



ARNOLD ABOUBACAR
MARGUERITA HOYLE
EDITORS

PUBLIC HEALTH IN THE 21ST CENTURY

ENCYCLOPEDIA OF
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PUBLIC HEALTH IN THE 21ST CENTURY

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PUBLIC HEALTH IN THE 21ST CENTURY

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ARNOLD ABOUBACAR

AND

MARGUERITA HOYLE

EDITORS



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PREFACE

This encyclopedia contains 22 volumes and a total of 552 chapters covering up-to-date research in the field of public health.

Chapter 1

ADOLESCENT ALCOHOL MISUSE

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"Fill with mingled cream and amber,
I will drain that glass again.
Such hilarious visions clamber
Through the chamber of my brain —
Quaintest thoughts — queerest fancies
Come to life and fade away;
I am drinking ale today."
Edgar Allan Poe (1809-1849)

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INTRODUCTION

Alcohol can be traced back to the neolithic period in human history which was the last period in the Stone Age of homo sapiens; during this truculent time ancient humans developed agriculture and utilized polished stone tools [1]. Ale is one of oldest liquids produced by humans dating back in the 5th millennium BCE; beer dates back to at least 3000 BC [2]. Alcohol was an important source of clean hydration for millennia when uncontaminated water was hard to find—even in modern times [3]. As noted by the famous French chemist and microbiologist of the 19th century who saved the wine industry: “*Wine is the most healthful and most hygienic of beverages.*” (Louis Pasteur: 1822-1895).

The Old Testament notes that wine “gladdens” the heart (Psalm 104:15), but also warns of the dangers of overuse of alcohol (Proverbs 20:1—10th century BCE) that includes poverty, strife, and injustice (Proverbs 23:20-21; 23:29-30; 31:4-5). Wine was prominently mentioned in the New Testament in the first century AD such as being used at weddings (John 2:3) or being associated with drunkenness and debauchery (Ephesians 5:18). Moderation in wine drinking was also linked to improved health (1 Timothy 5:23). Alcohol has been both celebrated and denounced by famous human beings for thousands of years.

“Alcohol may be man’s worst enemy, but the Bible says love your enemy.”
Frank Sinatra (1915-1998)

PREVENTION

We desperately need guidance in learning how to prevent alcohol and drug addiction in our youth and establish prevention programs to decrease the devastating toll it has and will take on billions of human beings in this century and beyond. We must be concerned and more cognizant about addiction and its effect on our youth including their alarming use of nonmedical analgesics. It is important to study youth in their communities and thus support more community-based research protocols [4]. It is useful to know what is positive in substance abuse management as well as what is not [5, 6].

PREDICTORS

Excessive drinking in adolescence can be a social and public health problem (violence, poor or missing school performance, drunk driving, suicide and risky sexual behavior as some examples) and prediction as well as prevention or abatement of adverse effects have both clinical and public health value.

Researchers [7] from the University of California San Diego School of Medicine have identified 34 neural factors that can predict adolescent alcohol consumption. Their study is a prospective investigation that used machine learning with demographic, neurocognitive, and neuroimaging data in substance-naive adolescents to predict alcohol use initiation by age 18 years.

There were 137 healthy substance-naïve adolescents aged 12-14 years in the study, who underwent neuropsychological testing and structural and functional magnetic resonance imaging (sMRI and fMRI), and then were followed annually.

At the age of 18 years, 70 out of the 137 (51%) started moderate to heavy alcohol use, while 67 remained non-users. The researcher used all the collected data to create a model containing predictors contributing to alcohol use by age 18 years:

- They were male with a higher socioeconomic background
- They reported dating, possessed more externalized behaviors, such as lying or cheating and believed alcohol would benefit them in social settings
- They performed poorly on executive function tests
- Their neuroimaging results indicated thinner cortices - the outer layer of neural tissue covering the brain

In this study neuropsychological, sMRI, and fMRI data increased the prediction accuracy of the model. Now the question is how to use this data in the clinical and everyday use of health professionals to predict, intervene and prevent excessive alcohol consumption in adolescence.

IMPRINT OF GENETICS

“We can do genetics. We can do experiments on fruit flies. We can do experiments on yeast. It’s not so easy to do experiments on humans. So, in fact, it helps us, to interpret our own genetic code, to have the genetic code of the other species.”

Craig Venter (b: 1946)

Alcohol use disorder is a complex condition with major underlying factors that involve one’s environment and genetic background [1]. Genetic components have been found to be highly contributory in some persons’ struggles with alcohol consumption [1, 8]. Genetic studies that have provided some insight into genetic features in these persons include candidate gene research, linkage research, twin studies, and genome-wide association studies (GWAS) [9].

Alcohol use disorder is found in some families and genetic factors account for 40% to 60% of this phenomenon that includes increase risk in monozygotic twin studies (versus the dizygotic twin) [10, 11]. The alcohol dehydrogenase gene cluster can lead to alcohol dependence in some persons while genes of alcohol metabolism (alcohol dehydrogenase [ADH] and aldehyde dehydrogenase [ALDH]) are protective [8, 9, 12].

Using genome-wide association studies (GWAS) some genes associated with alcohol dependence have also been linked with other substance abuse disorders [1, 8]. An example is that a number of genes in the gamma-aminobutyric acid-ergic system can increase the risks for nicotine dependence while changes in cadherin 13 may lead to methamphetamine dependence [13, 14]. Use of GWAS is aiding in finding new genes implicated in increasing risks for a person developing alcohol use disorder [1]. Another unique approach is to look at collections of data from state databases and use this so-called “big-data” tool to help identify

factors in the environment-genetics interaction in persons leading to problematic alcohol use [15].

Other genes under study include GABRA2 as well as alcohol dehydrogenases 1B and 4 [16]. Studies in adolescents have suggested that alcohol use disorder may be linked to certain circadian rhythm genes: NR1D1 and BHLHE41 [11]. Another gene of current interest is the GRIN2B gene that is linked to glutamatergic signalling and possible effects on alcohol use disorders via changes in the posterior cingulate cortex [17].

Also, ASTN1 (astrotactin neuronal protein) is a gene linked with alcohol dependence that is involved in glial-guided neuronal migration and has been linked by research to attention-deficit, hyperactivity disorder, autism spectrum disorders, bipolar disorder, and schizophrenia [8, 18]. Research also has seen a link between SNPs (single nucleotide polymorphisms) in the gene C15orf53 (located on chromosome 15q14); the number of alcohol-related symptoms and the greater number of alcohol symptoms leads to a higher chance of having a variant in this gene [19]. Variations in this gene may lead to augmented risks for bipolar disorder, a condition considered co-morbid with alcohol dependence [20].

CONCLUSION

What has emerged from 20th and now 21st century investigations is that alcohol use disorder is a neurobiologic-genetic disorder (brain disease) with different types such as the proposed Cloninger type 1 (harm avoidance type) with decreased dopamine and increased serotonin as well as type 2 (novelty seeking) with decreased serotonin [21]. The search for reliable biomarkers for this disorder (as healthful harbingers) will continue such as decreased platelet MAO activity, alcohol-induced dopamine (DA) release, measures of central glutamate levels, and studies using positron emission tomography of functional MRI as well as central glutamate tone using MR spectroscopy [22, 23].

Environment factors that intrinsically influence the development of alcohol use disorder that are under study include one's family milieu, exposure to childhood adversity, culture, and religion [24]. Further research will continue to overcome current inpasses and cul de sacs of ignorance in the complex interplay of one's milieu and genetics in the development of alcohol use disorder; such incessant, intrepid inquires involve animal work (i.e., rat models) and epigenetic studies (i.e., alterations and aberrations in DNA methylation and chromatin structure) [25-30]. The guidance of the U.S. National Institute on Alcohol Abuse and Alcoholism (NIAAA) has been important for nearly half a century in this exigent effort [30]. Such astute auspices is critical as clinicians and society saliently seek to circumspectly protect its children, adolescents, and adults from the doleful, deleterious dilemmas and cumbrous consequences of alcohol use disorder in the 21st century.

"I would not put a thief in my mouth to steal my brains."
William Shakespeare (1564-1616)

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Chapter 2

THE IMPACT OF EXPOSURE TO ALCOHOL ADVERTISEMENTS ON ADOLESCENTS: A LITERATURE REVIEW

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ABSTRACT

Alcohol consumption occurs worldwide and widespread among youth. Although, alcohol was once given to children as it was cleaner than water, neurological research continues to inform individuals of the toxicity of alcohol on the brain. The topic of interest is the subtle relationship between exposure to alcohol advertisements and alcohol consumption in children. The purpose of this literature review was to determine the current perception held by researchers concerning the relationship between exposure to alcohol advertisements and alcohol consumption by adolescents. Google scholars search engine was used to select published peer-reviewed journal articles related to the topic. The body of literature suggests exposure to alcohol advertisements does influence alcohol consumption among children around the world, including the United States, Germany and Australia. More specifically, increased exposure influences alcohol consumption by altering perceptions of alcohol. These findings indicate educating children and parents about the negative effects of alcohol on the developing child needs to begin at the start of secondary school. Although measuring the impact of exposure to alcohol advertisements is difficult, as technology advances, researchers in the fields of public health and neuroscience may be able to examine the subtle relationship between alcohol advertising and alcohol consumption more thoroughly. In addition, regulating alcohol advertisement content, location, and frequency to limit children's exposure is an ideal progressive policy reform that will serve to protect children.

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Keywords: adolescent health, alcohol abuse, Caribbean, Grenada, school health

INTRODUCTION

Alcohol consumption is a key component of cultures and economies around the world. The historical acceptance of alcohol use among cultures enables this substance's consumption in every country around the globe at almost any age [1]. The impacts of alcohol consumption on individual health and society at large make alcohol consumption a public health concern. The acceptance of alcohol consumption by society contributes to alcohols frequent promotion and alcohols frequent promotion contributes to alcohol's generational acceptance in society despite known health disadvantages of heavy consumption [2].

The long-term consequences of alcohol consumption during human development appears not to be communicated as well as the benefits of alcohol consumption as approximately 1-4% of infants are born with fetal alcohol syndrome [3, 4] and adolescents binge drink more than previous generations [5]. The health impacts of alcohol in adulthood are associated with age of consumption. The prevalence of alcohol abuse disorders among individuals who first consumed at age 12 years is 40% whereas the prevalence among individuals who first consumed at age 18 years is 16% [6].

A larger number of youth report heavy drinking compared to adults ranging from 50% of 12-14 year olds and 79% of 17-18 year olds [7]. Although the trends of binge drinking slightly differ by age and ethnicity, approximately 27% of 14-18 year-old males participate in binge drinking compared to 15% of females [5]. This is not just an American issue. A cross-sectional study of 13 year-old students in 6 European countries determined 27% reported consuming five or more alcoholic beverages at least once in their lives [8].

Alcohol consumption in general—especially binge drinking-- in children is a health risk for each child and others as alcohol consumption increases risky behavior [9]. Alcohol consumption by children increase the risk they will miss school, experience social (aggression), physical (headaches), and neurological problems (slowed memory, abnormal brain growth), abuse other drugs, partake in unprotected sexual activity, and die from alcohol poisoning. Alcohol consumption is a leading cause of disability [1] and the cause of avoidable injuries and deaths [1]. Underage drinking is related to the three leading causes of death among individuals aged 12-20 years, which are unintentional injury, homicide, and suicide [9].

Early adolescence is a critical period when the majority of individuals initiate alcohol consumption for a variety of reasons: primarily social [10]. Rarely do adolescents drink alone. A larger number of youth engage in alcohol consumption around other youth who are consuming alcohol. Youth aspire to drink to achieve euphoria from the sensation of breaking laws, social experience of drinking in a group, expectation of experiencing a positive emotional state [10]. Understanding that these perceived benefits of alcohol are not the only impacts of alcohol on society is important to convey to youth.

Although at the appropriate ages and doses alcohol consumption is relatively harmless, alcohol advertisements do not consistently convey this information to viewers. Children do not have the mental capacity to understand that marketing techniques are designed to persuade and manipulate viewers into becoming consumers [11]. The health risks and unique

vulnerabilities of children are overshadowed and underestimated by children due to the high influx of positive portrayals of alcohol consumption compared to realistic portrayals in advertisements [12].

The effects of alcohol exposure on the developing fetal brain are well documented under the spectrum of fetal alcohol syndromes [13]. Alcohol exposure in utero is one of the known preventable causes of a permanent intellectual disability. Due to the fact alcohol consumption by adolescents is commonly occurring without obviously disabling deficits; the effects of alcohol consumption on the adolescent brain were thought to be less significant until recent decades. The brains of children, just like the developing fetuses, are more vulnerable to the effects of alcohol compared to the mature brain. Neurological changes due to alcohol exposure are broadly predicted by two main behavioral patterns: early initiation of alcohol consumption and binge drinking during adolescence [14]. One beer will circulate in an adolescent's body at a much higher concentration than in a fully developed adult's body making smaller quantities of alcohol more toxic to developing children.

Human brains rapidly increase in size in the womb and in the first three years of life [15], but the second decade of life is important for improving the efficiency of the brain. Connections between neurons are strengthened and excess tissue is trimmed away in the normal developing brain. The brain naturally undergoes this process called "pruning" so that it relies on fewer important connections and can function with a higher speed of processing and accuracy. Research suggests that consistent consumption of alcohol from age 11-14, not only prevents the ability of the brain to prune itself [16], but increases a child's risk of developing alcohol dependent behaviors and suffering from the cognitive effects of neurodevelopmental delays, such as slowed cognition and impaired ability to control behavior [16].

Some adolescents may have a genetic predisposition to suffering from neurological changes from alcohol [16]. A study of monozygotic twins further disclosed some of the neurotoxic damages of alcohol exposure and potential inborn neurological differences that may increase risk for developing alcohol abuse disorders [17]. The study of twins revealed brain regions that were susceptible to neurotoxic damage in adolescents. The areas included the ventral diencephalon and middle temporal gyrus. These brain regions are important for processing sensory and motor information and emotions and memories, respectively.

Despite the health concerns for adolescents, they are frequently targeted and exposed to a high number of alcohol advertisements. Anderson, de Bruijn, Angus, Gordon and Hastings [17] discuss data demonstrating that children are more susceptible to the messages of alcohol advertisements compared to adults because they are inexperienced. The most common forms of alcohol advertisements encountered include television, billboard, poster, magazine, and radio. The Internet is also becoming a popular way to target youth with advertising as well [11]. The content of alcohol advertisements directed at youth, is a subject of concern. A five-year study of alcohol advertisements in American youth magazines revealed that one fourth of the alcohol advertisements, mainly beer and spirits, targeting youth sent messages with underlying sexual messages [18]. Interestingly, these underlying messages align with youth behaviors associated with alcohol consumption.

The content is more appropriate for an adult audience, yet is reaching many naive adolescents. Winter, Donaven, and Fielder [19] found that Australian adolescents ages 13-17 were exposed to the same number of alcohol advertisements as individuals 18-24, which was 75% of the advertisements viewed by 25 year-old individuals. In the United States, exposure

to alcohol advertisements increased for 18-20 year olds from 2005-2011 more than any other age group targeted by companies selling beer and spirits [20]. The tendency of the alcohol industry to target a vulnerable population suggests they are benefiting from the investment, which is a concern.

The hypothesis of this study was that alcohol advertisements do impact adolescents' choices to consume alcohol for the first time and to continue consuming alcohol. The purpose of this literature review was to determine the current perception held by researchers concerning the relationship between exposure to alcohol advertisements and alcohol consumption by children.

Goals

The goal of this literature review was to report a generalizable consensus on the relationship between alcohol advertisement exposure and alcohol consumption in adolescents to spread awareness and encourage action. To accomplish the goal, three objectives were established. The three objectives were to 1) review literature of published journal articles investigating the relationship between alcohol advertisement exposure and initiation of alcohol consumption and overall alcohol consumption in adolescents and 2) assess youths' reported perceptions of alcohol 3) assess other factors reported to influence alcohol consumption among adolescents. Key terms:

- Adolescent: individual between ages 10-19
- Youth: individual between the ages 20-26
- Alcohol advertisement: any form of communication that promotes alcohol consumption (e.g., individual drinking, posters, magazines, commercial).

METHODS

Google Scholars search engine was used to select published peer-reviewed journal articles related to the topic of interest. Google Scholars selects articles from search engines across the major academic fields including Public Health, Medicine, Neuroscience, Psychology, Anthropology, and many others. This enables a broad and thorough literature search that is not limited by the literature accessible through specific field-based search engines. In order to provide an understanding of the recent literature, articles were excluded if they were published—prior to 2005-- more than ten years ago. Articles published within the last seven years were preferentially chosen to the older articles to focus on current literature.

To search the literature regarding exposure to alcohol advertisements and alcohol consumption by adolescents, phrases such as “exposure to alcohol advertisements and age of consumption”, “exposure to alcohol advertisements and alcohol consumption among minors”, “impacts of alcohol advertisement exposure on children” were typed into the search engine.

To gather information on youths' perceptions of alcohol and alcohol consumption, phrases such as “youth's perceptions of alcohol”, “adolescents' beliefs about alcohol”, “adolescents' beliefs about alcohol consumption” were searched. Educational interventions

were searched using the same techniques. Phrases such as “alcohol education and consumption among minors”, “alcohol educational interventions for children”, “and impact of alcohol education on children” were searched in Google Scholars.

Fourteen published primary articles were chosen for review. The studies were completed in countries (Germany, Australia, New Zealand, United States) with a high rate of alcohol consumption among youth and high rate of alcohol advertisements. Longitudinal and cross-sectional study designs were included. The majority of the participants in each study were between the ages of 11 and 20 years. One study looked at children between the ages of 15 and 25 years.

Literature Analysis

Exposure to alcohol advertisements impacts adolescents’ preferences for alcohol and subtly encourages consumption. Caswell [21] found a positive correlation between exposure to alcohol advertisements and liking alcohol advertisements. In addition, the level of exposure to alcohol advertisements was more predictive of alcohol consumption for adolescents that reported liking the advertisements.

Whether or not some individuals are more inclined to like the advertisements by nature or if the advertisements are inherently attractive is a question researchers are trying to answer. Alcohol advertisements influence alcohol consumption in youth by associating desired outcomes, popular idols, and role models with alcohol consumption. Associating role models of adolescents and alcohol sends an underlying message to children that consuming alcohol is not only an acceptable activity, but also an enjoyable activity.

Moreover, Chen et al. [22] found a relationship between alcohol advertisement content and the development of positive expectations regarding alcohol consumption. Positive reactions to alcohol advertisements that target their audiences with humor, popular idols, and songs were positively related to adolescents’ intentions to purchase and consume alcohol. Although this study only related alcohol advertisements to the intentions of adolescents to drink alcohol and not alcohol consumption itself, the impact of alcohol advertisements on the intentions of adolescents is a subtle change in cognition.

Morgenstern et al. [23] found that attitudes toward alcohol consumption change in German youth, as they grow older and may mediate the effects of alcohol advertisements. At the follow up of the non-drinking German youth, 28% of the non-drinkers were current drinkers. In addition, 46% of the students reported more positive attitudes toward alcohol consumption. Only 15% of the participants reported less positive attitudes toward alcohol.

Ellickson, Collins and Hambarsoomians [2] investigated the relationship between exposure to in-store alcohol advertisements and alcohol consumption in a prospective cohort study of seventh grade South Dakotan students. For seventh grade non-drinking students, alcohol consumption in grade nine was predictable based on exposure to in-store alcohol advertisements. For seventh graders already consuming alcohol, exposure to magazines with alcohol advertisements and beer concession stands at sports or music events predicted frequency of alcohol consumption in the ninth grade. This study suggests that there is a possibility different forms of advertising uniquely influence different groups of children.

Collins et al. [27] conducted a longitudinal study of 11-12 year-old students in South Dakota to determine if there were any positive relationships between exposure to forms of alcohol advertisements and the students' odds of drinking within the past year. Collins et al. [27] found that 20% of the non-drinking fifth grade students in the 75th percentile of exposure to alcohol advertisements reported alcohol consumption by the seventh grade. Only 13% of the non-drinking fifth grade students in the 25th percentile of exposure to alcohol advertisements reported drinking in the seventh grade.

Snyder et al. [25] compared exposure to alcohol advertisements and industry data on the amount of money spent on alcohol advertisements with the number of alcoholic drinks consumed in the past month by individuals between the ages of 15-26. The results indicated that for each additional alcohol advertisements viewed in the previous month, the number of drinks consumed by individuals less than twenty years old increased by one percent. In addition, each additional dollar spent on alcohol advertisements increased overall alcohol consumption by 2.8 percent.

Henewinkel and Sargent [8] studied fifth through ninth grade students in Germany to examine the relationship between exposure to alcohol use in movies and initiation of alcohol consumption in this age group. Thirty-three percent of the participants initiated alcohol consumption without informing their parents and 14% were, at the point, binge drinking. The results of this study revealed that the mean exposure to alcohol advertisements in movie was 3.2 hours. Students were categorized into four different quartiles based on exposure to alcohol advertisements in movies. As exposure to alcohol advertisements increased, the risk ratio for initiation of alcohol consumption without parental knowledge and engaging in binge drinking increased.

Grenard, Dent, and Stacy [26] investigated exposure to alcohol advertisements, alcohol consumption and alcohol related problems in adolescents. Even after controlling for many covariates (drinking by peers, drinking by close adults, playing sports, parents' education, and others), alcohol ad exposure and liking of the ad in seventh grade predicted participants' alcohol consumption in ninth grade and alcohol use problems. This study suggested that, for some adolescents, alcohol advertisements are one of the major factors encouraging more alcohol consumption by youth and which ultimately lead to alcohol use problems. One factor contributing to consumption by adolescents may be that the alcohol advertisements of popular brands consumed by the age group are more appealing to them compared with the advertisements of unpopular brands [27].

Literature indicates alcohol advertisements on television, in-stores, and on the radio are not the only forms of advertising children notice. Pasch et al. [28] found that as exposure to alcohol advertising near schools increases the intention to drink increases as well. Pasch et al. [28] and Feighery et al. [29] both investigated the relationship between owning alcohol promotional items with adolescent alcohol consumption. Feighery et al. [29] found that two-thirds of the 11-14 year-old students reported weekly visits to retail stores in which alcohol advertisements were noticeable. Both exposure to alcohol advertisements in stores and possessing alcohol promotional items were associated with greater odds of ever drinking alcoholic beverages [29]. Moreover, the children who indicated they own alcohol promotional items were 1.5 times more likely to currently consume alcohol [29].

As the Internet continues to emerge as a platform for youth activities and an unlimited source of exposure to any type of advertisement, investigations on the impact of online alcohol advertisements determined that online alcohol advertisements are powerful marketing

tools for youth. Lin et al. [30] found that exposure to online alcohol advertisements increased 13-14 year olds' odds of drinking by 98% whereas exposure to offline (posters, television, radio) alcohol advertisements only increased the odds of alcohol consumption by 51%. Combined exposure to online alcohol advertisements and offline advertisements increased consumption among children already drinking [30]. In a cross-sectional study of Australian boys aged 12-15 years, similar results to Lin et al. [30] were found regarding the impact of alcohol advertisements and alcohol consumption. Jones and Magee [31] found exposure to alcohol advertisements on the Internet was associated with current alcohol consumption among the male youth. Interestingly exposure to alcohol advertisements in venues where alcohol is consumed (e.g., bars) was associated with alcohol consumption within the last year. When male youth were exposed to alcohol advertisements in bars and online, there was an association with alcohol consumption within the last month. This article suggests that exposure to online advertisements potentiates the effects of exposure in public areas of consumption.

Additional Influences

Many factors are involved in an adolescent's choice to consume alcohol for the first time and binge drink, such as peer relationships [32] and parenting styles [33]. Parental involvement is associated with decreased drinking age, but these effects may decline as age increases [34]. Sex and age impact age of consumption as males are more likely to consume at an earlier age compared to girls [14, 34]. The effects of alcohol advertisements likely changes throughout an individual's life, but children are the most susceptible. Gordon et al. [35] suggested that the impact of alcohol advertisements on children may increase after a child consumes alcohol for the first time. Adolescents who reported previously consuming an alcoholic beverage paid more attention to alcohol advertisements than adolescents who did not report prior alcohol consumption [35]. These influences, similar to alcohol advertisements exposure, were difficult to measure and not conclusively more powerful than the impact of alcohol advertisements. The choice to consume alcohol in adolescence is a myriad of influences acting in tandem.

Alcohol advertisements use the multifactorial relationship to their advantage; where as other influential factors do not or cannot join forces. Kenny, Hastings and MacKintosh [36] reported that alcohol advertisements are involved in the establishment of social norms and also use peers to potentiate the effects of alcohol advertisements on alcohol consumption. This suggests that peers contribute to the impact of advertisements and that advertisements may shape peers. Peers were often victims of the advertisement campaign and promote positive messages. It is not known whether or not parents and peers can work together to decrease the age of initiation of alcohol consumption and frequency among adolescents.

Counterarguments against the relationship between alcohol advertisements exposure and adolescent alcohol consumption are limited. Some individuals, primarily those working for the alcohol advertisement industry [37], promote that individuals will consume alcohol regardless of the presence of alcohol advertisements. According to the Drug Control Officer of Grenada, Mr. Dave Alexander, alcohol advertisements "promote brand choice" and serve as a reminder that alcohol is "present and available" rather than a form of coercion to

consume alcohol [38]. Alcohol companies agree with Dave Alexander as they claim advertisements promote brand choice, not consumption, as consumption is going to happen whether or not they advertise alcohol.

A recent study on the level of exposure to alcohol advertisements for a specific brand at a population level and the consumption of that specific brand among adolescents supported the claim that alcohol advertisements promote brand choice among adolescent consumers. The results revealed that exposure to brand specific advertisement was a predictor of consumption of that specific brand among adolescents [39]. The problem is alcohol advertisements are supposed to promote brand choice among adults, not adolescents.

Contrary to the argument that everyone will consume alcohol and will continue to consume alcohol is misleading. Data from the WHO indicates only 39% of the world's population actually consumes alcohol regularly [1]. The percentage of the population that consumes alcohol is less than 100 and varies from country to country—the highest being in Europe and lowest in Middle Eastern and North African countries. In Mali, 96% of the population abstains from alcohol consumption throughout their lifetime compared to 11% of Canadians. Although Grenada has a reputation for high alcohol consumption per capita, thirty percent of Grenadians over age fifteen report never having tried alcohol [1].

Limitations

Many biases may be embedded not only in the literature selection, but also in the literature selection of publishers. Determining the relationship between exposure to alcohol advertisements and alcohol consumption among adolescents is difficult for researchers due to the complexity of the relationship and inability to quantitatively measure the variable. Although the articles selected clarified that they accounted for confounded variables, the factors such as peer relationships and parental involvement are as challenging to measure as alcohol advertisement itself as the accuracy of the participants' reports are essential for determining the impact of the variable.

Moreover, quantitatively measuring each child's exposure to alcohol advertisements is not simple. There is not a straightforward test that tells researchers the exact amount of exposure. In spite of this limitation, studies used various techniques to measure the parameter as accurately as possible. The studies in this literature review were conducted on children who lived in areas with an elevated prevalence of alcohol consumption among youth. This study population may mask the persuasive influence of alcohol advertisements as everyone is exposed frequently.

Other limitations arise as a result of the study designs. Two types of observational studies were included in this literature review: cross-sectional and longitudinal. Limitations arise, as neither type of study is suited for this non-linear, multifactorial, problem. Both cross-sectional and longitudinal studies are inherently biased to a degree. Cross-sectional studies are often called snap-shots of situation because they involve collecting data over a very short time frame and analyzing it for correlations. The limitation of this type of study is that cross-sectional studies do not provide information about the variables before or after the point in time the data was taken; therefore, these studies are not useful for establishing causal relationships. However, each moment of a child's life is far more significant to a child than

the same moment is to an adult as children have hardly lived but a moment at all. With that in mind, the data provided through snap-shots was useful for interpreting one piece of a group of children's experiences.

Longitudinal studies are beneficial for establishing linear causal relationships and the impact of alcohol advertisements on youth is not a linear relationship. These studies examine the same group of participants over a long time frame. This involves collecting baseline and follow-up data on the variables of interest. Longitudinal studies allow researchers to examine the variable before and after exposure so to a certain degree one can estimate if overtime alcohol advertisement exposure increased and alcohol consumption by comparing baseline and follow up data of consumption with self-reported exposure to alcohol advertisements.

CONCLUSION

Correlations, associations, and other statistics do not and cannot suggest direct causation as conclusions on this topic frequently proclaim. The initiation and continued consumption of alcohol by youth is complex, yet simple. There is one factor that will influence nearly every adolescent consuming alcohol in every country and that is alcohol advertisements. Alcohol advertisements are influencing the alcohol consumption of youth and perhaps more than we can currently determine [40]. Ignoring the persuasive effects of advertisements on children in an attempt to preserve the freedom of the alcohol industry to target a vulnerable population ignores the responsibility of society to protect children. Moreover, alcohol advertisement exposure is a factor that public health interventions can effectively attempt to mediate through education and policy change.

In order to reduce alcohol consumption in youth, more than one action is necessary. The most important action is providing children with an education that enables them to think for themselves [21]. Children need to be informed that advertisements are only partially correct. They need to know that alcohol is not all fun and games rather alcohol is deadly. Regulating alcohol advertising is a common response, but may not help by itself. In the United States, the alcohol industry advertisement guidelines require 70% of the viewers be twenty-one or older. This is a voluntary compliance and is not well enforced. Therefore, it is not necessarily surprising that more alcohol advertisements target youth compared to adults and youth are being exposed more frequently [25]. In 2009 Israel implemented an alcohol policy prohibiting sales to minors and consumption in public, limiting advertising, and enforcing alcohol taxations. The policy changes combined with strict enforcement were beneficial to reducing alcohol consumption in public [41].

The United Kingdom adopted slightly more stringent guidelines as alcohol advertisements are not allowed at all during any event or television or radio programs with a primary audience less than the age of 18 years [42]. Norway and Sweden limit alcohol advertisements to the public by restricting alcohol advertisements completely on beverages containing greater than 2.5% and 3.5% of alcohol respectively [43]. The effects of these new regulations on alcohol consumption by youth may be documentable within the next decade.

The reported knowledge from the literature in this review is relevant to Grenada, West Indies. Grenada is a small island that depends on the alcohol industry to provide jobs for citizens and a source of revenue for the island. Despite popular belief that everyone in

Grenada consumes alcohol, everyone in Grenada does not consume alcohol. Similar to Europe and Australia, Grenada's adolescents are exposed to alcohol advertisements in their everyday environments and begin consuming alcohol in early adolescence. The average age is eleven [44]. According to a Drug Prevalence Survey of Grenadian secondary students [34, 44], 65% of students perceived that inhaling second hand cigarette and marijuana smoke was very harmful to your health compared to 54% of students who perceived getting drunk was very harmful to health. The fact that more students believe inhaling second-hand smoke is very harmful to health than students who believed consuming alcohol is very harmful to health suggests there may be an unbalanced understanding of the dangers of each alcohol consumption.

Government of Grenada [34], reported results from implementation of a pilot drug prevention program in pre-school and kindergarten programs during the 2007 school year. Twenty-eight Grenadian teachers attempted to complete the education program. Unfortunately, five did not receive the lesson plan manual. Teachers that did teach from the manual reported the manual as good overall, but lacked visual aids. Some teachers did not teach from the manual directly rather they taught concepts as they felt it contained information too advanced for the age group. Revision of the manual, distribution of the materials, and short training sessions for the teachers may improve the ability of teachers in Grenada to communicate the material to students and enhance the learning experience. Incorporating frequent short interactive alcohol and alcohol marketing education programs into secondary-school curriculums may be an efficient step towards increasing awareness of marketing tactics and decreasing unavoidable consequences of heavy alcohol consumption in adolescence.

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Chapter 3

ALCOHOL-RELATED ROAD TRAFFIC ACCIDENTS IN THE ENGLISH-SPEAKING CARIBBEAN: A CALL TO ACTION

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ABSTRACT

The alcohol consumption levels of a nation as well as government initiatives to monitor and control it can greatly influence the health status of a population. Road traffic accidents (RTA) are caused by numerous factors that range from faulty vehicles and poor road design to driver-related, which includes alcohol-impaired driving, speeding, and driver in the distractions. However, alcohol-impaired driving is responsible for a large proportion of RTAs in the Caribbean. This paper reviews the background of alcohol related RTAs in the Caribbean and examines policy options aimed at reducing alcohol and illicit drug related RTAs in the Caribbean region.

Keywords: alcohol consumption, Caribbean, public health, road traffic accidents

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INTRODUCTION

The UN General Assembly has declared 2011-2020 as the "Decade of Action for Road Safety". This is significant as road traffic accidents (RTAs) are a leading cause of morbidity and mortality in both developing and developed countries [1-4]. Annually over 1.3 million people worldwide die as a result of RTAs, and approximately 20-50 million sustain severe injuries, the majority of which require long-term treatment [5]. However, low and middle-income countries LMICs are disproportionately affected [6] where it is estimated that 94% of road traffic-related deaths occur. Though these countries have just over half of the world's registered vehicles. The burden of is higher among the youth and young adults as well as middle-aged individuals who, combined, constitute the economically most productive age groups of society [1, 3, 6, 7]. Consequently, RTA rates remains one of the most important health and social policy issues that spans all countries across all continents [5].

Understanding the risk factors associated with RTAs is as important as understanding the population at risk, for the development of policies to reduce the growing burden. Traffic incidences are multifactorial events that are caused by human factors, technical issues and environmental conditions [8], but the majority is attributed to human or driver-related factors [7]. A large proportion of RTAs are associated with driving under the influence (DUI) of either alcohol or drugs [2, 9-12]. Thus, while increased death rates in LMICs, like the Caribbean, are driven, at least in part, by rapid motorization, the lack of concomitant road safety strategy implementation and safe road infrastructure development is also largely responsible [13].

RTAs and their consequences, increased mortality and disabilities, can be reduced through preventive programs that tackle the multifactorial natures of RTAs. Such an approach would seek to address this public health concern, through a mechanism of public policies on road accident prevention and stricter enforcement of the regulations resulting from these policies. This approach recognizes that the impact of RTAs is both at the individual and the population level.

While RTAs are an issue throughout the Caribbean, this paper examined policy options aimed at reducing alcohol and illicit drug related RTAs in the Caribbean region. The specific expected outcomes are [1] improved data quality to quantify the true burden of alcohol and illicit drug related RTAs; [2] focused campaigns promoting safe driving habits; [3] increased public and governmental awareness of the realities of alcohol and illicit drug related RTAs and [4] decreased alcohol and illicit drug RTAs.

BACKGROUND

As early as 1962 the World Health Organization (WHO), through Resolution WHA27.59, challenged member states to address the urgent problem [14]. However, six and a half decades later RTAs remains a major public health concerns for countries around the globe. It is estimated that in the absence of increased efforts and new strategies and policies, the total number of road traffic deaths is expected to reach 1.9 million by the year 2020. Currently, the majority of such deaths are among vulnerable road users - pedestrians, pedal cyclists, and motorcyclists. In addition, the youth and young adults are disproportionately burdened.

It is well documented that traffic accidents are caused by numerous factors that range from faulty vehicles and poor road design to driver-related, which includes alcohol-impaired driving, speeding, and driver distraction [7, 11, 15, 16]. However, alcohol-impaired driving is responsible for the greater proportion of RTAs. Global Burden of Disease (GBD) estimates for 2010 indicated that almost 200,000 road traffic accident fatalities were the direct result of alcohol [17]. DUI of alcohol and illicit drug use presents unique challenges for public health and government officials [6]. Studies have documented that the relative risk of being involved in a RTA significantly increases at a blood alcohol content (BAC) level as low as 0.04g/dl [2, 12, 16, 18]. Movig et al. [19] provided substantial evidence that individuals involved in alcohol or substance related motored vehicle accidents have an increased risk of hospitalization.

According to the WHO's Global Status Report on road safety, raising public awareness is the first step to prevention of RTAs and is necessary to raise support for progressive legislation. In regards to alcohol consumption, such legislation may involve mandatory testing of drivers involved in RTAs, as exemplified by the Philippine Road Action Plan of 2011 [20]. It is well documented that substance use is influenced not only by individual choices, but also by a combination of social, economic, and environmental factors, and consequently a multipronged approach to raising awareness of the dangers of substance and alcohol use while driving is necessary. Such an approach should include policy changes along with educational and media campaigns as well as strict enforcement of the law [21]. Chile's experience suggests that traffic law reforms in order to have an effect on both traffic fatality and injury rates reduction require changes in police enforcement practices [15, 22]. The findings suggest that the police traffic enforcement increment registered after the introduction of its 2005 traffic law reform reduced traffic fatalities by 59% and severe injuries by 37% [15]. In addition, this case illustrated how the diffusion of successful road safety practices globally promoted by WHO and World Bank can be an important influence for enhancing national road safety practices.

CARIBBEAN REALITY

The alcohol consumption levels of a nation as well as government initiatives to monitor and control it can greatly influence the health status of a population. This paper seeks to examine English speaking Caribbean countries and the legalities of alcohol consumption in these countries.

The most populous of the countries examined is Jamaica with 2,741,000 people, followed by Trinidad at 1, 328,000. Saint Kitts and Nevis is the least populated with 52,000 people. Alcohol consumption varies from island to island, however, some themes remain consistent between them. See table 1 for a summary of the World Health Organization information regarding alcohol in the Caribbean [23].

In comparison to the rest of the English Speaking Caribbean, Antigua and Barbuda has the lowest national legal minimum age for off and on premises sales of alcohol at 10 years old. This indicates that pre-adolescent children can easily and legally access alcohol in Antigua and Barbuda. There is no set Blood Alcohol Concentration (BAC) when driving a vehicle in the nation of Antigua and Barbuda as well as in Barbados, Dominica, Grenada and

Saint Vincent and the Grenadines. The rest of the countries have a set standard of 0.08% BAC when driving a vehicle.

Despite being the country with the earliest minimum age for legal alcohol sale, Antigua and Barbuda does not have the highest Patterns of Drinking Score as of 2010. This composite measure of drinking patterns reflects how people drink instead of how much they drink, on a scale of 1 (least risky pattern of drinking) to 5 (most risky pattern of drinking). Attributes used to create this indicator include quantity of alcohol consumed per occasion, festive drinking, the proportion of drinking events when getting drunk, the proportion of drinkers who drink daily, drinking with meals, and drinking in public places [23]. On a scale of 1 to 5, with 1 being the least risky and 5 being the most risky Grenada has the highest patterns of drinking score in the English speaking Caribbean at 4.

Common to all the countries analyzed, spirits are the most consumed type of alcoholic beverage, usually almost at 50% in each country except Trinidad and Tobago. Trinidad and Tobago serves as the exception, where Beer at 54% is the main type of alcoholic beverage consumed as of WHO's survey in 2010. Trinidad and Tobago has a low Patterns of Drinking Score as of 2010 at 2, on a scale of 1 to 5, with 1 being the least risky and 5 being the most risky. Other countries, which also share the lowest Patterns of Drinking Score 2, are Bahamas, Barbados, Jamaica, Saint Kitts and Nevis and Saint Vincent and the Grenadines. Not surprisingly, these are the countries with the oldest legal minimum legal age for alcohol sales at 18 years old except Saint Vincent and the Grenadines where the legal age is 16 years.

Table 1. Summary of alcohol consumption

	AB	Bah	Bar	D	G	J	SKN	SL	SV	TT
Written national policy (adopted/revised)/National action plan	No	Yes	No	No	No	No	No	No	No	No
National legal minimum age for off-premise sales of alcoholic beverages	10	18	16	16	16	18	18	18	16	18
National legal minimum age for on-premise sales of alcoholic beverages	10	18	18	16	16	18	18	18	16	18
National maximum legal blood alcohol concentration (BAC) when driving a vehicle (general/young/ professional), in %		0.08				0.08	0.08	0.08		0.08
National Government Support for Community Action	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
National Monitoring System(s)		Yes			Yes	Yes		Yes		
Pattern of drinking score (1-5)	3	2	2	3	4	2	2	3	2	2
RTA-male (per 100,000)		4.9	9.9			5.2				12.6
RTA – female (per 100,000)		1.7	3.7			1.9				4.9
Heavy episodic drinking – males (%)				41.5	8	11.9	33.3	8.6	9.9	
Heave episodic drinking-females (%)				14.3	1	2.1	10.4	1.2	1.3	

Source: World Health Organization (2014) *Management of Substance Abuse. Country Profiles 2014*. Retrieved from http://www.who.int/substance_abuse/publications/global_alcohol_report/profiles/en/.

Note: AB – Antigua and Barbuda; Bah – Bahamas; Bar – Barbados; D – Dominica; G – Grenada; J – Jamaica; SKN – St. Kitts and Nevis; SL – St. Lucia; SV – St. Vincent and the Grenadines; and TT – Trinidad and Tobago.

The health consequences of alcohol consumption (morbidity and mortality) were quantified per 100,000 population (15 years and older) in 2012 in Bahamas, Barbados, Jamaica, Trinidad and Tobago only. Of these countries, Trinidad and Tobago had the highest Alcohol Attributable Fractions (AAF) for liver cirrhosis at 56.8% in males and 52.5% in females. Trinidad and Tobago also had the highest Age-standardized Death Rate (ASDR) for

road traffic accidents with males at 28.8 and Females at 13.6. The Years of Life Lost Score was 3 on a scale of 1 to 5 with 1 being the least risky and 5 being the most. These analyses were not made for most of the other countries, so it is uncertain whether Trinidad and Tobago would have ranked highest for these criteria if other countries were included.

The percentage of heavy episodic drinking was the highest in Dominica at 41.5% in males for the population and the least in Grenada at 8.0% in males for the population. In all the countries, males tended to consume alcoholic beverages more than females. In contrast, Grenada had the highest total alcohol per capita consumption in the region with males (15 years and older) at 29.9L/capita, females 19.6L/capita and both sexes 25.5L/capita.

Only Trinidad and Tobago and Bahamas have alcohol policies and interventions and a national action plan for alcohol. The rest of the examined countries all do not. Legal binding regulations on alcohol binding, placement, sponsorship and sales promotion are non-existent or limited in majority of the countries.

Within the Americas an estimated 5.4% of all deaths were attributable to alcohol consumption which is 68% higher than the world average [24]. Alcohol was responsible for approximately 10% the Disability Adjusted Life Years (DALY) lost in the Region in 2002 compared to the global figure of 4.4%. In Trinidad and Tobago, the per capita consumption per drinker in liters of pure alcohol, including unrecorded consumption, is 8.7 liters per person. Excess alcohol intake (>1-2 drinks per day) contributes an estimated 20-50% of road traffic fatalities in the region [24]. Alcohol use remains historically high in the Caribbean region [13]. Analysis of data from school surveys sponsored by Inter American Commission on Drug Abuse Control (CICAD) indicates that adolescents and youth in the Caribbean drink frequently and at an age when alcohol consumption is prohibited by law [24]. The lifetime prevalence of alcohol use among teens in the region ranged from 86.2% in Saint Lucia to 47.72% in Haiti. The mean age of first use of alcohol across the region was 11.7 years. One study noted that individuals drinking alcohol before age 15 are 5 times more likely to develop alcohol abuse or dependence than people who first used alcohol at age 21 or older. Other studies have noted that the acute consequences of underage drinking include unintentional death and injury associated with driving or engaging in other risky tasks after drinking [2, 9].

DISCUSSION

There is need for action on alcohol consumption control by English Speaking Caribbean countries. Improved alcohol consumption levels can serve to reduce mortality and morbidity, which can promote better health status for citizens and positively impacts countries. Because many countries do have an issue with alcohol and either no monitoring system or national plan, governments should develop a comprehensive road safety programme, which includes an information network and database, which will assist policy makers in addressing alcohol related RTAs more effectively. The programme should include standardized blood testing, mandatory hospital testing of all motor vehicle victims and a police officer alcohol and drug checklist.

Standardized blood testing for alcohol and other substance use in RTA should be conducted. This is to ensure comparability of data across all facilities. There is sufficiently strong evidence to indicate that having established BAC limit for drivers, supported by

standardized laboratory testing, can help reduce road traffic injuries and deaths [25-30]. A standard blood test that all hospitals use to test for alcohol and illicit drug levels in the blood of motor vehicle victims will streamline the process of collecting blood samples, remove any questions that may result from non-standardized blood samples. However, the use of blood alcohol concentration (BAC) levels, while it can, through legislation, help curb the number of RTAs, in and of itself is not enough. Successful implementation will also establish guidelines for enactment in other territories in the Caribbean. However the effectiveness of BAC levels testing is dependent on many factors aside from the availability of the test. It would require that traffic police resources be improved and further education provided to police on the general deterrence potential of BAC [31]. Its effectiveness would require heightened community education and public awareness campaigns to ensure improved knowledge of new drinking and driving regulations and how to stay within the confines of the law. The success of BAC testing is dependent on publicity and visible, rapid enforcement of BAC regulations. In addition, a decrease in trends would only be possible with support from other programmes. Alcohol misuse problems should be addressed, particularly for drunk driving offenders and repeat offenders [30].

Mandatory hospital testing should be conducted for all RTA victims. Through mandatory testing and subsequent data collection, government officials will be able to develop a more comprehensive picture of alcohol related RTAs. Improved, timely data will assist in informing policy and interventions for this major public health problem. It will also help public health practitioners to better quantify the relationship between blood toxicity (alcohol or illicit drugs) and RTAs and the proportion of the mortality and morbidity burden attributable to alcohol-related RTAs. Mandatory, routine testing will eliminate the question of whether to test or not test and make testing more objective, removing the element of subjectivity. In addition, it will remove the barrier of test results and the medical practitioner as a liaison between laboratories and the police.

The final component is police officers mandated to fill out a checklist, which includes an assessment of all individuals involved in RTAs for alcohol and drug use, at the scene of every accident that is investigated. A checklist will assist in the standardization of police protocols in quantifying the number of individuals involved in RTAs who are under the influence of alcohol or illicit drugs.

CONCLUSION

The goal of any traffic program or policy is to decrease road traffic injury, which is related to any specific issue in this case alcohol related incidences. Multicomponent programmes and policies, such as what is detailed is generally known to include a combination of efforts to limit access to alcohol or to have measures that deter alcohol use, responsible beverage consumption, sobriety checkpoints or other well-defined enforcement efforts, public education, and media advocacy all designed to gain the support of both policymakers and the general public for reducing alcohol-impaired driving and alcohol-related road traffic accidents. Studies suggest that carefully planned, well-executed multicomponent programmes that are implemented in conjunction with community

mobilization efforts are effective in reducing alcohol-related RTAs and at cost savings to the country [32].

There is need for action in the Caribbean to reduce the alcohol related mortality and morbidity of RTAs, and to establish data to support evidence or practice based decisions and programs. As data are collected policies and programs can be developed to focus educational awareness and campaigns targeting specific regions, age groups and other demographic groups that are most in need.

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Chapter 4

THE RELATIONSHIP BETWEEN ALCOHOL USE AND SOCIAL AND CULTURAL DETERMINANTS IN GRENADIAN ADOLESCENTS

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ABSTRACT

The purpose of this study was to assess the relationship between family structure, parental involvement and peer pressure and alcohol use among Grenadian adolescent. A secondary data analysis of the 2013 secondary school drug prevalence survey for Grenada was conducted. A nationally representative group of secondary school students were selected for the study through a two-stage sampling frame. Questionnaires were completed by students (n = 1,490) in forms 2, 4 and 5 from seventeen public and private secondary schools. The independent variables were family structure, parental involvement and peer pressure. The dependent variable was alcohol use. Continuous variables were summarized using a mean and standard deviation. Categorical variables were summarized using frequency and percent. Chi Square test A significant relationship was found between parental involvement and patterns of drinking ($X^2 = 91.9$, $p = <0.001$). Significance was also found between peer pressure and frequency of drinking. ($X^2 = 145.3$, $p = <0.001$). The findings from this study did not show any significant relationship between the different family structures and the use of alcohol among adolescents. ($X^2 = 13.78$, $p = 0.131$). A high perception of parental involvement was associated with being less likely to consume alcohol. Experiencing minimal peer pressure was associated with less use of alcohol, which was also related to strong parental involvement.

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Keywords: parental involvement, peer pressure, alcohol, family structure

INTRODUCTION

Global alcohol consumption in 2010 was rated at 6.2 liters per person 15 years and older. In 2014, Grenada was ranked as the country with the highest rate of alcohol consumption in the Caribbean, with a rating of 12.5 liters per capita [1]. It is not known how much adolescent alcohol consumption contributed to the rating. However, the lifetime prevalence of alcohol use among secondary school students in Grenada is 72% with an average age of initiation of 12 years [2]. This high rate of alcohol use during adolescence is a cause for concern specifically from a public health, economic and social perspective. Excessive use of alcohol can have health and social burdens on communities. Social and cultural factors such as peer pressure, family structure and parental involvement are major contributing factors to adolescent alcohol use in Grenada.

Adolescence is characterized as a time of experimentation. This age group is usually more vulnerable to alcohol-related harm because their brain is still developing [3]. Therefore, early introduction of alcohol, before age 14, is related to an increased risk of alcohol addiction and misuse, which can continue throughout an individual's lifetime [4]. Alcohol dependence and abuse can result in impaired health status, alcohol-related motor vehicle crashes and other unintentional injuries [4]. Thus, it is important to understand the factors associated with early adolescence alcohol consumption.

At the adolescent stage children go through physical, emotional, intellectual and social change. Although the consequences of alcohol use have been studied, the social and cultural factors underlying their early initiation of drinking is less understood [4]. Understanding the role socio-cultural factors play in adolescent alcohol consumption would help develop effective school and community based programs and alcohol policies directed towards adolescents. This can reduce the burden adolescent alcohol use place on communities thus improving the health and social well-being of these communities which is an important aspect of public health.

Alcohol has accounted for 3.3 million or 5.9% of all deaths worldwide [4]. Although the majority of deaths and disabilities are among adults, the use of alcohol is common during adolescence. Approximately 10.4 million adolescents between twelve and twenty years consumed more than "just a few sips" of liquor in 2009 [5]. Additionally, children drink more as they get older, 70% of adolescents consume at least one drink by age fifteen [5]. Research examining adolescent alcohol use patterns predicted that by age 16, a significant percentage of teenagers were consuming alcohol at levels considered harmful for adults. Furthermore Heron et al. found that early exposure to alcohol was strongly linked to its use later on in life [6]. Similarly, a report on Alcohol in Europe stated approximately all 15-16 year-old students (>90%) consumed alcohol during their life. On average, they began to drink at 12½ years, and got drunk for the first time at 14 years [7]. Possible predictors to adolescent alcohol use by age 15 were early parental drinking and heavy drinking by the father. Additionally, adolescents belonging to two-parent households were less intense alcohol users compared to those from single-parent households [8].

When observing adolescent drinking practices, attention should be paid to the direct social context in which they drink and how their patterns are structured based on differences

created within society [9]. Adolescent drinking patterns should be understood at the same level at which their practice is guided such as symbolic significances discussed through societal communications. Young people are “cultural agents” who construe their traditional values and meanings to create their own individual social worlds [9]. The way adolescents construct their social world is crucial in understanding their drinking habits.

Historically, the Caribbean has been a key producer of sugar cane and rum. Hence it is habitual for adults to drink alcohol in social gatherings since it is a part of their regular diet [10]. Although knowledge of adolescent health status in the Caribbean is limited, separate information on alcohol abuse indicated a cause for concern [11].

Previous studies suggested 49 to 67% of youths consumed alcohol during their lifetime [12]. Similarly, a Caribbean drug use survey found that previous year’s prevalence of 55.16% was distinct in ages 14 or less and 15-16 [10]. From age thirteen, adolescents are more susceptible to experiment with minor misbehavior since they are strengthening their identities [10]. Therefore higher incidence of alcohol use can be attributed to adolescent experimentation.

Prinstein, Boergers and Spirito, conducted a study on adolescents and their friends reported an adolescent’s health risk behavior was strongly determined by their association with friends who engage in risky behavior [13]. Thus, use of alcohol by peers was linked to use of alcohol by adolescents themselves. On the contrary, it was highlighted that adolescents who associated with non-deviant peers were likely to abstain from alcohol use [13]. Furthermore, assessment of adolescent vulnerability to peer influence utilized the social learning theory. For a behavior to be reinforced, adolescent’s observation of their peer’s behavior does not have to occur. Believing that peers approves of a certain behavior can encourage the behavior. Therefore, the perception that peers would approve of adolescents alcohol use may be the influential factor in early adolescent when direct pressure is not present [14].

Peer influence was also examined in relation to other variables such as parenting style, parental monitoring and family structure. Low levels of authoritative parenting and monitoring can increase the influence that peers have on adolescents [13]. Therefore, high peer influence along with high family dysfunction were linked to increased health risk behavior.

Family dysfunction was also directly associated with increased alcohol use. Research examining risk factors for adolescent substance use highlighted that adolescents in dysfunctional families turn to alcohol as a stress reliever if there was no family support [15]. Parental monitoring of adolescents behavior was not effective in these families due to poor communication. On the other hand, general communication, relationship between parent and child, parental involvement and parental monitoring were found to be predictors of delayed alcohol initiation and reduced levels of future drinking by adolescents [16]. It was emphasized that although parental monitoring is necessary it is not sufficient to influence adolescent’s behavior [17].

Although the various studies were consistent with the variables to be explored in this study, insufficient research has been done to examine their relationship to adolescent alcohol use in Grenada. A study on substance abuse among young people in Grenada stated that although there is quantitative statistics on substance abuse among young people, inadequate qualitative research has been done on the subject [18]. The social disorganization of society was seen as the major influencing factor for alcohol use. As stated by Douglas, the problem of

alcohol use and abuse is a social construction of the society we live [18]. Recommendation was made by the Drug Avoidance Secretariat to conduct a study to identify new findings to reduce the incidence of substance abuse among young people. Based on the preceding studies, and the gap in knowledge, it is important to continue the study of socio-cultural factors associated with adolescent alcohol use in Grenada.

Therefore, the purpose of this study was to assess the relationship between family structure, parental involvement and peer pressure and alcohol use among Grenadian adolescent. Results from the study would be used to make recommendations to a school-based program tailored towards delaying the initiation of adolescent alcohol use.

METHODS

The data for this study was retrieved from the 2013 secondary school drug prevalence survey inclusive of Grenada and Carriacou. An anonymous, self-administered questionnaire developed by the Drug Control Secretariat of Grenada and the Inter-American Drug Abuse Control Commission (CICAD) was used for the survey. This questionnaire contained 105 questions representing drug use, parental involvement, consequences of drugs and health risk behavior. For the purpose of this study, 36 questions were used. The items measured family structure, parental involvement, peer pressure and alcohol use.

The following describes the methods used to obtain the sample used in the drug prevalence survey. A random sample of 1,490 students in forms 2, 4 and 5 from seventeen public and private secondary school students throughout the island of Grenada and Carriacou were selected for this survey. A two-stage sampling frame was used to select the participants. The first stage randomly sampled the secondary schools. Sixteen schools were randomly selected from twenty secondary schools on the island of Grenada. To ensure representation of Carriacou and Petite Martinique, one secondary school was randomly selected from Carriacou. The second stage included a random selection of classrooms in forms 2, 4 and 5 within each of the selected secondary schools. All students ($n = 1,860$) in the selected classrooms were asked to participate. A total of 1,460 students participated, representing an 80% response rate. The demographic characteristics of the students are provided in Table 1.

The independent variables in this study were family structure, parental involvement and peer pressure. The dependent variable was alcohol use. The following describes the measurement of each variable.

Family Structure was defined as the composition of the adult figure (s) in the household. The family structures were two [2] parents, one [1] parent, and guardian/relative. When there when no mother, father, stepfather, stepmother, grandparent or guardian/ relative identified, then a sibling is used. When there is no sibling, a girlfriend or boyfriend is used. This represented the no parent family structure.

Seven questions were used to measure the perceived parental involvement of the students. They included:

1. Parent's expectation to be told of student's whereabouts
2. Parents control of the time students come in at nights
3. Level of attention parents pay to students activities at school

4. How often students had meals together with their parents
5. Parents knowledge of students close friends
6. Parents knowledge of TV shows watched
7. Parents knowledge of students whereabouts

Table 1. Student demographics

Demographic indicator	(%)
Type of school	
Public	97.1
Private	2.9
Age (in years)	
11-14	31.2
15-16	41.5
17+	16.8
Gender	
Female	51.3
Male	48.3
Form in school	
2 nd	37.5
4 th	35.5
5 th	27

For the purpose of analysis, parental involvement was rated using the following scale of 1-7. Minimally involved (less than or equal to 2), moderately involved [3-5], very involved [6-7].

Peer Pressure was defined as how much influence the student's friends had over their actions, specifically drinking habits.

Alcohol use was defined as the patterns in which the students consume alcohol. The following scale was used to classify the different patterns of drinking among the students: Non-drinker-never consumed alcohol. Infrequent drinker-consumed one or two alcoholic drinks a few times during the month. Weekend drinker-consumed alcohol only on weekends. Chronic drinker-consumed alcohol daily or several days of the week. Adolescence was defined as the period in human development that occurs between childhood and adulthood, from 10 to 19 years [1].

Data Analysis

The data from the survey was entered into Excel twice to ensure there was no risk of data entry errors. In order to tabulate the data, the final excel spreadsheet with the data was converted to SPSS format version 19.

Continuous variables were summarized using a mean and standard deviation. Categorical variables were summarized using frequency and percent. All analyses used a level of significance of 0.05.

To determine differences in drinking patterns by family structures chi-square tests were conducted. Chi-square tests were conducted between each parental involvement variable and drinking pattern. Chi-square tests were also conducted to determine differences in drinking patterns based on peer pressure.

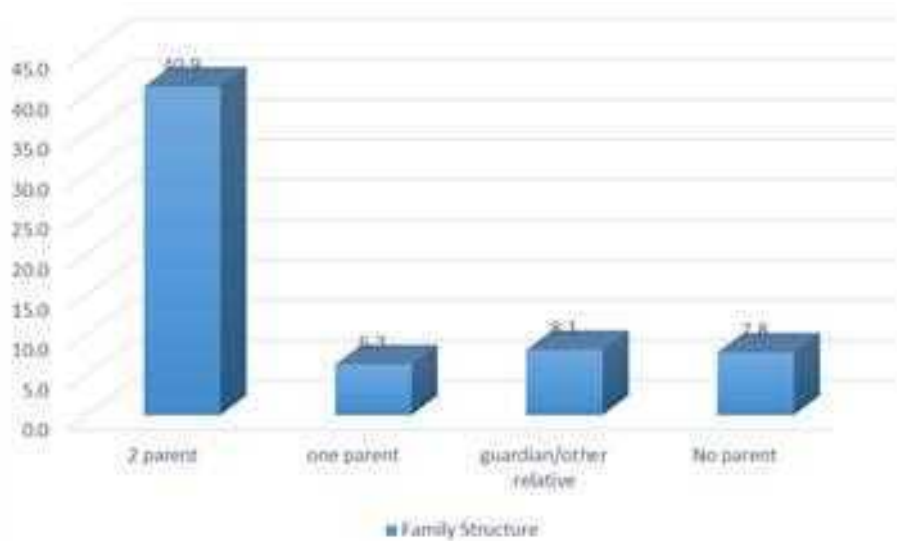
RESULTS

Approximately forty percent (40%) of students belonged to two parent households whereas households with one parent, guardian/other relative and no parents were six [6], eight [8] and eight [8] percent respectively (refer to Figure 1). The majority of students (26%) were categorized as infrequent drinkers. Approximately eighteen (18%) percent of students were categorized as non-drinkers, 13.4% of students were categorized as weekend drinkers and 12.1% were categorized as chronic drinkers (refer to Figure 2).

Table 2. Summary of family structure and students patterns of drinking

Family structure	n	Non drinker N (%)	Infrequent drinker N (%)	Weekend drinker N (%)	Chronic drinker N (%)
Two parent	265	67 (25.3)	101 (38.1)	48 (18.1)	49 (18.5)
One parent	3035	819 (27)	1103 (36.3)	585 (19.3)	528 (17.4)
Guardian/relative	362	87 (24)	141 (39)	78 (21.5)	56 (15.5)
No parent	167	27 (16.2)	66 (39.5)	37 (22.2)	37 (22.2)

Note: $X^2 = 13.8$, $p = 0.13$.



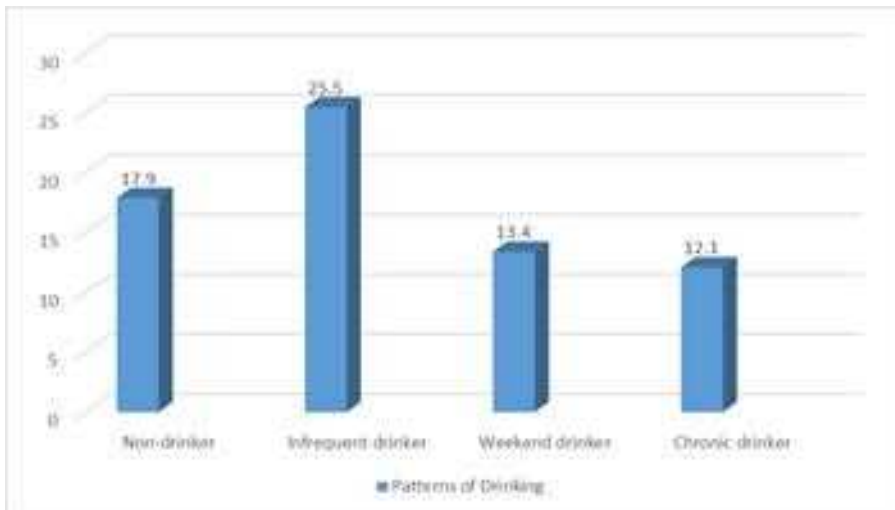
Note: Thirty seven percent (37%) percent of students did not disclose their family structure.

Figure 1. Family structure of students.

There was no significant difference among the percentages for patterns of drinking in two parent, one parent and guardian/relative households. Students in a no parent household (22%) were more likely to consume alcohol. Overall, there was no significant relationship between the different family structures and patterns of drinking among the students, $p = 0.13$. Therefore, a difference in family structure is not likely to have an impact on a student’s drinking patterns (refer to Table 2).

Students who perceived their parents to be very involved in their lives were less likely to consume alcohol. With the perception of minimal parental involvement, the percentage of students in the category of non-drinker decreased by 17%. Therefore, students who perceived

their parents to be minimally involved in their lives were more likely to consumed alcohol. This was represented by a six (6%) increase in students who were weekend and chronic drinker. There was no significant difference in drinking patterns among students who perceived their parent to be very involved or moderately involved in their lives. Represented by p values <0.05, significant results were found at all levels of parental involvement. Generally, there was a significant relationship between parental involvement and students patterns of drinking. Thus the level of parental involvement is likely to influence a student's alcohol use (refer to Table 3).



Note: Thirty one percent (31%) of students did not disclose their drinking patterns.

Figure 2. Summary of students' patterns of drinking.

Table 3. Summary of student's perception of parental involvement and patterns of drinking

Parental involvement (category)	n	Non drinker N (%)	Infrequent drinker N (%)	Weekend drinker N (%)	Chronic drinker N (%)
Very involved (6-7)	923	329 (35.6)	300 (32.5)	142 (15.4)	152 (16.5)
Moderately involved (3-5)	2057	500 (24.3)	821 (39.9)	404 (19.6)	332 (16.1)
Minimally involved (<3)	852	162 (19.0)	298 (35)	202 (23.7)	190 (22.3)

Note: $X^2 = 91.9$, $p < 0.001$.

Table 4. Summary of Peer pressure experienced and patterns of drinking

Peer pressure to drink	n	Non drinker N (%)	Infrequent drinker N (%)	Weekend drinker N (%)	Chronic drinker N (%)
Yes	2157	408 (18.9)	499 (37.7)	499 (23.1)	46 (20.2)
None - minimal	1635	570 (34.9)	593 (36.3)	242 (14.8)	230 (14.1)

Note: $X^2 = 145.3$, $p < 0.001$.

Students who experienced peer pressure were more likely to consume alcohol represented by an eight [8] and six [6] percent increase in weekend and chronic drinkers respectively. Students who experienced minimal peer pressure were less likely to consume alcohol

represented by approximately thirty five (35%) who were nondrinkers or infrequent drinkers. A significant relationship was found between the two spectrums of peer pressure and student’s patterns of drinking supported by p values less than 0.05. Results suggest that peer pressure is likely to have an effect on a student’s drinking patterns (refer to Table 4).

Table 5. Summary of parental involvement in relation to peer pressure experienced to drink alcohol

Peer Pressure to drink alcohol	n	Minimally involved (<=2) N (%)	Moderately involved (3-5) n (%)	Very involved (6-7) N (%)
Yes	2817	638 (22.6)	1587 (56.3)	592 (21)
None-minimal	2619	248 (13.3)	1389 (53)	882 (33.7)

Note: $\chi^2 = 148.5$, $p < 0.001$.

There was no significant difference between students who experienced peer pressure and perceived their parents to be minimally involved (23%) and very involved (21%) in their lives respectively. Students who perceived their parents to be very involved in their lives were less likely to experience peer pressure. This was represented by a twenty (21%) percent increase in students who perceived their parents to be very involved (34%) compared to those who perceived their parents to be minimally involved (13%) within the category of minimal peer pressure. The two spectrums of peer pressure yielded significant values as it relates to different levels of parental involvement. Therefore, the level of parental involvement can influence whether a student experiences peer pressure (refer to Table 5).

DISCUSSION

We examined the impact of family structure, parental involvement and peer pressure on adolescent alcohol consumption patterns. We did not find any significant relationships between family structure and patterns of alcohol use, which is inconsistent with the findings of other studies. However, associations were found between parental involvement and consumption patterns, with lower perceived involvement being associated with increased consumption. In addition, we found consistent evidence that peer pressure impacts alcohol use. Furthermore, parental involvement had a linear relationship with peer pressure with greater involvement resulting in less peer pressure.

No significant relationship between family structures and the pattern of alcohol consumption among adolescents were found. However, Podana et al. [7], found that adolescents from a single parent household use alcohol more intensely than adolescents from two-parent households. Additionally, Vanassche et al. [18] also found that adolescents living in single parent or step- families had a higher likelihood of being frequent drinkers than their counterparts from intact families. It is possible that the results of this study differ due to alcohol use being a social norm in Caribbean countries where alcohol consumption is an important part of cultural and social activities. As such differing parental structures may not significantly impact adolescent drinking habits. Nevertheless, consistent with a study by Soyibo and Lee [20], the prevalence of alcohol use among adolescents was found to be greater than 50%.

The students' perception of parental involvement had a significant effect on their pattern of drinking. Students who perceived their parents to be very involved in their lives did not consume as much alcohol as the students who perceived their parents to be minimally involved in their lives. This may be due to the practice of authoritative parenting styles, which is demonstrated to be associated with lower levels of alcohol use among adolescents [2]. A positive emotional attachment between parent and child, as well as acceptable levels of openness and control distinguishes this style of parenting from other styles. As such it serves as a protective factor against high risk behaviors such as alcohol use. The opposite is true for parents who practice more liberal styles of parenting. A student's perception of parental involvement may differ from the parent's perception; therefore, the results in the study related to parental involvement can be skewed.

Similar to the findings of a study by Nash et al. [22], results showed that students who experienced little or no peer pressure were less likely to binge drink or consume alcohol overall. The majority of students who experienced peer pressure were categorized as weekend or chronic drinkers. In relation to peer pressure and parental involvement, students who perceived their parents to be very involved in their lives experienced little or no peer pressure. The strong interpersonal relationship between parent and adolescent may act as a buffer against peer pressure. Prinstein et al. [13] also found that low levels of parental involvement could result in increased peer pressure experienced by adolescents thus leading to alcohol consumption. These results further support the notion that peer pressure is not the only factor that contributes to adolescent alcohol use.

The present study indicates that parental involvement through monitoring of activities in and out of school, knowing who their friends are, spending time together and having control of the time they return home at nights can act as protective factors against early alcohol use. Therefore, interventions aimed at delaying the initiation of alcohol use among adolescents should also target parents. Additionally, findings suggest that student's perception of their parents can influence their patterns of drinking. The inclusion of various aspects of parental involvement such as educational support, constructive parenting and efficient discipline into school-based alcohol prevention programs has been found to be successful [21]. Moreover, a variety of parenting strategies for reducing adolescent alcohol use can be tailored for use in this setting [16].

RECOMMENDATIONS

To curb the issue of increased alcohol consumption among the Grenadian population, the National Alcohol Policy should be revised to include a minimum drinking age. While this measure alone cannot reduce the incidence of alcohol use specifically among adolescents, the findings from this study suggest more emphasis needs to be placed on helping adolescents develop healthier relationships with their parents and peers. This in turn can assist in their decision making as it relates to their alcohol usage.

The Health and Family Life Education (HFLE) program is one of the few programs adolescents are exposed to within the school system that attempt to address issues related to family life, social life and alcohol use within one curriculum. These aspects are included under the theme of Self and Interpersonal relationship. Therefore it is a suitable existing

program to which recommendations can be made based on the variables examined in this study and the results obtained. However, the effectiveness of this program is frequently questioned especially as it relates to delaying the initiation of alcohol use among adolescents.

While the regional evaluation of HFLE in 2009 did not find a constant pattern of positive effects on the health outcomes of students [23], these findings support the importance of programs like Health and Family Life Education in the school systems throughout the Caribbean. Improving its effectiveness may help adolescents obtain the necessary skills to foster positive family and social relationships. This can contribute to decreased incidence of alcohol use among adolescents in Grenada.

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Chapter 5

ALCOHOL MISUSE IN ADULthood FOLLOWING EXPERIENCES OF PSYCHOLOGICAL MALTREATMENT DURING CHILDHOOD

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ABSTRACT

This study seeks to identify whether exposure to psychological maltreatment in childhood is predictive of alcohol misuse, in adulthood, among Jamaican university students. Systematic sampling techniques were utilized to gather data on 382 university students. Measures utilized were the Kessler Psychological Distress Scale (K10), the Adverse Childhood Experiences questionnaire, and CICAD drug use questions. Alcohol misuse was reported by 12.6% of the students, while 66.7% reported exposure to psychological maltreatment. Logistic regression analysis identified psychological maltreatment as being predictive of alcohol misuse (OR = 2.701; 95% CI 1.22 - 5.97; $p < .01$) as well as higher levels of psychological distress (OR = 1.988; 95% CI 1.211-3.265; $p < .01$) among select university students. Public health policies aimed at reducing psychological maltreatment may result in the reduction of alcohol misuse.

Keywords: alcohol misuse, child abuse, psychological maltreatment, substance misuse

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INTRODUCTION

‘Alcohol misuse’ refers to the excessive consumption of alcohol, which is a known risk factor for road accidents, injuries, risky sexual behaviours, violence, and the development of chronic illnesses such as liver cirrhosis, hypertension and heart disease [1]. A national survey had identified alcohol as being the most widely consumed psychoactive substance in Jamaica, with 39% of the adult population reporting alcohol consumption within the past month [2]. It was also noted that 6.9% of Jamaicans are alcohol misusers, consuming 60 grams or more of alcohol on one occasion, within the past month [3]. Furthermore, one of every five Jamaican road accident fatalities was found to be attributable to alcohol misuse [3]. As a result, alcohol misuse is a key public health concern in Jamaica and therefore it is essential to understand its drivers.

Within developed nations, exposure to psychological maltreatment during childhood has been implicated as a risk factor for alcohol misuse in adulthood [4, 5]. Psychological maltreatment consists of both emotional abuse and emotional neglect, therefore consisting of all cognitive and affective forms of maltreatment [5]. Emotional abuse includes restriction of movement as well as non-physical acts that emotionally damages a child such as threatening, exploiting, belittling or terrorizing a child [6]. While emotional neglect involves not providing for a child’s emotional need for love, support and belonging [6].

Psychological maltreatment is the least reported type of maltreatment [7] even though it is believed to be the most frequently occurring form, as it tends to accompany all other types of abuses [8]. Its low reporting frequency may be attributable to the difficulty in providing evidence that substantiates this type of maltreatment, as well as the cultural belief that ‘words’ do not have any longstanding negative impact. As such, within a Jamaican context, humiliating, threatening, demeaning and rejecting a child is widespread and is often seen as a viable, effective and less severe form of disciplining technique than spanking; and therefore is reserved for everyday offences [9, 10]. Consequently, many persons who have experienced this type of disciplining are often not aware that it constitutes or meets the criteria of maltreatment [11].

It has been postulated that exposure to psychological maltreatment may bring about psychological distress and thereby increase the likelihood of alcohol misuse [6]. Persons experiencing psychological distress are believed to be at an increased risk of psychoactive substance misuse, as they may try to alleviate their distress by self-medicating with psychoactive substances [12]. It has also been hypothesized that the type of psychoactive substance that is selected is associated with the nature of the distress; with alcohol misuse facilitating an emotional numbing, when faced with overwhelming negative emotions [12]. Therefore, alcohol may be the chosen drug subsequent to psychological maltreatment experiences.

The significant adverse outcomes associated with alcohol misuse, makes it necessary to explore the psychological maltreatment-alcohol misuse link. However, only scant research has been conducted in this area, within a Jamaican context. The goal of this exploratory research is to investigate the predictive relationship between exposure to psychological maltreatment and later alcohol misuse, within a Jamaican context; among a population that is expected to have an elevated frequency of alcohol misuse, university students.

METHODS

The data for this study were part of a larger multi-country research in Latin America and the Caribbean to investigate the relationship between adverse childhood experiences and psychoactive substance use. This segment of that research employed systematic sampling techniques within a cross-sectional survey design to gather information on 382 students from a select university in Jamaica. The measures utilized are the Emotional Abuse and Emotional Neglect scales from the Adverse Childhood Experiences questionnaire (ACE) (Centers for Disease Control and Prevention 2012), the Kessler Psychological Distress Scale (K10) [13] and substance use questions from the Inter-American Drug Abuse Control Commission (CICAD) Drug Use questionnaire.

Adverse Childhood Experiences Questionnaire

The Adverse Childhood Experiences Questionnaire (ACE) assesses the impact of exposure to childhood maltreatment and household dysfunction on development of public health issues. The ACE questionnaire is widely used by the Centers for Disease Control and Prevention and has been found to display adequate reliability and validity [14] in a variety of cultural settings. The emotional abuse scale of the ACE consists of two items: 'Did a parent or other adult in the household: 1) Often or very often swear at, insult, or put you down? 2) Often or very often act in a way that made you afraid that you would be physically hurt?' The potential response choices were 'almost never or never,' 'some of the time,' 'half of the time,' 'most of the time' and 'almost always or always.' An affirmative response to any question indicates the presence of emotional abuse and also gives a measure of the perceived frequency of the emotional abuse. The ACE Emotional Neglect Scale consists of five items originally derived from the Childhood Trauma Questionnaire [15]. The emotional neglect items assess the failure of a guardian to provide love, support, encouragement, and belongingness. These items are known to demonstrate good reliability and validity among university students [16].

Kessler Psychological Distress Scale

The Kessler Psychological Distress scale (K10) was initially developed to screen for the presence of non-specific psychological distress among the United States populace [13, 17, 18]. However, its concise nature and cross-cultural validity has resulted in the K10 and its abbreviated version, K6, being translated into numerous languages and being widely used by the World Health Organization. The 10 items of the K10 assess for anxiety and depressive symptoms that are commonly identified in many psychological disorders [19]. Therefore, high scores on this scale indicate an increased likelihood of being diagnosed with a psychological disorder [20, 21].

CICAD Drug Use Questionnaire

The Inter-American Drug Abuse Control Commission (CICAD) Drug Use Questionnaire has been translated into several languages and is widely used within Latin America and the Caribbean. Select questions were taken from this questionnaire to provide a measure of alcohol use and misuse in accordance with the DSM-V definition. These questions provided a measure of alcohol consumption frequency as well as a measure of the negative outcomes that occurred as a result of alcohol misuse.

Procedure

The research questionnaire was pretested among university students to ensure that they were being interpreted as intended. Using a table of random numbers, university faculties were randomly selected and every third student within the vicinity of the faculty office was invited to participate. Power analysis identified the minimum required sample size to be 311, when using a sampling error of 5%.

The data entry process involved the use of the double entry method to reduce the possibility of errors. Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 19. Univariate and bivariate statistics were employed to explore the relationship between alcohol misuse and exposure to psychological maltreatment in childhood.

RESULTS

Three hundred and eighty two students (279 females and 103 males) participated in this segment of the study. The mean age for the sample was 21.27 years ($SD = 4.389$) with 88.5% being young adults between the ages 18-24 years. The demographic and psychosocial characteristics of the sample are summarized in Table 1. A majority of the students reported being raised in middle class socioeconomic backgrounds. The most frequently used psychoactive substance was alcohol, with alcohol use within the past month being reported by 24.2% of the sample (19.5% of the females and 36.9% of the males). Twenty one percent (21.1%) of alcohol users reported consuming alcohol weekly, 11.4% reported a frequency of 2 or 3 days/ week, while 3.2% reported a frequency of 4 days or more each week. Alcohol misuse was reported by 12.6 % of the sample (9% of the females and 20% of males). Of note, 14.4% of the students reported that they lived with an alcoholic in their household. Psychological maltreatment was reported by 66.7 %, with exposure to emotional abuse being reported by 64.7% of the students. Half of the students (52.8%) who had experienced psychological maltreatment were not aware that their experiences had met the criteria for maltreatment.

The students' level of psychological distress was assessed and the results are displayed in Table 2. One third of the students (33.1%) reported moderate to severe levels of psychological distress, with an equivalent percentage of females and males reporting increased levels of psychological distress.

Table 1. Demographic and psychosocial characteristics of the sample

Characteristics	Total	
	(f)	(%)
Gender		
Female	279	73
Male	103	27
Age (years)		
18- 24	337	88.5
25-29	22	5.8
30-34	10	2.6
35-40	7	1.8
40 +	5	1.3
Socioeconomic Status (SES)		
High	50	13.3
Middle	246	65.4
Low	80	21.3
Psychological Maltreatment		
Emotional Abuse	247	64.7
Emotional Neglect	76	19.9
Psychoactive substances used in the last 30 days (not mutually exclusive)		
Alcohol	92	24.2
Tobacco/ cigarettes	24	6.3
Cannabis	18	4.7
Cocaine	3	0.8
Heroin	3	0.8
Ecstasy	3	0.8
Inhalants	5	1.3
Unprescribed use of prescription drugs	7	1.9

Table 2. Levels of psychological distress by gender

Level of Distress	Males		Females		Total	
	(f)	(%)	(f)	(%)	(f)	(%)
Minimal - Mild	67	67	179	66.8	246	66.8
Moderate - Severe	33	33	89	33.2	122	33.2

Table 3. Dysfunctional outcomes associated with alcohol misuse

Dysfunctional Outcomes	Alcohol Misuse	
	f (%)	p value
Repeatedly absent from classes	6 (1.6)	.008
Had unprotected sexual activity	17 (4.5)	.000
Had unintended sexual relations	12 (3.2)	.000
Family conflicts	7 (1.8)	.003
Had partner conflicts	17 (4.5)	.000
Financial difficulty	16 (4.2)	.000
Health problems	4 (1.1)	.019
Fighting resulting in arrest	2 (.5)	.140
Fines for driving under the influence	2 (.5)	.140
Motor vehicle accidents	3 (.8)	.150
Have been incarcerated	2 (.5)	.140
Legal problems	5 (1.3)	.004
Academic problems	11(2.9)	.000

Students who reported consuming alcohol with there being associated adverse outcomes were assessed to provide a measure of alcohol misuse. Table 3 outlines the frequency of alcohol misuse and the associated dysfunctional outcome. The most frequently identified dysfunctional outcomes occurring due to excessive alcohol consumption were unprotected sexual activity (4.5%) and experiencing partner conflicts (4.5%).

The relationship between alcohol use and psychological distress was investigated using the Chi-square statistic. A non-significant relationship was found between experiencing psychological distress and consuming alcohol ($p > 0.05$). However, a logistic regression examination of the relationship between experiencing psychological distress and alcohol misuse was found to be significant ($X^2 = 10.051$, $df = 1$, $N = 368$, $p = 0.002$). Students reporting increased levels of psychological distress were 2.76 times more likely to misuse alcohol (OR = 2.76; 95% CI 1.48 - 5.17). Additionally, exposure to psychological maltreatment was found to be predictive of experiencing higher levels of psychological distress ($X^2 = 7.774$, $df = 1$, $N = 364$, $p = 0.005$) (OR = 1.988; 95% CI 1.211 -3.265). Logistic regression analysis was also conducted to investigate whether or not there is a predictive relationship between exposure to psychological maltreatment during childhood and alcohol misuse in adulthood. A significant predictive relationship was identified ($X^2 = 7.109$, $df = 1$, $N = 378$, $p = 0.008$) (OR = 2.701; 95% CI 1.222 - 5.970). Therefore, students who had experienced psychological maltreatment had an increased likelihood of excessive alcohol consumption by a factor of 2.701.

DISCUSSION

Excessive alcohol consumption is a global phenomenon with grave public health implications for any nation. In accordance with international and local research, this study identified alcohol consumption as the psychoactive substance of choice for university students [22-24]. This preference for alcohol consumption may be attributable to its relatively low cost, easy accessibility as well as the misperception that its use is associated with minimal risks. Mirroring the results of several international studies, a greater percentage of males than females reported alcohol consumption [23, 25, 26]. Alcohol consumption being greater among males, may be attributed to a variety of reasons including a more positive attitude towards alcohol consumption and its associated outcomes, less refusal skills when with drinking peers, as well as the ease of accessibility [25].

Interestingly, most of the students were from a middle socioeconomic background and as seen in previous research, individuals from a higher socioeconomic status are more likely to misuse alcohol. Previous research has also revealed that “heavy episodic drinking” increased with higher SES [27].

Two-thirds of the students experienced psychological maltreatment (66.7%) but half of these students were unaware (52.8%) that their experiences had constituted a form of mistreatment. This lack of awareness highlights the cultural acceptance of verbal assaults as a practical and less severe disciplining technique in Jamaica. Nonetheless, this exploratory study found that experiencing psychological maltreatment during childhood almost tripled (OR = 2.701; 95% CI 1.222-5.970) the probability of alcohol misuse among select Jamaican university students. Furthermore, students who were exposed to psychological maltreatment

were more likely to have elevated levels of psychological distress, which may be indicative of a psychological disorder [17]. Therefore, this perceived innocuous disciplining technique has longstanding implications for individual mental health as well as public health.

Consistent with international studies, exposure to psychological maltreatment was predictive of alcohol misuse in adulthood [28-30]. This psychological maltreatment- alcohol misuse link may occur due to the need to cope or to self-medicate for the negative emotions arising from the psychological maltreatment experiences [30]. Therefore, alcohol misuse may occur to facilitate the numbing of negative emotions.

As anticipated, alcohol use did not exhibit a significant relationship with psychological distress ($p > 0.05$). This non-significant relationship was expected as alcohol consumption in Jamaica is culturally endorsed for a wide variety of significant events, such as weddings and funerals, as well as non-events. Therefore, identifying a specific pattern of alcohol consumption would be unlikely. On the other hand, experiencing psychological distress was found to almost triple the odds ($OR = 2.76$; 95% CI 1.48-5.17) that alcohol misuse would occur. This finding that psychological distress increases the likelihood of alcohol misuse further supports the self-medication hypothesis.

Of note, an equivalent percentage of males as well as females (33%) were found to be experiencing psychological distress, however a greater percentage of males (20%) misused alcohol than females (9%). These findings may indicate that excessive alcohol consumption may be the preferred method to deal with emotional difficulties among males, while females may utilize other methods. Additionally, it highlights that the psychological maltreatment - alcohol misuse link is not an automatic one. Being exposed to psychological maltreatment does not automatically bring about alcohol misuse as the level of psychological distress being experienced as well as other mitigating factors, are expected to have an influence.

CONCLUSION

This research has identified that among select Jamaican university students, psychological maltreatment is predictive of higher levels of psychological distress and also an increase probability of alcohol misuse. This finding reveals another target area for the creation of public health policies aimed at reducing excessive alcohol consumption. As by eliminating psychological maltreatment, a reduction in alcohol misuse may occur. However, this exploratory study should be interpreted with caution as the data collected was self-report in nature, and therefore the possibility exists that some participants may have responded in a socially desirable manner. Additionally, psychological maltreatment frequently accompanies other forms of maltreatment and on those occasions, it may not be possible to accurately measure the impact of each form of maltreatment.

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Chapter 6

GENDER AND SUICIDAL BEHAVIOUR AMONG ADOLESCENTS WHO USE ALCOHOL

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ABSTRACT

This study sought to determine the overall prevalence of suicidal behaviours and differences related to gender and alcohol use among a nationally representative sample of Jamaican secondary school adolescents. A cross-sectional survey design was used to gather information on suicidal behaviour and substance use in a sample of 3,471 students island-wide, using a self-administered questionnaire comprised of the Suicidal Behaviours Questionnaire-Revised (SBQ-R) and another standardized questionnaire. Suicide risk prevalence was 19.85%. There were no significant direct associations between alcohol use and suicidal behaviour ($p > 0.05$ in all cases). However females who used alcohol had higher suicide risk scores, more reports of lifetime suicidal ideation, past year ideation and lifetime suicide attempt than males who used alcohol ($p < 0.05$ in all cases). Females who used alcohol had higher means for past year suicide ideation and suicide risk scores than females who did not use alcohol ($p < 0.01$). There were no significant differences between male alcohol users and non-users and suicidal behaviour ($p > 0.05$). Suicide prevention measures for Jamaican adolescents should take gender differences and alcohol use into consideration when developing programmes or interventions to address these behaviours.

Keywords: suicidal behaviour, substance use, adolescents, Jamaican

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INTRODUCTION

Suicide is a complex, multi-causal public health issue and remains a leading cause of death with an estimated annual global burden of 800,000 suicide deaths [1] and a mortality rate of 16.7 per 100,000 which is projected to increase [2, 3]. Suicide behaviours exist on a continuum, ranging from suicide ideation to suicide plans, suicide attempts and completed suicide [4].

Nock et al. [5] pellucidly define suicide ideation as “thoughts of engaging in behavior intended to end one’s life and a suicide plan as “the formulation of a specific method through which one intends to die.” A suicide attempt is the “engagement in non-fatal but potentially self-injurious behavior for which there is evidence (either implicit or explicit) that the person intended at some (non-zero) level to kill himself/herself” [5, 6] whereas suicide may be defined as, “death caused by self-directed injurious behavior with any intent to die as a result of the behavior” [7].

The problem of suicidal behaviour is of great relevance among adolescents, with increased risk among adolescent females [8]. In the 15-19 year old age group it is ranked the fourth most common cause of death globally among boys, and the third for girls [9]. Overall, the mean suicide rate of 7.4 per 100,000 in this age group [9].

However, Abel et al. [10] concluded that the suicide rate in Jamaica is relatively low with a mean overall incidence of 2.1 per 100,000. In another 12-month prevalence of suicide ideation in a subset of Jamaican adolescents, 10-15 years old, was found to be 9.7% [11], and among school-children from grades 6, 9 and 11 surveyed in 1996, 11% reported attempting suicide at least once [12].

Among the main predisposing factors among adolescents are gender, alcohol and other substance use [8, 13]. Other factors identified in the literature include, prior suicide attempts, unstable family systems, family history of suicide attempt, low socioeconomic status and impulsive traits.

Gender is a major predisposing factor for suicidal behaviour [5]. Research indicates that adolescent females are two to three times more likely to attempt suicide than adolescent males, but males are five times more likely to complete suicide [8]. Adolescent females also have higher rates of suicidal ideation [13].

Additionally, alcohol has been found to account for the increase in suicide mortality among adolescents who express suicidal behaviour [14-16], with up to 63% of all persons completing suicide had substance use disorders, mostly alcohol [17]. The frequency of alcohol among adolescents is more predictive of suicide attempt than suicide ideation [8, 18] possibly due to the fact that alcohol use accelerates the transition from ideation to suicide attempt. In adolescent females, severity of depression predicted suicidal ideation, and alcohol consumption predicted severity of suicidal behaviour [19].

The present study was aimed at exploring the prevalence of suicidal behaviours among a cluster of secondary school adolescents and determining whether there were associations between suicidal behaviour, gender and alcohol use.

METHODS

This was a cross-sectional survey design consisting of 3, 471 participants were selected from a sample of public and private secondary schools in Jamaica which were stratified. The cluster sampling procedure was carried out in two stages, using the automated C-Survey program. Firstly, 38 school clusters were generated with the probability of selection proportional to size. Secondly, a grade was then selected from each stratum to represent key developmental periods that are typically investigated in health related, school based adolescent research [20]. This sampling technique resulted in the selection of the 2nd, 4th and 6th forms. However, as the number of students in the 6th form in Jamaica is comparatively low [21], both grades in the upper grade level were included in this study. All participants completed two self-administered questionnaires:

- A standardized questionnaire developed by the Inter-American Uniform Drug Use Data System (SIDUC) [22].
- The Suicidal Behaviors Questionnaire-Revised (SBQ-R).

The standardized SIDUC questionnaire has previously been used with secondary school students in Jamaica. It consists of items on socio-demographic, school performance and substance use.

The Suicidal Behaviors Questionnaire-Revised (SBQ-R) is a 4-item scale, developed by Osman et al. [23], that is available in the public domain. The SBQ-R is brief, with a completion time of approximately 5 minutes, and assesses lifetime suicidal behaviours, past year frequency of suicide ideation, and the likelihood of a future suicide attempt. The total score ranges from 3-18 points, with higher scores indicating higher suicide risk. This instrument has been previously standardized among secondary school students with Cronbach's alpha of 0.87 [23].

Approval to conduct this study was granted by the school principals, the Ministry of Education and the Ministry of Health. The Ethics Committee of the University of the West Indies, Mona, also granted ethical approval. Written informed consent was obtained from the parents or guardians of the students and the students themselves completed assent forms. Participants were provided with a list of mental health professionals, whom they could contact in the event that they felt distress during the process.

Statistical Analysis

Data were entered and cleaned in the Statistical Package for the Social Sciences (SPSS) version 17. Statistics were performed to produce frequencies for sociodemographic variables as well as to calculate the prevalence of the following dependent variables; suicide risk, ideation, attempt and plan. Independent variables included alcohol use, gender, geographical location, school factors, family factors and aggressive behaviour traits. Independent sample t-tests, and Chi Square analyses were used to explore gender differences in suicidal behaviour. Pearson's Correlation analysis was used to explore relationships between alcohol use and suicide risk scores.

RESULTS

The sample consisted of 3,289 participants, 41.2% male and 58.8% females. The response rate was 87.7%. The age of students ranged from 11-19 years, with a mean age of 14.97 years ($SD = 1.7$). The vast majority of students attended public (97.8%), co-educational schools (83%). The spread across a grade levels was as follows; 8th grade- 31%, 10th grade- 32.1%, 11th grade-26.5% and 12th grade-10.3%. The urban (50.6%) and rural (49.4%) representation were equivalent.

Scores on the suicide risk prevalence (SBQ-R Scale) revealed; suicide risk at 19.8%, lifetime suicide ideation was 35.6%, among those who expressed lifetime suicidal ideation, 70.2% reported past year suicide ideation. Additionally, 15.8% had a suicide plan, 6.1% suicide attempt, 27.4% suicide threats and 8.4% indicated a future intention to attempt.

Gender and Suicidal Behavior

Independent samples T test revealed that there was no significant difference between males and females for suicidal risk, ($t(1115) = -1.788$, $p = 0.074$). However, Table 1 shows that more females than males reported both lifetime ($t(903.5) = -3.013$, $p = 0.003$) and past year suicidal ideation ($t(311.8) = -2.438$, $p = 0.015$). Similarly more females reported lifetime suicidal attempts and suicidal threats. There was no statistically significant differences between gender and suicidal plan ($p > 0.05$).

Additionally Chi-square analysis revealed significant differences between gender and threatening suicide, with more reports of threatening suicide coming from females (%) than from males (%) ($X^2 = 18.44$, $N = 2951$, $p < 0.01$).

Alcohol Use and Suicidal Behavior

Most students admitted to using alcohol in their lifetime (56.7%). The past year use was 35.9% and 18% reported drinking in the last 30 days. However Pearson's Correlation analysis revealed no significant associations between alcohol use (lifetime, past year, or last 30 days) and suicidal behaviour (ideation, plan or attempt, $p > 0.05$).

Table 1. T-test and descriptive statistics for suicidal ideation and attempt by gender

	Sex						95% CI for Mean Difference	t	df	p value
	Male			Female						
	M	SD	n	M	SD	n				
Lifetime (ever) suicidal ideation	0.322	0.468	1147	0.38	0.486	1719	(-.093, -.022)	-3.164	2518.2	0.002*
Past year suicidal ideation	0.67	0.471	476	0.72	0.447	805	(-.106, -.002)	-2.023	956.46	0.043**
Suicide plan	0.24	0.428	1147	0.27	0.444	1719	(-.061, 0.004)	-1.703	2864	0.089
Lifetime (ever) suicidal attempt	0.043	0.202	1147	0.073	0.26	1719	(-.047, -.0136)	-3.526	27800	0.000*

Key: * $p < 0.01$, ** $p < 0.05$.

Gender Differences in Suicidal Behaviour among Alcohol Users

The data was split based on lifetime use of alcohol. Independent Sample t-test analysis on gender differences in suicidal behaviour among alcohol users revealed that females who used alcohol had higher suicide risk scores (SBQ-R scale) than males who used alcohol (see Table 2). Compared to males who used alcohol, more females who used alcohol also reported lifetime suicidal ideation, past year ideation, lifetime suicide attempt and were more likely to have a suicide plan ($p < 0.01$).

Table 3 shows that there were no significant differences between male alcohol users and non-users and suicidal behaviour ($p > 0.05$ in all cases).

When female alcohol users were compared to non-alcohol users analysis revealed that there were significant differences between female alcohol users and non-users and total suicide risk score as well as past year suicide ideation with female alcohol users displaying higher means than non-users (see Table 4).

Independent sample T-test analysis was also performed within gender, to explore differences between males who use alcohol and suicidal behaviour compared with males who do not use alcohol and their suicidal behaviours.

Table 2. T-test and descriptive statistics for suicidal ideation and attempt by gender among alcohol users

	Sex						95% CI for Mean Difference	t	df	p value
	Male			Female						
	M	SD	n	M	SD	n				
Lifetime (ever) suicidal ideation	0.316	0.465	667	0.399	0.49	976	(-.129, -.035)	-3.442	1477.7	0.001*
Past year suicidal ideation	0.67	0.472	273	0.79	0.411	470	(-.183, -.054)	-3.581	507.2	0.001**
Suicide plan	0.25	0.432	667	0.29	0.455	976	(-.089, 0.001)	-2.013	1478.5	0.04**
Lifetime (ever) suicidal attempt	0.03	0.183	667	0.079	0.27	976	(-.067, -.0209)	-3.98	1640.1	0.000*
Suicide risk scores	7.7	3.87	234	8.51	3.948	421	(-1.435,-1.432)	-2.541	489.8	0.011*

Key: * $p < 0.01$, ** $p < 0.05$.

Table 3. Differences in suicidal behaviours between male non-users and alcohol users

	Male Alcohol Non-users			Male Alcohol Users			95% CI for Mean Difference	t	df	p value
	M	SD	n	M	SD	n				
Lifetime (ever) suicidal ideation	0.3	0.461	276	0.32	0.465	667	(-0.007, 0.053)	-0.361	941	0.718
Past year suicidal ideation	0.72	0.452	103	0.67	0.472	273	(-0.053, 0.156)	0.979	191.2	0.329
Suicide plan	0.21	0.406	276	0.25	0.432	667	(-.099, 0.017)	-1.381	544.1	0.168
Lifetime (ever) suicidal attempt	0.05	0.22	276	0.03	0.168	667	(-0.013, 0.046)	-1.083	439.6	0.280
Suicide risk score	8.12	4.036	90	7.7	3.869	234	(-0.534, 1.377)	0.868	322	0.386

Key: * $p < 0.01$, ** $p < 0.05$.

Table 4. Differences in suicidal behaviours between female non-users and alcohol users

	Female Alcohol Non-users			Female Alcohol Users			95% CI for Mean Difference	t	df	p value
	M	SD	n	M	SD	n				
Lifetime (ever) suicidal ideation	0.37	0.484	429	0.4	0.49	976	(-0.081, 0.030)	-0.906	1403	0.365
Past year suicidal ideation	0.66	0.475	186	0.79	0.411	470	(-0.202, -0.046)	-3.124	300.8	0.002*
Suicide plan	0.27	0.443	429	0.29	0.455	976	(-0.075, 0.027)	-0.916	1403	0.36
Lifetime (ever) suicidal attempt	0.06	0.235	429	0.08	0.27	976	(-0.049, 0.007)	-1.448	931.9	0.148
Suicide risk score	7.66	3.775	163	8.51	3.948	421	(-1.552, -0.139)	-2.35	582	0.019**

Key: * $p < 0.01$, ** $p < 0.05$.

Additionally, cases were selected to reflect only those who reported lifetime alcohol use and suicidal behaviour ($n = 864$). Independent samples T test analyses were performed to explore associations between gender, sociodemographic, school and family factors and marijuana use. These analyses revealed that significantly more females ($M = 0.836$, $SD \pm 0.371$) than males ($M = 0.683$, $SD \pm 0.466$) reported lifetime marijuana ($t(285) = -4.072$, $p < 0.001$). Furthermore, significant more males ($M = 0.691$, $SD = 0.463$) than females ($M = 0.533$, $SD = 0.499$) who reported lifetime alcohol use and suicidal behaviours lived in urban communities ($t(346) = 4.047$, $p < 0.001$). Also significantly more males ($M = 0.54$, $SD = 0.50$) than females ($M = 0.32$, $SD = 0.466$) who reported lifetime alcohol use and suicidal behaviours lived in violence prone communities. However there were significant gender differences among those who reported alcohol use and suicidal behaviour and variables such as school type, school factors, relationship with parents, living arrangements and aggressive behavioural traits ($p > 0.05$ in all cases).

DISCUSSION

In this study 19.85% of secondary school students surveyed were found to be at risk for suicide based on their total scores on the SBQ-R scale. For specific suicidal behaviours; they reported suicidal ideation (35.5%), suicidal plan (15.8%), suicidal attempts (6%) reported. The estimated prevalence of suicidal behaviours in adolescents vary widely in the literature, not only because of socio-cultural differences but also because of inconsistencies in the operational definitions of suicidal behaviours.

The findings in this study, for suicidal ideation (35.6%) is consistent with what is reported widely in the literature, a meta-analysis of 128 international studies of both community and school-based adolescents reported a mean lifetime prevalence of 29.9% [24]. With regard to the lifetime prevalence of suicide attempts in adolescents, the result from this study (6.0%) is also consistent with cross-national figures which range from 1.5% to 12.1% [25].

GENDER AND SUICIDAL BEHAVIOR

Consistent with the literature [8, 26] this study found the rates of suicide ideation, plans and attempts were higher in females than in males. Numerous research studies have proposed explanations for this gender difference in suicidal behaviour. One proposed explanation is that gender roles may dictate the individual's response to psychological distress [27]. The idealized 'hyper-masculinity' [28] of the Jamaican male includes a cultural assumption that outward displays of emotionality are feminine. This may result in the channelling of psychological distress into more gender-acceptable forms including anger, antisocial behaviour and violence [27].

Furthermore, the wish to conform to this hyper-masculine ideal may also result in a conscious or unconscious denial of emotional distress. That is, males may consciously refuse to admit to suicidal behaviours for fear of appearing 'weak'. Alternatively, they may not have been socialized to develop an 'emotional language' to either recognize or appropriately communicate these feelings.

Alcohol Use and Suicidal Behavior

The majority of the participants in this study reported lifetime alcohol use 56.7%. While past year and one month alcohol use were reported at 35.9% and 18% respectively. There were no direction associations noted between alcohol use and suicidal behaviour in this study. These findings fail to support research finding that substance use is linked to adolescent suicidal behaviour [5, 29, 30].

However Sher [31] in his commentary article on alcohol consumption and suicide pointed out the relationship between alcohol use and suicide is not conclusive as it varies across countries. For example, Portugal which has the highest rate of alcohol consumption in Europe but has a relatively low rate of suicide and shows a negative relationship between alcohol consumption and suicide while this is not so for other countries in Europe such as France, Russia and Finland [31]. These differences were attributed to levels of alcohol consumption where alcohol use disorders and binge drinking practices were noted to contribute more suicidal behaviours than merely using alcohol. These aspects of alcohol use were not explored in the present study and would be important to investigate in future studies.

Gender, Alcohol Use and Suicidal Behavior

Interestingly, when alcohol use was explored with gender and suicidal behaviour distinct differences were noted. Females who used alcohol had higher suicide risk scores than males who used alcohol. There were no differences noted between male alcohol users and male alcohol non-users and suicidal behaviours. However, female alcohol users showed higher means for past year suicidal ideation and suicide risk scores than female alcohol non-users.

Additionally, significantly more females than males who used alcohol and reported suicidal behaviour also reported lifetime (ever use) use of marijuana. Light et al. [32] suggested that self-medication with substances is a mechanism used to cope with adverse life events. Also both substance use and suicidal behaviour may also be mediated by stressful life

experiences [33]. Consequently, future research among adolescents particularly females, should seek to explore the presence of stressful life experiences as a possible contributing risk factor for substance use and suicidal behaviour.

Noteworthy is the finding that more males than females who reported alcohol use and suicidal behaviour lived in urban communities and violence prone areas. Exposure to violence and aggressive behaviour especially during childhood are known to contribute to suicidal behaviours [34]. Exposure to violence may propel males to the use of alcohol which also contributes to impulsivity associated with suicidal behaviour. Here again further research is needed to explore this relationship among male adolescents.

CONCLUSION

This study was limited by the use of a cross-sectional design and the possibility of recall bias. The inability to concurrently assess and control for the presence of mood, psychotic and externalizing disorders was also a limitation, as these disorders have strong associations with suicide. Nonetheless, calculations of the contingency coefficient allowed for statistical quantification of the contribution of each of several independent variables to suicidal behaviour outcomes. Additionally, given that suicidal behavior is the result of a complex interaction of numerous biological, psychological and social variables, there were other factors such as personality traits, mental disorders, childhood trauma, familial psychopathology and exposure to suicide in the social environment that would have been worthy of investigation.

Nevertheless this study is important as it highlighted the relationship between gender, alcohol use and suicidal behaviour. These findings should be used to guide gender specific approaches to suicide prevention among Jamaican adolescents.

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Chapter 7

THE JAMAICAN SECONDARY SCHOOL SURVEY: PARENTAL INFLUENCES ASSOCIATED WITH ADOLESCENT ALCOHOL USE

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ABSTRACT

Alcohol is the most commonly used and abused psychoactive substance among adolescents and young adults in Jamaica. Several studies suggest that parental factors play significant roles in both the initiation and continuation of alcohol use among adolescents. This present cross-sectional study conducted by the National Council on Drug Abuse (NCDA) with technical support and funding by the Organization of American States' Inter-American Drug Abuse Commission (CICAD) sought to examine the association between parental involvement, parents' alcohol use and parent-adolescent relationship and adolescent alcohol use in Jamaica. The sample consisted of 3,365 secondary school students ages 13, 15 and 17 years drawn from 38 schools using a stratified random sampling method. The Inter-American Uniform Drug Use System (SIDUC), the standardised Questionnaire for Secondary Schools, a self-administered instrument, comprising 99 items was used to capture socio-demographic, parenting influences, drug use and other psychosocial data. Spearman's Rho and Pearson's statistics were performed on key variables based on the objectives outlined for this study. Results show adolescent alcohol use decreases as parental involvement increases; that

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adolescent alcohol use increases as parents' drinking habits increase and that as relationship with mother or father improves, adolescent alcohol use decreases. These results were significant ($p < 0.01$). The findings highlight the importance of parent training and public education on possible links between parental influences and adolescent alcohol use.

Keywords: parental influences, parents' drinking habit, adolescent alcohol use, Jamaica

INTRODUCTION

Adolescence spans the period from the dependence of childhood to the independence of adulthood [1]. It is the developmental phase commonly characterised by turbulence as adolescents attempt to negotiate Erikson's psychosocial challenge of identity versus role confusion [2, 3]. Experimentation with identity roles is not unusual during this critical developmental phase and substance use is one of the ways that teenagers engage in the risk taking which is typical of adolescence [4].

Drinking is among a constellation of high-risk behaviours engaged in by adolescents. Alcohol is the most commonly used and abused psychoactive substance among adolescents and young adults in Jamaica [5]. About 66% of students surveyed ($n = 4,536$) in Jamaica admitted to using alcohol compared to 22.2% admitting to cigarette use, 21.5% marijuana and 25.5% inhalants [5]. Some surveys indicate the age of first use for alcohol is 11.71 years, while others have found that most adolescents who drank in the last year (37%) admit to 14 to 15 years old as their initiation ages [5, 6]. The Jamaican adolescents' preferred alcoholic beverage is beers or stouts, 70.8%, followed by premix alcoholic coolers 56.5%, wine, 32.8% and liquor, 32.6% [6]. When preferred alcoholic beverages are disaggregated by gender, it was found that the premix alcoholic coolers were preferred by more adolescent females (72%) than males (44.9%) and beers or stouts were preferred by more adolescent males (84.6%) than females (52.2%) [6].

A review of the pattern of alcohol use among Jamaican youth indicates that lifetime prevalence is about 66%; past year prevalence is about 48% and past month prevalence is 34% [5]. Lifetime prevalence in other Caribbean states are also comparatively high, for example, in Antigua and Barbuda (71%); Barbados (76%); Guyana (61%) and Trinidad and Tobago (82%) [6].

Highest alcohol prevalence among youth by age group, in Jamaica, was in the 15 to 16 age group (55%) compared to 52% in the 17 and over age group and 36% in the 14 and under age group [5]. In terms of adolescent alcohol use by gender, lifetime prevalence for males was nearly 70% compared to 62% for females; past year prevalence was 52% males and 42% females; past month prevalence was 36% males and 30% females [5].

Alcohol use is a major public health concern [7]. An association has been made between adolescent use of alcohol or illicit drugs and increased risk for poor school performance, and vice versa [8]. Also, intoxicated adolescents, through impaired judgement, are more likely to engage in risky sexual encounters and create situations where unsuspecting members of the public, friends and family members can be harmed in vehicular accidents or in violent behaviours [7, 9]. These risky behaviours associated with hazardous alcohol consumption facilitate increased psychological, financial and economic burden in increased medical costs,

loss of workplace productivity, greater impact on the criminal justice system and emotional strain on family members and friends [7, 9].

Parental Influences

It is commonly assumed that peer factors play a more important role than parental influences in adolescent alcohol use [10]. However, several studies suggest that parental influences do in fact, play a significant role in both the initiation and continuation of alcohol use among adolescents [10]. The parental influences of interest in this study are parental involvement, parents' alcohol use and parent-adolescent relationship.

Parental Involvement

Parental involvement as defined in this study includes issues of parental monitoring and parental behaviour management of adolescents. Parental monitoring describes parents' awareness of and communication of concern about their child's or children's activities [10]. This parental factor has been linked with adolescent alcohol and substance use in various cross-sectional and longitudinal studies [11-15]. High levels of parental monitoring are associated with lower adolescent alcohol use and lower levels of parental monitoring have been consistently associated with higher levels of adolescent alcohol use, externalising behaviours, sexual risk-taking and internalising behaviours such as low self-esteem, maladjustment and poor academic achievement [10].

Parents' Alcohol Use

Research has found that parents' use of alcohol increases the likelihood that adolescents would also consume alcohol [16] and further, an extensive body of evidence indicates that parents' substance use is predictive of adolescent substance use [17-19]. Higher levels of alcohol use have also been found among adolescents whose parents are dependent on alcohol when compared with adolescents with non-dependent parents [20]; paternal, but not maternal, alcohol use has been found to have a direct effect on the alcohol use among adolescent boys [21] and maternal alcohol use, more so than paternal alcohol use, has been found in the literature to be related to adolescent psychopathology such as depression, conduct disorder and alcohol dependence [22].

Other family-related factors, laws and cultural norms have also been shown to be associated with adolescent alcohol use. Various studies have identified parents' norms, attitudes, and beliefs on the issue of adolescent alcohol as significant influences on adolescent alcohol [23, 24]. An Australian study of 650 teenage participants found that adolescents are less likely to drink if their parents show disapproval of adolescent drinking but, adolescents are likely to engage in more drinking when parents convey tolerance and permissiveness to drinking [25].

Parent-Adolescent Relationship

Parent-adolescent relationship quality underpins many aspects of parenting and is an ongoing interplay between parents and adolescents, affecting and being affected by other parenting factors such as parental monitoring and parenting style. Adolescents' perception of their relationships with their parents as warm and supportive has been associated with lower levels of adolescent alcohol use and lower rates of problematic use and misuse [10, 26]. A study with a sample of 493 adolescents who misused alcohol found that the participants were significantly more likely to report lower parental care [27]. Parent-adolescent relationship quality also mediated the effect of temperament on alcohol misuse among males with good parent-adolescent relationships reducing the contribution of temperament to alcohol misuse. However, the mediating effect was different among females as it was found that relationship quality and temperament separately predicted alcohol use, and good parent-adolescent relationship quality did not minimise the effect of temperament on alcohol use [28].

The aim of the present study is to examine the relationship between the dependent variable, adolescent alcohol use, and three independent variables, parental involvement, parents' alcohol use and parent-adolescent relationship.

METHODS

The present study was cross-sectional and conducted by the National Council on Drug Abuse (NCDA) in collaboration with the Organisation of American States' Inter-American Drug Abuse Commission (CICAD); the latter provided technical support and funding for this project. This was part of a regional project being conducted in Jamaica and 12 other Caribbean islands.

Sample

The target population included all public and private secondary schools in Jamaica. A randomly selected sample frame was used with school lists being provided by the Ministry of Education and the Private School Association of Jamaica. Thirty-eight schools were selected representing a target sample of 3,949 students at the lower, middle and upper levels of the school system representing ages 13, 15 and 17 years.

Instrument

The Inter- American Uniform Drug Use System (SIDUC), the standardised questionnaire for secondary schools was used in this study. This was a self-administered questionnaire comprised of 99 items which captured information related to socio-demographic characteristics, parental involvement, parental drug use, relationship with parents and other relevant information.

Procedure

Approval to undertake the study was granted through the Ministry of Health and Ministry of Education. Informed consent and assent forms were distributed to the identified schools by the NCDA prior to data collection. Trained researchers administered the questionnaires to students who returned the informed consent and assent forms. Students were assured of confidentiality and anonymity and reminded not to include any identifiable information on the questionnaire. They were also provided with a list of mental health professionals associated with the project although minimum harm was expected through their participation.

Data Entry and Analysis

The data were entered into a pre-constructed Microsoft Excel database constructed by OAS/CICAD. The data was cleaned using the double data entry technique. Individual school files were merged and exported to the Statistical Package for the Social Sciences (SPSS). Spearman's Rho and Pearson's statistics were performed on key variables.

RESULTS

This section presents the results of the study. First, descriptive statistics regarding the demographic variables are presented and then the results relating to dependent variable, adolescent alcohol use, by the independent variables parental involvement, parents' alcohol use and parent-adolescent relationship.

Descriptive Statistics

There were 3365 students who participated in the study, 42.7% were males and 57.3% were females. Most participants reported that they lived with their mother (75.1%), a significant number also lived with their brother(s)/sister(s) (47.9%), and father (37.3%). The lifetime prevalence of alcohol use was 64.1% while one year use was 44% and one month use, 33.6%.

Parental Involvement and Alcohol Use

Parental involvement was measured by the several questions (See Table 1) over lifetime, past year and one month periods. The Spearman's Rho and Pearson's were conducted to examine the association between parental involvement and adolescent alcohol use. Table 1 indicates that overall there were weak negative associations with parental involvement and adolescent alcohol lifetime, past year and one month use ($p < 0.01$). This indicates that as parental involvement increases, adolescent alcohol use decreases. Except in the case of 'how well do parents know friends' and student alcohol use in the past month ($r = -0.05$, $p > 0.05$) which was not significant.

Parents' Alcohol Use

Parents' alcohol use was measured by the several questions (See Table 2) over lifetime, past year and one month periods. The Spearman's Rho and Pearson's were conducted to examine the association between parents' alcohol use and adolescent alcohol use. Table 2 indicates significant weak positive associations between mother/guardian and father/guardian drinking habits and student alcohol use over lifetime, past year and one month use in all cases ($p < 0.01$ and $p < 0.05$). This indicates that as parental drinking habits increase, adolescent alcohol use increases. It also indicates that parents (mother/father/guardian) reaction if adolescents are caught drunk or tipsy was significantly associated with student alcohol use over lifetime, one year and one month. It was a weak negative relationship indicating that whereas parents' reaction became less negative, students' reports of alcohol use increases ($p < 0.01$).

Parent-Adolescent Relationship

Parent-adolescent relationship was measured by two questions (See Table 3) over lifetime, past year and one month periods. The Spearman's Rho was conducted to examine the association between parent-adolescent relationship and adolescent alcohol use. Table 3 shows that relationship with parents (mother, father or guardian) had a weak negative association with adolescent alcohol use over lifetime, last year and one month. These associations were significant at the $p < 0.01$ level except in the case of relationship with father/guardian and last 30 days use which was not statistically significant ($p > 0.05$). This result indicates that as relation with mother or father improves, student alcohol use decreases.

Table 1. Parental involvement by adolescent alcohol use

Parental Involvement	Alcohol Use by Adolescent		
	Ever used	Last 12 months Use	Last 30 days use
<i>Parents knowledge where student is</i>			
correlation co-efficient-Spearman rho	-0.109	-0.800	-0.114
p value	<0.01*	<0.01 *	<0.01*
<i>Parents knowledge TV shows watched</i>			
correlation co-efficient-Pearson's	-0.192	-0.138	-0.093
p value	<0.01*	<0.01*	<0.01*
<i>Parents attention to school work</i>			
correlation co-efficient-Spearman's rho	-0.195	-0.092	-0.090
p value	<0.01*	<0.01*	<0.01*
<i>Meals together with parents/guardians</i>			
correlation co-efficient-Spearman's rho	-0.145	-0.087	-0.070
p value	<0.01*	<0.01*	<0.01*
<i>Control time come in at night</i>			
correlation co-efficient-Pearson's	-0.078	-0.118	-0.133
p value	<0.01*	<0.01*	<0.01*
<i>Parent expects to be told where student is</i>			
correlation co-efficient-Pearson's	-0.067	-0.065	-0.080
p value	<0.01*	<0.01*	<0.01*
<i>How well do parents know close friends</i>			
correlation co-efficient-Spearman's rho	-0.131	-0.061	-0.05
p value	<0.01*	<0.01*	0.055

*p significant at $p < 0.01$ level.

Table 2. Parent/guardian substance use and attitudes by adolescent alcohol use

Parents/Guardians Substance Use and Attitudes	Alcohol Use by Adolescent		
	Ever used	Last 12 months Use	Last 30 days use
<i>Mother's/Guardian Drinking Habit</i>			
correlation co-efficient-Pearson's	0.115	0.017	0.067
p value	<0.01*	<0.01*	<0.05*
<i>Father's/ Guardian Drinking Habit</i>			
correlation co-efficient-Pearson's	0.178	0.066	0.083
p value	<0.01*	<0.01*	<0.01*
<i>Mother's/Guardian's reaction if catch you drunk/tipsy</i>			
correlation co-efficient-Spearman's rho	-0.110	-0.117	-0.162
p value	<0.01*	<0.01*	<0.01*
<i>Father's/Guardian's reaction if catch you drunk/tipsy</i>			
correlation co-efficient-Spearman's rho	-0.134	-0.154	-0.146
p value	<0.01*	<0.01*	<0.01*

* p significant at $p < 0.01$ level, ** p significant at the $p < 0.05$ level.

Table 3. Relationship with parents/guardians and student alcohol use

Relationship with Parents/Guardians	Alcohol Use by Student		
	Ever used	Last 12 months Use	Last 30 days use
<i>Relationship with Mother/Guardian</i>			
correlation co-efficient-Spearman's rho	-0.071	-0.112	-0.092
p value	0.006**	0.000**	0.000**
<i>Relationship with Father/Guardian</i>			
correlation co-efficient-Spearman's rho	-0.140	-0.057	-0.032
p value	0.000**	0.012**	0.220

** p significant at $p < 0.01$ level.

Summary

Results show adolescent alcohol use decreases as parental involvement increases; that adolescent alcohol use increases as parents' drinking habits increase and that as relations with mother or father improves, adolescent alcohol use decreases. These results were significant ($p < 0.01$).

DISCUSSION

In this study, we found that overall as parental involvement increases, adolescent alcohol use decreases ($p < 0.01$). This finding is consistent with the literature that generally indicates that parents who show greater awareness of their adolescent's activities and openly communicate their concern about their adolescent's activities, which may include monitoring television shows watched, school work, friends, and schedule, tend to report lower adolescent alcohol use [11-15]. The converse of low parental monitoring of adolescent activities has been associated, both in cross-sectional and longitudinal studies, with increased adolescent alcohol use [10]. Seemingly simple but nurturing activities such as parents and adolescents

having dinner together and parents paying attention to their adolescents' homework have consistently been shown to amount to large pay-offs not only in reducing adolescent alcohol use but also in managing other high-risk behaviours that characterise the turbulence of this developmental [2, 3, 29]. The reality, based on the literature, is that parenting behaviours that are responsive to the needs of children and adolescents and which exude nurturance and monitoring continue to play influential roles in late adolescent alcohol use, and other high-risk behaviours, even when placed against formidable peer influences such as alcohol offers, social modelling and perceived norms [23].

To a large extent, parental involvement in their adolescents' lives is mediated by the adopted parenting style which includes methods of adolescent behaviour control and disciplining. Baumrind [30] isolated three main parenting styles – authoritarian, authoritative and permissive – based on variations in control or monitoring and warmth or nurturance exhibited by parents towards their children and adolescents. The authoritative parenting style that is high on warmth, rational, flexible, though firm and clear about expectations with limited use of punitive disciplinary practices when compared to authoritative parenting styles has been credited with producing more well-adjusted adolescents [30, 31]. In fact, the protective effect of authoritative parenting style against adolescent alcohol and other substance use has been well established in the literature [29].

Parents' Alcohol Use

We found that as parental drinking habits increase adolescent alcohol use increases over lifetime, past year and 30-day periods ($p < 0.001$ and $p < 0.05$). This positive association between these two variables is consistent with other findings in the literature. While this present study was cross-sectional in design and carries limitations in terms of making cause-and-effect statements, there is an extensive body of evidence making parental alcohol use and dependency predictive of adolescent alcohol use [17, 18, 19]. The study by Zhang et al. [21] has found that in relations to male adolescent drinking, it is paternal alcohol use rather than maternal drinking that plays the crucial link between the variables. This association could quite possibly be explained in behaviour modeling by boys of the same sex parent, particularly as they move into adolescence and are clarifying issues of identity formation [32]. However, while the boys may be modelling paternal behaviour, maternal drinking is not without its pitfalls as it has been associated, far more than paternal drinking, with adolescent psychopathology such as alcohol dependence, depression and conduct disorder [22]. This differential in adolescent outcome between paternal and maternal drinking could be the subject of further studies in a Jamaican and Caribbean population.

It was also found that parents' attitude towards alcohol use was negatively associated with adolescent alcohol use with less negative reaction by parents being associated with increased adolescent alcohol use. It could be argued that parents' attitudes, norms and beliefs underpin their own alcohol use and it is therefore not surprising that various studies in the literature have reported similar negative association [23, 24].

Parent-Adolescent Relationship

In this study, it was found that as relationship with mother or father improves, adolescent alcohol use decreases ($p < 0.01$), except in the case of relationship with father and last 30-day use which was not statistically significant ($p > 0.05$). This finding is consistent with those reported by several researchers [10, 26, 27]. The relationship between parents and adolescents, as previously discussed, is largely mediated by parenting style adopted. Authoritative parenting, which is high in nurturance and control, has been found to be protective against adolescent drinking and other substance use that authoritative parenting style protects adolescents against drinking and smoking while parenting styles that were more inflexible and administered more punitive disciplinary methods were associated with more substance dependency in adolescent [31].

CONCLUSION

In conclusion, the findings indicate that adolescent alcohol use decreases as parental involvement increases; that adolescent alcohol use increases as parents' drinking habits increase and that as relations with mother or father improves, adolescent alcohol use decreases. These findings were significant ($p < 0.01$) and consistent with the findings of other studies in the literature. The findings highlight the importance of parent training and public education on possible links between parental influences and adolescent alcohol use.

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Chapter 8

SMASHING BABASH: AN EVALUATION OF UNREGULATED RUM IN GRENADA

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ABSTRACT

Much of the research on the public health implications of alcohol consumption focuses on high-wealth nations in the Americas and Europe, alcohol is a problem in many developing countries. However, there are a proportion of alcoholic beverages that are illegally produced and considerably unregulated. Much of the alcohol consumption in Grenada comes from illegally distilled rum, colloquially called babash or bush rum. The public health complications of babash consumption is currently an un-researched public health issue. *Methods:* Bottles of locally and illegally produced babash were collected from three different regions in Grenada. Three of the bottles were randomly selected to be analyzed for toxicological impurities by the Grenada Bureau of Standards and St Louis Testing Laboratories. *Results:* Methanol analysis performed determined that while the ethanol concentrations varied between samples, the methanol concentrations of all three samples were well below both the maximum tolerable concentration (MTC; 2.0%). Heavy metal analysis tested for 32 different analytes and determined elevated levels of aluminum, calcium, chromium, copper, sulfur, silicon, and zinc. *Recommendations:* Based on this chemical analysis, there is sufficient evidence to suggest that babash, beyond the effects of ethanol, may pose a public health risk to consumers. Although none of the samples reached the hazardous or toxic limits found in the human body, they can

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still have acute and chronic effects on the body depending on the consumption rates and chemical content.

Keywords: alcohol consumption, Grenadian Bureaus of Standards (GBS), illegal distillation, public health, heavy metal poisoning, babash, bush rum, methanol toxicity, ethanol

INTRODUCTION

Many nations have severe problems with alcohol abuse and over-consumption, and the morbidity and mortality associated with alcohol is well researched [1, 2]. Alcohol use is therefore the subject of much interest for public health interventions. The global burden of alcohol is difficult to determine, because there are many facets involved, which include healthcare costs, criminal justice costs and collateral damage from accidents. Current estimates suggest that 3-8% of global deaths and 4-6% of global disability-adjusted life-years (DALYs) are attributable to alcohol consumption [2]. In economic terms, a 2011 study estimated the 2006 cost of alcohol in the United States to be \$223.5 billion, most of which was due to lost productivity and specifically attributable to binge-drinking; this enormous sum averages to approximately \$1.90 per alcoholic drink consumed [3]. While much of the research on the public health implications of alcohol consumption focuses on high-wealth nations in the Americas and Europe, alcohol is a problem in many developing countries.

Grenada, for example, is the largest consumer of alcohol per capita in the western hemisphere, and many other countries in the Caribbean region are just as high [4], yet there is a noticeable void in the public health research on alcohol in the Caribbean region. Specifically, in Grenada, alcohol abuse is a large concern for the Ministry of Health (MoH) and the MoH has been investigating interventions to help reduce the burden of alcohol abuse in Grenada [5]. Emergency department (ED) studies found that in the Caribbean and Latin American Regions alcohol consumption has an extremely high prevalence among injured prevalence in the ED, and ED doctors in Grenada report that the ED is full of alcohol-related injuries and co-morbidities [6, 7].

The production of most alcohol consumed worldwide is subject to regulation by government authorities [8]; however, there are a proportion of alcoholic beverages that are illegally produced and considerably unregulated. According to the World Health Organization (WHO) an estimated 24.8% of alcohol consumed worldwide was unrecorded [4]. Part of the problem is that small batch distilleries have become extremely popular over the past decade in the creation of low volume, personalized craft liquors [9, 10].

Much of the alcohol consumption in Grenada comes from illegally distilled rum, colloquially called babash or bush rum [6, 11]. Babash provides a cheap, strong source of alcohol for many and is strongly tied to the culture of Grenada, as many social events will feature babash in some amount [6, 12].

In Grenada babash is typically produced in stills using copper pots or iron pots for the boiling process, bamboo, cut fire hoses and copper for tubing, and plastic barrels for cooling [11]. The production of babash takes place in the “bush” – a heavily wooded area- that is well hidden. Because of the less than sanitary conditions of production and bottling, and no standard formula, babash can have different levels of ethanol, methanol, arsenic, copper, lead, zinc and other contaminant levels. Because there is no regulatory oversight, it is difficult to

assess the toxicological safety. Potentially exposing consumers to highly toxic levels of substances such as lead, methanol, and pure ethanol leading to subsequent adverse health effects [13]. Raising public health concerns of consumption of possible contaminants. Illegal spirits have been found to have high levels of methanol [14] and lead [15], suggesting acute and chronic toxicities from consumption.

The consumption of illegally produced alcohol is by no means a new occurrence, as there has been much research into consumption of moonshine in the United States [16, 17] and other countries [4], however, there is an absence of research on babash in the Caribbean region. This is potentially troubling, as unregulated alcohol, such as babash, is estimated to account for 30% or more of total alcohol consumed worldwide [18].

The public health complications of babash consumption are currently un-researched public health issues. Two major public health concerns are: (1) the direct physical effects of consumption, which include methanol-, ethanol-, and heavy metal poisoning; and (2) the social and cultural significance of babash in Grenada, which not only includes how babash is viewed by Grenadian communities, but babash's importance to its producers, merchants, and consumers. The social and cultural significance is crucial to help plan and develop any potential interventions and will help predict barriers to success.

The goal of this study was to assess if babash should be treated as a public health issue, or, if it is simply a cheaper means of alcohol for consumers. Specifically, the aims of this study were to assess the quality of babash and determine the potential health effects of consumption.

METHODS

Seven bottles of locally and illegally produced babash were collected from three different regions in Grenada (Grenville, Vincennes, and Beaton). Three of the bottles were randomly selected to be analyzed for toxicological impurities by the Grenada Bureau of Standards and St. Louis Testing Laboratories. The Grenada Bureau of Standards (GBS) completed a chemical analysis, reporting on the alcohol impurities and level of ethanol and methanol content for each sample. St. Louis Laboratories conducted a full metal analysis on each sample for the 33 of the most commonly sampled metals.

RESULTS

Methanol Analysis performed by the Grenadian Bureaus of Standards (GBS) determined that while the ethanol concentrations varied between samples, the methanol concentrations of all three samples were well below both the maximum tolerable concentration (MTC; 2.0%) and EU general limit for consumption (0.40%) (See Table 1). In the analyzed contents from sample 1, the level of ethanol was 85% and contained a higher level of methanol and ethyl acetate than what is safe to consume. There were other impurities whose concentrations were not significant enough to pose a threat to public health. The other two samples had above 40% ethanol and also contained constituents similar to those found in the sample 1.

Table 1. Methanol and ethanol content

Sample	Volume (mL)	pH	Brix (%)	Ethanol (%)	Methanol (%)	Methanol (ppm)
Standard (Pure EtOH)	-	6.95	19	-	0	-
#1	750	5.22	18.8	85.6	0.1	100000
#2	750	4.96	15.9	43	0.003	3000
#3	750	4.46	15.3	48.4	0.02	20000
Methylated Spirits	-	-	-	95	5.0	5000000

Table 2. Volatile impurities analysis

Sample	Impurities
1	Acetaldehyde, Methanol, Ethyl-Acetate, <i>N</i> -Propanol, <i>Sec</i> -Butanol
2	Methanol, Ethyl-Acetate, <i>N</i> -Propanol, <i>Sec</i> -Butanol
3	Acetaldehyde, Methanol, Ethyl-Acetate, <i>N</i> -Propanol, <i>Sec</i> -Butanol, Acetone, Isobutanol, Active Amyl Alcohol, Isoamyl Alcohol, <i>N</i> - Amylalcohol

Table 3. Alcohol metal analysis (in mg/L)

ANALYTE (mg/dl)	#1	#2	#3	MCL
Silver	<.0.05	<.0.05	<.0.05	0.1
Aluminum	1.13	28.7	0.31	0.02
Arsenic	<.0.05	<.0.05	<.0.05	0.01
Boron	<.0.05	<.0.05	<.0.05	2.4
Barium	<.0.05	<.0.05	<.0.05	2
Beryllium	<.0.05	<.0.05	<.0.05	0.004
Cadmium	<.0.05	<.0.05	<.0.05	0.005
Chromium	0.13	0.27	0.14	.1
Copper	12.2	4.98	18.5	1.3
Iron	0.15	0.69	0.54	0.015
Zinc	0.05	0.22	10.6	11

MCL Maximum contaminant level from the United States Environmental Agency.

Volatile impurity analysis was also performed by GBS using GC-Chromatography, but, due to a lack of an internal standard, the analysis was only qualitative. The volatile impurity analysis identified 9 unique compounds between the three samples are presented in Table 2. Because the quantity of the impurities of the compounds could not be determined, no health effects can be estimated, however the presence of the impurities is definitely still worth as they are carcinogenic.

Heavy metal analysis performed by St. Louis Testing Laboratories tested for 32 different analytes and determined elevated levels of aluminum, calcium, chromium, copper, sulfur, silicon, and zinc (Table 3). Of these analyzed, the levels of aluminum, copper, arsenic and chromium are of most concern. Heavy metal analysis of 32 different contaminants elucidated dangerously elevated levels of copper (>10X MCL). Chromium levels in the three samples were all found to be above the WHO MCL of 0.05 mg/L (>2X MCL). The levels of copper were also found to be over ten times the US EPA MCL of 1.3 mg/L. and chromium (>2X MCL), as well as high levels of zinc, sulfur, silicon, and calcium. Based on this chemical analysis, there is sufficient evidence to suggest that babash, beyond the effects of ethanol, may pose a public health risk to consumers.

DISCUSSION

Surrogate alcohol or unrecorded alcohol as it is known around the world is a threat to public health. The analyzed samples of babash showed a variance on levels of methanol, ethanol, arsenic, aluminum copper, iron and zinc. These results could be a single batch specific outcome, and could change in the next batch of babash, as producers do not use precise methodology for each production.

If improperly distilled at incorrect temperatures, the alcoholic beverage can be laden with impurities of carbons and metals that did not evaporate at their respective boiling point [18]. Methanol is hazardous to the human body if consumed at a rate of 2%/volume in liquid form can cause harmful effects on the liver leading to liver hepatitis and ultimately irreversible cirrhosis and possibly death if consumed in excess [19]. In the human body, methanol is converted to formaldehyde, which can subsequently effect the optic tract and lead to temporary or even permanently blindness if constantly consumed. Of the three samples analyzed, all three samples were well below the hazardous limit of methanol poisoning, however, sample 1 has a subsequently higher percentage (.1%/ volume) of methanol concentration compared to the other two samples (see Table 1). Although Sample 1 might be considered “safe,” as it is under the hazardous level, it can result in acute blindness.

Ethanol is the portion of the alcohol, which is consumed by humans, and is measured by ethanol percentage/ volume (proof). It is very subjective criteria to measure the quality of alcohol consumers are drinking, but instead measure the quantity of alcohol consumed. In the case of Babash, the variability in the three samples (Tables 1 and 3) shows that sample 1 (170 proof) is almost double the proof of the average rum (60-100 proof) and other two samples under the babash ‘moniker.’ The quantity (proof) of ethanol in legalized alcohol can be controlled to variable limits based on the manufacturer’s distillation process. However, in babash, as seen in the chemical analysis the variability between producers is all based on the distillation process and lead to serious health outcomes if not regulated properly. Excess ethanol consumption can lead to fatty liver (steatosis), which can progress to irreversible liver cirrhosis. Mentally, patients with ethanol poisoning will be confused, lack of movement (ataxia), signs of neuropathy, and a decreased respiratory rate which can lead to sudden death.

Aluminum is a neurotoxin and results in poorer psychomotor control and cerebral impairment leading to a decrease in IQ. While there is no agreed MCL for aluminum, chronic ingestion of aluminum has been linked to neuro-degenerative effects [21]. Altman [21] found that a water supply with excess in aluminum sulphate that was used in illegal alcohol production in England resulted in organic brain damage occurred.

Lead is a toxic metal that should not be found in the human body as once it gets into the bloodstream can cause renal failure, liver damage, and impaired hearing or cause mental retardation [20]. According to Morgan, Parramore, and Ethridge [17], the human lead toxicity level is 300 mg/dl, however, all of the samples of babash samples were <.05 mg/dl.

Excess iron can lead can also lead to neurological/physiological problems such as Parkinson’s disease [18]. Acute iron poisoning causes GI, cardiovascular, metabolic, hepatic and central nervous system toxicity [22] Liver is one of the organs most affected by cellular iron toxicity, but other organs such as the heart, kidneys, lungs, and the hematologic systems also may be impaired. Chronic iron overload, the deposit of iron into the heart may cause death due to myocardial siderosis

Cadmium poisoning can cause anaemia, emphysema or renal failure and cadmium may be a risk factor in the development of prostate (which is of interest in the Grenada Afro Caribbean population) or lung cancer.

Excess zinc inhibits the uptake of copper, which leads to aneurisms and cerebral dysfunction leading to increased risk of stroke. In addition, copper causes liver damage-hepatitis going on to cirrhosis. Excess copper spills into the liver, and leads to deposits in the RBCs, eye, and brain.

Finally, chromium was also found and known to impair kidney functions, reproductive capacity, hypertension, and hepatic dysfunction [20].

While the ethanol and methanol content is within safe limits the heavy metal analysis of the samples suggests that unregulated rum can have potential serious side effects.

CONCLUSION

Metal and chemical contamination is a problem when unregulated and poor quality control methods are used in the distillation process of the creating illegally produced alcohol [18]. Unregulated both in taxation and quality control Babash's demand has increased over the past decade and so has the number of illegal producers of the rum [23]. As a result of the analysis, there is variation in the chemical and metallic impurities there. Although none of the samples reached the hazardous or toxic limits found in the human body, they can still have acute and chronic effects on the body depending on the consumption rates and chemical content.

While the initial organic analysis provided optimistic results as a cheaper form of alcohol, with the ethanol and methanol levels within safety limits, the results of the heavy metals are of concern. The majority of results are below physiologically significant levels, however Aluminum and Copper are of some concern. These metals have significant mental and cognitive effects on the human brain. The limitation of this was that quantity of babash was not addressed. More research is needed to develop an evidence based protocol in considering the abovementioned concerns would potentially help reduce the potential harmful implications of babash consumption mentioned above.

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Chapter 9

INFLUENTIAL FACTORS AFFECTING UNDERAGE DRINKING AMONG CARIBBEAN YOUTHS

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ABSTRACT

Underage drinking is a problem among Caribbean youths, however little information is known of the interpersonal and intrapersonal factors that are seen in association with the consumption of alcoholic beverages. This article serves to highlight some socioecological aspects in the Caribbean that may contribute to underage drinking. Data was used from a regional survey conducted by Inter-American Drug Abuse Control Commission (CICAD). Interpersonal factors such as, increased shared meals between parent and adolescent decreases the risk of the adolescent engagement in underage drinking. Furthermore, good quality father-adolescent relationship, have shown to statistically significantly reduce underage drinking. Whereas, increase drinking habits exhibited parents and the increased number of peers who consume alcohol have shown to increase risk of underage drinking. A good mother-adolescent relationship and the adolescent's perception of the harmfulness of regular consumption of alcohol, have shown statistical significance. These results suggest that greater efforts need to be implemented at the intrapersonal and interpersonal levels in the Caribbean, to reduce underage drinking.

Keywords: adolescence, alcohol, underage drinking, Caribbean

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INTRODUCTION

Globally, 14% of females and 17% of males engage in underage drinking, which is defined as the consumption of alcohol before the legal age [1]. In 2013, it was reported that, 35% of school aged children in the United States consumed alcoholic beverages within the 2last 30 days [2]. In the Caribbean 43% of adolescents 14 years or younger, 58% of 15-16 year olds and 17% of those 17 years or older engage in underage drinking [3].

The perceptions and beliefs by the adolescent are critical in understanding the contributing factors of underage drinking and its continuance into adulthood [4]. Adolescents perceive that drinking is associated with being recognized as an adult, hence they engage in such behaviours [5]. Although adolescents are quite knowledgeable of the increased risk associated with the consumption of five or more alcoholic drinks once or twice a week, alcohol consumption has increased from 38.2% to 40.7% between 2002 and 2011 [4], thus indicating that underage drinking continues to be an issue within this developmental age group.

Interpersonal factors such as parents and peers play a key role in social support and initiation of underage drinking [6]. A collapse within the support system or the involvement of parents and peers who consumes alcohol can result in the early onset of underage drinking that may further progress into difficulties due to ingestion of alcohol early adulthood [7]. It has been shown that the adolescent whose father drinks is at an increased risk of underage drinking [3,21], whilst the mother increases the risk to a lesser extent to 2.14 times [8]. Nevertheless, the consumption pattern of both parents may influence the adolescent's premature drinking habits. Despite the drinking habits exhibited by parents, the quality of the relationship between the adolescent and parents can serve as a protective factor against underage drinking [6]. Adolescents who feels respected and are familiar with a sense of belonging, within the family has shown to be an integral protective factor against deviant behaviours [9]. In addition to the adolescents "placement" within the family structure, the parents' type of disciplinary approach can promote or delay early onset of underage drinking. Parents who have a permissive attitude towards underage drinking while informing them about the dangers of alcohol usage, have shown to reduce underage drinking in comparison to an authoritarian approach whereby, consumption of alcohol is strictly prohibited without any communication of its harmfulness, leaving curiosity within the adolescent's psyche [5]. Dishion and Loeber [10], stated that adolescents who are closely monitored by parent(s) are at lowered risk of engaging in alcohol consumption and are less likely to have peers that also do so [11].

Despite parental influences, peers interactions, can too influence the adolescents to engage in underage drinking. Studies have shown that the adolescent's family interaction decreases and time spent with peers increases age the adolescent becomes older [12]. Thus, in search for acceptance by peers, adolescents become increasingly vulnerable to delinquency and substance abuse behaviour [13]. A 5.17 fold increased risk has been observed among adolescents who had friends who consumed alcohol [14].

Drinking alcoholic beverages during adolescence poses a public health issue due to lack of brain development which may result in increased disability-adjusted life years lost. Ingestion of alcohol during this developmental stage has been shown to significantly impact the adolescent's brain morphology causing deceleration or under-development of the brain

[15]. The lack brain development can result in, decreased sustained attention is experienced followed by delayed academic progression [15] which may further result in a lowered Grade Point Average and missed days among adolescent males [16]. A study conducted by the Centres for Disease Control and Prevention [17] findings suggested that 1 in 10 adolescents between 15 and 20 years drive under the influence moreover, and found a 17 times increased risk of being in motor accidents can occur when the adolescent drives under intoxication. Thirty – four (34%) percent of adolescents have reported being driven by their peers or family members who were under the influence of alcohol [18]. Difficulties in completing every day task due alcohol consumption in early adulthood has shown to be related to increased frequency of drinking alcohol during middle adolescent period [19]. Furthermore, an increased risk of 1.06 in developing cancer correlates to moderate drinking habits [20]. This current study aims to explore the adolescents' perception, parents' drinking habits and relationship with the adolescent as well peers' influence on underage drinking in the Caribbean, thus reducing the prevalence of underage drinking among the Caribbean islands.

METHODS

Secondary data was obtained from a regional cross sectional survey conducted by the Inter-American Drug Abuse Control Commission (CICAD). The survey assessed the prevalence of alcohol and drug use among nine Caribbean countries, as well as possible risk factors that may contribute to the adolescent's usage. Nine Caribbean countries were surveyed; Trinidad and Tobago, Antigua and Barbuda, Jamaica, St. Kitts and Nevis, St. Vincent and the Grenadines, Grenada, Guyana, St. Lucia and Haiti. To ensure random selection of participants, a two stage cluster sampling design was performed by secondary schools and later by classrooms (Forms 2, 3 and 5) which included pupils from between ages 12-16 years.

Fifteen questionnaire items based on alcohol use and possible risk factors were exclusively selected for the purpose of this study. The variables assessed were sex; age; parents' knowledge of whereabouts of the adolescent; number of meals in the company of their parents; parents' knowledge of close friends; reactions of the father and mother to the adolescent coming home drunk/tipsy; the relationship with father and mother; drinking habits of the mother and father; the number of the adolescents' peers that consume alcohol; the adolescents' perception of regular alcohol use to their health and the adolescents' perception of the harmfulness of getting drunk.

Data were analyzed Using IBM Statistical Package for the Social Sciences Version 23. Descriptive statistics were utilized to describe the sample population and alcohol consumption and comparisons between males and females were done using Chi Square analysis in relation to the variables. Lastly, logistic regression was used to estimate the influence of the intra- and interpersonal factors on adolescents who consumed alcohol.

RESULTS

The total sample included 19,376 students aged between 12 to 17 years from 10 Caribbean countries. The mean age was 15.4 years, with 46% being males and 21.4% of the sample group being predominantly from Trinidad and Tobago (Table 1). The highest proportion (39%) of the respondents stated their parents' marital status as married followed by the second highest as being single (26.6%). Furthermore, more than half (64.6%) of the study participants engaged in underage drinking, with 54.2% being female when compared to males (45.8%).

A large percentage in each gender reported that parents rarely knew of their whereabouts; females (80.6%) and males (62.0%). Forty – seven percent (47%) of males and sixty percent (60%) of female adolescents disclosed that their father would be extremely upset if they were to arrive home intoxicated. However, more adolescents (males 52.5%; females 61.0%) reported that their mother would be extremely upset in contrast to the father's reaction. When comparing the relationship between the adolescent and their parents, majority of males (48.4%) and females (51.1%) described the relationship existing between themselves and their father as moderate, but reported that the relationship with their mother as good (males 65%; females 59.9%). Whilst majority within each gender stated they had no friends who consumed alcohol regularly (males 45.8%; female 56.7%), there was a statistically significant difference of the number friends of adolescents who consumed alcohol between males and females ($p < 0.001$).

There was statistically significant difference ($p < 0.001$) of the perception of the harmfulness of getting drunk and regular consumption of alcohol between genders. More females than males had perceived that regular consumption of alcohol (males, 45.6%; females, 54.1%) as well as getting drunk (males, 55.5%; females, 61.1%) is very harmful. When considering the parents' reactions to the adolescent coming home drunk or tipsy, there was a statistically significant difference between males and females ($p < 0.001$).

There was no statistically significant difference between the relationship with the mother and the adolescent's consumption of alcohol ($p > 0.05$). On the contrary, the association between the father's relationship with the adolescent and drinking was statistically significant ($p < 0.05$).

The odds of underage drinking among adolescents who had meals with parents for 3 to 5 days and 6 to 7 days compared with those who had meals for 0 to 2 days per week was 0.76 (95% CI 0.66, 0.88) and 0.67 (95% CI 0.61, 0.74) respectively (Table 3). A protective effect was noted when comparing fathers who reacted extremely (OR 0.45; 95% CI 0.31, 0.63) or moderately (OR 0.57; 95% CI 0.40, 0.83) to knowledge of their child consuming alcohol in comparison to the father who was not upset. Adolescents were found to be 1.3 (95% CI: 1.01, 1.69) times more likely to drink alcohol when the perception of its harmfulness was moderate and 0.94 (95% CI: 0.73, 1.2) when adolescent's perceptions were very harmful in comparison to adolescent's perception that it was not harmful. Furthermore, adolescents who had one friend that drank alcohol have an increased risk of 1.9 (OR 1.9, 95% CI: 1.59, 2.29), whilst adolescents with some friends and a lot of friends has shown a further increased risk of 2.854 (95% CI: 2.57, 3.17) and 3.981 (95% CI: 3.22, 4.93) respectively.

Table 1. Characteristics of the study sample

Characteristics	N (%)
Gender	Male
	Female
	Single
	Married
Parents' marital status	Divorced
	Separated
	Widow(er)
	Living together/common law
	Other
Country	Antigua and Bermuda
	Grenada
	Guyana
	Haiti
	Jamaica
	St. Kitts and Nevis
	St. Lucia
	Trinidad and Tobago
	St. Vincent and the Grenadines
Consumption of alcohol	Yes
	No

Table 2. Cross-tabulation of the risk factors of alcohol consumption by gender

Variables	Gender		P value
	Male (%)	Female (%)	
Parents knowledge where student is			
No	33.3	17.4	<0.001
Rarely	62.0	80.6	
Yes	4.7	1.9	
Meal together with parents			
0-2 days	46.4	46.0	0.001
3-5 days	13.1	11.6	
6-7 days	40.4	42.5	
How well parents know close friend			
No knowledge	14.6	9.5	<0.001
Moderate knowledge	42.6	56.4	
Extreme knowledge	42.7	44.0	
Reactions to: Father catches you drunk or tipsy			
Not upset	7.3	3.3	<0.001
Moderately upset	28.9	21.8	
I have no idea how they would react	16.1	15.0	
Reactions to: Father catches you drunk or tipsy			
Not upset	6.2	2.9	<0.001
Moderately upset	30.1	25.6	
I have no idea how they would react	52.5	61.0	
Relationship with father			
Bad relationship	5.8	7.8	<0.001
Moderate relationship	48.4	51.1	
Good relationship	42.5	37.7	
Not applicable	3.3	3.5	
Relationship with mother			
Bad relationship	2.1	2.9	<0.001
Moderate relationship	31.9	36.5	
Good relationship	65.0	59.9	
Not applicable	1.0	0.8	

Table 2. (Continued)

Variables	Gender		P value
Drinking Habits: Father			
Never drink	26.7	23.4	<0.001
Moderate drinker	49.3	47.3	
Heavy drinker	19.9	24.2	
Not applicable	4.1	5.1	
Drinking Habits: Mother			
Never drink	43.4	39.6	<0.001
Moderate drinker	48.2	50.7	
Heavy drinker	5.9	7.4	
Not applicable	2.5	2.2	
How many friends drink alcohol regularly			
None	45.8	56.7	<0.001
One	6.9	6.3	
Some	34.8	30.5	
A lot	12.5	6.5	
Perception: Harmfulness of regular alcohol consumption			
Not harmful	6.5	4.9	<0.001
Moderately harmful	38.1	33.8	
Very harmful	45.6	54.1	
Do not know	9.7	7.2	
Perception: Harmfulness of getting drunk			
Not harmful	5.6	4.3	<0.001
Moderately harmful	29.1	26.9	
Very harmful	55.5	61.1	
Do not know	9.8	7.7	
Ever consumed alcohol			
Yes	68.5	67.5	0.19
No	31.5	32.5	
Consumed alcohol in the last 30 days			
Yes	52.3	47.7	<0.001
No	47.7	52.3	

Table 3. Logistic regression of adolescents' consumption of alcohol with risk factors (adolescent's perception, peers and parental influences)

Variables	OR (95% CI)	P value
Parents knowledge where student is		
No	Reference	
Rarely	0.64 (0.56, 0.72)	<0.001
Yes	0.62 (0.44, 0.86)	0.004
Meal together with parents		
0-2 days	Reference	
3-5 days	0.76 (0.66, 0.88)	<0.001
6-7 days	0.67 (0.61, 0.74)	<0.001
How well parents know close friend		
No knowledge	Reference	
Moderate knowledge	1.01 (0.86, 1.20)	0.858
Extreme knowledge	0.85 (0.72, 1.00)	0.055
Reactions to: Father catches you drunk or tipsy		
Not upset	Reference	
Moderately upset	0.57 (0.40, 0.80)	0.002
I have no idea how they would react	0.45 (0.31, 0.63)	0.000
Reactions to: Mother catches you drunk or tipsy		
Not upset	Reference	
Moderately upset	0.63 (0.43, 0.92)	0.017
I have no idea how they would react	0.53 (0.36, 0.77)	0.001

Variables	OR (95% CI)	P value
Relationship with father		
Bad relationship	Reference	
Moderate relationship	0.69 (0.55, 0.87)	0.001
Good relationship	0.56 (0.44, 0.70)	0.000
Not applicable	0.48 (0.30, 0.76)	0.002
Relationship with mother		
Bad relationship	Reference	
Moderate relationship	0.97(0.69, 1.4)	0.879
Good relationship	0.87 (0.61, 1.2)	0.435
Not applicable	0.85 (0.41, 1.8)	0.669
Drinking Habits: Father		
Never drink	Reference	
Moderate drinker	1.85 (1.64, 2.07)	<0.001
Heavy drinker	2.03 (1.77, 2.34)	<0.001
Not applicable	1.81 (1.33, 2.46)	<0.001
Drinking Habits: Mother		
Never drink	Reference	
Moderate drinker	1.63 (1.47, 1.08)	<0.001
Heavy drinker	1.71 (1.38, 2.13)	<0.001
Not applicable	0.75 (0.53, 1.06)	0.099
Perception: Harmfulness of regular alcohol consumption		
Not harmful	Reference	
Moderately harmful	1.30 (1.01, 1.69)	0.045
Very harmful	0.94 (0.73, 1.20)	0.644
Do not know	0.64 (0.47, 0.88)	0.005
How many friends drink alcohol regularly		
None	Reference	
One	1.905 (1.59, 2.29)	<0.001
Some	2.854 (2.57, 3.17)	<0.001
A lot	3.981 (3.22, 4.93)	<0.001
Perception: Harmfulness of getting drunk		
Not harmful	Reference	
Moderately harmful	1.16 (0.87, 1.54)	0.312
Very harmful	1.08 (0.82, 1.43)	0.588
Do not know	0.68 (0.49, 0.94)	0.021

DISCUSSION

In our study, the intrapersonal and interpersonal levels were assess to discover the possible influences on underage drinking. One of the fundamental aspects that initiates bond formation between the adolescent and parent are shared meals between adolescent and parent. From the analysis, it was observed that adolescents who has an increased number of shared meals with parents of 3 to 5 times and 6 to 7 times weekly showed a significant decrease risk of underage drinking by 24% and 33% respectively, in comparison to adolescents who had 0 to 2 shared meals. This can be related to the benefits of shared meals, which provides an open forum to building communication, monitoring as well as addressing issues that concerns the adolescent [21]. Additional studies have also shown to corroborate our findings, whereby increased number of meals together with the adolescent, decreases the risk of deviant behaviours including underage drinking and drug usage [22, 23].

Parents' reaction of moderate and extreme disdain, when the adolescent arrives home visibly intoxication has resulted as protective factors against underage drinking compared to parents who were showed no indication of disapproval. Our findings revealed that the father's

reaction was even a greater influence in reducing engagement of underage drinking of 55% (95%CI: 0.31, 0.63) when compared to a similar reaction by the mother is 45% (95%CI: 0.31, 0.63). This may be due to the stereotypical association that the father is disciplinarian of the household whereas the mother provides the comfort and assists with the emotional needs of the family [9]. Hence, the father reaction has a greater impact on the adolescent's consumption of alcohol. Other studies have discovered, however that parents with authoritarian tendencies have shown to increase high risk behaviours compared to parents with non – authoritarian attitudes [24].

The parent- adolescent relationship are critical elements during the adolescent's developmental phase which can deter them from a series of negative outcomes [25]. Having a moderate and good relationship, with the father significantly decreased the odds of underage drinking from 0.69 to 0.56 respectively in comparison to the adolescent who has a bad relationship with their father. Studies consistent with finding indicated that adolescents who have had their emotional needs met by their father fosters a father – adolescent connection, which have shown to prolong having to consume alcohol the future [26]. As such, the absence or existence of a good relationship between the father and the adolescent is an indicator in promoting or reducing underage drinking respectively. The mother's relationship showed no statistical significance in reducing underage drinking, thus does not impact adolescent consumption of alcohol.

Drinking habits exhibited by parents are related to underage drinking. In cases whereby the adolescent's father is moderate or heavy drinker have shown to increase the chances of the adolescent consuming alcohol by 85% and 103% respectively, compared to fathers who do not consume alcohol. The mother's drinking habits are also risk factors for underage drinking; with an increased odds of 63% as a moderate and 71% as heavy drinker. The father has a greater influence compared to the mother's influence on underage drinking. Fathers are more so the role models of the household, thus imitation of such behaviour are natural for the adolescent. The social learning theory can corroborate the findings of this study, whereby the learning process was facilitated by observation of the drinking habits exhibited by parents, followed by imitation of those behaviours by the adolescent [27].

The Health Belief Model (HBM) commonly serves as a template when addressing issues of behavioural change at an intrapersonal level. In this study, the construct of the HBM perceived severity was examined. Adolescents who are unaware of the harmfulness of getting drunk have shown a decreased odds (32%) of alcohol consumption when compared with adolescents who do not perceive getting drunk as harmful. On the contrary, when the perceived risk increased to moderate and very harmful there was no statistically significant difference in comparison to the perception of no risk. Invincibility is a key aspect within this developmental stage regardless of the consequences. Furthermore studies have shown that perception of the harmfulness of underage drinking is not sufficient to reduce the consumption of alcohol by minors [28], thus greater efforts should be made by using other constructs of the HBM such as perceived benefits.

There is an increased odds of alcohol consumption among adolescents who had a lot of friends (OR = 3.98; 95%CI: 3.22, 4.93) rather than some friends (OR = 2.84; 95%CI: 2.57, 3.17) when compared to adolescents with no friends. Social support of peers is important factors during adolescence, whilst too can be a burden. The Social Norms Theory can attest to our findings of increase number of friends, who consumes alcohol increases the risk of underage drinking [29].

This study has several limitations. Selection bias was introduced, since persons who attended school on the day of the survey were the included in the sample. Students who were absent may have different characteristics from those who were present. However, the random sampling of schools and form classes, allows for generalization of the wider population. The use of unweighted data of alcohol consumption of underage drinking between countries demonstrated a bias view. Furthermore, there was no controlling for confounders such as gender, socioeconomic status and ethnicity.

In conclusion, from our findings corroborating by similar studies that intra and interpersonal factors play a significant role in delaying the onset of underage drinking. Usage of all constructs of the HBM will provide a holistic approach in understanding and formulating intervention to address underage drinking. Furthermore, whilst both parents' negative attitudes are protective factors against underage drinking, the father's reaction is more of a protective factor compared to the mother based on the stereotypical role of the father figure. Thus, interventions should address the relations between the adolescent and father to delay the onset of underage drinking.

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Chapter 10

HOW MANY DRINKS HAS YOUR ADOLESCENT BEEN OFFERED TODAY?

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ABSTRACT

Traditional and non-traditional forms of alcohol advertisements are meant to entice adult consumers to drink as well as create a pipeline for new and upcoming drinkers, serving to establish brand loyalty through various promotions. While there has been much research of traditional and non-traditional forms of alcohol advertising, there has been little attention on the exposure of the byproducts of alcohol drinking on adolescents. The purpose of this observational study was to quantify the amount of indirect advertising, such as people drinking in public and alcohol posters, Caribbean children and adolescents are exposed to during an average day walking home from school. Two neighborhood routes students use to walk home were identified; one route for elementary school children and a second for high school students. Researchers walked the routes at the time students were dismissed from school on a weekday. The results demonstrate that

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children as young as 6 years old are exposed to many forms of indirect alcohol advertising.

Keywords: alcohol advertisements, adolescent alcohol consumption, public health, Caribbean

INTRODUCTION

Unhealthy alcohol consumption accompanied with abuse of alcohol is a significant problem globally. According to data obtained from the World Health Organization [1] in 2010 the global consumption of alcohol was equivalent to an estimated 6.2 liters of pure alcohol consumed per person aged 15 years or older; this is about 13.5 grams of pure alcohol daily. Despite the rise in the daily consumption of alcohol globally, there has been an alarming increase in underage drinking. In 2013, the National Institute on Alcohol Abuse and Alcoholism (NIAA) reported that 35.1% of 15 year olds have consumed at least one drink in their lives. In addition, approximately 8.7 million people within the ages 12-20 years indicated drinking alcohol in the past month. Of these current drinkers, 16% were heavy drinkers [2].

According to a 2008 WHO-initiated Global School-based Student Health Survey conducted in Grenada, approximately 45.6% of secondary school students reported having at least one drink in the previous 30 days and about 27.3% reported having been intoxicated at one point in their life. According to a study conducted by Shayota [3], who investigated the prevalence of alcohol use among 1542 secondary school students aged 11-16 years, it was discovered that the overall prevalence of alcohol use was highest among males; however, there was a growing rise in females consuming alcohols. An estimated 31.6% of males versus 29.4% of females in the age 11-12 cohort group were currently consuming alcohol. An increase to 44% amongst males in the 13-14 age group versus 37.9% for the females. Lastly, the highest prevalence was in the 15-16 age group, with 67.2% of males and 54% of females currently consuming alcohol [8]. Updated data from a 2013 Global School-based Student Health Survey indicated that around 70% of students had reported having a drink in their lifetime and 28.5% of students of the ages 12-13 had their first drink of alcohol compared to 22.8% at 10-11 years and 22.9% at 14-15 years.

The promotion of alcohol and targeted advertisement is universal as it exist in almost all countries with the exception of some of the countries with predominantly Muslim populations and where strong regulation limits focusing on adolescents and young adults [4]. Such case scenarios occur particularly among the public advertisement of alcohol across the Caribbean, where many island nation's economies and the promotion of tourism aggressively promote rum, beer and other exotic alcohol beverages. The production and promotion of alcohol are entrenched into the Caribbean's history and transcends into many cultural experiences. Thus, there is an ever presence and ease of availability of alcohol, and alcohol promotions may serve as encouragement for alcohol consumption in some individuals, such as adolescents and young adults. Within such contexts, factors such as parents and peers, are believed to influence alcohol consumption [5]. Other influential factors are alcoholic advertisements on television, which are disguised with appealing settings and memorable messages that may remain with the viewer. Other than television messages, alcohol advertising is observed

through products, special promotions, sponsorships of musical, educational and sporting events, hats, clothing, and other merchandising products. The convenience of having sale promotions such as 3 for \$10 dollar beers and “two for one” discount events at local bars, serve as advertisements to increase consumption [6]. The convergence of these issues in the Caribbean was the basis for this study, which explores the role of advertising as it relates to alcohol exposure among elementary and high school students (6-18 years) in a Caribbean island, Grenada.

Studies conducted have supported the theories that there is a lack of social control and education on the harms associated with alcohol consumption because it is highly integrated into the culture and, as such, traverses age and generation. Longitudinal studies have been conducted to support the theory that exposure to alcohol advertising results in a strong belief about drinking and is positively associated with increased adolescents and early adulthood alcohol consumption [7].

While alcohol consumption is a key component of cultures around the world, in the Caribbean, specifically Grenada, 31%-59% of children consume alcohol for the first time by the time they are eleven and half years of age. By age fourteen, 75%-86.5% of children report they have consumed at least one drink of alcohol [8, 9]. Adolescent brains are more vulnerable to the effects of alcohol compared the brain of an adult [10]. Research suggests that consumption of alcohol from age 11-14 years increases a child’s risk of developing dependent behaviors [10] and suffering from the cognitive effects of neurodevelopmental damages [11]. Natures versus nurture theories are instructive in this regard. Appreciably, while genetic components of human beings determine many factors of development, influences of environmental exposures cannot be ignored.

The impact of alcohol advertisements on the age of initial alcohol consumption is debatable. The intent of alcohol advertisements may be to promote brand choice and not alcohol consumption; however, the high frequency of alcohol advertisement in the environment inevitably influences the drinking choices of children [11] and possibly the regularity with which they drink. The goal of this study was to raise awareness of a child’s potential exposure to alcohol advertisements and alcohol consumption. The purpose of this study was to examine the exposure of school-aged children (in elementary and high schools) in Grenada to advertisements promoting the use of alcohol on a typical school day. To accomplish this, three objectives of this study were to observe and document the number of alcohol advertisements (posters, signs, umbrellas, bottles, bottle tops), stores selling alcoholic beverages, and individuals drinking alcohol.

The Law that overlooks alcohol consumption in Grenada is the Liquor Dealer License Act Chap 174. Within this legislation, there are rules on distribution, sale hours, limitation of drunkenness, but the legislation lacks in certain areas that should be addressed. There are not any regulations set in place that address advertising of alcoholic products, sponsorships and promotions. Also, there is a lack of regulation of health warning labels on alcoholic advertisements and bottles and containers that are produced within Grenada. Assessment of current legislation shows that the amount of support towards limiting the exposure and availability of alcoholic beverages is restricted and inadequate. Added to that, the sale of alcohol to minors remains, by and large, unregulated. As such, children and adolescents are frequently sent by adults to purchase alcohol. Granted that alcohol is a sustainable source of income, given the rate of consumption, proprietors are not inclined to turn away anyone from purchasing alcohol.

BACKGROUND

In the Caribbean region, there are a variety of factors that encourage people to heavily consume alcohol thus further exacerbating the problem of excessive alcohol consumption. Generally, alcohol is utilized to alleviate the societal pressures and physical stresses of working under the characteristic hot and humid Caribbean climate and provides a means of psychological escape [12]. In addition to this, alcohol is widely used in the region as a popular beverage in social occasions. This is exacerbated by the culture of 'fete' that is inherently Caribbean. Another factor influencing heavy alcohol consumption in the region is the cultural norm of consuming alcohol after work aside from being limited to social functions. The region's past also seems to fuel this issue because historically speaking the Caribbean islands are deemed as a place where people take vacations and participate in heavy drinking to alleviate the daily stresses of life. It is important to note that according to research carried out by Legion, Gregorowicz, and Jolly [13], it was established that a rise in income substantially increases the amount of alcohol consumed and the consumers have a tendency to upgrade from the local illicit brews towards heavily consuming the more refined drinks. Furthermore, most Caribbean nations were once European plantation colonies that produced sugarcane, molasses and rum as export products throughout the world [12].

Alcohol advertising is a very effective method of targeting current and future consumers on the availability of alcohol and alcohol related products. Alcohol advertising is responsible for initiating drinking among adolescents commencing at a young age and enhancing the transition from experimental drinking to hazardous drinking [14]. Given the problem of underage drinking, there are a multitude of factors, which contribute to this problem. These problems include access to cheap alcohol, access to alcohol from parents, long periods of unsupervised time, access to money to spend, early introduction to alcohol, alcohol advertising, poor educational achievement and truancy, exposure to adult binge drinking and alcoholism, a culture where drinking is the norm and is encouraged, peers who indulge in alcohol and bullying [16]. Taite, found that young adults (15-23 years old) had a high recall of advertisements on television for top beer and distilled brands. This recall was a factor found to predict drinking outcomes [14].

Chai and Politi [15] noted a gender difference in the messages received by alcohol advertisements. Young girls tend to absorb message more quickly and are more prone to influences because of the social and emotional effect of the ads. Most of these advertisements present messages of increasing attention from men, obtaining a successful life and appearing more attractive towards people of the opposite and same sex if one consumes alcohol. Thus, making young girls more susceptible to consuming alcohol from an early age [15] if one consumes alcohol.

Most of the literature provided state there is a link between alcohol advertising and early and increased drinking among youths. Despite the numerous supports to this claim, there are some studies, which refute this. However, despite the lack of conclusive evidence of alcohol consumption being influenced by alcohol advertising, there are studies, which show that adolescents are very vulnerable to the effects of advertising [17]. Adolescents who have higher exposures to alcohol advertising have a higher probability of developing positive attitudes and beliefs about alcohol. Also, the exposure to alcohol advertising results in

increasing the likelihood of early initiation of adolescent alcohol use and a rise in the amount of alcohol consumed [18].

METHODS

This observational study examined the frequency of alcohol exposure through direct and indirect advertising among elementary and high school students, separately. One elementary school and one high school were purposefully selected based on the major routes the students used to travel to and from school. Students were observed as they exited the school on the main roads and made their way home. Elementary school students observation stopped at the point the route traveled was not the main road. The route observed was approximately half a mile in distance. High school students were observed on their route from school to the main bus station, where students take separate buses to their home. The high school selected was in walking distance, approximately half a mile in distance, to downtown St. George. Many high school students travel the public bus system to their villages within and outside St. George. Because the high school system is one where you select the high school, students can travel from all parts of Grenada to attend high school in Grenada.

To quantify the frequency of advertisements to which elementary and high school students are exposed, an observation list was developed. The observation list included: alcohol advertisements, including signs, umbrellas, and posters; individuals drinking in public spaces, which included open-air bars; stores and stands selling alcohol; and other, to capture any unexpected forms of advertisements.

Two groups of observers collected data. One group observed the elementary route on a Wednesday and the second group observed the high school students on a Friday. Both groups collected data at the time students were walking home, which was 3:00 pm for the elementary students and 2:00 pm for the high school students. The results of the observation lists were compared to determine the degree of agreement. In the case of a disagreement, the observers discussed the form of advertisement and came to a consensus in its resolution.

RESULTS

Overall, both elementary and high school students are exposed to various forms of alcohol advertisements while they walk from school to their homes or in the cases of those travelling to the bus station. Table 1 presents the frequency of advertisements to which the students are exposed. All students were exposed to signs, umbrellas, public drinking and bottle caps. What was unexpected was both groups noted the extremely high number of labeled bottle caps on the ground of the routes traveled. With respect to the agreement of observers, the number of bottle caps was an issue, because not all observers had the same number of observed bottle caps, Table 1 presents the lowest number of bottle caps recorded. This is also true for the number of people who were consuming alcohol in public.

Table 1. Summary of checklist: Frequency of alcohol advertisements

	High school students	Elementary school students
Signs	11	6
Umbrellas	3	2
Public drinking	33	11
Vendors	12	10
Bottle caps	70+	35+
Brewery	0	1

Elementary Student Route Observations

From the checklist, it is evident that elementary school students are exposed to alcohol advertising. On this route, children passed a brewery, large billboard and bars that have open windows. In addition, the restaurants, provision stores, and open kiosks had alcohol visible at the eye level on the shelves. Additionally, none of the billboards advertising alcohol had any messages emphasizing the practice of healthy alcohol consumption behaviors’ such as not driving or operating machinery under the influence of alcohol. Moreover, they neither contained messages emphasizing the use of alcohol from the legal age of 18 years nor the negative effects associated with unhealthy alcohol consumption. There were absolutely no messages present to educate the consumers and raise awareness. Also, in the residential areas, there were small posters, stapled to power poles, along the routes used by the children advertising party functions with drinks offered and special discounts to purchase multiple drinks during one transaction. In addition to this, there were playing fields, where residents commune during the evening hours to hold party functions and play sports. This is another notable means of directly exposing children to alcohol and which contributes to indulgement at an early age. It is vital to point out that the public buses the elementary students utilized to travel home play loud Soca music, which contain messages of consuming alcohol. While walking on the route, the observers noticed a large number of bottles and bottle caps in the street. Also observed were children picking up the bottle caps and playing with them.

High School Student Route Observations

Along the high school student route were many stores, an outdoor produce market and kiosks serving alcohol, a shopping mall where cruise ships dock and which has stores that sell alcohol as well as alcohol paraphernalia. This is an area where high school students congregate to socialize and to wait on parents and guardians. Inevitably, these students would browse around the stores and, as a result, be exposed to alcohol advertisement. On Friday, there were many activities as it is the start of the weekend and adults drink more. Across the street from the mall entrance is a wall of advertisements, a bar and a library. It is interesting to note that to get to the children’s library one had to walk through the bar. The end point of the route is the bus station, which is the final point before continuing their journey home on the public bus. The bus station is a large structure similar to a 2-story parking structure that is open on all sides. In the bus station, there are kiosks where alcohol and snacks are sold. In addition, the bus station is where many alcohol advertisements are placed. Advertisements are

in the form of posters, signs and scattered bottle caps. The bus station also has men who are drinking in front of the bus station and inside the bus station.

DISCUSSION

This study provides evidence that elementary and high school students are exposed to alcohol outside the home from an early age. As alcohol is part of the culture, these indirect and by-products of direct marketing serve as messages that alcohol is readily available and accessible. As such, they also serve to strengthen the culture of alcohol consumption; having a potentially significant impact on underage drinking. Notably, alcohol is ingrained in the culture of Grenada. Similar to many other areas where alcohol is embedded in the culture, exposure to alcohol is a part of life from cradle to grave. A high frequency of alcohol advertisements on secondary children's route to and from school is therefore not surprising. On the Friday observed, the most alcohol advertisements were documented at the main bus station in St. George. Although the bus station is a public place, it is important to point out that the audience at the bus station at certain times each week day is primarily youths. Therefore, students may travel from areas of low-density alcohol advertising to areas of high density; where there is the constant bombardment of alcoholic advertising. This sort of constant enticement coupled with the pervasive alcohol culture creates a serious public health concern. Because there is no "school bus" and students use the public buses for transportation, the St George bus station is the school bus pick up and drop off for hundreds of Grenadian children attending school in St. George. Alcohol drinks can be purchased in the terminal and at nearby bars and street vendors.

A broad conclusion is that unconsciously or consciously children are exposed to a variety of alcohol advertisements on their walk to and from school. We venture that these promotions can and do impact their attitudes to and consumption of alcohol.

Alcohol advertisements can seep into a Grenadian child's life frequently to and from school will be as they are exposed to multiple alcohol advertisements, individuals drinking alcohol, and stores and kiosk stands selling alcohol on the student's walking route home.

The constant and consistent existence of alcohol promotion and purchasing opportunities makes it extremely difficult to create counter public health arguments and messages to discourage the consumption of alcohol, especially among young people. First, many points of purchase rely on alcohol sales to make a profit and support their livelihood of their families. Second, there are multiple points at which individuals can access alcohol, making it impossible to limit it to locations where school children are less likely to frequently visit. Third, the price of alcohol is very cheap; at times as cheap as purchasing bottle water. Fourth, the rum distilleries and beer breweries financially support many social events frequented by students, inclusive of sporting and educational events. Finally, these companies also advertise during prime time on television. A notable example is during the news broadcasts advertising alcohol. As a professional practice, teachers encourage their students to listen to and report on current issues; the news broadcasts being important sources of information. Consequently, students, during what was aimed at educational objectives, would be exposed to alcohol promotions. These factors are hurdles that must be overcome to limit young adult consumption.

Exposure to alcohol advertisements has negative implications on adolescents' preferences for alcohol and subtly encourages consumption [7]. Various alcoholic bottle caps are left in public spaces in Grenada and collected by children. These artifacts have the potential to incite interest in alcohol and to encourage consumption. In a resource-limited country where alcohol is tied to the economy and culture, it is a challenge to initiate policies and programs that reduce the prevalence of elementary and high school students drinking. It is better to have a weak policy, which is consistent with the cultural values and minimally impacts the revenue of established vendors that is enforceable than a strong policy that is an unenforceable one. Any attempts at programs and policies should therefore preferably be proactive, focusing on delaying the age of initiation of first drink rather than reactive, reducing the prevalence of youth drinking.

In developed countries tackling youth indulging in alcohol, the formulation and enforcement of policies governing the price of alcohol, location, density, operating hours of sale outlets alongside regulation of the alcohol market will have a greater impact than the simple ban of alcohol advertisements. In addition, enforcing harsh penalties and strict licensure requirements will assist in discouraging youth in engaging in hazardous drinking [17]. In a developing country where alcohol is connected with the economy, it is better to formulate policies and programs that are consistent with the values and culture, and do not impact the revenue that is generated from the local business owners.

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Chapter 11

ALCOHOL AND AVIATION: AN ASSESSMENT OF AERONAUTICAL DECISION MAKING AMONG CARIBBEAN PILOTS

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ABSTRACT

Over the past 25 years, the aviation industry has been motivated by the need to reduce accidents of which 95% is attributed to human error. This study assessed Caribbean pilots on their Aeronautical Decision Making (ADM) knowledge and skills and evaluated their ability to identify risk factors and make appropriate decisions with exposure to alcohol consumption. Design and methods: Cross sectional study utilizing an electronic survey to members of the Trinidad and Tobago Airline Pilots Association (TTAPA) that attended the 2015 annual general meeting. The survey collected data on pilots' career background, ADM knowledge, risk assessments and decision process in aviation case scenarios. Results: 110 pilots participated in the study among which were 103 (94%) males, with an average age of 47 years (range 24 – 59 years). 47 pilots were locally trained while 63 were foreign trained with all having received ADM training and continued training. Average number of logged flight time was 9,347 Hobbs (range 541 – 23,441) and routes flown were mainly the Caribbean and the Eastern coast of North America. Effects of alcohol of takeoff and climb and landing was identified by 23.4% and 24.1% of pilots as the most incident prone and ADM dependent phases of flight. 94% of pilots accurately identified alcohol consumption as contributing to anti-authority, impulsivity, invulnerability, macho and resignation as hazardous attitudes. Further operational pitfalls associated alcohol consumption with peer pressure (80%), mind set

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(74%), get-there-it is (51%), duck-under-syndrome (21%), continuing visual flight rules into instrument conditions (14%) and checklist neglect (7%). Conclusions: Alcohol consumption was assessed to be a risk factor that affects ADM as a critical skill set for pilots to protect the safety and lives of passengers than use air travel as a means of transportation.

Keywords: aviation safety, aeronautical decision making, alcohol in flight, Caribbean pilots airmanship

INTRODUCTION

The International Air Transportation Association (IATA) projected that two billion passengers will use air transportation to fly by the year 2024 [1]. Furthermore, IATA recognized there are over 104,100 pilots and 650,000 flight crew currently servicing the expanding aviation industry. Additionally, the potential risk to ground communities and infrastructure positions aviation as a significant global population based experience and potential for significant adverse public health consequences [2]. The risk potential that aviation poses has allowed for the establishment of a safety management system for aviation, which is primarily dependent on the health and safety of pilots [3]. Aeronautical Decision Making (ADM) is decision making in the unique environment of aviation, which comprises a mental process that pilots use to consistently determine the best course of action in response to a given set of circumstances [4].

Alcohol consumption is associated with various cultural and social practices such as celebrations and mourning traditions [5]. Alcohol beverages are used by many to “unwind” or relax, or act as a social “icebreaker” as it alters one’s mood by decreasing inhibition [6]. Alcohol consumption is widely accepted and has its genesis as a “rite of passage” into adulthood [7]. While alcohol consumption is an accepted social activity, piloting an aircraft is a highly demanding cognitive and psychomotor task, which takes place in an inhospitable environment of airline, passenger, maintenance and weather stress. Alcohol consumption is considered a sedative, hypnotic and addictive drug, which is rapidly absorbed from the stomach and intestines and transported by the blood throughout the body [8]. The effects of alcohol vary considerably from person to person and are influenced by variables of gender, body weight, rate of consumption (time) and total amount consumed (volume) [9]. Further, the rate of alcohol elimination from the body is fairly constant regardless of the amount consumed, which allows for effects to be sustained from 48 to 72 hours after consumption [10]. The majority of the adverse effects produced by alcohol consumption relate to the brain, eyes and inner ear, which are three crucial organs to pilots [11]. Brain effects include reduced reaction time, reasoning, judgment and memory as alcohol reduces the ability to utilize oxygen [12]. Specifically for pilots, the effects of alcohol on the brain are magnified with simultaneous exposure to altitude characterized by decrease partial pressure of oxygen. Visual impairments include eye muscle imbalance which leads to double vision and difficulty focusing and inner ear effects include dizziness and decreased hearing perception [13]. Pilots may also be exposed to conditions of sleep deprivation, fatigue, medication use, hypoxia, night flying or severe weather that can further magnify the negative effects of alcohol [14].

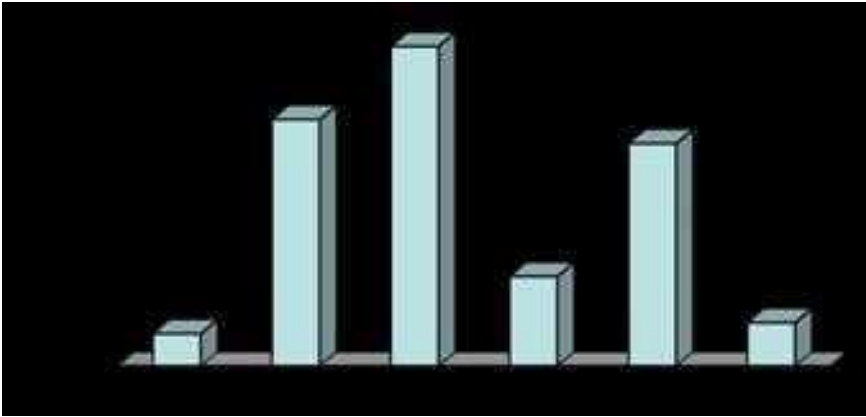


Figure 1. Effects of alcohol consumption on various stages of flight.

Studies on how alcohol affects pilots' performance have shown impairment in their ability to fly an Instrument Landing System (ILS) approach, fly Instrument Flight Rules (IFR) or even perform routine Visual Flight Rules (VFR) flight tasks [15]. The number of serious errors committed by pilots is shown to be dramatically increased at or above concentrations of 0.04% blood alcohol [16]. General aviation pilot fatalities reported by the Forensic Toxicology Research Section of the Federal Aviation Authority (FAA) Civil Aerospace Medical Institute identified Blood Alcohol Concentration (BAC) levels of 0.04% or more among an average of 8.9% of pilots [17]. The information based on analysis of blood and tissue samples from pilots involved in fatal aviation incidents demonstrates the need to attend to alcohol consumption in the aviation industry. The use of alcohol is regulated by civil aviation authorities around the world. The Federal Aviation Regulation (FAR) 91.17 is used to regulate the alcohol and drug use among pilots [18]. FAR 91.17 states that no person should operate or attempt to operate an aircraft within 8 hours of having consumed alcohol, while under the influence of alcohol, with a BAC of 0.04% or greater or while using any drug that adversely affects safety [19].

This study examined the ADM knowledge and skills based on an assessment of exposure to alcohol consumption among pilots. The objective was to understand the level of awareness of the potential risk to pilots, identify the main risks that require ADM among pilot as well as promote for effective alcohol regulation and health and safety for the Caribbean aviation community.

METHODS

The study population consisted of pilots who serve as active members of the Trinidad and Tobago Airline Pilots Association (TTAPA). Pilots that attended the 2015 Annual General Meeting (AGM) were invited to participate in the study. The study comprised of an electronic survey compartmentalized into five sections including the following:

Section 1: Background

Age, gender, location of training, whether ADM was years as a pilot, number of logged hours, routes flown, aircraft(s) flown.

Section 2: ADM Knowledge

- Identify the various phases of flight and what are the accidents associated with each phase.
- What are the five hazardous attitudes of pilots?
- Categorize the steps for good decision making.

Section 3: Risk Assessment

- What are the likelihood categories of risk in aviation?
- What are the levels of risk severity for aircrafts and passengers?
- What are the elements of risk mitigation in aviation?

Section 4: Case Scenario

Describe the process used and decisions made in each of the following scenarios:

1. A commercial jet pilot had only four hours of sleep the night before and was asked by the manager to fly to a meeting in a city 750 miles away. The reported weather was marginal and not expected to improve.
2. A pilot landing a small airplane just after a heavy cargo jet had departed a parallel runway. The pilot assumed that wake turbulence would not be a problem since landings had been performed using similar circumstances. Due to a combination of prevailing winds and wake turbulence from the heavy jet drifting across the landing runway, the airplane made a hard landing.
3. During a preflight, a pilot noticed a small amount of oil dripping from the bottom of the cowling. Although the quantity of oil was insignificant at the time, the pilot delayed a commercial jet liner to have a mechanic check the source of the oil.
4. On a cross Atlantic flight in marginal weather conditions, a pilot calculated the groundspeed and determined that the airplane would arrive at the destination with only 25 minutes of fuel remaining. The pilot was determined to keep on schedule by trying to mix the fuel supply instead of diverting to land for refueling. The flight landed on time with a low fuel state.

Section 5: Alcohol Consumption

- Do you consume alcohol?
- Is alcohol consumption done within 8 hours of flight time?
- What are the alcoholic beverages consumed within 8 hours of flight time?

Pilots who agreed to participate completed the survey at a computer terminal where responses were submitted and received in an electronic dataset that was analysed and reported.

RESULTS

110 pilots participated in the study of which 103 (94%) were males with an average age of 47 years (range 24 – 59). 47 (43%) of pilots were locally trained while 63 (57%) were foreign trained with 100% of pilots having received ADM training on the regulations and risks associated with alcohol consumption. The average number of logged flight time was 9,347 Hobbs (range 541 – 23,441) in routes flown across the Caribbean and the Eastern coast of North America. There were also 16 (15%) of pilots who reported incidents that were not fatal but was ADM related and occurred during their aviation careers.

Alcohol consumption was associated with effects on airmanship across different phases of flight including takeoff/climb, cruise and landing (Figure 1) as well as ADM operational pitfalls such as peer pressure, mindset and “get there it is” in commercial flying (see Figure 2).

All pilots responded to the case studies where ADM knowing and application was required to provide an accurate decision. The responses and pilot’s performance were rank as either adequate or not based on the required course of action for each case study. Pilots were assessed as adequate on the case studies ranging from 88% accurate in Case 2 to 100% accurate for Case 4 when compared to the standard ADM operational procedures expected. Figure 3 represents the performance of the pilots for each case.

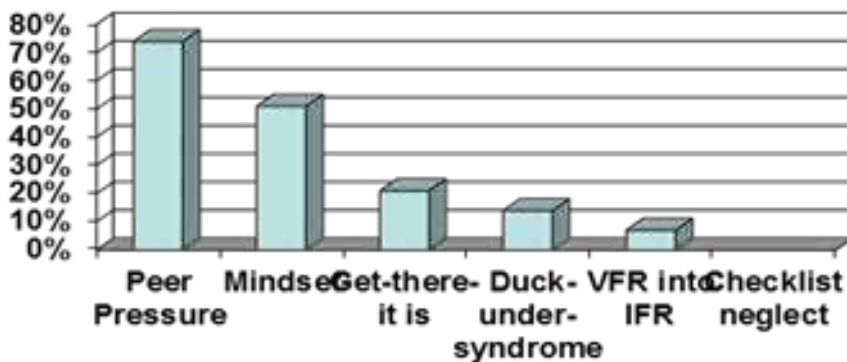


Figure 2. Effects of alcohol consumption on ADM.

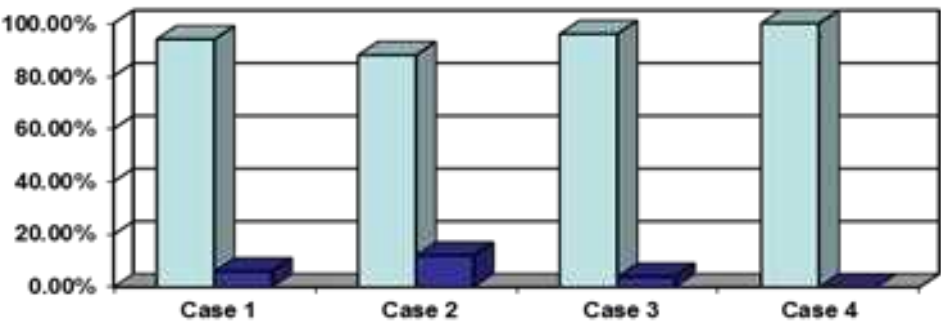


Figure 3. Performances in case study assessments.

Alcohol consumption was also assessed among pilots and was differentiated into flight time and non-flight time exposures. 84% of pilots reported alcohol consumption during non-flight time while 34% of pilots indicated consumption was within the 8 hours of flight time. Table 1 represents the alcohol consumption characteristics of the surveyed pilots.

The frequency of alcohol consumption among pilots who consumed alcohol within 8 hours of flight time was further evaluated. 76% of pilots who consume alcohol within 8 hours of flight time consumed 1 drink while 3% reported more than three drinks. The distribution is represented in Figure 4.

The assessment of alcohol consumption also surveyed the type of alcohol beverages consumed by pilots and ranged from whiskey, rum, vodka, beer, wines and cocktails. The frequency distribution of types of alcohol beverages consumed is reported in Figure 5.

Table 1. Alcohol consumption among pilots

	No of Pilots (%)
Alcohol consumption	92 (84%)
Alcohol consumption with 8 hours of flight time	37 (34%)
Alcohol consumption among male pilots	92 (89%)
Alcohol consumption among female pilots	0
Alcohol consumption among local trained pilots	37 (100%)
Alcohol consumption among foreign trained pilots	0
Alcohol consumption and its impairment of ADM	0

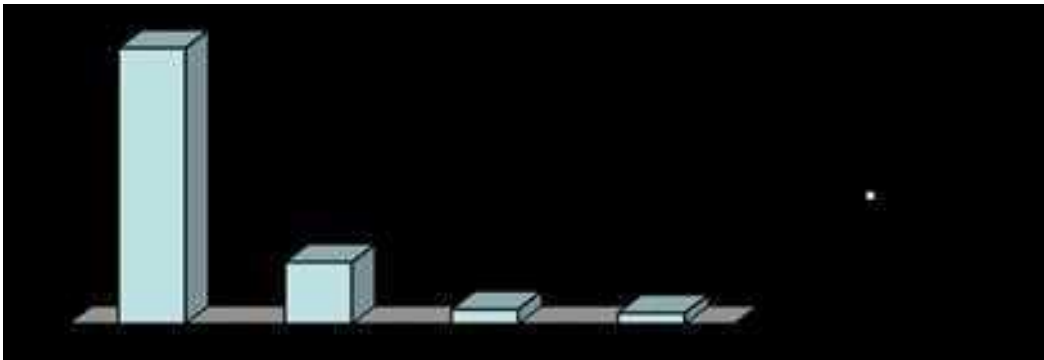


Figure 4. Number of alcohol drinks consumed within 8 hours of flight time.

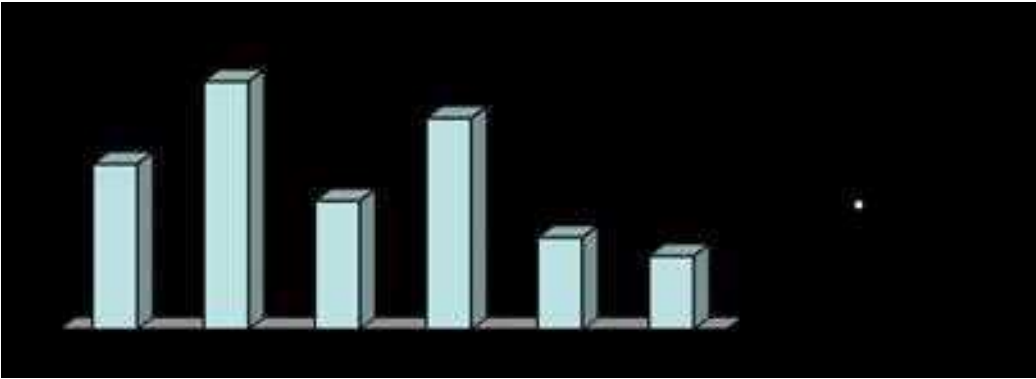


Figure 5. Distribution of alcohol beverage type consumed.

DISCUSSION

The majority of pilots surveyed were males that were significant they reported risk behavior of alcohol consumption within eight hours of flight time as opposed to their female counterparts. Locally trained pilots were also reported to be the ones that consume alcohol within 8 hours of flight time. The risky behavior of alcohol consumption within 8 hours of flight time was associated with locally trained male pilots. This risk profile is important towards identifying intervention strategies towards reducing at risk alcohol consumption among pilots. Additionally, 16 pilots, all male and locally trained reported having been part of incidents that was assessed as a compromise of ADM standards and operational procedures. Furthermore, all 16 pilots with previous incidents reported as having consumed alcohol within 8 hours of flight time. Alcohol consumption maybe associated with pilots with a history of aviation incidents.

ADM standards and operational procedures were well established and assessed as adequate among participating pilots with accurate decisions submitted based on aeronautical challenges presented. ADM and adverse consequences as a result of alcohol consumption was identified for the takeoff, cruise and landing phases of flight. The pilots in identifying the challenging phases also noted the most cognitive and psychomotor active phases of flight, which may be compromised with exposure to alcohol consumption. Peer pressure was the most reported consequence of alcohol as pilots identified as alcohol consumed seem to be familiar with each other and served as a pressure to continue to engage in the behavior among each other. Alcohol was also referred to as influential to the mindset of pilots, which would serve to influence their ADM skills set.

The surveyed pilots while representing an estimated 25% of pilots as part of the Trinidad and Tobago Airline Pilots Association (TTAPA) should be considered as representative of the alcohol consumption behaviors of pilots. Guidelines from the Trinidad and Tobago Civil Aviation Authority (TTCAA) and respective airline operators must provide assurance that pilots are maintaining the FAR 91.17, which is critical to the safety of the air travel passengers and the Caribbean aviation industry.

CONCLUSION

The risk profile for alcohol consumption among pilots in the Caribbean are locally trained males who are more likely to have a history of an aviation incident. ADM standards and operational procedures were however well established and practiced. Education and attention to regulations should be strengthened to maintain the occupational health of pilots and the safety of their passengers and communities that may be affected.

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Chapter 12

**ASSESSMENT OF HEALTH-COMPROMISING
BEHAVIOR PREVALENCE AND CLUSTERING AMONG
GRENADIAN ADOLESCENTS: FINDINGS FROM THE
2008 GLOBAL SCHOOL-BASED STUDENT
HEALTH SURVEY**

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ABSTRACT

Involvement in health-compromising behaviors amongst adolescents has serious, adverse implications for the individual, community and the public health system. While several studies have assessed the prevalence and clustering of health-compromising behaviors among youth, to the best of our knowledge, no such investigations have examined this issue within the Caribbean island nation of Grenada. As such, our aim was to assess health-compromising behavior (tobacco, alcohol, and drug use, gang involvement, and sexual activity) prevalence and clustering among Grenadian adolescents based on data obtained from the 2008 Global School-based Student Survey on Health. Alcohol consumption was the most commonly cited health-compromising behavior (62.4%), followed by sexual intercourse (25.1%) cigarette smoking (22.5%), drug use (15.7%), and gang involvement (13.5%) amongst all participants surveyed. Statistically significant relationships were evident between nearly all pairs of health-compromising behaviors for both males and females; we thereby conclude that behavior clustering was evident amongst Grenadian youth.

Keywords: Caribbean, alcohol, cigarettes, sex, gang, drugs

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INTRODUCTION

Involvement in health compromising behaviors including, though not limited to, cigarette smoking, alcohol and illicit drug use, sexual activity and gang involvement are not confined to particular adolescences in any one geographical region but are rather a global public health concern [1-10]. Interestingly, the clustering of these behaviors, defined as involvement in multiple concurrent activities, has become increasingly evident.

It is widely accepted that adolescence is a challenging transitional period in one's life. Imperative is that many behaviors established during these formative years persist through adulthood. Adolescent morbidity and mortality are most frequently the result of preventable behavioral, environmental and social factors, as opposed to pathologic disease [11, 12]. The adverse effects of these health-compromising behaviors should not be underestimated [10, 13].

While several studies have been carried out to assess the clustering of health compromising behaviors within the United States [14-19], only one such study was identified, which evaluated these factors within the Caribbean region at large [16]. As such, this paucity of data has rendered gaps in our knowledge and understanding of health-compromising behavior among Caribbean youth.

The aim of this study, therefore, was to assess health-compromising behaviors (tobacco, alcohol, and marijuana use, violence, gang involvement, sexual activity) among Grenadian youth. To achieve this aim we evaluated the prevalence and clustering of health-compromising behaviors among Grenadian secondary school aged students from data obtained from the 2008 Global School Based Student Survey on Health. Also examined were the role of drug use and sexual intercourse involvement as precipitating factors to engagement in additional health-risk behaviors.

Assessment of health compromising behavior prevalence and clustering within specified populations is essential for the establishment of health promotion programming [9] and overall improved health status of a nation. We anticipate that these findings will advance the current understanding of health-risk behavior trends and adolescent behavioral development among Grenadian adolescents. Moreover, we suspect that these findings will subsequently guide public health prevention and intervention programs of the future.

METHODS

The current investigation involved a secondary analysis of data obtained from the 2008 Global School Based Student Health Survey, which was administered to students' aged 11-16 attending Grenadian secondary schools. The GSHS was developed by the World Health Organization (WHO) in collaboration with the United Nations Educational, Scientific and Cultural Organization (UNESCO), the United Nations Children's Fund, and the Joint United Nations Program on HIV/AIDS with technical support provided by the Centers for Disease Control and Prevention (CDC). This collaborative surveillance project was designed and implemented to support the ongoing collection and assessment of behavioral risk and protective factors in 10 fundamental areas, across all countries served by the United Nations in order to develop priorities, establish programs, and advocate for resource allocation [20].

Country-specific data, including questionnaires and fact sheets, are made publically available from the WHO and CDC and have been cited elsewhere in peer-reviewed literature [21-24].

The GSHS utilized a standardized scientific sample selections processes and a common school-based methodology whereby a 2-stage cluster sample design was employed to produce data representative of all students in Grenada. During the first stage, schools were chosen with probability proportional to enrollment size. During the second stage, individual classes were randomly selected with all students enrolled in the class being eligible to participate. Core questionnaire modules, and a combination of core- expanded and country-specific questions were administered on a computer scannable answer sheet in Forms 1, 2, 3 and 4, during a single regular class period. The 85-question, self-administered survey, conducted on 1,542 Grenadian students, ages 11-16, yielded a 95% school response rate, 82% student response rate and 78% overall response rate [20].

Measures

The following five health-compromising behaviors were included in analysis: sexual intercourse activity, cigarette smoking, alcohol consumption, drug use and gang involvement. The questions used to assess these five health-compromising behaviors are described in Table 1. Indicating yes to gang involvement or sexual intercourse was taken as indication of behavior engagement. Endorsing use of cigarettes or alcohol consumption one or more times in the past 30 days or drug use within the course of one’s life was accepted as indication of use and therefore behavior involvement.

Data Analysis

The prevalence of each health compromising behavior was calculated, stratified by gender and age category: ≤ 11 , 12-13, 14-15, ≥ 16 years. To assess the relationship between health-compromising behaviors, amongst girls and boys, odds ratios were calculated. To address the hypotheses that drug use and engagement in sexual intercourse are associated with initiation of additional health-compromising behaviors, relative risks were calculated. Confidence intervals were calculated for both the odds ratios and relative risks. All analyses recognized a p-value < 0.05 as statistically significant. All outputs were generated via SPSS version 19.

Table 1. Survey questions measuring health-compromising behavior

Sexual Intercourse Activity	Have you ever had sexual intercourse?
Gang Involvement	Do you currently belong to a gang or violent group?
Cigarette Smoking	During the past 30 days, on how many days did you smoke cigarettes?
Alcohol Consumption	During the past 30 days, on how many days did you have at least one drink containing alcohol?
Drug Use	During your life, how many times have you used drugs, such as marijuana?

RESULTS

The study population under investigation included 1,542 students attending Grenadian secondary schools. A total of 1,521 students were included in this analysis as they met inclusion criteria for selection by responding to the specified survey questions under investigation (including but not limited to age and gender classification). Thus, a total of 681 male and 840 female students participating in the 2008 GSHS were included and ranged in age from 11-16 years.

Males were determined to have a higher prevalence of involvement among all five health-compromising behaviors across all 4-age categories, as compared with their female counterparts, with exception to alcohol consumption and drug use, which were reportedly higher among girls age 11 and younger, as described in Table 2. Alcohol consumption was the most commonly cited health-compromising behavior (62.4%) with 60.4% of those involved reporting their first drink at or before age 11. Sexual intercourse activity involvement proceeded in order of prevalence (25.1%) with 44.5% of students reporting their first experience at or before age 11 years. In descending order of prevalence were: cigarette smoking (22.5%), drug use (15.7%), and gang involvement (13.5%) amongst all participants surveyed. Involvement in four of the five health risk behaviors, including cigarette smoking, alcohol consumption, sexual intercourse and gang involvement were found to increase with age for both female and male students, ages 12 and older.

Additionally, odds ratios were calculated to describe the relationships between pairs of health-compromising behaviors as stratified by gender. The strongest relationship appreciated, for both females and males, was between drug use and cigarette smoking (OR = 6.37, 95% CI, 3.73, 10.89, OR = 7.90, 95% CI, 5.21, 12.0). The weakest relationships observed were between gang involvement and alcohol consumption (OR= 1.47, 95% CI, 0.873, 2.47) and between gang involvement and sexual activity (OR = 2.16, 95% CI, 1.40, 3.32) for females and males respectively. All odds ratios were statistically significant with exception of the relationship between gang involvement and alcohol consumption amongst female students (see Table 3 and 4).

Table 2. Prevalence of female and male involvement in health-compromising behaviors by age group

Prevalence of Involvement [n, (%)]								
Age	≤ 11		12-13		14-15		16 ≥	
Variable	Female	Male	Female	Male	Female	Male	Female	Male
Cigarette Smoking	0 (0.0)	2 (100.0)	40 (11.9)	43 (23.6)	78 (22.0)	97 (30.7)	32 (38.6)	50 (50.0)
Alcohol Consumption	3 (50.0)	3 (42.9)	160 (47.1)	125 (65.1)	242 (65.9)	250 (72.5)	71 (80.7)	104 (92.0)
Drug Use	3 (33.3)	0 (0.0)	9 (56.3)	25 (73.5)	42 (11.4)	90 (26.1)	20 (22.0)	50 (45.5)
Sexual Intercourse	0 (0.0)	4 (57.1)	20 (6.0)	51 (30.9)	67 (19.6)	141 (48.5)	40 (49.4)	59 (66.3)
Gang Involvement	1 (12.5)	4 (57.1)	22 (6.3)	30 (15.7)	37 (9.8)	61 (17.7)	13 (14.1)	37 (33.9)

Table 3. Association, by odds ratio (95% CI), of health-compromising behavior involvement among Grenadian males attending secondary school

	Cigarette Smoking	Alcohol Consumption	Drug Use	Sexual Intercourse	Gang Involvement
Alcohol Consumption	5.85 (3.42-10.02)	--			
Drug Use	7.90 (5.21-12.00)	5.70 (3.14-10.36)	--		
Sexual Intercourse	2.81 (1.90-4.14)	2.57 (1.70-3.90)	3.49 (2.28-5.34)	--	
Gang Involvement	2.57 (1.69-3.91)	2.82 (1.64-4.86)	3.49 (2.31-5.27)	2.16 (1.40-3.32)	--

Table 4. Association, reported as odds ratio (95% CI), of health-compromising behavior involvement among Grenadian females attending secondary school

	Cigarette Smoking	Alcohol Consumption	Drug Use	Sexual Intercourse	Gang Involvement
Alcohol Consumption	5.86 (3.56-9.65)	--			
Drug Use	6.37 (3.73-10.89)	2.65 (1.49-4.71)	--		
Sexual Intercourse	4.04 (2.61-6.24)	5.27 (3.12-8.90)	5.14 (2.92-9.02)	--	
Gang Involvement	2.86 (1.65-4.97)	1.47 ^{ns} (0.873-2.47)	4.52 (2.50-8.16)	1.98 (1.08-3.64)	--

^{ns} Not statistically significant, $p > 0.05$.**Table 5. Association between engaging in alcohol consumption and additional health-compromising behaviors, reported as relative risk, among both female and male adolescents**

Variable	≤ 11		12-13		14-15		16 $\geq$		Total	
	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
Cigarette Smoking	--	--	2.76 (1.45-5.23)	5.19 (1.94-13.91)	5.34 (2.53-11.26)	3.95 (2.08-7.49)	6.13 ^{ns} (0.91-41.32)	1.15 ^{ns} (0.54-2.45)	4.46 (2.84-6.99)	3.90 (2.45-6.21)
Sexual Intercourse	--	1.33 ^{ns} (0.38-4.72)	2.66 (1.05-6.75)	1.77 ^{ns} (0.99-3.17)	3.39 (1.74-6.60)	1.65 (1.17-2.33)	2.71 ^{ns} (0.97-7.55)	1.10 ^{ns} (0.53-2.28)	4.19 (2.60-6.75)	1.75 (1.34-2.31)
Drug Use	1.00 (0.10-9.61)	--	1.40 ^{ns} (0.38-5.12)	2.84 (1.02-7.93)	2.23 (1.06-4.68)	4.37 (2.10-9.10)	1.30 ^{ns} (0.43-3.94)	1.92 ^{ns} (0.57-6.49)	2.40 (1.40-4.11)	4.18 (2.44-7.17)
Gang Involvement	0.44 ^{ns} (0.02-7.52)	1.33 ^{ns} (0.38-4.72)	1.82 ^{ns} (0.77-4.27)	3.52 (1.28-9.65)	0.86 ^{ns} (0.44-1.65)	2.72 (1.28-5.78)	2.96 ^{ns} (0.41-21.20)	0.75 ^{ns} (0.34-1.64)	1.39 ^{ns} (0.86-2.24)	2.39 (1.45-3.86)

^{ns} Not statistically significant, $p > 0.05$.

Table 6. Association between engaging in sexual intercourse and additional health-compromising behaviors, reported as relative risk (95% CI), among both female and male adolescents

Variable	≤ 11		12-13		14-15		16 ≥		Total	
	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
Cigarette Smoking	--	--	2.33 (1.02-5.32)	3.03 (1.74-5.26)	2.46 (1.65-3.66)	1.80 (1.22-2.64)	1.58 ^{ns} (0.88-2.84)	0.94 ^{ns} (0.59-1.50)	2.79 (2.08-3.73)	2.00 (1.53-2.62)
Alcohol Consumption	--	1.50 ^{ns} (0.23-9.80)	1.55 (1.13-2.12)	1.27 (1.03-1.56)	1.45 (1.26-1.66)	1.26 (1.09-1.45)	1.31 (1.05-1.65)	1.02 ^{ns} (0.91-1.14)	1.61 (1.45-1.79)	1.26 (1.14-1.39)
Drug Use	--	--	2.22 ^{ns} (0.29-17.19)	2.78 (1.17-6.61)	2.80 (1.42-5.52)	2.06 (1.33-3.17)	3.25 (1.16-9.09)	2.18 (1.09-4.34)	4.25 (2.62-6.91)	2.59 (1.85-3.63)
Gang Involvement	--	--	0.82 ^{ns} (0.12-5.81)	1.66 ^{ns} (0.82-3.35)	1.72 ^{ns} (0.79-3.76)	1.72 (1.02-2.89)	1.79 ^{ns} (0.57-5.66)	1.31 ^{ns} (0.66-2.59)	1.85 (1.08-3.18)	1.85 (1.31-2.61)

^{ns} Not statistically significant, $p > 0.05$.

Also generated were the relative risks of initiation in the defined health-compromising behaviors, provided involvement in alcohol consumption (see Table 5). The strongest relative risk generated for females was between alcohol consumption and cigarette smoking (RR = 4.46 95% CI, 2.84, 6.99) whereas that for males was between alcohol consumption and drug use (RR = 4.18, 95% CI, 2.44, 7.17). Contrarily the weakest associated relative risk, provided alcohol consumption, for females was that of gang involvement (RR = 1.39, 95% CI, 0.86, 2.24), although this was not determined to be statistically significant, and for males was that of sexual intercourse (RR = 1.75, 95% CI, 1.34, 2.31). Additionally examined, were the relative risk values of health-compromising behaviors provided involvement in sexual intercourse activity (see Table 6). The strongest relative risk generated was that of drug use for both females (RR = 4.25, 95% CI, 2.62, 6.91) and males (RR = 2.59, 95% CI, 1.85, 3.63). The weakest proportional risk provided sexual intercourse involvement amongst both females and males, was engagement in alcohol consumption (female RR = 1.61, 95% CI, 1.45, 1.79; male RR = 1.26, 95% CI, 1.14, 1.39).

DISCUSSION

A plethora of studies have been carried out worldwide, which have appraised the clustering of health-compromising behaviors among adolescents [5, 15, 25-29]. However, a paucity of such studies were identified that assessed these factors within the Caribbean country of Grenada.

Amidst a culture where sexual activity and the use of tobacco, alcohol and marijuana are often celebrated [30], Caribbean teens are particularly susceptible to health-compromising behavior engagement. In the present study we examined these very factors amongst Grenadian youth and determined that alcohol consumption (62.4%) followed by sexual intercourse activity (25.1%) and cigarette smoking (22.5%) were the most frequently cited health-compromising behaviors.

The current investigation determined that 59.4% of females and 68.9% of males surveyed reported involvement in alcohol consumption, which, although lower amongst females and higher amongst males, paralleled previous studies by Blum and Ireland, which reported weekly alcohol consumption amongst Caribbean females and males to be 78.7% and 62.1% respectively [31]. With such a high prevalence of alcohol consumption reported, we further investigated the relative risk between engagement in this activity and the remainder of the health-compromising behaviors examined. It was determined that consumption of alcohol rendered both males and females at the highest relative risk for cigarette smoking. Interestingly, we found that sexual intercourse activity was the behavior that most weakly associated with alcohol consumption amongst male students, although it was the second strongest relative risk value calculated amongst female students. When stratified by gender, alcohol consumption was determined to leave individuals at a statistically significantly higher relative risk for engagement in each of the four remaining health-compromising behaviors, with exception of female gang involvement.

In conjuncture with Smikel et al. [32] report on Jamaican adolescent sexual intercourse onset, which determined the mean age of onset among males to be 12.5 years, we observed that 44.5% of sexually active Grenadian adolescents reported their first experience at 11 years of age or younger. This finding supported the findings of Ohene et al. that 82.0% of females and 52.0% of sexually active Caribbean youth reported their first sexual experience at or before the age of 13 years [9]. With current reports citing the Caribbean region as having both the second earliest age of sexual debut and HIV/AIDS prevalence [32] early sexual intercourse engagement is of particular concern to Grenada. As such, we further examined the role of sexual intercourse involvement in overall health-compromising behavior involvement by generation of relative risk values. It was determined that both female and males students were at greatest risk for drug use, provided they were sexually active. When stratified by gender, involvement in sexual intercourse activity was determined to render students at a statistically significantly higher relative risk for engagement in each of the four remaining health-compromising behaviors.

To further investigate the clustering of health-compromising behaviors, odds ratios were calculated. The associations between all pairs of health-compromising behaviors were determined to be statistically significant across both genders, with the exception of gang involvement and alcohol consumption in female students. The clustering of health-compromising behaviors among Grenadian youth is consistent with previous studies carried out both in the region [5] and the world [4, 8, 26, 34] However, these findings are of particular concern among Grenadian adolescents were alcohol consumption and early sexual intercourse debut are the prevailing norm.

The implications of health-compromising behavior initiation, and their clustering, should be cause for serious concern. With adolescents between the ages of 10-24 comprising up to 30% of the population [14] individuals and communities must come to realize that behaviors, which are adopted during the second decade of life, have lasting implications on the well-being of the individual, the community and the public health system [31]. Having established the presence of health-compromising behavior clustering among Grenadian youth, the authors suggest that these findings be utilized to guide future adolescent prevention and intervention programs, which address concurrent health-compromising behavior initiation. Despite the findings documented in this report, additional studies should be carried out to investigate the underlying variables posited for the clustering of such behaviors.

Limitations and Strengths

Limitations worthy of mention include the proceeding factors. As a secondary data analysis, assessments were limited to data obtained from the original study. Furthermore, use of a self-administered questionnaire allows for the possibility of reporter bias. Moreover, as this questionnaire was administered only to Grenadian adolescents attending school it may not be generalizable to all Grenadian youth. Additionally, as a cross-sectional study neither causality or directionality of health-compromising behaviors could be analyzed.

Several strengths were however, evident in this study. As to the best of our knowledge, this is the first study to date, to examine the clustering of health risk behaviors among Grenadian youth. Moreover, information generated from this study may be applied to the development of adolescent public health prevention and intervention programs, which seek to address concurrent involvement in multiple health-compromising behaviors, which is thought to improve upon previous programs which address sets of individual behaviors as opposed to whole persons.

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Chapter 13

DRUG CONSUMPTION IN SURINAME: INFLUENCE OF KNOWLEDGE OF CONSEQUENCES AND ACADEMIC PERFORMANCE

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ABSTRACT

The perception of risk of drug use has been associated with decreased substance use. This study was conducted to determine whether this association applied to university students in Suriname. It also aimed to find out whether academic performance served as a protective factor for drug use. Study design: A Cross-sectional study was conducted that involved male and female undergraduate students between the ages of 18 and 35 years. A randomized cluster sampling was used to select participants attending Anton de Kom University during the 2012-2013 academic years. Students over the age of 35 or below the age of 18 were excluded. Methods: Data was gathered using a survey administered by the Anton de Kom University of Suriname to 250 undergraduate students attending Anton de Kom University in Suriname. Drug consumption patterns, knowledge of consequences of drug use, and academic performance were evaluated using descriptive statistics. Inferential analysis, using correlation ratios (CR), was implemented to determine relationships. Results: Knowledge of consequences of alcohol, cannabis, and cocaine consumption was associated with a decreased tendency to participate in cocaine use (CR = -.23, -.23, and- .20; $p = .01, .01, .03$ respectively). Additionally, cannabis drug involvement was found to be associated with less knowledge of cocaine (CR = -.19; $p = .04$). Conclusion: University students with a less working knowledge of consequences of drug use are at a higher risk of participating in substance use. Therefore, the government

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of Suriname should continue to address substance use and the associated health risks through the integration of such information in both undergraduate and graduate curricula.

Keywords: drug consumption, Suriname, knowledge of consequences

INTRODUCTION

Despite the overwhelming evidence associating substance use with adverse health effects and poor social outcomes, illicit drug use remains a globally recognized problem with significantly increasing prevalence worldwide. According to the World Health Organization's (WHO) World Drug Report of 2012, approximately 3.4 to 6.6 percent of the adult population use illicit drugs such as alcohol, cannabis, and cocaine [1]. As such, the consumption of these drugs contributes appreciably to the global burden of disease. Drug consumption has been linked to poor health outcomes such as psychosis, organ failure, chronic inflammation, addiction and oftentimes death [2-4]. Due to the addictive nature of illicit drugs, users tend to continue abuse until severely ill or dead. In fact, according to the United Nations 1 in every 100 adult deaths are attributed to illicit drug use [1].

In addition to the negative consequences experienced by the individual, productivity losses are of major concern. Society is burdened with the costs of law enforcement, health care, and drug-related crime, i.e., illegal possession, fraud, stealing, and violence [1]. International comparative studies conducted to assess the costs of drug use on society have indicated that the majority of costs are as a result of illness and premature death. For the year 2007, productivity losses in the United States were estimated to be \$120 billion USD (.9 per cent of GDP), decreased labor participation and incarceration being the main causes [1]. This statistic is consistent with global trends, where current prevalence would require an expenditure of \$200-250 billion USD (0.3-0.4 per cent of GDP), to cover global productivity losses associated with illicit drug use and treatment [1]. The impact on national GDP is further exacerbated by the high prevalence of drug use among youth, whom represent the most productive sectors of society and contribute the most to national GDP [1]. Recent studies have also shown an increase in substance use in developing nations, especially those in the Caribbean. According to the United Nations' analysis of the illicit drug market, there are between 10 million-13million drug users in the Caribbean and South America and a 2.8 percent prevalence of cannabis users [1]. This raises major concern because developing nations lack the financial capacity to enforce drug laws and drug prevention programs or cope with drug related productivity losses.

Given the public health and economic concern surrounding substance use, attempts have been made on both national and international levels to discourage drug use worldwide. However, the multifaceted etiology of substance use makes it difficult to address. Fortunately, despite its complicated nature, research findings substantiate the notion that beliefs and attitudes regarding drug use, mainly the knowledge of the consequences (KOC) of drug use, influence the likelihood of engaging in substance use. Therefore, lack of KOC of drug use (or low perception of risk) may be associated with the high prevalence of drug use in the Caribbean and can be targeted as a point of intervention.

Bejarano conducted a study examining the perception of risk and drug use in six Latin countries through a survey distributed to high school students [5]. The perception of risk is a

cognitive process in which individuals allocate certain attributes, positive or negative, to a behavior; in this case, drug use [5]. The questionnaire asked respondents to identify the level of risk associated with particular consumption patterns. Results revealed that an average of 16.7% and 22.7% perceived risk were associated with cocaine and marijuana, respectively [5]. Low perception of risk was found among those more likely to use substances. However the question remains whether academic performance, or overall cognitive capacity, (possibly associated with KOC of drug use) is correlated with decreased drug use as well.

Currently, there is no information available for the Caribbean region, even less in Suriname, about the possible correlation between knowledge of consequences, academic performance, and substance use. It is important that such associations be assessed in this population in order to inform drug prevention programs in Suriname as it is becoming a growing concern. Therefore, the objective of this study was to examine the relationships that exist between perceived risks, drug use, and academic performance in Suriname. The purpose of this study was to provide government of Suriname with an assessment of the influence that academic performance and knowledge of consequences of drug use may have on drug use among university students in Suriname. This was accomplished through a secondary data analysis of the survey conducted in Suriname in order to address the following objectives: to determine association between knowledge of consequences of drug use and drug consumption among university students in Suriname and to determine association between academic performance and drug consumption among university students in Suriname.

METHODS

The Inter-American Drug Abuse Control Commission's (CICAD) International Drug Research Capacity-Building Program's cross-sectional study in Suriname involved a target population comprised of undergraduate students between the ages of 18 and 35 years. Randomized cluster sampling was used to select approximately 250 undergraduate students attending Anton de Kom University during the 2012-2013 academic years. Students over the age of 35 or below the age of 18 were excluded. Students were informed of the purpose of the survey and given an informed consent with information regarding procedural instructions, eligibility, risks, benefits, confidentiality, and contact information. All students who provided informed consent were given 20-30 minutes to complete the questionnaire. Students were allowed to discontinue participation at any time. The survey included questions addressing, socio-demographic information, and knowledge about consequences of drug use, academic performance, and drug consumption patterns. Refer to Appendix A for survey questions and additional information on sampling. The primary independent variables were KOC and academic performance. KOC was defined as the knowledge students had regarding the negative biological, psychological and social outcomes associated with the use of cannabis, alcohol, or cocaine. For each drug, correct answers corresponding to true or false statements were given the value of 1. Incorrect answers received a score of 0. Total knowledge scores ranged from 0 to 14 for each drug and the highest scores signified more knowledge. Academic performance was a number selected (by the student) to represent the student's perceived level of academic performance with classification as either low (1-3), average (4-

6), or high (7-10). The dependent variable, drug consumption (yes or no), was defined as the use and/or abuse of alcohol, cannabis, or cocaine.

Table 1. Summary of participant demographics (n = 250)

	n (%)
Gender	
Male	70 (28)
Female	180 (72)
Academic area	
Health	28 (11.2)
Social sciences	222 (88.8)
Residence	
At home	222 (88.8)
On campus	16 (6.4)
Off campus	10 (4)
Who live with	
Relatives/family	216 (86.4)
Friends	11 (4.4)
Roommates	9 (3.6)
Alone	12 (4.8)
Importance of Religion	
Very important	131 (52.4)
Important	99 (39.8)
Somewhat important	10 (4.0)
Not important	10 (4.0)
Year of study	
First	200 (80.0)
Second	38 (15.2)
Third	7 (2.8)
>=Fourth	5 (2.0)

The survey was conducted with the approval of the research Ethics Board of the Center of Addiction and Mental Health (CAMH) and the Board of Directors of the Anton de Kom University of Suriname.

Frequency and percentage distributions were determined to assess the prevalence of drug consumption, the distribution of knowledge scores, and academic performance levels. A correlation analysis was conducted to explore the relationship between these variables.

RESULTS

During the 2012-2013 academic year, 250 students participated in the study. The average age was 21.5 years, 180 (72%) were women, 222 (88.8%) studied social sciences and lived at home, and 200 (80%) were in their first year of study. Additional sociodemographic characteristics are shown in Table 1. When measuring the prevalence of drug use at the university in the past 12 months, alcohol was the most prevalent (62%) at the university, followed by cannabis (6.2%). Cocaine use was not seen however there was a minor increase in prevalence (1.8%) when examining lifetime drug use. Approximately 77% of the students have used alcohol and 11% cannabis in their lifetime. Problematic drug involvement was measured by using the ASSIST substance specific involvement approach to quantify

consumption patterns as described in appendix A. Approximately 11.2% of the students are at-risk for problematic alcohol involvement, 6.4% cannabis, and less than 1% for cocaine use.

Table 2 presents the correlation coefficients between knowledge of consequences, drug consumption and academic performance. Though significant, the correlations between cocaine drug involvement with knowledge of consequences for alcohol, cannabis and cocaine were weak, -.23, -.23, -.20, respectively ($p = .01, .01$, and $.03$). Cannabis drug involvement and knowledge of cocaine presented a minimally significant correlation as well of $-.19$ ($p = .04$). The relationships between knowledge of consequences had moderate relationships with each other, indicating that an increase in knowledge with one drug corresponded to an increase in knowledge with the other drugs.

Difference in the knowledge of cannabis and cocaine by students who consume cannabis and those who do not were statistically significant ($p < .05$) (see Table 3). On average, students consuming cannabis had a lower KOC score for cannabis (mean 10.41, s.d. 2.68) than those who did not (mean 11.48, s.d. 1.58). A similar trend was seen with the knowledge of consequences for cocaine. On average students who consumed cannabis had a lower KOC score for cocaine (mean 10.31, s.d. 2.14) than students who did not use cannabis (mean 11.62, s.d. 1.61). All other differences were statistically insignificant. There were no statistically significant differences in academic performance and drug use or in KOC scores and alcohol consumption (see Table 2).

Table 2. Correlations between knowledge of consequences, drug consumption and academic performance

	KOC: Alcohol	KOC: Cannabis	KOC: Cocaine
KOC: Alcohol	--	.400**	.306**
KOC: Cannabis		--	.461**
KOC: Cocaine			--
DI: Alcohol	-.028	-.119	-.097
DI: Cannabis	.003	-.108	-.186*
DI: Cocaine	-.226*	-.225*	-.203*
Academic Performance	.565	.578	.168

Note: ** Correlation is significant at the 0.01 level (2-tailed), * Correlation is significant at the 0.05 level (2-tailed).

Table 3. Comparison of average knowledge of consequences and cannabis use

	12-month cannabis consumption	N	KOC Ave. (sd)	t-test
KOC Alcohol	No	182	11.78 (1.59)	-1.81
	Yes	14	12.57 (1.45)	
KOC Cannabis	No	176	11.48 (1.58)	1.36 *
	Yes	12	10.41 (2.68)	
KOC Cocaine	No	172	11.62 (1.61)	2.78**
	Yes	13	10.31 (2.14)	

Note: ** Correlation is significant at the 0.01 level (2-tailed), * Correlation is significant at the 0.05 level (2-tailed).

Table 4. Consequences of past three months use: Alcohol

	Never	Once or Twice	Monthly	Weekly	Daily or almost Daily
	n (%)	n (%)	n (%)	n (%)	n (%)
Strong desire	95 (38)	80 (32)	13 (5.2)	17 (6.8)	5 (2)
Problems	96 (78.4)	11 (4.4)	0	1 (0.4)	0
Failed normally expected	191 (76.4)	12 (4.8)	0	1 (0.4)	0

DISCUSSION

Overall the data showed that knowledge of consequences (KOC) of drug use is associated, though minimally, to decrease in drug involvement. On average students consuming cannabis and cocaine displayed a lower knowledge of consequences of cannabis and cocaine. Thus suggesting that students using these drugs do so because they are unaware of the negative effects of consuming cannabis and cocaine. As stated before, a negative correlation was found between cocaine drug consumption and knowledge of consequences of alcohol, cannabis and cocaine indicating that increased knowledge of consequences of either drug was associated with a decreased tendency to participate in cocaine use. In addition, cannabis drug involvement was associated with less knowledge of cocaine ($r = -.19$). This coupled with the finding that increased knowledge with one drug coincides with increased knowledge with another suggests that efforts aimed at drug prevention should provide information concerning the consequences of using various drugs in order to discourage them from participating in substance use of all types, rather than just alcohol.

Unfortunately, a significant percentage of students answered incorrectly when asked to identify true statements regarding consequences of alcohol, cannabis, and cocaine use (avg. = 18.05%, 19.43%, 17.6% respectively). Misconceptions among students included beliefs that consuming alcohol, cannabis, or cocaine may result in improved muscular strength, expansion of one's mental capacity, and improvement of romantic relationships. Therefore, continued use of these drugs, regardless of the student's knowledge or experience of the consequences, may be attributed to incorrect perceived benefits. For instance, of those who have consumed alcohol in the past three months, a significant amount had a strong desire or urge to use alcohol once or twice (see Table 4), despite the fact that they experienced health, social, legal or financial problems and/or were unable to achieve what was normally expected of them. A similar pattern was seen with both cannabis and cocaine. Fortunately very few students expressed failure to control substance use at any given point in time.

Although the association between KOC of drug use and drug use itself is minimal, it exists and provides support for the implementation of a education-oriented drug prevention program in Suriname. Due to the correlation found between the increase in knowledge with one drug to another and the overwhelming use of alcohol (compared to cannabis and cocaine) among the university students, the governments drug prevention program should incorporate information about the consequences of using different types of drugs with an emphasis on alcohol. Also, the lack of correlation between academic performance and drug use suggest that the students' academic performance (avg. = 6.3) was not an indicator of the "type of student" who would participate in drug use. Students, whether performing well in school or not, are at risk and can benefit from information concerning the consumption of cannabis, alcohol, and cocaine.

Furthermore, additional research should be done to explore other underlying reasons of drug use such as age, gender, or familial dynamics. Very few students indicated that they've had a friend or relative express concern about their use of alcohol, cannabis and cocaine. This is surprising given the fact that 11.2% of the students are at-risk for problematic alcohol involvement. The program can therefore provide information to the families of students about the consequences of drug use in order to increase the perceived risk of drug use within communities in Suriname. However, further research should be conducted to examine the

degree of influence family and friends have, if any, on the choice students make to participate in such risky social behavior.

Because the majority of the students displayed working KOC of drug use, one goal of the program should be to focus on increasing the students' perceived vulnerability to experiencing those negative consequences. Thus far, Suriname's National Drug Master Plan supports efforts towards supply reduction, demand reduction, and control measures. Suriname has also ratified various bilateral anti-drug agreements with neighboring countries such as Guyana, Brazil, Venezuela and Columbia. The fight against drugs has primarily been the responsibility of the Narcotics Squad of the Suriname Police Corps and Customs and the Military Police Corps [7]. More resources are being allocated towards drug-law reinforcement as opposed to educational approaches for drug prevention. However, based on the evidence gathered, drug prevention through the introduction of curricula covering drug use, consequences, and related content in both undergraduate and graduate programs should also be the government's main focus.

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Chapter 14

COMMUNITY ENGAGEMENT: A COMMENTARY ON PROMOTING THE HEALTH OF COMMUNITIES

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ABSTRACT

The health of an individual is inherently intertwined with the elements of the environment and the community in which the individual lives. However, improving health and wellbeing at the community level is fraught with challenges. After framing social and community dimensions of health, we highlight four cases of personal involvement by the authors focused on varying approaches and lessons learned regarding community engagement in the pursuit of improved health conditions. Two cases highlight

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successful project interactions and insights, but problems with long-term sustainability. Two other cases show the value of sustained resources, infrastructure, and relationships between researchers and community partners. Key components of community partnerships and engagement are offered to inform successful health promotion efforts.

Keywords: public health, community, environment, partnership

INTRODUCTION

This paper is a product of a symposium held during the 11th Annual Break the Cycle Conference in Atlanta Georgia April 2016. Jasmine Williams, a student in the Department of Veterinary Science and Public Health, Fort Valley State University, Fort Valley, Georgia, participated in our 10th Annual Break the Cycle program by focusing on indoor triggers of asthma in children in the town of Fort Valley Georgia [1]. Fort Valley is a small, poor town of about 10,000 people, 80% of whom are African American, with a low literacy rate and limited resources. It is prototypic of the segregated towns that are relics of the shameful history of slavery and racism that was a part of the character of the US South: a town lost in time. This student planned to look at the relationship between the conditions of the houses in the town as factors in the prevalence of asthma among the children. What she found was a complex sociological study of a group of people in an almost intractable situation where poverty and lack of education perpetuate the cycle of environmental health disparities.

In order to carry out her project, she proposed a partnership involving community leaders, as well as medical, environmental, and public health professionals to create a forum to promote asthma awareness and empower members of the community to address the factors that are responsible for the high prevalence of asthma. In addition, she proposed raising funds and support to renovate housing units which were in a dilapidated state, and to provide more community based health literacy training.

The response of the community to her invitations to participate in her project was minimal, despite incentives. Indeed, the prevailing sentiment reflected one of distrust and a sense of resignation that had developed in the community over many years of neglect and failed promises as well as a fear that someone would want something from them and would take away what little they had – in terms of both material possessions and dignity. Although she was only able to open the lid of Pandora's Box, she also opened the door to explore ways to make a difference and break the cycle to improve the health and well-being of the children.

As a response to this challenge we organized a symposium on "Community engagement" at our 11th Annual Break the Cycle conference with a set of formal presentations and a workshop for the attendees to take on the challenge. The lessons learned from the exercise gave us additional insights into the issues of working with a community – generally poor, underserved and, to a significant degree disenfranchised – to help improve the health of the individuals in their community and, hence the health of the community as a whole. Although this is a noble sentiment it is by no means simple.

A community beset by adverse social, economic and environmental factors may be desperate for change for the better, but this is by no means a simple task. Often, communities such as these consist of many people in differing circumstances at different levels in society, and with many different and sometimes competing interests and agendas. Often, they have

had interactions with organizations and institutions of authority, whether government or private, that have left them disappointed and with failed hopes, therefore reluctant to let strangers in again. The challenge we set for ourselves was: how do we approach this community, how do we overcome their fears and suspicions that have been caused by previous negative experiences, and how do we make a difference by creating a collaborative partnership of trust and mutual respect to enable them to make a difference and become proud of who they are and where they live.

In this paper we will explore the concept of Community Engagement and provide examples of community engagement projects and programs that will illustrate some of the scope of the field as well as the successes and failures that can be associated with the activity.

HEALTH

World Health Organization (WHO) defines health as follows: “Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity” [2]. This definition has not been amended since 1948. Individual health and wellbeing are associated with a state of existence that encompasses a level of satisfaction with a sense of security, a physical ability to go where you need and do what you want, and a freedom to pursue happiness with your fellow human beings in your community and, if you wish, and are able, in the broader world. This is not a static situation, because the passage of time and circumstances generate constant challenges requiring active engagement to resist perturbations. Continually striving to overcome the challenges may result in moments of satisfaction and happiness. The health of an individual is inherently intertwined with the elements of the environment and the community in which the individual lives. The health, happiness, and wellbeing of each individual are part of the health, happiness, and well-being of the community and represent an ecological homeostasis.

HEALTH DISPARITIES

Healthy People 2020 characterizes health disparities as health differences that are closely linked with social, economic, and/or environmental disadvantage [3]. Health disparities adversely affect groups of people who have systematically experienced greater obstacles to health based on their socioeconomic status, racial or ethnic group, age; gender, religion, mental health, cognitive, sensory, or physical disability, sexual orientation or gender identity, geographic location, or other characteristics historically linked to discrimination or exclusion. These factors collectively predispose to adverse health outcomes as well as to limited access to quality healthcare, thus further exacerbating the health disparities [3].

SOCIAL DETERMINANTS OF HEALTH

The social determinants of health are the circumstances in which people are born, grow up, live, work, and age, as well as the systems in place to educate children, to provide safety

and security for the citizens, to provide means of safe transportation and to provide services to promote health and to prevent and treat health related conditions [4]. Social determinants of health are shaped by the distribution of money, power, and resources throughout local communities, nations, and the world [5]. These are the factors that contribute to health disparities.

The World Health Organization further defines social determinants of health as: a complex, integrated, and overlapping set of social structures and economic systems that are responsible for most health inequities. The WHO focused on the social determinants of health as a means to achieve global health equity by the articulation of a set of “Millennium development goals” (MDG 2015) [6] which represent the factors include eradication of poverty and hunger, universal primary education, gender equality, reduction of child mortality, improvement in maternal health, combating infectious diseases, ensuring environmental sustainability, and building global partnerships for development. Although these eight goals have since been supplanted by the 17 of the “Sustainable development goals for 2030” (SDG 2030) [7], they continue represent a core of concerns that affect the health and well-being of people across the world in in our global collective society.

HEALTH OF COMMUNITIES

A community can be seen as a collection of people who live and interact together as a group. This larger conceptualization considers the community as a number of individuals tied together by place and common characteristics, heritage, interests, and culture. In some cases, persons in a community may be tied more by common interests than by shared space place, given the current ease of communication and transportation across geographical space. As such, a healthy community is one in which all residents or group members have access to a quality education, safe and healthy homes, gainful employment, transportation, physical activity, and nutrition, in addition to quality health care.



Figure 1. Ecological framework of health.

Communities are collectively the building blocks of the society and the country in which they are located. The population health status of a country and factors that have the potential to influence health outcomes, such as health care access and quality, health behaviors, social factors and the physical environment are critically dependent on the political framework of the country, the economy, as well as the culture and social fabric of the society. Figure 1 represents such an ecological framework. Although the diagram appears 'nested' the elements need to be seen in a more dynamic, interactive manner that reflects reality in its many fluid dimensions.

APPROACHING THE HEALTH OF A COMMUNITY

When approaching the health of a community it might be helpful to frame the discussion in terms of an individual health encounter. The relationship and the intent are similar but the framework is different and the situation is far more complex. In the situation of a personal health encounter, an individual with an ailment is likely to seek out a health care professional who will diagnose the problem and offer a treatment plan. The process involves a face to face visit during which the 'patient' states what the symptoms are and the health care provider asks further questions that try to identify the cause and the diagnosis, performs a physical examination and may order relevant laboratory studies to establish a diagnosis and then to develop a treatment plan. This model can be readily adapted to the situation of a public health concern. The community raises a concern about the health of its community members; the public health team responds with further investigation into the nature of the situation, including the cause and its effects and then develops a plan of action for the community that may involve additional resources and strategies. The similarity between the two scenarios is valid, but clearly the public health concern involving a community has a greater degree of complexity and requires a greater degree of planning and organization to develop the plans of action and solicit active participation of the community in question to follow through with the recommendations. Lessons from the direct healthcare provider-patient care model are instructive. For example, we have learned that the active participation of the patient in the diagnostic and therapeutic process results in a better short-term and long-term set of outcomes [8].

There is substantial evidence that strategies for informing and empowering patients and involving them in their health and health care has a positive impact on health outcomes. Health literacy on the part of the patient plays a large role in this process and contributes to decision-making in the management of health related conditions. WHO stresses that, when patients have to make important health decisions that affect health outcomes for health concerns, especially for chronic health conditions, informing and empowering patients about health and healthcare enhances the health outcomes and ensures the future sustainability of health systems. WHO offers a number of strategies that include written and electronic information sharing, as well as education programs for physicians and their patients [8].

The application of this model in the relationship between a public health organization and the members of an affected community can be critical to the success of the intervention. This latter process can be referred to as community engagement.

COMMUNITY ENGAGEMENT

Community engagement is a relatively flexible term that can be characterized as a process of working collaboratively with and through groups of people affiliated by geographic proximity, special interest, or similar situations, to address issues affecting the well-being of those people [9]. The process involves building authentic partnerships, with mutual respect and active, inclusive participation; and power sharing and equity; towards mutual benefit. In general, the goals of community engagement are:

- to build trust,
- enlist new resources and allies,
- create positive patterns of communication, and
- improve overall health outcomes as successful projects evolve into lasting collaborations

CASE DISCUSSIONS

We present four case scenarios, in which the authors had personal involvement; each is different in its focus and intent, but the similarities are in the desire to improve the health of the members of the target communities. The process in each was dependent on the community in question, the particular health-related issue raised and the relationship that developed between the particular individuals and organizations initiating the interaction and the members of the community – the leaders, the stakeholders and the general citizenry.

In the following set of examples we will explore the elements of the particular issues and the process and then review the literature on the process of community engagement which offers suggestions to assure a greater likelihood of a positive outcome in terms of the health of the community and the sustainability of the community in terms of the strategies adopted by the community to maintain good health and have tools at their disposal to deal with related health issues in the future.

Case Study: Anniston, Alabama [10]

In the year 2000, the city of Anniston, Alabama was embroiled in a situation in which segments of the community were exposed to high levels of polychlorinated biphenyls (PCBs), which are by-products of the chemical industry and are known to have adverse health effects including acne-like skin conditions in adults and neurobehavioral and immunological changes in children as well as causing cancer in animals [11]. These chemicals had been produced in large quantities and were dumped into landfills, subsequently seeping into the water table and resulting in highly toxic levels in local rivers and in the fish in these waters. The resulting diseases and death of the fish alerted the Centers for Disease Control Agency (CDC) and the Agency for Toxic Substance and Disease Registry (ATSDR) to the presence of the toxin. In February 2000, CDC and ATSDR released a “Health consultation on the evaluation of soil, blood and air data from Anniston, Alabama” that summarized data available to that point.

The analysis showed widespread PCB-affected soil in Anniston, which posed a serious public health hazard [12]. Blood testing confirmed a pattern of human PCB exposure that identified Anniston as one of the most heavily exposed communities in the nation. These levels were much higher than the mean serum PCB levels of 0.9 to 1.5 ppb found in recent years in unexposed populations.

Community Reaction

Obviously when the news of this contamination became public, the affected citizens were distressed and wanted to be rid of the toxins in the environment and in their bodies. The reality of the situation was that the people most affected by the presence of the PCB's were the poorer members of the community who also happened to be African American. These residents worked in the factories, lived nearby, and were sometimes provided with soil contaminated with PCB's to use on their fence posts to prevent termites. A further complication occurred in that the factories, realizing that they were responsible for the contamination and the toxicity causing serious health related consequences, closed their operation and moved out of town. Although this resolved part of the problem by eliminating the further production of PCB's, it created massive job loss and eroded the tax base that had been the engine of the local economy. As a result, not only were the citizens of the community in West Alabama still contaminated by the remaining PCB's, they were plunged into a situation of greater unemployment, poverty, and anger. A number of community activists arose to form advocacy groups who sued the chemical company.

It was during this situation that the Southeast Pediatric Environmental Health Specialty Unit (PEHSU) based at Emory University in Atlanta was asked by the Region 4 Environmental Protection Agency (EPA) Office to provide information and guidance to the pediatric community in Anniston to help them deal with the concerns of the parents about the health of their children as a result of PCB exposure. PEHSU's had been established in 1998 through a joint agreement by EPA and ATSDR to provide an interconnected system of specialists located throughout North America, corresponding and related to the EPA regions, to respond to questions from public health professionals, clinicians, policy makers, and the public about the impacts of environmental factors on the health of children and reproductive-age adults [13]. Thus the Southeast PEHSU was tasked with responding to the environmental health situation in Anniston Alabama.

The original scope of that request focused on providing Continuing Medical Education (CME) sessions for Anniston physicians. Through this process, representatives of the Southeast PEHSU met concerned physicians and learned from them about existing programs for children and other community resources. Once in the community it became clear to PEHSU physicians that merely providing information about the chemical and its toxicity was not enough to make a difference. The situation in Anniston was much more complex than merely the toxic effects of the PCB's; it was a mix of psychological, social, economic and political elements that were difficult to disentangle and resulted in a fractious relationship between the predominantly African American community in West Anniston who were directly affected by the toxins and the economic fallout of the factories leaving town and the members of the predominantly white community on the other side of the tracks who were not

directly affected by the toxins but shared economic loss from factories leaving the area. In addition, they experienced an economic impact from the negative publicity about community health conditions.

This fractious situation was at an impasse; clearly a mere delivery of CME lectures to the pediatricians of the town was not going to make much difference. Fortunately, the support from the Region 4 EPA enabled the Southeast PEHSU to become more involved in the community. Over the course of two years PEHSU staff were able to create a viable and functioning steering committee which consisted of representatives from the different community stakeholders, including the mayor, as well as representatives from the business community, the pediatric community, the school system, the early intervention programs, leadership from the activist community and parent organizations. This steering committee met on a monthly basis to explore ways to overcome the dark cloud of toxicity and division within the community and to work together to promote the health and wellbeing of the children of Anniston. To this end the group held two community Health Fairs and ultimately, in 2002, helped to create a private not-for-profit organization called *Vision 2020: For the children of Anniston*, which had as its mission to assure that by the year 2020 all children in Anniston would graduate from high school. This meant that the children born in that year would be the beneficiaries of this organization.

Unfortunately, the funding for the Southeast PEHSU to work with the community came to an end and so did the carefully cultivated community relationship with PEHSU. The lawsuit against the chemical company was successful, but the plaintiffs received a pittance of the millions of dollars in awards and became further disenchanted. Vision 2020 was disbanded, and the community has returned to a new/old equilibrium – now almost at the time when the vision of Vision 2020 would be realized. A brief moment of success – a mere taste – like footprints in the sand on the beach – was erased with the tide.

What did we accomplish? Did we indeed make a difference? And, did we make a difference for the people of Anniston or only briefly for those who participated in the steering committee?

At PEHSU, we are continuing to take lessons from that experience and to translate it into new challenges and to continue to try to make a difference in the lives of those who endure adverse social, economic and environmental factors. In particular, we have learned that resources must be invested for an indeterminate time in order to make a difference in complex community issues. Whether those resources are externally or internally generated, they must be sustainable in order to realize a long-term plan. One outcome was the partnership between the Southeast PEHSU and a not-for-profit organization, Innovative Solutions for Disadvantage and Disability to develop the Break the Cycle of Environmental Health Disparities Program, which recently received an award from the US Environmental Protection Agency for promoting children's environmental health.

Case Study: Alaska

The incidence of diabetes among Alaska Native people is high. A 2007-2011 research project funded by the US EPA sought to investigate the health properties of wild Alaska berries and the role they play in traditional Alaska Native community life and knowledge that

might help mitigate health risks [14, 15]. Youth aged 5 to 18 years from three study communities (Akutan, Seldovia, and Point Hope) were engaged as research partners. They helped conduct interviews and surveys with community members, as well as field assays of wild berries. Beyond these important research roles, however, these young people, particularly in Point Hope, changed a researcher's mental model of community vulnerability forever.

Literature on social and environmental conditions in Alaska is full of examples of risk assessments. From every angle, it seems there are hazards and vulnerabilities threatening the wellbeing of people and nature. Alaska's far northern position increases the impacts of climate change and related stresses on natural resources and subsistence foods. Legacies of environmental contamination as well as threats from ongoing and planned resource extraction pose myriad problems. Health and behavioral health conditions and risks pose particular challenges for Alaska Native people and are exacerbated by the loss of traditional knowledge and practices. Based on this background information, the researchers went into the three study communities with a focus on risk, hazard, and vulnerability. The line of questioning often started with, "What threatens your community?"

Working with young people is a remarkable experience. Their diverse personalities are less shielded than adults and, often, they are less inhibited in communicating what they are thinking and feeling. This was the case in Point Hope, Alaska. During our second visit, one young woman spoke up during a group discussion and said, "I don't want to do this anymore. It's all so depressing. Why are you only asking us what's wrong with us? How come you never ask us what's good about our village and our land and our sea?" Needless to say, that was a pivotal moment for the sociologist on the project who from that moment on expanded the focus of her work to encompass wellbeing, rather than just risk and risk perception in changing environments. With the help of the young people in Point Hope, the study shifted to investigating quality of life and wellbeing as well as factors posing threats to community residents and the natural environment.

Empirical investigation yielded insights into how Point Hope's youth saw their future as compared to adults. While they shared adults' appreciation for how traditions were honored and how people supported each other, young people were more likely to articulate concerns about the safety and cleanliness of their environment and too few opportunities to be involved in local governance. They created long lists of things they liked best about their community and place and the benefits of living there, including freedom, abundant food from nature, hunting and whaling, fun outside in nature with family and friends, and longstanding traditions. It wasn't that they didn't speak of threats. They did. They indicated concerns about drugs and alcohol and loss of traditions, of the threat of oil drilling and possible spills and other contamination, and of climate change threatening their relationship with sea and ice and wildlife. As they learned from the research project about the health benefits of their wild berries, they simultaneously taught the researchers that studying environmental health is as much about assessing abundance and quality as it is about threats and risks. Furthermore, they showed the value of engaging a community, and its youth in particular, in order to move beyond vulnerability to promote a cycle of environmental health capacity that includes learning, fun and play, healthy food, community traditions, and time in nature.

Alas, the project ended as the funding ended. There is no ongoing relationship between the researchers and the people of these communities. Not only have we no way of tracking whether the project made any lasting impact on the lives and health of these people, but also

the ongoing local insights and experiences no longer have a conduit to informing scientific understanding. The longer-term sustainability of community empowerment and of relationships between local communities and researchers must be a higher priority in the realm of environmental health.

Case Study: The Georgia School-Based Health Center Project

PARTNERS for Equity in Child and Adolescent Health in the Department of Pediatrics at Emory University School of Medicine was developed to enhance the health and well-being of the underserved children and adolescents in the state of Georgia [16]. The purpose of PARTNERS is to increase access to quality health care, improve the delivery of health services and improve the overall health of the children of Georgia. The components and mission of PARTNERS includes: expansion of school based health clinics (SBHC) throughout the state; increased access and improved delivery of primary care services for underserved populations; improved academic outcomes through the development of innovative programs that link healthcare, education and community services; and the training of future pediatricians and other medical providers to provide medical care that addresses the social determinants of health. The vision of the program is to reduce health disparities ensuring that all Georgia children are more likely to be happy, healthy and productive members of society.

Twenty-eight million children nationwide come from economically disadvantaged households and are at risk for a variety of negative outcomes including 1) increased rates of health problems and mortality, and 2) increased risk of academic underachievement and school drop-out. School-based health centers (SBHCs) are safety net health organizations that increase access to healthcare and improve academic achievement for underserved students [17]. SBHCs were first introduced in late 1960s (Cambridge, Massachusetts) and early 1970s (Dallas, Texas and St. Paul Minnesota) to provide affordable and accessible healthcare for poor children and adolescents [18]. There is significant evidence in the literature to support the role of SBHCs in increasing access to healthcare, improving health outcomes and reducing health disparities (i.e., mental health, asthma) and reducing medical costs for the most needy children and adolescents in our nation [19].

There are approximately 2,400 SBHCs nationally, which reflects a four-fold increase within the past 20 years [20]. Less than 1% of public elementary schools house SBHCs despite strong evidence of effectiveness from model programs. Four issues must be addressed in taking SBHCs to scale: evidence of community need and support, sustainability, evidence of health and health cost impact, and fidelity to exemplar models [21].

Following an exemplar model (Whitefoord Elementary School-Based Health Center in Atlanta, Georgia) [22] and under the direction of PARTNERS for Equity in Child and Adolescent Health of the Department of Pediatrics at Emory University, the Georgia SBHC Project was created to expand SBHCs in Georgia with 3 phases – planning, implementation, and sustainability. One-year planning grants were awarded beginning in 2010 to Georgia counties for local stakeholders to provide evidence of community need and support. The purpose of the planning grants was to increase knowledge and public will around the development of SBHCs. Grantees were required to create a community advisory group

consisting of stakeholders in child and adolescent health and education. Members included representatives from the school system, health care providers, community agencies, parents, local politicians and child advocates. The planning grants included the following activities:

- **GRANTEES PARTICIPATED IN:**
 - developing a community advisory group to work towards accomplishing the goals of the grant,
 - conducting a needs assessment to define the health and academic need of students,
 - defining strategies to address needs,
 - identifying specific school(s) for clinic services, and
 - developing a business plan for establishing the SBHC.
- **PARTNERS:**
 - conducted three SBHC workshops at Emory with the assistance of staff from the national School-Based Health Alliance
 - held monthly conference calls to provide technical assistance, address challenges, celebrate successes, lend encouragement, and
 - conducted site visits and presentations to members of advisory groups and community leaders to educate and provide a forum for addressing concerns of the community.

Over the past six years, PARTNERS has awarded planning grants to 37 counties representing 41 communities throughout Georgia. Central to the planning process was the alignment of the resources, talents, and organizational vision of each stakeholder. Another critical element was the work of a SBHC champion who was vital in minimizing mission creep and in keeping the process going when faced with challenges within and without the advisory council (i.e., key member turn-over, opposition from medical providers, etc.). Called upon to define the needs of its children and to develop strategies to address these needs, each advisory council participated in conducting a needs assessment using primary and secondary data. Primary data collection was obtained through focus groups, key informant interviews and surveys of parents, teachers, school administrators and community leaders. Information obtained included knowledge of SBHCs, health (physical, psychosocial, oral) needs of students, barriers to access to medical providers, need for a SBHC, and likelihood of using or referring students to a SBHC. School system, state and county sources were used for secondary data collection. School achievement, absenteeism, percentage of children living in poverty, overall health status of children in the county as compared to the state, resources available to address the health and academic challenge for students were elements of the secondary data collection.

Using the data, the council was charged with developing specific strategies to address the needs through the creation of a SBHC. The strategies included:

- Which school would be best served by a SBHC
- What services should be offered by the SBHC
- What medical entity would serve as the medical sponsor of the SBHC
- What community resources were available to support the SBHC; and
- How to obtain funding for SBHC start-up.

As a result of these community grants, the number of SBHCs in Georgia has increased from two to 22 over the past 5 years. These are comprehensive, full-service SBHCs that provide primary health care to students and staff and, for some, both behavioral and oral health as well as primary care. These 22 SBHCs can potentially impact the health and well-being of approximately 11,000 students. Several other communities are poised to begin when funding is secured and continue to meet as an advisory council well beyond the planning process. In addition, other communities involved in the planning process that were not able to develop a comprehensive school based health center chose to expand existing school health programs using telemedicine or by adding behavioral health services alone. There are currently over 80 schools with telehealth and three with just behavioral health programs.

We have demonstrated the importance of community buy-in and support in expanding SBHCs throughout the state. Galvanizing community stake-holders around defining and addressing the needs of its children is key not only for planning but also for implementing and sustaining these centers as well.

Case Study: Community Engagement Adds Value to Environmental Health Science

When environmental health (EH) research omits community knowledge, it can lead to research results that are not easily translatable into actionable information for the public. In other words, community engagement can improve the relevance and benefits of EH research. Community-engagement in EH research lies on a continuum from outreach to collaborative research partnerships with shared leadership between the scientists and community. Ideally, in a collaborative EH research partnership, the community identifies an environmental exposure concern and participates in the translation of that concern into a research question and then into the design of a research study. Ultimately, the community partner may take a lead role in the use, translation, and dissemination of the research findings.

Of course, environmental exposures do not happen in isolation from the other determinants of health, as there are many influences on human health from genetic inheritance to economic factors. The Exposome is a new approach to better consider these multiple influences, including environmental exposures, into the study of human health. In simplistic terms, the Exposome is everything that influences health throughout a lifetime except the inherited characteristics with which we are born. Importantly, because Exposome science is an emerging approach, it represents a unique opportunity for community input into science at an early stage. The integration of community knowledge should be a key component of the newly developing Exposome science and is a primary aim of the HERCULES Exposome Research Center at Emory University in Atlanta, Georgia [23].

In order to engage the Atlanta community in the new Exposome approach to science, HERCULES needed to start where the community is and learn both the environmental health concerns of the local community and what other factors are priorities to the community. Before going into the community, HERCULES reached out to community leaders and stakeholders active in Atlanta's environmental health network. Many of these individuals agreed to serve on a stakeholder advisory board (SAB) not only to provide input into the scientific activities of the HERCULES center, but also to guide the center in its community

engagement efforts. The SAB emphasized the importance of bringing immediate benefits to the community-- in the form of knowledge, capacity building, resources, and partnerships – all components essential to community empowerment and the sustainability of community-led efforts to address local EH concerns.

Building trusting relationships with the community takes time. Part of that trust is supporting the community in their efforts to address local concerns. For HERCULES, this includes sharing both financial resources and expertise in the Clarence “Shaheed” DuBois Community Grant Program [24]. This program provides funding and technical assistance to organizations that aim to conduct outreach, to promote community awareness of local environmental health concerns, or to collect information needed to address local environmental health concerns. This program funds 4-5 community projects per year. Funded projects have ranged from an educational campaign to educate refugee parents about the health impacts of cigarette smoking indoors to urban agricultural gardens teaching local residents the skills to grow and cook their own healthy foods. An evaluation of the community grant program is currently being conducted in which four dimensions of community capacity are being examined: knowledge and skills, leadership opportunities, partnerships, and resources leveraged. Preliminary analyses of qualitative interviews with grantees suggest the community grants were successful in strengthening several dimensions of capacity.

As articulated above, the purpose of community-engaged EH research is to conduct research that is relevant to the community and produces scientific findings that can be translated into actionable information that improves overall health outcomes. The relationship building with both SAB members and in the community lays the foundation for the conversations and interactions between researchers and community members that may lead to research partnerships. As part of this process, HERCULES researchers participate in community-organized meetings focused on local environmental challenges. Two community-driven scientific projects have emerged from researchers being present in the community and learning of local concerns. Both of the projects were funded through a competitive pilot program offered to scientific faculty associated with HERCULES. The funding for both projects was shared between the community partnering organization and the scientific team, and community residents served as citizen scientists in both projects. The first project entailed a health survey in two impoverished Atlanta neighborhoods concerned about frequent flooding, indoor mold, and asthma. The project documented high rates of asthma and indoor mold in the homes, which garnered the attention of the city council. The second project is an assessment of tap water quality during rain events in another flood-prone neighborhood in which residents report smelly, brown tap water during heavy rainfall. This study is ongoing with residents collecting samples of drinking water and floodwater during rain events that will be analyzed for microbial and chemical contaminants.

Community-engagement in EH research can be successful if built on the understanding that the community has valuable knowledge that can improve the scientific process. Sharing financial resources with the community emphasizes the value of community knowledge and community leadership in addressing local EH concerns. It also helps build trust in the community. This trust is further established when researchers are present in and listening to the community. Community-engaged EH research can serve as a model for scientific investigations that both further the science and directly benefit the local community.

DISCUSSION

Of the four examples given above, the first two had limited funding and a direct focused project which had some immediate success in forging relationships and having some influence on the community and on creating new ideas and change. Their shortcomings however, were in their lack of sustainability and therefore limited impact. Although lessons were learned from these experiences, the communities they served were likely left with incomplete closure and possible frustration, which may have resulted in a measure of distrust towards potential future relationships of this kind.

The second two examples demonstrate that with ample resources and a stable and effective supportive infrastructure much can be achieved. In both, there is clearly stakeholder buy-in and active participation in making the project a success. This process speaks to the mutual satisfaction of the academic institution and the community agencies and organizations. PARTNERS had a singular focus – and the school-based clinics – with the seeding of a model of service that was found not only to become functional, but also documented real benefits for all. The Exposome concepts include a varied set of community-defined projects that organically grow from communities engaged with researchers. Both models are effective and also have demonstrated sustainability.

The challenge posed at the beginning of this paper, that of the town of Fort Valley Georgia, is a different. Because of past false steps and disappointments, the first challenge is to develop a relationship with the people of the town. We must begin to listen to the citizens about how they perceive both the healthy aspects of their community and the health issues facing their children. Our focus is on the environment, particularly indoor air, and the prevalence of asthma as well as the frequency of asthmatic episodes and the severity of the episodes. But that may not be the main concern of the community. Once we can hear their concerns and dreams, we can then work with them and empower them to take charge and ownership of their identified problem while we provide the necessary support, information and technical assistance to make it happen. To increase the probability of attaining the desired goals of all, we aim to work within the frameworks for effective community engagement outlined below. Community partnerships are not built overnight [25, 26]:

- A trusting partnership is developed over months or years.
- A partnership does not depend on a single grant, or even a succession of grants.
- The partnership continues even when there are no grants.
- A partnership means that resources and control are shared.
- The academic institution or government agency must be prepared to share funds with the community.
- The community should be the “senior partner” on issues that affect it.
- Community representatives should primarily be people who live in the community.

Notes on Community Engagement

Involving the community and collaborating with its members are cornerstones of building the public's health. In recent years, community engagement and mobilization have been

essential to programs addressing smoking cessation, obesity, cancer, heart disease, and other health concerns. Recognizing that community involvement is essential to the identification of health concerns and interventions, community engagement is increasingly recognized as a vital component of efforts to expand access to quality care, prevent disease, and achieve health equity for all Americans.

I am convinced that Americans need to live and work in environments where they can practice healthy behaviors and obtain quality medical care. Social, cultural, physical, and economic foundations are important factors in the overall health of the community. We must use our resources to increase availability of healthy foods, ensure that neighborhoods have safe places for physical activity, and provide access to affordable, high-quality medical services. Creating these healthy environments for people of all ages will require their active involvement in grassroots efforts. Private citizens, community leaders, health professionals, and researchers will need to work together to make the changes that will allow such environments to flourish.

Regina M Benjamin, US Surgeon General, 2011. [27]

In practice, community engagement is a blend of science and art. The science comes from sociology, political science, cultural anthropology, organizational development, psychology, social work, and other disciplines, and organizing concepts are drawn from the literature on community participation, community mobilization, constituency building, community psychology, and cultural influences. The art comes from the understanding, skill, and sensitivity used to apply and adapt the science in ways that fit the community of interest and the purposes of specific engagement efforts. We present below a few of the key concepts underpinning successful community health promotion.

Culture

In order to develop a relationship with the community it is critical not only to have an understanding the practicalities and the conditions in the community but also to understand the language and culture of the community. Culture can be seen as a complex integrated system of thought and behavior shared by members of a group — a system whose whole pattern allows us to understand the meanings that people attach to specific facts and observations. Culture shapes identities and fosters notions of community, and it shapes how individuals and groups relate to each other, how meaning is created, and how power is defined. Furthermore, culture shapes ideas about partnership, trust, and negotiation. Therefore, culture shapes the process of community engagement, and effective engagement requires an understanding of culture.

Empowerment

The process of empowerment is a particularly challenging one. Empowerment has been articulated as “a group-based participatory, developmental process through which

marginalized or oppressed individuals and groups gain greater control over their lives and environment, acquire valued resources and basic rights, and achieve important life goals and reduced societal marginalization.” Ideally, empowerment is both a process and an outcome of community engagement and should take place at three levels: the individual, the group, and the community [28].

Social Ecological Model

The social ecological model conceptualizes health broadly and focuses on multiple factors that might affect health. The social ecological model incorporates the understanding and appreciation of the interaction between the individual, the group or community, and the physical, social, and political environments incorporating the social determinants of health (see Figure 2).



Figure 2. The social-ecological model: A framework for prevention.

The Social Ecological Model (SEM) is a theory-based framework for understanding the multifaceted and interactive effects of personal and environmental factors that determine behaviors, and for identifying behavioral and organizational leverage points and intermediaries for health promotion within organizations [29].

CONCLUSION

Building trusting relationships takes time, but it is key not only to providing the most appropriate and useful information, but also to bringing the community into a lasting network of relationships they might draw upon for future needs (and to perhaps help others in similar situations or build regional networks of empowerment). Overall this process serves to improve the health of children who grow up in vulnerable circumstances and who would live more fulfilling and productive lives with good health and prospects for a future, with a good education and good health care. It is our job to help make this a reality.

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Chapter 15

MOMMY: A MATERNAL HEALTH SURVEILLANCE SYSTEM

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ABSTRACT

Maternal mortality is a global public health challenge, with 99% of deaths occurring in developing countries. Poor pregnancy outcomes reflect a cycle of vulnerability to risk factors, most of which can be prevented. We propose the creation of an electronic system ('Mommy') that will assist and monitor the health of pregnant women, minimize their exposure to risk factors and break the cycle of maternal mortality. We predict that implementation and widespread use of Mommy may lead to healthier pregnancies and reduce the number of both maternal and neonatal deaths. This project will help to break the cycle and reach the Sustainable Development Goal 2030 of reducing maternal mortality and improving infants' health.

Keywords: maternal health, surveillance, mobile application

INTRODUCTION

Maternal mortality is defined as the death of a woman during pregnancy or in the first year after delivery. The World Health Organization (WHO) estimated that 830 women die every day from preventable causes related to pregnancy and childbirth, with 99% of all

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maternal deaths occurring in developing countries, and predominantly among young women from low-income populations. The high rate of maternal deaths reflects the social determinants of health (e.g., race, income, education, physical environment, among other characteristics) and highlights the health gap between rich and poor [1, 2].

Pregnancy is a vulnerable period for both mother and fetus, and many factors can increase their risk [3-6]. These factors can be divided into five categories [7]: 1) Preexisting health conditions; 2) Age; 3) Life style; 4) Pregnancy conditions and 5) Environmental risks [8-9].

With advances in technology, it has become useful to apply existing resources to improve health and well-being. To this end, the term mHealth (mobile health) was created. mHealth is a general term for the use of mobile phones and other wireless technology in medical care [2]. The most common application of mHealth is the use of mobile phones and communication devices to inform users about preventive health care services anywhere in the world. Through smartphone technology, mHealth intends to change the face of modern medical assistance, creating mobile systems that collect and analyze data and interact with people.

The risks on the gestational period can be reduced and neonatal outcomes can be improved when the appropriate preventive measures are taken. Smartphone technology can be used as a preventive and efficient method that can be easily harnessed and implemented and it is also practical for women in childbearing age.

Objectives

To develop a computational system to monitor and assist pregnant women to prevent or minimize their exposure to environmental risk factors that can be harmful to themselves and/or their children.

Hypotheses

The technology of smartphones can be harnessed to prevent complications during pregnancy, and decrease maternal and neonatal death rates. This modern tool will allow improved patient monitoring, more personalized care and increase physician and patient satisfaction.

Contextualization

Maternal mortality is one of the major health problems in Brazil and other developing countries [10]. The direct causes of maternal mortality are hemorrhage, sepsis, hypertensive disorders, unsafe abortion, and prolonged and/or obstructed labor [11]. The indirect causes of maternal death are related to poor health before pregnancy, or diseases that women develop during pregnancy [12]. Virtually, all the direct causes are treatable and can be prevented if women receive appropriate prenatal care. Furthermore, some factors (sepsis, unsafe abortion,

hypertensive disorders) are clearly and directly related to the social determinants of health (SDH).

The Pan American Health Organization (PAHO) evaluated the maternal mortality ratio (MMR) in the Americas: the MMR fluctuated from 5.9/100,000 live births in Canada to 690/100,000 live births in Haiti, illustrating the extreme socioeconomic inequality in the region. In Brazil, the MMR has been reduced in the last 18 years from 120/100,000 live births in 1990, 64/100,000 live births in 2005 to 58/100,000 live births in 2008, but the rate did not reach the expected threshold defined by the United Nations [10]. According to the fifth Millennium Development Goal, the annual reduction for MMR in Brazil should have been 5.5%, but it was only 4% [9-10].

Neonatal mortality is frequently used as an indicator of quality of life and well-being of a population [13-15]. Mortality on the first days of life reflects the complex relationship between biological, socioeconomic and welfare factors where socioeconomic and welfare factors are strongly related to the care provided to pregnant women and the newborn [16, 17]. Neonatal mortality rates in developing countries remain alarming: in Bolivia there are 37.49 deaths per 1,000 live births [2], in Africa there are 55 deaths per 1,000 live births, and in Brazil the ratio is 13.82 deaths per 1,000 live births [16]. The major causes of neonatal mortality are related to diseases during pregnancy and childbirth: mainly preterm birth, low birth weight, respiratory and infectious diseases, and congenital malformations [9]. Neonatal mortality is inextricably connected with maternal health conditions [18]. The risk factors of pregnancy can be divided into five categories [7]:

- *Pre-existing health conditions:* These are conditions that are present before women become pregnant, for example diabetes and obesity.
- *Age:* Pregnant teenagers have higher probability of developing high blood pressure, anemia, and are more likely to deliver prematurely. Also, teenagers are less likely to access pre-natal care and do not always understand the risks of pregnancy. Women who have their first child after 35 years of age usually have a normal pregnancy, however they have a higher risk to have a caesarean section, to have complications in childbirth, and their child have higher risk of having genetic conditions, such as Down syndrome.
- *Life style:* Pregnant women who consume alcohol have a higher risk of premature birth, and infants with Fetal Alcohol Syndrome. Women who smoke during pregnancy also put their fetuses at risk of premature birth, genetic abnormality, and sudden death syndrome. Passive smoking or 'second hand smoke' also increases the risk of health problems in both fetus and mother.
- *Pregnancy conditions:* Multiple pregnancies (i.e., twins, triplets, or more) increase the risk of premature birth and frequently require cesarean section. Infants from multiple pregnancies, in general, are smaller and more likely to be premature than singletons. Also, premature infants are more likely to have respiratory distress with associated increase in morbidity and mortality.
- *Environmental risk factors:* Environmental exposures as, for example: air pollution and pesticides may cause premature birth, low birth weight, and congenital malformations. These babies have a higher risk of dying, and those who survive have

higher risk for brain, respiratory and digestive disorders. Environmental exposure is also related to the development of heart diseases and diabetes in adulthood [8-9].



Figure 1. International cycle of environmental health disparities [23].

According to the World Health Organization, maternal deaths significantly reflect social determinants of health, limited access to adequate health care and lack of timely information [1]. Neonatal mortality reflects complex relationship between environment, genes, socioeconomic status, access to health services, and maternal literacy status. Neonatal mortality can thus be prevented by stronger public health policy targeting antenatal and immediate postnatal care [19-22].

Figure 1 shows the cycle of environmental health disparities. This project focuses on to prevent the health risk factors and consequently to break this cycle by offering the pregnant women information, and a facilitated contact with the physician.

RELATED WORK

Many mHealth systems are currently in use, and those focusing on improving maternal and neonatal health have been well received [23]. “Wired mothers” is an mHealth application that combines communication, education on pregnancy, reminders of antenatal care visits, and an emergency medical response system, and has been demonstrated to decrease perinatal mortality rate by 50% [23]. “mMamee” is another mHealth application that does monitor and assess environmental exposures that could potentially affect the health of pregnant women [24]. The platform relies on the combination of user descriptive input and urban sensing

measurements. Their goal is to determine the long-term impact of various exposure factors on maternal and fetal health [24].

A study conducted by Sondaal et al., assessed the effect of mHealth interventions in improving maternal and neonatal care in low- and middle-income countries; the studies, however, have not reviewed used the sensors of the smartphone to obtain environmental data to allow preventive alerts [23].

Mommy is an innovative approach among mHealth applications in that it will use the full capacity of the smartphone by incorporating an environmental sensor to create a more effective prevention tool.

MOMMY ARCHITECTURE

The architecture of the system is shown in Figure 2. The system will have: 1) a mobile application that will be installed on the smartphones of pregnant women; 2) a web system that will be used by the health professional providing prenatal care; 3) a central system that will be responsible to process the information.

The smartphone of the pregnant woman will be the interaction interface of the system: 1) It will collect the environmental data 2) send it to the central system 3) which will process and store the data 4). After processing the data, the system will send alerts and tips to the woman [5 and 6], and include the crucial information into the health professional report [7]. This report can be visualized through the web interface [8].

Pregnant women will register with an email address and password. After that, they will be asked to input some additional information about the pregnancy such as:

- Stage: How many weeks of gestation have passed since last period?
- “Twins information”: How many fetuses is the pregnant carrying, i.e., is it a single fetus or multiple fetus pregnancy?
- Weight: Information about weight gain during pregnancy.
- Symptoms: There will be a list of common pregnancy symptoms that the patient will be prompted to check. There will be also an option to add additional symptoms.
- General well-being: The patient will be prompted to enter information on how she is feeling about sleep quality, mobility, appetite, and other factors during the pregnancy, using a five-star rating bar.

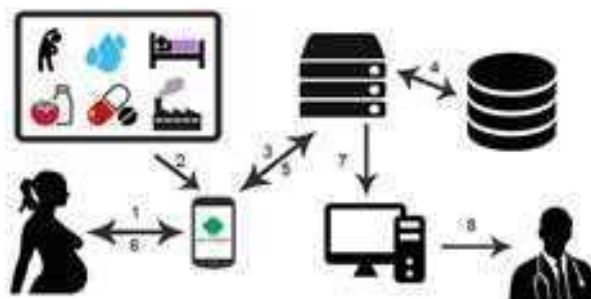


Figure 2. Mommy's architecture.

Shortly after registering, the system will invite her to fill in information about her medical information on conditions, such as personal medical history, family medical history, pregnancy history, and health habits (smoking, alcohol drinking, physical activity) to allow more accurate alerts.

The doctor's report will store the health related information including data such as medications, vaccines, high-risk travel, and physical activity. The doctor's report is crucial for better results, but the pregnant woman will have control over who can access her data. This is especially important for the empowerment of the patient.

The system will provide reliable information throughout pregnancy as the fetus develops. Mommy will also allow the pregnant woman to submit questions and concerns to health professionals. The system will provide instructions to help her recognize signs and symptoms that require further evaluation. A communication channel with the doctor will be available for emergencies.

Other proposed functionalities are the tracking of medication use, and the monitoring of sleep, physical activity, and fluid intake. Tips regarding healthy diet will also be included in the system. The location tracker is fundamental. The women will be alerted if they plan to travel to high risk areas, such as those with high pollution levels or areas with reported cases of Zika.

A prototype of the system was implemented and the Medication Tracker functionality was developed which manages medications that the pregnant woman is taking. Moreover, it reminds her when she needs to take another dose of medication, and it will alert her if the medication that she is taking is not deemed safe during pregnancy.

Although Mommy has been partially developed, it has not yet been tested, and, consequently, has not been released for general use. It was developed to test the system at the Hospital das Clinicas at Ribeirao Preto, Brazil. The technology is currently being elaborated along with the development of new functionalities. This is a work in progress.

DISCUSSION

mHealth interventions have been developed to improve maternal health, antenatal and postnatal clinic attendance, improved vaccination rates, and delivery at staffed facilities [23]. These interventions, however, have shown little impact on maternal and neonatal health outcome [23]. However, as shown by Sondaal et al., none of the methods utilized to develop mHealth applications used the environmental data of the pregnant women to access daily risks. In addition, none of the applications reviewed by the study put together all the functionalities that Mommy proposes.

Mommy intends to access and process the environmental data and send alerts to allow the woman to make changes on her daily habits. There will be also incentive messages seeking to motivate the pregnant women to improve their health habits, making use of multivariate visualization tools to make it easier to understand what the most important aspects are that need to be improved. Furthermore, the system has the potential to be a valuable surveillance tool for doctors in that they can monitor the status of their patients through the electronic reports that will be generated.

The next step of the system development is the medication tracker functionality which will be evaluated and a ‘first version’ will be released to users. Also, new functionalities of Mommy, such as the physical activity tracker will also be developed.

Mommy has the potential to be a functioning health care application that even low- and middle-income populations can access. Technology is becoming more accessible and smartphones are becoming cheaper. There are more than 281 million mobile phones in Brazil, with about three smartphones for each ten people [25]. With a population of 200 million, the number of cellphones exceeds the number of people in the country [26], while the number of doctors is not enough; there are on average only 1.95 doctors per thousand inhabitants with an uneven distribution favoring more urban affluent areas where there are 2-4 doctors per thousand inhabitants while in the poorer areas there are less than 1 per thousand, which is comparable to the poorest countries in Africa [27]. This scenario argues for the potential of Mommy in Brazil particularly for the people living in low resource areas.

By helping to change the mother’s habits that can be harmful to her health and her child’s health and improve her quality of life, we expect to break the cycle of environmental health disparities (see Figure 1) and contribute directly to a better maternal and neonatal health outcome.

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Chapter 16

DISPARITIES IN ACCESS TO EARLY INTERVENTION SERVICES FOR EXTREMELY PRETERM INFANTS BY FAMILY INCOME

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ABSTRACT

This analysis evaluates access to state-provided early intervention (EI) programs among extremely low birth weight (ELBW) infants based on family income. ELBW infants are at high risk for developmental delays in early childhood and at school age. Studies suggest that early intervention programs play an integral role in mediating the health and educational disparities that impact children from low-income households. The Neonatal Intensive Care Unit (NICU) follow-up clinic at Comer Children's Hospital at the University of Chicago has robust data on the developmental status of and early intervention receipt for 131 ELBW infants. Using linear regression analysis to assess this data, we found that for every \$10,000 decrease in median family income, the odds of receiving access to adequate EI services are decreased by 24% ($p < 0.05$). This data demonstrates that infants from low-income families who are at high risk for developmental delays face barriers to accessing EI. Healthcare professionals, EI service coordinators, and families must work together to identify mechanisms for low-income families to access the highest quality of care and support for their children.

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Keywords: early intervention, disability, preterm, extremely low birth weight, access, income, intensive care

INTRODUCTION

Infants who are of low birth weight are more likely to experience developmental delays or learning disabilities [1-4]; however, these delays or disabilities can be mitigated through early childhood interventions [5-7]. Children with disabilities or who are at high risk for developmental delays qualify for state-provided early intervention services under Part C of the Individuals with Disabilities Education Act (IDEA). Part C early intervention programs help children ages 0-3 learn basic physical, cognitive, social and emotional skills, while emphasizing the roles that the family and the environment play in a child's development. Despite the fact that these programs have the capacity to greatly enhance a child's development and the parents' ability to work with their child, not everyone who qualifies for EI services is able to receive them. This is especially true for children from low-income families, reinforcing the systemic disparities that these families experience. As such, children from low-income households and who are of low birth weight face a double jeopardy that only intensifies the need to ensure that these children are provided with crucial early childhood supports (see Figure 1).

Part C of IDEA was formulated to implement publicly funded, statewide systems of EI services for young children that may be delivered locally or regionally and mandates that services occur in "settings that are natural or typical for a same-aged infant or toddler without a disability, [which] may include the home or community settings" [8, 9]. Examples of EI services include speech, occupational, developmental, behavioral and physical therapies, family training and counseling, psychological and case management services, comprehensive health and social work services, vision and auditory services, assistive technology devices, and transportation services [10]. In addition to requiring that states provide EI to children with diagnosed disabilities or delays, Part C allows states to opt-in for the provision of EI services for children who are at highest risk for developmental problems [5]. Illinois includes at-risk children in its eligibility criteria, so this Chicago-based analysis studies infants born < 1,000 grams as well as children experiencing brain injury who are at high risk for developmental delays in early childhood and at school age.

Due to their broad scope, EI services benefit not only the child in isolation but also the child's family by fostering familial relationships that will create a less stressful and more supportive home environment. In the National Early Intervention Longitudinal Study conducted by SRI International, 59% of participants reported that their families were much better off after receiving EI services [7]. According to Adams et al. [8] infants who received EI services had improved verbal abilities, receptive language scores, and overall cognitive performance at 8 years of age [8]. Importantly, studies have also shown that EI particularly benefits children from low-income households [5]. Even further, significant economic returns make early intervention an especially attractive policy direction. James Heckman, a Nobel Laureate and University of Chicago economist, has demonstrated that investments in early childhood development, specifically among disadvantaged children, provides the largest rate of return compared to other human capital programs such as schooling later on in life or job

training [6]. Despite these demonstrated benefits, concerns of access arise for children and their families. In a 2008 study, Rosenberg et al. [11] found that at 24 months of age, only 10% of children who exhibited delays received early intervention, with particularly poor rates of access among black children from low-income households [11].

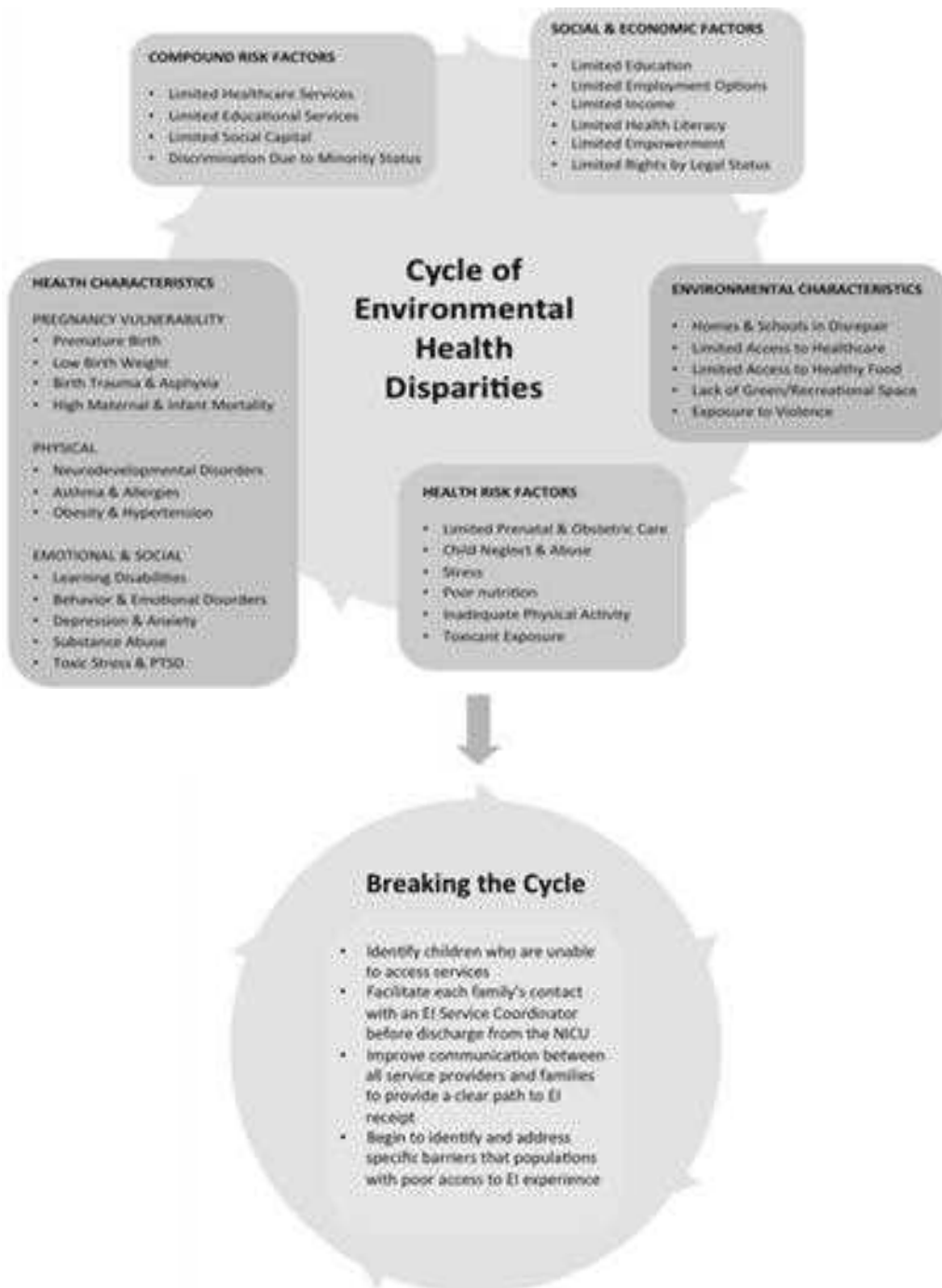


Figure 1. Breaking the cycle of environmental health disparities.

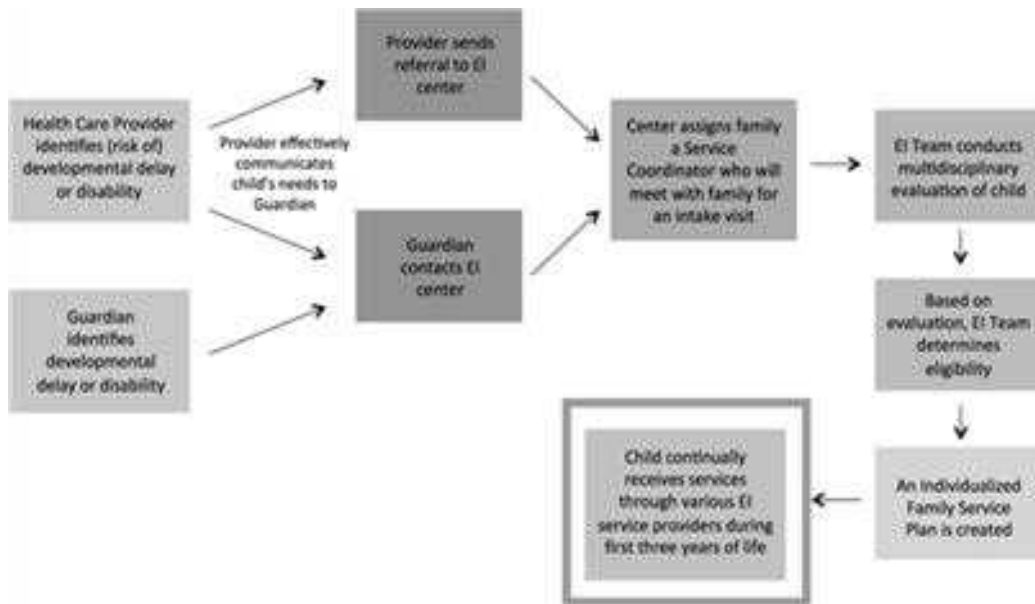


Figure 2. Steps to receive early intervention services.

In order to receive services, families must navigate through a series of steps (see Figure 2). First, the family receives an EI referral from a health, social service, or rehabilitation professional; alternatively, parents, upon noticing a potential delay in their infant, may contact their local EI center. It should be noted that the method by which EI services are distributed varies by state; for example, Illinois services are distributed via EI centers that are spread throughout the state, whereas some states' EI programs are organized through single state offices. Once families are connected with an EI center, the child is screened and evaluated in order to assess whether he or she is eligible for services. After eligibility is confirmed, the caseworker will conduct an initial assessment of both the child and the family in order to identify the specific areas of need. These assessments allow the caseworker to draft an individualized family service plan (IFSP), which describes the services that the child will receive, the child's current developmental status, payment details, steps to transition into and out of EI, when and where the child will receive services, and the anticipated results of the services [12].

The aim of this study is to identify and evaluate the factors that affect access to early intervention services among extremely low birth weight infants. Two factors are of primary interest: 1) family income and 2) the extent of neurological impairment after critical illness in the NICU. This paper also considers barriers that prevent families from receiving the necessary EI services and offers suggestions to overcome these barriers.

Extremely preterm infants were followed from the time they were admitted to the NICU until approximately three years of age, capturing the full eligibility age range for Part C services. Given their extent of prematurity, these infants experience significantly higher rates of learning disabilities and developmental delays than their term counterparts. Msall et al. [2] found that out of 149 children who were extremely premature at birth, 9% of them required intensive special education services, 42% of them required some level of special education services, and 15% of them were at risk for needing additional special education resources as

the educational curriculum became more challenging. Therefore, extremely low birth weight infants constitute a very high-risk population that is in need of support resources and systems of family-centered coordinated care after experiencing life-threatening neonatal illness. By focusing on children who experience the double jeopardy of an extremely preterm birth and poverty during early childhood, this study considers the interplay between the social and biological factors that influence a family’s ability to access developmental healthcare resources.

METHODS

From 2008 to 2014, the University of Chicago Hospitals enrolled 279 extremely low birth weight infants in a clinical trial consisting of two dosing schedules of inhaled nitric oxide for the purpose of evaluating the extent of conferred neuroprotection. Developmental status and provided services were documented for all patients within this “NOVA II” cohort. The patients within this cohort compose this study’s patient population.

Clinical Intuitions Study

The clinical intuitions study is an ongoing study directed by Dr William Meadow at the University of Chicago Hospitals. This study collects data on medical staff members’ longitudinal intuitions on infant mortality and morbidity and the extent of neurodevelopmental impairment in the Neonatal Intensive Care Unit at Comer Children’s Hospital. These infants require mechanical ventilation and have been enrolled in this study with parental consent. Nurses, residents, nurse practitioners, fellows, and attending physicians are asked the questions in Table 1 while the infant is ventilated in the NICU. To analyze these intuitions, the worst intuition on any given day was assigned a numerical score, excluding low-level confidence predictions (see Table 2). In most cases, this method provides an accurate demonstration of each patient’s predicted status; however, for a select few patients, the worst intuition was an outlier.

Table 1. Clinical intuitions study survey questions

Q: Do you think that the patient will live to go home with their family, or die before they are discharged from the hospital?
A: Live/Die
Q: How confident are you about your answer?
A: Low/Medium/High
<i>If staff member predicts that the patient will live to discharge, continue to next question.</i>
Q: Do you think that the patient will experience neurological delays?
A: None/Mild/Moderate/Severe
Q: How confident are you about your answer?
A: Low/Medium/High

Table 2. Clinical intuitions study scoring

• 0 – no impairment predicted
• 1 – mild impairment predicted
• 2 – moderate impairment predicted
• 3 – severe impairment predicted
• 4 – death before discharge predicted once
• 5 – death before discharge predicted by more than one healthcare team member on a given day
• 6 – death before discharge predicted by all healthcare team members on a given day

Table 3. Gender

Sex	%, n=131
Male	56.5
Female	43.5

Table 4. Race

Race	%, n = 130
Black	68.5
White	19.2
Hispanic	12.3

Table 5. Income

Income	%, n = 128
<\$30,000	21.9
\$30,000-40,000	19.6
\$40,000-50,000	14.8
\$50,000-60,000	9.4
\$60,000-70,000	18.0
>\$70,000	16.4

Table 6. Infant prematurity

	Mean, n = 131	SD
Gestational Age (Weeks)	25.9	1.8
Average Birth Weight (Grams)	784	200

Table 7. Early intervention (EI) access

Access to EI	%, n = 128
None	28.9
Inadequate	21.9
Adequate	49.2

The NOVA II trial and the clinical intuitions study were conducted in the same NICU at Comer Children's Hospital, and the patients who were enrolled in both studies are the subjects of this analysis. The sample consists of 131 extremely low birth weight (<1000 g) infants (mean gestational age: 25.9 weeks, SD: 1.8 weeks; mean birth weight: 784 grams, SD: 200 grams) (see Tables 3-8).

The Bayley Scales of Infant and Toddler Development is a standard assessment that evaluates a child's developmental status. The Bayley Scales of Infant and Toddler Development scores (see Table 9) were obtained through the NOVA II trial data and are included in order to validate the clinical intuitions scores. To do so, a linear regression evaluating the relationship between the Bayley scores and the clinical intuitions scores was performed, resulting in a significant and positive relationship that aligns the two measures of development (coefficient: 0.53, p-value: 0.05). For this regression, it was important to consider all three of the Bayley measures of development—cognitive, motor and language—and thus each infant was assigned a score that reflected the number of measures out of the three in which the child scored below a score of 85 (one standard deviation below the mean score of 100).

Therefore, although predictions from the clinical intuitions study are collected during the infant's first few months of life, they do have the power to predict neurodevelopmental outcomes for critically ill infants. Additionally, researchers from the University of Chicago have noted the predictive power of these clinical intuitions [13].

Table 8. Clinical intuitions study

Clinical Intuitions Score	%, n = 121
0	1.7
1	7.4
2	46.3
3	17.4
4	17.4
5	0.8
6	9.1

Table 9. Bayley Scale of Infant and Toddler Development Scores

Bayley Scale of Infant and Toddler Development Category	% scored < average, n = 90	% scored < 1 SD below average, n = 90
Cognitive	60%	37%
Language	74%	30%
Motor	63%	27%

Family Income

Family income was estimated based on the family's full address using 2010 U.S. census data. The family's full address as of January 2016 was entered into the FFIEC Geocoding/Mapping System to determine the 2010 median family income for each tract [14].

Access to Early Intervention Services

Physician notes in electronic health records were examined from the time of admission to the most recent physician note entry. These notes provide the primary care physician's assessment of whether or not the child received EI services and the extent of services received. Medical staff members including neonatologists, pediatricians, social workers, and speech pathologists referred all patients and families to early intervention services. Patients received a "0/None" if no EI services were received, "1/Inadequate" if a portion of indicated services were received but a clinician noted that the child or the family's needs were not being met, and "2/Adequate" if all referred services were received without undue complications. In order to run linear regressions, EI access codes were categorized into two groups: 1) adequate receipt and 2) not adequate receipt (none or inadequate).

Data Analysis

Logistic regressions and models were produced using StataSE 13. The model adjusts for sex, race, predicted neurodevelopmental impairment (clinical intuition score), and birth weight. Gestational age was originally included as a control but was later omitted due to collinearity concerns. Gestational age, birth weight, race, and sex were obtained from electronic health records. Studies demonstrate that race and sex are significantly related to receiving EI services, and children with delays are seven times more likely to receive services than children without delays [11].

RESULTS

Out of 128 families, 21.9% had a median family income below 150% of the 2016 federal poverty line for a household of three people [15]. The sample's demographics largely replicate those of the community surrounding the University of Chicago (see Tables 3-7). We hypothesized that family income and the extent of developmental delay would affect EI access with higher incomes and more severe delays being associated with a greater likelihood of receiving adequate EI. We found that for every \$10,000 decrease in median family income, the odds of receiving access to adequate EI services are decreased by 24% ($p = 0.025$). Figure 3 further illustrates the significant discrepancy in access by family income. The probability of receiving adequate EI services is 37% for families with a median income of \$20,000; in contrast, for a family with a median income of \$140,000, the probability of receiving adequate EI rises to 86%. Therefore low-income families with babies who 1) were extremely low birth weight and thus were at high risk for developmental delays; 2) received referrals to early intervention services; and 3) are in fact experiencing developmental delays (see Tables 8-9 for Bayley and clinical intuition scores) are not receiving adequate access to early intervention services. It is also worthwhile to note that even for a median family income of \$80,000, the probability of receiving adequate EI services is still only 65%. Furthermore, approximately half of the children in this sample did not receive adequate EI (see Table 7).

Predicted neurodevelopmental impairment (clinical intuitions scores) did not have a significant effect on access to adequate EI services. Among those who did not receive any EI services, 19% of them were predicted to have greater levels of neurodevelopmental impairment, whereas among those who received inadequate services, 64% were predicted to have greater levels of neurodevelopmental impairment (see Figure 4). The infants' clinical intuitions scores are concentrated around scores of 2, 3 and 4 (moderate impairment, severe impairment, and death before discharge predicted once, respectively). Both the clinical intuitions scores and the Bayley scores demonstrate that these extremely low birth weight infants are experiencing developmental delays.

For male children, the odds of receiving adequate EI services are decreased by 62.8% compared to female children ($p = 0.024$).

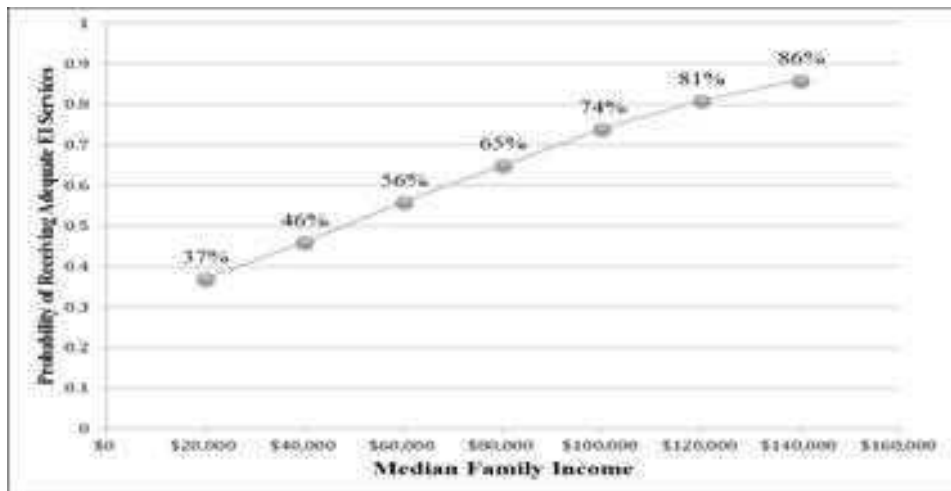


Figure 3. Access to early intervention services by median family income.

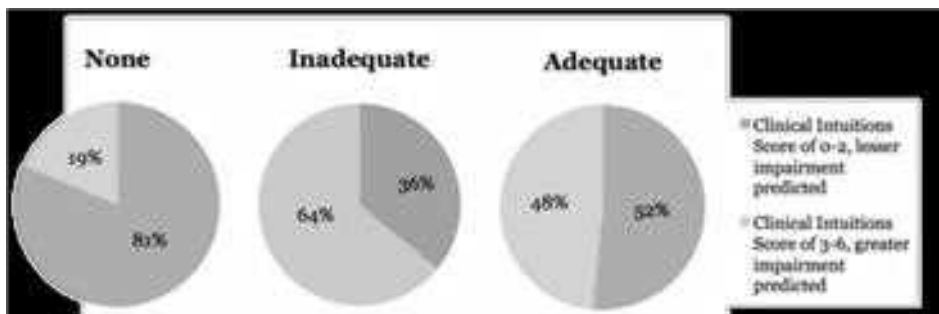


Figure 4. Access to early intervention services by clinical intuitions score.

DISCUSSION

This paper evaluates access to state-provided early intervention services for extremely low birth weight infants, specifically focusing on the relationship between family income and access to early intervention services. At the time of discharge from the NICU, there are

numerous social and public factors that impact how NICU ‘graduates’ access community support services. Early intervention programs take advantage of the crucial window of early childhood brain development, and recent studies suggest that interventions during the first few years of life play an integral role in mediating the health and educational disparities that low-income children experience in settings of high biomedical or social risk. Trajectories of developmental delays can widen during middle childhood and adolescence, setting the stage for lifelong physical, behavioral, and social health challenges. The consequences of these missed opportunities for secondary developmental prevention significantly impact the child, family, and community. Given our financial and societal constraints, developmental healthcare resources must comprehensively target those who are most vulnerable; specifically, our enabling efforts must prioritize children experiencing social disadvantage and who are at the highest biomedical risk for developmental delays or disabilities. The Bayley assessments provide valuable developmental information, but caretakers gain this information at a time when it is much harder to mobilize services. Bayley assessments are typically conducted between 18 and 24 months of age, leaving approximately one year for families to navigate the EI system (see Figure 2) and to start using EI services before their children age out of the system at 3 years of age. With the data from the clinical intuitions study, physicians and families may have an understanding of the delays that a child will have going into early intervention. Additionally, infants who are especially at risk may be identified well before they leave the NICU.

Biological Factors and Developmental Healthcare Resources: Prematurity

With 1 in every 10 US births being preterm, it is valuable to consider how we might use early interventions to manage the potential consequences of an early arrival [17]. Although preterm infants have an increased mortality rate, most neonates survive but experience a range of health and developmental adverse effects. Preterm infants face an increased chance of developmental delays, breathing problems, vision problems, and hearing impairments [17]. These issues only intensify as birth weight decreases [3]. The prevalence of preterm birth combined with the increased risk of physical and mental complications compels us to offer services, such as early intervention, that help families and children cope with the effects associated with prematurity. For the most part, experts have not discovered specific physiological mechanisms through which preterm labor occurs, so researchers have put their energy toward identifying risk factors. Various factors such as having a low-income, a lack of education, experiencing unemployment, or having limited support networks may put mothers at risk for preterm labor [1]. Race is also a significant risk factor, as almost 17% of black babies are preterm compared to less than 10% of white babies [1].

Social Factors and Developmental Healthcare Resources: Family Income

Social factors strongly influence a child’s developmental progress and existing social structures can make it nearly impossible for families to sufficiently support their child’s developmental growth. These challenges may lead to decreased kindergarten readiness rates,

suboptimal educational achievement on standardized assessments as part of the No Child Left Behind Act and decreased high school graduation rates and attendance at community college. Furthermore, there are often decreased life course outcomes in employment, income, and social independence. A study from the Center on Children and Families at Brookings Institution examines the relationship between family income level and the percentage of children who were school-ready by the age of five. Only 48% of children from poor families were kindergarten-ready, whereas 75% of children from moderate or high-income families were kindergarten-ready [18]. This 27-percentage point difference demonstrates that low-income families face more challenges regarding their child's developmental trajectory. Importantly, the age at which a child experiences poverty matters: poverty experienced during the first five years of life strongly influences the number of school years a child may complete. Poverty experienced after age five has a significantly smaller impact on school completion [19]. For low-income families with a child below the age of five, a \$10,000 increase in mean family income allowed for nearly one additional school year to be completed [19]. This crucial early childhood window demands that developmental health and educational resources are provided to high-risk children as early as possible.

Intensifying these considerations, poor neighborhoods may be less socially organized and are often complicated by issues such as high crime and school dropout rates as well as low employment rates [20]. All of these factors influence development, and this reality is only worsened by the lack of resources in poor neighborhoods such as limited access to day care programs, museums, libraries, playgrounds, healthcare facilities, and after-school programs [21]. These multidimensional and complex issues reveal a susceptible population that needs appropriate early interventions in order to provide the best support and care possible. With this in mind, early intervention becomes a critical source of support that can prepare children with delays or disabilities for success, especially among low-income populations. Although all children should receive the best education and healthcare possible, low-income families experience compounding risk factors that make them especially vulnerable to the cycle of disadvantage (see Figure 1) since poverty intensifies and reinforces the problems that are associated with healthcare and educational disparities.

Gender and Developmental Healthcare Resources

Male preterm infants experience worse developmental outcomes than female preterm infants, and male sex is a risk factor for poor neonatal, neurological, and respiratory outcomes [16]. Janet Peacock et al. [16] reported that some level of disability was present in 53% of preterm males compared to 39% of preterm females at 24 months of age. Considering this, it is particularly concerning that male children have more difficulty accessing adequate EI services (see Figure 5). Hintz et al. [23] asserts that worse neurodevelopmental outcomes in males are likely due to unmeasured biological variables. However, the discrepancy in access to EI for male children may call for a reanalysis: perhaps the lack of developmental support for male children plays a role in the developmental disadvantage that male infants experience, which adversely impacts this population throughout adolescence and adulthood.

Barriers to Early Intervention Services

Considering the numerous steps that families must go through to receive EI services (see Figure 2), the process can become quite complicated, often resulting in a failure to provide or receive services. Jimenez et al. [22] identified barriers to early intervention services by interviewing EI employees, families with EI referrals but who were not evaluated, and families with EI referrals but who were evaluated. Five main themes emerged: 1) parents described communication problems with their pediatrician; 2) many parents believed that they were the best judge of their child’s development, and thus they should be the ones to decide whether or not their child received services; 3) some parents wanted to wait and see how the child’s development progressed without services; 4) practical obstacles caused ambivalent parents to stop the EI process; and 5) EI employees expressed that they believe families avoid evaluation since they mistake EI employees for child protective services [22]. These perceived and real barriers, although substantial, may largely be resolved through improved communication between all of the involved actors (families, healthcare providers, and EI employees). It also seems that physicians may play a profound role in improving access since many families did not agree with their primary care provider’s decision to refer their child to EI. Among families who were not evaluated by an EI caseworker, 63.6% were in denial or disagreement about their child’s EI referral, whereas out of those who were evaluated, 18.2% were in denial or disagreement [22]. This suggests that working with families to illustrate the benefits of EI and explaining the reasons for referral will help children to receive the necessary services.

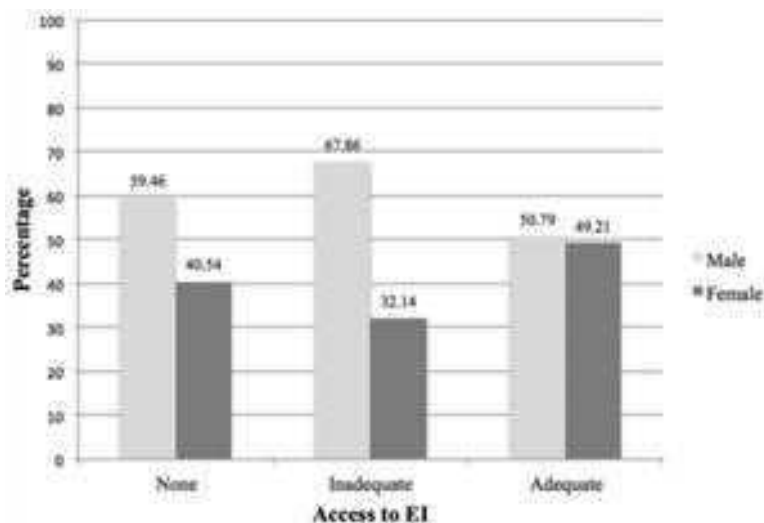


Figure 5. Access to early intervention services by gender.

Practices to Improve EI Service Delivery

All of the babies in this sample spent a number of months in the NICU before they could be discharged from the hospital. This provides an opportunity to ensure that families fully

understand the benefits of EI services and to guide them through the EI process. During their time in the NICU, families have easy access to physicians, nurses, and social workers who can and should help families connect to early intervention centers. In an attempt to guarantee that the highest-risk infants have access to services as soon as possible, the EI process should begin before the infant is discharged from the NICU.

According to Dr Bree Andrews, a neonatologist and the director of the NICU follow-up clinic at Comer Children's Hospital, EI caseworker reluctance to visit specific neighborhoods can substantially impact a family's ability to receive services [24]. Understandably, caseworkers may refuse specific cases out of concern for their own safety or comfort level. Although this is a reasonable feature of the program's organization, it means that families who live in certain neighborhoods have fewer caseworkers available to them, posing a serious threat to EI access. To moderate this issue, EI centers may co-localize services—a vast majority of infants who need EI require more than one type of service (i.e., both speech and physical therapy). These services may be packaged and delivered together, at the same time, in the same place. This could help with the issue of caseworker safety, but it would also relieve some of the burden that multiple EI appointments often place on busy families.

National Early Intervention Standards

Because early intervention systems are not standardized on the national level, EI organization and distribution varies by state. This federally granted freedom has led to significant differences in state eligibility criteria. For example, this paper examines at-risk infants; however, most states do not offer services for children who are at-risk, instead, these states only provide services to those who have diagnosed delays or disabilities [5]. This analysis shows that many high risk children require EI, and it seems most likely that these children would be overlooked in a state with less generous eligibility requirements than Illinois's. With a standard set of eligibility requirements that fully acknowledge the impact that EI services can have, more children may receive the appropriate developmental support.

Effectively Allocate Our Limited Resources

Early intervention funding increased from \$81 million in 2002 to \$146 million in 2009; however, from 2009 to 2013, funding has remained relatively stable [25]. Correspondingly, the number of Illinois children served increased from 11,100 children in 2002 to 19,100 in 2009 [25]. From 2009 on, the number of children served by EI has remained constant, mirroring the stagnant post-2009 funding levels [25]. EI funding has failed to account for both inflation and need, leading to an increase in the number of children who need EI but who are not receiving it. The Illinois state budget crisis puts EI programs in constant jeopardy, as EI centers are commonly unable to pay their employees for extended periods of time.

With our current resource limitations, there must be mechanisms in place to ensure that the neediest families are receiving services. This begins by ensuring that families are connected to an EI center before they leave the NICU, but it must extend further toward a cultural shift and a broad acknowledgement of the barriers to access for low-income families.

This data urges us to allocate more of our limited resources to families and infants who are underserved and thus are combatting a multiplicity of health and educational disparities. This engagement and this advocacy process will lead to improved developmental and educational outcomes.

Study Limitations

There are some limitations in generalizing this data since it was conducted in only one hospital system, Comer Children's Hospital at the University of Chicago, and healthcare practices vary by hospital and EI center. In addition, the sample is largely African American (68.5%) and though it reflects much of the concentrated minority status in Chicago, it may not be nationally representative across other urban centers.

CONCLUSION

Through linear regression analysis, we found that for every \$10,000 decrease in median family income, the odds of receiving access to adequate EI services are decreased by 24%, suggesting that low-income families face barriers to services that reach beyond physiological need alone. Male infants also experience discrepancies in access—their odds of receiving adequate EI services are decreased by 62.8% relative to female infants. Predicted neurodevelopmental impairment did not have a significant effect on EI access; however, these clinical predictions may account for the social factors that shape a child's life after they are discharged from the hospital in addition to giving healthcare professionals an early signal about the delays that the child may experience.

This disparity in access reflects a need to have more proactive engagement and support for vulnerable children and families. To try to do this, there must be improved family-centered engagement practices including better coordination and involvement of EI professionals, NICU discharge planners, and pediatricians. Poverty and prematurity feed into and nourish a cycle of environmental health disparities. This cycle travels from poverty to limited resources to premature birth, forcing the next generation of parents and their children into a disadvantaged reality. Figure 1 illustrates this cycle of disparity and illuminates the compounding factors that affect a family's ability to access services. Despite these families' need for support, this paper demonstrates that low-income families are not receiving the necessary and comprehensive developmental healthcare services to which they are entitled.

With the demonstrated discrepancy in access, EI and healthcare professionals, policymakers and families must work in tandem to acknowledge this problem, identify barriers to receiving services, and discover mechanisms to overcome these barriers. By considering a child's developmental needs as early as possible, physicians can proactively help families work with their children to optimize neurodevelopmental outcomes. This consideration must begin while the critically ill child is in the hospital and continue after hospital discharge when low-income families with infants who are extremely high risk need the highest level of family-centered support and care coordination.

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Chapter 17

AN ECOLOGICAL MODEL OF HEALTH CARE ACCESS DISPARITIES FOR CHILDREN

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ABSTRACT

The southern region of the United States (US) is home to approximately 20% of the US total pediatric population. Previous research has shown that children in the South experience higher poverty and poorer health outcomes, including higher rates of infant mortality, asthma, and obesity. Access to health care and utilization of preventive medical services are both essential determinants for the well-being of children and youth in the United States. Additionally, the local neighborhood environment has also been shown to be associated with child health and access to health care. Poverty, southern residence, and adverse community characteristics may serve as compounding risk factors for children's access to health care. In order to explore this issue, we analyzed data from the 2011-12 National Survey for Child Health. The primary measures of access to care include having a medical home, preventive medical visit a preventive dental visit. The multivariate logistic regression models included covariates of individual sociodemographic and health characteristics. Poverty, southern residence, unsupportive neighborhoods, measures of built environment, and community marked by decay were independently associated with worse access to health care, after adjusting for all other covariates. Children from low-income households who also live in southern communities

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with disadvantaged characteristics experience multiple factors undermining their access to health care. In order to help break the cycle of disadvantage, an ecological model should be used to guide future interventions for improving access to comprehensive health care services for all children.

Keywords: health care access, medical home, preventive care, health care utilization, poverty, geography, neighborhood environment

INTRODUCTION

Access to health care and utilization of preventive medical services are both essential determinants for the well-being of children and youth in the United States (US). Improving access to quality health care services and promoting timely and appropriate use of preventive services can allow children and youth to achieve the best health outcomes and achieve their full potential [1]. In the past two decades, public health insurance programs, including the enactment of the State Children's Health Insurance Program (SCHIP) initiative and the expansion of the Medicaid program, have expanded insurance coverage for the pediatric populations in the US [2]. Despite these efforts, inequities and disparities in health care access have persisted as a major problem for many American children, especially those from vulnerable and underserved communities.

While a wide range of ecological factors can influence children's access to health care, poverty is often considered one of the most prominent risk factors. The associations between childhood poverty, poor health status, and decreased access to medical care are well documented in the literature [3-6]. In general, children in families living below the poverty threshold are less likely to obtain appropriate health insurance coverage and have a usual source of health care [6]. These children are also more likely to report unmet medical needs and experience more frequent delays of care [7].

Another important factor potentially affecting health care access is geography. The influence of geographic variation in health care access, which is less frequently examined in population health research, is often overshadowed by racial and ethnic disparities [8]. Nevertheless, some researchers argue that regional differences may contribute to a significant portion of the overall health disparities in the US [9, 10]. Home to approximately 20% of the US pediatric population, the South is a distinct geographic region in the United States. The unique identity of the South is brought by its history of racial segregation and discrimination, religious values and traditions, and social conservatism. More importantly, the region has experienced persistent disparities in both poverty and health care for children. Compared to other regions, the South has consistently had the highest child poverty rate in the country [11]. National data provide evidence of regional health disparities for children in the South, including higher rates of infant mortality, childhood asthma, and obesity [12-15]. Additionally, a previous study indicated that living in this region is a strong predictor of poor child health outcomes [10].

In addition to the macro level of regional geographic variations, the local community and neighborhood characteristics are considered micro level of geography which are also important socioecological determinants of children's physical health and their access to care. Researchers have found that the local built environment, such as parks and recreational

facilities, is associated with both increased child physical activity and lower rates of obesity [14, 16, 17]. Another dimension of neighborhood is the social connectedness as measured by human capital and social cohesion. Studies have demonstrated significant associations between parental perceptions of the cohesion and safety of their neighborhood and their children's access to a medical home [18].

While current research has identified disparities in child health outcomes related to poverty, geographic region, and neighborhood characteristics independently, few studies have investigated the combined impact of these risk factors. Furthermore, to our knowledge, none have studied poverty and geography in relationship to children's access to care in the context of preventive care utilization and the presence of a medical home. Using an ecological framework called "Break the cycle" [25], this study examined the role of poverty and geography (as measured by Southern U.S residence and local community characteristic of social cohesion and the built environment) while adjusting for health insurance and other socio-demographic and health status characteristics. The findings of this study will help advance knowledge and understanding of the ecological characteristics and barriers of access to care for the pediatric population in the South. The results of the analyses will help raise awareness and support the development of region-based health interventions that aimed at breaking the cycle of environmental and other child health disparities in the South.

METHODS

Our study is built upon the ecological model of "Break the cycle" created by colleagues at Southeast Pediatric Environmental Health Specialty Unit in Atlanta, GA (see Figure 1). The model takes a systematic approach to understanding the interconnectedness between social, economic, and environmental risk factors as related to health care disparities among children. It posits that the personal socioeconomic circumstances, compounded by environmental disadvantages, can lead to limited access to social and health care services for children, and as a result, increasing their chances of having developmental disabilities and other chronic medical conditions. Children who fall short of their full potentials and well-beings may ultimately encounter further issues and disadvantages as they transition into adulthood, as the cycle continues. This ecological framework offers a creative guidance to address health care challenges by looking broadly at various factors on both individual and community level, and by doing so to break the cycle of disadvantages [25].

Data Source

This study used cross-sectional data from the 2011-2012 National Survey of Children's Health (NSCH). The NSCH is a national population-based telephone survey designed and conducted by the National Center for Health Statistics at the Centers for Disease Control. The survey generates a broad range of information about children's health and well-being to help guide healthcare providers, researchers, advocates, and policymakers. Using a random-digit-dial sample of both landline telephone and cell phone numbers, the survey identified and sampled households with one or more children under 18 years old. Within each household, a

parent or guardian was interviewed about a child randomly selected in the family. A total of 95,677 surveys were collected nationally for the 2011-2012 NSCH with each state having at least 1,800 completed surveys. The survey results were adjusted and weighted to represent the demographic composition of non-institutionalized children 0-17 nationally [24].



Figure 1. Breaking the cycle at two locations.

Measurements of Health Care Access

Access to care was measured by three dichotomous variables: having a preventive medical care visit in the past 12 months, having a preventive dental care visit in the past 12 months, and receiving care in a medical home. The medical home measure used in NSCH is consistent with the definition developed by the American Academy of Pediatrics (AAP) and includes five sub-components: having a usual source of care, having a personal physician or nurse, receiving all needed referrals for specialty care, receiving needed help coordinating care between multiple providers, and receiving care that is family-centered and culturally sensitive. Respondents were required to meet all five sub-components to qualify as attaining a medical home.

Key Predictors

The main predictor variables were poverty, southern residence, and community characteristics. Poverty is defined as below 100% of the Federal Poverty Level. The household poverty level was imputed from reported family income and size by the NSCH with standards based on Department of Health and Human Services (DHHS) guidelines. The operational definition of the South is from the study by Goldhagen and his colleagues in 2005, where they found significant disparities in children’s health outcomes in nine southern states as compared to other regions of the United States [10]. The Goldhagen’s definition of the South includes these following states: North Carolina, South Carolina, Georgia, Florida,

Alabama, Mississippi, Louisiana, Arkansas, and Tennessee [10]. Children who live in one of these nine states are identified as living in the South while those living outside of these states are considered “Non-South.”

The NSCH includes several questions to assess community characteristics based on the parents and guardians’ perceptions of their children’s neighborhood environment. Our study included the following factors: supportive neighborhood, positive built environment, and community marked by decay. These community environment measurements in the NSCH survey were originally developed and used in other social surveys and were derived from validated measures [18].

Supportive neighborhood also refers to social cohesion or social capital in various contexts. This variable was measured by responses to four statements: 1) People in my neighborhood help each other out; 2) We watch out for each other's children in this neighborhood; 3) There are people I can count on in this neighborhood; 4) If my child were outside playing and got hurt or scared, there are adults nearby who I trust to help my child. The parent or guardian of the child was asked about the level of their agreement to each statement, ranging from strongly agree to strongly disagree. Item responses were then imputed in a numeric scale between zero to four and the average is calculated for eligible cases (those who with valid responses to at least three items). The cases with an average score equal to or above the population mean (2.25) qualify as living in a supportive neighborhood.

Positive built environment was characterized by the positive aspects of the physical environment in the neighborhood. Respondents were asked four questions about the presence of neighborhood amenities, including sidewalk, parks/playground, recreational center and library. For this study, only cases with affirmative responses to all four questions met the requirement of having a positive built environment.

Community marked by decay refers to the negative aspects of the physical environment in the neighborhood. The variable was derived from three survey questions on the presence of detracting elements within the community, including litter or garbage, dilapidated housing, or vandalism. Respondents with affirmative response to just one or more of the three questions were considered living in a community marked by decay.

Covariates

Covariates included age, gender, race / ethnicity, insurance status and type, types of family structure (such as two-parents or single-parent), primary language, highest education level of the parent / guardian, the overall health status of the child, and the presence of special health care needs which was identified through the validated Children with Special Health Care Needs (CSHCN) screener tool used in numerous national surveys.

Statistical Analysis

For the entire sample, diagnostic analyses (collinearity, linearity, independent variance) were conducted to assure that the data met all required test assumptions. A descriptive bivariate analysis was conducted for all variables in the model. For all three outcome

variables, weighted percentages were tabulated for each of the main predictors and covariates. Unadjusted chi-square tests were then used to ascertain statistical associations between the independent variables and dependent variables. The independent effects of the main predictors on the outcome variables were evaluated using multivariate logistic regression analyses while controlling for all other confounders. Covariates that were found statistically insignificant were removed from the subsequent analyses. There were less than 15% missing percentage for all given analyses. All statistical tests were conducted using SPSS software (version 23.0). A p-value of less than 0.05 was considered the indication of statistical significant.

RESULTS

Table 1 presents the overall distribution of sociodemographic characteristics and health care access among all children aged 0-17. There were 95,677 cases in the 2011-2012 NSCH, which represents approximately 73 million children in the U.S. Within the weighted study population, 20.4% of children lived in the South. 22.4% of the population are children living below the poverty threshold. In addition, 17.4% of American children reported they lived in an unsupportive neighborhood, 44% lacked positive built environment, and 28.1% lived in community marked by decay. Nationally, 44.1% of the total population of children lack access to a medical home, while 15.5% and 21.4% respectively did not have a preventive medical care visit and dental care visit in the previous year.

Chi-Square Analysis

Table 2 lists the proportion of children with access to a medical home, preventive medical visit and dental visit in the past 12 months according to demographic, socioeconomic, health status, and health insurance. Statistical differences among the percent of preventive care visits and medical home attainment rates are apparent across our main predictors. Prevalence of medical homes was much lower among children below the federal poverty threshold than those above (36.4% vs 59.5%). Children in poverty also reported lower rates for preventive medical visit (78.5% vs 86.1%) and dental visit (68% vs 79.8%). 53.4% of children from the South had access to a medical home, which was slightly less than children in other parts of the US (54.7%). In comparison, children with southern residence also had lower likelihood of attaining either preventive medical visit (82.1% vs 85%) or dental visit (74.4% vs 77.9%).

In addition, all three community indicators are statistically associated with children's health care access. Nearly 38.8% of children who lacked a supportive neighborhood reported having a medical home compared to 58.3% of those living in supportive neighborhood. Children without a supportive neighborhood also had lower rates for preventive dental visit (70.3% vs 78.8%). Similar observations were found in the measure of positive built environment. Compared to children who have positive built environment, those lacking positive built environment reported worse access to medical home (51.4% vs 57.7%), preventive medical visit (82.2% vs 86.6%) and dental visit (75.4% vs 79.4%). Additionally,

only 46.9% of children from a community marked by decay received care from a medical home compared to their counterparts (57.8%). These children were also slightly less likely to have obtained a preventive medical visit (83.8% vs 84.8%) and dental visit (73.6% vs 78.7%) in the past year.

Table 1. Characteristics of the study population of children aged 0–17 years in United States (95,677), National Survey of Children’s Health, 2011–2012

Characteristics	N	%	Characteristics	N	%
Have preventive medical visit in the past 12 m			Age		
Yes	80,586	83.6	0-5 yrs old	29,997	32.7
No	14,337	15.5	6-11 yrs old	31,079	33.2
Have preventive dental visit in the past 12 m			12-17 yrs old	34,601	34.1
Yes	72,299	72.4	Race and Ethnicity		
No	17,941	21.4	Hispanic	12,682	23.0
Have a medical home			White, non-Hispanic	61,381	51.1
Yes	56,257	52.7	Black, non- Hispanic	8,875	13.2
No	36,493	44.1	Multi-racial/Other, non-Hispanic*	10,446	10.0
Southern Residency			Highest Educational Level		
Yes	16,745	20.4	Less than high school	12,837	19.1
No	78,932	79.6	High school graduate	30,691	29.8
Poverty Status			More than high school	46,688	43.5
Poor	14,928	22.4	Family Structure		
Non-Poor	80,749	77.6	Two parent-biological/adopted	66,287	64.6
Live in Supportive Neighborhood			Two parent-step family	6,563	8.6
Yes	80,333	79.7	Single mother-no father present	15,113	18.7
No	13,136	17.4	Other family type [†]	6,549	6.6
Have a Positive Built Environment			Type of Insurance		
Yes	49,270	51.8	Private Insurance	63,079	56.5
No	43,354	44.0	Medicaid/SCHIP	27,381	36.5
Live in Community Marked by Decay			Uninsured	4,040	5.5
Yes	25,627	28.1	Overall Health Report		
No	68,254	69.7	Excellent/Very Good	83,895	84.1
Gender			Good	9,269	12.7
Male	49,219	51.1	Fair/Poor	2,392	3.2
Female	46,349	48.8	CSHCN		
Primary Language			Yes	19,687	19.8
English	88,163	84.4	No	75,990	80.2
Language other than English	7,451	15.5			

*Non-Hispanic children reporting only one race category of Asian, American Indian, Alaska Native, Native Hawaiian, or Pacific Islander, or who are more than one race (multi-racial) are grouped as "Multi-racial/Other, non-Hispanic" because of small sample sizes in many states. [†]Households identified as having two mothers of the same type (biological, step, foster, or adoptive) were classified as "other family type."

Results of the unadjusted chi-square analysis showed the children of minority race or ethnicity (versus white) have lower access across all three measures. Children from families whose primary language was not English were dramatically less likely to have a medical home than children with families where English was primarily spoken (26.5% vs 59.3%); in addition, their likelihood of having a preventive medical visit within the past year was also lower (77.2% vs 85.7%). Only 27.8% of uninsured children had access to a medical home compared to those with public (43.9%) and private (64.0%) insurance. These large discrepancies related to insurance type were also present for preventive dental visits (uninsured 47.7% vs public 73.5% vs private 82.5%). More than 62% of children of parents with more than high school education received care in a medical home, compared to less than 39% of children of parents with below high school education. Interestingly, although children

with the special health care needs were reported to have higher rates of preventive medical and dental visits, they were less likely to have a medical home when compared to children without special health care needs (46.8% vs 56.3%).

Table 2. Factors associated with access to care among Children 0-17 years in United States (95,677), National Survey of Children's Health, 2011-2012

Variables***	Have a Medical Visit (%)	Have a Dental Visit (%)	Have a Medical Home (%)
Southern Residency			
Yes	82.1	74.4	53.4
No	85.0	77.9	54.7
Poverty Status			
Poor	78.5	68.0	36.4
Non-Poor	86.1	79.8	59.5
Live in Supportive Neighborhood			
Yes	84.7	78.8	58.3
No	84.0	70.3	38.8
Have a Positive Built Environment			
Yes	86.6	79.4	57.7
No	82.2	75.4	51.4
Live in Community Marked by Decay			
No	84.8	78.7	57.8
Yes	83.8	73.6	46.9
Gender			
Male	83.7	76.7	53.4
Female	85.2	77.6	55.4
Primary Language			
English	85.7	78.4	59.3
Language other than English	77.2	70.5	26.5
Age			
0-5 yrs old	89.7	54.3	58.2
6-11 yrs old	82.0	87.6	53.7
12-17 yrs old	81.7	85.1	51.4
Race and Ethnicity			
Hispanic	80.7	73.9	37.2
White, non-Hispanic	86.4	79.7	65.7
Black, non- Hispanic	84.2	75.9	44.7
Multi-racial/Other, non-Hispanic	84.7	73.5	50.5
Highest Educational Level			
Less than high school	79.1	73.4	38.4
High school graduate	83.9	78.5	56.8
More than high school	88.1	79.1	62.5
Family Structure			
Two parent-biological/adopted	85.8	77.4	58.6
Two parent-step family	80.4	81.8	49.6
Single mother-no father present	83.4	75.1	45.3
Other family type	79.9	74.6	47.4
Type of Insurance			
Private Insurance	87.8	82.5	64.0
Medicaid/SCHIP	84.1	73.5	43.9
Uninsured	53.7	47.7	27.8
Overall Health Report			
Excellent/Very Good	85.1	78.1	58.4
Good	80.2	72.2	34.9
Fair/Poor	82.2	73.8	23.1
CSHCN			
Yes	90.6	83.1	46.8
No	82.9	75.6	56.3

***All results are statistically significant at $p < 0.001$.

Multivariate Logistic Regression Analysis

Table 3 presents adjusted odds ratios, 95% confidence intervals and p-values from the multivariate analysis of the factors that influence children's health care access. After the adjustment for covariates, poverty remained as a significant factor for health care access. Compared to those who are not in poverty, children from families below poverty threshold were less likely to have a preventive dental visit in the past year (OR = 0.74, $p < 0.001$), less likely to have a preventive medical visit in the past year (OR = 0.79, $p < 0.001$, and less likely to have access to a medical home (OR = 0.82, $p < 0.001$). Southern residence also had an independent effect on health care access. Compared to children living outside of the southern region, children from the South were less likely to have a preventive medical visit (OR = 0.86, $p < 0.001$) and a preventive dental visit (OR = 0.94, $p < 0.05$). However, in contrast to the bivariate results, children from southern states had slightly higher odds of having a medical home than those not living in the South (OR = 1.08, $p < 0.001$).

In addition, the multivariate analysis also showed that measures for community characteristics were each directly associated with health care access. Children living in neighborhoods rated as not supportive had decreased odds of access to a medical home (OR = 0.59, $p < 0.001$) and preventive dental visit (OR = 0.78, $p < 0.001$); but no significant relationship was found with access to preventive medical visit. Children living in communities that lacked a positive built environment were less likely to have a medical home (OR = 0.86, $p < 0.001$), preventive medical visit (OR = 0.81, $p < 0.001$) and dental visit (OR = 0.86, $p < 0.001$) than children living in communities with all four aspects of the built environment. Lastly, compared to children living in communities without decay elements, children living in neighborhoods marked by decay showed lower odds for the attainment of medical home (OR = 0.879 $p < 0.001$) and the receipt of a preventive medical visit (OR = 0.93, $p < 0.001$) and a preventative dental visit (OR = 0.86, $p < 0.001$).

In addition to key predictor variables, other covariates also had individual effects on health care access. Being uninsured, having only public insurance, and low parental educational attainment were all significant risk factors for not obtaining recommended preventive medical visit and dental visit as well as not having a medical home. Race and ethnicity are independently associated with health care access. Adjusting for other factors, children from minority racial and ethnic groups still showed lower odds for the attainment of a medical home, but higher odds of having a preventive medical visit in the past year compared to White children. Statistical significance were found in the direct association between primary language and access to medical home or preventive medical visit but not with dental visit. The presence of special health care needs was associated with higher likelihood of getting timely preventive medical visit and dental visit, but was associated with a lower odds of access to a medical home.

DISCUSSION

Utilizing data from a nationally representative sample of families and children, we found that children were less likely to have access to timely preventive health care if they are poor, living in the South, and come from neighborhoods characterized as unsupportive, lacking a

positive built environment or marked with decay. These associations remained independently significant even after controlling for demographic, socioeconomic, health status and health insurance characteristics of the children and their families. Therefore, our study provides additional evidence that poverty and both macro and micro geographic characteristics are important factors in supporting equitable access to care for all children.

Table 3. Adjusted rates for health care access among children aged 0–17 years in United States (95,677), National Survey of Children’s Health, 2011-2012

Variables	Have a Medical Visit		Have a Dental Visit		Have a Medical Home	
	aOR	95% CI	aOR	95% CI	aOR	95% CI
Southern Residency (Reference = No)						
Yes	0.86***	0.82-0.91	0.94*	0.89-0.98	1.08***	1.04-1.12
Poverty (Reference = Non-Poor)						
Poor	0.79***	0.74-0.84	0.74***	0.70-0.79	0.82***	0.78-0.86
Live in Supportive Community (Reference = Yes)						
No	0.96	0.91-1.02	0.78***	0.73-0.82	0.59***	0.56-0.61
Have Positive Built Environment (Reference = Yes)						
No	0.81***	0.77-0.84	0.86***	0.83-0.89	0.86***	0.84-0.89
Live in Community Marked by Decay (Reference = No)						
Yes	0.93**	0.89-0.98	0.86***	0.82-0.90	0.79***	0.77-0.82
Gender (Reference=Male)						
Female	1.08***	1.04-1.13	1.11***	1.07-1.16	1.07***	1.04-1.10
Primary Language (Reference = English)						
Language other than English	0.80***	0.73-0.87	0.97	0.89-1.06	0.41***	0.38-0.44
Age (Reference=0-5 yrs old)						
6-11 yrs old	0.39***	0.37-0.41	8.67***	8.23-9.12	0.82***	0.79-0.85
12-17 yrs old	0.42***	0.40-0.44	7.01***	6.68-7.36	0.72***	0.70-0.75
Race and Ethnicity (Reference=White, non-Hispanic)						
Hispanic	1.13**	1.05-1.21	1.08*	1.01-1.16	0.69***	0.66-0.73
Black, non- Hispanic	1.26***	1.17-1.36	1.06	0.99-1.14	0.59***	0.56-0.63
Multi-racial/Other, non-Hispanic	0.96	0.90-1.03	0.89***	0.83-0.94	0.68***	0.65-0.72
Highest Educational Level (Reference=More than high school)						
High school graduate	0.82***	0.78-0.85	0.95*	0.91-0.99	0.93***	0.90-0.96
Less than high school	0.76***	0.72-0.81	0.89***	0.84-0.95	0.82***	0.78-0.86
Family Structure (Reference = Two parent--biological/adopted)						
Two parent-step family	0.88***	0.81-0.94	0.81***	0.75-0.88	0.82***	0.78-0.86
Single mother-no father present	0.95	0.90-1.01	0.87***	0.82-0.92	0.88***	0.84-0.91
Other family type	0.82***	0.76-0.88	0.74***	0.69-0.81	0.79***	0.74-0.84
Type of Insurance (Reference = Private Insurance)						
Medicaid/SCHIP	0.92**	0.87-0.98	0.89***	0.84-0.93	0.79***	0.75-0.82
Uninsured	0.26***	0.24-0.28	0.20***	0.18-0.22	0.37***	0.34-0.40
Overall Health Report (Reference = Excellent/Very Good)						
Good	0.91**	0.85-0.97	0.72***	0.67-0.77	0.60***	0.56-0.63
Fair/Poor	0.99	0.86-1.15	0.78***	0.68-0.88	0.47***	0.42-0.52
CSHCN (Reference = No)						
Yes	2.24***	2.11-2.38	1.38***	1.31-1.46	0.68***	0.65-0.70

***p < 0.001 **p < 0.01 *p < 0.05. Abbreviations: aOR, Adjusted Odds Ratio; CI, Confidence Interval.

Our study focused on the potential health care access disparities among children living in the southern region as compared to the rest of the US. The results of the multivariate logistic regression analysis demonstrate that children from the South lag behind their peers on both timely preventive medical care visits and dental visits compared to their counterparts outside the south even after adjusting for all other socioeconomic and health factors. However, the southern region is associated with slightly greater adjusted odds for access to a medical home than non-south. The concept of medical home is relatively more complex, subjective and relative to parents' expectations for care. Therefore, the higher rates of medical home attainment in the South could result from potential bias towards overestimation within the rural and poor population that perhaps has lower health literacy.

Why do children in the South have worse access to preventive health and dental visits? Past research has indicated that the receipt of preventive health care services is strongly associated with insurance status [19]. While our analysis controlled for type of insurance (private, Medicaid and uninsured), we did not measure other insurance-related barriers such as the relative payment rates. Southern states have the highest child uninsured rate in the country [15]. Southern states' Medicaid programs (with some exceptions) have some of the lowest reimbursement rates in the country. This is reflected in the fact that all southern states in our study ranked below the US average for Medicaid spending for pediatric enrollees [20]. The combination of low overall insurance rates and lower reimbursement rates are associated with worse access to health providers that decline to accept Medicaid patients or limit the number of Medicaid patients in their practice.

The significant association between child poverty and lack of health care access has been documented in multiple studies [3-6]. Consistent with previous research, our study found that children living below the poverty threshold had worse access to primary healthcare services. Poor children were less likely than their non-poor counterparts to report having a medical home and were less likely to have preventive medical and dental visits in the previous year. While poverty has been a common topic in the discussion of healthcare disparities, it nevertheless is an important driver for other social determinants of health, and as such, it acts as a centerpiece for our research. As stated previously, the child poverty rate has been disproportionately higher in southern states than other parts of the US [11].

Despite a growing interest in the relationship between social environment and health, there are few studies that measure the impact of neighborhood characteristics on health and health care of children. Some studies assess neighborhood environment using individual-level variables, such as personal income and employment status, which may not be sensitive to structural, social and environmental impact of neighborhoods on service utilization [21]. Additionally, we found very few pediatric articles focused on the interplay between community environment and health care access [18, 22], as a majority of research were focused on the adult population. Our study assesses the association between neighborhood characteristics, as rated by the parents, including social supportiveness, built environment, and decay elements in the neighborhood, with children's health care access, which in turn can impact children's health outcomes. We found that the lack of supportive neighborhood and positive built environment, along with the presence of community decay is associated with worse access to medical home and lack of adherence to preventive visits in addition to southern residence and poverty.

What are the mechanisms or pathways that lead to decreased service utilization for children in these neighborhoods? Parents in less supportive neighborhoods may face

increased obstacles to access health care for a number of reasons. Medicaid transportation only allows the parent and the patient in the transport. Parents in unsupportive neighborhoods may lack neighbors who can watch their other children when they need to go to a medical appointment. The distance to health facilities from impoverished neighborhoods is, on average, greater than from more wealthy neighborhoods. In addition, public transportation may be lacking to allow easy and timely access for parents from these neighborhoods. Lack of a built environment, such as sidewalks, may make it very difficult for parents of young children to walk to public transportation. Lastly, communities marked by decay have increased rates of violence, limiting the ability of families with children to leave their homes, especially at night. Our findings underscore the need to foster collaborative relationships among health care providers, families, and community leaders to identify innovated local solutions to improve health care access for children from neighborhoods with disadvantaged characteristics.

The model of “Break the cycle” in our study signifies a new approach of examining the complex interactions of the impact of socioeconomic (poverty), geographic (southern residence) and ecological (community characteristics) factors on children’s health care access. At-risk children may often experience multiple disadvantaged conditions simultaneously, which can lead to serious implications for the health care access. In our study, we found that both micro and macro geography were independently associated with access to care, compounding the effect of poverty. Therefore, poor children in the South who live in neighborhoods which are less supportive, marked by decay and lack dimensions of the built environment can be subject to multiple risk factors that are cumulative and greatly reduce their access to appropriate health care. In previous research it was found that children experiencing multiple risk factors reported 68% lower odds of having a medical home than those with only one risk factor [5]. Combined risk profiles can lead to larger shortfalls in having appropriate access to quality health care for children. These observations suggest that in addition to acknowledging the single, unbiased effect of each risk factor in research, it is equally important to account for the collective influence of multiple characteristics for healthcare access disparities.

There were several limitations in our study. First, we were not able to determine causal inferences from our data due to the cross-sectional nature of the NSCH. In addition, all questions measured in the NSCH were based on parental reports, such as the measurements for medical home, children’s health conditions, and perceptions of social cohesion and community characteristics. The answers provided by parents in the survey are limited by their knowledge and recollection. To minimize such self-report bias and recall bias, future research may consider triangulating parents’ responses with youth and healthcare providers’ responses or other ecologic studies of access to care. Finally, the design of NSCH may have been subject to selection bias as some groups of children are underrepresented or not represented in the survey, including children living in homeless shelters, those in institutional settings, and those without either landline telephones or cell phones.

Despite these limitations, this study has depicted a detailed and comprehensive examination of the persisting disparities in children’s health care access. This research contributes to the existing body of literature on the impact of poverty, southern region, and adverse neighborhood environment for children’s access to quality medical home and utilization of preventive care services. Our findings also demonstrate the need for applying an ecologic framework, such as the Break the Cycle, to understand the interrelationship and

cumulated effects among regional, community, and personal-level characteristics for access to primary care. Utilizing an ecologic framework may help inform policy changes to support greater access to primary health care delivery and encourage the development of ecologic and population-based interventions that aim in breaking the cycle of disparities for children.

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Chapter 18

**GRANDPARENTS RAISING GRANDCHILDREN
WITH DISABILITIES: ASSESSING HEALTH STATUS,
HOME ENVIRONMENT AND IMPACT OF A FAMILY
SUPPORT CASE MANAGEMENT MODEL**

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Elham Laghaie, MS, Fatima Ali, MPH, Shaaz Fareed, BS
and Lilly Immergluck, MD, MS, FAAP***

ABSTRACT

There are 4.2 million households in the United States where grandchildren live with their grandparents. Grandparents who raise grandchildren are at risk for financial strain, poor health outcomes, and poor housing conditions; this is compounded when the grandchildren have developmental disabilities or other chronic medical conditions. We partnered with Project GRANDD (Grandparents Raising And Nurturing Dependents with Disabilities), a program that provides support to grandparents who are the primary caregivers for their grandchildren with disabilities, to determine if family-centered case management, (phone calls, nurse visits, home visits, monthly group meetings, and referrals) had an impact on the grandparents' perception of their own health and their own home environment. We evaluated the impact of the program retrospectively, by reviewing case management documents and prospectively, by administering surveys to grandparents who were enrolled in Project GRANDD. From the 46 grandparents who participated in our study, we determine that Project GRANDD services resulted in overall perceived improved health and home environmental conditions. Specifically, 44 percent of enrolled grandparents reported a health improvement since joining Project GRANDD and 39 percent of grandparents reported an improvement on the condition of their home through the services provided by the program. The potential benefit of this particular family-centered case management model on health and home environment requires

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further exploration and study, but our preliminary study suggests that such a model has a positive impact on the health and wellness for these families.

Keywords: multigenerational, grandparents, grandchildren, disabilities, caregivers, health, environment, condition of home, role strain, family support, case management

INTRODUCTION

Families where grandparents are the primary caregiver for their grandchildren are becoming more prevalent in the US as compared to 30 years ago [1, 2]. In 2012, 4.2 million US households were comprised of grandparents living with grandchildren [3] and 2.7 million grandparents were primary caregivers for their grandchildren under the age of 18 years old [4]. Caring for a child while in a later stage of life requires many adjustments on the part of the grandparent. For example, a grandparent who must tailor a home environment to meet the needs of a grandchild, especially one with a disability, can be challenging financially and emotionally, and thus, be a source of stress (see Figure 1). This, and other stressors can result in feelings of isolation and depression among these senior citizens [1, 5]. Also, grandparents are more likely to need to manage their own health conditions alongside their grandchildren's health; often times, these health conditions (hypertension, heart disease, diabetes, and arthritis) which are more likely to occur in older populations are chronic in nature, and thereby, require more frequent visits to healthcare providers, medications, and limit their mobility. Consequently, managing these chronic conditions along with the needs of their grandchildren, particularly if the children have disabilities, can negatively impact the health and wellbeing of all members of the household [6, 7]. In these situations, elderly primary caregivers have been found to neglect their own health in order to properly care for their grandchildren [7]. Grandparents, many of whom are on a limited and fixed income, must address the added financial burden associated with the care of their grandchildren with disabilities or chronic medical conditions. Costs tied to medical treatment or transportation to medical facilities [8] diverts funds from maintaining the home environment [9].

Innovative Solutions for Disadvantage and Disability (ISDD) is a not-for-profit organization, based in Atlanta, Georgia that supports children, with or at risk for disabilities, from low income, primarily minority and underserved communities [10]. They work with community leaders and support community-based participatory research that helps reduce health disparities among vulnerable children. Project GRANDD, a program of ISDD, uses a family-centered support model to specifically address the needs of grandparents who are the primary caregivers for their grandchildren with disabilities. Educational support, forum to share common experiences with other grandparents in similar predicaments, home visits by trained social workers, and appropriate referrals to legal and other necessary social service agencies are examples of the type of family-centered case management provided through Project GRANDD.

The impact of financial, physical, and mental stressors on the health of grandparents is an issue that deserves serious consideration. The purpose of Project GRANDD is to "break the cycle" of intergenerational disadvantage by reducing stress and improving health outcomes through family-centered case management (Figure 1). In this study, we examined the direct and indirect impact of family-centered case management offered through Project GRANDD

on enrolled grandparents' quality of life, using indicators of their perceived health benefit and the safety of their place of residence.

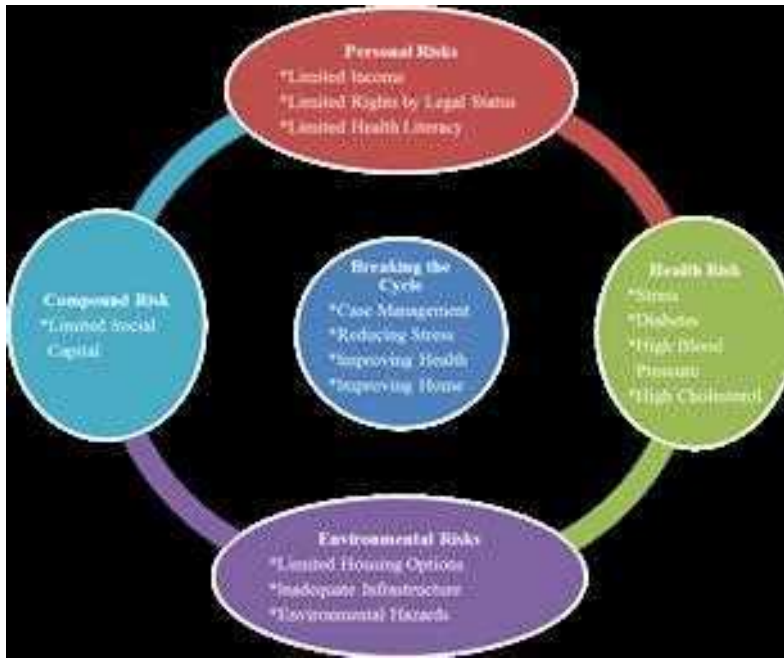


Figure 1. Potential risk factors for grandparents raising grandchildren with disabilities and the impact of Project GRANDD.

METHODS

This study is a cross-sectional survey of grandparents who were actively enrolled in a case management program offered through Project GRANDD.

Study Participants

Grandparents who were members of Project GRANDD and had at least one grandchild with a disability under their direct care were eligible to participate. Participants were required to be residents of the state of Georgia, speak and understand English, and live in a rented or owned property. Active members of Project GRANDD were defined as those grandparents who had consistent contact with program staff through calls, emails, and group meetings since joining the program. Inactive members of Project GRANDD were defined as those grandparents who had joined the program but did not have any further interaction with the program. The active/inactive distinction was made by the staff social worker in Project GRANDD [11].

Recruitment and Enrollment

Letters with information about the study and a notification that contact would be made by research staff were sent both through the US Postal Service and electronically to all members of Project GRANDD. Within 20 days of mailing, study staff telephoned all active and inactive members to inquire about participating in the study.

After informed consent was obtained from the phone call, study staff administered the survey questionnaire through personal phone interviews. The survey questionnaire included demographic information and was divided into two components: a) health survey explored grandparents' medical conditions which and b) home environmental survey assessed the participant's perception of home safety [12]. All information collected was entered into a relational electronic database [13]. A chart review of documents was also conducted incorporating completed intake forms at the time of grandparent entry into Project GRANDD, records of home visits made by the case manager or nurse, written logs of attendance at monthly grandparent support group meetings, any referrals made, and records of all phone contact. Information was collected, beginning at the point of entry into the program through the date of enrollment into the study.

Data Analysis

Standard frequency data (mean, range, and percentile) were determined for various characteristics describing participants. The independent variables consisted of the length of time the participant spent in Project GRANDD and the total number of resources received in the program (e.g., referrals, home visits, phone calls, monthly group meetings, and nurse visits). The dependent variables were self-reported health status, home environment condition status, and the composite score of the environmental survey. The composite score was created from a subset of ten questions taken from the 32-item questionnaire [12]. Odds ratios and corresponding 95% confidence intervals (CI) were calculated for health status, environmental status, and home environment improvement status. Multivariate logistic regression analysis was performed to assess the association between case management and perceived health and home conditions. Statistical analyses were conducted, using SAS Software package (SAS version 9.2) [14].

RESULTS

Of the 120 grandparents in Project GRANDD, 68 were active and 52 were inactive (see Figure 2). From the 68 active and 52 inactive members, 40 active and six inactive members were enrolled into the study. The average age of the grandparents in our study was 61.5 years. Of the 46 participants enrolled in the study, 97.8% [45] of the participants were female and 95.7% [44] of the participants were African-American (see Table 1). The average median household income reported was in the category of \$20, 000 - \$29,000; only one family reported a household income of greater than \$60,000. Seventy-six percent of grandparents reported at least one health condition: hypertension [24], stress [15], diabetes [12], and

hypercholesterolemia [6] (see Figure 3), while 11 grandparents reported having no chronic medical conditions. The average number of grandchildren per household was two (range: 1 – 7) (see Figure 4), and 15 grandparents reported caring for multiple grandchildren, with and without developmental disabilities. Of the 108 grandchildren, the most common disabilities reported among the grandchildren were: Attention Deficit Disorder (ADD), Attention Deficit Hyperactivity Disorder (ADHD) (38.9%), asthma (23.1%), behavioral disorders (23.1%), autism (18.5%), learning disabilities (18.5%), and developmental disorders (15.7%). Twenty-six (24.1%) grandchildren had no associated conditions and 38 (35.2%) had two or more (see Figure 5).

Table 1. Participant’s characteristics

Total Grandparent Participants n = 46		
Variable	Category	n (%)
Age (years)	Mean	61.5
Sex	Female	45 (97.8)
Race	Black*	44 (95.7)
Annual Income	< \$10,000 - ≥ \$60,000**	41 (89.1)
	Unknown/Declined	5 (10.9)

*1 participant: Black/Hispanic; 1 participant: American Indian.

**Average Median Household Income: \$20,000 - \$29,999.

Table 2. Length of time in program vs. health status, environmental status, Environmental Composite Score

Impact of Length of Time in Program	Odds Ratio	95% CI
Health Status	1.08	0.98 – 1.28
Environmental Composite Score	0.99	0.83 – 1.17
Environmental Improvement Status	1.37	1.05 – 1.78

Table 3. Total resources received in program vs. health status, environmental status and Environmental Composite Score

Impact of Total Resources in Program	Odds Ratio	95% CI
Health Status	0.985	0.906– 1.071
Environmental Composite Score	1.014	0.931 – 1.105
Environmental Improvement Status	1.16	1.047 – 1.283



Figure 2. Enrollment scheme for study population.

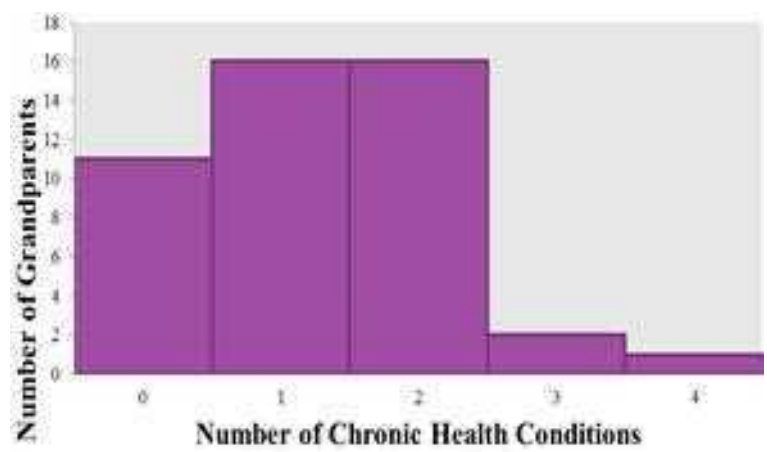


Figure 3. Number of chronic conditions per grandparent.

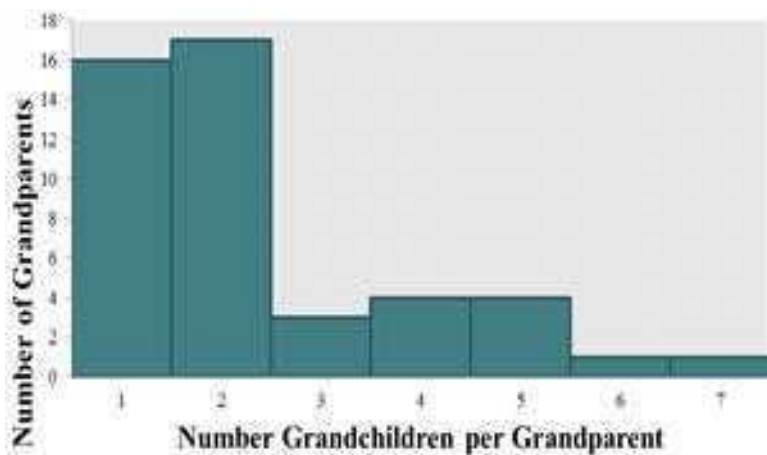


Figure 4. Number of grandchildren per grandparent.

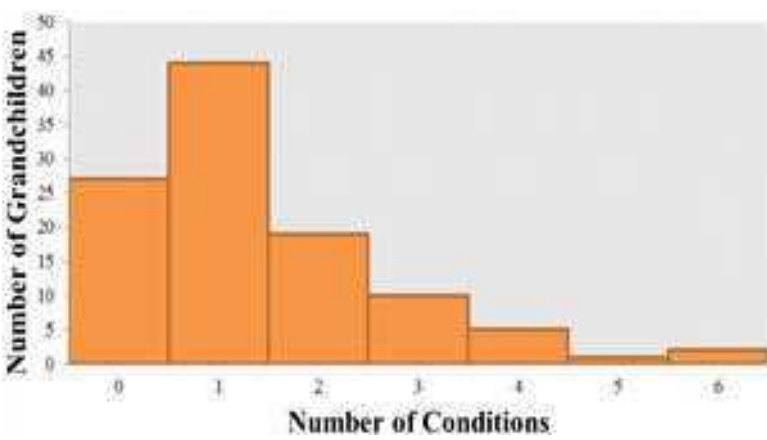


Figure 5. Number of disabilities per grandchild.

Impact of Program

We looked at the association between length of time in Project GRANDD and the grandparent's health and home environmental score. The odds ratio for the health status, environmental status, and environmental composite score were 1.08 (95% CI: 0.98 – 1.28), 1.37 (95% CI: 1.05 – 1.78), and 0.99 (95% CI: 0.83 – 1.17), respectively (see Table 2). We also assessed the relationship between number of resources received in the program on grandparent's health and composite home environment and found that the odds ratio on health status, environmental status, and environmental composite score were 0.985 (95% CI: 0.906–1.071), 1.16 (95% CI: 1.047 – 1.283), 1.014 (95% CI: 0.931 – 1.105), respectively (see Table 3). We tested for confounding factors (length in the program and total number of resources = covariates) and none were found.

The average length of time grandparents were in the program was four years (range: 1 month – 15 years). With each year in the program, the odds of a perceived improved effect on the home environment increased by 1.37 (95% CI: 1.05 – 1.78). Health status improved by 1.08 (95% CI: 0.98 – 1.28) for each additional year in the program. The average number of resources (i.e., referrals, home visits, phone calls, monthly group meetings, nurse visits) received by the grandparents while in the program was eight (range: 0 – 22). The odds of a perceived environmental home improvement increased by 1.16 (95% CI: 1.047 – 1.283) for each additional resource received by grandparents. Our data also showed that 43.5% and 39% of the grandparents reported a health improvement and home improvement when asked directly.

DISCUSSION

Grandparents who are the primary caregivers for their grandchildren are disproportionately women of color [15]. In our study, we also found a majority of the participants who self-identified as African-American females with the average age of 62 years. It has been postulated that historically, African American families who were living in impoverished conditions, tended to live with extended family members in order to pool resources, which included financial means and caregiving roles [16]. This finding may account for why we have such a significant number of grandparents who serve as the primary caregiver of their grandchildren, often for more than one.

Caring for a child with a disability or chronic medical condition is associated with increased stresses, however, perceptions of stress differ among caregivers, depending on the levels of stress, the number of stressors and the experiences, outlook and support that each individual has [9, 15]. Only 32 percent of grandparents in our study reported experiencing stress; we did not explore the reason why some grandparents reported stress and others did not, but other studies also show conflicting responses when grandparents are put into the position of caring for their grandchildren [9, 14, 17, 18]. One possibility for the discrepancy may be related to the observation that some grandparents felt invigorated in this role as primary caregiver, thereby, giving them a sense of purpose, while others may have felt burdened and isolated by having such a large responsibility [19]. There are clearly significant personal, experiential, emotional and practical reasons as well as the phenomenon of

resilience that ought to be considered, when accounting for how much ‘stress’ is added by serving as the primary caregiver of a grandchild.

Caregivers of children with disabilities benefit from practical and concrete services such as stipend programs and respite care [15]. However, in our study, the length of time and total number of resources received in the program showed no statistically significant positive impact on the perceived health status or the environmental composite score. We did observe the relationship between supportive case management and the grandparents’ perception of improved health and home environment. This perceived improvement on the home may have occurred because the grandparents received assistance through referrals and stipends. Referrals made through case management enabled repairs to be done on the home itself, with companies who provided repairs at reduced costs. A consistent support provided to grandparents was the regular opportunity for grandparents to share their experiences with other grandparents in similar situations. This “support group” might have contributed as an indirect benefit to perceived improved health by participating grandparents. This allotted time to share created a sense of community among these grandparents and may have reduced feelings of isolation which may have reduced their overall stress levels. Additional studies are needed to further explore the relationship between family-centered case management and benefits to improved health and home conditions.

Limitations

Our study used a cross-sectional design and we were limited in our findings. We were unable within the time frame to conduct a case control study, which may be able to ascertain more clearly the impact of case management on specific health outcomes of grandparents and their grandchildren. In our study, we had no comparison control group to assess the true impact of the interventions. We were also limited by findings based on self-reports given by participants. During the recruitment process prior to enrollment, some grandparents declined to participate reporting that they had limited free time and hectic schedules, so our findings were limited by selection bias—only grandparents who could set aside time for the study were able to join, thereby excluding possible valuable information from those unable or unwilling to participate. There may have been a recall bias present as well, since participants were asked to remember situations and events that occurred prior to joining Project GRANDD in order to get a before/after effect when collecting data which would require a more accurate recall of events in the distant or recent past.

FUTURE DIRECTIONS

Moving forward we recommend a prospective case-control study to more clearly and accurately evaluate the impact of the program on the health and well-being of the grandparents and their grandchildren, as well as on their home environment. Greater focus should be on the nature of resources each grandparent receives through Project GRANDD, in order to identify the resources with the greatest beneficial impact on their lives. A well-designed home environment survey could be used to shed light on the living conditions of the

families. The information used could help to enhance relationships between the grandparents, their landlords and other service agencies. Social workers who work directly with the elderly could then use the data to evaluate the needs of the people they serve and advocate for improved living conditions. Researchers are in the position to shed light on the nuanced experience of multigenerational families and suggest interventions that aid in healthy family dynamics. We feel that, in the US, priority should be placed on helping grandparents who raise grandchildren, especially grandchildren with disabilities in order to “break the cycle” of intergenerational disadvantage and reduce the likelihood of disabilities and health disparities.

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Chapter 19

ADDRESSING SOCIAL DETERMINANTS OF HEALTH AT A FEDERALLY QUALIFIED HEALTH CENTER

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ABSTRACT

Social determinants of health (SDH) are the external conditions in which a child and his or her family live, work, learn, and play that can impact quality of health. The impact of SDH is often negative when a child is living in poverty. We utilized the HealthBegins Upstream Risks Screening Tool to evaluate children and families attending a low-income clinic in Southern Ohio/Northern Kentucky. Results were used to connect the children and their families to local community resources to address the SDH areas of greatest need. Population data on these children and their families informed the screening process and reinforced the need for this non-clinical, social service. Undergraduate and graduate students were effective in obtaining information to address SDH in the primary care setting.

Keywords: social determinants of health, federally-qualified health center, students, asthma, public health

INTRODUCTION

Margaret Whitehead, DBE was one of the first to establish inequity in health as unfair and unjust [1]. In cities across the United States health inequity can result in a life expectancy gap between the rich and the poor of up to fifteen years [2]. Limited access to medical care

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and unhealthy behaviors have traditionally been accepted as causes for poor health outcomes [3]. However, limited access to medical care and unhealthy behaviors only account for a portion of poor health outcomes [4]. A broader explanation for health disparities may be attributed to a person's social environment, or "the circumstances in which people are born, grow up, live, work, and age" as the social determinants of health (SDH) [5]. Children living in poverty with its associated SDH, are at greater risk for adverse health outcomes such as asthma and are less likely to receive consistent preventive care (e.g., Well-Child Checks) than children from families with high incomes [6-8].

Pediatric primary care providers have long provided primary prevention, and the screening necessary for secondary prevention [9] with a variety of guidelines and screening tools to address SDH in the primary care setting [10, 11]. It is currently recommended that SDH screening tools be used for families of pediatric patients during well-child checks and paired with education on available community resources [12, 13]. Despite the growing evidence of the important role of SDH in child health, addressing SDH is not a standard of care and does not systematically occur in the primary care setting. Common barriers to addressing SDH include minimal financial incentive, a lack of professional awareness and training, limited familiarity with screening tools, and disconnection with community resources to address SDH [11, 14].



Figure 1. Study purpose: Breaking the cycle at five points.

The quality improvement project assessed in this paper explored the process of systematically screening pediatric patients and their families for SDH risks within a federally qualified health center (FQHC) clinic serving Southwestern Ohio/Northern Kentucky. FQHC care sites provide health care service regardless of the client's ability to pay; largely serving patients in households with income at or less than the 200% poverty level (90% of FQHC clients) [15]. FQHC patients, particularly children, are at the greatest risk for negative physical and social/emotional outcomes due to SDH. Incorporating regular SDH assessment and support into pediatric FQHC appointments is one strategy for "Breaking the cycle" in health disparities among low-income populations. This project sought to affect the SDH cycle at these points: compound risk factors, personal characteristics, environmental risk factors, environmental characteristics, and health risk factors (see Figure 1).

METHODS

Data Source: Our quality improvement project focused on pediatric patients and families attending a primary care clinic within a FQHC in Southwestern Ohio between January and April 2016. As the project's intent was to improve current clinic operations, the FQHC did not require IRB approval for this quality improvement assessment.

Patients and families who registered at the clinic were invited into a side consultation room prior to their clinic appointment to learn about the new operational screening. They met with one of four volunteer students; undergraduates and graduates who were recruited and trained in Health Insurance Portability and Accountability Act (HIPAA) regulations, cultural competency, and professionalism. The student described the screening, its potential benefit to the patient and family, and its use for improving clinic services. The pediatric patients and families who chose to participate were screened immediately, and those who chose not to participate returned to the clinic waiting room for their regular clinic visit. Regardless of screening participation, all patients saw the clinic provider per their scheduled appointment.

The screening lasted approximately 6 minutes. Overall, 114 families participated out of 128 who were approached. Reasons given for non-participation included distrust, disinterest, or lack of time. The small scale of the project allowed the assessment team to learn from the screening process, and understand the time investment needed to provide patients and families with SDH screening and support.

Data Tools

The “HealthBegins’ Upstream Risks Screening Tool” was selected as the pilot screening tool of SDH for this study by the clinical staff at the FQHC (see attachment 1). It was administered by the trained students through conversation with the participants and scored immediately for use in the patient’s clinic appointment.

The tool included 26 questions grouped into 14 different social need categories: education, employment, social connection and isolation, physical activity, immigration status, financial strain, housing insecurity, food insecurity, dietary pattern, transportation, exposure to violence, stress, and civic engagement (see Table 1). Within these categories, previously established criteria were used to determine whether or not the patient was positive for a social risk on a given question.

Table 1. Pediatric patients and families identified at-risk by screening procedure

Pediatric Patients and Families Screened At-Risk by Categories	
# Screened At-Risk with 0 < Positive Categories	111 (97.4%)
# Screened Not At-Risk with 0 > Positive Categories	3 (2.8%)
Total (N)	114
Pediatric Patients and Families Screened At-Risk by Questions	
# Screened At-Risk with 0 < Positive Questions	113 (99.1%)
# Screened Not At-Risk with 0 > Positive Questions	1 (0.9%)
Total (N)	114

Each question was categorized as a binary variable (i.e., 1 if the patient was at-risk and 0 if the patient was not at-risk). These variables were then summed to assess each patient’s total social need score, ranging from 0-26. Additional social need sub-scores were summed within each social need category. If 50% or more of the questions within a category had a score of 1, then the whole category received a score of 1, for a potential score range of 0-14 across the 14 categories.

The second tool involved a community resources guide with a one-page educational handout. Following the SDH assessment, at-risk results were cross-walked to a community resources guide built to identify local Southwestern Ohio/Northern Kentucky agencies and programs that addressed the social needs covered by the screening tool. The guide listed for each supporting program or agency: resource eligibility requirements, contact information, and any additional access information. The guide was made available during the in-office consult to the screened participants, and published online (www.letschangeourcity.org). Non-screened patients and families were not directly notified of the guide’s online availability at this pilot improvement stage, but could have accessed it directly on their own. For those receiving the educational handout, it listed the community resources reflective of the patient’s identified social need. Patients and families were offered assistance in making contact with the referred community resource(s), as well as help in accessing other supportive services not listed in the community resources guide.

Data Measures

The operational utility of the quality improvement screening used three measures: SDH, visit type, and asthma diagnosis. SDH was measured using the overall (0-26) and sub-category (0-14) scores from the HealthBegins’ Upstream Risks Screening Tool. Visit type was tracked by the clinic appointment as child check-up [1] or acute [2], to determine if patients’ SDH risks varied with whether the clinic visit was planned or unplanned. Asthma diagnosis was tracked by the patient’s medical chart as positive [1] or negative [0] (see Table 2). Asthma was selected as a key variable because the literature suggests it is a physical health condition with higher prevalence among children in poverty; the predominant population attending our FQHC clinic [7].

Table 2. ICD-10 codes considered positive diagnosis for asthma

ICD-10 Code	Description
J45.2x	Mild Intermittent Asthma
J45.3x	Mild Persistent Asthma
J45.4x	Moderate Persistent Asthma
J45.5x	Severe Persistent Asthma
J45.90x	Unspecified Asthma
X = 0	Uncomplicated
X = 1	With Exacerbation
X = 2	With status

Data Analysis

Our operational analyses used SAS 9.4 for logistic regression models. SDH risk (overall, sub-category) was independently compared against visit type and asthma diagnosis using two-tailed T-tests.

Table 3. Summary statistics for analysis variables

Question	Category	Variable	N	N (%)
1A	Education	Highest Ed	113	27 (23.9%)
1B	Education	Highest Deg	89	63 (70.8%)
1C	Education	Child Prob	100	21 (21.0%)
2	Employment	Employment	110	29 (26.4%)
3	Social Connection & Isolation	Marital	113	80 (72.7%)
4A & 4B	Social Connection & Isolation	Social	112	11 (9.8%)
4C	Social Connection & Isolation	Faith Year	113	64 (56.6%)
4D	Social Connection & Isolation	Club Year	113	89 (78.8%)
5A & 5B	Physical Activity	Exercise Week	110	73 (66.4%)
6	Immigration	Immigration	113	9 (8.0%)
7A	Financial Strain - Overall	Financial Strain	113	28 (24.8%)
7B	Financial Strain - Overall	Financial Basics	113	47 (41.6%)
8A	Housing Insecurity	Housing	112	2 (1.8%)
8B	Housing Insecurity	Housing Quality	113	13 (11.5%)
8C	Housing Insecurity	Housing Move	112	2 (1.8%)
9	Food Insecurity	Food Security	113	1 (0.9%)
10A	Dietary Pattern	Fruit Day	113	44 (38.9%)
10B	Dietary Pattern	Veggie Day	113	97 (85.8%)
11	Transportation	Transport	107	12 (11.2%)
12	Exposure to Violence	Safety	112	18 (16.1%)
13A	Exposure to Violence	Emotional Abuse	112	13 (11.6%)
13B	Exposure to Violence	Fear Partner	112	7 (6.3%)
13C	Exposure to Violence	Rape	112	6 (5.4%)
13D	Exposure to Violence	Physical Abuse	112	5 (4.5%)
14	Stress	Stress	112	47 (42.0%)
15	Civic Engagement	Help Vote	112	9 (8.0%)
-	-	Acute	114	65 (57.0%)
-	-	Asthma	108	22 (20.4%)

RESULTS

Of the 114 patients completing the SDH screening tool, 97.4% were identified as being at-risk for at least one of the 14 SDH tool sub-categories, while 99% were found to be at-risk for at least one of the 26 screening questions (see Table 1). The screening tool items incurring the highest percentage of at-risk SDH scores represented the categories of dietary pattern, social connection and isolation, and physical activity (see Table 3).

Log-risk models of overall SDH screening scores were not significant by appointment type (Wald Chi-square test statistic = 1.50, $p = 0.21$) or asthma diagnosis (Wald Chi-square test statistic = 1.3, $p = 0.25$). The same non-significance was found for SDH sub-category scores (appointment type: Wald Chi-square test statistic = 1.16, $p = 0.28$; asthma: Wald Chi-square test statistic = 0.34, $p = 0.56$). Still, mean score testing of overall and sub-category

SDH scores by appointment type showed that acute care appointment patients had higher SDH risks, compared to well-child check patients; although the difference was not significant (overall: unpooled mean difference = -0.74, $t = -1.26$, $p = 0.21$; sub-category: unpooled mean difference = -0.35, $t = -1.07$, $p = 0.29$). Likewise, mean score testing of overall and sub-category SDH scores by asthma diagnosis showed higher SDH risks for positive compared to negative diagnoses; although the difference was not significant (overall: unpooled mean difference = -0.87, $t = -1.26$, $p = 0.22$; sub-category: unpooled mean difference = -0.24, $t = -0.63$, $p = 0.53$).

DISCUSSION

Our assessment stems from a quality improvement project that examined the systematic screening of pediatric patients and their families for SDH risks within a FQHC. The screening tool effectively captured the estimated risk levels of our FQHC families showing the majority (97%) of our pediatric patients at-risk for at least one SDH. The most frequent SDH issues were dietary pattern, social connection and isolation, and physical activity.

In the literature, these findings are not uncommon with SDH experiences reported by persons in poverty; particularly a greater risk for obesity given poor dietary options and lower physical activity [16]. Although variations exist, common barriers to proper nutrition and physical activity for low income individuals often include limited flexible time in travelling to food stores or for exercise), and poor access to healthy food areas or safe green spaces [17]. For issues of social isolation, limited social support is linked to poverty, as it limits one's access to supportive resources used in sharing burdens around childcare, finances, or stress [18].

Our assessment also found observable, but non-significant, differences in SDH scores by appointment type and asthma diagnosis. As expected, SDH risks were greater for pediatric patients and their families seeking acute care, and for pediatric patients with asthma and their families. These findings also align with the current literature where children in poverty are less likely to receive consistent preventative care [8], which may delay timely diagnosis or treatment of chronic conditions, including asthma. Additionally, housing conditions, smoke exposure, and traffic air pollution are all environmental conditions that contribute to asthma and are related to poverty [7, 19].

Finally, our quality improvement assessment suggests that systematic SDH screening of pediatric patients within a clinic environment is feasible and, anecdotally, beneficial for both the patient/families and the clinic provider. We used a trained cadre of four student volunteers to administer the screening tool and refer patients/families to appropriate social services. We believe that the patients and families benefited from the time, talent, and energy of the SDH screening, as perceived by patients' informal expressions of appreciation toward the new information on their SDH risks and local resources, and our provider reflecting on an increased confidence in addressing SDH issues.

Still, there are potential limitations in our process improvement findings. For example, fear of adverse consequences may have limited participation and led to underreporting of social needs. In the future, we may consider a standard form for parents to complete prior to the visit or use of self-guided technology to collect SDH information; strategies that have had

successful application in other primary care settings [20, 21]. We also do not have information on whether participants who received the educational handout used it to access community resources tailored to their SDH needs. It would be interesting to reach out to these families to assess the resource's utility and limitations, as well as to reach out to families that missed their appointments to perform the screening by phone. It is possible that continuing SDH barriers, including transportation, clinic hours, or child care issues, limits the resource or health care utilization for much of our patient population. However, these issues were not explored in our assessment.

Going forward, it is apparent that the majority of families at our FQHC had unmet social needs. The primary care setting is an ideal opportunity to screen for and identify SDH and match families in need with appropriate community resources. Substantial organizational and community coordination is necessary to ensure ethical and effective screening [22]. Stronger and more direct primary care-community resource partnerships would provide greater opportunity for success in addressing SDH and matching families to community resources for long-term support [22, 23]. Further training of alternative workforces, such as volunteer students, clerical staff, or intake workers to address SDH has potential to make SDH screening cost-effective despite limited financial incentive or reimbursement.

Our work also indicates that implementing a brief screening tool into already busy clinic operations is feasible, and may likely improve care coordination between providers and at-risk families, improve health outcomes for pediatric FQHC patients, and reduce SDH-related disparities.

Regardless, policy makers, legislators, and individual citizens must be educated as to the influence of SDH on adverse health outcomes and together should develop implement effective strategies for screening and for connections with resources.

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APPENDIX



Upstream Risks Screening Tool

"Everyone deserves the opportunity to have a safe, healthy place to live, work, eat, sleep, learn and play. Problems or stress in these areas affect health. We ask our patients about these issues because we may be able to help."

Date of screening: ____/____/____

What's your name? First: _____ Last: _____	What's your date of birth? ____/____/____
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1. Education

- a. What is the highest level of school you have completed?
 - i. Elementary school
 - ii. High school
 - iii. College
 - iv. Graduate / Professional school
- b. What is the highest degree you earned?
 - i. High school diploma
 - ii. GED
 - iii. Vocational certificate (post high school or GED)
 - iv. Associate's degree (junior college)
 - v. Bachelor's degree
 - vi. Master's degree
 - vii. Doctorate
- c. Are you concerned about your child's learning, performance, or behavior in school?
 - i. Yes
 - ii. No
 - iii. Not applicable

2. Employment

- a. Choose one of the following. Which best describes your current occupation?
 - i. Homemaker
 - ii. Employed full-time
 - iii. Employed part time
 - iv. Employed, but on leave for health reasons
 - v. Employed but temporarily away from my job (other than health reasons)
 - vi. Unemployed or laid off 6 months or less
 - vii. Unemployed or laid off more than 6 months
 - viii. Unemployed due to disability
 - ix. Retired from my usual occupation and not working
 - x. Retired from my usual occupation but working for pay
 - xi. Retired from my usual occupation but volunteering

3. Social Connection & Isolation

- a. What is your marital status? Check one.
 - i. Married
 - ii. Living with partner
 - iii. Widowed
 - iv. Divorced
 - v. Separated
 - vi. Never married

4. Social Connection & Isolation

- a. In a typical week, how many times do you talk on the telephone with family, friends, or neighbors?
 - i. Number of times per week _____
- b. How often do you get together with friends or relatives?
 - i. Number of times per week _____
- c. How often do you attend religious or faith-based services?
 - i. Number of times per year _____
- d. How often do you attend meetings of the clubs or organizations you belong to?
 - i. Number of times per year _____

5. Physical Activity

- a. On average, how many days per week do you engage in moderate to strenuous exercise (like walking fast, running, jogging, dancing, swimming, biking, or other activities that cause a light or heavy sweat)?
 - i. Days per week _____
- b. On average, how many minutes do you engage in exercise at this level?
 - i. 0
 - ii. 10
 - iii. 20
 - iv. 30
 - v. 40
 - vi. 60
 - vii. 90
 - viii. 120
 - ix. 150 or greater

6. Immigration

- a. Do you have concerns about any immigration matter for you or your family?
 - i. Yes
 - ii. No

7. Financial Strain

- a. Do you ever have problems making ends meet at the end of the month?
 - i. Yes
 - ii. No
- b. How hard is it for you to pay for the very basics like food, housing, medical care, and heating? Would you say it is:
 - i. Very hard
 - ii. Somewhat hard
 - iii. Not hard at all

8. Housing Insecurity

- a. In the last month, have you slept outside, in a shelter, or in a place not meant for sleeping?
 - i. Yes
 - ii. No

- b. In the last month, have you had concerns about the condition or quality of your housing?
 - i. Yes
 - ii. No
- c. In the last 12 months, how many times have you or your family moved from one home to another?
 - i. _____

9. Food Insecurity

- a. Which of the following describes the amount of food your household has to eat?
 - i. Enough to eat
 - ii. Sometimes not enough to eat
 - iii. Often not enough to eat

10. Dietary Pattern

- a. How many pieces of fruit, of any sort, do you eat a typical day?
 - i. _____ pieces/day
- b. How many portions of vegetables, excluding potatoes, do you eat on a typical day?
 - i. _____ portions/day

11. Transportation

- a. How often is it difficult to get transportation to or from your medical or follow-up appointments?
 - i. Does not apply
 - ii. Never
 - iii. Sometimes
 - iv. Often
 - v. Always

12. Exposure to Violence

- a. Do you have concerns about safety in your neighborhood?
 - i. Yes
 - ii. No

13. Exposure to Violence

- a. Within the last year, have you been humiliated or emotionally abused in other ways by your partner or ex-partner?
 - i. Yes
 - ii. No
- b. Within the last year, have you been afraid of your partner or ex-partner?
 - i. Yes
 - ii. No
- c. Within the last year, have you been raped or forced to have any kind of sexual activity by your partner or ex-partner?
 - i. Yes
 - ii. No

- d. Within the last year, have you been kicked, hit, slapped, or otherwise physically hurt by your partner or ex-partner?
 - i. Yes
 - ii. No
- 14. Stress
 - a. Stress means a situation in which a person feels tense, restless, nervous, or anxious, or is unable to sleep at night because his/her mind is troubled all the time. Do you feel this kind of stress these days?
 - i. Not at all
 - ii. A little bit
 - iii. Somewhat
 - iv. Quite a bit
 - v. Very much
- 15. Civic Engagement
 - a. Would you like help registering to vote?
 - i. Yes
 - ii. No

Name of screener:

Survey #:

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Chapter 20

HEALTH VULNERABILITIES OF UTAH'S IMMIGRANT CHILDREN: BREAKING THE CYCLE

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ABSTRACT

The health-related vulnerabilities of immigrant children are numerous, but information related to their needs is limited, especially in new immigrant destination states like Utah. In order to examine these vulnerabilities, this study incorporates responses from a variety of social service agencies that offer a broad range of health services for immigrant and refugee populations. Semi-structured qualitative interviews were conducted with sixteen respondents (N = 16) to elaborate on the health-related vulnerabilities of immigrant children and the specific practices that have been developed to address them. The respondents identified gaps in the medical system faced by immigrant children and outlined general health-related trends faced by the group as a whole. These social service providers were also familiar with a wide range of strategies that have been employed in an effort to “break the cycle” of vulnerabilities faced by immigrant children in Utah. The respondents specifically noted that the vulnerabilities to which the children of unauthorized immigrant children are exposed are fundamentally different than those faced by refugee children. This difference highlights the need for unique solutions for each group of children.

Keywords: health vulnerabilities, immigrant health, healthcare services, social services

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INTRODUCTION

It is difficult to imagine a more vulnerable population than children of immigrants. They face numerous environmental and health-related challenges, including low-quality housing, transient lifestyles, and limited provision of legal rights and healthcare services. They and their parents experience unique cultural, linguistic, and transitional difficulties on a daily basis. While there are various types of immigrants, this project emphasizes the vulnerabilities faced by the children of undocumented immigrant families and those faced by the children of refugee families. An undocumented immigrant in the United States is “a foreign national residing in the United States without legal immigration status” [1]. A refugee is “a person who is unable or unwilling to return to their country of nationality because of persecution or a well-founded fear of persecution... the practice of accepting such refugees is that of offering political asylum” [1]. The term “immigrants” will be used in this paper for findings that describe both of these groups.

According to existing literature, many immigrant children form part of the “undeserving poor”: a demographic that is perceived by the majority population as being undeserving of socially-provided services [2]. They also face many vulnerabilities such as poverty, low English proficiency, mental anguish, and availability of only episodic health care [3-6]. All of these issues result in rates of poor health for immigrant children that are more than twice as high as those of native children [7]. For undocumented immigrant children, the situation is further compounded by the ever-present fear of deportation and family separation due to the family’s precarious legal status [3]. While the refugee population does not face the same legal barriers as the unauthorized population, parents and their children may carry lingering stress from circumstances faced in leaving their home country and still face many challenges in attempting to access health care. They face linguistic and cultural difficulties that make it difficult for refugees to navigate the complicated healthcare system of developed nations. A 2015 study found that refugees in Utah have “only a very basic understanding of how insurance and healthcare function” [8].

The impact of these differing vulnerabilities is especially powerful in states like Utah, where the presence of immigrant families is relatively new. Utah is a historically homogeneous state, with a traditional white majority and a conservative constituency. From 1990 to 2013, however, the percentage of foreign-born Utah residents more than doubled in size from 3.4% to 8.2% [9]. Based on 2010 census data, the Hispanic population alone grew from 201,000 to 358,000, a 78% increase in the last decade making them the fastest growing minority group in Utah [10]. Currently about 56% of immigrants in Utah are documented (including refugees) and 44% are undocumented [11]. This drastic change in the state’s demographics has had a variable impact on state politics.

Regarding immigration, the rhetoric of Utah decision makers vacillates between welcoming and condemning. In 2010 almost every political, economic, and religious leader in the state banded together to sign a document entitled the Utah Compact, which advocated for the humane treatment of unauthorized immigrants. The document represented a statewide concern for the wellbeing of immigrant families and identified Utah as a pioneer in the national immigrant debate. Utah’s governor, Gary Herbert, was the only Republican governor who did not reject acceptance of Syrian refugees into his state in the aftermath of the Paris attacks in February 2016 [12]. Today, Utah takes in roughly 1,100 refugees annually from

various countries including Burma, Somalia, and Iraq [13]. Various state policies, however, take a punitive stance toward immigrant families despite this compassionate rhetoric. Such policies include SB-81, which denies funding to social service agencies that fail to prove that their client bases are legal. The law effectively denies any state funds to unauthorized immigrants [11].

This inconsistent policy context provides an ideal backdrop in which to examine the health vulnerabilities of immigrant children. Developed states and nations all over the world are, like Utah, struggling to determine how best to respond an influx of immigrants. This project contributes to that ongoing discussion by asking the following questions: “What are the health vulnerabilities of Utah’s immigrant children?” and “Are there difference in vulnerabilities between the children of refugees and the children of undocumented immigrants?” Based on our literature review, we hypothesized that the health vulnerabilities faced by immigrant children in Utah would be greater than those faced by the general public and that they would face significant barriers to accessing health-related services. We further hypothesized that the vulnerabilities faced by undocumented immigrant families would be different than those faced by refugee families and thus that unique solutions would be required to serve each population.

METHODS

While overarching trends in immigrant health are well documented, a relatively small number of people are privy to information related to the medical needs of specific enclaves of immigrant families. Social and medical service providers based in states and communities often have the greatest appreciation for the vulnerabilities faced by the groups that they serve. Our study was designed with this understanding in mind.

The study consisted of sixteen semi-structured interviews with a variety of social service agencies that offer a broad range of health services for immigrant and refugee populations. Participants were selected via criterion and snowball sampling methods. We generated our original contact list using information from the public domain on clinics and other social services within Utah working directly with immigrant populations. Once the initial participants were selected and interviewed, we asked them to identify additional respondents who might have insights related to immigrant vulnerabilities in the state. Every participant directed us to other organizations, many of which were not well known to the public. The study’s participant pool thus represents large organizations with an established web presence as well as grassroots entities known only to other professionals in the field. Of the sixteen participants, ten occupied management-level positions in their organizations and six worked directly with immigrant and refugee populations on a regular basis. Those in management positions (often executive directors) had many years of experience with their organizations and were thus able to discuss overarching trends in immigrant or refugee care. The direct-care workers offered intimate perspectives on the daily lives of immigrant families and their efforts to access health services. The pool of participants also differed by the population served by the respondent’s organization. Six offered services exclusively to refugee populations, two offered services only to undocumented immigrant populations, and eight offered services to both groups. The combined responses of these overlapping groups

illuminated the scope of the vulnerabilities into which Utah's immigrants fall and provided insight into the range of solutions that are currently being used to break that cycle.

The interview questions consisted of four main categories, all of which invited participants to outline differences between vulnerabilities faced by undocumented immigrants and those faced by refugees. First, we asked general information about the participant's organization to obtain an understanding of where they fit into the hierarchy of the institutions and what health services were offered to immigrants at their facilities. Second, we asked participants to identify the health vulnerabilities of immigrant children served by their organization. Third, we asked if there were any barriers that immigrant children faced in attempting to access health care services. Finally, we asked participants to report any successes by their agency in addressing immigrant vulnerabilities and their thoughts on future actions that could be taken by the agency or the government to further alleviate these vulnerabilities. The interviews lasted between 20-40 minutes. Fifteen of the sixteen participants consented to have their interviews recorded; their interviews were transcribed to ensure fidelity to the responses of our interviewees. Extensive interview notes were taken for the participant who preferred not to be recorded.

The interview process was discontinued when participants began to consistently refer our team to organizations with whom we had already spoken and when we began to hear repeated themes and few new insights across interviews. The interview notes and transcripts were then qualitatively analyzed to identify trends among the responses. These trends are explored in the following section.

RESULTS

Our results fall under four main categories: health vulnerabilities of immigrant children, health-related barriers faced by immigrants, barriers for service provision faced by agencies and solutions that had been or could be employed to address these barriers.

Health Vulnerabilities

When asked about specific health-related vulnerabilities faced by immigrant children, participants reported various similarities between the children of refugees and the children of undocumented immigrants. One of the most commonly referenced health issues that affected both groups was low dental health. Many participants said that it was difficult to help immigrant families take the health of their children's teeth seriously, given that it rarely represented an urgent need and was often not included in immigrant insurance plans, if they had any insurance at all. These dental health issues are exacerbated by distrust that immigrants have for tap water, which is fluoridated in the United States and thus has the capacity to improve dental health. One interviewee, in reference to the fact that the tap water in many less-developed countries is not potable, said that "the water [from the tap] is perceived as unclean and so they don't want to drink out of the faucet." This lack of trust excludes immigrant children from the benefits of the fluoridated public water. Immigrant children, given their life in often low-income homes and neighborhoods, are also exposed to a

wide variety of environmental health hazards, especially lead exposure. Speaking about the dangers of lead exposure, one interviewee said “[it] will go into the brain and actually permanently short-circuit parts of the brain...their IQ drops oftentimes by ten percent; they have a variety of behavior issues.” In fact, the American Academy of Pediatrics reports that that “no amount of lead exposure is safe for kids” [14]. Mental health issues such as anxiety and depression also affect both immigrant groups. The mental health issues reported were often related to the trauma of moving to a new country. This finding matches the underlying trends in immigrant health discussed in the literature review. Finally, many participants pointed to transition-related symptoms, such as respiratory difficulty, and skin ailments that affected undocumented immigrants and refugees equally. These transition-related symptoms were often the result of elevation and atmospheric differences between Utah and the immigrants’ home countries.

While refugees and undocumented immigrants shared many health vulnerabilities, as discussed above, some vulnerabilities were specific to just one group. Participants reported that undocumented children faced much higher rates of obesity and pesticide exposure than either native-born children or refugee children. The regular pesticide exposure was due to the high rate of employment in the agricultural sector by undocumented immigrant parents. Refugee children, on the other hand, were more likely to be underweight or malnourished and have parasites upon arrival in the United States. These observations were attributed to the fact that most of them arrive in the U.S. after extended stays in refugee camps with little access to nutritious diets. Participants noted, however, that refugee families struggle to maintain a balanced diet even after having spent some months in the country. “All of a sudden,” one reported, “they [refugees] were able to go grocery shopping ... they're not even exposed to what the different foods in the grocery are.” This unfamiliarity with the resources provided in developed countries was a common theme among respondents: many health vulnerabilities faced by refugee children were the result of the “cultural illiteracy” of the refugee families.

Comparing Refugees and Undocumented Immigrants on Barriers to Health-Related Services

According to participants, both refugee and undocumented immigrant families have difficulty receiving health-related services due to the regularly scheduled operating hours of most clinics. Given various circumstances faced by immigrant parents, including low English proficiency, many of them work in positions that pay by the hour. This makes the decision to take time off to take a child to the doctor a difficult one. Participants explained that many immigrant families also have restrictive insurance plans because Utah is one of the 19 states that has not expanded Medicaid [15]. Given that many immigrant families fall within the low-income demographic of the state’s population, participants reported that this Medicaid restriction is particularly devastating to them. A previous study found that “the high costs and confusing nature of medical costs and insurance coverage [are] stressful issues for refugees” in Utah [8]. Even when affordable health-related services are available, however, immigrant families face a knowledge barrier in regards to health-related services: they often do not know what programs are available to them and their children. While services are available to them

in some cases, many immigrant families are unaware of where to find them and lack the language skills or social networks to learn more.

Interviews highlighted that some barriers to health-related services apply specifically to undocumented immigrant families, the greatest of which is fear. Many undocumented immigrant families fear that if they seek out medical services they will be forced to provide documentation that will reveal their non-legal status, potentially resulting in deportation and separation from the rest of their family. Participants reported that many services are available for this population that do not require any documentation, but the fear felt by undocumented families immobilizes many of them to the point that they do not receive even the treatments for which they are eligible. This phenomenon, among others, has resulted in a situation in which, according to one participant, “Utah has the worst rate of insurance for Latino children in the United States... 22 percent of Hispanic children don't have health insurance in Utah compared to 11 percent nationwide.”

Interviews revealed that other barriers to services are faced by refugee families to a larger degree than undocumented families. Participants indicated that refugees struggle when trying to access services due to their lack of familiarity with the United States' healthcare system and society in general. This lack of familiarity does not extend solely to the healthcare sector, but also incorporates transportation difficulties, literacy barriers, language skills, and limited social networks. A combination of these barriers has led to a significantly high “no show” rate for medical appointments made by refugees. One participant reported that this rate of refugee absences is as high as 50% at their clinic.

The differences in barriers faced by undocumented immigrant families and those faced by refugee families can largely be explained by what we have labeled the “fear / familiarity dichotomy” rather than a lack of cultural awareness of how the system works. Whereas many undocumented immigrant children lack access to healthcare given the fear that they face due to their non-legal status, many refugee children miss out on services because neither they nor their parents are familiar with the medical bureaucracy of a first-world country. The dichotomy was best illustrated by one participant, who said, “[Refugees] don't have the same fears as undocumented immigrants. [Undocumented immigrants] often fear applying for services due to the chance of deportation... [Refugees] often just don't know when or where to go for certain services. For instance, many will go to the ER for a simple cold. They just don't know how to navigate the medical system.”

Barriers to Health-Related Services Faced by Agencies

Interview participants also looked inward to their organizational efforts and identified some of the complications that they face in their attempts to provide services to immigrant children. Many reported a general lack of funding from the state and federal governments, low political will to serve immigrant families given Utah's history as a conservative state, immigrant housing checks being thwarted by landlords who refused to allow inspections of rented property, and issues with accessing the (often nonexistent) medical records of immigrants from their home countries.

For organizations that seek to provide services specifically for undocumented immigrants, the most common inhibitor was said to be the lack of state funding, which (due

to SB-81) is often tied to the agency's ability to prove that its clients are legal residents. Once an agency finds out that a client is undocumented, the range of services that it is able to offer and referrals that it is able to make narrows dramatically. Aside from the difficulties associated with procuring state funding, organizations that serve undocumented immigrants even struggle to acquire funding or grants from private donors. Many such grants come with "strings attached" that indicate which groups of people are eligible to receive services and which are not. Undocumented immigrant populations are regularly excluded from these eligibility pools for private grants. Many participants also reported that various would-be volunteers with their organization had indicated that they would be unwilling to serve undocumented immigrant families. These responses highlight the reality of undocumented immigrant families falling within the "undeserving poor" category, as described above, and also illustrate the indifference that some of Utah's conservative constituency feels towards this population.

Participants from refugee-oriented organizations reported that their biggest issue with funding is the expiration date associated with newly arrived refugee clients. After these refugees reach a certain threshold of time spent in the U.S., often at eight months, many of the funding opportunities that were available to them when they first arrived are removed because they are no longer considered "recent arrivals." This loss of funding severely restricts the agencies' abilities to assist refugee families in attaining long-term stability, even though they would like to do so. Another problem specific to refugee-oriented organizations is associated with the high refugee "no show" rate for medical appointments, which was referenced above. High refugee "no show" rates indicate a loss of revenue for clinics that rely on the income derived from the steady flows of patients through fee-for-service reimbursement. Also, many refugee-oriented organizations have struggled to find interpreters with an adequate medical vocabulary to serve a new influx of refugees from places like Somalia, Syria, and Burma. This dearth of medically-trained interpreters restricts the abilities of many organizations to effectively address the health-related vulnerabilities of their refugee clients.

Solutions: Breaking the Cycle

The combined influences of fear, cultural unfamiliarity, low English proficiency, low income, reluctant donors, and many other factors described above contribute to a destabilizing cycle of vulnerabilities that results in poor access to health-related services for immigrant children. Figure 1 shows the array of health disparities found in this study of Utah's immigrant children.

While the prospects for healthy immigrant families might appear dismal given the existence of this cycle, nearly all of our respondents reported that they and their organizations had found successful ways to navigate the complicated social, political, and economic difficulties associated with immigrant health in order to effectively serve their disadvantaged clients. The following is a list of creative solutions that Utah's organizations are *currently* using to help immigrant families break out of this cycle of health-related vulnerabilities (see Figure 1):

- Many immigrant-oriented agencies have developed informal partnerships with other health providers and refer their clients to the services provided by their partners. This practice effectively addresses the difficulties associated with the small social networks that many immigrants have when they first arrive and also enables agencies to advertise their services to a broader pool of potential clients.
- Various refugee-oriented organizations have adopted cultural education programs to help their clients learn to ride the bus, navigate a grocery store, or learn basic English. These programs help refugee families overcome their unfamiliarity with the complicated social dynamics in their new country of residence.
- Many organizations have identified unconventional yet practical locations in which they can advertise their services. Advertisements situated in churches, mosques, WIC clinics, preschools, ethnic restaurants, and other such places were particularly effective.
- One participant mentioned that her organization, aware of the fear that many undocumented immigrant families faced when arriving at a clinic to receive medical care, instructed its staff members to act like they worked for a private practice rather than a non-profit organization. The participant indicated that trust barriers dissolved if clients were treated with the respect and concern that are normally shown to full-paying customers.
- One refugee-oriented organization, hoping to expand its services to new immigrant populations, developed a creative way to hire culturally competent staff members who were invested in the community. The director of this organization went into the community and asked residents to identify a local leader who spoke both English and the language commonly spoken in the community, had a car and a cell phone, and was trusted by his/her neighbors. When such a person had been identified, this organization director simply approached the leader and hired the person on the spot, offering money if he or she would consent to acting as an intermediary between him (the director) and the community. This grassroots hiring strategy enabled this organization director to provide culturally competent services to many refugee communities about which he had very little personal knowledge.
- One particularly innovative solution involved the creation of a “Mobile Medical Clinic”—essentially a mobile home converted into a doctor’s office. Many of the services that immigrant families need are compacted into this portable clinic, which is then brought directly into immigrant communities. The Mobile Medical Clinic eliminates many of the barriers associated with low social networks, low access to public or private transportation, fear of straying too far from one’s community, and lack of familiarity with the bureaucratic atmosphere of a doctor’s office. Service providers working for the clinic are often able to work with immigrant families in their homes, making the patients feel more comfortable and also giving medical professionals an opportunity to examine their living conditions.

Participants were also asked about solutions to immigrant health vulnerabilities that they hoped could be instituted *in the future*. A list of their responses follows (see Figure 1):

- Various participants indicated that if Utah opted to expand Medicaid it would improve the wellbeing of the state's immigrant population dramatically. Some reported clients had moved to states where Medicaid had already been expanded in order to find more affordable services and insurance for their families.
- Other participants suggested that the expectations for newly arrived refugees be changed to include English education. The current system, according to the respondents, is focused on funneling newcomers directly into the labor market with no thought given to their long-term employment prospects. If English education were given priority over immediate job placement, they argue, newly-arrived refugees would be competitive to work in more lucrative industries that would enable them to pull out of the low-income demographic faster than they are currently able to do.
- Some agencies hope to circumvent the unavailability of medically trained interpreters by creating programs within their organizations to teach and/or hire staff members that speak the languages commonly spoken by their client base.
- One large-scale idea involved the creation of a multi-facility "Immigrant Care Campus": a plaza of services that would provide medical, housing, legal, educational, and other assistance for immigrant families in a single location. The participant raising this idea indicated that such a suite of services has been built into clinics in Phoenix, Arizona (affiliated with the University Medical Center) and in Boise, Idaho (affiliated with St. Alfonso's Hospital) with remarkable success.

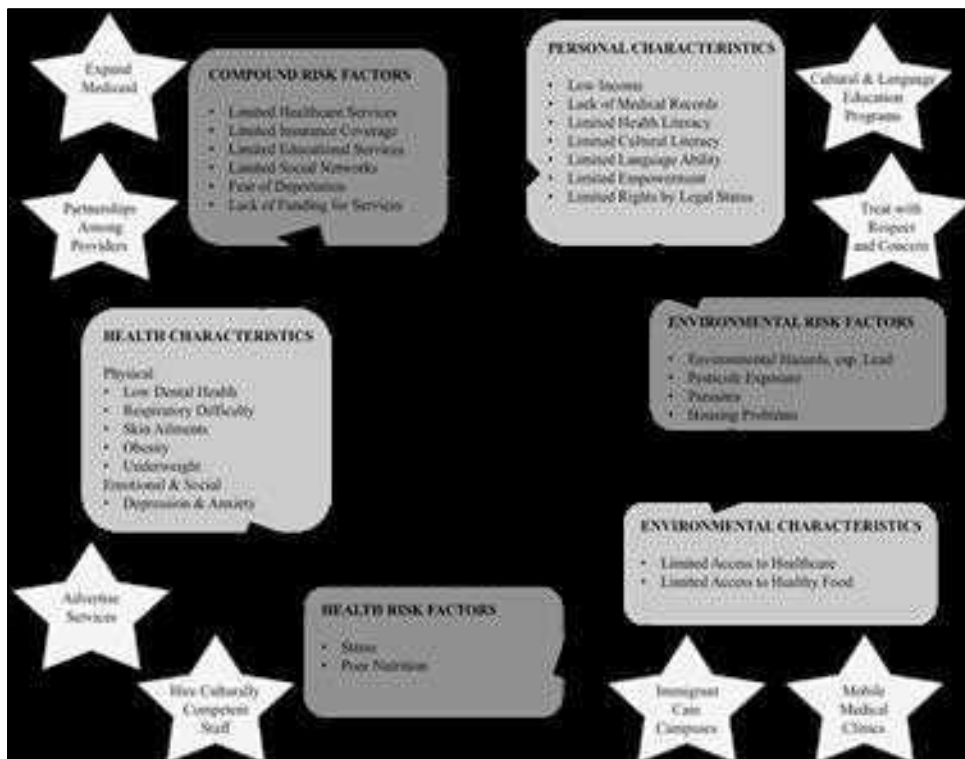


Figure 1. Health disparities facing Utah's immigrant children (boxes) and opportunities to "break the cycle" (stars) as articulated in project interviews. Adapted from <http://www.isdd-home.org/#!/break-the-cycle/crkn>.

DISCUSSION

Many of the results of this study speak for themselves. The health-related vulnerabilities faced by immigrant children in Utah are undeniably real, as are the barriers that are faced by immigrant families and medical providers. Many of the health vulnerabilities faced by undocumented and refugee immigrant children relate to compound risk factors that pervade their lives beyond health considerations, such as cultural and educational services, social networks, and legal status.

We expect the findings highlighted in this report to be useful to a wide range of audiences who are seeking to address this reality. We hope that everyday citizens, especially Utahns, are exposed to this report and understand the depth of immigrant disadvantage in their state and begin to embrace a commitment to address it. We further hope that any immigrant families who are exposed to this study are able to see what kinds of services are available to them in Utah today. While our study focuses on the state of Utah in the United States, we note that immigration is a global issue and our findings are likely to resonate with health service providers around the world.

In the ongoing discussion designed to break the cycle of vulnerabilities faced by immigrant families, it is vital to recall that different solutions are required for undocumented immigrant families than are required for refugee families. While many of the needs and vulnerabilities of these populations are similar, the “fear/familiarity dichotomy” requires agencies, in many cases, to approach the same problems in different ways depending on which demographic they serve. The provision of social and health-related services to newly arrived immigrants is a growing sector that has many lessons to learn, but it will become only more important as world conflicts continue to direct disadvantaged families to advantaged countries. Raising the level of cultural literacy related to navigating complex services and bureaucratic systems will be essential to breaking the cycle of vulnerability [8], and the participants in this study framed specific and tangible ways to improve the health of immigrant children and their families. Above all else, we hope that this study adds to the ongoing conversation between health-related professionals who are providing medical services to immigrant children across the world, the United States, and especially in Utah. It is through the steady accumulation of knowledge, research, experience, and collaboration that organizations like these will truly be empowered to, once and for all, fully and effectively break the cycle.

ACKNOWLEDGMENTS

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APPENDIX A

Social Service Interviews

We prefer to make an *audio recording* of our interviews, whenever possible, to guarantee that we represent your comments correctly. We have every intention of *maintaining your confidentiality*. May we make an audio recording of this interview to ensure the accuracy of our report?

Thank you for participating in our study! Your opinion and expertise is very important to our project. Our focus is on immigrant children and their health and medical vulnerabilities.

We realize that there are different categories of immigrants –

- There are refugees who are fleeing conflict or persecution and are protected by international law.
- Then there are migrants who move for various reasons.
- Within the migrant population, there are also undocumented or unauthorized migrants who lack legal documentation or status.

It would be very helpful if you could speak to the differences in these groups as it pertains to your organization and your answers.

I expect this interview to last approximately 20-30 minutes. *You may choose not to answer any of our questions or ask that we conclude the interview at any time.*

Do you have any logistical questions for me before we begin?

1) Information about you/your organization

- A. Can you please state your name and the organization with which you work? (probe for details)
- B. How long have you been working with this organization?
- C. What is your current role and responsibilities with this organization?
- D. What kinds of healthcare-related services does your organization provide for children of immigrant families (age 0-18)?
- E. Does your organization target a specific population of immigrant families? (Probing: A particular type of immigrant as we discussed above? A certain region? A certain age? A certain gender?)

2) Now we'd like to ask you about HEALTH ISSUES of Children of Immigrant Families

- A. In your opinion, what are the most common medical or health *issues* experienced by the children of immigrant families that your organization serves?
- B. Are there any significant differences between immigrant boys' health-related needs and immigrant girls' health-related needs? (age 0-18)

- C. Are there any significant differences between the health-related needs of *refugee children, undocumented immigrant children, other immigrant children, and non-immigrant children*?
- D. One of the things we are interested in on this project is *environmental health* – health issues related to factors that are external to a person – such as air, water or soil conditions or in the built environment like houses, schools, or other places, or due to contaminants (like lead) or other exposures.

In your opinion, what are the most common *environmental* health issues experienced by the immigrant children that your organization serves? [Probing: pre-existing vulnerabilities? Or did they arise upon arrival?]

3) Next we'd like to ask you about HEALTHCARE ACCESS for Children of Immigrant Families

- A. Do children of immigrant families need to meet any *eligibility* requirements in order to access your organization's services?
- B. (if not addressed above) Are there any significant differences between the health-related *access* of the children of *refugee* families and the access of children of *undocumented immigrant* families?
- C. Are there any significant differences between boys' *access* to health care and girls' *access* to health care?
- D. What barriers do immigrants face in trying to access healthcare services?
- E. What barriers do organizations like yours face in attempting to provide healthcare related services to the children of immigrant families in Utah?

4) Finally, we'd like to ask your thoughts about reducing vulnerabilities faced by children of immigrant families in Utah

While our project is designed to identify these vulnerabilities, we are also very interested in identifying strategies to overcome them. [If appropriate, acknowledge successes mentioned above here.]

- A. What successes has your organization had in addressing the vulnerabilities faced by children of immigrant families in Utah?
- B. What actions do you believe could be taken by organizations – yours or others – to more successfully address these vulnerabilities?
- C. Are there any governmental actions you see as needed to address these issues?

Final Questions

- A. Is there anything we haven't asked or anything else that you would like to tell us about your experience in providing healthcare services to immigrant children?

- B. We would like to speak with representatives from as many social services as possible that provide healthcare services to immigrants. Can you think of anyone that is also familiar with the medical vulnerabilities faced by children of immigrant families with whom we should speak?

If so:

Do you know this person's email address? Phone number? Is this person affiliated with an organization like yours? What is that organization? Would it be okay for us to identify you as the source of the contact information? (It's not vital that we do so, but it's helpful). [if this gets complicated – suggest follow up email]

- C. Would it be okay if we email you with any additional questions that we might have?
- D. [Ensure we have email contact info] We will be sure to send you a report of our findings when we have it in mid-summer.

Thank you so much for your time!

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Chapter 21

PARENTS' AND TEACHERS' BELIEFS ABOUT SCHOOL READINESS: WORKING TOWARD DEVELOPING MORE CULTURALLY RELEVANT INTERVENTIONS

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ABSTRACT

The persistent disparity on educational measures between students from different socioeconomic backgrounds is often referred to as the achievement gap. To mitigate this achievement gap, many prior interventions have been designed to promote children's linguistic skills and overall school readiness. These interventions are often built upon majority-culture standards and traditions, despite the differing values and practices of many diverse communities. To more effectively support language and academic outcomes of children growing up in low-income households, we need to ground our interventions in the cultural values of specific communities, and better understand how parents and teachers are preparing children for their early academic careers. To further this understanding, the current work used focus groups with parents and teachers of preschool and Pre-K students. Focus group discussions revolved around two primary questions: 1) how do you conceptualize school readiness for your children and 2) what are the current oral language practices in the home and classroom? Differences in school readiness beliefs and practices were present across all three groups. Parents and teachers emphasized different school readiness skills. Additionally, mismatch between parents' and teachers' beliefs about students' learning may result in tension between the home and classroom environments. Future interventions might promote stronger communication between these two groups – allowing for a shift in perspective about the value of specific developmental and educational activities.

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Keywords: preschool, pre-K, language, school readiness, cultural competency, focus groups, thematic analysis

INTRODUCTION

Poverty is pervasive across the United States. It affects both adults and children, but has especially significant ramifications for children who are exposed from a young age – specifically from birth to the preschool years [1]. The poverty rate for United States (U.S.) children has been increasing since 2000. Approximately 22% of Americans under the age of 18 grow up in poverty [2]. High concentrations of wealth have exacerbated growing income disparity across the country. Such disparity results in inequalities in access to quality healthcare, housing and education.

Young children growing up in low-income and impoverished homes experience challenges in both developmental and academic realms [3]. Prior work demonstrates that children from low-socioeconomic households face poorer outcomes in both verbal and math achievement, as well as on more basic cognitive tasks [4]. Children growing up in poverty may also demonstrate more emotional, social, and behavioral problems, due in part to their increased exposure to stress [5].

Two significant influences on young children's future academic success are their language facility and their overall school readiness, which includes elements such as social-emotional competency, attention, and motivation. To better support children growing up in low-income households, many interventions have been designed to bolster these foundational abilities. As verbal ability supports success in other academic domains, language and reading interventions are particularly prevalent for these children. These interventions, however, often neglect to account for cultural differences across communities. Views and practices of specific communities influence how language and school readiness are fostered and what elements and skills are preference. Effectively supporting children's language and school readiness necessitates understanding their ecological influences by learning about individual community's beliefs and practices. Incorporating culturally relevant practices would strengthen the effectiveness of existing interventions. Understanding a community's cultural values and beliefs is understood to be of utmost importance in public health communication [6], and should be included in early childhood educational interventions as well.

Within the community, children's early caregivers (e.g., teachers and parents) play a significant role. The supportiveness of the home and classroom environment can strengthen or impede children's healthy development. The views of both parents and teachers are thus vital to creating a clear and thorough understanding of the child's cultural context. The current study used focus groups to learn about the views of parents and teachers regarding young children's language and school readiness to inform more culturally relevant interventions.

The Importance of Children's Early Language Environments

Prior work has shown that culture influences the role and purpose of language, particularly in regard to how adults expect their children to learn and use language [7]. Children absorb the language spoken around them. Adults – particularly the children's primary caregivers – thus play an important role in what and how a child learns language. The quantity and quality of a caregiver's speech affects components of language ranging from vocabulary size to language processing efficiency [8]. Hearing greater quantities of speech typically improves children's vocabulary size and diversity, as well as increases the length of spoken sentences. Children whose caregivers speak more also tend to develop greater speech processing efficiency [9]. These individual differences in language among children – specifically regarding lexical quantity and sophistication – can be seen as early as one year of age, highlighting the importance of promoting language within the early caregiving environment [10]. In addition to the grammatical and functional elements of language that children learn via adults, they also absorb the social functioning of language [11]. Language allows children to understand their role in the community, as well as what is expected of them as they age. This strong social component reinforces the impact that the community's beliefs and views have on their children's language development.

Research investigating the specifics of children's language outcomes based on differing language input has produced mixed results. This may in part be due to different measures of home language. While some studies define home speech as the entirety of language spoken in the home, others focus more on child-directed speech [12]. When in the home, parents may differ in the quantity of speech directed to other adults as compared to the quantity of speech directed to their child. Some researchers contend that this child-directed speech is even more critical than the overall spoken language [13, 14]. Child-directed speech, however, can serve multiple purposes. Parents can use directive speech – speech that is instructing children in some manner – or can use more elaborative speech, which serves to bolster conversation through back-and-forth communication. Differences in these types of speech can be seen among parents of different SES levels as well as among different ethnicities [13, 15]. For instance, among lower-income African American families, conversations are more likely to involve commands and directives, where children are expected to argue their positions when conversing with adults [11]. These elements may not prepare children for success in the mainstream education system, where more referential and elaborate language and more formal grammar are used.

In addition to the language spoken in the home, parents' literacy practices – both formal and informal – impact their children's language development. In general, formal literacy activities refer to those that focus specifically on the code, or print, whereas informal activities often involve exposure to print material, but concentrate on meaningful components such as story content or question-asking [16]. Joint activities such as shared book reading increase emergent literacy skills such as phonological and print knowledge, as well as more conceptual knowledge. Acquisition of such skills may take place at different times during storybook reading [17], but all are critical components to a child's later ability to read and comprehend. Parents may view certain language and literacy practices as ways to support their children's success in school. For this reason, the current work aimed to better understand parents' home language practices by eliciting conversations about school readiness.

Early School Readiness

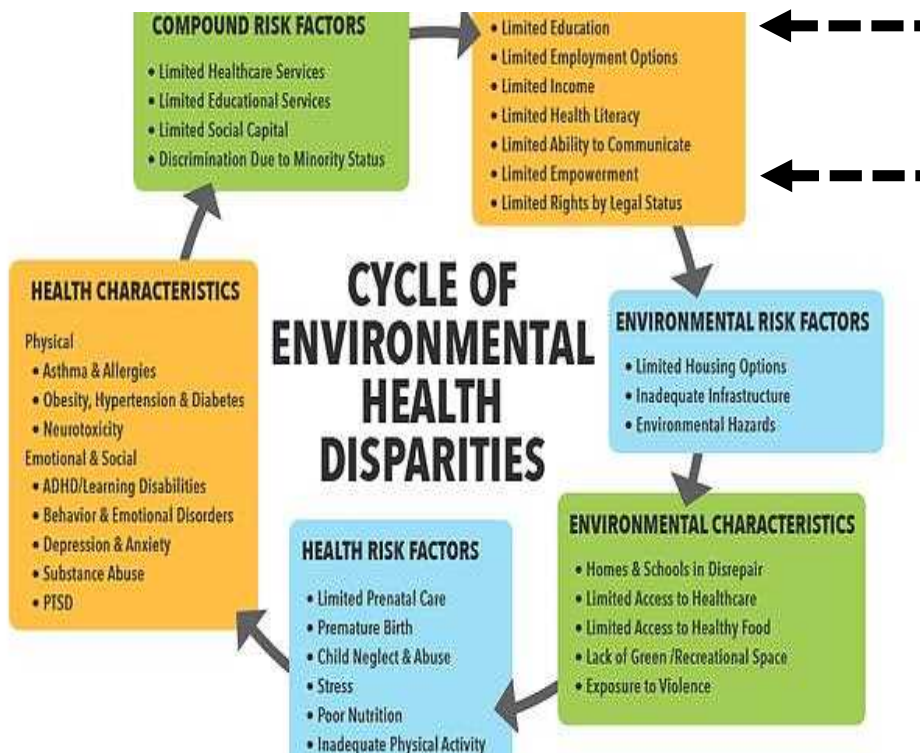
Children's early success in school is not solely dependent upon their language abilities. School readiness encompasses a variety of skills ranging from academic to social-emotional to physical development. School readiness is particularly critical as children move from preschool to kindergarten. Children who meet the relevant school readiness goals demonstrate a greater likelihood of later success in school, both socially and academically [18]. At a young age, children are transitioning from spending the majority of their time in the home with their immediate family members to the classroom where they participate in structured interactions with peers and teachers. As children make this transition from primarily family interactions to peer/teachers' interactions, they are learning expectations and standards from both parents and teachers. Due in part to the differences between the home and classroom environments, parents and teachers may emphasize different skills – and consequently prioritize specific goals in a different manner. The current study led separate focus groups with parents and teachers in order to allow for an accurate representation of each group's beliefs to emerge.

Prior research has emphasized distinct differences between parents' and teachers' views on school readiness. In general, parents emphasize the importance of formal academic skills over social and behavioral skills [19]. Other studies have revealed that parents' views on school readiness are often related to their education level and socioeconomic status. Parents living in low-income areas felt that skills such as knowing phone numbers, how to count, and letters of the alphabet, were the most important readiness skills [20]. In an urban school district in New York, there was a greater home emphasis on compliance with authority and basic knowledge, such as knowing body parts, colors, and the alphabet [21]. Teachers' conceptions of readiness tend to include a range of social, emotional and cognitive skills. For instance, a study of kindergarten teachers tended to view preparing children for satisfying the social demands of schooling as of higher priority than academic skill development [22]. In regards to these social expectations, teachers typically refer to whether a child can verbalize their needs and desires, take turns with other students, and follow classroom directions. Teachers' expectations for students entering kindergarten also influence their judgments of children's problems and direct their attention to specific areas [23].

While research regarding parents' and teachers' conceptions of school readiness was robust over a decade ago, few recent studies have continued to examine these differences. This is in spite of the fact that readiness standards have changed dramatically over the past decade, and thus academic and developmental expectations for children may be quite different. To best prepare children for later success, it is important to understand the emphases of parents and teachers on school readiness components. More specifically, it is important to understand the emphases of parents and teachers within culturally, economically, and ethnically diverse settings. Both school readiness and language usage have been conceptualized as culturally dependent constructs [6]. The future societal roles caregivers envision for their child may influence what elements of school readiness they deem most important. As such, uncovering a specific community's beliefs about school readiness is vital to the development of future academic interventions.

The Current Study

Many prior interventions designed to promote children's linguistic, social, and academic development are grounded in middle class, majority practices, despite the differing values and practices of many diverse communities. To more effectively support developmental outcomes of children growing up in low-income households, we need to ground our interventions in the cultural values of the community, and better understand how parents and teachers are preparing their children for their early academic careers. We can understand the cycle of environmental health disparities as being perpetuated in part by cultural practices, but in order to determine how we can most effectively break this cycle – specifically in regards to education and language/literacy and communication (Figure 1), we need to understand what those cultural practices are. The goal of this work was to understand how parents and teachers of preschool and pre-K students, specifically those growing up in low-income households, conceptualize “school readiness,” how they subsequently help their children prepare for success in school, as well as what types of oral language practices are occurring in the home and classroom. The current study used focus groups to uncover the views and beliefs of parents and teachers. The two guiding research questions underlying the discussions within the focus groups were: (1) How do parents and teachers conceptualize school readiness? (2) What are the characteristics of oral language practices in the home and in the classroom?



Note: Arrows indicate where the current project intervenes to break the cycle of environmental health disparities.

Figure 1. Breaking the cycle of environmental health disparities.

METHODS

Research was conducted at one early childcare center in a large metropolitan city. The center provides services for children age birth through five and has multiple preschool and pre-K classrooms. The center is part of a larger organization that serves children growing up in low-income households. Teachers and parents of both preschool and pre-K children were invited to participate in this research. Recruitment occurred via flyers posted in the center as well as announcements sent to parents and teachers from center administrators.

Focus groups for teachers and parents were conducted separately. Three focus groups were held. One focus group was for preschool and pre-K teachers, one focus group was for parents of preschool students, and one focus group was for parents of pre-K students. One or two graduate research assistants led all focus groups.

Twenty-three African American men and women participated in the three focus groups. Three participants were male and 20 were female. Eight preschool parents participated, four pre-K parents participated, and eleven preschool and pre-K teachers participated. Prior to beginning the focus groups, participants were given consent forms to sign. After consent was acquired, all focus groups were audio-recorded. Focus group participants' comments directed the conversations, but research assistants provided guidance via additional questions as needed. Sample focus group prompts are included in Table 1. The duration of each focus group varied from one to one and a half hours.

Table 1. Sample focus group prompts

Research Question 1: How do parents and teachers conceptualize school readiness?	What do you do to help your child (student) succeed in school?
	What skills do you think are most important for your child (student) to succeed in school?
	What are some things you tell your child (student) about being a good student?
	What are the important things you think your child (student) should know at this age?
Research Question 2: What are the characteristics of oral language practices in the home and in the classroom?	How often do you have long talks with your child (student)? What kinds of things do you talk about?
	Do you make up stories to tell to your child (student), if so, what kinds of stories are these?
	What types of questions do you ask your child (student)? How often do you do this?
	What type of books do you and your child (student) like to look at? How often do you all read together?

Data Analysis

A trained graduate research assistant transcribed all focus groups. Focus group transcripts were analyzed using the thematic analysis framework developed by Braun and Clarke [24]. Thematic analysis follows six primary stages: 1) familiarizing yourself with the data, 2) generating initial codes, 3) searching for themes, 4) reviewing themes, 5) defining and naming themes, and 6) producing the report. Themes are intended to capture elements relevant to the research questions that emerge consistently throughout the data set.

A key step within thematic analysis is determining how to qualify or quantify the 'prevalence' of themes. One method for doing so is taking an exact count of conversational elements that are present. A potential weakness within this technique, however, is that the most prevalent conversational elements may not answer the research questions. Elements mentioned less often might provide more direct insight into those questions. For this reason, rather than relying on exact counts, the current research specifically examined conversational components that captured an important element related to the research question. Exact counts of themes are thus not included within the results.

RESULTS

Conversations from the focus groups revealed four primary themes. Two themes revolved around differences in beliefs or practices between the groups of participants, one theme depicted the language practices that parents and teachers felt were important for children's school readiness, and one theme emphasized group similarities.

Differences in Beliefs between Parents and Teachers

In both the pre-K parent focus group and the teacher focus group, elements of miscommunication between teachers and parents and misalignment between their beliefs regarding school readiness arose. For instance, teachers emphasized informal opportunities for teaching and learning, whereas parents – specifically pre-K parents – felt that their children's primary learning took place in formal, structured activities. The majority of Pre-K parents felt that skills such as knowing how to write your name properly, or being able to trace letters and numbers, were vital to their success in school. Supporting these skills required parents to sit with their child one-on-one, guiding them through their practices. One parent mentioned how these home experiences were different from what her children received in the classroom. She said, "They just letting you have circle time all day, and you just getting the learning when I'm home with you at the table." Parents of pre-K children also discussed the influence that technology had on their children's learning. Many parents referenced using educational programs, videos or applications as learning supplements for their children. Pre-K parents mentioned wanting more communication with teachers to guide their practices, and there was a sense of bitterness when one parent said "...But I haven't had a report from the teachers, so I'm not even really sure they're still doing it."

In contrast to the formal activities emphasized by pre-K parents, both preschool and pre-K teachers believed that children's learning experiences were richest in moments of play and exploration. Teachers viewed these activities as more developmentally appropriate than the formal learning activities they believed parents preferred. Moreover, teachers believed that parents thought that the children's playing was "just playing" – rather than "developing skills while they're playing."

The misalignment between parents' and teachers' views arose in the teacher conversation as well. Teachers appeared to sense parents' emphasis on formal education over informal education – referencing how parents gave them more respect when they led organized

activities rather than letting students have time for free play or exploration. One teacher stated, “Parents need to know what school is and what is developmentally appropriate for children.” Teachers also felt that parents expected them to do more behavioral management than teaching. There was substantial frustration due to the fact that they were viewed more as nannies than educators. Many teachers believed that parents used them to provide the discipline when they themselves didn’t want to; “They make you be the bad guy to do the parenting for them.” In general, teachers wanted parents to take more responsibility for their actions, teaching their children by example. Referring to a parent who didn’t follow the classroom hand-washing policies, one teacher said, “...it starts at home. It starts with the parent. You’re the child’s first teacher, your child sees you doing that, and then they’ll automatically do it too.”

Regarding differences in philosophies of education, one teacher mentioned that she had witnessed a generational gap in what constitutes education. This teacher discussed how this generational gap is seen in both parents and teachers. In teacher training sessions, the developmental emphasis within education had only recently arisen, and was influencing practices within the classroom. Just as teachers were exposed to multiple educational philosophies, groups of parents from different generations have had different academic experiences. Their academic experiences influence their perception of what type of education is most effective and how it should be structured. According to some teachers, parents expect the same type of education for their child that they themselves received. Understanding what educational activities are developmentally appropriate for their children is important not just for teachers, but for parents as well.

Differences in Beliefs between Preschool and Pre-K Parents

Two separate focus groups were held for parents of preschool students and parents of pre-K students. Themes discussed in each of these focus groups were strikingly different. Parents of preschool students emphasized the importance of supporting character traits such as independence, self-awareness, creativity, and responsibility. For them, these abstract qualities were vital to their child’s future success in school. One parent said, “I encourage him to be very independent, so that he feels that he can do anything. I allow him opportunities to [...] accomplish things. I try to encourage creativity because I feel that is something that in many ways lacks with our little ones.” To support this creativity and independence, many parents discussed strategies for extending conversation, “not ask[ing] yes or no type questions,” in order to support their child’s interest in specific areas. Several parents mentioned scenarios in which they could support their child’s interests, such as taking field trips, conducting science experiments within the home, and participating in music classes.

Parents’ desire to support their children in these more abstract and creative qualities was not present in the conversation with pre-K parents. Instead, the primary emphasis was behavioral compliance. All parents mentioned that having good behavior was the most important component of being a good pre-K student. One parent said, “Behavior is most important to me ‘cause they can’t learn anything if you’re acting loud and crazy.” Paying attention to authority figures and being respectful to them were key component of maintaining good behavior. References to listening to the teacher were common; “I tell my

kids to sit down and listen to the teacher. Don't over-talk your teacher. Listen to what she says, then respond." These behavior rules were especially important to those parents whose children were girls. Whereas parents felt that their male children listened to instructions, the girls were consistently referred to as "having a sassy mouth," "doing what they want to do," and "playing the parents against each other."

Parents' Beliefs about Oral Language Practices

One aim of the current study was to learn more about oral language practices within the home and classroom. Separating references to language practices from discussions of school readiness, however, was challenging. Parents talked about strategies to promote their children's language abilities, such as reading and writing practices, as they related to their child's success in school. Within the context of school readiness, a dichotomy between directive and elaborative language arose between pre-K and preschool parent discussions. As previously mentioned, directive speech is meant to instruct, whereas elaborative speech is meant to foster back-and-forth communication. Pre-K parents used more directive language strategies, discussing their use of formal teaching practices to support their children's verbal and writing ability. These parents mentioned components such as tracing letters, teaching their children to spell and write their names, and learning how to count to 100. Preschool parents, however, discussed using more elaborative techniques. These parents talked about using open-ended questions to promote language development, and capitalizing on their child's interests. As one parent said, her daily goal was to "try to dialogue with my son and do conversation."

Groups' Shared Investment in Supporting Their Children

An important component of all three focus groups was that both parents and teachers strive daily to support their children. While this support may not manifest itself in the same manner among the different stakeholders, the entire community's desire to provide a better future for their children was evident in all conversations. When asked what the best thing about being a parent was, parents responded with statements such as, "We build and we grow and we learn together," "Being a great example to your child," and "We have these two little people who love us unconditionally." Teachers shared this same enthusiasm for supporting their children, saying, "You know, family has support here, but my stake is for the children."

DISCUSSION

Overall, parents and teachers talked more about general school readiness concerns, rather than focusing solely on language. Both groups did mention certain language practices, but these comments were primarily embedded within readiness goals. This shift may reflect broader policy changes affecting early childcare centers' learning standards and frameworks.

These frameworks have begun to focus on more than just reading and math, to include social, emotional, and cognitive aims as well.

The current work confirmed prior research findings regarding parents' and teachers' beliefs about school readiness [20-22]. Definitions of school readiness are common, but these definitions vary among different groups of individuals. Among parents and teachers, school readiness goals ranged from abstract qualities such as independence and self-esteem, to learning numbers and letters, to knowing how to behave appropriately. Even after the components are delineated, beliefs regarding their relative importance differ. In the current work, there were philosophical differences regarding the purpose, practices, and theories of early childhood education between parents and teachers. Perhaps more importantly it appeared that these differences in beliefs about education practices negatively impacted the relationship between parents and teachers. The misalignment between parents and teachers resulted in tension – despite both groups having the same goal of best supporting the development of their children.

One limitation of the current work is related to recruitment issues. Parents who elected to participate in the focus groups may not provide an accurate representation of the beliefs and practices of all parents within the childcare center. Teachers who referenced struggles with parents may be referring to less involved parents, likely those who did not participate in a focus group. Future work should attempt to recruit a wider sample in order to gain a more holistic view of the beliefs and practices of specific communities. Obtaining a larger sample, specifically one including parents of varied levels of involvement, would promote greater generalizability to other populations. An additional limitation of the study was related to the two research questions. The study aimed to better understand parents' home language practices as well as their beliefs regarding school readiness. Separating discussions of language from discussions of school readiness was challenging, perhaps because parents had already been primed with the first question to discuss school readiness. Future studies using focus groups should develop more nuanced questions in order to understand language as separate from formal readiness practices.

Findings from the current work have wide-ranging policy implications, specifically for parent and teacher development. Understanding the views of key stakeholders, such as parents, teachers, and community leaders, provides a method to encourage bottom-up policy development. Head Start, the largest federally funded childcare provider, considers parent-teacher communications to be of utmost importance to children's early learning. Head Start emphasizes that parents are true partners in their children's development and education. Activities such as parent-teacher conferences, and individual goal-setting within those conferences, make up a central portion of parent-teacher communication. Some programs, however, have experienced lower levels of parent involvement than desired. While beneficial, communication strategies may suffer if parents' and teachers' beliefs about basic school readiness are not aligned. Knowing how each set of caregivers views children's school readiness may promote more productive conversations within teacher-parent conferences. Future interventions need to capitalize on the shared investment of parents and teachers in the lives of the children they support. Enhancing parent and teacher collaborations may require more opportunities for interaction, in safe spaces outside of conferences. If parents are to believe that they are truly partners in their child's education and development, then their beliefs must be heard and validated more by teachers. Conversely, teachers need to share their views about what classroom activities are most developmentally appropriate for their

children. The results from this work emphasize this need - indicating that common educational and developmental goals and standards for children need to be established. For a community to best support their children, interventions must be grounded in their beliefs – but their beliefs must first be better aligned.

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Chapter 22

“I WAS SCARED OVER THERE.” FAMILY WELL-BEING AFTER RELOCATION FROM A DISTRESSED PUBLIC HOUSING DEVELOPMENT

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ABSTRACT

This study examines changes in well-being among families relocated from the Boulevard Homes public housing development in Charlotte, North Carolina. Prior to demolition, Boulevard Homes had high rates of violence, drug use, and teen pregnancy relative to other neighborhoods in the city. Households were relocated to another public housing development or to private-market housing with a voucher and were provided case management services for up to five years. Fifty-five percent of those living in Boulevard Homes were children under the age of 19 years. Methodology: This study utilizes mixed-methods and a socio-ecological approach to understanding the context of adverse childhood experiences, while living in a distressed public housing development. We asked how well-being was affected five years after relocation. Quantitative methods examine which variables of interest were most affected by the move and associated with an improvement in overall quality of life. Semi-structured interviews conducted in 2015 contextualize the quantitative findings. Results: Both the quantitative and qualitative data indicate that relocation resulted in significant improvements in perceptions of safety amongst those individuals who stated their life was “much better” than when they lived in Boulevard Homes. Parents cited safety and well-being concerns for their children when discussing the positive outcomes of the move. Discussion: Results confirm previous housing mobility studies – providing quality housing in safe neighborhoods improves well-being. To break the cycle of adverse childhood experiences and poverty leading to

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health disparities, communities must seek to improve living conditions of vulnerable populations while providing services to increase economic mobility.

Keywords: public health, public housing, well-being, adverse childhood experiences, toxic stress, health disparities

INTRODUCTION

Adverse childhood experiences (ACE) such as abuse, neglect, household dysfunction, and exposure to violence have been linked to poor behavioral decision-making and increased incidence of mental health diagnoses and chronic health conditions [1]. Adverse experiences during childhood, which continue over a long period of time as opposed to single events or brief periods, may result in the development of toxic stress [1]. Toxic stress occurs when the body's stress response system is activated over a long period of time. Children exposed to extreme poverty or hunger, repeated acts of violence, and abuse or neglect as a result of parental substance abuse and maternal depression experience chronic insecurity and fear resulting in toxic stress [1]. The physiological responses to toxic stress causes the body to biologically embed these early adverse experiences and triggers the neuroendocrine, autonomic, metabolic, and immune systems to malfunction leading to an increased risk of early mortality [1].

While not specifically intended to address ACE or toxic stress, the Department of Housing and Urban Development's HOPE VI program delivered interventions that addressed both concerns. From 1993–2010, HOPE VI provided funding to local housing authorities to redevelop highly distressed public housing developments [2]. During redevelopment, households could opt to relocate to another public housing development or to private-market housing with a Housing Choice Voucher (HCV) also known as Section 8. Many households – especially those relocating with a voucher – moved to higher-quality and safer neighborhoods, resulting in a reduction of ACE and improvements to health and well-being [3].

This paper explores how HOPE VI affects individual and family well-being when mothers with dependent children relocate from a highly distressed public housing development to better quality living environments. It adapts Shonkoff's framework of health disparities [4] to examine how the environment in which families live contributes to maternal health and well-being and how these, in turn, affect children's current and future well-being. We hypothesize that:

- Parents who report greater safety and neighborhood satisfaction post-relocation will report improved measures of well-being.
- Children will benefit from the move to better neighborhoods due to reductions in exposure to harmful environmental factors, increases in healthful factors, and improvements to maternal health and well-being.

We find that moving families away from a community marked by violent crime to new neighborhoods where families feel safer from violence and property crime had a significant impact on feelings of well-being.

In this paper, we explore how the socio-ecological environment in which individuals live affects their health and well-being either through increased exposure to stressors and risk, or protections from these potential harms. We then examine how housing mobility interventions may serve to remove households from many of the environmental risks associated with reductions in health and well-being. Finally, we discuss how HOPE VI, which combines mobility and support services interventions, seeks to address the socio-ecological environments of highly vulnerable public housing residents by moving the household from distressed public housing developments to better living conditions while providing up to five years of community support services to improve household economic mobility. Our study of the Charlotte Boulevard Homes HOPE VI project is used to illustrate how HOPE VI aims to intervene in the cycle of environmental health disparities experienced by children and adults living in distressed public housing. Finally, we recommend how policy makers can intervene in the cycle of health disparities and improve overall well-being by providing services to address the social determinants of health.

Neighborhood Effects on Well-Being

We begin with a brief introduction to well-being. Since the World Health Organization (WHO) declared in 1946 that "health is not the mere absence of diseases but a state of well-being" [5], researchers, physicians, policy makers, and others have sought to define and measure the concept [6]. Well-being is complex; it encompasses the quality of individual health and relationships as well as an individual's sense of security and agency. These are, in turn, intrinsically linked to the individual's environment and access to resources. Well-being was defined by Shin and Johnson as "a global assessment of a person's quality of life according to his own chosen criteria" [6] and by the WHO [6] as,

People's perception of their position in life in the context of the culture and value systems in which they live, and in relation to their goals, expectations, standards, and concerns. It is a broad ranging concept affected in a complex way by the person's physical state, personal beliefs, social relations and their relationships to salient features of their environment

As a multidimensional concept, it takes into account many aspects of an individual's life that combine to produce an overall feeling of well-being [6]. Although well-being is sometimes established through application of a set of objective criteria such as income, chronic disease, and access to key resources such as housing, safe water, nutrition, and education, it can also be measured by asking the individual to rate his or her own sense of well-being or overall quality of life [7]. The individual considers the many dimensions – health, income, safety, happiness, and achievement – and determines whether these dimensions combine to produce either a global feeling of positive or negative affect [6].

Socio-ecological models explore how the ecology of the environment impacts the well-being of those living within the environment [7]. Our social ecology includes our immediate

family environment as well as the neighborhood in which we live, work, play, go to school, and meet friends. Children present a special case of social ecology as they have very little control over their environments. They live within families, families live in houses, and houses are located within neighborhoods. This “nested” aspect of social ecology means that to understand health and well-being, we must take into account not only the characteristics and biology of the individual, but also their family, home, and neighborhood environments. These linked environments are collectively referred to as the social determinants of health: the quality and quantity of access to resources as a result of education, of income and of where we live, work, and play [8].

In the United States, the resources provided through municipal services such as schools, police, and parks are largely funded by local tax revenues, particularly property taxes. As a result, neighborhoods with higher concentrations of low-income residents generally have lower-quality schools, strained public services, fewer parks, and a less robust business community [4]. Historical practices of legal segregation and on-going practices of social and economic segregation have produced many low-income neighborhoods with significant minority populations [5].

These low-income neighborhoods are also more likely to be burdened by extremely poor housing conditions and locally unwanted land uses (LULUs) such as high speed roads and pollution sources such as transportation depots. The social, economic, and physical factors of low-income neighborhoods also increase the incidence of crime and violence [4]. Environmental risks in the neighborhood and poor quality housing contribute to the development of chronic health conditions such as asthma, anxiety, and depression as well as acute injuries such as those related to unsafe traffic, poor housing conditions, and violence [4]. The physical, economic, and social conditions of these neighborhoods often isolates residents from environmental resources such as grocery stores and parks and from the social and economic resources of job and educational opportunities [7].

Poverty, violence, and isolation from opportunity contribute to stress, fear, and distrust within these communities making them less able to mobilize the benefits of social capital [7, 9]. Collective efficacy, one form of social capital, comes from the social cohesion born of a sense of shared experience and responsibility. Social cohesion empowers neighbors to address problems within their community. When neighbors are stressed and fearful, they are reluctant to become involved and invested in their communities [11]. Bridging social capital is another form of social capital which occurs when diverse groups of people share a wide range of knowledge, access to jobs, and other resources across informal networks. The information shared through these networks provides greater opportunities to improve household and neighborhood conditions than does more traditional bonding social capital which tends to occur between family and friends with similar sociodemographic characteristics [12]. Individuals who live in neighborhoods that lack diversity of economic and social resources are less likely to benefit from the information sharing resulting from bridging social capital, resulting in further isolation of the household [12].

Stress resulting from living in high-poverty neighborhoods with significant social disorder and insufficient resources may lead to depression and anxiety for many of the individuals living there [13, 14]. Residents in these neighborhoods are almost twice as likely to suffer from depression as residents living in higher-income neighborhoods, even after controlling for socioeconomic and health factors [15, 16]. The individual does not need to be directly affected by social disorder and crime to develop mental health disorders such as

anxiety and depression. Perception of social disorder and fear of future risk of becoming a victim also increase the odds of adult depression [17]. Neighborhood stressors and the lack of social supports contribute to the development of chronic mental health disorders [13, 14, 17].

Children in high-poverty areas are at even greater risk as a result of the reduced opportunities and greater exposure to negative experiences and of the negative effects these neighborhoods have on their caregivers [9]. High-poverty neighborhoods lack access to quality resources such as schools and parks, and children living in these neighborhoods are exposed to greater rates of social disorder and environmental hazards such as air, water, and noise pollution [4, 9]. These children are also more likely to grow up in female-headed households that lack financial, social, and emotional resources and security to protect them from these hazards [9, 11].

Children suffer as a result of familial poverty and maternal stress. Poor, single, mothers living in high-poverty neighborhoods are at higher risk for developing mental health disorders, particularly depression and anxiety [6–9, 12–14]. These mothers are less capable of effective parenting and more likely to neglect or abuse their children as a result of their mental health status or substance use [14, 15]. Maternal neglect and inconsistent parenting practices negatively affects children's health [20] and their educational outcomes [21]. These outcomes remain even after controlling for socioeconomic factors [6–10, 16]. Children living in high-poverty neighborhoods have a greater risk for increased harm not only because they are exposed to environmental and social hazards but also because their families do not have the financial and emotional resources to adequately protect them and mitigate the harm [12–15].

Toxic Stress: Its Timing and Impacts on Adult Outcomes

Stress is one of the body's mechanisms for protecting itself; the complex psychophysiological response serves to keep us safe in times of danger. Not all stress, however, is protective [1]. Stress can be managed and normalized when experienced within the context of safe and supportive relationships. Tolerable stress includes those experiences which could potentially alter brain structure due to increased and prolonged cortisol production but which are mitigated through experiences of safe and supportive relationships. Toxic stress occurs when an individual is exposed to prolonged, frequent, or particularly intense events which trigger the body's stress-response system in such a way that brain architecture and other body systems are significantly and permanently affected [1].

Thus, stressful experiences during childhood can produce debilitating life-long effects if not sufficiently mitigated by the care of supportive relationships. Extreme poverty, caretaker abuse or neglect, family or community violence, maternal depression, and parental substance abuse can trigger a heightened and prolonged stress-response resulting in cognitive impairment, chronic mental illness, and physical disease. These adverse childhood experiences (ACE) impact children differently from adults because of their specific developmental, psychological, and physiological vulnerabilities [16]. Exposures occurring at particularly susceptible periods can permanently alter the body's regulatory physiological processes. Adverse childhood experiences that contribute to toxic stress have been linked to increased risk of chronic heart and lung disease, cancer, anxiety and depression, and

behavioral risks such as substance abuse and addiction, teen pregnancy, obesity, smoking, and physical inactivity [1].

Children who grow up in poverty are at greater risk for ACE and toxic stress due to their disproportionate exposure to family chaos, environmental stressors, and traumatic experiences [1]. Residing in high-poverty neighborhoods increases children's risk for toxic stress because of their exposure to the ACE of extreme poverty and community violence and the likelihood that their mothers will suffer from depression and anxiety [16]. These mothers are less likely to be able to protect their children and more likely to neglect or abuse their children due to the environmental stressors experienced [1, 17–21]

Theory of Mobility on Individual and Family Outcomes

Recognizing the potential harm of concentrated poverty, some scholars and policy makers argue that households living in neighborhoods of concentrated poverty should be “deconcentrated” by moving them to economically and socially integrated neighborhoods [3, 10–12, 22]. These policies seek to address the enduring interconnectedness of race, poverty, and disadvantage which contribute to the social determinants of health [8, 11, 22]. Programs and policies that have sought to address concentrated poverty have included Gautreaux, Moving to Opportunity, HOPE VI, and the expansion of the housing choice voucher (HCV) program [3, 22, 23].

One of the first “tests” of deconcentration came as a result of a 1966 lawsuit brought by Chicago public housing residents and the NAACP against the Chicago Housing Authority. The suit alleged that the housing authority had violated the 5th Amendment and the 1964 Civil Rights Act by siting their public housing developments in neighborhoods that were majority African-American with high concentrations of poverty and social disorder. In 1976, a US Supreme Court decision, *Hills v. Gautreaux*, ordered the Chicago Housing Authority to provide HCVs to residents so they could move out of the disadvantaged neighborhoods [3]. Eligible households were given an HCV and assigned housing in neighborhoods that were less than 30% African-American.

After several years, those individuals living in suburban neighborhoods reported much better outcomes. These residents were more likely than their urban counterparts to be employed and off welfare, report better mental and physical health, and have completed educational programs (such as high school for children living in the household) [3]. The results provided some of the first evidence that deconcentration was an effective strategy to combat urban poverty, and provided support for a major policy and funding shift away from traditional public housing developments and toward increased funding for HCVs and mixed-income developments [23].

Moving to Opportunity (MTO) and HOPE VI

As part of this funding and policy shift, Congress and HUD also funded two new programs: the Moving to Opportunity (MTO) housing experiment and the HOPE VI housing redevelopment program. Amongst other goals, both 1993 initiatives sought to expand

understanding of the impact of deconcentration on the outcomes of households living in public housing [3].

MTO was an experiment designed to rigorously test the results of Gautreaux. It randomly assigned public housing households to one of three groups. A 'treatment' group received an HCV and relocation counseling that required the households to initially relocate into a neighborhood with less than a 10% poverty rate. A "comparison" group received an HCV without any location restrictions or counseling, and a "control" group remained in public housing. Families in all three groups were tracked between 1995 and 2005 [3].

To the disappointment of policy makers, findings from MTO did not match those of Gautreaux. Within the experimental group, adults reported little to no improvement in employment or income, children's educational outcomes did not improve, and there were even some increases in delinquency among young males [3]. Despite this, there was some cause for optimism. Women and girls experienced significant improvements in physical and mental health which were attributed to changes in the women's sense of safety. Adult women experienced reductions in obesity, and both women and girls reported reductions in depression and psychological distress comparable to effective psychotherapeutic treatments [3]. New research has found that although parents did not experience economic benefits from the move, their children, who were under age 13 at the time of the move, did benefit. These children were more likely than their comparison or control counterparts to attend college and attend better colleges (by 2.5 percentage points), had better annual incomes by roughly \$3,500 (31%), and more likely to marry (by 2 percentage points) [24]. Together, these findings suggest that mobility strategies may prove to be an effective intervention for the social determinants of health [3, 7, 8, 23].

HOPE VI was another policy experiment to improve housing conditions for and reduce the concentration of public housing residents in high-poverty neighborhoods. HOPE VI provided funding to: (i) help households in developments targeted for demolition move to either another public housing development or to private rental housing with the support of a HCV during redevelopment; (ii) provide community support services (CSS) to ease families' transitions from the original housing unit to their new communities and help them make economic gains, and (iii) redevelop the original site to new, mixed-income housing. The program envisioned that displaced residents, would return following redevelopment [25].

Like Gautreaux and MTO, one of the goals of HOPE VI was that families would experience gains in employment, education, income, and health once they were removed from their poor living environments. HOPE VI, however, sought to expand upon the mobility intervention by requiring housing authorities to provide community supportive services (CSS) to relocated residents in an effort to increase household economic mobility. These services assessed household needs and then helped connect residents to education and job training support as well as referrals for physical and mental health interventions and family counseling or other child-focused supports [3, 25].

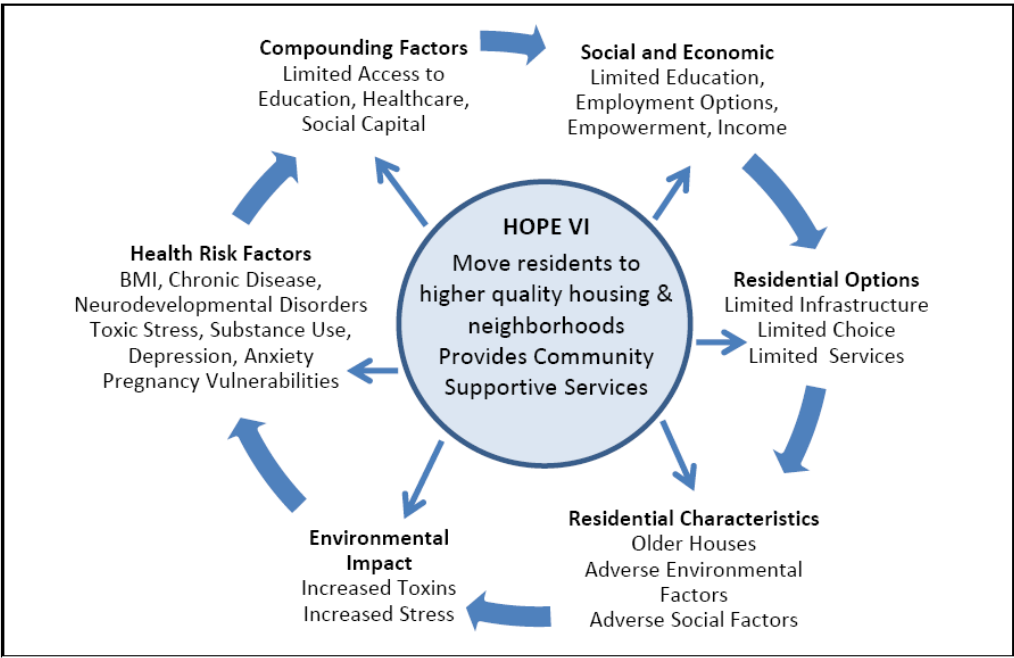
HOPE VI has produced mixed results. It largely succeeded in demolishing distressed public housing developments, reducing crime, and improving property values in the surrounding neighborhoods [25]. It has not, however, significantly increased the economic mobility of residents or effectively returned former residents to the redeveloped sites [25]. Most did not return because they could not meet income and employment qualifications for the mixed-income site or because they did not want to move out of their HCV-funded rental apartments or homes [25].

HOPE VI as a Health Intervention

Despite these criticisms, HOPE VI has positively affected the well-being of many relocated residents [3, 25, 26]. Although not envisioned as a health intervention per se, many of the program’s elements address the origins of health disparities [4, 7, 8]. Two of HOPE VI’s major goals – improving affected residents’ housing and neighborhood conditions and enhancing their economic mobility – can be viewed as environmental health interventions to reduce health disparities [4, 7, 8].

Figure 1 displays the cycle of environmental health disparities. HOPE VI interrupts this cycle by relocating residents into higher-quality housing and neighborhoods. Further, CSS addresses educational, employment, and health barriers by connecting the residents to education, job training and placement, and health services [3, 25].

Although the quality of public housing is regulated [18], public housing developments targeted for redevelopment through HOPE VI were older and suffered from inadequate maintenance and upgrades. Plumbing, HVAC, and roofing tended to be at or beyond their intended lifespans resulting in leaks and mold and mildew within units. Construction codes, in place when the developments were built, have since been upgraded to reflect increased knowledge of building materials and potential hazards. Improved understanding of physical plan and building design has also resulted in newer public housing developments that increase defensible space and promote positive social engagement [20].



Adapted from Shonkoff’s biodevelopmental framework for understanding health disparities [4] and Break the Cycle of Environmental Health Disparities [28].

Figure 1. HOPE VI as an intervention into the cycle of health disparities.

While the physical conditions of public housing developments targeted for demolition under HOPE VI contributed to poor physical health, the social conditions of these developments contributed to poor mental health. HOPE VI housing developments tended to be located in highly segregated communities with little access to retail stores or employment opportunities. Drug trafficking and other crimes were common in these neighborhoods. Few adults were likely to have completed high school or be employed. Finally, early child bearing and single parenthood contributed to these conditions which tended to be intergenerational [27].

In addition to these stressors, in order to qualify for traditional public housing, household income must generally be 30% or less of the federal poverty level [23]. Public housing in the US is not an entitlement: therefore, local housing authorities establish "preferences" to help them prioritize households on the waiting list [23]. Preferences often include homelessness, domestic violence, or child neglect or abuse. Together, these socioeconomic factors make public housing residents highly vulnerable to health disparities [1, 8].

As a result of these vulnerabilities and exposures to adverse childhood experiences, most residents subject to HOPE VI relocation reported very poor overall health, high rates of chronic health conditions and mental health disorders, and body mass index (BMI) scores indicative of obesity. These health conditions are not only worse in comparison to the overall population but also worse than comparable cohorts, including those in poverty and racial minorities [26].

STUDY SITE

Understanding the significant socio-ecological risks that households are exposed to while living in highly distressed public housing, our study seeks to understand how the wellbeing of mothers with dependent children is affected by a move from Boulevard Homes in Charlotte, North Carolina. We employ data collected as part of a larger evaluation of the Charlotte Housing Authority's (CHA) HOPE VI Boulevard Homes redevelopment. Using the 2010 and 2015 surveys in conjunction with resident interviews we seek to better understand the stressors experienced while living at Boulevard Homes and how these stressors were affected by moving to new residences and neighborhoods.

Boulevard Homes was originally constructed in 1969 on a 34-acre site, 4.5 miles west of downtown Charlotte. The development comprised 300 housing units in 121 buildings. By 2007, the development had significant physical and social problems; CHA's application to HUD notes that "demolition of all structures on the site is justified based on the extreme physical obsolescence of the units, buildings, and systems" [23]. Much of the deterioration was attributed to site and building design flaws which contributed to the development of mold and mildew within the units. Poor grading also led to flooding. Homes were damaged by obsolete construction standards and materials life cycles that contributed to roof leaks, plumbing prone to recurring problems including bursting pipes, and inadequate cooling and heating. Asbestos was also detected in the flooring materials and joint compound used in construction. All of these factors suggest residents were exposed to significant levels of environmental toxins prior to relocation. Access to the site and layout of the buildings also

contributed to physical isolation from the rest of the city and creation of “indefensible” spaces that fostered criminal activity and a sense of insecurity among residents [23].

Boulevard Homes was considered a “crime hot spot” defined as a location where there were five or more overlapping monthly incidences of crime. Incidences of violent crime (homicide, rape, robbery, and aggravated assault) were five times greater than the city average, juvenile crime was 2.8 times greater than the city average, and property crime was twice that of the city average [23].

METHODS

Quantitative data for this study are drawn from two surveys completed by Boulevard residents: one prior to relocation and a second five years after relocation. These surveys had response rates of 76% (223 of 291) and 52% (108 of 204) respectively. The sample is restricted to households that completed both surveys and included at least one child under the age of 19 at the time of the 2010 survey prior to relocation. This results in a survey sample of 44 households.

Qualitative data are drawn from the open-ended survey questions and from interviews with a randomly selected group of former Boulevard residents still living in CHA housing five years after relocation. While 20 heads of household were interviewed for the larger study, only 13 had a child under the age of 19. All interviews were recorded and transcribed.

Analysis

We were interested in learning how quality of life or well-being was affected by the move. We analyzed quantitative data using paired T-tests and Chi Square as determined by the data’s structure to measure for significant differences in the 2010 and 2015 variables associated with health and well-being and an individual’s likelihood to rate their overall well-being in 2015 as “much better” than when they lived in Boulevard Homes. Heads of household were asked, “Comparing your household’s overall quality of life, to that of Boulevard Homes, would you say your household’s current overall quality of life is: much better, somewhat better, about the same, somewhat worse, or much worse?”

Variables tested include perceptions of individual health, housing, and neighborhood (see Table 1). Health questions included overall health, number of chronic conditions, depression, anxiety, and a measure of food (in)security. Housing and neighborhood questions included perception of crime, perception of safety, opinion of current home, opinion of current neighborhood, and an index measure of social capital. Other variables of interest include age of the head of household and educational attainment, the household income as reported in June 2010 and June 2015, and the number of children age 17 years or under living in the home in December 2015.

Prior to analysis, we explored the presence and patterns of missing data that were found to be moderate and appropriate for imputation. Multiple imputations using Stata were conducted to create complete data sets. Standard statistical tests confirmed that the data were normally distributed within acceptable limits and did not require adjustment.

Table 1. Variable of interest

Variable	Survey Question	Type	Measure
Self-rated Health	In general would you say your health is...	Ordinal	1= Excellent - 5= Poor
No. Chronic Health Conditions	Asthma, Hypertension, Type2 Diabetes	Continuous	Sum 0-3
BMI	Calculated by reported weight and height	Continuous	Obese = >30
Accomplish Less Due to Anxiety	During the past four weeks, how often did y	Ordinal	0= None - 4=All of time
Work Less Carefully Due to Anxiety	During the past four weeks, how often did y	Ordinal	0= None - 4=All of time
CES-D Score	10 questions used to screen for depression	Continuous	Possible depression = >10
Age of Head of Household	Calculated by birthdate	Continuous	
Number of Children	Housing authority administrative records	Continuous	
Income in Thousands	Housing authority administrative records	Continuous	
Ran Out of Food	How often during past 12 months did you run out of food before you got money to buy more?	0/1	Sometimes or Often = 1
Sense of Safety	How safe would you feel being out alone in the parking lots, the lawns, the street, or sidewalks right outside your home at night?	Ordinal	4=Very Safe - 1=Very Unsafe
Social Capital	Do you know any neighbors who... have a car you could borrow, would babysit your children, are good at using a computer, are active in a community organization, would bring you medicine or food if you were ill, you can discuss personal matters with, would lend you a \$100"	Continuous	Sum yes/no responses, household assigned a score reflecting deviation above or below median
Months Active in Case Management	Housing authority administrative records	Continuous	0 - 57
Better House	Comparing your current housing situation to that of Boulevard Homes, would you say your current housing situation is...	Ordinal	5=Much Better - 1=Much Worse
Better Neighborhood	Comparing your current neighborhood to that of Boulevard Homes, would you say your current neighborhood is...	Ordinal	5=Much Better - 1=Much Worse
Overall Quality of Life	of life to that of Boulevard Homes, would you say your household's current overall quality of life is...	Ordinal	5=Much Better - 1=Much Worse

As mentioned above, qualitative data are drawn from two sources: open ended survey questions and semi-structured interviews with heads of household. The two open-ended survey questions were "What have been some of the best things about relocation from Boulevard Homes?" and "What have been some of the worst things about relocation from Boulevard Homes?" The semi-structured interviews asked about a wide range of experiences related to the move from Boulevard Homes including: finding and settling into a new home and neighborhood, children's adjustments to the new community and new school (if applicable), the health of the head of household and household members, employment and educational experiences, perspectives on the helpfulness of the CSS case management experience, aspirations for the future, and family interest in, or barriers to, moving back to the redeveloped site.

Qualitative data were uploaded into the data analysis program Atlas.ti and analyzed using deductive and inductive coding. Deductive codes included those based on the variables of interest such as health, safety, well-being, children, and violence. Inductive codes were also generated and applied as they emerged from the data. These included subjects related to fear, independence, and self-worth. Once coded, frequencies and co-occurrences were compared to findings from the quantitative data seeking themes of convergence or divergence across the two data sources.

RESULTS

The residents living in Boulevard Homes experienced a number of markers of social distress, particularly in comparison to other Charlotte area residents (see Table 2) [23]. In 2010, Boulevard residents had a median household income of \$8,088, 92.8% of households received food stamps, and only 20.4% of residents indicated employment as a source of income. In comparison, Charlotte residents reported a median household income of \$52,148 and only 13.1% received food stamps. Only 51% of the heads of household in Boulevard Homes have a high school diploma or GED. Youth living in Boulevard also struggled to complete high school — 14.3% were high school dropouts as compared to 5.1% — and reported very high rates of teen pregnancy — 21.6% as compared to 6.4% of Charlotte residents [23]. At the time of the move, there were 286 households with a total population of 828, 55% of whom were children; 152 were ages 0-5 (18%), 199 were ages 6-12 (24%), and 108 were ages 13-17 (13%) [23].

Tables 3 and 4 provide a summary of the quantitative variables. The age range for the head of household spans from 27 to 86 years and is indicative of grandparents either cohabitating with adult children and grandchildren or assuming parenting responsibility for their grandchildren. On average, Boulevard heads of household dropped out of high school sometime before reaching the 11th grade. Household income shows a broad range from zero to roughly \$36,000. When one high-income outlier is removed from the average, the new mean income is \$10,860.

Table 2. Boulevard Homes Compared to Charlotte Residents

	Boulevard Homes	Charlotte
Household Income	\$8,088	\$52,148
Food Stamps	93%	13%
High School Dropout	14%	5%
Teen Pregnancy	22%	6%

Table 3. 2010 Variable of Interest

Variable	Obs.	Mean	Std. Dev.	Min.	Max.
No. of Children	44	2.36	1.60	1	8
Avg Household Income	44	\$9,784	\$8,131	\$0	\$32,988
Overall Health	44	3.02	1.13	1	5
BMI	44	34.09	7.85	21.1	51.28
CES-D 10	44	9.20	5.25	2	24
Accomplished Less due to Anxiety	44	2.27	1.25	1	5
Worked Less Carefully due to Anxiety	44	1.82	1.11	1	5
No. Chronic Health Cond.	44	0.89	0.95	0	3
Food Ran Out	44	1.61	0.72	1	3
Perception of Safety	44	2.59	0.92	1	4
Social Capital	44	0.35	0.31	0	1

Table 4. 2015 Variable of Interest

Variable	Obs.	Mean	Std.Dev.	Min	Max
No. of Children	44	2.41	1.73	0	8
Avg Household Income	44	\$11,426	\$9,107	\$0	\$35,605
Overall Health	44	3	0.99	1	5
BMI	44	34.29	9.43	23.22	57.78
CES-D 10	44	9.25	5.26	0	23
Accomplished Less due to Anxiety	44	2.11	1.13	1	5
Worked Less Carefully due to Anxiety	44	1.82	1.15	1	5
No. Chronic Health Cond.	44	0.91	1.07	0	4
Food Ran Out	44	1.89	0.62	1	3
Perception of Safety	44	3.14	0.88	1	4
Social Capital	44	0.41	0.35	0	1
Age HOH	44	47.14	13.28	27	86
School Completed	44	10.98	2.13	0	14
Live in Section 8	44	0.91	0.29	0	1
Live in Better Home	44	4.16	1.20	1	5
Live in Better Neighborhood	44	4.20	1.09	1	5
Overall Quality of Life	44	4.20	1.07	1	5

Boulevard Homes had an unusually high number of children because it was one of the few developments with four and five bedroom units. Households that included children had between two and three children on average, but several households had between six and eight children. The average age of the children at the time of the relocation was just under nine years old. Households were given a choice of moving to another public housing unit or to move using an HCV, and 64% of all relocatees moved using an HCV. Almost all (91% or 40 of 44) households in our sample moved to a privately owned apartment or house with the assistance of an HCV. The percentage of HCV movers is higher in our sample because it is restricted to families with children, many of whom were anxious to trade public housing for their own home with a yard.

We began the analysis by conducting significance tests to understand which conditions in both 2010 and 2015 had a statistically significant effect (at the 0.05 level or above) on the household's overall quality of life in 2015. As seen in Table 5, those households that experienced lower levels of safety in 2010 while living in Boulevard Homes reported a much better quality of life after relocation.

Table 6 reviews the same variables of interest but also contains several variables that asked households to compare their current living situations to Boulevard Homes. Households that moved using a housing choice voucher, had higher household incomes, and reported that their homes and neighborhoods were better than when they lived in Boulevard Homes also reported higher overall quality of life in 2015. None of these results are surprising given the conditions at Boulevard Homes, many tenants' wish to live in a private rental home, and the fact that higher incomes improve most people's quality of life.

In contrast to these results, however, households that reported better overall quality of life were also more likely to report that they had run out of food in the past 12 months. This outcome is most likely due to the additional costs associated with renting a private home

rather than living in public housing. Also, individuals in this group may have been making enough money to lose benefits such as Medicaid and to have their food stamp benefits reduced.

**Table 5. T-test* of 2010 Variables' Impact on Overall Quality of Life
(Much Better or Not Much Better)**

		Obs.	Mean	Std. Err.	Std. Dev.	[95% Conf. Interval]		Pr(T , t)
Self-rated Health	QOL Better	24	3.13	0.22	1.08	2.67	3.58	0.52
	QOL Not Better	20	2.9	0.27	1.21	2.33	3.47	
	difference		-0.23	0.34		-0.92	0.47	
No. Chronic Health Conditions	QOL Better	24	0.92	0.19	0.93	0.53	1.31	0.82
	QOL Not Better	20	0.85	0.22	0.99	0.39	1.31	
	difference		-0.07	0.29		-0.65	0.52	
BMI	QOL Better	24	34.41	1.57	7.68	31.17	37.66	0.77
	QOL Not Better	20	33.71	1.84	8.24	29.85	37.56	
	difference		-0.71	2.4		-5.56	4.14	
Accomplished Less Due to Anxiety	QOL Better	24	1.29	0.25	1.23	0.77	1.81	0.91
	QOL Not Better	20	1.25	0.29	1.29	0.65	1.85	
	difference		-0.04	0.38		-0.81	0.73	
Worked Less Carefully Due to Anxiety	QOL Better	24	0.96	0.24	1.16	0.47	1.45	0.36
	QOL Not Better	20	0.65	0.23	1.04	0.16	1.14	
	difference		-0.31	0.34		-0.98	0.37	
CES-D Score	QOL Better	24	8.17	1.06	5.21	5.97	10.37	0.15
	QOL Not Better	20	10.45	1.15	5.15	8.04	12.86	
	difference		2.28	1.57		-0.88	5.45	
Age of Head of Household	QOL Better	24	29.88	2.39	11.7	24.94	34.81	0.44
	QOL Not Better	20	30.45	3.41	15.27	23.3	37.6	
	difference		0.58	4.07		-7.63	8.78	
Number of Children	QOL Better	24	2.54	0.37	1.79	1.78	3.3	0.43
	QOL Not Better	20	2.15	0.3	1.35	1.52	2.78	
	difference		-0.39	0.49		-1.37	0.59	
Income in Thousands	QOL Better	24	10.26	1.69	8.3	6.75	13.77	0.68
	QOL Not Better	20	9.21	1.81	8.1	5.42	13	
	difference		-1.05	2.49		-6.06	3.97	
Ran Out of Food* (χ^2)	QOL Better	24						0.75
	QOL Not Better	20						
	difference							
Sense of Safety	QOL Better	24	2.33	0.2	0.96	1.92	2.74	0.04
	QOL Not Better	20	2.9	0.18	0.79	2.53	3.27	
	difference		0.57	0.27		0.2	1.11	
Social Capital	QOL Better	24	0.3	0.07	0.32	0.16	0.43	0.24
	QOL Not Better	20	0.41	0.07	0.3	0.27	0.55	
	difference		0.11	0.09		-0.08	0.3	

* Unless otherwise noted as Chi-square

Table 6. T-test* of 2015 Variables' Impact on Overall Quality of Life (Much Better or Not Much Better)

		Obs.	Mean	Std. Err.	Std. Dev.	[95% Conf. Interval]		Pr(T > t)
Self-rated Health	QOL Much Better	24	3.04	0.19	0.91	2.66	3.43	0.76
	QOL Not Better difference	20	2.95 -0.09	0.25 0.3	1.1	2.44 -0.7	3.46 0.52	
No. Chronic Health Conditions	QOL Much Better	24	0.79	0.21	1.02	0.36	1.22	0.43
	QOL Not Better difference	20	1.05 0.26	0.26 0.33	1.15	0.51 -0.4	1.59 0.92	
BMI	QOL Much Better	24	35.09	1.9	9.32	31.15	39.02	0.55
	QOL Not Better difference	20	33.33 -1.75	2.17 2.88	9.71	28.79 -7.56	37.66 4.05	
Accomplished Less Due to Anxiety	QOL Much Better	24	1.29	0.24	1.16	0.8	1.78	0.25
	QOL Not Better difference	20	0.9 -0.39	0.24 0.34	1.07 -1.08	0.4 0.29	1.4 0.92	
Worked Less Carefully Due to Anxiety	QOL Much Better	24	0.92	0.25	1.21	0.4	1.43	0.54
	QOL Not Better difference	20	0.7 -0.22	0.24 0.35	1.08	0.19 -0.92	1.21 0.49	
CES-D Score	QOL Much Better	24	9.38	1.08	5.29	7.14	11.61	0.87
	QOL Not Better difference	20	9.1 -0.28	1.2 1.61	5.35	6.6 -3.52	11.6 2.97	
Age of Head of Household	QOL Much Better	24	46.9	2.39	11.7	41.93	51.8	0.89
	QOL Not Better difference	20	47.45 0.58	3.41 4.07	15.27	40.3 -7.63	54.6 8.78	
Number of Children	QOL Much Better	24	2.5	0.38	1.8	1.72	3.28	0.71
	QOL Not Better difference	20	2.3 -0.2	0.36 0.53	1.63	1.54 -1.27	3.06 0.87	
Income in Thousands	QOL Better	24	13.7	2.1	10.28	9.36	18.04	0.07
	QOL Not Better difference	20	8.69 -5	1.51 2.68	6.74	5.54 -10.41	11.85 0.4	
Ran Out of Food* (χ^2)	QOL Better	24						0.4
	QOL Not Better difference	20						
Sense of Safety	QOL Better	24	3.2	0.17	0.83	2.86	3.56	0.56
	QOL Not Better difference	20	3.05 -0.16	0.21 0.27	0.94	2.6 -0.7	3.49 0.38	
Social Capital	QOL Better	24	0.4	0.08	0.37	0.24	0.55	0.74
	QOL Not Better difference	20	0.43	0.07	0.32	0.28	0.58	
Educational Attainment	QOL Better	24	11	0.53	2.6	9.86	12.05	0.47
	QOL Not Better difference	20	11	0.32	1.45	10.32	11.7	
Moved with a HCV	QOL Better	24	1	0	0	1	1	0.02
	QOL Not Better difference	20	0.8 -0.2	0.09 0.08	0.41	0.61 -0.37	0.99 -0.03	
Months Active in Case Management	QOL Better	24	49.38	3	14.73	43.15	55.6	0.08
	QOL Not Better difference	20	55.45 6.08	0.96 3.41	4.3	53.44 -0.82	57.46 12.96	
Better House	QOL Better	24	0.96	0.04	0.2	0.87	1.04	0.0008
	QOL Not Better difference	20	0.55 -0.41	0.11 0.11	0.51	0.31 -0.64	0.79 -0.18	
Better Neighborhood	QOL Better	24	4.7	0.13	0.62	4.44	4.54	0.0004
	QOL Not Better difference	20	3.6 -1.11	0.28 0.29	1.23	3.02 -1.69	4.18 -0.53	

* Unless otherwise noted as Chi-square

Table 7. T-test of Change in Variable from 2010 to 2015 Impact on Overall Quality of Life

		Obs.	Mean	Std. Err.	Std. Dev.	[95% Conf. Interval]		Pr(T . t)
Self-rated Health	QOL Better	24	-0.08	0.22	1.06	-0.53	0.36	0.66
	QOL Not Better difference	20	0.05	0.21	0.94	-0.39	0.49	
			0.13	0.31		-0.48	0.75	
	QOL Better	24	-0.13	0.2	0.99	-0.54	0.29	
No. Chronic Health Conditions	QOL Not Better difference	20	0.2	0.11	0.52	-0.04	0.44	0.19
			0.33	0.25		-0.17	0.82	
BMI	QOL Better	24	0.67	0.93	4.56	-1.25	2.3	0.52
	QOL Not Better difference	20	-0.37	1.38	6.19	-3.27	2.52	
			-1.05	1.62		-4.32	2.23	
	QOL Better	24	0	0.27	1.32	-0.56	0.56	
Accomplished Less Due to Anxiety	QOL Not Better difference	20	-0.35	0.26	1.18	-0.9	0.2	0.36
			-0.35	0.38		-1.12	0.42	
Worked Less Carefully Due to Anxiety	QOL Better	24	0.21	0.35	1.69	-0.51	0.92	0.75
	QOL Not Better difference	20	0.05	0.34	1.5	-0.65	0.75	
			-0.16	0.49		-0.35	0.62	
	QOL Better	24	1.21	1.48	7.27	-1.86	4.27	
CES-D Score	QOL Not Better difference	20	-1.35	1.14	5.13	-3.75	1.05	0.19
			-2.56	1.94		-6.46	1.34	
Income in Thousands	QOL Better	24	3.44	2.67	13.06	-2.07	8.96	0.24
	QOL Not Better difference	20	-0.52	1.75	7.85	-4.19	3.15	
			-3.96	3.33		-10.69	2.77	
	QOL Better	24						
Ran Out of Food* (χ^2)	QOL Not Better difference	20						0.69
Sense of Safety	QOL Better	24	0.88	0.22	1.08	0.42	1.33	0.03
	QOL Not Better difference	20	0.15	0.22	0.99	-0.31	0.61	
			-0.73	0.31		-1.36	-0.09	
	QOL Better	24	0.1	0.08	0.39	-0.06	0.26	
Social Capital	QOL Not Better difference	20	0.02	0.1	0.43	-0.18	0.22	0.54
			-0.08	0.12		-0.33	0.17	
Educational Attainment	QOL Better	24	11	0.53	2.6	9.86	12.05	0.47
	QOL Not Better difference	20	11	0.32	1.45	10.32	11.7	
Moved with a HCV	QOL Better	24	1	0	0	1	1	0.02
	QOL Not Better difference	20	0.8	0.09	0.41	0.61	0.99	
			-0.2	0.08		-0.37	-0.03	
	QOL Better	24	49.38	3	14.73	43.15	55.6	
Months Active in Case Management	QOL Not Better difference	20	55.45	0.96	4.3	53.44	57.46	0.08
			6.08	3.41		-0.82	12.96	
Better House	QOL Better	24	0.96	0.04	0.2	0.87	1.04	0.0008
	QOL Not Better difference	20	0.55	0.11	0.51	0.31	0.79	
			-0.41	0.11		-0.64	-0.18	
	QOL Better	24	4.7	0.13	0.62	4.44	4.54	
Better Neighborhood	QOL Not Better difference	20	3.6	0.28	1.23	3.02	4.18	0.0004
			-1.11	0.29		-1.69	-0.53	

* Unless otherwise noted as Chi-square

Overall, the quantitative data supports our hypothesis that moving mothers with dependent children from a highly distressed public housing does improve the lives of many households. Moving with the support of an HCV was fully predictive of households reporting a much better overall quality of life. Also, most households reported feeling safer after relocation, which also positively impacted quality of life (see Table 7).

Despite these gains, the data did not reveal significant improvements in any of our measures of health. This may be related to the size of the sample but is most likely due to extremely poor health within the sample. The move and provision of community supportive services may be insufficient to alter the course of the adverse childhood experiences that have already marked the health of mothers and other caretakers within our sample.

Qualitative Results

Qualitative results confirm and expound on the quantitative findings. The top four responses to the open-ended survey question asking about the "best things about moving away from Boulevard Homes" (see Table 8) included having a better house (29%), living in a situation that is better for their family (18%), living somewhere that is safer with less violence (15%), and living in a better neighborhood (14%).

In describing what is best about her new home, one resident captured the sense of relief that comes from moving to a neighborhood that is safe and a home that is devoid of environmental toxins, "New surroundings, very pleasant place to live. I am more comfortable. Enjoy the neighborhood and I am also more [able to] relax." Another respondent referenced the difference in the property crime rate in her new neighborhood compared to Boulevard Homes: "Being in a house where my kids have a yard of their own to play in with no worries about their bikes being stolen." One mother wrote that, "My children was able to graduate and receive some college without the Boulevard Homes influence." Others were more succinct, writing, "Better for my kids" and "Don't have to deal with the high crime rate."

In responding to "the worst things about moving away from Boulevard Homes," 21% could not name any negatives associated with the move. However, some wrote that they had more expenses ("Having to pay more than one bill"), regretted moving away from friends, family, and familiar places, ("The neighbors are truly missed. I worry about the children and wonder how they are getting along"), or complained that they were forced to select housing or a neighborhood that was no better than Boulevard Homes ("Bad heating problem in this home. Can't find a home that is decent with accepting voucher amount").

Those who reported that their lives were "not much better" after relocating from Boulevard Homes reported higher social capital scores in 2010 (a mean of 0.41 vs. 0.3) and seemed to feel safer while living there (a mean of 2.9 vs 2.33) than those whose lives were much better. This group experienced greater social cohesion within Boulevard Homes and didn't feel the same sense of urgency for their personal safety. Increased expenses and less responsive landlords also made the move difficult for some.

While the open-ended survey questions confirm the quantitative findings that improved housing and neighborhood conditions are important to well-being, the interviews provided compelling stories about the fear and anxiety that came from living in Boulevard Homes. In their stories, we see clear evidence of the development of toxic stress among some of the mothers and accumulation of adverse childhood experiences (ACE) among the children.

Dania is a Black woman in her mid-fifties with an eight-year-old son. She uses a motorized wheelchair after rheumatoid arthritis disabled her in her forties. She moved into Boulevard Homes after she was disabled, could no longer work as an industrial restaurant kitchen manager, and became pregnant with her last son. She lived at Boulevard for five years during her pregnancy and then, after he was born, for roughly the first four years of his life.

When we met, she was quick to tell us that her life has been “excellent [since moving away from Boulevard Homes because she is no longer] around drug lords or in between drug battles.” She recalled “My car was shot up, like 18 times, had 18 bullet holes in it, and it got broken into like ten times.” She continued,

I have to praise God because even though the car was broken into and shot up, we were never broken into and none of those bullets ever came through our house to injure me or my sons. So I was blessed but still it was traumatic. Every night. Every night. I really still don’t sleep at night

Living at Boulevard Homes was a traumatic and potentially deadly experience for Dania. One Sunday morning she headed out of her apartment with her son, who was two at the time, when they were confronted with a young man brandishing and shooting a handgun. “Going round and round in a circle, shooting. He shot four people that day... And I’m trying to get to my child, I’m running to get him.” She finished her story telling us that she managed to grab her son, get in her car, and drive away to the safety of family. “It was something every day. I have not had any incidents, traumatic incidents like that, since I’ve been in my house.”

Table 8. Qualitative Response Categories for Best and Worst Things about Moving from Boulevard Homes

Best Things About Moving	
Reason	# (%)
Better house	25 (29)
Better for family	15 (18)
Safer/Less violence	13 (15)
Better neighborhood	12 (14)
More convenient location and better transportation	11 (13)
Better neighbors	9 (11)
Peace and quiet	6 (7)
Greater independence and privacy	5 (6)
Relocation support provided	5 (6)
Nothing	12 (14)
Worst Things About Moving	
Reason	# (%)
Poor housing quality	15 (19)
Missing family and friends	11 (14)
Relocation process and expense	11 (14)
Inconvenient location	10 (13)
Neighborhood and/or neighbors are bad	10 (13)
More expenses	9 (11)
Nothing bad about moving away	17 (21)

Her new home includes a back yard for her son, a space for him to play basketball, and a big front yard where she has planted flowers with her next-door neighbor who has become a good friend. She describes her new home as "really serene ... gardening, peace, to be able to sit on my front porch in the morning and just be at peace."

Kathy also shared a story of fear while living at Boulevard Homes. She is a White woman in her late sixties who is disabled by obesity, diabetes, and a heart condition. She told us that she worked fulltime her whole life until she had a heart attack. She used the HCV to move outside the city to a small house close to where she grew up and raised most of her five children. She shares the house with her adult daughter, Mary, who is in early thirties, and her daughter's three children ages 17, 8, and 2 years. Although the house is somewhat crowded, Kathy is committed to continuing to live with her daughter and grandchildren. Her daughter was diagnosed with bi-polar disorder and borderline schizophrenia. The family moved to Boulevard Homes after their home burned down.

When we asked her if their lives are better or worse since leaving Boulevard, she told us, "This is better. This is where I grew up. I know everybody. It's more comfortable." She continued,

I didn't like living in Boulevard Homes, 'cause I never lived in that type of environment before. Drugs and shootings and killings. When we were there, eight people got killed...Yeah, people got killed while we lived there. One right across the street and one on the corner across the street from us. The only time I come out of my house was to go to work or to the grocery store. I didn't get out to socialize with people

The children also had a hard time while living at Boulevard. Their mother became involved with drugs, developed an addiction, and the two children she had at the time were taken into child protective services custody. Eventually, the children were returned to the family's custody. Kathy told us that the children didn't like living at Boulevard Homes. "[The eldest child] couldn't ride her bicycle 'cause you never knew what was going to happen over there."

Kathy differentiates the experience of being poor from being poor and living in an environment like Boulevard Homes. "We grew up in the mountains. We were so poor! I can adjust to just about anything ... except killings. ...I was scared over there."

Five years after leaving Boulevard, the family seems to have stabilized. The oldest daughter was preparing to graduate from high school. The middle child was doing well in middle school and the two year old displayed all the developmentally appropriate behaviors of a two year old. The HCV has given Kathy an opportunity to return home to a place she feels safe and that she believes will be a better environment for her daughter and grandchildren. "I like it out here, 'cause it feels like coming home."

Although Dania and Kathy are only two of the 13 former Boulevard Homes parents we interviewed, their stories are not atypical. Many of the families interviewed had suffered some major setback in their lives that necessitated the move to public housing such as a significant health problem, domestic violence, or loss of a home. Public housing would not have been their first choice but it offered what they believed would be a safe and affordable refuge at a time of crisis in their lives. And while not all of the women we spoke with told such vivid stories of the violence and fear experienced while at Boulevard Homes, all of them believed that moving away from Boulevard was better for their children.

Dania and Kathy also referenced the social isolation they felt while living at Boulevard Homes. Although most of those we interviewed indicated that they had made some friends while living in the public housing community, their interactions were severely limited by the fear they experienced while living there. It was common to hear that the former residents had made new friends in their new neighborhoods.

For most of those interviewed, a sense of safety and peace were the overwhelming advantages to the move from Boulevard Homes. Most also found their new residences were of better quality and in better condition.

DISCUSSION

What emerges from the quantitative and qualitative data confirms that residents living in Boulevard Homes were exposed to violence, social disorder, and poor quality housing. The parents and caretakers indicated high rates of chronic physical illness and disability and experienced high rates of depression and anxiety. The children living there were exposed to these same negative experiences but were placed at greater risk as a result of their developmental vulnerabilities and their caretakers' fragile physical and mental health.

Our findings are consistent with other studies of HOPE VI [20]. Prior to relocation, the Boulevard Homes residents suffered multiple measures of social distress: low educational attainment, high unemployment, and poor health. They experienced statistically significant improvements in perceptions of increased safety, and overall quality of life was improved by moving to better housing and neighborhoods with the use of a housing choice voucher (HCV). These results were tempered, however, by the additional costs associated with living in private rental housing. These findings confirm our hypotheses that adults who express satisfaction with their housing and reductions in their fear of crime will experience improvements in an overall measure of well-being.

Consistent with other studies, heads of household did not make major gains in their education, employment, or health while receiving community supportive services [25, 26]; however, they experienced slight improvements in some of these measures including employment and income [3, 25]. The adults in our sample continue to report extremely high rates of chronic physical and mental health conditions. The move to better housing and a better neighborhood improved feelings of overall well-being and seems to have reduced some symptoms of anxiety and resulted in slight increases in individual's access to social capital.

The move did not, however, reduce depression scores and could not alter a diagnosis of rheumatoid arthritis or reverse a chronic heart condition. The high percentage of tenants who moved with an HCV meant that many individuals in our sample were more likely to have moved to better neighborhoods and better quality housing. This also means, however, that the household assumed increased expenses associated with private rental and that they were more likely to have been separated from family and friends and easy access to public transportation. Boulevard residents who were older at the time of the move and who had fewer financial resources were more likely to experience reductions in their overall quality of life due to these factors of expense and location.

It is also important to note that not all relocatees reported lives that were "much better" after leaving Boulevard Homes. This finding is also consistent with other research on HOPE

VI relocations [25, 26]. Some of the households relocated from Boulevard Homes had lived there most, or even all, of their lives. Although flawed, Boulevard Homes represented a familiar community, and moving separated these householders from people they cared about and, in some cases, a neighborhood and resources they knew. Moving is a highly stressful event for most individuals and is more so when those affected have few resources.

Children under the age of 19 years comprise 55% of those affected by the move from Boulevard Homes, and 75% of these children were aged 12 years or younger at the time of the move. Given the research regarding the developmental and physical effects of toxic stress and biodevelopmental vulnerabilities, this age pattern suggests reasons for both concern and optimism. The experience of living at Boulevard is cause for concern because women who were pregnant while living there were exposed to environmental toxins, potential physical injury, and the likely neurophysiological effects of prolonged and extreme stress. Also, children exposed to the hazards of highly distressed housing and neighborhoods have the potential to be negatively affected, the stressful experiences becoming biologically embedded and making them susceptible to disease and negative behavioral responses. Mothers who were depressed and stressed while living at Boulevard would have been more likely to engage in inconsistent or neglectful parenting, increasing the likelihood that the children would have experienced more ACE. Outside the home, the children would also have been exposed to the violence and social disorder of Boulevard Homes.

Despite these concerns, many of the children who were under age 12 years at the time of the move had the opportunity to attend different and better schools and to experience their teen years in neighborhoods that were less isolated and socially dysfunctional. The timing of the move also indicates their exposure to the Boulevard homes and neighborhood environment would have been of a shorter duration, suggesting that they potentially experienced fewer ACE and environmental toxins. Finally, this group of children is also more likely to benefit from the educational and employment outcomes that emerged from the more recent evaluation of the MTO data [19].

Limitations and Next Steps

Neither the HOPE VI program nor our surveys were designed to directly address trauma or toxic stress in either caregivers or their children. However, these topics emerge in both the quantitative and open-ended survey data and in the interviews held with residents. Conclusions about the well-being and trajectory of children impacted by living in Boulevard Homes and the subsequent move must also be inferred as both the surveys and interviews were conducted with the head of household who is the child's caregiver. As there is substantial evidence linking caregiver well-being to child outcomes [1, 4, 7–9, 17–19, 21, 26, 28], we feel this is not a significant limitation on our conclusions and recommendations. In future research, we hope to link this data to Charlotte-Mecklenburg Schools' data to better understand how the move away from Boulevard Homes and to better housing and neighborhoods affected the educational outcomes of the children.

Finally, this study did not demonstrate statistically significant improvements in any of our measures of health. Extremely high rates of trauma exposure and disease burden within this sample may be obscuring statistically significant improvements in some of these

measures of mental health [26]. Despite this, interviews suggest parents and children did experience meaningful improvements in their overall sense of well-being linked to feeling less anxious and depressed.

Recommendations

While the last HOPE VI grants were awarded in 2010, lessons learned from the program and this study can provide valuable insight into intervention programs for other highly vulnerable families living in public housing. The new Housing and Urban Development grant initiative, Choice Neighborhoods, incorporates many of the lessons learned from HOPE VI by seeking to improve overall housing and neighborhood quality to increase the economic mobility and well-being outcomes of public housing residents [29].

HOPE VI has made a significant and positive impact on the eradication of severely distressed public housing and has funded the construction of units that not only provide “defensible space” but are also intended to encourage positive interactions between neighbors of different income levels. The new units are built with environmental health in mind and many ban smoking. Perhaps most significant, efforts have been made to increase the physical safety of residents through careful screening of applicants, strict enforcement of rules of conduct, and enhanced surveillance of public space. All of these measures should help to improve the physical and mental well-being of residents [25].

Individuals and families who qualify for public housing are at high risk for health disparities due to their poverty status, race, and previous exposure to trauma [8, 30]. Adults living in public housing are less likely to have completed high school or to have completed additional education and training [27]. Poverty and low educational attainment are two of the greatest risk factors for chronic mental and physical health disease [8]. Interventions that help adult residents increase their educational attainment and obtain better quality higher paying jobs are not only strategies to improve economic mobility but also strategies to improve health and well-being [7, 22, 26].

Housing authorities and communities have an opportunity to intervene in the cycle of poverty. Fifty-five percent of those living in Boulevard Homes at the time of the relocation [27] and 37% of all those living in public housing nationally [30] are children under the age of 19. These children are highly vulnerable to poor outcomes in education, health, and employment [1, 7], however, they also have access to a vital resource – safe and affordable housing [22, 24, 28].

In addition to ensuring that families have safe housing and neighborhoods that protect residents from environmental hazards, the delivery of targeted programs to address mental and physical health, and educational and employment deficits will improve the outcomes of public housing residents [7, 22, 24]. Housing authorities and community stakeholders are well aware of the significant needs of this population and of the significant costs incurred when these deficits are not effectively addressed [5, 9]. In particular, families with young children represent an important opportunity to halt the cycle of intergenerational poverty and health disparities [1, 4, 7]. Partnerships that provide early childhood interventions such as pre- and perinatal care, nutrition assistance, parenting support to improve developmental and educational outcomes, and preschool have all been found to be highly effective at improving

the outcomes for these children and families [22]. Intervening in the cycle of health disparities will produce a lasting and intergenerational effect [4, 8].

If public housing authorities prioritize addressing the health needs of their residents, they will not only improve the health of residents but also increase the economic mobility of the entire household [22, 24]. As the health, well-being, education, and income of the household increases, so too, does the likelihood that children living in the homes will escape the cycle of environmental disparities, ACE, and toxic stress that limits their future and the future of their children [4, 8].

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Chapter 23

LEARN, EAT, GROW: THE HEALTHY LIVING INITIATIVE

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ABSTRACT

In order to address the health disparities and challenges resulting from the unequal availability of healthy, fresh, affordable food in the Greater Atlanta area, we implemented an intervention for school children to encourage better nutritional choices. This entailed a six-week partnership with a local school introducing a curriculum geared toward gaining knowledge about healthy food and lifestyle options, through the means of urban gardening. Students were surveyed regarding their dietary intake and knowledge regarding nutrition and gardening before and after the intervention. The six sessions included curriculum centered on gardening, cooking, exercise and components of a healthy lifestyle and encompassed hands-on-sessions regarding tasting, cooking, and growing vegetables and herbs. Surveys prior to the start of the intervention confirmed that students in this metropolitan Atlanta classroom were not knowledgeable about dietary recommendations and consumed below the suggested daily portions of fruits and vegetables. At baseline, few knew basic nutritional facts and 56% of students reported that they had never previously had a gardening experience. The average number of fruit and vegetables consumed daily was 2.7, ranging from none to 7. After the six educational sessions all but two students out of 33 knew the recommended daily intake of fruit and vegetables, and their average reported intake rose from 2.7 to 3.2 servings. Every student could name three healthy snacks, and at least two benefits of gardening. Teaching about healthy living and gardening during this six-week period led to an increase in the consumption of fruit and vegetables and a greater knowledge regarding healthy eating, and gardening.

Keywords: urban gardening, food deserts, nutrition, healthy choices, intervention

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INTRODUCTION

Lack of access to healthy fresh food contributes to the cycle of health disparities and obesity facing lower income children in inner city America. The aim of this project was to break the cycle of health disparities resulting from poor understanding of nutrition and limited access to nutritious foods. As a pilot study, an intervention was planned and executed targeting high school students in inner city Atlanta, Georgia.

Disparities in Atlanta and Food Deserts

Several economic, social, and health disparities plague the Atlanta area. Eighteen percent of Georgia's residents live at or below the poverty line, which is an increase of almost one million more people experiencing poverty since 2000 [1]. Twenty-eight percent of Georgia's children live in food insecure households, and cannot afford to buy healthy food on a regular basis [2]. This leads to what is known as a "food desert." A food desert is an urban area in which it is difficult to buy affordable or good-quality fresh food [3]. There are many factors that contribute to food deserts, including environmental factors that affect local growing efforts such as soil, climate, and space, behavioral factors which impact communities' acknowledgement of food related issues in their area and educational factors that reflect consumer's knowledge of healthy food choices. A food desert results from limited food options, supermarket wars, and the lack of knowledge and choice when it comes to food choices, especially in lower income areas. Food deserts contribute to increasing obesity rates, as well as unhealthy eating habits because of limited access to fresh and or affordable produce. Access to fresh food is strongly correlated with economic status and low income communities have limited access to healthier food options [3]. This statewide issue is reflected at the local level in Atlanta where significant gaps in neighborhood food availability exist. There are 35 food deserts located inside Atlanta's perimeter, impacting two million Georgia residents, including 500,000 children who live in food deserts [2].

Urban Gardening

The concept of urban gardening is that fresh food can be grown locally, even within the confines of the city. Urban gardens are focused around cultivating, processing and distributing food in a town or city setting, making the necessary accommodations in order to grow produce in an unconventional agricultural setting. Urban gardening has been shown to help combat food deserts [4]. Urban gardening also has been shown to promote greater community collaboration while producing home grown, healthy food that is accessible and affordable [5, 6].

Previous Cases Studies

Previous studies have shown that urban gardening increases nutritional food intake and helps individuals develop an appreciation and knowledge of healthy habits. Urban gardening increases children's connection with their food, which results in an improved awareness of the nutritional content of the foods that they eat. It introduces them to new choices, allowing them to gain access to healthy fresh food that in many areas are difficult to obtain. Urban gardening brings communities together, can reduce crime, and promotes obtainable healthy life options [7].

According to an article entitled "A garden pilot project enhances fruit and vegetable consumption among children" [7], children who grow their own produce are more likely to eat healthier, because they are connected to the food they grow. They describe a program titled "Delicious and Nutritious Garden" created in Emmaus, Pennsylvania. During the course of this 12-week program, 4th through 6th graders worked in a garden and created healthy snacks out of the produce they helped to cultivate. By the end of the study, they found that, "98 percent of kids said they liked the taste tests, 93 percent said they liked the cooking aspect, 96 percent liked working in the garden, and 91 percent said they actually enjoyed learning about fruits and vegetables". This form of "seed-to-table" program was shown to be successful and engaging for the children. The study demonstrated that the gardening program led to better eating habits for the participants, and that this "hands-on" learning approach presented the students with a cost effective way to grow food, instead of relying solely on items available in the grocery store [8].

Another example of an effective intervention was conducted by Stephen Ritz, a teacher based in the Bronx borough of New York City. Ritz addressed the problem of food deserts in his area by addressing the food desert by teaching students how to grow produce. He turned his classroom into the National Health, Wellness, and Learning Center. An article in the Wall Street Journal describing his project states, "We're harvesting hope and cultivating minds" in the Bronx neighborhood where his school is located [9]. Ritz and his students helped create urban gardens throughout the Bronx, even in classrooms. He taught his students how to grow and cook with fresh produce. Ritz's goal was to "send students home with 100 bags of fresh, school-grown fruits and vegetables a week, 50 weeks a year." These students often did not have enough food at home in general, and they had no prior experience with organic fruits and vegetables [9, 10].

Another study conducted in Lawrence Massachusetts focused further on the role of urban gardening in nurturing community ties and reducing inner city violence [11, 12]. The author concluded that "Community garden programs can strengthen civic engagement and foster neighborhood stability, while simultaneously cut down on youth violence [11]"

Nutritional Education

There are many resources regarding good nutritional choices available; however, many educators and students do not know how to access them. These resources are rarely used in a school setting. Such tools include Choose My Plate [13], the Environmental Protective

Agency (EPA) guidelines [14], and local area gardening initiatives. These tools can be used to educate individuals as to a balanced and healthy lifestyle.

ChooseMyPlate is an initiative of the United States Department of Agriculture's (USDA) Center for Nutrition Policy and Promotion. Its two primary goals are to "advance and promote dietary guidance for all Americans, and conduct applied research and analyses in nutrition and consumer economics." ChooseMyPlate provides information regarding how to prepare a healthy meal, and the daily servings recommendations for each of the major food groups; fruit, vegetables, grains, protein, and dairy, based on age and body mass index [13].

The purpose of the United States Environmental Protection Agency is to develop policies to protect human health and the environment. The EPA has been working to create a lesson plan designed to engage and excite children about different forms of environmental health, and to empower them to take action in their communities to lessen the many environmental risks that they face. The students learn about environmental health and how to positively impact their communities through an "Ask, do, and explain" campaign with hands-on learning [14]. This program is very promising, however it is not yet implemented nationwide, and many school districts are unaware of this resource.

Education is necessary to improve dietary habits. Poor nutrition is a factor in the high rates of obesity and heart disease in America [15].

Community gardens are another means to engage participants in a "real life" educational experience. These gardens bring people together, have the potential to reduce crime in "high-risk" neighborhoods, and produce fresh fruits, vegetables, and herbs for the whole community to enjoy [11]. Efforts at urban agriculture such as community gardens improve food security and safety. The growers are involved in the entire process, from the soil and seeds to harvesting the end product. Community gardens reduce the carbon footprint, while teaching city residents about agriculture and how to achieve a nutritious food balance [16].

METHODS

Participants: Druid Hills High School was identified as an ethnically and socioeconomically diverse Atlanta public school located in close proximity to Emory University. In 2015, enrollment in this school included 1,353 students. Fifty percent of the student body is self-described as African American, 23% as White, 12% Asian, 10% Hispanic, and 4% as Multi-racial [17]. The school administration agreed to participate in the study and proposed conducting the intervention in a science course, after consultation with the science department. The participants in the project consisted of 33 ninth grade biology students at Druid Hills High School. The gender composition of the classroom was 52% female, 48% male, and students were 14 to 15 years of age. High School students were chosen as participants because the topic was compatible with their curriculum.

An Institutional Review Board exemption was obtained from Emory University. However, since the participants were minors, consent forms explaining the project were distributed and signatures were obtained from both the students and their parents.

Description of survey: Two surveys were administered to the students, a preliminary survey before the intervention began, and a concluding survey to evaluate the impact of the intervention. Baseline eating and gardening habits and knowledge about nutritious eating was

assessed. Demographic information regarding age and gender were collected. Students were asked how many fruits and vegetables they consumed daily, as well as the specific number consumed during the past 24 hours. Participants were asked if they had any prior gardening experience, and surveyed regarding their favorite foods, allergies, and previous experience with home grown foods. The final survey included similar questions regarding both knowledge and habits related to maintaining a well-balanced lifestyle and the benefits of urban gardening. It also questioned students as to how they would act in the future regarding food choices and whether or not they found the intervention to be worthwhile.

Intervention: The intervention was conducted over a six-week period, and the investigator visited the classroom once a week, interacting with students during their science class period. The six-week lesson plan included instruction regarding the growing of plants and gardening. Students were taught the importance of making healthy choices. During the first week of the intervention, students answered the initial survey, and planted one of the following vegetables/herbs in a compostable seed-starting container; snap peas, basil, dill, or lavender, with store-bought all-purpose gardening soil. Herbs were selected for the project because they grow rapidly and require relatively little intervention. During the second week they learned about the national food plate, which corresponds with the recommended daily food intake of fruits, vegetables, protein, grains, and dairy, as well as how to incorporate these foods into everyday meals. During the third week they prepared and sampled healthy snacks including non-fat yogurt parfaits with granola and fruit, edamame, apple slices with cinnamon, and guacamole. In session four they learned about the components of a healthy well-balanced life, as well as the cost effectiveness of growing fruits and vegetables. During week five, the students helped to start a school garden outside, and played games that promoted physical activity. For the last session, students brought in healthy recipes that were compiled to make a class cookbook. They also reviewed all that they had learned, took the closing survey, and received seeds to enable them to continue their gardening efforts at home.

Throughout the six weeks, the seeds planted during session one were tended to by providing them with water and sunlight. Students brought the plants home on the final day of the intervention.

Data Analysis

Surveys were distributed to the study participants prior to the intervention and again following the intervention. The results were compiled by the primary investigator. Quantitative results were examined in Excel spreadsheets and presented graphically. The responses to qualitative questions were analyzed and recorded independently. Qualitative answers were categorized based on the extent of nutritional knowledge demonstrated. For example, students were asked to name three benefits of urban gardening. If they provided these items correctly, they received a score of one, and if they were unable to do so. They received a score of zero.

RESULTS

The data collected from the preliminary and final surveys were analyzed independently and then the results were compared to assess the effectiveness of the intervention.

The results of the initial survey indicated that 56% of the students had no prior gardening experience. The preliminary survey revealed that the average number of fruits consumed per day by the students was 2.3 servings. The average number of vegetables consumed per day was 2.0 servings. The average number of fruits and vegetables combined eaten by the students in the previous 24 hours was 2.7 servings, ranging from none to 7. The results are shown in Figure 2. Few participants knew the correct recommended number of daily servings of fruits and vegetables. The students' favorite foods included choices ranging from salads to jelly beans, and the foods varied vastly in nutritional value.

Learn, Eat, Grow: Initial Survey

Name (First and Last Initial): _____

Age: _____

Gender: _____

What is your favorite food?

Are you allergic to any foods? Yes / No

If yes, which foods?

How many fruits do you eat per a day?

How many vegetables do you eat per a day?

How many servings of fruits and vegetables are you supposed to have every day?

Which fruits and vegetables have you eaten in the last 24 hours?

Have you ever had a garden?

Have you ever eaten homegrown fruit or vegetables? If yes, which ones?

LEARN, EAT, GROW: END SURVEY

Name: _____

Age: _____

How many fruits do you eat per a day?

How many vegetables do you eat per a day?

How many cups of fruits and vegetables are you supposed to have every day?

Which fruits and vegetables have you eaten in the last 24 hours?

Can you name 3 healthy snacks?

Do plan to start a garden in the future?

Name 2 advantages to creating homegrown food:

Did you enjoy this project? Why?

What was your favorite class session? Why?

What was your favorite class session? Why?

What would you change or improve about this project?

Figure 1. Learn, Eat, Grow surveys.

After the six educational sessions all but two of the 33 students knew the correct recommended daily number of serving of fruit and vegetables per day (see Figure 3). The survey revealed that after the intervention, the average number of servings of vegetables consumed per day increased from 2.0 to 2.6. The concluding survey also showed that after the intervention the average number of servings of fruits consumed increased from per day 2.3 to 2.4, which does not reflect a significant change. However, when specifically queried regarding their intake of fruits and vegetables during the 24 hours prior to the survey, the results reflected a change from 2.7 to 3.2 servings (see Figure 4). Every student could name three healthy snacks, and at least two benefits of gardening. Forty-one percent of students wrote that they definitely would like to start a garden in the future; whereas, before the study half of the students were not at all familiar with home-grown food.



Figure 2. Preliminary survey: Fruit and vegetable intake in the previous 24 hours.

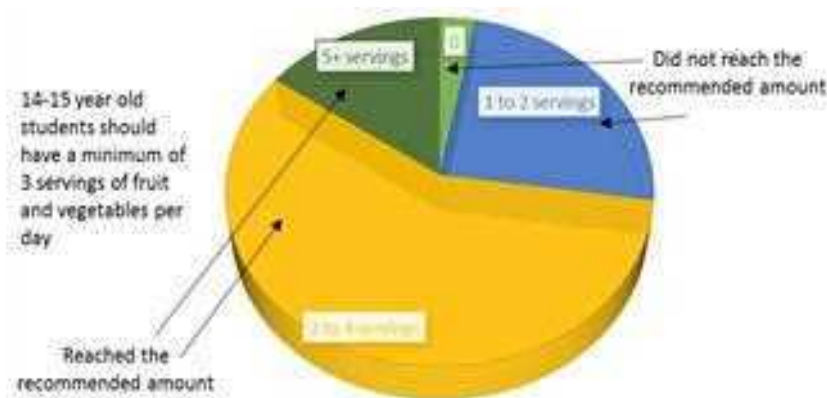


Figure 3. Concluding survey: Fruit and vegetable intake in the previous 24 hours.

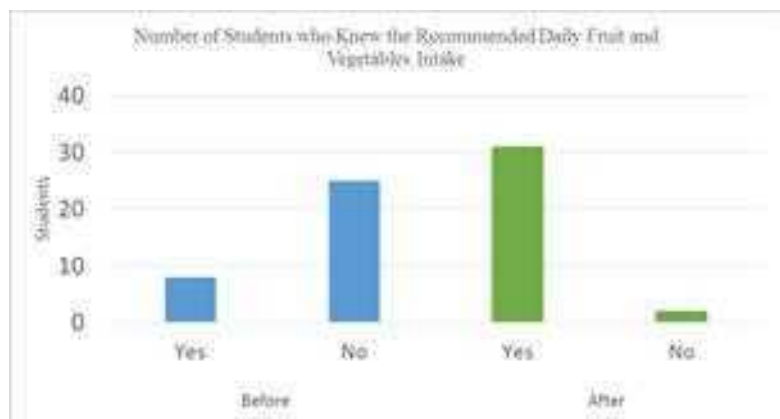


Figure 4. Students regarding their intake of fruits and vegetables 24 hours prior to the survey.

The participants reported that their favorite classes included the sessions when they planted their own herbs, learned about nutrition and prepared healthy snacks, and helped to create a school garden. All of the students reported that they enjoyed participating in this project and they praised its implementation in the classroom. Overall, healthy food intake increased, albeit not dramatically, and so did their knowledge regarding nutrition and

gardening. The intervention showed a positive trend of increased knowledge and participation in maintaining a healthy lifestyle and developing a connection and awareness about homegrown fruits and vegetables.

DISCUSSION

This project adds to existing literature on the subject of urban gardening and nutritional choices and suggests that simple interventions can make a difference in improving healthy living. Other studies have similarly demonstrated the impact of the introduction of gardening to school aged children, but these were generally conducted over longer time periods. For example, a model study performed in Minneapolis evaluated an urban gardening program that continued for 12 weeks [8]. A project conducted in five elementary schools in Texas involved introducing growing vegetables throughout the school year [18]. They observed an increased appreciation and consumption of fresh produce as a result of the project.



Figure 5. Break the Cycle Chart.

From this study, it appears that even after six weeks learning about urban gardening and nutrition had an impact on 14 to 15-year-old school children. As their understanding of these issues grew, they began to consider healthier choices. The project increased nutritional

awareness, which resulted in the ability to make healthier food choices. The positive results of this and other pilot programs suggest that the implementation of larger and longer interventions in schools could have a significant impact.

The strengths of this study included the successful engagement of the students and the collaboration of dedicated teachers. A highlight of the intervention was that students actively participated and wanted to learn more. Some students came to the primary investigator eager to share new healthy recipes that they had identified, and others expressed their eagerness to continue to grow plants.

Unfortunately, this six-week project did not provide enough time to plant and harvest fruits and vegetables. Future project should be at least three months long to allow a full harvest cycle [19]. During this intervention, students planted herbs. In order to develop a deeper connection to their produce, it would be ideal if the children were able to plant other fruits and vegetables. For example, focusing on a vegetable such as the zucchini squash would enable the students to learn to grow a product with nutritional value that could then be introduced in numerous recipes.

The investigators were not able to evaluate how race or income influenced the students' access to and knowledge about healthy eating. This data was not available for analysis.

High school students were chosen for this program because they are more able to make independent diet choices compared to younger children. The topic of the study fit in well with their biology curriculum, because students could relate what they were learning about health and nutrition with other concepts taught in class [20].

During the time that this project was conducted other issues came to light. The school meals were noted to consist of unhealthy processed foods, and fruits and vegetables used were often canned or frozen. A greenhouse has been proposed to allow year round gardening and access to fresh produce. The school has set aside dedicated garden space in front of the school, which will facilitate the continuation of the basic concepts of gardening introduced in this project. The school and especially a few dedicated teachers have embraced the urban gardening initiative and look forward to future collaborations. Based upon the success of this pilot intervention, the faculty is interested in possibly adding similar units to the school curriculum in biology and environmental science courses.

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Chapter 24

SHOULD PARENTS BE ALLOWED TO REFUSE VACCINATIONS FOR THEIR CHILDREN?

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ABSTRACT

Vaccine hesitancy and parental refusal to vaccinate their children have been a subject of vigorous debate, especially in the United States, where the incidence of vaccine preventable diseases is low. In addition to medical contraindications, vaccine refusal based on personal philosophical or religious beliefs poses challenges to sustain effective mass immunization programs and herd immunity. In United States, where, recommended childhood vaccinations are mandated to attend school, a question often raised is, “Should parents be allowed to refuse vaccination for their children?” This article explores some basic ethical and practice implications implicit in this question.

Keywords: vaccine, immunization, parental rights, herd immunity, Gilovich’s taxonomy, free-riding

INTRODUCTION

A vast array of factors including geographic, political, economic, disease epidemiological, cultural, and other local factors influence health behaviors of people in different parts of the world, including parental attitudes towards vaccination for their children. Therefore, this discussion is limited to issues regarding vaccination of infants and children in the United States.

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PARENTAL RIGHTS

Do parents have the right to make medical decisions for their children? In the United States, most vaccinations are given during infancy and early childhood. It is generally agreed that at this age, children, because of their limited cognitive maturity and life-experiences, are not considered competent to make medical decisions for themselves [1, 2]. Therefore, the law grants parents (or other legal guardians in some cases) the right to make medical decisions for their children. In that sense, the legal rights of parents, under most circumstances are clear regarding their right to make medical decisions for their child.

In addition to the legal rights, what are other considerations for parental rights? In medical decision making, it is widely accepted that one must consider any decisions based on the best interests of the patient. Physicians apply this logic in their daily practice when faced with multiple choices in management decisions for their patients. The same argument can be extended to the issue of parental decisions for their children. It is generally agreed upon that parents make medical decisions for their child based on what is in the best interest for the child. It is important to recognize that in this case what constitutes best interest for the child is determined by parents, and that others may disagree with parental reasoning.

Dawson [2] has explored the issue of “best interest” in relation to childhood vaccinations. According to Dawson [2], there are two main views of what constitutes “best interests,” namely the objective view and the subjective view. Based on the objective view, the concept of best interests is explained in terms of maximizing the individual welfare, well-being, or good. Such a determination of best interests can be arrived at independently of what the individual might believe or desire to be relevant to be maximal welfare or well-being. Taking this view, “...the judgment as to what is in an individual’s best interests is to be determined by the outcome which would maximize welfare, even if we are ignorant or mistaken about which outcome that might, actually be” [2]. On the other hand, taking the subjective view of best interests, “...the concept is to be defined in terms of what the individual themselves does choose, or if they are incompetent, what they would be expected to choose if they were able to do so” [2]. In addition to legal rights and best interest considerations, the parental right to vaccinate or not to vaccinate their child is also considered on the basis of ethical principles of respect for autonomy and individual right to privacy [3].

REASONS FOR PARENTAL REFUSAL OR HESITANCY TO VACCINATION

Given that parents have the right to make medical decisions for their child, they have the right to make decisions about vaccination for their child, including the right to refuse to vaccinate. Thus, it is important for medical professionals to understand why parents are hesitant or refuse to vaccinate their child.

Parental perspectives and attitudes on vaccination are influenced by a complex interaction of medical, social, personal, and religious factors [4, 5]. Parents may be hesitant or refuse to allow vaccination for their child on the basis of medical information they have received from various sources including medical professionals, public health agencies, and the media [1, 3]. The scientific accuracy of such information, how such information is

communicated or presented, and how it is interpreted by parents influences their decision [6, 7]. Parental trust or mistrust of various sources of information is also an influential factor. Healthcare providers should provide evidence-based, unambiguous information for parents regarding vaccination, addressing any specific fears or concerns. Providing information about vaccine preventable diseases, morbidity, and sequelae in an honest and open manner is important for parents to understand the potential risks of refusing or delaying immunization for their child [6, 8, 9].

Well established medical conditions or diagnoses for which certain vaccines are contraindicated are not the main subject of contention. However, there are numerous parental fears and misconceptions regarding vaccines that in general do not outweigh the benefits of immunizations. These fears or misconceptions include: fear of pain or discomfort of the child, concern for potential ill effects on child's immune system from multiple immunizations, belief that acquiring "natural" immunity is healthier by contracting the vaccine preventable disease, or belief that some vaccines are not as important as others. In other cases, parents may fail to grasp the seriousness of vaccine preventable diseases because they have not encountered them in daily life or the perception that vaccine preventable illnesses are uncommon in the United States.

Parents or caregivers may also truly believe that there is no need for their child to be immunized because the majority of other children are, and the chances of contracting a disease is very low (as in "herd immunity"). In this case, some may believe that the purported benefits of vaccination do not justify the potential risks to their child. Objections to immunizations that are based on parental understanding of available information can be addressed adequately in medical practice. However, objections to vaccination based on personal religious or philosophical beliefs, or based on principles, pose significant ethical dilemmas and public health challenges, and is the subject of much debate.

RELIGIOUS OR PERSONAL OBJECTIONS TO VACCINATION

Grabenstein [10] in a review on religion and vaccine practices identified more than sixty reports or evaluations of vaccine-preventable infectious disease outbreaks that occurred within religious communities or that spread from them to broader communities. He found that the religious reasons to decline immunization reflected concerns about vaccine safety or personal beliefs among a social network of people organized around a faith community, rather than theologically-based objections per se. This is an important consideration when evaluating religious objection to vaccinations.

In the review of reasons for vaccine refusal, Jacobson et al. [11], found that flaws in personal reasoning and information interpretation played a role in decision making. Jacobson et al. [11] also cited the work of Gilovich [12] to provide the basis for such flaws. The Gilovich's taxonomy [12] of common flaws in reasoning include the cognitive determinants (desire to find order and predictability in random data, difficulty in detecting and correcting biases in incomplete and unrepresentative data, eagerness to interpret ambiguous and inconsistent data to fit theories and expectations) and motivational or social determinants (wishful thinking and self-serving distortions of reality, pitfalls of second-hand information

and miscommunication including mass communication, exaggerated impressions of social support).

ETHICAL IMPLICATIONS OF PARENTAL REFUSAL TO VACCINATE THEIR CHILDREN

First, what are the implications of parental refusal to vaccinate their child? For the child, one might consider the obvious risk of contracting the vaccine preventable disease. From a public health perspective there is the risk for spreading the disease to others who are not immunized for various reasons. There is also the risk of reducing herd immunity and thereby diminishing the overall protection from the disease for the community.

According the American Academy of Pediatrics, pediatricians should respect parental decision not to vaccinate their children and engage in an ongoing dialogue to address their concerns about vaccines [1]. AAP considers a pediatrician's decision to dismiss family from further care on the basis of vaccine refusal as an option. However, if access to care for children whose parents refuse vaccinations is limited, the AAP recommends caution against dismissing them from practice [1].

At present time, given that under most circumstances the risk of contracting a vaccine preventable disease is very low from those who are not immunized, one can invoke the harm principle [3]. Based on the harm principle, parents may refuse vaccination because such a decision does not pose substantial risk to others in a highly immunized population such as that in the United States.

In considering parental vaccine refusal, the issue of "free-riding" has also been discussed in the literature [3, 13-16]. "Free-riders" are individuals who benefit from programs in which they have not contributed. Free-riders benefit from conditions created by individuals in the community who have contributed and participated to create the beneficial conditions in the first place. These individuals therefore have not taken any risks associated with a given action that others in the community have. In consideration of the mass immunization programs, free-riders specifically benefit from the herd immunity created by others who have taken the risks associated with getting immunized. Some have argued that this practice is not unethical or morally wrong, on the basis that free-riding does not necessarily increase the risk to others or threaten the viability of a mass immunization program in any way. So in terms of the consequentialist approach, no specific harm is done. On the other hand non-consequentialist theories posit that free-riding is morally wrong on its own merit. Based on the precepts of virtue ethics, if refusal to vaccinate is based on deeply held personal religious or philosophical beliefs, then one could argue that free-riding is not necessarily immoral. It is important to note in the United States, most states do grant personal belief exemptions from immunization based on religious or philosophical beliefs.

Under what circumstances is parental vaccine refusal not justified and is there any basis for the right of the state to override the parental decision not to vaccinate their child? Based on a number of cases, the United States Supreme Court has upheld the legal and constitutional right of the state (police power) to require and enforce vaccination [16]. In legal terms, the right of the state has been historically established. The constitutional basis of vaccination requirements in the United States is based on the police power of the state [16]. According to

the American Academy of Pediatrics, if the harm from non-immunization is significant, it may constitute an actionable medical neglect on the part of parents [1]. According to the literature [8], if there is a risk for serious and imminent harm to the child from vaccine refusal, the state may override parental refusal. Lyen and Leonard [8] also refer to the issue of distributive justice as a consideration for overriding parental refusal to vaccination. It is also important to consider the fact that the risks and benefit equation may vary over time.

Based on the utilitarianism one could argue that the state can require vaccinations to prevent harm to others who are not immunized [3]. In some cases the exact benefits or risks may not be known, and in this situation one could apply the precautionary principle to justify mass immunization requirements by the state [3]. Because children are considered a vulnerable population one could also apply the precept of weak paternalism to justify mandatory immunization requirements by the state. According to Dawson [2], in some cases the presumption that parents represent the best interests of the child is misconceived, and this justifies overriding the decision by the state. As Dawson [2] observed, "Such a situation arises where there is a substantial risk of significant harm resulting from the decision to either vaccinate or not to vaccinate" (p 189). Dawson [2] in fact went as far as suggesting that in such cases it is not only justified for the state or third party to act, but it is their obligation to act.

Holland [3] evaluated the strong general duty thesis that states that based on moral considerations, there is a general duty for each one of us not to infect others and therefore accept vaccination. The main objection to such an argument is based on the distinction between what are considered acts and omissions. Weak paternalism and libertarian paternalism can also be applied to support the state's right to enforce vaccination mandate.

Lantos et al. [17] argued that personal belief exemptions to the mandate for childhood immunizations should not be allowed. They base their argument on the basis of risk to others who are not immunized for well-founded medical reasons. On the other side of the argument, Opel and Diekema [18] contended that "a just vaccine policy need not prohibit parents from claiming personal belief exemption. We think a more effective approach is one that offers greater flexibility in balancing competing goods and greater opportunity to favorably influence public opinion toward encouraging vaccination. Personal belief exemptions need not be eliminated, just revised" [18].

HEALTHCARE PROVIDERS' ROLE IN ADDRESSING PARENTAL VACCINE REFUSAL

A physician or other primary healthcare provider plays an instrumental role in addressing parental concerns regarding vaccine refusal. At times, family counseling on various concerns may be time consuming, but establishing a trustworthy relationship with parents and their children forms the basis for accurate and nonjudgmental dialogue regarding immunization concerns. Literature supports that even parents with serious concerns about vaccines report their child's healthcare provider as the most important influence and most trusted source for information about vaccines.

CONCLUSION

The answer to the question, “Should parents be allowed to refuse vaccinations for their child?” remains complex and nuanced. In evaluating of all the elements and implications involved in this parental decision, we must consider multiple viewpoints and factors in an attempt to resolve this question. The most plausible conclusion is that the answer will vary and depend on given circumstances at that time. Among the multiple variables to be considered in such an evaluation include disease severity and epidemiology, disease prevalence, the basis of parental reasoning, available information, misinformation, relative risks and benefits of a given vaccine, evolving science, and many others. As this review illustrates, public health ethical principles could be applied to argue for and against parental vaccine refusal for their child.

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Chapter 25

FOOD SECURITY, GENDER, AND OCCUPATIONAL SEASONALITY IN URBAN LOW-INCOME HOUSEHOLDS

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ABSTRACT

This paper examines an adaptive strategy using occupational choice that can be undertaken by household members especially women in urban poor areas to help ensure their access to food. Our investigation focuses on working women and men in seven predominantly slum communities in North, South, East and West. This study tries examines how women in urban low income households through self-mechanism ensure their households access to food by being employed in some or the other kind of enterprise. This paper attempts to answer following questions: Does concern for household food security influence the choice of women's work in urban low income households? Does seasonality affect the income and skills of women? To answer these questions we analyze the possible relationship between household food security and occupational constraints in slums of Delhi spread across seven clusters. We have used both qualitative and quantitative information from the field interviews. This study takes into account the likely influence of occupational choice of women on gender ascribed roles, seasonality and many more factors which affect the condition of women and adds to their vulnerability status.

Keywords: food security, occupation, seasonality, slums, India

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INTRODUCTION

The “State of food insecurity in world” [1] in 2014 presents updated estimate of undernourishment and progress towards Millennium Development Goals and World Food Summit hunger targets. A stock taking of where we stand on reducing hunger and malnutrition shows that progress in hunger reduction at global level and in many countries has continued but substantial effort is needed in many others. The latest estimates indicate that global hunger reduction continues about 805 million people are estimated to be chronically undernourished in 2012–14, down more than 100 million over the last decade, and 209 million lower than in 1990–92 [1]. This shows the poor state of food security over period of years. The “Gender equality and women’s empowerment operational plan, 2013–2020” [2] emphasizes the need for deepening gender mainstreaming and for direct investments in women and girls to close remaining gender gaps and achieve better gender equality outcomes. Another argument put forward in this respect is fully 55% of the gains against hunger in these countries during those 25 years were due to the improvement of women’s situation within society [3]. Another interesting argument put forth is that countries ranking highest on the index of global hunger are also those where such inequalities (gender) are more severe [4].

Recognition of women’s unpaid work in the care economy breaks down the common dichotomy that, while men (or women who join the labor market) produce, women at home consume [5]. The ILO Committee of experts notes that “measures designed to promote harmonization of work and family responsibilities, such as child-care services, should not be specific to women” [6]. The condition for slums are more worst firstly, because the rate at which urbanization is increasing, attracts migrants from the different parts of the countries towards metropolitan areas thus swinging the demand of labour in terms of supply and demand which is leading to more unemployment and underemployment. Secondly, lack of opportunities throughout the year leads to variation in income of women which affects the health status of women and their children. This paper argues that woman through being employed in some or the other form of employment which is even not available throughout the year tries to make their household more food secure and which have positive impact on their health, nutrition and related factors.

METHODS

It may also be noted that the list of ‘jhuggi-jhopdi’ colonies provided in the DDA (Delhi Development Authority) list is neither comprehensive nor exhaustive. Various illegal squatter settlements and marginal settlements located in various parts of the city are not necessarily covered by the list primarily slums have been included in the list. The list of Notified slums was also obtained from the slum wing and notified slums were identified in consultation with experts. A brief description of the sampling procedure used to select the 400 households is given below. In order to select the 400 sample slum households, we have used a two-stage stratified random sampling framework. The basic document we used for our sampling strategy, as mentioned above, is the list of slums called as ‘jhuggi-jhopdi’ clusters (which gives the specific areas where the slums are located) provided by DDA for the year 1994.

This is the latest document available, which lists the number of constituencies, the number of clusters in each constituency, and the number of slums in each cluster. In the first step, we divided Delhi into nine zones on the basis of the geographical location of the 70 constituencies given in the DDA list; thus zones one through seven are respectively, north, north-east, east, south, west, and central Delhi.

Selection of State

The state of Delhi was purposively chosen for the study as it is National Capital Region with large number of slums. Delhi is known for migration of poor people from different states in search of economic opportunities. All these have led to demographic change in Delhi population. Hence, Delhi slums were purposively taken for the study.

Selection of Districts

In the first step, we divided Delhi into seven zones on the basis of the geographical location of the 70 constituencies given in the DDA list; thus zones one through seven are respectively, north, north-east, east, south, west, north-west and central Delhi. Out of seven zones four zones were selected purely on the basis of number of slum in these zones based on the report from MCD list.

Selection of Clusters

As detailed around 400 household has been selected from four Non-notified and three notified slums spread across Delhi in four different directions in order to make the sample more representative. Total of 1997 person were surveyed in all 400 households and to be precise 1,061 persons from Non-notified and 936 from notified were surveyed during the course of the study which includes males, females and children.

RESULTS AND DISCUSSION

Table 1 shows the employment status of women in seven clusters across Delhi but data is restricted only for persons who are aged above fifteen. Under work categories, we can see the number of women who were not working are significantly high around 72.7% while 27.3% of male were also not working. Within all major categories of work women are affected majorly as they are unemployed. Under self-employment category only 16% have taken their own initiative as there is lack of skills and capital among most of the women in slums. There are many reasons for women not being employed apart from the cultural and social reasons. Seasonality appears to be an important factor which affects women's work as work is not available throughout the year which leads to variation in income of the household and directly or indirectly affects their food security status. Women use most of the liquid cash for

purchasing essential items which are required on daily basis such as milk, vegetables oils and many other things if there is significant variation in their income this directly affects their food security. Lack of opportunities make women more susceptible to vulnerability and thus makes households more prone to insecurity in terms of food and many other basics of life.

The gender segregation in terms of occupation is presented in Table 2. It is clear from this that most of the women do not participate in the labour market as they do not have enough skills, training, education and moreover household compulsions, which do not facilitate their entry into the labour market [7]. However, some women out of economic compulsions do participate in the labour market so as to supplement the income of the family which also provides them with food security for their households. It is remarkable to note that though women do not participate in the labour market on full time basis but their mean hours of work were almost similar to those of their counterpart males. An important issue which needs to be discussed here is that women are almost absent from trade, commercial services, transport, security and repairing of machinery activities. However, over the years the state of women occupation has declined significantly, and the most conceivable explanation to this is most of the activities require full time work and travelling which women cannot afford to practise because of household compulsion.

Table 1. Employment status of surveyed households by location and sex above 15 years of age group

Work categories	Slum A		Slum B		Slum C		Slum D		Slum E		Slum F		Slum G		Total	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
No Work	18 21.2	67 78.8	23 32.9	47 67.1	31 30.7	70 69.3	14 20.3	55 79.7	26 31.7	56 68.3	23 26.1	65 73.9	38 27.3	101 72.7	173 27.3	461 72.7
CL	32 80	8 20	31 77.5	9 22.5	42 87.5	6 12.5	51 87.9	7 12.1	45 83.3	9 16.7	50 90.9	5 9.1	90 73.8	32 26.2	341 81.8	76 18.2
RW	20 83.3	4 16.7	11 78.6	3 21.4	5 100	0 0	5 100	0 0	2 100	0 0	2 100	0 0	5 100	0 0	50 87.7	7 12.3
SE	5 100.	0 .0	6 75	2 25	2 66	1 33.3	0 .0	0 .0	2 66.7	1 33.3	1 100.0	0 .0	5 100.0	0 .0	21 84.0	4 16.0
Total	75 48.7	79 51.3	71 53.8	61 46.2	80 51.0	77 49.0	70 53.0	62 47.0	75 53.2	66 46.8	76 52.1	70 47.9	138 50.9	133 49.1	585 51.6	548 48.4

^a Note: This is based on the ILO definition of informal employment and it includes own-account workers and employers employed in their own informal sector enterprises, contributing family workers, employees holding informal jobs, whether employed by formal sector enterprises or informal sector enterprises, or as paid domestic workers, etc.

^b Note: The percentage in this table is row-wise.

^c Note: CL- Casual labour, RW- Regular Wage, SE- Self Employed.

The income-wise gender divide is quite large, the figure shows average income of both the sexes in all categories of work, whereas men income is quite considerably high as compared to female. The construction sector has the highest average earning for both men and women and lowest has been recorded in security for men and personal services for women. It is surprising to note that average income of construction workers for both men and women are significantly high when compared with other occupational groups. This was due to the fact that the construction workers include skilled labour like plumber, carpenter and mason (Raj mistri) who also works overtime this makes his per day income is quite high

when compared with the daily wage labourer. Another reason supporting this argument is that construction activities are on rise in Delhi which enables these workers to find work for most of the time during the year.

Public distribution system (PDS) is an Indian food security system. Established by the Government of India under Ministry of Consumer Affairs, Food, and Public Distribution and managed jointly with state governments in India, it distributes subsidized food and non-food items to India's poor. This scheme was launched in India on June 1997. Major commodities distributed include staple food grains, such as wheat, rice, sugar, and kerosene, through a network of fair price shops (also known as ration shops) established in several states across the country.

Table 2. Occupational category

Occupations	Male	Female	Average Income Rs (Male)	Average Income Rs (Female)	t-test
Professional	26(6.20)	8(8.6)	5050	3229	1.835**
Sales	98(23.3)	12(13.0)	5035	4375	1.492**
Trade	8(1.90)	0	4833	0	0
Personal services	46(10.97)	44(47.8)	3400	2046	6.521*
Manufacturing	40(9.5)	11(11.9)	4345	2250	4.60*
Commercial services	20(4.7)	2(2.17)	4500	0	0
Transport	60(14.3)	1(1.08)	4604	0	0
Tailoring and knitting	12(2.8)	2(2.17)	5222	2250	3.014*
Construction	91(21.7)	12 (11.9)	5712	4750	2.88*
Security	3(0.7)	0	3000	0	0
Repairing	15(3.5)	1(1.08)	4909	0	0
Total	419	92			

Note: Figure in parentheses gives the percentage from the respective total. T- test is the test statistics examining the statistical significance of the differences in male and female wage differentials "0" indicates No women work was found ** Not significant Significant at .05 level.

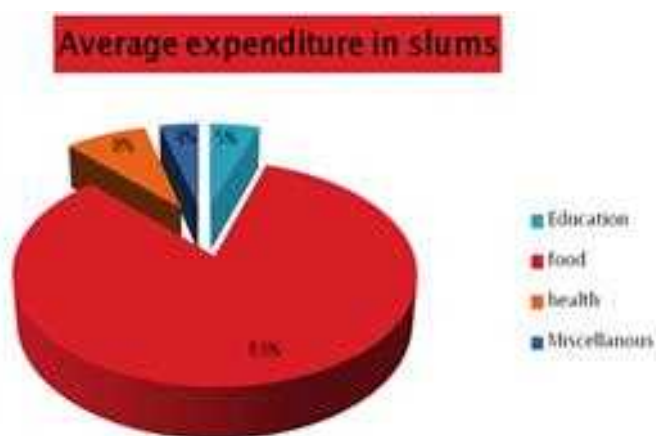


Figure 1. Average expenditure for slum dwellers.

Table 3. Below poverty line card holding

Type of Card	Non-Notified	Notified	Total
No card	177 (88.5)	150 (75)	327 (81.8)
Red card	19 (9.5)	5 (2.5)	24 (6)
Yellow card	4 (2)	34 (17)	38 (9.5)
White card	0	11(5.5)	11(2.8)
Total	200	200	400

Table 4. Amenities provided under different types of BPL cards

Type of Card	Wheat (Quantity dispersed)	Rice (Quantity dispersed)	Kerosene Oil (Quantity dispersed)	Sugar (Quantity dispersed)
Red card	20kg/3	10kg/4	5lit/60	5kg/14
Yellow card	No of persons in family@Rs 3	No. of persons in family @Rs/4	No oil	5kg/14
White card	No of persons in family@Rs 3	No. of persons in family@ Rs/4	No	No

**Table 5. Reasons for indebtedness
(coping strategies)**

Reason for Indebtedness	Did Not Answer	Yes	No	Total
Not indebted	83(30)	10(3.6)	184(66.4)	277
Family exp (mainly food)	0(0)	66(100)	0	66
Health problem	0(0)	29(100)	0	29
For setting shop	0(0)	2(100)	0	2
Health of father	0(0)	5(100)	0(0)	5
Childs operation	0	1(100)	0	1
For making home at village	0	4(100)	0	4
Marriage	0	1(100)	0	1
Sister marriage	0	4(100)	0	4
Husband operation	0	9(100)	0	9
Total	83(20.9)	131(32.9)	184(46.2)	398(100)

Table 3 and 4 provide the total numbers of below poverty line card holders in the studied slums, where three types of BPL (Below Poverty Line) cards holders were found. These cards are red, yellow and white, where the red card holders get 20 kg of wheat at Rs. 3 per kg, 10 kg rice at Rs. 4 per kg and 5 kg sugar at Rs 14 per kg. But for the yellow and white cardholders the scenario is quite different, where the ration given to these families depends on number of members in the family. The yellow and white cardholders get wheat and rice at Rs. 3 and Rs. 4 per kg per number of persons in the family. While the white card holders also get ration based on the number of persons with exception for sugar and kerosene oil. However, there are lot of problems within the public distribution system (PDS) which leads to black marketing of these food grains as reported by these people.

In the next section we have examined the extent to which households in the urban poor areas are vulnerable to food security. Common measures of food insecurity are based on food expenditures, consumption and household members and nutritional status. These indicators are subject however, to measurement problems as well as conceptual issues [8]. The above figure shows that average expenditure pattern in slums of Delhi. From this we infer that 80% of income is spend on food, expenditure on health is less than 8% and education is even less

than 5%. Income from all sources is so less that the entire money is spends on food. Lack of work both among male and female leads to underemployment and this affect their income as well as food security status of household more decisive.

In order to cope up the seasonality of work during different periods of the year the slum dwellers resort to different kind of strategies or measures which include the use of strategies such as borrowing for food, pawning and selling of assets, reducing food consumption, or just cook once in a day (in bulk) etc. The above table represents the reason for indebtedness among the households, around 32.9% of 400 households were indebted due to one or the other reason while 46.2% of households were not indebted. During the period of survey it was found that most of the households exchanged money among themselves as part of coping strategy in order to run their current expenditure which was short during the particular month.

Skills and knowledge are the driving forces of economic growth and social development for any country. Countries with higher and better levels of skills adjust more effectively to the challenges and opportunities of world of work. Potentially, the target group for skill development comprises all those in the labour force, including those entering the labour market for the first time (12.8 million annually), those employed in the organized sector (26.0 million) and those working in the unorganized sector (433 million) in 2004-05. The current capacity of the skill development programs is 3.1 million. India has set a target of skilling 500 million people by 2022. In terms of skilled labour, that most of the workers both men and women have low basic skills which have significant impact on their wage level. Most of the activities that persist in slums requires low level of basic skills such as truck driver, construction workers, plumber, and hinge (kabja) worker were dominated by men. For women, the major domain of work was part-time, contractual activities that did not require even basic skills and is actually an extension of household activities. This was also the major reason for their wage differentials cross gender. Both the counterparts male (10.26) percent and female (5.4) percent have low levels of skills while around (89.73) percent are employed in non-skilled activities.

Seasonal variation (or seasonality) refers to the degree to which employment rises and falls because of the seasonal pattern (caused by climate and/or institutional events). It governs the extent to which employment estimates must be changed in order to remove the seasonal pattern. In order to address the issues of poverty and food security the seasonal availability of work within low income households has to be addressed so that year round employment can benefit the people at large. Table 7 provides information on different kind of activities prevalent in slums all the year round. It is quite clear from the table that available work opportunities for women is quite minimal as compared to men, further, the labour market was segregated and female participation in the labour market was unremittingly much lower than male participation. Women account for most of unpaid work and when they are paid they face significant wage differentials vis-a-vis their male counterpart. An observation made by Mitra, who has argued that physical segmentation that is seclusion of certain kinds of jobs to certain group of individuals was primarily because of the distance factor within the city and even inexpensive intra-city transport for commutation which does not eliminate these barriers. Women under these circumstances are more ungaurded; they bear major burden of unpaid work which doesn't permit them to travel long distances.

Table 6. Type of skilled labour

Type of Work	Male	Male Income (Avg Income)	Female	Female (Avg Income)	Total
Skilled	43(10.26)	5712	5(5.4)	4833	48(9.3)
Non-skilled	376(89.73)	4500	87(94.56)	2733	463(90.6)
Total	419		92		511

Table 7. Seasonality in work

Month	Activities	Wage /Day	Time/ Day
January, February	Peeling of peas, Making of garlands, removing unused material from zip and jeans, making nut bolt sharper.	1 Dirai=5kg7/dirai 2 Per Garlands, 30 paise/piece 50 paise/piece.	5-6 hrs
			4-5 hrs
			6-8 hrs
			6-8 hrs
March, April	Making of <i>Papads</i> , Taking out stickers from cloth.	20/kg for making <i>papads</i> , 5/piece, 30 paise/piece	6-8 hrs
			5-6 hrs
			5-7 hrs
July, August	No activity	No activity	—
September, October, November	Putting cushion inside vaseline box, removing of unwanted material from finished goods, basket, making of chandeliers (<i>Jumars</i>)	Rs2/bottle, 5Paise /piece, 10/basket, Rs10/piece.	6-8 hrs
			5-6 hrs
			7-8 hrs
			5-6 hrs
Notified Slums			
January, February, March	Packaging of soaps, Refining and Cleansing of copper Making of papads	For 1000 soaps they get Rs 30 Rs 300/day Rs 20/kg	5-6 hrs / day
May, June, July, August	Making of garlands	For one piece they get Rs 1.	4-6 /day

CONCLUSION

Women and girls are affected in two different ways. One is the limits on their access to education and employment opportunities, which curtails their economic autonomy and weakens their bargaining position within the family. Secondly, their weakened bargaining position translates into little or no voice in household decisions, differential feeding and care giving practices favouring boys and men, food and nutrition insecurity, lower health and nutrition outcomes. This paper tries to conclude that women's income makes positive contribution to the household nutritional status. Women in slums do not have regular source of income through being employed in some or other type of enterprise they make significant contribution to their household income and thus making themselves more food secure. This implies that being employed in some kind of enterprise (work as option), and they also make use of other adaptive or coping strategies such as undertaking two or more jobs, which gives them regular source of income. However, it does not allow them to develop their skills in any particular enterprise thus making them more vulnerable. This in turn suggests that there are factors that influence their occupational choice (taking up of two work together) other than food security concern.

Seasonality, was most important factor that affects women work and income quite sharply where certain period no work is available. There are two sets of arguments put

forward in this respect by the slum dwellers, firstly opportunities of work was dependent upon season, and secondly, even within the season the work was not available throughout the year which leads to variation in income which finally makes significant impact on the nutritional status of women and children and household on the whole. Most of the income which is earned from the above said activities is spent on food items. Household with economically dependent adults and larger household were most vulnerable. Thus, women under these circumstances act as catalyst towards household nutrition as most of the surveyed women around 73% spent their income on food, followed by their children education and health. It is also clear through seasonality calendar that during the months of July, August and December there are no activity which can substantiate the income of the women which affect the food security status of the entire household. Improved food intake translates into better health and nutritional outcomes only if accompanied by access to adequate education, health services, water, and sanitation. This paper shows how gender-sensitive policies that empower women within households can contribute to nutritional security.

APPENDIX

Occupational Groups

Professional: Auxiliary Nurse Midwife, accredited Social Health Activist, lady Health Visitor, anganwadi Worker and Helper, supervisor, computer operator, NGO worker, registered medical practitioner, engaged in field work (as assistants), teacher, tutor (home based who are in their graduation), doctors.

Sales: Fruit seller, vegetable seller, baas ki tokri maker and seller, toy seller, kachori seller, small peddlars and hawkers (Peddlars are mainly associated with Food products), seller of food products (Kiranewala), acid and phenyl Seller.

Trade: Butcher, fish seller, worker in hotel, worker in community centre, worker in private tent firm, assistant in shop, tea shop owner/worker, milkman, petty traders, contractors.

Personal services: Barber, cobbler, cook, domestic labour (engaged in cleaning), bathroom cleaner, domestic maid, helper in house (for keeping the child), clothes washer, ironing clothes, Roti maker.

Manufacturing: Workers involved in utensils (barthan maker and polishing it with acid), confectioner, cover maker, dial maker, metal processor, worker in workshop, skilled labour, peeling of peas, making of garlands, removing unused material from zip and jeans, making nut bolt sharper, making of Papads, taking out stickers from cloth. putting cushion inside vaseline box, removing of unwanted material from finished goods, basket, making of chandeliers (Jumars).

Commercial services: DJ operator, drum player, MCD worker, musician, peon, worker in office (like sweeper, multitasker, attendant, etc.).

Transport: Auto driver, taxi driver, cab operator, rickshaw puller, conductor, ticket checker.

Construction: Construction labour, carpenter, marble cutter, painter, Raj Mistri, sanitary worker.

Security: Security guard in private hospital, constable, homeguard, security guard in private enterprise.

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Chapter 26

TRADITIONAL HEALTH CARE PRACTICES OF WOMEN IN URBAN SLUMS: FOCUS ON MATERNAL HEALTH AND NUTRITIONAL STATUS

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ABSTRACT

This study examines the health, nutritional status, and health care seeking behaviour of a community based sample of 400 postpartum women from an urban slum in Delhi, India. It describes physically impoverished environment, where malnutrition is serious, and non-trivial morbid episodes as a consequence of childbirth are very common. Malnutrition was found to be widespread among women residing in slums. During the first few weeks postpartum over three-quarters of the women reported non-trivial illness. The frequency of reported illnesses was significantly associated with both increasing age and parity. As severe poverty persisted, most of the women reported complications (63.5%) and received some form of health care from a wide range of medical practices and traditional health care providers, with traditional birth attendants (TBAs) and unqualified medical care providers being the most frequently utilised. This study highlights the plight of these women in a precarious environment and showed how their health was compromised by cultural and political constraints. We conclude that while the burden of postpartum morbidity is very high, the incorporation of traditional practitioners and unqualified western care providers into maternal health training programs, together with efforts to empower women, could be effective in improving the health status of mothers in this marginalised and fragmented community. To achieve this outcome, a clearly articulated and integrated approach to development in slum communities is required.

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Keywords: malnutrition, body mass index, intrapartum, postpartum, slums, public health, India

INTRODUCTION

Maternal health refers to the health of women during pregnancy, childbirth and the postpartum period. While motherhood is often a positive and fulfilling experience, for too many women it is associated with suffering, ill-health and even death. The “State of the world’s mothers” 2015 focuses on vulnerable group of mothers and children mainly from low income group in urban areas and it highlights the key causes for mortality in Sub-Saharan Africa and South Asia [1].

Bhutta et al. [2] argued for strategies to promote complementary feeding with or without provision of food supplements, micronutrients intervention, general measures to improve recurrence of diseases and thus improving overall health status of the people. On the other hand Gupta [3] argued that in the majority of cases there was a lack of knowledge and correct practices regarding newborn care among mothers, which should be promoted through improved coverage with existing health scheme. Ghosh and Sharma [4] suggested that better antenatal care, safer delivery practices and post-natal visits observed among women resulted in less morbidity and mortality. Another remarkable argument forwarded by Paula and Stephenson [5] asserted that poor quality of service offered at government institutions was a motivating factor for delivery at home. On a similar note Parashar [6] found that inadequate knowledge and adverse practices regarding neonatal care among mothers was revealed in the study area, while Iyengar [7] argued that the quality of services administered was adequately addressed.

Even though much work has been done on health issues, there is still a paucity of data on the kind of complications and morbidity pattern among low income households. Sundar and Sharma [8] in their paper examined the pattern of morbidity and healthcare utilization by urban poor living in slums and resettlement colonies of Delhi and Chennai. The findings of their study suggested that women were at an added risk. Lack of awareness about hygiene, low levels of education, low social status, and stigma about gynecological problems may have resulted in higher actual morbidity and lower utilization of health care. Izugbara [9] also argued that in many developing countries like for example Nigeria maternal reproductive health has long been recognized as a most urgent public health and social policy priority. Krishnaraj and Chanana [10] argued that female education plays a major role in determining health, particularly that of their children. Fronczak [11] in their paper described associations among delivery-location, training of birth attendants, birthing practices, and early postpartum morbidity in women in slum areas of Dhaka, Bangladesh. Associations among maternal characteristics, birth practices, delivery-location, and early postpartum morbidity were specifically explored. Self-reported postpartum morbidity was associated with maternal characteristics, delivery-related complications, and some birthing practices. Dais (a term used for untrained traditional birth attendants in rural and urban slum areas) with more experience were more likely to use potentially-harmful birthing practices, which increased the risk of postpartum morbidity among women with births at home. Postpartum morbidity did not differ by birth-location. Safe motherhood programmes must develop effective strategies to

discourage potentially-harmful home-based delivery practices demonstrated to contribute to morbidity.

Khan et al. [12] argued that pregnant women inhabiting urban slums were a “high risk” group with limited access to health facilities. The study examined whether hazardous maternal care practices existed and whether there were differences in the utilization rates of health services in two different slums.

The current paper aims to highlight the maternal health status of women in slums of Delhi, which includes antenatal care access, child birth practices, and complications during pregnancy and morbidity pattern among the women during their last delivery.

METHODS

A descriptive research design was used in this study in order to meet the objectives and justify the hypothesis. The study employed both quantitative as well as the qualitative methods. Descriptive research included surveys and fact-finding enquiries of different kinds. The major purpose of descriptive research is description of the state of affairs as it exists at present. There are three ways a researcher can go about doing a descriptive research.

- Observational, defined as a method of viewing and recording the participants Case study, defined as an in-depth study of an individual or group of individuals.
- Survey, defined as a brief interview or discussion with an individual about a specific topic.

Thus, in order to see interlinkages between health, work and education the above design was considered most suitable.

Sampling Procedure

The state of Delhi was purposively chosen for the study as it is national capital region with a large number of slums. As a first step, we divided Delhi into seven zones on the basis of the geographical location of the 70 constituencies given in the DDA (The Delhi Development Authority was created in 1955 under the provisions of the Delhi Development Act to promote and secure the development of Delhi) list; thus zones one through seven are respectively, north, north-east, east, south, west, north-west and central Delhi. Out of seven zones four zones were selected purely on the basis of the number of slum in these zones based on the report from the *Municipal Corporation of Delhi (MCD)*.

Selection of Clusters

A “non-notified slum” is a compact urban area with a collection of poorly built tenements, mostly of temporary nature, crowded together usually with inadequate sanitary and drinking water facilities in unhygienic conditions, if at least 20 households lived in that

area. Urban areas notified as slums by respective municipalities, corporations, local bodies or development authorities were treated as “notified slums”. A total of 400 household has been selected from both non-notified and notified slums spread across Delhi. 1,997 persons were surveyed in a total of 400 households. Thus, 1,061 persons from non-notified and 936 from notified were surveyed during the course of the study, which includes males, females and children.

RESULTS AND DISCUSSION

Gravida indicates the number of times the woman has been pregnant, regardless of whether these pregnancies were carried to term or not. A current pregnancy, if any, is included in this count. The section below focuses on health status of women which covers antenatal care, health complications among women, morbidity pattern among women, complications during postpartum period. The second section focuses on intrapartum morbidities and birth practices in slums of Delhi and the last section focuses on the postpartum problem and nutritional status of females in slums.

Table 1 provides information on gravida of women in urban slums of Delhi. The term gravida can be used to refer to a pregnant woman. A “nullgravida” is a woman who has never been pregnant, a “primigravida” is a woman who is pregnant for the first time or has been pregnant one time, a “multigravida” or “secundogravida” is a woman who has been pregnant more than one time. From the table it is very clear that women in slums marry at a very early age. Most women conceive in their early adulthood. Out of 155 women in the 20-29 year age group category, 27.1% completed their third pregnancy. Out of 139 women in the 30-39 year age group, 23.7% completed their fourth pregnancy, which means that women in slums conceive at a very early age and the parity between the children is very short. Lack of spacing between the children also results in poor maternal health status of women in slums of Delhi.

Antenatal Care

Prenatal care is preventive healthcare with the goal of providing regular check-ups that allow physicians, nurses or midwives to treat and prevent potential health problems throughout the course of the pregnancy, while promoting healthy lifestyles that will benefit both mother and child.

The World Health Organization defines antenatal care as recording medical history, assessment of individual needs, advice and guidance on pregnancy and delivery, screening tests, education on self-care during pregnancy, identification of condition detrimental to health during pregnancy, first time management and referral services. Table 2 shows the pattern of antenatal care utilisation for their last child birth among urban slum dwellers. Respondents interviewed among eight slum clusters from all around Delhi displayed a very small proportion of women that had received full antenatal care services during their last pregnancy. Similarly, out of 400 women interviewed only 75 women responded, when asked about antenatal care services. Out of 75 women only 69.3% had measured their weight during the last pregnancy, while 24% who made partial visits to facility had measured their weight

and 6.7% did not pay even a single visit to a facility. Similarly, out of 79 women only 59.5% who had received full antenatal care services. While 15.2% of women got their hemoglobin measured and 25.3% did not make even a single visit to the facility. The major reason for not accessing ANC (antenatal care services) during their last pregnancy was lack of knowledge and education (40%) followed by mother in law who did not allow (20%). However, 20% did not consider it mandatory and only 12% responded socio-economic condition to be a major factor.

Table 3 provides information on various types of complications reported during their last pregnancy. Complications such as night blindness, blurred vision, swelling on legs and face, excessive fatigue and anemia together amounted to 52.3%. Nonetheless, women in very small percentage reported problems like anemia (8.5%), oligohydramnios (0.5%), urine infection (0.5%), infection in uterus (0.5%), problem in stomach (0.5%), pain in abdomen (5%), body swollen (4.5%), pain in legs (1%), low blood pressure (2.5%) and jaundice (0.5%). Around 58.5% of women in notified slums (these slums are recognized/ registered by their respective municipalities) faced any complication during their last pregnancy, as compared to 14.5% in non-notified slums (these slums are not recognized /registered with their respective municipalities).

Table 1. Age group with pregnancy status of the women

Age Group	Number of Children						Total
	1	2	3	4	5+	No Children	
15-19	7(100)	0(0)	0(0)	0(0)	0(0)	0(0)	7(1.75)
20-29	42(27.1)	35(22.6)	42(27.1)	12(7.7)	5(2.6)	19(12.9)	155(38.75)
30-39	3(2.2)	23(16.5)	51(36.7)	33(23.7)	29(20.8)	0(0)	139(34.75)
40-49	9(11.3)	12(15)	16(20)	19(23.8)	24(30)	0(0)	80(20)
50-59	1(50)	0	1(50)	0	0	0	2(0.5)
>60	0(0)	0(0)	0(0)	8(47.1)	9(52.9)	0(0)	17(4.25)
Total	62(16.1)	70(18.2)	110(28.6)	72(16.9)	67(14.6)	19(5.7)	400(100)

Note: Figure in the parenthesis shows percentage to their respective total.

Table 2. Type of antenatal care accessed and participation of women (N = 400)

Type of Antenatal Care	Full		Partial	Not a Single Visit to Facility	Total
Weight measurement	52(69.3)		18(25)	5(6.7)	75
Blood test	54(72)		17(22.7)	4(5.3)	75
Urine check-up	54(66.7)		22(27.2)	5(6.2)	81
Abdominal examination	54(69.2)		19(24.4)	5(6.4)	78
Haemoglobin test	47(59.5)		12(15.2)	20(25.3)	79
X-ray	43(84.3)		6(11.8)	2(3.9)	51
Whether ultrasound	34(65.4)		17(32.7)	1(1.9)	52
TT injection	One dose	13(23.6)	10(18.2)	32(58.2)	55
	Two dose	22(73.3)	4(13.3)	4(13.3)	30
Blood pressure was monitored.	43(79.6)		8(14.8)	3(5.6)	54

Note: Figure in the parenthesis shows percentage to their respective total.

Table 3. Complications during pregnancy (N = 400)

Complications during Pregnancy	Non Notified	Notified	Total
No problem diagnosed	29(14.5)	117(58.5)	146(36.5)
Night blindness	5(2.5)	66(33)	71(17.75)
Blurred vision	12(6)	17(8.5)	29(7.25)
Swelling on legs and face	31(15.5)	0(0)	31(7.75)
Excessive fatigue	44(22)	0(0)	44(11)
Anaemia	34(17)	0(0)	34(8.5)
Oligohydramnios	2(1.0)	0	2(0.5)
Urine infection	2(1)	0	2(0.5)
Infection in uterus	2(1.0)	0	2(0.5)
Problem in stomach	2(1)	0	2(0.5)
Pain in abdomen	20(10)	0	20(5)
Body swollen	9(4.5)	0	9(2.25)
Pain in legs	2(1)	0	2(0.5)
Low BP	5(2.5)	0	5(1.25)
Jaundice	1(.5)	0	1(.25)
Total	200(100)	200(100)	400

Note: Figure in the parenthesis shows percentage to their respective total.

Table 4. Types of communicable and non-communicable disease among women during OPD visits (N = 400)

Communicable Disease		Non-Communicable		Total
Jaundice	132(65)	Kidney problem	26(31)	158(55.05)
Pneumonia	21(10)	Respiratory distress	18(22)	39(13.5)
Malaria	3(1)	Fracture in hand	1(1)	4(1.3)
Tuberculosis	8(4)	Pregnancy related complication	3(4)	11(3.8)
Cough and cold	24(12)	Operated	3(4)	27(9.4)
Gastroenteritis	2(1)	Brain problem	4(5)	6(2.09)
Dengue	7(3)	Whitish discharge	1(1)	8(2.7)
Typhoid	5(2)	Infection in heart	3(4)	8(2.7)
Diarrheal problem	2(1)	Joints pain	9(11)	11(3.8)
		Fit problem	4(5)	4(1.39)
		Cancer	1(1)	1(.348)
		Problem in uterus	2(2)	2(.696)
		Menopause problem	1(1)	1(.348)
		Thyroid problem	1(1)	1(.348)
		Anaemic	6(7)	6(2.09)
Total	204		83	287

113 women did not made any OPD visit in 3 months preceding the survey.

Note: Figure in the parenthesis shows percentage to their respective total.

Antenatal Morbidities among Women

Table 4 shows various types of communicable and non-communicable diseases prevalent among women in slums three months preceding to the survey. Out of 400 respondents, 113 (28.25%) did not make any OPD (outpatient department it means a person is not admitted in hospital he/she just makes a visit for consulting a doctor) visit within three months preceding the survey. From the table it is evident that 65% of women suffered from jaundice,

pneumonia (10%), malaria (1%), tuberculosis (4%) cough and cold (12%), gastroenteritis (1%), dengue (3%), typhoid (2%) and diarrheal problem (1%). However, women suffered more from non-communicable diseases, as to communicable diseases. Problem such as kidney disorder and respiratory distress makes up around 51% of non-communicable diseases. The major reason for spreading of communicable diseases in these low income households is because of the poor quality of water supply they have been receiving, which makes them prone to water borne diseases. Besides, lack of maintenance of proper sanitation and hygiene further adds to the agony of these low income settlements.

Intrapartum Morbidities and Practices during Child Birth

In obstetrics, the period from the onset of labor to the end of the third stage of labor is called the intrapartum period. In India, maternal mortality is estimated at 540 per 100,000 live births [13]. The intrapartum period, although a limited time span, is of critical importance, as at this stage a seemingly normal labour can suddenly degenerate into a crisis.

Among women with deliveries at home, self-reported postpartum morbidity was significantly associated with risk parity (primiparity or grand-multiparity of five or more births), poorest economic strata, under nutrition, anemia, meeting operational definitions for delivery-related complications, and malposition of the infant (see Table 6). With regard to delivery practices, postpartum morbidity was significantly associated with having two or more vaginal examinations and reports of practices to expel the placenta or stop bleeding (forced gagging, applying hard manual pressure to the abdomen or pulling on the umbilical cord). Table 7 shows various kinds of practices which were prevalent during birth in slums at home. These practices are quite hazardous, which often results in morbidity or mortality either in children or mother. During the survey period many women said that after delivery they were immediately transferred to the hospital as emergency cases for excessive bleeding as one of the major problem after delivery.

Table 7 provides information on various kinds of problems reported by women during postpartum period in low income settlements. The majority of women reported complication such as excessive blood clots, foul smelling discharge and pain in lower abdomen as major complications during the postpartum period. The major reason for these complications are the lack of any antenatal visits before delivery (see Table 2).

Table 5. Problems during intrapartum period

Intrapartum Problems	Given Tea	Given Hot Milk	Nothing Given	Total
No problem	36(85.7)	4(9.5)	2(4.8)	42
Inadequate labour pain	5(2.6)	136(69.4)	55(28.1)	196
Prolonged labour	2(1.5)	27(20.5)	103(78)	132
Heavy bleeding during labour	4(16)	14(56)	7(28)	25
Loss of consciousness	1(50)	0	1(50)	2
Heavy bleeding after labour	0	3(100)	0	3
Total	48(12.1)	184(45.7)	168(42.2)	400

Table 6. Delivery practices

Delivery Practices	Categories	Number	Share (%)	Medical Practices
Cleaning of the floor prior to delivery	Yes	96	23.8	Yes
Washed hands with disinfectants	Yes	88	22	Yes
Boiled instruments used for cutting cord	Yes	92	23	Yes
Boiled the thread for tying umbilical cord	Yes	101	25.25	Yes and use of clamp
Wore gloves	Yes	43	10.75	Yes
Given hot milk and egg during delivery	Yes	237	59.25	
Posture during delivery	Squatting	213	53.25	Supine
	Supine	187	46.75	
Abdominal massage after delivery	Yes	157	39.25	Not ideal practice
Cord Cut	Blade Scissors	144	44.72	
		178	55.27	
Cord tied	Thread Cloth	228	57	
		172	43	
Cord application	Ghee Turmeric	213	53.25	No application
		187	46.75	
Resuscitation	Slapping	212	53	Slapping
	Tilting baby upside down	119	29.75	
	Ringling bell	69	17.25	
Encourage to walk before delivery	Yes	148	37	-
Oxytocis injected	Yes	131	32.75	-
Delivery on floor of slums	Yes	43	10.75	No
	No	357	89.25	
Multiple vaginal examinations	Yes	128	32	No
	No	272	68	
Manual removal of placenta	Yes	43	10.75	Trained personnel
	No	357	89.25	could do it.

Table 7. Complications reported by women during postpartum period (N = 400)

Complications	Non-Notified	Notified	Total
No complications	25(32.9)	51(67.1)	76(19)
Excessive blood cloths	30(17.8)	139(82.2)	169(42.5)
Foul smelling discharge	37(78.7)	10(21.3)	47(11.75)
Fever	23(100)	0	23(5.75)
Pain in lower abdomen	42(100)	0	42(10.6)
Infection of vaginal wound	24(100)	0	24(6)
General weakness	16(100)	0	16(4)
Failure to lactate	1(100)	0	1(0.25)
Arthritis	1(100)	0	1(0.25)
Swollen body and blood transfusion	1(100)	0	1(0.25)
Total	200	200	400

Note: Figure in the parenthesis shows percentage to their respective total.

Table 8 shows cross-classification of nutritional status of women with respect to various age groups. However, with increase in age most of the women surveyed faced problems of inadequate calorie intake. Around 11.7% of women within different age group were found to be underweight, while around 7% of women within different age group were severely underweight. Many of the women suffered deficiency in necessary vitamins and micronutrients found in fruits, vegetables, and dairy products. During the course of the survey it was found that many families in slums do not have access to pulses, green leafy vegetables

and dairy products. During the past few years, due to consistent rise in the prices of milk, vegetables and pulses, many slum dwellers are unable to get these products. Women who consume milk or curd everyday are less likely than other women to have CED (chronic energy deficiency). Similarly, women who consume fruits or chicken, meat or fish on a daily basis are less likely than other women to have CED. Apart from CED, a significant proportion of women suffers from overweight and obese, which clearly indicate that this problem cannot be ignored. This phenomenon is becoming a well-recognized aspect of nutrition transition, with change in dietary pattern and levels of physical activity leading to increase in overweight.

Table 8. Nutritional status of women analyzing body mass index (N = 382)

Age categorical	Less than 15 (very severely underweight)	15-16 (severely underweight)	16-18.5 (underweight)	18.5-25 (normal)	25-30 (overweight)	30-35 (moderate obese)	35-40 (severe obese)	Total
15-19	0	0	0	4 (66.6)	2 (33.3)	0	0	6 (100)
20-29	7 (4.09)	4 (2.33)	22 (12.86)	83 (48.50)	43 (25.14)	12 (7.07)	0	171 (100)
30-39	2 (1.1)	6 (4.3)	14 (10.14)	56 (40.57)	31 (22.4)	24 (17.3)	5 (3.6)	138 (100)
40-49	4 (5.9)	4 (5.9)	9 (13.43)	22 (32.83)	17 (25.37)	10 (14.9)	1 (1.49)	67 (100)
Total	13 (3.4)	14 (3.6)	45 (11.7)	165 (43.1)	93 (24.34)	46 (12.04)	6 (1.57)	382 (100)

Note: Figure in the parenthesis shows percentage to their respective total.

CONCLUSION

This study demonstrated that the health of women in slums was very poor, as an outcome of severe economic, environmental and social deprivation. In addition, housing, sanitation and health services are grossly inadequate. Low status is reflected in high levels of malnutrition, as shown in low body mass indices. Further, the women reported significant morbidity following child-birth. The data gathered from this urban slum in Delhi were consistent with the relatively scarce information available on comparable populations in Delhi. Perhaps surprisingly, given the poverty of these people, there is a wide range of untrained medical practices and traditional practitioners who ply their services to the slum dwellers and the respondents used their services fairly frequently. These women and their families clearly consider health care services to be desirable, and prove this by voting with their feet and using their meagre resources to do so.

Not only do these slum dwelling women live in appalling physical conditions, but they also suffer high rates of illiteracy and have little decision making power, which serves to reinforce their inferior status. Furthermore, they are often denied the support of an extended social network due to the highly fragmented and mobile nature of the population. It is clear that the low status of women in Delhi in general, and in slum communities in particular, is a severe impediment to bringing about improvements in their overall health. Any attempts to improve the status of these women must take as a starting point an in-depth understanding of

their particular circumstances. Such an understanding may reveal, as this study has, that in spite of everything, women are surprisingly active in pursuing health care services, particularly those they could access within the bustee or slums. It is this positive motivation which should be mobilised in any community-based initiatives.

Long-term programs aimed at improving women's status, education and employment must be part of an integrated program for development in slum communities. We consider such initiatives need to go hand in hand with comprehensive community based health care services that reach out to women within the slums, rather than services that wait for powerless women to come to them. This study also offers some practical scope for potential improvement.

In short, we would recommend that the growing problem of urban slum health needs urgent attention, and that the primary health care approach, emphasising basic and accessible low-level services linked to, and supported by, the community, holds the best hope for improvement. It is clear that this group of poor urban mothers is at a very high risk, and should be recognised as such and targeted by health planners and policy makers. Clearly, overall economic improvement is fundamental, and policies should be directed to documenting and improving the living conditions of the urban poor, perhaps especially those in the present group, who are an impoverished sub-group within the deprived underclass. This study has contributed to the scant information we have on health problems and their management among mothers living in the urban slums of Delhi.

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Chapter 27

**CHINESE BELIEFS ABOUT ADVERSITY:
THEIR ASSOCIATION WITH TREATMENT FEARS
AMONG YOUNG PSYCHOTROPIC SUBSTANCE
ABUSERS IN HONG KONG**

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ABSTRACT

Mainstream Chinese cultural values have their roots in Confucian, Taoist, and Buddhist teachings that have been transmitted through generations. This study examines Chinese beliefs about adversity and their association with treatment fears among young psychotropic substance abusers undergoing residential drug treatment in Hong Kong. Results showed that young substance abusers' levels of current treatment fears and anticipated discharge fears were negatively correlated with the Chinese Cultural Beliefs about Adversity Scale. The findings imply that young substance abusers under treatment who have a stronger endorsement of positive Chinese cultural beliefs about adversity are expected to have a lower level of anticipated discharge fears. The role of Chinese beliefs about adversity in the treatment of young substance abusers is discussed.

Keywords: Chinese beliefs about adversity, treatment fears, young substance abusers, residential drug treatment, Hong Kong

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INTRODUCTION

According to the statistics of the Central Registry of Drug Abuse (CRDA) maintained by the Government of the Hong Kong Special Administrative Region (2015), the average age for reported adult drug abusers was 38 years, and the mean age for first use of drugs was 18 years. For the drug abusers under 21 years, the average age was 18 years, and the mean age for first abuse was 15 years. Most of them (87.8%) were psychotropic substance abusers. The most commonly abused drugs reported by young substance abusers were methamphetamine (40.9%), ketamine (36.7%), and cocaine (29.2%).

The CRDA statistics (2015) showed that about half of the current drug abusers reported that their main reason for drug use was relief of boredom, depression, or stress [1]. These findings echoed the findings of Shiffman and Wills [2] who found that coping ability of an individual in handling stress and temptation was a determinant of substance abuse. Research studies suggested that youngsters tended to use drugs as a coping strategy when they wanted to evade encountering their problems and negative emotions [3-5]. Echoing the results of the above studies, Aebi et al. [6] reported associations among avoidant coping pattern, psychosocial adversities, and substance use. Their findings showed that adolescents who frequently showed avoidant coping would have lower ability to deal with their psychosocial adversities, such as family violence, imprisonment of a family member, financial problems, school failure, and sexual abuse, which subsequently predicted their substance use behaviour. In addition, Shek [7] found that a lower level of endorsement of Chinese cultural beliefs about adversity was associated with a higher level of substance abuse.

With specific reference to the Chinese culture, Confucian, Taoist, and Buddhist teachings form the main roots of Chinese cultural values. These traditional values and rules that passed down through generations tend to govern the behaviour of individuals [8]. Besides, the ways that Chinese cope with adverse life events can be explained by the cultural values and attitudes that have been transmitted down through the generations. According to Shek [9], Chinese cultural beliefs about adversity include those concepts about the nature of adversity such as its causes, consequences and the proper coping behaviour.

Life adversity in Confucian teaching can be interpreted as fate. According to Xunzi, people should not challenge or change their fate. Life adversity is pre-assigned and should be regarded as an opportunity in life. People should seize adverse situations as a chance for personal development and subsequently overcome the hardship in life [10]. Similar to the Confucian teaching, Taoism also regards adversity as part of the life path of an individual. People are advised to accept it with endurance and a peaceful mind, trying to embrace it as a learning process. In Buddhist teaching, adverse events are regarded as karma, which refers to a consequence driven by the intent of the action. It can be viewed as a retribution or transmigration that people should accept. In summary, Chinese cultural beliefs about adversity accept that adversity is inevitable. However, people are encouraged to adopt an optimistic and positive attitude rather than taking it as a suffering. They can seize it as an opportunity for personal development and a chance to succeed. For people who admit that adversity is retribution, they can rebound from the situation when they commit to doing more benevolent acts to compensate for their bad deeds. As such, people will demonstrate their strong capacity for enduring frustration and encouraging themselves to rebound from adverse situations. This could positively inspire or enlighten people to deal with their adversities

positively and to maintain good mental health. On the contrary, people will view adversity as suffering or a failure if they adopt a negative attitude towards adversity.

Every society has its own unique cultural value system for raising its children. Masten [11] pointed out that special cultural customs, beliefs and values can become protective factors for individuals facing adversity. Even though today's social environment is rather complicated, and children's exposure to adversity is not the same, traditional wisdom provides a sound framework for individuals in responding to social environments and dealings with others. Likewise, Chinese people also have cultural beliefs about adversity, which serve as protective factors for Chinese people to overcome life adversities. Research findings suggest that people who identified with more positive Chinese cultural beliefs about adversity (such as "where there is a will, there is a way") have a stronger sense of mastery in life and adapt easier to their environment [12]. People may become more resilient to cope with stress when they can work through hardship and gain benefits through exposure to difficulties [13, 14]. On the contrary, people may have more fears when their life adversities are not properly dealt with. They may turn to other coping options (such as substance use) to alleviate their emotional distress arising from the adversity.

Based on the above background, we asked the following research question in this study - is there any relationship between Chinese beliefs about adversity and treatment fears? Consistent with the existing literature, it was hypothesized that there would be a negative relationship between Chinese beliefs about adversity and treatment fears among young psychotropic substance abusers undergoing residential drug treatment (Hypothesis 1). Besides, it was hypothesized that the level of endorsing Chinese beliefs about adversity would be negatively related to anticipated treatment fears amongst young substance abusers undergoing residential treatment (Hypothesis 2).

METHODS

To explore the relationship between Chinese beliefs about adversity and treatment fears, a cross-sectional study was designed to collect information from young psychotropic substance abusers undergoing residential drug treatment in Hong Kong. As a result, 303 participants were recruited from various residential drug treatment centers by means of convenience sampling.

The age of these 303 participants ranged from 14 to 25 years with a mean age of 20.03 (SD = 2.9). Their age of first drug use ranged from 9 to 24 years with a mean age of 14.71 (SD = 2.09). About 82.8% of them had been poly-drug users at the time they admitted to residential drug treatment. The most popular drugs among the participants were ketamine (83.2%), cocaine (63.0%), cannabis (45.5%), methamphetamines (39.9%), and nimetazepam (37.3%). About 40% of them had an educational attainment of above Secondary 3 (equivalent to Grade 9 in the US). The majority of the participants were Chinese (96%). Most of the participants (83.7%) were recommended by forensic orders (probation order, superintendent's discretion scheme, supervision order, or bound over) to receive residential drug treatment. About 16% of the participants stated that they chose residential drug treatment reluctantly. 20 participants (6.6%) were diagnosed with mental disorders at the same time. The participants

had undergone an average of 9.08 months of drug treatment at a residential drug treatment agency, with a range from 2 weeks to 8.5 years ($SD = 13.5$ months).

The data in this study were collected within a time span of 13 months from June 2011 to July 2012. The objectives of the research, procedures of data collection, and the use of the data so collected were explained to the participants. In addition, the participants were informed of their rights to participate on a voluntary basis and to withdraw from the study at their free will. After obtaining their consent, the participants were invited to self-administer a questionnaire. Ample time was given to the participants to answer the questionnaire which took them roughly 45 to 60 minutes to complete.

Instruments

The 35-item Early Treatment Fears Scale was developed and validated in this study to measure the fear level of young psychotropic substance abusers arising from different causes in their early treatment phase when they underwent residential drug treatment. The scale was developed mainly by reviewing the literature on substance abuse, generating qualitative data from the focus group interviews with young substance abusers and experienced social workers in the drug field, as well as using the clinical experience of the first author [15]. The overall reliability analysis with Cronbach's alpha showed that the Early Treatment Fears Scale (ETF) was reliable ($\alpha = .93$), showing good internal consistency. The Early Treatment Fears Scale (ETF) and its subscales showed good item-total correlations, reliability, validity, and dimensionality in measuring early treatment fears of young psychotropic substance abusers in a Chinese context.

Anticipated Discharge Fears Scale (ADF)

The 39-item Anticipated Discharge Fears Scale was developed and validated in this study to measure the treatment fears of the young psychotropic substance abusers who were about to be discharged from residential drug treatment programs. The scale was formulated from reviewing of substance abuse research [15], qualitative data generating from focus group interviews with young substance abusers and experienced social workers in the drug field, as well as the clinical experience of the first author. The overall reliability analysis with Cronbach's alpha showed that the Anticipated Discharge Fears Scale (ADF) was reliable ($\alpha = .94$), showing good internal consistency. In addition, the ADF and its subscales showed good item-total correlations, reliability, validity and dimensionality in measuring anticipated discharge fears of young psychotropic substance abusers in the Chinese context.

The Chinese Beliefs about Adversity Scale (CBA)

The 9-item Chinese Beliefs about Adversity Scale (CBA) focusing on Chinese beliefs about adversity was developed by a group of psychologists and social workers in this study. For each item, respondents were requested to indicate their degree of agreement with the item

on a 6-point Likert scale ranging from strongly disagree to strongly agree. Adequate reliability of this scale was reported [7, 9]. There are 9 items under this scale, namely, (1) “hardship increases stature”; (2) “whether a life is good or bad depends on fate”; (3) “where there is a will, there is a way”; (4) “if you work hard enough, you can turn an iron rod into a needle through grinding”; (5) “poverty stifles ambition”; (6) “diligence is an important factor to overcome poverty”; (7) “man is the master of his own fate”; (8) “a contented person is always happy”; and (9) “man is not born to greatness, he achieves it by his own effort.” In this scale, item 2 and item 5 are negative cultural beliefs about adversity, while the rest of the items are positive items about adversity.

RESULTS

Results showed that participants’ endorsement of the Chinese beliefs about adversity were significantly related to their level of early treatment fears ($r = -.105$, $p < .05$, one-tailed test), thus supporting Hypothesis 1. In addition, the findings also showed that participants’ level of early treatment fears was negatively correlated with the negative Chinese Cultural Beliefs about Adversity Scale ($r = -.097$, $p < .05$, one-tailed test), suggesting that the strong endorsement of participants on negative Chinese cultural beliefs about adversity with a higher level of early treatment fears.

Besides, participants’ level of anticipated discharge fears was negatively correlated with the Chinese Cultural Beliefs about Adversity Scale ($r = -.130$, $p < .05$, two-tailed test), giving support to Hypothesis 2. In addition, the findings also showed that participants’ level of anticipated discharge fears was negatively correlated with the negative Chinese Cultural Beliefs about Adversity Scale ($r = -.204$, $p < .001$, two-tailed test), implying that the strong endorsement of participants on negative Chinese cultural beliefs about adversity with a higher level of anticipated discharge fears (see Table 1).

Table 1. Correlations among Early Treatment Fears Scale, Anticipated Discharge Fears Scale, and Chinese Beliefs about Adversity Scale and their Subscales

	CBA	Positive CBA	Negative CBA
ETF	-.105a	-.067	-.097a
ADF	-.130*	-.042	-.204**

** Significant at the 0.01 level (2-tailed).

* Significant at the 0.05 level (2-tailed).

^a Significant at the 0.05 level (one-tailed).

Note: ETF = Early Treatment Fears Scale;

ADF = Anticipated Discharge Fears Scale,

CBA = Chinese Beliefs about Adversity Scale;

Positive CBA = Positive Chinese Beliefs about Adversity;

Negative CBA= Negative Chinese Beliefs about Adversity.

DISCUSSION

Generating a representative sample of illicit drug users for substance abuse research can be challenging because there is no sampling frame. According to Hendricks and Blanken

[16], a random sampling methodology with a drug-using population is impossible for three reasons: potential legal and social sanctions; inability to estimate sample size from an accurate sampling frame; and hidden nature of the drug use population. In response to this research barrier, the use of service-based samples (convenience sampling) of young psychotropic substance abusers undergoing drug treatment at non-government residential treatment institutes to collect data did help solve the data collection problem, and it provided a means to gather information from this population group.

Consistent with our hypothesis, this study showed that the young substance abusers' total scores of endorsement of Chinese cultural beliefs about adversity were significantly related to their level of early treatment fears. Besides, their endorsement of Chinese cultural beliefs about adversity was negatively correlated with their anticipated discharge fears.

The findings underscore the importance of cultural beliefs in influencing the adjustment and well-being of substance abusers. Some deep-rooted values for adversity in the Chinese culture inherited for generations like "hardship increases stature," "one must be testified by sustaining hardship in the way of success" gave positive influences to young substance abusers in facing their treatment fears. The cultural beliefs encourage people to overcome stress associated with negative emotions and to provide a cognitive structure that gives a sense of control over life [9, 19]. Under proper counselling, young substance abusers will understand that both physical and mental discomforts arising from drug treatment can be alleviated gradually. Programs designed with integrated traditional Chinese beliefs about adversity can surely help much in this area, in particular, in the development of resilience. Owing to the lack of research study about the relationship of Chinese beliefs about adversity and treatment fears of young substance abusers in the Western and local context, the present findings can be regarded as pioneering in nature. It is suggested that similar attempts should be carried out to examine this issue in western contexts.

Practically, the use of the indigenous Chinese Cultural Beliefs about Adversity Scale in this study helped illuminate how young psychotropic substance abusers perceive adversity and the relationship of those perceptions with treatment fears. Service practitioners may include cultural beliefs about adversity in the intervention process by adopting a cognitive orientation to change clients' beliefs and thinking. For instance, they can help clients maintain positive thinking when they encounter adversity. It would also be worthwhile to identify subcultural beliefs about adversity in different Chinese societies and to investigate the relationships between such beliefs and the factors affecting the relapse of young substance abusers. The program can include service learning program like serving poor children, so that young substance abusers can enhance their awareness of developing positive thinking in encountering adversity.

Of course, it is noteworthy that a cross-sectional design was adopted in this study. Obviously, cross-sectional data always limits certainty on the direction of causality between variables. Hence, researchers should collect longitudinal data using large samples in the future to illuminate the relationship between cultural beliefs about adversity and treatment fears among young substance abusers.

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Chapter 28

VALIDATION OF THE NON-CONFLICT-RELATED MARITAL QUALITY SCALE FROM THE PERSPECTIVE OF CHINESE ADOLESCENT CHILDREN

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ABSTRACT

Based on two samples of Hong Kong Chinese adolescents, the psychometric properties of a scale assessing adolescent perceptions of non-conflict related attributes in the marital life of their parents were examined. Results from both samples showed that the scale possessed good internal consistency, test-retest reliability, criteria-related validity and convergent validity. For the dimensionality of the measure, results suggested that there was one factor of the scale. The present study is a pioneer attempt to examine the psychometric properties of a scale assessing perceived non-conflict related attributes in parental marital relationship amongst Chinese adolescents.

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Keywords: marital quality, children's perspective, adolescents, Chinese, psychometric properties

INTRODUCTION

Inter-parental relationship affects adolescent development and mental health in many ways [1, 2]. For instance, a high level of inter-parental conflict and overt inter-parental violence are risk factors for both depression and aggression in adolescents [3, 4]. Besides, inter-parental conflict was related to adolescent internalizing and externalizing disorders, conduct problems, poor peer interaction, poor health, depression, anxiety, attachment insecurity, and low self-esteem [1, 5, 6-11].

In addition to conflict-related attributes, there are studies showing that non-conflict related attributes of inter-parental relationship, such as the degree of care and concern, also influenced adolescent development. Unfortunately, compared with inter-parental conflict, non-conflict related attributes received less research attention. Lack of studies and assessment tools on non-conflict related attributes is particularly obvious for non-conflict related aspects of perceived marital quality from the perspective of adolescent children (i.e., inter-parental relationship perceived by adolescents).

Developing assessment tools for adolescents' perceptions of inter-parental non-conflict related attributes is important for three reasons. First, as the concept and the theories related to non-conflict-related attributes are under-developed, a validated measurement tool would facilitate empirical studies in this area, which would make theorization and conceptualisation of the related concepts and theories possible. Second, inter-parental non-conflict related attributes might be particularly important for Chinese people because relationship harmony is strongly emphasized in the Chinese culture [12]. As conflict behavior is not easily expressed in Chinese families (thus its occurrence may be low), inter-parental conflict may not be a sensitive indicator of inter-parental marital quality perceived by children [12]. Therefore, to understand inter-parental relationship perceived by adolescent children, development of assessment tools for adolescents' perceptions of inter-parental non-conflict-related attributes is necessary. Third, assessment tool in this area helps researchers understand how family relationship impacts adolescents in Chinese society. This would help the development of indigenous Chinese family concepts which would enhance our understanding of Chinese families and construction of relevant family models [13, 14].

The purpose of the paper was to report two studies on the psychometric properties of a scale assessing perceived inter-parental non-conflict related attributes among adolescents in Hong Kong. The scale was developed based on a literature review of marital quality and measurement tools of marital relationships and interactions [15-17]. Furthermore, two focus groups of adolescents and two focus groups of social workers with family services experiences were interviewed separately to understand adolescents' views on inter-parental relationships and interaction qualities. Based on both literature review and focus groups findings, 60 items were generated and were categorized in terms of twelve themes, including Togetherness, Communication, Appreciation, Criticism, Concern, Helping, Understanding and Acceptance, Trust, Satisfaction, Indigenous Chinese concepts, Passion, and Commitment.

Before the scale can be objectively used in research and practice contexts, it is important to establish the psychometric properties of the scale. In the context of assessment, researchers commonly examine three psychometric properties of a scale. First, reliability of the measure, such as internal consistency and test-retest reliability, should be assessed. Second, validity of the scale, such as criterion-related validity and convergent validity, should be explored. Finally, the dimensions of a measure (i.e., factorial validity) should be examined. In this paper, data were collected from two adolescent samples to evaluate these psychometric properties of the measures.

METHODS

Study 1 was based on a small convenience sample of adolescents aged 12 to 16 years. Adolescents with intact (i.e., a family in which parents remain married) and non-intact family (i.e., a family in which parents are divorced or separated) were recruited in a school social work service unit of a non-governmental organization. Altogether 23 male and 24 female adolescents were recruited from the school social work service unit. Their average age was 14.45 (SD = 1.30; Min = 12; Max = 16), with 28 of them coming from intact families while 19 of them were from non-intact families.

Instruments

Participants were requested to fill in a scale assessing adolescents' perception of inter-parental non-conflict related attributes and some basic demographic information.

Data Collection and Data Analysis Plan

Invitation letters of Study 1 were sent to adolescents' parents through the school social work unit. The objective of the study was explained and confidentiality of the data was emphasized in the letter. After obtaining written parental consent and adolescents' own consent, participants were asked to fill in a scale assessing adolescents' perception of inter-parental non-conflict related attributes on a 6-point scale, ranging from never [1] to always [6]. They were also asked to report basic demographic information including gender and age.

To assess internal consistency of the scale, Cronbach's α was computed for the overall scale. To assess criteria-related validity, a series of independent sample t-test with family type (i.e., intact or non-intact family) as the independent variable and scores of each item of the scale as dependent variables were conducted.

RESULTS AND DISCUSSION

The data from this small convenience sample of adolescents showed that the scale had high internal consistency, with the overall Cronbach's α of .98. The mean inter-item

correlation was .51, which had moderate effect size. In addition, the mean corrected item-total correlation was .71. These indicators showed that the scale had excellent internal consistency.

For criteria-related validity, 43 out of 60 items as well as the total score across 60 items showed that adolescents in intact families were significantly different from adolescents in non-intact families. The effect size of the 43 items (i.e., Cohen's *d*) ranged .61 to 1.39, which was large. Table 1 lists the results of the independent sample *t*-test of each item.

Table 1. Result of independent sample *t*-test of the 60 items

Domain/Item				
Togetherness	t-value	Df	p-value	Cohen's <i>d</i>
01	2.78	45	.008*	.83 (large)
02	3.34	45	.002*	.99 (large)
03	1.85	45	.071	.55 (medium)
04	-1.82	45	.076	-.54 (medium)
05	-1.76	45	.086	-.52 (medium)
Communication	t-value	Df	p-value	Cohen's <i>d</i>
06	3.82	45	.000*	1.13 (large)
07	3.19	45	.003*	.95 (large)
08	4.20	45	.000*	1.25 (large)
09	4.65	45	.000*	1.39 (large)
10	4.30	45	.000*	1.28 (large)
11	-1.25	45	.217	-.37 (medium)
12	-2.59	45	.013*	-.77 (large)
13	2.79	45	.008*	.83 (large)
14	3.03	45	.004*	.90 (large)
Appreciation	t-value	Df	p-value	Cohen's <i>d</i>
15	2.17	45	.036*	.65 (large)
16	2.38	45	.022*	.71 (large)
17	3.34	45	.002*	1.00 (large)
18	2.31	45	.025*	.69 (large)
19	3.22	45	.002*	.96 (large)
20	2.85	45	.007*	.85 (large)
21	2.41	45	.020*	.72 (large)
Criticism	t-value	Df	p-value	Cohen's <i>d</i>
22	-.87	45	.390	-.26 (small)
23	-1.05	45	.300	-.32 (medium)
24	-.61	45	.526	-.18 (small)
25	-.99	45	.329	-.30 (medium)
Concern	t-value	Df	p-value	Cohen's <i>d</i>
26	2.36	45	.023*	.70 (large)
27	2.23	45	.031*	.66 (large)
28	3.47	45	.001*	1.03 (large)
29	3.37	45	.002*	1.00 (large)
30	3.17	45	.003*	.95 (large)
Helping	t-value	Df	p-value	Cohen's <i>d</i>
31	3.46	45	.001*	1.03 (large)
32	-.37	45	.715	-.11 (small)
33	3.01	45	.004*	.90 (large)
34	2.06	45	.045*	.61 (large)

Domain/Item				
Understanding and Acceptance	t-value	Df	p-value	Cohen's d
35	2.45	45	.018*	.73 (large)
36	1.55	45	.129	.46 (medium)
37	2.62	45	.012*	.78 (large)
38	2.20	45	.033*	.66 (large)
Trust	t-value	Df	p-value	Cohen's d
39	-1.71	45	.094	-.51 (medium)
40	1.57	45	.123	.47 (medium)
41	2.27	45	.028*	.68 (large)
42	2.01	45	.051	.60 (large)
Satisfaction	t-value	Df	p-value	Cohen's d
43	3.04	45	.004*	.91 (large)
44	3.96	45	.000*	1.18 (large)
45	3.98	45	.000*	1.19 (large)
46	.64	45	.529	.19 (small)
47	4.27	45	.000*	1.27 (large)
48	1.11	45	.275	.33 (medium)
49	3.92	45	.000*	1.17 (large)
50	3.25	45	.002*	.97 (large)
51	-3.48	45	.001*	-1.04 (large)
Indigenous Chinese Concepts	t-value	Df	p-value	Cohen's d
52	2.03	45	.049*	.61 (large)
53	2.93	45	.005*	.87 (large)
Passion	t-value	Df	p-value	Cohen's d
54	2.18	45	.034*	.65 (large)
55	2.17	45	.035*	.65 (large)
56	1.92	45	.061	.57 (medium)
Commitment	t-value	Df	p-value	Cohen's d
57	1.18	45	.244	.35 (medium)
58	1.51	45	.138	.45 (medium)
59	2.46	45	.018*	.73 (large)
60	2.03	45	.048*	.61 (large)
Overall Mean	t-value	Df	p-value	Cohen's d
Mean of All Items	3.77	45	.000	1.12 (large)

* p-value < .05.

Study 2

In this study, 253 participants were recruited from two local secondary schools. The participants were asked to fill in two sets of questionnaire within a two- week interval. While 53 participants failed to complete the first set of questionnaire, 63 participants failed to respond to the second set. The demographic information of the participants in both Time 1 and Time 2 are presented in Table 2. At Time 1, the average age of the participants was 14.70 (SD = 1.55; Min = 12; Max = 16), with 138 male participants and 66 female participants. At time 2, the average age of the participants were 14.58 (SD = 1.68; Min = 12; Max = 16), with 132 participants being male and 62 being female.

Invitation letters of Study 2 were sent to adolescents' parents through the secondary schools. The objective of the study was explained and confidentiality of the data was

emphasized in the letter. After obtaining written parental consent and adolescents’ own consent, participants were asked to fill in a short questionnaire.

Table 2. Demographic information of the participants in both Time 1 and Time 2

	Mean of Age	No. of Male	No. of Female	No. of Intact	No. of Non-Intact
Time 1	14.70 (SD = 1.55)	138	66	185	19
Time 2	14.58 (SD = 1.68)	132	62	176	18

The questionnaire at Time 1 contained the 8 items from a scale of adolescents’ perception of inter-parental non-conflict related attributes. The items were selected based on the criterion-related validity findings in Study 1. These items had the largest t-values in the study. The questionnaire also included other assessment tools listed below. All participants were also asked to report their demographic information, including age and gender.

Participants filled in the short questionnaire in a self-administered format. Adequate time was provided. Participants generally took around 20 minutes to complete the questionnaires. Internal consistency, test-retest reliability, construct validity and factorial validity of the scale were examined.

Instruments

Children’s Perceptions of Non-Conflict Related Attributes in Parental Relationship. Based on Study 1, 8 items with the largest differentiation power in terms adolescents perception of inter-were selected. The scale generally measures positive attributes of inter-parental relationship from adolescents’ perspective. Higher score represents higher level of perceived non-conflict related attributes.

Conflict intensity subscale of the Chinese version of Children’s Perceptions of Inter-parental Conflict Scale (C-CPIC-CI). Grych et al. [18] developed a 49-item child-completed questionnaire assessing 10 dimensions of inter-parental conflict, including frequency, intensity, content, resolution, threat, coping efficacy, content (child related vs. non-child related), triangulation, stability and self-blame. Research findings showed that CPIC possessed good psychometric properties. Besides, compared with other commonly employed indicators of marital conflict and satisfaction, Conflict intensity subscale scores were more predictive of child adjustment [18]. Higher score represents a higher level of perceived conflict intensity. The Chinese version of the scale was translated by Zhao and Mo [19] who found that Conflict intensity subscale is reliable and valid in Chinese samples across developmental ages.

Chinese version of Life Satisfaction Scale (C-LIFE). Diener et al. [20] developed the Satisfaction with Life Scale to assess global evaluation of quality of life. There are 5 items in the scale with a six-point scale. The scale was found to be internally consistent and valid in Chinese [21]. A higher LIFE scale score indicates a higher level of life satisfaction.

Chinese version of Hopelessness Scale (C-HOPEL). Beck, Weissman, Lester, and Trexler [22] developed the Hopelessness Scale (HOPEL) to measure the sense of hope in a person. The Chinese HOPEL scale was developed and proved to be reliable and valid by Shek [23]. A

higher HOPEL scale score indicates a lower sense of hope. Yip and Cheung [24] suggested a four-item Chinese version of the scale. They found that the four-item Chinese version predicted depression and suicide in Hong Kong Chinese sample.

Chinese version of short form of the Marlowe–Crowne Social Desirability Scale (CMCDS). The scale has 14 items which assess whether a person responds in a socially desirable manner [25]. The Chinese version of the Marlowe–Crowne Social Desirability Scale (Short Form) was reliable and valid in Chinese people [25].

Except CMCDS which was used at Time 2 only, all other instruments were used at both Time 1 and Time 2. To establish the convergent validity of the scale, it was expected that the mean scores of the scale assessing adolescent perceptions of inter-parental non-conflict related attributes would have negative relationships with mean scores of C-CPIC-CI and C-HOPEL but a positive relationship with C-LIFE at Time 1 and Time 2.

Results and Discussion

Results showed that scores of adolescents' perception of inter-parental non-conflict related attributes were not significantly related to the participants' gender, age, parental educational level, and family income.

Results showed that the scale had high internal consistency, with the overall Cronbach's α of .95 for both Time 1 and Time 2 data. The mean inter-item correlations were .70 for Time 1 and .69 for Time 2 data, which had strong effect size. In addition, the mean corrected item-total correlation coefficients were .81 for Time 1 and .82 for Time 2 data. These indicators showed that the scale had excellent internal consistency. To assess the temporal stability of the measure, test-retest reliability was performed. The correlation coefficient, the Pearson's r , between two equivalent tests was taken as an estimate of the reliability of the test. Test-retest reliability coefficient, in terms of Pearson's r was .81 ($p < .001$). Analyses using paired t-test showed that the Time 1 ($M = 3.92$) and Time 2 ($M = 3.88$) mean scale scores were not significantly different, $t(132) = .14$, ns . These findings suggested that the scale showed good test-retest reliability.

For the convergent validity of the proposed scale, correlation coefficients between C-CPIC-CI and C-LIFE, C-HOPEL and CMCDS were computed. For the Time 1 data, it was found that the total scores of adolescents' perception of inter-parental non-conflict related attributes showed a significantly negative relationship with the score of CPIC-CI and C-HOPEL but positive with the score of C-LIFE. The Pearson r were $-.41$ ($p < .01$), $-.40$ ($p < .01$), and $.60$ ($p < .01$) respectively, which were considered as a moderate effect size according to Cohen's [26] suggestion.

For Time 2 data, mean scores of adolescents' perception of inter-parental non-conflict related attributes showed a significantly negative relationship with CPIC-CI ($r = -.47$, $p < .01$) and HOPEL ($r = -.35$, $p < .01$) but positive with LIFE ($r = .58$, $p < .01$). These correlations were considered barely moderate to moderate in term of effect size (Cohen, 1988). The scores of adolescents' perception of inter-parental non-conflict related attributes was positively correlated with that of CMCDS. The Pearson r was $.32$ ($p < .01$). The correlation was considered to be weak [26].

To examine the underlying dimensionality of the scale, we used principal component analysis followed by varimax rotation. For Time 1 data, initial factor extraction, change of eigenvalue and the scree plot suggested a one-factor solution. The eigenvalue was greater than unity, and the solution explained 74.16% of the total variance. The loadings of all items exceeded .70. The factor had all 8 items. This factor corresponded to the domain of communication, appreciation, satisfaction and helping in content validation in Study 2.

For Time 2 data, initial factors extraction, change of eigenvalue and the scree plot also suggested a one-factor solution. The factor had eigenvalue greater than unity, and the solution explained 73.00% of the total variance. The loadings of all items exceeded .70. The factor had all 8 items. This factor corresponded to the domain of communication, appreciation, satisfaction and helping in content validation. Table 3 illustrates the rotated component matrix of the items at Time 1 and Time 2.

Table 3. Component matrix of revised adolescents' perception of inter-parental non-conflict related attributes for time 1 data

Items	Factor at Time 1	Factor at Time 2
1. My parents talk to each other and have fun together.	.803	.830
2. My parents talk to each other when having dinner.	.831	.819
3. My parents get along well.	.896	.857
4. My parents have good communication.	.844	.855
9. My parents express that the other party is a good partner.	.865	.849
10. My parents express their appreciation of each other.	.872	.881
16. My parents actively help when the other party faces difficulties.	.888	.869
20. My parents feel that the other is the ideal companion.	.885	.874

OVERALL DISCUSSION

In view of the non-existence of validated assessment tools for adolescents' perception on inter-parental non-conflict related attributes, the present paper describes two studies examining the psychometric properties of the scale. There are two unique characteristics of the studies. First, an indigenous measure of adolescents' perception of inter-parental non-conflict related attributes was employed. Second, reliability (internal consistency and test-retest reliability) and validity (convergent validity and factorial validity) were investigated.

The studies generated empirical evidence on the psychometric properties of adolescents' perception of inter-parental non-conflict related attributes, which is considered as pioneering in this field. The scale showed good results in internal consistency, test-retest reliability, convergent validity and factorial validity, suggesting that the scale possesses good psychometric properties. As related research in this area is almost non-existent, this study is an important addition to the literature.

Results of Study 1 indicated that items with highest ability to differentiate adolescents from intact and non-intact families mainly come from the domains of communication and satisfaction. This is highly consistent with the literature on marital quality, relationship and

interactions [15-17] as well as on positive relationship features of marriage [27-29], suggesting that communication and satisfaction are sensitive indices differentiating distressed from non-distressed couples from both couples' and adolescents' perspectives.

However, inconsistent with previous literature on the positive relationship features of marriage [27-29], results of Study 1 showed that appreciation and concern were also important elements of differentiating distressed from non-distressed couples because items from these two domains demonstrated high differentiation power. This supplements theorization and conceptualisation of positive relationship features of a marriage [27-29]. There are two possible explanations for this observation. First, the difference may be attributed to different perspectives between couples and adolescents. Previous studies on the positive relationship features of marriage mainly used couple samples whereas the present studies used data from adolescents. Empirically, Joshi [30] showed that children's perceptions of inter-parental relationships were different from those of parents.

Second, it may be due to cultural differences in perceptions of positive relationship features of marriage. Previous assessments of marital quality were developed in Western culture [31] whereas the scale of adolescents' perception of inter-parental non-conflict related attributes was developed and validated in a Chinese society. There are studies showing that conceptualisation of positive elements of romantic relationship and marriage varies across cultures [31-33]. Researchers are suggested to examine the role of appreciation and concern in differentiating distressed from non-distressed couples from both couples' and adolescents' perspective across cultures.

There are six implications of the present findings. First, the studies deepen our understanding of the dimensionality of the construct of adolescents' perception of inter-parental non-conflict related attributes. As there are only limited theoretical conceptualizations of the construct, the present findings sharpen our ideas on the underlying facets of inter-parental non-conflict related attributes. Second, the present findings provide evidence for an indigenous measurement tool that may be useful for further exploration of indigenous Chinese concepts as well as construction of Chinese family models. Third, a reliable and valid measurement tool may bring special value for further research on the association between inter-parental relationship and adolescents' development. Previous studies on the association between inter-parental relationship and adolescents' development focused on parental conflict [1, 2], with little attention paid to positive aspects of inter-parental relationship, including non-conflict-related attributes. The proposed measure developed in this study makes it possible to examine the unique contribution of different aspects of inter-parental relationship to adolescent development.

Fourth, practically speaking, the scale helps social workers enhance adolescents' mental health by teaching parents the skills that foster inter-parental non-conflict related attributes such as active response to partners' need and appreciation. Fifth, as a measure of positive feature of marriage from adolescents' perspective, the scale enables clinicians to assess how adolescents perceive non-conflict related family processes and design the intervention plan. The use of this measure in the context of an emotionally close relationship with the counselor may help more defensive adolescents deal with the resistance in talking about and facing poor inter-parental interaction [34]. This may be particularly important for Chinese people because inter-parental conflict behavior might not be a sensitive indicator of inter-parental relationship quality [12]. Absence of non-conflict related attributes may indicate poor inter-parental

interaction as perceived by children. Sixth, this measure could also be used as a means for children and adolescents to express their feelings about the marital quality of the parents [34].

There are several limitations of the present findings. First, as two adolescent samples were not randomly sampled, generalizability of the findings may be limited. Second, the small sample size in parent's study may restrict stability in factor analysis. Thus, there is a need to conduct factor analysis using larger samples. Third, research findings showed that adolescents' perception of inter-parental relationship and interaction was influenced by their developmental progress and cognitive maturity [35, 36] as well as the indicators under focus [37]. Therefore, the factor structures of the scale of adolescent perception of inter-parental non-conflict related attributes may vary across age and gender of adolescents [34]. It is essential to conduct further studies using multi-group confirmatory factor analysis to investigate the dimensionality of the scales with different samples of adolescents. Fourth, as only Chinese adolescents and parents in Hong Kong, we have to examine the generalizability of the findings in other contexts.

Despite the above limitations, the studies are pioneer in assessing the reliability, validity and dimensionality of the measure. It clearly demonstrates that the scale of adolescents' perception of inter-parental non-conflict related attributes possesses good psychometric properties that can be used objectively in Chinese parents and adolescent samples. As commented by Shek [14] that "there were few validated Chinese assessment measures and the effort to validate the developed measures was inadequate" (p. 282), the studies are regarded as positive response to Shek's suggestion.

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Chapter 29

SUBJECTIVE OUTCOME EVALUATION OF A TRAINING PROGRAM OF TIN KA PING P.A.T.H.S. PROJECT IN CHINA

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ABSTRACT

The first training workshop for the Tin Ka Ping P.A.T.H.S. Project for 2015-2016 school year was held in December 2015 in Zhaoqing, mainland China. To gauge the impact of the training program, 134 participants completed a subjective outcome evaluation survey during the last training session. Results showed that the vast majority of trainees were highly satisfied with the training program regarding perceived program benefit, program quality, administrative arrangements, instructor performance, and their own performance. Consistent with the previous findings, overall satisfaction and the perceived benefits were positively predicted by the perceived program quality. Besides,

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instructor quality, administrative arrangements, and participants' own performance also predicted perceived program benefits. The favorable evaluation findings suggested that the training program for Tin Ka Ping P.A.T.H.S. Project training program was well-designed and well received by the program participants in mainland China.

Keywords: professional training, subjective outcome evaluation, Tin Ka Ping P.A.T.H.S. Project, positive youth development

INTRODUCTION

The transition from childhood to adulthood is not an easy task for adolescents. During this transitional phase, adolescents face dramatic changes in every aspect of their life, including physical growth, sexual maturation, cognitive development, social development and emotional changes [1]. ADOLESCENTS going through such a turbulent transition period often engage in different risk behaviors and are vulnerable to developmental problems, such as mental health problems, addictive behaviors, self-harm behaviors, bullying behaviors and delinquent behaviors [2-5]. In view of these rising concerns, efforts to promote healthy adolescent development such as the development of positive youth development (PYD) programs have emerged. Unfortunately, programs devoted to reducing adolescent developmental problems and promoting positive adolescent development are grossly inadequate in different Chinese societies [6].

To promote positive youth development amongst Chinese adolescents in Mainland China, a PYD program entitled "Tin Ka Ping P.A.T.H.S. (Positive Adolescent Training through Holistic Social Programs) Project" was introduced in Mainland China with the financial support from the Tin Ka Ping Foundation. This Project was transplanted from the Project P.A.T.H.S., which is a systematic and holistic PYD program that has been implemented for Hong Kong junior secondary school students for many years. Studies utilizing a broad range of systematic evaluation strategies, including both quantitative and qualitative evaluation methods, have shown that the Project P.A.T.H.S. is effective in promoting the PYD and in slowing down the development of risk behavior among Hong Kong adolescents [7-10].

Tin Ka Ping P.A.T.H.S. Project is a curriculum-based universal program targeting all students studying in secondary schools. The curriculum is based on the 15 positive youth development constructs identified in the existing successful programs [11]. As a transplant of the Project P.A.T.H.S. in Hong Kong, the Tin Ka Ping P.A.T.H.S. Project has the benefit of learning from the experience in Hong Kong. With reference to the socio-cultural contexts in mainland China, the curriculum of junior secondary school program was adapted and modified. For example, the modified program incorporated traditional Chinese virtues and moral values, as well as topics relevant to the development of young people in mainland China. Besides the junior secondary school curriculum, the Research Team also developed curriculum materials for the senior secondary school program which are applicable to Secondary 4 to Secondary 6 students.

Table 1. The first training program of the Tin Ka Ping P.A.T.H.S. Project in Zhaoqing, mainland China

Junior Group

Day 1 (6.5 hours)	
Themes and Objectives	Activities Conducted
a) Introduce the implementation progress of the Tin Ka Ping P.A.T.H.S. Project; and	1. Introduce the Tin Ka Ping P.A.T.H.S. Project and the professional team, ice-breaking exercise;
b) Offer opportunities for participants to share their experiences;	2. Explain how to use teaching materials and other resources of Tin Ka Ping P.A.T.H.S. Project;
	3. Introduce the Co-Walker Scheme.
	4. Schools presentation on:
	a. Experience of pilot implementation (3 schools);
	b. Implementation progress and achievements (5 schools);
	c. School policy and administration (4 schools);
	d. Teaching and training experience (5 schools).
Day 2 (6.5 hours)	
Themes and Objectives	Activities Conducted
a) Demonstrate teaching techniques;	1. "Collaborative teaching" technique demonstration by participating schools;
b) Familiarize the participants with teaching methodology of the Tin Ka Ping P.A.T.H.S. Project; and	2. Lesson demonstration by participating schools;
	3. Group discussion and Q&A session;
	4. Wrapping up and Self-reflection.
Day 3 (6.5 hours)	
Themes and Objectives	Activities Conducted
a) Offer opportunities for participants to share their experiences;	1. Schools presentation on teachers' personal growth;
b) Clarify participants' questions on project implementation; and	2. Discussion and Q&A session on project implementation; and
c) Familiarize the participants with the evaluation methods of Tin Ka Ping P.A.T.H.S. Project.	3. Interactive lecture on the evaluation instruments of the program (form A, form B, and weekly report) and data analysis methods;
	4. Wrapping up and Self-reflection; and
	5. Conclusion.

Senior Group

Day 1 (6.5 hours)	
Themes and Objectives	Activities Conducted
a) Introduce the implementation progress of the Tin Ka Ping P.A.T.H.S. Project; and	1. Introduce the Tin Ka Ping P.A.T.H.S. Project and the professional team, ice-breaking exercise;
b) Offer opportunities for participants to share their experiences;	2. Explain how to use teaching materials and other resources of Tin Ka Ping P.A.T.H.S. Project;
c) Familiarize the teachers with the constructs and teaching units.	3. Introduce the Co-Walker Scheme.
	4. Schools presentation on implementation progress and achievement.
	5. Lecture on the constructs and the contents of Units.
Day 2 (6.5 hours)	
Themes and Objectives	Activities Conducted
a) Demonstrate teaching techniques;	1. "Collaborative teaching" technique demonstration by participating schools;
b) Familiarize the participants with teaching methodology of the Tin Ka Ping P.A.T.H.S. Project; and	2. Lesson demonstration by participating schools;
	3. Group discussion and Q&A session;
	4. Wrapping up and Self-reflection.
Day 3 (6.5 hours)	
Themes and Objectives	Activities Conducted
a) Familiarize the teachers with the constructs and teaching units;	1. Lecture on the constructs and the contents of Units.
b) Offer opportunities for participants to share their experiences;	2. Discussion and Q&A session on project implementation; and
c) Clarify participants' questions on project implementation; and	3. Interactive lecture on the evaluation instruments of the program (form A, form B, and weekly report) and data analysis methods;
d) Familiarize the participants with the evaluation methods of Tin Ka	4. Wrapping up and Self-reflection; and
	5. Conclusion.

Researchers suggest that five factors contribute to the implementation quality of PYD programs, including program, people, process, policy, and place (5Ps) [12]. Among them, “people” is one of the most significant elements for successful program implementation [13]. Studies also consistently showed that program effectiveness could be explained by the perceived quality of program implementers [14, 15]. Thus, effective training for program implementers is extremely important because program implementers must understand the philosophy of the program, program content and related theories, teaching philosophy and techniques, and related success factors. As such, systematic training for the implementers is an indispensable prerequisite for effective program implementation in Mainland China. Besides, potential program implementers should be properly empowered and motivated to teach the program, which is always taxing and challenging for the program implementers.

As training is regarded as the cornerstone of successful PYD programs, the Tin Ka Ping P.A.T.H.S. Project places a great emphasis on training program implementers. Before the formal launching of the project, four training workshops were conducted in 2014-2015 school year. In 2015-2016 school year, three 3-day training workshops were conducted. All potential program implementers and school management, including teachers and principals from 30 participating schools all over Mainland China joined the training. The first 3-day training workshop took place in December 2015 at Zhaoqing, Guangdong province. This training workshop was intended to help trainees to (a) understand the concepts and rationale of positive youth development and relevant research and program; (b) understand the nature of youth development and to develop positive attitudes to adolescent development; (c) appreciate the rationales, design, implementation, and evaluation of the Tin Ka Ping P.A.T.H.S. Project; (d) understand the training contents and activities developed; (e) review and obtain attitude, knowledge, and teaching skills that are beneficial to the success of the program implementation; and (f) develop a self-help network among the training participants [16]. The details about the schedule, themes, and contents of this training workshop are shown in Table 1.

To understand the effectiveness of the training programs, post-training evaluation is indispensable. According to Salas and Cannon-Bowers [17], program evaluation enables the researchers to understand whether the program objectives have been achieved. In particular, evaluation can help researchers understand the acquisition of teaching skills and identification with the training philosophy.

More importantly, evaluation helps to answer theoretical and practical questions of what factors (such as program quality, implementer qualities, perceived benefits of the program) are related to training impact. Similarly, Robson, Sebba, Mittler and Davies [18] pointed out that training evaluation is essential because it helps identify what works and what does not work before program implementation.

To understand the effectiveness of training programs for the Tin Ka Ping P.A.T.H.S. Project, subjective outcome evaluation was conducted for all the training programs where participants' views toward the training (e.g., instructor quality and program quality), benefits of the training, satisfaction toward the program administrative arrangements and their own performance during training were the focuses in the evaluation study. There are several justifications for using subjective outcome evaluation [19]. First, it is not expensive to carry out. Second, it is an efficient way to understand the personal views of the trainees. Third, instead of relying on the evaluators' judgment, the voice of service recipients can be heard

[19]. Fourth, there is evidence suggesting that subjective outcome evaluation is closely associated with objective outcome evaluation findings [20, 21]. In this paper, evaluation findings from the first training workshop held in Zhaoqing in December 2015 are reported.

METHODS

In the school year of 2015-2016, three training workshops were held for implementers of the Tin Ka Ping P.A.T.H.S. Project in China in different cities, including Zhaoqing, Shaoguan, and Changchun. For the first workshop, a total of 166 teachers from 25 Junior Secondary schools and 19 Senior Secondary schools registered. The workshop lasted for 3 days in Zhaoqing, China. The participants were invited to fill in a subjective outcome evaluation questionnaire at the last session of the training workshop. One hundred and thirty-four questionnaires were collected finally. Not all participants responded because some of them left early due to transportation constraints. Among the respondents, 40 were males (29.9%) and 94 were females (70.1%). Almost all respondents were teachers ($n = 133$), apart from one school administrator. Forty-two of them were from senior secondary school and 92 were from junior secondary school. The average work experience for the teachers was 14.75 years ($SD = 8.37$).

Instruments

The subjective outcome evaluation questionnaire was utilized to assess participants' perceptions of the program content, instructor quality, administrative arrangement, and their own performance. A total of 31 items on a 5-point Likert-scale and two open-ended questions were included in the questionnaire. Regarding the two open-end questions, participants were asked about the things they most appreciated and the areas that they think need further improvement. In the present study, only the quantitative rating scales were analyzed.

There are four parts in the rating scales. The first part measures participants' perception of the training program content, including program benefits (9 items), program quality (5 items), and overall satisfaction (2 items). The second part measures participants' satisfaction with the program instructors (5 items). The third part assesses participants' satisfaction of program administrative arrangements (6 items). The last part measures participants' perceptions of their own performance in the workshop (4 items). Participants were asked to respond all items according to their own perceptions and feelings from "1 (strongly disagree/very dissatisfied)" to "5 (strongly agree/very satisfied)". The items can be seen in the tables. Previous training evaluation studies showed that the scale has achieved good psychometric properties [22-25].

RESULTS

All subscales and the overall scale were proven to be reliable, according to the results of reliability analyses. As shown in Table 2, the Cronbach's alpha ranged from .65 to .91 for all

the subscales. The overall rating scale also showed good internal consistency ($\alpha = .95$). The mean score for every subscale in both senior and junior secondary schools exceeded 4.0 with 5.0 as the maximum score, indicating that respondents generally had high satisfaction ratings on the program content, instructor quality, administrative arrangement, and their own performance. A one-way ANOVA was performed to compare the satisfaction ratings between senior and junior secondary school teachers. No significant differences were found which suggest that the satisfaction levels of the junior and senior year students over different domains were similar.

Table 2. Means, standard deviations, Cronbach's alphas, and mean of inter-item correlations and the comparison between Senior and Junior Secondary school participants

Subjective Outcome Evaluation Scales	Total (N = 134)		Senior (N = 42)		Junior (N = 92)		F
	M (SD)	α (Mean ^a)	M (SD)	α (Mean ^a)	M (SD)	α (Mean ^a)	
Program content (16 items)	4.33 (.37)	.91 (.38)	4.30 (.35)	.89 (.34)	4.34 (.38)	.92 (.41)	.29
Perceived benefits (9 items)	4.40 (.40)	.86 (.41)	4.40 (.38)	.86 (.42)	4.40 (.40)	.87 (.42)	.00
Program quality (5 items)	4.27 (.41)	.74 (.37)	4.20 (.40)	.72 (.34)	4.30 (.41)	.75 (.38)	1.51
Overall satisfaction (2 items)	4.16 (.49)	.65 (.49)	4.13 (.46)	.47 (.31)	4.18 (.51)	.72 (.56)	.35
Program instructor (5 items)	4.35 (.44)	.83 (.51)	4.31 (.41)	.78 (.43)	4.37 (.45)	.86 (.56)	.49
Administrative arrangements (6 items)	4.15 (.60)	.91 (.63)	4.09 (.60)	.91 (.65)	4.19 (.60)	.91 (.62)	.82
Self-performance (4 items)	4.15 (.47)	.83 (.55)	4.14 (.44)	.78 (.47)	4.16 (.49)	.85 (.59)	.03
Total scale (31 items)	4.28 (.38)	.95 (.37)	4.24 (.36)	.94 (.34)	4.29 (.38)	.95 (.38)	.52

In Table 3-6, the participants' positive perceptions (i.e., ratings of 4.0 and 5.0 scores) of the training program in different aspects are presented. Table 2 shows that almost all participants agreed that the training program had strengthened their understanding of the nature of adolescent development (97.76%) and positive youth development (96.27%), and helped them cultivate a positive attitude to adolescent development (97.01%). Generally speaking, most of the respondents agreed that the training program benefited them in several domains (95.35%). Participants also had a quite positive evaluation of program quality (82.58%) and they agreed that the training methods and activities were appropriate (96.27%).

Overall speaking, the participated teachers had a very positive perception of the instructor(s)' teaching performance (99.25%). They perceived that the instructor(s) showed good professional attitude (99.25%) and had a good mastery of the curriculum (96.27%). As for the satisfaction ratings on administrative arrangements, 82.84% of the participants were satisfied with the information obtained before attending the workshop (82.84%) and the reception provided by training team (84.33%). Besides, the participants were also satisfied with their own performance (82.84%). After attending the training program, 91.79% of the participants had confidence in program implementation.

As demonstrated in Table 7, significant positive correlation coefficients (r s ranged from .46 to .78, p s < .001) were found among the key evaluation components, including program quality, instructor quality, perceived benefits, overall satisfaction, self-performance, and administrative arrangement. Two multiple regression analyses were further conducted to test

the relationships among the ratings of participants' satisfaction towards different domains of the training program (see Table 8). Results showed that perceived benefits were significantly predicted by perceived program quality ($\beta = .30, p < .001$), perceived administrative arrangements ($\beta = .24, p = .001$), and perceived self-performance ($\beta = .27, p < .001$), and marginally significantly predicted by perceived instructor quality ($\beta = .15, p = .051$). The whole model explained 61% of the variance of the perceived benefits of the workshop. Besides, overall satisfaction was significantly predicted by the perceived program quality ($\beta = .61, p < .001$). The whole model explained 64% of the variance of overall satisfaction.

Table 3. Summary of the positive views (options 4-5) of the participants towards the training program content

Perceptions of the Program Content			N	Agree (4)		Strongly Agree (5)		Positive Response (Options 4-5)		M	SD
				n	%	n	%	n	%		
Perceived Benefits ^a			129					123	95.35	4.40	.40
1.	It has strengthened my understanding of the nature of adolescent development.		134	60	44.78	71	52.99	131	97.76	4.51	.55
2.	It has helped me to cultivate positive attitude to adolescent development.		132	59	44.03	71	52.99	130	97.01	4.52	.53
3.	It has strengthened my understanding of positive youth development, including its concept, design, and research.		133	65	48.51	64	47.76	129	96.27	4.45	.56
4.	It has helped me to understand the Project P.A.T.H.S., including its basic philosophy, design, implementation, and evaluation.		134	66	49.25	63	47.01	129	96.27	4.43	.57
5.	It has strengthened me to understand the content of the Tier 1 Program.		134	77	57.46	54	40.30	131	97.76	4.37	.56
6.	It has helped me to acquire the attitude, knowledge, and skills that are conducive to the successful implementation of the Tier 1 Program.		134	74	55.22	46	34.33	120	89.55	4.24	.63
7.	It has helped me to establish self-help support network and share teaching experiences among the program participants.		134	75	55.97	49	36.57	124	92.54	4.29	.60
8.	It has promoted self-reflection.		133	61	45.52	67	50.00	128	95.52	4.47	.57
9.	It has helped me to recognize factors affecting teaching.		133	76	56.72	49	36.57	125	93.28	4.31	.58
Program Quality ^a			132					109	82.58	4.27	.41
1.	The training methods and activities are appropriate (e.g. lecture, games, group discussion).		134	71	52.99	58	43.28	129	96.27	4.40	.56
2.	Training time is appropriate.		134	84	62.69	24	17.91	108	80.60	3.98	.63
3.	It has met my expectation.		132	83	61.94	31	23.13	114	85.07	4.10	.60
4.	There was much peer interaction amongst participants.		133	68	50.75	59	44.03	127	94.78	4.40	.58
5.	Instructor(s) encouraged participants to do the best.		134	63	47.01	67	50.00	130	97.01	4.47	.56
Overall Satisfaction ^a			133					111	83.46	4.16	.49
1.	Overall speaking, I am satisfied with the training program.		134	87	64.93	42	31.34	129	96.27	4.28	.53
2.	I think participants are satisfied with the training program.		133	83	61.94	29	21.64	112	83.58	4.06	.61
Perceptions of the Program (Whole Scale) ^a			129					115	89.15	4.33	.37

Note: ^a: Scores on the scale/subscale higher than or equal to 4 were treated as positive views.

Table 4. Summary of the positive views (options 4-5) of the participants towards the program instructor(s)

Perceptions of the Program Instructor(s)	N	Agree (4)		Strongly Agree (5)		Positive Response (Options 4-5)		M	SD
		n	%	n	%	n	%		
1. The instructor(s) had good mastery of the curriculum.	134	86	64.18	43	32.09	129	96.27	4.28	.53
2. The instructor(s) understood the needs of participants.	134	74	55.22	39	29.10	113	84.33	4.13	.66
3. The instructor(s) showed good professional attitude.	134	43	32.09	90	67.16	133	99.25	4.66	.49
4. The instructor(s)' teaching was clear and easy to understand.	133	79	58.96	39	29.10	118	88.06	4.18	.61
5. Overall speaking, I have positive evaluation of the instructor(s)' teaching performance.	134	64	47.76	69	51.49	133	99.25	4.51	.52
Total Scale ^a	133					117	87.97	4.35	.44

Note: ^a: Scores on the scale higher than or equal to 4 were treated as positive views.

Table 5. Summary of the positive views (options 4-5) of participants towards administrative arrangements

Perceptions of the Administrative Arrangements	N	Satisfied (4)		Very Satisfied (5)		Positive Response (Options 4-5)		M	SD
		n	%	n	%	n	%		
1. Information obtained before attending the workshop.	134	76	56.72	35	26.12	111	82.84	4.08	.67
2. Workshop assigned.	134	79	58.96	41	30.60	120	89.55	4.20	.61
3. Location of the workshop.	132	65	48.51	38	28.36	103	76.87	4.02	.82
4. Reception provided by training team (e.g., transportation arrangement, refreshments).	134	57	42.54	56	41.79	113	84.33	4.22	.83
5. Facilities of the venue.	133	65	48.51	44	32.84	109	81.34	4.11	.79
6. Overall speaking, I am satisfied with the administrative arrangement.	133	73	54.48	51	38.06	124	92.54	4.31	.62
Total Scale ^a	131					96	73.28	4.15	.60

Note: ^a: Scores on the scale higher than or equal to 4 were treated as positive views.

Table 6. Summary of the positive views (options 4-5) of participants towards their own performance in training

Perceptions of Self-Performance	N	Agree (4)		Strongly Agree (5)		Positive Response (Options 4-5)		M	SD
		n	%	n	%	n	%		
1. I participated actively during discussion.	134	86	64.18	27	20.15	113	84.33	4.04	.60
2. I am willing to apply the specific skills and theories learned from this training program.	134	73	54.48	55	41.04	128	95.52	4.37	.57
3. After attending the training program, I have confidence in program implementation.	134	86	64.18	37	27.61	123	91.79	4.19	.57
4. Overall speaking, I am satisfied with my performance.	133	88	65.67	23	17.16	111	82.84	4.04	.72
Total Scale ^a	133					104	78.20	4.15	.47

Note: ^a: Scores on the scale higher than or equal to 4 were treated as positive views.

Table 7. Correlations among the key evaluation components

Variables	1	2	3	4	5	6
Program quality (5 items)	-					
Perceived benefits (9 items)	.67***	-				
Instructor quality (5 items)	.65***	.62***	-			
Administrative arrangement (6 items)	.59***	.63***	.56***	-		
Self-performance (4 items)	.46***	.60***	.51***	.48***	-	
Overall satisfaction (2 items)	.78***	.63***	.55***	.58***	.48***	-

Note: *** $p < .001$.

Table 8. Multiple regression analyses predicting perceived benefits and overall satisfaction

Predictors	Perceived Benefits				Overall Satisfaction			
	<i>B</i>	<i>SE</i>	β	R^2	<i>B</i>	<i>SE</i>	β	R^2
Program quality	.29	.08	.30***	.61	.72	.09	.61***	.64
Instructor quality	.14	.07	.15 [^]		-.03	.09	-.02	
Administrative arrangements	.16	.05	.24**		.11	.06	.13	
Self-performance	.23	.06	.27***		.09	.07	.09	
Perceived benefits					.14	.11	.11	

[^] $p = .051$; * $p < .05$; ** $p < .01$; *** $p < .001$.

DISCUSSION

The Tin Ka Ping P.A.T.H.S. Project aims to promote holistic development of Chinese adolescents. As a pioneering PYD program in mainland China, systematic training for the potential implementers is a must [26]. As reviewed by Lauer et al. [27], short-term face-to-face professional development training programs with effective design features have steady positive impacts on education workers. A well-designed pre-service training could serve to enhance participants' knowledge and beliefs, cultivate their professional competency and skills, and further to improve their teaching practices [28]. In the present study, the effectiveness of a training program for Tin Ka Ping P.A.T.H.S. Project was evaluated. Responses to a subjective outcome evaluation from 134 participants revealed that the training program in Zhaoqing city in the year 2015 was successfully and smoothly implemented. In agreement with the evaluation studies [22-25] for the training programs in the preparatory year (i.e., 2014-2015 school year), participants expressed overwhelmingly positive perceptions towards the first training program in the full implementation year.

Several observations can be highlighted from the findings. First, favorable reactions towards the program benefits were found. Participants agreed that the training program had strengthened their professional attitude, knowledge, and skills in positive adolescent development. Second, many participants agreed that the training program promoted their self-reflection. As the Tin Ka Ping P.A.T.H.S. Project emphasizes much on the importance of reflection in students, the potential program implementers must be able to appreciate the value of reflection. Third, the respondents opined that program quality, instructor quality, and administrative arrangements had successfully met participants' expectations. These observations echo the model proposed by Shek and Sun [12, 13] that "program," "process,"

and “people” are important determinants of success of PYD programs. Theoretically, it can be argued that program instructors and the program itself serve as a bridge to motivate and encourage participants to have self-reflection and to establish their own peer networks. Finally, most of the participants were satisfied with their own performance in the training program. Such experience would obviously promote the self-efficacy of the potential program implementers to facilitate them to apply the knowledge and skills acquired from training to teach and help the youths.

Besides the above observations, several findings of the study deserve further attention. First, comparison of the perceptions between participants in senior and junior sections showed no significant differences. The findings suggested that junior and senior high school teachers perceived the training programs positively and the findings were consistent with findings in previous studies [22-25]. Second, regarding predictors for perceived benefits, besides program quality, the other three components (including instructor quality, administrative arrangements, and participants’ own performance) also played a positive role. These findings suggested that multiple factors should be taken into account when examining the impact of training programs.

It is noteworthy that there are several limitations of the present study. First, a general criticism on subjective outcome evaluation is its deficiency in predicting future behavior or performance [29]. Obviously, it would be helpful to look at the change of the trainees in the real world using objective outcome evaluation such as follow-up observations of trainees. The association between subjective and objective outcome evaluation findings could help verify the favorable conclusions in the present study. Second, the quantitative evaluation could hardly explain the complexity and details of participants’ feelings and reactions. Hence, qualitative data collected through structured interviews and focus groups could be constructive and helpful. Third, increasing sample size could better generalize the findings. Despite these limitations, the present positive findings showed that the training program for the Tin Ka Ping P.A.T.H.S. Project training program in Zhaoqing was well received and welcomed by the potential implementers in mainland China.

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Chapter 30

SUBJECTIVE EVALUATION OF A TRAINING PROGRAM OF THE TIN KA PING P.A.T.H.S. PROJECT IN MAINLAND CHINA

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ABSTRACT

Subjective outcome evaluation approach was used to investigate the participants' views of Tin Ka Ping P.A.T.H.S. Project training program held in Shaoguan, China. A total of 63 junior teachers and 63 senior teachers responded to the satisfaction questionnaires. Results revealed that almost all participants highly appreciated all components of the program. Compared to participants in the senior high school training program, participants in the junior high school training program rated the program in a more favorable manner. Consistent with previous studies, perceived program quality positively predicted both perceived benefits and overall satisfaction. Perceived instructor quality and perceived self-performance were also significant predictors of perceived

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benefits of the program. The present study suggests that the training program of Tin Ka Ping P.A.T.H.S. Project in Shaoguan was effective in promoting the knowledge, attitudes, and skills of the participants in the training program.

Keywords: Tin Ka Ping P.A.T.H.S. Project, training evaluation, adolescent, positive youth development

INTRODUCTION

Adolescents are important assets for a society if they can develop their potential to the fullest extent. However, they can also be burdens for the society if they fail to develop in a healthy way [1]. During their transition to adulthood, contemporary adolescents face many challenges, such as high expectations from parents, stressful school life, temptations such as Internet addiction and moral confusion, and highly competitive job market [2]. Under such pressure, adolescents are vulnerable to a plethora of developmental issues, such as substance abuse, early sexual involvement, addictive behaviors, self-harm/suicide intentions or behaviors, and juvenile crimes [3, 4]. Based on a systematic review conducted by Muehlenkamp and her colleagues [3], non-suicidal self-injury and deliberate self-harm behaviors were prevalent among adolescents across nations, with an average rate of 18.0% and 16.1%, respectively. In China, Shek and Yu [5] did a survey among over 3,000 secondary school students in Hong Kong. They found that during the year of 2011, 32.7% of the participants reported at least one form of deliberate self-harm behaviors. Furthermore, they found that self-harm and suicidal signals were more likely to be present among students with lower cognitive, behavioral, and emotional competencies. Besides self-harm behaviors, Internet addiction has also become a common health problem for adolescents [4]. Research findings showed that the prevalence of addictive Internet use was high in both mainland China (10%) and Hong Kong region (16%).

Two main approaches have been adopted to “solve” adolescent developmental issues [6]. Initially, the prevention science approach was proposed for reducing problematic behaviors of troubled adolescents. Single-problem-focused prevention programs emerged since the 1980s in response to the existing crises, such as substance abuse [7], teenage pregnancy [8], academic failure [9], dysfunctional family [10], and mental health problems [11]. However, evaluation studies showed that the positive effects of “problem-based” prevention programs were not ideal [e.g., 12]. Though longitudinal studies and evaluation findings were later incorporated to help service providers and researchers diagnose the predictors of specific problem behaviors [13], it is still uneconomical and impractical to develop prevention programs for each specific adolescent problem behavior. Therefore, the positive youth development (PYD) approach emerged as an alternative approach to promote and enhance adolescents’ psychosocial competencies from an ecological perspective [14]. As stated by Larson [14], “development, after all, is a process of growth and increasing competence. In the important subdomain of social and emotional development, however, we are often more articulate about how things go wrong than how they go right” (p. 170). Therefore, instead of viewing young people as troublesome, PYD approach emphasizes the intrinsic strengths and values of youths [9, 15]. Many PYD programs aim to reduce youth problems by promoting their strengths and competencies. For example, a PYD program enhancing effective decision-

making skills successfully reduced adolescents' use of drugs, alcohol, and marijuana one year after commencement of the program [15].

Although the notion of PYD has been widely accepted [16], insufficient work has been done in developing and implementing PYD programs in different Chinese contexts [17]. Shek and his colleagues have led a Project entitled "P.A.T.H.S. (Positive Adolescent Training through Holistic Social Programmes)" in Hong Kong. The P.A.T.H.S. Project aims to promote the holistic development of adolescents in Hong Kong by providing both school-based and community-based programs [17-19]. Evaluation studies have shown that the P.A.T.H.S. Project received high satisfaction ratings from various stakeholders, and consistently demonstrated the success of the project in reducing the growth of adolescent risk-taking behaviors such as drug use and Internet addiction, and promoting the positive psychosocial constructs including cognitive competence, social and emotional competence, and moral competence [20-23].

Obviously, it is important to ask how we can disseminate the successful experience of the Project P.A.T.H.S. to other Chinese communities. Upon the invitation of Tin Ka Ping Foundation, the Research Team adapted and implemented the Project P.A.T.H.S. in mainland China since 2011. After the initial trial from 2011 to 2014 and the training provided to the potential schools in the 2014-15 school year, the project was in a full implementation mode that engaged around 30 schools in China participating in the project. As pointed out by Shek and Sun [24], "people" is the most important factor that influences program quality. Besides, previous studies have found that implementer performance could explain the effectiveness of a program to a great extent [23, 25]. Obviously, implementers act as gatekeepers to transmit the program content from the program developers to the program receivers. Hence, implementers' mastery of the knowledge and their understanding of the program rationales are the prerequisites of effective program implementation [26].

Given the above considerations, starting from the preparatory year (i.e., 2014-2015 academic year) of the full implementation of the project, the Research Team began to offer training programs for implementers, including teachers, social workers, and school principals. During 2014-2015 academic year, four training workshops were held in different cities in mainland China, including Shanghai, Suzhou, and Chongqing. These training programs attempted to fulfill the following objectives: 1) strengthening implementers' understanding of the nature of positive youth development; 2) cultivating and summarizing the rationales, concepts, and latest development of the Tin Ka Ping P.A.T.H.S. Project; 3) offering opportunities for implementers to share successful experiences during the implementation; 4) reviewing the obstacles and obtain feedbacks from frontline implementers; 5) motivating implementers to have self-reflections; and 6) facilitating implementers to develop peer networks among the training participants and learn collaborative teaching strategies [27].

Shek and Wai [28] did a systematic review of training programs in positive youth development programs. They found that although there was a proliferation of PYD programs in the recent two decades, few offered systematic training programs for the potential program implementers, and even fewer evaluated the effectiveness of the training programs [29, 30]. However, training program evaluation deserves much more attention than it actually receives because once the PYD program is off-course, the intended learning effects may disappear [28]. Therefore, evaluating the effectiveness of the training program can give the program developers some ideas whether the potential program implementers indeed understand the program and implement it according to the philosophy of the program. Besides, feedbacks

from the trainees also shed light on future improvement of the training content, training method, and trainers' performance [27].

Different aspects have been assessed in the existing training evaluation studies. For example, Kealey et al. [31] evaluated the in-service training program for a school-based smoking prevention by assessing teachers' perception of the content of the program, perceived usefulness of the training, and quality of the facilities and arrangements. Nunnery et al. [32] evaluated teachers' perceptions and feelings of a pre-implementation training in the domains of quality of training (organization, trainers' performance, and perceived effectiveness), participants' self-perception, and the enthusiasm and confidence towards implementing. However, very few evaluation studies on PYD training program have been published. To fill in this research gap, Shek [33] developed an evaluation questionnaire to test the participants' perceptions of the training program for Project P.A.T.H.S. in Hong Kong. There are four main domains in the questionnaire, including perceptions of the training program (e.g., objectives, activity formats, and designs), instructor quality, own performance, and administrative arrangements. Evaluation findings supported that the training programs for Project P.A.T.H.S. were effective and satisfactory [26, 33]. The questionnaire has also shown good reliability and validity based on the data collected in mainland China. The subjective outcome evaluation findings collected in the academic year of 2014-2015 showed that the related training programs were successful [34-37].

It is noteworthy that some improvements were made for the training program content in the year 2015-2016, such as acquainting new-added teaching materials, sharing successful implementing experiences in mainland China, and separating training workshops for senior and junior secondary teachers. Therefore, to replicate the positive findings in previous years and to examine whether the implementation of the training program in the full implementation year (i.e., the academic year 2015-2016) was equally effective and smooth, the present study attempted to evaluate the second training program in 2015-2016 academic year held in Shaoguan of mainland China. The details of the training program can be seen in the appendix.

METHODS

The second training workshop for the Tin Ka Ping P.A.T.H.S. Project in China in 2015-16 school year was held in Shaoguan. The workshop lasted three days. Two separate training sessions were held in parallel for junior secondary school teachers and senior secondary school teachers, respectively. A total of 108 teachers from 24 junior secondary and 81 teachers from 23 senior secondary schools participated in the training program. At the last session of the workshop, the participants were invited to fill in a structured subjective outcome evaluation questionnaire. Some teachers were not able to complete the questionnaire since they left earlier because of transportation reasons. Finally, a total of 126 questionnaires were collected from 63 junior teachers and 63 senior teachers. Among all the respondents, 38 (30.2%) were males and 88 (69.8%) were females. A large proportion (59.5%) of the teachers had more than 10 years of extensive teaching experience. The average teaching experience of the participants was 13.35 years ($SD = 9.48$).

Instruments

To assess participants' perceptions of the training program in the present study, five parts were included in the questionnaire:

1. Perception of the training program content (16 items), including the perceived program quality (5 items), perceived program benefits (9 items), and overall satisfaction (2 items).
2. Perception of the program instructor (5 items).
3. Perception of the administrative arrangements (6 items).
4. Perception of own performance (4 items).
5. Two open-ended questions, including the things that they most appreciated and the areas that they think need further improvement during the workshop.

For the first four parts, participants were asked to rate their agreement/satisfaction on a 5-point Likert scale (from 1 = strongly disagree/very dissatisfied to 5 = strongly agree/very satisfied), with a higher score indicating a more positive perception. The rating for each scale/subscale was indicated by the average score of corresponding items. The present study attempted to investigate participants' perceptions of the program in terms of content, instructor, administrative arrangements, and self-performance. Hence, only data based on the rating scales were analyzed.

RESULTS

The overall scale and all subscales were reliable according to the results of reliability analyses as shown in Table 1. Except the overall satisfaction subscale, the overall rating scale and all subscales showed medium to high internal consistency with Cronbach's alpha ranging from .75 to .93. For the overall satisfaction subscale, insufficient number of items (only two items) could possibly account for the relatively low reliability (α ranged from .47 to .63) [38].

Table 1. Cronbach's alphas and mean of inter-item correlations of the scales/subscales

Subjective Outcome Evaluation Scales	Total (n= 126)		Senior (n= 63)		Junior (n= 63)	
	α	Mean [#]	α	Mean [#]	α	Mean [#]
Program content (16 items)	.91	.39	.90	.37	.91	.40
Program quality (5 items)	.76	.41	.75	.39	.76	.40
Perceived benefits (9 items)	.86	.40	.86	.41	.86	.40
Overall satisfaction (2 items)	.58	.41	.47	.31	.63	.47
Program instructor (5 items)	.80	.45	.80	.46	.78	.42
Administrative arrangements (6 items)	.85	.49	.86	.51	.82	.44
Perceived own performance (4 items)	.80	.49	.79	.49	.79	.49
Total scale (31 items)	.93	.32	.93	.32	.93	.31

Note: Mean[#]: inter-item correlation.

Perceptions of the Program Content		Senior						Junior						Total			
		N	M	SD	Positive Responses ^b		N	M	SD	Positive Responses ^b		N	M	SD	Positive Responses ^b		
					n	%				n	%				n	%	
Overall Satisfaction ^a		61	4.07	.41	50	81.97	63	4.21	.54	51	80.95	124	4.14	.48	101	81.45	
1.	Overall speaking, I am satisfied with the training program.	61	4.21	.52	57	93.44	63	4.38	.58	60	95.24	124	4.29	.57	117	94.35	
2.	I think participants are satisfied with the training program.	60	3.93	.52	50	83.33	63	4.03	.67	52	82.54	123	3.98	.60	102	82.93	
Perceptions of the Program (Whole Scale) ^a		61	4.25	.37	47	63	4.36	.40	49	77.78		4.30	.39	96	77.42		

Note: ^a: Scores on the scale/subscale higher than or equal to 4 were treated as positive views. ^b: For every item, respondents with positive responses (Options 4-5) are shown in the Table.

Table 3. Summary of the positive views (options 4-5) of the participants towards the program instructor(s)

Perceptions of the program instructor(s)		Senior				Junior				Total								
		N	M	SD	Positive Responses ^b		N	M	SD	Positive Responses ^b		N	M	SD	Positive Responses ^b			
					n	%				n	%				n	%		
1	The instructor(s) had good mastery of the curriculum.		61	4.33	.51	60		98.36	63	4.51	.56	61	96.83	124	4.42	.54	121	97.58
2	The instructor(s) understood the needs of participants.		61	3.93	.65	46		75.41	63	4.19	.67	56	88.89	124	4.06	.67	102	82.26
3	The instructor(s) showed good professional attitude.		61	4.72	.49	60		98.36	63	4.78	.46	62	98.41	124	4.75	.47	122	98.39
4	The instructor(s)' teaching was clear and easy to understand.		61	4.02	.76	46		75.41	62	4.15	.70	51	82.26	123	4.08	.73	97	78.86
5	Overall speaking, I have positive evaluation of the instructor(s)' teaching performance.		61	4.49	.57	59		96.72	62	4.68	.47	62	100.00	123	4.59	.53	121	98.37
Total scale ^a		61	4.30	.45	46	75.41	63	4.45	.44	58	92.06			124	4.38	.45	104	83.87

Note: ^a: Scores on the scale higher than or equal to 4 were treated as positive views.

Table 4. Summary of the positive views (options 4-5) of participants towards administrative arrangements

Perceptions of the Administrative Arrangements																
Senior							Junior					Total				
N	M	SD	Positive Responses ^b		N	M	SD	Positive Responses ^b		N	M	SD	Positive Responses ^b			
			n	%				n	%				n	%		
63	4.06	.62	55	87.30	63	4.14	.67	53	84.13	126	4.10	.64	108	85.71		
1.	Information obtained before attending the workshop.															
2.	Workshop assigned.															
3.	Location of the workshop.															
4.	Reception provided by training team (e.g., transportation arrangement, refreshments).															
5.	Facilities of the venue.															
6.	Overall speaking, I am satisfied with the administrative arrangement.															
Total Scale ^a		63	4.04	.56	39	61.90	63	4.26	.49	49	77.78	126	4.15	.53	88	69.84

Note: ^a: Scores on the scale higher than or equal to 4 were treated as positive views.

Table 5. Summary of the positive views (options 4-5) of participants towards their own performance in training

Perceptions of Self-Performance															
Senior						Junior						Total			
N	M	SD	Positive Responses ^b		N	M	SD	Positive Responses ^b		N	M	SD	Positive Responses ^b		
			n	%				n	%				n	%	
63	4.14	.69	54	85.71	63	4.29	.58	59	93.65	126	4.21	.64	113	89.68	
63	4.38	.61	59	93.65	63	4.57	.50	63	100.00	126	4.48	.56	122	96.83	
63	3.98	.58	54	85.71	63	4.10	.69	56	88.89	126	4.04	.64	110	87.30	
62	3.97	.68	49	79.03	62	4.08	.71	51	82.26	124	4.02	.69	100	80.65	
63	4.12	.50	46	73.02	63	4.26	.49	55	87.30	126	4.19	.50	101	80.16	
Total Scale ^a															

Note: ^a: Scores on the scale higher than or equal to 4 were treated as positive views.

To have a comprehensive understanding of the participants' satisfaction with the training program, the numbers and percentages of positive ratings (i.e., options 4 and 5 on the 5-point Likert scale) on each scale/subscale were aggregated as shown in Table 2-5. In general, both junior and senior teachers rated over 4.0 on every subscale with 5.0 as the maximum score, indicating their high satisfaction with the program content, instructor quality, administrative arrangement, as well as their own performance.

Specifically, Table 2 illustrates that over 80% of the participants expressed positive views towards almost every aspect of the program quality, except for the training time (71.77%). Regarding perceived benefits of the program, almost all participants (99.19%), especially participants in junior session (100.0%), agreed that the training workshop had strengthened their understanding of the nature of adolescent development and it had helped them cultivate positive attitudes to adolescent development. In addition, over 80% of the participants had overall satisfaction with the training program.

Participating teachers (83.87%), especially junior school teachers (92.06%), expressed highly positive ratings towards the program instructors. Almost all participants agreed that the instructors had a good mastery of the curriculum (97.58%) and they had shown good professional attitude (98.39%). With respect to the administrative arrangements, approximately 90% of the participants had overall satisfaction. Besides, over 90% of the participants held positive views towards the workshop assigned. Results in Table 5 indicate that 96.83% of the participants were willing to apply the specific skills and theories learned from this training program, and 89.68% of the participants participated actively during the discussion.

To compare the perceptions between senior and junior school teachers, a MANOVA analysis was performed. As demonstrated in Table 6, significant differences were found in the perception of program quality ($F(1,122) = 4.86, p = .029, \eta_p^2 = .038$), perceived administrative arrangements ($F(1,122) = 5.14, p = .025, \eta_p^2 = .040$), and the total score ($F(1,122) = 4.77, p = .031, \eta_p^2 = .038$). Marginally significant difference was found in perceived program instructor attributes ($F(1,122) = 3.82, p = .053, \eta_p^2 = .030$). In general, the training program for junior teachers received relatively higher satisfaction ratings than did the program for senior teachers, although the satisfaction ratings can be regarded as quite positive.

Table 6. The comparison between Senior and Junior Secondary school participants on the perceptions of the training program

Subjective Outcome Evaluation Scales	Senior (n = 63)		Junior (n = 63)		F	η_p^2
	M	SD	M	SD		
Program content (16 items)	4.25	.37	4.36	.40	2.24	.018
Program quality (5 items)	4.17	.45	4.35	.46	4.86*	.038
Perceived benefits (9 items)	4.34	.39	4.39	.41	.58	.005
Overall satisfaction (2 items)	4.07	.42	4.21	.54	2.35	.016
Program instructor (5 items)	4.30	.45	4.45	.44	3.82 [†]	.030
Administrative arrangements (6 items)	4.04	.56	4.26	.49	5.14*	.040
Self-performance (4 items)	4.12	.50	4.26	.49	2.22	.018
Total scale (31 items)	4.19	.36	4.34	.35	4.77*	.038

Note: * $p < .05$, [†] $p = .053$.

Table 7. Correlations among the key evaluation components

Variables	M	SD	1	2	3	4	5	6
Program quality (5 items)	4.26	.46	-					
Program benefits (9 items)	4.36	.40	.72***	-				
Program instructor(s) (5 items)	4.38	.45	.62***	.58***	-			
Administrative arrangement (6 items)	4.15	.53	.43***	.35***	.35***	-		
Self-performance (4 items)	4.19	.50	.61***	.64***	.37***	.37***	-	
Overall satisfaction (2 items)	4.14	.48	.71***	.65***	.50***	.40***	.50***	-

Note: *** $p < .001$.

Table 8. Multiple regression analyses predicting perceived benefits and overall satisfaction

Predictors	Perceived Benefits				Overall Satisfaction			
	<i>B</i>	<i>SE</i>	β	R^2	<i>B</i>	<i>SE</i>	β	R^2
Program quality	.34	.08	.39***	.613	.49	.11	.47***	.548
Instructor quality	.20	.07	.23**		.00	.09	.003	
Administrative arrangements	-.01	.05	-.02		.10	.06	.11	
Self-performance	.26	.06	.33***		.01	.08	.01	
Perceived benefits					.32	.12	.27**	

Note: * $p < .05$; ** $p < .01$; *** $p < .001$.

Pearson correlation analyses revealed that the key evaluation components, including perceived program quality, program benefits, program instructor, administrative arrangement, self-performance, and overall satisfaction, were significantly and positively correlated with each other (r s ranged from .35 to .72, p s $< .001$; see Table 7). Two multiple regression analyses were further performed to examine the predicting effects of the key evaluation components for perceived benefits and overall satisfaction (see Table 8). Results revealed that perceived benefits were significantly predicted by perceived program quality ($\beta = .39$, $p < .001$), instructor quality ($\beta = .23$, $p = .002$), and perceived self-performance ($\beta = .33$, $p < .001$), but not perceived administrative arrangements ($\beta = -.02$, $p = .772$). The whole model explained 61.3% of the variance of perceived benefits of the training program. Besides, overall satisfaction was significantly predicted by perceived program quality ($\beta = .47$, $p < .001$) and perceived program benefits ($\beta = .27$, $p = .008$). The whole model explained 54.8% of the variance of overall satisfaction.

DISCUSSION

There has been a shifting from problem-oriented to strength-oriented interventions for young people in Western societies in recent decades [39]. However, there is a lack of validated and effective positive youth development (PYD) programs in China [40]. The Tin Ka Ping P.A.T.H.S. Project was carried out to fill this gap which attempted to promote positive development in Chinese adolescents. Numerous researchers have reiterated the importance of professional training and development for youth workers [29, 31, 41]. For example, Bowie and Bronte-Tinkew [41] pointed out that effective pre-service and in-service training for youth workers not only benefit individual trainees but also improve program

quality. As training is important, the current study evaluated the effectiveness of the training program for potential program implementers in the “Tin Ka Ping P.A.T.H.S. Project” in China based on the responses of 126 participants.

The present findings suggest that the training program in Shaoguan in 2016 was an overall success. Generally speaking, feedbacks from the program participants were extremely positive. Consistent with the evaluation studies for the training programs in the previous year [34-37], participants highly appreciated every component of the program. Specifically, a considerable proportion of the participants acknowledged the benefits of the training program. They strongly agreed that the training workshop helped them strengthen professional skills and cultivate positive attitudes to adolescent development. Besides, participants had fairly positive perceptions towards program quality, instructor performance, and program administrative arrangements. The findings suggest that the training program for the Tin Ka Ping P.A.T.H.S. Project was well designed and implemented, and the instructors showed professional attitudes and good performance. Furthermore, most of the teachers expressed their satisfaction with their own performance during the training program. Almost all participants expressed their willingness to apply the learned skills and theories in providing service and help to adolescents.

Although the perceptions of the participants in the junior high school program and the senior high school program were fairly positive, participants in the junior high school program had more positive responses than did participants in the senior high school program. A possible explanation for this observation may be due to differences in teaching materials. The teaching materials for junior school students have been used and validated through over ten years’ implementation of the “P.A.T.H.S. Project” in Hong Kong. However, the teaching materials for the senior high school program are newly developed for mainland Chinese students, which are trial version only. Hence, potential implementers from senior school may still have concerns about the program content while junior teachers may not. Nevertheless, differences between senior and junior training sessions were not found in the first training program in the year 2015-2016 at Zhaoqing [42]. Therefore, the present finding should be treated as tentative which requires replication.

Consistent with previous studies [34-36], participants’ overall satisfaction was predicted by perceived program quality and perceived benefits of the program in the current study. It implies that participants’ endorsement of the program content and rationales is indispensable for a successful training program. Furthermore, participants’ perceived benefits of the program was positively predicted by perceived program quality, perceived instructor quality, and perceived self-performance. These findings have some implications for the design of training programs with benefits to trainees. First, the program itself should include rich and suitable materials. Second, the instructors should show professional attitudes and skills. Finally, the program should promote participants’ engagement in the training and their self-efficacy. As reflected in the 5 Ps theory proposed by Shek and Sun [24], the importance of “program,” “people,” and “process” elements are highlighted in the present study.

Three limitations of the present study should be addressed in future studies. First, the participants’ extremely positive responses may be due to demand characteristics. For example, the participants might rate positively on the survey because they wish to play the role of good program participants. Hence, measures assessing demand characteristics should be included in future studies. Second, as we could only access potential implementers’ perceptions in the present study, this would not be sufficient to enable the Research Team to

claim that the Tin Ka Ping P.A.T.H.S. Project is beneficial for the youths. As such, follow-up outcome evaluation studies should be conducted. Third, a larger sample size could give a clearer picture about the views of the trainees. Despite the above-mentioned limitations, the present study gives support to the effectiveness of the Tin Ka Ping P.A.T.H.S. Project training program in Shaoguan which paves the way for the successful implementation of the project in China.

APPENDIX

The second training program of the Tin Ka Ping P.A.T.H.S. Project in the 2015-2016 school year in Shaoguan, mainland China

Junior Group

Day 1 (6.5 hours)	
Themes and Objectives	Activities Conducted
a) Introduce the latest advances of the Tin Ka Ping P.A.T.H.S. Project during the full implementation phase (2015-2016); b) Offer opportunities for school delegates, school principals, and experienced teachers to share their implementation experiences; and c) Familiarize the teachers with the constructs and teaching units.	1. Introduce the Tin Ka Ping P.A.T.H.S. Project and the professional team; 2. Warm-up activities; 3. Introduce the training schedules of the Project; 4. Guide the participants how to use the updated teaching materials and other resources of Tin Ka Ping P.A.T.H.S. Project; 5. Introduce the Co-Walker Scheme; 6. Introduce the results of first training program evaluation; and 7. Lecture on the rationales and the frameworks of units.
Day 2 (6.5 hours)	
Themes and Objectives	Activities Conducted
a) School delegates share their teaching experiences and demonstrate teaching techniques; and b) Familiarize the participants with teaching methodology of the Tin Ka Ping P.A.T.H.S. Project;	1. Lesson demonstration by school delegated from participating schools; 2. Group discussion and Q&A session; and 3. Wrapping up and Self-reflection.
Day 3 (6.5 hours)	
Themes and Objectives	Activities Conducted
a) Familiarize the teachers with the constructs and teaching units; b) Clarify participants' questions on project implementation; and c) Familiarize the participants with the evaluation methods of Tin Ka Ping P.A.T.H.S. Project.	1. Lecture on the constructs of "Resilience (RE)" and the contents of units; 2. Lecture on the constructs of "Emotional Competence (EC)" and the contents of units; 3. Lecture on the constructs of "Prosocial Involvement (PI)" and the contents of units; 4. Lecture on the constructs of "Behavioral Competence (BC)" and the contents of units; 5. Interactive lecture on the evaluation instruments of the program (form A, form B, and weekly report) and data analysis methods; 6. Wrapping up and Self-reflection; and 7. Conclusion.

Senior Group

Day 1 (6.5 hours)	
Themes and Objectives	Activities Conducted
a) Introduce the latest advances of the Tin Ka Ping P.A.T.H.S. Project during the full implementation phase (2015-2016); b) Familiarize the teachers with the constructs and teaching units.	1. Introduce the Tin Ka Ping P.A.T.H.S. Project and the professional team; 2. Warm-up activities; 3. Introduce the training schedules of the Project; 4. Guide the participants how to use the updated teaching materials and other resources of Tin Ka Ping P.A.T.H.S. Project; 5. Introduce the Co-Walker Scheme; 6. Introduce the results of the first training program evaluation; 7. Lecture on the constructs of “Bonding (BO)” and the contents of units; 8. Lecture on the constructs of “Self-Efficacy (SE)” and the contents of units; 9. Lecture on the constructs of “Prosocial Involvement (PI)” and the contents of units; 10. Lecture on the constructs of “Social Competence (SC)” and the contents of units; and 11. Lecture on the constructs of “Self-Determination (SD)” and the contents of units.
Day 2 (6.5 hours)	
Themes and Objectives	Activities Conducted
a) Offer opportunities for school delegates to share their implementation experiences and teaching plans; and b) Familiarize the participants with teaching methodology of the Tin Ka Ping P.A.T.H.S. Project;	1. Lesson demonstration by school teachers from participating schools; 2. Group discussion and Q&A session; 3. Wrapping up and Self-reflection.
Day 3 (6.5 hours)	
Themes and Objectives	Activities Conducted
a) Familiarize the teachers with the constructs and teaching units. b) Clarify participants’ questions on project implementation; and c) Familiarize the participants with the evaluation methods of Tin Ka Ping P.A.T.H.S. Project.	1. Warm-up activities; 2. Lecture on the constructs of “Prosocial Norms (PN)” and the contents of units; 3. Lecture on the constructs of “Moral Competence (MC)” and the contents of units; 4. Lecture on the constructs of “Prosocial Involvement (PI)” and the contents of units; 5. Interactive lecture on the evaluation instruments of the program (form A, form B, and weekly report) and data analysis methods; 6. Wrapping up and Self-reflection; and 7. Conclusion.

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Chapter 31

HOW DO TEACHERS VIEW AND EXPERIENCE A NEW GENERAL EDUCATION PROGRAM IN HONG KONG? A STUDY BASED ON DESCRIPTORS AND OPEN-ENDED QUESTIONS

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ABSTRACT

General education has become more important in higher education to nurture students' capacities in different domains for their thriving in an increasingly globalized world. Through qualitative evaluation based on descriptors and open-ended questions, the present study examined teachers' views and experiences of a new general education program "General University Requirements" (GUR) developed by The Hong Kong Polytechnic University (PolyU) when its undergraduate program was reformed from three to four years. Seventy-eight teachers teaching subjects in different GUR

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components in Semester 1 of the 2014-2015 academic year completed the evaluation form. Results suggested that teachers had highly positive feelings and impressions of the subjects they taught. They perceived their subjects as helpful to students' development with respect to the five desired graduate attributes of PolyU. Teachers also identified important merits of and challenges to the GUR curriculum.

Keywords: general education, higher education, Hong Kong, qualitative evaluation, teachers

INTRODUCTION

General education has a long history in educational philosophy and practices. Its idea stems from the idea of liberal education in Ancient Greek and Roman times. In that time, liberal education was a privilege of upper class with an aim of creating freemen through a curriculum of seven liberal arts: grammar, logic, rhetoric, arithmetic, geometry, astronomy, and music [1]. In modern universities, general education has become a comprehensive education for all university students. It inherits the essential idea of ancient liberal education that aims to nurture rounded persons and effective citizens through developing common knowledge and intellectual skills such as higher-order thinking and effective communication [1].

Several core concepts and related curricular models have been developed during the development of general education. Robert Maynard Hutchins (1899-1977) [2], the former president of the University of Chicago, argued that the aim of general education should be the cultivation of intellectual virtues and habits. These intellectual virtues were contained in classical books and formed the core of the intellectual heritage of Western civilization. Therefore, through this cultivation, general education contributed to the unity and continuity of Western society. In other words, general education helped "to connect man with man, to connect the present with the past, and to advance the thinking of the race" [2]. Based on this concept, the great book model of general education curriculum was developed. The model consisted of learning of great books in Western civilization together with some fundamental subjects on thinking, communication and mathematics [3]. Similarly, the Harvard Committee on General Education in 1945 [4] proposed that the broad social aim of general education was for the unity and continuity of Western cultural heritage and Western societies. However, they claimed that the curricular mean for this education was one that consisted of learning of three knowledge areas including natural science, social science and humanities, and stressed cultivation of five traits of mind including effective thinking, communication, judgment making, and value discrimination. Related to this concept, the scholarly discipline model of general education was developed. This model introduced students to major disciplines of college that were regarded as the best storage of the human intellectual heritage [3].

The above concepts of general education were classic. However, they were criticized by other modern educators such as John Dewey (1859-1952) for their separation of theory and practice and their neglect of the role of student experience in education [5]. Dewey [6] argued that education should be built on or should take into account students' experience and genuine development of thinking was based on reflection on experiences. Therefore, Dewey [6] perceived education as a social and interactive process with the aim of having students learn to live as effective citizens and realize one's potentials rather than obtain pre-determined

knowledge. Related to Dewey's philosophy of education, the effective citizen model of general education was established. The aim of the model was to develop in students the values and skills for effective citizenship through studying issues concerning contemporary society [3]. Particularly, Dewey's ideas influence the development of experiential education and some new modes of curriculum such as service learning in contemporary general education programs.

With regard to the practice, general education has been promoted and implemented in higher education in many places in contemporary society. In the context of Hong Kong, in response to challenges of the globalized knowledge economy and civic construction of Hong Kong society after its return back to China, the University Grants Committee (UGC) of Hong Kong mandated a reform to undergraduate education of all public universities of Hong Kong. Commencing from the 2012-2013 academic year, the eight public universities of Hong Kong transformed their undergraduate programs from three to four years. As an integrated part of this reform, each university introduced a significant component of general education in its new four-year curriculum. The reform aimed "to strike a new balance between breadth and depth" [7] of students' learning and to put greater emphasis on the development of students' foundational and generic skills in higher education [7].

As a key player of the above reform, The Hong Kong Polytechnic University (PolyU) extended its undergraduate degree program from three to four years. In the new four-year curriculum, a general education component named "General university requirements" (GUR) was introduced. The GUR aims to develop students in five desired graduate attributes, including effective communication, critical thinking, innovative problem solving, lifelong learning, and ethical leadership. The curriculum is comprised of six major components: Freshman Seminar (FS, 3 credits), Leadership and Intrapersonal Development (LIPD, 3 credits), Language and Communication Requirements (LCR, 9-credit English and 3-credit Chinese subjects), Cluster Area Requirements (CAR, 12 credits), Service Learning (SL, 3 credits), and Healthy Lifestyle (HLS, non-credit-bearing). Active teaching and learning methods are incorporated in the teaching and learning of the GUR, including cooperative and experiential learning, writing practice, as well as other innovative teaching strategies. A brief summary of each curricular component is listed as below:

- FS: introduce students to their disciplines and potential majors, and develop higher-order thinking, entrepreneurship, and self-learning.
- LIPD: nurture inter- and intra-personal qualities that lead to effective and ethical leadership.
- LCR: develop language proficiencies in English and Chinese.
- CAR: expand intellectual horizons and develop reading and writing skills.
- SL: cultivate social responsibility, empathy and attitude of serving the others.
- HLS: develop healthy lifestyle through learning knowledge and theories, and sports skills training.

The structure of the GUR is comprehensive and active teaching and learning methods are adopted. Although it was assumed that such pedagogies are welcomed by students, scientific evaluation findings are needed. To understand the functioning and effectiveness of the GUR, systematic evaluation studies should be conducted. To this end, qualitative evaluation is one

good approach to understand the impact of GUR on students. Qualitative evaluation is commonly used in educational field. Through a variety of methods such as focus group, individual interview, open-ended written question, self-reflection, and others [8-10], qualitative evaluation investigates viewpoints of important stakeholders to provide in-depth information and develop a more context-based understanding of program implementation [11-13]. Qualitative methods might be particularly useful in educational evaluation since “there is no single determination of worth for any educational endeavor. Worth is complex and personal” and “part of an evaluator’s responsibility is to indicate who finds merit in what, and what criterial and standards they appear to exercise” [14].

Teachers are important stakeholders of general education programs. Therefore, to understand views of teachers and listen to the voices to teachers as major stakeholders are important. To understand teachers’ views of the GUR, qualitative evaluation based on teachers’ written responses to open-ended questions were conducted. Comparing with other qualitative evaluation methods such as focus group and individual interviews, collection of written responses has several unique features. First, this method is more cost-effective and resource-saving. Second, data gathered from written responses might be more logical and consistent in expression than data gathered from focus groups in which participants’ expression might be more impromptu and less thoughtful. Thirdly, some forms of written responses such as descriptors and short phrases could also be analyzed in a more quantified approach. Based on this, the present study examined teachers’ views and experiences of the GUR through their written responses collected from the qualitative evaluation forms to understand the implementation and effects of the GUR at PolyU.

METHODS

At the end of the first semester of the 2014-2015 academic year, a total of 128 staff members who were involved in teaching of subjects in different components of the GUR curriculum were invited to fill in an online qualitative evaluation form. These teaching staff was sampled mainly based on nomination of subject leaders and important teachers in different GUR components and direct invitation of teachers based on the list of some GUR components. By early February of 2015, 78 staff members had completed the online form, with a response rate of 60.94%. The numbers of participants in different GUR components were: FS (n = 8), LIPD (n = 12), English LCR (n = 10), Chinese LCR (n = 7), CAR (n = 19), SL (n = 11), and HLS (n = 11). Detailed information is shown in Table 1.

Instrument

The online qualitative evaluation form was developed by the authors. It was comprised of two major parts. The first part required staff members to use “three descriptors or short phrases” to describe their general impression and feelings about the GUR subjects they taught in the first semester of the 2014-2015 academic year. The second part consisted of two open-ended questions:

- Have you observed any changes in your students after studying the GUR subject you taught in this semester? If yes, please describe the changes.
- Have you encountered any difficulties or challenges in your teaching of the GUR subject in this semester? If yes, what might be the reason(s) for these difficulties or challenges?

Data Analysis

All the written responses collected from the online evaluation forms were input into an Excel file for analyses. For the analysis of descriptors, the unit of analysis was a meaningful unit instead of a mere statement. All the meaningful units were carefully read by a researcher. The researcher in the first step coded these units into four broad categories, namely “positive,” “negative,” “neutral” and “undecided.” Under each category, the meaningful units were further coded into different themes. For the analysis of teachers’ responses to each of the two open-ended questions, all teachers’ written responses were carefully read by a researcher for several times and were coded into different themes and subthemes. Furthermore, all codes were carefully checked to ensure their accuracy.

Table 1. Number of participants in teacher qualitative evaluation

Component of GUR Curriculum	Numbers of Teaching Staff Being Invited	Numbers of Teaching Staff Completing the Form
FS	17	8
LIPD	12	12
English LCR	10	10
Chinese LCR	9	7
CAR	50	19
SL	19	11
HLS	11	11
Total	128	78
Response Rate	60.94%	

Note. FS = Freshman Seminar, LIPD = Leadership and Intrapersonal Development, English LCR = English Language and Communication Requirements, Chinese LCR = Chinese Language and Communication Requirements, CAR = Cluster Area Requirements, SL = Service Learning, HLS = Healthy Lifestyle.

Table 2. Summary of descriptors/short phrases teachers used to describe their general impression and feelings towards the GUR subjects

Descriptors/Short Phrases	GUR Component							Total	%
	FS	LIPD	ELCR	CLCR	CAR	SL	HLS		
Positive	17	29	24	14	40	28	23	175	82.16
Neutral	1	3	0	2	1	9	0	16	7.51
Negative	1	1	2	5	4	3	2	18	8.45
Undecided	0	0	0	1	2	0	1	4	1.88
Total	19	33	26	22	47	40	26	213	100.00

RESULTS

The first question in the evaluation form asked the teachers to use three descriptors or short phrases to describe their general impression and feelings of the GUR subjects they taught. A total of 213 descriptors/short phrases were collected. Among these descriptors/short phrases, 175 (82.16%) were classified as positive descriptors, 16 (7.51%) were classified as neutral descriptors, and 18 (8.45%) were coded as negative descriptors. Detailed information about classification of descriptors/short phrases in total and by each GUR component is shown in Table 2. The 175 positive descriptors/short phrases were further coded into six themes, namely “Impact of Subject Teaching on Teachers,” “Teachers’ Perceived Benefits of Their Subjects and Related Teaching to Students,” “Teachers’ Perceived Merits of GUR Subjects,” “Teachers’ Relationship with Students,” “Teachers’ Perceived Engagement of Students,” and “Others.” Table 3 provides a detailed summary of the positive descriptors/short phrases under each theme and subtheme.

Table 3. Summary of positive descriptors/short phrases given by teachers to describe their general impression and feelings of the GUR subjects

Descriptors	FS	LIPD	ELCR	CLCR	CAR	SL	HLS	Total (%)
<i>Impact of Subject Teaching on Teachers</i>								
<i>Sense of Achievement</i>								
A sense of achievement	1	1	1		2	2	2	9
A fair/moderate sense of achievement		1	2		1			4
A good/great/strong sense of achievement	2		2		3	1	2	10
							<i>Subtotal</i>	23
<i>Sense of Satisfaction</i>								
A great/strong sense of satisfaction	1					1	2	4
A sense of satisfaction					1	1	1	3
(Very) satisfied	1		1		1		1	4
							<i>Subtotal</i>	11
<i>Enjoyable</i>								
Enjoyable		2					3	5
Feeling of pleasure during the lesson							1	1
							<i>Subtotal</i>	6
<i>Rewarding</i>								
(Very) rewarding		2				2		4
A busy but rewarding experience						1		1
							<i>Subtotal</i>	5
<i>Others</i>								
Grateful		1						1
Fulfillment						1		1
Passionate		1						1
Enthusiasm					1			1
Sense of mission					1			1
Being a mentor		1						1
Paid a lot of efforts		1						1
Learnt a lot					1			1
Learnt (a lot) from the students		1				1		2
Rich educational experience		1						1
Strong sense of responsibility		1						1
Watching my students grow		1						1

Table 3. (Continued)

Descriptors	FS	LIPD	ELCR	CLCR	CAR	SL	HLS	Total (%)
Important communication skills			1					1
Learn how to communicate better					1			1
Learn how to present their ideas better					1			1
More open multilateral communication					1			1
Remind the importance of Chinese writing					1			1
Communication skills being lifelong beneficial to students				1				1
<i>Thinking</i>								
Provides new ways of thinking about the world					1			1
Promoted students' comprehensive and objective thinking to one problem				1				1
<i>Problem Solving</i>								
Students' problem solving skills enhanced					1			1
Encouraged students to solve problems actively				1				1
<i>Lifelong Learning</i>								
Useful for their lifelong learning					1			1
Effectively promoted students' self-learning after the class				1				1
<i>Self-Reflection and Self-Understanding</i>								
Understanding themselves							1	1
Realize the importance of reflection for students' development		1						1
<i>Social Responsibility</i>								
Socially responsible						1		1
Contented to learn that some students will continue to do voluntary work thereafter						1		1
<i>Others</i>								
A successful endeavor in nurturing future leaders		1						1
Promotes literacy					1			1
							<i>Subtotal</i>	<i>19</i>
<i>Others</i>								
Mutual benefits		1						1
Helpful for their future career				1				1
Learn how to enjoy lectures					1			1
Valuable for students' university life and beyond			1					1
Show how business can do some good					1			1
Sending the message of authorial ownership to students					1			1
A strong sense of meaningful contribution to the society						1		1
Aroused students' interests in sports and exercise participation							1	1
Helping students own a piece of work as their own creation					1			1
							<i>Subtotal</i>	<i>9</i>
							<i>Subtotal</i>	<i>53 (30.29%)</i>

Descriptors	FS	LIPD	ELCR	CLCR	CAR	SL	HLS	Total (%)
Teachers' Perceived Merits of GUR Components								
<i>Content</i>								
New and interesting topics to them					1			1
Strong focus on referencing skills			1					1
Strong focus on research skills			1					1
Rich content				2				2
Sufficient content			1					1
Practical					1			1
Practical "life skills" that they will use long after they have left PolyU			1					1
Topics including earth history, cosmology and evolution are indispensable for all students					1			1
							<i>Subtotal</i>	9
<i>Method</i>								
Engaging teaching methodology	1							1
Hands-on						1		1
Interactive	1	1						2
Student-oriented			1					1
							<i>Subtotal</i>	5
<i>General and Others</i>								
Impressive						1		1
Influential					1			1
Insightful	1							1
Inspiration			1					1
Inspiring introduction to the subject	1							1
Interesting	1				2			3
Invigorating			1					1
Meaningful	2					1	1	4
Meaningful course						1		1
Motivated							1	1
Reflective	2							2
Self-reflection	1							1
Effective application of theories					1			1
Good linkage between theories and practices					1			1
This subject is well-organized					1			1
Well-organized			1					1
Diversified assessment				1				1
Having fun	1							1
							<i>Subtotal</i>	24
							<i>Subtotal</i>	38 (21.71%)
Teachers' Relationship with Students								
Close relationship with students							1	1
Develop good relationship with students							1	1
Enjoyed interaction with students	1							1
Good communication with students							1	1
Good interaction with freshmen	1							1
Strong bonding with students						1		1
Smooth and effective communication between me and students			1					1
An enjoyable time with the students who have curiosity for language or communication issues					1			1
							<i>Subtotal</i>	8 (4.57%)

Table 3. (Continued)

Descriptors	FS	LIPD	ELCR	CLCR	CAR	SL	HLS	Total (%)
Teachers' Perceived Engagement of Students								
The students are committed						1		1
Active participation of the majority of students				1				1
Having motivated some students					1			1
Generally engaging students			1					1
Students have high motivation					1			1
I saw passion in my students when they presented their project results		1						1
						<i>Subtotal</i>	6 (3.43%)	
Others								
Proud of my students						1		1
Relief							1	1
Students were lovely							1	1
Continue improvement				1				1
Becoming better day by day				1				1
Appreciate the strengths of students from different disciplines						1		1
Nice class of students (way beyond my expectation because it was a male-only group)			1					1
						<i>Subtotal</i>	7 (4.00%)	
Total	17	29	24	14	40	28	23	175

Under the theme “Impact of Subject Teaching on Teachers”, 63 (36.00%) descriptors were collected. These descriptors were further coded into five subthemes, namely “sense of achievement” (n = 23), “sense of satisfaction” (n = 11), “enjoyable” (n = 6), “rewarding” (n = 5), and “others” (n = 18). This indicated that at least more than one third of the teachers had perceived benefits from their teaching of GUR subjects, particularly that they developed sense of achievement and satisfaction, and felt enjoyable and rewarding from their teaching experience.

Under the theme “Teachers’ Perceived Benefits of Their Subjects and Related Teaching to Students”, 53 (30.29%) descriptors/short phrases were collected. These descriptors/short phrases were further coded into five subthemes: general benefits, character building, multi-disciplinary learning, competence, and others. Notably, in the subtheme “competence,” six major competences in alignment with the five desired graduate attributes of PolyU were identified, including effective communication, critical thinking, problem solving, lifelong learning, self-understanding, and social responsibility. Under the subtheme “character building”, teachers perceived their GUR teaching as beneficial to resilience, confidence and creativity of students.

Under the theme “Teachers’ Perceived Merits of Curriculum”, 38 (21.71%) descriptors/short phrases were collected and further coded into three subthemes: content, method, and general and others. In the subtheme “content”, descriptors/short phrases such as “rich content,” “sufficient content,” and “practical” were collected. The subtheme “method” included descriptors such as “engaging teaching methodology,” “hands-on,” “interactive” and “student-oriented”. Some teachers also perceived their subjects as “impressive,” “influential,” “insightful,” and “invigorating” in general. Finally, descriptors under the themes “Teachers’ Relationship with Students” and “Teachers’ Perceived Engagement of Students” suggested

that some teachers established close relationship with students through their teaching of GUR subjects and some perceived their subjects as highly motivating and engaging.

Table 4. Summary of neutral and negative descriptors/short phrases teachers used to describe their general impression and feelings towards the GUR subjects

Descriptors	FS	LIPD	ELCR	CLCR	CAR	SL	HLS	Total
Neutral								
A challenge to the teaching team						1		1
A good challenge in handling a lecture class of 300+	1							1
Challenging		2				2		4
Somewhat challenging						1		1
Meet the challenge			1					1
A room for improvement					1			1
There always has a room for improvement						1		1
Motivation of students is very important			1					1
Keeping the interest of students is important						1		1
Roller coaster		1						1
Students can achieve more if they are given chances						1		1
Time management is very important						1		1
Need to have more respect from Office of Service Learning						1		1
Total	1	3	0	2	1	9	0	16
Negative								
Lonely						1		1
A feel of toil						1		1
High workload						1		1
Disappointed					1			1
Disappointment					1			1
Frustration					1			1
It is a challenging topic	1							1
Not enough course time				1				1
Some bumps remained			1					1
Not strong sense of achievement (from teaching effects)				1				1
Limited creative/critical thinking/problem solving			1					1
Too much assignments, hard for teachers and students				1				1
Have some regrets: some students only show up for quiz					1			1
Lack of a sense of achievement because the comment from OGUR on HLS is negative but without sound evidence							1	1
Many arguments among colleagues on the evaluation method of different stage of HLS							1	1
Under-estimated and misunderstood by both students and other faculty members		1						1
Gain a superficial understanding through cursory observation (from subject credit and content)				1				1
Helpless (from student composition and course scheduling)				1				1
Total	1	1	2	5	4	3	2	18

In addition to the positive descriptors presented above, there were also 16 (7.51%) and 18 (8.45%) descriptors/short phrases that were classified into “Neutral” and “Negative” categories, respectively (see Table 4). Among the neutral descriptors, some indicated a feeling of “challenging” in teachers regarding to their GUR teaching (such as “a challenge to the teaching team”, “somewhat challenging”, and “meet the challenge”). Some indicated teachers’ perceived importance of motivating students in their subjects (such as “motivation of students is very important”; “keeping the interest of students is important”). The negative descriptors were much diversified. Some indicated teachers’ heavy workload in teaching SL and Chinese LCR subjects. Some suggested that few teachers lacked a sense of achievement through their teaching of GUR subjects, particularly the Chinese LCR subjects.

Teachers’ Observed Changes in Their Students after Studying Their Subjects

For the first open-ended question “have you observed any changes in your students after studying the GUR subject you taught in this semester?” 90 meaningful responses were collected. The detailed information is presented in Table 5. Among these responses, 83 (92.22%) were classified as positive responses. The positive responses were further coded into four themes, namely “Desired Graduate Attributes of PolyU,” “Intended Learning Outcomes of GUR Components,” “Broadening Knowledge/Horizon”, and “Others.” Remarkably, the theme “Desired Graduate Attributes of PolyU” was comprised of 47 (56.63%) responses, and these responses were further coded into five subthemes including effective communication, ethical leadership, critical thinking, problem solving, and lifelong learning. The theme “Intended Learning Outcomes of GUR Components” included 17 (18.89%) responses. These responses were further categorized into the intended learning outcomes of four GUR components including HLS, FS, SL, and LIPD. These findings indicated that teachers perceived a general alignment of their GUR subjects with the desired graduate attributes of PolyU and with their intended learning outcomes.

Specifically, among the 47 responses in the theme “Desired Graduate Attributes of PolyU,” 20 responses were related to the competence of effective communication. A detailed view of these responses revealed that teachers teaching different GUR subjects, particularly the subjects in LCR component, perceived that their students had become more confident in both oral and written communication through studying ELCR and CLCR subjects. The following written responses of teachers help to illustrate this benefit:

- “Some students were shy to share their ideas in front of their classmates. But they became more confident as the semester progressed. They learned to communicate well with their groupmates and applied different problem solving skills in the preparation of their presentation.”
- “Absolutely. I have seen some dramatic and very positive changes not just in students’ approach to academic research and writing, but also in their understanding of research ethics, the importance of developing effective communication skills, becoming confident speakers and effective presenters.”

The CAR and LIPD teachers also perceived students' improvements in their understanding of leadership and problem-solving skills after studying the related subjects, as illustrated by the following written responses:

- “Students become more reflective and mature. They started to realize that self-leadership is the first step for leading other people and they were willing to apply the knowledge and strategies learned in this subject (a CAR subject on service leadership) in their future university life.”
- “At the beginning of the semester, the students were quite passive in problem solving, no matter for the problems developed from class activities or the problem in group projects. ... [But] they became more mature in handling the conflicts among their group-mates after studying ‘relationship building, team building and conflict management’ and ‘social competence.’ At first, they might think the attribute of ‘social competence’ was a bit abstract to them. When they faced real and contextual problems and they could be able to apply the knowledge into the practice, they became clear about the attribute.”

With regard to the theme “Intended Learning Outcomes of GUR Components,” teachers teaching FS subjects in different faculties/schools noted that their FS subjects increased students' knowledge about their broad disciplines and related professions, as well as students' appreciation of their majors. Teachers teaching SL subjects observed an increase in empathy and social understanding of their students. Teachers wrote that through their subjects, students “become more mature and some develop a compassionate heart for the needy,” and “have developed a better understanding towards diversity.” These improvements in students can be further illustrated by the following responses of teachers:

- “Students from different disciplines and backgrounds can work together on a group project (in a FS subject). Each of them contributed to the project by employing their different backgrounds. It is a great subject as it helps the students to understand more about the construction industry and the responsibility of different professions.”
- “Students have developed a deeper appreciation to their chosen disciplines. They are more confident in tackling problems and issues pertaining to the study, exploration, and practice of their own disciplines.”

Table 5. Teachers observed changes in students after studying the GUR subject

Themes/Codes	FS	LIPD	ELCR	CLCR	CAR	SL	HLS	Total
Negative, Neutral, and Undecided Responses	1		1		4	1		7
							Subtotal	7 (7.78%)
Positive Responses								
Desired Graduate Attributes of PolyU								
<i>Effective Communication</i>								
Communication	1	5	7	6	1			20
<i>Ethical Leadership</i>								
Civic responsibility						6		6
Leadership	1	5				1		7
<i>Critical Thinking</i>								
Critical thinking			2	1	3			6

Table 5. (Continued)

Themes/Codes	FS	LIPD	ELCR	CLCR	CAR	SL	HLS	Total
<i>Problem Solving</i>								
Problem solving	1		1	1				3
<i>Lifelong Learning</i>								
Improve learning mode	1							1
Increase learning motivation				2	1			3
Lifelong learning			1					1
							<i>Subtotal</i>	<i>47 (52.22%)</i>
Intended Learning Outcomes of GUR Components								
<i>Healthy Lifestyle</i>								
Healthy lifestyle							5	5
<i>Freshman Seminar</i>								
Introduce students to their broad discipline and major	4							4
<i>Service Learning</i>								
Social caring and social understanding						4		4
<i>Leadership and Intrapersonal Development</i>								
Self-reflection	3							3
Self-awareness and self-understanding	1							1
							<i>Subtotal</i>	<i>17 (18.89%)</i>
Broadening Knowledge/Horizons								
Knowledge broadening						3		3
Eye-opening						1		1
Perspective broadening						1		1
							<i>Subtotal</i>	<i>5 (5.56%)</i>
Others								
Academic ethics		1						1
Approach to academic research		1						1
Chinese ability and cultural quality			1					1
Mature						1		1
Openness	1							1
Organization skills						1		1
Personal and professional development						1		1
Resilience						1		1
Social network				1				1
Confidence		1						1
Students' engagement in learning		1						1
Students' high interests and engagement							2	2
Teamwork skills and spirits						1		1
							<i>Subtotal</i>	<i>14 (15.56%)</i>
							<i>Subtotal</i>	<i>83 (92.22%)</i>
Total	7	17	14	10	17	18	7	90

Table 6. Difficulties/challenges teachers encountered in their teaching of the GUR subjects

Themes/Codes	FS	LIPD	LCR-E	LCR-C	CAR	SL	HL	Total
No challenge/major difficulty	1		1	4	3	2		11 (19.64%)
Teaching and Learning								
More efforts needed for class/lecture preparation		1					1	2
Student motivation and interests		2	3	2	1	1		9
Students' difficulty in team teaching	1							1
Online tutorial on academic integrity	1							1

Themes/Codes	FS	LIPD	LCR-E	LCR-C	CAR	SL	HL	Total
Teach students with different disciplinary knowledge	1				1	1		3
Teacher-student interaction	1							1
Need more guidance in assignments	1							1
Teach large class					1			1
Collaboration with the service partners						2		2
Learn SL subject offered by other disciplines						1		1
Teach students with a great variety of English and Mandarin proficiency	1	1	1					3
Great learning difference and achievements among students							1	1
							<i>Subtotal</i>	26 (46.43%)
Course Design and Scheduling								
Impact of shortened semester length		2				1		3
Course length							1	1
Morning class	2	1						3
Subject content				1				1
Subject registration and application						2		2
							<i>Subtotal</i>	10 (17.86%)
Others								
Lack of manpower					1			1
Language issue					1			1
Students' heavy workload			1		1	1		3
Students' study habits					1			1
Too big and unrealistic goal setting				1				1
Blackboard problem	1				1			2
							<i>Subtotal</i>	9 (16.07%)
Total	5	6	7	7	13	12	6	56

Difficulties/Challenges Teachers Encountered in Their Teaching of GUR Subjects

For the second question “Have you encountered any difficulties or challenges in your teaching of the GUR subject in this semester?” 56 meaningful responses were collected. Detailed information is presented in Table 6. Among the 56 responses, 11 (19.64%) indicated no challenge and problem encountered in teaching. The remaining 45 responses were coded into three themes: “Teaching and Learning,” “Course Design and Scheduling,” and “Others.” Around a half of the responses ($n = 26$, 46.43%) were coded under the theme “Teaching and Learning.” Several major challenges were identified under this theme, including student motivation and interests, teaching students from a variety of disciplines and with great variety of language proficiency, and students’ heavy workload. For example, one challenge expressed by the teachers was the lower motivation and engagement of some students in studying GUR subjects. Teachers perceived that students’ lower motivation might be due to their utilitarian mindset, heavy workload in undergraduate study and less knowledge about general education and the GUR. Meanwhile, some teachers perceived that it was difficult to teach students from different disciplines.

DISCUSSION

Through qualitative methods based on descriptors and open-ended questions, this study investigated views and experiences of teachers in a new general education program “General University Requirements” (GUR) which was an integral part of the new four-year undergraduate curriculum of PolyU. Several major observations could be made from the findings.

Firstly, the teachers gained positive feelings in their teaching. As indicated by the descriptors/short phrases given by the teachers, a lot of teachers developed a sense of achievement and satisfaction during their teaching. Some also felt rewarding and enjoyable. Teachers’ positive feelings were much important for the implementation and success of the GUR curriculum. A sense of achievement and satisfaction can generate high commitment to teaching as research indicated that a lack of job satisfaction was associated with serious withdrawing behavior of teachers and a sense of low achievement might lead to apathetic attitudes of teachers towards their teaching [15]. Particularly, in modern universities, the research-directed and specialized education dominated culture heavily undermined faculty’s devotion to teaching in general education [3, 16]. In this circumstance, a general education program that can promote teachers’ positive feelings could be regarded as successful and these positive feelings may further sustain and promote teachers’ good teaching.

Secondly, teachers perceived that the GUR curriculum benefitted the all-round development of students, particularly with respect to the desired graduate attributes of PolyU. The most significant impact was on communication skills. There might be three possible reasons for this learning outcome of the GUR. The first reason was the positive effects of LCR subjects that were specially designed to improve students’ language and communication skills. The second reason was the positive effects of the active and cooperative teaching and learning methods that were adopted in different GUR subjects, as identified from teachers’ responses. This was supported by the literature that cooperative learning was effective in promoting communication skills in adolescents and university students [17-19]. Students’ improvement in oral and written communication was also identified through active learning strategies [20]. The third reason was that students’ improvement in communication skills might be more easily observed by teachers in class than other attributes.

Thirdly, findings from the descriptors suggested some merits of the GUR curriculum, including rich and practical subject content, active and interactive pedagogy, as well as a close teacher-student bond. This is basically in line with the studies suggesting that good general education program might create community through collaborative learning and evaluating students’ learning through active experiences [21]. Fourthly, findings suggested several possibly pivotal challenges in implementation and teaching of general education. One critical challenge was the lower motivation of some students in studying general education subjects. This has been identified by the existing literature. Zhang’s [22] study indicated that one major challenge to teaching in general education in Chinese universities was how to arouse students’ motivation in learning these subjects in an environment in which undergraduates’ studies were dominated by specialized education. In universities in Hong Kong, students’ motivation in learning in general education might also be lower under the influence of the previous British model of undergraduate education [23] and the utilitarian philosophy of Chinese education. To promote students’ motivation and interests in learning

general education, two measures might be considered. One is to strengthen students' understanding of rationales of general education through all kinds of channels. Another is to incorporate more active and engaging teaching and learning methods in curriculum design to foster students' active and deep-level learning [24]. The second major challenge was students' increased study load under the structure of new four-year curriculum. This might diminish their engagement in study of GUR subjects. To tackle this problem, the university needs to reevaluate students' whole workload in the four-year curriculum and to take appropriate action to adjust students' workload.

The present study had three limitations. Firstly, although the use of descriptors could quickly gather teachers' general feelings and impressions, and could be analyzed in a more quantified way, this approach is limited when obtaining in-depth information about teachers' views. For example, in this study, few teachers used descriptors such as "disappointed" and "challenging" to describe their general feelings about the GUR subjects they taught. It would be hard to know in detail these feelings of teachers. Also, many teachers used descriptor "a sense of achievement" to describe their feelings. However, these descriptors could not reveal what achievement and in what context it was developed. Therefore, to enrich understanding of teachers' views, other qualitative studies such as focus group and individual interview should also be performed. For example, the use of repertory grid test may be helpful [25]. Secondly, although teachers were important observers of students' study and changes, some changes of students could not be easily observed by teachers in a short time such as improvements in critical thinking and ethical leadership. To gain a solidier understanding of the effects of the GUR, the method of objective outcome evaluation using validated instruments should be conducted to assess students' longitudinal changes during their studies of the GUR. Thirdly, to increase the trustworthy of the data collected from the teachers, views of other important stakeholders such as students could also be investigated.

Despite these limitations, the findings from the present study indicated a smooth implementation of the GUR curriculum and its positive effects on students' holistic development based on teachers' perspectives.

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Chapter 32

CONDOM USE, ALCOHOL, AND ALCOHOL-RELATED PERSONALITY CHANGES: A VIEW FROM RUSSIA

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ABSTRACT

Abortion rate in the former Soviet Union was reported to be the highest in the world, which was caused by insufficient availability of modern contraception and frequent non-use of condoms. Alcohol abuse and heavy binge drinking were generally perceived as factors contributing to the non-use of condoms. The association between alcohol abuse and high-risk sexual behavior is explainable within the scope of the alcohol myopia theory, according to which, alcohol reduces the cognitive capacity and causes people to focus on the cues that are most salient in the environment. The prevailing opinion in the literature is that heavy binge drinking and alcohol consumption at sexual relations are risk factors for the non-use of condoms. Moreover, the irresponsible behavior is apparently favored by slowly progressive personality changes developing under the influence of chronic alcohol abuse and heavy binge drinking.

Keywords: condoms, alcohol, alcohol-related dementia, sexually transmitted infection

INTRODUCTION

The abortion rate in the former Soviet Union has been reported to be the highest in the world [1], which was obviously caused not only by insufficient availability of modern contraception, but also by irresponsible behavior expressed by non-use of condoms. There is evidence that the abortion rate in Russia has declined dramatically during the last decade [2] and the heavy binge drinking seems to be declining as well [3, 4]. Current trends in abortion and contraception are beyond the scope of this review, which is trying to analyze

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psychological aspects of condom use in relation to the alcohol consumption. According to our observations from the Soviet past, individual carelessness acted in some cases synergistically with the alcohol abuse resulting e.g., in neglectful sabotage of the withdrawal method of contraception [5]. Condoms were of poor quality and imported ones were scarce, while Soviet-made condoms were notoriously thick and, at the same time, tore easily. Of oral contraceptives, mainly infecundin and bisecurin (both produced in Hungary), were known in the 1980s and they required prescription and were used infrequently. An unofficial directive from the late 1940s to enhance fertility was apparently behind it, effectuating e.g., poor quality and limited availability of contraceptive appliances, prohibition of abortions till 1955, as well as certain behavioral stereotypes.

ALCOHOL AND SEXUAL RISK BEHAVIOR

The association between alcohol consumption and high-risk sexual behavior is explainable within the scope of the alcohol myopia theory [6, 7]. According to this theory, alcohol reduces cognitive capacity and causes people to focus on the cues that are most salient in the environment. Less salient cues require additional cognitive resources to process and are, therefore, less likely to be acted upon by an inebriated person [7]. Furthermore, the effect of alcohol on cognition is supposed to be linear: the more intoxicated a person is, the more pronounced the “myopia” becomes [8]. In sexual encounters, the most salient cues are usually those that involve immediate sexual engagement. More distant cues, such as a suspicion that the partner could be infected by a sexually transmitted infection (STI), are less salient. Therefore, when intoxicated by alcohol, the ability to consider less salient cues decreases and the protective behavior is less likely to be enacted [7]. Interestingly, according to a study performed in women, alcohol directly increased the risk through weaker future condom use intentions, but indirectly decreased the risk for women who are higher in condom use self-efficacy through stronger in-the-moment condom negotiation intentions [9]. This is understandable as alcohol might help to overcome communicative barriers enabling a momentarily more decisive condom negotiation. According to other research, people intoxicated with alcohol reported more prudent intentions than sober ones, provided that the most salient features of the situation emphasized the risks of unprotected sex [10], which is also in accordance with the alcohol myopia theory.

The role of alcohol in the safer sex decision making is discussed in the literature, the prevailing opinion being that heavy binge drinking and alcohol consumption at sexual relations are risk factors for non-use of condoms [11-17]. Furthermore, heavy binge drinking is associated with severe hangover sometimes accompanied by a transitory depression, while depressive symptoms were demonstrated to be associated with unprotected sex [18]. In particular, alcohol use was reported to be significantly associated with unprotected sex among people with HIV/AIDS [19]. Moreover, sexual violence often coincides with heavy alcohol use [20, 21]; whereas use of condoms within the context of violence would be less probable than on average [22]. The topic alcohol and condom use is, however, not without controversy: drinking was reported to be inconsistently related to protective behaviors such as the condom use among college students and youth [23]. Some researchers did not find any relation between drinking and lower condom use [24]. There is an opinion that people who use

condoms when they are sober would use them also when they are drinking, while those who fail to use condoms when drinking probably also fail to use them when sober. However, empirical exceptions from this rule are recognized by the same researchers [7]. In the author's opinion, sexual behavior largely depends on personal features; but, taken on average, heavy binge drinking and alcohol consumption at sexual relations are risk factors for the non-use of condoms.

PERSONALITY TRAITS

Among various personality traits, the non-use of condoms is apparently favored by those developing as a result of prolonged alcohol abuse in relation to the deficit in frontal inhibitory control and cognitive impairment [25] i.e., beginning alcohol-related dementia, the latter overlapping with such entities as the frontal or prefrontal syndrome [25, 27] and organic personality disorder [28]. The cortical changes and symptoms of alcohol-related dementia are partly similar to those found in frontotemporal dementia [29], also known as Pick's disease [30]; demarcation of these conditions is beyond the scope of this review. It should be mentioned that the term "alcoholic dementia" used in Russia does not exactly correspond to the internationally used term "alcohol-related dementia" as nutritional deficiency, brain injury, e.g., old subdural hematoma [31], and chronic diseases, can play a role in its pathogenesis [32], especially, if chronic diseases are not adequately treated. Frontal lobe dysfunction is regarded to be a hallmark of alcohol dependence [33]. Among manifestations are social and personal neglect, lack of insight [29], faulty foresight, disinhibition in the affective and emotional sphere, disinhibition of instinctual behavior [26], impulsivity i.e., inability to forego small, immediate rewards for larger, delayed rewards [34]. This means that not only an immediate impact of alcohol intoxication is conducive to the non-use of condoms but also slowly progressive personality changes under the influence of chronic alcohol misuse, the heavy binge drinking in particular. Poor quality of alcoholic beverages i.e., other substances than ethanol may be of importance in this connection [35], which should become a topic of further toxicological research.

SURVEYS

It should be commented that data on alcohol consumption and use of condoms obtained by means of surveys in Russia are of limited validity. Many studies on the alcohol consumption in Russia e.g., [36-38] and other countries have been based on surveys. However, there are international differences in this regard. Evaluating results of surveys and opinion polls, it should be taken into account that these research tools have been largely discredited in Russia since the 1990s by means of widespread obtrusive solicitations to partake in different surveys, often asking for private information: in the streets, per telephone, and also by agents coming to private homes. Accordingly, people in Russia are generally "sick and tired" of questionnaires; and many of them tend to conceal their true opinions [39]. This pertains to opinion polls and scientific surveys, both being discredited. The tendency to discredit surveys and opinion polls can be seen as a continuation of the Soviet-time attitude,

when the “frame of mind of the working population” was monitored but the data were kept secret or published after a trimming to adjust them to the official ideology [39]. Answers to the questionnaires can be biased, especially in regard to such delicate topics as alcohol consumption and condom use. The statements with references to foreign literature, e.g., that the “earlier research has suggested that, at least for drinking behavior, reports (by adolescents) can be regarded as being generally valid” [36] are in fact not supported by the references to studies from West Europe [40], where the attitude to the surveys is probably more responsible.

Here follows an example. The study [36] was based on a survey carried out among adolescents 13-17 years old. “In terms of sexual behaviour, there was no difference in the odds ratios between binge drinking and non-binge drinking girls and boys for non-condom use during last sex” [36]. In other words, the adolescent binge drinking was reported to be not associated with “non-condom use during last sex”. However, it can be reasonably assumed that the study subjects answered the question “The last time you had sex did you or your partner use a condom?” [36] with “yes” without pondering that it is a research having potential significance for the public health etc. Respondents were probably unwilling to admit to the disapproved practices such as non-use of condoms.

CONCLUSION

In conclusion, according to the literature and our observations since the 1970s [3, 5], heavy binge drinking and alcohol consumption at sexual relations are risk factors for non-use of condoms and hence of STI and unintended pregnancy. Moreover, the chronic alcohol abuse and heavy binge drinking are apparently associated with progressive personality changes conducive to the irresponsible behavior including non-use of condoms.

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Chapter 33

FACTORS ASSOCIATED WITH SUICIDAL IDEATION AMONG IN-SCHOOL ADOLESCENTS, URUGUAY

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ABSTRACT

The study examined the prevalence of suicidal ideation and associated factors among students in Uruguay in grades 2 CB, 3 CB and 1BD in 2012 in a Global School-based Student Health Survey. Both bi-variate and multi-variate logistic regression analyses at 95% confidence level were conducted to assess associations between relevant predictor variables and suicidal ideation within the previous twelve months. Out of a total of 3,524 students who participated in the survey, 3,480 of them responded to the question on suicidal ideation among other questions. Overall, 12.3% of the students reported having had suicidal ideation in the previous 12 months (7.2% among males and 16.6% among females). Being anxious, lonely, having no close friends, bullied, physically attacked or involved in a physical fight just like smoking cigarettes or marijuana, alcohol consumption and abuse were all significantly associated with suicidal ideation. Having parents or guardians who did not understand the adolescent's problems and worries was also significantly associated with suicidal ideation. Interventions that address issues of violence against students, fighting with peers, initiation of smoking, alcohol and illicit drug use and those that encourage supportive roles of parents may reduce the risk of suicidal ideation.

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Keywords: suicidal ideation, prevalence, associated factors, Uruguay

INTRODUCTION

Suicide is a global public concern as more than 800,000 people commit it every year and for every suicide there are many more who attempt it [1]. A prior suicide attempt is the single most important risk factor for suicide in the general population [1]. In 2012, suicide was the second leading cause of death among 15-29 year olds worldwide and occurs throughout the life span [1, 2]. The Global Burden of Disease Study in 2004 estimated that suicide contributes to 6% of all deaths among young people aged 10-24 years worldwide [3]. Suicide does not just occur in high-income countries, but is a global phenomenon in all regions of the world [1]. Notably, in 2012, 75% of global suicides occurred in low and middle income countries [1, 2]. Previously, suicide rates were found to be low in Latin American countries, but that has been expected to change [4, 5]. In Uruguay, literature on suicide or suicidal ideation is scarce [6, 7]. Suicide is preventable with timely, evidence-based and often low-cost interventions [1, 8].

Suicidal ideation is both a strong risk factor and a stage in the suicidal process from planning to committing suicide [9, 10]. Although not all suicidal ideation materialize into suicide attempts or suicide, it is the first step on to the path to suicide [11]. A 60% rate of transition has been observed from suicidal ideation to first suicide attempt within the first year of ideation on-set [12]. Hence, prevention of suicidal ideation may in turn prevent suicide. To date, several environmental, psychosocial and behavioural factors have been associated with suicidal ideation, suicidal attempts and suicide. Physical, sexual and emotional abuses have also been associated with adolescent suicidal ideation and attempts [8, 12, 13].

In Brazil, the prevalence of suicidal ideation was observed to be 14.0% and was associated with violent behaviour, smoking and alcohol consumption [14]. Bullying of students was found to be common in Chile and was associated with suicidal ideation [14]. Family problems, social pressure, economic struggle, racism and violence introduce constant emotional stresses and challenges among Peruvian adolescents [14]. In addition, a strong association was observed between peer victimization and emotional, and mental stress among adolescents in Peru [14] may lead to having suicidal thoughts. The prevalence of suicidal ideation and its associated factors among junior high school students in Uruguay is unknown. Therefore, the objective of this study was to estimate the prevalence of suicidal ideation as well as identify factors associated with this phenomenon.

METHODS

The study was conducted in Uruguay (see Figure 1), a country on the east coast of South America, and south of Brazil and east of Argentina. The country consists of a low, rolling plain in the south and a low plateau in the north. Uruguay is a high-income country with a gross national income per capita of US\$ 16,810 in 2014 and there is no extreme poverty [15].



Source: <http://uruguaymap.facts.co/>.

Figure 1. Uruguay and its neighbouring countries.

The Global School based Health Survey (GSHS) was developed by the World Health Organization (WHO) in collaboration with UNICEF, UNESCO and UNAIDS with technical assistance from Centers for Diseases Control and Prevention, Atlanta, Georgia, United States with the aim of providing data on health and social behaviours among school-going adolescent students. This paper presents results of a secondary analysis of the data obtained from the GSHS conducted in 2012 students in Uruguay. The survey measured alcohol use; dietary behaviours; drug use; hygiene; mental health; physical activity; protective factors; sexual behaviours; tobacco use; violence and unintentional injury.

The Uruguay GSHS used a two-stage cluster sampling design, in which in the first stage, schools were selected with probability proportional to enrolment size. In the second stage, classes were randomly selected and all students in selected classes were eligible to participate. The school response rate was 100%, the student response rate was 77% and the overall response rate was 77%. A total of 3,524 students participated in this survey. Students self-reported their responses to each question on a computer-scannable answer sheet.

Variables that were used for our analysis included socio-demographic characteristics, having seriously considered attempting suicide, smoking, loneliness, parental understanding, involvement in a fight, truancy, anxiety, close friendship and food security. Assessments of associations were conducted using both bi-variate and multivariate logistic regression analyses with 95% confidence intervals using SPSS Version 16.0.0.

RESULTS

A total of 3,524 students participated in the Uruguay 2012 Global School-based Students Health Survey, of which 46.0% were males. Most of the students were either of age 14 years (30.1%) or 15 years (30.2%). About 1 in 4 students (26.7%) missed classes or school without permission. Overall, 18.6% of students reported being bullied and 16.0% were physically attacked. Significantly, more males (38.4%) than females (17.2%) were involved in a physical fight ($p < 0.001$). Altogether, 13.1% of the students reported that they smoked cigarettes 30 days prior to the survey, and 12.7% reported that they smoked marijuana in their lifetime. About half (48.6%) of both males and females consumed alcohol, while 28.9% abused it. Overall, 60.9% of students indicated that their parents or guardians understood their problems and worries. The prevalence of suicidal ideation was 12.3% with significantly more female students (16.6%) than male students (7.2%) ever seriously considered attempting suicide ($p < 0.001$). These results are shown in Table 1.

Table 2 shows factors that were associated with suicidal ideation. All the factors that were considered in the analysis were significantly associated with suicidal ideation in bivariate analyses. However, in multivariate analysis, food security was no longer significantly associated with suicidal ideation.

Compared to students who were aged 16 years or older, students of age less than 14 years (AOR = 0.77, 95% CI [0.73, 0.81]) and of age 15 years (AOR = 0.95, 95% CI [0.91, 0.99]) were less likely to seriously consider attempting suicide; while students of age 14 years (AOR = 1.23, 95% CI [1.18, 1.28]) were more likely to have suicidal ideation.

Male students were 41% (AOR=0.59, 95% CI [0.58, 0.61]) less likely to have suicidal ideation than female students.

In relation to anxiety and loneliness, students who were worried about something that they could not sleep at night were 75% (AOR = 1.75, 95% CI [1.68, 1.81]) more likely to have suicidal ideation than students who were not anxious. Meanwhile, students who felt lonely were 2.03 (95% CI [1.96, 2.09]) times more likely to have suicidal ideation than students who did not.

Students who did not have close friends were more likely to have suicidal ideation than those who had close friends (AOR = 1.11, 95% CI [1.04, 1.18]). Compared to students who did not miss classes or school without permission, students who were truant were 15% (AOR = 1.15, 95% CI [1.12, 1.18]) more likely to seriously consider attempting suicide.

Being bullied, physically attacked and involvement in a physical fight were significantly associated with suicidal ideation. Students who were bullied were 39% (AOR = 1.39, 95% CI [1.35, 1.43]) more likely to have suicidal ideation compared to students who were not bullied. Compared to students who were not physically attacked, those who were attacked were 1.38 (95% CI [1.35, 1.42]) times more likely to have suicidal ideation. Students who

were involved in a physical fight were 14% (AOR = 1.14, 95% CI [1.11, 1.17]) more likely to have suicidal ideation compared to those who were not in a physical fight.

Table 1. Distribution of factors considered in the analysis by gender among students in the Uruguay 2012 Global School-based Health Survey

Factor	Total n ¹ (%) ²	Males n ¹ (%) ²	Females n ¹ (%) ²
Age			
<14	740 (22.8)	350 (23.1)	387 (22.7)
14	1073 (30.1)	503 (29.5)	563 (30.6)
15	1070 (30.2)	502 (31.3)	561 (29.2)
16+	605 (17.0)	256 (16.2)	344 (17.6)
Gender			
Male	1621 (46.0)	-	-
Female	1867 (54.0)	-	-
Food security			
No	53 (1.5)	28 (1.7)	25 (1.4)
Yes	3432 (98.5)	1579 (98.3)	1819 (98.6)
Anxiety			
Yes	192 (5.8)	50 (3.2)	140 (8.1)
No	3278 (94.2)	1540 (96.8)	1705 (91.9)
Loneliness			
Yes	246 (7.1)	64 (4.1)	181 (9.8)
No	3247 (92.9)	1545 (95.9)	1668 (90.2)
Close friends			
No	107 (3.1)	55 (3.7)	49 (2.6)
Yes	3373 (96.9)	1541 (96.3)	1800 (97.4)
Truancy			
Yes	928 (26.7)	440 (27.3)	483 (26.3)
No	2544 (73.3)	1153 (72.7)	1362 (73.7)
Bullied			
Yes	635 (18.6)	271 (17.2)	359 (20.0)
No	2780 (81.4)	1297 (82.8)	1453 (80.0)
Attacked			
Yes	556 (16.0)	297 (18.0)	251 (14.1)
No	2949 (84.0)	1311 (82.0)	1610 (85.9)
In a fight			
Yes	955 (27.0)	633 (38.4)	310 (17.2)
No	2565 (73.0)	985 (61.6)	1556 (82.8)
Smoked cigarettes			
Yes	445 (13.1)	155 (10.1)	290 (15.8)
No	3022 (86.9)	1427 (89.9)	1563 (84.2)
Smoked marijuana			
Yes	469 (12.7)	242 (14.4)	227 (11.5)
No	3024 (87.3)	1362 (85.6)	1626 (88.5)
Consumed alcohol			
Yes	1641 (48.6)	795 (51.1)	833 (46.8)
No	1697 (51.4)	743 (48.9)	933 (53.2)
Abused alcohol			
Yes	995 (28.9)	455 (28.9)	531 (29.0)
No	2408 (71.1)	1102 (71.1)	1280 (71.0)
Parental understanding			
Yes	2102 (60.9)	980 (62.0)	1104 (60.1)
No	1342 (39.1)	598 (38.0)	727 (39.9)
Suicidal ideation			
Yes	422 (12.3)	117 (7.2)	302 (16.6)
No	3058 (87.7)	1477 (92.8)	1549 (83.4)

¹ unweighted frequencies. ² weighted percents.

Table 2. Factors associated with suicidal ideation among students in the Uruguay 2012 Global School-based Health Survey

Factor	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Age (years)		
<14	0.56 (0.54, 0.58)	0.77 (0.73, 0.81)
14	1.13 (1.10, 1.17)	1.23 (1.18, 1.28)
15	1.04 (1.01, 1.07)	0.95 (0.91, 0.99)
16+	1	1
Gender		
Male	0.62 (0.61, 0.64)	0.59 (0.58, 0.61)
Female	1	1
Food security		
No	1.54 (1.45, 1.63)	-
Yes	1	
Anxiety		
Yes	2.72 (2.65, 2.80)	1.75 (1.68, 1.81)
No	1	1
Loneliness		
Yes	3.04 (2.96, 3.12)	2.03 (1.96, 2.09)
No	1	1
Close friends		
No	1.33 (1.27, 1.39)	1.11 (1.04, 1.18)
Yes	1	1
Truancy		
Yes	1.50 (1.47, 1.53)	1.15 (1.12, 1.18)
No	1	1
Bullied		
Yes	1.71 (1.67, 1.74)	1.39 (1.35, 1.43)
No	1	1
Attacked		
Yes	1.89 (1.85, 1.93)	1.38 (1.35, 1.42)
No	1	1
In a fight		
Yes	1.34 (1.31, 1.36)	1.14 (1.11, 1.17)
No	1	1
Smoked cigarettes		
Yes	2.16 (2.11, 2.21)	1.61 (1.56, 1.66)
No	1	1
Smoked marijuana		
Yes	1.86 (1.82, 1.90)	1.08 (1.04, 1.12)
No	1	1
Consumed alcohol		
Yes	1.61 (1.57, 1.64)	1.22 (1.19, 1.25)
No	1	1
Abused alcohol		
Yes	1.66 (1.63, 1.70)	1.16 (1.13, 1.19)
No	1	1
Parental understanding		
Yes	0.62 (0.61, 0.63)	0.81 (0.79, 0.83)
No	1	1

Smoking (cigarettes (AOR = 1.61, 95% CI [1.56, 1.66]); marijuana (AOR = 1.08, 95% CI [1.04, 1.12]) were significantly associated with suicidal ideation. Students who consumed alcohol were 22% (AOR = 1.22, 95% CI [1.19, 1.25]) more likely to have suicidal ideation compared to students who did not consume alcohol. Meanwhile, students who abused alcohol were 1.16 (95% CI [1.13, 1.19]) times more likely to have suicidal ideation compared to those who did not abuse alcohol.

Students who reported that their parents or guardians understood their problems and worries were 19% (AOR = 0.81, 95% CI [0.79, 0.83]) less likely to seriously consider attempting suicide.

DISCUSSION

In this study, the prevalence of suicidal ideation was 12.3% which is low when comparing with the result from China [16]. The prevalence of suicidal ideation among males was about half that among females (7.2% vs 16.6%). This finding was also observed in a similar study done elsewhere [14]. It is, however, surprising that this is the case, as globally, actual suicide deaths occur more among males than females [16].

With regard to age, the study found that there was an association between age group and suicidal ideation which indicates some unequal risk of suicidal ideation among different aged adolescents. Students who were less than 14 years of age and those that were 15 years of age were less likely to consider attempting suicide. This finding contradicts the findings in the Peru study which did not find any association between age and suicidal ideation and therefore reported an equal risk of suicidal ideation among different aged adolescents [14, 17]. The study by Muula et al. found that adolescents who were less than 14 years of age were more likely to consider committing suicide [11]. This finding and our finding are different from the findings of Liu et. al. who found increasing age to be correlated with suicidal behaviour [16]. We are, however, unable to offer a plausible explanation as why students who were 14 years of age (compared to other age groups in the study) were less likely to have suicidal ideation because in most cases, it is the slightly older adolescents who would think of committing suicide more than the younger ones. Muula et al. in their paper explain that younger children may not have developed problem solving skills and as such they are more likely to consider committing suicide than the older ones [11].

In this study, being anxious, lonely, having no close friends, missing classes or school without permission were all associated with suicidal ideation. Being bullied, physically attacked and involvement in a physical fight were all significantly associated with suicidal ideation. Students who were bullied were 39% more likely to consider attempting suicide and those involved in physical fights were 14% more likely to have suicidal ideation. This indicates that adolescent violence and bullying is common in Uruguay. In a similar study among Brazilian adolescents, being involved in a physical fight was associated with a higher rate of suicidal ideation [14]. Similarly, being bullied has been seen as an important risk factor of suicidal ideation in study findings in other countries [11, 14]. This indicates that physical and emotional violence against adolescents is related to suicidal ideation.

The study revealed a significant association between smoking and suicidal ideation. Similarly, another study also observed cigarette smoking as a risk factor for suicidal ideation [14]. Alcohol consumption and abuse were both associated with suicidal ideation. This association has also been reported in a similar study [11]. Students who consumed alcohol were 22% more likely to consider attempting suicide. We therefore assume that preventing initiation of smoking, alcohol consumption among adolescents in Uruguay may in turn prevent suicide.

We observed that students whose parents or guardians understood their problems and worries were 19% less likely to consider committing suicide. A similar finding has been reported Randall et al. [18]. Poor parenting may cause physical and emotional stress as well as impaired social and cognitive development [19-21].

In conclusion, although the prevalence of suicidal ideation was found to be relatively low, a number of factors were significantly associated with this phenomenon among the participants in the study area. We propose that preventive interventions measures of suicidal behaviours that have been found to be significantly associated with suicidal ideation be put in place. These should focus on prevention of violence against adolescents, encouraging peer relationships and controlling health risk behaviours, particularly initiation of smoking, alcohol use and abuse

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Chapter 34

PREVALENCE AND FACTORS FOR SUICIDE IDEATION AMONG ADOLESCENTS ATTENDING SCHOOL IN GHANA

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ABSTRACT

Suicide in adolescents has become a major health concern for many countries especially African countries where conditions of living are generally poor. However, there is paucity of data regarding the prevalence of suicidal ideation and its correlates in most African countries including Ghana where the vice is on the rise. The purpose of this study was to determine the prevalence and correlates of suicidal ideation among adolescents in grades SS1-3 in Ghana. Analyses are based on the 2012 Global School-Based student Health Survey (GSHS) conducted in Ghana. Logistic regression analyses were conducted to determine associations between the factors (i.e., food security, current alcohol use, bullying victimization, loneliness, anxiety, having no close friends, missed school, parental understanding, smoking, physical fights, physical attacks) and suicidal ideation for all students that participated in the study. The prevalence rate for suicidal ideation among adolescents (N = 1648) attending schools was 20%. Significantly (p < 0.001) more females (21.7%) contemplated on committing suicide than males (19.2%). Being of age <14 or 15 years and male gender were protective against suicidal ideation.

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No food security, current alcohol abuse, bullying victimization, loneliness, anxiety, having no close friends, truancy, parental understanding, smoking, physical fights, and physical attacks, were all found to be risk factors of suicidal ideation. The prevalence of suicidal ideation in Ghana was high and could lead to high suicide rates. Therefore, there is an urgent need for additional studies in this area to greatly up regulate suicide prevention efforts.

Keywords: suicidal ideation, adolescents, risk factors, Ghana

INTRODUCTION

Suicidal ideation is a thought about how to kill oneself, which can range from a detailed plan to a feeling consideration and does not include the final act of killing oneself [1]. Approximately one million people die from suicide every year; which translates in a “global” mortality rate of 16 per 100,000, or one death per 40 seconds [1]. Pompili et al. [2] reported that suicide is now a major health concern for many countries. Across the world, it is estimated that 71,000 adolescents die due to suicide and 40 times as many adolescents attempt to commit suicide, a fact that categorises suicide as the third leading cause of death among adolescents [1].

In Ghana, the Ghana Statistical Service’s report of 2013 shows 18,938 deaths recorded and categorised as accidents, homicide, or suicide within 12 months preceding the census which was conducted in 2010 [3]. It should be stated that official statistics on adolescent suicide in Ghana is lacking. The data that seems to be available concerns deaths amounting to 6467 adolescents categorised under accidents, violence, homicide or suicide [3]. A study conducted by Adinkrah [4] using police recorded information, shows 9.1% suicides among adolescents. Although this information on suicides appears to be unreliable, it can act as an indication to the implication that, adolescent suicide cases are on the rise in Ghana [5]. More reliable data were determined in the Global School-based Student Health Survey (GSHS) conducted in 2012 in Ghana, where 19.0% adolescents reported to have had suicidal thoughts in the previous 12 months [6]. In studies done elsewhere in Africa, the prevalence rates of suicide ideation have been found to be high [7, 8]. In order to reduce these prevalence rates, investigation of risk factors is cardinal.

The risk factors for suicidal ideation have been categorised as follows: psychiatric, biological, social, environmental and factors related to an individual’s life history [9]. The effects of these factors tend to vary according to countries. In a study conducted in 2015 by Quarshie et al. [10], on adolescent suicide in Ghana, five subthemes were used as key drivers in the motivation for this adolescent suicidal behaviours, these were; psychological factors, conflictual relationships, loss of significant other, poor school work, and socio-economic factors. However, there are differences in the prevalence of suicide ideation and factors associated to it across gender, race cultures and countries in the world [11].

There are few quantitative studies that have been conducted on the magnitude of suicide ideation among adolescents attending school in Ghana. Furthermore, it sets out to add to the knowledge over the factors associated with suicide ideation. It is hoped that the outcome of this study will serve a heuristic and seminal function for much broader socio-demographic

and epidemiological enquiry into the phenomenon aimed at uncovering the nuances regarding the factors and prevalence rate of suicidal ideation in Ghana among in-school adolescents.

METHODS

The study utilised secondary data from the 2012 Ghana Global School Health Survey (GSHS) organised by World Health Organisation (WHO) and Centres for Disease Control and Prevention (CDC). This was a school-based survey of students in grades SS1-3, which are mostly attended by students aged 13-17 years. The study used a two-stage cluster sample design in order to produce data representative of all students in grades SS1-3. In the first stage, schools were selected with probability proportional to enrolment size, while at the second stage, classes were randomly selected and all students in selected classes were eligible to participate. The school response rate was 100%, the student response rate was 82%, and the overall response rate was 82%. A total of 1648 students participated in the Ghana GSHS.

Data analysis was conducted using SPSS version 16. The variables that were used for analysis included sociodemographic characteristics, having considered suicide in the last 12 months, smoking, loneliness, parental understanding, involvement in a fight, whether someone was attacked or not, whether bullied or not, truancy, anxiety, alcohol abuse, alcohol intake, close friendship and food security. The frequencies were weighted. The determination of associations between the independent variables and dependent variable were done by using univariate and multivariate logistic regression analysis at 95% Confidence Interval (CI).

RESULTS

The total number of students that participated in the survey was 1,648, out of which 52.4% were males. Out of the total number of participants, 27.5% were aged less than 14 years, and 31.3% were 16 years or older. Table 1 presents selected characteristics of the study population. The analysis of these characteristics showed that 15.2% of the students did not have enough food. It was also found that 13.0% were anxious. Students who reported to have been lonely accounted for 13.2%. Students who reported truancy were 41.9%, and those bullied and attacked accounted for 62.1% and 48.5%, respectively. Among the students, it was also found that 10.0% and 48.4% smoked and were involved in a fight, respectively. The prevalence of suicidal ideation was 20.6% (21.7% among females and 19.2% among males).

Table 2 indicates variables that were associated with suicidal ideation. Age was associated with suicide ideation. Those students, who were less than 14 years old, were 12% less likely to contemplate on committing suicide than those aged 16 years or older. While those that were 15 years old were 7% less likely to think about committing suicide than those aged 16 years or older.

Male students were 7% less likely to entertain thoughts about suicide than females. Students with challenges with food security were 9% more likely to have suicide ideas compared to those without food challenges. Students with anxiety were 37% more likely to have thoughts about suicide compared to those without anxiety. Those students who were lonely were 39% more likely to contemplate on committing suicide. In addition to this,

students who were truant and had no close friends were 4% and 28%, respectively, more likely to have suicidal ideation.

Table 1. Distribution of factors considered in the analysis by gender among adolescents attending school in Ghana, 2012

Factor	Total n ¹ (%) ²	Males n ¹ (%) ²	Females n ¹ (%) ²
Age			
<14	481 (27.5)	235 (25.2)	240 (30.1)
14	351 (21.2)	172 (19.4)	175 (23.3)
15	318 (20.0)	167 (19.7)	150 (20.6)
16+	486 (31.3)	290 (35.6)	187 (26.0)
Gender			
Male	867 (52.4)	-	-
Female	754 (47.6)	-	-
Food security			
No	246 (15.2)	128 (15.2)	114 (15.2)
Yes	1394 (84.8)	733 (84.8)	638 (84.8)
Anxiety			
Yes	213 (13.0)	112 (13.4)	98 (12.7)
No	1424 (87.0)	748 (86.6)	652 (87.3)
Loneliness			
Yes	218 (13.2)	111 (12.9)	105 (13.6)
No	1421 (86.8)	752 (87.1)	649 (86.4)
Close friends			
No	182 (11.3)	85 (9.7)	93 (13.0)
Yes	1437 (88.7)	775 (90.3)	641 (87.0)
Truancy			
Yes	676 (41.9)	340 (40.1)	322 (43.3)
No	941 (58.1)	507 (59.9)	422 (56.7)
Bullied			
Yes	905 (62.1)	486 (61.4)	405 (63.1)
No	548 (37.9)	305 (38.6)	234 (36.9)
Attacked			
Yes	791 (48.5)	411 (48.2)	369 (49.0)
No	840 (51.5)	445 (51.8)	380 (51.0)
In a fight			
Yes	800 (48.4)	444 (50.5)	345 (46.2)
No	844 (51.6)	423 (49.5)	405 (53.8)
Smoked cigarettes			
Yes	150 (10.0)	83 (10.4)	62 (9.2)
No	1436 (90.0)	756 (89.6)	660 (90.8)
Parental understanding			
Yes	526 (31.9)	283 (32.9)	235 (31.0)
No	1096 (68.1)	569 (67.1)	508 (69.0)
Abused Alcohol			
Yes	152 (9.8)	87 (10.6)	62 (8.8)
No	1398 (90.2)	734 (89.4)	643 (91.2)
Consumed alcohol			
Yes	235 (15.9)	135 (17.3)	97 (14.3)
No	1260 (84.1)	654 (82.7)	586 (85.7)
Suicidal ideation			
Yes	328 (20.6)	161 (19.2)	159 (21.7)
No	1283 (79.4)	687 (80.8)	578 (78.3)

¹ unweighted frequencies. ² weighted percents.

Table 2. Factors associated with suicidal ideation among adolescents attending school in Ghana, 2012

Factor	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Age (years)		
<14	0.87 (0.86, 0.87)	0.88 (0.87, 0.89)
14	0.92 (0.91, 0.92)	1.01 (1.00, 1.02)*
15	0.94 (0.93, 0.95)	0.93 (0.92, 0.94)
16+	1	1
Gender		
Male	0.93 (0.92, 0.93)	0.93 (0.93, 0.94)
Female	1	1
Food security		
No	1.31 (1.31, 1.32)	1.09 (1.08, 1.10)
Yes	1	1
Anxiety		
Yes	1.60 (1.59, 1.61)	1.37 (1.36, 1.38)
No	1	1
Loneliness		
Yes	1.37 (1.36, 1.38)	1.39 (1.38, 1.40)
No	1	1
Close friends		
No	1.04 (1.03, 1.04)	1.04 (1.03, 1.04)
Yes	1	1
Truancy		
Yes	1.48 (1.48, 1.49)	1.28 (1.27, 1.28)
No	1	1
Bullied		
Yes	1.34 (1.33, 1.34)	1.10 (1.10, 1.11)
No	1	1
Attacked		
Yes	1.32 (1.32, 1.33)	1.06 (1.05, 1.06)
No	1	1
In a fight		
Yes	1.26 (1.25, 1.26)	1.11 (1.11, 1.12)
No	1	1
Smoked cigarettes		
Yes	1.81 (1.80, 1.82)	1.34 (1.33, 1.35)
No	1	1
Parental understanding		
Yes	1.00 (0.99, 1.00)	1.09 (1.08, 1.09)
No	1	1
Abused alcohol		
Yes	1.77 (1.76, 1.78)	1.16 (1.14, 1.17)
No	1	1
Consumed alcohol		
Yes	1.65 (1.64, 1.66)	1.11 (1.10, 1.12)
No	1	1

*P = 0.068.

Bullied and attacked students were 10% and 6%, respectively, more likely to think about suicide than those who were not bullied or attacked, while those that smoked and involved in a fight were 34% and 11%, respectively, more likely to have thoughts about suicide than those that did not smoke and got involved in a fight. Students who abused alcohol and those that consumed alcohol in the previous 30 days to the survey were 16% and 11%, respectively, more likely to have suicidal thoughts than those who did not abuse alcohol and consume alcohol in the previous 30 days to the survey, and students without parental understanding

were found to be 9% more likely to have suicidal ideas than those with parental understanding.

DISCUSSION

This study found that the prevalence of suicidal ideation was 20.6%. Out of this, 21.7% females reported to have thought about committing suicide compared to 19.2% males who contemplated on suicide. The finding of this study is similar to what Omigbodun et al. [6] reported of 20% suicidal ideation prevalence among Nigerian students. In another study done in Zimbabwe [12], the prevalence was found to be 21.6% which is also similar to the finding of the present study.

According to a study done by Muula et al. [13] among Zambian students, suicidal ideation prevalence was established to be 32.2%, a finding that is higher than the finding of the present study. However, the prevalence of suicidal ideation among in-school adolescents in Ghana is still high at 20.6%, and there is need for proper measures to be put in place to reduce the vice.

In our study, students less than 14 years old and those aged 15 years were less likely to think about committing suicide than those aged 16 years old or older. This finding is similar to Liu et al. [14] and Rudatsikira et al. [15] findings who reported that the odds of suicidal ideation increased with increasing age. In another study done in Zambia by Muula et al. [13], they found that adolescents less than 14 years old were more likely to have considered committing suicide than those aged 16 years old or older, which is a direct opposite of our finding. The explanation could be that, the Zambian study enrolled more students who were less than 14 years of age. In addition to this, the period around 12-14 years in children is very critical, as this is when hormonal influence gets to be strong; therefore, more students are likely to be frustrated with little things which might drive them to wanting to take their own lives.

The finding that males were less likely to think about suicide than females differs with the results obtained by Muula et al. [13] who reported that males were more likely to consider committing suicide than female students. Nevertheless, Liu et al. [14] found a similar result to what the present study established, where it was found that females were more likely to seriously consider committing suicide than males. This is also supported by Ovuga et al. [16] who reported females to have had higher chances of committing suicide than males in two rural districts of Uganda. Despite having more females thinking about suicide in the present study and many others, it is the males who top in terms of deaths due to suicide [17]. This situation could be attributed to the differences in temperaments between males and females. Usually, females will just talk or think about suicide, but are not courageous enough to undertake the vice.

We also found that adolescents who had challenges with food were more likely to think about suicide than those without these challenges. This finding is congruent with a study done in Benin by Randall et al [18], who reported higher chances of those with food challenges to have had suicidal thoughts. It can therefore, be speculated that hunger can also lead to serious considerations of committing suicide due to its adverse health effects. However, many studies have not established the association of food security and suicidal ideation.

Our study found that students who reported anxiety were more likely to seriously consider committing suicide than those that did not report anxiety. This finding is similar to the finding by Omigbdun et al. [7] and Rudatsikira et al. [12] who found that anxiety was positively associated with suicidal ideation. However, the finding of the present study is contrary to the results of Dunlavy et al. [19] who reported that there was no association between anxiety and suicidal ideation among the school attending adolescents in Dar es Salaam, Tanzania. The reasons for this disparity are speculated to be due to the fact that, anxiety in the study by Dunlavy et al. [19] was not operationalised to capture the somatic experience and also, anxiety alone was not sufficient to warrant the association. In addition to this, the definition of anxiety in Dunlavy et al.'s study was different from the present study.

Loneliness was also found to be a risk factor in the present study. Students who reported loneliness were more likely to consider suicide than those who were not lonely. The finding is in tandem with Rudatsikira et al. [23] who found that loneliness was positively associated with suicide ideation. However, the finding from the present study contradicts the finding of Muula et al. [13] and Dunlavy [19], who reported loneliness to be negatively associated to suicide ideation. The difference in the findings may be as a result of the religious differences that exist among the countries. In some religions (i.e., Christianity), difficulties might strengthen them to fight on till a break through comes. In addition to this, they will even get examples from their religious figures who could have gone through difficulties and who could have led lonely lives. Therefore, students from such backgrounds will not entertain thoughts of suicide because it would be sinning against their supreme being.

Adolescents who had close friends were less likely to have thoughts about suicide. This result from the present study is similar to other studies done by Rudatsikira et al. [12] and Dunlavy et al. [19], who reported that adolescents who had no close friends were significantly more likely to have had suicidal thoughts. Nevertheless, Randall et al. [18] reported a higher chance of suicidal thoughts among those adolescents with close friends. This may be due to the violence acts that are very common in Benin where the study was conducted. The violent acts are normally done in gangs or groups who may all be friends.

Students who reported truancy in the present study were more likely to have suicidal thoughts than those who did not. This finding is not in agreement with the results obtained by Dunlavy et al. [19] who found that those students who reported truancy were less likely to consider committing suicide than those that did not report truancy. The disparity between the results could be explained by the differences in the prevalence rates of factors such as bullying, attacks, hunger, and alcohol abuses, which were lower in the study done by Dunlavy et al. [19] than the present study. The factors that have been listed above have been found to greatly influence truancy among adolescents according to Siziya et al. [20]. Therefore, it can be speculated that, in the event where truancy is not significantly associated with suicide ideation, those factors could be missing or having little influence in causing someone to have suicidal thoughts.

It was also observed in the present study that adolescents who were bullied were more likely to contemplate on suicide than those that were not bullied. The result is consistent with the results obtained from studies done by Rudatsikira et al. [21] and Omigbodun et al. [7] who reported higher chances of those bullied students thinking about suicide than those that were not. However, Dunlavy et al. [20] found no association between being bullied and having thoughts of suicide. This could be attributed to the lower prevalence rates of bullying

in that Tanzanian study done by Dunlavy et al. [20]. Another reason could be due to the differences in bullying rates by geography [21, 22].

Another finding from the present study was that being attacked was found to increase the chances of one thinking about suicide. This finding is similar to those found by Omigbodun et al. [7], Randall et al. [18] and Rudatsikira et al. [15] who established that being attacked was likely to increase the chances of one thinking about committing suicide. This finding might be due to the fact that, some attacks might leave the victims injured or raped as can be the case for the female students. This might make students to think about committing suicide to cover up the shame of rape, or avoid perpetual pain due to the injuries from the attacks.

Our study also found that students that smoked were more likely to consider committing suicide than those that did not report to have smoked in the previous 30 days. The finding is consistent with Rudatsikira et al. [15, 23], Muula et al. [13] and Omigbodun et al. [7] who reported an association between smoking and having thoughts about suicide. Generally, smoking makes people do things they can't do when they are normal, for young minds such as for these students, smoking may lead them to be involved in sexual activities. As a result, they may contract diseases such as HIV and STIs. These are some of the reasons that may cause students who may have been smoking to think about suicide. Others might even be involved in crime. Out of fear to be shamed or jailed, they might start thinking about committing suicide.

Adolescents in the present study that were involved in a fight were more likely to think about committing suicide than those that did not get involved in any fight. However, this finding differs from the finding by Randall et al. [18], who found that students, who were involved in a fight, were less likely to think about committing suicide than those that did not report getting into a fight. The difference may be attributed to the fact that, students that fight usually relieve their psychological pain, especially when they manage to beat the opponent. Therefore, the thoughts of being a hero override thoughts of wanting to end their lives. The opposite is true when they are involved in fights and lose.

In the present study, students with parental understanding were surprisingly found to be more likely to think about committing suicide than those without parental understanding. This is contrary to a study conducted in Guyana by Rudatsikira et al. [23] who reported students having parental understanding to be less likely to consider committing suicide compared to those that lacked the parental understanding. Other studies have also shown that parent-child conflict is one of the most common precipitating factors of suicide attempts [24]. In another study done by Heider et al. [25], they reported that among adults in the European Study of Epidemiology of Mental Disorders project, suicidality was associated with low parental care. Therefore, parental understanding is cardinal in reducing suicidal thoughts among adolescents in many other studies despite it not being an important positive factor in the present study.

Parents normally offer a listening ear that a child would not get from anyone in society; hence many would be comforted and abort all the thoughts of killing one-self. Despite all the good reasons of parental understanding, we have a certain type of parental understanding that can lead or encourage children/adolescents to entertain these suicidal thoughts. Such a type would be influenced by cultural or religious beliefs that may offer suicide as a solution whenever one is aggrieved. In addition to this, suicide is like a reward for whomever, dares to take such a path. These are some of the factors that could have been at play to produce such a result in the present study, where parental understanding was found not to be protective against suicidal thoughts like many studies have suggested or found.

Alcohol abuse was found to be significantly associated with suicidal ideation. Students that abused alcohol were more likely to think about committing suicide than those that didn't abuse alcohol. This finding is consistent with results obtained by Rudatsikira et al. [12, 15, 23] who reported that students that were in the habit of abusing alcohol were more likely to seriously consider suicide than those that didn't. An explanation to this could be that alcohol is a depressant, and many adolescents take alcohol in times of confusion as a result of social issues. After getting sober, reality dawns and are faced with more problems than ever, a recipe that is more likely to lead them to end their lives.

In conclusion, the prevalence of suicidal ideation in Ghana was high and could lead to high suicide rates. Therefore, with this understanding of the factors that are likely to influence the suicidal ideation among in-school adolescents in Ghana, strategies aimed at reducing adolescent suicide cases can focus on these factors.

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Chapter 35

PREVALENCE AND CORRELATES FOR SUICIDAL IDEATION AMONG ADOLESCENTS IN SCHOOL IN GAZA STRIP

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ABSTRACT

Suicidal ideation is considered to be an important precursor to later attempted and completed suicide. Suicide among children, even in developed nations, has been a neglected issue until recently. This situation has created a paucity of data on suicidal ideation, attempted suicide and suicide among adolescents in such populations. The objectives of the study were to estimate the prevalence of suicidal ideation as well as to determine factors associated with suicidal ideation among in-school adolescents in Gaza strip. We conducted secondary analysis of the Gaza strip Global School-Based Health Survey-2010 data. Assessments of associations were conducted through both weighted bivariate and multivariate logistic regression analyses at 95% confidence interval. The study recruited 2,607 students. Close to one fifth of both male (18.9%) and female (19.7%) students reported having seriously considered committing suicide. Having no close friends, current smoking, anxiety, victim of bullying, loneliness and experiencing challenges of food security were positively associated with suicidal ideation, while being male and having understanding parents were negatively associated with suicidal

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ideations. Suicidal ideation is a major public health issue in Gaza strip. Measures aimed to prevent suicide should incorporate our understanding of the factors associated with suicidal ideation identified in this study together with pure Islamic values, principles, traditions and cultural issues that uphold parental support.

Keywords: suicidal ideation, prevalence, associated factors, adolescents, Gaza strip

INTRODUCTION

Suicidal behavior is a major contributor to morbidity and mortality worldwide [1]. World Health Organization (WHO) estimates that globally, approximately one million people kill themselves every year [2]. According to Anderson and Smith [3], suicide is the third leading cause of death among 15-to-24 year olds [4] and the work by Schwartz 2016 show that suicide is actually the second leading cause of death among college students. Therefore, WHO ranks suicide as the major global public health problem that needs implementation of national suicide prevention strategies.

While most research and prevention of suicide is carried out in the more affluent countries and receiving increased attention in many developed countries, it remains largely ignored in developing countries [5]. Some researchers are for the view that suicide should be considered as an important area of research in developing countries, especially impoverished rural populations because it is highly associated with mental health problems [6]. This perceived association with mental illness tends to impede the implementation of successful preventive programs hence the need for more research in such populations. Challenges impeding on research into suicide attempts and completed suicide among people with severe mental disorders in low-middle-income countries are many. For instance, such research is mostly limited to patients attending psychiatric facilities where selection bias is likely to be high [1]. It is also important to note that suicide is a hidden cause of death in traditional societies because of the high levels of stigma and associated religious and cultural condemnation [7].

Recent epidemiological evidence suggests that suicide is soaring among young people in the Middle Eastern countries, including Gaza strip. A number of factors have been associated with suicidal ideation in Gaza strip and studies [8] indicate that children and adolescents in Gaza Strip have been under continuous violence since the beginning of the second Intifada (Uprising). Other studies also indicate that alcohol drinking has negative effects on mental health and that this leads to a condition that causes psychiatric disorders and increases the risk of suicide [9], but we are not sure if this is relevant for this population in the Gaza strip. Therefore, the objectives of the study were to estimate the prevalence of suicidal ideation as well as to determine factors associated with suicidal ideation in order to suggest a framework for prevention of suicide among school going adolescents in the Gaza strip.

METHODS

Secondary data analysis was conducted using data obtained in the 2010 Gaza Strip Global School based Health Survey (GSHS) survey. The GSHS was developed by the WHO and the aim was to provide research data on health and social behaviors among school-going adolescents.

Table 1. Distribution of factors considered in the analysis by gender among junior high school students in Gaza strip, 2010

Factor	Total n ¹ (%) ²	Males n ¹ (%) ²	Females n ¹ (%) ²
Age			
<14	991 (37.2)	421 (33.2)	546 (40.7)
14	784 (30.8)	344 (32.0)	433 (30.0)
15	749 (27.8)	370 (30.7)	369 (25.0)
16+	112 (4.1)	50 (4.1)	60 (4.2)
Gender			
Male	1191 (51.0)	-	-
Female	1416 (49.0)	-	-
Food security			
No	303 (11.7)	147 (12.3)	146 (10.9)
Yes	2332 (88.3)	1023 (87.7)	1253 (89.1)
Anxiety			
Yes	433 (16.4)	143 (12.4)	278 (20.4)
No	2169 (83.6)	1001 (87.6)	1117 (79.6)
Loneliness			
Yes	405 (15.3)	161 (13.7)	229 (16.5)
No	2212 (84.7)	990 (86.3)	1170 (83.5)
Close friends			
No	224 (8.8)	105 (9.1)	107 (8.0)
Yes	2354 (91.2)	1022 (90.9)	1281 (92.0)
Truancy			
Yes	1008 (39.4)	460 (40.8)	519 (37.5)
No	1557 (60.6)	661 (59.2)	862 (62.5)
Bullied			
Yes	1463 (59.3)	692 (63.4)	731 (55.0)
No	1029 (40.7)	400 (36.6)	602 (45.0)
Attacked			
Yes	1193 (46.6)	633 (54.0)	526 (38.6)
No	1449 (53.4)	539 (46.0)	876 (61.4)
In a fight			
Yes	1047 (40.9)	589 (49.8)	427 (31.4)
No	1607 (59.1)	588 (50.2)	980 (68.6)
Currently smoked			
Yes	291 (11.9)	213 (19.0)	66 (4.6)
No	2253 (88.1)	883 (81.0)	1318 (95.4)
Parental understanding			
Yes	875 (33.7)	354 (31.6)	502 (36.0)
No	1700 (66.3)	771 (68.4)	884 (64.0)
Suicidal ideation			
Yes	496 (19.3)	211 (18.9)	274 (19.7)
No	2056 (80.7)	894 (81.1)	1112 (80.3)

¹ unweighted frequencies. ² weighted percents.

The survey used a two-stage probability sampling technique, in which for the first stage, primary sampling units were schools which were selected with a probability proportional to their enrolment size. In the second step a systematic procedure was conducted among adolescents clearly indicating that they would not like to participate or by submitting a non-completed questionnaire. The overall response rate in the Gaza 2010 GSHS was 95% (School response rate of 100% and student response rate of 95%).

Variables that were used for analysis included having considered suicide, smoking, loneliness, parental understanding, in a fight, truancy, anxiety, close friendship, food security and key socio-demographic characteristics. Assessments of associations were conducted using both weighted bivariate and multivariate logistic regression analysis at 95% confidence interval.

RESULTS

The study recruited 2,607 school adolescents of which 51.0% were males. Results in Table 1 presents distributions of factors considered in the analysis by gender among the participants in Gaza strip, 2010. Selected characteristics of the study population showed that 88.3% of students had food security problems (most of the time or always went hungry because there was not enough food in the home). Female students reported anxiety and loneliness more than their male counterparts (20.4% and 16.5% among females compared with 12.4% and 13.7% among males, respectively). Few students (8.8%) reported having no close friends but truancy was common both among females (37.5%) and males (40.8%). A large proportion of students reported having been bullied (63.4% of males and 55.0% of female).

Slightly more than half (54.0%) of males and 38.6% of females reported having been attacked, and 49.8% of males and 31.4% of females reported being involved in a fight. Smoking was mainly reported among male students (19.0%) while parental understanding was reported in about one third (33.7%) of both male and female students. About 1 in 5 of both male (18.9%) and female (19.7%) students reported having seriously considered committing suicide.

Table 2 shows factors associated with suicidal ideation among junior high school students in the Gaza strip. Male students were 16% less likely (AOR = 0.84, 95% CI [0.82, 0.86]) to have suicidal ideation compared to female students. Students with food insecurity were 1.13 times more likely (AOR = 1.13, 95% CI [1.09, 1.17]) to consider committing suicide compared to students with food security. Anxious students were 58% more likely (AOR = 1.58, 95% CI [1.54, 1.63]) to have suicidal ideation compared to students who did not experience anxiety. Students who reported not to have close friends were 66% more likely (AOR = 1.66, 95% CI [1.60, 1.72]) to experience suicidal ideation compared to students who had close friends, while lonely students were 1.23 times more likely (AOR = 1.23, 95% CI [1.19, 1.26]) to consider committing suicide compared to students who did not report loneliness. Students with a history of involvement in a fight were 1.19 times more likely (AOR = 1.19, 95% CI [1.16, 1.22]) to consider committing suicide compared to students who never reported having been involved in a fight. Bullied students were 1.31 times more likely (AOR = 1.31, 95% CI [1.28, 1.35]) to have suicidal thoughts compared to students who were

not victims of bullying. Students who reported currently smoking were 65% more likely (AOR = 1.65, 95% CI [1.59, 1.70]) to have suicidal ideation compared to currently nonsmoking students. Students with parental understanding were 14% less likely (AOR = 0.86, 95% CI [0.84, 0.88]) to have suicidal ideation compared to students who did not have parental understanding.

Table 2. Factors associated with suicidal ideation among junior high school students in Gaza strip, 2010

Factor	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Age (years)		
<14	0.86 (0.84, 0.89)	0.92 (0.88, 0.96)
14	0.85 (0.82, 0.88)	0.94 (0.90, 0.98)
15	1.02 (0.99, 1.06)	1.01 (0.97, 1.06)
16+	1	1
Gender		
Male	0.98 (0.96, 1.00)	0.84 (0.82, 0.86)
Female	1	1
Food security		
No	1.26 (1.22, 1.29)	1.13 (1.09, 1.17)
Yes	1	1
Anxiety		
Yes	1.73 (1.69, 1.77)	1.58 (1.54, 1.63)
No	1	1
Loneliness		
Yes	1.58 (1.54, 1.61)	1.23 (1.19, 1.26)
No	1	1
Close friends		
No	1.77 (1.72, 1.82)	1.66 (1.60, 1.72)
Yes	1	1
Truancy		
Yes	1.26 (1.24, 1.28)	1.10 (1.07, 1.12)
No	1	1
Bullied		
Yes	1.53 (1.50, 1.57)	1.31 (1.28, 1.35)
No	1	1
Attacked		
Yes	1.39 (1.37, 1.42)	1.08 (1.05, 1.11)
No	1	1
In a fight		
Yes	1.26 (1.23, 1.28)	1.19 (1.16, 1.22)
No	1	1
Currently smoked		
Yes	1.91 (1.87, 1.96)	1.65 (1.59, 1.70)
No	1	1
Parental understanding		
Yes	0.84 (0.82, 0.86)	0.86 (0.84, 0.88)
No	1	1

DISCUSSION

The current study found a prevalence of suicidal ideation of 19.3% among in-school Gaza strip adolescents. This prevalence is lower than the rate found by Ghrayeb and colleagues [6]

among the Palestinian adolescents of 24.6%. However, our study finding is comparable to the reported rates in the neighboring countries of the Eastern Mediterranean Region and results of the previous international research work [10].

Results of the present study show that male students were 16% less likely to seriously consider committing suicide than female students. This finding is contrarily to the findings of the study among the Palestinian adolescents [6] and other previous reports [10, 11] that globally, the prevalence of suicidal behavior is consistently greater in males as compared to females. This is also supported by most previous studies [12, 13] that indicate that prevalence of suicidal ideation is higher among females than males. Age was found to be significantly associated with suicidal ideation and adolescents aged 14 years and below were less likely to have suicidal thoughts compared to the older participants. The result agrees with a finding in another study [14] and the explanation to this lays in part to higher prevalence of substance abuse and greater suicidal ideation in older adolescents.

Adolescents who reported to have food security challenges were found to be more likely to have suicidal ideas and this finding corresponds to the finding obtained elsewhere [15]. None availability of food in homes may have serious mental health problems for the young people that may result in a feeling that it is not worthy to live.

In the present study, anxiety was significantly associated with suicidal ideation. Similar finding has been reported elsewhere [16, 17] in which it has been reported that a preexisting anxiety disorder is an independent risk factor for subsequent onset of suicidal ideation.

Loneliness was associated with suicidal ideation in the current study and this is in conformity with other research work that found that living alone increased the risk for suicidal ideation among college students [18], suggesting that engagement in various activities with friends and having a well-established support system of friends can help in reducing suicidal ideas among in-school adolescents [19].

In addition, school adolescents in Gaza strip who reported truancy were more likely to have suicidal ideas compared to adolescents who did not have the habit of truancy. Other researchers also agree with our findings and in a European study [20], the analysis showed that there is a correlation between skipped school and suicidal behavior. Skipping school may be as a result of running away from being bullied. Alternatively, seriously thinking about committing suicide may result in skipping school. Because a cross sectional design was used in the current study, we are unable to ascribe causation in the relationship between truancy and suicidal ideation. Adolescents who had an experience in bullying were more likely to think of committing suicide compared to the others who did not experience bullying. Another study found a similar result and the finding was that adolescents who were being bullied and those who were bullies were at an increased risk of suicidal ideation [21].

Involvement in a fight has been associated with suicidal ideation in the present study. A study in the USA found that suicidal behavior might be associated with involvement in less extreme forms of violent behaviors, such as physical fighting [22]. In a similar finding, having been attacked was significantly associated with suicidal ideation in the present study, and another study in Peru [23] found that adolescents who had been attacked were more likely to have suicidal ideas compared to those that did not experience an attack. There is strong evidence that violence among adolescents is associated with suicidal ideation and efforts should be made to curtail this vice.

Smoking was significantly associated with suicidal ideation and this is in accord with the finding in another study elsewhere [24] where being a non-regular smoker was significantly

associated with lower odds of suicidal ideation. People may smoke to relieve stress that may in turn result in suicidal thoughts. Hence, further studies to directly link smoking to suicidal ideation are suggested.

Lack of parental understanding was significantly associated suicidal ideation and this is in accord with the observation in another study [25] in which the relationship of parental bonding to suicide ideation was examined. The study findings indicate that low parental care and high over-protection that indicate lack of parental understanding are associated with adolescent suicidality in general. Parental understanding would equally reduce levels of anxiety in the young population because in our findings, students who reported anxiety were 58% more likely to experience suicidal ideation which has also been noted as a risk factor for suicide in another study [24]. Improving the social, economic and political situation in the Gaza strip would help in reducing the levels of loneliness, increasing chances of students having close friends and encouraging positive parental-adolescent relationship.

In conclusion, most of the factors associated with suicidal ideation among in-school adolescents in Gaza strip are consistent with the prevailing situation in the Gaza strip. There is need to recognize suicidal ideation as an important issue among school adolescents in the Gaza strip. The design, implementation and evaluation of public health interventions aimed at reducing suicide rate in Gaza strip should incorporate our understanding of the factors associated with suicidal ideation that have been identified in the current study. Interventions should address the issue of violence against adolescents, fighting with peers, health risk behaviors especially initiation of smoking, and uphold supportive role of parents.

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Chapter 36

PREVALENCE AND CORRELATES OF SUICIDAL IDEATION AMONG SCHOOL-GOING ADOLESCENTS IN OMAN

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ABSTRACT

Worldwide, suicide is increasingly becoming an important public health problem. However, adolescent suicidal behaviour is a neglected public health issue especially in middle and low-income countries like Oman. The purpose of this study was to establish the prevalence and factors associated with suicidal ideation among adolescents in Oman. Analyses were based on secondary data from the 2010 Global School-Based student Health Survey (GSHS) conducted in Oman. Logistic regression analyses were performed to establish associations between the factors (i.e., food security, current alcohol use, bullying victimization, loneliness, anxiety, having no close friends, missed school, parental understanding, smoking, physical fights, physical attacks) and suicidal ideation. Suicidal ideation prevalence among adolescents (N = 1648) attending school was 10.2%. Out of this, more males (58.4%) contemplated on committing suicide than females (41.6%). There were no significant associations between exposure factors and suicidal ideation, except for cigarette smoking. Students who smoked were 2.43 (95% CI [1.38, 4.26]) times more likely to have considered committing suicide than those who did not

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smoke. Although suicidal ideation in Oman was relatively low, smoking should be considered in the designing of interventions to further reduce suicidal ideation rate and subsequently suicide rate.

Keywords: suicidal ideation, prevalence, smoking, Oman

INTRODUCTION

An estimated 20% of the world's adolescents have a mental health or behavioural problem [1]. This has resulted in many of the children considering suicide. Suicidal behaviour is an important public health problem worldwide. According to World Health Organisation (WHO), more than 800,000 people died of suicide in 2000 [2]. In another report by WHO, more than one million people die annually as a result of suicide [3]. Suicide ranks as the fourth leading cause of mortality among adolescents aged 15-19 years [4]. In the age group 10-24 years, suicide is ranked the second leading cause of death [4]. These statistics show that suicide is a growing global public health problem among adolescents. In addition to this, suicidal ideation among adolescents is on the rise [5].

Dunlavy et al. [6] reported a prevalence of suicidal ideation of 7%. In a study conducted in the United States of America by Eaton et al. [7] among 14-18 years of age, a prevalence of suicidal ideation of 15% was reported. Rudatsikira et al. [8] found a prevalence of suicidal ideation of 18.4% among adolescents in Guyana. According to Randall et al. [9] and Muula et al. [10], 23.2% and 31.3% of the adolescents enrolled in their studies reported suicidal ideation, respectively. Despite these statistics, and the grave consequences of suicidal ideation among the adolescents and youth, suicidal ideation has remained a neglected public health issue across the entire globe; this includes developing and developed countries.

Oman is a 1000 mile long, coastal plain at the southeast tip of the Arabian Peninsula lying on the Sea and gulf of Oman. It is bordered by the United Arab Emirates, Saudi Arabia, and Yemen. There is paucity of data regarding suicidal ideation among adolescent in Oman. However, in a study conducted by Khalid et al. [11], 16.15% of the adolescents reported to have considered committing suicide in the United Arab Emirates, a country sharing a boarder with Oman. Nevertheless, there are no studies that have been done in Oman regarding suicidal ideation, though certain factors related to suicidal ideation have been studied such as bullying [12]. In that study, Al-Saadoon et al. [12] indicated that studies on bullying in Arab/Muslim countries are scarce, so are studies on suicidal ideation.

Suicidal ideation among adolescents is associated with several factors that include alcohol abuse [13-15], low parental understanding [16], bullying [17, 18], loneliness [19] and low social support [20]. There have been various reports on suicidal ideation and its correlates in developed countries [21, 22] but developing countries like Oman has limited data concerning the vice. We, therefore, carried out this study to estimate the prevalence and establish the correlates for suicidal ideation among adolescents in Oman.

METHODS

The present study used secondary data obtained from the Oman Global School-based Health survey (GSHS) organised by the World Health Organisation (WHO) and Centres for Disease Control and Prevention (CDC). Participants were students in grades 8 to 10. In order to produce data representative of all students in grades 8 to 10 in Oman, a two-stage cluster sample design was employed. During the first stage, schools were selected with probability proportional to enrolment size, while in the second stage, classes were randomly selected and all students in selected classes were eligible to participate in the survey. The response rate for the schools was 94%, while that of the students was 94%, and the overall response rate was 89%.

SPSS version 16 was used to conduct the analyses. Variables that were used in the analysis included socio-demographic characteristics, having considered suicide, smoking, loneliness, parental understanding, involvement in a fight, truancy, anxiety, close friendship and food security. Frequencies were weighted. Determination of associations between exposure variables and outcome variable was done using univariate and multivariate logistic regression analyses at 95% Confidence Interval (CI).

RESULTS

The Oman Junior High School survey (GSHS) enrolled a total of 1606 students, out of which 58% were males. The majority (36.4%) of students were aged less than 14 years. The rest were 15 and 16 years or older.

Table 1 presents characteristics of the participants in the study population. The results indicated that 11.9% of students had less food and 29% of them reported truancy. Analysis also showed that 31.1% of the students were bullied and 36.6% were attacked. Students who were involved in fighting accounted for 29.8% and those who smoked were 12.4%. It was also noted that among the participants, 25.4% abused alcohol, 24.0% lacked parental understanding and 10.2% were reported to have thought of committing suicide.

Table 2 shows factors that were associated with suicidal ideation. There were no significant associations between factors considered in the study and suicidal ideation, except for cigarette smoking. Students who smoked were 2.43 (95% CI [1.38, 4.26]) times more likely to have considered committing suicide than those who did not smoke.

DISCUSSION

The findings from this study indicate a prevalence of suicidal ideation of 10.2%. Out of this, 6.9% of the males reported suicidal ideation compared to 15.3% females who thought about committing suicide. This result is close to the finding by Dunlavy et al. [6] who reported 7% suicidal ideation among adolescents in Tanzania. However, it is significantly lower than rates found among school-going children of 20% in Nigeria [23], 14.5% in the United States [7], 31.3% in Zambia [10], 18.4% in Guyana [8] and 21.6% in Uganda [19].

The prevalence rate in the present study is also congruent with what was reported among Americans of Caribbean decent [24] of 10.7%.

Table 1. Distribution of factors by gender among students in Oman, 2010

Factor	Total n ¹ (%) ²	Males n ¹ (%) ²	Females n ¹ (%) ²
Age			
<14	50 (36.4)	25 (32.4)	25 (41.9)
14	16 (11.6)	11 (12.4)	5 (10.8)
15	23 (16.6)	15 (17.1)	8 (16.2)
16+	52 (35.4)	32 (38.1)	20 (31.1)
Gender			
Male	83 (58.4)		
Female	58 (41.6)		
Food security			
No	16 (11.9)	13 (17.3)	3 (5.4)
Yes	125 (88.1)	70 (82.7)	5 (94.6)
Truancy			
Yes	41 (29.0)	24 (30.0)	17 (28.2)
No	94 (71.0)	56 (70.0)	38 (71.8)
Bullied			
Yes	41 (31.1)	22 (30.2)	19 (32.4)
No	90 (68.9)	54 (69.8)	36 (67.6)
Attacked			
Yes	48 (36.6)	26 (32.7)	22 (41.9)
No	93 (63.4)	57 (67.3)	36 (58.1)
In a fight			
Yes	43 (29.8)	31 (36.5)	12 (20.3)
No	98 (70.2)	52 (63.5)	46 (79.7)
Currently smoked cigarettes			
Yes	18 (12.4)	11 (12.7)	7 (12.2)
No	122 (87.6)	71 (87.3)	51 (87.8)
Alcohol abuse			
Yes	37 (25.4)	24 (28.2)	13 (21.1)
No	101 (74.6)	58 (71.8)	43 (78.9)
Parental understanding			
Yes	34 (24.0)	19 (22.5)	15 (26.0)
No	104 (76.0)	62 (77.5)	42 (74.0)
Suicidal ideation			
Yes	16 (10.2)	6 (6.9)	10 (15.3)
No	122 (89.8)	75 (93.1)	47 (84.7)

¹ unweighted frequencies. ² weighted percents.

The lower suicidal ideation rates in Oman could be explained by the good economy that the country has. This good economy for the country enables easy access to various needs of humanity, ranging from shelter to food, and thus prevents change in behaviour that can lead to suicide. In a study conducted by O'Donnell et al. [25], it was established that those with unmet needs were at greater risk of thinking about committing suicide than those that had their needs met. This clearly shows a possible explanation for the low suicidal ideation rates in Oman. The needs of a larger population in Oman have been taken care of; therefore, the suicidal ideation is quite low. Though the suicidal ideation is quite low, there is need for the Oman government to put in place measures that will further reduce the prevalence rate of suicidal ideation.

Table 2. Factors associated with suicidal ideation among students in Oman, 2010

Factor	Unadjusted odds ratio (95% CI)
Age	
<14	0.60 (0.23, 1.55)
14	0.61 (0.14, 2.69)
15	2.38 (0.97, 5.83)
16+	1
Gender	
Male	0.63 (0.38, 1.04)
Female	1
Food security	
No	0.69 (0.26, 1.88)
Yes	1
Truancy	
Yes	1.23 (0.73, 2.04)
No	1
Bullied	
Yes	1.13 (0.67, 1.92)
No	1
Attacked	
Yes	1.19 (0.72, 1.95)
No	1
In a fight	
Yes	1.43 (0.87, 2.35)
No	1
Currently smoked cigarettes	
Yes	2.43 (1.38, 4.26)
No	1
Alcohol abuse	
Yes	1.26 (0.74, 2.13)
No	1
Parental understanding	
Yes	0.78 (0.41, 1.49)
No	1

The results from the present study show no significant associations between suicidal ideation and all the factors (age, gender, food security, truancy, bullying, being attacked, having been involved in a fight, alcohol abuse and parental understanding) except for cigarette smoking. Students who smoked cigarettes were 2.43 times more likely to have considered committing suicide compared to students who were not smokers. This finding is in tandem with various studies [15, 26]. Smoking as a drug may have ill-effect on the brain that may in turn lead to suicidal thoughts of the affected persons.

The factors that were not significantly associated with suicidal ideation in the present study have been reported to be positively associated with this vice in many studies [8-10, 18]. The non-significance of the associations between the exposure variables and outcome variable could be due to the similarities between students who had seriously thought about committing suicide and those who had not thought so in the present study. Having similar background characteristics between the two groups of students could result into non-significant associations. The other explanation would be the effect of confounders. If other factors that influence the outcome are unevenly distributed between the groups, these other factors can distort the apparent association between the outcome and the primary exposure of

interest; this might be the reason why the findings in this study show no association between the independent variables and outcome variable.

In conclusion, we found an overall relatively low prevalence of suicidal ideation among school going adolescents in Oman. Smoking should be considered in the designing of interventions to further reduce suicidal ideation rate and subsequently suicide rate.

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Chapter 37

FACTORS ASSOCIATED WITH SUICIDAL IDEATION AMONG ADOLESCENTS ATTENDING SCHOOL IN PHILIPPINES

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ABSTRACT

Research on suicidal ideation and its correlates has not been given the right attention in Philippines; this is despite suicidal ideation being an important public health issue among adolescents. The aim of the present study was to determine the prevalence and correlates of suicidal ideation among adolescents in Philippines. The study used secondary data that was collected in a Global School-based Student Health Survey in 2010. Both bivariate and multivariate logistic regression analyses were performed to establish associations between the factors (i.e., food security, current alcohol use, bullying, loneliness, anxiety, having no close friends, missed school, parental understanding, smoking, physical fights and physical attacks) and suicidal ideation. Altogether, 5290 students participated in the survey. Overall, the prevalence of suicidal ideation was 17.0% (12.0% among males and 21.8% among females). Being of age <15 years, male gender and parental understanding were protective against suicidal ideation. The rest of the correlates were found to be risk factors of suicidal ideation. Among the risk factors that were established were; food security, anxiety, loneliness, having close

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friends, truancy, bullying, physical attacks and fights, smoking and alcohol abuse. Suicidal ideation in Philippines was significantly high. Knowledge of the associated factors from the current study will enable implementation of interventions to reduce the suicide burden.

Keywords: suicidal ideation, suicidal behaviours, correlates, adolescent, Philippines

INTRODUCTION

Suicide is the fourth leading cause of death globally among the youth with age ranging from 15 to 19 years [1]. In addition to this, 6% of global deaths among youth aged 10-24 years are attributed to suicide [2]. Therefore, this makes suicide a major public health problem. Suicide has enormous social and economic costs to individuals and communities [3]. WHO [4] reported that suicide is a primary cause of death in the youth population worldwide. In Philippines, suicide is on the rise. Radaniel et al. [5] reported that there was an increase in the incidence of suicide cases in Philippines between 1984 and 2005, from 0.23 to 3.59% with the more females committing the act than males. These statistics indicate the need to formulate preventive measures that would curb the rising prevalence of suicide especially among the youth in Philippines.

According to Peter et al. [6], research on youth with suicidal thoughts is critical as suicidal ideation is a precursor to suicide completion. Studies among youth are cardinal due to the fact that many cases are occurring in this sub-population, especially among adolescents [7]. In a study by Page et al. [8] conducted in one of the towns in Philippines, suicidal ideation in adolescents was reported at 17.1%. Besides this study, other studies on suicidal ideation in both low and middle income countries have reported varying prevalence rates; 16% in Lebanon [9], 17.8%, in China [10] and 24% in Philippines. In African countries, the prevalence of suicide ideation is generally higher; 19.6% in Uganda, 23.1% in Botswana, 27.9% in Kenya and 31.9% in Zambia [8].

Philippines is an archipelago nation comprising 7107 islands that are mainly divided into three groups (Luzon, Visayas, and Mindanao) located in South East Asia [11]. In 2008, 21% of the estimated 90 million people living in Philippines were adolescents. Young people (aged 10-24 years) accounted for 30.5% of the population. The country has an active economy, with good rates of employment among youth that are aged between 15 and 19 years [12]. Although this is the case, many working youth are considered poor because they normally work for less than 1.25 dollars a day, a factor that is likely to affect adolescents and lead them to contemplate on committing suicide as a way of running away from economic hardships. Due to limited information on the suicidal ideation and its risk factors, the present study aimed to explore this area in order to provide knowledge that will be useful for interventions against suicide and suicidal ideation in Philippines.

METHODS

Our study utilised secondary data obtained from the Philippine Global School-based Health Survey (GSHS) carried out in 2011. This survey involved students in grades 1st to 4th. In order to rule out selection bias, the survey used a two-stage probability cluster sampling technique. Besides ruling out selection bias, the technique was used in order to produce data representative of all students in grades 1st to 4th. In the first stage sampling, the primary level involved the selection of schools which were chosen with probability proportional to the enrolment size. In the second stage, classes were randomly selected from the selected schools, and all students in selected classes were eligible to participate. A self-completed questionnaire was used to capture the information. The rate of response from the schools was 97%, while that of students was 82%; giving an overall response rate of 80%.

The outcome variable was self-reported suicidal ideation. The participants were asked to provide answers to questions about: their thoughts on suicide, age, gender, food security, their experiences on smoking and abuse of alcohol, their relationship with parents, whether they had close friends or not, having been bullied and attacked and truancy.

In order to reflect the likelihood of sampling each student, a weighting factor was utilised. In addition to this, the weighting reduced bias by compensating for differing patterns of non-response. SPSS version 16 was used to conduct logistic regression analyses in order to estimate associations between predictor variables and suicidal ideation at 95% Confidence Interval (CI). We reported unadjusted and adjusted odds ratios for selected predictor variables while considering suicidal ideation as the dependent variable.

RESULTS

A total of 5,290 adolescents participated in the Philipino Global school-based Health Survey (GSHS) in 2011. Out of the total number of participants, 50.2% were females. Most (26.9%) of the students were aged 16 years or older. Those aged less than 14 years accounted for 26.2%.

Table 1 gives the sample characteristics of the study population. Among the respondents, 6.8% reported not to have had enough food, 11.4% were anxious, 14.8% were lonely, 3.6% had no close friends and 33.9% reported missing school without permission. Furthermore, 47.6% were bullied, 33.2% were attacked, and 36.6% were involved in a physical fight. Other students reported smoking (13.9%) and abusing alcohol (20.6%). The prevalence of suicidal ideation was 17.0% (12.0% among males and 21.8% among females).

Table 2 presents variables that were associated with suicidal ideation. In terms of age, students less than 14 years old were 27% less likely to think about committing suicide than those aged 16 years or older. On the other hand, those students aged 15 years old were 21% more likely to contemplate on suicide than those aged 16 years or older. The table also shows males being 41% less likely to think about committing suicide than females. Students with anxiety were 18% more likely to entertain thoughts of committing suicide than those without it. Students who reported loneliness were 55% more likely to have thoughts about committing suicide than those who were not lonely. Furthermore, students who were truant and those who

had no close friends were 8% more likely to have suicidal thoughts compared to students who were not truant and those who had close friends, respectively.

Table 1. Distribution of factors considered in the analysis by gender among adolescents attending school in Philippines, 2011

Factor	Total n ¹ (%) ²	Males n ¹ (%) ²	Females n ¹ (%) ²
Age			
<14	1198 (26.2)	485 (26.4)	713 (26.0)
14	1348 (22.1)	553 (20.8)	795 (23.3)
15	1305 (24.8)	549 (24.3)	756 (25.3)
16+	1378 (26.9)	679 (28.5)	702 (25.3)
Gender			
Male	2279 (49.2)		
Female	2985 (50.2)		
Food security			
No	375 (6.8)	195 (8.1)	176 (5.4)
Yes	4872 (93.2)	2071 (91.9)	2801 (94.6)
Anxiety			
Yes	584(11.4)	239(10.4)	345 (12.4)
No	4670 (88.6)	2033 (89.6)	2637 (87.6)
Loneliness			
Yes	781(14.8)	290(12.7)	491 (16.9)
No	4374 (85.2)	1940 (87.3)	2434 (83.1)
Close friends			
No	165 (3.6)	86 (4.4)	79 (2.8)
Yes	50151 (96.4)	2161 (95.6)	2890 (97.2)
Truancy			
Yes	1643 (33.9)	806 (37.1)	837 (30.7)
No	3573 (66.1)	1442 (62.9)	2131 (69.3)
Bullied			
Yes	2384 (47.6)	964 (46.0)	1420 (49.1)
No	2602 (52.4)	1171 (50.0)	1431 (50.9)
Attacked			
Yes	1699 (33.2)	836 (37.3)	863 (29.1)
No	3540 (66.8)	1431 (62.7)	2109 (70.9)
In a fight			
Yes	1763 (36.6)	897 (42.8)	866 (30.6)
No	3454 (63.40)	1360 (57.2)	2094 (69.4)
Smoked cigarettes			
Yes	609(13.9)	445 (20.4)	164 (7.7)
No	4614 (86.1)	1799 (79.6)	2815 (92.3)
Parental understanding			
Yes	1415(27.1)	555 (25.3)	860 (28.9)
No	3800 (72.9)	1694 (74.7)	2106 (71.1)
Abused Alcohol			
Yes	926(20.6)	525 (24.8)	401(16.6)
No	4206 (79.4)	1678 (75.2)	2528 (83.4)
Consumed alcohol			
Yes	1024 (23.2)	597 (28.7)	427 (17.9)
No	4125 (76.8)	1618 (71.3)	2507 (82.1)
Suicidal ideation			
Yes	857 (17.0)	264 (12.0)	593 (21.8)
No	4317 (83.0)	1958 (88.0)	2359 (78.2)

¹ unweighted frequencies. ² weighted percents.

Students that were bullied and attacked were 26% and 3%, respectively, more likely to think about suicide than those that were not bullied and attacked. Those that were involved in a fight and smoked were 15% and 32%, respectively, more likely to ponder over committing suicide than those who were not. In addition to this, students who consumed alcohol were 31% more likely to consider committing suicide than those who did not, while those that had parental understanding were 17% less likely to cogitate on committing suicide than those that did not have.

Table 2. Factors associated with suicidal ideation among adolescents attending school in Philippines, 2011

Factor	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Age (years)		
<14	0.76 (0.75-0.76)	0.73 (0.73-0.74)
14	0.90 (0.90-0.91)	0.98 (0.97-0.98)
15	1.22(1.21-1.22)	1.21(1.21-1.22)
16+	1	1
Gender		
Male	0.70 (0.70-0.71)	0.59 (0.59-0.60)
Female	1	1
Food security		
No	1.14 (1.14-1.15)	1.06 (1.05-1.06)
Yes	1	1
Anxiety		
Yes	1.47 (1.46-1.47)	1.18 (1.18-1.19)
No	1	1
Loneliness		
Yes	1.77 (1.77-1.78)	1.55 (1.55-1.56)
No	1	1
Close friends		
No	1.21 (1.20-1.21)	1.08 (1.07-1.08)
Yes	1	
Truancy		
Yes	1.22 (1.22-1.23)	1.08 (1.07-1.08)
No	1	1
Bullied		
Yes	1.36 (1.36-1.37)	1.26 (1.26-1.27)
No	1	1
Attacked		
Yes	1.18 (1.18-1.19)	1.03 (1.03-1.04)
No	1	1
In a fight		
Yes	1.27 (1.27-1.28)	1.15 (1.14-1.15)
No	1	1
Smoked cigarettes		
Yes	1.40 (1.40-1.41)	1.32 (1.31-1.32)
No	1	1
Parental understanding		
Yes	0.76 (0.76-0.77)	0.83 (0.83-0.84)
No	1	1
Consumed Alcohol		
Yes	1.40 (1.40-1.41)	1.31 (1.30-1.31)
No	1	1

DISCUSSION

Our study found that overall 17% (12% males and 21.8% females) had seriously cogitated on committing suicide. This finding is much higher than the rate of suicidal ideation among the adolescents in Thailand (8.8%) [13], Myanmar (0.7%), Indonesia (4.0%) [14] and in Sri Lanka 9.9% [14]. The difference in the rates can be attributed to religion. In countries like Thailand, most people are Buddhists. In Buddhism, one has to train oneself against destroying life, as this would be practicing one of the immoral actions in the religion. Therefore, this religion practiced by Thai people or adolescents may play a role in preventing them from thinking about suicide as opposed to Filipinos who are mostly Christians. However, Christianity also speaks against suicide but might not be as strict as Buddhism.

Similarities in the prevalence rates of suicidal ideation between Philippines and other countries where Christianity is also practiced exist; 17.1% in Brazil [15] and 18.4% in Guyana [16]. Previous studies have reported similar findings with regard to more female adolescents considering suicide than males [17-19].

Results from the present study indicate that students less than 14 years together with those aged 14 year were less likely to contemplate on committing suicide than those aged 16 years or older. This result is similar to that found by Liu et al. [20] and Rudatsikira et al. [21] who established that increase in age was correlated with suicidal ideation. Contrary, Muula et al. [22] reported that adolescents aged less than 14 years were more likely to consider committing suicide than those aged 16 years or older. The explanation for the difference is not entirely clear. It might be speculated that in Muula et al.'s [22] findings, younger minds were more likely to succumb to life's pressures, hence the wish to take one's life. It might as well be that younger adolescents may not be as stressed as the older ones to result in having suicidal thoughts because the 'adolescence crisis' might not have taken its toll on the younger adolescents.

We also observed that adolescents who had no food were more likely to ponder on committing suicide than those that had enough to eat. This finding is in line with a study done by Randall et al. [23], who concluded that adolescent students who were hungry were likely to think about suicide compared to those that had enough food. The effect of lack of food causes various effects in young people, such as missing school which later leads to failure or school stoppage. Siziya et al. [24] also reported an association between lack of food and being truant or missing school without permission. This could explain why such adolescents with challenges of food could possibly and constantly think about killing themselves.

The present study also established that students who reported to have been anxious were more likely to contemplate on committing suicide compared to those that were not. This ties in very well with the finding by Omigbun et al. [25] who reported a positive association between anxiety and suicidal ideation. However, the finding in the current study differs with that obtained by Dunlavy et al. [26] in Tanzania. In that study, students who were anxious were less likely to think about suicide. We are unable to offer an explanation for this difference.

Lonely students were also found to be more likely to think about suicide compared to those who were not lonely. This is congruent with the finding of Rudatsikira et al. [21] who established a positive association between loneliness and suicidal ideation. However, Muula et al. [22] finding is not in tandem with the result from the present study. The difference may

be as a result of the social and cultural training that adolescents are exposed to in the setting where Muula et al. conducted the study. Otherwise, Stravynski and Boyer [27] also reported a positive association between loneliness and suicide ideation.

In the present study, lack of close friends was positively associated with suicide ideation. This is also reported by various studies [21, 22, 25]. However, Randall et al. [23] finding contradicts the results from the current study. The reason might not be very clear as to why having close friends might lead one to consider committing suicide, but, it can be explained by considering various frustrations that can be brought by close friends. Sometimes peers might introduce unnecessary competition as regards to material possessions. When one does not have what others who are close have, they might start thinking that it's not worth to live in a world full of struggles.

Truancy is defined as missing school without permission. Students who were truant in the present study were more likely to ponder over committing suicide compared to students that were not. Truancy may be necessitated by various factors such as bullying, attacks and fights at school. These factors might prevent adolescents from attending school regularly [24]. In studies where these factors were low in prevalence rates, like in Dunluvy's [26] study of adolescents in Tanzania, truancy was negatively correlated with suicidal ideation. The present study has higher prevalence rates of bullying, attacks and physical fights.

Bullying or victimization tends to influence negative thoughts in adolescents. Many begin to feel unwanted and hence the thought of ending it all through committing suicide. In the present study, students that reported having been bullied before were more likely to have thoughts of committing suicide compared to those that never experienced the vice. These findings are in line with those of Omigbodun et al. [25] and Owusu et al. [28] who established a positive association between Bullying and suicidal ideation. Other studies have found no association between the two variables [26]. The disparity in the results can be due to the lower rates of bullying in the later study and the effects of recall bias by some participants when it comes to recalling whether they had experienced the vice in the previous months before the study was conducted.

Another finding from the present study is an attack on an adolescent increases the chance of thinking about committing suicide. This finding is similar to results established by Omigbodun et al. [25] and Randall et al. [23]. Attacks may bring negative thoughts about one's life, a feeling that is likely to culminate into suicide. In some countries where suicide is considered to be a tool for retribution, when one is attacked, they are forced to start thinking about suicide so as to avenge the attacks they could have gone through in the past. This is common in Islamic countries where suicide is commonly practiced as it is part of the beliefs.

According to the findings of the present study, students that smoked were more likely to seriously consider committing suicide than those that did no smoke. This finding agrees with what Rudatsikira et al. [21] and Muula et al. [22] reported. Smoking tends to affect the normal operation of the brain; adolescents who indulge in such vices are likely to have thoughts about suicide. However, smoking might be linked to various factors such as having close friends and parents who are involved in the habit of smoking [29]. Other studies have also associated psychiatric illnesses to smoking [30-32]. These illnesses eventually might lead to someone getting frustrated with life, after which thoughts about killing oneself will be inevitable.

Our study also found that adolescents who had parental understanding were less likely to think about suicide. The present study agrees with the findings of Cash and Bridge [33] who established that having parental understanding was protective against suicidal ideation. The presence of parents who understand in one's life just makes things better, amidst of troubles; adolescents having parents who understand quickly find solutions as parents offer solutions and good listening ears. However, it is not everyone who has understanding parents who enjoys this privilege of care. In certain instances some adolescents are driven to start thinking about suicide due to the uncaring attitudes from their parents.

A significant association between alcohol abuse and suicide ideation was observed in the current study. Students who consumed alcohol were more likely to consider suicide than those that did not consume alcohol. The result is similar to what Rudatsikira et al. [21] found. It has been observed among adolescents that alcohol consumption is looked at as a solution to many social problems that might be prevalent in their lives. However, the habit of abusing alcohol just increases these problems and leads the adolescents to start thinking about suicide so as to alleviate the sufferings brought as a result of alcohol consumption.

In conclusion, suicidal ideation among school going adolescents in Philippines was high and risk factors associated with suicidal behaviour were identified. This information from the present study can be taken into consideration when developing and implementing interventions to prevent suicide.

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Chapter 38

CORRELATES OF SUICIDAL IDEATION AMONG SCHOOL-GOING ADOLESCENTS IN BAHAMAS

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ABSTRACT

Suicidal ideation and its correlates have not been addressed within the Bahamian society despite its enormous effects on adolescents not only in Bahamas, but also all over the world. Statistics have indicated a rise in suicide cases in Bahamas. However, there is paucity of information regarding suicidal ideation and its correlates in Bahamas. The objectives of the current study were to estimate the prevalence of suicidal ideation and determine its correlates among adolescents in Bahamas. Secondary analyses were conducted using data obtained from the Global School-based student Health Survey (GSHS) carried out in 2013 in Bahamas. A backward logistic regression analysis was conducted to determine independent factors associated with suicidal ideation (i.e., food security, current alcohol use, bullying, loneliness, anxiety, having no close friends, missed school, parental understanding, smoking cigarettes and marijuana, physical fights, physical attacks) and suicidal ideation. Suicidal ideation prevalence among adolescents (N=1357) was 18.2% (13.8% among males and 22.3% among females). Male gender was protective against suicidal ideation. Other variables were found to be risk factors for suicidal ideation and these were; age below 16 years, anxiety, loneliness, bullied, physical fights, smoking cigarettes and parental understanding. Suicidal ideation in

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Bahamas was notably high. Hence, the needs for interventions addressing the risk factors that have been identified in this study in order to curtail the prevalence rate of suicidal ideation.

Keywords: suicidal ideation, prevalence, risk factors, adolescent, Bahamas

INTRODUCTION

Suicide is the 14th leading cause of death worldwide. It accounts for 1.4% of the global burden of disease and 1.5% of all mortality [1, 2]. It is also known to be 3rd cause of death in adolescents, mainly those aged 15 years [3]. When compared to mortality rate due to war and homicide combined, the annual mortality rate as a result of suicide is greater [4]. The situation about suicide is more alarming as indicated by reports given about people that harm themselves through suicide. It is known that 2,000 people every day harm themselves through suicide. Suicide and suicidal attempts in Bahamas has become a major public health concern [5], with steady increase in the cases.

In other countries such as the United States of America, suicide is the tenth leading cause of death. It is observed that there are more deaths due to suicides than car accidents in that country (USA) [6]. According to the first report on suicide by WHO, one person commits suicide every 40 seconds [7]. Suicide starts with a thought before it can be completed. In Bahamas, there has been studies done in order to ascertain the rate of suicide cases, however, studies on suicidal ideation and its correlates have not been undertaken to greater detail. This fact is supported by Kava et al. [5] who stated that mental health was insufficiently addressed within the Bahamian society.

The Bahamas is a stable, developing nation with an economy heavily dependent on tourism and offshore banking. Though this country has been shown to be developing, it is one of the wealthiest Caribbean countries. In terms of poverty, 8.7% of the households are living in poverty, and poverty levels are significantly higher in family islands than in New Providence (12.4%) and in Grand Bahama (9.4%) islands. According to Kava et al. [5], one of the leading causes of these thoughts about suicide is a feeling of shame. The theory suggests that the shame gap usually occurs when one struggles with high expectations versus reality. The result of this will be someone contemplating on suicide. It would mean that someone is not dealing with the problem but with shame of failing to meet the expectations.

The above effects of thoughts on suicide can lead to increased death rate if not addressed in Bahamas. Kava et al. [5] reported a 3.7% suicide rate from 2000 to 2013. Though suicide rate of 3.7% is low, the rate of suicide attempts was reported to be between 6% and 23%, spanning from 2000 to 2012. Though the government through Central Detection Unit (CDU) is doing everything possible to reduce the cases, there are still deficits in the information pertaining to risk factors and prevalence rates of suicidal ideation. These missing elements are critical to prevention programmes. Hence, the objectives of the study were to estimate the prevalence of suicidal ideation and determine its associated factors.

METHODS

The present study involved secondary analysis of data for the Bahamas Global School-based Health Survey (GSHS) carried out in 2013. This survey was organised by World Health Organisation (WHO) and Centres for Disease Control and Prevention (CDC). The aim of the GSHS was to avail data on the prevalence of health behaviours and protective factors that could be used in evaluating school health and youth health programmes among young people aged 13 to 17 years. In the Bahamas GSHS, most young people in this age group were students in grades 8, 9, and 10. The GSHS used a two-stage cluster sampling method in order to produce data representative of all students in grades 8, 9, and 10 in Bahamas survey.

The first stage included schools being selected with probability proportional to enrolment size, while the second stage involved the random selection of classes. All students in selected classes therefore, were eligible to participate in the survey. Participants in this survey were required to self-report their responses to each question on a computer scannable answer sheet. The process was guided by well-trained research assistants that encouraged the students to answer all the questions; however, they were not forced to answer questions they were not comfortable to respond to. In the process, not all eligible students participated in the survey. The student and school response rates were 87% and 90%, respectively, giving an overall response rate of 78%.

Students indicated their age and gender on the questionnaire. They were also questioned on whether they had; challenges with food, experienced anxiety, been lonely in the previous 12 months, any close friends and whether they had missed school without permission. Information on how many students were bullied and attacked was also collected. Furthermore, participants were asked to state whether they had been involved in physical fights and smoked cigarettes and marijuana. The survey also sought to establish whether adolescents had parents who understood their problems and worries. Questions on whether students ever consumed alcohol and had ever thought about committing suicide were posed to establish the prevalence rates and later on determine factors that are associated with suicidal ideation.

The outcome variable was suicidal ideation that was experienced by the student in the previous 12 months before the study was undertaken. The independent factors were; age, gender, food security, anxiety, loneliness, having close friends, truancy, victimisation or bullying, physical attacks and fights, cigarette and marijuana smoking, alcohol abuse and consumption, and having parental understanding.

A weighting factor that was used in this analysis took into account differing patterns of non-response. The weight was:

$$W=W1 * W2 * f1 * f2 * f3 * f4,$$

where W1= the inverse of the probability of selecting the school

W2= the inverse of the probability of selecting the classroom within the school

f1= a school-level non-response adjustment factor calculated by school size category (small, medium, large)

f2= a class-level non response adjustment factor calculated for each school

f3= a student-level non response adjustment factor calculated by class

f4= a post stratification adjustment factor calculated by grade.

Using SPSS version 16, we generated weighted frequencies as estimations of prevalence rates of factors. Bivariate and multivariate logistic regression analysis was conducted at 95% Confidence Interval (CI) to establish the associations between the independent variables and suicidal ideation within the previous 12 months to the survey.

RESULTS

Adolescents who participated in the Bahamian Global school-based Health Survey (GSHS) in 2013 were 1357. Out of the total number of the enrolled students, 53.1% were females. About half (50.8%) of students were less than 14 years of age. Those aged 16 years or older accounted for 3.6%.

Table 1 shows the sample characteristics of the study population. Of the enrolled students, 7.0% reported to have had challenges with having enough food to eat, 14.1% experienced anxiety, 11.1% were lonely, 9.0% had no close friends and 14.5% were truant. In addition to this, 23.2% were bullied, 29.6% were attacked, and 39.5% were involved in a physical fight. Some students reported smoking cigarettes (5.4%) and marijuana (10.1%). Students that abused alcohol were 20.6%, and those that had cogitated on committing suicide were 18.2% (13.8% of males and 22.3% of females).

Table 2 presents factors that were associated with suicidal ideation after logistic analysis. Students less than 14 years old were 2 times more likely to seriously consider committing suicide than those aged 16 years or older. Meanwhile, students aged 14 and 15 years were 55% and 35% more likely to think about committing suicide than those 16 years or older. The table further indicates males being 23% less likely to consider committing suicide than females. Those students with anxiety were 89% more likely to puzzle over committing suicide than those without. Students who were lonely were 48% more likely to have thoughts about committing suicide than those who were not.

Students that were bullied and were involved in physical fights were 57% and 17%, respectively, more likely to contemplate committing suicide than those that were not bullied and involved in fights. Those that smoked cigarettes and marijuana were 17% and 51% respectively, more likely to think about committing suicide than those who did not. Furthermore, students who consumed alcohol were 19% more likely to seriously consider committing suicide than those who did not. On the other hand, those that had parental understanding were surprisingly 42% more likely to ponder over committing suicide than those that did not have.

Table 1. Distribution of factors considered in the analysis by gender among junior high school students in Bahamas, 2013

Factor	Total n ¹ (%) ²	Males n ¹ (%) ²	Females n ¹ (%) ²
Age			
<14	760 (50.8)	351(47.7)	409 (53.7)
14	403 (31.8)	185(32.6)	218 (31.1)
15	150 (13.8)	68(14.7)	82 (13.0)
16+	35 (3.6)	21 (5.1)	14 (2.2)
Gender			
Male	626 (46.7)		
Female	724 (53.1)		
Food security			
No	95 (7.0)	43 (7.1)	52 (6.8)
Yes	1247 (93)	579 (92.9)	668 (93.2)
Anxiety			
Yes	181 (14.1)	60 (7.1)	52 (6.8)
No	1141 (85.9)	547 (89.3)	668 (93.2)
Loneliness			
Yes	148 (11.1)	52 (8.4)	96 (13.5)
No	1188 (88.9)	566 (91.6)	622 (86.5)
Close friends			
No	124 (9.0)	64 (9.6)	60 (8.4)
Yes	1202 (91.0)	547 (90.4)	655 (91.6)
Truancy			
Yes	180 (14.5)	115 (20.4)	65 (9.2)
No	1108 (85.5)	473 (79.6)	635 (90.8)
Bullied			
Yes	287 (23.2)	140 (24.3)	147 (22.1)
No	977 (76.8)	438 (75.7)	539 (77.9)
Attacked			
Yes	393 (29.6)	210 (33.5)	183 (26.0)
No	921 (70.4)	401 (66.5)	520 (74)
In a fight			
Yes	532 (39.5)	281 (44.8)	251 (34.7)
No	810 (60.5)	342 (55.2)	468 (65.3)
Smoked cigarettes			
Yes	64 (5.4)	46 (8.4)	18 (2.6)
No	1252 (94.6)	561 (91.6)	691 (97.4)
Parental understanding			
Yes	470 (36.2)	218 (36.2)	252 (36.1)
No	817 (63.8)	371 (63.8)	446 (63.9)
Abused alcohol			
Yes	260 (20.4)	143 (24.3)	117 (16.9)
No	1029	447 (75.7)	582 (83.1)
Consumed alcohol			
Yes	353 (27.9)	168 (29.5)	185 (26.4)
No	939 (72.1)	435 (70.5)	504 (73.6)
Smoked marijuana			
Yes	120 (10.1)	75 (13.8)	45 (6.8)
No	1153 (89.9)	508 (86.2)	645 (93.2)
Suicidal ideation			
Yes	235 (18.2)	81 (13.8)	154 (22.3)
No	1068 (81.8)	516 (86.2)	552 (77.7)

¹ unweighted frequencies. ² weighted percents.

Table 2. Factors associated with suicidal ideation among junior high school students in Bahamas, 2013

Factor	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Age (years)		
<14	0.91 (0.83-1.00)	2.00 (1.64-2.42)
14	1.35 (1.23-1.48)	2.55 (2.10-3.10)
15	1.26 (1.13-1.40)	2.35 (1.91-2.89)
16+	1	1
Gender		
Male	0.75 (0.71-0.78)	0.77 (0.72-0.81)
Female	1	1
Food security		
No	1.36 (1.26-1.47)	-
Yes	1	
Anxiety		
Yes	2.29 (2.17-2.41)	1.89 (1.76-2.03)
No	1	1
Loneliness		
Yes	2.05 (1.93-2.17)	1.48 (1.37-1.60)
No	1	1
Close friends		
No	1.15 (1.07-1.24)	-
Yes	1	
Truancy		
Yes	1.19 (1.12-1.26)	-
No	1	
Bullied		
Yes	1.74 (1.66-1.83)	1.57 (1.47-1.67)
No	1	1
Attacked		
Yes	1.44 (1.38-1.51)	-
No	1	
In a fight		
Yes	1.27 (1.22-1.33)	1.17 (1.10-1.24)
No	1	1
Smoked cigarettes		
Yes	1.70 (1.56-1.84)	1.17 (1.10-1.24)
No	1	1
Parental understanding		
Yes	0.63 (0.60-0.67)	1.42 (1.25-1.62)
No	1	1
Abused alcohol		
Yes	1.51 (1.43-1.58)	-
No	1	
Consumed alcohol		
Yes	1.53 (1.46-1.60)	1.19 (1.12-1.27)
No	1	1
Smoked Marijuana		
Yes	1.55 (1.45-1.65)	1.51 (1.38-1.65)
No	1	1

DISCUSSION

Statistics from the current study show an 18.2% prevalence rate of suicidal ideation among adolescents attending school in Bahamas. The majority (22.3%) of participants who considered committing suicide were females. On the other hand, 13.8% of the males

experienced suicidal thoughts. The findings of the present study are similar to those obtained by Liu et al. [8] who reported 19% suicidal ideation in China. The results are also in line with the results found among adolescents in Nigeria [9]. However, the estimates are significantly lower than the 39.7% suicidal ideation among Viennese students [10] and 21.6% of the vice reported by Rudatsikira et al. [11] among Ugandan adolescents. Differences in the rates could be due to differences in the age structure, a relatively older population would likely have a higher prevalence of suicidal ideation because suicidal ideation rates increase with age [12].

The finding from the present study that males were 23% less likely to consider suicide is in congruent with findings of Liu et al. [8], Ovuga et al. [13], Lam et al. [14], Borges et al. [15], and McKeown et al. [16]. However, Muula et al. [17] established that males were more likely to consider committing suicide than females. This finding contradicts various studies [8, 13]. Although gender disparity in suicidal ideation in many studies is that females are more seriously going to ponder over committing suicide than males, males on the other hand are more likely to commit suicide and in a more violent manner [18]. It can further be assumed that females just think about committing suicide but they actually don't go on to kill themselves. In addition to this, Brezo et al. [19] found that female gender was also associated with a 2-3 times much likelihood of suicide attempts among Canadian-French participants.

We also observed that adolescents who experienced anxiety were more likely to cogitate on committing suicide than those that did not. The findings are similar to what Omigbun [9] found among adolescents in Nigeria. However, there was a difference with results obtained in Dunlavy's study [20]. The explanation for this disparity is not very clear, however, the Dunlavy's study could have been affected by recall bias.

Results from the current study shows that students less than 14 years old were more likely to think about committing suicide than those that were 16 or older. This is in line with findings of Muula et al. [17]. However, Liu et al. [8] found that adolescents who were less than 14 years were less likely to consider committing suicide than those 16 years or older. The explanation for the difference might not be clear, however, it might be that younger minds are likely to give in to life's problems hence the wish to commit suicide.

Students who reported to be lonely were found to be more likely to have considered committing suicide than those who were not. This finding is similar to that obtained by Stravynski and Boyer [21]. The finding from the present study is also in line with that of Rudatsikira et al. [11] who as well established a positive association between loneliness and suicidal ideation. However, Muula et al. [17], found loneliness to be protective against suicidal ideation. This finding from Muula et al. [17] is surprising because loneliness is a subjective experience of isolation. Therefore, persistent loneliness can alter behaviour and lead to mental disorders [5]. In addition to this, loneliness interferes with the ability to control emotions and can overtime derange perception of others. In the case of adolescents, this distortion in perception is what might bring about suicidal thoughts.

In the current study, bullied students were more likely to seriously consider committing suicide than those that were not. This finding is similar to what Owusu et al. [22] reported. However, Dunlavy et al. [20] observed no significant association between bullying and suicidal ideation. Bullying has bad effects on the victim; one of which is alienation, hence; suicidal thoughts linger in minds of adolescents who may experience bullying in order to escape from this vice. Students who were involved in physical fights were more likely to think about committing suicide than those that were not. This finding is not in tandem with what Randall et al. [23] reported in a study conducted among students in Benin. The disparity

in the results can be due to recall bias by some adolescents when it comes to recalling whether they had experienced the vice in the previous months before the study was carried out.

Another finding from the current study was that adolescents who smoked cigarettes were more likely to seriously consider committing suicide than those who did not. This finding is in tandem with that of Rudatsikira et al. [11] who also establish a positive association between smoking cigarettes and suicidal ideation. Burge et al. [24] also found that alcohol or cannabis use was positively associated with suicidal ideation. The effects of smoking and alcohol consumption may range from mental confusion to mental illnesses. This situation is likely to lead to alienation from others. The shame as a result of these mental confusions may trigger thoughts of wanting to kill one self.

We also found that students who had a good relationship with their parents were more likely to think about suicidal ideation than those that did not. This finding contradicts the findings of several authors [11, 25] who found that having a good relationship with a parent protected adolescent students against suicidal ideation. The finding in the current study suggests that a sound relationship between parents and children may not always yield positive results. Adolescents may take advantage of this good understanding attribute of the parents and indulge in various activities such as unsafe sexual activities and end up being infected. Adolescents in such situations may likely think about committing suicide.

According to the findings of the present study, students that consumed alcohol were more likely to ponder over suicide than those that did not. This finding is congruent with the finding of another study [11]. Alcohol has several effects on the mental health of an individual. The mental stability is distorted if one indulges in alcohol consumption. These effects are even worse for young people. Due to the depressant effects of alcohol, adolescents who engage in beer drinking are left with no option but think of a way to remove the shame that comes as a result of activities associated with drunkenness. Such adolescents contemplate on committing suicide more than they would focus on constructive activities. Furthermore, the present study found that students that smoked marijuana were more likely to consider committing suicide than those who did not. The finding is in agreement with that obtained by Muula et al. [17] study who reported that marijuana use was associated with suicidal ideation. Marijuana also known as cannabis has been used by adolescents to self-medicate in times when they have experienced the thoughts of wanting to kill themselves [26].

The present study had several limitations. The data was collected from school-going adolescents and may not represent all the adolescents in Bahamas. The mode of reporting or responding to questions in the questionnaire was self-reporting and therefore, mis-reporting was possible whether on purpose or just to avoid giving right answers about themselves. Due to the cross sectional design of the study, causation could not be ascribed to the associations that were observed in the current study.

In conclusion, suicidal ideation among adolescents in Bahamas was notably high. The factors associated with suicidal ideation from the current study might be useful in the development and implementation of measures to reduce the prevalence of suicidal ideation.

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Chapter 39

**SUICIDAL IDEATION IN JAMAICA:
PREVALENCE AND ITS CORRELATES AMONG
SCHOOL-GOING ADOLESCENTS IN A
GLOBAL SCHOOL HEALTH-BASED SURVEY**

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ABSTRACT

Suicide is a global public health problem which may start with seriously thinking about how to commit it. Although a study was previously conducted on the prevalence and correlates for suicidal ideation in Jamaica, it was based on a limited sample size and possible factors for suicidal ideation. Weighted logistic regression analyses (bivariate and multivariate) were conducted to establish significant factors associated with suicidal ideation. Unadjusted odds ratio (OR) and adjusted odds ratio (AOR) together with their 95% confidence intervals (CI) are reported. Of the 1,623 students who participated in the survey. Overall, 24.8% (23.0% of male and 25.8% of female) students reported suicidal ideation. Factors associated with suicidal ideation were age, gender, food security, anxiety, loneliness (AOR = 2.01, 95% CI [1.97, 2.05]), close friends (AOR = 1.25; 95% CI [1.22, 1.28]), truancy, bullied (AOR = 1.11; 95% CI [1.10, 1.13]), currently smoked cigarettes (AOR = 1.19; 95% CI [1.17, 1.22]), alcohol consumption [currently drank

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alcohol (AOR = 1.21; 95% CI [1.19, 1.23]) and alcohol abuse (AOR = 1.22; 95% CI [1.20, 1.25]) and parental understanding (AOR = 0.95; 95% CI [0.93, 0.97]). The prevalence of suicidal ideation in Jamaica among adolescents is high. In designing interventions for adolescent mental health and suicide prevention, unhealthy lifestyles and social relationships should be considered.

Keywords: suicidal ideation, prevalence, associated factors, adolescents, Jamaica

INTRODUCTION

Suicide is a global public health problem with 6% of all deaths among young people aged 10-24 years worldwide being attributed to suicide [1]. The rate for suicide in Jamaica is estimated at 2.0–2.7/100,000 population [2]. Suicide is an act of taking one's own life in response to overwhelming, unbearable emotional pain [3] and it can be prevented. One way to prevent suicides is to avoid suicidal ideation that is defined as thoughts, ideas and the desire to commit suicide [4].

The World Health Organization (WHO) and Centers for Disease Prevention and Control (CDC) have conducted a survey, the Global School-Based Health Survey (GSHS), in over 80 countries worldwide to assess health of adolescents aged 13–17 years [5]. Data from this survey have been used to determine magnitudes of adolescent suicide ideation [6] and variety of factors associated with suicidal ideation [4, 7-11]. The prevalence rate of suicidal ideation varies between countries and continents but risk factors have not varied [12]. However, risk factors may differ across surveys due to differences in study populations and sets of risk factors that are considered in analyses.



Source: http://www.worldatlas.com/webimage/countrys/printpage/printpage.php?l=/img/areamap/content/caribbean_map.gif.

Figure 1. Map of Jamaica with its neighbouring countries.

Although a study was conducted on suicidal ideation in Jamaica [13], this study only covered Western Jamaica and the significant factors associated with suicidal ideation were sexual abuse, mental health diagnoses other than depression, self-violence, and ease of access to lethal substances/weapons. A limited sample of 342 adolescents aged 10-19 years from 19 schools in Western Jamaica participated in the survey. The GSHS obtained data from a nationally representative sample and covered more variables different from the ones covered by Kukoyi et al. [13]. It is thus imperative that further studies on suicidal ideation be conducted in Jamaica. High rates of suicidal ideation of 19.8% among boys and 25.7% among girls (overall 23.0%) aged 13-15 years have been reported in Jamaica [14] but not the correlates for suicidal ideation in the same sample of students in the GSHS. Hence, the objective of the current study was to determine prevalence of suicidal ideation as well as factors associated with suicidal ideation among students in grades 7-12 in Jamaica.

METHODS

Further analysis of the 2010 Jamaica GSHS data [15] was conducted. The survey assessed among other factors, mental health of the students. Details of the survey have been described elsewhere [16]. However, in brief, the 2010 Jamaica GSHS was a cross sectional study administered to individual students in grades 7-12 by a self-administered questionnaire.

Students were selected using a two-stage cluster sampling technique. Schools were first selected with probability proportional to enrollment size. Classes were then randomly selected and all students in selected classes were eligible to participate. All the schools that were selected to participate in the survey agreed to do so. An overall response rate of 72% was achieved.

Although the surveys are run by CDC and WHO, the data sets belong to countries. However, two years after completing the survey, the data set and code book associated with the core GSHS questionnaire modules are made available to the public. Only data from core GSHS questions are made public and no school or student identifiers are available.

Data was analyzed using SPSS version 16. The dependent variable was suicidal ideation that was obtained by asking the question 'During the past 12 months, did you ever seriously consider attempting suicide?' Variables were recoded as shown in Table 1. Frequencies were weighted using the following weighting factor:

$$W = W1 \times W2 \times f1 \times f2 \times f3 \times f4$$

where W1 = the inverse of the probability of selecting the school, W2 = the inverse of the probability of selecting the classroom within the school, f1 = a school-level non-response adjustment factor calculated by school size category (small, medium, large), f2 = a class-level non-response adjustment factor calculated for each school, f3 = a student-level non-response adjustment factor calculated by class, and f4 = a post stratification adjustment factor calculated by grade.

Weighted logistic regression analyses (bivariate and multivariate) were used to establish significant factors associated with suicidal ideation. Unadjusted odds ratio (OR) and adjusted odds ratio (AOR) together with their 95% confidence intervals (CI) are reported.

Table 1. Global School-Based Health Survey questions used in the analysis of adolescent suicidal ideation

Variable	Question	Coded	Recoded
Dependent variable			
Suicidal ideation	During the past 12 months, did you ever seriously consider attempting suicide?	1 = Yes; 2 = No	1 = Yes; 2 = No
Independent variables			
Age	How old are you?	1 = 11 years old or younger; 2 = 12 years old; 3 = 13 years old; 4 = 14 years old; 5 = 15 years old; 6 = 16 years old or older	1-3 = 1; 4 = 2; 5 = 3; 6 = 4
Gender	What is your sex?	1 = Male; 2 = Female	1 = 1; 2 = 2
Food security	During the past 30 days, how often did you go hungry because there was not enough food in your home?	1 = Never; 2 = Rarely; 3 = Sometimes; 4 = Most of the time; 5 = Always	4-5 = 1; 1-3 = 2
Anxiety	During the past 12 months, how often have you been so worried about something that you could not sleep at night?	1 = Never; 2 = Rarely; 3 = Sometimes; 4 = Most of the time; 5 = Always	4-5 = 1; 1-3 = 2
Loneliness	During the past 12 months, how often have you felt lonely?	1 = Never; 2 = Rarely; 3 = Sometimes; 4 = Most of the time; 5 = Always	4-5 = 1; 1-3 = 2
Close friends	How many close friends do you have?	1 = 0; 2 = 1; 3 = 2; 4 = 3 or more	1 = 1; 2-4 = 2
Truancy	During the past 30 days, on how many days did you miss classes or school without permission?	1 = 0 days; 2 = 1 or 2 days; 3 = 3 to 5 days; 4 = 6 to 9 days; 5 = 10 or more days	1 = 2; 2-5 = 1
Bullied	Bullied during the past 30 days, on how many days were you bullied?	1 = 0 days; 2 = 1 or 2 days; 3 = 3 to 5 days; 4 = 6 to 9 days; 5 = 10 to 19 days; 6 = 20 to 29 days; 7 = All 30 days	1 = 2; 2-7 = 1
Attacked	During the past 12 months, how many times were you physically attacked?	1 = 0 times; 2 = 1 time; 3 = 2 or 3 times; 4 = 4 or 5 times; 5 = 6 or 7 times; 6 = 8 or 9 times; 7 = 10 or 11 times; 8 = 12 or more times	1 = 2; 2-8 = 1
In a fight	During the past 12 months, how many times were you in a physical fight?	1 = 0 times; 2 = 1 time; 3 = 2 or 3 times; 4 = 4 or 5 times; 5 = 6 or 7 times; 6 = 8 or 9 times; 7 = 10 or 11 times; 8 = 12 or more times	1 = 2; 2-8 = 1
Currently smoked cigarettes	During the past 30 days, on how many days did you smoke cigarettes?	1 = 0 days; 2 = 1 or 2 days; 3 = 3 to 5 days; 4 = 6 to 9 days; 5 = 10 to 19 days; 6 = 20 to 29 days; 7 = All 30 days	1 = 2; 2-7 = 1
Parental understanding	During the past 30 days, how often did your parents or guardians understand your problems and worries?	1 = Never; 2 = Rarely; 3 = Sometimes; 4 = Most of the time; 5 = Always	1-3 = 2; 4-5 = 1
Alcohol abuse	During your life, how many times did you drink so much alcohol that you were really drunk?	1 = 0 times; 2 = 1 or 2 times; 3 = 3 to 9 times; 4 = 10 or more times	1 = 2; 2-4 = 1
Currently drank alcohol	During the past 30 days, on how many days did you have at least one drink containing alcohol?	1 = 0 days; 2 = 1 or 2 days; 3 = 3 to 5 days; 4 = 6 to 9 days; 5 = 10 to 19 days; 6 = 20 to 29 days; 7 = All 30 days	1 = 2; 2-7 = 1

Table 2. Distribution of factors considered in the analysis by gender among junior high school students in Jamaica, 2010

Factor	Total n ¹ (%) ²	Males n ¹ (%) ²	Females n ¹ (%) ²
Age			
<14	236 (13.1)	117 (11.1)	112 (14.4)
14	510 (27.8)	254 (27.3)	253 (28.4)
15	479 (29.3)	220 (28.9)	257 (30.1)
16+	375 (29.9)	184 (32.7)	190 (27.1)
Gender			
Male	778 (51.4)	-	-
Female	817 (48.6)	-	-
Food security			
No	167 (13.5)	93 (15.3)	69 (11.7)
Yes	1425 (86.3)	671 (84.7)	734 (88.3)
Anxiety			
Yes	278 (19.0)	105 (14.4)	166 (23.6)
No	1337 (81.0)	669 (85.6)	647 (76.4)
Loneliness			
Yes	292 (19.5)	106 (14.5)	182 (24.6)
No	1263 (80.5)	643 (85.5)	600 (75.4)
Close friends			
No	156 (11.6)	75 (11.8)	77 (11.2)
Yes	1425 (88.4)	674 (88.2)	727 (88.8)
Truancy			
Yes	517 (39.2)	276 (42.8)	232 (35.2)
No	1067 (60.8)	476 (57.2)	573 (64.8)
Bullied			
Yes	551 (41.8)	271 (43.1)	265 (39.2)
No	931 (58.2)	428 (56.9)	492 (60.8)
Attacked			
Yes	657 (45.8)	353 (47.8)	289 (42.4)
No	956 (54.2)	420 (52.2)	526 (57.6)
In a fight			
Yes	719 (50.2)	412 (58.1)	287 (41.0)
No	900 (49.8)	364 (41.9)	529 (59.0)
Currently smoked cigarettes			
Yes	309 (24.6)	182 (32.0)	120 (16.8)
No	1267 (75.4)	570 (68.0)	681 (83.2)
Parental understanding			
Yes	499 (33.9)	249 (35.6)	241 (32.0)
No	1077 (66.1)	504 (64.4)	556 (68.0)
Alcohol abuse			
Yes	510 (39.2)	293 (46.7)	203 (30.0)
No	1035 (60.8)	440 (53.3)	586 (70.0)
Currently drank alcohol			
Yes	819 (55.4)	430 (60.8)	375 (50.3)
No	712 (44.6)	305 (39.2)	394 (49.7)
Suicidal ideation			
Yes	343 (24.8)	138 (23.0)	197 (25.8)
No	1187 (75.2)	590 (77.0)	582 (74.2)

¹ unweighted frequencies. ² weighted percents.

RESULTS

Of the 1,623 students who participated in the survey, 51.4% were males and 13.1% were aged less than 14 years. Overall, 13.5% of the students reported that they had no food security. About 1 in 5 students reported being anxious (19.0%) and lonely (19.5%). Most

(88.4%) of the students had close friends. About a third (39.2%) of the students missed school or classes without permission. Over 4 in 10 students were involved in violence: 41.8% were bullied, 45.8% were attacked and 50.2% were involved in a fight. Current cigarette smoking was reported by 32.0% of males and 16.8% of females. Meanwhile, alcohol abuse was reported by 46.7% of males and 30.0% of females; and current alcohol use by 60.8% of males and 50.3% of females. About 1 in 4 of the students reported that they had suicidal thoughts: 23.0% of males and 25.8% of females with an overall rate of 24.8%. These results are shown in Table 2.

Table 3. Factors associated with suicidal ideation among junior high school students in Jamaica, 2010

Factor	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Age (years)		
<14	1.44 (1.41, 1.48)	1.19 (1.14, 1.23)
14	0.85 (0.84, 0.87)	1.02 (0.99, 1.05)
15	0.88 (0.86, 0.90)	1.10 (1.07, 1.13)
16+	1	1
Gender		
Male	0.93 (0.92, 0.94)	0.86 (0.84, 0.87)
Female	1	1
Food security		
No	1.62 (1.59, 1.64)	1.44 (1.41, 1.47)
Yes	1	1
Anxiety		
Yes	1.54 (1.52, 1.56)	1.08 (1.06, 1.10)
No	1	1
Loneliness		
Yes	1.99 (1.97, 2.02)	2.01 (1.97, 2.05)
No	1	1
Close friends		
No	1.41 (1.38, 1.43)	1.25 (1.22, 1.28)
Yes	1	1
Truancy		
Yes	1.36 (1.34, 1.38)	1.07 (1.05, 1.09)
No	1	1
Bullied		
Yes	1.46 (1.44, 1.48)	1.11 (1.10, 1.13)
No	1	1
Attacked		
Yes	1.34 (1.33, 1.36)	-
No	1	1
In a fight		
Yes	1.19 (1.17, 1.20)	-
No	1	1
Currently smoked		
Yes	1.54 (1.52, 1.56)	1.19 (1.17, 1.22)
No	1	1
Alcohol abuse		
Yes	1.58 (1.56, 1.60)	1.22 (1.20, 1.25)
No	1	1
Current alcohol use		
Yes	1.28 (1.27, 1.30)	1.21 (1.19, 1.23)
No	1	1
Parental understanding		
Yes	1.03 (1.02, 1.04)	0.95 (0.93, 0.97)
No	1	1

Correlates for suicidal ideation are shown in Table 3. All the factors considered in the analysis were significantly associated with suicidal ideation in bivariate analyses. However, in Multivariate analysis, the variables 'attacked' and 'in a fight' were not significantly associated with suicidal ideation. Students aged less than 14 years (AOR = 1.19; 95% CI [1.14, 1.23]) and those of age 15 years (AOR = 1.10; 95% CI [1.07, 1.13]) were more likely to have suicidal thoughts than students aged 16 years or older. Male students were 14% (AOR = 0.86; 95% CI [0.84, 0.87]) less likely to have suicidal ideation compared to female students. Students from homes that had no food security were 44% (AOR = 1.44; 95% CI [1.41, 1.47]) more likely to have suicidal ideation.

Compared to students who were not anxious, students who were anxious were 8% more likely to have suicidal ideation (AOR = 1.08; 95% CI [1.06, 1.10]). Meanwhile, students who were lonely were 2.01 (95% CI [1.97, 2.05]) times more likely to have suicidal thoughts compared to students who were not lonely. Students who had no close friends were 25% (AOR = 1.25; 95% CI [1.22, 1.28]) more likely to have suicidal thought compared to students who had close friends. Missing school or classes was positively associated with suicidal ideation (AOR=1.07; 95% CI [1.05, 1.09]).

Students who were bullied were 11% (AOR = 1.11; 95% CI [1.10, 1.13]) more likely to have suicidal ideation compared to students who were not bullied. Compared to students who did not smoke cigarettes, students who smoked cigarettes were more likely to have suicidal ideation (AOR = 1.19; 95% CI [1.17, 1.22]). Alcohol consumption was positively associated with suicidal ideation: alcohol abuse (AOR = 1.22; 95% CI [1.20, 1.25]); and currently drank alcohol (AOR = 1.21; 95% CI [1.19, 1.23]). Students who had parental understanding were less likely to have suicidal ideation (AOR = 0.95; 95% CI [0.93, 0.97]).

DISCUSSION

About 1 in 4 of the students in the current study reported that they had suicidal thoughts: 23.0% of males and 25.8% of females with an overall rate of 24.8%. The following factors were associated with suicidal ideation in the current study: age, gender, food security, anxiety, loneliness, close friends, truancy, bullied, currently smoked cigarettes, alcohol and parental understanding. The observed rate of 23.0% in the current study is much higher than the 9.7% that was previously reported by Abel et al. [17] among the school-going children aged 10-15 years. The observed high rate of suicidal ideation in the current study can partly be explained by the economic hardship that the population had been facing in Jamaica. The Jamaican economy was in recession between 2004 and 2010 and worsened by hurricanes in 2004 and 2007. The heavy rains caused widespread damage to agriculture and mining [18]. The effects of the hurricanes and floods may have had untold mental health effects on the population, and life might not have been worth living for the affected persons; and adolescents are at the greatest risk for suicidal ideation [19].

The prevalence of suicidal ideation was higher in females than males. Similar findings have been reported before [20, 21]. The higher rate of suicidal ideation in females may be due to the higher rate of depression in this gender than male gender [22] as a result of more girls experiencing sexual abuse than boys [23]. However, in some studies [24, 25] no significant associated has been reported between gender and suicidal ideation. Yet in a study by Muula et

al. [26], males were more likely to have suicidal thoughts than females. Cultural differences in different populations relating to gender may partly explain differences observed in the relationship between gender and suicidal ideation.

The finding that students aged less than 14 years were more likely to have suicidal thoughts compared to those aged 16 years or older accords the finding by Muula et al. [26]. Adolescence is a period of identity crisis that may result in mental ill health. However, this finding is not universal as other researchers have not found a significant association between age and suicidal ideation [11, 27-29].

Anxiety has been reported to be significantly associated with suicidal thoughts [11] and so is it from the current study. Information is needed to understand what is making students anxious so that interventions can be implemented to curtail suicidal ideation. The finding from the current study that those who were lonely were about twice likely to have suicidal thoughts compared to those who were not lonely contradicts the finding by Muula et al. [26] who reported that those who were lonely were less likely to have suicidal thoughts. By the cross sectional design of both studies, it is possible that loneliness may lead to suicidal thoughts and conversely because of thinking about taking one's own life, the individual may be withdrawn from public. In either case, companionship is encouraged to avoid suicide. Truancy has been associated with suicidal ideas in the current study. This finding accords that of D'Aulerio et al. [30]. It is possible that skipping school that may be as a result of depression may lead to suicidal ideation. Alternatively thinking about taking one's own life may make one abscond from school. Further studies are needed to elucidate this relationship between truancy and suicidal ideation.

Bullying that can be physical or emotional has been reported in previous studies to be associated with suicidal ideation [8, 11, 28, 31]. A similar finding is reported in the current study. In bullying, bullied students are rejected and abused by their peers and could lead to suicidal thoughts [32]. Bullying can be stressful and it is important to stop bullying in schools [33]. It is thus important that violence is prevented among adolescents to avoid suicidal thoughts.

Substance abuse has been shown to be associated with suicidal ideation. The present study revealed a significant association between smoking and suicidal ideation. Similarly, previous studies have also observed smoking to be significantly associated with suicidal ideation [9, 27, 29, 34, 35]. Alcohol consumption has frequently been reported to be associated with suicidal ideation [8, 11, 26, 36]. Further, alcohol abuse was also associated with suicidal thoughts in the present study and in other previous studies [11, 34]. Rossow et al. [37] argued that substance abuse may augment depressive thoughts and trigger ideation, suggesting that substance use may not directly affect suicidal ideation. Because early initiation of smoking and alcohol consumption are associated with adolescent suicidal ideation [38, 39], prevention of smoking and alcohol consumption among adolescents may be useful in preventing suicide thoughts and in turn suicides. However, not all people with suicidal thoughts end up committing suicide [40].

Poor child-parent relationship may cause developmental issues [41, 42] such as poor physical and emotional status, as well as social and cognitive development that may lead to suicidal thoughts [43]. Lack of parental support was also reported to be associated with suicidal ideation [11]. In the present study, students without close friends were more likely to have suicidal thoughts compared to those with close friends. Social support is important in preventing suicidal thoughts and eventually suicide.

In conclusion, the prevalence of suicidal ideation in Jamaica among adolescents is high. In designing interventions for adolescent mental health and suicide prevention, the following should be considered: prevention of bullying among adolescents, encouraging healthy relationships with friends and parents, and discouraging initiation of smoking and alcohol consumption.

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Chapter 40

SUICIDAL IDEATION PREVALENCE AND ITS ASSOCIATED FACTORS AMONG SCHOOL-GOING ADOLESCENTS IN PAKISTAN

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ABSTRACT

Suicidal ideation and its factors have not received attention in Pakistan despite it being a global public health problem among adolescents. Although suicidal ideation is still of major public health importance, some studies indicate a drop in suicide rates in the last decade. However, there are few studies that have been conducted in Pakistan to address this vice. The aim of the present study was to determine the prevalence and factors of suicidal ideation among in-school adolescents in Pakistan. Therefore, the findings from the current study will aid the formulation of prevention programmes aimed at reducing the prevalence of suicidal ideation. Secondary data from the 2009 Pakistan Global School-Based student Health Survey (GSHS) was analysed using bivariate and multivariate logistic regression analyses at 95% confidence interval. The prevalence of suicidal ideation among in-school adolescents (N = 5192) was 7.2% (7.6% of males and 6.7% of females). Being of age <15 years, male gender, being attacked and parental understanding were protective against suicidal ideation. The rest of the correlates were found to be risk factors (food security, anxiety, loneliness, having close friends, truancy,

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bullying, fights and smoking cigarettes) of suicidal ideation. The results from the present study indicate the need to provide adequate intervention programmes that will effectively curb the prevalence rates of suicidal ideation in Pakistan.

Keywords: suicidal ideation, prevalence, risk factors, adolescent, Pakistan

INTRODUCTION

Worldwide, suicide accounts for an estimated 6% of all deaths among young people [1] and is the fourth leading cause of death globally among the youth with age ranging from 15-19 years [2]. Thus, suicide is a major public health problem. Low and middle-income countries are home to more than 90% of the world's children and youth and also account for over 75% of global suicide deaths [3]. According to a study by WHO [4], it was reported that suicide is a primary cause of death in the youth population around the World. In Pakistan, suicide ideation has been under studied.

According to a study by Nock et al. [5], suicidal ideation often emerges in adolescence and is more common among females. There is need for more research on youth with suicidal thoughts as it is a precursor to suicide completion [6]. Studies on suicidal ideation in both low and middle income countries have produced varying suicidal rates; lower rates of 16% in Lebanon [7] and 17.8% in China [8]; higher in prevalence in some African countries: 19.6% in Uganda, 23.1% in Botswana, 27.9% in Kenya, and 31.9% in Zambia [9]. In Pakistan, Masood [10] reported a prevalence of 3.3%.

Factors associated with risk of adolescent suicidality have been identified as; being female, exposure to bullying and violence, alcohol and drug use, mental disorders and weak family and peer relationships [11-13]. However, the risk factors that influence suicide can be summarised as; psychiatric, biological, social and environmental. In Pakistan, Shaikh [10] found that anxiety, having close friends, parents checking homework and smoking were significantly associated with suicidal ideation. However, the results of this study [10] cannot be compared with results from similar studies because of differences in statistical methods, categorization of factors and factors considered in the analyses. Nevertheless, factors associated with suicidal ideation may vary according to populations within and among different countries. Thus, it is important that studies are conducted to establish factors that may be useful in formulating interventions to curb suicidal ideation in specific populations.

METHODS

The present study utilised secondary analysis of existing data from the Pakistan Global School-based Health Survey (GSHS) conducted in 2009. This survey involved students in grades 8 to 10. The survey used a two-stage probability cluster sampling procedure in order to rule out bias. In addition to ruling out selection bias, the procedure aided the production of data representative of all students in Pakistan. The first stage of sampling involved the selection of schools chosen with probability proportional to the enrolment size. On the other hand, the second stage comprised selecting classes from the selected schools. A self-

completed questionnaire was implored to capture the information. The response rate from the schools was 88%, while that of students was 87%.

The dependent variable was suicidal ideation, while independent variables were: age, gender, food security, smoking cigarettes, parental understanding, close friends, having been bullied and attacked and truancy. A weighting factor was utilised in the current study with the aim of reflecting the likelihood of sampling each student. Furthermore, weighting the sample further reduced bias by compensating for differing patterns of non-response. As a result, data analyses were weighted. SPSS version 16 was used to conduct a backward logistic regression analysis so as to determine associations between independent variables and suicidal ideation at 95% confidence interval.

RESULTS

A total of 5,192 adolescents participated in the survey of which 61.2% were males. The majority (38.9%) of the students were aged 14 years. Those aged 16 years or older accounted for 3.1%. Table 1 shows the sample characteristics of the participants. Among the respondents, 5.8% reported to have had challenges in accessing food, 8.4% were anxious, 12.2% were lonely, 8.0% had no close friends, and 23.4% reported to have been truant. In addition, 41.3% were bullied, 34.1% were attacked and 37.4% were involved in physical fights. Other students reported to have smoked cigarettes (6.3%). The prevalence of suicidal ideation was 7.2% overall.

Table 2 presents variables that were significantly associated with suicidal ideation. Students less than 14 years old were 13% less likely to cogitate about committing suicide than those aged 16 years or older. Furthermore, students aged 15 years old were 5% more likely to contemplate on suicide than those aged 16 years or older.

In addition, Table 2 also shows males being 7% less likely to ponder over committing suicide than females. Students with anxiety were 72% more likely to have thoughts of committing suicide than those without. Students who reported loneliness were 21% more likely to consider committing suicide than those who did not. Furthermore, students who were truant and had no close friends were 19% and 43%, respectively, more likely to have suicidal thoughts. Students that were bullied were 19% more likely to think about committing suicide than those that were not bullied. Surprisingly, students that were attacked were 2% less likely to have considered committing suicide than those who were not attacked. Students that were involved in a fight and smoked were 12% and 41%, respectively, more likely to ponder over committing suicide than those who were not. Furthermore, students who had parental understanding were 11% less likely to cogitate on committing suicide than those that did not have understanding parents.

DISCUSSION

Our study found an overall suicidal ideation prevalence of 7.2% (7.6% among males and 6.7% among females). This finding is similar to the rate of suicidal ideation among the adolescents in Thailand (8.8%) [14] and Sri Lanka 9.9% [15]. However, the suicidal ideation

rate in the current study is higher than that reported by Shaikh [10], despite both studies using the same data set. It is possible that the difference could have been due to transcribing error.

Table 1. Distribution of factors considered in the analysis by gender among adolescents attending school in Pakistan, 2009

Factor	Total n ¹ (%) ²	Males n ¹ (%) ²	Females n ¹ (%) ²
Age			
<14	963 (22.7)	689 (19.8)	274 (27.3)
14	2145 (38.9)	1630(39.6)	515 (37.7)
15	1897 (35.3)	1427(36.8)	470 (33.0)
16+	172 (3.1)	147 (3.8)	26 (1.9)
Gender			
Male	3897 (61.2)	-	-
Female	1285(38.8)	-	-
Food security			
No	311 (5.8)	253 (6.6)	58 (4.5)
Yes	4815 (94.2)	3597 (93.4)	1218 (95.5)
Anxiety			
Yes	442 (8.4)	318 (8.1)	124 (8.8)
No	4717 (91.6)	3557 (91.9)	1160 (91.2)
Loneliness			
Yes	621 (12.2)	442 (11.5)	179 (13.3)
No	4505 (87.8)	3412 (88.5)	1093 (86.7)
Close friends			
No	393 (8.0)	272 (7.1)	121 (9.5)
Yes	4724 (92.0)	3575 (92.9)	1149 (90.5)
Truancy			
Yes	1312 (23.4)	1139 (30.1)	173 (12.8)
No	3832 (76.6)	2724 (69.9)	1108 (87.2)
Bullied			
Yes	2025 (41.3)	1589 (45.1)	436 (35.5)
No	2643 (58.7)	1886 (54.9)	757 (64.5)
Attacked			
Yes	1876 (34.1)	1520 (38.6)	356 (26.9)
No	3297 (65.9)	2368 (61.4)	929 (73.1)
In a fight			
Yes	2116 (37.4)	1815 (46.9)	301 (22.5)
No	3051 (62.6)	2066 (53.1)	985 (77.5)
Smoked cigarettes			
Yes	386 (6.3)	375 (9.8)	11 (0.9)
No	4753 (93.7)	3479 (90.2)	1274 (99.1)
Parental understanding			
Yes	2717 (54.6)	1903 (49.0)	814 (63.4)
No	2408 (45.4)	1948 (51.0)	460 (36.6)
Suicidal ideation			
Yes	375 (7.2)	286 (7.6)	89 (6.7)
No	4731(92.8)	3542 (92.4)	1189 (93.3)

¹ unweighted frequencies. ² weighted %.

Previous studies have reported findings with regard to more female adolescents considering suicide than males [16-18]. The finding in the current study confirms this finding. The results from the current study also show that students less than 14 years and those aged 14 years were less likely to consider committing suicide than those aged 16 years or older. This result is similar to that found by Liu et al. [19] who established that increase in age was

associated with suicidal ideation. However, Muula et al. [20] reported that adolescents aged less than 14 years were more likely to consider committing suicide than those aged 16 years or older. The explanation for this difference is not well known. It might be that younger adolescents may not be as stressed as the older ones to result in having suicidal thoughts because the ‘adolescence crisis’ might not have greatly affected younger adolescents. Alternatively, younger adolescents may not have developed coping strategies for stress arising from the ‘adolescent crisis,’ resulting in the younger adolescents being more likely to have suicidal thoughts than older adolescents as reported by Muula et al. [20].

Table 2. Factors associated with suicidal ideation among adolescents attending school in Pakistan, 2009

Factor	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Age (years)		
<14	0.78 (0.77-0.79)	0.87 (0.86-0.88)
14	0.92 (0.91-0.92)	0.94 (0.93-0.95)
15	1.05 (1.04-1.06)	1.05 (1.04-1.06)
16+	1	1
Gender		
Male	1.07 (1.07-1.08)	0.93 (0.93-0.94)
Female	1	1
Food security		
No	1.44 (1.43-1.45)	1.24 (1.22-1.25)
Yes	1	1
Anxiety		
Yes	2.10 (2.08-2.11)	1.72 (1.71-1.73)
No	1	1
Loneliness		
Yes	1.68 (1.67-1.69)	1.21 (1.20-1.22)
No	1	1
Close friends		
No	1.51 (1.50-1.52)	1.43 (1.42-1.44)
Yes	1	1
Truancy		
Yes	1.24 (1.23-1.24)	1.19 (1.18- 1.20)
No	1	1
Bullied		
Yes	1.36 (1.36-1.37)	1.19 (1.18-1.19)
No	1	1
Attacked		
Yes	1.17 (1.17-1.18)	0.98 (0.98-0.99)
No	1	1
In a fight		
Yes	1.27 (1.26-1.27)	1.12 (1.12-1.13)
No	1	1
Smoked cigarettes		
Yes	1.66 (1.65-1.67)	1.41 (1.40-1.42)
No	1	1
Parental understanding		
Yes	0.83 (0.83-0.84)	0.89 (0.88-0.89)
No	1	1

It was also observed in the current study that adolescents who had challenges with food were more likely to think about committing suicide than those that had enough to eat. This finding is congruent with a study done by Randall et al. [21], who concluded that adolescent

students who did not have enough to eat were likely to ponder on committing suicide compared to those that had enough food. Biologically, food plays a role in thinking abilities. Adolescents that lack food may be prone to engaging themselves in a cluster of unhealthy behaviours such as alcohol abuse, stealing and sexual intercourse that would depress them and later lead to suicidal thoughts.

The current study also found that students who reported to have been anxious were more likely to ponder on committing suicide compared to those that were not. However, the finding in the current study differs with that obtained by Dunlavy et al. [22] in Tanzania. In that study, students who were anxious were less likely to consider committing suicide than those who were not. A clear explanation for this difference is difficult to find and calls for further studies in establishing the association between anxiety and suicidal ideation.

We further established that lonely students were more likely to think about committing suicide compared to those who were not. This is in line with the finding of Rudatsikira et al. [23] who found a positive association between loneliness and suicidal ideation. On the contrary, the finding by Muula et al. [20] is not congruent with the result from the current study. The disparity may be as a result of the social and cultural teachings that adolescents are exposed to in the setting where Muula et al. carried out the study.

Lack of close friends was found to be positively associated with suicidal ideation. This is also reported by Omigbodun [24]. However, the result by Randall et al. [21] contradicts the finding from the present study. The explanation for this difference is not clear. However, while positive social support from close friends might protect adolescents from suicidal ideation, peer pressure arising from close friend may in turn result in thoughts of committing suicide. The current study could not establish causation and, hence, the need for further studies.

Students who were truant in the current study were more likely to think about committing suicide than students who were not. However, Dunlavy et al. [22] established a negative association between truancy and suicidal ideation. Truancy may be brought by various factors such as bullying, attacks and fights in school. Such factors might deter adolescents from attending school regularly [25]. Therefore, the link between truancy and suicidal thoughts may not be direct and the current study could not establish that.

In the current study, students that reported having been bullied before were more likely to contemplate on committing suicide compared to those who were not. The findings are in tandem with those of Owusu et al. [26] who found a positive association between bullying and suicidal ideation. Bullying tends to traumatise and alienate the victimised adolescents who may think of committing suicide. We also observed that students who were attacked were less likely to consider committing suicide. This is contrary to the finding established by Omigbodun [24]. Attacks may bring negative thoughts about one's life. However, if the frequency of attacks is high, adolescents may not worry so much about the act and not think about committing suicide.

Students that smoked were more likely to ponder over committing suicide than those that did no smoke. This result is similar to what Rudatsikira et al. [23] and Muula et al. [20] reported. Adolescents who indulge in smoking are likely to be stressed and in turn likely to think about committing suicide. Adolescents who abuse substances are likely to be unhealthy (physically and psychological) and should be targeted for intervention to curb suicide.

Our study also established that adolescents who had parental understanding were less likely to cogitate about suicide. The findings from the current study agrees with those of Cash

and Bridge [27] who found that having parental understanding was protective against suicidal ideation. The presence of parents who understand gives children a platform to share problems. Such adolescents are given guidance over issues affecting them and therefore, they are able to withstand life's pressures.

In conclusion, although the prevalence of suicidal ideation among school going adolescents in Pakistan is low, interventions must be put in place to curtail suicidal ideation by considering factors that have been identified in the current study.

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Chapter 41

SUICIDAL IDEATION IN GUYANA: PREVALENCE AND ITS ASSOCIATED FACTORS AMONG ADOLESCENTS IN A GLOBAL SCHOOL HEALTH-BASED SURVEY

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ABSTRACT

Guyana is the ninth top most suicidal country in the world. A series of Global School-based Health Survey (GSHS) are conducted to monitor trends in the prevalence of health behaviors and establish protective factors among school-going adolescents. Two surveys were conducted in 2014 and 2010. The current study presents results from the second survey conducted in 2010. Weighted logistic regression (univariate or multivariate) analyses were conducted to determine factors associated with suicidal ideation. Unadjusted odds ratios (OR) and adjusted (AOR) together with their 95% confidence intervals (CI) are reported. A total of 2,392 students participated in the survey of which 48.5% were males. Suicidal ideation was reported by 23.5% (16.4% of male and 29.7% of female) participants. Correlates for suicidal ideation were: age, gender (AOR = 0.63, 95% CI [0.61, 0.65]), anxiety (AOR = 1.29, 95% CI [1.24, 1.34]), loneliness (AOR = 1.42, 95% CI [1.37, 1.47]), close friends, truancy, bullied (AOR = 1.36, 95% CI [1.32, 1.40]), attacked (AOR = 1.19, 95% CI [1.16, 1.23]), currently smoked cigarettes, alcohol abuse (AOR = 1.21, 95% CI [1.17, 1.25]), current alcohol use (AOR = 1.22, 95%

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CI [1.18, 1.25]) and parental understanding (AOR = 0.75, 95% CI [0.73, 0.78]). Healthy lifestyles, peer and parental relationships should be promoted in order to avoid suicidal thoughts.

Keywords: suicidal ideation, prevalence, correlates, adolescents, Guyana

INTRODUCTION

Suicide is a major health problem in many countries worldwide [1]. In particular, in Guyana, suicide was the leading cause of death among persons in the age group 15-24 years in the period 2004-2006 [2]. Overall, Guyana has the highest suicide rate in the Caribbean countries and is the ninth top most suicidal country in the world with an incidence of 45 suicides per 100,000 population [3]. The process of ending up with an attempted or complete suicide may start with thinking about committing suicide, planning it and finally executing it. However, this progression may not always hold [4]. An estimate of 60% rate of transition has been observed from suicidal ideation to first suicide attempt within the first year of ideation onset [5]. Another study by Kessler et al. [6] reported the following rates of transition of 34% from ideation to a plan, 72% from a plan to an attempt, and 26% from ideation to an unplanned attempt. Suicidal ideation is a risk factor for complete suicide [7] and it is thus important that efforts are directed to curtailing thoughts about committing suicide by investigating its correlates.

While data is available on suicidal ideation in developed countries, it is limited in developing countries [8, 9], including Guyana. The Global School-based Health Survey (GSHS) was developed by the World Health Organization (WHO) in collaboration with United Nations' UNICEF, UNESCO, and UNAIDS; and with technical assistance from CDC to obtain data on young (aged 13-17 years) people's health behaviour and protective factors for leading causes of morbidity and mortality among children and adults worldwide [10]. Using this survey, trends in the prevalence of health behaviours and protective factors are established for use in evaluation of school health programs [11].

The first Guyana Global School-based Health Survey (GSHS) was conducted in 2004. In this survey, 18.4% of the students (14.9% of males and 21.6% of females) had suicidal ideation [12]. We are not aware of any intervention that was implemented in Guyana since the 2004 GSHS was conducted. However, even in the absence of any intervention, the survey itself may have had an impact on the prevalence of suicidal ideation and its associated factors. It is thus important to keep track of the prevalence of suicidal ideation and its correlates. Moreover, only a limited number of factors were considered in the 2004 analysis of factors associated with suicidal ideation. Furthermore, there is growing literature on the occurrence of suicidal thoughts and its correlates in developing countries: Seychelles, Kenya, Botswana, Namibia, Zimbabwe, Tanzania, and Uganda [12-14] that needs to be updated with new evidence for use in suicide prevention among adolescents.

In line with the GSHS object of tracking the occurrence of mental health situation among the young population, we conducted the current study to determine the current prevalence rate of suicidal ideation and its correlates. We considered more factors in the 2010 that were identified in the growing evidence of factors associated with suicidal ideation than 2004 Guyana GSHS analysis.

Table 1. Variable definition and codes

Variable	Coded	Recoded	Redefined variable
Outcome variable			
During the past 12 months, did you ever seriously consider attempting suicide?	1 = Yes; 2 = No	1 = 1; 2 = 2	Suicidal ideation
Independent variables			
How old are you?	1 = 11 years old or younger; 2 = 12 years old; 3 = 13 years old; 4 = 14 years old; 5 = 15 years old; 6 = 16 years old or older	1-3 = 1; 4 = 2; 5 = 3; 6 = 4	Age
What is your sex?	1 = Male; 2 = Female	1 = 1; 2 = 2	Gender
During the past 30 days, how often did you go hungry because there was not enough food in your home?	1 = Never; 2 = Rarely; 3 = Sometimes; 4 = Most of the time; 5 = Always	4-5 = 1; 1-3 = 2	Food security
During the past 12 months, how often have you been so worried about something that you could not sleep at night?	1 = Never; 2 = Rarely; 3 = Sometimes; 4 = Most of the time; 5 = Always	4-5 = 1; 1-3 = 2	Anxiety
During the past 12 months, how often have you felt lonely?	1 = Never; 2 = Rarely; 3 = Sometimes; 4 = Most of the time; 5 = Always	4-5 = 1; 1-3 = 2	Loneliness
How many close friends do you have?	1 = 0; 2 = 1; 3 = 2; 4 = 3 or more	1 = 1; 2-4 = 2	Close friends
During the past 30 days, on how many days did you miss classes or school without permission?	1 = 0 days; 2 = 1 or 2 days; 3 = 3 to 5 days; 4 = 6 to 9 days; 5 = 10 or more days	1 = 2; 2-5 = 1	Truancy
During the past 30 days, on how many days were you bullied?	1 = 0 days; 2 = 1 or 2 days; 3 = 3 to 5 days; 4 = 6 to 9 days; 5 = 10 to 19 days; 6 = 20 to 29 days; 7 = All 30 days	1 = 2; 2-7 = 1	Bullied
During the past 12 months, how many times were you physically attacked?	1 = 0 times; 2 = 1 time; 3 = 2 or 3 times; 4 = 4 or 5 times; 5 = 6 or 7 times; 6 = 8 or 9 times; 7 = 10 or 11 times; 8 = 12 or more times	1 = 2; 2-8 = 1	Attacked
During the past 12 months, how many times were you in a physical fight?	1 = 0 times; 2 = 1 time; 3 = 2 or 3 times; 4 = 4 or 5 times; 5 = 6 or 7 times; 6 = 8 or 9 times; 7 = 10 or 11 times; 8 = 12 or more times	1 = 2; 2-8 = 1	In a fight
During the last 30 days, on how many days did you smoke cigarettes?	1 = 0 days; 2 = 1 or 2 days; 3 = 3 to 5 days; 4 = 6 to 9 days; 5 = 10 to 19 days; 6 = 20 to 29 days; 7 = All 30 days	1 = 2; 2-7 = 1	Currently smoked cigarettes
During the past 30 days, how often did your parents or guardians understand your problems and worries?	1 = Never; 2 = Rarely; 3 = Sometimes; 4 = Most of the time; 5 = Always	1-3 = 2; 4-5 = 1	Parental understanding
During your life, how many times did you drink so much alcohol that you were really drunk?	1 = 0 times; 2 = 1 or 2 times; 3 = 3 to 9 times; 4 = 10 or more times	1 = 2; 2-4 = 1	Alcohol abuse
During the past 30 days, on how many days did you have at least one drink containing alcohol?	1 = 0 days; 2 = 1 or 2 days; 3 = 3 to 5 days; 4 = 6 to 9 days; 5 = 10 to 19 days; 6 = 20 to 29 days; 7 = All 30 days	1 = 2; 2-7 = 1	Currently used alcohol

METHODS

The 2010 Guyana GSHS was conducted among students in Forms 2, 3, 4, and other. Details of the methodology that was used in the survey are described elsewhere [11]. In summary, the sample was drawn using a two-stage cluster sampling method in which at the first stage of sampling, schools were selected with probability proportional to enrolment size. At stage two of sampling, classes were randomly selected and all students in selected classes were eligible to participate. The overall response rate was 76% with a school response rate of 97% and student response rate of 78%.

A self-administered questionnaire was used to collect the information. The questionnaire included sections on alcohol use, dietary behaviours, hygiene, mental health, physical activity, protective factors, sexual behaviours, tobacco use, violence and unintentional injury. The variables in this study included: age, gender, food security, anxiety, loneliness, close friends, truancy, bullying, being attacked, involvement in a fight, smoking cigarettes, alcohol consumption (use and abuse) and parental understanding as independent variables and suicidal ideation as the outcome variable. Table 1 shows how the variables were originally coded and re-coded.

Logistic regression (univariate or multivariate) analyses were conducted to determine factors associated with suicidal ideation. Unadjusted odds ratios (OR) and adjusted (AOR) together with their 95% confidence intervals (CI) are reported. Analyses were weighted with the following weight to allow results to be generalized to the entire population, not just to those that took part in the survey.

A weighting factor was used in the analysis to reflect the likelihood of sampling each student and to reduce bias by compensating for differing patterns of non-response. The weight used for estimation is given by the following formula:

$$W = W1 \times W2 \times f1 \times f2 \times f3 \times f4$$

where W1 = the inverse of the probability of selecting the school, W2 = the inverse of the probability of selecting the classroom within the school, f1 = a school-level non-response adjustment factor calculated by school size category (small, medium, large), f2 = a class-level non-response adjustment factor calculated for each school, f3 = a student-level non-response adjustment factor calculated by class, and f4 = a post stratification adjustment factor calculated by grade.

RESULTS

A total of 2,392 students participated in the survey of which 48.5% were males. Overall, most of the participants were of age 14 years (30.9%) or 15 years (29.1%). Altogether, 14.2% of the participants were anxious, 17.8% were lonely and 10.4% had no close friends. About a third of the participants reported being truant (33.7%), bullied (37.3%), attacked (39.2%) and involved in a fight (37.7%). In relation to drug use, 12.7% (17.2% of male and 7.6% of female) participants smoked cigarettes and 41.1% (46.5% of male and 35.8% of female)

participants consumed alcohol. Suicidal ideation was reported by 23.5% (16.4% of male and 29.7% of female) participants. These results are shown in Table 2.

Table 2. Distribution of factors considered in the analysis by gender among junior high school students in Guyana, 2010

Factor	Total n ¹ (%) ²	Males n ¹ (%) ²	Females n ¹ (%) ²
Age			
<14	546 (24.8)	205 (20.8)	328 (28.0)
14	709 (30.9)	359 (34.0)	346 (28.3)
15	737 (29.1)	312 (29.7)	420 (28.6)
16+	388 (15.2)	158 (15.6)	230 (15.1)
Gender			
Male	1034 (48.5)	-	-
Female	1328 (51.5)		
Food security			
No	176 (7.8)	87 (8.6)	83 (6.8)
Yes	2200 (92.2)	942 (91.4)	1237 (93.2)
Anxiety			
Yes	341 (14.2)	127 (12.5)	210 (15.7)
No	2032 (85.8)	902 (87.5)	1108 (84.3)
Loneliness			
Yes	448 (17.8)	149 (13.9)	297 (21.7)
No	1926 (82.2)	877 (86.1)	1023 (78.3)
Close friends			
No	249 (10.4)	104 (9.8)	139 (10.7)
Yes	2129 (89.6)	925 (90.2)	1182 (89.3)
Truancy			
Yes	786 (33.7)	404 (40.3)	369 (27.2)
No	1527 (66.3)	593 (59.7)	920 (72.8)
Bullied			
Yes	825 (37.3)	365 (37.8)	448 (36.5)
No	1387 (62.7)	595 (62.2)	780 (63.5)
Attacked			
Yes	928 (39.2)	461 (44.6)	448 (33.5)
No	1451 (60.8)	570 (55.4)	872 (66.5)
In a fight			
Yes	857 (37.7)	508 (49.6)	332 (25.7)
No	1524 (62.3)	520 (50.4)	991 (74.3)
Currently smoked cigarettes			
Yes	304 (12.7)	192 (17.2)	101 (7.6)
No	2026 (87.3)	814 (82.8)	1193 (92.4)
Parental understanding			
Yes	834 (36.4)	374 (37.8)	450 (35.1)
No	1511 (63.6)	641 (62.2)	853 (64.9)
Alcohol abuse			
Yes	653 (30.0)	333 (35.5)	317 (25.3)
No	1608 (70.0)	631 (64.5)	956 (74.7)
Currently used alcohol			
Yes	926 (41.1)	457 (46.5)	456 (35.8)
No	1330 (58.9)	525 (53.5)	790 (64.2)
Suicidal ideation			
Yes	541 (23.5)	157 (16.4)	374 (29.7)
No	1789 (76.5)	845 (83.6)	928 (70.3)

¹ unweighted frequencies. ² weighted percents.

Table 3 shows factors associated with suicidal ideation. Food security and involvement in a fight were not significantly associated with suicidal ideation in multivariate analysis. Students aged less than 14 years were more likely to have suicidal thoughts compared to students aged 16 years or older (AOR=1.08, 95% CI [1.03, 1.14]). Compared to female

students, male students were 37% (AOR=0.63, 95% CI [0.61, 0.65]) less likely to have suicidal thoughts.

Anxiety or loneliness were associated with suicidal ideation (AOR=1.29, 95% CI [1.24, 1.34] for anxiety and AOR=1.42, 95% CI [1.37, 1.47] for loneliness). Students who were truant were less likely to have suicidal thoughts (AOR=0.92, 95% CI [0.89, 0.95]).

Table 3. Factors associated with suicidal ideation among junior high school students in Guyana, 2010

Factor	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Age (years)		
<14	1.03 (0.99, 1.07)	1.08 (1.03, 1.14)
14	1.00 (0.96, 1.04)	0.95 (0.91, 1.00)
15	0.98 (0.95, 1.02)	0.97 (0.92, 1.01)
16+	1	1
Gender		
Male	0.68 (0.67, 0.70)	0.63 (0.61, 0.65)
Female	1	1
Food security		
No	1.09 (1.05, 1.13)	-
Yes	1	
Anxiety		
Yes	1.58 (1.53, 1.63)	1.29 (1.24, 1.34)
No	1	1
Loneliness		
Yes	1.64 (1.60, 1.68)	1.42 (1.37, 1.47)
No	1	1
Close friends		
No	1.21 (1.17, 1.25)	1.17 (1.12, 1.23)
Yes	1	1
Truancy		
Yes	1.06 (1.04, 1.09)	0.92 (0.89, 0.95)
No	1	1
Bullied		
Yes	1.49 (1.46, 1.53)	1.36 (1.32, 1.40)
No	1	1
Attacked		
Yes	1.30 (1.27, 1.33)	1.19 (1.16, 1.23)
No	1	1
In a fight		
Yes	1.13 (1.11, 1.16)	-
No	1	
Currently smoked cigarettes		
Yes	1.44 (1.40, 1.49)	1.13 (1.08, 1.18)
No	1	1
Parental understanding		
Yes	0.74 (0.72, 0.76)	0.75 (0.73, 0.78)
No	1	1
Alcohol abuse		
Yes	1.32 (1.29, 1.36)	1.21 (1.17, 1.25)
No	1	1
Currently used alcohol		
Yes	1.32 (1.29, 1.35)	1.22 (1.18, 1.25)
No	1	1

Being bullied or attacked were significantly associated with suicidal thoughts (AOR=1.36, 95% CI [1.32, 1.40] for being bullied and AOR=1.19, 95% CI [1.16, 1.23] for being attacked). Drug use was associated with suicidal ideation. Students who currently smoked cigarettes were 13% (AOR = 1.13, 95% CI [1.08, 1.18]) more likely to have suicidal thoughts compared to students who did not currently smoke cigarettes. Meanwhile, students who abused alcohol were 21% (AOR = 1.21, 95% CI [1.17, 1.25]) more likely to have suicidal thoughts compared to students who did not abuse alcohol; and students who currently consumed alcohol were 22% (AOR = 1.22, 95% CI [1.18, 1.25]) more likely to have suicidal thoughts compared to students who did not currently consume alcohol.

Students with no close friends were 17% (AOR = 1.17, 95% CI [1.12, 1.23]) more likely to have suicidal thoughts compared to students who had close friends. Students with had parental understanding were 25% (AOR=0.75, 95% CI [0.73, 0.78]) less likely to have suicidal thoughts compared with students who did not have parental understanding.

DISCUSSION

In the current study, suicidal ideation was reported by 23.5% (16.4% of male and 29.7% of female) participants. Factors associated with suicidal ideation included: age, gender, anxiety, loneliness, close friends, truancy, bullied, attacked, smoking, alcohol consumption and parental understanding. The rate of suicidal ideation increased from 18.4% (14.9% among males and 21.6% among females) in 2004 [12] to 23.5% (16.4% of male and 29.7% of female) in 2010, partly due to the effects of the global financial crisis of 2008-2009 [15]. The overall rate of suicidal ideation in the present study of 23.5% compares well with the rates reported in some sub-Saharan African countries [14] of Uganda (19.6%), Botswana (23.1%), Kenya (27.9%) and Zimbabwe (25.5%) but higher than those found in the Seychelles (16%), Tanzania (11.2%), some eastern Asian countries of Thailand, China, Taiwan, Vietnam, and the Philippines [16-19] and in some developed countries of 12.5-16.7% [22, 21]. Variation in rates of suicidal ideation between and within regions of the world may partly be due to differences in coping strategies for depression emanating from life or family events between people of different cultures.

Students of age less than 14 years in the current study were more likely to have suicidal thoughts compared to students who were aged 16 years or older. This finding contradicts that obtained in a 2004 Guyana GSHS in which no significant association was observed between age and suicidal ideation [12]. The difference in the finding from the same population in the two surveys (2004 GSHS and 2010 GSHS) may partly be due to differences in the factors considered in the multivariate analyses. More factors were considered in the analysis of the 2010 GSHS data than in the 2004 GSHS that might have confounded the relationship between age and suicidal thoughts, making the comparison difficult to make. Adolescence is a time of rapid physical, cognitive and emotional growth that is challenging for the adolescent [22]. Younger adolescents (under 15 years of age) may be less likely to cope with the stressors and thought of ending their lives may be a way to escape the experiences. They may not have developed problem solving skills and emotional maturity [9, 23].

Suicidal ideation was more prevalent in females than males (16.4% and 29.7%, respectively) in the present study which contradicts findings of no association between gender

and suicidal ideation in other studies [13, 14]. However, our finding of suicidal ideation being more common in girls than boys is similar to those reported by Lee and Choi [12, 24]. The differences in the relationship between gender and suicidal ideation may indicate gender differences in emotional and behavioural problems [25].

Being anxious or lonely was associated with suicidal ideation in the present study. A similar finding was reported by Rudatsikira et al. [12] in the same study area and Randall et al. [31] who suggested that suicidal behaviour may be a way of expressing distress culturally.

Having close friends and parental understanding were protective factors for suicidal ideation in the present study and in the 2004 Guyana GSHS [12]. In seeking autonomy during the adolescence period, conflicts usually arise between parents and adolescents. Adolescents may turn to their peers for support. It is thus important that healthy adolescent-parent and adolescent-peer relationships are fostered to maintain good mental health.

The current study reports that smokers were more likely to have suicidal thoughts than non-smokers, similar to a finding made by Rudatsikira et al. [12] in the same study area. However, it contradicts the finding by McGee et al. [27] who did not find a significant association between cigarette smoking and suicidal ideation. However, a similar finding to the current study has been reported by Innamorati et al. [28] and Fuller-Thomson et al. [29]. Other studies also found a significant association between smoking and suicidal ideation [30, 31]. In a multinational study, Hockenberry et al. [31] reported an association between tobacco use and suicidal ideation, specifically among girls in Africa. The association between cigarette smoking and suicidal ideation may not be causal because smoking may mediate other psychosocial causes of suicidal ideation such as depression. Adolescents may perceive smoking as a possible solution to stressful events.

Students in the current study who used or abused alcohol were more likely to have suicidal thoughts compared to students who did not use/abuse alcohol. This finding is similar to one obtained by Rudatsikira et al. [12] earlier on in the same population. Another study in three Asian cities of Hanoi, Shanghai and Tapei reported a similar finding that drunkenness is positively associated with suicidal ideation [32]. Curtailing early initiation of alcohol use that has been associated with suicidal ideation [33] could be one of the strategies to prevent suicide.

The association between violent behavior (being bullied or attacked) and suicidal thoughts in the current study may partly be as a result of displacement behavior resulting from stressful events. Violent behavior may be a reaction to stressful events. A similar finding was made by Rudatsikira et al. [12] earlier on in the same study area.

Students who were truant were less likely to have suicidal thoughts in the current study. Students may stay away from school without permission to avoid bullying, for example. Bullying is positively associated with suicidal ideation, and staying away from bullying by skipping school may have a protective effect for suicidal ideation. Skipping school should not be encouraged but efforts should be directed at preventing violence at school.

In conclusion, psychological, behavioral, family and social factors should be considered in designing suicide prevention programs. Healthy lifestyles, peer and parental relationships should be promoted in order to avoid suicidal thoughts.

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Chapter 42

FACTORS ASSOCIATED WITH SUICIDAL IDEATION AMONG ADOLESCENTS ATTENDING SCHOOL IN SAMOA

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ABSTRACT

Suicidal ideation is an important factor in completed suicide. There is scarce information on suicidal ideation in developing countries. The objective of the study was to determine correlates for suicidal ideation among adolescents in Samoa. The current study used secondary data obtained in a Global School-based Health Survey (GSHS) which was conducted in Samoa in 2011. Frequencies and logistic regression analyses (bivariate and multivariate) were weighted. Unadjusted odds ratio (OR) and adjusted odds ratio (AOR) together with their 95% confidence intervals (CI) are reported. A total of 2418 students participated in the survey of which 48.4% were males. Suicidal ideation was reported by 33.3% of students (37.8% of males and 29.5% of females). Factors correlated with suicidal ideation were age, gender, food security, loneliness, bullied,

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attacked (AOR = 1.24, 95% CI [1.11, 1.39]), involvement in a fight (AOR = 1.23, 95% CI [1.11, 1.37]), currently smoked cigarettes (AOR = 1.32, 95% CI [1.16, 1.51]), used marijuana (AOR = 1.25, 95% CI [1.09, 1.42]), current alcohol consumption (AOR = 0.76, 95% CI [0.66, 0.88]), alcohol abuse (AOR = 1.53, 95% CI [1.32, 1.76]) and parental understanding. The many factors identified to be associated with suicidal ideation in the current study suggest a multifactor intervention to include social and behavioral factors in curtailing suicidal ideation among adolescents in Samoa.

Keywords: suicidal ideation, prevalence, associated factors, adolescents, Samoa

INTRODUCTION

Suicide rates in populations of the Pacific islands are amongst the highest in the world [1], probably as a result of modernizing social structures [2]. Suicide ideation is an important factor in completed suicide. It is estimated that 60% of persons with suicidal ideation end up with attempted suicide [3]. Other reported transition rates are 34% from suicidal ideation to planning suicide, 72% from planning suicide to attempted suicide, and 26% from suicidal ideation to unplanned attempted suicide [4].

Samoa is located in the Pacific Ocean and its closest islands include American Samoa, Tokelau, Wallis and Futuna, Niue, Fiji and Tonga. There is limited information on suicidal ideation in this region and in Samoa, in particular. In a study of four Pacific island countries in Oceania, the prevalence of suicidal ideation in Samoa (33.8%) was comparable to that of Kiribati (34.7%) but higher than that of Solomon Islands (27.7%) and Vanuatu (17.2%). In all these countries, males had a higher prevalence of suicidal ideation than females; 37.8% of males had suicidal thoughts compared to 29.5% of females [5].

Across the four islands: Samoa, Kiribati, Solomon islands and Vanuatu, current substance use and their initiation (smoking, alcohol use and drug use) were significantly associated with suicidal ideation [5]. It is important to exclusively examine the correlates for suicidal ideation for Samoan school-going adolescents so that interventions to prevent suicidal ideation may be tailored for this population because correlates may be population specific. Furthermore, only a limited number of factors were considered as correlates for suicidal ideation in the study above. The objective of the current study was to determine correlates for suicidal ideation among adolescents in Samoa.

METHODS

The survey was conducted in the Polynesian group of islands known as Samoa that consists of two main islands Upolu and Savai'i and seven smaller islets. Upolu is home to nearly three-quarters of Samoa's population (Figure 1). The population for Samoa was 187,820 in 2011 of which 51.6% were males; 38.3% were aged below 15 years and 80% resided in rural areas [6]. The study was based on secondary data obtained from the 2011 Samoa Global School-based Health Survey (GSHS). The study design was a cross sectional study in which a questionnaire was self-administered to individual students in grades 9-10 in Samoa. Details of the survey have been described elsewhere [7].



Source: https://www.lib.utexas.edu/maps/australia/samoa_rel98.jpg.

Figure 1. Map of Samoa and surrounding countries.

In order to obtain a representative sample of students on the island, students were selected using a two-stage cluster sampling method. During the first stage of sampling, schools were selected with probability proportional to their enrollment size. Classes were then randomly selected during the second stage of sampling and all students in selected classes were eligible to participate. The survey achieved a school response rate of 83%, a student response rate of 96% and an overall response rate of 79%.

Although the survey was run by CDC and WHO, the data set belong to Samoa. However, the data set and code book associated with the core GSHS questionnaire modules were made available to the public two years after the survey was conducted. Only data from core GSHS questions were made public and no school or student identifiers were indicated in the data set.

The questionnaire included questions on alcohol use; dietary behaviors; drug use; hygiene; mental health; physical activity; protective factors; sexual behaviors; tobacco use; and violence and unintentional injury. Responses were made on a computer scannable answer sheet.

Table 1. Global School-Based Health Survey questions used in the analysis of adolescent suicidal ideation

Variable	Question	Coded	Recoded
Dependent variable			
Suicidal ideation	During the past 12 months, did you ever seriously consider attempting suicide?	1 = Yes; 2 = No	1 = Yes; 2 = No
Independent variables			
Age	How old are you?	1 = 11 years old or younger; 2 = 12 years old; 3 = 13 years old; 4 = 14 years old; 5 = 15 years old; 6 = 16 years old or older	1-3 = 1; 4 = 2; 5 = 3; 6 = 4
Gender	What is your sex?	1 = Male; 2 = Female	1 = 1; 2 = 2
Food security	During the past 30 days, how often did you go hungry because there was not enough food in your home?	1 = Never; 2 = Rarely; 3 = Sometimes; 4 = Most of the time; 5 = Always	4-5 = 1; 1-3 = 2
Anxiety	During the past 12 months, how often have you been so worried about something that you could not sleep at night?	1 = Never; 2 = Rarely; 3 = Sometimes; 4 = Most of the time; 5 = Always	4-5 = 1; 1-3 = 2
Loneliness	During the past 12 months, how often have you felt lonely?	1 = Never; 2 = Rarely; 3 = Sometimes; 4 = Most of the time; 5 = Always	4-5 = 1; 1-3 = 2
Close friends	How many close friends do you have?	1 = 0; 2 = 1; 3 = 2; 4 = 3 or more	1 = 1; 2-4 = 2
Truancy	During the past 30 days, on how many days did you miss classes or school without permission?	1 = 0 days; 2 = 1 or 2 days; 3 = 3 to 5 days; 4 = 6 to 9 days; 5 = 10 or more days	1 = 2; 2-5 = 1
Bullied	Bullied during the past 30 days, on how many days were you bullied?	1 = 0 days; 2 = 1 or 2 days; 3 = 3 to 5 days; 4 = 6 to 9 days; 5 = 10 to 19 days; 6 = 20 to 29 days; 7 = All 30 days	1 = 2; 2-7 = 1
Attacked	During the past 12 months, how many times were you physically attacked?	1 = 0 times; 2 = 1 time; 3 = 2 or 3 times; 4 = 4 or 5 times; 5 = 6 or 7 times; 6 = 8 or 9 times; 7 = 10 or 11 times; 8 = 12 or more times	1 = 2; 2-8 = 1
In a fight	During the past 12 months, how many times were you in a physical fight?	1 = 0 times; 2 = 1 time; 3 = 2 or 3 times; 4 = 4 or 5 times; 5 = 6 or 7 times; 6 = 8 or 9 times; 7 = 10 or 11 times; 8 = 12 or more times	1 = 2; 2-8 = 1
Currently smoked cigarettes	During the past 30 days, on how many days did you smoke cigarettes?	1 = 0 days; 2 = 1 or 2 days; 3 = 3 to 5 days; 4 = 6 to 9 days; 5 = 10 to 19 days; 6 = 20 to 29 days; 7 = All 30 days	1 = 2; 2-7 = 1
Used marijuana	During your life, how many times have you used marijuana (also called bo da)?	1 = 0 times; 2 = 1 or 2 times; 3 = 3 to 9 times; 4 = 10 to 19 times; 5 = 20 or more times	1 = 2; 2-5 = 1
Currently consumed alcohol	During the past 30 days, on how many days did you have at least one drink containing alcohol?	1 = 0 days; 2 = 1 or 2 days; 3 = 3 to 5 days; 4 = 6 to 9 days; 5 = 10 to 19 days; 6 = 20 to 29 days; 7 = All 30 days	1 = 2; 2-7 = 1
Alcohol abuse	During your life, how many times did you drink so much alcohol that you were really drunk?	1 = 0 times; 2 = 1 or 2 times; 3 = 3 to 9 times; 4 = 10 or more times	1 = 2; 2-4 = 1
Parental understanding	During the past 30 days, how often did your parents or guardians understand your problems and worries?	1 = Never; 2 = Rarely; 3 = Sometimes; 4 = Most of the time; 5 = Always	1-3 = 2; 4-5 = 1

Data was analyzed using SPSS version 16. The dependent variable was suicidal ideation that was obtained by asking the question ‘During the past 12 months, did you ever seriously consider attempting suicide?’ The dependent and independent variables were recoded as shown in Table 1. Frequencies and logistic regression (bivariate and multivariate) analyses were weighted using the following weighting factor:

$$W = W1 \times W2 \times f1 \times f2 \times f3 \times f4$$

where W1 = the inverse of the probability of selecting the school, W2 = the inverse of the probability of selecting the classroom within the school, f1 = a school-level non-response adjustment factor calculated by school size category (small, medium, large), f2 = a class-level non-response adjustment factor calculated for each school, f3 = a student-level non-response adjustment factor calculated by class, and f4 = a post stratification adjustment factor calculated by grade.

Unadjusted odds ratio (OR) and adjusted odds ratio (AOR) together with their 95% confidence intervals (CI) are reported.

RESULTS

Altogether, 2,418 students participated in the survey of which 48.4% were males. Most (40.4%) of the participants were of age 14 years. About a third of the participants had no food security (36.1%). About 1 in 4 of the students reported anxiety (27.8%) and loneliness (23.1%). Most (83.5%) of the students had close friends. Over half (55.4%) of the students missed school or classes without permission. The majority of students was bullied (74.2%), attacked (71.7%) and involved in a fight (68.3%). Current cigarette smoking was reported by 44.1% of males and 27.0% of females. Similarly, 44.4% of males and 27.1% of females reported using marijuana. Alcohol consumption was also reported by a third of the students (overall 35.9% of students, 45.2% of males and 27.3% of females currently consumed alcohol; 36.6% of all students abused alcohol with 48.0% of males and 26.5% of females having done the same). About a third of the participants had parents who understood their problems and worries. The prevalence of suicidal ideation was 33.3% (37.8% among males and 29.5% among females). These results are shown in Table 2.

Table 3 shows factors associated with suicidal ideation. Students aged 14 years were 22% (AOR=0.78, 95% CI [0.67, 0.90]) less likely to have suicidal ideation than students of age 16 years or older. Other factors associated with suicidal ideation were gender (AOR = 1.14, 95% CI [1.04, 1.25]), food security (AOR = 1.10, 95% CI [1.00, 1.21]) and loneliness (AOR = 1.15, 95% CI [1.03, 1.28]). Violence was associated with suicidal ideation (bullied (AOR = 1.18, 95% CI [1.05, 1.32]), attacked (AOR = 1.24, 95% CI [1.11, 1.39]) and involvement in a fight (AOR = 1.23, 95% CI [1.11, 1.39])). Drug abuse was also associated with suicidal ideation (AOR = 1.32, 95% CI [1.16, 1.51]) for currently smoked cigarettes and AOR = 1.25, 95% CI [1.09, 1.42]) for used marijuana and AOR = 1.53, 95% CI [1.32, 1.76]) for alcohol abuse). Students who drank alcohol were 24% (AOR=0.76, 95% CI [0.66, 0.88]) less likely to have suicidal thoughts compared to students who did not drink alcohol. Students with parental understanding were 19% (AOR = 0.81, 95% CI [0.74, 0.89]) less likely to have suicidal thoughts compared to students who did not have parents who understood their problems and worries.

Table 2. Distribution of factors considered in the analysis by gender among junior high school students in Samoa, 2011

Factor	Total n ¹ (%) ²	Males n ¹ (%) ²	Females n ¹ (%) ²
Age			
<14	615 (23.9)	234 (22.3)	381 (25.4)
14	964 (40.4)	393 (39.6)	571 (41.1)
15	614 (28.4)	265 (29.1)	349 (27.7)
16+	150 (7.4)	76 (9.1)	74 (5.8)
Gender			
Male	970 (48.4)		
Female	1376 (51.6)		
Food security			
No	825 (36.1)	342 (36.3)	483 (36.0)
Yes	1466 (63.9)	609 (63.7)	857 (64.0)
Anxiety			
Yes	631 (27.8)	247 (27.0)	384 (28.6)
No	1625 (72.2)	672 (73.0)	953 (71.4)
Loneliness			
Yes	523 (23.1)	220 (23.8)	303 (22.5)
No	1714 (76.9)	695 (76.2)	1019 (77.5)
Close friends			
No	336 (16.5)	143 (17.4)	193 (15.7)
Yes	1759 (83.5)	700 (82.6)	1059 (84.3)
Truancy			
Yes	1089 (55.4)	499 (62.2)	590 (49.4)
No	905 (44.6)	299 (37.8)	606 (50.6)
Bullied			
Yes	1460 (74.2)	640 (79.2)	820 (69.6)
No	516 (25.8)	162 (20.8)	354 (30.4)
Attacked			
Yes	1635 (71.7)	704 (74.1)	931 (69.4)
No	657 (28.3)	245 (25.9)	412 (30.6)
In a fight			
Yes	1516 (68.3)	683 (73.7)	833 (63.3)
No	714 (31.7)	235 (26.3)	479 (36.7)
Currently smoked cigarettes			
Yes	710 (35.1)	370 (44.1)	340 (27.0)
No	1370 (64.9)	468 (55.9)	902 (73.0)
Used marijuana			
Yes	661 (35.2)	344 (44.4)	317 (27.1)
No	1296 (64.8)	435 (55.6)	861 (72.9)
Currently consumed alcohol			
Yes	714 (35.9)	380 (45.2)	334 (27.3)
No	1337 (64.1)	459 (54.8)	878 (72.7)
Alcohol abuse			
Yes	674 (36.6)	364 (48.0)	310 (26.5)
No	1220 (63.4)	391 (52.0)	829 (73.5)
Parental understanding			
Yes	661 (33.1)	238 (30.0)	423 (35.8)
No	1304 (66.9)	543 (70.0)	761 (64.2)
Factor	Total n ¹ (%) ²	Males n ¹ (%) ²	Females n ¹ (%) ²
Suicidal ideation			
Yes	618 (33.3)	276 (37.8)	342 (29.5)
No	1270 (66.7)	452 (62.2)	818 (70.5)

¹ unweighted frequencies. ² weighted percents.

Table 3. Factors associated with suicidal ideation among junior high school students in Samoa, 2011

Factor	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Age		
<14	0.94 (0.86, 1.03)	0.91 (0.77, 1.08)
14	0.83 (0.76, 0.90)	0.78 (0.67, 0.90)
15	0.80 (0.73, 0.87)	1.00 (0.86, 1.17)
16+	1	1
Gender		
Male	1.20 (1.14, 1.27)	1.14 (1.04, 1.25)
Female	1	1
Food security		
No	1.16 (1.10, 1.22)	1.10 (1.00, 1.21)
Yes	1	1
Anxiety		
Yes	1.27 (1.20, 1.34)	-
No	1	
Loneliness		
Yes	1.23 (1.16, 1.31)	1.15 (1.03, 1.28)
No	1	1
Close friends		
No	1.08 (1.00, 1.16)	-
Yes	1	
Truancy		
Yes	1.32 (1.25, 1.40)	-
No	1	
Bullied		
Yes	1.80 (1.68, 1.94)	1.18 (1.05, 1.32)
No	1	1
Attacked		
Yes	1.65 (1.55, 1.75)	1.24 (1.11, 1.39)
No	1	1
In a fight		
Yes	1.54 (1.45, 1.63)	1.23 (1.11, 1.37)
No	1	1
Currently smoked cigarettes		
Yes	1.86 (1.76, 1.98)	1.32 (1.16, 1.51)
No	1	1
Used marijuana		
Yes	1.65 (1.56, 1.75)	1.25 (1.09, 1.42)
No	1	1
Currently consumed alcohol		
Yes	1.56 (1.48, 1.65)	0.76 (0.66, 0.88)
No	1	1
Alcohol abuse		
Yes	1.83 (1.72, 1.94)	1.53 (1.32, 1.76)
No	1	1
Parental understanding		
Yes	0.86 (0.81, 0.91)	0.81 (0.74, 0.89)
No	1	1

DISCUSSION

In the current study, age, gender, food security, loneliness, violence (bullied, attacked and involvement in a fight), substance use (smoking cigarettes or marijuana, alcohol consumption and abuse) and parental understanding were significantly associated with suicidal ideation. It is not entirely clear why the age of 14 years was protective, while students aged below this age were at higher risk, suggesting an inconsistency finding. Muula et al. [8] found that

students aged below 14 years were at increased risk for suicidal ideation. Meanwhile, Randall et al. [9], Silva et al. [10] and Sharma et al. [11] found no significant association between age and suicidal ideation. Establishing an association between age and suicidal ideation is important so that age at which to intervene to reduce adolescents having suicidal thoughts could be established. Studies have shown no consistent finding between gender and suicidal ideation, reflecting the different impact of culture on gender. While in the current study females were a higher risk for suicidal ideation than males, similar to what was reported by Garrison et al. [12] and Abel et al. [13], no association was reported by Hallfors et al. [14] and Jorgensen et al. [15]. Contrary, Muula et al. [8] found males to be more likely to have suicidal ideation than females. It was observed that females have a higher rate of depression than males and may explain the higher suicidal ideation prevalence in females than males.

Students who went hungry in the current study because there was not enough food in the home who may also have been lonely were more likely to have suicidal thoughts. Provision of food security may also curtail violence (bullying, physical attacks and fighting) and substance abuse (smoking cigarettes and marijuana and abusing alcohol) in adolescents which have been associated with suicidal ideation [16, 17].

Stress leading to depression as a result of lack of enough food may be an important factor in the occurrence of suicidal ideation. It is, however, interesting that students in the current study who consumed alcohol were less likely to have suicidal ideation. How can alcohol consumption in moderation be protective, while abusing it is a risk for suicidal ideation? This is a research question that should be answered. However, Rossow et al. [18] suggested that substance use may not directly result in suicidal ideation but that it compounds depression to result in suicidal thoughts.

Wagner et al. [19] reported that poor child-parent relationship may cause poor physical and emotional status that may result in suicidal thoughts. Randall et al. [9] also reported that lack of parental support is associated with suicidal ideation. Good parenting involving discussing problems and worries adolescents may be faced with is important in curtailing suicidal ideation.

In conclusion, the many factors identified to be associated with suicidal ideation in the current study suggest the need to have a multifactor intervention to include social and behavioral factors in curtailing suicidal ideation.

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Chapter 43

PREVALENCE AND CORRELATES FOR SUICIDAL IDEATION AMONG SCHOOL-GOING ADOLESCENTS IN IRAQ

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ABSTRACT

Adolescent suicidal behavior is a neglected public health issue especially in middle and low-income countries. However, it is an important precursor to later attempted and completed suicide which is of major public health significance. It is in view of this that this work was conducted and the main objective was to determine prevalence and associated factors for suicidal ideation among school-going adolescents in Iraq. Secondary data from the Global School-based Health Survey conducted in 2012 was analyzed. Bivariate and multivariate analyses at 95% confidence interval were conducted to determine factors associated with suicidal ideation. Out of 2027 students, 17.6% (18.0% of males and 17.2% of females) had considered committing suicide. Factors positively significantly related with adolescents' suicidal ideation among Iraq school-going adolescents were male gender, food insecurity, anxiety, loneliness, having no close friends, truancy, history of attack and bullying, having been involved in a fight and current smoking. Parental understanding and age less than 15 years of age were the protective factors against suicidal ideation. Intervention measures to curb the vice should

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target peer pressure and build adolescent self-esteem through establishing and advocating for social support networks.

Keywords: suicidal ideation, prevalence, correlates, adolescents, Iraq

INTRODUCTION

Suicidal behavior among school-going adolescents is an important global concern. It is considered to be an important precursor to later attempted and completed suicide and is of major public health significance. Suicide has not been considered as an important area of research in most developing countries. It still remains a neglected issue especially in middle and low-income countries like Iraq [1].

According to the World Health Organization (WHO), nearly one million people commit suicide every year [2]. WHO reports that suicide is a global problem and in 2012, countries in low and middle income regions recorded 75% of global suicide cases. It was estimated in the same year that suicide accounted for 1.4% of all deaths worldwide, making it the 15th leading cause of death [3]. Each year, about 4 million adolescents world-wide attempt suicide and suicide is the third leading cause of death among adolescents [4] and in the 15-24 years age group [5] and the second leading cause of death among college students [6].



Source: http://www.mojahedin.org/images/2014/2014815103328488699241_Map-of-Iraq-and-neighboring-countries.jpg.

Figure 1. Map of Iraq showing its neighbouring countries.

Although the overall rate of suicide among youth has declined slowly since 1992, it is still unacceptably high [7]. A 5.0% prevalence rate of suicidal ideation was obtained in the 2007 Global School-based Health Survey (GSHS) among secondary students in Kut City, Iraq [1]. Interventions targeting suicidal ideation are important because most of suicidal acts start with seriously thinking about how to commit them. A study among secondary school adolescents in Kut city [1] indicated depression, anxiety, poor school grade, and subjection to corporal punishment at home as factors significantly related to adolescents' suicidal behavior (suicidal ideation or attempted suicide). These factors may be biased towards suicidal attempt

because over ninety percent of the students with suicidal behavior attempted suicide [1]. Further, Kut city may not represent the entire country. Furthermore, confounding factors were not adjusted for in the analysis. Clearly, there is need to ascertain factors associated with suicidal ideation in Iraq. Therefore, the objectives of the current study were to determine the prevalence of suicidal ideation and its correlates using the most recent 2012 GSHS.

METHODS

The study setting was Iraq, bordered by Iran, Jordan, Kuwait, Saudi Arabia, Syria, Turkey and a small stretch of the Persian Gulf as shown in Figure 1. Secondary data from the 2012 Global School based Health Survey (GSHS) developed by WHO to provide data on health and social behaviors among the school-going adolescents in Iraq was used in the analysis. The survey measured a number of variables including age, gender, food security, anxiety, loneliness, lack of close friends, truancy, history of attack, bullying, involvement in a fight, current alcohol use, alcohol abuse, marijuana use and parental understanding. The analysis involved the assessment of factors that could be associated with suicidal ideation in this group of adolescents.

The Iraq GSHS was a two-stage cluster sample design, in which in the first stage, schools were selected with probability proportional to enrollment size. In the second stage, classes were randomly selected and all students in selected classes were eligible to participate. Assessments of associations were conducted using both bivariate and multivariate logistic regression analyses at 95% confidence interval.

RESULTS

Out of the 2027 school-going adolescents recruited in the 2012 Global School-based Health Survey, 57.3% were males. Table 1 shows factors that were under consideration and distributed according to gender. The characteristics of the study population included in the analysis showed that 42.7% of adolescents had problems regarding food security (most of the time or always went hungry because there was not enough food in the home). Female adolescents reported anxiety and loneliness more than their male counterparts 18.1% and 20.0% compared with 9.3% and 14.0%, respectively. Only 6.3% adolescents reported having no close friends. Truancy was common among both females (26.7%) and males (31%). Similarly, bullying was common at 24.4% among females and slightly high among males at 32.6%. More male adolescents reported having been attacked (36.3%) compared to females (22.4%) and close to half (46.8%) of male adolescents were involved in a fight compared to 23.6% of female. Reports of current smoking were more common among males at 14.7% compared to 5.3% among female students. Parental understanding was reported as lacking in a lot of female and male students, 38.9% and 42.4% respectively. Close to 1/5th of both male (18.0%) and female (17.2%) students reported having considered suicidal ideation, with an overall prevalence of suicidal ideation of 17.6%.

Table 1. Distribution of factors by gender among school-going adolescents in Iraq, 2012

Factor	Total n ¹ (%) ²	Males n ¹ (%) ²	Females n ¹ (%) ²
Age			
<14	577 (28.4)	302 (25.7)	271 (31.8)
14	494 (22.5)	266 (20.9)	227 (24.8)
15	492 (24.4)	288 (25.9)	202 (23.2)
16+	455 (24.5)	277 (27.5)	174 (20.1)
Gender			
Male	1145 (57.3)	-	-
Female	882 (42.7)	-	-
Food security			
No	174 (57.3)	102 (9.0)	71 (8.4)
Yes	1847 (42.7)	1036 (91.0)	801 (91.6)
Anxiety			
Yes	271 (13.1)	106 (9.3)	163 (18.1)
No	1750 (86.9)	1029 (90.7)	712 (81.9)
Loneliness			
Yes	338 (16.6)	158 (14.0)	178 (20.0)
No	1679 (83.4)	974 (86.0)	696 (80.0)
Close friends			
No	124 (6.3)	64 (5.8)	59 (6.8)
Yes	1874 (93.7)	1058 (94.2)	806 (93.2)
Truancy			
Yes	586 (29.2)	345 (31.0)	237 (26.7)
No	1412 (70.8)	773 (69.0)	632 (73.3)
Bullied			
Yes	549 (29.1)	348 (32.6)	198 (24.4)
No	1335 (70.9)	718 (67.4)	610 (75.6)
Attacked			
Yes	609 (30.3)	415 (36.3)	193 (22.4)
No	1394 (69.7)	718 (63.7)	666 (77.6)
In a fight			
Yes	745 (37.0)	530 (46.8)	209 (23.6)
No	1263 (63.0)	592 (53.2)	666 (76.4)
Currently smoked			
Yes	204 (10.6)	156 (14.7)	47 (5.3)
No	1772 (89.4)	946 (85.3)	816 (94.7)
Parental understanding			
Yes	812 (40.8)	470 (42.4)	340 (38.9)
No	1170 (59.2)	639 (57.6)	522 (61.1)
Suicidal ideation			
Yes	345 (17.6)	191 (18.0)	152 (17.2)
No	1641 (82.4)	925 (82.0)	707 (82.8)

¹ unweighted frequencies. ² weighted percents.

Factors found to be associated with suicidal ideation among school-going adolescents in Iraq in the 2012 GSHS study are presented in Table 2. Results in the table show that age of adolescents was significantly associated with suicidal ideation; less than 15-year-old adolescents were less likely to have suicidal ideation compared to those who were 16 years or older (AOR = 0.69, 95% CI [0.68, 0.70] for 14 year-olds and AOR = 0.69, 95% CI [0.68, 0.70] for aged less than 14 years). Adolescents aged 15 years were 1.22 times more likely to commit suicide compared to those who were 16 years or older (AOR = 1.22, 95% CI [1.21, 1.23]). Adolescents with food insecurity were 1.07 (95% CI [1.06, 1.08]) times more likely to consider committing suicide compared to those with food security. Anxious adolescents were 50% more likely (AOR = 1.50, 95% CI [1.49, 1.51]) to have suicidal thoughts compared to those who never reported anxiety. Adolescents who reported to have no close friends were 1.29 (95% CI [1.28, 1.31]) times more likely to experience suicidal ideations compared to

those who did not have close friends while lonely respondents were 67% (AOR = 1.67, 95% CI [1.66, 1.68]) more likely to consider committing suicide compared to those who did not report loneliness. Those with a history of having been attacked were 1.15 (95% CI [1.20, 1.22]) times more likely to consider committing suicide compared to those not been attacked before. Having been involved in a fight was 1.12 (95% CI [1.20, 1.22]) times more likely to consider suicide compared to those with no history of having been involved in a fight. Adolescents who reported current smoking were 45% more likely to think of committing suicide (AOR = 1.45, 95% CI [1.44, 1.46]) than nonsmokers. Adolescents with parental understanding were 9% less likely (AOR = 0.91, 95% CI [0.90, 0.91]) to have suicidal ideation compared to students who did not have parental understanding.

Table 2. Factors associated with suicidal ideation among school-going adolescents in Iraq, 2012

Factor	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Age (years)		
<14	0.88 (0.88, 0.89)	0.92 (0.91, 0.93)
14	0.68 (0.67, 0.68)	0.69 (0.68, 0.70)
15	1.16 (1.15, 1.17)	1.22 (1.21, 1.23)
16+	1	1
Gender		
Male	1.03 (1.02, 1.03)	1.01 (1.00, 1.01)
Female	1	1
Food security		
No	1.32 (1.32, 1.33)	1.07 (1.06, 1.08)
Yes	1	1
Anxiety		
Yes	1.98 (1.97, 2.00)	1.50 (1.49, 1.51)
No	1	1
Loneliness		
Yes	2.04 (2.03, 2.05)	1.67 (1.66, 1.68)
No	1	1
Close friends		
No	1.71 (1.70, 1.72)	1.29 (1.28, 1.31)
Yes	1	1
Truancy		
Yes	1.28 (1.27, 1.28)	1.05 (1.04, 1.05)
No	1	1
Bullied		
Yes	1.34 (1.33, 1.34)	1.05 (1.04, 1.06)
No	1	1
Attacked		
Yes	1.26 (1.26, 1.27)	1.15 (1.14, 1.15)
No	1	1
In a fight		
Yes	1.39 (1.38, 1.39)	1.21 (1.20, 1.22)
No	1	1
Currently smoked		
Yes	1.83 (1.82, 1.84)	1.45 (1.44, 1.46)
No	1	1
Parental understanding		
Yes	0.77 (0.77, 0.78)	0.91 (0.90, 0.91)
No	1	1

DISCUSSION

The current study findings indicate a prevalence of 17.6% of school-going adolescents with suicidal ideation, a finding that is in accord with other similar studies [8, 9]. A number of factors have been negatively and positively associated with suicidal ideation. Young age (less than 15 years) and having parental understanding were negatively associated with suicidal ideation while anxiety, having close friends, loneliness, having been attacked, having been involved in a fight and current smoking were positively associated with suicidal ideation.

Male adolescents were more likely to consider committing suicide compared to females. This is in accord with another study finding which indicated that males are more likely to think of committing suicide compared to females [10]. The explanation could be that female adolescents mature earlier than males in such a way that they are able to cope with the challenges faced during adolescence period.

The findings of our study show that suicidal ideation among school-going adolescents in Iraq is influenced by psycho-social factors such as anxiety and loneliness. Loneliness and anxiety have been found to be significantly associated with suicidal ideation in many other studies [11, 12]. However, we are unable to ascribe causation in the current study because the design was cross sectional. It is possible that because of suicidal ideation, adolescents may tend to be lonely or anxious while thinking about how to commit suicide. Alternatively, because they are lonely or anxious due to other reasons, they may in turn think about committing suicide.

The results of our current study show that adolescents involved in current smoking were significantly more likely to have suicidal ideas compared to those that were not involved in smoking. Other unhealthy behaviors such as been bullied, attacked and involvement in a fight were also significantly associated with suicidal ideation. Adolescents involved in smoking at an early stage usually risk getting involved in other unhealthy behaviors and they are significantly more likely to have suicidal ideation as is the case in another study elsewhere [13].

Having close friends and parental understanding were both significantly associated with suicidal ideation in the present study. Supportive parental relationships have been associated with less suicidal ideation in other cross sectional studies as well [14, 15] and in a longitudinal study [16] and support from friends may decrease the risk of mental health [16].

The findings highlight a number of possible intervention targets for the earliest stage of suicidal ideation similar to previous findings [17] which indicated the need for strengthening a network of social support among students on campus, parents and family. Violence should also be considered in these interventions.

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Chapter 44

**CORRELATES OF SUICIDAL IDEATION
AMONG IN-SCHOOL ADOLESCENTS
IN TRINIDAD AND TOBAGO**

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ABSTRACT

Suicidal ideation is a public health concern in many countries. There is need for robust research to establish factors associated with suicidal ideation among in-school adolescents. In Trinidad and Tobago, considerable level of research has been conducted on suicidal ideation among adolescents. However, more research is still needed in order to establish and profile factors associated with suicidal ideation among in-school adolescents. The objective of the study was to determine factors associated with suicidal ideation among in-school adolescents in Trinidad and Tobago. Analysis of the secondary data from the 2011 Trinidad and Tobago Global School-Based Health Survey was conducted using bivariate and multivariate logistic regression at 95% confidence interval. The study recruited a total of 2,811 students. The results showed that the proportion of students who reported suicidal ideation was 16.3% and female (19.3%) students reported a higher ($p < 0.001$) proportion than males (13.3%). Having understanding parents, history of bullying, being of male gender and being 15 years of age were negatively associated with suicidal ideation, while food security, anxiety, lack of close friends,

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loneliness, history of attack, involvement in a fight, truancy, currently smoking, alcohol abuse, current alcohol use and marijuana use were all positively associated with suicidal ideation. Therefore, issues relating to family and parental support structure, age and gender, violence among peers and substance abuse should be considered when planning and implementing public health intervention programs against suicidal ideation among in-school adolescents in Trinidad and Tobago.

Keywords: suicidal ideation, prevalence, associated factors, adolescents, Trinidad and Tobago

INTRODUCTION

Adolescent suicidal behavior is a major public health concern in many countries, developed and developing alike [1]. Suicide behavior includes suicidal thoughts and suicide attempt. Suicide is a global phenomenon in all regions of the world; statistically, suicidal behavior is the third leading cause of premature death in the adolescent age group [2]. Deaths due to suicide have been estimated to be over 800 000 every year [3] and it is the second leading cause of death in 15-29-year-olds [1]. Suicidal attempts are estimated to range between 2.8% and 13.2% among adolescents [4]. A number of studies have been done and various possible explanations have been suggested for the rising suicide trends, however, a lot still needs to be done [5, 6].

Work to establish trends and rates of suicide have been done worldwide and some analyses still do not present consistent information regarding the causes of death and suicide rates among young people aged 15-19 years [1, 7, 8]. In the Caribbean region suicide is a major public health problem and there are indications that mental health problems are common in the Caribbean and may have a role to play in this health problem [9, 10]. According to previous research [10], Trinidad and Tobago has the second highest suicide rates in the region. Although the rates of suicide are high in the Caribbean, research in this field is still low and speculations are that the paucity of research on suicide in the Caribbean is due to little priority given to the issue by researchers and mental health professionals working within the region. Some researchers attribute this lack of robust research in this area to the sensitive nature that is involved in working with suicidal patients [11]. In Trinidad and Tobago, other than gender, studies on suicide have established a number of other factors associated with suicide. In a study by Hutchinson and Simeon, social distress was noted as an important contributor to the rate of suicide in Trinidad and Tobago, particularly among men [12].

Generally, suicidal behavior predetermines suicides. It is thus important that suicidal behavior is characterized. In a study conducted by Rodriguez and colleagues, social predictors of suicidal behavior in Nicaragua included involvement in family issues and alcohol abuse, other social demographic factors such as education and poverty were not identified as factors associated with suicidal expressions [13]. Other studies have reported low rates of suicidal behavior in African population [11, 14] and this is said to signify a cultural and ethnic difference. Cultural predispositions have been identified as some of the reasons for low rates of suicidal behavior. Certain cultural predispositions such as varying concepts of distress among different population groups for instance concepts of distress among east Indians

involved in suicidal behavior may not be the case among people of African-Caribbean heritage.

One of the suicidal behaviors is suicidal ideation. Some researchers have indicated that there are a number of factors that contribute to suicidal ideation and some of the factors include loss of social cohesion, violence, traditional family structure breakdown, economic instability, lack of employment opportunities, and mental health issues such as rising prevalence of depressive disorders (9, 10, 13]. The factors may vary according to populations within and between countries. Therefore, it is important that studies are conducted to establish factors that may be useful in designing interventions that are population-specific to curtail suicidal thoughts and eventually suicide. Thus, the objectives of the current study were to determine correlates for suicidal ideation including its prevalence among in-school adolescents in Trinidad and Tobago.

METHODS

The study was conducted in the Republic of Trinidad and Tobago, a twin island *country* bordering the Caribbean to the north and sharing maritime boundaries with other *nations*. It is situated off the northeast coast of South America at the extreme southern end of the Lesser Antilles as shown in Figure 1.



Source: <http://www.worldatlas.com/webimage/countrys/namerica/caribb/ht.htm>.

Figure 1. Trinidad and Tobago and its surrounding islands and countries.

This chapter presents results of the secondary data analysis obtained from The Global School based Health Survey (GSHS) on health and social behaviors of in-school adolescents in Trinidad and Tobago. The survey measured demographic characteristics of age and gender; social behaviors such as involvement in a fight, truancy, food security, alcohol use and abuse, current smoking in general and use of marijuana, bullying, loneliness, close friendship, anxiety and attack; parental understanding, and the social and health outcome of having considered suicide.

The secondary data was analyzed in order to assess factors that are associated with suicidal ideation among in-school adolescents in Trinidad and Tobago. Assessment of association was conducted through both bi-variate and multivariate logistic regression analysis.

RESULTS

The in-school adolescents aged less 14 years old had the largest proportion of representation (42.9%) in the current study and more than half (54.6%) of the participants were male. Factors under consideration were distributed according to sex as shown in Table 1. The study population features included in the analysis showed that less than 10% of both male and female adolescents had challenges with food security, reported anxiety and lack of close friends. As for loneliness, 11.4% of females reported having experienced loneliness compared to males at 8.2%. More than three quarters of both male (82.0%) and female (79.9%) students practiced truancy. A high proportion of both female (87.9%) and male (82.7%) adolescents were victims of bullying. Majority of male students (40.3%) reported having been attacked compared to females (25.7%). In a similar way, close to half (46.5%) of male students reported having been involved in a fight compared to 26.0% of female students. Reports of current smoking were more common among males at 13.0% compared to 6.2% among female students ($p < 0.001$). Almost a similar proportion of pupils reported lack of parental understanding in female (40.1%) and male students (39.7%). Close to 1/5th of male (19.7%) and slightly more than 1/5th (23.7%) of female students reported having abused alcohol. More than half of both male students (65.6%) and female students (69.0%) reported that they were currently not taking any alcohol and only 10% of male pupils reported using marijuana. Suicidal ideation was reported in 19.3% of female students compared to 13.3% of their male counterparts.

The factors associated with suicidal ideation are presented in Table 2 and results show that age was significantly associated with suicidal ideation, students aged fifteen [15] years were 12% less likely (AOR=0.88, 95% CI [0.84, 0.92]) to have suicidal ideation compared to those aged sixteen years and above. Students aged 14 years and those less than 14 years were 1.07 times (AOR=1.07, 95% CI [1.02, 1.12]) and 1.14 times (AOR=1.14, 95% CI [1.09, 1.20]) more likely to commit suicide compared to students who were 16 years old and above. Male students were 33% more likely to commit suicide compared to female students.

Table 1. Distribution of factors considered in the analysis by gender among junior high school pupils in Trinidad and Tobago

Factor	Total n ¹ (%) ²	Males n ¹ (%) ²	Females n ¹ (%) ²
Age			
<14	1316 (42.9)	710 (42.3)	606 (43.4)
14	665 (25.5)	383 (25.7)	282 (25.3)
15	524 (21.6)	282 (22.6)	242 (20.7)
16+	269 (10.1)	140 (9.5)	129 (10.7)
Gender			
Male	1515 (54.6)	-	-
Female	1259 (45.4)	-	-
Food security			
No	212 (6.4)	124 (7.8)	88 (5.0)
Yes	2521 (93.6)	1369 (92.2)	1152 (95.0)
Anxiety			
Yes	202 (7.2)	87 (5.4)	115 (9.1)
No	2558 (92.8)	1419 (94.6)	1139 (90.9)
Loneliness			
Yes	290 (9.8)	134 (8.2)	156 (11.4)
No	2486 (90.2)	1379 (91.8)	1107 (88.6)
Close friends			
No	249 (8.8)	138 (8.6)	111 (9.1)
Yes	2506 (91.2)	1361 (91.4)	1145 (90.9)
Truancy			
Yes	2196 (82.0)	1162 (79.9)	1034 (84.0)
No	505 (18.0)	307 (20.1)	198 (16.0)
Bullied			
Yes	2227 (85.3)	1183 (82.7)	1044 (87.9)
No	441 (14.7)	270 (17.3)	171 (12.1)
Attacked			
Yes	972 (32.9)	644 (40.3)	328 (25.7)
No	1789 (67.1)	865 (59.7)	924 (74.3)
In a fight			
Yes	1078 (36.1)	729 (46.5)	349 (26.0)
No	1650 (63.9)	764 (53.5)	886 (74.0)
Currently smoked			
Yes	259 (9.5)	181 (13.0)	78 (6.2)
No	2486 (90.5)	1311 (87.0)	1175 (93.8)
Parental understanding			
Yes	1047 (39.9)	572 (39.7)	475 (40.1)
No	1644 (60.1)	886 (60.3)	758 (59.9)
Alcohol abuse			
Yes	618 (21.7)	374 (23.7)	244 (19.7)
No	2026 (78.3)	1066 (76.3)	960 (80.3)
Current alcohol			
Yes	917 (32.7)	524 (34.4)	393 (31.0)
No	1712 (67.3)	918 (65.6)	794 (69.0)
Marijuana			
Yes	197 (6.6)	149 (10.0)	48 (3.3)
No	2482 (93.4)	1305 (90.0)	1177 (96.7)
Suicidal ideation			
Yes	443 (16.3)	200 (13.3)	243 (19.3)
No	2243(83.7)	1266 (86.7)	977 (80.7)

¹ unweighted frequencies. ² weighted percents.

Table 2. Factors associated with suicidal ideation among junior high school students in Trinidad and Tobago

Factor	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Age (years)		
<14	0.69 (0.67, 0.71)	1.14 (1.09, 1.20)
14	1.05 (1.02, 1.09)	1.07 (1.02, 1.12)
15	1.10 (1.06, 1.12)	0.88 (0.84, 0.92)
16+	1	1
Gender		
Male	0.80 (0.78, 0.82)	0.67 (0.65, 0.69)
Female	1	1
Food security		
No	1.68 (1.63, 1.74)	1.28 (1.22, 1.35)
Yes	1	1
Anxiety		
Yes	2.41 (2.34, 2.49)	1.54 (1.48, 1.61)
No	1	1
Loneliness		
Yes	2.44 (2.38, 2.51)	2.04 (1.97, 2.11)
No	1	1
Close friends		
No	1.28 (1.24, 1.32)	1.06 (1.01, 1.11)
Yes	1	1
Truancy		
Yes	0.88 (0.54, 0.90)	1.08 (1.05, 1.12)
No	1	1
Bullied		
Yes	0.64 (0.63, 0.66)	0.81 (0.78, 0.84)
No	1	1
Attacked		
Yes	1.41 (1.38, 1.44)	1.27 (1.24, 1.31)
No	1	1
In a fight		
Yes	1.35 (1.32, 1.38)	1.05 (1.01, 1.08)
No	1	1
Currently smoking		
Yes	1.62 (1.56, 1.67)	1.20 (1.14, 1.25)
No	1	1
Parental understanding		
Yes	0.54 (0.53, 0.56)	0.63 (0.61, 0.65)
No	1	1
Alcohol abuse		
Yes	1.53 (1.49, 1.56)	1.19 (1.16, 1.23)
No	1	1
Current alcohol		
Yes	1.51 (1.48, 1.54)	1.26 (1.22, 1.30)
No	1	1
Marijuana		
Yes	1.70 (1.64, 1.76)	1.55 (1.47, 1.63)
No	1	1

Students with food security problems were 1.28 times more likely (AOR = 1.28, 95% CI [1.22, 1.35]) to consider committing suicide compared to students with food security. Anxious students were 1.54 times more likely (AOR = 1.54, 95% CI [1.48, 1.61]) to have suicidal thoughts compared to students who never reported anxiety. Students who reported not to have close friends were 1.06 times more likely (AOR=1.06, 95% CI [1.01, 1.11]) to experience suicidal ideations compared to students who had close friends while lonely pupils

were 2.04 times more likely (AOR=2.04, 95% CI [1.97, 2.11]) to consider committing suicide compared to students who did not report loneliness. Students having been attacked were 1.27 times more likely (AOR = 1.27, 95% CI [1.24, 1.31]) to consider committing suicide compared to those having not been attacked before. Students who have been involved in a fight were 1.05 times more likely to consider suicide (AOR = 1.05, 95% CI [1.01, 1.08]) compared to those with no history of having been involved in a fight. Respondents who reported current smoking were 1.20 times more likely to think of committing suicide (AOR=1.20, 95% CI [1.14, 1.25]) compared with non-smokers. Students who reported having understanding parents were 37% less likely (AOR = 0.63, 95% CI [0.61, 0.65]) to have suicidal ideation compared to students who did not have parental understanding. Students who reported alcohol abuse were 1.19 times more likely to commit suicide compared to those who did not report alcohol abuse (AOR=1.19, 95% CI [1.16, 1.23]). Respondents who reported current alcohol use were 1.26 times more likely to commit suicide compared to those who did not report current alcohol use (AOR = 1.26, 95% CI [1.22, 1.30]). Students who took marijuana were 1.55 times more likely to commit suicide (AOR = 1.55, 95% CI [1.47, 1.63]) compared to those who did not report use of marijuana.

DISCUSSION

The current study examined the correlates for suicidal ideation among in-school Trinidad and Tobago adolescents using Global School Health Survey data. This study found that 16.3% of in-school adolescents seriously considered committing suicide and this prevalence is consistent with the prevalence of Lebanese adolescents (16%) who thought of committing suicide in a previous study [15]. Having understanding parents, history of bullying, being of male gender and being 15 years of age were negatively associated with suicidal ideation, while food security, anxiety, lack of close friends, loneliness, history of attack, involvement in a fight, truancy, currently smoking, alcohol abuse, current alcohol use and marijuana use were positively associated with suicidal ideation.

Suicidal ideation in younger age is not a common finding in many studies, however, the finding in this study is in accord with the result in another study elsewhere [6] which observed an increase of suicide mortality at a lower age and related it to an early age onset for depressive disorders. In view of this previous finding, it can be assumed that an increase of suicidality at a lower age may indirectly suggest evidence of an early age onset of depressive disorder.

The results of our study show that gender was significantly associated with suicidal ideation and females were more likely to have suicidal ideas compared to male adolescents. This is contradicting the finding by Wasserman et al. [1] in which suicide rates for young people in the 15-19 age group are, as for other age groups, higher in males than in females.

Adolescents who reported food-insufficient were significantly more likely to think of suicide than those that did not have food security challenges. A study among US adolescents [16] agree with this result. The other findings of the current study showed that poor mental health issues such as loneliness, anxiety and no close friends were significantly associated with suicidal ideation. This is reaffirmed by several studies [17, 18] that have shown that suicidal ideation is associated with loneliness and anxiety.

Our study results showed that incidences of victimization significantly increased the likelihood of suicidal ideation among in-school adolescents in Trinidad and Tobago. Similarly, another study [19] elsewhere showed that involvement in fight, attack or bully—victim problems at school, was significantly related to suicidal ideation. Substance abuse was found to be significantly associated with suicidal ideation and a lot of research has been conducted on this subject [14, 20, 21] and most of the results agree with our findings.

In conclusion, the current study indicates the public health importance of highlighting the commonly observed factors associated with this public health problem of suicidal ideation. It is essential to consider unhealthy behaviors such as substance abuse, violent behavior among peers and social support structures as the main determinants of suicidal ideation among in-school adolescents in Trinidad and Tobago. Therefore, parental and social support, age and gender of adolescents should also be considered when planning and implementing public health intervention programs against suicidal ideation among in-school adolescents in Trinidad and Tobago.

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Chapter 45

FACTORS ASSOCIATED WITH SUICIDAL IDEATION AMONG ADOLESCENTS ATTENDING SCHOOL IN KUWAIT

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ABSTRACT

Suicide rates in Kuwait are on the increase and information on suicidal ideation which may lead to suicide is scanty. The objective of the study was to determine factors that are associated with suicidal ideation. Weighted frequencies to estimate proportions and logistic regression analyses (bivariate and multivariate) to establish significant factors associated with suicidal ideation were conducted using secondary data obtained in a 2011 Kuwait Global School-based Health Survey. Unadjusted odds ratio (OR) and adjusted odds ratio (AOR) together with their 95% confidence intervals (CI) are reported. Of the 2672 students who participated in the survey. Overall, 19.9% (18.7% of male and 21.3% of female) students reported suicidal ideation. Factors associated with suicidal ideation were age, gender (male gender: AOR = 0.75; 95% CI [0.73, 0.78]), food security, anxiety (AOR = 1.43; 95% CI [1.39, 1.46]), loneliness (AOR = 1.61; 95% CI

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[1.57, 1.65]), close friends (AOR = 1.33; 95% CI [1.24, 1.42]), truancy (AOR = 1.20; 95% CI [1.17, 1.23]), bullied (AOR = 1.54; 95% CI [1.50, 1.58]), attacked, in a fight (AOR = 1.39; 95% CI [1.35, 1.43]), currently smoked cigarettes, used marijuana (AOR = 1.84; 95% CI [1.73, 1.95]) and parental understanding (AOR = 0.70; 95% CI [0.68, 0.72]). The prevalence of suicidal ideation in Kuwait among adolescents is high. Suicidal ideation is prevalent in Kuwait. Interventions designed using the factors identified in the current study are needed to curb the rate of suicidal thoughts.

Keywords: suicidal ideation, prevalence, associated factors, adolescents, Kuwait

INTRODUCTION

Suicide rates in Kuwait increased from 3.2 in 2002 to 6.1 per 100,000 population in 2010 [1]. While not all suicidal thoughts materialize in suicide, prevention of suicidal ideation may curtail suicide rates. Information on suicidal ideation among adolescents is scanty in Kuwait and in the region as a whole partly due to the illegality of suicide. El-Sayed Badr [2] obtained a prevalence rate of suicidal ideation of 20.0% among participants in a 2010 Kuwait Global School-based Student Health Survey. Factors associated with suicidal behaviours (ideation, planning and attempts) in that study were gender, smoking, physical violence, loneliness, bullying and parental understanding. Literature suggests that more factors are associated with suicidal ideation. These include: age [3-5], food security [6-9], anxiety [7, 10-14], having close friends [15-17], truancy [10, 18], attacked [7, 11, 19] and involvement in a fight [7, 20, 21]. The current study aimed to further determine factors that are associated with suicidal ideation.

METHODS

Kuwait is a high income country located in the Middle East and North Africa region [22]. Preliminary results of the 2011 census indicated a population of 3.1 million of which 65% was non-national and about 83% of the total population resided in the capital, Kuwait city [23]. This high level of non-nationals poses a challenge to estimate the population size for Kuwait because the Kuwait government rarely grants citizenship to foreigners. Kuwait borders with Iraq and Saudi Arabia (Figure 1). About a quarter (25.3%) of the population is aged below 15 years [23]. The study population comprised school-going adolescents in grades 8 to 10, country-wide. The study design was cross sectional.

A total of 2,672 students participated in the 2011 Kuwait Global School-based Health Survey (GSHS) resulting in a school response rate of 97%, the student response rate of 88%, and an overall response rate of 85%.

A two stage cluster sampling method was used to select participants for a sample that is representative of school going adolescents mainly in the age group 13-15 years. The school was the sampling unit in the first stage of sampling. Schools were randomly selected proportional to their enrolment size. In the second stage of sampling, classes were then randomly selected and all students in selected schools were eligible to participate in the study irrespective of their ages.



Source: <http://www.worldatlas.com/webimage/countrys/asia/kw.htm>.

Figure 1. Map of Kuwait and its neighbouring countries.

The 2011 Kuwait GSHS questionnaire had the following sections: dietary behaviours; drug use; hygiene; mental health; physical activity; protective factors; tobacco use; and violence and unintentional injury. Table 1 shows variables that were considered in the analysis. The dependent variable was suicidal ideation, while the independent variables were age, gender, food security, anxiety, loneliness, close friends, truancy, bullied, attached, in a fight, smoking cigarettes/marijuana and parental understanding.

Data Analysis

Data was analysed using SPSS version 16. Frequencies and logistic regression analyses were weighted using the following equation:

$$W = W1 \times W2 \times f1 \times f2 \times f3 \times f4$$

where W1 = the inverse of the probability of selecting the school, W2 = the inverse of the probability of selecting the classroom within the school,

f1 = a school-level non-response adjustment factor calculated by school size category (small, medium, large), f2 = a class-level non-response adjustment factor calculated for each school, f3 = a student-level non-response adjustment factor calculated by class, and f4 = a post stratification adjustment factor calculated by grade.

Table 1. Global School-Based Health Survey questions used in the analysis of adolescent suicidal ideation

Variable	Question	Coded	Recoded
Dependent variable			
Suicidal ideation	During the past 12 months, did you ever seriously consider attempting suicide?	1 = Yes; 2 = No	1 = Yes; 2 = No
Independent variables			
Age	How old are you?	1 = 11 years old or younger; 2 = 12 years old; 3 = 13 years old; 4 = 14 years old; 5 = 15 years old; 6 = 16 years old or older	1-3 = 1; 4 = 2; 5 = 3; 6 = 4
Gender	What is your sex?	1 = Male; 2 = Female	1 = 1; 2 = 2
Food security	During the past 30 days, how often did you go hungry because there was not enough food in your home?	1 = Never; 2 = Rarely; 3 = Sometimes; 4 = Most of the time; 5 = Always	4-5 = 1; 1-3 = 2
Anxiety	During the past 12 months, how often have you been so worried about something that you could not sleep at night?	1 = Never; 2 = Rarely; 3 = Sometimes; 4 = Most of the time; 5 = Always	4-5 = 1; 1-3 = 2
Loneliness	During the past 12 months, how often have you felt lonely?	1 = Never; 2 = Rarely; 3 = Sometimes; 4 = Most of the time; 5 = Always	4-5 = 1; 1-3 = 2
Close friends	How many close friends do you have?	1 = 0; 2 = 1; 3 = 2; 4 = 3 or more	1 = 1; 2-4 = 2
Truancy	During the past 30 days, on how many days did you miss classes or school without permission?	1 = 0 days; 2 = 1 or 2 days; 3 = 3 to 5 days; 4 = 6 to 9 days; 5 = 10 or more days	1 = 2; 2-5 = 1
Bullied	Bullied during the past 30 days, on how many days were you bullied?	1 = 0 days; 2 = 1 or 2 days; 3 = 3 to 5 days; 4 = 6 to 9 days; 5 = 10 to 19 days; 6 = 20 to 29 days; 7 = All 30 days	1 = 2; 2-7 = 1
Attacked	During the past 12 months, how many times were you physically attacked?	1 = 0 times; 2 = 1 time; 3 = 2 or 3 times; 4 = 4 or 5 times; 5 = 6 or 7 times; 6 = 8 or 9 times; 7 = 10 or 11 times; 8 = 12 or more times	1 = 2; 2-8 = 1
In a fight	During the past 12 months, how many times were you in a physical fight?	1 = 0 times; 2 = 1 time; 3 = 2 or 3 times; 4 = 4 or 5 times; 5 = 6 or 7 times; 6 = 8 or 9 times; 7 = 10 or 11 times; 8 = 12 or more times	1 = 2; 2-8 = 1
Currently smoked cigarettes	During the past 30 days, on how many days did you smoke cigarettes?	1 = 0 days; 2 = 1 or 2 days; 3 = 3 to 5 days; 4 = 6 to 9 days; 5 = 10 to 19 days; 6 = 20 to 29 days; 7 = All 30 days	1 = 2; 2-7 = 1
Used marijuana	During your life, how many times have you used marijuana (also called khushkhash)?	1 = 0 times; 2 = 1 or 2 times; 3 = 3 to 9 times; 4 = 10 to 19 times; 5 = 20 or more times	1 = 2; 2-5 = 1
Parental understanding	During the past 30 days, how often did your parents or guardians understand your problems and worries?	1 = Never; 2 = Rarely; 3 = Sometimes; 4 = Most of the time; 5 = Always	1-3 = 2; 4-5 = 1

RESULTS

Of the 2,672 students who participated in the survey, 52.3% were males and 87.2% were aged less than 16 years. Overall, 9.3% of the students reported that they had no food security. About 1 in 5 students reported being anxious (20.2%) and lonely (18.7%). Most (96.7%) of the students had close friends. Overall, 57.9% of the students (53.8% of males and 62.2% of females) missed school or classes without permission. Violence was common ($p < 0.001$) among males than females (bullied: 36.2% males and 19.6% females; attacked: 41.3% males and 24.8% females; in a fight: 59.9% males and 28.6% females). Cigarette smoking was reported by 26.0% of males and 8.2% of females. Meanwhile, marijuana was used by 5.7% of males and 0.4% of females. Altogether, 39.3% of students indicated that their parents understood their problems and worries. About 1 in 5 of the students reported that they had suicidal thoughts: 18.7% of males and 21.3% of females with an overall rate of 19.9%. These results are shown in Table 2.

Correlates for suicidal ideation are shown in Table 3. All the factors considered in the analysis were significantly associated with suicidal ideation in both bivariate and multivariate analyses. While students aged 14 years (AOR = 1.20; 95% CI [1.15, 1.24]) were more likely to have suicidal ideation, those of age 15 years were less likely to have suicidal thoughts (AOR = 0.75; 95% CI [0.72, 0.78]) compared with students of age 16 years or older. Male students were 25% (AOR = 0.75; 95% CI [0.73, 0.78]) less likely to have suicidal ideation compared with female students. Students from homes that had no food security were 6% (AOR = 1.06; 95% CI [1.02, 1.10]) more likely to have suicidal ideation compared with students from homes with food security.

Compared with students who were not anxious, students who were anxious were 43% more likely to have suicidal ideation (AOR = 1.43; 95% CI [1.39, 1.46]). Meanwhile, students who were lonely were 1.61 (95% CI [1.57, 1.65]) times more likely to have suicidal thoughts compared with students who were not lonely. Students who had no close friends were 33% (AOR = 1.33; 95% CI [1.24, 1.42]) more likely to have suicidal thought compared with students who had close friends. Missing school or classes was positively associated with suicidal ideation (AOR = 1.20; 95% CI [1.17, 1.23]).

Violence was associated with suicidal ideation. Students who were bullied were 54% (AOR=1.54; 95% CI [1.50, 1.58]) more likely to have suicidal ideation compared with students who were not bullied. Compared with students who were not attacked, students who were attacked were 9% (AOR=1.09; 95% CI [1.06, 1.12]) more likely to have suicidal thoughts. Involvement in a fight was associated with suicidal thoughts (AOR = 1.39; 95% CI [1.35, 1.43]).

Smoking was significantly associated with suicidal thoughts. Compared with students who did not smoke cigarettes, students who smoked cigarettes were more likely to have suicidal ideation (AOR = 1.18; 95% CI [1.13, 1.21]). Students who used marijuana were 84% (AOR=1.84; 95% CI [1.73, 1.95]) more likely to have suicidal thoughts than students who did not use marijuana. Students who had parental understanding were 30% less likely to have suicidal ideation (AOR=0.70; 95% CI [0.68, 0.72]) than those without.

Table 2. Distribution of factors considered in the analysis by gender among junior high school students in Kuwait, 2011

Factor	Total n ¹ (%) ²	Males n ¹ (%) ²	Females n ¹ (%) ²
Age			
<14	614 (23.1)	245 (18.2)	365 (28.4)
14	813 (30.7)	415 (33.4)	396 (27.8)
15	875 (33.4)	459 (34.1)	414 (32.8)
16+	362 (12.8)	216 (14.3)	144 (11.0)
Gender			
Male	1336 (52.3)		
Female	1320 (47.7)		
Food security			
No	240 (9.3)	138 (10.6)	100 (7.8)
Yes	2404 (90.7)	1172 (89.4)	1219 (92.2)
Anxiety			
Yes	547 (20.2)	214 (16.2)	331 (7.8)
No	2077 (79.8)	1079 (83.8)	984 (92.2)
Loneliness			
Yes	492 (18.7)	177 (13.6)	314 (24.3)
No	2138 (81.3)	1121 (86.4)	1002 (75.7)
Close friends			
No	91 (3.3)	51 (3.8)	39 (2.8)
Yes	2558 (96.7)	1267 (96.2)	1276 (97.2)
Truancy			
Yes	1535 (57.9)	713 (53.8)	811 (62.2)
No	1114 (42.1)	606 (46.2)	503 (37.8)
Bullied			
Yes	712 (28.3)	452 (36.2)	254 (19.6)
No	1821 (71.7)	797 (63.8)	1014 (80.4)
Attacked			
Yes	862 (33.4)	539 (41.3)	316 (24.8)
No	1781 (66.6)	769 (58.7)	1003 (75.2)
In a fight			
Yes	1161 (44.9)	781 (59.9)	370 (28.6)
No	1486 (55.1)	530 (40.1)	950 (71.4)
Currently smoked cigarettes			
Yes	450 (17.6)	342 (26.0)	102 (8.2)
No	2163 (82.4)	952 (74.0)	1202 (91.8)
Used marijuana			
Yes	84 (3.2)	77 (5.7)	6 (0.4)
No	2559 (96.8)	1234 (94.3)	1310 (99.6)
Parental understanding			
Yes	1029 (39.3)	575 (43.6)	446 (34.5)
No	1618 (60.7)	737 (56.4)	873 (65.5)
Suicidal ideation			
Yes	519 (19.9)	238 (18.7)	278 (21.3)
No	2132 (80.1)	1083 (81.3)	1036 (78.7)

¹ unweighted frequencies. ² weighted percents.

Table 3. Factors associated with suicidal ideation among junior high school students in Kuwait, 2011

Factor	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Age (years)		
<14	0.86 (0.83, 0.89)	0.95 (0.91, 1.00)
14	1.10 (1.07, 1.14)	1.20 (1.15, 1.24)
15	0.82 (0.80, 0.85)	0.75 (0.72, 0.78)
16+	1	1
Gender		
Male	0.92 (0.91, 0.94)	0.75 (0.73, 0.78)
Female	1	1
Food security		
No	1.43 (1.39, 1.47)	1.06 (1.02, 1.10)
Yes	1	1
Anxiety		
Yes	1.90 (1.86, 1.94)	1.43 (1.39, 1.46)
No	1	1
Loneliness		
Yes	2.05 (2.01, 2.09)	1.61 (1.57, 1.65)
No	1	1
Close friends		
No	1.40 (1.34, 1.46)	1.33 (1.24, 1.42)
Yes	1	1
Truancy		
Yes	1.35 (1.32, 1.38)	1.20 (1.17, 1.23)
No	1	1
Bullied		
Yes	1.87 (1.84, 1.91)	1.54 (1.50, 1.58)
No	1	1
Attacked		
Yes	1.56 (1.53, 1.59)	1.09 (1.06, 1.12)
No	1	1
In a fight		
Yes	1.52 (1.50, 1.55)	1.39 (1.35, 1.43)
No	1	1
Currently smoked cigarettes		
Yes	1.60 (1.57, 1.64)	1.18 (1.13, 1.21)
No	1	1
Used marijuana		
Yes	2.54 (2.43, 2.65)	1.84 (1.73, 1.95)
No	1	1
Parental understanding		
Yes	0.68 (0.67, 0.70)	0.70 (0.68, 0.72)
No	1	1

DISCUSSION

In the current study, prevalence rate of suicidal ideation of 19.9% overall (18.7% among males and 21.3% among females) was observed. Factors associated with suicidal ideation were age, gender, food security, anxiety, loneliness, close friends, truancy, bullied, attacked, involvement in a fight, smoking (cigarettes or marijuana) and parental understanding. Using

the same data set and methods of data analysis, the prevalence rate of suicidal ideation in the current study was 19.9% as opposed to 20.0% reported by El-Sayed Badr [2]. It is possible that the difference is due to rounding off error.

Findings on demographic factors associated with suicidal ideation have not been consistent. In the current study, while students aged 14 years were more likely to have suicidal thoughts, students aged 15 years were less likely to have suicidal ideation compared with students of age 16 years or older, contradicting the notion that younger adolescents may be less likely to cope with the stressors. In another study by Rudatsikira et al. [16], no association was observed between age and suicidal ideation.

Male students were less likely to have suicidal ideation compared with females in the present study. This finding accords those of Rudatsikira et al. [16] and Lee and Choi [24]. However, no association was observed between gender and suicidal ideation in other studies [25, 26]. Differences in the association between gender and suicidal ideation are partly a reflection in gender differences in emotional and behavioural reactions [27] in different cultures.

Adolescents in homes with not enough food were more likely to have suicidal ideation in the current study. Lack of enough food may trigger anxiety and loneliness that have been associated with suicidal ideation in adolescents. Similar findings have been reported by Rudatsikira et al. [16] and Hockenberry et al. [28].

In the current study, violence (bullied, attacked or fighting) has been associated with suicidal thoughts. Rudatsikira et al. [16] observed that students in Guyana who were bullied were more likely to have suicidal ideation compared with students who were not bullied. Because of fear of being bullied, attacked or involved in a fight, school going adolescents may miss classes or school without permission. Prevention of violence should be addressed at school.

Apart from McGee et al. [29] who did not find a significant association between smoking and suicidal ideation, most studies have reported a significant association between smoking and suicidal ideation [16, 28, 30-32]. Smoking marijuana was also significantly associated with suicidal ideation in the current study. Smoking (cigarettes or marijuana) may mediate depression in its association with suicidal ideation and students may perceive smoking as a way out of their stressful situations.

Good relationships with friends and parents are important so that any negative changes in the adolescents can be identified and addressed before situations become unmanageable.

In conclusion, suicidal ideation in Kuwait is prevalent and interventions utilizing information obtained in the current study should be designed to curtail the rate of suicidal ideation.

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Chapter 46

SUICIDAL IDEATION IN FIJI: PREVALENCE AND ITS CORRELATES AMONG SCHOOL-GOING ADOLESCENTS IN A GLOBAL SCHOOL HEALTH-BASED SURVEY

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ABSTRACT

There is scanty information on suicide in general and in particular suicide ideation in Fiji. Fijian Indians have one of the highest rates of suicide in the world. The objectives of the study were to determine the rate of suicide ideation and its correlates among adolescents in Fiji. Secondary data obtained in a 2010 Fiji Global School-based Health Survey was used in the analysis. Weighted frequencies to estimate proportions and logistic regression analyses (bivariate and multivariate) to establish significant factors associated with suicidal ideation were conducted. Unadjusted odds ratio (OR) and adjusted odds ratio (AOR) together with their 95% confidence intervals (CI) are reported. A total of 1673 students participated in the survey. Overall, 17.6% (16.4% of male and 18.5% of female) students reported suicidal ideation. Factors associated with suicidal ideation were age, gender (male gender: AOR = 0.75; 95% CI [0.73, 0.77]), food security, anxiety (AOR = 1.46; 95% CI [1.41, 1.51]), loneliness (AOR = 1.26; 95% CI

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[1.21, 1.31]), bullied, attacked (AOR = 1.28, 95% CI [1.24, 1.32]), in a fight (AOR = 1.23; 95% CI [1.19, 1.27]), smoking cigarettes (AOR = 1.39, 95% CI [1.34, 1.45]) and alcohol use (AOR = 1.41, 95% CI [1.36, 1.46]). The prevalence of suicidal ideation in Fiji is of concern and efforts should be made to design interventions that may lower the prevalence, considering the information obtained in the current study.

Keywords: suicidal ideation, prevalence, correlates, adolescents, Fiji

INTRODUCTION

Fiji is one of the happiest countries in the world with 93% of people indicating as such [1] despite unstable political past and only in 2006 were democratic elections held [2]. Fiji has a tight-knit society that is mostly village based with the extended family, where children are cared for by the community; and there is low crime rate [3]. Fiji is located in the South Pacific Ocean with more than 300 islands of which 110 are permanently inhabited [4]. Although the overall suicide rate for Fiji was 19 per 100,000, the suicide rate for Fijian Indians aged 15-24 years of 34 per 100,000 population was higher than those for other countries in the world in 1982-1983 [5, 6]. In 2014, Fiji with a rate of 7.50 per 100,000 population ranked 100 out of 172 countries in suicide in 2014 [7]. Clearly, there are unhappy faces in the happiest country in the world.

There is limited information on suicidal ideation in Fiji. A prevalence of suicidal ideation and related behaviors was reported to be 22.5% among ethnic Fijian adolescent girls in Fiji [8]. In order to contribute to the body of knowledge on suicide ideation, a study was conducted to determine the extent of the problem and establish factors associated with it.

METHODS

Fiji is a developing country in the upper middle income group [9] located in the East Asia and Pacific region (Figure 1). The population of Fiji at the time of the survey was 860,559 in 2010 [10] and it is now 905,949 consisting of 51% Fijian, 44% Indian and 5% others. The 0-14 years age group makes up 31.1% of the population. In terms of religion, 52% of the population is Christian, 38% Hindu, 8% Muslim and 2% belong to other regions or are none believers [11]. The study population comprised school-going adolescents in Forms 2, 3 and 4 in Fiji nation-wide [12].

A cross sectional study was conducted in which 1,673 students participated in the 2010 Fiji Global School-based Health Survey (GSHS) resulting in a school response rate of 100%, the student response rate of 90%, and an overall response rate of 90%.

A two stage cluster sampling technique was used to select participants for a sample that is representative of students in Forms 2, 3 and 4 in Fiji. The school was the primary sampling unit that was selected with probability proportional to enrolment size. The second stage of sampling involved randomly selecting classes in the selected schools and all students in the selected classes were eligible to participate in the survey.



Source: <https://www.tourismfiji.com/fiji-map.html>.

Figure 1. Fiji islands.

The questionnaire that was used in the 2010 Fiji GSHS had the following sections: alcohol use, dietary behaviours; mental health, physical activity, sexual behaviour, tobacco use, and violence and unintentional injury. Table 1 shows variables that were considered in the analysis. The dependent variable was suicidal ideation, while the independent variables were age, gender, food security, anxiety, loneliness, close friends, bullied, attached, in a fight, cigarette smoking and alcohol use/abuse.

Data Analysis

Data was analysed using SPSS version 16. Frequencies and logistic regression analyses were weighted using the following equation:

$$W = W1 \times W2 \times f1 \times f2 \times f3 \times f4$$

where $W1$ = the inverse of the probability of selecting the school, $W2$ = the inverse of the probability of selecting the classroom within the school, $f1$ = a school-level non-response adjustment factor calculated by school size category (small, medium, large), $f2$ = a class-level non-response adjustment factor calculated for each school, $f3$ = a student-level non-response adjustment factor calculated by class, and $f4$ = a post stratification adjustment factor calculated by grade.

Table 1. Variable definition and codes

Variable	Coded	Recoded	Redefined variable
Outcome variable			
During the past 12 months, did you ever seriously consider attempting suicide?	1 = Yes; 2 = No	1 = 1; 2 = 2	Suicidal ideation
Independent variables			
How old are you?	1 = 11 years old or younger; 2 = 12 years old; 3 = 13 years old; 4 = 14 years old; 5 = 15 years old; 6 = 16 years old or older	1-3 = 1; 4 = 2; 5 = 3; 6 = 4	Age
What is your sex?	1 = Male; 2 = Female	1 = 1; 2 = 2	Gender
During the past 30 days, how often did you go hungry because there was not enough food in your home?	1 = Never; 2 = Rarely; 3 = Sometimes; 4 = Most of the time; 5 = Always	4-5 = 1; 1-3 = 2	Food security
During the past 12 months, how often have you been so worried about something that you could not sleep at night?	1 = Never; 2 = Rarely; 3 = Sometimes; 4 = Most of the time; 5 = Always	4-5 = 1; 1-3 = 2	Anxiety
During the past 12 months, how often have you felt lonely?	1 = Never; 2 = Rarely; 3 = Sometimes; 4 = Most of the time; 5 = Always	4-5 = 1; 1-3 = 2	Loneliness
How many close friends do you have?	1 = 0; 2 = 1; 3 = 2; 4 = 3 or more	1 = 1; 2-4 = 2	Close friends
During the past 30 days, on how many days were you bullied?	1 = 0 days; 2 = 1 or 2 days; 3 = 3 to 5 days; 4 = 6 to 9 days; 5 = 10 to 19 days; 6 = 20 to 29 days; 7 = All 30 days	1 = 2; 2-7 = 1	Bullied
During the past 12 months, how many times were you physically attacked?	1 = 0 times; 2 = 1 time; 3 = 2 or 3 times; 4 = 4 or 5 times; 5 = 6 or 7 times; 6 = 8 or 9 times; 7 = 10 or 11 times; 8 = 12 or more times	1 = 2; 2-8 = 1	Attacked
During the past 12 months, how many times were you in a physical fight?	1 = 0 times; 2 = 1 time; 3 = 2 or 3 times; 4 = 4 or 5 times; 5 = 6 or 7 times; 6 = 8 or 9 times; 7 = 10 or 11 times; 8 = 12 or more times	1 = 2; 2-8 = 1	In a fight
During the last 30 days, on how many days did you smoke cigarettes?	1 = 0 days; 2 = 1 or 2 days; 3 = 3 to 5 days; 4 = 6 to 9 days; 5 = 10 to 19 days; 6 = 20 to 29 days; 7 = All 30 days	1 = 2; 2-7 = 1	Cigarette smoking
During your life, how many times did you drink so much alcohol that you were really drunk?	1 = 0 times; 2 = 1 or 2 times; 3 = 3 to 9 times; 4 = 10 or more times	1 = 2; 2-4 = 1	Alcohol abuse
During the past 30 days, on how many days did you have at least one drink containing alcohol?	1 = 0 days; 2 = 1 or 2 days; 3 = 3 to 5 days; 4 = 6 to 9 days; 5 = 10 to 19 days; 6 = 20 to 29 days; 7 = All 30 days	1 = 2; 2-7 = 1	Alcohol use

RESULTS

Of the 1,673 students who participated in the survey, 49.8% were males and 11.1% were aged 16 years or older. Overall, 10.7% of the students reported that they had no food security. Less than 3 in 20 students reported being anxious (14.0%) and lonely (12.3%). Most (93.1%) of the students had close friends. Overall, 43.0% of the students were bullied. Physical attack and fighting were more common ($p < 0.001$) in males than females (attacked: 52.1% males and 39.6% females; in a fight: 60.2% males and 36.6% females). Cigarette smoking was reported by 18.1% of males and 7.9% of females.

Meanwhile, alcohol abuse was reported by 19.2% of males and 8.2% of females; alcohol use by 22.1% of males and 11.2% of females. Suicide ideation was reported by 17.6% of students (16.4% of males and 18.5% of females). These results are shown in Table 2.

Correlates for suicidal ideation are shown in table 3. While students aged 14 years (AOR = 1.12; 95% CI [1.07, 1.17]) were more likely to have suicidal ideation, those of age <14 years were less likely to have suicidal thoughts (AOR = 0.84; 95% CI [0.80, 0.89]) compared with students of age 16 years or older. Male students were 25% (AOR = 0.75; 95% CI [0.73, 0.77]) less likely to have suicidal ideation compared with female students.

Students from homes that had no food security were 6% (AOR = 1.06; 95% CI [1.01, 1.10]) more likely to have suicidal ideation compared with students from homes with food security. Compared with students who were not anxious, students who were anxious were 46% (AOR = 1.46; 95% CI [1.41, 1.51]) more likely to have suicidal ideation. Meanwhile, students who were lonely were 1.26 (95% CI [1.21, 1.31]) times more likely to have suicidal thoughts compared with students who were not lonely.

Violence was associated with suicidal ideation. Students who were bullied were 16% (AOR=1.16; 95% CI [1.13, 1.19]) more likely to have suicidal ideation compared with students who were not bullied. Compared with students who were not attacked, students who were attacked were 28% (AOR = 1.28; 95% CI [1.24, 1.32]) more likely to have suicidal thoughts. Involvement in a fight was associated with suicidal thoughts (AOR = 1.23; 95% CI [1.19, 1.27]).

Smoking was significantly associated with suicidal thoughts. Compared with students who did not smoke cigarettes, students who smoked cigarettes were more likely to have suicidal ideation (AOR = 1.39; 95% CI [1.34, 1.45]). Students who consumed alcohol were 41% (AOR = 1.41; 95% CI [1.36, 1.46]) more likely to have suicidal thoughts than students who did not consume alcohol.

DISCUSSION

The prevalence rate of suicidal ideation in the current study was 17.6% overall (16.4% among males and 18.5% among females). Factors associated with suicidal ideation were age, gender, food security, anxiety, loneliness, bullied, attacked, involvement in a fight, cigarette smoking and alcohol use. In the present study, while students aged 14 years were more likely to have suicidal thoughts, students aged <14 years were less likely to have suicidal ideation compared with students of age 16 years or older, contradicting the finding by Rudatsikira et al. [13] who reported no association between age and suicidal ideation. The inconsistencies in the finding on the relationship between age suicide ideation suggest further research.

The finding that males were less likely to have suicidal thoughts accords the findings by Rudatsikira et al. [13] and Lee and Choi [14]. Contrary, no significant association was observed between gender and suicidal ideation in other studies [15, 16]. Differences in the association between gender and suicidal ideation are partly a reflection of cultural influence on gender roles which differ between populations.

Food security was associated with suicidal thoughts in the current study and so was anxiety and loneliness. Because of lack of enough food homes, adolescents may be anxious for where to find the next meal and in the process become lonely. Rudatsikira et al. [13] and

Hockenberry et al. [17] also reported similar findings. Further analysis to establish interactions among factors associated with suicidal ideation is suggested.

In the current study, being bullied, attacked or involved in fighting were associated with suicidal ideation. Rudatsikira et al. [13] observed a similar finding in Guyana. Prevention of violence at school may reduce the prevalence of suicidal thoughts.

Smoking cigarettes and consuming alcohol were positively associated with suicidal ideation in the current study. Other studies [13, 17-19] have reported similar findings. However, McGee et al. [20] did not find a significant association between smoking and suicidal ideation.

Table 2. Distribution of factors by gender among students in Fiji, 2010

Factor	Total n ¹ (%) ²	Males n ¹ (%) ²	Females n ¹ (%) ²
Age			
<14	340 (27.0)	139 (25.0)	200 (29.1)
14	603 (31.4)	257 (32.5)	345 (30.3)
15	553 (30.5)	231 (29.4)	319 (31.5)
16+	168 (11.1)	81 (13.1)	87 (9.2)
Gender			
Male	714 (49.8)	-	-
Female	952 (50.2)	-	-
Food security			
No	176 (10.7)	74 (10.5)	102 (10.9)
Yes	1488 (89.3)	634 (89.5)	847 (89.1)
Anxiety			
Yes	230 (14.0)	100 (14.2)	128 (13.7)
No	1439 (86.0)	611 (85.8)	823 (86.3)
Loneliness			
Yes	221 (12.3)	83 (11.1)	135 (13.4)
No	1402 (87.7)	607 (88.9)	791 (86.6)
Close friends			
No	120 (6.9)	52 (7.0)	67 (6.7)
Yes	1540 (93.1)	653 (93.0)	881 (93.3)
Bullied			
Yes	683 (43.0)	304 (45.8)	375 (40.2)
No	896 (57.0)	352 (54.2)	541 (59.8)
Attacked			
Yes	757 (45.9)	371 (52.1)	381 (39.6)
No	906 (54.1)	339 (47.9)	566 (60.4)
In a fight			
Yes	757 (48.5)	422 (60.2)	330 (36.6)
No	910 (51.5)	291 (39.8)	618 (63.4)
Cigarette smoking			
Yes	219 (13.1)	135 (18.1)	79 (7.9)
No	1439 (86.9)	568 (81.9)	869 (92.1)
Alcohol abuse			
Yes	211 (13.7)	134 (19.2)	75 (8.2)
No	1451 (86.3)	573 (80.8)	873 (91.8)
Alcohol use			
Yes	269 (16.6)	161 (22.1)	107 (11.2)
No	1392 (83.4)	545 (77.9)	841 (88.8)
Suicidal ideation			
Yes	295 (17.6)	116 (16.4)	175 (18.5)
No	1361 (82.4)	585 (83.6)	773 (81.5)

¹ unweighted frequencies ² weighted percents.

Table 3. Factors associated with suicidal ideation among students in Fiji, 2010

Factor	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Age (years)		
<14	0.92 (0.89, 0.96)	0.84 (0.80, 0.89)
14	1.06 (1.02, 1.10)	1.12 (1.07, 1.17)
15	1.05 (1.01, 1.10)	1.05 (1.00, 1.09)
16+	1	1
[p = 0.058]		
Gender		
Male	0.93 (0.91, 0.95)	0.75 (0.73, 0.77)
Female	1	1
Food security		
No	1.23 (1.19, 1.28)	1.06 (1.01, 1.10)
Yes	1	1
Anxiety		
Yes	1.75 (1.70, 1.80)	1.46 (1.41, 1.51)
No	1	1
Loneliness		
Yes	1.73 (1.68, 1.78)	1.26 (1.21, 1.31)
No	1	1
Close friends		
No	1.11 (1.07, 1.16)	-
Yes	1	
Bullied		
Yes	1.47 (1.44, 1.51)	1.16 (1.13, 1.19)
No	1	1
Attacked		
Yes	1.48 (1.44, 1.52)	1.28 (1.24, 1.32)
No	1	1
In a fight		
Yes	1.42 (1.39, 1.46)	1.23 (1.19, 1.27)
No	1	1
Cigarette smoking		
Yes	1.69 (1.64, 1.74)	1.39 (1.34, 1.45)
No	1	1
Alcohol abuse		
Yes	1.50 (1.45, 1.54)	-
No	1	
Alcohol use		
Yes	1.62 (1.58, 1.67)	1.41 (1.36, 1.46)
No	1	1

Alcohol consumption was also associated with suicidal ideation in the present study. Kandel et al. [21] and Swanson et al. [22] have also reported similar findings. Adolescents may perceive cigarette smoking and consumption of alcohol as a way to get rid of stress that may lead to suicidal thoughts. Because the study design was a cross section, we can not ascribe causation. Further research utilizing higher study designs are recommended.

In conclusion, the prevalence of suicidal ideation in Fiji is of concern and efforts should be made to design interventions that may lower the prevalence, considering the information obtained in the current study.

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Chapter 47

PREVALENCE AND CORRELATES FOR SUICIDAL IDEATION AMONG ADOLESCENTS IN SCHOOL IN WEST BANK

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ABSTRACT

Although suicide rates appear to be lower in Muslim populations than in those of other religions, it is important that interventions are identified and put in place before the rates reach unmanageable levels. Suicidal ideation among adolescents is one such area that can be targeted to curtail suicide rates. The objectives of the study were to determine the prevalence and correlates for suicidal ideation among school-going Arab adolescents in the West Bank Judea and Samaria). Secondary data obtained in a 2010 West Bank Global School Health Survey was used in the study. Weighted analyses were conducted to obtain weighted frequencies, unadjusted odds ratios (OR), adjusted odds ratios (AOR) and their 95% confidence intervals (CI). The survey recruited 1908 students of which 50.7% were females. About 1 in 4 of the students (overall 23.7%; Males 25.8% and Females 21.8%) ever seriously considered attempting suicide. The following factors were significantly associated with suicidal ideation: age gender, food security 1.51 (95% CI [1.45, 1.56]), anxiety (AOR = 1.25; 95% CI [1.21, 1.28]), loneliness (AOR = 1.62; 95% CI [1.57, 1.67]), having close friends (AOR = 1.54, 95% CI [1.48, 1.61]), truant, bullied

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(AOR = 1.26; 95% CI [1.23, 1.30]), physically attacked, involvement in a fight, smoking cigarettes (AOR = 1.35; 95% CI [1.31, 1.39]) and parental understanding. Suicidal ideation in the West Bank is prevalent among adolescents. In designing interventions for prevention of suicidal ideation, the following should be considered: prevention of violence in form of bullying, physical attack and fighting, encouraging socialization and discouraging smoking.

Keywords: suicidal ideation, prevalence, associated factors, adolescents, West Bank

INTRODUCTION

The worldwide suicide rate is estimated at 11.6 per 100,000 inhabitants [1]. An act of suicide may be preceded by suicidal thoughts, planning for suicide and suicidal attempt. Intervention should, thus, be targeted at an earlier stage of suicidal thoughts. Suicidal ideation may be influenced by social, economic, cultural, political and geographic factors [2]. The West Bank (Judea and Samaria) has been at war, exposing adolescents to destructive and violent events, and also to personal losses; self-destructive behaviours; exposure to suicide of other people; and access to means to complete suicide [3]. Suicide in the Middle East cannot be explained by Islam, a religion that is predominant in the region. The Quran prohibits taking away own life. Quran 4:29-30 says

“... nor kill yourself: for verily God hath been to you Most Merciful! If any do that in rancor and injustice, soon shall He cast them into the Fire: And easy it is for God.”

This is for the Arab population, but in fact the Jewish Torah also prohibit suicide. Hence, the low suicide rates in the region may be due to underreporting because suicide is prohibited by the Quran. However, despite the possible underreporting, Lester [4] argued that suicide rates appear to be lower in Muslims than in those of other religions. Another possible consequence for this prohibition is the scarcity of information on suicide in the Arab West Bank.

A study conducted in the East Mediterranean Region (EMR) in Jordan, Lebanon, Morocco and United Arab Emirates reported suicidal ideation rates of 24.7%, 19.6%, 17.8% and 16.2%, respectively [5]. Factors associated with suicidal ideation in the EMR varied across the four countries. While gender was not associated with suicidal ideation in Jordan and UAE, males were less likely to have suicidal ideation than females in Lebanon and Morocco. Age was only significantly associated with suicidal ideation in Lebanon with students less than 15 years being less likely to have suicidal thoughts. Only bullying, no friendship and feeling sad were consistently associated with suicidal ideation across the four countries. It is, hence, important that correlates for suicidal ideation are established to inform interventions for each country. The objectives for the current study were to determine prevalence and correlates for suicidal ideation among adolescents in the West Bank.

METHODS

The study population comprised of Arab students in grades 7th, 8th, and 9th in the West Bank. Arab West Bank with a population of about 2 million and a growth rate of 3.4% [6] (see Figure 1). The population comprises of 45% children under the age of 15 years. Thirty percent of the population is refugee and 27% of these refugees live in refugee camps [7]. Study is cross sectional.



Source: <http://www.mapsofworld.com/israel/>.

Figure 1. Map of West Bank (Judea and Samaria) and neighbouring countries.

Table 1. Global School-Based Health Survey questions used in the analysis of adolescent suicidal ideation

Variable	Question	Coded	Recorded
Dependent variable			
Suicidal ideation	During the past 12 months, did you ever seriously consider attempting suicide?	1 = Yes; 2 = No	1 = Yes; 2 = No
Independent variables			
Age	How old are you?	1 = 11 years old or younger; 2 = 12 years old; 3 = 13 years old; 4 = 14 years old; 5 = 15 years old; 6 = 16 years old or older	1-3 = 1; 4 = 2; 5 = 3; 6 = 4
Gender	What is your sex?	1 = Male; 2 = Female	1 = 1; 2 = 2
Food security	During the past 30 days, how often did you go hungry because there was not enough food in your home?	1 = Never; 2 = Rarely; 3 = Sometimes; 4 = Most of the time; 5 = Always	4-5 = 1; 1-3 = 2
Anxiety	During the past 12 months, how often have you been so worried about something that you could not sleep at night?	1 = Never; 2 = Rarely; 3 = Sometimes; 4 = Most of the time; 5 = Always	4-5 = 1; 1-3 = 2
Loneliness	During the past 12 months, how often have you felt lonely?	1 = Never; 2 = Rarely; 3 = Sometimes; 4 = Most of the time; 5 = Always	4-5 = 1; 1-3 = 2
Close friends	How many close friends do you have?	1 = 0; 2 = 1; 3 = 2; 4 = 3 or more	1 = 1; 2-4 = 2
Truancy	During the past 30 days, on how many days did you miss classes or school without permission?	1 = 0 days; 2 = 1 or 2 days; 3 = 3 to 5 days; 4 = 6 to 9 days; 5 = 10 or more days	1 = 2; 2-5 = 1
Bullied	Bullied during the past 30 days, on how many days were you bullied?	1 = 0 days; 2 = 1 or 2 days; 3 = 3 to 5 days; 4 = 6 to 9 days; 5 = 10 to 19 days; 6 = 20 to 29 days; 7 = All 30 days	1 = 2; 2-7 = 1
Attacked	During the past 12 months, how many times were you physically attacked?	1 = 0 times; 2 = 1 time; 3 = 2 or 3 times; 4 = 4 or 5 times; 5 = 6 or 7 times; 6 = 8 or 9 times; 7 = 10 or 11 times; 8 = 12 or more times	1 = 2; 2-8 = 1
In a fight	During the past 12 months, how many times were you in a physical fight?	1 = 0 times; 2 = 1 time; 3 = 2 or 3 times; 4 = 4 or 5 times; 5 = 6 or 7 times; 6 = 8 or 9 times; 7 = 10 or 11 times; 8 = 12 or more times	1 = 2; 2-8 = 1

Variable	Question	Coded	Recorded
Currently smoked cigarettes	During the past 30 days, on how many days did you smoke cigarettes?	1 = 0 days; 2 = 1 or 2 days; 3 = 3 to 5 days; 4 = 6 to 9 days; 5 = 10 to 19 days; 6 = 20 to 29 days; 7 = All 30 days	1 = 2; 2-7 = 1
Parental understanding	During the past 30 days, how often did your parents or guardians understand your problems and worries?	1 = Never; 2 = Rarely; 3 = Sometimes; 4 = Most of the time; 5 = Always	1-3 = 2; 4-5 = 1
Marijuana	During your life, how many times have you used marijuana (also called khushkhash)?	1 = 0 times; 2 = 1 or 2 times; 3 = 3 to 9 times; 4 = 10 to 19 times; 5 = 20 or more times	1 = 2; 2-5 = 1

A total of 1,908 students participated in the West Bank GSHS resulting in a school response rate of 100%, the student response rate of 94%, and an overall response rate of 94%. A two stage cluster sampling method was used to draw the sample. The primary sampling unit was the school. Schools were randomly selected proportional to their enrolment size. Classes were then randomly selected. All students in selected schools were eligible to participate in the study.

The 2010 West Bank GSHS questionnaire comprised of modules on dietary behaviours; drug use; hygiene; mental health; physical activity; protective factors; tobacco use; and violence and unintentional injury. Table 1 shows variables that were considered in the current study. The dependent variable was suicidal ideation, while the independent factors were age, gender, food security, anxiety, loneliness, close friends, truancy, bullied, attached, in a fight, currently smoked cigarettes and parental understanding.

Data Analysis

Data was analysed using SPSS version 16. Frequencies and logistic regression analyses were weighted using the following weighting factor:

$$W = W1 \times W2 \times f1 \times f2 \times f3 \times f4$$

where $W1$ = the inverse of the probability of selecting the school, $W2$ = the inverse of the probability of selecting the classroom within the school,

$f1$ = a school-level non-response adjustment factor calculated by school size category (small, medium, large),

$f2$ = a class-level non-response adjustment factor calculated for each school,

$f3$ = a student-level non-response adjustment factor calculated by class, and

$f4$ = a post stratification adjustment factor calculated by grade.

RESULTS

The survey recruited 1,908 students of which 50.7% were females. Females tended to be younger than males with 35.5% of males aged <14 years compared to 43.5% of females in the same age group. Overall, 9.2% of the students reported that most of the time or always they went hungry because there was not enough food in the home. The proportions of students who indicated that they felt lonely and anxious were 13.4% and 16.0%, respectively. Overall, 7.4% of the students reported that they had no close friends. About a third (34.1%) of the students was truant. Altogether, 53.3% of students were bullied. Significantly more male (50.1%) than females (27.1%) students were attacked. Similarly, 67.0% of male and 26.1% of female students were involved in a fight ($p < 0.001$). Regarding smoking, significantly more male (32.7%) than female (8.4%) students smoked cigarettes ($p < 0.001$). Significantly ($p < 0.001$) more female (43.3%) than male (33.9%) students indicated that their parents or guardians understood their problems and worries. About 1 in 4 of the students (overall 23.7%; Males 25.8% and Females 21.8%) ever seriously considered attempting suicide. These results are shown in Table 2.

Factors that were associated with suicidal ideation are shown in Table 3. All the factors that were considered in the analysis were significantly associated with suicidal ideation at both bivariate and multivariate logistic regression analysis. As a result of the effect of confounding, the association between gender and suicidal ideation changed from males being more likely to have suicidal ideation at bivariate analysis to less likely to have suicidal ideation in multivariate analysis. The directions of associations for the rest of the variables remained the same.

Students of ages 14 (AOR = 0.89; 95% CI [0.85, 0.93]) or 15 (AOR = 0.93; 95% CI [0.88, 0.97]) years were less likely to have suicidal ideation compared to those aged 16 years or older. Male students were 13% (AOR = 0.87; 95% CI [0.85, 0.90]) less likely to have suicidal ideation compared with female students.

Students without food security were 1.51 (95% CI [1.45, 1.56]) times more likely to have suicidal ideation compared with students who had enough food in their homes. Compared to students who were not anxious or lonely, students with anxiety or those who were lonely were 25% (AOR = 1.25; 95% CI [1.21, 1.28]) and 62% (AOR = 1.62; 95% CI [1.57, 1.67]), respectively, more likely to have suicidal ideation. When compared with students who had close friends, students who did not have close friends were 1.54 (95% CI [1.48, 1.61]) times more likely to have suicidal ideation.

Truant students were 10% (AOR = 1.10; 95% CI [1.07, 1.13]) more likely to have suicidal ideation compared with students who did not miss classes or school without permission. Students who were bullied were 26% (AOR = 1.26; 95% CI [1.23, 1.30]) more likely to have suicidal ideation compared with students who were not bullied. Students who were physically attacked were 1.19 (95% CI [1.17, 1.22]) times more likely to have suicidal ideation compared to students who were not attacked. Similarly, students who were involved in a fight were 12% (AOR = 1.12; 95% CI [1.09, 1.15]) more likely to have suicidal ideation compared with students who were not involved in a fight.

Students who smoked cigarettes were 35% (AOR = 1.35; 95% CI [1.31, 1.39]) more likely to have suicidal ideation compared with non-smokers. Compared with students with parents or guardians who did not understand their problems and worries, students with

understanding parents or guardians were 17% (AOR = 0.83; 95% CI [0.81, 0.85]) less likely to have suicidal ideation.

Table 2. Distribution of factors considered in the analysis by gender among junior high school students in Arab West bank, 2010

Factor	Total n ¹ (%) ²	Males n ¹ (%) ²	Females n ¹ (%) ²
Age			
<14	662 (39.5)	283 (35.5)	368 (43.5)
14	701 (34.8)	372 (36.4)	317 (32.9)
15	479 (23.0)	243 (25.3)	233 (21.1)
16+	54 (2.7)	26 (2.8)	26 (2.5)
Gender			
Male	927 (49.3)	-	-
Female	948 (50.7)	-	-
Food security			
No	166 (9.2)	80 (9.3)	79 (8.5)
Yes	1713 (90.8)	832 (90.7)	857 (91.5)
Anxiety			
Yes	297 (16.0)	117 (13.3)	176 (18.6)
No	1567 (84.0)	783 (86.7)	758 (81.4)
Loneliness			
Yes	250 (13.4)	110 (12.5)	137 (14.4)
No	1626 (86.6)	794 (87.5)	805 (85.6)
Close friends			
No	138 (7.4)	64 (7.3)	69 (7.3)
Yes	1714 (92.6)	815 (92.7)	872 (92.7)
Truancy			
Yes	632 (34.1)	347 (39.4)	271 (28.7)
No	1217 (65.9)	532 (60.6)	669 (71.3)
Bullied			
Yes	947 (53.3)	464 (55.8)	469 (51.3)
No	840 (46.7)	381 (44.2)	444 (48.7)
Attacked			
Yes	710 (38.3)	451 (50.1)	248 (27.1)
No	1166 (61.7)	458 (49.9)	687 (72.9)
In a fight			
Yes	871 (46.1)	616 (67.0)	242 (26.1)
No	1023 (53.9)	302 (33.0)	702 (73.9)
Smoked cigarettes			
Yes	363 (20.0)	276 (32.7)	80 (8.4)
No	1444 (80.0)	574 (67.3)	847 (91.6)
Parental understanding			
Yes	720 (38.8)	302 (33.9)	406 (43.3)
No	1133 (61.2)	584 (66.1)	530 (56.7)
Suicidal ideation			
Yes	423 (23.7)	215 (25.8)	203 (21.8)
No	1396 (76.3)	643 (74.2)	729 (78.2)

¹ unweighted frequencies. ² weighted percents.

Table 3. Factors associated with suicidal ideation among junior high school students in Arab West Bank, 2010

Factor	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Age (years)		
<14	0.91 (0.88, 0.95)	0.99 (0.94, 1.04)
14	0.77 (0.74, 0.80)	0.89 (0.85, 0.93)
15	0.90 (0.87, 0.94)	0.93 (0.88, 0.97)
16+	1	1
Gender		
Male	1.11 (1.09, 1.14)	0.87 (0.85, 0.90)
Female	1	1
Food security		
No	1.54 (1.49, 1.58)	1.51 (1.45, 1.56)
Yes	1	1
Anxiety		
Yes	1.54 (1.50, 1.57)	1.25 (1.21, 1.28)
No	1	1
Loneliness		
Yes	1.94 (1.89, 1.99)	1.62 (1.57, 1.67)
No	1	1
Close friends		
No	1.75 (1.70, 1.81)	1.54 (1.48, 1.61)
Yes	1	1
Truancy		
Yes	1.38 (1.36, 1.41)	1.10 (1.07, 1.13)
No	1	1
Bullied		
Yes	1.55 (1.52, 1.58)	1.26 (1.23, 1.30)
No	1	1
Attacked		
Yes	1.47 (1.44, 1.50)	1.19 (1.17, 1.22)
No	1	1
In a fight		
Yes	1.31 (1.29, 1.34)	1.12 (1.09, 1.15)
No	1	1
Smoked cigarettes		
Yes	1.64 (1.61, 1.68)	1.35 (1.31, 1.39)
No	1	1
Parental understanding		
Yes	0.75 (0.74, 0.77)	0.83 (0.81, 0.85)
No	1	1

DISCUSSION

Suicidal ideation was prevalent in the Arab West Bank with 23.7% (25.8% of males and 21.8% of females) reporting it. All the factors considered in the study were significantly associated with suicidal ideation; i.e., age, gender, food security, anxiety, loneliness, close friends, truancy, bullied, attacked, involvement in a fight, smoking cigarettes and parental understanding. The rate of suicidal ideation obtained in the Arab West Bank is similar to those reported by Khalid [5] of 24.7% in Jordan, 19.6% in Lebanon, 17.8% in Morocco and 16.2% in United Arab Emirates.

Students in the current study aged 14 or 15 years were less likely to have suicidal ideation compared with students aged 16 years or older. This finding contradicts findings in Jordan, Morocco and UAE where no significant association was observed between age and suicidal ideation [5] in Jordan (24.7%) and Lebanon (19.6%). Further, in Lebanon, students aged <15 years were less likely to have suicidal thoughts compared with students who were aged 16 years or older. Further research is suggested to determine which age groups are risk factors for suicidal ideation so that tailored interventions may be targeted to the at risk age groups. The relationship between gender and suicidal ideation has not been consistent in the region. While males were less likely to have suicidal ideation than females in Lebanon and Morocco, no association was observed between gender and suicidal ideation in Jordan and UAE. The finding from the current study suggests that males were less likely to have suicidal thoughts than females. Generally, there is evidence from this region that males may be less likely to have suicidal thoughts than females. Abel et al. [8] argued that females are at higher risk for suicidal ideation because females have a higher rate of depression than males.

Hunger or family food insufficiency has been associated with psychosocial outcomes and suicide symptoms, respectively [9, 10], and it is no wonder that students who had no food security were more likely to have suicidal thoughts in the current study.

Students who have no close friends are more likely to be socially isolated, feel lonely, anxious and depressed. Anxiety, loneliness and depression have been associated with suicidal ideation [11-13]. The findings from the current study support these findings. Lack of parental understanding of the problems or worries facing adolescents has been associated with suicidal ideation in the current and previous study [13]. It is important that adolescents receive social support to avoid suicidal thoughts.

Truancy may be linked to bullying, being attacked and involvement in a fight. Students may be truant in fear of being bullied, attacked or involved in a fight. These factors have been associated with suicidal thoughts in the current study and accord findings from other studies. King et al. [14] reported a significant association between physical fighting and suicidal ideation. Bullying was associated with suicidal ideation by Brunstein et al. [15]. Bullied students are rejected by their peers and stressed [16, 17] and can result in depression that is associated with suicidal ideation. Truancy has been associated with suicidal ideation in the current study. This finding accords that of D'Aulerio et al. [18].

Smoking has been associated with suicidal ideation in the current study. Similar findings have been reported before [19-23]. Students may smoke when they are depressed. Hence, smoking may not be directly associated with suicidal thoughts. Alternatively, students with suicidal thoughts may smoke as they think about how to end their lives. Because the study design was cross sectional, we cannot ascribe caution to the observed associations.

In conclusion, suicidal ideation in the Arab West Bank is prevalent among adolescents. In designing interventions for prevention of suicidal ideation, the following should be considered: prevention of violence in form of bullying, physical attack and fighting, encouraging socialization and discouraging smoking.

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Chapter 48

SUICIDAL IDEATION PREVALENCE AND ITS ASSOCIATED FACTORS AMONG IN-SCHOOL ADOLESCENTS IN MOROCCO

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ABSTRACT

Suicidal behaviour is still of major public health significance among the younger generation despite some research work indicating that there has been a dramatic decrease in the youth suicide rate during the past decade. The objective of the current study was to determine the prevalence of suicidal ideation and associated factors among the in-school adolescents in Morocco. The Moroccan 2010 Global School-based Health Survey (GSHS) data was analyzed using bivariate and multivariate logistic regression analyses at 95% confidence interval. The prevalence of suicidal ideation in Morocco among in-school adolescents was 16.6% (13.9% among males and 20.0% among females) and was positively associated with increase in age (being 15 years or older), issues of food insecurity, anxiety, lack of close friends and loneliness, victimization – attack, bullying; substance abuse – cigarette smoking and use of marijuana. Being male and presence of parental understanding were negatively associated with suicidal ideation. These results underscore the need to provide effective public health intervention programs in Morocco

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among in-school adolescents that target issues of substance abuse and address parental/social support in general.

Keywords: suicidal ideation, prevalence, associated factors, adolescents, Morocco

INTRODUCTION

Suicidal behaviour is one of the major causes of injury and mortality globally. It is considered to be an important precursor to later attempted and completed suicide [1]. World Health Organization (WHO) estimates that by the year 2020 about 1.53 million people will die from suicide and about 10-20 times more people will attempt to commit suicide worldwide. If the current trends estimated by WHO continues, it is estimated that on average, there will be one death every 20 seconds and one suicide attempt every 1-2 seconds [2]. While WHO reports that the African region has almost no data available on suicide, countries of the European region submit suicide data to WHO on regular basis [2]. However, according to the crude estimates for suicide in Africa, there are over 34,000 suicides in a year, giving an overall incidence rate of 3.2 per 100,000 population [3]. These figures may be underestimating the extent of the problem of suicides in Africa because deaths that result from suicide are misclassified as an accident or another cause of death to avoid familial, religious and social stigmatizations [4] or as a taboo [1].

Suicidal behaviour is still of major public health significance among the younger generation despite some research work indicating that there has been a dramatic decrease in the youth suicide rate during the past decade [5]. It is ranked third among the leading causes of mortality among 15-to-24 year olds and second among college students [6, 7]. Despite suicide being such an important public health concern among the younger generation, there is still a paucity of data on suicidal ideation in many African countries. In the past years suicidal ideation was not considered as a common issue, however recent research has shown that it actually accounts for a significant public health burden [8]. So far the research work done in African countries such as Uganda, South Africa, Zambia and Nigeria indicate that the challenges faced by suicidal ideation cannot be ignored and the problem is relatively common in this region [9]. Therefore, the study aimed to determine the prevalence of in-school adolescent suicidal ideation and associated factors in Morocco.

METHODS

The Global School-based Health Survey (GSHS) for Morocco was conducted among in-school adolescents. Morocco is located in the southern Mediterranean zone, in the extreme northwest of the African continent as shown in Figure 1. The secondary analysis of the GSHS data on health and social behaviors of students was carried out using bivariate and multivariate logistic regression analyses at 95% confidence interval. The demographic characteristics of age and gender; social behaviours such as involvement in a fight, truancy, food security, alcohol use and abuse, current smoking in general and use of marijuana,

bullying, loneliness, close friendship, anxiety and attack; parental understanding, and the social and health outcome of having considered suicide were considered in the analyses.



Source: http://farm5.static.flickr.com/4107/5023100732_93c26d3914.jpg.

Figure 1. Map of Morocco and its neighbouring countries.

Data representative of all students was produced using a two-stage cluster sampling design. Schools were selected with probability proportional to enrollment size at the first stage. At the second stage, random selection was employed to select classes and as long as students belonged to selected classes, they were eligible to participate. The response rate was 100% for school and 92% for students with an overall response rate of 92%.

RESULTS

Altogether 2,924 students participated in the survey. Table 1 shows the distribution of factors considered in the analysis by gender among the in-school adolescents in Morocco in 2010. There were more female participants (52.3%) and the majority (43.4%) of the participants was 14 years old or younger. Less than 20% of pupils reported food insecurity (10.6%), anxiety (15.5%), having no close friends (8.9%), currently smoking (6.7%) and marijuana use (3.5%). However, 23.1% of female pupils reported loneliness compared to only 13.8% of male pupils ($p < 0.001$). Truancy was reported in 42.1% of male pupils compared to 29.7% of females ($p < 0.001$). Involvement in a fight, being attacked was highly reported among male students at 56.6% and 35.7% respectively compared to 24.5% and 21.7% among females respectively, ($p < 0.001$). Bullying was reported in 21% of female students and only

17.5 % of males reported having been bullied. Parental understanding was lacking in 30.7% of females compared to 24.7% of males, while 20.0% of females had considered committing suicide compared to 13.9% of males. The overall suicidal ideation prevalence was 16.6%.

Table 1. Distribution of factors considered in the analysis by gender among junior high school students in Morocco, 2010

Factor	Total n ¹ (%) ²	Males n ¹ (%) ²	Females n ¹ (%) ²
Age			
<14	1072 (36.5)	596 (30.9)	476 (43.4)
14	763 (26.9)	365 (27.0)	365 (26.9)
15	578 (20.7)	253 (22.3)	253 (18.7)
16+	443 (15.9)	147 (19.8)	147 (11.0)
Gender			
Male	1495 (52.3)	-	-
Female	1361 (47.7)	-	-
Food security			
No	302 (10.6)	190 (12.5)	112 (8.2)
Yes	2537(89.4)	1300 (87.5)	1237 (91.8)
Anxiety			
Yes	449 (15.5)	189 (12.5)	260 (19.2)
No	2378 (84.5)	1298 (87.5)	1080 (80.8)
Loneliness			
Yes	519 (17.9)	206 (13.8)	313 (23.1)
No	2339 (82.1)	1294 (86.2)	1045 (76.9)
Close friends			
No	259 (8.9)	115 (7.6)	144 (10.6)
Yes	2594 (91.1)	1373 (92.4)	1221 (89.4)
Truancy			
Yes	1019 (36.6)	623 (42.1)	396 (29.7)
No	1809 (63.4)	863 (57.9)	946 (70.3)
Bullied			
Yes	539 (19.0)	261 (17.5)	278 (21.0)
No	2291(81.0)	1224 (82.5)	1067 (79.0)
Attacked			
Yes	831 (29.4)	540 (35.7)	291 (21.7)
No	2042 (70.6)	967 (64.3)	1075 (78.3)
In a fight			
Yes	1185 (42.3)	854 (56.6)	331 (24.5)
No	1677 (57.7)	649 (43.4)	1028 (75.5)
Currently smoked			
Yes	179 (6.7)	36 (10.0)	143 (2.6)
No	2645 (93.3)	1319 (90.0)	1326 (97.4)
Parental understanding			
Yes	775 (27.3)	368 (24.7)	407 (30.7)
No	2056 (72.7)	1121(75.3)	935 (69.3)
Marijuana			
Yes	93 (3.5)	76 (5.3)	17 (1.2)
No	2692 (96.5)	1359 (94.7)	1333 (98.8)
Considered suicide			
Yes	481 (16.6)	207 (13.9)	274 (20.0)
No	2355(83.4)	1276 (86.1)	1079 (80.0)

¹ unweighted frequencies. ² weighted percents.

Table 2. Factors associated with suicidal ideation among junior high school students in Morocco, 2010

Factor	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Age (years)		
<14	0.72 (0.71, 0.72)	0.75 (0.74, 0.76)
14	0.78 (0.78, 0.79)	0.84 (0.83, 0.85)
15	1.20 (1.93, 1.21)	1.17 (1.16, 1.19)
16+	1	1
Gender		
Male	0.80 (0.80, 0.81)	0.73 (0.72, 0.73)
Female	1	1
Food security		
No	1.29 (1.28, 1.30)	1.06 (1.05, 1.07)
Yes	1	1
Anxiety		
Yes	1.71 (1.70, 1.72)	1.29 (1.28, 1.30)
No	1	1
Loneliness		
Yes	1.77 (1.76, 1.78)	1.34 (1.33, 1.35)
No	1	1
Close friends		
No	1.42 (1.40, 1.43)	1.26 (1.25, 1.28)
Yes	1	1
Truancy		
Yes	1.37 (1.36, 1.38)	1.15 (1.15, 1.16)
No	1	1
Bullied		
Yes	1.78 (1.77, 1.79)	1.36 (1.35, 1.37)
No	1	1
Attacked		
Yes	1.44 (1.43, 1.45)	1.19 (1.80, 1.20)
No	1	1
In a fight		
Yes	1.17 (1.17, 1.18)	0.95 (0.95, 0.96)
No	1	1
Currently smoking		
Yes	2.01 (2.00, 2.03)	1.44 (1.42, 1.46)
No	1	1
Parental understanding		
Yes	0.82 (0.82, 0.83)	0.85 (0.84, 0.85)
No	1	1
Marijuana		
Yes	2.19 (2.16, 2.21)	1.52 (1.50, 1.55)
No	1	1

Table 2 shows factors associated with suicidal ideation among in-school adolescents in Morocco, 2010 GSHS study. Age of students was significantly associated with suicidal ideation. Students aged less than 14 years old were 25% less likely (AOR = 0.75, 95% CI [0.74, 0.76]) while those aged 14 years old were 16% less likely (AOR = 0.84, 95% CI [0.83, 0.85]) to consider committing suicide compared to those aged 16 years or older. On the contrary, students aged 15 years were 1.17 times more likely to consider committing commit suicide compared to students who were aged 16 years or older (AOR = 1.17, 95% CI [1.16, 1.19]). Male participants were 27% less likely (AOR = 0.73, 95% CI [0.72, 0.73]) to have suicidal ideation compared to female students. Students who reported food insecurity were 1.06 times more likely (AOR = 1.06, 95% CI [1.05, 1.07]) to have suicidal ideation compared to students with no food security problems. Anxious students were 1.29 times more likely

(AOR = 1.29, 95% CI [1.28, 1.30]) to have suicidal thoughts compared to students who never reported anxiety. Students without close friends were 1.26 times more likely (AOR = 1.26, 95% CI [1.25, 1.28]) to experience suicidal ideations compared to students with close friends and lonely students were 1.34 times more likely (AOR = 1.34, 95% CI [1.33, 1.35]) to consider committing suicide compared to students who did not report loneliness. Students reported attacks were 1.19 times more likely (AOR = 1.19, 95% CI [1.80, 1.20]) to consider committing suicide compared to those who did not report attacks. Students with an experience of a fight were 5% less likely (AOR = 0.95, 95% CI [0.95, 0.96]) to consider committing suicide compared to those no experience of a fight. Bullied students were 1.36 times more likely (AOR = 1.36, 95% CI [1.35, 1.37]) to think of committing suicide compared to students who were not bullied. Students who reported currently smoking (AOR = 1.44, 95% CI [1.42, 1.46]) and using marijuana (AOR = 1.52, 95% CI [1.50, 1.55]) were 1.44 and 1.52 times, respectively, more likely to consider committing suicide compared to those who did not smoke with cigarettes or marijuana. Students with understanding parents were 15% less likely (AOR = 0.85, 95% CI [0.84, 0.85]) to have suicidal ideation compared to students who did not have parental understanding.

DISCUSSION

The prevalence of suicidal ideation in the current study was high at 16.6%. This prevalence is in accord with results of many other studies, for example, by Zarrouq et al. [1]. However it is not in agreement with what Moroccans believe in and this could be a possible drop in religious ethics and religiosity among Moroccans since suicide is considered as a taboo and a disgraceful act prohibited by religion, condemned by society, and hampered by legal consequences [4].

The factors that were positively associated with suicidal ideation included older age group, female gender, food insecurity, anxiety, lacking close friends and loneliness, history of attack, and bullying; cigarette smoking and use of marijuana. Meanwhile, involvement in a fight and a finding that males were less likely to have suicidal thoughts compared to females have been reported elsewhere [10, 11]. The younger adolescents in the current study were less likely to experience suicidal thoughts possibly because adolescents tend to have exposure to other risk behaviors such as substance abuse as they grow and interact more with peers.

Loneliness and lack of close friends have been significantly associated with suicidal ideation in the current study. The study by Stravynski and Boyer [12] also revealed that the prevalence of suicidal ideation increased with the degree of loneliness. However, it is not clear whether loneliness and lack of close friend may have resulted in suicidal thoughts or vice versa since causation is not implied in a cross sectional study. Anxiety among in-school adolescents in Morocco has also been significantly associated with suicidal ideation. Results of another study elsewhere [13] generally supports the conclusion that anxiety disorders convey risk for suicidal ideation.

Violent behaviors defined as bullying, attacks and fights among peers have been observed to be significantly associated with suicidal thoughts among adolescents in the present study. Adolescents who were involved in a fight or been attacked or bullied were more likely to think of committing suicide compared to those that did not experience such violence. Similarly, findings in other research [14, 15, 16] indicate that violent behaviors such

as fight, bullying and attack are significantly associated with suicidal ideation. It is more likely that students experiencing violence may be more likely to think that it is not worthy live than the converse that suicidal thoughts may be resulting in violence.

The other major factor associated with suicidal thoughts according to the current study is substance abuse. Adolescents who reported cigarette smoking and marijuana were more likely to have suicidal ideas compared to non-smokers. This result is not different from the findings of other studies [9, 17, 18]. Further, low parental monitoring has associated with increased risk of suicidal ideation [18]. Hence, effective public health intervention programs in Morocco among in-school adolescents should consider substance abuse and address parental/social support in ascertaining components of suicide prevention programs are effective in order to optimize use of limited resources.

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Chapter 49

SUICIDAL IDEATION IN VIETNAM: PREVALENCE AND ITS ASSOCIATED FACTORS AMONG ADOLESCENTS IN A GLOBAL SCHOOL HEALTH-BASED SURVEY

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ABSTRACT

Literature is scant on suicidal behaviours and their correlates in developing countries, including Vietnam. The objectives of the study were to estimate the suicidal ideation rate and determine its associated factors. Proportions of exposure factors were estimated using weighted frequencies and logistic regression analyses (bivariate and multivariate) were weighted to establish significant factors associated with suicidal ideation. Unadjusted odds ratio (OR) and adjusted odds ratio (AOR) together with their 95% confidence intervals (CI) are reported. Altogether, 3331 students participated in the survey. Overall, 16.9% (12.2% of male and 21.1% of female) students reported suicidal ideation. Factors associated with suicidal ideation were age, gender (male gender: AOR = 0.64; 95% CI [0.63, 0.64]), food security (no food security: AOR = 0.68; 95% CI [0.67, 0.69]), loneliness (AOR = 1.82; 95% CI [1.81, 1.83]), close friends (no close friends: AOR = 1.65; 95% CI [1.64, 1.66]), truancy, bullied, attacked, in a fight (AOR = 1.22; 95% CI [1.21, 1.22]), currently smoked cigarettes (AOR = 1.40; 95% CI [1.39, 1.41]), used marijuana (AOR = 0.73; 95% CI [0.72, 0.74]), currently consumed alcohol, alcohol

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abuse (AOR = 1.45; 95% CI [1.45, 1.46]) and parental understanding (AOR = 0.70; 95% CI [0.70, 0.71]). The prevalence of suicidal ideation in Kuwait among adolescents is high. The suicidal ideation rate in Vietnam is of concern. Interventions should be designed using information obtained in this study and implemented to lower the rate of suicidal thoughts.

Keywords: suicidal ideation, prevalence, associated factors, adolescents, Vietnam

INTRODUCTION

Suicidal ideation is thought about engaging in behaviour intended to end one's life [1]. It is thinking about, considering, or planning suicide [2] without suicidal actions such as attempted and completed suicide. These thoughts come about when it seems there is no other way but suicide to solve problems and end the pain. Literature on suicidal ideation is abundant in developed countries but limited in developing countries, including Vietnam a middle-income country.

In a study to determine the prevalence of suicidal ideation/attempts and socio-demographic correlates of suicidality among 15-24 year-olds in Vietnam, China, and Taiwan, Blum et al. [3] found a rate of suicidal ideation of 2.3% in Hanoi, Vietnam. Nguyen et al. [4] studying 15-19 year-olds found that 26.3% of the students reported that they had seriously considered attempting suicide. The above rates of suicidal ideation are higher than the reported rate among medical students in years 1, 3 and 5 throughout Vietnam of 8.7% [5]. In other national population based surveys, the prevalence of suicidal ideation was 5.3% in the first survey conducted in 2003-2004 and 12.2% in the second survey conducted in 2009-2010 among adolescents in Vietnam [6].

The correlates for suicidal ideation across the three countries: Vietnam, China, and Taiwan [3] were female gender, younger age, family structure, parental support, family history of suicide, migration status and substance use. Nguyen et al. [4] found the following factors to be associated with suicidal ideation: anxiety, depression, gender, alcohol, abused by parents/other adults, having a tutor after school, seriously quarreled with teachers or other staff and school type. The above studies were not standardized and comparing the results across the studies may not be valid. CDC and WHO designed a Global School-based Health Survey (GSHS) which would make it possible to compare the findings across the surveys in different regions of the world and countries. Some of the factors in the GSHS have not been considered in the above studies. Hence, the objectives of the study were to determine the prevalence and associated factors for suicidal ideation among adolescents in Vietnam that would be comparable with findings from similarly designed surveys.

METHODS

Vietnam became a middle-income country in 2011 from being one of the poorest countries 25 years ago [7]. Estimates suggest that Vietnam was the 14th most populous country in the world with a population of 92.5 million in 2014 [8]. About a quarter of the population (23.1%) was aged less than 15 years [9]. Two thirds (66%) of the population lived

in rural areas [10]. The study population comprised school-going adolescents in grades 8-12 country-wide in Kuwait. The study design was cross sectional. A total of 3,331 students participated in the 2011 Vietnam GSHS resulting in a school response rate of 100%, the student response rate of 96%, and an overall response rate of 96%.



Source: <https://viet-nam.wikispaces.com/Neighbours>.

Figure 1. Map of Vietnam with its neighbouring countries.

Table 1. Global School-Based Health Survey questions used in the analysis of adolescent suicidal ideation

Variable	Question	Coded	Recoded
Dependent variable			
Suicidal ideation	During the past 12 months, did you ever seriously consider attempting suicide?	1 = Yes; 2 = No	1 = Yes; 2 = No
Independent variables			
Age	How old are you?	1 = 11 years old or younger; 2 = 12 years old; 3 = 13 years old; 4 = 14 years old; 5 = 15 years old; 6 = 16 years old or older	1-3 = 1; 4 = 2; 5 = 3; 6 = 4
Gender	What is your sex?	1 = Male; 2 = Female	1 = 1; 2 = 2
Food security	During the past 30 days, how often did you go hungry because there was not enough food in your home?	1 = Never; 2 = Rarely; 3 = Sometimes; 4 = Most of the time; 5 = Always	4-5 = 1; 1-3 = 2
Loneliness	During the past 12 months, how often have you felt lonely?	1 = Never; 2 = Rarely; 3 = Sometimes; 4 = Most of the time; 5 = Always	4-5 = 1; 1-3 = 2
Close friends	How many close friends do you have?	1 = 0; 2 = 1; 3 = 2; 4 = 3 or more	1 = 1; 2-4 = 2
Truancy	During the past 30 days, on how many days did you miss classes or school without permission?	1 = 0 days; 2 = 1 or 2 days; 3 = 3 to 5 days; 4 = 6 to 9 days; 5 = 10 or more days	1 = 2; 2-5 = 1
Bullied	Bullied during the past 30 days, on how many days were you bullied?	1 = 0 days; 2 = 1 or 2 days; 3 = 3 to 5 days; 4 = 6 to 9 days; 5 = 10 to 19 days; 6 = 20 to 29 days; 7 = All 30 days	1 = 2; 2-7 = 1
Attacked	During the past 12 months, how many times were you physically attacked?	1 = 0 times; 2 = 1 time; 3 = 2 or 3 times; 4 = 4 or 5 times; 5 = 6 or 7 times; 6 = 8 or 9 times; 7 = 10 or 11 times; 8 = 12 or more times	1 = 2; 2-8 = 1
In a fight	During the past 12 months, how many times were you in a physical fight?	1 = 0 times; 2 = 1 time; 3 = 2 or 3 times; 4 = 4 or 5 times; 5 = 6 or 7 times; 6 = 8 or 9 times; 7 = 10 or 11 times; 8 = 12 or more times	1 = 2; 2-8 = 1
Currently smoked cigarettes	During the past 30 days, on how many days did you smoke cigarettes?	1 = 0 days; 2 = 1 or 2 days; 3 = 3 to 5 days; 4 = 6 to 9 days; 5 = 10 to 19 days; 6 = 20 to 29 days; 7 = All 30 days	1 = 2; 2-7 = 1
Used marijuana	During your life, how many times have you used marijuana (also called bo da)?	1 = 0 times; 2 = 1 or 2 times; 3 = 3 to 9 times; 4 = 10 to 19 times; 5 = 20 or more times	1 = 2; 2-5 = 1
Currently consumed alcohol	During the past 30 days, on how many days did you have at least one drink containing alcohol?	1 = 0 days; 2 = 1 or 2 days; 3 = 3 to 5 days; 4 = 6 to 9 days; 5 = 10 to 19 days; 6 = 20 to 29 days; 7 = All 30 days	1 = 2; 2-7 = 1
Alcohol abuse	During your life, how many times did you drink so much alcohol that you were really drunk?	1 = 0 times; 2 = 1 or 2 times; 3 = 3 to 9 times; 4 = 10 or more times	1 = 2; 2-4 = 1
Parental understanding	During the past 30 days, how often did your parents or guardians understand your problems and worries?	1 = Never; 2 = Rarely; 3 = Sometimes; 4 = Most of the time; 5 = Always	1-3 = 2; 4-5 = 1

A three stage cluster sampling method was used to select participants for a sample that is representative of school going adolescents mainly in the age group 13-17 years. A province was a primary sampling unit that was selected with probability proportional to school enrolment size. Selection of schools then followed. Schools were also selected with probability proportion to school enrolment size. At the final stage of sampling, classes were randomly selected and all students in selected classes were eligible to participate in the survey.

The 2013 Vietnam GSHS questionnaire was divided into the following sections: dietary behaviours; drug use; hygiene; mental health; physical activity; protective factors; tobacco use; and violence and unintentional injury. Table 1 shows variables that were considered in the analysis. The dependent variable was suicidal ideation, while the independent variables were age, gender, food security, loneliness, close friends, truancy, bullied, attached, in a fight, currently smoked cigarettes, used marijuana, currently consumed alcohol, alcohol abuse and parental understanding.

Data Analysis

Data was analysed using SPSS version 16. Frequencies and logistic regression analyses were weighted. Unadjusted odds ratio (OR) and adjusted odds ratio (AOR) together with their 95% confidence intervals are reported.

RESULTS

Of the 3,331 students who participated in the survey, 46.9% were males. Only 1.1% of the students reported that they had no food security. Overall, 11.5% of the students indicated that they were lonely, 5.5% reported that they had no close friends and 19.4% reported that they missed classes or school without permission. About 1 in 5 students reported violence: bullied (22.7%), attacked (20.9%) and involved in a fight (16.6%). Regarding smoking, 4.7% of the students currently smoked cigarettes and 0.6% used marijuana. Alcohol consumption was reported by a quarter of the students (current consumption of alcohol: 24.9% overall, 33.2% of males and 17.6% of females; alcohol abuse: 22.5% overall, 30.8% of males and 15.3% of females). Overall, 30.4% of students reported that parents understood their problems and worries. These results are shown in Table 2.

Correlates for suicidal ideation are shown in Table 3. All the factors considered in the analysis were significantly associated with suicidal ideation in both bivariate and multivariate analyses. Students aged less than 16 years (AOR = 0.87; 95% CI [0.86, 0.87]) were less likely to have suicidal ideation compared with students of age 16 years or older. Male students were 34% (AOR = 0.64; 95% CI [0.63, 0.64]) less likely to have suicidal ideation compared with female students. Students from homes that had no food security were 32% (AOR = 0.68; 95% CI [0.67, 0.69]) less likely to have suicidal ideation compared with students from homes with food security.

Students who were lonely were 1.82 (95% CI [1.81, 1.83]) times more likely to have suicidal thoughts compared with students who were not lonely. Students who had no close

friends were 65% (AOR = 1.65; 95% CI [1.64, 1.66]) more likely to have suicidal thought compared with students who had close friends. Missing school or classes was positively associated with suicidal ideation (AOR = 1.05; 95% CI [1.05, 1.05]).

Table 2. Distribution of factors considered in the analysis by gender among junior high school students in Vietnam, 2013

Factor	Total n ¹ (%) ²	Males n ¹ (%) ²	Females n ¹ (%) ²
Age			
<15	890 (33.8)	418 (33.8)	472 (33.8)
15	854 (35.3)	391 (35.1)	463 (35.5)
16+	541 (30.8)	252 (31.0)	289 (30.7)
Gender			
Male	1557 (46.9)	-	-
Female	1765 (53.1)	-	-
Food security			
No	34 (1.1)	16 (1.0)	18 (1.1)
Yes	3273 (98.9)	1533 (99.0)	1740 (98.9)
Loneliness			
Yes	367 (11.5)	159 (10.8)	208 (12.1)
No	2901 (88.5)	1375 (89.2)	1526 (87.9)
Close friends			
No	173 (5.5)	93 (6.2)	80 (4.9)
Yes	3129 (94.5)	1453 (93.8)	1676 (95.1)
Truancy			
Yes	596 (19.4)	343 (23.9)	253 (15.4)
No	2718 (80.6)	1206 (76.10)	1512 (84.6)
Bullied			
Yes	742 (22.7)	338 (21.5)	404 (23.9)
No	2449 (77.30)	1158 (78.5)	1291 (76.1)
Attacked			
Yes	731 (20.9)	438 (26.6)	293 (15.9)
No	2576 (79.1)	1111 (73.4)	1465 (84.1)
In a fight			
Yes	576 (16.6)	399 (24.2)	177 (9.9)
No	2722 (83.4)	1144 (75.8)	1578 (90.1)
Currently smoked cigarettes			
Yes	137 (4.7)	116 (8.8)	21 (1.1)
No	3165 (95.3)	1424 (91.2)	1741 (98.9)
Used marijuana			
Yes	18 (0.6)	14 (1.1)	4 (0.2)
No	3280 (99.4)	1530 (98.9)	1750 (99.8)
Currently consumed alcohol			
Yes	721 (24.9)	454 (33.2)	267 (17.6)
No	2468 (75.1)	1037 (66.8)	1431 (82.4)
Alcohol abuse			
Yes	645 (22.5)	408 (30.8)	237 (15.3)
No	2543 (77.5)	1084 (69.2)	1459 (84.7)
Parental understanding			
Yes	1034 (30.4)	518 (32.5)	516 (28.6)
No	2278 (69.6)	1033 (67.5)	1245 (71.4)
Suicidal ideation			
Yes	538 (16.9)	186 (12.2)	352 (21.1)
No	2742 (83.1)	1350 (87.8)	1392 (78.9)

¹ unweighted frequencies. ² weighted percents.

Table 3. Factors associated with suicidal ideation among junior high school students in Vietnam, 2013

Factor	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Age (years)		
<15	0.84 (0.84, 0.85)	0.87 (0.86, 0.87)
15	0.82 (0.81, 0.82)	0.87 (0.86, 0.87)
16+	1	1
Gender		
Male	0.72 (0.72, 0.72)	0.64 (0.63, 0.64)
Female	1	1
Food security		
No	1.39 (1.38, 1.40)	0.68 (0.67, 0.69)
Yes	1	1
Loneliness		
Yes	1.99 (1.99, 2.00)	1.82 (1.81, 1.83)
No	1	1
Close friends		
No	1.64 (1.64, 1.65)	1.65 (1.64, 1.66)
Yes	1	1
Truancy		
Yes	1.17 (1.17, 1.17)	1.05 (1.05, 1.05)
No	1	1
Bullied		
Yes	1.39 (1.39, 1.40)	1.18 (1.18, 1.19)
No	1	1
Attacked		
Yes	1.23 (1.22, 1.23)	0.98 (0.98, 0.98)
No	1	1
In a fight		
Yes	1.34 (1.34, 1.35)	1.22 (1.21, 1.22)
No	1	1
Currently smoked cigarettes		
Yes	1.41 (1.40, 1.41)	1.40 (1.39, 1.41)
No	1	1
Used marijuana		
Yes	1.93 (1.91, 1.95)	0.73 (0.72, 0.74)
No	1	1
Currently consumed alcohol		
Yes	1.31 (1.31, 1.32)	1.11 (1.10, 1.11)
No	1	1
Alcohol abuse		
Yes	1.43 (1.43, 1.44)	1.45 (1.45, 1.46)
No	1	1
Parental understanding		
Yes	0.65 (0.65, 0.65)	0.70 (0.70, 0.71)
No	1	1

Violence was associated with suicidal ideation. Students who were bullied were 18% (AOR = 1.18; 95% CI [1.18, 1.19]) more likely to have suicidal ideation compared with students who were not bullied. Surprisingly, being attacked was negatively associated with suicidal thoughts (AOR = 0.98; 95% CI [0.98, 0.98]). Students who were involved in a fight were 22% (AOR = 1.22; 95% CI [1.21, 1.22]) more likely to have suicidal thoughts compared with students who were not involved in a fight.

Smoking was significantly associated with suicidal thoughts. Compared with students who did not smoke cigarettes, students who smoked cigarettes were more likely to have suicidal ideation (AOR = 1.40; 95% CI [1.39, 1.41]). Interestingly, students who used marijuana were 27% (AOR = 0.73; 95% CI [0.72, 0.74]) less likely to have suicidal thoughts than students who did not use marijuana. Alcohol consumption was positively associated with suicidal ideation (AOR = 1.11; 95% CI [1.10, 1.11]) for currently consumed alcohol and AOR = 1.45; 95% CI [1.45, 1.46]) for alcohol abuse).

Students who had parental understanding were 30% (AOR = 0.70; 95% CI [0.70, 0.71]) less likely to have suicidal ideation compared with students who did not have understanding parents.

DISCUSSION

Suicidal ideation in the current study was reported by 16.9% (12.2% of male and 21.1% of female) respondents. The following factors were associated with suicidal ideation: age, gender, food security, loneliness, close friends, truancy, bullied, attacked, involved in a fight, smoking (cigarettes or marijuana) alcohol (use or abuse) and parental understanding. Students younger than 16 years were less likely to have suicidal ideation compared with students who were of age 16 years or older, contradicting the argument by Muula et al. [11] and Spirito et al. [12] that they are more likely to have suicidal thoughts than the older ones partly because they have not developed problem solving skills and emotional maturity to handle stressful events. The finding that male students were less likely to have suicidal thoughts suggests that males and females are at different developmental stages in relation to how to handle stress and its resultant, depression. Females mature earlier than males and may be more likely to have suicidal thoughts than males in the same age group.

While lack of food security was associated with suicidal thoughts in other studies [13], the finding in the current study that students from homes with no food security were less likely to have suicidal thoughts is interesting. The observed relationship between food security and suicidal ideation in the current study could partly have been due to the effects of school feeding program.

Students who were lonely, had no friends or without parental understanding were more likely to have suicidal ideation. Social interaction is important in relieving stress and subsequently avoiding depression that is associated with suicidal ideation. Generally, studies have shown that loneliness [15, 16], having no close friends [11, 14, 15] and lack of parental understanding [16] are associated with suicidal ideation.

Students who were bullied, attacked or were involved in a fight might also have been truant. All these factors were associated with suicidal ideation in the current study and in other studies [17-19]. Targeting violence in interventions to reduce rates of suicidal ideation rates may in turn curtail suicide rates.

Interventions targeting substance use among adolescents, in particular discouraging students from smoking cigarettes or marijuana and consuming alcohol or abusing it, would help in curtailing suicidal thoughts and in turn reduce suicidal rates. Rudatsikira et al. [14] also found that alcohol abuse is associated with suicidal ideation. Adolescents may perceive substance use/abuse as a reliever of pain.

In conclusion, the suicidal ideation rate in Vietnam is of concern and interventions should be designed and implemented to lower the rate. In designing interventions, the factors established in the study should be considered.

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Chapter 50

PREVALENCE AND CORRELATES FOR SUICIDAL IDEATION AMONG ADOLESCENTS IN SCHOOL IN BOLIVIA

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ABSTRACT

The study examined the prevalence of suicidal ideation and associated factors among junior high school students aged 13-15 years in 2012, in Bolivia. Both bivariate and multivariate logistic regression analyses at 95% confidence level were conducted to assess the association between relevant predictor variables and suicidal ideation within the previous twelve months to the survey. A total of 3,477 junior high school students responded to the question on suicidal ideation among other questions in a structured questionnaire from the Global School-based Student Health Survey (GSHS). Overall, 18.2% of the students (13.2% of males and 23.5% of females) reported having had suicidal ideation in the previous 12 months. Significant factors associated with suicidal ideation were: being anxious, lonely, having no close friends, being bullied, being physically attacked or involved in a physical fight, smoking cigarettes or marijuana, alcohol consumption and abuse, and parental understanding. Interventions that address issues of violence against students, fighting with peers, initiation of smoking, alcohol and

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illicit drug use and those that encourage supportive roles of parents and peers may reduce the risk of suicidal ideation.

Keywords: suicidal ideation, prevalence, risk factors, Bolivia

INTRODUCTION

Adolescent suicide and suicidal behaviour have become major public health issues in recent years [1]. Suicide is widely recognized as major cause of mortality in young people and non-fatal suicidal behaviours in young people are associated with considerable morbidity. Suicidal behaviour in adolescence covers a wide spectrum of phenomena [1]. Rates of suicide increase markedly from childhood into adolescence representing a significant public health concern [2].

Suicide, in general, is a global public concern as more than 800,000 people commit it every year and for every suicide there are many more who attempt it [3]. A prior suicide attempt is the single most important risk factor for suicide in the general population [3]. In 2012, suicide was the second leading cause of death among 15-29 year olds worldwide and occurs throughout the life span [3, 4]. In a global burden of disease study, it was estimated that suicide contributes to 6% of all deaths among young people aged 10-24 years worldwide [5, 6]. Notably, 75% of global suicides occur in low and middle income countries [3, 4].

Previously, suicide rates were found to be low in Latin American countries, but that was expected to change [7]. In Bolivia, in a study conducted by analysing data from four different sources between 2007 and 2012, it was found out that more females attempted suicide whereas more males realized it and suicide attempts were most numerous among adolescents in contrast to suicides being most prevalent in the older age groups [8]. In Brazil, a neighbouring country to Bolivia, suicide rates among children and adolescents were reported to be relatively low compared with other countries before 2000 [9].

Although not all suicidal ideation materialize into suicide attempts or suicide, it is the first step on the path to suicide [10-12]. Suicidal ideation is a common mental health problem. The lifetime prevalence of suicidal ideation in Western countries has been reported to be around 10% [1, 2]. In Brazil, the prevalence of suicidal ideation was observed to be 14% and it was associated with violent behaviour, smoking and alcohol consumption [9].

A 60% rate of transition has been observed from suicidal ideation to first suicide attempt within the first year of ideation onset [12]. Suicidal thoughts are preventable with timely and low cost interventions [13]. To date, several environmental, psychological and behavioural factors have been found to be associated with suicidal ideation [14]. Physical, sexual and emotional abuses have been associated with adolescent suicidal ideation [14-16]. Family problems, social pressure, economic struggle, racism and violence, introduce constant emotional stresses and challenges among Peruvian adolescents [17], and these may be associated with suicidal ideation. While there have been reports on the prevalence and correlates of suicidal ideation in the developed world, data from the developing world is limited [10]. In order to contribute to the body of knowledge on suicidal ideation in developing countries, this study was conducted to determine the prevalence and identify associated factors for suicidal ideation.

METHODS

Bolivia is a landlocked country in South America. Brazil forms its eastern border; its other neighbours are Peru and Chile on the west and Argentina and Paraguay on the south (see Figure 1).

The Global School-based Health Survey (GSHS) was developed by the World Health Organization (WHO) in collaboration with UNICEF, UNESCO and UNAIDS with technical assistance from Centers for Diseases Control and Prevention, Atlanta, Georgia, United States with the aim of providing data on health and social behaviours among school-going adolescent students. This paper presents results of a secondary analysis of the data obtained from the GSHS conducted in 2012 among the junior high school students in Bolivia. The survey obtained data on alcohol use; dietary behaviours; drug use; hygiene; mental health; physical activity; protective factors; sexual behaviours; tobacco use; violence and unintentional injury.

The Bolivia GSHS was a two-stage cluster sample design, in which for the first stage, schools were selected with probability proportional to enrolment size. In the second stage, classes were randomly selected and all students in selected classes were eligible to participate. The school response rate was 99%, the student response rate was 89% and the overall response rate was 88%.

Students self-reported their responses to each question on a computer-scannable answer sheet. Variables that were used for our analysis included socio-demographic characteristics, having considered suicide, smoking, loneliness, parental understanding, involvement in a fight, truancy, anxiety, close friendship and food security. Assessment of associations was conducted through both bivariate and multivariate logistic regression analyses at 95% confidence interval.



Source: <http://boliviamap.facts.co/boliviamapof/boliviamap.php>.

Figure 1. Geographical location of Bolivia.

RESULTS

A total of 3696 students participated in the survey, of which 50.5% were males. Most of the students were either of age 14 years (27.4%) or 15 years (29.2%). About 1 in 3 students (32.8%) missed classes or school without permission. Overall, 31.3% of the students reported being bullied and 34.8% were physically attacked. Significantly, more males (44.4%) than females (21.2%) were involved in physical fights ($p < 0.001$). More females (14.8%) than males (7.3%) reported being lonely ($p < 0.001$). Altogether, 15.4% of the students reported that they smoked cigarettes 30 days prior to the survey, and only 3.5% reported that they smoked marijuana in their lifetime. About half (18.6%) of both males and females consumed alcohol, while 15.1% abused it. Overall, only 32.4% of students indicated that their parents or guardians understood their problems and worries. Significantly, more female (23.5%) than male students (13.2%) ever seriously considered attempting suicide ($p < 0.001$). These results are shown in Table 1.

Table 2 shows factors that were associated with suicidal ideation. All the factors that were considered in the analysis were significantly associated with suicidal ideation in both bivariate and multivariate analysis. Compared to students who were aged 16 years or older, students of age of 14 years (AOR = 0.86, 95% CI [0.85, 0.87]) were less likely to seriously consider attempting suicide; while students of age less than 14 years (AOR = 1.06, 95% CI [1.04, 1.08]) and age 15 years (AOR = 1.18, 95% CI [1.16, 1.20]) were more likely to have suicidal ideation. Male students were 34% (AOR = 0.66, 95% CI [0.65, 0.67]) less likely to have suicidal ideation than female students.

In relation to anxiety and loneliness, students who were worried about something that they could not sleep at night were 37% (AOR = 1.37, 95% CI [1.34, 1.39]) more likely to have suicidal ideation than students who were not anxious. Meanwhile, students who felt lonely were 1.75 (95% CI [1.73, 1.77]) times more likely to have suicidal ideation than students who did not.

Students who did not have close friends were more likely to have suicidal ideation than those who had close friends (AOR = 1.03, 95% CI [1.02, 1.05]). Compared to students who did not miss classes or school without permission, students who were truant were 26% (AOR = 1.26, 95% CI [1.24, 1.27]) more likely to seriously consider attempting suicide.

Been bullied, physically attacked or involvement in a physical fight were significantly associated with suicidal ideation. Students who were bullied were 32% (AOR = 1.32, 95% CI [1.31, 1.33]) more likely to have suicidal ideation compared to students who were not bullied. Compared to students who were not physically attacked, those who were attacked were 1.30 (95% CI [1.29, 1.31]) times more likely to have suicidal ideation. Students who were involved in a physical fight were 99% (AOR = 0.99, 95% CI [0.98, 1.00]) more likely to have suicidal ideation compared to those who were not involved in a physical fight.

Smoking cigarettes (AOR = 1.27, 95% CI [1.26, 1.29]); marijuana (AOR = 1.17, 95% CI [1.15, 1.20]) were significantly associated with suicidal ideation. Students who consumed alcohol were 26% (AOR = 1.26, 95% CI [1.24, 1.27]) more likely to have suicidal ideation compared to students who did not consume alcohol. Meanwhile, students who abused alcohol were 1.10 (95% CI [1.09, 1.12]) times more likely to have suicidal ideation compared to those who did not abuse alcohol.

Table 1. Distribution of factors considered in the analysis by gender among junior high school students in Bolivia, 2012

Factor	Total n ¹ (%) ²	Males n ¹ (%) ²	Females n ¹ (%) ²
Age			
<14	842(22.9)	412(22.4)	430(23.4)
14	983 (27.4)	477 (26.3)	506 (28.5)
15	967 (29.2)	485 (28.7)	482 (29.7)
16+	677 (20.5)	379 (22.5)	298 (18.4)
Gender			
Male	1753 (50.5)	-	-
Female	1716 (49.5)	-	-
Food security			
No	309 (8.4)	185 (9.8)	124 (6.9)
Yes	3187 (91.8)	1592 (90.2)	1595 (93.3)
Anxiety			
Yes	266 (7.2)	101 (5.4)	165 (9.1)
No	3208 (92.8)	1660 (92.7)	1548 (90.6)
Loneliness			
Yes	395 (11.0)	131 (7.3)	264 (14.8)
No	3126 (89.0)	1652 (92.7)	1474 (85.2)
Close friends			
No	299 (8.4)	154 (8.5)	145 (8.2)
Yes	3212 (91.6)	1623 (91.5)	1589 (91.8)
Truancy			
Yes	1148 (32.8)	629 (34.7)	519 (30.8)
No	2358 (67.2)	1146 (65.3)	1212 (69.2)
Bullied			
Yes	1055 (31.3)	549 (32.4)	506 (30.2)
No	2251 (68.7)	1128 (67.6)	1123 (69.8)
Attacked			
Yes	1233 (34.8)	690 (38.7)	543 (30.7)
No	2288 (65.2)	1097 (61.3)	1191 (69.3)
In a fight			
Yes	1171 (33.0)	789 (44.4)	382 (21.2)
No	2358 (67.0)	1000 (55.6)	1358 (78.8)
Smoked cigarettes			
Yes	515 (15.4)	343 (20.5)	172 (10.0)
No	2960 (84.6)	1419 (79.5)	1541 (90.0)
Smoked marijuana			
Yes	121 (3.5)	75 (4.4)	46 (2.6)
No	3347 (96.5)	1678 (95.6)	1669 (97.4)
Consumed alcohol			
Yes	615 (18.6)	354 (21.1)	261 (16.0)
No	2789 (81.9)	1374 (78.9)	1415 (84.0)
Abused alcohol			
Yes	491 (15.1)	306 (18.4)	185 (11.8)
No	2918 (84.9)	1423 (81.6)	1495 (88.2)
Parental understanding			
Yes	1120 (32.4)	564 (31.4)	556 (33.5)
No	2373 (67.6)	1202 (68.6)	1171 (66.5)
Suicidal ideation			
Yes	655 (18.2)	248 (13.2)	407 (23.5)
No	2822 (81.8)	1518 (86.8)	1304 (76.5)

¹ Unweighted frequencies. ² Weighted percents.

Table 2. Factors associated with suicidal ideation among junior high school students in Bolivia, 2012

Factor	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Age (years)		
Age		
<14	0.88 (0.87, 0.89)	1.06 (1.04, 1.08)
14	0.81 (0.80, 0.82)	0.86 (0.85, 0.87)
15	1.22 (1.21, 1.24)	1.18 (1.16, 1.20)
16+	1	1
Gender		
Male	0.49 (0.49, 0.50)	0.66 (0.65, 0.67)
Female	1	1
Food security		
No	1.19 (1.17, 1.20)	0.97 (0.96, 0.99)
Yes	1	1
Anxiety		
Yes	2.25 (2.23, 2.28)	1.37 (1.34, 1.39)
No	1	1
Loneliness		
Yes	2.45 (2.43, 2.47)	1.75 (1.72, 1.77)
No	1	1
Close friends		
No	1.22 (1.21, 1.24)	1.03 (1.02, 1.05)
Yes	1	1
Truancy		
Yes	1.38 (1.37, 1.39)	1.26 (1.24, 1.27)
No	1	1
Bullied		
Yes	1.67 (1.66, 1.68)	1.32 (1.31, 1.33)
No	1	1
Attacked		
Yes	1.55 (1.54, 1.56)	1.30 (1.29, 1.31)
No	1	1
In a fight		
Yes	1.23 (1.22, 1.24)	0.99 (0.98, 1.00)
No	1	1
Smoked cigarettes		
Yes	1.67 (1.66, 1.69)	1.27 (1.26, 1.29)
No	1	1
Smoked marijuana		
Yes	1.86 (1.83, 1.89)	1.17 (1.15, 1.20)
No	1	1
Consumed alcohol		
Yes	1.66 (1.65, 1.67)	1.26 (1.24, 1.27)
No	1	1
Abused alcohol		
Yes	1.61 (1.60, 1.63)	1.1 (1.09, 1.12)
No	1	1
Parental understanding		
Yes	0.69 (0.69, 0.70)	0.75 (0.75, 0.76)
No	1	1

Students who reported that their parents or guardians understood their problems and worries were 25% (AOR = 0.75, 95% CI [0.75, 0.76]) less likely to seriously consider attempting suicide.

DISCUSSION

In this study all the factors that were considered in the analysis were significantly associated with suicidal ideation in both bi-variate and multi-variate analysis. Although the prevalence of suicidal ideation of 18.2% is lower than the rates reported in similar studies in various parts of the world [10, 18, 19], it is common in Bolivia. The prevalence of suicidal ideation among males was about half that among females (13.2% vs 23.5%). This finding was also observed in similar studies done elsewhere [18]. It is, however, surprising that this is the case, as globally, actual suicide deaths occur more among males than females [10]. One study explained that girls had higher suicide attempt risk than boys and 45% of the risk was explained by socio economic, school, mental difficulties and violence [18]. With regard to age variation in relation to suicidal ideation, the study found that some younger age groups were protective, while others were not when compared to the oldest age group. Students who were less than 14 years of age and those that were 15 years of age were more likely to consider attempting suicide. This finding contradicts the findings in the Peru study which did not find any association between age and suicidal ideation and therefore reported an equal risk of suicidal ideation among different aged adolescents [18, 19]. The study by Muula et al. [10] found that adolescents who were less than 14 years of age were more likely to consider committing suicide. This finding and our finding are different from the findings of Liu et al. [20] where increasing age was correlated with suicidal behaviour. We are, however, unable to offer a plausible explanation as to why students who were 14 years of age (compared to students of ages 16 years or older in the current study) were less likely to have suicidal ideation because in most cases, it is the slightly older adolescents who would think of committing suicide more than the younger ones. Muula et al. [10] in their paper explained that younger children may not have developed problem solving skills and as such they are more likely to consider committing suicide than the older ones.

In the present study, being anxious, lonely, having no close friends, missing classes or school without permission were all associated with suicidal ideation. In addition, being bullied, physically attacked, involved in a physical fight were all significantly associated with suicidal ideation. Students who were bullied were 32% more likely to have suicidal ideation while those who were attacked were 30% more likely to have suicidal ideation. This indicates that adolescent violence is an important factor in the study area in Bolivia. Curtailing violence may result in reduced suicidal ideation. In a similar study among Brazilian adolescents, being involved in a physical fight was associated with a higher rate of suicidal ideation [18]. Similarly, being bullied has been observed as an important risk factor of suicidal ideation in study findings in other countries [10, 18]. This indicates that physical and emotional violence against adolescents is related to suicidal ideation.

The current study revealed a significant association between smoking and suicidal ideation. Similarly, in Benin, cigarette smoking was observed as a risk factor of suicidal ideation (14 = 18). Alcohol consumption and abuse were both associated with suicidal ideation in the current study. This association has also been reported in a similar study in Zambia [10]. Students who consumed alcohol were 26% more likely to have suicidal ideation in the current study. We, therefore, assume that preventing initiation of smoking, alcohol consumption among adolescents in Bolivia may be one of the useful strategies to prevent suicidal ideation and in turn prevent suicide.

We observed that students whose parents or guardians understood their problems and worries were less likely to consider committing suicide. Together with the finding that students who had close friends were less likely to have suicidal ideation, healthy parental and peer relationships should be encouraged for adolescents to have good mental health.

In conclusion, adolescent suicidal ideation is a common experience among adolescents in Bolivia. Creating a supportive environment both in school and at home will help adolescents to express their feelings and this will translate into reducing negative incidents of suicidal thoughts. We propose that preventive measures against suicidal ideation be put in place considering the factors that have been found to be significantly associated with suicidal ideation in this study.

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Chapter 51

FACTORS ASSOCIATED WITH SUICIDAL IDEATION AMONG ADOLESCENTS ATTENDING JUNIOR HIGH SCHOOL IN SURINAME

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ABSTRACT

Adolescent suicidal behavior is a neglected public health issue especially in middle and low income countries. Informed policy decision-making on suicidal behavior will need reliable information on the factors associated with suicidal ideation, which is one of the determinants of suicidal behaviour. The study aimed to identify factors associated with suicidal ideation among junior high school students in Suriname. Both bivariate and multivariate logistic regression analyses at 95% confidence interval were conducted to assess the association between relevant predictor variables and suicidal ideation within the previous twelve months. A total of 1,674 junior high school students responded to the question on suicidal ideation among other questions in a structured questionnaire from the Global School-based Student Health Survey (GSHS). Overall, 13.6% (9.1% of male and 17.9% of female) students reported having had suicidal ideation in the previous 12 months. The analysis showed that being anxious, lonely, having no close friends, being bullied, physically attacked or involved in a physical fight just like smoking cigarettes, alcohol consumption and abuse were all significantly associated with suicidal ideation.

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Interventions that address issues of violence against students, fighting with peers, initiation of smoking, alcohol consumption and abuse may reduce the risk of suicidal ideation.

Keywords: suicidal ideation, prevalence, correlates, Suriname

INTRODUCTION

Suicide is a global public concern as more than 800,000 people commit it every year and for every suicide there are many more who attempt it [1]. A prior suicide attempt is the single most important risk factor for suicide in the general population [1]. In 2012, suicide was the second leading cause of death among 15-29 year olds worldwide and occurs throughout the life span [1-3]. The Global Burden of Disease Study [4] estimated that suicide contributes to 6% of all deaths among young people aged 10-24 years worldwide. Notably, 75% of global suicides occur in low and middle income countries [1, 2]. Suicide is preventable with timely, evidence based and low cost interventions [1, 5]. Suicidal ideation is both a strong risk factor and a stage in the suicidal process from planning to attempt dying [6, 7]. Although not all suicidal ideation materialize into suicide attempts or suicide, it is the first step on to the path to suicide [8]. A 60% rate of transition has been observed from suicidal ideation to first suicide attempt within the first year of ideation on set [7].

Suicidal ideation often emerges in adolescence and is prevalent in this age group, particularly among females [9]. Across 17 European countries, the lifetime prevalence of ideation among students aged 15-16 years ranged from 15% to 31.5%. Across 49 low and middle income countries, 15.3% of adolescents aged 13-15 years had seriously considered suicide in a year prior to the survey. In neighbouring countries to Suriname, the prevalence of suicidal ideation was 14% in Brazil [10] and 18.4% in Guyana [11]. Given that ideation strongly and prospectively relates to suicide attempts and suicide, identifying potentially modifiable risk factors is essential for preventing these deaths [9]. Several environmental, psychosocial and behavioural factors have been found to be associated with suicidal ideation [9, 10] and include: physical, sexual and emotional abuses [8, 9, 12, 13], family problems, social pressure, economic struggle, racism [12, 13], smoking and alcohol consumption [12]. Correlates for suicidal ideation may vary from subpopulation to subpopulation in a country; among countries and continents and, hence, is important that these correlates are established for specific populations. Suicidal ideation prevalence and its associated factors among junior high school students in Suriname are unknown. Therefore, the objectives of the study were to estimate the prevalence of suicidal ideation and identify factors associated with this phenomenon.

METHODS

Suriname is a small country in South America (see Figure 1). It is a sovereign state on the northeastern Atlantic coast of South America. It is bordered by French Guyana to the east, Guyana to the west and Brazil to the south. At just under 165,000 km², it is the smallest

country in South America with a population of approximately 566,000, most of whom live on the country's north coast, in and around the capital and largest city, Paramaribo. It's defined by vast swaths of tropical rainforest, Dutch colonial architecture and a melting-pot culture. On its Atlantic coast is the capital, Paramaribo, where palm gardens grow near Fort Zeelandia, a 17th -century trading post. Paramaribo is also home to Saint Peter and Paul Basilica, a towering wood cathedral consecrated in 1885.

The Global School-based Health Survey (GSHS) was developed by the World Health Organization (WHO) in collaboration with UNICEF, UNESCO and UNAIDS with technical assistance from Centers for Diseases Control and Prevention, Atlanta, Georgia, United States with the aim of providing data on health and social behaviors among school-going adolescent students. This paper presents results of a secondary analysis of the data obtained from the GSHS conducted in 2009 among the junior high school students in Suriname. The survey measured alcohol use; dietary behaviors; drug use; hygiene; mental health; physical activity; protective factors; sexual behaviors; tobacco use; violence and unintentional injury.

The Suriname GSHS used a two-stage cluster sample design in which in the first stage, schools were selected with probability proportional to enrollment size. In the second stage, classes were randomly selected and all students in selected classes were eligible to participate. The school response rate was 100%, the student response rate was 89% and the overall response rate was 89%.

Students self-reported their responses to each question on a computer-scannable answer sheet. Variables that were used in the analysis included: socio-demographic characteristics, having considered suicide, smoking, loneliness, parental understanding, involvement in a fight, truancy, anxiety, close friendship and food security. Assessments of associations were conducted using both bivariate and multivariate logistic regression analyses at 95% confidence interval.



Source: <http://www.mapsofworld.com/suriname/surinam-location-map.html>.

Figure 1. Map of Suriname and its neighbouring countries.

RESULTS

A total of 1698 students participated in the survey of which 51.0% were males. Most of the students were either of age 16 years or older (38.1%) or 15 years (22.2%). About 1 in 4 students (27%) reported being bullied. Overall, 22.1% of students missed classes or school without permission and 24.7% were physically attacked. Significantly ($p < 0.001$), more males (29.9%) than females (12.6%) were involved in a physical fight and also more males (30.5%) than females (13.9%) reported to have missed classes or school without permission. Altogether, 12.2% of the students reported that they smoked cigarettes 30 days prior to the survey. Overall 38.1% of both males and females consumed alcohol, while 19.1% abused it. Overall, 41.4% of students indicated that their parents or guardians understood their problems and worries. Significantly, more female students (17.9%) than male students (9.1%) ever seriously considered attempting suicide. The overall suicidal ideation prevalence rate was 13.6%. These results are shown in Table 1.

Table 2 shows factors that were associated with suicidal ideation. All the factors that were considered in the analysis were significantly associated with suicidal ideation in both bivariate and multivariate analyses. Compared to students who were aged 16 years or older, students of age less than 14 years (AOR = 0.52, 95% CI [0.47, 0.57]) were less likely to seriously consider attempting suicide while students of age 14 years (AOR = 1.22, 95% CI [1.12, 1.33]) and 15 years (AOR = 1.33, 95% CI [1.23, 1.44]) were more likely to have suicidal ideation. Male students were 40% (AOR = 0.60, 95% CI [0.57, 0.63]) less likely to have suicidal ideation than female students.

In relation to anxiety and loneliness, students who were worried about something that they could not sleep at night were 52% (AOR = 1.52, 95% CI [1.43, 1.62]) more likely to have suicidal ideation than students who were not anxious. Meanwhile, students who felt lonely were 1.27 (95% CI [1.20, 1.35]) times more likely to have suicidal ideation than students who did not.

Students who did not have close friends were more likely to have suicidal ideation than those who had close friends (AOR = 1.16, 95% CI [1.09, 1.22]). Compared to students who did not miss classes or school without permission, students who were truant were 7% (AOR = 0.93, 95% CI [0.88, 0.99]) less likely to seriously consider attempting suicide.

Been bullied, physically attacked or involvement in a physical fight were significantly associated with suicidal ideation. Students who were bullied were 41% (AOR = 1.41, 95% CI [1.34, 1.48]) more likely to have suicidal ideation compared to students who were not bullied. Compared to students who were not physically attacked, those who were attacked were 1.11 (95% CI [1.05, 1.17]) times more likely to have suicidal ideation. Students who were involved in a physical fight were 17% (AOR = 1.17, 95% CI [1.11, 1.24]) more likely to have suicidal ideation compared to those who were not involved in a physical fight.

Smoking cigarettes (AOR = 1.26, 95% CI [1.19, 1.34]) was significantly associated with suicidal ideation; Students who consumed alcohol were 13% (AOR = 1.13, 95% CI [1.07, 1.19]) more likely to have suicidal ideation compared to students who did not consume alcohol. Meanwhile, students who abused alcohol were 1.32 (95% CI [1.24, 1.39]) times more likely to have suicidal ideation compared to those who did not abuse alcohol.

Students who reported that their parents or guardians understood their problems and worries were 22% (AOR = 0.78, 95% CI [0.75, 0.82]) less likely to seriously consider attempting suicide.

Table 1. Distribution of factors considered in the analysis by gender among junior high school students in Suriname, 2009

Factor	Total n ¹ (%) ²	Males n ¹ (%) ²	Females n ¹ (%) ²
Age			
<14	332 (19.2)	142 (16.5)	190 (21.9)
14	346 (20.5)	157 (18.0)	189 (22.9)
15	370 (22.2)	193 (22.6)	177 (21.8)
16+	630 (38.1)	366 (43.0)	264 (33.4)
Gender			
Male	858 (51.0)	-	-
Female	820 (48.9)	-	-
Food security			
No	173 (10.6)	86 (10.6)	87 (10.7)
Yes	1498 (89.4)	767 (89.4)	731 (89.3)
Anxiety			
Yes	166 (9.9)	77 (9.0)	89 (10.8)
No	1519 (90.1)	783 (91.0)	736 (89.2)
Loneliness			
Yes	246 (14.9)	119 (14.1)	127 (15.6)
No	1434 (85.1)	737 (85.9)	697 (84.4)
Close friends			
No	287 (17.5)	135 (16.1)	152 (18.9)
Yes	1372 (82.5)	710 (83.9)	662 (81.1)
Truancy			
Yes	365 (22.1)	254 (30.5)	111 (13.9)
No	1277 (77.9)	581 (69.5)	696 (86.1)
Bullied			
Yes	437 (27.0)	223 (27.5)	214 (26.5)
No	1176 (73.0)	588 (72.5)	588 (73.5)
Attacked			
Yes	417 (24.7)	250 (29.3)	167 (20.2)
No	1262 (75.3)	607 (70.7)	655 (79.8)
In a fight			
Yes	359 (21.1)	255 (29.9)	104 (12.6)
No	1321 (78.9)	601 (70.1)	720 (87.4)
Smoked cigarettes			
Yes	205 (12.2)	126 (14.8)	79 (9.7)
No	1470 (87.8)	728 (85.2)	742 (90.3)
Consumed alcohol			
Yes	569 (38.1)	322 (41.5)	247 (34.7)
No	935 (61.9)	462 (58.5)	473 (65.3)
Abused alcohol			
Yes	312 (19.1)	217 (26.3)	95 (12.1)
No	1319 (80.9)	618 (73.7)	701 (87.9)
Parental understanding			
Yes	673 (41.4)	347 (42.4)	326 (40.5)
No	949 (58.6)	472 (57.6)	477 (59.5)
Suicidal ideation			
Yes	223 (13.6)	77 (9.1)	146 (17.9)
No	1451 (86.4)	773 (90.9)	678 (82.1)

¹ unweighted frequencies. ² weighted percents.

Table 2. Factors associated with suicidal ideation among junior high school students in Suriname, 2009

Factor	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Age (years)		
Age		
<14	0.59 (0.54, 0.54)	0.52 (0.47, 0.57)
14	1.07 (1.00, 1.14)	1.22 (1.12, 1.33)
15	1.43 (1.34, 1.52)	1.33 (1.23, 1.44)
16+	1	1
Gender		
Male	0.68 (0.65, 0.70)	0.60 (0.57, 0.63)
Female	1	1
Food security		
No	1.15 (1.09, 1.21)	0.91 (0.84, 0.97)
Yes	1	1
Anxiety		
Yes	1.91 (1.83, 2.00)	1.52 (1.43, 1.62)
No	1	1
Loneliness		
Yes	1.75 (1.68, 1.82)	1.27 (1.20, 1.35)
No	1	1
Close friends		
No	1.20 (1.14, 1.25)	1.16 (1.09, 1.22)
Yes	1	1
Truancy		
Yes	1.13 (1.08, 1.18)	0.93 (0.88, 0.99)
No	1	1
Bullied		
Yes	1.64 (1.58, 1.70)	1.41 (1.34, 1.48)
No	1	1
Attacked		
Yes	1.32 (1.26, 1.37)	1.11 (1.05, 1.17)
No	1	1
In a fight		
Yes	1.29 (1.23, 1.34)	1.17 (1.11, 1.24)
No	1	1
Smoked cigarettes		
Yes	1.46 (1.39, 1.53)	1.26 (1.19, 1.34)
No	1	1
Consumed alcohol		
Yes	1.36 (1.31, 1.41)	1.13 (1.07, 1.19)
No	1	1
Abused alcohol		
Yes	1.43 (1.37, 1.49)	1.32 (1.24, 1.39)
No	1	1
Parental understanding		
Yes	0.69 (0.66, 0.72)	0.78 (0.75, 0.82)
No	1	1

DISCUSSION

In the current study all the factors that were considered in the analysis were significantly associated with suicidal ideation. The prevalence of suicidal ideation was 13.6% which is higher than the prevalence of suicidal ideation of 10.7% among Americans of Caribbean

descent but lower than the prevalence of suicidal ideation of 17.1% in Brazil [10]. The prevalence of suicidal ideation among males was about half that among females (9.1% vs 17.9%, respectively). This finding was also observed in similar studies done elsewhere [12]. It is, however, surprising that this is the case, as globally, actual suicide deaths occur more among males than females [8].

With regard to the distribution of suicidal ideation by age, the present study found that there was an association between age and suicidal ideation. Students who were less than 14 years of age were less likely to consider committing suicide. This finding contradicts the finding in Peru which did not find any association between age and suicidal ideation [12]. The study by Muula et al. [8] found that adolescents who were less than 14 years of age were more likely to consider committing suicide. Our finding and the finding by Liu et al. [14] indicate that age is correlated with suicidal ideation. We are, however, unable to offer a plausible explanation as why students who were 14 years of age (compared to older age groups) were less likely to have suicidal ideation because in most cases, it is the slightly older adolescents who would think of committing suicide more than the younger ones. Muula et al. [8] in their paper, however, explained that younger children may not have developed problem solving skills and as such they are more likely to consider committing suicide than the older ones.

In the current study, being anxious, lonely, having no close friends, missing classes or school without permission were all associated with suicidal ideation. Been bullied, physically attacked, involved in a physical fight were also significantly associated with suicidal ideation. Students who were bullied were 41% more likely to have suicidal ideation and those who were anxious were 52% more likely to have suicidal ideation. In similar studies elsewhere being involved in a physical fight and bullying were significantly associated with higher rates of suicidal ideation [8, 11, 12]. These findings indicate that physical and emotional violence against adolescents should be considered in efforts to design interventions to prevent suicide.

The present study revealed a significant association between smoking and suicidal ideation. Similarly, another study also observed cigarette smoking as a risk factor of suicidal ideation [9]. Alcohol consumption and abuse were both associated with suicidal ideation in the current study. This association has also been reported in another study [8]. Students who consumed alcohol were 13% more likely to consider committing suicide than those who did not consume alcohol while those that abused alcohol were 32% more likely to consider committing suicide. Therefore, preventing initiation of smoking and alcohol consumption among adolescents in Suriname may be one of the useful strategies to prevent suicide.

In conclusion, suicidal ideation is a significant public health issue among in-school adolescents in Suriname that requires attention. We propose that the design, implementation and evaluation of preventive measures should incorporate the knowledge of the associated factors obtained in the current study.

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Chapter 52

CORRELATES OF SUICIDAL IDEATION AMONG IN-SCHOOL ADOLESCENTS IN MYANMAR

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ABSTRACT

Information on the epidemiology of suicidal ideation is scanty in low and middle income countries. In order to contribute to the body of knowledge on suicidal behaviour, a study was conducted to examine the correlates of suicidal ideation among adolescents attending junior high school in Myanmar. Both bivariate and multivariate logistic regression analyses at 95% confidence interval were conducted to establish associations. A total of 2,803 junior high school students responded to the question on suicidal ideation among other questions in a structured questionnaire from the Global School-based Student Health Survey (GSHS). Overall, 1.1% students reported having had suicidal ideation in the previous 12 months. The analysis showed that having no food security, being anxious, lonely, having no close friends, being bullied, physically attacked or involved in a physical fight, alcohol consumption were all significantly associated with suicidal ideation. The study also found that having parents or guardians who do not understand the adolescent's problems and worries was significantly associated with suicidal ideation. Interventions that address issues of food security, violence against students, fighting with peers, initiation of alcohol consumption and those that encourage supportive roles of parents may reduce the risk of suicidal ideation.

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Keywords: suicidal ideation, prevalence, correlates, Myanmar

INTRODUCTION

Suicide is a global public concern as more than 800,000 people commit it every year and for every suicide there are many more who attempt it [1]. A prior suicide attempt is the single most important risk factor for suicide in the general population [1]. In 2004, suicide was the fourth leading cause of death among young males and the third among young females aged 15-19 years, worldwide [2]. The Global Burden of Disease Study [3] estimated that suicide contributes to 6% of all deaths among young people aged 10-24 years worldwide. It is, however, worthy noting that over the past 25 years there have been major shifts in causes of mortality and morbidity among young people aged 10-24 years [4]. Notably, 75% of global suicides occur in low and middle income countries which are home to more than 90% of the world's children and youths [5]. Compared to high income countries, relatively little is known about the epidemiology of adolescent suicide and suicide behaviours in low and middle income countries [5].

Studies among adolescents from low and middle income countries seem to show considerable rates of prevalence of suicidal ideation: 17.8% in China, 17.1% in Philippines, and in African countries; 19.6% in Uganda, 23.1% in Botswana, 27.9 % in Kenya and 31.9% in Zambia [6]. Local studies in Thailand found a prevalence of suicidal ideation of 4.0% among high school students [6, 7].

Suicide is preventable with timely and low cost interventions [1]. It is reported that 85.7% of those who make a suicide attempt have seriously thought about doing so earlier. To date, several environmental, psychosocial and behavioral factors have been found to be associated with suicidal ideation, suicidal attempts and suicide in studies conducted in various countries. Physical, sexual and emotional abuses have been associated with adolescent suicidal ideation and attempts [7-9].

Although not all suicidal ideation materialize into suicide attempts or suicide, it is the first step on to the path to suicide [10]. Suicidal ideation is both a strong risk factor and a stage in the suicidal process from planning to attempt dying [11, 12]. A 60% rate of transition had been observed from suicidal ideation to first suicide attempt within the first year of ideation on set [12]. Hence, one of the key challenges for preventing suicide among adolescents is improving the prediction of suicide risk [13]. Given that suicide ideation strongly and prospectively relates to suicide attempts and suicide, identifying potentially modifiable risk factors is essential for preventing these deaths [5]. Many factors associated with youth suicidal behaviours in low and middle income countries overlap with established risk factors from high income countries [5].

In a study conducted in 2008 in Thailand, a neighbouring country to Myanmar, the overall prevalence of suicidal ideation was 8.8%, and factors that were associated with suicidal ideation were sadness, lack of parental attachment and current alcohol use [6]. Studies were conducted between 2003 and 2012 in China [14], another neighbouring country to Myanmar. Meta-analysis of these studies estimated the lifetime prevalence of suicidal ideation as 3.9%. This figure cannot, however, be compared to the prevalence of suicidal

ideation found in Myanmar because the studies in China were conducted in age groups above 15 years.

Suicidal ideation and its associated factors among junior high school students in Myanmar are unknown. Therefore, the objectives of this study were to determine the prevalence of suicidal ideation as well as factors associated with this phenomenon.

METHODS

The study setting for the current study was Myanmar. Myanmar (formerly Burma) is a Southeast Asian nation of more than 100 ethnic groups, bordering India, Bangladesh, China, Laos and Thailand (see Figure 1).

The Global School-based Health Survey (GSHS) was developed by the World Health Organization (WHO) in collaboration with UNICEF, UNESCO and UNAIDS with technical assistance from Centers for Diseases Control and Prevention, Atlanta, Georgia, United States with the aim of providing data on health and social behaviors among school-going adolescent students. This paper presents results of a secondary analysis of the data obtained from the GSHS conducted in 2007 among the junior high school students in Myanmar. The survey measured alcohol use; dietary behaviors; drug use; hygiene; mental health; physical activity; protective factors; sexual behaviors; tobacco use; violence and unintentional injury.



Source: <http://i.infopls.com/images/mburma.t.gif>.

Figure 1. Myanmar and its neighbouring countries.

In the Myanmar GSHS, a two-stage cluster sample design was used. In the first stage, schools were selected with probability proportional to enrollment size. In the second stage, classes were randomly selected and all students in selected classes were eligible to participate. The school response rate was 100% and that for students was 95%, with an overall response rate was 95%.

Variables that were used in the current study included socio-demographic characteristics, having considered suicide, smoking, loneliness, parental understanding,

involvement in a fight, truancy, anxiety, close friendship and food security. Assessments of associations were conducted using both bivariate and multivariate logistic regression analyses at 95% confidence interval.

RESULTS

A total of 2806 students participated in the Myanmar 2007 Global School-based Students Health Survey, of which 49.8% were males. Most of the students were either of age less than 14 years (40.7%) or 14 years (25.2%). About 1 in 4 students (21.8%) missed classes or school without permission. Overall, 20.7% of students reported being bullied and 23.1% were physically attacked. Significantly, more males (21.7%) than females (9.8%) were involved in a physical fight ($p < 0.001$). Altogether, 2.9% of the students reported that they smoked cigarettes 30 days prior to the survey, and none reported that they smoked marijuana in their lifetime. Only 1.4% of both males and females consumed alcohol, while 2.6% abused it. Overall, 60.9% of students indicated that their parents or guardians understood their problems and worries. There was no significant difference ($p = 0.303$) in suicidal ideation rates between female students (1.2%) and male students (1.1%). These results are shown in Table 1.

Table 2 shows factors that were associated with suicidal ideation. All the factors, except gender, that were considered in the analysis were significantly associated with suicidal ideation in bivariate analyses. However, in multi-variate analysis, cigarette smoking, and alcohol abuse were no longer associated with suicidal ideation.

Compared to students who were aged 16 years or older, students of age less than 14 years were 2.71 (95% CI [2.61, 2.81]) times more likely to have suicidal ideation than students who did not. Students who were 14 years (AOR = 0.45, 95% CI [0.43, 0.48]) were less likely to seriously consider attempting suicide; while students aged 15 years (AOR = 0.62, 95% CI [0.59, 0.66]) were less likely to consider attempting suicide. Gender was not significantly associated with suicidal ideation.

In relation to anxiety and loneliness, students who were worried about something such that they could not sleep at night were 2.17 (95% CI [2.10, 2.24]) times more likely to have suicidal ideation than students who were not anxious. Meanwhile, students who felt lonely were 1.82 (95% CI [1.76, 1.88]) times more likely to have suicidal ideation than students who did not.

Students who did not have close friends were more likely to have suicidal ideation than those who had close friends (AOR = 1.14, 95% CI [1.07, 1.21]). Compared to students who did not miss classes or school without permission, students who were truant were 19% (AOR = 1.19, 95% CI [1.16, 1.22]) more likely to seriously consider attempting suicide.

Been bullied and physically attacked were significantly associated with suicidal ideation. Students who were bullied were (AOR = 1.00, 95% CI [1.00, 1.02]) more likely to have suicidal ideation compared to students who were not bullied. Compared to students who were not physically attacked, those who were attacked were 2.38 (95% CI [2.32, 2.44]) times more likely to have suicidal ideation. Students who were involved in a physical fight were 18% (AOR = 0.82, 95% CI [0.80, 0.85]) less likely to have suicidal ideation compared to those who were not in a physical fight.

Table 1. Distribution of factors considered in the analysis by gender among junior high school students in Myanmar, 2007

Factor	Total n ¹ (%) ²	Males n ¹ (%) ²	Females n ¹ (%) ²
Age			
<14	840 (40.7)	377 (38.1)	463 (43.3)
14	628 (25.2)	307 (25.0)	321 (25.4)
15	770 (21.0)	391 (21.4)	379 (20.5)
16+	549 (13.2)	313 (15.5)	236 (10.8)
Gender			
Male	1388 (49.8)	-	-
Female	1399 (50.2)	-	-
Food security			
No	91(3.3)	48 (3.2)	43 (3.3)
Yes	2700 (96.7)	1340 (96.8)	1360(96.7)
Anxiety			
Yes	67 (2.2)	41 (2.7)	26 (1.8)
No	1340 (6.7)	1349 (97.3)	1375 (98.2)
Loneliness			
Yes	123 (4.2)	63 (4.5)	60 (3.9)
No	2672 (95.8)	1330 (95.5)	1342 (96.7)
Close friends			
No	98 (3.7)	52 (4.2)	46 (3.3)
Yes	2695 (96.3)	1336 (95.5)	1359 (96.7)
Truancy			
Yes	609 (21.8)	352 (25.4)	257 (18.2)
No	2177 (78.2)	1032 (74.6)	1145 (81.8)
Bullied			
Yes	504 (23.1)	283 (24.4)	221 (17.0)
No	1933 (79.3)	909 (75.6)	1024 (83.0)
Attacked			
Yes	586 (23.1)	369 (29.1)	217 (16.8)
No	22.8 (76.9)	1023 (70.9)	1185 (83.2)
In a fight			
Yes	402 (15.9)	278 (21.7)	124 (9.8)
No	2390 (84.1)	1113 (78.3)	1277 (90.2)
Smoked cigarettes			
Yes	106 (2.9)	95(5.0)	11 (0.8)
No	2635 (97.1)	1263 (95.0)	1372 (99.2)
Consumed alcohol			
Yes	48 (1.4)	40 (2.2)	8 (0,5)
No	2677 (98.6)	1297 (97.8)	1380 (99.5)
Abused alcohol			
Yes	97 (2.6)	85 (4.4)	12 (0.7)
No	2706 (97.4)	1310 (95.6)	1396 (99.3)
Parental understanding			
Yes	1714 (60.9)	771 (55.8)	943 (66.2)
No	1065 (39.1)	611 (44.2)	454 (33.8)
Suicidal ideation			
Yes	30 (1.1)	13 (1.1)	17 (1.2)
No	2773 (98.9)	1382 (98.9)	1391 (98.8)

¹ unweighted frequencies. ² weighted percents.

Table 2. Factors associated with suicidal ideation among junior high school students in Myanmar, 2007

Factor	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Age (years)		
Age		
<14	1.70 (1.66, 1.74)	2.71 (2.61, 2.81)
14	0.69 (0.67, 0.72)	0.45 (0.43, 0.48)
15	0.52 (0.50, 0.54)	0.62 (0.59, 0.66)
16+	1	1
Gender		
Male	0.99 (0.98, 1.01)	-
Female	1	-
Food security		
No	2.66 (2.61, 2.72)	2.03 (1.96, 2.11)
Yes	1	1
Anxiety		
Yes	3.43 (3.36, 3.50)	2.17 (2.10, 2.24)
No	1	1
Loneliness		
Yes	2.38 (2.34, 2.44)	1.82 (1.76, 1.88)
No	1	1
Close friends		
No	1.53 (1.49, 1.47)	1.14 (1.07, 1.21)
Yes	1	1
Truancy		
Yes	1.45 (1.43, 1.47)	1.19 (1.16, 1.22)
No	1	1
Bullied		
Yes	1.72 (1.68, 1.75)	1.00 (1.00, 1.02)
No	1	1
Attacked		
Yes	2.40 (2.37, 2.44)	2.38 (2.32, 2.44)
No	1	1
In a fight		
Yes	1.96 (1.93, 1.99)	0.82 (0.80, 0.85)
No	1	1
Smoked cigarettes		
Yes	1.39 (1.34, 1.44)	-
No	1	-
Consumed alcohol		
Yes	3.63 (3.55, 3.72)	1.81 (1.74, 1.89)
No	1	1
Abused alcohol		
Yes	0.87 (0.82, 0.92)	-
No	1	1
Parental understanding		
Yes	0.67 (0.66, 0.69)	0.94 (0.92, 0.96)
No	1	1

Students who consumed alcohol were 81% (AOR = 1.81, 95% CI [1.74, 1.89]) more likely to have suicidal ideation compared to students who did not consume alcohol.

Students who reported that their parents or guardians understood their problems and worries were 6% (AOR = 0.94, 95% CI [0.92, 0.96]) less likely to seriously consider attempting suicide.

DISCUSSION

The prevalence of suicidal ideation in the current study was 1.1% which is lower than what has been reported in similar studies in various parts of the world [10, 15]. The low rate of suicidal ideation in Myanmar may be due to Buddhism. About 95% of the population is Buddhist and one of the five actions of Buddhism requires a lay Buddhist to train himself or herself to avoid destroying life [6]. Religious affiliation and practice among Burmese people may play an important role in preventing them from suicidal behaviour when they encounter hopeless feelings in their lives [6]. Some studies have reported strong sociocultural influence especially among middle and high income families in relation to suicide attempt reports [16]. In various studies conducted in China between 2003 and 2011 among the aging populations, there were vast variations in the prevalence of suicidal ideation between various regions. The prevalence ranged from 2.2% to 41.2% [17]. In a meta-analysis study to establish the prevalence of suicidal ideation and suicide attempts in the general population of mainland China in the age range 15 to 18 years, the prevalence of suicidal Ideation ranged from 2.8 to 4.9 % [14].

The prevalence of suicidal ideation was similar in males and females (1.1% vs 1.2%). This finding was also observed in another study elsewhere [15]. It is, however, surprising that this is the case, as globally, actual suicide deaths occur more among males than females [10]. With regard to age variation, the study found that there was an association between age and suicidal ideation which indicates some unequal risk of suicidal ideation among different aged adolescents. Students who were less than 14 years of age were 2.71 times more likely to consider attempting suicide than those who were of age 16 years or older. Meanwhile students who were of age 14 or 15 years were less likely to have suicidal thoughts compared to students of age 16 years or older. This finding contradicts the findings in Peru and Uganda which did not find any association between age and suicidal ideation and therefore reported an equal risk of suicidal ideation among different aged adolescents [15, 18]. The study by Muula et al. [10] found that adolescents who were less than 14 years of age were more likely to consider committing suicide. This finding and our finding are different from the findings of Liu et al. [19] who found increasing age to be correlated with suicidal behaviour. We are, however, unable to offer a plausible explanation as why students who were less than 14 years of age were more likely to have suicidal ideation because in most cases, it is the slightly older adolescents who would think of committing suicide more than the younger ones. Muula et al. [10] in their paper, however, explained that younger children may not have developed problem solving skills and as such they are more likely to consider committing suicide than the older ones.

In the present study, being anxious, lonely, having no close friends, missing classes or school without permission and parental understanding were all associated with suicidal ideation. Being bullied, physically attacked, involved in a physical fight and alcohol use were also significantly associated with suicidal ideation. Students who were attacked were 2.38 times more likely to have suicidal ideation than those who were not and those who were lonely were 82% more likely to have suicidal ideation. In a similar study conducted in 2008, among Thai adolescents, being sad, anxious, lack of parental understanding, alcohol use and use of illicit drugs were associated with a higher rate of suicidal ideation [6]. Similarly, being bullied is an important risk factor of suicidal ideation in study findings in other countries [10,

15]. These results suggest that many factors will have to be considered in designing interventions to curtail suicidal ideation, although the prevalence was low.

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Chapter 53

BREAK THE CYCLE OF CHILDREN'S ENVIRONMENTAL HEALTH DISPARITIES

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ABSTRACT

Break the Cycle of Children's Environmental Health Disparities (*Break the Cycle*) is an annual collaborative interdisciplinary research and training program involving university students in academic tracks that focus on the impact of adverse social, economic and environmental factors on children's health and development. The target populations are communities where poverty is associated with social and political marginalization exposing children to environmental hazards with risks to their health and well-being. Each participating student develops a project that focuses on preventing or reducing adverse environmental factors in order to benefit the children who live in these communities by reducing the likelihood of health disparities and improving their health and well-being. At the end of the project period, students present their findings at a national conference and write papers, which are published in this volume. The projects in any given year cover a range of social, economic, environmental and political factors that operate over the lifespan, and have an influence on individual, family, community, and societal elements. Most importantly, they inform us about children's environmental health disparities and propose solutions to reduce and eliminate health disparities and promote health equity for all children. The phrase *Break the Cycle* in this context uses the ecological construct of the cycle of environmental health disparities (Figure 1) and represents a framework for reducing health disparities and promoting health equity among vulnerable children. The student projects are intended to break the cycle and liberate children from the intergenerational cycle of health disparities, so they can grow and develop to their full potential. Through their participation in this academic process, the students gain knowledge, insight and skills to enable them to advance in their careers and become future leaders in children's environmental health research, clinical practice and advocacy. The papers in this publication represent the work of students who participated in the 13th Annual *Break the Cycle* program 2017-2018.

INTRODUCTION

Children who grow up in poverty are often exposed to poor indoor air quality, which increases the risk for asthma and respiratory disorders, and to high lead levels from old paint and plumbing in older houses which can result in adverse health outcomes [1]. In addition, the children are at risk for a variety of other environmental exposures because their poor neighborhoods are more likely to be located near roadways where the air is polluted with exhausts from motor vehicles, or near factories, and even toxic waste sites. Their neighborhoods and schools are often poorly serviced with visible litter, trash and general degradation, not to mention poor lighting at night which increases risks of assault and other

crimes, as well as absence of green spaces for recreation [2]. Furthermore, the emotional toll on the children from multiple stressors, including food insecurity, housing insecurity, and fear of physical injury from neglect and abuse which, cumulatively, can result in the physiological phenomenon of chronically elevated cortisol levels and “toxic stress” [3]. The toxic stress syndrome is associated with adverse structural and functional changes in the brain resulting in life-long consequences that can be associated with a reduction in brain volume in white matter, in grey matter, and specifically in the hippocampus and amygdala with developmental, learning, behavior and other functional consequences [4]. As they reach adolescence, they are more likely to experience school failure and engage in risky behaviors, including substance abuse, gang membership, and crimes which can result in incarceration or death from drugs or gun violence. The chronically elevated cortisol levels associated with toxic stress also affect the cardiovascular, immune and hormonal systems, resulting in an increased likelihood of adverse health outcomes in adulthood including obesity, diabetes, and hypertension, with associated morbidity and mortality [3].



Figure 1. Cycle of environmental health disparities [9].

The risks for children are greater than they are for adults, because children breathe more air, drink more water, and eat more food for their body weight than adults, so their exposure load through polluted air, water and soil is greater [5]. Yet, as vulnerable as the children are, so much more sensitive is the fetus. Therefore, the exposure of a pregnant woman to environmental toxins not only affects her health and well-being but can have serious and permanent effects on her fetus. Despite the physiological protective elements in the placenta, many toxins do enter the fetal circulation and can affect organ system development, anatomically and physiologically. Many substances can cross the blood-brain barrier and adversely affect the developing brain resulting in disorders of development and learning with

risks for learning disabilities, such as ADHD, and Autism [6]. These children also have the misfortune of living in poor neighborhoods and attending older, more dilapidated, schools, with teachers who are also suffering from the stress of adverse environmental factors. The combined effects of environmental stresses and negative educational experiences result in high drop-out rates and low graduation rates [7]. Limited education leads to poor employment opportunities, or work with low pay, trapping the young people in the poorer neighborhoods with the older houses in states of disrepair, contributing to exposures to indoor hazards of lead, mold, and other possible contaminants, as well as emotional stress with depression, anxiety about the future with despair and social isolation [8].

This assault of adverse social, economic and environmental factors results in unfavorable health, developmental, and educational outcomes that compromise the child's opportunity for economic and social success and devolves into the perpetuation of an intergenerational cycle. It is the codification of this ecological construct that embodies the concept of the cycle of children's environmental health disparities (see Figure 1).

BREAK THE CYCLE PROGRAM

"Break the Cycle of Children's Environmental Health Disparities" (*Break the Cycle*) is an annual collaborative interdisciplinary research and training program involving university students in academic tracks that explore the impact of adverse social, economic, and environmental factors on children's health, development, and education. Each student develops a project that focuses on preventing or reducing environment related disorders for children who live in communities where environmental hazards are related to circumstances of social and economic disadvantage. At the conclusion of the project, the students present the results of their projects at a national conference and write papers which are published in a journal supplement devoted to the collection of projects from each given year [9].

Each annual program begins with a call for proposals from students which are then subjected to a competitive review process that evaluates the quality of the proposal, relevance to children's environmental health disparities, creativity, and feasibility. The 10 best proposals are selected to work with their academic mentors and with the *Break the Cycle* faculty to complete their projects. The students and their mentors are required to participate in monthly conference calls, during which the progress of each project is reviewed, additional perspectives are explored, and constructive guidance is provided. During these conference calls, the students and their mentors also have an opportunity to communicate and collaborate with their counterparts at other universities.

Since the inception of the Break the cycle program in 2004-2005, we have had 13 annual programs and worked with over 100 students representing 30 different university departments in 10 states in the United States (US), as well as students from countries in Latin America, Europe, and Africa. To date, we have had 10 monographs published in international journals and 10 books in a public health series. In 2012, we completed a survey of past students who rated their experience with *Break the Cycle* valuable, and many reported that they pursued careers relating to their *Break the Cycle* projects [10].

The program was started with the expectation that the projects would make a positive difference by improving the health and well-being of children, their families, and their

communities. It was also envisioned that the students would be inspired to pursue careers that focused on reducing health disparities and in becoming the leaders of the future. Furthermore, because each student has a mentor in the home university, we anticipated that the faculty mentors would add elements of the concept and literature on the subject into their curricula, and thereby promote further research and academic interest in this field (see box 1).

We also expected that the participating students would inspire peers in their academic, social and professional circles, and that the interdisciplinary nature of the program with participation of students at other universities around the world would be stimulating and inspiring (see box 2). The 2012 survey also showed that students derived significant benefit from all aspects of their participation in the process, which included the practical aspects of conducting a research project, experience in preparing and delivering a presentation and writing a manuscript. Each student gained knowledge about children's environmental health and environmental health disparities as well as being exposed to different perspectives from the other student projects. Many participants reported that their participation in the program influenced their career choice [10].

Box 1. Project guidelines

- University faculty identify students with an interest in this topic area and support the student in the selection of an idea for projects that explore environmental factors that adversely affect the health of children living in circumstances of social and economic disadvantage. Alternatively, students interested in a specific project can initiate the application process and identify mentors to work with them.
- The students submit their proposals which are reviewed by the *Break the Cycle* faculty. The process is competitive with only 10 projects being selected each year.
- During the project period, there are monthly conference calls with all students and mentors to monitor the progress of the projects, share ideas, and assure that the projects are consistent with the spirit of the *Break the Cycle* concept.
- At the end of the project period, the students present the results of their work at a conference.
- The students are then required to write papers on their projects, which are submitted for publication in an international journal as a monograph of the *Break the Cycle* projects. The papers are also published as chapters in a book.
- Funding for travel expenses within the United States and accommodation for the conference is provided for the student and faculty mentor. A modest stipend is provided to the students once they have completed the project and submitted their paper.
- The progress and careers of the participating students are tracked to evaluate the impact of their participation in the *Break the Cycle* program

Box 2. Desired outcomes

- To inspire students from a variety of academic disciplines to explore the relationship between adverse social, economic and environmental factors and the health, development and education of children and to creatively generate strategies to address the challenges
- To collaborate with an interdisciplinary team of academic leaders from variety of different universities and colleges to get a perspective on the broader issues of this topic area
- To encourage faculty at universities who participate in this program to promote academic interest and social awareness in children's environmental health disparities
- To cultivate future leaders among the students

BREAK THE CYCLE 13 PROJECTS

The papers in this publication represent the interdisciplinary array of creative work by students from universities in six states in the US who participated in the 13th Annual *Break the Cycle* program. The papers in this volume cover the lifespan from consideration of prenatal vulnerabilities of the fetus, supporting mothers in breastfeeding their newborn infants and reading to their children, exploration of the impact of maternal adverse childhood experiences on the infant and child development, considerations of diet, sleep, obesity and school engagement, looking at the impact of neighborhoods and natural disasters on the vulnerability of children. The following are brief reviews of the *Break the Cycle* 13 student projects:

Evaluating Fish-Consumption in Pregnancy: An Opportunity for Neurodevelopmental Health Promotion

Ivorie Stanley, MD, MPH from the University of Illinois in Chicago, looked at the question of fish consumption among pregnant women to determine risks of mercury toxicity for the fetus. Although her findings showed that very few of the women she studied in Chicago did consume fish, the question she raised and the discussion she generated were meaningful and thought-provoking. We have been concerned about mercury toxicity in fish since the dramatic episode in the 1950's when the Chisso chemical company in Japan dumped tons of mercury-containing toxic waste into the Minamata Bay in Japan resulting in almost 1,000 deaths and over 2,000 people were poisoned as a result of eating fish contaminated by the mercury in the bay, most significantly children and pregnant women, resulting in severe neurological consequences [11]. This episode sensitized us to the neurotoxic effects of mercury, particularly in children and pregnant women. Although this was a dramatic episode and alerted us to the risks of dumping toxic waste from factories into our rivers and streams, it also alerted us to the dangers of mercury toxicity in humans. Unfortunately, over time, there has been a contamination of many of our lakes, rivers and streams, and, in the US, this is readily recognized in the Great Lakes region where, during the great industrial age in the USA from the late 19th century well into the middle of the 20th century, industries lined the Saint Lawrence waterway and the burning of fossil fuels in industry sent mercury into the atmosphere which then precipitated into the river and lakes, was converted to methyl mercury by microorganisms and consumed by fish. As a result, today, most waterways and fish contain mercury. Different fish contain different levels of mercury, with the predators having the highest bioaccumulation. Consumption of contaminated fish, therefore, puts vulnerable populations at risk for mercury toxicity. The interesting challenge in this situation is that fish is a healthy food containing omega-3 fatty acids, that have been shown to be a positive factor in brain development. Furthermore, many populations, particularly those who live on the coast or on islands, are almost exclusively dependent on fish for nutrition especially for their protein [12]. This dilemma is addressed by having fish advisories generated by the EPA and other advisory and governmental bodies, that recommend which fish are safe for children and pregnant women and specify the quantities that are safe. Dr. Stanley may not have found what she was looking for in her study, but she certainly presents a thoughtful consideration of fish

consumption among different populations, socioeconomic as well as ethnic, and how to balance the concern about mercury with the importance of good nutrition.

Risk of Preeclampsia in Teen and Inexperienced Mothers in East and Central Harlem

Alexandrah Gichingiri, BS, from the Department of Environmental Medicine and Public Health, Icahn School of Medicine at Mount Sinai in New York, studied a group of pregnant teenagers at Little Sisters of the Assumption Family Health Service Maternal Outreach Program, a local charitable organization situated in East Harlem where the poverty rate is almost 50%. Although she was specifically looking at the clinical condition of preeclampsia in this population, she opened the discussion on the prevalence and demographics of teen pregnancies and the health consequences for the young women and their offspring [14]. Although teen pregnancies in the US are on the decline, the rate remains substantially higher than in other countries in the western world with significant disparities in the rates for different ethnic and racial groups, by socioeconomic status, and by state. Social determinants of teen pregnancies include poverty, low educational achievement, degraded neighborhoods with racial segregation, and dependence on welfare, especially children in foster care. Rates are also a third higher in rural versus urban populations and 4 times higher in some southern states compared to the northeastern states. One of the most powerful determinants of teen pregnancies is the cumulative effects of Adverse Childhood Experiences (ACE's), with more than 50% of young women with ACE's scores of 8 becoming pregnant as teenagers [15]. There is also a disproportionate level of health problems among pregnant teens which compounds their existing health risks, including nutritional disorders such as obesity, and cardiovascular disorders such as hypertension, which, in turn, is associated with preeclampsia. Furthermore, there are increased rates of adverse pregnancy outcomes with increased risks for premature and low birth weight infants with a higher infant mortality rate [14]. One of the more disturbing statistics of pregnancy outcomes (not necessarily for teens only) is maternal mortality in the US, which is more than double what it is in most of the western world, and the disparity within the US of a greater than 3 times pregnancy related death rate for black women compared to white women [16].

The resulting challenge is to improve the education of girls and young women, well before they are likely to become pregnant, and provide healthcare to all, with a special attention during pregnancy because of the risks to mother and baby.

Barriers and Promoters to Initiating and Sustaining Breastfeeding among African American Women

Danielle Dimacali, BS, from the Emory University Nell Hodgson Woodruff School of Nursing in Atlanta, Georgia explored the positive factors that were associated with breastfeeding among a group of African American mothers. Breastfeeding is the identifying characteristic of all mammals; after all, the term mammal was derived from the Latin word *mamma* which means breast [17]. Breast feeding is a critical part of the human condition.

This biological imperative is clearly associated with a positive outcome for the mother, the baby, the family, the community, and the species [18]. In premodern communities where the mother may not have had sufficient milk or was absent for reasons of tribal necessity or had died, another woman would have substituted as a 'wet nurse,' providing the necessary nutrients through surrogate breast feeding. From about 10,000 years ago, humans began domesticating and herding animals rather than hunting and gathering, and, in so doing, had access to animals with a ready supply of milk. So, if human mothers were not able to feed their babies for one reason or another, they could resort to milk from their domesticated animals, such as cows, sheep, goats, donkeys or even camels. They would probably have done this directly at first, before developing appropriately configured drinking vessels for their babies. The value of milk in infant nutrition could not have been missed by our ancestors in seeing the potentially fatal consequences of lack of milk. The word *Kwashiorkor* refers to infants and children who have protein deficiency malnutrition with characteristic physical appearances of swelling of limbs with edema, abdominal distention with skin, hair and teeth changes [19]. The origin of the word comes allegedly from Ghana in Africa and refers to the effects of the birth of a second child, when the mother stops breastfeeding the first child, often in the 2nd year of life. The first child may then be fed adequate calories from the staple starch of the area, but no protein from the milk. As a result of the lack of protein in the diet metabolism is disordered and many organ systems suffer, resulting in a characteristic appearance with loss of pigment in the skin and hair giving them a reddish coloration rather than the usual highly pigmented skin color of African people, with thin limbs and a protuberant abdomen and a sad countenance. If not corrected, this can lead to death, most commonly from susceptibility to an infection such as gastroenteritis (often from drinking contaminated water) or even measles (the children are often inadequately immunized).

Some form of dehydrated or partially dehydrated milk products have been present in past civilizations, but, after the industrial revolution, large scale production of dried milk was a positive development in assuring adequate infant nutrition and saving lives especially in difficult times, because it lasts longer than regular milk, could be transported great distances, and could be readily reconstituted with clean water. One of the major problems in developing countries, particularly in Africa, is the limited availability of clean water, resulting in reconstitution of the milk formula with contaminated water, introducing pathological bacteria which results in gastroenteritis and can be fatal, especially in undernourished children (see above). Another problem with reconstituted powdered milk is that it is costly, especially to poor mothers. In order to save they may put less powder and more water, to make the supply last longer, and, in so doing, reduce the protein intake for the children, which can also result in malnutrition.

With the development of powdered infant formulas and industrial production and marketing, the nutritional value of milk became more readily available and accessible, which improved infant nutrition in poor areas of the world but, in the process, resulted in the reduction in the prevalence of breast feeding. In the mid-20th Century, formula feeding was favored across socioeconomic boundaries [18]. However, as we came to appreciate the benefits of breastfeeding and the potentially negative health outcomes of exclusive formula feeding, there has been an increasing trend to breastfeeding. While the trend to breastfeeding has been positive, it has not been uniformly adopted in US society. For a variety of factors, low income minority women are less likely to breast feed [20]. In her exploration of the barriers to breastfeeding, Danielle Dimacali, examines the characteristics of African

American women who have successfully breastfed their infants, giving her insights into strategies that can help to encourage breastfeeding among groups of African American women who are less likely to breast feed, and improve the health and wellbeing of their offspring.

Maternal Childhood Adversity and Early Parenting: Implications for Infant Neurodevelopment

April L. Brown, MA, MPH, in the Department of Psychology at Emory University in Atlanta, Georgia explored the concept of the Cycle of Environmental Health Disparities in the context of children who grow up in poverty or in marginalized communities, and who are also more likely to be exposed to environmental hazards, and experience cumulative and prolonged stresses which can have long term impacts on their health, development, learning, behavior and general well-being. The recognition of this phenomenon has been codified in the concept of Adverse Childhood Experiences (ACEs) and is a major focus of public health efforts of the Centers for Disease Control and Prevention (CDC) [21]. The ACEs have a scoring system that is measured by the number of adverse experiences, on a scale from 1-10 (where 1 is the lowest score and 10 is the highest). The higher the score, the more predictive the adverse long-term outcome. Measured long term outcomes have revealed increases in health-related problems, such as diabetes and hypertension, learning disabilities and difficulties with focus and attention, behavior disorders with increased risks of substance abuse, violence and early death. As was stated in the paper on preeclampsia among teenagers in this volume, the greater the ACEs score, the more likely is a young teenager to become pregnant – with the likelihood increasing with increasing scores [15]. So, too, is there a likelihood that the greater the ACEs score, the greater the likelihood of consequences, but it should also be noted that even the lowest score in vulnerable children can have significant consequences [22], while even for relatively high scores, the phenomenon of resilience can result in a positive outcome particularly associated with high levels of social support and working with the parents [23, 24]. It is therefore, critical to identify the children early and provide appropriate interventions to assure a positive impact of growth and development. The CDC also promotes strategies to prevent ACEs and their effects (see Figure 2).



Figure 2. From the CDC about adverse childhood experiences [21].

In her project looking at the impact of maternal ACEs scores on the children, April Brown is in the early stage of her research and has just scratched the surface by looking at very young infants. In other studies on children of mothers who have high ACEs scores, the findings do reflect a correlation between maternal ACEs and children's development and behavior, as well as correlation the ACE score and likelihood of adverse outcome [25].

Young Minds, Young Readers: Dialogic Reading with Adolescent Mothers and Their Children

Diana Abarca, BS, University of Central Florida, Orlando, FL, focused on adolescent mothers who are living in poverty, dropping out of high school, unemployed, and at risk for mental health issues, which may compromise their parenting skills and leave them trapped with their children in the cycle of environmental health disparities. Her project looked at how to break the cycle by teaching the young mothers to read to their young children, expecting that the mothers would be empowered to learn and build their own self esteem at the same time as they encouraged their children to become familiar with books, with reading and with learning. This is expected to help with their language acquisition and increase the likelihood of academic success, which in turn, leads to improved employment opportunities and higher income when they grow up, thus breaking the intergenerational cycle of health disparities.

Unfortunately, as the timing of her project was short and with the challenge of recruitment, she was only able to work with 1 mother who had twin boys. Although she was not able to demonstrate an objective benefit with the two boys in such a short time, she was able to demonstrate that the young mother was able to learn how to read to her children.

There is, ample evidence that exposure of young children to books and reading has a positive impact on their language development and learning, with the promise of a brighter future for them academically by improving school readiness. One program that addresses this need among vulnerable children is called Reach Out and Read, which offers books to children from low income families and encourages reading in these young families [26, 27]. Reach Out and Read was started almost 30 years ago and has grown from its original site at the Boston Medical Center to thousands of sites around the US, reaching millions of children [28].

Another program initiated at the University of Chicago is the Thirty Million Words initiative, which encourages early use of language from birth by talking and singing to the infant [29]. In a recent Monthly Feature in the AAP journal *Pediatrics*, the title of which, *Talk, Read, Sing: Early Language Exposure As an Overlooked Social Determinant of Health* clearly links early exposure to language and language acquisition to developmental, academic and social success in life [30].

There is no question that improving a child's ability to read and encouraging a spirit of learning is the beginning of a promising academic experience in school, and with the improved education, improved opportunities for employment and a stable and secure income. This also promotes resilience in the children should they experience adverse events and stresses in their lives. Thus, early exposure to language and reading, can reverse the effects of poverty and other adverse childhood experiences and break the cycle of children's environmental health disparities.

Breaking the Cycle: Changing Sleep Habits to Decrease Obesity

Kristina Caffey, a student at the College of Nursing, University of South Alabama, in Mobile, Alabama, evaluated the sleep characteristics of children from a low-income urban area and the barriers these children have in developing healthy sleep behaviors. She worked with a team of mentors from the Nursing School and the School of Psychology to look at the relationship between sleep habits, nutrition and learning. What she found was that the ecological set of environmental factors, barriers and habits factors associated with poverty contributed to the adverse health outcomes. The adverse health outcomes she studied were those of obesity with its associated health impacts, school performance, which is impacted by the adverse personal experiences associated with poverty, the environmental factors associated with the built environment of the neighborhood, and the structural and educational realities of schools in the poor neighborhoods. All these factors contribute substantially and cumulatively to the cycle of environmental health disparities among children who grow up and live under these circumstances.

In this project, she connected with families through questionnaires and focus groups, obtaining information directly from the families primarily about sleep practices for their children. What she found were not unexpected barriers to sleep, i.e., electronic use by the children before bed, co-sleeping, and waking at night for a drink or snack, all of which resulted in reduced quantity and quality of sleep that affected daytime behavior, learning and physiological well-being. The environmental realities of poor households with limited space, often malfunctioning indoor climate control, ambient noise and, more often than not, parental stress leading to insecurity, all affect sleep patterns and result in the adverse developmental, behavioral, learning and health outcomes.

She also demonstrated that involvement with the families, in identifying potentially modifiable environmental and behavioral elements, could break the cycle and alter the negative trajectory into a more positive and healthier lifestyle. The lessons from this study include the importance of getting to know the families, learning about their specific patterns of behavior, around sleep in this case, and helping to guide and direct changes in behavior and practices that foster healthier patterns of behavior with consequent improvements in quality of life, health and function.

Study of Childhood Obesity in Neighborhoods Undergoing Gentrification

Brennan Rhodes-Bratton from Columbia University, Mailman School of Public Health, Department of Sociomedical Sciences in New York City, looked at the impacts of gentrification of poor neighborhoods on children's health, with a focus on nutrition and obesity. This topic is especially vexing because, in the historical context of urban living in the US, cities once thrived, but then with increases in wealth in the population and the explosion in automobile use, the more affluent and mobile populations moved to open spaces in suburbs. As the wealthier families moved into the suburbs, the poorer citizens moved into the cities. In the last decade of the 20th Century, large cities in the US were predominantly populated by poor people of color, with degraded and dilapidated housing and neighborhoods. In fact, the combination of poor maintenance of city infrastructure, with the low tax base that

could not provide enough resources to make a positive difference, resulted in the dramatic picture of urban blight. Poor schools provided poor education, with high rates of school failure, high drop-out rates, high unemployment, high rate of teenage pregnancies, and a dystopian picture with high rates of drug abuse and crime. With the changing social, economic, cultural and demographic forces that emerged in the late 20th and early 21st Centuries, urban renewal and revitalization became an emerging and expanding pattern across the country. With businesses and more highly paid workers moving back into the cities, buildings were renovated, neighborhoods were rehabilitated, and the tax base was increased to fuel the process of urban growth and development. As the picture began to look good for the cities, the new or returning residents, and for city governments, the plight of the low-income, low-resource, indigenous residents came under stress. If the residents could financially and culturally remain in the areas, they could see some benefits to the health and well-being of children from the neighborhoods in the process of gentrification [31]. However, for many, if not most, the financial and cultural stress would be too great, and, not only would they not benefit from the new riches, but they would suffer the loss of familiarity, of home, of community and of culture. As a result, they would have to move to other neighborhoods outside of the city, find affordable housing and maybe a new job, new schools for their children, new friends, and, try to rebuild a community. These stresses to families can result in adverse health outcomes particularly affecting mental health, and, in consequence, physical health as well [32].

In her project, Rhodes-Bratton chose to look at food and food options for families in the changing neighborhoods. Although there were more and healthier food options in the form of high-end supermarkets and restaurants, these were financially out of reach for the average poor resident of the neighborhood. At the same time, the familiar stores and foods were dwindling, leaving the heads of families with less affordable food options for their children. What she found was that, where a number of fast food options remained, there was no change in the children's BMI, however, in the areas where there was an increase in the number of healthy food options, the children had a significant decrease in BMI scores.

The conclusion of this study is that, while gentrification is good for cities, businesses and the people who work in them, and for a limited number of children of long-term residents, it is disruptive and stressful for the low-income, long-time residents of the areas, particularly those who become displaced. The importance of this realization is that there needs to be more planning in the process with mental health and community support services for the families who are displaced, and assistance with integration into their new neighborhoods and communities [32].

Relationship between Community Characteristics and School Engagement among U.S. Children, National Survey of Children's Health, 2011–2012

Breyanna M. Mikel, in the Department of Epidemiology, School of Public Health at Georgia State University in Atlanta, Georgia, explored the relationship between the built environment and the social and cultural context of neighborhoods and communities, with the concept of school engagement among children K-12. In this project, the usual characteristics of a poor neighborhood are presented as determinants of school engagement and school

performance among the children. The results demonstrate that there is indeed a correlation between the child's social, cultural and physical environment, and school performance. What also emerges is how small differences can have great impacts, which provides further proof of resilience, and the importance of identifying resilience and resilient factors in a child's life. Indeed, she reports that "children living in communities with at least one amenity in their neighborhood (i.e., recreation or community center, library, sidewalks) were more likely to have higher levels of school engagement."

We know that children who live in poor neighborhoods and go to poor schools tend to have more learning disabilities, experience school repetition and school failure, tend to drop out before graduation, and are less likely to be employed [33]. We know that graduation from high school is associated with a greater likelihood of going to college and of finding better jobs with a higher earning potential, enabling the individuals to live in better neighborhoods with better schools which provides better educational opportunities for their children. In this context, school engagement becomes an imperative for children, not only for the sake of school performance in the present, but for the cultivation of long-term intergenerational impacts in securing a future for the next generation, thus breaking the cycle of poverty through enhanced academic achievement.

This project makes the case for societal investment in education and, significantly for this vulnerable population, in schools in communities and in neighborhoods. For poor and vulnerable populations in the US, schools also provide a safety net in providing good nutrition for the children who suffer from food insecurity, counselling for the children who are having emotional difficulties at home, nursing services, and, in some situations, therapies and pediatric care for children with special health care needs, and for children who have learning and other related functional difficulties, there is speech therapy, physical therapy and occupational therapy. As James Heckman, the Nobel Laureate in Economics commented in his long term assessment of the benefits of early intervention for low income vulnerable preschool children in the Perry Preschool Project, "Our estimates of the overall rate of return hover in the range of 7% to 10%, and they are statistically significantly different from zero in most cases." That rate is quite substantial and better than can be realized in many other investments [34].

Schools also provide a forum for community engagement, as was demonstrated by another of our Break the Cycle students during the financial depression beginning around 2009, when families were suffering. The schools not only provided a place to feel welcome, but also to receive food and community support for families [35].

Invisible Threats: Legal Methods to Confront Airborne Hazards in the Home

Prathyusha Chenji, now at Emory University School of Law, did this project while she was at Georgia State University School of Law in Atlanta, Georgia. She looked at the impact of poor housing conditions on the health of children, with a focus on asthma. Recognizing that low income populations are more likely to live in older homes where there was a greater likelihood of asthma triggers which can aggravate asthma in children, she sought to develop guidelines for the families to advocate on behalf of their children. She also recognized that there might be hesitation on the part of families to challenge their landlords fearing retaliation

and possible eviction. In order to help the families secure the necessary modifications and remediations to their rental homes, she developed a ‘worksheet’ for parents to use as a guide to assess the presence of asthma triggers in the home. She also provided the families with information on their legal rights as renters, and offered recommendations for them on how to go about securing legal aid, if necessary, in order to make their case with the landlord. The relationship between poor housing conditions and children’s health has been a focus of Federal agencies like HUD (Housing and Urban Development) which developed the Healthy Homes Initiative in 1999 to protect children and their families from housing-related health and safety hazards [36]. A previous Break the Cycle student had looked at this initiative in relation to asthma reinforcing the importance of the comprehensive approach to addressing children’s asthma by developing a comprehensive approach to dealing with asthma triggers in the home [37].

Children’s Health and Safety Risks Posed by Irrigation Water in Northern Utah

Kristen R. Koci, BS, in the Department of Sociology, Social Work, and Anthropology, Utah State University, Logan, Utah looked at a unique situation to Northern Utah, where irrigation water runs through city streets and is used for residential purposes. She noted the potential risk to children’s health and safety, both in terms of the risks for drowning of young children as well as the risks of the possible chemical or bacterial contaminants from runoffs, with children in lower socioeconomic communities experiencing more exposure pathways and greater levels of vulnerability. Her project involved a survey of two groups of stakeholders, one of which were the families who had grown up with the irrigations ditches and had fond memories of playing in the ditches from their childhood, took it as a fact of life, and were not concerned in the least; the other group was represented by the scientific research community who expressed concern about the risks. What emerged, apart from the interesting dichotomy of response was that there was no data on the water quality and, without objective data, each group can claim that they are correct.

In general, water quality of runoff, which contributes to the water in the irrigation channels, is different in urban, suburban, and rural areas. In urban areas, the runoff is potentially more complex and toxic, depending on local industries. It can contain chemical compounds as well as coliform bacteria. In the rural areas, the contaminants are mainly from the pesticides and herbicides from agricultural applications. In suburban areas, the runoff can also include pesticides and herbicides from garden applications [38]. Thus, an assessment of water quality is a very important step in determining the relative safety or risk for children playing in those irrigation ditches.

Environmental Justice for Vulnerable Florida Children in Hurricane Aftermath

Manmit Singh, BS and Dylan Avery, from the Nell Hodgson Woodruff School of Nursing, at Emory University, in Atlanta, Georgia, performed a literature review to identify

environmental and socioeconomic factors that affect vulnerability and resilience of communities in the event of a hurricane, particularly in selected parts of South Florida. They found that, while environmental vulnerability is a reality in the entire state of Florida, socioeconomic vulnerability varies widely throughout the state. Interestingly, they found that the counties in Florida that are highly vulnerable according to the Social Vulnerability Index (SVI) were the inland counties with the greatest proportional population of children under the age of 18 years old. The realities of vulnerability to natural disasters is that the low resource communities are more vulnerable because of location. Furthermore, the families are less likely to have insurance or other resources to recoup their losses and may find themselves homeless. Images of Hurricane Katrina of 2005 showed how the poor African American families found themselves forced to take refuge in the Superdome for lack of other feasible alternatives. After the destruction of their property, many had to leave the state to find work and live elsewhere [39].

As the impact of climate changes result in increases in natural disasters like hurricanes, floods, snowstorms, droughts, wildfires, and other extreme weather phenomena, we are going to see the impact on society, the economy and the most vulnerable populations especially the children [40].

Social Media as a Tool for Breaking the Cycle of Children's Environmental Health Disparities

Talia Bernhard from the College of Arts and Sciences and Faith Bygrave from the Nell Hodgson School of Nursing, at Emory University in Atlanta, Georgia, raised our awareness of the current phenomenon of Social Media by presenting a case for the potential value of social media in promoting children's health and children's environmental health, to help to Break the Cycle of children's environmental health disparities. There is no question that social media, in all the diverse and often consuming forms, has been a force in our society for the good and for the not so good. Like all forces that we encounter, the question becomes how we harness it for positive effect on the health and well-being of our society, and how we control the negative and potentially destructive power that it has and can unleash.

These two students surveyed children's environmental health professionals, asking about social media habits, measures of success, challenges, and communication strategies. From the health disparities perspective, they asked about whether the respondents focused their efforts on vulnerable populations. Although many used a range of social media, a minority focused on vulnerable populations, and only a few exclusively. As this is a new and emerging field of endeavor with a significant potential impact, we are still in the early stages in our understanding and application of social media in promoting children's health, children's environmental health and children's environmental health disparities.

In a review of literature on social media interventions and promotion of health equity, a group in Canada found that social media interventions were effective in certain populations at risk for disadvantage, including youth, older adults, low socioeconomic populations and in rural communities [41]. They then created a list of highlights based on their findings:

- The use of social media interventions has been increasing in the field of public health as they can cross geographical and physical access barriers.
- Eleven systematic reviews found mixed effects of social media interventions on improving health outcomes and healthy behaviors.
- Some of the reviewed studies found benefits from social media interventions while others found no change or found that outcomes were worse than those from non-social media interventions.
- We know little about how the design and implementation features and the intensity and duration of interventions could improve health or whether they could increase negative behaviors, stigmatization, or exacerbation of health inequities.
- Many of the studies used social media platforms that were developed by the researchers. The effects of using existing social networks with commercial platforms, such as Facebook and Twitter, as part of social media health interventions are unknown.

This paper was published in 2016 using data from previous studies therefore was not quite up to date for 2019, but the gist is clear: there is value in harnessing social media for improving health communication. Because social media can reach vulnerable populations, it can serve to Break the Cycle of children's health disparities and promote greater health equity. This student project contributes to the accumulating experience with current active social media platforms and how they can be adapted for use in health education and health promotion especially for vulnerable population. We appreciate the glimpse that the two students have provided into harnessing the power of this new technology and its potential application to promoting the health and well-being of all children. However, we need to be highly sensitive and cognizant of the potential negative use and impact of social media and factor this awareness into all strategies to use social media on the public.

CONCLUSION

This publication of student projects from our 13th Annual *Break the Cycle* program reflects the diversity of perspectives on the expressions of environmental health disparities in our society and provides strategies that break the cycle. It is gratifying to see that the efforts of each student make a positive difference in our understanding of the health and well-being of children most impacted by adverse social, economic, and environmental factors.

In this collection, we recognize some familiar themes, such as adverse childhood experiences, and the impact of home, school and neighborhood, as well as other social, economic and environmental factors on the health and development and development of children. This year, however, we were brought into the common elements of our time, social media and the impact of climate change. If we are to ensure a safe and secure future for all children, we need to be cognizant of the factors that can affect their health, in all settings at all times. The social media opportunities and options need to be harnessed to positive use in health promotion. We need to harness technology to try to avert the escalation of natural disasters in light of climate change, by reducing greenhouse gases and by utilizing conservation and sustainability practices. In the process of helping our most vulnerable

citizens, we will be helping the entire population and secure a more promising future for generations to come. To this end, we are dedicating our next *Break the Cycle* symposium to exploring the impact of climate change and the rising prevalence and intensity of natural disasters on vulnerable populations.

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Chapter 54

BREAK THE CYCLE OF ENVIRONMENTAL DEGRADATION

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ABSTRACT

Humans have unique abilities among all other living creatures. They have the ability to move about in many different ways and in many different terrains. They have the power of making choices. They have the ability to think ahead and plan ahead. They have the ability to make use of objects in their environment to assist them in their quests. Collectively they have the ability and power to dominate and modify their environment and other living creatures in the environment in order to advance their causes. They have the ability and power to harness natural resources and energy and interact collectively to change the world they live in. They are able to see and assess the consequences of their actions and take action to make necessary changes on what they have found or have done. This collection of characteristics makes them powerful, formidable and dangerous. In the context of this exploration we will marvel at their achievements, celebrate their undeniably exceptional advances, and examine the destructive environmental consequences of their actions, some unanticipated and some ignored. In this commentary, we will look at a local microcosm that illustrates the consequences of environmental neglect and abuse and its inevitable impact on human health, and the subsequent realization and revitalization by collective community action. We will cover a brief history of human habitation on the planet and the associated environmental degradation, accompanied by what has been done to address the process, and recommend a constructive approach to breaking the cycle of environmental degradation toward the promise of a positive future for our planet in good ecological balance with health and well-being for generations to come.

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INTRODUCTION

This commentary was inspired by a symposium entitled ‘Envisioning community-based solutions to environmental health disparities’ held during the 13th Annual Break the Cycle of Children’s Environmental Health Disparities Conference in Atlanta, Georgia, in April 2018. The symposium focused on a waterway in northwest Atlanta called Proctor Creek. The Proctor Creek area was once a pristine site with clean, clear water, rich with natural flora and fauna. The creek had once been the source of food, recreation, and pride for the local community but, over time, through economic, social, cultural and political neglect, the community became impoverished, houses and neighborhoods fell into disrepair, and the creek became polluted with sewage runoff, bacteria, chemicals and debris to the extent that it was no longer a source of pride, but of shame.

After many years of tireless grass-roots, collective community effort and advocacy, positive change eventually came from many different social, economic and political trajectories. Urban flight reversed and was replaced by urban renewal, awareness of the impact of the natural and built environment grew, and collaboration among local residents, citizen’s advocacy groups, university schools of public health, the business community and political representatives proliferated. These collective forces came together to clean up the area and restore it to its former source of pleasure and pride [1]. Although this scenario is local to the Atlanta area, it is representative of similar scenarios and patterns that currently play out in many cities and towns in the United States (US) and around the world and provides a lesson on how to break the cycle of environmental degradation.

This paper will attempt to briefly review our human history of settlement on this planet, with our tendency for exploitation and abuse of our environment, and examine critical events in our recent past that have been transformative in breaking the cycle of environmental degradation to reclaim a clean and healthy environment for ourselves, for future generations and for the ecological balance of our planet.

PROCTOR CREEK

Proctor Creek is a waterway that is fed by many minor tributaries before it enters the Chattahoochee River, which then feeds into the Apalachicola River, a relatively short river formed by the confluence of the Chattahoochee and Flint rivers and flows from Florida into Apalachicola Bay in the Gulf of Mexico. The modern settlement of the Proctor Creek area was comprised predominantly of African American families in the early part of the 20th Century on the west side of the growing and bustling city of Atlanta. By mid-Century, the west side of Atlanta had evolved into a culturally rich African American community, home to the largest complex of historically black colleges and universities in the Southeast US. This area was also a major focal point in the Civil Rights Movement of the 1950s and 1960s with a lengthy list of important leaders who have called the watershed home, including WEB Dubois, Dr Martin Luther King, Jr, Maynard Jackson, and Julian Bond [2].

With the dramatic growth of the city of Atlanta in the last quarter of the 20th Century, associated with changing economics and demographics, infrastructural challenges in dealing with sources of water and sewage disposal had to keep pace with the growth. As has been the

case with so many human settlements, the use of natural waterways have been co-opted to serve the interests of the settlements, not only as a source of water for personal and collective consumption, but also for the disposal of wastes and, in the case of larger waterways, the transportation of goods. Proctor Creek, being a relatively small waterway, was not suited to transportation of cargo but was used in the disposal of sewage and other debris of human settlement. As the city of Atlanta grew, notably from the late 1970s, and more dramatically after the Olympic Games in the mid-1990s, so did the amount of waste that was channeled into the Creek, resulting in increasing pollution including human waste, particularly enterocolic pathogens. Although sewage treatment plants were developed, they had limited capacity, with the consequence that major storms often created overflow from the sewage systems into the combined drainage systems, and the contamination of the Creek continued and accumulated [3].

Over time, with ongoing changes in demographics associated with political, economic and environmental forces, Proctor Creek neighborhoods experienced advancing impoverishment. Progressive contamination of the waterways caused by neglect and abuse of the area, with increased illegal dumping of refuse into the waters of the Creek and its tributaries, worsened the environmental degradation. The accumulation of trash coupled with the bacterial contamination and pollution of the water contributed to the degradation of the neighborhoods and their communities. People who could leave did, while those who remained experienced increasing poverty with limited resources. As happens in many poor and unpoliced neighborhoods, the houses fell into disrepair to the point of becoming uninhabitable, with the void filled by the socially destructive combination of drugs, prostitution and crime. As a consequence, not only was the land and water polluted, but the built environment and the culture became a toxic mix of dystopian elements. Proctor Creek neighborhoods and communities became unhealthy and unsafe. Not only were the dwelling structures in disrepair, but the tax base was depleted, leading inevitably to the compromise of the institutions that support the growth and development of children such as schools and other cultural community centers. The resultant effect on the children was a critical undermining of their opportunities to learn, which compromised their opportunities for gainful employment in the future.

By 2010, the population in the area around Proctor Creek was greater than 13,000, over 80% of whom were African American. A Health Impact Assessment for County performed by the Region 4 of the US Environmental Protection Agency (EPA) revealed that the most common emergency room visits for adults were for mental and behavior disorders, asthma and assault, with the most common causes of death being hypertension, mental and behavior disorders and human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS). For children, emergency room visits were most often for unintentional injury [3].

As happens with low income, minority and often disenfranchised communities, there is limited social and political capital, so desires and attempts by the local communities to make changes and improve the situation through an appeal to local municipalities and government often go unheeded and even unanswered. As a result, not only is the situation perpetuated, but aggravated, resulting a spiral of physical degradation along with social and emotional despondence and despair, that perpetuates the cycle of environmental health disparities across generations [4].

Fortunately, human beings are endowed with innate qualities of resilience and determination to survive and to care for their young [5]. For Proctor Creek communities, this was manifest in local citizens coming together to advocate for positive change, for a cleaner and healthier living space. Over the course of years, advocacy groups grew in number, size and influence, and connected with universities and businesses to make significant progress in reaching relevant organizations and members of the Atlanta business community as well as local political representatives [1]. This collective action has resulted in a process of revitalization of the Proctor Creek watershed, along with other major gentrification projects in inner city Atlanta such as the Atlantic Station, an upscale business, residential and social complex, the largest urban Brownfield redevelopment program of that time, which was built on an abandoned factory, foundry and steel mill [6]; and, more recently, the Atlanta Beltline Project, a residential, business and recreational project, which was developed on an abandoned railroad track [7]. Both of these revitalization projects have been instrumental in bringing city residents of all ethnicities and socioeconomic strata together in common cause, and represent vibrant examples of breaking the cycle of environmental degradation in a local area, with lessons for tackling much of what remains to be done to restore a safe and healthy environment with benefits to all.



Figure 1. Ecosystems services – conceptual framework for a healthy and supportive environment [8].

The US Environmental Protection Agency (EPA) considers a healthy environment in the context of an overarching principle of Ecosystems Services, which refers to those benefits to health and well-being that humans receive from nature, including our food and water, security, and economy [8]. It requires that we remain conscious and aware of the links between our surrounding environment and our well-being when we are engaged in making decisions about develop community infrastructure or managing the land surrounding our communities (see figure 1).

HUMAN PRESENCE ON THE PLANET

Human beings, known as *Homo Sapiens*, the genus of animals with knowledge and wisdom, emerged onto the planet tens of thousands of years ago. While the exact date is not clear, it is relatively recent in the history of the earth and its other inhabitants. Over the course of human history, there are landmarks and milestones that create a compelling historical narrative. The domestication of animals and plants to serve human needs was one such milestone that, through the lens of extended time, was associated with changes that transformed the ways humans lived as individuals, families, communities and societies. The continued and growing opportunities for previously unimaginable creativity and industry, where advances in knowledge and the sharing of knowledge, ideas, and technological innovations, resulted in the remarkable improvements in living conditions for the people of the time with increasing likelihood for survival of the individual and the collective. In this meteoric rise to power and domination of this planet, the history of the species is littered with artifacts that document this journey through time.

The earliest times are recognized by the discoveries of stones and bones that had been fashioned as tools for the survival for groups of individuals, because, after all, the species lives and thrives in groups. The groups could be of different sizes, the smallest being those of families or clans, that would hunt and forage for food. The earliest artifacts in stone are those presumably used for hunting and processing of animals successfully caught in the hunt [9]. With the advent of agriculture around 10,000 years ago, the groups became larger and the impact on the environment became greater [10]. The debris of the larger groups became more plentiful and varied as the need for shelter, equipment for agriculture, and for domestication animals grew. The nature of an agricultural community is such that not all people are involved all the time in planning for or actively seeking food, resulting in free time for creativity and productivity, which further added to the number of objects produced in that society. Indeed, it was the production and proliferation of artifacts in these societies that have enabled archeologists and anthropologists to extrapolate how the societies might have looked, lived and functioned. One of the earliest examples of environmental degradation was a consequence of repeatedly farming on a particular plot of land, which results in depletion of nutrients in the soil, that lowers the yield and contributes to soil erosion with negative effects on the natural flora and fauna in the settled area [11]. It is likely that early farming communities became aware of this phenomenon, as reference to it appears in the Biblical texts where there is a directive to work the land for six years then let it rest for the 7th or Sabbatical year, promising that it will increase the yield [12, 13].

The critical human need for water for personal consumption as well as for agriculture dictated that the early societies necessarily settled near sources of water, such as rivers, streams, or lakes. Two obvious examples in western history are the civilizations of Mesopotamia, which settled and flourished between the Tigris and Euphrates rivers, and in Egypt where the Nile provided water for agriculture, for human consumption, for transportation to support the society's physical and economic needs, and to serve as a domain for deities for society's spiritual needs. Bodies of water, particularly those that flow, also served in the convenient disposal of waste, inevitably resulting in the pollution and degradation of the water source with the risks of bacterial contamination. We know today from societies and communities living near water sources into which waste is disposed, that infectious diseases are a major health hazard, and that the most vulnerable are infants and young children who succumb to diarrhea, with consequent dehydration which is a major contributor to death, especially in low income developing countries in Africa and Asia to this day [14, 15].

In early agricultural times, communities were relatively small by today's standards, so the degrees of pollution and contamination may have been at a relatively modest scale. However, by the time of the Roman civilization in the western hemisphere approximately 2,000 years ago, city states had become quite large and sophisticated in the spheres of administration, engineering, architecture, politics and warfare, with the result that they were able to support larger populations. The city of Rome was built by the river Tiber, which provided the water and accepted the waste of the Roman society. Predictably, when the Roman population grew, more water was required, and more waste generated, which was channeled to the Tiber. As a result, the Tiber became dangerously polluted with a high concentration of bacteria and other toxins associated with the waste of that society in those days [10]. In order to satisfy the water needs of the people of Rome, engineers created aqueducts to bring clean water from the north to the city which became available to the population through the many fountains for which Rome is famous. The Romans, through their engineering ingenuity, not only channeled water from sources at higher elevations through a system of aqueducts, but developed a pipe system to carry the water to the fountains for domestic use for drinking as well as in their famous baths. They also developed toilets and sewage draining systems, which emptied into the rivers and the ocean. Roman pipes were constructed primarily from lead [16], which is a potent neurotoxin, particularly for children. So, not only would lead be found in the water for drinking and other domestic uses, but lead would also accumulate in the waste water that went into the Tiber. In addition, the pipes needed to be manufactured, which required fire and smelting. Lead fumes would inevitably be released into the air, eventually settling to the ground and found in the soil and sediment in the rivers. Furthermore, lead vapor and particulates were carried by winds far from the smelting source, to be found 2,000 years later in the analysis of a core of ice extracted from the subarctic ice cap in Greenland [17]. To this day, despite the banning of lead from gasoline and paint, it remains an environmental hazard as a result of the legacy of using lead pipes, recently creating a crisis involving lead-contaminated drinking water from the Flint river in Michigan [18].

Interestingly, the fall of the Roman Empire in 476 CE coincided with the ice core becoming relatively clean again, but not for too long. By the 16th century, the ice core reveals that the air on earth once again became contaminated and polluted with lead and other metals. That occurred when the Spanish Conquistadors defeated and subjugated the native peoples of South America and began to mine and extract silver and gold on a large scale. Their use of

large fires in smelting, released the fumes of metal into the South American air that also found its way into the ice caps hundreds of miles away in the Andes [19]. These examples of the Roman and the South American mining and metallurgic practices provide evidence that local pollution is not confined to local areas, but can be wide-spread, particularly where air and water are contaminated.

Another example of contamination of the air came from the large-scale domestication of livestock, presumably to feed the growing affluent populations with meat and milk and its products, such as cheese. Herding of domestic animals probably began around a similar time to the development of agriculture as a way of life and a way of supporting larger groups of people. Records on the condition of polar ice caps document a dramatic increase in the presence of methane gas around 2,000 years ago [20]. This increase was associated with the expansion in size of societies during the Roman Period, which coincided with growth in Chinese civilizations at the same time on the other side of the world. The increase in the presence of methane is considered to be a result of the emission of gases by the domestic livestock [21]. This period of high methane production subsided somewhat as the civilizations of the time fell to less organized groups. It rose again when greater degrees of social order were re-established during the middle ages and progressively through modern times as the growth in size of settled communities required more food. This necessitated the development of more agricultural lands and more livestock to feed the people, which in turn, resulted in the release of more methane gas. While low ambient levels of the gas may not play an appreciable role in modifying the climate, the larger amounts and concentrations in the air that have accumulated over the past half century have had a substantial and escalating effect on our climate as one of the ‘greenhouse gases’ [22].

INDUSTRIAL REVOLUTION

For the early centuries of writing, accessibility of reading matter was confined to the elite and educated. This changed dramatically with the invention of the printing press, which made written material readily available and accessible to the ordinary citizen in intelligible common vernacular, resulting in a burst of creative and cumulative advances in knowledge and technology. This coincided with the beginning of science and scientific experimentation that was ignited after the renaissance in Western society following the oppressive middle ages. The invention of machines and the establishment of factories in the late 18th and early 19th Centuries across Europe gave rise to the industrial revolution, which changed the course of human history.

In England, the plentiful presence of coal gave fuel to the fires of industry which was characterized by productivity and prosperity. The ideas, inventions and practices generated at that time were shared between countries and cultures to bring similar success and wealth to those countries. But along with the dramatic changes that brought success, there were unanticipated social, economic and environmental changes that were no less dramatic. The large-scale transformation of the society from being primarily agricultural to having a strong industrial base resulted in the movement of people from the rural areas into the cities where there were promising economic opportunities. This mass migration disrupted centuries of culture, community and socioeconomic balance to create a society with much wealth as well

as much poverty now concentrated in the cities, such as London, as captured so effectively in the novels by Charles Dickens.

At an environmental level, the burning of coal created significant air pollution which caused rampant respiratory problems, particularly among the poorer citizens who lived in the middle of this smoky toxic mix of pollution and poverty. The consequences of air pollution on health was noted relatively early in the process of industrialization, particularly in Great Britain where laws were progressively developed from as early as 13th Century when the use of coal in London was prohibited as being “prejudicial to health”, but really took off in the mid-19th Century to address the problem of coal burning and pollution [23]. However, it took an environmental disaster in London in December 1952, when 4,000 people died as a result of smog trapped in a thermal inversion, to bring about the United Kingdom’s (UK) Clean Air Act in 1956 [10, 23]. The phenomenon of the industrial revolution with its advances in technology, transportation and mass manufacturing as well as its unintended negative consequences, was not confined to the UK or Europe but was also advancing significantly in the US as well. On October 26, 1948 in the small industrial town of Donora, Pennsylvania, a weather anomaly in the form of a thick fog trapped malodorous toxic waste emissions from the town’s zinc smelting plant and stayed on the ground for five days [10]. Twenty people died and 7,000 were hospitalized with respiratory problems. The Donora disaster brought air pollution into focus in the United States, and paved the way for the Clean Air Act, established in 1970, and then amended in 1977 and 1990 [24]. One of the goals of the Clean Air Act was to address the public health and welfare risks posed by certain widespread air pollutants by setting pollutant standards coupled with directing the states to develop implementation plans, applicable to controlling industrial sources of pollution, in order to achieve these standards [25]. The pollution and health related problems as a result of industrialization and the use of fossil fuels are by no means over. Air pollution dramas continue to occur around the world, particularly in low- and middle-income countries, and in rapidly industrialising countries resulting in significant morbidity and mortality requiring urgent attention [26]. Air pollution from industrial sources consisting of gases and particulates not only leads to serious morbidity and mortality due to acute and chronic respiratory diseases as well as other disorders in exposed populations including an impact on reproductive health [27], but also contributes significantly to greenhouse gases and broader environmental consequences manifesting in climate change [28].

Smoke from coal-fired power plants also releases sulfur dioxide and nitrogen oxides into the air, which mixes with water and results in acid rain [29]. Corrosive and deadly to plants and trees, acid rain falls and drains into rivers, streams and lakes where it accumulates, polluting the water and altering the ecology by damaging the flora and fauna and rendering the water undrinkable in some areas. Furthermore, toxic by-products of coal burning, including mercury, are precipitated by rain and drain into waterways where, through biological transformation, the mercury enters the food chain and is consumed by fish where it bioaccumulates. Subsequent human consumption of mercury-infected fish can be toxic, especially to children and pregnant women, and can result in significant neurological damage [30]. The EPA regularly issues fish advisories that recommend which fish are to be avoided and which are safer to eat [31].

The relationship between the presence of mercury in fish and neurological damage of children became clear in the mid-1950s when an epidemic of children with severe neurological disorders was being seen in the clinics of the Chisso Corporation in Minamata

Bay, Japan. The disorders were eventually linked to the consumption of fish from the Minamata Bay, which were heavily contaminated with mercury. The mercury found in the fish was a result of the discharge of tons of mercury-containing waste into the Minamata Bay by the Chisso Chemical Corporation. There were an estimated 900 deaths attributed to the mercury poisoning and over 2,000 people who directly suffered from mercury poisoning [32]. This awareness has led to international efforts to reduce mercury levels in our environment through the Minamata Convention on Mercury [33].

This scenario has played out in the Great Lakes region of the US, which contains about one-fifth of the world's fresh surface water supply and nine-tenths of the US supply. Because the Lakes are part of a chain on the St. Lawrence waterway situated between the US and Canada feeding into the Atlantic Ocean, it has been ideal for shipping and transportation. For these reasons many factories and industries were established along the banks of the river and lakes so that the products of industry could be readily loaded onto large ocean-going vessels and shipped to harbors anywhere in the world. These industries discharged large quantities of toxic waste into the rivers and Great Lakes, creating substantial pollution, with the result that swimming and fishing in the rivers and lakes were prohibited [34]. The extent of pollution reached epic proportions in Lake Erie, the fourth-largest of the Great Lakes and the eleventh-largest globally if measured in terms of surface area. Lake Erie seemed to become more contaminated than the other Lakes, in part because of the location of industries along its shores, but also because the Lake is shallow and consequently less resilient. In addition to heavy contamination of Lake Erie, the Cuyahoga River, that runs through Cleveland, Ohio on the banks of Lake Erie, became so contaminated with a mix of pollutants, that it caught fire, presumably because of the oil slick on the surface of the river with other toxic chemicals and flammable debris from indiscriminate dumping of waste from steel factories, sewer disposals and larger scale littering saturating the river, ignited by a passing train that sent sparks into the oil-soaked river [35]. The Cuyahoga river did not just catch fire and burn once, it happened 13 times, the last time was in 1969. Although the fire of 1969 was not the most destructive or costly, for a variety of reasons, it was of high profile and, as a result, ultimately led to the creation of the EPA and passage of the Clean Water Act in 1972 [36, 37]. This Act established the basic structure for regulating pollutant discharges into the waters of the US and gave the EPA authority to implement pollution control programs such as setting wastewater standards for industry and maintaining existing requirements to set water quality standards for all contaminants in surface waters [38].

CHEMICAL REVOLUTION

During World War II (1939-1945), there was a compelling stimulus to science in the development of weapons of war and destruction on a diabolically grand scale. Each side in the conflict developed new technologies to gain military advantage in the seemingly endless battles that raged around the world. Innovations in machinery, aviation, metallurgy, explosives, chemicals and ultimately nuclear energy surged, and with these efforts came newer technologies that, after the end of the war, were turned to civilian commercial use and function in the new peacetime societies. Rapid development of the chemical industry led to newer chemicals and mass production to meet the needs of the recovering and fast-growing

post-war societies. All this activity helped to fuel the economy and bring increasing standards of living to many parts of the world, especially industrialized countries, while other, poorer parts of the world continued to suffer from societal disruption, ongoing conflicts, droughts, famines and exploitation, particularly for natural resources to feed the industrial needs.

One such chemical in this revolution was dichlorodiphenyltrichloroethane (DDT), which was developed to kill insects that plagued the crops of the farming industries [39]. This new pesticide was very effective and became widely distributed and used on a mass scale, being sprayed on large agricultural areas, often by airplane with ‘crop dusters.’ It was also used in suburban areas to promote greener lawns and, significantly in large parts of the world where insect borne diseases, like malaria, were endemic [40]. Therefore, not only did DDT help to increase agricultural yield but dramatically reduced the morbidity and mortality from malaria for people living in heavily insect-infested areas, particularly in the continents of Africa, Asia and Latin America. Unfortunately, the mass production and indiscriminate and injudicious use of DDT (and other chemicals), with the widespread dumping of the waste byproduct of chemical production, led to the chemicals leaching into the soil and waterways where they flowed into the rivers and streams and became part of the food cycle, having unintended consequences on the health of flora and fauna, from insects to birds, fish, amphibians, mammals and humans [39].

In 1962, Rachel Carson, who was an environmental scientist, wrote the book “*Silent Spring*”, an exposé condemning the indiscriminate use of long-lasting pesticides in general, and DDT in particular [41]. Her carefully researched material and its masterful presentation were the driving force behind the emerging environmental movement in the US and around the world. It is believed that many pollution control laws were influenced by “*Silent Spring*”. The use of DDT in many nations was subsequently banned. Globally, the use of DDT is limited and currently approved only for control of insect-borne diseases such as malaria, while safer alternatives are being researched. Despite the banning of DDT in the US, there is, however, a report that birds are dying in the area where the chemical company that had manufactured the pesticide was located in Michigan, presumably from residual DDT in the soil [42].

The widespread use of insecticides on crops has also had the unexpected and untoward effect of indiscriminately killing other insects that are beneficial to agriculture, particularly bees and other pollinators. The potential loss of this group of insects could have a dramatic impact on food production. The cause of the phenomenon of dramatic losses of bee populations, known as Colony Collapse Disorder, is, as yet, unclear and, according to the EPA, not necessarily exclusively the result of poisoning with pesticides [43], that climate change and other factors may be playing a significant role as well [44].

The story of DDT plays out in a similar pattern for tens of thousands of different chemicals that have been manufactured over the years, many of which have been demonstrated to be toxic to animals and humans, and tend to remain in the soil, water or even the air, long after manufacture has ceased. Part of the problem is that only a small percentage of the thousands of chemicals has been tested for safety, hopefully more will be tested in the future as a result of a chemical safety act which was passed in 2016 [45]. These chemical compounds are referred to as Persistent Organic Pollutants (POPs) because they are not readily biodegradable and can bioaccumulate in ecosystems, particularly in the food chain. POPs can be toxic to humans leading to increased cancer risk, reproductive disorders, alteration of the immune system, neurodevelopmental and neurobehavioral disorders,

endocrine disruption, genotoxicity and increased birth defects [46]. Just as with DDT, the POPs are of international concern as the chemicals are distributed globally. This challenge was addressed in the Stockholm Convention of 2001, the goal of which is ‘to protect human health and the environment from POPs [47].

Another distinct benefit to humans of the chemical revolution has been the discovery of increasingly effective medications in the treatment of human and animal diseases. This has been particularly effective at a global scale in the development of vaccines as protection against infectious diseases and the use of antibiotics in the treatment of infectious diseases. At the same time as the proliferation of increasingly potent antibiotics has been beneficial in treating the most recalcitrant infectious agents, widespread, often indiscriminate and, at times, injudicious uses of antibiotics by prescribers, has led to increasing resistance to existing antibiotics among bacteria and other microorganisms. The current challenge in modern hospitals is dealing with drug resistant bacteria, so-called ‘multi drug resistant organisms’ (MDRO), most notably the methicillin resistant staphylococcus aureus (MRSA) [48].

Antibiotics are also used in mass quantities in livestock farming to reduce risk of infection and promote healthier growth among the animals. This industrial-scale use of antibiotics in animals and widespread use of chemicals in agriculture, used to enhance human food supply, has played a part in modifying the human microbiome [49]. Connections are now being made between microbiota dysbiosis and a variety of different diseases such as rheumatoid arthritis, inflammatory bowel disease, type 1 diabetes, atopy, and obesity [50]. Over time, there are likely to be more conditions identified that are linked to the disturbance of the human microbiome.

Among the most useful yet concerning products of the chemical revolution are plastics [51]. The term “plastic” is derived from the Greek word “plastikos”, meaning fit for molding. It is an apt term because the products of the chemical process involving polymerization of basic carbon-based material are multiple in form and function. Plastics are used expansively in items in everyday use, from clothing to utensils to components of medical equipment, machinery and building materials, even spaceships. Indeed, our modern society is wedded to the use of plastics and plastic products. The problems for the environment come from several different levels of manufacture, use and after-use. In the manufacture, there are releases of harmful chemical compounds into the air. After-use and disposal of plastics, however, have created an environmental catastrophe. Because they are not biodegradable, they remain in our environment unchanged as pollutants in their original forms, as microplastics or larger pieces, such as plastic bottles and grocery bags. Although there is some recycling, most of used plastic products are found in waste sites like trash dumps, where they may become part of landfill, slowly degrading over millennia, or washed into waterways and into the oceans [52]. Each year, an estimated 18 billion pounds of plastic waste enters the world’s oceans from coastal regions where they can be ingested by small and large sea creatures endangering their lives and killing individual animals, as well as threatening species [53]. There is an estimated 100 million tons of plastic debris in our oceans at present, 80-90% of which has come from land-based sources which could have been recycled [54]. The use and disposal of plastic material is one of the challenges of our times. It is critical that we reduce consumption of single-use plastic objects; which is an appeal to consumers and manufactures to restrict the use of plastics, and for policy makers to pass laws regulate the use of certain plastics as well as on the need to recycle. The bigger challenge is the cleanup and removal of plastic debris

particularly from shorelines [55] and of the massive floating islands of plastic in the world's oceans [56].

Apart from the global challenge of plastic pollution, there is a real threat to human health, particularly for children who are more vulnerable because their organ systems are developing, especially the brain, endocrine and immune systems [57]. Concerns have long been documented and a list of specific hazardous chemicals associated with production of plastics is growing [58].

WASTE DISPOSAL

The impact of gravity and the relatively porous nature of the earth's soil results in accumulation of chemicals and substances in the soil and, with rains, they are likely to seep into the water table beneath the surface and into the rivers and streams. When the amount of chemical pollutant is great, the potential saturation of the soil can be correspondingly great and last for a long time, posing significant risks to life for people and animals. A notable dramatic example of this scenario took place at Love Canal in New York in the late 1970s, which has been described as one of the "most appalling environmental tragedies in American history" [59, 60]. In the early part of the 20th Century, William T Love imagined a model community in New York, on the edge of Niagara Falls and dug a canal to supply water power to what he envisioned would be a combination of industrial and residential areas in the community. Unfortunately, his dream was not fulfilled, and the empty canal was then filled with approximately 21,000 tons of toxic chemical waste from the Hooker Chemical Company. The city of Niagara Falls then built houses and an elementary school on the site. Over the years, the underground containers filled with of chemical waste corroded and, in 1977, after record rainfall, chemicals leaked into the soil. Dissolved chemicals leached into people's homes, backyards, and playgrounds, resulting in serious adverse health effects in the community, with high rates of birth defects and miscarriages [59].

As a result of this tragedy, the US Congress enacted the Comprehensive Environmental Response, Compensation and Liability Act to address toxic waste dumps [61]. This became known as the Superfund Program which is designed to protect human health and the environment by cleaning up polluted sites, make responsible parties pay for cleanup work, involve communities in the Superfund process, and return the Superfund sites to productive use [62]. In addition, in 1995, the EPA launched the Brownfields program "to empower states, communities, and other stakeholders in economic redevelopment to work together in a timely manner to prevent, assess, safely clean up, and sustainably reuse" land which may be complicated by the presence or potential presence of a hazardous substance, pollutant, or contaminant [63]. Examples of the Brownfields programs were provided earlier in the discussion on the revitalization of the city of Atlanta with the Atlantic Station and Beltline projects [6, 7]. Of note is that as part of the decision criterion for the Atlanta Beltline Brownfield redevelopment project, a health-impact assessment was conducted to look at how the proposed changes in access and equity, environmental quality, safety, social capital, and physical activity would maximize health benefits and reduce negative effects [64]. The findings were ultimately incorporated into the design to fulfill the EPA Ecosystems Services model (Figure 1) [8].

The disposal of waste is not necessarily confined to a neighboring location or regional site. Because of the large-scale generation of toxic waste by industrialized countries, it had become a practice to transport waste from the high income industrial countries to low income developing countries adding to their toxic burdens [65]. Although historically, there has been relatively limited regulation on this transaction, the EPA notes that several international agreements address transboundary transportations of hazardous waste including the Basel Convention [66], the Organization for Economic Cooperation and Development (OECD) Council Decision, and local and regional agreements such as exist between the United States and Canada, Mexico, Costa Rica, Malaysia, and the Philippines [67].

NUCLEAR AGE

In addition to the proliferation of chemical production during and after World War II, there was the discovery that the phenomenon of nuclear fission could be applied to and used in weapons of mass destruction, far greater than had been previously imagined. The testing of these devices took place in the desert in the Southwest US, on tropical islands in the Pacific Ocean and in the atmosphere, resulting in such powerful explosions that it surprised and shocked even the scientists charged with developing them [68]. Neither did scientists predict the destructive impact of the radiation released from these atomic devices on plant and animal life far from the site of the explosion. At test locations in the Pacific, not only was there total destruction of ecology of the islands, but the inhabitants of the islands were subjected to dangerous levels of radiation, and they remain displaced and disenfranchised to this day as they continue to suffer adverse health consequences [68, 69]. The use of the atomic bomb by the US during the war resulted in the almost total destruction of the Japanese cities of Hiroshima and Nagasaki and the immediate death of over 200,000 citizens near the epicenters of the explosions, as well as the deaths of those within range from acute radiation sickness. Those further away from the epicenter suffered long-term adverse health consequences [70].

The adoption of the nuclear option in war then became part of the weapons manufacture and proliferation in the US and in the Union of Soviet Socialist Republics (USSR), or the Soviet Union, during the ‘Cold War’. These two so-called Super Powers accumulated nuclear stockpiles for more than four decades following the end of World War II, which posed an existential threat to human survival. The threat of mutual annihilation, so-called ‘Mutually Assured Destruction’, or the appropriate acronym MAD, was a term attributed to John Von Neuman [71], one of the prominent scientists of the time and part of the team that developed the hydrogen bomb. This insanity came to an end with the mutually agreed limitations in use of nuclear weapons, starting with the Strategic Arms Limitations Treaties (SALT) between the leaders to the US and USSR [72]. The United Nations Office for Disarmament Affairs enacted a number of treaties progressively addressing the control of nuclear weapons, including the Treaty on the Non-Proliferation of Nuclear Weapons in 1968 and, most recently, the Treaty on the Prohibition of Nuclear Weapons in 2017 to prevent destruction of life and the environment [72, 73].

After the dramatic use of the Atomic Bomb and its consequences, attention was turned to peaceful use of nuclear energy in the generation of electricity and nuclear power plants were developed in the 1950s by both the USSR and the US [74]. Once hailed as a safe

source of energy, human exploration of nuclear power has come with substantial and dramatic risk. In April 26, 1986, a sudden surge of power during a reactor systems test destroyed Unit 4 of the nuclear power station at Chernobyl, Ukraine, in the former Soviet Union, releasing massive amounts of radioactive material into the environment [75]. The consequent mortality and morbidity of the disaster resulted in the deaths of 28 workers in the first four months with another 106 workers received high enough doses to cause acute radiation sickness. In the immediate aftermath of the disaster many children in the area drank milk contaminated with radioactive iodine, which resulted in a high rate of thyroid cancers among the children among other long term adverse health effects on the population, however, it was the long-term psycho-social impacts on residents and evacuees from the disaster that has been the greatest realization with findings of higher rates of depression, alcoholism and anxiety, with negative self-assessments of health, as well as unexplained physical symptoms [76].

There have been other nuclear accidents of a similar nature, such as the Three Mile Island commercial nuclear power plant partial meltdown in 1979 in the US [77], and, in 2011, following a massive earthquake and tsunami affecting Japan, the Fukushima Nuclear Reactor was damaged resulting in release of radioactive material [78]. Neither of these accidents had the same consequences as the Chernobyl disaster, but they certainly raised alarm and concern of the risks of nuclear power plants.

Overall, the resultant increase in atmospheric radiation and radioactive isotopes from all sources has the potential for adverse health outcomes, especially for children [79]. Furthermore, the disposal of hazardous radioactive waste remains a grave concern in avoiding human exposure and reducing the likelihood of environmental damage especially to flora and fauna. There are very clear criteria for how the waste is stored, depending on the half-life of the particular radioactive material and the levels of waste being of low, intermediate or high, which will determine how and where the waste is stored. Although the criteria are accepted globally, each country is responsible for its own details of management [80], the potential risk remains.

SOIL DEGRADATION

Soil degradation of the land likely began in early agricultural times when repeated farming of the same plot of land resulted in degradation of the quality of the soil. As mentioned above, this phenomenon was recognized in biblical writings, with the requirement to work a particular field for a limited number of years then allowing the land to replenish its nutrients for year before resuming farming [12, 13]. There is speculation that the Akkadian Empire which ruled the region between the Tigris and Euphrates rivers four millennia ago, may have collapsed as a result of soil exhaustion and desertification, the process of making a desert of previously fertile soil [81]. Soil degradation and desertification is of grave concern in sub-Saharan Africa, as it seriously depresses food production and, along with other dramatic unpredictable climate events, like droughts and floods, increases the likelihood of food insecurity and famine [82]. Famine can lead to restive populations and large-scale migration to find food and work, which can destabilize not only the local and neighboring communities, but beyond country borders as famine-affected refugees [83]. In recent years, wars, drought and famine have caused refugee migration from Africa and the Middle East to

Europe, which has dramatically altered political and social dynamics within and between countries, and appears likely to play out again as the impact of climate change will continue to affect weather patterns and hence the quality of the soil which affects agriculture and food production [84].

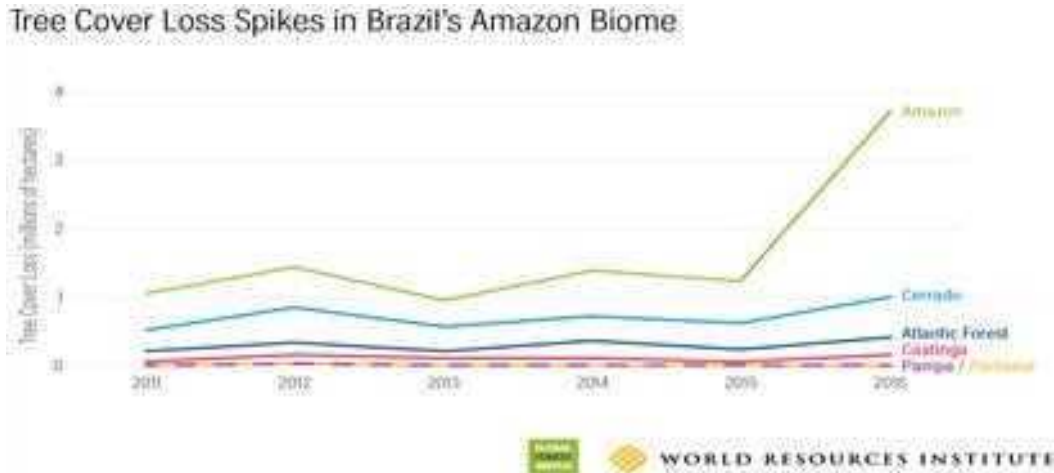


Figure 2. Global tree cover loss rose 51 percent in 2016 [85].

The other major impact on the quality of soil by human activity is the process of deforestation which has dramatically increased in pace and magnitude (see Figure 2) [85]. The consequences of deforestation, particularly in the large rain forests of Brazil, and equatorial Africa, not only results in degradation of the soil causing erosion but increases the risk of desertification [86]. As an example, natural forests in Indonesia have been destroyed by burning, for mining and natural resources as well as for monoculture of palm oil groves for the yield of the fruit [87]. This large-scale deforestation and widespread destruction of critical vegetation in our ecological balance has drastically reduced the natural source of carbon dioxide consumption and oxygen generation resulting in an increase in atmospheric carbon dioxide which is a 'greenhouse gas' and major contributor to climate change. In addition, as a result of the disruption of the local ecology, there is an increased risk for floods, mudslides and forest fires which further aggravate the situation [88]. The changes in natural forests especially rain forests are sadly also resulting in a reduction in biodiversity [89].

CLIMATE CHANGE

The rather narrow range of atmospheric temperatures on Earth has resulted in the proliferation of plant and animal life in the waters of the rivers, lakes and oceans, as well as on the land and in the air. For all life on this planet there is a temperature range from summer to winter and day to night for comfortable survival and maintenance of the Earth's homeostatic and current ecological character.

Over the course of the past two millennia, but particularly in the past 150 years, and rapidly accelerating in the past 70 years, human activity has progressively and cumulatively changed the climate on earth by the burning of coal and other fossil fuels, particularly in

industry, by the emissions of exhaust gases from the consumption of gasoline as a result of the increasing number of motor vehicles, by the emission of methane gas from livestock, and by deforestation. At present there is overwhelming evidence that we are experiencing dramatic climate change associated with global warming that is distinctly related to human activity [90].

According to NASA's Goddard Institute for Space Studies (GISS), the average global temperature on Earth has increased by about 0.8° Celsius (1.4° Fahrenheit) since 1880. Two-thirds of the warming has occurred since 1975, at a rate of roughly 0.15-0.20°C per decade see Figure 3 [91].

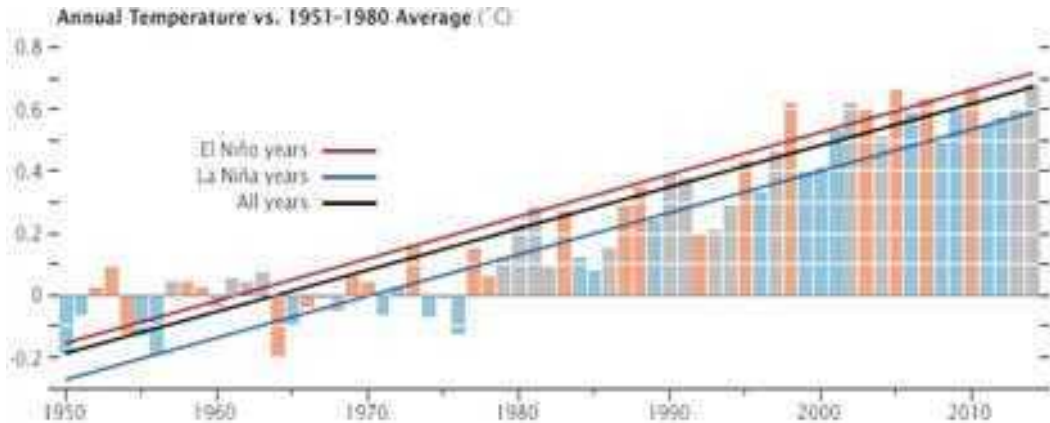


Figure 3. Annual temperature from 1951-present vs average between 1951-1980 [91].

As the world population of humans increases exponentially, there is a greater impact on the earth, with the result that the land, waters and atmosphere are becoming attenuated, and the natural flora and fauna of the Earth's biosphere are increasingly threatened. At the same time, there is a growing need to assure adequate food production and a critical need to feed the increasing number of people in the world. This is a compelling reason to take immediate action to reverse current trends in order to secure a more settled ecological homeostasis.

Another consequence of climate change and warming of the planet, is a dramatic change in the occurrence, frequency and intensity of extreme weather phenomena, such as heat waves, droughts, hurricanes, floods, snowstorms, and wildfires [92]. Not only do these disasters cause destruction and devastation to the built environment, but the after-effects on the natural and built environment, with disruption of communities, all come at a high financial toll.

The health impacts of the extreme weather events can result in immediate deaths or serious physical injuries or illnesses and disabilities that can appreciably reduce functional well-being and life expectancy, as well as have an impact on mental health of individuals, families and communities [93]. Significantly, the progressive changes wrought by the rising global temperatures affect the ecological and ecosystem balance manifesting in changes in ambient temperature and humidity, air quality, water quality, and agricultural conditions that have implications on food production and food security, as well as alter the insect and microbial populations resulting in increases in human diseases and mental health consequences (see figure 4).



Figure 4. Climate change and health [93].

These health impacts fall most heavily on vulnerable populations, especially children, pregnant women, older adults, low income groups, some communities of color, immigrant groups, Indigenous peoples, persons with disabilities, and persons with preexisting or chronic medical conditions. Furthermore, at a global level, the most vulnerable populations tend to live in high-density communities in areas that are also more vulnerable to floods and, as a consequence, suffer great losses of life. The concern is that, as the global temperatures continue to rise and extreme weather phenomena occur more frequently, the cumulative consequences, particularly on health, has significant implications on development of health policy [94].

BREAKING THE CYCLE

This exploration of the cycle of environmental degradation began with an examination of the microcosm of the Proctor Creek neighborhood in Atlanta. The lessons of the Proctor Creek experience demonstrate the critical importance of a consortium of concerned participants with an understanding of the situation, with ideas on how to break the cycle, with financial resources and a determination and commitment to work together to make changes for the good of all [1].

Just as the citizens of the Proctor Creek community took action to clean up their creek and restore an environment that is clean, pleasant and healthy, there are a multitude of similar efforts at many levels in neighborhoods, towns, states, countries and globally that have successfully broken the cycle of environmental degradation and restored a healthier ecological balance. In many places, these efforts have enhanced opportunities for healthier

physical, emotional and social activities for the citizens, characterized by the EPA as Ecosystems Services (see figure 1). Figure 5 represents a conceptual model of how the natural environment becomes degraded and how efforts to break the cycle can reverse the trend towards a more natural and healthy ecological balance.



Figure 5. Diagram depicting the process of environmental degradation followed by regeneration through environmental stewardship.

Efforts to break the cycle can and do occur at many different levels including a personal commitment to reduce waste by not using single use plastics, by driving cars that do not use fossil fuels, by recycling, and many other changes to personal behavior that are sensitive to the environment, and by extending the commitment to local community action, and advocating national and international governing bodies to likewise take up the charge and develop strategies to make positive changes and laws to assure maintenance and compliance with the standards expected for a healthy environment. Each organization and agency, government or Non-Governmental Organization (NGO), or international body, plays a significant role in the process. The greater the number of entities involved, and the greater the interaction and coordination among them, and the greater the resolve, the greater will be the impact on improving the health and well-being of all living beings and of the ecological balance of our planet. In this context, three examples of bodies whose missions and visions to make a difference are worthy of our support are offered for consideration.

THE UNITED STATES ENVIRONMENTAL PROTECTION AGENCY (EPA)

The mission of EPA is to protect human health and the environment. EPA's Strategic Plan identifies the measurable environmental and human health outcomes the public can expect from EPA and describes how the EPA intends to achieve those results [95].

In 1970, as a result of heightened public concerns about deteriorating city air, natural areas littered with debris, and urban water supplies contaminated with dangerous impurities, the EPA was formed [37]. At the time, given the dramatic environmental realities of air pollution, water pollution and pollution of the soil, President Richard Nixon requested billions of dollars of funding for a rather far reaching and visionary set of challenges:

- setting national air quality standards and stringent guidelines to lower motor vehicle emissions;
- launching federally-funded research to reduce automobile pollution;
- ordering a clean-up of federal facilities that had fouled air and water;
- seeking legislation to end the dumping of wastes into the Great Lakes;
- proposing a tax on lead additives in gasoline;
- forwarding to Congress a plan to tighten safeguards on the seaborne transportation of oil; and
- approving a National Contingency Plan for the treatment of oil spills.

In order to achieve these goals, the EPA was given the following mandates [37]:

- The EPA would have the capacity to do research on important pollutants irrespective of the media in which they appear, and on the impact of these pollutants on the total environment.
- Both by itself and together with other agencies, the EPA would monitor the condition of the environment, biological as well as physical.
- With these data, the EPA would be able to establish quantitative "environmental baselines", critical for efforts to measure adequately the success or failure of pollution abatement efforts.
- The EPA would be able, in concert with the states, to set and enforce standards for air and water quality and for individual pollutants.
- Industries seeking to minimize the adverse impact of their activities on the environment would be assured of consistent standards covering the full range of their waste disposal problems.
- As states developed and expanded their own pollution control programs, they would be able to look to one agency to support their efforts with financial and technical assistance and training.

In the almost 50 years since its inception, the EPA has played a significant role in improving the quality of our environment, with cleaner air, cleaner water and strategies to clean up polluted lands. It has also responded to the impact of natural disasters such as Hurricane Katrina in New Orleans, and man-made disasters such as the 2001 destruction of the World Trade Centers in New York. It has also worked collaboratively with international

organizations to help make positive changes in the environment around the world. Significantly, it has worked with the international community to address the challenges of climate change, despite the changing stances of the leadership in the US [96]. Unfortunately, changing leadership in the US affects the philosophy and policy of the EPA so that the path forward is not necessarily a straight one, but deviates, at times from its core mission. This situation requires constant vigilance by concerned citizens and organizations who monitor the environment and the impact of the environment on health, especially for children and other vulnerable populations.

THE WORLD BODY: UNITED NATIONS (UN) AND WORLD HEALTH ORGANIZATION (WHO)

Both the UN and the WHO are intimately involved in improving the environment towards improving the health of all people in the world.

The WHO's Health and the Environment [97] program mandate is to support Member States to improve health outcomes linked to environmental risks such as:

- Unsafe water and inadequate sanitation
- Poor indoor and outdoor air quality
- Exposure to toxic or hazardous waste and chemicals
- Climate change

The 2017 annual report of the UN Environment states [98]:

“Throughout the past year, UN Environment campaigned on many fronts against the spiraling pollution of air, water and land around the world. Climate change, wildlife crime, micro-plastic pollution and land degradation are just a few examples of environmental ills that affect the health and well-being of communities and economies, global efforts to achieve the Sustainable Development Goals and even the security of nations.”

UNITED NATIONS FRAMEWORK CONVENTION ON CLIMATE CHANGE (UNFCCC)

The United Nations Framework Convention on Climate Change (UNFCCC) is an international environmental treaty adopted in 1992 and signed at the Earth Summit in Rio de Janeiro, Brazil to “stabilize greenhouse gas concentrations in the atmosphere at a level that would prevent dangerous anthropogenic interference with the climate system” [99]

The UNFCCC serves as the foundation of an evolving global climate effort and sets a long-term objective of avoiding dangerous human interference with the climate system. Toward that end, the agreement:

- commits all nations to take steps to mitigate greenhouse gas emissions;
- establishes the principle of “common but differentiated responsibilities and respective capabilities” (CBDRRC), recognizing that countries vary in their

contributions to climate change and capacities to address it, so their obligations will likewise vary; and

- commits developed countries to assist developing countries in reducing emissions and coping with climate impacts.

There have been a number of international meetings, initially in Kyoto, Japan in 1995, where the Kyoto Protocol was developed, followed by the Paris Agreement in 2015 and most recently in Katowice Poland in 2018. Although these successive conferences have affirmed the commitment of participants to respond to the real and immanent dangers of climate change, there are so many competing factions among different nations and within each of the countries, that the resolve melts away while there remains much to do as the time slips away.

CONCLUSION

Over the millennia of human habitation on this planet, we have multiplied and conquered the land, seas and air. In the process, we have exploited the Earth's natural resources and irrevocably altered the quality of the natural environment to the detriment of almost all living beings. Human-caused environmental degradation has been progressive and cumulative and creates an existential threat that must be addressed. Rising global temperatures and consequent ecological changes are scientifically irrefutable. In this commentary, some of the more dramatic elements, episodes and disasters have been presented and discussed with meaningful responses at local, national and international levels being highlighted.

The continued threat of environmental degradation to our health and, arguably, to human existence and the deepening disruption of the ecology of our planet, compel further immediate and sustained action. Historically, we have been more reactive than strategic in our approach, responding to environmental disasters and the immediate consequences. While these responses have been, in many instances, demonstrably effective, they fall short of a broader approach to environmental degradation with a longer view. Our objective must be to avoid the disaster and our public policy and practice must be informed by science and dedicated to environmental recovery.

In order for humans to continue to flourish on Earth, we must acknowledge the link between the environment and health, human health and the health of all other living species, and on the ecological health of our planet. We must continue to reverse the trends of environmental degradation and the local, regional, national, international and global realities that accompany it. As outlined in this commentary and captured in figure 4, actions can be taken by individuals, groups of individuals or by larger organizations and agencies, to break the cycle of environmental degradation and improve the quality of our environment to assure the health and viability for all species in our current ecological system for the future. We must build on the successes of, and lessons learned by previous generations, dedicate ourselves to the depth of contributions we will make, and leave a legacy and a positive direction for the generations who will follow us. *It is not incumbent upon on any one of us to finish the task, but neither are any of us free to absolve ourselves from the undertaking of it.* [100]

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Chapter 55

RISK FACTORS FOR PREECLAMPSIA IN A HIGH-RISK COHORT OF WOMEN SERVED BY A NURSING-BASED HOME VISITING PROGRAM

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ABSTRACT

In this chapter we aimed to identify the impact of psychosocial risk factors on pregnancy outcomes for high risk women in an urban setting. Women in this category tend to experience adverse pregnancy outcomes, like preeclampsia, at greater rates than low or medium risk women. A retrospective paper chart review of East Harlem women served by LSA Family Health Service (LSA) Maternal Outreach Program (MOP) was conducted. All women who enrolled in the MOP with a singleton pregnancy from January 2015 to December 2017, were eligible for inclusion in our analyses. Data were analyzed using SPSS (version 23). Of 379 total charts reviewed, 68.6% (n=203) were Hispanic/Latina women, 44.8% (n=163) were English only speakers, 67.4% (n=226) were identified as overweight/obese, 90.6% (n=328) were mothers over the age of 20 among those for whom data were available. Sixty-two percent (n=235) initiated prenatal care in their first trimester, and 71.5% (n=271) were referred to the MOP by a hospital or other healthcare provider. The percentage of preeclampsia among mothers was 26.9% (n=102). After adjustment for type of LSA services received, and race/ethnicity, there were no associations between psychosocial risk factors and preeclampsia diagnosis in this population. Further research is needed on the relationship between psychosocial risk

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factors and preeclampsia to identify potential areas of intervention and reduce the burden of disease.

INTRODUCTION

Preeclampsia is a disorder of pregnancy that is characterized by new onset hypertension along with cerebral or visual symptoms, pulmonary edema or laboratory abnormalities indicating thrombocytopenia, transaminitis or renal dysfunction, during pregnancy or immediately postpartum [1]. The diagnosis can be present at any stage of gestation but is more commonly encountered in the third trimester or up to six weeks postpartum [2]. The prevalence of preeclampsia and other pregnancy related hypertensive disorders is estimated to be between 2-8% globally [3-5]. Hypertensive pregnancy disorders are responsible for more than one quarter of maternal deaths in Latin America and the Caribbean [3]. In the United States, racial and ethnic disparities in the prevalence of preeclampsia persist. One study found that Mexican American women had higher preeclampsia rates compared to non-Hispanic White and East Asian women [6]. Another study of pregnant New York City women found that among women with pre-existing diabetes, Hispanic and non-Hispanic Black women were more likely to have preeclampsia than non-Hispanic White women after adjustment for confounders [7].

Hospital discharge data show that African American women have higher rates of and more severe preeclampsia compared to other racial and ethnic groups [8]. Known risk factors for preeclampsia include: nulliparity, chronic hypertension, diabetes and obesity [9-10]. Mothers younger than 20 years or older than 35 years of age are also more likely to be diagnosed with preeclampsia [10]. Preeclampsia is associated with poorer birth outcomes such as increased likelihood of having a preterm or low birth weight infant, since delivery via induction of labor continues to be the mainstay of treatment for affected women [11-12]. Although the maternal comorbidities associated with this disorder have been well documented, there is less research on the psychosocial risk factors associated with this important pregnancy complication. The purpose of our descriptive study is to identify social risk factors for preeclampsia in a high-risk cohort of mothers who received skilled home nursing visits through the Maternal Outreach Program (MOP) at LSA Family Health Service (LSA) to identify additional areas for intervention.

OUR STUDY

LSA Family Health Service (LSA) is a non-profit community organization located in East Harlem, New York. This neighborhood has historically been the home to several immigrant communities, becoming one of the largest minority communities in New York City with more than three quarters of the population identifying as Latino/Hispanic or Black/African American [13]. The median income is approximately \$38,000 in both East and Central Harlem with about 30% of residents living below the federal poverty level [14-15]. This organization provides social and health services to address many aspects of family health; and is designed to empower those who are vulnerable and have limited access to

necessary resources needed to cultivate a healthy life. The LSA Maternal Outreach Program (MOP) consists of a team of community nurses who provide care to prenatal and postpartum women residing in East and Central Harlem by conducting home-visits and providing individualized prenatal and infant care education as well as breastfeeding classes. Additional services provided by LSA to promote community health/wellness and family support include: The Advocacy and Food Pantry Program, Environmental Health Services, Parenting and Child Development, and Preventive Services—a support program that works to strengthen fragile or crisis-impacted families.

The study population consisted of pregnant and postpartum women served by LSA. Women were referred to the MOP if there was a perceived need and potential benefit from receiving home nursing care and community support. Women also self-referred if interested, based on community awareness of the organization and services offered. All women with singleton pregnancies, who were clients of the MOP during 2015-2017, were eligible for inclusion in our study.

Table 1. Demographic information by type of service received

	All (n=379)	Prenatal Only (n=28)	Postpartum Only (n=257)	Prenatal- Postpartum (n=94)	P-value
Race/Ethnicity*					<0.001
Black/African-American	27.7%	8.7%	37.7%	12.2%	
Hispanic/Latina	68.6%	87.0%	57.9%	85.6%	
Other	3.7%	4.3%	4.4%	2.2%	
Language*					<0.001
English Only	44.8%	29.6%	56.8%	18.1%	
Spanish Only	28.8%	44.4%	16.4%	56.4%	
Bilingual	23.4%	22.2%	23.9%	22.3%	
Other	3.0%	3.7%	2.9%	3.2%	
BMI Class*					0.043
Underweight	3.7%	8.0%	3.3%	3.4%	
Normal	28.9%	28.0%	27.3%	29.7%	
Overweight/Obese	67.4%	64.0%	69.4%	66.9%	
Maternal Age <20 yrs*					0.644
Yes	9.4%	7.1%	10.4%	7.4%	
No	90.6%	92.9%	89.6%	92.6%	
Trimester of Prenatal Care Initiation					<0.001
First	62.0%	64.3%	80.9%	54.9%	
Second or Later	4.0%	****	5.3%	3.9%	
Unknown	34.0%	35.7%	13.8%	41.2%	
Referral Source					<0.001
Hospital or healthcare provider	71.5%	39.3%	87.2%	38.3%	
Self or other individual	12.1%	35.7%	2.3%	31.9%	
LSA or other organization	8.7%	25.0%	0.8%	25.5%	
Missing/Unknown	7.7%	N/A	9.7%	4.3%	

*Of the participants for whom data were available.

A retrospective paper chart review of program data on mother-infant dyads was conducted by trained research assistants. Data were analyzed with SPSS software (SPSS version 23). Chi square analyses and logistic regression were used to model associations between preeclampsia and psychosocial risk factors identified by the nurses during program intake. Risk factors of interest included: being a teen or inexperienced parent, (defined as

being a mother less than 20 years or being a first time mother); having food insecurity, insufficient income; low maternal education, (defined as less than a 10th grade education or leaving school before age 17), poor housing quality, and perceived neighborhood safety.

OUR FINDINGS

The study population consisted of a total of 379 mothers with singleton pregnancies. More than two thirds of the women (n=257) were enrolled in the postpartum-only component of the MOP. About one quarter (n=94), enrolled in both the prenatal and postpartum components of the MOP. Less than 10% (n=28) participated in the prenatal program only. Table 1 summarizes the demographic information of the MOP participants stratified by type of LSA services received. More than two thirds (68.6%) of the women identified as Latina and, 28% were African American. The group of women who received only postpartum services had the lowest percentage of Latina women (57.9%) and the highest percentage of Black women (37.7%) compared to the other groups ($p<0.001$). The postpartum only group also had the highest percentage of women who spoke primarily English (56.8%). In comparison, the group with the highest percentage of Spanish only speakers, was the prenatal-postpartum group (56.4%). BMI was elevated in about two thirds of the women in all three groups with minimal between group differences. Eighty-seven percent of women enrolled in the postpartum-only program were referred by a hospital or clinic compared to less than 40% in the prenatal only and prenatal-postpartum participants of the MOP combined.

Table 2. Psychosocial risk factors by type of LSA services received

	All (n=379)	Prenatal Only (n=28)	Postpartum Only (n=257)	Prenatal- Postpartum (n=94)	P-value
Teen/Inexperienced Parenting*					0.635
Yes	44.6%	50.0%	45.3%	40.9%	
No	55.4%	50.0%	54.7%	59.1%	
Low Maternal Education*					<0.001
Yes	24.6%	35.7%	16.1%	44.6%	
No	75.4%	64.3%	83.9%	55.4%	
Food Insecurity*					<0.001
Yes	23.1%	21.4%	18.4%	36.7%	
No	76.9%	78.6%	81.6%	63.3%	
Insufficient Income*					<0.001
Yes	34.0%	28.6%	28.5%	51.1%	
No	66.0%	71.4%	72.5%	48.9%	
Substandard Housing Quality*					<0.001
Yes	26.9%	32.1%	15.8%	57.5%	
No	73.1%	67.9%	84.2%	42.5%	
High Risk/Unsafe Neighborhood*					0.007
Yes	13.3%	N/A	11.9%	21.6%	
No	86.7%	100%	88.1%	78.4%	

*Of the participants for whom data were available.

Table 2 outlines the prevalence of our psychosocial risk factors by LSA service type. Generally, participants who were only enrolled in the postpartum program were the least likely to report low maternal education, food insecurity, insufficient income, substandard housing quality and living in a high risk or unsafe neighborhood (all $p < 0.001$).

Table 3. Percentage of pre-eclampsia diagnosis by psychosocial risk factor stratified by LSA service received

	All (n=379)	Prenatal Only (n=28)	Postpartum Only (n=257)	Prenatal- Postpartum (n=94)	Overall P-value
Total Prevalence					N/A
	26.9%	3.6%	34.2%	13.8%	
Teen/Inexperienced Parenting					0.058
Yes	22.1%	7.1%	27.9%	10.5%	
No	30.9%	***	40.6%	14.5%	
Low Maternal Education					0.002
Yes	13.6%	***	27.0%	4.9%	
No	30.5%	5.6%	35.7%	17.6%	
Food Insecurity					0.724
Yes	25.3%	16.7%	29.5%	18.2%	
No	27.3%	***	35.2%	10.5%	
Insufficient Income					0.122
Yes	21.8%	12.5%	30.4%	10.6%	
No	29.3%	***	36.2%	15.6%	
Substandard Housing Quality					0.018
Yes	17.5%	***	28.9%	12.0%	
No	29.9%	5.3%	35.6%	10.8%	
High Risk/Unsafe Neighborhood					0.695
Yes	24.5%	***	34.7%	10.5%	
No	27.2%	3.6%	33.3%	13.0%	

PREECLAMPSIA IN THE MOP

Table 3 summarizes the percentage of women with preeclampsia by psychosocial risk factor, stratified by type of LSA services received. Preeclampsia rates were lower among women with less maternal education (13.6% vs 30.5%, $p = 0.002$) and those with poor housing (17.5% vs 29.9%, $p = 0.018$). Table 4 highlights the odds of preeclampsia in clients of the MOP with select risk factors. Consistent with the findings in Table 3, the odds of preeclampsia were 64% lower in women with low maternal education (OR 0.36, 95%CI 0.19-0.70) and 50% lower in women who lived in poor quality housing (OR 0.50, 95%CI 0.28-0.89). However, after adjustment for race/ethnicity and type of LSA services received, these differences were no longer statistically significant (Adj OR 0.53, 95%CI 0.24-1.13 and Adj OR 0.67, 95% CI 0.32-1.38). There were no statistically significant associations between preeclampsia and food insecurity, income, teen/inexperienced parenting or perceived neighborhood safety.

Table 4. Odds of preeclampsia by psychosocial risk factor

	Unadjusted OR (95%CI)	Partially Adjusted OR (95%CI) ^a	Adjusted OR ^b (95%CI)
Teen/Inexperienced Parenting	0.63 (0.40, 1.02)	0.61 (0.37, 0.99)	0.63 (0.35, 1.12)
Low Maternal Education	0.36 (0.19, 0.70)	0.51 (0.26, 1.02)	0.53 (0.24, 1.13)
Food Insecurity	0.83 (0.48, 1.45)	1.03 (0.57, 1.87)	1.05 (0.52, 2.11)
Insufficient Income	0.67 (0.40, 1.16)	0.79 (0.46, 1.34)	0.65 (0.34, 1.23)
Substandard Housing Quality	0.50 (0.28, 0.89)	0.79 (0.42, 1.51)	0.67 (0.32, 1.38)
High Risk/Unsafe Neighborhood	0.87 (0.43, 1.75)	0.91 (0.44, 1.86)	0.91 (0.38, 2.18)

^aAdjusted for type LSAFHS Services type ^bAdjusted for type of LSAFHS services type, and race/ethnicity.

DISCUSSION

The present study is among the first to explore the potential impacts of various psychosocial risk factors on preeclampsia for an at-risk, minority population receiving skilled home nursing visits. Demographic analysis of our study population confirms that the MOP at LSA serves a high-risk population. The group was primarily comprised of English-speaking Latina women categorized into overweight and obese groups by their calculated BMI, which is consistent with previous research identifying an increased risk of preeclampsia in women with this risk factor [16].

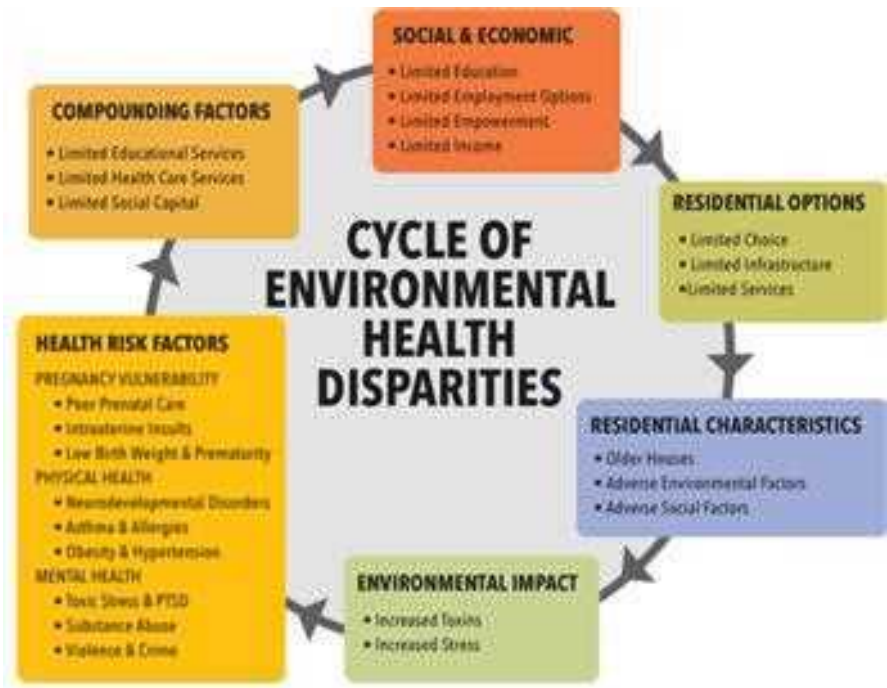


Figure 1. Areas in the cycle of health disparities targeted by LSAFHS.

Fewer women in the teen/inexperienced parent category had a diagnosis of preeclampsia, but this relationship was not significant after adjustment for race/ethnicity and type of LSA

service received. These results differ from existing literature on teen and inexperienced parenting as a preeclampsia risk factor. Other studies have associated young maternal age (under 20 years old), with an increased risk of preeclampsia, especially among racial and ethnic minorities [17]. LSA's definition of 'inexperienced parent' also includes nulliparous women who may have more anticipated stress related to preparation for becoming a first-time parent. There is literature which suggests that perceived stress and nulliparity may be associated with the development of preeclampsia during pregnancy [18-19]. The LSA category for teen and inexperienced parents was a combination of these two populations. Therefore, it is possible that the association between teen parenting and preeclampsia, as well as the association between parenting experience and preeclampsia, may have been masked. Further research should explore teen parenting, parenting experience and parental stress as individual risk factors for this disorder within this population. Women with low maternal education also had lower rates of preeclampsia. However, this relationship appeared to be explained by differences in the distributions of LSA service type and race/ethnicity. This finding disagrees with existing works that associate low maternal education with a greater risk of preeclampsia [19-20]. One possible explanation is differences by nativity status. Foreign-born women tend to have better birth outcomes than those born in the United States regardless of racial or ethnic background [21]. Therefore, a study population with a higher percentage of foreign-born women may have lower education but better birth outcomes nonetheless. Nativity was beyond the scope of our data analyses.

Teen/Inexperienced parent: Mother less than 20 years of age, or being a first time mother.
Low maternal education: Mother who left school before age 17 or had less than 10 th grade education.
Food insecurity: Defined as a report of not enough food or only nutritionally deficient food in the home.
Insufficient income: Not enough income to meet basic needs such as food, housing, healthcare and supplies.
High-risk/unsafe neighborhood: Perceived presence of or concern for safety in the building where they reside.
Substandard Housing: Presence of less than adequate housing conditions such as apartment or building fixtures in poor condition, non-functioning windows, deteriorating flooring and walls.

Figure 2. Risk factor definitions used by LSAFHS nurses.

We did not find any significant association between nurse-reported insufficient income or food insecurity and having preeclampsia. This too, is in contrast with relevant literature that cites low socioeconomic status as being positively associated with preeclampsia development [22]. Household income data were not available for analyses so we were unable to identify discrepancies between mothers' perceived income insufficiency, and measured income that could have provided additional insight into our findings. It is possible that the mothers' perception of whether the household income was sufficient may not have correlated well with their true income. Additional research with more direct, quantitative measures of income insufficiency is warranted. Similarly, there were no differences in preeclampsia rates among those who reported and those who did not report food insecurity. One explanation is that the nurses' intake form did not note the type of food that was available at home or the nutritional content of what the women ate. Research shows that risk of preeclampsia may be increased by diets that are high in fat or deficient in calcium [23-24]. Other studies suggest that

increased intake of added sugars is associated with the development of preeclampsia [25]. Therefore, mothers with preeclampsia may have had access to a greater quantity of food of poorer quality which may have impacted our results.

After adjustment for the covariates, there was no significant association between housing quality or neighborhood safety and preeclampsia. Established literature cites that residents who live in substandard housing are more likely to have additional socioeconomic risk factors, such as living in an unsafe neighborhood that increase levels of chronic stress and poorer mental health, which then increases risk of adverse birth outcomes, including preeclampsia [26]. While this study's results diverge from these findings, it is possible that these two risk factors are less important than medical comorbidities risk factors, like BMI. The distribution of BMI was similar among the three groups of women and modelling BMI in relation to preeclampsia was beyond the scope of our analysis. Alternatively, the risk factor definition may have been too heterogeneous to identify specific environmental housing factors that are associated with preeclampsia.

Of great significance is the finding that women who only participated in the postpartum component were by far more likely to be referred by health care providers for medical conditions. Many of these women had preeclampsia as the referral diagnosis, which is reflected in our data since the postpartum-only group had the highest preeclampsia percentage overall. Though they had higher rates of protective risk factors for preeclampsia, such as higher maternal education level and more income, they were also more likely to identify as Black or African American which is a well-documented preeclampsia risk factor [8, 27]. Most of these women did initiate prenatal care within their first trimester but were not referred to MOP for secondary preventive care. This highlights a gap in referrals for participants and a failure to identify high-risk women for additional support for preeclampsia earlier in their pregnancy. Potential reasons for lack of referral include lack of provider awareness of MOP, patient preference, or competing priorities especially for medically complex or hospitalized mothers and infants. Since preeclampsia is associated with both maternal and infant comorbidity, early detection and disease management are public health priorities. Referrals to skilled, home nursing programs that connect clients to community resources could mitigate some of the adverse outcomes associated with this disorder; and serve as an additional window of opportunity to decrease the maternal and child health disparity gap.

Our study has several limitations, including the small sample size after stratification by program type and risk factors; and the lack of validation of the LSA criteria used for the different psychosocial and environmental risk factors. Other challenges include the inability to assess inter-observer reliability amongst the nurses and members of the data collection teams, as well as the lack of specificity in criteria used to define some of the risk factors of interest.

Nevertheless, we did demonstrate the ability of a community-based organization to track data with great public health significance in a systematic way and provide much needed home-base services during and after pregnancy. The neighborhood served by the MOP has a significant proportion of mothers who often have less access to traditional health care venues and our study contributes to the body of literature on this important population. Additional pilot projects could explore ways of helping community-based organizations improve their data management strategies in a self-sustaining way; and increase their capacity to evaluate their program outcomes and further identify need gaps for the populations they serve.

CONCLUSION

We found no association between any of the psychosocial risk factors examined and preeclampsia, after adjustment for race/ethnicity and the type of MOP services received in our population. Though our findings differ from existing literature, they do highlight the importance of carefully considering the criteria used to screen mothers for common risk factors. Further research is still needed to better characterize risk; and to reveal additional links between socioeconomic factors and preeclampsia. Given the long-term negative consequences of this disorder for both mothers and infants, understanding the environmental risk factors for this condition is critical in order to break the cycle of birth outcome disparities in ethnic minority communities. Many of the root causes of maternal and child health disparities are challenging to solve; and organizations like LSA provide much needed support and care to marginalized communities.

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Chapter 56

EVALUATING FISH-CONSUMPTION IN PREGNANCY

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ABSTRACT

For children particularly burdened by social and economic disadvantages, exposure to toxic substances is an important contributor to adverse health outcomes and health disparities. Maternal consumption of fish high in methylmercury during pregnancy is associated with increased risks for preterm delivery and adverse neurodevelopmental outcomes in the children. In this chapter we evaluate a single fish-consumption screening question to identify pregnant women at risk for elevated mercury levels. The question “In general, do you eat more than two fish meals per week?” was asked and a single test for total blood mercury level was obtained from pregnant women presenting to an urban hospital Labor and Delivery Triage Unit. In this limited study (n=42), participants were mainly Black (48%) and Latina (43%), and 71.4% had a median household income (estimated from zip code) below 200% of the federal poverty level. No participant had an elevated mercury level. Indeed, this population had a very low geometric mean mercury level of 0.32 µg/L (64% below the US geometric mean for women of childbearing age; from NHANES 2009-2010), indicating a likely low frequency of fish intake. In this sample population, prenatal exposure to elevated methylmercury was not an issue and the utility of this screening question was not supported. However, in these women already at risk for disparate health outcomes, the potential health benefits for brain development from omega -3 fatty acids in fish are being missed.

INTRODUCTION

For children particularly burdened by social and economic disadvantages, exposure to toxic substances in the environment is an important contributor to environmental health

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in 2015, with preterm births highest among non-Hispanic Black, American Indian/ Alaska Native, Native Hawaiian/Pacific Islander, and subgroups of Hispanic women. Additionally, the percent of infants born with low birth weight (weighing less than 2,500 g) saw a 1% increase, from 8.07% in 2015 to 8.17% in 2016; the highest rates of which were among non-Hispanic Blacks and Hispanic subgroups [7, 8].

In contrast, it is important to point out that fish and shellfish are excellent sources of the long-chain omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). These fatty acids are essential nutrients (only obtained through the diet) that confer significant neurodevelopmental benefits and may promote healthy gestational length [9]. There are other sources of short-chain omega-3 fatty acids, such as flax seed, which are less potent. As a result, the American College of Obstetricians and Gynecologists (ACOG) conferred with the US Food and Drug Administration (FDA) and the US Environmental Protection Agency (EPA), and encourages women who are or who may become pregnant or who are breastfeeding to eat at least 8 oz., up to 12 oz. (approximately 2-3 servings) of low mercury fish per week [6, 10].

Considering both factors, maternal fish consumption practices can have significant implications for children's health and development. Currently, pregnant women are not screened for fish consumption to assure adequate intake of omega-3 fatty acids and minimal mercury intake. Through the use of a simple screening question that can be incorporated into busy outpatient prenatal care, this study aims to evaluate use of a single screening question to identify pregnant women with elevated total blood mercury levels.

Among socioeconomically disadvantaged pregnant women, evaluating fish consumption practices may offer insight into dietary contributions to suboptimal neurodevelopment. By identifying pregnant women at risk for high dietary mercury exposure, we can provide additional monitoring and targeted interventions to limit potential gestational and neurotoxic effects. For those at risk for low DHA/EPA intake, we can directly promote neuro-protective dietary choices. Recognizing both high methylmercury and low DHA/EPA intake, informs opportunities to slow the gears of premature birth, poor nutrition, toxicant exposure, and neurotoxicity in order to help break the cycle of environmental health disparities (see Figure 1).

OUR STUDY

This cross-sectional study was conducted at a state hospital in Chicago, IL that serves a large proportion of minority and low socioeconomic status patients. The main study components were a brief, in-person interview and a single blood test for total mercury. Study participation was voluntary. Potential participants were eligible if: a) an adult woman (age $\geq$ 18 years), b) currently pregnant, c) able to consent to participate in the study, and d) their care required a venipuncture during the time of recruitment. Potential participants were recruited from the Labor and Delivery Triage Unit when they met study eligibility. Out of respect for the patients and the flow of care, women presenting in critical condition or in distress were not approached for recruitment. All recruitment, consent, and research was conducted by the single physician researcher and approved by the University of Illinois at Chicago Institutional Review Board.

Consent for participation in the study required a level of English language proficiency to understand the consent form and to answer the screening and demographic questions. Consent forms were available in English and all study materials were approved by the University of Illinois Institutional Review Board. Participants provided written consent to participate in the interview and allow the collection of a single blood sample.

The question “In general, do you eat more than two fish meals per week?” was asked of consenting pregnant women. Each participant was assigned an ID number, and then their medical record number, due date, date of birth, zip code, ethnicity, and response to the fish consumption question were recorded. The ID number served as a code to link the patient to their medical record number, which was kept separate from the remaining study documentation. This was necessary for the follow up required for results greater than or equal to the EPA reference dose-equivalent of 5.8 µg/L. In the event of an elevated result, a site provider would be contacted and provided the medical record number to access the patient’s contact information. The provider would notify the patient of their result by telephone.

The ID code was written on the vacutainer tube by the researcher and was the only information on each tube. A single blood sample was collected by the patients’ provider at the time they performed any other necessary venipuncture. The samples were refrigerated onsite before being shipped to the designated lab holding an ISO 9001-2000 certification and accreditation by the College of American Pathologists. All lab results were analyzed at the same lab. During the encounter, the researcher was also available to discuss low-risk fish consumption, answer questions, and provide pamphlets in English (“Eat fish, choose wisely. Protect against mercury”) or Spanish (“Advice about eating fish. What pregnant women and parents should know”) for the women and their families to keep (see Figure 2A, Figure 2B).

On research days, over the course of five months in 2017, an attempt was made by the researcher to recruit all eligible patients who presented to Labor and Delivery Triage Unit. Participants were excluded if not mentally competent to provide consent ($n = 1$). There were also 15 consented patients who met eligibility requirements but were excluded after no blood sample was collected for reasons that included: provider forgot to draw the additional tube, an inability to acquire adequate blood sample, the care plan changed and no longer required a venipuncture, or their care didn’t progress to include the venipuncture during the window of researcher availability. Approximately 22 women declined study participation, with seven women citing an unwillingness to participate in research and approximately 15 woman citing labor pain or other discomfort. There were 10 Spanish-speaking only patients who couldn’t be consented based on language. Numerous patients ($n = 50+$) were ineligible because their care plan did not include venipuncture. In total, 42 participants were successfully recruited, with data available for analysis.

Descriptive and analytical statistics were used to characterize the study population, and to evaluate the fish consumption practices and mercury level of participants by demographic factors like age, ethnicity, and income. To evaluate the utility of the screening question, sensitivity, specificity, positive predictive value, and negative predictive values were calculated. Results were also compared to national levels published by NHANES. Statistical analyses were performed using SAS Enterprise Guide 6.1 (SAS Institute Inc, Cary, NC).



Source: https://www1.nyc.gov/assets/doh/downloads/pdf/edp/mercury_brochure.pdf.

Figure 2A. Informational pamphlet, English.



Source: <https://www.fda.gov/downloads/Food/ResourcesForYou/Consumers/UCM536614.pdf>.

Figure 2B. Informational pamphlet, Spanish.

The geometric mean was calculated by taking the natural logarithm of each concentration, computing the mean of those log-transformed values, and exponentiating the value to the original scale. Fifteen (35%) blood mercury levels were below the limit of detection (LOD) and assigned a value equal to the detection limit divided by the square root of two. Income level was approximated by the zip code reported by each participant at the time of the study. The incomes used for analysis were the median household incomes for a family of four, as populated from an online search of the respective zip codes. The data was from the American Community Survey 2016 5-year estimates, using comparable income statistics available from the US Census Bureau, with values in 2016 inflation-adjusted dollars [11].

FINDINGS

Table 1 shows the demographic characteristics of the 42 study participants. The mean participant age was 27 years (+ 5.6 years), with a range from 18 to 37 years old (43% were aged 18-24 years). Regarding country of ethnic origin, 48% self-identified as Black and 43% as Latina, with the remaining identifying themselves as White (7%) and Other (2%). Thirty (71.4%) of the participants had a median household income (estimated from zip code) below 200% of the federal poverty level.

Table 1. Demographic characteristics of study participants

	Total (N=42)	
Age (years)	Frequency	Percent
18-24	18	43%
25-29	7	17%
30-34	12	29%
35-39	5	12%
40+	0	0%
Mean Age (SD=)	27	(SD = 5.7)
Race/Ethnicity		
White, Non-Hispanic	3	7%
African-American	20	48%
Hispanic/Latina	18	43%
Other	1	2%
Asian/ Pacific Islander	0	0%
Trimester		
1	12	29%
2	3	7%
3	27	64%
Mean Gestational Age (weeks) (SD =)	27.2	(SD = 13.2)
Income (by zip code)		
<\$46, 435/year	30	71%
>\$46, 435/year	12	29%
Mean Income (SD=)	\$ 56,084.26	(SD = 13,849.86)

Of those who reported eating fish more than twice weekly ($n = 4$), the mean blood mercury level was $1.11 \mu\text{g/L}$ compared to a mean blood mercury level of $0.37 \mu\text{g/L}$ for those who do not ($p = 0.05$). Age was also found to be associated with mercury level; participants aged 27 years (the median participant age) or older had a mean mercury level of $0.55 \mu\text{g/L}$, compared to $0.31 \mu\text{g/L}$ in those aged 26 years or younger ($p = 0.05$). No significant difference in mercury levels were found for the remaining variables related to ethnicity, income, and trimester (see Table 2). The screening question was not found to have utility in this study population with low mercury levels. Using both the $>5.8 \mu\text{g/L}$ and $>3.5 \mu\text{g/L}$ limits, we found a sensitivity of 0.0% (95% CI: n/a), specificity 90.5% (95% CI: 76.5%, 96.9%), negative predictive value 100% (95% CI: 88.57%, 100%), and positive predictive value 0.0% (95% CI: 0%, 60.4%).

Table 2. Distribution of blood total mercury ($\mu\text{g/L}$), by select demographics

	N	Arithmetic Mean		Geometric Mean		p-value
		(95% CI)		(95% CI)		
Fish Consumption ^a						
Eat Fish > 2x/week	4	1.11	(-0.15,2.37)	1.35	(1.22,1.50)	P = 0.05
Eat Fish < 2x/week	38	0.37	(0.28,0.45)	0.29	(0.49,0.36)	
Age						
> 27 years	22	0.55	(0.34,0.77)	0.41	(0.28,0.58)	P = 0.05
< 26 years	20	0.31	(0.20,0.42)	0.24	(0.18,0.34)	
Income ^b						
> \$46,435	12	0.41	(0.07,0.76)	0.25	(0.14,0.46)	P = 0.12
< \$46,435	30	0.45	(0.32,0.57)	0.35	(0.27,0.46)	

^a Participant response to question: "In general, do you eat more than two fish meals per week?"

^b Income based on median household income for a family of four in participants zip code.

DISCUSSION

This small study of mainly young, urban, Black or Latina, low-income women looked at a single question about fish-consumption during pregnancy to assess for a possible association with mercury levels. No participants were found to have elevated total blood mercury levels, but this population had a low geometric mean mercury level of 0.32 µg/L. This compares to studies in this geographic area (the great lakes coast region) with a geometric mean of 0.78 µg/L (95% CI: 0.75, 0.82) [12] and to the national mean among non-Asian women of childbearing age of 0.58 µg/L [13]. When looking specifically at Black and Latina women of reproductive age, estimates of the geometric mean of blood mercury were 0.50 µg/L (95% CI: 0.44, 0.57) for non-Hispanic Blacks and 0.35 µg/L (95% CI: 0.30, 0.40) for Mexican Americans (NHANES 1999—2002) [14].

Given the low sample size, the statistical analyses in this study were limited. Total blood mercury level was found to be associated with whether someone typically eats fish more than twice a week. We also found that older age (i.e., age greater than or equal to the median participant age of 27 years) was associated with increased fish consumption, as seen in other studies [12, 13]. No other variables were found to have a statistically significant association with mercury levels. The screening question was not found to have utility for this study population due to the low prevalence of fish consumption and the absence of elevated blood mercury levels.

While not formally part of the research, during conversations with each participant, the researcher noted that most women (over 90%) did not eat fish regularly and were unaware of the health benefits of omega-3 fatty acids for developing babies and children. The health care professionals (to include physicians, midwives, and nurses) in the unit also expressed limited knowledge and understanding of what to communicate about fish and seafood consumption in pregnancy. The providers, participants and their families were very receptive to the educational materials; they were particularly interested to learn about types of fish to avoid and types considered recommended choices.

Consistent with other literature on women of reproductive age [10, 12], most participants reported eating fish at rates much lower than the recommended twice a week (8–12 ounces per week). As a result, the offspring from this study population may not be getting the benefits of optimal omega-3 fatty acid intake. Maternal consumption of the omega-3 fatty acids found in fish supports fetal brain and neurologic development and is associated with increased birth weight and longer gestation [9]. These are key areas where lower income and/or Black and Latina women continue to experience disparate health outcomes. By encouraging consumption of fish high in omega-3 and low in mercury, there is an opportunity to intervene and potentially improve outcomes for child health and development, and reduce health disparities.

This study has several limitations. Participants self-selected into the study, thus patients choosing to participate may be more attentive to their health and have different nutritional habits and exposures than those who did not participate. Additional bias may be introduced by participants' responses to the screening question, including inaccurate recall of fish consumption practices or the desire to provide a seemingly socially desirable response. The small sample size and study design considerably limited the strength and detail of analyses that could be performed. The inclusion of additional variables for stratification, including

varying levels and types of fish consumption and other dietary habits (including the use of omega-3 supplementation), would allow more detailed assessments of the risks.

CONCLUSION

In the face of numerous social and environmental threats to health, it is important to look for opportunities to promote health and build resiliency. By evaluating fish consumption practices, particularly for vulnerable pregnant women, there is an opportunity for neurodevelopmental health promotion. The very low rates of fish consumption among low income Black and Latina pregnant women in this study may signal suboptimal omega-3 fatty acid (DHA/EPA) intake and therefore the loss of health benefits to neurodevelopment of their offspring, potentially contributing to the achievement gap already well documented among these populations. Consuming low mercury fish at least twice a week, or ensuring comparative supplementation of omega-3 fatty acids, would likely help address some of the health disparities suffered by African American and Latino communities in the United States.

Considerations from this study may be used to guide further investigations and to target outreach to populations at risk for poorer health outcomes. Appropriate dietary choices can help limit further toxic insult and build developmental resilience, to ultimately help break the cycle of children's environmental health disparities.

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Chapter 57

BARRIERS AND PROMOTERS TO INITIATING AND SUSTAINING BREASTFEEDING AMONG AFRICAN AMERICAN WOMEN

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ABSTRACT

According to the Centers for Disease Control and Prevention statistics, African American women are less likely to breastfeed compared to other racial/ethnic groups. Just over 60% of African American mothers initiate breastfeeding, with only 14% continuing to exclusively breastfeed until their infant is six months of age. Despite this persistent disparity, few studies have explored the barriers and promoters to initiating and sustaining breastfeeding specific to African American women. In this study we used a “positive deviant” model to help understand the factors that have influenced the experiences of African American mothers who have exclusively breastfeed for at least six months. Ten African American women who had given birth within the previous year were recruited through a lactation center located in the southeastern region of Atlanta, GA. Semi-structured interviews were conducted with these women regarding the initiation and sustaining of breastfeeding for six months or longer, as well as the social, cultural, environmental, and economic factors that may have acted as barriers and/or promoters to breastfeeding. Interviews were transcribed and general qualitative data analyses using MaxQDA utilizing intra-and inter-rater reliability techniques were carried out. Results: The majority of the participants described the following as positive factors:

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supportive family, workplace autonomy, and support groups. Barriers included: long commute, work hours, stressful environments and difficulty latching. Conclusion: This group of African American women are positive deviants and key informants in identifying barriers and promoters of exclusively breastfeeding for at least six months. Our findings will help generate hypotheses on community and culturally tailored interventions to encourage more African American mothers to initiate and sustain breastfeeding.

INTRODUCTION

Breastfeeding is regarded as the optimal form of infant feeding because of the many benefits it provides to infant and child health and development [1]. The American Academy of Pediatrics (AAP) policy on breastfeeding recommends exclusive breastfeeding for six months, followed by continued breastfeeding as complementary foods are introduced, with continuation of breastfeeding for one year or longer as mutually desired by mother and infant [1].

Breast milk affords protection against many health problems in infancy, such as obesity, diabetes, infections including necrotizing enterocolitis, and allergic disease [2]. Additionally, Bar et al. reviewed the long-term neurodevelopmental benefits of breastfeeding and found that children who breastfeed for longer than six months have better cognitive outcomes, including a lower risk of developing attention-deficit/hyperactivity disorder, and higher intelligence quotient [3].

Additionally, breastfeeding benefits the infant's immune system through contributing to the seeding of the microbiome by introducing new microbial communities and stimulating the maturation of the neonatal gut microbiome [4]. The microbiome matures in parallel with the infant's immune system, setting up the framework for the adult immune system and microbiome, by developing regulatory T-cell populations [5-7]. Bacteria located in both colostrum and mature milk can stimulate the anti-inflammatory response, helping to reduce the risk of developing a broad range of inflammatory diseases and immune-mediated pathologies, such as asthma, inflammatory bowel disease and atopic dermatitis [4, 8]. According to Houghteling, the nature of infant environmental exposures, acting through the microbiome, affects the likelihood of developing other diseases such as obesity and food allergies [4]. Hence, the best way to promote and maintain a healthy neonatal microbiome is through exclusive breastfeeding [6].

Health concerns for children such as asthma, obesity, hypertension, diabetes, and neurodevelopmental disorders are often caused or exacerbated by socioeconomic and ecological factors. Children who are breastfed for longer periods have lower infectious morbidity and mortality and higher intelligence quotient (IQ), than do those who are breastfed for shorter periods, or not breastfed [9]. This inequality persists until later in life [10]. Through increasing the breastfeeding initiation and sustaining rates, we can help to break the cycle of health and developmental disparities in children that lead to poor physical health in adulthood.

According to the Centers for Disease Control and Prevention, African American women have a breastfeeding initiation rate of 64.3% compared to 81.5% of white women [11]. Furthermore, African American mothers exclusively breastfed for 6 months at a rate of 14%

compared to 22.5% of white women. Hence, African American mothers and their babies are at higher risk for poorer health and developmental outcomes. Little is known about what promotes and helps to maintain exclusive breastfeeding for the 14% of African American mothers who are successfully breastfeeding up to six months.

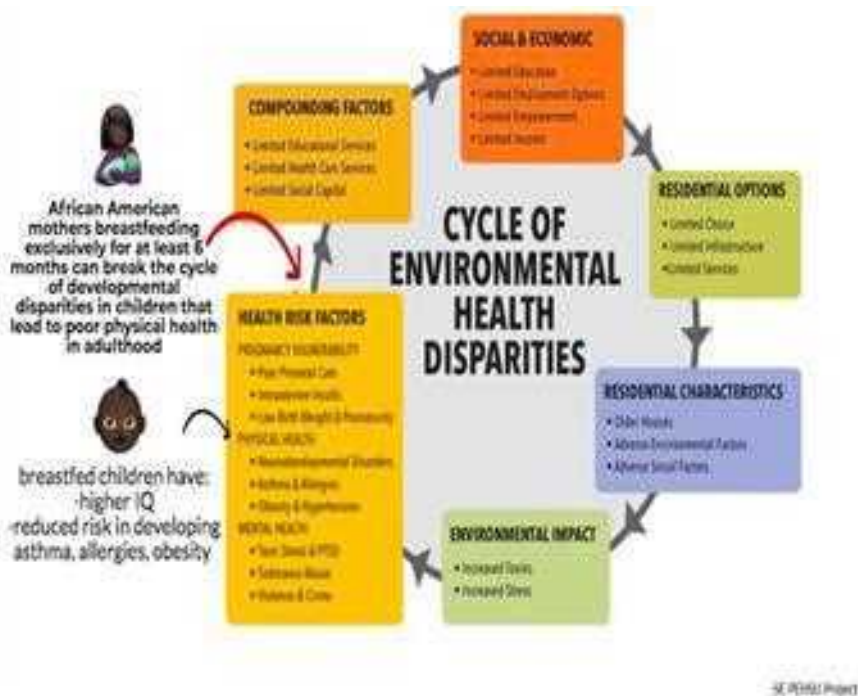


Figure 1. Cycle of environmental health disparities.

Despite the lower rates that exist with African American mothers' breastfeeding initiation and sustaining practices there is a lot to learn from women who have been successful. Through their narrative we are able to identify and highlight positive promoters of breastfeeding and learn about the challenges African American mothers overcome to reach their breastfeeding goals. Rather than focus on the black-white disparity in research as it reinforces a deficit model, we sought to humanize the gaps in research through narratives and input from African American mothers who have successfully breastfed [12]. We chose to validate the significant improvements of African American breastfeeding rates through the behaviors of positive deviants.

African American women who do breastfeed may be considered positive deviants. A positive deviant approach examines behavior that deviates from the norm to produce favorable outcomes. According to a pioneer on the study of positive deviance, this approach allows a participatory approach to identify solutions to community problems within the community [13]. In every community, there are exemplary individuals who display unconventional and uncommon practices and behaviors that enable them to find creative solutions compared to their counterparts who have access to the same resources [14, 15]. Through identifying individuals with better outcomes than their peers and analyzing their behaviors, other members of the communities could be encouraged to adopt the behaviors as an effective method to produce sustainable and locally sourced change [16]. Rather than

identifying a problem and creating a solution, we seek to identify the solution and work backwards to solve the problem [17]. In healthcare, the positive deviance approach is successful through presuming that the knowledge about ‘what works’ exists in identified communities [18].

In order to bring about sustainable and applicable improvements in breastfeeding rates among African American women, it is essential to ask those mothers who have exclusively breastfed to share their insight on how they overcame barriers and accomplished their desired goals. The aim of this study was to understand the lived experience of African American women who have exclusively breastfed their infants through 6 months of age. This research design was inspired by a 2017 study by Gross titled “*Long-term breastfeeding African American mothers: A positive deviance inquiry of women, infant, and children (WIC) participants*,” in which she conducted semi-structured, in-depth interviews from exclusively breastfeeding mothers from the Women, Infant, and Children (WIC) programs in three local health districts in Georgia to gain insight on their breastfeeding experiences [12, 19]. WIC is a federally funded health and nutrition program for pregnant, breastfeeding, and postpartum women whose household income is under the federal poverty line [12]. For breastfeeding mothers, WIC offers lactation counselors to provide information and support breastfeeding.

We sought to develop a similar study with interviews from African American mothers who utilize lactation counselors outside the realm of WIC. We focused on the lived experiences of exclusively breastfeeding African American women recruited from a community partnership with Breastfeed Atlanta, a network of lactation centers serving the metropolitan Atlanta area. Breastfeed Atlanta is a private lactation center in Atlanta, which employs trained professional lactation consultants who take a thorough breastfeeding history, assist with feeding, and provide evidenced-based information for a customized breastfeeding care plan to individualize care and education to increase breastfeeding rates [20]. Breastfeed Atlanta accepts some insurance plans but also allows clients to pay out of pocket for lactation services at Breastfeed Atlanta’s office or in the client’s home. These services can range from \$75 to \$220 per visit [20]. Thus, the network of African American mothers recruited from this lactation center could either have insurance coverage or afford out of pocket expenses.

Through examining factors that served as barriers and promoters of breastfeeding within the African American community, we sought to generate hypotheses on community and culturally tailored interventions to encourage African American mothers to initiate and sustain breastfeeding. The results of this study will be used to build future interventions to address barriers to breastfeeding among African American women and support the creation of community tailored breastfeeding education and interventions in lactation centers, hospitals, workplaces, and society to break the cycle of infant health disparities.

OUR STUDY

Ten African American mothers who had exclusively breastfed for at least six months were given the opportunity to reflect on their breastfeeding experience identifying factors that helped them to breastfeed and factors that may have been barriers; such as cultural expectations, social support, economic conditions, education and environmental factors.

Table 1. Demographic data

Gender	%
Female	90
Non-binary	10
Age	%
25-30	10
30-35	60
35-50	30
Head of household	%
Yes	90
No	10
Marital Status	%
Married	80
Divorced	10
Never Married	10
Education level	%
Some grade school	10
Bachelor's Degree (BA, AB, BS)	30
Master's Degree (MA, MS, MBA)	50
Doctorate (PhD)	10
Employment status	%
Full time	80
Part time	10
Self-Employed	10
Number of children	%
1	70
2	20
3	10
Number of children breastfed 6 months or longer	
1	90
2	10
Number of months exclusively breastfed	
6-7 months	30
8-9 months	30
10-11 months	20
12 months and above	20
Introduction of formula	%
Newborn	40
1-2 months	10
5-6 months	10
7-8 months	10
9-10 months	10
No formula	20
Added supplement to breastmilk or formula (e.g., rice cereal)	%
Yes	10
No	90
Introduction of solid foods %	90
6-7 months	100
Breastfeed, Pumped, or both	%
Both	100

The ten semi-structured interviews were conducted by three researchers (DD, CM, JF). The interviews were conducted in February and March 2018 at the mother's choice of time and location ranging from homes, workplaces, the lactation center, and coffee shops. The geographic context for this study was within the metropolitan Atlanta area. In collaboration with the lead Lactation Consultant of Breastfeed Atlanta who did the recruiting using a

recruitment flier and capitalizing on Atlanta Lactation Center's ListServ and Facebook contacts. To be eligible for interviews, women were required to self-identify as African American adult women, 18 years or older, be able to read and understand English, be able to consent for study participation, and have breastfed their infant for at least six months. Furthermore, the breastfeeding experience should have been initiated no longer than 12 months prior to the present interview and the infant that was breastfed was a singleton birth and was appropriate for gestational age in size at birth. Exclusion criteria were infants born at less than 37 weeks gestation, spent more than one week in the neonatal intensive care unit after birth, or had a medical condition such as gastroesophageal reflux disease or cerebral palsy, that could make breastfeeding difficult.

There were 32 women who expressed interest and were screened via telephone. Ten mothers did not meet the inclusion criteria, twelve were unable to schedule interviews, and ultimately ten interviews were conducted. Informed consent was obtained, and demographic questions were asked, including age, ethnicity, gender, marital status, educational level, employment status, household income, number of children, and number of children exclusively breastfed for six months. Demographic forms were based on the CDC Questionnaires: Breastfeeding and Infant Feeding Practices [21]. During the 1-1.5-hour semi-structured interviews we asked questions about initiating and sustaining breastfeeding, social, cultural, educational, environmental, and economic factors (see figure 3). The interviews were recorded and given an interview code to ensure participant confidentiality, pseudonyms were created using the participant initials and number of the participant. Participants received a \$10 gift card to Amazon or Target as compensation for their time.

The content of the tape-recorded interview was fully transcribed by their respective interviewers. Interrater reliability was checked with one person having experience and training conducting qualitative interviews. The interviews were then analyzed using maxQDA with training from a trained qualitative faculty researcher, HB. Codes were generated by topics that mimicked the interview guide: initiating, sustaining, education, and environmental factors.

FINDINGS

There were ten breastfeeding mothers interviewed. The participants self-identified as female (90%) and (10%) as gender non-binary, between the ages of 30-35 (50%), were married (80%), academically had a Bachelor's degree or higher (90%) and worked full time (70%), with a median income of between \$60,000-\$90,000. All participants (100%) shared that they both breastfed and pumped. The demographic data is seen in Table 1. Key results from the major areas on the questionnaire explore promoters and barriers regarding: initiating breastfeeding, sustaining breastfeeding, social support, educational resources, and environmental impacts that affect breastfeeding (see Table 2).

Table 2. Interview guide

Initiation	1) I want you to think back to your pregnancy. Please describe what motivated you to breastfeed when you were pregnant. 2) Now I want you to think back to when you gave birth to your baby. Please describe your experience initiating breastfeeding after birth. 3) Now think back to the first few weeks after you had your baby. What was your breastfeeding experience like during this time?
Sustaining	1) What were your initial goals for breastfeeding, meaning how long did you plan to breastfeed for? 2) Please describe what helped you continue breastfeeding for 6 months or longer. 3) In as much detail as possible, please describe and compare your very last experience breastfeeding as compared to your first breastfeeding experience. 4) What were some barriers that you had to overcome in order to sustain your breastfeeding goals? 5) How did you overcome these barriers?
Social/Cultural	1) What impact do you think your culture had on your breastfeeding experience? 2) Was your family supportive of your decision to breastfeed? How so? 3) Was your work supportive of your decision to breastfeed? How so? 4) Did you have childcare arrangements? 5) Who were your role models or support people while you were breastfeeding? 6) What role do you think the media plays in people's decision to breastfeed?
Education	1) To your understanding, what benefits does breastfeeding give the baby? 2) How about to yourself (mother), and/or community? 3) Did you have access to breastfeeding education? 4) What prompted your decision to come to the Atlanta Lactation Center? 5) How was your relationship with your counselor at the "Atlanta Lactation Center"?
Environmental	1) To your understanding, what environmental factors (e.g., smoking, drinking, medications, illicit drugs, cosmetics, birth control) influence breastfeeding? 2) Do you know of any other environmental factors that influence breastfeeding that maybe out of your control (e.g., stress, unemployment, inadequate safety, lack of access to education, air pollution, water access)? 3) Did the environment you were in (work/school/home) have any affect on your breastfeeding? 4) I want you to now imagine your ideal environment for breastfeeding. What would that look like?
Economic	1) Can you talk a little about the expenses associated with breastfeeding, including coming to Atlanta Lactation for professional support?
Final Questions	1) I want to better understand the breastfeeding experiences of African American mothers. Is there anything that I missed? Is there anything else that you would like to share? 2) If you had the chance to give advice on how to help African American mothers to breastfeed, what advice would you give?

Initiating

Initiating, or deciding to breastfeed within the first hour after birth, is a major component to the start of the breastfeeding experience to ensure that the infant receives colostrum, or "first milk" which is rich in protective factors [22]. The first theme to emerge was regarding initiation of breastfeeding. In this sample, all mothers gave birth at a hospital and first initiated breastfeeding in a hospital setting.

Motivation to Breastfeed

When asked about motivation to breastfeed, 80% of mothers stated that they were motivated to breastfeed because they knew it was inherently a healthier option. Of those who said it was the healthier option, 25% described breastfeeding as a ‘natural’ thing to do.

“I just knew it was healthiest and I just had read research on how it helps with the health of your gut and how that kind of leads to so many health benefits and there's still research going on, but basically, I just want it to set my baby up with the best start possible now” -JF#1

“It seemed like that was the natural thing to do. It was my first option I haven’t even thought of the formula option.” -DD#3

30% of mothers interviewed stated that the fact that breastfeeding was free and was a significant motivator for them initially.

“The health benefits, and I'm very cheap, so I should add that that's a huge motivator for me at all times. There's just a cost benefit to breastfeeding as well. I mean, it's insane how much formula is while [breastmilk] you could just produce it and it's free.” -JF#3

30% of mothers were initially allured by skin to skin and the bonding aspect of breastfeeding.

“It's a moment or an opportunity for bonding. You have those, I think they say, or endorphins or whatnot that's being produced. So it just feels, I've already said it, but super satisfying, right. Um, and then you get those kind of quiet moments with your child, so you're just kind of able to be in the moment and absorb what's happening.” -DD#3

This initial foundational knowledge of the benefits of breastfeeding could be seen as motivators to mothers to initiate breastfeeding.

Goal Setting

A major recurring motif was goal setting prenatally, 80% of mothers had a goal of breastfeeding for one year, with 50% of the mothers quoting American Academy of Pediatrics (AAP) recommendations they received from AAP’s book “Caring for your baby” or from their pediatrician.

“I knew that I wanted to do it at least for the first year. That was my personal goal, just because I knew that based on research, the first year even up to two years is really beneficial for baby. So that was my goal, but I was flexible with myself and knew that that may or may not change when I went back to work. I actually made it past that. So I would say just putting the emphasis on helping before delivery and then also in the hospital” -DD#2

Furthermore, one mother cited that her initial goal was only to breastfeed for three months which correlated with her maternity leave. However, she found her breastfeeding experience getting easier and less cumbersome over time.

“My initial goal was three months and while I was on maternity leave to see how we can do this and take it from there. Then I got to 3 months and was like man 3 months came kind of fast and then I was like let’s try to 6 months.” -DD#3

While actively making the decision to breastfeed helped establish a mindset to breastfeed, however, upon initiation and their first breastfeeding experience, 60% mothers described difficulties they encountered when initially breastfeeding.

Sustaining

In order to sustain breastfeeding many mother stated that having determination was a positive promoter. Of the mothers interviewed, 50% talked about having determination to reach their goals.

“Sheer perseverance, partially being stubborn.” -JF#2

“Just prayer and determination. I mean I just set a goal and I just, I’m just keeping with it. There are times where my supply goes up and down and I recently had to travel for a week and pumped milk for that, but it’s just through consistency and discipline. I believe you can do it.” -JF#1

“It’s that determination from friends and family and support groups.” -DD#3

Difficulty Latching

An initial barrier encountered described by 60% of the mothers was difficulty latching. Of those who had difficulty latching, 50% said they found it painful to nurse which escalated into stress for the mothers, who became concerned that their babies lacked adequate nutrition.

“I think she had a shallow latch, which really made it excruciatingly painful to nurse” -CM#1

“And so, every time to try to make her latch was kind of really stressful for me because the way that it was suggested by the doctor that we saw, the pediatrician was like ‘push her head into the breast’. And then it was, it just looks so stressful for both of us. She’s so tiny and she was six pounds 15 ounces and then she was straining and crying and all that stuff.” -DD#4

90% mothers described methods to overcome these initial barriers, such as utilizing breastfeeding equipment and seeking outside help initially from a lactation consultant.

“I ended up using an SNS [Supplemental Nursing System] to put him back at the breast to try to get him to latch because there got to be a point where he wouldn’t latch at all. Christy evaluated his latch, which was horrible, so he really wasn’t really getting anything. He might’ve been getting colostrum in the hospital, but slowly but surely it just wasn’t happening.” -JF#2

Other barrier mothers in this study had to overcome included breastfeeding pain due to cracked and sore nipples, low milk supply production, time management, birth trauma and getting used to breastfeeding in public. Although barriers presented themselves during the

initiation phase, these mothers overcame them and were able to sustain breastfeeding for six months or longer.

Social Support

70% of the mothers interviewed were married and a 86% of those mothers who were married described having a supportive partner.

“He was very supportive. He was kind and encouraging me because we went to a hospital tour at Dekalb Medical, they have a breastfeeding kind-of segment because they actually have a lactation consultant do the tour so that she can kind of plug breastfeeding in there. So, he was able to hear like the importance of breast milk on his own and he knew it from before and he had always been supportive before but just to have a lactation consultant speaking to the both of us and telling us the importance of the nutrients, so he was supportive” -CM#1

One mother described how at first her partner was reluctant about breastfeeding, in particular in public, but how his views have changed over time.

“And the look on my husband's face was like, oh, like I think he could have freaked out, but he didn't want to freak out in front of everybody because nobody else was freaking out. And he slowly but surely got used to it and now he'll say ‘I can't believe the stigma of people!’” -JF#2

Another mother described how breastfeeding not only helped her bond with her baby, but it helped her husband bond with their baby as well.

“I think exclusively pumping gave me some flexibility in actually helped her get very close with her dad. She's super close with him, but we split the tasks after the two weeks when she stopped latching where it wasn't all about me. And he would feed her her bottle half the time too. So she has a really strong attachment to him as well, so I do think that was good about exclusively pumping.” -DD#4

For partners that were not described as supportive, barriers to breastfeeding included feeling like bottle feeding was more convenient.

“My husband, we're still working on him. He's cool with it and he understands that this is the most healthy option but he doesn't feel like it has to be the only option either. He's more of a convenience thing. Uh we got to stop for 30 minutes because she needs to breastfeed, why can't you just give her a bottle, or you know” -DD#3

Another barrier encountered was the stigma of breastfeeding in public and how it subsequently makes husbands uncomfortable. This particular mother described how she overcame that barrier.

“My husband's not comfortable with me not covering. So if I had it my way I would just do like the 2 shirt method. So if I nurse in public it's either in the car, in the backseat, my windows tinted or I try to find a room that no one's in, i usually try to do that at church or kind of struggled with the cover” -CM#1

Scheduling and Preparation

Of the 90% full time working mothers, 55% described how they faced barriers with scheduling and how they had to had to schedule and prepare how to pump while at work which in turn affects their production.

“The other challenge is just in the industry that I was in, it was just hard at times to pull away to go do that. My work schedule, the amount of times that you're pumping affects your ability to produce it. So that went down for me once I started working during the work day and then you get home, you're tired and so that negatively affect my production for sure.” -JF#3

Although barriers were faced, promoters discovered were active planning and preparation for optimal time management.

“So it just took a lot of planning and preparation, make sure that I had enough water and snacks because I get really thirsty and hungry when I'm pumping and nursing.” -DD#2

“I would pump when I got to work. I would pump when I got up at like six and that was hard too because I do mornings with her so then when I got to work I would pump before class and then right after class I would come, then I would hold office hours then a couple of pumps later on” -DD#4

Furthermore, of the full-time working mothers, 22% described how a long commute to work itself that served as a barrier. The two mothers described driving an hour to and from work and how they had to figure out how to pump on their nursing schedule.

“I traveled for work. I'm on the road every day. Sometimes that entails staying overnight. So having to be prepared whether that was with a cooler planning out my route so that, you know, I had time built in to stop” -DD#2

“The biggest barrier is the fact that I work full time. I have to go back to work right before her 12 weeks, but the biggest challenge that I have to pump in order to send bottles to daycare and that's really hard to get that time in. I talked to a lot of people and went to several lactation support groups here in the city and just talked to other moms and getting tips on how to make it convenient and getting a manual pump or getting the adapter that allows you to pump in the car while driving.” -DD#3

Improvements over Time

Additionally, 50% of mothers stated they were motivated because they saw marked improvements in the breastfeeding relationship over time.

“I just know so much more, I know the cues, it doesn't hurt anymore. She's a lot faster now, at the beginning it was like four-five minutes at a time and an hour and she used to fall asleep in the beginning” -DD#3

“I would say just the, probably the confidence that I gained those first few weeks helped me to realize that it was actually very easy for me.” -DD#2

Education

A major source of support for many of the participants included lactation consultants. 90% of the mothers had prior knowledge of the role of lactation consultants and knew to reach out for their help when encountering barriers.

The majority of our participants (70%) took a breastfeeding class prenatally and stated that it helped them to feel more prepared and had an idea of how to latch the baby. Of those that took a breastfeeding class, 2 out of the 7 women stated that in theory they knew what to do after taking a class but felt that they needed more support to overcome barriers:

“I had gone to a breastfeeding class at the same hospital I delivered but it was like a theory. Afterwards, I was in pain and healing and extremely tired even though I did have my mom there.” - DD#3

90% of the mothers also started receiving their education through online support groups like Facebook and reading books such as “The big letdown” and “What to expect when you're expecting.”

Knowing Your Rights

This year, 2018, Utah and Idaho enacted laws making breastfeeding in public a legal right in all 50 states plus the District of Columbia, Puerto Rico and the Virgin Islands. A few mothers mentioned the importance of knowing breastfeeding rights in order to advocate for themselves in the workplace. While the majority of our participants had supportive work environments they encountered other women on their online support groups for which this was a huge barrier.

“Learning about the state regulations that protect your right to breastfeed at work, like having lactation areas and having an area designated for you and have to make a reasonable attempt to allow you space and time to pump. Learning all of those helped me to advocate for myself was important and learn how to talk to my CEO.” -DD#4

Health Benefits for Mother, Baby, Community

70% of the mothers mentioned mother–infant bonding as a benefit of breastfeeding to mothers, babies and the community. For the breastfeeding benefit to babies the most common responses included overall healthier babies, brain development, complete nutrition, and reduction of SIDS. One mother stated that the reduction of SIDS was the strongest motivating factor for her decision to breastfeed her second baby.

“So, I think just overall healthier babies and healthy parent-infant relationships, and maybe more confident babies.” - CM#1

“I think it helps the community because it sets a healthy example for mom and baby. I think it helps baby be happier. I think it helps baby be healthier.” - DD#2

“Health benefits for the baby, it reduces SIDS. That really turned me on because that’s really scary part when you first have kids. The health benefits.” -CM#3

Environmental

We asked mothers what environmental factors served as barriers to their breastfeeding experience, 40% cited stress as a barrier to breastfeeding.

“I would say stress, because I am a single mom... stressing sometimes does sometimes affect your milk supply, so I can empathize with ones who are financially struggling having or having housing or shelter struggles, and how that stress can affect your decision.” JF#1

“Stress will kill your breastfeeding journey.” CM#3

“If you have at home stress, if you're not a stable living situation. I definitely understand how I'm breastfeeding can be very difficult.” DD#2

We concluded our interviews with asking this study group to give advice on how to help African American mothers to breastfeed they stated these pearls of wisdom:

“Have a support system of other African American mothers”
 “Realize why you want to do it and push beyond previous generations assumptions”
 “Find people that are going through what you’re going through”
 “Know that you are all they [babies] need”
 “Reward yourself. If I make it to 6 months, what am I going to do for myself?”
 “The benefits outweigh the difficulty in the beginning.”
 “Support and encourage each other. Be willing to give someone a demonstration.”
 “Know that you’re doing what’s best for her.”

Table 3. Benefits of breastfeeding

Benefits for babies	Benefits for mother	Benefits for the community
Mother-Infant Bonding	Mother-Infant Bonding	Healthier communities
Overall healthier babies: • Brain development • Complete nutrition • Decrease SIDS	Saves time	Cost savings for healthcare system
Changes specifically to babies needs	Saves money	Environmental benefits
	Cancer reduction	
	Losing weight	

DISCUSSION

Breastfeeding has been shown to benefit mothers, babies, and the overall community. The rates of breastfeeding initiation and breastfeeding exclusively for 6 months or more are lower among African American women (14%) compared to white women (22.5%). In this study we conducted qualitative semi-structured interviews with ten African American women who had exclusively breastfed for at least six months, each with their own personal narratives, promoters, and barriers they faced. Each mother expressed interest in trying to better

understand why the breastfeeding initiating and sustaining rates among African American women were significantly lower. We hoped to understand the factors that have influenced the experiences of African American women that have exclusively breastfed their infant through six months of age. We chose to use the ‘positive deviants’ model by identifying women who had successfully breastfed for 6 months or more, and learn about the factors that have been promoters and barriers in their breastfeeding experience.

In Gross’ study, her positive deviants were African American mothers from the WIC programs, which primarily serve mothers with household incomes below the federal poverty line [12]. In this study, the positive deviants were African American mothers recruited through Breastfeed Atlanta, a metropolitan lactation center, who have higher median income to be able to afford lactation services. In our sample, all ten mothers had a median income between \$60,000-\$90,000 and were educated, informed, affluent, motivated, employed and had supportive families and social networks. The mothers from Breastfeed Atlanta are in accordance with those mothers in the Gross study from WIC who sought African American lactation support personnel and African American breastfeeding support groups [12]. Despite having higher income levels, this study of mothers also emphasized the importance of having a community of other African American mothers to support and encourage each other. Thus, the desire to have support within the African American community transcends poverty lines and socioeconomic status.

Furthermore, the breastfeeding mothers in this study also offered insight for working African American mothers above poverty level who are navigating the unique workplace challenges related to breastfeeding. For example, 55% of the mothers encountered barriers around scheduling pumping time at work in order to maintain their milk supply. Ultimately, most of the advice the mothers provided were free and accessible and could be utilized by other African American women as well as by online educational resources and support groups.

Learning about the promoters and barriers for women that have successfully breastfed for up to 6 months, offers valuable insight on social, cultural, economic and environmental factors that influence breastfeeding rates among African American women. The promoters identified were: prenatal goal setting, cost savings, educational resources, knowing your rights, Facebook groups, and knowing multisystem health benefits for the baby, mothers, and community. The women in this study felt that their determination and the support of lactation consultants, online support groups and friends and family acted as positive promoters in reaching their breastfeeding goals. These mothers showed a passion and ardor to reach their goals, especially through prenatal goal setting and partners who support their goals. Thus, the internal determination and steadfastness to commit to goals of these mothers ultimately led to their success.

This study also revealed barriers that the women had to overcome such as: difficulty latching, stigma, work schedules, commutes, and stressful environments. An overwhelming 60% of mothers reported difficulty latching as a major barrier to breastfeeding exclusively. The mothers stated were able to overcome this barrier because they were motivated by improvements in the breastfeeding relationship with their infants after gaining the knowledge, the experience and the skill to persevere. In this context, lactation consultants were crucial in educating women on breastfeeding frequency, latching, increasing their milk supply and assuring mothers that their babies were getting enough milk. Furthermore, community groups such as online support groups on Facebook created a sense of community and gave

representation and role models of other African American women breastfeeding. Therefore, proper knowledge of how to improve latching and when to seek out additional help is important in educating and affirming African American women that they are capable, and it is possible.

Another barrier encountered was the stigma regarding breastfeeding, including how it inconveniences their partner or makes them uncomfortable, however, emotional and social support was crucial for sustain breastfeeding longer than six months. Ultimately 70% of the mothers described having supportive partners whether it was initially, because of early education efforts, or over time throughout the breastfeeding experience. These mothers highlighted the importance of including the partner in early education efforts about the multisystem health benefits for the baby, mothers, and community, allowing the partner to build a bonding relationship with the baby, and breastfeeding using blankets and covers.

Additionally, 90% of the full-time working mothers described scheduling and lengthy commutes as barriers to breastfeeding. The mothers described combatting this with active planning and preparation including food, water pumping supplies and chargers, and portable refrigeration systems. Furthermore, carving out the time around the work schedule was difficult but a few mothers mentioned the importance of knowing breastfeeding federal laws in order to advocate for themselves in the workplace. Thus, through a knowledge base of the rights, and with advanced scheduling, breastfeeding can be possible despite a full-time schedule and lengthy commute. All the mothers in this study reported pumping in their breastfeeding journeys.

Based on the barriers and promoters identified in the study, our recommended breastfeeding community interventions for African-American mothers include helping new mothers establish breastfeeding goals prenatally and equipping them with evidence-based education. Furthermore, it is important to encourage providers and hospitals to make referrals to lactation consultants and incorporate lactation education for expectant mothers and families. The mothers in this study felt more prepared in initiating breastfeeding after receiving breastfeeding education. Additionally, women should receive education on their breastfeeding rights and other environmental factors that influence breastfeeding and the health of our communities overall. This study group received their education about breastfeeding through their healthcare providers, nurses, online support groups, breastfeeding class and lactation consultants. Breastfeeding education is readily available and free for mothers who have internet access and know how to navigate resources online. Access to lactation consultants was integral in helping the mothers overcome physical and emotional barriers to breastfeeding.

Some of the mothers in this study benefited from insurance coverage for lactation consultants and breastfeeding pumps. Hence, having health insurance coverage for lactation consultants and for breastfeeding supplies helps to alleviate monetary constraints and promotes the sustaining of breastfeeding.

The mothers we interviewed had relatively high autonomy in their workplace and most were able to breastfeed during work hours. Regardless of socioeconomic status, African American mothers should be equipped with knowledge of the laws surrounding adequate breastfeeding and accommodations in the workplace and tools on how to advocate for themselves. For example, in the state of Georgia, Ga. Code An. § 34-1-6 states “An employer may provide reasonable unpaid break time each day to an employee who needs to express breast milk for her infant child. The employer may make reasonable efforts to provide a room

or other location (in close proximity to the work area), other than a toilet stall, where the employee can express her milk in privacy.” Thus, break times could be used to schedule adequate pumping schedules to not affect milk supply.

It is important for healthcare providers to educate African American women on their resources and services available to them, whether it be through their insurance coverage with lactation support services or community resources available. Lactation consultants were integral in helping mothers overcome physical and emotional barriers to breastfeeding. Ultimately, it is crucial to build community by linking African-American women with other African-American mothers who practice exclusive breastfeeding. Equipping mother prenatally with resources in their local community or on an online forum such as the Facebook group “Black Moms Do Breastfeed” [23]. Fundamentally, 100% mothers found reassurance that they were doing what they thought was best for the baby. It is important as health care professionals and society to provide affirmations and reassure mothers they are capable of adequately feeding their baby solely through breast milk.

The sample in this study was from a highly selective population that may not reflect the general African American population. The majority of mothers interviewed in this study were married, with higher levels of education, and above the poverty line which revealed promoters and barriers that may not be relatable to other African American mothers who lack similar resources. Another limitation was mother’s self-reporting on exclusivity of breastfeeding. Although our inclusion criteria required exclusively breastfeeding for six months, 80% of mothers divulged that they supplemented with formula for short periods due to overcome latching and milk supply difficulties. During the inclusion screening these mothers self-identified as exclusively breastfeeding (Figure 2). During our phone screening, we relied on self-reporting of the mother to deem themselves exclusively breastfeeding for 6 months. Therefore, a major limitation in this study was failing to include any type of “formula supplementation” as an exclusion criterion.

CONCLUSION

Although the Centers for Disease Control and Prevention reports that African American mothers do not initiate or sustain breastfeeding at the same rate as white mothers, there are African American mothers who do breastfeed and from whom lessons can be learned that can encourage other African-American mothers to breastfeed successfully and overcome this disparity in breastfeeding practices. The insight gained in this study from the positive deviants can be amplified to address this public health issue of racial disparities in breastfeeding. Health care professionals serving diverse populations should actively and encourage a supportive culture surrounding breastfeeding through the establishment of prenatal breastfeeding goals, educational support for healthcare providers and mothers, African American community groups, and providing affirmations during the breastfeeding experience particularly for all African American mothers. Thus, the lessons from the breastfeeding African American mothers in this study can help break the cycle of children’s environmental health disparities by providing insight on barriers African American women face regardless of income level or access to services, and offers valuable promoters that can be utilized by other African American mothers to overcome breastfeeding difficulties.

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Chapter 58

MATERNAL CHILDHOOD ADVERSITY AND EARLY PARENTING: IMPLICATIONS FOR INFANT NEURODEVELOPMENT

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ABSTRACT

In this chapter we aimed to examine associations between maternal childhood abuse and maltreatment, early parenting behaviors, and infant neurodevelopment among African American mother-infant dyads. Maternal adverse childhood experiences (ACEs) were assessed during pregnancy using the Childhood Trauma Questionnaire, and early parenting behaviors were assessed by coding videotaped observations using an adapted version of The Three-Bag Assessment when infants were 3-months of age. Infant neurodevelopment was assessed using the cognitive and motor subscales of the Bayley Scales of Infant and Toddler Development. At the time of this analysis, 59 mother-infant dyads had ACEs exposure, early parenting, and infant neurodevelopment data available from the infant 3-month assessment. Preliminary findings suggest no main effects of maternal adversity on infant neurodevelopment and indicated no significant interaction effects between maternal adversity and early parenting behaviors, although this study may have been underpowered to detect a small effect given the sample size available. It is still possible that these factors predict the rate of neurodevelopment beyond the first three months of life, which will be examined using growth curve analyses in future studies. The overall goal of this ongoing research is to explore parenting behaviors as a key point

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of intervention that may reduce the intergenerational impact of ACEs on child neurodevelopmental outcomes, thereby breaking the cycle of risk.

INTRODUCTION

Exposure to adverse childhood experiences (ACEs), such as poverty, abuse, or neglect, represents one of the most prevalent and detrimental risk factors for abnormal biological, psychological, and behavioral sequelae [1]. Over the years, empirical studies have suggested that childhood adversity is associated with dysfunction within the neuroendocrine system [2], increased risk of psychopathology [3], and later perpetration of violence [4]. Recent studies have also indicated that the effects of ACEs have the potential to cross generational lines and impact offspring's socio-emotional and developmental outcomes [4]. Much of the research on the long-term outcomes associated with ACEs has been guided by the Life Course Model, which considers how chronological age, relationships, and social factors shape people's lives from birth to death [5]. There is overwhelming evidence that ACEs can impact later outcomes well into adulthood across behavioral, social, and cognitive domains [6, 7], and studying ACEs from a life course perspective acknowledges that there is a unique relationship between time, experience, and human development. While individual trajectories vary, patterns can be predicted based on environmental exposures and experiences.

For example, evidence continues to amass that individuals who reside in lower socioeconomic status (SES) communities are disproportionately exposed to early life adversity [8]. Low SES has been cited as a risk factor for child abuse perpetration among caregivers [9], and children who live in low SES communities are also more likely to be exposed to violence, neglect, various forms of abuse, and caregiver substance use or serious mental illness [9]. Further, researchers examining the long-term impact of childhood abuse have suggested that early childhood victimization affects later economic stability [10-12]. Zielinski [10], for example, found victims of child maltreatment to be at an increased risk of financial and employment-related difficulties in adulthood. Poverty thus serves as both a consequence of and a risk factor for other ACEs and may play an important role in the intergenerational transmission of adversity (see Figure 1).

Importantly, children of mothers with a history of childhood adversity, even in the absence of ACEs themselves, are at increased risk of internalizing and externalizing problems, such as anxiety, emotion dysregulation, aggression, delinquency, and overall worse adjustment over time [13, 14]. Maternal ACEs have been linked to child emotional development and behavioral problems at ages 4 and 7 years [13] and disruptive behavior during adolescence [15]. The impact of maternal ACEs on child cognitive and motor development in infancy is less well studied and is the focus of the current investigation.

Poor parenting practices may be one mechanism by which maternal ACEs negatively impact infant neurodevelopmental outcomes. Empirical studies have demonstrated that maternal childhood exposure to violence, neglect, emotional maltreatment, and sexual abuse are significantly associated with mothers' observed hostility toward their children and concerns related to their parenting competence [16]. Maternal ACEs have also been linked to decreased maternal responsiveness, sensitivity, and positive affect, which reflect her ability to have a prompt and appropriate response to her child's needs [17]. Maternal childhood adversity may therefore impair her ability to form secure attachments with her child [18],

which aligns with Bowlby's attachment theory [19]. This theory suggests individuals develop an "internal working model" during infancy that serves as the basis of their worldview. The infant signals its needs for care, and differences in the quality of attachment are due to the caregiver's responsiveness and sensitivity to the child's needs. From this interaction, infants then form their basic expectations about the environment. Abuse, inconsistency, or rejection from a primary caregiver can diminish the quality of the bond, thereby negatively impacting the child's developmental outcomes.



Figure 1. Factors that maintain the cycle of disadvantage and disparities.

On the other hand, positive parenting might ameliorate the potential negative impact of maternal ACEs on child outcomes. Warm, supportive, and stable relationships have consistently been cited as protective factors across a number of studies [20] and are thought to be critical to normal child development. Indeed, positive parenting strategies are believed to promote child independence, facilitate the achievement of other developmental outcomes, and are frequently linked to increased child cognitive performance [21]. For example, positive mother-child interactions have been linked to higher scores on infant mental development indices at 12-weeks [22], and child cognitive development has been described as a function of maternal responsiveness [23]. Responsiveness often includes providing appropriate levels of stimulation in ways that support children's learning [23]. Additionally, it has been theorized that maternal responsiveness affects mother-infant attachment, which consequently determines the degree to which the infant feels secure enough to explore his or her surroundings [23]. Positive parenting behaviors are therefore beneficial for young children's development of emotional security, social competency, and independence. Previous studies have primarily focused on the impact of negative parenting practices that are associated with maternal ACEs. However, maternal ACEs and poor parenting do not always go hand in hand. One of the aims of the current study is to examine positive parenting as a potential moderator of the relationship between maternal ACEs and infant neurodevelopment.

Notably, very few studies have examined the association between maternal childhood adversity and infant neurodevelopment as a function of early parenting behaviors. Such studies might elucidate that early parenting behaviors are a key point of intervention for

breaking the cycle of adversity that is especially maintained in lower SES and minority populations. Black Americans, for example, experience twice the rate of poverty of White Americans [8], and results from studies using the Centers for Disease Control and Prevention's ACEs module indicate that Black Americans are also disproportionately exposed to ACEs when compared to their White counterparts [24]. Although social scientists have dedicated many years to unfolding the short- and long-term consequences of early life adversity, most of the research in this area has relied on cross-sectional studies and retrospective accounts. It is therefore crucial that the influence of ACEs on parenting and infant neurodevelopment is examined using prospective research designs in samples that may be at increased risk. The present study attempts to fill this gap in the literature.

This pilot study aimed to explore the effects of maternal ACEs on infant neurodevelopment. It was hypothesized that maternal experiences of childhood abuse and neglect would predict lower scores on measures of infant neurodevelopment at three months of age. Secondly, this study aimed to examine whether positive parenting behaviors would mitigate the effect of maternal childhood adversity on infant neurodevelopment. It was therefore hypothesized that the association between maternal ACEs and infant neurodevelopment would be weaker in cases where mothers displayed more positive parenting behaviors.

OUR STUDY

Study participants were African American mother-infant dyads (N=59) currently enrolled in a larger, ongoing study focusing on infant development. All participants were originally recruited during pregnancy from hospitals in a large metropolitan city in the southeastern United States. Inclusion criteria for the pregnancy study were: 1) African American race (as determined via self-report); 2) Maternal age of 18-40 years; 3) No chronic medical conditions; 4) Singleton pregnancy; and 5) Fluency in written and spoken English. During their participation in the pregnancy study, mothers were asked if they would be willing to be contacted for future studies. Women were then recruited for the infant study if their infants were born without congenital disorders. Informed consent was obtained from the women prior to participation in the infant study using procedures approved by Emory University's Institutional Review Board. Participants were included in the current study if mothers reported on their history of childhood adversities and mothers and infants completed the postnatal follow-up study visit when the infant was 3-months-of-age.

Data for the present study were collected at two study time points: during pregnancy (T1) and when offspring were 3-months-of-age (T2). Ongoing follow-up visits occurred at 6-months (T3), 12-months (T4) and 18-months (T5) of age, but these time points were not included in the present study due to insufficient sample size to date. Maternal demographics (i.e., age and socioeconomic status) and history of adversity were collected at T1 via questionnaires and medical chart record abstraction. At T2, mothers and infants completed videotaped observation tasks and infants were administered an assessment of mental development status. Study visits were conducted by trained Master's level research assistants either at participants' homes or during a visit to the laboratory at Emory University.

Sociodemographic Factors and Statistical Controls

Information about mothers' age in years and socioeconomic status were collected at T1 and examined as potential control variables. Socio-economic status was operationalized as the mother's federal poverty level and highest level of education.

Maternal Childhood Adversity

Maternal adversity was assessed at T1 using the Childhood Trauma Questionnaire (CTQ) [25], which asks about experiences of abuse and neglect during childhood and adolescence and has been shown to yield reliable and valid retrospective assessments [26]. Responses were collected on a 5-point Likert scale, with response options ranging from Never True [1] to Very Often True [5]. A visual inspection of the CTQ score histogram suggested scores were non-normally distributed. Therefore, dichotomous indicator variables were derived to denote maternal history of physical abuse, sexual abuse, and neglect, where 0 = Never and 1 = Some Exposure.

Early Parenting Behaviors

Parenting behaviors were assessed using five-minute free-play situation videos for mother-infant dyads obtained at T2. An adapted version of the Three-Bag Assessment [27] was used to code each interaction task video for maternal sensitivity and positive regard. Maternal sensitivity refers to the mother's capacity to recognize the child's emotional state and respond with comfort, consistency, and warmth, and positive regard refers to behaviors such as having a warm tone or smiling [28]. Each parenting behavior variable (i.e., maternal positive regard and sensitivity) was coded on a scale ranging from 1 to 4 points, where 1 represents no evidence of the particular variable, and 4 represents the highest relative demonstration of that variable. A single positive parenting summary score was computed by combining the two positively-valenced domains and could range from 1-8, where higher scores indicated more positive parenting behaviors.

All coders underwent an initial coding training sequence to achieve independent levels of greater than or equal to 80% reliability for previously determined "gold standards" of each coded variable. Coders included trained graduate and undergraduate students who were blind to levels of maternal distress and infant mental development. A trained graduate student supervised ongoing reliability of 20% of the coded videos, maintaining greater than or equal to 70% reliability for each coded variable across interaction tasks, and holding weekly coding meetings, as needed. Intraclass correlations of inter-rater reliability on all coded variables ranged from 0.81 to 0.94.

Infant Neurodevelopment

Infant neurodevelopment was assessed at T2 using the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) cognitive and motor subscales [29]. The Bayley-III was designed to evaluate developmental functioning through a series of standardized items. After each assessment, raw scores for each subtest were calculated by the test administrator and double-scored by two trained undergraduate research assistants. Raw scores were then converted to standardized scores to determine each baby's cognitive and motor skills composite scores, which were used in current study analyses. The cognitive composite score reflects the infant's ability to think, react, and learn about the world around him or her. The motor skills composite score combines gross motor and fine motor skills, which gauge how well the infant can manipulate objects with his or her hands and examines static positioning, movement of limbs, and balance. The Bayley-III Scales have been well validated and are a reliable indicator of infant mental status [30].

Data Analyses

Descriptive analyses were performed to assess sample characteristics. Data were examined for multicollinearity and normality using univariate procedures, and bivariate analyses were conducted to identify statistical controls. To assess study aims and hypotheses, a series of multiple linear regression analyses were performed using maternal childhood adversity and parenting variables as predictors of infant neurodevelopmental outcomes at T2 (i.e., cognitive composite score and motor skills composite score, respectively). To test moderation hypotheses, interaction terms were computed by centering each independent variable of interest and obtaining the product (i.e., maternal physical abuse $\times$ positive parenting, maternal sexual abuse $\times$ positive parenting, and maternal neglect $\times$ positive parenting, respectively). Multiple linear regression analyses were then conducted in SPSS [31] to assess whether maternal childhood adversity interacted with parenting behaviors to predict infant neurodevelopmental outcomes at T2. Estimates were considered statistically significant at $p < 0.05$.

FINDINGS

The average age of mothers in this sample ($N=59$) was 25.34 ($SD = 5.40$). The majority of the sample had a high school diploma or GED ($n = 28$; 47.5%) and were at less than 100% of the federal poverty line ($n=23$; 39%). Approximately one third of mothers reported experiencing physical abuse ($n=20$), sexual abuse ($n = 20$), and/or physical neglect ($n=22$), and the average positive parenting score was 6.78 ($SD = 1.34$). Additional sample characteristics are reported in Table 1.

Preliminary analyses examining maternal age, education, and income as covariates were conducted using Pearson correlations and independent samples t-tests. Results indicated a significant correlation between maternal age and infant motor skills composite scores at 3-months ($r = -0.24$, $p = 0.048$), with older mothers' infants having lower scores. Maternal age

was not significantly associated with infant cognitive scores ($p = 0.59$). Additionally, there were no significant differences in either motor or cognitive scores by maternal education or income level ($ps > 0.05$).

Table 1. Sample characteristics (N=59)

Variable	n	%	Mean (SD)	Range (Min-Max)
Education				
Some High School or Less	6	10.2		
High School Diploma/GED	28	47.5		
Some College/Technical School	14	23.7		
College Grad or Higher	11	18.6		
Household Income				
< 100%	23	39.0		
100-149%	14	23.7		
150-299%	11	18.6		
300% or Greater	7	11.9		
Maternal Childhood Adversity				
Physical Abuse	20	33.9		
Sexual Abuse	20	33.9		
Physical Neglect	22	37.3		
Maternal Age			25.34(5.4)	18 - 40
Positive Parenting Score			6.78 (1.34)	3 - 8
3-mo Bayley Composite Scores				
Cognitive			110.85 (14.95)	65 - 140
Motor Skills			110.64 (12.80)	85 - 139

**Table 2. Preliminary results: Summary of main effects
(3-month follow-up)¹**

	Coefficient	SE	t-statistic	p-value
Main Effects - Cognitive				
Physical Abuse	-1.60	5.25	-0.3	0.76
Sexual Abuse	-6.10	5.35	-1.14	0.26
Neglect	-1.25	4.10	-0.31	0.76
Main Effects - Cognitive				
Positive Parenting	1.26	1.46	0.86	0.40
Interaction Effects Models (Cognitive)				
Maternal Physical Abuse*Parenting	2.14	3.18	0.67	0.50
Maternal Sexual Abuse*Parenting	-7.83	4.08	0.62	0.54
Maternal Neglect Abuse*Parenting	0.58	3.07	0.04	0.85
Main Effects - Motor				
Physical Abuse	-3.67	4.43	-0.83	0.41
Sexual Abuse	-2.92	4.45	-0.66	0.52
Neglect	1.29	3.43	0.38	0.71
Main Effects - Motor				
Positive Parenting	-0.87	1.27	-0.70	0.49
Interaction Effects Models (Motor)				
Maternal Physical Abuse*Parenting	2.78	2.62	0.16	0.29
Maternal Sexual Abuse*Parenting	2.70	2.62	1.03	0.14
Maternal Neglect Abuse*Parenting	1.25	2.55	0.49	0.63

¹ All interaction effects models run separately. Models using motor composite scores as the primary outcome control for maternal age.

To examine study aims and hypotheses, a series of multiple linear regression analyses were performed. Results indicated that there were no significant main effects of maternal childhood physical abuse, sexual abuse, or neglect on infant cognitive or motor skills development at 3-month follow-up ($p > 0.05$; see Table 2). There was also no significant main effect of positive parenting on infant cognitive or motor skills at 3-months-of-age. Finally, results indicated that there were no significant interaction effects between maternal childhood adversity and parenting ($p > 0.05$; see Table 2).

DISCUSSION

ACEs have been cited as significant environmental risk factors for a host of negative outcomes. Minority populations and those who reside in socio-economically depressed areas are disproportionately exposed to ACEs [8, 24], and studies have provided evidence that ACEs may have intergenerational effects on offspring development [13, 14]. There is evidence that maternal ACEs decrease maternal responsiveness, sensitivity, and positive affect, which in turn, impede infant neurodevelopment [17]. Recently, associations between maternal ACEs and child brain anatomy have been observed [32]; but the majority of research in this area has relied on cross-sectional studies and retrospective accounts. This study aimed to examine associations between maternal childhood abuse and maltreatment and infant neurodevelopment and assess whether early parenting behaviors moderated these associations. Preliminary findings from this pilot study, however, suggest no main effects of maternal adversity on infant neurodevelopment at 3-months and indicated no significant interaction effects between maternal adversity and early parenting behaviors.

It is important to acknowledge several possible methodological limitations in the current study. First, this pilot study was limited in its ability to detect significant effects due to a small sample size, which was supported by post hoc power analyses ($1 - \beta = 0.31$). Secondly, it is possible that infant neurodevelopment scores at 3-months of age are less reliable and stable than later time points. The Bayley manual provides test-retest reliability values that range from .67 to .80 for infants aged 2 to 4 months; but these indices were calculated using very short retest intervals (approximately 6 days). There will likely be significant developmental changes as time progresses since milestones are achieved more rapidly in the early stages of life [33], and scores are expected to stabilize. Thus, by 6- and 12-month follow-up, Bayley scores may be more reliable and valid.

It is also possible that there are nonlinear associations between maternal childhood abuse and neglect, where effects at the tail ends of the distribution have the greatest effects on infant neurodevelopmental outcomes. The present study assessed maternal history of adversity using the CTQ but derived dichotomous indicators of abuse and neglect, because of the non-normal distribution of scores. Dichotomous variables inherently have no range and less variability, which may deflate the significance of effects. Mothers with severe levels of exposure to abuse and neglect, however, may be at greatest risk, as previous researchers have noted worse outcomes among individuals with severe exposure to adversity [3, 34]. Future studies should therefore consider the severity of experiences to identify potential risk thresholds for negative outcomes.

Finally, parenting measures, while objective, were conducted in participants' homes under video-taped conditions. The literal act of video-taping the mother-child interaction subsequently necessitates that mothers are highly aware of their behaviors, words, and emotions, particularly those that are directed towards their 3-month old infant. While this paradigm allows for researcher standardization (across all observed videotaped home-visits of participants) it also leaves room for artificially positively-valenced observations. This artificial increase may have contributed to mothers' high scores on sensitivity and positive regard, the two variables that were captured within our positive parenting variable. Mothers' positive parenting ranged from 1 to 8, but on average, fell at 6.78 (1.34). Mothers may have been more likely to behave positively towards and around their children, due to 1) the presence of the study researchers, 2) the presence of video cameras, and 3) the knowledge that their behaviors were being captured for purposes of scientific study. As such, it is possible that we could not adequately capture a full range of parenting behaviors. This phenomenon can be likened to the Hawthorne Effect, or the concept that research study participants often change their behavior simply as a function of the fact that they are observable participants [35]. This phenomenon has been reported in parenting intervention programs [36], and previous studies have hinted at a need to control for the emergence of the Hawthorne Effect, particularly when studying young children [37]. To address this issue, future studies could incorporate self-report measures of parenting for purposes of reliability and comparison. Although parents are often unreliable raters of their own behaviors and often rate themselves more positively than other reporters [38], the combination of observer ratings and self-report may be preferable to including only one of these methods on their own. Lastly, it is possible that 3-months of age is too young to elicit a varied range of behaviors from mothers. We would expect more variability in infant temperament and maternal parenting as the infants age [39].

Despite the above stated limitations, this study has notable strengths. First, the usage of a prospective longitudinal design is quite promising and will provide the ability to examine rates of infant neurodevelopment using growth curve analyses in the future. Data collection on our postnatal cohort will continue at 6, 12, and 18 months, with a goal to eventually enroll study participants in a second longitudinal study with time points at 2, 3, 4, 5, and 6 years. We are also utilizing a well-validated, reliable tool for the assessment of infants' neurodevelopment. Infant mental assessments are notoriously challenging, but the Bayley-III is widely used and is frequently cited as a reliable and valid measure for this early infancy age group [30].

Strengths and limitations considered, one possible interpretation of these preliminary findings is that despite having experienced adversity, most mothers are actually engaging in positive parenting strategies. At least one-third of study participants experienced some form of abuse or neglect, yet positive parenting scores were elevated (see Table 1). It is therefore possible that these mothers have already taken the steps necessary to disrupt the cycle of adversity via their interactions with their child. As such, parenting behaviors may still be viewed as a key point of intervention in breaking the potential intergenerational effects of ACEs among at-risk populations who are disadvantaged and disproportionately experience early life stress. Future studies will explore child neurodevelopment and parenting behaviors at later time points in hopes of elucidating a clearer relationship, as children's neurodevelopmental patterns become more reliable and valid, and parenting behaviors become more variable (in response to children who are more mobile and verbal).

Furthermore, maternal childhood adversity and parenting behaviors may predict the rate of neurodevelopment over the first year of life, rather than mean levels of cognitive and motor skills scores at 3-months of age, as reflected by composite scores. Expansion of our pilot study to a larger body of work is promising both analytically and clinically, and ongoing work on this pilot study will delve further into breaking this cycle of risk.

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Chapter 59

YOUNG MINDS, YOUNG READERS: DIALOGIC READING WITH ADOLESCENT MOTHERS AND THEIR CHILDREN

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ABSTRACT

Adolescent mothers are at risk of developing mental health issues, living in poverty, dropping out of high school, and becoming unemployed, which may lead to compromised parenting skills. Adolescent mothers have the potential to use effective practices, such as dialogic reading (DR), when given the appropriate levels of support and education to facilitate their children's language and literacy development. The purpose of this chapter was to evaluate the feasibility of teaching DR strategies to adolescent mothers as measured by DR strategy use during shared book reading with their children. The secondary purpose was to determine the impact of adolescent mothers' implementation of DR strategies on their preschool children's single word vocabulary. A single subject multiple baseline across behaviors research design was implemented with one adolescent mother and her twin boys. Based on visual analysis of graphical representation of the data, it was determined there was a functional relation between educating an adolescent mother on DR and her implementation of DR strategies during shared book reading with her children, depending on the DR strategy. However, children's receptive and expressive scores on the individual book assessments decreased from baseline to intervention. These results provide preliminary evidence that adolescent mothers have the potential to implement new strategies during shared book reading when provided with direct support. Future research should focus on developing an intervention for adolescent mothers and their children that enhances children's language and literacy development.

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INTRODUCTION

In 2014, nearly 250,000 infants were born to teenage mothers aged 15-19 years in the United States [1]. Birth rates were highest for Hispanic adolescents ages 15 to 19 years, followed by black adolescents, and then white adolescents [1]. Young women characterized by risk factors across several developmental domains have been found to be at an increased risk for teenage pregnancy [2]. These factors include being reared by a teenage mother, being born into a single parent family, a high rate of exposure to parental change, educational underachievement, conduct issues, early onset of menarche, engaging in high rates of sexual activity, and involvement with deviant peers [2]. While rates of teenage births have steadily declined from 52% in 1991 to 9% in 2013 [1], teenage pregnancy remains a serious issue requiring attention within a life course developmental model due to the risk factors associated with childhood and adolescence and the negative and lasting effects it has on teenage mothers and their children (figure 1 depicts the cycle of teenage pregnancy).

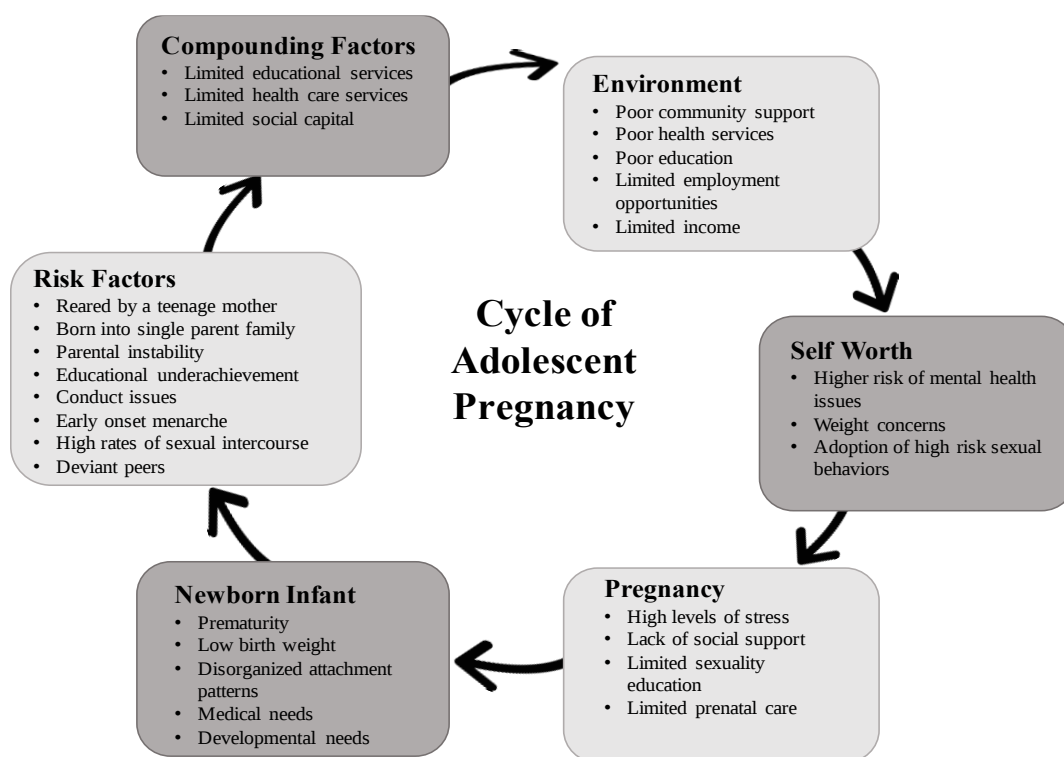


Figure 1. Cycle of adolescent pregnancy.

Teenagers who become parents during their adolescent years are subject to multiple risk factors. In fact, the leading cause of school dropout among adolescent girls is pregnancy or parenthood, with only 40% of teenage mothers finishing high school, and less than 2% of teenage mothers finishing college by age 30 years [3]. Low achievement in education may leave adolescent mothers at a disadvantage in the job market, therefore leading to financial hardships [4]. Eighty-three percent of parenting adolescents come from poor or low-income families and more children born to adolescent mothers live in poverty than children born into

traditional families [4]. Mothers living in poverty and with little education are less likely to provide the necessary resources, support, and care to their children [5].

Mental health concerns are prevalent among the adolescent parent population. It has been widely documented that depression rates in young mothers are much higher compared to rates in adult mothers and typical adolescents [5]. Stressors connected to depression among teenage mothers are described as high levels of parenting stress, little to no social support, and weight concerns [4, 6]. As depression rates increase, adolescent mothers display less positive parenting practices, such as maternal warmth and sensitivity, contingent responsiveness, and general talkativeness [5].

The lack of educational achievement, persistence of financial difficulties, and high rates of depression reported by adolescent mothers have an impact on parenting behaviors and ultimately child development [7]. Many factors such as high depression rates, low socioeconomic status (SES), low levels of resources, and higher rates of health complications (e.g., low birth weight) affect children's cognitive, language, and temperament development [7-10]. Children of teenage mothers are at-risk for developing disorganized attachment patterns with their mothers as infants [9], perform less well on emerging literacy and math measures as two-year-olds compared to those born to adult parents [8], and score lower on language performance measures as toddlers [11]. Furthermore, children of teenage mothers are at risk for language delays as toddlers when compared to children born to adult mothers [11] and of being retained a grade in elementary school [10].

Keown and colleagues [11] reported increased maternal intrusiveness (i.e., ill timed, restrictive, and directive maternal behavior) and lack of verbal stimulation and involvement accounted for the difference in early expressive and receptive language competence between children born to adolescents and children born to adult mothers. Expressive and receptive language delays in children of teenage mothers are also linked to low maternal ability and a poor quality linguistic home environment [10].

Therefore, interventions focused on the literacy practices and reading behaviors of teenage mothers when interacting with their children must be developed [12]. There are several studies that attempt to understand and facilitate interactions between teenage parents and their children. For example, Neuman and Gallagher [13] coached teenage mothers on behaviors and strategies during literacy-related play activities. They reported an increase in the labeling, scaffolding, and contingent responsivity used by teenage mothers, as well as a statistically significant increase in vocabulary measures in the children [13].

In a study conducted by Scott and colleagues [12], teenage mothers were coached on emergent literacy skills to be used when reading to their children, including teaching vocabulary, phonemic awareness, and print concepts. Participants demonstrated a statistically significant improvement before and after the intervention in the use of questioning, vocabulary, and book and print features. This study, along with Neuman and Gallagher's [13] study, suggests a change in parent reading strategies is possible when taught by a clinician. However, the effect of these skills on the teenage mothers and their children have not been specifically explored.

Dialogic reading (DR) is a specific type of shared interactive reading intervention reported to enhance preschool children's oral language [14, 15]. DR is designed to reduce adults' straight reading from the book and encourage children to become more participatory during the reading experience [14]. During DR, adults use a series of prompts (completion, recall, open-ended, wh-questions, and distancing; i.e., CROWD) and a prompting hierarchy

(prompt, evaluate, expand, repeat; i.e., PEER) to facilitate children's storytelling during the shared reading experience. First, the adult prompts the child using one of the CROWD prompt types centered around a specific word, illustration, or word in the book. Then, the adult evaluates the child's response, providing positive feedback for a correct response, and corrective feedback for an incorrect response. Next, the adult expands the child's response by adding some linguistic element, an adjective or phrase, to enhance the child's response. Finally, the adult repeats the original prompt so that the child may repeat the expanded response. During the first step (i.e., prompt), a variety of prompts may be used (CROWD): completion prompts encourage children to complete an utterance the adult begins, often using a repeated text element from the book; recall prompts are used to ask children about events that occurred previously in the story; open-ended prompts are used to ask children what is happening in a picture, encouraging children to respond more than yes/no; wh-questions highlight specific vocabulary or language features utilizing what, where, when, why, and who questions related to the story's illustrations; and distancing prompts are utilized to connect the book's events to children's real life experiences [14]. These behaviors are adopted to enhance the sophistication of a child's descriptions of a story's characters, objects, and plot.

The effectiveness of this intervention has been evaluated across populations and contexts. Whitehurst and colleagues [15] first reported an effect on expressive language ability with middle to upper-SES participants. These effects were later seen with children from low-income families [14]. Children exposed to this intervention were also found to be more likely to exhibit a higher mean length of utterance, higher frequency of phrases, and a lower frequency of single words [15].

While researchers have reported an increase of DR strategies present in shared book reading by adults when trained to use the strategies, it is the level of implementation of DR that has been found to positively influence children's oral language [14]. Yet, there is limited report of low-income parents' responses to a DR training. Furthermore, researchers who have included low-income families in their studies have neglected to track the fidelity of the use of DR strategies when parents are trained to use them [16]. Compliance to the intervention has been reportedly tracked through parent interviews after intervention, reading logs filled out by parents during the intervention, and parent surveys but not by tracking of implementation fidelity by researchers [16].

Breaking the Cycle

Because adolescent pregnancy and parenting is such a complex and involved issue, limited investigation has been done to understand what interventions can disrupt this cycle. To break the cycle of economic, educational, and developmental delays, it is essential to understand what specific interventions and support are most beneficial for adolescent mothers and their children - it may be that the use of a literacy program is advantageous, providing multiple opportunities for communication between mother and child [12]. In a study conducted to investigate the factors that lead to an achievement gap among children born to adolescent mothers, Luster and colleagues [10] found the most successful children were those that experienced more supportive care and higher levels of parenting, were read to frequently, and had mothers who progressed further in their schooling. While young mothers are heavily

impacted by early onset pregnancy, the majority of adolescents feel a sense of maternal responsibility towards their baby, indicating they are not receiving the support and education necessary to offset the many effects their children are reportedly experiencing [2, 10].

Immediate concern needs to be focused on literacy and language development of adolescent mothers' children because of the documented negative impacts that early onset parenting has on children's language and literacy skills [7, 9, 10]. Therefore, interventions should focus on training teenage parents on how to expose their children to literacy and its importance [6]. Research has repeatedly shown that professionals and caregivers are able to learn the DR protocol, which can positively influence oral language and literacy development in preschool-aged children [14, 16]. However, there is a lack of information on adolescent parents' ability to learn and implement the DR strategies with fidelity.

The primary purpose of this study was to evaluate the feasibility of teaching DR strategies to adolescent mothers as measured by DR strategy use during shared book reading with their child. The secondary purpose was to determine the impact of adolescent mothers' implementation of DR strategies on their preschool children. The research questions are: 1) To what extent does a DR intervention taught to adolescent mothers in a one-on-one setting affect their shared reading behaviors as measured by their use of the DR strategies as measured by a fidelity checklist? 2) What is the impact of an adolescent mother's fidelity of implementation of DR strategies during a shared book reading and her child's single word expressive vocabulary? 3) What is the impact of an adolescent mother's fidelity of implementation of DR strategies during a shared book reading and her child's single word receptive vocabulary? 4) What are the perceptions of the teenage mothers regarding the goals, procedures, and outcomes of the DR intervention as measured by a survey?

OUR STUDY

A single subject multiple baseline across behaviors a priori research design was utilized to measure the impact of a DR intervention on the use of the CROWD and PEER strategies implemented by adolescent mothers during shared book reading. Phase changes were based on predetermined time points, instead of based on criterion. Each reading session was recorded to determine inter-observer agreement and training fidelity. Reading behaviors were coded live during each session or from the video as necessary to track frequency or percentage of use.

Recruitment Procedures

After IRB approval, three adult participants and their children were recruited from a charter school in the southeastern United States. The researcher visited the regularly scheduled playgroup with a staff member to explain the study, potential benefits and risks, inclusion criteria, and compensation to potential participants. Inclusionary criteria for mothers were as follows: 1) 15 to 19 years old, 2) have a child 2 to 5 years old, and 3) be enrolled in the teen parent program at the charter school. All eligible participants were 18 years or older, so they signed consent immediately. While three participants signed consent, one participant

withdrew from school and another did not meet the 50% attendance criteria during the baseline phase, so they were excluded from the data analysis. Only one adolescent mother, Isabel (all names included in this paper are pseudonyms), participated in the entire study.

Participants

Isabel was an 18-year-old African American mother of twin boys, Jack and John. Isabel was matriculated in 11th grade and self-reported a grade point average (GPA) of 2.8 at the beginning of the study. She was fifteen when she had her twin boys. Isabel lived at home with her parents and spoke English only. She reported an annual household income of less than \$24,999, which indicates that she was from a low SES household. When asked about her home literacy practices, Isabel reported she read to her children daily, taught her children new words “all the time” (quoted from Isabel), owned four picture books for her children at home, and never took her children to the library. Isabel scored a total of 54 out of a possible score of 94 on the researcher developed Perceptions of Reading Abilities. Her responses ranged from 1 (never) to 5 (always) on the individual components of the survey. This result indicated that Isabel had a moderate perception of her capabilities in reading abilities, such as sounding out words, answering questions based on a passage, and reading fluently. Isabel's Total Reading standard score was 73 on the Woodcock Reading Mastery Test (WRMT-R/NU; 17), almost two standard deviations from the mean, which indicated a moderate to significantly below average score.

Jack and John were twin brothers who were 33 months at the start of the study. They were both African American, spoke English at home, and had a medical diagnosis of asthma. Jack had a total language score of 95 on the Peabody Language Scale 5th Edition, with a 93 on the auditory comprehension subtest and a 97 on the expressive communication subtest. He had a standard score of 106 on the PPVT-4 and a standard score of 100 on the EOWPVT-4. John received a total language score of 96, with a 98 on the auditory comprehension subtest and a 95 on the expressive communication subtest. He earned a standard score of 92 on the PPVT-4 and a 92 on the EOWPVT-4. All language scores for both children were in the average range. During the pretesting period, it was observed that both children were easily distracted and had difficulty attending to one task for a long period of time.

Setting

This study was conducted at a charter school in the southeastern United States during regularly scheduled weekly playgroups for adolescent mothers and their children to provide an opportunity to interact during the school day and during group therapy for adolescent mothers. For this study, arrangements were made prior to the start of the intervention that the participants could attend an intervention session during their group therapy period so there would be two intervention sessions per week. Participants also attended a newly created group specific to the study during the intervention program, instead of their regular weekly playgroup.

Independent Variable

Isabel was educated on each reading strategy by the researcher. The training consisted of: 1) naming the strategy, 2) defining the strategy, 3) providing examples, and 4) answering questions. Isabel received a handout which summarized the reading strategy during the first session of each strategy. Books were provided and scripted with 12 CROWD prompts each. Isabel was asked to read the entire book and include the scripted prompts. During the sessions following the introduction of a new DR strategy, the researcher reviewed the DR strategy prior to the book reading using the same components of the training (i.e., naming the strategy, defining the strategy, providing examples, and answering questions). Isabel was reminded and encouraged to continue use of the previously learned reading strategies, as the DR steps are cumulative.

The adherence to the DR intervention was assessed by a trained research assistant (RA B) according to the following elements: 1) session started with a hello song, 2) children were invited to play, 3) during training or review, the strategy was named, 4) during training or review, the strategy was defined, 5) during training or review, examples were provided 6) during training or review, any questions were answered, 7) children were invited to read a book, 8) the parent read a book to children together, 9) children were invited to play, 10) feedback was provided, 11) new questions were answered and 12) session ended with a goodbye song. Twenty-five percent of videotaped sessions were observed and scored. The sessions were randomly selected prior to the start of the study. Fidelity was measured by the number of behaviors observed divided by the total number of behaviors that should have been observed and multiplied by 100. Fidelity was 91.7%.

Materials

Seven books were randomly selected from the “Read together, talk together” kit as done in past studies. (RTTT; 17). The books used included “A summery saturday morning” (1998), “Pigs aplenty, pigs galore!” (2008), “The wolf’s chicken stew” (1996), “I took my frog to the library” (1992), “The dinosaur who lived in my Backyard” (1990), “Spike in the city” (2000) and “Oonga Boonga” (1990). One book was provided for baseline without any alterations. Five intervention books were used during the intervention phase. Each intervention book was prepared with twelve scripted questions based on CROWD prompts taped into the book following the written text. There were at least two scripts of each CROWD prompt type. Five vocabulary words were targeted through these scripts. The researcher consulted the RTTT teacher notes to choose the book specific vocabulary. Vocabulary words had to be mentioned in the text, as well as depicted in the illustrations. One book (book 7) was provided for generalization without any alterations on the last intervention session.

Procedures

After IRB approval and consent to participate, Isabel was individually tested on the Reading Comprehension Cluster of the Woodcock Reading Master Test Revised-Normative

Update (WRMT-R/NU) during her group therapy sessions. She also completed the self-efficacy questionnaire on her reading abilities and a demographic survey. Each child was assessed using the PLS-5, EOWPVT-4, PPVT-4, and near-transfer receptive and expressive vocabulary tests.

After testing was complete, Isabel entered the baseline phase for five sessions for the first behavior (i.e., prompt), eight for the second behavior (i.e., evaluate), eleven for the third behavior (i.e., expand), and fourteen for the fourth behavior (i.e., repeat). After baseline, Isabel entered the intervention phase which included DR training and using pre-scripted books. After the intervention, Isabel entered the generalization phase (see Table 1).

Table 1. Dialogic reading intervention overview

Session	Focus	Book
Baseline sessions 1-5	Read as you normally would	1
Intervention sessions 1-3	Prompt your child (i.e., CROWD prompts)	2 & 3
Intervention sessions 4-6	Evaluate what your child says	2 & 4
Intervention sessions 7-9	Expand what your child says	2 & 5
Intervention sessions 10-12	Repeat the prompt	2 & 6
Generalization sessions 1-2	Read without intervention supports	7

Baseline. Baseline data were taken for five sessions during the biweekly playgroups. Isabel was instructed to read to her children as she normally would with no intervention present. One book was used only for baseline. After five predetermined baseline sessions, the DR intervention for the first behavior began.

Intervention. The intervention was an eight-week program completed during the biweekly playgroup sessions. Each session lasted 30 minutes and was led by the researcher. Three sessions were dedicated to each strategy (i.e., prompt, evaluate, expand, repeat). During the first of these three sessions, the researcher educated Isabel on the strategy (see Independent Variable) and Isabel practiced the strategy through the reading of one book (i.e., *Pigs Aplenty*, *Pigs Galore!*) to her children. During the next two sessions, the strategy was reviewed and Isabel read a new book to her children to practice the strategy. A new book was introduced for each new reading strategy (i.e., four new books). Each session was structured consistently, but the focus of the session differed every three sessions (see Table 1 for an overview of the intervention). The following schedule was followed every session: 1) hello song, 2) training/review of reading strategy, 3) book reading, 4) discussion and feedback for the mother during playtime and 5) goodbye song.

Generalization. Isabel was provided a new book on the last intervention session and was asked to prepare to read to her children using the DR reading strategies. Isabel was videotaped while reading to her children without the support that was present in the intervention (i.e., unscripted books, no feedback from the researcher, and no review of dialogic reading strategies). This occurred during playgroup, just as baseline did, for two sessions.

Data Analysis

Isabel's use of the DR strategies was coded by the first author to track implementation fidelity of the CROWD and PEER strategies. One undergraduate research assistant was trained to code prior to the start of the study by observing and coding sample videos with direct instruction from the first author to criterion. The research assistant had to reach 80% agreement with the first author before she could begin coding [19].

During baseline and generalization, questions posed by Isabel were coded as any of the CROWD prompts or as "other" questions (e.g., yes or no questions, questions eliciting pointing) based on Isabel's intentions. During intervention, however, the books were scripted with CROWD prompts. Isabel's reading behaviors were coded based on whether she asked the scripted questions. Any questions outside of the twelve scripted prompts were coded as any of the CROWD prompts and "other" questions as determined by the coder. CROWD prompts were measured as an average frequency per phase.

The presence of the PEER hierarchy was coded as to whether Isabel used each strategy for all phases. Evaluate, expand, and repeat strategies were measured as average percentages per phase (number of times the strategy was used divided by number of opportunities for the strategy to be used multiplied by 100). The number of opportunities was equal to the number of questions Isabel asked during the book reading, because she had the opportunity to use the strategies anytime she asked a question.

Inter-observer agreement (IOA) was established through the coding of 25% randomly selected videotaped sessions by a trained research assistant which was compared with the original coding sheets. A minimum of 80% agreement was required for IOA. Inter-observer agreement was calculated by dividing the amount of agreements by the total sum of disagreements and agreements between the raters and multiplying by 100. Reliability was 85% between the first author and the research assistant. Disagreements in the coding were resolved by the first author and the research assistant.

Effects of the DR intervention on the reading behaviors of an adolescent mother were examined through visual analysis [19]. Line graphs were constructed to display the data for each behavior. The four steps for conducting visual analysis were as follows: 1) "document a predictable baseline pattern of data", 2) "examine the data within each phase of the study to assess the within-phase patterns," 3) "compare the data from each phase with the data in the adjacent phase to assess whether manipulation of the independent variable was associated with an effect," 4) "integrate all the information from all phases... to determine whether there are at least three demonstrations of an effect at different points in time" (which in the present study were baseline, intervention, and generalization) [19]. The features examined to assess the effect of an intervention were: 1) level, 2) trend, 3) variability, 4) immediacy of the effect, 5) overlap and 6) consistency of data patterns across phases [19]. Changes in level (the average of the data in a phase), trend (the slope of the line of best fit within a phase), and variability (the range of data surrounding the best-fitting straight line) were displayed on each graph and examined. Data patterns across phases (immediacy of effect, overlap, and consistency of data in similar phases) were examined to further determine the effect size of the intervention. Immediacy of effect is measured by the change in level in the last three data points and first three data points in adjacent phases; a more rapid effect signifies a stronger relationship between the intervention and effect. Overlap refers to the amount of data that

converges in between phases; the larger the separation between data of two neighboring phases, the more convincing it is that there has been an effect [19]. Consistency of data in similar phases will not be considered in the present study because each phase of this study is unique. The steps outlined above were followed using the assessment features to determine what effect the DR intervention had on adolescent mothers’ reading behaviors.

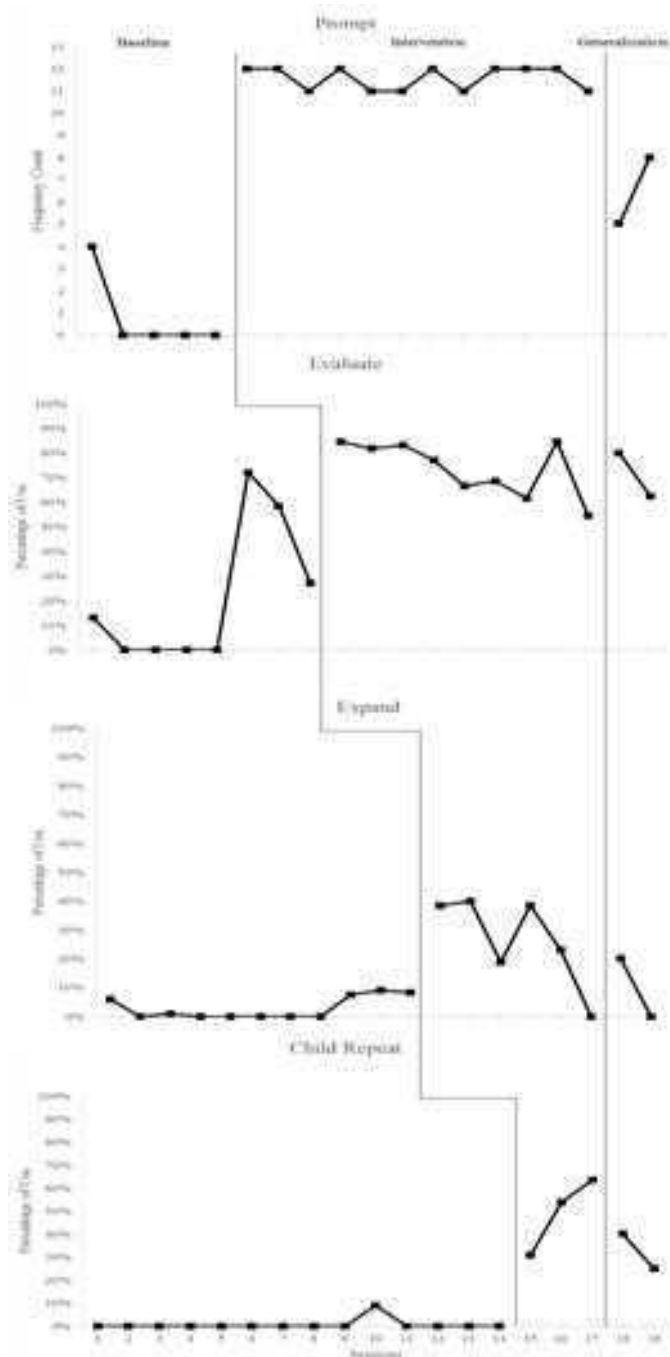


Figure 2. Isabel’s use of DR strategies.

Isabel was asked to complete a social validity survey [20] at the end of the intervention. The survey measured Isabel's views of the goals, procedures, and outcomes of the study through seven items on a seven point Likert scale and four open ended questions. The survey included seven questions to be answered on a seven point Likert scale. Scores were totaled and an average score was calculated.

During the last intervention session of each book, the children were assessed on the five book-specific vocabulary terms targeted in the books that were read through an expressive and receptive task. For the expressive test, the children were shown a scanned illustration from the book depicting each vocabulary word and were asked "What is this?" The administrator waited five seconds for a response before recording a non-response. Each verbal response was recorded and the total number of correct responses was scored. For the receptive test, children were shown four scanned pictures- one of them was the targeted vocabulary word, and three were foils. The administrator said, "Point to the ____." and again waited five seconds before recording a non-response. Each response and the total number of correct responses were recorded. Prior to the start of the study and after the intervention was complete, the children were assessed on all twenty vocabulary words targeted in the four intervention books. The same procedures were used as in the individual book vocabulary tests.

FINDINGS

Research question 1 (see figure 2). During the baseline, there was a low degree of variability, with a mean of 0.8 (range 0 to 4), and a moderate downward trend on the issue of prompt. Isabel was then trained to use the different types of prompts as established by the DR protocol (i.e., CROWD). Following intervention, there was an immediate increase in the level of the variable ($M = 11.58$), little variability, and no overlap with the baseline. The level decreased ($M = 5$) from intervention to generalization.

Evaluate. During the baseline, there was a high degree of variability with a mean of 21% (range 0% to 72%) and a moderate negative trend. Immediately following intervention, there was a rapid increase in the level of the dependent variable ($M = 74\%$) with moderate variability, and 44% overlap with the baseline. The level slightly decreased ($M = 71.25\%$) from intervention to generalization.

Expand. During the baseline, there was minimal variability with a mean of 3% (range 0% to 9.10%) and a moderate negative trend. Immediately following intervention, there was a slow increase in the level of the dependent variable ($M = 13\%$) with little variability, and 17% overlap with the baseline. The level from intervention to generalization slightly decreased ($M = 10\%$).

Repeat. During the baseline, there was minimal variability with a mean of 0.65% (range 0% to 9.10%) and a low negative trend. Immediately following intervention, there was a rapid increase in the level of the dependent variable ($M = 49\%$) with little variability and no overlap with the baseline. The level decreased ($M = 32.5\%$) from intervention to generalization.

Research questions 2 and 3. To determine if there was an effect of the adolescent mother's training on DR behaviors and her sons' receptive and expressive vocabulary, the mean scores on the near-transfer assessments for the baseline and intervention phases per

child were calculated. Children’s vocabulary scores were reported per child. Table 2 demonstrates the book-specific vocabulary per phase and per book. Both John and Jack’s expressive scores were 3 (out of 5) for baseline and 2.25 (out of 5) for intervention. Their receptive scores were 5 (out of 5) for baseline and 3.25 (out of 5) for intervention. The expressive and receptive near-transfer vocabulary decreased from baseline to intervention in both children.

Table 2. Book-specific vocabulary per phase

Book		Vocabulary targeted			
Baseline					
Book 1	Cat	Dog	Bike	Goose	Sandals
Intervention					
Book 2	Oatmeal	Plane	Pizza	Broom	Bed
Book 3	Wolf	Chicken	Pancakes	Doughnuts	Cake
Book 4	Librarian	Card catalog	Skin	Pelican	Hyena
Book 5	Dinosaur	Basketball	School bus	Tent	Kite
Book 6	Leash	Parking meter	City	Frisbee	Skateboard

Research question 4. The adolescent mother’s experience related to the DR intervention was evaluated through a 7-item social validity questionnaire. Samples of Isabel’s answers to the open-ended questions of the survey were included to address the aspects of the intervention that were most and least enjoyable. Isabel responded with an average of 6.42 (range 6 to 7) on the seven items, indicating a high level of acceptance of the DR intervention. Responses to open-ended questions also indicated positive reactions to the experience. Isabel reported that she enjoyed the intervention because “[her] boys are learning more vocabulary” and that she “learned new ways to read to [her] boys.”

DISCUSSION

Adolescent mothers have the potential to use effective practices when given the appropriate levels of support and education to facilitate their children’s language and literacy development [3, 21]. Dialogic reading has been shown to be effective in developing children’s expressive and receptive language skills when implemented by a variety of adults, including parents [14-16]. However, there are limited reports related to implementation of DR strategies and the degree of fidelity when implemented with low SES adolescent parents.

We examined the feasibility of teaching DR strategies to an adolescent mother from a low SES home by measuring her use of DR strategies (i.e., CROWD and PEER) during shared book reading with her children. The data indicated that when trained on the four DR strategies separately and provided with consistent feedback and in-book scripts, the adolescent mother was able to learn and implement the DR strategies more frequently than in baseline. The data suggested a highly effective intervention on the prompt and repeat DR strategies for Isabel, and a moderately effective intervention on the evaluate and expand DR strategies. These results are consistent with previous studies in which adults have been trained, specifically parents, to implement DR strategies during shared book reading [16]. Given that adolescent mothers have responded well to other direct supportive services, such

as prenatal fitness, stress management classes, and maternal nutrition classes, when employed in their school curriculum [21], they demonstrate potential to learn and implement new strategies. This potential coupled with adolescent mothers' instinctive maternal care and sense of responsibility for their children [22] may begin to explain Isabel's success in implementing the DR strategies. It may be important to note that the "expand" strategy had the least immediate increase out of the other DR strategies, which is consistent with past studies [16]. This may indicate that this strategy is the most difficult to implement because it requires the adult to have knowledge on what components can be provided in an expansion, a skill typical parents, especially young mothers, may not obtain. In future studies, this strategy may require additional training or support to be implemented accurately.

During generalization, there was a decline for all behaviors. The consistency in Isabel's implementation of the DR strategies may have been affected by known stressors in her life during the study and because support (i.e., feedback and in-book scripts) was not provided. It may be that a slower phasing out of support is needed for adults to be able to transfer these strategies to new contexts. However, Isabel showed marked improvement in the quality of the questions she asked. During baseline, Isabel presented many questions ($M = 9.4$) that fell out of the scope of the CROWD prompts during shared book reading, such as yes/no questions and questions that elicited a pointing response and during generalization, Isabel used the CROWD prompts more frequently than in baseline, even without scripts in the books, and used very little 'other' prompts ($M = 1.5$). Although the average number of CROWD prompts used during generalization declined from intervention, the intervention had an impact on the quality of questions Isabel used. However, the decline in this strategy and the three other strategies suggest that a more gradual decrease in support may be necessary for the intervention to have a lasting impact on participants' reading behaviors.

We also examined the effect of the use of DR strategies with fidelity on preschool aged children's expressive and receptive vocabulary related to the storybooks. Receptive and expressive scores on the individual book assessments decreased from baseline to intervention. These data suggest that exposure to DR strategies during shared-book reading with their adolescent parents does not promote children's learning of book-specific vocabulary given the design of this study. While the majority of past studies that have reported child outcomes found increases in language and/or emergent literacy skills [18], the results of the current study may have been inconsistent due to an uneven distribution of vocabulary difficulty across phases. For example, baseline vocabulary words included "dog" and "cat" while intervention vocabulary words included "librarian" and "Frisbee". Only one book was used during baseline and it was repeated five times, in comparison to four different books used during intervention that were read only twice each. This uneven distribution of complexity and increased exposure to the vocabulary during baseline may have compromised the results for research questions two and three. Another factor which may have affected the children's success on the near-transfer vocabulary task was their attention to the book during the book reading. There were many times when the children were distracted by toys in the room and wandered off during the book reading. If they did not receive repeated exposure to the vocabulary during the book reading because of distractions, their success on the vocabulary task may have been compromised. This result was unlike the positive gains in near-transfer vocabulary reported in other studies [23, 24].

Acceptance of the DR intervention was evaluated through a seven-item survey using a seven point Likert scale. Isabel reported an average score of 6.42 on the seven items,

suggesting positive acceptance of the intervention. Responses to open-ended questions aligned with this finding. In one study, Heubner [25] included adolescent mothers in the study sample and reported positive parental satisfaction of a DR intervention program. Positive satisfaction may be attributed to adolescent mothers' perceived success to implement a new strategy as opposed to feelings of nonfulfillment other areas of their life, such as school [21].

Teenage pregnancy and parenting is a multigenerational cycle including issues of low income, low academic attainment, low achievement in education, specifically in literacy, and higher risk of mental health and medical issues (see Figure 1) [4, 5, 7, 8]. We sought to address the issue at hand through one possible angle which included investigating the feasibility of using a shared reading intervention, dialogic reading, to impact an adolescent mother's reading behaviors. While this study included only one participant, we demonstrated that it is feasible to teach DR behaviors to an adolescent mother. With this data, we intend to continue in this line of research to further develop a mutually beneficial intervention, centered around literacy, for adolescent mothers and their children on a larger scale. The most successful children born to adolescent mothers are those that are read to frequently, experienced more supportive care, and had mothers who completed higher levels of education [10]. Therefore, by educating adolescent mothers on the importance of reading to their children and providing direct training on their reading behaviors, the adverse effects of early onset pregnancy may be offset and we may advance towards breaking the cycle of teenage intergenerational pregnancy.

Limitations and Future Directions

While this single case study suggests an encouraging relationship between a DR intervention and adolescent mothers' use of DR strategies, there are several limitations that must be noted. This study included only one adult participant, which may have affected the participant's learning of the strategies- whether the one-on-one attention was conducive to her learning or the lack of watching others utilize the strategies negatively impacted her learning. Future studies should obviously include a larger number of adolescent mothers. Another limitation of the current study was the uneven distribution of complexity of the book specific vocabulary across phases. The near-transfer vocabulary may have been too difficult for the age of the child participants. Another limitation was that the children were read to together, which may not have been conducive for their focus, potentially affecting the children's success on the near-transfer vocabulary assessments. Future researchers should consider participants' age range and knowledge level to choose appropriate vocabulary. Because the near-transfer vocabulary assessments measure only short-term effects, researchers may also consider analyzing the long-term effects of DR on children's oral language in facets other than vocabulary, such as mean length of utterance (MLU) and type token ratio (TTR).

Future studies should explore the minimal increases in the implementation of the expand strategy. During the expand strategy, the adult models a longer and more detailed sentence, which gives children a chance to practice longer utterances during the repeat strategy. Researchers should explore what makes this strategy more difficult to implement and what extra support is needed to implement it with fidelity. Due to the effects associated with teenage parenting, it is critical that interventions that affect adolescent mother's literacy skills

be developed. Future research should investigate the impact of implementing DR strategies during shared book reading on adolescent mothers' literacy. Developing a mutually beneficial intervention for both the mother and child is critical in breaking the intergenerational cycle that is associated with teenage pregnancy and parenting.

CONCLUSION

This study demonstrated that an adolescent mother from a low SES background was able to utilize DR strategies following a systematic training of the DR protocol. However, positive changes on children's receptive and expressive book-specific vocabulary due to implementation of DR strategies were not seen. This study contributed to the limited information that is available concerning literacy and language interventions for low income adolescent mothers and their children. Adolescent mothers' potential to effectively implement a new strategy when given the appropriate support should inspire continued research with this population. Future research must strive to understand adolescent mothers' interactions with their children in order to develop interventions that will target the areas that are lacking in order to break the multigenerational cycle seen in families of adolescent mothers.

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Chapter 60

CHANGING SLEEP HABITS TO DECREASE OBESITY

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ABSTRACT

In this chapter we evaluate the sleep characteristics of children from a low-income urban area and the barriers these children have in developing healthy sleep behaviors. A multiphase mixed-methods exploratory research design was used to provide a deeper understanding of the perceptions of parents/caregivers from low-income urban areas regarding their children's sleep. Sleep was identified as a "very important" contribution to their children's health by 97.1% of participants (options being "not important," "somewhat important," and "very important"); however, a high proportion reported a home environment that is not conducive to healthy, restful sleep. Problematic sleep habits of children, including parasomnias, sleep anxiety, and night wakening, were noted by 88.2% of the participants on the Children's Sleep Habits Questionnaire. Focus groups identified several barriers to healthy sleep hygiene practices such as television/electronics before bedtime, co-sleeping, and night waking (paired with eating/drinking). During the focus groups, many parents/caregivers reported daytime tiredness and drowsiness of their children. Discussion: Culturally-appropriate education is needed to guide parents/caregivers in creating a healthy home sleep environment. Simple measures such as removing televisions from bedrooms and discontinuing electronic use before bedtime, night waking food/beverage feeding, and co-sleeping may lead to the increased occurrence of healthy sleep with this population. Culturally-appropriate education may be

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an essential element to helping this community learn strategies on creating a healthy home environment that promotes optimal sleep habits.

INTRODUCTION

The cycle of environmental health disparities in children is multifactorial and must be viewed through a health care lens which investigates and intervenes from multiple vantage points. Children from low-income communities in the United States experience greater health burdens than do those from middle- to high-income communities and are more likely to be of black race and/or Hispanic ethnicity [1]. These children are at an increased risk for asthma, infant mortality, and teen pregnancy. Upon becoming adults, these individuals are at a higher and earlier risk of hypertension, diabetes, cardiovascular disease, and stroke, the foundations for which are often established during childhood [1]. Black mothers and their children who reside in low-income areas are at highest risk for being overweight or obese [1–4]. Nationally across the U.S., 82% of black women and 55% of black children are classified as overweight, obese, or extremely obese [4]. Mobile, Alabama has the second highest obesity rates in the United States and the highest rates of adults with diabetes in the nation, tied with Charleston, West Virginia [5–7]. Despite these numbers, black women and their children are underrepresented in behavioral weight management research [5, 6, 8]. This shortage of research led the Institute of Medicine to identify obesity interventions among diverse ethnic groups as an urgent need [9].

It is important to focus on targeting modifiable risk factors such as sleep which may create an opportunity for reducing adverse health outcomes such as obesity with high risk vulnerable populations. A modifiable risk factor that can help play a role in preventing and decreasing obesity is ensuring adequate sleep for children. Poor sleep patterns contribute to obesity risk. This risk is related to identified shorter sleep duration, poor quality/less restful sleep, and increased sleep curtailment (restricting sleep time below needed amount) at an increased rate in economically disadvantaged children, black children, and Hispanic children [10]. Research has found that twenty percent of parents reported daytime fatigue in their children several days per week, and 70% report negative sleep behaviors in their children [10]. According to the age-based sleep recommendations issued by The National Sleep Foundation, preschool children should have 10-13 hours of sleep each night, and school-age children should have 9-11 hours [10]. The incidence of sleep problems is increasing at higher rates in black and Hispanic children, ranging from 25-50% [10].

Etiologies for inadequate sleep in children are dependent upon many biological, psychological, social, and environmental factors [11]. Sleep can be adversely affected by a child's temperament, neurocognitive status, and behavior. Parental contributors to sleep habits include the parents' mental health, ages, education levels, parenting styles, and sleep perceptions [10, 11]. Decreased sleep duration can be related to the failure of an individual during infancy to attain adequate self-soothing and self-regulating behaviors which initiate and maintain sleep [12]. Sleep quality and duration may also be affected by co-sleeping, delayed bedtimes, the presence of a television (TV) in the child's room, ineffective bedtime routines, and adverse dietary behaviors [10].

The detrimental psychosocial effects of poor sleep are well-documented in the literature. Children who do not sleep well are twice as likely to develop symptoms of attention-deficit

hyperactivity disorder and are three times as likely to have a conduct disorder [13]. Longer sleep has been positively correlated with improved academic performance, emotional regulation, and quality of life in children [14]. Furthermore, sleeping problems in children, including prolonged sleep latency (length of time to fall asleep) and refusal to sleep alone, were predictive of longitudinal anxiety and depression [15]. Mothers of minority children with poor sleep behaviors have also identified symptoms of depression, anxiety, and post-traumatic stress disorder in their children [16].

Research has demonstrated that poor sleep contributes to obesity. Conversely, the presence of obesity increases the incidence of obstructive sleep apnea (OSA) and other respiratory sleep disorders, circadian rhythm sleep-wake disorders, insomnia, and hypersomnolence [10, 17–21]. Thus, those who conduct sleep research, education, and interventions must consider obesity as a contributor and the outcome as well. The association between poor sleep habits and obesity is especially concerning since childhood obesity has become a severe public health concern [2]. Obesity in children is particularly prevalent in the Deep South, and black and Hispanic children of low socioeconomic status are disproportionately affected [22, 23]. Excess weight early in life increases the risk of an individual to be overweight or obese in adulthood, and Malhotra, Ostbye, Riley, and Finkelstein [24] found that, in 18 years, adults typically gained 1.2 pounds per year. Obesity in adulthood substantially increases an individual's risk for hypertension, type 2 diabetes, stroke, cardiovascular disease, osteoarthritis, and some cancers [24, 25]. The disparities found in racial and ethnic cohorts contain factors contributing to childhood obesity starting early in life [26].

The most common adverse effect of obesity on sleep is the development of OSA. The incidence of OSA in obese children exceeds 50% [27], and leads to increased sleep fragmentation resulting in daytime sleepiness and diminished physical activity, which further accelerates obesity. Sleep fragmentation from OSA also contributes to and/or exacerbates adverse cardiovascular and metabolic effects throughout the life span, such as lipid disorders and diabetes which are commonly found in individuals with obesity [25].

tolerance and sensitivity, increased evening concentrations of cortisol, changes in phospholipids, and alterations in thyroid functioning [28, 29]. One of the most marked effects of sleep disruption occurs in the hormonal processes that regulate hunger. Levels of ghrelin, a hormone that stimulates the appetite, increase in the presence of sleep deprivation. Conversely, leptin, a satiety hormone, is decreased by sleep deprivation [30]. Thus, sleep-deprived individuals experience increased feelings of hunger, particularly for carbohydrate-rich foods, and report a decreased feeling of fullness after eating [19, 20]. Also, there is an increased opportunity to snack and consume food because the individual is awake to eat.

The effects of poor sleep and obesity are far-reaching. Affected individuals are at high risk for negative health outcomes due to an unhealthy home environment. Through research and observation, it is incumbent upon healthcare providers to identify strategies to reverse negative health risk factors, including sleep disruption and obesogenic influences that contribute to the cycle of environmental health disparities.

The specific aims of this research study are to: 1) identify the sleep characteristics of children from a low-income urban area, 2) explore barriers to healthy sleep behaviors, and 3) identify the content needed for a future sleep intervention. The study was designed to investigate a component of the cycle of environmental health disparities (see Figure 1); thus,

the setting of study and recruitment of participants occurred at a child-care center located in a low-income urban area where residents experience substantial health disparities.

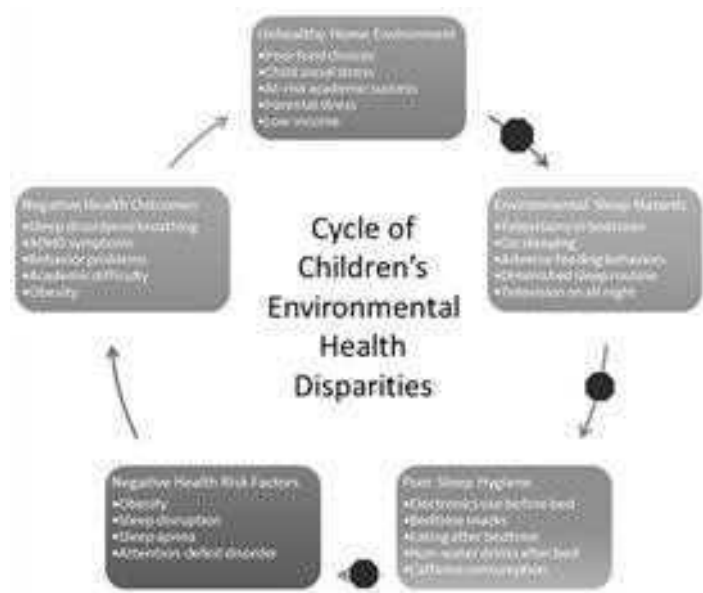


Figure 1. Breaking the cycle by addressing barriers to healthy sleep.

Obesogenic biochemical processes resulting from poor sleep include decreased glucose

Family members play a critical role related to the actions of each other. When parents actively participate in sleep routines and sleep hygiene, they serve as examples to their children [11]. Family Systems Theory has been used to investigate health behavior extensively and effectively [31]. The research team in the current study selected this theory to guide the understanding of sleep habits and sleep hygiene within families.

OUR STUDY

A multiphase mixed-methods exploratory research design employing concurrent and sequential phases was used to obtain data and provide context [32] and allowed for a deeper understanding of perceptions of parents/caregivers about their children's sleep. The setting of the study and recruitment of participants occurred at a child-care center located in a low-income metropolitan area where residents experience substantial health disparities. Participants were asked to complete a questionnaire (quantitative data collection) before participating in a one-hour focus group (qualitative data collection).

Quantitative Method

The Children's Sleep Habits Questionnaire (CSHQ), a validated, reliable questionnaire, was administered to parents/caregivers of children at the child-care center to identify patterns

related to the children's sleep [33]. The CSHQ is a 45-item measure of multiple sleep domains for children. The overall score of the CSHQ has demonstrated internal consistency of 41, sensitivity of 0.80, and specificity of 0.72 when used in school-age children. Evaluative subscales of the CSHQ include bedtime resistance, sleep onset delay, sleep duration, sleep anxiety, night waking, parasomnias (abnormal or unpleasant perceptions while falling asleep or waking up), sleep-disordered breathing, and daytime sleepiness [33]. The research team gained permission to use this copyrighted instrument [33].

A questionnaire (see appendix 1) was developed by the research team to obtain demographic data, bedtime routines, barriers to sleep hygiene, and dietary practices. The demographic questions included inquiry about participants' financial concerns and use of Government-sponsored programs of assistance, including Supplemental Nutrition Assistance Program and Temporary Assistance for Needy Families.

Qualitative Method

Four one-time one-hour focus groups were held at the child-care center, providing participants an opportunity to express personal experiences regarding their children's sleep practices, bedtime routines, and sleep habits. The focus group discussion was steered by a semi-structured interview guide composed by the research team with input from national experts. Upon receipt of the completed questionnaires, the research team added/adapted questions on the interview guide to further explore concepts or comments based on questionnaire responses and/or patterns as the sequential phase of the mixed-methods design.

Procedure

An expedited Institutional Review Board approval was obtained from the University of South Alabama. Parents/caregivers of children who utilize the child-care center were recruited by means of a flyer displayed in the center. The director of the center was instrumental in the recruitment and helped explain questions on the questionnaires to the participants if requested. Participants who returned the completed questionnaires were eligible to sign up for one of the focus group sessions. Completion of a questionnaire was mandatory prior to focus group session attendance to avoid bias.

The questionnaires had a waived consent with a cover sheet explaining the nature of voluntary completion. Participants who attended a focus group session consented at the beginning of the focus group. Focus groups were conducted using established methodology [34]. After consent was obtained, the sessions were audio recorded to aid in understanding and transcription. The principal investigator led each session while other members of the research team, including faculty, a graduate student, and undergraduate students, facilitated the discussion and added questions when appropriate. The investigator greeted the participants and asked the open-ended questions. A second researcher took notes of participants' comments as well as non-verbal behavior. At the end of each question, the researcher verified the discussion points, summarized responses from the discussion, and

welcomed input from participants on any missed points. Each focus group session lasted about 60 minutes.

Participants who completed the questionnaires and attended a focus group session were compensated at the end of the focus group with a \$25 gift card and were encouraged to keep all discussions confidential. Later, one researcher transcribed the recordings, and two other researchers reviewed the transcripts for accuracy. Audio recordings, notes, and transcripts were stored in a secure site.

Data Analysis

The quantitative and qualitative data were analyzed simultaneously as the concurrent phase of the mixed-methods design. Data collected from participants were cleaned and entered into a database and analyzed using SPSS v. 24. Due to the small sample size, missing data were deleted likewise. Subscale scores for the CSHQ were calculated using author-provided guidelines [33]. For this study, quantitative sample descriptive statistics, including measures of central tendency were analyzed. Additionally, scores on the CSHQ were compared using Welch's unpaired t-tests to community sample subscale scores published by Owens, Spirito and McGuinn [33] to ascertain the degree to which the current sample resembles other community samples.

Analysis of qualitative data involved examining, categorizing, tabulating, mapping, and interpreting the transcripts. The transcripts were reviewed by the research team for general themes in the discussion. The researchers identified the content and entered larger, broader themes as a distinct line item in a spreadsheet, and the items were sorted into categories. The larger categories were formed by grouping similar idea units together and then were sorted to create distinctions among them. The themes were reviewed by the researchers independently, and discussion and debate ensued until consensus was met.

OUR FINDINGS

Thirty-four participants completed the questionnaires and focus group discussions. Thirty-three participants were female, and one was male. The majority of participants (85%) were mothers of children enrolled at the child-care center. Participants were primarily black (91.2%) and non-partnered (20.6% married or partnered). The average age of participants was 32.29 years (SD 11.12). Participants varied in their levels of education, with 8.8% having less than a high-school education, 32.4% graduating from high-school/obtaining a GED, 35.3% having some college education, and 23% holding a college degree. The children of the participants had an average age of 4.43 years (SD 3.68), and 52.9% were male. When asked about perceptions of weight, more than half (53%) of the participants/caregivers answered they consider themselves to be "somewhat overweight." Almost all (91%) answered that they consider their children to be "Normal/average weight."

Household income varied widely with a mean of \$21,468 (SD \$16,711) ranging from \$5,000 to \$75,000 with a median of \$17,000; however, 12 of the participants (35%) did not answer the demographic question related to household income. When removing the outlier of

\$75,000, the mean income ($n = 21$) was \$18,919 (SD \$11,964), median was \$16,000, and the range was \$5,000 to \$50,000. The majority (58.8%) of families reported some degree of financial difficulties, and most were enrolled in Government-sponsored financial assistance programs (Supplemental Nutrition Assistance Program (SNAP) = 58.8%; Temporary Assistance for Needy Families (TANF) = 67.7%).

Participants reported on various sleep habits of their children (see table 1). Most felt that their child sleeps the right amount (67.7%), and 70.6% reported that their child “rarely” receives too little sleep. Participants reported that their children usually sleep the same amount each day (71.0%), that they felt sleep was “very important” to their children’s health (97.1%), and that bedtime routines were “very important” (88.2%).

Participants also completed the CSHQ as described above. Based on published cut-off scores [33], 88.2% of the participants indicated that their children had problematic sleep habits (Table 2). When CSHQ subscales were compared with demographic variables, a significant correlation was found between child age and daytime sleepiness ($r = .348$, $p = .044$). No other significant differences or correlations were found between the CSHQ and demographic variables.

Table 1. Children’s bedtime habits and environments (N = 34)

	n(%)		
	“Yes”	Male (n = 18)	Female (n = 16)
Child eats after bedtime	16(48.5)	7(41.2)	9(56.3)
TV on one hour before bedtime	29(85.3)	15(83.3)	14(87.5)
TV on where child sleeps	15(44.1)	6(33.3)	9(56.3)
TV in child’s room	29(85.3)	15(83.3)	14(87.5)
Child uses electronics before bed	18(52.9)	9(50)	9(56.3)
Child has own bed	30(88.2)	15(83.3)	15(93.8)
Child usually sleeps with someone else	15(44.1)	10(55.6)	5(31.3)
Child drinks caffeinated beverages	12(36.4)	7(38.9)	5(31.3)

Table 2. CSHQ subscales with comparison to the normative sample

	Mean	SD	Welch’s Unpaired t-test
Bedtime Resistance	3.12	2.81	$t(35) = 4.1911$, $p = .0002$
Sleep Onset Delay	2.59	.61	$t(37) = 12.3909$, $p < .0001$
Sleep Duration	3.94	1.37	$t(430) = 3.0553$, $p = .0024$
Sleep Anxiety	5.50	1.89	$t(36) = 1.8347$, $p = .0748$
Night Wakening	4.27	1.22	$t(36) = 3.6719$, $p = .0008$
Parasomnias	8.53	1.71	$t(36) = 1.3983$, $p = .1706$
Sleep Disordered Breathing	3.53	1.05	$t(35) = 1.5418$, $p = .1321$
Daytime Sleepiness	13.68	2.90	$t(413) = 8.0379$, $p = .0001$
Total CSHQ	48.24	7.91	$t(41) = 5.5544$, $p < .0001$

Scores on the CSHQ for the current sample were compared to the normative/non-sleep disordered sample reported by Owens et al. [33], and several significant differences were found (see table 2). Overall, the current sample reported a significantly greater disruption in sleep habits than the sample reported by Owens et al. [33].

Topics regarding current practices and barriers to healthy sleep in children that were discussed in focus groups were: 1) current bedtime sleep routines and challenges related to healthy sleep habits; 2) parent/caregiver description of restful sleep for their children and

facilitators and barriers to restful sleep; 3) effects of children's eating and physical activity behaviors related to sleep; and 4) association between the sleep and health of their children.

The focus group findings identified several major barriers to healthy bedtime sleep routines in children:

- *Electronics before bedtime:* A familiar theme that surfaced from the focus group was TV watching and/or electronic use at bedtime. One participant reported, "My baby and my child likes the noise, they just have to hear something going on." Another reported, "My daughter has to have her phone in her hand to go to sleep."
- *Co-sleeping:* Many participants reported that their children sleep with them. One participant reported, "I feel like my son just likes to have me, if he ain't got me, he won't even go to sleep, period."
- *Night waking accompanied by consumption of food/drink:* Many participants identified that their child expects/requires food or drink upon waking up during the night. The most common drinks mentioned were milk, juice, and water. Several mentioned Gatorade and Pedialyte. In terms of food during the night, several identified fruits, crackers, yogurt, jello, and leftovers.
- *Inadequate nighttime sleep resulting in daytime fatigue:* Several participants agreed with the following statements from other participants, "My children often fall asleep in the car on their way to school in the morning" and, "I often get calls from the school that my daughter fell asleep during class."

The themes, or barriers, identified in the qualitative data were echoed by findings in the quantitative data. Thus triangulation, or confirmation, was achieved through the use of the mixed-methods design.

DISCUSSION

The current research highlights the experiences and challenges faced by low-income, primarily black families related to the sleep habits of children. This study identified habits and challenges that will guide the development of interventions to help families create healthier sleep habits and make positive changes in the home environment for at-risk children. Identifying obstacles to children's sleep is critical to planning effective interventions.

Looking at children's sleep patterns among low income black families and the health and educational implications, this study identified that 97.1% of parents/caregivers identified that sleep was "very important" to their children's health. However, a high proportion reported a home environment that does not ensure restful sleep for their children. It was interesting that more than two-thirds of the parents/caregivers believe their children get enough sleep (67.7% said the child gets the right amount of sleep, and 70.6% think the child rarely gets too little sleep); however, on the CSHQ, 88.2% of the parents/caregivers identified that their children had problematic sleep habits. It appears that most parents/caregivers value the importance of sleep but may not be able to identify factors that interfere with adequate sleep quality and amounts or may not be aware of the specific sleep hygiene practices that are needed to promote healthy, restful sleep. Creating a healthy home sleep environment requires specific

strategies and interventions to ensure high-quality sleep. These findings align with previous research that children from minority, economically disadvantaged homes have decreased sleep duration, poor quality/less restful sleep, and more sleep curtailment than children who are not from minority, economically disadvantaged households [10].

The focus groups identified specific bedtime behaviors that threaten healthy sleep hygiene practices. Several themes that were reported were parents allowing electronics use consistently before bedtime, co-sleeping, and providing food and drinks upon waking during the night. The parents/caregivers also reported that children were often tired and drowsy during the day. The survey identified that many children had TVs in their bedrooms, and one of the emergent themes from the focus group indicated that the TV is frequently on before bedtime and, at times, throughout the night. This corresponds to research that identifies that these bedtime routines adversely affect healthy sleep patterns [10].

Promotion of healthy sleep with this population can play a role in preventing daytime sleepiness, a contributor to poor academic performance [14]. Healthy sleep habits can also help prevent depression, anxiety, attention-deficit hyperactivity disorders, and obesity [13]. Promoting longer sleep times can improve academic performance, emotional regulation, and quality of life in children [14].

It appears that an intervention which includes culturally-appropriate education could guide parents/caregivers on creating a healthy sleep environment to contribute to breaking the cycle of children's environmental health disparities by addressing barriers to healthy sleep [35] (Figure 1). Simple measures such as removing TVs from bedrooms and discontinuing the practices of electronic use before bedtime, night waking food and beverage consumption, and co-sleeping can lead to promoting healthy sleep with this population. Education is one of the key elements to helping this community help develop and maintain healthy sleep habits for their children.

Despite the small sample size and geographic location, this study illuminated a need for an educational intervention on healthy sleep habits and provided helpful insights about practices and barriers to healthy sleep patterns with children in a low-income urban area in the Deep South. Further research is needed in this area to validate, elucidate, and explore strategies to improve sleep practices and hygiene.

Through the current mixed-methods research design, the research team was able to become increasingly acquainted with the experiences and challenges of low-income, minority families regarding the sleep habits of children with opportunities for correlations, exploration, and increased perspective. The findings suggest that household practices supporting a more structured home environment are needed to promote healthy sleep hygiene practices with this high-risk population.

CONCLUSION

This research study identified sleep characteristics of children from a low-income urban area and explored barriers to healthy sleep behaviors. The study contributes to the understanding and appreciation of the cycle of environmental health disparities in children by highlighting the environmental factors among low-income black families relative to their children's sleep hygiene and the contribution to adverse health outcomes like obesity and its

complications. It further illuminates potential strategies and intervention research to help vulnerable populations create a healthy home environment. Promoting healthy sleep routines is an excellent starting point. Data collected during the questionnaires and focus group sessions will be used to inform future intervention research related to promoting adequate sleep.

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APPENDIX 1. DEMOGRAPHIC QUESTIONNAIRE

ABOUT YOUR CHILD (Child enrolled at daycare, preschool, or after-school)		
Child's Date of Birth: / /	Child's Gender: ☐ Male ☐ Female	
Child's Race: ☐ Asian ☐ Black/African American ☐ White ☐ Other (Specify)		
Child's Ethnicity: ☐ Hispanic ☐ Non-Hispanic		
ABOUT YOURSELF		
Relationship to child: ☐ Mother ☐ Grandmother ☐ Aunt ☐ Sister ☐ Other		
Your Age: _____ years	Current Zip Code: _____	
Your Race: ☐ Asian ☐ Black/African American ☐ White ☐ Other (Specify)		
Your Ethnicity: ☐ Hispanic ☐ Non-Hispanic		
Your highest grade completed: ☐ Less than high school ☐ Graduated high school/GED ☐ Some college/vocational school ☐ Graduated college/vocational school ☐ Some graduate school ☐ Completed graduate school		
YOUR RELATIONSHIP STATUS		
☐ Single ☐ Married/Partnered ☐ Separated/Divorced ☐ Other: _____		
WHAT LANGUAGE IS USUALLY SPOKEN AT HOME?		
☐ English ☐ Spanish ☐ Other (describe) _____		
PLEASE INDICATE THE TYPE OF HOME YOU LIVE IN:		
☐ House	☐ Mobile home	
☐ Apartment	☐ Condominium	
☐ Townhome	☐ Other _____	
In an average week, how many times do all of the people in your family who live with you eat dinner together? (circle one): One Two Three Four Five Six Seven		
In an average week when YOU were a child, how many times did all of the people in your family who lived with you eat dinner together? (circle one): One Two Three Four Five Six Seven		
WHAT IS YOUR CURRENT WORK STATUS?		
☐ Employed- FULL TIME	☐ Disabled, not able to work	☐ Unemployed and looking for work
☐ Employed- PART TIME	☐ Student	☐ Unemployed and not currently looking for work
☐ Retired	☐ Temporarily laid off	
DO YOU OR ANY OTHER MEMBER OF YOUR HOUSEHOLD RECEIVE ASSISTANCE FROM ANY OF THE FOLLOWING? (Please check all that apply)		
☐ Social Security/SSI	☐ Worker's Compensation	☐ Unemployment Benefits
☐ SNAP (Supplemental Nutritional Assistance)	☐ Alimony/Child Support	☐ Veteran's Benefits
	☐ Cash Assistance/TANF	☐ Other: _____
WHAT IS YOUR FAMILY'S CURRENT HOUSEHOLD YEARLY INCOME? (estimate)		
IS YOUR FAMILY CURRENTLY EXPERIENCING ANY FINANCIAL DIFFICULTIES? (Please check one)		
☐ No ☐ Some problems ☐ Many problems ☐ It is hard to meet our basic needs		
IN WHAT AREAS DO YOU HAVE FINANCIAL DIFFICULTIES? (Please check all that apply)		
☐ None ☐ Phone/Utility bills ☐ Rent/Mortgage ☐ Buying food ☐ Vehicle-related ☐ Medical		
WHO LIVES IN THE HOME WITH THE CHILD? (including you and the child)		
Number of Adults (18 years and older): _____		Number of Children (Under 18 years): _____
What is YOUR height and weight? Height: _____ feet _____ inches		Weight: _____ pounds
Do you feel YOUR weight is (circle one):		
Underweight	Normal/Average Weight	Somewhat Overweight
		Very Overweight
Do you feel YOUR CHILD'S weight is (circle one):		
Underweight	Normal/Average Weight	Somewhat Overweight
		Very Overweight

Please circle "yes" or "no" to each of the following questions

1.	Does your child have a diagnosis of ADD or ADHD?	YES	NO
2.	Does your child have behavior problems?	YES	NO
3.	Does your child have problems learning in school?	YES	NO
4.	Does your child have breathing problems during sleep?	YES	NO
4a.	If "yes" have you discussed the problem with your child's doctor?	YES	NO
5.	Does your child eat after bedtime?	YES	NO
6.	In the hour before your child's bedtime, is there a TV on near your child?	YES	NO
7.	Is the TV on all night where your child sleeps?	YES	NO
8.	Is there a TV in your child's room?	YES	NO
9.	Does your child use a cell phone, tablet, or computer before bed?	YES	NO
10.	Does your child have a bed to sleep in?	YES	NO
11.	Does your child have their own bed?	YES	NO
12.	Does your child usually sleep alone?	YES	NO
13.	Does your child usually sleep with someone else?	YES	NO
14.	Does your family have a set dinner time?	YES	NO
15.	Does your child eat dinner with the family?	YES	NO
16.	Does your child drink caffeinated soda, tea, or chocolate drink with dinner?	YES	NO
17.	Does your child drink anything besides water during the night?	YES	NO

Please circle your response to the following questions

- How important do you think sleep is to your child's health?
Not important Somewhat important Very important
- How important is a bedtime routine for your child?
Not important Somewhat important Very important
- Please rate the quietness of the place where your child sleeps:
Noisy Somewhat quiet Very quiet

Please write in your answer to the following questions

- How many hours of sleep do you think your child needs in a 24-hour period? _____
- What things help your child to sleep well?
- What things keep your child from sleeping well?
- If your child wakes up at night, what do you do to help them get back to sleep?
- When is your child's bedtime during the week on school days? _____
- When is your child's bedtime on the weekends or when out of school? _____
- How many days each week does your family eat take out or fast food for dinner? _____

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Chapter 61

**THE RELATIONSHIP BETWEEN CHILDHOOD OBESITY
AND NEIGHBORHOOD FOOD ENVIRONMENT
EXPLORED THROUGH THE CONTEXT OF
GENTRIFICATION IN NEW YORK CITY**

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ABSTRACT

Inequity and health disparities can be exacerbated as a result of gentrification when long-term residents are displaced, or remain but are not able to take advantage of new opportunities. The disappearance of old and emergence of new food establishments may increase the proximity to and density of healthy food options, however, affordability and consumption of healthy food, nor a decrease in risk of adverse health outcomes are not guaranteed. Our study aims to understand the relationship between gentrification, neighborhood food environment, and childhood obesity. We describe food opportunities changes in New York City using National Establishments Time Series Database stratified by gentrification status. Using data from the Columbia Center for Children's

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Environmental Health birth cohort study, we evaluate the impact of the area-level changing food chances on the body mass index z-scores of children at age five. Overall, gentrifying neighborhoods have the highest number of food chances and experience the most substantial increase in both healthy ($p < 0.001$) and unhealthy ($p < 0.001$) food chances between 1990-2010. After adjusting for covariates, higher access to healthy food chances was associated with both lower BMI z-score ($p < 0.01$) and less likelihood of being overweight or obese ($p < 0.001$) for five-year-old children. Our results suggest gentrification was associated with contemporaneous changes in the neighborhood food chances in NYC and children exposed to greater healthy foods experienced a lower probability of excess body weight by five years old. Further research is needed to understand other potential pathways connecting gentrification to childhood BMI.

INTRODUCTION

In the United States over the last five decades, the percentage of children and adolescents affected by obesity has more than tripled [1]. Nationally, nearly 1 in 5 school age children and young people (6-19 years) is obese. These trends are similar in New York City, where almost half of elementary school children and Head Start children are not at a healthy weight [2]. Obesity prevalence also impacts the very young; 1 in 5 kindergarten students, and 1 in 4 Head Start children (birth to age five), are obese [2]. Adults and children who are overweight are at increased risk for diabetes, heart disease, stroke, high blood pressure, arthritis, and some cancers [3]. Marginalized communities bear a disproportionate share of the burden of obesity and related health conditions, i.e., diabetes [4, 5]. Given that obesity begins early in life [6], childhood obesity has immediate and long-term effects on physical, social, and emotional health; the gravity of this public health issue is of great concern.

Obesity results from an imbalance of energy consumption and expenditure. The food environment provides the key ingredient in the energy equation -- the energy. The availability [5, 7-10], accessibility [11, 12] and proximity [13-15] of healthy and unhealthy food purchasing and consumption opportunities [9, 15, 16] have been associated with obesity. Also, food prices and food affordability are influential determinants of the food choices, and therefore determinants of obesity, and other metabolic chronic diseases [17-19].

The influx of investment that accompanies gentrification, reinvestment of capital, social upgrading of locale by incoming affluent groups, and landscape change, results in direct or indirect displacement of low-income groups [20]. Gentrification also brings a change in the urban food environment, affecting the access to and availability of various forms of food and beverages, grocery stores, restaurants, large big-box stores, farmer's markets, bodegas, and other food establishments [21-25]. Recent studies have indicated that shifts in the food environment in the United States (US) are transforming urban centers [11, 13, 26] from food deserts (i.e., low-income areas where a significant number of residents are located more than one mile from a supermarket) [27] to areas with abundant food options, including fresh food markets and sit-down restaurants. Breyer and colleagues report that the growing abundance of food options does not necessarily correlate with increased consumption of healthy foods for all residents. They posit that while healthy food options appear plentiful, healthy foods are economically inaccessible for socioeconomically marginalized households [28]. Healthy foods closer to home does not guarantee these healthful foods reach the tables of marginalized

residents. Breyer and colleagues [28] state this type of disconnect is most stark in gentrifying neighborhoods.

The food-related opportunities shaped by gentrification and residents' associated food choices can be described regarding the sociological concept of habitus that links structural factors to individual behavior or practices [29]. "Food habitus" can be thought of as a set of dispositions and tastes towards food that account for food and nutrition-related practices that become apparent in an individual's body, including one's weight [30]. Thus, food habitus represents the dialectical relationship between the individual's food-related choices and the opportunities afforded by the food environment. Insights to obesogenic environments can be illuminated by focusing on the interplay between the structural opportunities, or food chances (i.e., chance to purchase and consume food), that exist within the food ecology and individual-level food choices. Understanding the trends in the food environment is integral to addressing whether shifts in capital investments and shifts in the demographic composition of the neighborhood as a consequence of gentrification has an impact on the long-term health of residents.

This project focuses on the structural opportunities within New York City's (NYC) food environment. We examined associations between obesity measures of five-year-old children and 1) neighborhood healthy food chances 2) neighborhood unhealthy food chances 3) neighborhood gentrification status during 1990-2010 in NYC. Secondly, the relationship between gentrification and food chances was examined, to provide greater context to the relationship between obesity measures and the neighborhood food environment.

OUR STUDY

The project involves secondary longitudinal data analyses that integrates information from the Columbia Center for Children's Environmental Health's (CCCEH) prospective birth cohort, National Time-Series Establishments Database (NETS), New York University Furman Center, and New York City Department of Planning Community District Profiles. This work aims to evaluate the role of gentrification and food environment in the cycle of children's environmental health disparities, specifically obesity. The combination of these data sources provided the opportunity to examine how participants' neighborhood food environment influence the weight of children in the context of gentrification. The Institutional Review Board at Columbia University Medical Center approved research protocols related to CCCEH and NETS.

CCCEH has conducted a longitudinal birth cohort study beginning in 1998 that has been described extensively elsewhere [31, 32]. Briefly, CCCEH enrolled 727 women ages 18–35 years old during their third trimester of pregnancy. Women were included if they self-identified as either African American or Dominican and resided in Northern Manhattan or the South Bronx for at least one year before pregnancy. Exclusion criteria included mother's report of cigarette smoking or use of other tobacco products during pregnancy, illicit drug use, diabetes, hypertension, known HIV, or a first prenatal visit after the 20th week of gestation. Research staff abstracted medical records of mother and infant at delivery to ascertain prenatal medical history and birth outcomes. Mother-child dyads participate in follow-up visits every three months throughout the first two years and annually thereafter.

During the follow-up visit of five-year-olds, body size measurements (weight and height) were collected ($n = 486$). Children were measured in bare or stocking feet while wearing light clothing (i.e., pediatric gown, underwear, or shorts and a t-shirt). Weight was assessed using a digital scale.

A Detecto Cardinal 750 digital scale/stadiometer (Cardinal Scale Manufacturing Company) was used to collect standing height measurements until January 2010. After January 2010, CCCEH researchers assessed standing height with the Holtain-Harpenden Wall Mounted Stadiometer Counter 602VR (Holtain Limited). Body mass index z-scores (BMIZ) were quantified using the SAS programs provided by the CDC [33]. According to the CDC child growth charts, the overweight category is defined as BMI 85th to less than the 95th percentile while obese is defined as 95th percentile or greater for age and sex. The mothers' weight before pregnancy was self-reported during the third trimester.

New York City Food Environment and Gentrification

The NETS database (Dun and Bradstreet data from January of each year to create an annual census of businesses and many nonprofit and government agencies) [34-36] was used to develop a food environment measure for each sub-borough areas (SBA; geographical unit similar to community district) in NYC for each year from 1990-2010. Kaufman and colleagues [37] recently analyzed NETS to measure health-relevant business over the same 21-year time span in the NYC metropolitan area. Of the 25 categories defined by the research team, 13 relate to food establishments. Aggregate level data for unhealthy and healthy food chances are the central interest in our analyses. Unhealthy food chances are defined as fast food restaurants, pizza restaurants, bakeries and candy/confectionary stores, meat markets, and corner store/deli often described as “bodegas.” Convenience stores were not included in the aggregate measure because corner stores represent this category in NYC. Healthy food chances are defined as fruit and vegetable markets, natural food markets and nut stores, fish markets, small grocery stores, and large supermarkets. Our analyses operationalized the food environment by the average food chances per square kilometer. To increase accuracy, bodies of water are excluded from the area of the neighborhoods.

Second, we used the Furman Center of New York University [38] gentrification classification system to measure gentrification status of NYC's neighborhoods during the same period that food chances were estimated (1990-2010). In brief, the criteria defining the classification systems relate to the median income of the neighborhood in 1990 and the median rent growth between 1990-2014. NYC is comprised of 55 SBAs. “Gentrifying” neighborhoods consist of SBAs that meet two criteria: 1) low-income in 1990 and 2) experienced rent growth above the median SBA rent growth between 1990 and 2014. “Did not gentrify” neighborhoods also started as low-income in 1990 but experienced no growth or more modest rent growth. “Not eligible to gentrify” neighborhoods” are the city's remaining SBA, which had higher incomes in 1990.

Primary Analyses

We aimed to understand the relationship between childhood obesity and the changing food environment of children in the context of gentrification. This overall analysis required evaluation the several relationships including a) food chances, time and gentrification status; b) obesity and food chances trajectories c) obesity and gentrification. Below we provide details of these three analyses conducted.

To assess how food chances change throughout the 21-year timeframe, we conducted group-based trajectory model estimation (GBTM) on the number of food chances in the SBAs where CCCEH children lived at age five during 1990-2010. GBTM models the number of food chances as a continuous function of time (measured annually) and estimates the probability of trajectory membership for each food category. GBTM was conducted on healthy and unhealthy food chances separately to generate specific trajectories for each category. We log-transformed the count of food chances to better approximate a normal distribution and estimated models with varying numbers of groups [1–6] and shapes (linear, quadratic, cubic). We evaluated model fit using the Bayesian Information Criterion (BIC), as well as the magnitude of group membership posterior probabilities. The relationship between food trajectories and gentrification status (gentrifying, did not gentrify, and not eligible to gentrify) was assessed using chi-square Fisher Exact tests. The analyses GBTM were performed using the Stata command “traj” developed by Bobby L Jones and Daniel S Nagin [39]. Table 1 provides the number of groups, shape, and BIC for both healthy and unhealthy food chance trajectories.

Table 1. Food chances trajectories according to the number of groups, shapes, and BIC

Food Chances Category	Number of groups	Trajectory shapes ¹	BIC ² (N = 24)
Healthy Food Chances	2	1 1	1.1
	2	1 2	8.3
	2	2 1	10.3
	2	2 2	17.9
	2	3 3	24.7
	2	4 4	32.5
Unhealthy Food Chances	2	4 4	-26.9
	3	1 1 4	26.6
	2	4 1	-30.5
	3	1 1 4	51.66
	2	1 4	-53.1

¹ Trajectory shapes: 1 = linear; 2 = quadratic; 3 = cubic; 4 = quartic.
² BIC = Bayesian information criterion (for the total number of Sub-boroughs).
* One or more of the groups had a very small proportion of the observations.
* The food ecology is described concerning food chances to reflect the sociological construct of habitus that provides insights to obesogenic environments by focusing on the interplay between food chances and food choices. Food chances are the food establishments available in a neighborhood.

The relationship between obesity and the previously calculated trajectories were examined through linear regression of BMI z-scores and logistic regression of overweight/obesity status based on the CDC classification [33] of five-year-old children. Given that enrollment for CCCEH occurred from 1998-2006, children reached age five between 2003-2011. This period falls within the years covered by the NETS dataset and the

Furman Center's gentrification classification of NYC neighborhoods (199-2010). CCCEH participants turned five-years-old between 2003 and 2011. This period is one year beyond the period covered by NETS and the Furman Center. For those children that turned five in 2011 ($n = 26$), the food chance trajectories experienced in 2010 were included in the study.

Fisher Exact tests were conducted between the binary variable of overweight/obese status and gentrification status. Similar to the previous analysis, the relationship between obesity and gentrification was assessed through linear regression of BMI z-scores and logistic regression of overweight/obesity status as the dependent variables and the gentrification status of the child's SBA.

Three adjustment strategies were considered for each of the aforementioned linear and logistic regressions: univariate model, individual-level only model, and full model with both individual and area-level covariates. Individual-level covariates include children's age, gender, race/ethnicity (African American or Dominican American), mother's pre-pregnancy BMI, mother's years of education, and use of public assistance at least once from the period during pregnancy through the child being five-years-old. Area-level covariates include SBA average population size between 1990-2010, the land area of SBAs (square km, excluding bodies of water), percent of households with SNAP benefits in the past 12 months, and percent of residents with less than high school diploma. The population size was derived from the United States Census Bureau decennial census; the American Community Survey data (2006-2010 5-year estimates) was the source of all remaining area-level covariates.

Contextual Analyses

To graph changes in the food environment of CCCEH participants over time, we used locally weighted scatterplot smoothing (lowess) on the NETS data for the SBA in which CCCEH participants resided while the child was five-years-old. Lowess bandwidth of 0.4 was used to provide locally weighted scatterplot smoothing that narrowly followed the data. CCCEH participants with completed data on all variables of interests (BMI z-scores, BMI percentile, neighborhood, child's gender, child's age, child's ethnicity, maternal education, pre-pregnancy BMI, and use of public assistance) reside in 24 of NYC's 55 SBAs. Thus, only these 24 SBAs were used in the lowess plots to capture the food environment that CCCEH participants experienced. Figures 1 and 2 display the average number of food chances per square kilometer stratified by the gentrification status from 1990 to 2010.

Software

We performed all statistical analyses with Stata version 15 and graphics were developed with grystyle software [40]. All regression analyses used cluster-robust standard errors to account for participants clustering within SBAs.

FINDINGS

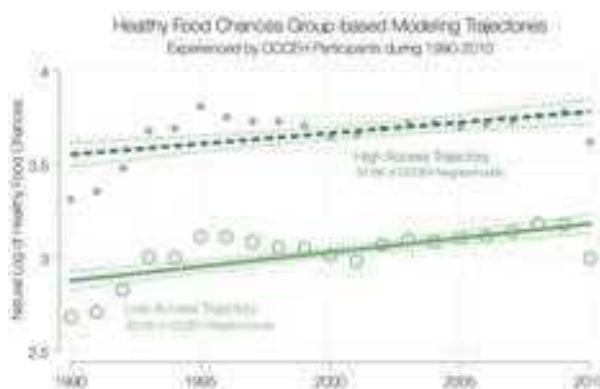
The sample included 486 mother-child pairs from CCCEH with 54% female children. The majority of participants self-identified as Dominican, obtained at a least high school diploma (or GED) and never received public assistance before or while the child was five years old. Mothers’ pre-pregnancy BMI places nearly half as overweight or obese before pregnancy. At age five years, children predominantly lived in gentrifying neighborhoods and over a third of the sample of children were overweight or obese. Table 2 provides demographic information about the CCCEH mother-child dyads.

Table 2. CCCEH participants characteristics at child age five

Participant Characteristics	(N = 486)
Race	
Dominican/Dominican American	92 60%
African American	194 40%
Gender	
Female	261 54%
Caregiver Education Level	
GED, HS Diploma or more	354 73%
Ever Received Public Assistance	
Yes	80 17%
Child Body Mass Index	
Overweight or Obese	187 39%
Maternal Body Mass Index	
Overweight or Obese	222 46%
Gentrification Status and SBAs	
Gentrifying	11 68%
Mott Haven/Hunts Point	
Morrisania/East Tremont	
Bedford Stuyvesant	
Bushwick	
North Crown Heights/Prospect Heights	
Lower East Side/Chinatown	
Morningside Heights/Hamilton Heights	
Central Harlem	
East Harlem	
Washington Heights/Inwood	
Astoria	
Did not gentrify	4 26%
Highbridge/S. Concourse	
University Heights/Fordham	
Kingsbridge Heights/Mosholu	
Soundview/Parkchester	
Not eligible to gentrify	9 6%
Riverdale/Kingsbridge	
Throgs Neck/Co-op City	
Pelham Parkway	
Williamsbridge/Baychester	
Park Slope/Carroll Gardens	
East Flatbush	
Elmhurst/Corona	
Rockaways	
North Shore	

Trajectory Analyses of Food Chances

GBTM of unhealthy and healthy food chances in CCCEH SBAs result in models with two trajectory groups that follow parallel increasing slopes (see Figures 1 and 2). The trajectories for healthy food chances were best fit with a linear term function of time and the trajectories for unhealthy food chances were best fit with a more complex model that requires a quadratic function of time. Results of these analyses are provided in Table 1. The food chances trajectories are classified as either low or high access. However, it should be recognized that the “low” and “high” descriptors are relative to the type of food chances category and lack an equivalent numeric representation. In other words, SBAs classified as “high access” to healthy foods is not equivalent to the number of food chances available in “high access” unhealthy food SBAs.



* The food ecology is described concerning food chances to reflect the sociological construct of habitus that provides insights to obesogenic environments by focusing on the interplay between food chances and food choices. Food chances are the food establishments available in a neighborhood.

Figure 1. Group-based modeling trajectories for healthy food chances in neighborhoods where CCCEH participants resided when child was five-years-old.



* The food ecology is described concerning food chances to reflect the sociological construct of habitus that provides insights to obesogenic environments by focusing on the interplay between food chances and food choices. Food chances are the food establishments available in a neighborhood.

Figure 2. Group-based modeling trajectories for unhealthy food chances in neighborhoods where CCCEH participants resided when child was five-years-old.

Table 3. Food chances trajectories and gentrification status among CCCEH participants at age five

Exposure	Gentrifying	Did not gentrify	Not eligible to gentrify	Total	P> z Fisher's Exact Test
HEALTHY FOOD CHANCES ANALYSES					
Low Access	174 (55%)	127 (40 %)	15 (5%)	316	0.000 ***
High Access	158 (93%)	0 (0.0%)	12 (7%)	172	
Total	332 (68 %)	127 (26%)	27 (6%)	486	
UNHEALTHY FOOD CHANCES ANALYSES					
Low Access	151 (50%)	127 (42%)	25 (8%)	303	0.000 ***
High Access	181 (99%)	0 (0.0%)	2 (1%)	183	
Total	332 (68%)	127 (26%)	27 (6%)	486	

* (p < .05) ** (p < 0.01) *** (p < 0.001).

The range for healthy food chances per square kilometer is between 2 and 7; while the range for unhealthy food chances is 8 to 54, indicating that it is more likely, in any SBA, that an individual will come in contact with an unhealthy vs healthy food outlet. This indicates that within an SBA, it is far more likely that an individual will interact with an unhealthy food establishment vs. a healthy food establishment. The healthy food chances GBTM suggests that 63% of SBAs where CCCEH participants resided during 1990-2010 were low access healthy food chances trajectories, while the remaining neighborhoods are classified as high access. GBTM of unhealthy food chances found 75% of SBAs contain low access trajectories.

Gentrification Status and Trajectories of Food Chances

In the CCCEH sample, the majority of households resided in gentrifying SBAs (see Table 3). Nearly a quarter of the participants resided in SBAs that did not gentrify between 1990-2010. These SBAs that did not gentrify only include the low access trajectories of healthy and unhealthy food chances. Only 27 participants resided in SBAs not eligible to gentrify. Low access to unhealthy foods is more common in SBAs that are not eligible to gentrify. There are statistically significant ($p < 0.001$) differences between gentrification status and unhealthy and healthy food chances trajectories.

Regression Analyses of Children's BMI and Food Chances Trajectories

We analyzed the relationship between children's BMI z-score and food chances GBTM. Across all models, children residing in neighborhoods with high access to healthy foods have lower BMI-z scores and less likely to be overweight or obese compared to children who resided in neighborhoods with low access to healthy foods (see Table 4). BMI-z is significantly lower in adjusted models at the individual level (beta = -0.32; 95% CI: 0.5, -0.1).

Children are less likely to be overweight or obese controlling for individual and area-level covariates respectively (OR = 0.58; 95% CI: 0.4, 0.8; OR = 0.35; 95% CI: 0.2, 0.8). Across all models, children residing in neighborhoods with high access to unhealthy food chances trajectories had slightly lower BMI-z scores. The logistic regression model predicting overweight or obesity adjusted for individual-level covariates was significant (OR = 0.68; 95% CI: 0.5, 1.0).

Table 4. Obesity measures and food chance trajectories regression analyses for CCCEH participants at age five

Exposure	BMI-Z			Overweight/Obese		
	Model 1 ^a (N = 486)	Model 2 ^b (N = 486)	Model 3 ^c (N = 486)	Model 1 ^a (N = 486)	Model 2 ^b (N = 486)	Model 3 ^c (N = 486)
	Beta (95% CI)	Beta (95% CI)	Beta (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
HEALTHY FOOD CHANCES ANALYSES:						
Low Access Trajectory	ref	ref	ref	ref	ref	ref
High Access Trajectory	-0.19 (-0.4 to 0.0)	-0.32** (-0.5 to -0.1)	-0.43 (-0.9 to 0.0)	0.78 (0.5 to 1.2)	0.58*** (0.4 to 0.8)	0.35** (0.2 to 0.8)
UNHEALTHY FOOD CHANCES ANALYSES:						
Low Access Trajectory	ref	ref	ref	ref	ref	ref
High Access Trajectory	-0.09 (-0.3 to 0.2)	-0.19 (-0.5 to 0.1)	-0.18 (-0.6 to 0.3)	0.88 (0.6 to 1.3)	0.68* (0.5 to 1.0)	0.59 (0.3 to 1.3)

* (p < 0.05) ** (p ≤ 0.01) *** (p ≤ 0.001).

^a Univariate model.

^b Adjusted individual-level model (individual level covariates included gender, age, ethnicity, maternal education, maternal pre-pregnancy BMI, and public assistance).

^c Adjusted model with individual and neighborhood level covariates (including SBA population, area in kilometers squared excluding bodies of water, SNAP recipients, and educational attainment).

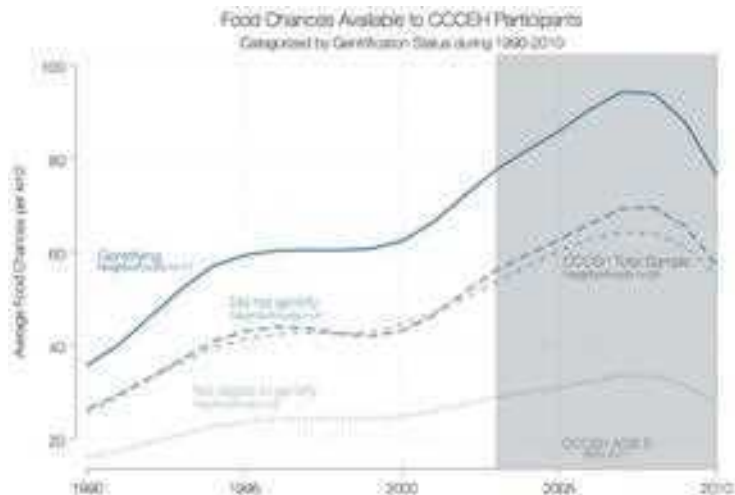
Regression Analyses of Children's BMI and Gentrification Status

The majority of children in the study are not overweight or obese (n = 299), and 71% of them live in gentrifying neighborhoods. A small percentage (5%) of healthy weight children reside in SBAs not eligible to gentrify and the, remaining 24% lived in SBAs that did not gentrify during 1990-2010. Similar to their healthy counterparts, overweight or obese children (n = 187) primarily live in gentrifying SBAs (65%), a small percentage live in SBAs not eligible to (6%), and a slightly higher percentage live in SBAs that did not gentrify (29%). There are no statistically significant differences between these groups (see Table 5).

Table 5. Overweight/obese status and gentrification status among CCCEH participants at age five

Exposure	Gentrifying	Did not gentrify	Not eligible to gentrify	Total	P> z Fisher's Exact Test
Neither overweight nor obese	211 (70.57 %)	73 (24.41 %)	15 (5.02 %)	299	
Overweight or obese	121 (64.71 %)	54 (28.88%)	12 (6.42 %)	187	
Total	332 (68.31%)	127 (26.13%)	27 (5.56%)	486	0.386

SBA that did not gentrify (as compared with gentrifying neighborhoods) were associated with higher BMI z-scores. However, this was only statistically significant in the unadjusted model (beta= 0.18; CI: 0.0, 0.3). This positive relationship was also present in the logistic regression analyses of overweight or obesity status but also lacked statistical significance. SBAs not eligible to gentrify (as compared with gentrifying neighborhoods) were also associated with higher BMI z-scores and being overweight or obese, but also lacked statistical significance. Full details are presented in Table 6.



n = Neighborhoods defined by NYC sub-borough areas.
* Area of neighborhood excludes bodies of water.
** The food ecology is described concerning food chances to reflect the sociological construct of habitus that provides insights to obesogenic environments by focusing on the interplay between food chances and food choices. Food chances are the food establishments available in a neighborhood.

Figure 3. Average food chances available to Columbia Center for Children’s Environmental Health participants categorized by gentrification status during 1990-2010.

Table 6. Obesity measures and gentrification status

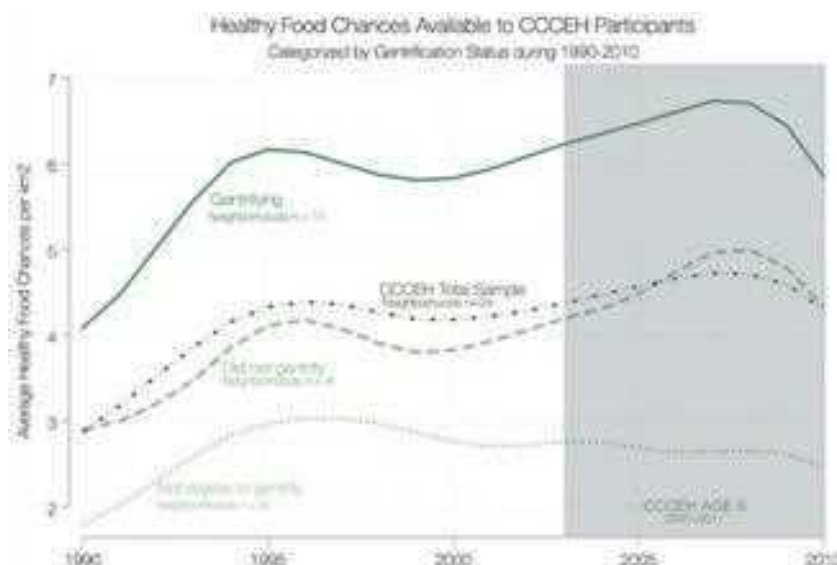
	BMI-Z				Overweight/ Obese	
Exposure	Model 1 ^a (N = 486)	Model 2 ^b (N = 486)	Model 3 ^c (N = 486)	Model 1 ^a (N = 486)	Model 2 ^b (N = 486)	Model 3 ^c (N = 486)
	Beta (95% CI)	Beta (95% CI)	Beta (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
GENTRIFICATION STATUS						
Gentrifying	ref	ref	ref	ref	ref	ref
Did not Gentrify	0.18 * (0.0 to 0.3)	0.13 (-0.1 to 0.3)	0.06 (-0.6 to 0.3)	1.29 (0.9 to 1.9)	1.23 (0.8 to 1.8)	1.13 (0.7 to 1.8)
Not eligible to gentrify	0.36 (-0.1 to 0.8)	0.31 (-0.2 to 0.8)	0.24 (-0.6 to 1.1)	1.40 (0.7 to 2.9)	1.32 (0.6 to 3.1)	.91 (0.3 to 3.1)

* (p < 0.05); ** (p ≤ 0.01) *** (p ≤ 0.001).
^a Univariate model
^b Adjusted individual-level model (individual level covariates included gender, age, ethnicity, maternal education, maternal pre-pregnancy BMI, and public assistance).
^c Adjusted model with individual and neighborhood level covariates (including SBA population, area in kilometers squared excluding bodies of water, SNAP recipients, and educational attainment).

Food Chances and Gentrification Status

The SBAs where CCCEH participants resided, food chances increase over time, across all categories of gentrification, there seems to be a surge in food chances around 1995, with a steady increase from 2000 until 2008 where the number of food chances declines (see Figure 3). This pattern is present in all three categories of food chances; however, the sum, mean and range vary between healthy and unhealthy food chances (see Figures 4 and 5).

Gentrifying SBAs have the most food chances across all years, (mean = 49.4; median = 47.8; range = 17.7-104.4). SBAs that did not gentrify followed (mean = 68.2; median = 57.4; range = 14.9 -253.1). SBAs not eligible to gentrify offered the lowest number of food chances per square kilometer during 1990-2010 (mean = 26.1; median = 24; range = 5.2-70.5).



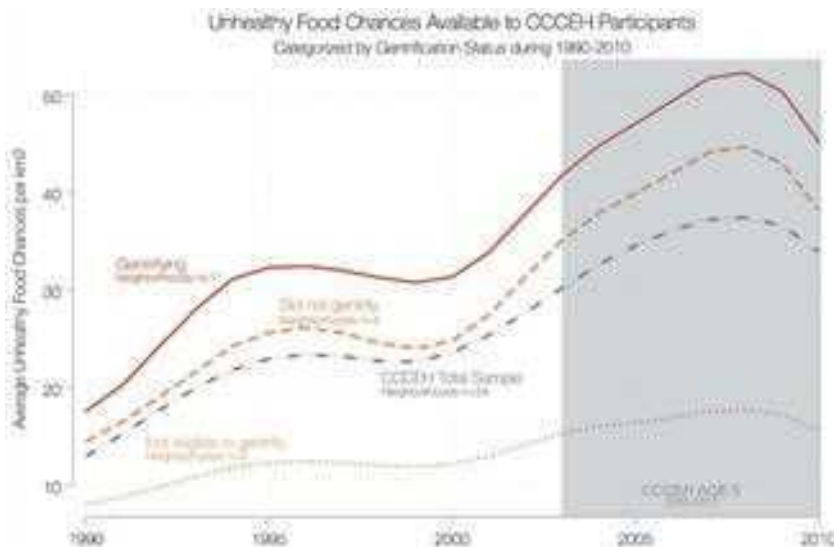
n = Neighborhoods defined by NYC sub-borough areas.

* Area of neighborhood excludes bodies of water.

** The food ecology is described concerning food chances to reflect the sociological construct of habitus that provides insights to obesogenic environments by focusing on the interplay between food chances and food choices. Food chances are the food establishments available in a neighborhood.

Figure 4. Average healthy food chances available to Columbia Center for Children's Environmental Health participants categorized by gentrification status during 1990-2010.

Overall there are fewer healthy food chances than unhealthy food chances available to CCCEH participants across all years and gentrification categories. Gentrifying SBAs have both the greatest number of healthy (mean = 6; median = 5.5; range = 1.2-14.9), and unhealthy (mean = 36.7; median = 31.7; range = 9.1-93.2) food chances across all years. Food chances afforded by SBAs that did not gentrify had fewer healthy (mean = 4.1; median = 4.1; range = 1.7 -7.9) and unhealthy (mean = 30.2; median = 26.9; range = 9.6-68.1) food chances are less than gentrifying SBAs. SBAs not eligible to gentrify offered the lowest number of food chances per square kilometer for both healthy (mean = 2.7; median = 2.7; range = 0.4-5.7) and unhealthy (mean = 13.5; median = 12.1; range = 2.1-35.7) food chances.



n = Neighborhoods defined by NYC sub-borough areas.

* Area of neighborhood excludes bodies of water.

** The food ecology is described concerning food chances to reflect the sociological construct of habitus that provides insights to obesogenic environments by focusing on the interplay between food chances and food choices. Food chances are the food establishments available in a neighborhood.

Figure 5. Average unhealthy food chances available to Columbia Center for Children's Environmental Health participants categorized by gentrification status during 1990-2010.

DISCUSSION

This study evaluated shifts in food chances as a function of gentrification, and the relationship between area-level healthy and unhealthy food chances and the BMI of five-year-old children in a birth cohort study. An increase in food chances was noted between 1990-2010. Gentrifying neighborhoods experienced the most significant increase of opportunities to purchase foods, including both healthy and unhealthy food chances, and participants living in areas that were not eligible to gentrify experienced lower availability of healthy and unhealthy food sources throughout the time period. Greater area-level availability of healthy foods was associated with lower BMI at age five. Although unhealthy food sources were more abundant, there was no observed relationship between area-level availability of unhealthy foods and excess weight in this sample. While most of the birth cohort sample lived in areas classified as gentrifying, there was no statistically significant association of area-level gentrification with BMI at age five.

Changes in urban food ecology as a function of gentrification have not only taken hold in New York City but across the nation. Our findings provide insights to study the effect of gentrification on health retrospectively. Despite the lack of a universally accepted operational definition, gentrification connotes images of a capital investment that often create a flourishing food ecology. For instance, communities defined as food deserts are transformed into an abundance of food opportunities. Some researchers are not convinced that these new establishments will transfer into actual uptake of healthier food consumption [28, 41]. We

hypothesized that gentrification would increase healthier food chances. The NETS data indicate that there was an overall increase in food chances throughout the city regardless of gentrification status, including an overall increase in healthy food chances in gentrifying neighborhoods until 2008. However, gentrifying neighborhoods held not only the greatest abundance of healthy food chances but also the greatest abundance of unhealthy food chances. The simultaneous increase suggests that all food chances are increasing, but there are more opportunities to choose unhealthy options. In terms of food habitus, residents may lean towards what is more available, accessible, and affordable to obtain in their neighborhoods. The food habitus formed by the historic lack of healthy foods chances will take time to change, even when healthy foods become available and affordable.

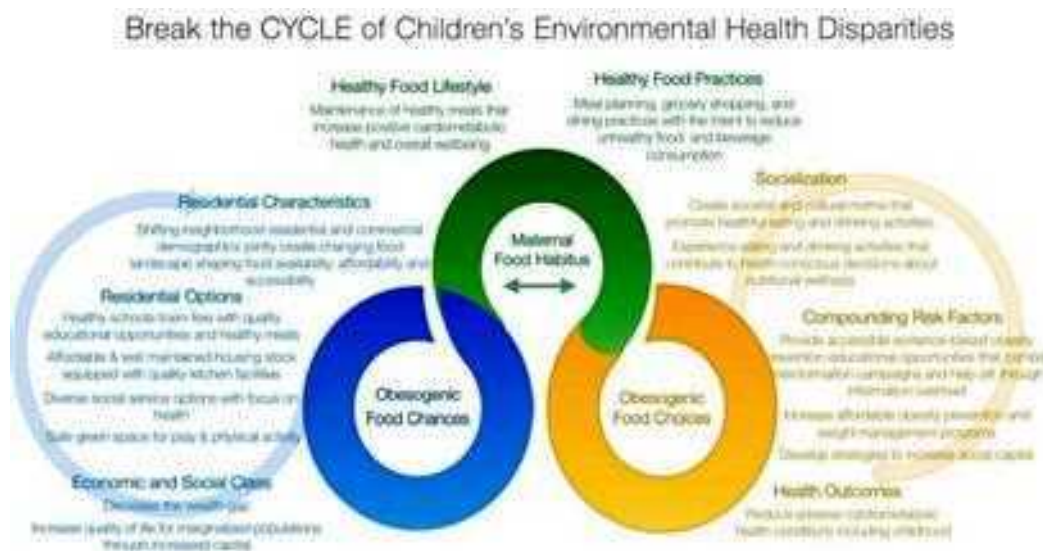
Moreover, a change in habitus does not occur immediately. Thus, lasting dispositions towards one's food choices may remain. Residents that have formed a less health-promoting food habitus due to a past absence of healthy food chances could be more susceptible to continuing to choose the unhealthy options that are becoming increasingly available in their neighborhood.

Given the literature on the abundance of fast food outlets in marginalized communities [27, 42-46], it was surprising that gentrifying SBAs experienced more of an increase in unhealthy food chances as compared with SBAs that did not gentrify. This may be a result of overall growth and opportunities for capital investment of food businesses signaling broader changes to the retail ecology irrespective of healthfulness. Lastly, it should be noted that we believe the decline near the end of our observation period and across all gentrification statuses may be a result of the 2008 economic crisis as well as trends toward more online food retail.

The two trajectories identified by the GBTM analyses for healthy and unhealthy food chances resemble the lowess curves for both of these categories confirming the latter analyses. The significant relationships between a) gentrification status and food chances and b) healthy food chance trajectories and obesity would suggest an association between gentrification status and obesity. However, this was not detectable, and future investigations may provide insight as to whether such an association would be observed with sufficient statistical power and variation in the environment. It is clear that the process of gentrification may influence the food ecology, and a food environment higher in availability healthy foods may be protective against children developing obesity. The relationship between gentrification and childhood obesity, and the causal nature of links along this pathway, would benefit from further research.

The lack of association between increased access to unhealthy foods and obesity is contrary to public discourse about the association between fast-food outlets and BMI. Yet, this finding is consistent with prior work in NYC [47]. The ubiquitous nature of bodegas, fast food restaurants, and other unhealthy food chances in NYC may have oversaturated the environment such that healthy food access is more of a limiting factor, constraining food choices of CCCEH participants.

Availability of healthy foods as measured in this study is only one of many factors that play into household food purchases. If household food purchases are determined largely by cost, there may be a preference toward familiar, less expensive foods, limiting the risk of dissatisfaction and potential food waste. Moreover, highly processed foods are less likely to be wasted due to perishability. As previously mentioned, habitus takes time to change therefore an expanded time frame for future research efforts to capture potential changes in habitus is needed.



* The food ecology is described concerning food chances to reflect the sociological construct of habitus that provides insights to obesogenic environments by focusing on the interplay between food chances and food choices. Food chances are the food establishments available in a neighborhood.

Figure 6. Breaking the cycle of children's obesity and environmental health disparities.

Beyond the household, it is important to consider policy-related influences from our community and government on children who are five-years-old. In our sample, 17% of families received public assistance at least once during the time of this study. Some programs, i.e., the Women, Infants, and Children (WIC) only benefit families until the child's fifth birthday. Thus, nutritional intake may suffer once no longer eligible. Further research beyond the age of five can provide more insights to the impact of aging out of WIC. Also, children of this age may participate in meals provided by his or her public school; as many as, two meals and one snack per school day. United States public school meal programs are notoriously underfunded and often provided ultra-processed foods. Food choices of under-resourced families become limited while a child's palate adapts to a constrained menu. Gentrification may exacerbate the lack of resources for local public schools in the most economically disadvantaged areas, and increase segregation as a result of the decision not to attend local schools in which children are assigned. [48, 49]. Currently, 40 percent of NYC kindergartners do not attend his or her assigned school; leading to concentrated poverty in zoned schools [49].

There are several limitations to this study that should be acknowledged. First, the sample is limited to less than half of NYC neighborhoods and a specific cohort associated with CCCEH. A city-wide sample and better yet, a national sample would provide a better representation of gentrification in the United States. Secondly, the complexity associated with measuring gentrification limits our understanding of the multifaceted social process. Using the Furman Center's definition relies on the assumption that gentrification can be distilled to a simple categorical variable for the entire time period rather than varying in intensity and dynamic over time. There may be nuances or levels of gentrification that change the status of

a neighborhood during the period of study. Future analyses may consider creating a continuum measure of gentrification that is informed by input from community residents.

Moreover, food chances categories may not have been able to capture gradations within the food environment. For example, food chances labeled as “healthy” may offer “unhealthy” items (e.g., candy at a supermarket) and vice versa (e.g., apple slices or salads at fast food restaurants). Also, there may be differences in the food choices made by individuals shopping and eating at these food establishments, such that our categorization oversimplifies the multi-faceted nature of variation in the food environment. As previously mentioned, including an investigation of food habitus (the interplay between food chances and food choices) can provide useful insights for understanding food practices and reducing disparities in childhood obesity. We were limited to data collected during CCCEH follow-up visits that did not capture household food choices or diet quality.

Despite these limitations, this study had substantial strengths. The multiple sources of data coalesced to provide a multi-faceted picture of the food environment experienced by CCCEH five-year-old children. The longitudinal nature of the NETS data allowed for the food environment changes associated with the social process of gentrification to be captured over time. As a single measure of food availability is unlikely to describe the food environment, we were able to measure both unhealthy and unhealthy food chances for 21 years. Lastly, we applied GBTM, enabling the identification food chance trajectories that provided an empirical basis for identifying and describing groups.

CONCLUSION

Our results suggest gentrification influences neighborhood food environment in NYC and children exposed to plentiful food chances as well as greater healthy foods experienced a lower body mass index by age five. The interplay between obesogenic food chances and choices is integral to preventing childhood obesity. Figure 6 provides a visual representation of how our work builds on a foundation of children’s environmental health research that aims to reduce inequities. Further research is needed to understand the pathways through which gentrification impacts childhood obesity and to inform policy and community actions that can break the cycle of childhood obesity in minoritized populations.

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Chapter 62

**RELATIONSHIP BETWEEN COMMUNITY
CHARACTERISTICS AND SCHOOL ENGAGEMENT
AMONG UNITED STATES CHILDREN,
NATIONAL SURVEY OF CHILDREN'S HEALTH,
2011–2012**

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ABSTRACT

Neighborhood conditions and the built environment are social determinants and influences for various health outcomes – including chronic diseases, such as heart disease and obesity. However, there is limited information about how the specific structural aspects of the built environment have an impact on educational outcomes among school-aged youth. This chapter provides insight into this area by examining the association between the presence of school amenities and school engagement among children 6-17 years of age in the United States. Data from the 2011-2012 National Survey of Children's Health were analyzed. Bivariate and chi square analyses were conducted to analyze the affect that community amenities have on school engagement among school-aged youth across the United States. The results showed that children living in communities with at least one amenity in their neighborhood (i.e., recreation or community center, library, sidewalks) were more likely to have higher levels of school engagement (OR = 1.37; 95% CI = 1.24-1.52). Findings revealed that males (2.31, 2.20-2.40), youth in middle and high school (1.77; 1.69-1.85), and non-Hispanic Black students (1.15; 1.07-1.23) have increased likelihoods of having lower school engagement. Further, the findings from this study indicate and highlight the significance of identifying subgroups and demographics of youth with low school engagement living in communities lacking amenities to help build academic engagement.

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INTRODUCTION

With education strategies constantly evolving and the rigor of the curriculum increasing, students across the United States face growing challenges and responsibility within the classroom. Aside from the textbook lessons that students work on, there is an increased focus on a more holistic education that includes the development of various skills through social interactions and activities. Outside of the classroom, schools and other youth-centered institutions offer additional organizations, clubs, and activities for students to participate in and create a positive environment for students in which to flourish. These strategies cumulatively contribute to establish a concept of school engagement among school-aged youth.

The concept of school engagement, also referred to as student engagement, is one that includes:

- a student's participation in school and extracurricular activities
- the emotions, motivation, attention, and effort demonstrated by students
- the way that students identify themselves within the hierarchical setting of school [1].

Specifically, the definition of school engagement consists of students having meaningful involvement and learning experiences in an academic environment. School engagement encompasses various levels of involvement from the student – including, emotional, behavioral, and cognitive – and is considered to be multidimensional [1-3]. Moreover, school engagement is manifest when students actively participate and identify with the school and the school community resulting in positive outcomes from the student [1]. School engagement is operationalized through academic success, active participation, and awareness on multiple levels by the student. There is a connection and relationship established and maintained by the student with other prominent players related to the school environment – such as the parents, the teachers, the administration, the peer network, and the community.

School engagement is a significant precursor to of school and academic success among youth. There is evidence in the literature that decreased school engagement threatens educational and professional success. Specifically, it contributes to growing dropout rates, poverty, limited employment opportunities, and crime. There are various determinants that influence school engagement among school-aged youth. Previous research by Quin et al. [4], provides an ecological framework to identify potential correlates impacting school engagement – also referred to as academic engagement in the literature – which focuses on the individual, family, peer, school, and community levels [4]. When utilizing the ecological framework as a guide, the individual level includes inter- and intrapersonal factors, such as genetic factors, personal attitudes and belief systems, and lived experiences as determinants of school engagement. Examples of this include participating in extracurricular activities, and personal involvement, motivation, and interest as well as such negative elements such as truancy and absences. Additionally, the student's gender, age, grade level, overall health and well-being plays a significant role in the student's school engagement. As part of the student's individual level of school engagement in the ecological framework, is the influence of family. Students who come from households where the parent/guardian plays an active role in the child's academic success are likely to have increased school engagement [5].

Moreover, as students get older and advance in their grade level their peer group and social network posit into the overall trend in decreased school engagement. Finally, the school level focuses primarily on the teacher's support, while the community level fundamentally accounts for how students feel about the community that they reside in.

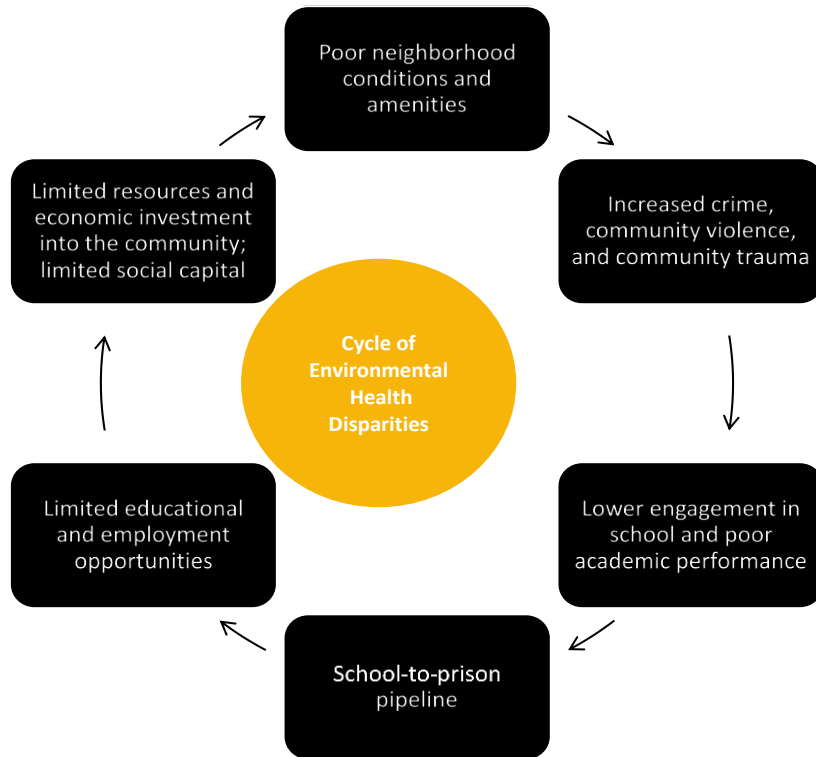


Figure 1. Diagram of how limited neighborhood amenities acts a determinant.

Additional community and/or neighborhood characteristics have not been used in previous literature to determine whether they had some influence on school engagement. Community and neighborhood level issues do result in individual level outcomes and performances ranging from chronic diseases (i.e., heart disease and obesity) to behavioral and mental health (i.e., depression and posttraumatic stress disorder) [9]. With community disarray and disorder present, individuals, specifically, youth, living in neighborhoods with dilapidated buildings, inadequate amenities, crime, and poverty have an increased likelihood of having delayed development socially, emotionally, and cognitively – all of which impact academic outcomes [10]. This is contextualized through the poem entitled “‘Cause I ain’t got a pencil”, which depicts the domino effect of living in a neighborhood with limited resources and/or residing in a community in disarray (see Figure 2).

In the ecological model, individual contexts had the greatest influence among school engagement [4]; however, when analyzing community level influence, only two characteristics were analyzed: low attachment and disorganization. Based on the Quin, et al. [4] study, the characteristic of disorganization is one that consists of the presence of dilapidated housing, which is a variable used in our current study. While the literature

surrounding the built environment and neighborhood amenities influencing school engagement and other academic outcomes is limited, there is research about poverty, violence, and community relationships as they serve as an attribute of neighborhood amenities [11, 12].



Figure 2. “Cause I ain’t got a pencil” by Joshua T. Dickerson.

Specifically, Galster et al. [5], conducted a study on how various neighborhood characteristics, including the presence of community violence and environmental pollution (e.g., ambient noise and presence of lead,) operate through intermediate variables that result in decreased school engagement, such as school absences and trancies [5]. Additionally, Sastry and Pebley [6] posited that aside from the school environment, students spend most of their time in their respective neighborhoods and communities. Because of this, there is concern that the socioeconomic inequalities present in poor and disorganized neighborhoods have an impact that widens the achievement gap and contribute to educational health disparities [6, 7]. Furthermore, researchers have studied the importance of a neighborhood’s social and cultural characteristics on both academic engagement and success. This is measured through the social capital and interactions present in the neighborhood and its residents. Those neighborhoods with stronger social networks and cohesion result in a culture that fosters security, resiliency, and overall success among youth in an academic setting [8].

Due to the alarming trends surrounding school engagement and the limited literature dedicated solely to the built environment of neighborhoods, it is important to analyze the relationship between the built neighborhood amenities and school engagement. The focus on the built environment – particularly, the presence of community amenities – is important because it addresses the toxic cycle that continues to plague and perpetuate poor communities across the United States. Neighborhoods with dilapidated conditions lacking community amenities are at increased risk for crime, community violence, and community trauma (see Figure 1). Those negative characteristics have a direct negative effect on school attendance, academic success, and academic engagement. Students who do not feel a sense of belonging at their schools have a greater likelihood of not completing high school, engaging in crime, and/or participating in other risky behaviors. Ultimately, these three outcomes are gateways to

limited educational and employment opportunities and incarceration. Overall, the burden on the community increases due to the limited social capital and resources that need to be invested in neighborhoods with poverty and crime. We hypothesize that school engagement decreases when school-aged youth are exposed to negative structural elements of the community and low neighborhood amenities that potentially diminish and devalue a community.

OUR STUDY

We analyzed data from the 2011–2012 National Survey of Children’s Health (NSCH). The NSCH employs a cross-sectional sampling design and uses random digit dialing and telephone surveys to collect detailed information from households with at least one child, on topics related to health and well-being, community amenities and school activities, and medical coverage [13]. From each eligible household, one child was randomly selected to be the subject of the survey and the parent or guardian that has knowledge of that child’s health completed the survey. The complete description of the 2011–2012 survey is available at <http://www.cdc.gov/nchs/slait/nsch.htm> [13]. Because the NSCH is a public data set, institutional review board (IRB) approval was not required for this analysis.

Sample

The overall NSCH sample consisted of 95,677 children ranging from the ages of 0 to 17 years ($M = 8.85$, $SD = 5.23$), 51.6% of participants were male, while 48.4% were female. For the purpose of this analysis, only data on children between 6 and 17 years of age were used because the children 5 years of age and have not been in a school setting long enough to gauge academic performance ($N = 59,192$; $M = 11.16$, $SD = 3.18$).

Dependent Variable

The outcomes of interest for this analysis are: a. child cares about doing well in school and b. child completes all required homework. At the time of data collection, parents were asked to report whether their child cared about performing well in school (never, rarely, sometimes, usually, always) and completed all required homework in the previous month (never, rarely, sometimes, usually, always). Together, these variables comprise the NSCH child health indicator of “school engagement”. For the purpose of this analysis, each variable was dichotomized into either rarely (never, rarely, or sometimes) or often (usually or always).

Independent Variables

Sociodemographic characteristics. Individual-level sociodemographic covariates included race/ethnicity (white, black, Hispanic, other), sex (male, female), and age (6–11, 12–17

years). We were also interested in family-level sociodemographic covariates, including household income based upon the federal poverty level (<100%, 100–199%, 200–399%, and >400%) and family structure. Categories for family structure included two-parent household (two biological or adopted parents), two-parent household—step (two-parent household with at least one step parent), single mother (one parent household with biological, step, foster, or adoptive mother and no father), and “other”.

Neighborhood characteristics. For this analysis, we were primarily interested in the presence of neighborhood amenities and detracting neighborhood elements. The NSCH identifies both the presence of neighborhood amenities and the presence of detracting neighborhood characteristics as child health indicators. We defined presence of neighborhood amenities by affirmative answers to three or more of the following questions: 1) Do sidewalks or walking paths exist in your neighborhood?; 2) Does a park or playground area exist in your neighborhood; 3) Does a recreation center, community center, or boys’ or girls’ club exist in your neighborhood and 4) Does a library or bookmobile exist in your neighborhood?

We defined presence of detracting neighborhood elements by affirmative answers to at least one of the following questions: 1) In your neighborhood, is there litter or garbage on the street or sidewalk? 2) How about poorly kept or rundown housing? or 3) How about vandalism such as broken windows or graffiti?

Analysis

We used SAS 9.4 to conduct a secondary analysis of the 2011–2012 National Survey of Children’s Health dataset. We conducted Wald’s chi square tests and bivariate analyses to provide descriptive statistics and determine the association between school engagement and the various sociodemographic variables. We calculated crude and adjusted odds ratios (ORs) and 95% CI to examine the association between the presence of neighborhood characteristics and school engagement. Children whose parents reported that their child usually or always cared about doing well in school and completed all required homework served as the referent group, respectively. Logistic regression models were built separately for the presence of neighborhood amenities and the presence of detracting neighborhood elements to calculate odds ratios.

FINDINGS

The majority of the sample of 6 to 17 year old children were non-Hispanic White (66.8%), followed by Hispanic (12.9%), non-Hispanic Black/African-American (9.7%), with Multi-racial/Other, non-Hispanic (10.6%) making up the rest of the sample. Table 1 shows the number and percentages of children with various sociodemographic and neighborhood characteristics in 2011–2012 as well as the odds ratios comparing those with no or low school engagement and those with moderate or high school engagement. There was a higher prevalence of children who come from a two-parent household with an income more than 400% above the FPL and living in neighborhoods with a high presence of amenities.

We analyzed the association between the two components of school engagement – cares about school and completes all homework – using chi-square tests (see Table 2). Table 1 provides the odds ratios for the components of school engagement and the covariates that were included in the model, while Table 2 highlights the presence of community amenities – or lack thereof. When we analyzed the 2011-2012 NSCH, we found an adjusted odds ratio of 0.92 (95% CI = 0.89-0.93) for children caring about school and living in a neighborhood with at least one detracting element. Further, for youth living in neighborhoods with at least one amenity present, they were 1.37 (95% CI = 1.24-1.52) more times to have high school engagement compared to their counterparts living in neighborhoods with detracting community elements. Finally, when analyzing covariates, several yielded significant findings, including males (2.31; 2.20-2.40), non-Hispanic Blacks (1.15; 1.07-1.23), middle and high school-aged students (1.77; 1.69-1.85), having any poverty level greater than 100%, and having a family structure other than two-parent biological (see Table 1).

Table 1. Characteristics of youth and bivariate association with school engagement and without school engagement

Participant Characteristics	No/Low School Engagement N = 10,778	School Engagement N = 48,488	OR (95% CI)
N = 59,266			
Age, years Median (IQR)	12 (10-15)	11 (8-14)	
Sex			
Male	7261 (67.4)	23298 (48.1)	2.31 (2.20, 2.40)
Female*	3511 (32.6)	25122 (51.8)	1.00
Missing	6 (0.1)	68 (0.1)	-
Race/Ethnicity			
Non-Hispanic White*	6669 (63.4)	31978 (67.6)	1.00
Non-Hispanic Black	1386 (13.2)	4194 (8.9)	1.15 (1.07, 1.23)
Hispanic	1365 (12.9)	6088 (12.9)	0.88 (0.81, 0.94)
Other	1095 (10.4)	5057 (10.7)	0.97 (0.90, 1.04)
Missing	263 (0.02)	1171 (0.02)	-
Age Groups			
6-11 Years of Age*	4442 (41.2)	26637 (54.9)	1.00
12-17 Years of Age	6336 (58.8)	21851 (45.1)	1.77 (1.69, 1.85)
Missing	-	-	-
Poverty Level			
Less than 100%*	2229 (20.7)	6155 (12.7)	1.00
100-199%	2340 (21.7)	8059 (16.6)	0.86 (0.80, 0.92)
200-399%	3289 (30.5)	15096 (31.1)	0.69 (0.65, 0.75)
400% or more	2920 (27.1)	19178 (39.5)	0.51 (0.47, 0.55)
Missing	-	-	-
Family Structure			
Two-parent Biological*	5593 (52.6)	33902 (70.8)	1.00
Two-parent Step	1345 (12.7)	3832 (8.0)	1.86 (1.73, 1.99)
Single Mother	2438 (22.9)	6872 (14.4)	1.77 (1.66, 1.88)
Other	1249 (11.8)	3294 (6.9)	1.93 (1.79, 2.08)
Missing	153 (0.01)	588 (0.01)	-

Abbreviations: IQR, interquartile range.

* Referent group are those variables coded as 1 per the SAS Code.

* Bold indicates significant difference.

Table 2. Characteristics and bivariate association of youth aged 6-17 years living in a community without any community amenities present and living in a community with at least one community amenity present

Participant Characteristics N = 59, 266	No Amenities Present N = 2,115	At least one amenity present N = 57,151	OR (95% CI)
Age, years Median (IQR)	12 (9-14)	11 (8-14)	
Sex			
Male	1112 (52.6)	29447 (51.5)	1.01 (.92, 1.11)
Female*	1000 (47.3)	27633 (48.4)	1.00
Missing	3 (0)	71 (0)	-
Race			
Non-Hispanic White*	1461 (69.9)	37186 (66.7)	1.00
Non-Hispanic Black	183 (8.8)	5397 (9.7)	0.69 (0.59, 0.82)
Hispanic	268 (12.8)	7185 (12.9)	0.73 (0.64, 0.84)
Other	179 (8.6)	5973 (10.7)	0.70 (0.60, 0.82)
Missing	24 (0)	1410 (0.02)	-
Age Group			
6-11 Years of Age*	1020 (48.2)	30059 (52.6)	1.00
12-17 Years of Age	1095 (51.7)	27092 (47.4)	1.20 (1.10, 1.31)
Missing	-	-	-
Poverty Level			
Less than 100%*	469 (22.2)	7915 (13.9)	1.00
100-199%	476 (22.5)	9923 (17.4)	0.74 (0.65, 0.85)
200-399%	650 (30.7)	17735 (31.0)	0.53 (0.46, 0.60)
400% or more	520 (24.6)	21578 (37.8)	0.34 (0.29, 0.39)
Missing	-	-	-
Family Structure			
Two-parent Biological*	1354 (64.6)	38141 (67.6)	1.00
Two-parent Step	191 (9.1)	4986 (8.8)	0.87 (0.74, 1.02)
Single Mother	331 (15.8)	8979 (15.9)	0.77 (0.68, 0.88)
Other	219 (10.5)	4324 (7.7)	1.16 (0.99, 1.35)
Missing	20 (0)	721 (0)	-

Abbreviations: IQR, interquartile range.

* Referent group are those variables coded as 0 per the SAS Code.

* Bold indicates significant difference.

DISCUSSION

Within the NSCH, the variable school engagement is a proxy for academic success. Both academic success and the level of school engagement can be influenced by both individual level and community level determinants. Neighborhood amenities act as a protective factor for the two components that make up school engagement – student cares about school and student completes required homework. Despite the results indicating that there is a statistical significance among all variables – with the exception of race/ethnicity and presence of neighborhood amenities - there was very little difference between the two groups. However, the variable of sex of the student was the only significantly different result that did not include 1 within the confidence interval.

In order to address community disorder and amenities, there is a need for bottom-up, rather than top-down, policy and interventions to obtain qualitative and quantitative data from

the communities. There is a need to create buy-in and ensure that residents of communities and neighborhoods with limited amenities are interested stakeholders with a seat at the table. Moreover, to continue this research, analyses can occur at the state and local levels to determine trends and gather information that can be used for policy change.

With academic performance and success being influenced by a multitude of factors, such as socioeconomic status, belonging to an ethnic and/or racial minority, parental educational level, and the safety of both the school and community environment - there is a little priority placed on how community amenities that include the built environment impact school-aged youth's academic performance. Despite the NSCH capturing a few structural amenities, it must be noted that children living in neighborhoods with ample street lighting; well-maintained structural amenities (i.e., sidewalks); and, the presence of sidewalks, green space, playgrounds, crosswalks, community centers, and other youth-centered facilities are pertinent to childhood development.

The built environment has a profound impact on youth prior to them beginning primary school. With early childhood development, youth that live in communities with limited resources are more prone to be experience behavioral health issues and encounter developmental disabilities. These same problems that arise during early childhood can also appear at any point during childhood and adolescence due to the built environment. Because of this and the outcome it has on school engagement and academic success, there is a need for further research, program planning and implementation, and policy change on approaches to increase community amenities and improve the built environment while allowing residents to have a voice and have buy-in.

Addressing the built environment and the lack of protective and positive community amenities in a neighborhood or community is essential in breaking the perpetuating cycle that creates health disparities among children and adolescents. As indicated in Figure 1, neighborhoods with poor conditions and/or limited amenities in the built environment have a greater likelihood of having crime, violence, and community trauma due to both the crime and violence. Youth are just as likely to be victims of crime or violence in their neighborhoods and to develop PTSD and other signs of trauma. The trauma and PTSD is a form of behavioral and mental health that leads to disruptions in the classrooms and school settings among youth – posing a risk for grade repetition, poor grades, and dropping out of school early.

With the decreased likelihood of graduation stemming from modifiable problems - such as the built environment - youth from the neighborhoods with inadequate amenities are more likely to have limited employment and career opportunities because they do not possess a high school diploma. Because of the limited career opportunities, there will also be limited income and capital for the individual, which promotes poverty among the individual and family level. At the neighborhood and community level, this reduces the capital in the area – resulting in limited investments, upgrades, and improvements to the community. For example, rather than the addition of parks and grocery stores or repairing cracked sidewalks and reducing blight, there will be the continuous presence of dilapidated housing, graffiti, litter, pawn shops, and liquor stores. The latter is what begins the cycle again in terms of poor neighborhood conditions, which impacts another generation of youth.

There are several limitations to this study. First, the measure of school engagement is based on the perception of the parent/guardian. The operationalization of the NSCH definition of school engagement does not include quantitative data on how often a child completes

homework or the duration of homework and studying. The same can be said about whether a child cares about their schoolwork – a component of the school engagement variable in the dataset. Additionally, there is potential of bias with parents self-reporting is an issue as it cannot be validated. Moreover, the questions included in the NSCH survey are ones that are not necessarily indicative of poor community characteristics. For instance, the question of whether sidewalks are present in a neighborhood, does not equate to a neighborhood or community being in disarray or having negative community characteristics. In some cases, affluent neighborhoods and communities do not have sidewalks present; however, those neighborhoods have other amenities not captured in the survey that serve as protective factors for youth – indicating that there are culminating factors that impact school engagement among youth. Lastly, survey data for the NSCH were collected in a cross-sectional manner.

CONCLUSION

The study, despite its limitations, adds to a growing body of literature that highlights the influence of the built environment on childhood development. Children who care about doing well in school and complete their homework often perform better in future academic and professional careers. Using data from a nationally representative survey, this study examined the relationship between community characteristics - specifically, residential neighborhood amenities and detracting elements - and school engagement among US school-aged children. The availability of community amenities, such as presence of sidewalks and/or walking paths; presence of park or playground; presence of a recreation center; and, the presence of a bookmobile or library had a positive association with overall high school engagement. Similarly, the presence of negative and risky community characteristics, such as the presence of graffiti, litter, and abandoned homes were found to increase the likelihood of poor school engagement among school-aged youth. It must be noted that this study was observational and utilized a secondary data analysis for sample that reflected the entire United States. Future studies conducting a longitudinal survey would be useful to see if findings would be similar to those in this study.

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Chapter 63

INVISIBLE THREATS: LEGAL METHODS TO ADDRESS ASTHMA TRIGGERS IN RENTAL HOMES

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ABSTRACT

Federal housing laws dictate certain fundamental rights for tenants living in federally subsidized housing. Most state jurisdictions acknowledge a tacit “implied warranty of habitability” provision in residential lease agreements, which enforces the duty of landlords to fix defects on properties to ensure that rented living spaces are habitable for tenants and comply with local housing codes. Yet these legal baseline standards have not effectively secured healthy and safe living conditions for low-income, minority families. Environmental health hazards found in substandard housing, such as mold, lead, dust mites, and rodents serve as asthmatic triggers for children. When these health risks are eventually identified as triggers for their child’s ill health, parents may still forgo opportunities to confront their landlord for fear of retribution in the form of increased rent, penalties, or eviction. The scope of this project is to develop a resource that would facilitate a “know your rights” education for vulnerable families, offering guidance on how to negotiate with landlords for better housing conditions. The primary goal is to create an educational legal worksheet for families renting substandard housing and to guide them in seeking resources and relief to improve their living environment. This project strives to empower families by developing a resource that raises awareness, facilitates making housing rights more accessible, and highlights legal tools to help address asthmatic triggers within the home, thereby improving the health of vulnerable children.

INTRODUCTION

Substandard housing environments have a significant connection to pediatric asthma morbidity and present persistent challenges for low-income, minority families particularly [1,

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2]. Racial, ethnic, and income disparities in housing stock have deep roots in the history of American law and commerce. Through the middle of the twentieth century, some housing developers embedded private legal covenants in deeds to prevent sale of single-family homes to minority families [3]. Early federal housing initiatives incorporated government regulations, zoning restrictions, and lending policies to intentionally favor accommodating middle or higher-income, white households over low-income, minority communities [4, 5]. With the enactment of the Fair Housing Act of 1968, the federal government has established numerous public programs, policies, and incentives to help create better housing options for minority communities, including home ownership available to low-income and minority buyers [6]. Still, current trends suggest there remain marked disparities in home ownership rates among householders who identify as both low-income and minorities [7].

Subsidized rental housing initiatives have created affordable rental housing options for minority and low-income candidates [6], however, prominent zoning, tax, and financial policies in the United States strongly favor development of owner-occupied housing and make renting costly for tenants [8]. Even where low-income, minority families qualify for the US Department of Housing and Urban Development's Section 8 Housing Choice Voucher program, the promise of finding a better place to live may never materialize for many low-income renters. Vouchers are often difficult to secure through sporadic lotteries, and redistribution of poverty and racial segregation in suburban neighborhoods continue to disadvantage low-income and minority renters [6, 8]. The effect of these skewed dynamics on renting is that many low-income families must compete for relatively few affordable housing units, especially after the housing bubble surrounding the Great Recession of 2008. In 2016, a National Low-Income Housing Coalition study found that supply of affordable housing for low-income renters fell 7.2 million units short of demand [9].

Where tenants are able to secure rental accommodations, they must contend with whims and requirements of landlords who understand that affordable housing is scarce and demand from low-income families is high. Black and Hispanic tenants are more likely than white tenants to be cost burdened, with at least half of their income funneled into rent payments and little budget for necessities like food or healthcare [10]. Threat of eviction is also a reality that many tenants face if they fail to comply with a landlord's expectations. Formal evictions are generally the product of rent nonpayment, but many landlords also practice undocumented, informal evictions, where they change the locks to ensure tenants cannot return [11]. Low-income black and Latina female tenants, especially single mothers heading households with children, face higher rates of eviction than men or adult-only families [11].

A single eviction on tenants' records could classify them as problematic, resulting in their future housing applications being rejected and preventing them from securing quality housing for their children [11]. Ultimately, low-income, minority communities facing increased levels of forced displacement within the renters' market suffer tremendously in terms of decreased financial health and quality of life in pursuit of housing accommodation. Low-income and minority tenants are increasingly relegated to substandard housing options: black tenants are 1.7 times more likely to live in substandard housing, while low-income families are 2.2 times more likely occupy such spaces, often as a trade-off for keeping food on the table or ensuring a roof over their children's heads [12].

Substandard housing is broadly defined as a dwelling with moderate to severe physical defects which may contribute to adverse health effects or threaten the safety of individuals [13]. Evidence of the relationship between housing deficiencies and health effects has

previously been established, including studies which proved that interventions targeting housing defects improved householder health [13-18]. Examples of defects in substandard homes which may threaten the health of householders include physical conditions like inadequate ventilation, temperature exposure, low air quality or biological conditions such as pests, cockroaches, mice, mold, and other allergens [13]. Since low-income, minority families disproportionately occupy substandard housing, often in high poverty, predominantly minority neighborhoods, these populations may suffer heightened exposure to these defects [12, 19, 20]. One of the most prevalent diseases linked to substandard housing defects is childhood asthma. Increased asthma morbidity, hospitalizations, and mortality have been identified among low-income, minority children exposed to in-home, deteriorating housing defects [13, 19, 21].

Asthma is a common chronic disease in children. Exposure to asthma triggers and allergens within the home is strongly linked to asthma diagnosis, exacerbation, and morbidity in children in locales with substandard housing [15, 22, 23]. Children who live in substandard housing have higher sensitization to allergens, as well as increased exposure to asthmatic triggers such as mold, cockroaches, rodents, pet dander, cigarette smoke, and strong fumes or odors [2, 22].

Tenants encounter at least two challenges when attempting to address substandard housing conditions. First, tenants do not immediately recognize that deficiencies within a rented unit may be contributing to adverse health effects, lacking the knowledge to identify in-home asthma triggers [24]. Second, tenants also may not be aware of the legal rights and remedies which entitles them to have the issue mitigated or resolved [25]. Fear of eviction and landlord retaliation also contributes to tenant inaction [24, 25]. Unfortunately, there are too few legal tools available to low-income, minority tenants that educate and promote access to justice in landlord-tenant issues.

In most housing or landlord-tenant cases, the first step in a legal process is to survey the tenants' residence to identify issues for potential legal claims. If tenants can ensure a landlord takes responsibility for substandard housing, then the process could prove both educational and empowering. However, trying to understand the various aspects of the legal rights and due process may be overwhelming for non-lawyers, particularly low-income tenants who have few alternate housing options and fear retaliation from the landlord. The concept of informing laypeople with no legal degree on how to fight for their rights is a challenging process. The "informed layperson" perspective is the lens through which this project was developed.

This project creates a resource in the form of a legal worksheet to inform and empower tenants who have recognized that they have asthma-related health hazards within the home but have not been successful in confronting or convincing the landlord to make the necessary changes. to tenants. In the event that the landlord cannot be contacted or does not simply agree to make the necessary repairs to address health hazards in the home, the worksheet comes into play.

This worksheet also provides tenants with access to local legal aid organizations. In the event that they meet certain qualifications, e.g., proof of low-income or nature of the case, these organizations may be able to connect tenants to a lawyer at little or no cost. A lawyer would then require tenants to analyze how much their child or family has suffered due to environmental hazard in the home and to a landlord's failure to perform repairs.

Although this worksheet lists generic advice on strategies directed to all potential clients in a landlord-tenant issue, the legal services listed are specific to Atlanta tenants. Apart from the local references, the worksheet, could prove beneficial for any tenant in a similar situation, regardless of geographical location. In addition to highlighting the advantages of seeking legal representation, it is a tool that orients tenants on how to prepare to be a more successful potential claimant and legal client. Finally, it challenges tenants to consider the legal recourse and damages they deserve for what their child has suffered due to the landlord's failure to address a hazardous home condition.

Tenants would then meet with the legal representative to help identify goals and potential options for recourse. When working towards legal redress, tenants are expected to make personal decisions about why or how they intend to seek legal help. Tenants may have several potential options, but the first step is helping householders realize and articulate what relief they might be able to secure in addressing the current living situation.

- Do the tenants want to break the lease? If so, a lawyer can help review the contract, work through communications with the landlord, identify conflicts which may arise, and discuss possibilities of investing in an alternate living situation.
- Do the tenants want to move, but would also consider moving to another property owned by the same landlord? If yes, a lawyer may help the tenant negotiate with a landlord, or consider location, affordability, and costs the landlord should waive given his failure to repair the current home.
- Do the tenants want to force a landlord to make repairs to the current home situation. In this case, a legal representative can assess expected fixes, enforce action from the landlord, and advise remedies that may be owed to the family for what they have endured. In some cases, a lawyer may choose to file a lawsuit on behalf of the tenant. In this way, seeking legal help in light of living in hazardous home conditions can be an advantageous decision.

THIS STUDY

By (a) researching applicable legal literature, (b) reviewing state and local laws in Georgia, and (c) interviewing local lawyers, this project distills information and considerations that are likely to be significant for tenants seeking available legal relief.

Georgia Housing Statutes and Local Ordinances

Landlord-tenant law is not uniform across the fifty states. Each state adopts and adjudicates its own landlord-tenant laws. Federal Fair Housing laws have nationwide application, but their focus on eliminating discrimination in certain housing-related matters. As a result, legal research pertaining to this project was focused on Atlanta, Georgia. Limiting the scope to a localized population allowed for working more closely with applicable laws in order to maximize the benefits of this resource for troubled tenants. State law contained in the Official Code of Georgia and local ordinances, such as the Atlanta Housing Code, DeKalb

County Property Maintenance Code, and Gwinnett County Code of Ordinances, sets forth laws governing housing conditions in the metro-Atlanta area. These laws also describe the landlords' duty to maintain habitable living spaces for their tenants and provide the legal backbone of any tenant's potential claim against a landlord.

Interviews with Housing Lawyers

Interviews with housing lawyers on housing and tenant issues and discussing the types of legal relief and housing rights available to potential clients helped detail how landlord-tenant issues resolve in real-time application. This understanding was crucial to creating a resource that would be beneficial to tenants.

Legal Literature

The Georgia Department of Community Affairs has a rich, comprehensive resource available to the public titled the "Georgia Landlord-Tenant Handbook," which furnishes a background for relevant law and basic tenant rights. This handbook also details various issues tenants may encounter [25]. This handbook provided a reliable tool against which to verify the information presented on the worksheet.

FINDINGS

Based on review of applicable Georgia laws and interviews with Georgia housing lawyers, this worksheet was drafted to provide Georgia tenants with a guide to key questions concerning putative in-home environmental health risks (see Figure 1). The worksheet helps tenants answer questions that are critical to evaluating whether and how to secure assistance from counsel. Additionally, there are opportunities to acquire legal services for free or low costs for low-income tenants who may qualify. This fact would be comforting to tenants who might not pursue a legal consultation for fear of the costs involved. The following are quotations directly from the worksheet, along with corresponding explanations.

1. WHY Should a Tenant Seek Legal Help?

The worksheet begins by orienting tenants to think about the rights to which they are entitled, starting with the basic legal provisions specific to the resident state. For example, under Georgia law, the landlord has the duty to maintain the premises. Landlords do not always do their job, but the tenant has certain essential rights.

The worksheet goes on to provide context for a situation which might require legal help. It addresses the tenant directly. The following quotations are from the worksheet:

"If you or a loved one is facing a health condition because of your housing situation, but your landlord fails to make repairs, you may have grounds for a legal claim. You always have options. Even when it seems like you do not. Think about what you want, work with a lawyer. Be ready to ask questions. Set Goals."



Healthy Rental Housing Know Your Legal Rights

WHY seek legal help?

Under Georgia law, the landlord has the duty to maintain the premises. *They don't always do their job. But you HAVE RIGHTS too.*

If you or a loved one is facing a health condition because of your housing situation, but your landlord fails to make repairs, you may have grounds for a legal claim.

You always have options. *Even when it seems like you don't. Think about what you want, work with your lawyer. Be ready to ask questions. Set Goals.*

1. Do you want to force the landlord to make repairs? *What are the expected fees? How can landlord make it up to you? Is a settlement possible? Would you want to file a lawsuit?*
2. Do you want to break the lease early? *What penalties are in your contract? How would your landlord react? Will there be moving costs?*
3. If the landlord owns another property, is moving there an option? *How is the new location? Is it affordable?*

WHEN to start prepping?

Start now. *If you have any doubt something might be hazardous, start documenting with pictures and/or written communications with landlord.*

The earlier the evidence begins, the more compelling your story becomes. *Reach out to a lawyer for a consultation. Is it an easy fix? Could it go to court?*

BETTER TO GET LEGAL HELP EARLY THAN TOO LATE!

WHAT to know?

Do NOT withhold rent! *Even if you think it would force landlord to make repairs, not paying rent will make you look like a bad tenant! You may also risk eviction.*

Being a model tenant will make your story credible.

You will need the following documents: *copy of lease, all landlord correspondence, proof of rent payments, receipts of repairs, doctor's visits, medical bills.*

WHO do you call?

Atlanta Legal Aid Society
Pulaski Courthouse (404) 524-5811
P.O. Box 10000 (404) 377-5381

Atlanta Volunteer Lawyers Foundation
Adams (404) 521-0790

Health Law Partnership (HELP)
Adams (404) 787-2005

Atlanta Bar Association Rental Service
Adams (404) 521-0777

HOW to be ready?

Take pictures. *Leaks, pest, feces, mold, carpet stains, everything.*

Put everything to landlord in writing. *i.e. don't ask for fixes in-person, text or email instead.*

Keep track of everything relevant to your story. *Ex: child's doctor visits, medical bills & inhaler costs, clothes purchased/thrown away due to pests, TV ruined due to pipe leak, food spoiled because of fridge mold, etc.*

Collect necessary documents.

WHERE to start?

Inform your landlord of the problem **IN WRITING**. *Instead of talking in-person, deliver a letter, keep a copy. Write a text, email, take a video, be creative! Point is, you have proof if your landlord says "I didn't know!"*

Provide your landlord a deadline along with the notice.

Start thinking about damages. *End goal is to get repaid for your suffering, but you have to be able to prove your side of the story.*

Break the Cycle©

CREATED BY PRATHYUSHA CHENJI

Figure 1. Legal worksheet for tenants.

The worksheet goes on to challenge clients to consider their options by relaying a list of possible end-goals that clients may want to pursue with the help of their lawyer. It also shares potential factors or consequences to consider with each goal:

1. “Do you want to break the lease early? What penalties exist in your contract? How would your landlord react? Will there be moving costs associated with breaking the lease early?”
2. “If the landlord owns another property, is moving there an option? How is the new location? Is it affordable? Do you trust the landlord enough to negotiate this situation with him?”
3. “Do you want to force the landlord to make repairs in your current living situation? What are the expected fixes? How can the landlord make it up to you? Can you negotiate? Is a settlement possible? Would you want to file a lawsuit?”

2. WHEN Should a Tenant Start Preparing for Legal Representation?

This section advises a tenant to “start now.” Even if tenants are not sure about getting legal help immediately, they can begin gathering key information and evidence documenting their story about the adverse health conditions their children have encountered, i.e., ‘the case’.

“If you have any doubt that something [in the home] might be hazardous, start documenting with pictures and/or written communications with the landlord.” “The earlier the evidence begins, the more compelling your story becomes. Reach out to a lawyer for a consultation. Is [your problem] an easy fix? Could it go to court? Better to get legal help early than too late!”

3. WHO Does the Tenant Call for Help?

A list of legal resources is provided, tailored to the potential client living in Atlanta, Georgia. This is the only section of the worksheet that is specific to a geographic location, and should be edited based on the target audience, i.e., population intended to be helped. Additional resources which may be included in this section are online tools, app details, and alternative language tools. Services listed include: Atlanta Legal Aid Society, Atlanta Volunteer Lawyers Foundation, Health Law Partnership (HeLP), and the Atlanta Bar Association Referral Service.

4. WHAT to Know?

This section highlights key considerations for seeking legal help. For example, it asks the tenant not to withhold rent from the landlord, even if she believes that it would force the landlord to make repairs. The reasoning behind this advice is that not paying rent may undermine the strength of the tenant’s case and, in certain states like Georgia, may cause the tenant to risk eviction.

This section also encourages tenants to be “model tenants” because it makes their story, or case, more credible in the eyes of third parties. Finally, it provides a list of documents that tenants should start collecting in preparation for their first meeting with a legal representative. “You will need the following documents: copy of lease, all landlord correspondence, proof of rent payments, receipts of repairs, doctor’s visits, medical bills.”

5. WHERE Does a Tenant Start the Process of Improving a Home Situation?

This section orients tenants on what to do immediately after recognizing health hazards:

“Inform your landlord of the problem in writing. Instead of relying on a verbal request, deliver a letter with receipt of delivery, and keep a copy. Write a text, email, take a video, be creative! The point being that it provides evidence of the request if the landlord says, ‘I did not know!’”

“Give your landlord a deadline along with the notice.”

“Start thinking about damages. The ideal end goal is to get repaid for your suffering, but you have to be able to prove your side of the story.”

6. HOW Does a Tenant Get Ready to Seek Relief?

This section advises tenants to be vigilant and deliberate in their actions from the moment they begin to notice a need for a potential fix in the home:

“Take pictures. Leaks, evidence of bugs or mice, mold, carpet stains, everything.”

This section also pushes a tenant to keep a record of every communication with the landlord in writing, and substitute in-person interactions with text or email at every possibility.

“Keep track of everything relevant to your story, e.g., child’s medical bills, inhaler costs, clothes purchased/thrown away due to pests, T.V. ruined due to pipe leak, food spoiled because of fridge mold, cleaning supplies to clean black mold off of walls, etc.”

“Collect necessary documents.”

DISCUSSION

This project aims to raise awareness among low-income, minority renters about environmental factors within rental homes that produce adverse health outcomes. Additionally, this project offers tenants guidance on how to work with their landlords to resolve housing defects. It uses a worksheet to educate the renter of the potential situations that may arise after a health hazard has been recognized in the home. The worksheet also seeks to advise tenants on how to communicate the existence of a defect with the landlord and the options tenants may have to seek legal help if the landlord fails to make necessary repairs.

The legal worksheet is directed toward tenants who have recognized health hazards within the home but are unsure on how to confront them. Most individuals do not immediately consider seeking legal help. In the best-case scenario, the job of the tenants’ lawyer is to encourage an action from a landlord that is favorable to the tenants. The resource created from this project attempts to diminish assumptions that getting a lawyer is “too big for such a small issue,” or acquiring a lawyer to be too expensive or inaccessible. The worksheet

accomplishes this by referring the potential client to local nonprofit legal clinics and consultation resources. There is need for a tool which informs tenants about their own rights, as well as the legal process and encourages tenants to take that first step in pursuit of remediation. This worksheet presents one such intervention for addressing this need.

For example, consider tenants who may have recognized a potential in-home asthma trigger but have not confirmed whether it has had a detrimental impact on their child's health. Here, the tenants may have doubts about whether a housing defect is an asthma trigger. Parents may also be uncertain as to how urgent the situation is. They may notice an unusual odor emitting from the A/C unit but may not realize it is an issue that warrants a landlord's attention or responsibility. As a result, tenants may not reach out to the landlord, may disregard the defect, or consciously decide to postpone a confrontation with the landlord.

Alternatively, consider tenants who may have identified and confirmed the existence of asthmatic triggers in the home which affect their child. Here, parents are certain because a physician has confirmed that the child's health condition is being triggered by certain indoor environments. For example: parents were informed that mold is an asthmatic trigger. After investigating, they discovered black colored, foul-smelling residue behind the A/C unit. They then immediately attempted to inform the landlord, and either did not receive a response, or the landlord refused to accommodate the request for timely repairs. In both of the above scenarios, tenants are likely not thinking about legal recourse as an option.

In the first hypothetical, even if the tenants had been thinking about getting a lawyer, they likely believed they did not have a claim. In this case, the legal worksheet would encourage tenants to begin documenting any repairs in the home with photographs and informing the landlord in writing. The important message is that it is never too early to document observations or concerns that might ultimately be helpful in the case of a legal claim.

In the second hypothetical, tenants have done what they can and have informed the landlord about the situation. A landlord has the duty to repair where a home situation proves hazardous or unlivable. In this case, fungal spores are health hazards which trigger asthmatic episodes in children, making an environment unsuitable for a child. When a landlord fails to act upon such a request, there is potential for a legal claim.

The worksheet does not show tenants how to force the landlord to make repairs. In a successful scenario, this outcome would be achieved by a lawyer. Instead, the legal worksheet familiarizes parents with guidance in preparing for a possible legal proceeding. Additionally, the legal worksheet encourages tenants to consider how best to maintain and manage a good tenant-landlord relationship. Tenants who are in good standing with their landlord and have all correspondence to the landlord in writing can best prove their assertions about adverse health conditions. For this reason, these tenants are more likely to be considered credible by a court or mediator. Therefore, if the tenants take prudent steps in preparing their claim, then tenants would have the best possible chance of securing an outcome in their favor.

The worksheet serves to accomplish more than simply providing tenants an opportunity to educate themselves about their rights and the legal process. It also serves to aid a lawyer with her job. A lawyer representing tenants requires a narrative upon which to build a case favorable to her client. By structuring the information in a "who, what, when, where, why, how" format, the legal worksheet encourages tenants to prepare by gathering information the lawyer may require. Once the narrative has been acquired, the lawyer has more time to counsel clients on viable options and work with clients to set goals. Overall, the interactions between a lawyer and clients are most efficient when both parties know what to expect. For

that reason, the legal worksheet seeks to guide tenants prior to consultation with a lawyer. An efficient lawyer-client team is most effective in providing a greater chance for tenants to win the case and acquire damages for what their child has suffered.



Figure 2. Breaking the cycle of adverse health disparities relating to childhood asthma within substandard rental homes.

This project helps break the cycle of environmental health disparities by providing an intervention to childhood asthma morbidity among low-income and minority families renting substandard housing options (see Figure 2). Once residential exposure to health hazards have been recognized and tenants have confirmed that these environmental triggers pose a serious threat to their child's asthmatic condition, this resource educates tenants of their rights and empowers them to consider legal recourse. After tenants consult with a lawyer, they are in a better situation to confront the landlord to make necessary repairs within the rented unit. If successful, a child within the home experiences decreased exposure to environmental, asthma triggers and improved health outcomes.

RECOMMENDATION: FRAMEWORK FOR APPLICATION OF LEGAL WORKSHEET

The sample worksheet can be made available to users either in paper or electronic form. The worksheet is designed as a resource for families renting substandard housing units from unresponsive landlords. If distributed among tenants living with hazardous home conditions, the worksheet should enable and empower tenants to consider how to proceed and how to consider legal recourse. By encouraging action to remediate indoor hazardous conditions, and thereby decreasing exposure to asthmatic triggers, this worksheet would be a cost-effective intervention for preventing childhood asthma.

The worksheet may be suitable for distribution in environments like children's hospitals, community schools, or legal clinics. Health provider offices may distribute the worksheet as

an informational resource to parents after recognizing that a home environment might be worsening a child's asthmatic condition. Public health nurses performing in-home visits, social workers and community organization that work with children with asthma could also use the worksheet. The worksheet may also be made available in schools or day care centers where parents would expect to receive other educational resources. Legal aid clinics may share this resource with potential clients during an initial consultation regarding hazardous home conditions. This resource would be the most impactful if available online to tenants who may be researching their children's health or in-home living environment. Social media provides another channel that could help make the content from this worksheet widely accessible to the public as an educational resource. The content can be creatively organized into interactive videos or online platforms. Additionally, the content can be expanded for inclusion in an educational handbook or tutorial.

CONCLUSION

Once parents who are renting homes in low income neighborhoods have recognized that indoor environmental risk factors affecting children's health may be present within the home, it is time to act. The legal worksheet aims to educate tenants to be vigilant and to prepare for possible legal support as soon as they are aware of potential health risks. Where tenants are in a compromised living situation and cannot rely on their landlord to address and reduce environmental health hazards, the worksheet lays out the "who, what, when, where, why, how" of seeking a legal solution. The worksheet presents an overview of information and advice for tenants to consider prior to securing a lawyer. It also provides low income families with a list of legal resources in their geographic area (in this case, local Atlanta resources). The intent of this worksheet is that it demystifies how legal services could resolve landlord-tenant issues, improve living situations among low-income renters, and improve and maintain children's health.

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Chapter 64

CHILDREN'S HEALTH AND SAFETY RISKS POSED BY IRRIGATION WATER IN NORTHERN UTAH

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ABSTRACT

In Northern Utah communities, irrigation water runs through city streets and is used for residential purposes, posing a potential risk to children's health and safety. Children may be exposed to these waters in various ways, including through gardening, play, ingestion, or other unintentional contact. These waters are typically not treated and may contain potentially harmful contaminants. In this chapter we explore perceptions of health and safety risks children may face when exposed to irrigation water in Logan, Utah and surrounding areas. A qualitative analysis was employed for this study. Specifically, semi-structured interviews were conducted with key stakeholders in the area (N=13) to assess local and scientific knowledge and risk perceptions on water quality, health risks, and safety risks associated with the urban irrigation system. Members of the scientific research community expressed concern that irrigation water may expose children to various health and safety risks, and that children of a lower socioeconomic status may experience more exposure pathways and have greater levels of vulnerability. Conversely, civic stakeholders expressed a lack of concern about health risks from irrigation. Strategies are identified to remedy divisions in perspectives on children's health and safety risks and break the cycle of vulnerability.

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INTRODUCTION

Children possess a distinct vulnerability to environmental hazards that may result in negative consequences for their health and safety. From a general environmental health standpoint, children have greater sensitivity to harmful chemicals due to their unique physiology and behavior patterns [1-4]. Additionally, children are more vulnerable to unintentional injuries than adults, including drowning, which is the leading cause of death for children between the ages of 1 and 4 years [5].

One environmental factor that may pose considerable health and safety risks for children is irrigation water. Irrigation waters are used in areas throughout the United States for various residential and agricultural purposes. In Utah, irrigation water is managed by over 1,000 irrigation companies who handle farms' and households' access to irrigation water throughout the state (from single neighborhoods to thousands of acres) [6]. Irrigation waters in Utah are sometimes piped directly to households for residential irrigation use, though they may also flow through town in open canals and ditches or through the gutter system to be used for residential landscaping or more widespread agriculture. Irrigation water is not treated to the same standards as drinking water, if indeed it is treated at all, and often varies in quality based on location and source [7]. Additionally, irrigation water often gets less attention than drinking, waste, and recreational waters, leading to a lack of appropriate monitoring of irrigation water quality [7]. However, a report issued by the Utah State University Foundation, and in partnership with the Federal Water Pollution Control Administration, stated that the major contaminants of concern commonly found in irrigation water include soluble mineral constituents, fertilizers, nitrate, pesticides, and in some cases, treated wastewater [8]. As such, irrigation waters may pose considerable risks for children's health and safety when exposure occurs, and there are multiple potential ways children could be exposed to these waters (including through play, gardening, ingestion, and other unintentional contact). Figure 1 shows a picture of children playing in irrigation water flowing through a street gutter in Logan, Utah.

Considering that surface waters are most often used for irrigation and are open to a broad range of potential contamination, researchers have examined the quality of these waters world-wide [9]. Most of these efforts are focused in the developing world, though there are some studies that examine these issues within a US context. One such study examined the quality of waters in irrigation reservoirs and canals in Ohio [9], finding total coliforms in all water samples and *E. coli* in most collected water samples. A study examining surface water quality in an agricultural watershed of Louisiana found that sediment, phosphorus, nitrogen, dissolved solids, and acidity/alkalinity were the most important factors associated with poor surface water quality in this watershed [10]. While these studies focus on irrigation water quality, additional studies have also discussed human health in relation to decreased water quality. For example, Gilliom et al. [11] found that pesticides and herbicides pose the most significant concern for human health, especially those found in urban streams and rivers. Other studies have provided suggestions for the best way to monitor irrigation water quality [7, 9].



Figure 1. Children playing in irrigation water flowing through a street gutter in Logan, Utah (Photo by C. Flint with permission from parent).

Previous studies on irrigation water quality and related risks, while valuable in their contributions, are sparse. In general, there is not much information available on the quality of irrigation waters and potential risks to local populations. More extensive knowledge on the quality of irrigation water is needed to better understand associated risks to those exposed to it, especially for children due to their increased vulnerability and contact with these waters.

In addition to sparsity, the extant research on irrigation water exposure is limited in several ways. Previous research does not specifically address safety-related risks that may occur due to human access to open irrigation water sources such as open ditches and canals, and it neglects to account for health and safety risks specific to *children* exposed to these waters. Further, existing research explicitly focuses on microbial risk assessment, failing to account for the social dimensions of risk that may exist. Specifically, this research fails to account for the ways that local populations *perceive* issues of health and safety risk due to irrigation water exposure. While analyzing the quality of and specific harmful constituents in irrigation water is undoubtedly of great importance, it is equally important to understand water risk perceptions to better comprehend the complexity of the issue. Beyond research on levels of contamination within irrigation water, local perceptions of risk from irrigation water exposure may differ from those expressed in scientific settings and may influence broader community awareness and concern for these issues [12]. Additionally, vulnerabilities experienced on an everyday basis contribute to environmental risk situations that are socially constructed in various and potentially conflicting ways among community residents [13].

This study addresses perceptions of risk related to children's irrigation water exposure in Northern Utah by focusing on the following broad questions: 1) Are there perceived health and safety risks for children exposed to irrigation water in Northern Utah and 2) If so, are there ways to minimize these risks? Additionally, this research seeks to provide a deeper understanding of the ways that perceptions of risk are constructed within certain social

contexts and how this could influence levels of concern surrounding issues of risk within communities [12].

OUR STUDY

This study was conducted in Northern Utah, with a predominant focus on the City of Logan. Logan, Utah is the largest city in Cache County. Based on US Census 2017 statistics, Logan has an estimated population of 51,115 [14]. In terms of race, the city's population is predominantly non-Hispanic or Latino white (75.4%) [14]. The Hispanic or Latino population makes up 15.5% of the local population, followed by individuals of Asian origin (4.2%) [14]. In terms of age, 24.1% of Logan's population is under 18 years of age, and 9.2% of the population is under 5 years of age [14]. Some statistics for Logan are skewed by the presence of a large student population in the city (considering that it is home to Utah State University). For example, only 40.5% of the population owns their home and 25.4% are classified as living in poverty [14].

Semi-Structured Interviews

Semi-structured interviews were conducted with 13 key stakeholders from the area who represent various local social fields. Local social fields are groups of people in local settings that represent different identities and interests [15]. Local social fields may make up a community field when the perspectives of each field converge toward locality-based action for the common good [15]. Key stakeholders interviewed for this study who represent local social fields include university researchers whose work focuses on water and water quality, individuals affiliated with University Extension (a program providing state-wide services and outreach connected to land grant universities), city officials, state government officials, individuals associated with local irrigation systems, and individuals affiliated with other community organizations. These stakeholders fall into two main categories: 1) university informants (university researchers and individuals affiliated with Extension) and 2) civic informants (city officials, state government officials, individuals associated with irrigation systems, and individuals affiliated with community organizations). In total, six university informants were interviewed (three university researchers and three individuals affiliated with Extension) and seven civic informants were interviewed (two individuals affiliated with irrigation systems, two state government officials, two city officials, and one individual affiliated with a local community non-profit organization). While these stakeholders represent distinct social fields, it is important to note that they also overlap. In other words, individuals affiliated with one social field (such as city government) may also be affiliated with other social fields (such as community organizations and irrigation systems). Many stakeholders are also local residents in the study area. Figure 2 shows the local social fields represented in the study and the number of informants interviewed within each field.

Interviewees were selected via criterion and snowball sampling. An initial list of interviewees was compiled based on known connections to irrigation systems and/or irrigation water quality. Individuals selected for the study were invited to participate via

email. During each personal interview, interviewees were asked to identify additional individuals who they thought may provide relevant information on the topic. These individuals were contacted and invited to participate in the study as well. Interviews lasted approximately 30-45 minutes. Most interviewees agreed to have their interviews recorded. Notes were taken during all interviews and recorded interviews were transcribed for subsequent thematic analysis. The interview process continued until data saturation was reached and interviewees began to consistently refer us to individuals already contacted.

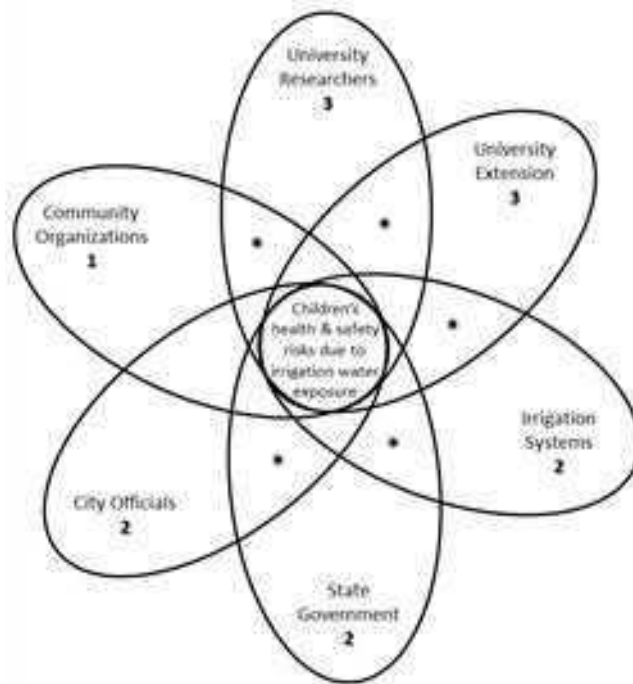


Figure 2. Social fields represented in the study and the number of informants interviewed within each field. Asterisks (*) represent points of overlap. Adapted from Theodori [15].

Interview transcripts were analyzed to assess perceptions on children's health and safety risks due to irrigation water exposure, and efforts made or suggested to address these issues. Interviewees were initially asked to discuss their role in the city or organization they are affiliated with, and their involvement with irrigation water or irrigation systems. Next, they were asked several questions focused on water quality and safety risks associated with the urban irrigation system, water risk communication efforts by area authorities, and associated links to children's environmental health vulnerability. All interviewees were asked how they believe capacity can be built within the existing systems to break the cycle of identified or potential health and safety risks for children exposed to irrigation water now and in the future. While Logan was the city of focus in this study, some informants provided answers to the above questions from a vantage point beyond this study area. For example, some informants discussed these issues from a broader county (Cache County) or regional (Northern Utah) focus.

FINDINGS

Study findings are discussed below organized by four main themes: 1) identified contaminants of concern in irrigation water; 2) perceived health and safety risks for children exposed to irrigation water; 3) perceived risks for disadvantaged populations and 4) strategies for breaking the cycle of risks to children posed by irrigation water.

Contaminants of Concern

When asked about specific contaminants that may be present in Northern Utah irrigation water, some informants – most notably university informants – reported concern for potentially harmful contaminants introduced into irrigation water through runoff from streets, fields, and agricultural lands. One university informant expressed considerable concern for how there is little to no treatment of these waters:

“I guess the biggest concern about irrigation water in general, depending on where it comes from, there may be no treatment whatsoever of it. In fact, there’s very little treatment ever. So, I’m thinking again about the place where Hyrum gets their water. If there are people camping or – well, I guess it’s primarily camping – or a place like at rest stops where there might be a problem with waste treatment systems up there, there’s a pretty good potential for those sources to impact that irrigation water. I know, for example, we have Giardia up in Logan Canyon from backpackers and hikers and so on. So, any of that irrigation water that might have been infected by that contaminated stream water from sources of human camping, hiking, fishing, stuff, that’s going to have no treatment whatsoever.”

Some specific contaminants identified by university informants that may be in irrigation water include agro-chemicals (such as pesticides, herbicides, and fertilizers), pathogens (bacteria or other microorganisms that could cause disease in humans), animal materials, and human contaminants from recreation. One university informant said “...(D)efinitely if the water is traveling in uncovered canals, there is unlimited exposure potential and unlimited contamination potential.” Another university informant said:

“We actually had a situation in Smithville Canyon where there was a raccoon that got into the water storage tank and died. So, there was high levels of bacterial contamination, if there were any diseases that raccoon had, there was a potential. So, even things like that where animals just fall in and die and decay, there’s a potential of risk from that as well.”

Additionally, a university informant suggested that maintenance of irrigation canals can introduce potentially harmful chemicals into irrigation water:

“We also have the maintenance of the canals themselves which, ironically, produce some of the worst chemicals. So, we have the people that manage these ditches, they call this stuff moss – it’s a growth that happens in these unlined canals. They used to throw xylene on them... I don’t know what the current practice is, that was when I first arrived. So, they would simply tell the people near the ditch that if it’s running milky colored, don’t use it. But kids play in these ditches all the time.”

While some university informants were unsure whether identified contaminants exist at high enough levels to cause significant negative health effects, they expressed the critical

need for greater concern and research on the topic to determine the specific contaminants in irrigation water and if the levels of these contaminants are harmful to human health.

Perceived Health Risks

After discussing contaminants that may be present in irrigation water, informants provided their perspectives on children's health risks due to irrigation water exposure. University informants expressed a general concern for children's health, specifically perceiving that exposure to irrigation water may lead to risks from ingestion and other physical health-related issues. One university informant explained why children are at a higher risk for health-related issues from exposure to irrigation water than adults. This informant described how children have a lower tolerance for fighting off bacteria than adults and do not need to be exposed to as many infectious organisms as adults to become sick, specifically saying:

"So, a couple of things. The dose, the infectious dose, is typically based on body weight and so they [children] don't need as many infectious organisms that they're exposed to in order for them to get a disease. That's an issue, certainly, because of their size. They also tend to be, kids tend to be less worried about eating dirt. Pica's an issue, so if there's organisms or contaminants that absorb to soils, then they can get higher doses than adults would normally get because of ingestion of the solids. So, yeah... the exposure routes and the infectious dose are much, much more for the kids because of their body weight, higher surface area to volume through skin, those sorts of things. When I think of routes of exposure, I'm thinking of inhalation or dermal exposure or ingestion... (T)he kids are the ones that are primarily going to be running in the sprinklers and drinking that water. So, their potential... well, it could be in the canals. So, if canals are there, kids can jump in them and play in them and so on, but once the water gets to the user, the water that's sprayed or sprinkled or whatever, then the kids are going to tend to have higher exposures. They tend to be worried less about skin exposures. They're going to drink the water, they have the larger surface area to body mass ratios because they're smaller, they worry less about drinking the water, and all of those kinds of things. So, yes. Certainly, the exposure, the potential duration, and number of exposures for the kids are going to be higher."

Other university informants explained specific ways children may become sick from irrigation water exposure. Some examples of responses include:

"I mean, it's not treated. So, then you're looking at potential gastrointestinal issues... So, if it's piped or pressurized, there's still that health risk of ingesting that water and it hasn't been treated to drinking water standards. I mean, in this country, our tummies and guts are not equipped to deal with bacteria and things..."

"I think the pathogens are the ones I'd worry most about. You know, just because you not only have animals, but you also have potential for septic systems to drain into these [irrigation systems], especially the older ones. Exposure to fecal matter is never a good thing, you know. So, I think that's probably the biggest risk."

While university informants suggested there is a potentially significant health risk for children exposed to irrigation water, civic informants generally did not believe a health risk exists – at least not one of concern. When asked if they believe there are any health risks associated with children's exposure to irrigation water, civic informants responded in the following ways:

"You know, I honestly don't. Again, maybe I'm misinformed, but that's the honest answer. I don't really see that as a problem here."

"Not that I would be openly concerned about. I mean, if there's an outbreak in the water, that's a different story... (W)hen I grew up, it [the irrigation water] was water from the creek that had been diverted upstream and was run through this ditch and then flowed back in the creek. So, it was part of creek water which was, you know, it was clear water. It wasn't muddy, it wasn't real contaminated. We just had a lot of fun playing in it."

"I mean, we're a society of cleaning ourselves up and it can almost be debated both ways whether that's good or bad because if I'm too clean, any bacteria gets me sick and if I'm a little dirty, I can handle those bacteria and germs and things like that. So, I don't know where I stand on that. It's always a potential. It's a problem when you have outbreaks and, to me, an outbreak's more than, I don't know, 20 or 30 – a larger number."

As exemplified by the above discussion, there is a significant divide between perspectives of university informants and civic informants about children's health risks due to irrigation water exposure. University informants perceived a potentially significant health risk and civic informants perceived little to no risk at all. Furthermore, not only did civic informants rarely mention health risks, they more commonly expressed placing a high value on the irrigation water. Civic informants expressed sincere appreciation for irrigation water and consistently spoke of fond memories regarding their experiences with these waters:

"...(W)e irrigate with it around my house exclusively. So, my lawn, my garden, about a half an acre of property. I'm grateful to have it based a lot on cost. I mean, I pay like 12 bucks a month for it no matter if I use none or as much as I want. It's not metered; I just pay for a flat fee. So, it's really neat. Of course, I don't like to waste water either, so I don't over-irrigate. But my kids play in it, you know. They love to. You know, kids like to play in sprinklers and water in the summer, so they'll run through the sprinkler or put the sprinkler under the trampoline and jump on that. I've done it with them too, it's pretty fun. Nobody thinks about the water quality really."

"Growing up next to a ditch my whole childhood life, I really had a lot of fun and honestly it was a big part of growing up and being a kid. I mean, climbing in the ditch and getting wet and throwing moss around, and getting muddy and that kind of stuff—it was a lot of fun."

"That canal that I mentioned to you about that failed? People used to float that all the time. I've floated it and it was really fun. It was cold water, but it was really fun to do that and that's no longer an option."

Perceived Safety Risks

After discussing potential health risks, informants were asked whether they believe there are any safety risks associated with children's exposure to irrigation water. Both university and civic informants expressed concern for safety-related risks. University informants suggested many specific ways that exposure to irrigation could produce safety-related risks, saying things like:

"I think probably kids playing in it is the biggest risk. And, you know, just drowning. We have a remarkably laissez-faire attitude about kids being near the water. It just breaks my heart when people go camping with a little kid by the river and, 'we just took our eyes off for 30 seconds.' 10 seconds, 5 seconds is all it takes for a kid to fall into the water and then they're gone."

"So, a small child could easily drown in a canal. Easily. In addition, the water tends to be very cold, so there's a risk for hypothermia. And those are just physical risks. That's completely putting aside whether or not they might ingest that water. I mean, it's not treated."

"I mean, cars run into those canals too. People drowned, and kids get in the culverts and get sucked through the inverted syphon or something."

Civic informants also expressed concern for children's safety due to irrigation water exposure. When asked, "Do you believe there are any safety risks associated with open canals and ditches?" some civic informants replied:

"Yeah, I always worry about that. And again, you know, that was one argument for covering them. Some of the canals they've done liners on, so they're a little slippery on the edges and it's like, "what if a kid gets in?" ... It's always a risk."

"Oh yeah! Absolutely! I mean, you talk to the Bear River Canal Company in Box Elder county – they irrigate 70,000 acres and they have 2 major canals and they're open, you know. People play in them and swim in them and whatever, but people have drowned in them. They drowned last year in one of Bear River Canal Company's canals. So, the conveyance system – typically these irrigation companies are using these open canals and ditches because that's what they put in a hundred and fifty years ago."

Both university and civic informants also consistently referred to an instance where a "hundred-year-old" canal failed in Logan, Utah, and described how these sorts of scenarios introduce unique safety risks for children and adults alike. One informant explained the event as follows:

"They piped it finally, but there was a canal at the edge of USU [Utah State University] and above the Island and it was failing. They had knowledge it was failing. There were little mudslides here and there, but someplace it broke. When that starts happening it dissolves the hill away and you get a mudslide before you realize the canal's failing. It came right down on top of this little house right down in the Island and killed a mother and her 2 children. Certainly, these were low-income people living in this place. It was heart-breaking. That's a maintenance issue. The canal company and university and city people were fighting over this for years rather than fixing the damn thing. It's your problem, no it's your problem, no it's your problem, and it never gets fixed. They just argued over who was going to pay for it and when they did finally fix it [after the mudslide], they put it into a pipe. The pipe sometimes breaks now too, so, water's funny that way."

Perceived Risks for Disadvantaged Populations

In addition to providing perspectives on general health and safety risks for children exposed to irrigation water, university informants suggested that there could be unique risks for socially and economically disadvantaged populations. One university informant suggested that children who are more disadvantaged are more at risk. This informant specifically stated:

"I will note that it's the children who are poorer or in socially disadvantageous situations, meaning they have maybe parents that aren't as educated, or their diet is not as good as a wealthier family, who are more at risk. If we have a relatively poorer community where we have these children who encounter the water more and, also, maybe their health status isn't as good as we would like, it's incumbent upon us to protect them as best as we can. So, there is a demographic and socioeconomic aspect of this work..."

Another university informant proposed that children in rural areas are more at risk for health and safety risks due to irrigation water exposure, saying:

"We have kind of a laissez-faire attitude about this kind of stuff. So, in terms of social justice and economic stuff, it would be kids out in rural areas that [are exposed more]. You know, when I was a kid, I remember playing in the irrigation ditches because it was fun! I can't imagine kids are any different here."

Strategies for Breaking the Cycle of Risks to Children Posed by Irrigation Water

Interviews revealed a combination of factors that collectively create vulnerability to environmental risks posed by irrigation water. The combined influences of personal characteristics (including increased susceptibility to injury and disease, limited communication ability, and limited education), environmental characteristics (including lack of regulation for irrigation water treatment, access to both open and piped irrigations waters, and exposure through ingestion), environmental risk factors (including exposure to pathogens, agro-chemicals, and human and animal contaminants), health risk factors (including skin irritation and gastrointestinal issues), and safety risk factors (including potential for injury and drowning/death) contribute to the cycle of children's irrigation water-related risks that result in compound risk factors including potential long-term health effects and prolonged issues from injury, limited communication, limited educational services, and limited regulatory policy. While this cycle of children's irrigation water-related risks may appear disheartening, university and civic informants alike suggested numerous strategies during interviews that could be implemented now, and in the future, to mitigate and break the cycle of children's health and safety risks posed by irrigation water in Northern Utah. University informants suggested strategies such as:

- Raising the general level of awareness and informing the public about potential irrigation water risks
- Increasing the general concern about the use of irrigation water and risks that may associated with it
- Communicating with the public about appropriate ways to use the water
- Piping and pressurizing open irrigation waters

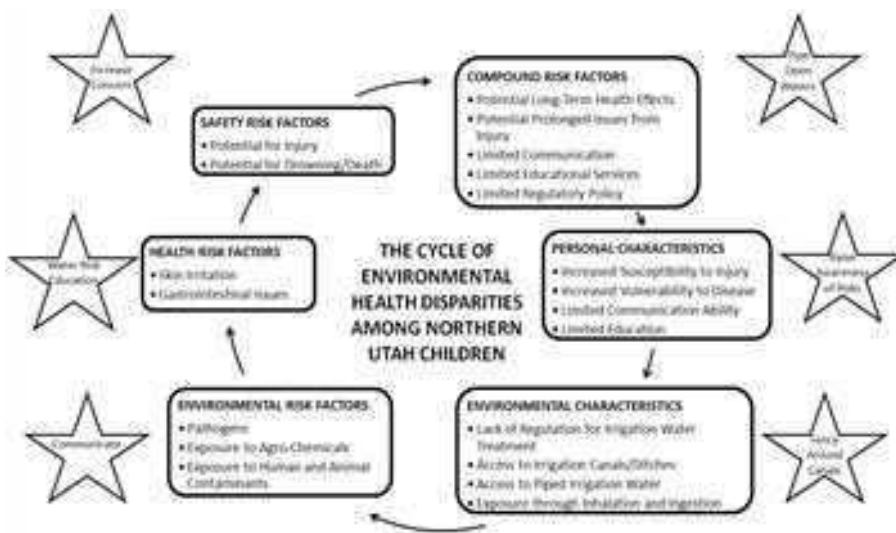


Figure 3. The cycle of irrigation water-related environmental health disparities among northern Utah children and strategies to “break the cycle” (stars) as suggested in interviews. Adapted from <https://www.isdd-home.org/break-tp>.

In addition to those strategies suggested by university informants, the most consistently suggested strategy proposed by civic informants to break the cycle of children's irrigation water-related risks was fencing off open irrigation canals. Figure 3 shows the array of children's health and safety vulnerabilities illuminated in this study and some strategies informants proposed to break the cycle of this type of children's environmental health problem.

DISCUSSION

As exemplified in the discussion above, perceptions of children's' health and safety risks posed by irrigation water in Northern Utah, especially regarding health risks, are divided between university and civic informants. University informants suggested health risks from irrigation water exposure are always present, potentially significant, and should be imminently addressed. In contrast, civic informants believed little to no health risk exists and attention to the issue is not necessary. This division in perspectives represents the absence of a community field (due to the lack of convergence of perspectives toward locality-based action for the common good) [13, 15]. These divided perspectives also represent what Irwin [12] terms 'situated knowledge' versus 'scientific knowledge'. In the case of the university and civic informant perspectives, the university informants possess scientific knowledge, or knowledge constructed or given meaning in a scientific setting, and the civic informants possess situated knowledge, or knowledge constructed or given meaning in a local setting. This highlights the way that pollution issues such as the one that is the focus of this paper are constructed and viewed differently in different settings. Irwin [12] suggested

"...(T)he extent to which pollution issues are viewed as matters of concern cannot simply be established in scientific or technical terms... Rather than seeing problems as simply given, we have viewed 'sense-making' as a process of active construction within particular contexts and settings."

Accordingly, the extent to which irrigation water pollution issues are viewed as matters of concern cannot simply be established in scientific terms. Researchers need to better understand how these issues are constructed in non-academic settings as well to attain a broader understanding of the complexity of the issue. Scientific knowledge may ignore or discredit the power of collective memory held within a local population that enhances a higher risk tolerance or aversion to thinking about risk [12].

Considering the scientific research perspective that there are threats to children's health and safety from irrigation water exposure, future research is warranted. In addition to physical water sampling and testing to identify risks, it is important to understand the differences in perceived risks (university versus civic perspectives) in order to establish a means of communication between the public and public leaders in an effective way. Irwin [12] discusses the need to carefully address disconnections between scientific and local perspectives:

“From one point of view, the accounts offered by local people...can be seen as reflecting an information shortage (or ‘deficit’). If only residents had access to more complete and authoritative information, then they would not need to bring together such partial information and clues – they could simply deal with the ‘real’ situation... Of course, this formulation also grants privileged status to the experts (whether scientific, industrial, governmental, or, indeed, sociological) who might be expected to understand best what the situation really is.”

As this quote suggests, without an established communication flow among the public, local leaders, and the scientific community, information presented to the public from “experts” could easily be dismissed and this wouldn’t be beneficial to any of the actors involved. Finding middle ground between polarized perceptions is essential to mitigating risks while being mindful of different vantage points among local stakeholders. Creating forums for multi-directional dialogue are key to community-based risk management.

Future inquiries into irrigation water-related risks should emphasize evidence-based inquiry into water quality, while also addressing the socioeconomic context of local exposure. Analyzing secondary data on sociodemographic characteristics of residents in areas with increased access to open irrigation waters (including irrigation ditches, canals, and gutters) is warranted. This assessment could provide insight into whether those of a lower socioeconomic status have more irrigation water exposure routes, allow for more specific consideration of how children from a lower socioeconomic status may experience more exposure pathways and greater levels of vulnerability, and aid in the development of targeted educational and outreach materials to address potential irrigation water-related risks. Furthermore, extending qualitative research into perspectives of local residents, particularly parents, would be informative.

ACKNOWLEDGMENTS

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Chapter 65

ENVIRONMENTAL JUSTICE FOR VULNERABLE FLORIDA CHILDREN IN HURRICANE AFTERMATH

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ABSTRACT

In this chapter we conduct a literature review to identify environmental and socioeconomic factors that affect vulnerability and resilience of communities in the event of a hurricane, particularly children in selected communities in South Florida. Qualitative data analyses mobilizing GIS visualization were used to display spatial patterns of hurricane hazards and demographic vulnerability factors across Floridian counties. Results showed that, while environmental vulnerability is a reality in the entire state of Florida, socioeconomic vulnerability varies widely throughout the state. Further, counties in Florida that are highly vulnerable according to the Social Vulnerability Index (SVI) are also the counties with the greatest proportional population of children under the age of 18 years old. While conducting analyses, several challenges in vulnerability assessment were identified, including but not limited to, the need for more refined indicators of environmental risk to better represent vulnerable populations.

INTRODUCTION

A projected 4 degree Celsius increase in global temperatures (see Figure 1) and an average global sea level rise of from 45 to 82 centimeters by year 2100, with increasing intensity and frequency of natural disasters, should be recognized as significant indicators that climate change is an emergent threat to global health [1]. While the impacts of climate change

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have detrimental effects on both the environment and the population [2], children and the elderly are the most vulnerable. Children are dependent on the resources of their caregivers and communities and, therefore, are arguably some of the most climate-vulnerable members of society, including vulnerability to climate-related environmental exposures. Compounding the structural vulnerability of children, this population is also physiologically vulnerable, with increased absorption of toxicants due to increased consumption of water, air, and foods for their size, and immature metabolic systems compared to adults [3]. Environmental exposures may impact a child's lifelong health trajectory as a result of both the interruption of healthy living during childhood and longer periods to develop chronic diseases as a result of exposures, predisposing these children to poorer long term-health trajectories [1, 3]. The global burden of disease index identifies global climate change as a growing contributor to global disease burden, of which children making up 88% of the disease and disability impact attributed to climate change [4]. Socio-economic status compounds the risk and impact of environmental exposures to children, and climate change will increasingly be a contributing cause of disease and disability among this vulnerable population [5].

The vulnerability of children, related to their developmental status, lack of autonomy, and sociological displacement in the aftermath of an extreme weather event is often overlooked [5]. Previous studies have identified vulnerability and resilience as factors predictive of the severity of detrimental effects of adverse weather events such as hurricanes [6]. This vulnerability is further compounded by multiple risk factors associated with socioeconomic status of the child's family and community [5]. Examples include rate of illness, nutritional status, infrastructure quality, and community resources (see Figure 2a and Figure 2b). While many factors, both environment and social, have been identified, the complexity of the interaction with child health remains poorly understood. The current motivation for research is identifying these vulnerable populations, based on geographical and social risk factors, in order to allocate resources to promote resilience for these children.

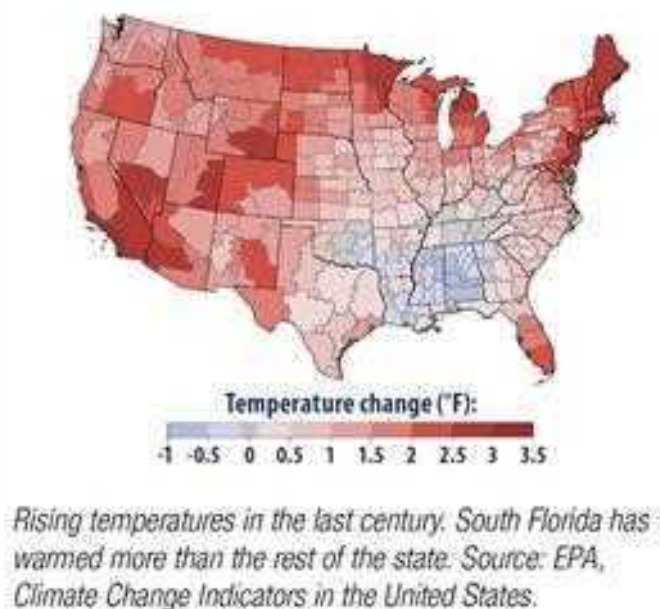
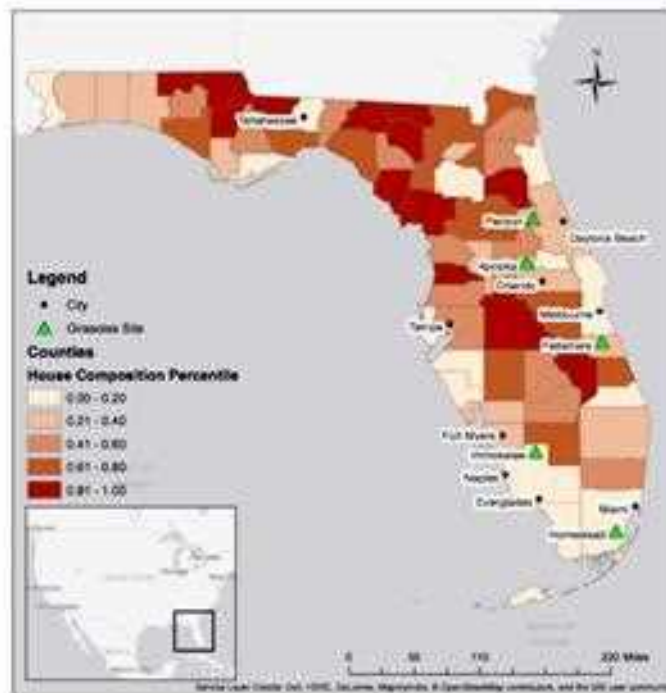


Figure 1. Historical US rising temperature map [2].

U.S. Census Household Composition Percentile Ranking



U.S. Census Socioeconomic Percentile Ranking

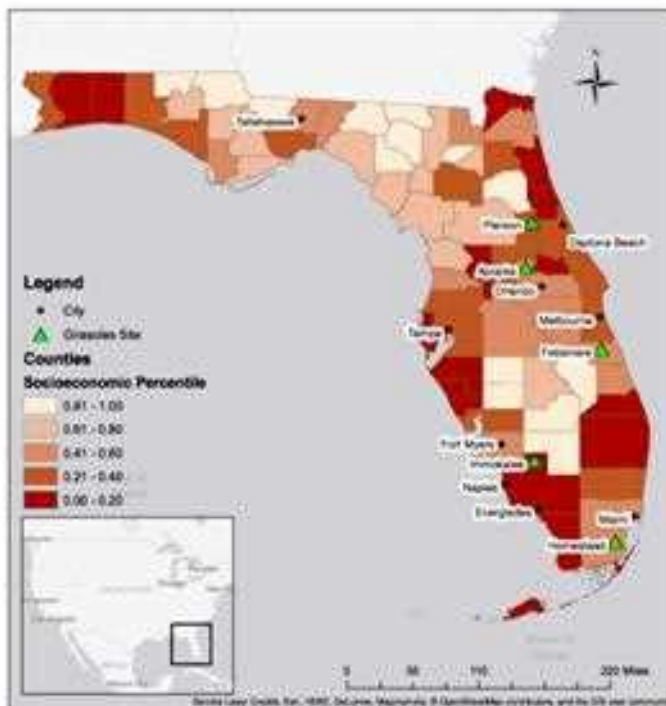


Figure 2a. Florida SVI by state by category (Top: Household composition, Bottom: Socioeconomic status).

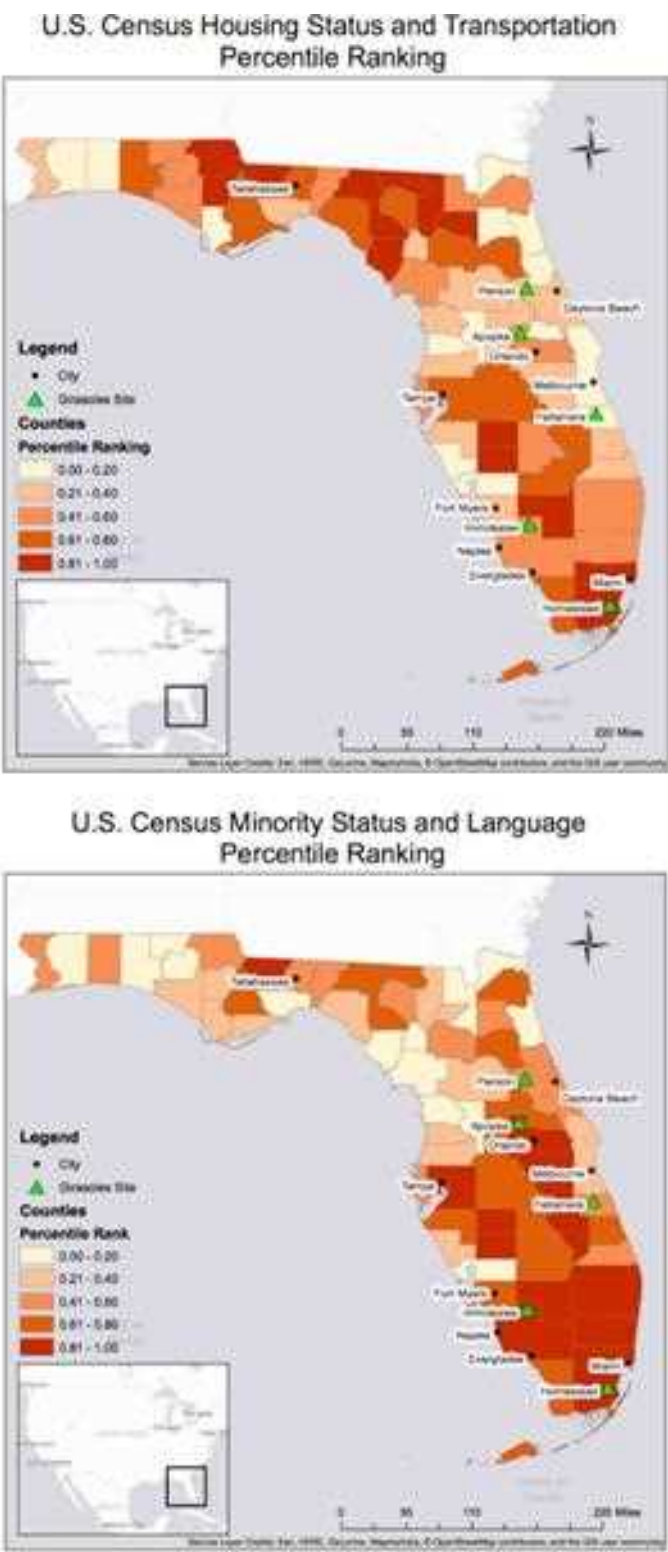


Figure 2b. Florida SVI by state by category (Top: Household and transportation, Bottom: Minority status and language).

The implications of climate change and the associated environmental impacts have long been studied and proven to have detrimental effects on children's health [1, 4, 7, 8]. With this evidence, it is imperative that children are specifically considered when assessing the vulnerability and resilience of a community. The combination of environmental hazards, socioeconomic inequity and developmental vulnerability create an interconnected cycle of children's environmental health inequity represented in. Each element of the cycle of health disparities represents a key area where interventions have the potential to break this cycle in children.

In the recent hurricane season of 2017, Hurricane Irma on September 10, 2017 revealed the intersectional effects of poverty and inequity on populations in Florida. The extreme effects of the storm in communities such as Immokalee, Florida, primarily made up of immigrant families, was left with meager resources following the storm in obliterated housing units and many days without power, resulting in severe food insecurity and no source of income due to flooding of crops [9]. Vulnerable communities like Immokalee, and the children residing within them, exist throughout the state of Florida, and need identification with further representation and accounting to counteract their heightened vulnerability. These efforts will lead to the development of strategies to build resilience in the face of future effects of climate change.

The specific vulnerability faced by these children in the aftermath of a hurricane (from impacts of storms and sea level rise on infrastructure like roads, railways and drinking water) includes scarcity of basic natural resources [2] resulting in undernutrition, and displacement, which leads to risks to security, adverse physical and mental health consequences, and disruptions in education [1]. In 2016, Garcia and Sheehan conducted a literature review to examine the direct and indirect effects of extreme weather events (EWEs) on children's health. The review compared a traditional model of climate change-based health impacts with a nonlinear and more complex model that takes into account biopsychosocial interactions [10]. Common health impacts identified in the current literature included:

- direct impact health effects (i.e., trauma, injury, drowning, infections, asthma exacerbations, dust/toxin exposure, medication disruption, crowding and increased cumulative stress)
- indirect impact health effects, which occur due to ecosystem and social systems being negatively impacted (i.e., infectious disease outbreaks, waterborne illnesses, poor nutrition, disruption of vaccine schedules, displacement from their homes, and food contamination), all of which eventually lead to undernutrition
- direct and indirect mental health effects (i.e., post-traumatic stress disorder (PTSD), chronic "survival mode," or prenatal maternal stress that affects the fetus) [10–13].

It is evident that the health effects of hurricanes and other EWEs are vast and complex. However, several studies show that cultivating resilience is the key to dampening the health effects that children face [10, 12, 13].

As a result of the effects of Hurricane Irma on Floridian communities, this project explores social vulnerability metrics as they relate to pediatric populations and the cycle of environmental disparities. Susan Cutter et al. [14] developed a social vulnerability index (SoVI) by identifying perceived vulnerability based on 11 identified factors at the county

level of resolution [14]. This index was utilized to classify and rank counties by their measured vulnerability. The Center for Disease Control and Prevention's (CDC) social vulnerability index, that is calculated using demographic variables from the US Census American Community Survey which are then ranked by county, was identified during the literature review as a tool to explore environmental vulnerability and disparities that Floridian children face [15].

With all intricacies in mind, the following question was posed: "Are certain Floridian populations of children more vulnerable to the effects of hurricanes based on their geographical location and sociodemographic factors?" We utilized key principles of children's environmental justice to identify areas of potential impact within the Cycle of Environmental Health Disparities framework (Figure 3). This project aimed to identify areas where pediatric populations are most vulnerable and will most greatly benefit from interventions in the community, socioeconomic and environmental hazard domains of the Break the Cycle framework.

OUR REVIEW

Initially, existing literature relevant to the topic was assessed utilizing the keywords: 'hurricanes,' 'Florida,' 'resilience,' 'vulnerability,' and 'children.' Databases utilized in this search included PubMed and JSTOR in the initial search conducted December 12, 2017. Key search terms included 'disasters,' 'Florida,' 'children,' 'vulnerability,' and 'resilience.' Inclusion criteria consisted of an assessment of external validity, publication within the last 20 years, and geographic region. Articles older than 20 years or not relevant to the Florida climate were excluded. The review was performed to assess vulnerability and resiliency factors relevant to hurricane disasters. Measures of resiliency and vulnerability were reviewed in the search in order to develop a measure of social vulnerability. Measures of environmental risk were also reviewed in order to classify disaster records consistent with current studies.

In order to promote reproducibility at a level that can inform disaster preparedness best serving children in the future, we utilized the CDC Agency for Toxic Substances and Disease Registry's (ATSDR) Social Vulnerability Index (SVI) developed from the US Census American Community Survey as a preliminary index to inform the social factors in our study [15]. This index consists of 15 descriptive factors that are recorded from census data during the American Community Survey every five years. This index was chosen primarily due to the incorporation of several variables that represent children as this is the focus of our research. We also utilized this index for the sake of reproducibility and accessibility. These variables were recorded at a county level, which is the level at which emergency preparedness resources in Florida are disseminated.

The 15 factors considered by the CDC's Social Vulnerability Index (SVI) are broken up into four sections that collectively represent social vulnerability:

- "Socioeconomic status" which consists of the factors: percent of individuals below poverty, percent of civilians unemployed, per capita income, and percent of adults over age 18 years with no high school diploma

- “Household composition and disability” which consists of the factors: percent of persons 65 years of age or older, percent of persons 17 years of age or younger, percent of persons more than 5 years old with a disability, and percent of single male or female householder, no spouse present, with children under 18
- “Minority status and language” which consists of the factors: percent of minority and percent persons 5 years or older who speak English less than “well”
- “Housing and transportation” which consists of the factors: percent of multi-unit structure, percent of mobile homes, crowding (at household level, more people than rooms, percent total occupied housing units (i.e., households) with more than one person per room), percent of households with no vehicle available, and percent of persons in group quarters (i.e.,: correctional institutions, nursing homes, college dormitories, and military quarters).



Figure 3. Cycle of health disparities and hurricanes.

Each of these four categories were classified, ranked by quantile and visualized using choropleth mapping (see Figure 3). Quantile ranking for all raked variables are listed from lowest ranked vulnerability to highest ranked vulnerability. Total SVI was ranked by county and classified by percentile (higher SVI ranking being more vulnerable) for visualization using choropleth mapping by quantile (see Figure 4).

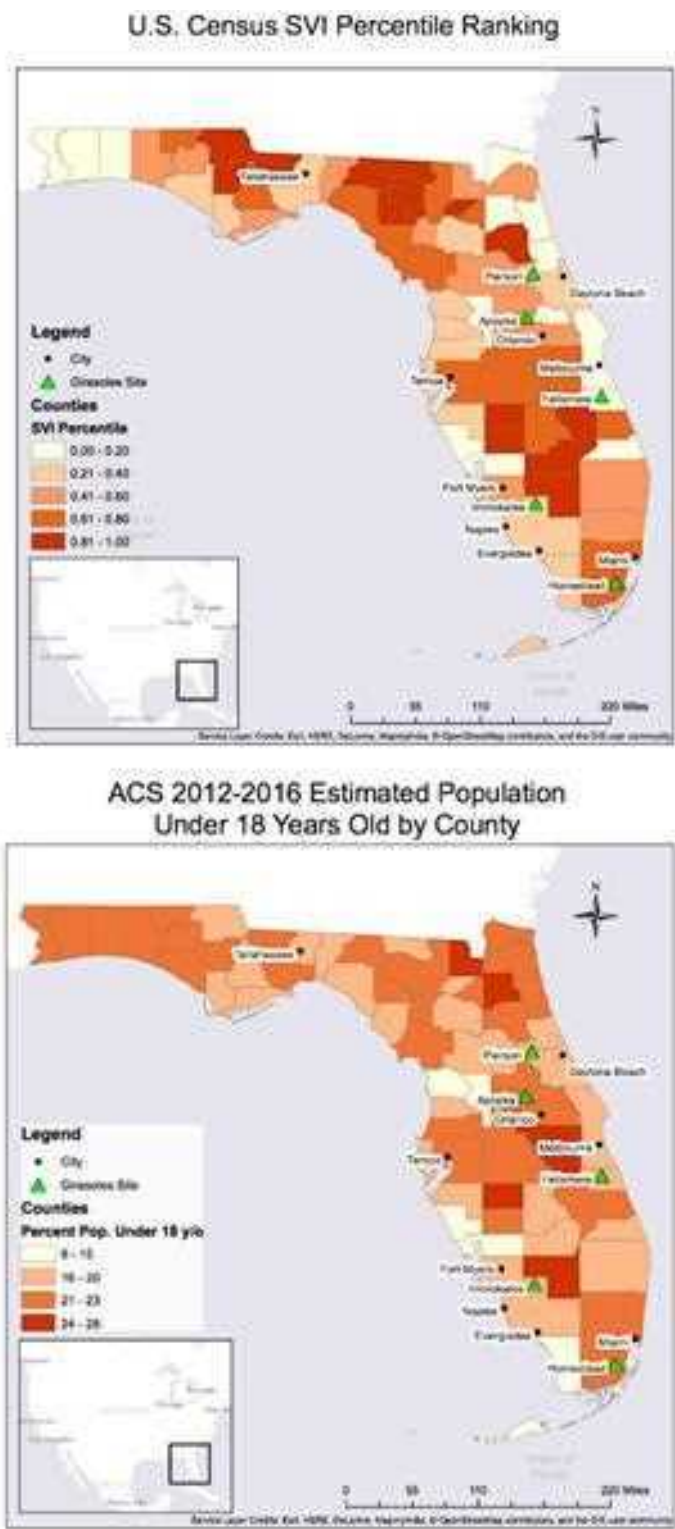


Figure 4. Choropleth visualization of SVI and percent of pediatric population (a. Top SVI, b. Bottom: Pediatric population).

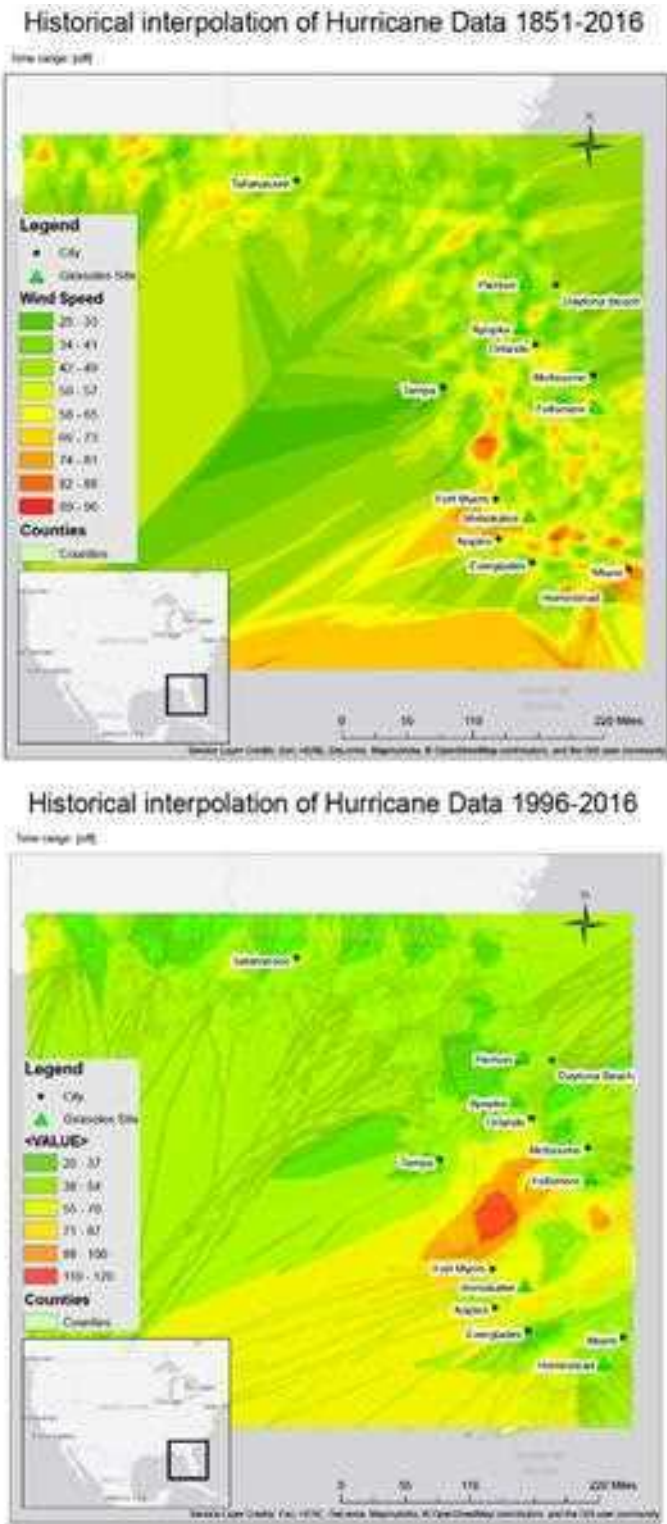


Figure 5. Linear interpolation of hurricane discrete path winds (a. Top: Total hurricane history, b. Bottom: 20-year history).

The Rstudio® (Version 1.0136) platform for statistical computing and graphics was utilized to manage and process data provided by the US Census and National Oceanic and Atmospheric Administration (NOAA). RStudio® scripts and records managed in a Git repository were used to manage the project for collaboration and open access. Environmental System's Research Institute's (ESRI) ArcGIS® software was utilized to perform geographic information system (GIS) visualization and data analysis. The 15 components of the CDC's Census SVI were mapped utilizing RStudio® and GIS technology. Each component was mapped individually and another map compiling all 15 indices was created to reflect overall social vulnerability at the county level for all Florida Counties.

Historical hurricane data was utilized to classify future risk. All hurricane paths classified by wind speed from 1851 to 2016 were mapped to assess for any patterns predictive of future hurricane paths. Hurricane path centroids (a point vector) were calculated for each line vector data point. Linear interpolation was then performed to qualitatively visualize regional historical hurricane wind trends utilizing raster format, a dot matrix data structure. Hurricane wind data from the Florida State Hazard Mitigation Plan was mapped for both the total recorded history and the last 20 years to observe differences in recent history (see Figure 5). In order to further analyze environmental risk, a storm surge hazard map was created reflecting storm surge by storm category (1 through 5) from NOAA data.



Figure 6. State of Florida: State Hazard Mitigation Plan, 100 Year probabilistic scenario [17].

FINDINGS

Spatial interpolation of hurricane wind speed using NOAA data of recorded hurricanes from 1851 to 2016 (see Figure 5a) shows a dispersed distribution of wind speed compared to an interpolation using a 20 year timeframe between 1996 and 2016 (see Figure 5b). This visualization of the 20 year interpolation represents a utilization of a time frame consistent

with current literature [14, 16]. Despite this, the results of whole history (1851 to 2016) interpolation more consistently resembles the Florida State Hazard Mitigation Plan assessment of hurricane disaster geographic probability (see Figure 6) [17].

Classification of census demographic information by county in Florida based on the CDC's SVI provides evidence of disparities between counties. Choropleth maps denoting areas of statistical variability utilizing shading in proportion to measurements of the SVI ordered, ranked and classified the data into quintiles, highlighting distinct differences in SVI between counties. SVI ranking by subcategory is depicted as well. The resulting map (see Figure 4a) shows the central southern counties in general making up a larger proportion of the high SVI areas than the coastal counties (with some exceptions, namely Miami-Dade County). Choropleth visualization of the county proportional population of people under the age of 18 (see Figure 4b) reveals a pattern similar to SVI ranking.

DISCUSSION

Results from the review of historical hurricane track data for the past 20 years (depicted in Figure 5) reveals that hurricane wind hazard risk is broadly dispersed across the state, with wind speed intensity increasing in Floridian counties of lower latitude. This suggests that hurricane force wind risk as a variable in vulnerability remains relatively constant between contiguous counties. These risk models are based on historical assessment data, which for the most part do not account for trends in storm intensity. Recent research suggests that global climate change trends will be associated with an increase in the intensity and impact of hurricane force winds in the Gulf Coast region [2]. Therefore, with the majority of the global burden of disease affecting children being attributed to climate change, the inclusion of effects of climate change on hurricane risk in future assessments is extremely important [1, 4]. Because we were unable to perform any correction based on spatial or temporal autocorrelation, our ability to draw conclusions was limited to preliminary qualitative assessment. Despite this, our results were consistent with the state of Florida's hazard mitigation plan.

GIS visualization of CDC's SVI from data provided by the U.S. census reveals several potential patterns in vulnerability across the state of Florida. By reviewing the raw population count by county and total pediatric population (<18 years old) by county (see Figure 2), it is evident that a larger proportion of the total Floridan population resides within coastal counties. Further, visualization of the county SVI ranked quintiles (see Figure 4a) reveals that, while the inland counties make up a smaller proportion of population, they inversely make up a larger proportion of social vulnerability compared to other counties in the state. Further, inland Floridian counties make up a larger proportion of counties with a higher proportion of children (<18 years old) when compared to counties statewide (see Figure 4b), with a few exceptions in the larger metropolitan centers. This suggests that a future direction should be to explore this pattern in greater detail to confirm and explain any disparity in environmental vulnerability impacting children.

Hurricane storm surge hazard data from the NOAA was classified into quintile and visualized on a choropleth display (see Figure 7)). The map depicts the storm surge depth (in feet) based on the presentation of a category 5 storm. The figure depicts that the coastal

counties face the largest impact from storm surges, including several coastal counties that ranked in the highest SVI quantiles (i.e., Miami-Dade County). With increasing sea level rise [2], storm surge risk will continue to encroach on more inland areas including counties in the southern central region of Florida that represent a larger proportion of the state's social vulnerability (see Figure 4). One major limitation in our storm surge assessment was the lack of resources to analyze trends in flooding risk, which could demonstrate the effects of higher sea levels and other climate change on the coastal regions of Florida.



Figure 7. NOAA storm surge risk disaster visualization.

An important impact to note regarding environmental disasters in the Gulf Region is that Hurricane Irma also displaced Puerto Ricans and other Caribbean country residents, many of whom sought refuge in Florida counties. Such countries are extremely vulnerable in that they have large poor populations that are may become climate refugees due to likely increases in EWEs in this region. The effects of EWEs on poor populations can be seen in the aftermath of Hurricane Maria in Puerto Rico for instance. Due to their high vulnerability low resilience state, they are still without power in many regions. Therefore, these populations must be considered in future emergency preparedness efforts in Florida, as these refugees are vulnerable to further secondary displacement in the eye of future storms if unaccounted for. Assessing the risk and needs of pediatric populations within refugee and local undocumented populations living in Florida counties is beyond the scope of this manuscript, but should certainly be considered in future efforts to create equitable change in Florida.

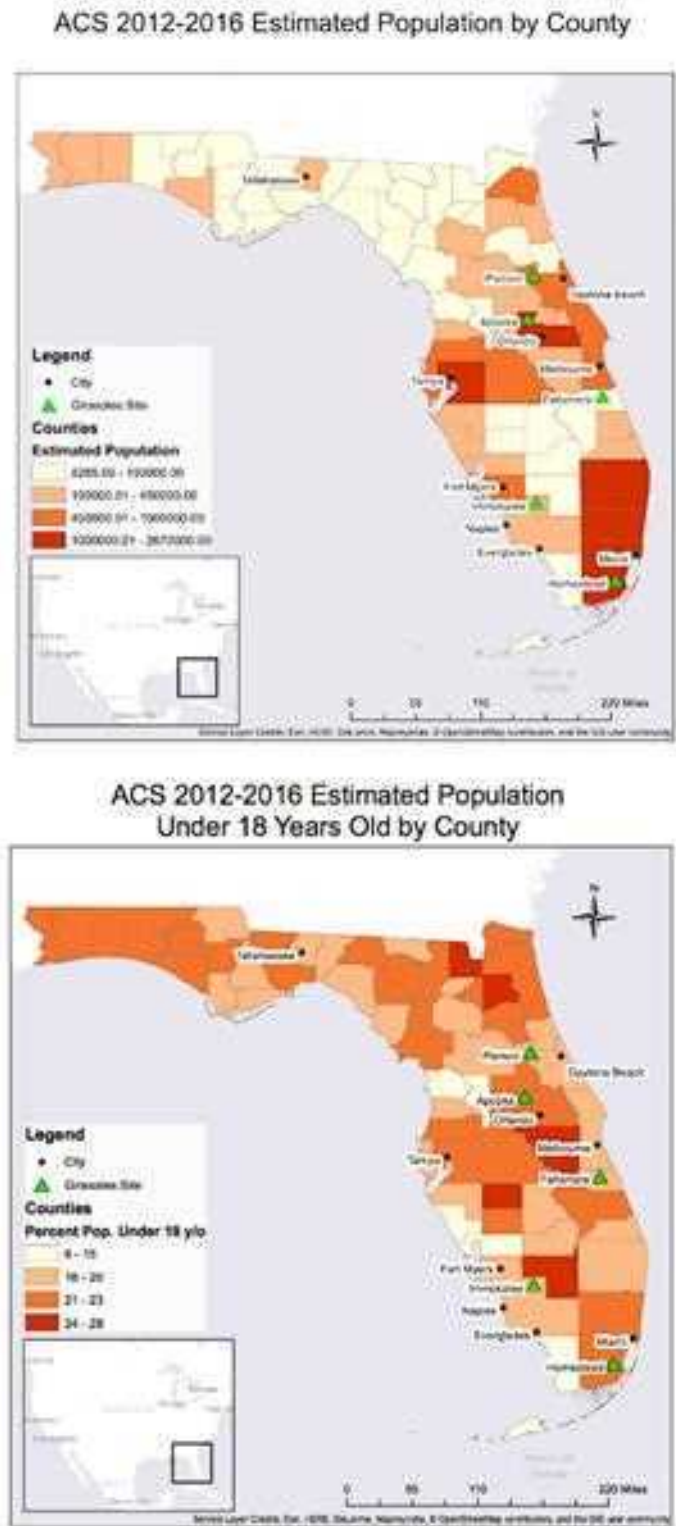


Figure 8. Florida population count choropleth by county (a. Top: Total population count, b. Bottom: Total pediatric population count).

Future directions will include a more intensive look at the demographic patterns suggested in our demographic analysis of Census data. Inland regions appear to make up a larger proportion of the State's vulnerable communities and proportional population of children, as ranked by the ATSDR's SVI. Detailed analysis needs to be performed on the risk factors for pediatric vulnerability and health outcomes related to environmental disasters in Florida counties. Specifically, a focus on risk factors relevant to the vulnerability of pediatric populations needs to be explored (see figure 8). Additionally, future efforts need to be made to incorporate migrant and refugee populations in Florida to better represent the whole population (including children) and gauge overall need across counties in Florida. Another future focus will be incorporating probabilistic modeling of climate change into our risk assessment, to provide a better picture of future risk in vulnerable communities, specifically considering the vulnerability of pediatric populations. This ideally will include a more comprehensive integration of hurricane hazard assessment with factors such as infrastructure quality, community resiliency indicators, and demographic risk factors that are sensitive to child health. We hope to accomplish these future aims through partnership with local organizations including researchers and advocates at the University of Florida, the Farmworker Association of Florida, and the Nell Hodgson Woodruff School of Nursing to gather original data for further analysis.

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CONFLICT OF INTEREST

None to disclose.

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Chapter 66

SOCIAL MEDIA AS A TOOL FOR BREAKING THE CYCLE OF CHILDREN'S ENVIRONMENTAL HEALTH DISPARITIES

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ABSTRACT

Social media plays a role in many current public health practices, although the details of online activity among children's environmental health professionals is unknown, which inspired this project. Twenty-five children's environmental health (CEH) professionals completed an online survey about their organizations' use of social media in promoting CEH and in addressing CEH disparities. The survey examined social media habits, measures of success, challenges, and communication strategies. Based on qualitative feedback, most indicated that social media supports the goal of their organization. Results indicated a range in online activity levels and several difficulties in using social media in professional settings. This project also probed whether or not CEH professionals focus their online efforts on vulnerable populations (minorities, low SES or those with limited education). A majority of respondents declared they do not focus their online efforts toward any particular population group. This findings of this project illustrate a need for further efforts on how to effectively utilize social media for public health communication to improve CEH and reduce CEH disparities.

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Figure 1. Factors that contribute to children's environmental health disparities (this project pertains to Compound Risk Factors and Personal Characteristics).

INTRODUCTION

Social media networking platforms such as Facebook, Instagram and Twitter give individuals the ability to “make connections by sharing expressive and communicative content,” [1]. Facebook and Twitter link organizations and diverse populations to share information through virtual communication [2]. Instagram allows individuals to share and search for photographs and videos online [2]. These platforms play an important role in everyday communication and connections between individuals and organizations. The use of such platforms as a resource for mass communication makes them very useful in the creation and dissemination of on-line sites that can reach and influence human behavioral interactions. The reach of such platforms makes them important for health communications and for public health research on health communications. About 44 million individuals use Facebook to communicate and browse online for posts about science and health-related areas [3]. However, use is not evenly distributed: there is an imbalance in the time spent on social media among different age ranges [4]; and Hispanics and African American are proportionally higher user groups than Caucasians of platforms such as Facebook, Instagram, and Twitter [5]. While these platforms could serve to promote children's environmental health (CEH) and to reduce CEH disparities, we need to explore ways to best use social media to reach those who are disproportionately affected by environmental health disparities due to risk factors such as limited educational services, limited social capital and limited health literacy. The cycle of environmental health disparities has many factors that could

adversely affect a children's health (see Figure 1). As children are more vulnerable and likely to be adversely affected by environmental toxins and stresses, it is important to emphasize the roles of two elements relating to disparities in this cycle which are the 'compound risk factors' and 'personal characteristics' (see Figure 1). This project addresses to these areas by attempting to understand how different organizations that focus on CEH, target audiences that are disproportionately affected by environmental health disparities.

To date, there has been very little research regarding CEH communication through social media, likely because the use of social media is relatively new in healthcare research and communication [6]. While social media may be considered an unconventional tool for health communication by some, there are many potential benefits to its use for health communication, such as more shared information between the healthcare professionals and the general public, more peer support, a role in advocacy, and the potential to influence government policy [7]. According to the Children's Environmental Health Network (CEHN), a national nonprofit working to protect children from environmental hazards, 73.5% of the 82 respondents to their 2017 Eco-Healthy Child Care Survey expressed interest in education to promote awareness about environmental hazards that significantly affect children [8]. Paired with the sparse literature about best practices for social media messaging and CEH, this interest in education provides a stimulus for new research into how social media can help advance CEH. This project analyses a survey of a set of CEH stakeholders to assess their use of social media with regard to promoting children's environmental health literacy.

OUR STUDY

Survey participants were individuals involved in CEH consisting of primary care physicians, leaders of children's environmental health centers in the US, environmental community group leaders, and child care professionals. This group was chosen to provide a diversified perspective on the current use of social media in local communities and public health centers. Participants were drawn from lists of individuals connected to the Pediatric Environmental Health Specialty Unit (PEHSU) network and Children's Environmental Health Centers (CEHC). The PEHSU's are regional centers throughout the USA as national network of healthcare providers and academics with a mandate to provide knowledge and awareness about children's environmental health hazards to health care professionals and the public and offer effective and practical ways to combat these hazards [9]. The CEHC's are a nationwide set of academic based programs that conduct research focused on improving children's environmental health [10]. Both organizations make extensive contributions to knowledge and awareness of children's environmental health for a diverse set of communities.

A survey containing a mixture of open-ended and multiple-choice questions was developed (see Figure 2) exploring familiarity and functional use of social media in the work of these organizations. The survey was placed on Google Forms, a convenient and accessible survey platform. Respondents were given the option of completing the survey online or participating in a phone interview. The first and second sections of the survey sought basic details of the responding organization, and in the use of social media platforms. The third section used multiple-choice questions to inquire about target populations, and to record the

Break the Cycle Project Survey (Adults: Adults & Children's Environmental Health)

Please print your name, title, organization, address, phone number, fax number, email address, website URL, and other contact information at the bottom of this page. Please print clearly. If you are unable to print, please email us at info@breakthecycle.org.

Your email address: _____

Part I

What is the name of your institution, agency, organization, etc? _____
 - Most relevant link: _____

Where are you based? (City, State) _____
 - Most relevant link: _____

What social media platforms does your group use to publicly communicate about children's environmental health issues and/or issues? (Mark all that apply.)

- Facebook
- Instagram
- Twitter
- YouTube
- Email Group
- Podcast(s)
- Print material (booklets, brochures, etc.)
- Blog website

Part II

Does your group attempt to reach particular ethnic groups or racial/ethnic groups? If yes, which of the following groups do you attempt to reach? (Mark all that apply, or select the two options if your answer is both.)

- We do NOT target any group in particular
- Asian
- Black/African American
- Hispanic or Latino

How active is your group on social media?
 Once a month or less
 A few times a month
 Once a week
 Once a day
 Multiple times every day

Does your group measure social media outreach success?
 Number of tweets/followers:
 Number of likes/views
 Number of retweets/reposts
 Number of participants at in-person events

Does your group use any particular social media strategies?
 No, we do not use any particular strategies
 Live! Twitter chat
 Facebook to Instagram Live! video format
 Links to videos
 Social media challenges

Can describe some challenges your group has faced in successful social media outreach.
 Limited content to share
 Limited financial resources
 Limited staff capacity/time
 Difficult to engage with audience
 Difficult to increase followers/viewers
 Difficult to understand how to use different platforms
 Technological difficulty

Native Americans and Alaska Natives
 Native Hawaiian or Other Pacific Islander
 White/Caucasian
 Other

Does your group attempt to reach people of any particular socioeconomic status (SES)? If yes, which of the following groups do you attempt to reach? (Mark all that apply, or select the one option if your answer is no.)

- We do NOT target any group in particular
- Household income < \$10,000/year
- Household income between \$10,000/year and \$20,000/year
- Household income between \$20,000/year and \$30,000/year
- Household income > \$30,000/year

Does your group attempt to reach people of a particular education level? If yes, which of the following groups do you attempt to reach? (Mark all that apply, or select the one option if your answer is no.)

- We do NOT target any group in particular
- High school or less
- Some college
- College
- Graduate training

Which of the following groups are included in your organization's membership or target population? (Mark all that apply.)

- At-risk/At-Disadvantaged (wealth protection)
- Educators (schools)
- General public
- Government (local, state, federal)
- Healthcare providers (physicians, nurses, etc.)
- Non-profit organizations
- Parents
- Researchers

Part IV

How do you see your group's work as breaking the cycle of childhood environmental health disparities? (e.g., My organization incorporates environmental justice into our mission and work). Please be as detailed as possible.

- Long answer text

Part V

Does social media help your group accomplish its goals?

- Yes
- No

Please describe why you answered yes or no to the previous question.

- Long answer text

Does your group offer non-social media based measures or materials to reach vulnerable/high risk populations?

- Yes
- No

Please describe why you answered yes or no to the previous question.

- Long answer text

Part VI

Would you or someone from your organization be willing to participate in a 15-minute interview (by phone or in person)?

- Yes
- No

If you answered yes, please provide your email and a phone number which we can contact you.

Figure 2. Components of the survey given to healthcare providers and community partners.

FINDINGS

Of the 30 individuals contacted, 25 responses were received between February 20th, 2018 and March 14th, 2018 (response rate = 83%). Of these, ten were from Atlanta, Georgia, five were from Washington, DC, three from Illinois, two from California and one each from Alabama, Mississippi, New York, North Carolina and Tennessee (see Figure 3).

The first part asked about the use of social media and, as displayed in Figure 4, the most commonly used social media platform was Facebook (21/25; 84%). A total of 19 out of 25 respondents reported using a blog or website; 15 reported using Twitter, nine reported using Hootsuite (a social media platform which allows users to disseminate and track content on multiple social media channels simultaneously); and nine reported using Instagram. Twenty-two organizations reported using print sources, such as flyers and brochures, to inform their audiences.



Figure 3. Geographic representation of survey respondents.

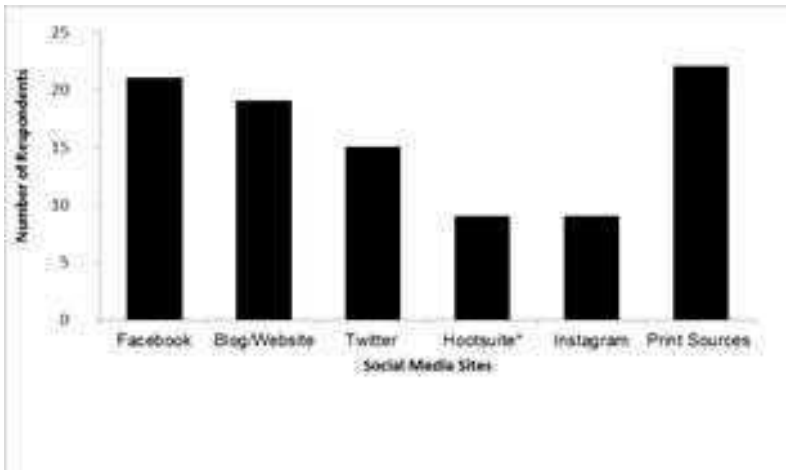


Figure 4. Most used social media sites by survey respondents.

Part II of the survey asked respondents which demographic groups they target through social media (respondents could select more than one group on the survey). Fourteen of the 25 reported not targeting any particular group. Ten reported that their organizations attempt to reach a Black/African American audience, five targeted the Hispanic/Latino audience, four reported targeting Asian populations, and three organizations (or fewer) each marked Native American/Alaska Native, Native Hawaiian or Other Pacific Islander, and White/Caucasian. The survey also questioned respondents about whether they target particular socioeconomic (SES) groups; 18 out of 25 reported not targeting any specific SES. Four respondents reported trying to reach people with an annual household income of \$20,000 or less. Respondents were also asked to identify the targeted education levels they sought to reach (identifying as many as applied); 16 of 25 reported not trying to reach any particular education level in their audience. Eight reported targeting those with a high school education or less with some college or college education; one organization focused particularly on those with some college or college education. A majority of respondents marked the following in their organization's stakeholder or target population: advocates, educators (health promotion and school), general public, government (local, state, federal), non-profit organizations, parents, and researchers.

Part III of the survey focused on gauging how the organizations use social media. To the question 'How active is your group on social media?', six organizations reported using social media once a day and six others reported social media activity a few times a month. Others ranged broadly from never using social media to using it multiple times a day. To the question 'How does your group measure social media outreach success?' 18 out of 25 indicated they refer to the number of 'likes,' reactions to an online post, and/or views; 16 used the number of new online followers as a marker; and 11 considered the number of re-posts or re-tweets, as indicative of an increase of online recognition. Ten respondents considered the number of people at in-person events, as opposed to online activity, as a marker of success. Six reported not measuring success; some even acknowledged that they are unsure how to do so. To the question 'Does your group use any particular social media strategies?' 16 of the 25 individuals reported not utilizing any strategies. Of those who do use specific strategies, six reported posting links to videos and others include 'live' features, such as Twitter chats, and Facebook or Instagram videos which are real-time 'conversations,' either posts on Twitter in a question and answer format, or 'Live' video on Facebook or Instagram which allows people to live-stream themselves and answer questions that are sent by viewers, contests and giveaways, e.g., "Share photos of your local parks and greenspaces using the hashtag #gogreenATL to be entered in our iPad raffle," and referring to popular hashtags.

The last question in Part III of the survey asked about challenges respondents face in using social media. Eighteen reported limited staff capacity and time, ten cited limited financial resources, and seven reported difficulty with increasing followers and viewers. Other challenges that respondents faced, though less frequently reported, included difficulty engaging with the audience, limited content to share, difficulty understanding how to use different platforms, and public affairs oversight.

Part IV of the survey allowed individuals to share how they see their group's work addressing the issue of CEH disparities. Many work for organizations that strive to address underserved communities through social media, in addition to in-person events. Some referred to social media as a medium for direct participation and citizen science, while others use media-based learning modules for environmental justice content.

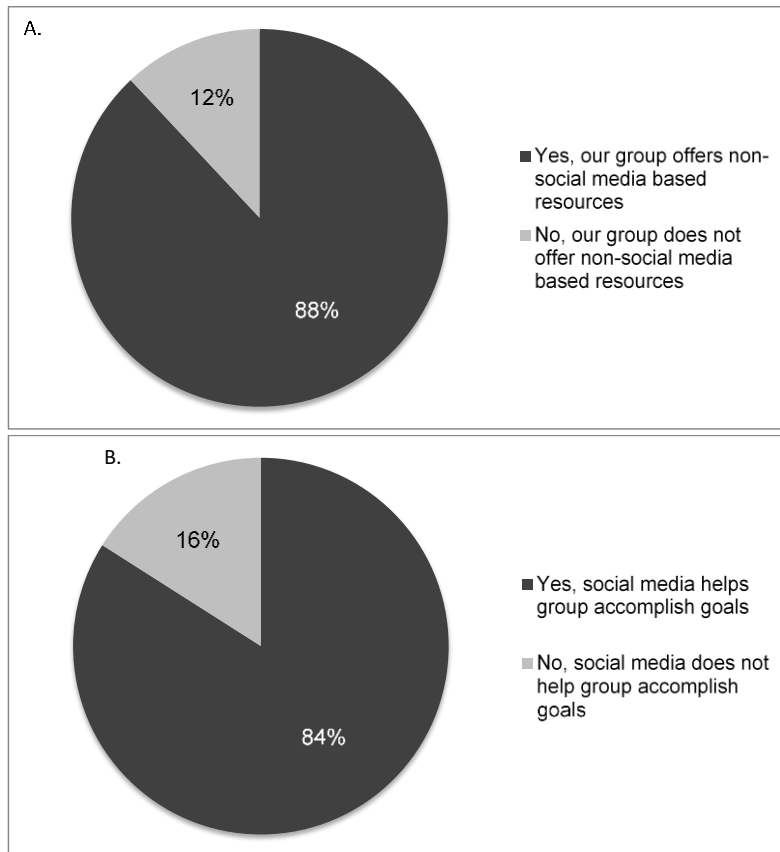


Figure 5. Survey results of social media use and effectiveness. (A) Responses to the question, "does your group offer non-social media-based resources or materials to reach vulnerable/high risk populations?" (B) Responses to the question, "does social media help your group accomplish its goals?"

Part V sought to ascertain how respondents see social media in helping their organizations accomplish their goals and queried whether respondents offer non-social media-based resources to reach vulnerable populations. Eighty-four percent, 21 individuals, responded 'Yes, social media helps my group accomplish our goals', as indicated in Figure 5. Respondents were then asked to describe why they answered yes or no. According to those who responded positively, meeting their goals was accomplished by spreading awareness, engaging people, contributing to advocacy work, tightening their message and broadening their reach. For the four respondents who did not view social media as helpful in accomplishing their organization's goals, they pointed to a lack of community engagement with their organization's online media.

To reach vulnerable or high-risk populations who may lack access to electronic media, 88% reported offering non-social media-based resources, as shown in Figure 5. Those include print materials, meetings and workshops, and training, which provide additional educational access and support, according to their free response answers. This finding may have implications for the efficacy of social media in reaching vulnerable populations, creating a need to probe more effective engagement strategies.

DISCUSSION

Education, advocacy, and engagement all can be promoted through social media, and these activities are congruent with the goals of CEH organizations. The purpose of this survey was to gauge how CEH organizations use social media, to ascertain the benefits and challenges they experience in their social media activities, and to determine whether they focus on reaching vulnerable populations. A total of 25 individuals, from different organizations in the United States who work in various capacities addressing CEH, completed our survey.

Given that respondents generally reported positively that social media helps their organizations accomplish their goals, social media activity clearly serves a valuable purpose as a form of public health communication. However, six out of 25 (almost one quarter of the respondents) reported not measuring social media outreach success. The discrepancy between a large proportion pointing to the benefits of social media and the individuals who declared they do not evaluate social media outreach success is concerning. Without measuring the effects of social media activity, some may overstate or underestimate the true benefits, and opportunities for improving social media use may be missed.

Facebook, Twitter, Instagram, Hootsuite, blogs and websites were used by most of the respondents. The reported levels of activity varied greatly, ranging from posting once a month to multiple times a day. While the results of this survey suggest there is a high rate of social media use among organizations that work toward improving CEH, there are other groups working in public health who have not yet engaged with online social media. In 2012, a study found that only 60% of state public health departments reported using at least one social media account, suggesting, “social media use by public health agencies is in the early adoption stage” [11]. In the six years since those findings, the number of public health organizations participating in social media outreach for public health communication has likely increased as social media platforms have expanded and become more popular and more accessible. Given the growing popularity of social media among all age groups, races, and genders [12], it will be important for organizations with a public health mission to consider the use of social media for outreach along with other traditional approaches.

Over half of the survey respondents confirmed their organizations do not have a formal social media strategy. Further research may elucidate the varying levels of efficacy in different social media strategies. For example, comparing knowledge and attitude changes between two different social media campaigns might offer evidence to better guide CEH professionals’ work on social media. Additionally, considering the high percentage of respondents (88%) who indicated they offer non-social media-based resources to reach vulnerable or high-risk populations, another potential point of improvement lies in making education through online and social media more accessible for all. For example, more concise and plain-language content can be helpful for reaching less educated individuals.

Despite the high number of respondents offering non-social media-based resources for vulnerable populations, most respondents did not target any particular education level, SES, or ethnic group on social media. For those who did report targeting specific groups, the pattern tended toward focusing on typically more disadvantaged communities. As a result of not focusing on vulnerable communities, organizations may not effectively reach such populations. By developing a comprehensive social media strategy that includes culturally

relevant, plain-language content, dedicating appropriate staff and resources, and using analytics to evaluate the effectiveness of the outreach, organizations can better position themselves to address vulnerable populations and break the cycle of CEH disparities.

Eighty-nine percent of American adults use the internet [13], and the figure is only increasing. Now more than ever individuals are and will continue to be empowered to learn, challenge, and act, given almost nine-in-ten have constant access to information and can express themselves at the push of a button. ‘Science for the People’ was a slogan adopted by activists in the 1970s. ‘Science by the people’ is a more inclusive aim and is becoming a distinctly 21st century phenomenon” [14]. The benefits of widespread access to social media and the internet enables collaborations between citizens and researchers along a continuum of public engagement in scientific research. For example, a scientist or research team may have a specific focus of interest and engage the community to help develop research questions, design a study, and collect data. In contrast, citizen science efforts are driven by community concerns, where community-initiated projects may involve a partnership with an academic or research institution, and both parties work together to collect and share data. The goal is to address a community concern through collaborative research, and to translate the research findings into public health action that benefits the community [15].

It is expected that the use of social media in health communication and in research will evolve and, in the process, serve to improve the health and wellbeing of the general population and for the purpose of this project, advocacy to improve CEH and help to reduce CEH disparities.

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Chapter 67

AN ASSESSMENT OF ANTI-VACCINE: REASONS AND RESPONSES

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ABSTRACT

The Wakefield study on measles-mumps-rubella (MMR) vaccine and autism with the subsequent spread of misinformation by various media outlets have resulted in an increase in vaccine refusal by parents and a reemergence of vaccine-preventable diseases, which we see now with the spread of measles, which has resulted already in several deaths. The rise of echo chambers on social media has made it difficult to reach members of the anti-vaccine movement to change their beliefs about vaccines, even when presented with quality scientific evidence. If the trend does not reverse on its own, the situation may escalate to a point where immunizations must be made legally required to protect herd immunity. Simultaneously, we must work to educate upcoming generations about the Wakefield study, its fallout, and the dangers of vaccine refusal so that they will be better equipped to protect themselves and their children from the ramifications of misinformation.

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INTRODUCTION

As St George's University, Master of Public Health (MPH) program celebrates its 20th anniversary in 2019, there have been significant gains and challenges to the public's health. The old adage, At the end of this second decade of the 21st century, one of the main tools of public health, vaccination, is having an anti-vaccination experience. Lost memory of diseases prevented by vaccines and misinformation has led to an increase in vaccine refusal. This has resulted in the return of many cases of preventable communicable disease, including measles. This editorial will explore how the anti-vaccine movement came about and what needs to be done to address this issue to prevent it from recurring in the future.

IMMUNIZATION

Immunization is the world's most cost-effective preventative health intervention. Immunization prevents 2-3 million deaths per year and vastly reduces the burden of disease around the globe. Therefore, enhancing access to immunization is a top priority for every nation and is, "crucial to achieving the (World Health Organization's) Sustainable Development Goals [1]." There are many examples of the successes of vaccination: accelerated immunization programs decreased the worldwide mortality rate of measles by 84% from 2000 to 2016; meningitis A epidemics have been nearly eliminated in Africa after introducing the vaccine to the region in 2010 and "the world is closer than ever to eradicating polio" [1].

However, in 1998, Dr Andrew Wakefield published a paper in *The Lancet* that suggested a link between the measles-mumps-rubella (MMR) vaccine and autism. His study prompted the scientific community to spend millions of additional research dollars trying to validate his findings. In the meantime, news of a potential link between autism and vaccines spread around the world. Dr Wakefield's paper was used as ammunition in lawsuits against vaccine manufacturers and he was allegedly paid a sum of \$674,000 by lawyers who profited from these cases [2]. As a result, parents increasingly turned down vaccinations for their children and outbreaks of these vaccine-preventable diseases began to surface in numbers not seen since the vaccines were introduced decades beforehand.

Dozens of additional studies have been conducted in the years since the initial report and not a single study has found a link between autism and vaccinations, thoroughly debunking Dr Wakefield's original claims. This includes a 2012 study that was, "a review of 27 cohort studies, 17 case control studies, six self-controlled case series studies, five time series trials, two ecological studies, and one case cross-over trial covering over 14,700,000 children [3]." In 2004, 10 of the 12 original authors of that paper issued their own retraction, stating that, "We wish to make it clear that in this paper no causal link was established between MMR vaccine and autism as the data were insufficient [4]." Richard Horton, *The Lancet's* editor, "said he should not have published the study and that Wakefield's links to litigation against the manufacturers of the MMR vaccine were a 'fatal conflict of interest [4]." Despite this, *The Lancet* took until 2010 to officially retract the original paper, after 12 years of misinformation spread around the world. The chief of infectious diseases at the Children's Hospital of Philadelphia, Dr. Paul Offit, gave an opinion shared by many in the medical

community that, “This retraction by the Lancet came far too late. It's very easy to scare people; it's very hard to unscare them [4].” In other words, the damage was done and we are currently faced with a generation of parents who refuse to vaccinate their children, because of a fabricated link printed over 20 years ago.

VACCINES CAUSE AUTISM: ORIGIN AND PROPAGATION OF THE MYTH

Dr. Wakefield and his falsified report have already been introduced, but the spread of the myth he created required more than just a single paper. There is no doubt that his study, which proposed a link between autism and the MMR vaccine based on a case report of 12 children was dubious science. As it was a case report, every child in the study had autism and since the MMR vaccine was widely available in Great Britain at the time, it is likely that most of them had received the vaccine. Not only does the size of the study call its significance into question, but it is typically accepted that only a randomized clinical trial can truly establish causation.

So, what happened then? How did this study become so widespread and erroneously accepted as fact? For one, his study happened to be published around the time when the internet was beginning to take shape. Millions of people were starting to explore it for the first time and media outlets were still trying to figure out how to make the best use of it. Additionally, “Wakefield has been given ample opportunity either to replicate the paper's findings or to say he was mistaken. He has declined to do either.” Other studies were done using the Wakefield paper as a reference. One of these was the Rimland/McGinnis paper, which was published in the journal, *Lab Medicine*, in 2002. “The Rimland/McGinnis paper, citing more than 100 other papers, including Wakefield's 1998 paper, established connections between “patterns” of autism and immune response, as well as the timing of the vaccines.” This paper was not retracted by *Lab Medicine* until 2018! All these factors came together at the perfect time to make this story one of the first to go ‘viral’.

“Wakefield was at the center of a media storm about the MMR vaccine, and is now being blamed by journalists as if he were the only one at fault. In reality, the media are equally guilty. The media repeatedly reported the concerns of this one man, generally without giving methodological details of the research, either because they found it too complicated, inexplicably, or because to do so would have undermined their story.” Many of the journalists reporting on the story were not trained in the concepts of ‘association versus causation’ and their reporting reflected their lack of knowledge on the difference between the two. Mark Zweig, a medical doctor who also teaches reporters how to cover medical research, believes that, “an important part of reporting results of research in health news lies in attention to language that may in subtle ways imply cause-and-effect relationships, where the underlying study design does not warrant such language. We urge health care journalists to be mindful of when causal language is warranted by the study design and when it is not [9].” In other words, the media's lack of skill in interpreting medical research caused them to write stories that were factually incorrect. The rise of the internet and social media allowed these stories to spread like wildfire.

THE ROLE OF CELEBRITIES AND SOCIAL MEDIA

The internet and social media have created an environment where everyone is connected, all the time. It is possible for someone to use Twitter to engage in a conversation with their favorite celebrity or to share a story on Facebook and have it go instantly to their friends... and their friends' friends... and so on. This has brought us to an era of communication and information sharing that is unprecedented in all of human history. Unfortunately, much of this information is shared without fact-checking and misinformation runs rampant. It can also lead to the proliferation of certain biases simply because some people are more vocal on social media than others. The proponents of the anti-vaccine movement tend to be more active on social media regarding this issue than people who are pro-vaccine, for example, including celebrities.

Perhaps the most well-known celebrity member of the anti-vaccine movement is Jenny McCarthy. After her son, Evan, was diagnosed with autism she made numerous well-publicized statements on social media, the Oprah Winfrey show, and in Time Magazine that are not based on actual scientific data and have been very damaging to the medical community's efforts to maximize vaccinations. Here is a selection of some of her comments:

To Time Magazine: "I do believe sadly it's going to take some diseases coming back to realize that we need to change and develop vaccines that are safe. If the vaccine companies are not listening to us, it's their fault that the diseases are coming back. If you give us a safe vaccine, we'll use it. It shouldn't be polio versus autism."

To Oprah: "The University of Google is where I got my degree from... And I put in autism and something came up that changed my life, that led me on this road to recovery, which said autism—it was in the corner of the screen—is reversible and treatable."

On Social Media: "People are also dying from vaccinations. Evan, my son, died in front of me for two minutes. You ask any mother in the autism community if we'll take the flu, the measles, over autism any day of the week. I think they need to wake up and stop hurting our kids. Without a doubt in my mind, I believe that vaccinations triggered Evan's autism."

The power of celebrities lies in the fact that their fans take actions based on opinions that are shaped, in part, by their commentary. Jenny McCarthy's comments have influenced many people who share her beliefs to refuse vaccinations for their children. These people then go onto their social media channels to further propagate their beliefs.

THE MYTH'S EFFECT ON VACCINE-PREVENTABLE DISEASES

The Wakefield paper, outspoken celebrities, social media have all resulted in the anti-vaccine movement, which has culminated in a resurgence of vaccine-preventable diseases. Measles, mumps, rubella, pertussis, and polio have all been declared either eliminated from the Americas or vastly reduced since the introduction of their respective vaccines. However, all of them have had numerous outbreaks in the western hemisphere in recent years due to a combination of migrating travelers who carry the disease and waning herd immunity due to lower vaccination rates.

CONCLUSION

The Wakefield study and the subsequent spread of its misinformation by various media outlets have resulted in an increase in vaccine refusal and a reemergence of vaccine-preventable diseases. The rise of echo chambers on social media has made it difficult to reach members of the anti-vaccine movement to change their beliefs about vaccines, even when presented with quality scientific evidence. If the trend does not reverse on its own, the situation may escalate to a point where immunizations must be made legally required to protect herd immunity. Simultaneously, we must work to educate upcoming generations about the Wakefield study, its fallout, and the dangers of vaccine refusal so that they will be better equipped to protect themselves and their children from the ramifications of misinformation.

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Chapter 68

DEPRESSION IN THE SKIES: AN OCCUPATIONAL HEALTH ISSUE AMONG PILOTS

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ABSTRACT

Depression is a global concern that affects individuals from every walk of life. It has been shown to have potentially significant impacts on a person's judgement, cognition, and motor function. This is of particular concern if an individual requires a high degree of mental and physical function in order to effectively perform their job and minimize risk to others. In the airline industry, pilots are responsible for multimillion-dollar aircrafts and the transportation of millions of passengers every year. However, recent events such as the crash of Germanwings flight 9525 have reinforced the notion of a proactive mental health screening among pilots. The studies reviewed here demonstrated that, although there are FAA protocols in effect for subjective interpretation of mental health status in airline pilots during a routine medical clearance, an underreporting of depression or depressive symptoms were present. This, in combination with associated risk factors such as stress and fatigue from extended hours and early shift work, household disputes, significant life stressors, and family history of depression create an environment that compromises flight safety. There is a need, therefore, to further investigate the causes of the underreporting of depressive symptom to encourage pilots to seek early and appropriate treatment.

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INTRODUCTION

Depression is a serious medical condition that affects a person's mood, cognition, and physical functioning [1, 2]. Globally, the World Health Organization has estimated that in 2017 over 300 million people globally are suffering from depression, affecting all walks of life, and is on the rise [3]. The severity of this condition, it fact could have significant impacts on lifestyle and job performance [4]. This becomes particularly concerning if those suffering have significant responsibility for human life and safety as part of their job responsibilities. Within the airline industry, pilots are responsible for the lives of hundreds of passengers per day while controlling multimillion-dollar equipment. According to the International Air Transport Association (IATA), airlines carried 4.1 billion passengers in 2017, an increase of 7.3% over 2016 [5]. There have been several recent events that have highlighted the severe impact of mental health issues in pilots including the crash of Germanwings Flight 9525 on March 24, 2015 [4, 6, 7]. More frequently, effects of depression among airline pilots contribute to less catastrophic events but still have the potential to lead to compromises in safety if left unchecked [4, 8].

Currently, there are protocols for regular medical examinations in order to screen pilots for mental health issues. This involves a short series of questions and observational data by the medical examiner [8, 9]. However, some articles suggest that current protocols may not be sufficient to adequately identify and manage depression currently present in airline pilots [8]. This paper aims to review the current literature for the risk factors for depression in airline pilots.

METHODS

The Federal Aviation Administration (FAA) provides very specific guidelines for aviation medical examiners to use when clearing pilots for flight. These guidelines involve regulations, medical history, medical examinations and disposition [9]. To receive a certification, a candidate must not have any established history of severe personality disorders that cause an individual to display impulsivity or poor judgement, psychosis, bipolar, substance dependence (or demonstrating abstinence during the preceding two years), substance abuse within the previous two years, and any other medical or psychiatric condition that would inhibit the pilot from safely performing their duties at the judgement of the medical examiner [9]. The medical examiner is not required to conduct a formal psychiatric interview, but must instead 'formulate their evaluation based on medical history, demeanor, and information gathered from a genuine curiosity into the patient's life [9]. While it is critical for pilots to be truthful with their examiner, both for maintaining the integrity of the individual as well as receiving necessary treatments, these conditions could jeopardize their chances for obtaining their medical clearance and maintaining their career. Therefore, underreporting of mental health conditions is likely given these negative consequences [7].

DEPRESSION PREVALENCE AMONG PILOTS

According to the American Psychiatric Association (APA), there are very specific criteria required to diagnose major depressive disorder. These include depressed mood, anhedonia, disturbances in sleep and eating behaviors, psychomotor retardation, lack of energy, poor concentration, and suicidal ideations [10]. A survey in 2016 noted that the rate of mental health issues among airline pilots are similar to that of the US population [7, 8]. In his cross sectional survey, Wu et al. [7] received completed Patient Health Questionnaire (PHQ-9) information and determined that 12.6% of pilots studied met the depression threshold, and 4.1% of pilots reported suicidal thoughts. The FAA has stated as of December 31, 2018, there are 99,880 commercial pilots in the US, this number equates to 4,095 commercial pilots with suicidal thoughts [11].

RISK FACTORS ASSOCIATED WITH DEPRESSION

Although there are no specific causes that can be attributed to depression, there are several risk factors that must be taken into consideration. Generally, medical examiners are guided to determine certain aspects of one's medical history in order to determine risk for depression [9]. The APA denotes first-degree family members with major depressive disorder, adverse childhood experiences, neuroticism, and stressful life events as significant to increasing one's risk to developing depression [2]. Stress and fatigue have been found in multiple studies to have a significant impact on the development of depression among pilots [4, 8, 12].

One cross-sectional study found that pilots who experienced longer work hours per week (41 to 45 hours) were twice as likely to develop depression and anxiety than those with fewer work hours per week (less than 25) [4]. Additionally, the presence of early morning shift work has been demonstrated to significantly contribute to increased levels of fatigue and stress [4, 13]. Bostock and Steptoe [13] found that shift work that required waking prior to 0530h contributed to increased amount of the stress hormone as a response to awakening as well as an overall increased amount of cortisol throughout the day. A cross-sectional study by Widyahening [14] interviewing select airline pilots during their medical examinations confirmed the above findings as well as noting that household tension also contributed to overall stress levels and thereby increased risk for depression.

ANTIDEPRESSANT USE IN AVIATION

Antidepressants such as selective serotonin reuptake inhibitors (SSRIs) are commonly used to treat those suffering from depression [15]. However, the FAA was reluctant to grant pilots the use of these medications while on duty primarily due to the underlying medical condition that it was treating [16]. However, on April 5, 2010, the FAA removed this restriction and allowed the use of antidepressants for active pilots. Recent studies into fatal injuries of airmen determined that there is no correlation between SSRI use and flight safety [16]. While a 2016 article by the American College of Physicians recommends both

pharmacologic and cognitive behavioral therapy as effective approaches to treat depression [15], a 2014 statistical survey by the FAA determined that only 0.09% of those seeking certification or recertification that year applied for antidepressant medication use [17].

DISCUSSION

300 million people across the world and currently increasing. This review demonstrates from the studies of Wu et al. [7] that the prevalence of major depression among airline pilots is 12.4% with 4.1% of the sample population reporting suicidal ideations. As this cross-sectional study was based on self-reported data, it is possible that these results be an underrepresentation of true prevalence within the population. Therefore, the medical community must be aware that many active pilots are currently experiencing symptoms that are diagnosable for depression and putting their passengers and crew and increased risk for catastrophic accidents. The underreporting may be due to the stigma associated with mental illness, the onerous process of getting adequate mental health therapy once a diagnosis has been made, or the threat of negative consequences to one's career if depressive symptoms were ever identified [7, 8]. In order for those suffering from depression symptoms to seek treatment, they must first be encouraged that help-seeking behavior will not have negative consequences on their career. Reducing this stress will allow pilots to seek the help they need in a timely manner in order to prevent potentially fatal accidents as a result of impaired judgement or motor functioning.

Antidepressants

The data demonstrated in this review illustrates that there are effective treatments available for depression that do not inhibit a pilots ability to safely operate an aircraft. This includes both cognitive behavioral therapy as well as pharmacological therapy. The process for acquiring approval for antidepressant use while on duty is still arduous despite the research demonstrating minimal risk of flight safety with use of these medications. A reevaluation of the current FAA clearance protocols may be warranted in order for pilots experiencing these depressive symptoms to begin the therapy they need to recover. Additionally, it is interesting to note the differences between the amount of SSRI approvals granted in 2014 by the FAA (0.09%) to pilots seeking medical certification and the percentage of pilots meeting threshold for depression (12.6%) in the 2016 study by Wu et al. [7]. As SSRIs have been allowed by the FAA since 2010, further study is required to better understand the discrepancy between these values.

Risk Factors

There are many known risk factors that have been noted to significantly contribute to the development of depression among pilots. Notably, high occupational stress from increased workloads have been recognized to be a predisposing factor for depressive symptoms. Fatigue

from early morning shift work has been shown to further increase the amount of stress hormone in the body, both at the time of awakening and throughout the day, which ultimately cause an increase in stress levels. This effect is prominent within pilot populations as flights are commonly ranging from early morning to late evening and can cross multiple time zones during the flight. Therefore, although there are regulations currently in effect for shift work limits [18], it is important to keep in mind personal limitations that can be stress-inducing when scheduling extended work hours. Medical examiners must be able to identify other risk factors commonly associated with depression as described above. As such sensitive topics may take time to reveal due to the trust established between the pilot and the physician, it is therefore critical for pilots to be seen consistently with the same provider in order to establish the continuity of care necessary for building a trusting relationship.

CONCLUSION

In conclusion, mental health within the aviation industry is well established and is currently an integral component of the pilot medical certification. However, with recent events such as the crash of the Germanwings flight 9525, the medical community has a continued obligation to improve our understanding of mental health and depression in pilots. This review demonstrates that, though there are guidelines in place to protect passengers and crew from potentially dangerous mental health conditions, much can be improved. Current data have shown predictable risk factors for depression as well as a trend of underreporting of depressive symptoms to authorities for fear of negative consequences to their careers. We must create an environment that we can encourage pilots experiencing these symptoms to divulge this information to seek help and ultimately protect the safety of the millions of passengers these pilots serve.

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Chapter 69

AN ASSESSMENT OF MENTAL HEALTH AMONG REFUGEE COMMUNITIES

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ABSTRACT

This chapter is a review of current literature and research focused on exploring the impacts of experiences, stressors, and stigma that contribute to mental health and mental illness being underprioritized in the population and within certain vulnerable communities. Specifically, it will be focused on studying various refugee communities, including Afghan, Vietnamese, and Syrian populations, to explain how unique stigmas are perpetuated and why a lack of health seeking behavior is seen utilizing the five hierarchical levels of influence within the Social Ecological Model (SEM): intrapersonal, interpersonal, and combining community, organizational, and societal levels. The paper further examines a few current interventions implemented in different countries that target the different levels of influence on mental health stigma perpetuated within the SEM. In addition, it will show that the lack of resources contributes to only part of the issue of limited health-seeking behavior seen within the refugee community-at-large. Lastly, recommendations in support for further efforts in mental health to reduce mental illness with implementation and future research in developing possible interventions will be addressed in attempts to develop more effective and efficient ways to overcome the current barriers and stigma experienced within refugee mental health.

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INTRODUCTION

Mental health, and subsequent mental illness, is a major public health issue today that is underdiagnosed undermanaged on a global scale. Mental health-related issues, like depression, are the leading cause of disability worldwide and is a major contributor to disease burden [1]. Individuals continue to feel stigmatized and isolated from seeking care, especially within the refugee community [2].

By utilizing an ecological model framework, mental illness can be demonstrated on a multilevel system of mutual interaction and influences that contribute to its perceived worth and importance. In particular, the Social Ecological Model (SEM) of health delves into the intrapersonal (individual belief and cognition), interpersonal (family and peers), organizational (community health centers and medical providers), community (identity factors of ethnicity and culture), and societal levels (policy and government) have been explored to better understand the beliefs and barriers of mental health acceptance and health-seeking behavior within this population. Research has indicated that various interconnected factors in the mismanagement of refugee mental health continue to occur and a need for targeted interventions must be implemented if optimal mental health outcomes are to be attainable [2].

MENTAL HEALTH

Numerous studies have been conducted on mental health to assess the current global and national impacts, stigmatization, and interventions that are correlated with the treatment of mental illness, especially within refugee communities. The intricate involvement of multiple factors within the SEM framework has been used within this literature review to describe the barriers and global interventions developed in attempts to improve mental health outcomes for refugees.

DISCUSSION

The most widely accepted definition of health encompasses the complete physical, mental and social wellbeing despite the absence of disease or infirmity [1]. As a result, mental health is an essential piece in achieving optimal health. The burden of mental health and resulting illness is significant and debilitating for an individual and community-at-large [2]. Mental illness has detrimental effects on multiple aspects of health including social and physical wellbeing. Internationally, 25-33% of the population report having at least one mental illness [1]. Within the United States, mental illness affects one in five adults in a given year [3]. About \$193.2 billion in lost earnings are estimated per year due to mental illness [4]. Research [5, 6] has also shown that neuropsychiatric disorders are the leading cause of disability in the U.S. Mental health profoundly impacts an individual's ability to maintain physical health and participate in healthy behaviors [7]. These adverse health behaviors, as a result of mental illness, compromise an individual's ability to live a healthy life. People

suffering from poor mental health and mental illness have been shown to have higher disease and death rates than the general population [8].

Impact of Mental Illness: Refugee Communities

The Refugee experience is a unique situation where an individual has to flee their home due to a variety of compromising positions. Refugee communities end up developing a higher risk of poor mental health leading to illness due to the unique experiences they must endure in fleeing and relocating to a new area along with post-migration experiences within their host country [9]. Extreme conditions of civil war, fear of persecution, and forced displacement, as a result, negatively impact refugee mental health. In 2016, 65.5 million people worldwide were refugees, which has increased from previous years [9]. Pre-and post-displacement factors, such as human rights violations, trauma, and limited access to resource have been found to consequently leave refugees in emotional distress years and decades after resettlement [10]. Recent research [11], indicates that certain risk factors, such as the trauma load experienced by a refugee, affects the severity and likelihood of mental illness. Other research [12, 13] found that social determinants like continued poverty from the post-migration period have also severely impacted the evolution of poor refugee mental health, leaving a lasting effect beyond the resettlement period.

Nevertheless, specific mental illnesses including anxiety, depression, and PTSD were found to be most prevalent in the refugee community due to the to the accumulating circumstances and stressors unique to their experience [14, 15]. accumulating circumstances and stressors unique to their experience [14, 15].

Stigmatization of Refugee Mental Illness and Health Seeking Using SEM

Stigmatization is a social construct that has been an ongoing issue in acceptance and health-seeking behavior within individuals, communities, and societies overall. A couple of factors have been suggested to contribute to the unique stigma seen within refugee mental health and health-seeking behavior. Literature has been reviewed to understand how different levels within SEM influence and affect the overall stigma that is perpetuated within the refugee community as barriers to diagnosing and receiving treatment for mental health.

Intrapersonal level. In general, individuals suffering from mental illness struggle with motivation and behavior [8]. The impact of stereotypes, prejudice, and discrimination all negatively affect an individual's self-determination, beliefs and behaviors toward mental health [8]. This severely influences the intrapersonal level in analyzing the SEM framework, which accounts for non-modifiable (genetics and age) and modifiable characteristics (knowledge, attitude, behavior, and perception) within an individual [2]. One study [8] describes a Regressive Model of Self-Stigma to describe stigma development within an individual through four stages: perceived stigma, agreement with the stigma, self-application of the stigma, and the negative impact on self-esteem and self-efficacy which consequently affects the perception of health seeking. In an already disenfranchised community, refugees are especially susceptible to developing and perpetuating stigma beliefs resulting from

perceived discrimination due to lack of social support, cultural differences, socio-economic issue, and difficulty with asylum processing [16]. As a result, these experiences and circumstances negatively impact the intrapersonal characteristics in accepting mental illness and the likelihood of initiating health-seeking behavior. In further exploring the effects of mental illness stigma on seeking care within an individual, lack of knowledge, insight, and subsequent unawareness of one's mental state acted as a barrier to health seeking [8].

Interpersonal level. Beliefs and expectations within familial and social networks addressing mental illness differ within each ethnic group and refugee experience, but these groups still have a significant influence on mental illness progression and outcomes. Groups within the interpersonal level have been found to endorse stereotypes of mental illness, which results in discrimination amongst friends and family members with mental illness [8].

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Familial Influence. Mental health stigma perpetuated within families for some Asian groups, for example, is due to the collective perception that disabilities of mental illness reflect weakness or flaws within a family [8]. Guo et al. [17] found that Vietnamese American students from refugee families had a significantly higher mental health need when compared to European American students, but were less likely to seek mental health care due to cultural values of family responsibility and correlated shame.

Peer Influence. Another influential group within mental illness stigmatization is one's social network and peers. Social isolation was found to be a salient determinant of mental health amongst older refugees [18]. As a result, there was a higher risk of mental health issues encountered due to more difficulty assimilating to post-migration conditions along with pre-migration stressors within this population [18]. Displacement experienced within the refugee experience disrupts one's original social support in their home country and results in a new social dynamic where they are seen as marginalized and alienated by their peers in their host country [16].

Organization, community, and societal levels. Together, the organizational, community and societal levels of mental health go beyond an individual and their immediate social support network. As a result, they collectively have a more indirect effect on stigmatization that gets transferred down to the interpersonal and intrapersonal level of mental health beliefs and behaviors [2]. Research [16] suggests that the high mental illness rates and continued barriers of coping with mental illness collectively seen within Afghan refugee community are due to their inability to unify as a group to deal with the shame perceived from their new surroundings in the United States. This has contributed to their collective acceptance of being marginalized [16].

Within a health care system, changing demographics secondary to refugee relocation significantly impact medical management and perpetuate a perceived stigma felt within the medical field. The unique healthcare needs, inexperience interacting with the health system unfamiliar to providers, and physically identifiable differences leave providers susceptible to race-based stigma and discrimination in treating this population [19]. Many healthcare settings are not prepared to provide the patient-centered and culturally competent care required for this population, which leads to the under-diagnosing and limited awareness of

mental health in refugee patients [19]. This stigma transfers onto patients who are already hesitant to seek care and more reluctant to speak about mental health illnesses based on intrapersonal and interpersonal influences. Research [20] shows that mental health services in non-war stricken countries who see an influx of refugees are generally more poorly equipped to meet the complex needs of war refugees, as seen within the recent Syrian refugee community in Canada.

On a societal level, government and health policy play significant roles in perpetuating mental health stigma in the general population. Research [2] focused on understanding North Korean refugee attitudes toward mental illness as a group showed that, like other refugee communities, they face the same stressors of economic hardship, discrimination, cultural barriers, and family separation issues, which contributed to their high incidence rates of PTSD, anxiety, and depression [21]. The social restrictiveness and lack of resources available for the treatment of mental illness for the general public in North Korea perpetuated the resistance and lack of knowledge seen after the refugees settled within South Korea. Through strict government restrictions in controlling the nation's media, positive aspects of the society were only allowed to be reported as opposed to negative realities like mental illness [21]. Limitations in mental health services also perpetuate a nation's view of not prioritizing mental health in health policy. Research [22] showed that refugees within Canada, especially the youth population, were found to utilize the emergency department as the first point of contact for mental illness due to their perception and experience of having limited outpatient mental health services available.

SEM Targeted Approaches to Mental Illness Intervention

Some evidence-based services have been demonstrated to be effective in treating mental illness [8]. Globally, many nations have made efforts to implement targeted programs to address mental health across the different levels of the SEM. To target an individual's own stigma beliefs of mental health and health seeking, the World Health Organization [23] has developed a self- help program targeting changes in behavior and beliefs within the intrapersonal level while providing scalable mental health interventions within settings with limited resources faced in refugee post-resettlement. By educating and empowering the individual, they became more proactive in seeking help and accepting their mental illness rather than perpetuate the stigma that they previously believed. On an interpersonal level, research [24] showed the success of an integrated community and primary care approach with dedicated mental health services that had properly trained medical teams in cultural competency to alleviate the stigma and perceived discrimination felt within the refugee community when attempting to access care within a foreign country. Other research [20] targeting medical providers suggests the need of a transcultural approach to mental health services, targeting practice-based skills needed in trauma- informed care beyond cultural competency to meet the needs of refugees effectively. Lastly, a broader approach of achieving support from leadership and co-coordination within a national, regional, and district level of government was required in successfully addressing widespread stigma and low mental health awareness in refugee-origin countries like Ethiopia [25].

There is no doubt that mental health is a major influencer in the outcome of health for any individual. In addition to the debilitating effects it has on an individual's productivity, state of mind, and future health outcomes, there is an issue of mental health being underdiagnosed and undertreated globally [8]. This issue is magnified when focusing further on the vulnerable population of refugees that continues to grow to this day due to civil war and political persecution [20]. Refugee mental health is a multilayered and complex issue [20]. The unique stressors from violence, fear, trauma, and loss felt before and during relocation combined with the post-relocation experiences such as discrimination, resource instability, and cultural isolation from a sponsor nation contribute to their higher likelihood of mental illness [11]. As a result, it is not surprising to see higher rates of depression, anxiety, and PTSD reported within refugee communities [14]. Mental health needs for this community is greater and will continue to exceed the requirements of those from non-refugee origins because of the unique stigmatization and perceived marginalization experienced after refugees resettle within a sponsor nation [16].

Utilizing SEM, intrapersonal factors of one's own beliefs, education, and self-stigma toward mental health influences their likelihood to accept and eventually seek care [2]. By internalizing the negative perception of mental health illness and applying it to one's own beliefs, self-esteem and self-efficacy become compromised. Subsequently, the value and need for seeking care are no longer considered [8]. When analyzing the interpersonal level of family and social support, certain refugee communities which value family at a higher level stigmatized mental illness and endorsed it as a flaw that reflects upon their family's reputation resulting in lack of health seeking behavior [17]. Social support in refugee communities have also been lacking due to the nature of relocation and losing a pre-establish social population from their origin country. Research [18] revealed that older refugee communities are likely to experience social isolation and lack social support to encourage them to accept and seek care for their mental health showing the impact of one's social network. Lastly, analyzing organizational, community, and societal levels together demonstrated the broad influence of reinforcing stereotypical beliefs and marginalization seen within the public. Research [16] showed how the distress felt from an Afghan refugee community within California contributed to perceived discrimination and marginalization that perpetuated mental illness but stigmatized mental health and subsequent care within the sponsor community. Other research [19] showed an inherently biased and prejudice within the health system and healthcare providers due to lack of cultural competency and training to deal with this community. Lastly, societal impacts of government power controlling social perceptions, as seen in research [21] studying North Korea refugees in South Korea, reinforced the stigma and negative association of mental health that was accepted within this population. Interventions have been developed targeting the different levels of SEM involved with stigmatization and subsequent lack of health seeking behavior [2]. Various studies [20, 23-25] have demonstrated interventions involving self-empowerment programs, transcultural approaches in proper provider training, implementation of dedicated mental health services within the community, and ensuring adequate support from leadership in a variety of refugee communities to improve refugee mental health.

Mental health resources within health systems are inadequate on a global standpoint [1]. As a result, more interventions and resources need to be provided for all individuals who have a mental illness, especially those within high-risk populations like refugees. Unfortunately, there has been recent research [17] indicating that providing interventions within the refugee

community are not enough to effectively overcome refugee mental health stigma and lack of health seeking. Research [17] showed that increasing mental health resources was correlated to increase health seeking in European groups, but not within Vietnamese refugee communities, suggesting that other refugee-specific factors need to be considered in developing interventions [17]. Despite the existing evidence-based services for refugee mental health already used in practice, many refugees still do not seek the care they need because of the overwhelming influence of stigma [8].

CONCLUSION

Refugees are part of a vulnerable population seen within mental health and illness that are need of cultural competency, support, and acceptance amongst all levels within the SEM. To adequately understand the complexity of refugee mental health requires the acknowledgment and awareness that personal beliefs, family, social groups, communities, health care providers and national governments all perpetuate the stigma perceived in mental illness and health seeking.

As a result, there is no simple solution to providing mental health services for this community as each ethnic group and individual has a unique refugee experience. Research needs to target refugee-specific interventions that emphasize effective changes in stigma on a multitude of levels and promote cultural competency. Lastly, research needs to explore what specific aspects are required to be addressed by policymakers in developing health policy to better prepare a nation for the influx of refugee needs and refugee mental health care. By implementing better policies and laws to protect refugee rights and resources, it will inevitably cause a trickle-down effect on the community, family and individual level to hopefully promote mental health acceptance and health-seeking behavior.

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Chapter 70

**ENVIRONMENTAL ATRAZINE EXPOSURE
AND ENDOCRINE HEALTH:
IMPLICATIONS FOR RURAL COMMUNITIES
IN MIDWESTERN UNITED STATES**

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ABSTRACT

Pesticides are used daily in agriculture to limit the amount of unwanted plants and organisms in crops. Atrazine (6-chloro-N-ethyl-N'-(1-methylethyl) -1,3,5-triazine-2,4-diamine), a well-known and controversial pesticide used in the United States, is classified as a herbicide in the triazine family. Although its use is advantageous in the production of corn in midwestern United States, atrazine poses a threat to individuals due to its endocrine disrupting health effects and persistence in water systems. By extrapolating data from animal models, potential public health implications in humans can be hypothesized. The results of this review attempt to demonstrate the current gaps in the assessment of risk and potential health implications of continued atrazine use among individuals living in midwestern United States.

INTRODUCTION

Pesticides are subdivided into several broad categories, including insecticides, herbicides, biopesticides, rodenticides, and fungicides to name a few [1]. Herbicides are used specifically to limit the quantity of weeds in agricultural crops and are classified based on their effect on specific plant metabolic processes, such as lipid synthesis, amino acid synthesis, and growth

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regulator inhibitors, in addition to the chemical family each herbicide belongs to [2]. Atrazine, a widely used herbicide in the United States, is classified in the triazine chemical family and acts as a photosynthesis inhibitor by inhibiting the photosystem II, a system crucial for energy production in plants [3].

Atrazine was first registered for use in the United States in 1958 and since then, has played an important role in agriculture, specifically corn production in midwestern United States, as well as weed control in sugarcane, pineapples, sorghum, macadamia nuts, and evergreen trees [2, 4]. In 2016, approximately sixty million pounds of atrazine was applied to corn crops in the United States, with concentrated application in the midwestern United States, a region known as the “corn belt” [5]. In the state of Iowa, out of the 97% of herbicides applied to corn fields, 58% were applied with atrazine [6]. Commercial use of atrazine for corn production has shown to increase the yield and market value of corn, as well as play an environmental role in the reduction of soil erosion through conservation of tillage [4, 7]. Due to these facts, atrazine has proved to play an important role in the production of corn in midwestern United States.

Application of atrazine occurs through one of two methods: aerially via plane or helicopter or sprayers mounted on tractors [8]. The method of application depends on terrain, soil type, and crop; however, mounted sprayers are recommended due to lower rates of drift to surrounding areas [8]. For atrazine to properly elicit effects, it must dissolve in the liquid phase of soil to become activated, allowing for entry into roots of unwanted plants [2]. Following activation, atrazine has a half-life of approximately four months in surface water and demonstrates little biodegradation during this time period [2, 3]. However, when present in surface soil, atrazine shows little persistence due to interactions with sediments and demonstrates a significantly lower half-life, ranging from half a month to three months [2, 9]. Nonetheless, atrazine can be classified as persistent in the environment when in surface waters and poses a potential threat to the public health of surrounding communities.

Individuals can become exposed to atrazine through contaminated water systems via runoff from nearby fields, direct exposure during the application process, living near fields where atrazine was applied and digging in atrazine applied dirt [2]. Following exposure to atrazine, potential health implications becomes a grave concern for the surrounding population. In both human and animal models, the endocrine, or hormonal, system acts as the major target for atrazine [3]. The endocrine system is made up of the pituitary gland, adrenal glands, thyroid gland, parathyroid gland, and portions of the pancreas [10]. Atrazine has been shown to have direct implications on both the pituitary and thyroid glands through interference of circuitry and hormones necessary for growth and reproduction [10–13]. Despite compelling evidence regarding endocrine and reproductive disruption following atrazine exposure in animal models, little evidence remains for the carcinogenic effects in human populations, thus the International Agency for Research on Cancer has classified atrazine in Group 3, a group considered not carcinogenic to humans [14].

Concern surrounding the health implications of atrazine fuels the controversial discussion between its advantageous uses in agriculture and its disadvantageous effects in human health. In the European Union, atrazine is banned due to persistent water contamination and the evidence of atrazine acting as an endocrine disruptor [15, 16]. On the other hand, in the United States, atrazine is legal, but is considered a restricted use pesticide, meaning that only registered professionals can purchase and use it [2, 3]. Due to concern of implications associated with atrazine, several regulations and programs are in place in the United States to

monitor pesticides, such as the development of the Iowa Groundwater Protection Strategy directed by the Iowa Department of Natural Resources and the Pesticide Environmental Stewardship Program directed by the Environmental Protection Agency [3, 4]. Regardless, discussions and future research demonstrating the public health implications associated with atrazine exposure must continue to allow for a holistic review of the role atrazine plays in United States' agriculture.

The aim of this review was to establish the link between atrazine exposure and the potential for endocrine disruption in humans, identify sources of exposure and risks of exposure to atrazine in midwestern United States, examine and compare current views on atrazine exposure in the United States and European Union, with a view to identifying knowledge gaps and elucidating the implications for population health in midwestern United States.

OUR SEARCH

General supporting information on pesticides and atrazine were sourced on government websites and scientific textbooks, including the Environmental Protection Agency, Agency for Toxic Substances and Disease Registry, United States Department of Agriculture, and International Agency for Research on Cancer. Information and documents from these websites aided in defining the role of atrazine in agriculture, specific uses of atrazine, and regulation of atrazine usage. Specific studies were identified by searching the PubMed database using the key word “atrazine exposure” in combination with “endocrine system,” “endocrine disruption,” “pituitary,” “thyroid,” and others. Information from these studies guided the discussion on the health implications associated with atrazine exposure. 226 citations were identified through the combination of the mentioned keywords (see Figure 1). Out of the 226 citations, forty-five had full read text available (see Figure 1). Titles were then screened based off inclusion of atrazine and topics related to the endocrine system. After a final review of titles and abstracts, ten relevant studies were identified that examined the relationship between atrazine exposure and endocrine disruption (see Figure 1).

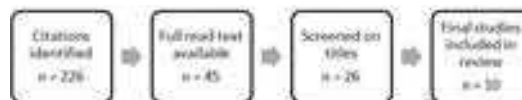


Figure 1. Diagram for identification of literature sources (adapted from Nahar et al, 2018).

Inclusion and Exclusion Criteria

Studies were included based on exposure to atrazine, amount of exposure to atrazine, and implications associated with the endocrine system, such as decreased tissue size, decreased production of hormones and disruption of hormonal circuitry. Due to the limited number of studies examining the effects of atrazine exposure in humans, the results were extrapolated from animal models for the estimation of risk in humans. Additionally, due to limited number of recent studies in both human and animal models, studies from 2000 to 2018 were considered. Studies were excluded based on exposure to pesticides beside atrazine, results that did not include the endocrine system, and studies that did not include full read text.

FINDINGS

Results from the Agricultural Health Study were among the first used to evaluate the adverse health effects associated with long-term pesticide exposure, such as leukemia, non-Hodgkin's lymphoma, and prostate cancer to name a few [17]. Since the Agricultural Health Study, a multitude of studies have elaborated on those health implications, especially those related to atrazine. Humans have demonstrated decreased levels of pituitary hormones, shortened estrous cycle length, reduction of luteinizing hormone surge, and ovarian pathologies, all of which result in regulatory disruption of endocrine and reproductive systems [18]. Experimental animal models have demonstrated similar effects, especially in mice and fish models (see Table 1). In addition to the specific disruption of the pituitary and thyroid glands, animal models have also demonstrated induction of inflammatory responses, abnormal expression of genes involved in structural stability and stress regulation, neurotransmitter disruption in the brain, and feminization of male species [19–21]. These findings aid in the discussion of potential atrazine toxicity in humans outside the scope of the endocrine system.

DISCUSSION

Effects of Atrazine Exposure on the Pituitary Gland in Animal Models

The role of the pituitary gland is to receive signals from the hypothalamus, produce hormones, and release hormones which are then sent out to other parts of the body. Hormones produced and released from the pituitary gland play pivotal roles in growth and reproduction; therefore, interference with these processes can severely disrupt an organism's ability to grow and reproduce properly [10].

Due to disruption of the pituitary gland and processes associated with reproduction, atrazine exposure during specific time periods in life resulted in severe disruption of reproductive processes in zebrafish and mice models (see Table 1) [12, 22, 23].

During embryonic exposure to atrazine in male mice, Hao et al. [23] discovered decreased numbers of spermatozoa and disruption of meiosis and spermiogenesis, key processes in the growth and reproduction of male mice. Researchers also discovered that offspring of these atrazine exposed mice can have altered genes involved in the same processes [23]. Thus, Hao et al. concluded that genetic changes caused by atrazine exposure can potentially transfer across generations, creating a worrisome discussion when applied to human populations [23].

During pre-pubertal exposure, Weber et al. discovered altered genes for organ and reproductive development of both testis and oocytes in zebrafish, as well as abnormally smaller adrenal glands, prostate, pancreas, and kidneys (see Table 1) [22]. Identification of these altered genes can aid in defining mechanisms for atrazine toxicity in human models. Lastly, during adult exposure to atrazine, researchers discovered oxidative stress in oocytes and disruption of follicle formation in female mice, a process crucial to the reproductive capability of organisms [12]. These results can pose a threat when applied to human models, especially atrazine exposed women who intend to become pregnant.

Decreased growth hormone expression has also been observed as a result of direct pituitary gland disruption. Fakhouri et al. studied the effects of pre-pubertal exposure in rats by exposing pituitary cells to various levels of atrazine (see Table 1) [11]. Atrazine exposure resulted in abnormally low levels of genes that encode for growth hormone and luteinizing hormone, hormones responsible for growth and gonadal development, as well as decreased circulating levels of these hormones in adult rats [10, 11]. Atrazine is able to cause these effects through direct disruption of the pituitary gland “by binding to the growth hormone releasing hormone receptor and inhibiting GH [growth hormone] expression at the mRNA and protein levels” [10]. According to researchers, this was the first time a specific receptor for atrazine was identified, serving as a framework for future research on atrazine exposure in humans [11].

Effects of Atrazine Exposure on the Thyroid Gland in Animal Models

The thyroid gland is an endocrine organ that secretes thyroid hormones and plays an important role in the regulation of metabolism [10]. Pesticides are one of the major toxicants that can interfere with the circuitry and production of hormones by the thyroid gland [10]. Studies conducted by Rajkovic et al. [13], Stoker et al. [24] and Laws et al. [25] researched the effects of atrazine exposure on the thyroid gland in rat models.

Stoker et al. [24] discovered no adverse effect on the thyroid glands of rats at pre-pubertal and adult atrazine exposure but did discover abnormalities in the developmental of male rat genitalia (see Table 1). It was shown that male rats exposed to atrazine had delayed preputial separation, decreased weight of prostate, and decreased circulating levels of testosterone. However, Rajkovic et al. [13] found compelling evidence for thyroid damage due to peripubertal and adult atrazine exposure in rat models (see Table 1). Following different exposure concentrations to atrazine, rat thyroid mast cells were shown in decreased amounts due to the cells destroying and expelling their cellular contents, a process known as degranulation [13]. Normally, mast cells function as mediators of allergic and immune responses, saving organisms from adverse effects caused by toxicants [26]. By understanding the disturbance of thyroid functions in animal models, such as the studies conducted by Stoker et al. [24] and Rajkovic et al. [13], future researchers can investigate the potential thyroid disturbances and threat atrazine poses on human populations.

Environmental Distribution of Atrazine

These well documented adverse effects of atrazine exposure represent a serious risk to the public health of communities in the United States especially when considered in the context of its fate and transport in the environment. In a study conducted by the EPA on contaminants in ground water, atrazine was found as a common contaminant in several regions, especially the Midwest [1]. In Iowa, it was found that 8% of private drinking water wells were contaminated with low concentrations of atrazine [27]. However, contamination levels in drinking water did not exceed the EPA Maximum Contaminant Level of 3 µg/L, adapted from the original World Health Organization guidelines set at 2 µg/L [18].

Table 1. Effects of atrazine exposure on the endocrine system and other

Reference	Model	Exposure	Time Frame of Exposure	Age at Exposure	Major Endocrine Findings and Conclusions/Implications Related to Human Health
Weber et al., 2013	Animal (zebrafish)	0, 0.3, 3, or 30 ppb (µg/kg)	1 to 72 hours post fertilization	Embryonic	Major Findings: Altered genes (transcriptomes) responsible for organ and reproductive development (testis, oocytes); congenital adrenal hyperplasia; carcinogenesis for prostate, pancreas, kidneys Conclusion: Identification of altered genetic targets can aid in defining mechanisms for atrazine toxicity
Hao et al., 2016	Animal (mice)	100 mg/kg/day	9 days	Embryonic	Major Findings: Decreased spermatozoa, disrupted meiosis (spermiogenesis), impaired RNA expression Conclusion: Genetic changes that result from atrazine exposure can transfer across generations.
Gely-Pernot et al., 2017	Animal (mice)	100 mg/kg/day	9 days	In utero and adult	Major Findings: Oxidative stress in oocytes disrupts processes associated with meiosis; delay of puberty due to disruption of hormones; disruption of follicular development and reduction of follicles in female mice Implication: Pregnant women exposed to atrazine can have babies with lower birth weights
Fakhouri, Nunez, and Trail, 2010	Animal (rat)	1 ppb (µg/kg) and 1ppm (mg/kg)	7 days	Pre-pubertal	Major Findings: Pituitary cells exposed to atrazine resulted in decreased levels of genes encoding for GH and LH Conclusion: Atrazine targets GHRHR of pituitary cells and decreases levels of GH. To the knowledge of the researchers, this is the first time a receptor has been identified. This can aid in future research on atrazine exposure.
Stoker et al., 2002	Animal (rat)	6.5, 12.5, 25, 50, 100, 200 mg/kg/day	Post-natal depression (PND) 23 to 53 days	Pre-pubertal and adult	Major Findings: Delayed preputial separation; Decreased weight of prostate and anterior pituitary; Decreased serum testosterone levels; No effect on the thyroid Conclusion: Both atrazine and its metabolites alter the development of puberty in male rats and can pose a potential threat to human populations

Reference	Model	Exposure	Time Frame of Exposure	Age at Exposure	Major Endocrine Findings and Conclusions/Implications Related to Human Health
Rajkovic et al., 2012	Animal (rat)	50 and 200 mg/kg/day	28 days	Peripubertal and adult	Major Findings: Degranulation of thyroid mast cells; Decrease in the density of thyroid mast cells Conclusion: Results provide framework for future research that investigates the role atrazine exposed mast cells play in thyroid function
Laws et al., 2000	Animal (rat)	50, 100, 200 mg/kg/day	PND 22 to 41 days	Pre-pubertal	Major Findings: Decrease in body weight and weight of kidneys, adrenals, pituitary gland, and uterus; Delayed age of vaginal opening; Delayed menstrual cycle Conclusion: Results aid future research on the effects of atrazine exposure on the central nervous system and the hormonal control of gonads
Mizota and Ueda, 2006	Animal (mice)	.0001 – 1.0 µM	0 – 20 minutes	Pre-pubertal	Major Findings: Induction of inflammatory effects, mast cell degranulation and action of Gq/11-protein coupled neurosteroid receptor, PLC and intracellular Ca ²⁺ mobilization
Huang, Yang, and Song, 2014	Human (female breast cells)	0.1 µg/mL (100 ppb)	3, 6, and 12 hours	Adult	Major Findings: Abnormal protein expression of genes involved in signaling, protein translation, gene transcription, structural stability, stress regulation, and glycolytic metabolism; changes in genes necessary for growth and development; acetylcholinergic and dopaminergic system dysfunction in the brain Conclusion: Exposure to environmentally relevant concentrations of atrazine cause dysregulation of several processes; however, mechanisms of action are unclear and future research is needed
Suzawa and Ingraham, 2008	Animal (zebrafish)	.1, 1, 10 µM	6 months	Pre-pubertal and adult	Major Findings: Feminization of male fish; Increased number of genes involved in endocrine signaling in adrenal cell lines, human liver cell lines, and primary endometriotric cell lines Conclusion: Atrazine exposure affects hormone signaling and endocrine networks in fish and can potentially disrupt similar circuitry in more advanced vertebrates (i.e. humans)

Rice et al. [9] studied the degradation process for atrazine to determine if the presence of sediments in water altered the half-life of atrazine. Atrazine can persist in the environment for approximately four months [9]. The authors discovered that levels of atrazine in surface water containing sediments were significantly lower compared to water free of sediments. Results demonstrate that sediments present in water can play a synergistic role in the degradation process of atrazine and can serve as a foundation for future public health studies looking at the persistence of atrazine in water systems.

Atrazine Monitoring and Regulation

In midwestern United States, atrazine exposure through contaminated water systems is estimated at the level of 0-3 µg/L, based off the EPA Maximum Contaminant Requirements [18]. This means that concentrations of atrazine in water sources can vary depending on the time course of atrazine application and persistence of atrazine in water sources. This creates a public health issue for individuals using private water wells as their main source of drinking water, as private wells may not undergo the same amount of monitoring as larger water systems do. It remains important to identify communities in midwestern United States as a susceptible population to atrazine exposure due to the fact that atrazine is heavily applied to corn crops in this area.

Monitoring levels of atrazine in the environment remains an important aspect due to the persistence of atrazine in surface water and the public health threat this causes to surrounding communities. Unfortunately, monitoring levels of water contaminated with atrazine can prove difficult in the United States, especially in areas, such as Iowa, where are a large number of individuals receive their water from private drinking wells. From 2006 through 2008, the University of Iowa Center for Health Effects of Environmental Contamination conducted a survey to sample private drinking wells throughout several counties in Iowa [27]. In all the wells sampled, 8% had low concentrations of atrazine present. The survey also noted that wells less than 100 feet deep and wells constructed before 1991 had higher detectable levels of herbicides compared to deeper and newer wells. In addition to private drinking wells, atrazine has also been detected year-round in streams of the Midwest United States, posing a risk to the various wildlife living in and near these streams [9].

In the United States, the production and usage of pesticides is monitored by the United States Department of Agriculture. Following the 1990 Farm Bill, the United States Department of Agriculture required private applicators, by law, to keep a detailed record of application of restricted use pesticides, including atrazine [6]. Unfortunately, due to budget cuts, this program, known as the Pesticide Record Keeping Program, was eliminated in September 2013 [6]. In 1994, the Environmental Protection Agency established the Pesticide Environmental Stewardship Program with hopes of reducing the risks of pesticide risks in the United States [1]. Currently, the Pesticide Environmental Stewardship Programs has several initiatives aimed at reducing pesticide risks in every sector, including school education programs, landscaping initiatives, and tick monitoring [1]. Although this program does not single out atrazine, it does provide an educational framework for individuals unaware of the risks associated with pesticides.

When discussing regulations of atrazine in the United States, it remains useful to view the state of atrazine in other parts of the world. Currently, atrazine is banned in the European Union due to the unpreventable nature of repeated water contamination, as well as the discovery of atrazine as an endocrine disruptor [15, 16]. In 1999, the European Union began its discussion of regulating hazardous chemicals, such as chemicals that act as endocrine disruptors, by creating a series of categories to classify hazardous substances [15]. In addition, information regarding safe drinking water and contamination with hazardous substances spawned further discussion in the European Union regarding its role in agriculture [15, 16]. During the late 1990s to mid-2000s, the European Union conducted several reviews of atrazine regarding its adverse health effects and water contamination. Although the evidence regarding the adverse health effects of atrazine in humans was inconclusive, due to its persistence in environmental media, the European Union still voted to ban atrazine in 2003, with the exception of essential use in parts of the United Kingdom and Ireland for forestry and maize use until 2007 [15]. Fifteen years following the European Union's decision to ban atrazine, organizations in the United States, especially the EPA and USDA, still continue to discuss the role of atrazine in agriculture in the United States.

CONCLUSION

The results of the reviewed studies identify a multitude of health implications associated with atrazine exposure, specifically disruption to the pituitary and thyroid glands. These tissues are crucial to human development and processes involved with the regulation of growth, reproduction, and metabolism. Although little research has been conducted in humans, results extrapolated from animal models provide compelling evidence for potential health implications in human populations. This information, coupled with the persistent nature of atrazine and regulations of atrazine worldwide, aids in the public health discussion of atrazine and the role it plays in humans and the environment. This review addressed the knowledge gaps of atrazine in the United States and provides insight for the need of continued research on atrazine and its effects on human populations.

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Chapter 71

COMMUNICABLE DISEASES IN THE WINDWARD ISLANDS IN THE CARIBBEAN: A REVIEW OF HEALTH STATUS, 1990-2016

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ABSTRACT

There has been notable progress in the eradication of communicable diseases in the Caribbean islands. The region, however, still faces public health challenges from endemic and emerging infectious diseases. There were differences in the health outcomes between the Windward Islands. In this chapter, health status is compared in the islands to indicate progress in addressing communicable diseases. Comparing data in the Pan American Health Organization database for the years reported, the lowest overall rate of mortality from communicable diseases was in St. Lucia and the sharpest decline in rates was in St. Vincent and the Grenadines between 2010-2015. There was a notable decline in HIV mortality rate from 44.5 per 100000 population in 2000 to 20.3 in 2015 in St. Vincent and the Grenadines. The tuberculosis mortality rate was especially low, less than 2 per 100000 population, in all the islands except in St. Vincent and the Grenadines which had a slightly higher rate. Reported cases of dengue increased sharply in each island. There were slight increases in leptospirosis cases, except in Grenada. From 1995-2012, cholera cases were not reported in any of the islands. Apart from Grenada and St Lucia, measles cases were not reported after 1990 in any of the other islands. The factors that account for the differences in health status between the islands should be further examined. Local and

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regional health agencies should also facilitate more robust reporting, sharing information on best practices, and interventions to address challenges related to achieving SDG #3, health for all.

INTRODUCTION

The Windward Islands (WI), comprising of four independent island states - Grenada, St Vincent and the Grenadines, St Lucia, and Dominica - are located in the southern part of the Caribbean archipelago. The small islands have a total population of 472,000. The demographic, social and economic landscape of the islands are generally similar. Within close proximity, the WI also commonly experience similar issues related to the spread and burden of communicable diseases. Various factors, however, contribute to differences in health status between the islands.

Overall, the Caribbean islands made great strides in combating communicable diseases. The last cases of measles occurred in the WI in 1995 and cases of cholera were not reported from about the mid-1990s [1]. Polio was eradicated in the Caribbean region from 1991 although a few cases were diagnosed in Haiti and the Dominican Republic in 2000 [2]. Rubella was not diagnosed in the region since 2002 [3]. The successes in eradicating communicable diseases are attributable to a vaccination coverage of 94% - 100% over the last ten years for communicable diseases like measles and polio [1]. Improvements in access to water and sanitation services, nutrition and primary health care were also recognized by the Pan American Health Organization (PAHO) as having a significant part in contributing to control and eliminate the spread of diseases in the Caribbean region [4].

Despite the notable progress in curbing some infectious diseases, there is still a relatively high prevalence of other diseases in the WI and other regional countries, indicating that health challenges persist in the Caribbean region. A major challenge still facing the WI and the Caribbean region, in general, is the emergence and re-emergence of vector-borne diseases such as dengue, Chikungunya and Zika [5, 6]. In the last decade, there were recurrent outbreaks of dengue every 3-5 years in the Americas with a major outbreak in 2010 [6]. Chikungunya virus infections rose to epidemic proportions in 2013 and, two years later, in 2015, the Zika virus epidemic was declared in the region [5]. Data in the PAHO database shows the highest number of reported cases of dengue in 2010 in each of the WI [1]. The increase in dengue transmission in the Americas (including the Caribbean) is linked to the increased spread and multiplication of the *Aedes aegypti* mosquitoes (vector for dengue) throughout the Americas [5]. The presence of all four serotypes of dengue (DENV 1, 2, 3, & 4; previously only 2 & 3 were present) was associated with the failed eradication program in 1947 – 1970 [6].

Tuberculosis, leprosy, cholera and leptospirosis were of concern since the late 1980s [7]. Two of those diseases, tuberculosis and leptospirosis continued to be of concern in the region as relatively consistent rates of infection were reported to PAHO [1]. High prevalence of sexually transmitted infections (STIs), in particular HIV, is another major infectious disease challenge in the WI [8]. HIV disease is the primary cause of death among Caribbean people aged 25 years to 44 years [9]. Albeit, there was success in reducing the rate of mother-to-child transmission, increased use of drug therapy, increased use of condoms by female sex workers, and improved safety in blood transfusion processes [9]. In general, there has been a shift in

focus away from communicable to non-communicable diseases. Nonetheless, the continuing high prevalence of HIV and other infectious diseases warrants more attention to communicable diseases in the Caribbean region [3].

This study was conducted to compare morbidity and mortality from communicable diseases in the four WI. The study focused on six diseases that have had major impacts on health and the health care systems in the sub-region, that is, HIV, tuberculosis, dengue, leptospirosis, cholera, and measles. Data was extracted from PAHO's database, spanning the period 1990-2016, and compared to provide an indication of progress in addressing communicable diseases in the region. The authors also discussed the implications for achieving Sustainable Development Goal (SDG) #3 - good health for all - in the WI.

OUR STUDY

This study constitutes a review and comparison of data on health outcomes related to six communicable diseases that have had major impacts on health and the health care systems in the sub-region - HIV, tuberculosis, dengue, leptospirosis, cholera, and measles. The data was extracted from PAHO's electronic database to compare morbidity and mortality rates and the number of deaths from communicable diseases [1]. The authors compared data, as provided by the countries, at six points - 1990, 1995, 2000, 2010, 2015, and 2016. Mortality data were reported for the years 2000-2015 in Dominica, 2000-2012 in St Lucia, 2010-2016 in Grenada, and 2000-2015 in St Vincent and the Grenadines. Mortality data were reported for dengue, tuberculosis and measles from 1990-2016. For the other diseases, data was provided for 2015-2016. Data on morbidity from cholera were reported for all the islands in 1995-2012. Gender disaggregated data is also reported in this study, but not shown. The results provide an indication of trends in health status over the extended period and show differences that indicate progress in addressing communicable diseases in the sub-region. The authors discuss the implications for achieving SDG #3 - good health for all - in the individual islands and, collectively, in the WIs.

FINDINGS

In the years reported, the mortality rate from communicable diseases was mostly steady in St Lucia, which also had the lowest overall rate among the four islands. In Dominica, there was an increase in the rate from 89.7 in 2010 to 111.5 per 100,000 population in 2015. Over the same period, the rate of mortality from communicable diseases also increased slightly in Grenada from 90.8 to 107.3 per 100,000 population but decreased to 89.9 per 100,000 in 2016. In St Vincent and the Grenadines, there was a sharp decrease in the reported rate from 2010-2015. Over the years, the reported mortality rate show decrease among females and increase among males in Dominica and was consistently higher among males in St Vincent and the Grenadines, Grenada, and St Lucia.

Table 1. Total mortality rate from communicable diseases and from HIV and tuberculosis infections in the Windward Islands

	1990	1995	2000	2010	2012	2015	2016
Total Communicable Diseases Mortality Rate (100000 population)							
Dominica	-	-	-	89.7	108.1	111.5	-
Grenada	-	-	-	90.8	97.7	107.3	89.9
St. Lucia	-	-	67.3	66.4	69.2	-	-
St. Vincent and the Grenadines	-	-	131.4	145.3	114.8	107.5	-
HIV Mortality Rate (100000 population)							
Dominica	-	-	-	4.1	11	2.8	-
Grenada	-	-	-	8.6	6.7	4.7	5.6
St. Lucia	-	-	0	3.5	0	-	-
St. Vincent and the Grenadines	-	-	44.5	13.5	11.2	20.3	-
Tuberculosis Mortality Rate (100000 population)							
Dominica	-	-	-	0	1.4	1.5	-
Grenada	-	-	-	1	0	1.9	0
St. Lucia	-	-	0.7	0.6	0.6	-	-
St. Vincent and the Grenadines	-	-	3.6	5.7	3.7	0.9	-

Table 2. Morbidity related to HIV, Dengue, leptospirosis, tuberculosis, cholera and measles in the Windward Islands

	1990	1995	2000	2010	2012	2015	2016
HIV Diagnosis Rate (100000 population)							
Dominica	-	-	-	-	-	27.2	31.2
Grenada	-	-	-	-	-	38.4	28.9
St. Lucia	-	-	-	-	-	-	-
St. Vincent and the Grenadines	-	-	-	-	-	61.2	32.8
Reported Cases of Dengue (total)							
Dominica	6	293	15	635	29	11	351
Grenada	3	74	27	152	75	25	151
St. Lucia	2	52	0	74	33	25	196
St. Vincent and the Grenadines	9	224	5	218	193	13	89
Reported Cases of Leptospirosis (total)							
Dominica	-	-	-	-	-	10	16
Grenada	-	-	-	-	-	12	3
St. Lucia	-	-	-	-	-	8	11
St. Vincent and the Grenadines	-	-	-	-	-	10	14
Tuberculosis Incidence Rate (100000 population)							
Dominica	8.6	11.2	-	11	9.6	9.5	6.8
Grenada	0	4	0	3.8	0.9	4.7	5.6
St. Lucia	9.4	7.5	5.7	5.2	6.3	7.9	1.7
St. Vincent and the Grenadines	1.9	12	14.8	13.7	27.4	6.4	5.5
Reported Cases of Cholera (total)							
Dominica	-	0	0	0	0	-	-
Grenada	-	0	0	0	0	-	-
St. Lucia	-	0	0	0	0	-	-
St. Vincent and the Grenadines	-	0	0	0	0	-	-
Reported Cases of Measles (total)							
Dominica	13	0	0	-	0	0	0
Grenada	6	3	0	-	0	0	0
St. Lucia	30	2	0	-	0	0	0
St. Vincent and the Grenadines	1	0	0	-	0	0	0

There was a notable decline in HIV mortality rate in St Vincent and the Grenadines from 44.5 per 100,000 population in 2000 to 20.3 in 2015. The HIV mortality rate was consistently higher among males in all countries. The reported tuberculosis mortality rate was extremely low, less than 2 per 100,000 population in all the islands, with slightly higher rates in St Vincent and the Grenadines, 3.7-5.7 per 100,000 in 2000-2012. The rate, however, dropped to 0.9 per 100,000 population in 2015. The HIV mortality rates were significantly higher among males in St Vincent and the Grenadines. Table 1 shows the total mortality rate from communicable diseases in the four islands and the mortality rate from HIV and tuberculosis infections.

Morbidity from Communicable Diseases

Between 2015-2016, the total HIV diagnosed rate increased slightly in Dominica but decreased slightly in Grenada over the same period. The most significant decrease in new diagnosis was in St Vincent and the Grenadines over the two-year period from 61.2-32.8 cases per 100,000 population. The highest number of reported cases was among males in each island. In each island, the number of reported cases of dengue increased sharply over the years reported. There were also slight increases in reported cases of leptospirosis in all the islands, except in Grenada. The incidence rate of tuberculosis decreased in Dominica and St Vincent and the Grenadines in 2015-2016. From 1995-2012, cholera cases were not reported in any of the islands. Apart from Grenada and St Lucia, measles cases were not reported after 1990 in any of the other islands. Table 2 shows data on morbidity related to communicable diseases.

DISCUSSION

It is evident that while noncommunicable diseases have surpassed communicable diseases as the major cause of death and disease, the latter still poses a major challenge to the health systems in Latin America and the Caribbean [10]. Communicable disease mortality rates in the WI, in general, are more than double what is seen in North America [2]. Consequently, these resource-limited small island nations must find the wherewithal to address simultaneously both communicable and non-communicable diseases. At the same time, governments must prioritize the provision of basic services for citizens. Addressing the high prevalence of communicable diseases and risk factors can place severe strain on the small and fragile economies of Caribbean countries, including the WI.

Many of the health achievements made in the WI, and in the Caribbean as a whole, are as a result of solid regional and international partnerships [11]. It is well recognised that the first sub-region in the Americas to eliminate poliomyelitis and the first to eliminate indigenous measles and rubella was the Caribbean [11]. Notwithstanding these achievements, because of their small scale, a common feature among these islands is a lack of both human and financial capacity to provide health services. Through PAHO, the World Health Organization provided technical and financial support for many years to the countries to address both communicable and noncommunicable diseases and their determinants. Other organizations and donor

agencies such as the Caribbean Community (CARICOM), President's Emergency Plan for AIDS Relief (PEPFAR), United Nations Programme on HIV/AIDS (UNAIDS) and the Pan Caribbean Partnership Against HIV and AIDS (PANCAP) have contributed significantly through cooperation in health for the reduction in the incidence of diseases, such as HIV, and to improve conditions and the standard of living of individuals. The Windward Islands still stands to benefit more from this regional approach to address communicable diseases. In the absence of benefiting from technical cooperation and financial support, it is difficult for small island states, such as the WIs to achieve SDG #3 - Ensure healthy lives and promote well-being for all at all ages.

Some infectious diseases like measles and cholera have been eliminated in the WI for over a decade [1]. Effective vaccine coverage, availability of clean drinking water and improved sanitation contributed to the reduction in communicable disease prevalence [12–14]. The HIV mortality rate decreased in the WI between 2010 and 2015, except in St. Vincent and the Grenadines (but the rate is lower than in 2000) [1]. The decline in the mortality rate has been as a result of improved prevention and control programs, for example, early initiation of antiretroviral therapy (ART) [8]. Good progress has been made in the fight against HIV in the Caribbean region, including in the WI, but significant work still needs to be done. The incidence of tuberculosis increased in the 1990s and early 2000s, then started decreasing by 2015 in the Windward Islands [1]. The increase may have been mainly due to co-morbidity with HIV infection. Improved control programs may have led to the eventual decrease in cases of tuberculosis.

Insufficient and ineffective vector control programs and the effects of globalization are factors that may have contributed to the increase in vector-borne illnesses in the WI [12, 15]. The WHO encourages governments to foster and enable social and health equity to improve health outcomes through three main measures: 1) improve daily living conditions, 2) tackle the inequitable distribution of power and resources and 3) measure the scope and magnitude of the problem and assess the impact of action [16]. SDG #17 promotes multi-national partnerships for sharing resources to facilitate poorer countries to achieve the goals including creating the environment for the healthy development of individuals [17]. HIV testing, counseling and treatment are offered at no cost to the residents in the WI. Most of the HIV/AIDS response programs are funded through PEPFAR, which provides 57% of HIV funding in the Caribbean [18]. In 2017, PEPFAR announced the reduction of funding for HIV programs in the larger Caribbean islands [8]. The WI and other members of Organization of Eastern Caribbean States (OECS) have retained their funding but are also vulnerable to the reduction of HIV financing by external donors [6, 8] which can have a negative impact on achieving the SDG goals for health and wellbeing. With increased financial input (both local and international) greater success can be achieved in the fight against HIV and AIDS and other communicable diseases in small island states. Additionally, compliance with ART treatment has been a long-standing problem in the Caribbean (including the Windward Islands), this needs to be addressed urgently to boost the fight against HIV/AIDS [18].

CONCLUSION

This study highlights the situation with communicable diseases in the WI. Lessons can be learned from the achievements of the WI in controlling and eliminating vaccine-preventable infectious diseases like measles, polio, diphtheria and pertussis through consistently high levels of population vaccination coverage, starting in infancy. These achievements prove it is possible for low and middle-income countries to control/eliminate other communicable diseases using cost-effective sustainable strategies. The increase in vector-borne diseases like Dengue, evident in the Windward Islands is a reflection of failed vector control programs within the Caribbean region and globally. Also, the effects of globalization, like increased international trade and travel, urbanization and climate change have enhanced the proliferation and geographical reach of vectors like *Aedes aegypti* mosquitoes. Additionally, although HIV infection and mortality rates have decreased in the Windwards Islands due to improved HIV prevention and treatment programs, vulnerability to loss of funding from international agencies threatens to hinder this progress. This highlights the need for low and middle-income countries to invest their own resources in HIV and other communicable disease prevention programs to ensure sustainability. Stakeholders at multiple levels must be involved in public health action to achieve better health outcomes, including government and non-governmental organizations, civil society, community-based organizations and business organizations.

Finally, there is a need to also improve surveillance and reporting at local and regional levels to increase access to current data and evidence to support policy development and appropriate responses. There were gaps in PAHO's data for several years, highlighting data collection and reporting may not be done on a consistent basis in the WI. This paucity in data creates a limitation for PAHO, the region's health authority, to make evidence-based decisions and to be guided by the principles of health equity in its programs. Governments must improve and monitor institutional structures to improve the performance of the health sector within the local and regional contexts [18].

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Chapter 72

MEASLES OUTBREAK 2019: RE-EMERGENCE IN THE UNITED STATES

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ABSTRACT

The measles outbreaks have been occurring in multiple areas in the United States. The number of confirmed measles cases for the first half of 2019 has already recorded the highest in the last twenty years since the government had declared its elimination in 2000. Measles is a highly contagious disease that is responsible for millions of deaths in the past; however, it is almost completely preventable with vaccination nowadays. Maintaining herd immunity in the population is crucial. The declining rates of vaccination in certain communities or groups of people have led to a sharp spike of measles cases in a short period of time. Methods: Epidemiological data for recent measles outbreaks were collected from CDC and corresponding local health departments to examine the facts about recent outbreaks and their reasons. Results: Data have shown that the vast majority of measles cases occurred in younger children whose parents chose not to vaccinate them. The local health authorities have been putting efforts to stop the chains of infections by ordering mandatory vaccination and eliminating non-medical exemptions based on religious or personal beliefs. Conclusion: The skepticism around autism spectrum disorder and the MMR vaccine still persists among those who are reluctant to get vaccinated despite numerous scientific research studies proving the safety of vaccines. The effects of current interventions are yet to be visualized but it would require concurrent education and health policy adaptation to sway the social norms and make changes in people who are not adhering to vaccination requirements.

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INTRODUCTION

The fear of measles is sweeping again among young children and parents in multiple geographic locations in the United States. The United States government had declared the elimination of endemic measles two decades ago in 2000 [1]. This means measles is no longer circulating among the population, or more specifically, the absence of sustained transmission of the virus for more than 12 months. However, sporadic outbreaks continue since there are introduced cases from abroad by international travelers that have spread the virus locally to susceptible individuals. The problem is that the number of measles outbreaks and the number of confirmed disease cases have dramatically increased since 2018. As of July 25, 2019, the Centers for Disease Control and Prevention (CDC) had reported 1,164 cases of measles since the beginning of 2019 [1]. This is the largest number of cases reported in the United States in the past two decades. In April 2019, New York City declared a public health emergency because of a massive spike in measles cases, especially in areas of Brooklyn [2].

Measles was once considered as one of the deadliest infectious diseases because it is highly contagious and it has been responsible for millions of deaths in human history. Most people who contract the disease will fully recover, but a portion of infected individuals will develop some complications including pneumonia, which is the most common cause of measles-related deaths in children, laryngotracheobronchitis, otitis media, and potentially fatal viral encephalitis. The development of the measles vaccine has dramatically changed the disease transmission and mortality rates. Measles, being a viral disease, requires a new host to sustain. However, with effective vaccination, the number of susceptible hosts will be reduced, which will prevent the virus from replicating, causing it to eventually vanish from the population.

One clear reason why the disease might be re-emerging in the United States is because there is an increasing number of unvaccinated children. Laws governing vaccination requirements and exemptions are currently at the center stage of debate regarding whether implementing laws to mandate vaccination or allowing exemptions would impact positively or negatively on public health outcomes.

The purpose of this narrative review is to examine the current measles outbreaks and illustrate some of the existing laws and policies that are in effect to prevent the spread of measles.

METHODS

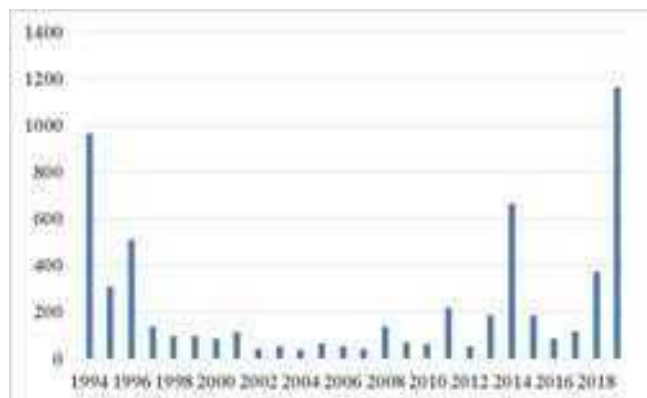
Epidemiological data for the 2019 measles outbreaks were collected from the CDC website and corresponding local health authorities: Clark County Public Health, NYC Department of Health, California Department of Public Health, and Rockland County Department of Health. These data are publicly available online and the most up-to-date information was obtained as of July 29, 2019. The numbers for reported measles cases per year in the United States from 1994 to 2019 were collected for comparison. The yearly data prior to 2010 were obtained from Morbidity and Mortality Weekly Report, Summary of Notifiable Diseases, published in 2009 as this information is not available on the CDC website. Yearly cases prior to 1994 were not considered for comparison in this review.

because the number of measles cases prior to the introduction of the second dose of MMR (measles, mumps, and rubella) is ranged in several thousand per year and the difference is obvious.

The most recent and current measles outbreak cases occurred in four geographic locations (Clark County, WA; New York City, NY; California State; Rockland County, NY). The data were categorized by age groups and vaccination status. Age ranges were constructed differently per outbreak location as the original source from local public health authorities used different age categorization. In places where the original data are not reported in number of cases, age groups and vaccination status were compared as percentages.

FINDINGS

CDC reports that there are five jurisdictions in the United States with currently ongoing measles outbreaks and there have been 1,164 confirmed measles cases since the beginning of 2019 in 30 states as of July 25, 2019 [1]. As shown in Figure 1, the number of measles cases in this year is significantly greater than any other years since the declaration of the elimination of measles in 2000. The numbers of yearly cases have been kept near the one hundred range since 1997, when the two-dose MMR recommendation had stabilized measles outbreaks across the country; the second dose of MMR was first introduced in 1989. The only exception is the year 2014 in which there were 667 reported measles cases. This was as a result of an outbreak in Amish communities in Ohio, which was responsible for more than half of the total cases in that year [1]. The vaccination rates in these communities at the time were found to be very low due to personal and cultural beliefs. There was also a large measles outbreak in California that started in December 2014, which was associated with an initial exposure at Disneyland theme park, resulting 147 cases between December 2014 and April 2015 [1]. A modest increase in measles cases is observed in 2018 and it is worth noting that some of 2018 outbreaks have continued into 2019. For example, Rockland County and NYC outbreaks, which are believed to originate from a suspected international traveler case in September 2018, have continuously contributed new cases in 2019, representing the degree of severity of disease transmission in these regions.



Sourced from CDC data) [1] [22].

Figure 1. Reported measles cases per year in the United States, 1994-2019.

Table 1. Age groups and vaccination status of confirmed measles cases in Clark County, WA during 2019 outbreak (Sourced from Clark Country Public Health) [3]

Ages	Cases	Vaccination Status	Cases
Under 1 year old	0	0 MMR doses	61
1~10 years old	52	1 MMR dose	3
11~18 years old	14	2 MMR doses	0
19+	5	Unknown	7
Total	71	Total	71

There is a total of 71 confirmed cases in Clark County as a result of the outbreak [3]. As shown in Table 1, 61 out of 71 cases occurred in individuals who previously did not have any MMR vaccine. The cases in terms of age group were as follows: 52 in the 1-10 years old, 14 in the 11-18 years old and 5 in the 19 years and older. The local health authority of Clark County declared that the outbreak was over as of April 2019 with no further cases being reported, however, there are a few other regions in Washington State with ongoing incident cases [3].

The outbreak in New York City is currently ongoing with new cases emerging. There have been 642 confirmed cases as of July 29, 2019 (see Table 2), which date back to September 2018 [2]. Of these cases, 466 out of 642 occurred in unvaccinated individuals, 46 in individuals with one MMR, 31 in individuals with two MMR, and 99 in individuals with an unknown vaccination status. More than three quarters of the cases occurred in the pediatric population and 129 cases were in adults. The NYC outbreak is heavily concentrated in certain neighborhoods in Brooklyn. Of all 642 NYC cases, Borough Park had 122 cases and Williamsburg had 461 cases. All other neighborhoods in Brooklyn and the other 4 boroughs have confirmed measles cases mostly ranging from 0 to 5.

Table 2. Age groups and vaccination status of confirmed measles cases in New York City during 2018-2019 outbreaks (Sourced from NYC Department of Health) [2]

Ages	Unvaccinated	1 MMR	2 MMR	Unknown	Total
Under 1 year	98	2	None	None	100
1 to 4 years	241	33	1	None	275
5 to 17 years	122	4	10	2	138
18+ years	5	7	20	97	129
Total	466	46	31	99	642

In California State, there have been a total of 64 confirmed measles cases statewide with several different outbreak origins [4]. The vaccination status was known in 69% of the total cases reported while in the remaining 31% of the cases the vaccination status was unknown. In the cases with a known vaccination history, 100% of pediatric cases and 48% of adult cases occurred in unvaccinated individuals; while 44% of adult cases occurred in individuals with two or more MMR doses and 7% with one MMR dose (see Table 3).

The current outbreak in Rockland County had a total 289 confirmed cases as of July 30, 2019. The case count started during September 2018 when the first suspected international traveler case was identified [5]. Of the total cases, 78.2% of the confirmed cases had no previous MMR vaccination, 5.9% had 1 dose of MMR, 3.5% had 2 or more MMR doses, and 12.5% had an unknown vaccination history (see Table 4). Among cases, 12.1% belonged to

the age group of under 1 year old, 40.5% were 1-6 years old, 26.3% were 7-18 years old, and 21.1% were over 19 years of age.

Table 3. Known vaccination status of confirmed measles cases in California State during 2019 outbreaks (California Department of Public Health) [4]

Vaccination Status	Pediatric Cases	%	Vaccination Status	Adult Cases	%
Unvaccinated	12	100%	Unvaccinated	13	48%
1 dose	-	-	1 dose	2	7%
2 doses	-	-	2 doses	12	44%
Total	12	100%	Total	27	100%

Table 4. Age groups and vaccination status of confirmed measles cases in Rockland County, NY during 2018-2019 outbreaks (Rockland County Department of Health) [5]

Ages	Cases %	Vaccination Status	Cases %
Under 1 year old	12.1%	0 doses	78.2%
1~6 years old	40.5%	1 dose	5.9%
7~18 years old	26.3%	2 or more doses	3.5%
19+	21.1%	Unknown	12.5%
Total	100%	Total	100%

DISCUSSION

The number of measles cases in 2019 thus far is the reason for concern. It has already surpassed the number of cases in 1994, a long time before the declaration of the elimination of measles in the United States. The number of incident cases is on a trajectory to increase even further by the end of the year. In addition, the current outbreak trend suggests that there are areas with high vulnerability to the measles infection. There are multiple foci of local communities with highly concentrated measles cases when compared to the rest of the United States. These foci also recorded low vaccination rates in their communities. Data from four different geographic locations concordantly showed that the vast majority of confirmed measles cases in these outbreaks are clustered among younger children who did not receive any MMR vaccine. This highlights the importance of the preventive effectiveness of vaccination against measles.

However, a contrasting scenario was shown in California where a large proportion of adults who had measles were previously vaccinated with two doses of MMR. This is most likely attributed to the waning effect of vaccine-induced immunity [6]. Although two doses of MMR vaccine during childhood usually provide sufficient protection until adulthood, waning of immunity differs from person to person and the antibody titer could shrink below sufficient level within several years [7]. In such cases, the serum antibody titer would provide sufficient evidence of current immunity against measles. Alternatively, these adult cases of measles may have been as a result of immunodeficiency, either from immune function related diseases or from the effects of immunosuppressive medications used for other diseases. Nevertheless, the majority of the measles infections to this date have occurred among unvaccinated young children.

Measles and Vaccinations

Due to the nature of its mode of transmission by air and by contact with body fluids, measles is highly contagious and it spreads rapidly to susceptible individuals. It's severity of contagiousness is marked by the fact that 9 out of 10 people who come into contact with an infected person would also become infected, if they were not already immunized. Because of this high transmissibility the disease was responsible for the loss of millions of human-lives worldwide prior to the development of the measles vaccine. At a population level, it is crucial to achieve the herd immunity threshold. The herd immunity threshold for measles is known to be about 93~95%. The estimated MMR vaccination coverage among children aged 19–35 months in the United States is 91.5% for 2017 [8]. This number seems reasonably high but the problem is that there are pockets of geographic areas in the vaccination map where the community vaccination rate is far below 80%. Rockland County had only 72.9% of people in the ages of 1-18 years vaccinated with two doses of MMR despite the effort from the local health authority [9]. Clark County estimated overall measles vaccination rate of 78%, which is also too low for herd immunity [10].

It is practically impossible to have everyone vaccinated in any given population because there are always individuals who may elect not to get immunized, nor to have their children vaccinated. There are also individuals who have contraindications to the MMR vaccine. MMR is a live attenuated vaccine and people with immunocompromised state or pregnant women should not get the vaccine due to the risk of a full-blown infection. Another consideration is for children under the age of 1 year. According to the CDC immunization schedule, the first dose of MMR vaccine is generally administered between 12 to 15 months of age and the second between 4 to 6 years of age [11]. MMR vaccine is typically not given before 12 months of age because young children do not respond adequately to the vaccine. Special consideration could be applied if the child has to travel to an endemic region in which case the vaccine may be given as early as 6 months of age, but still have to follow up with regular two doses afterwards. Systematically, this schedule leaves out children under the age of 1 year relatively unprotected even with the consideration of passive immunity transferred from mother, which would mostly disappear several months after being born. This is another reason the herd immunity is so important in order to maintain a population-level protection against measles. These individuals, who cannot achieve their own immunity through the MMR vaccine due to the aforementioned reasons, can passively avoid the infection if the herd immunity remains strong.

While the reasons for the low vaccination rate may vary between these measles “hotspot” communities, it is clear that a low vaccination rate is strongly correlated with the number of measles cases. There has been a big spike of measles occurrences in these communities when there is an introduction of measles from travelers and, also, the disease spreads very quickly. In the end, the victims of low vaccination rates are the young children who cannot express their opinions since the decisions were made for them by their parents.

The MMR Myth

One of the reasons for the anti-MMR movement stems from data purporting an association of MMR vaccine and autism. A former British physician, Andrew Wakefield, published a research paper in *The Lancet* claiming there is an association between the MMR vaccine and colitis and autism spectrum disorder [12]. This MMR vaccine controversy was proved to be fraudulent due to the manipulation of the research evidence and the presence of multiple undeclared conflicts of interest. However, the fear about the possibility of their children developing autism spectrum disorder still persist among some parents in spite of numbers of scientific studies refuting such associations and the fact that the original paper was retracted from *The Lancet* [13]. The original claim by Wakefield gained such a massive media attention at the time that it engraved anti-vaccination in a lot of people's minds distracting their focus from the scientific evidence. There is still much more advocacy that individual healthcare providers need to take part in to increase MMR vaccination rates.

Non-Medical Exemptions (NMEs)

Most states require children to have appropriate vaccination prior to entering kindergarten or grade school. But the parents may ask for non-medical exemptions based on their religions or personal beliefs although not all states allow such exemptions. Olive et al. [14] revealed in their study that the number of NMEs has risen since 2009 in 12 of the 18 states that allow this policy and they also identified that there is an inverse relationship between NME rates and MMR vaccination rates in these states. Suffice it to say, communities with higher NME rates have a larger portion of vulnerable pediatric population against vaccine preventable diseases such as measles and these communities correlate with several measles outbreak locations during 2018-2019. On the contrary, the same study also concluded that the states which have banned NMEs exhibited higher MMR vaccination coverages among kindergarten children [14].

One aspect of non-medical exemption concerns the religious or personal beliefs. The outbreaks in New York City and in Rockland County seem confined to Orthodox Jewish residents who have chosen not to vaccinate their children for the religious beliefs. In some neighborhoods, the belief that the supernatural is in control of illness rather than a vaccine, have contributed to low vaccination rates [15]. This brings an ethical dilemma about the freedom of religious belief and the freedom to choose not to vaccinate. There may not be one true answer to this situation but the outbreak would only grow larger if no changes are made.

California SB277 – Elimination of NMEs

California was the first state to step forward to address the non-medical exemption issue. After the outbreak occurred between December 2014 and April 2015, which was originated from an initial exposure at Disneyland theme park and resulted 147 measles cases mostly in unvaccinated younger children, California implemented Senate Bill 277 (SB277) in June 2015, which eliminated non-medical exemptions from childhood immunization requirements

and it also encompassed the removal of religious objections [16]. This bill mandated all children to meet the vaccination requirements for entry to grade schools as well as day care centers in California unless they are exempted by medical reasons. Despite the challenges of implementing the law, this change in health policy resulted in modest success. Delamater et al. [17] revealed that the percentage of kindergartners entering school while not up-to-date on vaccinations decreased from 7.15% to 4.42%. However, Delamater et al. [17] has also stated that the previous geographic patterns of vaccine refusal persisted after the law's implementation.

Rockland County, NY – Barring Unvaccinated from Public Space

In Rockland County, measles outbreak had occurred since September 2018 and there have been continuous occurrences of new confirmed cases until this date. The county declared public health crisis in March 2019 and barred unvaccinated children from public places where more than 10 persons are intended to congregate [18]. The ban was soon put on hold several days later by a state judge in response to lawsuits filed by the parents of local school children. The judge concluded that the current outbreak didn't meet the definition of an epidemic that the law permitting emergency declarations requires [19]. Despite multiple efforts from the local health authority to encourage MMR vaccination through campaigns and free vaccination clinics, the vaccination rates linger in 70's in particular communities and the health officers are concerned as more occurrences are expected.

New York City – Mandatory Measles Vaccination

On April 9, 2019 New York City declared a public health emergency over the measles outbreak and the health commissioner ordered mandatory vaccinations for anyone in the neighborhood with certain zip codes including people with religious objections and children between 6 to 12 months of age [2]. People who ignored the order could be fined \$1,000 if found out, even retrospectively [20].

This is certainly a more stringent version of the prevention efforts. While it is very clear that the city wants to put a stop to the spread of measles in its jurisdiction, there are also voices criticizing the mandatory vaccination order. Cantor [21] wrote in the *New England Journal of Medicine* that forcible vaccination should represent an unconstitutional intrusion on the liberty of competent adults. Yet the legal justification is far more complex because the constitutional law clearly states that the state governments may require individual liberty to yield to reasonable public health regulation [21]. The degree of reasonable interventions may be interpreted differently depending on the person and situation. Cantor [21] also stated that the force, whether economic or physical, does not educate, develop trust, or protect human dignity. This implies that the order may work as a solution for a temporary measure but would not help change the public awareness regarding vaccination. In June 2019, New York State signed legislation which removed nonmedical exemptions from school vaccination requirements. Under the legislation, New York City health officials then enforced closure of schools in the city that failed to comply with the measles-related emergency order. The long-

term effects of current interventions are yet to be found out. Nonetheless, the explosive public attention gained for the current measles outbreaks definitely provides an ideal opportunity to educate everyone about the importance of vaccination.

CONCLUSION

The United States is currently experiencing the worst measles outbreak in the past twenty years stemming from low vaccination rates in certain communities and groups of people. The current trend with rapidly increasing number of new cases is certainly alarming. It would be prudent to take preventive countermeasures before the disease starts to spread out of control. The reasons for people refusing vaccination are all too well known: fears of adverse effects of the vaccine, religious and personal beliefs. Despite numerous scientific literature claiming no association between MMR vaccine and developmental disorder, obstinate skepticism persists and the anti-vaccination is still being propagated within the population. In the case of MMR vaccination, education and litigation methods have to be applied concurrently because either one would not succeed on its own.

MMR vaccine has been shown to be highly effective and safe. The government has to become more proactive in educating the public with specific and correct information; reasons why we need measles vaccine, scientific evidence demonstrating the safety of vaccine, and false rumors circulating around the vaccination. Primary healthcare providers are likely an underused resource in conveying accurate information and advice on vaccination to the public. Advancing by a small step where the changes could be widely accepted is the key to the successful transformation. For example, instead of eliminating non-medical exemptions altogether there should be step-wise procedures implemented to the non-medical exemption process such as first having mandatory consultation with health professionals to exchange their views about vaccination in order to proceed further. If the reason not to vaccinate their children have arisen from religious or cultural beliefs, these need to be properly addressed in order to prevent negative stigmatization of the particular groups. In the end, the public awareness has to be improved so that people acknowledge that vaccination is a societal responsibility; it is a form of altruistic behavior. Maintaining the herd immunity is essential for protecting our communities, the immunocompromised, pregnant women, and most importantly young children who are yet to get vaccination.

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Chapter 73

VACCINE AWARENESS FOR CERVICAL CANCER

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ABSTRACT

Cervical cancer, caused by the human papillomavirus (HPV) is the third most prevalent cancer in women, globally. Worldwide application of the HPV vaccine varies, ranging from thorough administration of immunizations in the first world to practically nonexistent in various developing countries. We survey the state of HPV vaccine awareness and cervical cancer mitigation worldwide and propose a framework for improving education on the vaccine's benefits and implementation of vaccination programs in the developing world. We also discuss how health care professionals can communicate with parents and policy makers to ensure that this framework is sustainable.

INTRODUCTION

The HPV is a double-stranded DNA virus that produces pathological effects on epithelial cells. This virus is a sexually transmitted infection (STI), spread through direct skin to skin contact [1]. The greater percentage of sexually active adults will be infected with HPV at least once in their lives, with the highest rates of infection occurring with women younger than 25 [2]. HPV is the most common STI because of its high transmissibility [3].

There are 100 different strains of HPV, some of which cause active disease, though most are cleared by the immune system. HPV can progress to different pathological presentations such as head and neck cancers and anogenital cancer including: vulval, vaginal, anal and penile. The most common result of HPV infection is progression to cervical cancer and/or genital warts. About 4% of all cancers are related to HPV [4]. The high-risk oncogenic types

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of HPV, HPV 16 and HPV 18, are associated with 99.7% of cervical cancer cases [1]. The carcinogenicity of these types of HPV is due to the activity of oncoproteins E6 and E7, which impair the growth regulatory pathways leading to the slow accumulation of host genetic mutations [5].

The third most common cancer in women worldwide, often affecting women under 40 years, is cervical cancer [6]. Cervical cancer robs women of many productive years and requires resource-intensive treatment. However, this cancer is preventable due to the HPV vaccine. There are two HPV vaccines available: the quadrivalent, which protects against the most common oncogenic strains of HPV, 6, 11, 16 and 18, and the nine valent which protects against five additional oncogenic types 31, 33, 45, 52 and 58 [7]. Studies carried out in the US where HPV vaccines are recommended have shown a reduction in cervical cancer incidence since the implementation of HPV immunization [8]. The HPV vaccine needs to be administered before people become sexually active because of HPV's high transmissibility and prevalence, infection is possible at the first sexual contact [9].

SAFETY OF THE HPV VACCINE

The Advisory Committee on Immunization Practices (ACIP) in 2006 recommended the HPV vaccine for routine vaccination of adolescent girls at age 11 or 12 years, and in 2011 for adolescent boys ages 11 or 12 years [10]. The HPV vaccine can be administered safely with other routinely recommended vaccines at a well-child visit to the physician. A post-licensure safety assessment carried out between 2006 and 2009 shows that there was no statistically significant increased risk for any pre-specified adverse events after vaccination such as Guillain-Barre, stroke, allergic reactions, and anaphylaxis [11]. Randomized controlled clinical trials of the HPV vaccine provide evidence of an excellent safety profile; the vaccine continues to be well-tolerated and immunogenic up to 9 years following vaccination [12]. The HPV vaccine, like all vaccines recommended by the WHO, had to go through multiple safety trials and its efficacy supported by scientific data, before it was deemed safe and an internationally recommended vaccine.

EFFICACY OF THE HPV VACCINE

The efficacy of the HPV vaccine for protecting against cervical cancer is widely accepted. The quadrivalent HPV vaccine, which is more widely used, protects against 70% of all cervical cancer. The nine valent vaccine increases this protection to about 90% of cervical cancer [7]. Ten years post vaccination the HPV 16/18 vaccine demonstrates continued efficacy against cervical intraepithelial neoplasia irrespective of HPV type [13]. The HPV vaccine protects not only against cervical cancer but other HPV related pathologies.

The HPV vaccine was initially only administered to young women to protect against cervical cancer; however, the administration was expanded to young men to protect against anogenital cancers and genital warts caused by HPV. In males who are 16 to 26 years old, the quadrivalent HPV vaccine prevents infection with HPV and the development of genital lesions such as warts and anogenital cancers [14]. Vaccinating both males and females

facilitates herd immunity. The efficacy of widespread HPV vaccination of both males and females has been proven. However, the WHO does not recommend the vaccine to males because the disease burden of HPV on men is not as great as on females [15].

WHO RECOMMENDATIONS

According to the WHO [15], 90% of deaths from cervical cancer globally occur in low- and middle-income countries. The HPV vaccine can significantly decrease the number of deaths as a result of cervical cancer. Developing countries contribute the most to cervical cancer deaths because there is limited access to the HPV vaccine for primary prevention, the pap smear screening test for secondary prevention and treatment of cervical cancer.

All girls between the ages of 9-14 years should be given the HPV vaccine as part of routine vaccination, before they start sexual activity [15]. This is seen as a form of primary prevention to protect against HPV. The aim is to proactively block infection; secondary prevention such as pap smear screening is still necessary but with the widespread use of the HPV vaccine, fewer people will require tertiary prevention. The WHO recommends vaccinating girls and not boys, though HPV prevents genital warts and anogenital cancers in males, as this is the most cost-effective measure against cervical cancer [15]. Implementing vaccinations in girls has been proven to be cost-effective, but there has not been enough research to support the recommendation to vaccinate boys in resource-poor countries. It is likely that as more research and evidence on the safety, efficacy and cost-effectiveness of HPV vaccine in males becomes available a recommendation for vaccinating both girls and boys may be made.

BARRIERS TO SUCCESS OF WIDESPREAD VACCINATION

There are many barriers to successfully implementing widespread vaccination. One of the major impediments in developed countries, where the vaccine is readily available, is lack of healthcare provider recommendation [16]. Parents willingness to vaccinate their children is higher when physicians recommend the vaccine. This vaccine is recommended for females aged 9-14 years old so parental consent is required to administer the vaccine. In countries where the HPV vaccine is readily available, healthcare providers have found that parental resistance is often the reason for the low rates of the HPV vaccine uptake [17]. Potential barriers to parents consenting to the HPV vaccine include concerns about the effects of the vaccine on sexual behavior, low perceived risk of HPV infection, vaccine costs, social influences and irregular preventative care [18].

Anti-vaccination campaigns have threatened existing HPV vaccination programs in many countries [19]. The spread of false information on the HPV vaccine and its efficacy and safety has hindered the US from reaching its 80% vaccine coverage target for 2020 [16].

The cost of the cervical cancer vaccine is a barrier to its widespread adoption in the developing world. The three-dose series of the quadrivalent vaccine costs approximately \$360 USD [20]. Despite the vaccine's cost in the developing world, from 2013, Gavi, the Vaccine

Alliance has negotiated lower prices for eligible low-income countries [21]. Policy makers in developing countries and Gavi need to work together to source subsidized HPV vaccines.

COUNTRIES WITH HPV VACCINE IMPLEMENTATION

Australia implemented a government funded school-based HPV vaccination program in 2007 for females aged 12-13 years and a catch-up program in 2009 for young females 13-26 years [22]. The school-based program is key as it removes the barrier of parents having to take children to the doctor for immunization. There has been a significant reduction in the incidence of genital warts among vaccine eligible females since the initiation of the vaccination program [23]. Herd immunity is also present because there was a reduction of 44% of new cases of genital warts in young males who are not part of the program, documented in the same time period [22].

Likewise, the US has implemented widespread HPV vaccination with the aims of having 80% vaccine coverage for females aged 13-15 years by 2020 [24]. HPV vaccine coverage among US females has increased since vaccine licensure but it remains low compared with other recommended adolescent vaccines [18]. Parents often consent for the other adolescent vaccines but not HPV as there is often lack of education on the benefits of the HPV vaccine.

Also, studies carried out in the US have demonstrated a reduction in cervical cancer incidence since the implementation of HPV immunization [8]. Furthermore, a cost-benefit analysis performed in the US demonstrated that vaccinating girls between 9 and 14 was cost effective when compared to current practice, US \$14,538 per quality-adjusted life year (QALY) gained [25]. There have been clear benefits to the implementation of an HPV vaccination program in the US. However, it is concerning that the vaccine coverage is falling below the target.

In Israel during the school years 2015-2016 through 2018-2019 the Gardasil-4 vaccine was administered to girls and boys in the eighth grade at school. During the school year 2014-2015, the Gardasil-4 vaccine was administered to eighth grade girls in schools and during the school year 2013-2014, the Cervarix vaccine was administered to eighth grade girls at school and to ninth grade girls at the health bureaus. As of the 2019-2020 school year the Gardasil-9 vaccine will be provided to girls and boys in the eighth grade at school. Two doses six months apart will be administered.

SUSTAINING VACCINATION

The priority of all healthcare providers who work with adolescents should be to increase the rates of HPV vaccination. In countries where the HPV vaccine is readily available providers need to recommend it like they would other scheduled vaccines and collaborate with parents to ensure maintenance of the vaccine schedule [24]. Widespread HPV vaccination requires not only healthcare provider support but government policies and mandates to improve coverage and unhindered access to the HPV vaccine [26]. Health education and health promotion programs to raise awareness on HPV, its related pathologies and the HPV vaccine, are essential to sustaining vaccination rates [27]. Policy makers need to

recognize that parents, the key decision makers for consent of this vaccine, are hesitant in complying with vaccine administration; strategies to educate parents and ensure optimal vaccine uptake are required [28]. It will be a waste of resources to make the vaccine readily available and it is not utilized.

Moreover, the decisions made to implement widespread HPV vaccination should be financially sustainable. Healthcare systems must ensure that vaccine purchasing mechanisms prioritize cost-saving interventions, have support to confront challenges in procuring vaccines, and use accurate vaccine demand forecasting [29]. Gavi, the Vaccine Alliance, helps low-income countries source funding for HPV vaccination programs and helps facilitate a vaccine demonstration program to help countries make informed decisions for subsequent national introduction of the vaccine [30]. Countries can use vaccine demonstration programs to help them map out the wider implementation plan and make it more effective.

DISCUSSION

There needs to be a framework in both developing and developed countries for broadening the application of the HPV vaccine for the prevention of cervical cancer and related illnesses. The cost-effectiveness of the vaccine has proven its necessity. The widespread implementation of this vaccine will require greater awareness and a community-based effort to vaccinate.

A large proportion of general population is unaware of HPV and its impact. In countries where the HPV vaccine is readily available, parents tend to deny consent because they have not been educated on the vaccine. Education campaigns targeting policy makers, healthcare practitioners and parents have shown an increase in compliance with the HPV vaccine [27]. Parents who are assured of the efficacy and safety of the vaccine are more likely to allow vaccination of their children. Targeted education campaigns are necessary to facilitate the implementation of an HPV vaccine program.

Similarly, the effort to vaccinate should be community-based, carried out by healthcare community workers to educate the parents so they will consent to vaccination. Community health workers are more trusted and are better able to communicate with community members. They better understand the culture and may be more successful at educating parents on HPV. Additionally, administering the vaccines in schools, to relieve parents of the responsibility of taking their child to the doctor, is another promising measure. Many countries have school vaccination programs, adding the HPV vaccine to the vaccination schedule increases compliance. The HPV vaccine has two or three doses and school vaccination programs are a more efficient way to stay on the vaccination schedule. Community healthcare workers can also be used to remind parents to comply with the vaccination schedule. Likewise, the children receiving the vaccine should also be educated on the benefits as part of a wider conversation on sexual health.

Furthermore, countries annually spend an exorbitant amount on the treatment of cervical cancer and related conditions. In the US the annual average cost of treating one patient <65 years old with cervical cancer in the last year of life is US \$117,830 [31]. The three-dose series of the quadrivalent vaccine costs approximately \$360 USD [20]. Modeling studies have demonstrated that HPV vaccination can be cost-effective [32]. The decrease in the resource

burden of cervical cancer and other HPV related pathologies on health systems is reason enough to implement HPV vaccination.

Resources are not only spent on the treatment of cervical cancer; in the event of an abnormal pap smear, the procedures carried out following can be costly. These procedures may show results that do not indicate a precancerous or cancerous state, however, the changes in the cervix are due to HPV. The HPV vaccine prevents these abnormal changes, which would result in costly medical procedures.

Moreover, the disease burden of cervical cancer is great, particularly in resource-poor countries. Often, by the time patients present with symptoms of cervical cancer, treatment is costly. The treatment of pre-cancer lesions on the cervix, cryotherapy, is resource intensive. Primary prevention of cervical cancer, HPV vaccine, prevents infection and therefore progression to a precancer or cancer state. Developing countries will be less burdened by cervical cancer if they implement HPV vaccination programs. Gavi, the vaccine alliance, facilitated programs will help low income countries with widespread implementation of HPV vaccination.

In addition, cervical cancer affects women who are still productive and are likely part of the workforce. In the US in 2014 \$2.1 billion was the total productivity loss due to cervical cancer [33]. Not only is the cost of diagnosing and treating cervical cancer great, there is a significant loss in productivity. A loss that would likely be decreased if women from that generation had been vaccinated against HPV.

It is important that low- and middle-income countries develop HPV vaccine programs speedily because delays mean another group of females miss the window to be vaccinated. The vaccine's implementation in these nations is imperative, as every five-year delay in roll-out contributes to 2 million cervical cancer deaths [34]. These deaths are avoidable, and a concerted effort needs to be made to effect policy changes that will lead to widespread HPV vaccination.

CONCLUSION

Cervical cancer is one of the few cancers that its etiology is well-understood and a reliable prevention tool developed. The safety and efficacy of the HPV vaccine has been proven and supported by scientific data; however, widespread vaccination is not a reality globally. The cost-benefit analysis of HPV vaccination programs has proven the programs cost effective. These vaccination programs help relieve the financial burden of HPV on health systems. Despite tremendous advances made towards implementing the HPV vaccination programs, throughout the world, developing countries still lag in this regard. Several developed countries, which have the vaccine readily available, also fall short of vaccination coverage goals. Initiatives to design and establish a comprehensive vaccination framework in these countries could be tremendously beneficial, especially those heavily focused on educating the patients and their communities on the risks of cervical cancer, and necessity of implementing proactive measures against it. This is a preventable cancer that should be eradicated.

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Chapter 74

**EFFICACY OF COMBINATION ANTIMICROBIAL
THERAPY AND IMPACT ON EMERGING
ANTIMICROBIAL RESISTANCE:
A TWENTY-FIVE YEAR SYSTEMATIC REVIEW**

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ABSTRACT

Antimicrobial resistance is a growing threat to public health. We quantified concerning trends in the development of antibiotic resistance across multiple species against a variety of antibiotics from 1996-2015. The systemic increase in the percentage of antimicrobial resistance demonstrated a decline in the percentage of the population that was susceptible. An emerging strategy to combat these trends is to use combination antimicrobial therapy in order to shift population percentages to favor the growth of susceptible strains. In order to support the viability of this strategy, we performed a systematic review of the literature to evaluate the evidence for combination therapy significantly affecting the relative population of susceptible versus resistant strains of microorganisms in vivo. In six of the eleven studies, we found a significant association between efficacy in drug combinations and a population shift towards the drug resistant strain for the microorganism of interest.

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INTRODUCTION

The CDC (Center for Disease Control and Prevention) estimates antibiotic resistant strains account for more than two million infections and 23,000 deaths each year [1]. From 1997 to 2006, hospitalizations related to antibiotic resistant infections each year increased by 359% [2]. The increased antibiotic resistant infection proportion is believed to be associated with increased consumption of antibiotics. Antimicrobial resistance can occur via specific mechanisms of resistance transfer that include conjugation, transduction, and transformation [3].

Table 1. The CDC classification of significant antibiotic resistant threats [1]

Hazard Level	Antibiotic Resistant Microorganisms
Urgent	<i>Clostridium difficile</i> (<i>C. difficile</i>) Carbapenem-resistant <i>Enterobacteriaceae</i> (CRE) Drug-resistant <i>Neisseria gonorrhoeae</i> (cephalosporin resistance)
Serious	Multidrug-resistant <i>Acinetobacter</i> Drug-resistant <i>Campylobacter</i> Fluconazole-resistant <i>Candida</i> (a fungus) Extended spectrum β -lactamase producing <i>Enterobacteriaceae</i> (ESBLs) Vancomycin-resistant <i>Enterococcus</i> (VRE) Multidrug-resistant <i>Pseudomonas aeruginosa</i> Drug-resistant Non-typhoidal <i>Salmonella</i> Drug-resistant <i>Salmonella typhi</i> Drug-resistant <i>Shigella</i> Methicillin-resistant <i>Staphylococcus aureus</i> (MRSA) Drug-resistant <i>Streptococcus pneumonia</i> Drug-resistant tuberculosis (MDR and XDR)
Concerning	Vancomycin-resistant <i>Staphylococcus aureus</i> (VRSA) Erythromycin-resistant <i>Streptococcus</i> Group A Clindamycin-resistant <i>Streptococcus</i> Group B

Drug resistance variations between different strains of bacteria and viruses exist and contribute to this resistance. For example, in the human immunodeficiency virus (HIV), the level of resistance to antiretroviral drugs differs amongst different HIV variants. In the treatment of *human immunodeficiency virus* (HIV), the level of resistance to antiretroviral drugs differs amongst different HIV variants [4]. As of 2010, animal antibiotic consumption was estimated to be 63,151 tons with predictions for consumption to increase to 105,596 tons by 2030 [5]. As of 2013, animal antibiotic consumption was 131,109 tons, and new projections for 2030 are 200,235 tons [4]. The use of antibiotics increase significantly every year, and projections are often exceeded. In a study that analyzed *E. coli* from 1998-2007 in the United States, *E. coli* increased in resistance against ampicillin, ciprofloxacin, ampicillin/sulbactam, levofloxacin, and trimethoprim/sulfamethoxazole [5]. The prevalence of *Helicobacter pylori* resistance to clarithromycin (1993-2014), metronidazole (1993-2014), and levofloxacin (1999-2014) has steadily increased over time in many countries [2]. As shown in table 1, the CDC has been tracking and classifying antibiotic resistant organisms to better understand the impact on the healthcare system and identify areas of focus for researchers to address increased resistance to currently available antibiotics [1]. These high

priority microorganisms are showing new resistances in recent years and an increased percentage of the respective populations are showing antimicrobial resistance. This systematic review seeks to quantify the trends in antimicrobial growth and analyze the evidence of population shifts in response antimicrobial combination therapy.

This paper will examine combination antimicrobial therapies with respect to their efficacy and effects on antimicrobial resistance during a 25-year period from 1992-2017.

BRIEF INTRODUCTION TO COMBINATION DRUG THERAPY

Combination drug therapy involves using drugs for the purpose of creating an effect that could not be achieved individually [8]. In order to fully understand combination drug therapy, figure 1 adapted from Pimenta et al. places an emphasis on drug effectiveness and drug interactions, including antagonism, additivity, synergism, inertism, and coalism.

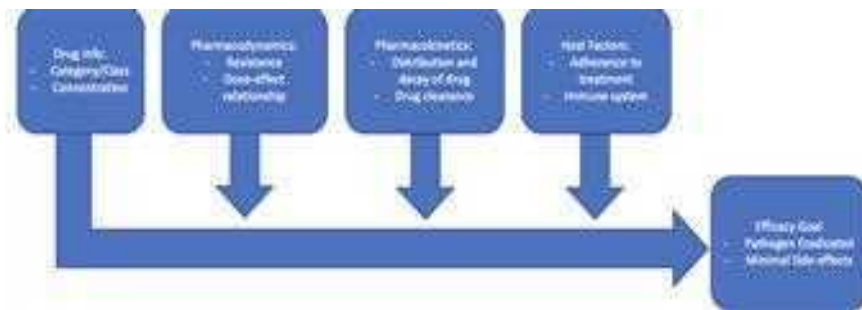


Figure 1. Considerations of drug combination therapy are all considered for the purpose of the efficacy goal.

Both inertism and coalism occurs when a single drug alone has no effect on the pathogen of interest and an additional drug is required for an effect. Synergy is the interaction of drugs to yield a greater combined effect than the sum of their individual effects. Additivity is when the interaction of combined drugs is equal to the sum of their individual effects. Lastly, antagonism interaction of drugs has one drug inhibiting the action of the other.

Drug interactions occur as a result of the characteristics of the drug, the effects of the drug on the body (pharmacokinetics), the way the drug moves through the body (pharmacodynamics), and characteristics of the host itself. Therefore, the same factors are studied to know how efficacious a drug is against a certain microorganism. An emerging understanding of combination therapies suggests that efficacy and resistance are related in shifting the proportion of antibiotic resistant versus antibiotic susceptible populations.

By utilizing an ecological model framework, mental illness can be demonstrated on a multilevel system of mutual interaction and influences that contribute to its perceived worth and importance. In particular, the Social Ecological Model (SEM) of health delves into the intrapersonal (individual belief and cognition), interpersonal (family and peers), organizational (community health centers and medical providers), community (identity factors of ethnicity and culture), and societal levels (policy and government) have been explored to better understand the beliefs and barriers of mental health acceptance and health-seeking behavior within this population. Research has indicated that various interconnected

factors in the mismanagement of refugee mental health continue to occur and a need for targeted interventions must be implemented if optimal mental health outcomes are to be attainable [2].

MIXED EFFICACY OF MONOTHERAPY VERSUS COMBINATION THERAPY

There has been a great deal of controversy about the best treatment options. The results of both in vivo and in vitro investigations are mixed in regards to whether monotherapy or combination therapy is the superior treatment. To illustrate this, a study for each of the urgent hazard level organisms will be discussed: *Clostridium difficile* (*C. difficile*), carbapenem-resistant enterobacteriaceae (CRE), drug-resistant *Neisseria gonorrhoeae* (cephalosporin resistance). In the first meta-analysis, the authors compared the results of metronidazole monotherapy with vancomycin monotherapy and combination therapy in patients infected with *Clostridium difficile* (*C. difficile*) [9]. The results showed an equal efficacy for both drugs individually, but they noted that the combination produced additional side effects without increasing the efficacy synergistically [9]. In another meta-analysis that looked at carbapenem-resistant enterobacteriaceae (CRE), the evidence suggested that use of combination therapy relative to polymyxin monotherapy produced lower 28-day or 30-day mortality [10]. An investigation of drug-resistant *Neisseria gonorrhoeae* (cephalosporin resistance) chose to look at the varying efficacies across different pairs of combination therapy [11]. The results showed varying degrees of efficacy, but those with the highest efficacy were not effective against a certain strain that was affected by the lower efficacy combinations [11]. The best available treatment options in terms of efficacy vary in effect depending on the organism, and even some cases the individual strains will determine the treatments with the highest efficacy.

CONSEQUENCES OF TREATMENT

Since the antibiotics that are used to treat patients provides a competitive advantage for resistant strains, patients who were exposed to antibiotics in general were more likely to be colonized by MRSA in a hospital setting according to a meta-analysis [12]. This occurs primarily by indiscriminately disrupting the normal microflora, which in turns provides more room and resources for colonization by drug resistant bacteria [13]. Although most antimicrobials approved by the FDA are safe and contain minimal side effects, some can have life-threatening side effects [14]. The severity of the side effects is dependent on the patient themselves with factors such as immunodeficiency, age, and comorbidity coming into play [15].

In 2016, the CDC published a study that found the manner of prescribing antibiotics had not changed significantly from 2006-2012. More than 50% of patients staying at a hospital had been prescribed at least one antibiotic during their stay [16]. This led to the implementation of stewardship programs for hospitals [17]. These programs include tracking and reporting the prescription and use of antibiotics. Perhaps the most important involves

educating physicians about the emerging resistance and optimal prescription methods following clinical guidelines provided by the hospitals [17]. The CDC has also implemented the program, Be Antibiotic Aware, that includes evidence-based methods to improve and control for the use of antibiotic therapy given to patients in hospitals, clinics, and private practice settings [18].

OUR SEARCH

An initial search was conducted on September 17, 2018 using Google Scholar to look at trends in antibiotic resistance in the last 25 years. A systematic review using peer reviewed journal articles published on the Internet was performed to analyze trends in antimicrobial resistance. Any publications that were not peer-reviewed publications were thrown out. The search was then narrowed down to include resistance of combinational antibiotic drug therapy use and its efficacy using the PubMed database. MeSH terms for “combinational drug therapy” and “antibiotic resistance” were defined using this database yielding a total of 2029 results. The MeSH terms were further defined to include the following subheadings: adverse effects, analysis, statistics and numerical data, drug chemistry, ethics, etiology, mortality, physiology, therapeutic use, therapy, toxicity, trends, treatment outcome. These subheadings included information pertinent to obtaining peer-reviewed articles that encompassed the efficacy of drug treatment. This refined search resulted in a total of 212 non-duplicated research articles, which were screened using the inclusion/exclusion criteria defined in the sections below. The primary screening included collecting the date of publication, bacterial organism, study design, and sample size of each article. After articles were excluded, the remaining 11 articles were analyzed. Additionally, the results of the systematic review were categorized according to year of publication, organism of interest, and classification of organism in figures 2-4.

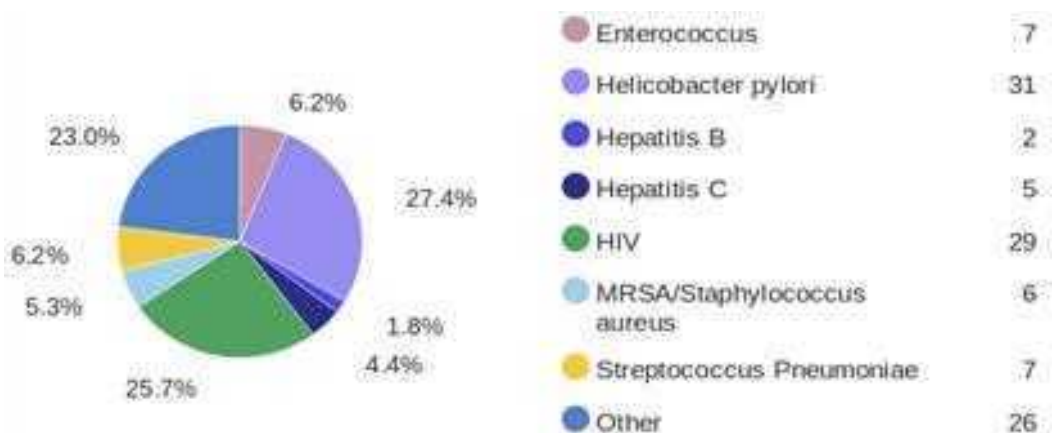


Figure 2. This pie chart breaks down the distribution of primary research articles that were focused on the resistance or susceptibility of different microorganisms elicited in the investigation. The other category was comprised of single mentions of microorganisms or neutropenia. The results are shown in both percentages as well as raw numbers.

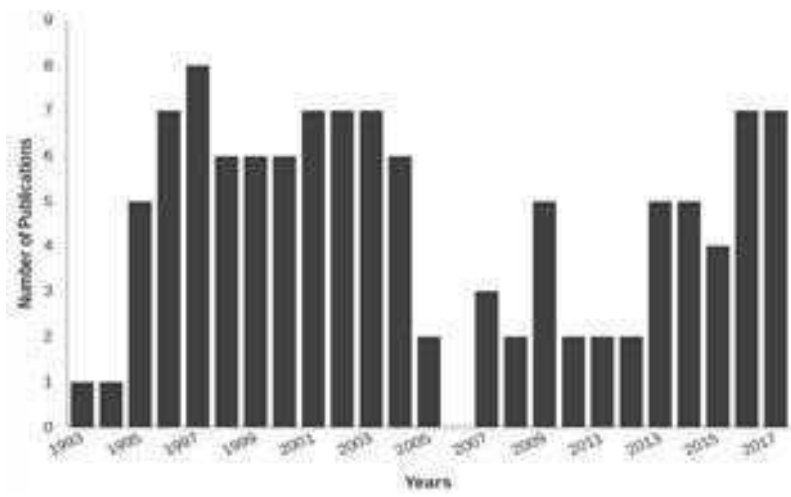


Figure 3. This pie chart breaks down the distribution of primary research articles that further quantified susceptible and resistant strains in in vivo experiments.

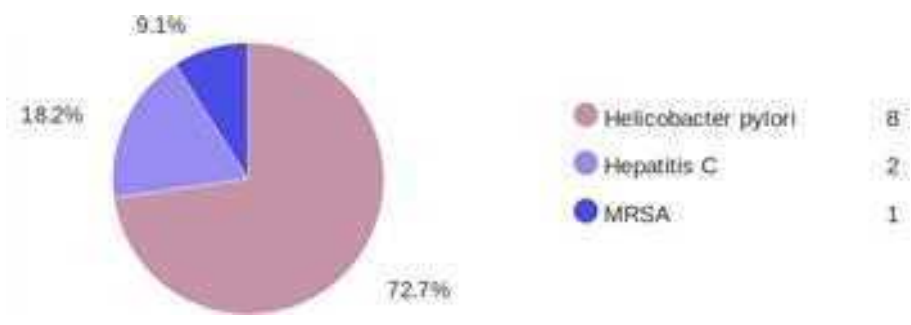


Figure 4. This bar chart breaks down the distribution of primary research articles by quantifying the distribution of the publications analyzed by year of publication.

Inclusion Criteria

The target population of this study included published articles that included both the effect and efficacy of combinational drug therapy on antimicrobial resistance. They were separated by microorganisms and ranked by year of publication. The studies that included similar microorganisms were grouped together and reviewed. Those organisms that had the highest frequency of studies conducted were included in this review. Drug resistance trends that stood out in the screening included the following bacterial organisms: Hepatitis C, MRSA, and *Helicobacter pylori*.

Exclusion Criteria

Case studies, narrative reviews, meta analyses, and opinion pieces were excluded from this review. Articles that included comorbid bacteria resistance seen with a chronic disease were excluded.

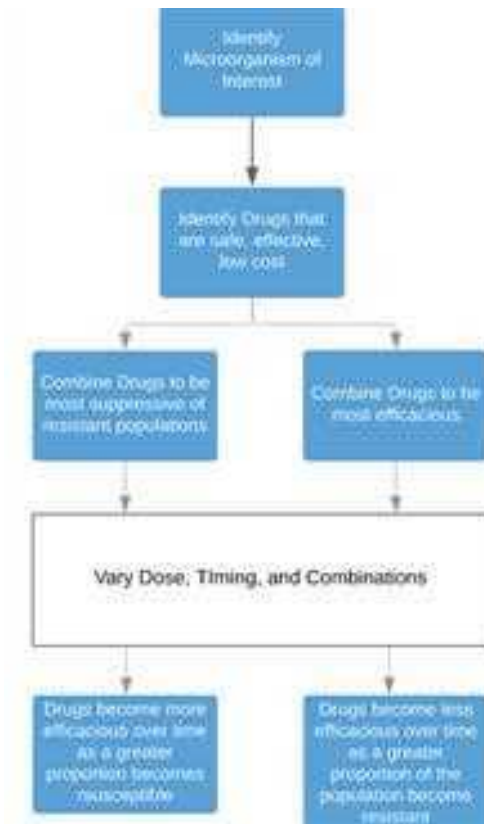


Figure 5. This flow chart simplifies the decision process in how the choices currently being made are affecting the future of antimicrobial therapy.

Data Collection and Analysis

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) model was used in order to reduce the potential for bias in the study and to standardize the evaluation of the evidence. Data was gathered from the 11 articles. The name of the organism and antimicrobial drugs were collected on a table along with the efficacy and p value.

To further analyze the trends of antimicrobial resistance within the last 25 years, graphs were made summarizing four extensively studied microorganisms affecting humans: *Salmonella*, *Shigella*, *Escherichia coli* and *Campylobacter jejuni*. The information from the four organisms was extracted from the Center for Disease Control and Prevention National Antimicrobial Resistance Monitoring System's database.

FINDINGS

The history of the development of antimicrobial resistance was analyzed from 1996 to 2015 for four bacteria: *Salmonella*, *Shigella*, *Escherichia coli*, and *Campylobacter jejuni*. Four antibiotics were tracked for each bacteria for a total of sixteen trends to be analyzed. The

data was originally collected as part of the National Antimicrobial Resistance Monitoring System published by the CDC. Two important trends appear in each of the four microorganisms analyzed: an antibiotic resistance develops in a bacteria where none had existed before and a substantial increase in resistance is observed across many years for those antibiotics under observation. A gain of new resistance was seen in salmonella for ciprofloxacin, in shigella for cefoxitin, in *Escherichia coli* for nalidixic acid, and in *Campylobacter jejuni* for telithromycin. In 1996, less than one percent of the salmonella population was resistant to nalidixic acid, but by 2015 almost five percent of the population was resistant to nalidixic acid. In 1999, less than sixty percent of shigella was resistant to streptomycin, but by 2015 almost a hundred percent of the reported population was resistant to streptomycin. In 1996, only two percent of the reported *Escherichia coli* was resistant to streptomycin, but by 2015 the percentage had risen to over twelve percent. In 1997 less than twenty percent of the *Campylobacter jejuni* population was resistant to either ciprofloxacin or nalidixic acid, but by 2015 almost thirty percent were resistant to both [16].

Relationship between Resistance and Efficacy

Eleven studies met the inclusion criteria for quantifying the efficacy of combination therapy regimens in vivo in both susceptible and resistant strains in microorganisms. Among these studies, eight studies examined *Helicobacter pylori*, two studies examined hepatitis C, and one study examined methicillin-resistant *Staphylococcus aureus*. The study by Song et al [19] found that among those strains of *Helicobacter pylori* that undergo a quadruple therapy of esomeprazole, amoxicillin, clarithromycin, and tinidazole, there was a significant association found in the strains that were resistant to clarithromycin and metronidazole. The resistant group for amoxicillin only contained three people, which is the most likely reason that no significant association was found between the susceptible and resistant group. This significance demonstrates a significant population shift towards the resistant strains in both the cases of clarithromycin and metronidazole resistant strains following exposure to the quadruple therapy. Before the quadruple therapy, there were 72 populations of clarithromycin susceptible strains and 63 populations of clarithromycin resistant strains. After exposure, there were 6 populations of the susceptible strain in the patients and 16 populations of the resistant strain. In the metronidazole groups, the susceptible populations shifted from 44 to 3, while the resistant populations shifted from 91 to 19 populations. This observation is consistent with the shifting of antimicrobial resistance that has been shown in the United States. Among the studies that found a significant population shift following combination therapy, most populations shifted towards a predominance of the resistant strain. This was seen in both the *Helicobacter pylori* as well as *Hepatitis C* virus studies. It should be noted that the in vivo experiments analyzed in this systematic review were not optimized for the purpose of preventing the increasing proportions of antimicrobial resistance. Among the five papers analyzed that did not show a significant population shift, they all had comparison groups that involved less than twenty patients and in some cases the groups contained zero people. These studies were likely underpowered to show a significant difference. The studies used multiple different timings, drug combinations, and doses. These differences are likely to play a role in the shifting of the populations seen in these studies.

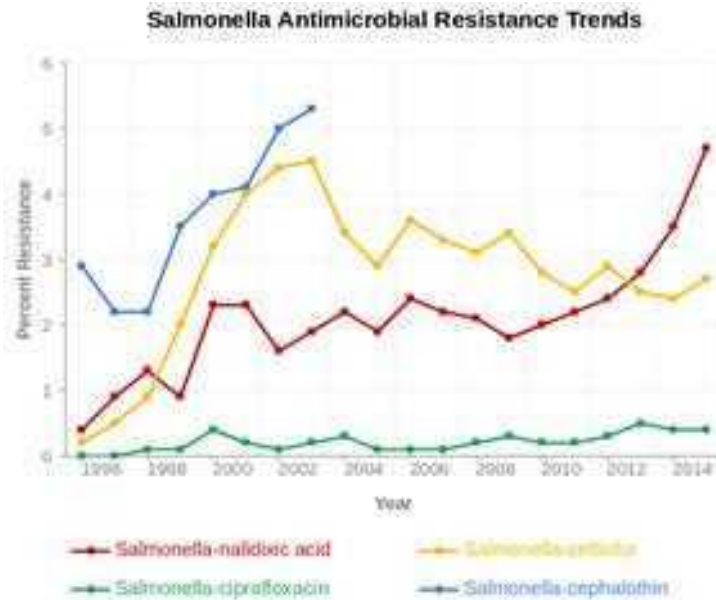


Figure 6. The CDC surveillance of *Salmonella* antimicrobial resistance trends from 1996 to 2015 shows an increase in the proportion of *Salmonella* strains that display a resistance to one or more of the following antibiotics: cephalothin, cefixime, ciprofloxacin, and nalidixic acid [24].

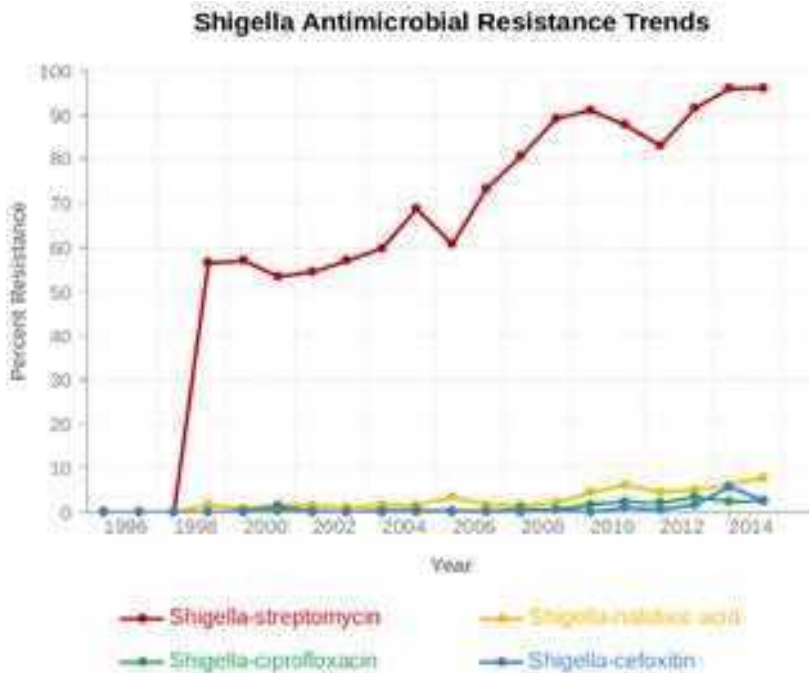


Figure 7. The CDC surveillance of *Shigella* antimicrobial resistance trends from 1996 to 2015 shows an increase in the proportion of *Shigella* strains that display a resistance to one or more of the following antibiotics: cefoxitin, ciprofloxacin, nalidixic acid, and streptomycin [24].

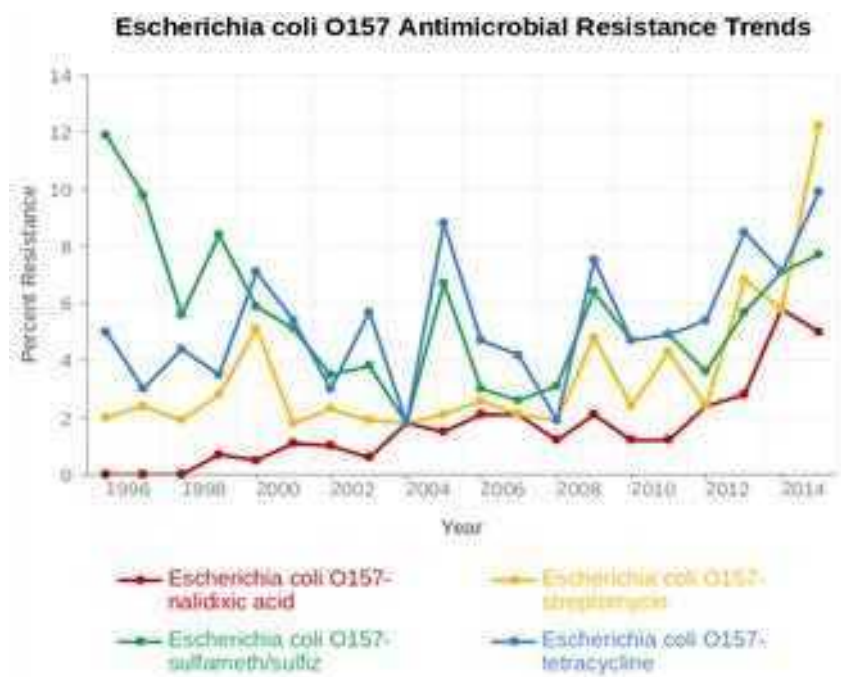


Figure 8. The CDC surveillance of *Escherichia coli* antimicrobial resistance trends from 1996 to 2015 shows an increase in the proportion of *Escherichia coli* strains that display a resistance to one or more of the following antibiotics: nalidixic acid, streptomycin, sulfameth/sulfiz, and tetracycline [24].

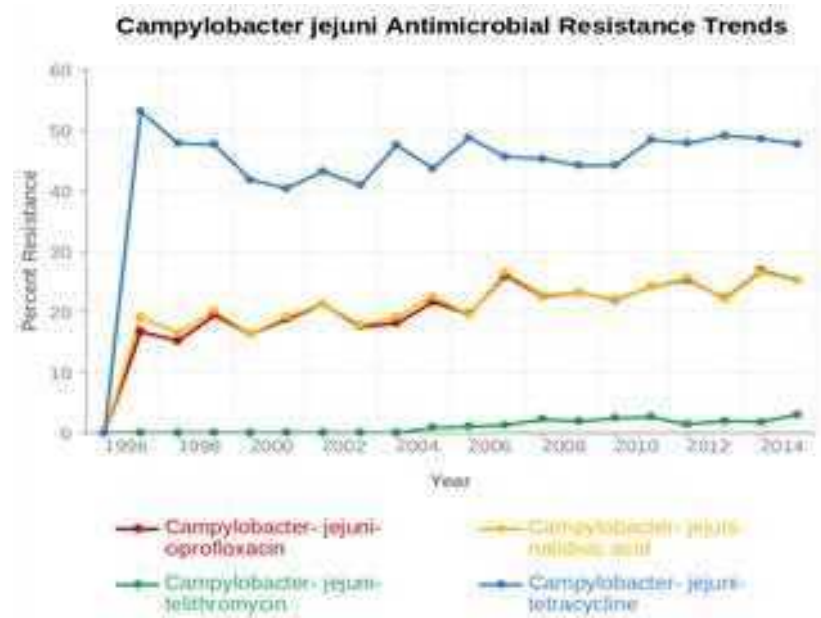


Figure 9. The CDC surveillance of *Campylobacter jejuni* antimicrobial resistance trends from 1996 to 2015 shows an increase in the proportion of *Campylobacter jejuni* strains that display a resistance to one or more of the following antibiotics: ciprofloxacin, nalidixic acid, telithromycin, and tetracycline [24].

DISCUSSION

The CDC created a tool to view the data regarding antibiotic resistance in bacteria isolated from humans through the National Antimicrobial Resistance Monitoring System. Figures 6-9 show trends over time of the resistance of four bacteria: *Salmonella*, *Shigella*, *Escherichia coli*, and *Campylobacter jejuni* against four common antimicrobials. The general trend is consistent with an increase of bacterial resistance to commonly used antibiotics [16]. These trends are heavily influenced by the current application of antibiotics in clinical practice. The variety of regimens currently employed to maximize efficacy are shifting the proportion of the population to favor resistant strains. This is the result of most experiments focusing on maximizing short term gains at the expense of long term losses. This decision process is simplified in figure 5.

Suppressive drug combinations are combinations of drugs that have a lower combined efficacy than the sum of its parts. One or more drugs must at least be partially antagonistic. The treatment with the highest efficacy is typically the favored treatment as long as cost and side effects are minimal.

Until recently the bias towards choosing the highest clinical efficacy did not appear to have major drawbacks, because the effect on antimicrobial resistance was not well understood. To illustrate this effect, researchers compared a suppressive drug combination versus a synergistic drug combination with high efficacy [20]. In the experiment, doxycycline-resistant and doxycycline-sensitive *Escherichia coli* were treated with either the additive drug combination of doxycycline and erythromycin or the suppressive combination of doxycycline and ciprofloxacin [20]. The suppressive combination resulted in the doxycycline susceptible strain out competing the doxycycline resistant strain, while synergistic pair resulted in the doxycycline resistant strain overtaking the population [20]. The results in the synergistic pair are in line with current clinical approaches and the observed population trends. The results of the suppressive combination provides in vitro evidence that demonstrates that these resistant strain population trends can be reversed. Another research group was able to demonstrate in vivo a specific mechanistic relationship among antagonistic suppressive antimicrobial combinations [21]. Specifically they tested a wide range of bactericidal and bacteriostatic pairs [21]. They were able to observe a population shift towards the bacteriostatic susceptible strain [21]. The strains that became resistant to the bacteriostatic drug went on to grow and incorporate a bactericidal drug, which resulted in the death of the bacteria that developed resistance to the bacteriostatic drug [21].

There are also exceptions to antagonistic combination being the best tradeoff between efficacy and drug resistance prevention. Mathematical models based upon *P. aeruginosa* have shown that under certain conditions the synergistic pair will have the highest efficacy and the highest prevention of antimicrobial resistance such as at the onset of infection when populations are low and competition for resources is limited [22]. The models suggest that prevention of antibiotic resistance is better served by antagonist combinations [22]. This understanding can help clinicians understand the best treatment for preventing resistance by discerning the microbial growth patterns in response to early interventions versus late interventions. Recent modeling of clinical interventions has capitalized on this understanding of competition for resources in population of susceptible versus resistant strains of bacteria. The models take advantage of an initial stage, where the susceptible strain over takes the

resistant strain [23]. There are several potential mechanisms to bring about this effect. The carrying of a resistant plasmid comes with the cost of reduced fitness in the absence of an antibiotic particularly when competition for resources is at its highest [23]. At capacity, the susceptible strain out competes the resistant strain [23]. Another example is activating the resistant genes that activate efflux pumps, which has the net effect of increasing the carrying cost of the resistant genes [23]. Once the population of resistant strains has been greatly reduced or altogether eliminated through competition, the synergistic combination of drugs would have optimal effects for highest efficacy as well as drug resistance prevention. These in vivo based models collectively represent a new approach to treating infectious disease and an evidenced based approach to reducing antimicrobial resistance.

CONCLUSION

This study provided a systematic review of the efficacy of combination drug therapies and their relationship with shifting the population of susceptible versus resistant strains of microorganism in in vivo studies. None of the in vivo study findings were significant for suppressive relationships that shifted the populations in favor of the susceptible strains as has been found in in vitro studies; however, none of the studies reviewed intended to use the combination therapy with the intent of suppression of the resistant populations. It is pertinent that physicians keep up to date with the recent studies pertaining to multi drug therapies and their effects on organisms. Further research should continue to be conducted in order to fully understand the efficacy of using multiple drugs in treating pathogens. Additionally, adherence to antimicrobial stewardship programs (ASPs) set out by the CDC can improve the spread of infections and therefore help to reduce the antibiotic resistance [25].

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Chapter 75

KNOWLEDGE, ATTITUDES AND PRACTICES OF DIABETIC PATIENTS AT A CLINIC IN GRENADA: IMPLICATIONS FOR HBA1c LEVELS

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ABSTRACT

In Grenada, data on patients' knowledge and practices regarding the management of diabetes is virtually absent. The prevalence of diabetes is, however, relatively high in the country. The authors conducted this pilot study with a convenient sample of 20 patients in one clinic of which 8 had a low average HBA1c level (6-8%), 5 had a middle average HBA1c level (9-11%) and 7 had a high average HBA1c level (12->14%). Overall, 13 respondents used medication to manage the disease of which 4 also used diet and exercise. Fifteen respondents correctly identified diabetes as "higher than normal levels of sugar in the blood," however, only 12 correctly identified all the symptoms of diabetes in a list that was provided. Sixteen respondents stated they engaged in physical activities and 12 respondents did not follow a diet plan. The number of patients that regularly tested blood glucose levels and did eye checks was not exceptionally high. The results are indicative of a disconnect between knowledge and practice by the patients. An education program may be necessary, designed to reinforce knowledge leading to behavior change towards reducing blood sugar levels. The findings also highlight the need to monitor the impact of current programs and to develop new evidence-based interventions for the management of diabetes in Grenada. Finally, this pilot study can serve as a reference to guide in designing a study for a larger sample and serve as a baseline to compare findings regarding the management of diabetes in Grenada.

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INTRODUCTION

Diabetes is a major global public health problem with increasing prevalence in middle and low-income countries [1]. The chronic condition develops when the pancreas does not produce sufficient insulin (type I diabetes) or when insulin is not efficiently metabolized in the body (type II diabetes) resulting in consistently high blood glucose levels [2]. Type 1 diabetes is diagnosed mostly in children and young adults while type II diabetes mostly affects middle-aged and older adults [2]. Diabetes can lead to progressive and debilitating complications of the brain, kidneys, heart, muscles and eyes [3]. Some of the complications caused by diabetes include weight gain, hypertension, blindness, amputation, neuropathy, stroke, coronary artery disease, end-stage renal disease, dialysis and eventually death [3].

The International Diabetes Federation (IDF) 2017 Atlas reported that approximately 425 million people worldwide or 8.8% of adults aged 20-79 years had diabetes and four million died from the complications. Approximately 79% of people with diabetes reside in low and middle-income countries. Based on the trends, it was estimated that by 2045, 629 million people within the age group will develop diabetes. Among the age group 20-79 years, 10.7% of all-cause global mortality was due to diabetes [4].

Diabetes has a considerable financial impact on the healthcare systems of countries as well as the affected individuals and their families. In many developing countries, diabetes treatment consumes 5-20% of the health care budget, with more than 50% of the cost arising from the treatment of complications [5]. Among the seven IDF regions, the North American and Caribbean region spend the highest amount on diabetes (20-79 years) estimated at 383 billion international dollars (ID). This corresponds to 52% of the total amount spent on diabetes treatment globally in 2017 [4]. In the Caribbean, the economic burden of diabetes was estimated by the Caribbean Public Health Agency (CARPHA) to be between 1.4% and 8% of the gross domestic product (GDP) [6].

In 2017, the prevalence of diabetes among persons aged 20-79 years in Grenada was 10.7% of the population [7]. Diabetes also ranked third among diseases that caused death on the island [8]. Between 1990-2013, the annual mortality rate (per 100,000 people) from diabetes has increased by 57.5% [9]. Additionally, since 1990, there has been an increase of 41.2% of annual years of healthy life lost (per 100,000 people) from diabetes. Alcohol, drug use, smoking tobacco, low physical activity, unhealthy diet, high body mass index and high fasting plasma glucose were some of the risk factors cited as contributing to deaths from diabetes in 2013 [9]. Exercise, diet and medication are beneficial for the prevention and management of diabetes.

The existing data shows diabetes is prevalent in Grenada and provides a basis for the development and implementation of interventions to prevent and manage the disease. To be effective, however, interventions must address gaps in knowledge, attitudes and behaviors of persons at risk and those affected by the disease. There is a paucity in published information regarding knowledge, attitudes and practices in relation to the management of diabetes in patients. The authors, therefore, conducted this pilot study at one clinic to understand factors that may be critical for addressing high blood glucose levels in Grenada. Further, the findings can be a useful reference for current programs to improve the effectiveness in addressing gaps in the system and behavioral risk that contribute to the high prevalence of the disease on the island. This pilot study does not allow for extrapolation to the wider population of patients

with diabetes. Nonetheless, the results can also provide an indication of the significance of variables for inclusion in future studies involving samples that are representative of the diabetic patient population.

OUR STUDY

This pilot study was approved by the Institutional Review Board (IRB) at St. George's University in Grenada [10]. The study was conducted at one clinic in the parish of St. George. Fifty patients who attend the outpatient clinic with a minimum of one record of abnormal HBA1c level were initially identified in the Patient Laboratory Database at the clinic, for participation in the survey. The selected patients were categorized according to high (12-14%), middle (9-11%) and low (6-8%) HBA1c levels. The inclusion and exclusion criteria for participation in the study were as follow:

Inclusion criteria

- Patients aged 20-79 years
- Male and female patients
- Diagnosis of type 2 diabetes
- A minimum of 1 record of abnormal HBAIC levels ranging from 6% - >14%
- Utilize the services at the outpatient clinic .

Exclusion criteria

- Diagnosis of type 1 diabetes
- Patients not diagnosed with abnormal HBAIC levels ranging from 6% - >14%

Development of the Data Collection Instrument

The data collection instrument consisted of 41 questions adapted from the study conducted by Beaubrun-Toby in Trinidad in 2014 [11] and from the Diabetes Attitude Survey provided online by the University of Michigan Diabetes Research and Training Center [12]. Open-ended, closed-ended and Likert scale questions were included in four sections: demographics, knowledge of diabetes, attitude towards diabetes, and diet and health practices in relation to managing diabetes. Pilot testing for clarity and comprehension of the instrument was done with five staff members and patients at the clinic. The instrument was revised to include recommendations from the pilot group and other revisions to improve clarity and ease of use of the instrument.

Recruitment and Administration and Analysis

Participants were contacted by the principal investigator (PI) to secure approval for their participation in the study. Informed consent was required for participation in the survey. Patients who consented were invited to do the survey at the clinic. Of the 46 patients contacted, 25 consented to participate in the study, however, questionnaires were completed by 20 patients. Convenience sampling was therefore used in this study.

The survey was administered face to face by the PI over a twelve-week period between November 26th, 2018 to February 15, 2019. Responses were recorded on the questionnaire. The responses were entered into a Microsoft Excel spreadsheet and imported into SPSS. The frequency of responses was analyzed and reported. Compensation was not provided for participation in the study.

FINDINGS

The study was conducted with 20 patients, with the majority (11, 55.0%) residing in the parish of St George. More females (11, 55.0%) participated in the study than males (9, 45.0%). The majority, (13, 65.0%), of respondents were in the age group 51-65 years. The most frequent weight of the respondents (8, 40.0%) was 151-200 pounds. The most frequent heights were 5 ft 6 inches - 5 ft 12 inches (7, 35.0%) and 5 ft - 5 ft 5 inches (6, 30.0%), respectively. Most respondents were married (11, 55.0%) and employed full time (11, 55.0%). The highest levels of education attained by respondents were primary school (5, 25.0%) and secondary school (6, 30.0%). Table 1 shows the demographic information for the respondents.

Table 1. Demographic information for the respondents

Demographic indicator	Number (n)	Percentage (%)
<i>Parish of Residence</i>		
St. George	11	55.0
St. David's	3	15.0
St. Mark's	1	5.0
St. John's	3	15.0
St. Andrew's	1	5.0
St. Patrick's	1	5.0
Carriacou & Petite Martinique	0	0.0
<i>Gender</i>		
Male	9	45.0
Female	11	55.0
<i>Age (years)</i>		
20-35	2	10.0
36-50	2	10.0
51-65	13	65.0
66+	3	15.0
<i>Height (ft & inches)</i>		
5'-5'5"	6	30.0
5'6"-5'12"	7	35.0
6' & over	4	20.0
Don't know	1	5.0

Demographic indicator	Number (n)	Percentage (%)
No response	2	10.0
<i>Weight (lbs)</i>		
100-150	2	10.0
151-200	8	40.0
201-250	1	5.0
>250	3	15.0
Don't know	2	10.0
No response	4	20.0
<i>Marital Status</i>		
Never married	7	35.0
Married	11	55.0
Widowed	2	10.0
Common Law Union	0	0.0
Separated/Divorced	0	0.0
<i>Employment</i>		
Attending an educational institution	0	0.0
Full-time, 35 hours or more a week	11	55.0
Part-time, less than 35 hours a week	1	5.0
Unemployed and looking for a job	0	0.0
Unemployed and not looking for a job	1	5.0
Homemaker	2	10.0
Retired	4	20.0
Disables, not able to work		
Other: Self employed	1	5.0
<i>Level of Education</i>		
Primary school	5	25.0
High school	6	30.0
College	2	10.0
Technical or trade school	2	10.0
University graduate	1	5.0
Postgraduate degree	3	15.0
Other: None	1	5.0
<i>Diagnosis of Diabetes</i>		
<1 year	1	5.0
1-2 years	3	15.0
3-5 years	1	5.0
6-10 years	3	15.0
>10 years	5	25.0
Don't know	1	5.0
No response	6	30.0

DIAGNOSIS AND TREATMENT

The respondents reported on the time they were diagnosed with diabetes. One quarter (5, 25.0%) reported they were diagnosed more than ten years ago while (6, 30.0%) reported they were not diagnosed. One (5.0%) reported they were diagnosed less than one year ago and 3-5 years ago, respectively; three (15.0%) reported 1-2 years ago and 6-10 years ago, respectively. Table 1 shows the time at which patients reported they were diagnosed with diabetes. Of the 20 respondents, 8 (40.0%) had a low average HBA1c level (6-8%), 5 (25.0%) had a middle average HBA1c level (9-11%) and 7 (35.0%) had a high average HBA1c level (12->14%). Figure 1 shows the proportion of respondents by HBA1c levels.

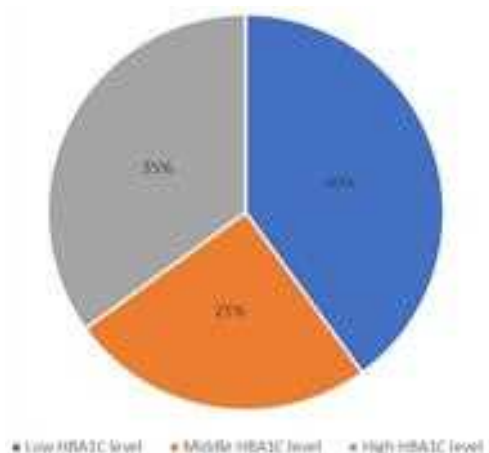


Figure 1. HbA1c categories of the respondents.

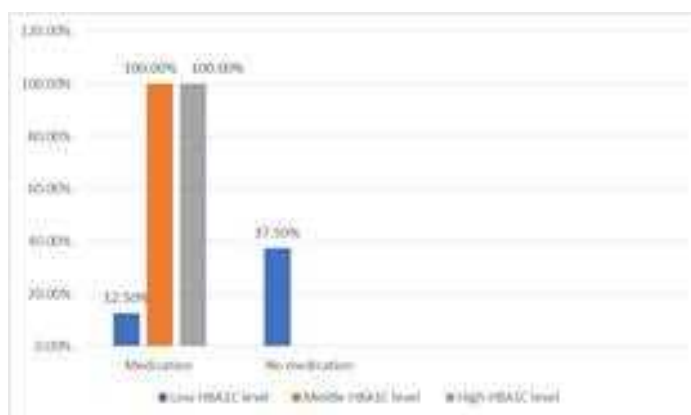


Figure 2. Patient responses regarding the use of medication to manage diabetes.

Table 2. Patients responses on measures to control diabetes

Method of Control	Low HbA1c levels n=8	Middle HbA1c levels n=5	High HbA1c levels n=7	Total HbA1c levels n=20
Insulin only	0 (0.0)	0 (0.0)	1 (14.3%)	1 (5.0%)
Diabetes Medication only	1 (12.5%)	2 (40.0%)	2 (28.6%)	5 (25.0%)
Insulin + Diabetes Medication only	0 (0.0)	1 (20.0%)	2 (28.6%)	3 (15.0%)
Diet only	1 (12.5%)	0 (0.0)	0 (0.0)	1 (5.0%)
Exercise only	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diet + Exercise only	2 (25.0%)	0 (0.0)	0 (0.0)	2 (10.0%)
Diabetes medication + Diet+ Exercise	0 (0.0)	1 (20.0%)	0 (0.0)	1 (5.0%)
Insulin + Medication + Diet	0 (0.0)	1 (20.0%)	0 (0.0)	1 (5.0%)
Insulin + Diet + Exercise	0 (0.0)	0 (0.0)	1 (14.3%)	1 (5.0%)
Insulin + Medication + Diet + Exercise	0 (0.0)	0 (0.0)	1 (14.3%)	1 (5.0%)
No answer	2 (25.0%)	0 (0.0)	0 (0.0)	2 (10.0%)
Not applicable	2 (25.0%)	0 (0.0)	0 (0.0)	2 (10.0%)

In the Low HBA1c level category (n=8), only 1(12.5%) respondent used medication to manage their diabetes, one (12.5%) used diet only and 2(25.0%) used diet and exercise. One quarter (25.0%) in that category did not respond and an equal percentage indicated that the question was not applicable to them. In the middle (n=5) and high HBA1c level category (n=7), all respondents used insulin or other medication to manage the disease. In the middle category, two (40.0%) also used diet and exercise along with insulin/medication. In the high category, two (28.5%) used diet and exercise along with insulin/medication. Overall, 13 (65.0%) of the respondents used insulin/medication of which four (30.0%) also used diet and exercise and three (15.0%) only used diet and exercise to control the disease. Table 2 and Figure 2 show information about the measures used by the respondents to manage diabetes.

Knowledge of Diabetes and Control Measures

Regarding the definition of diabetes, the majority (15, 75.0%) of respondents correctly selected “higher than normal levels of sugar in the blood.” Regarding identifying symptoms of diabetes, most of the respondents (12, 60.0%) correctly selected “all of the above” which included slow healing of wounds, increased tiredness, increased frequency of urination at night and increased thirst and hunger. Eighteen (90.0%) of respondents stated the correct way to monitor diabetes is to “check blood glucose levels.” Two (10.0%) respondents did not know of any way to correctly monitor diabetes. Twelve (60.0%) respondents stated blood glucose levels should be checked once “every day” if using another measure to control diabetes. Seven (35.0%) respondents felt diabetic patients should have their eyes checked “once every six months,” an equal number of respondents felt the check should be done “once a year” and five (25.0%) stated they “did not know” how often the check should be done.

Table 3. Patients agreement with statements regarding diabetes

	Strongly Agree		Agree		Neutral		Disagree		Strongly Disagree	
	n	%	n	%	n	%	n	%	n	%
In general, I believe that what I do as a diabetic patient has more effect on my health than anything that a doctor, nurse or dietician can do	11	55.0	6	30.0	2	10.0	1	5.0	0	0.0
In general, I believe that as a diabetic patient, I should learn a lot about the disease so I can manage my own diabetic care	12	60.0	7	35.0	1	5.0	0	0.0	0	0.0
In general, I believe that I can prevent the complications of diabetes by keeping my blood sugar close to normal	12	60.0	7	35.0	1	5.0	0	0.0	0	0.0
In general, I believe that people whose diabetes is treated by just a diet do not have to worry about getting many long-term complications	0	0.0	6	30.0	3	15.0	7	35.0	2	10.0
In general, I believe that it is frustrating for people with diabetes to take care of their disease	1	5.0	10	50.0	2	10.0	3	15.0	2	10.0

Eight (40.0%) of respondents correctly stated regular urine test will help monitor “how well the kidneys are functioning” and seven (35.0%) stated they “did not know” what regular urine test would help monitor. Regarding proper foot care, the respondents were allowed to

select more than one answer. Eight (40.0%) respondents selected “choose the best possible footwear,” 10 (50.0%) selected “inspect and wash feet every day” and seven (45.0%) selected “not walk barefoot inside and outside the house.”

When asked about control factors for blood sugar, most of the respondents (14, 75.0%) selected the option “all of the above” which included regular exercise, a well-balanced diet and medication. In relation to the treatment of diabetes, 16 (80.0%) indicated diabetes can be treated by blood sugar lowering medication of which three (19.0%) also selected eating bitter vegetables. When asked about problems that may arise from untreated diabetes, the majority (18, 85.0%) selected the option “all of the above” which included eye problems, kidney problems, foot ulcers and heart problems.

Attitude towards Diabetes

The respondents were asked to state their level of agreement with statements about diabetes. Table 3 shows the responses. Generally, the majority (55-60.0%) of respondents strongly agreed or agreed with correct statements while 10.0-20.0% disagreed with statements.

Diet and Health Practices

The respondents were asked about diet and health practices. The majority (16, 80.0%) stated they exercised or engaged in physical activities. Some of the activities included walking (8, 40.0%), going to the gym or exercising on a machine (5, 25.0%), running (1, 5.0%), gardening (1, 5.0%), playing sports (1, 5.0%). Three (15.0%) of the respondents did not state an activity but indicated that were active, generally.

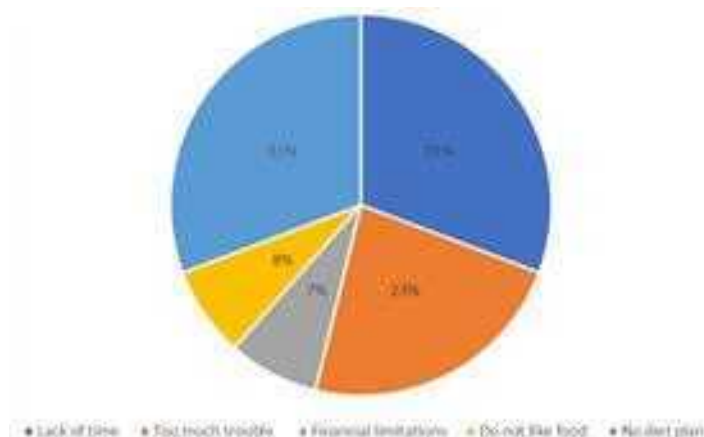


Figure 3. Patients responses regarding reasons for not following controlled diet/meal plan.

With regards to following a controlled diet/meal plan, 12, (60.0%) of the respondents did not follow a plan. The reasons indicated for not following a controlled diet/meal plan included lack of time (4, 20.0%), not having a diet plan (4, 20.0%) too much trouble (3,

15.0%), financial limitations (1, 5.0%), not liking food (1, 5.0%). Figure 3 shows reasons for not following a controlled diet to manage diabetes.

Table 4. Patient responses regarding diet and health practice

Questions	Low HBA1c level n (%)	Middle HBA1c level n (%)	High HBA1c level n (%)	All HBA1c levels n (%)
Exercise/ Engage in physical activity	6 (75.0)	4 (80.0)	6 (85.7)	16 (80.0)
Follows controlled diet plan	1 (12.5)	3 (60.0)	3 (42.9)	7 (35.0)
*Does not miss medication	1 (12.5)	2 (40.0)	3 (42.9)	6 (30.0)
Eye examination 1 year ago or less	5 (62.5)	3 (60.0)	4 (57.1)	12 (60.0)
Urine check 1 month ago or less	2 (25.0)	0 (0.0)	3 (42.9)	5 (25.0)
HBA1c/blood glucose test 1 month ago or less	3 (37.5)	3 (60.0%)	5 (71.4)	11 (55.0)
Fruit consumption > 3x per week	4 (50.0)	5 (100)	5 (71.4)	14 (70.0)
Green vegetables, non starch vegetables and legumes > 3x per week	4 (50.0)	3 (60.0)	3 (42.9)	10 (50.0)
Food not prepared at home < 1x per week	5 (62.5)	2 (40.0)	4 (57.1)	11 (55.0)
Sweetened drinks <1x per week	4 (50.0)	4 (80.0)	5 (71.4)	13 (65.0)
Alcohol <2x per week	7 (87.5)	5 (100)	7 (100)	19 (95.0)
Does not smoke	8 (100)	5 (100)	7 (100)	20 (100)

*One patient in the low HBA1c category took medication for their diabetes. All patients in the middle and high HBA1c category took medication for their diabetes.

Twelve (60.0%) respondents had their eye examination within the last year, 5 (25.0%) had their urine checked within the last month and 11 (55.0%) had their blood glucose/HBA1c test done within the last month. Fruits were consumed more than three times per week by 14 (70.0%) respondents while 10 (50.0%) have meals which consist of green leafy vegetables, non-starch vegetables and legumes more than three times per week; 11 (55.0%) consumed food not prepared at home less than one time per week; 13 (65.0%) drink sugar-sweetened drinks less than one time per week; 19 (95.0%) consumed alcohol less than twice per week and none of the respondents smoked. Table 4 shows the diet and health practices of the respondents.

DISCUSSION

This pilot study was conducted to investigate knowledge, attitude and practices of patients with type 2 diabetes at one clinic in Grenada. Published data is virtually absent on the KAP of diabetic patients in Grenada. This study, therefore, provided an indication of the factors that may be critical for developing interventions to prevent and manage diabetes in Grenada. The findings can also be used to inform changes in current interventions to improve effectiveness by targeting specific issues in relations to knowledge and practices. The results can provide an indication of the significance of variables for inclusion in future studies involving samples that are representative of the diabetic patient population. This small pilot study does not allow for extrapolation to the wider population of patients with diabetes.

The study in Grenada was indicative of the patients having extensive knowledge about diabetes. It appeared that the results of the study, regarding knowledge about diabetes, may differ from the general findings in a study in Trinidad, a neighboring Caribbean country. The findings from the KAP study in Trinidad indicated that the knowledge of the patients with

diabetes was above a basic understanding [11]. However, their knowledge seemed to be limited to understanding symptoms, possible complications of diabetes, what is required to control blood sugar levels and diabetic diet requirements. There appeared to be a lack of knowledge about the causes, nature and treatment of diabetes [11].

Although the respondents in Grenada seemed to be generally knowledgeable about diabetes, the findings also indicated they did not engage sufficiently in practices to manage the disease. The frequencies of activities such as regularly testing blood glucose levels, doing regular eye checks, and following a diet plan were not exceptionally high among the patients. This shows a disconnect between knowledge and practice which is an important point of entry for intervention. An education program may be necessary, designed to reinforce knowledge leading to behavior change. The finding also highlights the need for monitoring the impacts of programs. A system should be developed to ensure that patients who access care in both private and public facilities are monitored to determine how the type of care provided impacts the patient health outcome.

Although most of the patients selected the correct response for how diabetes can be treated, it is interesting to note that a small percentage of participants also indicated that the disease can be treated by eating bitter vegetables. Although this may appear to be insignificant in this study, this response can be an indication of a practice that should be explored further especially within Caribbean societies where herbal medicines are commonly used to manage health problems. Regarding proper foot care, the responses varied with approximately half of the patients selecting one response although the question consisted of more than one correct answer choice. This pattern in the response indicated gaps in knowledge regarding healthy practices to minimize complications.

With regards to attitude towards diabetes, most of the respondents agreed with correct statements. Similar results were obtained from the KAP study in Trinidad and the authors found that the patients may be receptive to diabetes education [11]. However, half of the patients in the Grenada study indicated that it was frustrating for people with diabetes to manage the disease. Frustration may be a deterrent to accessing education. Other factors, such as family support and stigmatization, may also be deterrents. Data from a study with diabetic patients in Malaysia showed that factors outside of knowledge and attitude also had a significant bearing on patient management of the disease [13]. Some possible factors identified in Malaysia were poor self-management, lack of motivation and lack of resources to maintain modification of behavior or lifestyle [13]. Apart from education programs, intra-personal, community, organizational and policy support should be considered to create a holistic enabling environment for behavior change in the management of diabetes. Such change will not only benefit the individual but is vital to reduce the national economic burden associated with providing care for diabetic patients. CARPHA estimated between 1.4% and 8% of the GDP in Caribbean countries was allocated for treating diabetes and related complications [6]. Such allocations may instead be diverted to also provide preventive care.

These findings were similar to the study done in Trinidad where close to half of the patients reported that they did not adhere to the recommended diet [11]. In addition to physical activity, following a proper diet also plays a major role in the management of diabetes. The issue of diabetic patients not having a diet/meal plan needs further evaluation. Meanwhile, some interventions should be developed to address this issue among patients that use the facilities at the clinic. On the other hand, it was commendable that more than half of the patients reported they engaged in physical activities. Physical activity is an important

factor for metabolic improvements and to decrease mortality from the disease. Maintaining physical activities can be a difficult routine for patients. Less than half of the participants in the Malaysian KAP study reported that they exercised regularly [13]. Facilities and programs should be established to motivate patients to exercise regularly. Such programs may include incentives for maintaining healthy behaviors.

It was also interesting to note that some respondents with HBA1c levels between 6.4% and 6.7% did not believe they were diabetic. Therefore, they did not believe some of the questions in the questionnaire were applicable to them or did not adhere to some of the diet and health practices that were necessary for the management of diabetes. According to the American Diabetes Association, the range for pre-diabetes is 5.7%-6.4% and for diabetes is 6.5% or higher [14]. While these patients may not be on medication and their HBA1c levels may fluctuate between the pre-diabetic and diabetic ranges, it is imperative that proper diet and health practices be utilized to prevent an increase of blood glucose to unhealthy levels.

CONCLUSION

In conclusion, findings from this study indicate slightly above-average levels of knowledge, attitude and practices among the patients with diabetes attending the outpatient clinic in Grenada. Albeit, there may be no direct relationship between knowledge and practices as the frequencies of taking action to manage diabetes was not exceptionally high. This study is limited by the small sample size and the findings cannot be extrapolated to the general population of persons with diabetes in Grenada. The patients, however, should engage more actively in self-management and remain committed to lifestyle changes. Additionally, adequate social support has been linked to improved long term disease management, glucose control and health outcomes [13]. Possessing the ability to adapt is also an important skill for managing the disease. Overall, a collaborative effort between patients, health care professionals, family members and peers are essential for creating a supportive environment towards managing diabetes. Support can also be provided through accommodating patients' lifestyle changes and dietary needs and monitoring behavioral change progress. Providing critical support can empower the patient to understand and manage diabetes effectively [13].

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Chapter 76

CARNIVAL BACCHANAL CULTURE AND THE SILENT HIV RISK AMONG FEMALE CARIBBEAN PROFESSIONALS

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ABSTRACT

The feminisation of HIV and AIDS globally has significantly impacted Caribbean nations. Within the last 10-15 years, West Indian females have been disproportionately affected by the spread of HIV at a 3-6 times higher rate than males. This qualitative study explored the sexual behaviours and practices of professional, Caribbean women and their perceived susceptibility to HIV and AIDS: generally, in the broad context of everyday life, and specifically, during the Carnival season. The study also examined the extents to which, in the context of Caribbean culture, professional women felt in command of their health. The study therefore sought to determine if the sexual behaviours and practices of professional women, increased their vulnerability to HIV. Participants were selected from Grenada and Trinidad, known HIV low and high-risk islands respectively. Carnival activities are dominated by women between ages 18-40 years. As such, the study population comprised professional women aged 25-40 years. A cross sectional approach using qualitative research methods was employed: participant observations, interviews and focus groups. It was found that education was not a significant driver of safe sex decision-making. Rather, it was the varying attitudes and perspectives regarding sexuality and the degree of empowerment in relation to physical, sexual, mental, emotional and social well-being that determined safe sex practices. These findings lay a comprehensive and preliminary foundation that can be used to buttress future research on this, traditionally, underexplored area related to the socio-cultural factors that lead to the feminisation of HIV and AIDS in the Caribbean.

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INTRODUCTION

HIV and AIDS is the leading cause of death in the Caribbean among male and female persons between the ages 20-59 years; unprotected sexual encounters between heterosexuals account for the primary means of transmission [1]. Females currently contract HIV at a significantly higher rate than males [2]. Such statistics have been the driving force that catalysed and intensified the amalgamation of efforts among health and gender agencies, at both local and regional levels. The frequency and disproportionate manners in which West Indian women are contracting HIV, as compared to men, has led to the feminisation of HIV; a development with far reaching public health and social consequences that has been largely overlooked in academia.

HIV and its transmission pose a greater threat to Caribbean women as a result of circumstances such as: anatomical composition, geographic location, finance, education, social conditioning and culture. In Trinidad and Tobago, 49.5% of the existing HIV positive cases are men, and 45% are women [3]. Among this population, 40% of them are in the age range of 15-24 years, and 70% of those infected between the age range 15-54 years were females [4]. This represents a much higher percentage of women being infected compared to women living in countries of the Organisation for Economic Co-operation and Development, which includes Grenada [5]. In the male population, HIV is usually prevalent in the age group 45-49 years [6]. In Grenada, in early 2013, 43% of HIV patients were women. There were 334 males and 183 females diagnosed with or currently living with HIV [7]. In 2010, 95% and 91% of pregnant women received HIV testing in Grenada and in Trinidad respectively [8]. This data clearly shows that although HIV is a public health issue, it is also an urgent gender issue [9].

The American Psychological Association [10] asserts that there is a link between low socio-economic status and high-risk sexual behavior among women. Impoverished women may engage in riskier practices making them more susceptible to HIV [11]. The increased accessibility to robust income sources and medical care that is facilitated by completion of higher education should, logically, result in a lower risk of the professional woman contracting HIV. However, a dearth of available research and literature to support this hypothesis demonstrates that the target population: professional Caribbean women, remains under explored.

Carnival is an annual festival of music, dance, alcohol consumption, fetes and masquerade parades. It has become synonymous with bacchanal and abdication of sexual inhibition. In Trinidad, Carnival is a national event, drawing thousands of tourists to the capital city, Port of Spain [12]. It is an enormous party and ranks alongside the Rio de Janeiro Carnival in Brazil in popularity [13]. Grenada's Carnival or 'Spicemas' is substantially smaller than that of Trinidad, but equally renowned for its sensory splendour, colour and revelry.

The purpose of this study has been to investigate a significantly important, yet under researched area in the HIV discourse: the perception of professional women towards themselves; their cultural perspectives on gender and sexual relationships; and how these attitudes influence their sense of empowerment on expressions of their sexuality and safe sex experiences. Using Carnival bacchanal as a hypersexualised site for examination of sexual behaviour, the following have been queried: the degree to which participants demonstrate

self-love and self-efficacy by protecting themselves, both physically and emotionally, in their intimate liaisons; their locus of control vis-à-vis HIV risk exposure; and the influence of tertiary and sex education on their ability to manage their mental and sexual welfare.

OUR STUDY

Carnival activities are dominated by women in the age group 18-40 years. As such, the target population was professional Caribbean women aged 25-40 years, from Grenada and Trinidad. ‘Caribbean woman’ was defined as a woman who spent her formative years in the Caribbean. ‘Professional woman’ was defined as one who attended university and had at least one degree. Sixty participants (see table 1) were randomly selected, from a pool of 80 candidates, and comprised the total sample population. All participants engaged in interviews and/or focus group discussions. To anonymise the participants, different identities were given. The investigation adopted a cross sectional approach using qualitative data collection methods (see figure 1) [14].

Table 1. Participant demographics

Demographics	Variables	Participants
Ages		
	25-30	21
	31-35	19
	36-40	20
Religion		
	Christian	47
	Hindus	5
	Muslim	4
	Other	2
	Atheist	2
Marital Status		
	Married (includes common law)	20
	Separated	2
	Single	35
	Divorced	3
Offspring		
	Children	15
	No children	45
Total		60

An ethnographic map (see figure 2) was drawn up to select participants, where, according to Heckathorn [15], ‘an initial sample [forms] the basis for network sampling’ [15]. This approach was utilised because of its effectiveness to obtain a wide cross-section of participants who met the study criteria. Multiple data collection methods were used for fieldwork to provide depth to the research design and interpretation [16, 17]. Primary data collection involved a complementary methodology (see figure 3) [18]: participant observations, interviews, focus groups and stakeholders’ meetings.



Figure 1. Qualitative research data.

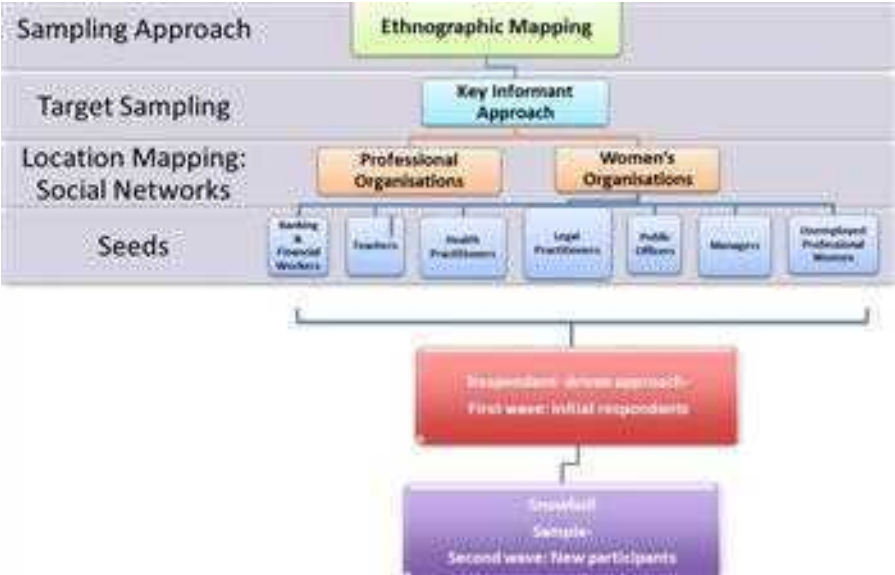


Figure 2. Ethnographic map.



Figure 3. Data collection methods.

Observations were made at 10 different Carnival events. This method offered more credible, first-hand information to describe happenings and arrive at interpretations of them [19]. Interviews and focus groups were held at two universities in Trinidad and Grenada, in a three-week period leading up to the Carnivals. There were 30 semi-structured interviews (see table 2) lasting 1.5 hours each. Six focus groups (see table 3) lasting two hours each, consisting of 5-7 persons were held. Twenty stakeholder meetings, which involved both open and close-ended questions, occurred at the participants' workplaces, and lasted two hours each.

Ethics approval required focus groups to be held centrally in University settings, resulting in a lack of flexibility in hosting sessions in multiple locations. Since protection of privacy was of paramount importance, this kind of variance in venues would have decreased the likelihood of participants being grouped with an acquaintance. This may or may not have contributed to some reticence on the parts of participants who would have preferred to fully maintain their privacy.

Table 2. Interview questions Part A, Part B, and Part C

Part A
Objective: Perception of professional woman toward herself and her sexual partners
<i>To find out how professional women view themselves in relation to men</i>
Would you consider yourself a femme fatale (i.e., an irresistibly attractive woman, especially one who leads men into difficult, dangerous, or disastrous situations)? Why?
Do you consider yourself a sex goddess (i.e., knowing that when you walk into a room, you look fantastic, you are going to turn heads, and that men there are looking at you, thereby giving you that power which makes you feel like a sex goddess)? Why?
Do you consider yourself a sexually adventurous (i.e., bold, daring, exciting, willingness to try new things, fascinated to learn about sex) young woman? Why?
Can you suggest some of the other ways women may consider themselves and why?
<i>To evaluate whether professional women believe in equality between the sexes</i>
Do you believe in feminism (i.e., belief in the social, political, and economic equality of the sexes)? In what ways?
What do you think about equality between the sexes? Is it important to you and your partner in your relationship? To what extent and why?
<i>To assess the role of men in the lives of professional women</i>
Can you tell me a little about whether or not it is important for you to have male partner in your life? Can you give some of your reasons for this?
Generally, do you think that the presence of a male contributes to your happiness? Please explain.
Do you ever give much consideration to your partners' earning capacity in relation to your own? Is this an important issue for you and why?
Part B
Objective: To investigate the attitudes of professional women toward safe sex practices and HIV/AIDS and how these are reflected in their behaviours
<i>To understand the impact of tertiary education on safe sex practices</i>
Do you think that your educational positively and/or negatively influences the application of knowledge about safe sexual practices and behaviours in the everyday living of professional Caribbean women?
With regard to your decisions around sex, have you been contented with the decisions in the past compared with those you are currently making? Do you care to share how so?
<i>To learn about the types of sexual relationships of interest to professional women</i>
What kind of sexual relationships are you interested in- a short or a long term? Can you explain the reasons for this?
Generally, do you feel in control of your choice of sexual partners? Please explain.
Are you interested in engaging in relationships of convenience? (i.e., relationships that fulfil some of your needs as opposed to most of your needs)? If yes, why? If no, why not?
How do you and your partner handle the issue of fidelity? (e.g., is it openly discussed, do you have an open relationship?)

<i>To investigate the safe sex practices of professional women</i>
What does safe sex mean to you? Does this include any medical testing for STIs/HIV? Are you encouraged by your sexual partner/s to practise safe sex? Do you encourage your sexual partners to practise safe sex?
Have you thought about whether or not economic empowerment directly influences safe sex practices for women? In what ways do you think?
<i>To explore professional women's views on various relationship choices in Caribbean culture</i>
What do you think about sex in a monogamous relationship? (i.e., the practice or condition of having a single sexual partner during a period of time)? Is it one that should be physically gratifying, emotional, for safe sex practices etc.?
How do you regard partners who engage in a in a down-low lifestyle (i.e., the behaviour of men who have sex with other men [MSM], as well as with women, but who do not identify as gay or bisexual)? What would you do if you became aware that your partner is on the downlow?
What do you think about women who engage in social prostitution (i.e., where a person may have a sexual relationship with a person in exchange for material gains)?
What are your thoughts on polygamy? (i.e., the practice or condition of having more than one spouse, especially wife, at one time)? Why?
Do you think that professional women engage in multiple sexual partnering (i.e., having more than one sexual partner at the same time)? If so, what in your view might be the reasons?
In your opinion, are professional women open to polyamorous relationships (i.e., the practice pertaining to participation in multiple and simultaneous loving or sexual relationships)? Why do you think this might be so?
Part C
Objective: The influence of Carnival on certain kinds of sexual behaviour on the part of professional women
<i>To find out about professional women's perceptions of Carnival culture</i>
How would you define a Carnival party animal? Would you consider yourself a party animal when it comes to the Carnival season?
Do you believe that wearing revealing clothing to Carnival events influences professional women's own behaviour and how they are viewed by the opposite sex?
<i>To enquire about the value of Carnival celebrations and its impact on the lives of professional women</i>
What do pre-Carnival events (e.g., fetes, cruise, shows etc.) mean to you? Are they considered an important part of the build up to Carnival?
Do you play mas (i.e., join in a Carnival costume band and parade on the streets) for Carnival? Do you enjoy them?
Is alcohol use during Carnival an integral part of enjoying your Carnival activities? If yes, why? If not, why not?
Do people's perceptions of your behaviour (e.g., dancing, alcohol consumption etc.) influence your behaviour around Carnival time?
Generally, do you think that professional women engage in more sexual activity during Carnival time? Why would you say so?

Table 3. Focus group questions Part A and Part B

Part A
Objective: Cultural perspectives of professional women on gender and sexual relationships
<i>To find out whether women are regarded as being repressed or dominated by men</i>
What are your thoughts on patriarchal society (i.e., society being under the repressive domination of men) in the Caribbean context?
<i>To discover whether or not women believe that machismo is a reality in Caribbean society</i>
Do you believe that machismo (i.e., the belief that the man is the provider and dominant one; he is independent, strong and willing to face danger) is a pervasive reality in our Caribbean societies today?
<i>To determine whether or not women believe in marianismo</i>
In what ways is marianismo (i.e., it is the portrayal of the ideal woman as being modest, pure, dependant, weak, vulnerable and abstinent until marriage. When married, the woman becomes subordinate and obedient to her spouse) manifested in the lives of professional women?
<i>To ascertain how professional women view themselves in relation to men</i>
Do you think that women view themselves as equal to men? Why?
Do you think that patriarchal practices are still upheld in their relations with men? How?
Do you believe that there are times when a woman should be submissive to a man based on religious or social norms?
Does emotional dependence on a male partner play a role in determining your self-worth?
Do you think sexual intimacy with a man is important for women to feel loved? Why?

<i>To establish whether or not particular age groups of men are more appealing or sexually attractive to professional women</i>
Which groups of men do you find most appealing to you and why? (e.g., employed or unemployed professional men OR employed or unemployed unprofessional men).
<i>To investigate the kinds of relationships professional women would consider having with men</i>
What kinds of relationships do you think professional women are interested in? Short-term or long-term relationship? (e.g., sexual intimacy, financial partnership, emotional bonding, fathering of kids, companionship etc.)
<i>To uncover whether professional women feel that they are more capable of finding partners over other non-professional women</i>
In today's Caribbean societies, do you think that professional women are at an advantage or disadvantage over other women in securing the best possible choices of sexual partners? (Are they seen as more appealing or less appealing to the opposite sex?) Why?
<i>To learn how women view women's self-empowerment and sexual liberation</i>
Would you say that a woman's independence gives her the 'permission' to make liberated choices regarding her sexuality (e.g., have multiple sexual partners, short term relations etc.)?
Part B
Objective: Attitudes of professional women toward safe sex practices and HIV/AIDS during Carnival time.
<i>To find out whether the practice of masturbation assists in reducing unsafe sexual practices</i>
Do you think that women who engage in masturbation (the stimulation or manipulation of one's own genitals, especially to orgasm; sexual self-gratification) are less likely to seek out a sexual partner in these modern times? Why?
<i>To elicit information about the perceptions of Carnival and the human psyche</i>
Based on what you've experienced in previous years, do you think that the Carnival culture perpetuates the objectification of all women certain groups of women? (e.g., younger aged women, women dressed in a particular way, less educated women, women with lower earnings etc.) How and why?
Carnival is a time when people tend to free themselves from life's daily challenges. It is culturally rich in music and dance and people tend to spend time engaging in parties and other pleasure and leisure times. Do you think that Carnival is also seen as a time to be sexually free?
<i>To probe whether Carnival music, dress and use of alcohol are considered conducive to heightened sexual activity and why?</i>
There has been a significant increase in births 9 months post-Carnival, which provides evidence that women are engaging in more unprotected sexual activity around that time. Are you of the belief that Carnival provides the opportunity for women to engage in unsafe sexual practices?
<i>To uncover if particularly provocative dance movements and music influence sexual practices and behaviours</i>
Do you think that the wine and jam culture associated with Carnival influences the sexual choices that professional women make? If so, in what ways?
<i>To determine if professional women think differently from other women about making sexual choices</i>
Professional women are perceived as being financially independent. Does this independence give them a feeling of being sexually liberated by having several non-committal sexual partners?
<i>To explore whether or not professional women are considered to be at risk of STIs because of sexual practices</i>
Can the attainment of a tertiary education be seen as having a positive impact on all aspects of a woman's life? As such, are professional women more inclined to practise safe sex all the times, sometimes, not sure?

DATA ANALYSIS

Recorded data from interviews and focus group discussions were transcribed and processed using NVivo software. Field notes from observations were also collated. Key issues were identified and organised according to themes and subthemes using word document files. NVivo was then used to store, categorise and code the data. Triangulation of data to see where key themes intersected [20, 21] involved descriptive and explanatory data coding. Clearly defined codes, consisting of key words and phrases for location of specific themes, were created. Using the associations among themes, a thematic analysis was carried out and conclusions were drawn [22] on the sexual practices of the participants, and their role in the feminisation of HIV.

The sexual practices of professional Caribbean women, and their HIV risk have not been researched in-depth prior to this study. The field work's focus entailed examination of what was happening within a specific time frame, with a specific group of women. It was not intended to show what could have happened in the future, so it was irrelevant to gauge dependability of the study. The project did not necessitate transferability [23] to other countries or other groups of women. Precedence was given to documenting insights into what was happening, and why, as opposed to the extent to which attitudes, behaviors and practices among professional women were the same. Given the project's phenomenological nature, the emphasis targeted procedural rigour [23] and what Gray [17] described as 'contextual description and analysis' [17]. Research was conducted in low and high-risk islands and produced similar findings, which was indicative of some measure of generalisability within the Caribbean.

Confirmability of findings [24] was important, thus, field observations as participant observer and experiences and sentiments of interviewees were shared with focus group participants. The study's validity was maintained through researcher analytic reflexivity and evaluative rigour [17, 25]. Through respondent validation, the participants as judges of their own experiences, confirmed or refuted findings. Their views in the data triangulation process lent further credibility to the study.

FINDINGS

Participants gave a multiplicity of perspectives on the feminisation of HIV and their role in the epidemic. This was contextualised through these women's gendered stories on the politics of self-identity and self-awareness; femininity and womanhood; sexual health education discourse; and the hypersexualised Carnival culture.

Feminism

In examining feminist consciousness, most participants identified as feminists. After exploration was made into the cultural nuances regarding what it meant to be male and female in that social context, the prevailing sentiment was that men and women were different and having 'equal status' in relationships was not a necessity. Overall, participants claimed that independence, in the form of economic imperatives, was very important to them. Self-sufficiency and self-worth were crucial to their notion of the feminist ideal.

Many respondents believed that for women, feminists or not, forming bonds with men was natural and important. They wanted men to care for them, but not have automatic power and control over them. Participants concluded that, for many, it was more alluring to be in an unsatisfying relationship than in none at all. In fact, some women willingly assumed submissive roles, while giving in to men's feelings of entitlement and authority.

Female Sexual Identity and the Femme Fatale

Participants believed that women who were considered sex goddesses were sexually audacious and self-loving. Conversely, participants articulated that some women with exaggerated displays of self-confidence were deliberately trying to mask low self-esteem. There was consensus that female sexual identity was shaped by inner workings and by other people's perceptions. Women relished attention often couched in sexual innuendos. Participants averred that women's preoccupation with physicality was inextricably linked to attempts at using the body as a tool to tantalise the opposite sex.

Personal attributes like a love of danger and short-lived thrills might have made it easier to engage in risky sexual encounters. Participants claimed that educated women might have been more aware of HIV risk and that may or may not have influenced their sexual partnering decisions. As the interviews addressed sexual risk more personally, there was more reticence; women disassociated themselves from the femme fatale mentality when addressing their own personal escapades. Focus group participants established that risk taking behaviour showed ignorance and naivety, which resulted in detrimental consequences. In theory, these educated women claimed that there was a need to be sexually responsible, yet their actions showed the antithesis to self-love and protection of the body.

Male-Female Relations and Gender Equality

This study demonstrated that long term bonding from relationships was a vital self-esteem booster. Ubiquitous interference and pressure from society was noted to be humiliating for women without partners. Women with companions gave the impression that they had fewer episodes of insecurity. Data findings revealed a paradigm shift in the assignment of gender roles. Although participants praised their heritage, they were critical of the social norms that did not seek to uphold gender justice. As ostensible lovers of modernity and progressive thinking, they embraced a new social mandate that promoted equality and anti-patriarchal politics.

There was unanimous agreement that in this system of entrenched male privilege, men were granted a license for sexual freedom. Some contributors expressed they were disenchanted with the ways women acquiesced to Caribbean machismo culture. It was affirmed that women simply tolerated it as their fate; as a means of attaining a partner and social acceptance. It was not clear as to the degree to which empowered women accepted or rejected equality in its various manifestations in romantic relationships.

Safe Sex Education and Sex Talk

The maxim that 'sex sells' contributed to the success of Carnival advertising strategies, aimed at attracting individuals from every socio-economic status. Increased sexual energy, which accompanied Carnival celebrations, was highly anticipated. Some study participants believed Carnival could be regarded as the annual sex festival in the Caribbean. The erotic

overtones arising out of the tuneful compositions, the melodious rhythms and sensual body movements collectively acted as enabling factors for this so-called sex-fest.

Judging from stakeholder reports, authorities were actively engaged in public sensitisation on sexually transmitted infections (STIs), particularly around Carnival. Stakeholders advised that more collaborative work to develop an inter-sectoral approach to HIV prevention was needed. There was agreement among participants that recent decreases in HIV cases was indicative of public health drives; however, the problem of feminisation of HIV was yet to be adequately addressed. Participants admitted that their attitudes towards safe sex had undergone a metamorphosis over the years. More explicitly, they identified maturity; and personal research on risky sex as major game changers.

Hesitance of Caribbean couples to converse openly on their sexuality was highlighted. The crux of this silence was fear of confronting issues related to infidelity, STIs and sexual dissatisfaction. Participants neither expected their spouses to cheat nor put their lives at risk; however, they acknowledged the possibility. A few women disclosed that they were not oblivious to the realities; therefore, they often had conversations on sexual matters with their partners. Some believed that women felt that they had control over their partners' behaviour. It was debated that many women looked through rose-tinted glasses: seeing only the pleasant aspects of their relationships, while ignoring warning signs associated with infidelity or STIs.

Safe Sex Behaviours and Practices

Respondents argued that the most empowered women were no better off than women in more vulnerable positions. The conclusion was made that regardless of educational background or financial capabilities, women were all susceptible to HIV because of unwise sexual choices. For the participants, a safe sex utopia was one where women got into monogamous relationships; however, they admitted that this model was difficult to find and emulate. Alternatively, the approach of one relationship at a time was seen as a solid alternative.

In discussing past sexual decisions, generally and around Carnival, respondents claimed that in spite of their ability to take protective action, they had not been sexually responsible. Fixation on nourishing the body, and getting it physically fit, especially prior to Carnival was a plain contradiction. In the heart of heightened sexual pulls, preserving the body from life threatening diseases through risky sex was often neglected, resulting in post Carnival regrets. In addition to sex education, values, morals and personal grounding were seen as important for sex behaviour modification. In the final analysis, it was decided the true test of self-love was one's ability to protect oneself.

DISCUSSION

Feminism was recognised among Caribbean women; however, wariness over the doctrine was deeply entrenched in patriarchal influence and interference. The appraisal of and consequent leniency by professional females acknowledged the prevailing impact of triple jeopardies: 1) intergenerational miseducation on feminism; 2) androcentric cultural

indoctrination; and 3) the social construction of female identity and self-acceptance through male-female bonding. As the struggle for recognition of feminism prevails up to today, the fabrication of a new socio-political movement is still lacking.

Education and socio-economic latitude afforded to women in the patriarchal structure can have a huge impact on gender relations. Women as empowered beings have had sobering implications for the male ego. Females have had to pander to the 'fragile' image and esteem of men; some, even, have downplayed their influence to appear less intimidating as a means of securing their relationships. Professional women's inability or refusal therefore to consciously embrace equality in their partner relationships can have detrimental effects on their politics of equality; sense of self; and overall well-being.

The presentation of the female sexual self appears to be in a constant state of flux: moving from a conservative projection of self to a more unconventional identity. Passion for sex without limitations translates into a refusal to conform to previously accepted trajectories of traditional female sexuality, free of sin or fault. Simultaneously, the power of cultural restrictions imposed on women around sexual individuality cannot be denied. Women may disguise themselves by putting on masks to protect their socially fabricated fickle 'good girl image.'

The social order has successfully upheld a seemingly infallible, but falsified, image of the sexual health lifestyle of professional Caribbean women. This image has been created on the specious basis that academically accomplished women are likely exemplars of female virtue. Tertiary qualifications and intellect do not automatically imply acquisition of sex education, let alone safe sex habits. The same is applicable to women from other educational backgrounds who, may or may not, make wise safe sex choices. In reality, there is no benchmark test to determine a woman's awareness and her subsequent use of this information to protect against HIV. Knowledge and application of knowledge are distinct, and they may or may not intersect.

Carnival acted as a catalyst for removing everyday barriers. Women deliberately 'shelved' their inhibitions to be able to 'get on bad' at Carnival time. Free of gender prescriptions, women stepped out from behind the veils of piety and used their bodies in the public domain to unleash the 'bad' girl inside. This signified the extent to which sexuality or hypersexuality was repressed at other times. In the metaphorical sense, the road, on which the Carnival masquerade takes place, is her canvas for feminist consciousness, expressions of physicality and identity. Within these parameters, professional women like all other women, become unapologetically active, visible, players in the Carnival bacchanal. There are no clear lines of demarcation on behaviour of the different women at Carnival.

Quintessentially, Carnival was an aphrodisiac for the body and mind: a springboard for sexual expression. The contranormative setting with sexual innuendos provided the environment for sexual affairs, and the ability to coerce women into acting in more sexualised ways. Women who engaged in safe sex over the Carnival period without detailed knowledge of HIV contrasted sharply with the obfuscating actions of women who had the knowledge but did not practise safe sex. Involvement in unsafe practices might have been a conduit through which some women attained yet another cerebral high at Carnival. Like the femme fatale who thrives on risk taking behaviour, these Carnival lovers might have wanted to engage in thrill seeking escapades to fuel the bacchanalian women within. Unfortunately, even if these experiences resulted in mind-blowing eroticism and heavenly, bodily pleasures, there was always the prospect of sabotage to either their physical or emotional welfare.

A new version of the sexual life script of professional women has been unmasked: during Carnival, these women became inexorable 'silent players' who actively contributed to sexual misconduct of the female collective; post Carnival, they disappeared and reverted to socially prescribed behavioural norms. This secrecy and shame forced women underground whenever they deviated from traditional 'good girl behaviour.' Although the Caribbean region is far from embracing concepts such as sex-positive feminism, the sanguine hope of the research subjects was to be in a superlative position to metamorphose the way they regarded their womanhood, sexuality and sexual agency.

This study concretised the fact that, in their daily living, and as well during Carnival, professional women may be prone to error. In pursuit of happiness, they may discover pain; on a quest for euphoria, they may find danger; and in search for rebirth, they may discover death. Can a truly self-loving, mentally and emotionally sound and self-respecting woman be willing to die for sex? Professional women's silence; denial of the problem and its root causes; and refusal to call authorities to action are inimical to reducing the overall impact of the feminisation of HIV in the Caribbean. As a people, mouthing the same platitudes about privilege and empowerment to and about professional women is futile. Acknowledgement must be made of Caribbean gender politics and its obliteration of true female agency. The negative repercussions of cultural indoctrination on all women within a patriarchal system must also be given prominence. To curb the acquisition and transmission of HIV and the overall feminisation of HIV in the Caribbean- this is quintessential.

Venturing into uncharted research territory can be meritorious in its own right; however, what remains unclear is which socio-cultural factors have the greatest influence on sexual practices. With the burden of an HIV epidemic, and the economic restrictions in developing nations, it is imperative that key players prioritise which issues to concentrate on more closely through additional research. Once sufficiently understood, investment can be made in the relevant strategies to address the most critical socio-cultural issues.

CONCLUSION

The women's stories gave understandings of female sexuality, safe sex and Carnival culture in ways not described before. This study showed that sexual health education and promotion on HIV had been carried out ad nauseam; however, female complacency had set in on the problem. Education or knowledge does not necessarily influence safe sex practices. The harsh reality is that certain perilous sexual behaviours have become the norm; so much so that many women became inured to them. There are numerous commonalities among Caribbean women apropos of sexual health attitudes, behaviours and practices. In varying degrees, the socio-cultural environment influences women's individuation and sexual relationships. Society often minimalises the perceived threat of HIV to professional women. These West Indian women hold substantial socio-economic power, making them privileged on one hand, but on the other, they are vulnerable to compromised health in some of the same ways as other non-professional women. Collectively, Caribbean women are at continued risk of HIV if the necessary precautions are disregarded. Finally, findings from this project can be utilised for health programming tailored to women, as part of the wider HIV prevention strategies in the Caribbean.

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Chapter 77

PET OWNERSHIP AND STRESS AMONG UNIVERSITY STUDENTS

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ABSTRACT

The purpose of this chapter was to determine whether there is an association between pet ownership and the reported level of stress among college students. The additional variables investigated were the students' academic achievement, their age, gender and school term. To this day, most research into the probable correlation between owning a pet and an individual's stress level focused on the elderly. However, young people, especially students, can experience equally severe stress levels. Such students may be at elevated risk for poor academic performance and the onset of anxiety or depression. The method used in the study was a cross-sectional survey, conducted between June 7 and December 13 2016. Data analysis was performed using Statistical Analysis Systems (SAS) and statistical significance set at $p = 0.05$ if not stated otherwise. The measures were tested with Wilcoxon's two-tailed rank sum and Spearman's rank. 187 of 780 veterinary students completed the survey, 87% of them were female. 39% of them had at least one pet and the median self-reported stress level was 7 out of 10. Pet ownership was significantly associated with stress level ($p = 0.02$, Spearman's rank correlation -0.17), increased age and later term in school. However, there was no correlation between pet ownership or stress and gender or academic success. Additionally, the number, type and effects of pets on stress were investigated. The study affirms the negative association between pet ownership and stress among college students and thus has implications for further research in this field amid younger people.

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INTRODUCTION

The role of animal companionship in stress management has gained scientific attention in recent years. Owning a dog appeared to buffer elderly people against the effects of stressful life events [1], and at least one study found dog ownership was more effective than standard drug therapy for stress-induced hypertension [2]. Likewise, dog owners were less depressed than non-owners following bereavement [3] especially if they had few or no human confidants. Some of these associations may be mediated by better self-care, including increased physical activity, among dog owners in particular [4], and/or reverse confounding, with pet owners generally healthier and younger than non-owners [5]. However, the association also exists in prospective studies: dog owners who had a heart attack were more likely to survive one year than those who did not own a dog at the time of the attack [6].

To this date most research into the association between pet ownership and stress has focused on the elderly. However, stress may be equally severe in young people. Of the ten most stressful life events according to the well-known Holmes-Rahe scale [7] none are limited to the elderly and many occur only in working-age adults (e.g., dismissal from work). High stress levels have been reported in college students for over 20 years: in 1994 a majority reported moderate to severe stress [8] and this has, if anything, increased with time [9]: in 2011 over 90% of sampled students reported average or above-average stress, and 27% reported that their stress was severe enough to cause academic problems. In addition to academic problems, stress can also cause anxiety [10] and depression [11] which in their clinical forms are among the leading causes of morbidity [12] and mortality [13] in young adults. This morbidity is likely to become worse if the stress is severe enough to interfere with performance and directly cause stressful events. Clearly college students are at risk for stress and its sequelae, and thus might benefit from stress relief interventions.

Most studies of the role of animals in stress relief among students rely on trained therapy animals, rather than the students' own pets. However, they suggest similar protective effects. College students exposed to a therapy dog reported lower stress after the encounter [14] and students' stress biomarkers were lower after exposure to a novel dog than either a human friend, or no exposure [15]. This research is convincing enough that many universities, such as Harvard [16], provide therapy dogs for stress relief. However, therapy dogs are not pets. Pets, especially dogs, often represent a significant investment of time and attention that may conflict with other priorities, while the therapeutic relationship is limited in time and space. Thus, while it is possible that pet ownership protects college students against stress in a similar manner to the use of a therapy animal, it is also possible that the benefits do not translate.

In this study, we specifically investigate whether pet-owning college students are less stressed than those who do not own pets. We also investigate whether these students are at elevated risk for poor academic performance.

OUR STUDY

After obtaining IRB approval, a cross-sectional poll was distributed to all veterinary students attending St George's University. Written informed consent was collected from all

participants. Responses were collected between June 7 and December 13, 2016. Data were collected on the following measures:

Demographics

- Age, years
- Gender (male/female)
- Term of school

Academic Performance

- GPA, categorized by quarter of a point and ranging from 0–4
- Percentage of lectures attended, categorized as follows
- Under 50%
- Over 50%
- Over 75%
- Over 90%

Pet Ownership

- Pet ownership: has at least one pet at home

Stress

- Stress, rated on a scale from 1 (lowest) to 10 (highest)

Data Analysis

All data analyses were conducted using Statistical Analysis Systems, SAS. All graphics were produced using Excel. P-value for significance was 0.05 unless otherwise stated. Because many measures were non-normally distributed, descriptive statistics are presented as N, % or median (25th and 75th percentiles) unless otherwise stated.

Each measure was tested to see if it was associated with pet ownership (using Wilcoxon's two-tailed rank sum, a nonparametric test) and/or stress (Spearman's rank). Those which were statistically significant at $p > 0.10$ were entered into a multivariable logistic regression predicting pet ownership from stress and confounders. Backwards selection took place at $p = 0.05$.

Because many studies of therapy animals use dogs, we conducted a subgroup analysis within the pet-owning group to see if those who owned one or more dogs were more or less

stressed than those who owned no dogs. We then conducted a further subgroup analysis to see if stress varied depending on the number of dogs, or the number of non-dog pets. In the pet-owning subgroup no multivariable models were run.

Table 1. Population characteristics

Trait ¹	% or median (25 th , 75 th percentile)	Associated with pet ownership P-value ²	Associated with stress Spearman's rank, (P-value)
N	187	--	--
Age	25 (24, 26)	0.001	0.03 (0.66)
Male	12.8	0.47	-0.12 (0.09)
Term of school	4 (2, 5)	0.007	0.14 (0.06)
Lives with a pet	39	--	-0.17 (0.02)
GPA ³	3.6 (3.1, 3.9)	0.60	-0.0006 (0.99)
Percent of classes attended ⁴	95 (75, 95)	0.16	-0.01 (0.84)
Stress level (1-10, ascending)	8 (7,8)	0.019	--

- N for N, % for binary measures, otherwise median (25th, 75th percentile).
- P-value from nonparametric test, Wilcoxon's two-tailed rank sum test.
- GPA reported in quarter-point increments. Average taken from the middle of each range, e.g., 3.64 was reported as "3.5 to 3.75."
- Attendance reported as "under 50%", "over 50%", "over 75%", and "90-100%. Average taken from the middle of each range, e.g., "under 50%" was recorded as 25%.

All measures are self-reported.

FINDINGS

Of 780 students who attended the vet school, 187 (24%) completed the survey. 87% were female. Median age was 25 years (25th and 75th percentiles 24 and 26). The median subject was in the 4th term out of 5 (2,) and reported a GPA of 3.6 (3.1, 3.9).

39% of students, N = 73, had at least one pet living with them on Grenada. Pet ownership was significantly associated with increased age ($p = 0.0001$) and with later term in school ($p = 0.007$) in addition to stress ($p = 0.02$). However, it was not associated with gender, GPA, or class attendance (all $p > 0.10$).

Stress

Median self-reported stress was 7 out of 10, and most students reported their stress as being 7 or 8 (25th and 75th percentiles 7, 8). Students who reported higher stress were less likely to report owning pets, with a clear trend visible (figures 1 and 2). This association persisted in statistical models: stress was significantly associated with pet ownership ($p = 0.02$, Spearman's rank correlation -0.17). It was also associated borderline significantly with term of school ($p = 0.06$, rank correlation 0.14). Males were nonsignificantly less stressed

than females ($p = 0.09$). However, there was no association between stress and either age, GPA, or school attendance (all $p > 0.50$).

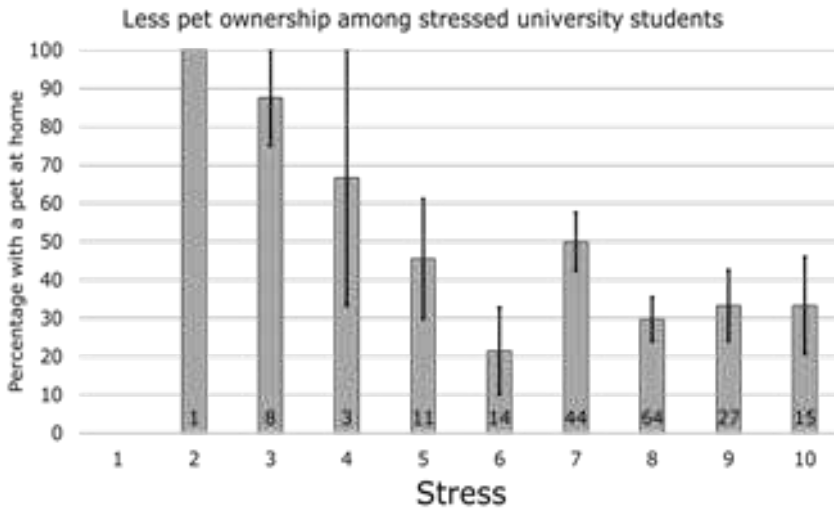


Figure 1. Less pet ownership among stressed university students.

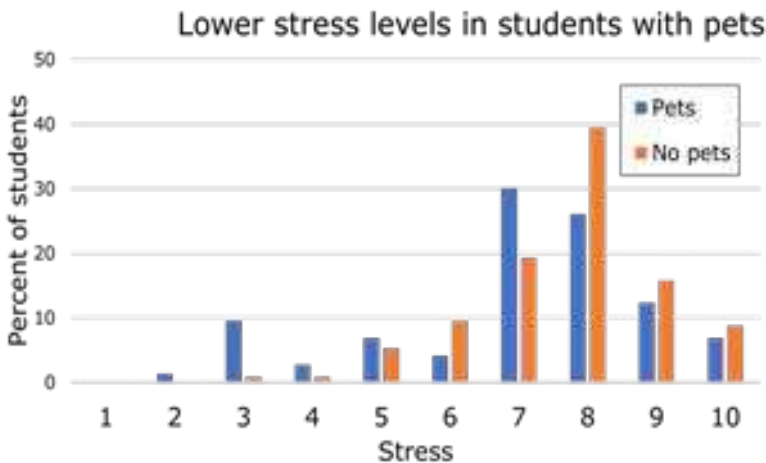


Figure 2. Lower stress levels in students with pets.

Number, Type and Effect of Pets on Stress

Among students with any pets, the median number of pets was 1 (75th percentile, 2; see table 2). 58% owned one or more dogs, and 41% owned one or more other animals. Within pet owners there was no association between stress and either species or number of pets (all $p > 0.5$). Almost all (93%) of pet owners reported that their pet decreased their stress, while only one (1.5%) reported that the pet increased their stress.

Table 2. Profile of pet owners

Trait ¹		Associated with stress (Spearman's rank, p-value)
N	73	--
Male		
Total number of animals	1 (1, 2)	0.04 (0.77)
Any dogs	58 (79%)	0.17 (0.16)
Number of dogs, among those with any	1 (1,1)	0.03 (0.78)
Any other animals	30 (41%)	-0.04 (0.75)
Number of other animals, among those with any	1 (1, 2)	-0.03 (0.79)
Effect of pet on stress levels		
Increase	1 (1.5%)	-0.04 (0.72)
No change	4 (5.8%)	0.02 (0.89)
Decrease	64 (93%)	-0.04 (0.74)
(missing data)	4 (5.8%)	--

- 39% of subjects (N = 73) had pets living with them.
 - N for N, % for binary measures, otherwise median (25th, 75th percentile).
 - P for difference from nonparametric tests (Wilcoxon's two-tailed rank-sum test).
 - GPA reported in quarter-point increments. Average taken from the middle of each range: e.g., 3.64 was reported as "3.5 to 3.75."
 - P for global null.
- All measures are self-reported.

Corrected Association between Pet Ownership and Stress

In the raw data, each one-point increase in stress was associated with about a 23% reduction in the odds of having a pet (odds ratio 0.767, $p = 0.005$). However, students in later terms of school were both more stressed and more likely to own pets, so the association got stronger after correction for term. In corrected models the odds ratio dropped to 0.746 ($p = 0.0003$, see table 3). After correction for term, age was not independently associated with pet ownership.

Table 3. Correlates of pet ownership

Predictor	Odds ratio	95% confidence interval	P-value
Age	(removed)	--	--
Term of school (from 1 to 5)	1.333	1.10 – 1.61	0.003
Stress (from 1 to 10)	0.746	0.62 – 0.91	0.003

DISCUSSION

This study confirms the known negative associations [1, 2] between pet ownership and stress and extends these associations to college students. It also appears that resources invested in a pet did not interfere with academic success, since pet ownership was not associated with either GPA or class attendance.

Previous research into the association between animal companionship and stress has suggested that dogs are the most beneficial [1] and therapeutic interventions also tend to focus on dogs. However, other animals may be equally beneficial: we found no association between stress and either species or number of pets. We encourage future researchers with greater statistical power to replicate this part of our study.

This study has three major limitations, of which the largest is a complete reliance on self-reported data. Social desirability bias may have led subjects to report higher GPAs or more class attendance than was in fact the case. However, the bias may be nondifferential with respect to pet ownership, and perceived stress is necessarily self-reported.

Similarly, selection bias almost certainly took place. The survey was distributed through the university's Facebook page and thus may have oversampled those who were more engaged in their education. 87% of sampled subjects were female compared to only 81% of the veterinary school, and almost all reported good grades and low absenteeism (25th percentiles for GPA and attendance were 3.1 and 75% respectively). Reported pet ownership was also relatively low-intensity, with most pet owners reporting only a single animal, and thus pet-induced stress may not have been sufficient to interfere with academic performance. Care should be taken when applying our findings to poor students, those with limited resources, or those with large numbers of pets.

Lastly, reverse causation is a concern. Our data are consistent with a protective effect of pets on stress, but also with a lower rate of pet acquisition among people with high stress levels, with pet-friendly environments being less stress-inducing, or with a non-causal relationship. No cross-sectional study can address this issue, and a controlled trial of pet ownership is unlikely, but a longitudinal study would help to establish the existence and direction of causation.

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Chapter 78

QUANTIFICATION OF ANTIMICROBIAL PRESCRIBING PRACTICES WITHIN HAMPSHIRE HOSPITALS NHS FOUNDATION TRUST

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ABSTRACT

Antimicrobials are considered the foundation of modern medicine facilitating exponential improvements in patient care. Antimicrobial resistance (AMR) is defined as “the loss of effectiveness of antimicrobial agents upon pathogenic microbes” caused by inappropriate use of antimicrobials. AMR is an ever-growing problem recognized as one of the greatest public health threats worldwide.

Objectives: To identify variation in adherence to antimicrobial standards among the Winchester and Basingstoke hospitals within the Hampshire Hospitals NHS Foundation Trust (HHFT). Study group: Electronic records of all patients on antimicrobials within the HHFT between April 8th and May 10th, 2019.

Methods: This cross-sectional point prevalence study reviewed antimicrobial prescriptions using the HHFT's Electronic Patient Records (EPR), e-prescribing system (JAC) and medical notes against Public Health England's audit standards.

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Results: Out of 660 patients, 213/215 (99%) patients on antimicrobials were reviewed. Clinical indications were documented in 86% of cases with appropriate samples taken in 75% of cases. There was a significant difference between documented indication for antimicrobial ($p = 0.046$) and taking of appropriate sample for antibiogram before initiation of antimicrobial ($p = 0.047$) between the two hospitals within the Trust.

Conclusion: Improvements across HHFT are required in order to improve the quality and standard of prescribing practices to decrease AMR. Additional research is needed on appropriate step-down plans and stop dates agreed on for each prescription.

INTRODUCTION

Antimicrobials have been proven to be extremely important developments in medicine. They are considered to be the foundation of modern medicine which has facilitated exponential improvements in patient care [1, 2]. Antimicrobial resistance (AMR) is defined as “the loss of effectiveness of antimicrobial agents upon pathogenic microbes”. AMR is not a new phenomenon [3, 4], yet there is currently no systematic surveillance systems in place to monitor AMR [5]. It has become an ever-growing problem and is recognized as one of the greatest threats to human health worldwide, both in the present and in the coming decades [1, 6, 7].

Within the last decade, there has been a dramatic increase in the proportion and number of bacterial pathogens that are resistant to multiple antibacterial agents and especially regarding resistance to quinolones, carbapenems and third-generation cephalosporins. This is driven by inappropriate prescribing, over-the-counter availability and self-medication, which reflects a general lack of awareness on the global threat that AMR poses to society [8]. Antibiotic prescription in primary care settings has been shown to directly affect AMR [9]. During the period 2010 to 2014, most antimicrobial prescribing in the UK occurred in general practice. In 2014 specifically, 74% of antimicrobial prescribing occurred in general practice, 11% for hospital inpatients, 7% for outpatients, 5% for patients seen in dental practices and 3% in other community settings [9]. Resistance is primarily driven by the use of antimicrobial agents [3] used in a variety of settings such as hospitals, out-patient clinics, long-term care facilities as well as in animal-associated settings like veterinary clinics, farms and feedlots [10].

In addition, there is also growing resistance to even second and third-line forms of treatment making it difficult to treat these diseases. One example is *Klebsiella pneumoniae* which is rapidly becoming untreatable using last-line antibiotics. This is especially problematic in hospitals where it causes a range of acute infections [11] and it is compounded by the burden of resistant hospital-acquired infections (HAIs).

THE DWINDLING PIPELINE OF ANTIMICROBIAL AGENTS

Not only is the problem of AMR increasing but over the last 30 years, antimicrobial drug development has slowed having a compounding effect [9]. In response to the growing penicillin resistance, new beta-lactam antibiotics were developed which restored confidence in antibiotics but this was short-lived as the first case of methicillin-resistant *Staphylococcus*

aureus (MRSA) was identified in the same decade, first in the UK in 1962, and then in the US in 1968 [12, 13].

In the initial periods of the discovery of antimicrobials, drug development occurred at a relatively fast rate with twenty new classes of drugs making it to the market between 1930 and 1962 [5]. This meant that when resistance developed, a new drug was simply created to treat the increasingly resistant bacteria [9, 14]. After the 1960s there were only three completely new classes of drugs that were approved [5] and since 1998, only 10 new antibiotics have been approved and only two of these (linezolid and daptomycin) have new targets of action [9].

AMR WITHIN THE HOSPITAL

Even though a fair amount of antimicrobial usage occurs in communities, the intensity of use is higher in hospitals, therefore hospitals are particularly important in the containment of AMR [3]. It is estimated that up to 50% of antibiotic orders in hospitals are unnecessary or inappropriate and this is the setting where the broadest of spectrum agents are rampantly being used [15, 16].

This cross-sectional point prevalence study explored existing variation in adherence to antimicrobial prescription standards within the HHFT. We hypothesized that there would be variation in antimicrobial prescribing standards among the wards within each hospital as well as between both Royal Hampshire County Hospital (RHCH) and Basingstoke and North Hampshire Hospital (BNHH), two hospitals within the Trust.

OUR STUDY

A prospective chart review was conducted for adult patients that were admitted to the Royal Hampshire County Hospital [RHCH] and Basingstoke and North Hampshire Hospital [BNHH], hospitals within the Hampshire Hospitals National Health Service [NHS] Foundation Trust (HHFT). Approval for this study was obtained from the HHFT. Data were collected from the HHFT's Electronic Patient Records (EPR) and were anonymized regarding both patients and practitioners. A single auditor prospectively reviewed all patients on new prescriptions of antimicrobials between April 8th to May 10th, 2019. Data was obtained from the following wards: acute and medical; critical care (intensive care unit [ICU] and high dependency unit [HDU]); surgical; orthopedic; and maternity.

Inclusion Criteria

The study included all adult patients on the selected wards who were prescribed new antimicrobial agents (antibiotics, antifungals and antivirals) on their current admission.

Exclusion Criteria

Pediatric patients, patients who were admitted and were already on antimicrobials, patients admitted only for same-day surgery, and patients seen at the Accident and Emergency Department were excluded from the study. Patients who were prescribed antiretrovirals or antimicrobials for surgical or medical prophylaxis, patients who were prescribed any topicals medication, and patients who were prescribed any anti-parasitic medication, were also excluded.

The auditor accessed the EPR system, medical notes, and the electronic prescribing system, JAC. The number of patients on antimicrobials was recorded as well as the number of patients' notes seen and evaluated. Antimicrobial prescriptions and practices were reviewed against the following audit standards:

- 100% of antimicrobial prescriptions have the clinical indication documented.
- 100% of cases have appropriate samples (sputum sample, MSU, wound swab, blood cultures etc.) taken before initiating antimicrobial treatment in order to provide targeted antimicrobial therapy.
- 100% of antimicrobial prescriptions that are greater than 72 hours have been reviewed.
- 100% of intravenous (IV) antimicrobial prescriptions that are suitable for the therapeutic switch to an oral alternative are appropriately stepped down (criteria as per 'IV to oral switch therapy' guidance as per MicroGuide™).
- 100% of antimicrobial prescriptions follow the Trust's antimicrobial prescribing guidelines or are according to documented specialist advice.

Antimicrobial prescriptions exceeding 72 hours comprised of a documented collaboration between a microbiology consultant, an infectious disease specialist, an antimicrobial pharmacist, or documentation of "continue antimicrobial/ antibiotic plan". Patient notes that were documented as "continue the plan" was considered as an inadequate review. Step-down treatment that was documented in patient notes but was not documented in the electronic prescribing system was considered as "not documented."

Data Analysis

The information collected from the patients' EPR was compiled and summarized according to the categories established for this study. Chi-square tests and Fisher's Exact tests were used to examine if there was a significant association between adherence to Trust guidelines, documented indication for antimicrobial treatment, and other factors relating to antimicrobial prescription practices, by hospital sites and wards among the total sample. Trust guidelines followed were categorized as: yes, no, off guideline but justified, guideline unavailable, and treatment unknown. For Table 1, trust guideline followed were further classified as yes, no and other. For Table 2 and Figure 2, analysis was done only if trust guidelines followed were documented as yes and no. Statistical significance was reported at

an alpha level of 0.05. All data were analyzed with SPSS statistical software package, version 24 (Armonk, NY).

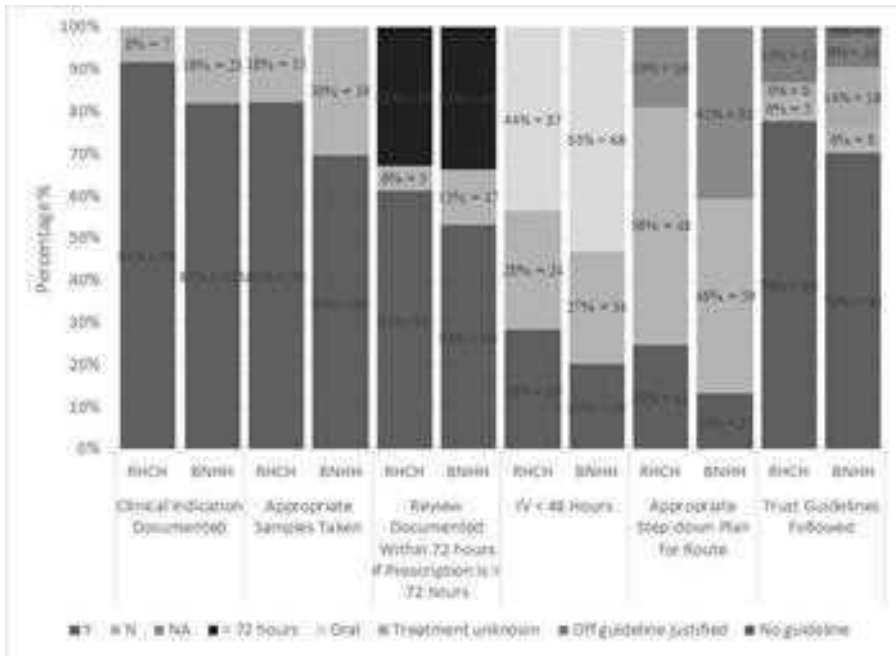


Figure 1. Audit standards tested across RHCH and BHNN hospitals within HHFT.

FINDINGS

Our sample included a total of 660 patients on thirty-seven selected wards in RHCH and BNHH; 215 (33%) were on antimicrobials, of which 213 (99%) had medical notes available to enable quantification of antimicrobial prescription management indicators. Of the 213 patients on antimicrobials, 183 (85.9%) had a clinical indication documented. Appropriate samples were taken in 160 (74.4%) patients. There were 142 (66.7%) patients who had an antimicrobial prescription for longer than 72 hours. Of those who had an antimicrobial prescription for longer than 72 hours, a review had been documented within 72 hours for 120 patients (84.5%). There were 106 (49.8%) patients who had oral prescriptions and 107 (50.2%) who had IV prescriptions. Those who had IV prescriptions, 50 (46.7%) of them were prescribed for more than 48 hours. There were 38 patients (17.4%) who had an appropriate step-down plan. Trust guidelines were followed in 156 (71.6%) patients, 13 (6%) cases did not follow Trust guidelines, (73%), the indication was unknown in 21 (9.6%) cases, treatments were off-guideline but justified in 21 (9.6%) cases, and there were no guidelines available in 2 (0.9%) of cases. Detailed descriptions are found in Figure 1.

Categorical analysis showed that there was a discrepancy in prescription practices between the two hospital sites regarding type of antimicrobial prescribed ($p < 0.001$), documented indication for antimicrobial use ($p = 0.046$) and taking of appropriate sample for antibiogram before initiation of antimicrobial ($p = 0.047$). Details are shown in Table 1 and Figure 2.

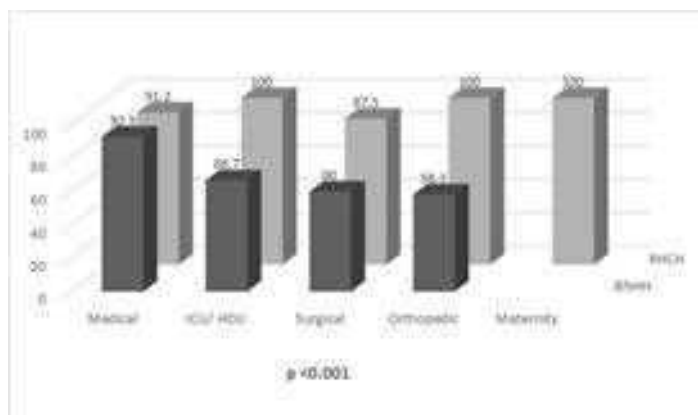


Figure 2. Percentage of AM indication that was documented according to hospital and ward.

Table 1. Antimicrobial (AM) prescription and practices according to hospital sites

Variables	BNHH	RHCH	Values
Ward, n (%)			0.865
Medical	85 (59.9)	57 (40.1)	
ICU/ HDU	6 (66.7)	3 (33.3)	
Surgical	25 (59.5)	17 (40.5)	
Orthopaedics	12 (66.7)	6 (33.3)	
Maternity	3 (42.9)	4 (57.1)	
Type of AM, n (%)			<0.001
Antibacterial	110 (59.1)	76 (40.9)	
Antifungal	18 (85.7)	3 (14.3)	
Antiviral	0 (0.0)	6 (100.0)	
AM Indication Documented, n (%)			0.046
Yes	105 (57.4)	78 (42.6)	
No	23 (76.7)	7 (23.3)	
Sample Taken, n (%)			0.047
Yes	90 (56.3)	70 (43.8)	
No	38 (71.7)	15 (28.3)	
AM Route, n (%)			0.138
IV	59 (55.1)	48 (44.9)	
Oral	69 (65.1)	37 (34.9)	
AM >72 Hours, n (%)			0.921
Yes	85 (59.9)	57 (40.1)	
No	43 (60.6)	28 (39.4)	
Review Documented within 72 hours, n (%)			0.070
Yes	68 (56.7)	52 (43.3)	
No	17 (77.3)	5 (22.7)	
Step-down Plan Followed, n (%)			0.270
Yes	17 (44.7))	21 (55.3)	
No	59 (55.1)	48 (44.9)	
Trust Guidelines were Followed, n (%)			0.452
Yes	90 (57.7)	66 (42.3)	
No	8 (61.5)	5 (38.5)	
Not Applicable	30 (68.2)	14 (31.8)	

However, analysis according to if the Trust guidelines were followed or not did not show any statistical difference for prescription practices relating to antimicrobial therapy. Further details are shown in Table 2 and Figure 3.

Table 2. AM prescription and practices according to if trust guidelines were

Trust Guidelines were Followed			
Variables	Yes	No	Values
Site, n (%)			0.787
BNHH	90 (91.8)	8 (8.2)	
RHCH	66 (93.0)	5 (7.0)	
Ward, n (%)			0.079
Medical	110 (90.2)	12 (9.8)	
ICU/ HDU	5 (100.0)	0 (0.0)	
Surgical	29 (100.0)	0 (0.0)	
Orthopaedics	11 (100.0)	0 (0.0)	
Maternity	1 (50.0)	1 (50.0)	
Type of AM, n (%)			1.000
Antibacterial	144 (91.7)	13 (8.3)	
Antifungal	7 (100.0)	0 (0.0)	
Antiviral	5 (100.0)	0 (0.0)	
AM Indication Documented, n (%)			0.145
Yes	149 (93.1)	11 (6.9)	
No	7 (77.8)	2 (22.2)	
Sample Taken, n (%)			0.466
Yes	126 (91.3)	12 (8.7)	
No	30 (96.8)	1 (3.2)	
AM Route			0.120
IV	73 (89.0)	9 (11.0)	
Oral	83 (95.4)	4 (4.6)	
AM >72 Hours, n (%)			0.380
Yes	103 (93.6)	7 (6.4)	
No	53 (89.8)	6 (10.2)	
Review Documented within 72 hours, n (%)			0.420
Yes	96 (94.1)	6 (5.9)	
No	7 (87.5)	1 (12.5)	
AM IV 48 Hours, n (%)			0.483
Yes	37 (92.5)	3 (7.5)	
No	36 (85.7)	6 (14.3)	
Step-down Plan Followed, n (%)			0.279
Yes	35 (97.2)	1 (2.8)	
No	74 (89.2)	9 (10.8)	

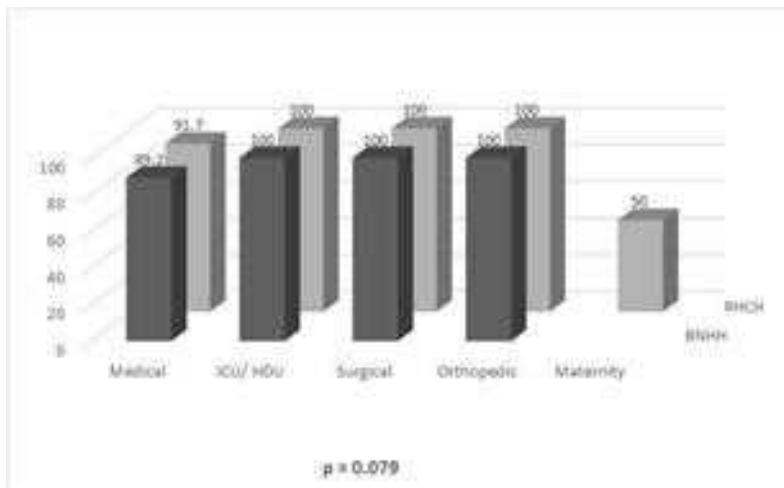


Figure 3. Percentage of Trust guidelines followed according to hospital and ward.

DISCUSSION

The results confirmed the hypothesis that antimicrobial prescribing practices did differ among the wards within each hospital and across hospital sites within the HHFT. The results were slightly better at RHCH than BNHH across all audit standards tested. This showed a level of inconsistency regarding antimicrobial prescribing practices between both hospital sites within the HHFT. This difference in practice raises a concern about the need for systematic approaches to ensure adherence to established guidelines in all hospitals within the HHFT. The results show there is room for improvement specifically for BNHH to reach the same level of prescribing practices as RHCH.

While the majority of cases reviewed were in compliance with HHFT guidelines, over one-quarter of these demonstrated some issue. In 7% of the cases, guidelines were either absent or not followed. While there was no statistical difference regarding adherence to Trust guidelines, this non-compliance is not the best evidence-based practice regarding prescribing antimicrobials.

The above non-compliance represents 13 patients over the sample size of 213 patients. The results of this study show that 32.6% of patients reviewed were on antimicrobials. This is in accordance with WHO suggestion that up to 30% of all hospital inpatients should be on antimicrobials at any one time.

The results show that in all aspects reviewed medical wards tended to have better overall prescribing practices compared to the surgical wards. The critical care wards had a higher percentage of patients on IVs longer than 48 hours, but this is expected based on the typical patient profiles on these wards. The critical care wards also had less plans for stepping down treatment but again this is understandable given the more severe nature of the patients' condition on these wards.

RECOMMENDATIONS

It is vital to have the clinical indication documented in the patients' notes so that all members of the team can be aware of what the patient is being treated for. It was interesting to note that in all 15 cases where a clinical indication was not recorded, reviews for those cases were also not done. Having indications documented will encourage reviews to take place.

Taking appropriate samples is important in making or confirming a correct diagnosis to be able to narrow and target treatment accordingly based on sensitivities.

It is important to ensure that patients are not unnecessarily on long courses of IV treatments. There are risks to being on extended IV treatments such as the risk of line infections and thrombophlebitis. In addition, it is more expensive to treat patients with IV treatments than oral equivalents when they are medically stable enough to use oral forms.

Having stop dates included in the online prescribing system can facilitate the assessment of whether course length planning is being actively considered. Appropriate step-down planning was difficult to measure in this study so it may be more helpful to have stop dates put in place for future studies. Having hard stop dates may however pose problems in cases where patients with more serious infections may require a longer duration of treatment.

Having to renew prescriptions based on stop dates may prove onerous to clinicians and can lead to human errors. On the other hand, if clinicians are forced to continuously review prescriptions, this may lead to better prescribing practices and improved antimicrobial stewardship. This topic is recommended for further discussion and consideration outside the scope of this paper.

Professor Dame Sally Davies, Chief Medical Officer of England said “Antimicrobial resistance poses a catastrophic threat. If we do not act now, any one of us could go into hospital in 20 years for minor surgery and die because of an ordinary infection that cannot be treated by antibiotics” [9]. The WHO shares this sentiment as they claim that “A post-antibiotic era — in which common infections and minor injuries can kill — far from being an apocalyptic fantasy, is instead a very real possibility for the 21st century” [17]. India has reported a prevalence of 41% with methicillin resistant *Staphylococcus aureus* (MRSA) and additional high prevalence of Gram-negative bacterial resistance [18]. The WHO has estimated that worldwide there are 3.7% of new cases and 20% of previously treated cases are estimated to have multidrug resistant TB [18].

In 2013, the Centers for Disease Control and Prevention (CDC) estimated that over two million Americans develop hospital-acquired infections (HAIs) as they are infected with antibiotic-resistant infections each year [19, 20]. Methicillin-resistant *Staphylococcus aureus* (MRSA) alone kills more Americans annually than emphysema, HIV/AIDS, Parkinson’s disease and homicide combined [21, 20]. In 2006, two common HAIs alone (sepsis and pneumonia) were responsible for almost 50,000.

American deaths and cost the US health care system over \$8 billion. In 2007, annual deaths due to these infections accounted for 23,000 and 25,000 deaths respectively in the European Union and the United States [6, 15, 22, 23, 19]. In India, there are 58,000 deaths per annum due to drug-resistant infections [5]. Currently, it is estimated that there are 700,000 deaths globally each year due to AMR [7]. Without policies in place to stop the worrying spread of AMR, this number is predicted to rise to a disturbing 10 million deaths per year, more than cancer and diabetes combined [7]. The CDC suggested that the world was losing the battle on AMR when it stated in 2013 that the human race is now in the “post-antibiotic era” [19]. A year later, the WHO also warned that the AMR crisis is becoming dire [17].

In order to solve this paradoxical problem of resistance, public education and awareness is critical as this is a major contributing factor to AMR. In addition, a much higher degree of precision is required in antimicrobial stewardship and more prudence needs to be exercised in prescribing practices.

Antimicrobial stewardship is a broad term used to encompass appropriate selection, dosing, route of administration and duration of antimicrobial treatment [16]. It has been described as “the optimal selection, dosage, and duration of antimicrobial treatment that results in the best clinical outcome for the treatment or prevention of infection, with minimal toxicity to the patient and minimal impact on subsequent resistance” [24].

Through stewardship programs, one can ensure that the limited agents we have available are put to optimum use with the utmost discretion across all settings including the hospital and wider community. These programs have significantly reduced the incidence of infections and colonization with antibiotic-resistant bacteria and *C. difficile* infections in hospital inpatients [25].

There are many ways to tackle AMR. One incredibly important recommendation is to have a significant increase in surveillance to track resistance, especially in the emerging

world [7]. The UK government has taken on this task and initiated the Fleming Fund providing 375 million USD to improve disease surveillance focused on drug-resistant infections in low and middle-income countries [1, 7].

It is also recommended that more funding be allocated to research into new antimicrobials and improved diagnostic tests [7]. Both the UK and Chinese governments have taken the initiative to achieve this recommendation by each contributing 50 million GBP (72 million USD) to a new Global Innovation Fund [7].

AMR requires a One Health approach as it is recognized that human, animal and environmental health are all inextricably linked through the use of antimicrobials. The widespread use of antimicrobial agents in animals and the food chain contribute a significant source of AMR. This One Health approach is necessary to develop comprehensive and integrative measures to address AMR and should include whole-genome sequencing surveillance of pathogens in humans, animals and the environment to developing a better understanding of AMR [2].

LIMITATIONS

An important limitation was the appropriateness of the diagnosis given to each patient. This audit was testing whether the chosen antimicrobials were appropriate for the given clinical indication assuming the diagnosis made was correct.

It was not established whether IV prescriptions were given as a result of no oral options being available.

Assessing whether an appropriate step-down plan was established proved difficult as the auditor's access was restricted to the online prescribing system, JAC, for all previous prescriptions the patient was on for their current admission. The current prescriptions the patient was on may not have been reflective of their initial prescriptions and therefore it may have been missed if their treatment was stepped down.

It was difficult to ascertain whether a prescription was off-guideline justified vs off-guideline not justified particularly when the auditor was not a member of the team on the ward and they did not know the patient.

CONCLUSION

According to the WHO guidelines, no more than 30% of hospital patients at any given time should be on antimicrobials. This study indicated that some 32% of the sample size was on antimicrobials and therefore underscores the fact that hospitals do play a big role in antimicrobial stewardship and the global AMR challenge. It is therefore imperative that guidelines are clearly articulated and followed by all institutions within a Trust.

Based on the results of the study, there is an overall need for improvement in both hospital sites with regards to documenting indications, taking appropriate samples and having better reviews conducted and documented. In addition, proper planning of stepping down treatment from IV to oral should be made, clear stop dates should be agreed upon and improvements made in the following of Trust guidelines.

If all these criteria are improved on, prudent antimicrobial prescribing practices can be improved. This will enhance overall clinical outcomes for patients while impacting the wider community by helping to curb the growing problem of AMR.

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Chapter 79

ALCOHOL CONSUMPTION AND SELF-REPORTED VIOLENCE AMONG SECONDARY SCHOOL AGED CHILDREN (12-16 YEARS) IN 14 CARIBBEAN COUNTRIES: A CROSS SECTIONAL STUDY

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ABSTRACT

Cross sectional study using secondary data analysis from the Global School-based Student Health Survey (GSHS) examining the relationship between alcohol consumption and violence among adolescents in 14 countries across the Caribbean region. Objectives: To determine (i) the association between alcohol consumption and violence and (ii) to identify the predictors of alcohol use and violence among Caribbean adolescents. Study Group: 22,525 (44.6% boys and 53.4% girls) adolescent students (12-16 years), were sampled using two stage sampling design, from Secondary schools across the Caribbean. Methods: Logistic regressions to obtain crude odds ratios between alcohol use and three forms of violence. Likelihood ratios tests for variables identified as potential confounders were conducted to determine which variables should be included in the final model. Further analyses using logistic regression to determine the predictors of violence included the primary exposure (alcohol) and confounding variables. Results: Alcohol consumption was (i) associated victims of violence, OR = 1.47, CI: (1.37-1.58), $p < 0.0001$, (ii) associated with those who instigated or participated in physical fights, OR = 1.92, CI: (1.77-2.09), $p < 0.0001$ and (iii) associated with self-directed violence, OR = 0.49, CI: (0.44-0.55), $p < 0.0001$. The predictors of violence are (i) cigarettes use, (ii) other drugs, (iii) insomnia and (iv) parental involvement. Conclusions: This study confirms what has been found in European and North American cultures where alcohol consumption is positively associated with violence among adolescents. Further, there are demographic, psychological, and environmental factors that may also influence adolescent alcohol use and violent behaviors.

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INTRODUCTION

Alcohol use among adolescents represents a major global public health concern due to its immediate and long term physical and mental health effects [1]. Reasons for drinking are complex and many factors contribute to this behavior. Previous research has established links between personality factors and alcohol consumption and between metacognitions (one's ability to understand, control and manipulate his/her thinking) [1].

There are three main direct mechanisms of harm caused by alcohol consumption in an individual: (i) toxic effects on organs and tissues, (ii) intoxication that leads to impairment of physical coordination, consciousness, cognition, perception, and behavior and (iii) dependence, loss of self-control on drinking behavior [2]. Even when consumed in small amounts, alcohol use has a number of consequences, such as risky sexual behaviours, juvenile delinquency, conflicts with friends, familial conflicts, elevated suicidal rates, illicit drug use, violence and many more [3]. Some of these risks associated with alcohol consumption by adolescents may be immediate, for example, road traffic accidents, and injuries from sports and drowning or long term such as development of substance use disorders: tobacco, cannabis and stimulants [3].

The drinking patterns of people in different age groups are difficult to compare internationally because different age groupings and varying measures of alcohol consumption used in different countries [4]. Ahlstrom study reports that most surveys that compare drinking in various age groups were conducted in established market economies of Europe and North America, and not in developing regions. However, gender and age have emerged from these studies as important factors that affect drinking behaviours [4]. In almost every society, young adult males drink more frequently than young adult females whereas during adolescence the drinking patterns are less differentiated by gender. This convergence is especially obvious in Nordic countries, Ireland, United Kingdom and United States [4]. In the Caribbean this differentiation by gender for alcohol consumption among adolescents is not known.

A study on alcohol consumption among adolescents reports that in Australia 19.2% consumed one or more drinks within the previous three months, in Portugal approximately 50% experimented (first time drink only) with it [5]. This study further reports that studies carried out in Brazil claims that the prevalence values of alcohol experimentation ranges from 48.3% to 71.4% in adolescence at some time in life in addition to an 8.9% frequency of heavy use [5]. Another study on Caribbean-Americans adolescents found that they drank more frequently, became drunk more often, consumed more per drinking occasion, and planned to drink more in the future than African-American adolescents [6]. However, these studies did not determine the predictors of alcohol use for these groups.

In addition, parental alcohol use is thought to be a strong predictor of alcohol use among adolescents [6]. Other research also shows that peers and friends play a significant role in influencing teenagers to drink [7]. This supports the notion that observation of a particular behaviour by significant others, leads to the imitation of that behaviour and once started, the original models reinforce the behaviour. This social learning process of behaviour through observation, modelling, imitation and reinforcement influences alcohol use among adolescents [6].

It can be argued, that generally the social learning process is universal, whereas the specific social influences to consume alcohol may depend on culture or ethnicity [6, 7]. Therefore, to accurately assess which social characteristic influences one to drink, studies must include a complete range of these influences among different groups in different regions. According to Epstein et al. [6] and Behaviour Theory, alcohol use results from an interaction of personal, physiological, genetic, and environmental factors. The theory proposes that some adolescents find deviant behavior such as drinking and smoking, functional because it helps them to achieve personal goals. This is a gap in our knowledge that must be filled through scientific investigations [6].

Exposure to violence and traumatic stressors among children and adolescents has both short and long term effects on multiple health behaviours, for example, smoking, substance abuse and physical inactivity [8]. In addition to the effects on multiple health behaviours, there are negative health outcomes later, in life such as higher prevalence of heart, lung and liver disease, diabetes and depression [8]. Moreover, the exposures (alcohol and peer to peer violence) appears to influence health behaviours and outcomes through a cumulative process affecting the liver and the nervous system [3, 8].

Several studies have found a relationship between alcohol consumption and interpersonal violence including individual and group fighting, hand gun use, violent attacks, intimate partner violence, forcible rape and homicide. Therefore, adolescents experiencing violence, particularly peer to peer violence is common [8]. Further, evidence from prospective studies indicate that alcohol use during adolescence increases the risk for violence during that period and into adulthood [9]. Most recently in 2012, a study using the Global School-based Student Health Survey (GSHS) data for Argentina found that both male and female adolescent's drinkers were significantly more likely to engage in violence when compared to their non-drinking classmates [1].

The GSHS survey investigates the health and risk behaviours of middle school students living in low and middle-income countries across the world. Participating countries use the results from GSHS to identify public health policies and interventions that will improve the health of adolescents. Its purpose is to provide data on health behaviors and protective factors among students to (i) help countries develop priorities, establish programs, and advocate for resources for school health and youth health programs and policies (ii) allow international agencies, countries and others to make comparisons regarding the prevalence of health behaviours and protective factors and (iii) establish trends in the prevalence of health behaviours and protective factors [10, 11].

Currently, there are no studies that have looked at this relationship in the Caribbean. As a result an understanding of the risk factors associated with early exposure to alcohol and its association with violence among adolescence in the Caribbean is needed. This will contribute to the development and or refinement of intervention programs aimed at reducing alcohol use and violence among Caribbean adolescents.

Therefore, this study hypothesizes that Caribbean adolescents who drink alcohol are involved in a significantly higher frequency of violent activities because research has shown that alcohol affects judgment, behavior and the expression of emotions.

As a result the purpose of this study is to determine the association between self-reported violence (primary outcome) and alcohol consumption (primary exposure) among adolescents in the Caribbean. In addition the predictors of alcohol use will also be determined in an effort to guide interventions aimed at reducing alcohol use and violence among adolescents. To

achieve this, this study will be guided by the following objectives: (i) To determine the association between alcohol consumption and violence among Caribbean adolescents and (ii) to identify the demographic, environmental and psychological predictors of alcohol use and violence among Caribbean adolescents. To achieve this the following questions will be answered:

The findings of this study will set the foundation upon which further studies can build increasing our knowledge and understanding of alcohol use and participation in violent activities. Further, the results of this study will provide evidence that justifies the need for interventions aimed at reducing alcohol intake and violence among teenagers in the Caribbean.

OUR STUDY

Cross Sectional Study using secondary data from the Global School-based Student Health Survey (GSHS) examining the relationship between alcohol consumption and violence among adolescents in 14 countries across the Caribbean region. The methods used in the survey have been described elsewhere in detail [10-12].

Setting

The Caribbean is a region of the Americas with a population of approximately 44 million and consisting of islands from the Bahamas and Cuba in the north to Trinidad and Tobago in the south. Some islands are surrounded entirely by the Caribbean Sea and others are bordering with both the Caribbean Sea and the North Atlantic Ocean. This study uses data from 14 Caribbean English speaking countries.

Participants

Twenty two thousand five hundred and twenty five adolescent students (12-17 years), comprising of 44.6% boys and 53.4% girls was sampled from secondary schools across the Caribbean. The GSHS used a standardized scientific 2-stage sampling design. Stratum reflects the first level of the GSHS sample selection process, that is, schools. Stratum is assigned sequentially starting with the school with the largest enrolment of students in the grades/sections/levels/forms that 12-17 year olds usually attend and continuing through the list to the school with the smallest enrolment [10, 11]. At the second stage, classes were randomly selected and all students in selected classes were eligible to participate. Students enrolled in the sampled classes were invited to complete an anonymous self-reported questionnaire during school hours [10, 11].

Table 1. Demographic and general characteristics related to violence and alcohol consumption in 14 Caribbean countries

Country	Year of GSHS Survey	Sample size	Response rates (%)	Gender: Female (F) Male (M) in sample (%)	Drinkers (%) 95% CI	Victims of violence (%) 95% CI	In Physical Fights or Instigators (%) 95% CI	Suicidal thoughts (%) 95% CI
Anguilla	2009	951	84	F:52.9 M:47.1	44.7 41.4-48.1	27.8 25.0-30.1	33.3 30.3-36.4	81.1 78.4-83.6
Antigua/Barbuda	2009	1266	67	F:53.3 M:46.7	44.2 41.6-47.3	40.1 37.4-42.9	46.6 43.8-49.4	81.6 79.4-83.8
Bahamas	2013	1357	78	F:53.6 M:46.4	27.6 25.1-30.1	30.1 27.7-32.7	39.7 37.1-42.4	81.9 79.7-83.9
Barbados	2011	1629	73	F:54.8 M:45.2	47.7 45.2- 50.3	29.2 27.0-31.5	36.9 34.5-39.3	No Data
British Virgin Island	2007	1664	90	F:55.5 M:44.5	34.9 32.6- 37.4	30.6 28.4-32.9	35.6 33.3-38.0	84.9 83.2-86.7
Cayman Islands	2009	1299	79	F:51.4 M:48.6	40.2 37.4- 43.2	51.1 48.2-54.0	47.0 44.1-49.9	74.6 72.1-77.0
Dominica	2009	1642	84	F:56.4 M:43.6	51.5 49.0- 54.0	35.0 32.7-37.4	36.5 34.1-38.9	78.6 76.5-80.6
Grenada	2008	1542	78	F:55.1 M:44.9	49.4 46.6- 52.1	48.5 45.8-51.2	41.9 39.3-44.6	73.9 71.6-76.1
Guyana	2010	2392	76	F:56.2 M:43.8	41.0 39.0-43.1	39.0 37.0-41.0	35.9 34.1-38.0	76.8 75.0-78.5
Jamaica	2010	1623	72	F:51.2 M:48.8	53.5 51.0-56.0	40.7 38.3-43.1	44.4 42.0-46.9	77.6 75.4-79.7
St. Kitts/Nevis	2011	1740	70	F:55.9 M:44.1	53.4 51.0-56.0	33.9 31.7-36.2	36.7 34.4-39.0	83.2 81.3-85.0
St. Lucia	2007	1276	82	F:57.5 M:42.5	56.1 53.1-59.0	46.1 43.2-49.1	42.0 39.2-44.9	75.7 73.2-78.0
St. Vincent	2007	1333	84	F:52.7 M:47.3	54.5 51.6-59.0	46.2 43.2-49.2	39.3 36.5-42.2	71.2 68.7-73.7
Trinidad & Tobago	2011	2811	90	F:45.4 M:54.6	35.0 33.2 – 36.9	35.4 33.6-37.2	39.7 37.9-41.5	83.5 82.4-84.9

Data Collection Procedures

The GSHS is a school based self-administered survey primarily for students 12-17 years. This survey included core questionnaire modules, core expanded questions, and country specific questions that are combined to form a questionnaire which can be administered during one regular class period [1, 9]. The core questionnaire modules address the leading causes of morbidity and mortality among children adolescents worldwide [1]. These include three items on demographics (age, gender and current class grade), six items on alcohol use including age of first exposure, seven items on dietary behaviours, four items on drug use including age of first exposure, four items on hygiene, six items on mental health including feelings of loneliness, four items on physical activity including number of days student attended physical activity classes within school year, six items on protective factors for example missing classes without permission, five items on sexual behaviours that contribute to HIV infection, other sexually transmitted infections, and unintended pregnancy, six items on tobacco use and seven items on violence and unintentional injury. Participating countries must include at least six of the 10 core modules with no changes in the questions [1, 10]. Core-expanded questions are used to collect more detailed information on selected core questionnaire module topics. Core-expanded questions measure behaviors, knowledge, attitudes, skills, access to resources or information, or module-specific protective factors. These questions share the same format characteristics as the core questionnaire modules and is not available for public use. The data use for this analysis comes from the public-use data files. CDC (Center for Disease Control and Prevention) serves as the Data Coordination Center. All data processing (scanning, cleaning, editing, and weighting) is conducted at CDC [10, 12].

Data Analysis

Alcoholic drinkers are defined as participants reporting consumption of one or more alcoholic beverages in the previous month. This was recoded to a dichotomous scale of drinkers and non-drinkers. In the GSHS violence is measured with three questions about the previous year: (i) being the victim of violence (being physically attacked) (ii) instigating or participating in violence against others (being in a physical fight), and (iii) self- directed violence (whether student had seriously considered suicide). These were all recoded to a dichotomous scale.

Data analysis accounted for clustering by country using country as a fixed term in analyses. Crude Prevalence estimates and estimates by country were obtained for alcohol consumption, and the three forms of violence. Chi-square test of independence between all three forms of violence were performed.

Logistic regressions indicating which factors are associated with both alcohol (main exposure) and the three forms of violence determined which ones were confounding factors. Factors assessed were age, gender, feeling of loneliness (mental health), insomnia producing anxiety, cigarettes use, parental involvement (parents checking homework, parent's knowledge of their adolescent whereabouts, parents understanding of their adolescent), physical activity, skipping school without permission, and having no close friend. Likelihood

ratio test was done to determine whether or not age and gender were modifying the effect of alcohol on violence.

The final model included variables identified as potential confounders (associated with both alcohol and violence) to obtain the adjusted association between alcohol use and the three forms of violence. Analyses were performed using STATA 14. All p-values lower than 0.05 showed evidence against the null hypothesis of no association between exposure(s) and the outcome.

FINDINGS

The study population consisted of 46.6% males and 53.4% females with an age range of 11 to 16 years categorized into the following age groups: 11-12 year olds 12.0%, 13 year olds 23.2%, 14 year olds 27.9%, 15 year olds 23.3% and 16 year olds 3.6% (see Table 2).

Alcohol consumption (main exposure) had a crude prevalence of 43.8%, 95% CI: (43.1%- 44.5%), and showing a steady increase from the youngest age group to the oldest. 10 of the 14 participating countries had a prevalence >40 (see Table 3).

Table 2 shows the crude prevalence for the three forms of violence: (i) Victims of violence: 37.6%, 95% CI: (36.9 -38.3), (ii) Participated in physical fights: 39.4%, 95% CI: (38.8- 40.1), (iii) Serious thoughts of suicide (self-directed violence): 79.1%, 95% CI: (78.6 – 79.7).

Table 2. Age distribution of participants by country (n = 22,382)

Country	Age groups				
	11-12 years % (n)	13 years % (n)	14 years % (n)	15 years % (n)	16 years % (n)
Anguilla	13.6 (129)	19.5 (185)	22.18 (210)	19.3 (183)	25.3 (240)
Antigua/Barbuda	3.3 (42)	31.8 (400)	33.5 (421)	29.8 (377)	1.4 (18)
Bahamas	18.2 (246)	38.2 (517)	29.9 (404)	11.1 (150)	2.7 (36)
Barbados	2.2 (35)	22.0 (357)	38.8 (631)	30.0 (487)	7.1 (116)
British Virgin Island	20.6 (341)	17.0 (281)	20.9 (346)	17.6 (290)	23.9 (394)
Cayman Islands	16.9 (219)	24.9 (323)	29.7 (385)	17.5 (227)	11.0 (143)
Dominica	19.5 (318)	21.1 (345)	20.4 (333)	21.2 (347)	17.9 (292)
Grenada	12.5 (191)	25.0 (383)	25.3 (388)	23.4 (358)	13.8 (211)
Guyana	1.6 (39)	21.3 (507)	29.8 (709)	31.0 (737)	16.3 (388)
Jamaica	2.1 (33)	12.7 (203)	31.9 (510)	29.9 (479)	23.4 (375)
St. Kitts/Nevis	1.2 (20)	21.1 (366)	33.8 (585)	29.2 (506)	14.6 (253)
St. Lucia	16.6 (211)	21.4 (272)	22.5 (286)	24.0 (306)	15.6 (198)
St. Vincent	13.0 (170)	31.6 (414)	29.4(385)	17.6 (230)	8.4 (110)
Trinidad & Tobago	24.4 (682)	23.0 (641)	23.9 (668)	18.9 (527)	9.8 (273)
Total % in sample	12.0 (2676)	23.2 (5194)	27.9 (6261)	23.3 (5204)	13.6 (3047)

Linear Trends

Likelihood Ratio Tests (LRT) for linear trends between alcohol consumption and age ($p = 0.0004$) confirmed that a linear trend exists between alcohol consumption and age showing that there was an increase in alcohol consumption as age increased.

LRT for linear trends (evidence decline) between age and violence provided evidence against the null that there was no linear trend between (i) Victims of violence and age $p = 0.0113$, (ii) instigators and those who participated in fights $p = 0.014$.

LRT test for trend between Self-directed violence and age did not find evidence against the null of no linear trend $p = 0.3430$.

Table 3. Chi Square test of independence between different types of violence

Victim of Bullying	Instigating or participating in physical fights (n)%		Total (n)%	Probability of Chi Square
No	No 10, 447 (80.9)	Yes 2,914 (34.4)	13,361 (62.5)	<0.001
Yes	2,468 (19.1)	5,557 (65.6)	8,025 (37.5)	
Total % (n)	12,915 (100)	8,471 (100)	21,386 (100)	
Victim of Bullying	Self-directed violence (thoughts of suicide) (n) %			<0.001
No	No1,999 (50.1)	Yes10,077 (65.5)	12,076 (62.3)	
Yes	1,994 (49.9)	5,301 (34.5)	7,295 (37.7)	
Total % (n)	3,993 (100)	15,378 (100)	19,371 (100)	
Self-directed Violence	Instigating or participating in physical fights (n) %			<0.001
No	No 2,110 (17.7)	Yes 1,940 (25.4)	4,050 (20.7)	
Yes	9,815 (82.3)	5,688 (74.6)	15,503 (79.3)	
Total % (n)	11,925 (100)	7,628 (100)	19,553 (100)	

Factors Associated with Alcohol Use

Environmental and psychological factors associated with alcohol use were: gender (male), loneliness, insomnia, cigarettes use, the use of other drugs, parental involvement, victims of bullying, physical activity on less than two days in past week, skipping school and having no close friend (see Table 4).

Factors Associated with Violence

- *Alcohol*: Crude association showing odds ratios (OR, 95% CI) adjusted for country between self-reporting alcohol consumption and all forms of violence were. (i) Victims of violence OR = 1.75, CI: 1.64 – 1.86, (ii) Participant and instigators of physical fights OR = 2.09, CI: 1.97 – 2.22) and (iii) self-directed violence OR = 0.53, CI: 0.49 – 0.57 (see Table 4).
- *Age and gender*: Table 4 shows crude associations (OR and 95% CI) for age and three forms violence and adjusted for country. Chi square test for gender (males compared to females) and the three forms of violence gave $p < 0.0001$ for all associations. Logistic regression controlling for country also produced odds ratios showing a positive association between gender and violence when males are compared to females. Other predictable variables associated with all forms of violence are loneliness, insomnia, cigarettes use, use of other drugs, parental

involvement, victims of bullying, physical activity on less than two days in past week, skipping school and having no close friend are shown in Table 4.

Table 4. Crude association of demographic, environmental, and psychological factors with 3 forms of violence (main outcome) and alcohol (main exposure) adjusted for country

Variable	Victim of violence	Instigating or participating in physical fights	Self-directed violence	Alcohol
Age				
11-12 years	1	1	1	1
13 year	1.08 (0.97-1.19)	0.94 (0.85-1.04)	0.86 (0.76-0.98)	1.57 (1.41-1.76)
14years	1.14 (1.03-1.26)	1.01 (0.92-1.12)	0.73 (0.64-0.82)	2.35 (2.10-2.61)
15years	(0.91-1.12)	0.90 (0.81-0.99)	0.68 (0.59-0.77)	2.89 (2.58-3.23)
16 years	1.05 (0.94-1.18)	0.91 (0.81-1.01)	0.60 (0.52-0.69)	3.95 (3.50-4.47)
Gender				
Female	1	1	1	1
Male	1.68 (1.59-1.78)	2.04 (1.93-2.16)	1.67 (1.56-1.80)	1.39 (1.35-1.42)
Alcohol	1.74 (1.64-1.86)	2.08 (1.96-2.22)	0.53 (0.49-0.57)	-
Mental Health				
Loneliness	1.44 (1.36-1.53)	1.14 (1.07-1.20)	0.41 (0.38-0.45)	1.40 (1.31-1.49)
Insomnia anxiety	1.67 (1.58-1.77)	1.37 (1.30-1.45)	0.31 (0.29-0.33)	1.71 (1.62-1.82)
Use of other substances				
Cigarettes	2.26 (2.21-2.73)	2.76 (2.48-3.06)	0.45 (0.40-0.50)	7.12 (6.25-8.14)
Other drugs	3.22 (2.88-3.60)	3.14 (2.82-3.51)	0.38 (0.34-0.43)	5.76 (5.05-6.60)
Parental Involvement				
Checked homework	0.87 (0.80-0.94)	0.96 (0.83-1.03)	1.65 (1.49-1.83)	0.74 (0.68- 0.81)
Knew of whereabouts	0.79 (0.73-0.87)	0.73 (0.67-0.79)	1.54 (1.39-1.71)	0.70 (0.64-0.77)
Understood participants	0.86 (0.80-0.94)	0.99 (0.91-1.06)	2.04 (1.86-2.25)	0.88 (0.81-0.96)
Victim of Bullying	2.90 (2.71-3.10)	2.08 (1.95-2.22)	0.43 (0.40-0.46)	1.33 (1.24-1.43)
Physical Activity	1.14 (1.06-1.22)	1.12 (1.05-1.20)	0.91 (0.84-0.99)	1.28 (1.19-1.37)
Skipping school	1.62 (1.51-1.73)	1.72 (1.62-1.85)	0.89 (0.82-0.97)	1.65 (1.53-1.78)
Having no close friend	0.87 (0.79-0.96)	0.90 (0.82-0.99)	1.58 (1.41-1.76)	1.04 (0.94-1.15)

Assessment of Confounding Factors

Confounding factors associated with victims of violence and alcohol use were cigarette use, use of other drugs, and insomnia (see Table 5). Likelihood ratio test ($p < 0.0001$) identified cigarette use, use of other drugs and insomnia as factors to be included in the final model.

Confounding factors associated with participants who instigated or participated in physical fights and alcohol use were cigarette use, use of other drugs, and parental involvement (parents checking homework, parents knowledge of adolescents whereabouts and parents who understood participants problems) (see Table 6). Likelihood ratio test ($p < 0.0001$) identified cigarette use, use of other drugs and parents knowledge of participants whereabouts as factors that should be included in the final model.

Confounding factors associated with self-directed violence and alcohol use were parental involvement parents checking homework, parents knowledge of adolescents whereabouts and parents who understood participants problems) (see Table 7). Likelihood ratio test ($p <$

0.0001) identified all three variables (parent checking homework, parents knowledge of child whereabouts, and parents understanding child's problems) as factors that should be included in the final model.

Table 5. Alcohol and Victims of Violence: Crude and adjusted odds ratios

Variable adjusted for (potential confounders)	Crude Association OR, 95% CI	Adjusted OR's, 95% CI	LRT for confounding factors p-value
Gender	1.75 (1.64 – 1.86)	1.72 (1.61- 1.82)	-
Mental Health Loneliness Insomnia anxiety	1.75 (1.64 – 1.86)	1.71 (1.60-1.82) *1.64 (1.55-1.76)	- P < 0.0001
Use of other substances Cigarettes Other drugs	1.75, (1.64 – 1.86)	*1.57 (1.45-1.67) *1.56 (1.47- 1.67)	P < 0.0001 P < 0.0001
Parental Involvement Checked homework Knew of whereabouts Understood participants	1.75, (1.64 – 1.86)	1.69 (1.56-1.82) 1.69 (1.56- 1.83) 1.70 (1.58-1.85)	- - -
Victim of Bullying	1.75, (1.64 – 1.86)	1.71 (1.61-1.83)	-
Physical Activity	1.75, (1.64 – 1.86)	1.75 (1.64-1.87)	-
Skipping school	1.75, (1.64 – 1.86)	1.69 (1.58-1.81)	-
Having no close friend	1.75, (1.64 – 1.86)	1.70 (1.60-1.82)	-

* Indicates confounding factors.

Table 6. Alcohol and adolescents who instigated or participated in physical fights: Crude and adjusted odds ratios

Variable adjusted for (potential confounders)	Crude Association OR, 95% CI	Adjusted OR's, 95% CI	LRT for confounding factors p-value
Gender	2.09, (1.97 – 2.22)	2.06 (1.94-2.20)	-
Mental Health Loneliness Insomnia anxiety	2.09, (1.97 – 2.22)	2.08 (1.96-2.21) 2.02(1.90- 2.15)	- -
Use of other substances Cigarettes Other drugs	2.09, (1.97 – 2.22)	*1.88 (1.76-2.01) *1.90 (1.78-2.02)	P < 0.0001 P < 0.0001
Parental Involvement Checked homework Knew of whereabouts Understood participants	2.09, (1.97 – 2.22)	*2.18 (2.01-2.35) *2.15 (1.99-2.33) *2.20 (2.04-2.39)	P = 0.7970 P < 0.0001 P = 0.6905
Victim of Bullying	2.09, (1.97 – 2.22)	2.06 (1.94-2.20)	-
Physical Activity	2.09, (1.97 – 2.22)	2.08 (1.94-2.22)	-
Skipping school	2.09, (1.97 – 2.22)	2.00 (1.87-2.14)	-
Having no close friend	2.09, (1.97 – 2.22)	2.08 (1.96-2.22)	-

*Indicates confounding factors.

**Table 7. Alcohol and self-directed violence (serious thoughts of suicide):
Crude and adjusted odds ratios**

Variable adjusted for (potential confounders)	Crude Association OR, 95% CI	Adjusted OR's, 95% CI	LRT for confounding factors p-value
Gender	0.53, (0.49 – 0.57)	0.51 (0.47-0.55)	-
Mental Health			
Loneliness	0.53, (0.49 – 0.57)	0.54 (0.50-0.59)	-
Insomnia anxiety		0.58 (0.54-0.63)	-
Use of other substances			
Cigarettes	0.53, (0.49 – 0.57)	0.57 (0.52-0.62)	-
Other drugs		0.57 (0.52-0.62)	-
Parental Involvement			
Checked homework	0.53, (0.49 – 0.57)	*0.49 (0.44-0.54)	P < 0.0001
Knew of whereabouts		*0.49 (0.44—0.54)	P < 0.0001
Understood participants		*0.48 (0.43-0.53)	P < 0.0001
Victim of Bullying	0.53, (0.49 – 0.57)	0.54 (0.49-0.58)	-
Physical Activity	0.53, (0.49 – 0.57)	0.52 (0.48-0.56)	-
Skipping school	0.53, (0.49 – 0.57)	0.51 (0.47-0.56)	-
Having no close friend	0.53, (0.49 – 0.57)	0.54 (0.50-0.59)	-

*Indicates confounding factors.

Final Models for Alcohol Consumption and the Three Forms of Violence

Adjusted odds ratios (OR), 95% CI, for factors associated with victims of violence and alcohol use (exposure) identified cigarette use, use of other drugs, and insomnia producing anxiety confounded the effect of alcohol on adolescent victims of violence (see Table 5). Likelihood ratio test to assess the contribution of each confounding factor to the final model, that is, to test the null hypothesis that adding them does not improve the fit of the model. All variables (cigarette use, use of other drugs and insomnia producing anxiety) showed very strong evidence against the null hypothesis ($p < 0.0001$).

Alcohol use and victims of violence: This model produced OR = 1.47, CI: (1.37-1.58), $p < 0.0001$, after adjusting for Cigarette use, use of other drugs, insomnia producing anxiety, age and country.

Alcohol use and Instigating or participating in physical fights: This model produced OR = 1.92, CI: (1.77-2.09), $p < 0.0001$, after adjusting for Cigarette use use of other drugs, parents knowledge of whereabouts of adolescent, age and country

Alcohol use and self-directed violence: This model produced OR = 0.49, CI: (0.44-0.55), $p < 0.0001$, after adjusting for parents checking homework, parents knowledge of whereabouts of adolescent.

DISCUSSION

The prevalence of the three forms of violence (i) victims of violence 37.6% (ii) instigating or participating in physical fights 39.4% and (i) self-directed violence 79.4%, among adolescents in the Caribbean is relatively high. Alcohol consumption among

participants 43.8% was quite high and positively associated with (i) victims of violence and (ii) instigators and participants who engaged in physical fights but negatively associated with self-directed violence (thoughts of suicide). Behavioral and environmental predictors such as: use cigarettes, use of other drugs, parental involvement, victims of bullying, limited participation in physical activities, skipping school and having no close friends were associated both with alcohol consumption and the three forms of violence. Although the prevalence of alcohol increased with age, the prevalence of violent activities decreased among older participants.

Alcohol consumption in the Caribbean among adolescents was not explored in the past. However consumption among adolescents in the Americas varies widely by country, from 15% to 51% [1]. In South America frequent alcohol consumption and binge drinking are common among secondary school students [1, 13]. This study brings new evidence supporting the notion that alcohol consumption in the Caribbean maybe very similar to its surrounding regions, the Americas.

Alcohol consumption is largely a social behavior, where individuals learn from practice with other members of their culture: family members, peers and significant others [4]. Consequently the drinking behavior of adolescents in any country, culture or region is a reflection of the drinking behavior of the entire population [4]. This is of concern since early exposure to alcohol is associated with an increased risk of addiction in adults [1, 14]. In addition, economic, psychosocial and environmental factors are also associated with alcohol consumption at an early age, some of which were identified as predictors of alcohol and violence in this analysis.

Alcohol use by adolescents is also associated with violence and suicide attempts [15, 16]. While these associations suggest that alcohol use and violent behavior are part of a larger lifestyle, they do not necessarily indicate that adolescents engage in these behaviors while under the influence of alcohol. Very few studies have examined adolescent involvement in alcohol related violent behaviors. This study supports the findings of a similar study done on Argentine's adolescents where adolescent's drinkers were more likely to engage in violent behaviors [1].

In the Caribbean culture, parents value a punitive, restrictive approach to discipline and child rearing such that obedience and docility is valued [6]. This harsh and punitive parenting style has been associated with aggressive, deviant, and acting out behaviors among adolescents [6]. As a result the tendency to act out or engage in violent behaviors are more likely to occur and is associated with alcohol consumption. The vast majority of studies available in the literature did not assess different forms of violence, nor used identical age groups, making them very difficult to compare. In addition they targeted European and North American adolescents [1]. This analysis, takes a more comprehensive approach examining the association of alcohol consumption with both active and passive violence

This study found many psychosocial and environmental predictors of alcohol and violence. An unexpected but interesting finding is that adolescents who consumed alcohol was less likely to have serious thoughts of suicide. Little information is available about the possible role of alcohol in suicide by non-alcoholics, but some studies indicate that a proportion had been drinking shortly before their death, perhaps to bolster their courage [4]. This protective association, found between alcohol consumption and thoughts of suicide maybe as a result of reverse causality, where adolescents who had thoughts of suicide may have drank alcohol which in turn caused them to have less thoughts of suicide.

Parental involvement, a strong predictor for three forms of violence is of much concern. The positive association found emphasizes the importance of parenting skills, communication, and the overall parent-child relationship. Poor parental monitoring is also relatively strongly linked to delinquency [17]. Parental monitoring: parental knowledge of the child's whereabouts, the active tracking and tracing of the child's whereabouts by parents, and child disclosure, all having links to delinquency that are relatively similar in magnitude [17]. Given that both parenting dimensions of support and control are linked to delinquent behavior, parenting styles could be important risk factors for delinquency (that is, the combination of the dimensions support and control). In particular, a neglectful parenting style may be linked to delinquency which is linked to deviant behaviors [17, 18].

The African-Caribbean family has unique mating and childrearing patterns. Some of these patterns include absent fathers, grandmother-dominated households, frequently terminated common-law unions, and child-shifting, where children are sent to live with relatives because the parents have migrated or have begun a union with another spouse [19]. Families tend to have a matri-focal or matri-centric structure. Approximately 30 to 50 percent of African-Caribbean families are headed by a female: Jamaica: 33.8%; Barbados: 42.9%, and Grenada: 45.3%. [19] Single-parent families have more difficulty in providing the necessary conditions that prevent crime and deviant behaviours. The demands of single parenting can make monitoring their child difficult and others in the community. Thus a higher proportion of single parent families result in a greater opportunity for an adolescent to participate in deviant behaviours [19].

Predictors such as cigarette use and use of other drugs and their confounding effect on the association between alcohol and violence is well known [9]. The easy access to alcohol, cigarettes and other drugs must be examined to determine how access acts as an enabling factor that influences their use among adolescents. Further, in Caribbean societies, law-enforcement related to underage drinking is not emphasized because alcohol is not regarded as a drug that can cause harm when consumed in moderation [6]. Social functions and festive seasons, especially the annual celebrating of the abolishment of slavery (carnival) and Christmas, is marked by excessive alcohol consumption among the population. This acceptance of alcohol consumption and the easy access, may very well act as enabling factors that encourage alcohol consumption, cigarette use and other drugs among Caribbean adolescents. Another drug, Cannabis (marijuana), not identified separately as a drug in the GSHS, must be examined in the future to determine how its use is associated with violence, alcohol consumption and deviant behavior among adolescents.

The results of this analysis underscores the complexity of this issue and the urgent need to focus on the adolescent population. Prohibitive national measures as minimum drinking ages have had little effect [5]. Public Health interventions to discourage and decrease adolescent alcohol consumption would alleviate other pressures on teenagers such as, marketing of alcohol to youths and teenagers [5]. Many different efforts involving individuals and the environment to improve the success of youth anti-alcohol behaviors at varying levels must be employed. Further, programs that alert parents on the dangers of youth drinking and provides parenting tips will be critical for the success of anti-alcohol youth programs [1, 20].

These interventions will provide tools that foster open communication between parents and children about alcohol thereby reducing the pressures placed on adolescents to make decisions by themselves. Schools based and health care programs may also be useful in combatting the enabling factors that encourage adolescent drinking. This issue merits much

reflection since alcohol consumption is associated with many outcomes, road traffic accidents, violence and consequently the risk of death [5].

Mental health and parental involvement predictors identified in this analysis must be considered seriously. Psychological support services in schools and communities must be available to adolescents [21]. The adolescent period is marked by significant physiological changes that may affect an adolescent in many ways. Feelings of loneliness and insomnia producing anxieties are only two of the many intra-personal challenges adolescents face during this unstable and ever changing period. Intervention programs should focus on training parents on how to actively monitor and guide their children in order to enhance parent's knowledge on the whereabouts of their children [17]. Training should emphasize improvements in parent-child relationship and trust, since this will enhance disclosure by adolescents. Further, practitioners, should be alert to parents who neglect their children because of its association higher levels of delinquent behavior [17].

The strengths of this analysis include, nationally selected samples using multi stage sampling techniques, coupled with high participation rates. As a result representative samples were obtained minimizing the possibility of selection bias and preserving external validity. However, there are limitations that must be acknowledged. The low numbers of 11-12 year olds (1-2%) participating from 5 countries is of concern and could have introduced selection bias skewing the results in the direction on increased prevalence of alcohol use and therefore inflating the association between alcohol use and violence because older teens tend to consume more alcohol and more likely to participate in violent activities. Secondly, there was no data on suicidal thoughts from Barbados. This would have introduced some form of selection bias depending on prevalence of suicidal thoughts in that country and may have contributed to an over estimation or underestimation of the prevalence of and the association between alcohol use and suicidal thoughts. Further, the GSHS is a self- administered survey, so some participants may have misinterpreted or misrepresented their behaviors and perceptions with no validation by parental or social data. This misrepresentation is influenced by the participant's perception of desired and undesirable behaviors resulting in over reporting or under reporting of exposures and outcomes depending on their interpretation of acceptability in their community or their belief system.

Additionally, this cross sectional design used different time scales for alcohol consumption (previous month) and violence (during past year). As result it is not clear whether the exposure preceded the outcome or the outcome led to the exposure, reverse causality. Further the cross sectional design does not allow for the interpretation of results based on causality. Notwithstanding these limitations, the results of this study identifies a possible link between alcohol consumption and various types of violence in Caribbean adolescents aged 12-16 years.

CONCLUSION

The findings of this study confirms what has been found in European and North American cultures about the association between alcohol consumption and violence. Since most information acquired about drinking patterns and violence is based on data from European and North American countries, global comparisons are difficult to make.

Furthermore studies on drinking have used different age groups making it even more difficult to compare and contrast these patterns.

The apparent increase in alcohol consumption for adult populations in developing countries maybe also be reflected in the increase of alcohol use in adolescents. However there are demographic, psychological, environmental and cultural factors that also influence adolescent alcohol use and violent behaviors. Exposures to cigarettes and other drugs are important predictors that must be considered. Further the access to these, in Caribbean cultures may be enabling factors that encourage alcohol use and its related outcomes.

An important predictor that should not be ignored is parental involvement in their child's life. Parents directly and indirectly influence their adolescent's behavior through modeling, and parent-child relationship [6, 17]. The effective monitoring and support, as well consistency with positive parental modelling cannot be overlooked. Further single parent living environments reduce social control and may lead to an increase in deviant behavior. In addition, anti-social behaviors (no close friends, limited participation in physical activities) among adolescents are also predictors of violence.

Interventions to reduce alcohol consumption and violence among adolescents must focus on varying levels of society (advertising, access, enforcement of laws), adolescents and parents. In particular strengthening of the parent-child relationship will benefit both parents and children [1, 20]. Future studies must focus on standardized measures for international, regional and local comparisons. This will allow for a better understanding of the true patterns that may exist. Finally this study findings are particularly important in today's climate, in which violent behavior in youth has increased over the years.

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Chapter 80

MANAGING INFLUENZA PANDEMICS: PAST AND FUTURE

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INTRODUCTION

Influenza (flu) is a disease that we expect to see each year. Many engage with the flu, if only to prevent it, by washing hands or getting the annual vaccine. While it can be deadly, for most people the flu merely causes intense misery and then passes. In 1918, however, the world witnessed a global influenza pandemic that was radically different from any that has been recorded before or since: at least 20 million people died worldwide, and unexpectedly, otherwise healthy young adults proved to be particularly vulnerable. These factors, among others, ensured that the 1918 pandemic (often called the Spanish influenza) was disruptive and fearsome. That is the pandemic that Nancy Bristow will discuss, with a particular focus on who suffered. Like many episodes in public health, the answers are not simply tied to the scientific and medical realms, but also include factors in the social and political arenas.

Because physicians and scientists did not know the cause of the Spanish influenza in 1918, they could neither treat nor prevent it effectively. Local boards of health and governments tried various solutions from banning large public gatherings to requiring the wearing of face masks in public and instituting quarantines. Over the last century, the growth in knowledge about the flu, the increased organization of the public health infrastructure, and practice with flu preparedness have influenced the development of contemporary public health plans. Some of these plans grapple with issues in historically important ways, such as finding methods for massive, safe disposal of contaminated bodies in urban communities or determining how to provide medical care for a population in need that has suddenly increased

in size. The plans vary at the state and municipal level, and may need to be implemented or adapted in unforeseen ways during actual crises. Tim Soucy and Dora Mills will speak to situations based upon their experiences at the local and state level, respectively.

LECTURE

THE HISTORICAL PERSPECTIVE: THE 1918 INFLUENZA PANDEMIC

*Nancy Bristow,
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Early in the evening of Wednesday, September 25, 1918, a woman named Agnes L. Swenson died in Rye, New Hampshire. Her obituary said that she had worked at the First National Bank, was a Christian woman, and was known for her “kindly nature and fine qualities of heart and mind.”¹ Just a few days short of turning 36, Ms. Swenson had contracted influenza and left work early the previous Friday. Five days later, she died of pneumonia. *The Portsmouth Herald* acknowledged her passing saying news of her sudden death was a sad blow to her family and friends: “All who knew her can sympathize with the family in their deep bereavement.”²

For the people of Rye, New Hampshire, it was, indeed, a sad day, but soon, people throughout the US and around the world would know the same kind of bereavement. Agnes Swenson was one of the early casualties in the worst pandemic in the history of human beings. Perhaps 50 million people died of this influenza pandemic in the winter and spring of 1918–1919.³ Within days of Swenson’s death, it had reached epidemic proportions in New Hampshire. Between October 6 and 15, 205 people died in the single city of Manchester, New Hampshire. The worst losses for the state followed in the week of October 12 when 393 people died—this in a population smaller than 450,000.⁴

When the pandemic struck, public health leaders moved quickly to try to stamp out the grim epidemic. As early as September 18, *The Portsmouth Herald* reported on a “steady increase” in the number of victims, but noted that “the entire force of the public health service is working on the cases and hope to check it.”⁵ Within a week, the local Board of Health, in collaboration with the US Public Health Service, had opened the city’s first emergency hospital; a second would follow.⁶ By September 25, 1,000 people were sick and the Board of

¹ “Obituary—Agnes L. Swenson,” *The Portsmouth Herald*, September 26, 1918), 8.

² “Obituary—Agnes L. Swenson,” *The Portsmouth Herald*, September 26, 1918), 8.

³ It is difficult to know the figures worldwide, but the most impressive accounting suggests perhaps 50 million deaths. See Niall P. A. S. Johnson and Juergen Mueller, “Updating the Accounts: Global Mortality of the 1918–1920 ‘Spanish’ Influenza Pandemic,” *Bulletin of the History of Medicine* 76 (2002): 107, 111, 115.

⁴ “Your State—New Hampshire,” feature on The Great Pandemic, The US in 1918-1919, US Department of Health and Human Services website, accessed September 8, 2013 and April 9, 2017, https://cybercemetery.unt.edu/archive/allcollections/20090305005652/http://vietnamese.pandemicflu.gov/pandemicflu/envi/24/_1918_pandemicflu_gov/your_state/new_hampshire.htm.

⁵ “Influenza Spreading in This City,” *The Portsmouth Herald*, September 18, 1918, 6.

⁶ “Open Emergency Hospital for Grippe Patients—Will Care for Non-Residents Mostly and Those with Pneumonia,” *The Portsmouth Herald*, September 24, 1918, 5; “Elks’ Hospital Opened with 15 Patients,” *The Portsmouth Herald*, October 4, 1918, 4.

Health, on behalf of the Mayor, ordered the closure of schools, churches, dance halls, and theaters; all public gatherings were banned, and even the county fair had to be cancelled.⁷ Public funerals were prohibited as well.⁸ Next they turned to the soda fountains and near beer saloons, which were closed several days later.⁹ The bans remained in effect for several weeks. Yet despite it all, the obituary section of the paper continued to run story after story of the city's losses to influenza. By early January 1919, more than 2,000 residents of New Hampshire had died in the pandemic.¹⁰

Fortunately, today we have many additional tools to use in our fight against influenza, and so our relationship to a flu pandemic might be a bit different. We have preventive vaccines. We have antivirals that can lighten the symptoms and shorten the course of an illness. We have antibiotics that can lessen the danger of certain secondary infections that were so costly in 1918. The reality, though, is that influenza remains a serious public health danger, even in the twenty-first century. For that reason, I believe that the voices of 1918 have much to tell us about how we might best handle our next influenza crisis.

One insight, based on research by scholars at the University of Michigan and the Centers for Disease Control and Prevention (CDC), is both very important and deceptively simple. Exploring public health outcomes in 43 of the 66 largest cities in the country, they have confirmed that non-pharmaceutical interventions, or NPIs, actually worked. What is an NPI? In this instance it means implementing social distancing measures—keeping people away from one another—such as cancelling public gatherings, closing down public spaces, and keeping people quarantined. NPIs worked by slowing down the progress of the disease, and lowering “the overall and peak attack rate,” a finding with great relevance to our own time.¹¹ With the availability of effective vaccines and antiviral treatments, slowing a pandemic's spread and delaying its worst impact would be still more effective today, giving us time to develop and put in use such prophylactic and treatment measures. Such practices, though, would raise significant civil liberties concerns, just as they did in 1918.

We know that in 1918 Americans didn't always accept the restrictions on their freedom of movement during the pandemic. Now that we know just how valuable these restrictive measures were in combatting influenza, it is all the more important to understand why people did or did not follow the rules. What led so many Americans to accept such tight restrictions on their liberty in the early days of the pandemic? Why, in turn, did many of those same Americans later withdraw their cooperation? And were there other populations whose relationship with the authorities was troubled from the beginning? I want to focus on answers to those questions, arguing that in 1918 the American public, widely accepting of public health measures initially, later rejected the authority of governmental and health officials when they felt misinformed, misled, and even lied to—in short, when they found the words of

⁷ “Will Stamp Out the Grip Epidemic,” *The Portsmouth Herald*, September 25, 1918, 1; “Four Deaths from Influenza,” *The Portsmouth Herald*, September 25, 1918, 3; Editorial Comment, *the Portsmouth Herald*, October 3, 1918, 4.

⁸ “Must Have No Public Funerals,” *The Portsmouth Herald*, September 25, 1918, 5.

⁹ “Soda Fountains and Saloons Closed,” *The Portsmouth Herald*, October 8, 1918, 6.

¹⁰ “Influenza Causes 2,106 Deaths in New Hampshire,” *The Portsmouth Herald*, January 9, 1919, 8.

¹¹ See Howard Markel et al, “Nonpharmaceutical Interventions Implemented by US Cities During the 1918–1919 Influenza Pandemic,” *Journal of the American Medical Association* 298 (August 8, 2007): 644–654; Howard Markel, Alexandra M. Stern, and Martin S. Cetron, “Nonpharmaceutical Interventions Employed by Major American Cities During the 1918–1919 Influenza Pandemic,” *Transactions of the American Clinical and Climatological Association* 119 (2008):129–142.

those leaders dishonest and empty. Furthermore, some Americans had a conflicted relationship with public health authorities throughout the pandemic because they found themselves the targets of discriminatory, unjust, or culturally insensitive treatment. The takeaway lesson from 1918 that I wish to offer us is the value not only of NPIs, but of honest and ethical leadership.

To make sense of the choices Americans made during the pandemic we must begin with the context within which they made those choices. As the example of Portsmouth suggests, when the pandemic struck, Americans faced it with a new confidence in the ability of medicine and public health to protect them from such a scourge. In the late nineteenth century, the new field of bacteriology had allowed scientists to discover the causative agents for several diseases, including dysentery, malaria, scarlet fever, leprosy, bubonic plague, typhoid, yellow fever, gangrene, and whooping cough, and as a result to begin to control some of these illnesses. By the early twentieth century germ theory had gained traction, and “regular” allopathic practitioners dominated the American medical scene.¹² Many people, including health care professionals, began to imagine a world without infectious disease.¹³

These changes in medicine had enormous implications for the field of public health as well. To get a sense of this, note that in the mid-nineteenth century, Americans’ health had declined, with rising death rates and falling life expectancy brought on by urbanization.¹⁴ But this worsening situation offered new opportunities to increasingly professionalized public health practitioners, who pushed for the creation of city and state health boards and the reform of what was evolving into the US Public Health Service. Facilitated as well by the Progressive Era’s broad-based efforts to reform American cities, public health leaders employed new measures ranging from garbage removal and basic hygiene education to clean water and sewage systems to make significant contributions to Americans’ health. The nation’s entry into World War I only heightened the stature of the public health profession, as the field contributed to soldiers’ health.

And then the pandemic hit. Perhaps originating in Kansas—we call it Spanish Flu for reasons that are not relevant here—it might accurately be called the American Flu.¹⁵ It passed through in a first wave in the spring of 1918 largely unnoticed because it sickened lots of people but killed very few.¹⁶ When the second wave started its rampage in Boston in late

¹² Allopathic medical professionals are individuals who practice what is generally viewed as mainstream medicine today. Allopathic medicine contrasts with homeopathic or alternative medicine.

¹³ Nancy Tomes, *The Gospel of Germs: Men, Women, and the Microbe in American Life* (Cambridge: Harvard University Press, 1998), 92, 94; William H. McNeill, *Plagues and Peoples* (Garden City: Anchor Press, 1976), 278–279, 284–286, 289; Arno Karlen, *Man and Microbes: Disease and Plagues in History and Modern Times* (New York: Touchstone, 1995), 139–140.

¹⁴ John Duffy, *The Sanitarians: A History of American Public Health* (Chicago: University of Illinois Press, 1990), 93; David Rosner, “Spanish Flu, or Whatever It Is...”: The Paradox of Public Health in a Time of Crisis,” *Public Health Reports* 125 (2010, Supplement 3): 39–40. On the problem of garbage, see Martin V. Melosi, *Garbage in the Cities: Refuse, Reform, and the Environment*, 3rd ed. (Pittsburgh: University of Pittsburgh Press, 2005).

¹⁵ Although the Spanish people were not the only victims of the disease, since Spain was a neutral country during World War I, there was less censorship there than in other nations. News of the influenza flowed out of the country, and thus it gave its name to the disease.

¹⁶ Alfred Crosby, *America’s Forgotten Pandemic: The Influenza of 1918* (New York: Cambridge University Press, 1989), 18–19. Military camps were the notable exception. See Carol Byerly, *Fever of War: The Influenza Epidemic in the US Army during World War I* (New York: New York University Press, 2005), 70–71. For a useful account of the first spring wave of the epidemic, see John Barry, *The Great Influenza: The Epic Story of the Deadliest Pandemic in History* (New York: Penguin, 2004), chap. 14.

August, however, there was no question that Americans were facing a new and different disease.

How did they know it was different? First of all, the symptoms were simply horrific. Some people suffered only what we think of as the flu: you feel terrible, you have a fever, you're achy, you feel just awful. But with this new influenza, the vast majority would suffer a much more serious disease with very high fevers, very serious muscle and joint pain, and immobilizing prostration and weakness. Other symptoms included chills, and edema in the lungs—the lungs would literally begin to fill with liquid. Some patients would begin to recover at that point, but others would get sicker still, facing delirium and a descent into unconsciousness. Watching these symptoms develop was traumatic for family caregivers, as patients suffered from bloody fluids leaving their bodies. Then, finally, because of cyanosis, extremities and faces would turn blue or black as the person was sickening and dying. As three military doctors reporting on the pandemic at Camp Upton in New Jersey conceded—and, remember, these were people who were familiar with the horror of illness—"the memory of this sight will haunt for life the minds of those who saw it."¹⁷

The shock of the illness was reinforced by the rapidity with which it spread. By the end of the pandemic, 28%—more than a quarter of all Americans—had been sickened by the flu. The epidemic was serious enough to lower life expectancy in the US in 1918 by 12 years; it was 25 times as deadly as regular seasonal flu.

Also strange, and destabilizing, was the reality of who was sickening and dying. When you plot the age of normal influenza victims on an x-y graph, you get a U shape—the young and the old are the most common victims of the disease. But deaths from influenza in 1918 charted as a W—almost half of its victims were people between the ages of 20 and 40.¹⁸ Imagine moms and dads as common victims, or the people who work to keep communities running. That's who was passing away in this catastrophe. And it was in this chaotic context that public health leaders tried to take control.

The reality is that, in 1918, we still had a very uneven public health structure in the US. It varied enormously from state to state and city to city in terms of infrastructure. Political and cultural realities varied across and within communities as well. Even so, there are certain patterns in the public health efforts that were broadly shared, and looking back, are easily discernible.

The common first step in the effort to prevent influenza and contain the pandemic was education—public health leaders knew they needed people to understand what was happening. Officials worked very hard to publicize their message and make it accessible; they used cartoons and translated the information into multiple languages.¹⁹ The point of education

¹⁷ Irving P. Lyon, Charles F. Tenney, and Leopold Szerlip, "Some Clinical Observations on the Influenza Epidemic at Camp Upton: From Sept. 13 to Dec. 1, 1918," *Journal of the American Medical Association* 72 (June 14, 1919): 1726.

¹⁸ Jeffery K. Taubenberger and David M. Morens, "Influenza: The Once and Future Pandemic" *Public Health Reports* 125 (2010 Supplement 3): 19–21; Jeffery K. Taubenberger and David M. Morens, "1918 Influenza: The Mother of All Pandemics," *Emerging Infectious Disease* 12 (January 2006): 19.

¹⁹ Rupert Blue, "Epidemic Influenza and the U.S. Public Health Service," *Modern Hospital* 11 (December 1918): 425; "Droplet Infection Explained in Pictures," *Public Health Reports* 33, no. 46 (November 15, 1918): 1969; "Red Cross Bulletin—Spanish Influenza," File 803.7: Epidemics—Influenza—Publicity and Publications, Box 688, Record Group 200, National Archives, College Park, MD. By pandemic's end the US Public Health Service had produced 6 million copies of a brief pamphlet entitled "'Spanish Influenza,' 'Three Day Fever,' 'The Flu,'" and a multitude of posters, articles and a "daily bulletin" for use by the press, while the Red Cross published a pamphlet, "Spanish Influenza," which it translated into eight languages. As the noted influenza

was to teach people basic public health practices such as washing their hands, avoiding public drinking cups, and ceasing “promiscuous” (as it was called then) coughing, sneezing, and spitting.²⁰

Then, as things got worse, public health officials looked to more invasive measures. The Surgeon General of the US recommended the closing of “all public gathering places” if a community was “threatened with the epidemic” as in Portsmouth, New Hampshire. Many cities and towns did just that.²¹ Some institutions found ways to work within these rules. For example, in San Francisco church services might be held outdoors but the worshippers had to wear masks. New Hampshire College (a former name of the University of New Hampshire) reopened for classes but held them outside.²² (This was in October when it was getting quite chilly, of course.) Some cities varied transportation schedules, changed the times that people shopped, or did whatever they could do to try to cut down on overcrowding. Less common, but sometimes employed, was a requirement for people to wear masks in public or for the ill to remain quarantined until their illness passed.

As public health restrictions moved from voluntary to mandatory measures, and from simple to more invasive restrictions, initially most Americans continued to obey. But, as the pandemic persisted, public reaction began to shift as people resisted and sometimes simply stopped cooperating altogether.

The first question is, “Why would so many people be supportive of these public health measures at the beginning?” Certainly the months of war had given the public plenty of opportunities to cede power to the government and to obey new interventions in their lives—consider the draft, for instance. In fact, when mobilizing the public in the pandemic, authorities employed the war very intentionally, suggesting it was patriotic and part of the war effort to help fight the flu. As one poster from the Connecticut State Director of Health and the State Council of National Defense declared, “Help fight the Grippe [the flu], Kaiser Wilhelm’s ally.”²³ This call to the public was framed to capitalize on the war as a mechanism for motivating citizens to cooperate with public health demands. Another important factor was the confidence that Americans had in science: they were believers in its possibilities in 1918. Americans wanted to believe that those who had controlled yellow fever and diphtheria might help them against this new illness. Their confidence in the capabilities of science and

historian Alfred Crosby suggested, “If influenza could have been smothered by paper, many lives would have been saved in 1918.” Alfred Crosby, *America’s Forgotten Pandemic*, 49.

²⁰ Memo from Lieutenant Commander J.R. Phelps, Medical Corps, USN to Dr. Biggs, in reference to the memo of November 6 from the Governor’s Commission on Epidemic Influenza, Box 79, Series 3, Manuscript Group #749, Charles-Edward Amory Winslow Papers, Sterling Library, Yale University; “Guarding Against Influenza,” *Public Health Reports* 33, no. 51 (December 20, 1918): 2259; Rupert Blue, US Public Health Service, “Spanish Influenza” ‘Three-Day Fever’ ‘The Flu,’” *Public Health Reports* (September 25, 1918, Supplement 34), 4.

²¹ Surgeon General Blue quoted in Crosby, *America’s Forgotten Pandemic*, 74. Massachusetts led in the closures, and was soon followed by others. For examples see Rupert Blue, “Epidemic Influenza and the U.S. Public Health Service,” 426; Charles V. Aiken, “Influenza in South Carolina, 1918,” *Journal of the South Carolina Medical Association* 15 (January 1919): 346; “Controlling the Influenza Epidemic in Ohio,” *Ohio Public Health Journal* 9 (November 1918): 453; Judith Walzer Leavitt, *The Healthiest City: Milwaukee and the Politics of Health Reform* (Madison, Wisconsin: University of Wisconsin Press, 1982), 229–238.

²² “College to Resume Out of Doors,” *The Portsmouth Herald*, October 11, 1918, 1; Editorial Comment, *The Portsmouth Herald*, October 16, 1918, 4.

²³ Kaiser Wilhelm was the emperor of Germany during World War I. “Help Fight the Grippe,” poster produced by the Connecticut Department of Health and the Council of National Defense, Broadside 1918 H44, Special Collections Department, University of Virginia Library.

medicine encouraged them to trust the authorities and hope this trust would preserve their own and their community's health.

This mood, though, didn't last. Fairly quickly people began to resist, and the response worsened as the pandemic dragged on. Given the civil liberties issues involved in the restrictiveness of some of the public health measures, this may seem unsurprising. What is noteworthy, though, is how rarely questions of civil liberties were raised, even by those who resisted the public health controls.

And so we come to the second question, "Why do they begin to say no?" I want to suggest that the failure to communicate honestly with the American people undercut the relationship between the public and the authorities. I do want to preface this, however, by noting that leaders were motivated, at least in part, by a concern for the public calm. Indeed, the possibility of public panic was of enormous concern. So, the first thing that many public health officials did, and some did it over and over again, was tell people that everything was going to be OK, to downplay the risk. Most notable, perhaps, was the case of Royal S. Copeland, the health commissioner for New York City, who downplayed the danger beforehand, minimized its impact once influenza struck, and asserted many times over that the pandemic was under control when it was not.²⁴ Similar voices could be heard in New Hampshire. *The Portsmouth Herald* routinely reported "epidemic conditions improving," or that "the physicians are of the opinion that with three or four days of warm sunshine the disease may be brought under control."²⁵ Educational materials, too, almost never portrayed the depth of the dangers facing Americans, instead painting the pandemic as something familiar, as similar to the common cold, failing to prepare Americans for the realities they faced.²⁶

Such a calming story was often reinforced by overblown promises about the effectiveness of medicine and public health practices to protect against influenza. These narratives, whether born of concerns for public calm or an inflated over-confidence, created heightened expectations among lay people. When these were unmet, the people rejected the authority of public health officials, and began to resist. In Sanford, New Hampshire, for instance, a clergyman took a case about the closure of churches to court.²⁷ In eastern and northern Maine, people complained when their liquor was seized for use in the pandemic.²⁸ When the third

²⁴ On reassurances before the pandemic hit, see "No Quarantine Here Against Influenza," *The New York Times* August 15, 1918, 6. For an example of his statements of the pandemic being under control, on October 6, 1918, for instance, when influenza had sickened 2,070 additional New Yorkers in the previous 24 hours, Copeland argued that given the population New York, he did not "consider that the city is stricken." He would not create an emergency committee to deal with the flu until mid October. "Revise Time Table in Influenza Fight," *The New York Times*, October 6, 1918, (1) 8; "Asks Experts' Aid to Check Epidemic," *The New York Times*, October 13, 1918, 18.

²⁵ "Epidemic Conditions Improving," *The Portsmouth Herald*, October 2, 1918, 6; "One Death From Influenza Wednesday," *The Portsmouth Herald*, September 26, 1918, 5.

²⁶ The widely-circulated USPHS pamphlet, "*Spanish Influenza*" "*Three-Day Fever*" *The Flu*," for instance, reassured citizens that epidemic influenza was a common occurrence and compared Spanish flu to the common cold and the yearly flu, and though acknowledging that more severe symptoms arrived more quickly and that deaths had resulted, noted that ordinarily the "patient recovers" and deaths were the result of "a complication." Rupert Blue, "*Spanish Influenza*" "*Three-Day Fever*" *The Flu*," reprinted in *Public Health Reports*, (September 25, 1918, Supplement 34).

²⁷ "Opening of Church at Sanford Will Make Test Case," *The Portsmouth Herald*, 25 October 1918, 7.

²⁸ Editorial Comment, *The Portsmouth Herald*, 8 November 1918, 4. Clergymen in Lawrence, Massachusetts protested against the closure of their churches, a response prompted in part by the continued functioning of saloons. Editorial Comment, *The Portsmouth Herald*, 15 October 1918, 4.

wave came raging through communities, Americans were even less cooperative, and public health and political authorities found themselves unable to control the citizenry any longer.²⁹

There is one last issue I want to raise. I can't say that there was a definitive connection between resistance and mistreatment, but I think we have to wonder whether the neglect or abuse of certain populations undercut a positive relationship between segments of the public and authorities, decreasing the citizen's willingness to cooperate with officials. Continuing a long history of medical neglect, the government's treatment of African Americans during the pandemic was notoriously discriminatory. When Richmond, Virginia, opened an emergency hospital in John Marshall High School, black patients were initially placed in beds in the basement until a segregated, all-black hospital could be established. Philadelphia, worst hit of all American cities, opened several emergency hospitals for its white citizens, but none for African Americans.³⁰ Native Americans also faced hostile behavior from the authorities. Already suffering poverty and poor health as a result of government policies and reservation life, Indians experienced the dual trauma of influenza and cultural displacement as public health officials used the influenza crisis on the reservations as another opportunity to replace traditional health-care practices.³¹ Officials referred openly to the "average case with the Indian" and the problems of "combativeness" and "Indian philosophy" that interfered with their work.³²

In urban areas, poor communities also found themselves the target of condescension and cultural misunderstanding in the midst of the pandemic. Already living on the edge of material want, an influenza illness or death often left poor families destitute and reliant on the assistance of both state-run and private aid organizations. Visiting nurses and social workers routinely described the "dirt and lack of order" they observed in the homes of the poor, and often assumed such conditions reflected deeper moral problems.³³ As one student nurse working in Boston explained, "To nurse in an epidemic was like meeting a creeping foe allied

²⁹ For one example, see "Guarding Against Influenza," *Public Health Reports* 33 (December 20, 1918): 2258.

³⁰ Marian Moser Jones, "The American Red Cross and Local Response to the 1918 Influenza Pandemic: A Four-City Case Study," *Public Health Reports* 125 (2010, Supplement 3): 101; Vanessa Gamble, "'There Wasn't a Lot of Comforts in Those Day': African Americans, Public Health, and the 1918 Influenza Epidemic," *Public Health Reports* 125 (2010 Supplement 3): 119.

³¹ These efforts are recounted, for instance, in a memo from D.A. Richardson, MD to P.T. Lonergan, Superintendent, Subject: Influenza Epidemic at Pueblos of Albuquerque Day School Section, available online as "Letter from visiting doctor reporting situation to superintendent, Albuquerque Day School, New Mexico, December 20, 1918, Bureau of Indian Affairs," available online at "The Deadly Virus—The Influenza Epidemic of 1918," National Archives and Records Administration Online Exhibit, accessed September 12, 2013, <https://www.archives.gov/exhibits/influenza-epidemic/records/visiting-doctor-letter.pdf>. The removal of many children to Indian schools, too, created a context during the pandemic in which families suffered the additional pain of separation and the inability to provide appropriate burial rites when children sickened and died. As one mother wrote when her daughter died, "I would have felt better if I could have seen her." Mrs. Annie Murphy to Mr. Harwood Hally [sic], October 16, 1918, Mary Murphy File, Student Files, Chemawa Indian School, Box 66, Record Group 75, National Archives, Pacific-Alaska Region, Seattle, WA. On Indian schools, see David Wallace Adams, *Education for Extinction: American Indians and the Boarding School Experience, 1875–1928* (Lawrence, KS: University of Kansas, 1995).

³² "Letter from visiting doctor reporting situation to superintendent, Albuquerque Day School, New Mexico, 20 December 1918," available online at "The Deadly Virus—The Influenza Epidemic of 1918," National Archives and Records Administration Online Exhibit, accessed April 20, 2017, <https://www.archives.gov/exhibits/influenza-epidemic/records/visiting-doctor-letter.pdf>.

³³ Miss Condell, "Personal experiences during the epidemic," Student nurse epidemic accounts, Folder 1, Box 8, RG 22.1, Department of Nursing, Academic Departments, College Archives, Simmons College.

with ignorance, poverty, superstition, immorality, and hopeless fear.”³⁴ Suspicion of the poor’s motives made it more difficult for them to seek aid, even as aid workers assumed moral failings and sometimes intervened in the private life of families.³⁵ Such mistreatment could produce resistance, and likely always damaged the relationship between communities and the state, mitigating against the embrace of the public health leadership and its policies.

Thus, we are offered two additional lessons that might guide our future efforts to manage influenza pandemics. First, while preventing panic will remain a priority, Americans must be told the truth if we again face pandemic influenza. The seriousness of the situation, the unpredictability of pandemic influenza, the complexity of public health officials’ efforts, and the uncertainty about the effectiveness of those efforts must all be acknowledged and discussed. Given the value of NPIs but acknowledging their corresponding conflict with civil liberties, encouraging public cooperation with the needs of the moment will be vital. In turn, we must not only commit to the equitable treatment of all, but must also do the hard work of interrogating our own culture in order to understand how (and whom) we might stereotype, underserve, and over-police. The crisis of a pandemic must not again be an occasion for the punishment of our most vulnerable citizens. The voices of 1918 have much to tell us about the risks a pandemic might present. Only we can do the hard work of understanding those lessons for our own time.

MODERN PUBLIC HEALTH PERSPECTIVE: THE VIEW AT THE STATE LEVEL FROM SOMEONE ON THE GROUND

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and Former Head of Maine’s CDC***

Between 1996 and 2009, I spent a lot of time working on pandemic preparedness as the head of Maine’s Bureau of Health [now called Maine’s CDC]. We had an emergency team at the state level, and we would spend time doing pandemic flu exercises. We based our exercises on the 1918 pandemic flu. In fact, I had spent some time going through old newspaper clippings from around the state from the years of the Spanish influenza. One of the big lessons we learned was that it had been an extremely severe pandemic, and most pandemics aren’t that extreme. Nevertheless, in our office, we always thought that if we prepared for the worst, we could scale down if necessary—but actually it was harder to scale down than we thought.

³⁴ Miss Franklin, “Personal experiences during the epidemic,” Student nurse epidemic accounts, Folder 1, Box 8, RG 22.1, Department of Nursing, Academic Departments, College Archives, Simmons College.

³⁵ On the suspicions about a family’s need, see Case #13369, Reel #194—Family Welfare, Minneapolis Family and Children’s Service Case Records 1895–1945 (SWF19), Social Welfare History Archives, University of Minnesota Libraries. The example of a poor immigrant family living in Minneapolis illustrates social workers’ pre-occupation with the habits of their working-class clients, their assumptions about the immorality of those clients, and their use of the family emergency created by the epidemic as an opportunity to intervene. See Case #3126, Reel #16, Children’s Protective Society, Minneapolis Family and Children’s Service Case Records 1895–1945, Social Welfare History Archives, University of Minnesota Libraries.

The 2009 influenza pandemic started the third or fourth week of April, 2009. I know exactly where I was because it was spring vacation week, and my children were in elementary school at the time. My husband is a Civil War buff and we were driving through the back roads of southern Virginia looking for Appomattox. My cell phone rang; it was the US Centers for Disease Control (CDC) Emergency Operation Center. It was Thursday the 23rd. They said we had an emergency conference call I needed to be in on in about 20 minutes, to talk about an emerging pandemic. I thought it was some sort of joke; it just didn't seem real. I was like, "Well, we're trying to look for Appomattox." Anyway, it turned out to be the real thing, and we did go to Appomattox but high-tailed it back up to Maine immediately after. Fortunately, I had an air card in my laptop and a cell phone, so I was able to put out a health alert and convene conference calls with the state team while on the road.

We brushed up our pandemic plans. In fact, I was re-reading them as my husband was driving us up the highway to Maine. Of course, the plans talked about this pandemic starting somewhere in Asia or Africa, or somewhere else, and taking weeks to get here. In 2009, though, we had some cases of a new strain of influenza in Texas and California. We knew that there were hundreds of young people hospitalized or dead in Mexico. That was about all we knew. We did not have a lot of time to prepare because, again, it was spring vacation week and, guess what? A lot of people from Maine had gone to southern California, Texas, and Mexico to vacation.

We had five days to prepare—our plans had predicted that we'd have weeks. By the following Wednesday, we had our first cases in Maine, and we had closed two daycares and a school. It really was on our doorsteps within days.

As Nancy Bristow mentioned, an influenza pandemic is very different from even a bad seasonal influenza year. In a pandemic, there is a shift in the virus, and in 2009 there was a particular shift in who was impacted. Normally, with seasonal flu, 90% of the deaths are amongst people 65 and older. With the 2009 pandemic flu, 90% of the deaths were *under* 65 years of age. That's important because over the years we had geared up the 65-years and older population to want vaccine and took precautions. We hadn't really geared up the younger people. There are also waves in pandemics that are often not present during the seasonal flu seasons. There is higher transmission, and it can impact different areas differently. To show you how quickly the progression of H1N1—which was the strain of the 2009 flu—spread, in April of 2009 there were two countries with this particular form of influenza: the US and Mexico. By the summer, it was in more than 200 countries.

This raised many concerns. I had very intelligent people asking me if we should close the bridge between Maine and New Hampshire to close the borders. I said, "You know what? As much as there are some things that work, that is not going to work." One of the goals for addressing a pandemic in public health is to limit the burden of disease. That's obvious, but it's also important to minimize social disruption. Yes, we could close everything down, but we know that that's impractical for many reasons. The role of medication in public health is to delay the pandemic, and to lower its effects, because when you have too many patients, the health care system is overwhelmed and can't respond very effectively.

To go back to the 2009 influenza as a case study, there are three big challenges that I'd like to talk about, and I don't have all the answers. These challenges hit me because we hadn't really prepared for them, and partly because this wasn't as severe a pandemic as that of 1918. Again, that ability to scale down was challenging.

The first action when fighting a pandemic is in surveillance, particularly during the early detection phase. The four pillars of public health functions are surveillance, medication, vaccination, and communication. I always hesitate to use the term “surveillance” in public—I always call it disease tracking—because we’re not part of the NSA, the CIA, or any other intelligence agency.

In the world of public health, however, we do use the word surveillance. One of the key actions early in a pandemic is to detect whether the disease has hit an area early: this is early detection. As the pandemic evolves, surveillance is used both to monitor the evolution of the virus and to monitor outbreaks. It becomes less important that people get tested.

Challenge #1: Need to Know vs. Privacy

One challenge is to balance the public’s need or desire to know versus an individual’s privacy. Most people have heard of the Health Insurance Portability and Accountability Act (HIPAA). There are laws in the US that state that health information needs to be kept confidential with certain parameters. Most state laws mirror HIPAA, and HIPAA is actually fairly silent in terms of what public health agencies can provide for the information that they have.

HIPAA is very clear that health care providers have to report to public health agencies, but HIPAA is less clear about what public health agencies can do with that information. State law in Maine, and in most states, basically leaves it up to the public health agencies to decide the extent of the information that they are going to make public. In April of 2009, we had those first few cases, and suddenly everybody wanted to know: Who were they? Where did they live? At the state public health board we had decided early on that we would give data by county, and so we said that our first few cases were in Kennebec and York counties. (York County is just a few minutes from the New Hampshire border.)

It wasn’t hard for people to figure out who some of the first cases were because we had closed two daycares and a school. In that small town in York County, everyone knew which family had gone to Mexico and had come back sick, and had thus caused the school to be closed. Still, we were not giving out names. We did give the school name, but it was hard not to. We didn’t give out the daycare names. (One of the daycares did get in to the press and unfortunately went out of business a while later. I’m not sure if the pandemic and the closure were connected, but they may have been.)

We were under a lot of pressure to provide more information about the early cases, and not just from the media. The reporters I worked with mostly understood why we were trying to protect people’s privacy. Instead, with all due respect to my colleague Tim Soucy from the city of Manchester, New Hampshire, it was local officials who pressed us. It was not local public health officials, particularly, but first responders—fire fighters, and police—who said, “We need to know who these people are. If they’re in our town, what if we get called to their house? We want to know that they have flu.”

Now, what disease from 25 or so years ago—30 years ago—taught us that you don’t need to know who those people are? HIV/AIDS. It wasn’t until 1987 that universal precautions were recognized as a *bona-fide* strategy so that if you’re going to be in contact with blood or respiratory secretions or whatever, you use barriers because you don’t know who is positive

and who is not. With this in mind, I was trying to educate our first responders by saying, “You don’t need to know who those people are because if you go into a household and they’re coughing, you should take precautions...” Just as you would for HIV/AIDS.

Then, the first responders said that in other states the public health authorities for surveillance and disease control at the county or municipal level gave out specific information about sufferers. For example, fire fighters and police at the local level in many other states had the names and addresses of early sufferers in the pandemic. In some states that was true, and in some states it wasn’t. Now, I don’t think that this issue really existed to the same extent in 1918. We are in the information age these days, and we’re in the information dissemination age, too. I propose that this is an issue that impacts our civil liberties in a way that we have not clearly figured out, although I’ve asked for guidance from the CDC a number of times over the years, including when we had Severe Acute Respiratory Syndrome (SARS) back in 2002–2003. The CDC has been fairly quiet on this issue, so that is challenge number one.

Challenge #2: Vaccinations

I can’t tell you how many hours I have spent in the Maine State Legislature because politicians have asked me to talk about the laws and details about mandatory vaccination. We have all kinds of laws concerning when and how you can mandate vaccines, what the exceptions are, etc. One of the issues that has interested me the most is to do with vaccine distribution. I’ve analyzed, in a report, the need for government authorities to distribute a vaccine—when there’s a shortage of that vaccine—in a fair and equitable way. That was a huge issue in 2009, and I will give you some data that show why.

First of all, we didn’t have any vaccine until October. The pandemic started in April, and while we had some waves of it in the summer, we knew the severe wave probably wasn’t going to come until the fall. It didn’t. We also didn’t have any vaccine until about late September/early October. In the meantime, with the help of the CDC, in Maine we began to plan who would get the vaccine and how to get it to them once it arrived.

During the late summer and early fall, the CDC got some influenza samples, at least enough to be able to characterize the virus better and to determine whom it was impacting most severely. This is great, except that the CDC’s guidance included almost half of the population of Maine, and Maine’s population was approximately 1.3 million people. I remember saying to CDC, “Thanks a lot. You really narrowed the population down,” because we knew we weren’t going to get 625,000 doses in the first week of the vaccine being distributed.

The people in the priority groups are those whom the pandemic flu impacts the most severely—plus significant others like health care workers. Including the Emergency Medical Service (EMS), this group of health care workers totals about 43,000 people in Maine. Ironically, most health care workers I’ve heard from think they’re in the priority group because they’re dealing with patients with flu and are, therefore, at risk. In fact, they are in the priority group primarily to protect their patients. A health care worker with the flu—and remember a sufferer is contagious for a couple of days before they come down with the symptoms—can be passing flu on to patients who are already sick for other reasons.

Next we had to figure out how many people could vaccinate others. According to the state's licenses, we have approximately 25,000 health care providers able to vaccinate. We actually passed emergency legislature in May, 2009, allowing pharmacists, for the first time, to vaccinate. People asked us, what about dentists? I said, "Well, you know what? We've got almost 20,000 nurses." That's whom we really focused on this time around. We recruited nurses, particularly many retired nurses and nurses at home with kids, to see if they would volunteer to vaccinate.

So, in September we had half of Maine's population as a high priority for vaccine and 25,000 or so people who were vaccinators. We had predictions of 80,000 doses of vaccine becoming available each week starting September 30th. We looked at the data and realized that our biggest problem was getting vaccinators out, specifically getting clinics up and running. We spent a couple of months establishing clinics in all kinds of schools, shopping centers, restaurants, and all over the place, and getting the vaccinators ready. When the vaccine arrived, we wanted to be able to flip the switch and everybody would start vaccinating. Then we got a call at the very end of September—the vaccine was not going to arrive as predicted.

What we didn't know was that we had five manufacturers of the vaccine, and four of them were offshore. We found out later that the Food and Drug Administration (FDA), who is responsible for licensing vaccine manufacturers, wasn't really monitoring the progress of the vaccines being manufactured overseas. We also had nine formulations of vaccine coming, and each could be used for a different group... So, we were supposed to start getting vaccine October 1st, but we didn't get the first batch until October 9th, and then only 8,700 doses.

Now, when you have 625,000 people in the highest priority list and they hear there are only 8,700 doses, each person thinks that there's one dose with his or her name on it. Keep in mind that the disease at the time was surging in many other parts of the country. On the nightly news, there were stories of kids dying and emergency hospitals being set up in parking lots. It was on the news every single night. We heard that the surge was on our doorstep, and we had but a drop of vaccine. The challenge, over those coming weeks, was to figure out how to get the vaccine to the high-priority people in a fair and equitable way. The first month, the vaccine that came to Maine was almost all nasal spray, which can only be given to healthy people from toddler age to age 50—it doesn't fit a lot of the high-priority people. We sent it out to our in-patient health care workers, and we got right into schools and vaccinated school children. We got a lot of push back.

We got push back from people who said, "Why are you vaccinating healthy school children and not me?" whoever the "me" was. To be fair, they were used to the fact that flu usually impacts a population other than grade school kids. However, we also know that school children are major transmitters of flu within a community. If you want to stop the transmission, you go to schools. That helps, but you are vaccinating a healthy population when you do this.

The disease surge came in November, and the biggest surge was Thanksgiving week. Now, we were also taking other actions. It wasn't as if we were just focused on the vaccine, and we did talk about the non-pharmaceutical inventions as Nancy Bristow mentioned. For example, hand-washing was one of the things that I thought was interesting. This is one of the

many posters the CDC put out at the time: “Are you the office sprinkler?”³⁶ It’s very reminiscent of the 1918 flu prevention posters.

Challenge #3: Balance of Authority within the Government

The third and last big challenge is the balance of authority. We always talked about the balance of power in government being judicial, legislative, executive, and we always prepared around that, because we had prepared for the worst case scenario where peoples’ civil liberties would be greatly impacted. We worked with the judicial branch and the legislative branch. The real issue in 2009 was the balance of power between the state, the federal, and local officials who are our partners. We all had to work in partnership, but the balance was really tenuous and difficult.

I should just quickly mention that, in 1918, the balance of authority was at the municipal level in Maine, as it was in many states. That changed in January of 1919: the state Legislature passed a law that gave public health authority in Maine to the state government. I think one of the lessons we learned was the very important role of our local partners—private and public—and that there needs to be a delicate balance of authority between local, and state and federal officials. This paraphrases Kierkegaard’s philosophy a bit: influenza epidemics are lived forward and understood backward.

Also, the state health officers in the New England states stayed in very close contact with each other. We met by phone every Monday morning at 7:00 AM, and we had very similar strategies. We had the highest vaccination rates in the country. I’m very proud to say that Maine—and I believe several other New England states—was one of the few states that had no child fatalities from the pandemic flu in 2009. One of the big reasons was that we got the vaccine into schools immediately.

To wrap up, I’ll leave you with a few facts: the most predictable thing about influenza is its unpredictability, and the influenza vaccine suppliers also are very unpredictable. Massive unpredictability is absolute certainty. It also takes a village to vaccinate and we have shared responsibilities, and being prepared is always good.

THE MUNICIPAL PERSPECTIVE: MANCHESTER, NH, AS A CASE STUDY

***Tim Soucy, Director of the Manchester Health Department
in Manchester, New Hampshire***

Before I start, let me apologize because you’re going to see some similar information from me regarding influenza. But, I do want to give you a slightly different perspective. I’m

³⁶ An example of a poster with this message, although one published by a state, can be found at the Utah Government Digital Library. Bureau of Epidemiology, Center for Disease Control and Prevention, Utah Health, “Are You the Office Sprinkler?” (Utah: Department of Health, 2010) in the Utah State Publications, Utah Public Health Library Collections at the Utah Government Digital Library, accessed January 31, 2017, <http://digitallibrary.utah.gov/awweb/awarchive?type=file&item=35510>.

the Public Health Director for the city of Manchester, which is the largest city in the state New Hampshire. When it comes to flu, we learned quite a bit from 1918. We learned quite a bit from each epidemic, including the one in 2009. I want to share with you some of the challenges that we face, because sometimes we think we have really great ideas and plans, and when it comes to implementing them, we realize that maybe there are things we haven't considered. These are some of the questions I'm going to pose to you to consider.

First, though, I want to tell you *my* story of how I first learned about the 2009 epidemic. My daughter was playing travel soccer in the spring. It was April, and I was on a soccer field, and for whatever reason I parked near the fence. A stray ball came and took my windshield out. My windshield was shattered and the inside of my car was full of glass. I was on the phone with my insurance company when Doctor José Montero, who was Director of the Division of Public Health Services for the state of New Hampshire in 2009, called and said, "We're going to have an emergency conference call in 20 minutes." I was balancing between my insurance agent and José; José won. I did get a new windshield eventually.

Flu Basics

Let's talk a little bit about the difference between seasonal and pandemic flu, especially the potential impacts and some numbers. In particular, I want to take it down one more notch to the local level so you can see what some of the issues are that any local public health director would manage. Then, I want to talk about some of the strategies that we thought were really great, as well as some of the issues that we realized were going to be a problem.

To start, how do we get the flu and what happens when we do? Some of this is redundant, but it's important to know. How is influenza transmitted? In droplets, spread person-to-person. For this reason, we're always saying "try to stay three feet away from someone." Then there's indirect transmission. For example, you pick up a handset of a telephone, you handle a doorknob, and then you go back and touch your face.

Next is the incubation period. How long does it take to get sick? Probably one to five days. And when is a person contagious? A couple of days *before* symptoms become present. That's very important when we talk about isolation and quarantine as a strategy.

What about the impact on a community? To begin with, seasonal flu is a deadly illness. Every year about 36,000 people die in the US from influenza. Manchester, New Hampshire, has a population of approximately 110,000 and the hospitals serve about 180,000. About 21 people die from influenza every year in Manchester, and another 154 require hospitalization. We have two acute-care hospitals each with about 200 to 250 beds. I think, since the legislature cut some of their reimbursements, those numbers have gone down in the past two years, which is a problem. But, these are numbers that are easy to handle. We're not going to see all the patients all at once. We're going to see them over a period of time, but they're manageable in a regular influenza year.

Today, though, we keep talking about this term pandemic. I think any public health official during 2009 spent a lot of time talking about what pandemic means. Actually, technically, all the term pandemic does is refer to geography; it has nothing to do with severity. People hear the word pandemic, and they think something horrible is happening. I think Dora Mills mentioned that more than 200 countries had influenza cases in a matter of

months in 2009—that’s what determines pandemic; it has nothing to do with severity of illness.

How does a pandemic emerge? You may know that there are bird flus and swine flus, but how do either of them get to humans? Well, there are a couple of different ways. We did a lot of risk communication during H1N1, which was the pandemic influenza strain in 2009.³⁷ If I were a virus, there’s a couple characteristics I would want to have. I would want to be able to infect a lot of people, but I don’t necessarily want to kill them all, because if I kill them all, then my virus strain is going to stop. If I’m a virus, I want to be a villain. I want to be a bad guy. I want to be easily transmissible from person to person, but I don’t want to kill everyone.

So, transmission happens in one of two ways. The first is direct transmission of a non-human virus. Where do we see this? At the beginning of the H1N1 2009 pandemic, the first people to be infected had direct contact with poultry. That’s how they were getting infected. The genetic drift and shift that allowed humans to transfer this strain of influenza to other humans hadn’t occurred yet. It’s interesting because there are different types of flu viruses. There’s bird flu. There’s pig flu. There’s dog flu. There’s people flu... a little bit of everything. The first cases had to have direct contact with infected poultry. If you ever saw the pictures of some of the markets in Asia with the ducks hanging, and the birds, the live chickens everywhere, you know there were opportunities for exposure. In another case, maybe one or two years ago, we were concerned with a new strain of swine flu. It was coming from county fairs because people were chasing pigs. You would get in the pen and try to catch a pig, and some of the pigs had this particular virus. That caused direct transmission.

The other way that you can end up with a new virus, a novel virus that creates a pandemic, is that a human virus mingles with either a bird or swine virus, and creates a new virus. If the virus has the right characteristics—easily transmissible, virulent but not too virulent—then it has great opportunity. This new virus can take off very, very quickly, which we’ve seen happen.

What are some of the impacts? What do I worry about when we are talking about a pandemic? You heard some of these numbers earlier, they are the number of deaths. The 1918 Spanish flu pandemic probably killed between 20 and 40 million people around the world. Compare that to World War II, World War I, Ebola, SARS. The numbers of deaths from the influenza in 1918 were staggering.

SARS taught us a couple of interesting lessons; one was about health care workers. When SARS—a respiratory illness, a novel virus, a Coronavirus—struck, it taught us, especially in Toronto, that health care workers were the most susceptible for transmission, and that becomes important. The other interesting thing with SARS—Dora Mills talked about closing the bridge between Maine and New Hampshire—was that Manchester airport had direct flights from Toronto. All of a sudden we were thrust into a whole new world of international travel. I can’t tell you how many nights I stood at the airport. We had little cards to give people who had gone to Toronto. As people were coming in, I’d say something like, “Welcome to Manchester.” Then I would hand them a card that said, “If you get sick in the next five to seven days,” this is what you need to do. Additionally, we developed plans for what to do if there was a sick person on an airplane. Guess what? There are sick people on airplanes every day. They don’t all end up at the quarantine station at Logan or La Guardia

³⁷ “Risk communication” is the process of communicating information about risks, including those about public health risks.

airports, or anywhere else. Now, if you know Manchester at all, the airport is between the cities of Manchester and Londonderry. It's right on the line, and the authority is actually in Londonderry. Talk about a rift within the state! I only have legal jurisdictions in the city of Manchester, while Dr. Montero has state jurisdiction in Londonderry. My plan was to park the plane on the Londonderry side, and then I wouldn't have to deal with it. Dr. Montero's plan was a little bit different! You can really see the potential impact of a novel virus that is virulent, and the 1918 strain was virulent. We've seen much less virulent strains over time.

Managing the 2009 Influenza

After the H1N1 influenza strain appeared, the CDC came up with a program called Flu Surge. Essentially, it was a computer model that allowed you to enter demographic data, and then it would make projections. We got a copy of the program, and some of the assumptions that we built in for our particular model were that if you had true influenza, your length of hospital stay would be about seven days. About 15% of the people admitted would have to go to intensive care. The length of stay in the ICU was about 10 days, and about 7.5% of those people admitted were going to need a ventilator, because of the severe respiratory problems. These were some of the assumptions that we built into our program.

We also looked at a best-case scenario and a worst-case scenario. The best case was a six-week period when the flu would hit our community the hardest. For this, we projected 467 hospital admissions over and above the normal admission number. Now, remember we have about 400 beds. Motor vehicle accidents don't stop, heart attacks don't stop, ruptured appendices don't stop. Every hospital bed is pretty much full on a daily basis. Hospitals don't keep wards open in case something bad happens—that's a money loser. Hospitals operate in real time. We're looking at an additional 467 admissions in a best-case scenario; the worst case is 1,100 admissions. Then we looked at the total number of deaths and the logistics of someone dying from influenza. Funeral homes are funeral homes; once again, they can only deal with so many people at any given time. There were some real issues around these numbers.

What did we do to try and prepare? To try and get ready? Isolation and quarantine. We use the terms interchangeably all the time, but they are not the same. You isolate someone who's already sick. You quarantine someone who's been exposed to someone who's sick, but may not have developed the illness yet. Isolation and quarantine, in my opinion, will never work in a pandemic for two reasons. Number one: what did I say earlier about when do you begin to become infectious? There are one to two days before symptoms show up. How do I quarantine people who have been exposed to a sick person when the sick person doesn't know he or she is sick yet? It is almost impossible. Then, isolation is very, very difficult. You can do it on a very small scale, and even then it is hard to do. Isolation orders have to come from the state, but I've had to enforce isolation orders on a tuberculosis (TB) patient within the past year. Short of putting a cop outside the house 24 hours a day, it is almost impossible. He was a bread winner, and he was undocumented. He was on a construction job in Boston. So, he would get in a car in the morning, go to Boston, and come back. We would check with him and ask, "Were you here all day?" Of course, he said he was, right? It is almost impossible to track and to enforce isolation.

Also, if someone is under an isolation order, what about their family who may need to be quarantined? What if they need food? What if they are not handling it very well, and you have to provide some mental health services, clergy, whatever the case may be? Are all of those logistics lined up to support your isolation plan? Lots of times they aren't; sometimes they are. One of the great things about being at the local level is the connections that you make. For the longest time I served on the board of a homeless shelter in Manchester. They have a soup kitchen and food pantry. I would call and I'd say, "Hey, I need a couple of boxes of food, no questions asked," and they'd say, "All right, come over and pick it up." I'd be able to go over pick up food, and bring it to people under home isolation. That's not a bad system when it's one person.

It is not very practical, though; isolation and quarantine are not practical solutions. If I can't do it completely for one guy, I am not going to be able to do it for a lot of people in a pandemic.

To try and get a law enforcement officer to execute an order, to arrest someone who is not complying with an isolation order, is very difficult. In the case I just described, we had a patient who wasn't complying, so I ended up having two orders in my back pocket. One order said, "Let's go to the hospital voluntarily and get treatment." The other order said, "Let's go in the back of the sheriff's van, and lock you up." We went to visit the patient, and I had two vehicles outside, an ambulance and a sheriff's van. Fortunately, the person made the smarter choice of the two, but these are the realities.

There are a lot of issues with issuing quarantine or isolation orders. Who enforces them? Isolation and quarantine are really not practical.

So, we've reviewed community-based initiatives, non-pharmaceuticals, and we've heard about isolation and quarantine. Now, let's talk about social distancing—a good reason to stay away from people. It's an important factor to keep three feet away from folks. Don't go to public gatherings.

I also want to emphasize that public education is so important, especially with regard to social distancing and basic hygiene. I agree with both Nancy Bristow and Dora Anne Mills. People trust public health authorities at the beginning of an epidemic. As time moves on, people become less trusting, so the education piece is vital. It's not rocket science; we're telling you to "sleeve your sneeze" or "catch your cough." There are all these catchy phrases. Also, you need to wash your hands, singing the alphabet or something similar to make sure you do it long enough. Another tactic is to use hand sanitizer. I love hand sanitizer; it's my favorite thing in the world. These are public education tips that you give to people because they're pretty simple.

It isn't always easy to implement techniques, though. For example, think about social distancing again and come back to those funerals. What do you do? How do we mourn? We wake. We hug each other. We say, "I'm sorry for your loss." We get together. We eat together. How do I, as a local public health guy, say you can't do that anymore? I can, but it's very, very difficult.

What about other activities? After the Boston Marathon bombing in 2013, the Boston Bruins cancelled a hockey game, and look at the disruption that caused. We're talking about a bombing at a marathon, a terrorist event. Now, what if we're talking about the cancellation of a Bruins' hockey season because people are sneezing and coughing? If I'm a guy with \$4,000 invested in tickets, I might be a little miffed. Or, what about when common sense says stay home from work or school? Great idea. In Manchester, 52% of kids live below the poverty

line, and they get free and reduced lunch. OK, so if both their parents are working, what do we do with those kids? Keeping them home from school is great from the perspective of epidemic prevention, but it may not be a good idea for other reasons. This isn't 1918 when there was probably a woman at home in every household—a mother, a grandmother, someone. Today, our family dynamics do not support keeping kids home from school. It's a great strategy, but there are logistical issues with it.

Then there are the ethical issues that are linked to some of the logistical concerns. What about mass dispensing of vaccines or antivirals? Yes, we have plans to do that. At one point in time, when we thought the smallpox vaccine was going to be used again, we wrote all these plans about how we could treat someone with a vaccine or antiviral within a very short period of time. But, how are we really going to do it? Are we going to have the staff to do it? Also, people don't always want to come to work when things are bad. If there's a chance that they might get sick, they may not show up for work.

What about the ethics of who gets the vaccine? Who gets the antivirals? At a vacation place in Maine, there's a sign that says, "You never know how many friends you have until you have a beach house." Well, I believe you never know how many friends you have until you have a refrigerator full of vaccine. I get calls from people I've never heard from, saying, "Hey, could I have a little dose?" It's amazing, and there are some real ethical dilemmas there.

Here's another issue: who gets space in a health care facility? There are pictures from 1918 of beds lined up in gyms and other places as temporary hospitals, and we developed this great plan: We were going to create an acute care center, an ACC, with 100 beds in a middle school to use once the hospitals were full. That's awesome, but in a severe epidemic, 100 beds are probably going to be filled in an hour. We feel great because we've got the beds, and we've got these cool sheets, but there are issues with the ACCs—there are not enough beds.

There is another concern: the ethics when standards of care are going to be much lower. Does an ACC become a place where you go and die? You don't want to die at home, so you go there, but you're not going to get the same level of care. We don't have ventilators there. You're going to be lucky if someone walks around and changes the bedpan every so often. These are some of the realities that we face.

Then, after the epidemic, what about re-occupancy? If I used a middle school for my ACC, our families are not going to want to re-use the school as a school when everything is calmed down.

Moving away from the ACC issues. What about special populations? In Manchester, there are 70 different languages spoken in our schools. I'm not talking about common languages like French and Spanish. I'm talking about 70 different languages for which I need translators and written materials. That's not easy to pull off. Special populations include more than those who speak other languages. What about the elderly, the hearing impaired, and the physically impaired? Those with mental health issues? What do you do with them? Shelter in place? It's not a bad plan, if people will abide by it.

What about the whole community, during and after an epidemic? What would be the mental health status of our communities? Will there be continuity of operations? Can businesses still run? Will there be enough food out there? Anyone know how much food is in the state of New Hampshire on any given day? Three days' food supply. That's what we have; we're real-time-economy based.

Yes, I have concerns. I think a lot of folks have done a lot of great work, but we certainly don't have all the answers ready for the next pandemic. People always say, "It's not going to happen." But, it is going to happen. It's not a matter of *if* it will, it's a matter of *when* it will. It will happen again. We were lucky in 2009 because the influenza pandemic wasn't that virulent. It will happen again and the questions are: Is public health ready? Is health care ready? And, probably more importantly: is the public ready?

DISCUSSION QUESTIONS FROM THE AUDIENCE

Question #1: Did World War I exacerbate the spread of the Spanish influenza?

Response:

Professor Bristow: I'll confirm that everything Tim Soucy just said about prevention and preparedness is true. Here is a specific example that really brings it home: I was doing research in The Portsmouth Herald to prepare for today, because I wanted to have some local examples. The stories in the midst of the epidemic in Portsmouth were often on pages 6, 7, and 8. Sometimes, on the editorial page, there would be two sentences about influenza following a major editorial about the discussions for the peace after World War I. The flu was relegated to the back pages of the newspapers and of public attention, and that led to really bad decision making in some cases. For instance, the government did manage to slow one round of the draft once the pandemic was really underway, but because we had soldiers living in crowded and rough conditions in Europe, the US, and around the world, the war was a factor. The movement of troops around the world was a factor in spreading it. Things like the Liberty Loan drive (to encourage people to buy war bonds) that was concluding on November 11, 1918, led to parades. The peace (which started on November 11, 1918, too) also led to victory parades, and there were all kinds of meetings to raise money for the war. These were tremendously costly in terms of health. Even so, communities across the country employed some really smart and, as it turns out, effective public health measures. I think, even without the war, the influenza in 1918, because of the particular strain of the virus and what we now know about it, was going to be a problem. Could they have saved a lot of lives if we hadn't had a war? I'll turn it over to my colleagues because I actually don't know enough of the science to answer. Was the war a factor in what did happen? Absolutely.

Dr. Mills: I always think the corollary to your question is: Would we have had the Spanish influenza of 1918 if we hadn't had World War I? I don't know if anybody could really answer that. I do think it certainly would have been a different type of pandemic, because we know that those large troop ships were such a petri dish for the virus.

In addition, President Wilson had expanded the draft down to age 18—right in the group that was highly affected. All of those young men during the late summer and early fall were travelling from very remote places from all over New England, often going to Fort Devens, Massachusetts. Then there was a ship that came into port in Boston and landed at Fort Devens, and they had flu.

There were just thousands of men. You had Fort Devens with tens of thousands of people, mostly young men, and they were the age that was severely impacted. They were in

extraordinarily tight quarters. They wouldn't have been there if it hadn't been for World War I. Then, as the flu went through Fort Devens, to reduce the impact they actually discharged all these men back home. A lot of them seemed well when they left the camp. There were accounts in the Maine newspapers of trains arriving in Portland and Falmouth, and other places in Maine, with the passengers dead. Young men who had been sent home, and they died on the train. You just have to think that, yes, we might have had a pandemic anyway, but it would have been a lot different if we hadn't had World War I.

Mr. Soucy: I agree.

Professor Bristow: Also, we are still arguing about where the actual virus had its source. The best argument, as far as I can tell, is that it started in Haskell County, Kansas, and it's at Fort Riley, Kansas, a military installation, that the first cases appeared.

Question #2: What is the role of the media, and do members of the press hype things up?

Response:

Dr. Mills: The old newspaper saying is "if it bleeds, it leads." I think I found the media to be our best friends during H1N1 in 2009 and with many other public health issues because, as a public health official, you have to work very closely with them to get your message out and get it out clearly. Can it be hyped up? Sure. Can that be detrimental? Sure. You have to be very careful, but one thing we did during 2009, and many other public health emergencies, actually, was to have very frequent media briefings. That ensured that the media partners in Maine understood what was going on. The meetings were so that I could publicize my main point, but also I wanted to answer questions and help educate our media partners. That went a long way to making sure that they got the right sound bite and did a good job of covering it. You have to have relationships with the media in the world of public health. They are your best friends, but they can also be your worst enemies. I found that you have relationships and you build on those.

Mr. Soucy: If you don't establish those relationships with the media and give them information, they're going to find the next person to give them information—whether it's correct or not—or they'll make it up. That timely honest piece of information is so critical. If you remember after H1N1, there was a made-for-TV movie about this pandemic coming across the country. I was asked to go to the local TV stations and watch it with a few folks and then react to it. One thing I distinctly remember was that they had so many dead people that they were wrapping them up in plastic and loading them up into dump trucks, and burying them in open pits in landfills. The media can be responsible, and the media can be very irresponsible. When you start putting images like that in people's heads, it's very hard for the most honest, ethical public health people to overcome them. Fear is always more powerful than reality, and when those false, fearful messages get delivered, they're very hard to overcome.

Dr. Mills: I think it goes back to what Nancy Bristow was saying earlier, too: it's about being honest. When you are in public health, you have to be exceedingly honest with the media in terms of what you know and what you don't know. It was very important in 2009 early on in the pandemic when the data from Mexico showed that hundreds of young people were in the hospitals and dying. I don't know if that ended up being true or not—we do know that the impact was not as severe as we thought it could have been—but it was much, much

more severe than seasonal flu, and a lot of young people did die, and a lot of pregnant women died—a lot of hospitals were overrun in many other countries.

We had to be very careful and make sure that we clearly communicated, “This is what we know right now, but there’s a lot that we don’t know.” Also, you have to be careful to make sure you tell people what they can do to protect themselves. You can’t just keep saying, “We have 8,700 doses of vaccine for the entire state, and there are 625,000 of you who need vaccine right now.” We had to give people things to do, and we had to give updates about the vaccine. We also told the public that there are some things that everybody can do. You can make sure you wash your hands frequently. Cover your coughs either with your sleeve or your tissue, and stay home if you’re sick. I can still say those three things very quickly in my sleep. Everybody has something they can do, and that helps to empower people so that they are not overwhelmed by the fear.

Professor Bristow: I think there’s some onus on us, as the consumers. I’m actually not a public health person. I’m a professor of history. I watch these pandemics happen from the same seat that you, the audience, sits in. It’s OK if they tell us a possible epidemic could be worse than it ends up being. That’s part of my point that we have to educate well enough to help people understand the unpredictability of these things so that we prepare for that worst case scenario. It’s on us not to say afterwards, “Why did they say it was such a big deal and then it wasn’t?” The influenza is unpredictable. I’m up in the Northwest, and I’m impressed about how effectively they really did warn us about something before it happened, and we were lucky that time. I kept trying to tell people: consider ourselves lucky, not misinformed.

Question 3: What can everybody do? One of the things I noticed that ran through all three of your talks is the reality of inequality in epidemics. It’s true in other realms of our lived experiences as well. Obviously, a virus can kill anybody, whether you’re rich or poor, but poor people are going to suffer disproportionately. This is something that you’ve all addressed explicitly. I guess what I put out there—especially for the students in the audience—is to think about our role as citizens in demanding that no person is going to have to go to work when they are sick just so they can feed their children.

It is important that we have good public health education, which is just a huge challenge because I think everybody, on some level, knows to wash their hands, and yet we haven’t found a way to really create a culture of disease prevention awareness among adults and children. Not to go on and on, but those are the structural issues in our society.

I had wondered about international comparisons with countries with a greater social safety net where nobody is going to go hungry, or lose their job, or their house if they get sick. Do they have lower rates of infection in those kinds of countries? Again, this isn’t so much a question as a comment, but I would be curious to hear if anybody wanted to comment on that.

Response:

Mr. Soucy: I’ll just say two quick things. One is you can’t underestimate the social determinants of health. Health does not simply depend on whether or not you go to the doctor. There are a lot of underlying factors of social determinants of health.³⁸

³⁸ According to the World Health Organization, “social determinants of health are the conditions in which people are born, grow, live, work and age. These circumstances are shaped by the distribution of money, power and

The second is the point of having sick time. If you're the person who's in a minimum-wage job, and you either show up or you're fired the next day because there are 10 people waiting for that job, you're going to show up to work whether you're sick or not. Those are some of the hurdles we need to cross.

Dr. Mills: I should say that in Maine, we actually got criticized for putting out the message that you should stay home if you're sick; we got push back saying there are a lot of people who can't stay home if they're sick.

There is also the question about how to handle the demand for vaccine. I think that as a public health official you have to look at who is at the highest risk for severe flu and who fits the criteria specific to each kind of vaccine. In 2009, we had nine different types of vaccine, and each had different criteria that dictated to whom they could be given. Often the loudest advocates for the vaccine weren't people who were demanding the vaccine and writing letters to the editor and on TV saying, "We need vaccine." They're often the ones who didn't meet the highest need, and I can't tell you how difficult that is. I fortunately had been a state health official for years by then, so I had pretty thick skin, but it's tough. I would ignore it, but I would come home, and my husband would say, "Do you know how many people are criticizing you because you're not giving the vaccine to XYZ?" I felt that our ethical duty was to look at the data and advocate for those who often can't advocate for themselves. One example I remember is when I got an e-mail from a woman, a mother of a young college-age student who had cystic fibrosis. She was going to one of the University of Maine campuses. She said something like: "Dr. Mills, I know you're getting a lot of criticism right now because a lot of first responders are saying you shouldn't be giving the vaccine to young people, that you should be giving it to them first. I want to tell you my daughter is critical to me, and I'm so grateful. She will die if she gets this flu. I'm so grateful that she's getting the vaccine and the students around her as well, so she's got a circle of protection." It reminded me in the middle of it all that our job is to try to be as ethical as possible. It's to ensure that the distribution of the vaccine—or whatever our treatments and decisions are—is as fair and accurate and equitable as possible.

Professor Bristow: The part that makes that really hard, of course, is that we carry prejudices that we don't recognize. We're more attuned to certain kinds of fairness and we may be missing others. We have to be constantly interrogating ourselves about who it is in our society that is going to be most vulnerable in this context? Will it be an issue of economics? Will it be an issue of the ability to speak English? Or will it be because you have a pre-existing illness? What are those factors that make populations vulnerable? And again, this is why I'm glad you're in your seats and I'm in mine, because I think you run into some very, very complicated ethical questions. You have to be one step ahead of where society is in terms of its fair treatments of its citizens.

Dr. Mills: I'll just give one example. I don't want to keep going on, but we were very transparent. Every week we did a press conference and reported exactly where the vaccine was going. Not the actual addresses, but the populations and how much was going to each county, so people could see we were distributing it equitably, geographically by population. I will say that, although I didn't lie about it, I never said we sent a bunch of vaccines fairly

resources at global, national and local levels. The social determinants of health are mostly responsible for health inequities - the unfair and avoidable differences in health status seen within and between countries." "What are social determinants of health?" World Health Organization, 2016, accessed March 2017, http://www.who.int/social_determinants/sdh_definition/en/.

early on to the prisons, we just embedded it in the data by county. I wanted the jails and the prisons to be vaccinated, and if somebody had asked me about it, I would have told them. However, I knew that if I announced this decision we would get a lot of heat because we were vaccinating prisoners before a lot of other people on priority list. You never lie, but you don't always have to tell. You can tell the truth in such a way that you don't always necessarily unveil everything. I was prepared to take the heat. That was fine, but I didn't have to put it on the mark either by announcing, "Oh, and by the way, we sent 5,000 doses to prisons, jails, and youth detention centers this week." We just put it by counties.

Mr. Soucy: My biggest dilemma is that I work very closely with our police and fire departments on a daily basis. We began to vaccinate EMS in the city of Manchester, and the fire department rolls on EMS calls. If someone is in respiratory distress, the fire department goes. Well, we vaccinated firefighters but not police. Now, they don't like each other to begin with anyway. Once you start vaccinating one half and not the other half, it leads to upsets. I used to say that the police officers' ABC is "ambulance before a cruiser," so I actually used that against them so that I could put things into perspective for them.

Dr. Mills: On another note—I haven't read up on it recently—but we don't really know if pandemics do tend to hit younger people harder. The one in 2009, the one in 1957 and in 1968... one thing they have in common besides the viral shift is that they also hit young people, particularly pregnant women, much harder than others. It's not fully understood. I've heard some theories that maybe some of the older people have been exposed to something similar from years ago, so they have lingering immunity when a similar strain appears later. But that doesn't fully explain why in all these pandemics, it is primarily young people who are more severely affected. There's some part of physiology that I've read that did somewhat explain it, but not entirely.

Professor Bristow: I'll try to talk about the part of physiology here. The question was: Why did more young people die when it's supposed to be the young and the old? One theory is that it has to do with the immune response of healthy young adults, and is called a "cytokine storm." The problem is you have edema in the lungs, and many of these people are literally drowning in their own bodily fluids, the result of a powerful immune response to the virus. It is because the healthy have a better immune response, and so their bodies actually fight against them in addition to all of those other factors.

The other thing is that the research on the connection between the 1890 pandemic and the 1918 pandemic suggests that getting the former did not provide immunity for the latter. They've done quite a bit of study on where immigrants were from; who had been isolated and who had not; who had had the flu in 1890; and it doesn't seem to play out to have been a protection. That doesn't mean that the more recent influenza wouldn't have been a factor.

Mr. Soucy: Yes, and going back to the main question, it is really about the ethics of social justice versus health care justice, if I'm saying it correctly. I'll go back to what Dr. Mills said—I think you make the best decision based on the information that you have. Are there going to be ethical dilemmas on either sides of the equation? Absolutely, but I think if I'm basing my decisions on the science that I have in front of me at that time, then I can sleep at night. It's not always easy to make those decisions. Do you vaccinate all school age kids? Or do you vaccinate elderly folks?

Some people will say, and I'll be very harsh characterizing that point of view, that the elderly have led a good life, so why are we wasting the limited vaccine on them? If the data

suggests that's the most susceptible population, though, then from the public health perspective, that's where the vaccine should be going.

I don't know if we'll ever conquer some of the social justice and economic issues. I think we look at the data that's presented to us, and make the best ethical decision based that data.

Dr. Mills: I think you're absolutely right. During my 15 years as a state health officer in Maine, I don't think there was a day when I didn't deal with some sort of ethical issue. Public health is social justice; you can't separate the two. If you don't believe in social justice, please don't go into public health. I don't mean to be blunt, but that's the reality. You have to believe in that. With that said, particularly with an increasingly for-profit health care system, it gets complex. You get into some interesting dilemmas when you're working with a partner whose main mission is profit. It can be difficult, but there are also ways to work together. In 2009 we had a lot of pharmacists who were very upset that they didn't get the flu vaccine early on because they wanted to put it out there and market it. In some states, they gave it to the pharmacies very early and others said, "no, instead we are putting it into the schools." If we put it in places like schools then we are using a social justice strategy because we're getting all kids, rich and poor alike. You're getting the kids who live in the remote areas, whose parents do not have the gas or car to get to a pharmacy, you're getting everybody. We actually—we and the other New England states who used that strategy—had the highest vaccine rates in the country. Again, we were one of the very few states who did not have a child who died of flu in 2009. I think it had a lot to do with the fact that we put it in the schools.

We also had for-profit companies who helped us out. Once we had sufficient vaccine—around the third week of December—those companies offered to vaccinate all their employees, their employees' families, and anybody else. One company, during the week or two before Christmas when it was completely overrun with handling mail-order gifts, hired nurses on its own who went in and offered—24/7—vaccine to all of its employees and all their families. One company vaccinated more than 5,000 people, and one of the other big employers in Maine did the same thing, vaccinating more than 10,000. Those two employers are for-profit, but they also have a belief in "the common good" as a value. In other words, just because somebody is for-profit doesn't mean that they're bad.

Question #4: As we move more and more into a for-profit medical system, what are the implications for these ethical questions? They get harder, I suppose.

Response:

Mr. Soucy: There's actually been research on whom people trust. The question is: How do you maintain credibility with the media when, even in 1918, if you're not telling the truth, people aren't going to believe you? In the field of risk communication, there's been research that shows that people tend to believe health care officials more than politicians. It's been proven scientifically. I think that's probably one thing that we have to our advantage. That becomes very important when you decide who your public information officer is.

You need someone who not only can read the prepared statement, but also can answer questions honestly and ethically and openly to maintain the credibility moving forward. I'll tell you that someone did do that very thing in 2009. At the end of every press conference

he'd say, "This is ever changing, and what I told you today might be different tomorrow." You have to tell people that, it will help maintain your credibility.

Dr. Mills: I totally agree, and in many different types of public health scenarios, you want to have a variety of spokespeople. For instance, I have a lot of history with the tobacco war that is still ongoing. Very early on, I decided that I was not going to go on TV to talk about tobacco unless it was something about a bill and the legislature. If we were going to have people on TV, for instance, telling people to quit smoking, it needed to be a smoker—it needed to be a former smoker. It didn't need to be me. In fact it shouldn't be me. When there's a top-down approach, like preaching, telling people, "you should stop smoking," it doesn't work; it turns people off.

In a crisis, it may be different. I remember very early on in 2009, our media people in government said, "Dora, you're going to be the spokesperson." I said, "Really? Can't it be the governor or somebody else?" They said, "No, no, you do not want the governor." In fact, in some states they had the governor on quite a bit. In Maine, though, we had a communications director who was very savvy, and he said that it was not the right approach.... Anyway, it got tiring but it was also the right thing. That's when you want public health officials doing a lot of communication.

Question #5:

Professor Bristow: Can I ask a follow-up question? To what extent are you engaging with things like social media and some of the new ways of communicating? Is that a big part of what you do?

Response:

Mr. Soucy: We're getting there slowly but surely. I can't speak for Maine, but I think New Hampshire is a little behind the eight ball when it comes to social media. I think we still have a long way to go to capitalize on these new methods of communicating. We're starting, but I think we still have a long way to go.

Dr. Mills: I think that it was the spring of 2009 when we went on social media. We reassigned a lot of people at the Maine CDC (it used to be called the Bureau of Health) to work on the pandemic. We had this really hip young woman who worked in HIV and did a lot of social media on HIV—which you have to do if you're in HIV. We moved her up to do pandemic flu communications, and she immediately got us on social media. At the time, the big platforms were Facebook, Myspace, and Twitter. She got me plugged in so that we had several people who could post, and she set it up so I could post something, even in the middle of the night, and it would go to all of these Twitter feeds. It was the first time that I'd gone on Facebook. We did a lot of social media, and it was helpful because we were trying to reach a younger group. We weren't used to communicating about flu to 20 year olds. We were used to talking to senior citizens. We learned a lot of lessons from it.

CLASS EXERCISES

From the Past to the Present

Divide the class into three groups (or multiples of three). Each group should consider one of the following questions:

- What can we learn from the Spanish influenza to help us with annual influenza recurrences today?
- What can we learn from the Spanish influenza to help us with pandemics, in general, today?
- What can we learn from the Spanish influenza to help us with public health-preparedness educational initiatives today?

After each group has brainstormed, ask a representative from each one to share what the group recorded. Then, ask all the students to engage in a discussion: What are the differences in the answers to each question? Why? What are the similarities? Why?

Individual Views

Influenza pandemics encompass stories of medical challenges, political organization, and individual experiences. Ask students (as individuals or in small groups) to look up stories about personal experiences with the 1918 influenza in newspapers, either from your local area or around the country. How do these stories differ from one another? How might they be the same or different from experiences that people undergo today during an epidemic?

Priorities in a Crisis

Divide the class into groups, each one representing a state. If each group had two weeks' notice that there was a flu pandemic coming to its state, what would it prioritize out of the following list?

- Vaccination, education, isolation, preventative supplies (masks, etc.), treatment (such as antivirals), hospital and medical care
- In what order?
- What could you do quickly? What would take longer?
- Why would you make those choices? Are you hoping to cover certain populations? What would be the most effective measures? The most just? The quickest to implement?
- If you had a limited number of vaccines, which groups of the populations would you seek to cover first? Make a list of your top three and explain why. (For this exercise,

assume that any vaccine will be appropriate to use on any individual and that you can cover 90% of each group you choose.)

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Nancy Bristow is a teacher and scholar at the University of Puget Sound where she has been a Distinguished Professor for 11 years. She earned a BA from Colorado College and an MA as well as a PhD from the University of California at Berkeley. She published a monograph on the 1918 Spanish influenza entitled *American Pandemic: The Lost Worlds of*

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Dora Anne Mills has served as the State Health Officer and then the Director of the state's Center for Disease Control in Maine. She was raised in Maine and earned a BA from Bowdoin College, her medical degree from the University of Vermont College of Medicine, and her masters of public health degree from Harvard. Before she focused on public health, she practiced medicine in the US and abroad. In 2010, the American Academy of Pediatrics gave her a Special Achievement Award, and the Association of State and Territorial Health Officers gave her the McCormack award for her work during the 2009 H1N1 influenza epidemic.⁴⁰ She currently works as the vice president for clinical affairs at the University of New England (UNE).

Timothy Soucy is the Public Health Director of the Manchester Health Department in New Hampshire. In this role, he was instrumental in the development of Manchester's Pandemic Preparedness Influenza Plan. (Manchester, New Hampshire, represents approximately 10% of the state's population and is the largest city in the state.) Mr. Soucy manages the current challenges of maintaining the health of the state's most ethnically and racially diverse population in the face of a potential flu pandemic. He grew up in New Hampshire, earned a BS from the University of Vermont and an MPH from Boston University. He has additional training from the US Food and Drug Administration, Centers for Disease Control and Prevention, and Department of Homeland Security. Over the course of his career, he has focused on specialized areas in public health including environmental health and public health preparedness.⁴¹

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Chapter 81

THE DILEMMA OF TYPHOID MARY: PERSONAL LIBERTY VERSUS PUBLIC HEALTH

*Judith Walzer Leavitt**

INTRODUCTION

Professor Leavitt presents the story of an Irish immigrant woman in New York in the early decades of the twentieth century who was the first identified healthy carrier of typhoid, a potentially fatal disease, in the US. Healthy carriers are people who have recovered and are no longer sick with the disease but who can nonetheless still transmit it to others. Mary Mallon was, and is, well known by the name “Typhoid Mary,” a label that reduces her identity from that of an individual to that of a disease. She became a symbol for issues that confronted society both in her time and today, including decisions about what takes priority: individual liberty or public health. How did (and should) officials treat individuals whose health status threatens others? Was Mary treated justly? And how can we ensure that people in her position are treated justly today?

LECTURE

I am assuming that many of you have heard of Typhoid Mary, a woman whose real name was Mary Mallon. But even if you have heard of her, you will not necessarily know her full story. Today, I am going to discuss that story and some of the issues it raises.

Typhoid Mary was, and is, infamous. Almost any history of twentieth-century America will include something about her. Very frequently, it will not be completely correct, but at least she will be mentioned.

She is usually portrayed as a dangerous woman—don’t eat what she cooks or you might become ill and die. In one contemporary illustration there is a big shadow behind her, a sign

* Judith W. Leavitt, “Medical History & Bioethics,” University of Wisconsin-Madison, 2016, <https://medhist.wisc.edu/faculty/leavitt/index.shtml>.

that something is amiss with her. Another popular idea was that she shed germs wherever she went; there is at least one illustration in which those germs are shown falling off of her. Otherwise, she appears perfectly benign in that drawing, but that is part of the danger she poses—she looks benign, but she is not. You do not want to get near her. It has nothing to do with her sneezing and coughing all over you. The message is clear: just to be close is to be in danger.

To tell the story of Mary Mallon is to tell two stories: that of Mary Mallon and that of Typhoid Mary. These two tales help us to understand the contest of individual liberty versus the public health, two values that are very important in our culture, but which, at times, come right up against each other, forcing one to yield—the question is: Which one and by how much?

The other big question is that of justice. Through Mary's case we learn that justice is not always applied equitably. What we want to conclude—but cannot fully answer even today—is this: Can we protect the public's health without trampling on individual rights? This, surely, is the key question, and not merely a historical question—these issues occur in our time as well. For example, consider the case of Andrew Speaker. In 2007 he was diagnosed with multidrug-resistant tuberculosis (TB). But Speaker had destination wedding plans and so flew on an airplane, and thus exposed several individuals to a hard-to-treat form of TB. Should he have been allowed on to the plane? Could we, morally, have prevented him from boarding?

Now, let's return to typhoid fever. What is it? It is a bacterial infection with systemic, flu-like symptoms, fever, headache, and gastrointestinal issues caused by the *Salmonella typhi* bacterium. It is transmitted via food and water contaminated with the feces or urine of patients and carriers. Think about that: How does something that is in the feces or urine of one person get into the food of another person? Because the carrier prepares and serves food with unwashed hands. The disease can be transmitted by somebody who is ill but also by somebody who has been, but is no longer, ill...somebody who is a healthy carrier.

Mary Mallon

Mary Mallon was an Irish immigrant born in 1869. She came to the US in the 1880s, and found work as a domestic servant, and ultimately, as a cook. In the domestic hierarchy of her day, cooks were at the top of the ladder and Mary was proud of her skill and her position. She worked with various employment agencies in New York City and rarely went without a job.

She often cooked in the homes of very rich New Yorkers, sometimes living in servants' quarters in their homes, sometimes coming in on a daily basis.

In the summer of 1907, the family for whom Mary was working took her with them to Oyster Bay, Long Island, a summer resort frequented by fairly rich people. They had rented a house for the summer and Mary was to come out and cook for them. During the summer, some of the family became sick with typhoid fever. In the early 1900s typhoid fever was a common disease, and so, while obviously dismayed by the illness, the family was not unduly surprised.

The owners of the house, however, were afraid they would never again manage to rent it because it would become known as a house that somehow carried typhoid fever. They hired various people to look into the problem, among them, George Soper. Soper was a sanitary

engineer. He checked the cleanliness of the house and looked at the water supply. He also checked the clams in the bay to see if the seafood was contaminated. Yet, in all of his searches he could find no evidence of the bacterium and nor did anyone else in Oyster Bay fall sick with the disease.

This is the way George Soper tells the story, and I have to believe it, at least in part: He remembered reading that two years earlier a German physician, Robert Koch, had identified healthy people as possible carriers of typhoid fever—people who had recovered from a disease could sometimes continue to carry the bacilli somewhere in their gastrointestinal tract; usually it could be found in the urine or feces.

Once he remembered this article, Soper decided to find out if there was such a person involved with this particular outbreak. His interest focused on the cook. Since the typhoid outbreak, Mary had left the family's employ and gone to cook for another family. Soper went to all the employment agencies and ultimately found her. He wrote: "I had my first talk with Mary in the kitchen of this house... I was diplomatic as possible, but I had to say I suspected her of making people sick and that I wanted specimens of her urine, feces and blood."¹

Now, just stop for a minute. What would it feel like to have a complete stranger, not a person in authority, not a member of the Health Department or the government, turn up in your kitchen and say, "I want feces, urine, and blood from you." Needless to say, Mary was not happy, as Soper put it. She came at him with a carving fork, and chased him out of the house. Soper, however, would not give up. He tried to get to her a few times. And, all the while, Mary became angrier and tenser and more and more worried.

Finally, when Soper could not get her to come with him voluntarily, he went to the Health Department and reported that he thought she was a carrier of typhoid fever. In turn, the Health Department decided to go after her and see if it was true. They selected S. Josephine Baker, a physician and health inspector with the Health Department. Choosing a woman to go after a woman was one of the few humane things the Health Department would do over the course of Mary's story.

Baker went to Mary's place of work but could not find her. Indeed, in an act of class solidarity, none of the servants would tell her where Mary was, and so Baker searched and searched. She had five policemen with her. They searched the house. They went up into the attic, onto the roof, into the basement, everywhere. There was no sign. And then, just as they were giving up and preparing to leave, they spied a little piece of blue cloth sticking out of a door. They opened the door, and there was Mary Mallon. She had been there for hours, cowering in the corner.

They took her with them, but as Baker put it, "She came out fighting and swearing, both of which she could do with appalling efficiency and vigor. I made another effort to talk to her sensibly and asked her again to let me have the specimens, but it was of no use. By that time she was convinced that the law was wantonly persecuting her, when she had done nothing wrong." Baker continued, "There was nothing I could do but take her with us. The policemen lifted her into the ambulance and I literally sat on her all the way to the hospital; it was like being in a cage with an angry lion."² It is not hard to imagine that by now Mary was really upset; she wanted nothing to do with this, and so they took her away forcibly.

¹ George Soper, "Curious Career of Typhoid Mary," *Bulletin of the New York Academy of Medicine* 15 (October, 1939): 704 quoted in Judith Walzer Leavitt, *Typhoid Mary: Captive to the Public's Health* (Boston: Beacon Press, 1996), 43.

² Josephine Baker, *Fighting For Life* (New York: Macmillan Co., 1939), 74 quoted in Leavitt, *Typhoid Mary*, 46.

Mary was taken to Willard Parker Hospital, a New York hospital for contagious diseases, and she was put in bed. She was a healthy 37-year-old woman who had been doing her job, and they took her forcibly and put her in bed.

After a while at Willard Parker Hospital, Mary was moved to North Brother Island on the East River, a tuberculosis retreat. Here, there was a small tuberculosis hospital with nurses' quarters and doctors' quarters. They gave her a bungalow on the island, put her in it, closed the door, and went away. Every morning, apparently, somebody would bring a tray of food to her front door and run away as if just looking at her would infect them. She was really alone. Eventually she would make some friends among the patients and some of the nurses, but there she stayed for the rest of 1907, through 1908, and into 1909.

When, in 1909, the *New York American*—a William Randolph Hearst newspaper—broke the story of how the Health Department had been holding Mary all this time against her will, they called her “the most dangerous woman in America.”³ There are various images of Mary accompanying the story, but there is one drawing of particular interest. It shows Mary in 1909, when she was 39. In the artist's vision, she is fairly young and well dressed. Her hair is done up. She has an apron. She is a cook. But there are signs that she's not all sweetness and light. Her face is a little dark. The hair on her arm is pronounced. She is holding a skillet into which, instead of eggs, she is breaking skulls. In other words, she is not only killing people but is doing so wantonly and intentionally.



Figure 1. A Menacing Typhoid Mary. *New York American*, 1909, image available through Wikimediacommons.org at https://commons.wikimedia.org/wiki/File:Mallon-Mary_01.jpg#filehistory.

³ *New York American*, Sunday magazine sec., June 20, 1909, 6–7 quoted in Leavitt, *Typhoid Mary*, 132.

Curiously, the newspaper's story is actually very sympathetic. It tells of a woman who was doing her job, walking down the streets, living her life, when the Health Department grabbed her and took her in, and had kept her ever since. But the picture was very powerful, and despite the story, it was that image that lingered.

The officials continued to assess Mary, even as the public learned about her. Every other day, or at least three times a week, they took her feces and urine to test. There is a record of all these tests and she tested positive most of the time. However, the results were sometimes negative, and the Health Department concluded that she was an intermittent carrier (which many typhoid-fever carriers are). Of course, when her feces tested negative she could not transmit the disease, but from their records it is evident that most of the time she could.

Now, Mary was a smart woman. She decided that the Health Department lab may not have been acting in her interest, so she sent samples of her feces with her boyfriend down to a lab in Manhattan. There were not many samples, but every one of them tested negative... every single one.

At that point, Mary must have said to herself, "The Health Department is creating a case against me that isn't true because I now have scientific, laboratory proof—just like theirs—that my feces are not carrying live bacilli." Of course, with hindsight we realize that we know nothing about the samples: When were they delivered? How old were they? How often had her boyfriend visited her? How often had she given him samples? How long did it take him to get them to the delivered? It is very possible that they were negative samples simply because any germs within them had died by the time they reached the lab. Still, Mary was convinced that the evidence proved her innocence.

This is how she put it: "There was never any effort by the Board authority to do anything for me excepting to cast me on the Island & keep me a prisoner."⁴ Her perception was that "I have been in fact a peep show for Every body even the Internes had to come to see me & ask about the facts already Known to the whole wide World[.]"⁵ This quote is from the only letter extant in Mary Mallon's hand. It is five pages long.

It is clear that Mary was very sensitive to the stigma that was attached to her through the title of Typhoid Mary. She says, "Dr. Parks [sic] has had me Illustrated in Chicago." In other words, he gave a talk at the American Medical Association [AMA] meeting, and he had slides. Mary continues by stating, "I wonder how the Said Dr. W[ilia]m H. Park [the director of the Health Department's laboratory] would like to be insulted and put in the Journal & call him or his wife Typhoid William Park."⁶ She knew what the officials were doing, and she knew that she had very little power against the Health Department's efforts to portray her as dangerous.

As it turned out Mary picked on the wrong person. William Park was really very sympathetic to her situation. But, he was merely a bacteriologist in the Health Department; he was not the commissioner and had no power. Still, Park said one day: "Has the city a right to deprive her of her liberty for perhaps her whole life?"⁷

⁴ In the Matter of an Application for a Writ of Habeas Corpus for the Production of Mary Mallon, New York Supreme Court (June 28–July 22, 1909) in the New York County Courthouse quoted in Leavitt, *Typhoid Mary*, 185.

⁵ Ibid. quoted in Leavitt, *Typhoid Mary*, 187.

⁶ Ibid.

⁷ William H. Park, "Typhoid Bacilli Carriers," *JAMA* 51 (September 19, 1908): 982 quoted in Leavitt, *Typhoid Mary*, 47.

In 1910 a new health commissioner was appointed, Ernst Lederle. At last there was someone in power who was sympathetic. He said, "For Heaven's sake, can't the poor creature be given a chance to live? An opportunity to make her living, and have her past forgotten? She is to blame for nothing—and look at the life she has led."⁸

With the help of a *pro bono* lawyer Mary had sued for release in 1909, but it was not granted. Basically, the judge said, "Look. You are a carrier, you are dangerous to public health. The Health Department calls you a menace to the public's health. We can't let you out on the street." She was returned to North Brother Island, and there she stayed until Lederle came in 1910 and let her go. As he put it, "She has been released [now] because she has been shut up long enough to learn the precautions that she ought to take."⁹

Most public health people at the time agreed with him. They realized that it is not necessary to imprison a typhoid fever bacillus carrier. It is sufficient merely to restrict their activities. If you can prevent her from cooking, find her some other work, then it is safe for her to be walking around the streets. Lederle found Mary a job as a laundress in a laundry. It was a position far below that of cook—both in status as well as pay—and Mary was not happy. But, she did it for quite a while. Then, she went on to other work, and eventually returned to cooking, this time in a maternity hospital where she was tracked down in 1915. She had been out for five years, but now she was returned once more to North Brother Island.

And this, for me, is when the story gets really interesting. George Soper put it this way: "Whatever rights she once possessed as the innocent victim of an infected condition...were now lost. She was now a woman who could not claim innocence. She was known—willfully and deliberately—to have taken desperate chances with human life... She had abused her privilege; she had broken her parole. She was a dangerous character and must be treated accordingly."¹⁰

Second time around, public opinion was quite different. People who had once been sympathetic lost patience. She had gone back to cooking and more people had become sick with typhoid fever. Now, her one-time supporters said, "No, you're going back in and you deserve to go back in." One historian put it this way: "Consider that Mallon disappeared for five years [which she didn't—the Health Department actually kept in touch with her for most of that time], and used several aliases [which is true; she changed her name to Brown at least among other names] and went back to cooking... Now as far as I am concerned, this verges on assault with the possibility of second degree murder. Mallon knows she carries typhoid, knows she should not cook—and does so."¹¹

There is a point here. If you have somebody who willfully does not do as instructed by the Health Department, then the Health Department's authority over that person seems more valid, more solid. But that is not how Mary Mallon saw it. She said, "Before God and in the eyes of decent man my name is Mary Mallon. I was christened and baptized Mary Mallon. I lived a decent, upright life under the name of Mary Mallon until I was seized...[and] rechristened 'Typhoid Mary.'"¹²

⁸ *New York American*, February 21, 1910, p. 6 quoted in Leavitt, *Typhoid Mary*, 65–66.

⁹ *New York Times*, February 21, 1910, p. 18 quoted in Leavitt, *Typhoid Mary*, 65.

¹⁰ George Soper, "Typhoid Mary," 13, quoted in Leavitt, *Typhoid Mary*, 67.

¹¹ Robert J.T. Joy, quoted in Leavitt, *Typhoid Mary*, 248.

¹² *New York World*, July 20, 1909, 18 quoted in Leavitt, *Typhoid Mary*, 163.

Other Carriers

These are the issues: How far can the state infringe on personal liberty? Whose liberty historically has been abridged in the name of public health? I looked for other healthy carriers in New York City and tried to see how Mary's story matched theirs and what was really going on.

One comparison I found was Alphonse Cotils, a Belgian immigrant. (Almost everybody I found was an immigrant, which is, in itself, interesting.) Cotils was a baker and a healthy carrier of typhoid fever. He was found to be transmitting disease through the food he prepared in his bakery—usually the icing on the cookies and tarts he made. When he was taken, he said to the newspaper, “I am not a Typhoid Mary...I always wear a white coat and a white hat and white working pants. I am a clean man.”¹³ This, then, is the contrast—even Mary's fellow healthy carriers disowned her by saying, more or less, that “she was dirty and she deserved what she got, but me, I'm pure.” The judge agreed with Cotils. He wrote, “I am thoroughly impressed with the extreme danger from these typhoid fever carriers, particularly when they are handling food [just as Cotils was. But] I could not legally sentence this man to jail on account of his health.”¹⁴ So, there is Mary Mallon sitting on a North Brother Island, and yet Alphonse Cotils goes free.

Another carrier was Tony Labella who had actually caused typhoid fever in many more people than Mary Mallon had. He was an Italian dairy worker. In the early 1900s, raw milk was sold loose and handled without much care. If handled by a healthy carrier, it could easily be contaminated and carry disease to many people. Labella infected 122 people, killing five of them. Yet, the Health Department isolated him for two weeks and then released him. Whereupon, he did it again. Here, then, is another case of a repeat offender—just like Mary Mallon. However, unlike Mary, the officials again released Labella and found him a job. He was never heard from again, so, presumably, that time the warnings worked or he may have moved out of the jurisdiction of the New York City Health Department.

Then there was Fredrick Moersch, a German immigrant confectioner—he sold ice cream. A healthy carrier, he was described as being well disposed and quite amenable. He was temporarily isolated, and in his record the Health Department wrote that he was worthy of special note: “His wife is not in good health and cannot help with earning money. They have four small children... He is a skilled workman, and...he was suddenly excluded from work in his trade.”¹⁵ To all intents and purposes, he was a male Mary Mallon, and yet the Health Department let him go but followed him. Because of the Mary Mallon case, the Health Department had a new regulation concerning the following of healthy carriers, and Moersch was required to register with the city at least once a year. Thus, with most healthy carriers, the Health Department showed sympathy and gave help. They simply required regular registration with address changes, and they informed all carriers that they should not cook for anybody.

In Chicago, I found an interesting case of a woman named Jennie Barmore who ran a lodging house and cooked for her lodgers, and in the process, transmitted typhoid fever to

¹³ Cotils in Gene Fowler, “Health Board Bars Robust Baker, Typhoid Carrier,” *New York American*, March 14, 1924, p. 13 quoted in Leavitt, *Typhoid Mary*, 162.

¹⁴ *New York Times*, March 15, 1924, p. 19 quoted in Leavitt, *Typhoid Mary*, 58.

¹⁵ Memo from G.L. Nicholas to Director of the Bureau of Infectious Diseases, Department of Health, February 14, 1916 quoted in Leavitt, *Typhoid Mary*, 122.

them. The Chicago Health Department essentially put her under house arrest and said that, while she could stay in her house, she could not take in more lodgers. She could not even feed her children, but she was not taken into any custody. How different from the isolated, stigmatized Mary Mallon.

Justice Denied?

While I cannot go into it all here, my research reveals that class, ethnic, and gender issues helped to construct the response to Mary Mallon's case. But if there is a discriminatory pattern in the justice meted out, then surely there is no justice. The question that must be asked, therefore, is this: What criteria did the Health Department use in Mary Mallon's case that they did not use in other cases?

There is much in the records of both the Health Department and George Soper that indicate that they were not just interested in Mary's status as a healthy carrier of typhoid fever. There were other things they did not like about her, things to do with her gender, class, and immigrant status. They justified taking her: she was tall; she was too heavy; she had a determined mouth and jaw—all things that were completely irrelevant to her being a carrier. Soper went even further: "Nothing was so distinctive about her as her walk, unless it was her mind. The two had a peculiarity in common. Mary walked more like a man than a woman and...her mind had a distinctly masculine character, also."¹⁶

And so, Mary Mallon spent the rest of her life on North Brother Island. She had arrived in 1907, was released in 1910, returned in 1915, and stayed until her death in 1938. At the time of her death, her public image was just as it had ever been: she remained a dangerous character, "Typhoid Mary," someone to be avoided. There is one image in which Mary is bringing tea; following in her wake is a host of pathogenic bacilli; she appears to be very malevolent. Clearly she is putting something into the food of the sick persons behind her—she is deliberately infecting them and looking on as they suffer. This is how Mary Mallon, Typhoid Mary, is remembered.

But how did this happen? Clarence Darrow, the lawyer who defended Jennie Barmore in Chicago, believed that health officials were permitting "one carrier complete liberty to go about in his usual manner...while another may be confined under the strictest quarantine."¹⁷ He was arguing that Jennie Barmore should not be contained simply because officials were saying, essentially, "If you let her out she's going to cook again, that's what women do. You can't stop a woman from cooking, and therefore women, more than men, must stay in quarantine."

This was Darrow's interpretation of how health departments viewed carriers, and if you look at the regulations of the time, they were sufficiently vague to be so interpreted. Indeed, they were so vague that a health department could label one person a danger to public health and another—to all intents in the same condition—as no danger to anyone. One person can be trusted, but not the other; one person can be allowed out, but not the other. Clarence Darrow pointed out that this is capricious. It was really up to the Health Department's whim—if they

¹⁶ George Soper, *Curious Career*, 698 quoted in Leavitt, *Typhoid Mary*, 106–107.

¹⁷ *Illinois ex rel. Barmore v. Robertson*, 302 Ill. 422 (1922). Quotation from the Application for Rehearing, 9 quoted in Leavitt, *Typhoid Mary*, 124.

did not like somebody because she walked too much like a man, then they could just arrest her and keep her isolated. Darrow was trying to make the case that the law had to be clear and more fairly applied. He was not arguing against isolation *per se*, but rather, that if you were going to isolate, you had to do so fairly and equitably, and I agree.

As I said before, there is every reason to believe that Mary Mallon was smart. She understood that there were two kinds of justice in America. She said, "All the water in the ocean wouldn't clear me from this charge, in the eyes of the Health Department. They want to make a showing; they want to get credit for protecting the rich, and I am the victim." She also said, "I will get justice somehow, sometime."

Maybe it is up to us to give her that justice.¹⁸

There are, essentially, two different perspectives in this story. On the one hand we have the Health Department saying that Mallon posed a threat to their efforts to preserve the public health. On the other, we have Mallon herself, saying the health officials were persecutors who unfairly took away her identity (by changing her name), her independence (by locking her up), and her ability to earn a living. The "unfairly" part you can debate, but the rest was true—they did take away her identity, she was never again called Mary Mallon, she was Typhoid Mary, and this most certainly took away her independence and her ability to earn a living.

One of the lessons, one of the important lessons, is to understand how labeling people can affect a story. Mary Mallon was identified not just as Typhoid Mary, but also as someone who was dangerous to public health. It was a dehumanizing stigma. It said, "We can do this to you. You're over there. We are not dangerous to the public health, but you, over there, you are dangerous."

To be able to identify someone that way is to have control. Mary was, as she put it, banished like a leper simply because the Health Department had the authority to banish if they wanted to. The label, and its associated stigma, surely affected ensuing events and made controlling the disease more difficult. Mary's back was up right from the start and she was in no mind to cooperate. She was angry and frustrated; in the ambulance Mary was like a caged lion. Perhaps if the authorities had treated her differently, had not been so swift to stigmatize and isolate her, she might have acted very differently.

Behavior labeling has far-reaching consequences. As Jonathan Mann, head of the International AIDS Center in the 1990s, said, "Stigma and discrimination are the enemies of public health."¹⁹ The phrase sums it up very well. Stephen Joseph, a New York City health commissioner in the 1980s, said, "The issue...is not whether quarantine is a legitimate tool for protecting the public health,"—which he agreed it was—"The issue is: Under what circumstances should it be employed, and with what safeguards against its abuse?"²⁰ And that is, indeed, how we have to think about Mary Mallon's case. To put it into a contemporary setting, think about AIDS sufferers in Cuba where the initial response was to isolate anyone who tested positive for HIV. Some of the victims have said, "It is very difficult to be just sitting here waiting to die. We have lost our freedom; that is the most important thing there

¹⁸ *New York World*, July 20, 1909, 18 quoted in Leavitt, *Typhoid Mary*, 183.

¹⁹ "Preface," *The Impact of Homophobia and Other Social Biases on AIDS* (San Francisco: Public Media Center, 1995), p. 3 quoted in Leavitt, *Typhoid Mary*, 237.

²⁰ Stephen C. Joseph, "Quarantine: Sometimes a Duty," *New York Times*, February 10, 1990, 15 quoted in Leavitt, *Typhoid Mary*, 237.

is.”²¹ When she was out on the island, Mary Mallon was asked, “We take good care of you. We feed you. You have a bungalow. What are you complaining about?” She said, “How about my freedom?” It was as simple as that.

Sandor Katz, another AIDS activist in the 1990s, said, “Given the stigma of AIDS and the vulnerability of the groups hardest hit by it—gay men, drug addicts—there is an ever present danger that the public health officials will trample on civil liberties in their zeal to do something.”²² This raises a specter of discrimination in employment, housing, health insurance, etc. Katz understood that if the sufferer is unlike you in some way, it is easy to say, “OK. OK. Yeah, we can isolate you.” But what if the issues apply also to you, to me, to all of us?

It is important to ask: Was Mary Mallon, in some way, to blame for her treatment? Did she consciously bring sickness and death? Was she the demon, breaking skulls? Was the Health Department to blame? Did it act too quickly and without sensitivity to Mary Mallon’s situation? The easiest answer is that they shared the blame, right? The Health Department, however, had the power in this situation, and therefore I believe that makes their blame a little more significant than Mary’s blame.

When my book about Typhoid Mary was published, I was criticized for being too sympathetic to her. I was sympathetic to her, and I still am. I am sympathetic to anybody who gets caught in a machine as powerful as city government, state government, federal government. It is too easy to get caught in a way that makes your behavior look worse. As Mary Mallon lashed out against it, she became the one who was, and is, blamed more; government behavior is rarely criticized because they are the ones in authority; they define the situation.

Thus, in the end, I conclude that the Health Department was more to blame. George Soper’s presence muddies the water because he was not part of the Health Department, but he was the first one to get to Mary. It is Soper who comes to her and he says, “I want your blood, feces and urine.” If somebody came to your door, you wouldn’t give him those, would you? You’d be upset. So even before the Health Department was part of the story, Mary was upset. But did she have reason to be? And should her reaction have influenced the officials’ treatment of her?

I ask the question, “Have we been too quick to override individual liberty with the perceived larger good of protecting the public’s health?” I think we need to pay attention to the injury that was caused by the stigmatizing labels and “othering.” We need to apply public health equitably—much easier to say than it is to do—but I think it is really important to think about providing fairness in our public health policy. We need to develop a trusted system that does not discriminate. We need to educate the general public to lower risk behaviors. And, indeed, that is what the Health Department has been trying to do throughout the twentieth century and into today.

We need to gain public cooperation, not resistance. In recent years there has been a big push for health departments to try to figure out ways to build cooperation in the community so that if something were to happen, people would not just get angry and say “no.” Instead, they would try to work with the authorities to make the situation better.

²¹ Tim Golden, “Patients Pay High Price in Cuba’s War on AIDS,” *New York Times*, October 16, 1995, 4 quoted in Leavitt, *Typhoid Mary*, 242.

²² Sandor Katz, “HIV Testing—A Phony Cure,” *The Nation*, May 28, 1990: 738–42 quoted in Leavitt, *Typhoid Mary*, 239.

Perhaps we should use isolation only as a last resort, although in cases such as SARS (Sudden Acute Respiratory Syndrome) you do have to act very quickly. In a case like SARS, officials might need to resort to isolation more rapidly, but the isolation should be temporary. Regardless, we always have to pay attention to due process and, of course, in Mary Mallon's case, there was none.

Historically, I can see that immigrants and racial minorities have experienced the greatest inequality from health policies. If you look into public health anywhere in the US in the late nineteenth and way into the twentieth century—probably even today—you will see that the people most likely to be caught in the system, are people like Mary Mallon—immigrants, racial minorities, women—and all have fewer resources with which to defend and protect themselves, to ensure that they receive due process.

CONCLUSION

Is the protection of public health a higher national priority than individual rights and the liberty of the stricken? I think they are both very strong national priorities, and because of that we continue to struggle with the dilemma. But, justice must always be in our minds as we consider these issues.

Finally, we must always think of these issues as if they apply to *us*, not just to *them*. For only by placing ourselves in the dilemma, will we ever be able to achieve justice.

Discussion Questions from the Audience

Question #1: I was wondering if Mary talks about facing discrimination even before the health officials discriminated against her? Was she discriminated against in other ways—in employment or anything like that?

Response: She doesn't talk about that all.

Many immigrant women did feel they were at the lower end of the work world and didn't like it there very much, but no, I never came across that from her.

That said, she sees it so clearly in the medical case that she must have understood or felt discrimination in some way earlier, she just never talked about it. I think people had a view of the world from their own position in it, and she was at a lower position. She understood that most of the other people she dealt with—employers or the government in this case—had a lot of power that she didn't have. At some very basic level she understood that or she wouldn't have been able to make that connection. But whether she ever consciously made it earlier, I just don't know.

Question #2: Did she feel responsible for the typhoid patients around her?

Response: To her employers, absolutely, she felt a responsibility. In fact, when people got sick in the houses where she cooked, she stayed around and took care of them and so, of course, made it worse. It could be interpreted that she felt responsible for making them ill, but

I think she saw it as her responsibility for other reasons. She was always thanked by her employers for being so loyal and kind and taking care of the people who were sick in the house. Yes, she felt that responsibility very much. But, did she feel responsible for giving them the sickness? No. She never felt that.

Question #3: Did Mary understand the science used by the Health Department?

Response: One of the things that happened on the island after she was isolated the second time is enlightening. Mary was always applying to do some job, and they finally gave her a job in the island laboratory checking TB sputum samples to see if they were active tuberculosis. Now, Mary didn't believe in bacteriology, certainly didn't believe she was a carrier—after all, she kept saying, “How I can be dangerous to anybody? I'm not sick”; she had accepted that if you were sick, you might give a disease to somebody, but she never accepted that if you were healthy you might give the disease to somebody. Yet there she was, working in a lab.

She was very much a woman of her time. Most people in America at that time didn't believe that a healthy person could make another person sick. Intuitively, it just didn't make sense, and it took a lot of convincing even among physicians. I have found many contemporary physicians who said, “They're crazy. I might accept that sick people who are carrying a bacterium might make somebody else sick, but a well person, never.” So, Mary was in good company.

I interviewed a woman who knew Mary on North Brother Island, and she was convinced that Mary Mallon never believed—never to the day of her death—that she was responsible for those deaths. It complicates the story because we have to understand how people comprehend things in order to know how to handle them, and, in Mary's case, the Health Department didn't try to understand that part of her.

Question #4: One of the factors regarding how Mary was treated was the fact that she was an immigrant—among other things, including maybe gender—but a lot of the typhoid carriers you talked about were also immigrants and yet were allowed to go about their normal life. Could you talk about that?

Response: That's a good point. It's not just immigrants, obviously. There were class issues, too, at least in a couple of the cases. Some of the carriers could be seen as middle class, and that made the Health Department respond a little differently to them. But Mary's story puts the gender issue pretty front and center. It turns out that more women than men become healthy carriers after having typhoid fever. I don't think anybody understands why. But it may be that the Health Department officials felt they had to be harsher with women to keep them away from food.

However, I don't think that's what they did. They made Mary out to be an unnatural woman, which is why they were able to persecute her, as she put it. I think also it was relevant that she was a single woman who lived with a man when she wasn't living in her employers' houses. Thus, she was seen as someone who wasn't living the life that she should live, someone who was already immoral. Also, she had her back up more than anybody else that I was able to find, and I think the officials didn't like being challenged, so they acted more harshly towards her. The other thing, of course, is that she was the very first carrier to

be identified, and you could argue that the Health Department was making an example of her and felt that they had to do that.

Question #5: Is the fact that Mary always had her back up what really inspired most of the Health Department's actions, or was it because she was the first case? Do you think it was primarily because of her attitude?

Response: Definitely. If somebody repeatedly defies you, you retaliate, and I think that was part of it. Of course, they blamed her actions on her Irish temper more than anything else, which is where the immigrant stereotyping played a part. And that was, certainly, a factor. The Health Department people themselves were not deliberately malicious. Yet, when the long-term health commissioner of Providence, Rhode Island, wrote to the New York Health officials and said, "You shouldn't be keeping her anymore," they either ignored him or agreed, but did nothing. The officials were challenged by a variety of different people and organizations, not just by Mary. If you act in a particular way—such as keeping Mary in isolation—the longer you keep doing it, the harder it is to stop. That was also a significant factor.

Question #6: Why did Mary return to cooking after her release, even though she had been told not to?

Response: I don't think she ever thought about it that consciously. I think she tried to make a living—what she thought was a decent living—in various other ways and just couldn't make it. That was one frustration. I also think she didn't understand that she was dangerous. She really did believe that somehow they had found her and made an example out of her unjustifiably—I believe that was very important to Mary. After all, she was healthy...she just couldn't accept that she had caused any of the outbreaks.

Another thing I should say is in regard to typhoid fever. Although the number of cases had come down by the early twentieth century as water supplies were increasingly filtered, it was still a very prevalent disease. There were about 5,000 cases in New York City every year. The one case, three cases, five cases that Mary may have caused were like a drop in the ocean. So, Mary probably wondered something like, "Why don't you go after those people who were sick? Don't go after me. I couldn't have caused it. I'm healthy. There are a lot of people around who have typhoid fever who could have caused it." I think she really didn't believe it.

Question #7: Did any of the known carriers continue in risky endeavors?

Response: They did, and they were arrested again and released again. Now, once the authorities began registering healthy carriers, they soon had hundreds and hundreds of them in a city like New York, probably thousands. They were following all of them and 99% were cooperative—they didn't go back to cooking, or at least they never again came under the Health Department's purview. But there were some who came back time and again, who were recidivist in that sense, yet they were treated better than Mary.

Question #8: What happened to Soper afterwards?

Response: He continued in an engineering career. He had a very good engineering career, but he no longer did specifically health-related work like finding typhoid carriers. He was involved in health-related work like developing sewers, for example. He was very interested in sewers. But he never forgot Mary Mallon, and periodically he would write or call the Health Department to ask what was happening with her. He was just curious. They usually didn't answer him, which is interesting.

Question #9: How do we handle cases similar to Typhoid Mary's today?

Response: In the modern era tuberculosis would be a good analogy, as would SARS. I'm sure we can think of others. In all cases, the assumption is that the person you identify as "dangerous" understands that they are dangerous, right? That's a difficult assumption. Maybe it's that assumption that we should pay attention to: How do people understand the situation in which they find themselves?

I've spent many hours trying to figure out if Mary believed she was a carrier, and I spent a lot of time with a woman who worked with her on North Brother Island day in and day out for five years. I asked her what she thought because, after all Mary had been through, it was hard for me to think that she still refused to believe that healthy carriers were a possibility. That's something we can't really answer, but Mary's colleague was convinced that Mary believed in her own innocence. Mary would, for example, occasionally bring her an apple. It is hard to imagine that Mary would do that if she understood she could be risking her colleague's life.

Question #10: I wonder if education could have been the answer to helping Mary believe that she was a healthy carrier and what that meant.

Response: If we could only teach people what they need to know, then the world would be a good place. It's very interesting to think of it in those terms. Thank you.

Question #11: What happened to Jennie Barmore, the woman in Chicago who ran a boarding house until she was labeled a healthy carrier?

Response: Her children were grown and out of the house at the time. She had a husband who was disabled and couldn't work, which is why they ran the boarding house and why it was their only source of income. The Chicago Health Department didn't have a North Brother Island type of facility to put her in, or I believe they might have done so. Instead, they chose home isolation. They repeatedly put a sign in front of her house that read, "Typhoid fever. Danger" or something like "Do not eat any food. Do not leave milk." (I've never understood why somebody couldn't leave milk.) Anyway, the signs listed various things that you shouldn't do, and Jennie Barmore kept tearing them down. She resisted her treatment, for sure. Yet, they did nothing other than put her under house arrest.

Question #12: Did you look at other states to see how they treated healthy carriers?

Response: I looked at many other states and their regulations for the handling of carriers. I found no other example like Mary Mallon.

Any regulations were written after Mary Mallon, and were based on her case. New York came first and then states around followed suit. Before Mary the rules referred to people who were sick. Unfortunately for her, the New York authorities had no problem attaching those rules to Mary.

Class Exercises

Who is Typhoid Mary? Does her Role Change over Time?

Judith Leavitt told the story of Typhoid Mary not only as a window into history, but also as a way of studying public health issues that we still confront today. Has Mary's story—or more precisely, her label and legend—been used to help the public understand similar issues? To find out:

- Do a search in a newspaper or magazine database for articles that liken sufferers of diseases or potential victims to Typhoid Mary.
- Read the articles and create a list to determine how often and when the phrase “Typhoid Mary” is used as a metaphor for a danger to public health or an imprisoned individual. Is it ever used as a symbol for another issue?
- Decide whether Mary's story is used correctly or whether it has been reinterpreted over time.
- From your answers, assess whether our society remembers Typhoid Mary's story accurately or whether it has reinterpreted it.
- Is it problematic if Mary's story is used inaccurately or in a new way—why? Is it helpful to use her story, correctly, incorrectly, or in a new way—how? What do your answers tell you about the need to know the historical context as well as the current context of medical issues?

Variation 1: One variation on this activity is to ask different groups to find and analyze stories from different newspapers or time periods and then to compare the results. Is Mary's story more relevant to one area of the country than another? Is her story more relevant to one decade than another? How can you interpret the patterns that you find?

Variation 2: Another variation is to ask students to interview people outside of the class about the phrase “Typhoid Mary” and find out what they associate with that term. Then follow steps 3-5 above.

Public Health Protection in the Law versus Personal Freedom

Did Mary commit murder?

- Divide the class into groups to debate: “Should Mary have been convicted of manslaughter in 1915, after she returned to work as a cook in a maternity hospital

despite promising not to take a job as a cook? Why or why not?” Note that 25 people became ill because of her cooking, and two died.²³ Remember that, while murder in the first degree usually requires deliberate intent to kill and a plan to commit homicide, there are other kinds of murder charges. A defendant is guilty of a lesser murder charge—involuntary manslaughter—when he or she commits homicide “because of criminally negligent or reckless conduct.”²⁴

- After the debate, assess the following question in a class discussion or an essay: What do your answers reveal about expectations to do with personal responsibility, individual liberty, and public health?
- Then, students should compare their responses. Why do they differ, or why are they similar? Did arguments rest on science, political ideals, justice, personal experience, and/or other grounds? What do people consider when making judgments? Are the grounds or reasons different from the ones used when Mary’s contemporaries judged her? Why or why not?

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Judith Walzer Leavitt is the Ruppel Bascom and Ruth Bleier Professor Emerita at the University of Wisconsin at Madison. She is a prolific scholar whose interest in the history of medicine has led to research on public health and gender on topics ranging from municipal health issues to contagious diseases, to childbirth. Perhaps her most famous work is *Typhoid Mary: Captive to the Public's Health*. That book inspires the story she recounts, as well as the issues she raises below.

Chapter 82

PREPAREDNESS IN PUBLIC HEALTH: A NEVER ENDING NEED

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ABSTRACT

Due to the ease with which people and goods are able to move within and between countries via efficient transportation means, the probability of the general population being exposed to a novel pathogen exists. Dr. Montero's lecture emphasizes the importance of public health and healthcare systems being prepared to handle the unknown and the inevitable. This chapter highlights the key aspects of the public health science—known as epidemiology—that are required to prepare for, control, and ultimately prevent disease outbreaks. Dr. Montero utilizes several renowned pandemics, including Severe Acute Respiratory Syndrome (SARS), Influenza, and the Middle Eastern Respiratory Syndrome (MERS), to illustrate the tools he and his staff use on a daily basis, as well as the necessary systems that are required to detect an outbreak of disease, educate the public, and limit its spread. This chapter presents a comprehensive overview of how important it is that our public health and healthcare systems work efficiently and in an integrative manner to keep populations across the globe healthy.

LECTURE

Public health emergencies are always happening, so we need to be prepared. How we prepare, and what we prepare for, is the focus of this lecture. To present the historical context of public health preparedness, I am going to start with Severe Acute Respiratory Virus, SARS.

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In February of 2004, the World Health Organization (WHO) detected some unusual epidemiological activity going on in China. Unusual health events in China are not unexpected—there are a billion people in China and there’s always something going on. This time, 300 people had atypical pneumonia, or infections in the lungs, in one particular area of the country. When the WHO started to investigate, they found that this unusual health event had been occurring since November 2003. Now, in February 2004, as WHO began to investigate these cases, they noted that there were also cases in Vietnam. The WHO sent a great team to investigate those cases. Unfortunately, later on, the team leader got infected and died. At that point, the WHO issued a travel advisory, which means, “Don’t go to this place, and don’t go to this other place. If you are traveling, you need to make sure that you are not sick. If you have a cold, a fever, respiratory symptoms, we won’t let you on an airplane because you may be transporting a particular infection, and we still don’t know what this is.”

In the middle of March 2004, the WHO developed an international network of laboratories. To do this, they go to places around the world with great technical experts and say, “Guys, here are some samples. Help us. We need to learn what’s cooking? What is this disease that is killing people?”

Then, on around March 20, 2004, the health officials in Hong Kong said, “We think we know how this is happening.” There was a doctor, a lung specialist, who’d come from the Guangdong province and gone to Hong Kong. He’d stayed at a hotel called the Metropole. When he’d arrived, he’d been kind of sick so the officials started looking into it. They found out exactly when the doctor had been at the hotel and who had been in the rooms near his. They tracked down those people to see who’d been where and when. They found out that the doctor had come from Guangdong to the Metropole and had infected somebody from Hong Kong; and then somebody else who went to Vietnam got infected, and then somebody else who went to Singapore got infected, and then somebody else who came to the US got infected, and then somebody else went to Ireland and he was infected, and then somebody else went to Canada . . . and so the nightmare, SARS, occurred.

What else happened? Well, the Chinese asked the US government, “Help us. We really can’t manage this.” For the Chinese to say that, it had to be really dramatic, really dramatic, because there’s a lot of international politics at play. By March 27, 2004, Chinese health officials were telling the Chinese public that they could not go to Canada in an airplane, no one could go to Singapore, and no one could or should go to Hong Kong. Imagine the economic and social impact of those recommendations and decisions.

Steps were then taken to manage the disease at a more local level. The Chinese started to see a lot of cases in one particular high-rise building in the Guangdong province and decided to restrict people’s movement—something that’s kind of hard to do in the US. People had to stay put in the building—there were around 300 people actually sick in that one building. Other residents were told to wear masks. In China, people have no problem with this. You tell them, “Use a mask because that will help you to prevent transmission of the disease to others,” and they do. Can you imagine that happening in the US? You’d never get the same level of compliance. In Guangdong, though, they started doing the right thing and used masks. Furthermore, people who were allowed to travel were screened for respiratory signs and symptoms. They still had to use masks if anything seemed abnormal and several used masks just because they thought it would help prevent them from acquiring the infection themselves.

Finally, in April 2004, we started to see the disease come under control, but by then camps had been set up for people who were infected. How? In China, you tell a couple of thousand people that they cannot leave a building, and then you tell them you need to move them to a place where they cannot infect anybody. All these steps require a mix of quarantine and isolation and social skills that simply don't exist in the West.

In Toronto, Canada, one patient of Chinese descent came from Hong Kong and infected his family. He was admitted into the hospital where he infected the hospital employees, who, in turn, infected a lot of other people. By the end, there were 400 cases in Toronto and 44 people died. Travel, conferences and business coming to the city were dramatically decreased. A billion dollars were lost to the city's economy because of SARS.

Thus was the chain of events: A guy went to a hotel, somebody was in the next room, got infected, went to Toronto, and more than 40 people died. This was the twenty-first century; it was not the Middle Ages. This was your highly developed, technological world.

This kind of event reminds us that the world is really a small place. You are incubating a disease, and you can go wherever. From this one SARS event, we had about 8,000 cases and 774 people died. But the world came together to tackle the problem, to manage it and to prevent further spread.

Now, let's bring this to a more local picture: New Hampshire, the third healthiest state in the country, a state where we have really great health indicators. But the reality is that it doesn't matter how good our indicators are when we have an infectious situation like the one just described. I'm going to look at several different situations to show you what we have done, what we can do, and what we should do in the face of health crises.

One big problem is how to communicate about such an event. It's always scary when I go on TV and say, "Well, we have this thing going on and we need to close this place, or we need to do X, or we need to do B," but the reality is that the media has a day-to-day duty to report on such topics, so I do need to go on TV to present information. I don't know how many of you still watch TV, maybe you only read Yahoo or Google news. But, either way, you'll have seen stories that say something like, "Authorities identified this patient with whatever flesh-eating bacteria. It was in whatever place, and we're all going to die by 11 o'clock tonight." Wait a minute... you're a parent and you've just been told that your kids are going to die by tonight at 11. Everything is a big emergency. This news becomes the regular news, the regular coverage, and we move into emergency mood and mode!

But is that reaction appropriate? How do we manage the right level of awareness? What is news and what is important are not necessarily the same things. We need to be careful about how we announce a situation, how we educate, and how we bring information to the public. Once informed, people can choose their risk level based upon their own reasons. For example, they can choose to get vaccinated or not.

We also need to consider what causes an epidemic. First, we're talking about infectious stuff. What can happen? Viruses change. They mutate. They are engineered to survive and they are incredibly good at that. But, if somebody brings a SARS-type virus into our society, we are all susceptible to that. In addition, we could have an enhanced mode of transmission—enter bioterrorism. And that is now part of what we do: we prepare and plan for the management of a bioterrorism event, whatever it is—ricin, anthrax, or smallpox, for example.

Then there is the consideration of the differences in susceptibility of the disease hosts. There are people who are immunosuppressed for particular reasons: a cohort of cancer patients, a group of the elderly, a bunch of diabetics—all of them have immunity issues. If

they are exposed to something then, as a group, they have the possibility of developing something. What do we do? Well, we have 10 steps that we follow every time we have such a situation so that we can investigate and determine what's going on and what to do.

The process is to verify, index, and scan. We collect samples. You get sick, so we come and take blood, saliva, feces, urine, your liver, your brain (not really, just kidding) ...whatever we need we take from you because we need to figure out what's going on. You may not like it—especially if it's your brain—but you know, all for the public good! We talk to the providers who saw you. In my job, I don't see patients: I just get the reports of the cases so we can try to figure out what's going on out there. Then we start to create lists. Who else has something like this? Who else has reported something like this? We start looking at ways in which we can determine the extent of the problem. Is this the first case, or has it already been happening, or has it already expanded somewhere else? It's detective work. That's what we do.

We look all over, at schools, absentee lists, death certificates, outpatients, and national databases. Then we question: Is this really abnormal? We look at epidemic curves and see whether this is truly a situation. Is this situation on the baseline, or above it? For example, in situations like some gastrointestinal outbreaks, we find that there are peaks and valleys. If it's January, I know that people are going to suffer outbreaks of diarrhea. It's called the winter vomit, or Norovirus, and it happens every winter. If you're reading this in December, then in a few weeks you are going to get sick because you didn't wash your hands and you eat bad food. It's expected. That doesn't mean that it's not a problem. Nor does it mean it's not something we need to act upon. But if I start to see a peak at a different time, *that* may be something unusual. For example, we've had abnormal peaks that accompany the emergence of a new strain of Norovirus. When that happens, we need to decide what to do. Do we have the resources to tackle the situation? Is it important? Or do we decide that, yes, although we have a few cases of this illness, it's so mild that it's not worth investing any resources to control it because no one is going to get severely ill or die.

Next, we try to define the epidemiology of the information that starts to come up. For example, in New Hampshire from 2004 to 2006, we placed all of the information we had for West Nile Virus or Eastern Equine Encephalitis on a map. We looked to see if there was a particular geographical pattern, a particular ecological pattern, or indeed, any particular factor that could help us determine how the disease was moving. And, again, we did our epidemic curves. (Epidemiologists are funny people. They need their numbers and their graphics and all that geeky stuff—I'm a recovering epidemiologist... I don't do that much anymore!).

Now, we are able to start to construct the hypothesis about how the virus works. To do this, we need to go back to our lessons in biology and in ecology. We know that things like West Nile Virus or Eastern Equine Encephalitis come through mosquitoes, but mosquitoes bite birds most of the time, and then in some cases they bite humans, so we need to figure out what the reservoir is.¹ Where do the reservoirs stay? How do they transmit the disease? Once we know that, we can generate hypotheses about how we're going to control the disease, who will do the controlling, and what extra samples we need. Then we implement the measures that we need to utilize. We can quarantine people. We can isolate people. We can recommend immunizations. We can recommend antibiotics. We can recommend that everybody stay

¹ A disease reservoir is the species that hosts the disease; the host may not become seriously sick or sick at all from the disease.

home. Recommendations depend upon what we need in order to manage a particular condition under particular sets of circumstances. For example, one disease may require one type of management when the weather is cold and another when the weather is warm. This kind of decision-making requires a lot of science and a touch of art.

(One important thing to remember here is the difference between isolation and quarantine. You isolate people who are infected: if you are coughing, and I have a diagnosis for you, I can isolate you. Then I will quarantine those people who have been in close contact with you. They are not sick, but they were close to you and so need to be quarantined so they don't spread the disease as they develop symptoms).

Now comes the issue of reporting. If deemed necessary, I have to go to the public and say, "Hey guys, this is happening." Sometimes we don't report it. However, by law, health care providers must report to us, the public health officials. Because we have their reporting we can keep track of things and see how they evolve in the future—that is our long-term surveillance, without it, we cannot hope to control health crises. Finally, if we are successful and the danger passes, we hug and kiss and sing "Kumbaya." We deserve that hug. Sometimes it's the only thing we have.

Those are the principles. Now, how do we play this in New Hampshire? I'm going to pepper the New Hampshire examples with some national data and references to some particular examples in history.

We manage health situations in four ways. First, we create an infrastructure that allows us to keep track of things. Then we develop a system that allows us to analyze the information that we collect in order to keep track and forecast. This is not a guessing game. Next, we implement our protocols to control a health situation. Finally, we conduct the long-term surveillance, as we move into recovery.

First things first: We keep track of you. How? You went to the clinic and you had a funny disease that I have a particular interest in, so your provider reports you to the Department of Health. (The Department of Health has a list of reportable conditions. Should doctors diagnose a case that is on the list, they are supposed to call us to notify the Department of Health. Reportable conditions include sexually transmitted infections such as gonorrhea or syphilis, vaccine-preventable conditions such as whooping cough, diphtheria, or polio, and a handful of really severe, weird diseases.) We also look at death certificates and have a link to veterinarians who tell us about particular diseases. In a sense, it's all a bit Big Brother-ish.

Our work is facilitated by automated systems. We look into emergency rooms in a live fashion. I have a system of computers with all of the de-identified information of every diagnosis that comes to us. But I don't get names; we don't create big databases of whom you are or what you do. What I do get is information so that I can see if there is a big increase in, for example, respiratory illness or cases of meningitis or particular skin rashes that may tell us that a bioterrorism event has occurred. All of that information comes into our office and we create tables that allow us to study trends and so see if something abnormal is happening.

If we do spot an abnormality, then we reach out to the clinicians. We say, "Hey, be alert. You have something cooking in your region. Pay attention," and they do. In some cases, we ask for specific samples and those go to our public health laboratory, where we do a lot of testing. In 2012, for instance, there was a rise in the number of cases of Hepatitis C in southeastern New Hampshire. In order to investigate the matter, we basically did DNA fingerprinting. The New Hampshire Public Health Laboratories is one of the few laboratories that can do this. We can identify all of the patients whose Hepatitis C strains match, which in

turn allows us to identify the original source of the infection. By doing that, we can either prevent future outbreaks or prevent a current outbreak from spreading. In the 2012 case, many people became infected before we knew it was happening, but after the source was identified nobody else was infected. That's the purpose of what we do.

How do we forecast things based on the information at hand? Well, we need to keep track of data. Take the West Nile Virus. In 1999, it was present only in the New York metropolitan area. It spread in 2002, 2003, 2005, 2006, 2013 . . . and by May 2014, it was all over the place. That's an epidemic. It spread that quickly.

Studying and tracking the data allows us to forecast when and where things will come. We see that there is something new...West Nile Virus. The last time we checked the Nile River was not in the US, but here it is a virus that was identified there. Thus, somebody must have imported it. The first issue is that we have no idea how the virus will evolve in our climate and ecology. We need to keep track of it so we can begin to forecast how it will create cycles and what the vectors are going to be. We have identified several mosquitoes that are involved in the transmission. One is the *Aedes japonicus*. In other words, we have an African virus that can use a Japanese mosquito to transmit infections in the USA. How does *that* work? We don't know how it began, but once identified we can and do keep track of it.

But that's not the only type of thing that we need to keep track of in the infectious diseases world. Let's talk about Bambi. Bambi, and other deer like him, carries ticks that are approximately 1 mm in length, hard to find, and can give you Lyme disease. Twenty years ago, we had 60 cases per year in New Hampshire. In 2012, there were 1,300 cases. Fifteen to twenty years ago, Lyme was only found in the southeastern part of the state. Now it's all over, although most cases are still found in southeastern New Hampshire. By tracking the data, public health officials could see that the disease was moving north. Thus, we could forecast that it was going to reach a particular region before it did. This allowed us to focus our education and prevention messages in that region. We worked with local clinicians so they knew how to diagnose the condition. Prior to our training, they were unfamiliar with the disease and so a case could have been missed, resulting in chronic issues for the patient.

Now let's look at a different example in another part of the world. Around 1 billion people are mandated to go to Mecca at least once in their lifetime, if possible.² As you may imagine, with such a mass of people arriving in one place from all over the world, space becomes extremely tight and you create the ideal situation in which to exchange viruses or bacteria. After this pilgrimage, the *hajj*, outbreaks of meningitis have been often reported around the world. OK, but why should we care about that here in the US? Because there are other global events that can trigger similar outbreaks—the World Cup or the Winter Olympics for example. By tracking and understanding the *hajj* and the locations many of the attendees came from and go back to, we can predict what will happen at other large-scale gatherings. If we pay attention, we can foresee potential health threats.

There are things that are emergencies and there are things that are kind of day-to-day. Is the *hajj* an emergency? No, it's a huge task for surveillance, but it's not an emergency because we know that it's happening. There's a big difference between the focus of day-to-day surveillance work and a public health emergency. Public health preparedness requires a lot of work all the time.

² The pilgrimage to Mecca, or *hajj*, is one of the five pillars of Islam.

The world today has become really small. People can get on airplanes and go places and a disease can spread quite quickly. Consider air flights over a 24-hour period. In that short time, you can connect North America to Europe to Africa to Australia. If you study the patterns, you can understand how a Japanese mosquito can infect people in New York City with an African virus. In the same way, meningitis travels around the world when people depart from Mecca to return to their homelands, and this doesn't even touch on shipping containers and the maritime transfer of goods. Transportation of cargo allows huge numbers of mosquitoes to migrate around the world. When you bring tires from China, for example, mosquitoes hitch a ride and breed for weeks in the water in the ship's hold.

Nevertheless, air travel is the most significant issue when it comes to prevention. We need to manage the prevention of infection in planes, but we also need quarantine stations in ports of entry to this country. The main international ports have quarantine stations staffed by employees of the Centers for Disease Control and Prevention (CDC). This means that if we are tracking a rise in a particular disease and then we detect symptoms of that disease in a passenger entering the US, we can stop the person, bring them to the station, test them, and thereby determine whether or not they should be allowed to enter the country.

For any investigation, there are protocols and resources. Principles have been developed that allow us to identify and predict. The problem is determining for what we are planning. Are we planning for flu? Tornadoes? The H7-M9 virus? An ice storm? Hurricanes? The short answer is: yes. We need to plan for all types of emergencies. But what we don't want to do is create so many systems that it gets too complicated. Thus, at the end of the day, it is essentially the same people who respond to all emergencies. It's Public Health—whether it's an infection, a dirty bomb, or a hurricane... My team responds to them all.

We follow national standards called the National Incident Management System, and we create a structure called the Incident Command Structure. This set up was developed by firemen who, when managing big wild fires, need 5,000 people working in several places. To coordinate and control their efforts, there's an Incident Commander and four sections: operations, planning, logistics, and finance. We keep track because when we need funds, I have to go to the governor and say, "Hey, I need money." Then I have to go back and say "Guess what? I need more money." That's something that nobody ever likes to hear.

As you might imagine, national standards are complex and multi-faceted and involve a lot of paperwork. In New Hampshire, we follow them as much as we can. We choose a few things to prioritize and we work with the healthcare system. In the past, we worked almost entirely with hospitals. Now, we realize that we need to include the whole healthcare infrastructure. In the event of an approaching hurricane, you can get people out of a hospital, but what do you do with the 300 people in a nursing home? Where do you move them? How fast can you move them? There's a dementia unit with Alzheimer's patients. Where do you move them, and who will take care of them when you are moving them? Seven percent of our society has diabetes and half of them are using insulin. How do you handle that? There's a bunch of people with COPD who require portable ventilators. If we need to move them out of their houses, they will need access to power for their ventilators so that they can stay alive. They can't get it from a hospital.

In the event of an emergency, we track different things, and plan for things that previously we were not looking for. That's why we engage in all kinds of theoretical discussion about how we plan for disasters and what we learn from each of our emergency responses. In New Hampshire, we have the Department of Health at the state level but only

Manchester and Nashua have full service local health departments, so we had to create a system of regions that will work with us to respond at the local and regional level. Within each of those regions, we created a system so they will know how to respond, whom to ask for help, and who makes the final decision so no one is confused.

We decide where and what to prioritize. We know that we need to work more on community preparedness or on medical surge capacity. For example, what happens if I have flu pandemic and I need to increase the number of available hospital beds by 20%? It doesn't just happen because I say so, and even if it did, who would take care of the patients? Where will the healthcare workers come from?

For illustration, the best example is flu pandemics. Flu can be quite deadly and the possibility of fatalities is quite high.³ The most famous flu pandemic, known as the Spanish flu, occurred in 1918. But it was by no means the first—Hippocrates described one way back in 400 BCE! Flu pandemics are like moving targets, you never know for sure which flu virus is going to get you. Four years ago, we were planning for a flu pandemic coming from China and instead we got one from Mexico.

There are many ways to try to stop the flu. We have a flu epidemic every year. And yet, even with all the years of surveillance, we still have been unable to crack the flu nut. Around 20,000 to 30,000 people still may die from flu-related conditions every year in the US. Our problem is that flu viruses change all the time. They are RNA viruses with no self-control. When DNA and RNA are replicated, you have a form of quality control that allows you to see if the replication process didn't work and therefore cannot be used. That doesn't apply here: The flu RNA changes all the time; there is no quality control; and it just keeps mutating.

Flu viruses may have antigenic drifts or antigenic shifts. Shifts are major changes and can cause pandemics. There is a huge interaction between flu viruses and animals. There's the well-known chicken flu and swine flu, but other animals, such as dolphins, are susceptible, too. And viruses can jump from species to species, which puts us at risk.

What kind of risk? Well, the Los Alamos laboratory in New Mexico is famous for nuclear stuff, but they also do incredible advanced math work and modeling. They can tell us how quickly infections can spread in today's world. Thanks to a model they developed, we know that in just three months, the whole of the US could be fully infected with a flu virus. That's the kind of thing we need to plan for.

There are many variants of viruses and several different strains that we track around the world. In 2012, a flu strain came from pigs in Mexico. Kids apparently went to a fair, interacted with the pigs and then played and touched and kissed one another just as kids do all over the world. Next thing you know, the flu is spreading. Then there's the bird flu that came from China. In some areas in China, people and animals live and work in close proximity with one another. A person will be exposed to viruses coming from their animals, be they chickens or dogs, and those viruses will spread from species to species and be re-assorted.

Getting a system in place that allows for worldwide control of diseases is complex because countries and cultures are different the world over. It's tough because we are one society asking another, often underdeveloped, society to act in a certain way. With bird flu, for example, we asked people with no industry and no way to earn a living other than by raising chickens to kill all their birds in an effort to fight the virus. And they did. The WHO has tried to create a worldwide system by which we agree on the best practice for raising

³ See Chapter 1 in this book for a more detailed discussion of flu pandemics.

birds and how to do things, in order to avoid another outbreak and spread of bird flu, but until we have a more developed and equitable world, we will have no way of controlling all social conditions.

So how can we create this fair and equitable world? It's not going to happen with just the WHO, it will need Harry Potter's "Ministry of Magic" and all its partners. We need a concerted effort worldwide. We need to provide assistance to poorer communities so they can do better surveillance, so we can find things early, and intervene early. If we can do that then, hopefully, we will be able to prevent future epidemics from happening.

Let's return to New Hampshire and the flu pandemic of 2012. We did four things: We carried out surveillance; we provided medical research, dissemination, and met other clinical system needs; we did prevention; and we implemented actions to contain things at the community level.

Let's start with the surveillance. People keep asking me, "How is the flu season going to be this year?" I have no answer, I don't know. We cannot predict how the viruses will evolve and how they will move each year because of the re-assortment and the antigenic drifts. Nevertheless, we do keep track. We look at emergency rooms. We ask doctors to tell us how many of their patients have flu symptoms. We find out which school districts have above-normal absenteeism. We map all of this and track it so that, if a pandemic does happen, I can flatten the curve. Let me explain: If I don't have a vaccine—and I will explain why I may not have a vaccine—I need to prevent all of the cases from happening at once. It's one thing if I need to provide care to 50,000 people over three months, but quite another if I have to provide care to 50,000 people in three weeks—I simply don't have that kind of capacity. Truth be told, I probably don't have the capacity for the first scenario, either, but it would certainly be easier and fewer people would die from lack of service.

Let's talk about space. Here you all are, together in a classroom. I need to spread you out. But how? I send you home because the space that you have at school versus the space that you have at home is quite different. We use social distancing. We cancel mass gatherings. We use non-pharmaceutical interventions. If you are somewhat ill but don't know what you have, we ask you to stay home. We do that on a regular basis—every day with pertussis (whooping cough) or tuberculosis patients.

When people don't want to stay home and we really feel that there is a high risk, we use police powers—these give public health authorities the right to write and sign an order restricting a person's movements, even put a person in jail if need be. Such measures would not be my choice; we always try to get people to stay home or move them to a hospital. Nevertheless, in the last 10 years we have needed to go to these extreme measures a couple of times. The next step is then to use formal isolation and quarantine.

How and when we implement all of these measures depends on how severe the disease is and where we expect it to be. We need to plan for the impact of a disease, and we want businesses to plan, too. What will happen if, for example, 10% of your people are sick? Can 20% of your people work from home? Can your business telecommute more? If all our worksites add in telecommuting, do we have the infrastructure to support that? Actually, no, we don't. If, for example, we put all of the University of New Hampshire on the Internet, it wouldn't work. We also have to consider how long we'll need to use any of these measures. It depends on both the disease and the severity of the particular pandemic. It may be three days, seven days, or two weeks.

We need to plan in order to minimize the impact. If we're sending people home and they cannot work, who will bring them food? If we isolate and quarantine people and we don't want them to leave the house, how will they eat? Who will bring food if they may be exposed to the disease? We've been planning for this type of thing and trying to provide proper training for many, many years. At the end of the day, most things actually come back to the basics: Wash your hands and use some protection against respiratory infections. It's not the complete answer, but it does help, dramatically. Do we have the capacity to care for large numbers of people being isolated in a hospital? Normally, for the severe diseases that we've encountered, the answer is no, so New Hampshire has invested in a bunch of respirators that have been placed across the state ready for use in an emergency.

Then we have to think about vaccines. If we're talking about flu, do we have flu vaccines? It's the same every year: We worry that we won't have enough flu vaccine. The production system of flu vaccine is quite archaic. We're still making it in eggs! Each year, in December, we look at what's going on in the other hemisphere. From those observations, we forecast what type of viruses is going to come here next year. Then, in January, we place an order with pharmaceutical companies around the world to produce the vaccine that the northern hemisphere is going to need. That goes into production to be ready by August, to be distributed in September, to start vaccinating in October. It's a nine-month process. But if we have an unexpected pandemic, we don't have nine months.

There has been a good deal of investment to provide different vaccines; different techniques have been developed in an effort to identify better antigens, better components in the capsule of the virus, to provide a long-term vaccine that won't be so impacted by the shifts in the virus. But, we're not there yet. During the 2009 pandemic, we had half a million doses of vaccine, which we got out to the general population as soon as we could. Within the first four weeks, we didn't have enough vaccine to treat everyone. And yet, at the end of the pandemic, I was left holding 150,000 doses of unused vaccine — by the time we'd actually got it through production, it was too late, the pandemic was over.

We do have other weapons in our arsenal. We can use antivirals—medications that, in theory, kill the virus. So far, most flu viruses are susceptible to the antiviral, Tamiflu. We have supplies to treat thousands of people. We keep them in a secure location because if we do need to use them, we need to pick and choose how we distribute them.

Basically, when it comes to flu, we do everything we can to buy time in the hope that we can get a vaccine.

If we have a vaccine, the key question is ethical: Whom do I vaccinate first? Me. If I'm not here, I can't run the show, right? Right. So, who's second? You? OK. Why should I vaccinate you second? Beyond the fact that you are awesome, do you meet any other criteria that might demand that I vaccinate you second? We may choose to vaccinate younger people because there is a higher chance of them infecting others. After all, if I want to stop the transmission, I need to stop the transmitters. I'm not calling the young bad, infectious vectors, but they may be.

We may do that but we also have to consider social value. Do we vaccinate the oldest or the youngest? Do I vaccinate the 65-year-old, like my father, or the 5-year-old, like my daughter? How do we, as a society, come to those decisions, and who makes the call? Who would you think should make that call? Who wants my job?

I'm not alone in all this. I am helped in my decision making by an ethics committee. We have criteria and we know that our decisions will be different in every pandemic. There are

pandemics that will kill more of the young. There are pandemics that will kill more of the old. We need to balance and there is no pre-determined right and wrong.

There are some funky things to be considered, too. For instance, what happens if people start dying? What do I do with all those bodies? If we had the million fatalities that occurred during the pandemic of 1918, we wouldn't have the capacity to process the bodies—I need to figure out where to put them. Then there are the volunteers. Great! Except, please don't help me. Please, don't. If you don't have a clue what you are trying to do you will actually cause me trouble. With the best intentions you leave your work and family to help with the disease, but then, because you don't know what you're doing, you will become sick and I'll have to use other people to help you, to keep you alive.

Volunteers are good news when they've had the training, when they are part of the system, and part of a team. Imagine I need nurses and doctors to take care of you and your mother. Somebody shows up and says to me, "Hi, I'm a doctor. Do you need one?" I can't just say, "Sure, great, go and treat them." I can't do that! My lawyers won't let me because I have no idea who that person is. Thus, we have a system through which we register volunteers ahead of time, and we manage it as well as we can.

What happens if you don't speak English? What happens if you are homebound in a wheelchair? How do we get the vaccines to you? How do we get food to you? How do we get you out of your house if we need to evacuate you? We need to look at all these things, and we need to look at the socioeconomic impact of all our decisions—when we close a school; when we close a public space; when we quarantine somebody; when we don't allow a person to go out for a week, for two weeks, a month, three months, as can sometimes be the case for tuberculosis.

We need to be creative. We know that every time we implement a plan, we'll see that, "Oh, look, this doesn't work as we thought." We learn, and we improve. Hopefully, we'll be ready when the big one comes.

For example, there is a new SARS-type situation happening right now (2013). It's called the Middle Eastern Respiratory Syndrome (MERS). We have cases coming from Saudi Arabia and other countries. It's a new type of Coronavirus that is from the same family of SARS viruses that we had years ago. So far, we have identified the disease in people, bats, and camels. It's not as transmissible as some infections that we have had in the past, but it has the potential to be and is quite severe in those who develop the disease. What we don't know is why some people develop the disease while others do not. Most of the people we've identified have contacts who are healthy. Nevertheless, we're paying close attention because it has the potential to become the next pandemic, the next SARS. What happens if this actually grows a little more in Saudi Arabia and many affected Saudi nationals travel around the world? It won't just be the Metropole hotel, it'll be the Metropole multiplied 100,000 times.⁴

What's going to be the next pandemic? I have no idea. We have systems that allow us to project and try to predict, but we have no way of really knowing. All we can do is keep track of things, and keep the information public so that people know what we are working on. Only

⁴ Stephanie R. Bialek, MD, *et al.*, "First Confirmed Cases of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) Infection in the United States, Updated Information on the Epidemiology of MERS-CoV Infection, and Guidance for the Public, Clinicians, and Public Health Authorities — May 2014," *Morbidity and Mortality Weekly Report*, Centers for Disease Control and Prevention, May 16, 2014, accessed March 3, 2017, <https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6319a4.htm>.

then can we dispel the perception that we're hiding information or doing something inappropriate. We need to be out in public communicating with people. It's a tricky balance because some people will think we are just trying to create fear, while others will say we're making it too easy to prevent disease, which goes against nature. Every time we announce something, we open a whole new can of worms.

So, that's what the Centers for Disease Control and Prevention does: They lead the US Public Health system as we prepare for whatever type of emergencies might occur; we plan for them. Only by preparing and planning can we properly respond. We know that we will never be done because diseases will never stop changing. That's the nature of biology, the nature of ecology, the nature of science. We keep discovering things and the mark keeps moving.

DISCUSSION QUESTIONS FROM THE AUDIENCE

Question #1: I'm curious about surveillance and Big Brother. You said that clinicians are recording outbreaks and incidences, but are people who don't have health insurance represented? Are any groups over-represented?

Response: I am Big Brother, by definition. Who am I looking at? Everybody, as much as I can, in the sense that we get clinical information from different clinical encounters. We get information if you go to your doctor with whooping cough, and if you are uninsured and in the emergency room, I will still get the information. But, if you don't go to the healthcare system, and you don't get a diagnosis, I won't get a diagnosis until you die, and then I will see your death certificate.

Are some groups over-represented? Well, yes, those with better access to healthcare. The reality is that in most cases, the information that we are looking for is there. I try to keep track of population trends. I also try to identify individual cases, so we can prevent spreading disease around them.

If you have a disease, in general, it's not public health's responsibility to treat you. By the time you are reported to us, you have been already prescribed a treatment. My concern is to prevent the disease from spreading, to identify the people who have been near you so we can advise and protect them. "Hey, you were less than four feet away from her. You should get Cipro, or whatever antibiotic is appropriate, right now, because if you don't, you will have this disease." That's the purpose of this Big Brother; we're not here just to keep track of you.

Question #2: What is Norovirus and how is it transmitted?

Response: Norwalk virus—now called Norovirus—is a gastrointestinal infection that has a quick incubation period, around 24 hours or even less. It is easily transmitted by hygiene improprieties like not washing your hands after you go to the bathroom, which is apparently quite a frequent practice around the world, including in this country. You look at schools and the kids go to the bathroom, and then they come out and blow their nose. They say, "Hey, how are you?" and touch and kiss and hug. That's the way that it goes around. Then, there are volunteers at the cafeteria. They touch the food and give you the salad. Then you get sick, and

that afternoon you vomit. Then, when people come and clean, they spread it around even more. That's how Norovirus works.

It is essential for us to identify sick food workers. It's something to which we pay close attention: You have Norovirus; are you a food worker? If you are a food worker, I'd rather not have you working for a couple of days because, even with good hygiene, there is a chance that you're going to infect others.

You have Hepatitis A. Are you a food worker? I would rather not have you working while you are acutely infectious because you may contaminate the food. If you do, then I will have to do a clinic as we did three months ago in Hopkinton, NH. We vaccinated 1,000 people—maybe only 300 went to the affected restaurant but 700 others came for the vaccine. That's the way that these things work.

Question #3: New Hampshire is famous for being a libertarian, “Live Free or Die” state.⁵ Does that make your job harder than it might be in another state? Do you get people and politicians complaining that you're infringing too much on individual liberty more than you would in, say, New York or California?

Response: Yes. As you say, New Hampshire is a libertarian state. That's the ethos of our society, and as an organization we are quite careful and respectful of that. We have had interesting discussions with elected officials over the years. Actually, there is one official who openly calls me Big Brother, and we have a really good working relationship. He's an incredibly smart fellow, and we just have a different philosophical construct about what we should do. Most people, including the elected officials, understand our purpose.

Question #4: It strikes me that these bugs don't respect political boundaries very well, and I've always been curious why we have a state public health mechanism to respond to these things. Why don't we do it at the national level or even at the international level? Is there a particular advantage in dealing with these problems at the state level?

Response: That's federalism for you. We are a union of equals and each state has the sovereign right to do as it feels appropriates—“Don't tell me what to do, federal government.” However, we do have the Centers for Disease Control and Prevention (CDC), which is a broad national organization that does a lot of research, develops strategies, and consolidates data so that we can look at things nationally or regionally.

The list of reportable conditions is different state by state. We don't have a national, unified list. The state epidemiologists get together every year and look at the list and add things, but then every state needs to adopt the list and not every state will. As an example, New Hampshire has never adopted Hepatitis C as a reportable condition. I think we might be the only state that still hasn't done so.⁶

That said, when emergencies do happen, we work with the other states and with our regional partners. In New England, the six directors of public health speak every Monday morning at 7:30 am via phone. We go over what's cooking and what we are doing. We realize that a lot of the things we need to do are education-related. If I come and say everybody needs

⁵ The New Hampshire state motto is “Live Free or Die.”

⁶ Since Dr. Montero's talk, Hepatitis C has been added to New Hampshire's list of reportable conditions.

to stay home, and the commissioner in Massachusetts says, “I don’t care,” that is a big mess because, in addition to us, there are the talking heads who make big bucks every time they talk in and to the media. And you *know* they’ll talk about this.

So, we do work in a coordinated manner. For example, we are trying to figure out regionally what to do with Lyme disease. We’re not going to kill all the deer, so what messages can resonate across the region? We have a significant media market in Boston and then smaller media markets—Burlington, VT; Augusta, ME; Portland, ME; Manchester, NH—that don’t have the same penetration. How do we manage those media markets and unify messages between all of us? We are working on those types of things. There is hope, but there will never be a fully unified system because, as I say, we are a union of equals. We have the right to do as we please; it’s the people who elect the officials, and they are the ones who decide... I just execute.

Question #5: Do you think the Affordable Care Act will make your job easier?

Response: I don’t know if it’ll have a huge impact on emergencies. In general, we manage the treatment of infectious diseases. If you have tuberculosis but don’t have insurance, we figure out a way to get you treatment. If you have whooping cough and you don’t have the antibiotics, we figure out ways to help you.

In a big emergency, I don’t know how much the hospitals would bill for each individual thing. We had this discussion when we talked about preparing for the flu pandemic: Who will pay? In general, insurance will pay for those who are insured. From that perspective, having everybody insured will decrease the financial risk. Also, with the Affordable Care Act came the creation of the Health Information Exchanges. Health Information Exchanges give us a quicker reporting system for health diagnoses that may be of public health interest, and from that we may detect or keep track of things in different ways.

Right now, we keep track of the trends in emergency rooms and when we identify a patient of special significance, we go back to the hospital and ask that they talk to their doctors. Or, we ask the hospital to contact the patient and confirm the diagnosis so we can then get to that patient. Those are matters with which the Affordable Care Act can help us, from an emergency response perspective.

Question #6: Do the public health authorities ever consider withholding information that might be useful to individuals when deciding on appropriate action, because you’re afraid of how we will act if we have that information?

Response: No, I do not consider withholding information as a standing principle. However, what information is relevant at any particular time will vary. Let me give you three real-life examples:

There’s a 57-year-old woman with meningitis, living with her husband. Meningitis is quite infectious, has a high risk of transmission, and in general, a 10% mortality rate, give or take. We investigate and discover that this person stays home most of the time. We cannot identify the source of the disease; other than her husband, nobody was ever really exposed to her. We treat the husband. We don’t treat the woman; she’s not our patient; she’s the doctor’s patient. She interests us, but only because we’re concerned about the population around her.

What benefit does it bring to put out a press release every time a case of meningitis occurs? None, because it doesn't have any direct impact on the health of the public.

This is actually an ongoing discussion with a couple of media outlets in New Hampshire that get quite upset every time they realize there was a case that I didn't tell them about, but there is no information to give them in that particular case.

Now, what if you have a case of meningitis in a 14-year-old high schooler? You start looking. What does he do? Where does he go? Almost as soon as you start the investigation, you find a second case. Right then, I go public, not to create panic, but because I need the information to flow incredibly quickly. What if we are missing something because this kid is unconscious in an intensive care unit, or, perhaps, he won't tell me whom he kissed; whom he had sex with; whom he smoked marijuana with or shared a cigarette or toothbrush with? I go public.

Now we have two cases of a particular disease in a school. We are investigating, identifying the cases. We never identify the patient, but that's tricky for us because if we're asking for information without identifying the person we're talking about it becomes complicated. Most of the time, though, the community knows and will help us identify things.

In another example, a month ago we received a report of a patient who died and the clinician thought the person had Creutzfeldt-Jakob disease—a protein-particle disease related to Mad Cow Disease. Just the mention of Mad Cow creates anxiety in a lot of people, but we don't release the information because we don't actually have Mad Cow Disease; we have somebody who died with a disease that you see once in maybe a million deaths a year. What we do, however, is start investigating and, in this case, we found out that the person had brain surgery before he died—the alarm bells start ringing.

Confirmation of the diagnosis takes a month. Do I sit on that, or do I act? Typically, we would act, and we did. I called a bioethicist and asked him to help me out, because nobody in recent American history has dealt with a situation like this. You have a person who had dementia symptoms and had brain surgery, and the equipment that was used on this person was then used on eight others. There was a piece of equipment that came from out of the state, was used on this patient, and was then sent back out of the state and used on patients in two other hospitals outside of New Hampshire. The national recommendations are to wait until the case is confirmed. But what is the balance of risk? What if this is a case of Creutzfeldt-Jakob disease? What if any one else was exposed to it? Should we wait the four weeks not knowing? We decided not to wait. Dealing with the information that we found, thought, or feared, was really important to the public so we went public.⁷

These were three different scenarios, all of them real. Getting it right is incredibly tricky. The media's mantra is "if it bleeds, it leads." That's why the news broadcasts start with the fire, follow with the car accident, and *then* get to the change in national policy. As consumers, we ask for that and they deliver. When you open the browser on your computer, you typically don't go to see what the latest change in policy was; you go for the funky picture with the bleeding car.

I am incredibly careful and mindful of our interaction and relationship with the media and make every effort to provide proper information. No one other than the infected patients needs to worry about the flesh-eating bacteria, and I don't want people panicking and doing stupid things. But at the same time, I'm not going to lie to the public—everything I say is on

⁷ This diagnosis was eventually confirmed.

camera and live. Somebody is going to come back to haunt me with whatever I said in a particular forum or setting.

No no, we don't withhold information. Rather, we strive to be first, to be accurate, and to be right. When I don't know, I will say so. I'm not going to make it up. If I make it up and I'm wrong, somebody's going to let me know and it won't be fun.

Question #7: I'm curious about your take on the concept of eradication—like with smallpox. The virus does still exist [in labs] and the vaccine does exist, so from the point of view of preparedness... what if? How do you approach that as a public health officer, practically? What's your take on the decision, for example, not to vaccinate people for a disease like smallpox? Is that smart, because the risks outweigh the chance of getting the disease?

Response: We don't have polio in the US and we do still vaccinate. In general, we don't have diphtheria in the US but we still vaccinate because the virus is circulating around the world. In Syria right now [in 2013], with the civil war, they've had outbreaks of polio—it's a disease that can still come.⁸ The problem that we face as a society, and I face as the head of public health, is that nobody in this room has ever seen a case of polio. Nobody here has ever seen a case of diphtheria. I have seen only one case of tetanus in my life, and that was in a different country. People don't realize that these things can actually happen and when they do, they are quite severe. For such diseases that are still circulating, we still need to vaccinate everybody—if we don't, they will come back. It may not impact me, because I am already vaccinated and immune, but it will impact our children, and they will die, and that's the problem.

Smallpox is a whole different animal—it's the only disease that, through vaccination, we have eradicated from being a human harm. But we are faced with different discussions: Do humans have the right to kill the virus? If we do, we will have eradicated something that was natural in the world—that's one dilemma. In theory, there are two big reservoirs of smallpox in the world, one at the CDC and one in Russia, somewhere in Russia. So, a second discussion is: Do we vaccinate or not?

My opinion is no, we don't. The disease is not circulating and there is no imminent risk of it re-emerging. However, that doesn't mean that we shouldn't vaccinate selected groups. I was vaccinated against smallpox 10 years ago because if we do have an outbreak, we need a group that can take care of the first set of patients as we start vaccinating people again. Smallpox vaccine was developed at a time when the disease was fatal to 30 or 40% of sufferers. In the face of that statistic, a vaccine that caused severe complications in 10% of recipients was acceptable. But I won't give that vaccine to the general populace when the disease does not exist. I simply cannot afford the risk. People get really mad at me when they get a fever or headache from a flu vaccine. Imagine the uproar if people died or developed encephalitis or other big, severe complications from a smallpox vaccine! So, we don't vaccinate, and I won't ask people to be vaccinated population-wide. In fact, we are now struggling because we should give boosters of the smallpox vaccine every 10 years—who among the people I vaccinated in my office 10 years ago are still with me and should be re-

⁸ Polio is not endemic in Syria in March of 2017.

vaccinated so that I have a small, five-person cohort ready to go out and immunize the whole population should we ever need to?

CLASS EXERCISES

Management of SARS

- Divide the class into groups that will represent Hong Kong, Vietnam, Canada, and the United States.
- Each group is responsible for researching—via the Internet—how their respective country first identified Severe Acute Respiratory Syndrome (SARS), the number of cases of those sick with the disease, and the number of those who died from the disease.
- Each group is responsible for researching—via the Internet—how their respective country managed SARS (i.e., who was involved in disease management and what specific policies were implemented).
- Each group will critique their respective country's response to SARS and propose a new management strategy for the next novel disease outbreak.
- Each group will present their strategy to the class.

Public Health Preparedness

- Divide the class into groups that will represent different states in the nation.
- Each group is responsible for researching—via the Internet—the pandemic flu preparedness plan for their respective state.
- Each group should identify as many components in the plan as possible that relate to Dr. Montero's lecture. For example, what is the organizational structure in the event of a flu pandemic? Who is in charge? Identify any other organizations that are involved. Is there an organization that is not involved but which you think should be involved? Explain.
- Describe the plan to identify those you should vaccinate first. Do you agree with the state's rationale? Explain.
- When will isolation and quarantine measures be implemented in the plan?
- Describe the plan to manage mass casualties.
- Each group will present a brief overview of their respective state's plan, highlight the two or three most important points in the plan, and explain the rationale for their selection.

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Chapter 83

FROM SMALLPOX TO POLIO: HOW AMERICA EMBRACED VACCINES

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INTRODUCTION

The theme of the Sidore lecture series inspired Dorsey's essay in which she discusses events and decisions related to personal liberty and bodily integrity. This chapter is included in the book to show a historical trend that deepens our understanding of American society's general willingness to use vaccines. The three examples she discusses are smallpox inoculation in colonial Boston, diphtheria toxin-antitoxin injections in early twentieth century New York City, and the polio vaccine trials of 1954. While Dorsey acknowledges that not all Americans react positively to all vaccines at all points in the history of the US, she demonstrates that there are noteworthy examples when significant portions of the lay population involved in key vaccination drives embraced vaccines. This occurred even at times when science had not proven a vaccine's effectiveness, such as in colonial Boston, or when there were no governmental mandates driving vaccination, such as in the polio trials. Sometimes popular support for a vaccination campaign occurred even in the face of official and expert opposition or debate among experts. In other words, these campaigns were not solely driven by governments or even scientific or medical experts attempting to convince lay populations to accept vaccinations because of legal compulsion or simply because of trust in science. Thus, at key points in US history we see that there has been a partnership between a lay population and segments of the scientific or governmental communities to adopt vaccines; implementation of vaccines has not always been the result of a top-down imposition of policy, nor has the growing acceptance of vaccines been a strictly scientific or legal story.

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ESSAY

Polio scholar Jeffrey Kluger tells a story about an anonymous woman in 1955 who was so desperate for her child to receive an early version of Jonas Salk's polio vaccine that she acquired it illegitimately, visited a doctor's office, told the physician to inject her child, and ordered him to ask no questions about the vaccine's origin.¹ The new vaccine was not 100% effective, as a recent study had proven. It certainly was safe, and it provided protection against polio, but some children who received it would nevertheless succumb to the disease.² Still, at a time when there was no cure and no effective treatment, this was the best that medicine had to offer during a decade when polio attacked tens of thousands of children every year in the US. The public embraced the vaccine and parents *chose* to have nearly two million children—an incredible number—take part in the polio vaccine trials in 1954; they did not participate because the law compelled immunization. Hundreds of thousands of citizens volunteered to help administer the national trial; they did not take part because the government pressured them to do so.³ Instead, people participated—as recipients of the experimental vaccine and as enablers of the trial—because they had been educated about the vaccine's potential and because they believed in the need for a polio vaccine.

It is not inevitable that vaccines be accepted by laymen as standard tools for disease prevention. Vaccines are, by definition, an intrusion into personal autonomy. To prevent a disease, someone injects chemical and biological matter into another's body or, in the case of inhaled vaccines like FluMist, blows the matter into the patient's nose. Today, most vaccines are given to children, people who have no say in whether or not they get a vaccine. Thus, the debate about vaccines infringing upon personal liberty is really centered on whether the government may *compel* someone to get a vaccine or whether an individual (or his or her parents) may *elect* to get the vaccine. It must be said that as it is always illegal, in this country, to hold someone down in order to administer a vaccine; there has to be some element of volition.

Today, studies reveal that the vast majority of Americans accept vaccination as a shield against disease.⁴ While no one looks forward to getting a shot, anecdotally it is clear that for most who do get vaccinated it is, at worst, a routine chore, and at best, a moment to be grateful for modern medicine. The majority of concerns are inconvenient side effects, such as fevers or sore arms, and the bulk of frustrations are about scheduling and cost. There are legal requirements in place, but probably they serve as tools to encourage families to vaccinate children on a particular schedule—it is more of an incentive to take the time to visit the doctor in a timely manner than to convince patients of the benefits of vaccination in the first place.

No attitude is universal, of course. There is a recognizable minority that resists vaccines for religious or philosophical reasons, and there are others who abstain from optional vaccines, such as the annual flu shot, for reasons of convenience or lack of faith in that

¹ Jeffrey Kluger, *Splendid Solution: Jonas Salk and the Conquest of Polio* (New York: Berkley Books, 2004), 308.

² *Ibid.*, 294.

³ David M. Oshinsky, *Polio: An American Story* (New York: Oxford University Press, 2005), 286.

⁴ Monica Anderson, "5 Facts about Vaccines in the U.S." *FactTank: News in the Numbers*, Pew Research Center, July 17, 2015, accessed January 19, 2017, <http://www.pewresearch.org/fact-tank/2015/07/17/5-facts-about-vaccines-in-the-u-s/>.

particular vaccine.⁵ There are some who cannot be given vaccines because of medical reactions to the ingredients. There is also a distinct minority who rejects vaccines because it fears government conspiracies about the ingredients or is convinced that they cause harms such as autism. In general, though, vaccines are a normal, accepted part of medicine, and a very common part of standard medical care for children.

It has not always been so. At different times in American history, vaccines have not been embraced for a variety of reasons. At times vaccines have been forced upon the public and challenged by patients fleeing syringe-wielding officials. For example, these reactions occurred in some US cities around the turn of the twentieth century in response to localized campaigns to vaccinate against smallpox.⁶ One of the most famous instances of resistance was Pastor Jacobson's stand against the mandatory smallpox vaccine in turn-of-the-century Boston: Jacobson believed the vaccine endangered him because of his physical or genetic make-up. The case was immortalized in *Jacobson v. Massachusetts*, the US Supreme Court case that rejected the pastor's appeal and that authorizes mandatory vaccinations to this day.⁷

At other times, scientists and governmental authorities have sold vaccination, and its forerunner, inoculation, to the American public as a legitimate, useful tool, and sometimes, a medical marvel.⁸ The fact that vaccines are now considered routine by most people is proof that they have become effective and safe. However, this is not just a top-down, one-way story of governmental and medical officials selling or compelling the public to get vaccines. At times significant segments of the public have helped to sell—as well as to buy—the idea of vaccinations. A key thread of the vaccination narrative, therefore, is that of a partnership, with the public seeking to engage actively in vaccination campaigns. In specific campaigns, the audience has sought to participate through fundraising and vaccine administration, as well as by seeking access to both experimental and proven vaccines.

Furthermore, the campaigns to sell vaccines have not always revolved—or at least, not solely—around confidence in science. They have depended upon non-scientists, upon techniques associated with advertising, upon parental desires to protect children, and upon other factors beyond the world of laboratory science and medical professionalism. The story of our embrace of vaccines, therefore, includes case studies that illustrate that scientific progress and acceptance does not happen in a vacuum; emotional factors, lay enthusiasm, accessibility, and other factors, all helped to shape the increased popularity of vaccines.

While vaccines have traditionally been seen as a battlefield between the government and the individual, sometimes the government plays a very minor role—as in the Salk vaccine

⁵ Gretchen Gavett, "The Vaccine War: Why Aren't Parents Vaccinating their Children?" *PBS: Frontline*, November 28, 2011, accessed January 19, 2017, <http://www.pbs.org/wgbh/frontline/article/why-arent-parents-vaccinating-their-children/>. Regarding popular reasons for not getting the flu shot, see, for example, McLaren Greater Lansing, "5 reasons people skip the flu shot but shouldn't," *Lansing State Journal*, December 24, 2015, accessed January 19, 2017, <http://www.lansingstatejournal.com/story/sponsor-story/mclaren-greater-lansing/2015/12/24/5-reasons-people-skip-flu-shot-but-shouldnt/77851410/>; "10 bad reasons for skipping the flu shot this year," *Consumer Reports*, January 2013, accessed January 19, 2017, <http://www.consumerreports.org/cro/2013/01/10-bad-reasons-for-skipping-the-flu-shot-this-year/index.htm#>; and Jane E. Brody, "Myths about the Flu Vaccines," *The New York Times*, March 11, 2013, accessed January 19, 2017, http://well.blogs.nytimes.com/2013/03/11/myths-about-the-flu-vaccine/?_r=0.

⁶ In Michael Willrich's book about the history of smallpox vaccination in the United States, he describes several protests in a variety of locations and over time. Michael Willrich, *Pox: An American Story* (New York: Penguin Books, 2011).

⁷ Willrich, 285–366 describes the story of *Jacobson v. Massachusetts* in detail.

⁸ Note that the very title of Kluger's book about polio is *Splendid Solution*, which refers to the Salk vaccine to prevent polio.

trials or the New York diphtheria campaign—or an unexpected one—as in colonial Boston. Sometimes, the public even makes the free choice to be on the same side as the government.

To illustrate this, and to understand how the long-term history of American vaccination has helped shape cultural attitudes and behaviors towards the process today, it is worth looking at three major diseases and key points in the distribution of their associated vaccines: smallpox in colonial Boston; diphtheria in New York City, 1929 – 1931; and the Salk polio vaccine trials across the US in 1954.

SMALLPOX INOCULATION

The first major vaccination effort in what would become the United States involved neither vaccinations, technically speaking, nor a governmental campaign. Instead, the focus of effort was on the *opportunity* to get inoculated against smallpox in colonial Boston.

Smallpox is a disease that once terrified the world's populations. Today, it is eradicated, living on only in a few laboratories and in our fears of bioterrorism. When it circulated naturally in the world, smallpox was a disease that could appear anywhere, any time. When it did emerge, it could cause epidemics with fatality rates of up to 30%. Scars often disfigured survivors and blindness could handicap them. As with many viruses, there were versions of the disease that were relatively minor. The worst strains, however, demanded fear and attention. They not only killed in great numbers, but also in a gruesome manner. Victims died slowly, painfully, and visibly, suffering from high fevers, vomiting, and erupting pustules.⁹ There was nothing anyone could do for victims except provide palliative care. The one method of prevention was to avoid the disease, through isolating the sick or quarantining the potentially sick. The one blessing was that if you caught the disease and survived, you were immune for life.

In colonial Boston, news of a technique to stave off fatal smallpox caught the attention of physician Zabdiel Boylston. As importantly, it also intrigued Cotton Mather, the most prominent clergyman in Boston in an era when religious figures wielded enormous social as well as religious power.¹⁰ The technique was inoculation—the insertion of a minimal amount of smallpox from one victim's pox into a cut in the arm or leg of a healthy individual. Ten days or so after the procedure, the recipient would become sick with smallpox. If everything were done correctly and the patient had a robust immune system, the case would be mild; the recipient would get well and possess a lifetime immunity to any kind of smallpox. He traded a short-term illness, albeit a serious one, for lifelong protection.

This is, of course, not quite vaccination but is, rather, the forerunner of it and served the same purpose. It was not invented in Boston in 1722—as Boylston and Mather knew—but had been practiced in Africa for some time. Still, it was new to Boston, both because it was a novel way to prevent smallpox in North America and because inoculation was an innovative idea to the settlers.¹¹ Even so, for some residents of Boston, the risk of inoculation seemed

⁹ For more details, see “Smallpox Fact Sheet: Smallpox Overview,” *Centers for Disease Control and Prevention*, updated January 15, 2016, accessed January 19, 2017, http://www.ct.gov/dph/lib/dph/communications/cerc/smallpox_fs_web.pdf.

¹⁰ John B. Blake, “The Inoculation Controversy in Boston: 1721–1722,” *The New England Quarterly*, 25, no. 4 (Dec., 1952): 490–492, accessed January 19, 2017, <http://www.jstor.org/stable/362582>.

¹¹ *Ibid.*

much smaller than the risk of catching smallpox naturally, and approximately 200 people came to Boylston to try it.¹²

In eighteenth-century Boston, religion influenced law, public opinion, and culture, and it was vital that both a clergyman and a doctor together endorsed the new approach. This was an era in which physicians did not dictate medical matters, and supporters—as well as those who underwent inoculation—faced substantial opposition. One might think that people scared of smallpox, people who knew how grisly dying from smallpox could be, to say nothing of the high rate of mortality associated with it, would embrace any method of avoiding the disease or limiting the damage it inflicted, especially in the middle of a local epidemic. That was not the case, however.

There were clearly some potential philosophical and scientific problems with inoculation. First, it is dangerous to infect an individual deliberately with the contents of a pox gleaned straight from someone else's body. Consider the following issues: Is that the right disease? Will the right amount be transferred? Will the technique communicate another disease, perhaps through an unsterile tool, that will make the recipient ill? Second, once the recipient has been inoculated, will he communicate smallpox to someone else, perhaps a caretaker or a member of the public, while he is sick? Will he, in fact, start an epidemic? There were also moral and philosophical problems: should doctors insert diseased material into a healthy person? If the Hippocratic oath orders, "First do no harm," then how can a doctor deliberately make someone sick, even if the goal is to protect him or her for the future?

Dr. William Douglass, a powerful and vocal physician, was a leading opponent to Boylston's inoculations. It was wrong, he said, according to the laws of God and man, to poison someone. Furthermore, it was dangerous, risking the health of the recipient and his community, especially since Boylston did not take strict precautions to quarantine the recipient and his caregivers while he was contagious. In return, Mather argued that Africans had been inoculating for years; this was not a new-fangled or unproven technique.¹³ Rather, it was a confirmed method of preventing a great danger: an epidemic.

Boston's epidemic lasted just over a year. Of Boylston's roughly 200 inoculated patients 2–3% died, and he claimed that those victims died not from the inoculation but from other causes. Overall, in a city of 11,000, some 6,000 caught smallpox and 15% of those sufferers died.

Nevertheless, officials were not convinced. Instead, the tried-and-true method of quarantines remained the only legal, as well as the dominant, method of preventing smallpox. Soon, the city enacted laws banning inoculation.¹⁴ Unlike today's arguments that compel an injection for the sake of the general public's health, here was an authority banning individuals from taking a personal risk for fear that it would endanger others. Yet, some 200 people believed that the risk was worth it, and they were sufficiently convinced to go against the

¹² "The Boston Smallpox Epidemic, 1721," *Harvard University Open Collections Program, Contagion: Historical Views of Diseases and Epidemics*, accessed January 19, 2017, <http://ocp.hul.harvard.edu/contagion/smallpox.html>.

¹³ Matthew Niederhuber, "Special Edition on Infectious Diseases: The Fight Over Inoculation during the 1721 Boston Smallpox Epidemic," *Harvard University, The Graduate School of Arts and Sciences*, December 31, 2014, accessed January 19, 2017, <http://sitn.hms.harvard.edu/flash/special-edition-on-infectious-disease/2014/the-fight-over-inoculation-during-the-1721-boston-smallpox-epidemic/>.

¹⁴ "Mass Moments: June 26, 1721: Dr. Boylston Experiments with Smallpox Inoculation," *Massachusetts Foundation for the Humanities*, June 26, 2005, accessed January 19, 2017, <http://www.massmoments.org/moment.cfm?mid=186>.

majority and to take the time, effort, and risk to seek out a doctor for a procedure that was new and had no proven track record. Of course, the danger of the disease itself partially convinced them, as did the support of two prominent members of society. Specifically, Mather's public verbal support, as well as his evidence—although based on hearsay—of African experiences with the technique helped to persuade people. And Boylston's evidence that he had subjected his six-year old son and two slaves to inoculation also provided convincing data.¹⁵ Some Bostonians were, indeed, sold on the idea that science could provide protection, even when the medical technique was, in some ways, outlandish. It is all the more remarkable when one remembers that medicine at the time lacked knowledge about the germ theory, antisepsis, and many other scientific discoveries that have since helped make doctors effective healers.

Smallpox vaccination did become more accepted over time, especially once Englishman Edward Jenner developed the cowpox variolation technique of transferring cowpox to humans in 1796, which provided humans with immunity to the related smallpox but did not risk an epidemic. However, during the eighteenth century, when inoculation was still the method used, and even into the twentieth century, after vaccination had been developed, people have rejected smallpox vaccines in different places, at different times, for a variety of different reasons.¹⁶ It has certainly not been a universally popular vaccination, partly because of its side effects.

However, to recap, it is important to realize that even before the science behind vaccination (and inoculation) gained the trust of the wider population, there were debates in public between those trying to prevent inoculation and those trying to sell it to the public. The legal role was the opposite of that seen today: it sought to prevent vaccination rather than require it. Yet, a substantial minority in Boston actively risked public censure to seek out a vaccine with no local track record. This group, then, participated in a partnership with Dr. Boylston to gain immunity. It is true that 200 or so people did not constitute a majority or even sizable portion of the population, but it is still an impressive number when one recognizes the novelty of the inoculation process and that the patients hazarded social and legal consequences in order to take a stand. Today, it is the “anti-vaxxers,” those who reject vaccines, who are the minority, but in colonial Boston, with the “pro-inoculators” we begin to see the first steps in the general public embrace for vaccines.

So, what happened next?

THE DIPHTHERIA PREVENTION COMMISSION

A major turning point occurred in the 1920s and 1930s when New York focused on diphtheria, one of the next diseases for which doctors developed a preventive. Unlike smallpox, diphtheria is still in circulation, although the CDC says there have been fewer than five cases in the last ten years in the US. Diphtheria is the “D” in the DPT (diphtheria-pertussis-tetanus) shot that every schoolchild gets and that many adults receive as a booster.

¹⁵ Blake, 492.

¹⁶ For some examples, see Willrich and “The 1730 and 1774 Marblehead Riots against Smallpox Inoculation,” *New England Historical Society*, accessed January 19, 2017, <http://www.newenglandhistoricalsociety.com/1730-1774-marblehead-riots-smallpox-inoculation/>.

While pertussis (better known as whooping cough) and tetanus are the diseases of most concern today, diphtheria, in its heyday, was a killer, particularly of children. It could have a fatality rate of 50% of its victims before a treatment was developed, and as an example, more than 200,000 children caught it in the US in 1921.¹⁷ It was a major threat.

What is diphtheria? Diphtheria does not kill everyone, nor does it kill as spectacularly as smallpox. It is an upper respiratory illness in which bacteria produce toxins that can damage many parts of the body. It is most well-known for destroying parts of the respiratory tract, and the dead cells make it challenging, if not impossible, to breathe.¹⁸

The facts that it was not only a potentially fatal disease, but also one that targeted children, particularly those of nursery-school age, were major factors in the campaign to convince parents to protect their children in the early twentieth century. Another key element was the timing of the effort. The 1920s and '30s were a golden age of advertising development; the confidence in marketing and the techniques available made it reasonable and feasible to mount a widespread and varied campaign.

Then, of course, there was the science. Medical science had made great strides since the days of colonial Boston. The development of the germ theory of disease, new technology such as x-rays, and new medications such as aspirin, made mainstream medicine more effective and trustworthy. The most important of these was the germ theory. The recognition of germs, particularly bacteria, led to a focus on scientific medicine in laboratories, and applications of this work included the tests for diphtheria immunities as well as anti-toxins.

The most famous diphtheria vaccine was, as in the colonial smallpox story, not actually a vaccine. It was a toxin-antitoxin, and its spectacular popular success belied the fact that it may not, actually, have been responsible for all the drops in the number of annual cases of diphtheria in New York between 1929 and 1931. Since the disease peaked and ebbed in New York in multi-year cycles, reductions in childhood diphtheria cases may have been the result of natural ebb as well as the impact of the vaccine, especially during the first year of the campaign. Still, the campaign of the late 1920s was and is recognized as a successful vaccination effort.¹⁹

The key component of this so-called vaccine was an antitoxin. An antitoxin is a mixture that treats, or combats, the toxins in a disease. A vaccine, of course, prevents the disease in the first place. Yet, by mixing the diphtheria antitoxin with the toxin, and then injecting it into healthy children, the effect was, in laymen's terms, to give them and treat them for the disease simultaneously. Before this—even once scientists knew about the efficacy of antitoxin—antitoxins were only administered to an already sick child. Thus, unlike with smallpox, there was a treatment before a vaccine was available.²⁰ However, the antitoxin alone did not always work.²¹ Children could, and did, still die, and those around them could, and did, still get sick. The toxin-antitoxin injections thus logically appeared to be a much better approach, not only in decreasing fatalities but also in avoiding the disease entirely.

¹⁷ "About Diphtheria," *Centers for Disease Control and Prevention*, updated January 15, 2016, accessed January 19, 2017, <http://www.cdc.gov/diphtheria/about/>.

¹⁸ "Diphtheria Symptoms," *Centers for Disease Control and Prevention*, updated January 15, 2016, accessed January 19, 2017, <https://www.cdc.gov/diphtheria/about/symptoms.html>.

¹⁹ Evelyn Maxine Hammonds, *Childhood's Deadly Scourge: The Campaign to control Diphtheria in New York City, 1880–1930* (Baltimore: The Johns Hopkins University Press, 1999), 216.

²⁰ Jacob Heller, *The Vaccine Narrative* (Nashville: Vanderbilt University Press, 2008), 35 and 36.

²¹ Hammonds, 123.

There was another development that made the campaign worthwhile: the ability to test for diphtheria immunity. There are some diseases, such as smallpox, that leave visible traces on their victims. Smallpox survivors are known for the scarring that the pustules leave behind, including on their faces. Anyone can recognize them. Until recently, recipients of the smallpox vaccine revealed their protected status because of the special scars that the vaccines left on their arms: lines and dots in a pattern an inch or so wide, that indicated where a stylus (or point) scratched the skin to inject the cowpox derivative. What could not be shown, however, was how long ago the vaccine had been administered and whether it had immunized or still protected the recipient. (The smallpox vaccination was not like the smallpox inoculation that gave permanent protection to those who received it.) In 1902 in Cambridge, Massachusetts, for example, the authorities required revaccination if an individual's last vaccination was five or more years ago.²² Diphtheria was different: a test was developed to indicate whether or not an individual was susceptible—the Schick test.

In the Schick test a tiny bit of toxin was injected beneath the surface of the skin to see if a red or brown skin reaction developed. A medical expert “read” the site every 24-hours for four days. The true “positive,” or “absence of immunity to diphtheria,” could be distinguished from false positives, or “pseudo” reactions, partly by recording the length of time that the injection site remained discolored.²³ Depending upon the results, it was proven that the tested individual either had or did not have current immunity to diphtheria. While the test was theoretically simple to administer and read, the clearest results came from using control tests and true Schick tests simultaneously. A patient received heated toxin (one in which the diphtheria proteins remained but the toxin was inactivated) in one arm and the live toxin in the other arm, thus ensuring that any redness did truly come from the toxin and not the proteins.²⁴ Giving the test could save time and money as well as provide reassurance. Medical practitioners and parents would know whom to vaccinate. As important, perhaps, was the confidence it inspired: parents *knew* their child was safe from diphtheria, and they had more reason than before to believe in scientific methods providing that protection.

The ability to provide such a shield against diphtheria, an invisible shield, was believable—and so easier to sell—if you could prove that it truly was an effective barrier to the disease. Yet those who pushed the importance of the diphtheria toxin-antitoxin did not leave it just to logic. Non-legal tools and community members, from individuals to non-profits and commercial businesses, actively participated in a campaign of education, the administration of a campaign to vaccinate young children, and the provision of patients to vaccinate.

Of course, the campaign also involved medical personnel, but not the same medical personnel as would be most heavily involved in vaccine efforts today. Before the 1929 campaign, people did not usually go to a doctor's office for the diphtheria toxin-anti-toxin shot either routinely or preventively.²⁵ Instead, you consulted a doctor for antitoxin after you caught the disease or were exposed to it. New York wanted to change that. Here was a chance to show that laboratories and public health could work miracles. If enough children were

²² Willrich, 285.

²³ Association of Schools of Public Health, “The Schick Test and Active Immunization Against Diphtheria,” *Public Health Reports (1896–1970)*, 34, no. 20 (May 16, 1919): 1064–1065, accessed January 19, 2017, <http://www.jstor.org/stable/4575155>.

²⁴ Hammonds, 181 and 259–260.

²⁵ *Ibid.*, 203.

vaccinated, perhaps a whole disease could be “eliminate[d] . . . in New York City within two years,” or at least fatalities could be greatly reduced among the vulnerable population of children.²⁶

How should or could New York do this, though? How do you find the appropriate-aged children? How do you convince them (or rather their parents) to get the toxin-antitoxin? How do you keep track of the records? What about the costs? The fact that family doctors were not particularly involved—this was a public health measure, not a private medical endeavor—made it all the more confusing.

It turns out that among the most important tools at the disposal of the campaign were volunteer groups, but not necessarily ones with any medical training. The local branches of the Junior League, a national women’s group, and the Lions, a national men’s service group, were two of the most active organizations. In the town of Newburgh, near New York, Junior League women took on the painstaking job of searching through census records to find the names, ages, and (hopefully) current addresses of nursery-school age children. The Lions Club offered lollipops to those who received shots.²⁷ (Decades later, Dr. Jonas Salk would provide lollipops when he gave the first polio vaccines, too.)²⁸

Still, more efforts had to be made to inform children and their families at the neighborhood level. Some of this information did come from organized public health entities—nurses visited homes trying to sell the idea. But why not make it fun and add a dash of peer pressure? Public schools competed with one another to see which could get the most children vaccinated. Others gave out tokens indicating that someone had been vaccinated, such as a badge one could wear and show off.²⁹

The media sold the campaign in myriad ways, in newspapers and on the radio, through editorials, news stories, and advertisements. Politics and the media combined when one mayor created a photo op out of his children’s vaccinations—it was one more way to promote the toxin-antitoxin.³⁰

Yet, it was not simply a competition or an advertising campaign. This was serious business, and the organizers noted that in their approaches. In the nineteenth century, for example, women had been told that, since cleanliness and health were connected and they were in charge of housekeeping, they were responsible for much of their family’s well-being. Now they were told that it was their fault if a family member fell ill with a disease associated with diphtheria, in part because they could prevent the disease through vaccination.³¹ Thus, the stick of moral persuasion was used as well as the carrot of possible protection. What was not part of this campaign was the legal compulsion we see today, even though it did exist for smallpox in some districts at the time. No school banned children who had not been

²⁶ Ibid., 192.

²⁷ James Colgrove, *State of Immunity: The Politics of Vaccination in 20th Century America* (Berkeley: University of California Press, 2006), 90.

²⁸ Kluger, 257 and Eileen Ogintz, “The Polio Pioneers,” *Chicago Tribune*, August 7, 1990, accessed January 19, 2017, http://articles.chicagotribune.com/1990-08-07/features/9003060335_1_polio-pioneers-dead-polio-virus-salk-vaccine/.

²⁹ Colgrove, 90–92.

³⁰ Ibid., 91–92.

³¹ For a more in-depth discussion of housekeeping, health, and women, see Nancy Tomes, *The Gospel of Germs: Men, Women, and the Microbe in American Life* (Cambridge: Harvard University Press, 1998), 135–156. Hammonds, 192–193 and Heller, 40.

vaccinated. Such leniency avoided the resistance— sometimes violent resistance—that had been seen towards the smallpox vaccine at various times around the country.³²

There is one other factor that was critical to the campaign: how to pay for it all. The campaign organizers were clever and sought substantial private funding, both from business and from a charity. Met Life, an insurance company, was a smart choice.³³ It had a vested interest in having children grow up to buy insurance, and also saw campaign support as a way to increase its positive profile among those who could already buy insurance.³⁴ Met Life had more utilitarian motives, too. As the company's leading statistician, Louis Dublin, determined, "childhood illnesses such as diphtheria cost American society some \$200,000,000 [in 1920s dollars] per year in medical and nurses costs and lost parental wages."³⁵ It was only smart to try to eliminate diphtheria. On the other hand, the Milbank Memorial Fund had a very different motive. The Milbank Memorial Fund is a non-profit organization set up in 1905 to apply health policy.³⁶ While it had sponsored work with other diseases, such as tuberculosis, diphtheria hit close to home: one of the founder's son had died of it in the late 19th century.³⁷ It is, perhaps, not astonishing that the Milbank Memorial Fund provided the majority of support for the New York City diphtheria toxin-antitoxin efforts.³⁸

With so many groups working towards the same goal, it is not surprising to learn that diphtheria rates did fall after the campaign got underway.³⁹ However, there were problems.

The first was that the lowered death rate did not stay lowered.⁴⁰ As the first flush of campaign effort fell away, fewer children were vaccinated. But each year there is a new crop of young children who are the right age to vaccinate, so any vaccination project is, by its nature, never-ending.⁴¹ Another issue arose some time after the campaign: only then did scientists recognize that healthy carriers (those who did not get sick from diphtheria but could infect others) also had to be controlled, if the disease were to be eradicated.⁴² However, the problem that most directly related to the ending of the campaign was that attention and sponsorship faded. It required more effort to get the vaccine after the campaign ended; innovative ideas like the "snow-removal trucks that...[carried] physicians and nurses [and] toured the city" to immunize "thousands" were no longer employed.⁴³ In addition, there were other diseases and issues that caught peoples' attention. There is a loss of excitement once the first wave of success has been felt, and the fact that the campaign's leaders declared "success," may have led some families to believe diphtheria was no longer, or at least less of,

³² Willrich discusses these in detail. Note that there have been a variety of reasons for smallpox vaccine resistance including catching diseases from contaminated tools used for vaccinating and side effects such as sore arms that make it difficult for working class men to earn a living temporarily.

³³ Hammonds, 210–211 and Margaret McMahon and Carl L. Erhardt, "Highlights of the First 100 Years: New York City Department of Health," *Public Health Reports (1896-1970)* 81, no. 1 (January 1966): 100, accessed January 19, 2017, <http://www.jstor.org/stable/4592654>.

³⁴ Hammonds, 210.

³⁵ Colgrove, 88–89.

³⁶ Daniel M. Fox and Samuel L. Milbank, "Milbank Memorial Fund Centennial Report," Foreword, accessed January 19, 2017, <http://www.milbank.org/uploads/documents/centennialreport.pdf>.

³⁷ *Ibid.*, 5.

³⁸ Edward F. Brown, "New York City's Diphtheria Campaign," *The Milbank Fund Quarterly Bulletin*, 9, no. 1 (Jan. 1931): 21, accessed January 19, 2017, <http://www.jstor.org/stable/3347528>.

³⁹ Hammonds, 216–217.

⁴⁰ Heller, 47.

⁴¹ Hammonds, 217.

⁴² Heller, 47–48.

⁴³ McMahon and Erhardt, 100.

a threat, even though the city had not met its goal of eradicating the disease.⁴⁴ For these, and more, reasons, rates of vaccination decreased and rates of illness increased.

Nevertheless, the very fact that the campaign worked to increase rates of vaccination meant that public perception was that the campaign was a success. In many ways, it was.⁴⁵ First of all, it was an example of cooperation between many groups; it was not a top-down campaign aimed at a passive public. The 1929 Diphtheria Prevention Commission, for example, brought together more than 50 leaders within the New York City community, and its sub-commissions included a technical consulting board (representing private physicians and five medical societies) as well as an editorial consulting board (with 32 newspaper editors).⁴⁶ In addition, there were politicians and public health professionals who endorsed the campaign, as well as volunteers who helped on a day-to-day basis. Schools, and their teachers and administrators, also fostered immunization, as did others. Parents voluntarily brought their children to be vaccinated. In short, respected and helpful individuals from myriad fields came together to create a multi-pronged campaign.

While the focus of the project had been to eradicate diphtheria in New York City (something it failed to do), it had the subsidiary goals of raising public awareness of diphtheria and creating the view that it was a disease that could be defeated.⁴⁷ It also championed science; science, in the form of bacteriology and medicine had led to a routine use of a test to check for diphtheria antibodies (and thus immunity levels) as well as a way to prevent (not just treat) diphtheria through vaccination. The narrative made science the hero, and those who failed to protect their children (particularly the parents, and especially the mothers) the villains. Such ideas could be used in the future. Indeed, even today, those who opt out of vaccination are often vilified as rejecters of science and reckless with regard to their children's health, whether that is their rationale or not.

Ironically, many scientific issues were ignored at the time of this story. For one thing, global experts did not necessarily believe that the best way to prevent diphtheria was through the toxin-antitoxin immunization at the core of the 1929 campaign. Instead, for instance, the French believed that a diphtheria toxin could be inactivated chemically, such as with formalin, and that the resulting "toxoid" could be used to vaccinate children. This version did not require injecting live toxin into children, nor did it need animal serum to make it; the toxoid could be frozen, was more stable, required fewer boosters, and immunized children for a longer period of time. On the other hand, it could produce side effects in older children.⁴⁸ In New York, the public did not hear about these options or this debate. Instead, the official story was straightforward; scientific nuances were unimportant.

Thus, in sum, once medicine produced the vaccine and the goal to eliminate diphtheria had been announced, there was widespread ownership of the efforts to achieve the goal. The methods used during the campaign itself were not particularly scientific, nor political, nor legal; instead, they were emotional, commercial, and voluntary—ones a lay population could engage and wield. The city government did not solely organize or run the campaign, either; as

⁴⁴ Hammonds, 217.

⁴⁵ *Ibid.*

⁴⁶ *Ibid.*, 204.

⁴⁷ Hammonds, 211 and Heller, 40–41.

⁴⁸ Colgrove, 106.

one scholar noted, the “public sector” was critical if they were to vaccinate 522,243 children.⁴⁹

As impressive as these numbers are, though, the Salk polio trials involved almost four times as many children. How was that possible?

THE SALK POLIO VACCINES TRIALS

The third real-life example to consider is the development of the Salk polio vaccine. This is only one part of the polio story, but it is a more modern example of how vaccines—even experimental ones—need not be mandated to be popular. By virtue of the process that made it available, the Salk polio vaccine became known as the “people’s vaccine.”⁵⁰

As one scholar wrote recently, for most people in the US today the word “‘polio’ describes a vaccine to be taken, not a disease to be feared.”⁵¹ However, through history, at least as far back as ancient Egypt, polio has caused a potentially paralyzing illness and sometimes death. There are three strains of polio, each one of varying virulence. Thus, many victims of polio were only slightly affected; others were partially paralyzed; a few spent the remainder of their lives in an iron lung, largely immobile (there are still some iron-lung patients alive today); and some died.⁵²

Polio has come and gone over the years. At its height in the US, it was a disease that appeared in summer, and whether or not it hit hard in any particular year, people dreaded it. Families might not let their children swim in public pools or go to the movies in case they caught polio from someone in the crowd.⁵³ And it was children who were hit.

The fact that polio’s casualties escalated in the twentieth century—especially in mid century—is one reason that it drew so much attention.⁵⁴ The fact that, like diphtheria, it attacked children is another. Finally, one of its most prominent victims was Franklin Delano Roosevelt, a member of a famous and powerful family as well as a future US president. While FDR worked hard to hide visible reminders of his disability from polio, he could not hide the fact that he had suffered from the disease. He became associated with the National Foundation for Infantile Paralysis (NFIP—better known today as the March of Dimes, although currently that organization has turned its focus from polio to birth defects) and his profile and work on behalf of that organization drove a campaign to care for polio victims and then to prevent the disease. Its work provided the basis for what has become a global effort to eradicate polio.

Efforts to create and distribute the first successful polio vaccine in the US began in 1955 and resulted in Jonas Salk’s creation. This was not the first time scientists had tried to prevent polio, nor even to find a vaccine.⁵⁵ Until there was an effective vaccine, however, the only

⁴⁹ Hammonds, 217 and 227.

⁵⁰ David M. Oshinsky, *Polio: An American Story* (Oxford: Oxford University Press, 2005), 211.

⁵¹ *Ibid.*, 282.

⁵² Jonel Aleccia, “60 years in an iron lung: US polio survivor worries about new global threat,” *NBC News: Health*, November 30, 2013, accessed January 19, 2017, <http://www.nbcnews.com/health/60-years-iron-lung-us-polio-survivor-worries-about-new-2D11641456>.

⁵³ Ogintz.

⁵⁴ Daniel J. Wilson, *Living with Polio: The Epidemic and Its Survivors* (Chicago: University of Chicago Press, 2005), 14.

⁵⁵ For example, see Kluger, 51–56.

thing families could do was try to avoid the disease—and anyone carrying it. Local authorities would quarantine houses and, if they deemed it necessary, hospitalize affected children with or without their parents' consent.⁵⁶

Unlike diphtheria, polio is caused by a virus, and it was well into the twentieth century before there was even a solid understanding of viruses. Once the understanding was there, there were issues about how to create a vaccine if, indeed, one could even be created. The largest debate was whether it should be a killed injected vaccine, or a live oral vaccine. (A killed, or inactivated, virus vaccine is one that takes the disease-causing virus and “kills” it—some scientists argue that a virus is not truly alive on its own, and cannot be “killed” in a technical sense—so that it cannot cause the disease but is still in a form that the immune system will recognize. This contrasts with a live, or attenuated, virus vaccine in which the disease-causing virus is weakened so that it should do no harm; this often results in better immunity but also risks giving the individual a case of the disease. Even once the question was settled, scientists would have to decide which polio strain should be used, what other chemicals would be in the vaccine, and other details.)⁵⁷

While the March of Dimes did not make the vaccine, it did provide financial support and guidance. It moderated the conversation between the top polio scientists in the US, in order to focus research efforts and encourage exchange of ideas. The vaccine was not the organization's only goal—it also raised money to provide care for those stricken—but it did become the focal point.⁵⁸

First, however, the March of Dimes had to raise money on an ongoing basis. In the Diphtheria Prevention Commission campaign in New York, the goal had been short-term: immunize the young children of New York City and eradicate the disease in two years. In the case of polio, the vaccine had to be invented and then children had to be vaccinated—it would not be a short-term project and those involved knew this.

There were, nevertheless, similarities to the diphtheria campaign. Firstly, the public would have to be informed about the campaign before it could take off so that ordinary citizens would want to participate and would know how to get involved. Next, the population had to believe that science could provide the answer—eventually in the form of a vaccine. Broadcasts, like the one given on CBS radio in 1953 announcing trials for a vaccine, would help spread the message.⁵⁹ Thirdly, the public would have a role to play: providing funding, moral support, and ultimately people—children to be injected with the true vaccine and the control substance, as well as adults to raise money, run trials, and help with vaccination drives.

The fundraising predated Salk's work on the vaccine and is worth looking at because it was wildly successful, even during the Depression and World War II when there were major societal events that, understandably, demanded the nation's money and attention.

Unlike the diphtheria drive, the March of Dimes sought most of its money from the grassroots level. The original signature event was the Birthday Ball. Held for the first time in 1934, this became an annual event and was replicated around the country. Nominally celebrating the President's birthday, the ball's main purpose was to raise awareness of, and fundraise for, the fight against polio. The balls would ultimately raise \$1 million—despite the

⁵⁶ *Ibid.*, 10-12.

⁵⁷ *Ibid.*, 237.

⁵⁸ Ogintz.

⁵⁹ Kluger 200–201. Other announcements were made, too. See, for example, Kluger, 222.

Depression.⁶⁰ Roosevelt's law-practice partner Basil O'Connor, who later led the March of Dimes, helped organize the balls. Any money raised went to Roosevelt's favorite polio center in Warm Springs, Georgia, and to the local communities that sponsored the event. Once the March of Dimes was established, the birthday balls became an integral part of the organization's fundraising.⁶¹

The March of Dimes not only raised funds, but also concentrated on increasing awareness of the disease and what the public could do to help combat its spread. In these efforts the organization decided to target the average individual. The benefit of seeking numerous donors, rather than just a few generous ones, was that smaller donations could add up to a large amount of money while simultaneously spreading the word about the March of Dimes and its activities. These were hard economic times and it was important to do much with the few cents that was all many people could spare. The "mile of dimes" fundraiser encouraged people to donate, literally, dimes—in the first year alone donated dimes amounted to \$200,000.⁶² Later, fundraising drives focused on mothers, the individuals perhaps most concerned about the disease and perhaps best able to encourage donations. By 1941 the March of Dimes mothers had raised \$435,000. And fundraising would become ever more creative. In 1950 there was a Mothers' March—a short but intense fundraising effort during which mothers went door-to-door collecting change—that brought in tens of thousands of dollars.⁶³

Nor did the NFIP stop with dimes. Its chapters held fashion shows, exhibitions of Harry Winston jewelry, and created official posters featuring children. After World War II, "federated giving" to the United Way lessened the amount of money that the March of Dimes gathered through its traditional methods.⁶⁴ But, the NFIP increased its commitment to protecting children from polio, and strengthened its determination to fund efforts to eradicate it. Ironically, the March of Dimes was assisted in its efforts by polio itself: Just as veterans were settling into peacetime life, starting families, and chasing the American Dream of a house with a picket fence and kids in the yard, waves of polio struck increasing numbers of children throughout the country. As one scholar noted, it "turn[ed] the postwar culture upside down."⁶⁵ The dangers of war now turned into dangers for babies and children. Awareness and horror spiked and the NFIP was in place to help spread the word. In 1946, a poster depicting a child victim of the disease placed polio front and center in the lives of all Americans, even if the disease was not a current threat in their neighborhood.⁶⁶

It was in 1947 that the NFIP began to fund Jonas Salk, just as it continued to fund other scientists. In need of a new project and research money, Salk applied to the NFIP, but for some time received support not for the exciting prospect of vaccine development but rather for the more basic work of typing strains of polio. Despite the March of Dimes' years of

⁶⁰ Oshinsky, 67, and "Birthday Balls: Franklin D. Roosevelt and the March of Dimes," *Franklin D. Roosevelt Presidential Library and Museum*, accessed January 19, 2017, <http://docs.fdrlibrary.marist.edu/bdtext.html>.

⁶¹ "Bill Kemp, "FDR birthday balls helped raise funds, awareness in polio battle," *Pantagraph*, January 29, 2012, accessed February 10, 2017, http://www.pantagraph.com/news/local/fdr-birthday-balls-helped-raise-funds-awareness-in-polio-battle/article_6e36fe84-49f6-11e1-99a1-001871e3ce6c.html.

⁶² "Eddie Cantor and the Origin of the March of Dimes," *March of Dimes*, accessed January 19, 2017, <http://www.marchofdimes.org/mission/eddie-cantor-and-the-origin-of-the-march-of-dimes.aspx>.

⁶³ Oshinsky, 68 and 87–88.

⁶⁴ *Ibid.*, 86, 87, 80.

⁶⁵ *Ibid.*, 84.

⁶⁶ "In Memoriam: Donald Anderson, First Poster Child, 1940–2014," *March of Dimes*, accessed January 19, 2017, <http://www.marchofdimes.org/news/in-memoriam-donald-anderson-first-poster-child-1940-2014.aspx>.

raising funds and awareness, so little was known about polio that scientists were still trying to determine how many strains there were—a prerequisite for any vaccine development. It was not headline-worthy work, but it was straightforward, dangerous, and important.

Soon Salk had proven himself, and after some political wrangling within the NFIP, he managed to secure the organization's blessing, and funds, to start work on a killed-virus vaccine.⁶⁷ Before long he had developed a vaccine to his satisfaction, but even then he faced numerous challenges before the medical community could offer it to children as part of their regular preventive care.

Inevitably there were arguments within the NFIP. Not everyone was convinced that a killed vaccine could be both safe and effective. The prevailing thought was that a live vaccine would provide more protection—certainly longer protection—because it would stimulate the immune system more thoroughly. Albert Sabin, the man who would eventually develop the live vaccine, was particularly outspoken on this issue.⁶⁸ Then there was the dilemma about how large a dose and how many doses would be necessary to protect children with a killed vaccine. What kind of additional substances would be mixed with the vaccine, and would they be safe? In particular, the debate centered on adjuvants—in this case oil—added to the vaccine to stimulate the immune system and increase the longevity of protection. The problem was that if the adjuvant entered the blood stream it could cause death.⁶⁹ Injecting it just beneath the skin would work, but some scientists wanted Salk to omit adjuvants completely.⁷⁰ Another question was whether the vaccine would be safe: could it, in fact, give someone polio? This is always a risk in a live vaccine, of course, but might it be a problem with a failed killed vaccine? And, of course, there was the biggest question of all: would the vaccine actually protect against polio?

There were, then, political and scientific debates, but there were also emotional ones. Earlier attempts to find a vaccine had backfired and caused polio in those who received the shots.⁷¹ Such past experiences made officials less eager to approve vaccine trials. How could one really know that a new one would be safe?

Scientific debates led first to animal testing, and thence to small-scale testing on humans. At the time, American scientific protocol demanded both that the vaccine did not harm the test subjects and also that it might do them good. Some of the first children to be inoculated were in a home for young victims of polio. The idea was that they could not get polio again—at least not the strain that had originally felled them—but they would benefit from not getting another strain. Next, children from a home for severely developmentally disabled were tested, the rationale being that they would be particularly vulnerable to contagious diseases since they lived in close quarters.⁷² The children could not, however, be tested without the consent of their guardians—enough did give permission to provide sufficient positive outcomes to instill confidence in the vaccine.

⁶⁷ Kluger, 159.

⁶⁸ “Jonas Salk and Albert Bruce Sabin,” *Chemical Heritage Foundation*, updated July 21, 2015, accessed January 19, 2017, <https://www.chemheritage.org/historical-profile/jonas-salk-and-albert-bruce-sabin> and *ibid*.

⁶⁹ Kluger, 164–165.

⁷⁰ *Ibid.*, 165 and Oshinsky, 179. Note that in the 1990s, debate about additives centered around thimerosal—a preservative made from mercury—in the measles-mumps-rubella (MMR) vaccine amid claims that it caused autism.

⁷¹ Gilbert King, “Salk, Sabin and the Race against Polio,” *Smithsonian.com*, April 3, 2012, accessed January 19, 2017, <http://www.smithsonianmag.com/history/salk-sabin-and-the-race-against-polio-169813703/>.

⁷² Kluger, 175.

Finally, plans were made for a widespread trial in 1954. First among many important decisions to be made was who would produce the vaccine. During the trial, the March of Dimes planned to vaccinate approximately two million children, and corporations were required to manufacture doses on a massive scale. The scales were huge, but so too were the potential profits for those companies that could get in on the ground floor. It is worth recounting a conversation between a March of Dimes official and prospective pharmaceutical corporations in 1953. He asked how effective the vaccine had to be for its manufacture to be worth their time and energy. The numbers they gave were staggeringly low—one even said 15%. In other words, they believed there would still be a market for a vaccine that was only slightly useful; indeed, a vaccine that would be so ineffective in preliminary testing that the March of Dimes would not have approved it for large-scale human trials.⁷³

Once the companies were selected, they had to be trained in a very finicky process—purity and precision were vital if they were to reach the necessary standards of safety and efficacy. There were failures. The trial nearly lost government approval because some test batches seemed to cause polio in animal subjects. (In fact, the test monkeys had a different disease.)⁷⁴

Next, there was the structure of the trials to be considered. The gold standard by then, as now, was double-blind studies in which no one personally involved knew who received the real vaccine and who received a placebo. That way, no one could analyze the results influenced by their knowledge. However, Salk and others were concerned: would anyone sign up for a study in which their child might not get the magic preventive? Morally, how could Salk and the organizers deny children the vaccine? Because of this, several states agreed to participate without the double-blind system in place, planning instead to use children in first and third grade as controls. Second graders would be injected, since they were young enough to be at high risk of polio but old enough to be in school for regular attendance, while first and third graders would simply be observed to see if they caught polio more often than the second graders.⁷⁵

A few communities did agree to the double-blind procedure, but they joined the trials late. Scientist Tommy Francis—one of Salk's former mentors before the polio research—had a sterling reputation and was asked to oversee the analysis of the results. He refused unless the double-blind procedure was used. He believed that a trial without the double-blind procedure would not be legitimate science, and thus would be worthless. At the same time, the trial organizers did not think that morally they could deny the vaccine to those who had already agreed to participate. And so, new communities had to be found, ones eager enough for the vaccine that they were willing to take the chance that their children might be in the control group and thus get no protection—as long as there was a chance that they would be assigned to the group that got the miracle vaccine, they were willing to participate.^{76 77}

So it was that, in 1954, two million children, hundreds of thousands of volunteers, and numerous medical personnel came together. Volunteers tracked down parents who had not signed consent forms, washed needles (so they could be reused), offered lollipops to children,

⁷³ *Ibid.*, 236.

⁷⁴ *Ibid.*, 271–272.

⁷⁵ Oshinsky, 184–185 and 186.

⁷⁶ Kluger, 241–243.

⁷⁷ Oshinsky, 186–187.

found no-show children, and on and on.⁷⁸ Then came months of waiting. Waiting by families to see if the vaccine would work: would their children emerge unscathed from the current polio season? Waiting by scientists and the public for Tommy Francis's team to analyze the results: was the vaccine safe and effective?

Finally, in an almost circus-like atmosphere at the University of Michigan—Francis's professional home—he announced the results live.⁷⁹ The vaccine worked. Not perfectly—it had varying degrees of effectiveness for different strains—but it worked and it was safe. The path was open for tweaking and perfecting. And there was to be no charge for the patent, so corporations would receive it for free. It would become known as the “people's vaccine.”⁸⁰ Millions of people had helped finance the work to produce it, and millions would now benefit.

It was a major moment for Salk. He received piles of mail and an invitation to the White House, but his scientific colleagues were less impressed.⁸¹ He never received a Nobel Prize because the science behind his work was considered derivative rather than original.⁸² On the other hand, no one could deny that its application was incredibly successful.

The story does not simply end on that happy note, though. Later trials and batches did have failures. In the ensuing years, some children did get polio from poorly produced batches.⁸³ Eventually, Albert Sabin developed a live vaccine that subsequently dominated the market, partly because it was easy to administer and less expensive.⁸⁴ However, the last case of “wild” polio in the US was in 1979, and the country reverted to using a version of Salk's vaccine for reasons of safety.⁸⁵ (This vaccine is now bundled into the numerous shots babies get during their first few years of life, and the CDC recommends four doses by age six.)⁸⁶ The oral vaccine is still used in an effort to eradicate polio globally partly because it can be easily administered by anyone to anyone.⁸⁷ As of January 2017, the disease does still exist, but is endemic only in Pakistan, Afghanistan, and Nigeria.⁸⁸ (This is a reversal of the trend since polio has re-emerged in Nigeria since 2015).⁸⁹

Even now, volunteers outside the medical field are still deeply involved in eradicating polio. The Rotary Club, an international volunteer organization, has taken on polio as one of its major missions.⁹⁰ The Bill & Melinda Gates Foundation, so well-known for its anti-

⁷⁸ Ibid., 197, 198, Kluger, 277.

⁷⁹ Kluger, 294.

⁸⁰ Oshinsky, 211.

⁸¹ Ibid., 214 and Kluger, 306.

⁸² Heller, 5 and Kluger, 315.

⁸³ Heller, 6.

⁸⁴ King, “Salk, Sabin and the Race against Polio.”

⁸⁵ “Polio Elimination in the United States,” *Centers for Disease Control and Prevention*, updated June 21, 2016, accessed January 19, 2017, <https://www.cdc.gov/polio/us/index.html>.

⁸⁶ “Vaccination in the U.S.,” *Centers for Disease Control and Prevention*, updated October 3, 2014, accessed January 19, 2017, <https://www.cdc.gov/polio/us/vaccination.html>.

⁸⁷ “Polio,” *U.S. Department of Health and Human Services: Vaccines.gov*, accessed January 20, 2017, <https://www.vaccines.gov/diseases/polio/>.

⁸⁸ John Hewko, “6 Key Numbers in the Fight to End Polio,” *World Economic Forum*, published January 12, 2017, accessed January 20, 2017, <https://www.weforum.org/agenda/2017/01/6-key-numbers-in-the-fight-to-end-polio/>.

⁸⁹ “Does Polio Still Exist? Is it Curable?” *World Health Organization*, updated October 2015, accessed January 20, 2017, <http://www.who.int/features/qa/07/en/>.

⁹⁰ “End Polio,” *Rotary*, accessed January 20, 2017, <https://my.rotary.org/en/take-action/end-polio>.

malaria work, is another major donor.⁹¹ As in the years that led to the development of the vaccine, and through its major 1954 trial, there are major efforts from people wishing to see an end to the threat of polio. For the breakthrough—the Salk vaccine’s development and trial—people volunteered money, from pocket change (like dimes) to thousands of dollars.⁹² The NFIP, a non-profit, supervised most of the research and treatment efforts at the national level for decades. A President championed polio and brought it to the public eye because it was one of his personal philanthropic causes. Volunteers collected money and staffed trials. Children were the “polio pioneers,” as Salk called them, who received the first vaccines.⁹³ Whether or not they chose to participate in the trial, it was those children who bared their arms, received the shot, and took the chance. While the March of Dimes and the President helped to publicize the dangers of the disease and the possibility that science could prevent it, it was the public who chose to buy into the messages and actively promote the campaigns. The public—as donors, as fundraisers, as volunteer administrators during the trials, and as vaccine recipients—made this possible. Coercion was not involved.

CONCLUSION

Today, most Americans get their children vaccinated because of legal mandates, medical recommendations, and their trust in science. However, there have been times in our history when laymen have actively sought vaccines, sometimes in spite of government recommendations and experts’ debates, such as in colonial Boston. At other times, such as during the New York City diphtheria campaign and the Salk vaccine trials, segments of the public and lay organizations have sought to promote vaccination drives. Public embrace of vaccination has not always been a top-down process led by experts or promoted solely because of scientific trust, and understanding this may help future campaigns designed to educate the public and to convince them to trust their children to the doctor’s needle.

Class Exercises

The Great Debate

Think about the colonial smallpox inoculation debate. Break into two groups, one on the side of Boylston and Mather and one on the side of Douglass.

- What were some of the reasons raised in favor of inoculations and some of the reasons raised against it?
- Each side should argue one side or the other in a debate.

⁹¹ “Polio,” *Bill & Melinda Gates Foundation*, accessed January 20, 2017, <http://www.gatesfoundation.org/What-We-Do/Global-Development/Polio>.

⁹² Nicole Kappatos, “Birthday Balls,” *Richmond Times-Dispatch*, January 31, 2016, accessed January 20, 2017, http://www.richmond.com/from-the-archives/birthday-balls/article_094f319a-ada6-11e5-8a47-6fe2f1c7dae9.html.

⁹³ Ogintz.

- Considering the knowledge and technology available in colonial Boston, which side won in your class?
- Would the reasoning used during the debate apply to a debate about vaccination today? Why or why not? If not, how would it be different today, and what does that tell you about how approaches to medical issues change over time?

Personal Motivations

All three of the diseases discussed in this chapter have been wholly or almost wholly eradicated in the US. Smallpox has been eradicated globally and polio has been almost entirely eradicated worldwide, too. It is challenging to understand how deeply people feared these diseases in the US, or why they might risk subjecting their children to vaccine trials on a large scale. To develop a more complete—and personal— understanding of these issues, do one of the following:

- Interview someone who was vaccinated for polio during the 1950s. In particular, find someone who remembers the advent of the Salk vaccine, if possible. Ask them if their parents prohibited them from certain activities before the vaccine, whether they were scared of polio, and how they felt when news of the vaccine broke.
- Research newspaper articles from April and May of 1954 through 1955—the period between the beginning of the large-scale Salk vaccine trials and Dr. Francis’s announcement. Look for articles that interviewed individuals or explained how people felt about the possibility of a safe, effective vaccine. Note what they said about their previous attempts to avoid polio, fears of it, and feelings about the trials and vaccine.

Discuss your findings with your classmates. Do they change your understanding of the history of the polio vaccine and lay involvement in the trials? Do you think that people feel the same way about vaccinations today? Why or why not?

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Chapter 84

IMMUNIZATION: RIGHTS, RESPONSIBILITIES, REGULATIONS, AND RESULTS

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INTRODUCTION

The practice of immunizing against infectious diseases is steeped in history and has been shown to be a very effective means by which to promote health, yet many parents still refuse to vaccinate their children against life-threatening diseases. Dr. Hinman's lecture explores the tension that exists between this very cost-effective means of keeping populations healthy and the perception that this public health approach trumps one's personal freedom. This chapter highlights the key aspects of the role of human rights, vaccine regulation, responsibility of the public health and healthcare systems, and their integration. Dr. Hinman focuses on several significant examples—including measles and the human papillomavirus—to emphasize the roles that the media, personal-belief exemptions, and cultural norms play in our inability to eliminate or eradicate vaccine-preventable diseases. This chapter also presents a comprehensive overview of the importance of vaccination in our everyday lives and the tremendous efforts to assure the efficacy and safety of this cost-effective public health measure—one of the greatest public health achievements to date.

LECTURE

Historical Background

Immunization is one of the most effective and cost-effective measures we have to protect health and prevent disease. We've saved millions of lives around the world through immunizations. Nonetheless, immunizations have been controversial ever since Englishman

Edward Jenner first transferred pus from a cowpox blister on the hand of the milkmaid, Sarah Nelms, into the arm of 12-year-old James Phipps in 1796. Two months later, Jenner inoculated James Phipps with pus from a smallpox victim and found that James did not develop smallpox himself. Jenner named the procedure “vaccination” after *vaccinia*, the Latin for cowpox. Such a study would never be allowed today. Informed consent? This was before the germ theory of disease.

In the centuries before Jenner's experiments, smallpox had been a major killer of kings and peasants alike, with millions of deaths over the years. The introduction of smallpox and measles into the Americas in the wake of the Spanish colonization decimated the indigenous populations of North, Middle, and South America.

Since the fifteenth century, practitioners in Asia and the Middle East had practiced something called variolation. This involved taking small amounts of pus from smallpox lesions—smallpox was then called *variola*—and inoculating that into the skin of individuals. The inoculated then developed a mild form of smallpox from which they recovered, and were subsequently immune.

Unfortunately, 1% to 2% of those who were variolated died as a result of the procedure. However, although this was a pretty high adverse event rate, it was much lower than the 30% death rate from naturally acquired smallpox. Clearly, the benefits of variolation outweighed the risks, and it was a fairly widespread practice. It was introduced to the Americas, and in the 1700s Cotton Mather was a practitioner of variolation.¹

So, Jenner's experiment gave the world a new and safer approach with which to prevent smallpox. But, it immediately attracted critics. Some claimed that inoculating cowpox into humans might turn them, or parts of them, into cows. Some objections were based on religious belief; others came simply from the fear of inoculating animal tissues into humans.

One result was that anti-vaccination societies developed. Anti-vaccination leagues were formed in England in the mid-nineteenth century, and in the US, at least as early as 1879. In addition, there were anti-vaccination demonstrations, and even riots, when compulsory vaccination laws were enacted in England in the mid- nineteenth century.

Rights

Human rights are a set of beliefs about the societal basis for human well-being. They represent a series of non-provable statements about what people need to maintain their human dignity, and they primarily describe the relationships between individuals and society, usually in the form of the state (as in government).

Human rights are rights of individuals, inherent to individuals just because they're human. They don't have to be earned; they don't have to be purchased. You have them simply because you are a human being. Human rights apply to all people around the world.

Global codification of human rights in formal documents really began in the wake of World War II and the Holocaust. Several human-rights documents have been developed and enacted. There are actually dozens, but three represent the primary legal basis for human rights: the Universal Declaration of Human Rights (UDHR), issued in 1948; the International

¹ Cotton Mather was a famous clergyman in colonial Boston. His influence spread beyond the religious realm into issues that had an impact on the wider society. See chapter 4 for more details.

Covenant on Economic, Social and Cultural Rights (ICESCR), created in 1966; and the International Covenant on Civil and Political Rights (ICCPR), created in 1966.

I'm going to quote a few of the important statements from these documents that have a bearing on immunization. Article 1 of the Universal Declaration of Human Rights says, "All human beings are born free and equal in dignity and rights. They are endowed with reason and conscience and should act towards one another in a spirit of brotherhood."²

Article 2 of UDHR says that, "Everyone is entitled to all the rights and freedoms set forth in this Declaration without distinction of any kind, such as race, colour, sex, language, religion, political or other opinion, national or social origin, property, birth or other status."³ This, remember, was written in 1966, and the issue of sexual orientation was not then being discussed in society. If this was written today, it would probably contain a statement about sexual orientation.

These two articles outline the major parameters of human rights. Article 25 of UDHR addresses the right to health: "Everyone has the right to a standard of living adequate for the health...of himself and of his family."⁴ Health is not necessarily inherent, but may be something that requires a standard of living and some ability to purchase or obtain things. This sentence is also interesting because it says, "himself and of his family." Remember, this is post-World War II, and these things were mainly written by men. Again, were it written today, it would probably have a different orientation. However, it is worth noting that one of the prime movers behind the development of the Universal Declaration was a powerful and famous woman—Eleanor Roosevelt.

There are further statements on the right to health. In the International Covenant on Economic, Social and Cultural Rights, Article 12 describes, "the right of everyone to the enjoyment of the highest attainable standard of physical and mental health." It also says that, "The steps to be taken by the states parties to the...Covenant" include those necessary "for the provision for the reduction of the stillbirth-rate and of infant mortality... [t]he improvement of all aspects of environmental and industrial hygiene... the prevention, treatment and control of epidemic, endemic, occupational and other diseases... [and t]he creation of conditions which would assure... medical service."⁵ There is a further elaboration specifically regarding immunization in a general comment to the treaty.

The treaties, these covenants, are formal legal documents. They're usually not long, but they do inspire the question: What does that mean? There are international committees established around each of these human rights documents, which try to elaborate on what they really mean. The committees draft "general comments."

For example, general comment 14 on the ICESCR describes the core obligation of governments to provide immunization against the major infectious diseases occurring in the community.⁶ In other words, we have a human right to be immunized.

² United Nations, "Universal Declaration of Human Rights" (General Assembly Resolution 217A, December 10, 1948), accessed January 23, 2017, <http://www.un.org/en/universal-declaration-human-rights/>.

³ Ibid.

⁴ Ibid.

⁵ United Nations, "International Covenant on Economic, Social and Cultural Rights" (General Assembly Resolution 2200A, December 16, 1966), accessed January 23, 2017, <http://www.ohchr.org/EN/ProfessionalInterest/Pages/CESCR.aspx>.

⁶ Office of the High Commissioner for Human Rights, "CESCR General Comment No. 14: The Right to the Highest Attainable Standard of Health (Art. 12), accessed March 28, 2017, <http://www.refworld.org/pdfid/4538838d0.pdf>.

These documents describe the rights of individuals to make choices, and the obligation of states to respect, protect, and fulfill those rights. “Respect,” in this situation, means that the states must allow individuals to exercise their rights; they must not impede the exercise of their rights. “Protect” means that states must not allow others to infringe upon the exercise of these rights. “Fulfill” represents an obligation on the state to provide conditions in which the rights can be exercised. These statements of rights, statements of responsibilities of states or governments, are pretty broad.

Are there any circumstances in which the exercise of human rights can be limited? Well, yes, there are. Article 29 of the Universal Declaration says that, “In the exercise of his rights and freedoms, everyone shall be subject only to such limitations as are determined by law solely for the purpose of securing due recognition and respect for the rights and freedoms of others and of meeting the just requirements of morality, public order and the general welfare in a democratic society.”⁷

This phrase, “just requirements of public order and the general welfare,” is the basis by which the state—the nation—commonly acting through state departments of health in the US, can infringe upon the exercise of rights by isolating or quarantining individuals, compelling treatment of communicable diseases, etc.

In 1984, there was a meeting of 31 experts in Siracusa, Sicily, to consider further the issue of how you can limit the exercise of the rights guaranteed through the International Covenant on Civil and Political Rights (ICCPR). The participants agreed on the need for a close examination of the conditions for permissible limitations and derogations. They went on to enunciate that a restriction of rights guaranteed under the ICCPR is allowable if the restriction is provided for and carried out in accordance with the law, and it is in the interest of a legitimate objective of general interest such as public safety, public order, and public health.

The participants also stated that this kind of restriction is strictly necessary in a democratic society in order to achieve the objective, *if* there are no less intrusive and restrictive means available to reach the same goal, *and* the restriction is based on scientific evidence and is not imposed arbitrarily. These principles are, in fact, being put into place.

For example, in New York City in the 1990s, there was a resurgence of tuberculosis (TB) with multi-drug resistant tuberculosis occurring primarily in HIV-infected individuals, many of whom were addicted to drugs. Many were homeless, and many didn’t want to take treatment. So, the question arose: Is it legal and ethical and respectful of human rights to do nothing?

Essentially, the system that developed was this: Step one, you say, “OK, you need to take these drugs for the next 12 or 18 months [in the case of multi-drug resistant TB]. Yes, some of them are going to make you feel sick, but you need to take them. You need to take them throughout the whole period.” What’s the likelihood that somebody is going to do that? Even if that someone is an affluent, middle class, fully employed individual? Not great.

Step two, you try to establish a contract with the person. They will say, “OK, I will sign my name here that I’m going to do this.” Once again, the likelihood of success is not too high.

Step three, you use Directly Observed Therapy (DOT). An individual—typically a representative of the health department, but sometimes a family member—physically watches the patient take the drugs every day. DOT has been the strategy that has enabled us, around

⁷ Declaration of Human Rights.

the world, to bring some degree of control over tuberculosis. It's used in affluent and impoverished areas alike, and it works most of the time. But, if you can't find a person to administer the therapy, then even DOT doesn't work.

Step four, you may have to confine the individual. This is, in essence, the last step and the process of getting to it represents the whole roster of principles laid out in the Siracusa principles: to take the least restrictive measure possible to achieve the legitimate goal.

Responsibilities

We all have rights. Those rights can be restricted under certain circumstances to protect the public's health. What are society's responsibilities as opposed to our own personal responsibilities? Let's consider the ethical basis on which public health rests. This is often considered to be utilitarianism, a philosophical belief that prioritizes achieving the greatest good for the greatest number. It's achieving an ecstasy index, if you will. Its approach is basically democratic, but it will always value utility over justice, and it can be heartless—it could result in decisions being made solely on the basis of cost-benefit or cost-effectiveness reasoning. In many ways, this would be antithetical to public health's concern for the most vulnerable and underserved and for the achievement of social justice.

Utilitarianism is probably not the right theory to use for the ethical basis for public health. I think public health is based more on a communitarian ideal in which we balance individual rights and interests with those of the community as a whole. This considers that individuals are shaped by the cultures and values of their communities. The community may be a family unit, but is usually understood in the wider sense of interactions between a community of people in a geographical location or people who have a shared history or shared interest.

I used to serve on the Task Force on Community Preventive Services that assessed the evidence base for what we do in public health. The Task Force defined communities as groups of people who share a common characteristic. Characteristics may be geographic, cultural, sexual orientation, country of origin, whatever.

Communities tend to be groups of people who share customs, institutions, and values. In pursuit of the common good, individuals and communities are usually willing to yield some aspects of their individuality. This might be reflected, for example, in restrictions on smoking areas where smokers willingly—mostly willingly—forgo smoking in certain areas in order to protect the health of the community. Public health is fundamentally an effort to promote the common good and the shared values of reducing disease, saving lives, and promoting good health while minimizing restrictions on human rights.

Another manifestation of communitarianism is in the immunization arena. With the exception of tetanus, all of the diseases we try to prevent using vaccines are transmitted from person to person. That means that a decision about immunization is not strictly an individual decision; it affects the community. If I decide not to immunize my child, for whatever reason, and my child becomes ill with measles, she may transmit the disease to other children who may be especially vulnerable as a result of, for example, undergoing chemotherapy for leukemia; or to other children too young to be vaccinated; or even to other children who have been vaccinated but are not protected—vaccines are not perfect.

For example, three to five percent of people who receive the measles vaccine won't be protected. This is not an abstract example. Measles is no longer an indigenous disease in the

US. Since 1999, all cases of measles that have occurred in the US have originated in another country. Recently, many cases have occurred in persons who consciously have not been vaccinated. They have traveled to another country, become infected there, and brought the disease back to the US.

In 2008, a seven-year-old unvaccinated boy in San Diego who had recently been with his family in Switzerland was diagnosed with measles. He was responsible for a total of 11 additional measles cases in unvaccinated infants and children aged 10 months to 9 years. These 11 cases included both of the boy's siblings, five children in his school, and four additional children who had been in the pediatrician's office at the same time as the boy—transmission was occurring in a healthcare facility!

Among the four patients who had been in the pediatrician's office, three were infants less than 12 months of age and therefore too young to have been vaccinated. Also, they were so young that they were at greater risk of experiencing complications. One of the three was hospitalized for a couple of days and another traveled by airplane to Hawaii, while infectious, potentially exposing others. Fortunately, I don't think there were any tertiary cases.

Among the other nine patients—all of whom were old enough to have been vaccinated—eight were unvaccinated because of parental beliefs. There were approximately 70 children exposed to the disease in the school, day-care center, pediatrician's office, and other community settings who were unvaccinated and exposed because their parents either declined measles vaccination, or they were too young to be vaccinated—these 70 were placed under voluntary home quarantine.

The San Diego outbreak illustrates the risk for measles transmission in healthcare settings. Airborne transmission of measles has been reported in emergency departments, physicians' offices, and pediatric ambulatory care settings. I believe some of the measles cases that occurred in New York City in 2014 resulted from transmission in healthcare settings.

Individuals have a responsibility to the community. If I do not vaccinate my child, I endanger my community. I'm proud to be a member of Voices for Vaccines, a parent-led group providing science-based advocacy for vaccines. Our motto is, "Pro-child, pro-community, pro-vaccine."

Regulations

There are two kinds of regulations that I wish to talk about: regulations about the vaccines themselves and regulations about the use of vaccines.

Modern vaccines are safe and effective. However, they are neither perfectly safe nor perfectly effective. That means that some persons who receive vaccines will have adverse effects, and some persons who receive vaccines will not be protected.

Regulations about vaccine composition, safety, and efficacy antedate the Pure Drug and Food Act of 1906, which has a role of overseeing vaccines. Vaccines are among the most highly regulated of any products in the US. For example, the manufacturing process and the manufacturing plant are separately regulated, so that each lot of vaccine is separately inspected before being released.

Vaccine developers go through a multi-step process to obtain licensure of vaccines. After initial laboratory investigation indicates the possibility that an entity might be useful as a

vaccine, it is tested in animals to determine whether it induces protection and whether it causes adverse reactions.

Next, if deemed potentially suitable, vaccine developers submit a plan for testing in humans under an Investigational New Drug (IND) permit. This testing has three phases.

Phase one entails administration of the vaccine to a limited number of humans—typically dozens—to determine whether the vaccine induces an immune response and whether it causes immediate apparent adverse effects.

Phase two typically involves up to a few hundred individuals to determine appropriate dosing and, again, to look at potential adverse events.

Phase three typically involves several thousand individuals to determine the immune response, adverse events, and natural protection against disease of the potential vaccine.

Recent trials of rotavirus vaccine involved some 50,000 to 60,000 infants before the vaccine was licensed for release and use in the US. This large test number was used because the original rotavirus vaccine, introduced in the 1990s, was found to be associated with an additional risk of intussusception—an intestinal blockage—that occurred at an excess rate of about one in 10,000 of those vaccinated. Think about finding an excess risk of one in 10,000. Obviously, you have to have at least 10,000 in the study population.

After phase three testing, the developers submit a Biologics License Application (BLA) to the Food and Drug Administration (FDA) that, if approved, enables them to produce and distribute the vaccine. The Biologics License Application is reviewed by an independent committee, the Vaccines and Related Biological Products Advisory Committee, or VRBPAC. This body recommends to the administrator of FDA whether or not to license the product for use in defined populations for defined purposes.

Following licensure, the Advisory Committee on Immunization Practices (ACIP) reviews the evidence about safety and efficacy and then issues recommendations about how the vaccine should be used. The ACIP is an independent committee comprising 15 authorities who are knowledgeable in the fields of immunization practices and public health, who have expertise in the use of vaccines and other immunobiological agents in clinical practice or preventive medicine, and have expertise with clinical laboratory vaccine research or in the assessment of vaccine efficacy and safety.

The ACIP also includes a person or persons knowledgeable about consumer perspectives and/or social and community aspects of immunization programs. In addition to these 15 individual members—none of whom is a government employee—the ACIP includes liaison representation from the American Academy of Pediatrics, the American Academy of Family Physicians, the American Academy of Physicians—which is the internal medicine group—the American College of Obstetrics and Gynecology, the American Medical Association, and many other organizations.

ACIP recommendations are proposed to the director of the Centers for Disease Control and Prevention (CDC) and the Assistant Secretary of Health in the Department of Health and Human Services. Once accepted, they are widely published and endorsed by all of the aforementioned organizations. These are truly national recommendations that are harmonized among the various medical specialty organizations. They become a standard of practice for healthcare practitioners and typically are included as covered services by health-insurance organizations.

The ACIP has a unique power under the Vaccines for Children Act of 1993 to declare that vaccines recommended for universal application to children under the age of 18 must be

provided as an entitlement, free of charge, to children who are on Medicaid, uninsured, or are under-insured for one or more vaccines, are American Indians, or Alaska natives. This action removes financial barriers to access to vaccines for those who are less well-off, and has resulted in a dramatic reduction in disparities and immunization coverage among population groups in the US. Nearly half of all US children are entitled to free vaccines through the Vaccines for Children Program, a program that currently costs about \$3 billion annually. It is an extraordinary investment with extraordinary returns.

Our challenge is to maximize effectiveness while minimizing adverse consequences. To deal with the fact that vaccines aren't perfectly safe, the National Childhood Vaccine Injury Act of 1986 created the National Vaccine Injury Compensation Program. This is a no-fault alternative to using the traditional court system for resolving vaccine injury claims and provides compensation to people found to be injured by certain vaccines.

As of February 3, 2014, 3,511 compensation awards had been made since the first claims were filed in 1989. More than \$2.7 billion in compensation awards had been paid with more than \$100 million paid to cover attorney fees and legal costs. In addition to these 3,500 awards, more than 9,700 claims had been dismissed as not reflecting vaccine causation.

This program has resulted in a stabilization of the supply of childhood vaccines in the US. At the time the Act was passed in the 1980s, several manufacturers had left the market, or were threatening to do so, because of a growing number of lawsuits filed against them alleging that the vaccines had improperly caused injury. Regulations ensure that our vaccines are as safe and effective as possible, *and* provide a mechanism for compensating those who are injured by vaccines.

Compulsory Vaccination Regulations

What about regulations that *require* some people be vaccinated? Immunization mandates have a long history, starting with requirements that the entire population be vaccinated against smallpox. In England, the Vaccination Act of 1855 ordered mandatory vaccination of infants, and in 1867, this was extended to 14-year-olds. These Acts prompted the formation of anti-vaccination leagues, journals, demonstrations, and even riots.

In 1902, during an epidemic of smallpox in Boston and surrounding areas, the Cambridge Board of Health in Massachusetts passed a regulation requiring all citizens who had not been vaccinated in the previous five years to undergo the procedure again. A minister named Henning Jacobson refused vaccination, and he also refused to pay the \$5 fine that he was levied as a result of violating the law. This initiated a series of lawsuits that ultimately reached the Supreme Court of the United States. In 1905, the Supreme Court issued its decision in *Jacobson v. Massachusetts*. Justice John Harlan wrote, in part, the liberty secured by the Constitution of the United States to every person within its jurisdiction does not import an absolute right in each person to be, at all times and in all circumstances, wholly freed from restraint. There are manifold restraints to which every person is necessarily subject for the common good. On any other basis, organized society could not exist with safety to its members. Society based on the rule that each one is a law unto himself would soon be confronted with disorder and anarchy.⁸

⁸ *Jacobson v. Massachusetts*, 197 U.S. 11 (1905). See previous chapter for more details about this case.

The Supreme Court's decision has been reaffirmed since, and in many ways, is the basis for many of the police powers that health departments have today.

An approach that has been taken in the US—more than in other countries—has been for states to require that children be immunized before entering school. This approach began in the mid-nineteenth century as public schooling began to be obligatory, resulting in smallpox outbreaks amongst school children. The first statewide school immunization requirement was enacted in Massachusetts in 1850.

By the turn of the twentieth century, nearly half of all states had such requirements, although we don't know how strongly they were enforced. In 1977, there was a Childhood Immunization Initiative, in which I was heavily involved, that incorporated a request from the Secretary of what is now the Department of Health and Human Services, Joe Califano, to every governor in the US, asking them to enact and enforce school immunization requirements.

As of 1980, all 50 states have laws requiring that all children be immunized before entering school. Remember, this is not a national mandate; these are state laws. The specific requirements under which vaccines are necessary vary from state to state, as do the allowances for exemptions to the law based on medical condition, religious belief, and personal or philosophical beliefs. (The last are often called PBEs, Personal Belief Exemptions).

What has been the effect of these regulations? Measles transmission in schools was common in the era before interruption of endemic disease transmission. School requirements for vaccination have been a successful strategy for achieving high vaccination coverage in school kids and decreasing transmission in school settings.

However, while all states do require children to be vaccinated before entering school, all states also offer medical exemptions to immunization requirements for day care and school attendance. If, for example, a child has hypersensitivity to one of the components in a vaccine, or is immunocompromised and therefore should not get a live virus vaccine, he may be exempt on a medical basis. In addition, as of 2014, all states, except Arkansas and West Virginia, allow religious exemptions, although the question of how one defines a religious belief varies from state to state.

Twenty-one states, including California, offer non-medical personal belief exemptions.⁹ These exemptions are defined differently in each state. Some states require that a parent obtain a notarized statement that he or she has philosophical beliefs that preclude immunizations. Others may have a simple check-off box on a form that says parents have personal beliefs that preclude immunization.

Studies have shown that the easier it is to get an exemption, the higher the exemption rate, and the greater the risk of vaccine-preventable diseases. Some parents reportedly check the exemption box, not out of opposition to immunization, but to avoid the hassle of having to go find the immunization record and produce it.

The personal belief exemption allowed in California requires only a parental affidavit. If you compare people who are exempted from vaccination because of personal beliefs with those who are vaccinated, those who have exemptions are between 22 and 224 times more

⁹ California does not allow non-medical exemptions as of 2016 and other states have different options now, too. There is a map and chart with updates at "States with Religious and Philosophical Exemptions from Immunization Requirements," National Conference of State Legislatures, August 23, 2016, accessed April 9, 2017, <http://www.ncsl.org/research/health/school-immunization-exemption-state-laws.aspx>.

likely to contract measles. Some of us have said—including in print—that it should not be easier to get an exemption than it is to get your child vaccinated. However, in California that is the case: all you have to do is say “Don’t want it.”

School immunization requirements were originally enacted to prevent outbreaks of disease, such as measles, that occur among school children, and they were highly effective. But, because they were so effective, they began to be viewed as a convenient way to rapidly ensure high levels of protection among children for diseases that were not necessarily epidemic in schools, but for which the vaccines had recently become available.

I believe this began with the ACIP recommendation for universal application of the hepatitis B vaccine in 1991. In the US, hepatitis B is primarily transmitted by sharing needles or through sexual contact. Many parents felt that their children were not at risk of such behaviors. They thought, “My child is never going to have sex. My child is never going to shoot up.” In addition, these are not behaviors that are acceptable at schools. Nonetheless, most states established requirements for hepatitis B vaccination before school entry. Many parents oppose this for the very reasons that I gave: “This isn’t something that’s transmitted in school and my child is not risk.” This opposition has carried forward to newer vaccines, such as the varicella (chickenpox) vaccine, and human papillomavirus (HPV) vaccine.

However, chickenpox should not be compared to hepatitis B. Chickenpox is a disease that is often transmitted in school settings. In fact, the primary mode of transmission of chickenpox in the past was school-based outbreaks. It’s usually a mild disease, but it can result in complications like pneumonia or encephalitis. Before the varicella vaccine was introduced, there were about 100 deaths per year from chickenpox in the US. Still, the disease was often viewed just as a part of growing up.

However, a child who has chickenpox has to stay home from school for 5 to 10 days, which means that a parent has to stay home also for 5 to 10 days to take care of them. If there’s more than one child in the house with the infection, you have another week. In fact, cost-effectiveness studies have shown that varicella vaccination can be justified on the basis of lost parental earnings, not just on the basis of illness prevented.

Human papillomavirus (HPV) is a somewhat different story. HPV is the main cause of cervical cancer, and causes other cancers and genital warts in both men and women. It is spread through sexual contact, including non-penetrating sexual contact, and it is acquired by most people soon after initiating sexual activity.

The development and licensure of HPV vaccines containing several serotypes of HPV, of which there are about 100, provided a major opportunity to prevent a substantial proportion of the 3,700 cervical cancer deaths a year that still occur in the US, despite a quite effective program of Pap smear screening and treatment. In many developing countries, cervical cancer is the leading cause of cancer deaths in women, and often there’s no infrastructure to do Pap screening.

HPV vaccines provide a major mechanism to prevent needless death. They represent the second cancer vaccine we have. Hepatitis B vaccine was the first cancer vaccine—to prevent liver cancer—and now we have HPV to prevent cervical cancer. In spite of the fact that this offers a great opportunity, introduction of HPV vaccines elicited a major negative response on the part of some parents in the United States who claimed it would result in promiscuous sexual behavior. However, studies have actually shown that girls who receive the HPV vaccine are more likely to postpone intercourse to a later age than girls who don’t receive it.

To compound the problem in the US, a vaccine manufacturer provided financial support to groups who lobbied state legislatures to enact laws requiring HPV vaccine as a condition of middle or high school attendance. This provoked a significant backlash that has still not been overcome in this country. Our performance with HPV vaccine in the US is not as good as Rwanda, for example, which has reached 90% coverage in 10- to 12-year-old girls. In the US, coverage is about 50 to 60%.

RESULTS

Now that we've covered rights, responsibilities, and regulations. Let's talk about results. Before turning to specifically immunization, I'd like to consider some of the results relating to general progress in health. I like to think about the health progress that's been made in what I consider to be living memory—the period dating from the birth of my father up to the present.

My father was born in 1904. At that time, the median life expectancy of a white male at birth was 46.6 years. I was born in 1937. When I was born, the median life expectancy was 59.3 years. We'd gone up by nearly 13 years.

My older daughter was born in 1970. At that time, the median life expectancy was 68.0 years, more than a 20-year increase in life expectancy in the 66-year period since my father was born. The median life expectancy of a white male born in 2009 is 76.4 years. This represents an increase in median life expectancy at birth of nearly 30 years in just 100 years. To look at it another way, for every week of the twentieth century, median life expectancy at birth increased by two days. That is an incredible achievement.

The increase in life expectancy is primarily a result of prevention, rather than treatment. It is mostly a result of reductions in infant and young child mortality, primarily with regard to reductions in infectious diseases. As Ben Franklin is said to have pronounced, "An ounce of prevention is worth a pound of cure." (An ounce is 6.6% of one pound so, by Franklin's reckoning, we should be investing approximately 6.6% of all health expenditures in prevention. We actually invest about 1%).

Improvements in sanitation, nutrition, and immunizations have been the driving factors in the increase of life expectancy. Immunization has been one of the most spectacular lifesaving measures known to humankind. Thanks to immunization, smallpox, which killed millions every year, has been eradicated from the face of the earth, and exists only in laboratory conditions.

In the past century, there has been an explosion in the number of vaccines available in the past century. When my father was born, the only vaccine administered to infants was smallpox. The same was true when I was born. By the time my daughter was born, there were eight different antigens, and for the child born in 2009, there are 16 different diseases that can be prevented with immunization. As a result, our immunization schedule is really complicated. Children may get as many as five injections at a single visit, and we only have four arms and legs—one reason why there is so much interest in making combination vaccines!

Today, we have opportunities that we have never had before to prevent illness and death. In the US, we've seen dramatic reductions in the occurrence of diseases that are now preventable by vaccination.

Declines of more than 90% have been achieved for almost all of these diseases. The exception to this is whooping cough (pertussis), which is now being seen in levels higher than those of 20 years ago; this is partly because we now recognize that whooping cough is a serious problem in adults, as well as children; also because we now have much more sensitive diagnostic techniques; and also partly because the acellular pertussis vaccine we now use apparently does not give as long-lasting immunity as did the whole-cell vaccine we used to use, but the whole-cell vaccine caused more reactions.

Even vaccines that have been recently introduced, such as pneumococcal conjugate vaccine, have resulted in major declines in the incidence of diseases. The pneumococcal conjugate vaccine is particularly interesting. It is given to infants to prevent pneumococcal pneumonia, meningitis, and other systemic infections. Administration of this vaccine to infants has resulted in dramatic declines in incidence among those under five. It has also resulted in a 50% decline in the incidence of invasive pneumococcal disease in people of all ages, including those who are certainly not targets for vaccination. In fact, in terms of numerical value, the number of cases prevented by pneumococcal conjugate vaccine is greater among adults than it is among the children who received the vaccine. This apparently is a result of the fact that vaccinated infants are not infecting their grandparents.

Immunization levels in the US are at an all-time high. They are at, or above, 90% for nearly all the vaccines that have been recommended for several years. (HPV is not on that list.) Reflecting the enactment and enforcement of school immunization requirements, immunization levels in children entering school are at about 95%.

Thus, it can be said that we've had spectacular success in the US, and the same is true globally. Global immunization levels rose rapidly in the 1980s although they have risen much more gradually since 1990. Nonetheless, as of 2012, 83% of one-year-old children around the world have received at least three doses of DTP vaccine to protect against diphtheria, tetanus, and whooping cough. There do, however, remain marked disparities in immunization coverage in different regions of the world.

We've seen major declines in deaths from vaccine-preventable diseases around the world just in the last 10 years. In 2000, it was estimated that there were approximately 2.7 million child deaths due to vaccine-preventable diseases. By 2008, this number had decreased by 45%. This is an impressive achievement. But, to put it into perspective, the 1.5 million deaths from vaccine-preventable diseases in children in 2008 is approximately 4,110 deaths each day, or 171 deaths every hour, or one vaccine-preventable death every 21 seconds. We still have a lot to do.

Before the measles vaccine was developed in the 1960s, it was estimated that there were between 5 and 8 million deaths every year due to measles. It was such a common and severe problem that in some African countries children were not given names until they'd survived measles—the names were handed down from generation to generation, and you didn't want to waste a name on a child who wasn't going to survive. By 1980—more than 15 years after measles vaccine had been introduced globally—the number of deaths from measles had been reduced by only about 50%. But, as a result of the widespread application of the measles vaccine, which really began in the late 1970s, the estimated annual death toll from measles fell by nearly 80% from 1980 to 2000. Between 2000 and 2012, there was a further 75%

reduction, down to 122,000 deaths. To go from 5 to 8 million to 122,000 is a remarkable achievement, but it's still 122,000 deaths too many, because virtually all of these deaths are preventable if we can only get the vaccine to the children.

New vaccines are being developed that give hope that we may be able to bring diseases such as AIDS, tuberculosis, and malaria under control, but we're having problems with each of these because they're very complex immunologically. Smallpox has been eradicated. We are close to eradication of poliomyelitis. As of 2014, there are only three countries in the world that have never interrupted transmission of polio: Afghanistan, Nigeria, and Pakistan. Afghanistan's polio currently is all coming from Pakistan.

Many of us believe that measles eradication is inevitable, and just to demonstrate that, an article was published nearly 32 years ago entitled "The Case for Global Eradication of Measles."¹⁰ Eradication is for everyone, everywhere, and forever. Eradication represents the ultimate in equity.

CONCLUSION

The use of vaccines involves a consideration of the interplay of rights, responsibilities, and regulations. We have a continuing need to balance the tensions between individual rights and the meeting of "just requirements of public order and the general welfare."¹¹ We yield some degree of personal freedom, in order to protect the community.

Vaccines are not perfect. They are neither perfectly safe nor perfectly effective, but there exists an extensive regulatory process to ensure they're as safe and effective as possible. Vaccines have made critical contributions to improvements in human health over the past 218 years. There's every indication that they'll make even more contributions in the years to come as we develop new vaccines for infectious diseases, as well as vaccines to prevent non-communicable diseases and therapeutic vaccines. For me, the message is very clear: "Disease is bad. Vaccines are good."

DISCUSSION QUESTIONS FROM THE AUDIENCE

Question #1: What are your thoughts about mandating the flu shot for healthcare workers?

Response: That's a very interesting question. We have, for decades, recommended that healthcare workers get annual influenza immunization to protect themselves and their patients. An infected healthcare worker can infect someone who is on immunosuppressive therapy and has a high risk of complications or death. In spite of these annual recommendations and a great deal of effort trying to improve immunization levels in

¹⁰ Donald R. Hopkins, Jeffrey P. Koplan, Alan R. Hinman, and J. Michael Lane, "The Case for Global Eradication of Measles," *The Lancet*, 319, 8286 (June 19, 1982): 1396–1398, accessed January 27, 2017, [http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(82\)92510-7/abstract](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(82)92510-7/abstract).

¹¹ Declaration of Human Rights.

healthcare workers, we rarely get above about 60%. If we go so far as to send immunization carts onto the ward, go to different shifts, you name it, then we get up to 70%.

Implementing a requirement of annual influenza immunization results in spectacular increases in immunization coverage. I think Virginia Mason Hospital was the first to implement such a requirement, and they went from about 65 or 70% to about 98%. I don't think they fired anyone. People either got vaccinated or left, but I don't think anyone was actually discharged.

The approach of "OK, if you have an objection, we're going to put a scarlet A on you—like in *The Scarlet Letter*—and make you wear a mask and stay away, may, in principle, have some advantages...¹² There is no question that the healthcare worker who gets infected is a potential source of danger to patients. Healthcare workers like to tough it out. They think, "It's just the flu. I'm going to go to work." If you happen to be working in a cancer ward, that might not be a good thing—it can be an infringement of some rights to behave this way. I think this situation and Virginia Mason Hospital's approach to it meets the Siracusa principles. It is necessary, I think, to protect public welfare and the public's health. It would be lovely if we didn't have to enforce vaccination, but it works wherever it's been done.

Question #2: What about school immunization requirements?

Response: The University of New Hampshire (and others) requires students to be vaccinated with MMR before allowing them to attend classes. For workers in New Hampshire healthcare institutions hepatitis B vaccine is required. We are at an odd point with respect to immunization mandates, though. There is increasing opposition. People who are called "vaccine hesitant," "vaccine resistant," or sometimes "anti-vaxxers," exist in clusters in the American population, and are often quite vocal.

In 2014, *JAMA: the Journal of the American Medical Association* published a research letter by Saad Omer, myself, and a couple of others.¹³ After a review of attempts to modify school immunization requirements in several states over the last several years, we had found that none of the efforts to expand exemptions had passed, whereas a substantial proportion of the efforts to make exemptions harder to get did pass.

In spite of the public debate and the publicity, there still seems to be substantial support for the notion that our kids should be safe in school, at least with respect to infectious diseases. I think it's entirely plausible that the influenza vaccine may join the mandatory vaccination group in the future. There are some logistic issues with the influenza vaccine because it is an annual immunization, and so there would be a lot more record keeping involved.

At present, since the required vaccination schedule is based upon school age, and all you have to do is check the year the child enters day care or kindergarten to see which vaccinations a child should have by a certain point. Registries can provide the information that makes an annual determination of immunization status simple. Immunization registries are becoming more and more common in the US. Currently, between 85 and 90% of all

¹² In Nathaniel Hawthorne's novel, *The Scarlet Letter*, set in colonial America, a woman who violated social norms by becoming pregnant out-of-wedlock had to wear a scarlet "A," for adulteress, on her bodice as a punishment.

¹³ Saad B. Omer, *et al.*, "Legislative Challenges to School Immunization, 2009-2012," *JAMA* 311, no. 6(2014):620-621.

children less than six-years-old in the US have at least two immunizations recorded in an immunization information system or immunization registry. At this time, New Hampshire is the only state in the United States that doesn't currently have an immunization registry, but it is working on one.

Several years ago, we did an economic analysis of the cost and savings from the use of immunization registries and found that far and away the biggest positive factor, economically, of immunization registries would be a reduction in staff effort in pediatrician's offices, typically in August. Right now, those practices may not allow their staff to take vacation because they have to be generating so many immunization records. There would also be a reduction in the overtime paid in schools to review immunization records. The registry can do all that work automatically. In Michigan, each school says, "Here are the kids entering this year." The registry sends back messages like "These kids are OK, but these two need those vaccines."

When it comes to influenza however, the disease is not as feared as many of the other vaccine-preventable diseases, and the influenza vaccine is not as good as many of our other vaccines. Depending on the year and the match between a circulating strain and the strains in the vaccine, it may be only 50% effective, or it could be 75% or even 80% effective. But that contrasts with the 90+% effectiveness of the measles vaccine.

The issue is further complicated by the fact that so many things are called flu that aren't actually the flu. We hear people say, "I had a stomach flu last week." Yet, the influenza virus infection doesn't cause gastrointestinal symptoms. If you had diarrhea last week, it probably wasn't influenza, but you still call it flu. Then there are many things that cause symptoms similar to flu. We hear people say, "I got the flu shot, and then I got the flu." But influenza vaccine does not protect against rhinovirus infections, for example. We don't normally get diagnostic tests done to tell us what the cause of the illness is, so we may not know for sure in any particular case—it may be influenza, but it may just as likely not be.

Thus, I would conclude that the influenza vaccine is a little harder to consider mandating than, for example, the measles vaccine. But it may happen.

Question #3: What happens to influenza vaccine that is not used in the US?

Response: For physicians' offices that don't do a lot of immunization, it may be much more convenient to have the patient go to the pharmacy and get immunized. They are important partners of some interest, compared to in the early 2000s.

At the end of a recent flu season, Walgreens Pharmacy discovered that they had 350,000 doses of influenza vaccine that they couldn't use. They were going to throw it away, but didn't want to. They called the Centers for Disease Control and Prevention (CDC) and said, "We really don't want to throw this out—it's perfectly good vaccine—but we're not going to be able to use it. Can you find a use for it?"

Very soon, 350,000 doses of influenza vaccine were on their way to Laos where they were administered to pregnant women and healthcare workers and other high-risk individuals. Everybody liked that. Indeed, they liked it so much that the following year, the effort was repeated and extended to include Nicaragua for use in pregnant women and healthcare workers.

The Bill and Melinda Gates Foundation got interested in providing some funding to us and the CDC to try to expand this effort into something called Partnership for Influenza

Vaccine Introduction. I hope, by now, that 763,000 doses of influenza vaccine have finally been unpacked in Vientiane, Laos. They were shipped from Frankfurt a few days ago [in 2014] in refrigerated containers by plane to Bangkok and then over land in refrigerated trucks from Bangkok to Vientiane. The last trucks were being unloaded earlier today, so I hope it's all there.

We hope to be able to expand this activity in the future in a somewhat different way; because this program started on the basis of goodwill and excess vaccine, it's not easy to plan around. So, now, we're trying to get advanced commitments from donors—manufacturers or other donors—for some level of support, so we can say to countries, “OK, you're going to get at least this much support to introduce influenza vaccine.” That enables those countries to establish an infrastructure for delivery and have in their mindset that they're going to be doing it. Then, later in the year, if more vaccine becomes available, they have the infrastructure to be able to absorb it. So, we're hopeful that this will expand successfully. We'll see.

Question #4: Why do some diseases require more than one dose of vaccine?

Response: It depends on the disease and how readily it spreads. For example, with polio, we have historically thought that if we had community immunity on the level of about 80% or so, it would be adequate. On the other hand, with measles—about the most highly contagious disease we know—you have to reach 95+% immunity. This is not just immunization of the population, but immunity in the population in order to interrupt transmission.

What that means is that we give two doses. One dose will protect 90% of people who receive it. The second dose will protect 90% of those who didn't respond to the first dose, because, as far as we can tell, the vaccine failures are essentially random. We can get very good levels of population immunity by using two doses of measles vaccine.

It depends on the disease.

Question #5: You spoke about the anti-vaccine sentiment here in the US and also in the UK. I was wondering if you can talk about the anti-vaccine sentiment at the global level right now.

Response: There is anti-vaccine sentiment, I think, in virtually every country in the world. The reasons for it differ from country to country. In some places, it's based on religious belief. For example, in Zimbabwe a few years ago, they had a major epidemic of measles with thousands of cases among followers of an apostolic sect that rejects vaccination.

In northern Nigeria, in 2003, political and religious leaders claimed that the oral polio vaccine was contaminated with HIV or that it contained a sterilizing agent to sterilize their children. They stopped vaccinating against polio, and it took the effort of sending the vaccine for testing in labs in Muslim countries to show that it had no HIV or contraceptive in it. Then, finally, after obtaining oral polio vaccine manufactured in Indonesia—the largest Muslim country in the world—the campaign started up again. During the year that they weren't vaccinating, Nigeria exported the disease to 23 other countries around the world that had previously been free of polio, some for as long as 10 years. That's an extraordinary setback in the campaign to eradicate the disease.

There are groups that are opposed to Western influence. In fact, in Nigeria, the leaders who were talking about HIV and contraceptives actually admitted publicly that they didn't believe that the vaccine was contaminated, but they spoke out against it because they were opposed to the polio eradication initiative because it was a Western-led initiative. That same view has been expressed in Pakistan, and to a lesser extent, in Afghanistan.

There have been some instances where, for example, the wrong diluent was used in reconstituting a vaccine. There was an instance in, I think, Guatemala a few years ago where succinylcholine, a muscle relaxant, was mistakenly used as a diluent for the measles vaccine. The children who were immunized collapsed within a half hour. Fortunately, very few died.

Understandably, such things lead to concern about vaccination and about immunization.

There are differing issues in differing countries, but I do think there is an overall growing amount of vaccine hesitancy, vaccine reluctance, vaccine refusal, anti-vaccination sentiment, whatever you wish to call it.

Question #6: What is the basis for those who oppose immunization requirements?

Response: As I say, I think the opposition to immunization requirements is based on a number of factors—religious belief, philosophical belief, libertarian beliefs captured by the sentiment: “Get your damn government fascist boots out of my door.” It's a range of things.

It is of some interest that fewer than 2%,—it may be even fewer than 1%—of children in the US have never received any dose of vaccine. A lot of the opposition to vaccines is selective, and HPV vaccine is a prime example of that currently. If you look at unvaccinated, versus under-vaccinated or partially vaccinated children, the partially vaccinated children tend to be children of higher socioeconomic status than the children who are totally unvaccinated.

Question #7: Can you speak more about the movement to reduce the exemptions for not having your child vaccinated?

Response: This is a state-by-state movement, because each of the requirements is a state requirement. Pro-vaccine parents have mobilized in many areas. Voices for Vaccines, the group that I mentioned, is very interested in this.

The anti-vaccine voices are also pretty well organized and have more years of experience in the use of the Internet and social media than pro-vaccine people do. After all, who's going to go around and protest something you like? As they say, nobody bleeds to death from prevention, so you take it for granted. The great fun in prevention is sitting around and watching nothing happen as a result of what you've done!

Question #8: Jenny McCarthy is a celebrity in the media who's opposed to vaccines because she claims that her son developed autism after getting the measles, mumps, and rubella (MMR) vaccine. Is there any truth in that?

Response: Ms. McCarthy has “mom science”—that's the term she uses—on her side. There have been at least 10, possibly more, studies that have clearly shown that the MMR vaccine is not associated with an increased risk of autism, but mere facts do not decide things.

I'm a recovering epidemiologist. I often say that data doesn't drive decisions, stories drive decisions.

Where we have failed as public-health officials and epidemiologists is in finding and using the stories that exemplified what the data show. We have to learn how to do that better. It's not just a question of providing the facts—facts don't counter beliefs. Facts can counter ignorance, but not beliefs, nor values, which are based on a variety of factors, only one of which is reason.

It's easy to understand why, if something bad happens to your child, you start asking, "What might have caused this?" As an example, about 30 years ago, there was a lot of discussion around whether DTP vaccine—diphtheria, tetanus, and pertussis—caused sudden infant death syndrome (SIDS).

Assertions were made that SIDS is precipitated by DTP. If you look into it, it turns out that the DTP vaccine is given in the US at two months, four months, and six months of age. The peak incidence of SIDS is between three and six months of age. We went through the statistics on this to find that, by chance alone, there would be 50 times a year in which a child died in the 24 hours following a DTP vaccination. It is also true that, by chance alone, there would be 50 times a year when a child had SIDS the night *before* being scheduled for DTP vaccine.

But, OK, here I am, a mealy-mouth epidemiologist talking with the mother of a child who died suddenly the night after receiving DTP vaccine. Is she going to believe me when I say, "Studies have shown that the DTP vaccine doesn't cause sudden infant death syndrome." When I'm a grieving a parent, I want to know what might have caused it, and here is an identifiable event that resulted in the child crying and having a fever. I may make an association between the vaccine and SIDS. It is impossible to deal with such circumstances, and you absolutely understand it. Even though I'm a recovering epidemiologist, if it had been my kid, I would have said, "Well, I don't know. Maybe not, but perhaps in this case." The National Vaccine Information Center—something of a misnomer—says "If it happens to you or your child, the risk is 100%," which is, in fact, a fair reflection of perception.

Question #9: What's the current situation for managing potential vaccine complications?

Response: The National Vaccine Injury Compensation Act provides coverage for side effects from vaccines that are recommended for universal use in children, even if those vaccines are administered to adults. This is a no-fault system, but it also means you cannot go to court to sue the manufacturers unless you've gone through this system. If you go through the system, you can reject the finding and then sue. For example, if the compensation program says, "No, this was not a vaccine-induced injury." Then you can say, "OK, the hell with you. I'm going to go sue." On the other hand, all of the material that was presented to the Vaccine Injury Compensation Program is also available as part of a lawsuit. Equally, if you're given an award by the compensation program, you can say, "Oh, that's not enough. I want to go sue." You can do that, but once again, the information and findings of the compensation program are part of it, *and* you forgo the award from the compensation program.

The compensation program doesn't apply for vaccines that aren't recommended for universal use in children. There still is tort liability there. The program has, though, had a remarkable impact on liability relating to childhood immunization. On the other hand, we're not vaccinating as many adults.

Question #10: Why don't physicians want to schedule the vaccines all at once?

Response: It's because of a range of things. There are some people who claim—and even some physicians who say—“Giving five vaccines at once...that's too much antigen for a baby.” Well, it turns out that if you look into the vaccines, they have a lot fewer antigens than the wild organisms. Children are constantly exposed to different antigens.

There is also concern about simultaneous injections. Who wants to watch their child get five shots at one time? Well, actually, parents do! If you say, “OK, Johnny needs five injections. I'll give him all five now, or we can schedule for you to come back every two weeks and give him two today, two in two weeks from now, and the fifth one at the end of the month.” Which would you rather do? You'd rather give him all five shots today. There are variety of reasons for making this choice: Spreading out the shots means taking time off from work to bring Johnny in two more times. It means paying for two more office visits. Besides, Johnny is already crying. Why make him cry two more times? It's a fascinating thing. There have been surveys on this, and it turns out that healthcare workers, particularly nurses, are more concerned about the impact than mothers are!

CLASS EXERCISES

Vaccine Controversy

- The instructor will poll the class, as a whole, about whether they are pro- or anti-vaccination. The instructor will then randomly divide the class into two groups that will represent the pro-vaxxers and the anti-vaxxers.
- Each group is responsible for researching, via the Internet, their respective positions.
- Each group is responsible for preparing a 15-minute presentation about their position. This presentation should rely on historical references, public health data, applicable regulations, and the role of rights in the argument.
- Once the presentations are completed, the instructor will facilitate a general class discussion about the information that was presented.
- The instructor will poll the class following the discussion to see if the initial poll response has shifted.

Public Health Protection versus Personal Freedom

- Divide the class into two or three groups.
- Each group is responsible for researching, via the Internet, a historical example that represents the tension between protecting the health of a population at the expense of one's personal freedom.
- Each group is responsible for preparing a 15-minute presentation to the class about their specific example. This presentation should rely on historical references, public health data, applicable regulations, and the role of rights in the argument.

- Following each presentation, a brief discussion is held to determine whether the class agrees with the outcome of the case or not.

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ABOUT THE AUTHOR

Dr. Hinman is the Director for Programs at the Center for Vaccine Equity, a program of the Task Force for Global Health, a non-profit organization affiliated with Emory University. He received his Bachelor of Arts from Cornell University, his medical degree from Western Reserve University, and his Masters of Public Health degree from the Harvard School of Public Health. Since 1965, he has been involved in public health programs at state, national, and global levels, primarily working with the Centers for Disease Control and Prevention based in Atlanta, Georgia. At the Centers for Disease Control and Prevention, he served as

Director of the Immunization Division from 1977 to 1988 and of the National Center for Prevention Services from 1988 to 1995.

In addition, Dr. Hinman has worked for the State Health Departments of New York and Tennessee. He retired from the United States Public Health Service in July, 1996, having attained the rank of assistant surgeon general. He has authored or co-authored more than 400 publications. He has served on the Executive Board of the American Public Health Association and the Board of the Global Alliance for Vaccines and Immunizations, as well as chaired an Advisory Committee for the World Health Organization. He is an Adjunct Professor of global health and epidemiology at the Rollins School of Public Health of Emory University, where he teaches courses on immunization programs and policies, as well as on health and human rights.

Chapter 85

REFUGEE HEALTH IN THE US: FROM INTERNATIONAL POLICIES TO THE AFFORDABLE CARE ACT

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INTRODUCTION

Refugees are the tragic consequences of the unrest that occurs in and between certain countries. Dr. Geltman's lecture outlines the process by which one becomes a refugee and the refugee resettlement process, with emphasis given to the unfortunate consequences that can befall refugee children. Examples specific to the Lost Boys and Girls of Sudan and the conflict in Kosovo are used to highlight the mental health outcomes for these children. Since the health-care system landscape is changing, Dr. Geltman's lecture also introduces the impact the Affordable Care Act may have on health services that refugees receive during the resettlement process.

The question about whether refugee children suffer from discrimination in health care in the realm of public health underlies this lecture, although Dr. Geltman does not address it explicitly. This chapter presents an overview of how small the world truly is with respect to the importance of addressing the health of all populations and why, from a humanitarian standpoint, we need to continue to work to improve the social determinants of health for all. It also reveals a current population that is particularly vulnerable to discrimination because of its needs, as well as its lack of means and power.

In addition, by discussing the process by which refugees come to the US, the process of resettling them here, and the health-care needs that their experiences both abroad and in the US might create, he shows that tensions between public health, individual liberty, and government authority can depend upon factors that are outside of the field of health care itself. These may not be the tensions that we traditionally consider in the US, nor the ones discussed in the other chapters in this book, but they are still important to understanding the interrelationships of liberty and health. Specifically, the crisis situations that turned the

children he discusses into refugees help to explain why those children may have particular health needs—especially mental health needs—even once they arrive in the US. Yet, because the US government and other agencies assist in the resettlement of child refugees in the US, and because the refugees have little means, their care is dependent upon domestic and international politics, especially upon definitions created by treaties and laws, such as the UN Refugee Convention; organizations supported by the government, such as the State Department; and funding provided by political institutions, such as Congress. The US federal government's authority provides the opportunities for refugees to come to the US, as well as the resources upon which they can draw for their needs, thus both opening the door for care and limiting how widely that door is open. Public health issues, very broadly defined, arise because the government, through programs like Medicaid, subsidizes much of the early care for refugees. In addition, (nearly) universal health care is one of the goals of the Affordable Care Act, thus making all kinds of health care a public interest. Finally, because of their political status and means, refugees have little liberty to control their own health care.

LECTURE

About 13 years ago, a group of refugees started arriving in the US from southern Sudan. They became known as the Lost Boys of Sudan. After a group of the youngest of them had been in the US for about a year, I had the privilege of doing what was, in effect, a very unique health-outcomes assessment of them.

As you learned in the introduction, I am a pediatrician, and when I talk about refugee health, usually my preference is to focus on children, although what I say about children is not necessarily specific just to children; some of the issues are much broader, in terms of high-risk groups, even within refugee populations.

I want you to think about how well our current system of refugee resettlement actually works and whether, somehow, we are failing children along the way in this process. I'm going to start with some background about the topic. The United Nations Children's Fund (UNICEF) estimates that of the 57 million plus people displaced by war, more than half are children. Of these millions of children, it's the unaccompanied who are the most likely to be killed, tortured, raped, robbed, and recruited to be child soldiers. Historically, the scope of the problem can be seen when you look at Cambodia in the 1980s: around half of the entire population was under 15 years of age, which is extraordinary; in Rwanda in 1994: in a matter of two months more than 100,000 minors were left unaccompanied as a result of the genocide and the refugee situation and its immediate aftermath; in Angola a year later: during their civil war more than 20% of the nation's children were deemed to have been separated from their parents at some point. Finally, there are known to be more than 100,000 unaccompanied minors in the Great Lakes Region of Africa—the area around Lake Victoria, Lake Kivu, Lake Malawi, places like Burundi, Rwanda, Uganda, southern Sudan.

Many years ago, I had a calendar that featured a picture and a quote from Graham Greene: "There's always one moment in childhood when the door opens and lets the future in."¹ This quote could be a metaphor for child development. Child development occurs in

¹ Graham Greene was a twentieth-century author of fiction. Graham Greene, *The Power and the Glory* (London, Penguin, 1940, reprinted 1991), 12.

spurts and transitions. The image of the door opening and letting the future in struck me as relevant to refugee children, because it's such a time of turbulence in their lives and their development. What happens if something goes wrong and that door doesn't open, or they're not there, or they're at the wrong door, or they're coming from a very non-western culture and they don't know how to use the doorknob? There are so many things that can go wrong for children, in terms of their future development; I keep that old calendar page on my office bulletin board at the State Laboratory in Boston just to remind me of that fact.

Who Is a Refugee?

Who is a refugee? Who am I actually talking about? My work in refugee health is with the government. I do not work with undocumented immigrants because, in the eyes of the government, they are not refugees. They don't have a visa with the government's imprimatur on it so that there's a process to their resettlement.

How does a person become a refugee with a capital R, not a refugee with a little r? Refugee status was defined in 1951 by the UN Convention. It was a time when many of the international human rights documents came into existence [such as the United Nations Declaration of Human Rights], following the European refugee crisis in the wake of World War II. A refugee was defined then as any person who, "owing to well-founded fear of being persecuted... is outside the country of his nationality and is unable or... unwilling to avail himself of the protection of that country... or... return to it."²

In 1980, the Refugee Act formally incorporated this international definition of a refugee into US law. The hope was that the Act would remove the prevailing Cold War geographic and geopolitical or ideological preferences from the determination of refugee status and refugee populations. It established specific procedures about how to deal with refugees, how to resettle them, and how to integrate or assimilate refugees into US society; it also established what programs and services would be provided for refugees and how long they'd be eligible for those programs and services.

Why don't we see refugees from Central America? Well, because we didn't exactly depoliticize this, and, in fact, refugee resettlement is very much a part of our foreign policy and government policy. We really did not recognize the refugee situation in Central America, and so all of the Central Americans who wound up in the US are—in the eyes of the government—undocumented immigrants, not refugees.

Making refugee determinations through official international and governmental channels begins overseas. A refugee, by definition, is someone overseas, and most will be referred to the United Nations High Commissioner for Refugees, usually referred to as UNHCR. Representatives of UNHCR will take referrals, and then they will refer them to the US representatives in refugee camps overseas.

Overall, fewer than 1%—substantially fewer than 1%—will actually ever be resettled in a third country like the US. The most prominent countries currently engaged in refugee resettlement are Canada, Sweden, Australia, New Zealand, and a smattering of other

² United Nations, "Conventions Relating to the Status of Refugees," United Nations Conference of Plenipotentiaries on the Status of Refugees and Stateless Persons, July 28, 1951, accessed January 23, 2017, <http://www.ohchr.org/EN/ProfessionalInterest/Pages/StatusOfRefugees.aspx>.

countries. A smaller number of refugees will self-refer themselves to US consulates and embassies, although usually there has to be some kind of special status that permits such self-referral. Even fewer are referred by NGOs (non-governmental organizations), which make up what's called the overseas processing entity that works with refugees overseas and handles their cases.

The US Refugee Admissions Program is run by the State Department and gets help from the Department of Homeland Security, specifically the US Citizenship and Immigration Services. They have to determine whether individuals meet the definition of refugees. Are they non-combatants? Are they non-perpetrators? Then, in the wake of 9/11, approved applicants undergo a pretty thorough background check, and that can take a long time. If they're approved, they'll be assigned back to the NGOs for sponsorship. All refugees coming to the US have to have a sponsor, someone who's responsible for them.

The NGOs often will help prepare the refugees' applications in the first place, so they're often familiar with the refugees when they come back for sponsorship and processing. They will also often do a cultural orientation prior to departure for the US.

Lastly, the Centers for Disease Control and Prevention (CDC) and their partners at the International Organization for Migration, do an overseas medical screening and arrange for the logistics and transportation involved with migrating to the US.

Refugee Experiences and the Process of Resettlement

Back in November of 2001, I took a photograph of six young men. They were the first Lost Boys of Sudan to enter Massachusetts. They were probably among the first hundred or so to come to the US.

I'm going to use some recordings to try to give you a better sense of what it's like being a refugee and what their experiences were, because I think it resonates much more than hearing me talk about it. This first is a clip from *60 Minutes*:

Narrator: They were known as the Lost Boys because they were between five and 11 when their Christian villages in southern Sudan were attacked by Islamist forces from the north. When they saw their villages burning, they started running. Streams of boys became rivers. Hundreds became thousands until an exodus of biblical proportion was underway. They walked for three months across Sudan, barefoot. Twelve thousand found refuge in Ethiopia. But after four years, they were chased out at gunpoint, chased to the Gilo River where the waters did not part. For Joseph Tabin, that day will never go away.

Joseph Tabin Rufino: We saw so many people who were just floating on the river.

Bob Simon: Dead bodies.

Joseph Tabin Rufino: Dead bodies, yeah, who are floating on the river. ... Many were shot. Many drowned. Many were eaten by crocodiles. Zachariah Magok was there.

Zachariah Magok: One thousand to 2,000 who died in that river.

Bob Simon: One thousand or 2,000 died in that river?

Zachariah Magok: Yes.

Narrator: It wasn't much better on the other side. They walked across deserts, over mountains. They had no food or water. Paul Deng was seven when he started the walk.

Paul Deng: You have to urinate so that you drink your own urine.

Bob Simon: Did you ever do it yourself?

Paul Deng: Yeah. I didn't want to die. Other people didn't want to die.

Narrator: In the spring of 1992, after walking more than a thousand miles, the boys made it over the border into Kenya, to a desolate place called Kakuma. For the UN, it was an emergency of vast proportions, these emaciated children. For the boys, it was the safest they'd been in five years.

Joseph became a medical assistant at the camp clinic.³

So, to summarize, these young people spent 13 years fleeing violence and living in refugee camps; three years first in Ethiopia, then 10 more years in the refugee camp, Kakuma, in Kenya. Can you imagine that? That guy they were interviewing is probably about 22 years old; he probably started this process when he was about eight. Think about him, without his parents, walking across Africa alone. The youngest were preschool-aged children, and they endured severe deprivation as well as the loss of their parents, who were either missing or dead. They walked anywhere from 700 to 1,000 miles, often barefoot. They were stalked by hyenas and lions along the way, and they watched their peers being eaten. They were attacked by Sudanese militias first, then by the Ethiopian military. They had to cross the Gilo River, which was infested with Nile crocodiles. Many of them didn't know how to swim. In one of the interviews, one of them talks about how they figured out that the crocodiles look at you on the surface, so the only way to get across was to swim underwater. If you didn't know how to swim, you were in trouble. Thousands died, not just the 1,000 that the young man talks about, but multiple thousands died crossing that river. Sudan's a pretty big place, of course, and today it is two countries. The area the boys came from, Equatoria, is in southern Sudan, within a triangle including the towns of Bor and Juba and Rumbek. It is estimated that about 30,000 set out; 30,000 kids walking to Ethiopia.

When the Ethiopians attacked them and kicked them out—with helicopter gunships, by the way, firing into the refugee camps—they walked back into southern Sudan and then crossed a mountain range. The southern end of the range includes Kilimanjaro, the Great Rift Valley in Kenya and Tanzania and the Thousand Hills of Rwanda. The boys were at the northern end; they had to cross a 10,000-foot mountain peak, barefoot, emaciated, on their own, starving.

By the time they got down to Kakuma, in about 2001, it's estimated there were only about 6,000 of the original 30,000 left. In photos, the camp in Kakuma looks kind of neat and orderly, but imagine it during the rainy season when all the dirt turns into mud. It was a very hostile and inhospitable environment in which to grow up. In about 2000, the camp had about 50,000 residents, of whom 70% or so—about 35,000—were children. Most of them, or many of them, were unaccompanied.

Lots of kids live in refugee camps. When you have a refugee crisis like this, the internal agencies and other groups involved, the governments, try to come up with what's called a durable solution. So, what can be done with large numbers of refugees in a massive camp like this? Basically, there are three durable solutions.

First, send them back, repatriate them to their home country, if possible; that's the ideal solution. Second is local integration, absorb them into the surrounding community. Sometimes that actually does happen over time. But, Kakuma was in the middle of nowhere. There was no local community into which the refugees could assimilate. Third, which only a tiny percent will ever see, is resettlement in a third country like the US. To get to that point,

³ "The Lost Boys of Sudan: 12 Years Later," *60 Minutes*, Transcript, Produced by Draggan Mihailovich, March 31, 2013, <http://www.cbsnews.com/news/the-lost-boys-of-sudan-12-years-later-21-07-2013/>.

the agencies will often do the “best interest determination,” and this is where we start to get into policy issues.

The best interest determination seeks to identify the most appropriate solution for the refugee crisis; that is, what to do with the refugee population. Sometimes the decisions are population-based; sometimes they focus on specific individuals or subgroups like high-risk groups. For children—unaccompanied children in the case of the Lost Boys—the task is, to quote Anna Freud, to do “what’s in the best interest of the child.”⁴

Health Challenges for Refugee Children

Now, I want to give you my second example of a child refugee: a boy from Kosovo. In the 1990s, Yugoslavia fell apart in civil war. First came the “Bosnian crisis” involving Bosnia and Croatia and Serbia, and then Kosovo, part of Serbia, tried to split away. But Kosovo seceded without the consent of the Serbians. The action spawned a brutal civil war between Serbia and Kosovo.

The video clip that I’m going to share with you, is probably the best narration of a refugee story that I’ve ever heard.

New England Cable News (NECN) had interviewed me previously—very early in my career, when I was working for the Department of Public Health. They came to the State Lab and interviewed me, and I gave them my usual spiel about infectious diseases and trauma. I guess they liked it, and the crisis was unfolding, so the following week they asked me to come into the studio for a live on-air interview.

I thought it was going to be more of the same. They didn’t give me any kind of preparatory materials or anything, and after about 30 seconds they turned to me and said, “You know, we have an example of that. Let’s show the video clip.” The host, Margie Reedy, is a very forceful, eloquent, tall woman. She was around 6 feet tall plus wearing heels, a very empowered presence. I’m a reasonably confident person, but as I say, it was early in my career, and I was thoroughly intimidated. At the end of a brief introductory exchange, she turned to the camera and said, “Let’s watch the clip.”

Margie: This reporter, Dan, has the story of one 10-year-old dealing with the horrors of the war.

Dan: When you’re 10 years old you believe in the Boogeyman. You believe evil visits at night, Dren Caka believed. This morning, Dren describes what he saw.

Dren: [foreign language]

Dan: It was the most difficult night I’ve seen, he said. A group of Serbs came to his home, accused his family of hiding Kosovo rebels, and began shooting.

It was at the Albanian border, and they’ve heard about this happening before, but not with someone this young. He arrived here a few minutes ago with a bullet wound in his arm and a big, a big hole in his life.

Dren: [foreign language]

Dan: They killed my mother and my three sisters, he says. They put guns to their head and shot, and all 19 members of his family died that night.

He told the French medics who flew him to Tirana that people who did this were his Serbian neighbors. “I knew them,” he says. “I’ve seen them around town.” He told the American Air Force medics who treated him when he arrived at the airport that his father escaped just before that terrible night. Then later the Serbs were killing them.

Dren: [foreign language]

⁴ See Joseph Goldstein, Anna Freud, and Albert J. Solnit, *Beyond the Best Interests of the Child* (New York: Free Press, 1973) for more details.

Dan: "After they shot me, I played dead," he said, and waited until they set the house on fire, and then he jumped out the window. He ran to his aunt's house nearby.

Nimate: [foreign language]

Dan: "At first I didn't believe him," she says, "but then I saw his arm." And for this 10-year-old boy, the last memory of his family is his sister lying on the floor.

Dren: [foreign language]

Dan: "I didn't know if they were dead or alive," he says, "but I couldn't help them." The boy had broken his arm and he couldn't even carry his two-year-old sister. "I feel very bad about that," he says.

Don't tell Dren Caka the boogeyman isn't real; he believes.⁵

And that's when Margie turns to me and says, "Dr. Geltman, what did you think of that tape?" I couldn't even speak. This kid is 10 years old. People he knows break into his house in the middle of night with guns; they kill 16 or 19 of his family members, assassination style, bullet to the head. They shoot him in the arm and he only survives because he plays dead in the pile of bodies on the floor of his home. As they're setting the house on fire with him inside it, he climbs out the window, and he sees his two-year-old sister on the floor. He doesn't know if she's dead or alive, but he can't pick her up because his arm is broken. He flees to his aunt's house, and they flee together and escape to safety.

If you're 10 years old, what does that mean in terms of your development, your psyche, your future, and your emotional status? The whole narration centered on the boogeyman and night fears. Kids at this age are supposed to have fears; part of growing up is facing your fears, understanding them, overcoming them, and that's totally shot to pieces for this kid. He's watched his family being killed by people they knew. How is this kid ever going to develop the capacity for trusting relationships and emotional engagement with other people? What about overcoming the fear he's always going to feel in new situations and new environments with new people? How can he trust anybody?

Kids are truly the hidden casualties. There is an article by Bonnerjea entitled "Disasters, Family Tracing, and Children's Rights: Some Questions about the Best Interests of Separated Children," that emphasizes this point.⁶ It goes back a long time in terms of the impact of violence on refugee children.

Dr. Richard Mollica is a Harvard psychiatrist who works with Mass General Hospital. Back in the late 1970s, early 1980s, he did classic studies of adolescent Cambodian refugees in the camps in Thailand, and he showed that even low-level ongoing violence exposure in refugee camps is extremely deleterious, extremely harmful, for the mental health status of these adolescents. Mollica wasn't talking about witnessing a big bomb explosion or being involved with a firefight, after which you're done and you're safe. This was about ongoing violence in the camps—assault, robbery, stuff like that—just the ongoing sort of petty violence that refugee kids will be exposed to on a daily basis. Imagine you're a Lost Boy of Sudan at Kakuma—this is going to be your life for 10 years while you're a child and adolescent.

When processing unaccompanied children, agencies try to trace and reunite families. It's right to prioritize this. But it can be a long process. It can take months, even years. Around a third of the unaccompanied minors in the Great Lakes Region, particularly Rwanda, were reunited with family members—maybe not their parents, but a close family member. That's

⁵ Paul Geltman, interview by Margie Reedy, *New England Prime Time with Margie Reedy and R.D. Sahl*, New England Cable News, April 6, 1999.

⁶ L. Bonnerjea, "Disasters, Family Tracing, and Children's Rights: Some Questions about the Best Interests of Separated Children," *Disasters*, 18, no. 3 (September 1994): 277–83.

pretty successful, but what are the consequences of going through this process? What's the potential impact of that long drawn-out process, and what's going on in that child's life in the meantime? What are the prospects for successful reunification with their family, especially if the child is a youngster and years have gone by? The child might no longer even know their family. Is that really in the child's best interest at that point? And, what happens to all those unaccompanied children in the meantime?

There is this great debate that's been going on historically about orphanages versus foster care of some sort versus group homes. In Rwanda, they did this big push to do foster care placements of kids and get them into homes. That worked out pretty well. They did that pretty effectively. There were a number of big groups like Save the Children and UNICEF. They had a big presence there, and it was a very sophisticated operation starting with the tracing and then foster care placements. How you do that in Kakuma where there are no families? They created families. They essentially did group homes with a family structure where they grouped younger kids with older ones who could help look after them, kind of like a big brother, big sister relationship. That was the best they could do; certainly it was not a true family.

The reality is that in terms of the impact of all of this on kids, studies have estimated that more than 90% of recent refugee populations, at this point, have experienced pretty significant physical and psychological trauma. This is now the universal experience of refugees. It wasn't always that way, but it has become that. I took a picture of a boy in Rwanda. He was just walking along the roadside, hobbling, not walking very quickly. I looked at him for a while and noticed that his ankle was at a right angle. Clearly he had fractured his ankle at some point in the recent past, and it hadn't been taken care of or set properly. He's permanently deformed unless at some point he somehow manages to get some surgical correction. He was just wandering around by himself. I have no idea what his situation was.

Another time I encountered a girl at a Rwandan orphanage at which I did some work with Doctors of the World. She had a zigzagging scar that wrapped all the way around from the back across the side of her head. It was a wound sustained when somebody attacked her with a machete during the Rwandan genocide.

Again, what is the impact of all of this repeated trauma and its aftermath on refugee children? Even if they are not forced to flee, these children live with daily reminders of horror. In Rwanda, it's everywhere: bones lie here and there; there are bullet shells; there are burned out church buildings. Rwanda is a Catholic country and many of the Tutsi population sought refuge in churches. Their attackers blocked the doors and set the churches on fire. There were burned-out church buildings all around Kigali and other municipalities.

In order to talk about the developmental issues, you have to understand a little bit about early childhood and early school-aged children; that age is a process of change and maturation. It's a period of rapid progression in imagination, in communication skills and relationship formation, in knowledge base, and just in how we understand and interact with the world around us. Stress and trauma are known to alter brain neurobiology and neurodevelopment in very young children, particularly in the hippocampus. That creates concrete and predictable cognitive behavioral and emotional impacts or difficulties for kids coming out of this kind of environment. In particular, you need to have a certain basic sense of trust and security to allow for the exploration and mastery of your own environment—that's what you do when you're a school-aged kid: you explore and master your environment.

One day I took another photo in Rwanda and made a slide that you see here. [The lecturer projected a slide.] It's a stunningly beautiful setting. This is Lake Kivu by Cyangugu, Rwanda, and Bukavu, Congo, on the other side of this inlet, which is the beginning of the Kivu River. You can see the rolling hills of the Kivu Mountains in the background, the purple and oranges of the sunset. The water is actually a deep emerald green. It's spectacular.

About a month before I took this picture this whole lagoon was filled with dead bodies.

On this particular day, we were walking along and came upon these two little kids who looked pretty young. They had no pants, just shirts. They were dirty and grubby-looking. They just stopped where they were, squatted down, and did their business on the side of the road. If you look closely, you can see they're squatting over their little puddles of diarrhea. I use this slide when I talk about parasites and malnutrition, but today I'm using it because these kids were clearly displaced children. Whether they were with families or adults, I don't know.

The whole roadway from Kigali, the capital of Rwanda, to this southwest corner of the state was lined with little stick lean-tos that people had constructed while they were fleeing the capital area. Kids just get lost and caught up in all this stuff. There's the whole issue of trauma and PTSD—the kids will attribute responsibility to themselves in the role of guilt and mourning.

It's critical in human development for young children to develop a sense of guilt. This concept goes back to Freud. You have to understand guilt to have a sense of morality. You have to be able to self-regulate yourself. Think of Dren Caka and his boogeyman. Not only is he at an age when kids will attribute magical meaning to objects and events they experience normally, but also there are the issues of guilt. He will blame himself for his sister's death. He will blame himself because he left her there not knowing if she was alive or dead, and that's his fault. Somehow, it's his fault because he lived. It was his fault that his family members died. This kind of magical interpretation of events will heighten fears of reoccurrence and re-experiencing—a hallmark of post-traumatic stress disorder, or PTSD. This re-experiencing will come out of kids in traumatic fantasies and play behavior, like re-enacting a scene or drawing pictures of it. You'll be sitting in class, drawing pictures, and some kid will draw the picture of his family being killed. Children will relive and reenact and remind themselves, and as they do, they will blame themselves for what happened.

Such events impart a sense of vulnerability when a child should be feeling invulnerable. Kids who go through this kind of stuff will have continuing fear and hypervigilance, but no understanding of the concepts of protection and safety, which are necessary for that successful exploration of your environment. That will lead to difficulty with trust and relationships, as well as social withdrawal and numbing of responsiveness, which again, are hallmarks of post-traumatic stress disorder. It can even lead to identification with the aggressors; somehow they were powerful and magical. The aggressors must be the good guys if they were so strong and we were so weak. We let this happen.

In the case of the Lost Boys, the UNHCR hired consultants, specifically mental health experts, to interview the minors in the camp. One of them was Julianne Duncan, someone whom I got to know. She actually wrote the mental health report in the best interest determinations for the unaccompanied minors in Kakuma. She predicted that compared to children fleeing with their family, children fleeing alone would be more likely to be traumatized, to feel responsible for the deaths happening around them, and to develop a sense of insecurity and mistrust. It is basic mental health and social science, and predictable.

In her report, Julianne Duncan wrote that virtually all the children interviewed were experiencing symptoms of trauma. For the boys, it was typically prolonged sadness and grief, sort of an internalizing behavior. For the girls, it was depressive symptoms, specifically around the reality or the prospects of being a girl and being forced into an unwanted marriage. All of them very strongly equated education with safety—it was their opportunity to find safety. There was a strong sense of altruism and a desire to return to Sudan in adulthood to help rebuild their country.

When I did my study, we asked a small subset of our sample to dictate audio narratives about their most difficult or challenging experiences. We intended to do a formal qualitative analysis, but we ended up using them just to give us context to the quantitative responses that we were looking at in assessing their health outcomes. I've never let anybody listen to them, other than my colleagues, but I've created one segment of excerpts from one of these tapes for you. This is a girl, actually one of the Lost Girls of Sudan, who at the time she was telling the story, was, I think, about 16 years old. Her name is Veronica. (We asked them to do it anonymously, but most of them wanted their names to be known.) [Dr. Geltman repeats some of the Lost Girl's words for clarity and comments on others.]

Veronica: We was walking and no car. We're just walking barefoot, no water, nothing to eat. We ate soil sometimes.

Dr. Geltman: She's talking about that first migration to Ethiopia. [They had] no cars, had to walk barefoot, [had] no food, [and] no water. We ate soil. Like in the *60 Minutes* tape, she talks about them drinking their own urine.

Veronica: We were there—like one year on the way coming to Ethiopia. There was lion eating people; people died.

When you're a boy and you are 16, you go fight, or you're 14, you must fight.

Dr. Geltman: Here she's talking about all of the boys being forced or recruited into the Southern Sudanese Liberation Army.

Veronica: ... in Sudan, the school was hard for us.

Dr. Geltman: The desire to go to school.

Veronica: ... and the school was hard. They have brothers or sister who are back in Sudan. The school is too hard for them because they cannot go to school. You don't have parent, you don't have brothers and sisters ...

Dr. Geltman: She's talking about being unaccompanied.

Veronica: When you're a girl, you need to go to work every morning and fetch water.

Dr. Geltman: Talking about being taken in by another family as a girl.

Veronica: ... you don't go to school. You cannot do anything. If you don't clean, you don't wake up in the morning. They beat you. They beat you everyday. Everyday they beat you hard.

Dr. Geltman: You clean, or they beat you everyday.

Veronica: ... until you cleaned the house. You stay home. You don't go to school. You don't go anywhere. You don't. Don't forget us. We're still in Sudan or in Kenya ...

Dr. Geltman: She was talking about all the people who are left behind now. Her friends, people she knows who weren't resettled.

Veronica: ... one time who still meet and who still go back to our country. Go to America, but remember your brothers and sisters who are back in Sudan. They know that you are there for them. You are there in America.

Dr. Geltman: Talking about the feeling of responsibility to go back and give back and do something for their brothers and sisters, which she calls them.

Veronica: Go back to Kenya. It's still hard for somebody. What's important is education ...

Dr. Geltman: This theme of education is safety.

Veronica: I want someone to tell you that I'm going to school. Do this one. Do this one at home. You're excellent. You must go to school. You must ...

Dr. Geltman: Talking about all the help they're getting in the US, which they didn't get in Kenya.

Veronica: ...or they feel we're not people.

Dr. Geltman: They feel we're not people.

Veronica: God made everybody the same. You drink, you eat, you sleep, you talk ...

Dr. Geltman: God made everybody the same. You eat, you sleep ...

Veronica: God made everybody the same.

Dr. Geltman: You talk, you drink.

Veronica: But why that holocaust? Why kill us? Slaving us? Why, God? Why that happened to us?⁷

That's where she ends. And there it is: the whole theme of trust and guilt and blame.

Treatment of and for Resettled Refugees

Let's return now to the US and our laws and regulations about refugee resettlement.

I mentioned the Refugee Act of 1980. That created funding streams called refugee cash assistance and refugee medical assistance. Cash assistance is welfare or, as it's now called, transitional assistance. Medical assistance is Medicaid, basically health insurance.

Refugee medical assistance is the funding stream that pays for short-term Medicaid for refugees who would not otherwise be categorically eligible. You don't just get Medicaid because you're low income, you also have to meet certain other demographic criteria, like having dependent children, being a minor yourself, stuff like that. If you're a young adult, a Sudanese male, like the guy in the *60 Minutes* clip we heard, or the six I also discussed, and you don't have dependent children, you will get Medicaid, but it's only guaranteed for eight months. After that, it is not guaranteed.

Immigration status is very important in our safety-net laws and policy in the US. Back in the 1990s, in that first hundred days' "Contract with America" when the Republicans captured the House of Representatives for the first time in decades with Newt Gingrich, the Congressman from Georgia, in the lead, the Republicans were going to reform welfare.⁸ Bill Clinton went along with it since he had pledged to do something. So, they enacted welfare and immigration reform legislation, which dramatically limited access to any kind of public benefits and programs, such as the ones I mentioned, for most immigrant classes in the US. They did exempt refugees and asylees from most of these exclusions for five to seven years after coming to the US, which is the time it takes to become a citizen. It created a climate of fear, and the whole concept of a "public charge" became an issue.

There are organizations that take care of refugee resettlement in the US. They work under contracts with the Department of State, and they provide a package of benefits and support that includes "resettlement and placement services." Those include housing placement, some case management for a few months, job training, English language courses, and the eight-month eligibility for cash and medical assistance. The funding for this goes to each state that participates—most states do—usually through a single state agency that then disperses it to a local group.

I'm going to just quickly go through some of the outcomes of the Lost Boys. I don't want to dwell on it too much, because it's not really the point of this talk. We found that in our sample of those who filled out the trauma questionnaire, which was 241, 20% met diagnostic criteria for posttraumatic stress disorder. You can look at that two ways—you can say well, only 20%, that's great, or you can say 20%, that's huge.

⁷ Anonymous, research communication to Paul Geltman, December 12, 2001.

⁸ The Republican party released a document titled "Contract with America" in 1994 during the congressional election campaign. In it they detailed the legislation and Congressional action that would be introduced during the first 100 days of their term.

I will say that those 20% had histories that clearly explained why they were the 20%, why they were still showing signs of trauma. The ones who had been in the village when the attacks came had a substantially lower risk of PTSD, because they knew what had happened. Even if their family had been killed, they knew it. But, the Sudanese are a herding people, especially of cattle, and typically, it was the boys who would be out herding the cattle. When the bombs fell, they ran. They fled without knowing what was happening to their families.

We also found that the Sudanese who were placed in group homes, or in foster care alone with an American family, had a much higher risk of PTSD. We think that's because of the sense of feeling isolated and lonely. If they were in a group home, they weren't getting enough individual attention, and if they were alone with the foster family, they felt isolated from their peers and alienated by the cultural divide.

We did a functional-health-outcomes assessment called the Child Health Questionnaire [which is not solely for refugee children], on which, overall, the scores were actually quite good. They dropped significantly on sections about family cohesion and activities, which is not surprising if you're an unaccompanied minor. They were quite low in terms of self-rating general health, mental health, and bodily pain. I'm going to explain bodily pain in a minute.

These functional health scales ask daily-life questions like, "How well do you do at school? Can you go down the street and engage in a pickup game of basketball?" What was interesting was that all of the scores were significantly lower for the kids with PTSD, falling into ranges that were clearly indicative of functional and behavioral health problems. There was a direct linear relationship between their functional health score and their trauma score. You could use the measure of how they did in their daily life, to determine if, in fact, they were suffering from mental health problems.

We looked at their coping and, again, the kids with PTSD were about three times more likely than the kids without PTSD to blame themselves when bad things happened, not to feel close to anyone, and to keep problems to themselves, harkening back to some of those developmental issues that I talked about earlier.

But, remember that Rwandan girl with the scar across the back of her head? Well, she is doing well despite what happened to her. It's not all bad. Some kids will do just fine coming through this kind of a horrible refugee crisis.

Actually, 97% of the Sudanese kids had pretty good active adaptive coping skills, and they were generally able to draw on those skills to help them cope. Largely, they coped well when asked to adjust to life in the US, but there were some, those with PTSD, who had very passive, maladaptive coping skills.

Then there is the bodily pain element. People who have emotional stress or distress will manifest physical signs and symptoms of that distress. It's called somatization. Three-quarters of the Sudanese kids were exhibiting signs that we attributed to somatization, such as problems with their bowels, lack of energy, chest pain, loss of appetite, sleep disturbances, stomachaches, headaches. It was very, very common. They were seeking medical care for this stuff.

We also wanted to know if they were actually getting mental health services specifically to help them with their individual issues. Almost half said they were getting some kind of mental health counseling, but only 31% said they were getting any specific medical care for emotional and behavioral problems that they were suffering. We realized that a lot of this mental health counseling that they were reporting were things like support groups led by a social worker or psychologist that wasn't individualized to them. They weren't being

identified, and they weren't getting individualized services for their needs. In fact, the kids who had PTSD were no more likely than others to report getting individual mental health services.

The Sudanese provide a great example of how this process of coming to the US can create health risks for refugee children or refugees. They also have been the subject of many separate studies. For example, in Canada there was a study that reported that among the Sudanese who ended up in that country those who experienced economic hardship and food insecurity reported poor overall health and greater symptoms of psychological distress nearly four times more than those who did not experience economic hardship in Canada.

There was also a study about the Sudanese who went to Omaha, Nebraska. (Why did they go to Omaha, Nebraska? Because there's lots of beef in Omaha, and the kids were into cattle, so they wanted to go there. Some of the kids wanted to go to Chicago. Why Chicago? Because the Chicago Bulls are in Chicago, and they thought they were going to find cows.) The Sudanese in Nebraska encountered significant barriers to their access of health care and preventive services while engaging in some pretty risky typical adolescent health behaviors.

So, what happened if you were a Lost Boy who came to the US after you turned 18 years of age? You were no longer in the refugee foster-care program for unaccompanied minors. Or what if you were a Lost Boy in the unaccompanied minors program and you aged out of the program at—depending on the state—between 18 and 22 years of age? What happened to you? Nearly all of these young males lost their health insurance and cash support just eight months after arriving in the US. Many of them became destitute, suffered economic hardship, and had no health insurance. They had all their mental health problems and health issues, but could no longer access care.

It is not unusual to cut off aid to refugees. In fact, there's a fact sheet that the State Department actually writes for prospective refugees called "Refugee Resettlement in the US." Most Americans value self-reliance and hard work. They expect newcomers to find jobs as soon as possible and take care of themselves. Assistance provided to refugees is not enough to fully support oneself or family. The message is, "we're going to help you a little bit, but then you're just going to have to suck it up and get on with life." In fact, the airfare to get here is a loan—refugees are expected to pay back the money for their flight to the government.

In the fiscal year 2015 Statement to Congress on the Refugee Admissions Program, Assistant Secretary of State, Anne Richard said, and this is a quote, "Achieving durable solutions..."—there's that policy term again—"including third country resettlement is a critical component of the State Department's work....[T]he US Refugee Admissions Program... [is] an important humanitarian undertaking...by offering a solution to displacement when voluntary return and local integration are not possible."⁹ In other words, we'll resettle you, but that's our last choice.

Resources—meaning the funding refugee resettlement communities seek—will be used to fund the cost associated with the overseas processing and initial resettlement services including housing, furnishings, clothing, food, medicine, employment, social services referrals. This sounds great, doesn't it? Our policy makers and lawmakers believe this is what's happening out there. But what about health insurance? Well, good health, I think, is essential for successful resettlement. Access to health care certainly is a part of that process.

⁹ US Department of State, *Migration and Refugee Assistance, Emergency Refugee and Migration Assistance, Fiscal Year 2015*, Congressional Presentation Document, accessed January 23, 2017, <https://www.state.gov/documents/organization/228806.pdf>.

Health insurance clearly plays an important role—not the whole role, but an important role in access to health care.

The Affordable Care Act

Now, we come to the present day [2014]. Shouldn't the Affordable Care Act [ACA] be a solution?

Well, it could help, perhaps, with access to care. At least, it should, we think, and that certainly is a good place to start if you believe that health insurance is the doorway to access to care. That's not necessarily the case, as we're finding out, but it's certainly a good place to start.

How might this affect refugees? Well, it extended the eligibility for Medicaid to 12 months, which is the usual recertification interval. You may be thinking, "Well, twelve, eight, what's the big deal?" Well, it is a big deal because it puts them in the normal cycle; it gives the refugees a little more time to adjust; it gives them more time to prepare their recertification materials. The ACA also provides the availability to subsidize private insurance for individuals who are not eligible for Medicaid at that 12-month point. Previously, the kinds of policies available to individuals in the private insurance market place were extremely expensive and well beyond the reach of refugees.

Then politics happened. The Supreme Court weighed in and said, in effect, that states do not have to do the Medicaid expansion portion, and so this is what happened.

Let's map this to refugee resettlement now. There are approximately 35,000 refugees in the US who are still in states where, after eight months, they will lose all their benefits and health insurance. In the states that have opted out of Medicaid expansion, refugees will still lose their financial support after eight months. Then they can have access to the commercial insurance marketplace and government subsidies, under the Affordable Care Act, but purchasing new insurance still requires precious financial resources that most refugees can't afford to pay because they're frequently working in very low income, menial jobs.

Conclusion

Let's go back to my first two questions. How well does our current system of refugee resettlement work? Are we failing the children? I will allow you to make up your own minds, but there's no doubt in my mind that we are, indeed, failing. How do we move forward in this area?

The State Department does seem to get it a little bit, I have to say. Some examples of recent initiatives are about unaccompanied alien minors. There are Guatemalan 16-year-olds, picked up by the border patrol in Texas. Previously they would have been detained in a Department of Justice or Homeland Security immigrant detention facility. But, recently, jurisdiction was transferred from the Department of Justice to the Office of Refugee Resettlement, and that made those Guatemalans eligible for the Unaccompanied Minors Foster Care Program. Also, now the State Department is trying to do the overseas best interest determinations much earlier and much more quickly than in the past. Truly, the Refugee

Assistance Program does have the best of humanitarian intentions. Clearly, as in Anne Richard's statement, that's the mission. That's what they believe. It's just a question of how we get there.

So, are we being a little naïve about the consequences of all these policies and how we do things for children? Does the system look good on paper but does it fail when viewed against the developmental trajectories and needs of children? I think, probably, yes. I think we are moving in the right direction, and, honestly, what alternative is there other than peace and not having refugees? We try to do the best we can. Hopefully, we can do it a little better in the future and address some of these issues of refugee children. There are great groups out there who are working really hard towards a better future. I mentioned Save the Children and their work in Rwanda. UNICEF works hard as well, so it's hopefully getting better, bit by bit, but for now, there is much more to be done.

DISCUSSION QUESTIONS FROM THE AUDIENCE

Question #1: Earlier you gave us the definition of who qualifies to be regarded as a refugee. How easy is it to distinguish between immigrants and refugees when you are working with them?

Response: Most people in health care don't care what your immigration status is. They're going to provide services and care for you, period. My work is for a government program that's specifically authorized to work with refugees and people with other equivalent visa statuses, like recipients of political asylum, Cuban entrants, Haitian entrants, temporary-protected-status individuals, victims of trafficking, etc. If you're an undocumented immigrant who might meet an international definition of being a refugee from El Salvador, or a country in Africa, and you come here without proper documentation, or perhaps you had a student visa and you overstayed it, you can still apply for political asylum.

In the late 1990s, the laws changed from having no time limit on the filing process to having to file within one year after your arrival in the US. In the larger picture of being able to get health care or working with physicians, immigration status doesn't matter, but that's not all there is about health. If you don't have money, if you're starving, if you're living on the street because you don't have legal status or proper documentation to be in this country, that's going to impact your health. It also restricts your eligibility for health insurance.

Even if you want to use the doctor, and the doctor's willing to see you, how are you going to pay for that? In Massachusetts, they did away with the uncompensated care pool, and there are some very limited insurance programs for which undocumented immigrants are eligible. Often, they don't have even that insurance, though, so we still have people with this dilemma, even in Massachusetts.

An example of why this whole issue of immigration status is a very important matter in Boston right now has to do with lead poisoning. Today, we see very little lead poisoning, but it used to be a huge issue. About 10 years ago, I realized that the only kids I was still seeing with elevated blood lead levels were undocumented immigrants. They were not able to live in any kind of decent housing because they were poor, or because they did not have legal status

and were therefore not eligible for public housing or subsidized housing under the Section VIII Federal Government Support.

Thus, even today, it's important. I wish it wasn't, but it is. I will, on occasion, ask people what their immigration status is because I want to know if I can help them with health insurance or some kind of benefits or housing. If it's an undocumented immigrant, and they're telling me they're homeless, I can't help them. I can't even get them on a waiting list somewhere. Just forget about it. That's how it plays out.

Question #2: You were talking about the Sudanese, and you also talked about some studies in Canada and Nebraska. You also mentioned earlier that there are a few other countries that actually take a great interest, I guess, in resettlement. I'm thinking that they are countries with a very different health-care system to ours. Could you talk a little bit about how that's played out?

Response: Well, I can't answer that in broad terms because the study I did of the Sudanese here in the US was unique.

It is hard to know, because you can't identify refugees easily. They don't wear a badge or anything; they don't wave a flag saying, "I'm a refugee." Once refugees are here, and they're in the community, after we conduct the refugee health assessment, my program is no longer associated with them. Once they're done, we have no legal authority to be tracking them, following them, pursuing them, doing any further evaluations of them.

The project I did with the Sudanese was not through the state government; I did it in my role as an academician with Boston University. It was facilitated by connections through the state government, but I did it on my own time with funding from Boston Medical Center and Boston University.

I don't know about broader refugee health, so I really can't answer that question. This study is like the Holy Grail, because generally it is unclear how you track the outcomes of refugees. Still, I think it's important to know because the outcomes of refugees are relevant to the larger immigrant communities, or to other similar communities that may face similar situations but don't have refugee status.

For example, we have a lot of immigrants from Uganda and Nigeria. While there's a lot of violence and persecution in those two countries, these immigrants are coming here with green cards and immigrant visas. They blend in very easily because they're English-speaking and they've established communities here. There's a huge Ugandan and a huge Nigerian community in the Boston area, but because they're not refugees, they don't get health screening. We have no contact with them. There's no way really to identify or find them or track them in any systematic way without getting some kind of a big research grant and getting out there and pounding the pavement and finding them. It's a challenge.

Question #3: You stated that 34,000 people would be left out of the Medicaid expansion... Could you try to flesh out the demographic by discussing the states that have refugees? I know you said that the tracking you just mentioned is difficult, but might you have some idea where they came from and how long they stay in a Medicaid program in the states that might be expanding it?

Response: Well, eligibility for benefits is not a strong motivator for people to move from state to state. We call that secondary migration. It's going to affect particular groups in the sense that family reunification is a strong driver of refugee resettlement. You tend to see people gravitate to areas where those communities already exist.

Georgia, for example, has a big Burmese refugee population, so that's been a magnet for current Burmese refugee resettlement. Georgia is one of those states that opted out. So, it's predictable that the Burmese who are going to Georgia are going to be disproportionately affected compared to their peers going to other states. Some secondary migration will occur but not as much as you might think.

Question #4: I was wondering how much information refugees actually get when they come across. For example, you mentioned refugees going to Chicago because of the Chicago Bulls.

Response: They largely would go where they were told, unless there was some family connection dictating it.

Question #5: With respect to the information refugees are given and the choices they are given, is the information being updated with the effects of the ACA?

Response: No. That's not going to happen. The information they're given is quite limited. There're some wonderful videos on YouTube about the cultural orientation, specifically when you look at some of the groups that really need it, like the Sudanese. I mean, these are kids who have never used a flush toilet, they've never seen a doorknob, and maybe not even an electric light switch. The Somali Bantu population, which came in about seven years ago, was the same way. Completely non-Western. They were a rural agrarian persecuted minority in Somalia. They had no clue how to function in our society. The stories about them were just mind-boggling. I have some pictures that I took from the cultural orientation website, which showed them looking up at the skyscrapers; staring at the television, not knowing what it does; and preparing their food on the kitchen floor. Stuff like that. They get this mini-intensive cultural orientation session that the Center for Applied Linguistics does and the International Organization for Migration [IOM] helps with.

There was a guy from Massachusetts named Sasha Chanoff. He was very involved with the Lost Boys, and he did sessions in Kakuma. He's in the *60 Minutes* videos. He's trying to get them ready for winter. I mean, it's not just health you have to consider. Think about it. You're living in the African savanna, never having to put on a coat or long pants or shoes, and then you're going to the winter in New England. They don't even know what that's about. So, Chanoff had a big snowball or ice ball that he kept in the freezer. He would pass it around the audience and say, "This is winter. This is what it's going to feel like. You have to be ready and dress warmly and dress appropriately."

Resettlement education (called "cultural orientation") is about much more than just health care, and there's not a lot of time to do it. It would be wonderful if the refugees could get some kind of intensive ongoing work, but once they are in the pipeline to go, there's not a lot of time. They do what they can, but when the plane's ready to go, they're either on it or they're not going.

Question #6: Who makes decisions about where the refugees are going to go, and how is the decision made?

Response: Once there's a determination made and they pass through their background security clearance, they're assigned to the overseas processing entity, which has representatives from all the different NGOs and the governments. It's like they are playing poker. "OK, this refugee's got family in Boston," says an NGO. "It looks like we have capacity to take somebody in our Boston site, so we'll take them." That's how it works. They are divvied up according to where the capacity is, and where the family reunification dictates. Then that assignment gets passed along to the local affiliate, and that group gets a week or two weeks' notice. The local group will hear, "Refugee X from Camp Y is coming your way next week. Here's the flight information. Be ready. You have to have a house for them. Just get the paperwork going." It all happens very, very quickly.

Sometimes, when there are refugees with health issues, they might have to be expedited into medical care. There have been plenty of instances where people travel with a medical escort, and they've gone straight to a hospital after arrival. The transition period into the US is a very stressful grueling time.

Question #7: How much ongoing social casework is done with them? I use a book with some of my students called *Outcasts United* about a refugee soccer team that ends up in the Atlanta area.¹⁰ I have no idea how typical that experience is, but it sounds like they get inadequate furniture, very limited social work, and no ongoing case management. Is that typical?

Response: That's all true, but didn't it sound great when I read from Anne C. Richard's statement? That made it seem like we're looking after these people and taking care of them, but then there's that other quote that I read to you that said, basically, "Sorry. Government support is not enough. To really support yourself, you've got to work." That's the reality check, but that's not the public face of it.

I remember being stunned when I realized this; maybe I was naïve myself at the time. I went to a national meeting sponsored by the federal Office of Refugee Resettlement (ORR). Back in the last few years of the Clinton administration the head of the Office of Refugee Resettlement gets up at her plenary—this is at the height of the welfare and immigration reform debates—and proudly declares that refugee resettlement was the first welfare reform program. She says, in effect, "We get refugees to work. We cut their public support at eight months, and they have to be self-sufficient." She was proud of this, and I was thinking that this is awful because six to eight months is when they're all crashing. That's when the euphoria is ending, and the reality is setting in.

There's a whole system called mutual assistance associations that the ORR actually helps fund. These are like ethnic refugee community organizations. Typically, they're very small groups that provide some support to refugees going forward, but they're not big, well-established social service agencies. I used to be on the board of the Somali Development Center in Boston. I remember there were plenty of days when they would pass a hat around

¹⁰ Warren St. John, *Outcasts United: An American Town, a Refugee Team, and One Woman's Quest to Make a Difference* (New York: Spiegel and Grau, 2009).

the table for the six of us saying, “There’s this family in crisis. We need to help them. Give them some money.”

Question #8: Looking into the crystal ball of climate change and the forced migrations that will be brought about and the populations that will be on the move fleeing droughts or fleeing floods—if you believe the American Academy of Sciences’ strategy for climate change—what challenges will that pose for this kind of statutory framework here in the US or globally? What would you recommend to beat those kinds of challenges as a pediatrician and epidemiologist?

Response: It’s a good question, and really gets into the larger picture. In terms of its potential effects limiting the world food supply and clean water, is climate change going to exacerbate refugee crises as well as sectarian tensions leading to more civil wars? I would say clearly the answer is, yes.

Already, we’re seeing it in Sudan where they’re having a drought that, in the context of the Nuer-Dinka Civil War, they’re predicting is going to be on the scale of the Ethiopian famine in the 1980s.

It’s going to be a problem, and the reality is, as I mentioned, far fewer than 1% of the world’s refugees ever get resettled, so the misery that these people are going to live in is going to continue. We’re probably going to be seeing more and more of these kinds of situations unless we start dealing with it. At least in the US, we seem to have our heads in the ground trying our best to ignore it. Or, sometimes you get responses like the one from the mayor of Manchester, New Hampshire: “Stop sending us refugees. We don’t want any more refugees. End it.” Or, perhaps Congress will say, “OK. This isn’t working. You don’t like it? Not enough money? Let’s cut it. End the budget. No more refugee resettlement to the US.”

I don’t think anybody involved wants to see that happen because all of us—even if we’re not doing it well or well enough—recognize that it needs to be done for humanitarian reasons.

CLASS EXERCISES

Lost Boys of Sudan

- As a class, watch the video, *The Lost Boys of Sudan*, available at <http://www.lostboysfilm.com/>.
- Following the film have the class spend 10 minutes writing a short reflection piece on what they have seen. What surprised them the most? What is their overall reaction to the plight of this population?
- What health issues were, or should have been, touched upon?
- Lead a class discussion on how the refugee resettlement process can be improved.

Refugee Resettlement Process

- Divide the class into groups that will represent different states in the nation (e.g., Massachusetts, New Hampshire, Maine, Nebraska, Georgia, etc.)
- Each group is responsible for researching, via the Internet, the refugee resettlement process in their state. Be sure to note the specific agencies and timelines involved, as well as what refugee populations have been resettled over the last 10 years and how this has changed over this time period.
- Develop three feasible ways in which the refugee resettlement process can be improved in your specific state. Be sure to include thoughts about managing health issues that might arise.
- Each group presents a brief overview of their respective state's refugee resettlement plan, highlights the two most important factors that should be implemented to improve refugee resettlement, and gives their rationale for the selection.

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Chapter 86

PUBLIC HEALTH THEMES: GRENADA AND THE CARIBBEAN REGION

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ABSTRACT

Over the past decade, the Caribbean governments have turned their attention to tackling the rising prevalence of non-communicable chronic diseases, in particular, hypertension, diabetes and cancer. The emergence and rising prevalence of these lifestyle diseases are suggestive of a correlation with the cultural transformation that overtook the region. In the first quarter of 2020, the region's health landscape turned another corner with the emergence of the COVID-19 pandemic, demanding urgent public health and clinical interventions to address an infectious disease. Improving the health status of Caribbean populations is at the forefront of the agenda of the regional public health institutions and, in producing this book, we provide support for evidenced-based public health practice in the Caribbean region. We hope readers find the issue informative to understanding the public health situation in the Caribbean and will motivate affirmative action to improve public health.

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INTRODUCTION

This book is a collection of research and reviews that reflect pertinent public health themes in countries in the Caribbean region. Those themes precipitated from recent research and the insights of the authors who actively engaged with the regional and local public health systems. Many studies have been published, albeit, never before was a production made, bringing an array of public health themes together in the literature to readily provide a comprehensive overview of public health successes and challenges in Caribbean countries. The motivation to write this book came from the expressed yearning to have a fuller understanding of the direction in which public health activities may be focused to improve health and wellness of the Caribbean peoples. Sharing the results and recommendations in this book is especially valuable within the context of the limited resources that is available in the region for a wide range of studies to generate evidence related to public health. This limitation in the region hinders proportional response to significant events.

The information in this book is valuable for many audiences, including public health practitioners, health planners, and policymakers. Incorporating the content in academic settings is a positive step towards developing a conscientious and well-informed next-generation workforce. In this issue, we highlight reviews of the regional public health systems and country-based research findings and recommendations. Readers can deduce information about health status and public health needs in the region. Apart from contributing to inform capacity building, the results and recommendations presented by the authors provide directions to guide in the development of affirmative actions to improve the responsiveness of the regional public health systems. The themes in this book highlight the need for collaboration of the local and regional agencies to mobilize for action and to be more effective in the responses.

The efforts of Caribbean governments and public health institutions to address vulnerabilities and risks, in particular, for non-communicable chronic diseases, are well recognized. This book highlights the current pertinence and complexities of this issue in the region. Readers have an opportunity to make judgments about progress in addressing the problems in respective countries as well as to extrapolate results to predict the situation regarding non-communicable diseases in a broader sphere. At the same time, in the current period of the COVID-19 pandemic, greater emphasis is needed to manage and tackle infectious diseases. Health practitioners, planners, and policymakers may do well to apply the findings and recommendations in strategizing to improve the health and well-being of the Caribbean people. The themes also highlight the need for ongoing research to deepen understanding about health in the region.

We extend special thanks to the authors and reviewers for their contributions to this edition. Thanks to the faculty at St. George's University (SGU) in Grenada and the staff at the Caribbean Public Health Agency (CARPHA) in Trinidad. Improving the health status of Caribbean populations is at the forefront of the agenda of the regional public health institutions and, in producing this book, we provide support for evidence-based public health practice in the region. We hope readers find the issue informative to understanding public health in the Caribbean region and that the information will be transformed into affirmative actions to improve the health and well being of the peoples.

Chapter 87

RESPONDING TO COVID-19 IN THE CARIBBEAN THROUGH THE NOVEL TOURISM AND HEALTH PROGRAM IN THE CARIBBEAN

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ABSTRACT

The health of Caribbean economies is closely related to the health of its travel and tourism industry, given that the Caribbean is the most tourism-dependent region in the world. The global spread of the novel coronavirus pandemic (COVID-19) was propelled by travel and is threatening the health security of the region while, at the same time, disrupting tourism and reducing revenues in Caribbean economies. The Caribbean Public Health Agency's Regional Tourism and Health/Travellers Health Program is an innovative program that is addressing the health, safety, and environmental sanitation threats to tourism, with the aim of strengthening regional and national health systems and enhancing the health of visitors and locals. This unique program adopts a multi-prong (real-time early warning and response tourism and health information system (THiS), regional guidelines, food safety and environmental sanitation training, hospitality health safety and environmental standards, policy), and multi-sectoral (regional and international health and tourism partners) approach for implementation. The program has built capacity and equipped countries with regional tools that support preparedness and response to public health threats like COVID-19. This is the first integrated program of its kind, setting an international precedent for improving sustainable tourism and regional health security.

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INTRODUCTION

The United Nations Sustainable Development Goals are the blueprint for achieving a better and more sustainable future for all. Goal 3 calls for ensuring healthy lives and promoting well-being at all ages and Goal 9 requires building resilient infrastructure, promote sustainable industrialization, and foster innovation [1]. The Regional Tourism and Health/Travellers Health Program (THP) was established to promote regional health security and sustainable development throughout the region. This paper describes how the THP is supporting the preparedness and response to the novel coronavirus outbreak, declared a pandemic on March 11, 2020.

Background

The Caribbean region is one of the world's most prominent travel destinations, famous for its tropical weather, crystal blue waters, white-sand beaches, and vibrant culture. These features make the region an attractive destination to foreigners, particularly those seeking to escape colder climates. The tourism industry is crucial for Caribbean economies as it a primary revenue source. According to the World Travel and Tourism Council's (WTTC), tourism is a principal source of employment, foreign currency and economic growth in the Caribbean, accounting for approximately 2.5 million jobs or 15.5% of total employment contributing to 5.8% (US \$9.2 billion) to region's Gross Domestic Product (GDP) [2], illustrating the dependency of the Caribbean region on the tourism industry.

Caribbean tourism is vulnerable to many external factors, health being one of them. Due to its tropical climate, the region is highly vulnerable to outbreaks associated such as Chikungunya, Malaria, Dengue, and Zika. Negative health publications against an island or unmanaged epidemics can seriously harm the inflow of tourists and tarnish the reputation of Caribbean tourism destinations. Without a market, the Caribbean economy suffers from a fall in tourism generated revenue.

REGIONAL TOURISM AND HEALTH PROGRAM

The Regional Tourism and Health/Travelers Health Program (THP) is a novel, innovative, multi-sectoral, multifaceted program that aims to strengthen regional and national health systems by addressing the health, safety and environmental sanitation (HSE) threats to tourism, and thereby enhance the health and safety of visitors and locals, regional health security, and the quality, reputation, and sustainability of Caribbean tourism (website: <http://carpha.org/What-We-Do/Tourism-and-Health-Programme>).

The program is being executed by the Caribbean Public Health Agency (CARPHA), the Caribbean's sole public health agency responsible for preventing disease, promoting and protecting health, in collaboration with the Caribbean Hotel and Tourism Association (CHTA), the Caribbean Tourism Organization (CTO) and countries. The program is improving countries' capacities to provide cost-effective, quality health, food safety and environmental sanitation (HSE) solutions to the HSE threats impacting on sustainable tourism

in the Caribbean through real-time, early alert and response monitoring systems for tourism-based health issues; training and certification, HSE standards, and multi-sectoral regional and international partnerships. Countries gain enhanced capacity to mitigate against HSE threats to sustainable tourism. This integrated, multi-sectoral program is the first Caribbean-wide and global effort of its kind, setting an international precedent for improving sustainable tourism. The program is timely as new threats to health and travel in the region emerge.

The Caribbean depends on visitor arrivals more than any other region in the world, with over 55M visitors in 2019 [3]. High and increasing numbers of visitors to the Caribbean region increase the health, safety, and security risks to local populations. Travel/tourism-related illnesses are not only a health and security risk but contribute to reputational damage and economic instability in Caribbean economies. This is evident through the introduction and spread of new and re-emerging diseases, such as SARs, H1NI, chikungunya, zika, norovirus, measles, and now, the novel coronavirus (COVID-19) pandemic, by visitor populations. The health of Caribbean economies is thus closely related to the health of its travel and tourism industry, given that the Caribbean is the most tourism-dependent region in the world.

However, even though more people visit the Caribbean than reside, current health monitoring surveillance systems are primarily based on the local population, and there is no ongoing visitor tourism-based surveillance and response system. There is also inadequate food and environmental sanitation training for the tourism sector, lack of cumulative HSE standards and certifying system, and a marked lack of integration between tourism and health stakeholders to address health in tourism in the Caribbean region. These gaps have all contributed to the spread of disease outbreaks, food safety, and environmental sanitation issues in the region; and without adequate information management systems, standards and training, these HSE threats can become a severe tourism crisis. These risks and the importance of the tourism industry in the Caribbean region highlight the need for a system to monitor both traveler's and resident's health, provide rapid dissemination of real-time information, and respond quickly to prevent and control outbreaks. It is within this context that CARPHA established a Regional Tourism and Health Program in 2014, with funding received from the International Development Bank in 2016 to execute.

The THP is strengthening countries' capacity to prepare for and respond to public health threats like COVID-19, which can transcend national boundaries and negatively affect access to goods and services, through the following regional public health goods which have the potential to strengthen regional health security:

- 1) Tourism and Health Information System
- 2) Regional Guidelines for a harmonized response to travel-related public health issues occurring among visitors to the Caribbean arriving by sea (passenger ships) and air (accommodations).
- 3) Advanced Food Safety, Environmental Sanitation capacity building, and certification.
- 4) Hospitality Health Safety and Environmental standards
- 5) Partnerships, Mandates, and Policy

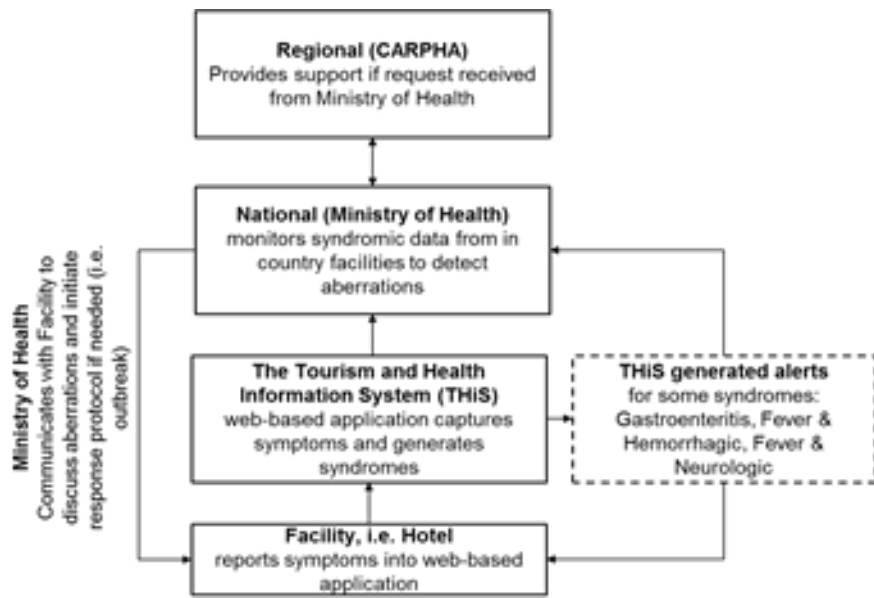


Figure 1. Primary surveillance pathway for the THiS web app.

Each of these components is discussed below and linked to possible COVID-19 preparedness and response actions.

Components

The Tourism and Health Information System (THiS) is a web-based application for syndromic surveillance of populations in tourist accommodations (website: <http://www.this.carpha.org>). This real-time, early warning system is confidential and only accessible by national authorities. It is currently being implemented in hotels and guest houses in eight countries (Bahamas, Barbados, Belize, Guyana, Jamaica, Trinidad and Tobago, Bermuda, Turks and Caicos Islands).

The THiS web app was designed to enhance national surveillance systems by monitoring illnesses in tourist accommodations to identify public health threats early. Figure 1 shows a schematic of how the THiS web app integrates into the existing national and regional public health surveillance mechanisms.

Data Collection and Reporting

Data collection in the THiS web app is conducted by staff from registered tourist accommodations, using an online questionnaire administered to an unwell guest or staff member. Accommodations are also required to confirm the absence of cases by epidemiological week using a “zero case” submission on the web app page. Also, the self-reporting page allows visitors and staff to independently report their illness using an online questionnaire located on the THiS web page: this.carpha.org.

The online questionnaires are similar for reporting by registered facilities and self-reporting. The questionnaire includes short questions that ask the user for necessary demographic information such as age and gender, potential exposure information such as recent travel and home country, and most importantly, which symptoms they are experiencing:

- 1) diarrhoea (≥ 3 loose or watery stools in past 24 hours)
- 2) vomiting and/or nausea
- 3) fever (sudden onset of fever $>38.0^{\circ}\text{C}$ or 100.4°C)
- 4) cough or sore throat
- 5) bleeding (gums, nose, blood pooling under skin coughing, stool) not due to physical trauma
- 6) headache
- 7) joint or muscle pains
- 8) eye pain/headache/facial pain,
- 9) generalized rash,
- 10) blurred vision or convulsions or altered consciousness

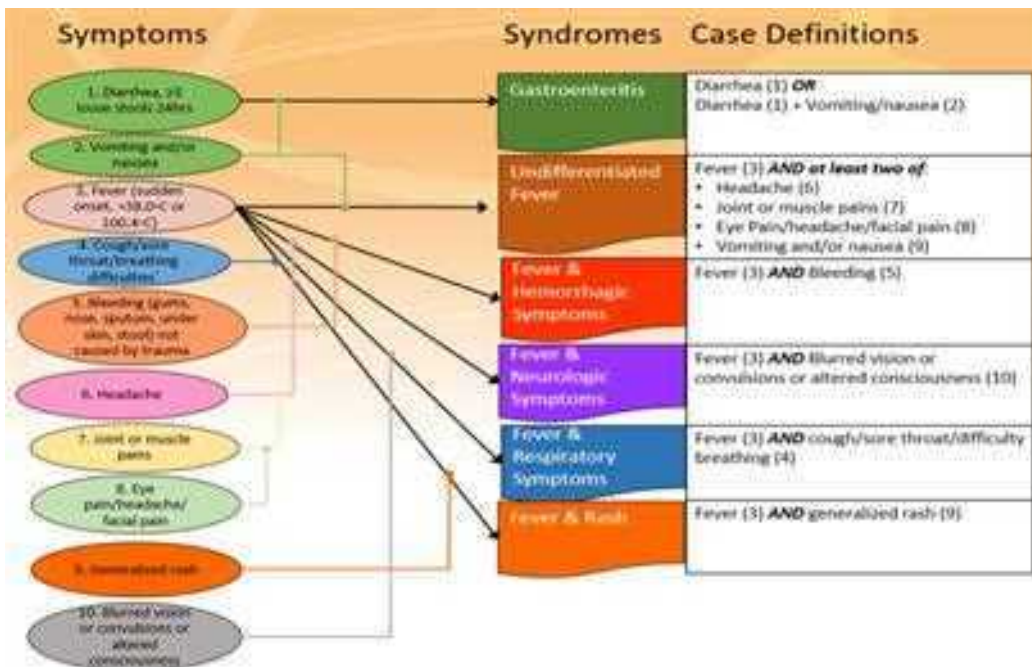


Figure 2. The logic used to generate syndromes from reported symptoms (based on Case Definitions for Syndromes under Regional Surveillance, CARPHA).

Responses to these symptoms are analyzed in the system to generate (see Figure 2) potential syndromes for each case:

- 1) Gastroenteritis
- 2) Undifferentiated fever
- 3) Fever and hemorrhagic symptoms

- 4) Fever and neurologic symptoms
- 5) Fever and respiratory symptoms
- 6) Fever and rash

Data Analytics

Data analytics are executed on the inputs from each facility on the THiS web app. The dashboard provides interactive data visualizations and allows the user to slice the information to view cases among guests vs. staff, by facility (for national users only), by country (for regional users only), and for all users by gender, age, and time (weeks vs. months vs. year) facility and national level—for MOH users), and time (case counts by day, week, month, or year). Access is limited to hotel management (i.e., hotel manager, health and safety manager), who would be persons engaging with public health staff at the MOH in the event of a potential public health issue such as an outbreak. At the Ministry of Health, access is given to users determined by the countries health focal point and typically includes an epidemiologist, surveillance officer, and/or Chief Medical Officer (CMO) or Environmental Health Officer. At CARPHA, access is limited to the THP epidemiologist and Project Coordinator.

Regional Guidelines

Two sets of regional surveillance guidelines were developed:

- Regional guidelines for managing issues of public health significance on passenger ships coming to the Caribbean (Caribbean Vessel Surveillance System (CVSS)), and
- Regional guidelines for managing issues of public health significance in stay-over arrivals (Tourist Accommodation-Based Surveillance) in the Caribbean

These guidelines, collectively called the “Regional guidelines” (see Figure 3), were developed to provide instructive guidelines for harmonized scientific response to travel-related public health issues occurring among persons aboard passenger ships and those in stay-over arrivals (tourist accommodations) in the Caribbean.

A key challenge in the tourism-dependent Caribbean countries is the marked variation and lack of standardization in the surveillance and response to travel-related public issues occurring among visitors arriving by sea and those in stay-over arrivals. Although the core competencies and protocols for investigating and reporting public health emergencies on passenger ships in the Caribbean are described in the 2005 International Health Regulations (IHR), how these are implemented vary by country, since each country is sovereign. The commonality of tourism-based illnesses, nearby borders, and frequent travel (both intra-regional and international) in the Caribbean necessitates the need for uniform and harmonized surveillance and response to travel-related public health events. This harmonized approach aims to avoid the introduction of new diseases, mitigate the spread of illnesses, and protect the health and security of visitors and locals.

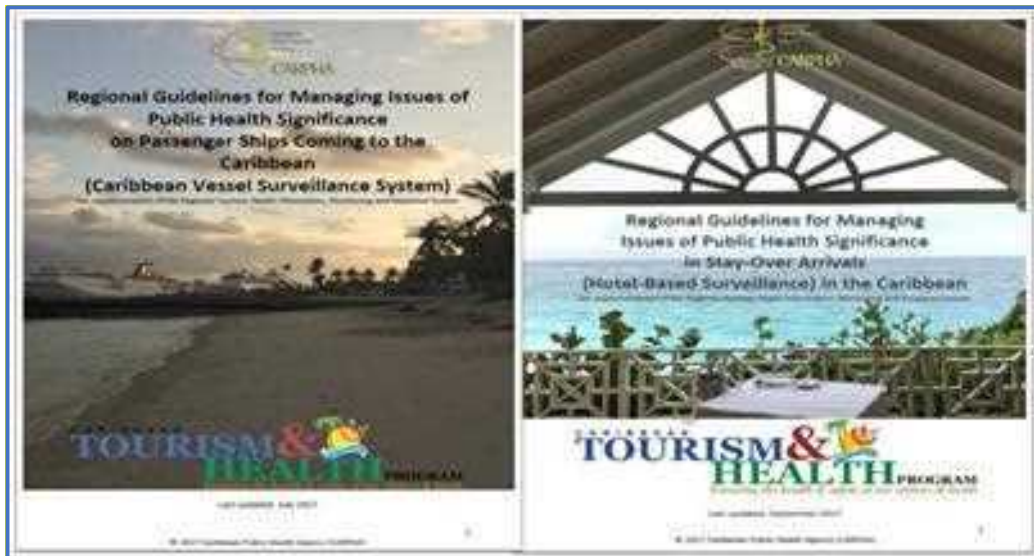


Figure 3. Regional guidelines.

CARPHA, as the Caribbean authority for public health surveillance, developed the Guidelines for harmonized surveillance and response to travel-related public health illnesses to prevent and mitigate public health events on passenger ships and in stay-over arrivals in the Caribbean region. It will support countries in carrying out public health action to manage issues of public health importance in a timely and coordinated fashion and thus protect the health and security of visitors and locals. It will also allow for the collection of surveillance data to establish baselines for outbreak detection and strengthen national surveillance.

The Guidelines are based on the IHR (2005), the World Health Organization (WHO) management of public health events onboard ships (2016) and other documents developed over a 3-year period involving country and agency consultations; and in close collaboration with the Cruise Lines International Association (CLIA) and CDC Vessel Sanitation Program (VSP). It was presented to the 33rd COHSOD, endorsed at the 2018 CARICOM CMOs meeting, and supported at the 2018 Regional Tourism & Health Stakeholder workshop (13 agencies, 14 countries).

Advanced Food Safety and Environmental Sanitation Training

Food safety affects the health, wealth, and reputation of countries. Diarrheal illness resulting from contaminated food or water (FBD) is the most common health problem faced by visitors to the Caribbean. In the last 15 years, the Caribbean has experienced an increase in the number of large and costly visitor-based outbreaks of illness, with negative impacts on the tourism industry. From 2010-2016, over 250 outbreaks of gastroenteritis (GE) from 23 countries were reported to the CARPHA, 15% occurring in hotels/resorts, and accounting for over 25,000 cases. One outbreak in 2012 resulted in over 800 ill persons, hotel closure, and a 20% decline in arrivals. Investigations of FBD outbreaks have repeatedly demonstrated that they were costly, yet preventable. The root causes of these illnesses were traced to inconsistent attention to existing food and environmental safety standards, inadequately

trained staff, and a lack of an effective monitoring and reporting system. Reducing the incidence of FBD is, therefore, a continuing challenge to the Caribbean hospitality industry. The most effective tools for preventing foodborne and other illnesses are science-based food safety management, education, and training.

The THP provides advanced food safety and certification train the trainer course for health and hospitality stakeholders This training is done by certified regional experts, using the globally recognized SERVSAFE food safety material uniquely infused with the Caribbean experience based on CARPHA's illnesses investigations of public health threats. SERV Safe is the internationally recommended comprehensive capacity-building proficiency course, using practical science-based knowledge and skills. It builds countries' capacities in the areas of advanced food safety, illness causation and prevention, outbreak response, and environmental sanitation (see Figure 4). It will also allow for globally recognized certification through the internationally recognized USA National Restaurant Association Educational Foundation (SERV Safe).



Figure 4. Topics covered in Advanced Food Safety and Environmental Sanitation Training.

Hospitality Health Safety and Environmental (HSE) Standards

Seven Caribbean-wide health safety and environmental (HSE) “clean and green” hospitality standards have been developed to improve health, safety, and environmental quality in the hospitality sector. These standards were developed under the authority of the CARICOM Regional Organization for Standards and Quality (CROSQ) through CARPHA THP. These are now being submitted for approval as the CARICOM Regional Hospitality Standards to the CARICOM Council for Trade and Economic Development (COTED):

- 1) Energy management and efficiency
- 2) Food safety and sanitation for the tourism industry
- 3) Environmental management systems for the tourism industry – Guidelines
- 4) Integrated pest management for the tourism industry
- 5) Sewage treatment and management for the tourism industry
- 6) Solid waste management for the tourism industry
- 7) Water treatment, management and efficiency for the tourism industry



Figure 5. Hospitality health safety and environmental (HSE) standards.

The adoption and implementation of these standards by the Caribbean tourism industry will significantly reduce the adverse impact of HSE issues, which in turn would increase the contribution of the sector to the economic well-being of the region. Implementing these standards will be the comparative advantage, as it would protect the region’s fragile environment and lead to a safer and better-quality environmental product, and a standards-based certified destination, which increases the comparative advantage of Caribbean tourism. Substantial benefits are possible if these standards are adopted and referenced in legislation/regulation that can be made sufficiently similar across the Caribbean Region. One such benefit is a substantial improvement in health food safety and environmental sanitary conditions in the hospitality sector throughout the region. The implementation of the standards would be recognized by the Association of British Travellers (ABTA) and other tour operators. Certified facilities would also be published on CTO, CHTA, CARPHA websites.

Partnerships, Mandates, and Policy

The THP developed a Regional THP Policy Framework to mandate the reporting of tourism/visitor illnesses to national authorities from the hospitality sector for the successful implementation and sustainability of the THP. The regional THP Policy Framework aims at ensuring an enabling environment for optimal implementation of the THP and its components. The Regional THP Policy Framework is a critical tool in the drive to secure the Caribbean Region's health security. Implementation of the Policy provides a basis for creating a sense of urgency among hospitality sector partners and travelers to reduce the risk posed to people in the Caribbean by communicable disease outbreaks and public health emergencies, through early detection and a strengthened rapid response.

- In 2017, the 33rd CARICOM Council of Health Ministers (COHSOD) mandated CARPHA through the THP to prepare a draft tourism/traveler's health policy for improving regional health security.
- During 2018-2019, through a consultative process, the Travellers Health Policy Framework was developed
- On September 29, 2019, the Regional Travellers Health Policy Framework was approved at the 37th COHSOD

Partnership

The THP involves the implementation of a new non-traditional health information and monitoring system (i.e., tourism/visitor-based illnesses), new clients/data users (private sector hotels, cruise ships, visitors), and new partners (Ministry of Tourism, tourism authorities, tourism agencies). In this regard, a critical factor for successful implementation and sustainability of the program is global and regional recognition, partnership development, and endorsement from international public and private health and tourism agencies. The THP, starting with an MOU between CTO and CHTA, is building multi-sectoral, multi-agency partnerships with regional and international health and tourism stakeholders to address travel-related public health threats in a rapid and well-coordinated manner for seamless information flow and response to traveler's illness across regional and international borders. Other key partners to date include CROSQ, VSP, Public Health Agency Canada (PHAC), and Public Health England (PHE) and Cruise Lines International Association (CLIA), Association of British Traveler (ABTA).

DISCUSSION

Surveillance is critical for protecting and improving population health. In particular, during a pandemic such as COVID-19, public health officials must be able to rely on a system that produces real-time and accurate data on the outbreak, collected and monitored over time, directly from the communities, so that they can rapidly identify and implement the most effective interventions. In a region such as the Caribbean, consisting of

small islands developing countries and territories, where tourists/travelers outnumber residents, there is a crucial need for a surveillance system that goes beyond national public health surveillance platforms. The Tourism and Health Information System (THiS) web app meets this requirement by monitoring illnesses among visitors and staff in tourist accommodations, in real-time. From January 2017-February 2020, the THiS was successfully implemented in 254 hospitality accommodations in eight countries (Bahamas, Barbados, Belize, Guyana, Jamaica, Trinidad, Tobago, Turks and Caicos Islands). Before its establishment, no system was in place to compile disease data on this population. The systems can detect aberrations in patterns of illness among travelers, which is even more important if they originate from multiple nations or regions. The strength of the platform is also that the visitors themselves are considered as part of the surveillance system. Being able to collect these data in the context of the COVID-19 pandemic cannot be overstated. It allows reporting of more comprehensive and timely data about the outbreak to public health officials.

Pre COVID-19, the THiS has been instrumental in identifying important clusters of illness that that would not have been reported through current national systems, resulting in a rapid action to prevent further spread. This innovative travel/tourism syndromic surveillance crucial during this COVID-19 pandemic for strengthening existing core national health surveillance systems of tourism-dependent Caribbean economies to collect real-time data for early alerts and triggering a rapid coordinated response. CARPHA is promoting the reporting of illnesses, including suspected cases of coronavirus, on THiS both by hospitality accommodation and self-reporting, as a proactive COVID-19 surveillance measure. This pandemic is a reminder that our first line of defense starts with people. We must consistently protect ourselves so that we are more prepared.

Advanced Food Safety Training

There is no evidence that food or food packaging is directly involved in the transmission of COVID-19 [4]. Unlike foodborne gastrointestinal viruses that can make people ill through contaminated food, SARS-CoV-2, which causes COVID-19, is a virus that causes respiratory illness. The main transmission occurs from person-to-person, either between people who are in close contact with one another or through respiratory droplets produced when an infected person coughs or sneezes [5]. However, a person can also contract COVID-19 by directly touching surfaces that have "cough or sneeze" droplets from an infected person, and then touching their mouth, nose, or eyes. For that reason, it is more critical for food handlers to follow the four key steps of food safety: clean, separate, cook, and chill [4]. The advanced food safety and environmental sanitation training contributes to COVID-19 prevention by building capacity and reinforcing behaviors that help avoid coming in contact with the virus (and pathogens in general): frequent washing and sanitizing of all food contact surfaces and utensils, frequent hand washing and glove changes before and after preparing food, frequent cleaning and sanitizing counters and condiment containers. To date, almost 600 health and hospitality workers were trained in the eight implementing countries, providing a solid platform of knowledge and training for proper hand hygiene, cleaning and sanitizing, and other behaviors to prevent COVID-19. Implementing and or reinforcing the food safety and environmental sanitation programs is essential to maintaining a hygienic and safe

environment, keeping the risk of infectious diseases and COVID19 outbreak low and customers and staff healthy.

Hospitality Health Safety and Environmental (HSE) Standards

According to WHO, “the provision of safe water, sanitation, and hygienic conditions are essential to protecting human health during all infectious disease outbreaks” [6]. Although the risk of contracting COVID-19 from the feces of a person is low and there is no evidence about the survival of the virus in water or sewage, implementation of the Caribbean-wide Health, Safety and Environmental “clean and green” Standards will further contribute to preventing transmission of communicable diseases, including the COVID-19 pandemic. In particular, the HSE standards encompass different components that are relevant to mitigate the spread of the virus: within the Food Safety and Sanitation component, frequent and proper hand hygiene is one of the key measures to prevent contamination and transmission and disinfection will facilitate more rapid die-off of the virus. These HSE standards constitute a critical component of a set of preventive interventions to enhance not only the region’s capacity to respond to the public health threats, but also to support the region’s drive towards achieving quality and sustainability and to remain competitive in this rapidly growing global tourism trade.

RESPONSE TO COVID-19 THROUGH THP

Regional Guidelines

The COVID-19 pandemic is causing worldwide disruption and challenge for response in countries. Responding to this pandemic and other emerging and re-emerging infectious diseases in the tourism-dependent, small island developing states like the Caribbean region requires a strong, harmonized coordinated regional approach, given the proximity and interconnection between the islands, their limited and varying capacity to quarantine to respond (test, isolate, treat, and contact tracing). CARPHA is leading the regional health response to COVID-19, in keeping with its Intergovernmental Agreement (IGA) mandate from CARICOM and recommendations from COHSOD- Health working group on regional coordination for management. As such, CARPHA convened the Regional Coordinating mechanism for Health Security (RCM-HS), consisting of Member States, regional and international agencies, to work with its partners and countries, towards a harmonized regional response.

Tourism and Health Information System (THiS)

The web-based application, THiS, allows monitoring and provision of alerts in real-time on the health of guests and staff members. In particular, when indicating the symptoms the tourist(s) or staff member(s) are experiencing, fever, cough/sore throat/difficulty breathing,

diarrhea [6-8] – known symptoms of COVID-19 – can be captured as well as information on recent travel history. Those symptoms can trigger an immediate response following the Regional Guidelines for Managing Issues of Public Health Significance in Stay-Over Arrivals in the Caribbean. Time is of the essence in the fight against the virus. Being able to detect and respond immediately to potential new COVID-19 outbreaks but also assess the impact of the measures taken on the trends of illness reported, can buy the world precious time to contain the spread.

Multisectoral Partnerships

Public health emergency preparedness and response aim to minimize the risks posed by communicable diseases and mitigate their impacts. Sharing and aligning activities in public health emergency preparedness adds value to efforts of single countries to strengthen their capacities and ensure coordinated, effective support with cross-border health threats. Responsibility for the preparedness and the response lies not only with public health agencies but involves every level of government, the private sector, non-governmental organizations, and individuals. In particular, tourism is currently one of the most affected sectors by the COVID-19 crisis as it is based on interaction amongst people. Guiding the tourism sector's response requires strong public-private intersectoral partnerships at national and regional levels between tourism, health, and environment stakeholders. This is the only way to support a rapid and well-coordinated approach to managing the pandemic – and this is what the Tourism and Health Program has executed since its inception. In response to the crisis, regular webinars were convened with CHTA, CTO members, and regional Ministers of Tourism to provide technical guidance to the hospitality sector for mitigating the spread of the virus throughout the region.

COVID-19 Situation reports, travel brief, and travel advisory providing a consolidated view of the health situation in the Caribbean are communicated every two days to countries, regional agencies (CARICOM, CDEMA, IMPACs) international development partners (World Bank, IDB, EU, ECDC, CARICOM, CHTA, and others). Guidelines for travelers, hotels and guesthouses, food and beverage industry, conveyances, front line workers, Ports of Entry in the region have also been developed with support from the THP and disseminated to promote a coordinated response. CARPHA THP, CHTA, CTO, and Global Tourism Resilience and Crisis Management Centre (GTRCMC) also established the COVID-19 Caribbean Tourism Task Force to formalize their efforts and harmonized the regional messaging.

CONCLUSION

In conclusion, the ongoing COVID-19 pandemic is causing worldwide disruption. It demonstrates that for new and emerging public threats, it is critical to capture and monitor the variables that drive illness occurrence in real-time, for informing strategies to tackle emerging and re-emerging infectious diseases. This requires a well-coordinated multi-sectoral response. In particular, the dependence of the Caribbean islands on tourism, the high volume of people

traveling to the islands, and the speed of international travel, heightens the public health challenges for the region. The novel regional Tourism and Health Program, through its multi-prong components and multi-sectoral partnerships, is supporting the regional fight against COVID-19. Efforts are already being made to expand this transdisciplinary approach to more countries regionally.

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Chapter 88

**WHITE PAPER ON VAPING:
ELECTRONIC CIGARETTES USE –
A CASE FOR RESTRICTIVE POLICIES IN GRENADA,
WEST INDIES**

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ABSTRACT

The use of electronic cigarettes (e-cigarettes) or the practice of vaping has emerged as a global public health concern. If this practice remains unchecked, all the gains due to public health efforts to reduce smoking of combustible cigarettes and thus reduce morbidity and mortality from tobacco-related deaths will be reversed. While e-cigarettes were initially introduced as a smoking cessation strategy, sufficient evidence for this has not been forthcoming. In fact, the use of e-cigarettes has produced more negative health outcomes than positive ones, as evidenced in the recent morbidity and mortality related EVALI. While this is more evident in developed countries, governments of low- and middle-income countries such as Grenada, need to protect youth and young adults from initiating and/or continuing use of these potentially harmful products. Many countries, as well as states in the United States, have implemented some level of restrictive policies on

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the use of e-cigarettes based on the available evidence of harm caused by these products. It is proposed that the same interventions that have worked for smoking of combustible cigarettes reduction should be applied to e-cigarettes.

INTRODUCTION

Within the decade, the practice of vaping, including the use of electronic cigarettes (e-cigarettes), has increased globally. Due to its significantly reduced cost per month when compared with regular cigarette smoking, e-cigarettes usage has become increasingly prevalent in high-income countries than in low- and middle-income countries. Vaping or e-cigarettes has been marketed as a strategy for smoking cessation tool. The advertisement strategy claimed that the tapering of nicotine delivery devices is more effective for quitting regular cigarette smoking without concerns about the adverse effects of combustible by-products. Studies have documented and demonstrated nicotine addictiveness through regular cigarette smoking among adults and teenagers.

The evidence of adverse effects of e-cigarettes on health is not clear. In the latter part of 2019, a brand of e-cigarette was linked to lung injuries and deaths among young people as a result of inhaling vitamin E acetate. However, for public health and preventive medicine experts, the concern is evident. Nicotine is highly addictive, and the increased use of nicotine-containing e-cigarettes among teenagers, youths, and adults will lead to greater nicotine dependence. Few studies have reported that vaping solutions and their emissions could contain more than nicotine but also aerosolized products (propylene glycol) and other contaminants which could lead to potential health hazards to e-cigarette users and non-users (passive users). Though using e-cigarette may decrease exposure to the risks associated with conventional cigarette use, the health effects of nicotine and aerosol exposures from e-cigarettes are not at present fully understood. Vaping aerosols and products are dangerous for passive users or non-users in environments with reduced ventilation or to those with disease comorbidities and compromised health conditions. A recently published manuscript (December 2019) in the American Journal of Preventive Medicine reported the first longitudinal analysis of the association between vaping and lung disease.

The research investigators followed e-cigarette users for three years and found that they had a 1.3-times higher risk of developing respiratory disease than people who did not use any tobacco product. Cigarette smokers had a 2.5-times higher risk, and those who both smoked regular cigarettes and vaped had a 3.3-times higher risk of developing respiratory disease [1]. Though the data from this study showed that using e-cigarettes appeared to show the minimal risk of developing respiratory disease, the three years follow-up is not a long time to follow vapers. It's also likely that many people who entered the study as smokers had likely started that habit much earlier, hence allowing risks to accumulate. In terms of the biological effects of e-cigarettes, it's likely that following e-cigarette users for 10 to 20 years will produce similar effects of risks associated with regular cigarettes smoking or worse. In light of this new publication that established an independent risk factor for respiratory disease among e-cigarettes users and dual users (e-cigarettes and regular cigarettes smoking), the latter being the most popular, we are proposing a more aggressive ban of e-cigarettes in Grenada. Further studies are needed to fully establish the adverse effects of e-cigarettes on developing respiratory diseases. Nonetheless, until these studies are available, and since the health

hazards and safety of vaping to users, non-users, and passive users are not completely understood, it is important to ban vaping or e-cigarettes use in Grenada. Grenada is a middle-income country and has no policy on e-cigarettes or vaping usage. The St. George's University is also located in Grenada. Most of the enrolled students are from the United States of America, and the probability of possessing vaping products and the use of e-cigarettes is high among these students. Policies are needed to be developed for the students at St George's University, and other institutions in Grenada. Presently, very few Caribbean countries such as Barbados, Jamaica, and Trinidad have policies that address e-cigarette or vaping. Specifically, in Jamaica, "Nicotine-containing e-cigarettes are classified as medicinal products under the Food and Drugs Act. As such, they must be registered before they can be imported (no approval has been granted for these products to date). The Food and Drugs Act prohibits the sale, distribution, importation, or manufacture of a drug that is not registered with the Ministry of Health. A tobacco control regulation prohibits the use of electronic nicotine delivery systems (ENDS) in public places and on public transportation." In Barbados, the Parliament in Barbados passed legislation on February 2, 2017 to ban smoking and vaping in public areas and to prohibit sales of vaping products to minors. On that date, the Minister of Health, Hon. John Boyce, concluded that the dangers that are associated with e-cigarettes are the same as the with combustible cigarettes. "The Health Service Amendment Bill 2017, which classifies e-cigarettes as electronic smoking devices, extends the prohibition on smoking to e-cigarettes."

In Trinidad and Tobago, "According to Chapter 30:04 #18 (Prohibition on toys or candy cigarettes) [1] No person shall (a) import or manufacture; or (b) sell, display for sale, distribute or supply, any sweets, snacks, toys or other non-tobacco items or objects in the form of tobacco products, or which imitate tobacco products. This act is to regulate tobacco products. Electronic Vaporizers or Electronic Cigarettes that do not contain tobacco or produces smoke." The Chapter 30:04 # 18 to e-cigarettes was designed to stop the importation of toy and candy that resembles traditional cigarettes. This act has resulted in debates and possibly not enforced. Countries that have banned e-cigarettes use include Argentina, Brazil, Brunei, Cambodia, Indonesia, Jordan, Oman, Qatar, Singapore, Taiwan, Thailand, United Arab Emirates, Uruguay, and Venezuela [2]. The experts at St. George's University, School of Medicine, Grenada, West Indies have concerns with the usage of e-cigarettes or vaping and recommends the following proposed solutions for consideration in order to protect the public from the health hazards that are associated with e-cigarettes or vaping in Grenada.

Develop and Add an Amendment to Legislation to Ban Importation, Sale, and Practice of Vaping Associated Products in Grenada

E-cigarette devices and the practice of vaping are relatively new to Grenada and, as such, are not considered under existing legislation to enforce regulation of its use. Vaping products are currently marketed as consumer goods, however, with reference to existing laws; it is an offense to sell nicotine vaping products to young people under age 18. The recommended amendment should include vape devices and e-liquids. The Drug Abuse (Prevention and Control) Act was not designed for vaping and does not include safety standards on what can

be sold. Moreover, flavoring used in vaping products are regulated under respective Food Standards and are not a part of the drug regulatory provisions. Options for consideration are:

- 1) In the absence of any specific legal framework for regulating vaping and its products, the government should draft and legislate vaping-specific laws and regulations as an amendment to existing legislation.
- 2) Primary and secondary schools, higher-educational institutions, and individual businesses can make their own policies and rules around vaping that include penalties such as fines for first and second violations and dismissal with persistent or chronic violations.

Establish Health Education and Promotion against Vaping as a Practice and Substances Used for Vaping

Health education and promotion efforts against vaping are a component towards prevention and control, which will complement a legislative agenda to include vaping within existing laws. Education and promotion campaign should focus on e-cigarettes/vapes and combustible cigarettes. Awareness campaigns should be designed to reach youth directly through a variety of channels:

- a) Online and social media advertisements on platforms popular with youth (e.g., Snapchat, Spotify, Instagram).
- b) Web page and Instagram account where youth can seek more information and resources.
- c) Through organizations such as schools and community-based organizations with posters, fact clings, and a handout.

Establish Policy and Legal Interventions against Vaping at Primary and Secondary Schools, Higher Educational Institutions, and Individual Businesses in Grenada. Review and Strengthen Current School Health Policy, Which Relates to Tobacco and Cigarette Smoking to Include Vaping. Themes to Include Are

- a) Educate: E-cigarettes and other vaping products are often not easily recognizable. Educating staff about these products and about the school's policy to address them is an important part of a strategy to reduce student use.
- b) Know more about vaping use: Collecting data on types of vaping products students are using and where they obtain vaping products can help inform education efforts and decisions about school health policies. Sample surveillance questions about vaping use, as well as questions about how students obtain vaping products, perceptions of harm, locations of use, are included.
- c) Share resources for quitting vaping: While the use of vaping on school grounds is not regulated, that doesn't mean they are not current vaping users. It is important to

support persons who use vaping products by providing them resources to address their own nicotine addiction.

- d) Know more about resources in your community: Work with student groups to provide support, education, and connections to resources to address issues of vaping use in their community.

ELECTRONIC CIGARETTES

The use of electronic cigarettes (e-cigarettes), also known as electronic nicotine delivery systems (ENDS) or the practice of vaping has emerged as a global public health concern. While this is more evident in developed countries, governments of low- and middle-income countries such as Grenada, need to protect youth and young adults from initiating and/or continuing use of these potentially harmful products. The US Surgeon General landmark report of 1964 linked smoking cigarettes to the development of lung cancer and heart disease. Following this report, a number of interventions, targeting the advertising, sale, and use of cigarettes, were successfully implemented and proven to be effective in reducing smoking rates [3]. However, the use of e-cigarettes, which was introduced as a potential cessation device and an alternative cigarette product, is threatening to reverse the successes of these interventions. To prevent this from occurring, governments need to take preventive measures. The most effective strategies involve examining best practices and evidence-based solutions that can be tailored to the local context and implemented. In this paper, we present evidence to make a case for the prohibition of some sort and/or restrictive policies in Grenada.

THE E-CIGARETTE DEVICE: BASIC STRUCTURE

Vaping is the practice of inhaling heated and aerosolized constituents of e-cigarettes liquids. The design of e-cigarette devices has changed over time. The change in size, shape, and style has evolved into an efficient nicotine delivery machinery capable of delivering greater concentration and volume of nicotine than older versions. The documented versions of these nicotine delivery devices are delineated into four generations [4].



Figure 1. Basic components of closed and open e-cigarettes, adapted from, Electronic cigarettes: what are they and what do they do? [5].

Common to these designs through all the generations is a battery, liquid that can be turned into vapor, an electrical heating system, and a tank (which serves as a reservoir for the liquid). These innovations are generally classified into two categories; open and closed. The open system is designed such that the components can be replaced; also, it has a system that serves as liquid storage (tank). The closed type has a less flexible design, devoid of the tank, and doesn't offer the option for part replacement. A classical representation of these designs is illustrated in Figure 1 below, showing the various essential components of an e-cigarette [5].

THE E-CIGARETTE DEVICE: HOW IT WORKS

E-cigarette devices comprise of a battery, a reservoir for holding a solution that usually contains nicotine, a heating element or a vaporizer, and a mouthpiece through which the user puffs. The user puffs on it but does not light it, and it does not produce smoke. The solution, which typically uses glycol or glycerine as a solvent for the nicotine and flavoring chemicals, is heated into an aerosol that is inhaled by the user [6]. The solution can also contain other harmful products such as volatile organic compounds (VOCs), nicotine, carcinogens, heavy metals, flavorings such as diacetyl; a chemical linked to a serious lung disease, and ultrafine particles that can be inhaled deeply into the lungs. Nicotine is highly addictive, toxic to the developing fetus, and harms brain development of adolescents. Peripartum, fetal, and developmental adverse effects of nicotine are well documented [7, 8].

The increased use of e-cigarette by female adolescents and women of childbearing age also raises concerns about the effects of e-cigarette during pregnancy and the safety of the fetus. Pregnant traditional smokers are making a switch to vaping because of the perceived lower risk noncombustible cigarette offers [9]. Bystanders can also breathe in this aerosol when the user exhales into the air, causing irritation of the upper airways and eyes and effects from nicotine, including palpitations and an increase of the systolic blood pressure [10]. As e-cigarettes have increased in popularity, their designs, due to a lack of standardization, have also become more diverse [11]. They come in many different shapes and sizes, resembling regular cigarettes, cigars, or pipes, pens, USB sticks, and other everyday items. The larger devices such as tank systems, or "mods," do not resemble other tobacco products [4]. The implications of these new delivery devices are that the level of nicotine and other chemicals inhaled by the user varies, thereby increasing the potential risk to the user. Moreover, there is the potential for e-cigarette devices to be used as illicit drug use delivery systems. Evidence shows e-cigarettes have been used to vape substances such as cannabis, methylenedioxy-methamphetamines, synthetic cannabinoids, methamphetamines, cocaine, heroin, and fentanyl [12]. The first device of what is currently used today was developed by Lik Hon, a Chinese pharmacist [13], and the original design has since evolved into the variety of e-cigarette devices that currently exist. This novelty was introduced into the Chinese market in 2004 and used as a potential cessation device or an alternative cigarette product [14]. The product was later introduced into the US market in the mid-2000s and quickly expanded into a variety of brands and flavors. The practice of vaping was promoted to assist smokers in quitting as it aimed to reduce and/or eliminate smoking withdrawal symptoms and cravings [15]. However, few robust studies have found e-cigarette use to be more effective than other traditional strategies. A recent Randomized Control Trial, which examined the effectiveness

of e-cigarettes versus nicotine replacement therapy as a smoking cessation strategy, found e-cigarettes to be more effective when accompanied by behavioral support [16]. On the other hand, evidence in support of the effectiveness of this intervention is inconclusive, as noted in several systematic reviews [17]. What has been found is that e-cigarettes reduce harm, in that exposure to poisonous and carcinogenic substances present in combustible cigarettes are reduced, thereby reducing adverse health outcomes. Nevertheless, while intended to be less harmful, the use of e-cigarettes has produced numerous biological effects resulting in injury and death. More rigorous studies are therefore needed to determine the effectiveness of e-cigarettes on harm reduction and quitting behavior. Furthermore, a study that compared the effect of co-use of traditional cigarettes with e-cigarette observed a quadruple increase in cigarette smoking compared to individuals who only smoked traditional cigarettes [18]. This result alludes to the body of academic evidence that questions the beneficial effect of vaping as an alternative to traditional smoking.

The recent trend in increasing prevalence, globally, is a cause for concern because there are reasons to believe that the public health gain from a decline in smoking tobacco could be reversed with the alarming rate of use of e-cigarette. In 2019, the prevalence of self-reported current e-cigarette use was high among US high school and middle school students, at 27.5% and 10.5%, respectively [19]. During 2017–2018, current e-cigarette use increased by 78% among high school students (from 11.7% to 20.8%), in 2011, it was 1.5%. Among middle school students, current e-cigarette use increased from 0.6% in 2011 (60,000 students) to 4.9% (570,000 students) in 2018 [20]. This increase in prevalence is also observed globally. In Canada, it was observed that 15.4% (4.6 million) reported the use of an e-cigarette. In 2017, 14.6 million Canadians who are 15 years and older had tried an e-cigarette, which translated to an appreciable increase from about 13% (3.9 million) in 2015 [21]. Among Korean youth use of e-cigarettes increased from 0.5% in 2008 to 9.4% in 2011 [22]; while in England among youth, the use of e-cigarette increased from 22% in 2014 to 25% in 2016 [23]. In Trinidad, in a study among young adults 18–40, the prevalence was 24.6%, and of that, 16.9% had never smoked tobacco [24]. These trends are worrisome, and use has recently been linked to deaths in the US. According to the US Centres for Disease Control and Prevention (CDC), as of November 20, 2019, 2,290 cases of electronic cigarettes, or vaping, product use-associated lung injury (EVALI) has been reported, including 47 deaths. Vitamin E acetate, an additive in some tetrahydrocannabinol (THC) containing products, was found in all analyzed bronchoalveolar lavage (BAL) fluid samples of patients. THC is the psychoactive mind-altering compound of marijuana that produces the "high." However, it is unclear whether other chemicals are also causing the lung injury and, for this reason, the CDC has advised persons to refrain from the use of all e-cigarettes or vaping products [25, 26]. Among youth and young adults, the use of e-cigarettes has also been shown to increase the likelihood of smoking combustible-cigarettes [27]. Some researchers believe that the unabated acceptance of vaping further perpetuates smoking habit and could serve as a portal for some tobacco naïve adolescents.

Furthermore, while the association of e-cigarette use and long-term health effects are unclear, evidence shows that e-cigarette use increases heart rate, increases cough and wheeze in adolescents, can induce acute endothelial dysfunction and oxidative stress of tissues. Potential pathological effects of vaping also include the development of pulmonary diseases such as COPD, cardiovascular diseases, neurodegenerative disorders such as Alzheimer's disease and cancer [28, 29]. More importantly, use of e-cigarettes can increase the number of

youth and young adults who are exposed to nicotine, increase the likelihood that former smokers will again become addicted to nicotine, encourage non-smokers to start smoking conventional cigarettes and other burned tobacco products and sustain nicotine addiction instead of quitting completely [30, 31].

While there is no data on e-cigarette use among youth and young adults in Grenada, a survey conducted among secondary school students in 2013 showed that the prevalence of lifetime use of combustible cigarettes is high, although it decreased from 37% in 2005 and 2007 to 27% in 2013. Overall, there was also a decrease in the prevalence of past-year use and current use of combustible cigarettes [32]. With access to e-cigarettes, these statistics can quickly be reversed.

DETERMINANTS/CONTRIBUTING FACTORS AND CHALLENGES

The use of e-cigarettes has been viewed by many users as a safe alternative to the use of combustible cigarettes. With a few brands being advertised as nicotine-free, consumers may regard e-cigarette use as a safe practice and one that may even contribute to lower nicotine craving. E-cigarettes are popularly used in many countries, including the US, UK, and Canada. The majority of e-cigarettes, however, contain nicotine [33] and, without making a deliberate choice to select non-nicotine products, the substance and its by-products are consumed by users, unawares. To date, the USFDA has not issued any advisory endorsing e-cigarettes as a quit aid.

Consumers may also fail to understand other risks associated with the use of e-cigarettes. In addition to nicotine, e-cigarettes also contain carcinogenic metals, such as cadmium, chromium, lead, manganese, and nickel that are added to e-liquids [34]. Although considered safer than combustible cigarettes [35], within the last five years, the evidence has also been mounting from research and epidemiological surveillance on the health effects of solvents, flavorants, and toxicants used in e-liquids. Compared to combustible cigarette, e-cigarette affords a more discrete use, and there is less disapproval of its use by the wider public. Although the electronic nicotine delivery systems (ENDS) are perceived and marketed as a safer alternative to traditional tobacco smoking; the anti-tobacco campaigns have largely succeeded in creating awareness about the dangers of second-hand smoke for bystanders from the use of combustible cigarettes. A similar second-hand smoke effect occurs among bystanders in close proximity to e-cigarette users. Increased levels of nicotine, tobacco-specific nitrosamines (TSNAs), propylene glycol, and copper were found in the exhaled breath of bystanders in a study, mediated by ventilation, size of the room, and behavior of the user [36]. When heated, the volatile particulates in e-cigarettes are quickly dispersed in the air, exposing non-users to the toxic chemicals.

Age

The teenage years are important for brain development, which continues into adulthood. At that stage, young people are also most susceptible to addictions and organ damage from drug use [37]. This stage of development is usually characterized by risky behaviors that

provide a sense of maturity and social acceptance for youth. Little regard is given for the implications of exposure to hazardous substances, such as drugs and alcohol, on future physical and mental health. E-cigarettes are popularly used by young people in the United States; a trend that signifies the potential for steady increase in the number of new users [38]. Between 2014-2018, e-cigarette use increased 160% among youth in the US [39]. The United States Surgeon General has continually warned of the use of tobacco products and other drugs during youth and young adulthood, which leads to habitual use in adulthood [40]. The copycat mentality perceived among young people in Caribbean countries towards the trends in the United States, in particular, favors an introduction and increase in the use of e-cigarettes in Grenada.

Apart from peer pressure, availability of the devices, alluring advertisements, attractive flavors, and the perception of a safe alternative appeal to young people. E-cigarette marketing projects vaping as glamorous and enchanting; this advertising style downplays and disguises the lethal effects of vaping to unwary teenagers and adolescents. The products and messages are packaged to appeal to the younger population as a harmless alternative method of recreation. The goal is to normalize the lifestyle of alternative nicotine consumption among teenagers and adolescents. Statistics show that there has been some degree of successes recorded by the vaping marketing industries, evident by the teeming and surging numbers of teenagers adopting vaping as a form of nicotine intake. Regulation of this industry has been described as a major part of several national strategies aimed at reducing the level of exposure of younger populations to these marketing strategies [41].

The perceived absence of stigmatization typically associated with the use of combustible smoking products may serve as an encouragement for the use of e-cigarettes. Nicotine is highly addictive and causes a plethora of problems in young people, including problems with cognition and attention, reduced impulse control, mood disorders, and physical damage to the brain and lungs [40]. These effects can contribute to a significant increase in morbidity and mortality in the youth and early adult population. With the emergence of concrete evidence of the dangers of smoking, public health agencies have ramped up campaigns against the practice over the years and were successful in securing support for banning or restricting the use of tobacco products in several countries. The Government of Grenada and governments and other small island states should consider the epidemiological and financial burdens that may emerge should e-cigarette use become widespread in these countries. Huge social and economic burdens may also be placed on young people, their families, and the wider Grenadian community to address any emerging epidemic related to the use of e-cigarettes. This burden will also extend to the state level, as the health care system in small island states quickly become stretched when confronted with new challenges.

Social Norms

The social acceptance of e-cigarette compared to combustible cigarette is discussed above. E-cigarette use is likely to be more popular among people who reside in communities and/or households where the practice is also acceptable. Young people usually obtain the devices from family members and friends [38]. In a study in four states in the US, young people reported that their families were aware of their use of e-cigarettes, and they also received positive messages about the use of the devices [38]. The media has also publicized

celebrities using e-cigarettes. Not only is the practice acceptable in many societies, but provisions are also made for smoking and e-cigarette use in highly patronized areas, such as in airports, universities (schools), and restaurants. Such provisions may project the impression that smoking and e-cigarettes use is “normal,” although confined to designated spaces. In August 2016, the FDA issued a Final Rule to regulate the manufacture and sale of e-cigarette in the US [42] and, by 2019, 98 countries had national or federal laws regulating manufacture, sale, and use of e-cigarettes [43]. Currently, there is no move towards prohibiting the importation and sale of e-cigarettes in Grenada. In order to follow the course of countries that have banned or prohibited the use of e-cigarettes to protect public health, the legal and policy provisions in Grenada need to be revised. The narrow focus of several laws and policies also need to be addressed to put Grenada in a more opportune position to respond to the new products that are constantly available on the market.

Cost and Availability

High taxation has been used as a mechanism to control the purchase and use of combustible cigarettes. In most cases, e-cigarettes do not attract the same high taxes that may deter sale. The Ministry of Health in Grenada has not produced any documentation on the local sale of the device and accessories nor the extent to which those are used on the island, although there are observations of e-cigarettes being used by tourists, international students, and other visitors. There may soon be a market in Grenada for the devices and refills. Should the products become available in markets in Grenada, other residents will also have access. Applying the precautionary principle or prevention measures may be most prudent and relevant to protect the health of Grenadians.

Other Drug Use

Recently, the CDC reported that some brands of e-cigarettes also contain the marijuana compound tetrahydrocannabinol (THC) [44], which is one of the main chemicals that produce physical effects when the leaves and other parts of the plant are used in smoking. Marijuana use and sale are illegal in Grenada. The use of e-cigarette, however, remains a legal and easy way to access and consume THC. In Canada, a study found that e-cigarette use was significantly associated with marijuana use among young people [45]. Another study in the US found that adults who used both marijuana and alcohol had increased odds of e-cigarette use [46]. The CDC also found that almost 90% of patients in two states in the US who developed lung injury reported they used vaping products with THC within three months before the study [44].

The CDC warned consumers of fake THC used in some e-cigarette brands and which also heighten the risk for damage to the lungs and other organs [44]. The study in 2013 among students in secondary schools in Grenada indicated that a relatively high number of young people had smoked combustible cigarette or marijuana in their lifetime and/or used alcohol [20]. Alcohol and marijuana can be gateway drugs to the use of e-cigarettes [46]. In another study, the reverse trend was also found; e-cigarette use was associated with subsequent use of

other drugs [33, 47]. Young people may experience several years of healthy life lost and high social and economic burdens associated with chronic diseases from the use of e-cigarettes. Similar to the situation in the US during the opium crisis, the health care system in Grenada may also become stretched to deal with a new challenge.

PROPOSED SOLUTIONS

The same interventions that have worked for youth smoking reduction are recommended to be applied to e-cigarettes. The approach, therefore, should be multipronged. In the US, seven states have taken action to ban or restrict the use of e-cigarettes [48]. According to a recent WHO survey, the sale of ENDS with nicotine is banned in 13 of 59 countries in which there are regulations. However, the majority of the 13 report availability of ENDS through illicit trade and cross border internet sales [49]. The WHO, therefore, advises countries to consider the following when designing a regulatory strategy for ENDS (a) impede ENDS promotion to and uptake by non-smokers, pregnant women, and youth; (b) minimize potential health risks to ENDS users and non-users; (c) prohibit unproven health claims from being made about ENDS; and (d) protect existing tobacco-control efforts from commercial and other vested interests of the tobacco industry [49]. Based on the WHO guidelines, the following are recommendations for Grenada:

Amendment to Legislation to Regulate Importation and Sale Practice of Vaping Associated Products

The recommendation is for vaping and its tobacco-based products to be listed for regulation under the Drug Abuse (Prevention and Control) Act No. 7 of 1992, Amended, January 2002, Amended by SRO 16 of 2011. E-cigarette devices and the practice of vaping are relatively new to Grenada and, as such, are not considered under existing legislation to enforce regulation of its use. Vaping products are currently marketed as consumer goods, however, with reference to existing laws; it is an offense to sell nicotine vaping products to young people under age 18. There are no legal restrictions on where people can vape, although the Drug Abuse Act which makes provisions for the demarcation of smoking free spaces. The recommended amendment should include vape devices and e-liquids to be regulated under respective and comparable laws.

The Drug Abuse (Prevention and Control) Act was not designed for vaping and does not include safety standards on what can be sold. Moreover, flavorings used in vaping products are regulated under respective Food Standards and are not a part of the drug regulatory provisions. Options for consideration are:

- 1) In the absence of any specific legal framework for regulating vaping and its products, the government should draft and legislate vaping-specific laws and regulations as an amendment to existing legislation.

- 2) Institutions and individual businesses can also make their own policies and rules around vaping, which is the only current measure for them to decide where persons can vape.

Any proposed legislative and policy initiatives should consider the following:

- a) Provide protection from environmental (second-hand) smoke and vapor by prohibiting smoking and vaping of tobacco, nicotine or related products except in the established outdoor designated smoking areas and prohibiting all smoking and vaping;
- b) Foster health and wellness by restricting the consumption, promotion, advertising and sale of smoking and vaping related products;
- c) Recognize the permitted burning of traditional medicines during Traditional Aboriginal Ceremonies;
- d) Communicate restrictions on smoking, vaping, and use of tobacco, nicotine, and cannabis.

Health Education and Promotion against Vaping as a Practice and Substances Used for Vaping

Health education and promotion efforts against vaping is another component towards prevention and control, which will complement a legislative agenda to include vaping within existing laws. Education and Promotion campaign should focus on e-cigarettes/vapes and combustible cigarettes. These are different products that pose the same dangers. A public information campaign to raise awareness among school-aged youth about the dangers of e-cigarettes/vapes is critical towards informing healthy behaviors. Reference is made to a campaign by the CDC as resources available to schools and community-based organizations, and ideas for utilizing the resources [50, 51]. Awareness campaigns should be designed to reach youth directly through a variety of channels:

- a) Online and social media advertisements on platforms popular with youth (e.g., Snapchat, Spotify, Instagram).
- b) Web page and Instagram account where youth can seek more information and resources.
- c) Through organizations such as schools and community-based organizations with posters, fact clings, and a handout.

The CDC recommends use of organizational resources for these campaigns. Some examples include:

- a) Reinforce adult education about the topic. The youth campaign and materials are a great way to reinforce educating parents/guardians and staff in organizations about e-cigarettes. Adults may not be up to date with information regarding vaping and should be considered for a presentation with basic information about e-cigarettes.

- b) Hang campaign posters. The Vapes and Cigarettes: Different Products. Same Dangers posters were created to deliver messaging to youth. Consider hanging them throughout schools where they are visible. Ideas for placement include bathrooms, locker rooms, classrooms, counselor's office, nurse's office, coach's office, bulletin boards, hallways, lunchroom walls, concession stands at school events, and meeting rooms.
- c) Hang fact clings. Each of the four main facts on the campaign poster is printed as small "clings" that adhere to windows, mirrors, doors, and other surfaces. Because young people reported during the campaign focus groups that school bathrooms are often a favored vaping location, the clings were developed with school bathrooms in mind—but they can be used in other areas of the organization's building as well.
- d) Distribute the campaign handout. A two-sided handout or fact sheet contains more facts about the dangers of vaping/using e-cigarettes. The handout expands upon the four main facts in the poster and fact clings and provides resources for youth.

Examples of Schools Based Awareness Campaigns include CATCH My Breath program. CATCH (Coordinated Approach to Child Health) is a school-based initiative which uses relevant, youth-friendly lesson plans. CATCH a youth e-cigarette prevention program targeting ages 11-18. The program uses a Tobacco Prevention Toolkit for teachers with in-classroom units and lesson plans on e-cigarettes, tobacco, and nicotine. The toolkit includes PowerPoints, discussion guides, worksheets, and activities. ASPIRE is also a free, bilingual, online tool that helps middle and high school teens learn about being tobacco-free, and smokescreen is a Smoking Prevention Videogame – play2PREVENT [52, 53].

Policy and Legal Interventions against Vaping

Review and strengthen current school health policy which relates to tobacco and cigarette smoking to include vaping. Themes to include are:

- a) Educate: E-cigarettes and other vaping products are often not easily recognizable. Educating staff about these products and about the school's policy to address them is an important part of the strategy to reduce student use.
- b) Know more about vaping use: Collecting data on types of vaping products students are using and where they obtain vaping products can help inform education efforts and decisions about school health policies. Sample surveillance questions about vaping use, as well as questions about how students obtain vaping products, perceptions of harm, locations of use, are included.
- c) Share resources for quitting vaping: While the use of vaping on school grounds is not regulated, that doesn't mean they are not current vaping users. It is important to support persons who use vaping products by providing them resources to address their own nicotine addiction.
- d) Know more about resources in your community: Work with student groups to provide support, education, and connections to resources to address issues of vaping use in their community.

BENEFITS

Support for smoke and tobacco-free policies in public spaces continue to be implemented over the last several years as the benefits of preventing second-hand smoke and reducing primary use of cigarettes is well documented. The advent of vaping and its associated adverse health effects have also led to current efforts to support policies that prohibit vaping in public spaces. Additionally, the numbers of higher education institutions with comprehensive smoke or tobacco-free policies are now extending their regulations towards vaping in an effort to prevent the adverse effects of vaping. Working to prevent vaping use among youth is especially important because 99 percent of vaping use starts at a young age. Similarly, citizen groups and professional organizations of healthcare providers have started advocating for the adoption of prohibiting vaping practices and vaping products out of an abundance of precaution towards preventing the established burdens associated with vaping exposure. Four particular benefits of prohibiting vaping practice and products for Grenada are:

Decline in Use

The lessons learned from the increase in smoke and tobacco-free policies have led to a decline in the number of persons who smoke cigarettes. Data describing the downward trends in cigarette use was also reported for other tobacco products, including e-cigarettes, hookah, little cigars, and traditional cigars. The expectation is for the practice of vaping to also be reduced through the implementation of policing prohibiting vaping together with an anti-vaping campaign.

Health Promotion

Additional benefits are also derived besides helping to reduce vaping use through education. Changing attitudes towards other substance use and eliminating second-hand exposure make it easier for users to quit. From a health behavior and health promotion perspective, a vaping free policy presents opportunities to educate persons about other health-related issues and the benefits of a health-seeking lifestyle.

Clean Environment

A policy prohibiting vaping will benefit the environment through reduced emission in the air, reduced litter, and reduction in the risk of fire. The policy on vaping prohibition will also reduce maintenance costs associated with cleaning and restoring spaces affected by vaping use and litter.

Professional Preparation

Policies aimed at reducing practices such as vaping also prepare persons to be functional for the workforce and other professional settings. An increasing number of worksites are prohibiting tobacco and other substance use, including through vaping. Smokers/vapers have a harder time getting hired and the chances of getting a job are reduced for unemployed job seekers who smoke/vape.

Reduced Healthcare Cost from Managing Adverse Health Effects

In 2019, vaping has become a public health priority after accidents of sudden lung diseases reported in the US and UK. Active research is currently underway to find out more negative side effects of vaping, but it will be a while before results are available. Vaping side effects can be from short-term, minor issues to something so severe affecting multiple organ systems in the body. From a cost perspective, per capita, health care costs for smokers are higher than those of non-smokers. For example, smoking is the largest single cause of preventable illness and premature death within the UK and places a significant financial burden each year. When applied to projected costs associated with vaping, the scale of use and effects is not comparable, but the cost of treating effects is considerable and increasing. The financial impact of vaping, like smoking, extends to businesses and its workforce productivity; smoking/vaping breaks are said to cost billions of dollars per year, and increased absenteeism is estimated in the billions. There is also a reduced life expectancy and decreasing the country's workforce and its productivity.

CONCLUSION

The use of electronic cigarettes (e-cigarettes) or the practice of vaping has emerged as a global public health concern. If this practice remains unchecked, all the gains due to public health efforts to reduce smoking of combustible cigarettes and thus reduce morbidity and mortality from tobacco-related deaths will be reversed. While e-cigarettes were initially introduced as a smoking cessation strategy, sufficient evidence for this has not been forthcoming. In fact, the use of e-cigarettes has produced more negative health outcomes than positive ones, as evidenced in the recent morbidity and mortality related EVALI. While this is more evident in developed countries, governments of low- and middle-income countries such as Grenada, need to protect youth and young adults from initiating and/or continuing use of these potentially harmful products. Many countries, as well as states in the US, have implemented some level of restrictive policies on the use of e-cigarettes based on the available evidence of harm caused by these products. It is proposed that the same interventions that have worked for smoking of combustible cigarettes reduction should be applied to e-cigarettes. With the reported high prevalence of conventional cigarette smoking among secondary school students in Grenada, the recommendation is for vaping and its tobacco-based products to be listed for regulation under the Drug Abuse (Prevention and Control) Act No. 7 of 1992, Amended, January 2002, Amended by SRO 16 of 2011. Health

education and promotion against vaping is another component of the effort towards prevention and control, which will complement a legislative agenda to include vaping within existing laws. Also, there should be a review and strengthening of current school health policies that relate to tobacco and cigarette smoking to include vaping. Benefits of prohibiting vaping practice and products for Grenada are health promotion with a decline in the use and associated reduction in healthcare costs, cleaner environment and promoting health seeking behavior, and professional conduct among youth and young adults.

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Chapter 89

PROTECTING HEALTH SECURITY IN THE CARIBBEAN: A COORDINATED REGIONAL RESPONSE TO THE NOVEL CORONAVIRUS DISEASE (COVID-19) AND OTHER GLOBAL PUBLIC HEALTH THREATS

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ABSTRACT

Small island developing states like those of the Caribbean Region need strong Regional Coordination of Health Security to mitigate the impact of emerging and re-emerging infectious diseases. The importance of countries working together to achieve functional cooperation and ensure a strong emphasis is placed on Regional Health Security is especially evident with the Caribbean's response to the pandemic of novel coronavirus disease (COVID-19). The aim of this chapter is to describe health security in the Caribbean region and how this has been addressed in the context of a coordinated regional response to the coronavirus disease epidemic. The Caribbean Community (CARICOM) Member States were among the last countries in the world to see an introduction of the COVID-19 infection. The health security efforts of multiple CARICOM regional institutions and stakeholders saw a level of coordination to achieve increased vigilance, early detection of importation of the novel coronavirus and the provision of additional critical care resources to deal with the rapid increase of illness which has come to characterize the progression of disease in affected countries around the world. While it is still early days in the COVID-19 pandemic, the Regional Coordinating Mechanism for Health Security has continued to be the mechanism by

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which CARPHA has gained agreement on policy and operational issues among the multiple stakeholders determining a more cohesive and transparent method for Health Sector action in CARICOM.

INTRODUCTION

The Caribbean consists of many small island developing states, which makes them extremely vulnerable to public health emergencies and disasters (hurricanes, floods, earthquakes). This is due to several factors, including variability in their capacity to respond to public health threats, geographical vulnerabilities to disasters, limited resources for health sector response and surge (human, financial, infrastructural), capacity. Traditionally the CARICOM Member States have individually only been able to respond to a moderate degree of threat. The porous borders and interconnectedness of countries through travel and trade further increases the risk from health threats [1]. The Caribbean also boasts one of the highest numbers of travelers per population worldwide. However, whilst tourism is the key economic driver for the region and is adversely impacted by emergencies and disasters, the high number of travelers per population increases the health, safety, and security risks to the local populations. This has been evident through the introduction and spread of several new and re-emerging diseases [2], as exemplified by outbreaks of Norovirus, H1N1, Chikungunya, Zika, and the current novel coronavirus (COVID-19).

Over the past five years, the Caribbean region has been negatively impacted by repeated outbreaks of new and emerging infectious diseases that have tested the regional health security capacity. The emergence of mosquito-borne diseases Chikungunya and Zika [3]; H1N1, and the preparedness for the possible introduction of Ebola are more recent events that have required the building of internal and regional capacity for emergency response and have highlighted the need for boosting regional health security. The Caribbean has been impacted by multiple hurricanes over the past years. In 2017, Hurricanes Irma and Maria devastated several of the Member States. According to one report, Hurricane Irma's impact from insured losses was estimated at around \$2 billion in 2019 [4]. The collective experiences gained across multiple sectors from many years of preparing for responding to public health emergencies and natural disasters have contributed to building resilience and adaptive capacity of the Caribbean people to the impacts of disasters.

Public health emergencies and disasters have the potential to adversely affect the health of the population. Hence public health systems must play an integral role in preparing communities to respond to and recover from hazard impacts. The public health consequences of disasters and emergencies can be far reaching. During the initial response, the people and communities that are impacted must rely on local community resources and then on external support. As a result, all local, national and regional emergency response stakeholders must be prepared to coordinate, cooperate, and collaborate with cross-sectoral partners and organizations at all governmental levels when emergencies occur, regardless of the type, scale, or severity.

The novel coronavirus disease outbreak in late 2019/early 2020 occurred following recent outbreaks, including Chikungunya and Zika, in multiple countries across the Caribbean region. Outbreak preparedness activities, as well as activities aimed at building core

capacities for the IHR (2005) by health sector stakeholders, should have provided the foundation to build regional cooperation to any new and emerging health threat.

The COVID-19 pandemic initially created international anxiety because of its novelty, coupled with extensive media coverage, and a plethora of fake news and misinformation. The ease of modern-day global travel meant that people from the original and subsequent epicenters traveled freely to several parts of the globe. The importance of travel in the movement of infected people from one geographical area to the other has been evident in the current COVID-19 pandemic. The heightened risk of importation of cases facilitated by tourism travel has been an important consideration for the island nations and the regional governance mechanisms of the Caribbean.

Some of the health issues observed in the region, including a combination of the increased burden of non-communicable diseases (NCDs), and injuries, new, emerging and endemic infectious diseases, and an aging population, will increase the vulnerability of populations and health systems in Member States [4, 5]. A significant proportion of Caribbean people have underlying health conditions that place them in the high-risk categories for severe outcomes from COVID-19. Health security measures must consider the NCD issues and prepare to mitigate the risk to the most vulnerable population.

The Caribbean Community (CARICOM), the regional body for governance, has established various institutions and mechanisms in partnership with regional stakeholders and international development partners to safeguard the health security of the region. The Caribbean Public Health Agency (CARPHA) as the sole regional public health agency, is leading the regional health response to COVID-19, in keeping with its Intergovernmental Agreement (IGA) mandate from Heads of CARICOM Government and recommendations from Council for Human and Social Development (COHSOD) - Health working group on regional coordination for the management of COVID-19.

The aim of this chapter is to describe the health security situation in the Caribbean region and how the Security Cluster of CARICOM has been mobilized to provide the foundation of a coordinated regional response to the Pandemic of COVID-19 disease. The paper also highlights the leading role of the CARPHA, in the CARICOM regional health response to COVID-19 and the importance of strong partnerships with non-Health sectors in achieving functional cooperation for regional health security.

HEALTH SECURITY IN THE CARIBBEAN

The World Health Organization defines global public health security [6] as the activities required to minimize the danger and impact of acute public health events that endanger the collective health of populations living across geographical regions and international boundaries. The goal of global public health security is to demonstrate how collective international public health action can build a safer future for humanity. Many of the lessons learned from the West African Ebola Outbreak have catalyzed actions that have enabled faster and more effective response to outbreaks and emergencies [7]. The Health Security Interface is the point where two systems - the public health sector and the security sector meet and interact in a variety of situations. Some examples where the health security interface occurs are: outbreak response operations in non-permissive environments, such as highly

politicized contexts, conflicts, and wars; deliberate events, including the intentional use of chemical or biological agents in order to cause harm; Issues related to mass gatherings, such as major sporting events, festivals, and regular religious migrations; and activities that may arise in the course of a natural disease outbreak.

The interconnectedness of the globe is now facilitated by the ease of travel from one end to the other by aircraft, and infectious disease threats can now spread much faster across geographical regions. The travel industry is vulnerable to public health emergencies and, in the context of the COVID-19 outbreak, the impact on travel is well noted. The updated and expanded International Health Regulations (2005) provides the legislative framework to enable international collaboration for public health emergencies of international concern. It also facilitates the mobilization of essential resources for effective and timely implementation of actions and, at the country level, requires national core capacity in disease detection. In the last five years up to 2017, WHO reported that more than 1100 epidemic events were verified worldwide; 48 of these in the region of the Americas [8]. Securing the health of the Caribbean surpasses keeping residents safe but extends to the millions of tourists and other visitors that travel to the Caribbean region each year. Implementing systems to eliminate, prevent, and control the spread of infectious diseases is essential for regional health security.

Regional Health Security in the Caribbean describes the capacities required for CARICOM Member States to prepare for and respond to public health threats, issues, and concerns that transcend national boundaries and potentially impact on economic and political stability, trade, tourism, and access to goods. The Caribbean region has a long history of cooperation for health, evidenced by the establishment of various regional organizations from as far back as the 1940s [9, 10]. While multiple efforts have targeted health security over the years, various activities have been carried out in the region in the last six years as part of efforts to bolster regional capacity and coordinated regional response.

The Caribbean Public Health Agency (CARPHA), is the sole public health agency of the Caribbean and commenced operations on Jan 1, 2013, with the aim of delivering the functions of five previous regional health institutions (Caribbean Epidemiology Centre, Caribbean Environmental Health Institute, Caribbean Food and Nutrition Institute, Caribbean Health Research Council, and Caribbean Regional Drug Testing Laboratory) through one platform for greater synergy and cost-effectiveness and as the principal institutional expression of the Caribbean Cooperation in Health [11]. CARPHA provides public health surveillance, emergency response, laboratory, information, research, training, and policy development services that benefit a diverse population of 17 million people in 26 English, French, Spanish and Dutch-speaking member states and territories.

As the regional public health agency, CARPHA plays a pivotal role in defining the scope of health risks associated with many emergencies, including those associated with the natural occurrence of highly infectious diseases, such as COVID-19. In health emergencies, CARPHA serves as a key leader in the regional health response, working closely with other regional and international agencies, to design protective strategies, to instruct health professionals about preventive or treatment interventions and to provide guidelines and technical input to inform the health sector and mechanisms involved in the health security interface. Mechanisms at CARPHA for supporting and coordinating regional health security include:

- CARPHA's Medical Microbiology Laboratory (CMML) which includes a biosecurity level 3 (BSL 3), that serves as the CARICOM regional reference laboratory.
- Health Information, Communicable Diseases and Emergency Response (HCE) Unit, well equipped with qualified epidemiologists, and other technical experts experienced in addressing public health emergency and response.
- Incident Management Team: multi-skilled team consisting of experienced scientists ranging from epidemiologists, laboratorians, risk communicators, behavioral scientists, non-communicable diseases, and other public health experts. This team is activated, once an emergency is verified, to provide real-time daily response to CARPHA member states.
- Regional travelers/tourism and health program (THP) that addresses health, safety, and environmental issues impacting on tourism through an integrated approach and works closely with regional and international tourism sector partners for health security. This unique program adopts a multiprong (surveillance, guidelines, standards, capacity building, policy) and multisectoral (partnerships with CLIA, WTO, VSP Travelers Health: PHE, CDC, PHAC, WHO) approach for implementation and endorsement from Ministers of Health and Tourism across the region. The THP provides a real-time Early Warning and Response Travel Health Information Monitoring (THiS; website <http://this.carpha.org>) that can serve as a proactive measure to help fight the importation and spread of this novel viral illness. Facilities housing stay over arrivals, such as hotels and guesthouses can register to report illness confidentially, and visitors can also self-report. The system will provide information to help identify and confidentially manage early warning COVID-19 symptoms reported by employees and guests in a rapid manner.
- Medicines Quality Control and Surveillance Department (MCQSD) forms part of the robust mechanisms for regulating medicines in CARICOM, in close collaboration with Member States, the CARPHA/PAHO Caribbean Regulatory System (CRS) and other partners such as PAHO/WHO. In health emergencies, they monitor the effectiveness, safety of medicines in use and on the market.
- Environmental Health and Sustainable Development (EHS) Department of CARPHA supports the Caribbean's sustainable development agenda by playing a lead role in key areas related to environmental management for optimal public health. There is a full-service microbiological and analytical laboratory that is accredited to ISO 17025 and provides environmental analyses, including water quality monitoring, plant, soil and tissue analyses, microbiological food testing, indoor environmental quality monitoring, and noise testing. Some of the areas where EHS supports Member States include monitoring, alert and outbreak response for communicable diseases, conducting Environment Impact Assessments (EIAs), and environmental auditing services led by certified ISO 14001 lead auditors.

In response to the Ebola emergency in West Africa in 2014, CARICOM Heads of Government at their Seventeenth Special Meeting in Port of Spain, Trinidad and Tobago in 2014 called for the establishment of a Regional Coordination Mechanism on Ebola (RCME) with a ten-point plan of action. Recognizing the vulnerability of the region and the likelihood

of future health threats, this RCME was then extended into the Regional Coordination Mechanism for Health Security (RCM-HS) to help counter any risk to regional health security from new and emerging threats. In recognition of the issue inherent in a region of very small, highly vulnerable and inter-connected countries and territories coupled with the political and economic integration movement, a regional approach to health security was considered necessary.

The RCM-HS provides oversight of the coordinated planning and implementation of the regional response to public health threats and emergencies with a focus on strengthening the capacity of member states, including those capacities related to the revised International Health Regulations (2005). The members of the RCM-HS are the Caribbean Public Health Agency (CARPHA) (Chair), Caribbean Community (CARICOM), Organisation of Eastern Caribbean States (OECS), CARICOM Implementation Agency for Crime and Security (IMPACS), Caribbean Disaster Emergency Management Agency (CDEMA), Pan American Health Organization/World Health Organization (PAHO/WHO), and selected Member States based on their lead roles in CARICOM. In 2017, participants from CARPHA Member States, regional and international organizations came together in Trinidad and Tobago to discuss the implementation of a Regional roadmap for health security.

Caribbean Regional governments have recognized that the Global Health Security Agenda complements the WHO IHR and has the ability to accelerate compliance through a multi-stakeholder approach. The CARICOM Council for Human and Social Development (COHSOD) agreed that the development of a five-year Roadmap for CARICOM would assist the regional governments in accelerating their national IHR compliance. The mechanism recognized that the region must focus on means of leveraging existing regional capacities, prioritize the importance of Regional Health Security at the political levels to garner continued support and develop means of sustainable financing through mechanisms such as the Stop the Epidemic There and Here (SETH) Fund.

A COORDINATED REGIONAL RESPONSE TO COVID-19

The coronavirus disease (COVID-19) outbreak was first reported in December 2019. The newly identified SARS-COV-2 virus, which was first detected in Wuhan City, China, with suspected links to an animal source, has rapidly spread from person to person. On January 30, 2020 the Director-General of the World Health Organization (WHO) declared the outbreak of a novel coronavirus disease (COVID-19) to be a Public Health Emergency of International Concern. Whilst the outbreak originated in China, in just over three months, the virus rapidly spread to more than 197 countries affecting more than 400,000 persons, as of March 25, 2020. On March 11, 2020 WHO characterized the outbreak to be a pandemic considering the 13-fold increase in COVID-19 cases outside of China with a tripling of the number of affected countries within the previous two weeks. The concerns associated with the rapid spread include the severity of disease and the disturbing lack of action observed in some countries. These, along with other factors, are expected to result in an increase in the number of cases and deaths in affected countries.

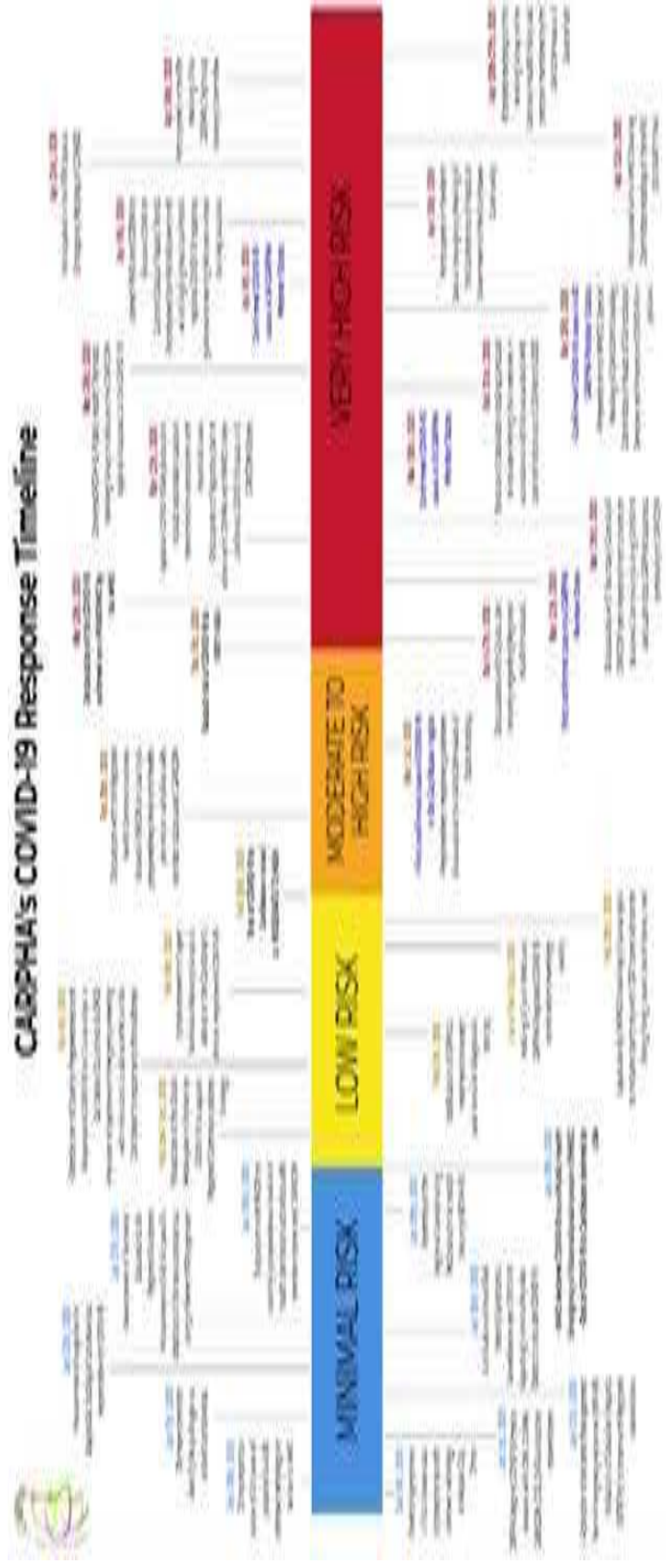


Figure 1. Timeline of CARPHA's key actions carried out in the context of COVID-19 preparedness and response.

Within a few weeks, the numbers of cases reported from China and countries reporting imported cases made it evident that the outbreak was spreading globally quite fast. It became obvious that it would only be a matter of time before an outbreak of great magnitude would impact the Caribbean. Early epidemiological assessments revealed that the elderly, those with chronic diseases, and smokers are among the high-risk groups for poorer outcomes [12, 13]. In the Caribbean context, there is a high prevalence of these risk factors, among others. The Caribbean region has one of the oldest populations in the world. Non-communicable diseases are the leading causes of morbidity and mortality in many countries in the region [4, 5].

According to the WHO, the public health security of all countries depends on the capacity of each to act effectively and contribute to the security of all. The early actions of China to quarantine people and restrict movements have been described as beneficial to the containment of the COVID-19 outbreak in China and delayed the spread of disease to other regions of the world. According to the Director General of WHO in a Statement on March 5, 2020 a collective, coordinated and comprehensive approach that engages the entire machinery of government is what is necessary to push back this COVID-19 epidemic [14].

Recognizing the vulnerability of the region and in keeping with its mandate, CARPHA sought an early audience with key experts in infectious disease internationally in January, 2020 prior to the spread of the disease outside of Wuhan. The advice obtained was acted upon to inform the initial health preparedness and response actions to the outbreak in the region.

Multi-Sectoral Response

CARPHA has been coordinating the CARICOM regional health response, conducting regular update meetings with Member States and partners including tourism partners, producing situation reports every two working days, performing tests on suspected cases from its Member States, enhancing its syndromic surveillance to capture suspected COVID-19 cases, developing technical guidelines including those on sampling, laboratory testing, ports of entry, algorithms for response, management of cases on ships, aircrafts, hotels and their staff, infection prevention and control, health sector response plan; regional communications plans, convening expert groups and participating in CARICOM Heads of Government meetings.

The Regional Coordinating Mechanism for Health Security was activated on January 29, 2020 as a means of bringing order and coherence to the responses of the Health and non-Health sectors as this outbreak evolved. Support for the RCM-HS was garnered from the highest level of regional governance. The CARICOM Council of Human and Social Development convened two Emergency Meetings and the CARICOM Heads of Government convened an emergency meeting of Heads of Government to discuss COVID-19 response and establish guidance for the region, including guidelines for cruise ships and other conveyances.

In keeping with CARICOM recommendations, various key actions were taken across multiple sectors, including:

- Coordination with the national Ministries of Health and Disaster Preparedness Offices
- Participation in national emergency preparedness planning processes
- Receiving training on critical areas such as: infection prevention and control

Health Sector

As a leading health agency, CARPHA took early actions to activate its Incident Management Team for Emergency Response and worked closely with regional and international health partners to define the response needed to this health threat and provide timely advice and assistance to its Member States. As the outbreak emerged, CARPHA convened multiple meetings to provide updates and information to assess the level of readiness and provide support for preparedness and response planning. CARPHA provided technical support and a plethora of technical guidance in keeping with international standards and best practice to ensure as uniform a response as possible across the region.

For COVID -19, CARPHA's Medical Microbiology Laboratory (CMML) is the regional reference laboratory and primary testing site initially, while internal capacity was subsequently built in various CARICOM countries by PAHO to enable testing for COVID-19, including Barbados, Suriname, Guyana, Dominica, Jamaica, Belize, Bahamas, and Haiti. Other countries in the region with capacity for testing included Martinique, French Guiana, Curacao, Aruba, St Martin, and the British territories of Cayman Islands, and Bermuda.

Another area where the strength of regional coordination was evident was in the actions of the Regional Security System facilitating the prompt transportation of samples to be tested at the CARPHA CMML from Member States and the adjustments made by the host country, Trinidad and Tobago, to expedite the clearance of samples by their Customs Department.

Most Caribbean countries have national emergency response plans and designated health emergency coordination structures in place. The last critical outbreak of similar nature in the region would have been Influenza H1N1 in 2009. Countries were advised to use the window of opportunity created by the delay in the importation of cases to the region, to review, update and adapt their pandemic influenza response plans for COVID-19, implement the necessary structures and legislative frameworks, ensure staff was trained and regular exercises carried out to prepare for an epidemic response. A decision was made by the COHSOD working group that a coordinated regional approach would be needed should the epidemic become escalated to a pandemic. CARPHA was tasked to develop a Health Sector Pandemic Response Plan for COVID-19 in this regard for a consistent approach among Member States. Figure 1 outlines the timeline of key actions carried out in the region in the context of COVID-19 response.

CARICOM reaffirmed CARPHA's responsibility and adopted their recommended Regional Approach to the Coronavirus – COVID-19 at the 31st Inter-Sessional Meeting of the Conference of Heads of Government of CARICOM 18-19 February 2020. In recognition of the rapid spread of the disease both at the epi-center and subsequently globally, CARPHA asked Member States to step up their preparedness and response actions as a matter of urgency.

A summary of other key actions recommended in the preparedness phase for the health sector includes:

- Public health authorities providing information to travelers to reduce the general risk of acute respiratory infections, via health practitioners, travel health clinics, travel agencies, conveyance operators, and at Points of Entry.
- Revision of stockpiles of medical equipment and logistical support tools.

- Revision of the list of medical and response personnel with adequate training and identification of staff with prior experience with the diagnosis and management of severe acute respiratory infection (SARS) and Influenza H1N1 cases.
- Member States should incorporate planning for health crisis responses into national disaster risk reduction preparedness and response mechanisms and plans.
- Engagement of all relevant stakeholders to identify response capacities and resources for a whole of government response.
- Development of pandemic plans and carry out simulation exercises for all relevant responders, including security forces.
- Implementation of routine measures, train staff, identify appropriate space and stockpile of adequate equipment in place at points of entry for assessing and managing ill travelers detected before travel, onboard conveyances (such as planes and ships) and on arrival at the points of entry.

Tourism Sector

The COVID-19 outbreak sent shockwaves through the cruise ship industry, and this was exacerbated by an outbreak aboard a cruise ship that docked and became quarantined at a port in Japan for an extended period of time. By March 13, 2020 there had been 696 cases and seven deaths associated with the ship. Development of disease during cruise ship voyages and the ability of their passengers to disembark at ports of entry continues to be a major challenge across the region. Multiple countries across the region have issued travel advisories, and some have banned travel to and from certain affected countries; the list is changing as the disease spread across regions.

In response, the Cruise Lines International Association (CLIA), the leading voice in the cruise ship industry, initially issued a series of enhanced policies for guests and crew who have recently traveled from or through China, including Hong Kong and Macau [15]. On March 8, 2020 the boarding restrictions were extended to South Korea, Iran, and any municipality in Italy subject to lockdown (quarantine) measures by the Italian government [16]. Five cruise ships (Diamond Princess, World Dream, Anthem of Seas, Westerdam and Costa Smeralda) have been quarantined after news of possible coronavirus infections emerged. The Diamond Princess in particular, represents the largest concentration of coronavirus cases outside China with 634 infections and two deaths. Another cruise ship, the Grand Princess, had been quarantined off the US coast with 21 people that have tested positive for coronavirus [17]. Several cruise operators have either canceled or changed their itineraries as countries across the world implement travel restrictions to curb the disease spread [18].

Airline travel has also been impacted globally, with multiple airlines canceling flights on multiple routes. In the Caribbean region, the regional carrier, Caribbean Airlines implemented measures to ensure their readiness in case of any eventualities, although none of their destinations had travel bans imposed. They also were permitting travelers on Caribbean Airlines with connections to or from mainland China, Iran, Italy, Japan, South Korea, and Singapore to rebook the Caribbean Airlines travel segment without change fees, subject to conditions [19].

In recognition of the significant contribution of the travel and tourism industry to the financial health and wealth of the region, CARICOM Heads and COHSOD - Health working group on regional coordination for the management of the virus, mandated CARPHA to lead the development of various regional guidelines for the management of cases on cruise ships, aircrafts, hotels, and among hotel staff.

Other organizations, such as the Global Tourism Resilience and Crisis Management Centre (GTRCMC), are working closely with CARPHA as the regional health lead in the GTRCMC, to promote a multisectoral coordinated response with academia, private and public health care providers, and tourism agencies for protecting Caribbean travel and tourism during the global coronavirus global crisis. During the response, the Head of the GTRCMC called upon the global travel and tourism industry to play a pivotal role in shaping global response efforts, with a focus on preventing exposure beyond the currently affected areas as well as to isolate infected persons from uninfected populations” [20].

CARPHA is also working with the Caribbean Tourism Organization (CTO), the region’s tourism development agency, and the Caribbean Hotel and Tourism Association (CHTA) with which it shares an MOU to enhance the health and safety of tourism and protect the tourism product. In keeping with their mandate of sustainable tourism, they facilitate the sustainability of tourism in the region through liaising with their partners, members, and stakeholders and providing technical advice on important issues e.g., standards development; the execution of projects on issues such as climate change, disaster risk management, energy efficiency [21].

Recognizing that tourism is the lifeblood of the Caribbean region and the essential need to safeguard the health and safety of residents and visitors to mitigate the impact of the COVID-19 threat to the region; and further recognizing the importance of building upon the collaborative efforts which are already underway, and the need to pool organizational resources to do so. On March 4, 2020 CARPHA, CHTA, GTRCMC formalize their efforts and messaging through the establishment of the COVID-19 Caribbean Tourism Task Force (CCTTF). The organizations acknowledged concerns about the high level of misunderstanding about the virus, which has elevated the panic level globally and resulted in the dissemination of a high level of misinformation. The CCTTF aim is to focus on sharing accurate information; strengthening monitoring at airports, sea ports, and hotels and accommodations; improving coordination among stakeholder organizations and locally between tourism and health officials; sharing best practices; training and education; and conducting tourism impact research. This agreement allows for rapid cross-sectional movement of resources, planning, targeted response, and messaging in response to this emergency. Other tourism specific response actions that were recommended include:

- Ensuring an inventory of the tourism properties with preparedness action plans and supporting plan development and testing
- Ensuring knowledge of protocols for management of illness among staff and guests
- Ensuring a protocol for reporting any illness to the Ministry of Health is in place
- CTO/CHTA work with CARPHA for Regional Level Training and Communications

Immigration, Customs and Security Sectors

The Caribbean Community (CARICOM) Implementation Agency for Crime and Security (IMPACS) was established by the Conference of Heads of Government in July 2006, as the implementation arm of a new Regional Architecture to manage CARICOM's action agenda on crime and security [22]. IMPACS played a significant role in the RCM-HS primarily through their Joint Regional Communications Centre (JRCC), that has responsibility for the operations and management of the Advance Passenger Information System (APIS), which screens approximately forty (40) Million passengers annually, specifically those entering, and traveling within the CARICOM Region by air and sea ports [23]. The information provided from APIS enabled countries to effectively monitor passengers arriving from high-risk settings, in the early stages of the outbreak.

In addition, immigration and customs departments were advised to take various sector-specific actions; viz:

- Provision of national protocols for personal protective equipment (PPE) use by Immigration and Customs personnel
- Receiving training on critical areas such as: infection prevention and control and handling of specimens or reagents for testing of COVID-19; strengthening passenger surveillance; and granting practice for cruise ships
- Participate in national emergency preparedness planning processes

The Security Sector engaged in various sector-specific actions, including:

- Ensuring the Security of Government Ministers and Key Officials as identified by the Cabinet
- Ensuring areas requiring additional security are identified as requested by Ministries of Health, e.g., quarantine or isolation centers, the main government stores of PPE, specialized health equipment and medicines, and the supply chain.

The Caribbean Disaster Emergency Management Agency

The Caribbean Disaster Emergency Management Agency (CDEMA) is a regional inter-governmental agency for disaster management in the Caribbean Community (CARICOM). The agency operates based on the principles of Comprehensive Disaster Management (CDM): an integrated and proactive approach to disaster management and seeks to reduce the risk and loss associated with natural and technological hazards and the effects of climate change to enhance regional sustainable development [24]. Through its Regional Response Mechanism (RRM) - a network of CDEMA Participating States (PSs), national, regional and international disaster stakeholders through which external response and relief operations in support of an impacted CDEMA Participating State (PS) are coordinated, CDEMA is recognized as the leader in regional disaster management. During the COVID-19 response, CDEMA's role was to identify the combined resources available and appropriately match

these to the needs of the impacted state(s), and effectively coordinate a response in the context of a global health threat [25].

Recognizing the wide-scale impact of COVID-19 across multiple sectors and the need for a coordinated response from whole of government, in addition to the key actions taken across multiple sectors, specific actions recommended for those in the private and education sectors included:

Private Sector

- Determining critical processes for maintaining operations of the Businesses
- Determining numbers and persons for maintaining operations
- Development of alternate working arrangements e.g., telework

Education Sector

- Establishment of reporting protocols for illness in staff and students
- Determining critical levels of staff required to keep schools open
- Ensuring parents receive instructions re reporting illness
- Ensuring that for institutions with residential facilities/health stations, there are guidelines for managing illness, quarantine, and reporting illness to the Ministry of Health for staff and students.

CONCLUSION

Caribbean Countries have rallied together to mount a regional response to the COVID-19 pandemic. Preparedness efforts in the region may have contributed to delayed importation of cases and afforded countries in the region time to shore up their health sectors and enabled a more robust whole of government response. The heightened level of vigilance not only at the country level, but across regional health security systems, is evidence of the early recognition of the risks of importation of cases on the health and wellbeing of the region's population (see Figure 2).

The regional coordination efforts, including the leadership of CARICOM and CARPHA as health lead, brought together a wide range of stakeholders and resulted in a coordinated approach to regional health security. The regional response was based on the utilization of existing networks and support systems for health security that saw cohesion and rapid response among key stakeholders. The ability to mobilize regional partners and their respective resources are based on these existing relationships between and within agencies and systems that facilitated ease of understanding amongst the various players.

Notwithstanding there were gaps in the regional response, some of which were influenced by the general lack of knowledge and understanding of the effect of the novel virus on human health, the lack of epidemiological evidence to inform response and the fragility of the CARICOM region to a new and emerging health threat. While there is no scientific evidence of whether the measures implemented by Member States were effective to delay the importation of cases to the region, the earliest confirmed cases imported to the region were exposed outside of the region in areas where containment measures had failed.

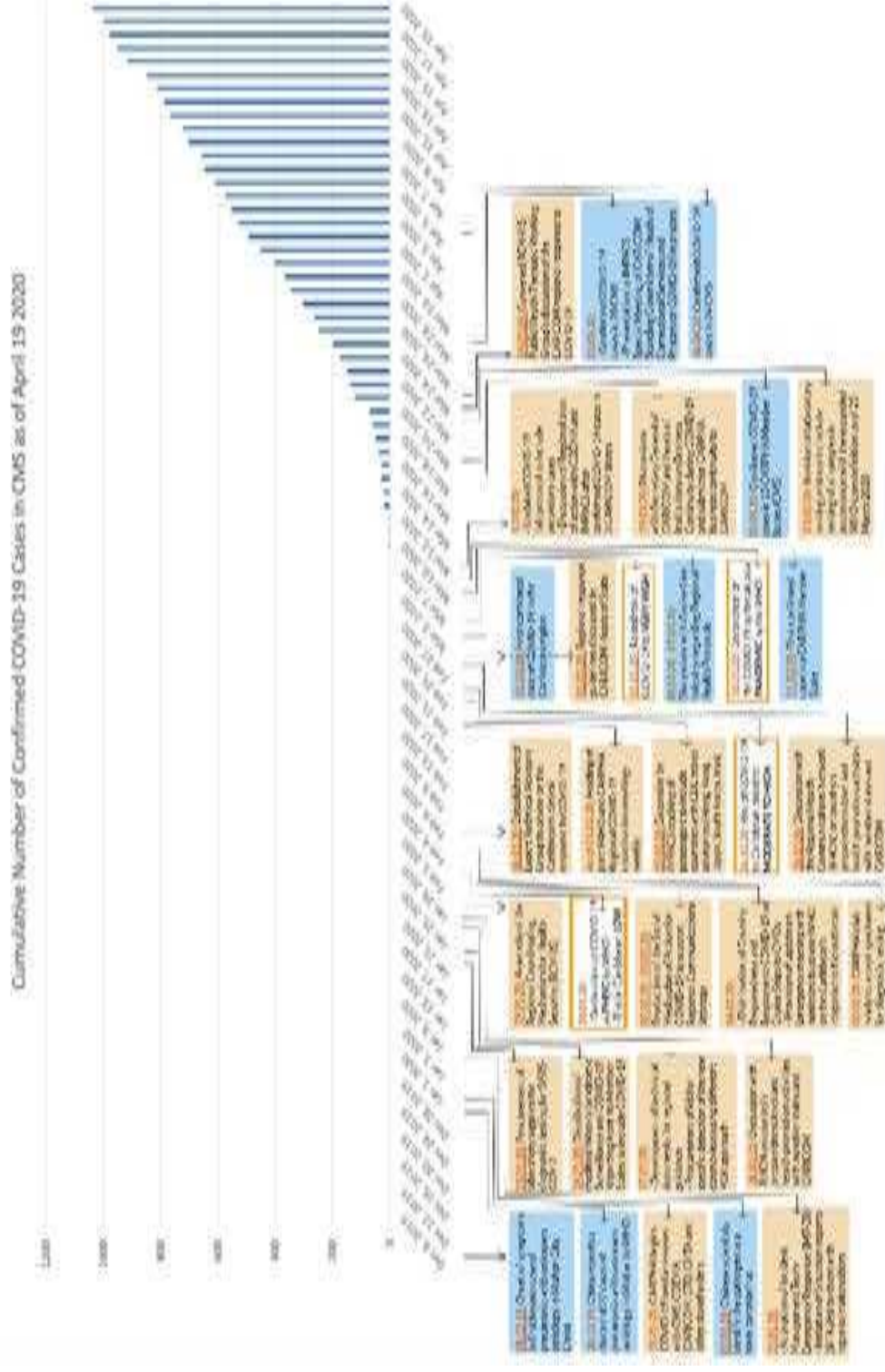


Figure 2. Timeline of Regional Actions and initial imported cases of COVID 19 to CARICOM Member States up to April 19, 2020.

The COVID-19 outbreak provided an opportunity to test the regional mechanisms for health security. The early response, support from regional Heads of Government, and the subsequent level of preparedness revealed that there is strong regional capacity for health security, despite the gaps identified in some areas. The Regional Coordinating Mechanism for Health security should continue to assess the internal capacity of its members and devise more cohesive and transparent methods for collaboration between members.

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CONFLICT OF INTEREST

The authors declare that they do not have any conflicts of interest with respect to this paper.

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Chapter 90

**RAINWATER HARVESTING WATER QUALITY
PARAMETERS RELEVANT
TO THE CARIBBEAN REGION:
A SHORT OVERVIEW**

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ABSTRACT

Harvesting rainwater for domestic use has been practiced for millennia and in recent historical times in the Caribbean. It is increasingly being put forward as a climate adaptation strategy. However, if it is to be promoted, due consideration has to be given by authorities to water quality. Although there is much literature on rainwater harvesting, the absence of specific regulatory responsibility for domestic rainwater harvesting means that there are few definitive guidelines for monitoring and testing. This short chapter aims to contribute to a better understanding of which water quality parameters might be of interest. This, though, needs to be coupled with a systematic approach to water safety assessment and planning.

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INTRODUCTION

Rainwater harvesting, as a source of domestic water use, has been practiced around the world for millennia [1]. In recent times it has been increasingly put forward as a resilience and adaptation response to climate change and climate variability [2], and a water security response in the aftermath of extreme events when formal water systems might be compromised to a greater or lesser extent. The technicalities around the sizing, design, and configuration of systems for harvesting rainwater are relatively straight forward and understood. However, as more attention is given to rainwater harvesting as a climate adaptation intervention, what might be called the ‘governance aspects’ are coming under increasing scrutiny. These include the relationship with public health and questions of responsibility for ensuring appropriate water quality if authorities encourage the adoption of rainwater harvesting. A key part would be understanding what water quality parameters might be appropriate for the different potential uses of harvested rainwater.

This paper is a brief overview of water quality aspects that have been associated with domestic rainwater harvesting systems (DRWHS). It is based on a literature review of some 60 published reports, guidance documents, and peer-reviewed journal articles. The focus of the review is to indicate the water quality issues that have been associated with DRWHS and, in particular, those that have been identified as having a potential impact on water safety and human health. It should be stated that there is a great deal of literature available on the quality of harvested rainwater and there is a high degree of consensus around which are the most important aspects potentially affecting human health. Another important point is that many of the studies reported in journal articles are concerned with a particular water quality aspect peculiar to a set of environmental conditions that are seldom widely replicable. An example of such a study is reported by Báez et al. [3], which considered the chemical composition of rainwater collected in Mexico City. One of the purposes of the study was to determine the extent to which the atmospheric pollution present in Mexico City affected rainwater quality. Given its focus, the study looked at an extensive range of parameters. A similar study, also in Mexico City, considered rainwater used to provide drinking water fountains on a university campus. Such studies are informative as they consider the role and impact of atmospheric conditions, albeit under circumstances that are unlikely to be replicated in the Caribbean.

It is also apparent from the review that water quality standards are an issue. In general, there are no specific water quality standards covering DRWHS. That said, in most instances, it is the World Health Organisation Drinking Water Quality Standards that are used as the benchmark. A further difficulty with the application of appropriate standards is that DRWHS tend to fall outside of the drinking water quality regulatory regime and, as a result, monitoring and testing tend to be carried out on an ad hoc basis. The main focus of concern relates to risks associated with bacteriological contamination and the effects on human health associated with gastrointestinal diseases.

The presented evidence with respect to links between bacteriological contamination of water used for domestic purposes e.g. drinking, washing, cooking, but not outdoor uses and gastrointestinal diseases, is ambiguous. The guidance on use of rainwater tanks produced by the Commonwealth of Australia [4] notes that studies;

“found no measurable difference in rates of gastrointestinal illness in children who drank rainwater compared to those who drank mains water. However, there are examples of *Campylobacter* and *Salmonella* enteritis associated with rainwater tanks and one example of cryptosporidiosis/ giardiasis associated with an underground tank.”

On the other hand, several case studies have linked gastrointestinal illnesses with the consumption of untreated rainwater sources [5]. This is supported by evidence from the Caribbean, particularly studies of DRWHS water quality in the Grenadines, West Indies. Ahmed et al. [5] concluded that health risk assessment models should be used to manage and mitigate health risks associated with drinking and non-potable uses of harvested rainwater. In general, though, harvested rainwater, when properly collected, stored, and treated can provide a safe and reliable source of supply.

CONTAMINATION SOURCES AND HEALTH CONCERNS

Following the approach adopted in the “Handbook of rainwater harvesting in the Caribbean” [6], the following section sets out the potential sources of contamination and their associated health risks.

Contamination from Atmospheric Sources

Rainwater, as it starts to fall, is a very pure form of water. However, as it falls, it interacts with pollutants in the air, either reacting with them or absorbing them into raindrops. For example, the atmosphere contains carbon compounds, and their interaction with water gives rise to a weak carbonic acid, which can corrode materials it comes into contact with. However, the concentrations are so low that they pose no threat to human health. The presence of other physical particles and chemical compounds that may be entrained or react with rainwater depends on the activities and sources of pollution that emit or otherwise give rise to them. These do not have to originate in the local vicinity as contaminants can be carried by air currents and winds over considerable distances; the finer the particles, the further they can be transported. Airborne contaminants can either be of geomorphic or anthropogenic origin; Sahara dust, for example, is of geomorphic origin. Anthropogenic activity has substantially increased the concentration of trace metals in the atmosphere as well as manufactured chemicals emitted through industrial processes or other activities such as the burning of fossil fuels and the use of pesticides, insecticides, and fertilizers. Generally, airborne contamination is a problem in developed countries where industrial activity contributes to poor air quality and airborne pollution. Studies, such as those carried out in Mexico City indicate that in urban settings, air pollution is a risk factor that requires monitoring as high concentrations of trace metals have been associated with increased health risks. Agriculture, too, can pose a threat where there is widespread use of chemicals and fertilizers.

In the Caribbean, the main sources of ambient airborne pollution are associated with vehicle and transport emissions, industrial and waste disposal operations. As already mentioned, Sahara dust is a known source of airborne pollution, which varies intra- and inter-

annually and has been associated with respiratory difficulties. In the Pacific region, the presence of volcanic ash was noted as a potential risk factor. Wet and dry deposition of the dust particles could be an issue but is unlikely to have any significant water quality impact. Of more concern would be airborne particulates associated with bushfires or of geomorphic origin, mobilize from dry surfaces by wind, particularly during dry periods. With increasing aridity associated with climate change, greater influxes of dust, and mobilization of geomorphic particles (soil and trace elements e.g. magnesium), some consideration of their impact on operation and maintenance procedures should be given. Peters [7], in his study of rainwater harvesting practices in Carriacou noted that poor harvesting practices, particularly with respect to the maintenance of collection surfaces, were correlated with poor water quality.

Contamination during Rainwater Capture

Catchment contamination can be physical, chemical, or biological. Physical contamination refers to the dry deposition on the catchment surface of airborne particulate matter or the deposition of organic and non-organic matter. The airborne particulate matter has been considered above and would be washed off the surface during rainfall events. Organic matter (biological contamination) refers to vegetation and fecal matter deposited on the rainwater collecting surfaces. The fecal matter could be of either avian or other animal origins and is probably one of the main hazards of concern noted in the literature. Fecal matter is of concern because it is associated in the literature with the transmission of harmful pathogens, such as legionella, cryptosporidium, and giardia lamblia. These are of concern if there is a direct connection to sources of water, but there are other risk factors to consider, such as the time between deposition and entry through flushing. The risk can be significantly reduced by a combination of disinfection and ultrafiltration. In general, most fecal pollution from man and animals occurs at or below ground level, so water collected from raised roof catchments is likely to be of better bacteriological quality than that collected from ground-level catchments. Studies have highlighted the high variability in the presence of contaminants among different systems, their configuration, operation, and maintenance.

Decaying vegetation would affect physical characteristics such as color and taste, and chemical properties such as level of dissolved oxygen as well as chemical and biological reactions (e.g., algal growth). Under certain circumstances, high levels of chlorine used during disinfection interacting with naturally occurring organic material can give rise to the production of harmful by-products; but as the WHO states, “the risks to health from these by-products are extremely small in comparison with the risks associated with inadequate disinfection.” Non-organic matter, other than the particulates referred to above, could be materials and items that are on the collection surface, concrete blocks, and discarded items.

Chemical contamination may occur if the catchment surface consists of materials that have a coating that can leach or be dissolved in water that collects on the surface. This could be related to the use of roofing sheets coated with toxic paints (containing lead and other compounds), asphalt coverings, shingles, or other forms of covering. Although the use of lead-based paints has been phased out, there are still roofs that could be painted with them. A further potential hazard noted in the literature is the potential chemical reaction between deposited material and the roofing materials. Research, though, indicates that chemical

contamination is not a major concern, while geographic location and type of exposure are more important factors.

Contamination during Storage

This is probably the most important part of the linkages between harvested rainwater and humans as it is from storage that water is taken for use and consumption. The quality of stored water depends on factors such as the measures to prevent contamination before it enters storage, the residence time, maintenance practices, and the environmental exposure of the storage vessel. The inclusion of a filtration and disinfection system as part of the system greatly reduces the risk of infection and the use of contaminated water, which would otherwise pose a risk.

A common issue with storage is that it can provide a breeding place for mosquitos, which, although it does not pose a direct health threat through ingestion, puts people at risk of vector-borne diseases transmitted via mosquitoes, such as Dengue, Chikungunya, Zika, Malaria, and other potentially emerging vector-borne diseases. Prevention and control are, therefore, highly important. Traditional vector control measures have included the introduction of predatory fish that feed on mosquito larvae. In addition, other animals need to be excluded from access to the water storage, such as vermin (rodents, other insects), frogs, and toads, as they too can transmit potentially harmful pathogens. Once storage tanks are fitted with properly fitting lids, all openings are screened, and water extracted using a tap or pump, the likelihood of contamination can be reasonably reduced. With control over the introduction of new contamination (through the use of screens and first-flush diverters), any bacteria and other pathogens that are in the tank will eventually die-off, resulting in improvement of the stored water over time.

There are additional risks associated with the use of below-ground cisterns. Poor construction practices could allow seepage through cistern walls. In areas where use is made of septic tanks and soakaways, there is a further risk of contamination via groundwater ingress. Other risks are associated with potential flooding. Polluted floodwaters, particularly when contaminated with human septage, might inundate below-ground cisterns. If this happens then the water would be unusable and have to be drained, and the cistern disinfected.

Whilst above ground storage would not be as susceptible to flooding, exposure to outdoor elements may pose minor risks. For example, stored water temperatures are likely to be higher, and if pathogens are present, such as legionella, then this would provide favorable reproduction conditions.

The message with respect to storage is that minimizing health risks and maintaining good water quality can be achieved through the proper design of a DRWHS, preventing sources of contamination entering the storage together with proper maintenance procedures that prevent the build-up of sediments and conditions for algal growth.

Contamination during Maintenance

The last link in the chain where risks to human health may occur is during the cleaning and maintenance of the collection and storage components of the DRWHS. Maintenance

tasks include the cleaning and disinfection of collection surfaces, guttering, and piping; desilting, tank cleaning and disinfection; cleaning or replacement of screens, and traps. These are hands-on activities that use cleaning chemicals. Care needs to be exercised that material is not transferred from one part of the system to another or foreign material is introduced, such as on footwear.

WATER QUALITY TESTING

As indicated above, there are not any water quality standards specific to harvested rainwater. The applicable standards are those which would relate to the use of the water, whether for potable or non-potable use. In the absence of national standards for drinking water, the WHO standards have been widely adopted. The problem is not, therefore, an absence of standards but rather of a regulatory regime that addresses and enforces a requisite level of water quality sampling, testing, monitoring, and reporting requirements, and lays down codes of practices governing the installation, operation, and maintenance of DRWHS. Some jurisdictions have developed regulatory regimes, particularly where DRWHS are an important part of the national water supply landscape. Water quality criteria depend on the political and social setting as well as resources and capacity available. Generally, the better off a country, the more developed its regulatory system would be. Examples from the literature of countries that have regulations include; Australia, Bermuda, the United States, US Virgin Islands, United Kingdom, though this is not exhaustive.

Parameters

The following parameters have been mentioned in papers and reports in connection with the testing of the water quality of harvested rainwater. This is an extensive list, and it is unlikely that these would all normally be tested for. In the literature where proposals are made with respect to which parameters to test for, the range is very limited. This probably reflects the understanding of the practical challenges and difficulties involved. Most propose between 4 and 5 parameters, with an emphasis on biological parameters associated with gastrointestinal illnesses.

Parameter		Comment
Physical		
X	pH	Frequently mentioned
	Conductivity	Frequently mentioned
	Alkalinity	Mentioned
	Hardness	Probably not necessary
	Turbidity (NTU)	Mentioned
	Temperature	Infrequently mentioned
	Odour	Seldom mentioned
	Colour (Hazen Units)	Seldom mentioned
	Total Dissolved Solids (TDS)	Mentioned
	Total Suspended Solids (TSS)	Mentioned

	Parameter	Comment
	Chemical	
	Chemical Oxygen Demand (COD)	Mentioned
	Dissolved Oxygen	Infrequently mentioned
	NO ₃ – N Nitrate	Frequently mentioned
	Nitrites	Seldom mentioned
	Physical	
X	NH ₄ – N Ammonia	Frequently mentioned
	SO ₄ Sulphate	Mentioned
	Cl- Chloride	Mentioned
X	Cl Residual	
	PO ₄ Phosphorus	Frequently mentioned
	Pb Lead	Infrequently mentioned
	Fe Iron	Infrequently mentioned
	Al Aluminium	Infrequently mentioned
	Cd Cadmium	Infrequently mentioned
	Zn Zinc	Infrequently mentioned
	Br Bromide (Residual)	Seldom mentioned
	B Boron	Seldom mentioned
	Mg Magnesium	Seldom mentioned
	Na Sodium	Seldom mentioned
	Ni Nickel	Seldom mentioned
	K Potassium	Infrequently mentioned
	Mn Manganese	Seldom mentioned
	Cu Copper	Seldom mentioned
	As Arsenic	Seldom mentioned
	Cr Chromium	Infrequently mentioned
	Se Selenium	Seldom mentioned
	TOC Total Organic Carbon	Infrequently mentioned
	DOC Dissolved Organic Carbon	Infrequently mentioned
	TPC Total Particulate Carbon	Infrequently mentioned
	Biological	
X	TC Total Coliforms	Frequently mentioned
	Faecal Coliforms	Frequently mentioned
X	Escherichia coli (E-coli)	Frequently mentioned
	Enterococci	Not frequently mentioned
	Legionella	Not frequently mentioned
	Giardia lamblia	Not frequently mentioned
	Salmonella	Not frequently mentioned
	Cryptosporidium	Not frequently mentioned
	Campylobacter	Not frequently mentioned
	Shigella	Not frequently mentioned
	Psuedodomenas	Not frequently mentioned
	Vibrio	Not frequently mentioned
	Mosquito larvae	Mentioned
	Dead animals & faecal droppings	Frequently mentioned
	In a few cases mention was made of testing for viruses and pathogens	
	Mentioned by the UK Environment Agency	
	Mentioned by Texas RWH Manual	
X	Suggested parameters for testing – taken from the literature	

CONCLUSION

Harvested rainwater is used around the world as a source of water for domestic purposes. Under certain circumstances, contact with sources of pollution can result in adverse health outcomes, especially among more vulnerable members of the population. If authorities are going to promote DWRHS as a climate adaptation strategy or a response to the adverse effects of extreme events that disrupt normal supplies, then more attention will have to be paid to the public health dimensions. This paper has aimed to make a contribution to the discussion that has to be had around what an appropriate monitoring and testing regime might look like and which parameters should be considered for inclusion. It is recommended that this has to be part of a process of water safety assessment and planning to ensure that whatever systems are put in place are appropriate, fit for purpose, and responsive to the potential hazard exposure.

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Chapter 91

BACTERIAL VAGINOSIS IN WOMEN OF REPRODUCTIVE AGES IN LATIN AMERICA AND THE CARIBBEAN: A LITERATURE REVIEW

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ABSTRACT

The objectives of this chapter are to (i) to summarize the prevalence of bacterial vaginosis (BV) in Latin America and the Caribbean and (ii) review risk factors associated with BV and (iii) review health complications associated with BV. Using key search terms such as bacterial vaginosis, Latin America, and the Caribbean, a combination of 1,206 articles from EBSCO and PubMed were assessed for inclusion. Six articles met the inclusion criteria, and were retrieved and used in this review. Columbia had the highest prevalence of BV (39.6%), while Grenada in 2009 had the lowest prevalence (16.1%). Other regions had a prevalence ranging from 21.0-32.0%. In Bogota (Columbia), the most common co-infection was between BV and *C. trichomatis* 78 (14.0%) followed by BV and *Candida* 41 cases (7.5%), and occasional sexual relationship, being a sex worker, weekly consuming alcohol, and older ages were significantly associated with BV. Of this, 10% of women who had co-infection in Pacoti (Brasil), BV, and human papillomavirus (HPV) were the most common (14%). In Grenada, the most common co-infection was *Candida* (3.6%, 95% CI: 2.9-4.5). Parity was significantly associated with cervical pathology (OR = 0.51, 95% CI: 0.31, 0.83, $p = 0.007$) among women with BV. Studies within the Latin American and Caribbean regions had a low to average prevalence of BV. However, only limited studies have been conducted, and there may be possibilities of increasing patterns within different study populations. Therefore, more population-based studies with scientifically appropriate methodologies should be conducted in order to determine the population-based prevalence, associated risk factors, possible co-infections, and the trend in the prevalence of BV in Latin America and the Caribbean.

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INTRODUCTION

Bacterial vaginosis (BV) is a polymicrobial vaginal infection which causes an alteration in the naturally occurring vaginal microbiota, as a result of a reduction in the naturally occurring *Lactobacillus* and an invasion of aerobic pathogens such as *Gardnerella vaginalis*, *G. prevotella*, *Mycoplasma hominis*, *Peptostreptococcus*, and *Bacteroides* spp. which rapidly multiplies in the vagina of women of reproductive ages [1-5]. Formerly known as *Gardnerella vaginitis*, the infection derives its name from *G. vaginalis*; a microbe which was first isolated from the genital of infected females, and was implicated as the causal microbe in 1892 [6, 7]. Although the presence of *G. vaginalis* remains strongly associated with BV, subsequent scientific findings have been able to isolate *G. vaginalis* from women who are asymptomatic and never end up with BV, thereby disputing the primary role *G. vaginalis* plays in the identification of BV [8-10]. About 50% of women infected with BV are asymptomatic; however, symptoms of BV may include milky discharge from the vagina, which often has a foul smell, and abdominal pain, which could get worse after the menstrual cycle [10].

To diagnose BV, a swab of vaginal discharge of the lateral and posterior vagina wall and assayed for an alkaline pH (>4.5) or clue cells using wet mount microscopy [11, 12]. Gram staining and Nugent scoring are widely considered the gold standards for BV. This criteria identifies and estimates the number of *Lactobacillus* and *G. vaginalis*, bacteroides, or mobiluncus in each field of a microscope slide and categorizes BV as normal bacterial flora (0-3 morphotypes), intermediate (4-6 morphotypes) and 4-7 morphotypes for the presence of BV [11, 12]. Because this assay technique may not be practical in some sites, an alternative known as Amsel's criteria is usually considered as an alternative to the aforementioned techniques. Amsel's criteria identify BV using four key properties such as a fishy odor of vaginal discharge, pH above 4.5, thin homogenous discharge, and = 20% clue cells in saline microscopy [11, 12].

BV is considered one of the most common vaginal infections in women of reproductive ages, with 1 of 3 women getting infected with BV at some time in their life. The etiology is unknown as no clear case definition for the disease has been determined. While previous studies suggest BV to be sexually transmitted, some studies also suggest otherwise [13, 14]. However, promiscuity remains a significant risk factor for BV among sexually active women with a greater risk among females who have sex with females, females who have oral sex and unprotected anal sex [15-17]. Because this infection may be asymptomatic and poses no direct implications on infected females, it is usually not considered a major public health concern. However, evidence has identified BV as a significant risk factor for pregnancy/birth complications as well as sexually transmitted infections (STIs) such as herpes simplex virus type 2, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Trichomonas vaginalis*, and human immunodeficiency syndrome (HIV) among women of reproductive age. The risk for these infections highlights the significance of BV in causing multiple complications and the need to implement public health actions to control this infection/risk [18, 19]. Some of the related birth complications associated with BV are preterm delivery and low birth weight in pregnancy [1, 20]. Preterm birth could result in poor cognitive functioning and other respiratory problems in low birth weight babies [1, 20].

Scientific studies in the United States (2000-2001) and the United Kingdom show a disproportionate distribution of BV among African American and Afro-Caribbean women when compared to other ethnicities, with higher risk amongst women of older ages and/ with multiple sexual partners [20-24]. Studies in Africa also identified multiple sexual partners, previous history of spontaneous abortion orthodox religion followers, douching practices, and male circumcision as significant risk factors associated with this infection [20-24]. Similar practices may exist among women of reproductive ages in Latin America and the Caribbean, which may elevate the risk and burden of the disease; however, only a few studies have been conducted to generate such findings from Latin America and the Caribbean. A review on the global epidemiology of BV revealed an intermediate prevalence of BV among subpopulations (Afro-Caribbean, African, Hispanic women) in developed countries, which may suggest there are similar trends within these regions [15]. Given the undeniable importance of researching and controlling the burden of BV as it relates to other STIs and health complications, it may also be important to understand the level of risk in individual countries to recommend evidence-driven solutions.

Table 1. Studies in countries within Latin America and the Caribbean

Country	Countries where studies were selected
Caribbean	Grenada
Latin America	Brazil, Chile, Colombia, Chile, and Haiti

This study aims to summarize the epidemiology of BV in Latin America and the Caribbean. This review provides an understanding of the current BV epidemiology and will help raise awareness regarding the prevention and control of BV in women of reproductive age (14-49 years) in Latin America and the Caribbean. The objectives are; (i) To summarize the prevalence of BV in studies conducted within Latin America and the Caribbean, (ii) review risk factors associated with BV within the regions (iii) review health complications associated with BV in Latin America and the Caribbean.

OUR STUDY

In August 2016, the St George's University Library was used to conduct a literature search using EBSCO HOST and PubMed, and cited references were evaluated for inclusion. The search terms were bacterial vaginosis, lower genital tract infection, prevalence, women of reproductive age, and 15-54 years. This literature search resulted in 1,206 publications (873 articles from EBSCO, 318 articles from PubMed, and 15 articles from references).

Inclusion and Exclusion Criteria

All articles in English (or English translation) and free full-text articles published within the past ten years were considered for inclusion. Peer-reviewed articles that were assessed for inclusion provided information on the prevalence and risk factors associated with BV in Latin America and the Caribbean. Publications that used random sampling technique, population-

based studies, antenatal/health care based samples, and reproductive health care center studies were preferably included in the review. When studies based on representative samples were not available, other studies conducted on special groups (pregnant women, women attending medical centers for HIV testing), were considered for inclusion. Only studies conducted on women of reproductive age (14-59 years), and studies using retrospective and cross-sectional designs were considered for inclusion in this review.

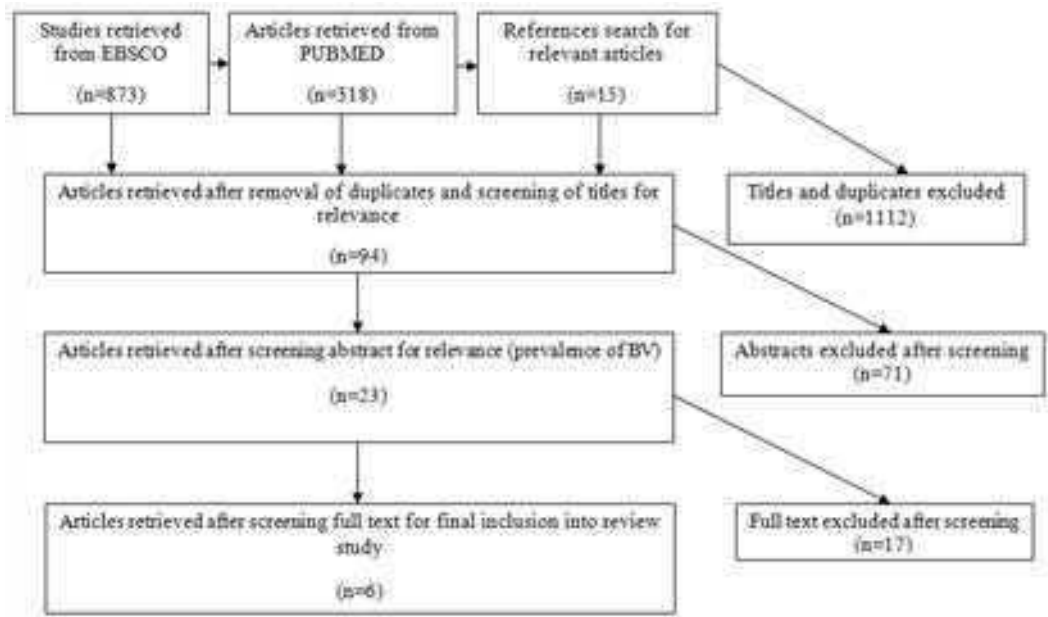


Figure 1. Summary of literature search.

Selection of Studies

Figure 1 shows a flow diagram describing the stages of the study selection based on the inclusion and exclusion criteria, which led to the final selection of studies used in this review.

Data Extraction

Six peer-reviewed articles from Latin America and the Caribbean were written in English (or English translation) and met the inclusion criteria for selection in the review. For each individual study, the following data were extracted; Age group, study design, country and city of study, study population, diagnostic criteria, sample size, sampling technique, and prevalence of BV. Figure 2 shows a summary of the sample sizes of studies conducted in Latin America and the Caribbean.

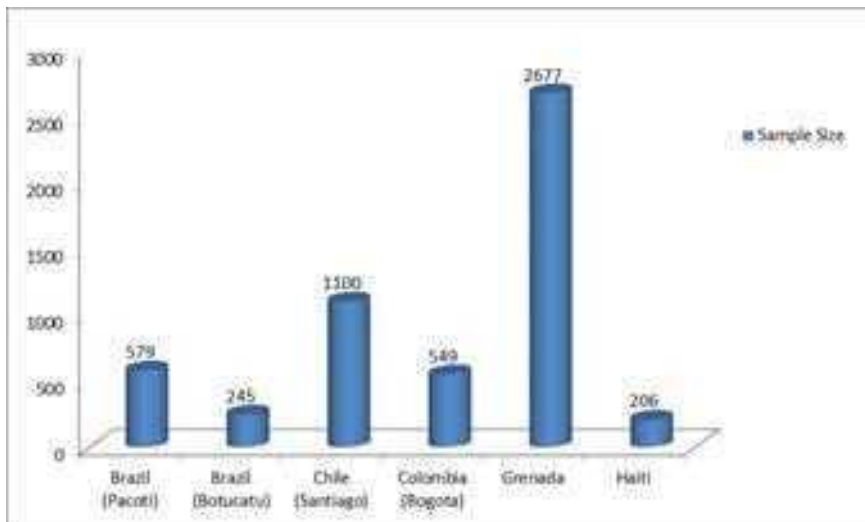


Figure 2. Summary of the sample sizes of students conducted in Latin America and the Caribbean.

Table 2. Prevalence of bacterial vaginosis of four countries in the Caribbean and Latin America

Location	Study location, age group and date of study	Study design, Selection process, and Sample size	Diagnostic Procedure	Prevalence of BV % (Number)
Brazil	Pacoti, 12-49 years ⁽²⁶⁾ 2007	Population based cross-sectional study of women of reproductive ages from 7 hamlets of and centre of Pacoti, (579 examined for BV)	Nugent scoring system	20.0 (116)
	Botucatu, 2006-2007 ⁽²⁷⁾	Cross-sectional study of pregnant women (5-40 weeks of gestation) from 8 family health strategy units of primary care services, (245 examined for BV)	Nugent scoring system	21.6 (53)
Chile	Santiago, 16 -54 years 2006 ⁽²⁸⁾	Cross sectional study of 100 randomly selected sexually active women attending Family Planning clinics.	Nugent Scoring System	32
Colombia	Bogota, 14-49 years, Feb-Dec 2010 ⁽²⁹⁾	Cross-sectional study of women with lower genital tract infection at 3 healthcare attention centers, (549 examined for BV)	Nugent scoring system	39.6
Grenada	Grenada, 15-49 years, Jan 2009-Dec 2011 ⁽³⁰⁾	Retrospective study of women of reproductive ages who had pap smear with a reported diagnosis of BV (2677 eligible women with BV within this period) 2009	Pap smear test	19.5
		2010		16.1
		2011		21.0
Haiti	Rural Haiti, >18 years, Mar 2013 ⁽³¹⁾	Cross-sectional systematic sampling of consecutive women complaining of vaginal itching, discharge, pain or lesion associated urinary symptoms, (206 examined for BV)	Amsel criteria	21.4 60.9

FINDINGS

Figure 3 summarizes the prevalence of BV in the studies in Latin America and the Caribbean. Table 2 shows the prevalence of BV in the studies. Bogota, Columbia, had the highest prevalence (39.6%) followed by Chile (30.0%) when compared to other regions with prevalence ranging between 16.1%-28.2% (25-31). In Bogota, the largest co-infection was found between BV and *C. trichomatis*, 78 (14.0%), and BV and *Candida*, 41 (7.5%) [25]. Also, a significant association between STIs and occasional sexual relationship, sex workers, weekly alcohol consumption, and older age was identified [25]. In Pacoti, out of 10% of women who had co-infection, BV with HPV was the most common (14%) [23]. However, not significant, BV was higher in women in older populations [23]. In Grenada, the highest co-infection was found with *Candida* (3.6%, 95% CI: 2.9-4.5) [26]. Parity was significantly associated with cervical pathology (OR = 0.51, 95% CI: 0.31, 0.83, $p = 0.007$) when nulliparous women were compared to women with 2 or more parity in women affected with BV [26]. In Botucatu, 66.0% of women infected with BV had symptoms; 35.8% ($p = 0.0026$) with vaginal odor, and 50.0% with white vaginal discharge. 57.1% of participants who had normal flora had clinical vaginal signs. No significant association was identified with age, ethnicity, marital status, education, parity, or time of sample collection in Botucatu [24]. Similarly, in rural Haiti, no risk factors were identified; however, 12.5% of infected women were identified to have increased vaginal discharge [27].

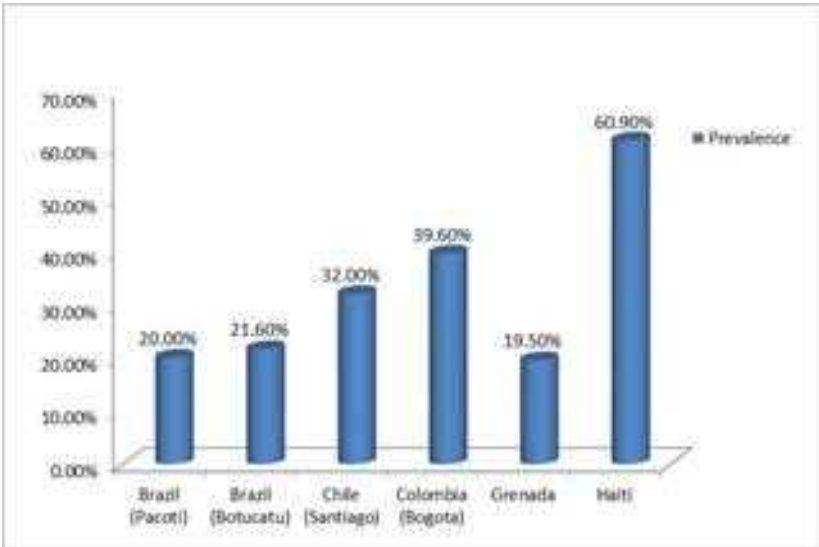


Figure 3. Prevalence of BV in studies conducted in Latin America and the Caribbean.

DISCUSSION

As illustrated in Figure 3, the prevalence of BV among women of reproductive ages in studies conducted within Latin America and the Caribbean was between 19.5-60.9%, with an average prevalence of 32.3% [30]. Due to the absence of prevalence studies in some countries

within the regions, the findings do not provide a generalized estimate of people who have been diagnosed with BV in the past ten years. We can suggest that due to the existence of similar epidemiological, geographical, and data availability characteristics of the countries in these regions, there may also be a similar prevalence of BV in countries where studies are lacking. Therefore, this review may be valuable to inform stakeholders of the possible risks in countries where studies were not conducted.

In order to present a recent review of BV estimates within Latin America and the Caribbean, only peer-reviewed articles conducted within the past ten years were included in this study. Although a literature review was published on the global epidemiology of BV, this review is the first of its kind that looks at the prevalence, risk factors, as well as co-infections or health complications associated with BV in these regions. This is expected to raise awareness on the prevalence of BV within Latin America and the Caribbean and inform advocacy for public health action to mitigate the potential risks of other STIs and health complications.

There are, however, some limitations related to the representativeness, diagnostic assay, and bias in this study. Only studies conducted within the past ten years met the criteria, hence, a small number of articles were eventually included in the review. This, therefore, limits the ability to estimate the prevalence of BV in the wider population. All studies were conducted with convenient samples, which may have introduced selection bias and prevented direct comparison between study populations in the regions. Only six studies were conducted within these regions, and no standard criteria of the study population for the literature search was used, which resulted in the inclusion of different study populations (population-based, married women, antenatal care based, or reproductive health care based) and prevented comparison between groups. Also, different diagnostic criteria were used to diagnose BV in women of reproductive ages, and because these techniques have different specificity and sensitivity as well as other properties, it may also affect the validity and prevent comparison between studies. In order to protect the reliability of the review, comparisons between groups were avoided. Similarly, variation in the prevalence of BV within the regions is consistent with results from other reviews; this suggests that the study is reproducible. However, no conclusion was drawn about the study population based on the studies included in this review.

Although the study conducted in Grenada [30] identified increasing prevalence of BV, yearly data in most countries within the study region has not been generated or readily available. In other cases, the results of the studies were not evaluated to identify prevalence trends. This lack of readily available data at the country level affects the ability to conduct studies with representative samples, resulting in the use of non-representative samples used in prevalence studies. Trend evaluation is often very important in evaluating disease outbreak amongst populations and can indicate whether there is a need for immediate public health action to prevent and control the disease within the population. This evaluation can be achieved by instituting an active surveillance system that captures all cases of BV within the country and as related to other STIs. Surveillance would make data readily available to conduct public health studies and to identify prevalence and risk factors for the disease in order to develop and execute evidence-based public health actions to control BV.

Based on scientific findings, BV infection in women has a high propensity of co-infection with other STIs as well as to lead to other health complications [25]. BV infection was found to be strongly associated with HPV, which is also a significant risk factor associated with cervical cancers in females. Although insignificant, BV infection in pregnancy is associated

with the risk of low birth weight and preterm delivery. Evidence within the Latin America and Caribbean regions are most likely to be identified in reproductive healthcare and antenatal care facilities. Because this infection is 50% asymptomatic, only individuals who display symptoms for BV and women who are pregnant are likely to be tested for BV and, as a result, BV statistics from these sites may be underreported.

A higher risk of BV in young women of reproductive ages was demonstrated in most studies conducted within these regions except for the study conducted in Pacoti, Brazil. Although the study in Brazil identified increased risks among the older population, the sample was not representative and, therefore, not comparable to other older populations, which may have resulted in the unusual disparity in the prevalence of BV [26]. This shows there is a need for further standardized studies to be conducted across the regions to identify the prevalence of BV among different sub-groups.

Given the various risks from infections, it is important for BV to be included as a priority STI for reporting in Latin American and the Caribbean countries. Epidemiological studies with representative, multi-level, population-based samples should be conducted to accurately determine the prevalence, risk factors, and protective factors associated with BV in women of reproductive ages in these countries. Also, prospective studies should be conducted to determine existing trends in the prevalence of BV risk factors associated with BV and possible BV co-infections that may exist in the regions. A standard diagnostic criterion should be adopted to allow for comparison of findings of the burden of BV. From studies conducted so far in these regions, prevalence of BV is intermediate and may potentially increase with time. It is important to conduct awareness programs in the form of sex education in schools, media campaigns, amongst others, to enhance the knowledge base and increase individual and public health actions to prevent BV among women in Latin American and the Caribbean.

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Chapter 92

RECOMMENDATIONS FOR DEVELOPING PESTICIDE EXPOSURE PREVENTION PROGRAMS IN CARIBBEAN COUNTRIES

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ABSTRACT

On a global scale, pesticides are commonly used in agriculture production, despite increasing awareness of the hazardous nature of many of these products. Pesticides have been classified by the World Health Organization (WHO) according to their potential for adverse effects on human health. Community and occupational exposures were found to be associated with increased risk for acute and chronic health problems such as reproductive disorders, neurological problems, flu-like symptoms, skin rashes, eye irritation, and nausea. Agricultural workers and members of their households experience high exposure to pesticides through dermal, inhalation, and ingestion routes. Studies have shown that health problems from pesticide exposures are more prominent in low-income countries that also have fewer resources to develop and adopt modern agriculture technologies. In the Caribbean, pesticide use is high in agricultural production, and studies have shown that agricultural workers do not commonly use personal protective equipment. These practices in the Caribbean region increase health risks for agricultural workers and members of their households. Developing effective interventions to improve safety in the use of pesticides among agricultural workers is necessary and should be a public health priority. To our knowledge, there is no published literature that describes approaches to developing and implementing effective interventions to improve pesticide stewardship - that is, the safe use of pesticides, in Caribbean countries. This chapter

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provides approaches to developing experiential, participatory, and learner-centered interventions aimed at behavior change, to minimize pesticide exposure and health risks among agricultural workers in the Caribbean region.

INTRODUCTION

On the global level, pesticides are commonly used in agriculture production. Increasingly, and more so in recent years, however, studies suggest that some pesticides can have significant negative impacts on human health, increasing risk to various chronic diseases such as Parkinson's disease, end-stage renal disease, and different types of cancers [1–5]. Besides, acute and chronic symptoms in humans, such as reproductive disorders, neurological problems, flu-like symptoms, skin rashes, eye irritation, and nausea have been found to be among common health problems that result from exposure to pesticides [6]. The World Health Organization (WHO) has classified pesticides based on their toxicological potential for human health and the environment [7].

The WHO expressed concerns about exposure to pesticides, among agricultural workers and other communities, particularly in low-income countries [7]. Pesticide exposure can occur through dermal contact, inhalation, and ingestion. Generally, the low-income countries lack innovative practices that are more common in high-income countries to maintain and improve occupational safety [7]. Safety precautions in pesticide usage also tend to be limited among agricultural workers in low-income countries as compared to the practice among workers in high-income countries [7]. The Caribbean has been described to be on a “pesticide treadmill,” indicating the high and increasing usage of pesticides in agriculture production [8]. As a result, concerns have been raised about food safety and the health of agricultural workers in the region from pesticide exposure [8].

The agriculture sector remains a significant contributor to the gross domestic product (GDP) in many Caribbean countries [9]. As such, it is imperative to take measures to reduce the burden of disease among the workers in the sector. Studies have suggested that unsafe usage of pesticides and poor pesticide protective behaviors, resulting in the increased exposure among workers, are due to the lack of knowledge and misperceptions of the risks associated with the use of the products [6]. In the absence of effective preventive interventions, a high percentage of workers in the agriculture sector in the Caribbean continue to be exposed to hazardous pesticides. The Pan American Health Organization (PAHO) has emphasized the need for countries to establish and enforce regulations to address occupational and environmental factors that constitute risks for diseases [10]. For the Caribbean, recommendations to minimize pesticide exposures among agricultural workers may also have significant implications for reducing the incidence of diseases.

In order to address the incidence of diseases associated with pesticide exposures in the Caribbean region, public health interventions must target behavioral change among agricultural workers. Studies have found few agricultural workers in the Caribbean region use protective equipment while handling and applying pesticides [11–14]. A study conducted in the Dominican Republic found that cytotoxic and genotoxic effects were associated with exposure to pesticides among applicators [15], showing the potential health effects pesticides may have on disease risk. To our knowledge, there is no published literature describing interventions aimed at improving pesticide stewardship- that is, safe use of pesticides, in an

effective and participatory manner in the Caribbean. This chapter provides recommendations for experiential, participatory, and learner-centered approaches in developing pesticide exposure prevention programs, focused on behavior change, for agricultural workers in the Caribbean countries. Lastly, this chapter includes a discussion about the benefits of social change for agricultural workers and the regional public health systems.

Application of Behavior Change Theory

Agriculture is the traditional livelihood in many Caribbean countries from colonial times. Although tourism, service, and manufacturing industries variably dominate the highest contributions to GDP across countries, the agriculture sector maintains a prominent role in economies and to ensure food security in the Caribbean. In most of the Caribbean countries, a significant segment of the population engages in commercial or subsistence farming. Small scale farmers dominate the sector [16,] which, in most islands, have only been moderately transformed into using modern technologies. Traditional and labor-intensive methods that resulted in hazardous exposures to pesticides are utilized even in contemporary times [9, 17]. Because many traditional practices are the norm, behavior change may be slow or resisted among agricultural workers.

The Transtheoretical model is a suitable framework on which to premise a preventive health program for the Caribbean region. On the belief that people do not change their behavior quickly, the Transtheoretical model postulates that people go through five incremental stages in behavior change: pre-contemplation, contemplation, preparation, action, and maintenance [18]. These stages represent a build-up in actions towards compliance and maintaining new behaviors. The model shows a progression from mental processing of information to contemplating action to adopting the action (behavior change) and, finally, to maintain the behavior change. Self-pacing and readiness are core principles that underpin the interventions at every stage. This learner-driven approach to change can easily transform into high acceptance of the interventions by agricultural workers. The progressive approach can also be critical to ensuring agricultural workers have both interest in and absorptive capacity for the behavior change interventions. Apart from applying a model that may be effective for positive behavior change among agricultural workers, the other sections of this paper highlight factors that should also be incorporated across the stages of implementation.

SETTING THE PACE FOR INTERVENTIONS

To develop a health promotion campaign, the first step is to determine the situation in the community. This step is referred to as formative research or situational analysis. This analysis is critical for informing the design of an intervention. Interventions that were developed for other contexts or previously implemented may not offer the best fit in the current environment and time. As for establishing a pesticide protective program, the intention is to investigate the situation pertinent to the handling and application of pesticides by agricultural workers. Community-Based Participatory Research (CBPR) approach is suitable for application in this investigation, requiring the target group, that is, the agricultural workers, to contribute their

knowledge and experiences in planning and developing the research. A wide cross-section of the workers should be consulted to create a stakeholder map and tools for the inquiry. Public health practitioners, academicians, and other preventive health experts should participate in this initial research designing consultations to ensure that scientific methods and best practices are considered and appropriately applied at this initial phase. Broad-based participation at this early stage can be advantageous to generate interest and increased participation in subsequent activities.

The formative research should incorporate a variety of themes that address agricultural workers' knowledge, interests, perspectives, attitudes, and practices related to pesticide usage and health. Such information would be valuable to guide in framing messages and activities to address gaps in knowledge about pesticide safety, poor attitudes, and unsafe practices. Data, which describe morbidity and mortality rates related to pesticide use, can be collected from registries and other authoritative sources, such as from government surveillance reports. Analysis of secondary data may serve to provide crucial evidence of the magnitude of the problem in the sector. Representatives for the agricultural workers and institutions, public health practitioners, academicians, policymakers, and other public health experts should review all results and consult in the development of the interventions, ensuring proper alignment of the interventions with the needs and expectations of the agricultural workers.

GOAL-DRIVEN PROGRAMS

Interventions should be developed with the ultimate goal of reducing the prevalence of health problems among agricultural workers. To achieve this goal, the interventions should focus on addressing gaps in knowledge and practices regarding the safe use of pesticides. Heightening awareness about the possible adverse effects of exposure to pesticides and, at the same time, increasing knowledge about safe practices is paramount to behavior change. Behavior change should aim to increase pesticide stewardship through: 1) use of personal protective equipment such as using masks and gloves, and 2) practicing good agriculture hygiene, such as washing clothes after using pesticides and washing hands before eating and using the toilet. By reducing exposure to pesticides, agricultural workers will also decrease the risk for developing health problems such as cancers and reproductive and neurological disorders [1-5]. The support of public health experts and policymakers can be instrumental in affirmative actions to address agricultural workers' health needs.

Interventions should seek to be both systematic and strategic. Purpose-driven interventions can have the most substantial effect on the knowledge, attitudes, and practices of the agricultural workers. Some key components in a campaign to address exposure to hazardous pesticides can include: 1) call for attention to the public health issue and its impact on health, 2) identification of the target group of agricultural workers in which pesticide exposure is present, 3) documentation of current behaviors regarding the use of pesticides, 4) assessment of the potential adverse health effects due to pesticide exposure in the target population, 5) a plan to protect the health of the agricultural workers and their communities, and 6) evaluation of the overall social and economic benefits. Contact information for the program implementers and sources of additional information should be provided to the workers. The interventions should be progressive – reflecting the tenets of the

Transtheoretical model, from pre-contemplation to action to maintenance of the new behavior. This approach is highly practical, although the timeframe could vary for individual workers to achieve the goal - safe use of pesticides - and subsequently reduce pesticide-associated health disease and conditions.

COMMUNICATION MEDIA

Three communication tools that are variably but highly accessible to Caribbean agricultural workers are television, radio, and telephone. Within the last decade, telephone access increased significantly in the Caribbean region, in particular, with cellular (or mobile) phone usage. The competition between the increasing numbers of telecommunications service providers and government regulations have been beneficial to keeping the cost of telephone and television services at affordable rates. Messages to be used for mobilization and in the interventions should be prepared in formats for dissemination through these various media to reach the largest cross-section of agricultural workers. Radio is advantageous for use in various locations, including in workplaces such as farms. Using the radio to disseminate information would increase the amount of time for which messages can be aired, even during prime time, at an affordable cost. Radio production is also relatively cheap. Using television is advantageous to disseminate information using interactive formats such as stories, charts, and pictures. These formats may be more suitable for persons with lower literacy. Television and radio are also suitable for persons with hearing and vision impairment, respectively. Texting, via cellular telephone, allows for disseminating and receiving short instant messages.

ENSURING APPROPRIATENESS IN MESSAGING

Age, literacy, and media appeal must be considered in developing messages to explain pesticide exposure risks and protective measures. While television and radio are more commonly accessed by middle-aged to older people, social media platforms, such as Whatsapp and Facebook, have greater appeal for young people in the Caribbean. Messages should be presented in formats that are suitable for agricultural workers with different literacy levels. The messages may also be crafted for the attention of the other household members and the wider community that interact with and support the agricultural workers. The channels for dissemination of messages will need to be selected based on suitability to accommodate formats such as tables, still charts, interactive charts, pictures, verbal presentations, and short or long text. Local dialects can be useful to express the meaning of some content or to simplify messages [19]. Representative groups of agricultural workers' can be consulted to review messages and to provide feedback to improve appropriateness and relevance for the wider group. Segments of the workers' group can also be involved in piloting messages.

MARKETING AND GETTING ATTENTION

Marketing of the pesticide prevention intervention should be conducted through direct and indirect means. Firstly, branding has the benefit of allowing the target group to identify with interventions through the use of distinctive design, content, and images [20]. For example, indirect marketing of the programs can include Caribbean- or island-flavored songs, jingles, theatricals, and posters via television and radio. These activities are symbolic of Caribbean traditions and can readily capture the attention of the agricultural workers. Cultural features, such as calypso beat in songs, local theater groups performing plays and displaying national colors on posters, can enhance the marketing strategy to capture the attention of the agriculture workers. Carnival and religious symbols may also be appropriate to grab attention to public health messages in the Caribbean setting.

Secondly, the aim of breakthrough inattention is to attract and engage the target group [20]. The messages should be crafted to appeal specifically to the agricultural workers and provide a sense of urgency for behavior change. Some practical and feasible new behaviors should also be presented to attract attention.

Peer-to-peer marketing among agricultural workers may result in increased support for participation in the interventions. Information about time, place, and format for interventions should always be provided in intervention marketing campaigns. Community groups, agriculture organizations, and other influential organizations, such as donor agencies, can be instrumental in marketing programs to the agricultural workers. The influence of gatekeepers and influential local leaders can affect the community's reception to marketing [19]. Influential members and leaders can reject intervention or messages, based on how it personally impacts them, and also influence the decisions of the wider group. In such cases, the message or intervention will need to be revised to increase its appeal to both the leaders and workers.

POSSIBLE CHALLENGES AND SOLUTIONS

The choice of the communication channel can determine the reach of messages to agricultural workers. It is beneficial for a wide range of media to be used to disseminate information. This, however, may have cost implications leading to fewer media being used segments of the target population not having access to information. This lack of access to information can have a significant impact on the success of the program. To address this issue, media accessibility and preference for the agricultural workers should be identified in the formative research. In pre-testing messages, the reach through various media should also be investigated. The most widely accessible media should eventually be used in the campaign.

Developing a non-specific message is another challenge. Messages that are not sufficiently tailored for a specific group may not attract interest and participation in the intervention. This challenge can be addressed by doing stakeholder mapping to identify the particular characteristics of the agricultural workers that should be targeted in messaging. Documenting the demographic characteristics of the agricultural workers, such as literacy,

age, and preferred communication medium, is also useful for ensuring messages about risk and protection from pesticide exposure, are appropriate and appealing.

An ethical issue may constitute unrealistic and unreasonable promises regarding behavior change and outcomes. Messages can be exaggerated and lead to disappointment when benefits are not perceived as proportionate to the effort for adopting the behavior change. To avoid this challenge, evidenced-based interventions should be adopted, with clearer indications of cause/effect relationships [19]. Such an approach may include the application of public health theories and results from scientific studies [20].

The introduction of excessively costly or unaffordable practices to replace current practices can be considered as unethical as it introduces bias by limiting participation of segments of the target group [19]. For example, large farmer holders may be able to purchase respirators for use when applying pesticides while small farm holders are deprived of acquiring this protective equipment. If cheaper alternatives are not available, the agriculture workers may be forced to resort to using ineffective methods, such as covering the mouth with a cloth while applying pesticides. The inability of the target group to maintain a behavior will also be counter-productive to achieving intervention goals. Although social marketing can result in ready adoption of alternative behaviors, the capacity, and resources that reside among agricultural workers and in the wider community should be assessed in the formative research and considered in the development of interventions.

METHODS FOR EVALUATING THE EFFECTIVENESS OF PESTICIDE EXPOSURE PREVENTION INTERVENTIONS

Evaluation is an essential component in the intervention cycle and should be planned during the initial development phase. This process should cater to agricultural workers reflecting on their experiences during interventions, identifying changes in behaviors, and evaluating the potential impacts of the changes on their health and well-being. These steps support experiential learning - learning through practice and being able to identify and define the outcomes. Formative, process, and summative evaluations should be conducted. The formative evaluation includes an assessment of the situation – for example, determine which workers use pesticides, how are pesticides applied in work settings, frequency of pesticide use, compliance with good agricultural practices, and pesticide stewardship. Process evaluations should determine whether a behavior is changing during the intervention and what factors contribute to positive or negative responses to the intervention. The summative evaluation should focus on what impact was achieved, unintended effects, and cost-effectiveness of the intervention upon completion. The summative evaluation should indicate the quantity and quality of change from the formative evaluation. Text messaging, surveys, and feedback via radio and television may be used to collect both qualitative and quantitative information for these evaluations. A final report should be prepared and submitted to all stakeholders.

CONCLUSION

Social change is the process of improving the conditions of individuals and communities through the use of interventions [21]. The campaign among agricultural workers caters for social change with a focus on the behavior of workers to improve pesticide stewardship in the agriculture sector. Achieving positive behavior change towards minimizing exposure to pesticides has implications for the health and well-being of the Caribbean population. The agriculture industry is one of the oldest establishments in the Caribbean, and many learned traditional behaviors are still dominantly practiced despite increasing evidence of the hazardous nature of some pesticides and their effect on one's health. The recommendations in this paper draw on the Transtheoretical model, which postulates an incremental approach to behavior change. The recommendations, such as applying a self-driven behavior change model in interventions, facilitating community-based participatory learning, and identifying behavior change through reflection support experiential, participatory, and learner-centered approaches in the development and implementation of the interventions to address health risks from pesticide exposures among Caribbean agricultural workers. Social change can also arise from sharing information about innovations and results [20, 22]. This intervention may be replicated in local communities with the results from the evaluation of each cycle disseminated to improve subsequent deliveries of the intervention. The results can also be disseminated across the Caribbean countries; however, each country should ensure that the recommendations are adapted to its specific context.

Finally, reducing exposure to pesticides can result in significant improvement in the health outcomes of agricultural workers in Caribbean countries. The spin-off effect is reducing the burden of diseases and the burden on the health care system while allowing resources to be reallocated to development. Generally, an effective campaign on safely using pesticides among agricultural workers in the Caribbean can contribute to protecting their health and improving the overall health status of the region.

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Chapter 93

BREAST CANCER IN GRENADA, WEST INDIES: A TREND ANALYSIS OF NEWLY DIAGNOSED BREAST CANCER CASES FOR THE PERIOD 2001-2010

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ABSTRACT

Though the burden of breast cancer is on the rise globally, data in the Caribbean region is limited. We examined the trend of breast cancer in the tri-island state of Grenada, Carriacou, and Petit Martinique between 2001 and 2010 in women over 20 years old. A cross-sectional study was conducted. Surveillance and biopsy data from Grenada General Hospital were used to analyze the trend in breast cancer. Data were extracted on biopsies with confirmed breast cancer. The data was collated using an EXCEL spreadsheet and analyzed using EpiInfo to summarize the demographic and pathologic characteristics of each case. Grenada reported 207 breast cancer cases between 2001 and 2010. The incidence rate was 26.4/100,000. St. David's parish had the highest incidence rate (54.5/100,000), and St. Patrick's parish reported the lowest (24.2/100,000). Invasive ductal carcinoma was the most common subtype of breast cancer (76.8%), followed by invasive lobular carcinoma (8.2%), undefined ductal carcinoma (3.4%), mixed carcinoma (2.9%), Ductal in situ carcinoma (2.4%), and invasive adenocarcinoma (1.0%). Other sub-types of breast cancer that were less than 1% include; lobular in situ carcinoma, undefined adenocarcinoma, differentiated carcinoma, undifferentiated carcinoma, invasive squamous cell carcinoma, sarcoma, and others. The majority of the

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cases occurred in the age range of 40-49 years old. Between 2001 and 2010, Grenada showed a decreasing trend in breast cancer rates, and the incidence rate was lower than those reported by other Caribbean islands. Reasons for elevated incidence rates in St. David deserve further study.

INTRODUCTION

Breast cancer is the leading type of cancer frequently diagnosed in women globally, with an estimated 1.4 million incident cases and 459,000 deaths in 2008 [1]. Breast cancer account for 25% of all cancer cases and 15% of all cancer deaths among females [2]. In the Caribbean region, 24.6% of all cancer diagnoses are breast cancer cases, and 15.8% of all cancer-related deaths are due to breast cancer [3]. In 2008, Trinidad and Tobago reported an incidence rate of 36/100 000, and Barbados reported a rate of 74/100 000 [4].

Research has shown that there has been an increase in global incidence rates of breast cancer. There are few studies that have examined the growing incidence rate of breast cancer in the Caribbean region; therefore, further exploration in this region is needed. In the tri-island state of Grenada, Carriacou and Petit Martinique, health service personnel have reported an alarming increase in the number of newly diagnosed breast cancer cases in women under the age of 50 years [5]. The purpose of conducting this study was to better understand the incidence of breast cancer amongst the Grenadian population. The objective of the study was to determine the trend (person/place/time) in the newly diagnosed cases of breast cancer in the tri-island state of Grenada, Carriacou, and Petit Martinique during the years of 2001-2010 [6].

OUR STUDY

A descriptive epidemiologic study was performed to analyze the trend(person/place/time) of all the reported diagnosed cases of breast cancer over a defined period of January 1, 2001 through December 31, 2010. The study utilized secondary, passive surveillance data from the Pathology Department at the General Hospital in Grenada, West Indies. The surveillance data provided information on each individual who had undergone breast tissue biopsy at the General Hospital and was confirmed as breast cancer cases. Breast tissue biopsy, followed by histological examination, was used as the primary mode of identifying cancer cases.

Target Population

The study area was the Caribbean tri-island state Grenada, Carriacou, and Petit Martinique. Grenada is located northwest of Trinidad and Tobago, northeast of Venezuela and southwest of Saint Vincent and the Grenadines. The target population included all the female citizens and or legal residents of Grenada, Carriacou, and Petite-Martinique.

Study Population

The inclusion criterion was outlined as all the confirmed cases of breast cancer in women under the age of 50 years in Grenada for the ten-year period 2001-2010 identified in the Pathology Surgical Entry Book, available at the Grenada General Hospital. For the purpose of the research, the definition of a case was the medically confirmed (breast tissue biopsy followed by histological examination) presence of an invasive/non-invasive ductal or lobular carcinoma of the breast.

The study excluded all breast cancer cases that were not identified in the surveillance data described in the Pathology Surgical Entry Book. All the diagnosed cases of breast cancer in men on the islands of Grenada, Carriacou, and Petit Martinique were excluded from the study. Furthermore, all cases reported out of the demarcated ten-year period that began on January 1, 2001 and ended on December 31, 2010, were excluded from the study.

Ethical Justification

Prior to the start of the research, ethical approval was sought through the Institutional Review Board (IRB) at St. George's University, Grenada-West Indies. Ethical approval was granted. All ethical protocols were observed during the research process.

Data Collection

A formal written request of permission to access the surveillance data and perform the research was sent to the Permanent Secretary in the Ministry of Health in Grenada. After permission was granted, the data collection process began.

All the confirmed cases of breast cancer were identified from the Pathology Surgical Entry Book. This book provided data on patient demographics and pathologic characteristics. For this study, the variables under investigation were as follows: date of diagnosis, age at diagnosis, parish of residence, and the specific sub-type of breast cancer. The data collected was inputted into a spreadsheet and exported into EpiInfo for data analysis. One data collector was responsible for the data collection process.

Statistical Analysis

Descriptive statistics from EpiInfo were used to summarize the demographic and pathologic characteristics of the identified cases. An analysis of the data was carried out to investigate the frequency of the different breast cancer sub-types amongst the cohort. Annual age-adjusted incidence rates of breast cancer over the specified period were calculated and analyzed on a graph to observe the trend. A time-trend analysis for the reported annual age-adjusted incidence rates was then applied to the data. In addition, the breast cancer incidence rates in the various parishes were assessed and compared.

FINDINGS

There were 207 confirmed cases of breast cancer that were identified from the Pathology Surgical Entry Book (General Hospital) in the tri-Island state Grenada, Carriacou, and Petit Martinique between 2001 and 2010.

Annual age-adjusted incidence rates for the period were calculated and illustrated graphically (see Table 1, Figures 1-2). When a time-trend analysis was applied to the age-adjusted incidence rates, no clear trend was established. Instead, there were relatively unstable and inconsistent changes in the age-adjusted incidence rates across all age categories.

Table 1. Annual age-adjusted incidence rates for breast cancer in Grenada

2001	Number of Cases	Female Population	Crude Rate	WHO World Standard Population	Age-adjusted Rate/100 000
20-29	1	10158	9.8	0.1615	1.6
30-39	4	6203	64.5	0.1471	9.5
40-49	8	5115	156.4	0.1263	19.8
50-59	5	4690	106.6	0.0992	10.6
>60	10	5282	189.3	0.1195	22.6
All Ages	28	31448	526.6	0.6536	64
2002	Number of Cases	Female Population	Crude Rate	WHO World Standard Population	Age-adjusted Rate/100 000
20-29	0	7046	0	0.1615	0
30-39	2	6701	29.8	0.1471	4.4
40-49	4	5526	72.4	0.1263	9.1
50-59	2	3279	61	0.0992	6.1
2002	Number of Cases	Female Population	Crude Rate	WHO World Standard Population	Age-adjusted Rate/100 000
>60	6	7170	83.7	0.1195	10
All Ages	14	29722	246.9	0.6536	29.6
2003	Number of Cases	Female Population	Crude Rate	WHO World Standard Population	Age-adjusted Rate/100 000
20-29	1	7096	14.1	0.1615	2.3
30-39	3	6747	44.5	0.1471	6.5
40-49	6	5565	107.8	0.1263	13.6
50-59	1	3302	30.3	0.0992	3
>60	6	7220	83.1	0.1195	9.9
All Ages	17	29930	279.8	0.6536	35.4
2004	Number of Cases	Female Population	Crude Rate	WHO World Standard Population	Age-adjusted Rate/100 000
20-29	0	7145	0	0.1615	0
30-39	1	6795	14.7	0.1471	2.2
40-49	7	5604	124.9	0.1263	15.8
50-59	5	3325	150.4	0.0992	14.9
>60	5	7271	68.8	0.1195	8.2
All Ages	18	30140	358.8	0.6536	41.1

2005	Number of Cases	Female Population	Crude Rate	WHO World Standard Population	Age-adjusted Rate/100 000
20-29	0	7195	0	0.1615	0
30-39	1	6842	14.6	0.1471	2.1
40-49	4	5643	70.9	0.1263	9
50-59	3	3348	89.6	0.0992	8.9
>60	2	7322	27.3	0.1195	3.3
All Ages	10	30350	202.4	0.6536	23.3
2006	Number of Cases	Female Population	Crude Rate	WHO World Standard Population	Age-adjusted Rate/100 000
20-29	0	7255	0	0.1615	0
30-39	6	6892	87.1	0.1471	12.8
40-49	13	5683	228.8	0.1263	28.9
50-59	6	3372	177.9	0.0992	17.7
>60	7	7373	94.9	0.1195	11.3
All Ages	32	30575	588.7	0.6536	70.7
2007	Number of Cases	Female Population	Crude Rate	WHO World Standard Population	Age-adjusted Rate/100 000
20-29	0	7277	0	0.1615	0
30-39	10	6939	144.1	0.1471	21.2
40-49	9	5723	157.3	0.1263	19.9
50-59	9	3375	266.7	0.0992	26.5
>60	9	7625	118	0.1195	14.1
All Ages	37	30939	686.1	0.6536	81.6
2008	Number of Cases	Female Population	Crude Rate	WHO World Standard Population	Age-adjusted Rate/100 000
20-29	0	7347	0	0.1615	0
30-39	1	6987	14.3	0.1471	2.1
40-49	8	5763	138.8	0.1263	17.5
50-59	2	3419	58.5	0.0992	5.8
>60	10	7478	133.7	0.1195	16
All Ages	21	30994	345.3	0.6536	41.4
2009	Number of Cases	Female Population	Crude Rate	WHO World Standard Population	Age-adjusted Rate/100 000
20-29	1	7399	13.5	0.1615	2.2
30-39	3	7036	42.6	0.1471	6.3
2009	Number of Cases	Female Population	Crude Rate	WHO World Standard Population	Age-adjusted Rate/100 000
40-49	4	5803	68.9	0.1263	8.7
50-59	4	3443	116.2	0.0992	11.5
>60	1	7528	13.3	0.1195	1.6
All Ages	13	31209	254.5	0.6536	30.3
2010	Number of Cases	Female Population	Crude Rate	WHO World Standard Population	Age-adjusted Rate/100 000
20-29	0	7450	0	0.1615	0
30-39	5	7085	70.6	0.1471	10.4
40-49	3	5783	51.9	0.1263	6.6
50-59	0	3467	0	0.0992	0
>60	9	7583	118.7	0.1195	14.2
All Ages	17	31368	241.2	0.6536	31.1

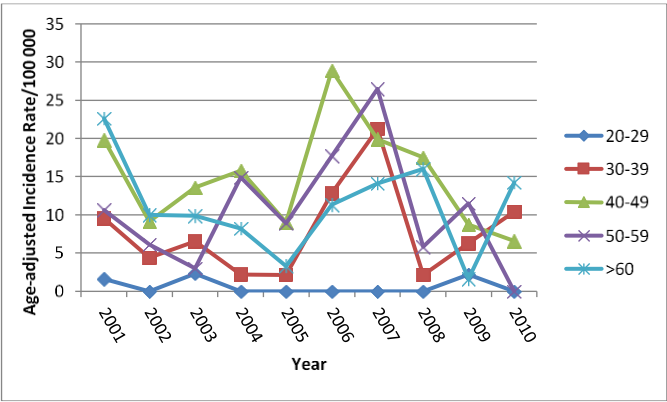


Figure 1. Distribution of newly diagnosed breast cancer using age-adjusted incidence rates (across all age categories).

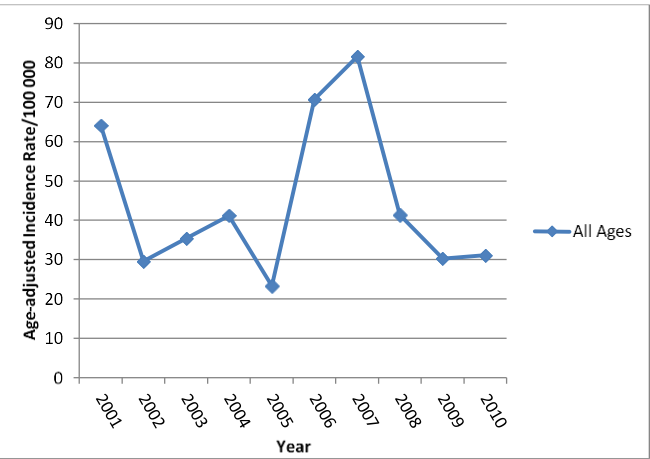


Figure 2. Distribution of newly diagnosed breast cancer of all ages between 2001-2010, using age-adjusted incidence rates.

Distribution of Breast Cancer by Type

The most common type of breast cancer reported in the population was invasive ductal carcinoma (76.8%). This was followed by invasive lobular carcinoma of the breast (8.2%), lobular in situ carcinoma (LCIS) (0.5%), differentiated carcinoma of the breast (0.5%), undifferentiated carcinoma of the breast (0.5%), undefined adenocarcinoma of the breast (0.5%), sarcoma of the breast (0.5%), and invasive squamous cell carcinoma of the breast (0.5%).

Age-Distribution

The youngest confirmed case of breast cancer was 26 years old, diagnosed in 2001. The case was reported as residing in the parish of St. John and was diagnosed with invasive ductal

carcinoma with no metastasis. The oldest confirmed case of breast cancer in this study was 90 years old and was diagnosed in 2010. The patient was a resident of the parish of St. George and was diagnosed with invasive ductal carcinoma with no metastasis.

Table 2. Summary of breast cancer sub-types in the population, 2001-2010

Sub-type of Breast Cancer	Frequency	% Frequency
Invasive ductal carcinoma	159	76.8
Invasive lobular carcinoma	17	8.2
Ductal in situ carcinoma	5	2.4
Lobular in situ carcinoma	1	0.5
Undefined ductal carcinoma	7	3.4
Invasive adenocarcinoma	2	1.0
Undefined adenocarcinoma	1	0.5
Mixed carcinoma	6	2.9
Differentiated carcinoma	1	0.5
Undifferentiated carcinoma	1	0.5
Invasive squamous cell carcinoma	1	0.5
Sarcoma	1	0.5
Other	5	2.4
Total	207	100

The most commonly occurring age for confirmed breast carcinoma was 46 years. The average age was 53 years, with a standard deviation of 14.53 and a variance of 211.15. The median age was 49 years. Inter-quartile age range distributions were 41 (25%) and 65 (75%) respectively. When an analysis of the incidence rates of breast cancer by age-distribution was applied to the data, the highest rate was noted in the 40-49 age category followed by the >60 and 50-59 age categories (see Table 3).

Table 3. Total incidence rates (un-adjusted) of breast cancer in Grenada 2001-2010

Age Category	Number of Cases	Female Population	Incidence Rate/100 000
20-29	3	10158	29.5
30-39	37	6203	596.5
40-49	65	5115	1270.8
50-59	37	4690	788.9
>60	65	5282	1230.6
All Ages	207	31448	3916.3

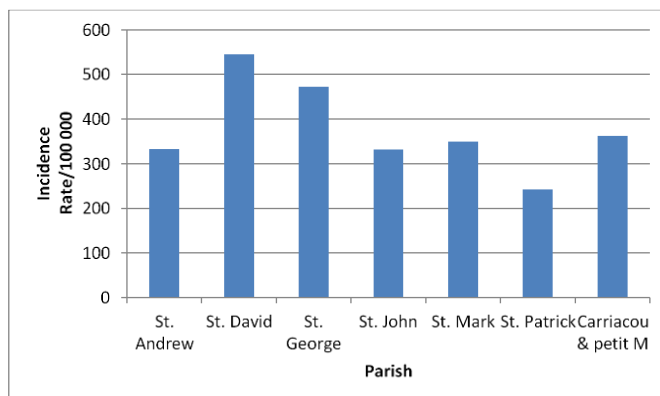


Figure 3. Distribution by parish of newly diagnosed breast cancer in Grenada 2001-2010.

The highest incidence rates of breast cancer were reported in St. David (544.8/100 000). The second highest rate was reported in St. George (472.9/100,000), followed by Carriacou and Petit Martinique (362.7/100,000). The lowest rate was reported in St. Patrick (242.4/100 000) (see Figure 3). Overall, out of all the confirmed cases of breast cancer in each parish, invasive ductal carcinoma was the most common sub-type noted throughout (Tables 4-5).

Geographical (Parish) Distribution

Table 4. Distribution by parish of newly diagnosed breast cancer in Grenada 2001-2010

Parish	Number of Cases	Female Population	Incidence Rate/100 000
St. Andrew	42	12636	332.4
St. David	30	5507	544.8
St. George	90	19033	472.9
St. John	14	4219	331.8
St. Mark	7	2003	349.5
St. Patrick	13	5363	242.4
Carriacou & Petit Martinique	11	3033	362.7
Total	207	46431	2636.5

Table 5. Newly diagnosed breast cancer (%) sub-types by parish between 2001-2010

Type of cancer	St. Andrew	St. David	St. George	St. John	St. Mark	St. Patrick	Carriacou & Petit Martinique
Invasive ductal carcinoma	75	77.8	80	78.6	71.4	69.2	72.7
Invasive lobular carcinoma	5.0	14.8	7.8	7.1	0	7.7	9.1
Ductal in situ carcinoma	5.0	0	3.6	0	0	0	0
Lobular in situ carcinoma	2.5	0	0	0	0	0	0
Undefined ductal carcinoma	5.0	3.7	2.2	7.1	14.3	0	0
Invasive adenocarcinoma	0	0	1.1	0	0	0	0
Undefined adenocarcinoma	0	0	0	7.1	0	0	0
Mixed carcinoma	2.5	0	2.2	0	0	7.7	18.2
Differentiated carcinoma	2.5	0	0	0	0	0	0
Undifferentiated carcinoma	0	0	0	0	0	7.7	0
Invasive squamous cell carcinoma	0	0	0	0	0	7.7	0
Sarcoma	0	0	1.1	0	0	0	0
Other	2.5	3.7	2.2	0	14.3	0	0
Total:	100	100	100	100	100	100	100

DISCUSSION

Between January 1, 2001 and December 31, 2010, 207 breast cancer cases were identified. The most recent calculated age-adjusted incidence rate was 31.1/100,000 for the year 2010. Upon regional evaluation, Grenada still has a fairly low incidence rate when compared to Jamaica (56.8/100,000), The Republic of Trinidad and Tobago (36/100,000), and the Dominican Republic (32.7/100,000) [4]. From a global perspective, Belgium has the highest incidence rate of breast cancer, with an age-adjusted incidence rate of 109.2/100,000

[4]. Compared to other countries around the world, the low incidence rate of breast cancer in Grenada can be due to demographic factors, such as the country having a predominantly black population. The Centers for Disease Control and Prevention (2015) stated that white women had a higher risk of developing breast cancer compared to black women.

Overall, the highest incidence rates across the time period were observed in the 40-49 age category, and the lowest incidence rates overall were observed in the 20-29 age category. Like in many other countries, we can conclude that in Grenada, new breast cancer cases is not a common disease amongst a younger population. Breast cancer is the most common cancer amongst females globally [7]; hence, there has been a global rising of attention to the disease. Breast cancer awareness has increased on the island of Grenada in the last decade, and this could explain the periods of increase where more people might have been seeking professional care.

On September 7, 2004 and July 13, 2005, Hurricanes Ivan and Emily hit the island of Grenada. Significant changes were noted in the year 2005, with a downward trend of breast cancer incidence rates observed for all age-categories. The population may have suffered psychological trauma following the environmental disasters and, as a result, may have been oblivious to the statuses of their health, resulting in the decreased identification of cases. More significantly, the disasters caused severe destruction and devastation to the island, both physically (landscape) and economically. The island's water and electrical supplies were interrupted for a long period. With this, health services were only available on a limited scale to the population. This resulted in a major disruption to the health care system and could explain the observed decline in the trend of breast cancer incidence rates.

An unstable economic situation has been reported for Grenada over the last five years. This instability is reflected in the results collected between the years 2007 and 2010 that demonstrate instability and inconsistency (no trend established). Prior to the July 2008 elections, high inflation rates were seen in the price of basic commodities-food and fuel. In 2009, the economic performance was recorded as -5.7% of the GDP. The recession could be an explanation for the downward trend seen in the years 2007 and 2009.

The recession has considerably affected the Grenadian economy and, overall, the functioning of the Grenadian health care system over the years. Grenada's health care system is predominantly universal; however, the system is overburdened and lacks sufficient human and financial resources to offer universal coverage for all. Therefore, this results in long waiting times when patients seek health care services. Reluctantly, many people are forced to pay out-of-pocket for the services they need. To those who cannot afford this service, they are subjected to waiting for long periods of time to have procedures performed, such as breast tissue biopsies. This would result in many cases remaining undiagnosed.

Invasive ductal carcinomas followed by lobular carcinomas have been described as the most common pathologic breast cancer types. Medullary, mucinous and papillary carcinomas of the breast have been described in the literature as rarer histological subtypes of breast cancer [6-8]. Medullary cancers have been said to account for 2% of all breast cancers globally [9]. It is most commonly found in women who have the mutated BRCA-1 gene. Current research suggests that medullary carcinomas have a more favorable prognosis compared to invasive ductal carcinomas of the breast [6, 8]. Mucinous carcinomas are said to account for approximately 2% of all breast carcinomas globally [10]. They are slow growing tumours, with close to none or very slight lymph infiltration, and usually have a more favorable prognosis compared to other types. Tubular carcinomas of the breast account for

approximately 1% of all breast cancers, globally [11]. This statistic is consistent with the findings of this study. The recurrence rate of this sub-type is very low. Papillary carcinomas of the breast usually does not infiltrate other body parts and normally affect older people [12]. This demonstrates a good prognosis. Papillary carcinoma subtypes were noted in very insignificant proportions in the population of this study.

A recent study carried out to assess breast cancer morbidity in peri-menopausal women found that 42.7% of the cases identified from the population were pre-menopausal [13]. This study shows that the majority of the population with breast cancer were pre-menopausal women. Fifty one percent of the reported cases in the Grenada population were under the age of 50 years. Furthermore, 34% of the reported cases were between the ages of 30-45 years. With reference to an earlier study, the age of menopause is observed to be 50 years [14]. A significantly large proportion of the cases reported were pre-menopausal, and this may suggest the possible existence of a BRCA-1 mutation within the population. BRCA 1 and BRCA 2 mutations are associated with early onset of breast cancer in women [15].

Age is a known risk factor for breast cancer; there is an increased risk with age. However, there is a much poorer prognosis for younger diagnosed cases [16, 17]. This is because younger cases have more aggressive forms of breast cancer with poor prognosis [16]. With a significantly large percentage of cases in the population identified under the age of 50 years, there is a need for the Grenadian government to design health promotion programs that encourage screening for breast cancer with the goal of early diagnosis.

The survival rate from breast cancer is considerably lower in the younger population. It is believed that this is due to the strong association with BRCA gene mutation [18]. In our study population, 19% of all the cases were below the age of 40 years. This is a significant proportion, and preventive measures should be applied to the population to ensure early diagnosis, which increases survival chances and improved quality of life.

Significant spatial distributions (by parish) of breast cancer were described in the findings of the research. Current research is proposing possible associations between geographically distributed environmental toxins and the development of mutations on the BRCA-1 genes [19]. The parish of St David reported the highest incidence rate followed by St. George, and St. Patrick having the lowest incident rate. In Grenada, families are normally clustered by geographical region (in this case, parish). With this, further research needs to be conducted to see if an association exists between the distribution (parish) of incidence and familial history of breast cancer and mutation in the BRCA1 gene.

In conclusion, the Ministry of Health in Grenada needs to make a commitment to develop and establish appropriate surveillance systems for breast cancer. A local cancer registry for breast cancer was commissioned in 2008 but, to date, it still requires much work in order to be considered fully functional. A true estimate of the burden of breast cancer on the population can only be analyzed when proper surveillance systems are put into operation.

Furthermore, in the effort of prevention, the Ministry of Health should promote early breast cancer detection through screening by mammography. The American Cancer Society currently has guidelines for age at mammography to begin at 40. Much research has been carried out to assess the benefits of early detection of breast cancer mainly through screening by mammography. Studies have indicated that early detection substantially decreases mortality rates [20, 21]. One study claimed that mammography screening had been shown to have the greatest effect on breast cancer mortality reduction in the age group of 50-69 years [19]. Another study claimed that early detection through mammography decreases breast

cancer mortality by up to 25% [22]. It is claimed that the promotion of screening by mammography for women between the ages of 40-49 years results in increased low-grade detections, decreased treatments, and decreased recurrence rates [23]. These findings may be applied to the population of this study, which reported an alarming fraction (51%) of the cases as being under the age of 50. In addition to this, continuous awareness campaigns, the promotion of self-breast examinations from age 20, and biennial clinical breast exams should be encouraged.

The limitation of the study was the chosen surveillance medium used to identify the cases of breast cancer in Grenada. The study only reported cases that were identified through breast tissue biopsy and histological examination at the Pathology Department in the General Hospital, Grenada. Consequently, many cases were excluded from participation. Therefore, this would have affected the trend (person/place/time) analysis and resulted in an under-estimation of the true burden of breast cancer in the population.

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Chapter 94

PROSTATE CANCER IN GRENADA, WEST INDIES: A SEVEN-YEAR TREND ANALYSIS FOR THE PERIOD 2008-2014

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ABSTRACT

Prostate cancer is the second most commonly diagnosed cancer in men worldwide, with countries such as the United States showing a higher incidence of prostate cancer in African American men. Studies performed in neighboring Caribbean countries show a high incidence of prostate cancer. Grenada is a small island country in the Caribbean with a population that is predominantly of African descent. Currently, there is limited data regarding the burden of prostate cancer in Grenada. This chapter seeks to determine the incidence, distribution, and mortality rate of prostate cancer in Grenada from 2008-2014. A cross-sectional study was performed utilizing secondary surveillance data available from national registries. Analytical software was used to determine the incidence, mortality, and distribution of cases by parish in Grenada during the period of study. Local incidence rate was as high as 91.03/100,000 (average 70.1/100,000). Mortality rate averaged 83.4/100,000. St. John was the parish with the highest recorded rate of 210/100,000 during the study period, with the parishes St. George and St. John having the highest overall 7-year average. Grenada has incidence levels comparable to Caribbean regional figures. There were higher mortality rates than expected. The geographical

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distribution of cases shows the parish of St. John having the highest individual incidence rate during the period.

INTRODUCTION

Grenada is a tri-island nation consisting of Grenada, Carriacou, and Petite Martinique. It has a population of 105,539 people, 53,008 male, and approximately 89.4% of African ancestry [1]. Since the end of the 18th century, the vast majority of the population in the Caribbean region is of African descent [2]. The ethnic profile of a geographical region is important to consider when examining disease rates. Prostate cancer has an increased incidence in African American men in the United States, and similar trends are seen in the mortality rate trends during the past 15 years [3]. Worldwide, prostate cancer is the second most commonly diagnosed cancer in men in over 12 of the planet's most populated nations [4]. In fact, there were 1.1 million men worldwide who were diagnosed with prostate cancer in 2012 alone [5].

Before the advent of screening using prostate-specific antigen (PSA) testing, prostate cancer often went undiagnosed and, therefore, untreated. When PSA testing became more commonly used, the rate of diagnosed prostate cancer began to spike [6]. This increase in the number of identified cases was seen in the US during the 1980s; it was also corroborated by similar rises in the incidence of many European countries during the 1990s [4].

According to a study done recently in Barbados, the Caribbean region generally has similarly high rates of prostate cancer in its black populations [7]. In fact, Martinique, which is another Caribbean country with similar ethnic profile, had the highest rate of prostate cancer worldwide in 2011 [8]. There are also four other Caribbean countries ranked in the top twenty highest prostate cancer incidence rates worldwide, which include Trinidad and Tobago, Barbados, Guadeloupe, and Puerto Rico [9].

According to the National Vital Statistics System, cancer was the number one cause of death among men and women in 2014. In relation to morbidity, prostate cancer has the highest rates; however, prostate cancer was the third most commonly diagnosed after cervical cancer and breast cancer, respectively [10]. A study conducted by Asulin et al. revealed that between the years 1990-2000, prostate cancer accounted for 61.4% of the male cancer cases and 53.6% of the cases associated with mortality [11].

Studies have shown that men are less likely to visit their doctor than women [12], and as such, it is quite often that cancer has already progressed to an advanced stage by the time it is diagnosed [13]. This would have more of an impact on mortality than an early diagnosis potentially would. The authors of this paper noted a lack of research on prostate cancer in Grenada over the past 15 years. Other cancers, such as cervical and breast cancer, have both been investigated within the past five years [10].

The goal of this chapter is to perform a review of prostate cancer trends in Grenada within the last seven years with the hope of contributing to future interventions to decrease its impact. The specific objectives were to identify the incidence of prostate cancer in Grenada within the last seven years (2008-2014); to identify the mortality of prostate cancer in Grenada during the years (2009-2013) and to determine the distribution, by parish, of prostate cancer incidence and mortality in Grenada (2009-2014).

OUR STUDY

A cross-sectional study was conducted utilizing secondary information derived from the National Cancer Registry, the National Statistics Office, and the Births and Deaths Registry. The analysis of the data was conducted utilizing the software: Microsoft Excel 2016, Epi Info7, and IBM SPSS Statistics 20.

The three existing resources were reviewed for data on prostate cancer during the period extending from 2008-2014. Data from the National Cancer Registry was used to determine the number of prostate cancer cases over that 7-year period among the male population of Grenada. That value was subsequently used to calculate the incidence rate per 100,000 of the male population. A case was defined as a male patient entered into the National Cancer Registry with a diagnosis of prostate cancer with corresponding histopathological confirmation. The age standardization rate was also calculated (ASR).

The National Cancer Registry also provided geographical information permitting the categorization of the cases by parish in Grenada. Grenada has seven parishes: Carriacou, St. Andrew, St. David, St. George, St. John, St. Mark, and St. Patrick. The Grenada Births and Deaths Registry was consulted in order to determine the deaths between the years 2009-2013 due to prostate cancer. The cases in which prostate cancer was the primary cause of death were included in this study.

FINDINGS

The data for prostate cancer incidence was collected from the period between January 2008 and December 2014. During this time period, 263 men were diagnosed with prostate cancer with a histopathological confirmation. The collection period for the data on the mortality rate of prostate cancer was January 2009 to December 2013. During this time period, there were 200 recorded deaths in which prostate cancer was the primary cause. Table 1 reports the distribution of new diagnoses of prostate cancer each year from 2008-2014. The distribution showed that 2014 had the highest frequency, with 50 new cases (19.1%) that year, closely followed by 2008, which had 39 new cases (14.8%). 2013 had the lowest frequency with 23 new cases (8.7%). Table 1 and Figure 1 also show the distribution of prostate cancer cases according to parish in Grenada. The parish of St. George had the greatest proportion of cases with 117 cases (44.5%). It was followed by the parish of St. Andrew with 19.8% of the cases (52). St. Mark and Carriacou had the lowest proportion of cases over the collection period with 4.2% and 4.9%, respectively.

Figure 2 shows the distribution of new prostate cancer cases by age group. The 71-75 year age group has the highest occurrence of new cases over the collection period, with the 61-65 age group having the second highest number of new cases of prostate cancer. The age group with the lowest number of cases was 31-35 years, with just one case in 2014, which was the year with the highest incidence overall. This patient was diagnosed at age 32 years. The average age for diagnosis of prostate cancer in Grenada during this period was 68–72 years, which was also the most commonly occurring age in the data set. Figure 3 and Table 2 present the deaths attributed to prostate cancer in the study period 2009-2013. The number of deaths from prostate cancer showed a progressive increase with age until it peaked and then

declined. The age group, which had the most prostate-related deaths, was 71-75, which is also where we saw most of the new cases. The mean age of death primarily due to prostate cancer is around 76.7 years, with 78 years being the most common age of death; similar trends for prostate cancer mortality appear in the UK [7] as well as in the United States [8].

Table 1. The frequency of new prostate cancer cases by year 2008-2014 and by parish

Variables		Frequency	Percentage (%)	Cumulative Total
Years	2008	39	14.8	14.8
	2009	48	18.3	33.1
	2010	40	15.2	48.3
	2011	33	12.5	60.8
	2012	30	11.4	72.4
	2013	23	8.7	80.9
	2014	50	19.1	100
Total		263	100%	100%
Parishes	Carriacou	13	4.9	4.9
	St. Andrew's	52	19.8	24.7
	St. David's	22	8.4	33.1
	St. George's	117	44.5	77.6
	St. John's	27	10.3	87.9
	St. Mark's	11	4.1	92.
	St. Patrick's	21	8.0	100
Total		263	100	100%

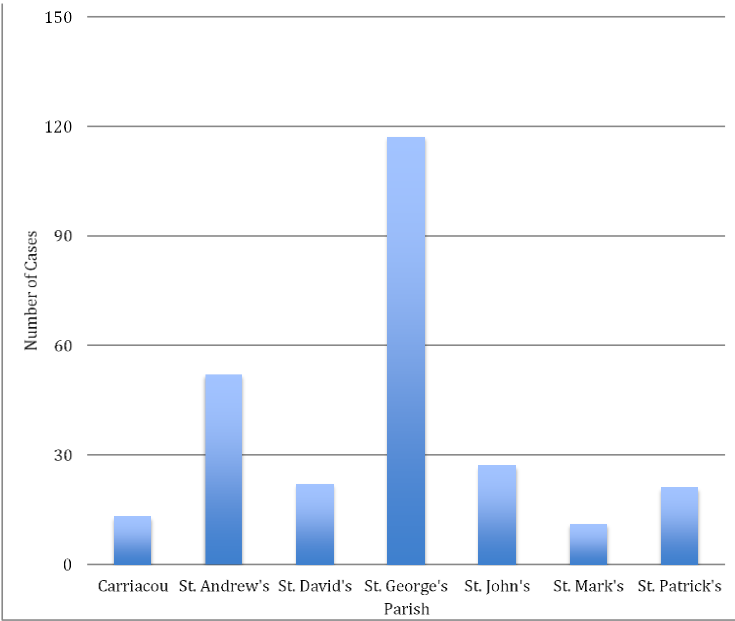


Figure 1. Frequency of new prostate cancer cases by Parish in Grenada 2008-2014.

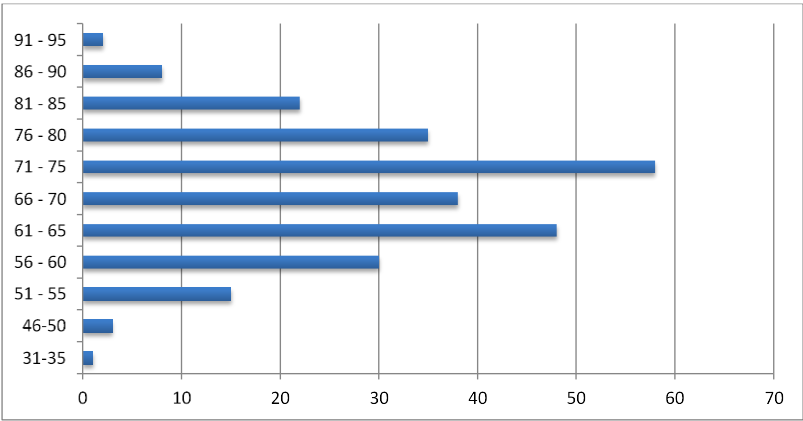


Figure 2. Prostate cancer distribution by age group in Grenada, 2008-2014.

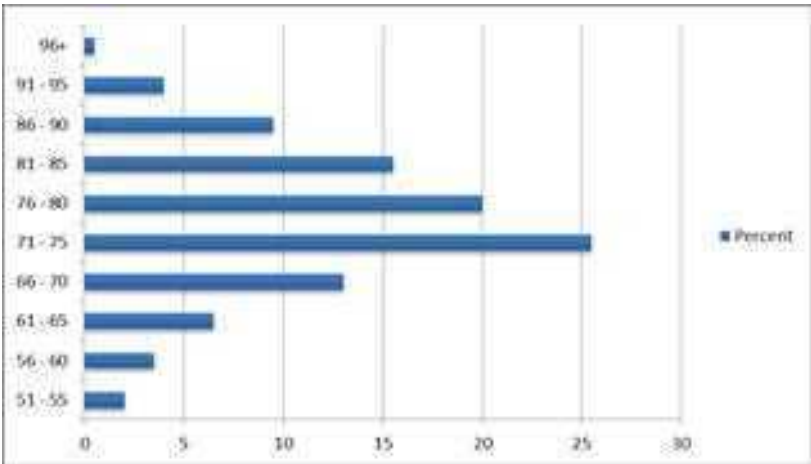


Figure 3. Prostate cancer mortality in Grenada, 2009-2013.

Table 2. Prostate cancer mortality by age group, Grenada, 2009-2013

		Frequency	Percent
Valid	51 - 55	4	2.0
	56 - 60	7	3.5
	61 - 65	13	6.5
	66 - 70	26	13.0
	71 - 75	51	25.5
	76 - 80	40	20.0
	81 - 85	31	15.5
	86 - 90	19	9.5
	91 - 95	8	4.0
	96+	1	0.5
Total		200	100.0

Figure 4 presents the incidence of prostate cancer per 100,000 as it compares to the mortality rate. Unlike what is seen in the US [8], but similar to the trend in Barbados [9], the mortality rate appears to be relatively high and has surpassed the incidence rate from 2010-

2013. The highest incidence seen was in 2014 (91.03), with the lowest rate noted in 2013(41.87). The highest mortality rate was in 2010 (83.35), which then declined to the lowest rate in 2013 (65.54). Figure 5 shows the age-specific incidence of prostate cancer for the Grenadian male population as it compares to the US population of African American men and the overall incidence in the US. In all cases, the age group of 65-74 years had the highest incidence. The incidence in the US nearly doubled the incidence in Grenada. Of all the cases, the 20-49 year age group has the fewest cases among all the countries whose populations were compared. The population standardized incidence rate of Grenadian men when calculated according to the Surveillance, Epidemiology and End Results (SEER) US 2000 population was 60.47, though, among Grenadian men, it averaged 70.89 and was as high as 91.03 in 2014. The incidence in Grenada is lower than the Barbadian incidence rate over the 2002-2008 study period (158.80) [9].

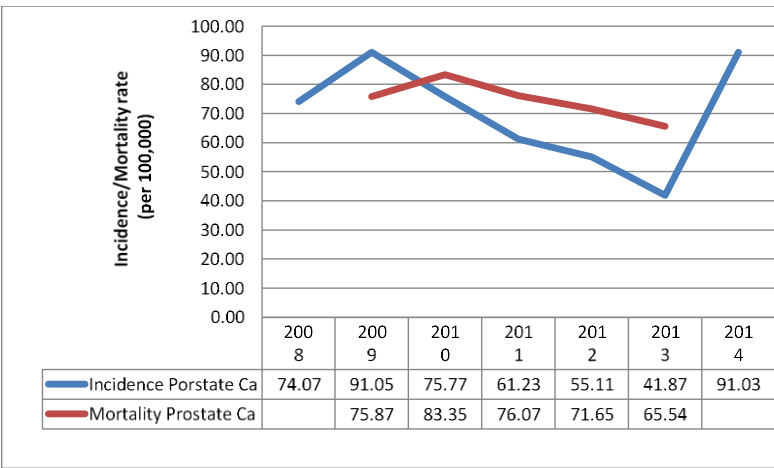
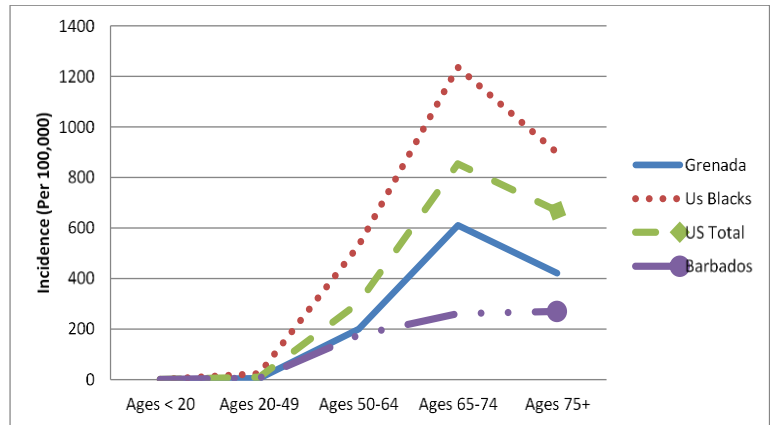


Figure 4. Prostate cancer in Grenada, incidence (2008-2014) vs. mortality (2009-2013).



*Population standardization was not done to US 2000 population as the other regional and US Black population were seen as sufficiently similar not to warrant it.

Figure 5. Age specific incidence of prostate cancer in Grenada (2008-2014) * Barbados (2002-2008) and US (2006-2012).

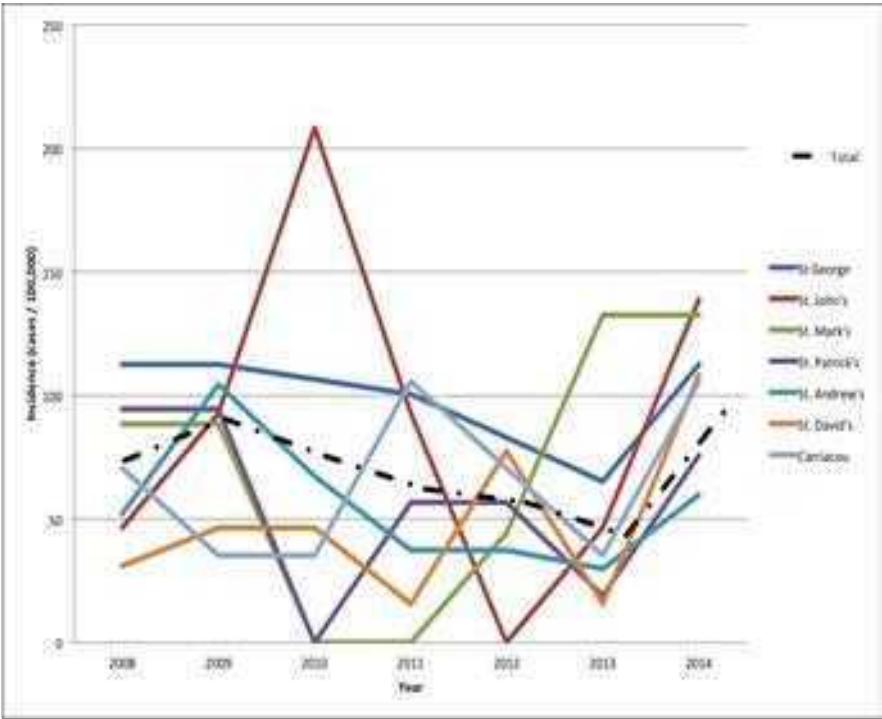


Figure 6. Distribution of incidence rates by parish between 2008-2014.



Figure 7. Distribution of prostate cancer incidence rates (2008-2014) and mortality rates (2009-2013) by parish in Grenada.

Figure 6 shows the incidence rate throughout the 7-year study period with respect to the seven parishes in Grenada (per 100,000). The highest recorded incidence during this period was in the parish of St. John in 2010, which was as high as 208.48; this is about three times higher than the national rate during that year. St. John retained the highest incidence rate for three consecutive years (2009-2011) and again in 2014. St. George had the highest rate in 2008 (112.42), Carriacou in 2011 (105.67), and St. Mark in 2013 (132.5) despite having two years without any cases (2010, 2011). Figure 7 shows a graphical representation of the distribution of the cases by parishes over the 7-year period. St. George had the highest number of cases of prostate cancer (117), and St. Andrew had the second highest (52 days). St. Mark had the lowest number of cases [11].

DISCUSSION

A prostate cancer registry was first established in Grenada by Dr. Robert Yearwood, and from 1996-2007 reportedly, it had recorded 300 cases of prostate cancer [8]. Grenadian males, during the seven-year study period from 2008-2014, had a total of 263 incident cases. Grenada's incidence per 100,000 for prostate cancer in its male population had an incidence rate in 2014 was 91.03/100,000. During the 7-year study period, the average incidence was 70.1. According to the World Cancer Research Fund (WCRF), the incidence rate recorded in Grenada in both 2009 and 2014 (91.05 and 91.03 /100,000 respectively), would place Grenada as having the 18th highest incidence of prostate cancer globally [5].

The 2004 study conducted in Grenada by Asulin et al., which was done between 1990-2000, recorded an incidence rate of 61.4 /100,000, which was lower than our currently recorded national 7-year incidence rate. This implies that there has been an increase in the number of new cases over the past 14 years in Grenada. According to the study by Gibson et al. from 1998-2002, the average incidence in Jamaica was 65.6/100,000, which was still lower than the 7-year average in our study in Grenada [11].

The Grenadian incidence rate over the collection period was still lower than that recorded in Barbados by Hennis et al. [7] in 2011, which was 160.4/100,000 for their 7-year study between 2002-2008. This rate ranked Barbados as number 4 by the WCRF [5]. The trend between 2009-2013 showed a decrease in the prostate cancer incidence rates in Grenada from 91.05/100,000 to 41.87/100,000, which was similar to the pattern shown in the US rates according to SEER for that time period (2009-2012). During that period, black Americans showed an incidence rate that was higher at 223.7/100,000 [8]. However, Grenada showed a rise in its incidence rates once again up to 91.03/100,000 in 2014. The mortality rate for prostate cancer between 2009-2013 was 83.4/100,000. This rate was higher than the incidence rate between 2010-2013, a trend that was not seen in the other compared populations in the region or amongst African Americans in the US [11].

The rate in the previous study done in Grenada was lower at 53.6/100,000. This mortality rate was also higher than the 7-year average incidence in Barbados of 63.7/100,000 and in African Americans in the US of 82.7/100,000. It is suspected that this difference may be attributed to the limited screening and treatment options currently available in the country. Additionally, it was observed in a previous study that male patients tend to visit their doctors

less frequently than females resulting in diagnoses occurring at a more advanced stage of cancer [4].

The parishes with the highest individual 7-year average incidence rates were St. George, St. John, St. Mark, and Carriacou, respectively (98.90, 89.35, 69.41 and 69.42 per-100,000). These parishes all share the western coast of the Caribbean Sea. As far as the author of this study is currently aware, there is no comparative study done in the Caribbean, which considers the distribution of prostate cancer incidence rates by location with which this finding can be compared. Strengths in the study are:

- Histopathological confirmation is the most accurate form of definitive prostate cancer diagnosis.
- Use of a functional cancer registry.
- Use of updated census data (2011)
- Regional comparisons to recently conducted studies.

Weaknesses in the study are:

- Loss of data: There is a private urology practice on the island, which occasionally sends patients to external diagnosis labs outside of Grenada. These patients were not included in the data from the hospital pathology laboratory, making the true incidence rates slightly higher than those reported.
- Co-morbidities are not always considered in the cause of death. For our study, the morbidity figures were compiled from prostate cancer being either a definitive or a probable cause of death.
- Undocumented cases may contribute to reduced prostate cancer diagnoses. As discussed in the paper, men tend to neglect visiting their physicians, which may contribute to unreported cases. Along with this, a lack of screening in specific age groups could contribute to the undocumented cases.

In conclusion, prostate cancer incidence rates in Grenada are overall trending high compared to other regional rates. Prostate cancer mortality was higher than expected; in some years, it was higher than the incidence rate. The distribution of prostate cancer by parish shows higher incidences in the parish of St. John and all of the other west coast (Caribbean Sea) parishes. Further studies are needed to formulate and investigate hypotheses to explain and corroborate some of these findings. In addition, major public health concerns have been raised in terms of the high local incidence rates as well as the geographical distribution of the cases. These also need to be addressed.

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Chapter 95

EPIDEMIOLOGIC SURVEILLANCE OF AMPUTATION IN GRENADA, 2010-2017

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ABSTRACT

The prevalence of limb amputation related to peripheral arterial disease (PAD) and diabetes has attracted global attention as a major health problem. Recently published studies, however, are virtually absent on diabetes foot and lower limb complications in the Caribbean region. A retrospective descriptive study was conducted in Grenada, a small Caribbean island, with secondary data from January 2010 to December 2017 of patients having amputations at the Grenada General Hospital. Data on demographics, reason for amputation, type of amputation, and comorbidities were also collected in the study. A total of 654 persons were recorded that had an amputation at the General Hospital; 370 (56.6%) males, 284 (43.4%) females, and median age 64 years (<1 to 105 years). The overall annual incidence of amputations ranged from 50.5 to 102.4 per 100,000 per year. Lower limb amputations ranged from 39.0 to 87.8 per 100,000 per year. Diabetes was comorbidity in 51.1% of amputations. Amputations can have negative effects on the quality of life of individuals. With indications of a potential global increase in the number of persons with diabetes, effective and timely diabetes prevention and management programs are of utmost importance in Grenada to address risk factors for amputations. Other Caribbean countries may benefit from this study, which creates awareness of the significance of the issue and the relevance for interventions to improve health outcomes in the region.

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INTRODUCTION

The prevalence of limb amputation related to peripheral arterial disease (PAD) and diabetes has attracted global attention as a major health problem [1]. An amputation is the removal of part of, or an entire, limb by surgery or trauma. Diabetes can cause microvascular and macrovascular complications that compromise immune response and blood circulation in the limbs resulting in the need for amputation to preserve life and health [2]. Worldwide, between 40-60 million people are affected by diabetic foot and lower limb complications [3]. Data from 12 countries in Europe and Australasia participating in the VASCUNET collaboration show the prevalence of diabetes among people who had amputations ranged from 25.7% in Finland to 74.3% in Slovakia, while the mean annual incidence of major amputations varied between 7.2/100,000 in New Zealand and 41.4/100 in Hungary [1]. In a study in Canada, 81% of persons who had a lower limb amputated also had diabetic complications [4]. In the United States, the Centers for Disease Control and Prevention (CDC) reported a decline in leg and foot amputations among people with diabetes from 1996-2008 [5]; however, a recent study reported a reverse in the trend between 2009-2015 [6]. The CDC reported that 108,000 diabetes-related amputations were done in 2014 [7]. The likelihood of having an amputation related to diabetes increased 4.9 times among people ≥ 65 years [1].

Overall, the risk for lower limb amputation is 10-fold higher among people with diabetes as compared to non-diabetic people [8], rendering diabetes as a significant cause of amputation and needing interventions for preventing the surgery. Lower limb amputation is the most common type of amputation among people with diabetes, while upper limb amputation related to diabetes is significantly fewer and usually associated with traumatic injury [8]. Limb amputation is associated with emotional disturbances and trauma as well significant decline in the quality of life of the individual, particularly when there is minimal support to provide for basic needs and to access appropriate health care [9]. High mortality rate, comorbidities, and high health care cost are major issues that contribute to poor health outcomes among people who had amputations [8].

This study describes the trends in amputations at the General Hospital in Grenada over eight years, 2010–2017. Grenada is a small island located in the southern part of the Caribbean archipelago, with a population of approximately 111,500 people. Few studies have been published recently on the prevalence and incidence of diabetic foot and limb complications and amputations in Caribbean countries. Older studies show an increasing rate of diabetes and related health problems, including amputations, in some Caribbean countries [10]. In a study published in 2004, Barbados had among the highest rate of lower extremity amputations in the world [10]. This study is, therefore, of value in determining the prevalence and potential impact of amputation in the Grenadian population. Other Caribbean countries may benefit from this study, which creates awareness of the significance of the issue and the relevance for interventions to improve health outcomes in the region.

OUR STUDY

A descriptive retrospective study was conducted using secondary data collected for the surveillance of amputations performed at Grenada General Hospital from the period 1st January 2010 to 31st December 2017. Grenada General Hospital is the main general medical and public surgical hospital in the state. It is the final referral hospital for both the public and private health sectors. It is a 198-bed facility, and the services offered include; accident and emergency, internal medicine, pediatrics, general surgery, obstetrics and gynecology, intensive care, ophthalmology, orthopedics, oncology, radiology, and laboratory services.

The Epidemiology and Information Department of the Ministry of Health routinely collects data on amputation as part of its surveillance of all health events in the country. Data on amputations were gathered from the paper-based operating theatre and surgical ward registers. A descriptive analysis of these data was undertaken to characterize the occurrence of amputations in Grenada.

The data elements selected for analysis included age, sex, parish of residence, dates of admission and discharge, reason for amputation, type of amputation, and comorbidities. The data were entered into a Microsoft Excel spreadsheet and analyzed to identify trends in the occurrence of amputations and the frequency of accompanying comorbidities.

OUR FINDINGS

A total of 654 patients underwent one or more amputations at the General Hospital during the study period. Of that total, 370 (56.6%) were male, and 284 (43.4%) were female. The average age of the patients who had amputations varied by year, ranging from 63.2-65.9 years in 2011-2017. In 2010, the average age was 56.3 years. Table 1 shows the distribution of patients by sex.

The parish with the largest proportion of cases over the eight-year period was St. George (32.1%), followed by St Andrew (17.9%). The years with the highest incidence of amputations were 2012 (91.1/100,00), 2014 (102.4/100,000), and 2016 (90.2/100,000). Tables 2-3 show the parish/residence of the patients having amputations and incidence per year.

Type of Amputation and Diagnosis

Overall, lower limb amputation was the most common type of amputation at the Grenada General Hospital. Below-knee amputation (BKA) was the most frequent procedure (281, 42.8%) followed by removal of toes and above-knee amputation (AKA). Upper limb amputation was more common in males and individuals in younger age groups. Loss of finger(s)/hand was more common than amputation at the forearm or arm. The most common reason for amputations in the upper limbs was injury. Tables 4-6 show the total number of amputations and the type and cause of upper limb amputations.

Table 1. Distribution of patients that had amputations by sex

Sex	2010		2011		2012		2013		2014		2015		2016		2017		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Female	19	35.8	28	42.4	43	44.8	34	45.3	59	52.2	38	39.2	41	41.4	22	40.0	284	43.4
Male	34	64.2	38	57.6	53	55.2	41	54.7	54	47.8	59	60.8	58	58.6	33	60.0	370	56.6
Grand Total	53	100.0	66	100.0	96	100.0	75	100.0	113	100.0	97	100.0	99	100.0	55	100.0	654	100.0

Table 2. Number and proportion of persons having amputations distributed by parish

Parish	2010		2011		2012		2013		2014		2015		2016		2017		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
St. Andrew	17	32.1	15	22.7	14	14.6	12	16.0	18	15.9	16	16.5	18	18.2	7	12.7	117	17.9
St. David	7	13.2	13	19.7	12	12.5	8	10.7	14	12.4	20	20.6	11	11.1	11	20.0	96	14.7
St. George	22	41.5	19	28.8	37	38.5	20	26.7	45	39.8	22	22.7	31	31.3	14	25.5	210	32.1
St. John	1	1.9	4	6.1	10	10.4	15	20.0	10	8.8	12	12.4	12	12.1	9	16.4	73	11.2
St. Mark	1	1.9	4	6.1	6	6.3	6	8.0	8	7.1	4	4.1	3	3.0	3	5.5	35	5.4
St. Patrick	3	5.7	9	13.6	13	13.5	8	10.7	12	10.6	8	8.2	9	9.1	6	10.9	68	10.4
Carriacou	2	3.8	2	3.0	3	3.1	6	8.0	6	5.3	5	5.2	2	2.0	4	7.3	30	4.6
Cruise ship	-	0.0	-	0.0	1	1.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	1	0.2
NA	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	10	10.3	13	13.1	1	1.8	24	3.7
Grand Total	53	100.0	66	100.0	96	100.0	75	100.0	113	100.0	97	100.0	99	100.0	55	100.0	654	100.0

Table 3. Incidence of amputations in Grenada by year

Year	Overall per 100,000	Upper limb amputations per 100,000	Lower limb amputations per 100,000	Finger/hand amputations per 100,000	Forearm/arm amputations per 100,000	Toe amputations per 100,000	Partial foot amputations per 100,000	BKA per 100,000	AKA per 100,000
2010	50.5	11.4	39.0	11.4	0.0	12.4	1.0	21.9	3.8
2011	61.9	8.4	53.4	8.4	0.0	15.0	2.8	30.0	5.6
2012	91.1	15.8	75.3	14.9	0.9	18.6	2.8	36.2	17.7
2013	69.1	12.9	56.2	12.0	0.9	20.3	1.8	25.8	8.3
2014	102.4	14.6	87.8	13.7	0.9	11.0	6.4	44.8	25.6
2015	89.0	10.9	78.1	9.1	1.8	20.9	6.4	32.7	18.2
2016	90.2	2.7	87.5	0.9	1.8	22.5	0.9	42.4	21.6
2017	48.4	2.7	45.8	2.7	0.0	18.8	0.0	24.2	2.7

BKA: Below knee amputations, AKA: Above knee amputations.

Table 4. Number and percentage of amputations, 2010-2017

Location of amputation	No.	%
Finger(s)/Hand	79	12.0
Forearm/Arm	7	1.1
Toe(s)	152	23.2
Partial foot (Trans metatarsal)	24	3.7
Below knee	281	42.8
Above knee	113	17.2
Total	656	100.0

* At least one patient had multiple amputations.

Table 5. Distribution of amputations of finger(s)/hand by gender and year

	2010	2011	2012	2013	2014	2015	2016	2017	Total									
	No.	%	No.	%	No.	%	No.	%	No.									
Finger/hand amputation																		
Males	11	91.7	8	88.9	13	81.3	11	84.6	11	73.3	6	60.0	1	100.0	2	66.7	63	79.7
Females	1	8.3	1	11.1	3	18.8	2	15.4	4	26.7	4	40.0	-	-	1	33.3	16	20.3
Total	12	100.0	9	100.0	16	100.0	13	100.0	15	100.0	10	100.0	1	100.0	3	100.0	79	100.0
Forearm/arm amputation																		
Males	-	-	-	-	1	100.0	-	-	1	100.0	2	100.0	2	100.0	-	-	6	85.7
Females	-	-	-	-	-	-	1	100.0	-	-	-	-	-	-	-	-	1	14.3
Total	-	-	-	-	1	100.0	1	100.0	-	-	2	100.0	2	100.0	-	-	7	100.0

Table 6. Diagnosis or reason for upper limb amputation

Diagnosis/reason for amputation	Amputations of fingers/hand		Amputations of forearm/arm	
	No.	%	No.	%
Infection (including osteomyelitis, abscesses, etc.)	22	27.8	2	28.6
Gangrene	11	13.9	-	-
Injury	42	53.2	4	57.1
Congenital (polydactyly)	3	3.8	-	-
Cancer	1	1.3	-	-
Other	-	-	1	14.3
Total	79	100.0	7	100.0

A total of 152 toe amputations were recorded, which represented 23.2% of the total. The highest number of toe amputations was in 2015 [23] and 2016 [25].

The number of partial foot (trans metatarsal) amputations was 24 (3.7%) in total. The highest number of these procedures was in 2014 and 2015 with seven [7] and eight [8] cases, respectively. Below-knee amputations were the most common type of lower limb amputation with a total of 281 (42.8%) procedures during the eight-year period. The largest number of below-knee amputations were recorded in 2014 [49] and 2016 [47]. A total of 113 (17.2%) above-knee amputations were recorded during the eight-year period, with the highest number in 2014 [28] and 2016 [24]. Gangrene was listed as the most common reason for toe, below-knee, and above-knee amputations, while infections were the most common reason for partial foot amputations. Tables 7-8 show the number, type, and cause of lower limb amputations.

Comorbidities

Of the 656 amputations, 335 (51.1%) patients had diabetes, 107 (16.3%) had hypertension, and 33 (5.0%) had peripheral vascular disease recorded as comorbidity. The highest proportion of amputations was of the lower extremities among patients with diabetes as a comorbidity. Table 9 shows comorbidities in patients that had amputations by gender. Table 10 shows the number of amputations in patients with diabetes.

DISCUSSION

The rising prevalence of noncommunicable diseases is a global problem that has negative implications for small island states, such as Grenada and the other Caribbean islands, with limited and stretched resources for health care systems. Few recent studies have been published, estimating the prevalence and incidence of diabetes foot and limb complications and amputations in Caribbean countries. In the absence of collecting and analyzing data, a dearth may remain in recognizing and understanding the “true” burden of amputation on the population and the health care system. This study is among the first in Grenada to provide information showing trends in the incidence of all types of amputations in the recent period. Given the scantiness of recently published information, this study may also create awareness of the significance of the issue in the Caribbean region and spur heightened action to address the risk factors, primarily diabetes, and peripheral arterial disease.

The findings in this study were consistent with that of other countries. Among 12 countries in Europe and Australasia, between 25-75% of persons who had amputations also had diabetes [1]. It was found that 50% of the persons in Grenada who had an amputation during the reporting period also had diabetes. This pattern affirms the value of strengthening diabetes prevention and management programs as important interventions towards curbing the number of amputations. The data in Grenada is suggestive of the possibility of having prevented about half of the amputations.

Table 7. Lower limb amputation by year

	2010		2011		2012		2013		2014		2015		2016		2017		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Toe amputation																		
Males	9	69.2	8	50.0	12	60.0	9	40.9	2	16.7	20	87.0	15	60.0	11	52.4	86	56.6
Females	4	30.8	8	50.0	8	40.0	13	59.1	10	83.3	3	13.0	10	40.0	10	47.6	66	43.4
Total	13	100.0	16	100.0	20	100.0	22	100.0	12	100.0	23	100.0	25	100.0	21	100.0	152	100.0
Partial foot amputation (trans metatarsal)																		
Males	1	100.0	2	66.7	1	33.3	1	50.0	5	71.4	5	62.5	1	100.0	-	-	15	62.5
Females	-	-	1	33.3	2	66.7	1	50.0	2	28.6	3	37.5	-	-	-	-	9	37.5
Total	1	100.0	3	100.0	3	100.0	2	100.0	7	100.0	8	100.0	1	100.0	-	-	24	100.0
Below knee amputation																		
Males	11	47.8	17	53.1	19	48.7	15	53.6	26	53.1	17	47.2	27	57.4	19	70.4	151	53.7
Females	12	52.2	15	46.9	20	51.3	13	46.4	23	46.9	19	52.8	20	42.6	8	29.6	130	46.3
Total	23	100.0	32	100.0	39	100.0	28	100.0	49	100.0	36	100.0	47	100.0	27	100.0	281	100.0
Above knee amputation																		
Males	2	50.0	3	50.0	9	47.4	5	55.6	9	32.1	11	52.4	13	54.2	-	-	52	46.0
Females	2	50.0	3	50.0	10	52.6	4	44.4	19	67.9	10	47.6	11	45.8	3	100.0	61	54.0
Total	4	100.0	6	100.0	19	100.0	9	100.0	28	100.0	21	100.0	24	100.0	3	100.0	113	100.0

Table 8. Diagnosis or reason for lower limb amputations

Diagnosis or reason for amputation	Toe amputations		Partial foot amputations		Below knee amputations		Above knee amputations	
	No.	%	No.	%	No.	%	No.	%
Infection	64	42.1	15	62.5	81	28.8	30	26.5
Gangrene	68	44.7	8	33.3	175	62.3	71	62.8
Injury	12	7.9	-	-	1	0.4	-	-
Congenital (polydactyly)	6	3.9	-	-	-	-	-	-
Cancer	-	-	-	-	1	0.4	1	0.9
Ischemia	1	0.7	-	-	21	7.5	8	7.1
Ulcer	1	0.7	-	-	-	-	-	-
Other (e.g. necrosis unspecified)	-	-	1	4.2	2	0.7	3	2.7
Total	152	100.0	24	100.0	281	100.0	113	100.0

Table 9. Distribution of comorbidities among patients who had amputations

Comorbidity	Diabetes Mellitus		Hypertension		Renal Failure		Congestive heart failure		Peripheral Vascular Disease		Cerebrovascular accident		Unknown/none	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Female	177	52.8	73	68.2	5	55.6	5	62.5	16	48.5	4	80.0	-	-
Male	156	46.6	34	31.8	4	44.4	3	37.5	17	51.5	1	20.0	-	-
Total	335	100.0	107	100.0	9	100.0	8	100.0	33	100.0	5	100.0	159	100.0

Table 10. Number and proportion of types of amputations in patients with diabetes

Location of amputation	Total No. of amputations		Amputations with diabetes recorded as a comorbidity	
			No.	%
Finger(s)/Hand	79		9	11.4
Forearm/Arm	7		1	14.3
Toe(s)	152		79	52.0
Partial foot (Trans metatarsal)	24		18	75.0
Below knee	281		163	58.0
Above knee	113		65	57.5
Total	656		335	51.1

Additionally, as in other international countries, the incidence of lower limb amputation in Grenada was significantly higher than upper limb amputations. Owing to the high incidence, preventive interventions should also be streamlined to address the specific risk factors for lower limb amputation.

Behrendt et al. [5] reported that people above 65 years in the United States were at higher risk for amputation. In Grenada, the average age of the persons who had amputations ranged from 63.2-65.9 years in the latter seven years of reporting. In the first reporting year, the average age was 56.3 years. While older people are more likely to experience poor health, having an amputation can significantly decrease the quality of life for the individual. Given that average life expectancy in Grenada is approximately 71 years, having an amputation translates into prolonged years of disability. The health, economic, and emotional consequences may be more dire after retirement when the individual has less access to financial resources for care and likely to become dependent on others. In 2004, a study was published citing diabetes foot care was a problem in Barbados and that the country had among the highest rate of lower extremity amputations in the world [10]. Limited access to prosthetic devices and rehabilitation services in the region were also deemed to increase hardship for persons who had amputations [10]. These conditions may not have improved much in the Caribbean region, particularly, as data is also lacking to highlight the extent of this problem and the need for redress.

Currently, there is no national or community-based program in Grenada to provide psychosocial and other support for people who had amputations. Additionally, until the National Health Insurance (NHI) is commissioned in Grenada, older people, in particular, may be confronted with a high cost for health services, particularly for services provided at private facilities. Behrendt et al. (2018) found that countries with fee-for-service reimbursement had a lower incidence of major amputations compared to a higher incidence in countries with population-based reimbursement system. This finding shows a potentially important function of the NHI in the management of major amputations. Driven by financial reward, a fee-for-service- system may serve to motivate health care workers to provide high quality care for patients to prevent or to reduce the risk for amputation. Serious consideration should, therefore, be given to ensure the NHI facilitates adequate preventive care for Grenadians.

The results show a higher incidence of upper limb amputation among men in Grenada with injury as the major cause. There was less variability between the number of men and women who had lower limb amputations, highlighting the need for prevention and care equally for both genders. Geiss et al. [5] found the number of persons, particularly aged 18-64 years (young and middle-aged adults), who had amputations in the United States increased between 2009-2015 compared to the CDC's findings for 1996-2008 [5]. The trends in the United States and in Grenada suggest the need for all age groups and genders to be targeted by interventions, rather than selected groups. In Brazil, Santos [11] found that men lived longer following amputation, losing more years of healthy life. Healthy life expectancy must be considered in planning with the aim of improving the quality of life for men who had amputations and ensuring that adequate services are provided, including health education [11].

Global data and projections do not give reassurance for a decrease in amputations. The World Health Organization (WHO) estimates show that about 422 million people were affected by diabetes in 2014, rising from 108 million in 1980 [12]. The number of people with

diabetes worldwide has increased steadily, and the number is expected to continue to rise [8]. PAD, the other main cause of amputation, has affected an increasing number of people, estimated at 202 million [1]. Considering the high and increasing prevalence of noncommunicable diseases in Grenada and other Caribbean countries [13, 14], not only are appropriate measures needed to prevent and manage diabetes, but these measures need to be implemented in a timely manner. While the number of amputations may appear insignificant, the overall social and economic burden is huge, extending to family and community members. Retrofitting physical infrastructure and social adjustments may also incur a significant burden on society.

Based on human rights, deliberate efforts should be made to relieve the trauma and discomfort associated with illness. Traumatic experiences may persist for several months after an amputation. Quite often, persons having amputations, especially those of the lower limbs, are pitied and/or stigmatized and, as such, the individual may withdraw from the society and normal functions. In the absence of adequate rehabilitation services, the level of the disability created by the amputation is magnified. Support groups and networks may serve an important role in rehabilitation and reintegration in the society of people who had amputations. The physical and social infrastructure must also be adequate for use by people with disabilities.

Recent publications on diabetes complications and amputation in the Caribbean are virtually non-existent. In the absence of data, there may not be sufficient understanding of the significance of amputation on the population health outcomes. The need for strengthening current interventions may not be sufficiently highlighted. As such, this study is useful to address the information gap to inform policy and interventions in Grenada. Other Caribbean countries may benefit from this study, which creates awareness of the significance of the issue and the relevance for Caribbean population health outcomes. Amputation can have serious effects on quality of life and may also put a strain on resources to make adjustments to accommodate persons with severe disabilities. These burdens, however, can be managed through the timely implementation of appropriate measures to address risk factors. Finally, Behrendt et al. [1] suggest that countries should also focus on improving data collection and analysis of amputation procedures and results, ensuring standardization of procedural and diagnosis codes with international protocols.

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Chapter 96

HAZARD AND RISK ASSESSMENT OF RAINWATER HARVESTING SYSTEMS IN CARRIACOU, GRENADA

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ABSTRACT

The structure and operation of 20 rainwater harvesting systems in households in Carriacou were observed to identify hazards and estimate the risk associated with the systems. A semi-qualitative assessment methodology was adopted from the World Health Organization and International Water Association Water Safety Plan Manual. A matrix was used to calculate risk scores based on the frequency and severity of hazardous events. This study focused on three types of hazards: physical (esthetics), chemical and microbial. The observations were conducted in June, 2019. Of the nine parameters assessed, more than 50% of the 15 concrete tanks received high to very high scores in six areas. More than 50% of the five plastic tanks also received high to very high scores in six areas. When the overall risk score was calculated, three systems received low scores, ten systems received medium scores, and seven systems received high scores. Overall, the findings are indicative of moderate risk associated with rainwater harvesting systems in households in Carriacou. Public health safety can be improved through educating householders, regular monitoring of the systems, and enforcement of safety measures, such as first flush devices and filters. These findings can be applied to develop guidelines for the replication of rainwater harvesting technology on the mainland in Grenada.

INTRODUCTION

Rainwater harvesting is well recognized for obtaining potable water in many countries [1]. The technology is commonly used in dry areas and where surface water is virtually non-

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existent. Harvested rainwater is also used to supplement municipal supplies with the additional benefits of risk substitution, low service and maintenance cost, and quality service [1, 2]. The technology is considered environmentally friendly, reducing runoff that can cause flooding and soil erosion [3].

Rainwater harvesting is significant for public health [4]. Harvested rainwater can become contaminated at several points along the system – catchment, conveyance, storage - up to levels that exceed recommended guidelines. Microbial contamination of the water can result in significant health problems; usually, severe diarrhea and vomiting, leading to other secondary problems and death, particularly in young children [5]. Poor sanitation in the environment is a major factor that contributes to high bacterial concentration in rainwater systems [6, 7]. Failing to treat harvested rainwater, such as by application of chlorine tablets, and improper installation of safety devices, such as for first flush diversion and filtering debris from the water, also make the systems prone to contamination [7]. Contaminants, such as chemicals and microorganisms, can enter stored rainwater from soils through cracks in underground tanks. The materials used to construct the system can also be hazardous, and leached into the water, posing a threat to human health from consumption of the water [8].

Although only a few major outbreaks of gastrointestinal illnesses were reported in Caribbean countries from the consumption of harvested rainwater, there were health challenges in some countries. Salmonella outbreaks were found to be associated with the consumption of rainwater in Trinidad and Jamaica [9]. In some situations, technical issues presented challenges in ensuring the systems were designed for safety and efficiency [10]. Another significant issue was the discovery of elevated levels of pollutants from African origin, including arsenic and pesticides, deposited in cisterns in the Caribbean region [11–13].

This research was conducted as a pilot study to identify hazards and estimate the risk associated with rainwater harvesting systems in Carriacou, a small dependency in the State of Grenada. The structure and operation of the systems were analyzed using a semi-qualitative matrix approach published by the World Health Organization (WHO) and the International Water Association [14]. Risk scores were calculated based on the frequency and severity of hazardous events associated with the location and operation of the systems. To our knowledge, this semi-qualitative matrix methodology has not been applied to conduct risk assessment in previous studies in Carriacou. The results from this study should allow for better streamlining of interventions to improve water safety in Carriacou and on the mainland in Grenada. The information can also be used to inform the designing of future research, with a wide range of variables, to get in-depth knowledge of the significance of rainwater harvesting for public health in Grenada and other Caribbean islands. Financial support for this study was provided by the Windward Island Research Foundation (WINDREF) at St. George's University in Grenada.

OUR STUDY

This research involved observations and assessment of rainwater harvesting systems in Carriacou in the State of Grenada to identify potential hazardous events and evaluate the risk related to those events. Two systems were randomly selected from among households in the larger communities and one system from among households in the smaller communities for

observation and evaluation. A total of 20 systems were included in this study. Four systems were in the communities in the southern part of the island, three systems in communities in the northern part, and 13 systems in communities in the central part of the island. Table 1 shows the community and number of systems included in the study.

Table 1. Selected communities and the number of systems included in the study

Community	Number of Systems Assessed
Laurenston	2
L'Esterre	2
Dunfries	1
Hillsborough	1
Harvey Vale	1
Brunswick	2
Grand Bay	1
Mt. Royal	1
Windward	2
Bogles	1
Prospect	1
Beausejour	1
Six Roads	1
Hermitage	2
Mt. Dor	1
Total	20

Observation and Evaluation

The approach for this study was adopted from the WHO and the International Water Association *Water Safety Plan Manual* [14]. Specific parameters were considered in the assessment and a matrix provided for calculating risk scores from potentially hazardous events based on the frequency of events and severity. This study focused on three types of hazards: physical (esthetics), chemical and microbial. The observations were conducted on June 29-30, 2019. Information on frequency and type of maintenance was deduced from a survey conducted in Carriacou in collaboration with the Caribbean Regional Pilot Program for Climate Resilience (PPCR). All other information for the assessment was deduced from the observations of the systems.

Evaluation and Calculation of Risk Scores

Table 2 shows the semi-quantitative matrix from the *WHO Water Safety Plan Manual* (2009). The likelihood/frequency of a hazardous event and the severity were both measured on a scale of 1-5. The likelihood of an event was ranked as rare (1 point), unlikely (2 points), moderate (3 points), likely – once a week (4 points) and almost certain – once a day (5 points). The severity was ranked as insignificant or no impact (1 point), minor compliance impact (2 points), moderate esthetic impact (3 points), major regulatory impact (4 points), catastrophic public health impact (5 points). The risk scores were derived from multiplying the number corresponding to the likely frequency of the event (3 monthly, 4 weekly, and 5

daily) by the hazard severity score for specific likely events (4 mosquito larvae/algae, 4 leaves and debris, 3 fine particulates, 4 light industrial activities, 2 traffic exhaust and dirt, 5 agrochemicals, 5 excreta from rats, bats, etc. dead animals, etc. in the catchment area, 5 excreta, urine from dogs, sheep, chickens, etc. on the compound, 5 sewage from septic tank/pit latrine).

Table 2. Semi-quantitative risk matrix approach for calculation and interpretation of risk score

		Severity or consequence				
		Insignificant or no impact - Rating: 1	Minor compliance impact - Rating: 2	Moderate aesthetic impact - Rating: 3	Major regulatory impact - Rating: 4	Catastrophic public health impact - Rating: 5
Likelihood or frequency	Almost certain / Once a day - Rating: 1	3	6	15	30	25
	Likely / Once a week - Rating: 2	4	8	12	16	20
	Moderate / Once a month - Rating: 3	5	6	9	12	15
	Unlikely / Once a year - Rating: 4	2	4	6	8	10
	Rare / Once every 5 years - Rating: 5	1	2	3	4	5
Risk score		<6	6-9	10-15	>15	
Risk rating		Low	Medium	High	Very high	

Source: WHO Water Safety Plan Manual (2009). Available at http://apps.who.int/iris/bitstream/handle/10665/75141/9789241562638_eng.pdf?sequence=1&isAllowed=y.

A maximum of 25 points was achievable, indicating that the highest level of risk was associated with the specific hazard. In cases where several hazardous events were present, the most regular frequency score was used in the calculation. A risk score <6 reflects low risk, 6-9 reflect medium risk, 10-15 reflect high risk, and >15 reflect very high risk. Table 3 shows the hazardous events and likelihood and severity scores used in calculating the overall risk scores for the systems in Carriacou.

FINDINGS

Of the 20 systems observed, five had plastic storage tanks, and 15 had concrete cisterns for storage, located fully or partially below ground level. Of the nine parameters, more than 50% of the 15 concrete tanks received high to very high risk score, attributable to six events (leaves and debris; fine particulates; chemicals from light industrial activities; chemicals from traffic exhaust; microbes in excreta and dead vectors (catchment area); and microbes from animal excreta and urine (tank area)). Of the nine parameters, more than 50% of the five tanks received high to very high risk score, attributable to seven events (mosquito/algae; leaves and debris; fine particulates; chemicals from light industrial activities; chemicals from traffic; chemical from agricultural activities; and microbes from excreta and dead animals (catchment area)). When the overall risk score was calculated, three systems received low risk scores, ten systems received medium risk scores, and seven systems received high risk scores. Table 4 shows the number of systems deriving specific risk scores for each event.

Table 3. Hazardous event, likelihood and severity scores used for calculating risk scores

Hazard	Severity Score	Events Frequency Score									
		1	2	3	4	5	6	7	8	9	10
		Windy	No filtering device	No first flush device	Crack in underground cistern	Concrete roof	No yearly maintenance of tank/filter/gutter	Mosquito larvae/algae	Animals on compound with cistern	Agriculture/ agrochemical use in vicinity	Catchment/ system close to road
		Daily [5]	Daily - dirt, leaves, debris, dead animals in catchment area [5]	Weekly - accumulated matter on catchment area [5]	Daily - particulates, chemicals, microorganisms [5]	Weekly - accumulated matter [4]	Daily - accumulated matter [5]	Daily - uncovered storage tank [5]	Daily - excreta, urine, [5]	Monthly - agrochemicals [3]	5 Daily - fine particles [5]
Esthetics											
<i>Mosquito larvae/algae</i>	Major impact: Physical contamination [4]							X			
<i>Leaves, debris</i>	Major impact: Physical contamination [4]	X	X	X			X				
<i>Fine particles</i>	Moderate Impact: color and taste change [3]	X	X	X	X	X	X				X
Chemical											
<i>Light industrial activities</i>	Major impact: Chemical contamination [4]			X			X				
<i>Traffic exhaust and dirt</i>	Minor impact: color change [2]			X			X				X
<i>Agrochemicals</i>	Catastrophic public health impact [5]			X	X		X		X		
Microbial											
<i>Excreta from rats, bats, etc. dead animals, etc.</i>	Catastrophic public health impact [5]			X							
<i>Excreta, urine from dogs, sheep, chickens, etc.</i>	Catastrophic public health impact [5]				X				X		
<i>Sewage from septic tank/pit latrine</i>	Catastrophic public health impact [5]				X						

Table 4. Number of systems attracting specific risk scores by event and type of system

Hazard	Number of Systems with Concrete Tanks	Systems with Plastic Tanks
Esthetics		
Mosquito larvae/algae	VH – 2 L- 13	VH – 3 L - 2
Leaves, debris	VH - 14 L-1	VH – 4 L-1
Fine particulates	0	L – 1 H- 2 VH - 2
Chemical		
Chemicals from catchment area (industrial activities, compounds, adhesives, etc.)	VH - 11 H-1 L-3	VH - 3 H-1 L-1
Chemicals from traffic exhaust and dirt	VH-10 H-3 L-2	VH - 3 H -1 L-1
Agrochemicals		
Microbial		
Microorganisms from animal excreta, dead animals, etc. in catchment area	VH – 12 L-3	VH - 1 L-4
Contamination from animals on compound	VH-2 L - 13	0
Microorganisms from septic tank/pit latrine	VH-3 L-12	0

VH – Very High, H – High, L- Low, M- Medium.

DISCUSSION

For many years, the Caribbean Public Health Agency (CARPHA) and other public health agencies have encouraged the use of rainwater harvesting technology in Caribbean countries to augment municipal supplies and as a measure to mitigate climate change impacts in areas that are prone to water-stress [15–18]. Rainwater harvesting systems are, however, also highly susceptible to pollution from various sources and have implications for public health when the contaminated water is consumed. In the study in Carriacou, there was moderate public health risk associated with consuming water from the systems, which received a mixture of high, very high a low scores attributable to specific hazard and likely frequency of the events. Half of the systems received overall scores in the category of medium risk. A medium-level risk score indicates a moderate presence of environmental factors that have the potential to compromise the quality of harvested rainwater, and that could affect human health. The presence and effect of those factors may vary by season. For example, during the dry season, due to windier conditions and low volume of water in tanks, there may be an elevation in the concentration of pollutants. According to the WHO, weather, chemicals, microorganisms, and organic matter can have mild to significant impacts on the quality of harvested rainwater [1].

A few systems did not have filters to prevent the entry of pollutants into storage tanks. Diversion of the first set of water was also not commonly practiced. In the absence of filters/mesh and first flush devices, debris can be easily transported into tanks and

compromise the physical, chemical, and microbial quality of the water. Organic matter facilitates the growth of microorganisms, protect organisms from the effects of disinfection, and increase the demand for chlorine in water [8]. Concrete roof, which was present in some households in Carriacou, is usually flatter than galvanize roof and favors lodgment and buildup of particulates on the uneven surface. Dissolved solids can increase the turbidity of the water and affect the taste and appearance. Systems that do not contain filters or first flush devices are more prone to changes in the quality of water from weather events. The WHO encouraged the use of effective devices to minimize the entry of organic matter into harvested rainwater, as well as the practice of regular maintenance of systems and disinfection of the water [8].

Fishing is the dominant livelihood in Carriacou. The island is also well known for its boat building trade. Many chemicals that are toxic to humans are used in the construction of boats. Carriacou is windy, and chemicals can be easily transported to water collection surfaces and later washed into the storage tanks. On the small island, applying pesticides in residential areas by spraying also increases the potential for chemical pollution of the water. The concentration of pollutants may be lower in the wet season due to the regular exchange of stored water. In the dry season, however, the concentration of pollutants may be elevated due to the low volume of water present in the tanks. The deposition of chemical pollutants from African origin, carried in dust blows that typically occur in the dry season, and detected in water tanks in the Caribbean [11–13] is proof that large quantities of particulates can be transported in the wind and accumulate to levels that may pose a risk to human health. Health problems such as cancer, neurological and developmental disorders, and irritation may result from exposure to toxic chemicals [19]. Residents should be encouraged to improve safety practices, including the installation of flush diversion valves. Flush systems can be manually operated and require human intervention for effective use in each rainy period. A more practical approach is to install an automated system that also requires low maintenance. An effective flush system can significantly reduce pollutants in stored rainwater. This can eventually reduce the incidence of waterborne disease on the island, although the incidence is generally low in the wet season with an increase in the dry season.

Rearing livestock, poultry, and other domesticated animals such as cats and dogs in close vicinity to cisterns can constitute a biohazard for ingress of polluted groundwater into cracked tanks. Cats and rats can also climb onto catchment areas, such as on roofs, and deposit excreta which can introduce pathogens to rainwater systems. Animal fences were not commonly seen in Carriacou although animals were left untethered. This situation may increase the risk for transmission of disease-causing organisms from animal sources to humans. Salmonella outbreaks were found to be associated with the consumption of rainwater in Trinidad and Jamaica [9]. Zoonotic diseases can cause serious illnesses in humans and even death [20]. Precautions should be taken to prevent animals and animal waste in the immediate vicinity of rainwater harvesting systems.

This pilot study was conducted, including 20 systems in Carriacou. The small sample size is not representative of households in Carriacou, and the results of this study only provide an indication of some environmental factors that may have an impact on public health in Carriacou through the water sector. Further research is needed to understand better the magnitude and extent to which the events, identified in this study, affect the quality of the harvested rainwater. It is important to identify public health risks in the water sector in Caribbean countries for several reasons: water is becoming scarce as a direct consequence of

climate change [15]; rainwater harvesting systems are increasingly used as a source for potable water, globally and in the Caribbean [1, 10]; waterborne diseases account for a significant burden on the health care systems in the region [21, 22]; and the region, comprising mostly of small island states, has limited resources to combat waterborne infectious diseases.

Other countries, such as Antigua, Barbuda, St. Lucia, and Barbados, in which rainwater harvesting is a common practice, may benefit from this pilot study to guide water quality studies. This study can be used as a reference to inform steps to improve water safety in the most precarious situations. Irrespective of the countries in which studies are conducted, it is beneficial to share data and technical resources to strengthen the capacities for monitoring rainwater harvesting systems in the Caribbean region. Finally, agencies such as CARPHA, the Pan American Health Organization (PAHO) and the Caribbean Development Bank (CDB) should collaborate with regional governments and local organizations to mobilize and provide resources for the introduction of new technologies in the region and to improve water safety for the Caribbean people.

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Chapter 97

KNOWLEDGE, ATTITUDES AND PRACTICES REGARDING RAINWATER HARVESTING IN CARRIACOU, GRENADA

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ABSTRACT

Rainwater harvesting is well established in Carriacou, a small dependency island in the State of Grenada in the Caribbean. Owing to a high dependence on rainwater for domestic purposes, it is essential to regularly monitor practices and the quality of water on the island. This pilot study was conducted to assess the knowledge, attitudes, and practices of residents in 20 households in Carriacou. A survey was administered face to face to the residents in June, 2019. The survey questions led to the collection of information on household water supply, knowledge about and attitudes to rainwater harvesting, rainwater harvesting practices, and the use and treatment of rainwater for domestic purposes. Fifteen respondents stored water in concrete tanks, while five used plastic tanks for storage. The overwhelming majority of respondents stated they used the water for one or more of the following purposes: drinking, bathing, cooking, cleaning, flushing toilet, and washing vehicles. More than half of the respondents stated that water was always available from their household system. Eighteen respondents reported they did maintenance at least once per year. Four respondents did not have a mesh to filter the water entering the tank, and 16 respondents did not practice first flush diversion. Water safety education programs can be beneficial to improve rainwater harvesting practices in Carriacou. Monitoring practices and providing support for improvements may greatly benefit the water sector on the island and minimize the risk of waterborne illnesses.

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INTRODUCTION

Rainwater harvesting is becoming more commonplace to augment municipal supplies. The technology is regarded as reliable to mitigate the impacts of climate change and with significant potential to reduce the risk of contracting pathogenic waterborne illnesses, particularly in areas where wastewater recycling is practiced [1, 2]. Rainwater harvesting is a common practice in the Caribbean countries, especially in Trinidad, Antigua and Barbuda, Tortola, Barbados, and the Bahamas. Increasingly, the need to collect and store water to maintain adequate supplies is recognized as the region experiences harsher and extended dry seasons [3–5]. About 500,000 Caribbean residents depend entirely or mostly on harvested rainwater to meet domestic, recreational, and agricultural water needs [6]. Although governments have taken steps to extend the supply of pipe-borne water in some countries, rainwater harvesting is also promoted as an environmentally friendly approach to supplement municipal supplies [7–9].

The points of collection, conveyance, and storage are susceptible to pollution. Wind and water can be vehicles to transport dust, chemicals, and bio-waste from the vicinity into the system. Studies have shown microbial and chemical pollution resulting from poor environmental sanitation and usage of hazardous construction materials for the systems [2, 10–12]. Additionally, discharges from industrial activities are significant sources of pollution from deposition on catchment areas and directly into storage tanks. In addition, studies have shown elevated levels of pollutants in cisterns in the Caribbean from trans-national sources, such as arsenic from dust blows originating from as far as the Sahara desert region in North Africa [13, 14].

Rainwater harvesting is the primary source of water in Carriacou, a small dependency island in the State of Grenada. Grenada is located in the southern part of the Caribbean. Approximately 5,000 persons reside in Carriacou. Surface water is virtually non-existent on the island, and it is not uncommon for most residents to experience a shortage of water during the dry season. The dry season typically lasts from January-June. During the dry season, there is an elevated risk of pollution from wind transportation. At the same time, the concentration of pollutants can build up faster in the small volume of water in storage tanks. Syndromic data from the Ministry of Health in Grenada show a consistent peak in the number of cases of diarrheal illness during the dry season each year [15], which may be indicative of the higher concentration of pollutants in water. The findings from the Burden of Illness (BOI) study in Grenada in 2008-2009 highlighted the need for closer monitoring of water safety practices, both on the mainland and in Carriacou and Petite Martinique.

This pilot study was conducted in partnership with the Caribbean Regional Pilot Program for Climate Resilience (PPCR) with a small sample of residents to investigate knowledge, attitude and practice (KAP) regarding rainwater harvesting in Carriacou. The regional project was designed to provide information on the feasibility and need for replicating rainwater harvesting technologies on the mainland in Grenada. In this study, we collected information on household water supply, knowledge about and attitudes to rainwater harvesting, rainwater harvesting practices, and the use and treatment of rainwater for domestic purposes. The study was conducted in the first month of the rainy season. The results of this study should inform future research with larger samples to obtain a more comprehensive understanding of the quality of water for potable uses. The findings also provide insights on some appropriate

interventions for water safety in Carriacou. Lastly, the findings will complement the PPCR to propose recommendations for safety in adopting rainwater harvesting technologies on the mainland, where communities also experience water shortage from pipe-borne sources during the dry season.

OUR STUDY

This pilot study was conducted with residents in 20 households across 15 communities in Carriacou. Two households were randomly selected in larger communities and one household in smaller communities. A total of four households were selected in the communities in the southern part of the island, three households in the communities in the northern part, and 13 households in communities in the central part of the island. The geographic spread in the sampling was representative of the number of communities and residents in the respective parts of the island. Table 1 shows the communities and number of households included in this pilot study.

Through the PPCR, a 3-day consultation was held in St. Lucia in March, 2019 to develop and test a questionnaire for use in the regional study in three Caribbean islands - Grenada, Jamaica, and St. Lucia. This questionnaire was modified slightly for use in the study in Carriacou. The modified questionnaire was further piloted with a small group, and the recommendations were incorporated to improve comprehension and answer choices suitable for the context on the island.

At the household level, one adult above 18 years, preferably the head of the household, was selected to participate. The survey was administered face to face by trained surveyors on June 29-30, 2019 in the first month of the rain season. Questions were included to collect information about household water supply, knowledge about and attitudes to rainwater harvesting, rainwater harvesting practices, and use and treatment of rainwater for domestic purposes. Participants were required to provide written consent before being interviewed. Responses were recorded on the questionnaire and later entered into a database for analysis.

Table 1. Number of households selected in each community in Carriacou for inclusion in the study

Community	Number of systems assessed
Laurenston	2
L'Esterre	2
Dunfries	1
Hillsborough	1
Harvey Vale	1
Brunswick	2
Grand Bay	1
Mt. Royal	1
Windward	2
Bogles	1
Prospect	1
Beausejour	1
Six Roads	1
Hermitage	2
Mt. Dor	1
Total	20

FINDINGS

Of the 20 respondents in the pilot study, 14 (70.0%) were males, and 6 (30.0%) were females. The majority of respondents (15, 75.0%) also identified themselves as the head of the households. Half (10, 50.0%) of the respondents were between 41-65 years, and more than half (12, 60.0%) had lived in the community for more than 26 years. The majority (14, 70.0%) of respondents lived in concrete houses, and 14 (70.0%) also had toilet facilities with a flush to septic tank system. Table 2 shows the demographic characteristics of the respondents.

Household Water Supply

Residents were asked about the main source of water for their households, disruptions, and alternative sources. Fifteen (75.0%) respondents reported a private concrete cistern was the main source of water for the household, while 5 (25.0%) reported a private plastic tank was used. More than half of the respondents (12, 60.0%) reported water was always available from the private supply, 6 (30.0%) stated water was available for most of the year, and 2 (10.0%) reported water was available for about half of the year or less. Nine (45.0%) respondents stated they had the most disruptions during the period of December to May. Of the respondents who experienced shortages during the year, 5 (55.5%) stated they sourced water from friends and neighbors as an alternative. About one-third of the respondents (6, 30.0%) stated their supply was more than adequate throughout the year, 10 (50.0%) stated adequate and 4 (20.0%) stated they experienced scarcity for the household.

Table 2. Demographic characteristics of the respondents

	Number	Percentage		Number	Percentage
Gender			Floor material		
Male	6	30.0	Dirt/Sand	0	0
Female	14	70.0	Wood	6	30.0
			Plywood	0	0
Position in household			Concrete	14	70.0
Head	15	75.0			
Other member	5	25.0	Roof material		
			Thatch	0	0
Age (years)			Wood	0	0
18-24	1	5.0	Galvanize/metal	17	85.0
25-40	4	20.0	Clay/shingles	0	0
41-65	10	50.0	Concrete	3	15.0
65+	5	25.0			
			External wall material		
Household Size			Dirt	0	0
1-3	7	35.0	Plywood	1	5.0
4-7	12	60.0	Galvanize	2	10.0
8+	1	5.0	Concrete	14	70.0
			Wood	3	15.0
Residence in community (years)					
<1 year	0	0	Toilet facility		
1-5	2	10.0	Flush to septic	15	75.0
6-10	1	5.0	Pit latrine	5	25.0
11-25	5	25.0	Bucket	0	0
26+	12	60.0	Bush/field	0	0

Rainwater Harvesting Practice

In reporting on the location of the storage facility, 19 respondents stated the facility was underground. Almost half of the respondents (9, 45.0%) reported they did not make preparations to secure their systems during the passage of a hurricane, storm or an earthquake; half (10, 50.0%) did not have a water line indicator in their system, and 4 (20.0%) did not have a mesh to filter the water entering the tank. The majority, 16 (80.0%), did not use a first flush system. A little more than half (12, 60.0%) of the respondents reported they treated the water before consumption; six added bleach, two added chlorine tablets, and three had small fishes to consume mosquitoes and larvae.

Only two (10.0%) respondents reported they used additional filtration or treatment methods after the water left the tank. Half of the respondents also stated they did not have a mesh to stop mosquitoes from going up into the pipes. Eighteen (90.0%) respondents reported they did maintenance or cleaning of the system. Table 3 shows the type and frequency of maintenance by respondents. Six (30.0%) respondents stated they felt they should do more maintenance while 13 (65.0%) felt they did not need to do additional maintenance.

Table 3. Frequency and type of maintenance performed by respondents

	Number	Percentage		Number	Percentage
Maintenance/cleaning			Clean Storage tank		
Yes	18	90.0	Every 5 years	1	5.0
No	2	10.0	Every 2 years	3	15.0
			Yearly	4	20.0
Maintenance			Dry season	6	35.0
Every 4-5 years	1	5.0	Twice yearly	1	5.0
Every 3 years	3	15.0	3-4 months	1	5.0
Every 2 years	2	10.0			
Dry season	6	30.0	Clean roof/gutters		
Twice yearly	2	10.0	Yes	16	80.0
Occasionally	1	5.0	No	4	20.0
No response	2	10.0			
			Clean roof/gutters		
Clean storage tank			Every 2 years	8	40.0
Yes	18	90.0	Yearly	4	20.0
No	1	5.0	Dry season	1	5.0
			Twice yearly	1	5.0
			Every 3 months	1	5.0

Use and Appearance of Drinking Rainwater

The overwhelming majority of the respondents (19-20, 95.0-100%) reported they used the harvested rainwater for one or more of the following purposes: drinking, bathing, cooking as well as for cleaning, flushing toilet, and washing vehicles. Nine (45.0%) also used the water for lawns/gardens. Eighteen (90.0%) respondents stated the water tasted good, and a similar proportion felt it was safe for drinking. Sixteen (80.0%) respondents stated the water was clear during most of the year.

Knowledge and Attitude to Rainwater Harvesting

Respondents were asked to state their level of agreement with statements that demonstrate their knowledge and attitude to rainwater harvesting. The most variance in the responses was to the question of whether the government was responsible for providing residents in Carriacou with safe water. While six (30.0%) of respondents agree, only two (10.0%) strongly agreed, five (25.0%) neither agreed nor disagreed, and seven (35.0%) disagreed. The responses differed more significantly on the question of the safety of using chlorine to treat drinking water. Five (25.0%) respondents strongly agreed that chlorine was safe to treat the water, seven (35.0%) agreed, three (15.0%) were neutral, and five (25.0%) disagreed. There was also variance in the responses regarding the safety of water after diverting the first set from the tank. Almost half (9, 45.0%) of the respondents neither agreed nor disagreed that the water was safer from using a first flush system, seven (35.0%) disagreed and four (20.0%) respondents, in total, strongly agreed and agreed. Table 4 shows the respondents' agreement with the statements.

Table 4. Respondents level of agreement with statements regarding rainwater harvesting

	Number	Percentage		Number	Percentage
Untreated rainwater is safe to drink			Rainwater treated with bleach is safe to drink		
Strongly agree	3	15.0	Strongly agree	5	25.0
Agree	10	50.0	Agree	7	35.0
Neutral	3	15.0	Neutral	3	15.0
Disagree	4	20.0	Disagree	5	25.0
Strongly disagree	0	0	Strongly disagree	0	0
Diverting the first set or rainwater makes the water safe to drink			Untreated rainwater is safe for bathing		
Strongly agree	2	10.0	Strongly agree	10	50.0
Agree	2	10.0	Agree	7	35.0
Neutral	9	45.0	Neutral	3	15.0
Disagree	7	35.0	Disagree	0	0
Strongly disagree	0	0	Strongly disagree	0	0
Filtered rainwater is safe to drink			Untreated rainwater is safe for cooking		
Strongly agree	9	45.0	Strongly agree	8	40.0
Agree	8	40.0	Agree	12	60.0
Neutral	3	15.0	Neutral	0	0
Disagree	0	0	Disagree	0	0
Strongly disagree	0	0	Strongly disagree	0	0
Boiled rainwater is safe to drink			It is the responsibility of government to supply us with safe water		
Strongly agree	15	75.0	Strongly agree	2	10.0
Agree	4	20.0	Agree	6	30.0
Neutral	1	5.0	Neutral	5	25.0
Disagree	0	0	Disagree	7	35.0
Strongly disagree	0	0	Strongly disagree	0	0

DISCUSSION

Rainwater harvesting is considered a safe alternative to municipal water supplies having a lower risk of contamination from sources such as lead pipes and chemicals and microorganisms in recycled water [1]. Rainwater systems, however, are susceptible to microbial and chemical pollution, in particular [11, 16, 17]. Constant monitoring is necessary to ensure that a consistent and safe supply of water is available in communities that are prone to experience water stress. KAP studies can be beneficial to understand risk and inform appropriate interventions to improve water safety. The findings from the BOI study in 2008-2009 and other studies in Carriacou suggest there is a need for close monitoring of the rainwater harvesting systems.

The results of this study indicate there is some level of efficient management of water supply by residents in Carriacou, with about half of the respondents stating they had a consistent supply of water throughout the year. This study did not focus on the extent and practices related to the management of supply. In the context of climate change mitigation, the issue is important, relating to the efficiency of the technologies that are currently used versus alternative technologies. The results show extremely high dependency on rainwater for drinking, cooking, bathing, laundry, and cleaning. This high dependence on harvested rainwater shows, not only the social impact of the practices but also the public health implications relating to water quality in Carriacou.

While there was a general positive indication about the management of water supplies in households, about half of the respondents also stated their supply was only "adequate" with an additional 20.0% stating they experienced scarcity. Together, these statistics indicate a potentially high risk for water shortage by a significant segment of the Carriacouan population. Climate change exacerbates this challenge, calling to attention the need to monitor and manage the balance between water demand and supply. The size of households, rainfall patterns, and other factors should be given consideration in determining what systems are adequate for households. Currently, pipe-borne water is the main supply on the mainland in Grenada. In promoting the replication of rainwater harvesting on the mainland, it may be best to develop policies that support diligence in water supply and address the gaps found in this pilot study in Carriacou. This approach can ensure that the measure becomes an effective climate change mitigation strategy and attract long term use by a significant segment of the population.

There were notable differences in the responses regarding the government's responsibility for providing safe water for residents in Carriacou. Several factors may account for the differences, including individual perception about the need and influence of laws and policies to direct the management of individual and communal water supplies. In the absence of a structured program by the government that actively directs and monitors rainwater harvesting in Carriacou, residents are left to make choices regarding how they manage household supplies. This autonomy may translate into little understanding and appreciation of the government's responsibility for oversight of public health, which also extends into the water sector. The government's failure to construct a modern water system on the island at the time of the interview may be another reason for the mixed responses.

Governments have ultimate responsibility for public health [18], and their agencies should ensure water safety measures are implemented and maintained within their

jurisdictions. In the BOI study in 2008-2009, the third highest prevalence of acute gastrointestinal illness (AGI) was found in Carriacou and Petite Martinique [15]. Despite a few reports of major issues related to water consumption in the dependency islands, a monitoring system is still prudent to maintain a potable quality of water in all households on the island and to reduce the seasonal increases in AGI cases. Inconsistency in the responses regarding the use of chlorine for sterilization also shows a possible need for education and health promotion to demonstrate best practices in rainwater harvesting including the WHO recommended usage of chlorine tablets for sterilization [10], first flush system and filters or mesh to reduce the potential for pollution of water in storage tanks.

More than half of the residents reported they did not make preparations to prevent disruption of their water supply in the event of a disaster, such as a hurricane or an earthquake. Given the island's close proximity to Kick 'em Jenny, an active submarine volcano, attention should be given to ensure there is a safe and consistent supply of water in the event of an emergency situation. Grenada and its dependencies are also located within the Atlantic Ocean's hurricane track, which could increase vulnerability to catastrophic climatic events. Ensuring a safe supply of water during an emergency reduces the chances of water-and/or food-related mortality and morbidity.

The results indicate most of the respondents performed maintenance of their rainwater system. The extent of maintenance parts of the system (collection surfaces, conveyance, and storage facility) was not investigated in this study. While most of the respondents stated they did yearly maintenance, some also felt they should do more. This may be an indication of the need for training to maintain the systems. Financial constraints may also limit maintenance, especially in households headed by women. The replicating the technology in Grenada, residents should be made aware of associated costs and educated on plans to provide for the maintenance of the system. All parts of a rainwater harvesting system should be systematically maintained as a measure to ensure the water is safe for consumption. The following recommendations may also be appropriate to address gaps and improve rainwater harvesting management in Carriacou as well as for application in replicating the technology on the mainland in Grenada:

- Conduct a follow-up risk assessment study in Carriacou with a representative sample to identify hazards and estimate the risk associated with the conditions. The information from this study should be used in the development or modification of interventions to improve water safety in Carriacou.
- Conduct community-based national education programs on best practices in rainwater harvesting technology. The messages should be communicated through various channels to ensure reach to the widest cross-section of the population.
- Establish a team/unit with responsibility for all activities related to rainwater harvesting at the national level.
- Monitor the condition of rainwater harvesting systems and operations on a regular basis. Ensure systems contain all appropriate safety devices such as first flush devices, rodent-proof, and drain taps in plastic tanks.
- Create policies that promote safety in rainwater harvesting. Address non-compliance with public health policies.

- Conduct a national survey to collect baseline data from residents on the mainland prior to the construction of systems. Post-training and post-adaptation surveys should also be conducted to evaluate differences in knowledge, attitudes, and practices.

Although a small sample was included in this study, useful information was provided on household water supply, knowledge about and attitudes to rainwater harvesting, rainwater harvesting practices, and the use and treatment of rainwater for domestic purposes in Carriacou. Recommendations are made to address gaps and to improve the management of rainwater harvesting systems in Carriacou. The recommendations can be referenced in the regional PPCR initiative to highlight an evidence-based approach in its work. Further studies are needed, however, to validate the situation in Carriacou. Meanwhile, the Government of Grenada, through the Environmental Health Department, can begin to take steps towards replication with improved practices on the mainland while ensuring an appropriate supportive environment for rainwater harvesting practice to thrive. Climate change has significant impacts on water supply and quality. Water security, however, is crucial for public health and to ensure a high quality of life for all the citizens.

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Chapter 98

ASSESSMENT OF RECREATIONAL WATER QUALITY IN THE SOUTHERN COASTAL AREAS OF GRENADA

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ABSTRACT

The microbial quality of recreational coastal waters along the southwestern coast of Grenada was assessed. A total of 120 samples taken from 12 sites were analyzed for enterococcus faecalis, fecal coliform, pH, temperature. Two samples per day from six sites were collected bi-weekly between 8 a.m. and 12 p.m. during the period of November-December 2008. Rainfall data for the sampling period was obtained from the Grenada Meteorological Office. The highest percentage of sampling days exceeding the World Health Organization's (WHO) recommended limits for enterococcus faecalis was recorded at two sites—Beausejour-Bay (70%) and Carenage-Bay ((60)%). The Carenage-Bay sampling site had the highest percentage of sampling days exceeding recommended limits for total fecal coliform ((60)%). Overall, 30% of the samples analyzed showed enterococcus faecalis and total coliform levels above the recommended limits. Other measured variables were inconsistent with increased microbial content. No correlation was observed between rainfall and enterococcus faecalis. This study found that the majority of beaches along the Southwestern coast of Grenada exceeded the recommended limits by WHO for fecal coliform and enterococcus faecalis period.

INTRODUCTION

In 2017, the United Nation World Water Development Report stated that over 80% of all wastewater worldwide, released into the environment, was untreated [1]. On a global level, countries are working towards ensuring good water quality for sustainable growth and

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productivity in accordance with the Sustainable Development Goal 6 (SDG 6) [2]. In order to measure the achievement of this sustainable development goal, water quality measures have been established for recreational waters, both freshwater and coastal water bodies. Poor recreational water quality measurements are usually associated with health problems and environmental concerns [3]. On the other hand, high quality recreation water indicators have a concomitantly reduced level of adverse health problems [3]. Many European countries have reported excellent recreational bathing waters in the last 40 years, which they have attributed to robust water quality monitoring systems [4].

In the Caribbean, recreational waters are almost exclusively located on the coasts of small island states. These coastal recreational waters can be contaminated through point and non-point sources such as agricultural and industrial runoffs, sewage discharges, and industrial effluents [5]. Contamination of the coastal environment has been found to be associated with an increase in the incidence of infectious diseases [6]. Some diseases and infections acquired through bathing in contaminated waters include acute febrile respiratory illness, infections of the eye, ear, nose and throat, and serious infections such as meningitis, hepatitis A, typhoid fever and poliomyelitis [7]. Other diseases caused by bathing in contaminated recreational waters or consumption of contaminated seafood include swimmer’s itch, gastroenteritis, dermatitis, viral hepatitis, and dysentery [8].



Figure 1. Sampling sites, river outlets, and sewage outfalls along the West coast of Grenada.

Environmental problems arise when sewage is discharged inappropriately into coastal areas. This can lead to very high nutrient loads from phosphates and nitrates, which cause localized eutrophication, which in turn is associated with toxic algal blooms [7]. The temperature and pH levels can also play a significant role in coastal water quality since both affect the growth and multiplication of aquatic organisms and fecal indicator organisms [5]. Caribbean countries, which depend on coral reefs as a natural defense for coastal areas and for the survival of fish populations, already face social and economic threats as a result of the degradation and loss of reefs [9].

Coastal waters are used for several activities, including transportation, food production, hydroelectricity generation, and for the deposition of sewage and industrial waste [7]. In the Caribbean, many islands market themselves through the promotion of clean, white sandy beaches; safe for swimming, snorkeling, diving, and bathing. Beach recreational activities are largely hosted around holiday activities and festivals. Not many Caribbean countries, however, have given sufficient attention to the importance of monitoring their recreational water quality. Regulations for sewage treatment and other sources of contamination, such as agricultural runoff, are either non-existent or not adequately implemented in the Caribbean countries. In 2012, the Caribbean Regional Fund for Wastewater Management (CREW) estimated that approximately 85% of the wastewater entering the Caribbean Sea was not treated [10]. As a result, many Caribbean coastal water areas are vulnerable to contamination, and those who use these areas are exposed to pathogenic microorganisms that can cause severe infections.

Grenada, approximately 133 square miles, is located 12.07° North and 61.0° West and is home to approximately 110,000 people. The island is divided into seven parishes with the parish of St. George, located in the South West, being the most populated with approximately 37,057 residents [11] (see Figure 1). The capital city, St. George's, is also located in this parish, which is the most developed on the island. One of the areas most visited by tourists is Grand Anse, located in the south of St. George parish and popular for shopping and the Grand Anse Beach. Wastewater, mainly greywater from residential, commercial, and industrial establishments, from the Grand Anse area is channeled through a 15-mile conveyor and discharged to a marine outfall. There is currently no secondary treatment of sewage in Grenada. During the rainy season, because of the island's mountainous topography, there is also severe soil erosion and land degradation [12] which affects the quality of the coastal recreational waters. Due to recent changes in the climate, however, rainfall has become less predictable and there has been a 61% increase in rainfall during the dry season (January to May) over the period 1990-2009 [13]. Coastal dynamics also play an intrinsic role in determining the status of water quality [14]. Closed bays are subjected to higher concentrations of contaminants since they have a low renewal frequency compared to open bays [15].

A study investigating the prevalence of *escherichia coli* and *enterococcus faecalis* in coastal environments located in the Southern parts of Grenada was limited to four coastal sites located on the furthest end of the parish of S. George [16]. In another study conducted in 2006 on the West coast of Grenada near the St John's Bay river, measurements of *enterococcus faecalis* levels were taken and found to be low [17]. A report from the Government of Grenada's Epidemiological Department stated that gastroenteritis was one of

the major acute illnesses affecting infants on the island. Approximately 1067 cases were reported in March 2012 as compared to 319 reported in March 2011 [18].

In recognition of the importance of having adequate monitoring systems in place, the Caribbean Environmental Health Institute (CEHI), subsumed into the Caribbean Public Health Agency (CARPHA) as at January 2012, produced and published guidelines for the region's coastal water quality [7]. The recommended limits for marine waters for *escherichia coli* is 126 CFU/100 ml, for fecal coliform 200 CFU/100 ml, and for *enterococcus faecalis* 35 CFU/100 ml [7]. In assessing water quality, multiple microbial indicators are used to make correlations between the number of microbes and possible contamination. According to the WHO, *enterococcus faecalis* meets all regulatory parameters standards as opposed to total coliform, which is not specific to fecal material [19]. The United States Environmental Protection Agency (EPA) also recommended the use of *enterococcus faecalis* as the best indicator for assessing recreational water health risk [20]. It is expected that by assessing Grenada's coastal waters using WHO and EPA recommended indicators, data can be obtained to provide a better understanding of the quality of the coastal waters of the Southern part of Grenada.

In this study, the quality of recreational waters of Grenada's most populated coastal regions was assessed and compared with WHO and EPA recommended standards. Sources of possible contamination were examined along with possible health-related outcomes to determine whether water quality monitoring is necessary to ensure safe water-related recreational activities in Grenada.

OUR STUDY

A cross-sectional sampling for *enterococcus faecalis* and fecal coliforms in the coastal waters located in the Southwestern regions of Grenada was taken from November 4th to December 3rd, 2008.

Sample Sites

Of the 45 beaches in Grenada, 12 beaches located in the South Western region of the island were selected for this study. The 12 sampled sites were Halifax-Bay ((HA)), Beausejour-Bay ((BA)), Flamingo-Bay ((FB)), Grand-Mal (GM), Carenage-Bay (CA), the Lagoon (LA), Mt-Pandy-Beach (PA), Morne-Rouge-Beach (BBC), Pink-Gin-Beach (PG), and Grand-Anse-Beach (GA) (see Figure 1). The GA site, which is approximately three miles long, was divided into three zones: Grand-Anse-Top (GAT), Grand-Anse-Middle (GAM), and Grand-Anse-Bottom (GAB). Each of these sampling areas is subjected to major exposures to contaminants from various water sources such as rivers, stormwater runoff, and sewage discharge. All of the Grand Anse (GA) sampling sites were heavily patronized by the local residents and tourists. The Grand Mal (GM) area is also a heavily populated zone and subject to runoffs from construction sites. GM site also has a sewer outfall that empties directly into its waters from the Queens Park area. Two of the other sampling sites, the

Lagoon (LA) and the Carenage (CA) sites, are major docking areas for ships, cargo boats, yachts, and barges.

Physical Parameters

To better assess the quality of the recreational waters, physical parameters such as surface temperature, pH, amount of rainfall, and general weather conditions were recorded. Temperature was measured directly after sampling and noted in degrees Celsius.

Rainfall

Rainfall data for the sampling period was obtained from five meteorological stations operated by the Grenada Meteorological Office. These meteorological stations were chosen based on their location and the direction of the runoff water caused by the rainfall. The chosen stations were located in Vendomme, Mardigras, Annandale, Botanical Gardens, and the Maurice Bishop International Airport. Rainfall data, measured in millimeters (mm), was collected to allow for investigation of possible relationships between water quality and land runoff associated with rainfall. For this study, a low level of rainfall was defined as levels < 10 mm, a moderate level of rainfall as 10 > 100 mm, and a high level of rainfall as >100 mm.

Sample Collection

Water samples were collected during the rainy season, between November 4 to December 3, 2008. Samples were collected bi-weekly for five weeks. Six sites were visited each day, and two samples were taken at each site, amounting to 24 samples per week. Samples were collected between 8 a.m. and 12 p.m. so that any variation in the levels of contamination due to downpours, wind direction, and tidal levels could be evaluated. Serial dilution techniques were used to reduce the density of the organisms present in the samples and to improve measurement accuracy.

The equipment and reagents used for collecting water samples were prepared according to protocols specified by the EPA [20]. All equipment was sterilized using detergent and hot water, followed by distilled water. Sampling bottles were autoclaved for 15 minutes up to 121°Celsius and kept closed after sterilization. All samples were taken 5 ft offshore and at a depth of 40 cm below the surface every Monday and Thursday of the week. This sampling protocol was recommended, given the majority of beach users occupy up to this area and where subsurface currents move much slower compared to surface currents [22]. For each sample, 100 ml of water was collected leaving space for the sample to be shaken. Testing was done within one hour of sampling. Samples that were not analyzed within this timeframe were refrigerated at or below 4°Celsius.

FINDINGS

Fecal coliform counts for HA, PB, GAM, BB, and FB were above recommended acceptable limits for 10% of the sampling days. This was the lowest observed percentage compared to all other sampled sites. Both BBC and PG sampling sites exceeded recommended fecal coliform limits 20% and 30% of collected samples, respectively, followed by GM, LA, GAT, and GAB in which 40% of samples at these sites exceeded the recommended acceptable limits. At CA, 60% of sampling days were above the recommended limits and was the highest in comparison to all other sites sampled (see Figure 2).

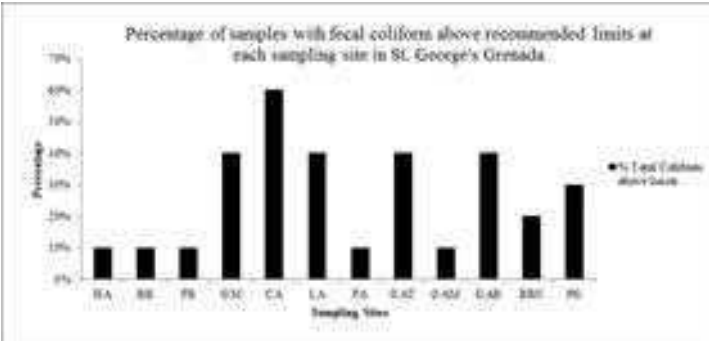
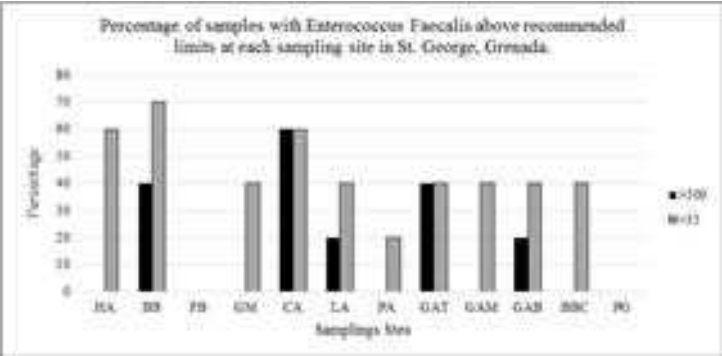


Figure 2. Fecal coliform levels above recommended limits by sampling sites for November 4 to December 3, 2008.

Enterococci faecalis

The recommended acceptable *Enterococcus faecalis* limits were exceeded at all sampled sites except FB. PA exceeded recommended limits in 20% of sampling days, and GM, LA, GAT, GAM, GAB, and BBC exceeded recommended limits for 40% of the sampling days.



*Black bars indicate percentage of *Enterococcus faecalis* counts > 200 CFU/100 ml samples out of the total that exceeded recommended limits. Example: BB shows percentage of samples exceeding recommended limits (35 CFU/100 ml) in grey (70%) and percentage of samples exceeding 200 CFU/100 ml (40%) of the total in black. NB: This is to emphasize the severity of contamination.

Figure 3. Percentage of *Enterococci faecalis* above recommended limits by sampling site in St. George's Grenada for November 4 to December 3 2008.

Sample sites LA and GAB had counts over 200 CFU/100 ml on 50% of those sampling days and GAT on all of those days. HA and CA showed similar results exceeding recommended limits on 60% of the sampling days, however, CA level reached counts > 200 CFU/100ml on all sampling days, whilst HA remained below 200 CFU/100ml in all samples. BB exceeded recommended limits on 70% of the sampling days, with 57% of those samples reaching counts above > 200CFU/100 ml (see Figure 3).

Temperature

The temperature for all bays ranged 20.4-31.6°C (see Figure 4). The greatest temperature range was recorded for CA, 20.4°C to 30.1°C.

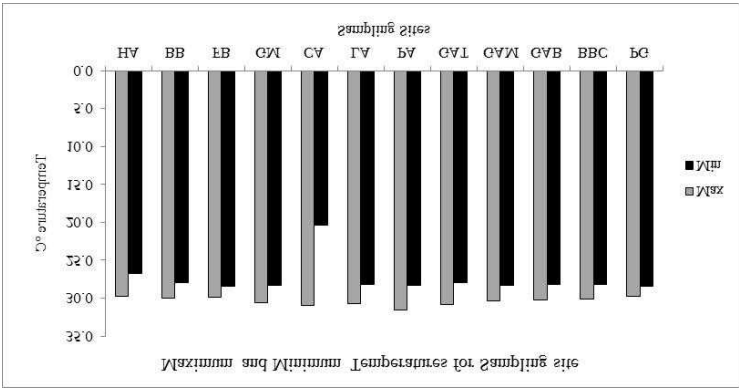


Figure 4. Maximum and minimum temperatures by sampling site for the period November 4 to December 3 ,2008.

pH

Recorded pH readings remained within the acceptable range for all sampling sites throughout November, 2008.

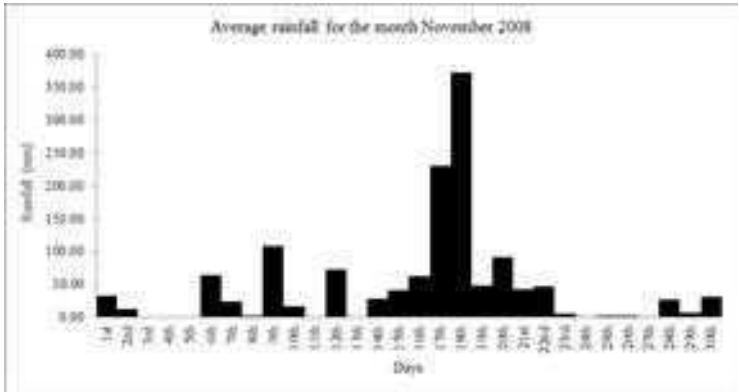


Figure 5. Average rainfall for the month of November in St. Georges, Grenada.

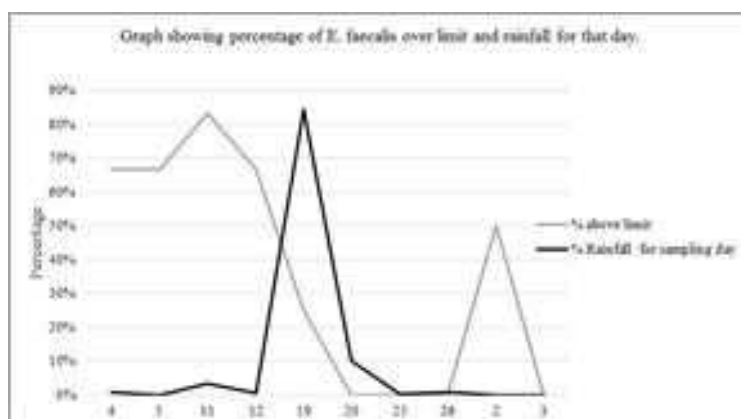


Figure 6. Percentage of enterococcus faecalis above limit and rainfall for the same sampling day.

Rainfall

High levels of rainfall were reported on the following sampling days: November 12, 19, and 20 (see Figure 5). It was observed that the rainfall pattern varied greatly with the corresponding high microbial counts (see Figure 6). Chi square analysis revealed that rainfall and *enterococcus faecalis* were independent as observed throughout the sampling period (χ : 0.63, p : 0.42).

DISCUSSION

Several studies have shown the presence of fecal indicator organisms in coastal waters of Grenada [16, 23, 24]. In 2008, an assessment of samples collected from the HA revealed readings that exceeded recommended fecal coliform levels for 10% of the sampling days when the amount of rainfall was low on the same day and moderate the previous day. This study found that *enterococcus faecalis* counts exceeded recommended acceptable levels for 60% of the samples when rainfall levels were low on the same day and moderate 24-hours before testing. Temperatures in the HA bay ranged from 26.8- 29.8°C.

This level was observed with the lowest temperature and exceeding levels of *enterococcus faecalis* and moderate levels of rainfall on the same day and high on the previous day. Halifax Bay is an enclosed bay and subjected to low water renewal and high accumulation of sediment. The area is in the vicinity of the island's main landfill. Runoff from the landfill most likely also accounted for the increased microbial levels recorded at this location by Garrido-Perez in 2008 [15].

BA samples exceeded recommended fecal coliform levels at a similar rate as HA (10%) when rainfall levels were low on the same day and on the previous day. *Enterococcus faecalis* levels exceeded recommended levels in 70% of the sampling sites which, correlated with low, moderate levels of rainfall on the same day, and low-high levels of rainfall 24 hours before testing. This was the highest recorded percentage amongst all tested sites. Of these samples, 57% were >200.5 CFU/100ml and showed a low correlation with high levels of rainfall.

Studies have shown that high rainfall has been associated with increased microbial counts [24]. The temperatures measured in BA ranged from 28-30.0°C. Further, no strong correlations were noted with temperature, exceeding levels of *Enterococcus faecalis*, and high levels of rainfall, either on the same day and 24 hours before testing. A reason why rainfall correlations may have been weak is that the BA is more open and, therefore, more amenable to the flushing of any contaminants [15]. The *enterococcus faecalis* levels may be high for this location due to continuous contamination by untreated septic tanks that enters the river, as indicated by previous studies [25]. The marine estuary located at the mouth of this bay can also present major problems when contaminated from upland sources [26].

The FB samples exceeded the recommended fecal coliform levels at rates similar to HA and BA (10%) when rainfall levels fell at low levels on the same day and moderate on the previous day. The temperatures measured in this bay ranged from 28.4-29.9°C. Recorded *enterococcus faecalis* levels did not exceed recommended levels at any sampling site. Highest rainfall levels 24 hours before and on the same day resulted in the lowest level of *enterococcus faecalis*, which pattern was also observed in previous studies [27]. This may have been as a result of protective factors such as increased dilution, the absence of potential sources of pollution, such as runoff from drains, and the bay's long distance from residential areas. No observed correlations could be made between either temperature and high levels of *enterococcus faecalis* or high levels of rainfall on the same day and 24-hours before testing.

The GM samples exceeded recommended acceptable fecal coliform limits for 40% of the sampling days when rainfall levels were low on the same day and low to moderate on the previous day. The temperature at this bay ranged from 28.3-30.6°C. *Enterococcus faecalis* levels exceeded recommended limits for 40% of the samples, however, none exceeding 200 CFU/100 ml. This correlated with low levels of rainfall on the same day and low to moderate levels 24-hours before testing. There was no correlation with the lowest temperature and exceeding levels of *enterococcus faecalis* and high levels of rainfall both on the same day and 24-hours before testing. The BM beach is an open area, therefore, frequent flushing of contaminants with high levels of rainfall may be the reason for the low microbial counts occurring with rainfall. Other parameters such as tidal flow and height could have been important factors that help explain the increase in microbial indicators at this sample site [28]. The observed occurrence of a high level of fecal coliform and *enterococcus faecalis* with high temperatures may also be the cause of conflicting results. Temperature is known to affect the rate at which bacteria grow and multiply [5]. Other factors, such as contamination from rivers, may have played a role in the increased microbial counts [7].

The CA samples exceeded recommended fecal coliform levels on 60% of the sampling days when rainfall levels fell to low to moderate levels on the same day and low, moderate, and high levels on the previous day. Temperature at this bay ranged from 20.4-31.0°C. This was the highest range noted for the month at all sites and may have been due to the area being completely surrounded by concrete infrastructure which contributes to a higher rate of runoff and flushing when rainfall occurs. *Enterococcus faecalis* levels exceeded recommended levels in 60% of the sampling sites, exceeding >200.5 CFU/100 ml on all days, and was not observed to occur in conjunction with high levels of rainfall. The high level of *enterococcus faecalis* could be attributed to the densely populated Carenage area which is a docking station for barges, cargo boats, and ships. Runoff from these facilities drains directly into the site. Studies have suggested *enterococcus faecalis* level increase in such areas [7, 19]. Low levels of *enterococcus faecalis* were observed with high levels of rainfall, which may have been due

to dilution of contaminated water. The LA samples exceeded recommended fecal coliform levels 60% of the sampling days when rainfall levels fell to low 1 on the same day and low to moderate on the previous day. Temperature on that bay ranged from 28.2-30.7°C. *Enterococcus faecalis* levels exceeded recommended levels in 40% of the sampling sites, exceeding >200.5 CFU/100 ml on 50% of those days and was not observed to occur in conjunction with high levels of rainfall. High level of *enterococcus faecalis* could be attributed to the highly developed commercial activities in the area as well as a docking station for barges, cargo boats, and ships. Runoff from facilities also drains directly into the site. Construction activities were noted to have occurred during that period [30]. Low levels of *enterococcus faecalis* were observed with high levels of rainfall, which may be due to the dilution of contaminated water, similar to the situation at CA. PA samples exceeded recommended fecal coliform levels 40% of the sampling days when rainfall levels fell at mostly low levels on the same day and low levels the previous day although one day was noted to produce heavy rainfall. Temperature at this bay ranged from 28.2-30.7°C. *Enterococcus faecalis* levels exceeded recommended levels in 20% of the sampling sites and were observed when rainfall levels fell at mostly low to moderate levels on the same day and low levels the previous day. A number of protective factors were present on this beach, including the high amount of flora and absence of drains emptying directly unto to beach.

GA samples (top, middle, and bottom) exceeded recommended fecal coliform levels in 40%, 10%, and 40% samples, respectively, when rainfall levels were at mostly low to high levels on the same day and low the previous day. Temperature at these sites ranged from 28.0-30.8°C (GAT), 28.3-30.4°C (GAM) and 28.2-30.2°C (GAB). *Enterococcus faecalis* counts exceeded recommended levels in 40% of the sampling sites GAB, GAM, and GAT. GAT and GAB, however, reported samples exceeding level >200.5 CFU/100ml in 40% and 20% of all samples, respectively. This was thought to be associated with drains which were observed to empty runoff directly into the swimming area of both sites (GAT and GAB) but were not present at GAM. There are several factors affecting this beach, including being frequently populated with tourists and local residents engaging in recreational activities.

BBC exceeded recommended fecal coliform levels on 20% of the sampling days when rainfall levels fell at mostly low levels on the same day and low levels the previous day, although one day was noted to produce heavy rainfall. The temperatures measured at this bay ranged from 28.2 -30.1°C. *Enterococcus faecalis* levels exceeded recommended levels in 20% of the sampling sites and did not occur in conjunction with high levels of rainfall.

PG exceeded recommended fecal coliform levels 30% of the sampling days, which was in conjunction with low to moderate rainfall the same day and low the previous day. Temperatures measured at this bay ranged from 28.5°-29.7 C. *Enterococcus faecalis* levels did not exceed recommended levels. This may be mostly due to the open bay and high flushing which may have carried contaminants away from the sample site.

Limitations of this study include possible errors in sample collection and preparation. These samples were collected over 12 years ago in 2008 and, therefore, it might be questioned whether the same results would be achieved today if a new batch of samples were collected. It should be noted that most of the factors that likely contributed to the observed high microbial levels, such as high levels of development and anthropogenic activity, have further increased over the years [31]. Additionally, the St. George's sewage outfall still releases untreated sewage and no major improvements in the quality of the water have been found [31, 32].

In conclusion, measurements of two recreational water quality indicators, fecal coliform and *enterococcus faecalis*, at 12 coastal sites located along the southwestern end of Grenada found results that exceed acceptable WHO recommended limits. The sampling site with the highest percentage of samples exceeding recommended levels was BB (70%), which is most likely due to sewage leakages from points along the river leading into this bay. Following BB were HA and CA (60%), LA GAT, GM, GAM, BBC, LA, and GAB (40%). FB (0%) had the best compliance with WHO's recommendations and had no samples that exceeded the recommended limits. The sampling site with the highest levels of fecal coliform was CA (60%), followed by GAT, GAB, GM and LA (40%), PG (30%), BBC (20%), and PB, BB, HA, PB (10%), respectively. The amount of rainfall and *enterococcus faecalis* was shown to have a negative association, possibly due to several factors affecting site flushing and protective mechanisms. Due to inconsistencies in the correlations between rainfall and microbial contamination, it is recommended that water quality monitoring systems be put in place to ensure that persons frequenting the beaches located along the southwestern coast are made aware of the safe days for swimming in these areas. Given that this study was done within an approximate one-month time period, this assessment should be replicated, extending over other months of the year, which can allow for a better assessment of the relationship between rainfall and microbial indicators. Additionally, an extended period of monitoring is necessary so that a comparative analysis can be done between the dry and wet seasons in Grenada. It is also anticipated that the data from this study will provide key information for the Government of Grenada on where best to install proper drainage systems to ameliorate the risk of contaminating coastal sites.

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Chapter 99

METABOLIC SYNDROME, ANXIETY, AND DEPRESSION IN ARUBAN ADULTS

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ABSTRACT

Metabolic syndrome is a collection of risk factors that include insulin resistance, dyslipidemia, visceral adiposity, and hypertension. Studies have shown contrasting results regarding its association with anxiety and depressive symptoms. The primary aim of this study was to evaluate the association of metabolic syndrome and the severity of anxiety or depression. Our objectives were to estimate the prevalence of anxiety and depression in Aruba. We conducted a cross-sectional study in Aruba in November 2016. Participants were assessed for metabolic syndrome using the harmonized criteria and were screened for depression and anxiety using the Patient Health Questionnaire-9 and the General Anxiety Disorder-7 questionnaires, respectively. We used the χ^2 test/Fisher's Exact test to compare proportions, and the unpaired t-test to compare continuous variables between groups. Statistical significance was reported at the 0.05 significance level. Our sample included a total of 181 participants, 103 (56.9%) of whom were women. A total of 67 (37.0%) people reported signs of anxiety, while 72 (39.8%) people reported signs of depression. In comparing metabolic syndrome status, there was a statistically significant difference for severity of anxiety ($p = 0.013$) but not for severity of depression ($p = 0.228$). The mean PHQ9 ($p = 0.027$) and the mean GAD7 ($p < 0.001$) scores were both significantly higher in people without metabolic syndrome. Participants with metabolic syndrome had decreased levels of anxiety and depression. There is a high prevalence of anxiety and depression in Aruba.

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INTRODUCTION

Metabolic syndrome (MetS) is a collection of risk factors that include insulin resistance, dyslipidemia, visceral adiposity, and hypertension [1]. Studies have shown there is a direct relationship with metabolic syndrome and the development of cardiovascular diseases [2] and type 2 diabetes mellitus [3]. Moreover, the risk of myocardial infarction and cerebrovascular disease triples in those with metabolic syndrome [3]. However, in addition to having an increased risk of cardiovascular diseases, metabolic syndrome has been shown to have an increased association of mood disorders, notably anxiety [4] and depressive symptoms [5]. Those with metabolic syndrome components manifest a low-moderate, chronic inflammatory state [6]. Concurrently, inflammation has been related to the development of some depressive disorders [7]. Other studies suggest that chronic systemic inflammation might explain the link between metabolic syndrome and anxious-depressive syndromes [6].

The relationship between mood disorders and metabolic syndrome has been considerably investigated. However, there are contrasting findings which are likely due to variation in sample demographics. Nonetheless, these investigations have shown to be commonly rooted in the correlation between mood and anxiety disorders with an increased risk of cardiovascular morbidity and mortality [8]. In addition, a study by Ellouze et al. showed that patients with type 2 diabetes and depression displayed poorer glycemic control and less medication compliance as compared to those without concurrent depression [9]. Thus, there may be other clinical implications relating to pharmacological treatment of patients with metabolic syndrome components and mood disorders. Therefore, a better understanding of the relationship between metabolic syndrome and anxiety or depression can potentially target their etiologies and consequently, provide a foundation for the development of novel therapies.

The primary aim of this study was to evaluate the association of metabolic syndrome and the different levels of severity of anxiety or depression in a sample of Aruban adults. Our objectives were to screen participants with the General Anxiety Disorder-7 [10] questionnaire and the Patient Health Questionnaire-9 [11] to estimate the prevalence of anxiety and depression, respectively. We hypothesized that there would be a positive association between metabolic syndrome and increasing levels of severity of anxiety and depression.

OUR STUDY

This study was approved by the institutional review board of Xavier University School of Medicine, Aruba. Written informed consent was obtained from all study participants. A cross-sectional study was conducted at Xavier University School of Medicine, in November 2016, during its Annual Health Fair.

The health fair was held at the campus of Xavier University School of Medicine, from 7 AM to 11 AM. Participants were recruited by announcements on local radio and television, and by flyers posted at popular supermarkets four weeks before the event.

We collected data on sociodemographic variables, health behaviors, depression, anxiety, and metabolic syndrome by using a structured questionnaire. The interviews were conducted in English, Papiamentu, and Spanish. Occupation was based on the International Standard for

Classification of Occupations (ISCO-08) [12] and was grouped as professionals, skilled workers, unemployed, and retired.

Assessment of Depression and Anxiety

We screened participants for depression and anxiety with the Patient Health Questionnaire-9 (PHQ9) [11] and the General Anxiety Disorder-7 (GAD7) [10] questionnaires, respectively. Participants were asked whether they had experienced symptoms of depression or anxiety within the past two weeks. Depression and anxiety were categorized as mild, moderate, or severe, using the cut-off points of 5, 10, and 15, respectively.

Assessment of Metabolic Syndrome

Metabolic syndrome was defined according to the harmonized clinical criteria [1] which require that at least three of the following five criteria have to be met: fasting plasma glucose (≥ 100 mg/dL and or diabetes medication), triglycerides (≥ 150 mg/dL and or drug treatment for elevated triglycerides), HDL cholesterol (< 40 mg/dL in males and < 50 mg/dL in females and or drug treatment for reducing HDL cholesterol), blood pressure (systolic ≥ 130 mm Hg and or diastolic ≥ 85 mm Hg and or use of antihypertensive medication), and waist circumference (ethnicity and country-specific cut-off; we used the International Diabetes Federation [13] cut-offs for Euroid: 94 cm for men and 80 cm for women). If patients had met the criteria for metabolic syndrome, they were contacted by the laboratory with the results and were recommended to visit their health care provider.

Measurements and Biochemical Analyses

Waist circumference was measured with a soft tape, on standing subjects, at the level of the umbilicus. Blood pressure was measured on the right arm using a manual mercury sphygmomanometer after the subject had rested for 10 minutes. Systolic and diastolic blood pressures were recorded as the first and last Korotkoff sounds, respectively.

Venous blood samples were taken from the antecubital vein after an overnight fast (participants were advised to fast overnight) and serum total cholesterol was measured by standard enzymatic assays within 4 hours of collection. Blood glucose level was measured using a glucometer (ACCU-CHEK® Active strips in Accu-Chek® Active test meter, Roche Diagnostics, Germany).

Statistical Analyses

Data were analyzed using SPSS version 24 (IBM Corp., Armonk, NY, USA). Descriptive statistics (mean $\pm$ standard deviation [SD] or percentages) were computed for socio-demographic factors and the prevalence of metabolic syndrome according to the severity of

depression and anxiety. We used the unpaired *t*-test to compare continuous variables and the χ^2 test/ Fisher's Exact test to compare proportions between groups. Statistical significance was reported at the 0.05 significance level.

FINDINGS

Our sample included a total of 181 participants, 103 (56.9%) of whom were women. Most of the participants (38.1%) were between the ages of 51-70 years. Hispanics comprised 51.4% of the sample. Metabolic syndrome was present in 21.5% of the participants. A total of 67 (37.0%) people showed signs of anxiety, of which 13 (7.2%) of them had severe anxiety. Similarly, 72 (39.8%) people showed signs of depression, 11 (6.1%) of whom met the criteria for severe depression. Detailed characteristics of the sample are shown in Table 1.

Table 1. Sociodemographic characteristics of the study participants (n=181)

Variables	
Sex, n (%)	
Men	78 (43.1)
Women	103 (56.9)
Age, n (%)	
18 – 30	32 (17.7)
31 – 50	42 (23.2)
51 – 70	69 (38.1)
≥ 71	38 (21.0)
Race, n (%)	
Hispanic	93 (51.4)
Caucasian	8 (4.4)
Mixed	21 (11.6)
Other	59 (32.6)
Occupation, n (%)	
Professional	50 (27.6)
Skilled	49 (27.1)
Unemployed	41 (22.7)
Retired	41 (22.7)
Education, n (%)	
High school	95 (52.5)
Undergraduate	38 (21.0)
Graduate	23 (12.7)
Other	25 (13.8)
Exercise, n (%)	
No regular exercise	60 (33.1)
1-2 hours/ week	55 (30.4)
>2 hours/ week	66 (36.5)
Alcohol consumption, n (%)	
Never	101 (55.8)
Current	80 (44.2)
Smoking, n (%)	
Never	164 (90.6)
Current	17 (9.4)
Metabolic syndrome, n (%)	
Yes	142 (78.5)
No	39 (21.5)

Variables	
Anxiety, n (%)	
None	114 (63.0)
Mild	35 (19.3)
Moderate	19 (10.5)
Severe	13 (7.2)
Depression, n (%)	
None	109 (60.2)
Mild	45 (24.9)
Moderate	16 (8.8)
Severe	11 (6.1)

Table 2. Metabolic syndrome, anxiety, and depression

Variables	MetS	No MetS	p values
Sex, n (%)			0.423
Women	20 (19.4)	83 (80.6)	
Men	19 (24.4)	59 (75.6)	
Age, n (%)			<0.001
18 – 30	1 (3.1)	31 (96.9)	
31 – 50	2 (4.8)	40 (95.2)	
51 – 70	20 (29.0)	49 (71.0)	
>70	16 (42.1)	22 (57.9)	
Race, n (%)			0.989
Hispanic	20 (21.5)	73 (78.5)	
Other	19 (21.6)	69 (78.4)	
Education, n (%)			0.066
High school	23 (24.2)	72 (75.8)	
Undergraduate	5 (13.2)	33 (86.8)	
Graduate	2 (8.7)	21 (91.3)	
Other	9 (36.0)	16 (64.0)	
Occupation, (%)			0.004
Professional	9 (18.0)	41 (82.0)	
Skilled	6 (12.2)	43 (87.9)	
Unemployed	7 (17.1)	34 (82.9)	
Retired	17 (41.5)	24 (58.5)	
Exercise, n (%)			0.728
No regular exercise	15 (25.0)	45 (75.0)	
1 - 2 hours/ week	11 (20.0)	44 (80.0)	
> 2 hours/ week	13 (19.7)	53 (80.3)	
Smoking, n (%)			0.764
Never	35 (21.3)	129 (78.7)	
Current	4 (23.5)	13 (76.5)	
Alcohol, n (%)			0.204
Never	18 (17.8)	83 (82.2)	
Current	21 (26.3)	59 (73.8)	
Depression, n (%)			0.228
None	27 (24.8)	82 (75.2)	
Mild	10 (22.2)	35 (77.8)	
Moderate	2 (12.5)	14 (87.5)	
Severe	0 (0.0)	11 (100.0)	
Anxiety, n (%)			0.013
None	33 (28.9)	81 (71.1)	
Mild	4 (11.4)	31 (88.6)	
Moderate	2 (10.5)	17 (89.5)	
Severe	0 (0.0)	13 (100.0)	
PHQ9, mean ($\pm$ SD)	3.41 (3.52)	5.05 (5.52)	0.027
GAD7, mean ($\pm$ SD)	2.38 (2.70)	5.35 (5.62)	<0.001

Participants who were 50 years and older were more likely to have metabolic syndrome. There was no association between metabolic syndrome and sex, race, or education. In comparing metabolic syndrome status, there was a statistically significant difference for age ($p < 0.001$), occupation ($p = 0.004$), and severity of anxiety ($p = 0.013$).

However, there was no statistically significant difference for severity of depression ($p = 0.228$) based on metabolic syndrome status. Of patients who had metabolic syndrome, 30.8% of them had depression, whereas 42.2% of those who did not have metabolic syndrome had depression. Patients who had metabolic syndrome were less likely to have anxiety (15.4%) compared to those who did not have metabolic syndrome (43.0%). Interestingly, as severity of both anxiety and depression increased, participants had a lower likelihood of having metabolic syndrome. In fact, 100% of participants who had severe anxiety or depression were free from metabolic syndrome. In addition, the mean PHQ9 ($p = 0.027$) and the mean GAD7 ($p < 0.001$) scores were both significantly higher for those without metabolic syndrome when compared to those with metabolic syndrome. Results are shown in Table 2, and Figures 1 and 2.

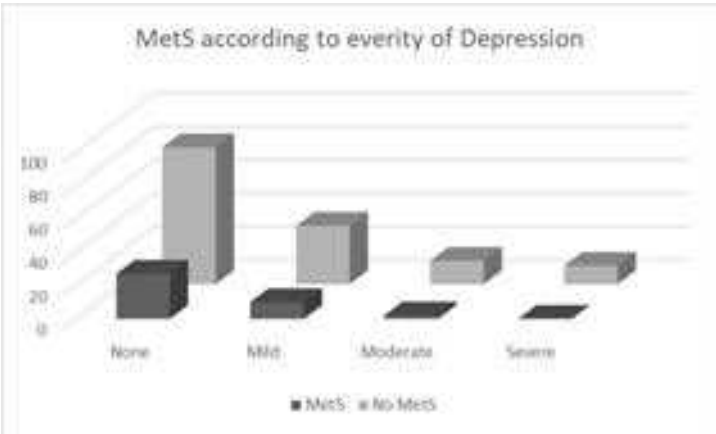


Figure 1. Prevalence of metabolic syndrome according to severity of depression.

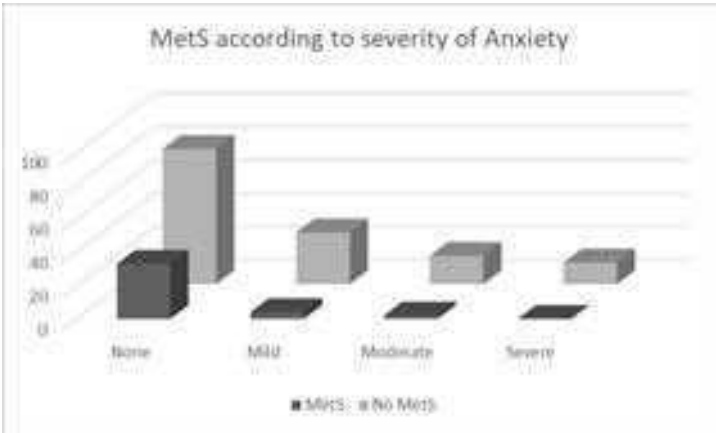


Figure 2. Prevalence of metabolic syndrome according to severity of anxiety.

DISCUSSION

To the best of our knowledge, this is the first study in Aruba to investigate the association between metabolic syndrome and anxiety or depression. Our results showed that anxiety and depression were both associated with metabolic syndrome reciprocally, contrary to expectation, wherein we hypothesized that there is a positive association.

In contrast to previous studies [14, 15], we found that anxiety and depression were more prevalent in participants without metabolic syndrome. Our results were similar to those of Glaus et al. [16], Herva et al. [17] and García-Toro et al. [18], even though their study samples were comprised of different demographics. A meta-analysis of eighteen cross-sectional studies showed that there was a slight increase in anxiety in patients with metabolic syndrome, with a pooled odds ratio of 1.07 (95% CI 1.01-1.12) [4]. Of significance, in this study, we screened participants for anxiety with the GAD-7 questionnaire [10] and for depression with the PHQ-9 questionnaire [11]. Both of these scales assess for anxiety or depression within two weeks of presentation. However, most of the studies in the meta-analysis [4] utilized the Spielberger Trait Anxiety Inventory (STAI) [19] and the Hospital Anxiety and Depression Scale (HADS) [20] for assessing anxiety. Nevertheless, there were inconsistent findings with these scales, even though both the STAI and HADS have more items compared to the GAD-7 or PHQ-9.

Our study showed that 37.0% of the participants had some level of anxiety, and 38.9% of participants had some level of depression. These are relatively high rates when compared to other studies on anxiety [21] and depression [22] in Latin America and the Caribbean. Even though our study found no significant association between metabolic syndrome and symptoms of depression, this might be accounted for by the lack of distinction of depression subtypes. Previous research emphasizes the importance of subtyping depression. Specifically, there have been significant findings with atypical depression and substance misuse [16].

The reciprocal association for metabolic syndrome and anxiety or depression in our study is not clearly understood. We suggest conducting large-scale longitudinal studies to investigate these relationships. However, one possible explanation for the positive association of metabolic syndrome and anxiety is the increase in sympathetic firing which, in turn, leads to an increase of metabolic syndrome components, such as hypertension and insulin resistance [23]. In interpreting the contradictory findings between metabolic syndrome and anxiety or depression, we should consider the varying diagnostic criteria for metabolic syndrome, and the different instruments utilized to measure the symptoms of anxiety and depression. Unlike the other studies, we used the Harmonized criteria [1] to establish the presence of metabolic syndrome. Furthermore, the varying demographics of sample populations in the different studies should also be taken into consideration.

An important strength of this study is seen in the reliability and reproducibility through use of the GAD-7 [24] and PHQ-9 [25]. Recruitment of the sample via media announcements and flyers in catchment areas optimized a randomly diverse group. The cross-sectional design eliminated the common obstacle of diminished participant retention. However, our study has constraints due to limitations of statistical power and the possibility of self-selection bias, as our data was collected at a health fair. In addition, the GAD-7 and PHQ-9 are not intended to reflect a diagnosis but were used as screening tools to detect symptoms of anxiety or depression within a narrow window. Moreover, the dynamics of our cross-sectional study

design does not allow for elucidation on cause and outcome for our study variables, notably metabolic syndrome and anxiety or depression.

In conclusion, the prevalence of anxiety and depression in Aruba is relatively high. Participants with metabolic syndrome had decreased levels of anxiety and depression. However, only anxiety and metabolic syndrome showed a significant statistical association. Future research should concentrate on comprehensive measures within large populations, thus allowing for isolation of variables, specifically anxiety/depression comorbidity as well as subtypes for both disorders. Conducting a longitudinal study would prove beneficial to explore the bidirectional association between metabolic syndrome and anxiety or depression. In addition, screening for depression and anxiety disorders is recommended in Aruba, which can lead to improved clinical care and implications for public health.

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Chapter 100

PREVALENCE OF METABOLIC SYNDROME AND OBESITY AMONG ADULTS IN ARUBA

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ABSTRACT

According to global data, the estimated prevalence of metabolic syndrome (MetS) in adults ranges from 11.9% in the Philippines to 43.3% in Puerto Rico. This study investigated the prevalence of MetS and obesity in Aruba. We hypothesized that there would be a relatively high prevalence of MetS and obesity in Aruba. We conducted a cross-sectional study in 2016. Data were collected on adults between the ages of 18 and 91 years during a Free Health Fair. Data collection methods included taking anthropometric measurements, blood pressure, and fasting blood glucose from the participants. Descriptive statistics were computed for socio-demographic variables, clinical characteristics, and the prevalence of MetS and obesity. The independent samples t-test was used to compare continuous variables, and the χ^2 test was used to compare proportions between groups. The overall prevalence rate of MetS in our sample was 21.5%, with men (24.4%) having a slightly higher prevalence rate than women (19.4%). Notably, 40.9% of the participants had pre-obesity (BMI: 25–29.9) and 32.6% were obese (BMI ≥ 30), giving rise to 73.5% of the sample having a BMI ≥ 25 . Our results have shown that metabolic syndrome and obesity are highly prevalent among adults in Aruba. Preventive measures should be taken to curtail these chronic conditions. In addition, patients with a body mass index higher than 25 should be screened for metabolic syndrome.

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INTRODUCTION

Metabolic syndrome (MetS) is defined as a cluster of metabolic disorders with features of visceral obesity, elevated blood pressure, hyperglycemia/ insulin resistance, and atherogenic dyslipidemia (elevated triglycerides and decreased high density lipoprotein cholesterol levels [1]. According to global data, the estimated prevalence of metabolic syndrome in adults ranges from 11.9% in the Philippines [2] to 43.3% in Puerto Rico [3].

In the United States (US) the prevalence of MetS in adults has substantially increased in the past decade, averaging approximately 34% between 2007–2012 [4]. In the Caribbean region, the prevalence is estimated to be 21.1% in Jamaican adults [5] and 20.5% in adults of Saint Croix, US Virgin Islands [6]. To date, there is no published data on the prevalence of MetS in Aruba. However, recent studies on the prevalence rates for MetS in cities in nearby countries were reported as 34.8% in Bucaramanga, Colombia [7], and 35.3% in Zulia, Venezuela [8]. The prevalence rates reported above were based on the definition of MetS according to the National Cholesterol Education Program's Adult Treatment Panel III criteria (NCEP ATP III) [9], one of several definitions of MetS.

MetS has become a significant worldwide problem and it is associated with increased risk of cardiovascular disorders and all-cause mortality [10, 11] type 2 diabetes mellitus [12] and the most common types of cancers [13]. Risk factors for developing MetS include obesity, visceral adiposity [14], and insulin resistance [15]. With the increasing pandemic of obesity [16], there is a parallel increase in MetS [17].

The primary aim of this study is to determine the prevalence of MetS and obesity in Aruba. We hypothesized that there will be a high prevalence of MetS and obesity in the country.

OUR STUDY

We conducted a cross-sectional study during a one-day free health fair in Oranjestad, Aruba, in November 2016. The main purpose of this study was to assess the prevalence of metabolic syndrome and obesity among adults in Aruba.

Assessment of Metabolic Syndrome

We used the harmonized clinical criteria [1] to define metabolic syndrome, which requires that at least three of the following five criteria have to be met: fasting plasma glucose (≥ 100 mg/dL and or diabetes medication), triglycerides (≥ 150 mg/dL and or drug treatment for elevated triglycerides), HDL cholesterol (< 40 mg/dL in males and < 50 mg/dL in females and or drug treatment for reducing HDL cholesterol), blood pressure (systolic ≥ 130 mm Hg and or diastolic ≥ 85 mm Hg and or use of antihypertensive medication), and waist circumference (ethnicity and country-specific cut-off; we used the International Diabetes Federation [18] cut-offs for Europid: 94 cm for men and 80 cm for women). Patients who had abnormal laboratory results were contacted by the laboratory and were recommended to visit their health care provider.

Study Population and Setting

The health fair was publicized on local radio and television, and on flyers at popular supermarkets four weeks before the event. The health fair was held at Xavier University School of Medicine from 7 AM to 11 AM. The study was approved by the institutional review board of Xavier University School of Medicine, Aruba, and all participants provided written informed consent.

Adults who attended the health fair were eligible to participate in the study. A structured questionnaire was used to collect data on age, sex, race, occupation, education, marital status, and self-rated health of the participants. Other questions included diagnosis of diabetes, hypertension, and hypercholesterolemia, family history of known metabolic syndrome in at least one first-degree relative (father, mother, or sibling). Interviews were conducted in English, Papiamentu, and Spanish.

Measurements and Biochemical Analyses

The three criteria used for the assessment according to the harmonized clinical criteria [1] were: measurement of waist circumference, measurement of blood pressure, and blood samples.

Waist circumference was measured with a soft tape, on standing subjects, at the level of the umbilicus. Bodyweight and height were measured with subjects in light clothing and without shoes. Body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared (kg/m^2) and grouped according to the World Health Organization (WHO) international classification [19].

Blood pressure was measured on the right arm using a manual mercury sphygmomanometer after the subject had rested for 10 minutes. Systolic and diastolic blood pressures were recorded as the first and last Korotkoff sounds, respectively.

Venous blood samples were taken from the antecubital vein after overnight fast, and serum total cholesterol was measured by standard enzymatic assays within four hours of collection. Blood glucose level was measured using a glucometer (ACCU-CHEK® Active strips in Accu-Chek® Active test meter, Roche Diagnostics, Germany).

Statistical Analyses

Due to a small sample size, race was grouped into Hispanic and Other (which included Caucasians, people of African ancestry, mixed-race, and other races).

Occupation was based on the International Standard for Classification of Occupations (ISCO-08) [20] and was grouped as professionals, skilled workers, unemployed, and retired. Professionals included groups 1-4 of ISCO-08 (managers; professionals; technicians and associate professionals; and clerical support workers) and skilled workers included groups 5-9 of ISCO-08 (service and sales workers; skilled agricultural, forestry and fishery workers; craft and related trades workers; plant and machine operators, and assemblers; and elementary occupations).

Descriptive statistics (mean $\pm$ standard deviation [SD] or percentages) were computed for socio-demographic variables, clinical characteristics, and the prevalence of MetS and obesity. We used the independent samples *t*-test to compare continuous variables and the χ^2 test to compare proportions between groups. All variables were reported as statistically significant at the 0.05 significance level. Analyses were performed using SPSS version 24 (IBM Corp, Armonk, NY, US).

FINDINGS

Detailed demographic and clinical characteristics are summarized in Table 1. A total of 181 participants were evaluated, in which there were 78 (43.1%) men and 103 (56.9%) women. There was a statistically significant difference between men and women regarding occupation ($p < 0.001$), exercise ($p = 0.019$), and alcohol consumption ($p = 0.01$). There was also a significant difference ($p = 0.01$) in waist circumference for men (100.1 cm [SD $\pm$ 17.8]) compared to women (93.8 cm [SD $\pm$ 14.4]).

Table 1. Demographic characteristics of the study participants (N = 181)

Variables	Men	Women	Values
Age, years, mean (SD)	55.7 (18.3)	50.8 (19.2)	0.086
Race, n (%)			0.150
Hispanic	32 (34.4)	61 (65.6)	
Other	46 (52.3)	42 (47.7)	
Occupation, n (%)			< 0.001
Professional	21 (42.0)	29 (58.0)	
Skilled	26 (53.1)	23 (46.9)	
Unemployed	6 (14.6)	35 (85.4)	
Retired	25 (61.0)	16 (39.0)	
Education, n (%)			0.609
High school	45 (47.4)	50 (52.6)	
Undergraduate	14 (36.8)	24 (63.2)	
Graduate	10 (43.5)	13 (56.5)	
Other	9 (36.0)	16 (64.0)	
Diabetes, n (%)			0.293
Yes	16 (51.6)	15 (48.4)	
No	62 (41.3)	88 (58.7)	
Hypertension, n (%)			0.390
Yes	53 (41.1)	76 (58.9)	
No	25 (48.1)	27 (51.9)	
Hypercholesterolemia, n (%)			0.173
Yes	21 (52.5)	19 (47.5)	
No	57 (40.4)	84 (59.6)	
Exercise, n (%)			0.019
No regular exercise	26 (43.3)	34 (56.7)	
1-2 hours/week	16 (29.1)	39 (70.9)	
>2 hours/week	36 (54.5)	30 (45.5)	
Alcohol consumption, n (%)			0.010
Never	33 (32.7)	68 (67.3)	
Current	45 (56.3)	35 (43.8)	
Smoking, n (%)			0.729
Never	70 (42.7)	94 (57.3)	
Current	8 (47.1)	9 (52.9)	
Family history of obesity, n (%)			0.845
Yes	23 (44.2)	29 (55.8)	
No	55 (42.6)	74 (57.4)	

Variables	Men	Women	Values
Metabolic syndrome, n (%)			0.423
Yes	19 (48.7)	20 (51.3)	
No	59 (41.5)	83 (58.5)	
Body mass index, kg/m ²	28.8 (5.2)	28.0 (5.7)	0.350
Body mass index, kg/m ² , n (%)			0.266
18 – 24	20 (41.7)	28 (58.3)	
25 – 29	29 (39.2)	45 (60.8)	
30 – 34	17 (50.0)	17 (50.0)	
35 – 39	10 (62.5)	6 (37.5)	
> 40	2 (22.2)	7 (77.8)	
Waist circumference, cm	100.1 (17.8)	93.8 (14.4)	0.010
Waist-hip-ratio	0.982 (0.152)	0.998 (0.724)	0.866
FBG	106.9 (62.2)	98.7 (30.4)	0.273
Blood pressure, mmHg			
Systolic	129.0 (9.8)	125.5 (14.6)	0.098
Diastolic	81.3 (9.9)	80.6 (9.7)	0.641

Table 2. Prevalence of metabolic syndrome according to BMI categories

Variables	Normal Weight	Pre-obesity	Obesity	P values
Sex				0.468
Men	5.0	31.0	31.0	
Women	3.6	15.6	40.0	
Age				
18 – 30	5.6	0.0	0.0	< 0.001
31 – 50	0.0	5.0	8.3	
51 – 70	7.7	30.8	36.7	
>70	0.0	36.8	75.0	
Race				1.000
Hispanic	6.9	20.0	41.7	
Other	0.0	23.5	31.4	
Education				0.066
High school	4.5	25.0	36.4	
Undergraduate	0.0	5.9	28.6	
Graduate	0.0	12.5	25.0	
Other	12.5	44.4	50.0	
Occupation				0.008
Professional	0.0	19.0	33.3	
Skilled	0.0	0.0	35.3	
Unemployed	14.3	23.5	10.0	
Retired	0.0	50.0	52.9	
Diabetes				< 0.001
Yes	20.0	41.7	85.7	
No	2.3	17.7	20.0	
Hypertension				< 0.001
Yes	16.7	21.1	66.7	
No	2.4	21.8	9.4	
Hypercholesterolemia				0.190
Yes	0.0	18.8	45.0	
No	4.5	22.4	30.8	
Exercise				0.766
No regular exercise	7.1	22.2	42.1	
1 - 2 hours/ week	0.0	24.0	27.8	
> 2 hours/ week	4.5	18.2	36.4	
Smoking				0.764
Never	2.4	19.7	36.8	
Current	14.3	37.5	0.0	
lcohol				0.204
Never	5.9	16.7	32.3	
Current	0.0	26.3	39.3	

The overall prevalence rate of MetS in our sample was 21.5%, with men (24.4%) having a slightly higher prevalence rate than women (19.4%). Notably, 40.9% of the participants had pre-obesity (BMI 25–29.9) and 32.6% were obese (BMI ≥ 30), giving rise to 73.5% of the sample having a higher than normal body mass index (BMI ≥ 25).

The prevalence of MetS in the different BMI categories according to WHO's classification [19] are presented in Table 2. Our data showed that there was a statistical difference in the prevalence rates of MetS among the different BMI categories regarding age ($p < 0.001$), occupation ($p = 0.008$), and the presence of diabetes ($p < 0.001$) and hypertension ($p < 0.001$).

Figure 1 shows that the prevalence of MetS is higher for both men and women who have a BMI greater than 25. However, even though there is no linear trend with prevalence of MetS and increasing BMI levels, there is an increased prevalence of MetS with increased severity of obesity for men. This pattern was not observed for women. Interestingly though, half of the men and half of the women with moderate obesity (BMI 35.0 – 39.9) had MetS and 100% of the men and 42.9% of the women with severe obesity had MetS.

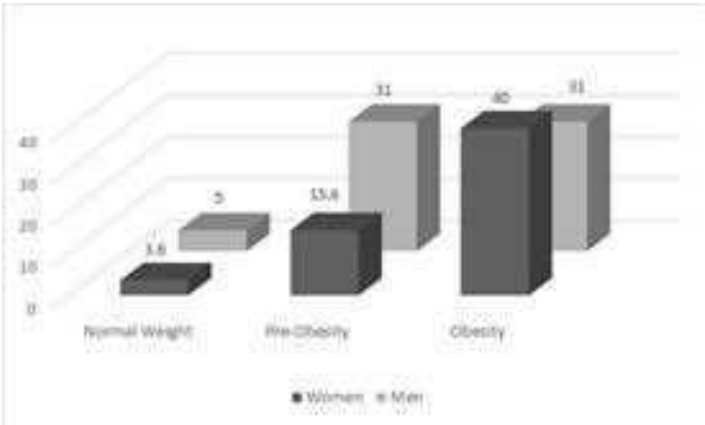


Figure 1. Prevalence of metabolic syndrome in BMI categories.

DISCUSSION

To our knowledge, this is the first study to assess the prevalence rate of metabolic syndrome (MetS) in Aruba. Results from this study confirmed our hypothesis that Aruba has a high prevalence of MetS and obesity among adults. This high prevalence of MetS in Aruba is supported by data from previous studies with similar demographics [21]. In addition, findings from our study corroborated with the prevalence rates of obesity from global data, especially those of the United States and countries in Latin America [22]. We found that the prevalence of MetS was slightly higher among men. However, among the obese, women had a higher prevalence of MetS. Our results also showed that increasing age was a significant predisposing factor for developing MetS. Individuals over the age of 70 years showed a drastic increase in risk. However, our results differed from a study by Florez et al. [8], which showed that the 50-59 years old age group had the highest proportion of MetS.

The prevalence of MetS was disproportionate among the different occupational groups. Of particular interest, those who were retired and having a BMI greater than 25 were more likely to have MetS. Thus, a sedentary lifestyle may have contributed to having an increased prevalence of both obesity and MetS. However, a study by Browne et al. [23] showed that those who have a sedentary occupation but have met the requirements for physical activity have a reduced risk of developing MetS. However, on closer examination, we did not find a significant association between occupation and exercise.

Our results clearly show that the prevalence of MetS was independently associated with pre-obesity and obesity, hypertension, and diabetes. Thus, these findings suggest the importance of screening patients with diabetes, hypertension, and BMI greater than 25 for metabolic syndrome. Årnlöv et al. showed that insulin resistance, higher BMI levels, and MetS had higher incidence rates of cardiovascular events [24].

The following methodological considerations have to be taken into account when interpreting our findings: firstly, the sampling approach was self-selection and, therefore, may not be representative of the entire population. Thus, the prevalence rate obtained in our study may not reflect the true prevalence rate for MetS in Aruba. However, our study may have underestimated the actual prevalence of MetS in Aruba because of the following reasons: we used the International Diabetes Federation cut-offs of waist circumference for Europid: 94 cm for men, instead of 90 cm, which is the suggested value for Ethnic Central and South American. Our sample comprised of 17.8% Hispanic men. In addition, biological measurements were obtained for fasting total cholesterol only, and not for triglycerides or HDL cholesterol levels. Thus, these criteria were not assessed in our diagnosis of MetS. Moreover, a study by Tull et al. [6] showed that Hispanic ethnicity was associated with an increased risk of MetS, high triglycerides, and low HDL-C. Secondly, our sample size was relatively small and may not have adequate statistical power.

We recommend that a population-based study with a larger sample size should be conducted to confirm our findings and to determine the country-wide prevalence of MetS in Aruba. The 51-70 years and >70 years age categories reported the highest level of MetS. In addition, those who were retired, had diabetes, and hypertension were at increased risk of MetS. Therefore, we suggest that people with these demographics should be screened for MetS. We also recommend having more health fairs and health-outreach programs for the people of Aruba. One of the benefits of health fairs is the increased likelihood of screening for chronic conditions, such as MetS, in individuals who may not otherwise get tested, due to their occupation or socioeconomic status.

CONCLUSION

In conclusion, our results have shown that metabolic syndrome and obesity are highly prevalent in the Aruban adult population. Preventive measures should be taken to curb these chronic and debilitating conditions. In addition, patients with a body mass index higher than 25 should be screened for metabolic syndrome.

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Chapter 101

OVERWEIGHT AND OBESITY AMONG GRENADIAN ADOLESCENTS

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ABSTRACT

In this chapter, we examine the prevalence of overweight and obesity among a representative sample of Grenadian adolescents. Recent studies have been equivocal on the degree to which the obesity epidemic has affected Grenada with high rates of overweight and obesity among Grenadian adults. A nationally representative sample of first-year students (i.e., Form 1) (n = 689) aged 11 to 14 years old from the twenty-three secondary schools in Grenada was assessed as part of the Grenada School Nutrition Study (GSNS). Height and weight were objectively assessed using standard measures. Standardized BMI percentile (BMIz score) was calculated using the Centers for Disease Control and Prevention (CDC) criteria. BMIz scores above the 85th percentile were classified as overweight and BMIz scores above the 95th percentile were classified as obese. Overall Grenadian adolescents have low rates of overweight (17.6%) and obesity (7.6%). Girls had nearly twice the rates of overweight compared to boys (i.e., 22.7% versus 12.2%) but similar rates of obesity (i.e., 8.2% versus 6.8%). Grenadian adolescents demonstrate low rates of obesity compared to both Grenadian adults and their

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US counterparts. This discrepancy in overweight and obesity between Grenadian adults and adolescents suggest Grenada is undergoing an epidemiologic transition with regard to the obesity epidemic.

INTRODUCTION

The two overarching goals of the Healthy People 2010 initiative are to 1) increase quality and years of healthy life and 2) eliminate health disparities. The rising prevalence of overweight and obesity (OW/OB) represents the primary threat to the achievement of these goals in the coming years [1-4]. Despite the growing awareness of the negative health impact of poor diet, physical inactivity, and excess weight, the prevalence of OW/OB has continued to increase in the United States (US) [2, 5]. During the last three decades, according to national surveys (i.e., NHANES), the US obesity rate has doubled in adults and tripled in children and adolescents and is leading to growing disparities in obesity risk among poor and minority populations [6-9]. The consensus among public health experts is that human genetic changes are not responsible for the rapid rise in obesity, and the explanation must lie in broad social determinants resulting in local environmental exposures that influence diet and physical activity [10-13].

Despite researchers having literally watched the epidemic of obesity unfold over the past three decades, not only in the US but across the globe, identification of the “drivers” of the epidemic remains contentious [14-16]. The effort to characterize the “drivers” of the epidemic involves the identification of the factors responsible for upsetting the balance in the “energy intake/energy expenditure” equation over the past four decades. On the energy intake side, the global food system that provides a “Westernized” diet of cheap, palatable, energy dense-foods is implicated [14, 16, 17]. On the expenditure side, the transition to sedentary occupations with low energy expenditure is implicated [18, 19]. The inability to arrive at a consensus is attributed to the lack of research with designs sufficient to link local obesogenic environments - created by the societal drivers - with individual obesity-related behaviors [20-22].

The chance for characterizing the factors that “drove” the epidemic in the US over the past decades is gone. Even retrospective studies of dietary trends raise more questions than they answer, and they do not get at the role of obesogenic environments [23]. Consequently, research on the drivers of the pandemic of obesity requires a study among a population that has not yet undergone the epidemiologic transition. According to the World Health Organization’s (WHO) “Burden of disease” (GBD) approach, it is projected that non-communicable diseases (NCDs) will represent the greatest disease burden in low- and middle-income countries (LMIC) by 2030 [24, 25]. The onset of NCDs, including cardiovascular disease, diabetes, and cancer represents an epidemiologic transition that is attributed to the emergence of local obesogenic environments [26-28]. In addition, the epidemiologic transition in LMIC is believed to be occurring at a much faster rate due to the globalization of the corporate food infrastructure.

The current study was organized to determine the degree to which the epidemiologic transition with regard to obesity has affected Grenadian adolescents. A recent study by the CDC indicated the obesity epidemic has already impacted Grenadian adults. Consequently, it could be assumed that Grenadian adolescents were already also affected by the epidemic.

OUR STUDY

The current study is part of a project titled the Grenada School Nutrition Study (GSNS). The GSNS goal is to identify behavioral and environmental factors that might be intervened on to prevent the development of obesity among Grenadian adolescents.



Figure 1. Map of Grenada demonstrating location of the 23 GNS schools.

Study Sample

The GSNS was designed to be a representative sample of all first-year secondary students (i.e., Form 1) drawn from the 23 public and private secondary schools across the tri-island nation of Grenada. Form 1 students range in age from 11 to 14 years. Randomization was performed at the classroom level resulting in an eligible sample of 1,004 students in 35 classrooms (i.e., in schools with only one Form 1 class all students were included) making up roughly 55% of all Form 1 students in Grenada. Parental refusals ($n=276$) and students who were absent on the day or did not complete all the assessments or surveys ($n=39$) resulted in an effective sample of 689 students in the cohort. All students were assigned a unique identifier linked to their informed consent signed by their parents. Personal identifiers in the form of parents' names, phone numbers, and school identification were collected for possible followup.

Study Measures

Height, weight, and waist circumference were directly measured for each student in a privatized setting (e.g., trifold blind booth) in normal school clothing. Measurements using a portable stadiometer and electronic scale standardized before each session were repeated three times, and the average score reported.

Body mass index (BMI), calculated by dividing weight in kilograms by their height in meters squared, was used to assess excess body fat. Due to the greater sensitivity of the CDC classification system compared with the International Obesity Task Force (IOTF) classification system for characterizing excess body fat in a Caribbean adolescent population, the CDC age- and sex-specific cutoffs were used to characterize overweight (i.e., BMI≥85th percentile) and obese (i.e., BMI≥95th percentile) adolescents in terms of their standardized percentile [29].

Rural and urban designations were defined at the school level. Students attending school in the two largest towns in Grenada (i.e., St Georges and Grenville) were defined as urban students.

Statistical Analysis

Multilevel models of students nested within schools were developed to characterize the overall and between school prevalence of overweight and obesity across Grenada. For this descriptive analysis, demographic measures including age, and gender were included in the analyses.

The basic multilevel models used a random coefficient for the intercept. Thus, at student level, we have the following model,

$$Y_{ij} = \pi_{0j} + \pi_1(\text{Gender})_{1ij} + \pi_2(\text{Age})_{2ij} + \varepsilon_{ij} \qquad \text{Level 1}$$

where Y_{ij} is the outcome (e.g., obesity related behavior measurements or BMI z-score) for student i in school j . π_{0j} is the intercept, which we allowed to randomly vary across schools, which also is the estimated mean response for school j . We assume fixed effects for a vector of student level risk factors. ε_{ij} is the random effect of student i in school j , which is assumed to have normal distribution mean 0 and constant variance σ^2 for $i = 1, \dots, n_j$ and $j=1, \dots, 23$.

Table 1. BMIz scores for Grenadian adolescents by gender in the GSNS

	BMIz ≥ 95th	BMIz ≥ 85th
All	7.4%	16.6%
Male	6.8%	12.2%
Female	8.1%	21.4%

Note: Bolded prevalences are significantly different at $p < 0.05$.

The intercept π_{0j} , is allowed to randomly vary across all schools. Therefore, at the school level, we have the following model:

$$\pi_{0j} = \beta_{00} + u_{0j} \qquad \text{Level 2 (random intercept)}$$

FINDINGS

The overall rate of overweight and obesity among Grenadian adolescents in the first year of secondary schools was 16.6% and obesity 7.4%, respectively (see Table 1). There was significant sexual dimorphism in the rate of overweight Grenadians with females at greater risk than males (i.e., 21.4% versus 12.2%). The differences in obesity were not significantly different.

With regard to the difference in rates of OW/OB between adolescents attending rural versus urban schools there appeared to be significant differences in obesity rates such that urban students evidenced significantly higher rates of OW/OB compared with rural students (20.44% versus 13.43%) (see Table 2).

Table 2. Descriptive statistics for adolescents in GSNS schools by rural and urban areas

	N	Overall	Rural (N=283)	Urban (N=406)
Demographics				
Age, years	689	12.67	12.81	12.57
Race-Afro Caribbean, %	689	83.31	89.05	79.31
Gender, male%	689	48.91	55.83	44.09
Outcomes				
BMIz > 85 th , %	689	17.56	13.43	20.44

Note: Bolded prevalences are significantly different at $p < 0.05$.

An empty multilevel model (i.e., Model 1, see Table 3) with obesity risk as the outcome yielded an intraclass correlation coefficient of 0.037, indicating that 3.73% of the variance in obesity rates was between schools. Adding age and gender into the model explained most of the school level effect (see Table 3, Model 2). Adding whether or not the school was in an urban or rural area did not significantly predict obesity risk and only explained a small amount of the school level effect (see Table 3, Model 3). Finally, including age and gender in the model explained most of the urban-rural effect suggesting the greater risk of obesity in urban schools was primarily due to the greater number of female students, who are at higher risk for obesity, in urban schools.

Table 3. Parameters estimates from multilevel models predicting obesity risk among 689 students nested within 23 schools

	Model 1	Model 2	Model 3	Model 4
Individual level Measures				
Age		-0.1234		-0.1142
Male		-0.3229		-0.3159
School level Measures				
Urban School			0.1861	0.1168
Random Effects				
School level effect u_{0j}	0.0511	0.0208	0.0475	0.0212
Individual level effect r_{ij}	1.3241	1.3116	1.3237	1.3112
Fit Statistics				
AIC	2172.2	2162.5	2172.5	2164.4

Note: Bolded coefficients are significantly different from 0 at $p < 0.05$.

DISCUSSION

The results document a low risk of overweight (i.e., 16.6%) and obesity among Grenadian adolescents despite significant sexual dimorphism in the rate of overweight Grenadian adolescents. Female adolescents have far greater risk of obesity compared to their male counterparts. Furthermore, it appears that the greater risk of obesity among the urban students is primarily due to the greater presence of female students in urban schools.

Since the study used the same growth curve cutoffs and procedures used for US adolescents in the NHANES, these rates of OW/OB can be compared with US adolescents. US black female and male adolescents of the same age had three (26.1% versus 8.1%) and four (25.4% versus 6.8%) times the rates of obesity (i.e., BMIz > 95th percentile) compared to their Grenadian counterparts, respectively [30]. With regard to overweight (i.e., BMIz > 85th percentile), US females and male adolescents had two (44.7% versus 21.4%) and three (38.8% versus 12.2%) times the rates compared with their Grenadian counterparts, respectively.

These findings are significant in that they seem to contradict a recent study by the CDC indicating the obesity epidemic has already impacted Grenadian adults. In the CDC study, Block and colleagues [31] found that among Grenadian adults, 42% of women and 17% of men were obese, and across all adult age groups the rate of OW/OB reached as high as 72%. These findings suggest that adolescents in Grenada will undergo a dramatic transition in their rates of OW/OB, such that prevalence among the current female adolescent group has the potential to rise from a current rate of OW/OB of 21% to nearly 72% as they transition to adulthood.

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Chapter 102

ACTIVE AGING: WINDREF'S SPORTS FOR HEALTH PROGRAM AMONG THE ELDERLY IN GRENADA, WEST INDIES

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ABSTRACT

Life expectancy in Grenada is expected to increase by 10% in the coming decade and, with it, a simultaneous increase in the demand on the healthcare system. Supportive environments and services need to be provided for the aging population and those with chronic diseases. In this chapter, we assess the impact of the Windward Island Research and Education Foundation (WINDREF) Sports for Health program on the physical, social, and mental well-being of the aging population in Grenada. A total of 23 participants aged 65 years and older (22 females, 1 male) were included in this cross-sectional study. A survey was administered at baseline in July 2017 and again after being enrolled in the Sports for Health program for a minimum of seven months and at the end of one year in July 2018. An adapted version of the RAND Health Survey was used. A statistically significant correlation was found between the following quality of life scales among participants: health vs. pain ($p = 0.013$), emotion vs. pain ($p = 0.009$), emotion vs. health ($p = 0.008$) and emotion vs. energy ($p = 0.022$). WINDREF's Sports for Health program has demonstrated that the quality of life characteristics for the aging population improved after participating. Although the sample size was small, the results showed important outcomes that indicate a benefit in community-based programs for the aging population. It also demonstrated the need to encourage more men to participate in such community-based programs.

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INTRODUCTION

Internationally, average life expectancy at birth in 1960 was about 52 years, and today, it is over 70 years [1]. There are over one billion people aged 60 years and older in low- and middle-income countries around the world [2]. Countries vary in their life expectancies based on many factors, but this is a massive accomplishment. It is evidence of previous decades of success in coordinated research and practice implemented by leading medical, academic, and public health communities. The public health system has been a guiding force in improving health outcomes resulting in prolonged life and reduced disease burden. It has largely been accomplished by enhancing knowledge through research and establishing public health values around the world. But, with this success has come new challenges, including non-communicable or chronic diseases and the increasing incidence of health issues more closely related to human behavior.

Each decade, a broad theme emerges among the international community, which prioritizes specific challenges to populations on a global scale. Setting agendas in this way is important in order to maintain a coordinated and global effort to achieve new population health goals. The World Health Organization (WHO) has declared the decade 2020-2030 as the international decade for healthy aging, which the organization defines as *the process of developing and maintaining the functional ability that enables well-being in older age* [3]. Simply, every person should have an opportunity to live a long life with the ability to participate to the fullest extent in what they value.

Unfortunately, aging is often equated with an increasing burden of disease and a poor quality of life [4, 5]. It is important to better understand this population and its unique needs. Chronic disease and health-related behaviors are only two of the many factors that influence a person's ability to live a full life as they age. These factors greatly affect the quality of life and are important focus of many interventions. Chronic disease also represents a massive portion of health care expenditure and is likely to gain acceptance among a wide range of organizations as an area of focused intervention.

Influencing human behavior is complex and uniquely challenging, particularly in an age where everything that might be considered "unhealthy" is readily accessible. The ecological approach has been applied successfully in public health intervention planning and implementation aimed at health promotion and changing health-related behaviors [6]. This is a broad theory, but many of its principles focus on the influence of the environment on behavior and the importance of social process and collaborative effort [7]. Contemporary models apply the ecological model in more focused ways and have suggested variations in its application, including comprehensive guidelines on program planning [8, 9]. In general, community-based programs for health promotion have been shown to be effective and sustainable approaches in targeting risk factors of chronic disease and improving health education [10]. This framework may also be applied to programs specifically targeting the aging population.

Sports for Health, Grenada

In Grenada, life expectancy was estimated at 73 years between 2003 and 2005. It is estimated that life expectancy will increase by 10% in the coming decade, which will place an increasing demand on the healthcare system [11]. A recent Pan American Health Organization (PAHO) report stated the need for the Grenadian health system to develop supportive environments and appropriate services, specifically for the aging population [11]. Chronic disease is also an important target for health promotion and intervention among all age groups in Grenada. According to the Ministry of Health, in Grenada, 37% of deaths are due to cardiovascular diseases, 21% due to diabetes, and 26% are due to hypertension [11]. An increase in deaths due to complications of diabetes, along with deaths due to complications from cardiovascular diseases, has also been noted.

Access to health care and services plays a central role in health and well-being. In an effort to address health inequalities in the Caribbean, WINDREF recently established the Caribbean Center for Health Equity (CCHE) at St George's University (SGU) in Grenada. The goal of this center is to coordinate regional efforts and establish a network of partners across the Caribbean in support of education, research, and service in health equity. Among the ongoing projects at the CCHE is the Sport for Health program, which focuses on providing health and nutrition education, as well as a place where members of the community can participate in fitness activities and training. The program is available to all Grenadians, having locations across 5 sporting fields in the parishes of St George, St John, St Andrew, and St David. The implementation of the Sports for Health program appears to follow an ecological approach in its focus on community engagement and creating environments for health promotion activities.

Current Study

The purpose of this study is to assess the impact of Sports for Health on participants over the age of 65 years. While the program provides services to all ages among the Grenadian community, this study seeks to better understand its efficacy in the aging population. The information presented reflected the participant's quality of life and their performance in the program. Although multiple studies have been conducted on the positive impact of participation in health promotion activities in the aging population, there is a need for such studies in developing countries.

The study assessed whether the sports for health program improved the physical, mental, and social well-being of the participants after having completed 12 months in the program. This was determined by comparing baseline survey responses with responses gathered after 12 months. The anticipated primary outcome of the study is that the "Sports for Health Program" will have a positive impact on the physical health and quality of life from baseline to the 12-month time point. The outcomes should show, which scales of quality of life, such as physical functioning, energy, pain, social and emotional well-being will be improved by participating in this program.

Study Design

This was a cross-sectional study that collected survey responses from participants at baseline in July 2017 and after being enrolled in the study for one year, who are henceforth referred to as the 12-month point population in July 2018. The WINDREF Sports for Health program is located across five sporting fields in the parishes of St George, St John, St Andrew, and St David.

OUR STUDY

The survey used in this study was a combination of the RAND Health Survey, along with questions regarding demographic characteristics. The RAND Health Survey is a composition of questions from the RAND 36-Item Health Survey (Version 1.0), which targets the overall well-being of an individual. The validity and reliability of the RAND health survey were demonstrated through the usage of the survey in the Wilson, Hutson, and VanStry study comparing the quality of life amongst breast cancer patients.

The survey in this study was administered to the participants that met the inclusion criteria both at baseline and after one year of participation. These same participants that filled out the first set of surveys also completed the same surveys after one year of participating in the study.

Participants were enrolled for seven months to a year for 11 of the participants (43.5%), and over a year for 12 of the participants (56.5%). A total of 20 (87%) of the participants attend 3-5 exercise sections per week.

Inclusion Criteria

Inclusion criteria for the baseline population was having an age of 65 years or more at the time of enrollment in the Sports for Health program. Participants were expected to continuously attend the fitness sessions at least three days per week for a year. There were no exclusion criteria for the baseline information.

Study Population

The sample population was taken from the whole target population. A total of 23 participants, comprising 22 females and one male, met the inclusion criteria and were evaluated in this study. The average age of the participants was 67.6, with a standard deviation of 1.9. The ages of the participants ranged from 65 to 73 years.

Variables

The dependent variables are the scales for well-being from the RAND health survey and current health indicators found on the demographics survey. The independent variables are the rest of the questions in the demographic survey such as age, length of enrollment, attendance rate, and level of education.

Data Analysis

Descriptive narrative characteristics, such as mean, standard deviation, 95% confidence interval for the mean, upper limit, and lower limit for the continuous variables have been and will continue to be assessed by comparing the baseline and 12-month time point, the males and females, and other variables of interest, in order to visualize the distribution. SPSS was utilized to evaluate the results. Results were charted in Excel.

Table 1. RAND health survey

Characteristic	Mean	SD
Physical functioning	91.3	15.9
The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?		
Vigorous activities	67.4	35.7
Moderate Activity	95.7	14.4
Lifting or carrying groceries	95.7	14.4
Climbing several flights of stairs	89.1	21.1
Climbing one flight of stairs	100.0	0.0
Bending, kneeling, or stooping	82.6	24.3
Walking more than a mile	97.8	10.4
Walking less than a mile	93.5	22.9
Bathing or dressing yourself	100.0	0.0
Pain	82.2	22.9
How much bodily pain have you had during the past 4 weeks?	70.4	24.0
During the past 4 weeks, how much did the pain interfere with your normal work?	86.9	22.4
During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?	89.1	22.3
General health	77.9	18.8
I seem to get sick a little easier than other people	83.7	17.9
I am as healthy as anybody I know	70.7	25.7
I expect my health to get worse	94.6	10.5
In general would you say your health is?	63.0	21.1
Emotional well-being	77.4	13.1
Have you felt calm and peaceful?	75.7	13.4
Have you felt so down that nothing could cheer you up?	74.8	8.98
Have you been a happy person?	81.7	17.0
Energy and fatigue	74.8	12.4
Did you have a lot of energy?	49.6	13.3
Did you feel worn out?	62.2	12.8

Questionnaire Part 2, RAND Health Survey, was analyzed using a two-step scoring method designed by Hays, Shermbourne, and Mazel [11]. Step 1 in scoring the results was to recode the answer. Each answer was scored according to a range of 0 to 100, with 100 being

the most favorable health state. The questions were organized into scales representing the dependent variables of the study. Step 2 was to organize the questions according to their specific scale, and then the scores of the answers in each scale were averaged. The answers that were left blank were not represented in the average score for each scale. Using this method of determining the average (mean), standard deviation, and p-values helped to determine the reliability, central tendency, and variability of the scales. Statistical significance was considered when the p-value was less than 0.05. The null hypothesis can be rejected for the specific statistical test. All the required statistical tests were analyzed according to a 95% confidence interval, with statistical significance noted as a p-value of less than 0.05.

FINDINGS

The mean and standard deviation are depicted for the participant’s answers from the survey in Table 1. The questions are grouped into four categories; physical functioning, pain, general health, emotional well-being, and energy, and fatigue. Answers to the survey questions have been scored according to a range of 0 to 100, with 100 being *the most favorable health state*. The mean and standard deviation are also included.

The participant’s health vs. pain (p = 0.013), emotion vs. pain (p = 0.009), emotion vs. health (p = 0.008), and emotion vs. energy (p = 0.022) are found to be significantly significant, hence, a relationship could exist between these variables. Physical functioning compared to energy and fatigue are not statistically significant.

A Pearson’s correlation test was utilized to determine if age had a statistically significant relationship with the quality of life scales. According to Table 2, there is only one statistically significant relationship that can be assumed, which is age and emotion.

Table 2. Analysis of quality of life scales

Scales	Age	
Physical	Pearson Correlation	-.194
	Sig. (2-tailed)	.375
	N	23
Pain	Pearson Correlation	.248
	Sig. (2-tailed)	.253
	N	23
Health	Pearson Correlation	.426*
	Sig. (2-tailed)	.042
	N	23
Age	Pearson Correlation	1
	Sig. (2-tailed)	
	N	23
Emotion	Pearson Correlation	.543**
	Sig. (2-tailed)	.007
	N	23
Energy	Pearson Correlation	-.004
	Sig. (2-tailed)	.984
	N	23

* Correlation is significant at the p = 0.05 level (2-tailed).

** Correlation is significant at the p = 0.01 level (2-tailed).

Table 3. Analysis of participant's attendance rates and quality of life scales

Spearman's rho	Enrollment Length	
Physical	Correlation Coefficient	.117
	Sig. (2-tailed)	.595
Pain	Correlation Coefficient	.156
	Sig. (2-tailed)	.477
Health	Correlation Coefficient	.245
	Sig. (2-tailed)	.259
Age	Correlation Coefficient	.020
	Sig. (2-tailed)	.926
Emotion	Correlation Coefficient	.172
	Sig. (2-tailed)	.434
Energy	Correlation Coefficient	.117
	Sig. (2-tailed)	.595

A Spearman's correlation test was applied to determine if participant's attendance rates are associated with their quality of life scales and no significant associations were found between these factors; hence, conclusions cannot be made about their relationships (see Table 3). A graph of these results can be seen in figure 1. To confirm that attendance rates do not act as confounding variables for quality of life scales, an ordinal regression test was performed. The test of parallel lines in the ordinal regression test failed to reject the null hypothesis that the slope coefficients are the same across the response categories. An ordinal regression test assumed that pain, physical functioning, health, and emotion are not significantly affected by the participant's attendance rate.

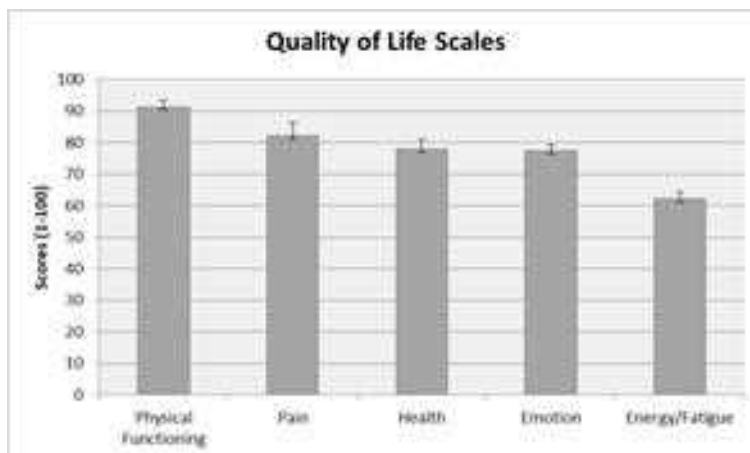


Figure 1. Quality of life scales.

A Spearman's correlation test was also used to determine if the participant's enrollment length had a significant association with their health scales. Conclusions cannot be made about the relationship between quality of life scales and enrollment length.

DISCUSSION

Community-based exercise interventions have become a growing theme for helping elderly persons improve their health. After the completion of this cross-sectional study, there is hope that this study will continue to recruit more male participants and persons aged 65 years and older, in order to form generalizations about the target aging population and improve validity. It is recognized that there are more females in Grenada's aging population than males, but the difference is not as extreme as shown in this study.

The quality of life and well-being of the participants were determined utilizing a RAND health survey, which categorized the responses according to five health scales. The responses to the survey were scored from 0 to 100, with 100 representing the *most favorable health state*. The highest scale was the participant's physical functioning with a mean score of 91.3, and the lowest score was found in the participant's energy and fatigue with a mean score of 74.8. Since the majority of these participants had been active members of the Sports for Health program for over seven months, additional reasoning behind these results could be that the Sports for Health program has quickly improved the participant's physical functioning.

The age of the participants is also an important independent variable, which is why a Pearson's correlation test was conducted to ensure that age did not act as an effective modifier of the health indicators. According to the test, the health scale for emotion can be assumed to have a statistically significant positive association with emotion ($p = 0.007$). Although the participants in the study might have been attending the exercise sessions in different quantities and at different rates, this shows that their participation appeared to be beneficial to their mental well-being when analyzing their health scales.

Increased knowledge about the effectiveness of community-based interventions can promote the expansion of the Sports for Health program as well as the implementation of programs specific to the aging population. It is an important area of research as Grenada's aging population is expected to increase significantly in the coming decade and will require effective health and well-being programs such as Sports for Health. WINDREF's Sports for Health program has demonstrated that quality of life characteristics for the aging population can be improved with a community-based exercise intervention. Lessons learned and best practices will be shared with other countries through publication of the results.

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Chapter 103

DIFFERENTIAL EXPOSURE TO SOCIAL DETERMINANTS OF OBESITY AMONG RURAL AND URBAN GRENADIAN ADOLESCENTS

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ABSTRACT

In this chapter, we examine rural and urban differences in exposure to social and environmental factors believed to be social determinants of obesity among Grenadian adolescents. A nationally representative sample of first-year students (i.e., Form 1) (n = 689) from the twenty-three secondary schools in Grenada was assessed as part of the Grenada School Nutrition Study (GSNS). Various measures of social and environmental determinants of obesity were obtained both at the individual and school levels using surveys or field observations, respectively. Urban (n = 13) and rural (n = 10) schools were determined by school location in relation to the two largest towns in Grenada. Exposure to unhealthy food outlets (i.e., shops selling sugar-sweetened beverages, candy, or highly processed foods) was determined by the density of either snack shops (i.e., bakeries, snack shops, markets, vending zones, tuck shops) or franchise fast food outlets (i.e., KFC, Subway) within a .75 km buffer around each school. Rural students were more

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likely to be Afro Caribbean (89.1% versus 79.3%) and male (55.8% versus 44.1%). Significant differences between rural and urban students were noted for car access (40.7% versus 53.3%), computer access (61.6% versus 73.5%), and snacking after school (83.6% versus 90.5%), respectively. Rural students' school environment had a lower mean density of snack shops (1.53 versus 3.39 shops/square km) and mean fast food outlet density (0 versus 1.17 outlets/square km) than urban students' school environment. For a number of measures, rural students in Grenada had significantly lower exposure to social and environmental factors believed to associated with overweight and obesity.

INTRODUCTION

The consensus among public health experts is that human genetic changes are not responsible for the rapid rise in obesity, and the explanation must lie in broad social determinants resulting in local environmental exposures that influence diet and physical activity [1-4]. A consequence of this new understanding is evidenced in a new overarching goal in Healthy People 2020 [5]. In addition to increasing years of healthy life and eliminating health disparities, the goal of – “creating social and physical environments that promote health” - has been added.

Despite the acknowledged importance of “obesogenic” environments in the epidemic there is little consensus on the aspects of the environment that have driven the epidemic as well as the factors that have given rise to the growing disparities in obesity-related outcomes by race and socioeconomic status [6, 7]. Although researchers have watched the epidemic of obesity unfold over the past three decades, not only in the US but across the globe, identification of the “drivers” of the epidemic remains contentious [8-10]. The effort to characterize the “drivers” of the epidemic involves the identification of the factors responsible for upsetting the balance in the “energy intake/energy expenditure” equation over the past four decades. On the energy intake side, the global food system that provides a “Westernized” diet of cheap, palatable, energy-dense foods is implicated [8, 10, 11]. On the expenditure side, the transition to sedentary occupations with low energy expenditure is implicated [12, 13]. The inability to arrive at a consensus is attributed to the lack of research with designs sufficient to link local obesogenic environments - created by the societal drivers - with individual obesity-related behaviors [6, 14, 15].

The current study is designed to begin to identify these drivers of the global epidemic of obesity in a country that has not yet been affected. The study was designed to identify modifiable factors in the school and local environment that were thought to lead to obesity among adolescents. The study targets adolescents entering secondary school because it is a critical developmental stage when adolescents exercise greater autonomy in their decisions regarding diet and physical activity [4]. Consequently, it is a period when the effects of the school and local environments will begin to have an impact on obesity-related behaviors.

OUR STUDY

The current study is part of a project titled the Grenada School Nutrition Study (GSNS). The GSNS goal is to identify behavioral and environmental factors that might be intervened on to prevent the development of obesity among Grenadian adolescents.

Table 1. Descriptive statistics for demographic, outcome, behavioral, and school environment variables by urban school status for GSNS schools

	N	Overall	Rural Schools (N = 283)	Urban Schools (N = 406)
Demographics				
Age, years	689	12.67	12.81	12.57
Race-Afro Caribbean, %	689	83.31	89.05	79.31
Gender, male	689	48.91	55.83	44.09
Outcomes				
BMIz > 85 th , %	689	17.56	13.43	20.44
Behaviors				
Car Access, %	687	47.89	40.07	53.33
TV Access, %	666	79.43	76.84	81.22
Computer, %	664	68.67	61.62	73.54
Snack after school, %	626	87.70	83.59	90.54
Junk snack, %	676	41.86	40.07	43.11
Walk to school, %	687	15.14	17.44	13.55
MVPA, % wear time	126	8.10	8.77	7.62
Sedentary, % wear time	126	58.90	57.86	59.63
School Environment				
Snack Store Density	23	8.24	1.53	3.39
Fast Food Density	23	0.664	0	1.17

Note: Bolded prevalences are significantly different at $p < 0.05$.

Study Sample

The GSNS was designed to be a representative sample of all first-year secondary students (i.e., Form 1) drawn from the 23 public and private secondary schools across the tri-island nation of Grenada. Form 1 students ranged in age from 11 to 14 years. Randomization was performed at the classroom level resulting in an eligible sample of 1,004 students in 35 classrooms (i.e., in schools with only one Form 1 class all students were included) making up roughly 55% of all Form 1 students in Grenada. Parental refusals ($n = 276$) and students who were absent on the day or did not complete all the assessments or surveys ($n = 39$) resulted in an effective sample of 689 students in the cohort. All students were assigned a unique identifier linked to their informed consent signed by their parents. Personal identifiers in the form of parents' names, phone numbers, and school identification were collected for possible follow up.

Data Collection

Throughout the academic school year, one school was assessed each week. Three formal visits were scheduled at each school during the week. The first day (i.e., Tuesday) involved the collection of anthropometric data: height, weight, and waist circumference. On the second day (i.e., Wednesday), the student survey and the principal survey were conducted. On the third day (i.e., Thursday), the students were instructed on the wearing of accelerometers. They were instructed to wear the device for four days from Thursday through Sunday.

The school food environment assessments were coordinated with the aid of a Geographic Information System (GIS) developed for the GSNS. The extent of the school environment was defined by a .75 km buffer around each school. Within each school environment, project field staff visited each food outlet and conducted a Store Assessment. The location of each school and store was recorded using a Garmin GPSMAO 76CSx. The reading was taken at the most central location within the school or store. The accuracy varied by 3 to 7 feet.

Study Measures

Height, weight, and waist circumference were directly measured for each student in a privatized setting (e.g., trifold blind booth) in normal school clothing. Measurements using a portable stadiometer and electronic scale standardized before each session were repeated three times, and the average score reported.

Body Mass Index (BMI), calculated by dividing weight in kilograms by height in meters squared, was used to assess excess body fat. Due to the greater sensitivity of the Centers for Disease Control and Prevention (CDC) classification system compared with the International Obesity Task Force (IOTF) classification system for characterizing excess body fat in a Caribbean adolescent population, the CDC age- and sex-specific cutoffs were used to characterize overweight (i.e., $BMI \geq 85^{\text{th}}$ percentile) and obese (i.e., $BMI \geq 95^{\text{th}}$ percentile) adolescents in terms of their standardized percentile [16]. Rural and urban designations were defined at the school level. Students attending school in the two largest towns in Grenada (i.e., St Georges and Grenville) were defined as urban students.

Percent time in moderate or vigorous physical activity (MVPA) was assessed using Actigraph GT3X+ accelerometers (ActiGraph, Pensacola, FL). A subsample of adolescents wore the accelerometer at their waist on an elasticized belt for two school days and two weekend days. Non-wearing time and cumulative time spent within specific intensity ranges were calculated using SAS (SAS Institute, Inc, Cary, North Carolina) syntax developed by the National Cancer Institute (http://appliedresearch.cancer.gov/nhanes_pam/). Non-wear time was defined as any sequence of at least 60 consecutive minutes of zero activity counts. The cut points of Evenson and Terry [17] for the various physical activity levels were used, as recommended by Trost and colleagues [18]. A valid day was defined as 8 hours or more of wear, and participants had to have a minimum of 2 valid days to be included in the analysis. Total time spent in sedentary and moderate-to-vigorous intensity physical activity was expressed as a percentage of wearing time.

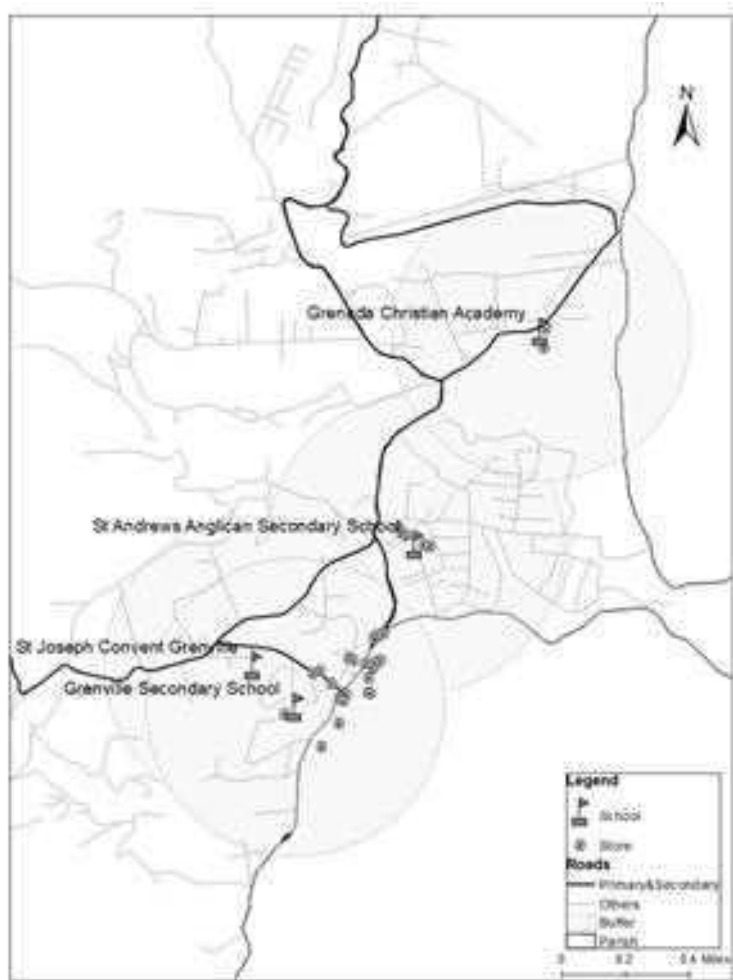


Figure 1. Map demonstrating school environments for the four schools with food stores.

Measures of the school food environment were developed using the GSNS Geographic Information System (GIS). In the GIS, data for each Store Assessment was linked to the location of the respective food outlet georeferenced relative to the school environments. Consequently, measures reflect the density of specific aggregated store conditions from the Store Assessments in the school environment. The measures included: 1) density of fast food outlets, 2) density of unhealthy food outlets (snack shop density), and 3) density of outlets with healthy foods. Density items were based on outlets per square kilometer in the school buffer area (see Figure 1).

Statistical Analysis

Multilevel models of students nested within schools were developed to characterize the overall and between school prevalence of overweight and obesity across Grenada. For this descriptive analysis, demographic measures including age, and gender were included in the

analyses. The basic multilevel models used a random coefficient for the intercept. Thus at student level, we have the following model,

$$Y_{ij} = \pi_{0j} + \pi_1(\text{Gender})_{1ij} + \pi_2(\text{Age})_{2ij} + \varepsilon_{ij} \quad \text{Level 1}$$

where Y_{ij} is the outcome (e.g., obesity related behavior measurements or BMI z-score) for student i in school j . π_{0j} is the intercept, which we allowed to randomly vary across schools, which also is the estimated mean response for school j . We assume fixed effects for a vector of student level risk factors. ε_{ij} is the random effect of student i in school j , which is assumed to have normal distribution mean 0 and constant variance σ^2 for $i = 1, \dots, n_j$ and $j = 1, \dots, 23$.

The intercept π_{0j} , is allowed to randomly vary across all schools. Therefore, at the school level, we have the following model:

$$\pi_{0j} = \beta_{00} + \beta_{01}W(\text{Urban School})_{1j} + u_{0j} \quad \text{Level 2 (random intercept)}$$

FINDINGS

Rural students were more likely to be Afro Caribbean (89.1% versus 79.3%) and male (55.8% versus 44.1%). Rural students were also less likely to be overweight or obese (i.e., BMIz >85th percentile).

With regard to obesity-related behaviors, significant differences between rural and urban students were noted for car access (40.7% versus 53.3%), computer access (61.6% versus 73.5%), and snacking after school (83.6% versus 90.5%), respectively. In addition, the rural students' school environment had a lower mean density of snack shops (1.53 versus 3.39 shops/square km) and mean fast food outlet density (0 versus 1.17 outlets/square km) than urban students' school environment.

Table 2. Parameters estimates (95% CI) from multilevel models for obesity related behaviors

	Model 1	Model 2	Model 3	Model 4	Model 5
Individual level Measures					
Computer		0.153 (-.041,0.347)		0.143 (-0.052,0.337)	0.154 (-0.052,0.337)
Male					-0.3279 (-0.524,-0.132)
School level Measures					
Urban School			0.1861 (-0.441,0.103)	0.169 (-0.103,0.441)	0.128 (-0.116,0.372)
Random Effects					
School level effect	0.0511	0.0450	0.0475	0.04334	0.0248
Individual level effect	1.3241	1.3258	1.3237	1.3253	1.3148
Fit Statistics					
AIC	2172.2	2095.2	2172.5	2095.7	2087.8

Table 3. Odds ratios (OR) and 95% CI from multilevel logistic models on individual nested within school level measures, predicting obesity (BMI $\geq$ 85^{pcd})

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Individual level Measures						
Male		0.52 (0.33, 0.80)		0.53 (0.34, 0.82)	0.53 (0.35, 0.81)	0.55 (0.36, 0.84)
Age, years		0.77 (0.57, 1.05)		0.79 (0.58, 1.08)	0.77 (0.57, 1.05)	0.80 (0.58, 1.09)
Computer					1.67 (1.04, 2.70)	1.61 (1.00, 2.60)
School level Measures						
Urban School			1.69 (0.96, 2.96)	1.49 (0.93, 2.40)		1.41 (0.90, 2.19)
Random Effects						
Tract level effect	0.2204	0.0699	0.1738	0.0500	0	0
Change from Model 1	--	-68.3%	-21.1%	-77.3%	-100.0%	-100.0%
Fit Statistics						
-2Res Log Pseudo-						

Note: Bolded OR are significantly different from 1 at $p < 0.05$.

Multi-level analyses were run to try and explain the urban-rural differences in obesity rates in terms of either individual or school environment level factors. In multilevel analysis predicting the risk of obesity, none of the individual behaviors or school food environment measures was observed to explain the urban-rural differences in obesity risk (see Table 2). For example, when access to computers was added to the model, the factor did not significantly predict obesity risk, although greater access to computers was positively associated with obesity risk. In addition, the inclusion of computer access to the model slightly reduced the effect of urban school status on obesity risk, but neither factor was significant (see Table 2, Model 3).

DISCUSSION

For several individual behaviors and school environment characteristics, rural students in Grenada had significantly lower exposure to social and environmental factors believed to be associated with overweight and obesity. However, in multilevel modeling controlling for demographic factors, the individual behaviors, and the school environment characteristics, individual behaviors did not explain the effect of urban school status on obesity risk.

While it is clear that students attending schools in rural parishes of Grenada have a lower risk profile with regard to presumed behavioral factors associated with obesity, explaining the rural versus urban differences were not explained by the individual behaviors measured in this study. Of note is the lack of a difference in MVPA level between the two groups. Consequently, it is unclear why the reported measures - computer use and car access - were significantly different between rural and urban students, given they imply differences in physical activity. Furthermore, the results suggest the difference in unmeasured factors associated with junk food consumption may be implicated. While the school level differences in the availability of junk food were not significant, the large difference in effect does appear to represent a trend given the sample size of only seven.

There were several weaknesses in the study. First, the gender difference related to urban and rural schools is an issue. The fact that females were more represented in urban schools may account for the urban-rural difference in overweight students in urban schools. However, higher socioeconomic status (SES) and high SES is related to car, computer, and junk food access in other studies. It may be that there is an interaction between rural versus urban school attendance and SES where overweight urban females attend rural schools and normal weight rural females attend urban schools, which were considered elite, thus biasing the results to the null. In addition, the accelerometer data was not ideal. In the analysis, students that did not complete the entire program were included in the analysis. Consequently, the lack of difference between rural and urban areas could be due to measurement error.

Finally, there appeared to be urban-rural differences in rates of overweight adolescents. While individual behaviors did not explain the differences there appeared to be confounding by individual SES. For example, computer access, the one behavior associated with overweight status, was significant across all schools but controlling for school status resulted in an insignificant finding. Future studies of rural versus urban differences in overweight and obesity should acknowledge the role of SES interaction biasing results to the null.

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Chapter 104

ANALYSIS OF URINE SAMPLES FOR ANTIMICROBIAL RESISTANCE PROFILES IN GRENADA, 2015-2018

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ABSTRACT

Antimicrobial resistance (AMR) is a serious global public health problem. Worldwide, annual mortality is half-a-million people from AMR infections. AMR also results in additional healthcare spending for non-fatal cases. In the presence of growing levels of AMR, further use of antibiotics should conform to relevant current empirical findings. A retrospective secondary analysis was performed on data collected from 2018 for catheter and clean void urine specimens collected at the Grenada General Hospital for uropathogens. The data were compared to the average of the preceding three years, as reported in published literature, to determine their susceptibility to different antimicrobials. The data were submitted after the Institutional Review Board (IRB) approval and redaction of identifiable patient information. A total of 9,054 urine collections were tested and reported for 2018. There were 583 catheter specimens and 8,471 clean void specimens. Those microbes that met inclusion criteria for both specimen types were *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Pseudomonas aeruginosa*. *Klebsiella pneumoniae* and *Proteus mirabilis* were shown to have statistically significant differences in resistance patterns between the published average of the preceding three years (2015-2017) and the 2018 collection. This study provides information on bacterial antibiotic susceptibility profiles of isolates from urine specimens from the Grenadian population. The findings of a trend towards increasing resistance emphasize the necessity

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of continued surveillance as part of the multimodal strategies recommended in infection prevention control programs. The findings in this study can be extremely useful to assist healthcare providers in planning treatment regimes for patients with urinary tract infections (UTI) in Grenada. Further, the Ministry of Health in Grenada can use the evidence from this study to support framing its response to the World Health Organization's (WHO) call to countries to address AMR and to improve antibiotic stewardship.

INTRODUCTION

Modern use of antibiotics began with the development of penicillin by Alexander Fleming (1881-1955) in 1928. Almost immediately, however, there were concerns that the capacity of these drugs to combat infections would not last. By 1946, Fleming said, “the public will demand [penicillin]... then will begin an era...of abuses. The microbes are educated to resist penicillin and a host of penicillin-fast organisms is bred out which can be passed to other individuals... I hope the evil can be averted.” By 1962 methicillin-resistant staphylococcus aureus (MSRA) had developed in the United Kingdom [1]. Now, the WHO claims that, “without urgent action, we are heading for a post-antibiotic era, in which common infections and minor injuries can once again kill” [2].

There is substantial evidence that antimicrobial resistance (AMR) is a serious health issue. There is presently an annual worldwide mortality of half-a-million people from infections due to AMR [3]. If the situation is left unabated, it is estimated that mortality due to AMR will rise to 10 million people annually by the year 2050 [4]. There is also substantial morbidity in non-fatal cases that contribute to the environmental “resistome,” viz. collection of AMR genes that are cultivated and transmitted among pathogenic microbes. In turn, more robust resistomes require longer durations of treatment for infections. In the United States alone, this leads to an additional \$35 billion, or \$18,000 to \$29,000 per patient, per year [1, 3]. In addition, as the world becomes a global community, there is concern that AMR pathogens will spread to more places and in a shorter time. There is now evidence to suggest that even short durations in transit create more robust resistomes in places such as airplane sewage [5].

To control AMR related impacts, antibiotic stewardship is prudent. However, it has been found that the antibiotic choice for treatment is inappropriate in at least 30% of cases [6]. In Trinidad, it has been shown that at least 62% of surgical prescriptions were inappropriate [7]. To counter this problem, an evidence-based approach should be used to increase the effectiveness of antimicrobial interventions. However, information on AMR for the human population in Grenada is limited. Analyzed data for UTI antimicrobial patterns and other types of infections are very limited. Specifically, there are no data publicly available for uropathogens after 2017 either from private institutions or the global reporting systems such as the Global Antimicrobial Resistance Surveillance System (GLASS) of the World Health Organization [2, 8]. This study was performed to provide evidence of uropathogen AMR prevalence in the population of Grenada from 2018. This information can be extremely useful to assist healthcare providers in planning treatment regimes for UTI in Grenada. The Ministry of Health in Grenada can also use the evidence generated in this study to inform its response to the WHO’s call to countries to address AMR and to improve antibiotic stewardship.

OUR STUDY

A retrospective secondary data analysis was performed for urine samples collected over a one-year period, January 2018 to December 2018, at Grenada General Hospital Laboratory. The data received from the Ministry of Health for the analysis was anonymized. The IRB at St. George's University (SGU) granted approval for the study (St. George's University IRB Ref 19030).

The information provided was WHONET compatible antibiogram data including the year of collection, host, number of samples, type of specimen collected, as well as microbial organism cultured, antibiotic(s) used for susceptibility testing, and the results. Urine clean void and urine catheter specimens were included from both inpatients and outpatients. The microbial organisms isolated from the specimens and reported were *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Raoultella terrigena*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus* sp., and *Streptococcus* sp. The antibiotics used for susceptibility testing were amoxicillin/clavulanate i.e., augmentin, ampicillin, trimethoprim/sulfamethoxazole, ciprofloxacin, levofloxacin, norfloxacin, gentamicin, amikacin, cefazolin, cefuroxime, cefoxitin, cefotaxime, ceftazidime, ceftriaxone, imipenem, and vancomycin.

Inclusion criteria consisted of urine specimens from the Grenada General Hospital Laboratory in the year 2018. Data were excluded if they contained incomplete or unclear documentation, or if the total number of samples collected for a category was limited ($n < 30$). Data that did not meet the criteria nor were included in the publication of the selected preceding years were not used in the analysis. A chi-square analysis was done to assess the level of change in AMR as of 2018 in comparison to published average uropathogen findings in Grenada from 2015 to 2017 [8]. The data were extracted into Microsoft Excel and analyzed using Statistical Package for Social Sciences (SPSS) software.

FINDINGS

A total of 9,054 urine collections were tested, reported, and met minimum inclusion criteria over the 2018 period. Out of the total, there were 583 catheter specimens and 8,471 clean void specimens. Microbes meeting criteria for both specimen types were *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, and streptococci (see Table 1, Table 2). Of these microbial specimens, a chi-square analysis was performed of the 2018 antibiotic profiles that were of sufficient size ($n > 30$) and had existing data for comparison from the three years prior in the published literature [8, 9]. After implementing these criteria, *Klebsiella pneumoniae* with ampicillin, *Proteus mirabilis* with augmentin, as well as *Proteus mirabilis* with cefuroxime were available for statistical analysis. *Klebsiella pneumoniae* isolates showed a statistically significant increase in resistance against ampicillin, $X^2(1, N = 152) = 11.52$, $p < .05$. *Proteus mirabilis* isolates showed a statistically significant increase against augmentin, $X^2(1, N = 280) = 188.45$, $p < .05$. *Proteus mirabilis* isolates also showed a statistically significant increase against cefuroxime, $X^2(1, N = 146) = 100.03$, $p < .05$.

Table 1. Uropathogens and select resistances (2015-2017)

	Total number from all urine samples (as reported by [8])	Resistant to Augmentin	Resistant to Ampicillin	Resistant to Cefuroxime
<i>Klebsiella pneumoniae</i>	186	36%	80%	27%
<i>Proteus mirabilis</i>	96	36%	48%	24%

Table 2. Uropathogens and select resistances (2018)

	Total number from all urine samples	Resistant to Augmentin	Resistant to Ampicillin	Resistant to Cefuroxime
<i>Klebsiella pneumoniae</i>	271	55%	3%	54%
<i>Proteus mirabilis</i>	4321	92%	40%	84%

DISCUSSION

The data collected in this study show *Klebsiella pneumoniae* resistant to augmentin and cefuroxime, which is the same as reported in a prior analysis of uropathogens in Grenada analyzed from 2015 to 2017 [8]. The current findings shows that since then there has also been a statistically significant increase in *Klebsiella pneumoniae* against ampicillin. Additionally, the current analysis show a statistically significant increase in *Proteus mirabilis* resistance against augmentin and cefuroxime.

There were several limiting factors in this study. It is possible that high levels of AMR over the short time period of analysis were due to low statistical power for certain subsets of specimens. However, the period under investigation may have been of sufficient duration as it has been documented that up to 70% of *Staphylococcus aureus* strains can become resistant to antibiotics, such as erythromycin, within six months of exposure onset [3, 10]. Additionally, as this study used secondary data, there was no way to control factors such as whether there was a lack of refrigeration of the samples, broth contamination, use of a non-sterile container for collection, and less than the minimum recommended volume of urine being submitted for analysis. While the current study had a higher number of total samples, there was also no ability to remove repeated specimen testing or polymicrobial samples. Prior studies from the same population with more stringent criteria of non-repeat monobacterial clinical isolates have yielded fewer samples [11]. Future analyses can better parse patient information by accounting for subsections and collecting demographic data, such as age and gender. This would allow for comparisons to other Caribbean countries for prevalence rates of UTI as well as reported cases of AMR genes such as metallo-beta-lactamases [12].

Findings from this investigation, and similar studies, can support evidence-based prescribing of antibiotics. Constant exposure to antibiotics at low levels promotes virulence through hormesis since the factors that contribute to pathogenicity also act as chemical communication with other microbes when present at concentrations below the threshold of

inhibition [13]. Imipenem at sub-inhibitory concentration levels induces beta-lactamase production in pseudomonas strains, ampicillin at sub-inhibitory concentration levels induce pathogenicity in *Escherichia coli*, and ciprofloxacin at sub-inhibitory concentration levels increase the transfer of pathogenicity factors to *Staphylococcus aureus* [6]. Due to hormesis, it would be ideal to reduce the amount of constant low-level exposure to antimicrobials [1]. With sufficient recent AMR data, there can be shorter courses of antibiotic treatment that do not negatively affect mortality can be encouraged [14].

Novel, more cost-effective search methods, are on the horizon for discovering new antimicrobials. However, they are not yet fully integrated into business models and the effects are not fully understood [15]. Alternative treatment methods are pending but are not yet proven to be clinically or financially effective [16, 17]. The use of biomarkers, such as procalcitonin, and non-antibiotics that demonstrate antimicrobial activity, such as ticagrelor, have not been shown to work independently of antibiotics, rather than augment them [18, 19]. It has thus become increasingly ineffective to financially subsidize private industry as compared to enhancing public health measures, directly [20]. As such, it is more prudent for small island states like Grenada to apply intermediate steps to protect and prolong health through antibiotic stewardship and associated public health interventions.

The data on AMR collected here can work in tandem with extending antibiotic stewardship into agricultural use as well. In the United States, 80% of antibiotics sold are for agricultural and farm use and up to 70% of administered antibiotics exit the body unmetabolized through urine, leading to at least 10% of pharmacologically active compounds being retained even after conventional water treatment [21, 22, 23]. In Grenada, specifically, antibiotic stewardship for poultry farmers can be an important point of intervention [24]. Additionally, effective public health measures, such as vaccinations, should be extended as well. AMR of *Streptococcus pneumoniae* serotype 19A, which is prevalent after introduction of the seven valent vaccine, is decreasing in children under five years in the Latin American and Caribbean region [25]. Implementing vaccinations in aquaculture would not only prevent AMR in water sources but also produce greater yield for farmers [23]. Public health policies should support these measures to protect the health of Grenadian citizens.

In conclusion, AMR is a growing problem and the solution lies in a multidisciplinary approach to intervention as well as generating strong evidence on which to premise actions. The use of data can support the development of measures to promote the physical and fiscal wellbeing of the public, through infection control that reduces the cost and morbidity of infections. This study documents antimicrobial resistance profiles from uropathogens in Grenada collected in 2018. In comparison to published data for the three years prior, 2018 uropathogens showed statistically significant increases in AMR among *Klebsiella pneumoniae* to ampicillin, and *Proteus mirabilis* to augmentin as well as cefuroxime. Although the conclusions of this study should be taken with some caution until further confirmatory studies are performed, other studies have shown there is an overall trend towards increased AMR. This trend highlights the need for continued surveillance in order to adjust future antimicrobial guidelines. With other reported findings, the results from this study can be stored in a database that can be used for AMR reporting and to inform education campaigns for medical professionals and the public, and promoting evidence-based clinical guidelines as well as antibiotic stewardship in Grenada and, more widely, in the Caribbean.

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Chapter 105

TRENDS IN MORBIDITY AND MORTALITY OF COMMUNITY-ACQUIRED PNEUMONIA IN GRENADA DURING 2015-2019

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ABSTRACT

Lower respiratory infection is a leading cause of morbidity and mortality worldwide. Pneumonia is an acute form of lower respiratory infection that is characterized by inflammation of the lung parenchyma and ranks as the 4th leading cause of death in Grenada. Pneumonia is categorized either as community-acquired pneumonia or as hospital-acquired pneumonia and can be caused by many pathogens, including streptococcus pneumoniae, hemophilus influenzae, mycoplasma pneumoniae, chlamydophila pneumoniae, influenza virus, coronavirus, and respiratory syncytial virus. The main objective of this study was to describe patterns of morbidity and mortality for community-acquired pneumonia in Grenada during 2015-2019. We retrospectively analyzed the morbidity and mortality of community-acquired pneumonia in Grenada during 2015-2019. Extracted data included the total number of admissions for each month and year; demographic data, including age, and sex; and patient outcomes (survived/died) for those admitted with community-acquired pneumonia. A total of 1,165 patients with community-acquired pneumonia were admitted during 2015-2019. There were 606 (52.0%) women, 557 (47.8%) men, and 2 (0.2%) of unknown gender. The number of cases of community-acquired pneumonia admitted increased significantly over the 5-year period, with 2019 reporting the highest number of cases. The overall case fatality ratio for the 5-year period was 20.5%, with 2015 reporting the highest proportion (29.1%). The proportion of hospital admissions for community-acquired pneumonia

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increased significantly during 2015-2019 in Grenada. There is an exceedingly high case fatality ratio for community-acquired pneumonia.

INTRODUCTION

Lower respiratory infection is a leading cause of morbidity and mortality worldwide [1]. Pneumonia is an acute form of lower respiratory infection that is characterized by inflammation of the lung parenchyma. Pneumonia can be caused by many pathogens, including streptococcus pneumoniae, hemophilus influenzae, staphylococcus aureus, klebsiella pneumoniae, pseudomonas aeruginosa, mycoplasma pneumoniae, chlamydophila pneumoniae, rhinovirus, influenza, parainfluenza virus, coronavirus, and respiratory syncytial virus [2]. Pneumonia is categorized either as community-acquired pneumonia (CAP), in which infection is acquired outside of the hospital setting, or as hospital-acquired pneumonia (HAP), in which infection is acquired after 48 hours of being admitted to the hospital [3].

Data shows that lower respiratory infection is the 4th leading cause of death worldwide [4]. This statistic is mirrored by reported mortality data for Grenada [5]. However, recent data shows that the global mortality rate of pneumonia is on the decline, despite more people above age 70 years dying from pneumonia [6]. Healthcare utilization and cost of hospitalization relating to the treatment of pneumonia is also substantial [7].

The main objective of this study was to describe patterns of morbidity and mortality for community-acquired pneumonia in Grenada during 2015-2019. Our primary hypothesis was that there would be an observable decline in hospital admissions for community-acquired pneumonia in Grenada during this 5-year period.

OUR STUDY

We retrospectively analyzed the morbidity and mortality of community-acquired pneumonia in Grenada during 2015-2019. Data for this analysis were obtained from the Grenada General Hospital medical records department. Grenada General Hospital is the main referral hospital for all public and private health care providers in Grenada. It is a 198-bed secondary/tertiary hospital that includes the only intensive care unit (ICU) on the island and several specialist services. In this study, data were extracted from January 1, 2015 to December 31, 2019. All data obtained from the medical records were de-identified and uploaded in an Excel[®] sheet. Extracted data included the total number of admissions for each month and year; demographic data, including age and sex; and patient outcomes (survived/died) for those admitted with community-acquired pneumonia. The International Classification of Diseases 10th revision (ICD10) [8] coding system was used to categorize acute respiratory infections. Specifically, we analyzed data for Code J18 (pneumonia, unspecified organism). We compared the admission rates of pneumonia regarding age, sex, and month of admission, and examined the trends over the 5-year period. The case fatality ratio for pneumonia was compared for this time period.

Table 1. Number of cases of pneumonia admitted by year and sex

Year	Women	Men	Unknown	Total
2015	76 (51.4)	72 (48.6)	0 (0.0)	148
2016	127 (53.8)	108 (45.8)	1 (0.4)	236
2017	105 (52.8)	93 (46.7)	1 (0.5)	199
2018	147 (52.9)	131 (47.1)	0 (0.0)	278
2019	151 (49.7)	153 (50.3)	0 (0.0)	304
Total	606 (52.0)	557 (47.8)	2 (0.2)	1165

OUR FINDINGS

A total of 1,165 cases of community-acquired pneumonia were admitted during 2015-2019. There were 606 (52.0%) women, 557 (47.8%) men, and 2 (0.2%) of unknown gender. Details are shown in Table 1. The number of cases of community-acquired pneumonia admitted increased significantly over the 5-year period, with 2019 reporting the highest number of cases. In 2019 the number of admissions for community-acquired pneumonia doubled that for 2015. With the exception of 2019, more women were admitted for community-acquired pneumonia during the 5-year period.

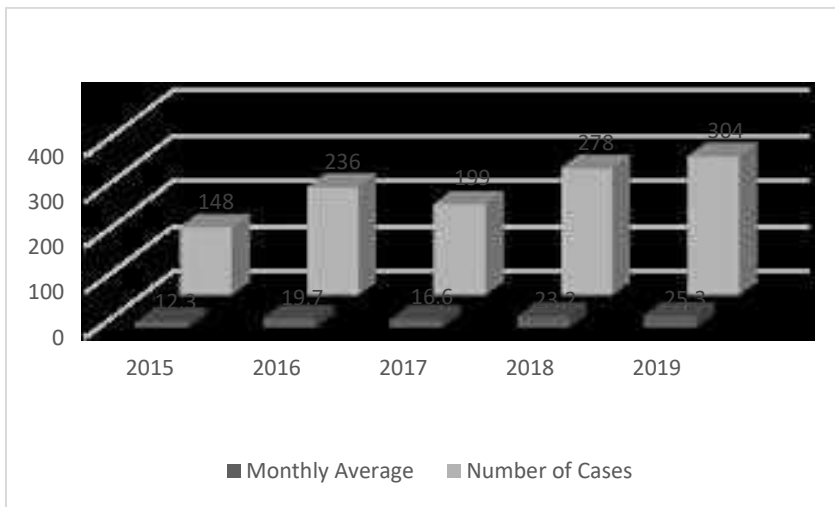


Figure 1. Number of cases of pneumonia admitted by year and monthly average.

There was a seasonal variation of hospital admissions for community-acquired pneumonia, with higher numbers being reported during the period of December to March. The annual total and average monthly number of admissions of community-acquired pneumonia cases are shown in Figure 1. The number of admissions for community-acquired pneumonia recorded in 2019 was 9.4% higher than in 2018. The average monthly number of cases has also increased over the same period. Additionally, the number of cases in December 2019 was 61.5% higher than the average over the previous three years (see Figure 2).

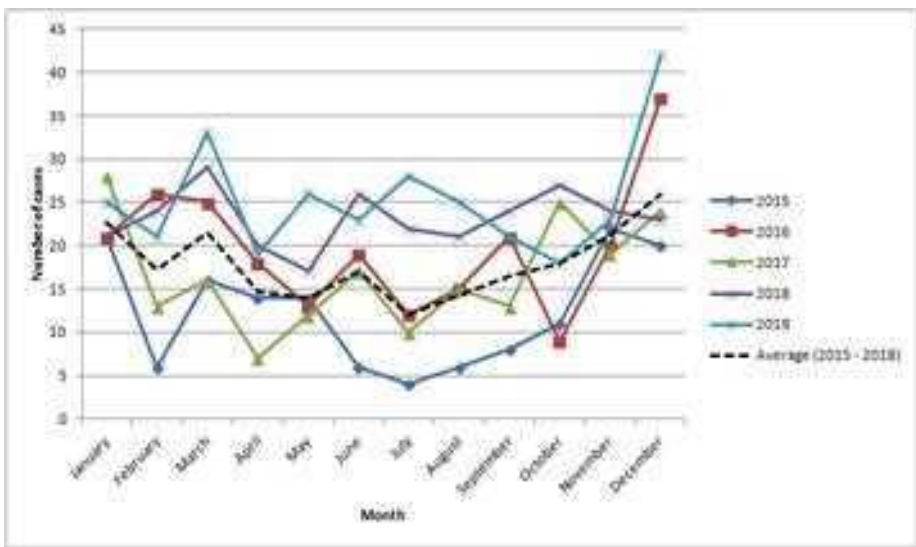


Figure 2. Number of cases of pneumonia admitted by year and month.

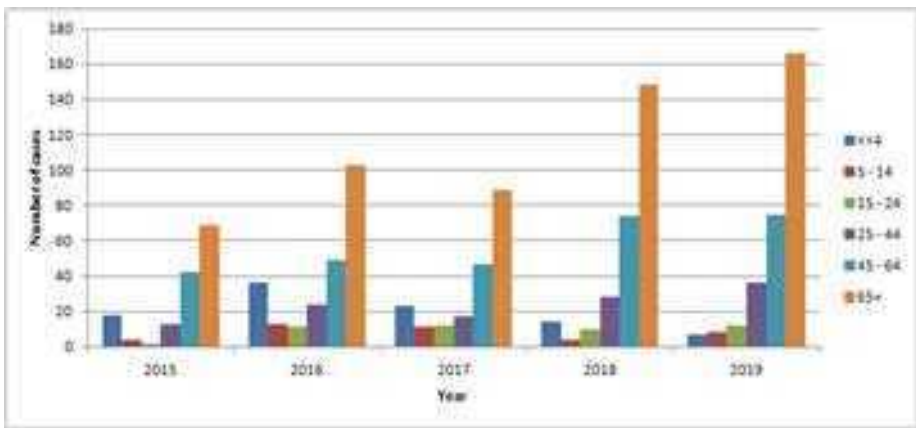


Figure 3. Number of cases of pneumonia admitted by year and age.

The 65-years and older age group consistently had the most hospitalizations for community-acquired pneumonia during 2015-2019 (with an average of 48.6% over this period). In 2019, 54.6% of all admissions for pneumonia were 65 years and older. The 45-to-64-years age group reported the second highest proportion of hospitalization for community-acquired pneumonia, averaging 24.8% over the 5-year period. An increasing trend in hospitalizations was also observed in this age group (see Figure 3).

The distribution of patients who died from according to year and age is shown in Figure 4. The total number of deaths recorded for the 5-year period was 239, with a yearly average of 48. The highest number of fatalities, 58, was recorded in 2019, in which 20.3% of the deaths were recorded occurred in December. Most of the patients who died from community-acquired pneumonia were 65 years or older, contributing to an average of 70.6% of deaths. The proportion of deaths in this age group ranged from 62.8% in 2015 to 74.6% in 2019.

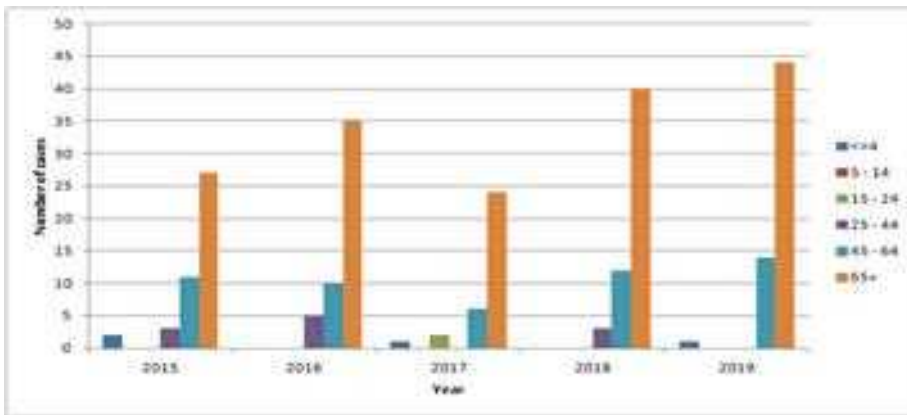


Figure 4. Number of cases died from pneumonia by year and age.

Table 2. Case fatality ratio for pneumonia during 2015-2019

Year	# Cases (% deaths)		Total
	Women	Men	
2015	76 (31.6)	72 (26.4)	148 (29.1)
2016	127 (22.8)	108 (19.4)	235 (21.3)
2017	105 (13.3)	93 (20.4)	198 (16.7)
2018	147 (16.3)	131 (22.7)	278 (19.9)
2019	151 (14.6)	153 (23.5)	304 (19.1)
Total	606 (18.6%)	557 (22.6)	1163 (20.5)

The case fatality ratio for community-acquired pneumonia during 2015-2019 is shown in Table 2. The overall case fatality ratio for the 5-year period was 20.5%, with 2015 reporting the highest proportion (29.1%). With the exception of 2015 and 2016, men had a higher case fatality rate compared to women. The case fatality rate for each year hovered around 20%, with the exception of 2015.

DISCUSSION

Over the study period, the frequency of community-acquired pneumonia increased significantly, rejecting our hypothesis that there would be an observable decline in hospital admissions in Grenada. Our results are in contrast to global data, which shows that there is a decreasing trend in the incidence of lower respiratory infections [1]. The reasons for this upward trend in incidence are unclear. One possible reason may be the underutilization of vaccination for streptococcus pneumoniae, hemophilus influenzae and the influenza virus. However, a recent report shows that Grenada has 95% immunization coverage [9], but the data did not specify for which diseases. Currently, pneumococcal vaccine is not included in Grenada's national vaccination program. Thus, the immunization data should be closely

examined to decipher whether this is a contributory factor for the increased incidence of community-acquired pneumonia.

Another possible reason for the increased incidence of community-acquired pneumonia may be as a result of increased infection by atypical pathogens [10]. However, our report lacks data regarding the specific pathogens causing community-acquired pneumonia in Grenada. This is because there is minimal testing for the causative agent of community-acquired pneumonia. Grenada has one state-owned clinical laboratory that performs public health functions. This laboratory does not have the capacity to test for and identify viral respiratory pathogens.

Similar to other data [11], our results showed that elderly persons were more likely to be diagnosed with community-acquired pneumonia. Thus, this demographic should be the target of interventions aimed at preventing the disease and its complications. Our results also showed a seasonal variation in the hospitalizations of community-acquired pneumonia, mirroring other studies [6, 12]. Grenada depends heavily on tourism as a pillar of its economy and increasing numbers of tourists visit the island each year. Moreover, the “flu season” in North America coincides with the winter tourist season and thousands of visitors travel to Grenada by air and sea. Thus, this increases the risk of importation of respiratory pathogens into Grenada, which can even initiate an epidemic. In addition, our report had similar findings to a study by Choi et al. [13] regarding gender differences in hospitalized for community-acquired pneumonia, in which men had increased risk.

Our results showed that pneumonia has a high fatality rate, particularly in the elderly. On average, about a fifth of patients admitted for pneumonia during 2015-2019 has died. The Ministry of Health, being the custodian of the healthcare system in Grenada, should consider the lessons of 2019 in preparing for future “flu seasons”. It is imperative that The Ministry of Health intensify its preventive efforts in order to curb the incidence of respiratory infections. Public service announcements should be released in the media outlining measures that can be taken to prevent the disease. Currently, hand hygiene and cough hygiene are being recommended as preventive measures. The influenza vaccine should also be promoted, targeting the groups at increased risk. There is also a need for effective surveillance at ports of entry so that respiratory infections can be rapidly and easily identified, and persons quarantined, if necessary. In this “flu season” and with the advent of COVID-19, surveillance has dramatically increased in Grenada and around the world. However, this initiative should continue in the years to come.

Even though there are challenges in detecting the cause-specific pathogen for pneumonia, with comprehensive molecular testing, pathogen detection can be significantly improved. However, adequate and appropriate treatment should be readily available for patients diagnosed with lower respiratory infections. Presently, there is no antiviral treatment available to treat patients requiring medication. Additionally, no antiviral influenza medication was available in Grenada in 2019, both in the private and public sectors. Seasonal influenza vaccines are usually made available to groups at risk.

This study had several limitations. Firstly, this study was conducted using secondary data from Grenada’s main public hospital. The study only represents cases with severe enough disease to require hospitalization and does not include cases treated ambulatorily. As such, morbidity and mortality due to community-acquired pneumonia in the state of Grenada cannot be generalized from these results. Secondly, data on comorbidities, laboratory confirmation information on cases and, apart from age and sex, data on other risk factors were

not available for this study. Underlying health issues and the pathogen causing disease may have had a great impact on the outcomes observed in the study. Lastly, information on the adequacy of the treatment regimens was not analyzed; this too may have provided further insight into the outcomes observed. Further research is therefore suggested to identify the factors associated with admission and mortality due to community-acquired pneumonia in Grenada.

In conclusion, the proportion of hospital admissions for community-acquired pneumonia increased significantly during 2015-2019 in Grenada, and the case fatality rate of community-acquired pneumonia is exceedingly high. Measures have to be taken to improve vaccination in order to prevent lower respiratory infections. In addition, comprehensive molecular testing should be done to accurately identify causative pathogens of lower respiratory infections. Finally, there is a dire need for medications to treat lower respiratory infections caused by viruses.

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Chapter 106

HEALTH IMPACT AND MULTISECTORAL RESPONSE TO A MAJOR FLOODING EVENT IN TRINIDAD, OCTOBER 2018

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ABSTRACT

In this chapter, we examine the effectiveness of the flood early warning system utilized by Trinidad and assess the multisectoral response to mitigate the health impact of flooding. The work consisted of two components. Firstly, a qualitative, key informant interview process was conducted, examining factors related to timeliness of early warning alerts, multisectoral impact including health, emergency response efforts, and recommended mitigation actions. Interviewees sampled were purposively selected from different sectors and were directly involved in the flood response. Consent was obtained before proceeding with interviews and transcriptions were analyzed using thematic analysis. The second component, targeted at assessing health impacts of flooding, collected and descriptively analyzed syndromic disease surveillance data from health centers serving flood-affected areas. Seven key informants in total were recruited from three organizations, including two local government regional corporations, the Ministry of Health, and a local Non-Governmental Organization. Major factors that led to the flooding included a combination of poor urban planning and development and unusually heavy precipitation within a short period of time that led to severe riverine flooding in

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North Central Trinidad. Households, entire communities, businesses, schools, and the agricultural and health sector were impacted. Syndromic surveillance conducted at health centers in the north-central area described a post-flooding rise in respiratory and gastrointestinal disease cases. The October 2018, Trinidad flooding event tested several organizational emergency response systems within the country. Climate resilience must be considered in health sector planning to strengthen surveillance systems and appropriately respond to health disasters.

INTRODUCTION

The Caribbean Region is particularly vulnerable to natural disasters, such as hurricanes, flooding, and drought. Climate change, which influences hydrometeorological events, is driven by global warming and is of major concern for Small Island Developing States (SIDS) in the Caribbean. The Intergovernmental Panel on Climate Change (IPCC) 2007 report details an observed 0.2°C increase per decade in the Caribbean region over the last 30 years [1].

The period June 1 to November 30 each year marks the Atlantic Hurricane season [2]. Over the past few years, the region has seen a rise in the frequency and severity of storms, including three Category 5 storms within the last two years [2], which heavily impacted human life and island economies. Over the last 30 years, climate variability, regional warming, and modifications in rainfall patterns have been recorded by Caribbean islands, however, climate change is responsible for a shift in the range and pattern of this variability [3].

Rainfall in Trinidad and Tobago varies across the two islands and within each island. Local and remote climate influencers such as El Niño and La Niña phases of the El Niño Southern Oscillation (ENSO) play important roles with respect to rainfall patterns. There also exists a strong relationship between local rainfall variability and the Inter Tropical Convergence Zone (ITCZ), which is linked to prolonged rainfall periods in Trinidad and Tobago [4].

On October 16, 2018 the Trinidad and Tobago Meteorological Service (TTMS) issued its first early warning message of a potential major flooding event in Trinidad, approximately 72 hours before the start of the event. This was followed by a yellow alert Common Alert Protocol (CAP) during the 17th – 19th October, which detailed an active ITCZ that would lead to flash flooding. On October 18, 2019 the TTMS upgraded their alert to the orange level, which was further escalated to the red level, projecting extensive riverine flooding along the Caroni River, and advising citizens to protect life, livelihood, and property (K. Kerr pers. comm. 11 February 2019).

Following this, a major flooding event occurred across the north-central and eastern parts of Trinidad, which resulted in the Trinidad and Tobago Government declaring a natural disaster and engaged all levels of response from national to local government, as well as civil society and community relief efforts. Communities along the Caroni flood basin were heavily impacted, with evacuations being necessary in some cases. Reports from the Trinidad Office of Disaster Preparedness and Management (ODPM) and the Caribbean Disaster Management Agency (CDEMA) indicated that flooding impacted 100,000 to 150,000 people, with 800 people being evacuated and 300 seeking shelter support [5].

This report aims to examine the effectiveness of the early warning system utilized by the Trinidadian authorities, assess the multisectoral response that evolved to mitigate the impacts of flooding, inclusive of the health outcomes, and make recommendations for future mitigation efforts.

OUR STUDY

This study consisted of two components; the first utilized information gained through semi-structured, key informant interviews. The interview protocol sought information on various factors, including timelines of alerts issued by the relevant authorities, factors that contributed to the flooding event, impact on various sectors including health, success of the response efforts, and recommendations for future mitigation actions. Interviewees sampled were purposively selected, held key positions within their organizations, and were directly involved in the flood response process. Interviewees were selected from different sectors, including emergency and disaster response, public health, and civil society. Consent was obtained before recording and assurances were given that anonymity would be preserved. No personal identifying information was collected. Notes and audio transcriptions were manually reviewed and categorized using thematic analysis. The results were summarized and are presented in the section below.

The second component, targeted at assessing health impacts of the flooding, was based on collecting and analyzing syndromic disease surveillance data from health centers serving flood-affected areas. Syndromes/disease classifications examined included respiratory infections, acute viral illness, and gastroenteritis.

FINDINGS

A total of seven key informant interviews were conducted, inclusive of four personnel from the local government regional corporations, two from the Ministry of Health, and one from a non-governmental organization (NGO). The local government corporations directly serviced the flood-affected areas.

Timeliness of Alerts

Official warnings from the Office of Disaster Preparedness and Management, as well as the Meteorological Office were dispatched, however, the reach and timeliness of the messages were not consistent throughout the response community. In one instance, the local government office acted independently of these alerts based on community reports received. Other response offices indicated satisfaction with timely alerts. Messages to the general Trinidadian population were disseminated on local television, radio channels, the TTMS website, and social media beginning three days prior to the start of the flooding event.

Factors Contributing to Flooding

The main contributors to the major flood event of October 2018 were proposed to be a combination of poor urban planning and drainage development, as well as the timing of hydrometeorological events. Main areas affected included North Central Trinidad (primarily the Caroni river flood basin) and Sangre Grande on the Eastern side of the island and Mayaro in the south. Communities built close to the river flood zone were impacted first. Between 17-19 October 2018, Trinidad experienced one month's worth of rainfall. Some meteorological weather sub-stations reported between 6-10 inches of rainfall over the three days, with areas such as Sangre Grande, North Oropouche, San Rafael, Carapo, Talparo and Guaico Tamana receiving 12-14 inches. This unusually large amount of rainfall in such a short space of time, coupled with high tides, prevented riverine and land runoff, resulted in the Caroni River overflowing its banks at several points, leading to inundation of surrounding communities and farms. Other factors included blockage of riverine systems due to improper solid waste disposal practices by local communities living near the river.

Impact of Flooding Event

Within the private sector, several whole communities in the north-central area, including St. Helena, Kelly, Las Lomas, Greenvale, as well as Sangre Grande in the east, and Mayaro in the south of the island were inundated with floodwaters. Levels reached greater than four feet high in the community of Greenvale, which required evacuation. Personal items such as clothing, household items, and appliances, furniture, and electronics were lost. Homes and buildings suffered infrastructural damages, and vehicles were also damaged by floodwaters. In the agricultural sector, crops and livestock were lost, and many local businesses suffered losses. Major transportation routes, such as the Uriah Butler Highway, were impassable to regular traffic for two days, and roads in and around the aforementioned communities were also impassable. The main commercial airport, Piarco, was also closed due to runway flooding. Schools in affected communities were closed.

Due to the impassable roads, some health facilities could not service the local population due to persons' inability to get to and from the health centers, more so in the Eastern region. Some of the facilities that were directly impacted were the Sangre Grande General Hospital, the Mayaro Emergency Health Services, and the St. Helena Health Centre. Health care staff servicing facilities were unable to commute and assist in response efforts.

Response Efforts

As reports were received about the severity of flooding, response teams from the Trinidad and Tobago Regiment, the Trinidad and Tobago Police Service, the National Fire Service, and staff members of the Regional Corporations and NGOs, were mobilized to help communities. The ODPM, under the Ministry of National Security, coordinated the national level response, whereas, the Regional Corporations, which have local emergency and disaster response units, coordinated the community-level response. Areas first affected were Sangre

Grande and Greenvale. Shelters were opened to accommodate those whose homes would have been affected by the floods. Rescue teams went out using boats and trucks to help rescue trapped persons in order to take them to the aforementioned shelters and health centers, where they could be assessed and treated as necessary. Some of the affected persons included vulnerable groups such as pregnant women, the disabled, and the elderly.

Mental health professionals were also deployed to shelters and health centers to provide counseling for persons who were traumatized by the event, however, the uptake of this service was limited, with affected persons focusing on accessing medical treatment services for illness and injuries. On the national level, citizens, faith-based organizations, businesses, schools, and NGOs mobilized resources from the population and supplied toiletries, food household items, and clothes to affected communities. The government of Trinidad and Tobago supplied monetary compensation to flood-affected victims to assist in the purchasing of clothing, furniture, and aid for small home repairs.

Syndromic Disease Surveillance

The flooding event occurred during epidemiological week 42. Limited syndromic surveillance data were available from health centers serving affected communities in the north-central area. Primarily respiratory and gastroenteritis data were collected. Health centers recorded no data recorded for undifferentiated fever syndrome. Increases were seen in acute respiratory infection in both the < and > 5-year age groups in the eight weeks following the flooding event (see Figures 1 and 2). A similar pattern was seen with gastroenteritis data in both the < and > 5-year age groups (see Figures 3 and 4). The local surveillance system also captures acute viral illness with the number of cases recorded higher during the eight weeks post-flooding (see Figure 5). No baseline or epidemic threshold data were obtained for the reviewed weeks.

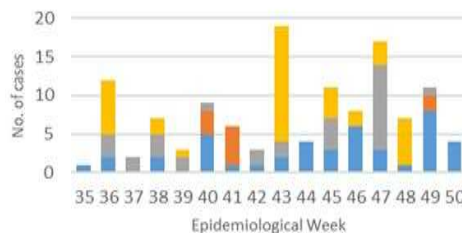


Figure 1. Cases of acute respiratory infection <5 years by epidemiological week, 2018, in North Central Trinidad Health Centres.

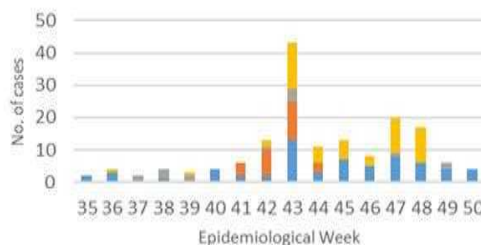


Figure 2. Cases of acute respiratory infection >5 years by epidemiological week, 2018, in North Central Trinidad Health Centres.

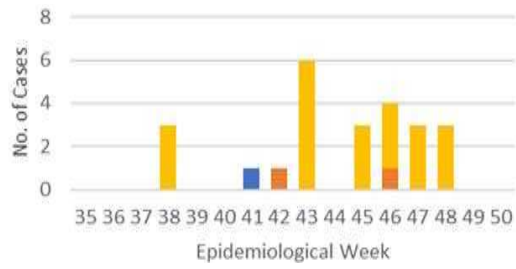


Figure 3. Cases of gastroenteritis <5 years by epidemiological week, 2018, in North Central Trinidad Health Centres.

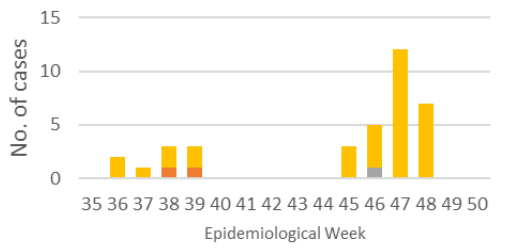


Figure 4. Cases of gastroenteritis >5 years by epidemiological week, 2018, in North Central Trinidad Health Centres.

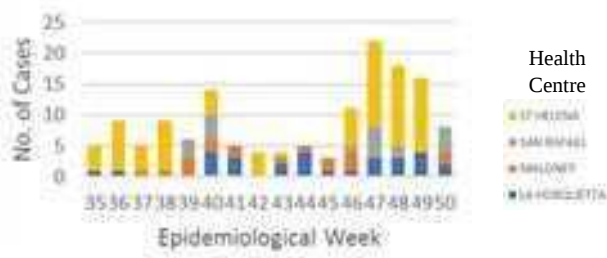


Figure 5. Cases of acute viral illness by epidemiological week, 2018, in North Central Trinidad Health Centres.

DISCUSSION

In Trinidad and Tobago, the highest rainfall and flood associated events are typically observed during November, however, over the last few years, a potential shift may be seen towards October [3, 4]. Above-average rainfall during three days in October 2018 precipitated what has been termed as an unprecedented flooding event in Trinidad, which impacted on a large scale communities, transportation routes, the agriculture, business, education, and health sectors. Additionally, the destruction of vegetation through bush fires/farming activities along the Northern and Central range of Trinidad, impacts on watersheds, further worsening flood events.

The early warning alerts issued by the TTMS were provided to the public and response agencies allowed most communities to prepare for the potential flooding event. The color-coded nature of these alerts targeted attention to the gravity of the developing situation, allowing response agencies and citizens time for some level of preparation. Social media was

noted as being heavily used in the dissemination of messages. In terms of the effectiveness of the response, a noted disparity was a certain degree of disconnect between the emergency/disaster response units of the Regional Corporations and the ODPM. The Corporations largely acted independently within their areas of responsibility with limited communication and coordination between the local and national level response systems.

Floodwaters pose immediate dangers to human health, and long-term effects result from displacement and worsened living conditions. Of particular concerns following flooding is the rise in communicable diseases, such as food and water-borne diseases, respiratory disease, and arboviral/mosquito-borne diseases [7]. While mosquito breeding sites may be washed away during flooding events, residual pooling post-flooding creates new breeding sites, increasing the transmission potential of viruses, such as Dengue, Chikungunya, and Zika [7]. Injuries during flood incidents are quite common, and the stress levels and trauma experienced by both flood victims, as well as relief and aid workers, are well documented [8]. Where flooding impacts transportation routes, this limits access to health services and medicinal supplies, which will also affect persons with chronic disease. In the October Trinidad flooding, access to health care was largely available, with the limitation more being seen in the inability of health care staff from flood-affected areas to commute and provide services at facilities. Future emergency response plans should describe mechanisms to mitigate the effects of major routes impacted by flooding.

Interpretation of the limited syndromic surveillance data available from health centers servicing affected communities was difficult. Baseline/threshold levels are not calculated at the local levels of the surveillance system and as records are paper-based, access to data to generate baselines is often not feasible. Data from local levels are aggregated and forwarded to the national level. Hence, for the weeks investigated, a determination cannot be made as to whether the rise in cases of acute respiratory infection and gastroenteritis was unusual for the period observed. The majority of health centers did not collect disease-specific data, either due to lack of human resources, limited coordination among sentinel physicians, lack of training, or limited collection of specimens to facilitate diagnostic testing confirmation. Of note, is that the St. Helena health center reported the highest number of cases across all syndromes (see Figures 1-5), however, a determination cannot be made about the reliability of this data or whether the pattern seen is an artifact due to a higher level of focus on reporting in this center.

In Trinidad, the classification of disease under acute viral illness is broad/nonspecific. In many instances, if regional syndromic classification guidelines are adhered to, the majority of viral cases would be reallocated under respiratory or undifferentiated fever syndromes [9]. This points to the need for continuous training and sensitization of physicians and surveillance personnel. Although no deaths resulted from the flooding event, the lack of continued post-disaster surveillance in the weeks/months that followed as services and lives were disrupted does not allow for an effective assessment of health impact. Post-disaster surveillance should also include shelter surveillance encompassing areas such as environmental health, food safety, water quality, and even pet/companion wellness. Syndromic, disease-specific surveillance, and mortality surveillance are critical.

Within the Caribbean, health systems need to rapidly increase their transition to climate resiliency to manage projected reductions in food quality and security, increases in water stress, increases in the magnitude and frequency of extreme weather and climate events, increases in the geographic range of mosquito-borne diseases, and changes in the burdens of

other climate-sensitive health outcomes. Resilience strategies can include improvements in emergency flood notifications; improvements to infrastructure that accommodate river flow; community education and outreach campaigns; restoration of watersheds and stricter enforcement of urbanization and development. The October 2018 Trinidad flooding event tested several response systems within the country. While the efforts at the local and national governmental levels are to be commended, improvements are required in terms of having coordinated, integrated responses. There is also a strong need to improve disease surveillance capacity at the local health center/sentinel site level to generate accurate, detailed data for timely public health action and response.

Key informant interviews were conducted with persons from the Regional Corporations, the Ministry of Health and NGOs/Civil Society. Groups such as the ODPM, Ministry of Social Development, faith-based organizations, and schools were unable to be included during the project time allotted for the interview process. Also, as baseline and threshold health data were unavailable for the weeks investigated, it is unknown if the rise in cases of acute respiratory infection and gastroenteritis was unusual for the period of time observed.

ACKNOWLEDGEMENTS

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Chapter 107

SERVICE LEADERSHIP EDUCATION FOR UNIVERSITY STUDENTS

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While it is good to see there are many leadership programs in the market in different parts of the world, there are several limitations of the existing leadership programs. Primarily, most of the programs focus on skills (i.e., doing) of leaders without much

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consideration of the inner qualities (i.e., being) of leaders. While skills are important, leaders with skills are just technicians or technocrats who are driven by their basic motives of acquiring fame or earning more money. However, true leaders are motivated by caring concern and moral values. Eight universities funded by a private foundation worked together to develop service leadership education. In this book we wish to document the achievements in different institutions and highlight the specific projects with different foci. We earnestly hope that through the publication of this book, service leadership education can flourish in different service economies.

INTRODUCTION

Leadership education is an important business for many sectors, particularly the business sector. Many leadership programs have been developed to nurture business leaders who can maximize the profits of the companies. There are also many elitist leadership training programs, which attempt to promote the leadership abilities of professionals in different disciplines. In the business world, leadership development programs are expensive. Meanwhile, there is a strong need to promote leadership development among students before they enter the workplace.

While it is good to see there are many leadership programs in the market in different parts of the world, there are several limitations of the existing leadership programs. Primarily, most of the programs focus on skills (i.e., doing) of leaders without much consideration of the inner qualities (i.e., being) of leaders. While skills are important, leaders with skills are just technicians or technocrats who are driven by their basic motives of acquiring fame or earning more money. However, true leaders are motivated by caring concern and moral values. Besides, with the change of the global economies shifting from the manufacturing mode to the service mode, the requirements for successful leadership under the service economies have changed [1]. For example, while leaders are expected to be authoritarian and top-down in the traditional manufacturing economies, desired leadership qualities include distributed leadership where bottom-up decisions are valued [2, 3].

Another important leadership quality that differentiates manufacturing economy and service economy is the role of moral character. While leaders emphasize “doing things right” in the manufacturing economies, the focus is shifted to “doing the right things” in the service economies. Finally, knowing how to care about other people is an important service leadership quality. As service providers, service leaders must care about the customers not simply because of maintaining good “PR” with the potential customers. In fact, genuine concern about people is intrinsic to service leadership. Furthermore, a successful service leader is one who shows concern about the followers [2, 4]. As Habecker remarked, “true leaders are motivated by loving concern rather than a desire for personal glory” [5].

The final observation of the leadership literature is that there are few validated leadership programs in the field. There are two main reasons why systematic and validated service leadership programs are important. First, with the emergence of service economies, university students should develop more “soft skills,” such as communication skills, ability to cope with adversity, and ethics, which are not systematically covered in the formal curriculum. Hence, when we talk about helping university students to develop in a holistic manner, service leadership education that emphasizes competencies, caring disposition and moral character is

indispensable. Second, service leadership education can help to enhance the employability of university graduates. In fact, many employers are complaining that university graduates do not really suit the job demands within service economies. There still remains a gap between what the employers want from their employees and what the graduates possess [6]. Service leadership education that is designed to meet the demands of service economies would help to fill this gap.

With reference to the above considerations, it is argued that there is a strong demand for service leadership in service economies. This is particularly the case for Hong Kong because service constitutes roughly 93% of the GDP of Hong Kong [7]. With the support of the Victor and William Fung Foundation, an initiative entitled “Fung Service Leadership Initiative” was launched in 2012 to support eight universities funded by the University Grants Committee (UGC) of the Government of the Hong Kong Special Administrative Region to develop service leadership education. In the past years, colleagues in the eight UGC-funded institutions have worked very hard to develop service leadership curriculum in Hong Kong with several major components. First, credit-bearing service leadership subjects covering the basic tenets, core beliefs and subject matters of service leadership have been developed. To illustrate this point, colleagues have developed a credit-bearing subject entitled “Service leadership” and symmetrically evaluated its effectiveness [8, 9]. Besides, credit-bearing subjects related to service leadership, such as social entrepreneurship, service learning, and general education have been designed. Second, non-credit-bearing service leadership programs have been developed. In particular, service learning programs have been developed and implemented to promote service leadership qualities in university students. Third, curriculum materials such as videos, exercises, experiential learning activities have been developed.

Finally, research projects have been carried out to expand the knowledge base of service leadership education in Hong Kong. For example, colleagues have done work to assess service leadership qualities. Effort has been made to examine the views of major business leaders on desired service leadership qualities. Most importantly, studies have been carried out to evaluate different service leadership initiatives and to examine the impact of different service leadership initiatives on the development of service leadership qualities in the students.

To document the achievement of the Fung Service Leadership Initiative, an international conference was held in May 2014. The keynote speeches and presentations are documented in a book [10]. To wrap up the Fung Service Leadership Initiative, a wrap-up conference was held in January 2016. Again, through this book, we wish to document the achievements in different institutions and highlight the specific projects with different foci. Same as the last book, we earnestly hope that through the publication of this book, service leadership education can flourish in different service economies.

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Chapter 108

SERVICE LEADERSHIP EDUCATION AT THE CITY UNIVERSITY OF HONG KONG

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ABSTRACT

At the City University of Hong Kong (CityU), quality professional education and whole-person development go hand in hand. With the advent of the four year curriculum and CityU's emphasis on Discovery-Enriched Curriculum, new opportunities exist for innovative teaching, knowledge transfer, and student service leadership education. In particular, a major development was the development of a 'Social Entrepreneurship Initiative' in 2011 that evolved rapidly into a broad interdisciplinary platform of 30 faculty members that is now branded as Project Flame, Social Innovation and Entrepreneurship@CityU (Project Flame). With generous sponsorship from the Victor and William Fung Foundation, and building upon the curriculum framework developed by the Hong Kong Institute of Service Leadership and Management, Project Flame is committed to improving Service Leadership in Hong Kong. Based on these inputs, with additional funding provided by CityU, Project Flame delivers a vibrant range of cross-disciplinary and sectoral programs to foster the emergence of a new generation whose members possess the service values and leadership skills required to become the service leaders in our region. This chapter introduces briefly Project Flame's key program areas - Professional and Academic Education; Social Innovation Incubation; Research and Knowledge Transfer; and - the focus of this paper - Student Service Leadership. With its multi-disciplinary and community-focused approach, Project Flame's social innovation and entrepreneurial activities enable students and staff to enhance their knowledge, skills

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and experience in service leadership. The chapter outlines Project Flame's unique approach, key activities, and concludes with brief reflections and a look at the future direction ahead.

INTRODUCTION

As a higher education institution, the City University of Hong Kong (CityU) is committed to fostering the growth of a new generation of leaders in various professional fields and sectors. With its wide range of taught, experiential courses; its hosting of international conferences on social innovation, social enterprise start-up and scale-up; and its research activities that include the development of the Hong Kong Social Enterprise Endorsement Mark, CityU is widely recognized as a leading player in promoting social innovation and entrepreneurship in Hong Kong. Supported by the generous sponsorship of the Victor and William Fung Foundation and building upon the curriculum framework developed by the Hong Kong Institute of Service Leadership & Management Ltd., CityU is determined to promote quality Service Leadership Education in Hong Kong. It is achieving this goal through a series of curricular and extracurricular programs designed to foster and sustain younger generations in becoming service leaders in the region.

In the fall of 2011, an informal 'Social entrepreneurship initiative' was established on a voluntary basis by a group of like-minded staff. This has since evolved into a broad interdisciplinary platform of 30 faculty members from 18 academic and support units. Now branded as Project Flame, Social Innovation and Entrepreneurship@CityU (Project Flame), Project Flame's vision and agenda encompass programs that directly address the core beliefs, ethics and concerns of Service Leadership and Management (SLAM) education. Keys amongst these are the beliefs in the importance of character, that everyone is a leader, that leadership is a service for satisfying the needs of others and oneself, that the server is the service, and that values relating to trust, respect and fairness are essential ingredients for leadership effectiveness [1, 2]. The synergies between SLAM Education and our social entrepreneurship initiatives distinguish Project Flame's and CityU's approach to Service Learning education from those of other institutions.

APPROACH AND ACHIEVEMENTS

From the start, Project Flame applied and adapted the original SLAM intellectual framework to its integrated framework of social innovation, entrepreneurship and student service leadership. The grant from the Li and Fung Foundation and the government matching scheme, augmented by internal funding for course and program developments, provided Project Flame with the resources required to build up a strong support team to carry out its programs.

Project Flame's approach to SLAM is infused with the values and programs of social innovation and entrepreneurship, and is implemented via four program areas, namely: *professional and academic education; student service leadership; innovation incubation; and research and knowledge transfer*. Our achievements thus far are outlined below.

Professional and Academic Education

The academic educational program provides a sustainable platform to deliver SLAM education. We have designed a coterie of Gateway Education (GE) courses and also Hong Kong's first Minor in Social Entrepreneurship. Our initiatives in undergraduate teaching of social entrepreneurship compares very favorably with universities abroad, most of which concentrate on postgraduate programs. In our pedagogical approach, our innovative teaching methods include experiential learning, practical orientation, student engagement, design thinking and practitioner sharing. Rich experiences of co-curricular learning are provided through student internships, study tours, competitions, service learning activities, seminars and media interviews on student projects.

Initial GE courses included: Enhancing Your Service Leadership for the 21st Century; Make a Difference: The Challenge of Social Entrepreneurship in a Globalized World; Changing Our Society: Turning Social Problems into Business Opportunities; Social Innovation and Entrepreneurial Venture Exploration; and Professions in Hong Kong: Critical Insights and Issues. Between them, these courses expose students critically to key knowledge, skills and values of effective service leadership that includes the characteristics and dimensions of quality service leadership as developed by Chung [1, 2]. They encourage deep learning through a combination of classroom teaching, experiences, reflection and application. They provide opportunities for practical training in service leadership through, for example, discussions of the roles of social innovation, entrepreneurship, civic engagement, and leadership in solving community problems. Guest lectures by local and international leaders in the fields of social innovation and enterprise, together with class visits to local social enterprises or service organizations, provide students with opportunities to identify role models and to learn from such individuals' and organizations' experiences, successes and failures. Students become engaged in social problems identification and social innovation incubation through participation in various team-based projects that require them to develop their own innovative solutions. Their ideas and plans are presented to panels of expert practitioners for their objective analysis and critical appraisal. The course entitled Professions in Hong Kong, Critical Insights and Issues broadens discussion of service leadership to the requirements of various service professions as well as to the career development of the students. The cumulated total enrolment in all our GE courses since the first offerings in 2012/2013, has already exceeded well over 1,000.

A milestone in curriculum development is the introduction of our interdisciplinary Minor in Social Entrepreneurship. This consists of a core course, Fundamentals of Social Entrepreneurship, and four elective courses that students select from a wide range of courses offered by the Departments of Public Policy, Applied Social Sciences, Management, Marketing, and the College of Business. One noteworthy elective course is Meeting Social Needs through Business Approach. This enhances the service leadership learning of the students and is also offered as a free elective to all other undergraduate students in the university.

Student Service Leadership

Our Student Service Leadership program aims to create direct experiences for students to participate, observe, and reflect on leadership qualities and challenges in various service settings. Particular attention is given to key aspects of service leadership and SLAM core beliefs, such as the importance of the concepts that leadership is a service and that everyone holds a position as a leader - whether in leading their own lives or been dealing with others and with complex situations. As such, there is always room for improving leadership effectiveness and this means that aspects of character, service commitment and various role and task competencies can and should be improved continuously.

Our student service leadership activities place an emphasis both on developing competencies and on learning from others who have proved successful in improving their own competencies and in serving the needs of others effectively and ethically. Agency visits for students have included those such as to the Hong Kong Observatory, North Point Police Station, New Life Psychiatric Rehabilitation Association, New Life Restaurant, Tung Wah Group of Hospitals, Dialogue in the Dark, Senior Citizens Home Safety Association, Green Ladies, Jockey Training School, Chef's Noodles, i-Bakery, Hong Kong Fair Trade Power, Microforest, and many more. Many social entrepreneurs have joined our classes to share their personal experiences and observations on leadership. For example, to kick-start the launch of our Minor, Professor Andreas Heinecke, the Founder of Dialogue in the Dark, gave guest lectures for three weeks with overwhelming response from the students such that he has since returned to hold even more classes for us.

Our international Internship Programs reflect the SLAM framework's recognition of the impact of globalization and the new opportunities this raises for caring, ethical service leadership. Internships provide the students with opportunities both to learn from those they are attached to, and to make a meaningful contribution to their activities. The first internships took place offered in Zhongshan City, Guangdong, with eight students working alongside interns from Beijing to undertake planning and promotion work for social innovation projects. In 2014, eight students took part in an internship program in Shanghai and, in June 2015, twelve students, selected from well over 100 applicants, undertook internships in a variety of social innovation and enterprise organizations in Singapore. In summer 2016, seven students were placed as interns with the Hondao Senior Citizens Welfare Foundation in Taiwan.

International study tours have included fifteen students going to study social enterprises in Singapore, fourteen students joining other students from Taipei, Shanghai and Hong Kong in a social enterprise exchange tour to Shanghai, and another fourteen students taking part in a study tour to social enterprises in Taipei. In January 2016, 14 students visited Social Enterprises in Shanghai and Suzhou where they gained exposure to social innovation ideas, issues and welfare practices in China.

In 2015, Project Flame was invited for the first time to take part in Project WeCan, a service project to provide leadership training and to meet needs of under-privileged secondary schools in Hong Kong. Initially, over 100 students were recruited to serve two schools in Kowloon East, and we are now serving three schools. Our students gain opportunities to serve and develop their leadership competencies while supporting the underprivileged or ethnic minority students from our partnering secondary schools. Activities have included holding experiential workshops to help school pupils to understand some of the practical issues facing

the elderly and to enhance their communication skills. Our students have led school pupils to visit an elderly center and a care and attention home, have facilitated English oral practice workshops, have led pupils on various outings, and have also hosted pupils from the schools for an experiential day visiting the CityU campus and learning about life as a university student. A particularly challenging activity has been holding an overnight student leadership camp that was designed and executed by Project Flame's student leaders together with one of our staff members. The first such camp served 20 pupils, the next, however, will be combining 60 pupils from three schools and will provide many opportunities for our students to gain valuable service learning experiences.

Perhaps the most significant highlight of our Service Leadership activities has been the partnering with the Junior Chamber International (JCI) to arrange three O! Love Tours in 2014, 2015 and 2016. Each tour matched twenty CityU students with twenty poor single elderly persons in Hong Kong to visit Taipei for a holiday. The students learn about communicating with and supporting the elderly and the tours provide excellent opportunities for them, not only to enrich their service learning and leadership experiences, but also to really understand the fundamental SLAM belief that the 'server is the service'. Both the elderly and student participants have found the tours to be truly life enriching experiences, and the O! Love Tour won the Best Social Service Project and also the Best of the Best of the 2015 JCI Outstanding Projects Awards.

Social Innovation Incubation

The ability to innovate is a very important leadership attribute. Our endeavors in innovation incubation have exposed students and faculty to key ideas and practices in social innovation and entrepreneurship. Activities have included: taking part in the Diamond Sedan Competition (winning third place), co-sponsoring the Social Enterprise Summit, and holding a 'Photo with a Message' Competition. We held a Mini-MaD (Make a Difference) Workshop on Zero Food Waste for 80 students in 2013-2014, with students working on implementable proposals to solve the chosen problem.

Our student volunteers operate 'Hand2Spot', which is our innovative campus second-hand shop, the first of its kind in Hong Kong. The students receive intensive training to run and lead the service and to innovate new marketing and service delivery strategies. For example, in 2015 student leaders initiated a book auction in addition to the more routine on-line and counter sales. Many of Hand2Spot student leaders have engaged also in activities such as our three Green Fashion Shows in which student models, with the support of a local fashion coordinator, make-up artists and sound engineers, wear donated second-hand clothing to highlight the needs for environmental consciousness and a new culture of re-use. In addition to the above activities, students taking the GE course, *Make a Difference: The Challenge of Social Entrepreneurship in a Globalized World*, work together in teams to identify social or environmental problems of their own choice. They then develop ideas to tackle their chosen problem. The students' innovations are required to be implementable and two projects have won particular praise. The first, "Transfriendly", developed a walking stick that can vibrate and help the elderly to navigate their way onto incoming buses. This won the

My Own Discovery Award 2014 in CityU. The second is called “Sonus” and entails a device that translates finger motion into speech. This won the Project Flame Social Innovation Award 2014 and has since been submitted for a patent application by CityU’s Knowledge Transfer Office.

In 2013 and 2014 we organized two international symposia that included pitching competitions with prizes to encourage young people to imagine, develop or implement their own social innovations and enterprises. Leading social entrepreneurs from the UK, Australia, Indonesia, USA, Malaysia, China, Taiwan and Hong Kong provided insights into how they identified the particular problems they wished to address. They then discussed the challenges, successes and failures encountered as they started or scaled up their enterprises. The speakers not only provided role models for exemplary service leadership and successful entrepreneurship, but also provided master classes for participants that included giving free advice to those starting or seeking to scale up their own social enterprises.

Research and Knowledge Transfer

Initial knowledge transfer activities included the Social Entrepreneur in Residence Program, a Community Forum on Social Innovation, a Workshop on Medicine Management Systems in Institutional Settings, and a visit to Social Innovation Parks in the cities of Shunde and Zhongshan that resulted in a student internship for eight students in Shunde in June 2013.

The above mentioned International Symposia in Discovery, Idea Incubation and Scalable Social Impact were co-organized with serial social entrepreneur and author Michael Norton OBE, the co-founder of UnLtd in the UK, India and South Africa, and also the co-founder of the International Centre for Social Franchising. By bringing together an impressive array of prize-winning international social innovators and service leaders to share their experiences and lessons with our students, staff and community participants, these symposia provided focused opportunities for knowledge transfer which, together with research, forms a key part of the core mission of the university. The social enterprises founded or managed by the speakers—for example Spark Inside, Buffed, Alternative Indigenous Development Foundation (AIDFI), Bike Works, Senior Citizens Home Safety Association, 18 Chefs, Diamond cab, Green Monday and many others, have all proved successful at providing new services or fresh opportunities for the socially disadvantaged – such as for the elderly, ex-offenders, ethnic minorities, rural poor, children and, together, have already served hundreds of thousands of people. Notably, all of these organizations possess mission statements in which the values of service and leadership are stated very clearly and thus provided excellent exemplars for our students.

In November 2013, Project Flame began a key applied research activity when it was awarded a contract by the Hong Kong General Chamber of Social Enterprises (HKGCSE) to develop a Social Enterprise Endorsement System for Hong Kong, which has now been known as the Social Enterprise Endorsement Mark (SEE Mark). The project was co-funded by Standard Chartered 150th Anniversary Community Foundation and by City University. Project Flame was responsible for developing the certification tool and for refining it through pilot-testing with 30 social enterprises to match the needs of the local social enterprise ecology. The SEE Mark is not only creating wide community impact and is also helping to enhance many aspects of service leadership in action. The scheme has been designed

specifically to cater for all social enterprises at different stages of development ranging from incubation through to advanced level. For every category, a particular emphasis is given to capacity building and to steps for enhancing both service and governance. One side benefit of the research has been the building up of new knowledge about social enterprise leadership and service - much of which is now being used in our classes with students. Another applied research activity is a new annual impact evaluation undertaken for the HUB Hong Kong, a local NGO that serves the poorest children and families in Sham Shui Po. The project engages students to help conduct interviews with children, their family members as well as with staff and volunteers in the HUB. This again enables the students to gain fresh insights into the nature of service and service leadership.

IMPACTS

We have no doubt that Project Flame has been successful in bringing forth positive impacts on its participants. In particular we emphasize: –

Proactive Engagement

Our programs, courses, internships, knowledge transfer and research activities provide excellent opportunities for both students and staff to reflect upon the many ways in which service leadership embraces the challenges of satisfying others' and one's own needs ethically, effectively and with prosocial values. Our initiatives in service leadership and social entrepreneurship have gone well beyond our pioneering classroom teaching and learning. In particular, we have sought to enhance students' learning and character development through a wide range of intra- and extra-curricular related activities such as inspirational guest talks, field trips, study tours, international internships and more. Such activities create positive impacts for students and for those they serve. They also reaffirm our belief in importance of adding value through proactive engagement between the university, students and members of the local and international communities.

Personal Growth

Student projects have shown excellent promise in social innovation and service design. A few projects have won prizes and have potential for patent development and production. The students participating in Project Flame activities have received highly complementary feedback from outside organizations. For example, several employers of students in the summer service leadership internships in Zhongshan, Shanghai and Singapore have stated their willingness to employ the interns once they are graduated. Feedback from the schools served by Project Flame's students under Project WeCan has also been very positive with our being asked to serve an additional school as a result. Students' own feedback and reflections on their learning continuously stress how their participation in our activities has added considerably to their personal growth and social awareness, with many students reporting that it has enhanced their commitment to serving the community in their later lives.

FUTURE DIRECTION

Our road down the service leadership and social entrepreneurship journey has been a rich and exciting experience. With the generous support from the Victor and William Fung Foundation we have built up an excellent foundation for Project Flame and our Service Leadership Initiative. We are now entering a new phase. New courses have been introduced including *Changing Our Society; Turning Social Problems into Services/Business Opportunities; Critical and Cultural Issues in Hong Kong's Service Economy; Writing Apps for Social Innovation; and Social Innovation and Entrepreneurial Venture Exploration*. Our study tours and internships are continuing with our most recent activities in 2016 being held in Shanghai and Taipei.

With the ending of the Li and Fung funding, we are taking steps both to enlarge collaboration and to create synergy between Project Flame and other units or organizations within or outside the university. Such bodies include, for example, CityU's Innovation Commons (IC) and the Hong Kong Jockey Club CarbonCare InnoLab (COIL), with whom we are organizing sustainability events. Study tours, internships, knowledge transfer workshops, applied research with local social enterprises and our service with Project WeCan are continuing, thus further enhancing the opportunities for students to develop their values, character and service leadership knowledge and skills.

In conclusion, through Project Flame's four broad programme areas, CityU has been able to enrich not only the learning experiences of its students, but also our service to the university and the wider community as well.

ACKNOWLEDGMENTS

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Chapter 109

SERVICE LEADERSHIP AT HONG KONG BAPTIST UNIVERSITY: A NEW CONCEPT IN GENERAL EDUCATION

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ABSTRACT

Amid the substantial increase in the role that the service sector plays in the economy of many countries, it is imperative to prepare graduates to provide service with care, and the ethical behavior that is a critical component of service. Institutions of higher learning have been instrumental in developing curriculum that is responsive to societal needs. In the case of service leadership, the Hong Kong Institute of Service Leadership and Management suggested that the Hong Kong tertiary institutions consider developing curriculum that will be responsive to the needs of the service industry and at the same time enhance leadership capabilities of the student-learners. In response to this suggestion, Hong Kong Baptist University (HKBU) initiated this project by designing General Education (GE) courses that addressed service leadership in a variety of disciplines and environments. In the last few years, HKBU has developed ten courses as part of the requirements in its General Education programme. Assessment of the effectiveness of the offerings shows that the students are valuing their exposure to the philosophy of service leadership, and have developed the valued characteristics of effective leaders, including empathy, openness in mind, being creative, socially responsible and reflective citizens.

INTRODUCTION

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Institutions of higher learning have been instrumental in developing curriculum that is responsive to societal needs. In the case of service leadership, the Hong Kong Institute of Service Leadership and Management started the Li and Fung Service Leadership Initiative, which suggested that the Hong Kong tertiary institutions consider the possibility of developing curriculum that will be responsive to the needs of the service industry and at the same time enhance leadership capabilities of the student-learners.

With the financial support from the Victor and William Fung Foundation, Hong Kong Baptist University initiated this project by incorporating service leadership courses in its General Education (GE) offerings. This meant giving the faculty from the different disciplines a chance to design and develop interdisciplinary courses that addressed service leadership in a variety of environments. GE provides a perfect platform for this type of curriculum as it exposes a large number of students to the concept of service leadership, and encourages integration of knowledge across the curriculum.

The aim of GE is to instill in students the ability to develop a broad knowledge, and intellectual skills necessary for lifelong learning as stated by Cuevas, Matveev, and Miller [1]. Specifically, our graduates today enter the world of work facing many complexities that are part of the realities of today. To be prepared to deal with these complexities, students need to be able to integrate knowledge from different disciplines. Xing and Ng [2] regarded professional competence, critical thinking, effective communication, innovative problem solving, and ethical leadership among the given and desired key attributes for the GE curriculum. GE hence becomes the bridge between the discipline specific majors and the values that university education espouses. One of those values is the ethical leadership that must go hand and hand with the increasing emphasis in providing services.



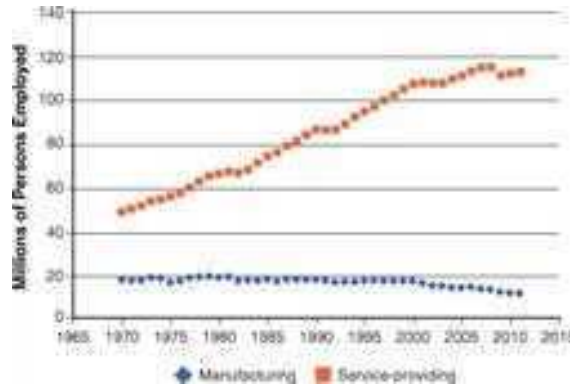
Source: The Global Economy.com ([http://www.theglobaleconomy.com/rankings/ Share_of_services/](http://www.theglobaleconomy.com/rankings/Share_of_services/)).

Figure 1. Service sector’s value added to the GDP of economies.

With increasing emphasis throughout the world on services and the contribution of the service sector to the GDP of economies as shown in Figure 1, it is imperative that the future graduates become familiar with the elements of services and the leadership needed to continue its growth path.

Aside from the significant contribution of the service sector to the GDP of countries, the most crucial aspect of the service sector's ascendance is thorough integration of services with virtually every other aspect of the present-day world economy. Service sector has become a critical source of new local jobs, as well as an essential ingredient in creating a commercial

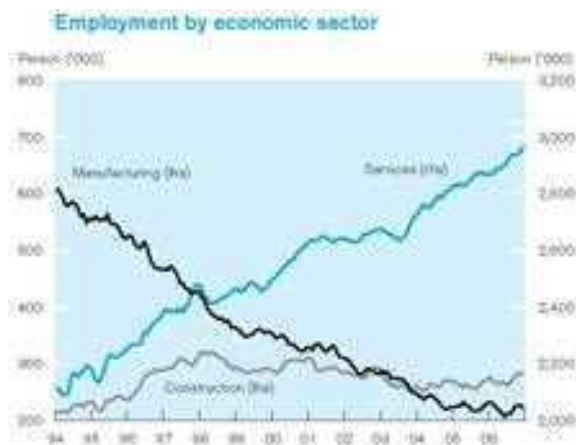
environment conducive to entrepreneurship, and a vital link to the wider world economies. On a global scale, the service sector is growing rapidly. It does not matter whether it is Hong Kong or New York, the employment generated by the service sector as compared with the manufacturing sector is unprecedented. According to Economy Watch [3] as of 2008, 87.7% of the workforce in Hong Kong is employed by the service sector. Similarly, if we were to look at the employment generated by the service sector in the U.S. between 1965 and 2013 [4], we observe an increasing growth over the decades as shown in Figure 2.



Source: Bureau of Labor Statistics, Employment, Hours, and Earnings from Current Employment Statistics survey (National), <http://data.bls.gov/cgi-bin/surveymost?ce> (Accessed on 03/03/2016).

Figure 2. Employment contribution of the service and manufacturing sectors.

According to Hong Kong Monetary Authority [5], stronger growth in employment relative to the labour force has driven down the unemployment rate from the peak of 8.5% in mid-2003 to a nine-year low of 4.2% in the second quarter of 2007. Distribution of employment by economic sector shows that growing labour demand in the service sector has been the key driver of employment growth over the past few years as shown in Figure 3.



Source: Hong Kong Monetary Authority Quarterly Bulletin, September 2007.

Figure 3. Employment by economic sector.

In view of such contributions to the welfare of an economy, it is essential for the graduates of institutions of higher learning to become familiar with the concept of service leadership and what role they can play in maintaining high quality service in their chosen disciplines.

Service-driven leadership begins with a fundamental shift in attitudes and actions. How to develop a curriculum that addresses a shift in attitude and action was an important element to be addressed. Our courses attempted to bring theory and practice to surface. We aimed at creating a number of courses so as to provide greater opportunities for the students to be exposed to the concept of service leadership. Besides the curriculum, we offered various kinds of co-curricular activities outside of the classroom, so that students can learn how to be good service leaders.

The ultimate goal of developing Service Leadership Education (SLE) courses at HKBU under the GE curriculum is to allow our students to experience service leadership in their university study and to cultivate in them the leadership capabilities for providing excellent services with care. The GE Programme is an ideal platform to initiate the SLE project because while students are broadening the scope of knowledge as foundation by taking courses from a wide variety of disciplines, they can also experience leadership through dynamic interactions with peers who are studying in different majors.

Course Development and Delivery

A total of ten SLE GE courses (see Table 1) were developed and over 400 students were enrolled in the courses offered in the past years. These GE courses incorporating the ideals of service leadership were purposely designed and delivered to build leadership competencies in our students. Ethical practices and the importance of positive social relationships are deeply emphasized in those SLE courses to equip students to be good service leaders. It is hoped that they can develop the valued characteristics of effective leaders, including empathy, openness in mind, being creative, socially responsible and reflective. All of the SLE courses developed aim at engaging the students in various kinds of teaching and learning activities, so that they can understand how service leadership is influenced by social perceptions.

In these holistic and interdisciplinary SLE courses, we have incorporated content and pedagogical strategies that help students to improve their ability to recognize the importance of trust and respect in social contexts, and how to deliver service with competence, and care. We believe that theories, research, and practices from a wide variety of academic disciplines and a wide range of scholar-practitioner experiences inform, support, and enhance service leadership curriculum and extra-curricular activities. We have achieved this goal in our courses which were well received by the students. The features of our SLE courses are shown in Figure 4 and the details of our SLE courses as well as the related publications can be viewed at <http://ge.hkbu.edu.hk/ge-programme/sle/>.

The approach taken by HKBU in offering GE courses with service leadership elements to our students is distinctive. From a programmatic perspective, we looked at two salient means through which our university could support service leadership: (a) curricular, and (b) extracurricular. Much of the work currently done in most universities relate to the extracurricular activities such as service learning. Our emphasis has been on the curricular

approaches to engage students in the community. We view service leadership as an integral part of a course that emphasizes the role of leadership in providing services to the community at large. Educational experiences in which students participate in an organized service activity that meets identified community needs (whether it is a business or a social organization) and reflect on the service activity in such a way as to gain further understanding of the course content, a broader appreciation of the discipline, and an enhanced sense of civic responsibility have been the hallmark of these courses.

Table 1. Courses

No.	Course title	Areas covered	Offering departments/offices
1	Leadership in Sustainability	Business, Science	Department of Management
2	Service Leadership in Action (Health Services)	Chinese Medicine, Social Sciences	School of Chinese Medicine & Department of Social Work
3	Service Leadership and Emotional Intelligence	Arts, Social Sciences	Department of Social Work & Office of Student Affairs
4	Paths to Service Leadership in Health Services	Arts, Chinese Medicine	Department of Religion and Philosophy & School of Chinese Medicine
5	Language and Service Leadership	Arts, Social Sciences	Department of English Language and Literature
6	From Responsible Citizenship to Service Leadership	Arts, Social Sciences	Department of Religion and Philosophy
7	Service Leadership and Meaning of Life and Death	Arts, Social Sciences	Department of Religion and Philosophy
8	Sharing Values: Interreligious Dialogue on Real Issues in the Real World	Arts, Social Sciences	Department of Religion and Philosophy
9	Service leadership in Learning Communities	Arts, Social Sciences	Department of Education
10	Service Leadership Practicum	Business, Social Sciences	Department of Marketing



Figure 4. Features of SLE courses at HKBU.

Developing service leadership at the institutional level required us to pay special attention to the following elements: awareness, planning, support, expansion, and evaluation. Research conducted at 44 institutions in the United States (US) that participated in a three-year study of integrating service with academic studies identified four constituencies that a service learning/leadership programme should focus its attention: institution, faculty, student, and community.

In the last three years, we have effectively engaged all parties in constructing courses that will have a significant impact on the lives of our graduates for years to come. The lessons learned from this project have been numerous. The success of the project needs proper planning, providing workshops to faculty, and supporting the extra-curricular activities that were a part of these courses. Assessment of the SLE courses all point to the positive impact these courses have on the lives of our students.

Faculty Activities on SLE

For faculty, we organized workshops on the design of SLE courses. Participating colleagues had an opportunity to discuss with their co-workers and identify potential partners for designing and delivering new courses. In addition, they had a chance to explore how they could facilitate student learning effectively inside and outside of the classroom in the SLE courses. Also, guest speakers from different backgrounds were invited to conduct seminars on the topic. Dr. Lu Yu, Assistant Professor in the Department of Applied Social Sciences, The Hong Kong Polytechnic University, was invited to deliver a seminar on “Character Strengths in Chinese Culture: Confucian Virtues and Service Leadership” in October 2013. Seminar on “General Education, Service Leadership and Management” was conducted in October 2014 by Mr. Po Chung, who shared his latest thoughts on the philosophy of service leadership and how GE makes an impact on the management in the real business world.

As a way to encourage more open dialogues on the teaching and learning in GE courses, we organized a retreat at the end of each semester. Colleagues teaching SLE courses were invited to share their experience and good teaching practices with other faculty. Through different kinds of training and workshops, faculty can become more effective facilitators in student learning. Successful strategies are also identified to develop sustainable service leadership curricula and activities at the university.

Student Co-Curricular and Extra-Curricular Activities on SLE

In addition to the SLE curriculum, various kinds of co-curricular activities were organized for the students so that they can learn how to be a good service leader outside the classroom. We provided abundant opportunities for the students to broaden their horizons on the concept of service leadership. We initiated the “Be eager to learn, to care, to lead” series in relation to the SLE project, which aims at providing opportunities for students to experience and learn how to be a leader in serving the people in need. The activities we organized over the years are shown in Table 2.

Table 2. Events

Date	Event
May 2016	Outing to New Life Social Enterprise
March 2016	Oxfam x Eldpathy Sociology Game on HK Elderly Poverty
January 2016	Theatre in the Dark: "The Choice of Hamlet"
November 2015	Guest talk on Service Holiday Co-organized with Department of Management, School of Business
October 2015	"Be eager to learn, to care, to lead" Series: GE x DiD Night (co-organized with Dialogue in the Dark for the 2 nd time)
October 2015 – March 2016	Youth Ambassadors for Social Inclusion Co-organized with Dialogue in the Dark
March 2015	"Be eager to learn, to care, to lead" Series: Breaking the Boundary! - Dialogue with Ricky Wong cum GE Outstanding Students Award Ceremony
February 2015	"Be eager to learn, to care, to lead" Series: GE x DiD Night (co-organized with Dialogue in the Dark)
November 2014	"Be eager to learn, to care, to lead" Series: Extraordinary 2 hours (Co-organized with i-dArt)
November 2014	Seminar on Service Leadership: Going Green in the Office Dr. William Yu, CEO of World Green Organization

We promoted the concept of Service Leadership among students through different channels and initiatives, such as cooperating with other offices or units to organize various kinds of activities for our students. The GE Office cooperated with the Office of Student Affairs to organize a global summit on "Explore the Unexplored" on 28 and 29 March 2015. Nearly 100 local and international students joined the event to discuss a couple of global and local issues. Through the implementation of the concept of "Act locally, Think globally," participants' awareness of global issues and understanding of what global citizenship means were enhanced.

Last year, the GE Office sponsored the Public Speaking Contest of the School of Business by giving a prize to the winner who delivered a speech on service leadership. Our office also sponsored a student to participate in the Change-Makers Programme of the Office of Student Affairs in which she conducted research on the theme of "Hunger and Poverty" in an 8-day service trip to Nepal. Through the above activities, we hope that students can be equipped with the qualities and capabilities of being good leaders while delivering excellent services.

Assessment of SLE Courses

To evaluate student learning in the SLE courses, we conducted focus groups to collect feedback from students who took those courses. Generally, they had very positive feedback on the course especially on the special teaching and learning methods used to stimulate their reflections on being service leaders. It is found that students who took our SLE courses show good indication on ways to improve their leadership capabilities and they have got more extensive understanding of different leadership models. Some of them reflected that they are now more caring and sensitive to others' needs. They understand deeper the essence of delivering excellent services to people as well.

For SLE co-curricular activities, post-event survey was distributed after each event and the average score of satisfaction of overall experience was over 8 out of 10. It shows that the SLE courses and activities gave students new perspectives on leadership and they are provided with the opportunities to apply what they have learnt in class to real situations.

CONCLUSION

The SLE project at HKBU is successful and is regarded as a significant step to further enrich the curriculum of HKBU's GE Programme. The SLE courses and co-curricular activities offered multiple opportunities and varied experiences for students to develop skills in service leadership. At the individual level, students can learn about their strengths and weaknesses as leaders and followers, experiencing leadership through action and reflections. At the community level, students are more willing to contribute their talents and knowledge through providing services to the people in need and bring positive impact to the community. They are better prepared to be more effective leaders in their career and in community life after graduation.

As for our future plans, HKBU will continue to develop courses on SLE under the GE Programme. We shall encourage more interdisciplinary collaboration between faculty members from different departments and across disciplines. Besides the co-curricular activities inside and outside of campus, we shall try to explore internships locally and overseas as a way of developing the competencies needed to be good service leaders. Overall speaking, the Li & Fung Service Leadership Initiative has added new and important elements of service leadership to our GE Programme that supports the ethos of "Whole Person Education" of HKBU.

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Chapter 110

EDUCATING STUDENTS AS THE LEADERS OF THEIR LIVES

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ABSTRACT

The Service Leadership Initiative (SLI) at the Chinese University of Hong Kong involved 1) a general education course “Service Leadership in an Uncertain Era,” 2) producing video assisted cases, 3) delivering modules on service learning through CUHK’s I-CARE program, and 4) a social website for the service leadership and learning community. The course was only a modest success, owing to the intense competition for students from many offerings in the Self and Humanity area and the course’s academic rigor. The video assisted cases showed far greater promise in the flipped classroom and discipline specific young service professional leaders than in the traditional long form case, even when videos augment cases. The service learning in Chinese and Taiwan NGOs increased mindfulness, soul-searching and communication skills. The social website had good initial frequency of usage but its social dimension has been lacking, suggesting a need for far greater focus in user groups.

INTRODUCTION

The Service Leadership Initiative (SLI) provided The Chinese University of Hong Kong (CUHK) in general and the writers in particular an opportunity to deepen and develop applied theory, teaching and student service learning. In line with the SLI’s philosophy [1], we encourage students to see themselves as leaders in their own lives and understand leadership as a process – how to engage stakeholders to make progress by facing “adaptive problems”

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together [2]. Competence in terms of educating the followers, providing stakeholders sufficient information, and skills in deliberation is important, but character and caring attitude are more fundamental in creating trust during this process. In view of this, we worked with leaders in companies and the community to provide students opportunities not only in practicing leadership skills, but also in building their characters and caring attitude. This chapter will discuss our achievements, impacts, and lessons learned. To understand SLI's impact, one must appreciate the CUHK background to SLI related activities: the context provides a lens through which to assess our successes or failures. SLI at CUHK involved

- [1] a general education course "Service Leadership in an Uncertain Era"
- [2] producing video assisted cases
- [3] delivering modules on service learning through CUHK's I-CARE
- [4] a social website for the service leadership and learning community.

For all but [4], CUHK has solid precedents in courses, programs and faculty and staff activities. We will discuss each of the four activities, SLI's impact and, drawing on lessons learned, how we can continue our student development of service leadership.

THE GENERAL EDUCATION COURSE: UGED 1250 SERVICE LEADERSHIP IN AN UNCERTAIN ERA

The Memorandum of Understanding stated that the main purpose of SLI was "...promoting a new model of leadership, service, and service leadership for the post-industrial age capable of being taught in universities" At CUHK we joined that promotion by developing and offering a general education (GE) elective course *UGED 1250 Service Leadership in an Uncertain Era*.

CUHK GE courses are offered by the GE Office, departments and colleges, of which CUHK has nine. CUHK's colleges, Chung Chi, New Asia, United, Shaw, Morningside, S.H. Ho, C.W. Chu, Wu Yee Sun and Lee Woo Sing College, are primarily responsible for student housing, extra-curricular life and pastoral care. The only for credit courses they offer are GE courses. Colleges have considerable discretion concerning the structure, content and rigor of their GE course. The GE Office offers a very few cross-disciplinary, rigorous courses. The GE Office's greatest task is teaching to the entire student body the required courses *UGFH 1000 In Dialogue with Humanity* and *UGFN 1000 In Dialogue with Nature*. With 363 GE courses already on the books at CUHK, the GE Office does not wish to offer new university-wide GE courses. They leave the task of launching new GE courses to departments and colleges.

We applied to the GE Office to launch UGED 1250, even though it required a lengthy application and vetting process, so that UGED1250 would meet the academic standards of the university, would not be restricted to only a single college, and would be perceived as a truly cross-disciplinary offering. We discuss elsewhere our GE course structure, and how it draws on sociological, business, political, and psychological classics works in leadership, uses case studies and brings in prominent business, third sector and political leaders [3]. Here we only summarize, report on impact and suggest lessons for future action to promote the SLI.

UGED1250 is team-taught by the authors, with several guest lecturers. The course is composed of five parts: 1) Theories of leadership; 2) Leadership in business; 3) Leadership in politics; 4) Leadership in non-profits; 5) Cross-sectorial leadership. Students are required to participate in group discussion in class, write reflection notes, and analyze a leader in a term paper. In the course offered in 2015-16, students are also required to work on a service design group project. In terms of quality, the course has been a success, at least judging from the excellent scores received from course evaluations. However, in terms of student enrollment, it has not been very impressive, drawing a total of 44 students in the three classes offered from 2013 to 2016. What lessons do we draw?

To answer this question, one needs to understand the competition among courses for student registration. All students at CUHK must take 21 credits (i.e., seven standard 3-credit courses) of GE. Six credits are taken up by *In Dialogue with Humanity* and *In Dialogue with Nature*. Each student must take at least three credits at his or her college, leaving 12 credits, which must be distributed among the four areas of GE as follows

- A. China Cultural Heritage
- B. Nature, Science and Technology
- C. Society and Culture and
- D. Self and Humanity

As one can see from the UGED1250 code, *Service Leadership in an Uncertain Era* is in *Area D: Self and Humanity*. Within *Area D: Self and Humanity*, 70 different courses (some with multiple sections) compete for students. Students may choose from *Area D* courses offered by departments, by colleges and by the GE Office, with UGED1250 being the only UGED course offered by the GE Office. In general, students perceive GE Office courses as more rigorous than department GE courses which are more rigorous than college GE courses. We require two written assignments and we actively mark class participation, so students perceive UGED1250 to have a moderately heavy workload. Students tend to prefer Cantonese but we give a substantial percent of the class in English. The grade a student receives does not reflect the rigor of the class – all classes are subject to the same proportions of As, A-s, B+s etc. So students rationally may choose a “softer” class than UGED1250 to fulfil their *Area D* requirement.

Furthermore, within *Area D*, UGED1250 is not the only course in the service leadership space. Not including UGED1250, nine UGED courses involve service learning or service to society and three involve leadership (inferred from course titles). These 12 courses do not include the GE College Senior Seminar offered by most colleges, which typically involve service learning projects and leadership issues.

Many students are hesitant to take our course because it appears to be very theoretical and demanding in terms of multiple assessments. A better promotion may help students understand the importance of learning service leadership in a service economy like Hong Kong. But it is more fundamental to restructure the course by reducing the amount of theories and adding elements of experiential learning such as practice in mindfulness.

Considerable promise exists for converting UGED1250 and other SLI content course offerings throughout Hong Kong into flipped classrooms [4]. The flipped classroom substitutes videos to be viewed at home by students for lectures and uses instructor-student contact hours that used to be occupied with lectures for discussions and other student-

centered learning. Promoting GE course with fully public video materials can make clear the content of the class to students before they enter the classroom. And a flipped classroom can present an attractive format whereby students use class time to explore service leadership in the context of human society's rich leadership tradition. But since requiring students to watch a video before attending each GE class can be seen by students as over-demanding, the advisability of using flipped classrooms should be carefully considered.

Since there is no hope for the course to become a required course in GE, we will have to face the keen competition from other GE courses in the year to come. The CUHK Department of Sociology is now considering hosting this course so that a stronger social dimension of leadership can be introduced. Their track records in providing quality GE course may also help branding the course. In order to spread more effectively the message of SLI, we believe that we need to go beyond the existing structure by developing SLI flipped classroom materials and introducing SLI teaching materials and modules into existing courses. This is an avenue we wish to pursue.

PRODUCING VIDEO ASSISTED CASES

CUHK's SLI team developed teaching materials and modules and produced video assisted cases. We discuss the effectiveness and challenges of the case method, our approach to supplementing traditional cases with YouTube videos of the protagonists, our methodology in developing case sets and our results up to May 2014 in our conference paper [5]. In this section, we report on progress since 2014 and the potential for further development.

To date, we have completed nine traditional Service Leadership Initiative cases with videos and are in the process of completing an additional three for a total of 12. We intend to continue producing cases at this rate for at least another year. In addition, we broadened the scope of video case development. We have completed 14 click-through videos that describe the service leadership of young Hong Kong financial professionals [6] and have completed 30 videos in a flipped classroom for introductory corporate finance. These two additional initiatives together have received up to 500 views per week (including views through CUHK's and CUHK Shenzhen's Moodle platforms). And we believe that they offer considerable promise, broadening service leadership pedagogy to specific industries, one discipline at a time.

In our work, we continue to face two major challenges: inability to motivate effectively professors to coauthor SLI cases and failure to promote completed cases effectively. The two problems are interconnected. Even though the interaction between academics and practicing leaders is absolutely critical to developing sound service leadership theory and practical knowledge, very few academics are willing to devote enough time to interact and subsequently develop usable teaching case materials. At CUHK, we relied on working with less than 10 instructors with a history of case development. No SLI colleague from outside of CUHK approached us about jointly developing cases, although we frequently requested the Action Research Team (ART) and approached several individual members directly.

The unique viewer numbers of the six videos developed for traditional teaching case use that have been on public YouTube display for over one year range from 108 to 398 per video. These low numbers lead us to believe that no class outside CUHK has directly used any of the

videos. The reason, we believe, is two-fold: 1) the SLI curricula developed by other ART members relies largely on non-business leaders, rendering our materials not useful, and 2) there is a preference for using materials that each instructor has already developed, or using globally prestigious materials rather than using materials from competitor schools within Hong Kong. We offer no solution to this reluctant uptake on traditional case development and use. We remain hopeful, however that we can contribute to critical mass development in the Hong Kong and Greater China. Commitment to build the service leadership community will result, in the long run, in world recognition.

DELIVERING MODULES ON SERVICE LEARNING THROUGH CUHK'S I-CARE

Soon after Professor Joseph J.Y. Sung became vice chancellor and president of CUHK, he launched in 2012, the I-CARE Framework for whole-person development of students:

- I: Integrity and Moral Development
- C: Creativity and Intellectual Development
- A: Appreciation of Life and Aesthetic Development
- R: Relationships and Social Development
- E: Energy and Wellness [7]

The student development goals of I-CARE are fully compatible with SLI. I-CARE uses civic engagement programs – service learning, social research projects, social enterprises and corporate social responsibility – to achieve this development.

We used SLI resources to support the I-Care NGO Internship Program. The program is highly popular with many more student applicants than allocated spots, so every year we select a small number of students from a large applicant pool. The program aims to develop students' sensitivity, resilience and leadership through serving in communities that challenge their adaptive power. Around 40 students are selected every year to serve in NGOs and social enterprises for eight weeks in Mainland China and Taiwan. The NGOs are mainly located in rural areas and they address poverty alleviation, environmental protection, cultural heritage preservation, and other social issues. SLI support for I-CARE was centered on pre-service training sessions on civil society, mindfulness and communication skills, and on post-service experience sharing and reflections. Students appreciated their exposures to very different social and economic conditions from Hong Kong: this culture shock enhanced mindfulness and promoted soul-searching.

Drawbacks of the program included the limited number of students enrolled and constraints not only from financial resources but also the limited number of qualified mentors. CUHK remains committed to continue the program, with funding permitting.

A SOCIAL WEBSITE FOR THE SERVICE LEADERSHIP AND LEARNING COMMUNITY

Since the launch of SLI, sponsors have voiced the need for an SLI internet presence and various ART members have suggested a need for a social SLI platform. In 2014 ART meetings, discussions of the difficulties of creating an academic journal for SLI research turned towards creating a research platform for placing of pre-submission papers as a first step. In the September 2014 ART meeting, we proposed to set up a digital platform. ART members warmly supported our proposal. Based on interviews with the teams of each ART member, we designed the platform.

The design was simple. Posting members would specify the title, identifying tags, whether the files may be downloadable with the click of an icon, whether the posting allows forum discussion, whether the posting member's email is given for contacting and the duration of the post. Each post would display the title, author, date and tags and (if appropriate) summary, download icon and email contact. Copyright of and control over posts would belong to posting member. The post could be edited or pulled off the platform by the posting member at any time. The administrator could also pull a post deemed insulting, obscene, infringing intellectual property or highly antagonistic to the philosophy of the platform. Only members could discuss posts by posting to a forum. The ultimate goal of the platform was to operate as a social media community centered on ART.

On August 1st 2015, after six months of development, the Fung Service Leadership Initiative Platform www.service-leadership.hk went public. After launch, we actively solicited postings from three groups over the next month:

- 1) Former UGED1251 students
- 2) Former student participants in the CUHK Vice Chancellor's Cup of Student Entrepreneurship and the Hong Kong Social Enterprise Challenge
- 3) Members of ART

From launch to October 6, 2015, there were 65 postings as follows: instructors: 32, students: 31, researchers: 1; community partners; 1. The website has attracted approximately 80 site visits per week since from late September 2015 to January 2016. Those who visited the website spent an average of just over six minutes there. So on the face of it, the website has enjoyed a modest success.

However, our attempt to build a *social* website has failed so far. *Social* websites have social interactions. Ours does not. We have solicited or made the posts ourselves. Not a single non-CUHK member of SLI has made a single posting to the platform. With the exception of one CUHK SLI team member, nobody has commented on anyone else's post although many have read them. Non-members can see most of what is on the site without going through the bother of signing up for membership. To the extent that some posts are for members only (this is within the power of the posting member to decide), non-members do not know what, if anything, they are missing.

We have attracted 54 members, but we personally invited all 54. We conclude that membership is not attractive. It confers the rights to post, to comment and to invite new members, but we have not developed a community that wishes to post, comment or invite

new members. To our knowledge, nobody has applied, unsolicited, for membership, even though such application is automatically accepted if it comes from one of the 20 some emails that had the suffix of a Hong Kong institute of higher learning. Our impact, during the first two months of the “social” website is disappointing.

A social website’s success is based on the 3 Cs: community, content and commerce [8]. What lessons can we draw from the preliminary usage of the site concerning our community, the content and the potential for commerce (i.e., high usage)? First, SLI itself is not a community with sufficient definition to give any of the corners of our website a critical mass. Asking ART members what they want, as we did in late 2014, was not enough. ART members’ responses suggested that SLI had four distinct communities leading us to design the four corners: a researchers’ corner for pre-publications drafts of service leadership research, a community partners’ corner for NGOs and companies in service learning, an instructors’ corner for the exchange of relevant teaching materials and a students’ corner for our primary community – the students whom we wish to instruct. However, each of those potential communities is very diverse and has a wealth of platforms to choose from. The question, “why should I post to www.service-leadership.hk?” does not even occur to members of these communities, unless they were asked to post by members of our team. So far, each has posted only as a favor to us.

There is some good news. Two constituencies offer glimmers of hope for the platform. First, in the instructors’ corner, we have used posting as a convenient way of sharing videos with students in the Mainland. The platform is not blocked by the Great Firewall. Over half of the platform’s usage comes from the Mainland. Hong Kong social enterprise startup planners form the second promising community. Twenty-two of the 31 student posts on the platform are business plans posted by or on behalf of former competitors in the Hong Kong Social Venture Challenge [9]. This Hong Kong-wide competition has been run annually by the CUHK Center for Entrepreneurship, since 2007. The organizers of the competition support our approach in two ways. They have asked past years’ teams to post their plans and they are asking the current year’s teams to read the posted plans to make their own plans better. From this interaction, we have discussed plans to build a targeted Hong Kong community that wishes to interact about social ventures. We anticipate that there may emerge a social element in the website. Following that, we will discuss with the HKSEC director about steps for tailoring the platform to meet their needs better.

We believe that the principle of an SLI platform remains good, notwithstanding the problems discussed above. If however, the digital needs of SLI can be satisfied by existing platforms, we must ask the question, “why develop our own?” Our students in Hong Kong and the Mainland have indicated that they are happy using, respectively, YouTube and Youku as video platforms and WhatsApp and WeChat for mobile social interaction. What advantage exists in building rather than using existing platforms? The answers lie in greatly sharpening focus onto specific communities whose needs can be met by our resources more efficiently.

CONCLUSION

SLI has provided CUHK in general and us in particular with a unique opportunity to teach our students about service leadership. The general education course on service

leadership is seen by students as a high quality course but one that is too rigorous in its student assessments. Without taking the course, students cannot differentiate the idea of service leadership from serve learning and are unable to appreciate the value of service leadership versus leadership in general. Further promotion of the importance of specific attributes of leadership in the service economy should be helpful in boosting enrollment. The flipped classroom as a new mode of teaching should also be explored. The production of video assisted cases provides researchers and teachers tools to study and disseminate knowledge of service leadership in the local context. Since each case is produced to illuminate specific academic themes, it is important to collaborate with scholars in diverse fields that interact with service leadership. Unfortunately, the number of scholars paying attention to service leadership (let alone studying it) is scanty even in a service economy like Hong Kong. The NGO internship has been remarkably successful as students can reflect on the meaning of service and leadership through experiential learning. The problems of this program include lacking resources and quality staff who can coach students in their services (in different professions) and help them in the soul-searching process so necessary to develop leadership. The website for service leadership and learning community is in an experimental stage. It could become a useful platform – for example for students in Hong Kong Social Enterprise Challenge – but to do so will require greater focus and promotion of a service leadership community in university education as well as in industry. We sincerely hope that the programs initiated and broadened by SLI will continue to prosper at CUHK and that our modest successes and our failures will provide valuable lessons to instructors, researchers, community partners and students, improving the quality of service leadership in Hong Kong.

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Chapter 111

GROOMING SERVICE LEADERS THROUGH DYNAMIC TEACHING

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ABSTRACT

The Service Leadership Initiative at CUHK involved producing locally sourced, globally applicable, teaching materials usable both in a general education SLI course and in modules concerning service leadership in other courses. This chapter reviews the production of nine video enhanced Harvard-style cases and 30 videos for the flipped classroom and discusses at greater length the 55 videos for the young financial professional videos.

INTRODUCTION

The Service Leadership Initiative (SLI) at CUHK, entitled “*Grooming Service Leaders through Dynamic Teaching*,” involved producing locally sourced, globally applicable, teaching materials usable both in a general education SLI course and in modules concerning service leadership in other courses. Other papers discuss CUHK’s achievements, impacts and lessons within SLI [1] and their use in CUHK’s general education course [2]. In this chapter, we discuss the production of teaching materials with special emphasis on videos concerning the young financial professional (YFP).

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VIDEO ASSISTED CASES AND THE FLIPPED CLASSROOM

If, as research indicates, recorded lectures are no worse than live lectures as tools for conveying information to students, one can legitimately question the efficiency of the traditional lecture system of post-secondary education [3]. Students can view, on their own, case-based videos, pre-recorded lectures, and other materials. Consequently, valuable instructor-student contact time can be used for student-centered learning. Video viewing can occur before or after class, before relevant assignments are due and examinations are held, and even after the completion of the course. Digital references can be easily shared among students and, subject to platform accessibility, to the wider learning community. In the flipped classroom, student-lecturer contact hours are devoted to student questions arising from video viewing, interactive discussions, exercises, problem solving, games, presentations, etc. Over the last decade, research has accumulated showing the effectiveness of the flipped classroom [3, 4].

CUHK sought to stimulate dynamic teaching in SLI partly through the production and distribution of video assisted cases of three types: *firstly*, the traditional Harvard-style case with a video, *secondly*, the recording and editing of video-lectures, and *thirdly*, the production of taping of YFP videos. Although this article primarily concerns the YFP videos, we will begin by introducing the traditional Harvard-style cases and video-lectures.

Harvard-style cases have been used to teach business in universities for over a century; that is for as long as business has been taught in the university. They are useful to develop students' discipline-specific skills and conceptual abilities [5] and are effective if student contributions to class analysis are assessed [6]. As I discussed in a precious article, a key part of SLI at CUHK was developing videos to enhance local cases that not only illuminated management theory but do so in the context of service leadership [7]. Each SLI video-enhanced case set consists of a Harvard-style written case, a 10 to 20-page instructor's note and 15 to 25-minute video posted to YouTube. As of the date of this article, we have produced nine written cases sets, have published all of the videos on *YouTube*, have six written cases in publication and another two accepted. Of those in or accepted for publication, seven are or will be cross-sold in *Harvard Business Publishing for Educators Network*. Notwithstanding the challenges we discussed in the earlier article, including the slightly less than even chance that a case begun will be successfully completed, we are currently working on another three cases and intend to continue working on new cases. See Table 1.

The flipped classroom involves two steps, first placing lectures on line and second, conducting a student-centric rather than a lecture-based class. We placed the lectures in two locations, publically on YouTube and privately on CUHK's course-specific Moodle e-learning website. Students were informed of both locations. Table 2 shows the lectures and the number of times they were viewed: in all there were 416 views of YouTube-posted lectures and 11,853 views of the same lectures on Moodle. Clearly, without the incentive of learning in order to gain course credit from passing a specific course, and with no separate promotion of the YouTube site, only a relatively small number of people seek out the flipped lectures that are publicly available.

Table 1. Video cases completed at CUHK under SLI[illegible]

RATIONALE FOR MAKING THE YFP VIDEOS

The YFP videos comprised CUHK's third set of SLI dynamic video teaching materials. SLI was initiated partly to promote ethical leadership among Hong Kong students about to embark on careers within services industries. Finance is one of Hong Kong's four Pillar Industries along with tourism, trading and logistics, and professional and producer services. Finance accounts for 16.6% of Hong Kong's GDP, less than the 23.4% of trading and

logistics. Finance accounts for 6.3% of the Hong Kong workforce, considerably below trade and logistics’ 20.4%. But these two facts combine to give finance a workforce per capita annual output of \$1.546 million versus trade and logistics’ \$0.673 million, a fact reflected in the high wages in finance [8]. Not surprisingly, students in Hong Kong consider a career in finance desirable.

Table 2. Videos in the flipped classroom

Number	Title	Length (min)	YouTube URL	Location	Public Views	Moodle Views
1	Introduction to Finance	10:00	https://www.youtube.com/watch?v=...	CUHK	120	150
2	Financial Statement Analysis	15:30	https://www.youtube.com/watch?v=...	CUHK	80	100
3	Investment Strategies	12:45	https://www.youtube.com/watch?v=...	CUHK	95	120
4	Corporate Governance	8:20	https://www.youtube.com/watch?v=...	CUHK	60	80
5	Financial Risk Management	11:15	https://www.youtube.com/watch?v=...	CUHK	70	90
6	Financial Markets	9:50	https://www.youtube.com/watch?v=...	CUHK	55	75
7	Financial Institutions	13:00	https://www.youtube.com/watch?v=...	CUHK	85	110
8	Financial Innovation	10:30	https://www.youtube.com/watch?v=...	CUHK	75	100
9	Financial Regulation	14:00	https://www.youtube.com/watch?v=...	CUHK	90	120
10	Financial Technology	11:45	https://www.youtube.com/watch?v=...	CUHK	80	110
11	Financial Ethics	9:10	https://www.youtube.com/watch?v=...	CUHK	65	85
12	Financial Law	12:00	https://www.youtube.com/watch?v=...	CUHK	70	95
13	Financial Accounting	10:45	https://www.youtube.com/watch?v=...	CUHK	85	115
14	Financial Management	11:20	https://www.youtube.com/watch?v=...	CUHK	75	105
15	Financial Planning	13:30	https://www.youtube.com/watch?v=...	CUHK	90	125
16	Financial Reporting	10:15	https://www.youtube.com/watch?v=...	CUHK	80	110
17	Financial Analysis	12:30	https://www.youtube.com/watch?v=...	CUHK	85	115
18	Financial Forecasting	11:00	https://www.youtube.com/watch?v=...	CUHK	75	105
19	Financial Modeling	14:15	https://www.youtube.com/watch?v=...	CUHK	95	130
20	Financial Simulation	10:00	https://www.youtube.com/watch?v=...	CUHK	80	110

The column Public Vides shows the numbers of unique viewer of videos posted publically on YouTube. If a single computer, smart phone, notepad, etc. views a video multiple times, it counts as a single view. The column Moodle Views shows the number of total views privately on the CUHK Moodle website, so if a single computer, notepad, smartphone, etc. views the video more than once, the site counts the total number of times that device views the video.

^The Moodle column understates the number of views because an amended video was posted part way through the term, erasing the exiting log of views.

*The Moodle column understates the number of views because for videos placed in a single root directory the number of entrants into the root directory were divided by the number of items in the root directory, assuming that the entrant did not view more than one video for each entry into the root directory.

Yet as an instructor with over two decades of experience in teaching finance, I have been struck by how little undergraduate students actually know about the work of finance service professionals. This lack of understanding, both before and after taking the course in financial management required to graduate with a bachelor of business administration, is especially worrying in the light of the public perception, strengthened after the global financial crisis, that the finance industry in particular and multinational corporations in general are cursed by “...a systemic breakdown in accountability and ethics...” [9, 10]. My casual observations as a former banker in Hong Kong together with current financial academic research leads me to believe that, in fact, financial professionals’ moral standards are insignificantly different from the general population and that progressing to a leadership position in finance is *facilitated*, not hindered by self-transcendence [11]. This observation and research is consistent with the emphasis on competence, character and care promoted by SLI [1]. We produced the YFP

videos to inform students of what careers in finance entail from not only a technical, but also a moral point of view.

Although CUHK's Office of Student Affairs, the CUHK School of Business Undergraduate Office's Student Career Planning and Development Division, each of CUHK's nine colleges, each specialized program and many of student societies bring senior financial professionals onto campus to speak with students about career prospects, we reasoned that students could learn more from *young* service professionals. Not only are they closer to our students' ages, not only is their work more like that which our students can expect to do upon graduation, but also they can illustrate our premise that every service employee is, by nature of the service industry, a leader at some time during each day [12].

THE PROCESS

We interviewed 15 alumni who had graduated within the last 10 years (i.e., no earlier than 2002). Each interviewee worked either in a financial service company or as a financial professional (involved in treasury or control) in a non-financial firm. Our interviews involved asking the open-ended questions shown in Table 3. We followed up interviewee answers with further unstructured questions. We asked questions largely in English but followed up in Cantonese, so that we could present the YFP as a global financial service provider with a local Hong Kong cultural base. We video recorded each interview, with each interview lasting from 45 minutes to 1.5 hours. We edited 15 sets of four, two to 10 minutes videos in which the interviewees discussed four aspects of their work *i. Work Content*, *ii. Theory and Practice*, *iii. Success*, and *iv. Improving Service*, giving us 60 videos. All but one YFP allowed us to use at least some part of the materials we had edited. Four YFPs required major editing of their videos and gave their permission on the basis that their companies' names should not be mentioned, or said that, if their companies' names were used, they would have to clear the videos through their corporate compliance departments. Our experience with corporate compliance departments led us to volunteer editing out of company names, a proposal that led all but one YFP to accept publication. The YFP who refused to give permission said that the editing quality of our work was not sufficiently high to warrant release and consequent lowering the reputation of CUHK. One YFP who allowed us to use his interview requested that we remove all of aspect *iv. Improving service* giving us 55 videos at the end of our work. Table 4 gives the names and titles of the 14 YFPs.

We placed all videos on the Instructors' Corner of the Service Leadership Website [13] discussed in our day one paper in this volume [1], rather than YouTube because in our approach to the YFPs we said that publication would be public but targeted towards the SLI community. We did not track visits to individual videos on the Service Leadership Website.

SUCCESS FACTORS

The YFP videos have so far been used in the Fina2010 *Financial Management* flipped classroom outlined in Table 2 from September to December 2015. Aspects *i. Work Content* and *ii. Theory and Practice* were used in classroom exercises to increase practical

understanding of material covered in the flipped lectures 1. *What is Finance*, 2. *Jobs in Finance*, 12. *Pro-forma forecasting*, 13. *Banks*, 14. *The Perspective of the Lender*, 19. *Bond and Stock Valuation*, 20. *Capital Budgeting*, 23. *Cost of Capital: WACC*, and 26. *The Weighted Average Cost of Capital: Equity – CAPM*. Materials from aspects iii. *Success* and iv. *Improving Service* were used in the first and the final class to place finance in a moral context. Students expressed interest in seeing their near-peers discussing important aspects of the work of financial professionals.

Table 3. Interview questions for young financial professionals

1.	Work Content
a.	How does your division of the company make money? i.e., what is the business model?
b.	Describe your job.
c.	How do you help your company's customers?
d.	Describe the percent of your time used on
	i. Meeting with customers
	ii. Meeting with colleagues
	iii. Researching and analyzing
	iv. Writing reports
	v. Other activities (specify if over 10%)
2.	Measuring Success
a.	Describe a highly successful incident at work
b.	Describe a failure at work. How do you find out how to improve your service?
c.	How is your success or failure in your job assessed?
3.	Improving Service
a.	What personal characteristics are most important to your continued success? [follow up with one of the following]
	i. How is empathy important to your success or failure?
	ii. How is self-control important to your success or failure?
	iii. How do you deal with inertia in your company?
	iv. In working with colleagues, do you primarily use authority or persuasion?
b.	One leader commented, "Everyone is a leader for at least 15 minutes each day." How true is this true in your organization?
4.	Theory and Practice
a.	Which concepts from introductory financial management are most important to you in your work and why?
b.	How do you use the following concepts in your work [Choose one, avoiding that covered in a. If the interviewee does not use your chosen topic, go on to the next one and so on until you come to one the interviewee uses. In subsequent interviews, start with the ones that were not chosen.]
	i. Financial Statement Analysis
	ii. Risk and return
	iii. Discounted cash flow analysis
	iv. Capital budgeting
	v. Correlation and diversification
	vi. Market efficiency
	vii. Cost of capital
	viii. Capital structure
	ix. Dividend Policy
	x. Cash and Liquidity Management
	xi. Options Valuation
	xii. Agency conflicts
5.	How have you improved your knowledge of finance since graduation?
6.	Would you be willing to appear in class on a Skype call?
7.	Can we release your email address to our students for them to directly contact you?

Table 4. Young financial professional interviewees

Surname	Given Name	Company	Job title	Customers	Work Content
Commercial Bankers					
Chan	Leo	JPMorgan	Investment Consultant Analyst	HNW Individuals	Private Banking
Yan	Elaine	a leading bank	Senior Direct Channels Manager	Retail	Web and Mobile
Hung	Raymond	Industrial Bank	AVP Financial Markets	Corporate	FX Options / Treasury
Tam	David	a leading bank	Manager of Regulatory Reporting	Corporates	Derivatives trading compliance
Investment Bankers and Asset Managers					
Ngai	Anthony	JP Morgan	Credit Trading Department	Asset Managers	Trading and advice
Cheng	Ben	BofA Merrill Lynch	Associate Investment Banking Dept	Financial Institutions, Large Corps	Sales
Chan	Michael	a leading bank	ECM Practitioner	Financial Institutions, Large Corps	Execution
Tang	Benson	Investco Hong Kong	Senior Analyst, Investment Risk & Performance	Institutional and Retail investors --	Fund Management
Insurance Professionals					
Chan	Herman	Manulife	Financial Planning Officer	Individuals buying Life Insurance	Sales
Wong	Ken	a leading insurance brokerage	Financial Analyst	Corporations buying P&C Insurance	Control budgeting, forecasting; reconciling
Financial Professionals in Non-Financial Institutions					
Leung	Fanny	HYVA Holdings	Senior Financial Analyst	Buyers of Construction Equipment	Control: budgeting, forecasting; reconciling
Tam	Carine	Pacific Plywood Holdings	Company Secretary and Controller	Investors and consulting clients	Filings, Listing compliance
Chau	Terence	Deloitte	Senior Consultant	Financial Institutions	Regulatory Advice, compliance
Li	Angela	McKinsey	Business Analyst	Financial Institutions, Large Corps	Strategic Advice

Here, I summarize the major success factors as reported by YFPs in the videos. I invite the readers to go to the videos to confirm my summaries, to share the videos with their students and to use the videos in their classes. Among the bankers, Leo Chan, private banker at JP Morgan saw good performance in the banker-client relationship as the key. Elaine Yen, Direct Channel Sales Manager at a leading bank, in charge of website interfaces for internet identified "... design for customer experience ..." as the key. Raymond Hung, AVP, Financial Markets at Industrial Bank saw the profit and loss statement – making money – as the number one success factor while David Tam, Manager of Regulatory Performance at a leading bank advised, "...be timely, precise and accurate." We interviewed four professionals in the field of investment banking and asset management: Anthony Ngai of JP Morgan Credit Trading, Ben Cheng of Corporate Sales at BofA Merrill Lynch, Michael Chan, equity markets execution at a leading investment bank and Benson Tang, Senior Analyst (quant modelling) at Investco. Their comments emphasized the necessity of preserving the franchises of their financial institutions through improving their institutional reputations. The clients' interests must come first. Communication with clients has to be timely, of high quality, accurate and good. Pricing (in IPOs) must be fair to clients on both the sell and the buy sides of each transaction. And the models designed for use by colleagues must not only work well but must be understood by colleagues so that colleagues are confident to use them to enhance

performance. Among all four answers, a strong commitment to service was evident. Our two insurance professionals, Ben Chan at Manulife and Ken Wong at a leading property and casualty brokerage, identified two key factors of success: winning and keeping the trust of customers and accuracy in work. Financial practitioners in non-financial corporations also identified key SLI factors. Fanny Leung, Senior Financial Analyst in regional control at HYVA Holdings, said that two factors were paramount: understanding her company's needs and meeting deadlines. Carine Tam, Company Secretary and Controller of Pacific Plywood Holdings said that her two key success factors were multi-tasking and staying calm. Two financial consultants rounded out our 14 YFPs: Terence Chau, Senior Consultant at Deloitte's financial intermediary compliance advisory practice and Angela Li, Business Analyst at McKinsey, came to identical conclusions using different words. The former said that the key was to "... make our customer happy..." while the latter said "...our customer's success is our success."

CONCLUSION

Using a dynamic approach helps link theory with practice in demonstrating to students the importance of SLI concepts. At CUHK we have achieved minor successes in adding a dynamic component to the teaching of service leadership: we have produced and tested 94 videos clips and 11 written cases. We are confident that the flipped classroom presents a medium for effective instruction. The YFP series demonstrates that students can be brought closer to their chosen finance careers before they leave school. The classroom can both inform them and instruct them concerning the moral dimension of a service industry career. Expansion of the YFP approach to other service disciplines beyond finance, including trade, logistics, business services, hospitality, healthcare, education etc., is viable. Tremendous potential exists for further applied research into service leadership in Hong Kong and the improvement of delivery of service leadership knowledge. To realize this potential, however, coordinated involvement of researchers and instructors at universities with practitioners' service industries is critical to create a truly Hong Kong-wide platform that is content-rich, useful, current, relevant and accessible.

ACKNOWLEDGMENTS

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Chapter 112

PROSPECTIVE SERVICE LEADERS ENHANCEMENT PROJECT

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ABSTRACT

In this chapter, we elucidate the experiences of service leadership development at The Education University of Hong Kong (EdUHK). Adopting the vision and missions of Fung Service Leadership Initiative, EdUHK launched the “Achiever” project in September 2012. The project aimed to develop service leadership qualities in students. In September 2015, this “Achiever” project was completed but the learning achievements generated from it will sustain. “Achiever” was developed in a co-curricular context and its development was based on three core beliefs of service leadership as well as a road map which comprised a three-phase training framework and a five-level student leadership development model. In the three-year duration of project development, over 1,000 students from different disciplines accumulated 73,698 learning hours in 13 designated co-curricular activities. Over 90% of the participating students reported that through “Achiever”, they enhanced their self-understanding, goal-setting skills and their abilities to appreciate others. Meanwhile, over 70% of students believed that caring and compassion were essential personal qualities of a service leader. We believe that the recognition of such qualities by our young generation will be beneficial to societal development as this shows their compassion to serve. The project aimed to be student-oriented by nature. EdUHK built a peer learning environment and an active sharing platform so that students could share their thoughts and experiences openly and freely. The development of supportive learning environment encouraged students to actively

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apply newly-acquired service leadership knowledge and skills to community development when they engaged in community service projects.

INTRODUCTION

With the sponsorship of Victor and William Fung Foundation and the support of the Hong Kong Institute of Service Leadership and Management (HKI-SLAM), The Education University of Hong Kong (EdUHK) conducted a three-year co-curricular learning project named “Prospective Service Leaders Enhancement Project” (hereafter called “Achiever”) from September 2012 to September 2015.

A number of scholars have been developing concepts of service leadership [1-3]. Following their footsteps, the “Achiever” aimed at grooming prospective students to become quality and committed service leaders through the provisions of different training activities and experiential learning opportunities. It was operated by the Student Affairs Office (SAO) in EdUHK. EdUHK emphasized providing practice opportunities for students with diversified learning needs and active reflections on learning achievements.

In particular, through the construction of a systematic student leadership development model and a three-phase training structure, EdUHK intended to develop a student-oriented service leadership development process. In this chapter, EdUHK shares the experiences with reference to the achievements, impacts and lessons learned from this “Achiever”. Students’ feedback is included to illustrate their learning.

SUMMARY OF ACHIEVEMENTS

“Achiever” was developed in a co-curricular context based on three core beliefs (see Figure 1): (a) everyone is a leader; (b) quality service leadership is built on three critical people factors: competency, character and care; and (c) the server is the service. These three core beliefs, found in *Service Reborn* [1], formed the backbone of students’ service leadership development in EdUHK. Kouzes and Posner [4] also posit that leadership is everyone’s business. They tend to inform that this “everyone” should include university students who are future leaders in the community. Posner [5] remarks that leadership development is an integral part of the educational programme of college students. His views are especially true for EdUHK as it nurtures teachers-to-be. Through “Achiever”, EdUHK communicated, encouraged, empowered and equipped students with the three core beliefs in a variety of student activities and prepared them to be service leaders.



Figure 1. Three core beliefs of service leadership.

Consolidation of a Three-Phase Training Structure

Komives [6] and her colleagues argue that leadership needs to be learnt and practiced. A three-phase training structure was thus established in “Achiever” (see Figure 2) which adopted experiential learning methods and also emphasized the importance of practice.



Phase One Foundation	Phase Two Self-Advancement	Phase Three Integration
Objective: - To help students build up fundamental knowledge on Service Leadership - To enhance self-understanding	Objective: To help students identify personal qualities that contribute to the nurture of a successful service leader	Objective: To apply and practise skills and knowledge acquired in real-life situations through experiential learning activities (<i>See Appendix 1 for experiential learning activities developed in EdUHK from 2012 to 2015</i>)

Figure 2. The three-phase training structure of “Achiever”.

Following this systematic training structure, programmes in the SAO were developed in which the participating students would go through a progressive learning process of acquiring fundamental knowledge and concepts of service leadership, setting their own learning goals (Phase One-Foundation), identifying their service leadership qualities through interviewing role models or joining adventure-based activities (Phase Two-Self-Advancement), and applying their newly-learnt service leadership knowledge and skills through various experiential learning activities in real-life context (Phase Three-Integration). Through this learning process, EdUHK nurtured students’ serving mindset as well as enhanced their capability in serving others when they led and engaged in activities that helped community development both locally and overseas. This training structure has also provided a good direction for SAO when designing learning activities for nurturing service leaders.

The Leadership Enhancement and Development (LEAD) Programme (Appendix 1) helps to illustrate how this structure was applied. In 2014/15, 205 selected students attended a talk on service leadership and two workshops on enhancing self-understanding and setting goals (Phase One). They then conducted interviews with role models, who were service leaders, to identify important service leadership qualities and explored areas for self-improvement in adventure-based training (Phase Two). In Phase Three, they applied and practised skills and knowledge acquired to serve overseas communities in developing countries such as Bangladesh, Cambodia or Vietnam. Upon their return to the campus, they took up mentors’ role and helped new participants of the programme.

Construction of a Student Leadership Development Model

To cope with the diversified developmental needs of students, EdUHK constructed a five-level student leadership development model. This model functioned as a road map guiding students to build up their leadership capacity through different leadership engagement levels in a variety of programmes.

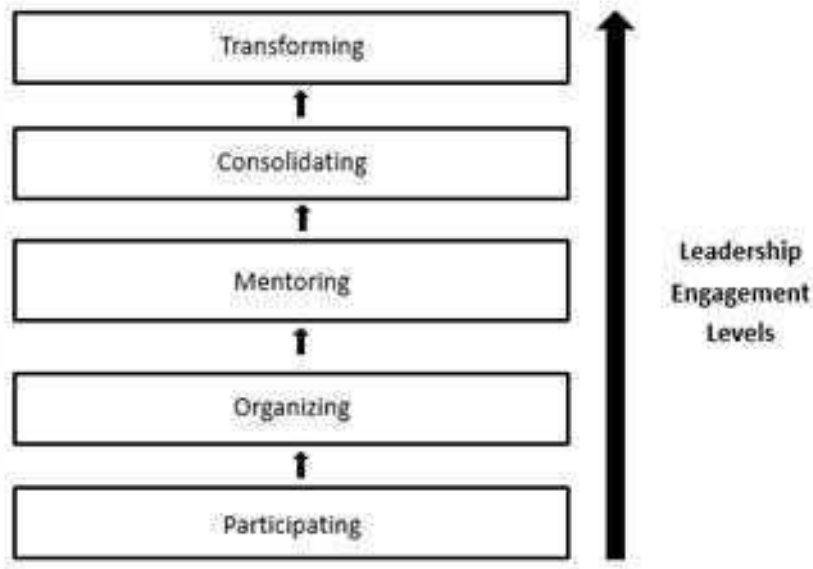


Figure 3. Five-level student leadership development model.

In a case study of a university conducted by Smith and Rodgers [7, p.479], they found that active student involvement in meaningful experiences was implemented through a multi-phase development model. Going through these phases, students would 1) act as participants, 2) have significant involvement and responsibility, 3) take up leadership role, and 4) assume a peer mentoring or training role. The EdUHK student leadership development model covered similar levels but a “Transforming” level was added. At this uppermost level, students continue to take initiative to serve the community after graduation and act as role models to undergraduate students in EdUHK. An alumni network will be developed and community development can be done with concerted efforts.

By participating in programmes that required different leadership engagement levels, students were expected to enhance their leadership competencies and commitment to serve others and to build a caring community. The following illustrates students’ learning achievements in different development levels.

1. Participating (Level One)

At “Participating” level, students acquired knowledge and skills through active participation in programmes and activities organized for them. Through active participation, students were expected to enhance their confidence and awareness of being service leaders. They were guided to form positive values towards community contribution. The following are

some students' feedback on positive experiences as a participant in an experiential learning programme:

"The goal setting workshop was beneficial to me on planning my long-term career and setting my own goals in the summer internship programme."

"The psychological testing and assessments (i.e., MBTI, Self-Directed Search) provided a great help in my career planning and self-understanding."

"Caring for others' feelings makes others feel being respected."

2. Organizing (Level Two)

At "Organizing" level, students were involved in planning and organizing functions with intensive coaching support. The Community Service Exposure Attachment (CSEA) programme served students' developmental needs at this level.

In CSEA, students were arranged to work for non-governmental organizations (NGOs) or social enterprises (SEs) to develop their leadership skills such as organizing skills and communication skills through assisting social welfare professionals in organizing service events. In 2015, 13 students took part in the programme. The following are some of their learning reflections:

"During the service attachment, I organized many activities for the children. It was not easy for me at the beginning since I was unfamiliar with the social welfare field. However, under the guidance of some experienced social workers, I gradually adopted practical methods to organize and conduct service activities."

"I have known more about how an NGO runs and what the general and complete procedure is for holding an activity."

3. Mentoring (Level Three)

Participants with outstanding performance in the programme were selected to take up coaching roles and served as mentors to new participants of various experiential learning activities, thereby building up a peer learning atmosphere. Boud [8] mentions that peer learning is a beneficial process for mutual sharing of knowledge, ideas and experience between participants. He tends to imply that students, by taking up the role of mentor and mentee, are peers and will become effective learners through presentation of their ideas and thoughts. In the LEAD Programme, students with mentoring roles coached and guided mentees to learn. They led small group meetings and team-building activities. A mentor in LEAD Laos group shared his own learning:

"I learned how to unite team members with different characters to work out challenging tasks. Being a translator between members and Laos' volunteers, I understood my strengths and weaknesses of being a leader."

4. Consolidating (Level Four)

At "Consolidating" level, students were expected to initiate new projects and fully apply their skills and knowledge acquired in previous developmental levels. The Service Exposure for Global Awareness (SEGA) Programme (Appendix 1) encouraged students to explore social issues in Hong Kong and Asia. The students worked on a highly autonomous level, formed their own teams, selected their study areas and planned their service tours. The following quotes show the learning achievements of two students:

“I can learn more about different social needs and issues from an international perspective, and be able to respect and appreciate human lives.”

“Through understanding the actual needs and listening to voices from the most disadvantaged groups, it makes me realize that life is not only about myself, but also the others in need.”

Activities at this level also included internship programmes, which allowed students to apply their skills and knowledge acquired in workplace. With actual practice in workplace, students expanded their circle of influence and strengthened their linkage with the wider community.

5. Transforming (Level Five)

When students can be self-initiative and self-directive in offering their services to the wider community after graduation, they then reach this uppermost leadership developmental level of “Transforming”. Graduates can engage in alumni network and work closely with other graduates to continue serving the community.

The Impacts of “Achiever”

Over 1,000 students participated in a variety of programmes developed under “Achiever”, accumulating a total of 73,698 learning hours. As mentioned earlier, while gaining their own learning, students also contributed to the learning of other students through different sharing platforms. This reciprocal learning mode built up a peer learning atmosphere in EdUHK and reinforced students’ acquisition of service leadership core beliefs, skills and knowledge. Frequent learning evaluation was a feature of “Achiever”. Under “Achiever”, EdUHK collected feedback and comments from students through different channels such as self-administered questionnaires, reflections in learning journals and direct sharing between students.

By way of filling in questionnaires students reported their experiences in talks and workshops. Over 90% of them experienced enhancement in their self-understanding, goal-setting skills and their abilities to appreciate others with diverse backgrounds. Meanwhile, many participants identified and planned to adopt four essential service leadership qualities: Care and Compassion, Happiness, Leadership, and Social Relationship after attending programmes developed at Phase Two of the training structure. From attending the experiential learning activities, many students gained positive experiences and understood the importance of teamwork. Through real-life practices, they identified their areas for improvement.

Two students, Helen and Michael, who took part in “Achiever”, presented their experiences in the International Conference on “Service Leadership Education in Service Economies” in January 2016. They shared their learning experience at the five levels of leadership development.

At the “Participating” level they were able to learn through observation. While making a presentation on Hong Kong films in an ambassador programme, Helen noticed the various styles among participants with different cultural backgrounds. For example, local Hong Kong students would give an overview of the issue, mainland China students would provide in-

depth information on a specific area, and international students would integrate their content into interactive games. Through observation, Helen was able to appreciate the strengths and weaknesses of other students, thus identifying those of her own.

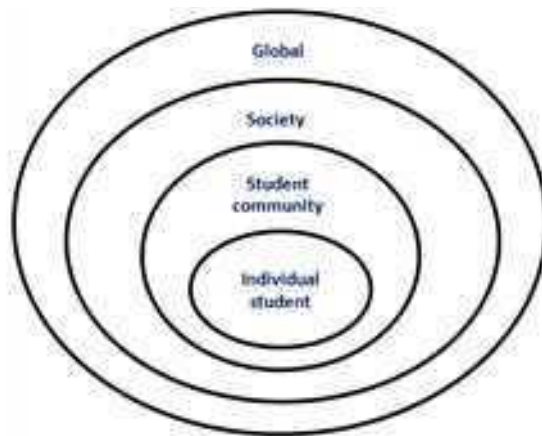


Figure 4. Impacts of learning achievements under “Achiever”.

After participating in the project, the students would take up a more significant role as organizer. During a New Student Orientation Camp at EdUHK, Michael was in charge of delivering a talk on campus activities to new students due to his good presentation skills, while other students were also appointed as persons in charge of activities based on their areas of excellence. This allowed Michael to understand the notion of “everyone is a leader” truly and to witness how this concerted effort was vital to the success of the camp.

When students successfully completed the first two levels of development, they were eligible to become a mentor to guide and take care of less experienced students. Helen became a mentor of a voluntary teaching trip to mainland China after drawing inspiration from her mentor. During the trip, she found a communication gap between two mentees and bridged it by bringing up common topics. The solution may be simple but Helen’s passion and care were crucial in nurturing a supportive peer learning community. We hope that this mentorship programme could encourage more students to take up mentoring role in the future.

At level four “Consolidating”, students would reflect constantly on their learning in the first three levels by using EdUHK’s online portfolio system. Through the writing of reflective journals or essays, they could reflect on their experiences as a whole and therefore acquired a better view of their talents and shortcomings. This realization process enabled the students to further explore new opportunities provided by EdUHK that matched their interests, whether it was to enhance their talents or to overcome their shortcomings. EdUHK is like an airport, offering a supportive learning environment and helping students to reach their desired destinations.

Finally, the character and mentality of the students became more mature after these experiences. They were able to step out of their comfort zone, cope with unfamiliar environments and conquer adverse circumstances. Michael’s internship in Germany confronted him with numerous challenges, but he overcame them by reminding himself of the training in “Achiever” and of the spirit “the server is the service.” He was able to manage his emotions immediately and to undertake his role as an intern with efficiency. Michael reflected

that his higher level of problem solving capability and adversity intelligence would not have been attained without his going through the different levels of leadership development. This showed the effectiveness of “Achiever” in developing students to be caring and responsible professionals.

Impacts on Student Community

A sharing platform was created for participants of “Achiever” to actively share their learning on service leadership to other EdUHK students. Through it, students expanded their sphere of influence in the student community and helped promote service leadership on campus when building up their leadership qualities.

A Poster Conference on Service Leadership was held in March 2015 with the aim to give an overview of the work completed under “Achiever”. During the conference, students who had attended different experiential learning activities reflected on and shared the core concepts of service leadership and their application experiences. Over 60 participants from EdUHK and partner universities attended the conference.

Besides, a Whole-person Development Activities Sharing Carnival was organized at the beginning of the first semester of 2015/16 to encourage new students to join student development activities and to build up a sharing culture in EdUHK students’ community.

Impacts on Society

At the final phase of each programme, students applied skills and knowledge in real-life context. Through serving society, students raised their social awareness and strengthened their connection with society. Some students shared their experiences in local newspapers. By doing so, students were promoting the notion of social responsibility and service leadership not only to the students on campus, but also to the public.

Critical Success Factors

“Achiever” is found to be developed from some critical factors. The first factor is a supportive learning environment which is built on the development of a variety of programmes. The other factors include the creation of a road map for student development and programme design, the emphasis on applications, the mutual peer learning opportunities, and the frequent assessments for continuous improvement of both the students and the programmes. These critical factors appear to equate with the learning facilitating conditions proposed by Brown [9], which include the development of a seamless learning environment, a focused picture of student development, the provision of rich array of learning experiences for students and the continued opportunities for student involvement.

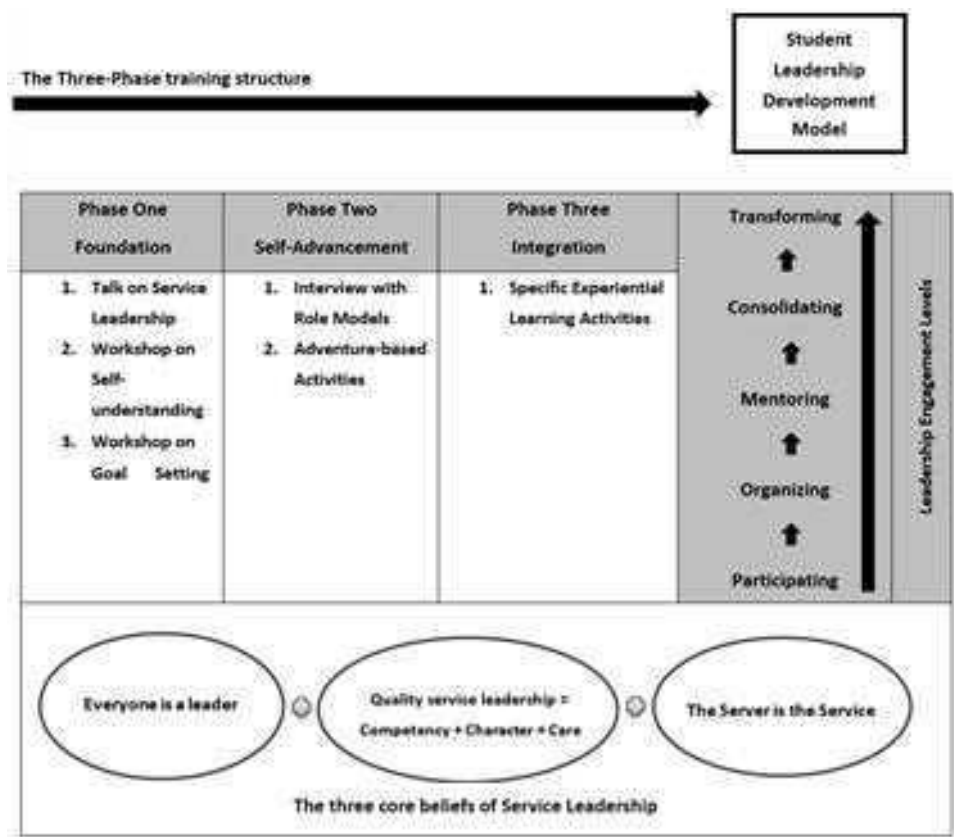
SUSTAINABILITY AND FUTURE DIRECTION OF SERVICE LEADERSHIP INITIATIVE

The advocacy of service leadership will continue to thrive in our society. EdUHK will continue to nurture students' social awareness, and help them to understand that service includes self-serving efforts which aim at ethically improving one's competencies, abilities, and willingness to help satisfy the needs of others. EdUHK will continue to apply the integrated structure of "Achiever" (Appendix 2) to its current and upcoming activities.

APPENDIX 1. EXPERIENTIAL LEARNING ACTIVITIES DEVELOPED IN EDUHK FROM 2012 TO 2015

	2012/13	2013/14	2014/15
Co-Curricular Activities	• Campus Life Advising Scheme (CLAS) • Study Tour Organizer Award Competition • Wofoo Community Service 5 Takes Service Leaders Competition • Leadership Enhancement and Development (LEAD) Programme	• Campus Life Advising Scheme (CLAS) • Study Tour Organizer Award Competition • Wofoo Community Service 5 Takes Service Leaders Competition • Leadership Enhancement and Development (LEAD) Programme • Service Exposure for Global Awareness (SEGA) Programme • Community Service Exposure Attachment (CSEA) • Intergeneration Learning and Elderly Service Academy • Sunshine in the Stroom • Pinchall Volunteers Project	• Campus Life Advising Scheme (CLAS) • Leadership Enhancement and Development (LEAD) Programme • Service Exposure for Global Awareness (SEGA) Programme • Community Service Exposure Attachment (CSEA) • Intergeneration Learning and Elderly Service Academy • Sunshine in the Stroom • Pinchall Volunteer Project • Career Development Summer Internship (Hong Kong) • Career Development Summer Internship (Overseas & Greater China Region)
Student Organization & Mentoring Scheme	NA	NA	• Campus Life Tutors Committee (CLTC) • Mentors of Leadership Enhancement and Development (LEAD) Programme • Mentors of Intergeneration Learning and Elderly Service Academy • Wofoo Leaders' Network (WLN) of the Student Affairs Office, HKIEd

APPENDIX 2. INTEGRATED STRUCTURE OF “ACHIEVER”



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Chapter 113

SERVICE LEADERSHIP EDUCATION AT THE HONG KONG POLYTECHNIC UNIVERSITY

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ABSTRACT

In this chapter we outline the achievements of The Hong Kong Polytechnic University (PolyU) in the 3-year Fung Service Leadership Initiative. In terms of curriculum development, PolyU has developed and offered several credit-bearing subjects and non-credit-bearing programs. Utilizing different evaluative strategies, both

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quantitative and qualitative data suggest that the credit-bearing subjects and non-credit-bearing programs yielded positive impacts on students' development. In terms of research, publications on service leadership have been generated from the project, including journal articles, conference paper presentations, books and book chapters. Reflections and lessons learned from the three-year journey are shared. Particularly, insights on collaboration, research and evaluation, as well as recommendations on how to take the initiative forward both in terms of research and practice are discussed.

INTRODUCTION

The present chapter outlines the achievements and related experiences pertinent to the Fung Service Leadership Initiative (2012-2015) implemented at The Hong Kong Polytechnic University. There are several sections in this paper. First, credit-bearing Service Leadership subjects developed in this period are presented. Second, non-credit-bearing Service Leadership programs are described. Third, research studies in the Service Leadership Initiative are outlined. Finally, experience gained and lessons learned are discussed.

Teaching Activities

As a part of the Fung Service Leadership Initiative sponsored by the Victor and William Fung Foundation to promote service leadership, four credit-bearing courses and four non-credit-bearing programs have been offered to students at The Hong Kong Polytechnic University (PolyU) and students of other tertiary institutions in Hong Kong. In addition, research activities have also been undertaken by the PolyU Team. The present report outlines both teaching and research activities at PolyU since the inception of the Initiative in 2012.

For credit-bearing subjects, four subjects were developed and offered to the students. Primarily, a 2-credit subject "Service Leadership" (APSS2820) was developed and offered to students studying under the 3-year undergraduate curriculum (i.e., old curriculum for A-level students). This subject was offered to students in the 2012/13 and 2013/14 academic years ($N = 190$). Upon completion of the subject, students are expected to gain knowledge on the theories and concepts related to service leadership and to appreciate and understand the importance of service leadership to one's personal development and the society. Modeled after the 2-credit subject, another 3-credit subject entitled "Service Leadership" (APSSA1A21) in the Cluster Area Requirement was developed for students of the 4-year curriculum (i.e., the new 4-year curriculum for graduates of the Diploma of Secondary Education Examination). This subject includes an additional component on the critical appraisal of the Service Leadership model proposed by HKI-SLAM and other major leadership models. To enhance the English proficiency of students, this subject also includes a component on English Reading and Writing requirements. The subject was offered twice since the 2014/15 academic year ($N = 176$). Based on APSS2820, a free elective 3-credit "Service Leadership" subject was developed for students studying in the 4-year curriculum. The subject is offered by the Department of Applied Social Sciences. This subject focuses on the critical evaluation of different leadership models, including the HKI-SLAM model.

In addition to the above credit-bearing subjects that are “classroom-based,” a service learning subject on service leadership utilizing both classroom and outside classroom teaching and learning strategies has been developed. A subject entitled “Service Leadership through Serving Children and Families with Special Needs” (APSS2S09) was designed to enable students to know the core attributes of service leaders, apply the service leadership concepts and skills through the engagement of community-based service activities, develop self-awareness of sharing and empathy with others and the community, and reflect on their service leadership qualities, particularly intrapersonal and interpersonal competencies. To date, students have provided services in special schools admitting boys with behavioral and emotional problems (Society of Boys’ Centres), a non-governmental organization providing service for pre-school children with developmental disorders and mental retardation (Heep Hong Society), a drug rehabilitation agency (Christian Zheng Sheng College) and schools admitting students with social and economic deprivation (schools in Project We Can initiated and financially supported by Wharf). The subject was offered to students since the 2013/14 academic year ($N = 341$).

Besides credit-bearing subjects, non-credit-bearing service leadership programs have also been designed. A modified version of the Service Leadership subject (4.5 days) was offered to students joining the Global Youth Leadership Program jointly organized by The Hong Kong Polytechnic University and Peking University in Beijing in July 2013 ($N = 48$). Several service leadership training workshops have also been developed and offered to members of Wofoo Leaders’ Network ($N = 312$) and as a part of the service learning scholarship program at the Hong Kong Polytechnic University as well ($N = 72$). In 2015, a condensed program on service leadership was offered to students joining the Silk Road Youth Leadership Program jointly organized by The Hong Kong Polytechnic University, Peking University and Xi’an Jiaotong University ($N = 50$).

In summary, since the inception of the Fung Service Leadership Initiative at PolyU, a total of 1,040 students were nurtured to become service leaders through participation in credit-bearing subjects and non-credit-bearing programs.

Research Activities

Primarily, evaluation research is central to the development of Service Leadership education at PolyU. Multiple evaluation strategies have been used to evaluate the credit-bearing and non-credit-bearing service leadership training programs. Quantitative (i.e., objective outcome evaluation, subjective outcome evaluation, and process evaluation) and qualitative (i.e., focus group interview and personal reflection) methodologies were employed. Taken as a whole, evaluation findings provide evidence that students were highly satisfied with the service leadership subjects and training programs. Most importantly, the subject and programs enabled students to gain service leadership attributes and yielded positive impacts on their development. To date, 12 refereed journal articles have been published or accepted for publication based on the evaluation studies [1-8].

In addition to evaluation research, the PolyU team has embarked on several research initiatives in terms of scale development. First, a scale assessing service leadership knowledge and qualities has been developed to gauge students’ changes after taking service

leadership subjects. Second, a research project on the relevance of Confucian virtues to service leadership was carried out. A Chinese Character Strengths Scale has been developed to assess students' Confucian virtues. Data have been collected from 2,887 students and journal articles will be published based on the findings. Third, The Service Leadership Scale research project was launched in July 2015 which aims to develop a multidimensional measure to assess the qualities of service leaders as outlined by the Service Leadership model, and to validate the developed instrument. Specifically, three scales (Knowledge, Behavior/Skills and Attitudes/Beliefs/Values Scales on Service Leadership) will be developed.

In order to allow scholars, practitioners, and the public to better understand service leadership, the PolyU team has presented papers at international conferences and published journal articles and a book. In terms of conferences, three papers on the key concepts and curriculum materials were presented at the Third International Congress on Pediatric Chronic Diseases, Disability and Human Development held on December 2-5, 2012 in Jerusalem, Israel. Moreover, a Service Leadership Roundtable was held on March 22, 2013, at The Hong Kong Polytechnic University, Hong Kong. In that roundtable, our research team gave multiple presentations about Service Leadership education and curriculum development at PolyU. Two papers were presented at the International Conference on Service Leadership Education for University Students: Experience in Hong Kong held on May 14-15, 2014 at The Hong Kong Polytechnic University. In the first paper, credit-bearing subjects and non-credit-bearing programs were described. In the second paper, evaluation studies were presented.

In terms of publication, two special issues of the *International Journal on Disability and Human Development* documenting evaluation studies' findings, the curriculum of the Service Leadership model, including the distinction between manufacturing and service economies and comparison between the Service Leadership model and existing major leadership models in the scientific literature, have been published [9-18]. Furthermore, Chinese articles have also been published in the Hong Kong and Macau Affairs discussing the importance of service leadership for Hong Kong's competitiveness and how to nurture service leaders among Hong Kong students. Lastly, a book entitled "Promoting Service Leadership Qualities in University Students: The Case of Hong Kong" was published in summer 2015 with Prof. Daniel Shek and Dr. Po Chung as Editors, and Dr. Hildie Leung and Dr. Li Lin as the Managing Editors. The book includes keynote speeches, welcoming addresses, and papers presented at the International Conference of Service Leadership Education: Experience in Hong Kong in May 2014 [19-22]. In summary, a total of 51 publications were produced by the PolyU team.

Reflections and Learning Points

There are several learning points from the project. Primarily, the development of the Service Leadership curriculum (including credit-bearing subjects and non-credit-bearing programs) forms a solid basis for Service Leadership education in Hong Kong. The related curriculum materials, assessment methods, and publications are important for the long-term sustainability of the initiative in the higher education sector. One obvious obstacle for Service

Leadership education in Hong Kong is the lack of curriculum materials and subjects. As such, development of the four subjects and the non-credit-bearing subjects at PolyU is helpful to take the Service Leadership education subjects forward.

Second, the project shows that experiential learning is a desirable learning approach in Service Leadership education. There were several features of Service Leadership subjects and programs developed at PolyU. Primarily, besides short lectures, interactive learning activities including role play and structured activities were used. In addition, collaborative learning through discussion, sharing, and presentation in groups was emphasized. Furthermore, students were encouraged to have reflective learning throughout the subject or program. Essentially, the students were encouraged to have reflections about their knowledge, attitudes and behavior with reference to the Service Leadership model.

Third, our experience suggests that Service-Learning is a good pedagogy for Service Leadership education. Through service-learning, students can have opportunities to reflect on their knowledge, attitudes and skills about Service Leadership, particularly moral character (such as sense of responsibility and trustworthiness) and caring dispositions (such as empathy and having passion about the needy). In essence, through the service-learning projects developed and service-learning hours performed by the students, the students can learn more about Service Leadership attributes.

Fourth, this project underscores the importance of using systematic evaluation methods to assess the impact of Service Leadership Initiative. In the present context, objective outcome evaluation adopting the one group pretest-posttest design was used. In the case of the Global Youth Leadership Program, multiple waves of data were in fact collected. Subjective outcome evaluation (i.e., the client satisfaction approach) was also adopted to gauge the views of the students. Besides, process evaluation was used to understand the implementation quality and adherence to the developed materials. Finally, qualitative evaluation is a good way to understand the subjective views of the students who take the subject or program. It is argued that Service Leadership subjects or programs developed should be properly evaluated to understand the impacts on the students.

Fifth, we must conduct systematic research on Service Leadership model. There are still many questions to be answered with reference to the SLAM model. Some questions include: What are the unique features of the model as compared to other mainstream leadership models? What antecedents influence the development of service leadership qualities? What are the consequences of having service leadership qualities? What should be the ingredients of moral character? How can we nurture trust in service leaders? Is Service Leadership related to productivity? Obviously, more research should be done to strengthen the body of knowledge on Service Leadership.

Sixth, it is important to document research and education on Service Leadership. In particular, there is a need to build up the literature on Service Leadership. Obviously, without published work on Service Leadership, it would be difficult to develop Service Leadership education. In particular, scientific reports on the effectiveness of Service Leadership education should also be stepped up.

Finally, the Service Leadership Initiative is an excellent example of collaboration between the commercial sector and the higher education sector. For the contribution of the commercial sector, the Victor and William Fung Foundation provides the financial support and the Hong Kong Institute of Service Leadership & Management Limited provides the Service Leadership model and curriculum framework. For the contribution of the higher

education sector, different curriculum materials, subjects, and programs have been developed. In the last three years, we can use the description of “let the hundred flowers bloom” to represent the work done. In future, consolidation of the work done and adoption of a more focused approach would be important.

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Chapter 114

SERVICE LEADERSHIP COMMUNITY BLOOMING

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ABSTRACT

After three years of seeding, watering and nourishing, the service leadership community of The Hong Kong University of Science and Technology (HKUST) is in full bloom. Diversified components in the community help students learn as apprentices, experience as practitioners and ultimately develop as service leaders. The leadership corner area at the Engineering Commons acts as a starting point to raise students' awareness of service leadership. The *EnG Chitchat*, an open idea-sharing forum, provides opportunities for students to inquire about service leadership and to learn how their expertise can be applied to satisfy people's needs. When students would like to practice service leadership, they can join the peer mentoring program (PMP). Over 200 senior students became peer mentors, providing academic advice, campus life information and social support to their mentees. In a survey of how first-year students adapt to university life, over one-third of students agreed peer mentors were helpful to them. Regarding service leader development, various service learning courses are available and open to students with different disciplines. From the trolley design for the elderly to the mobile App development for hearing impaired children, students apply their expertise to satisfy the needs of certain people in society. Students are also empowered to identify and satisfy people's needs on their own as we have a program of student-initiated service projects in our service leadership community. To keep improving the established community, we continuously conduct research, aiming to discover more effective and innovative ways to promote service leadership at the university.

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INTRODUCTION

In 2012, the Victor and William Fung Foundation and the Hong Kong Institute of Service Leadership and Management (HKI-SLAM) collaborated to provide financial and informative support to 8 UGC-funded institutions for the sustainable development and promotion of Service Leadership to tertiary students. At The Hong Kong University of Science and Technology (HKUST), the Center for Engineering Education Innovation (E²I) of the School of Engineering has established a Learning Community to nurture the mindset of service leadership in students [1]. The community provides different components to help students understand, practice, and develop service leadership. All components are also targeted to the personal development of students in leadership roles to become Service Leaders. The purpose of this chapter is to share the processes, outcomes, and experience gained by HKUST from the development of a service leadership community.

SERVICE LEADERSHIP COMMUNITY

In the community, the components are grouped into three types of platforms and each platform has its unique purpose so that students can achieve different levels of learning Service Leadership based on their interests. The apprentice platform serves as the starting point to raise students' awareness on service leadership. When students seek to practice and experience service leadership, they can join the peer mentoring program, a program to train senior students to serve first-year students. If students wish to develop as service leaders, various service learning courses are available for them to take.

Learn as Apprentices

To increase students' exposure to and understanding of service leadership, E²I set up a leadership area to display related information using slideshows, videos, publications and newsletters. Students can study and discover service leadership and how it is important to their future. During regular semesters, an open forum, *EnG Chitchat*, is held weekly for students to understand more about service leadership and how they can apply their technical knowledge to satisfy the people's needs. Based on the feedback of 31 participants from random sampling, 74% enjoyed the forum and over 65% agreed that it increased their interest in making contributions to the community. In addition, the concepts and beliefs of Service Leadership are introduced in a seminar of ENGG 1010 - Academic Orientation for the first-year students and of ENGG 2010 – Engineering Seminar Series. Over 800 students attended the seminars which present lecture materials enabling them to better understand service leadership and inspire them to practice it.

Based on the observations and feedback in *EnG Chitchat* and the students' interest in new technologies, tailor-made courses/workshops are designed to inspire students to learn and develop service leadership through the application of the latest technologies to satisfy people's needs. Service leadership concepts are described in a way of how they can be applied in engineering practice. Then with the understanding of the technologies, students are

asked to apply what they learn to fulfill the needs of the people mentioned in the case studies. A workshop called 3D Printing for Social Good is designed in this way and offered to students. As expected, students are very interested in the workshop and the quota is always completely filled by the second day of registration. In the recent feedback survey, 92% of respondents agreed that the teaching format of the workshop had been well designed to help them learn and the content of the workshop was clear to them. 42% rated the workshop “VERY GOOD” and the rest (58%) rated it “GOOD”. All respondents agreed that leadership is a service in which leaders satisfy the needs of people. 50% of the respondents also mentioned they would strongly recommend the workshop to other students. Thus, it can be observed that one of the feasible ways to attract engineering students to learn Service Leadership is to make a connection of new technologies and their interests with Service Leadership, i.e., how to apply the new technologies to satisfy people’s needs.

Experience as Practitioners

Practice is an indispensable component of leadership development, and clan-based Peer Mentoring Program (PMP) is a straightforward and useful approach for students to practice Service Leadership. In the program, senior students are trained to become peer mentors, providing academic and social support to first-year students who are grouped into respective clans. The mentors advise students in course registration and organize social activities enabling first-year students to adapt to university life. There are also some large events such as Team Building Camp and Rafting Competition for peer mentors and mentees to mingle more with one another, reinforcing their bonding. In addition, to broaden the peer mentors’ horizon, E²I has organized an Intercultural Peer Learning Program for peer mentors to serve the needs of visiting students from other foreign universities.

More than 200 senior students have so far joined the Program and based on the overall program evaluation survey, about 81% of the respondents agreed that leadership is a service aimed at ethically satisfying the needs of self and others, and it can be found all through society, professionally and personally. Also, over 80% believed leaders should self-improve themselves to serve others. From their written comments on their learning in the program, they mostly mentioned their communication skills were improved, implying they could understand the needs of their target people more effectively. They are more confident than before to communicate with students of different cultures and backgrounds, with some also putting themselves in others’ shoes to understand more about their mentees. Being competent at multicultural communication is an asset for students to compete in a service-driven economy like Hong Kong, with clients and customers from all around the world [2]. In the survey of how the first-year students adapt to university life, over 37% of respondents agreed peer mentors were helpful to them, and over 35% said the assistance of peer mentors was useful to them in ongoing professional careers.

It is indisputable that from the program evaluation, most peer mentors understand the main concepts of Service Leadership. However, the feedback of first-year students implied that the peer mentors can work better to serve first-year students. One possible way for improvement is to encourage peer mentors to be more proactive to understand the needs of first-year students through communication and observation. With more training on need

identification and satisfaction, the Peer Mentoring Program is a direct and handy way for students to understand and practice Service Leadership.

Develop as Service Leaders

To become service leaders, students need to learn leadership skills and have opportunities to practice. There are several service learning courses which are designed to help students develop as Service Leaders. ENGG 2900A (Community Service Project: The Way to Success) is a course to help students acquire leadership knowledge and foster their personal development using an interactive teaching approach. They are supervised by the instructor and mentors to design their own group service projects and handle the actual situations by themselves to learn leadership in a realistic way.

From the reflection papers, it is obvious that through the project design and implementation, students can learn and experience more profoundly the concepts of service leadership. In a group service project about selling cookies to raise funds to buy gifts for the homeless, some students recognized the uniqueness of each person and tried to understand their teammates' needs in order to be a successful leader with a sense of responsibility to serve others. In addition, since HKUST is located in a suburban area, some international and even local students may not be familiar with the area to find places for eating, shopping and other leisure activities, so another group developed an online guide for these students. This can show that students who took ENGG 2900A targeted the needs of people when designing their service projects. The other three courses are more technical than ENGG 2900A. They are:

- ENGG 2900B – Community Service Project: Innovative Trolley Design for the Elderly
- ENGG 2900C – Community Service Project: The Mobile App Development for Hearing Impaired Children
- ENGG 2900D – Community Service Project: Underwater Robot Competition Engagement Project

For these types of courses, students apply their technical knowledge to serve the targeted people. They first observe and communicate with these people, then identify the problems and satisfy those people's needs accordingly. In ENGG 2900B, students went outside the campus to talk with the elderly scavengers who collected cans and cardboard on the streets using trolleys. Through walking alongside the elderly to experience the challenges and hardship of collecting salable junk, students can recognize these elderly's needs so that they can effectively design an innovative and custom-made trolley for their end users. To help hearing-impaired children speak and communicate clearly with other people, students of ENGG 2900C applied their computer knowledge to develop mobile Apps for these children to learn how to pronounce Chinese words precisely. Also, in ENGG 2900D, students not only taught children and teenagers from primary and secondary schools to make robots but also assisted in organizing an underwater robot competition for these youngsters, with the aim to arouse their interest in science and technology.

Based on the overall evaluation of these courses, over 80% of the respondents agreed that the service learning courses helped them understand more about the needs of the community and increased their interest in making contributions to the community. About 88% replied that they would apply their expertise to help the needy in future and self-improve to provide the best approach to satisfy the community's needs as necessary. Also, in the participant feedback survey of the underwater robot competition, 75% of the responding schools are interested in joining the next competition. Also, the kids who joined the competition sent thank-you cards and photo albums to appreciate the students who taught them how to make robots.

Compared with the Peer Mentoring Program, service learning courses seem to help students understand and focus more precisely on satisfying the people's needs as the needs of targeted people are well defined and the ways to satisfy the needs are specified. Thus, service learning courses involving the application of technologies to satisfy the needs of targeted people is a good way to teach Service Leadership. To allow students to have more autonomy for applying their expertise to satisfy the needs of people, a program is set up to encourage students to initiate their own service projects. Students submit their proposals to the corresponding professors, and once approved, they can do their projects in an engineering design laboratory under supervision.

Impact of the Project

Traditionally, leadership development has not been the main focus in engineering education or a priority for engineering students [3-5]. These students have tended to concentrate their time on technical courses and group projects. With the implementation of the HKUST Service Leadership Initiative, engineering students are becoming aware of the dominance of services in our economy and the importance of leadership skills for their future development. The Initiative is also fostering a bonding between junior and senior students through the Peer Mentoring Program. This cohesion further extends within each engineering department, and graduates return voluntarily to HKUST to participate in school events, promoting their corresponding departments and the skillset necessary for professional practice.

With the influence of Service Leadership, more students put the factor of satisfying people's needs in designing their final year and capstone design projects. For example, one student project is the development of a Kinect-based physiotherapy system for patients who cannot go to clinics frequently for treatment. This project was also nominated and awarded in some public competitions. The University actively encourages more and more students to apply their knowledge and skills to make contributions to the community.

From the experience at HKUST, just three years ago, most students had little idea about Service Leadership. After the introduction of this ongoing initiative, students can apply Service Leadership in their projects, and we believe the outcomes of the project will continue to positively influence both students and HKUST.

CONCLUSION

With the aid of the Foundation and HKI-SLAM, HKUST has successfully established a Learning Community to help students develop a mindset of Service Leadership. They can achieve different levels of learning at the corresponding platforms based on their interests. After years of nurturing, each platform has achieved its purpose and provided insights for further developing the Community:

- The leadership area and *EnG Chitchat* act as an initiator to raise students' awareness on Service Leadership. The *EnG Chitchat* is also a good means to collect what students need and like so that tailor-made workshops can be developed to inspire students to learn Service Leadership.
- Peer Mentoring Program is a straightforward and handy way for students to practice Service Leadership. More training on need identification and satisfaction should be provided to help peer mentors effectively satisfy the needs of the first-year students.
- With the well-defined approaches to satisfy the needs of the targeted people, service learning courses are effective in helping students develop as Service Leaders. These courses produce profound impacts on both students and service receivers. In addition, an engineering design laboratory is set up to encourage students to start their own projects in which they can apply their expertise to help the people in need.
- More research about the comparison of the technology-based service learning course/workshop with the Peer Mentoring Program will be conducted to determine which one would be more effective in teaching certain core beliefs of Service Leadership.

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Chapter 115

**CHALLENGES IN THE DEVELOPMENT
OF AN EXPERIMENTAL COURSE SERIES
FOR MULTI-DISCIPLINARY
UNDERGRADUATE STUDENTS**

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ABSTRACT

The Hong Kong University of Science and Technology (HKUST) aims to engage undergraduate students in making contributions to the community as well as create and facilitate educational and leadership opportunities. Undergraduate students are encouraged to utilize their engineering knowledge and technology knowhow innovatively in projects contributing to the society. We collaborate with the School of Business, School of Science and faculty from School of Humanity and Social Science, and Interdisciplinary Program Office to design an undergraduate courses series to embed engineering knowledge and service leadership into two experiential learning programs.

INTRODUCTION

The objective of the experimental course is to provide students with opportunities to understand the fun of Inclusion, Science, Technology, Engineering, Art, and Mathematics (ISTEAM), and to nurture social inclusion and develop an understanding of the talents and needs of contestants from different backgrounds [1]. By integrating experience in service

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leadership into community engagement projects with fun and learning (an experiential learning approach), we provide a different learning environment to the undergraduate students.

The key design elements allow students to learn various types of knowledge from different professionals. These can be achieved by putting multi-disciplinary students together and forming teams to complete a goal. The students learn from their peers and understand different clients' views. The courses also aim to provide students experience in integrating their professional knowledge into community services. They can convert what they learn in the university and help to make changes to the society.

In the meantime, the courses allow students to make a decision when they face challenges from the clients. The clients in these courses are children, youth, students with special education needs and ethnic minorities. Our students need to understand and communicate with clients. As the author of the article "Inclusive education" [2] mentioned, people have gotten used to special education to mean "separate education." We believe that there will be a positive outcome for both academic and social interactions when the clients participate and educate each other.

Both courses receive support from departmental level to joint-school level in order to achieve multi-disciplinary problem-based learning. With the support from the other units like NGOs or engineering units, the students which participated in the course will have greater chance to learn and handle real-world problems by using their knowledge. Experiential learning encourages them to combine technical knowledge and skills with the creativity that leads to innovative ideas [1].

EXPERIMENTAL COURSE

In order to encourage multi-disciplinary learning and society collaboration, a mobile app design project has been embedded into an experimental learning course in 2015 [3]. This course has been set up for students coming from different disciplines such as engineering, business and science. They learn how to design Articulation Screening and Training Tool, a mobile app and server system for hearing impaired children. The students worked in sub-teams in different areas like mobile app design, data server construction and UI design. They also had to organize service learning activities in collecting speech samples.

The course is a good example in demonstrating the collaboration between NGO and academic research into a mobile app. The training tool can provide a simple platform for hearing impaired children to learn phonemes in a fun way. The course offers interactive modules that are different from conventional lecture-based engineering courses.

Two groups of undergraduate students were responsible for developing the apps for voice recording and the system. The junior undergraduate students developed the voice recording system, and the senior undergraduate students developed the system and the UI design. We also invited postgraduate students and research faculty to help develop the voice recognition algorithms. There were also a group of multi-disciplinary students and primary/secondary students that helped in voice collection among secondary students.

Over 8,000 voice samples were collected by HKSOD in summer 2015 and more than 35 enthusiastic students from a local secondary school helped with the voice sample collection

by HKUST in November 2015. There were around 50 HKUST students helping to verify over 25,000 Cantonese voice samples.

Another course is the Underwater Robot Community Engagement Project [4]. In 2015 March, HKUST invited students from Primary Four to Form Three to take part in a social inclusion project. Underwater robot technology was adapted for use in this social inclusion project. The HKUST Centre for Global and Community Engagement (GCE) offered an UG course with other units and recruited UG students for a two-and-half-day workshop for 18 school teams in robot-making skills. Through the course, the UG students were transformed from apprentices to mentors. Then, UG students became the mentors of contestants participating in an Underwater Robot Competition. The competition was held in HKUST indoor swimming pool.

The objective of the workshop and the competition was to provide students with opportunities to learn and experience in the Inclusion, Science, Technology, Engineering, Art, and Mathematics (ISTEAM) [5] and to nurture social inclusion and develop an understanding of the values and needs of students with different abilities and backgrounds. The contestants needed to design and assemble their robots, including both electronic and mechanical components on their own. The contest's aim is to spark junior students' interest in science and mathematics and it also gave the university students a chance to serve the community. Undergraduate students provided valuable lessons about teamwork for the contestants. It was really a pleasure to use engineering knowledge to serve the society.

In 2015 March, HKUST invited students from Primary Four to Secondary Three to take part in the competition. In the project, the contestants were coming from mainstream primary and secondary schools, and schools that teach students with special education needs and ethnic minorities. The students with special education needs included hearing impaired, visually impaired and students with learning disabilities. The HKUST students who took part in the course conducted a two-and-half-day workshop for all the 18 teams to teach them how to build a basic underwater robot. After the workshop, the underwater robot competition was held in HKUST indoor swimming pool and the student teams were required to improve their robot design by adding different parts and manipulators. To ensure the fairness, there was no fine adjustment for the scores even when the team consisted of students with different learning abilities.

FEEDBACK FROM THE STUDENTS

The reflective reports of UG students in these two courses indicated that they had a great experience in the teamwork in a multidisciplinary group. Here are some of the feedbacks from the undergraduate students and the secondary school participants:

"I used to be a person that works randomly, but now I would choose to make the work perfect so as to create a sweaty but worthwhile memory," said one of the HKUST undergraduate student mentors. A HKUST final year undergraduate business student mentor stated, "This is the first experience in working together with engineering and science students in a team."

The events also provided a chance to help the participant to gain confidence and engineering knowledge. One of the participants of the Underwater Robot Competition 2015 mentioned, “I am visually-impaired but it doesn’t mean I can’t do it.”

The Mobile App Design project and the Underwater Robot Community Engagement Project is the first trail of an undergraduate course in implementing “ISTEAM” education in HKUST. A lot of positive feedbacks were received. Also, many ways to improve the courses were also found. Many of the secondary and tertiary schools showed their passion for helping and willingness to have further cooperation in other experiential learning community projects. Our team was really pleased to see the concept of using engineering knowledge to serve the society in action and to see people of different backgrounds working together to bring a difference to society.

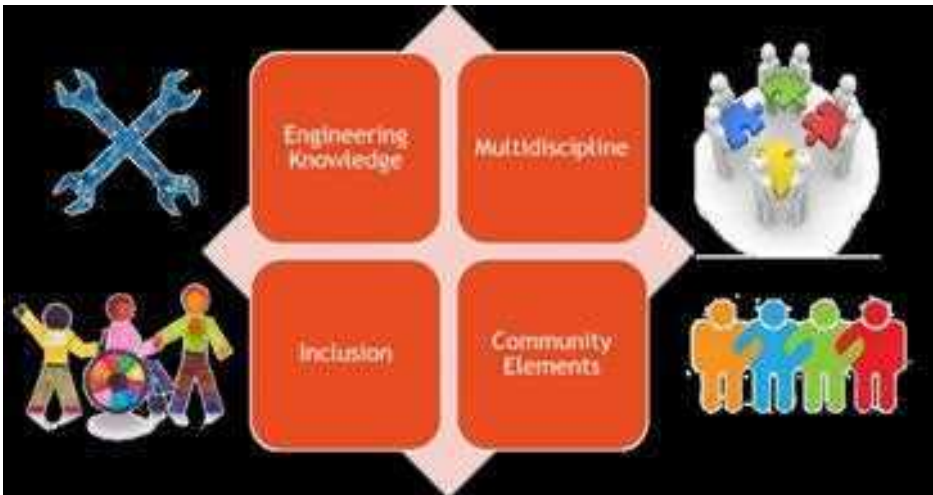


Figure 1. Key elements of experimental courses.

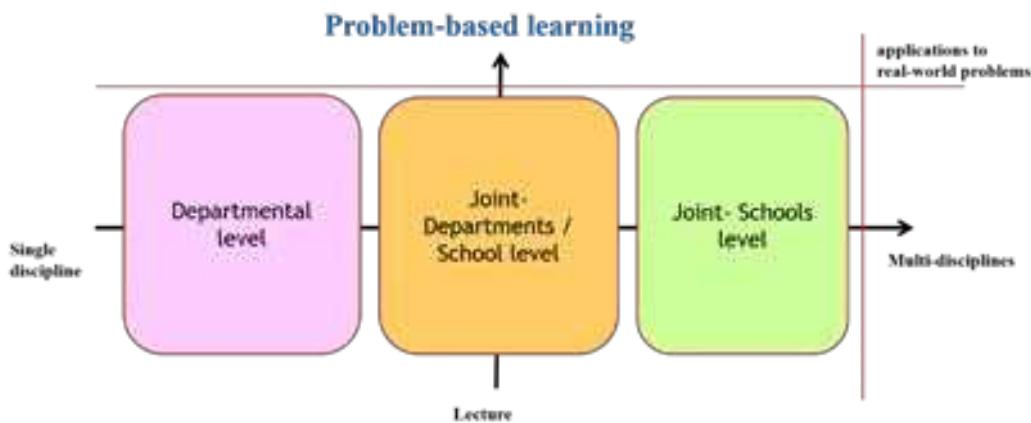


Figure 2. Structure of the experiential learning courses for multi-disciplinary students.



Figure 3. Design a mobile App and server system of Articulation Screening and Training Tool for hearing impaired children (The apps are applicable to all people).

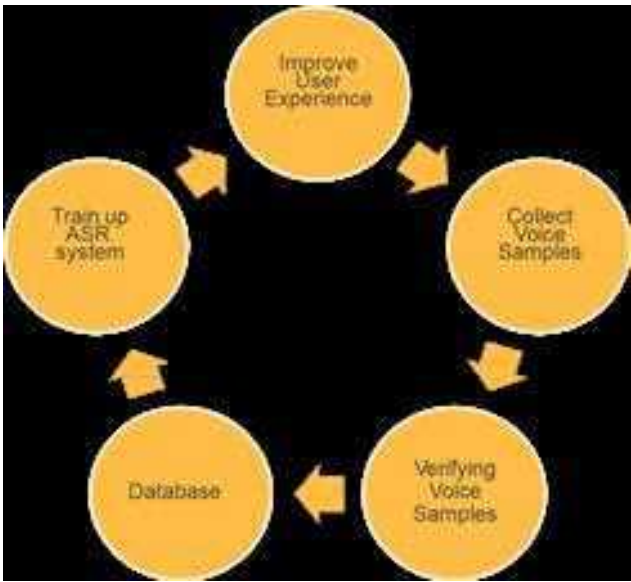


Figure 4. The development cycle of the Training tool for hearing impaired children.

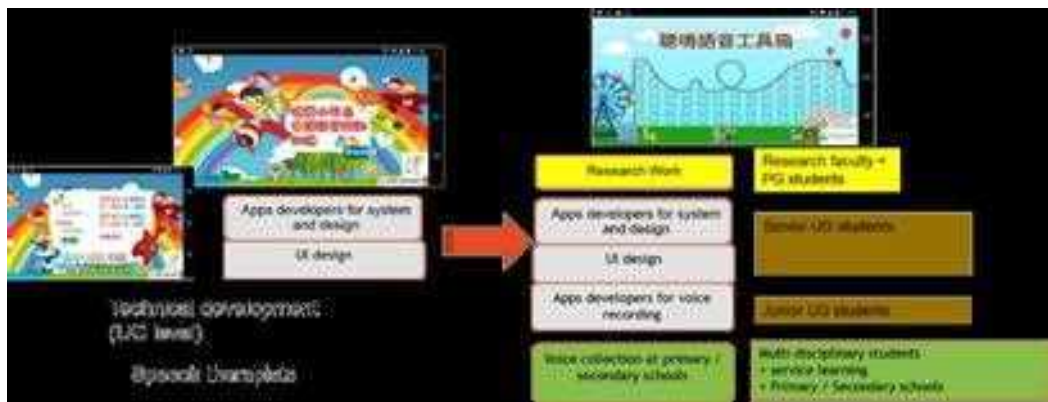


Figure 5. Co-operation between different students and units.



Figure 6. Underwater Robot Community Engagement Project.



Figure 7. Embedded “Art” and “Inclusion” into STEM Education.

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Chapter 116

KEY PRACTICES OF LEADERSHIP FOR SERVICE IN HONG KONG

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ABSTRACT

We conducted semi-structured, qualitative interviews with 17 Hong Kong based middle to senior managers from diverse service sectors about their own service leadership practices in helping their respective organizations to maintain effectiveness through establishing and meeting the needs of service-recipients and end-beneficiaries. Based on their explanations and illustrations, we identified four common practices. These were: entrepreneurial spirit and mindset, distributed leadership, building and sustaining productive relationships with stakeholders as strategic partners, and caring and respectful disposition. These practices and practical examples can inform the curriculum for undergraduate students in Hong Kong.

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INTRODUCTION

Advanced economies have entered a post-industrial era, with factory-based mass-production of standardized goods in decline, superseded by knowledge-intensive manufacturing wrapped in service [1], or by ‘pure’ service, tailored or adjusted to the unique needs of particular service recipients [2].

The leadership paradigm associated with the factory mode assumed that business operations require centralized, top-down command, imposition and enforcement, exerted by an elite few. While this leadership paradigm may linger on in the popular imagination, there have been calls for organizations to embrace a new leadership paradigm, better-suited for contemporary modes of value-creation [3].

Service leadership has been proposed as a new leadership paradigm for advanced economies [4]. Service leadership involves influencing people in positive ways, in accordance with sound ethical principles and in the context of employee empowerment, in order to achieve and improve upon excellent service. An associated organizing principle is that leadership responsibilities are distributed widely [5, 6], with organization members at all levels shouldering responsibility and taking initiative [7]. Associated core beliefs include that everyone is or can be a leader [8], that service quality depends on the quality of the server [9], and that caring disposition is an essential service leadership attribute [10, 11]. Servant leadership [12-15] may be regarded as a constituent of service leadership, but in service leadership there is additional concern to meet the leader’s own needs for health in body, mind and spirit [16].

The service leadership paradigm assumes that the effectiveness of human service organizations requires everyone, whether located at the frontline or responsible for designing the service habitat, to be sufficiently developed in terms of cognitive competence, emotional intelligence, spirituality, interpersonal skills, moral character, caring disposition, self-leadership and continuous self-improvement, and self-reflection [16]. These target developmental domains challenge contemporary educational institutions to provide effective service leadership education. We assumed that credible and inspirational case exemplars and practical explanations of service leadership would be cornerstones of such education. Our research sought to add to the existing body of local case material [17], while also identifying and explaining the associated dimensions of practice.

INTERVIEWS AND ANALYSIS

We constructed an interview guide, comprising open-ended questions on the following themes: organizational background; the interviewee’s approach to problem solving, meeting service-recipients’ needs, service innovation, influencing people, and developing people; sources of influence on the interviewee’s leadership approaches; how the interviewee had developed as a service leader; the interviewee’s motivation to provide service leadership; the interviewee’s recommendations on how to identify and meet service recipient needs; and organizational arrangements to support service leadership. Probing questions were included throughout the interview in order to seek critical incident accounts [18-20] as illustrations.

Based on the interview guide, semi-structured interviews [21] were conducted in Cantonese on a one-to-one basis with 17 Hong Kong based managers, who were occupying positions of seniority, ranging from project manager up to CEO. Among the interviewees, seven were employed by large multinational corporations, seven worked for local small businesses, one was a government employee, and two worked for NGOs. All interviewees were known by the authors to be seasoned practitioners of service leadership, and were contacted through the authors' personal networks, and hence constituted a criterion-based convenience sample [see 22, p. 28], covering a wide range of service industries.

Table 1. Background of the interviewees

Code Name	Position	Industry Sector
M1	CEO	Food
M2	CEO	IT/Marketing communications
F1	CEO	Education
M3	Executive director	Travel
M4	Managing director	Finance
M5	Managing director	Logistics
M6	General manager	Hospitality
F2	General secretary	NGO
F3	School principal	Education
M7	Director	Engineering services
F4	Vice president	Logistics
F5	Vice president	Logistics
M8	Senior unit manager	Insurance
M9	Senior unit manager	Insurance
M10	Training consultant	Management consultancy
M11	Design consultant	Engineering services
F6	Project manager	Travel

Table 1 lists the interviewees by codename, position, and industry sector. Each interview was transcribed on a near-verbatim basis into English.

Adopting a grounded theory approach [23, 24], the third author conducted open coding on the transcripts of the first six interviews, initially identifying over 100 categories and then, through axial coding, distilling these into 22 practice concepts. She was then able, without forcing, to categorize raw data from the transcripts of the remaining 11 interviews into these 22 practice concepts. These were: social values; personal values; seeing the big picture, looking forward; solving problems; using new approaches, taking risks, being flexible, being open; being persistent, hardworking, and conscientious; being customer-oriented; delegating, empowering, and developing subordinates, sharing responsibilities; connecting, relating, and integrating; collaborating and establishing partnerships; caring and respecting; learning new things and keeping updated; accepting mistakes; adjusting and improving; recognizing service leadership; professional knowledge and conduct; handling stress and managing emotions; setting a good leadership example; communication and interpersonal skills; providing training and giving guidance; recruiting and retaining the right people; and company support. Having identified these 22 practice concepts, the third author re-examined all 17 transcripts for instances and counted-up mentions thereof, arriving at four over-arching sets of service

leadership practices. A separate, more holistic reading of the 17 transcripts by the second author yielded a similar set of over-arching service leadership practices, thereby providing confirmation through analyst triangulation [25].

WHAT WE FOUND

The four main sets of service leadership practices were: entrepreneurial spirit and mindset; distributed leadership; building and sustaining productive relationships with stakeholders as strategic partners; and manifesting a caring and respectful disposition. Next, we shall explain these practices.

Entrepreneurial Spirit and Mindset

This involved leading for service innovation, embracing new approaches, taking risks, and being flexible and open-minded. All 17 interviewees mentioned aspects thereof. Service innovation could unfold along a continuum ranging from radical through connective to incremental innovation. Radical, “breakthrough” or “frontier” innovation involved reconfiguration of the firm’s business model. For example:

“I’m starting at this point to think about how to reintegrate all online sales, online services plus selling of offline shops or some true services we have to do when offline, like face to face service, to become a new model. And this is the new model that we, ‘---- Company’ wish to implement in the next one or two years.” (M2)

Connective innovation entailed the creation of novel service items to address needs that were newly-articulated by existing customers, while incremental innovation involved improvising upon existing service items to meet service recipients’ needs. Alluding indirectly to the latter, one interviewee commented:

“When you provide a professional service, being professional is not following what the books say, as it’s more like enforceability... the ability to do something beyond the codes and practice... this enables the company to have different skill sets to sell. Also, these skill sets are very unique, making our company different from other companies...” (M7)

Distributed Leadership

This involved delegating tasks to others for the twin purposes of mutual empowerment and service effectiveness. Every interviewee mentioned aspects thereof, which could range from “hands-off” empowerment within a flexible organization structure to “hands-on” guidance within a more settled structure. An example of “hands-off” empowerment was the adoption by all members of one organization of a system of using business cards with no job titles, representing a flat and flexible organization with no hierarchy, and with members being trusted to develop their own areas of expertise and responsibility in response to customer needs:

“Our company also does not officially define who is what. Actually, we call all employees that ‘Bro’ or that ‘Sis’. We don’t have titles. Even when we went out and did business with --- (a large international company), the business cards did not have titles. They looked at our cards. Then, we ... told them, ‘Oh. It’s fine. I’m responsible for this case. I can arrange it.’” (M1)

“Hands-on” guidance involved conveying basic principles to followers and nurturing them, though mentoring or coaching, to become independent solvers of the problems or needs of their service recipients, and was a step toward “hands-off” empowerment. The latter is illustrated in the following quote:

“A lot of ideas ... aren’t mine... it is the people from the floor (who) ... give them to me. ... For example, we have scan machines. How we continue to improve our scanners (comes from) the feedback from the people in the frontline. It is not from me. Because they do it day and night. They are in the best position to give me the most precious advice...” (M5)

Building and Sustaining Productive Relationships

All but one of the interviewees mentioned aspects of this set of practices, which included establishing and maintaining connection and dialogue with stakeholders, oriented to the diagnosis of service recipient needs. Such dialogue could take place via electronic media as well as face-to-face contact, and could be ongoing or extensive. For example:

“The first time I met this customer I already knew much information about her and understood her needs. ... Now, if she has any needs she will send WhatsApp messages to me.... Actually I don’t treat her only as a customer. I treat her as a friend. We were like old friends when we first met...” (M9)

Many interviewees mentioned the importance of being approachable and of inviting or initiating ongoing communication with service recipients. For example:

“After you get along with them for a long time, you will naturally become able to talk with them. Also, you will pay effort (to talk). You will think that it is unreasonable to fail to talk with them. Then, over time, you can communicate with them more effectively.” (F3)

Interviewees also mentioned the importance of open communication with subordinates. The following comment expressed the need to respect subordinates’ concerns about service requirements, the need to ensure that subordinates had sufficient resources to address such requirements, and the need to make corresponding adjustments in organizational policies.

“I will treat my role as a leader rather an administrator. That means, I think about the direction of the institution’s development, aligning with the different expectations of colleagues, and making it easier for them to achieve success in their jobs and to be happy.” (F3)

In cases where service recipients knew what they wanted and needed, the principle of strategic partnership required service leaders to be proactive and responsive in meeting articulated needs, to seek comments and feedback for service improvement, and to go beyond what was being asked for. For example:

“They ask you questions in the morning and want the answers in the afternoon.... Or sometimes they want the answer right away. To help our clients, instead of simply conveying the question to the related parties... we

need to think about and ask some further related questions so that we can synthesize the entire picture for the clients.” (F6)

In cases where service recipients were unsure about their needs, or were demanding inappropriate solutions, service leaders were careful to show that they were committed to meeting genuine needs while building around service recipients’ ideas. For example:

“There are things clients really need, but in many cases they don’t really need to have something but just think it’s good to have it. This is hard to directly ask them about. Especially, clients will search for information through various means, like the internet... So you will have to think how to explain this issue to the client...” (M7)

Caring and Respectful Disposition

This reflected that service leaders cared deeply about the best interests of their followers, customers and end-beneficiaries. Every interviewee mentioned related aspects, expressing passion for and enjoyment of their work, in the face of difficulties and demands. While some service leaders wanted to contribute to wider social causes, of primary and general importance was that they expressed heartfelt desire in their work to meet the needs of those around them as an end in itself. Interviewees articulated this in various ways, for example:

“Love is not just a matter of using the mouth to say it. You have to undertake. Yes.” (F3)

“Thus, it’s people... that are our biggest asset. I think it’s so ... We respect every customer. And (we) have a lot of trust in them...” (F4)

“When they (employees) bring their kids to the office, I hug the kids. Whoever brings their kids here and wants me to hug them, I hug them...” (F2)

Caring and respectful disposition appeared to constitute an essential foundation for service leadership, upon which all the other practices were built. One interviewee said that he tried to convey this principle to his subordinates:

“I advise them to be sincere in caring about people. In our job it isn’t really about caring about the finance. It’s about the person. Then, with this purpose, they (employees) may have greater enthusiasm at work, motivation to push themselves forward and to be mature. This is an important thing. True caring is the prerequisite of progression. True caring is more important than skills and luck.” (M9)

DISCUSSION

In identifying illustrative case exemplars of four key service leadership practices, we have adopted grounded theory [23, 24], and have explained and illustrated how service leaders meet their own needs by expressing entrepreneurial spirit and mindset, arranging for distributed leadership, building and sustaining productive relationships, and providing caring and respectful service from the heart. Appreciating and practicing service leadership may be an antidote to despair and anomie [26]. Our case exemplars can be shared with students as guidance and inspiration for their development as future service leaders.

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Chapter 117

**PREPARING SERVICE LEADERS FROM LINGNAN
UNIVERSITY THROUGH SERVICE-LEARNING
PRACTICUMS IN SOCIAL ENTERPRISES
AND NON-PROFIT ORGANIZATIONS**

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ABSTRACT

The full-time service-learning summer practicum programme organized by Lingnan University aims to provide internship experiences that empower undergraduates to practice service leadership in community organizations. We report on a qualitative evaluation study that identified three success factors, namely, task significance and challengingness, co-educator presence and supportiveness, and students' disposition for socially agentic self-initiation. The study broke these factors down into a number of sub-factors. We discuss the practical implications for service leadership development for undergraduates.

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INTRODUCTION

Internships involve hands-on workplace engagement [1]. They can address a range of educational purposes [2, 3]. Recently, a new purpose has emerged for some types of internship, which is nurturing service leadership attributes [4]. We shall first explain the concept of service leadership, and then summarize some factors that the broader literature on internships suggests might, by implication, also foster service leadership development through service-learning internships or practicums.

Service leadership is both an organizational process and a developmental domain. As an organizational process, it is a pro-socially-oriented, non-hierarchical and dispersed approach to leadership [5], with organization members from the front-line upwards sharing responsibility for service design and delivery [6]. In high-quality service organizations, senior service leaders develop open systems and cultivate a shared vision and spirit, inspiring leadership at the front-line and up to develop and sustain excellent service [6, 7]. Individual-level service leadership attributes and practices include active listening, anticipating and solving problems, caring disposition, originality in expressing opinions, building cohesive relationships, striving for service improvement, honouring promises and commitments, pro-community orientation, influencing others, and project coordination [8].

Although little prior research has been conducted on internships specifically intended for service leadership development, we inferred from prior literature that three factors would likely foster service leadership attributes, if they were present in service-learning practicums. The first inferred factor was the opportunity for students to create original solutions that address real needs [2]. The second inferred factor was co-educator supportiveness, which involves the provision of on-site coaching, guidance, encouragement, and support to students by their workplace supervisor(s) [1], as well as more basic orientation to the workplace and to task requirements [9, 10]. The third inferred factor was the student's level of developmental maturity [11], including his or her predisposition for active learning [1] and growth mindset [4, 12].

OUR STUDY

Our research focused on practicums undertaken between May and August 2014 by 16 students from Lingnan University (LU). Students worked full time for eight weeks at their respective community organizations, of which there were 10. These practicums differed from service leadership internships organized by The University of Hong Kong [4] in three respects. First, they were extra-curricular, not credit-bearing, and were not subsumed under students' major programmes. Second, they involved a portfolio of tasks, guided by a 'mini-mission', rather than being entirely focused on one project. Third, while the Office of Service-Learning (OSL) at LU intended that all practicum students would have abundant opportunities to perform work in collaboration with others, each had his or her own mini-mission and task portfolio. Thus, even though at some of the sites there were two practicum students from LU, and/or interns from other universities, the LU practicums were assigned individually rather than to project teams.

Our research questions (RQs) sought to identify success factors for service leader development through the practicums. Our first RQ was: what success factors relate to the type of tasks that the practicum students are empowered to undertake? Our second RQ was: what success factors relate to the student himself or herself? Our third RQ was: what success factors relate to the partner organization representatives (PORs) or to designated workplace supervisors?

Since the RQs were open-ended, focusing on issues that included organizational and socio-emotional dynamics, and addressing the relatively new topic of service leadership development through practicums in community organizations, we adopted a phenomenological approach [13]. The second author conducted semi-structured interviews with all 16 participating students, with PORs from all 10 host sites, and with a senior field coordinator from OSL, who had set up the practicums. The first and second authors analyzed the interview transcripts, and conducted documentary analyses of the learning diaries and reflective reports that students submitted as practicum requirements, along with PORs' formal appraisal reports on nine of the students.

Besides adopting a phenomenological approach, we also adopted a multiple case study research design [14]. In table 1, codenames 1-10 in column 1 denote the practicum sites, codenames 1a-10b in column 2 denote the PORs, and codenames M1-4 and F1-12 in column 3 denote the male and female practicum students, respectively. Ratings in columns 4-7 of Table 1 are interpretative syntheses based on comments by PORs, students and the senior field coordinator, and should be interpreted with caution.

FINDINGS

Through the research, we identified three broad success factors. These bore some correspondence to the factors, described above, that we had anticipated on the basis of the literature on internships, although our research led to their refinement and redefinition. We shall next explain and illustrate the success factors, before going on to summarize the overall effectiveness of the practicums and our suggested measures for improvement.

Task Significance/Challengingness

The first success factor concerns the significance and challengingness of the practicum tasks. It involves three sub-factors regarding the contributions that practicum students are empowered to make. The first sub-factor is that the students should perform work that conveys to them and others a palpable sense that they are meeting real community needs. The second sub-factor is that the students should perform work that involves facing difficulties and tackling problems while shouldering responsibility for overcoming/resolving them and not merely following orders and/or set procedures. The third sub-factor is that the work involves getting things done with and through people, rather than solo clerical or technical tasks.

Table 1. Sources of data and a summary of the findings

Practicum sites and type of service unit	Informants		Presence of Success Factors			Effectiveness in terms of leadership contributions and development
	POR code-names	Students code-names, gender, year & major	Task significance/challengingness	Co-educator presence & supportive-ness	Student's disposition for socially agentic self-initiation	
Site 1: Elderly education	1a 1b	F1 Yr 2, Soc Sci	High	High	High	Excellent
		F2 Yr 2, Soc Sci	High	High	Mod to high	Excellent
Site 2: Food collection & distribution	2a	M1 Yr 2, Soc Sci	Mod to high	Mod	High	Excellent
		F3 Yr 1, Trans	Mod to high	Mod	Initially low	Satisfactory
Site 3: Univ. service learning	3a 3b	F4 Yr 2, Phil	High	Mod	High	Excellent
		M2 Yr 2, Trans	High	Mod	Mod	Good
		F5 Yr 2, Trans	Low	Low	Low	Unsatisfactory
		F6 Yr 2, Soc Sci	Mod	Mod	Low to mod	Satisfactory
Site 5: Elderly recreation	5a	F7 Yr 2, Soc Sci	Mod	Mod	Mod	Satisfactory
		F8 Yr 2, Soc Sci	Low to mod	Low to mod	Low to mod	Unsatisfactory
Site 6: Clothes recycling	6a	M3 Yr 2, Cult St	Low to mod	Low to mod	Low to mod	Unsatisfactory
		F9 Yr 2, Soc Sci	Mod	High	High	Satisfactory
Site 7: Social enterprise corporate services	7a	F10 Yr 2, Mkt	Mod to high	High	Mod to high	Good
		F11 Yr 2, Soc Sci	Low	Low	Mod	Unsatisfactory
Site 8: Language education	8a 8b	M4 Yr 2, Soc Sci	Mod	High	Mod	Good
		F12 Yr 2, English	Mod to high	Mod	Mod to high	Good
Site 9: Rehabilitation/outdoor development	9a 9b					
Site 10: Refugee advocacy	10a 10b					

This success factor was illustrated at site 1, where the duties of F1 and F2 included designing classes on information technology and delivering them to elderly people, and conducting promotional visits about the classes. Rather than following pre-ordained protocols, F1 and F2 had opportunities to plan original solutions and improvise them in real time during service encounters. Illustrative quotes included the following:

“You can tell young people directly to type text on the monitor, but for elderly people, I discovered that you need to indicate first the place for typing the text.” (F1)

“Some elderly people said, ‘I am too old to learn’... To encourage them, I shared success stories of other elderly people, who hadn’t known anything about smartphones and finally learned how to use them to meet their needs.... I encouraged them to try.” (F2)

“(F1 and F2) were responsible for developing content and designing the teaching process all by themselves. They also prepared effective learning materials. They performed well.” (POR1a)

It appeared, however, that some PORs used students merely as ‘hired hands’ to perform routine technical or clerical tasks. The following quotes came from site 4:

“We expected a student to help with some light tasks.... She (F5) did not have much opportunity to perform service leadership here.” (POR 4a)

“For two weeks, my main task was ... simple but extremely time-consuming. It was very boring.” (F5)

Co-Educator Presence and Supportiveness

The second success factor concerns co-educator presence and supportiveness. It involves three sub-factors regarding the contributions of PORs or designated staff members responsible for providing on-site supervision. The first sub-factor is that the POR or designated supervisor should provide orientation at commencement of the practicum and before the practicum student’s assumption of new duties. The second sub-factor is that the POR or designated supervisor is available for *ad hoc* discussions about emerging issues. The third sub-factor is that the POR or designated supervisor should provide regular guidance, coaching and constructive feedback to the practicum student. This broad success factor was illustrated at site 7, where the approachability, guidance and support provided by POR 7a and other supervisors were appreciated by students F9 and F10. For example:

“From the beginning, they (POR 7a and other supervisors) provided us with something to read, to know more about the whole institution.... (POR7a) would come out of his office and would ask about our work and progress.... We were happy with him and he was willing to talk with us. We were free to voice out our opinions and he was also willing to listen.... He would also have casual talks with us. ... He would teach us how to do a proposal and even our reflective diaries.” (F9)

“(POR 7a and other supervisors) would point out our mistakes when we did something wrong..., but they would not use a complaining tone, and rather they would nicely tell us that, ‘Next time, when you want to ..., you can...’.” (F10)

Some PORs neither provided this kind of support nor arranged for another supervisor to provide it. Such omissions arose for various reasons, such as vacations, location elsewhere, or failure to appreciate the need. For example, at site 8, it appeared that POR 8a was a distant figure for the student, F11, and that supervision by POR 8b was perfunctory.

“(POR 8a) wouldn’t look after the operations of this company. (POR 8b) was my supervisor who introduced me to the office environment, who gave me an orientation and allocated tasks to me.” (F11)

“I told her (F11) that she is alone and is experiencing the real-life work environment. She may feel bored but it is the real-life environment and it would be good for her to learn about this sooner rather than later.... I was always away from the office ... I noted that someone had to take up the coaching role. But who? What to teach? ... When (F11) left, I told her that I was afraid that I couldn’t give what she wanted.... But interns also need to learn that in the real-life work environment, not everyone likes to be interrupted for questions when busy with work.” (POR 8b)

Disposition for Socially Agentic Self-Initiation

The third success factor concerns students’ disposition for socially agentic self-initiation during the practicum. It involves four sub-factors. The first sub-factor is that the student should be willing to initiate activities or proposals, rather than waiting passively for instructions. The second sub-factor is that the student should be prepared to “step out of the comfort zone” to face challenges. The third sub-factor is that the student should be proactive in building relationships with co-workers and service recipients. The fourth sub-factor is that the student should be oriented to getting things done with and through other people rather than burying themselves in solo clerical or technical tasks.

Contrasting student experiences at site 2 were attributable to differences between M1 and F3 in terms of this broad success factor, as illustrated in the following quotes:

“Without guidance, I handled contingencies and made decisions.... I was given opportunities for decisions about service provision. Although I encountered problems, I could handle them.” (M1)

“I dared not make decisions by myself, so I needed to wait to talk to [POR 2] for decisions.” (F3)

“(M1) demonstrated leadership qualities, such as coordination capacity, and responding to contingencies. ... He took initiative in expressing observations, thoughts and even things he was in doubt about.... (F3) may need some more time to understand the operations of the social service sector. She needs to understand people-orientated services.” (POR 2)

Overall Assessment

As listed in column 7 of Table 1, our effectiveness ratings, impressionistic as they are, indicate that of the 16 placements, 8 were “excellent” or “good”, 4 were “satisfactory”, and 4 were “unsatisfactory”. The unsatisfactory practicums were at case sites 4, 6, and 8, where we rated all three success factors as either “low” or “low to moderate” (see columns 4-6 of Table 1). The potential benefits arising from the co-presence of the three success factors are illustrated from the following quotes, regarding site 1:

“There was an obvious change in the atmosphere when they (the students) came.... Their lively presence affected the reactions of the elderly participants who were motivated to learn more positively and enthusiastically.” (POR 1a)

“I observed that the interns affected their colleagues. The colleagues had more communications and laughter. The work atmosphere was greatly affected.” (POR 1b)

DISCUSSION

Our research has indicated the need to make improvements in programme management to ensure that the three broad success factors are applied to each and every practicum.

Ensuring task significance and challengingness requires establishing a clear understanding with all PORs that they or a designated workplace supervisor should empower the practicum student(s) assigned to their organization to undertake tasks and mini missions that involve diagnosing and/or addressing significant needs. Furthermore, PORs need to be briefed that the practicum students should be entrusted to shoulder responsibility for tasks with sufficient complexity, and which engage service leadership attributes in working with and through other people. LU is continuing to seek third party sponsorship for the student stipends, in order to reinforce the message that the practicum programme is intended to empower students to practice service leadership for the greater good, and that they are not just “pairs of hands.”

Ensuring co-educator presence and supportiveness requires making clear to PORs that they and/or a designated workplace supervisor should serve as supportive co-educators. Thus, we expect that PORs or designated supervisors should provide orientation and background training at commencement of the practicum, and throughout, as necessary. We expect that PORs or designated supervisors; are available for *ad hoc* discussions with their practicum student(s) about emerging issues, and that they should provide timely guidance, coaching, encouragement and constructive feedback.

Ensuring that students enter into the practicum experience with sufficient disposition for socially agentic self-initiation requires more rigor and selectivity in recruiting them. Although everyone is a potential service leader, opportunities to undertake this kind of internship or practicum are relatively scarce, and some students may not (yet) be ready. It is important to target students, who are willing to initiate, are ready to face uncertainties and challenges, are sufficiently outgoing, and who ‘buy into’ and are interested in practicing the new model of shared and collaborative leadership for service rather than the traditional industrial model of autocratic bosses and meek, obedient, dependent subordinates.

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Chapter 118

THE EVALUATION OF SERVICE LEADERSHIP EDUCATION FOR UNIVERSITY STUDENTS IN HONG KONG

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ABSTRACT

In this chapter we investigate the outcomes of credit-bearing service leadership education at The Hong Kong Polytechnic University via pretest-posttest design. A total of 316 participating students completed an Objective Outcome Evaluation Questionnaire at the beginning and the end of the course "Service Leadership" measuring their positive youth development qualities, service leadership qualities and beliefs, as well as life satisfaction. Mixed ANOVA analyses comparing pretest and posttest revealed that students made improvements on all the variables of positive youth development, service leadership, and life satisfaction after taking the course. The positive changes did not vary across subject mode (2-credit-bearing vs. 3-credit-bearing). However, gender differences

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were found in which males but not females showed positive changes on positive identity, general positive youth development qualities, life satisfaction, self-leadership, and service leadership beliefs. The implications to further service leadership education were discussed.

INTRODUCTION

With the transformation of economic structure from manufacturing orientation (i.e., industrial mode) to service orientation (i.e., postindustrial mode), scholars, business professionals, and educational professionals are increasingly aware of the new demand of leadership qualities under the service economies [1, 2]. In fact, when conceptualizing effective leadership, “modern” leadership theories have focused on relationship, empowerment, integrity, trust, and service beyond strategic skills [3-6] instead of the inborn and elite nature of leadership. For example, transformational leadership emphasizes that leaders should act as an ethical role model and show individualized consideration toward subordinates [7]. Servant leadership advocates striving to meet the highest priority needs of others rather than personal interest [8].

As successful leadership qualities in the service economy are different from those in the industrial economy, Po Chung, the Co-founder of DHL International (Asia Pacific) [9], proposed the idea of service leadership which challenges the notion regarding leadership as a means to obtain fame and wealth. Instead, it regards leadership as a service that satisfies the needs of different parties involved. A successful leader is not only a competent person who is able to provide professional service, but also a moral person who deserves the trust from others and a caring person who is willing to satisfy others’ needs. The competence, the moral character and the caring disposition of a leader altogether determine the quality of the service and the effectiveness of one’s leadership. In this sense, a holistic development is highly needed in leadership education.

Bearing a mission to bring about a paradigm shift in people’s mindset of leadership and nurture a young generation of service leaders, Po Chung together with other academic professionals founded the Hong Kong Institute of Service Leadership and Management (HKI-SLAM) and designed the service leadership curriculum framework (i.e., SLAM framework). With the sponsorship of Victor and William Fung Foundation, the Fung Service Leadership Initiative was implemented in the eight UGC-funded institutions of Hong Kong, which developed and delivered service leadership education within the SLAM framework. Accordingly, The Hong Kong Polytechnic University (PolyU) has offered a credit-bearing subject for the undergraduate students since the 2013 Spring semester. Besides lecturing, this subject adopts experiential learning, reflective learning, and collaborative learning. The major goal of the current study is to examine the effectiveness of service leadership education in this credit-bearing mode. We used pretest-posttest design to understand the changes of the students who were taking the subject “Service Leadership” at PolyU. Although pretest-posttest design cannot lead to a causal conclusion, it is a typical and frequently used approach to understand the outcome of a program [10, 11].

To date, the subject “Service Leadership” was offered to two groups of students with different credits. The 2-credit-bearing subject (28 lecture hours) was offered to students under 3-year-curriculum while the 3-credit-bearing subject (39 lecture hours) was offered to

students under 4-year-curriculum. Three differences between these two subjects are noted. First, the 3-credit-bearing subject incorporates English Reading (ER) and Writing (EW) requirement, which is a language component of General Undergraduate Requirement (GUR) of PolyU, and thus the English requirement of the home assignment is higher than that of the 2-credit-bearing subject. Second, with more lecture hours, the 3-credit-bearing subject introduces other modern leadership theories (e.g., transformational leadership, servant leadership, and spiritual leadership), which is missing in the 2-credit-bearing subject. Finally, the 3-credit-bearing subject encourages students to critically appraise the model of service leadership, and thus, students could discuss the advantages and disadvantages of service leadership. Due to these differences, we were interested in whether the program difference would influence the pretest-posttest changes. Finally, as few previous studies found a gender difference in the effectiveness of leadership program and there were equivocal findings [12-14], we also explored whether male and female students showed different patterns of changes after taking the same subject.

OUR STUDY

Among 366 students taking the subject, 348 students took the pretest while 331 students took the posttest. In total, 318 students completed both the pretest and the posttest, in which 156 students were from the 2-credit subject (male = 66; female = 90; Mean age = 21.22 years, SD = 1.54) and 162 students were from the 3-credit subject (male = 66; female = 93; Mean age = 19.77 years, SD = 1.41). On average, the former was older than the latter, $t(315) = 8.75$, $p < .001$. Students provided individual informed consent before the pretest. The pretest was conducted on or before the third lecture; the posttest was conducted on or after the last third lecture.

Measures

The objective outcome evaluation questionnaire measured three aspects of students (i.e., positive youth development, life satisfaction, and service leadership) in a 6-point Likert scale. First, 10 positive youth development attributes were assessed using items selected and revised from the Chinese Positive Youth Development Scale [15]. Three composite scores were used in this study. Cognitive-behavioral competencies include the subscales of cognitive competence, self-determination, and behavioral competence; positive identity includes the subscales of belief in the future and clear and positive identity; general positive youth development qualities include the subscales of emotional competence, social competence, moral competence, resilience, and spirituality. The reliabilities of these three composite scales were good (see Table 1).

Second, life satisfaction was assessed by the five-item Satisfaction with Life Scale [16]. This scale was successfully used previously in other Chinese samples [17] and internally consistent in the current sample (see Table 1).

Finally, a new scale was created for this subject to measure service leadership qualities and beliefs according to the SLAM framework [18]. Service leadership qualities were

measured by self-leadership, caring disposition and character strength, and service leadership beliefs refer to the core beliefs of service leadership (e.g., “Leadership is a service for self, others, groups and the society”; “Leadership effectiveness is determined by situational task competencies, character strength and caring ability”). The reliabilities of all these scales were good (see Table 1).

FINDINGS

Several mixed ANOVA analyses were conducted to examine time (pretest versus posttest), gender (male versus female) and mode (2-credit versus 3-credit) effects on the indicators of positive youth development, life satisfaction, service leadership qualities and service leadership beliefs, respectively (see Table 2). Results showed that pretest-posttest changes were significant in all the indicators, which suggested that students changed in the positive direction after completing the subject on all indicators of positive youth development, life satisfaction, service leadership qualities and service leadership beliefs. However, no interaction effects of program and time were found, indicating that the positive changes did not vary across the old and new undergraduate curriculum. Interestingly, time interacted with gender in the domains of positive identity, general positive youth development, life satisfaction, self-leadership, and service leadership beliefs. Follow-up analyses adjusted by Bonferroni suggested that male students experienced significant changes in these indicators ($ps < .01$) while female students showed mild but insignificant trends of positive changes.

DISCUSSION

The objective of this study was to investigate the outcomes of the subject “Service Leadership” at PolyU. The pretest-posttest comparisons clearly indicate that students enhanced their positive youth development, life satisfaction, and service leadership qualities and beliefs after taking this subject. With the collective data from five classes of students, these results provide more convincing evidence than the previous study of a single class [18] about the program effectiveness. Besides, the positive results are congruent with the other evaluation studies based on subjective outcome evaluation [19], qualitative evaluation [20], focus group evaluation [21] and process evaluation [22].

In particular, students’ competencies indexed by positive youth development and self-leadership ability were improved and their character such as integrity was also enhanced. They become more caring, empathetic, and attentive to others. In addition, the subject fulfills the goal to bring about a paradigm shift in students’ mindset of leadership, as they tended to endorse service leadership beliefs to a greater extent after taking the subject. This finding is important because a leader’s practice such as decision-making and problem-solving is affected by his/her leadership beliefs [23].

Table 1. Means, standard deviations, and reliabilities of the variables

Variables	2-credit subject				3-credit subject			
	Male		Female		Male		Female	
	Reliability	Mean	SD	Mean	SD	Reliability	Mean	SD
Pretest								
1. Cognitive-behavioral competencies	.83	4.42	.56	4.55	.49	.82	4.51	.53
2. Positive identity	.82	4.46	.70	4.56	.57	.83	4.47	.62
3. General positive youth development qualities	.75	4.38	.48	4.64	.42	.75	4.39	.46
4. Life satisfaction	.84	3.97	.78	4.29	.68	.87	4.11	.80
5. Self-leadership	.79	4.47	.56	4.59	.52	.79	4.35	.56
6. Caring disposition	.91	4.49	.59	4.85	.52	.87	4.62	.50
7. Character strengths	.83	4.33	.47	4.56	.42	.86	4.37	.50
8. Service leadership beliefs	.89	4.59	.73	4.90	.53	.89	4.65	.67
Posttest								
1. Cognitive-behavioral competencies	.84	4.64	.54	4.64	.45	.85	4.64	.52
2. Positive identity	.85	4.71	.68	4.60	.64	.81	4.70	.57
3. General positive youth development qualities	.76	4.53	.49	4.69	.41	.80	4.57	.45
4. Life satisfaction	.87	4.32	.81	4.43	.71	.88	4.52	.77
5. Self-leadership	.81	4.60	.59	4.68	.49	.76	4.56	.58
6. Caring disposition	.90	4.65	.62	4.93	.44	.88	4.70	.50
7. Character strengths	.87	4.48	.56	4.67	.43	.88	4.56	.49
8. Service leadership beliefs	.93	4.82	.77	4.91	.57	.92	4.83	.60

Table 2. ANOVA results

Variables	Change		Gender		Mode		Gender*Change		Mode*Change	
	F	Partial η^2	F	Partial η^2	F	Partial η^2	F	Partial η^2	F	Partial η^2
1. Cognitive-behavioral competencies	13.69***	.04	.02	0	.16	0	3.54	.01	1.12	0
2. Positive identity	14.81***	.05	.84	0	1.34	0	5.80*	.02	.26	0
3. General positive youth development qualities	10.05**	.03	12.62***	.04	1.16	0	8.81**	.03	.11	0
4. Life satisfaction	24.31***	.07	.75	0	.01	0	8.10**	.03	0	0
5. Self-leadership	6.10*	.02	6.32*	.02	1.59	.01	4.84*	.02	.10	0
6. Caring disposition	5.18*	.02	19.48***	.06	.22	0	1.71	.01	.45	0
7. Character strengths	16.15***	.05	11.96**	.04	.07	0	1.60	.01	.47	0
8. Service leadership beliefs	6.19*	.02	7.56**	.02	.20	0	5.64*	.02	.07	0

* $p < .05$; ** $p < .01$; *** $p < .001$.

The enhancement after taking the subject was true for both students of 2-credit-bearing subject and students of 3-credit-bearing subject. Students who took the 2-credit-bearing subject were under the 3-year-curriculum, who are often regarded as more mature physically and psychological than those under the 4-year-curriculum. Our finding suggests that this subject is applicable for the students at different entry levels. Additionally, as no difference between the 28-hour subject and the 39-hour subject was found, future studies should examine the question of optimal teaching hours.

Nevertheless, it is worth noting that the enhancement was more salient among the male students than the female students, especially on positive identity, general positive youth development qualities, life satisfaction, self-leadership, and service leadership beliefs. The current findings are in line with the research findings of Dugan [13] and Dugan and Komives [24] which documented the advantages of female university students at multiple dimensions of the leadership capacities relative to male students. In sharp contrast to the traditional leadership style that requires “masculine qualities” such as authority, power, and self-assertion, the effective leadership style under service economies calls for emotion-skillfulness, cooperation, relation-orientation, empowerment, and mentoring, for which, women might have advantages [25]. Obviously, more studies should be conducted to examine how service leadership education is beneficial to students of different genders.

The present findings may have limited generalizability due to several reasons. First, without a control group, the cause-effect relationship between the subject and student change cannot be firmly established. Second, without a follow-up study, this study could not exclude the “honey moon” effect in which students’ self-evaluation was boosted right after the class but returned to the original level after a period of time [26]. Hence, longitudinal follow-up studies should be conducted. Finally, this study was only based on students’ self-report of performance, which may be different from the observant-report [27]. Obviously, teacher-report or peer-report information is needed in future studies.

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Chapter 119

DEVELOPMENT AND VALIDATION OF THE SERVICE LEADERSHIP KNOWLEDGE SCALE IN A CHINESE CONTEXT

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ABSTRACT

The notion of service leadership has been proposed to capture the ideal leadership model in service economies. However, there has been a lack of scientific measures that can operationalize the service leadership model. We thus developed a knowledge scale to capture the essential knowledge points of service leadership model in a format of multiple-choice question. The current study reported the development and content validation of this Service Leadership Knowledge Scale with four experts. The results showed that the majority of the items were rated as relevant to, clear, and representative of service leadership model. The development of this knowledge scale helps further construct a theoretical model of service leadership.

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INTRODUCTION

The service economy calls for leaders with qualities to serve others. It also calls for an updated leadership theory that can guide education, practice and research on effective leadership in the service era. This leadership theory and practice are highly important to Hong Kong, where the service economy constitutes 92.7% of the GDP [1]. Against this background, Po Chung, the co-founder of DHL International and the Chairman of the Hong Kong Institute of Service Leadership and Management Limited (HKI-SLAM), proposed the notion of service leadership and service leadership education (SLAM curriculum framework) to meet the demands of leadership education in the service era [2]. Po Chung believed that service leaders should provide high-quality services that meet the diverse needs of individuals, groups, communities, systems and environment [3]. He also believed that domain specific knowledge and skills, moral character and caring disposition are the bedrocks of successful service and effective service leadership [2]. Although these three qualities vary across individuals, service leadership notion upholds a belief that everyone can be a leader and has potential to improve their service leadership [4].

The content of the service leadership can be seen in two recently published special issues [4, 5]. There are several distinctive features of the service leadership model compared to other mainstream leadership models [6]. First, the model places equal importance on emotional, behavioral, cognitive, spiritual, and physical dimensions of a leader, and it has a comprehensive knowledge framework that covers service leaders' personal development, leadership practice, interaction with others and the systems with a service orientation. Second, the model emphasizes that "the server is the service" [3] by highlighting both the intrapersonal and interpersonal qualities of service leaders, with competencies, moral character and caring disposition as the fundamental qualities of successful service leaders. Third, self-leadership and reflection are critical service leadership qualities. Self-leadership includes self-management, self-reflection, intrinsic motivation to serve, goal setting and goal attainment. Service leadership is regarded as a constant reflection process for continuous improvement. Fourth, the service leadership model is applicable to multiple academic disciplines, professions in different service domains, and workers in different positions (e.g., from managers to frontline workers).

With the financial support of the Victor and William Fung Foundation, the Fung Service Leadership Initiative (FSLI) was launched in 2012 to support the development of service leadership education amongst the eight government-funded universities. As a member of the FSLI, The Hong Kong Polytechnic University (PolyU) has developed both credit-bearing courses and non-credit bearing programs on service leadership [7, 8]. In particular, multiple evaluation strategies including objective outcome evaluation, subjective outcome evaluation, and qualitative evaluation were used to evaluate the implementation and impact of the courses and programs [9]. Results generally revealed that the students showed positive changes in their service leadership qualities after joining the course or program and they generally had positive perceptions of the course and instructors. The related evaluation findings can be seen in two recent published special issues [9, 10].

While promoting service leadership education based on service leadership model is important, there is still a lack of measures to operationalize the service leadership model. In other words, how to judge if an individual is a service leader remains a question. What kind

of knowledge a service leader should have? What are the core beliefs of service leaders? What kind of behavioral qualities a service leader should demonstrate? Filling these gaps could help to further develop service leadership theory, improve service leadership education and provide guidance on the practice of service leadership. As such, The Hong Kong Polytechnic University initiated a research project entitled “Development and Validation of Measures Based on the Service Leadership Model” to develop and validate three scales on knowledge, attitude and behavior of service leadership. In this paper, we reported a study on the development of the knowledge scale on service leadership and the related content validation findings.

The purpose of developing the knowledge scale is to measure individuals’ understanding of the fundamental knowledge points that a service leader is expected to obtain, especially for those who receive service leadership education. The knowledge scale was created based on a knowledge framework of the service leadership education referring to different literature, including SLAM curriculum framework [2, 3], the “25 principles” of service leadership [11], 12 dimensions of personal brand of service leaders [12], and the lecture content of the subject “Service Leadership” [4, 5]. In details, the knowledge framework covers the following important domains of service leadership:

What is Service Leadership and What is It About?

The conceptualization of service leadership highlights service orientation [3, 6]. Service leadership is about providing high-quality services to satisfy the needs of oneself, others and systems [2]. Service leaders are the ones who could influence the subordinates with their good personal qualities instead of manipulating others or giving commands and penalties [2]. Character is more important than skills for job entrants in the service economy [3].

Service Leadership Has Three Realms: Self, Others and Systems

Service leadership can be carried out in three realms – self, others, and systems. Self-leadership takes place within individuals. Service leaders need to develop personal qualities and intrinsic motivation to serve others and systems, including improving one’s ability, skills and willingness to serve the needs of others and systems [2, 13]. Service leaders should be able to apply different motivation strategies to drive themselves to attain the goals [14-17]. Otherwise, they are not qualified to lead others. People-leadership takes place in a team environment. It is manifested in service leaders’ interaction with people and groups [2]. Systems leadership takes place in communities, including the local community, local society, and international markets. It is manifested in the control over the community and society rather than individuals. Different realms of service leadership correspond to different Chinese philosophies, with Buddhism related to self, Confucianism to others, and Taoism to systems.

Everyone Can Be a Leader

There is an important belief upheld by service leadership theory, which is “everyone can be a leader” [2, 6]. Service leadership model uses a broad definition of leadership, including leading oneself, leading people, and leading systems. Accordingly, people who are taking a leading role in any service transactions can be regarded as leaders and have the opportunity to practice and improve their leadership qualities. In addition, service leadership adopts an incremental belief about human attributes [18], and regards human attributes (including leadership) as changeable. In this tenet, service leadership qualities can be trained and improved. Therefore, everyone has the potential to be a service leader.

The General Principle of $E=MC^2$

The service leadership model proposes that leadership competencies, moral character, and caring disposition are three key attributes contributing to good service quality and effective service leadership [2]. It can be summarized as a formula $E=MC^2$, where “E” represents “effective service leadership,” “M” represents “moral character,” the two “Cs” represent “competence” and “caring disposition” [7]. Among the different elements, trust, fairness, respect, and care are considered as the “secret ingredients” to differentiate satisfactory service from unsatisfactory one [11]. Competencies, moral character, and caring disposition can enhance these “secret ingredients” so as to improve service qualities and leadership effectiveness. These three attributes are equally important for both leaders and followers in the service economy, and the attributes could be mutually influenced and improved between leaders and followers, thus raising their service leadership to a higher level.

Competencies

An effective service leader demonstrates good leadership competencies, service competencies, intrapersonal and interpersonal competencies to guide their personal development and leadership practice [19, 20]. Leadership competencies refer to possessing leadership skills and capacity that help service leaders attain personal and organizational goals, solve problems and satisfy different needs of self, others and systems. Service competencies of service leaders refer to their understanding and endeavors of creating and providing high-quality service with regards to particular contexts [2]. Moreover, intrapersonal competencies (i.e., IQ, EQ, AQ and SQ) and interpersonal competencies (e.g., conflict management, assertiveness, active listening) are core personal attributes that service leaders should continuously improve [19, 20].

Moral Character

The Service leadership model believes that professionals, elites or leaders without moral character are not true service leaders [20, 21]. Service leadership education fosters students' moral character by referring to two bodies of knowledge. The first one is about character strengths proposed by the Western researchers, which include six different domains – wisdom, courage, humanity, transcendence, temperance and justice [22, 23]. The second is about Chinese philosophies in Buddhism, Confucianism, and Taoism, particularly the Confucian virtues, such as benevolence, righteousness and propriety [24, 25]. According to the Principle of Personal Ethics of service leadership, service leaders should know how to do the right things by following moral codes and ethics. In this way, they can gain trust and respect from their followers [11].

Caring Disposition

A competent and moral service leader should also embrace caring disposition [2]. A caring service leader demonstrates sincerity to learn and meet others' needs and to show genuine care via love, empathy and active listening [26]. Caring disposition is commonly emphasized in many mainstream leadership models, such as servant leadership [6]. In the service leadership model, caring disposition covers not only the intention of caring (concern for others) but also action to care for one's followers, service clients and other people in need, which can be manifested in, for instance, developing the followers' growth [26].

Positive Social Relationship

Service leaders should be able to create, develop and maintain healthy and positive social relationships, while trust, fairness, respect, care, behavioral consistency, and loyalty are regarded as important to positive social relationships [27]. In particular, Chung and Bell [2, 11] repeatedly emphasized that trust is the key to successful service and leadership in service economy. Positive social relationships would comprise useful social capital that enables service leaders to operate their environment well [28].

Manufacturing Economy Versus Service Economy

Service leadership is connected closely to the context of the service economy, which is in sharp contrast to the manufacturing economy in economic structure, organizational structure, and requirements for leadership qualities [29]. In terms of the desirable leadership style and qualities, service economy calls for leaders that can carry out distributed leadership, in which they interact and communicate thoroughly with the followers and share the opportunity of decision-making with the followers. In addition, they can lead the organization in a transformational style, such as motivating followers to reach their potentials and empowering followers to work collaboratively and to achieve common goals [29]. These characteristics are incorporated into service leadership model.

Distinction of Service Leadership Model and Other Leadership Theories

As mentioned above, service leadership model adopts many ideologies from other leadership models, such as service orientation proposed by servant leadership. However, it has some unique features, which make it distinguished from other existing leadership models. For example, service leadership has seven core beliefs: 1) serve for oneself, others, and systems; 2) everyone can be a leader; 3) competencies, moral characters and caring are the three key attributes of service leaders; 4) competencies, willingness, abilities are important to service leaders themselves; 5) provide high quality of service; 6) evolutionary perspective of service leadership; 7) high pay and high position will go to people with service leader attributes [2, 10]. Moreover, service leadership adapts a maritime leadership style (vs. continental leadership style), which incorporates both top-down and bottom-up approaches in leader-follower interaction with regard to different situations (long-term planning, emergency or crisis) [2, 6].

Other Important Knowledge Points

There are some more knowledge points that a service leader needs to know. For instance, service reputation is critical to service industry. Hence, the integrity of service leaders is important and they must try their best to avoid errors or immoral conducts which bring bad reputation [11]. Service leaders should also understand the service, which is the core of humanity and has real value [11]. Besides, service leadership also highlights the importance of mentorship and choice of leadership style. Service leadership model is an evolving leadership model. From the evolutionary perspective, humans possess moral and caring intuitions in a long development history. Thus, service leadership could be considered as the oldest and longest surviving business model [2, 13].

After reviewing the above conceptual aspects of the service leadership knowledge framework, validated assessment tools that can measure the aforementioned knowledge of service leadership are needed. In particular, a knowledge scale with good validity and reliability is valuable for service leadership educators and researchers to examine the learning outcomes of effective service leadership education. First of all, the scale items need to be validated in terms of the extent to which scale items fall into the knowledge body of service leadership. As Rubio et al. [30] contended, “content validity refers to the extent to which the items on a measure assess the same content or how well the content material was sampled in the measure” (p. 94). Content validity usually informs us of “the degree to which elements of an assessment instrument are relevant to and representative of the target construct for a particular purpose.” (p. 238) [31]. The scale developers invited a panel of experts to evaluate the items and then the research team revised them according to the collected feedback [32]. The content of measures can be judged from several important perspectives: relevance, clarity, factor structure, representativeness, and comprehensiveness [20, 33]. In the current study, we mainly focused on relevance, clarity and representativeness of the knowledge scale.

OUR STUDY

In the current study we addressed the development of knowledge scale of service leadership and its content validation. The development of item pool was primarily based on the service leadership model [2, 5, 6] with reference to the previous literature regarding the knowledge points (e.g., self-leadership) [14, 15]. The content validation was conducted by inviting four experts to rate the relevance, clarity, and representativeness of each item. The process of scale development is described below.

Scale Development – Construction of Item Pool

The construction of item pool consists of three steps. First, we reviewed previous scales about leadership, which cover a wide range of leadership models: transformational leadership, authentic leadership, servant leadership, ethical leadership, leader-member exchange theory, spiritual leadership, participative leadership, relational leadership model, social exchange model of leadership development, and leadership identity development model. Via this practice, we found that measures tapping into the knowledge of a specific leadership model are missing in the literature. The majority of the leadership scales measures individuals' attitudes toward leadership and leadership behaviors [34-36]. There were also attempts to examine leadership knowledge. For example, Payne [37] designed 15 items to measure communication competence in leadership by asking the participants to select the most effective communication response in different communication scenarios.

In addition, considering the unique features of service leadership model, existing leadership scales that can be referred to are limited. In this case, we relied on the previous literature about service leadership, including Po Chung's books [3, 11, 12], Shek and colleagues' papers and book chapters [5, 6], as well as SLAM curriculum framework [2]. We first developed a conceptual framework based on this body of literature and developed items within this framework. The research team consisted of one senior researcher who provided supervision and three junior researchers who drafted, reviewed and cross-checked the items. All of them had doctoral degrees and had experience in research and teaching on service leadership.

The Service Leadership Knowledge Scale

With several rounds of iteration on items revision within the research team, 200 items of knowledge scale in a format of the multiple-choice question were generated. This scale includes following 11 categories (C1- C11):

C1. General description of service leadership (17 items). This category covers the definition, nature, and functions of service leadership. The items assess the understanding of the general feature of service leadership and service leader, such as the service-orientation.

C2. Three realms of service leadership (18 items). This category includes the knowledge about service leadership in three realms - self, others, and systems [2, 7, 11, 13-17]. The items measure knowledge about self-leadership, as well as the understanding of service leadership in oneself, teams and systems.

C3. Everyone can be a leader (11 items). This category includes the notion that everyone can be a leader. The items test the recognition of this notion and the theoretical root of this notion, including incremental theory about human attributes [2, 6, 11, 18, 38, 39].

C4. The general principle of $E=MC^2$ (11 items). This category includes the general description of the three determinants of effective service leadership – competence, moral character and caring disposition, as well as their nature and relevance to leaders and followers [2, 7, 11].

C5. Competencies (35 items). This category includes knowledge about competencies defined by SLAM framework (i.e., domain-specific competence, service competence, and leadership competence), as well as general intrapersonal competencies (IQ, EQ, AQ, and SQ) and interpersonal competencies (conflict management, assertiveness, and active listening) [2, 19, 20].

C6. Moral character (23 items). This category includes knowledge about moral character from a Western framework and Chinese philosophy. For the former, items assess the relevant concepts and knowledge about character strengths using Action in Value (VIA) model, which include wisdom, courage, humanity, justice, temperance, and transcendence [21, 22]. For the latter, items assess knowledge about Chinese virtue, particularly Confucian virtues, and its relation to service leaders [11, 24, 25].

C7. Caring disposition (17 items). This category includes knowledge about caring disposition within the SLAM framework [2]. The items assess knowledge about three core components of caring disposition – love, empathy and active listening [26], as well as the caring component of other leadership models [6].

C8. Positive social relationship (11 items). This category includes the knowledge about building, developing and maintaining positive social relationships. The items assess key factors to positive social relationship identified in the SLAM framework, general knowledge about relationship development (e.g., ABCDE model) [40] and social capital [2, 11, 27].

C9. Manufacturing economy versus service economy (18 items). This category includes knowledge about the differences of the features and leadership qualities between manufacturing economy and service economy [29] as well as the current societal status, particularly, the economic structure of Hong Kong.

C10. Distinction of service leadership and other leadership theories (24 items). This category addresses the knowledge about the unique features of service leadership model [2] compared with other leadership models in the literature. It is basically based on Shek et al.'s [6] paper reviewing differences of service leadership and other leadership models (e.g., transformational leadership, servant leadership, spiritual leadership, and ethical leadership).

C11. Other important knowledge points (15 items). This category includes the remaining knowledge points that are regarded as important in service leadership model, such as understanding of service, mentor-apprentice models and choice of leadership styles [2, 11, 13, 41].

The scale items were presented in various formats, such as filling the blank(s) of a concept or fact of service leadership, choosing the correct or incorrect descriptive statements of service leadership, and choosing a right combination of options to interpret a scenario of service leadership. Sample items of the scale can be seen in Appendix I.

Content Validation of the Developed Scale

With the item pool available, content validation was conducted to test how accurately the items assessed various aspects of service leadership knowledge. Four experts who are familiar with service leadership, especially the SLAM framework, were invited to judge the content validity of the 200-item Service Leadership Knowledge Scale. Three of them had a doctoral degree and were involved in the curriculum development and/or the teaching of the subject “Service Leadership.” The fourth one was an expert on service leadership working with Po Chung. A self-administered questionnaire was used to collect the opinions of the experts with the following procedure. First, they were invited to rate each item based on three criteria of content validity:

1. **Relevance**, the extent to which the item is appropriate in assessing the knowledge point and falls within the boundary of the SLAM framework on a 4-point rating scale:
 1 = *Irrelevant*, 2 = *Unable to assess the relevance without item revision or item is in need of revision or otherwise would no longer be relevant*, 3 = *Relevant but needs minor amendment*, 4 = *Relevant*
2. **Clarity**, the extent to which the item is concise, accurate, and direct on a 4-point rating scale:
 1 = *Very unclear*, 2 = *Unclear*, 3 = *Clear*, 4 = *Very clear*
3. **Representativeness**, the extent to which the item adequately represents and encompasses the essence of the knowledge point on a 4-point rating scale:
 1 = *Very unrepresentative*, 2 = *Unrepresentative*, 3 = *Representative*, 4 = *Very representative*

While giving the ratings, the experts were also invited to provide suggested modifications of the items for the negative responses (option 1 or 2). After rating all the items, they judged the overall quality of the whole scale based on the following items:

1. Does this batch of multiple choice questions cover all the essential knowledge in the service leadership framework?
2. Does this batch of multiple choice questions adequately represent the essential knowledge points in service leadership?
3. Overall speaking, are these multiple choice questions a valid measure of the basic body of knowledge covered in the Service Leadership and Management (SLAM) model?
4. Additional knowledge point(s), if missing from the knowledge scale (open-ended question).
5. Other comments (open-ended question).

The ratings from the four experts were used for analyses of content validity, while their suggested modifications and written feedbacks were taken into account when further revising the developed items.

OUR FINDINGS

Individual item content validity index (I-CVI) and average scale content validity index (S-CVI/ave) [30, 42] were calculated to indicate the content validity of the scale. I-CVI was computed by the number of positive responses in each item (option 3 or 4) divided by the number of experts. S-CVI/ave was an average score of the I-CVIs of all the items within each category or the overall scale. An I-CVI of .80 or higher indicates good content validity while S-CVI is at least .80, but preferably .90 or higher [42]. Considering we only had four judges, an I-CVI of .75 was considered to be acceptable. This approach has been used in previous scale validation studies in Hong Kong [43, 44].

As seen in Table 1, on individual level, most of the items had good I-CVI. All items had I-CVI(relevance) > .75, indicating that four experts agreed that all scale items were relevant to the service leadership knowledge under the SLAM curriculum framework. Except item 11, 17, 160 and 186, all items had I-CVI(clarity) > .75, showing that all experts considered most of the scale items were concise, accurate and direct. The four items with a fair I-CVI in clarity (I-CVI(clarity) = .50) were modified according to the suggestions from the experts. All items had I-CVI(representativeness) > .75, in the views of the experts, all the scale items could adequately represent the knowledge points of service leadership.

Table 1. The frequency of I-CVI and the S-CVI/ave for the whole scale

I-CVI	Number of items (percentage) (n=200)		
	Relevance	Clarity	Representativeness
0.25	0 (0%)	0 (0%)	0 (0%)
0.5	0 (0%)	4 (2%)	0 (0%)
0.75	9 (4.5%)	50 (25%)	14 (7%)
1.00	191 (95.5%)	146 (73%)	186 (93%)
S-CVI/ave	.99	.93	.98

Table 2. The S-CVI/ave for the subscales

No.	Category	No. of items	S-CVI/ave		
			Relevance	Clarity	Representativeness
C1	General description of Service Leadership	17	.96	.87	.96
C2	Three realms of Service Leadership	18	1.00	.93	1.00
C3	Everyone can be a leader	11	1.00	.91	1.00
C4	General description of the principle E=MC ²	11	.98	.91	.98
C5	Competencies	35	.99	.91	.99
C6	Moral character	23	1.00	.98	.99
C7	Caring disposition	17	.99	.91	.99
C8	Positive relationship	11	1.00	1.00	.98
C9	Manufacturing vs. service economies and current societal status	18	.99	.93	.99
C10	Distinction of Service Leadership and other leadership theories	24	1.00	.96	.98
C11	Other knowledge points in SLAM curriculum framework	15	.98	.88	.97

In regards to the overall scores, all the experts rated very positively the overall quality of the scale in terms of relevance, clarity, and representativeness, with $S-CVI/ave(relevance) = .99$, $S-CVI/ave(clarity) = .93$, and $S-CVI/ave(representativeness) = .98$, respectively (see Table 1). As can be seen in Table 2, for each category (total 11 categories), the results of $S-CVI/ave$ were also good, $S-CVI/ave(relevance) > .96$, $S-CVI/ave(clarity) > .87$, and $S-CVI/ave(relevance) > .96$.

DISCUSSION

The primary purpose of this chapter was to report the development of a scale to capture the knowledge of service leadership proposed by Chung [2] and the content validation of this study. The individual item content validity index (I-CVI) and average scale content validity (S-CVI) both indicate that the Service Leadership Knowledge Scale assesses various aspects of service leadership knowledge. The majority of the items were considered to be relevant to the body of knowledge about service leadership, clear and easy to understand, and representative of service leadership knowledge. The research team also reviewed and discussed the suggested modifications of particular items. Some items were modified before putting in the further validation studies.

The construction of the Service Leadership Knowledge Scale is a pioneering attempt to empirically assess the notion of service leadership proposed by Chung [2]. Since the launch of FSLI, substantial effort has been taken on promoting service leadership education, but the fundamental knowledge base of service leadership has been left unaddressed. The FSLI allows independent development of the curriculum of service leadership education, and thus the understanding of service leadership actually varies more or less across different institutions. This practice grants a great degree of autonomy for each institution to develop service leadership education and obtains great attainment to nurture a good number of university students into qualified service leaders [45]. However, there is still a strong need to specify the fundamental knowledge base of service leadership. Our current study initiated the endeavor to address this question, which indicates a good progress in the journey of the construction of service leadership theory. Of course, behind content validation effort, other means of scale validation should be conducted to clarify the content validity of the scale.

The present study had some limitations. First, we only had four experts for the content validation, although it still met the minimum acceptable number of three experts proposed by Lynn [46]. This is primarily because of the notion of service leadership is new and researchers or professionals who are working on it are rare. However, it limits the generalizability. Future research can consider inviting students who participated in service leadership course to rate the items. In addition, three out of four invited experts were academic researchers. Their understanding of the knowledge points of service leadership is mainly based on their research and teaching of the subject in an educational setting. They may not be fully aware of other practical knowledge point(s) of service leadership in an organizational field. Hence, experts from the field should be recruited. Lastly, the length of the current scale is very long, which possibly elicited fatigue in the raters. Hence, they might ignore some problems in the later part of the scale. Future studies may consider presenting the items in a different order to different raters, so as to reduce the effect of fatigue on the later part of the scale.

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APPENDIX I: SAMPLE ITEMS (WITH ADAPTATION) OF THE KNOWLEDGE SCALE

Knowledge Point	Multiple Choice Question
C1. General description of service leadership	
1. Leadership is a service that ethically satisfies a wide range of individual, group, community, system and environmental needs.	Bill has the following understanding of leadership. Which one is <i>NOT</i> consistent with the Service Leadership and Management (SLAM) Model? A. Service leadership includes ethically serving oneself. B. A leader should regard his/her leadership as a service. C. As a leader, individual needs should surpass service recipients' needs. D. As a leader, one should provide service to ethically satisfy a wide range of needs, including the needs of individual, group, and system. (correct answer: C)
C2. Three realms of service leadership.	
19. Service leadership claims that leadership can be carried out in three realms, including self, others, and system.	The realms of service leadership include_____. A. life, family, and work B. self, others, and system C. friendship, organization, and society D. microsystem, macrosystem, and ecosystem (correct answer: B)
Knowledge Point	Multiple Choice Question

C3. Everyone can be a leader.	
36. Every day, every human occupies a position of leadership and possesses the potential to improve his leadership quality and effectiveness.	Service Leadership and Management (SLAM) Model asserts that everyone can be a leader. Which of the following statements is <i>NOT</i> the rationale underlying this proposition? A. Self-development can be regarded as one sort of leadership. B. Every day, there are many service transactions in which one can take a leading role. C. Leadership quality is malleable and improvable. D. Leadership is an inborn quality. (correct answer: D)
C4. The general principle of $E=MC^2$.	
48. Learning and habituating leadership competencies, which include character strengths and a caring disposition, can enhance one's leadership effectiveness.	According to the Service Leadership and Management (SLAM) Model, if Kate wants to become an effective service leader, she needs to: ① develop her leadership, intrapersonal and interpersonal competencies. ② have excellent scholastic achievement. ③ enhance her moral character. ④ consider the needs of others and provide care to others when they are in need. A. ①② B. ①③ C. ①②③ D. ①③④ (correct answer: D)
C5. Competencies.	
65. Generally speaking, intrapersonal competencies process information of the self and involve a wide range of abilities related to self-understanding and self-management.	Generally speaking, intrapersonal competencies process information of _____ and involve a wide range of abilities related to _____. A. the service system; serving others B. the service system; serving the society C. the self; self-understanding D. the self; serving others (correct answer: C)
C6. Moral character.	
115. "Ai" is affection for one's fellow human beings, marked by interpersonal relationships with care, respect and humanity. "Ren" refers to benevolence or humanity, pertaining to "loving people."	Among different Confucian virtues, which one is most relevant to caring disposition required in service leadership? A. Trustworthiness B. Wisdom C. Harmony and Peace D. Benevolence and Affection (correct answer: D)
C7. Caring disposition.	
124. Three major components of caring disposition Three major components of caring disposition: 1) love; 2) listening; 3) empathy.	Which of the following attributes is one of the three major components of caring disposition covered in the Service Leadership and Management (SLAM) Model? A. Individual consideration B. Mentoring C. Listening D. Coaching (correct answer: C)

Knowledge Point	Multiple Choice Question
C8. Positive social relationship.	
140. Five stages of relationship building—the ABCDE Model Regarding the relationship development, the most influential theory is the five-stage model (i.e., ABCDE Model) proposed by Levinger (1983), a relationship begins with acquaintance (A), goes through building-up (B) and continuation (C), and (alternatively) experiences deterioration (D) and finally ends (E).	According to Levinger (1983)'s five-stage model of relationship building, what is the correct sequence of the stages? A. Acquaintance; building-up; continuation; deterioration (alternative); end B. Acquaintance; continuation; building-up; deterioration (alternative); end C. Building-up; acquaintance; continuation; deterioration (alternative); end D. Building-up; acquaintance; deterioration (alternative); continuation; end (correct answer: A)
C9. Manufacturing economy versus service economy and current societal status.	
153. Leaders in the service economy should be flexible, high in openness, collaborative and motivated. Trust, fairness, respect and care are the “secret ingredients” that distinguishes successful service experiences from unsuccessful ones.	Leaders in the service economy should primarily possess the following attribute: A. Show respect toward the followers B. High intelligence C. Good academic achievement D. Good political sensitivity (correct answer: A)
C10. Distinction of service leadership and other leadership theories.	
170. A maritime (distributed) leadership style that is both top-down and bottom-up is more productive, competitive, profitable, and sustainable in service industries.	A maritime leadership style is: ① Authoritarian in nature ② Distributed in nature ③ Top-down ④ Bottom-up A. ① ③ B. ② ④ C. ① ③ ④ D. ② ③ ④ (correct answer: D)
C11. Other important knowledge points.	
193. The value of service is co-created by the service providers and consumers.	Which of the following statements about service is correct? A. The value of service is determined by the service providers. B. The value of service is determined by the consumers. C. The value of service is co-created by providers and consumers. D. The value of service is determined by the product managers. (correct answer: C)

Chapter 120

VALIDATION OF THE SERVICE LEADERSHIP KNOWLEDGE SCALE: CRITERION-RELATED VALIDITY

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ABSTRACT

In order to assess the effectiveness of service leadership education, we developed the 200-item Service Leadership Knowledge Scale to measure knowledge related to service leadership. In this chapter, we report a validation study examining whether the developed scale could differentiate students who had received service leadership education from those had not (i.e., criterion-related validity). A posttest-only control group design was adopted to validate the scale, with 67 students in the experimental group and 93 students in the control group. As predicted, the experimental group scored higher on all domains and total scores compared to the control group. In terms of the individual item, the experimental group had higher scores on 163 items than did the control group, with statistically significant differences on 63 items. The present findings provide evidence supporting the criterion-related validity of the Service Leadership Knowledge Scale.

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INTRODUCTION

Leadership training and education for young people are growing in the higher education sector in both Western and Chinese societies [1, 2]. Generally speaking, leadership education programs aim at improving and transforming leadership knowledge, attitudes, skills, and behaviors in the program participants. With the development of leadership programs, scholars and practitioners argued that it is important to conduct rigorous evaluations to examine the outcomes of leadership training programs [3, 4]. Unfortunately, an examination of the leadership literature shows that rigorous evaluation is sparse, particularly in the Chinese culture.

With specific reference to Hong Kong, a large-scale leadership project entitled the “Fung Service Leadership Initiative” was implemented in eight government-funded public universities through the financial support of the Victor and William Fung Foundation. The main purpose of this initiative was to encourage universities in Hong Kong to develop curriculum and related materials on Service Leadership to nurture a new generation of leaders that fit the current service era. The idea of service leadership was initially proposed by Po Chung, the co-founder of DHL International and the Chairman of the Hong Kong Institute of Service Leadership and Management Limited (HKI-SLAM). Chung and Bell [5] argued that to meet the challenges created by the transformation from the manufacturing economy to the service economy, universities have a responsibility to train service leaders. According to Chung [6], service leadership is about “satisfying needs by consistently providing quality personal service to everyone one comes into contact with, including one’s self, others, groups, communities, systems, and environments” (p. 5). To be an effective leader, one needs to possess domain-specific competencies and to demonstrate moral character and caring disposition.

With a common objective to nurture university students’ leadership qualities in the areas of leadership competencies, moral character, and caring disposition, these eight institutions have developed their leadership courses and programs independently [7]. However, evaluation research on these curricula and programs remain to be done. To sustain service leadership education and to develop the body of knowledge surrounding service leadership, systematic evaluation of program effectiveness and benefits of the program to the participants is strongly needed [8]. Obviously, sound evaluation depends on sound assessment instruments. However, validated instruments on leadership qualities, particularly those related to Service Leadership are virtually non-existent in different Chinese communities. As such, the research team of The Hong Kong Polytechnic University (PolyU) has started to work on the development of a battery of assessment instruments on service leadership. The purpose of the current study was to examine the criterion-referenced validity of the Service Leadership Knowledge Scale which has been developed to assess service leadership knowledge.

To understand the outcomes of an educational program, researchers are usually concerned about participants’ knowledge, attitudes, skills, and behaviors. Numerous examples can be found in the literature that assessed the participants’ knowledge, attitudes, skills, and behaviors. For example, Hsu [9] measured participants’ pro-environmental behavior and environmental knowledge to assess the effectiveness of a 16-week environmental education course. Ergene, Cok, Tumer, and Unal [10] examined the knowledge, attitudes, personal behaviors and awareness of HIV/AIDS among students who

received or did not receive HIV/AIDS education. In the field of leadership education, most of the evaluation focused on the participants' attitudes and behavior. For example, in the report of Zimmerman-Oster and Burkhardt [11], students' cognitive visioning ability, visioning behavior, optimism, transformational leadership, and inspirational motivation were assessed before and after the leadership development program.

Comparatively, fewer evaluation studies tested leadership knowledge gained through a leadership program, though it is not uncommon to ask the participants to rate how much they have learned from the program (i.e., subjective estimation of knowledge change). For example, after attending the 5-day Washington Leadership Conference, Stedman, Rutherford, Rosser, and Elbert [12] asked the participants to rate the extent to which they perceived themselves to be able to describe authentic leadership, define character and the four-stage model for building relationship, and attain other knowledge delivered during the conference. Definitely, acquisition of leadership knowledge is a desirable outcome for a successful leadership program. Without obtaining any updated knowledge about leadership (e.g., what qualities an effective leadership should have), it is difficult, if not impossible, for the participants to change their attitudes and improve their leadership practice. Therefore, it is necessary to test program participants' knowledge about leadership in order to examine the effectiveness of a leadership program. Unfortunately, validated assessment tools on leadership knowledge are rare.

To facilitate the evaluation of service leadership education, we have developed the Service Leadership Knowledge Scale to assess individuals' understanding of service leadership knowledge. This body of knowledge was mainly based on the service leadership model within the SLAM framework, including SLAM curriculum framework [5, 6], 12 dimensions of personal brand of service leaders [13], the "25 principles" of service leadership [14], and other publications by Chung, Shek and colleagues [e.g., 15, 16]. A total of 200 multiple-choice questions were generated to assess 11 domains of knowledge, including general description of service leadership, three realms of service leadership, the belief that "everyone can be a leader," the general principle of $E=MC^2$ (i.e., competencies, moral character, caring disposition), positive social relationship, manufacturing economy versus service economy, distinction of service leadership and other leadership theories, and other important knowledge points. In an introductory class on Service Leadership, these knowledge points are covered in the class and/or required readings.

When we developed the Service Leadership Knowledge Scale, a content validation study with four judges who had expertise in service leadership research, teaching or practice was conducted [17]. The study provides initial evidence suggesting that the items are clear, relevant to, and representative of service leadership knowledge within the SLAM framework. Nevertheless, while the experts had positive evaluation of the scale items, whether this scale possesses good criterion-related validity is unknown. Criterion-related validation is important because it can tell us whether the test scores are related to certain external criterion such as whether the participants have studied in a course on service leadership.

The current study was conducted to address the question about whether Service Leadership Knowledge Scale has criterion-related validity. According to Rubin and Babbie [18], based on when the criterion occurs, criterion-related validity can be divided into two types, including predictive validity (which informs the ability of the test scores to predict a criterion occurring in the future) and concurrent validity (which informs the correspondence to a criterion that has been known). Typically, concurrent validity is assessed by known-

groups validity where the scale would be administered to two groups that are theoretically known to differ on the construct measured, such as different levels of knowledge [19]. As pointed out by Portney and Watkins [20], “using the known groups method, a criterion is chosen that can identify the presence or absence of a particular characteristic, and the theoretical context behind the construct is used to predict how different groups are expected to behave. Therefore, the validity of a particular test is supported if the test’s results document these known differences.” (p. 89).

In the current study, the criterion was taking up versus not taking up a 3-credit general education course entitled “Service Leadership.” This course provides 39 hours of class learning about service leadership through lectures, reflection exercises, group discussions, role plays, drawings, and other experiential learning activities. Students also enrich their knowledge via group presentation and individual term paper. For details of the curriculum of this course, readers can refer to the two special issues of *International Journal on Disability and Human Development* [15, 16]. According to the known difference, we hypothesized that the participating students would have higher scores than the non-participating students on the knowledge scale items and scale scores.

Posttest-only control group design was adopted to examine the criterion-related validity of the Service Leadership Knowledge Scale. In this design, one group of students who had ever participated in this course served as the experimental group and the other group of students who had never participated in any courses or programs related to service leadership served as the control group. Both groups were assessed during the same period of time. In the current case, we did not collect data before the course (i.e., pretest) because it was difficult to recruit a comparable control group before the course. The composition of the students could not be confirmed until the third lecture as the students were allowed to freely add or drop the course during the first three weeks of the academic semester. Hence, we had to assess their knowledge after completion of the course only.

Although the adopted design cannot provide information about the change within individuals, the between-individual comparison can still inform us about the effectiveness of the program by comparing the participating students and non-participating students. There were plenty of cases in the program evaluation literature that adopted this design. For instance, to understand the effect of an educational intervention on the students’ attitudes toward elderly people, Moriollo, Smey, Pescatello, and Murphy [21] measured the knowledge and attitude towards elderly people one week and ten weeks after the completion of this intervention. Results found that participants who received this intervention had better knowledge about aging than the non-participants at Week 1 assessment. More importantly, as the major objective of the current study is to test the criterion-related validity of the scale, the posttest-only control group design apparently meets this requirement.

OUR STUDY

A total of 67 students (Mean age = 20.13, SD = 1.42) were recruited from the classes on a 3-credit “Service Leadership” course who formed the experimental group. Among them, 30 took the course in the first semester while 37 in the second semester of 2014-15 academic year. Another 94 students (Mean age = 20.46, SD = 1.51) who had not taken the course “Service Leadership” were recruited from a convenience sample and they served as the

control group. However, one participant from the control group took the subject “Service Leadership through Service Learning” which is a course delivering service leadership ideology via a service-learning approach. With the removal of these participants, 93 students remained in the control group. During the recruitment, we tried to match the background characteristics of the control group with those of the experimental group. The characteristics of the participants are presented in Table 1.

Table 1. Descriptive statistics about participants (n=160)

Demographic variables		Experimental Group <i>n</i> = 67	Control Group <i>n</i> = 93
Gender	Male	26 (38.8%)	48 (51.6%)
	Female	41 (61.2%)	45 (48.4%)
Year of study	Year 1	54 (80.6%)	65 (69.9%)
	Year 2	4 (6.0%)	7 (7.5%)
	Year 3	9 (13.4%)	19 (20.4%)
	Year 4	0 (0%)	2 (2.2%)
Faculty	Faculty of Applied Science and Textiles	6 (9.0%)	8 (8.6%)
	Faculty of Business	0 (0%)	5 (5.4%)
	Faculty of Construction and Environment	15 (22.4%)	18 (19.4%)
	Faculty of Engineering	15 (22.4%)	18 (19.4%)
	Faculty of Health and Social Sciences	7 (10.4%)	12 (12.9%)
	Faculty of Humanities	4 (6.0%)	1 (1.1%)
	School of Design	2 (3.0%)	5 (5.4%)
	School of Hotel and Tourism Management	18 (26.9%)	26 (28.0%)
General university requirement (GUR) courses related to leadership taken	Have taken “Tomorrow’s Leaders”	31 (46.3%)	41 (44.1%)
	Have taken “Tango! Managing Self and Leading Others”	0 (0%)	3 (3.2%)
	Neither	36 (53.7%)	49 (52.7%)
Other leadership course or workshop taken	Yes, have taken before	1 (1.5%)	4 (4.3%)
	No	66 (98.5%)	89 (95.7%)
Knowledge of service leadership	No knowledge	1 (1.5%)	34 (36.6%)
	Little knowledge	5 (7.5%)	36 (38.7%)
	Some knowledge	49 (73.1%)	21 (22.6%)
	A lot of knowledge	11 (16.4%)	2 (2.2%)
	All the knowledge	1 (1.5%)	0 (0%)
Leadership position ever taken	Yes, have taken before	46 (68.7%)	46 (49.5%)
	No	21 (31.3%)	47 (50.5%)
Overall work experience	Have work experience	62 (92.5%)	83 (89.2%)
	No work experience	5 (7.5%)	10 (10.8%)
Entrance exam	Hong Kong Diploma of Secondary Education Examination (HKDSEE)	35 (52.2%)	46 (49.5%)
	Hong Kong Advanced Level Examination (HKALE)	7 (10.4%)	21 (22.6%)
	National College Entrance Examination (NCEE) - in mainland China	1 (1.5%)	1 (1.1%)
	Associate Degree/ Higher Diploma in Hong Kong	23 (34.3%)	23 (24.7%)
	Others	1 (1.5%)	2 (2.2%)

The experimental group and control group did not differ in age ($t(158) = 1.39, p > .05$) gender ratio ($\chi^2(1) = 2.57, p > .05$), distribution of study year ($\chi^2(3) = 3.27, p > .05$), distribution of faculties ($\chi^2(7) = 7.67, p > .05$), ratio of participation in General Undergraduate Requirements (GUR) leadership course ($\chi^2(2) = 2.21, p > .05$), ratio of participation in other leadership courses/workshops ($\chi^2(1) = 1.01, p > .05$), ratio of having work experience ($\chi^2(1) = .50, p > .05$), and ratio of entering university through HKDSE ($\chi^2(1) = .12, p > .05$). However, more students in the experiment group (vs. control group) had ever taken a leadership position in groups, clubs or associations ($\chi^2(1) = 5.87, p < .05$). It is possible that students who had ever taken leadership post were more interested in a leadership course. Taken together, the experimental group and the control group were generally comparable in terms of the demographic background.

Students completed the knowledge survey through an online platform in a self-administration manner. The assessment period was within two months after the completion of the course in the second semester of the 2014-15 academic year. The 200 multiple-choice questions were grouped into 20 blocks with 10 questions each. The blocks were randomly presented to exclude order effect. Individual consent was attained at the beginning of the survey.

Instrument

The Service Leadership Knowledge Scale consists of 200 multiple-choice questions. It covers 11 domains of knowledge points that are intrinsic to service leadership, particularly the SLAM framework, including general description of service leadership (17 items), three realms of service leadership (18 items), the belief that “everyone can be a leader” (11 items), the general principle of $E=MC^2$ (11 items), leadership competencies (35 items), moral character (23 items), caring disposition (17 items), positive social relationship (11 items), manufacturing economy versus service economy (18 items), distinction of service leadership and other leadership theories (24 items), and other important knowledge points (15 items). The details of this scale can be seen in the content validation study of the Service Leadership Knowledge Sale in this special issue (Shek et al., in press). The coverage of each domain is presented below.

1. *General description of service leadership*: the definition and general principles of service leadership model.
2. *Three realms of service leadership*: knowledge on the three realms of service leadership, i.e., self, other, and system.
3. *Everyone can be a leader*: knowledge on the belief about the notion “everyone can be a leader.”
4. *The general principle of $E = MC^2$* : the principle that moral character, competencies and caring disposition determine the effectiveness of service leadership.
5. *Competencies*: knowledge about intrapersonal (e.g., EQ, AQ, SQ) and interpersonal competencies (e.g., assertiveness, conflict resolution).
6. *Moral character*: knowledge about character strengths and Chinese virtues.

7. *Caring disposition*: knowledge about caring disposition, particularly, love, empathy, and active listening.
8. *Positive social relationship*: knowledge about building, developing and maintaining a positive social relationship.
9. *Differences of manufacturing economies and service economies*: knowledge about differences of the features and leadership qualities under manufacturing economy and service economy.
10. *Distinction between Service Leadership theory and other leadership theories*: knowledge about the distinction of service leadership and other leadership theories.
11. *Other important knowledge points of service leadership*: related knowledge that is important for a service leader to know, such as mentor-mentee model, understanding of service and service reputation.

Students also reported some demographic information (e.g., gender, year of study, and work experience, see Table 1). In addition, students rated how much they know about service leadership (i.e., self-evaluation of their own knowledge about service leadership).

Table 2. Independent t-test of the scale and subscales

No.	Category	Experimental Group M (SD)	Control Group M (SD)	t value	Effect Size (Cohens' d)
C1	1. General description of Service Leadership	.42 (.20)	.31 (.15)	4.08***	.65
C2	2. Three realms of Service Leadership	.41 (.17)	.33 (.14)	3.43**	.55
C3	3. Everyone can be a leader	.40 (.20)	.30 (.16)	3.54**	.56
C4	4.1 General description of the principle $E=MC^2$	.48 (.29)	.31 (.20)	4.39***	.70
C5	4.2 Competencies	.44 (.20)	.33 (.13)	4.23***	.67
C6	4.3 Moral character	.37 (.15)	.31 (.12)	2.95**	.47
C7	4.4 Caring disposition	.43 (.21)	.30 (.14)	4.66***	.74
C8	4.5 Positive relationship	.31 (.19)	.25 (.15)	2.46*	.39
C9	5. Manufacturing vs. service economies and current societal status	.40 (.20)	.30 (.15)	3.74***	.59
C10	6. Distinction of Service Leadership and other leadership theories	.38 (.19)	.32 (.15)	2.56*	.41
C11	7. Other knowledge points in SLAM curriculum framework	.34 (.20)	.27 (.14)	2.61*	.41
	Total mean score	.40 (.15)	.31 (.10)	4.79***	.76

Notes: "1" was given to the accurate answer, while "0" was given to the wrong answer.

* $p < .05$; ** $p < .01$; *** $p < .001$.

FINDINGS

This study was conducted to test the criterion-related validity of the Service Leadership Knowledge Scale. We first coded the items according to their accuracy. For the 200 multiple-choice questions, "1" was given to the items with correct answers, while "0" was given to the items with incorrect answers. Next, we performed independent t-test analyses to compare the scores of those students who had taken the subject "Service Leadership" and those who had not attended any courses or programs on service leadership. Analyses were conducted on the score of each domain and total scores. As shown in Table 2, the scores of the experimental

group were significantly higher than those of the control group in all domains, $t_s > 2.46$, $p_s < .05$, Cohens' $d_s = .39 - .74$. The effect sizes were about medium. Such difference was observed in the total score, with the effect size approaching large, $t(158) = 4.79$, $p < .001$, Cohens' $d = .76$. When assessing individual item, we found that the experimental group had higher scores on 163 items, with 63 items reaching a statistically significant level at $p < .05$. When the students were asked to rate their knowledge about service leadership, students in the experimental group perceived themselves knowing more about service leadership than their counterparts, $t(158) = 10.06$, $p < .001$, Cohens' $d = 1.60$.

DISCUSSION

In response to the lack of assessment instrument measuring individuals' knowledge level with regard to service leadership, we developed a 200-item Service Leadership Knowledge Scale. The purpose of the current study is to test its criterion-related validation through comparing students who had received service leadership education (i.e., experimental group) and students who had not (i.e., control group). The results showed that the scores of the experimental group were better than those of the control group in all 11 domains of knowledge points. When individual items were assessed, the experimental group had higher scores than the control group on 163 items. Amongst them, 63 items could statistically significantly differentiate the experimental group and the control group. To illustrate, the items about the definition of leadership competency items about desirable leadership qualities in service economy were able to differentiate the experimental group from the control group.

Overall speaking, the students who attended service leadership course knew more about service leadership, no matter in their self-perception or objective performance. Results suggest that this scale objectively assesses the basic knowledge on service leadership which could be acquired via service leadership education. Generally speaking, the criterion-related validity of this scale is good.

However, some items failed to differentiate the two groups. There are two possible explanations for this observation. First, this scale covers a wide range of knowledge points, perhaps, too wide for a student who only took 39-hour of class learning to capture. This scale includes not only the knowledge from the SLAM curriculum, but also other knowledge points regarded important by Chung and his colleagues [e.g., 14-16] in other publications. The comprehension of all these knowledge points depends not only on the class learning, but also the intensive reading on these papers and book chapters. For example, the knowledge about manufacturing economy and service economy was briefly taught in the first lecture, while the teacher highly recommended students to know more by reading Shek, Chung, and Leung [22]'s paper. Since there was no examination in this course, it is possible that not all the students read these papers though they were listed as required readings. Therefore, both the experimental group and the control group failed to answer some questions.

Second, as some knowledge points are not unique to service leadership, the students may learn them from other sources. For example, the knowledge about emotional intelligence, interpersonal competence, and positive social relationship can be acquired from psychology

courses, educational books, and other public channels. Therefore, some students from the control group were able to get a correct answer even without attending the service leadership course. However, these possibilities do not mean that the questions weak in differentiation are not important for a service leader. Further studies are needed to validate the current findings and examine what kind of knowledge is critical to the leadership effectiveness or work performance of service leaders. In the present study, there are at least 63 items that can differentiate the two groups which may form a short form of the Service Leadership Knowledge Scale.

Although the present study is a pioneer in the field of service leadership, there are four limitations. The first one is the lack of other methods to test criterion-related validation. We only used one criterion to assess the concurrent validity of the scale. In order to provide more validation evidence, future studies need to consider other criteria such as whether this scale is related to the likelihood of taking a leadership position in the future. The second limitation concerns the absence of pretest data. The current study only examined posttest without baseline assessment. Therefore, we should be cautious about making any causal inference that the occurrence of group difference in the knowledge is because of receiving the service leadership education. Future studies would benefit from a full quasi-experimental design with experimental group and control group assessed before and after receiving the service leadership education.

Another limitation of the study is that the homogeneity of the sample which may limit the generalizability of the findings to other population. The current experimental group was recruited from one course at the PolyU, while students that joined other service leadership courses or programs were not included. We knew that there are other approaches of service leadership education offered by the PolyU and other institutions in Hong Kong [7]. Therefore, the current findings need further replication with a more heterogeneous sample of students who joined other service leadership courses/programs. The final limitation is about the length of the scale, which may be too long for the participants. Students would be easily fatigued during the survey, which probably undermines their performance. Therefore, a short-version of knowledge scale is highly needed to quickly capture individuals' understanding of service leadership. As suggested by the current findings, we can develop a short form based on the 63 items which can detect significant differences between the two groups.

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Chapter 121

CONTENT VALIDATION OF THE SERVICE LEADERSHIP ATTITUDES SCALE

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ABSTRACT

The notion of service leadership has been proposed to meet the demands of service economies. However, there is no scientific measure of people's attitudes toward service leadership. We thus developed the 132-item Service Leadership Attitudes Scale (SLAS) with an objective to measure individuals' attitudes and beliefs toward leadership qualities and leadership practices upheld by service leadership model. In this chapter, we report on the content validation based on the responses of three judges of experts. Results showed that the items were perceived by the experts to be relevant to, clear, and representative of the construct measured. The development of SLAS has implications for leadership development and education.

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INTRODUCTION

There is a global trend of economic transformation from manufacturing mode to service mode [1, 2], which requires a paradigm shift in the conceptualization of leadership. In manufacturing economies, good leaders are often regarded as those with extraordinary competence and ability to achieve the greatest productivity. A stereotypical image of a leader in that era would be a person with power and authority who completely controls the operation. However, with the emergence of the service era, previous effective leadership qualities become increasingly inappropriate. Instead, the service era demands people-orientation (vs. task-orientation), relationship orientation (vs. man-machine interaction), service-orientation (vs. manufacturing orientation), morality (vs. maximization of profits), and soft skills (vs. hard skills) in leaders [3, 4]. The shifting economic environment calls for a new ideology of leadership that increases the competitiveness of team in the service economies.

In response to this call, Chung [5] proposed the notion of service leadership and asserted that service leadership “is about satisfying needs by consistently providing quality personal service to everyone one comes into contact with, including one’s self, others, groups, communities, systems, and environments” (p. 5). Chung and his colleagues further enriched the idea of service leadership within the framework of the Hong Kong Institute of Service Leadership and Management (SLAM) [6-9]. The idea of service leadership is in sharp contrast to the traditional leadership style in the manufacturing economies where leaders’ control, hierarchy, bureaucratic efficiency, and self-interest are of prime concern [10]. It is featured with seven core beliefs, which serve as the fundamental cognition of a service leader [11].

First of all, service leaders believe that leadership is “a service aimed at ethically satisfying the needs of self, others, groups, communities, systems, and environments” (Core Belief 1) [11]. In contrast to the view regarding leadership as an instrument to obtain profit and fame, service leaders serve the needs beyond the self. During service provision, service leaders also believe that high-quality personalized service is important as it will influence the commitment and loyalty of the followers toward the leader. As a result, service leadership “is about creating appropriate personal service propositions in real time and constantly striving to provide the highest quality service one afford to everyone one comes into contact with and whose lives are affected by one’s actions or leadership” (Core Belief 5) [11]. To service leaders, service activities are not regulated by external forces such as material reward or punishment alone. Instead, the drive for serving others and being served by others has been evolved over history and hard-wired into human nature. Service leadership is thus regarded as the “oldest, most competitive and longest serving business model” (Core Belief 6) [11].

Different from the idea that successful leadership is determined by one’s competence, service leadership model posits that “leadership effectiveness and service satisfaction are dependent on a leader or service provider possessing relevant situational task competencies plus being judged by superiors, peers, and subordinates as possessing character and exhibiting care” (Core Belief 3) [11]. In brief, effective service leadership (E) is a function of one’s moral character (M), competencies (C), and caring disposition (C) (i.e., $E=MC^2$). Service leadership model emphasizes moral character and caring disposition relative to competence, as they believe that demonstration of moral character and caring disposition helps to win trust

and respect from the followers, which further benefit leaders, followers, and the collective. The idea of “hire for character, train for skills” [7] well exemplifies this belief.

Besides service leadership skills, successful service leaders should also have positive beliefs about leadership development. Initially, they believe in average people’s capacity to be a leader, specifically, “every day, every human occupies a position of leadership and possesses the potential to improve his or her leadership quality and effectiveness” (Core Belief 2) [11]. By holding this belief, service leaders are more likely to adopt distributed leadership, which encourages the initiative-taking and participation of followers into decision-making. Chung deeply believes that distributed leadership is the formula for building up a successful corporate culture in service business, and he explained that “the formula is very simple: give people something within their ability to decide and the power to do it, make this part of their daily life” [12]. Furthermore, the Core Belief 2 implies the possibility for improving leadership. Actually, service leaders believe that “service includes self-development efforts aimed at ethically improving one’s competencies, abilities, and willingness to help satisfy the needs of others” (Core Belief 4). A commitment to continuous improvement is required by service leadership. Such efforts in self-development would pay off, because “now and in the future, high-paying, high status positions and management promotions will go to people who have domain specific knowledge and skills plus service leadership competencies, appropriate character strengths and a caring social disposition” (Core Belief 7) [11].

Although the service leadership ideology has been delivered to many college students in Hong Kong via educational activities in the Fung Service Leadership Initiative (FSLI) [13], the theoretical underpinning of service leadership is still in its infancy. The initial ideas were primarily based on the business experience and wisdom of Po Chung, in particular, his experience as the co-founder of DHL International. Later, with the implementation of FSLI, scholars from the eight government-funded tertiary institutions in Hong Kong contributed to the theoretical development of service leadership. However, the theoretical model with its underlying assumptions and inferred propositions has been left untested, which hinders the transition of service leadership model from experiential wisdom to scientific theory. A lack of validated assessment instrument is apparently an obstacle for the further advancement. As argued by Slavec and Drnovšek [14], “effective measurement is a cornerstone of scientific research ... reliable and valid measures contribute to the legitimacy and development of a research field” (p. 39).

With the measure that assesses the attitudes and beliefs toward service leadership, multiple research questions can be tested. For example, Chung and Bell [6] mentioned that despite the service industries have contributed a large share to the Hong Kong GDP, many leaders still hold the traditional attitudes toward leadership inherited from the manufacturing era. This observation can be tested by assessing the degree of endorsement of service leadership attitudes and beliefs among leaders in different organizations. Additionally, what are the consequences of service leadership attitudes and beliefs is one of the top questions awaiting to be solved in this field. For example, would such attitudes and beliefs predict service leadership practice? Would such attitudes and beliefs benefit one’s teamwork? As such, there is a need to develop and validate an assessment instrument that measures to what extent people evaluate service leadership.

LEADERSHIP ATTITUDES SCALES

How one behaves as a leader is affected by one's beliefs about ideal leadership [15]. However, compared to the abundance of measures assessing leadership behavior or practice, assessment instruments about leadership beliefs and attitudes are relatively rare. In the 1950s-70s, two scales were developed to understand the fundamental beliefs of people towards leadership, one is the Leadership Opinion Questionnaire (LOQ) developed by Fleishman [16] and the other is the leadership belief questionnaire developed by Haire, Ghiselli, and Porter [17]. LOQ asks participants to report their attitudes toward leadership practice by evaluating how frequently they thought they should do the described behavior. It consists of two dimensions of behavior, including consideration (e.g., "help people in the work group with their personal problems"; "back up what people under you do") and initiating structure (e.g., "emphasize meeting of deadlines"; "meet with the work group at regularly scheduled times"). This scale has been used in leaders from different kinds of organizations [16, 18]. However, as the concepts of consideration and structure were criticized by the leadership scholars [19, 20], this scale gradually received less attention in leadership research.

Another scale on attitudes toward leadership primarily measures leaders' fundamental beliefs toward democratic/participative vs. dictatorial/authoritarian leadership [17]. Specifically, it covers one's beliefs about average people's capacity for leadership and initiative, sharing information, participative management, and internal vs. external control of the individual toward the job. This scale was often used to examine the beliefs of leadership in different cultures [e.g., 17, 21]. However, the construct validity of this scale was questioned by Bottger, Hallein, and Yetton [22], as the items measuring beliefs about leadership capacity referred to average people, while the rest of them referred to subordinate, which are not consistent. Similarly, this scale has been rarely used nowadays.

After the millennium, the most commonly used scale nowadays is Leadership Attitudes and Belief Scale (LABS) developed by Wielkiewicz [23]. Adopting the ecological model of leadership [23, 24], he first developed a scale to assess serials of attitudes and beliefs about leadership in college students. In the original LABS (LABS-R), 86 items were generated with regard to attitudes toward authority (i.e., leaders' authority status), ethics (i.e., the importance of ethics in leadership), learning orientation (i.e., importance of learning in personal development and organization), relationship orientation (i.e., the importance of cooperation), change (i.e., consideration of change in leadership process), positional leader dependence (i.e., dependence of leadership on position), and systemic thinking (i.e., the influence of systemic process on leadership process). The initial scale later was narrowed down into two dimensions with 28 items (LABS-III) [25], including systemic thinking (e.g., "everyone's ideas and concepts could make contributions to the organizational success") and hierarchal thinking (e.g., "believing in the position determined organizational leadership"). In general, the LABS-III was widely used among college students regardless of whether they were taking a leadership position or not. For example, it was successfully used to investigate the role of gender and college experience in leadership attitudes [26, 27].

Other researchers also developed their own attitudes scales, but were rarely used by other researchers. For example, Rao [28] developed the Supervisory and Leadership Beliefs Questionnaire (SLBQ) to investigate the leadership beliefs of supervisor for effectively

guiding subordinates, and Hiller [29] developed the Orientation Toward Leadership Scale in the thesis aimed to measure of individuals' conception of leadership.

The scales reviewed above cover some concepts related to service leadership model. For example, the LOQ measures leaders' opinions about consideration which is similar to attitudes toward caring disposition in the service leadership model. Haire et al.'s [17] scale measures attitudes toward average people's capacity to take a leadership role, which is related to the attitudes toward the core belief "everyone can be a leader". LABS-R measures individual attitudes about to what extent ethics should play an important role in leadership process, which is similar to attitudes toward moral character. Finally, most of these measures concern democratic vs. authoritarian leadership attitudes, which is related to attitudes toward distributed leadership.

However, some essential components of service leadership were missing in the scale literature. The most obvious deficit is the lack of measures assessing individuals' attitudes toward the role of service in leadership (e.g., to what extent, a leader should serve others). Other critical attitudes such as the attitudes toward the importance of multiple competencies in leadership, self-leadership, and the nature of service are absent in the leadership assessment instruments. More importantly, most of the existing scales were developed for people occupying specific leadership positions (e.g., LOQ and SLBQ). As service leadership model uphold the belief in everyone's capacity and potential to be a leader, it is necessary to understand how average people think about service leadership irrespective of their experience in their positions.

THE SERVICE LEADERSHIP ATTITUDES SCALE [SLAS]

Against this background, we developed the Service Leadership Attitudes Scale [SLAS], which attempts to assess individuals' attitudes and beliefs about desirable leadership practices and leadership qualities within the SLAM framework. Specifically, it taps on one's attitudes and beliefs about what a desirable service leadership process should be, what kind of qualities a good leader is expected to possess, and what kind of functions a good service leader is expected to perform. A total of 10 aspects of attitudes/beliefs extracted from the core beliefs of the service leadership model were deemed important [7-9,30], which serve as the conceptual framework for the scale development.

First, according to the definition of service leadership, service leaders regard leadership as a sort of service rather than a means to obtain profit and frame. Thus, service leaders should have a service orientation, which includes regarding leadership as a service and having the willingness to surpass self-interest to serve others. This is the fundamental attitude toward leadership that differentiates service leadership from other traditional leadership developed in the manufacturing economies. Second, service leadership model upholds the belief that "everyone can be a leader and has the potential to develop leadership qualities" [11]. People who endorse this belief would have more confidence to assume leadership and improve their leadership qualities. Third, service leaders tend to regard distributed leadership as a desirable leadership practice. As noted by Chung and Bell [7], "distributed leadership suggests that an organization has been structured so that appropriate leadership decisions are pushed down to their lowest practical level" (p. 73). To adopt distributed leadership, leaders need to have

favorable attitudes toward 1) shared decision-making such as allowing their subordinate to voice out their opinions and contribute to the decision-making process, 2) empowerment of followers such as encouraging their followers to take initiative and delegating greater authority to their followers, and 3) trust and respect towards followers' views such as acknowledging their views and trusting their abilities to make good decisions.

Fourth, service leaders tend to believe that service leadership increases one's employability. Specifically, service leaders believe that high-status and high-paying leadership positions will go to leaders who are willing and capable to serve others. Fifth, in the service economies, one-size-fits-all service is no longer an optimal choice. Instead, a good leader needs to create high-quality personalized service and sensitive to individual needs. Service leaders would consider providing personalized service as a desirable leadership practice. Sixth, service leaders believe that providing service is intrinsically enjoyable to the service providers, as the tendency to serve others has been evolved into the core of humanity. Service leaders would not regard service provision as regulated by an external force such as reward and punishment but motivated by human nature, which has been evolved over history.

Seventh, service leaders believe that good leaders should have multiple intrapersonal competencies and interpersonal competence. There are four kinds of intrapersonal competencies that a good service leader should have, including IQ, EQ, AQ, and SQ. Intelligence quotient (IQ) includes comprehension and analytical abilities, independent thinking, critical thinking, logical reasoning and argumentation, flexibility (i.e., knowing how to improvise on the spot), and good problem-solving ability. Emotional quotient (EQ) includes understanding one's own emotions and others' emotions and managing one's own emotions and relationship with others. Adversity quotient (AQ) includes the ability to accept and cope with kinds of adversity and bounce back from the adversity. Finally, spiritual intelligence quotient (SQ) includes the ability to use meaning, vision, and other spiritual resources to solve personal problems and motivate the followers [31]. Service leaders would regard these competencies as important to a good leader. In addition, service leaders believe that good leaders should demonstrate interpersonal competencies in terms of being passionate about people, developing and maintaining a positive social relationship, being assertive, being able to collaborate and cooperate with people, being able to resolve conflicts within the team/in the services, and having good communication skills.

Eighth, service leaders hold a view that good leaders should demonstrate moral character. It includes maintaining a well-developed personal code of ethics characterized by integrity, fairness, and humanity, acting as an ethical role model, and believing in the power of morality, which is about winning trust and respect from the followers by one's virtues instead of power. Ninth, service leaders believe that good leaders should demonstrate a caring disposition, including care and concern about others as well as taking care of others. For the care and concern, they believe that empathy and compassion are two major qualities that good leaders should have. For taking care of others, they believe that good leadership involves loving followers by showing benevolence, affection, and forgiveness, supporting followers by providing physical and psychological resources to the followers, and developing followers by nurturing the growth of followers, coaching and mentoring the followers.

Finally, service leaders have a positive attitude toward a commitment to continuous improvement. They would have a growth mindset rather than a fixed mindset about leadership, believing that leadership can be changed and nurtured. Regarding the malleability of human attributes, people usually have two kinds of mindsets. People who adopt a growth

mindset believe that human attributes such as intelligence and personality could be developed through nurture while those who adopt a fixed mindset believe that human attributes are determined by nature [32]. In contrast to the notion of “elite” or “inborn” leadership, the service leadership model asserts that everybody is (and can be) a leader. It adopts a humanistic perspective that every individual has potential to be a leader and that leadership qualities can be changed and improved. It emphasizes self-leadership and self-reflection and considers them as good practices for a leader. Before one can lead others, one must first be able to lead oneself. In addition, service leaders must engage in constant reflection on one’s character, strengths, weaknesses, and service provision in order to seek for continuous improvement both professionally and personally. Generally, they believe in free will of human and tend to endorse Theory Y relative to Theory X about human behavior in organizations. Theory X and Y were proposed by McGregor [33] which concern the assumptions of human behavior in organizations. The underlying assumption of Theory X is that humans are inherently lazy, incapable of self-control, and have little to contribute to the effectiveness of the organization. On the contrary, Theory Y assumes that humans are not inherently lazy, but are capable of self-direction and self-control, and are able to positively contribute to the organization. Theory X implies that leaders must closely monitor the behaviors and performance of followers, whereas Theory Y encourages distributed leadership through delegation and autonomy. Service leaders are supposed to endorse Theory Y.

Based on the theoretical propositions of the Service Leadership Model, the scale development was conducted by a team of four researchers with teaching and research experience in service leadership. The three junior researchers drafted the items and the senior research modified items and supervised the whole process. With several rounds of re-iteration, a total of 132 items were created. Respondents are requested to report the degree to which they agree or disagree with the 132 statements that describe desirable leadership qualities or leadership practices on a 6-point Likert scale. With the items ready, the first question we would like to address is whether this batch of items measure the target constructs. Therefore, we examined the content validity of this scale. Content validity refers to “the extent to which elements of an assessment instrument are relevant to and representative of the targeted construct for a particular assessment purpose” [34]. In the scale development, many researchers used content validation as the first filter to select the good items [e.g., 35, 36]. In this study, we relied on the evaluation of three judges of expert for the content validation.

OUR STUDY

Three experts who were familiar with service leadership, especially the framework of the Hong Kong Institute of Service Leadership and Management (SLAM), were invited to judge the content validity of the 132-item Service Leadership Attitudes Scale. All of them had a doctoral degree and were involved in the curriculum development and/or the teaching of the subject “Service Leadership”.

Instrument

The experts evaluated the scale independently via content validation form. The raters judged the content validity in the following aspects for each item:

- Relevance (1 = Irrelevant, 2 = Unable to assess the relevance without item revision or item is in need of revision or otherwise would no longer be relevant, 3 = Relevant but needs minor amendment, 4 = Relevant)
- Clarity (1 = Very unclear, 2 = Unclear, 3 = Clear, 4 = Very clear)
- Representativeness (1 = Very unrepresentative, 2 = Unrepresentative, 3 = Representative, 4 = Very representative)

They were invited to provide justifications if negative responses were given. Besides the ratings for individual items, the experts were invited to evaluate the overall quality of the scale with reference to the following questions:

1. Does this batch of multiple choice questions cover all the essential attitudes/beliefs in the service leadership framework?
2. Does this batch of multiple choice questions adequately represent the essential attitudes/beliefs in service leadership?
3. Overall speaking, are these multiple choice questions a valid measure of the basic body of attitudes/beliefs covered in the Service Leadership and Management (SLAM) model?
4. Additional attitude(s)/belief(s), if missing from the scale (open-ended question).
5. Other comments (open-ended question).

FINDINGS

In the present study, content validity was determined by the judgements of experts. Individual item content validity index (I-CVI) and average scale content validity index (S-CVI/ave) [37, 38] were calculated to indicate the content validity of the scale. I-CVI was computed by the number of positive responses (option 3 or 4) divided by the number of experts [i.e., 3]. S-CVI/ave was a mean score of the I-CVIs of all the items within each category or the overall scale. This approach has been used in previous scale validation studies [35].

Table 1. The frequency of I-CVI and the S-CVI/ave for the whole scale

I-CVI	Number of items (percentage)		
	Relevance	Clarity	Representativeness
0.33	0 (0%)	0 (0%)	1 (0.8%)
0.67	3 (2.3%)	11 (8.3%)	2 (1.5%)
1.00	129 (97.7%)	121 (91.7%)	129 (97.7%)
S-CVI/ave	.99	.97	.99

Table 2. The S-CVI/ave for the subscales

No.	Domains	No. of items	Relevance	S-CVI/ave	
				Clarity	Representativeness
C1.	Service orientation	5	1.00	.93	1.00
C2.	Everyone can be a leader	4	1.00	1.00	1.00
C3.	Distributed leadership	13	.97	.95	.95
C4.	Employability	2	1.00	1.00	1.00
C5.	Personalized service	3	1.00	1.00	1.00
C6.	Attitudes toward service	2	1.00	1.00	1.00
C7.	Competencies	45	1.00	.99	1.00
C8.	Moral character	18	.98	.96	.98
C9.	Caring disposition	15	1.00	.98	1.00
C10.	Commitment to continuous improvement	25	.99	.96	.99

On an individual level, most of the items had good I-CVI (see Table 1). Among 132 items, 129, 121, and 129 items were regarded as relevant, clear, representative, respectively, by all the judges. The items were modified according to the judges' comments. The S-CVI/ave for the whole scale indicated an excellent content validity (see Table 1). For each category, S-CVI/ave was also very good (see Table 2). Finally, all the judges showed favorable responses to the questions about the overall quality of the scale. They regarded it able to cover all the essential attitudes/beliefs of service leadership, adequate to represent the essential attitudes/beliefs of service leadership, and valid to measure the basic body of attitudes/beliefs covered in the SLAM framework.

DISCUSSION

The purpose of this study was to examine the content validity of a newly developed scale – The Service Leadership Attitudes Scale (SLAS). Consistent with the SLAM framework [6-9], we developed the Service Leadership Attitudes Scale to measure how individuals think about service leadership regardless of their leadership experience. To our best knowledge, this is the first scale assessing individuals' attitudes and beliefs toward leadership qualities and leadership process upheld by the SLAM framework. Besides, as there are very few leadership attitude scales, this study is also one of the few attempts to validate leadership attitudes scale.

The first question regarding the development of the scale is whether it measures what it is supposed to measure. Our results support the content validity of the scale based on the views of three experts. Results showed that almost all items were rated as relevant to the construct by all three judges of expert except three items. All but 11 items were rated as clear by all three judges. Only one item was regarded as unrepresentative of the construct by two judges and two items were regarded as unrepresentative of the construct by one judge. Items were revised with the suggestion of the judges. For example, the item that “good leader upholds the principle of ‘leading by personal example’” was created to measure the construct of role modeling in moral character, but it was regarded as irrelevant, unclear and unrepresentative of the construct by one expert. This item was thus revised as “a good leader sets an example for others to follow”. Another item “the views of leaders are always better than those of their subordinates” was replaced by the item “a good leader does not let their followers participate

in the decision-making process” to represent the construct of shared decision making of distributed leadership, because it was regarded as unrepresentative of the construct by two judges. Generally speaking, the three judges regarded this batch of items covering the essential attitudes and beliefs within SLAM framework. Sample items were presented in Appendix 1.

The development of the SLAS has theoretical and practical significance to the field of leadership theory and education. The attention toward leadership attitudes in the academia seems to fade out after 1980s, with leadership scholars and practitioners focusing more on the overt leadership behavior [39]. The underlying attitudes/beliefs that a leader hold have been left under-examined or incorporated into leadership style (e.g., spiritual leadership) [40] for a long period of time. Although it is well-known that the link between attitudes/beliefs and actual behavior is not perfect [41], leadership attitude itself is important, as it assesses the cognitive aspect of leadership development [42]. Change in attitudes toward leadership (e.g., from a leader-centric perspective to a systemic perspective) signifies the development of leadership [27]. The development of SLAS would contribute to our understanding of service leadership development. Practically speaking, it also helps with educational program evaluation. Specifically, this scale will help us know whether the current service leadership education or other learning experience is effective to transform people’s views about leadership. Besides, understanding one’s attitudes towards leadership also helps to understand the training needs of the respondents.

This study is not free of limitations. Obviously, the number and heterogeneity of the experts involved in this study was limited. Only three experts rated the scale, although it still met the minimum acceptable number of three experts proposed by Lynn [43]. Obviously, the confidence in the robustness of the rating will increase with the increase in the number of judges [34]. Additionally, the three experts were all in the academia, and thus their feedbacks were more scholastic-oriented. It is difficult to recruit other experts outside academia as the idea of service leadership has not been widely and deeply delivered yet. However, as suggested by Haynes et al. [34], population sampling can be used, in which the people from the target population can be invited to rate the scale. Thus, we can ask colleagues in the business field who have received training in service leadership to share their feedbacks on the items in the future. Moreover, the judges were required to rate the items only instead of all the elements of the scale. As recommended by Murphy and Davidshofer [44], all the elements of an assessment instruction including instructions, response format, and scaling point should be under review. However, this study did not expressly request the judges to provide feedback on these elements, although one judge suggested to revise the scaling point from 6-point to 7-point in the open-ended question of “general comments”. We can draw attention of judges to these elements in the future studies of content validation.

Despite these limitations, this study shows an initial yet important step in developing a scientific measure to assess people’s attitudes toward service leadership. The scale was considered to be valid in terms of its content. Further studies on other aspects of validity await to be done.

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APPENDIX 1: SAMPLE ITEMS

Domains	Sample items
Service orientation	Above self-interest: A good leader puts the interests of his/her followers above the interests of his/her own. Readiness to serve: A good leader serves others with a genuine heart.
Everyone can be a leader	Everyone can be a leader regardless of his/her current role and position.
Competence	IQ: One of the main qualities of a good leader is to have good analytical skills. EQ: The capacity of managing his/her emotions in a healthy manner is an important quality of a good leader. SQ: A good leader is able to articulate his/her vision of the organization. AQ: Good leaders are able to bounce back from adversity. Passionate about people: Good leaders are people-oriented. Positive social relationship: A good leader maintains positive and healthy relationships with others. Assertiveness: Effective leaders can defend their views while respecting others' feelings and rights. Collaboration: A good leader is able to collaborate with others. Conflict resolution: Effective leaders resolve conflicts in creative and constructive ways. Communication skills: An effective leader effectively communicates his/her thoughts and ideas.
Moral character	Integrity: The overt behavior of a good leader is consistent with his/her inner principles. Fairness: A good leader evaluates followers' performance in an unbiased and objective way. Humility: A good leader accepts criticisms from followers and other people. Role model: A good leader acts as an ethical model for the followers. Belief in the power of morality: A true leader wins trust and respect from the followers by his/her moral virtues.
Caring disposition	Empath: A good leader looks at things from other people's perspective. Compassion: Good leadership requires compassion for other people. Love followers: A good leader extends his/her kindness to others without expecting repayment. Support followers: A good leader helps followers tackle problems that hinder their work progress. Develop followers: A good leader coaches his/her followers for their professional development.
Commitment to continuous improvement	Fixed vs. growth mindset: Leadership competencies can be developed. Self-Leadership: Leaders tend to be highly disciplined. Self-reflection: A leader should closely examine his/her own thoughts and behavior. Freedom vs. determinism: Human beings have the free will to change. Theory X: As most followers do not exercise self-control and self-motivation, leaders must exercise close supervision.

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Chapter 122

SERVICE LEADERSHIP EDUCATION IN THE UNIVERSITY OF HONG KONG

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ABSTRACT

Substantial research supports the idea that service-learning projects enrich students' leadership skills and nurtures leaders with a sense of social responsibility that is important in the twenty-first century. In view of this, the Faculty of Social Sciences of The University of Hong Kong has initiated the Service Leadership Internship programme to enhance the education of undergraduate students through project-based community service. The programme, which is supported by the Victor and William Fung Foundation, creates authentic platforms for students to work as shared leaders and develop important life skills like collaboration and conflict resolution. This chapter summarizes the learning outcomes of the programme and reflects upon the three-year learning journey. Future directions include the use of cross-disciplinary approaches and extending the programme beyond Hong Kong.

INTRODUCTION

Building the capacity of graduates to fulfill the human resource needs both in the business and the service sectors is increasingly important in higher education [1]. By reviewing the literature, the expert panel from the Horizon Project in 2014 [2] identified six important trends: 1) expanding the use of social media in teaching and learning, 2) engaging students in collaborative learning, 3) using students' data for improving learning outcomes, 4) seeing students as creators, 5) nurturing entrepreneurship in students and faculty, and 6) incorporating online learning. These signify a paradigm shift in higher education away from

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the traditional classroom environment to an interactive learning environment with a great deal of collaboration and social innovation.

Research into leadership education has suggested that experiential learning projects enhance students' leadership skills and nurture future leaders with a sense of social responsibility for the twenty-first century [3, 4]. Internship is one of the most effective experiential-learning pedagogical strategies in higher education. It promotes personal growth and improves the employment prospects of the students [5]. It also features a strong reflection component, onsite supervision, and students' exposure to career-related experiences [6]. About 90% of universities in the United States offer internships or similar experiences to undergraduate students [7].

In view of this, the Faculty of Social Sciences of The University of Hong Kong (HKU) has initiated the Service Leadership Internship (SLI) program. It is a 12-credit course (sponsored by the Victor and William Fung Foundation since 2013) aimed at fostering leadership skills in undergraduate students through a six- to eight-week community-service experiential learning program during the summer [8, 9].

THE OBJECTIVES OF THE SLI PROGRAM: THE HKU APPROACH

In line with the core beliefs underpinning the curriculum framework proposed by the Hong Kong Institute of Service Leadership Management, the SLI program at HKU aims to achieve the following four objectives:

- 1) To strengthen students' sense of the social responsibilities of leadership
- 2) To assist students in acquiring the personal competencies required for leadership, through the enhancement of
 - Self-efficacy and the ability to tackle novel challenges and ill-defined issues
 - Resilience to setbacks
 - Critical thinking and problem solving skills
 - Self-reflection on personal and professional growth
- 3) To help students acquire the social competencies needed in leadership by enhancing their
 - Collective efficacy and team building skills
 - Collaboration and conflict resolution skills
 - Communication skills
- 4) To enable students to hone their leadership skills in authentic services to the community. These skills include
 - Organization and management skills
 - Planning and decision making skills
 - Skills in exerting a positive influence on others

Students' Participation over the Years

The SLI program was launched in the summer of 2012. In its first three years, the program was solely designed for students from the Faculty of Social Sciences and the Faculty of Business and Economics, but is now (as of 2015) open to students from other faculties. This new move allows more students to benefit from the SLI program. Synergy arises from the interactions among students from different backgrounds, which also makes the learning experience more meaningful. The figures below give some of the program's descriptive data.

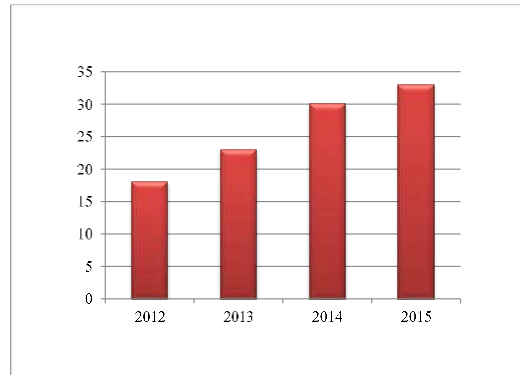


Figure 1. The total number of community partners since the inception of the SLI program.

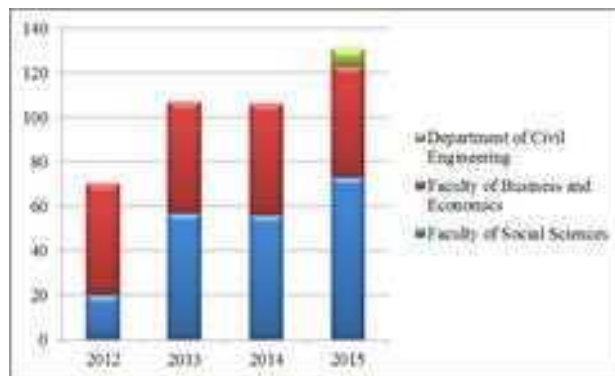


Figure 2. The total number of students from various faculties or departments since the inception of the SLI program.

Assessment and Impacts of the Program

Academic deliverables (ongoing participation in an online reflective forum, integrated essay, and a poster conference) have been structured alongside the internship. Students are assessed by their supervisors, academic tutors, peers, and themselves.

Each year an evaluation study of the program's impact on the students' mindsets—and of their gains in social awareness, personal and social competencies, and leadership skills—is conducted. Students have to complete a questionnaire before and after their internship. The

findings are then used to compare the students who joined the regular internship program (without the leadership component) and students who joined the SLI program.

The results in 2014 indicated that, after the internship ($t = 2.33$, $df = 143$, $p = .02$), students who had participated in the SLI program had lower fixed-mindset scores ($M = 3.08$, $SD = .86$) than the students who had participated in the regular internship program ($M = 3.32$, $SD = .89$) (Chow & Lam, 2015). Also, students with a less fixed mindset at the end of the program tended to be more forgiving ($r = -.30$, $p = .02$). They also tended not to attribute minor transgressions by their friends to personal traits ($r = .29$, $p = .02$). Further studies are required to explore the impact of SLI learning experiences on the students, preferably with a larger sample and across more time (over the medium and long term).

The data from a focus-group study conducted in September 2014 revealed that most of the students had very positive learning experiences in the SLI program. Students appreciated the diversity of project selection, the authentic project tasks, and the ample opportunities to apply their innovative social ideas. While some of them may experience challenges in team work, they learn how to adjust and negotiate their expectations and how to work towards common goals under shared leadership.

The SLI program has created an authentic platform for students to contribute through shared leadership and to develop important life skills, such as those needed for collaboration and conflict resolution. It has also enhanced the students' sense of social responsibility and improved the personal and social competencies of the students.

Reflection on the Three-Year Journey

There are four main reflections broadly covering the structure for service leadership and the wider learning environment.

Building the Structure for Service Leadership Education at HKU

The experiential learning approach at HKU is a very powerful and effective way to nurture the leadership skills of undergraduate students. The three-year journey has produced many successful cases involving students changing from a fixed mindset to a growth mindset and moving out of their comfort zone to collaborate and to lead the projects. By successfully completing different service tasks, students built up their confidence for participating in shared leadership and became committed to the betterment of the society in Hong Kong and beyond.

Through employing a wide range of project types with different organizations, we realize that community engagement is an authentic and practical way to nurture leaders with social awareness and to develop a commitment to the social responsibilities of leadership. Students were exposed to a wide range of contexts involving different social issues beyond campus life; as reflective learners, the students needed to integrate their academic knowledge with what they learned from the practical applications of it during the internship.

A team-based approach has been proven to be successful in nurturing shared-leadership skills. Throughout the internship process, students had to work towards common goals. Thus, they had to use their communication skills and collaborative skills at the same time as their problem solving skills.

Coaching is another important element of HKU's service leadership education. We aim to provide continuous, structured support to the students throughout the six- to eight-week internship. The dual supervision approach is critical to the students' learning processes: the supervisors from the community partner provide hands-on feedback to the student interns at the workplace, while the academic tutors from the university provide academic support. Tripartite meetings are conducted at different stages of the project so that students can receive timely feedback.

Co-Learning among Teachers, Intern Students and Community Partners

The teachers continue to reflect on the learning process to support the service leadership education. They add new elements so as to better structure the students' learning processes and achieve better learning outcomes.

In the fourth year of the program, we used social media to support the students' reflective learning process. Instead of submitting a written 1,500-word reflective journal, the students were required to participate in an interactive online forum throughout the internship. The students had to initiate a discussion thread and post a response in three different areas: problem solving, critical incidents, and personal growth and sharing. Although more effort was required for participation in an online discussion forum than for writing a single piece of academic work, the students' feedback regarding the forum was very positive.

We continue to heed students' feedback, which is garnered from various sources, including focus group interviews and self-evaluation data. We also encourage community partners to provide us with feedback regarding our program.

Building an Environment for Active Sharing among Students

Actively contributing to peers' learning processes is an indispensable element of HKU's service leadership education. Throughout the internship, we build in different peer learning and sharing environments at different times, so that students can contribute to others' learning outcomes through shared leadership.

During Week 7, students share in small groups, face-to-face, during the booster session at the HKU campus. In the pre-internship workshops students interact with all their counterparts; in the booster session, students meet with only two to three SLI project groups. They talk about their own difficulties and gather feedback from other students. Most students find this session very useful, as they collect feedback from other students and also receive support from their peers.

Students use the aforementioned online discussion forum as another effective platform for peer support. This is particularly true of the problem-solving area of the forum, where students pose questions regarding their SLI projects. For example, students ask questions related to project design, ask directions for locating different types of resources, and even ask for technical advice on how to use computer software. In the personal growth and sharing area of the forum, students continuously share with others new insights and knowledge. The platform is very effective in boosting team spirit and morale, as students find support in a timely manner and understand that other students also face different kinds of challenges as part of their learning process.

The poster conference at the end of the internship program creates a platform for students to celebrate their achievements. Students in each team decide among themselves who will fill the roles of presenters and assessors at the conference. While the presenters are responsible

for presenting the learning processes and learning outcomes of their SLI projects, the assessors appraise their peers' presentations and ask critical questions. The conference continues to be one of the highlights of HKU's service leadership education as it consolidates the students' learning and provides them with additional feedback.

Cross-Disciplinary Development

We understand that shared leadership is not only about working as a team; future leaders need to be able to work in multi-disciplinary settings too. We intend to extend our internship invitation to other disciplines and will continue to encourage students from different disciplines to work collaboratively in each SLI project. By working with students from different disciplines, individuals learn to understand their own limitations and, at the same time, appreciate inputs from other perspectives.

Another cross-disciplinary development involves the pilot project Glocal Solutions (GS). GS is a cross-disciplinary credit-bearing experiential learning project at the HKU that is aimed at nurturing global leaders who discharge their social responsibilities in diverse cultural settings. Based on a needs analysis of the community, an innovative small scale construction project will be implemented by the students, under the supervision of World Vision Vietnam. Students will work under shared leadership to create a design that will meet the community's needs, while utilizing their academic training (e.g., in social sciences or engineering) and remaining mindful of local constraints on capacity, resources, and time. We will continue our efforts to reach beyond the borders of Hong Kong and adopt a practice-oriented approach—so as to nurture global leaders with social awareness and a strong sense of commitment to global issues—by engaging community partners globally.

FUTURE DIRECTIONS

We are planning five major initiatives which will take place over the next three years.

Experiential Learning

The HKU Service Leadership Education will continue to be built around experiential learning, meaning that we provide leadership education through active experiences of students outside of regular classroom settings. We believe that transformative learning is more effective than informative learning at developing leadership attributes and at enabling students to become change agents [10]. Also, experiential learning provides a very valuable opportunity for students to gain new perspectives on their classroom learnings, so as to address real needs in society [11]. Lastly, it nurtures real and authentic collaborations amongst students, thereby building their teamwork and conflict resolution skills [12] that are critical parts of leadership development.

Cross-Disciplinary Approach

We will open up local Service Leadership Internship to students from other disciplines (e.g., engineering and architecture) and we will approach other Faculty staff to design SLI

projects that are cross-disciplinary in nature. Such cross-disciplinary collaboration in teams simulates real life situations and real work settings [13]. On one hand, this reflects how society actually functions, with work accomplished and achieved by interdependent disciplinary specialists [14]. On the other hand, cross-disciplinary collaboration is now critical to solving pressing global issues. The synergy creates insights and novel solutions to complex global problems [15]. Our students are encouraged to move out of their comfort zones by going beyond the limitations of their own disciplines and learning to approach the problems in a multiple-disciplinary, collaborative fashion.

Service Leadership Beyond the Borders

Students benefit academically, socially and culturally from overseas experiential learning projects [16]. Also, the University has clearly stated in the educational aims that our curriculum aims to develop students' capabilities in six key areas:

- 1) Pursuit of academic/ professional excellence, critical intellectual enquiry and life-long learning
- 2) Tackling novel situations and ill-defined problems
- 3) Critical self-reflection, greater understanding of others, and upholding personal and professional ethics
- 4) Intercultural understanding and global citizenship
- 5) Communication and collaboration
- 6) Leadership and advocacy for the improvement of the human condition (<http://tl.hku.hk/reform>)

In other words, the SLI must reflect the interconnectedness of the world and be aligned with HKU's educational aims and institutional learning objectives. We, therefore, have expanded the SLI program to reach beyond the borders of Hong Kong in order to further develop students' intercultural understanding and global citizenship. This allows our student leaders to develop cross-cultural communication skills [13] that would be otherwise difficult to develop in a local setting. As such, the pilot project Glocal Solutions was launched in summer 2015 and it will be carried on into the future.

Expertise Sharing Forum/Workshops

We aim to promote service leadership education at the university level by collaborating with other departments and also with community partners and organizations. For example, the Gallant Ho Experiential Learning Centre at HKU provides experiential learning support to all undergraduate students at HKU. We will take the opportunity to consolidate the conceptual aspect of service leadership and the teaching pedagogy.

Strengthening Experiential Learning at HKU through Evidence-Based Research

Lastly, the sustainability of the initiative rests with how well we transfer the lessons learnt and experience gained from the SLI program to the HKU's existing experiential learning curriculum. The Experiential Learning team at the Faculty of Social Sciences will: 1) systematically review the past four years' experience in order to identify the critical elements of the learning process (e.g., the enabling factors and barriers, and the roles played by the

different personnel involved in the process) embedded in the SLI program; and 2) make adjustments to the current experiential learning structure (e.g., working in small groups, specific project-based design, and shared leadership) to further improve the students' learning experience.

The Faculty is committed to nurturing global leaders through different types of experiential learning programs. We will continue to engage students from a wide variety of disciplines, as the skills acquired in interdisciplinary teams will be helpful for students in their future endeavours.

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Chapter 123

SERVICE LEADERSHIP EDUCATION IN AN ERA OF SERVICE ECONOMY

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INTRODUCTION

In different parts of the world, economies have been changing from an industrial mode to a service mode [1-3]. While industries such as computer and automobile manufacturing still exist in different parts of the world, there is a gradual integration of the traditional industrial production with service provision. Besides differences in production processes between the industrial and service economies (e.g., assembly line production versus production of reliable service), the desired leadership qualities of the two economies are also very different. While desired leadership in the industrial economy is more top-down, it is more bottom-up in the service economy [4].

In the “traditional” leadership models which are closely related to industrial economies, leadership generally focuses on production outcomes and is commonly conceived in terms of leadership competencies, such as effective problem-solving and skills to make wise

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management decisions. While these attributes are important, their sole existence is not adequate for effective leadership in service economies. As service provision involves both the service provider and the service recipient(s), whether service providers have ethics and moral responsibilities are particularly important because quality control is commonly performed by the service providers (e.g., teachers and brokers). In addition, whether a leader cares about other people, including the service recipients and the followers is an important leadership attribute in service economies. Basically, the mission of a service leader should not be just geared towards maximization of profit without caring about other people's benefits [5, 6].

Because of the changing requirements of effective leaders in service economies, there is a need to nurture leaders with leadership competence, ethics and caring attributes. The notion of "service leadership" was put forward by Po Chung, Co-Founder of DHL International. He argued that effective service leaders should have the attributes of generic leadership competence, moral character and caring disposition (3 Cs). Together with the support from the Victor and William Fung Foundation, Po Chung initiated the Service Leadership Education Initiative where eight Government-funded universities in Hong Kong were given grants to develop curriculum materials on service leadership. To mark the success of this initiative, two international conferences were held in 2014 and 2016, respectively [7, 8].

At The Hong Kong Polytechnic University (PolyU), both credit-bearing subjects and non-credit-bearing programs have been developed since the inception of this initiative. For credit-bearing subjects, a 2-credit subject was developed under the old 3-year undergraduate program and a 3-credit subject entitled "Service Leadership" was developed under the new 4-year undergraduate program. Besides Hong Kong, we also offered the "Service Leadership" subject in Cambodia and Xian in the form of intensive summer course. To promote service leadership attributes among the students, we also designed a service-learning subject to nurture the service leadership qualities among students through serving others. For non-credit-bearing programs, we designed leadership training programs for Wofoo Leaders' Network. We also included the intensive service leadership programs for students from PolyU, Peking University and Xian Jiaotong University.

To understand the impact of service leadership education on the development of students, we have conducted a systematic evaluation for the education programs developed. Primarily, we have used objective outcome evaluation via the one-group pretest-posttest design to assess the changes of the students after they completed the subjects or programs. Basically, there are research findings showing that students had positive changes in terms of improved knowledge, attitude and behavior on service leadership and enhanced well-being. Second, we used subjective outcome evaluation to understand the views of students toward the subject or training program, instructor or trainer, and the perceived benefits. Finally, qualitative evaluation via personal reflection worksheets, individual interviews or focus groups has been conducted to understand students' learning experiences and how they have benefited from the service leadership education. Taken as a whole, previous evaluation studies have demonstrated that service leadership subjects and programs are effective in promoting service leadership qualities and well-being among student participants [9-12].

In this book, we report evaluation findings based on different service leadership subjects and programs. Generally speaking, the reported findings replicated the previous evaluation findings of the Service Leadership Education Initiatives. These findings consistently and strongly suggest that these initiatives can help to promote service leadership attributes in young people. To build up the academic and professional foundation of service leadership

education, these evaluation initiatives are very important. When China is gradually evolving to the service economy, we earnestly hope that young people can be nurtured to be effective service leaders who possess competence, character and care.

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Chapter 124

IMPACT OF SERVICE LEADERSHIP EDUCATION ON UNIVERSITY STUDENTS IN HONG KONG

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ABSTRACT

In this chapter we assess the changes of students in universities in Hong Kong after studying a 3-credit subject about service leadership in two semesters. A total of 148 undergraduate students studying the subject conducted a questionnaire before and after the study. The questionnaire measures students' positive youth development, satisfaction with life, and qualities related to service leadership. Results revealed that students of both semesters had positive changes in different positive youth development indicators. Students' improvement in life satisfaction and qualities related to service leadership was also found in one semester. Findings of the study offer further support to effectiveness of service leadership subject in nurturing positive development and leadership development of students.

INTRODUCTION

Leaders are essential for the development of a society in any historical stage. Different leadership styles emphasize the cultivation of different characteristics and qualities [1]. Leadership was regarded as a process that a person exerts influence on a group of people to pursue a collective goal [2]. In the industrial time and manufacturing economy, the core activity in economy is mass production of goods or products; the production process is highly

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standardized; the organizational structure is highly hierarchy; and the workers are treated more as “screws” in a huge machine [3]. Accordingly, the leadership styles are normally autocratic and transactional [3]. In addition, the leadership mainly focuses on leaders’ own professional and task-related competences, that is, the “hard skills” [2, 4].

However, there has been a significant socioeconomic transformation in recent years. One prominent feature of this transformation is the prevalence and dominating of the service economy in the global landscape. According to different research studies and statistics, the service economy has become the major driver of economic development and major contributor of GDP in many countries and districts including the United States [5], countries of the Organization for Economic Co-Operation and Development [6], and Asian Pacific nations or regions [7]. Hong Kong is without exception. During the past two decades, there has been a rapid increase and expansion of service economy in Hong Kong’s economic development. The contribution of service industry to GDP of Hong Kong has increased from 87.3% to 92.2% between 2000 and 2016 [8]. Particularly, Hong Kong’s economic growth is driven by four key service industries including “financial services, tourism, trading and logistics, and professional and producer services,” which contributed to more than half of the GDP of Hong Kong [9]. In recent years, there has been rising of new service industries including medical and educational services, cultural industries, certification services, and innovation and technology, which helps together to shape Hong Kong’s competitive edge in global economic competition [9].

The economic activities, organizational structure, and manpower requirement are very different between manufacturing economy and service economy, so do the required leadership styles. In service-based economy, knowledge creation and service provision are core activities for economic development. The economic inputs are mainly knowledge and skills and the outputs are high-quality and individualized services provided to customers based on customer-producer negotiation and communication [3, 10]. Besides, tasks become highly complex in service-based economy for which leaders cannot make decisions solely by themselves but need shared decision making with their followers and even other stakeholders. Therefore, human assets, human interaction, and social relationship play an essential role in service economy and success of organization [4]. This requires organizational structures to be decentralized and flexible to allow for knowledge storing, sharing, and creation, and to give full support to autonomous and highly motivated workers [3]. This also requires leadership to focus on empowerment, relationship building, motivation, caring, support, and collaboration to maximize contributions of employees in service-based economy [3, 10]. In other words, possessing hard skills is far from enough for being effective leaders. Leaders’ generic competences, morality, character, and disposition of care become vital [11-13].

Envisioning the above mentioned socioeconomic transformation in Hong Kong society and required leadership styles, The Hong Kong Institute of Service Leadership and Management (HKI-SLAM) put forward a concept and related framework of service leadership. Service leadership was conceptualized as “satisfying the needs by consistently providing quality personal service to everyone one comes into contact with, including one’s self, others, groups, communities, systems, and environments” [14]. Besides, the service leadership effectiveness is dependent on three key qualities: care, character, and competence [15]. First, effective leadership requires not only domain-specific competences but also intrapersonal and interpersonal competences that are required for relationship building in service-based economy. Second, effective service leaders should be ethical role models of

their followers. Their moral characters are vital for gaining trust and commitment from their followers. Third, effective service leaders should love their followers, listen to their followers' views, and show empathy to their followers, which is "care" of leadership. As such, Po Chung [14], the co-founder of HKI-SLAM, argued that a successful service leader is a well-prepared, highly motivated, capable, and "on-the-spot socialized entrepreneur who possesses relevant task competencies and is judged by superiors, peers, subordinates, and followers to exhibit appropriate character strengths and a caring social disposition."

Although there are strong needs for service leaders in Hong Kong's society, the existing university education in Hong Kong shows worrying signs regarding students' healthy and holistic development. A body of research suggests that there are higher rates of developmental problems amongst students in Hong Kong universities. For instance, different studies suggest that Hong Kong university students may experience from moderate to high level of mental health problems such as stress, depressive symptoms, and anxiety [16]. Besides, employer surveys suggest that local employers were dissatisfied with the generic qualities of university graduates particularly for their interpersonal communication skills and psychological maturity [17]. One reason might be that the traditional three-year undergraduate education system overemphasized on specialized education and neglected students' holistic development [17, 18]. As such, it is imperative to nurture university students' holistic development including the development of soft skills and leadership qualities required by the service-based economy and society in Hong Kong.

In recent years, the university education of Hong Kong has experienced significant changes as a response to current socioeconomic change. Particularly, the three-year undergraduate education curriculum has been transformed to a four-year one since the 2012/13 academic year, with one additional year being devoted mainly to general education and students' holistic development [18]. Along with this transformation, there is an increasing awareness of leadership development among university students. Particularly, since 2012, the HKI-SLAM has collaborated with Victor and William Fung Foundation to launch the Li and Fung Service Leadership Initiative to fund the eight universities under the University Grants Committee (UGC) of Hong Kong to develop programs to nurture students' service leadership qualities [19].

Under this initiative, all the eight UGC-fund universities developed their own leadership programs according to the service leadership framework proposed by HKI-SLAM [20-22]. Among these programs, a prominent one was the "Service Leadership" (SL) subject developed by The Hong Kong Polytechnic University (PolyU). The SL subject is a credit-bearing (3 credits) subject developed combining the HKI-SLAM framework of service leadership with theories of positive youth development. It aims at fostering positive development of students as well as nurturing their related qualities of service leadership [23]. The subject content consists of 12 lectures on topics and qualities related to service leadership and positive youth developments [23]. Specifically, the content centers on leadership competences such as competences in intrapersonal and interpersonal dimensions, strength in character, and disposition of care [24]. Besides, an active and experiential-learning based pedagogy is adopted. Each lecture is delivered through combination of lecturing, group activities (such as group debate, discussion, and drawing), and class activities (such as personal reflection and sharing). With regard to the assessment, multiple assessment methods are adopted including group project, individual term paper, and class participation. The

subject has been implemented at PolyU in different semesters since the 2012/13 academic year as a subject of general education for undergraduate students.

Evaluation is one necessary component for a high-quality educational program. It helps not only assess subject outcomes but also identify possible rooms for further improvement. As such, evidence-based evaluation studies based on different methods were regularly conducted in 2012/13 – 2014/15 academic years as an integral component to monitor the implementation and examine the effectiveness of the SL subject. These methods included quasi-experimental design [25], students' subjective evaluation of the subject content and teaching [26], as well as qualitative evaluation methods such as individual interview and focus group [27]. In general, these evaluation studies revealed positive impacts of SL subject on students as well as students' positive perceptions of the subject [4, 13, 23]. For example, Shek, Yu, and Ma [25] conducted an objective outcome evaluation on a two-credit SL subject (a pilot subject of the three-credit SL subject) offered in the 2012/13 academic year based on quasi-experimental design. They found that students gained significant improvement in several positive youth development indicators such as behavioral and moral competences, and in overall service leadership qualities [25]. A qualitative evaluation study was also conducted on the same subject in the same academic year which illustrated that most students studying the subject used positive descriptors and/or metaphors to illustrate their experiences in the subject [28]. In addition, a subjective outcome evaluation was performed on the SL subject offered in the 2013/14 academic year, which found that most of the students had positive views of the subject content, teaching, and benefits to their development [13].

Although these existing evaluation studies suggest the effectiveness of the subject, they were still inadequate due to the following reasons. First, the existent evaluation studies mostly focused on evaluating the SL subject in its early years of implementation, i.e., from 2012/13 to 2014/15 [12, 25]. Few studies have been conducted to evaluate the subject after 2014/15 academic years. As evaluation is an integral and necessary component in program implementation, evaluation studies should be conducted in each academic year to ensure the smooth implementation and assess effects of the SL subject. Second, most of the existing studies adopted methods of subjective outcome evaluation or qualitative evaluation, few studies adopted pretest-posttest design to examine the subject impact. Although the existing few objective outcome evaluation studies suggest the positive impact of the subject on student positive development and development of service leadership qualities, the findings should be replicated by further evaluation studies based on the same methods.

Against the aforementioned background, this study aimed to examine the effectiveness of the SL subject at PolyU offered in the 2015/16 academic year. The study adopted the method of a single-group pretest-posttest design, which was widely adopted in educational, psychological, clinical, and evaluation fields [29-31]. Although it was criticized as having relatively weak internal validity, the method has its own value. For example, it can be used when there is a high difficulty to carry out control groups due to practical or ethical reasons [32]. In addition, it can also be used when the time span between pre- and post-tests is short to allow less influence of other confounding factors [32]. Considering it is difficult to find randomly assigned control and experimental groups in university settings and the pre- and post-test time span is short (one semester) for this study, the single-group pre- and post-test design was employed to assess the changes of students in positive developmental indicators after studying the SL subject.

OUR STUDY

The participants were 148 undergraduate students taking Service Leadership (SL) subject in either Semester 1 (S1) or Semester 3 (S3) of the 2015/16 academic year at PolyU. Among these students, 52 took SL subject in S1 and 96 took the subject in S3. Around one half (51.9%) of the participants in S1 group were female, while around one third (32.3%) of the participants in S3 group were female. The participants' mean age was 19.9 ± 2.30 years in S1 group and 23.7 ± 4.30 years in S3 group, respectively. Table 1 shows detailed demographic information of the participants.

In S1 and S3 of the 2015/16 academic year, all students taking the SL subject were invited to fill in a paper-and-pencil survey questionnaire at the first and the last lectures of the subject. In S1 group, 91 and 52 questionnaires were collected at pre- and post-tests, respectively. Fifty-two questionnaires were matched successfully. In S3 group, 96 questionnaires were matched successfully between 101 and 96 questionnaires collected respectively at pre- and post-tests.

Instruments

The survey questionnaire consisted of 70 items measuring demographic features of the participants and their performance in three constructs including Chinese Positive Youth Development Scale (CPYDS), Satisfaction with Life Scale (SWLS), and Service Leadership Scale (SLS). Description of the three measures is presented as below.

Chinese Positive Youth Development Scale (CPYDS)

The CPYDS attempts to measure the optimistic growth of Chinese adolescents [33]. It consists of 15 subscales, among which 10 were adopted in the study being indicators of students' positive development. The 10 subscales include "Social Competence" (SC, 3 items), "Emotional Competence" (EC, 3 items), "Cognitive Competence" (CC, 4 items), "Behavioral Competence" (BC, 2 items), "Moral Competence" (MC, 4 items), "Self-Determination" (SD, 3 items), "Clear and Positive Identity" (CPI, 2 items), "Belief in the Future" (BF, 3 items), "Spirituality" (SP, 4 items), and "Resilience" (RE, 3 items). All items are rated on a 6-point Likert scale (1 = "Strongly disagree" to 6 = "Strongly agree"). Three composite scores, i.e., "Cognitive-Behavioral Competencies" (CBC), "Positive Identity" (PI), and "Positive Youth Development Qualities" (PYDQ) are further computed based on the 10 subscales. CBC is composed of "Cognitive Competence," "Behavioral Competence," and "Self-Determination." PI includes "Clear and Positive Identity" and "Belief in the Future." PYDQ contains "Social Competence," "Emotional Competence," "Moral Competence," "Spirituality," and "Resilience." Previous studies reported that CPYDS had favorable psychometric properties [33]. The Cronbach alpha of CPYDS ranged from .90 to .92 in the present study, indicating excellent reliability of the measure.

Satisfaction with Life Scale (SWLS)

SWLS contains five items to assess people's overall judgement of their quality of life [34]. This study used the translated Chinese version of the scale which was revealed to

possess good reliability in previous research studies [35, 36]. All items are rated on a 6-point Likert (1 = “Strongly disagree” to 6 = “Strongly agree”). A higher score shows a higher degree of satisfaction with life. The Cronbach alpha of the scale ranged from .86 to .90 in the present study, which indicates good reliability.

Service Leadership Scale (SLS)

Referring to the HKI-SLAM framework of service leadership, the present study used four indicators to assess service leadership related qualities. The four indicators are “Self-Leadership” (SL, 5 items), “Caring Disposition” (CD, 8 items), “Character Strength” (CS, 15 items), and “Belief and Values of Service Leadership” (BVSL, 6 items) [25]. All items are rated on a 6-point Likert scale (1 = “Strongly disagree” to 6 = “Strongly agree”). Different subscales of service leadership quality all demonstrated good reliability in previous studies [25]. The Cronbach alphas of these subscales ranged from .92 to .94 in the present study, revealing high reliability of the measures.

Data Analyses

First, we analyzed demographic statistics of the participants (see Table 1). Second, we computed reliability test for each scale and subscale of the questionnaire. Third, we performed repeated measures MANOVA to assess the participants’ change in indicators of PYD, satisfaction with life, and qualities of service leadership with time (pre- and post-tests) being independent variable. Specifically, we performed multivariate analyses for the whole sample, S1 group, and S3 group, respectively.

Table 1. Demographic information of the participants

		Semester 1 (S1)		Semester 3 (S3)		Whole Sample	
		N	%	N	%	N	%
Gender	Male	24	46.2%	61	63.5%	85	57.4%
	Female	27	51.9%	31	32.3%	58	39.2%
	Did not indicate	1	1.9%	4	4.2%	5	3.4%
Age	Total	52		96		148	
	Mean	19.90		23.70		22.35	
	SD	2.32		4.27		4.11	

FINDINGS

Table 2 shows results of the repeated measures MANOVA on the overall effects of the SL subject offered in S1 and S3 of the 2015/16 academic year. The multivariate effect of time on the 10 subscales of CPYDS was statistically significant, $F(10, 136) = 4.58, p < .001$, partial eta squared = .25. Besides, multivariate effect of time on the three higher order factors of CPYDS was also found to be significant, $F(3, 143) = 5.19, p < .01$, partial eta squared = .10. Regarding the univariate effects of time, there was significant increase in participants’ scores on SC, EC, CC, BC, and CPI ($p < .01$ for EC, $p < .001$ for CC and CPI, and $p = .001$ for SC and BC), while the participants’ scores on MC, SD, BF, SP, and RE remained stable.

Regarding the univariate effects of time on the three higher order factors, the participants' scores for CBC, PI, and PYDQ all had significant increase ($p < .001$ for CBC, $p < .01$ for PI, $p < .05$ for PYDQ).

Table 2. Results of repeated measures MANOVA for the whole sample (S1+S3)

Variables	Pretest		Posttest		<i>F</i>	η^2
	<i>M</i> (<i>SD</i>)	α (mean) [#]	<i>M</i> (<i>SD</i>)	α (mean) [#]		
Chinese Positive Youth Development					4.58***^^^	.25
• Social Competence (SC)	4.53(.70)	.89(.74)	4.68(.58)	.83(.62)	10.48 ^a	.07
• Emotional Competence (EC)	4.38(.68)	.72(.46)	4.54(.57)	.63(.36)	10.29**	.07
• Cognitive Competence (CC)	4.40(.64)	.80(.50)	4.60(.57)	.76(.45)	16.55***	.10
• Behavioral Competence (BC)	4.34(.65)	.56(.38)	4.54(.62)	.48(.31)	12.21 ^a	.08
• Moral Competence (MC)	4.47(.56)	.35(.16)	4.44(.59)	.44(.21)	0.34	.00
• Self-Determination (SD)	4.47(.74)	.78(.55)	4.54(.62)	.73(.48)	1.96	.01
• Clear and Positive Identity (CPI)	4.10(.83)	.79(.65)	4.36(.76)	.79(.66)	18.27***	.11
• Belief in the Future (BF)	4.66(.77)	.79(.56)	4.74(.71)	.79(.55)	1.62	.01
• Spirituality (SP)	4.36(.75)	.52(.23)	4.43(.70)	.42(.20)	1.44	.01
• Resilience (RE)	4.50(.71)	.77(.52)	4.58(.71)	.84(.64)	2.43	.02
Higher Order Factors					5.19**^^	.10
• Cognitive-Behavioral Competencies (CBC)	4.41(.59)	.87(.44)	4.57(.50)	.84(.37)	14.84***	.09
• Positive Identity (PI)	4.44(.72)	.85(.53)	4.59(.67)	.86(.55)	8.76**	.06
• Positive Youth Development Qualities (PYDQ)	4.44(.50)	.84(.27)	4.52(.48)	.84(.29)	5.49*	.04
Life Satisfaction	3.97(.86)	.87(.58)	4.15(.81)	.88(.61)	8.44**	.06
Service Leadership Scale					2.66*^^	.07
• Self-Leadership (SL)	4.42(.66)	.83(.50)	4.53(.59)	.80(.44)	6.40*	.04
• Caring Disposition (CD)	4.58(.53)	.87(.45)	4.66(.55)	.89(.49)	5.03*	.03
• Character Strengths (CS)	4.42(.45)	.82(.24)	4.51(.47)	.85(.27)	7.82**	.05
• Beliefs and Values of Service Leadership (BVSL)	4.67(.68)	.87(.53)	4.79(0.7)	.92(.67)	3.75 ^b	.03

Mean inter-item correlation.

* $p < .05$; ** $p < .01$; *** $p < .001$; ^a $p = .001$; ^b $p = .055$.

^^^ Adjusted Bonferroni value = .005; ^^ Adjusted Bonferroni value = .017; ^ Adjusted Bonferroni value = .013.

The participants also had significant increase in their score of SWLS, $F(1, 146) = 8.44$, $p < .01$, partial eta squared = .06. Regarding SLS, a multivariate effect of time was also found, $F(4, 144) = 2.66$, $p < .05$, partial eta squared = .07. For univariate effects, three subscales (i.e., SL, CD, and CS) of SLS showed significant increase ($p < .05$ for SL and CD, $p < .01$ for CS) between pre- and post-tests. The fourth subscale, BVSL, also demonstrated marginalized significant increase ($p = .055$).

Table 3. Results of repeated measures MANOVA for the participants in S1

Variables	Pretest		Posttest		<i>F</i>	η^2
	<i>M</i> (<i>SD</i>)	α (mean) [#]	<i>M</i> (<i>SD</i>)	α (mean) [#]		
Chinese Positive Youth Development					1.50 ^{^^^}	.27
• Social Competence (SC)	4.71(.63)	.87(.69)	4.73(.51)	.78(.55)	.06	.00
• Emotional Competence (EC)	4.53(.58)	.62(.35)	4.65(.53)	.67(.41)	2.53	.05
• Cognitive Competence (CC)	4.46(.61)	.81(.51)	4.72(.54)	.75(.43)	11.31***	.18
• Behavioral Competence (BC)	4.43(.62)	.64(.48)	4.62(.53)	.48(.32)	4.32*	.08
• Moral Competence (MC)	4.44(.54)	.25(.12)	4.38(.50)	.25(.13)	.69	.01
• Self-Determination (SD)	4.54(.71)	.83(.62)	4.64(.57)	.80(.58)	1.14	.02
• Clear and Positive Identity (CPI)	4.32(.81)	.89(.80)	4.37(.68)	.77(.63)	.27	.01
• Belief in the Future (BF)	4.73(.75)	.81(.61)	4.73(.65)	.72(.47)	.01	.00
• Spirituality (SP)	4.37(.77)	.60(.31)	4.41(.64)	.19(.12)	.18	.00
• Resilience (RE)	4.54(.66)	.83(.62)	4.58(.69)	.86(.68)	.16	.00
Higher Order Factors					3.18* ^{^^^}	.17
• Cognitive-Behavioral Competencies (CBC)	4.48(.57)	.89(.47)	4.67(.46)	.84(.36)	7.47**	.13
• Positive Identity (PI)	4.57(.72)	.88(.62)	4.58(.61)	.83(.50)	.04	.00
• Positive Youth Development Qualities (PYDQ)	4.50(.47)	.83(.26)	4.53(.42)	.78(.25)	.26	.01
Life Satisfaction	4.13(.79)	.89(.63)	4.24(.76)	.90(.65)	1.15	.02
Service Leadership Scale					1.80 ^{^^}	.13
• Self-Leadership (SL)	4.47(.58)	.86(.54)	4.64(.53)	.84(.51)	5.21*	.09
• Caring Disposition (CD)	4.68(.54)	.89(.50)	4.77(.55)	.92(.60)	2.58	.05
• Character Strengths (CS)	4.45(.42)	.82(.24)	4.55(.42)	.82(.24)	4.00 ^c	.07
• Beliefs and Values of Service Leadership (BVSL)	4.78(.73)	.92(.67)	4.91(.56)	.91(.62)	2.36	.04

[#] Mean inter-item correlation.

* $p < .05$; ** $p < .01$; *** $p < .001$; ^c $p = .05$.

^{^^^} Adjusted Bonferroni value = .005; ^{^^} Adjusted Bonferroni value = .017; ^{^^} Adjusted Bonferroni value = .013.

Effects of the Subject in S1

Repeated measures MANOVA was also conducted separately to the participants in S1 group to identify effects of the SL subject offered in S1. The results are shown in table 3. Regarding the CPYDS, although there was no significant multivariate effect of time on the 10 subscales, the multivariate effect was found on the three higher order factors, $F(3, 48) = 3.18$, $p < .05$, partial eta squared = .17. The results of univariate effect revealed that the participants increased significantly in scores of CC ($p < .001$), BC ($p < .05$), and one higher order factor CBC ($p < .01$), while they did not change significantly in scores of other subscales and higher order factors. There was no significant multivariate effect of time on the participants' score on SWLS and SLS. Univariate effect tests showed that the participants increased significantly in the score of SL ($p < .05$) and CS ($p = .05$), while they remained stable in scores of BVSL.

Table 4. Results of repeated measures MANOVA for the participants in S3

Variables	Pretest		Posttest		<i>F</i>	η^2
	<i>M</i> (<i>SD</i>)	α (mean) [#]	<i>M</i> (<i>SD</i>)	α (mean) [#]		
Chinese Positive Youth Development					3.89***^	.31
• Social Competence (SC)	4.43(.72)	.90(.75)	4.66(.62)	.85(.65)	14.43***	.13
• Emotional Competence (EC)	4.30(.72)	.74(.49)	4.48(.59)	.61(.33)	7.74**	.08
• Cognitive Competence (CC)	4.37(.66)	.80(.50)	4.54(.58)	.76(.45)	7.06**	.07
• Behavioral Competence (BC)	4.29(.66)	.51(.34)	4.51(.66)	.47(.31)	7.87**	.08
• Moral Competence (MC)	4.48(.58)	.41(.19)	4.47(.64)	.52(.26)	0.02	.00
• Self-Determination (SD)	4.43(.76)	.75(.52)	4.49(.63)	.70(.43)	0.88	.01
• Clear and Positive Identity (CPI)	3.98(.83)	.74(.59)	4.36(.81)	.80(.67)	23.59***	.20
• Belief in the Future (BF)	4.63(.78)	.77(.54)	4.74(.75)	.81(.59)	2.37	.03
• Spirituality (SP)	4.36(.74)	.49(.21)	4.44(.73)	.52(.26)	1.47	.02
• Resilience (RE)	4.47(.74)	.74(.49)	4.58(.73)	.83(.63)	2.74	.03
Higher Order Factors					4.10***^	.12
• Cognitive-Behavioral Competencies (CBC)	4.37(.59)	.86(.42)	4.52(.51)	.84(.36)	7.63**	.08
• Positive Identity (PI)	4.37(.72)	.83(.49)	4.59(.71)	.87(.57)	11.69 ^a	.11
• Positive Youth Development Qualities (PYDQ)	4.41(.52)	.85(.27)	4.52(.52)	.86(.32)	6.11*	.06
Life Satisfaction	3.88(.89)	.86(.56)	4.10(.83)	.87(.59)	7.79**	.08
Service Leadership Scale					1.25^^	.05
• Self-Leadership (SL)	4.39(.7)	.83(.49)	4.47(.61)	.78(.41)	2.09	.02
• Caring Disposition (CD)	4.52(.52)	.85(.42)	4.61(.54)	.86(.43)	2.70	.03
• Character Strengths (CS)	4.41(.46)	.82(.24)	4.49(.50)	.56(.29)	4.11*	.04
• Beliefs and Values of Service Leadership (BVSL)	4.61(.64)	.83(.46)	4.72(.76)	.93(.68)	1.81	.02

Mean inter-item correlation.

* $p < .05$; ** $p < .01$; *** $p < .001$; ^a $p = .001$.

^ Adjusted Bonferroni value = .005; ^ Adjusted Bonferroni value = .017; ^^ Adjusted Bonferroni value = .013.

Effects of the Subject in S3

A significant multivariate effect of time on the 10 subscales of CPYDS was found based on repeated measures MANOVA, $F(10, 85) = 3.89$, $p < .001$, partial eta squared = .31, and on the three higher-order factors of CPYDS, $F(3, 92) = 4.10$, $p < .01$, partial eta squared = .12. Univariate effect tests showed that the participants increased significantly in scores of SC, EC, CC, BC, and CPI ($p < .001$ for SC and CPI, and $p < .01$ for EC, CC, and BC) and in scores of all three higher-order factors ($p < .01$ for CBC, $p = .001$ for PI, and $p < .05$ for PYDQ). The participants' score of SWLS was also significantly increased between pre- and post-tests, $F(1, 94) = 7.79$, $p < .01$, partial eta squared = .08. Although no significant multivariate effect of time was found on SLS, univariate effect tests showed that the participants' score on CD ($p = .046$) has increased significantly between pre- and post-tests.

DISCUSSION

This study assessed the impact of SL subject offered in two semesters of the 2015/16 academic year at PolyU through a single group pretest-posttest design. Students' improvements in a set of positive youth developmental indicators, satisfaction with life, and qualities related to service leadership were assessed. In general, the results revealed that the students gained significant improvement in positive youth development in general and some of its specific indicators, their satisfaction with life, and qualities related to service leadership after taking the subject. This indicates that the subject offered in the 2015/16 academic year was effective in fostering students' positive development, wellbeing, and development of qualities of service leadership.

The results are consistent with the findings of existing evaluative studies on the subject offered in previous academic years. For example, Shek, Yu, and Ma [25] evaluated a 2-credit SL subject (a piloted version of the 3-credit SL subject at PolyU) offered in early years based on objective outcome evaluation method. They found that students had positive changes in general positive youth development and some of its specific indicators, as well as in overall service leadership qualities. In another study objectively evaluating an intensive (3.5-day in length) SL subject offered to students in mainland China, it was found that the subject promoted students' development in most of the constructs indicating youth's positive development, satisfaction with life, and qualities related to service leadership [37]. While these previous studies provided evidence about the effectiveness of SL subject, they were either based on a piloted version or an adapted version for students outside of Hong Kong. These findings added strong evidence to the fact that SL subject is an effective program for promoting university students' positive, holistic, and service leadership development. It also suggests the quality implementation of the subject in different academic years.

Several specific observations deserve attention. First, univariate effects found that the participants gained significant improvement in most of the measured competences including social, emotional, cognitive, and behavioral competences, as well as their positive identity. This indicates that the subject is particularly useful in promoting students' development in these aspects. Social competence refers to interpersonal and social skills. Emotional competence refers to one's awareness of and abilities to manage emotions of oneself, and to understand and respond to others' emotions [38]. Cognitive competence means an individual's cognitive abilities such as logical and critical thinking. Behavioral competence refers to the ability of utilizing different strategies to shape socially desirable behaviors in social interactions and to make appropriate behavioral choice [39]. These different aspects of competences are vital to student development and are related to a set of positive developmental outcomes such as self-esteem [40], positive coping [41], and increased psychological wellbeing [42]. They were also negatively associated with a set of youth developmental problems such as internalizing and externalizing behaviors [43], depression [40] and substance abuse [44]. These competences were also important qualities for effective leadership development as shown by literature [45, 46]. Therefore, students' improvement in these positive development indicators indicates that SL subject is particularly useful and effective in promoting students' multi-facet and holistic competences.

Second, results indicate that SL subject is also effective in promoting students' subjective wellbeing indicated by life satisfaction. Life satisfaction means people's global evaluation

and perception of their quality of life as a whole [47]. It is regarded as an important psychological strength based on positive psychology [48]. Adolescents and university students with higher life satisfaction would have better psychosocial functioning [49], higher self-esteem [50], and better self-perceived health status [51]. They were also less likely to develop problem behaviors [52] and have reduced level of anxiety and depression [53]. As research revealed that adolescents in Hong Kong perceived lower-level satisfaction with life compared with US adolescents [54], it is necessary to promote adolescents and university students' life satisfaction to build up their strengths. Based on this, the results of the present study can help to show that SL subject could be one important mean or intervention strategy to help to elevate students' life satisfaction.

Third, students' service leadership qualities were promoted through studying the SL subject. This is important since that one of the major purposes of the subject is to foster students' development in important qualities related to service leadership including generic competences, morality, and disposition of care according to positive youth development theory and framework of service leadership put forward by HKI-SLAM [55]. As service leadership is an important quality that is highly needed for manpower in Hong Kong's economic and social development, the findings indicate that the SL subject can promote the required key service leadership qualities needed by the society. It also indicates that leadership knowledge, attitudes, and skills can be taught and nurtured through effective educational programs.

With regard to the result that students did not have change in some constructs such as "Moral Competence," "Self-Determination," "Spirituality," and "Resilience," this might be explained by several reasons. First, the effect of educational program on some developmental indicators such as morality and spirituality might take longer time to show. Second, the development of some qualities might also need more practice, life experience, and self-reflection in later life. It is hard to show significant improvement of students in these indicators in just one semester time. Third, although a lot of interactive, reflective, and experiential learning activities are integrated in the SL subject, the teaching of the subject still needs to be continuously examined and improved to further enhance the effectiveness of the subject in promoting these developmental indicators.

Moreover, the separated analyses on students' changes in S1 and S3 groups showed that students in S3 group gained more positive improvement than students in S1 group. This might be due to the reason that the intensive-teaching-and-learning design might be more effective compared to the normal design of the subject as students may have more intensive time to be engaged in and reflect on their learning. This is also supported by the results of previous studies that the intensive SL subject offered in mainland China had much positive impact on students' development of all the indicators [37]. Further studies need to be conducted to understand more about this issue. Of course, this is important to further examine the sustainability of the positive effects observed in the study.

This study had several limitations. First, although pre- and post-test design can help identify students' changes before and after studying the service leadership subject, students' improvement might also be influenced by their naturally maturing factors. Therefore, future studies should be conducted by adding control groups to better determine students' changes under the impact of SL subject. Second, as mentioned earlier, development of some indicators might need time, practice, and integration of experience; therefore, future studies might follow up with the students for a period of time after taking the subject to identify long-term

effects of the subject on student development. Third, as objective outcome evaluation method can only identify effectiveness of the subject but not the subjective viewpoints and feedbacks of different stakeholders to the subject, future studies may adopt both objective and subjective outcome evaluation methods to form a more comprehensive understanding of the effects of the SL subject and give more valuable suggestions to its further improvement. Fourth, to evaluate the effectiveness of the subject in a more vigorous approach, scholars developed validated measures to assess students' knowledge about service leadership, their attitudes towards service leadership, as well as their behaviors related to service leadership [56-58]. It is valuable and important to utilize these measures in the objective outcome evaluation to assess students' changes in knowledge, attitude, and behavior of service leadership to provide more evidence on effectiveness of the subject in future. Last but not the least, as previous research suggests an association between positive youth development and life satisfaction [52], it is worth to further examine the association between students' change in life satisfaction and PYD across studying the subject to further understanding of the impact of the subject.

Despite of the above limitations, this study provides significant evidence about the effectiveness of service leadership subject at PolyU, which is vital for continuous improvement and sustainable development of the subject.

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Chapter 125

**PROMOTION OF WELL-BEING AND LEADERSHIP
QUALITIES AMONG UNIVERSITY STUDENTS
AFTER TAKING A CREDIT-BEARING SERVICE
LEADERSHIP SUBJECT**

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ABSTRACT

With the increasing development of service economies, service leadership (SL) concepts and educational programs have been advocated in Hong Kong. To assess the impact of SL education initiative, the current chapter evaluated changes in SL attributes and well-being in 88 students after completing a credit-bearing General Education subject entitled “Service Leadership” at The Hong Kong Polytechnic University in 2017/18 academic year. Through a one-group pretest-posttest methodology, the research showed that students had positive changes in SL qualities indicated by “self-leadership,” “character strength,” “caring disposition,” and “SL beliefs” as well as personal well-being indexed by “life satisfaction” and “positive youth development.” This research also found that changes in SL qualities and well-being were positively correlated with each other. Our findings suggest that it is promising to nurture SL attributes and foster well-being among university students through formal leadership curriculum.

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INTRODUCTION

The world has stepped into a post-industrial era featured with the rapid development of new technologies and strong emphasis on knowledge, service, and human capital. Service sectors have occupied a much bigger share than manufacturing industries in some developed regions, such as the United States, the United Kingdom, and Hong Kong. For instance, in Hong Kong, the value added by service sectors in GPD (“gross domestic product”) has been over 92.0% since 2015 [1]. Developing countries, such as China and India, have also been paying more attention in service-sector-related fields, such as finance, in order to survive and thrive in the increasingly fierce global competition [2]. In mainland China, the service sector contributed to 52.2% of the GDP in 2018, compared to 41.2% of the GDP in 2004 [3]. The industrial era witnessed machines replacing human laboring which promoted productivity and efficiency. The post-industrial era, however, has a higher level of technological support as well as human resources contribution to service, creativity and other related fields, such as trades, finance, and technologies [1]. Obviously, one should ask what the desired leadership qualities are under service economies which emphasize human capital, particularly soft skills of the workers.

Characterized by empowerment, innovation, and creativity, the service economy calls for organizational changes and re-definition of youth leadership [4]. Therefore, holistic leadership qualities have been much stressed across the globe in the 21st century, as the society needs the younger generations to be equipped with integrative competencies including not only “hard skills” (e.g., professional knowledge), but also “soft skills,” such as “creativity and innovation,” “communication and collaboration,” “social and cultural skills,” and “critical thinking” [5]. In fact, employers now require university graduates to have these “soft skills” as one of the entry-level requirements [6]. In addition, some scholars proposed the “Service Leadership Theory” which specifies that effective “service leaders” in the contemporary service era need to possess three “Cs,” which denote “Competence,” “Character,” and “Care” [4]. This perspective of whole-person development should be kept in mind in providing leadership education for university students. However, such leadership training is far from sufficient in the context of higher education and to some extent, university graduates have failed to meet the requirements of being an effective “service leader.” The gap between the society’s demanding needs for university students’ service leadership (SL) qualities and their actual performance awaits to be urgently bridged.

Shouldering social responsibilities is one of the missions and visions of higher education institutes. Through education and research, making contributions to the society has been a tradition of universities which can be traced back to the establishment of University of Oxford and University of Cambridge, two of the oldest universities in the world. After hundreds of years, the mission and vision of contributing to “society through the pursuit of education, learning and research at the highest international levels of excellence” [7] and “benefit society on a local, regional, national and global scale” [8] are still included in the core values of the two universities for future development. In today’s rapidly transitioning world of the service economy, higher education plays an even more active role in sustaining societal development by continuingly fostering research and raising up future service leaders. For instance, Dugan and Komives [9] stated that “the education and development of students as leaders has long served as a central purpose for institutions of higher education” and leadership is “a critical

college outcome” (p. 8). Unfortunately, there are increasing voices criticizing that contemporary universities focus too much on ranking and student achievements without paying due attention to the holistic development of students.

To nurture youth leadership, both “hard skills” and “soft skills” need to be stressed, especially “soft skills” that are hugely emphasized in the service era but are somehow overlooked in the contemporary leadership education. Traditionally, when talking about leadership, people would think of leaders “doing things right” and leadership training accordingly focused mainly on hard skills and elitism, such as management skills and decision-making skills. As of today, comprehensive and effective leadership education proposes to train leadership in “knowing” (leadership knowledge), “being” (mindset, service orientation, character, and care) and “doing” (leadership skills) [4]. Such leadership education not only teaches young people how to “do things right,” but also to “do the right things.” This mode of leadership education has been proved to be effective in nurturing youth leaders in previous research. Students obtained significant growth in civic responsibility, personal and societal values, and holistic development [9-11]. A notable example is SL education guided by the “Service Leadership Theory” in Hong Kong [12]. The implementation of SL education highlighted “the importance of caring disposition and moral character in addition to competencies” (p. 97), and in practice efficiently deepened participating university students’ knowledge of SL and fostered their SL qualities [13].

As the name suggests, the concept of SL stresses service and leadership and refers to “ethically satisfying the needs of self, others, groups, communities, systems, and environments” [14]. In contrast to traditional leadership thoughts that are pertinent to elite leadership and leading others, SL notions manifest in stressing service orientation and equally emphasizing the development of competences, ethics and morality, and caring disposition (i.e., the 3Cs) [4, 12]. In addition, the SL proposition believes in young people’s strengths and potentials, thus it holds the belief that “every day, everywhere, everyone can take a leading role” [15]. To apply these SL concepts into practice, the “Hong Kong Institute of Service Leadership and Management” (HKI-SLAM) developed SL curriculum materials and initiated a SL education schema in eight government-funded universities in Hong Kong in 2012.

As one of the participating universities in the scheme, The Hong Kong Polytechnic University (hereafter PolyU) provided students with both credit-bearing General Education subjects (i.e., “Service Leadership” subject) and non-credit-bearing SL training programs since 2012/13 academic year. The SL education at PolyU aims to nurture leaders who possess leadership competencies, demonstrate concern, empathy, and sincerity to others, listen to and care for others’ needs, and show positive ethical traits. These intentions echo the core values of SL propositions that “leadership is service” and “everyone can be a leader” by serving [4]. To ensure the effectiveness of the SL education, course curriculum was rigorously developed and reviewed by the research team and instructors were well-trained to better deliver course materials. Specifically, the core concept of the course is the beliefs of SL, the importance of generic competencies, morality and caring disposition, and application of SL concepts in daily life and career development [16]. Furthermore, multiple teaching methods are used in the course to better engage students in active learning, such as the experiential teaching and learning pedagogy, reflective and collaborative learning. This provides more opportunities for students to be engaged in experiential learning emphasizing the importance of reflective learning, collaborative learning, and self-leadership. Previous research has demonstrated that

these teaching and learning approaches can effectively promote student engagement and deep learning [17, 18].

Theoretically, SL is an innovative concept. Practically, SL education has been well received by students and proved to be effective and fruitful in promoting student development. After years of implementation in Hong Kong, both qualitative and quantitative evaluation studies revealed positive perceptions held by teachers and students toward the implementation. They claimed significant positive changes among participating students in terms of leadership development and healthy functioning [19, 20]. Comparisons between student conditions before and after receiving the education revealed positive changes happened among the participants. For example, Shek, Yu and Ma [21] used a pre- and post-test method to analyze the effectiveness of the credit-bearing “Service Leadership” subject offered to students in 2012/13 academic year at PolyU. They found that the students who participated in the course displayed higher SL qualities, such as ethical attributes, after the completion of the course.

In addition, Shek and Lin [22] did pretest, immediate posttest, and follow-up test to examine the effectiveness of a 12-day intensive “Service Leadership” course as an academic component of a leadership training program jointly launched by PolyU and a university in Mainland China. The results suggested that the course effectively promoted students’ qualities and beliefs of SL as well as well-being. Similar positive findings were reported in Shek, Lin, Leung, and Zhu’s [22] study which analyzed student changes after taking another intensive SL course. Their findings further demonstrated the sustainable positive effects of the course as the authors put “students scored much higher on all indicators in the follow-up test than in the pre-test” (p. 69). Because of the positive impact, SL initiatives have won several teaching awards. In 2016, the subject entitled “Service Leadership” won the “Bronze Award (Ethical Leadership)” and the subject entitled “Service Leadership through Serving Children and Families with Special Needs” won the “Bronze Award (Social Enterprise)” in the “QS Reimagine Education Awards 2016” which was regarded as the “Oscar in Education.”

Despite the positive evaluation findings in previous studies, it is also necessary to further examine the beneficial influences of SL education in a continuous manner. Thus, the first research purpose of the current study is to replicate previous positive evaluation findings and unveil the effectiveness of the “Service Leadership” subject delivered in 2017/18 year at PolyU. To do it, this study analyzed student changes after they completed the course in the aspects of SL qualities and values, as well as well-being. In the realm of science, replication is always an important benchmark to evaluate stability of the findings. Besides, although previous evidence has demonstrated that SL education can foster student well-being, the underlying mechanisms contributing to such benefits remain unclear. Existing evidence showed that individuals’ well-being was linked to their leadership qualities [e.g., 23, 24]. Theoretically, it makes sense to expect that student attainment in SL qualities would promote their well-being. One possible explanation is that students’ positive learning experience and their personal development after learning enables students to have more positive feelings toward themselves and gain a sense of accomplishment and well-functioning [25]. Testing this possibility constitutes the second purpose of this study. Specifically, we explored whether student development of SL attributes and improvement in well-being are related to each other.

To achieve the above-mentioned two research purposes, this study utilized a “one-group pretest-posttest” methodology (also called “single-group pretest-posttest”). Although this methodology has some limitations because of the lack of a control group for comparison, Thyer [26] commented that it is a valuable strategy in the field of human services as a pre-

experimental design. To have a control group in an evaluation study helps exclude the effects of confounding factors such as maturation through comparing the experimental group and the control group. However, in practice, especially in the education field, it is not always applicable to have a control group concerning costs and sometimes ethical factors as well as its demanding requirements for administrative manpower and advanced research training in teachers. This is why McCall et al. [27] once asserted that conducting experimental evaluation research is “extremely difficult and often impossible” (p. 982). In this regard, one-group pretest-posttest design is a practical and cost-effective way to investigate outcomes of educational programs [28].

This evaluation methodology has been widely used in social science research fields, such as therapeutic service and education. For example, Williams, Poulsen, Chaguturu, Tobia, & Palmeri [29] used the one-group pretest-posttest methodology to evaluate an online training course which taught psychiatry residents about TUD (i.e., tobacco use disorder). Another example of the usage of this design is a research on the effectiveness of a training program called “Pakistani Educators’ Instructional Leadership Institute (PEILI),” which attempted to help educators in Pakistan acquire new professional knowledge and skills and build new supporting networks [30]. In our study, participating students filled out the same questionnaire before the first lecture of the “Service Leadership” subject (i.e., pretest) and after the last lecture (i.e., posttest). By comparing and analyzing the data collected from the pretest and posttest, the changes happened to the students after taking the course and the effectiveness of the SL education could be revealed.

OUR STUDY

Data used in this study were collected from students enrolled in the “Service Leadership” subject that was offered at PolyU in the first semester of the academic year of 2017/18. At the beginning of the first lecture in the first week, students were invited to fill out the pretest questionnaire forms. Upon the completion of the last lecture in the thirteenth week, students responded to the same questionnaire forms as the posttest. In both occasions of the test, participants were well informed of the data collection principles, such as the principle of anonymity and the usage of data provided by them for educational and research purpose without revealing any personal information in the reports or articles. Each participating student signed a written consent form before doing the pretest. Enough time was given to the participants during both pretest and posttest in filling out the questionnaire in a paper-and-pencil manner.

A total of 88 students completed both pretest and posttest. There were 33 (37.9%) male students and 54 (62.1%) female students and one participant did not report gender information. The average age of the participants was 20.6 ± 2.53 years old. Specifically, most participants were at the early twenties and aged between 19 and 22 years old (e.g., 6 participants aged below 18 years old while 4 aged above 23 years old). More details are depicted in Table 1.

Table 1. Demographic information of participants ($n = 88$)

Demographic variables	Frequency	Valid Percent (%)
Gender		
Male	33	37.9
Female	54	62.1
Age		
18 or below	6	6.8
19-year-old	17	19.3
20-year-old	29	33.0
21-year-old	21	23.9
22-year-old	11	12.5
23 or above	4	4.4
Mean age = 20.6 ± 2.53		

Instruments

The questionnaire used in the study included two outcome indicators: “well-being” and “SL qualities and beliefs,” Subjective and psychological well-being were assessed as two forms of well-being. To index subjective well-being, we measured life satisfaction which is pertinent to an individual’s cognitive appraisal of his or her overall life qualities. Positive youth development (PYD) was measured as an index of psychological well-being reflecting young people’s adequate and healthy functioning [31]. SL qualities were assessed by three subscales including “self-leadership,” “character strength,” and “caring disposition,” which were considered important for leadership effectiveness in the service era [21]. Values and beliefs held by students toward SL were also measured through a subscale. These four subscales related to qualities and beliefs of SL have been used in previous evaluation studies and showed good reliability [21, 22].

Assessment of Life Satisfaction (LS)

LS was measured by “Satisfaction with Life Scale” (SWLS) on a 6-point scale (“1” = “strongly disagree,” “6” = “strongly agree”) with a higher score representing higher LS. SWLS was designed to measure individuals’ perceptions of the qualities of their lives from a subjective point of view [32]. This scale has been widely used in youth development studies in Chinese contexts with a translated and validated Chinese version [22, 33]. The scale included five items, such as “I am satisfied with my life” and “so far I have got the important thing I want in life.” The level of LS was operationalized as the mean score of the five items. The Cronbach’s alpha coefficients of scale in the present study were .87 in both the pretest and posttest, indicating that the scale had good internal consistency (see Table 2).

Assessment of PYD

PYD attributes were measured by the “Chinese Positive Youth Development Scale” (CPYDS) on a 6-point scale (“1” = “strongly disagree,” “6” = “strongly agree”). CPYDS was developed as an objective measurement tool on “growth, cultivation, and nurturance of developmental assets, abilities, and potentials” in Chinese youths by taking into account both

PYD studies conducted in the Western context and features of Chinese culture [34].

Table 2. Outcome changes between pre-test and post-test (N = 88)

	Pre-test		Post-test		<i>F</i>	η^2_p
	<i>Mean (SD)</i>	α	<i>Mean (SD)</i>	α		
Higher-order PYD factors					3.43 [△]	.108
Cognitive-behavioral competencies	4.48 (.49)	.80	4.63 (.51)	.83	7.39 ^{**}	.078
Positive identity	4.41 (.65)	.79	4.59(.61)	.79	8.57 ^{**}	.090
General PYD qualities	4.55 (.50)	.87	4.63 (.46)	.83	4.17 [*]	.046
Total PYD	4.50 (.46)	.92	4.63 (.45)	.91	9.17 ^{**}	.095
Life satisfaction	4.03 (.85)	.87	4.18 (.81)	.87	3.70 [†]	.041
Service leadership qualities and beliefs					3.24 [△]	.134
Self-leadership	4.48 (.54)	.72	4.60 (.57)	.76	4.75 [*]	.052
Character strength	4.50 (.47)	.83	4.58 (.45)	.83	4.73 [*]	.052
Caring disposition	4.75 (.51)	.86	4.86 (.51)	.87	5.67 [*]	.061
Beliefs of service leadership	4.72 (.64)	.86	4.98 (.62)	.91	10.73 ^{**}	.110

Note. [†] $p < .10$; ^{*} $p < .05$; ^{**} $p < .01$; ^{***} $p < .001$. PYD = positive youth development. [△] Adjusted Bonferroni value = .013.

In this study, concerning the “Service Leadership” subject features, 10 out of 15 subscales included in the original CPYDS was utilized to measure ten PYD attributes (e.g., “cognitive competence,” “behavioral competence,” “clear and positive identity” and “moral competence,” etc.) [13]. Based on these subscales (thirty-one items), three higher-order factors including “cognitive-behavioral competencies” (CBC), “positive identity” (PI), and “general PYD qualities” (GPYD) were calculated to index PYD attributes. Specifically, CBC was comprised of three subscales: “cognitive competence” (4 items, e.g., “I know how to see things from different angles” and “I know how to find the causes of and solutions to a problem,” etc.), “behavioral competence” (2 items, e.g., “I can face criticisms with an open mind” and “I can express views that are different from others”), and “self-determination” (3 items, e.g., “I am capable of making wise choices” and “I believe things that will happen in my life are mostly determined by myself”). PI consisted of two subscales including “clear and positive identity” (2 items, e.g., “I am a person with self-confidence” and “I believe I have the qualities and abilities of a leader”) and “belief in the future” (3 items, e.g., “I have confidence to solve my future problems” and “I have confidence that I will be a useful person after I graduate”). GPYD included five subscales: “social competence” (3 items, e.g., “I know how to communicate with others” and “I understand the rules and expectations when interacting with others”), “emotional competence,” (3 items, e.g., “when I am unhappy, I can appropriately express my emotions” and “when I have a conflict with others, I can usually manage my emotions”), “moral competence” (4 items, e.g., “I have high moral standards about my behaviors” and “I have a habit of self-reflection”), “spirituality” (4 items, e.g., “I have found my purpose in life” and “I believe spiritual riches are more important than material prosperity”), and “resilience” (3 items, e.g., “when I face difficulties, I do not give up easily” and “my belief is that even though tomorrow becomes worse, I will still live in a good manner”). A total PYD score was also computed according to each participant’s responses to the ten subscales. Details of reliabilities of the higher-order PYD factors in pretest and posttest are presented in Table 2. This scale has been used in many studies and there are findings showing that the scale and the related subscales are valid and reliable.

Assessment of SL Qualities and Beliefs

As aforementioned, three subscales with 28 items in total were adopted to measure essential qualities and attributes related to SL including “self-leadership,” “character strength,” and “caring disposition.” The “self-leadership” subscale included 5 items with sample items as “I have a good planning on my life” and “I control my own behavior to avoid stepping out of line.” The subscale of “character strength” had 15 items and samples items were “I do not hesitate to fight against what I think wrong despite opposition” and “most of the time, I can keep my mind peaceful in face of gains or losses.” The third subscale, “caring disposition,” consisted of 8 items with two sample items as “I know how to appreciate others, even those who are completely different from me” and “I pay attention to others when they are talking to me.” Beliefs about SL were assessed by 6 items pertinent to one’s identification with SL notions. Sample items included “leadership effectiveness is determined by situational task competencies, character strength and caring ability” and “a successful leader should try his/her best to improve his/her competencies and satisfy others’ needs.” All the 34 items were rated on a 6-point scale (“1” = “strongly disagree,” “6” = “strongly agree”). In our study, the four subscales also showed good internal consistency as suggested by the Cronbach’s alpha coefficients ranging from .72 to .91 in the pretest and posttest (see Table 2).

Data Analysis

First, the internal consistency of the measurement tools used in the pretest and posttest was examined through a series of reliability test. Second, to compare participating students’ posttest scores with corresponding pretest scores on the outcome indicators, we performed three repeated-measures multivariate GLM (i.e., “general linear model”) analyses with three types of outcome measure (i.e., LS, PYD, and SL qualities and beliefs) as the DVs (“dependent variables”) and the time (i.e., pretest vs. posttest) as the IVs (“independent variables”). The Bonferroni adjustment procedure was used to reduce Type I error in detecting omnibus time effect. Following multivariate analyses, univariate analyses were performed for each indicator of PYD or SL qualities and beliefs. SPSS 25.0 was used to conduct reliability tests and GLM analyses.

Finally, AMOS 25.0 was used to do two cross-lagged path analyses to investigate associations between changes in well-being indicators and SL qualities. Figure 1 shows the cross-lagged models. Each model involved two scores (pretest and posttest) of two variables: a well-being indicator (LS or PYD total score) and SL qualities indicated by a composite score of self-leadership, character strength, caring disposition and beliefs of SL. In each model, there were six paths representing associations among different variables. Taking the cross-lagged model including SL qualities and PYD total score as an example, the six paths were:

- “Concurrent relationship” (CR): the correlational relationship between two pretest scores;
- “Temporal effect 1” (TE1): SL qualities pretest score predicted its posttest score;

- “Temporal effect 2” (TE2): PYD pretest score predicted its posttest score;
- “Cross-lagged effect 1” (CLE1): the effect of pretest score of SL qualities on PYD total score at posttest;
- “Cross-lagged effect 2” (CLE2): the effect of PYD total score at pretest on the posttest score of SL qualities;
- “Correlated change” (CC): the correlation between the residuals of SL qualities and PYD total score at posttest.

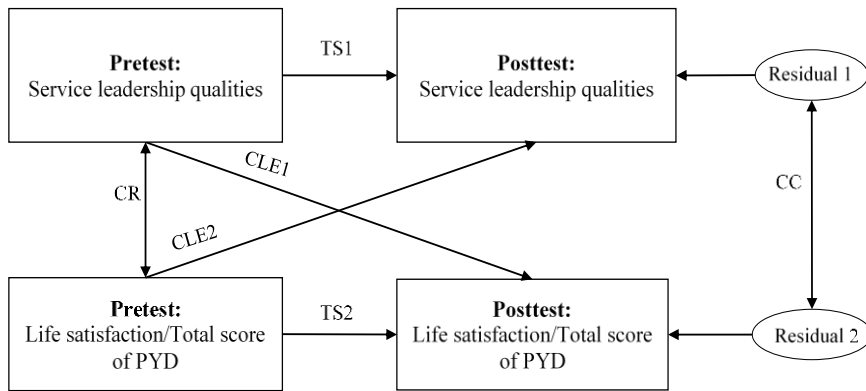


Figure 1. Cross-lagged models among service leadership qualities and well-being indicators in pretest and posttest. PYD: Positive youth development; CR: Concurrent relationship; TS1: Temporal stability of service leadership qualities; TS2: Temporal stability of well-being; CLE1: Cross-lagged effect of service leadership qualities on well-being; CLE2: Cross-lagged effect of well-being on service leadership qualities; CC: Correlated change.

As shown in Figure 1, there was an association between any two variables in one model. Thus, both cross-lagged models were saturated (i.e., $df = 0$ or Fitness statistics were perfect). Furthermore, after CR, TE1, TE2, CLE1, and CLE2 were statistically controlled, CC represented a valid estimated correlation between within-individual changes from pretest to posttest regarding well-being indicator and SL qualities measure [25, 35]. This analysis method has been widely used in personality studies to explore the common mechanism underlying the development of two different personality traits [e.g., 36]. In the present study, analyses of CC helped to inform whether well-being and SL qualities increased together. We expected that there would be significantly correlated changes between SL attributes and well-being.

FINDINGS

As shown in Table 2, there was a significant omnibus time effect for PYD attributes ($F(3, 85) = 3.43, p < .05, \eta^2_p = .108$). Thus, it can be concluded that students gained significant development in their PYD attributes. Follow-up univariate analyses showed that there was also a significant improvement in each higher-order PYD factor (“cognitive-behavioral competencies”: $F(1, 87) = 7.39, p < .01, \eta^2_p = .078$; “positive identity”: $F(1, 87) = 8.57, p < .01, \eta^2_p = .090$; “general PYD qualities”: $F(1, 87) = 4.17, p < .05, \eta^2_p = .046$; “total PYD

score”: $F(1, 87) = 9.17, p < .01, \eta^2_p = .095$). For LS, a marginally significant improvement was observed ($F(1, 87) = 3.70, p = .058, \eta^2_p = .041$). These findings suggested an increasing trend in students’ both psychological and subjective well-being after completing the “Service Leadership” subject which are consistent with the original prediction of the study.

Table 3. Standardized path coefficients of cross-lagged analyses ($N = 88$)

Variables in the cross-lagged analyses	Standardized path coefficients (β)					
	CC	CR	TS1	TS2	CLE1	CLE2
Service leadership qualities and life satisfaction	.40**	.30***	.61***	.59***	.08	.05
Service leadership qualities and total positive youth development score	.75***	.76***	.54***	.58***	.08	.11

Note. CC = Correlated change; CR = Concurrent relationship; TS1 = Temporal stability of service leadership qualities; TS2 = Temporal stability of well-being; CLE1 = Cross-lagged effect of service leadership qualities on well-being; CLE2 = Cross-lagged effect of well-being on service leadership qualities. * $p < .05$; ** $p < .01$; *** $p < .001$.

Similar to the results of PYD factors, the omnibus time effect for SL qualities was also significant ($F(3, 85) = 3.24, p < .05, \eta^2_p = .134$). A series of univariate analyses were also performed for each indicator and significant positive changes were identified for all indicators (“self-leadership”: $F(1, 87) = 4.75, p < .05, \eta^2_p = .052$; “character strength”: $F(1, 87) = 4.73, p < .05, \eta^2_p = .052$; “caring disposition”: $F(1, 87) = 5.67, p < .05, \eta^2_p = .061$; ‘beliefs of SL’: $F(1, 87) = 10.73, p < .01, \eta^2_p = .110$). Overall speaking, SL qualities and beliefs among students improved significantly after they completed the subject. Again, these findings are consistent with the original expectations.

Correlated Changes in Student Well-Being and SL Qualities

As aforementioned, we used cross-lagged models to detect the relationship between changes in well-being and SL qualities. The results are depicted in Table 3. After statistically controlled temporal stability of both well-being and SL attributes as well as cross-lagged effects between each other, significant correlated changes were identified in both models (SL qualities and LS, $\beta = .40, p < .01$; SL qualities and total PYD, $\beta = .75, p < .001$). In general, the improvement of university students’ well-being in terms of LS and PYD attributes was significantly associated with their positive changes in SL qualities.

DISCUSSION

The SL education initiative was launched in Hong Kong to sustain its competitive advantage in the service era through nurturing SL qualities and promoting well-being among university students. By using the one-group pretest-posttest quantitative evaluation method and collecting self-reported data from participating students, this study evaluated the effectiveness of the SL education based on the “Service Leadership” subject offered in one university in Hong Kong.

The present findings are encouraging as students generally achieved positive changes in both SL qualities and well-being after completing the subject. Specifically, in comparison to the baseline conditions in the pretest, students demonstrated better “cognitive-behavioral competencies,” “positive identity,” “general PYD qualities,” and “total PYD qualities” in the posttest, which reflected improved psychological well-being. In addition, there was also an increasing trend in student life satisfaction, despite that the improvement was marginally significant. Furthermore, students also gained significant improvement in their SL attributes in terms of “self-leadership,” “character strength,” “caring disposition,” and “SL beliefs.” These findings support our expectations. They are also in line with previous studies and provide support for the effectiveness of the subject in enhancing students’ SL qualities and well-being levels [16].

Regarding the question of why the “Service Leadership” subject influenced participants positively, not only in SL qualities but also in well-being, there are several points to be noted. First, the subject was created and designed based on the “Service Leadership Theory” which endorses the holistic development of university students in terms of a wide spectrum of competencies (e.g., emotional competence, spirituality, and relationship building, etc.) as well as moral character and caring for others. In addition, some propositions of this theoretical basis echo PYD theory that focuses on youths’ potentials and what they are capable of instead of the problems they have [20]. For example, the core belief of “everyone is (can be) a leader” reflects the PYD notion that “young people are resources to be developed.” In this regard, the subject teaching materials accordingly incorporated the perspective of positive and whole-person development. While being taught with knowledge or theories, students’ abilities and potentials were fully admitted so that they were encouraged to recognize their own strengths and make more growth. In the literature of PYD, the cardinal belief is that young people have strengths and potentials. The core issue is how to nurture their competences and unleash their potentials. In short, the present findings are consistent with the predictions of the positive youth development literature.

Second, the subject adopted various teaching modes based on teaching and learning purposes. These methods included lecture, group project and in-class activities (e.g., role play and drawing, etc.) which enhanced teacher-student, as well as student-student interactions. The mixed-mode teaching style also helped to create a better teaching and learning atmosphere which is conducive to students’ proactive involvement in learning. This conjecture is consistent with Larson’s [37] argument that youth activities can be useful in enhancing young people’s concentration and initiative in fostering their positive development. Evidence from previous studies also suggested that the mixed-mode teaching style can improve teaching effectiveness and students’ learning achievement [22]. In addition, in the “Service Leadership” subject, students also had plenty of opportunities to do individual or collaborative reflection excises for obtaining a better self-understanding, which is of great significance in personal and professional development [38, 39]. In the era of the Internet, the learning mode of young people has changed from passively listening to lectures to actively learning via collaboration with peers and teachers. Hence, the study underscores the importance of utilizing more active mode of teaching and learning for students. In future, studies should be conducted to evaluate how different modes of teaching and learning might influence the achievement of learning outcomes of the subject.

The present positive findings provide additional support for Lin and Shek’s [25] argument that SL qualities can be developed and well-being can be nurtured through proper

curriculum-based leadership education or training. This is different from conventional views of leadership that only those elite persons who occupy relatively higher positions can take a leading role [40]. Instead, curriculum-based leadership development approach is able to reach and benefit a general population of university students rather than only serving a small group of students (e.g., a certain kind of elite students). Although the “Service Leadership” subject under investigation in the present study was initially launched in Hong Kong where the service economies are overwhelming predominant, the application of formal curriculum-based leadership education is certainly not limited to Hong Kong or service-dominant economies. For example, SL education and training have also been implemented in mainland China and Cambodia, where the service economies are less developed compared with Hong Kong. In fact, empirical studies also showed that the SL programs in these two places also achieved a big success and effectively promoted participating students’ leadership development and well-being [20, 22].

Empirically, students’ positive changes in SL attributes were significantly related to their improvement in life satisfaction and PYD, index of subjective and psychological well-being, respectively. The results are in line with Lin and Shek’s [25] previous observation which showed that the increase in student life satisfaction was closely linked with their positive attitudinal changes regarding SL. Once again, the present findings inform the possibility that one’s endorsement of the new concept of SL notions, mindset change toward taking service-orientation as well as the development of SL qualities (e.g., moral character and concern for other’s welfare) is very much likely to enhance the one’s sense of accomplishment and good feelings about the overall quality of life. Theoretically speaking, the proposal of SL concepts stresses on a people-orientation in the service era, emphasizing on both others’ satisfaction and one’s own development and fulfillment [41]. Thus, the present study provides empirical support for this thesis. Furthermore, the findings are consistent with the previous observation of a close linkage between leadership qualities and well-being [24, 31]. Nevertheless, the present study only spoke a correlational relationship between changes, and future research is needed to directly detect the possible causal effect of leadership development on well-being.

Despite the important and positive findings, this study has some limitations. The first limitation is the lack of a control group to minimize threats over internal validity so that the cause-effect relationship between leadership education and student positive development can be concluded. However, it should be noted that the use of control group may not be easy in the educational context and there would be many confounding variables involved. Second, without follow-up tests, the influence of the subject in a long run is unknown. Previous research revealed that students showed even greater positive changes two weeks after the completion of an intensive “Service Leadership” subject [22]. It is necessary to conduct follow-up tests to examine the long-term sustainability of student positive changes after the end of the subject. In addition, there is a need to measure students’ actual leadership behavior and practice in addition to their self-perceptions in follow-up tests. In this way, the effectiveness of the SL education in promoting student SL behavior in daily life can be rigorously determined. Third, the research method used in this study was quantitative methodology and the data were collected solely from participants’ self-report questionnaire. In future studies, other methods such as objective observations, peer-report or teacher-report can be adopted to further strengthen the evaluation findings. Finally, the sample size of the study was not large (although the findings are quite robust). In future, it would be exciting to conduct a meta-analysis of the changes in the students based on the several studies conducted

previously. Despite these limitations and in conjunction of other studies utilizing the one-group pretest-posttest design [42-44], the present study underscores the usefulness of using this methodology in understanding the changes in the young people taking service leadership subjects or other kinds of training programs.

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Chapter 126

EVALUATION OF AN INTENSIVE SERVICE LEADERSHIP PROGRAM USING THE SUBJECTIVE OUTCOME EVALUATION APPROACH

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ABSTRACT

The fifth cohort of SOAR Youth Leadership Program 2017/2018 was launched in Beijing in the summer of 2018. A 21-hour intensive “Service Leadership” course was conducted with 43 undergraduate students who studied at The Hong Kong Polytechnic University (PolyU) and the Peking University (PKU). This study employed a mix-method approach that integrated both qualitative and quantitative data to evaluate the effectiveness of the “Service Leadership” course, including students’ views on the program content, lecturers, and overall satisfaction. Consistent with previous studies, the three dimensions were significantly correlated. Students’ responses collected through quantitative and qualitative methods were generally positive, suggesting that the program could promote service leadership qualities in the program participants.

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INTRODUCTION

Apart from providing professional knowledge, university also shoulders the responsibility to nurture future leaders for the society. In the book “Excellence without a soul,” Harry Lewis stated that although university has the responsibility to nurture students to obtain autonomy, resilience, and responsibility from higher education, not all universities achieve this fundamental purpose [1]. Moreover, over-emphasis on funding and research grants has become prevalence and universities have lost their mission to nurture students’ holistic development. Tull argued that Lewis’s observations can be applied to many other institutions of high education [2]. Instead of facilitating the development of students’ inner life and character, universities over-emphasize students’ achievements [3]. Unfortunately, this development cannot respond to emerging adolescent developmental issues such as substance abuse, mental problems, delinquency, narcissistic personalities, and egocentrism [4]. Also, employers are not satisfied with graduates’ interpersonal cooperation and maturity when they worked in their first jobs [4]. In view of this situation, how to promote adolescents’ holistic development becomes crucial and critical.

Shek and Ma [5] argued that it is helpful to nurture adolescents through the development of credit-bearing courses on positive youth development. The Service Leadership subject is grounded in the positive youth development approach, which emphasizes adolescents’ potentials and capability, instead of their problems. Positive youth development assets are closely correlated with adolescent developmental outcomes. Specifically, the more developmental assets adolescents have, the less risky behaviors they would display; hence resulting in more positive development outcomes [6]. There are two types of developmental assets: external (e.g., support, empowerment, boundaries, expectations, etc.) and internal assets (e.g., commitment to learning, positive values, and social competencies) [7]. Catalano and his colleagues [8] identified 14 developmental assets [5], including promotion of bonding, cultivation of resilience, promotion of social competence, promotion of emotional competence, promotion of cognitive competence, promotion of moral competence, cultivation of self-determination, and fostering prosocial norms. Shek and Ma [9] asserted that these positive youth developmental constructs would help to shape leadership qualities in university students. Since the Service Leadership subject is implemented, there are many students of different professional disciplines taking the subject. The subject has been kept updating and developing throughout the years. A range of evaluation studies have shown the effectiveness of the Service Leadership subject.

Quantitative and qualitative research methods, both of which has its own merits and shortcomings, are the two main strategies used in natural and social science. Quantitative research is used to examine the relationships among variables, which intends to predict, interpret, and control phenomenon [10]. The method has been widely adopted in social science. There are several characteristics of quantitative research methods. First, quantitative data, standardized measures, and uniform procedures in quantitative research can provide accurate and objective evidence to predict and explain the phenomenon [11]. The standardization and objectivity of quantitative research make it a practicable method to validate, compare, or repeat research study. Furthermore, probability sampling makes the findings generalizable [12]. Researchers’ biases can be minimized through standard procedure [13]. Compared to qualitative research, quantitative research is more economical in terms of

study duration or human and fiscal capacity [14]. Although there are many merits of the quantitative approach, whether it can be used in investigating social and human world remains controversial, especially on the sides that the reality could not be fully explained by numerals and it could be difficult for the observers to have total objectivity [13].

Qualitative research is employed to gather non-numerical data [15], which focuses on the essence of social phenomena [16]. As Peshkin [17] stated, the main objectives of qualitative research are description, interpretation, verification, and evaluation. To achieve these objectives, the most common methods used in qualitative research are interviews, documents, and observations [18]. Although the methods used in different studies might be varied, they shared the same strengths. First, the methods applied in qualitative research are diverse and flexible, which include action research, case study, ethnography, and other related methods. Second, qualitative research allows us to collect data without simplifying the complexity of reality. The research questions can function as a guide on choosing the most appropriate methods [19], which can facilitate researchers to be close to reality [11]. However, qualitative research highly depends on researchers' interpretation, which leads to the question of whether researchers' bias may affect the validity and reliability of findings. Sample representativeness and findings' generalization are also in doubt.

Integrating quantitative and qualitative research methods can provide a holistic perspective on understanding the reality of the social and human world. This approach may have various names, such as multi-methods [20], mixed methodology [21], mixed-methods [22], and multi-strategy research [23]. Researchers adopting the mix-method approach could reap the advantages of each method and minimize the shortcomings [24]. As a result, a more complete and comprehensive understanding of the subject matter can then be obtained [25, 26]. In other words, this type of approach can fulfill the needs to understand the information encoded in the variables, which makes the interpretation more meaningful and accurate [27, 28]. Greene, Caracelli, and Graham [29] illustrated five reasons to utilize mix-method approach, which are triangulation, complementarity, development, initiation, and expansion. Irrespective of the justifications in choosing mix-method research, participants and researchers' involvement in this approach is enhanced [30].

The objective of this paper is to evaluate the perceptions of undergraduate students on the "Service Leadership" course of the "SOAR Youth Leadership Program" (SOAR) using a mix-method approach. This one-year credit-bearing program was jointly hosted by The Hong Kong Polytechnic University and the Peking University. SOAR is the abbreviation of "Serving Heart," "Open-mindedness," "Aspiration," and "Responsibility." The goals and objectives of this program are to nurture all-rounded youth leaders of tomorrow and create an international exchange platform for youth leaders. In July 2018, SOAR Youth Leadership Program 2017/2018 was launched in Beijing. A total of 43 undergraduate students were recruited in the study, including 21 students from The Hong Kong Polytechnic University and 22 from Peking University.

The "Service Leadership" course was the conceptual framework of the program, which was defined by the Hong Kong Institute of Service Leadership and Management Limited (HKI-SLAM) as "satisfying needs by consistently providing quality personal service to everyone one comes into contact with, including one's self, others, communities, systems and environments" (Chung, 2011). Different from other paradigms of leadership, this theory emphasizes that it is equally significant to satisfy the needs of self, others, and systems (i.e., three realms of Service Leadership). Instead of manipulating others with the authority to

satisfy one's own needs, an effective service leader should respect others, care subordinates' needs and welfare, and transcend self-interest to satisfy the needs of others and systems. An excellent service leader will influence others with good character, such as empathy and caring [31]. According to the theory, the service object includes self, others, and systems, which means if one leads himself or herself well, then he or she can serve others well. Specifically, a capable service leader ethically improves his or her competence and manage himself or herself, which enables him or her to lead others and optimize the effect of the service to the communities, societies, and environment [32].

As Chung and Elfassy stated, $E = MC^2$, where "E" represents effective service leadership, "M" means leaders' moral character, and "C" stands for competencies and caring disposition [33]. Moral character refers to the moral values and integrity an effective leader should have, such as authenticity, honesty, and credibility. In other words, the leader should know what to do and what not to do. Competencies included leadership competence, interpersonal competence, intrapersonal competence, and business competence [34]. To guide leadership practice, an effective leader should possess the competencies listed above. Caring disposition is related to love, listening, and empathy. Rather than manipulating followers to fulfill his or her own needs, a leader with caring will respect his or her followers and concern with their benefits.

The HKI-SLAM proposed 7 core beliefs of Service Leadership. First, leadership is a kind of service, serving self, others, and systems in an ethical way. According to Chung's definition [35], service is the activities featured by human interaction. To serve is leadership's basic precondition. Second, everyone has the chance to assume a leadership position in daily life and has the potential to improve leadership's quality and effectiveness. Leadership is not inherent nor owned by the high-powered people. Everyone can practice his or her leadership skills through daily service transactions. Third, the effectiveness of leadership counts on both leader's specific competencies related to the task and his or her moral character and caring disposition valued by subordinators and receivers. The moral behavior [36] and caring disposition [37] of service providers have a profound effect on customers' loyalty and commitment. Fourth, to satisfy others' needs, a leader should ethically improve his or her competences, abilities, and willingness. Chung insisted that without a healthy mind, body, and spirit, leaders are unable to optimize their ability to serve others [35]. Fifth, personal service in high quality should be constantly provided to the people that the leaders encountered, including leaders themselves. Consistency and personalization of the service were highlighted in this belief. Sixth, as a business model, service leadership is not only the most competitive but also the longest surviving model of leadership. In other words, this is an adaptive group model, which focuses on collaborative service-focused thinking and behavior. Seventh, people who want to obtain leadership positions with high pay, high status and management promotions in current society should possess service leadership competencies, moral character, and caring disposition.

The primary goal of this course is to nurture students' holistic development. The knowledge of the service leadership model, seven core beliefs, and three components were included in the lectures through role play, group discussion, self-reflection, drawing, and other activities. The integration of academic content and students' real-life experiences are expected in the course. Several intended learning outcomes are: 1) understand the basic models of leadership and core beliefs about service leadership; 2) comprehend the three major elements (MC^2) of effective service leadership (E); 3) reflect on one's leadership qualities and

develop the basic qualities an effective service leader needs; and 4) appreciate the potential application of knowledge learned from this subject to oneself.

The positive outcomes of the Service Leadership subject and students' satisfaction have been evaluated by a variety of evaluation mechanisms, such as objective outcome evaluation, subjective outcome evaluation, process evaluation, focus group interview, and case study [38]. Generally speaking, the effectiveness of this course was supported and well received by the students. Specifically, the positive changes of students can be observed from the results of quantitative evaluations [39], especially in the outcome measures of moral competences and life satisfaction. On the other hand, the findings observed from the qualitative evaluation showed that students who attended this course valued it as useful, interesting, and meaningful. Besides, students stated they obtained practical knowledge of service leadership, and their leadership qualities were promoted after joining the course [40, 41]. These findings showed that the Service Leadership subject was well designed [42].

Date	Session	Lecture Topic
July 4, 2018 (Wednesday)	Afternoon (2pm-5pm)	Lecture 1 • Introduction to Service Leadership and SOAR Program • Realms, Models of Service Leadership, and differences between the manufacturing economy and service economy
July 5, 2018 (Thursday)	Morning (9am-12pm)	Lecture 2 • Seven Core Beliefs of Service Leadership • E (Effective Service Leadership) = MC^2 (Moral character $\times$ Competence $\times$ Care)
	Afternoon (2pm-5pm)	Lecture 3 • Intrapersonal Competencies and Service Leadership • IQ (task-relevant knowledge, problem solving, and decision making); EQ (understanding and managing emotion effectively); AQ (adversity quotient); SQ (spiritual quotient)
July 7, 2018 (Saturday)	Morning (9am-12pm)	Lecture 4 • Interpersonal competencies and Service Leadership (Communication skills; positive social relationship building; conflict resolution) • Promoting Positive Social relationship
	Afternoon (2pm-5pm)	Lecture 5 • Character Strengths and Service Leadership (love of learning, honesty, courage, perseverance, humility, and gratitude) • Character Strengths in Chinese Philosophies (integrity (lian), shame (chi), loyalty (zhong), filial piety (xiao), benevolence (ren), affection (ai), trustworthiness (xin), righteousness (yi), propriety (li), wisdom (zhi), harmony (he) and peace (ping))
July 8, 2018 (Sunday)	Morning (9am-12pm)	Lecture 6 • Caring Disposition and Service Leadership (Universal dimensions of social cognition (warmth and competence); primary elements of care (love, listening, and empathy) • Becoming Caring Service Leaders
	Afternoon (2pm-5pm)	Lecture 7 • Developmental Asset (Self-esteem, self-efficacy, purpose in life and optimism about future) • Self-Leadership and Service Leadership • Recap of Service Leadership and Core Beliefs • Sharing and reflections

Figure 1. Course arrangement and content outline of the 21-hour course in 3.5 days.

The course conducted in SOAR Youth Leadership Program 2017/2018 was a 21-hour intensive Service Leadership program. Whether the intensive course is as beneficial as the full-term service leadership course to the students, and whether this intensive course is well received are explored in this paper.

OUR STUDY

In the summer of 2017/2018 academic year, “SOAR Youth Leadership Program” conducted the intensive “Service Leadership” course in Beijing. The participants were students from The Hong Kong Polytechnic University (n=21) and Peking University (n=22). Upon completion of the course, the students were invited to complete two forms, namely course evaluation form and personal reflection form. Student consent was obtained to ensure voluntary participation which they were informed of their right to withdraw from the study without any consequences. A total of 41 sets of questionnaires were collected, with a response rate of 95.35%.

Instruments

The evaluation of this study consisted of quantitative and qualitative data which were collected through the Course Evaluation Form and Personal Reflection Form.

Course Evaluation Form (Quantitative and Qualitative Data)

The Course Evaluation Form was used to evaluate the effectiveness of leadership series courses with sound psychometric properties [43]. It composed of five parts as follows:

- 1) Students’ views on course content, which included 10 items covering course objectives, activities, classroom atmosphere, learning experience, etc.
- 2) Students’ views on lecturers, which included 10 items on teaching-skills, attitudes toward profession, class interaction, mastery of the course.
- 3) Students’ views on the extent to which the course has helped them, such as enhancement of social competence and resilience (18 items).
- 4) Overall satisfaction with the course (3 items), including whether suggesting this course to their friends, intend to participate in similar courses, and satisfaction with this course.

A 5-point Likert Scale was utilized in the first four parts, with ratings of “4” and “5” indicating positive responses.

- 5) Four open-ended questions: (a) important things they learned from this subject; (b) one thing they appreciate most in this subject; (c) comments about the lecturers; and (d) aspects should be improved.

Personal Reflection Form (Qualitative Data)

In the qualitative study, we used the Personal Reflection Form to capture the course’s effectiveness focusing on two parts:

- 1) Three words or phrases to express students' perception and comment on this course.
- 2) One metaphor with a brief interpretation that can represent the course.

Data Analyses

Quantitative and qualitative data are collected through the course evaluation form. For the quantitative data analyses, reliability analyses were first conducted to test internal consistency. Second, descriptive statistics were conducted to evaluate the participants' perceptions to better understand the responses of students. Thirdly, correlation analysis was conducted to explore the relationships amongst the subscales. Coding and counting positive response rates were used to analyze the qualitative data collected from the four open-ended questions.

Based on the previous studies [40, 44], responses collected from the Personal Reflection Form were transcribed and coded. If one descriptor had two or more meanings, they would be separated and categorized as two or more meaning units. For example, a student wrote "*touching and helpful*" as one descriptor, which could be divided into "touching" and "helpful" as two meaning units. On the other hand, if two or more descriptors shared one meaning, these descriptors would be merged as one category. The meaning units were subsequently categorized as "Positive," "Neutral," "Negative," or "Undecided."

The coding method was utilized in the metaphors as well. Metaphors were first classified as "Positive," "Neutral," "Negative," or "Undecided." If the explanation had more than one meaning units, the metaphor would be derived into several meaningful units accordingly. Then, the derived items would be coded into different categories. To test the consistency of coding, 20 descriptors and 20 metaphors were selected randomly to test the intra-rater and inter-rater reliabilities. Two coders coded the selected items separately to examine the intra-rater reliability; then, another two coders were invited to code the same set of items to test the inter-rater reliabilities.

Table 1. Mean, standard deviations, Cronbach's alphas, and mean of inter-item correlations amongst the variables

	Mean	Standard Deviation	Cronbach's alpha	Mean [#]
Program content (10 items)	4.50	.36	.77	.25
Program implementers (10 items)	4.73	.37	.90	.54
Program effectiveness (18 items)	4.25	.60	.96	.55
Total effectiveness (38 items)	4.44	.43	.96	.39
Overall satisfaction (3 items)	4.20	.69	.82	.66

Note: Mean[#]: inter-item correlation.

OUR FINDINGS

As shown in Table 1, the reliability analyses of Course Evaluation Form had an acceptable internal consistency: program content (Cronbach's alpha=0.77), program implementers (Cronbach's alpha=0.90), program effectiveness (Cronbach's alpha=0.96), total effectiveness (Cronbach's alpha=0.96), and overall satisfaction (Cronbach's alpha=0.82).

The descriptive analyses showed that the participants rated positively about this course in Table 2. In the ten items that assessed the course content, positive response ranged from 80.5% (n=33) to 100% (n=41). Specifically, all 41 participants agreed that curriculum objectives were clear and atmosphere of the class was pleasant, and they enjoyed the interaction between peers. In the open-ended question of “the most appreciate things in the course,” 28 out of 38 (73.68%) responded with positive comments (see Table 7). Those are related to the well-arranged activities, peer interaction, and pleasant atmosphere. For the metaphors about the program content, there were 19 meaningful units (see Table 9).

Referring to the perception of the lecturers (see Table 3), all participants (n=41) responded with a positive evaluation of the lecturers. There were 6 items with 100% positive responses, which included “*lecturer well prepare the lessons*,” “*showed good professional attitudes*,” “*lecturers involved in the class*,” “*encouraged students to join the activities*,” “*cared students*,” and “*ready to provide help to students*.” Although the positive response ratio of “teaching skills” was lower than other items, there were still 90.2% (n=37) students responded positively on the teaching skills of lecturers. “Professional,” “Caring,” and “Patience” were the most frequently appeared phrases in the open-ended question (see Table 7) as well as the interpretations of metaphors related to lecturers (see Table 9).

Table 4 presents the findings on the program effectiveness perceived by the students. All participants (n=41) admitted that the course has helped them to comprehend the importance of situational task competencies, character strength, and caring disposition in successful leadership. There were 97.6% (n=40) of the participants agreed that the course enabled them to cultivate compassion and caring for others; 39 out of 41(95.1%) participants gained knowledge (e.g., theories, research, concepts, etc.) covered in the course, which allowed them to understand the characteristics that successful service leaders need. Besides, students’ responses to the first question showed additional effects (see Table 7), such as accommodating others’ opinions and enhance communication skills. These effects also appeared in the descriptors and metaphors (see Tables 8 and 9).

Regarding overall satisfaction, 40 participants (97.6%) agreed that they were satisfied with the Service Leadership course. There were 85.4% of participants willing to recommend this subject to their friends, while only 25 out of 41 (61%) participants would consider to register a similar course in the future. The students also offered suggestions for course improvement in the fourth open-ended question (see Table 7), some of which also can be seen in the metaphors’ explanations. Furthermore, Pearson correlation analyses showed that all the subscales were significantly correlated (see Table 6).

Table 8 presents the results of descriptors coding. A total of 120 out of 134 (89.55%) descriptors were coded as positive. The top three most mentioned descriptors were “Inspiring/Inspired/Enlightening,” “Helpful/Useful/Benefit” and “Interesting/Fun/Attractive,” with 19, 15, 11 times mentioned respectively. The numbers of descriptors regarded as neutral, negative and undecided were 11 (8.21%), 2 (1.49%), and 1 (0.75%).

To test the consistency of coding, 20 items of the descriptors were randomly selected to examine the reliabilities. To assess intra-rater reliabilities, the raters who participated in the coding process are invited to rate the 20 items one more time. To assess inter-rater reliabilities, another two research assistants who were not involved in the original coding process were invited to rate the 20 items. The intra-rater agreements were 90% and 95%, and the inter-rater congruence were both 95%.

Table 2. Descriptive statistics of the participants' evaluations on the program content

Participants' views towards the program contents:	1		2		3		4		5		Content	
	Strongly Disagree		Disagree		Neutral		Agree		Strongly Agree		Positive responses (Options 4-5)	
	n	%	n	%	n	%	n	%	n	%	n	%
1. The objectives of the curriculum are very clear.	0	0	0	0	0	0	16	39.0	25	61.0	41	100.0
2. The content design of the curriculum is very good.	0	0	0	0	8	19.5	20	48.8	13	31.7	33	80.5
3. The activities were carefully arranged.	0	0	1	2.4	1	2.4	13	31.7	26	63.4	39	95.1
4. The classroom atmosphere was very pleasant.	0	0	0	0	0	0	8	19.5	33	80.5	41	100.0
5. There was much peer interaction amongst the students.	0	0	0	0	0	0	10	24.4	31	75.6	41	100.0
6. I participated in the class activities actively (including discussions, sharing, games, etc.).	0	0	0	0	4	9.8	18	43.9	19	46.3	37	90.2
7. I was encouraged to do my best.	0	0	1	2.4	1	2.4	16	39.0	23	56.1	39	95.1
8. The learning experience enhanced my interests towards the course.	0	0	1	2.4	2	4.9	15	36.6	23	56.1	38	92.7
9. Overall speaking, I have a very positive evaluation on the course.	0	0	2	4.9	1	2.4	12	29.3	26	63.4	38	92.7
10. On the whole, I like this course very much.	0	0	0	0	5	12.2	18	43.9	18	43.9	36	87.8

Table 3. Descriptive statistics of the participants' evaluations of the program implementers

Participants' views towards the program implementers:	1		2		3		4		5		Content	
	Strongly Disagree		Disagree		Neutral		Agree		Strongly Agree		Positive responses (Options 4-5)	
	n	%	n	%	n	%	n	%	n	%	n	%
1. The lecturer(s) had a good mastery of the course.	0	0	1	2.4	1	2.4	12	29.3	27	65.9	39	95.1
2. The lecturer(s) was (were) well prepared for the lessons.	0	0	0	0	0	0	7	17.1	34	82.9	41	100.0
3. The teaching skills of the lecturer(s) were good.	1	2.1	0	0	3	6.3	11	26.8	26	63.4	37	90.2
4. The lecturer(s) showed good professional attitudes.	0	0	0	0	0	0	9	22.0	32	78.0	41	100.0
5. The lecturer(s) was (were) very involved.	0	0	0	0	0	0	10	24.4	31	75.6	41	100.0
6. The lecturer(s) encouraged students to participate in the activities.	0	0	0	0	0	0	8	19.5	33	80.5	41	100.0
7. The lecturer(s) cared for the students.	0	0	0	0	0	0	5	12.2	36	87.8	41	100.0
8. The lecturer(s) was (were) ready to offer help to students when needed.	0	0	0	0	0	0	7	14.6	34	70.8	41	100.0
9. The lecturer(s) had much interaction with the students.	0	0	0	0	1	2.4	10	24.4	30	73.2	10	97.6
10. Overall speaking, I have a very positive evaluation on the lecturer(s).	0	0	0	0	0	0	13	31.7	28	68.3	41	100.0

Table 4. Descriptive statistics of the participants' evaluations of the program effectiveness

	Participants' views towards the program effectiveness	1		2		3		4		5		content	
		Strongly Disagree		Disagree		Neutral		Agree		Strongly Agree		Positive responses (Options 4-5)	
		n	%	n	%	n	%	n	%	n	%	n	%
1.	It has enhanced my social competence.	1	2.4	1	2.4	2	4.9	22	53.7	15	36.6	37	90.2
2.	It has improved my ability in expressing and handling my emotions.	0	0	2	4.9	6	14.6	18	43.9	15	36.6	33	80.5
3.	It has enhanced my critical thinking.	0	0	4	9.8	4	9.8	17	41.5	16	39.0	33	80.5
4.	It has increased my competence in making sensible and wise choices.	0	0	1	2.4	7	17.1	18	43.9	15	36.6	33	80.5
5.	It has helped me make ethical decisions.	0	0	2	4.9	4	9.8	18	43.9	17	41.5	35	84.3
6.	It has strengthened my resilience in adverse conditions.	0	0	0	0	7	17.1	24	58.5	10	24.4	34	82.9
7.	It has strengthened my self-confidence.	1	2.4	2	4.9	6	14.6	18	43.9	14	34.1	32	78.0
8.	It has helped me face the future with a positive attitude.	0	0	0	0	6	14.6	15	36.6	20	48.8	35	85.3
9.	It has enhanced my love for life.	0	0	2	4.9	6	14.6	16	39.0	17	41.5	33	80.5
10.	It has helped me explore the meaning of life.	1	2.4	1	2.4	9	22.0	14	34.1	16	39.0	30	73.2
11.	It has enhanced my ability of self-leadership.	0	0	0	0	3	7.3	16	39.0	22	53.7	38	92.7
12.	It has helped me cultivate compassion and care for others.	0	0	0	0	1	2.4	15	36.6	25	61.0	40	97.6
13.	It has helped me enhance my character strengths comprehensively.	0	0	2	4.9	4	9.8	18	43.9	17	41.5	35	85.4
14.	It has enabled me to understand the importance of situational task competencies, character strength and caring disposition in successful leadership.	0	0	0	0	0	0	20	48.8	21	51.2	41	100.0
15.	It has promoted my sense of responsibility in serving the society.	0	0	1	2.4	3	7.3	19	46.3	18	43.9	37	90.2
16.	It has promoted my overall development.	1	2.4	0	0	5	12.2	17	41.5	18	43.9	35	85.4
17.	The theories, research and concepts covered in the course have enabled me to understand the characteristics of successful service leaders.	0	0	1	2.4	1	2.4	18	43.9	21	51.2	39	95.1
18.	The theories, research and concepts covered in the course have helped me synthesize the characteristics of successful service leaders.	0	0	2	4.9	4	9.8	17	41.5	18	43.9	35	85.4

Table 5. Summary of the participants' perceptions toward other aspects

		1		2		3		4		5		content	
		Strongly Disagree		Disagree		Neutral		Agree		Strongly Agree		Positive responses (Options 4-5)	
		n	%	n	%	n	%	n	%	n	%	n	%
1.	Will you suggest your friends to take this course?	0	0	1	2.4	5	12.2	13	27.1	22	53.7	35	85.4
2.	Will you participate in similar courses again in the future?	1	2.4	2	4.9	13	31.7	13	31.7	12	29.3	25	61.0
3.	On the whole, are you satisfied with this course?	0	0	0	0	1	2.4	22	53.7	18	43.9	40	97.6

Table 6. Pearson correlations among program content, instructors, and effectiveness

Variables	1	2	3	4	5
1) Program content (10 items)	-				
2) Program instructors (10 items)	.61**	-			
3) Program effectiveness (18 items)	.70**	.73**	-		
4) Total effectiveness	.81**	.84**	.97**	-	
5) Overall Satisfaction	.68**	.67**	.89**	.88**	-

Table 7. Summary of students' written comments on the course (N=41)

	Positive responses	Total responses	Percentage (%)	Highlights
1) The most important thing(s) learned in the course	36	41	87.8	"I learned that sympathy and empathy are two different concepts and we should show empathy, not sympathy, to people in need." "The ways to be a self-leader" "I have learned the nature of intellectual quotient, AQ, EQ and emotional control"
2) The things that appreciated most in the course	38	41	92.7	"1. Pleasant atmosphere 2. Enough space and time for us to express and share 3. teachers are all caring" "I appreciate the efforts paid by the lecturers. It was really well-prepared. And the class atmosphere was really pleasant" "The interactive activities. The use of other medias (video, /role play), Many spaces for students to think deeply in topic."
3) Comments on the lecturer(s)	23	41	56.1	"The lecturers are nice and cheerful as they gave us physical and mental support throughout the trip" "I think the lectures are helpful and joyful. The lecturers are well-prepared, kind and willing to communicate with us" "They are professional, friendly. Warm-hearted"
4) Areas for improvement	24	41	58.5	"Can involve more interaction and discussion" "More videos and specific strategies. Some contents in the course is a little bit abstract" "Schedule too tight (sometimes), lack of interaction between groups"

In Table 9, 40 out of 41 (97.56%) original metaphors were considered as positive. Among the derived items, 49 (96.08%) of them were coded as positive, with only 2 (3.92%) items were coded as negative. A total of 13 categories were generated after coding. The three categories as examples are listed below:

The first category was bought up by seven students. The metaphors in this category indicated that this course included a wealth of knowledge.

- Buffet: "the lessons are fruitful and interesting. I gained much knowledge and fun during the lesson. The lessons provided me with a large variety of knowledge regarding leadership and equip me with the knowledge to deal with the challenge I may face in the future."

Table 8. Categorization of descriptors used by the participants to describe the course

Descriptors	Nature of the Response				Total
	Positive	Neutral	Negative	Undecided	
Inspiring/Inspired/Enlightening	19	-	-	-	-
Helpful/Useful/Benefit	15	-	-	-	-
Interesting/Attractive/Fun/Funny	11	-	-	-	-
Meaningful/Profound/Influential	10	-	-	-	-
Informative/Fruitful/Comprehensive	10	-	-	-	-
Enjoyable/Joyful/Happy/Cheerful	10	-	-	-	-
Eye-opened/Broaden my horizon/ Enrich inner self	8	-	-	-	-
Wonderful/Colorful/Extraordinary/ Serendipity	6	-	-	-	-
Touching/Warm/Beloved/Inter-connected	6	-	-	-	-
Impressive/Unforgettable/Memorable	4	-	-	-	-
Excited/Exciting	3	-	-	-	-
Creative/Flexible	3	-	-	-	-
Contact with excellent students/Cooperative	3	-	-	-	-
Efficient/Condensed	2	-	-	-	-
Satisfied/Worthy	2	-	-	-	-
Interactive	1	-	-	-	-
Practical	1	-	-	-	-
Other positive responses	6	-	-	-	-
Innovation/Cooperation/Role play/Challenging	-	5	-	-	-
Learnt service leadership/Think the part of service and leadership/Prefer group activities	-	3	-	-	-
Other neutral responses	-	3	-	-	-
Sad	-	-	1	-	-
Tired	-	-	1	-	-
999	-	-	-	1	-
Total Count (N):	120	11	2	1	134
Total Count (%):	89.55%	8.21%	1.49%	0.75%	100.00%

Four students expressed similar meanings in the second category. This category mainly referred to the diverse background of participants.

- Melting pot: “the people attendants are from different backgrounds, all the diverse thinking patterns, languages and cultures come together, melt with each other, forming an unbelievably perfect class. Everyone learns something about who they are, what other culture is like as well as most importantly, now to be a service leader.”

The third one was mentioned by three students, referring to the happiness that could be created by using the knowledge learned from the course.

- Lollipop: “we may change someone's life by doing something out of kindness.”

Table 9. Categorization of the metaphors used by the participants to describe the course

Metaphors	Nature of the Metaphor					Number of Codes Derived from the Metaphor and Its Nature				
	Positive	Neutral	Negative	Undecided	Total	Positive	Neutral	Negative	Undecided	Total
Crepe cake/Buffer/ A rich French dinner/Apple/Oliver fruit	7	-	-	-	-	10	-	1	-	-
Party/Melting pot	4	-	-	-	-	5	-	-	-	-
Lollipop/Candy	3	-	-	-	-	3	-	-	-	-
Light/Bulb	3	-	-	-	-	3	-	-	-	-
A sapling/An apple tree	2	-	-	-	-	3	-	-	-	-
Seed	2	-	-	-	-	2	-	-	-	-
Lighthouse	2	-	-	-	-	2	-	-	-	-
Gym room/Barbell	2	-	-	-	-	2	-	-	-	-
Knowledge trip/Train	2	-	-	-	-	3	-	-	-	-
a Doraemon	1	-	-	-	-	1	-	-	-	-
Butterfly	1	-	-	-	-	1	-	-	-	-
Other positive responses	11	-	-	-	-	13	-	-	-	-
Balsam pear	-	-	1	-	-	1	-	1	-	-
Total Count (N):	40	0	1	0	41	49	0	2	0	51
Total Count (%):	97.56	0.00	2.44	0.00	100.00	96.08	0.00	3.92	0.00	100.00

Similar to the descriptors, 20 items of metaphors were selected randomly to test the intra-rater and inter-rater reliability. The intra-rater agreement coded by two separate coders at two-time points were 90% and 100%, and the inter-rater reliability coded independently by two extra coders were both 95%. The results of both descriptors and metaphors supported the observation that the “Service Leadership” course was beneficial to the majority of the participants.

DISCUSSION

This study examined the perceptions of 43 undergraduate participants from The Hong Kong Polytechnic University and Peking University on the intensive “Service Leadership” course. Several observations are consistent with the previous studies [43, 45]: the internal consistency of Course Evaluation Form is acceptable; the content, lecturers, and effectiveness of the program were significantly correlated. The findings based on the quantitative and qualitative data are overwhelmingly positive.

Both quantitative and qualitative findings showed that student participants notably benefited from the “Service Leadership” course. First, students’ communication skills and the ability to regulate emotions were promoted. Students strongly agreed that they have learned the knowledge about how to control and express emotions as well as how to cultivate compassion and care for others. They practiced these skills through the activities organized in the courses, such as role play and self-reflection, which were rarely employed in other

subjects. Second, the “Service Leadership” course strengthened the student participants’ responsibility and capacity of self-leadership. Majority of them stated that they learned how to meet the needs of self, others, and community. Third, the “Service Leadership” course enhanced their willingness for service. Even though it was the first time they heard about the concepts related to Service Leadership, they developed the sense of the core components as a service leader and how to best serve others in such a role. Last but not least, many student participants revealed that the course fostered their confidence and awareness to be a leader. The theory behind “Service Leadership” upholds that every person has the potential to make use of their strengths and become a leader during the collaboration [31]. It raises the students’ awareness of acknowledging their potential and helps them to understand that everyone can occupy a position of leadership in daily life.

The quantitative and qualitative research employed in the study are complementary. On one hand, the credibility of the study can be promoted [46]. Besides, the validity and reliability of the study have been tested, which provide the base for replication and generalization available in the future. Besides, Toomela [27] stated that the mix-method approach provides a deeper understanding of the information we encoded.

Unlike other leadership models, Service Leadership Model starts from self-leadership and ends with serving others and the systems. Service Leadership theory emphasizes on self-leadership as the primary condition before one can serve others and systems [47]. Benefits of developing self-leadership have been explored in literature. For example, Prussia and colleagues’ [48] study showed that self-leadership could promote academic achievement effectively through enhanced self-efficacy. Also, Dolbier, Soderstrom, and Steinhardt [49] found that self-leadership is positively related to higher psychological function and better health status.

Furthermore, in another study which the corporate employees were employed, they found that self-leadership has positive correlation with not only health (e.g., greater perceived wellness, less work stress) but also work outcomes (e.g., more efficiency communication, greater work satisfaction, higher quality management, better working relationship) [49]. Learning service leadership can contribute to adolescents’ academic performance and their future work. In other words, not only a short-term effect but also long-term influence can acquire from service leadership training.

On the other hand, the Service Leadership subject is dedicated to nurturing adolescents to be caring service leaders [50]. Caring thinking and behavior facilitate leaders’ personal development and self-actualization [51]. For the ones whom they lead, caring will inspire them to be more autonomous in their daily work [51]. For the communities, the social atmosphere, which is full of caring, respect, and love, will be established. Self, others, and systems all can be benefited from the caring behaviors. Everyone can be benefited from the Service Leadership subject. In short, the significance of developing and broadcasting Service Leadership subject is profound.

Nevertheless, the present study has several limitations. First, after students completed the rating scales in the course evaluation form, they may be reluctant or impatient to answer the for open-ended questions in the last part which aimed at assessing the same aspect. Second, the “Service Leadership” course conducted in the SOAR program was an intensive mode. Although the result of the intensive course was positive, we could study further whether the differences between the intensive conducted courses and regular schedule courses exist.

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Chapter 127

**PROMOTION OF SERVICE LEADERSHIP
IN UNIVERSITY STUDENTS:
VIEWS OF UNIVERSITY STUDENTS**

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ABSTRACT

To nurture service leaders of tomorrow and to help university students develop in a holistic manner, the “Service Leadership” subject was established at The Hong Kong Polytechnic University (PolyU). In this chapter we examine the impact of the subject offered in 2015/16 academic year using the client satisfaction approach. A total of 106 university students completed an evaluation form assessing perceived program, instructors and effectiveness quality. The students reported a positive view of the program in both semesters. As predicted, there were significant inter-relationships amongst program content, instructor quality, and perceived effectiveness. Regarding predictors of program benefits, program and instructor quality showed a significant impact. For overall satisfaction, perceived benefits was the only significant predictor. The findings strongly suggest that the subject could promote the development of service leadership in students.

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INTRODUCTION

With Gross Domestic Product (GDP) in the service sector accounted for more than 93%, Hong Kong is fundamentally a service-oriented economy that has a percentage share of service sector much higher than other developed Asian economies [1]. Given the service sector has been the leading force of Hong Kong's economic growth, it is expected that it will continue to make a major economic contribution in the coming future [2]. After the handover of Hong Kong, there has been massive integration and collaboration with the fast-expanding Chinese market. For example, there is the development of the "Guangdong-Hong Kong-Macao Greater Bay Area" ("Greater Bay Area"), a major national strategy that sets new pursuit of Mainland China to unite the resources and unleash its full economic potential. The Greater Bay Area (GBA) includes nine municipalities in Guangdong Province and two Special Administrative Regions (i.e., Hong Kong and Macau). This area is fast growing and economically very active, which has a total population of around 70 million people and a total GDP of around US\$1.6 trillion in 2018 [3]. The joint cooperation platform highlighted the importance of giving completely distinctive strength of each of areas, elevating their role in the economic growth development, and building a globally competitive modern system.

With the launch of the Individual Visit Scheme under the Mainland China and Hong Kong Closer Economic Partnership Arrangement in July 2003, travelers from Mainland China permitted to visit Hong Kong for individual purposes, which has subsequently led to an explosive expansion in retail and tourism industries [4]. The scheme was implemented at different phases, with the first introduction at only 4 Guangdong cities and extended to cover 49 cities from 18 provinces. The number of total visitors to Hong Kong has increased tremendously in the past 15 years. The surge has led to a level that the number of visitors in Hong Kong alone surpassed the number of visitors in some countries. For example, Hong Kong provided warmth hospitality to 54.3 million tourists in 2013, compared to 31.1 million by the United Kingdom, 10.4 million by Japan, and 6.5 million by Australia. Meanwhile, the Mainland China tourists have a tendency to stay shorter and more frequent in Hong Kong and have a significantly higher level of average daily spending of HK\$3,593 than non-Mainland tourists of HK\$1,970 in 2013. It was estimated the scheme contribution to the Hong Kong economy in 2012 amounted to a total of HK\$26.1 million, 1.3% of the Hong Kong's GDP, and 114,280 in the number of jobs [4]. The change of policy has opened up a massive amount of employment opportunities in the service industry, which in some measure, supported the low unemployment rate sitting at 3.1 percent [5].

Despite the fact that unemployment rate at its record low in Hong Kong, the severe income and wealth inequality over the past years is growing recognition that moving up the ladder can be very challenging, suggesting most of the economy's income and wealth have been shifting to a small percentage of wealthy people and global corporations that have been accumulating assets and buying equities. Most societies that have prioritized economic growth have now reached a point where the disparity creates social tension and heightens the need for redistribution [6]. The phenomenon emerges not only in Hong Kong. The decline in mobility and growing inequality are also causing threats to the American dream in the United States [7]. Education is commonly considered as one of the known areas that can stop reinforcing inequalities generation to generation with its high correlation by increasing access to and improving the quality of education [8]. The higher education across developed

societies has substantially expanded in the last several decades. It is important that universities are ensuring the graduates have the knowledge and positive attributes that the evolving labor market needs. As in Hong Kong, the economy has presented both opportunities and challenges to the young people in entering the competitive labor market and having the chances of upward social mobility, which would typically opt for skilled and professional workers with good communication and management skills in leading and creating a society that thinks and innovates. In short, how to help university students to adapt to the challenges of the growing service economies is an important task for universities to achieve.

Besides the challenges of the changing service economies, young people in Hong Kong are also facing several other issues in their adolescence that might hinder them from bargaining for advantages in entering the competitive markets. For example, academic pressure in young people are particularly high in Hong Kong, and for those who cannot cope with academic pressure, they may have other mental health problems that required their attention, such as depression, anxiety, hopelessness, and even suicidal ideations [9]. Materialistic orientation has become an emerging issue among youth [10]. Contemporary young people in Hong Kong live in an age of material abundance that has led to many of them only targeted to get a step ahead in life and to accumulate wealth at an early age. According to the research by the Commission on Youth [11], 20% to 30% of Hong Kong adolescents had material orientations and agreed that they would use unethical ways to accumulate wealth. About 6.6% of high school students reported that they know classmates who are currently engaging in compensated dating [12, 13]. Adolescents and university students in Hong Kong were also described as egocentrism and a lack of social responsibilities and civic engagement [14]. Navigating the difficult job of teaching and the developmental challenges is certainly not an easy one, especially in Hong Kong. Along with the macro environment in society, there are many social obstacles from a global standpoint that are coming ahead of our younger generation.

Millennials, typically refer to individuals who were born between the early 1980s to the mid-1990s, are often being labeled as self-centered, unmotivated, and disrespectful [15]. This is a pivotal moment that Millennials are quickly advancing in their careers and taking leadership role inside of corporations, shifting from traditional leadership and hierarchical management style, and changing the work-life philosophies and company values along the way. The change is re-defining the power dynamics within organizations to a relatively flat culture and less bureaucracy where employees are empowered to contribute and make decisions through openness, collaboration, and transparency. Following the millennials are the Generation Z (i.e., a generation born between the mid-1990s to the early 2000s). Roughly speaking, these teenagers do not know life without internet and technology and about to start stepping onto universities around the world. It is undoubtedly that the world shall embrace and expect a different leadership outlook from Generation Z once they begin entering the workforce and taking up management roles in the future. Therefore, it is important that the universities are allocating and providing more resources in equipping and nurturing the next generation's competitiveness to become successful leader prior joining the labor force with a nearly seamless experience and in leading our society with social skills and social competence. The younger generation is not simply the future of tomorrow – they are the potential leaders of today. Leadership is never easy, especially in light of the enormous challenges coming after them.

With the aim of establishing and strengthening service leadership education to the undergraduates in Hong Kong, the Victor and William Fung Foundation and the Hong Kong Institute of Service Leadership and Management (HKI-SLAM) collaborated to launch the Fung Service Leadership Initiative. Eight public universities receiving funding from the University Grants Committee joined the project. In each university, courses, programs, and related educational materials were developed to meet its objectives of taking a holistic approach for nurturing and enhancing our university students with leadership competencies and capabilities for the most competitive service leadership mentality and practices. According to Chung [16], A service leader is “a ready, willing and able, on-the-spot entrepreneur who possesses relevant task competencies and is judged by superiors, peers, subordinates, and followers to exhibit appropriate character strengths and a caring social disposition.” In a study of Shek and colleagues [17], they have highlighted 12 dimensions of leadership desirable qualities as “*service orientation (self and others), systems orientation (self, followers, habitat, and larger system), leadership competencies, moral character, caring disposition, personal qualities of a leader, everyone is (can be) a leader, self-leadership, the need for continuous improvement, mentoring followers, Chinese cultural values, and comprehensiveness and breadth of the model*” (p. 218). For The Hong Kong Polytechnic University (PolyU), researchers have developed both credit-bearing subjects as well as noncredit-bearing leadership training programs.

In this chapter we evaluate the impact of the “Service Leadership” subject which was offered to students in semester 1 and 3 of the 2015/16 academic year at PolyU. The modified Subjective Outcome Evaluation Scale (SOES) was utilized for evaluation that examines the perceived satisfaction and impact of the subject. The scale included areas of assessment in program content (i.e., course design), program instructors (i.e., teaching skills), program benefits (i.e., enhancement of social competence), and overall satisfaction (i.e., global satisfaction of student participants). There are several expectations of the research findings: 1) if the program implemented as planned, most of the participants would give positive views towards all the measuring scales, and 2) in line with previous findings, we would expect significant correlation amongst the different aspects of client satisfaction, including program quality, instructor quality, benefits of taking the course, and overall satisfaction.

OUR STUDY

The “Service Leadership” subject was offered to students at PolyU in semester 1 and 3 of the 2015/16 academic year. In the end of the semesters, all the students (semester 1: 42 students; semester 3: 64 students; overall: 106 students) were invited to complete a subjective outcome evaluation form to evaluate their perception of the program. Before they complete the evaluation form, the student participants were told about the purpose of the evaluation and were asked to fill out a written consent form. The evaluation form was self-administrated in paper-pencil based mode. They were given adequate time to complete all the items in the form, and teaching assistants were on site for any questions that bought by the students. All evaluation forms were collected upon completion.

Instruments

A modified “Subjective Outcome Evaluation Scale” (SOES) was used to examine the student participants’ subjective perception of the “Service Leadership” subject. The SOES, which showed good psychometric properties (see Result section for details), was widely used in previous studies [18-20] to study the impact of the program based on the perception of program recipients (the students in the current study). The SOES is a 5-point Likert scale which comprised of several parts as follows:

- 1) Program Content (PC): Perception of students on the program, for examples, objectives and design of the program, interaction between students, and classroom atmosphere, etc. (10 items). Examples of the items are “The content design of the curriculum is very good.” and “The learning experience enhanced my interests towards the program.”
- 2) Program Instructors (PI): 10 items related to students’ perceptions of the instructor(s), including class preparation, professional attitude (i.e., “The instructor(s) showed good professional attitudes.”), teaching skills (i.e., “The teaching skills of the instructor(s) were good.”), class involvement (i.e., “The instructor(s) was (were) very involved.”), and quality of interaction with students (i.e., “The instructor(s) had much interaction with the students.”).
- 3) Program Benefits (PB): Student participants’ perception of the perceived program benefits, for instances, the promotion of their social competence and personal development (18 items). Examples of the items are: “It has increased my competence in making sensible and wise choices” and “It has enabled me to understand the importance of situational task competencies, character strength and caring disposition in successful leadership.”

In addition to the above-mentioned parts, there are two parts in the SOES that target on understanding the global satisfaction and student participants’ additional feedback:

- 1) Overall Satisfaction (OS): assessing the students’ global satisfaction, such as recommending the program to their friends (i.e., “Will you suggest your friends to take this program?”), their intention to join the similar program in future (i.e., “Will you participate in similar programs again in the future?”), and satisfaction with the program in general (i.e., “On the whole, are you satisfied with this program?”) through a 5-point Likert scale.
- 2) Four open-ended questions asking the student participants’ program experience and their feedback to the program, such as their learning experience (i.e., “the most important thing you have learned from the program”), things that they most appreciated (i.e., “appreciate most in this course”), instructors (i.e., “comments about the instructor(s)”), and areas for improvement (i.e., “suggestions on the improvement area”).

Data Analyses

The statistical package of SPSS 25 [23] was used to analyze the collected data from the participants. The psychometrics properties of SOES showed good reliability in previous studies [e.g.: 19, 20-22]. The psychometric properties, specifically the reliability, of the SOES was first examined. The score of each subscale items was added up and divided by the number of items in the subscale to create the composite measures of the subscale. Percentage analyses were then conducted to study the student participants' responses on the quantitative items (i.e., PC, PI, PB, and OS). The data was analyzed and reported separately by semesters (i.e., semester 1 and semester 3) and a combined group of student participants in overall score (i.e., combined both semesters). Correlation was performed to investigate the relationships amongst the subscales. The predictive effects of student participants' perception on PC, PI, PB, and OS were tested through multiple regression analyses.

FINDINGS

The mean, standard deviation, and reliability analyses of each subscale are shown on Table 1. Consistent with previous studies [19, 20], the SOES in the present study showed good reliability. For the combined group of students from both semesters, the overall Cronbach's alpha (α) in each of the subscales was .74 or above: PC (α = .87; Mean inter-item correlation = .41), PI (α = .93; Mean inter-item correlation = .58), PB (α = .94; Mean inter-item correlation = .48), and OS (α = .74; Mean inter-item correlation = .53). It supported that the SOES was internally consistent for the present study. The mean score in each of the subscale were above 4.0 (PC, M = 4.17; PI, M = 4.49; PB, M = 4.02; OS, M = 4.02).

As shown in Table 1 and 2, program content was positively perceived by the student participants (semester 1, M = 4.10; semester 3, M = 4.23; overall, M = 4.17). For instances, majority of the student participants rated agree or strongly agree that they liked the pleasant atmosphere in classroom (overall = 97.2%), the clear program objective (overall = 95.3%), and rated a very positive evaluation of the program (overall = 94.3%). There were also more than 90% of the student participants (n = 98, 92.5%) agreed or strongly agreed the activities were carefully arranged, a great amount of peer interaction, and the learning experience enhanced their interest towards the program. When they were asked to express their thoughts on what they most appreciated in this subject, they responded in several perspectives of the program, including *"This class has a lot of class activities and discussions, very interesting," "Relaxing environment to learn," and "Interactive lecture, using lots of activities and games for us to participate; instructor put lots of efforts to make the lectures more interesting."*

Supported by the findings shown in Table 3, over 93% of the students in both semesters reported positive responses in all the items in PI. The students were highly satisfied with the program instructors' performance (semester 1, M = 4.45; semester 3, M = 4.52; overall, M = 4.49). There were about 99% of the student participants (105 out of 106) perceived the instructors were very involved and encouraging for every students' participation. Also, about 98% of the students (104 out of 106) appreciated the instructors on their professional attitude, the caring for the students, and the help that offered to students when they are needed. The positive responses from the open-ended questions highlighted more to support the

quantitative part: students' responses mentioned about the well-organized and professionalism of the teaching team, such as *"Very (w)ell-prepared and caring lectures with a great team with passion for teaching, really learn a lot from lecture and also from the role model of the teacher."* and *"Instructor and other teachers were very well organized throughout all past lectures. I genuinely appreciate for involving many activities that I will not be able to find in other programs,"* and the teaching team's helpfulness and encouragement for students' participation, such as *"Willing to help students when they have questions. Encourage students to be active in class."*

The student participants' perception to program benefits (PB), shown in Table 4, were positively recognized (semester 1, $M = 4.03$; semester 3, $M = 4.02$; overall, $M = 4.02$). Majority of the student participants rated that the program massively improved their social competence (91.5%), for instance, a student responded that *"Though this subject teaches us how to be a good leader, more importantly, it teaches us how to get along well with the others."* They acquired a good and better understanding of the covered program content (i.e., theories, concept, and research) which related to a successful service leader (89.6% - 92.5%). There were similar responses from the students such as *"The $E=MC^2$, not only the theory, the knowledge but really how to practice it, how to use it applies to in daily life."* and *"I have learned how to be a professional service leader throughout participating in the lectures. Besides, I learned to accept others' ideas."* Compared with the other items in this subscale, items related to life, such as enhancing the love and meaning of life, were perceived particularly less influential to students (73.6% and 72.5%, respectively). This finding is consistent with previous findings [19, 24].

The responses to the three items that measure the student participants' overall satisfaction (OS) are shown in Table 5. They indicated high satisfaction with the subject (95.3%) and will recommend their friends to take this program (90.6%). However, they showed less interest in taking a similar subject in the future (67.9%). The pattern was similar to the previous studies (i.e., 19, 25, 26).

To study any differences in the subscales (i.e., PC, PI, and PB) across semesters, a one-way ANOVA was performed with the subscales as dependent variables and semesters (i.e., semester 1 and semester 3) as independent variables. Table 6 shows that there was no significant difference found in the analysis. This indicates the implication of no significant difference in how the student participants perceived the program in semester 1 and semester 3. Therefore, two sets of data from semester 1 and 3 were combined as a full set of overall group to perform correlation and multiple regression analyses to study the correlations between subscales and predictive factors.

Table 7 presents the results of the correlation of each subscale. Consistent with previous studies [19, 24], there were significant correlations amongst the different measures in the client satisfaction survey. We further conducted multiple regression analyses to examine the factors predicting perceived benefits and overall satisfaction of the program (see Table 8). Both the PC and PI were predictive factors of PB ($\beta = 0.76$, $p < .001$; $\beta = 0.24$, $p < .001$). For the overall satisfaction of the program, PB was the only predictive factor ($\beta = 0.44$, $p < .05$).

DISCUSSION

The study was to evaluate the impact of “Subjective Leadership” subject that was offered to students at PolyU in both semester 1 and semester 3 in the academic year 2015/16 based on the client satisfaction approach. Using the modified SOES with a 5-point scale, we examined four dimensions of the students’ perception towards the subject, including program content (i.e., the design and objective of the subject), program instructors (i.e., class preparation and teaching skills of instructor), program benefits (i.e., promotion of psychosocial competence and personal development), and overall satisfaction (i.e., program recommendation to friends and intention to take similar subject in the future). There were also four open-ended questions looking for comprehensive and constructive information that could support the statistical findings and provide a broader perspective in understanding the students’ perceptions.

The subject “Service Leadership” aimed to promote the service leadership qualities and overall development of university students. In summary, the results were consistent with our prediction that the students expressed positive perception with the mean score above 4.0 in each of the four subscales - PC, PI, PB, and OS. The results are reliable, as compared with the previous studies [18-20]. Results of the one-way ANOVA showed that the students in semester 1 and semester 3 had no significant difference in the results of all the subscales, which allowed to view and analyze the students in two semesters as one group on correlations between subscales and predictive factors of program benefits and overall satisfaction.

The student participants in both semesters with an overall mean score of 4.17 reported positive evaluation on the overall program content, such as clear program objective, carefully planned class activities, and a great environment for learning. The program was very stimulating to the students that they appreciated the interactive lectures which provided a sufficient amount of time on peer interaction to make the class more interesting and relaxing. In assessing instructors’ quality subscale, the majority of the students (more than 90%) with an average mean score of 4.49 rated with positive responses in all the measured items. All the students rated positively on the instructors’ evaluation. The results from open-ended questions echoed with the statistical findings that elucidated the professionalism and well-organization of the teaching instructors that they believed this type of quality teaching will not be able to find in other similar programs. The encouragement and helpfulness from instructors helped each of the students in getting involved in the activities and ensured that their needs were being met. Further, most of the students with an average response score of 4.02 in the program benefits subscale found that the program improved their social competence and helped them understand the concept of service leadership. The covered materials in the subject, such as the research concepts, supported them to better understand the attributes of being an effective service leader. However, there were only about 70% of the students perceived that the program enhanced their love for life and the exploration to finding the meaning of life. This may be due to the short duration of the subject. More than 90% of the students reported high overall satisfaction towards the program and would recommend to their friends in joining the program.

Table 1. Cronbach's alphas, mean, standard deviation, and mean of inter-item correlations of Subjective Outcome Evaluation

Variable(s)	Semester 1 (n = 42)				Semester 3 (n = 64)				Overall (n = 106)			
	Mean	SD	α	Mean [#]	Mean	SD	α	Mean [#]	Mean	SD	α	Mean [#]
Program Content (PC: 10 items)	4.10	.41	.84	.36	4.23	.39	.88	.44	4.17	.40	.87	.41
Program Instructors (PI: 10 items)	4.45	.47	.93	.59	4.52	.41	.93	.57	4.49	.43	.93	.58
Program Benefits (PB: 18 items)	4.03	.51	.95	.54	4.02	.39	.93	.43	4.02	.44	.94	.48
Total Effectiveness (TE: 38 items)	4.16	.40	.96	.37	4.21	.33	.95	.35	4.19	.36	.95	.36
Overall Satisfaction (OS: 3 items)	4.00	.49	.80	.62	4.06	.52	.69	.48	4.02	.51	.74	.53

Note. Mean[#]: inter-item correlation.

Table 2. Summary of the participants' positive responses towards Program Content (PC)

Perceptions of program content ^a	Semester 1 (n = 42)				Semester 3 (n = 64)				Overall (n = 106)			
	M [†]	SD	Positive Responses ^b		M [†]	SD	Positive Responses ^b		M [†]	SD	Positive Responses ^b	
			n	%			n	%			n	%
1. The objectives of the curriculum are very clear.	4.14	.52	39	92.9	4.20	.48	62	96.9	4.18	.49	101	95.3
2. The content design of the curriculum is very good.	3.98	.75	35	83.3	4.19	.53	60	93.8	4.10	.63	95	89.6
3. The activities were carefully arranged.	4.12	.63	38	90.5	4.19	.53	60	93.8	4.16	.57	98	92.5
4. The classroom atmosphere was very pleasant.	4.24	.57	39	92.9	4.41	.50	64	100.0	4.34	.53	103	97.2
5. There was much peer interaction amongst the students.	4.26	.62	38	90.5	4.31	.59	60	93.8	4.29	.60	98	92.5
6. I participated in the class activities actively (including discussions, sharing, games, etc.).	4.05	.79	32	76.2	4.03	.73	48	75.0	4.04	.75	80	75.5
7. I was encouraged to do my best.	3.90	.72	31	73.8	4.11	.65	54	84.4	4.03	.68	85	80.2
8. The learning experience enhanced my interests towards the program.	4.05	.49	38	90.5	4.23	.56	60	93.8	4.16	.54	98	92.5
9. Overall speaking, I have a very positive evaluation on the program.	4.21	.65	37	88.1	4.38	.52	63	98.4	4.31	.58	100	94.3
10. On the whole, I like this program very much.	4.02	.60	35	83.3	4.27	.54	61	95.3	4.17	.58	96	90.5

Note. ^a Scores on the scale/subscale higher than or equal to 4 were treated as positive responses. ^b For every item, respondents with positive responses (options 4-5) are shown in the Table. [†] 1=Strongly Disagree; 2=Disagree; 3=Neutral; 4=Agree; 5=Strongly Agree.

Table 3. Summary of the participants' positive responses towards Program Instructors (PI)

Perceptions of program instructor ^a	Semester 1 (n = 42)				Semester 3 (n = 64)				Overall (n = 106)			
	M [†]	SD	Positive Responses ^b		M [†]	SD	Positive Responses ^b		M [†]	SD	Positive Responses ^b	
			n	%			n	%			n	%
1. The instructor(s) had a good mastery of the program.	4.31	.60	39	92.9	4.33	.59	60	93.8	4.32	.59	99	93.4
2. The instructor(s) was (were) well prepared for the lessons.	4.45	.63	39	92.9	4.52	.56	62	96.9	4.49	.59	101	95.3
3. The teaching skills of the instructor(s) were good.	4.29	.74	37	88.1	4.38	.52	63	98.4	4.34	.62	100	94.3
4. The instructor(s) showed good professional attitudes.	4.48	.55	41	97.6	4.55	.53	63	98.4	4.52	.54	104	98.1
5. The instructor(s) was (were) very involved.	4.60	.54	41	97.6	4.61	.49	64	100.0	4.60	.51	105	99.1
6. The instructor(s) encouraged students to participate in the activities.	4.55	.50	42	100.0	4.61	.52	63	98.4	4.58	.51	105	99.1
7. The instructor(s) cared for the students.	4.43	.63	41	97.6	4.52	.53	63	98.4	4.48	.57	104	98.1
8. The instructor(s) was (were) ready to offer help to students when needed.	4.43	.59	40	95.2	4.61	.49	64	100.0	4.54	.54	104	98.1
9. The instructor(s) had much interaction with the students.	4.38	.58	40	95.2	4.53	.53	63	98.4	4.47	.56	103	97.2
10. Overall speaking, I have a very positive evaluation on the instructor(s).	4.55	.50	42	100.0	4.56	.50	64	100.0	4.56	.50	106	100.0

Note. ^a Scores on the scale/subscale higher than or equal to 4 were treated as positive responses. ^b For every item, respondents with positive responses (options 4-5) are shown in the Table. [†] 1=Strongly Disagree; 2=Disagree; 3=Neutral; 4=Agree; 5=Strongly Agree.

Table 4. Summary of the participants' positive responses towards Program Benefits (PB)

Perceptions of program benefits ^a	Semester 1 (n = 42)				Semester 3 (n = 64)				Overall (n = 106)			
	M [†]	SD	Positive Responses ^b		M [†]	SD	Positive Responses ^b		M [†]	SD	Positive Responses ^b	
			n	%			n	%			n	%
1. It has enhanced my social competence.	4.00	.66	38	90.5	4.09	.50	59	92.2	4.06	.57	97	91.5
2. It has improved my ability in expressing and handling my emotions.	3.95	.58	34	81.0	3.97	.50	55	85.9	3.96	.53	89	84.0
3. It has enhanced my critical thinking.	4.00	.58	35	83.3	3.92	.51	53	82.8	3.95	.54	88	83.0
4. It has increased my competence in making sensible and wise choices.	3.92	.64	34	81.0	3.94	.56	52	81.3	3.93	.59	86	81.1
5. It has helped me make ethical decisions.	4.12	.60	36	87.8	3.95	.58	51	81.0	4.02	.59	87	83.7
6. It has strengthened my resilience in adverse conditions.	4.21	.56	39	92.9	4.00	.64	51	79.7	4.08	.62	90	84.9
7. It has strengthened my self-confidence.	4.00	.70	34	81.0	4.00	.64	51	79.7	4.00	.66	85	82.0
8. It has helped me face the future with a positive attitude.	4.12	.63	38	90.5	4.17	.61	57	89.1	4.15	.61	95	89.6

Perceptions of program benefits ^a		Semester 1 (n = 42)				Semester 3 (n = 64)				Overall (n = 106)			
		M [†]	SD	Positive Responses ^b		M [†]	SD	Positive Responses ^b		M [†]	SD	Positive Responses ^b	
				n	%			n	%			n	%
9.	It has enhanced my love for life.	3.88	.80	32	76.2	3.83	.66	46	71.9	3.85	.71	78	73.6
10.	It has helped me explore the meaning of life.	3.95	.85	32	76.2	3.91	.68	48	75.0	3.92	.75	80	72.5
11.	It has enhanced my ability of self-leadership.	4.14	.65	38	90.5	4.06	.59	54	85.7	4.10	.61	92	87.6
12.	It has helped me cultivate compassion and care for others.	3.98	.72	33	78.6	3.97	.50	55	85.9	3.97	.59	88	83.0
13.	It has helped me enhance my character strengths comprehensively.	4.00	.66	35	83.3	4.06	.53	57	89.1	4.04	.58	92	86.8
14.	It has enabled me to understand the importance of situational task competencies, character strength and caring disposition in successful leadership.	4.12	.67	37	88.1	4.17	.58	58	90.6	4.15	.61	95	89.6
15.	It has promoted my sense of responsibility in serving the society.	3.90	.73	33	78.6	4.02	.60	53	82.8	3.97	.65	86	81.1
16.	It has promoted my overall development.	4.02	.78	34	81.0	4.11	.51	59	92.2	4.08	.63	93	87.7
17.	The theories, research and concepts covered in the program have enabled me to understand the characteristics of successful service leaders.	4.21	.72	40	95.2	4.16	.57	58	90.6	4.18	.63	98	92.5
18.	The theories, research and concepts covered in the program have helped me synthesize the characteristics of successful service leaders.	4.17	.70	40	95.2	4.09	.61	55	85.9	4.12	.64	95	89.6

Note. ^a Scores on the scale/subscale higher than or equal to 4 were treated as positive responses. ^b For every item, respondents with positive responses (options 4-5) are shown in the Table. [†] 1=Strongly Disagree; 2=Disagree; 3=Neutral; 4=Agree; 5=Strongly Agree.

Table 5. Summary of the participants' Overall Satisfaction (OS) with the program

Satisfaction with the program ^a		Semester 1 (n = 42)				Semester 3 (n = 64)				Overall (n = 106)			
		M	SD	Positive Responses ^b		M	SD	Positive Responses ^b		M	SD	Positive Responses ^b	
				n	%			n	%			n	%
1.	Will you suggest your friends to take this program? ^c	4.10	.48	39	92.9	4.20	.62	57	89.1	4.16	.57	96	90.6
2.	Will you participate in similar programs again in the future? ^c	3.74	.73	30	71.4	3.78	.84	42	65.6	3.76	.80	72	67.9
3.	On the whole, are you satisfied with this program? ^d	4.10	.48	39	92.9	4.20	.48	62	96.9	4.16	.48	101	95.3

Note. ^a Scores on the scale/subscale higher than or equal to 4 were treated as positive responses. ^b For every item, respondents with positive responses (options 4-5) are shown in the Table. ^c 1= Definitely will not, 2 = Will not, 3 = Not sure, 4 = Will, 5 = Definitely will. ^d 1= Very dissatisfied, 2 = Moderately dissatisfied, 3 = Neutral, 4 = Satisfied, 5 = Very satisfied.

Table 6. One-way ANOVA comparing the evaluations on the program of participants in different grade levels

		Sum of Squares	df	Mean Square	F
Program Content	Between Groups	.45	1	.45	2.81
	Within Groups	16.73	104	.16	
	Total	17.18	105		
Program Instructors	Between Groups	.14	1	.14	.76
	Within Groups	19.69	104	.19	
	Total	19.83	105		
Program Benefits	Between Groups	.00	1	.00	.00
	Within Groups	19.53	101	.19	
	Total	19.53	102		
Total Effectiveness	Between Groups	.06	1	.06	.49
	Within Groups	13.31	101	.13	
	Total	13.38	102		
Overall Satisfaction	Between Groups	.19	1	.19	.72
	Within Groups	27.17	104	.26	
	Total	27.36	105		

Table 7. Correlations coefficients among the subscales

Variable(s)	1	2	3	4	5
1) Program Content	1				
2) Program Instructors	.61***	1			
3) Program Benefits	.74***	.36***	1		
4) Total Effectiveness	.91***	.70***	.90***	1	
5) Overall Satisfaction	.64***	.39*	.58***	.64***	1

Note. * $p < .05$; *** $p < .001$.

Table 8. Multiple regression analyses predicting perceived benefits and overall satisfaction

Predictor(s)	Program Benefits				Overall Satisfaction			
	B	SE	β	R ²	B	SE	β	R ²
Program Content	0.69	.04	.76***	.86	0.40	.23	.31	.43
Program Instructors	0.20	.04	.24***		-.14	.125	-.12	
Program Benefits					0.63	.028	.44*	

Note. * $p < .05$; *** $p < .001$.

For inter-correlations between all the subscales of SOES, there were significant positive relationships with the strength ranging from 0.36 to 0.74. Inconsistent with the results in previous studies that only perceived program content predicted program benefits [19, 25], the current study found that both program quality and instructors' quality were significant predictors of program benefits. The relationship implies the importance of both the subject matter and performance of the instructors shape the learning outcomes. It was beyond any doubt that the perception of the students towards the benefits they received was highly dependent on the way of how an instructor in delivering a comprehensive program structure in the program content. The students highly valued the benefits of the program because of the combination of a wide range of skills and abilities that they have learned in the program along with the thoughtful instructors would be beneficial to them in having a competitive edge in

the labor market and advancing their personal development. In addition, program benefits was the significant predictor of overall satisfaction. It was not consistent with past studies that program content and program benefits explained overall satisfaction [25]. The high satisfaction could be due to the overall view of students towards the program benefits that were predicted by the program content and program instructors in order to willingly make a recommendation to their friends in joining this program.

The “Service Leadership” subject was found to be effective in satisfying the needs of university students in promoting the important qualities of successful service leaders and advocating positive youth development. The results were aligned with past studies that participants held a positive perception of the program in its content, instructors, and benefits [19, 20, 25, 26]. The results in current study also had evidently higher percentage of positive responses in program content, quality of program instructors, and program benefits as compared to the reported percentage of positive responses that collected from those who signed up for the “Service Leadership” subject in the academic years of 2012/13 [19], 2013/14 [20, 26], and 2014/15 [25]. The improved perception from students could be partly due to the fact of continuous revision on the program content based on the feedback from previous students and the instructors’ familiarity with ways of delivering the knowledge and experiences to the students.

However, we identified several weaknesses of this study. First, future studies should consider taking an approach that examines other factors which might have an influential effect over the perception towards the program for evaluation, such as program participation (e.g., attendance) and duration of the program lectures. Second, it might also worth exploring the gender relations interactions between instructors and students in the program, suggesting two gender effects that the views of male or female students have on the same- or opposite-sex instructors. Third, the comparison of different evaluation methods, such as objective measure and in-depth qualitative reflections and narratives, are necessary to explore their perception of the learning experience.

Traditionally, leadership style may have been associated with a stronger emphasis on the hierarchical structure to enable and empower the employees to excel. While millennials are gradually taking leadership roles and the Generation Z will begin entering the labor market, it is important for the universities to equip their students in reaching full potentials and advancing their personal development. Obviously, the subject “Service Leadership” is a good way to equip students with leadership qualities in the rapidly changing service economies.

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Chapter 128

IMPACT OF A LEADERSHIP PROGRAM ON THE HOLISTIC DEVELOPMENT OF UNIVERSITY STUDENTS IN HONG KONG

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ABSTRACT

In this chapter we examine the effectiveness of the SOAR Youth Leadership Program in the 2017-2018 academic year, using a mixed-method approach of both quantitative and qualitative evaluation method. There were 49 university students from three universities completed the evaluation on responding to subjective outcome evaluation form and personal reflection form. A significant percentage of student participants expressed positive responses with the program content, program instructors, and program effectiveness. Consistent with our expectation, there were significant positive correlations among program content, program instructors, program effectiveness, total effectiveness, and overall satisfaction. The participants described the program in positive descriptors and all the related metaphors were positive in nature. The results in this study supported the positive and strong influence of the program in promoting leadership skills and competence for our university students.

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INTRODUCTION

Fast changes in the economic and political environment led to a growing demand for effective leadership [1]. Under the influence of globalization, there is a pressing need to improve the leadership skills in meeting the uprising demands of effective management with reference to challenges and uncertainties [2]. Leadership skills are crucial for both personal and professional development, especially in times of crisis. The skills of trustworthiness, collaboration, as well as influencing and inspiring others were considered essential skills by leading experts in both Europe and the United States [3]. The concept of leadership is also transforming. As more millennials are progressing into leadership and management role, they become a major influence in transforming from traditional hierarchical style to a relatively flat culture with less bureaucracy. The conventional approach to managing a team in a rigid manner has shifted to leading a team with more flexibility and openness [4].

Effective leaders often need to be familiar with personal (e.g., be trustable, caring, and moral) and professional (e.g., setting mission, process, and procedures) leadership behaviors to constantly motivate people to willingly contribute their efforts [5]. Benevolent leadership can also bring considerable positive impact and favorable outcomes, such as employees' creativity [6], whereas poor leadership can be destructive and cause losses and damages [7]. Nurturing young talents with leadership has become a top priority in every society's development plan to ensure that young people are equipped with skills and competitiveness in making an impact and leading to create a positive influence on the world.

In response to the rapidly evolving environment, the Global Youth Leadership Institute as an education and research hub that was established by The Hong Kong Polytechnic University is dedicated to nurture their university students through a wide range of cross-cultural, innovative and reflective "Service Leadership" programs that focused on positive values and community engagement [8]. The institute provides training and courses to equip many university students to become leaders and bring positive influence to society. The key objectives of the institute are 1) to nurture global youth leaders with the vision and competence in thinking globally to make contribution to the society, 2) to develop excellence in youth leadership education worldwide through the implementation of pioneering and innovative youth leadership curricula, and 3) to push forward on researching global youth leadership and service-learning education. The programs can better prepare university students with exceptional leadership qualities and global competencies. Systematic evaluation studies showed that students benefit from the programs.

With the global economic integration that creates enormous room and opportunities in collaboration and operations without worrying geography or distance in modern technological landscape, the institute also attempts to support university students' in building capabilities to make connection to different parts of the world through joining an international platform of the University Social Responsibility Network for leadership development. The network was established in 2015 that has a total of 16 member institutions worldwide that covered six out of seven continents, including United States, Canada, Brazil, South Africa, United Kingdom, Israel, Kazakhstan, Korea, Japan, China, Hong Kong, and Australia. The missions of the network are 1) to establish a platform for exchanging concepts, resources, policies, practices, difficulties, and solutions to each of the network members, 2) to develop projects in a collaborative manner with varied scopes and scales within the network, and 3) to contribute to

discussions and development worldwide through networking and partnership within the network, as well as with other allied institutions.

In Hong Kong, the Global Youth Leadership Institute has teamed up with other universities to carry out non-credit programs, such as the SOAR Youth Leadership Program. The program serves as an international exchange platform for building cultural connection and cross-cultural competence. Sponsored by Si Yuan Foundation and Zeshan Foundation, Global Youth Leadership Institute, Peking University, and Xi'an Jiaotong University jointly organized SOAR (Serving heart, Open-mindedness, Aspiration, Responsibility) Youth Leadership Program. SOAR was an integration of two programs, namely the Global Youth Leadership Program and Silk Road Youth Leadership Program. The Global Youth Leadership Program (GYLP) aims at nurturing students at The Hong Kong Polytechnic University and Peking University on qualities of service leadership, such as competencies, character and caring disposition. The program attempts to support students in gaining knowledge, experiences, reflection and hands-on experience through lectures, dialogues, personal experience in activities and service in Mainland China, Hong Kong, and Cambodia.

In a study using six waves of data on objective outcome evaluation, university students from Hong Kong, mainland China, Korea, Taiwan, Thailand, and the United States enrolled in the GYLP program. A total of eighty-nine of them completed all the assessments. The results showed that significant improvement was evidenced across outcome measures on positive attributes of development, competencies in service leadership, and increased satisfaction to life [9]. With the launch of “Belt and Road Initiative” by the Central Government of China, there was an introduction to Silk Road Leadership Program (SRYLP) in the 2015-16 academic year to students at The Hong Kong Polytechnic University, Peking University, and Xi'an Jiaotong University. The evaluation on a 3.5-day (21 hours) service leadership program of SRYLP was highly positive on its program content, program instructors, and program benefits, with nearly 90% of the student participants showed program satisfaction [10]. The evaluations on different components of the program resulted in significant positive correlations. While perceived program content from the student participants predicted program benefits, the content and perceived program benefits predicted the overall satisfaction that was rated by the students. In a pre-and-post study using objective outcome evaluation that examined changes in university students after attending an intensive program under “Silk Road Youth Leadership Program” in mainland China, results showed that students experienced a positive impact on improving their knowledge on youth development, satisfaction to life, service leadership beliefs and qualities [11]. Over three assessment periods (i.e., pre-test before the program, post-test immediately after the program, and 12-day follow-up test after the program), the results also indicated a stable trend of improvement on these measures and significantly or marginally higher scores at post-test and follow-up test.

Evaluation of the leadership programs' effectiveness and participants' recommendation is essential in providing constructive feedback, which can be addressed in the planning and implementation of future programs [12, 13]. For example, a study found that particular personal characteristics of a program instructor, such as having a sense of humor and youth engagement strategies, could increase the effectiveness of positive youth development [14]. Therefore, the identification of staff members' characteristics and performance on how to engage with youth can provide a competitive edge. Gender differences in relation to leadership development programs were also revealed in other evaluation studies. When

participants' reflection in leadership development programs was used as a measure of effectiveness, the results found that there were subtle changes in the behavioral and cognitive responses along the way [15].

As leadership programs are at its infancy in Hong Kong, there is a need for collecting more supporting evidence on the effectiveness of leadership programs. In this study, we examine the Youth Leadership Program's effectiveness in the 2017-2018 academic year. The leadership program was developed to cultivate students in a holistic manner, including the promotion of their moral character (sense of social reasonability), leadership competencies (intrapersonal, interpersonal, and self-leadership), and caring disposition in maintaining a positive relationship. During the one-year program, the university students that enrolled were introduced to the basic models of leadership, basic attributes of leadership, reflection on their leadership qualities, application of knowledge as a promising leader, and the need for their development. The students also participated in study trips, youth forum, and service learning in the "Belt and Road Initiative" countries with a focus on the concept of service leadership and the development of China, Central Asia, and the Middle East. The opportunity in the discovery that was given in the program supported them to constantly reflect their personal values and build up self-confidence. All the knowledge and experience was important for the students to demonstrate their competencies in leading and understanding the needs of various stakeholders and to utilize their skills to lead others and the society in moving forward.

To assess the program effectiveness at The Hong Kong Polytechnic University, we have previously used several approaches for evaluation, such as objective and subjective outcome evaluations and qualitative evaluation. This evaluation study adopted the mixed-method approach (i.e., integration of quantitative and qualitative evaluation method) to assess program effectiveness. Mixed method research employs both approaches to evaluate a program from different perspectives. By integrating the quantitative data with qualitative data, it will provide a more comprehensive picture of the program impact in a more elaborated manner. This approach helps to explore broader perspectives and reveal relationships that occur between the layers of the multifaceted research questions [16]. The results of a mixed-method approach can increase findings of reliability and credibility by revealing concepts that are a representation of the phenomenon.

In this study, upon the program completion, the students were asked to provide their personal views and learning experience of the program. There are several expectations. First, if the program worked well, we would expect a high proportion of the participants showing positive responses. Second, based on previous research, we would expect significant correlations amongst different components of subjective outcome evaluation (i.e., program content, instructor quality, program effectiveness). Third, it was expected that the qualitative data would present the views of the students to be positive in nature.

OUR STUDY

In the 2017-2018 academic year, a total of 49 students completed the SOAR Youth Leadership program in Xi'an. There were 17 males (34.7%), 30 females (61.2%), and two students not indicating their gender status (4.1%). The students primarily came from three different universities - 22 from the Hong Kong Polytechnic University, 12 from Peking

University, 13 from Xian Jiaotong University, and two unknowns. The age range of the students was between the age of 17 to 21, with the mean age of 18.9 years.

The effectiveness of the SOAR Youth Leadership program in Xi'an in the 2017-2018 academic year was examined by the mixed-method approach of integrating both quantitative and qualitative analysis. Students' informed consent was obtained before the study, with the emphasis on confidentiality, anonymity and voluntary participation. They were also being informed of the rights to withdraw from this study without any consequences. All the data were collected by the program instructors that followed a standardized data collection protocol.

Instruments

The Subjective Outcome Evaluation Form targeted to measure students' views of the program. It is a validated measure that was used in previous studies on assessing participants' perceptions [17]. There were 10 items each on evaluating program content (e.g., such as objective, content design, and activities) and program instructor (e.g., mastery, preparation, and teaching skills). The possible responses are 1 (Strongly disagree), 2 (Disagree), 3 (Neutral), 4 (Agree), and 5 (Strongly agree). Further, there were 18 items on evaluating program effectiveness (e.g., enhancement on participants' social competence, self-awareness, and resilience). The possible responses are 1 (Very unhelpful), 2 (Unhelpful), 3 (Not sure), 4 (Helpful), and 5 (Very helpful). Following program effectiveness, there were 3 items also using five-point Likert scale that measure the participants' willingness in recommending the program to their peers, willingness in participating similar program from this time forward, and their contentment with the program. At last, there were 4 open-ended questions concerning the participants' program experience, including the most important thing(s) learned in the program, the things that most appreciated, comments about program instructors, and areas for improvement.

The Personal Reflection Form was used to measure participants' responses to the overall learning experience in the program. They were invited to give feedback on the program on a reflection sheet that consisted of two parts: 1) to ask participants to use three words or phrases as descriptors (e.g., interesting, boring, reflective) to describe their feelings, perceptions, and experiences of the program, and 2) to think of an object, an event, or state as metaphors that can be best described the program. (e.g., an enjoyable experience, a compass) and a brief explanation of the meaning of the metaphors they used. This method of narrating in descriptors and metaphors was effectively used in the previous studies [18, 19, 20, 21].

Data Analyses

For quantitative data, there were analyses on reliability to examine the internal consistency of the subjective outcome evaluation form. Descriptive statistical analyses were performed to assess the participants' responses to the content, program instructors, program effectiveness, and perceptions of other aspects. Pearson's correlation tests were used to

understand any inter-correlation coefficients between the program content, program instructors, program effectiveness, total effectiveness, and overall satisfaction.

For qualitative analysis, data of subjective outcome evaluation form and personal reflection form were coded and categorized by an independent researcher with training in social sciences, who was blinded and had no involvement in the study. Participants’ qualitative responses were categorized into 1) positive, 2) neutral, 3) negative, or 4) undecided. Coding of descriptors and metaphors of the personal reflection form was completed prior to categorization. A statement that consists of two meaningful units was separated into two independent meaningful units, for instance, “interesting and fruitful” into “interesting” and “fruitful.” Meanwhile, two statements with similar meaningful units were grouped into one meaningful unit, for instance, “funny” and “interesting” into “funny/interesting.” Descriptive statistical analyses with highlights were performed to examine participants’ responses to the program. Inter- and intra-rater reliability measures were computed.

FINDINGS

Table 1 shows the mean, standard deviation, and reliability analyses. The internal consistency of the subjective outcome evaluation form was high. Program instructors had the highest mean score (Mean = 4.33, SD = .51), followed by program content (Mean = 4.24, SD = .55) and total effectiveness (Mean = 4.19, SD = .55). The lowest mean score was overall satisfaction (Mean = 3.93, SD = .79). The Cronbach’s alpha of program content, program instructors and program effectiveness ranged from .90 to .96. The Cronbach’s alpha of total effectiveness is .97, whereas overall satisfaction is .88.

Table 1. Mean, standard deviation, Cronbach’s alphas, and mean of inter-item correlations

Variable(s)	Mean	Standard deviation	Cronbach's alpha	Mean inter-item correlations
Program content (10 items)	4.24	.55	.90	.47
Program instructors (10 items)	4.33	.51	.91	.52
Program effectiveness (18 items)	4.09	.63	.96	.57
Total effectiveness (38 items)	4.19	.55	.97	.49
Overall Satisfaction (3 items)	3.93	.79	.88	.73

Table 2 to 5 present the results of descriptive statistical analyses. Consistent with our expectation, a significant proportion of the student participants expressed their satisfaction. The evaluation on program content received 77.6% to 98.0% of positive responses that rated agree or strongly agree, with the highest percentage of positive responses were pleasant classroom atmosphere (98.0%) and a great amount of peer interaction (95.9%) (see Table 2). The lowest percentage of positive response on program content was the learning experience that enhanced interest in the lessons (77.6%). The evaluation of program instructors received 75.5% to 95.9% of positive responses (see Table 3). There were four items on program instructors received the highest percentage of positive responses (95.9%), including good preparation, encouragement for students to participate in activities, caring for students, and

much interaction with students. The lowest percentage of positive response on program instructor was the teaching skills were good (75.5%). A high proportion of student participants (71.4% to 95.9%) gave positive responses to items on program effectiveness (see Table 4). Two items exceed 90% of positive responses – cultivation for compassion and caring (95.9%) and enhancement on self-leadership ability (91.8%). The lowest percentage of positive response on program effectiveness was the program has strengthened self-confidence (71.4%). Further, as shown in Table 5, there were 44 out of 49 participants (88.9%) expressed positive satisfaction with the program. More than two-thirds of the participants (77.6%) reported their willingness to recommend other peers in taking the program. A total of 65.3% of participants also expressed their willingness to enroll in similar programs in the future. In summary, they were contented with the program and certain areas of improvement will be needed.

Table 6 shows the Pearson correlation analyses. As predicted, significant correlation coefficients were observed in program content, program instructors, program effectiveness, total effectiveness, and overall satisfaction. Both program content ($r = .86, p < .001$) and program instructors ($r = .81, p < .001$) were positively correlated with program effectiveness. Meanwhile, there was a significant positive correlation between program content and program instructors ($r = .81, p < .001$). Total effectiveness also showed a significantly positive correlation with program content ($r = .94, p < .001$), program instructors ($r = .90, p < .001$), and program effectiveness ($r = .97, p < .001$). Regarding overall satisfaction, significant positive correlation was observed with program content ($r = .78, p < .001$), program instructors ($r = .72, p < .001$), program effectiveness ($r = .76, p < .001$), and total effectiveness ($r = .80, p < .001$). To conclude, participants' evaluation on different aspects of the program appeared to be consistent and strongly inter-correlated.

Table 7 summarizes the participants' written comments on the program. A total of 91.8% of participants expressed positive responses to the most important things that they learned in the program, a finding which supports our expectation. For instance, one of the students commented that "Respect. Be humble to learn from different people. Serve before leading," while another student commented, "Different people have different angles, and other classmates/opinions force me to think critically more." In regards to the things that participants most appreciated in the program, 98% of the respondents expressed their appreciation, with 48 out of 49 participants rated positive responses. The quotes were "Instructors always give us much time to share our opinions, to play interactive games and to reflect what we've learned in the class." and "There are a lot of interactions within the students and also with the tutors." Meanwhile, there were 59.2% of the participants commented positively on the program instructors. They described the instructors as "a strong sense of caring disposition. She presents the content very well with passion. Listening to their sharing is indeed meaningful" and "patient and loving; very professional and caring." When asking for areas of improvement, there were 87.8% of the participants expressed their views, such as "can be taught with more academic way and more example of real cases about leadership," "more discussion with other groups may be better for us to make new friends and gain more ideas," and "more thorough explanations on theories or practical usages."

Table 2. Descriptive statistics of the participants' evaluations on the program content

Your views towards the program contents:	1 Strongly Disagree		2 Disagree		3 Neutral		4 Agree		5 Strongly Agree		Positive responses (Options 4-5)	
	n	%	n	%	n	%	n	%	n	%	n	%
1) The objectives of the curriculum are very clear.	1	2.0	4	8.2	0	0.0	31	63.3	13	26.5	44	89.8
2) The design of the curriculum is very good.	1	2.0	10	20.4	0	0.0	26	53.1	12	24.5	38	77.6
3) The activities were carefully planned.	1	2.0	4	8.2	0	0.0	20	40.8	24	49.0	44	89.8
4) The classroom atmosphere was very pleasant.	0	0.0	0	0.0	1	2.0	13	26.5	35	71.4	48	98.0
5) There was much peer interaction among the students.	0	0.0	0	0.0	2	4.1	12	24.5	35	71.4	47	95.9
6) I participated actively during lessons (including discussions, sharing, games, etc.).	0	0.0	1	2.0	5	10.2	26	53.1	17	34.7	43	87.8
7) I was encouraged to do my best.	0	0.0	3	6.1	4	8.2	24	49.0	18	36.7	42	85.7
8) The learning experience I encountered enhanced my interest towards the lessons.	1	2.0	2	4.1	8	16.3	25	51.0	13	26.5	38	77.6
9) Overall speaking, I have a very positive evaluation of the program.	1	2.0	0	0.0	7	14.3	23	46.9	18	36.7	41	83.7
10) On the whole, I like this curriculum very much.	1	2.0	0	0.0	8	16.3	23	46.9	17	34.7	40	81.6

Table 3. Descriptive statistics of the participants' evaluations of the program instructors

Your views towards the instructor(s):	1 Strongly Disagree		2 Disagree		3 Neutral		4 Agree		5 Strongly Agree		Positive responses (Options 4-5)	
	n	%	n	%	n	%	n	%	n	%	n	%
1) The instructor(s) had a good mastery of the curriculum.	1	2.0	0	0.0	5	10.2	31	63.3	12	24.5	43	87.8
2) The instructor(s) was well prepared for the lessons.	0	0.0	1	2.0	1	2.0	22	44.9	25	51.0	47	95.9
3) The instructor(s)' teaching skills were good.	1	2.0	1	2.0	10	20.4	26	53.1	11	22.4	37	75.5
4) The instructor(s) showed good professional attitudes.	0	0.0	2	4.1	5	10.2	25	51.0	17	34.7	42	85.7
5) The instructor(s) was very involved.	0	0.0	0	0.0	3	6.1	24	49.0	22	44.9	46	93.9
6) The instructor(s) encouraged students to participate in the activities.	0	0.0	0	0.0	2	4.1	17	34.7	30	61.2	47	95.9
7) The instructor(s) cared for the students.	0	0.0	0	0.0	2	4.1	19	38.8	28	57.1	47	95.9
8) The instructor(s) was ready to offer help to students when needed.	0	0.0	0	0.0	3	6.1	23	46.9	23	46.9	46	93.9
9) The instructor(s) had much interaction with the students.	0	0.0	0	0.0	2	4.1	25	51.0	22	44.9	47	95.9
10) Overall speaking, I have a very positive evaluation of the instructors.	1	2.0	0	0.0	3	6.1	22	44.9	23	46.9	45	91.8

Table 4. Descriptive statistics of the participants' evaluations of the program effectiveness

The extent to which the program has helped you:	1 Very unhelpful		2 Unhelpful		3 Not sure		4 Helpful		5 Very Helpful		Positive responses (Options 4-5)	
	n	%	n	%	n	%	n	%	n	%	n	%
1) It has enhanced my social competence.	1	2.0	1	2.0	3	6.1	29	59.2	15	30.6	44	89.8
2) It has improved my ability in expressing and handling my emotions.	0	0.0	2	4.1	6	12.2	25	51.0	16	32.7	41	83.7
3) It has enhanced my critical thinking.	1	2.0	2	4.1	7	14.3	26	53.1	13	26.5	39	79.6
4) It has increased my competence in making sensible and wise choices.	1	2.0	1	2.0	8	16.3	25	51.0	14	28.6	39	79.6
5) It has helped me make ethical decisions.	2	4.1	0	0.0	3	6.1	27	55.1	17	34.7	44	89.8
6) It has strengthened my resilience in adverse conditions.	1	2.0	0	0.0	11	22.4	24	49.0	13	26.5	37	75.5
7) It has strengthened my self-confidence.	1	2.0	2	4.1	11	22.4	19	38.8	16	32.7	35	71.4
8) It has helped me face the future with a positive attitude.	1	2.0	0	0.0	6	12.2	22	44.9	20	40.8	42	85.7
9) It has enhanced my love for life.	1	2.0	1	2.0	11	22.4	23	46.9	13	26.5	36	73.5
10) It has helped me explore the meaning of life.	1	2.0	2	4.1	8	16.3	23	46.9	15	30.6	38	77.6
11) It has enhanced my ability of self-leadership.	1	2.0	0	0.0	3	6.1	31	63.3	14	28.6	45	91.8
12) It has helped me cultivate compassion and care for others.	1	2.0	0	0.0	1	2.0	28	57.1	19	38.8	47	95.9
13) It has helped me enhance my character strengths comprehensively.	1	2.0	1	2.0	6	12.2	27	55.1	14	28.6	41	83.7
14) It has enabled me to understand the importance of	1	2.0	0	0.0	4	8.2	29	59.2	15	30.6	44	89.8
15) It has promoted my sense of responsibility in serving the society.	0	0.0	2	4.1	3	6.1	24	49.0	20	40.8	44	89.8
16) It has promoted my overall development.	1	2.0	0	0.0	7	14.3	29	59.2	12	24.5	41	83.7
17) The theories, research and concepts covered in the program have enabled me to understand the characteristics of successful service leaders.	1	2.0	0	0.0	7	14.3	27	55.1	14	28.6	41	83.7
18) The theories, research and concepts covered in the program have helped me synthesize the characteristics of successful service leaders.	1	2.0	1	2.0	6	12.2	26	53.1	15	30.6	41	83.7

Table 5. Summary of the participants' positive perceptions of other aspects

Item(s)	Positive responses (Options 4-5)	
	<i>n</i>	%
1) Will you suggest your friends to take this program? ^a	38	77.6
2) Will you participate in similar programs again in the future? ^a	32	65.3
3) On the whole, are you satisfied with this program? ^b	44	89.8

Note:

^a 1 = Definitely will not, 2 = Will not, 3 = Not sure, 4 = Will, 5 = Definitely will.

^b 1 = Very dissatisfied, 2 = Moderately dissatisfied, 3 = Neutral, 4 = Satisfied, 5 = Very satisfied.

Table 6. Pearson correlations among program content, program instructors, and program effectiveness

Variable(s)	1	2	3	4	5
1) Program content (10 items)	-				
2) Program instructors (10 items)	.81***	-			
3) Program effectiveness (18 items)	.86***	.81***	-		
4) Total effectiveness	.94***	.90***	.97***	-	
5) Overall Satisfaction	.78***	.72***	.76***	.80***	-

Note: *** $p < .001$.

Table 7. Summary of students' written comments on the program

Item(s)	Positive responses	Total responses	Percentage (%)	Highlights
1) The most important thing(s) learned in the program	45	49	91.8	"Respect. Be humble to learn from different people. Serve before leading." "I learned how to care about others" "Different people have different angles; and other classmates/ opinions force me to think critically more."
2) The things that appreciated most in the program	48	49	98.0	"The interactive atmosphere in the classroom, warm up activity also create a good atmosphere" "Instructors always give us many time to share our opinions, to play interactive games and to reflect what we've learnt in the class." "There are a lot of interactions within the students and also with the tutors."
3) Comments on the instructor(s)	29	49	59.2	"Very good activity planning, meaningful and interesting" "Patient and loving; very professional and caring" "The instructors show a strong sense of caring disposition. She presents the content very well with passion. Listening to their sharing is indeed meaningful."
4) Areas for improvement	43	49	87.8	"The program can be taught with more academic way and more example of real cases about leadership." "More discussion with other groups may be better for us to make new friends and gain more great ideas." "More thorough explanations on theories or practical usages."

Table 8. Categorization of descriptors used by the participants to describe the program

Descriptor(s)	Nature of the Response				Total
	Positive	Neutral	Negative	Undecided	
Fun / funny / interesting / enjoyable / exciting / happy / pleasant / satisfying / cheerful / warm / encouraging / active / energetic / optimistic	35				
Beneficial / benefits of personal all round development / helpful / help me to reflect / help me to understand / help to learn myself better / helpful for finding the meaning of my life / helpful in leadership-learning / helpful to let me interact more with my groupmate / helpful to my character development / helpful to my development / helpful to understand others / useful / useful to my social work discipline	20				
Meaningful / meaningful for me to think more / meaningful for my life	10				
Inspiration / inspirational / inspiring / inspiring new ideas / very inspiring in the end	9				
Reflective / have time for reflection / contemplative / provoking / think-provoking / thought provoking	9				
Fruitful/ fruitful program / full contents / diversified	5				
Interactive / interactive design for many sharing / full of interaction / very very very interactive for the activities and the sharing of students	5				
Informational / informative / intensive	4				
Novel / novel and different from normal program / unusual / different from any other programs I took before	4				
Unforgettable / impressing	4				
Better understanding of each other / building friendships	2				
Good learning opportunity / learn much	2				
Turn over a new leaf / morphing	2				
Well-organized	2				
Other positive responses	22				
Development		1			
Challenge		1			
Love		1			
Time-consuming / sometimes a little bit slow in path/ kind of slow			3		
Sometimes boring / boring at the beginning/ tired			3		
A bit aesthetic / too abstract			2		
A little noisy actually			1		
Less knowledge part will be better			1		
Total Count (N):	135	3	10	0	148
Total Count (%):	91.2%	2.0%	6.8%	0.0%	100.0%

Note: Other positive responses included the positive descriptors once or twice.

Table 8 presents the categorization of descriptors that were used by the student participants to express their description of the program. A total of 148 descriptors were found, with 91.2% (n = 135) were positive, 2.0% (n = 3) were neutral, and 6.8% (n = 10) were negative. The two positive responses that most frequently bought up by the participants were “funny / interesting / enjoyable / satisfying” (n = 35) or “beneficial / helpful / useful” (n = 20). Other noticeable and positive descriptors were “meaningful” (n = 10), “inspiring” (n = 9), “reflective” (n = 9), “fruitful” (n = 5), and “interactive” (n = 5). Three neutral descriptors were identified, including “development” (n = 1), “challenge” (n = 1), and “love” (n = 1). Negative descriptors were “time-consuming / slow in path” (n = 3), “boring” (n = 3), “too abstract” (n = 2), “a little noisy” (n = 1), and “less knowledge part will be better” (n = 1).

Table 9. Categorization of the metaphors used by the participants to describe the program

Metaphor(s)	Nature of the Metaphor				Number of Codes Derived from the Metaphor and Its Nature					
	Positive	Neutral	Negative	Undecided	Total	Positive	Neutral	Negative	Undecided	Total
A sour candy / candy / dark chocolate / pizza / smarties	5					12	1	2		
A window / an open door / key / the key to a new door	5					11		1		
Beacon / beacon light / flash light / light	5					5		1		
A novel trip / an enjoyable tour / an excursion to an old place / navigator / crossroad	5					10				
A big green tree / tree / a seed / fertilizer	4					6				
Book / an English book / dictionary	3					4	1	1		
Friend / a big party / a warm home	3					9	1			
A compass / compass in life	2					7				
A ripple / water surface	2					1	1			
Symphony / a comedy	2					6	1			
The head of fleet / a boat	2					3	1			
Other positive responses (e.g., butterfly, gas station, internet, mirror)	9					16	1	3	1	
Total Count (N):	47	0	0	0	47	90	7	8	1	106
Total Count (%):	100.0%	0.0%	0.0%	0.0%	100.0%	84.9%	6.6%	7.6%	0.9%	100.0%

Note: Other positive responses included the positive metaphors reported once or twice.

Table 9 is the categorization of metaphors that were used to describe their views on the program and codes that were derived from those metaphors. There were 47 metaphors identified and 106 meaningful codes derived. All the metaphors were positive in nature (100%), such as “candy / chocolate” (n = 5), “window / key” (n = 5), “beacon light / flashlight” (n = 5), or “tour / excursion” (n = 5). The nature of the metaphors was also categorized into meaningful pieces and codes. The codes derived from those metaphors were 84.9% positive (n = 90), 6.6% neutral (n = 7), 7.6% negative (n = 8), and 0.9% undecided (n = 1). The examples are as follows:

- Candy/chocolate: “The program is sweet and touch and I met a lot of interested persons in several days.”; “If you pay focus, you will find something useful. Like the sweet taste after a bar of dark chocolate.”
- Window/key: “It helps me to understand myself better and reminds the significant values and qualities to become a service leader. And, it encourages me to be more active and brave to speak out your mind in public”; “It’s hard for me to meet so many new friends from Hong Kong (PolyU) and Peking U and have such a long-term trip with them. This course is just like a key and help me open a new door for leadership-learning and so many interesting friends.”
- Light/flashlight: “I learn a lot in this program and the program is very different and it is full of energy and fun.”; “It is the course provide a platform that makes it a lot easier for me to understand it in a new way and it is like a flashlight to make my path clearer and brighter.”
- Tour/excursion: “I know more and think more about myself. I have met some interesting friends I have gained lots of fun through the class and game.”; “I have learned some of the knowledge and skills in this course and I am really thankful to know and recall the knowledge that strengthens my skills that can actually replenish the missing part of the previous course.”

DISCUSSION

Considering the SOAR Youth Leadership Program in the 2017-2018 academic year is a non-credit-bearing program, the enrollment of the participants evidently illustrates the potential upsides and the value of this program. In summary, the findings indicated that the program supported the hypothesis of positive and strong influence in promoting leadership skills and competence for our university students. The findings are consistent with past studies that examined similar program in both scale and sub-scale with good reliability [9, 10].

From the descriptive statistical analyses, the findings presented a significant percentage of the students expressed encouraging responses with the program content, program instructors, and program effectiveness. It reinforced the effectiveness of the SOAR Youth Leadership Program. The results of Pearson’s correlation analyses also supported that there were significant positive correlations among program content, program instructors, program effectiveness, total effectiveness, and overall satisfaction. The findings of both positive

responses and significant positive correlations may further provide evidence of the successful recognition of the program.

The qualitative component of the research echoed the quantitative phase of research, showing positive responses to the program effectiveness. The comments written by the participants indicated that they learned the important elements of a good leader, such as “respect,” “willing to serve,” “empathy,” and “self-reflection.” Many of them expressed the appreciation and described the program as “interactive” rather than the labeling of “inflexible” and “boring” lectures. More than half of the participants also rated positive for the instructors, with the description of “caring” and “patient and loving.” The participants also provided constructive feedback on future planning and implementation, such as “more example of real cases about leadership” and “more thorough explanations on theories or practical usage.” In line with the quantitative phase, subjective outcome evaluation form captured positive evaluation on the effectiveness and satisfaction with the SOAR Youth Leadership Program in the 2017-2018 academic year.

The data derived from personal reflection form also generated qualitative data that worth investigating more in-depth evidence of the effectiveness and outcome of the program. With over 90% of the descriptors given by the participants were categorized as positive responses, the most commonly used descriptors were “funny/interesting” and “beneficial/helpful/useful.” The results were very encouraging and promising. The results also revealed that the program was not only about having a “pleasant” experience but also providing opportunities to think more about “meaningful” for their lives. If looking into the negative descriptors, we could still find a certain percentage of the participants think that the program was “boring” and “slow.” It is important that the program implementation can be frequently reviewed to ensure that the elements of the program are meeting the needs of the students as much as possible and making necessary age- and gender-specific adjustments. Besides, the metaphors used by the participants in this study also showed great similarities in a previous study [19]. The students in both studies described the program as “candy,” opened a “window/door,” guided by “beacon” or “compass,” had a “journey,” fertilized as a “tree,” or read a “book.” The implication of the metaphors resonated with the descriptors.

There are several strengths of the study. First, the results of reliability analyses showed that the internal consistency was high, which indicates a reliable measure of the subjective outcome evaluation form. Second, the study adopted a mixed-method approach, integrating both quantitative and qualitative analysis. The results of using both analyses provided a more detailed view of the participants towards the program and increased reliability and credibility. Third, this is a continuous program that targeted at promoting positive youth development program of the Global Youth Leadership Institute. The results of the SOAR Youth Leadership Program in the 2017-2018 academic year echoed with studies that were examined in previous years. Such consistencies made the effectiveness of this program more conclusive. Finally, the results of the study allowed the program instructors to make corresponding adjustments that were reflected from the participants’ feedback and to contribute to the future planning and implementation of similar programs.

The study also has several limitations. First, as only program instructors, program content and program effectiveness were being evaluated, future studies should consider bringing in other aspects of the program for evaluation, such as administrative arrangement, program engagement, and duration for discussions. Second, the subjective outcome evaluation part can be hugely affected by a person’s subjective impression. Third, the study only examined the

student participants' perceptions of the program. It could be meaningful to also measure the perceptions of other stakeholders, such as program instructors, to provide a more comprehensive understanding of the interactions.

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Chapter 129

THE EFFECTIVENESS OF A SERVICE LEADERSHIP SUBJECT IN HONG KONG: A QUALITATIVE EVALUATION STUDY

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ABSTRACT

This chapter presents a qualitative evaluation of a credit-bearing, service leadership subject (2016/2017 academic year) at The Hong Kong Polytechnic University. It drew on data collected from three courses carried out in different semesters and venues, and with different degree of intensity. Students (n=76 for the semester 1 course, n=79 for the semester 3 course, n= 64 for the Cambodian summer camp) were invited to reflect on their learning experiences and report their perspectives towards the subject by using three descriptors and one metaphor. Findings demonstrated that the majority of students (more than 80%) evaluated the subject positively with positive perception of their learning experiences. They also perceived this service leadership subject to be effective to enhance their holistic development and nurture service leadership in them.

INTRODUCTION

The contemporary world has gradually shifted from an industrial society that emphasizes manufacturing to a post-industrial society that emphasizes service [1-3]. In Hong Kong, the services sector has occupied the dominant position with a contribution of more than 92% to Hong Kong GDP from 2008 to 2017 [4]. This transformation of society has given rise to an evolving demand in leadership of future generation from directive and autocratic to

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collaborative and empowering [2]. Only those who acquire good intrapersonal and interpersonal competencies besides their professional skills are able to provide high-quality services and thrive in the service economy [5].

Against this background, there have been a proliferation of theories and models in the field of effective leadership. For example, Conger and his colleagues [6-9] established a model of charismatic leadership, which perceives that leaders win reverence and trust from their followers not just because of the possessed authority and power but their extraordinary character.

Leaders should be a role model for their followers by exhibiting personal charisma such as an inspirational vision and impressive behavior. Greenleaf [10], as one of the pioneers, put forward the concept of servant leadership where he stressed on the power of leadership as a means to serve and empower followers and help them grow. However, Greenleaf's theory was argued by many as vague in definition and lacking of conceptualization and theorization [11]. Similarly, the model of spiritual leadership also underscores qualities of altruistic love, hope, and faith in being a leader. As spiritual leaders, they are expected to create a sense of membership among the team, motivate followers and leaders themselves, and promote the psychological well-being of the whole organization [12, 13]. However, it is argued that this model places less emphasis on the "functional abilities of leaders" [5]. Another influential model is Astin and Astin's Social Change Model [14], which also breaks away from the traditional roles of leadership and aims at using leadership to promote positive social changes. This model comprises eight interdependent core values of leadership, i.e., "consciousness of self, congruence, commitment, collaboration, common purpose, controversy with civility, citizenship and change."

In this model, leadership is perceived as a developmental process rather than a fixed and static position [15]. Studies have been carried out based on this perspective. For example, in a study aiming to examine the effectiveness of a 16-week, credit-bearing leadership course in an American university, the pre- and post-test results showed that college students, regardless of their age and gender, were able to develop more capabilities for socially responsible leaders, even more so for female students in terms of their development in the core values of collaboration and citizenship [16]. In a similar vein, Haber and Komives' [17] quantitative study also confirmed that for university students, participation in college student organization, among others activities, contributed the most to nurturing socially responsible leaders. These studies provided empirical evidence that leadership can be taught and trained at tertiary educational level.

Building on Chinese culture and context, Chung [18] carried forward the concept of service leadership and defined it as "satisfying needs by consistently providing quality personal service to everyone one comes into contact with, including one's self, others, groups, communities, systems, and environments." This notion was conceptualized as a 3Cs model that incorporates three major principles, i.e., competence, character, and care, in determining effective service leadership. In this model, the last two principles, character and care, were attached equal or even more importance than the principle of competence. There are seven core beliefs and several distinctive features developed within the model. For example, service leadership believes that everyone has the potential to be a leader, a perspective of which essentially distinguishes from the aforementioned charismatic leadership which underlines an idealized role of a leader [5, 18]. Service leadership also holds the belief that "leadership effectiveness and service satisfaction are dependent on a leader or service provider possessing

relevant situational task competencies plus being judged by superiors, peers, and subordinates as possessing character and exhibiting care” [18]. It underlines traditional leadership skills and competences as well as character and caring disposition. Another note-worthy belief is that service leadership lays emphasis on a balanced attention given to the needs of self, others and systems, and does not necessarily underscore the precedence of others over self [5, 18, 19]. In this sense, these scholars advanced the notion of servant leadership and spiritual leadership to service leadership by acknowledging that self-serving is also a type of service and also cannot be neglected [20]. Self-leadership and self-reflection are also highlighted in the model of service leadership, as they facilitate leaders to constantly monitor the goals they set and motivate themselves to seek continuous improvement in leadership [5, 18]. This notion, however, is not reflected in the model of servant leadership as well [5]. As a service leadership model rooted in Chinese culture, it incorporates Chinese values of Buddhism and Confucianism such as harmony, inner peace, self-reflection, and concern for others [3]. This service leadership, as Chung and Bell [21] argued, is essential to the current service economy of Hong Kong.

Higher education is an important incubator to nurture future leaders through curriculum and projects [14]. However, leadership education has often occupied a subordinate position in universities, and it has been considered inadequate at tertiary education level in reality [22, 23]. In addition, there have been relatively fewer leadership programs that aim to nurture students’ service leadership skills and beliefs oriented to our service-oriented society [2]. In order to meet the high demand of service leaders in Hong Kong society, the Hong Kong Institute of Leadership and Management was founded to assist various stakeholders such as higher educational institutions and government branches to promote service leadership education and practice [24]. Accordingly, the eight universities funded by the University Grants Committee (UGC) have then gradually introduced both credit-bearing and noncredit-bearing service leadership programs to bridge this gap [1]. For these programs, the aforementioned 3Cs model has been established as a theoretical framework for practice [25].

The present study is based on the data collected from one of the Service Leadership subjects entitled “Service Leadership,” which has been carried out in The Hong Kong Polytechnic University (PolyU) since 2012/2013 academic year. This credit-bearing course aims to enhance undergraduate students’ understanding of service leader, cultivate service leadership in them and promote the application of attributes of effective service leadership. To be specific, the intended learning outcomes are shown as below: “a) Understand the contemporary models of leadership with reference to the service sector, including their assertions, strengths and weaknesses; b) Demonstrate understanding of the basic leadership attributes intrinsic to effective service leaders; c) Reflect upon the need for developing the qualities of effective service leaders and their own leadership qualities; d) Appreciate the potential application of knowledge on effective service leadership gained in this subject to oneself” [26].

This subject has been evaluated by previous studies drawing upon both quantitative and qualitative methods, including objective outcome evaluation through pre- and post-tests and qualitative evaluation through analyzing descriptors and metaphors, e.g., Shek and his team’s evaluative work for this subject in 2013/2014 and 2014/2015 academic year respectively [2, 3, 24, 27-30]. Overall, these studies have supported the effectiveness of the subject over the years as well as the positive influence the courses exerted on students. In the objective outcome evaluations, positive changes were found in participants’ service leadership

qualities, positive youth development qualities, and life satisfaction. For example, in a quasi-experimental study that involved both experiential and control groups, Lin and Shek [30] found that participation in this course contributed to great improvement in terms of service leadership attitude and knowledge as well as life satisfaction, which confirmed that service leadership could be trained. With reference to the studies of qualitative evaluation, results showed that the overwhelming majority of students perceived their learning experiences very positively. Many students considered the course with good instrumental value and were “useful” and “helpful” for personal development, while also providing guidance or reference to students within a meaningful and interesting learning environment [e.g., 2, 27]. This subject has been conducted in different semesters, venues (e.g., Xi’an, Beijing, and Cambodia) and with different degrees of intensity. Many of these courses have been evaluated individually with regard to the effectiveness of the course and changes of students after participation. However, there has been a scarcity of research to take an overall perspective and compare the effectiveness of these courses within the same subject. This is the research gap the present study attempts to bridge.

For the present study, the overall dataset was based on three courses under the same subject, “Service Leadership,” which resembled each other in content, syllabus, assessment, and intended learning outcomes, but were carried out in different time and venues. The first course was a regular, 13-week module conducted in the 1st semester of 2016/17 in PolyU. The second was a more intensive module with two lectures given each week and a duration of 6.5 weeks in total in the 3rd semester of the same academic year. The third engaged students in a two-week intensive teaching and learning summer camp in Cambodia with field visits and course attendance in the 3rd semester.

The purpose of this study is to evaluate the overall effectiveness of the subject and compare across the three courses by drawing on a qualitative evaluation. A quantitative evaluation is considered more adequate in generalizing findings, validating assumptions and generating patterns [31]. However, it is often confined to prescribed variables, slicing up realities into discrete pieces [32]. Qualitative evaluation, on the other hand, has the potential to capture the dynamics and complexity of a phenomenon, experiences, live stories and deep emotions, etc., all of which may not be easily reduced to numbers, statistics, and quantification [33]. Therefore, it maintains a depth in understanding complex phenomena and multiple realities such as how respondents make sense of the social world [33, 34]. Second, as it is more open-ended by nature, a qualitative study also has the strength of generating rich data of perspectives and experiences from informants without the risk of neglecting factors that may be critical in explaining the data [35]. Moreover, it is able to provide researchers with a context for interpretation and analysis [34, 36]. Third, a qualitative study often allows more flexibility in design and is able to accommodate different methods such as interviews, observation, and focus group interview [34]. In the present study, we attempted to evaluate the effectiveness of the subject by investigating students’ perceptions, attitudes, and learning experiences in this course. In order to obtain a deeper insight, a qualitative study is considered more appropriate for the present study. To be specific, students were invited to provide written responses containing three descriptors and one metaphor to reflect on their learning experiences and perceptions.

Descriptors, as a type of qualitative description, offer a straightforward way of eliciting data on people’s views and experiences and brings researchers closer to the data [37]. Metaphors can incorporate rationality and imagination and associate cognitive and emotional

domains, allowing us to capture intangible aspects in respondents' experiences that would be more difficult to be otherwise grasped such as feelings and emotions [38-40]. Therefore, it is considered as a useful and complementary method for using descriptors. In addition, metaphors entail "culturally specific" meaning which can attend to feelings and emotions within a context in evaluation [40]. These reasons constitute the rationale of the employment of qualitative evaluation with descriptors and metaphors in the evaluation.

OUR STUDY

As stated previously, the subject "Service Leadership" was conducted in semester 1, 3 and Cambodia summer camp in 2016/2017 academic year. Except the intensity and locations were different, the content of the three courses was the same. At the end of the course, the students who took these three courses were all invited to share their points of view and give feedback to the course by filling the Personal Reflection Form after they accomplished the lectures. To be specific, students were first asked to write down three descriptors (words or phrases) to depict their learning experiences and express their feelings or perceptions about this subject (e.g., helpful, joyful, boring, tough). Second, they were invited to come up with a metaphor (e.g., book, sea, beacon, journey) that can best reflect the characteristics of the subject or their learning experiences, along with a short explanation of why this specific metaphor was selected in order to facilitate interpretation in analysis. Before the data collection, voluntary consent forms were distributed to students to explore their voluntariness of participation. Students were informed about the research project, purpose of data collection, confidentiality of their feedback, and anonymity of their responses. This consent form also made it explicit that participation was entirely voluntary and they could withdraw at any stage in the research. There were 76, 79, 64 questionnaires collected from the course of semester 1, 3, and Cambodian summer camp respectively.

Data Analysis

Two researchers who did not participate in the teaching and data collection were invited to code the responses, which were transcribed from the Personal Reflection Form. With regard to the descriptors, if two words shared a similar meaning, they would be merged into one category (e.g., useful and helpful, interesting and funny). This process of categorization was also applied to metaphors. However, metaphors were also broken down into different meaningful units if the short explanation of the metaphor entailed more than one meaningful unit. For example, a student used the metaphor "fitting room" with an elaboration that "this course provides a lot of idea on what attribute a good service leader should process, it likes the light in the room. This course also provides lots of chance for us to reflection, like mirror in the fitting room." In this case, the interpretation included two meaningful units, i.e., "the light in the room" which was related to the fact that the courses offered them knowledge and guidance, and "mirror in the fitting room" which was concerned with the enhancement of self-reflection and self-awareness. Therefore, this metaphor was divided into two meaningful units.

Then the descriptors, metaphors as well as the derived meaningful units were all classified by their nature into four categories: “positive,” “neutral,” “negative,” and “undecided.” The classification of descriptors was straightforward, while that of metaphors presented a more complex picture. The nature of a metaphor is depended on the nature of the derived meaningful units. For instance, the metaphor of “mother” entails positive meaning in a common sense. However, the student complemented it with an explanation that “sometimes it is really boring during the lecture, but I understand it is helpful and useful in my future.” According to the student, this metaphor included two meaningful units with one negative (“boring”) and one positive (“helpful and useful”). As the positive and negative units shared equal status, the metaphor of “mother” was considered neutral. If positive meaningful units outnumbered negative ones, the metaphor *per se* would be counted as positive, and *vice versa*. In addition, if those meaningful units were perceived as irrelevant, they would be classified into undecided.

Table 1. Categorization of descriptors used by the participants to describe the course in S1 of 2016/2017 academic year

Descriptors	Nature of the Response				Total
	Positive	Neutral	Negative	Undecided	
Helpful to personal growth/Useful subjects/useful to my development	37				
Interesting/Fun	32				
Inspiring/Encourage/Motivation/Enlightening	19				
Enjoyable/Relaxing/Joyful/Happy/No burden	17				
Caring/Warm/Full of love/Supportive/Love/Empathy	17				
Interactive	14				
Meaningful/Educative	13				
Informative/Knowledgeable/Fruitful/Comprehensive/Gaining lots of knowledge	13				
Impressive/Unforgettable	7				
Improvement	7				
Active/Lively/Vivid/Energetic	5				
Higher-level thinking/Involve many critical thinking	5				
Practical/Able to apply daily/Real life experience	4				
Other positive responses	20				
Participation/Cooperation/Mission& Vision/Night/Unit of my group		5			
Learn Caring/Moral character/Service leadership		4			
Unlike any others/Special/Challenging		3			
Other Neutral responses		6			
Total Count (N):	210	18	0	0	228
Total Count (%):	92.11	7.89	0	0	100

To examine the intra-rater and inter-rater reliabilities and improve validity, 20 descriptors and 20 metaphors were randomly selected from each course respectively. For the intra-rater reliability, the researcher who initially coded the responses recoded the randomly selected items in a different time. For the inter-rater reliability, the researcher who was not involved in the initial coding coded the randomly selected items independently.

Table 2. Categorization of descriptors used by the participants to describe the course in S3 of 2016/2017 academic year

Descriptors	Nature of the Response				Total
	Positive	Neutral	Negative	Undecided	
Helpful/Useful/Beneficial	54				
Interesting/Fun/Funny	43				
Meaningful/Thought-provoking/Educational	21				
Informative/Knowledgeable/Fruitful/ Rich content/Plentiful content	18				
Enjoy/Joyful/Happy/Delightful/Exhilarating/Relaxing	17				
Interactive/Engaging	15				
Broaden my horizon/Facilitates self- development/Develop perspectives/refresh mind	9				
Patience/Nice/Enthusiastic/Passionate	8				
Impressive/Impression/Unforgettable	7				
Inspiring/Encouraging/Enlightening	6				
Valuable/Worth learning	4				
Practical/Related to daily life	4				
Exciting/Excited	3				
Thankful	2				
Satisfaction/Fulfilled	2				
Other positive responses	17				
Unexpected		2			
Boring			2		
Too lengthy			1		
Hard to practice			1		
Busy to complete assignments			1		
Total Count (N):	230	2	5	0	237
Total Count (%):	97.05	0.84	2.11	0	100

FINDINGS

Table 1, 2 and 3 show the codes of descriptors collected from semester 1, semester 3 and Cambodia summer camp in 2016/2017 academic year, as well as their nature and classifications. The results in Table 1 (semester 1) reveal that 210 out of 228 descriptors (92.11%) were positive, and only 18 descriptors (7.89%) were considered neutral. The most frequently mentioned positive descriptors included “helpful/useful (to personal growth),” “interesting/fun,” “inspiring/encourage/motivation/enlightening” and “enjoyable/relaxing/joyful.” The intra-rater percent agreement reached 85% and the inter-rater agreement percentage reached 95%.

The data collected in semester 3 course generated a total of 237 descriptors, which were shown in Table 2. Positive descriptors accounted for 97.05% of all feedback. The percentage of neutral descriptors was 0.84% and negative was 2.11%. The most frequently used three positive descriptors were “helpful/useful/beneficial” “interesting/ fun,” “thought-provoking/educational” and “informative/knowledgeable,” the first three of which were similar to those in semester 1 course. The intra-rater and inter-rater agreements were 90% and 85% respectively.

Table 3. Categorization of descriptors used by the participants to describe the course in Cambodia summer camp of 2016/2017 academic year

Descriptors	Nature of the Response				Total
	Positive	Neutral	Negative	Undecided	
Interesting/Fun/Funny	29				
Helpful/Useful/Beneficial	25				
Inspiring/Encouraging/Motivating/ Heuristic/Eye-opening	17				
Achievement/Personal growth/Improvement	14				
Informative/Fruitful/Knowledgeable/content-rich	13				
Meaningful/Reflective	10				
Enjoyable/Joyful/Happy/Delightful/Relaxing	9				
Friendly/Nice/Patient/Caring	7				
Interactive	5				
Thankful/Appreciate/Grateful	4				
Impressive/Unforgettable/Memorable	4				
Great/Amazing/Wonder/Well	4				
Honest	2				
Easy to understand	2				
Practical/Learn and work it out	2				
Other positive responses	15				
Communication/Collaboration/Self-confidence/Self- esteem/Experience/Moral characters		14			
Know myself/Understand history/Understand Interpersonal competence		5			
Special/Complicated/Directly		3			
Hot			2		
Tough			2		
Tired			1		
Sad			1		
Too much lesson time			1		
Keep saying			1		
Total Count (N):	162	22	8	0	192
Total Count (%):	84.38	11.46	4.17	0	100

According to Table 3 (Cambodia summer camp), 84.38% (n=162) of the descriptors were considered as positive, 11.46% (n=22) as neutral, and 4.17% (n=8) as negative. The categories “hot,” “tough,” and “tired” comprised the majority in the negative descriptors. The intra-rater agreement and inter-rater congruence in Cambodia summer camp reached 95% and 90% respectively.

For the metaphors, 76 raw metaphors were collected from semester 1 (see Table 4). As shown in Table 4, 74 (97.37%) metaphors were regarded as positive, such as “light,” “tour/trip/journey,” and “book,” while two metaphors were perceived as neutral. The 76 raw metaphors were broken down into 91 meaningful items, with 89 responses (97.8%) considered positive and two responses (2.2%) considered negative. The first category, mentioned 20 times, was the most frequently mentioned one by students. It indicated that the course had given them directions and guidance in various dimensions in life and helped them grow. Three examples are listed below:

- **Road sign:** “Service leadership, stress on not only personal growth, but also other's growth. It guide you the right way and sense of achievement!”

- **Light:** “It guides me to understand what a leader should be equipped and give me the tips and clues of how to become a successful leader...”
- **Compass in life:** “My programme (Hotel mgt) is something related to service leadership, which is knowledgeable for my career path.”

The second category, mentioned by 15 students, emphasized that the course was informative which nourished them:

- **Tasty burger:** “A burger consists a wide range of ingredients, just like the course consisting different parts of knowledge.”
- **Fertilizer:** “If I were a tree, fertilizer can bring me nutrient to make me grow strong. Like the course inspired me how to be a better person comprehensively.”
- **Buffet:** “This course is very informative that provide a lot of useful information regarding service leadership which enrich my knowledge base.”

The third category was mentioned by 13 students, which contained 18 positive meaningful units. This category implied that the subject was a joyful and memorable experience, which enriched students’ knowledge and broadened their horizons:

- **An enjoyable tour:** “Every teacher just like every different tour guide, leading us to walk around and understand every scenic spot. All the content is interesting as well as helpful.”
- **A wonderful journey:** “I am able to learn more about service leadership and it enriches my horizon.”
- **Wonderful journey:** “In our daily life, we seldom try to study about how we control our emotion, how we care others. In fact, it is a good way for me to review how we treat others appropriately. It is a matter of caring about other's feeling. Try not to just care about own feeling & interest. This is selfish and not a good manner.”

Table 5 presents the 79 raw metaphors collected from the semester 3 course, and 91 derived meaningful units. Among the 79 raw metaphors, 75 were positive, comprising 94.94% of the total. There were two raw metaphors (2.53%) regarded as neutral and 2 (2.53%) as undecided. With regard to the derived meaning units, 84 out of 91 were positive, accounting for 92.31% of the overall units. There were two meaningful units counted as neutral, four as negative, and one as undecided, which accounted for 2.20%, 4.40%, and 1.10% respectively. The first category was mentioned by 19 students. It conveyed the perspective that the course provided direction and guidance to them:

- **A compass in life:** “I learnt a lot of valuable leadership qualities in this course. These elements are important to direct my future road to be a successful leader of self and others.”
- **Torch:** “It help to light up the life and guide the road of future.”
- **A beacon:** “It helps us to find out and understand our goals, and leads us to wherever we want to reach.”

Table 4. Categorization of the metaphors used by the participants to describe the course in S1 of 2016/2017 academic year

Metaphors	Nature of the Metaphor					Number of Codes Derived from the Metaphor and Its Nature				
	Positive	Neutral	Negative	Undecided	Total	Positive	Neutral	Negative	Undecided	Total
Light bulb/Light/Lamp/Compass/Google map/Road sign	20					20				
Burger/Buffer/Picnic/FertilizerWater/Battery/Lasagna/Tree	13	2				15		2		
Tour/Trip/Journey	13					18				
Book/Handbook/Notes/Dictionary/Smartphone	7					9				
A surprise present/Happy subject/3D movie/Puzzle	4					6				
Treasure/Treasure bag	2					2				
Marathon/A long hiking path	2					2				
A catalyst	1					2				
Fitting room	1					2				
A fairytale	1					1				
A butterfly	1					1				
Rainbow	1					1				
Other positive responses	8					9				
Total Count (N):	74	2	0	0	76	89	0	2	0	91
Total Count (%):	97.37	2.63	0	0	100	97.80	0	2.20	0	100

The next category, which was mentioned by 18 students, reflected the fact that the course was rich in knowledge and useful for their future:

- **Sandwiches:** “It contains many different kind of information and inspired me a lot about my future.”
- **Unforgettable buffet:** “There are so many useful information to put in my mind, it is so full.”
- **Fertile soil:** “The course itself provides us with lots of knowledge which it good for our personal growth just like fertile soil which provides lots of nutrients to the plants for them to grow healthily.”

The third frequent metaphors involved perceptions towards the overall learning experiences. Similar to the semester 1 course, their learning experiences were perceived as interactive, interesting, enjoyable and useful:

- **An interesting journey:** “The knowledge taught in this course are new for me. And it make me have an unforgettable experience.”
- **Life tour:** “It helps us to understand ourselves in different aspects based on the three components and we did self-reflection regarding to our past to our future.”

- **A mysterious tour group:** “I have to experience unknown, yet interesting interactive activities in each lesson with students I'm originally not familiar with, which is similar to that of a tour group.”

Table 5. Categorization of the metaphors used by the participants to describe the course in S3 of 2016/2017 academic year

Metaphors	Nature of the Metaphor					Number of Codes Derived from the Metaphor and Its Nature				
	Positive	Neutral	Negative	Undecided	Total	Positive	Neutral	Negative	Undecided	Total
Light/Bulb/Guiding star/Beacon Compass/Map/Torch	19					20				
Buffet/Seafood/An egg/Bread/ Sandwiches/Water	18					20	1	2		
Enjoyable tour/Interesting journey/Voyage	10					10				
Orientation camp/Party/Social media/Interactive forum	7					8				
Dictionary/Wikipedia/Guideline/ Encyclopedia	5					5				
Enjoyable workshop/Psychological emotional consultation	3					4				
Rainbow	2					3				
Tool box	1					2		1		
Flower	1					1				
Other positive responses	9					9				
Mother		1				1		1		
People in my life		1					1			
Moon				1					1	
Causal relationship				1		1				
Total Count (N):	75	2	0	2	79	84	2	4	1	91
Total Count (%):	94.94	2.53	0	2.53	100	92.31	2.20	4.40	1.10	100

Table 6 demonstrates the 64 raw metaphors and 73 derived meaningful units. 85.94% (n=55) raw metaphors were regarded as positive, while 12.50% (n=8) of metaphors were seen as neutral, and 1.56% (n=1) as negative. With regard to the breakdown of meaningful units, the proportion of positive ones was 87.67% (n=64). For the rest units, five meaningful units were classified as neutral and four as negative, and the proportion is 6.85% and 5.48% respectively. The first category in Table 6 suggested that students achieved personal growth via this course:

- **Tree:** “At the beginning of lecture, we know very little like a small sand seedling, and after having more than 10 lectures. We learnt much more and our mind is like a tree that grows into very strong.”
- **Palm tree:** “I learnt a lot and discovered that everyone has their own strength and we are unique, that everyone is born to be a leader, just like palm tree that grows tall and have a lots of uses.”
- **Bamboo:** “Growth fast. Can withstand in extreme environment. Adapt to change.”

The second category referred to the fact that this course gave them direction, meaning, and depth in life and enabled them to be on the right track:

- **A guidebook:** “It has many principles and practical insights for me to refer to when I meet adversity or lose confidence of myself. I will survive negative self-perception and develop a better-me. This course will guide me.”
- **Light bulb:** “It gave me a direction to become a good service leader so that I can set appropriate goal to improve myself.”
- **Road signs:** “As road signs help drives to find the way and guide them, so does this course.”

Table 6. Categorization of the metaphors used by the participants to describe the course in Cambodia summer camp of 2016/2017 academic year

Metaphors	Nature of the Metaphor					Number of Codes Derived from the Metaphor and Its Nature				
	Positive	Neutral	Negative	Undecided	Total	Positive	Neutral	Negative	Undecided	Total
Tree/Bamboo/Palm tree	9					9				
Dictionary/Guidebook/Light bulb/Lamp	8					9				
Tour/Journey	5					6				
Water/Fountain	4					4				
Dinner/Coconut/Egg	4					5				
Lamb/Lion/Cow	3					3				
Telescope/Magnifying glass	2					2				
Bingo/Game	2					4				
Heart/Love	2					2				
Road signs/Lego instruction	2					2				
Color pens	1					1				
Motorcycle	1					1				
Other positive responses	12					13				
Oven/Microwave oven		2				2		2		
Tight		1				1		1		
Other neutral responses		5					5			
Urgent			1					1		
Total Count (N):	55	8	1	0	64	64	5	4	0	73
Total Count (%):	85.94	12.50	1.56	0	100	87.67	6.85	5.48	0	100

The third category was mentioned by five students. Similar to the other two courses, students regarded the learning process as a meaningful and joyful journey:

- **Journey:** “The course just gave me some very inspiring experience. All the experience are learning for me and it does on me during my travelling experience.”
- **An enjoy trip:** “I made a lot of friends and visited places that I have never been before. So it is a precious and enjoyable trip.”

- **An enjoyable tour:** “The course is based on the trip to Cambodia and it's really enjoyable to learn with RUPP students and relate what we learned to reality in Cambodia. This course itself is full of knowledge also.”

It is noted that the aforementioned three courses showed high similarity in terms of students' perspectives. Meanwhile, the metaphors perceived as neutral and negative from Cambodia summer camp drew our attention. Examples of neutral and negative metaphors are given as below:

- **Oven:** “The classroom is so hot, just like an oven. Also the teachers are passionate and the students are energetic, thus we are enthusiastic as a heat and warm oven.”
- **Tight:** “It is quite an intensive course. We learnt 13 lecture in less than two weeks. It is quite a lot of knowledge and we also presented on our topic which give us more in-depth understanding.
- **Urgent:** “In the few days, we have finished our 13 lecture and a group presentation, and many course homework, so the time is quiet limit.”

The intra-rater agreement percentage of metaphors for semester 1, semester 3 and Cambodia summer camp is 100%, 95%, and 100% respectively. For inter-rater reliability, the percentage reached 95%, 90%, and 100% respectively. The inter-rater and intra-rater agreement percentages of both descriptors and metaphors suggested high reliability in coding.

A chi-square test was conducted to examine if there was any statistical difference in the nature of feedback between the three courses. To be specific, we divided the descriptors into two major categories, positive and non-positive, the latter of which combines neutral, negative and undecided responses. The result showed that there was a significant difference between the three with respect to the descriptors ($\chi^2 = 22.31$, $p < .05$). A post hoc test was run to explore which cells were significantly different, as χ^2 is an omnibus test. It can be seen from the result that the adjusted residual for positive feedback was -4.3 (smaller than -2.0) for Cambodian summer camp, which indicates that the number of positive responses were significantly smaller than expected. The same procedure applied to metaphors as well. It generated the χ^2 value of 6.42 and p value of .04, which also showed an association between the three courses and the nature of students' feedback. The post hoc test demonstrated that the adjusted residual for the Cambodian summer camp, positive responses was -2.1, and the major difference lay in between Cambodian and semester 1 courses (adjusted residual = 2.3).

DISCUSSION

The present study drew on a qualitative approach to evaluate the effectiveness of the subject “Service Leadership” and its influences on students in order to improve our understanding of students' learning experiences and the subject itself. The qualitative findings demonstrated that the positive feedback was predominant with more than 80% of students in all the three courses evaluating the subject positively. Positive responses reached more than 90% for the semester 1 and 3 courses. The overwhelmingly positive feedback provided

evidence that the well-designed curriculum and projects in higher education are a solid way to improve students' service leadership [14].

According to the written descriptors, the three courses shared the similarity that students considered the subject as useful, helpful or beneficial to them. Other commonly mentioned descriptors include "interesting," "funny" and "enjoyable," which denoted the courses had engaged students in a relaxing, delightful and interactive learning atmosphere; "inspiring," "thought-provoking," "eye-opening" and "heuristic," which expressed that students had broadened their horizons through attending these courses; "informative" and "knowledgeable," which were consonant with one of the objectives of the subject, i.e., imparting essential knowledge in the field of service leadership to students.

As to metaphors, the most frequently reported positive category was related to concepts or instruments that give directions, such as compass, map, beacon, lighthouse, and road sign. Based on students' explanations, these metaphors entail two different meanings: one is that these courses cultivated leadership in them and led them to the right path of how to be a successful service leader, and the other is that these courses directed their way to a successful career path in the future. Another common category shared by the three courses is "tree," "battery," "buffet," "seafood," "bread" and "sandwiches," which all denoted that students had achieved personal development as these courses had provided "nutrients," "fertilizers" or "essential knowledge" for students to grow. They also inspired them and added a competitive advantage to their profiles. In this sense, this category echoes the written descriptors such as "informative/knowledgeable" and "inspiring/thought-provoking." The third noticeable broad category shared by the three cohorts of students is that the learning experiences were an "enjoyable tour," "interesting journey" or a "party," which demonstrated that this subject was featured with an active and relaxing learning mode. Among the overwhelmingly positive feedback, there were several negative comments, especially in the Cambodian summer course such as "hot," "oven," "tight," and "tough." Their further elaborations of the metaphors showed that the negative meaning units were often associated with the intensive teaching and learning modes and students' inability to adapt to the hot climate in Cambodia during a short period of time. Despite several negative comments, the overall findings demonstrated the effectiveness of the subject "Service Leadership" in promoting students' holistic development and nurturing service leadership qualities. Students thought very high of this subject and of their learning experiences. The positive responses are consistent with previous studies [e.g., 27, 41], which centered around the instrumental and practical value of this subject, positive emotions emerged in this learning experiences, interesting and interactive teaching and learning styles, rich content, and personal development in competence, character, and caring disposition. In a sense, students' comments also echo that of previous objective outcomes evaluation [e.g., 2, 24] that participation in this subject facilitated personal growth and helped them thrive as it equipped them with necessary knowledge in service leadership and promoted caring disposition such as "how to treat others appropriately," and thus contributed to development in service leadership qualities and positive youth qualities.

In addition, this study adds to the literature by demonstrating the values of using descriptors and metaphors in evaluating a program. First, descriptors and metaphors provide a context for readers, and hence can facilitate interpretation and secondary analysis [40]. Second, metaphors are valuable in exploring informants' lived experiences as it attends to the depth of emotions and other intangible aspects in their lives [38, 42]. Third, compared with interviews or ethnographic observation, using descriptors and metaphors is efficient in

evaluating the effectiveness of a program, especially when dealing with large cohorts of informants. It allows them to encapsulate their learning experiences and complex emotions into small linguistic units.

Despite the overall encouraging and positive findings, there are several limitations of this study. Firstly, the efficiency of using descriptors and metaphors may bring about omission or misrepresentation in interpretation and analysis, as this method only allows a limited extent of elaboration from informants. For example, students described the course as “useful” or “helpful.” Researchers nonetheless had limited understanding that in what ways the course was beneficial to those students without their further elaboration. In order to reach a more comprehensive understanding of students’ learning experiences, in-depth interviews or focus group interviews should be involved in future studies. Second, as it was not designed as a pre- and post-test quantitative evaluation, the present study generated limited data on understanding in what aspects and to what extent students grew through attending the course. Despite the aforementioned limitations, the present study provides solid empirical evidence that the subject “Service Leadership” is effective in promoting students’ knowledge and competence in service leadership, and contributes to their personal growth.

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Chapter 130

A QUALITATIVE EVALUATION OF A SERVICE LEADERSHIP SUBJECT IN A HIGHER EDUCATIONAL INSTITUTION IN HONG KONG

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ABSTRACT

The chapter represents an attempt to evaluate the subject “Service Leadership” which has been conducted at The Hong Kong Polytechnic University as a credit-bearing subject. The dataset was collected from three courses under the subject in 2017/2018 academic year, which included 207 undergraduate participants in total (n=87 were from the Semester 1 subject, n=89 were from the Semester 3 subject, and n=31 were from the Cambodian summer school). By analysing students’ written feedback of descriptors and metaphors, researchers found that participation in this subject fostered students’ development in different areas including self-reflection, leadership competencies, moral characters as well as caring disposition, and hence equipped them to become qualified leaders in the future. This study also provides convincing evidence that it is important for higher educational institutions to incorporate service leadership education in their curricula.

INTRODUCTION

Service industries have contributed greatly to the development of many societies in the past decades. The remarkable transformation from a manufacturing economy to a service-based economy has led to a shift of the desired qualities of employees. In a product-based

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industry, the crucial attributes of employees were following instructions and conducting routine work by merely using their technical skills [1]. In sharp contrast, the critical requirement for employees in a service-based economy is to hone their soft skills (e.g., leadership, integrity, resilience, teamwork, and interpersonal skills) [2]. While in a manufacturing economy, leadership is often associated with centralised authority and personal power, a service industry calls for decentralised power, flexibility, and mutual influence [3]. Accordingly, there has been increased attention among scholars given to the shift of desired attributes of leadership and the application of new leadership models for university students since the 1990s [4].

Among the many leadership models, two widely recognized models which are highly relevant to the service-oriented economy are “servant leadership model” [5, 6] and “transformational leadership model” [7]. Servant leadership model proposes a servant-first philosophy in which servant leaders emphasize the needs of their followers, distinguishing itself from the conventional notion of leadership that highlights authority and dictation with top-down hierarchy [5, 6]. This concept encourages leaders to focus on the development and benefits of followers and the groups to which they belong [6]. Furthermore, Gregory and his colleagues [8] asserted that the servant leadership model offered the conceptual framework which can incorporate different leadership and facilitate empirical research. With regard to transformational leadership, Bass and Avolio [9] proposed four general components in leadership behaviours, i.e., “Idealized Influence, Inspirational Motivation, Individualized Consideration, and Intellectual Stimulation.” Building on and refining the previous theories, Kouzes and Posner [7] proposed their transformational leadership model, which presents five core practices in motivating followers and establishing effective leadership, i.e., “Model the Way, Inspire a Shared Vision, Challenge the Process, Enable Others to Act, and Encourage the Heart.” It is also a framework based on a large number of empirical case studies and surveys. For decades, the five elements of exemplary leadership have been verified by scholars to be positively correlated to the effectiveness of leadership, organizational commitment and work satisfaction [7]. They also hold the belief that not just great people can acquire exemplary leadership and mobilize others, but everyone can achieve that by receiving training and applying these practices. It is noted that despite their prevalence in service-oriented economies, they were developed in a Western context and rooted in Western culture, and therefore it is impractical to apply them in Hong Kong [10].

In answer to the call for a leadership model rooted in a Chinese context, Chung [11] and scholars from the Hong Kong Institute of Service Leadership and Management (HKI-SLAM) developed a service leadership model with the aim of promoting service leadership education at tertiary level in Hong Kong and providing advice and assistance to stakeholders such as government agencies and business communities. In this model, service leadership is defined as “ethically satisfying others needs by consistently providing quality personal service to everyone comes into contact with, including one’s self, others, communities, systems, and environments,” in which the core concept of leadership is essentially about service [11]. There are several core beliefs highlighted in this model. For example, the service leadership model upholds the belief that every individual is valuable with the potential of becoming a qualified leader [12]. Everyone also has opportunities to practice his or her leadership on a daily basis from self-serving improvement opportunities to more complicated service encounters. In addition, this model accents self-serving and self-management, a process during which people can improve their competences and other qualities, and are hence better

prepared to the needs of self and others [12]. Besides the core beliefs, HKI-SLAM also proposed a 3Cs model in which leadership competence, moral character, and caring disposition are introduced as the three major components in determining the effectiveness of service leadership [13]. This model distinguishes it from traditional leadership models that either highlight partial leadership skills that are primarily “related to individual achievement, sheer productivity and positional authority,” or claim that merely elites can achieve a good leadership [14]. Moreover, it is a leadership model which incorporates Chinese concepts and philosophies, including Confucianism, Daoism, and Buddhism. It reflects the Chinese culture and traditional values such as “harmony, righteousness, honesty, loyalty, benevolence and empathy” [4]. In general, this model is considered as a framework oriented to the service economy specifically under Hong Kong socioeconomic conditions [15].

Equivalent to the transformational leadership model, service leadership model cherishes a value that leadership can be acquired and not attributes one is congenital. However, the transformational leadership model mainly stresses on collective value and shared vision of groups and organizations. As a follower-centric model, it focuses on the leaders’ abilities to nurture, influence and mobilize followers but fails to place equal emphasis on self-management and self-improvement [12]. It is in sharp contrast to service leadership in which balanced consideration is given to self, others and the system [12]. Furthermore, transformational leadership primarily underlines high morality and personal charisma. Service leadership, on the contrary, pays significant attention to the comprehensive development of moral character, caring disposition as well as different leadership competencies in building up effective service leadership. A service leader shares several qualities in practice with a servant leader, such as the emphasis placed on service instead of autocratic and authoritative leadership, and on high moral characters and caring disposition. However, in comparison to the servant leadership model, it is firmly believed that service leadership model does not promote serving others and community at the expense of self-interest; instead, it includes self in service orientation [12]. In addition, it gives due attention to functional competencies and practical skills in being an effective service leader, which is not fully addressed in the servant leadership model [12].

In order to promote service leadership education in Hong Kong, the Service Leadership Initiative (SLI) was launched by the Victor and William Fung Foundation. Total eight higher educational institutions funded by the University Grants Committee (UGC), including The Hong Kong Polytechnic University, joined in this initiative and integrated the service leadership model in their curricula. Based on this framework, a credit-bearing subject entitled “Service Leadership” has been introduced to undergraduates at PolyU. In the 2012/13 academic year, a 2-credit service leadership subject was offered to students under the 3-year degree program at the initial stage. Since the 2014/15 academic year, 3-credit subject has been introduced to students studying in the 4-year degree program [16]. Its objectives include “1) understanding and integration of theories and concepts on service leadership, particularly the key propositions, core beliefs, and curriculum content strands of the HKI-SLAM conceptual framework; 2) acquisition of skills intrinsic to service leadership; 3) formation of strong identification with the attitudes and values emphasized in service leadership; and 4) recognition of the importance of service leadership to the development and wellness of oneself, other people and the whole society, particularly recognize the connection of learning in the subject to one’s own life” [17]. This subject highlights experiential learning, reflective learning and collaborative learning, which includes methodologies of lecturing, group work,

papers assignments with reflection, and experiential learning sessions [18]. It aims to facilitate students' understanding of contemporary models of leadership as well as the attributes of service leadership, nurture effective service leadership qualities in students, and encourage critical reflection and application of theories and knowledge from classroom to real life [18].

To examine the efficacy of service leadership course and improve teaching and learning experiences accordingly, evaluation is crucial [19]. In general, both quantitative and qualitative approaches have their own advantages. Shek and Sun [20] argued that a quantitative evaluation could utilize numerical data and statistics to validate assumptions, quantify perceptions, and measure at multiple time points effectively. Particularly, the use of quantitative method has the advantages of generalizing investigation results to "a larger population based on a representative sample, determination of causal relationship between given conditions and program outcomes, independence of results from investigator's standpoint, and standardized instruments and procedures that can be repeated in replication studies conducted by other researchers" [17]. It is also regarded as the mainstream methodology in social science research and has been used in the previous evaluation of the subject "Service Leadership" [21-23]. For instance, in a quasi-experimental study [21], the pretest-posttest results indicated that there was a greater enhancement for students who joined the course than those who did not, with regard to knowledge and attitudes related to service leadership, as well as life satisfaction.

Nonetheless, quantitative approach is criticized as less adequate in exploring subjective experiences and life stories as well as understanding in-depth meanings of participants in social and behavioral studies [24]. Qualitative methods can, therefore, capture detailed information with openness in eliciting data and at the same time maintain depth in analysis, objectives of which may be more difficult to achieve for structured methods [24, 25]. For an in-depth evaluation of program effectiveness, a qualitative study is considered more capable, as it contributes to the understanding of informants' experiences, perspectives and feelings in the learning process [26]. In this study, therefore, a qualitative method was selected to evaluate the effectiveness of the "Service Leadership" subject from the perspective of university students in Hong Kong. Notably, qualitative evaluation can also incorporate many approaches, such as "direct observation, focus group interview, and written reflections" [24, 25]. The qualitative evaluation has been adopted in previous studies. For instance, in a series of studies (e.g., 1, 4), Shek and his team provided convincing qualitative evidence of the positive influence this subject exerted on participating students by analyzing their written feedback.

In this study, we included a total of 207 students who attended the "Service Leadership" during the academic year of 2017/2018. We elicited their written responses by inviting them to give three descriptors and a metaphor to describe their learning experiences in and attitudes towards the course. Meanwhile, they were invited to elaborate with an explanation for their selected metaphors. The written descriptors allowed students to express their opinions in a straightforward and open manner. It also offered researchers a quick view of students' perceptions facilitated our identification of the nature of comments. The use of metaphor is an efficient way to understand some "emotionally difficult concepts" and explore intangible concepts [27]. According to Ma and her colleagues [28], conceptual metaphor theory is a frequently used method in evaluation research. A conceptual metaphor comprises two domains: the target (e.g., perceptions towards the course in the present study), and the source

(e.g., “beacon” or “journey” used by students in the present study) [29]. The target domain, as known as the conceptual domain, is what researchers pay particular attention to, while the source domain is the metaphorical expression to represent or describe the domain. Through pairing the target and the source, metaphors serve as a conceptual correspondence that sheds lights on abstract thinking and its connections to subjective experiences [28, 29]. As the present study mainly explores students’ perspectives and learning experiences to evaluate the effectiveness of the course, using written responses of metaphors and descriptors is considered adequate to reach our research objectives.

OUR STUDY

The purpose of the presented study was to evaluate the quality and effectiveness of the subject “Service Leadership” in the 2017/2018 academic year. This subject was carried out in Semester 1 and 3 in Hong Kong, and in the summer term in Cambodia. The Semester 1 subject was a regular module course with one lecture weekly and a duration of 13 weeks all-inclusively. The Semester 3 subject was with modest intensity, where two lectures were given each week during a period of 6.5 weeks. The Cambodia summer school was a two-week intensive module, which requested students to conduct field visits and attend classes in Cambodia. Students who participated in those three subjects were all invited to describe their subjective experiences in the program. They were first requested to use three concise words or phrases (i.e. descriptors) as their personal reflection of the program. They were also required to use a metaphor to give a written account of their perception towards the course with a brief elaboration. The student consent form was collected before the data collection. There is a total of 87 students in semester 1, 89 students in semester 3, and 31 students in Cambodia Summer School participated in this research.

Data Analyses

The coding of descriptors and metaphors was conducted by two independent researchers who were not associated in either lecturing the course or collecting data. To start with, the written descriptors were classified into four categories, defined by their nature of positive, neutral, negative and undecided. The coding of metaphor is more complex as a metaphor can entail more than one meaningful unit. By way of illustration, there was a student using “water” as the metaphor to describe this course with the interpretation that “the class seems simple or even boring, but when you look back, you will realize that it is so important to build up our character and leadership. Just like water, simple but important.” It was coded into two meaningful units. The first one is a negative comment which indicated the course was boring on the surface, while the second is about the benefits and development of the student during the course. As the negative and positive units share equal status in quantity, this metaphor was coded as neutral. If the metaphor was considered irrelevant to the context, it would be categorized into “undecided.” For descriptors and metaphors respectively, similar meanings were grouped into the same category. In order to examine intra-rater reliability in a reliable manner, the two research fellows randomly selected 20 descriptors and 20 metaphors from

each semester and coded them in a different time. These 20 descriptors and 20 metaphors were exchanged to and crosschecked by the other researcher to examine the inter-rater reliability.

Table 1. Categorization of descriptors used by the participants to describe the course in Semester 1 (HK) of the academic year of 2017/2018

Descriptions	Nature of the Response				Total
	Positive	Neutral	Negative	Undecided	
Fun/funny/interesting	44				
Inspiring/thought-provoking	30				
useful	30				
Meaningful	21				
Happy/joyful/enjoyable	13				
Interactive	13				
Helpful	11				
Reflective	9				
Informative	7				
Practical	5				
Creative	4				
Friendly	3				
Memorable	3				
Relax/relaxing	3				
Unique	3				
Other positive responses	51				
Social epitome		2			
Academic		1			
Information		1			
Listening		1			
Lollipop		1			
Mystery		1			
Self, others, system		1			
Loss of direction/slightly perplexed			2		
Regret			1		
Total Count (N):	250	8	3	0	261
Total Count (%):	95.79	3.07	1.15	0	100

FINDINGS

Tables 1, 2 and 3 show the descriptors of Semester 1, Semester 3 and Cambodia summer school respectively, together with the categories and the nature of them. As shown in Table 1, 250 out of 261 descriptors (95.79%) were positive, eight descriptors (3.07%) were neutral and three (1.15%) were negative. The descriptors with the same meanings were merged. Six categories were most frequently mentioned by students from semester 1, i.e., “fun/funny/interesting,” “inspiring/thought-provoking,” “useful,” “meaningful,” “happy/joyful/enjoyable” and “interactive.” Eight descriptors, i.e., “social epitome,” “academic,” “information,” “listening,” “lollipop,” “mystery,” and “self, others, system,” were regarded as neutral, while three were seen as negative, i.e., “loss of direction,” “slightly perplexed” and “regret.” Both the intra-rater reliability and inter-rater reliability reached 100%, indicating a high consistency in coding.

Table 2. Categorization of descriptors used by the participants to describe the course in Semester 3 (HK) of the academic year of 2017/2018

Descriptions	Nature of the Response				Total
	Positive	Neutral	Negative	Undecided	
Fun/funny/interesting	42				
Helpful/beneficial	27				
Inspiring/thought-provoking	24				
Informative	18				
Meaningful	15				
Useful	15				
Enjoy/enjoyable/happy/joyful	14				
Relax/relaxing	10				
Interactive	9				
Helpful	7				
Good/great	6				
Excited/exciting	4				
Applicable	3				
Attractive/intrigued	3				
Friendly	3				
Fruitful	3				
Fulfilling/satisfied/satisfying	3				
Impressive/unforgettable	3				
Responsible	3				
Other positive responses	33				
Hungry		3			
Long/long-duration		3			
Other neutral responses		4			
Unexpectedly		1			
Sympathy to others		1			
Boring			4		
Too many activities in class			2		
A little bit too fast			1		
Awkwardness			1		
Little sleepy			1		
Vague			1		
Total Count (N):	245	12	10	0	267
Total Count (%):	91.76	4.50	3.75	0	100

Similar results can be found in Table 2, where 245 out of 267 descriptors (91.76%) were categorized as positive, such as “fun/funny/interesting,” “helpful/beneficial,” “inspiring/thought-provoking” and “informative.” 12 descriptors (4.50%) were considered neutral in nature, such as “hungry,” “long/long-duration” and “abstract,” and 10 (3.75%) as negative, such as “boring” and “too many activities in class.” Both the calculated intra-rater and inter-rater agreement percentages attained 95%, which indicated that the codes were all highly consistent.

Table 3 displays the results of the descriptors from Cambodia summer school. It shows that 85 out of 93 descriptors (91.40%) were positive. The most commonly mentioned categories were “fun/interesting,” “helpful,” “informative” and “meaningful/profound,” which is similar to that of Semester 1 and 3 courses. Only four neutral descriptors (4.3%) and four negative descriptors (4.3%) were reported. The inter-rater reliability was 100% and the intra-rater reliability was 95%.

Table 3. Categorization of descriptors used by the participants to describe the course in Semester 3 (Cambodia) of the academic year of 2017/2018

Descriptions	Nature of the Response				Total
	Positive	Neutral	Negative	Undecided	
Fun/interesting	17				
Helpful	14				
Informative	7				
Meaningful/profound	6				
Inspiring	5				
Improving	4				
Happy/joyful	4				
Useful	3				
Interactive	3				
Fulfilling/satisfying	2				
Innovative	2				
Reflective	2				
Relaxing	2				
Other positive responses	14				
Dynamic		1			
I get a little about the service leadership		1			
Somethings new to me		1			
Communication		1			
Tired			2		
Sleepy			2		
Total Count (N):	85	4	4	0	93
Total Count (%):	91.40	4.30	4.30	0	100

Table 4. Categorization of metaphors used by the participants to describe the course in Semester 1 (HK) of the academic year of 2017/2018

Metaphors	Nature of the Metaphor					Number of Codes Derived from the Metaphor and Its Nature				
	Positive	Neutral	Negative	Undecided	Total	Positive	Neutral	Negative	Undecided	Total
Light/beacon/compass/map	24					25				
Enjoyable tour/trip	9					12				
Camping/workshop/forum	6					7				
Book/dictionary	6					8				
Tree	6					6				
Interesting party/club/games	4					4				
Gas station/supply station	3					4				
Dessert/lollipops	3					3				
Mirror	2					2				
Other positive responses	19					21				
A boat		1				1		1		
Organization		1					1			
People get along		1				1		1		
Poet		1				1		1		
Ripples				1					1	
Total Count (N):	82	4	0	1	87	95	1	3	1	100
Total Count (%):	94.25	4.60	0	1.15	100	95	1	3	1	100

Table 5. Categorization of descriptors used by the participants to describe the course in Semester 3 (HK) of the academic year of 2017/2018

Metaphors	Nature of the Metaphor					Number of Codes Derived from the Metaphor and Its Nature				
	Positive	Neutral	Negative	Undecided	Total	Positive	Neutral	Negative	Undecided	Total
Light/compass/ A travel guide/Map	16					18				
Book/encyclopaedia/Wikipedia	10					11				
Journey/tour	9					11				
Buffet	5					5				
Mirror	3					3				
Water	1	1				2		1		
Sun	2					2				
Tree/planting tree	2					2		1		
Other positive responses	34					39		1		
Detective game		1					1			
Durian		1				1		1		
Healthy food		1					1			
Mixer		1					1			
Beet			1					1		
Baby				1					1	
Total Count (N):	82	5	1	1	89	94	3	5	1	103
Total Count (%):	92.13	5.62	1.12	1.12	100	91.26	2.91	4.85	0.97	100

Table 6. Categorization of descriptors used by the participants to describe the course in Semester 3 (Cambodia) of the academic year of 2017/2018

Metaphors	Nature of the Metaphor					Number of Codes Derived from the Metaphor and Its Nature				
	Positive	Neutral	Negative	Undecided	Total	Positive	Neutral	Negative	Undecided	Total
Light bulb/a map/compass	7					7				
Mirror	5					5				
Tour/trip/travel blog	4					4				
Food/a baked toast/new style dish	3					3				
Plant/snowball/staircase	3					3				
Other positive responses	8					10				
My attention				1					1	
Total Count (N):	30	0	0	1	31	32	0	0	1	33
Total Count (%):	96.77	0	0	3.23	100	96.97	0	0	3.03	100

Tables 4, 5 and 6 show the codes of metaphors of the three courses as well as the categories and nature of them respectively. As can be seen from table 4, among the 87 metaphors, 82 (94.25%) were coded as positive, only four (4.6%) as neutral and one (1.15%) as undecided. The 87 metaphors were broken down into 100 meaningful units, in which 95.0% (n=95) were positive in nature, 1.0% (n=1) was neutral, 3.0% (n=3) were negative and 1.0%

(n=1) was undecided. The metaphors with similar meanings were categorized into the same group. For example, the “workshop” and “forum” that proposed by two students both implied interactive learning modes according to their explanations, therefore these two metaphors were considered as under the same category.

All categories were listed according to the frequency mentioned by students. The first category, that was recognized by 24 students, all indicated that this course of study gave them direction and guidance. Some examples are listed below:

- **Light:** “It leads us into a right way, and it lights up my career path.”
- **Compass:** “It gives me different ideas of service leadership, and it helps me to develop. Also, it shows the way to become a successful service leader.”
- **Map:** “It provides guidance to service leadership. It shows a clear path for my future leadership execution.”

The second category was pointed out by 9 students, which mainly suggested that it had been an enjoyable and memorable journey for them to attend the “Service Leadership.” During the process, they were able to acquire new knowledge and develop themselves. For instance:

- **Enjoyable tour:** “This course is very interested for learning how to become a successful leader and also helpful for my career and study after studying in this course.”
- **An interesting trip:** “I have learnt something more in each lecture. For example, I have learnt the basic concept of service leadership: $E=MC^2$. And the learning process was interesting.”
- **An inspiring journey:** “It would be like a journey to extremely new things, and concepts are really interesting and inspiring for me. I would be able to grow and learn through the journey.”

Other frequently mentioned positive categories include “camping/workshop” (n=6), “book/dictionary” (n = 6), and “tree” (n = 6). There were four neutral metaphors (i.e., “a boat,” “organization,” “people get along” and “poet”) and one undecided metaphor “ripples.” The intra-reliability was 95% while the inter-reliability was 100%.

Similar positive results of Semester 3 course can be found in table 5, where 82 (92.13%) out of 89 metaphors were positive, five (5.62%) were neutral, one (1.12%) was negative and one (1.12%) was undecided. In addition, these 89 metaphors were coded into 103 meaningful units, among which 91.26% (n=94) were perceived positive, 2.91% (n=3) were neutral, 4.85% (n=5) were negative and 0.97% (n=1) was undecided.

According to the frequency, topping the list of positive categories is “light/compass/travel guide/map,” which was stated by 16 students. This category expressed that the course gave them direction and guidance. Below are some examples of students’ illustrations:

- **Light:** “Bring me new information to explore the dark future.”
- **Compass:** “This course helps me reflect my position in life and provides guidelines that lead to successful leadership.”
- **Beacon:** “This course guides my direction of my future life like what beacon does in the sea.”

The second category, which chiefly implied that the course covered meaningful knowledge and sufficient information, was mentioned by 10 students. Three examples are listed as below:

- **Book:** “The course contains a lot of knowledge and methodology of the development and concept of service leadership.”
- **Encyclopedia:** “Meaningful, full of knowledge.”
- **Reading a meaningful book:** “Learnt a lot in the course.”

There are four neural metaphors, (i.e., “detective game,” “durian,” “healthy food” and “mixer”) stated by students. One negative metaphor, “beet,” and one undecided metaphor, “baby,” were recorded. Both the intra-agreement percentage and inter-agreement percentage calculated from these metaphors were 95%, which indicated high reliability.

For the metaphors used in the Cambodia summer school (see table 6), 30 (96.77%) out of 31 were positive and only one (3.23%) was considered undecided. With regard to the meaningful units, 32 (96.97%) were regarded as positive and one (3.03%) as undecided. The first frequently mentioned category, which was acknowledged by seven students, conveyed that the course gave them direction and guidance to develop their service leadership, bringing meanings to their life. Below are the examples of students’ explanations:

- **Light bulb:** “The course is helpful to my development and is meaningful to my life, just like a light bulb lighting my future.”
- **Compass:** “It leads me to the way to provide great service to others in the future, especially I am a nurse to be.”
- **A map:** “It guides us to different places and helps me to know more about service leadership.”

The second category, which was appreciated by five students, revealed that the course helped them to reflect and understand themselves in a better way. Three examples are shown below:

- **A mirror:** “I can reflect myself for “who am I” and “what I want to be” seriously during the lesson.”
- **Mirror:** “It helps me to do reflections frequently to understand more about myself.”
- **Mirror:** “I can know more about myself through several reflective activities.”

The only undecided metaphor was “my attention.” Both the intra-reliability and inter-reliability reached 100%, indicating a very high degree of consistency in coding.

DISCUSSION

The present study evaluated the quality and effectiveness of the subject entitled “Service Leadership” in the academic year of 2017/18. A qualitative evaluation methodology was used to reach an insightful comprehension of students’ perceptions and feelings towards the subject. Both intra-rater and inter-rater reliability of the descriptors and metaphors were all equal or greater than 95%, demonstrating that the qualitative findings are highly reliable.

The reported findings indicate that the subject was effective in nurturing service leadership of university students in Hong Kong. For the descriptors, the responses were dominantly coded as positive in nature as more than 90% of the students expressing their positive views of the course (95.79% in Semester 1, 91.76% in Semester 3, and 91.40% in Cambodia summer school). The positive views from the three courses have several features in common. According to the descriptors, this subject was positively depicted as “interesting” and “funny,” suggesting students had been engaged in a joyful atmosphere of learning. Another frequently mentioned category is “inspiring” and “thought-provoking,” which indicated this subject stimulated students’ deeper thoughts and vision. A large proportion of students across the three courses also used “helpful,” “useful,” “meaningful,” and “beneficial,” which manifested that students largely appreciated the value of utility in “Service Leadership” education. Many students used “informative” as a descriptor to convey that the subject had offered them useful and rich information and was helpful and useful for their future development.

Similarly, over 90% (94.25% in Semester 1, 92.13% in Semester 3, and 96.77% in Semester 3 Cambodia) metaphors were positively used by students to reflect their perception and experience of the learning process. The most frequently mentioned category of positive metaphor resembled each other between the three courses, i.e. “compass,” “beacon,” “map” and “light.” According to the written metaphors, the service leadership subject was regarded as an effective tool to bring meanings to life and to provide direction and guidance for students’ future development and how to effectively be a qualified service leader. To elaborate, one student pointed out that the course could give him/her different concepts of service leadership, showing him/her the way to become a successful leader in future. This category of metaphor demonstrated that one of the essential objectives of service leadership subject, i.e. “recognizing the importance of service leadership to the development and wellness of oneself, other people and the whole society, particularly recognize the connection of learning in the subject to one’s own life” [17], were achieved to a great extent.

The second most frequently mentioned metaphors were associated with joyfulness, which expressed the positive emotions of students. Students used metaphorical expressions such as “inspiring journey,” “interesting trip” or “tour” to reflect their enjoyable learning experiences, which are resonant with the aforementioned written descriptors, such as “happy,” “interesting,” “enjoyable,” and “relaxing. The concordance between descriptors and metaphors implied that the service leadership subject provided them an interesting and enjoyable learning experience where they also learnt and developed. It was also suggested by the explanations of metaphors that this subject has engaged students in interactive games and experiential learning activities, in which students could learn in a practical way. It reflected the highlighted features of teaching and learning methodology in this subject [17]. Students also used metaphors such as “book,” “Wikipedia,” and “encyclopedia” to describe the

subject, as they thought it provided useful and interesting information in the scope of “Service Leadership.”

Additionally, several participants revealed that the service leadership subject promoted reflective learning. It manifested itself in the use of “reflective” as the descriptors and “mirror” as the metaphors. According to students’ elaboration, they had learnt to have constant and deeper reflection and were able to achieve a better understanding of themselves. For example, a student perceived this course as a “mirror” as he/she could understand who he/she is and what he/she “wants to be seriously during the lesson.” Researchers discovered that reflective learning is one of the effective learning methods for students. It was believed that critical reflection contributes to their avoidance of premature cognitive mindset, development of accurate perceptions, improvement of flexibility, and enhancement of creativity [30]. Asserted by Begley and Branson [31], the use of self-reflection is an essential step that can foster leaders’ moral characters in their leadership development. Therefore, promoting students’ reflective learning has been one of the foci of attention in service leadership subject implementation [1]. This view is also shown in the Subject Descriptive Form of the subject. These results suggest that reflective learning was well perceived by participating students. Besides, the findings indicated that participation in service leadership program was a solid way to promote self-reflection.

Despite the remarkable positive responses towards the course, there was still dissatisfaction expressed by a few students. For example, several negative descriptors (1.15% in Semester 1, 3.75% in Semester 3, and 4.30% in Semester 3 Cambodia) were found across three different classes. Taking the class in Semester 3 in Hong Kong as an example, four students described the course using “boring,” and the other two interpreted it as “too many activities in class.” Although the negative perceptions were in minority, future evaluation studies such as focus group interviews can be conducted to understand negative views towards the subject and how to improve students’ learning experiences.

Overall, the findings in the current study are consistent with previous studies [e.g., 1, 4, 17] in that there were overwhelmingly positive responses in the form of both descriptors and metaphors. For the descriptors, several categories such as “helpful/beneficial,” “useful,” “inspiring/thought-provoking,” “fun/funny/interesting,” and “happy/joyful/enjoyable” repeatedly appeared across the past few years. For the metaphors, several objects like “light/light bulb/lighted candle/compass/map,” “(interesting/enjoyable/delightful) travel/journey/trip/tour,” and “mirror” were also commonly observed in the past years. The prevalence of similar positive feedback across years demonstrates that the subject of Service Leadership has been able to cultivate holistic development and leadership qualities in students. The overwhelming positive findings are also consistent with the findings from “objective outcome evaluation” where it relatively demonstrated a certain positive development for students who completed the subject [3].

The significant implications of the present study are as follows. First, our findings demonstrated that “Service Leadership” fostered students’ development in different areas including self-reflection, leadership competencies, moral character as well as caring disposition, and hence equipped them to become qualified leaders in the future. As the ideology of service leadership is well aligned with the post-industrial paradigm of leadership, university students were able to develop their leadership qualities oriented to the service society. Therefore, this study suggests that it is essential for the university to incorporate service leadership education in its curriculum. It confirms Hastings and Sunderman’s [32]

viewpoints that higher education institutes and their educators should uphold the responsibility to nurture socially effective leaders.

Regarding the evaluation of subject effectiveness, the current study demonstrates several advantages of using descriptors and metaphor in a qualitative evaluation. From the analytical process, the use of descriptors allows researchers to identify the features and nature of the subjective experiences efficiently. Metaphors also enable participants to efficiently encapsulate intangible meanings or abstract ideas into a concrete image or representation. It also facilitates researchers' interpretation of participants' subjective experiences and thoughts. As Shek, Siu and Merrick [17] put it, "using metaphor helps the students to express their mental representations regarding the effectiveness of the course, which at the same time allows researchers to access into students' cognitive representation." Of course, there is a need to assess the reliability of the coding and interpretations involved. According to Shek, Tang and Han [33], using intra- and inter-rater reliability procedures would be helpful.

Despite the inspiring and promising findings, several limitations are noted. Firstly, the present study only focused on addressing the perceived effectiveness of participating students. The evaluation of the subject was therefore significantly based on subjective but not objective approaches. Therefore, it is necessary to combine the current study with an additional assessment such as observation. However, as it is mentioned above, quantitative and qualitative evaluation findings in the existing literature conducted by the research team basically complement each other. Secondly, the data collection conducted at a single point of time for each class. It is regarded less adequate than approaches such as pre- and post-test which can evaluate the course at different points of time (i.e., at the outset and the end of the semester) and investigate students' behavioral changes after taking the course. Thirdly, as only limited explanations were obtained, it is challenging to ascertain the underlying reasons behind students' positive comments. For instance, despite the fact that the majority of students perceived the course as "useful," research staff could not fully understand how the course benefited the students. To obtain a more inclusive and comprehensive understanding of students' perception, in-depth interviews such as individual or focus group interviews could be incorporated into future researches. Nonetheless, the findings of this qualitative study demonstrate promising results for the effectiveness of the subject "Service Leadership" and the positive developments of participating students during the 2017/18 academic year.

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Chapter 131

DEVELOPMENT AND EVALUATION OF A SERVICE LEADERSHIP SUBJECT IN A BLENDED LEARNING MODE

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ABSTRACT

In view of the emergence of service economies in the global context, it is important to promote service leadership education in universities. In Hong Kong, many studies showed that service leadership education could successfully promote university students' service leadership attributes (competence, character, and care) and foster their well-being. To benefit more students and enrich their learning experiences, there is a need to develop blended learning tools in addition to traditional classroom-based service leadership education in Hong Kong. In this article, we outline the development of a leadership subject in blended-learning mode. Preliminary findings suggest that participating students generally showed positive perceptions of the course, instructors, and course benefits. Besides, students' service leadership qualities and well-being showed positive changes after completing the course. Limitations of the evaluation findings and challenges of implementing a blended service leadership course are discussed.

INTRODUCTION

In the 21st century, one of the most significant challenges faced by higher education is how to incorporate advanced technology to facilitate lifelong learning and to increase student

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achievement and success [1]. On the one hand, information technology has penetrated almost every sphere of human life and greatly reshaped human lifestyle including their learning mode and behavior. On the other hand, there are increasingly diversified profiles of university students in terms of different cultures, regions, socioeconomic backgrounds, personalities, learning motivation, and learning styles [2]. Both aspects have raised significant challenges to traditional face-to-face teaching mode, which has been criticized for its weak capability to promote higher-order thinking, active learning, and collaborative learning [2]. In response to these challenges, blended learning as a new and innovative teaching and learning mode has been increasingly adopted for its potential in learning transformation [3].

Generally speaking, blended learning refers to a hybrid mode of learning based on well-conceived and effective integration/combination of traditional face-to-face classroom learning and electronic learning [1, 4, 5]. The integration/combination implies a comprehensive transformation and redesign of traditional teaching in which course instruction includes both face-to-face and online instructions and the time for classroom teaching is reduced [6]. Through this integration, teachers could utilize both classroom and online teaching techniques to engage students in active learning. In blended learning, the nature of classroom teaching is a place for students to present, interact, share, discuss, and debate [6, 7]. In the classroom setting, students can consolidate and deepen their online learning results. Classroom teaching also plays a vital role in promoting students' social interactions and bonds establishment. In addition, classroom teaching provides instant support and feedback, which is often seen as an advantage compared to online learning [8]. Therefore, blended learning aims to "join the best features of in-class teaching with the best features of online learning to promote active, self-directed learning opportunities for students" [6].

Garrison and Kanuka [1] argued that blended learning could foster "a community of inquiry" through "multiple forms of communication" including face-to-face and online communication. This community of inquiry involves both cognitive and social functioning through interactive dialogues. During the process, students develop critical and reflective thinking, which implies that they have engaged in deep and active learning. In blended learning courses, learners could access and learn knowledge and information with no restriction of time and space [2]. They have higher autonomy to decide and schedule their own learning pace [9]. Students can be "together" physically through face-to-face classroom teaching and virtually through synchronized online learning; they can also be "apart" through asynchronous online learning [10]. All these features make students' learning highly flexible, which is essential for maximizing their learning achievements [10]. Furthermore, blended learning provides access to a large body of students with diversified backgrounds, such as students having commuting difficulties, owning part-time jobs, or having financial concerns, whose learning needs could not be easily met by traditional classroom teaching [8].

A growing body of empirical studies has focused on the impacts and effectiveness of blended learning courses [11, 12]. Some scholars found that well-designed blended learning courses could facilitate quality interactions among students and between students and teachers [13], increase student engagement [14], enhance learning satisfaction [8, 15], promote knowledge acquisition and learning achievement [16, 17]. Some studies also identified factors influencing the effectiveness of blended learning, including student engagement and perceptions about these courses [8], teacher support [18], and student learning styles and maturity [19]. Furthermore, a few studies outlined potential challenges of implementing blended learning courses in higher education institutions, such as a lack of new pedagogical

and technological skills among staff, insufficient learner support throughout the learning process, conventional conception, and staff resistance to change [6, 20].

Overall speaking, blended learning can be regarded as an irresistible trend in higher education due to its potential to improve student learning. With the continuous advancement of information technology, the inclusion of blended learning is increasing. However, Halverson and colleagues [3] claimed that one research gap was that a large body of existing work primarily focused on theoretical discussion on definitions and models while there were relatively limited empirical studies. Some scholars further discussed the limitations of blended learning at institutional level (e.g., complexity of its management and demanding for advanced learning management system) and student level (e.g., requirement of becoming self-directed learners, ineffective communication in an online environment) [21, 22]. In addition, there are studies showing no significant differences in course effectiveness between traditional learning and blended learning [23, 24]. Therefore, more studies should be conducted to understand the potentials, designs, practices, and effects of blended learning in different higher education settings. In addition, few studies have examined blended learning development in Asian contexts. It is necessary to advance scholarly knowledge on blended learning and provide useful guidance for administrators and educators to design and implement effective blended learning courses in higher education in non-Western contexts, such as Hong Kong.

Higher education in Hong Kong has been undergoing significant changes. One significant change is the transformation of the previous three-year undergraduate curriculum to the new four-year curriculum to offer more general education to students [25]. Another change is the usage of information technology in teaching and learning to enrich students' learning experience. To facilitate these changes, the University Grants Committee (UGC) provides funding to support the course development and staff professional training on blended learning and e-learning in different universities [26]. With this support, a notable project on blended learning entitled "The Responsive University: Appreciating Content Sharing in General Education" ("Responsive 4U" in short) was initiated in the academic year of 2018/2019. Four top-ranking universities in Hong Kong participated in the project, including The University of Hong Kong, The Chinese University of Hong Kong, The Hong Kong Polytechnic University (PolyU), and The Hong Kong University of Science and Technology. This project attempted to develop "sharable" blended learning general education and "cross-institutional learning system" among different participating institutions. Specifically, eleven blended-learning general education courses were offered to students. Among the eleven courses under the "Responsive 4U" project, one blended learning course entitled "Service Leadership" is offered by PolyU. Design of "Service Leadership" blended course and preliminary evaluation findings for its course effectiveness are presented in sections below.

DESIGN OF "SERVICE LEADERSHIP" BLENDED COURSE

The "Service Leadership" course is a 3-credit general education subject designed based on the Service Leadership Model proposed by Po Chung, the Co-founder of DHL International (Asia Pacific). According to Chung [27], service leadership is defined as "satisfying needs by consistently providing quality personal service to everyone one comes

into contact with, including one's self, others, groups, communities, systems, and environments." Effective service leadership consists of three key components: "competence," "character," and "care" [28]. Nowadays, the global economy is transforming from manufacturing to service economy. For university students to remain competitive, it is important to develop their service leadership qualities to accommodate themselves to the new requirements. As an innovative response to this call, the "Service Leadership" course aims to help students understand basic models of leadership, be aware of leadership qualities of themselves, and apply the principles and improve themselves in daily life.

This course has been previously taught in a traditional classroom face-to-face approach at PolyU. The evaluation of the traditional course has been very positive since its inception in 2012/2013 academic year [29-31]. The blended version of this course was developed in the first semester of the academic year of 2018/19 and implemented under the "Responsive 4U" project in the second semester. A total of 43 students enrolled in the course, including both PolyU and non-PolyU students. We used Blackboard as the Learning Management System for this blended course.

The blended course lasted for 13 weeks, including 10 online sessions and 3 face-to-face lectures. The main structure of all 13 lectures is shown below:

- 1st Week (1st Lecture): "Introduction of Service Leadership Model" (face-to-face)
- 2nd Week (2nd Lecture): "Core beliefs and key components of service leadership"
- 3rd Week (3rd Lecture): "Basic leadership competencies: Intrapersonal competencies"
- 4th Week (4th Lecture): "Basic leadership competencies: Interpersonal competencies"
- 5th Week (5th Lecture): "Character strengths and service leadership"
- 6th Week (6th Lecture): "In-class interactions and consultation" (face-to-face)
- 7th Week (7th Lecture): "Care and service leadership"
- 8th Week (8th Lecture): "Character strengths in Chinese philosophies"
- 9th Week (9th Lecture): "Contemporary leadership models and the dark side of leadership"
- 10th Week (10th Lecture): "Factors leading to creation, development, and maintenance of positive social relationships"
- 11th Week (11th Lecture): "Self-leadership and service leadership"
- 12th Week (12th Lecture): "Developmental assets and service leadership"
- 13th Week (13th Lecture): "Review of effective service leadership qualities and wrap-up" (face-to-face)

ONLINE MODULES

As mentioned earlier, the course aimed to help students to understand basic models of leadership, be aware of their own leadership qualities, and apply the principals and improve themselves in daily life. Online sessions contained both video lectures introducing concepts and theories related to service leadership, as well as different activities improving students' understanding and leadership skills. These activities included reflective activities, tests, discussion forum, group discussion, and class chat sessions. Table 1 summarizes the features of this blended course and the duration/frequency of different activities.

Online Video Lectures

In each week, students were required to watch several videos online under the same topic. The videos lasted for around 3-18 minutes with an average duration of seven minutes. Through watching videos, students were expected to gain knowledge of basic leadership attributes and contemporary models of leadership in the service sector. Online video lectures were convenient for students to arrange a flexible study schedule, especially for non-PolyU and part-time students.

Table 1. Features of a blended course of service leadership

Blended design	Participants	Duration of activity	Learning tools
Online modules			
Online video lectures	Individual	Average 7 mins/ per video, 4-6 videos/per week, 10 weeks	Videos on Blackboard
Reflective activity	Individual	3-7 topics per week, 10 weeks	Reflective activities on Blackboard (e.g., reflective writing, arguments, write metaphor, etc.)
Online test	Individual	5-7 items per week, 10 weeks	Tests function on Blackboard
Online discussion forum	Among all students	5 times under specific topic in Week 2, 5, 8, 11, and 12	Blackboard discussion group
Group discussion	Among group members	3 times in Week 3, 7, and 9	No specific tool is regulated. Only discussion record is required. Students can use WhatsApp, group forum function on Blackboard, etc.
Online chat sessions	Among all students and lecturers	1 hour per session, 2 sessions in Week 3 and 10, respectively	Blackboard Collaborate Ultra
Face-to-face modules			
Face-to-face lectures	All students and lecturers	3 hours per lecture, 3 lectures in Week 1, 6 and 13	

Reflective Activities

We developed reflective activities to deepen students' understanding and reflection, and cultivate their service leadership qualities. Through reflective activities, students could reflect on the importance of developing essential service leadership attributes, leadership qualities of themselves, and the way to apply knowledge in daily leadership practice. Reflective activities targeted on higher educational objectives of learning goals according to Bloom's taxonomy, including applying, analyzing, evaluating, and creating [32]. For example, after watching a video explaining different types of contemporary leadership models, students were required to further reflect on the differences between these models and the Service Leadership Model. Compared to face-to-face classroom reflective activities, students felt less time pressure or insufficient preparation when completing online reflective activities, and tended to share more genuine in-depth thoughts. In addition, after obtained their approval, we uploaded students'

anonymous sharing on Blackboard so that all students could learn from their classmates' reflections. Besides, we specifically selected those topics demonstrating their creative thinking, problem-solving skills, integrity, and leadership. For those questions receiving interesting or controversial responses, we brought them to class chat or face-to-face lectures to further share or discuss with students.

Test

After watching online video lectures in each week, students were required to complete a final test to recall the knowledge covered in service leadership. The test was used to evaluate student's recalling and understanding of the basic knowledge [32]. Multiple choices, true and false, and cloze were often used in the final test. In addition, some open-ended questions were asked to collect feedback on the online lecture each week.

Group Discussion

Students were also required to conduct group discussion on a topic from time to time. Group discussion helped students to practice their leadership through group activities and facilitate their group project preparations. Students had full autonomy in the way to arrange their group discussions. Students could do it online or offline. No specific tool or approach was suggested. They could use WhatsApp or group discussion board on Blackboard. The discussion record was required for our reference.

Online Discussion Board

Some lectures contained discussion tasks, which required students to share their opinions on a given topic and to give comments to others' posts. Students needed to present their own ideas, review and respond to other perspectives. For example, we asked students to recommend books or movies reflecting key elements of service leadership. We adopted the discussion board on Blackboard.

Online Chat Sessions

Online class chat aimed to establish direct and instant communication between students and lecturers. Students could receive instant feedback from lecturers and vice versa. We attempted to tackle the issues raised during the online learning. For each chat session, we provided two timeslots for students to choose. Blackboard Collaborate Ultra was used.

FACE-TO-FACE LECTURES

Three face-to-face lectures provided introduction and periodical wrap-up to students. Feedback on online activities was also covered in these face-to-face lectures. We also provided many opportunities for students to practice and reflect service leadership qualities during the face-to-face lectures. Based on the results of the online activities, we gave further feedback and explanation. For example, we shared the data of students' online learning to motivate them, shared the distribution of their opinions on different topics, disclosed ourselves, and invited them to share their experiences and reflections. In addition, we also gave feedback to some questions they mentioned in the online feedback.

Table 2. Assessment scheme of the blended course “Service Leadership”

Time	Requirements	Marks
Each week	Participate in required online activities and complete assignments of each respective online lecture	10
In Lecture 6	Participate in classroom interactions	1
In Lecture 13	Participate in classroom interactions	1
Before Lecture 3	The Pre-Test Objective Outcome Evaluation Form	1
Before Lecture 13	The Personal Reflection Form	1
Class chat session time	Participate in two class chat sessions	1
Total marks		15

*1 mark for each online lecture 10 online lectures in total.

Course Assessment

The assessment of the blended course included three parts: class participation, group project, and term paper. For class participation, students were required to watch videos, participate in activities and complete related assignments on time to get the participation marks. For students who successfully completed all tasks on time, a total of 15 marks for Class Participation/Preparation were given. The assessment scheme is shown in Table 2. For the group project, each group needed to produce a 30-minute video presentation on one of the key elements of effective service leadership. Group project presentation showed students' understanding of theories and concepts related to service leadership qualities, interpersonal skills, personal and group reflections, and the recognition of essential elements of service leadership covered in the course. For the individual term paper, all students were required to submit term papers on topics related to Service Leadership. Individual term paper indicated students' understanding of key concepts and theories, their self-assessment and self-reflection based on personal experiences.

EVALUATION

To examine the effectiveness of the blended “Service Leadership” course in promoting student leadership qualities and well-being, we conducted a preliminary evaluation study. We employed multiple evaluation approaches, including the one-group pretest-posttest method,

subjective outcome evaluation, and qualitative evaluation. All students gave their written consent to participate in the study. The evaluation study aimed to answer the following three questions.

- Question 1: Do students show positive changes in service leadership qualities and well-being after completing the blended “Service Leadership” subject?
- Question 2: How do students perceive the subject?
- Question 3: How do students evaluate their learning experiences in this blended course?

OUR STUDY

The one-group pretest-posttest used service leadership qualities (“knowledge,” “attitude,” and “behavior”) and well-being (“positive youth development” or PYD, and “life satisfaction”) as major outcome measures. Students participating in the blended course were invited to respond to these measures through an online survey before the delivery of the first lecture (i.e., pretest) and after the completion of all lectures (i.e., posttest). The data collected from 28 students were matched between the pretest and the posttest. The demographic information of the matched sample is presented in Table 3.

The 40-item “Service Leadership Knowledge Scale” (SLK) was employed to measure knowledge. The 40 multiple-choice questions are related to knowledge of service leadership, such as “manufacturing versus service economies in the modern world,” “the importance of 3Cs to effective service leadership,” “everyone can be a leader,” “features of the service leadership theory,” and so on. Students get “1” point for the correct answer or “0” point for any incorrect answers. This knowledge scale was developed following a standardized procedure of constructing a reliable and valid assessment tool. Previous studies have supported its good reliability and validity [33].

Attitudes toward service leadership practice were measured by a 23-item version of the “Service Leadership Attitude Scale” (SLA) which used a 6-point rating scale (“1” = “strongly disagree,” “6” = “strongly agree”). This scale was also constructed based on a solid scale validation procedure and has been demonstrated to possess good psychometric properties [34, 35]. The 23 items were pertinent to different elements, such as “self-reflection” (sample item: “a leader should closely examine his/her own thoughts and behavior”), “caring disposition” (sample item: “a good leader listens to his/her subordinates’ views”), “ethical role model” (sample item: “A good leader uses himself/herself as an example to influence the behavior of followers.”), and so forth.

The 19-item version of the “Service Leadership Behavior Scale” (SLB) was adopted to assess student leadership practice on a 6-point rating (“1” = “strongly disagree,” “6” = “strongly agree”). The good reliability and validity of SLB have been supported by a series of validation studies [36, 37]. The 19-item scale includes different aspects of desired service leadership practice, such as “self-improvement” (sample item: “I keep learning new knowledge”), “problem-solving” (sample item: “I am able to argue in a logical way”), “resilience” (sample item: “When difficulties or setbacks appear in my life, I do not give up easily”), and so on.

Life satisfaction was measured through the Chinese version of “Satisfaction with Life Scale” (SWLS) [38, 39]. The SWLS included five items (e.g., “In most ways, my life is close to my ideal” and “The conditions of my life are excellent”) and adopted a 6-point rating scale (“1” = “strongly disagree,” “6” = “strongly agree”).

Table 3. Demographic information of participants

Demographic variables	Frequency	Valid Percent (%)
Gender		
Male	13	46.4
Female	15	53.6
Age		
18-year-old	2	7.1
19-year-old	4	14.3
20-year-old	8	28.6
21-year-old	8	28.6
22 or above	6	21.4
Mean = 21.11; SD = 3.02		

(n = 28 matched sample).

PYD attributes of students were assessed by “Chinese Positive Youth Development Scale” (CPYDS), using a 6-point rating scale (“1” = “strongly disagree,” “6” = “strongly agree”). The present study utilized 31 items (e.g., “I know how to communicate with others” and “I can differentiate between the good and the bad aspects of things”) in relation to 10 subscales. Three higher-order PYD qualities can be computed based on the specific subscales: 1) “Cognitive-behavioral competence” calculated by three subscales including “cognitive competence,” “behavioral competence,” and “self-determination”; 2) “Positive identity” calculated by two subscales including “clear and positive identity” and “belief in future”; and 3) General PYD qualities calculated by the remaining five subscales including “social competence,” “emotional competence,” “moral competence,” “spirituality,” and “resilience.”

Subjective Outcome Evaluation

Students were invited to complete a “Subjective Outcome Evaluation Scale” (SOES) after the last lecture in Week 13. A total of 19 completed questionnaires were collected and used for data analysis. The SOES allowed students to express their views toward the blended course in terms of perceptions of “course contents” (e.g., “the content design of the curriculum is very good”), “lecturer” (e.g., “the lecturers showed good professional attitudes”), and “course benefits” (e.g., “it has strengthened my self-confidence”). In addition, the SOES assessed students’ overall satisfaction with the blended course through the following three questions: a) “Will you suggest your friends to take this program?” b) “Will you participate in similar programs again in the future?” and c) “On the whole, are you satisfied with this program?”. All items included in the SOES used a 5-point rating and the scale showed good internal reliability in previous studies [29, 40, 41].

Qualitative Evaluation

During learning, students were encouraged to express their personal views toward each online lecture after they completed all learning activities required for each online lecture. Besides, during the two online chat sessions, students were also invited to share their learning experience and feelings. After the completion of the course, a personal reflection form was further used to collect subjective evaluation of their learning experiences in the blended course. First, students were asked to use three words to describe their feelings and perceptions. Second, students were invited to think of a metaphor with a brief explanation to stand for the subject. In total, 37 completed personal reflection forms were collected and student responses were reviewed and analyzed.

FINDINGS

As shown in Table 4, there was a trend of positive changes in all eight outcome indicators. However, due to the small sample size ($n = 28$), participants' pretest and posttest scores did not follow a normal distribution, which violated the precondition of conducting repeated-measures multivariate general linear modeling analysis. As a result, we performed a binominal test based on the aggregated data. The result suggested that the positive change of the eight indicators was significant ($p = .008$), which gave tentative support for the claim that the subject was effective to promote the development of the students.

Table 4. Student changes in outcome indicators based on aggregated data ($n = 28$)

Outcome Indicators	Pre-test	Post-test	Positive change	Binomial Test (p)
Higher-order PYD factors				
Cognitive-behavioral competence	4.59	4.75	Yes	.008
Positive identity	4.45	4.66	Yes	
General PYD qualities	4.39	4.55	Yes	
Total PYD score	4.48	4.66	Yes	
Life satisfaction	4.00	4.14	Yes	
Service leadership qualities				
Service leadership knowledge	27.68	31.93	Yes	
Service leadership attitude	4.82	4.90	Yes	
Service leadership behavior	4.67	4.81	yes	

Subjective Outcome Evaluation

Summaries of student responses in the SOES are presented in Table 5 and 6. Results showed that most of the students expressed positive evaluations on most evaluation items. For example, over 78% of the respondents agreed that “the objectives of the curriculum are very clear,” “the activities were carefully arranged,” and “on the whole, I like this course very much”. In addition, nearly 85% of the participants expressed that the course lectures had good teaching skills and they were willing to help students. Furthermore, more than 78% of the participants felt that their critical thinking and self-confidence were enhanced after taking the course. Overall speaking, 78.9% of the respondents were satisfied with the blended course.

Despite these positive evaluation findings, only around 45% of the participants thought that the course was helpful for the pursuit of meaning in life.

Table 5. Summary of the positive views (options 4-5) of the participants in different aspects

Items		N	M	SD	Positive Responses ^a	
					n	%
Perceptions of course content						
1.	The objectives of the curriculum are very clear.	19	3.89	1.12	15	78.9
2.	The content design of the curriculum is very good.	19	4.05	.83	15	78.9
3.	The activities were carefully arranged.	19	3.84	1.09	15	78.9
4.	The classroom atmosphere was very pleasant.	19	3.84	1.09	13	68.4
5.	There was much peer interaction amongst the students.	19	3.89	.91	14	73.7
6.	I participated in the class activities actively (including discussions, sharing, games, etc.).	19	4.11	.85	15	78.9
7.	I was encouraged to do my best.	19	3.79	1.10	14	73.7
8.	The learning experience enhanced my interests towards the course.	19	3.74	1.02	13	68.4
9.	Overall speaking, I have a very positive evaluation on the course	19	3.79	1.10	14	73.7
10.	On the whole, I like this course very much.	19	3.84	1.09	15	78.9
Perceptions of lecturer(s)						
1.	The lecturer(s) had a good mastery of the course.	19	3.95	.94	14	73.7
2.	The lecturer(s) was (were) well prepared for the lessons.	19	4.05	1.00	15	78.9
3.	The teaching skills of the lecturer(s) were good.	19	4.05	.94	16	84.2
4.	The lecturer(s) showed good professional attitudes.	19	4.05	.94	16	84.2
5.	The lecturer(s) was (were) very involved.	19	4.05	.83	15	78.9
6.	The lecturer(s) encouraged students to participate in the activities.	19	4.16	.99	16	84.2
7.	The lecturer(s) cared for the students.	19	4.16	.81	16	84.2
8.	The lecturer(s) was (were) ready to offer help to students when needed.	19	4.26	.64	17	89.5
9.	The lecturer(s) had much interaction with the students.	19	3.95	.89	13	68.4
10.	Overall speaking, I have a very positive evaluation on the lecturer(s).	19	4.05	1.05	16	84.2
Perceptions of course benefits						
1.	It has enhanced my social competence.	19	3.63	1.09	12	63.2
2.	It has improved my ability in expressing and handling my emotions.	19	3.74	1.02	13	68.4
3.	It has enhanced my critical thinking.	19	3.84	1.09	15	78.9
4.	It has increased my competence in making sensible and wise choices.	19	3.74	1.07	14	73.7
5.	It has helped me make ethical decisions.	19	3.74	1.07	13	68.4
6.	It has strengthened my resilience in adverse conditions.	19	3.79	1.06	13	68.4
7.	It has strengthened my self-confidence.	19	3.89	.91	15	78.9
8.	It has helped me face the future with a positive attitude.	19	3.79	1.06	13	68.4
9.	It has enhanced my love for life.	19	3.32	1.38	8	42.1
10.	It has helped me explore the meaning of life.	19	3.58	1.14	9	47.4
11.	It has enhanced my ability of self-leadership.	19	3.95	.89	13	68.4
12.	It has helped me cultivate compassion and care for others.	19	3.95	.76	13	68.4
13.	It has helped me enhance my character strengths comprehensively.	19	3.84	.93	13	68.4
14.	It has enabled me to understand the importance of situational task competencies, character strength and caring disposition in successful leadership.	19	3.95	.83	14	73.7
15.	It has promoted my sense of responsibility in serving the society.	19	3.74	.91	12	63.2
16.	It has promoted my overall development.	19	3.63	1.09	12	63.2
17.	The theories, research and concepts covered in the course have enabled me to understand the characteristics of successful service leaders.	19	4.05	.83	15	78.9
18.	The theories, research and concepts covered in the course have helped me synthesize the characteristics of successful service leaders.	19	3.79	.95	12	63.2

Note: ^a For every item, respondents with positive responses (Options 4-5) are shown in the Table.

Table 6. Summary of students’ overall satisfaction with the course

Items		N	M	SD	Positive Responses ^a	
					n	%
1.	Will you suggest your friends to take this course?	19	3.89	.85	13	68.4
2.	Will you participate in similar courses again in the future?	19	3.74	1.07	12	63.2
3.	On the whole, are you satisfied with this course?	19	3.95	.76	15	78.9

Note: ^aFor every item, respondents with positive responses (Options 4-5) are shown in the Table.

Qualitative Evaluation

For comments on each online lecture, students mainly opined that they learned useful knowledge and concepts about service leadership which could help them to understand effective leadership in service economies and related determinants. Besides, those online reflective activities can help them to think deeply about own strengths and weaknesses and how to improve. Most importantly, students commented that blended learning is convenient for them to arrange a study plan. In this regard, most students agreed that learning through online lectures could give them more flexibility. For example, they could do the lecture activities several times and perform revision by going through the whole lecture by themselves whenever they wanted to. However, some students also complained that the workload was heavier compared with other face-to-face general education subjects.

Regarding personal reflections, students positively evaluated their learning experience in the blended course. Specifically, students frequently used positive descriptors to present their feelings and subjective experience in the course. The frequently used descriptors included “interesting,” “inspiring,” “joyful,” “fruitful,” “enjoyable,” “useful,” “helpful,” “meaningful,” “interactive,” “reflective,” and “innovative.” Regarding metaphors, students’ positive expressions were impressive. For example, a student claimed that the course “seems like a travel trip where I can look around the world to learn somethings that I have never touched or seen before in every other destination (lecture).” Another student used “a mirror” because “it reflects a lot of my own leadership strategies and imperfections, just like a mirror reflects physical appearance”.

DISCUSSION

Previous evaluation findings have repeatedly indicated that the “Service Leadership” subject delivered through traditional face-to-face mode is successful in nurturing university students’ service leadership qualities and promoting their well-being [29, 41-43]. The present evaluation findings further suggest that a well-designed blended “Service Leadership” course is also a promising approach to promote service leadership qualities and well-being among university students. As one of the innovative and technology-enriched teaching pedagogies, blended learning is considered increasingly important or even the “new normal” in higher education [44, p. 207-208]. The re-design of the traditional “Service Leadership” course into a blended one complies with this global trend. Past research suggests that blended learning can entail great learning achievement among students as compared to either sole e-learning or

sole face-to-face learning [45-47]. This may be because the blended design is flexible and technology-oriented, thus can enhance student engagement [48, 49]. This speculation is consistent with the present observations that students appreciated the flexible study plan including the convenient revision plan they can enjoy in the blended course.

Of course, we have to be mindful of the limitations of the blended learning approach. First, studies suggest that blended learning raises more demanding requirements for institutional management, teaching staff's mindset, and students' skills in mastering multiple learning strategies [21, 22]. Second, blended learning requires students to take a more active role in learning and become intrinsically motivated, which is not in line with the characteristics of Chinese students who normally prefer didactic teaching [50, 51]. Third, as blended learning takes up much time of the students (e.g., going through the online activities and assignments), students taking up part-time jobs may not like it as it may interfere with their earning activities. This point is important when we realize that students at PolyU are mostly from the grassroots.

There are several limitations of the current evaluation work. First, the sample sizes were small. In addition, due to the absence of a control group, objective outcome evaluation was unable to inform the causal effect of the blended course. Furthermore, all data were collected through self-report measures. Hence, while the present evaluation findings tended to support the effectiveness of the blended "Service Leadership" course, the findings were very preliminary. There is a great need to collect more data from multiple informants in the future to further evaluate the course effectiveness of a blended "Service Leadership" subject.

During the implementation of the blended course, we encountered several challenges, which should be further tackled for course improvement. The first challenge is related to student engagement. For example, some students were not able to complete online learning on time and some others came to face-to-face lectures without good preparation. Manwaring et al. [52] argued that while blended designs have been perceived to effectively engage students in learning, blended classes can also make engagement more difficult for some students. Students with low self-regulation may not perform well in navigating online learning modules independently without others' monitoring [53]. Besides, some students may still prefer regular face-to-face learning contexts. These students may feel "isolated" due to reduced classroom interaction with classmates and teachers, which in turn leads to a lower level of learning motivation [44]. In fact, some students in our course indicated that they expected more face-to-face interactions, which may be due to the "passive" learning style they have developed during primary and high schools.

The second challenge has to do with teachers' timely feedback. Students were required to do some individual reflective activities after completing certain online learning. For example, students were asked to think about self-leadership strategies they used in daily life and ways to improve self-leadership. After most of the students provided their reflective responses, we reviewed these responses and gave feedback to each of the questions. Besides, to facilitate student learning, especially learning from others' experience, we summarized and shared student opinions among all students. However, as students had different time schedules in completing online lectures, it was not easy for teachers to collect all students' responses and gave timely feedback. Last but not least, some students perceived that the workload of online learning was heavier than traditional classroom classes. In this case, some students may fail to complete all learning activities, which consequently hinder the achievement of intended learning outcomes.

To help students engage in online learning and better interact with peers and teachers, one feasible strategy is to design tailor-made group activities. For example, asking students to do a group discussion focusing on a specific topic where related concepts have been covered by online lectures. This will motivate students to learn and understand online learning materials and further digest knowledge through peer interactions (i.e., collaborative learning). Besides, it is also possible to have pre-lecture group activities, which may get students well-prepared for face-to-face lectures. Furthermore, group activities incorporating reflective learning may reduce students' workload. In short, we need to optimize online and offline activities to better engage students and facilitate their learning.

Despite the limitations of the preliminary positive evaluation findings and several challenges in implementing the blended "Service Leadership" course, the present study represents a pioneering effort in putting blended service leadership education into practice and examining its educational effects through multiple strategies. In conclusion, the blended mode can be regarded as an effective pedagogy to involve more students with diverse backgrounds and to provide them with flexibility in learning.

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Chapter 132

DEVELOPMENT AND VALIDATION OF ASSESSMENT TOOLS ON SERVICE LEADERSHIP KNOWLEDGE, ATTITUDE AND BEHAVIOR

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ABSTRACT

How can we develop and nurture leadership in service economies? This issue is of upmost importance, because the mode of production and requirements of the leaders are

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different in manufacturing and service economies. While the focus in manufacturing industries is on “do things right,” the focus of services economies is on “do the right things.” In this book we start out with the Service Leadership Model as well as the ingredients on Service Leadership knowledge, attitude, and behaviors (i.e., skills). Second, psychometric properties of three validated measures on Service Leadership knowledge, attitude and behavior are presented. In these chapters, the internal consistency, convergent validity and factorial validity of the measures are presented. Third, the psychosocial correlates and norms associated with these three measures of Service Leadership are presented. Through these chapters, we attempt to establish the psychometric properties and norms of the scales assessing Service Leadership knowledge, attitude and behavior. Finally, user manuals for the three assessment tools are also presented. It is our humble wish that the related work and the developed assessment tools can be used in the training, personnel decisions, intervention and research contexts.

INTRODUCTION

With the growth of service industries in the global world, there is a need to ask how we can nurture leadership in service economies. This is important because the mode of production and requirements of the leaders are different in manufacturing and service economies [1]. While the focus in manufacturing industries is on “do things right,” the focus of services economies is on “do the right things.” Besides, leadership style in service economies is often “bottom-up,” which is different from the “top-down” style in manufacturing industries. In view of the unique features of service economies, we need a leadership model which can meet the needs of service economies [2].

To address the issue of service leadership in the changing economies, Dr. Po Chung (Co-founder of DHL International and Chairman Emeritus of DHL Express (Hong Kong) Ltd. and Chairman of the Hong Kong Institute of Service Leadership and Management Limited (HKI-SLAM)) proposed the Service Leadership Model. According to HKI-SLAM [3], service leadership “is about satisfying needs by consistently providing quality personal service to everyone one comes into contact with, including one’s self, others, groups, communities, systems, and environments. A service leader is a ready, willing and able, on-the-spot socialized entrepreneur who possesses relevant task competencies and is judged by superiors, peers, subordinates, and followers to exhibit appropriate character strengths and a caring social disposition.” The Service Leadership Model is based on Chung’s seminal works on service reborn [4], 25 principles essential for service leadership [5] and 12 dimensions of one’s personal brand [6].

To promote Service Leadership education in the publicly-funded universities in Hong Kong, Li and Fung Foundation provided HK\$40 million to support a project on Service Leadership Education in Hong Kong. In the eight universities funded by the University Grants Committee, researchers developed credit-bearing subjects, non-credit-bearing programs and curriculum materials. In some programs, some evaluation work was done using some tentative measures of service leadership qualities [7, 8].

Unfortunately, Service Leadership education has been hindered due to its lack of validated measures of Service Leadership knowledge, attitude and behavior. Similarly, the lack of related validated measures also hinders the development of Service Leadership research. The development of measures based on the Service Leadership Model is important

for several reasons. First, as Service Leadership Model is still at its infancy and there is limited research underlying the concepts and theories of Service Leadership, validated measurement tools are vital to the future development of the model. Slavec and Drnovšek [9] argued that “effective measurement is a cornerstone of scientific research ... reliable and valid measures contribute to the legitimacy and development of a research field” (p. 39). Second, the scales would allow for investigations on the determinants and outcomes of effective Service Leadership qualities, and how these qualities are related to organizational effectiveness [2]. Third, assessment tools in Service Leadership are important because they can be used to examine the effectiveness of related intervention programs. For example, it would be extremely important to understand whether Service Leadership training programs really promote Service Leadership qualities in the program participants.

THREE AREAS OF IMPORTANCE

There are three areas that should be assessed as far as Service Leadership qualities are concerned. The first area is Service Leadership knowledge. Assuming that we are asked to create a credit-bearing subject on Service Leadership, we have to ask what fundamental knowledge on Service Leadership will be included. Basically, Service Leadership knowledge includes core beliefs of the Service Leadership Model (such as everybody can be a leader) and components of effective Service Leadership (competence, moral character and caring disposition). For example, as far as moral character is concerned, a service leader should appreciate the importance of morality and integrity and what constitutes an ethical leader (“know-what”). Besides, one must know the determinants of moral judgments such as motivation to act in a moral manner, moral reasoning, and reflection on one’s Personal Operating System. Regarding caring disposition, one should know its components, such as empathy, love, and sensitivity to others’ needs and emotions.

For attitude to Service Leadership, it basically addresses one’s beliefs and feelings about Service Leadership, such as whether one agrees to the core beliefs of Service Leadership and the basic ingredients of effective service leadership. Most important of all, it is important to assess whether one has a service mindset, such as care about oneself as well as others, and to be sensitive to others’ needs. Besides, whether one identifies with the importance of moral character, such as the degree of agreement with the importance of character strengths based on the Western literature and Confucian values based on Chinese philosophies.

For Service Leadership skills, an effective service leader should possess intrapersonal skills (such as resilience, emotional competence, social competence, courage and vision) as well as interpersonal skills (such as relationship building, team building and conflict resolution skills). Besides, service leaders should learn “maritime” leadership style combining both top-down and bottom-up leadership models and appreciate distributive leadership styles. As caring leaders, effective service leaders should also know the skills of developing others and mentorship abilities.

ABOUT THIS BOOK

Against the above background, there are several parts in this book. First, the Service Leadership Model as well as the ingredients on Service Leadership knowledge, attitude and behaviors (i.e., skills) are presented. Second, psychometric properties of three validated measures on Service Leadership knowledge, attitude, and behavior are presented. In these chapters, the internal consistency, convergent validity and factorial validity of the measures are presented. Third, the psychosocial correlates and norms associated with these three measures of Service Leadership are presented in three papers. Through these chapters, we attempt to establish the psychometric properties and norms of the scales assessing Service Leadership knowledge, attitude and behavior. Finally, user manuals for the three measures on Service Leadership knowledge, attitude, and behavior are also presented. It is our humble wish that the related work and the developed assessment tools can be used in the training, personnel decisions, intervention and research contexts.

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Chapter 133

LEADERSHIP ASSESSMENT TOOLS IN DIFFERENT CHINESE CONTEXTS

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ABSTRACT

Leadership research in different Chinese contexts is growing rapidly with plentiful assessment tools emerging in the field. Using a cross-cultural study framework, this chapter provides an overview of contemporary leadership assessment tools used in different Chinese contexts. The leadership assessment tools developed by the etic approach, emic approach and combined etic-emic approach all contribute to the knowledge advancement of leadership, yet their limitations should also be noted. This chapter ends with a critique of Chinese leadership assessment tools and recommendations for future directions.

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INTRODUCTION

Contemporary leadership theories commonly define leadership as a dynamic and reciprocal process in which one influences a group of people to achieve a collective goal [1, 2]. Leadership has been regarded as universal human behavior that has an evolutionary function for solving adaptive problems [3, 4]. However, the views toward the relationship between leadership and culture are not uniform. On the one hand, some scholars believe that there are some fundamental components of leadership shared by different cultures [5]. Additionally, the growing globalization over the world makes the leadership conceptualization and practices in Western and Eastern organizations become increasingly aligned over time [6]. On the other hand, some scholars believe that how people understand and practice leadership may vary across cultures [7, 8]. Cultural values may define what an ideal leader is in a specific culture, which influences how people practice their leadership in the organization and develop their leadership. Depending on their theoretical perspectives, researchers used different assessment tools to measure leadership in a particular culture.

There are three approaches to the inquiry of leadership in the Chinese contexts: the etic approach, the emic approach, and the combination of etic and emic approach [7]. First, researchers translated and validated the existing scales developed in Western cultures in order to test the generalizability of the existing leadership theories and models to Chinese contexts (i.e., etic approach). Second, researchers developed an indigenous leadership scale based on the Chinese leadership construct in order to capture psychological constructs that are not present in Western cultures (i.e., emic approach). Finally, researchers developed and validated a new scale based on both Western and Chinese concepts (i.e., etic-emic approach).

In this chapter, we reviewed the commonly used leadership assessment tools in Chinese contexts with reference to the related studies conducted in mainland China, Hong Kong and Taiwan. In the organizational realm, assessment tools of leadership usually measure leadership qualities including attitudes, beliefs, behavior and styles of people who take up a leadership post, using measures such as the Multifactor Leadership Questionnaire MLQ; [9], Authentic Leadership Inventory [10], and Paternalistic Leadership Scale [11]. In addition, in the realm of leadership development and education, based on the assumption that everyone has potentials and capacities to develop leadership [12], several scales have been developed to capture the leadership capacities of ordinary people regardless of their positions, such as Socially Responsible Leadership Scale SRLS; [12] and Leadership Practices Inventory [13]. This review covers leadership assessment tools for “positional” leaders and “ordinary” leaders. In particular, based on the scales reviewed, we identified the gaps and problems of the existing literature on leadership assessment tools in different Chinese contexts.

ASSESSMENT TOOLS BASED ON THE ETIC APPROACH

One of the major inquiries in Chinese leadership study is to test whether the imported assessment instruments measure the same construct across cultures. Therefore, validating the existing leadership measures developed in Western contexts is an initial step of leadership study in the Chinese academia. With validation evidence, researchers could test whether the Western leadership theories and models are applicable to Chinese contexts, and further extend

the theories by examining the mechanisms underlying the effects of a certain leadership practice or investigating the conditional boundary of these effects. This approach is called etic approach.

The characteristics of etic approach are top-down and Western in origin [14]. Guided by a Western leadership theory or model, researchers usually translate the assessment tools with literal adaption following a translation-back translation procedure [15]. For example, Chen and Farh [16] translated the Transformational Leadership Scale developed by Podsakoff, MacKenzie, Moorman, and Fetter [17], and found it well applied in Taiwan organizations. This scale assesses six features of transformational leadership practices, including identifying and articulating a vision, providing a role model, fostering the acceptance of collective goals, expecting high performance, offering individualized support and intellectual stimulation [17]. This translated version has been successfully used in many Chinese studies. For instance, Wang, Law, Hackett, Wang, and Chen [18] successfully validated the six-dimension structure via confirmatory factor analysis (CFA), and used it to examine the mediator that explained the associations between transformation leadership and positive performance and organizational citizenship behavior of followers in mainland Chinese organizations. Another example is Chan and Mak's [19] study that translated the 28-item Servant Leadership Scale developed by Liden, Wayne, Zhao, and Henderson [20] to examine the moderating effect of subordinates' organizational tenure in the association between servant leadership and subordinates' trust in leader and job satisfaction in Hong Kong organizations. This scale has seven factors – emotional healing, creating value for the community, conceptual skills, empowering, helping subordinates grow and succeed, putting subordinates first, and behaving ethically with good factorial validity. Additionally, Sun and Wang [21] translated the 23-item servant leadership scale developed by Barbuto and Wheeler [22] and examined the construct of servant leadership in mainland Chinese organizations. The original scale included five dimensions – wisdom, persuasive mapping, organizational stewardship, altruistic calling, emotional healing. This translated version demonstrated satisfactory reliability and similar internal structure (i.e., 5-factor structure) via exploratory factor analysis (EFA) and CFA, but there were slight differences in the number of items in each factor because some items were removed due to under loading.

In addition to leadership research in organizational settings, Chinese scholars also investigated leadership capacities of ordinary people, especially young people regardless of their leadership background. Therefore, similar to the case of leadership measures for positional leaders, Chinese translated versions of existing scales that assess leadership capacities are available in the literature. For example, based on the social change model, Dugan and Komives [12] developed the Socially Responsible Leadership Scale (SRLS) and its shortened version (SRLS-R2). These scales assess eight core values, including consciousness of self, congruence, commitment, courage, collaboration, common purpose, controversy with civility, and citizenship. Leung, Ha, and Yeung [23] translated the SRLS-R2 and tested it in Hong Kong university students. Results showed adequate evidence for the eight-factor structure, and the reliability for each subscale (factor) was satisfactory except for the change and controversy with civility dimensions. Additionally, Chan [24] created a Chinese version of 26-item self-reported Roets Rating Scale for Leadership (RRSL) [25] to measure three leadership capacities (i.e., leadership, ambition and desires) of Hong Kong students in grades 7-12, which showed satisfactory reliability and convergent validity with other leadership measures based on behavioral indicators reported by parents and teachers.

Because of the rapid development in psychology and organizational behavior in China, Chinese translated version of Western leadership scales are common. Besides the scales mentioned above, there are many other examples in the literature, such as the Chinese version of Authentic Leadership Questionnaire [26] translated by Qian, Lin, and Chen [27], the Chinese version of Leadership-Member Exchange Scale (LMX-MDM); [28] translated by Wang et al. [18], and the Chinese version of Ethical Leadership Scale [29] translated by Walumbwa et al. [30].

The application of Western assessment tools has made an important contribution to leadership knowledge development. Theoretically, it helps to advance the scientific understanding of general leadership process. The use of same assessment tool makes it possible to compare the findings derived from different cultures so as to identify cultural similarities and differences in the leadership process. Practically, it enables Chinese scholars to quickly catch up with the current trend of leadership research. It also facilitates the communication between Chinese scholars and Western scholars as they would have shared language. However, there are some intrinsic limitations of the etic approach [14], which constrain the development of leadership research in Chinese contexts. Primarily, these scales overlook the cultural component in leadership process (i.e., substantive limitation). For example, some cultural practices of leadership relevant to the Chinese context are not present in Western experience, and thus would not be included in the Western assessment tools. For example, the Leader-Member exchange (LMX) theory that focuses on the exchange within work domain was developed in the Western context. However, Chinese type of leader-member interaction goes beyond work issues and permeates into personal domains [31]. Hence, simple reliance on Western assessment tools leaves a large gap in understanding Chinese leadership and hinders researchers from a deep inquiry into the cultural variation in the field of leadership. It also constrains the initiative of Chinese scholars to construct leadership theories and models.

ASSESSMENT TOOLS BASED ON THE EMIC APPROACH

In response to the limitations of the etic approach that transplants Western leadership measures, some Chinese scholars proposed to focus on indigenous Chinese leadership [32, 33]. In contrast with the top-down orientation adopted in the etic approach, the emic approach tends to be bottom-up and to study leadership process from laypersons' perspectives. They usually construct leadership theories and leadership assessment tools according to local phenomena and experiences, and interpret the data using Chinese concepts, such as Confucian ideas.

Paternalistic leadership is an indigenous leadership style that has been well-studied in Chinese culture, which was proposed by Farh and Cheng [32] based on the Chinese history and the traditional ideologies (i.e., Confucianism and legalism). It refers to a leadership style with strong discipline and authority accompanied with fatherly benevolence and moral integrity [32]. Accordingly, Cheng, Chou and Farh [11] developed the 42-item Paternalistic Leadership Scale (PLS), which includes three unique components of Chinese leadership style – authoritarianism (i.e., “very strict with his/her subordinates”), benevolence (e.g., “encourages me when I encounter difficulties in work”), and morality (e.g., “sets an example

for me”). The PLS demonstrated satisfactory reliability and consistently showed a three-factor structure across Chinese societies, including Taiwan [34], mainland China [35], and Hong Kong [36]. It has become the most widely used scale that measures indigenous leadership style and demonstrated validity in predicting a wide range of leadership effectiveness indicators, such as employee’s trust in and satisfaction toward leaders [11], employees’ performance [34], and employees’ voice behaviors [37]. In particular, Cheng, Chou, Wu, Huang, and Farh [38] found that paternalistic leadership demonstrated a unique effect on employees’ responses above and beyond the effect of transformational leadership, which confirmed its cultural uniqueness in influencing leadership effectiveness. Furthermore, with revision on the items of morality, Cheng et al. [39] developed the Global Paternalistic Leadership Scale (GPLS), and successfully validated it across four Asian societies, including Taiwan, mainland China, Japan and South Korea.

In addition, several other scholars also attempted to construct a cultural-specific leadership style that can well describe the leadership features and predict leadership effectiveness in Chinese culture [40]. For example, Wang, Xin, and Xu [41] asked the participants of senior managers to articulate the leadership behavior of their CEO, upon which they developed a CEO leadership scale to understand the CEO leadership behavior during the economic transformation of China. This scale includes six dimensions of leadership behavior, including making innovation, coordination and communication, caring about subordinates, identifying visions, demonstrating authority, and monitoring operations. These dimensions were positively related to enterprise profit and employees’ attitudes [41].

The use of indigenous leadership assessment tools helps to explore and understand some culturally specific experiences in the leadership process. Indigenous leadership research makes a significant contribution to a growing body of literature documenting human behavior from a local perspective. Although many researchers are interested in developing a scale to capture Chinese specific leadership, not all of them provided adequate validation evidence. A rigorous emic approach requires evidence for the incremental validity of the indigenous scale. In other words, the indigenous construct should explain more of the leadership effectiveness than other existing scales, but this is often missing in the scale development. Furthermore, the indigenous leadership construct may not be totally specific to a certain culture. Instead, it may be a culturally specific manifestation of a general leadership concept. For example, paternalistic leadership does not only exist in Chinese culture. Indeed, it reflects a hierarchical leader-follower relationship, in which leaders are obliged to create a family-like environment and provide protection and guidance to their followers in both the work and non-work domain, and the followers are expected to show obedience and loyalty toward the leaders, which can be observed in multiple cultures [42]. However, people’s prototypical understanding of paternalistic leadership varies across culture. For example, Chinese people perceived typical paternalistic leadership incorporating more authoritarianism than Western people [43]. Therefore, simple reliance on indigenous leadership assessment tools may fail to capture the common component in leadership shared by different cultures. It also hinders the communication between Chinese researchers and Western researchers due to a lack of shared framework. In order to advance the field of leadership, we need to address both culturally universal and specific aspects of the leadership process.

ASSESSMENT TOOLS BASED ON THE ETIC-EMIC APPROACH

In different Chinese societies, an emerging effort has been made to study leadership by using a combined etic-emic approach. Researchers usually develop a leadership assessment tool based on Western literature theories, cultural theories, indigenous concepts and local leadership experiences [44]. This approach is able to link the indigenous leadership understanding with the so-called mainstream leadership understanding derived from Western research, and provide a more comprehensive framework to understand both the culturally universal and specific components in the leadership process.

The operationalization of transformational leadership in Chinese context can exemplify this approach. Transformational leadership refers to a leadership style, in which leaders strive to inspire followers to work toward common goals through setting up a role model for followers, showing individualized consideration toward followers, stimulating cognitive transformation of the followers, and inspiring their motivation to achieve higher [45]. However, Chinese researchers [44] argued that Chinese leaders may demonstrate different practices in order to reach the transformational goal due to the larger power distance between leaders and followers and stronger concern for interpersonal relationship. Thus, they asked Chinese managers to provide leadership behavior examples, upon which they worked out a new scale to measure Chinese transformational leadership. This scale contains four dimensions – moral modeling, charisma, visionary, and individualized consideration. The inclusion of moral modeling, which is missing in Bass's MLQ, shows the importance of moral modeling in Chinese people's understanding of good leadership. Additionally, in the dimension of individualized consideration, behavior of caring about the family and personal lives are included, which suggests the range of leader-follower interaction is expected to be broader than that in Western contexts.

A similar case was found in the construct of authentic leadership. There are at least two scales developed in the Chinese contexts to measure this leadership style [46, 47]. Taking Wang and Chen's [46] scale as an example, they developed this scale based on the previous scales developed in the Western contexts [e.g., 48] and their qualitative studies in Chinese organizations which examined employees and leaders' views toward authentic leadership. With this scale, they found the common components of authentic leadership shared by Chinese and Western cultures, including self-consciousness and internalized moral values, and an additional Chinese component of value-behavior congruency.

The use of combined etic-emic approach to developing leadership assessment tool has several merits. First, it is grounded in a larger body of literature and more integrated view about leadership, which likely provides a more comprehensive understanding on a certain leadership construct. Second, it helps to explicate both universal and cultural aspects of leadership process. It may provide generalizability evidence for a certain leadership theory and culturally unique findings that complement the theory. Finally, with a common conceptual framework, Western and Chinese researchers can better communicate their research findings and jointly endeavor to advance the field. However, the development of this combined approach in the leadership research in Chinese contexts is still in its infancy. Much more studies are needed to show the validation evidence, especially incremental validity of these scales.

UNSOLVED QUESTIONS AND FUTURE DIRECTIONS

The history of leadership assessment tools in Chinese contexts resembles that of many psychological assessment tools such as personality assessment [14]. It starts with an etic approach, an emic approach, and then a combined etic-emic approach. However, the etic approach still dominated the field of leadership, probably because of its ease of implementation. Obviously, this would hinder the contribution of Chinese experience to the leadership research and the initiative of Chinese scholars in the leadership theory construction. Emerging research has informed us that leadership is an integration of universal human nature and cultural influence [5]. For example, based on a study of 62 countries and areas, the Global Leadership and Organizational Behavior Effectiveness (GLOBE) Project found that some leadership qualities are universally desirable (e.g., charismatic and value-based leadership), while others are more culturally sensitive (e.g., participative leadership; [49]). Hence, to cover both universal and cultural elements of leadership, using a combined etic-emic approach to develop leadership assessment tools is an ideal direction. By doing this, researchers need to incorporate cultural variations by using samples from multiple cultural origins when developing and validating a scale [6]. The current validation of Chinese original leadership scales is often limited in one single culture, and thus requires more replications.

Additionally, there is an obvious lack of leadership assessment tools for ordinary people in Chinese contexts. The majority of the leadership scales were developed in an organizational context to assess leadership qualities or practices of formal leaders or positional authorities. However, in the field of leadership development and education, more and more researchers and educators believe that everyone has the potentials and capacities that enable him/her to carry out effective leadership no matter whether he/she takes up a leadership position [12, 50]. Increasing research has been conducted to understand how ordinary people develop their leadership capacities and how leadership program helps to enhance their leadership capacities [12, 51]. The dearth of leadership assessment tools for ordinary people in Chinese contexts hinders the advance of research on leadership development and education as well as the improvement of leadership programs. Moreover, leadership development and education would benefit if a norm of leadership capacities can be built, so that people can know how well their leadership capacities are by referring to the norm. It is thus necessary to develop a scale that measures leadership capacities for a wide range of population in Chinese contexts.

Indeed, a leadership scale is an instrument to operationalize a leadership concept, and thus whether the initial conceptualization is clear matters. Nowadays, there are plentiful leadership theories that try to capture an effective leadership style in contemporary organizational or social settings, including, but not limited to, transformational leadership [52], authentic leadership [53], servant leadership [22], and service leadership [50]. For the leadership development, theories and models are also growing, including relational leadership model [54], social change model [12], and leadership identity development model [55]. It remains a big challenge for Chinese researchers to synergize different perspectives and generate a suitable theoretical model of leadership that can well explain leadership experience in Chinese contexts but also contribute to the understanding of basic leadership process. Before developing a new assessment, Chinese researchers may need to adopt an integrated or cross-cultural view to conceptualize leadership. As suggested by Komives and Dugan [1],

contemporary leadership theories share three essential themes, including importance of leaders' self-awareness, morality and social responsibility in leadership, and shared leadership. Chinese leadership theory may need to integrate these three themes in the conceptualization of leadership, and develop the scales accordingly. In brief, we encourage future research to adopt an etic-emic approach in studying leadership and measuring leadership in Chinese contexts. We also call for developing reliable and valid assessment tools to measure leadership capacities of ordinary people. Addressing these unsolved questions requires a joint effort of Chinese scholars and collaboration of Western and Chinese scholars.

There are several recommendations regarding development of leadership scales in the Chinese contexts in future. First, a well-articulated conceptual model of leadership should be used. It could be a Western theory with or without adaptation, an indigenous theory derived from Chinese experience and/or theory, and integrated leadership model integrating Chinese and Western models of leadership. Second, validation is another task to be taken which includes several steps: a) development of an item pool; b) refinement of the pool by experts; c) empirical validation to ascertain the reliability and validity of the developed measures. For reliability, besides internal consistency (i.e., homogeneity of the items), there is a need to look at whether the scale is stable across time. For validity, besides examining content validity and criterion-related validities (such as concurrent validity and predictive validity), dimensionality of the measures based on the guiding conceptual model should also be tested to give support for the theory behind the measures.

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Chapter 134

CONCEPTUAL BACKGROUND AND THE DEVELOPMENT OF SERVICE LEADERSHIP KNOWLEDGE SCALE

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ABSTRACT

Knowledge plays a key role in shaping behavior in human beings. Leadership knowledge has been extensively studied for its contribution to productivity at both individual and organizational levels. With the service industries rooted as the key to the success of Hong Kong's economy, an appropriate service leadership knowledge framework should be developed based on the demand for leaders in the modern service economies. This chapter introduces the conceptual background of the Service Leadership Theory, and how Service Leadership Knowledge Scale was developed and validated based on the basic knowledge points under the Service Leadership Theory.

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INTRODUCTION

Knowledge refers to one's awareness of an objective, related processes, and how to do something [1]. It is widely believed that people's previous experience and knowledge shape not only people's judgement and attitudes but also the actual behaviors [2]. For example, people's level of environmental knowledge including environmental responsibility [3] and ecological awareness [4] was found to be associated with their ecological consumer behaviors, such as consumption, reuse and willingness to pay more for ecological products. In a systematic review [5], the importance of cardiac patients' knowledge was highlighted where patients' level of knowledge about cardiac care facilitates the health behavior change such as participating in physical activities, healthier dietary habits and smoking cessation. Moreover, increasing financial knowledge was a means of increasing people's responsible credit card use behavior [6].

Given the influence of knowledge on human behaviors in many fields, numerous theorists have explored the way in which knowledge influences behavior. For example, the mediated role of attitude has been emphasized. The Knowledge-Attitude-Behavior model proposes that accumulation of knowledge can motivate changes in attitude, thus further lead to behavioral changes [7]. The theory of planned behavior suggests that subjectively held information determines certain behavior [8]. Besides, the process of putting knowledge into action is considered worthy of attention. In the information-motivation-behavioral skills model, knowledge and motivation jointly influence behavior to the equivalent extent through the mediation of developing behavioral skills [9]. Knowledge-to-action cycle suggests knowledge phase can influence action phase at any point, and the process of translating knowledge to behavior is an iterative cycle in which knowledge and behavior update themselves anytime through dynamic interactions [10].

INFLUENCE OF LEADERSHIP KNOWLEDGE ON LEADERSHIP BEHAVIOR

As an important form of human behavior, leadership behavior is affected by leadership knowledge as well. Leadership knowledge includes three dimensions. First, leaders have to be equipped with hard leadership knowledge, which can be defined as a series of basic knowledge concerning managing different kinds of resources in organizations, including human resources [11], information resources [12], and financial resources [13]. Second, leaders are expected to have soft leadership knowledge, which can be defined as the knowledge used to establish emotional connections in a team. This form of knowledge includes how to build relationships with others, how to construct effective collaboration and how to improve management environment [14]. Third, an excellent leader needs to accumulate adequate or a very high level of leadership content knowledge, which was purposed and conceptualized by Stein and Nelson [15] as the technical or academic related knowledge in the industrial field. In other words, leaders are expected to be equipped with knowledge and technical skills closely related with industries before constructing and strengthening leadership among subordinates.

Leadership knowledge serves as a unique window to look inside the science of organizational behavior and has been found to exert influence on leadership behavior at the individual and organizational levels. At the individual level, Weitz and colleagues [16] emphasized the role of leadership content knowledge and suggested that content knowledge of service providers in understanding their customers may change the directions of their behavior towards a more effective way. Similarly, Yammarino and colleagues [17] demonstrated that basic management knowledge, soft leadership knowledge like perspective-taking, creative problem solving, and social judgment skills and leadership content knowledge related with industries all positively directed management behaviors, including assessing a solution, identifying limitations, making action plans, and organizing supporting resources as input to management activities. At the behavioral outcome level, by surveying 102 teams in hotel properties in the United States, Srivastava and colleagues [18] showed that leadership content knowledge and self-efficacy positively predicted service performance.

Several theoretical proposals can be utilized to explain how leadership knowledge as a complex management input can be connected to positive management behavior and outputs at the individual level. For instance, leadership knowledge as a general cognitive capability may have positive effect on leadership behavior through the mediation of improving positive management attitude, increasing self-efficacy and strengthening administrative behavioral control, the theoretical foundation of which is supported by the model of planned behavior [19]. The extended model of the planned behavior adds another two likely pathways connecting leadership knowledge to leadership behavior through self-identity and affective self-beliefs [20]. Similarly, based on the theory of reasoned action, leadership knowledge can impact on leadership behavior through shaping the positive attitude and positive subjective norms [21]. The similar technology model also supports the role of leadership knowledge in directing positive management behaviors [22]. In this model, leadership content knowledge as an external force motivates leaders to evaluate the usefulness and feasibility of purposed management plans, which further promotes positive leadership behavior through the effect on positive behavioral intentions [22].

At the organizational level, hard leadership knowledge improves the capacity of transforming resource into productivity; soft leadership knowledge spurs the potential of team and increases the motivation of its members, while leadership content knowledge helps leaders to expose organizations to external opportunities for development [23]. These mechanisms suggest a positive association between leadership knowledge and favorable organizational behavior and outcome. In line with this notion, soft leadership knowledge was proven critical to the success of organizations in terms of the performance of workers based on qualitative analysis in the study of Pearce and Manz [24]. In addition, with a sample of 144 U.S. employees in a network of university libraries, it was found that leadership content knowledge positively predicted organizational citizenship behaviors [25]. With a sample of 710 nurses in the South Korea, Lin and Hsiao [26] found leadership content knowledge and trust to subordinates were positively related to the organizational citizenship behaviors. Similarly, with a sample of industrial companies from four innovative industries in Spain, hard leadership knowledge and leadership content knowledge were found to promote organizational behavior and innovation through the effect of positive management practice [27].

As shown, a majority of pervious empirical studies connecting different types of leadership knowledge and leadership behavior (and behavioral outcomes) actively examined

the role of leadership content knowledge, and only a very small part of them aimed to investigate the importance of soft leadership knowledge. With the global transformation in economic structure from the manufacture economy to the service economy, the framework of leadership knowledge needs to be redefined. It needs to be transformed from a framework focusing on hard leadership knowledge and leadership content knowledge, which best responded to the production and cooperative mode in the manufacture economy, to the one emphasizing on soft leadership knowledge, which can maximize the effectiveness and quality of service in the service economy. When specifying the leadership in modern service economy, Chung and Elfassy [28] proposed the Service Leadership Theory, which displays 12 dimensions of positive attributes an effective service leader should be equipped with. Under the framework of the Service Leadership Theory, the basic knowledge points are summarized and presented in section below.

SERVICE LEADERSHIP KNOWLEDGE

Based on Service Leadership Theory, service leadership knowledge can be summarized in six domains. These domains are “general description of Service Leadership Theory,” “three realms of service leadership,” “everyone can be a leader,” “Principle $E = MC^2$,” “manufacturing versus service economies in contemporary world,” and “distinction of Service Leadership Theory and other leadership theories.” Knowledge points in these six domains are briefly outlined below.

General Description of Service Leadership Theory

Unlike the old paradigm of leadership where the relationship is hierarchical and the leader only places orders to those who are in lower positions for self-serving purpose, Service Leadership Theory emphasizes the importance of satisfying not only the needs of oneself but also others and the systems such as community, society, and environments [29]. The traditional concept of “leader” is signified with power and pride, and the leader is likely to be served by others instead of the opposite. To an extreme extent, the leaders might use their power to scarify others’ needs and benefits to fulfill their own needs. Such action is considered as unethical. In order to be an ethical service leader, one should work with others with care, value their wellness and benefits as much as oneself, and encourage to transcend self-interest to serve others and the system. According to Shek and colleagues [30], good service leaders are those who influence their subordinates with good personal qualities such as being caring and genuine, rather than manipulating others.

Three Realms of Service Leadership

Noteworthy, service leadership emphasizes not only personal interest and achievement, but also the intention to fulfill the needs of others and the systems. The three realms including self, other, and the system of service leadership indicate the importance for a person to

manage himself or herself before leading others. Chung [31] suggested that before a person becoming a competent service leader, one should focus on improving his or her intrapersonal competence. It is believed that “a leader is unable to optimize his or her ability to lead others well unless he or she is healthy in mind, body, and spirit.” In other words, one’s ability to lead oneself is one of the best indicators of his or her capacity to lead others [32]. Such concept shares similar value to a Confucianism thought in Daxue, which points out that if people are able to regulate the standpoint of showing love for others, interpersonal harmony and social stability will follow [33].

Everyone Can Be a Leader

In traditional beliefs, a leader normally carries a superior, talented, and competent image. Only these leaders in high positions need to be equipped with leadership capability [34]. Conversely, Service Leadership Theory believes that everyone has his or her strengths; hence, has the potential to lead. There are a wide variety of service transaction, ranging from self-serving personal achievement at work to complex service such as managing a team. Everyone has the potential to utilize his or her skills and strengths and become a leader in the collaborative process. It is important to be open-minded to see every person’s potential. With such beliefs, service leaders will serve and lead in a humble and respectful manner, which can help them fully utilize their followers’ skills, enhance their performance, and nurture the followers to become service leaders as well.

Principle E = MC²

According to Chung and Elfassy [28], effective service leadership (E) is a function of one’s moral character (M), competencies (C), and caring disposition (C) (i.e., $E = MC^2$). It is believed that effective service leaders should demonstrate good leadership competence, interpersonal competence, intrapersonal competence, as well as domain-specific knowledge in order to guide their leadership practice [30]. Moral character emphasizes the importance to serve others with integrity and moral values while taking the lead. Caring disposition emphasizes one’s sincerity to learn and to meet the needs of others. It is believed that a caring leader will not sacrifice the needs and benefits of others to fulfill one’s own.

Although it is emphasized that the three determinants are equally important, morality and integrity appear to be essential features of effective leaders in the service industry. It is believed that the subordinates as well as service-receivers have difficulties trusting a person who lies, breaks promise, and neglects the feelings and needs of others, regardless of his or her actual work performance. These qualities are particularly important in certain industries such as counseling and nursing, where the nature of the service relies heavily on the interpersonal relationship. In addition, effective leaders serve not only clients but everyone in life, including one’s self, peers, subordinates, followers, and surroundings. Good leaders should always be “ready,” “willing,” and “able” to serve. They are continuously being evaluated by superiors, peers, subordinates, and all other service-receivers. Hence, instead of merely being skillful and knowledgeable, service leaders should demonstrate character

strengths, moral character, leadership competency, and caring social disposition in order to perform effectively.

Manufacturing Versus Service Economies in Contemporary World

Traditional leadership education emphasizes the importance of knowledge and skills in the field. Such concept applies very well in industrialized societies, when the operation system required hands-on skills. However, in recent decades, the manufacturing industry is gradually replaced by the rapidly growing service industry, especially in Hong Kong. As a result, skills are no longer the only quality that makes one a competent leader. It is suggested that the new concept of effective leadership focuses on whether one is moral and caring to followers and service recipients, as the basic concept is that the person himself/herself is considered as the “service” [34].

Distinction of Service Leadership Theory and Other Leadership Theories

Different from other leadership theories, Service Leadership Theory puts great emphasis on the “collaborative service-focused” attitude and behavior. In addition, Service Leadership Theory purposes seven core beliefs, including 1) service means serving “oneself, others, and systems”; 2) “everyone can be a leader”; 3) “leadership effectiveness is dependent on possessing relevant situational task competences plus being judged by superiors, peers, and subordinates as possessing character and exhibiting care”; 4) “leaders should ethically improving one’s competences, abilities, and willingness to help satisfy the needs of others”; 5) “high quality personal service should be consistently provided to everyone that one comes into contact with, including oneself”; 6) “service leadership is the world’s oldest, most competitive, and longest surviving business model”; and 7) “high-paying, high status positions and management promotions will go to people who have domain specific knowledge and skills plus service leadership competences, character, and care” [30, 31].

Development of the Service Leadership Knowledge Scale

A validated service leadership knowledge assessment tool is indispensable to measure and investigate the influence of service leadership knowledge. Moreover, it is also a key to evaluate participants’ knowledge gain through service leadership education. In view of the lack of such validated scales, the research team at The Hong Kong Polytechnic University (PolyU) conducted a project entitled “Development and validation of measures based on the service leadership model,” which entailed the construction and validation of a knowledge scale aimed at “capturing the essential knowledge points of service leadership in a format of multiple-choice questions” [30, p. 164]. Accordingly, the Long-Form Service Leadership Knowledge Scale (i.e., SLK-LF-200), which comprises 200 multiple-choice items covering fundamental service leadership knowledge points as outlined above (also see Table 2 for the domains and several sample items). Each item has a “correct” answer with one point whereas

participants get zero point if they answer incorrectly. By adopting an objective method, the Service Leadership Knowledge Scale could reliably and validly show one's knowledge level [35]. Through several validation studies as outlined below, the trimmed versions of the knowledge scale were also created which were shown to be valid and reliable.

Table 1. Literature review on measures of leadership and service leadership

Steps	Details
Step 1: Literature Review on leadership knowledge measures, particularly in different Chinese contexts	Examples of references: – Chan, D. W. (2007). Leadership competencies among Chinese gifted students in Hong Kong: The connection with emotional intelligence and successful intelligence. <i>Roeper Review</i>, 29(3), 183-189. – Chiaburu, D. S., Huang, J. L., Hutchins, H. M., & Gardner, R. G. (2014). Trainees' perceived knowledge gain unrelated to the training domain: the joint action of impression management and motives. <i>International Journal of Training and Development</i>, 18, 37–52. – Farh, J.-L., & Cheng, B.-S. (2000). A cultural analysis of Paternalistic Leadership in Chinese organizations. In J. T. Li, A. S. Tsui, & E. Weldon, (Eds.), <i>Management and organizations in the Chinese Context</i> (pp. 84-127). London: Palgrave. – Peng, J., Liu, Y., Lu, H., Liu, Y., & Wu, W. (2014). Emotional leadership: Conceptualization, measurement, development and model construction. <i>Advances in Psychological Science</i>, 22(11), 1757-1769. – Sitzmann, T., Ely, K., Brown, K. G., & Bauer, K. N. (2010). Self-assessment of knowledge: A cognitive learning or affective measure? <i>Academy of Management Learning & Education</i>, 9, 169–191. – Stedman, N. L., Rutherford, T. A., Rosser, M. H., & Elbert, C. (2009). When leadership counts: Engaging youth through the Washington Leadership Conference. <i>Journal of Agricultural Education</i>, 50, 92–104.
Step 2: Literature Review on Service Leadership	Examples of references: – Chung, P. P. Y., & Elfassy, R. (2016). <i>The 12 dimensions of a Service Leader</i> (1st ed.). New York, NY: Lexingford Publishing. – Shek, D. T. L., Chung, P. P. Y., Lin, L., Leung, H., & Ng, E. C. W. (2018). Service Leadership under the Service Economy. In J. L. Chin, J. E. Trimble & J. E. Garcia (Eds.), <i>Global and culturally diverse leaders and leadership: New dimensions and challenges for business, education and society</i> (pp. 143–161). Bingley: Emerald Publishing. – Shek, D. T. L., & Leung, H. (2015). Service Leadership qualities in university students through the lens of student well-being. In D. T. L. Shek & P. P. Y. Chung (Eds.), <i>Promoting Service Leadership qualities in university students</i> (pp. 1-16). Singapore: Springer. – Shek, D. T. L., & Lin, L. (2017). Validation of the Service Leadership knowledge scale: Criterion-related validity. In D. T. L. Shek, P. P. Y. Chung, L. Lin & J. Merrick (Eds.), <i>Service Leadership education for university students</i> (pp. 189–204). New York, NY: Nova Sciences. – Shek, D. T. L., Lin, L., Leung, H., Yu, L., Ma, C. M. S., & Li, X. (2017). Development and validation of the Service Leadership knowledge scale in a Chinese context. In D. T. L. Shek, P. P. Y. Chung, L. Lin & J. Merrick (Eds.), <i>Service Leadership Education for University Students</i> (pp. 163–188). New York, NY: Nova Sciences. – Shek, D. T. L., Sun, R. C. F., & Liu, T. T. (2015). Evolution and realms of Service Leadership and leadership models. <i>International Journal on Disability and Human Development</i>, 14(3), 243-254.

Content Validation

The SLK-LF-200 was subjected to a content validation study administered by the research team at PolyU [30]. Four experts who were highly familiar with and involved in the development of the service leadership curriculum framework rated the 200 items based on three criteria, namely, i) relevance, ii) clarity, and iii) representativeness. The individual (I-CVI) and average scale content validation index (S-CVI/ave) based on experts' ratings on the three abovementioned criteria were employed to reflect the content validity of the scale. Both the I-CVI and S-CVI/ave metrics corroborated the meritorious content validity of the SLK-LF-200 on both the item and the scale levels [30].

Table 2. Initial Development of the Long-Form (SLK-LF-200) and Short-Forms (SLK-SF-50 and SLK-SF-40) Service Leadership Knowledge Scale

Steps	Details
Step 3: Development of the item pool (200 items) with reference to the main proposed domains	Seven key domains were conceptualized to be subsumed under the original, 200-item Long-form Service Leadership Knowledge Scale (SLK-LF-200). These include: General description of Service Leadership; Three realms of Service Leadership; Everyone can be a leader; Principle E = MC²; Manufacturing vs. service economies and current societal status; Distinction of Service Leadership and other leadership theories; Other knowledge points in SLAM curriculum framework. Three sample items are featured in the following: 2. According to the SLAM model, competence, _____, and _____ affect employees' loyalty and commitment. [Domain 1] A) fame; character; B) intelligence; care; C) intelligence; character; D) character; care (Correct answer: D); 27. Self-serving effort entails improving one's _____ in helping to satisfy others' needs. [Domain 2] A) fame; B) wealth; C) authority and power; D) competencies, abilities and willingness (Correct answer: D); 149. Which of the below is typically a desired behavioral attribute of employees in a manufacturing economy? [Domain 5] A) Flexible; B) Creative; C) Controllable; D) Unpredictable (Correct answer: C).
Step 4: Initial validation of the original scale (i.e., SLK-LF-200; 200 items)	The SLK-LF-200 was tested in a criterion-related validation study involving 161 PolyU students conducted in semester 2 of the 2014/15 academic year. Of those 161 participants 67 took the Service Leadership course before while the rest (N= 94) did not. Findings revealed that the former significantly performed better than the latter on 63 items of the SLK-LF-200. The first author of this paper commissioned a screening procedure on these 63 items, resulting in the removal of 13 items out of duplicity or face validity concern. Ultimately, a one-factor, 50-item short-form of Service Leadership Knowledge Scale (SLK-SF-50) was retained for the main study. See below for two sample items.
Step 5: Development of scale used in the main survey (i.e., SLK-SF-50; 50 items) and the major domains	<i>Single-factor, SLK-SF-50</i> 35. The two dimensions of social cognition include _____ and _____ . A) warmth; talent; B) warmth; competence; C) popularity; talent; D) popularity; competence (Correct answer: B) 43. The manufacturing economy emphasizes _____. A) Capital assets; B) Human assets; C) Financial assets; D) Social assets (Correct answer: A)

Note. All sample items were slightly re-worded to avoid familiarity effect.

Table 3. Refined scales based on exploratory factor analyses and confirmatory factor analyses

Steps	Details
Step 6: Refined scale based on exploratory factor analyses	N/A. No EFA was carried out.
Step 7: Refined scale based on confirmatory factor analyses (i.e., SLK-SF-40)	The whole working sample (N= 4,486) was utilized to validate the 50-item SLK-SF-50. Initial reliability analyses informed the deletion of 10 items due to low (i.e., < 0.30) item-total correlations. The resultant hypothesized one-factor, 40-item solution (i.e., SLK-SF-40) was accordingly subjected to CFA using the robust weighted least squares (WLSMV) estimator. The findings revealed the excellent fit of the SLK-SF-40 (i.e., CFI = 0.984; NNFI = 0.985; RMSEA = 0.029) to the data. The SLK-SF-40 also demonstrated excellent internal consistency ($\alpha = 0.94$, mean inter-item correlations = 0.28) as well as strong convergent validity (i.e., positive and significant correlations with all external criterion scales as well as other Service Leadership scales under validation). The SLK-SF-40 was accordingly accepted as the finalized solution. Three sample items are shown as follows: 8. A manager under the service economy wants to hire someone. Based on the Service Leadership model, which of the following advice would you give him/her? A) Hire for qualifications, train for character B) Hire for character, train for skills C) Hire for attitude, train for character D) Hire for efficiency, train for mindset (Correct answer: B); 22. In the four options below, which one belongs to an attribute of the intelligent quotient (IQ)? A) Raw power B) Attractiveness C) Sexual Orientation D) Problem-solving skills (Correct answer: D) 37. Which of the following statements is inconsistent with the concept of “respect”? A) Showing off one’s strength B) Accepting and appreciating differences C) Accepting and appreciating oneself D) Serving as a key element in nurturing authentic relationship (Correct answer: A)

Note. All sample items were slightly re-worded to avoid familiarity effect.

Criterion-Related Validation

The SLK-LF-200 was administered in the 2014-15 academic year involving 161 PolyU students [36]. The experimental group included 67 students who had taken credit-bearing training in service leadership before, while those who received no such training at the time of testing served as the control (N= 94). Results of the independent samples t-tests indicated that the experimental group scored significantly higher (i.e., all $t_s > 2.46$, $ps < .05$) in all seven component scores so as the total score (computed by summing all 200 items), indicating the criterion-related validity of the SLK-LF-200. Furthermore, analyses on the individual item

highlighted that the experimental group performed significantly better on 63 of those items (i.e., all χ^2 s > 2.46, ps < .05). These 63 items were subjected to a screening procedure conducted by the first author of this paper, leading to the deletion of 13 items after consideration of item redundancy and face validity. Consequently, 50 items (see Table 2 for the sample items) were retained to form the short version of Service Leadership Knowledge Scale (i.e., SLK-SF-50).

Large-Scale Validation

The SLK-SF-50 was administered in a large-scale validation study involving 4,486 undergraduates recruited from eight government-funded universities in Hong Kong. Initial reliability analyses suggested the removal of ten items with (i.e., < 0.30) item-total correlations. As a result, a single-factor, shortened 40-item solution (i.e., SLK-SF-40) was subjected to the Confirmatory Factor Analysis (CFA) using the robust weighted least squares (WLSMV) estimator. The goodness-of-fit indices underscored the excellent fit of this proposed solution with the data (see Table 3 for details). The SLK-SF-40 also demonstrated excellent internal consistency (α = 0.94, mean inter-item correlations = 0.28) and robust convergent validity, with the latter evidenced by the positive correlation between SLK-SF-40 and the list of theoretically-relevant constructs such as Servant Leadership [37] and Moral Self-concept [38]. Taken as a whole, this large-scale, joint-institution validation study underlined the adequacy of SLK-SF-40 (see Table 3 for the sample items) as a reliable, valid, and robust measurement tool in examining people's mastery of fundamental knowledge points on the Service Leadership Theory.

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Chapter 135

DEVELOPMENT OF THE ATTITUDE TO SERVICE LEADERSHIP SCALE IN HONG KONG

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ABSTRACT

Attitude is an important component of leadership qualities. Leaders who believe in the potential of the followers would allow more room for followers to make decisions. Leaders who believe in the importance of moral character would uphold moral principles in their work. With the gradual decline of manufacturing industries and the rise of service industries, there is a need to nurture leaders who can effectively lead in the challenging environment of service economies. In particular, fostering positive attitudes is an important task to be achieved. Unfortunately, measures of service leadership qualities are

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almost non-existent in the scientific leadership literature. In this chapter, the theory and concepts surrounding attitudes towards Service Leadership are outlined. The different steps underlying the development of the Service Leadership Attitude Scale are also described, including literature review, item development, initial validation and main survey.

INTRODUCTION

The 21st century has undergone paradigm shifts in the concepts, framework and application of leadership [1]. Hence, the traditional economic theory, which is based on the industrial paradigm, might not be applicable to the service world [2]. With the rapid evolution in information and communication technology, personalized services have become increasingly important. In fact, service has become the major economic sector in most developed nations. For example, service industry accounts for almost 80% of the economy in the United Kingdom and the United States [3]. In 2013, about 93% of the Gross Domestic Product in Hong Kong was comprised of a wide range of services, such as hotel and food services, banking and insurance, and professional and business services [4].

According to Shek, Chung and Leung [5], there are differences between manufacturing economy and service economy in terms of leadership qualities. For example, while leadership in manufacturing economy is more top-down, it is more bottom-up in service economy. Besides, service leaders need to be more sensitive to different needs and expectations of the customers [6]. Moving from a manufacture-oriented economy to a service-oriented economy means that the leaders need to be more responsive to customers' needs in the knowledge-intensive market [7].

THE NATURE OF SERVICE LEADERSHIP

With the rise of the service economy, customers have become part of the organizational system [8]. The increased diversity of customer backgrounds has imposed variability in the service provider-customer (supplier-customer) relationship [9] and led to a greater level of organizational uncertainty [7]. Hence, identifying and satisfying the needs of customers have become an integral cost of the firm [10]. In particular, emphasis on consumer experiences of services has become a key differentiator in this highly competitive world [11]. Leaders have to manage their organization effectively in order to stay ahead in the highly competitive market. Researchers proposed the use of "customer-centered" service-related competence models, which focus on the leadership behaviors and skills of Service Leadership to promote the quality of service.

Based on his experience in the service industries, Chung [12] proposed the Service Leadership Theory which posited that it is important to identify effective leadership competencies in the face of the competitive business environment. Under the framework of the Hong Kong Institute of Service Leadership and Management (SLAM), service leaders aim at "providing quality personal service to everyone one comes into contact with, including one's self, others, groups, communities, systems, and environments" [12, p. 5]. Compared with the conventional leadership theories (e.g., authentic leadership, transformation

leadership), Service Leadership focuses on changing the followers' beliefs and perceptions about themselves and promoting followers' positive behavior [13-15].

There are several unique characteristics of Service Leadership. First, meeting others' needs is a unique feature of Service Leadership. The major premise of the Service Leadership Theory is that leaders promote positive organizational outcomes by satisfying the followers' needs and facilitating their development. Through this empowering process, followers feel more attracted to their service leaders, see them as role models and thereby recognize their optimal level of performance. This is different from the leader-oriented and hierarchical nature of the previous leadership theories [5]. The de-emphasis of the hierarchical nature of leadership allows employees to act proactively and initiate changes from the bottom-up in order to address the needs at work [16]. Through this changing authority process, employees perceive themselves as part of the organization and feel that they have autonomy to exercise their personal judgment with greater job responsibilities, resulting in increasing job satisfaction and organizational commitment [17, 18]. Research studies show that adaptive employees reported better well-being [19, 20], a higher level of proactive skills [21] and greater organizational identification [16].

Second, development of followers' competence is another unique feature of the Service Leadership Theory. Effective leaders motivate others to excel themselves through achieving the organizational goals [22]. Service leaders encourage the followers to take challenges and to develop personal accountability. In order to differentiate themselves from others who are competitive and to keep staying ahead in the market, leaders seek ways to provide high-quality service for their customers [23, 24]. Providing high-quality service thus becomes a prerequisite for organizational success.

Third, high-quality service is provided when the service leaders possess effective intrapersonal and interpersonal competencies [5, 25, 26]. Effective service leaders should have high intrapersonal competencies in four areas, namely intelligence quotient (IQ), adversity quotient (AQ), emotional quotient (EQ) and spiritual quotient (SQ). IQ refers to the ability to critically analyze a problem and to search for innovative ways to solve the problem. AQ is defined as the ability to accept and overcome the difficulties by bouncing back from the challenges. EQ refers to the ability to understand one's own and others' emotions and to manage one's emotions when interacting with others. SQ refers to the ability to share the vision and mission with the followers and to solve problems by utilizing spiritual resources. Moreover, service leaders should have good interpersonal competencies so that they can communicate and work effectively with people of diverse backgrounds [27].

Fourth, moral character is an important attribute of effective service leaders. In particular, honesty and integrity are two major characteristics of a highly effective leadership [28]. Service leaders respond with trust and respect and express a strong preference for follower's needs over their own needs [29]. Ethical leaders are fully aware of the effects of their behavior on the development of the followers. They are always aware of their own moral values, perspectives and behaviors and transform their followers into moral agents [30]. Acting as change agents, service leaders transform followers into moral agents by behaving morally, developing a moral identity and creating ethical atmosphere [31]. Babalola et al. [32] highlighted the importance of ethical leadership in promoting followers' ability to handle conflicting situations. Empirical evidence [14, 33, 34] has shown the link between ethical leadership and followers' morality (i.e., moral identity, moral emotions, moral behaviors, and organizational commitment).

Fifth, effective service leaders must put the interests of the followers first. More specifically, the focus on helping and serving others is the central tenet of Service Leadership [35]. Service leaders show a genuine concern for the followers' welfare and focus on personalized care in creating an atmosphere that promotes the effectiveness of the team [29]. They serve as role models for intellectual stimulation and inspirational motivation [25]. Under this warm and supportive environment, employees feel secured and encouraged to explore innovative solutions in their work and to share their thoughts with their leaders [36].

Sixth, self-improvement is an important attribute of an effective service leader. Effective service leaders constantly evaluate their behavior and performance through reflection [37]. Self-reflection helps individuals to rethink or restructure their assumptions that underlie their own actions, beliefs and behaviors [38]. The significance of critical reflection has been demonstrated [39, 40]. Self-development is one of the significant competencies in the service industry [37, 41]. Customized service is characterized by complexity and utilization of specialized knowledge and skills [42, 43]. Effective service leaders are likely to rethink their own working performance, are more aware of others' needs and feel more motivated to promote personal growth. Reflection helps the individuals in personal growth and continuous improvement of leadership skills and knowledge. They are more willing to make changes and seek resources in order to adapt to the uncertain environment [37]. This leads to positive influence on the employees through the empowerment process [44, 45]. Employees become more welcome for changes and actively engage in continuous personal and professional development [46, 47].

Finally, the notion of "everyone can be a leader" is a defining characteristic of Service Leadership. In contrast to the concept of "elitist leadership" (i.e., only those who are talented can be leaders), the Service Leadership Theory emphasizes the notion that "everybody can be a leader." This notion suggests that everybody has potential to be a leader and the key is training and opportunities for development. This humanistic assumption is very empowering in nature, providing much space for development for the leaders and followers.

ASSESSMENT OF ATTITUDE TO LEADERSHIP

Facing the ever-changing business environment, new organization learning processes and informational activities have been rapidly increasing [2]. Leaders are expected to acknowledge individual differences and tailor their service to meet individual needs [15]. Yukl [48] argued that effective leadership may largely depend on the contexts [49]. The contemporary leadership theories often focus on how leaders' characteristics and behaviors influence the followers and organizational outcomes [50]. As such, some researchers began to study the factors related to effective leadership from the followers' perspective [17, 51-53]. In leadership research, attitude towards the leader refers to the degree of favorability one perceives a leader [54]. Wielkiewicz et al. [55] highlighted the importance of understanding of leadership development from the followers' perspective.

Recently, researchers have developed measurement tools to assess attitudes to leadership. For example, Wielkiewicz [56] developed the Leadership Attitudes and Beliefs Scale (LABS-III) which assessed both hierarchical thinking and systematic thinking about leadership. The scale has two dimensions with 14 items per subscale. This scale has been used to assess

college students' attitude towards leadership [55, 57, 58]. Also, the Operating Room Management Attitudes Questionnaire ORMAQ; [59, 60] was used to measure the attitudes towards six areas of leadership: assertiveness, teamwork, communication, leadership structure, awareness of personal limitations, and organizational issues. This scale has been tested in the fields of aviation [61] and medicine [59] but no factor analysis (e.g., confirmatory factor analysis) has been conducted.

Besides, the attitude towards service has been studied [23, 62, 63]. For example, customers' perception of service quality is an assessment of overall service excellence [23] and subjective evaluation of service quality has a close relationship with customer satisfaction [64]. Literature on service quality suggests that employees' attitude towards leaders are essential to determine customer satisfaction [65]. Parasuraman et al. [23] developed a 22-item tool assessing five dimensions of service quality, namely tangibles, reliabilities, responsiveness, assurance and empathy, and found support for the reliability and factor structure of the scale.

Unfortunately, although there are some measures assessing the attitude to service quality, existing scales for measuring the attitude towards Service Leadership are relatively scarce. For example, Wu [66] developed three items (e.g., "My service provider offers a larger choice of services for customers"; "My service provider satisfies customers' different needs with more diversified service"; "My service provider offers services of great variety") to assess Service Leadership and tested its impact on loyalty and brand equity via structural equation modeling which showed support for the reliability and validity of this construct. However, the coverage of these items on leadership qualities is not in-depth. In fact, despite the fact that service is playing an important role in the global economy, research on service development has lagged behind compared with the research on the manufacturing industry [67]. More research in this area can be helpful for the employers to understand which type of leadership style is the most suitable and appropriate in terms of the organizational and follower outcomes. Studying the attitudes of Service Leadership from employees' perspective is important because leaders need to create a positive atmosphere and accountability for employees so that organizational outcomes of interest (e.g., performance, satisfaction, leadership) can be achieved. Hence, psychometrically sound instruments would help researchers and practitioners understand individuals' attitudes towards Service Leadership.

Service is a process of applying one's knowledge and skills for the benefit of employees or customers [68]. Empirical findings showed that followers' attitudes toward leadership were positively related to follower positive outcomes, such as teamwork performance [62], job satisfaction [69] and organizational performance [70]. The establishment of psychometrically sound instruments will definitely increase our understanding of effective leadership in the service industry. Given the emergence of service-oriented economy which stresses the importance of intangible products, such as experiences and the quality of the goods, more research is warranted for helping us better understand effective leadership in this area.

Besides developing scales on Service Leadership, testing the psychometric properties of the developed scales is an important step. While the majority of research has mostly focused on assessing convergent/divergent validity [23] and content validity [71], little is known about the factor structure of the existing scales. More specifically, exploratory factor analysis has been commonly conducted when testing the factor structure [23, 56]. Although Service Leadership is perceived as a multidimensional concept [5, 25], a unidimensional tool has been

employed [66]. Clearly, more research should be conducted to test the generalizability of the Service Leadership Attitude Scale in different contexts and populations.

DEVELOPMENT OF THE SERVICE LEADERSHIP ATTITUDE SCALE

In Hong Kong, service industries account for nearly 93% of the GDP. Despite the importance of service industries, there is a gap in the development of Service Leadership in Hong Kong. In view of this deficiency, the Victor and William Fung Foundation made a donation of HK\$40 million to support the Service Leadership Education initiative with the participation of the eight institutions supported by the University Grants Committee. In each university, curriculum materials and subjects on Service Leadership were developed. With this good foundation, one unresolved question is on the availability of objective measures of Service Leadership knowledge, attitude and skills.

With further funding from the Victor and William Fung Foundation, the eight universities collaborated to develop scales on the Service Leadership knowledge, attitude and skills. As mentioned above, the Service Leadership Attitude Scale was developed within this context. As far as the Service Leadership Attitude Scale is concerned, several steps were involved:

- Step 1: Literature review on attitudes to leadership measures, particularly in different Chinese contexts
- Step 2: Literature review on Service Leadership
- Step 3: Development of the item pool (132 items) with reference to the main proposed domains
- Step 4: Initial validation of the original scale (132 items)
- Step 5: Development of scale used in the main survey (73 items) and the major domains
- Step 6: Refined scale based on exploratory factor analyses in the main survey (46 items)
- Step 7: Refined scale based on confirmatory factor analyses (46 items)

The details of different steps are outlined in Table 1-3. To assess the attitude to Service Leadership, Shek and colleagues [71] developed the 132-item long-form Service Leadership Attitude Scale (i.e., SLA-LF-132) and conducted the initial content validity test of the scale. This scale measures various aspects of service leadership, including service orientation, the belief that everyone can be a leader, leadership competence, moral character, caring disposition, and commitment to continuous improvement. The content validity of the scale has been established by the high content validity of the individual items and the overall questionnaires.

In this book, the findings on the psychometric properties of the Service Leadership Attitude Scale based on exploratory factor analyses are reported. We hope that from this book, it can be seen that the Service Leadership Attitude Scale possesses good psychometric properties and therefore can be used in research, assessment, education, evaluation and personnel decision contexts.

Table 1. Literature review on measures of leadership and service leadership

Steps	Details
Step 1: Literature review on attitudes to leadership measures, particularly in different Chinese contexts	Examples of references: – Casimir, G., & Waldman, D. A. (2007). A cross cultural comparison of the importance of leadership traits for effective low-level and high-level leaders: Australia and China. <i>International Journal of Cross Cultural Management</i>, 7(1), 47-60. – Chan, K. Y., & Drasgow, F. (2001). Toward a theory of individual differences and leadership: Understanding the motivation to lead. <i>Journal of Applied Psychology</i>, 86(3), 481-498. – Cheng, B. S., Boer, D., Chou, L. F., Huang, M. P., Yoneyama, S., Shim, D., ... & Tsai, C. Y. (2014). Paternalistic leadership in four East Asian societies: Generalizability and cultural differences of the triad model. <i>Journal of Cross-Cultural Psychology</i>, 45(1), 82-90. – Ho, J., & Nesbit, P. L. (2009). A refinement and extension of the self-leadership scale for the Chinese context. <i>Journal of Managerial Psychology</i>, 24(5), 450-476. – Lan, X. M., & Chong, W. Y. (2015). The mediating role of psychological empowerment between transformational leadership and employee work attitudes. <i>Procedia-Social and Behavioral Sciences</i>, 172, 184-191. – Liden, R. C., Wayne, S. J., Zhao, H., & Henderson, D. (2008). Servant leadership: Development of a multi-dimensional measure and multi-level assessment. <i>The Leadership Quarterly</i>, 19(2), 161-177. – Ling, W., Chia, R. C., & Fang, L. (2000). Chinese implicit leadership theory. <i>The Journal of Social Psychology</i>, 140(6), 729-739. – Spreitzer, G. M., Perttula, K. H., & Xin, K. (2005). Traditionality matters: An examination of the effectiveness of transformational leadership in the United States and Taiwan. <i>Journal of Organizational Behavior</i>, 26(3), 205-227.
Step 2: Literature review on Service Leadership	Examples of references: – Shek, D. T. L., & Li, X. (2015). The role of a caring disposition in service leadership. <i>International Journal on Disability and Human Development</i>, 14(4), 319-332. – Shek, D. T. L., & Lin, L. (2015a). Leadership and mentorship: Service leaders as mentors of the followers. <i>International Journal on Disability and Human Development</i>, 14, 351-359. doi: 10.1515/ijdhhd-2015-0456 – Shek, D. T. L., & Lin, L. (2015b). Intrapersonal competences and service leadership. <i>International Journal on Disability and Human Development</i>, 14(3), 255-263. – Shek, D. T. L., Lin, L., Leung, H., Yu, L., Ma, C. M. S., & Li, X. (2017). Content validation of the service leadership attitudes scale. In D. T. L. Shek, P. P. Y. Chung, L. Lin, & J. Merrick (Eds.), <i>Service leadership education for university students</i> (pp. 205-225). New York: Nova Sciences. – Shek, D. T. L., Ma, C. M. S., & Liu, T. T. (2015). Adolescent developmental assets and service leadership. <i>International Journal on Disability and Human Development</i>, 14(3), 275-283. – Shek, D. T. L., Ma, C. M. S., Liu, T. T., & Siu, A. M. H. (2015). The role of self-leadership in service leadership. <i>International Journal on Disability and Human Development</i>, 14, 343-350. doi: 10.1515/ijdhhd-2015-0455 – Shek, D. T. L., Yu, L., & Siu, A. M. H. (2015). Interpersonal competence and service leadership. <i>International Journal on Disability and Human Development</i>, 14, 265-274. doi: 10.1515/ijdhhd-2015-0407

Table 2. Initial development of the Long-Form (SLA-LF-132) and Short-Form (SLA-SF-73) Service Leadership Attitude Scale

Steps	Details
Step 3: Development of the item pool (132 items) with reference to the main proposed domains	Eight domains were proposed in 132-item long-form Service Leadership Attitude Scale (SLA-LF-132) including: [1] Service Orientation (e.g., Good leaders serve without expecting any rewards), [2] Everyone can be a leader (e.g., Only the elites can lead, reverse-item), [3] Distributed Leadership (e.g., Good leaders are open to challenge and criticism), [4] Employability (e.g., Lucrative leadership positions go to people who are eager and able to serve others), [5] Personalized Service (e.g., Sensitivity towards people's specific needs is an important trait for any leaders), [6] Attitudes towards Service (e.g., Service providers find it intrinsically enjoyable to render good-quality service), [7] Principle "E = MC²" (e.g., Moral character: Good leaders do not break promises; Competence: Good leaders make convincing arguments; Caring disposition: Good leaders are forgiving.), and [8] Commitment to Continuous Improvement (e.g., One can develop his/her ability to lead).
Step 4: Initial validation of the original scale (i.e., SLA-LF-132; 132 items)	The SLA-LF-132 was subjected to a quasi-experimental validation study in semester 1 of the 2016/17 academic year. A total of 208 PolyU students took the pre-test while 190 did the post-test. An exploratory factor analysis (EFA) was performed on 200 sets of pre-test questionnaires. Results of the EFA informed the retention of a 5-factor, 73-item solution (i.e., SLA-SF-73) which recorded good reliability and a significant and positive correlation with the short-form Service Leadership Knowledge Scale (SLK-SF-50). See below for the five factors extracted and two sample items for each factor.
Step 5: Development of scale used in the main survey (i.e., SLA-SF-73; 73 items) and the major domains	<i>Factor 1: Attitudes towards service and competences</i> 1. Good leaders serve with a genuine heart. 20. Good leaders can handle stressful situations calmly. <i>Factor 2: Attitudes towards moral character and caring disposition</i> 29. A good leader should be people-oriented. 39. Good leaders always tell the truth. <i>Factor 3: Attitudes towards self-reflection</i> 64. A good leader is self-restraint. 68. Genuine leaders are aware of their own strengths and weaknesses. <i>Factor 4: Everyone can be a leader</i> 5. Not everyone is able to lead others. (reverse-item) 6. Only the "best of the best" can lead. (reverse-item) <i>Factor 5: Implicit theory of leadership</i> 62. Leadership competence is not something that can be changed through learning. (reverse-item) 63. The ability to lead is inborn and not changeable. (reverse-item)

Note. All sample items were slightly re-worded to avoid familiarity effect.

Table 3. Refined scales based on exploratory factor analyses and confirmatory factor analyses

Steps	Details
Step 6: Refined scale based on exploratory factor analyses (i.e., SLA-SF-46E)	Nine items, which were demonstrated to possess low item-total correlation (i.e., <0.25), were dropped before the ensuing principal component analysis (PCA). Accordingly, the PCA was performed on the remaining 64 items of the SLA-SF-73 using a subset ($N = 2,246$) of the total sample ($N = 4,486$), resulting in a 7-factor structure demonstrated to be stable. Upon removing 18 items with loadings below 0.50, a 7-factor, 46-item solution (i.e., SLA-SF-46E) was retained to be subjected to CFA utilizing the other subset ($N = 2,240$). The SLA-SF-46E recorded excellent internal consistency and strong convergent validity, with the latter evidenced by its positive and significant correlations with the external criterion scales as well as other Service Leadership scales under validation. The seven factors of SLA-SF-46E include: Vision and competence (Factor 1), People Orientation (Factor 2), Caring Disposition (Factor 3), Ethical Role Model (Factor 4), Social Competence (Factor 5), Self-Reflection and Self-Understanding (Factor 6), and Positive Views about Human Beings (Factor 7). Three sample items are featured below: 28. Good leaders do not give in easily amidst adversity. (Factor 1) 38. Good leaders closely examine their thoughts and behaviors. (Factor 6) 41. Everyone has what it takes to be a leader. (Factor 7)
Step 7: Refined scale based on confirmatory factor analyses (i.e., SLA-SF-46)	The 7-factor SLA-SF-46E was subjected to CFA utilizing the Maximum Likelihood (ML) estimator, which showed acceptable fit to the data (i.e., CFI = 0.91; NNFI = 0.90; RMSEA = 0.048). Analyses were based on re-incorporating a previously removed seven-item subscale (from the PCA, due to low item-total correlations) back to the main factor structure. The 8-factor, 53-item factorial structure was subjected to CFA, whereby the fit indices (i.e., CFI = 0.87; NNFI = 0.86; RMSEA = 0.053) suggested an unsatisfactory fit. Inspection of the modification indices (MI) informed the removal of 7 items, due to their extreme MIs with multiple items on the same factor. The CFA was re-run on this 8-factor, 46-item structure where results suggested a much improved fit (i.e., CFI = 0.90; NNFI = 0.90; RMSEA = 0.054). Inspection of MIs revealed four pairs of parameters showing extreme covariance. After incorporating the correlation between errors for these four pairs of parameters, the findings corroborated the reasonable fit of this modified structure (i.e., CFI = 0.93; NNFI = 0.92; RMSEA = 0.041). This modified 8-factor, 46-item solution was accordingly accepted as the finalized solution (i.e., SLA-SF-46). The SLA-SF-46 comprises an <i>identical factor structure and labeling as the SLA-SF-46E</i>, with the addition of the eighth factor entitled “Unchangeable and Dark Human Nature”. Two sample items of this factor were shown below: 43. One’s ability to lead is inborn and hardly changeable (reverse-item). 45. People need to be checked to ensure they work as required (reverse-item). The SLA-SF-46 and the subscales showed good reliability and convergent validity, with the latter evidenced by the positive and significant associations with the external criterion scales and other Service Leadership scales.

Note. All sample items were slightly re-worded to minimize familiarity effect.

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Chapter 136

DEVELOPMENT OF SERVICE LEADERSHIP BEHAVIOR SCALE: BACKGROUND AND CONCEPTUAL MODEL

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ABSTRACT

The growth of the service economy in the contemporary world calls for a shift in the requirement of leadership qualities as compared to the manufacturing economy. However, contemporary leadership approaches and associated leadership behavior scales fail to fully encompass the required leadership qualities in the service economy. To satisfy the emerging needs of service economy which is predominant in Hong Kong, the Service Leadership Model has been proposed by the Hong Kong Institute of Service Leadership and Management Limited. To objectively assess service leadership behavior, the Service Leadership Behavior Scale (SLB) was developed. This chapter presents the background of the development of the Service Leadership Model, outlines its unique features as the

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theoretical foundation of the SLB, documents the content of the initial SLB (i.e., SLB-LF-97) regarding its four key domains, and summarizes the findings surrounding the validation studies on the SLB.

INTRODUCTION

Leadership has a long history as a universal human behavior that has evolved to solve adaptive challenges throughout history [1]. In the contemporary world, leadership is still indispensable for almost every aspect of human life to function effectively in different areas, such as the economic, professional, military, religious, and political fields. Traditionally, leadership is conceived as a dynamic process in which a leader exerts influence on a group to work enthusiastically towards a collective goal [2, 3]. However, traditional leadership theories are no longer able to encapsulate the contemporary leadership needs due to the substantial change in economic structure over the world.

During the past few decades, along with the growing globalization and technological innovation, the structure of global economy has transformed from an industrial to a postindustrial mode, which is characterized by the expansion of service industries and the shrinking of manufacturing industries [4]. For example, from 2000 to 2016, the share of the services sector (e.g., trades, financial, personal services, etc.) in Gross Domestic Product (GDP) has increased from 64.9% to 69.3% in Japan, from 87.3 to 92.2 in Hong Kong, and from 39.8% to 51.6% in mainland China [5]. The manufacturing economy makes tangible goods from tangible raw materials through standardized procedures, which involve little human interactions or employees' personal input. In such circumstance, leadership is usually task-oriented and the top-down leadership style with highly centralized decision-making and minimal empowerment of followers appears to be adaptive due to its high standardization in mass production process [6]. In contrast, the service economy produces intangible services through personalized interactions between service providers and recipients, which call for distributed leadership and "service leaders" who are service-oriented and people-oriented [6].

A number of leadership scholars came to realize the emerging requirements of service-oriented economy and regarded leadership as a relational process between leader and followers instead of merely focusing on the leader [7]. In fact, different leadership models have been proposed in the postindustrial era to highlight adaptive leadership styles as well as vital qualities associated with each style. For example, the transformational leadership theory highlights ethical behavior and willingness to change of an effective transformational leader, who demonstrates idealized influence, inspirational motivation, personalized consideration, and intellectual stimulation [8]. Similarly, servant leadership theory primarily focuses on the leader's motivation to serve others and give priority to others' needs rather than their own [9]. Based on these leadership models, a considerable number of instruments have also been developed to measure leadership qualities in terms of knowledge, attitude, skill or behavior. For example, Multifactor Leadership Questionnaire [10] and Transformational Leadership Scale [11] are two examples of widely used leadership behavior scales.

Apart from these endeavors, some scholars have explicitly highlighted the importance of people skills (or interpersonal competence) in determining leadership effectiveness, such as communication and team work, which are also highly desired by contemporary employers [12]. Additionally, shared decision-making has been gradually adopted in organizations and

new assessment tools have been developed to capture effective empowering leader behaviors [13]. Furthermore, there is a growing tendency to emphasize the ethical parts of leadership and value moral behaviors and qualities such as integrity, trust, honesty and caring [14, 15].

The above-mentioned developments in leadership literature have deepened our understanding of the leadership requirements in a postindustrial age. Unfortunately, these advances are not adequate to satisfy the needs of service economy. Particularly, there are still three problems need to be addressed. First, previous leadership theories or related studies stressed some of the requirements for an effective “service leader”, such as interpersonal competence or ethical concerns. In other words, there is a lack of holistic leadership framework which can fully encompass required leadership qualities in service economy. Second, the existing leadership behavior scales developed based on previous theories are not able to comprehensively assess effective leadership behaviors in service economy. For instance, transformational leadership scales primarily assess a leader’s skills in satisfying the needs of followers and the organization by motivating and stimulating the followers as well as demonstrating ethical behaviors as a role model [11, 16]. However, other constructs desired in service economy such as a leader’s people skills and caring characteristics were not included. Third, as mentioned above, the service industry is of dominance in Hong Kong and growing rapidly in mainland China. However, little effort has been devoted to delineating what an ideal “service leader” is with specific reference to the Chinese culture. Most important of all, leadership assessment tools including behavior scales that are tailor-made for Chinese people are also missing. This issue is particularly relevant when we consider the possibility that culture values may shape one’s understanding of leadership which lead to particular ideal leadership practices in a specific culture [17, 18]. Indeed, some scholars have advocated for considering cultural settings and traditional Chinese wisdom in studying contemporary leadership practices in China [19].

To address these issues, Chung [20] proposed the notion of “service leadership” which is conceived as “satisfying needs by consistently providing quality personal service to everyone one comes into contact with, including one’s self, others, groups, communities, systems, and environments” [20]. Based on this notion, the Service Leadership Model was developed as a theoretical foundation to guide service leadership education in Hong Kong [21, 22]. Moreover, based on the Service Leadership Model, service leadership scales were tentatively developed for the purpose of assessing service leadership qualities and evaluating the effectiveness of service leadership education [23-25]. This chapter will focus on one of the service leadership assessment instruments, namely “Service Leadership Behavior Scale” (SLB). In following sections, we will briefly introduce several distinguishing features of the Service Leadership Model, based on which the item pool of the SLB was constructed. Second, the work surrounding the development and validation of the SLB will be outlined as well.

UNIQUE FEATURES OF THE SERVICE LEADERSHIP MODEL

The notion of service leadership incorporates and goes beyond the propositions of the extant leadership theories in the postindustrial era by adopting the strengths of previous theories and adding new arguments that are seldom mentioned in other leadership approaches.

In other words, service leadership theory shares some commonalities with other classic leadership approaches, while it has its own distinct features [6]. In particular, the uniqueness of the Service Leadership Model is manifested in its seven core beliefs, which systematically address what is effective service leadership as well as its determinants. As the seven core beliefs have been presented elsewhere in details [22], we briefly highlight several notable ideas of the Service Leadership Model, which reflect the paradigm shift in leadership mindset and serve as the principle references of the development of SLB.

First, the Service Leadership Model strongly emphasizes service orientation. Instead of treating leadership as a means of achieving personal and organizational success, the Service Leadership Model holds that leadership is “a service aimed at ethically satisfying the needs of self, others, groups, communities, systems, and environments” [22]. The underlying belief is that people evolved service propensities as an outcome of natural selection, so that both serving others and being served by others are inherent tendencies hard-wired into human minds [26]. Therefore, leadership prioritizing service can reach the hearts of people and thus satisfy the needs of others and the leaders themselves.

Second, in strong contrast to traditional conception of leadership that leaders were “great men and women” [27], the Service Leadership Model contends that “every day, every human occupies a position of leadership and possess the potential to improve his or her leadership quality and effectiveness” [22]. Primarily, the notion of “everyone can be a leader” enhances confidence in every individual and encourages all employees to contribute to decision-making, constituting a timely response to the needs of distributed leadership in service economy. Besides, to take a leading role effectively whenever is necessary, one should take initiatives and be well-prepared by continuously improving one’s abilities and willingness to provide high-quality service. Therefore, self-leadership by means of actively engaging in self-reflection, self-management, and self-improvement is regarded as indispensable for one to achieve leadership success.

Third, it is believed that “leadership effectiveness is dependent on possessing relevant situational task competencies plus being judged by superiors, peers, and subordinates as possessing character and exhibiting care” [22]. To elaborate, the Service Leadership Model places equal importance on the three fundamental determinants in defining effective service leadership (E), namely moral character (M), competence (C), and caring disposition (C) (i.e., $E = MC^2$). By covering a wide range of personal qualities in multiple dimensions, this framework extends beyond conventional leadership theories focusing on leadership skills and establishes a more holistic model to explain how these characteristics jointly contribute to effective leadership in service economy.

Finally, the Service Leadership Model incorporates the Chinese traditional values and integrates the philosophy of Buddhism, Confucianism, and Taoism, aiming to “help East meet West” [28]. Concerning the notion of “thinking globally while acting locally”, one can argue that when participating leadership in the Chinese communities, in addition to the universally preferred leadership qualities such as problem-solving and efficiency, an effective leader should also be aware of and demonstrate the qualities historically valued in the Chinese culture such as the ability to maintain harmony and have constant self-reflection.

Table 1. Literature review on measures of leadership behavior and service leadership

Steps	Details
Step 1: Literature Review on leadership behavior measures, particularly in different Chinese contexts	Example of references: - Aycan, Z., Schyns, B., Sun, J. M., Felfe, J., & Saher, N. (2013). Convergence and divergence of paternalistic leadership: A cross-cultural investigation of prototypes. <i>Journal of International Business Studies</i>, 44(9), 962-969. - Chan, SCH., & Mak, W. M. (2014). The impact of servant leadership and subordinates' organizational tenure on trust in leader and attitudes. <i>Personnel Review</i>, 43(2), 272-287. - Chen, X. P., Eberly, M. B., Chiang, T. J., Farh, J. L., & Cheng, B. S. (2014). Affective trust in Chinese leaders linking paternalistic leadership to employee performance. <i>Journal of Management</i>, 40(3), 796-819. - Cheng, B. S., Chou, L. F. & Farh, J. L. (2000). A triad model of Paternalistic Leadership: The constructs and measurement. <i>Indigenous Psychological Research in Chinese Societies</i>, 14, 3-64. (in Chinese) - Li, C., Shi, K. (2005). The Structure and Measurement of Transformational Leadership in China. <i>Frontiers Bus Res China</i>, 2(4), 571-90. - Qian, J., Lin, X., & Chen, G. Z. X. (2012). Authentic leadership and feedback-seeking behaviour: An examination of the cultural context of mediating processes in China. <i>Journal of Management & Organization</i>, 18(3), 286-299. - Sun, J. M. & Wang, B. (2009). Servant leadership in China: Conceptualization and measurement. In: Mobley WH, Wang Y, Li M, eds. <i>Advances in global leadership</i>. Bingley: Emerald Group, 5:321-44. - Sheer, V. C. (2013). In search of Chinese paternalistic leadership: Conflicting evidence from samples of mainland China and Hong Kong's small family businesses. <i>Management Communication Quarterly</i>, 27(1), 34-60. - Wang, Y. & Chen, W. M. (2012). Study on the Structural Dimensions of the Authentic Leadership in Enterprises. <i>East China Economic Management</i>, 7, 98-101. (In Chinese)
Step 2: Literature Review on Service Leadership	Example of references: - Chung, P. P. Y. (2012). <i>Service reborn: The knowledge, skills and attitudes of service companies</i>. New York, NY: Lexingford Publishing. - Chung, P. P. Y. & Bell A. H. (2015). <i>The 25 Principles of Service Leadership</i>. New York, NY: Lexingford Publishing. - Shek, D. T. L., Chung, P. P. Y., & Leung, H. (2015). How unique is the service leadership model? A comparison with contemporary leadership approaches. <i>International Journal on Disability and Human Development</i>, 14(3), 217-231. - Shek, D. T. L., Chung, P. P. Y., & Leung, H. (2015). Manufacturing economy vs. service economy: Implications for service leadership. <i>International Journal on Disability and Human Development</i>, 14(3), 205-215. - Shek, D. T. L., & Lin, L. (2015). Core beliefs in the service leadership model proposed by the Hong Kong Institute of Service Leadership and Management. <i>International Journal on Disability and Human Development</i>, 14(3), 233-242. - Shek, D. T. L., Sun, R. C. F., & Liu, T. T. (2015). Character strengths in Chinese philosophies: Relevance to service leadership. <i>International Journal on Disability and Human Development</i>, 14(4), 309-318. - Shek, D. T. L., & Yu, L. (2015). Character strengths and service leadership. <i>International Journal on Disability and Human Development</i>, 14 (4), 299-307.

THE SERVICE LEADERSHIP BEHAVIOR SCALE (SLB)

With reference to the unique propositions of the Service Leadership Model, the research team at The Hong Kong Polytechnic University (PolyU), one of the eight universities funded by the University Grants Committee (UGC) in Hong Kong, developed a long-form of SLB

(SLB-LF-97) which consists of 97 items (see Table 1 for the list of related references). With each of the 97 items describing a specific leadership behavior desired in service economy, the SLB-LF-97 covers a wide range of constructs emphasized in the Service Leadership Model. Specifically, the content of the SLB-LF-97 can be subsumed to the following four key domains (see Table 2 for example items).

The first domain is “service provision” (4 items), which measures behaviors related to providing individualized service to others, going beyond one’s own interest, and being sensitive to others’ unique needs. These behaviors are indicative of a leader’s service mindset as well as automatic and genuine manifestation of care for others’ needs.

The second domain is related to the Principle “ $E = MC^2$ ”, which further includes three aspects: “competence” (38 items), “character” (14 items), and “caring disposition” (15 items). As a key determinant of effective service leadership, leadership competence in service economy has broad requirements including intrapersonal competencies [29] and interpersonal competencies [30]. More specifically, the SLB-LF-97 covers four types of intrapersonal competencies underlying effective leadership behaviors. First, 7 items are pertinent to intelligence quotient (IQ) which is manifested in problem-solving capacities, analytical abilities, independent and critical thinking, logical reasoning, and agile mindset. Second, 5 items measure emotional quotient (EQ), which serves as one of the most significant non-intellectual contributors to the success of personal life and career [31]. Behaviors pertaining to EQ in the SLB-LF-97 includes understanding, recognizing and managing emotions of oneself and others. Third, 4 items are on the adversity quotient (AQ), which reflects one’s ability not only to withstand loss, misfortune, or other types of adversity but also to rebound stronger than before [32]. AQ is conceptually similar to the idea of resilience and possessing AQ is deemed vital to one’s leadership quality [29]. The last type of intrapersonal competencies covered in the SLB-LF-97 is spiritual quotient (SQ), which is closely related to meaning, purpose and values in one’s life [33]. In the SLB-LF-97, 3 items assess the extent to which one can utilize meaning, faith, and other spiritual resources to solve problems.

Regarding interpersonal competencies, scholars have proposed a five-dimensional framework including “initiating relationships”, “self-disclosure”, “asserting displeasure with others’ actions”, “providing emotional support”, and “managing interpersonal conflict” [34]. These five dimensions have been further adapted and enriched based on Chinese culture and philosophy. Specifically, an effective service leader should be people-oriented (“*yi ren wei ben*” – people as the central focus) and able to maintain positive social relationships with others. In addition, a good service leader is expected to demonstrate good communication skills in order to build collaborative relationships with teammates and assert one’s personal thoughts and feelings when having conflicts with others. Apart from maintaining healthy social relationships, a competent service leader with adequate interpersonal competencies would also appreciate different opinions (“*he er bu tong*” – peace within diversity) and resolve interpersonal conflicts in a constructive way. As such, six revised components concerning one’s ability dealing with interpersonal competencies are intrinsic to the SLB-LF-97: “passionate about people” (2 items); “positive social relationships” (5 items); “assertiveness” (3 items); “collaboration and cooperation with people” (2 items); “conflict resolution” (3 items); and “communication skills” (4 items).

Table 2. Initial development of the Long-Form (SLB-LF-97) and Short-Form (SLB-SF-65) Service Leadership Behavior Scale

Steps	Details
Step 3: Development of the item pool (97 items) with reference to the main proposed domains	Four domains were proposed to be subsumed under the 97-item long-form Service Leadership Behavior Scale (SLB-LF-97) including: [1] Service Provision (e.g., I work for the best interests of others instead of just for my own benefit), [2] Principle “E = MC²” included three aspects (e.g., Moral character : I am aware of my weaknesses; Competence : I am able to argue logically; Caring disposition : I show kindness to those whom I had conflict with before.), [3] Commitment to Continuous Improvement (e.g., I am self-disciplined), and [4] Distributed Leadership (e.g., I respect others’ ideas and suggestions).
Step 4: Initial validation of the original scale (i.e., SLB-LF-97)	The SLB-LF-97 was subjected to a validation study involving 231 PolyU students in November 2016. Results of the exploratory factor analysis (EFA) informed the retention of 65 items, forming the trimmed version of the scale (i.e., SLB-SF-65). The SLB-SF-65, alongside its twelve factors (see the list below), overall demonstrated good internal consistency and robust convergent validity. See the paper by Shek, Ma, and Lin in this book.
Step 5: Development of scale used in the main survey (i.e., SLB-SF-65) and the major domains	Factor 1: Problem-Solving 6. I am capable of independent thinking. Factor 2: Self-leadership and Life-long Learning 47. I spare no effort in achieving my goal. Factor 3: Non-cognitive Intrapersonal Competences 10. I am often aware of my emotions. Factor 4: Distributed Leadership 65. I hold others’ ideas and suggestions in high regard. Factor 5: Integrity 31. Others often see me as a reliable person. Factor 6: Care Provision 44. I do not miss any chances to help others grow. Factor 7: Concern 36. I have no problem sharing my weaknesses with others. Factor 8: Self-Reflection 54. I often reflect on my expertise and shortcomings. Factor 9: Service Provision 3. I serve others based on their specific needs Factor 10: Positive Social Relationship 28. I am capable of developing a rapport with others. Factor 11: Communication Skills 24. I am adept at working with others. Factor 12: Fairness 35. Treating those around me equally is what I always do.

Note. All sample items were slightly re-worded to avoid familiarity effect.

“Character” (14 items) is another aspect under the second domain in the SLB-LF-97, which is also one of the three principle determinants for effective service leadership [35]. Drawing on the groundwork of defining universally valued character strengths (e.g., integrity and humility) in Western societies [36] and also taking into account traditional Chinese virtues such as benevolence (“ren”), affection (“ai”), and forgiveness (“shu”) [37], the SLB-LF-97 synthesizes strengths of character in both cultures and operationalizes the virtues of an effective service leader using “integrity” (5 items), “humility” (4 items), “fairness” (3 items), and “acting as an ethical role model” (2 items).

Table 3. Refined scales based on exploratory factor analyses and confirmatory factor analyses

Steps	Details
Step 6: Refined scale based on exploratory factor analyses (i.e., SLB-SF-48)	Utilizing a subsample (N = 2,246) of the whole dataset (N = 4,486), a principal component analysis (PCA) was performed on the SLB-SF-65. Findings of the PCA suggested that six factors can be extracted with 48 items (loadings above 0.50) retained for the trimmed scale (i.e., SLB-SF-48). The SLB-SF-48 was revealed to be a stable factorial structure and internally consistent. The SLB-SF-48 was also correlated positively and significantly to other external criterion scales and other Service Leadership scales under validation, thereby corroborating its convergent validity. The six factors, each of which forms a subscale, include: [1] Self-improvement and Self-reflection (e.g., I have a habit of reflecting my work and life), [2] People and Principles Orientation (e.g., I allow others to decide how to get things done), [3] Resilience (e.g., I have a sense of purpose in my life which helps me cope with stressful situations), [4] Social Competence (e.g., I can maintain positive relationships with others), [5] Problem-Solving (e.g., I am good at analyzing problems that I come across), and [6] Mentorship (e.g., I can facilitate other's growth by mentoring them). Details can be found in the paper by Shek and Ma in this book.
Step 7: Refined scale based on confirmatory factor analyses (i.e., SLB-SF-38)	The SLB-SF-48 was subjected to CFA on the other subsample (N = 2,240) using the Maximum Likelihood (ML) estimator. The results overall suggested that the fit was unsatisfactory (i.e., CFI = 0.86; NNFI = 0.86; RMSEA = 0.061). Ten items with extreme modification indices (over 40.0) with multiple items on the same factor were removed. The resultant 38-item structure was again subjected to CFA. Findings revealed a considerably better fit (i.e., CFI = 0.90; NNFI = 0.89; RMSEA = 0.056). Furthermore, three pairs of parameters showed particularly large covariance. Accordingly, the correlation between errors was incorporated for these three pairs of parameters. Results of the CFA performed on this modified 38-item solution (i.e., SLB-SF-38) demonstrated that the model fit adequately (i.e., CFI = 0.92; NNFI = 0.91; RMSEA = 0.055) with the data. The SLB-SF-38, which shared the same factorial structure and labeling as SLB-SF-48, was accepted as the final solution. The SLB-SF-38 and the six subscales recorded good internal consistency and were shown to be positively and significantly associated with all external criterion scales. The SLB-SF-38, inclusive of the subscales, also correlated significantly and positively to other Service Leadership scales, further supporting its convergent validity.

Note. All sample items were slightly re-worded to avoid familiarity effect.

The last aspect of the second domain is “caring” (15 items). A caring service leader is supposed to show concern to others as well as to oneself [38]. By referring to the Chinese culture, the SLB-LF-97 measures one’s caring disposition from two aspects: the qualities of concern (“guan xin”) including “empathy” (3 items) and “compassion” (3 items); and the qualities of providing care (“zhao gu”) for others in terms of “loving others” (3 items), “supporting others” (3 items), and “developing others” (3 items).

The third domain is “commitment to continuous improvement”. As aforementioned, one of the key features of the Service Leadership Model is its emphasis on the need for continuous improvement, through which everyone can be a leader at a certain time [39]. Besides, only through continuous professional and personal improvement could one be well prepared to serve oneself as well as others. Therefore, effective service leaders should put self-development efforts “aimed at ethically improving one’s competencies, abilities, and willingness to help satisfy the needs of others” [22] in terms of promoting self-leadership (5 items), engaging in constant self-reflection (4 items), and committing to life-long learning (4 items).

“Distributed leadership” is the last domain, which also represents a timely response to the belief that “every day, every human occupies a position of leadership and possesses the potential to improve his leadership quality and effectiveness” [22]. Distributed leadership in the service economy has two attributes. First, leaders encourage every team member to voice out and take initiatives and empower them to contribute to decision-making of a team. Second, leaders would trust and respect their followers by recognizing their views and trusting their abilities. As such, the domain of “distributed leadership” in the SLB-LF-97 includes three elements: “shared decision-making” (5 items), “empowerment of teammates” (4 items), and “trust and respect” (4 items).

The SLB-LF-97 is developed as a component of the scale development project supported by the Victor and William Fung Foundation. Several validation studies have been carried out to streamline the scale and provide evidence for its reliability and validity (see Table 2 and Table 3). It is worth noting that two papers based on the validation studies are included in this book and other related papers are under preparation. To show a full picture of the development of the Service Leadership Behavior Scale, the section below will briefly outline findings of these validation studies.

VALIDATION OF SERVICE LEADERSHIP BEHAVIOR SCALE (SLB)

First, an initial validation study involving 231 PolyU students was conducted to refine the original scale, i.e., SLB-LF-97. Based on the results of the exploratory factor analysis (EFA), 65 out of the 97 items were retained, forming the short form of the scale (i.e., SLB-SF-65). In addition, the SLB-SF-65 alongside its 12 sub-scales (e.g., “problem-solving”, “self-leadership and life-long Learning”, and “distributed leadership”.) demonstrated good internal consistency and robust convergent validity, as indicated by the significant positive correlations with several theoretically linked constructs such as moral self-concept and leadership efficacy. A paper by Shek, Ma, and Lin documenting the psychometric properties of the SLB-SF-65 is included in this book.

Second, using the refined SLB-SF-65, a large-scale validation project was jointly carried out in the eight UGC-funded universities in Hong Kong including PolyU, with the adoption of both exploratory factor analyses (EFA) and confirmatory factor analyses (CFA). Utilizing a subsample ($N = 2,246$) of the whole dataset ($N = 4,486$), the EFA revealed a six-factor solution with 48 items (loadings above 0.50) being retained. These 48 items formed the trimmed scale (i.e., SLB-SF-48) as well as the six subscales named as “self-improvement and self-reflection”, “people and principles orientation”, “resilience”, “social competence”, “problem-solving”, and “mentorship”. The SLB-SF-48 was also found to have good reliability and convergent validity. Details of this study and findings of EFA can be found in another paper by Shek and Ma in this issue as well.

Third, the SLB-SF-48 was further subjected to CFA using the other subsample ($N = 2,240$). After removing 10 items with extreme modification indices (over 40.0), the resultant 38-item structure demonstrated acceptable model fit. Thus, the 38-item scale (i.e., SLB-SF-38), which shared the same 6-factor structure and labelling as SLB-SF-48, was accepted as the final solution. Likewise, the SLB-SF-38 and its six subscales showed good internal

consistency and convergent validity. An article presenting the CFA and related findings is under preparation. Information on the related analyses can be seen in the User Manual.

Generally speaking, a well-developed and validated leadership behavior scale regarding service leadership is essential for educators and researchers to empirically evaluate individuals' service leadership qualities and assess their changes after service leadership education. By doing so, the Service Leadership Model as well as its associated propositions such as the principle "E = MC²" can be further validated as well. As such, the development as well as the validation studies for the Service Leadership Behavior Scale not only provide a pioneering assessment tool for contemporary service leadership education, but also represent an important progress in the journal of consolidating the Service Leadership Model.

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Chapter 137

PSYCHOMETRIC PROPERTIES OF THE SERVICE LEADERSHIP BEHAVIOR SCALE: PRELIMINARY FINDINGS

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ABSTRACT

Using a sample of 231 students recruited from The Hong Kong Polytechnic University (PolyU), this paper reports the findings of a validation study for the 97-item long-form of the Service Leadership Behavior Scale (SLB-LF-97), which was specifically designed to measure the behavioral characteristics of a quality Service Leader. Results showed that the SLB-LF-97 had high internal consistency and convergent validity. Exploratory factor analysis revealed that 12 factors were extracted from the data, with 65 items retained to form the short-form of the inventory (SLB-SF-65). Both the long-form (SLB-LF-97) and the short-form (SLB-SF-65) of the scale showed excellent

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internal consistency, with the latter demonstrating robust convergent validity as shown by its significant positive correlation with several theoretically linked constructs.

INTRODUCTION

Regarding the transformation of manufacturing-driven to service-driven and knowledge-based economies typical of advanced capitalist societies [1-3], Hong Kong has undergone the most complete and swift transition, despite the absence of any strategic political planning [4]. As such, Po Chung, Chairman of the Hong Kong Service Leadership and Management Limited (HKI-SLAM), strongly advocated the necessity to teach undergraduates in Hong Kong about effective leadership in a service economy which is vital to their career aspirations as well as personal growth [3, 5]. Indeed, the HKI-SLAM is committed to the development of sustainable Service Leadership education (i.e., SLAM curriculum framework) tailored to tertiary institutions in Hong Kong [6, 7].

Against such a background, a multi-year project entitled the “Fung Service Leadership Education Initiative (FSLEI)” was implemented in eight local universities funded by the University Grants Committee (UGC). The FSLEI was conceived with the financial support of the Victor and William Fung Foundation and the collaborative effort of the HKI-SLAM and the UGC. Under the FSLEI, each participating institution independently designs curriculum materials and programs on Service Leadership based on the SLAM curriculum framework [6-8]. Particularly, Chung [9, 10] contended that there are three fundamental building blocks of effective Service Leadership (**E**), namely, *competence* (**C**₁; “Expertise” dimension), *moral character* (**M**; “Moral” dimension), and *caring disposition* (**C**₂; “Compassion” dimension). Besides, the seven Core Beliefs [i.e., CBs 1 to 7] pertaining to Service Leadership and Management outlined by HKI-SLAM [11] also underlie the theoretical foundation of Service Leadership education under the FSLEI [7].

With the purpose of filling the research gap on the evaluation of leadership education [8, 12], as well as facilitating the objective assessment of qualities of an effective Service Leader [13], the research team at The Hong Kong Polytechnic University (PolyU) embarked on a project entitled “Development and validation of measures based on the Service Leadership model (i.e., “The Project” hereafter)” [14]. Through the construction and validation of three scales on attitude, behavior, and knowledge which constitute the three defining attributes of an effective Service Leader [12], Shek and colleagues [14] developed three related assessment tools. The present paper reports the findings of a validation study of the long-form of Service Leadership Behavior Scale (SLB-LF-97).

Designed to examine the “kind of behavioral qualities a Service Leader should demonstrate” [14], the SLB-LF-97 comprises 97 English items developed based on the SLAM curriculum framework, 25 principles of Service Leadership [9], 12 dimensions of a Service Leader [10], and other relevant publications from the leadership and management literature [15-17]. Each item describes a specific leadership behavior related to the Service Leadership model. Participants were asked to use a six-point Likert scale (1: very dissimilar to me; 6: very similar to me) to evaluate whether each statement appropriately describes one’s behavior in a situation which warrants his/her leadership (see Table 1 for the sample items). Resembling Yukl’s [18] proposed a hierarchical taxonomy of leadership behaviors, the SLB-LF-97 covered a wide range of component behaviors subsumed under four “metacategories”.

These “metacategories” included, i) service provision, ii) principle **E** (effective leadership) = **MC**² (Moral character * Competence * Caring disposition), iii) commitment to continuous improvement, and iv) distributed leadership.

Table 1. Four sample items of the SLB-LF-97

Items	Very Dissimilar to Me	Moderately Dissimilar to Me	Slightly Dissimilar to Me	Slightly Similar to Me	Moderately Similar to Me	Very Similar To Me
10. I can make convincing arguments.	1	2	3	4	5	6
18. I draw meaning from undesirable experience.	1	2	3	4	5	6
58. I find it hard to think from other people's perspectives. (Reverse-item)	1	2	3	4	5	6
89. I usually do not let others participate in the decision-making process. (Reverse-item)	1	2	3	4	5	6

Note. These sample items were slightly modified out of copyright concern.

The SLB-LF-97 was also examined in a content validation study which is described in detail in another paper under preparation. While it is crucial in scale development to examine content validity, which informs how each item represents the construct being measured [19], it is equally important to establish the convergent validity of the measure, which can be derived from “correlations with measures purporting to measure related constructs” [20, p. 179], as well as internal consistency for the measurement tool under validation. Hence, as a preliminary step paving the way for the main study, the present study utilized a sample of 231 PolyU students to examine the reliability, factorial validity, and convergent validity of the SLB-LF-97.

OUR STUDY

A total of 231 students at The Hong Kong Polytechnic University (PolyU) completed the questionnaire used in the present study via an online survey platform. Seventeen questionnaires were excluded from the working sample due to concern about response quality. Amongst the 214 valid questionnaires, 60 (28.0%) were male respondents while 154 (72.0%) were female respondents. Most participants (55.1%) were aged 20 to 24 years (mean age: 20.0 years, SD: 1.86). The majority of respondents had previous work experience (86.0%), had taken one (or more) credit-bearing Service Leadership course(s) at PolyU (52.9%), and received other prior leadership training (32.2%). Taken as a whole, 76.6 % of respondents claimed to possess “some” or “a lot of” knowledge about Service Leadership. Finally, 49.5% were admitted to PolyU based on performance on the Hong Kong Diploma of Secondary Education Examination (HKDSE). Details regarding other basic demographics of the sample are featured in Table 2.

Table 2. Demographic information for the current working sample (N= 214)

Demographic variables		N= 214
Gender	Male	60 (28.0%)
	Female	154 (72.0%)
Age group	15 to 19 years	92 (43.0%)
	20 to 24 years	118 (55.1%)
	25 to 29 years	4 (1.9%)
Year commencing on one's undergraduate study	2016	103 (48.1%)
	2015	52 (24.3%)
	2014	23 (10.7%)
	2013	30 (14.0%)
	2012 or before	6 (2.8%)
Faculty	Faculty of Applied Science and Textiles	17 (7.9%)
	Faculty of Business	36 (16.8%)
	Faculty of Construction and Environment	27 (12.6%)
	Faculty of Engineering	60 (28.0%)
	Faculty of Health and Social Sciences	47 (22.0%)
	Faculty of Humanities	3 (1.4%)
	School of Design	1 (0.5%)
	School of Hotel and Tourism Management	22 (10.3%)
Number of credit-bearing Service Leadership (SL) courses taken*	Others	1 (0.5%)
	0	101 (47.2%)
	1	105 (49.1%)
	2	7 (3.3%)
	3	1 (0.5%)
Participated in the non-credit bearing "Silk Road Youth Leadership Programme"	4	0 (0%)
	Yes	3 (1.4%)
Other leadership training or workshops taken?	No	211 (98.6%)
	Yes	69 (32.2%)
Previous work experience	No	145 (67.8%)
	Yes	184 (86.0%)
Self-proclaimed SL knowledge	No	30 (14.0%)
	No knowledge	11 (5.1%)
	Little knowledge	39 (18.2%)
	Some knowledge	128 (59.8%)
	A lot of knowledge	36 (16.8%)
Leadership position ever taken?	All the knowledge	0 (0%)
	Yes	152 (71.0%)
Entrance Exam	No	62 (29.0%)
	Hong Kong Diploma of Secondary Education Examination (HKDSE)	106 (49.5%)
	Hong Kong Advanced Level Examination (HKALE)	4 (1.9%)
	National College Entrance Examination (NCEE) in mainland China	21 (9.8%)
	Associate Degree/Higher Diploma in Hong Kong	35 (16.4%)
Grade Point Average**	Others (e.g., SAT, Cambridge International Examinations)	48 (22.4%)
	Average Grade Point Average (GPA) out of 4.50 (SD)	3.1 (0.5)
Time of completion	Average time (in minutes) taken to complete the survey (SD)	25.0 (6.7)

Note. * The list of credit-bearing SL courses offered by PolyU included i) APSS 1L01 Tomorrow's Leaders, ii) APSS 1A22 Promotion of Leadership Qualities in University Students, iii) APSS 1A21/1A21 M Service Leadership, and iv) APSS 2S09 Service Leadership through Serving Children and Families with Special Needs.

** As the present study was conducted in November 2016, this average GPA metric was computed based only on the responses given by 111 students who did NOT start their undergraduate study at PolyU in 2016.

Procedures

The study was conducted in a computer lab with each student seated in a separate cubicle. Participants were instructed to access the electronic survey implemented via the mySurvey@PolyU electronic survey system. The rationale of the study, instructions on how to participate, the principles of voluntary participation and withdrawal, and the pledge of data confidentiality were detailed in the invitation documents and on the e-survey. It was emphasized during the invitation and before the start that 30 minutes would be required for students to conscientiously complete the whole questionnaire. Each respondent was offered for his/her participation a supermarket gift voucher valued at HK\$50 (USD\$6.40) and an opportunity to win an iPad Air 2 via a lucky draw. Participants indicated whether they consented to join the study (or to withdraw) on the opening page.

We used time of completion as a proxy for gauging participants' seriousness in completing the survey. Specifically, we regarded responses submitted within half of our suggested time (i.e., 30 minutes) as invalid. Accordingly, 17 cases with a completion time below 15 (mean: 13.3, SD: 2.6) minutes were deleted, resulting in 214 valid cases.

Instruments

The present e-survey consists of items of the long-form of the Service Leadership Behavior Scale (i.e., the 97-item SLB-LF-97). As part of the project entitled "Development and validation of measures based on the Service Leadership model" [14], the SLB-LF-97 was developed based on the SLAM curriculum framework, 25 principles of Service Leadership [9], 12 dimensions of a Service Leader [10], and other published papers from the leadership literature [e.g., 17, 21]. The SLB-LF-97 is in English with a six-point Likert scale (1: very dissimilar; 6: very similar). Each item describes a certain leadership behavior whereby participants rate how each description resembles their own behaviors when they assume leadership roles in formal (e.g., workplace) or informal (e.g., family) contexts. Four sample items are illustrated in Table 1.

To assess the convergent validity of the SLB-LF-97, six additional measures based on the personality and leadership literature were administered alongside the SLB-LF-97. These validated criterion inventories included the Revised Servant Leadership Profile (RSLP; 20 items), the Paternal Leadership Scale (PTL; 5 items), the Leadership Attitude and Belief Scale (LABS; 28 items), the Interpersonal Reactivity Index (IRI; 14 items), the Moral Self-Concept Scale (MSC; 8 items), and the Leadership Efficacy Scale (LEF; 8 items). There were also a few closed-ended and open-ended items probing into the demographics of the respondents.

1. **Revised Servant Leadership Profile (RSLP):** The RSLP was developed by Wong and Page [22] as a self-assessment tool which assesses *Servant Leadership* as a multifactorial construct. Of the eight factors outlined in Wong and Page's [22] revised model of *Servant Leadership*, 20 items from five factors considered relevant to the SLAM framework were included in the present study. These five factors

included *Empowering and developing others* (5 items), *Serving others* (7 items), *Open, participatory leadership* (2 items), *Inspiring leadership* (2 items), and *Courageous leadership* (4 items). The RSLP operates on a seven-point Likert scale, with a higher composite score denoting a higher propensity to exhibit *Servant Leadership* behaviors. The RSLP was demonstrated to possess excellent internal consistency ($\alpha = 0.93$; mean inter-item correlations = 0.42).

2. **Paternalistic Leadership Scale (PTL):** Developed by Aycan and associates [23], the PTL (5 items) measures *Paternalism* as a leadership style epitomized by a strong sense of hierarchy combined with a fatherly benevolence and moral integrity bestowed upon followers [24, 25]. Items were rated on a six-point Likert scale, with a higher score illustrating a greater alignment with the mentality of a paternalistic leader. Reliability analyses underlined the acceptable internal consistency of PTL in the current study ($\alpha = 0.79$; mean inter-item correlations = 0.43).
3. **Leadership Attitude and Belief Scale (LABS):** Developed by Wielkiewicz [17] as a measure of college students' "attitudes and beliefs about regarding the nature of leadership" (p. 337), the LABS is formed of two independent dimensions probing into two distinct thinking styles regarding what leadership should be about. They included the *Systemic Thinking Scale* (ST; 14 items) which examines people's construal of leadership as a distributed and decentralized process, as opposed to the *Hierarchical Thinking Scale* (HT; 14 items) which assesses individuals' interpretation of leadership as involving centralization and hierarchies. Items were rated on a five-point Likert scale, with higher scale scores reflecting a greater likelihood to adopt a certain construal of the nature of leadership. Both ST ($\alpha = 0.84$; mean inter-item correlations = 0.28) and HT ($\alpha = 0.83$; mean inter-item correlations = 0.26) recorded meritorious reliability in the present study.
4. **Interpersonal Reactivity Index (IRI):** As a cross-culturally validated assessment tool [see 26-28], the IRI comprises four subscales with each assessing a dimension of empathy [29]. Subscales *Perspective Taking* (PT; 7 items) and *Empathic Concern* (EC; 7 items) were adopted in this study. Participants rated the 14 items on a five-point Likert scale, with higher subscale and composite scores indicating higher empathy, which constitutes the roots of compassion as a key dimension of a Service Leader [10]. Cronbach's alpha for subscales PT and EC and the composite IRI score were 0.66, 0.67, and 0.73, respectively.
5. **Moral Self-Concept (MSC):** As a subscale under the Chinese Adolescent Self-Esteem Scales [30], the MSC specifically examines students' self-evaluation on areas including i) *Conduct and virtues*, ii) *Self-control and discipline*, and iii) *Altruism*. Participants rated the eight items using a seven-point Likert scale, with a higher composite score representing the respondent's perceived significance of *morality* to oneself, which is a fundamental attribute of leadership effectiveness according to the SLAM curriculum framework [11]. The MSC was shown to possess a good internal consistency in the present study ($\alpha = 0.88$; mean inter-item correlations = 0.49).
6. **Leadership Efficacy Scale (LEF):** Developed by Murphy [31], the 8-item LEF constitutes a self-report inventory in which respondents rate their self-perceived capacity to lead. The LEF operates on a five-point Likert scale, with a higher score indicative of one's "level of confidence in the knowledge, skills, and abilities

associated with leading others” [32, p. 669]. Reliability assessment again highlighted a good internal consistency of the LEF ($\alpha = 0.84$; mean inter-item correlations = 0.41).

Data Analysis Plan

To explore the dimensionality of SLB-LF-97, we performed the exploratory factor analysis (EFA) in this validation study. Specifically, the present EFA was conducted using the principal axis analysis (PAA) with Promax rotation ($\kappa = 4$). Tabachnick and Fidell [33] argued that PAA should be preferred for studies which attempted to reach an uncontaminated theoretical solution and were designed on the basis of several underlying theoretical constructs. Both these criteria matched well with the objectives and nature of the present study. SPSS statistics version 24.0 (IBM) was used to perform descriptive analyses as well as internal consistency, convergent validity, and factorial validity.

Factorial Validity Analyses

Owing to the large number of survey items involved, we adopted the Minimum Average Partial (MAP) [34] to determine the number of factors to extract a priori as to avoid the issue of over-extraction [35]. The MAP, which involves “comparison of systematic and unsystematic variance remaining in a correlation matrix after each factor is extracted” [36, p. 108], has been shown in a simulation study to be the most accurate amongst a host of alternative extraction methods [36]. The MAP was administered using the SPSS R-Menu V 2.0 [see 35].

With the purpose of simplifying and enhancing the interpretability of the final factorial solution, we applied two exclusion criteria to help downsize the scale. First, double-loaded items were removed [37]. Second, only non- double-loaded items that are of substantive importance (i.e., highest loadings $\geq |0.40|$) to a factor were retained [see 19]. Table 3 details the post-rotation factor loadings of each item and other relevant statistics.

Reliability and Convergent Validity Analyses

We referred to the Cronbach’s alpha values and mean inter-item correlations as indicators of internal consistency of the scale and the factors derived (i.e., subscales). As regards the assessment of convergent validity, the composite scores calculated by averaging participants’ responses of both the scale and subscales were correlated with the six concurrently administered external criterion measures. Specifically, we hypothesized a positive and significant association between the behavior scale (and the subscales) and the i) RSLP (i.e., Hypothesis 1), ii) LEF (i.e., Hypothesis 2), iii) MSC (i.e., Hypothesis 3), and iv) IRI (i.e., Hypothesis 4), considering that *Servant Leadership*, *leadership efficacy*, *morality*, and *empathy*, respectively are all constructs theorized to underline the behavioral standard of a bona fide Service Leader [9, 10].

Table 3. Factor loadings of the SLB-LF-97 (N = 214)

M	SD	Factors extracted													Retained?
		1	2	3	4	5	6	7	8	9	10	11	12	13	
SLB-01	4.51	-0.01	-0.05	0.00	-0.16	-0.11	-0.04	-0.02	0.04	<u>0.77</u>	-0.02	0.06	0.09	0.15	Yes
SLB-02	4.28	-0.03	0.00	-0.03	-0.15	-0.04	0.09	0.01	0.05	<u>0.81</u>	-0.14	-0.10	0.12	0.18	Yes
SLB-03	4.76	0.15	0.16	-0.13	-0.10	0.15	-0.13	0.17	-0.20	<u>0.64</u>	0.01	-0.17	0.07	0.14	Yes
SLB-04	4.69	0.93	0.12	-0.11	-0.05	0.11	-0.02	0.11	0.06	<u>0.38</u>	-0.19	0.13	-0.01	0.48	No
SLB-05	4.59	0.92	0.09	0.16	0.01	0.08	0.07	0.00	-0.02	0.04	-0.18	-0.01	0.06	0.17	Yes
SLB-06	4.21	0.96	0.15	0.19	-0.01	-0.05	0.11	0.02	-0.13	-0.10	-0.11	0.02	0.08	0.04	Yes
SLB-07	4.66	0.98	-0.07	0.03	0.01	0.04	-0.09	0.00	0.07	-0.02	0.01	0.13	0.00	0.08	Yes
SLB-08	4.66	0.95	-0.01	-0.05	0.02	0.01	0.00	0.01	0.00	0.09	-0.15	0.17	-0.05	0.10	Yes
SLB-09	4.63	0.96	-0.13	-0.02	0.06	0.03	-0.08	-0.10	0.17	0.12	0.16	0.12	-0.16	-0.01	Yes
SLB-10	4.47	1.01	-0.01	0.00	-0.02	0.03	0.02	-0.03	0.10	0.04	0.22	0.07	-0.06	-0.04	Yes
SLB-11	4.27	0.92	0.08	0.35	-0.05	0.08	0.16	-0.06	-0.10	-0.20	-0.07	0.04	0.08	-0.01	No
SLB-12	4.87	0.93	0.02	<u>0.54</u>	0.27	0.05	-0.16	-0.02	0.04	0.03	0.03	-0.05	-0.20	0.11	Yes
SLB-13	4.71	0.92	-0.03	0.34	0.12	0.05	-0.12	-0.21	0.10	0.20	0.04	0.21	-0.15	0.53	No
SLB-14	4.22	1.14	-0.07	<u>0.73</u>	0.22	-0.24	-0.16	-0.19	-0.19	0.09	0.09	0.10	0.21	0.01	Yes
SLB-15	4.36	1.05	-0.01	0.42	-0.04	-0.05	0.01	-0.03	-0.02	0.14	0.19	0.36	-0.09	0.10	No
SLB-16	4.30	1.13	-0.04	<u>0.84</u>	0.20	0.09	-0.11	-0.06	-0.03	-0.15	-0.12	-0.12	0.15	0.02	Yes
SLB-17	4.51	1.07	-0.07	<u>0.55</u>	-0.08	-0.04	-0.01	0.18	0.19	-0.12	-0.14	0.27	0.08	0.09	Yes
SLB-18	4.42	0.95	-0.08	<u>0.42</u>	-0.08	-0.06	0.12	0.19	0.29	-0.04	0.01	0.13	0.03	0.02	Yes
SLB-19	4.60	0.88	0.05	<u>0.48</u>	-0.18	-0.07	0.11	0.03	0.08	0.19	0.00	0.05	0.05	0.01	Yes
SLB-20	4.42	1.07	0.24	<u>0.58</u>	-0.15	-0.05	0.02	0.11	0.13	0.07	0.06	-0.15	-0.07	0.09	Yes
SLB-21	4.29	1.11	0.31	<u>0.50</u>	-0.13	0.05	0.03	0.10	0.09	0.04	0.02	-0.21	-0.03	-0.14	Yes
SLB-22	4.42	1.07	-0.07	<u>0.80</u>	0.02	0.03	-0.10	-0.17	-0.05	-0.06	0.02	-0.11	0.05	0.01	Yes
SLB-23	4.42	1.11	0.06	<u>0.60</u>	-0.13	-0.01	-0.08	0.19	-0.01	-0.09	0.05	0.16	0.03	0.03	Yes
SLB-24	4.44	0.81	-0.21	0.12	-0.08	0.19	0.17	0.21	-0.05	0.26	0.25	-0.09	0.07	0.01	No
SLB-25	4.66	0.82	-0.25	0.17	-0.05	0.03	0.16	0.36	0.04	0.24	0.28	0.01	0.04	-0.08	No
SLB-26	4.91	0.82	0.07	-0.05	-0.05	-0.01	0.06	0.12	-0.11	-0.10	<u>0.77</u>	0.18	-0.09	-0.07	Yes
SLB-27	4.86	0.89	0.13	0.03	0.04	0.19	0.02	-0.08	-0.17	-0.09	<u>0.67</u>	0.12	-0.01	0.01	Yes
SLB-28	4.93	0.84	-0.07	0.01	0.10	0.10	-0.10	-0.06	0.14	-0.13	<u>0.77</u>	0.11	0.01	-0.09	Yes
SLB-29	5.00	0.93	0.00	-0.18	-0.12	<u>0.49</u>	-0.03	-0.10	0.14	0.22	0.28	-0.01	0.10	-0.05	Yes
SLB-30	4.87	0.89	0.04	0.01	0.12	0.19	-0.07	-0.17	0.08	0.26	0.21	-0.02	0.32	0.14	No
SLB-31	4.60	0.85	-0.11	0.02	0.33	0.07	-0.08	0.12	0.02	-0.02	-0.05	0.38	-0.11	-0.07	No
SLB-32	4.50	0.96	-0.16	0.16	-0.03	0.10	0.08	0.11	-0.17	0.10	0.16	0.04	0.01	-0.14	No
SLB-33	2.80	1.18	0.14	-0.05	-0.09	0.14	-0.27	-0.07	-0.08	-0.11	0.18	-0.10	-0.04	-0.29	No
SLB-34	4.60	0.89	-0.08	0.03	0.02	-0.05	0.15	0.07	-0.11	-0.06	0.23	<u>0.44</u>	0.05	0.18	Yes

Factors extracted															
M	SD	1	2	3	4	5	6	7	8	9	10	11	12	13	Retained?
SLB-35	4.63	0.86	-0.17	0.11	-0.09	0.17	0.28	-0.01	-0.10	0.03	0.28	0.27	0.04	0.15	No
SLB-36	4.55	0.98	-0.06	-0.01	0.14	0.39	0.26	-0.04	-0.09	-0.08	0.13	0.07	-0.12	-0.04	No
SLB-37	4.50	0.91	0.09	0.00	0.25	0.36	0.18	-0.18	-0.03	0.01	0.04	0.20	-0.12	-0.12	No
SLB-38	4.76	0.84	0.06	0.11	-0.05	0.31	0.04	0.28	-0.21	-0.14	0.25	0.25	-0.06	-0.05	No
SLB-39	4.35	1.09	0.17	-0.04	-0.05	-0.05	0.23	0.01	-0.03	-0.06	0.14	<u>0.67</u>	0.04	0.14	Yes
SLB-40	4.40	1.08	0.30	-0.06	-0.15	-0.10	0.25	-0.06	0.08	-0.17	0.17	<u>0.62</u>	0.05	0.04	Yes
SLB-41	4.64	0.92	0.12	0.03	0.04	0.12	0.06	-0.15	-0.01	0.05	-0.02	<u>0.49</u>	0.03	0.08	Yes
SLB-42	5.03	1.10	-0.12	0.16	0.24	0.33	-0.17	-0.03	-0.11	-0.08	0.11	0.03	0.07	0.08	No
SLB-43	4.50	0.93	0.20	0.05	0.08	<u>0.45</u>	0.03	0.00	-0.02	-0.08	-0.08	0.09	0.06	0.00	Yes
SLB-44	4.95	0.90	0.13	0.12	0.03	<u>0.81</u>	-0.03	0.00	0.01	-0.16	-0.05	-0.16	0.06	-0.02	Yes
SLB-45	4.97	0.85	0.05	-0.01	-0.08	<u>0.77</u>	-0.04	0.00	0.08	-0.01	0.04	-0.07	0.21	0.00	Yes
SLB-46	5.05	0.88	0.18	0.11	-0.14	<u>0.60</u>	-0.14	-0.03	0.01	-0.01	0.07	0.21	0.27	-0.02	Yes
SLB-47	4.71	1.01	-0.05	0.00	0.07	0.12	0.21	-0.11	0.02	0.23	-0.11	-0.06	<u>0.44</u>	0.01	Yes
SLB-48	4.39	1.06	0.00	-0.06	0.10	0.03	0.17	-0.09	0.04	0.07	-0.02	0.01	<u>0.68</u>	-0.08	Yes
SLB-49	4.66	0.91	0.02	0.08	0.09	-0.02	0.13	-0.03	0.06	0.12	-0.08	0.19	<u>0.43</u>	-0.08	Yes
SLB-50	4.39	1.08	-0.08	-0.18	0.10	0.07	0.17	-0.11	0.16	0.12	0.00	0.04	<u>0.60</u>	-0.08	Yes
SLB-51	5.04	0.82	0.04	-0.05	-0.12	0.28	0.03	0.31	0.11	0.04	-0.01	-0.13	-0.04	-0.02	No
SLB-52	4.27	1.20	0.02	0.03	-0.16	0.04	0.13	<u>0.61</u>	-0.18	0.13	-0.13	0.04	-0.12	-0.11	Yes
SLB-53	5.04	0.90	0.02	0.24	0.06	0.14	-0.05	0.24	-0.06	<u>0.51</u>	-0.19	-0.03	0.00	-0.17	Yes
SLB-54	4.82	0.82	-0.08	0.28	-0.03	0.30	-0.19	0.25	0.09	0.16	-0.02	-0.01	0.04	-0.27	No
SLB-55	4.10	1.03	-0.02	0.06	-0.01	0.08	0.13	0.18	0.01	0.05	0.06	0.22	0.24	0.01	No
SLB-56	4.39	0.94	-0.02	0.00	0.09	0.03	0.27	0.02	0.10	0.24	0.06	0.21	0.23	0.03	No
SLB-57	5.19	0.80	-0.05	0.04	0.16	0.18	0.04	0.14	-0.16	0.20	-0.08	-0.02	-0.04	0.11	Yes
SLB-58	4.25	1.20	0.08	-0.09	0.01	0.43	-0.37	-0.04	0.15	0.25	0.14	-0.05	-0.17	0.20	No
SLB-59	4.56	0.92	0.12	0.01	0.01	0.15	0.03	0.25	0.03	0.02	0.12	0.06	-0.11	0.38	No
SLB-60	4.70	0.80	0.16	-0.05	-0.10	-0.02	0.37	0.40	-0.05	0.00	0.07	-0.19	-0.02	0.22	No
SLB-61	4.87	0.89	0.05	-0.04	0.06	0.06	0.07	<u>0.64</u>	0.09	0.01	0.14	-0.21	-0.12	0.11	Yes
SLB-62	4.58	1.04	-0.05	-0.17	0.07	0.06	0.21	<u>0.48</u>	0.01	-0.08	-0.07	0.14	-0.07	0.12	Yes
SLB-63	4.48	0.99	0.00	-0.01	0.02	0.36	0.37	0.01	0.00	0.06	0.08	-0.01	0.09	-0.04	No
SLB-64	4.58	1.02	0.12	-0.09	-0.15	0.23	0.38	0.04	-0.11	0.14	0.01	-0.06	0.19	0.03	No
SLB-65	3.79	1.35	0.11	-0.01	0.11	0.05	-0.23	0.16	-0.15	0.13	0.34	-0.13	0.20	-0.05	No
SLB-66	4.75	0.84	-0.14	-0.02	-0.05	0.12	0.30	0.09	0.00	0.14	-0.06	0.03	-0.02	0.19	Yes
SLB-67	4.82	0.82	-0.13	0.07	-0.01	0.23	0.21	-0.03	0.06	-0.01	-0.05	0.03	-0.01	0.19	Yes
SLB-68	4.81	0.95	-0.07	0.10	0.07	0.05	0.22	0.28	-0.10	-0.06	0.00	0.13	-0.11	0.16	No
SLB-69	4.46	0.98	0.10	0.17	-0.10	-0.05	<u>0.58</u>	0.06	0.00	-0.01	0.06	0.24	-0.01	0.12	Yes
SLB-70	4.14	1.04	-0.03	0.07	-0.03	-0.09	<u>0.66</u>	0.17	0.07	-0.02	-0.06	0.18	0.06	-0.04	Yes

Table 3. (Continued)

	M	SD	Factors extracted													Retained?
			1	2	3	4	5	6	7	8	9	10	11	12	13	
SLB-71	4.21	1.09	-0.14	0.09	-0.11	-0.11	0.03	0.64	0.08	-0.03	0.12	-0.01	0.16	0.07	0.00	Yes
SLB-72	4.45	1.07	-0.07	0.71	0.23	-0.08	0.18	-0.16	-0.16	-0.04	-0.07	0.08	0.05	0.01	-0.01	Yes
SLB-73	4.88	0.89	-0.01	0.91	-0.10	-0.07	0.08	-0.03	-0.01	-0.04	0.08	-0.09	-0.02	-0.10	0.04	Yes
SLB-74	4.94	0.86	-0.10	0.58	0.05	0.10	-0.17	0.08	-0.04	0.18	0.24	-0.05	-0.03	-0.12	0.21	Yes
SLB-75	4.68	1.00	-0.09	0.77	0.03	-0.03	-0.03	0.00	-0.07	-0.02	-0.06	0.02	0.04	-0.05	-0.05	Yes
SLB-76	4.64	1.02	0.09	0.48	-0.05	-0.19	0.12	-0.21	0.19	0.23	0.00	0.10	0.20	-0.02	-0.15	Yes
SLB-77	4.92	0.94	0.05	0.23	-0.08	0.03	0.08	0.11	-0.17	0.69	-0.01	0.01	-0.05	0.01	0.09	Yes
SLB-78	5.00	0.93	0.08	0.00	-0.04	0.15	-0.12	0.09	-0.06	0.79	-0.02	0.01	-0.11	0.08	0.07	Yes
SLB-79	4.81	0.97	-0.02	0.04	0.16	-0.09	0.02	-0.05	-0.07	0.80	0.01	-0.08	0.05	0.10	0.08	Yes
SLB-80	4.80	0.95	0.01	0.04	-0.08	0.09	0.09	-0.06	0.09	0.72	0.01	-0.10	0.09	0.02	0.00	Yes
SLB-81	5.10	0.79	0.10	0.52	0.00	0.15	-0.11	0.05	0.05	0.77	-0.02	0.07	-0.06	-0.03	-0.15	Yes
SLB-82	5.08	0.83	0.05	0.46	-0.12	0.08	0.03	0.16	-0.02	0.27	-0.10	0.16	-0.03	0.04	-0.03	Yes
SLB-83	4.90	0.86	0.12	0.48	-0.04	0.23	-0.12	0.21	0.01	0.02	-0.03	0.05	-0.01	-0.03	-0.05	Yes
SLB-84	4.88	0.89	0.09	0.48	-0.10	0.23	-0.06	0.22	-0.09	0.14	-0.09	0.04	-0.09	0.07	-0.03	Yes
SLB-85	4.51	0.95	0.00	0.03	0.10	0.16	0.04	0.40	0.05	0.02	-0.05	0.15	-0.09	0.18	-0.10	Yes
SLB-86	5.11	0.79	-0.02	-0.05	0.07	0.62	0.12	0.12	-0.06	0.09	-0.04	-0.01	-0.03	0.10	-0.04	Yes
SLB-87	4.44	0.98	0.00	0.04	0.15	0.65	0.10	0.06	0.06	0.01	-0.20	-0.05	-0.10	0.04	-0.18	Yes
SLB-88	3.74	1.33	-0.09	-0.09	0.02	0.38	0.19	0.08	0.17	0.12	-0.19	-0.08	-0.06	-0.14	0.00	No
SLB-90	4.67	0.91	-0.07	-0.04	-0.04	0.50	-0.09	-0.25	0.33	-0.01	-0.06	-0.10	0.25	0.14	0.04	No
SLB-91	4.82	0.79	0.01	0.21	0.05	0.59	-0.16	-0.19	0.06	-0.11	-0.06	0.05	0.10	0.10	0.15	Yes
SLB-92	4.44	0.98	0.16	-0.03	-0.09	0.54	-0.02	-0.04	0.12	-0.02	-0.09	0.01	0.15	0.02	0.14	Yes
SLB-93	3.74	1.33	-0.13	0.08	0.08	0.13	-0.03	-0.44	0.12	-0.03	0.07	0.02	-0.04	-0.09	0.01	Yes
SLB-94	4.66	0.78	-0.01	0.07	0.09	0.32	-0.13	0.28	0.10	0.06	-0.14	0.03	0.03	0.02	0.13	No
SLB-95	5.16	0.78	-0.02	-0.04	-0.03	0.64	0.16	-0.08	0.15	0.06	-0.16	0.13	-0.02	0.04	0.10	Yes
SLB-96	4.78	0.95	-0.20	0.01	-0.03	0.37	0.03	-0.14	0.58	-0.02	-0.13	-0.01	0.11	0.08	0.04	No

		Factors extracted														
	M	SD	1	2	3	4	5	6	7	8	9	10	11	12	13	Retained?
S1	4.54	0.78														
S2	4.84	0.68	0.47													
S3	4.50	0.71	0.52	0.51												
S4	4.89	0.62	0.32	0.52	0.46											
S5	4.94	0.65	0.41	0.59	0.49	0.54										
S6	4.38	0.63	0.32	0.59	0.48	0.54	0.57									
S7	4.57	0.79	0.14	0.29	0.30	0.32	0.31	0.46								
S8	4.88	0.81	0.43	0.63	0.43	0.35	0.39	0.39	0.21							
S9	4.65	0.70	0.21	0.36	0.35	0.33	0.43	0.46	0.38	0.28						
S10	4.90	0.74	0.34	0.44	0.45	0.43	0.50	0.49	0.31	0.24	0.29					
S11	4.50	0.80	0.49	0.49	0.52	0.41	0.52	0.54	0.32	0.30	0.27	0.57				
S12	4.54	0.85	0.31	0.51	0.54	0.51	0.62	0.57	0.29	0.41	0.48	0.37	0.48			
SLB-LF-97	4.62	0.48	0.60	0.77	0.76	0.71	0.77	0.77	0.51	0.58	0.57	0.65	0.71	0.73		
SLB-SF-65	4.66	0.51	0.64	0.81	0.78	0.68	0.77	0.77	0.47	0.63	0.55	0.63	0.71	0.73		

Note. N = 214. M: mean scores; SD: standard deviation. Bold and underlined values are the highest loadings by a variable which are retained for subsequent analyses. Item SLB-89 was excluded here due to its unacceptable individual measure of sampling adequacy in the initial PAA (i.e., anti-image correlations diagonals < 0.50). Sixty-five items were retained to form the short-form of the behavior scale (SLB-SF-65) which were subjected to a large-scale validation study involving 4,486 Hong Kong undergraduates.

^aItem SLB-13, the only sufficiently-loaded (loading $\geq |0.40|$) item on Component 13, was removed together with the component. ^bAs component 13 only contained one item and was subsequently removed from the final solution, the total variance was computed by the summation of variance explained by the remaining twelve components. SLB-LF-97: 97-item Service Leadership Behavior Scale- Long-Form; SLB-SF-65: 12-factor, 65-item version of SLB-SF-65. S1: Subscale 1 (6 items, *Problem-Solving*); S2: Subscale 2 (9 items, *Self-leadership and Life-long Learning*); S3: Subscale 3 (10 items, *Non-cognitive Intrapersonal Competences*); S4: Subscale 4 (5 items, *Distributed Leadership*); S5: Subscale 5 (6 items, *Integrity*); S6: Subscale 6 (7 items, *Caring Behavior*); S7: Subscale 7 (3 items, *Compassion*); S8: Subscale 8 (4 items, *Self-reflection*); S9: Subscale 9 (4 items, *Service Provision*); S10: Subscale 10 (3 items, *Positive Social Relationship*); S11: Subscale 11 (4 items, *Communication Skills*); S12: Subscale 12 (4 items, *Fairness*). All correlation coefficients are statistically significant at $p < .001$ (two-tailed).

Furthermore, as the SLAM framework is catered to service economies which are characterized by *distributed leadership* and *decentralization* rather than *absolute control* and *centralization* [38], we expected a positive correlation between the behavior scale with the *Systemic Thinking Scale* (i.e., Hypothesis 5) while a negative association with the *Hierarchical Thinking Scale* (i.e., Hypothesis 6). Finally, while paternalistic leadership is characterized by a strong sense of hierarchy which contradicts the SLAM framework [7, 38], it also emphasizes leaders' exhibition of benevolence and integrity which correspond to the fundamentals of Service Leadership education [39]. As a result, a positive while mild correlation between the behavior scale (and the subscales) and the *Paternalistic Leadership Scale* (PTL) was predicted (i.e., Hypothesis 7).

OUR FINDINGS

Results of the MAP showed that the squared average partial correlation was at a minimum (0.00821) upon the extraction of the thirteenth factor, suggesting that thirteen factors should be retained [40]. Item 89 was deleted due to its poor (i.e., anti-image correlations diagonals below 0.50) individual measure of sampling adequacy [19]. Accordingly, the PAA was re-administered on the remaining 96 items specifying the extraction of thirteen factors. Each item's factor loadings, eigenvalues, the percentage of variance explained by each factor, and the correlations amongst the different factors are presented in table 3.

Applying the two exclusion criteria as abovementioned, nine double-loaded items were first eliminated. This was followed by the removal of 21 insufficiently-loaded items. Item 13, the only item loaded sufficiently on the thirteenth factor (see Table 3), was deleted as well. Ultimately, the resultant 65-item, twelve-factor solution—which accounted for 57.97% of the total variance—formed the short-form of the Service Leadership Behavior Scale (SLB-SF-65). The twelve factors, each of which forms a subscale, were accordingly named “Problem-Solving” (items 5 to 10), “Self-leadership and Life-long Learning” (items 72 to 76, 81 to 84), “Non-cognitive Intrapersonal Competences” (items 12, 14, 16 to 23), “Distributed Leadership” (items 86, 87, 91, 92, 95), “Integrity” (items 29, 43 to 46, 57), “Caring Behavior” (items 66, 67, 69 to 71, 85, 93), “Compassion” (items 52, 61, 62), “Self-reflection” (items 77 to 80), “Service Provision” (items 1 to 3, 53), “Positive Social Relationship” (items 26 to 28), “Communication Skills” (items 34, 39 to 41), and “Fairness” (items 47 to 50).

Reliability of the Total Scale and Subscales

As detailed in Table 4, both long-form (SLB-LF-97) and short-form (SLB-SF-65) of the behavior scale showed excellent internal consistency (all α values $\geq .95$, mean inter-item correlations $> .20$) in the whole sample ($N = 214$) and across two subsamples split based on participants' gender. All subscales, except for the three-item subscale “Compassion”, demonstrated at least acceptable internal consistency (all α values $\geq .70$, mean inter-item correlations $> .30$).

Table 4. Internal consistencies of SLB-LF-97, SLB-SF-65, and subscales across gender

	Whole Sample (N = 214)		Males (N = 60)		Females (N = 154)	
	α	Mean Inter-item correlations	α	Mean Inter-item correlations	α	Mean Inter-item correlations
Long-Form Service Leadership Behavior Scale (SLB-LF-97)	0.97	0.26	0.97	0.27	0.97	0.25
Short-Form Service Leadership Behavior Scale (SLB-SF-65)	0.96	0.28	0.96	0.29	0.96	0.27
Subscale 1: <i>Problem-Solving</i>	0.90	0.59	0.91	0.64	0.89	0.56
Subscale 2: <i>Self-leadership and Life-long Learning</i>	0.90	0.51	0.90	0.50	0.90	0.51
Subscale 3: <i>Non-cognitive Intrapersonal Competences</i>	0.88	0.42	0.90	0.47	0.86	0.39
Subscale 4: <i>Distributed Leadership</i>	0.79	0.44	0.78	0.43	0.79	0.44
Subscale 5: <i>Integrity</i>	0.84	0.46	0.85	0.49	0.83	0.45
Subscale 6: <i>Caring Behavior</i>	0.74	0.34	0.76	0.35	0.72	0.34
Subscale 7: <i>Compassion</i>	0.61	0.35	0.61	0.37	0.59	0.34
Subscale 8: <i>Self-reflection</i>	0.88	0.65	0.91	0.73	0.87	0.62
Subscale 9: <i>Service Provision</i>	0.73	0.40	0.70	0.36	0.73	0.41
Subscale 10: <i>Positive Social Relationship</i>	0.85	0.65	0.88	0.70	0.83	0.61
Subscale 11: <i>Communication Skills</i>	0.81	0.52	0.86	0.61	0.78	0.47
Subscale 12: <i>Fairness</i>	0.86	0.61	0.88	0.64	0.85	0.59

Note. α = Cronbach's alpha value.

Despite the seemingly unacceptable alpha values (i.e., 0.59 to 0.61), inspection of the range of mean inter-item correlations of subscale "Compassion" (i.e., 0.34 to 0.37) revealed that they all fell within the range (i.e., 0.20 to 0.40) of "optimal level of homogeneity" (p. 114) defined by Briggs and Cheek [41]. In short, the present findings provided support for the high reliability of the different forms of the behavior scale and its subscales.

Validity Assessment: Correlation with External Criterion Measures

Confirming Hypotheses 1 to 4, correlational findings (see Table 5) revealed a significant ($p < .05$, two-tailed), positive correlation between the SLB-SF-65 (and almost all the subscales) and the *Revised Servant Leadership Profile*, *Interpersonal Reactivity Index* (including the composite score and the two subscales), *Moral Self-Concept*, and *Leadership Efficacy*, respectively. Hypothesis 5 was also supported as the *Systemic Thinking Scale* (ST) was significantly and positively associated with the SLB-SF-65 alongside its subscales (see Table 5). Echoing Hypothesis 7, despite the statistical significance ($p < .05$, two-tailed), the SLB-SF-65 was only mildly correlated ($r = 0.25$) to the *Paternalistic Leadership Scale* (PTL). Similar findings (see Table 5) emerged when the subscales were correlated with PTL (r s ranging from 0.04 to 0.25), further supporting Hypothesis 7.

Meanwhile, contrary to Hypothesis 6, both SLB-SF-65 and the subscales were positively correlated to the *Hierarchical Thinking Scale* (see Table 5). This may be attributable to the non-mutual exclusiveness of *Hierarchical* (HT) and *Systemic Thinking* (ST) whereby people can be both hierarchical and systemic thinkers [17]. Hence, it is possible that the present positive link between HT and SLB-SF-65 ($r = 0.30$) was due to the moderate correlation between ST and SLB-SF-65 ($r = 0.51$) and that of HT and ST ($r = 0.44$). Indeed, once ST was

controlled for, the HT-SLB-SF-65 correlation was no longer significant ($p = .17$, two-tailed). In contrast, the ST-SLB-SF-65 link ($r = 0.44$) remained to be moderate even after controlling for HT. In short, while these results seemingly contradicted Hypothesis 6, further scrutiny revealed a pattern of findings that resonated with Wielkiewicz's [17] conceptualization of HT and ST.

Table 5. Correlations with external criterion scales (and subscales)

	RSLP	PTL	IRI	IRI-EC	IRI-PT	MSC	HT	ST	LEF
Long-Form Service Leadership Behavior Scale (SLB-LF-97)	0.81	0.26	0.51	0.28	0.56	0.75	0.28	0.51	0.56
Short-Form Service Leadership Behavior Scale (SLB-SF-65)	0.78	0.25	0.46	0.25	0.52	0.72	0.30	0.51	0.55
Subscale 1: <i>Problem-Solving</i>	0.33	0.04 ^{n.s.}	0.11 ^{n.s.}	-0.04 ^{n.s.}	0.22	0.27	0.20	0.28	0.43
Subscale 2: <i>Self-leadership and Life-long Learning</i>	0.58	0.24	0.26	0.09 ^{n.s.}	0.34	0.55	0.28	0.47	0.42
Subscale 3: <i>Non-cognitive Intrapersonal Competences</i>	0.52	0.10 ^{n.s.}	0.30	0.16	0.34	0.44	0.18	0.29	0.44
Subscale 4: <i>Distributed Leadership</i>	0.66	0.21	0.39	0.16	0.49	0.57	0.21	0.49	0.34
Subscale 5: <i>Integrity</i>	0.67	0.20	0.40	0.21	0.46	0.66	0.25	0.37	0.45
Subscale 6: <i>Caring Behavior</i>	0.71	0.24	0.39	0.22	0.42	0.65	0.22	0.44	0.33
Subscale 7: <i>Compassion</i>	0.49	0.15	0.43	0.42	0.29	0.49	0.04 ^{n.s.}	0.30	0.13 ^{n.s.}
Subscale 8: <i>Self-reflection</i>	0.35	0.17	0.30	0.20	0.30	0.36	0.27	0.38	0.29
Subscale 9: <i>Service Provision</i>	0.58	0.22	0.44	0.26	0.47	0.55	0.15	0.35	0.29
Subscale 10: <i>Positive Social Relationship</i>	0.54	0.14	0.37	0.24	0.38	0.54	0.10 ^{n.s.}	0.20	0.49
Subscale 11: <i>Communication Skills</i>	0.53	0.18	0.35	0.23	0.34	0.48	0.19	0.30	0.51
Subscale 12: <i>Fairness</i>	0.67	0.25	0.39	0.18	0.48	0.56	0.30	0.37	0.41

Note. N= 214. RSLP: Revised Servant Leadership Profile; PTL: Paternal Leadership; IRI: Interpersonal Reactivity Index; IRI-EC: Subscale "Empathic Concern"; IRI: PT: Subscale "Perspective Taking"; MSC: Moral Self-Concept; HT: Hierarchical Thinking about leadership; ST: Systematic Thinking about leadership; LEF: Leadership Efficacy. Unless otherwise specified by the superscript "n.s." which denotes statistical non-significance ($p > .05$, two-tailed), all correlation coefficients are significant at $p < .05$ (two-tailed).

Table 6. Comparison of the strength of correlations between SLB-SF-65 with the criterion scales

Correlations with the external criterion measures (and subscales)			Z-scores of difference between r s with SLB-SF-65:							
	Cronbach's alpha (Mean inter-item correlations)	r	PTL	IRI	IRI-EC	IRI-PT	MSC	HT	ST	LEF
1. RSLP	0.93 (0.42)	0.782***	8.91	6.92	8.89	6.14	2.51	8.47	6.04	4.96
2. PTL	0.79 (0.43)	0.249***	—	-2.71	0.04 ^{n.s.}	-3.65	-7.30	-0.69 ^{n.s.}	-3.55	-4.09
3. IRI	0.73 (0.17)	0.462***	—	—	5.94	-1.64 ^{n.s.}	-5.57	1.97	-0.77 ^{n.s.}	-1.44 ^{n.s.}
4. IRI-EC	0.67 (0.23)	0.245***	—	—	—	-3.96	-8.18	-0.54 ^{n.s.}	-3.50	-4.13
5. IRI-PT	0.66 (0.24)	0.523***	—	—	—	—	-4.12	2.95	0.20 ^{n.s.}	-0.49 ^{n.s.}
6. MSC	0.88 (0.49)	0.716***	—	—	—	—	—	6.62	4.09	3.22
7. HT	0.83 (0.26)	0.297***	—	—	—	—	—	—	-2.96**	-3.65
8. ST	0.84 (0.28)	0.511***	—	—	—	—	—	—	—	-0.64 ^{n.s.}
9. LEF	0.84 (0.41)	0.553***	—	—	—	—	—	—	—	—

Note. N= 214. *** $p < .001$ (two-tailed), RSLP: Revised Servant Leadership Profile; PTL: Paternal Leadership; IRI: Interpersonal Reactivity Index; IRI-EC: Subscale "Empathic Concern"; IRI: PT: Subscale "Perspective Taking"; MSC: Moral Self-Concept; HT: Hierarchical Thinking; ST: Systematic Thinking; LEF: Leadership Efficacy. Unless otherwise specified by the superscript "n.s." which denotes statistical non-significance, all other Z-scores of difference were significant at $p < .05$ (two-tailed) (i.e., $|Z\text{-score}| > 1.96$).

Furthermore, utilizing the statistical package *cocor* [42] which allows the comparison of strengths between two pairs of correlation coefficients using Steiger's [43] z-test, the results (see Table 6) highlighted that out of all significant associations, the SLB-SF-65 was most strongly correlated to the *Revised Servant Leadership Profile* ($r = 0.78$) while considerably more weakly associated with the *Paternalistic Leadership Scale* ($r = 0.25$) as well as the *Hierarchical Thinking Scale* ($r = 0.30$). Taken together, these findings are generally supportive of the convergent validity of the SLB-SF-65—which was shown to consistently correlate with various constructs theorized to underscore the behavioral qualities characteristic of an elite Service Leader.

DISCUSSION

Utilizing a sample of 231 PolyU students, the present study attempted to examine the internal consistency, factorial validity, and convergent validity of the 97-item long-form of the Service Leadership Behavior Scale (SLB-LF-97). Moreover, findings of the EFA suggested the retention of 65 items which formed the short-form of the behavior scale (SLB-SF-65). Besides recording meritorious internal consistency, the SLB-SF-65 and the subscales were shown to correlate significantly and positively with all the external criterion measures. Specifically, by confirming six out of seven hypotheses (i.e., Hypotheses 1 to 5 and 7), the present correlational findings underscored the convergent validity of the SLB-SF-65. In short, the present results not only vouch for the psychometric property of the 65-item SLB-SF-65, but also its utility in serving as a sound measurement tool to help evaluate whether an individual has exhibited adequate behavioral qualities representative of a genuine Service Leader.

There are several key contributions of this work. First, amidst the scanty evidence base of assessment inventory about leadership especially in the Chinese context [8, 12], the SLB-SF-65 constitutes a timely addition to the literature. As remarked by Ho and Nesbit [44], the interdependent construal of interpersonal relationships unique to a collectivist society such as China could constitute a fundamentally different interpretation of leadership. Hence, it is imperative that objective measurement tool be tailor-made for the Chinese population, especially considering that China accounts for about 20% of the global population. Second, the present paper informs the literature of Service Leadership education. Considering the paucity in robust evaluation methodologies as regards leadership training programs [13], the SLB-SF-65 would be useful for implementers attempting to gauge the effectiveness of a Service Leadership training program. A successful training should, in principle, enhance trainees' propensity to display behavioral qualities representative of a true Service Leader which can be operationalized by a post-program improvement in one's SLB-SF-65 score. Third, as a precursor to a validation study involving 4,486 Hong Kong undergraduates (i.e., the main event of "The Project"), the present findings justify the inclusion of the 65-item SLB-SF-65 by underscoring its excellent internal consistency and strong convergent validity. Moreover, the preliminary item-screening and eventual trimming of the scale did not only add to the ease of administration, but also facilitate the elicitation of quality responses which are crucial to the ensuing large-scale validation study.

Nonetheless, there are certain issues worthy of our attention. One glaring concern would be the legitimacy of the present EFA attributable to the sample size of the present study ($N=214$). As the present subjects-to-variables (i.e., STV) ratio only amounts to 2.23, which is below the commonly adopted “rule-of-thumb” STV ratio of 5 [see 45] for a list of “rule-of-thumb” STV ratios), there is inevitably a concern of under-sampling. However, previous research [e.g., 46, 47] had staunchly challenged the validity and utility of those “rules of thumbs”, as these researchers maintained that sampling adequacy should also depend on other factors such as communalities and size of loadings. Particularly, MacCallum and colleagues [45] specified that good recovery of population factors can be achieved “with communalities in the range of 0.5” (p. 96) and “a somewhat larger sample in the range of 100 to 200” (p. 96). Given that both these criteria were met in the present analysis (i.e., $N=214$; average communality = 0.53), there is no reason to outright dismiss the meaningfulness of the present EFA findings just because of the low STV ratio. Of course, there is a need to further assess the stability of the factors extracted because it is easy for multivariate statistics to capitalize on chance.

Additionally, owing to the exploratory nature of the present dimensionality assessment, there is a need to conduct a confirmatory factor analysis (CFA) to further examine the absolute and relative model fit of the current twelve-factor solution to participants’ responses [20]. Nevertheless, due to the sample size concern as outlined above, conducting a CFA by further splitting the present sample into two halves is just not workable. Therefore, to better ascertain the stability and fit indices of the current twelve-factor solution, both EFA and CFA need to be administered in the ensuing large-scale validation study ($N=4,486$) as mentioned above.

Furthermore, contrary to Hypothesis 6, the SLB-SF-65 was positively correlated to the *Hierarchical Thinking Scale* measuring people’s orientation toward leadership as a “leader-centric” concept whereby leaders ought to take the lion’s share of blames or credits for the organizational outcomes [17, 48]. As abovementioned, the non-mutual exclusiveness of Hierarchical (HT) and Systemic Thinking (ST) [17], coupled with the present positive, moderate correlation between the two and that between ST and SLB-SF-65, may account for the present positive association between HT and SLB-SF-65. Indeed, Wielkiewicz and colleagues [48] contended that an elite leader should in theory “embrace these two forms of leadership (beliefs)” (p. 4) owing to their more sophisticated understanding on and experience with leadership. Taken together, it is conceivable that the positive link between HT and SLB-SF-65 was attributable to those “elite leaders” in the present sample who scored high on both HT and ST. Findings from the partial correlation analyses implied just that. As ST was controlled for, the positive HT-SLB-SF-65 association became non-existent, while the ST-SLB-SF-65 link remained highly significant and moderate even after controlling for HT. Nevertheless, the question why is Service Leadership behavior insignificantly, instead of negatively, linked to Hierarchical Thinking remains an interesting research topic to be examined in future.

Notwithstanding the above concerns, the present paper constitutes a pioneer assessment on the convergent and factorial validity of the Service Leadership Behavior Scale. Not only did the current findings strongly corroborate the psychometric soundness of the SLB-LF-97, they also provided a glimpse into an interpretable factorial structure of SLB-LF-97 which warrants further empirical scrutiny. More importantly, as the precursor to the main event of “The Project”, the current study serves a preliminary screening purpose which informs the list

of scale items worthy of inclusion in the upcoming large-scale validation study. Last but not least, the current paper helps to bridge a well-documented literature gap in the systematic evaluation of Service Leadership education [8, 13] by introducing a valid and reliable tool to measure people's behavioral qualities as a good Service Leader.

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Chapter 138

CONTENT VALIDATION OF A SERVICE LEADERSHIP BEHAVIOR SCALE IN HONG KONG

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ABSTRACT

In this chapter we report the development of the 97-item Service Leadership Behavior Scale (i.e., SLB-LF-97) based on the Service Leadership framework proposed by Po Chung. To understand the content validity of the scale, the content validity of the developed items was examined. A panel of experts (n = 3) was formed to assess the content validity of the scale items in different domains (service provision, competence, character, caring, commitment to continuous improvement, and distributed leadership) in terms of relevance, clarity, and representativeness on each item. Results indicated that the SLB-LF-97 has an excellent content validity indexed by relevance, clarity, and representativeness for the whole scale and the different categories. The findings suggest the scale and subscales of the Service Leadership Behavior Scale possess excellent content validity.

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INTRODUCTION

Desirable leadership characteristics vary with the characteristics of different economic systems. The leadership qualities required by service economy are different from those required by manufacturing economy. Generally speaking, leadership in the manufacturing economy was regarded as inflexible, task-focused, and authority-based. In contrast, effective leadership in the service economy is characterized by people orientation, relationship orientation and service orientation [1]. Hong Kong has a service-oriented economy where the service industries shared 92.2% of the Gross Domestic Product (GDP) in 2016 [2]. With respect to the growth of service economy in the global context, Chung [3] proposed the notion of service leadership and developed the Service Leadership and Management Model (SLAM). As defined by Chung [3], service leadership “is about satisfying needs by consistently providing quality personal service to everyone one comes into contact with, including one’s self, others, groups, communities, systems, and environments”. It is also believed that effective service leadership is a function of leadership competencies, character, and caring disposition [4].

Although the notion of service leadership is newly proposed, its related components are not brand-new. Compared with other mainstream leadership theories and approaches, service leadership shares some similar features, such as the emphasis on integrity [5]. Nevertheless, the service leadership model has its distinctive features that are seldom mentioned in other theories. To begin with, not a single leadership theory emphasizes the importance of the service orientation, including servant leadership theory [6], authentic leadership theory [7], and ethical leadership theory [8]. Besides, these theories primarily conceptualize leadership at the individual level, dealing with the leadership behaviors of self and/or others. For example, while authentic leadership is mostly dependent on leaders’ behaviors in self-reflection, self-management, and self-improvement [7], service leadership theory adopts a more systematic multi-level perspective towards the service for self, others, as well as the ecological system [4].

Besides, some leadership theories argue that excellent leadership primarily relies on the competencies or certain personal qualities of the leaders. For example, managerial competencies are the core elements for top-down leadership theory [9], while a set of born characteristics is proposed to determine the success of a leader according to the trait approach to leadership [10]. In contrast, the service leadership framework asserts that competencies and character are not enough for an effective leader in the modern service economy [3]. The SLAM framework suggests three components that determine effective leadership, including moral character, leadership competencies, and caring disposition (for short, $E = MC^2$). This framework not only highlights the importance of service leaders’ personal qualities and competencies but also establishes a more comprehensive and systematic model to explain how these characteristics contribute to effective leadership [5].

Furthermore, although both service leadership and servant leadership focus on the development of followers through mentoring and teaching [11], servant leaders only focus on the followers rather than the leaders. Moreover, service leadership considers that everyone could be a leader and leadership requires life-long continuous improvement. Lastly, another new feature that service leadership goes beyond the other existing theories is that the SLAM framework incorporates Chinese cultural values and the philosophies of Buddhism,

Confucianism, and Taoism [3]. The incorporation helps to look at moral character from an integrated perspective. Overall speaking, service leadership theory is multidisciplinary in nature that it covers leadership in different domains [12].

As university students are the future leaders in society, service leadership education is essential for youths [13]. With the collaborative partnership of the Victor and William Fung Foundation, the Hong Kong Institute of Service Leadership & Management Limited (HKI-SLAM), and the eight universities funded by the University Grants Committee in Hong Kong, the Fung Service Leadership Initiative (SLI) was initiated in 2012 to promote service leadership education. The Hong Kong Polytechnic University (PolyU), among the eight universities, has developed and provided credit-bearing courses and non-credit-bearing programs/workshops on service leadership within the SLAM curriculum framework [14]. Both qualitative and quantitative evaluation strategies have supported the positive influences on the leadership capacities of students who have participated in the courses or programs [15-17]. In general, the service leadership education has obtained great achievement and recognition among university students.

Although some initiatives on service leadership education have been launched, there is little empirical research that assesses the qualities of service leaders. A survey of the literature shows that leadership behavior scales based on different leadership theories have been used, such as the Multifactor Leadership Questionnaire (MLQ) [18] that allows individuals to measure their own transformational, transactional, and passive-avoidant leadership behaviors. However, the MLQ has been criticized by researchers for having problematic construct validity issues as it focuses primarily on transformational leadership, rather than the other two leadership styles [19]. Other specific leadership behavior scales were largely developed with respect to its corresponding leadership theory, which has different conceptualizations from the Service Leadership theory. For example, the Transformational Leadership Inventory [20], the Authentic Leadership Inventory (ALI) [21], and the Servant Leadership Behavior Scale [22] were developed according to corresponding leadership theories. Therefore, there is an urgent need to develop a measurement specifically for the Service Leadership theory.

To fill this gap and to strengthen the assessment component of service leadership education, the Research Team at The Hong Kong Polytechnic University (PolyU) embarked on a research project entitled “Development and Validation of Measures Based on the Service Leadership Model”. In this project, three scales on service leadership (knowledge, attitude, and behavior) were developed and validated. Previous studies have documented the processes of developing the Service Leadership Attitude Scale and Knowledge Scale [23, 24]. Results of both studies showed that the items developed were perceived to be relevant, clear, and representative of the constructs of service leadership attitude and knowledge. In this paper, we reported the development of the 97-item Service Leadership Behavior Scale (SLB-LF-97) and its related content validation findings.

Generally speaking, three steps were involved in developing an assessment tool, including domain identification, item generation, and instrument formation [25]. For the present study, the SLB-LF-97 was developed based on the groundwork of the HKI-SLAM curriculum framework [3], 7 core beliefs of service leadership [26], 12 dimensions of the personal quality of service leadership [5], 25 principles of service leaders [4], and the existing literature. Specifically, the developed scale attempted to cover the behavior of service leaders in the following key domains:

1. **Service provision** – According to the Service Leadership theory, it is essential for service leaders to satisfy the needs of self, others, and systems, which is elaborated in the Core Belief 1 of the SLAM framework [26]. Also, as advocated by The Principle of Service Mindset [1], service leaders must have genuine care for others' needs. However, unlike servant leadership theory or spiritual leadership theory which overemphasizes followers' needs and neglects leaders' needs [5], service leadership theory adopts a more balanced approach in looking at the needs of the followers and leaders.
2. **Competence** – The traditional leadership approaches emphasize management skills or expertise [9], which is more applicable to the manufacturing economy. In contrast, leadership competency in the service economy has a broader coverage focusing on the importance of intrapersonal and interpersonal competencies [3]. Four types of intrapersonal competencies are concerned the most in the service leadership education [27]. First, intelligence quotient (IQ) is closely related to job performance as well as leadership performance [28]. The IQ of an effective service leader is manifested in good problem-solving, critical thinking, logical reasoning, and analytical abilities [27]. The second intrapersonal competence is emotional quotient (EQ), which is one of the most recognized non-intellectual factors that contribute to our work and daily life [29]. The ability to understand, recognize, and manage emotions of oneself and others will undoubtedly enhance the performance and leadership at work [30]. The other two essential intrapersonal competencies for service leaders are adversity quotient (AQ) and spiritual quotient (SQ). AQ addresses the ability to accept and successfully bounce back from failure, misfortune, or other adversity situations [31], while SQ is regarded as the ability to use meaning, faith, and other spiritual resources to solve problems [32]. A competent service leader possesses and utilizes intrapersonal competencies to serve oneself, others, and systems.

In addition, interpersonal competencies are also among the core personal attributes that service leaders should promote [33]. Five task domains of interpersonal competence were identified by Buhrmester, Furman, Wittenberg, and Reis [34], which included initiating relationships, self-disclosure, emotional support, conflict managing, and asserting personal thoughts and feelings. Besides, the SLB-LF-97 incorporates Chinese philosophy to enrich the model. As such, six components of interpersonal competencies are considered in the SLB-LF-97: passionate about people; positive social relationships; assertiveness; collaboration and cooperation with people; conflict resolution; and communication skills. Specifically, service leaders are supposed to be people-oriented (*"yi ren wei ben"*) and develop positive and healthy relationships with others. Meanwhile, an effective service leader shows great verbal and non-verbal communication skills, through which one could develop and maintain collaborative relationships with teammates and other people, as well as assert one's own rights when having conflicts. In short, service leaders with good interpersonal competencies can appreciate different opinions (*"he er bu tong"*) and create constructive ways to resolve interpersonal conflicts.

3. **Character** – Complying with the Principle of Competence, Character, and Care [4], and the Principle of Personal Ethics [4], leaders in the service economy are required to exhibit positive characters that are morally valued, which make followers more

willing to work with them [35]. In Western cultures, Park, Peterson, and Seligman [36] developed the VIA Classification and listed 24 virtues in action, such as integrity, gratitude, forgiveness, and bravery. However, Eastern cultural philosophies, particularly, Confucianism also uphold some traditional character strengths, such as benevolence (“*ren*”), affection (“*ai*”), and forgiveness (“*shu*”) [37]. The SLB-LF-97 synthesizes the Eastern and Western cultures and highlights the service leadership virtues by integrity, fairness, humility, and acting as an ethical role model.

4. **Caring** – This category covers the quality of caring disposition of the service leaders. The Principle of Trust, Fairness, Respect, and Care implies that successful service experiences cannot exist without caring service leaders [4]. A competent and moral service leader should also show concern for others and oneself [38]. Two aspects of caring disposition are measured in the SLB-LF-97. On the one hand, good service leadership involves the qualities of concern, such as empathy and compassion. On the other hand, caring leaders provide care for others by loving, supporting, and developing others.
5. **Commitment to continuous improvement** – The need for continuous improvement is one of the key characteristics of the service leadership model [5]. The HK-SLAM model emphasizes self-leadership and growth mindset, rather than the notion of “inborn” or “elite” leadership [26]. Besides, only through continuous professional and personal improvement could one be well prepared to serve oneself as well as others. Therefore, effective service leaders should make efforts to promote self-leadership, self-reflection, and life-long learning.
6. **Distributed leadership** – In response to the core belief of service leadership that “every day, every human occupies a position of leadership and possesses the potential to improve his leadership quality and effectiveness” (Core Belief 2) [26], distributed leadership style in the service economy encourages and empowers every teammate to voice out and contribute their insights to the team decision-making. Meanwhile, distributed leaders would show trust and respect to followers by acknowledging and respecting their views and abilities.

A well-developed Service Leadership Behavior Scale is indispensable for educators and researchers to empirically investigate students’ changes after taking service leadership education. Such a scale serves as an instrument for assessing one’s qualities of service leadership, which enables researchers to further validate the theory and hypotheses proposed by the service leadership model, such as the principle $E = MC^2$. Based on the Service Leadership model, the PolyU Research Team drafted a total of 97 items for the Service Leadership Behavior Scale. However, before formally utilizing the scale and interpreting scores with confidence, the validation process is a highly critical step in the test development [39]. To obtain judgmental evidence on whether the scale and items could adequately represent the content of service leadership behavior, content validation procedure was conducted in the present study.

Content validation was defined as “the degree to which elements of an assessment instrument are relevant to and representative of the targeted construct for a particular assessment purpose” [40, p.238], or “whether or not the items sampled for inclusion on the tool adequately represent the domain of content addressed by the instrument” [41, p.155].

One of the most frequently utilized approaches for content validation in previous research is the engagement of “content experts” [42], in which several knowledgeable people in a specialized area discuss and have consensus on the quality and representativeness of the instrument items. To minimize errors arising from subjective assessment and artificial consensus [43], content validity index (CVI) [44] was employed in the current study, which provides quantitative judgment evidence for the content validity of the test, including relevance, clarity, and representativeness [44]. In the present study, a panel of experts was invited to evaluate the items of the SLB-LF-97. Based on the quantitative and qualitative content validation findings, revisions were made to improve the scale.

OUR STUDY

The present study documented the development of the SLB-LF-97 and evaluated its content validation. Based on a thorough examination of the tenets of the Service Leadership Model [3] and leadership literature (e.g., spiritual quotient, [32]), an item pool on the behaviors and qualities of service leaders was established. The following six categories are included in the SLB-LF-97:

- C1. Service provision** (4 items). Items in this category assess respondents’ tendency of having a sensitivity to individuals’ needs and providing good service to others.
- C2. Competence** (38 items). This category addresses behaviors and qualities representing intrapersonal and interpersonal competencies within the framework of HKI-SLAM [27, 33]. For the intrapersonal competencies, items measure individuals’ IQ, EQ, AQ, and SQ. For the interpersonal competencies, items assess “passionate about people”, “positive social relationship”, “assertiveness”, “collaboration and cooperation with people”, “conflict resolution”, and “communication skills”. Basically, intrapersonal and interpersonal competencies are covered under this domain.
- C3. Character** (14 items). Items in this category measure a well-developed personal code of ethics as characterized by integrity, fairness, humanity, and whether a person is acting as an ethical role model.
- C4. Caring** (15 items). This category underlines caring disposition defined by the Service Leadership Model [3], including notions that deeply embedded in Chinese virtues, such as items assessing “guan xin” (concern) and “zhao gu” (providing care).
- C5. Commitment to continuous improvement** (13 items). This category involves the notion that effective service leaders put self-development efforts aiming at ethically improving their competencies, abilities, willingness, and resources to satisfy the needs of others. Based on the 25 principles of service leadership [4], items evaluating individuals’ self-leadership, self-reflection, and life-long learning were constructed.
- C6. Distributed leadership** (13 items). Items in this category assess the three core characteristics of distributed service leadership, including shared decision-making, empowerment of teammates, and trust and respect.

Three experts familiar with the Service Leadership literature were invited to assess the extent to which the SLB-LF-97 measured what it was intended to measure. All experts had a doctoral degree and were involved in the curriculum development and/or the teaching of the subject “Service Leadership” and they have professional knowledge in Service Leadership, especially the framework of the HKI-SLAM.

Instrument

A self-administered questionnaire was distributed to the three experts. They evaluated the content validity for each item in the following aspects:

- 1) **Relevance**, the extent to which the item falls within the body of knowledge of the SLAM framework. Experts were asked to judge on a 4-point rating scale: 1 = *Irrelevant*, 2 = *Unable to assess the relevance without item revision or item is in need of revision or otherwise would no longer be relevant*, 3 = *Relevant but needs minor amendment*, 4 = *Relevant*.
- 2) **Clarity**, the extent to which the item is concise, accurate, and direct. Experts were asked to judge on a 4-point rating scale: 1 = *Very unclear*, 2 = *Unclear*, 3 = *Clear*, 4 = *Very clear*.
- 3) **Representativeness**, the extent to which the item adequately represents and encompasses the corresponding concept. Experts were asked to judge on a 4-point rating scale: 1 = *Very unrepresentative*, 2 = *Unrepresentative*, 3 = *Representative*, 4 = *Very representative*.

Meanwhile, the experts were requested to give justifications or suggested modifications if they had negative ratings (option 1 or 2) on the items. After rating the individual items, the experts were also invited to judge the overall quality of the scale via the following questions:

- 1) Does this batch of items cover all the essential behaviors of qualities within the service leadership framework?
- 2) Is there any additional behavior(s) or qualities that you regard essential to service leader? If yes, please list the additional point(s) below.
- 3) Does this batch of items adequately represent the behavior(s) or qualities in service leadership?
- 4) Any other comments (open-ended question).

Experts’ ratings were used to analyze the content validity of the scale, while their written feedbacks and suggestions would direct further revisions of the developed items.

FINDINGS

With reference to the previous studies, the I-CVI index for each item was computed as the number of experts giving a rating of 3 or 4, divided by the number of experts [i.e., 3] —

that is, the proportion in agreement about relevance, clarity, or representativeness. Then, the S-CVI/ave for each category was an average score of the I-CVIs for all the items. As shown in Table 1, most of the items indicated good I-CVIs. Items that with an I-CVI value lower than 1.00 were modified according to the experts’ comments. For example, the original item 24 “I have passion for people” was revised to “I show passion for other people’s welfare” because one rater considered that the original expression was too subjective and abstract. For the whole scale, the S-CVI/ave manifested excellent content validity (see Table 1). For each category, the S-CVI/aves for all subscales were also very good (see Table 2).

Table 1. The frequency of I-CVI and the S-CVI/ave for the whole scale

I-CVI	Relevance	Number of items (percentage)	
		Clarity	Representativeness
0.33	0 (0%)	1 (1.0%)	0 (0%)
0.67	5 (5.2%)	10 (10.3%)	3 (3.1%)
1.00	92 (94.8%)	86 (88.7%)	94 (96.9%)
S-CVI/ave	.98	.96	.99

Table 2. The S-CVI/ave for the subscales

No.	Domains	No. of items	S-CVI/ave		
			Relevance	Clarity	Representativeness
	Service provision	4	1.00	1.00	1.00
	Competence	38	.98	.91	.99
	Character	14	.93	.98	.95
	Caring	15	1.00	.98	1.00
	Commitment to continuous improvement	13	1.00	1.00	1.00
	Distributed leadership	13	1.00	1.00	1.00

DISCUSSION

The primary purpose of the present study was to develop the SLB-LF-97 as well as to ensure the measure is relevant to the framework, appropriate and clear, and could represent the concept of service leadership. The construction and validation of a Service Leadership Behavior Scale could help educators and researchers to assess the behaviors and related qualities in an effective service leader as outlined by the HK-SLAM framework [3] in a valid manner. The content validity index (CVI) method based on expert ratings has been widely used to quantify content validity [44]. In the Hong Kong context, researchers also have used this approach to develop and validate scales [e.g., 45, 46]. Both item-level content validity index (I-CVI) and average scale-level content validity index (S-CVI/ave) were calculated in the present study.

Results showed favorable results based on the views of three experts. First, all experts agreed that almost all items were relevant to the HK-SLAM framework and only 5 items needed minor revisions. Second, one item was rated as unclear, ten items were regarded as in need of revision, and the rest 86 items were rated as clear by all three experts. Third, all but 3 items were judged as representative of the framework by all the three raters. Based on the judges’ suggestions, scale developers have carried out revisions of the wording. Therefore,

according to the three experts' judgments, the developed items for the SLB-LF-97 could successfully measure what it was intended to measure. Some sample items for each category are presented in the Appendix.

Theoretically, the development of Service Leadership Behavior Scale is valuable for the leadership literature. A sound understanding of leader behavior and leadership effectiveness can hardly be achieved without research findings based on rigorous assessments. Thus, well-established instruments would help further validate the theoretical propositions and hypotheses of the service leadership model. Although past research has yielded a number of measurements on leader behavior, such as Servant Leadership Behavior Scale [22] and Leader Behavior Description Questionnaire (LBDQ) [47], there is a need to develop new Service Leadership measures because it is a new type of leadership theory. The present study helped with an initial check on the content validity of Service Leadership Behavior Scale and also highlighted the criteria of effective service leadership behaviors.

Practically, a validated measurement is indispensable for effective service leadership education. Although the eight universities in Hong Kong were involved in the Fung Service leadership initiative, no systematic effort has been made to develop appropriate assessment tools to assess service leadership behavior. With the development of the Service Leadership Behavior Scale, the effectiveness of leadership education could then be examined. A simple evaluation strategy would be to collect both pretest and posttest data before and after the training program.

It is noteworthy that there are several limitations of the present study. First, although the involvement of three raters fulfills the minimum requirement of numbers of experts proposed by Lynn [48], future studies could invite more parties to help increase its generalizability, such as scholars from other universities, management professionals who have been trained with service leadership qualities, or students who excellently finished the study of service leadership courses [40]. Second, there is still a need for the continued refinement and validation of the scale. For example, psychometric properties of the scale including reliability and validity should be verified [49]. Furthermore, theoretical and empirical relationships among service leadership behavior, attitude, and knowledge should also be explored. This process could also provide support for the construct validity of the measures. Despite the abovementioned limitations, the present study contributes to our understanding of the service leadership qualities. It also provides another valid measurement to evaluate service leadership education programs [23, 24].

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APPENDIX: SAMPLE ITEMS (WITH ADAPTATION) OF THE SERVICE LEADERSHIP BEHAVIOR SCALE (SLB-LF-97)

Categories	Sample items
C1. Service provision	I provide service to others according to their specific needs. Readiness to serve: A good leader serves others with a genuine heart.
C2. Competence	<i>IQ</i> : When there is any issue that is out of my expectation, I can quickly come up with a workable solution on the spot. <i>EQ</i> : I can manage my negative emotions well so that it will not negatively affect my work. <i>SQ</i> : I have faith to deal with challenges in my life. <i>AQ</i> : Adversity such as failure and setback usually makes me stronger rather than weaker. <i>Passionate about people</i> : I value the well-being of other people. <i>Positive social relationships</i> : I am able to create a positive rapport with other people. <i>Assertiveness</i> : I uphold my own principles and stand firm to reject tasks that I think inappropriate. <i>Collaboration and cooperation with people</i> : I am good at collaborating with other people. <i>Conflict resolution</i> : I negotiate with others when we have conflict. <i>Communication skills</i> : I am able to effectively convey my thoughts and ideas to others.
C3. Character	<i>Integrity</i> : I am honest with people. <i>Fairness</i> : I treat people around me equally without favoritism. <i>Humility</i> : I recognize my limitations. <i>Role model</i> : People regard me as a person with ethical behavior.
C4. Caring	<i>Concern</i> : I am able to feel what other people are experiencing. <i>Provide care</i> : I do good things for other people without expecting them to return the favor.
C5. Commitment to continuous improvement	<i>Self-leadership</i> : I constantly seek to improve my character. <i>Self-reflection</i> : I give time to closely examine my own thoughts and behavior. <i>Life-long learning</i> : I keep learning new skills.
C6. Distributed leadership	<i>Shared decision-making</i> : When making decisions, I welcome critiques from my teammates. <i>Empowerment of teammates</i> : I delegate my power and authority to my teammates to facilitate their work. <i>Trust and respect</i> : I trust my teammates to make good decisions.

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Chapter 139

VALIDATION OF THE SERVICE LEADERSHIP KNOWLEDGE SCALE: FACTORIAL AND CONVERGENT VALIDITY

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ABSTRACT

Building on the previous work regarding the assessment tools developed based on the Service Leadership Education model, this chapter reports a large-scale validation study on the Service Leadership Knowledge Scale. A total of 4,486 Hong Kong undergraduates recruited from eight universities funded by the government were administered the Service Leadership Knowledge Scale (Short-Form) with 50 items (SLK-SF-50). After the initial internal consistency assessment, 40 items were retained to form

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the trimmed version (SLK-SF-40). Confirmatory factor analysis provided support for the hypothesized one-factor structure of the SLK-SF-40 and correlation analyses showed that the scale score was significantly related to different theoretically relevant constructs. The findings demonstrated that the trimmed Service Leadership Knowledge Scale (SLK-SF-40) is an objective measure in gauging individuals' knowledge about Service Leadership.

INTRODUCTION

As a result of the structural shifts in the global economic makeup over the past few decades, Hong Kong has transitioned from a manufacturing-based economy to a service-oriented economy [1]. Not only is such a transition characterized by the *production* aspects such as variability of the production process and GDP compositions and share of employment [1], the *people* aspects such as leaders' and organizations' perceptions of human nature and knowledge or competencies needed to excel also constitute the defining attributes of this transformation [2]. Owing to the evolution from an *Industrial* to a *Service* Age mentality [3], Chung [4, 5] argued passionately for the need of undergraduates in Hong Kong to learn effective leadership in a service economy, which is key to their survival and personal development in today's ultra-competitive business environment.

Against such a backdrop, a large-scale project entitled the "Fung Service Leadership Education Initiative", financially supported by the Victor and William Fung foundation and with the collaborative effort of the Hong Kong Institute of Service Leadership and Management Limited (HKI-SLAM) and the University Grants Committee (UGC), was implemented in eight UGC-funded universities in Hong Kong. Po Chung, Chairman of HKI-SLAM, instigated the concept of Service Leadership education targeting Hong Kong's undergraduates (i.e., SLAM framework). Specifically, the SLAM framework maintains that effective Service Leadership is embodied by "a leader or service provider possessing relevant situational task *competencies* plus being judged by superiors, peers, and subordinates as possessing *character* and exhibiting *care*" [6, p. 354]. Accordingly, the principle "Effective leadership = Moral character * Competencies * Caring disposition", summarized by the equation $E = MC^2$, is highly emphasized within the SLAM framework [6].

As each university would devise her curriculum on the nurturance of effective leadership attributes (i.e., MC^2) [7], it is imperative that systematic evaluation research is conducted to gauge the effectiveness of these independently developed curricula [8]. Particularly, Shek and Lin [9] argued that it is important to assess students' knowledge, attitudes, and behavior to assess an educational program's effectiveness. To facilitate the evaluation of Service Leadership education across universities, the research team at The Hong Kong Polytechnic University (PolyU) developed the long-form Service Leadership Knowledge Scale (SLK-LF-200; 200 items) to measure students' mastery of the fundamental knowledge points on the SLAM framework [10]. The assessment tool includes 200 multiple-choice scale items in seven domains based on the SLAM framework and the relevant literature [10]. These seven domains include the i) general descriptions of Service Leadership, ii) three realms of Service Leadership, iii) the belief that "Everyone can be a leader", iv) the principle " $E = MC^2$ ", v) manufacturing versus service economy, vi) distinction of Service Leadership and other leadership theories, and vii) other knowledge points in SLAM framework.

Utilizing a posttest-only control design, Shek and Lin [9] attempted to examine the criterion-related validity of the SLK-LF-200 with an undergraduate sample. The experimental group consisted of 67 students who took a three-credit “Service Leadership” course at the PolyU, whereas the control group was composed of 94 conveniently recruited PolyU students who had never taken the course. Inspection of each item revealed that the former significantly outscored the latter on 63 items. A follow-up inspection of these 63 criterion-valid items, led by the first author of this chapter, resulted in a further removal of 13 items due to duplication or face validity concerns. Ultimately, 50 items were retained to form the short-form of the Service Leadership Knowledge Scale (SLK-SF-50).

While Shek and colleagues [9, 10] pioneered the criterion and content validation of the initial knowledge scale (i.e., SLK-LF-200), the dimensionality and convergent validity of the short form (i.e., SLK-SF-50) remain to be ascertained. Against such a background, utilizing the responses of 4,486 undergraduates in Hong Kong, this chapter is primarily concerned with the psychometric properties of the 50-item SLK-SF-50 based on a large sample of students. Despite the fact that seven dimensions were theorized to be subsumed under the original scale (SLK-LF-200), the removal of three-quarters of items suggests that a re-examination of the trimmed scale’s (i.e., SLK-SF-50) dimensionality is necessary. Considering that the knowledge scale operationalizes respondents’ understanding of Service Leadership as “knowledge points” they acquired, and that a composite score which denotes overall proficiency is computed [9, 10], there is an implicit assumption that the knowledge scale is indeed unidimensional as the items cohere around one latent “knowledge” dimension [11, 12]. Hence, the proposed factor structure of the scale is a one-factor structure of the SLK-SF-50.

Convergent validity, which can be derived from “correlations with measures purporting to measure related constructs” [13], is also crucial in scale development as it informs whether the instrument can adequately probe into the target construct [14]. Utilizing several validated measures of relevant constructs outlined in the SLAM framework [see 15], including i) *Servant Leadership*, ii) *moral self-concept*, iii) *leadership efficacy*, and iv) *empathy*, this study sought to establish the convergent validity of the SLK-SF-50 via examining its correlations with these external measures.

OUR STUDY

Altogether 4,486 undergraduates (mean age: 20.47 years; SD: 1.67) from eight UGC-funded institutions completed the Short-Form Service Leadership Scale (SLS) validation study via an online platform. There were 1,517 (33.8%) male and 2,969 (66.2%) female respondents. The majority were aged 20 to 24 years (68.4%), had neither taken any credit-bearing Service Leadership (SL) subjects (74.3%) nor participated in any non-credit-bearing SL events a priori (82.0%), had previous work experience (91.4%), and had formerly served in leadership positions (61.4%). Additionally, 77.1% sat the Hong Kong Diploma of Secondary Education Examination (HKDSE). Table 1 highlights the demographic information for the present sample.

Procedures

All participants were administered the SLS online survey via the mySurvey@PolyU electronic survey system in March 2017. Students were asked to complete the survey in a self-administered fashion. Each participating university had her version of the online survey because the additional information asked is not the same. While the scale items were identical throughout, there were items probing into the respondents' demographics (e.g., faculty or school) and contact information of the person-in-charge that were unique to each university. The research objectives and guidelines on how to complete the questionnaire were detailed in the invitation emails and on the survey webpage. It was reiterated to students that it would take 45 to 60 minutes to conscientiously complete the whole survey. Each participant was given a supermarket voucher by the end of the study valued at HK\$100 or US\$12.80. Students indicated their consent or refusal to participate at the opening page.

Table 1. Basic demographic information for the current working sample (N = 4,486)

Demographic variables		N= 4,486
Valid responses from eligible participants from:	The Hong Kong Polytechnic University (PolyU)	1,000 (22.3%)
	The Chinese University of Hong Kong (CUHK)	505 (11.3%)
	The Education University of Hong Kong (EdUHK)	500 (11.1%)
	Hong Kong Baptist University (HKBU)	517 (11.5%)
	City University of Hong Kong (CityU)	464 (10.3%)
	Lingnan University (LU)	500 (11.1%)
	The University of Hong Kong (HKU)	500 (11.1%)
	Hong Kong University of Science and Technology (HKUST)	500 (11.1%)
Gender	Male	1,517 (33.8%)
	Female	2,969 (66.2%)
Age Group	15 to 19 years	1,344 (30.0%)
	20 to 24 years	3,070 (68.4%)
	25 to 29 years	69 (1.5%)
	30 years or above	3 (0.1%)
Year commencing on one's undergraduate study	2016	1,533 (34.2%)
	2015	1,164 (25.9%)
	2014	897 (20.0%)
	2013	742 (16.5%)
	2012 or before	150 (3.3%)
Number of credit-bearing Service Leadership (SL) courses taken*	0	2,962 (74.3%)
	1	951 (23.9%)
	2	71 (1.8%)
	3	2 (0.1%)
Number of non-credit-bearing SL events participated	0	3,680 (82.0%)
	1	506 (11.3%)
	2	230 (5.1%)
	3	62 (1.4%)
	4 or more	8 (0.2%)
Other leadership training taken	Yes	1,955 (43.6%)
	No	2,531 (56.4%)
Previous work experience	With work experience	4,102 (91.4%)
	Without work experience	384 (8.6%)
Self-proclaimed knowledge of Service Leadership	No knowledge	916 (20.4%)
	Little knowledge	1,590 (35.4%)
	Some knowledge	1,774 (39.5%)
	A lot of knowledge	195 (4.3%)
	All the knowledge	11 (0.2%)

Demographic variables		N= 4,486
Leadership position ever taken	Yes	2,753 (61.4%)
	No	1,753 (38.6%)
Entrance Exam	Hong Kong Diploma of Secondary Education Examination (HKDSE)	3,484 (77.1%)
	Hong Kong Advanced Level Examination (HKALE)	71 (1.6%)
	National College Entrance Examination (NCEE) in mainland China	221 (4.9%)
	Associate Degree/Higher Diploma in Hong Kong	495 (11.0%)
	Others (e.g., GCE A-Levels, IB, etc.)	215 (4.8%)
Grade Point Average	Mean converted Grade Point Average out of 4.00 (SD)	2.89 (0.45)
Time of completion	Average time (in minutes) taken to complete the survey (SD)	69.98 (383.13)

Note. *EdUHK does not provide any credit-bearing SL modules for her students.

Table 2. Number of cases retained in the main analyses

Participating universities	“Completed” cases as per record in mySurvey	Declined	Multiple participations	Deleted due to ineligibility of participants	Cases retained for the main analyses
EdUHK	506	0	6	0	500
CityU	477	0	3	10	464
HKUST	514	1	12	1	500
CUHK	511	2	0	4	505
LU	509	0	6	3	500
HKU	508	1	2	5	500
HKBU	522	2	0	3	517
PolyU	1008	0	4	4	1000
Total	4555	6	33	30	4486

Table 3. Three sample items of the SLK-SF-50

Items	Options	Model Answer
8. A manager under the service economy wants to hire someone. Based on the Service Leadership model, which of the following advice would you give him/her?	A. Hire for qualifications, train for character B. Hire for character, train for skills C. Hire for attitude, train for character D. Hire for efficiency, train for mindset	B
22. In the four options below, which one belongs to an attribute of intelligence quotient (IQ)?	A. Raw power B. Attractiveness C. Sexual orientation D. Problem-solving skills	D
37. Which of the following statements is inconsistent with the concept of “respect”?	A. Showing off one’s strength B. Accepting and appreciating differences C. Accepting and appreciating oneself D. Serving as a key element in nurturing authentic relationship	A

Note. All sample items were slightly re-phrased due to copyright concern.

Participants’ completed electronic responses were downloaded as an EXCEL file for a preliminary data cleaning process before being converted to an SPSS file and a DAT file for statistical analyses. Several procedures were involved regarding the 4,555 completed responses as recorded. First, six cases of which students refused to participate were removed. Thirty more cases were excluded due to ineligibility of participants. These included a) participants completing the wrong survey (i.e., University A’s students completed the survey designed for University B’s students), and b) participants revealing themselves to be

non-undergraduates (e.g., postgraduates) in those open-ended questions. Furthermore, thirty-three cases of multiple participations—as per inspection of participants' student ID—were excluded from the main analyses. Accordingly, 4,486 cases were retained for further analyses. Table 2 features a breakdown of the number of cases retained for the present sample.

Instruments

The current questionnaire comprised items of the short-forms of the Service Leadership scales, including that of i) the Service Leadership Attitude Scale (SLA-SF-73; 73 items), ii) the Service Leadership Behavior Scale (SLB-SF-65; 65 items), and iii) the Service Leadership Knowledge Scale (SLK-SF-50; 50 items). The present chapter is primarily concerned about the validation of the 50-item SLK-SF-50.

Developed based on the HKI-SLAM framework, twenty-five principles of Service Leadership [16], twelve dimensions of a Service Leader [3] and the relevant literature [e.g., 15], a 200-item Service Leadership Knowledge Scale (i.e., SLK-LF-200) was designed to “capture the essential knowledge points of Service Leadership model in the format of multiple-choice questions” [10]. Fifty items were ultimately retained to form the SLK-SF-50, following Shek and Lin's [9] criterion-validation study and a follow-up item screening. Table 3 features three sample items and the model answers. Participants' responses were coded based on accuracies. Each *correct* answer would earn the participants one point, whereas an *incorrect* answer entitles them to zero point. The scale items are in English.

Several well-validated inventories from the leadership and personality literature were also utilized, with the objective to establish the convergent validity of the SLA-SF-73, the SLB-SF-65, and the SLK-SF-50. These external criterion scales included the Revised Servant Leadership Profile (RSLP; 20 items), Leadership Efficacy Scale (LEF; 8 items), the Moral Self-Concept (MSC; 8 items), and the Interpersonal Reactivity Index (IRI; 14 items). A few forced-choice and open-ended items assessing students' background demographics were also included.

1. **Revised Servant Leadership Profile (RSLP):** Developed by Wong and Page [17], the RSLP measures *Servant Leadership* as a multidimensional construct. Twenty items from five factors relevant to the SLAM framework—namely, i) *Empowering and developing others* (five items), ii) *Serving others* (seven items), iii) *Open, participatory leadership* (two items), iv) *Inspiring leadership* (two items), and v) *Integrity and authenticity* (four items)—were adopted at present. Items were rated on a seven-point Likert scale, with a higher score indicating a greater alignment with a Servant Leader's mentality. Reliability analyses showed an excellent internal consistency of RSLP ($\alpha = 0.94$; mean inter-item correlations = 0.46).
2. **Leadership Efficacy Scale (LEF):** LEF was developed by Murphy [18] as a measure of one's perceived “generalized capability in the leadership role” [19, p. 270]. The LEF, which was utilized in the present study, entails eight items which are rated on a five-point Likert scale. Higher scores indicate one's perceived capability that he/she could lead effectively. Reliability analyses highlighted the acceptable

internal consistency of LEF on the present sample ($\alpha = 0.72$; mean inter-item correlations = 0.25).

3. **Moral Self-Concept (MSC):** As a subscale under the Chinese Adolescent Self-Esteem Scales developed and validated by Cheng [20], the eight-item MSC measures participants' self-evaluation on facets of i) *Conduct and virtues*, ii) *Self-control and discipline*, and iii) *Altruism*. A slightly modified, English-translated version of the MSC—which operates on a seven-point Likert scale—was adopted in the present study. A higher score reflects a greater perceived importance of *morality* to oneself, which is a fundamental attribute of effective Service Leadership according to the SLAM framework [21]. Reliability analyses revealed a high internal consistency among the items ($\alpha = 0.83$; mean inter-item correlations = 0.44).
4. **Interpersonal Reactivity Index (IRI):** Developed by Davis [22], the IRI constitutes the most widely adopted assessment tool of empathy. Not only was the IRI validated cross-culturally [e.g., 23, 24], some suggested that it was the sole 'published measure that allows a multi-dimensional assessment of empathy' [25, p. 620]. Two subscales of IRI, namely i) *Perspective Taking* (PT; seven items) and ii) *Empathic Concern* (EC; seven items), were adopted for the current study. Items were rated on a five-point Likert scale, with a higher score indicating a "higher level of empathy which is an essential quality of ethical leadership" [26, p. 44]. Component scores for subscales PT and EC were computed alongside a composite IRI score. Cronbach's alpha coefficients of the subscales PT, EC, and the composite IRI score were 0.58, 0.62, and 0.74, respectively.

Data Analysis Plan

SPSS Statistics version 24.0 (IBM) was used for the descriptive statistical analyses (i.e., demographics) and examination of internal consistency and construct validity. Owing to the dichotomous nature (i.e., *correct* versus *incorrect*) of the coded responses, assessment of the factorial structure of the SLK-SF-50 (i.e., Confirmatory factor analysis [CFA]) was conducted using Mplus version 6.12 [27].

We first inspected the reliability indices of the 50-item SLK-SF-50. A Kuder-Richardson 20 coefficient of 0.93 was observed, suggesting excellent reliability. Ten items with item-total correlations below 0.30 were excluded from the ensuing CFA. We then re-examined the reliability indices of the 40-item, trimmed SLK-SF-50 (i.e., SLK-SF-40 hereafter). Regarding CFA, the proposed one-factor structure was tested using the robust weighted least squares (WLSMV) estimator, which is appropriate for categorical items [28].

We examined the model fit using several indices including, a) Bentler-Bonett Nonnormed Fit Index (NNFI), b) comparative fit index (CFI), c) root mean square error of approximation (RMSEA; including also the 90% confidence interval [90% CI]), and d) weighted root-mean-square residual (WRMR). Based on the recommendations in the literature [29-31], a model with a NNFI exceeding 0.95, a CFI greater than 0.95, a RMSEA lower than 0.05 (with an upper CI value below 0.08), and a WRMR smaller than 0.90 would be considered an 'excellent' fit. Models with a 'good' fit should produce indices close to the above standards [28]. We also reported the STDY metric for each item, which denotes the change in standard

deviation units of outcomes (as per unit change in predictor). The STDY metric represents each item's standardized factor loading [32].

Lastly, the total scale score was correlated with the different criterion measures. Considering that the knowledge preached in the Service Leadership curriculum covers domains on *Servant Leadership*, *leadership efficacy*, *morality*, and *empathy*, we would predict a positive correlation between the SLK-SF-40 with each of these external criterion scales (and subscales). Correlational analyses with other Service Leadership scales (and subscales) under validation were also administered. Data of the entire sample ($N = 4,486$) were utilized throughout every step of the present validation study. Specifically, we hypothesized that the SLK-SF-40 would be positively and significantly correlated with i) RSLP, ii) LEF, iii) MSC, and iv) IRI (subscales EC and PT). We expected the SLK-SF-40 to also correlate positively with the validated versions of the SLA-SF-73 and SLB-SF-65 (and the subscales), considering that all these scales were constructed to assess the same underlying topic with different focuses (i.e., knowledge, attitude, and behavior).

FINDINGS

After removing ten items with low item-total correlations, reliability analyses revealed the excellent internal consistency of the 40 items retained ($\alpha = 0.94$, mean inter-item correlations = 0.28). All items had a corrected item-total correlation above 0.31.

Confirmatory Factor Analysis

Table 4 presents the model-fit indices of the proposed single-factor structure of SLK-SF-40, alongside the criteria for goodness-of-fit evaluation as abovementioned. Overall, the NNFI, CFI, and RMSEA all suggested that the present proposed one-factor structure fit excellently with the current data [29-31], while the WRMR exceeded the proposed cut-off of 0.90, suggesting a model misspecification [33]. Nevertheless, Newsom [34] cautioned against the sole reliance on WRMR as the only indicator of fit as it “does not always give sensible results (p. 3)”, and there is evidence [e.g., 35] that the three other metrics adopted at present (i.e., NNFI, CFI, and RMSEA) could perform well with categorical model estimations. Taken together, the examination of the goodness-of-fit indices offers preliminary support to the one-factor solution of SLK-SF-40.

We also scrutinized the individual parameter estimates of the present proposed one-factor solution. Table 5 presents every item's i) standardized factor loading (i.e., STDY estimates), ii) R-squared, iii) accuracy rate, iv) residual variance, and v) item-total correlations. As addressed in the table, the factor loadings and R-squared of all the SLK-SF-40 items were positive and significant at $p < .001$. The STDY estimates ranged from moderate to strong (0.32 to 0.90). No spurious findings were observed regarding the standard errors. These findings, in conjunction with the goodness-of-fit indices (see Table 4), again gave support to the proposed one-factor structure of the knowledge scale. Accordingly, this single-factor model was accepted as the final factorial solution, and each respondent's SLK-SF-40 score was computed via a simple summation of their *correct* responses to the 40 items.

Table 4. Model fit indices for the one-factor structure of SLK-SF-40

Model Tested	χ^2	Df	WRMR	NNFI	CFI	RMSEA (pclose)	RMSEA (90% C.I.)
One-factor	3,492.44	740	1.725	0.985	0.984	0.029 (1.00)	0.028/0.030
Criterion for goodness-of-fit	-	-	≤ 0.90	≥ 0.95	≥ 0.95	≤ 0.05	≤ 0.08

Note. WRMR= weighted root-mean-square residual; NNFI= Bentler-Bonett Nonnormed Fit Index; CFI= comparative fit index; RMSEA= root mean square error of approximation; pclose= probability of RMSEA ≤ 0.05 ; 90% CI= 90% Confidence Intervals (lower value/ upper value).

Table 5. Individual parameter estimates of the one-factor SLK-SF-40 (N= 4,486)

Items	Mean* (Standard Deviation)	Accuracy Rate**	Standardized factor loadings	R-squared	Residual variance	Corrected Item-total Correlations
SLK-01	0.391 (0.488)	39.12%	0.528	0.279	0.721	0.396
SLK-02	0.751 (0.433)	75.06%	0.545	0.297	0.703	0.396
SLK-03	0.830 (0.376)	83.01%	0.646	0.417	0.583	0.433
SLK-05	0.742 (0.438)	74.19%	0.537	0.289	0.711	0.391
SLK-06	0.439 (0.496)	43.87%	0.419	0.175	0.825	0.316
SLK-08	0.612 (0.487)	61.21%	0.570	0.325	0.675	0.444
SLK-10	0.447 (0.497)	44.72%	0.597	0.356	0.644	0.461
SLK-11	0.523 (0.500)	52.25%	0.522	0.272	0.728	0.399
SLK-12	0.607 (0.489)	60.65%	0.535	0.287	0.713	0.415
SLK-13	0.740 (0.439)	73.99%	0.831	0.690	0.310	0.621
SLK-14	0.592 (0.492)	59.16%	0.718	0.515	0.485	0.565
SLK-15	0.396 (0.489)	39.59%	0.676	0.456	0.544	0.509
SLK-16	0.604 (0.489)	60.43%	0.878	0.770	0.230	0.699
SLK-17	0.673 (0.469)	67.32%	0.869	0.755	0.245	0.682
SLK-18	0.597 (0.490)	59.74%	0.901	0.813	0.187	0.726
SLK-19	0.673 (0.469)	67.32%	0.558	0.311	0.689	0.422
SLK-20	0.624 (0.484)	62.44%	0.838	0.703	0.297	0.667
SLK-21	0.675 (0.468)	67.50%	0.570	0.324	0.676	0.433
SLK-22	0.685 (0.465)	68.46%	0.760	0.578	0.422	0.577
SLK-23	0.619 (0.486)	61.93%	0.819	0.672	0.328	0.652
SLK-24	0.542 (0.498)	54.19%	0.603	0.363	0.637	0.469
SLK-25	0.568 (0.495)	56.82%	0.755	0.570	0.430	0.598
SLK-26	0.594 (0.491)	59.38%	0.748	0.559	0.441	0.583
SLK-28	0.664 (0.472)	66.41%	0.316	0.100	0.900	0.653
SLK-30	0.672 (0.469)	67.23%	0.833	0.693	0.307	0.568
SLK-31	0.536 (0.499)	53.63%	0.731	0.534	0.466	0.573
SLK-32	0.552 (0.497)	55.19%	0.739	0.546	0.454	0.522
SLK-33	0.399 (0.490)	39.88%	0.662	0.438	0.562	0.494
SLK-34	0.536 (0.499)	53.59%	0.651	0.424	0.576	0.665
SLK-36	0.375 (0.484)	37.47%	0.820	0.673	0.327	0.462
SLK-38	0.429 (0.495)	42.93%	0.617	0.381	0.619	0.478
SLK-39	0.358 (0.480)	35.84%	0.618	0.382	0.618	0.318
SLK-41	0.608 (0.488)	60.81%	0.430	0.185	0.815	0.616
SLK-42	0.514 (0.500)	51.38%	0.772	0.596	0.404	0.580
SLK-44	0.343 (0.475)	34.26%	0.731	0.534	0.466	0.366
SLK-45	0.526 (0.499)	52.56%	0.497	0.247	0.753	0.591
SLK-46	0.649 (0.477)	64.87%	0.757	0.572	0.428	0.437
SLK-47	0.539 (0.499)	53.92%	0.563	0.317	0.683	0.343
SLK-48	0.363 (0.481)	36.31%	0.442	0.196	0.804	0.314
SLK-50	0.566 (0.496)	56.58%	0.421	0.177	0.823	0.575

Note. * Each correct (incorrect) response was coded "1" ("0"). ** Accuracy Rate = (Number of correct responses)/ (Total responses, i.e., 4,486) *100%. All standardized factor loadings and R² metrics were statistically significant at $p < .001$ (two-tailed).

Validity Analyses: Correlation with External Criterion Scales (and Subscales)

Confirming our hypotheses, findings of the correlational analyses (see Table 6) indicated that the SLK-SF-40 scores correlated significantly (all $ps < .001$) and positively with all external criterion scales (and subscales). Utilizing the *cocor* statistical package [36] which allows comparisons of strengths of association across two pairs of correlation coefficients e.g., Steiger’s [37] computation of z-score using average correlations), the findings (see Table 6) indicated that amongst the significant associations, the SLK-SF-40 correlated most strongly with the *Interpersonal Reactivity Index* ($r = 0.438$, $N = 4,486$) and least with the *Leadership Efficacy* ($r = 0.125$, $N = 4,486$). These findings should give substance to the convergent validity of the SLK-SF-40 as it was demonstrated to relate positively and significantly to a myriad of well-validated measures (e.g., IRI and MSC) on constructs that were highly emphasized in the SLAM framework (e.g., empathy and morality).

Table 6. Correlations between SLK-SF-40 and the presently adopted external criterion scales

	Correlations with the external criterion scales (and subscales)		Z-scores of difference between r s with SLK-SF-40 [36, 37]:				
	α (MITC)	r	MSC	LEF	IRI	IRI-EC	IRI-PT
1. RSLP	0.94 (0.46)	0.200***	-16.17***	4.83***	-16.92***	-14.15***	-10.09***
2. MSC	0.83 (0.44)	0.361***	—	15.11***	-6.25***	-4.31***	1.12
3. LEF	0.72 (0.25)	0.125***	—	—	-18.83***	-16.76***	-13.09***
4. IRI	0.74 (0.17)	0.438***	—	—	—	2.97**	12.91***
4a. IRI- EC	0.62 (0.19)	0.419***	—	—	—	—	5.64***
4b. IRI- PT	0.58 (0.19)	0.346***	—	—	—	—	—

Note. ** $p < .01$ (two-tailed). *** $p < .001$ (two-tailed). MITC: Mean inter-item correlations. RSLP: Revised Servant Leadership Profile; MSC: Moral Self-Concept; LEF: Leadership Efficacy; IRI: Interpersonal Reactivity Index; IRI-EC: Subscale “Empathic Concern”; IRI: PT: Subscale “Perspective Taking”.

Validity Analyses: Correlation with Other Service Leadership Scales under Validation

As detailed in Table 7, the SLK-SF-40 correlated significantly (all $ps < .001$) and positively with both composite scores of the six-factor, 38-item Service Leadership Behavior (i.e., SLB-SF-38) scale ($r = 0.178$, $N = 4,486$) and the eight-factor, 46-item Service Leadership Attitude (i.e., SLA-SF-46) scale ($r = 0.337$, $N = 4,486$). Discussions regarding the validations of both SLB-SF-38 and SLA-SF-46 are featured in two other papers within the current issue. The SLK-SF-40 also correlated positively with almost all the subscales of SLB-SF-38 and SLA-SF-46. These findings are consistent with our hypotheses that the three concurrently administered Service Leadership scales are positively and significantly associated with one another.

Furthermore, comparison via the *cocor* package highlighted that the strengths of correlations between SLK-SF-40 and SLA-SF-46 (and the subscales) were overall significantly greater ($ps < .05$) than those of SLK-SF-40 and SLB-SF-38 (and its subscales).

Table 7. Correlations between SLK-SF-40 and other Service Leadership scales (and subscales) under validation

Correlations with other Service Leadership Scales under validation		Z-scores of difference between rs with SLK-SF-40 [36, 37] ^a															
	r	α (MITC)	SLB-SF-38-F2	SLB-SF-38-F3	SLB-SF-38-F4	SLB-SF-38-F5	SLB-SF-38-F6	SLB-SF-38-Total	SLA-SF-46-F1	SLA-SF-46-F2	SLA-SF-46-F3	SLA-SF-46-F4	SLA-SF-46-F5	SLA-SF-46-F6	SLA-SF-46-F7	SLA-SF-46-F8	SLA-SF-46-Total
1.SLB-SF-38-F1	0.91 (0.53) 0.203***	-5.93	12.03	-0.20 ^{n.s.}	6.39	21.47	3.32	-7.57	-8.78	3.06	8.76	-11.35	-2.05	8.91	-10.53	-12.44	
2.SLB-SF-38-F2	0.87 (0.42) 0.269***	—	16.39	5.56	10.44	26.85	11.54	-3.36	-5.08	8.01	13.51	-7.81	2.31	13.37	-7.42	-8.87	
3.SLB-SF-38-F3	0.87 (0.50) 0.047**	—	—	-12.57	-5.26	9.64	-14.88	-16.03	-17.07	-6.42	-0.48 ^{n.s.}	-18.95	-10.93	0.53 ^{n.s.}	-17.40	-20.59	
4.SLB-SF-38-F4	0.86 (0.55) 0.205***	—	—	—	6.06	20.81	2.92	-7.19	-8.71	3.18	8.77	-11.25	-1.82 ^{n.s.}	9.17	-10.59	-12.14	
5.SLB-SF-38-F5	0.87 (0.56) 0.117***	—	—	—	—	13.36	-5.80	-12.20	-13.09	-2.22	3.35	-15.34	-7.05	4.06	-14.54	-16.32	
6.SLB-SF-38-F6	0.85 (0.65) -0.097***	—	—	—	—	—	-25.32	-23.05	-24.12	-15.34	-9.03	-25.78	-18.11	-7.35	-23.05	-28.03	
7.SLB-SF-38-Total	0.96 (0.37) 0.178***	—	—	—	—	—	—	-9.59	-10.91	1.61 ^{n.s.}	7.67	-13.46	-3.74	7.92	-11.54	-15.12	
8.SLA-SF-46-F1	0.90 (0.46) 0.315***	—	—	—	—	—	—	—	-2.35	12.83	18.20	-5.98	6.73	15.51	-4.97	-8.93	
9.SLA-SF-46-F2	0.87 (0.47) 0.337***	—	—	—	—	—	—	—	—	14.30	18.90	-3.52	7.80	17.93	-3.96	-5.44	
10.SLA-SF-46-F3	0.86 (0.47) 0.155***	—	—	—	—	—	—	—	—	—	8.28	-17.20	-5.85	7.01	-12.12	-24.59	
11.SLA-SF-46-F4	0.85 (0.53) 0.055***	—	—	—	—	—	—	—	—	—	—	-21.46	-11.92	1.05 ^{n.s.}	-16.15	-27.97	
12.SLA-SF-46-F5	0.83 (0.56) 0.373***	—	—	—	—	—	—	—	—	—	—	—	11.05	19.00	-2.09	-0.54 ^{n.s.}	
13.SLA-SF-46-F6	0.82 (0.49) 0.235***	—	—	—	—	—	—	—	—	—	—	—	—	10.41	-8.53	-13.48	
14.SLA-SF-46-F7	0.70 (0.54) 0.037***	—	—	—	—	—	—	—	—	—	—	—	—	—	-18.97	-22.18	
15.SLA-SF-46-F8	0.79 (0.42) 0.411***	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1.92 ^{n.s.}	
16.SLA-SF-46-Total	0.93 (0.28) 0.377***	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	

Note. ^aUnless otherwise specified by the superscript “n.s.” which denotes statistical non-significance, all other Z-scores of difference were significant at $p < .05$ (two-tailed) (i.e., $|Z\text{-score}| > 1.96$). ** $p < .01$ (two-tailed). *** $p < .001$ (two-tailed). MITC: Mean inter-item correlations. SLB-SF-38-Total: Scale score of the six-factor, 38-item Service Leadership Behavior (SLB) Scale; SLA-SF-46-Total: Scale score of the eight-factor, 46-item Service Leadership Attitude (SLA) Scale; SLB-SF-38-F1: SLB Factor 1 “Self-improvement and self-reflection”; SLB-SF-38-F2: SLB Factor 2 “People and principles orientation”; SLB-SF-38-F3: SLB Factor 3 “Resilience”; SLB-SF-38-F4: SLB Factor 4 “Social competence”; SLB-SF-38-F5: SLB Factor 5 “Problem-solving”; SLB-SF-38-F6: SLB Factor 6 “Mentorship”; SLA-SF-46-F1: SLA Factor 1 “Vision and competence”; SLA-SF-46-F2: SLA Factor 2 “People orientation”; SLA-SF-46-F3: SLA Factor 3 “Caring disposition”; SLA-SF-46-F4: SLA Factor 4 “Ethical role model”; SLA-SF-46-F5: SLA Factor 5 “Social competence”; SLA-SF-46-F6: SLA Factor 6 “Self-understanding and reflection”; SLA-SF-46-F7: SLA Factor 7 “Positive view about human beings”; SLA-SF-46-F8: SLA Factor 8 “Unchangeable and dark human nature”.

These findings suggested that while individuals knowing more about Service Leadership may be more prone to *think* or *feel* (i.e., attitude) and to *act* (i.e., behavior) as an effective Service Leader, there seems to be a weaker tie between “knowing” and “practicing what one was preached”.

DISCUSSION

The primary purpose of this study was to examine the factorial validity and convergent validity of the Service Leadership Knowledge Scale in a sample of Hong Kong undergraduates. Reliability analyses highlighted the excellent internal consistency amongst the 40 items which formed the SLK-SF-40. Consistent with our predictions, results of the CFA corroborated the unidimensionality of the SLK-SF-40, as both the goodness-of-fit indices and individual parameter estimates indicated that the proposed one-factor solution fits excellently with the data. Furthermore, the SLK-SF-40 correlated significantly and positively with all the external criterion scales. The SLK-SF-40 also correlated positively with the two other Service Leadership scales. Both these correlational findings offer convergent evidence for the SLK-SF-40, as instruments measuring i) the same underlying construct (i.e., SLB-SF-38 and SLA-SF-46) and ii) theoretically relevant constructs (i.e., IRI, MSC) all related consistently and positively to the SLK-SF-40. In summary, the present findings underscore the adequacy of SLK-SF-40 in measuring students' knowledge in Service Leadership.

While the findings overall support the validity and reliability of the SLK-SF-40, there are observations worthy of attention. First, the effect sizes of the *Knowledge-Servant Leadership* correlation ($r = 0.20$) and the *Knowledge-Efficacy* association ($r = 0.13$) are noticeably smaller compared to that of the *Knowledge-Empathy* ($r = 0.44$) and the *Knowledge-Moral Self-concept* ($r = 0.36$) associations. These findings may reflect the differential coverage of the constructs within the SLAM framework. As discussed above, *Moral character* constitutes the cornerstone of the SLAM framework (i.e., the “ $E = MC^2$ ” principle). Likewise, empathy is extensively covered as a fundamental attribute of *Caring Disposition* [38]. *Servant Leadership* and *Leadership Efficacy*, by contrast, are not as central to the SLAM framework despite being two highly relevant constructs. In particular, the disregard of self-interest, which is a hallmark attribute in the *Servant Leadership* theory [39], is even at odds with a Core Belief of the SLAM framework [21].

Second, comparison of the correlational strengths underlined a discrepancy between the *Knowledge-Attitude* ($r = 0.34$) tie vis-à-vis the *Knowledge-Behavior* association ($r = 0.18$), implying that Service Leadership may be easier-said-than-done. However, as theorized in the Theory of Planned Behavior (TPB) [39], while *attitude* and perceived behavioral control (which involves *knowledge*) constitute two key contributors of behavioral intention (BI), BI is also determined by a perception of whether a particular behavior would lead to others' approval (i.e., normative beliefs [NB]). In other words, although both *attitude* and *knowledge* are essential to the formation of intent to behave like a Service Leader, there is an additional element in NB (perception of whether acting as a Service Leader would be well-received by relevant others) to be taken into consideration. Hence, the current observed differential correlation strengths amongst knowledge, attitude, and behavior are actually in line with the TPB [39]. This would be an interesting direction for future research.

As a continuation of the PolyU research team's effort, the current study marks the concluding step of the creation (plus validation) of the assessment tool aimed to measure people's understanding of Service Leadership. Specifically, the present paper came up with a much-shortened version of the knowledge scale (i.e., SLK-SF-40) which was demonstrated to be valid and reliable. Not only is a shorter survey easier to administer, crucially, meta-analytic review findings had also consistently pointed to how shorter questionnaires are linked to higher response rates and avoidance of low-quality data due to response burden [40, 41]. In response to Shek et al.'s [10] appeal to develop an assessment instrument which facilitates cross-institutional comparisons on students' understanding of the SLAM framework, alongside adding to the literature on systematic evaluation of Service Leadership education, the present study produced a refined, "participant-friendly", and most importantly, a psychometrically sound measurement tool in the SLK-SF-40.

All in all, in conjunction with the previous studies, there is a strong evidence base for the different versions of the Service Leadership Knowledge Scale. In future, more work could be done to further examine the criterion-related validity of the different versions of the scale. Besides, the relationship between Service Leadership knowledge and actual Service Leadership behavior deserves investigation using longitudinal research designs.

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Chapter 140

VALIDATION OF THE SERVICE LEADERSHIP ATTITUDE SCALE IN HONG KONG

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ABSTRACT

To cultivate leadership of university students under the service economy, there is a need to help them develop positive attitude towards service leadership. Unfortunately, validated service leadership attitude measures do not exist. In this chapter, validation of the Service Leadership Attitude Scale was reported. Based on the responses of 4,486 students, internal consistency, convergent validity and construct validity of the 73-item Service Leadership Attitude Scale (SLA-SF-73) were examined. Exploratory factor analyses further showed that seven stable factors (Vision and Competence, Social Competence, Caring Disposition, People Orientation, Self-Reflection and Self-Understanding, Positive Views about Human Beings, and Ethical Role Models) were abstracted from the final 46-item scale (SLA-SF-46E), providing support for the factorial validity of the scale.

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INTRODUCTION

Hong Kong has shifted from a manufacture-oriented economy to a service economy since the 80s of the last century [1]. Till the end of 2016, four service-oriented pillars including banking and investment services, tourism services, logistics transportation and business support services have become the key engines driving the Hong Kong economy [2]. The number of working adults in the service-oriented sectors has increased from 3.14 million in 2011 to 3.31 million in 2016, accounting for 84.57% of all working adults [2], indicating the importance of service industries to the Hong Kong economy. Previous studies have devoted increasing attention to human capital and organizational climate in service sectors [3, 4], which are two primary mechanisms to obtain organizational success by influencing employees [5, 6]. Although traditional research emphasizes the positive influence of the bundles of Human Resource Management (HRM) Practice on human capital and organizational climate, Jiang and his colleagues [7] found other than HRM, both human capital and organizational climate are also positively shaped by a new ideology of leadership, service leadership, in service-economies.

Jiang and his colleagues [7] adopted the definition of service leadership in the study of Schneider and his colleagues [8], which claimed service leadership is essentially a behavioral focus on improving the service quality of an organization. Chung [9] extended the scope (i.e., not service manufacturing) and claimed that service leadership is essentially a behavioral focus on consistently offering quality personal service to meet the demand at individual, organizational, and social levels. Based on the framework of the Hong Kong Institute of Service Leadership and Management Limited (HKI-SLAM) [10], service leadership is featured by seven core beliefs which increase the competitiveness of the service-oriented economy in Hong Kong. First, service leaders believe service leadership is the service satisfying the needs of stakeholders at different levels, including individuals, groups, communities, systems and environments [10], which well responds to the service-dominant logic in the service-oriented economy that all social units compete with service, and compete through service [11]. Second, service leaders believe everyone can be a leader to improve service effectiveness and quality anytime [10], which spurs service innovation as the core competency of a service organization [12]. Third, service leadership supports the notion that leadership effectiveness and service satisfaction are jointly determined by task competencies, unique character and exhibiting care [10], which promotes the effectiveness of relationship marketing and emphasizes on keeping loyal customers by setting their satisfaction as priorities instead of emphasizing on the number of transactions completed. Researchers [1, 13] asserted that this is the most common strategy to retain customers in the service organizations. Fourth, service leaders believe that service leadership aims to ethically promote the competitiveness, abilities, and willingness of offering service to others [10], which is a particular prerequisite of improving service quality in Hong Kong, where the economic return of service does not wholly depend on service quality. Fifth, service leadership is focused on consistently creating personal service to change the life of others, responding to the transformation of profit model from indiscriminate commodities in the manufacture-oriented economy to customized service in the service-oriented economy [14]. Sixth, service leadership is seen as the longest and most competitive business model [10], which can be adopted as a main business model for Hong Kong, considering a majority of its domestic

production is supported by service-related industries. Last, other than specific skills and knowledge, leadership competencies, appropriate character strengths and caring social dispositions are also key requirements for high status positions in the service-oriented economy [10], which highlight that the soft skills are valuable assets in leading people-oriented projects in the service organizations [11].

In order to maintain the competitiveness of the service-oriented economy of Hong Kong in the global market, strengthening the service leadership in the service organizations is a necessity. With the requirement of cognitive and social-emotional competence, service leadership should be introduced before joining the labor market. Hence, the best time to conduct the related education is during tertiary education. To achieve this goal, HKI-SLAM and the Victor and William Fung Foundation cooperated and founded the Fung Service Leadership Education Initiative in 2012, and William Fung Foundation resolved to allocate HK\$40 million to design and conduct education programs of service leadership among college students in eight publically funded tertiary institutions in Hong Kong. The initiative aimed at promoting service leadership among local college students. Although the eight universities designed and implemented the courses and projects based on their own needs, there is a call for valid scales measuring service leadership attitude, knowledge and behavior to evaluate the effectiveness of these courses and projects as well as comparing the evaluation outcomes cross eight universities.

In the framework of cognitive and behavioral development, attitude plays an important mediation role connecting knowledge and behavior [15-17]. Knowledge can positively shape attitude, which in turn leads to the formation of a behavioral intention [15]. Ajzen [15] argued the more favorable the attitude, the stronger should be the person's intention to perform the specific behavior under consideration. Unfortunately, although attitude to service leadership is important, there has been no valid scales measuring service leadership attitude in Hong Kong-based college students. To fill the gap, a 132-item scale (SLA-LF-132) was initially developed to measure service leadership attitude among local college students by our team based on the SLAM framework, 25 principles of service leadership [18], 12 dimensions of a service leader [19] and relevant literature authored by Shek and his colleagues [20, 21]. The 132-item scale showed good content validity [22]. Based on the preliminary criterion-related validation results which are unpublished, 73 items were retained as the short version (SLA-SF-73). In this chapter we aim to explore the internal consistency, convergent validity and factorial validity of these 73 items.

OUR STUDY

The participants were sampled from undergraduate students of eight publically funded universities in Hong Kong. Students from each university were invited to fill out a customized online survey. The purpose of the research and how the data would be used were presented to students at the title page of the survey. Students were informed they have the rights to stop the online survey anytime. The title page also revealed that all information would be kept confidential and the individual identity of students would not be disclosed at any point. Students were informed that a supermarket voucher worth HK\$100 (roughly equivalent to US\$13) would be given to them upon successful completion of the whole

survey with 252 items which would be completed within 45-60 minutes. The survey would not be activated unless students gave formal consent to be the participants of this study.

The online survey covered the measures of service leadership attitude, knowledge, behavior, external criterion measures and demographic attributes. It was administered in English. The link to online survey was offered to students with the assistance of administrators in eight universities. The data were collected between late March and early June, 2017.

Measures

- 1) **Service Leadership Attitude Scale (SLA-SF-73).** Students were invited to respond to 73 items on a 6-point Likert scale ranging from “1” (strongly disagree) to “6” (strongly agree).
- 2) **Service Leadership Knowledge Scale (SLK-SF-40).** The original 200-item scale (SLK-LF-200) was also developed based on the literature related to the SLAM framework, service leadership and service leader [18-21]. The 200-item scale showed good content validity [23]. The initial criterion validation study shortened the 200 items to 63 items [24]. After considering the face validity and duplication of the items, 63 items were further shortened into 50 items (SLK-SF-50). After evaluating the internal consistency, 50 items were shortened into 40 items (SLK-SF-40). Factor analyses reported in a book chapter in this book showed that the scale possessed excellent factorial validity. These 40 items were used in this study and presented in the form of multiple choice questions. Value “1” was assigned to all correct answers and Value “0” was assigned to all incorrect answers. The Cronbach’s alpha cross all items was 0.93 (mean inter-item correlations = 0.21). The score of service leadership knowledge was calculated as the sum of all 40 items. A higher total score indicates a higher level of knowledge.
- 3) **Service Leadership Behavior Scale (SLB-SF-38).** Based on the aforementioned literature on service leadership and other published work on leadership [25, 26], a 97-item scale (SLB-LF-97) was developed to measure the extent to which the respondents demonstrated the behaviors that are representative of a service leader. On the basis of a Principal Axis Analysis (PAA) conducted, 97 items were shortened into 65 items (SLB-SF-65). After one round of Principal Component Analysis (PCA, see book chapter in this book) and one round of Confirmatory Factor Analysis (CFA) conducted, 65 items were further shortened into 38 items (SLB-SF-38), which demonstrated good convergent validity. Six stable factors were identified in the 38 items. They were Self-Improvement and Self-Reflection, People and Principle Orientation, Resilience, Social Competence, Problem-Solving, and Mentorship. The 38 items were adopted in this study. The items were formulated as statements, and responses were given on 6-point Likert items (1: very dissimilar to me; 6: very similar to me). The Cronbach’s alpha cross all 38 items was 0.96. The Cronbach’s alpha of the items of six subscales ranged from 0.85 to 0.91 (mean inter-item correlations ranged from 0.42 to 0.65). The score of service leadership behavior was calculated as the mean of all 38 items.

- 4) **Revised Servant Leadership Profile (RSLP).** RSLP is a 20-item instrument measuring attitudes toward servant leadership, commitment to developing others in the service, skills concerning servant leadership and capacity of leading a team in the service [27]. For each item, the respondent was invited to respond on a 7-point Likert scale with options ranging from “1” (strongly disagree) to “7” (strongly agree). The Cronbach’s alpha across all items is 0.94 (mean inter-item correlations = 0.46). The total score of Servant Leadership was calculated as the mean of all 20 items.
- 5) **Moral Self-Concept (MSC).** The Chinese Adolescent Self-Esteem Scales (CASES) consists of 60 items measuring overall self-esteem and six specific self-esteem including Cognitive, Family, Social, Moral, Body Image, and Physical Performance [28]. MSC is one of them consisting of 8 items [29], which was used to assess the moral self-concept of university students in this study. Students were invited to respond to a 7-point Likert scale with response options ranging from “1” (strongly disagree) to “7” (strongly agree). The Cronbach’s alpha across all items was 0.83 (mean inter-item correlations = 0.44). The total score of MSC was calculated as the mean of all 8 items.
- 6) **Leadership Efficacy (LEF).** LEF was measured by the 8-item scale developed by Murphy [30] with the focus on assessing the generalized capability in the leadership role [31]. Participants were invited to respond to items with a 5-point Likert scale with responses ranging from “1” (strongly disagree) to “5” (strongly agree). Three items were reversely coded. The Cronbach’s alpha across all items was 0.72 (mean inter-item correlations = 0.25). The total score of LEF was calculated as the mean of all 8 items.
- 7) **Interpersonal Reactivity Index (IRI).** IRI is a 28-item self-reported scale in which 7-item subscales were extracted: Empathic Concern (EC), Perspective Taking (PT), Fantasy (FS) and Personal Distress (PD) [32]. The present study only measured the first two aspects with a total of 14 items. Participants were invited to respond on a 5-point Likert scale ranging from “1” (Does not describe me well) to “5” (Describe me very well). The Cronbach’s alpha across all items was 0.74 (mean inter-item correlations = 0.17), while the Cronbach’s alpha across EC and PT were 0.62 and 0.59 respectively (mean inter-item correlations were 0.19 for both measures). The score of interpersonal reactivity, empathic concern, and perspective thinking were calculated as the mean of relevant items.

Data Analysis

The item-total correlation of each of 73 items was examined using SPSS 23 (IBM, New York), and those with item-total correlation less than 0.25 were dropped. Then we randomly and evenly split the data into two sets: A and B. Set A was adopted for main analysis and Set B was only used to test the factorial structural stability. We performed the Principal Components Analysis (PCA) with varimax rotation to investigate the factor structure. Coefficients of congruence [33] were computed to test the factorial stability by quantifying the similarity of the factor structure across two subsamples. Only items with the factor loading equaled to or above 0.50 were retained. Regarding reliability, the Cronbach’s alpha

value was adopted to examine the internal consistency. For convergent validity, correlation analysis was used to evaluate the association between the scores of SLA (and its subscales) and the scores of SLK-SF-40, SLB-SF-38 (and its subscales), RSLP, MSC, LEF, IRI, EC and PT respectively.

Considering the attitude of service-oriented organizational citizenship is positively related with the related knowledge [34], we hypothesized SLA would be positively correlated with SLK-SF-40 (Hypothesis 1). As how one believes about leadership to some extent directs one's behavior when performing the duties as a leader [15, 17], it was hypothesized that SLA would be positively associated with SLB-SF-38 and its subscales (Hypothesis 2a to 2f). Given that the basic propositions are consistent with those of service leadership, it was hypothesized that SLA would be positively correlated with RSLP (Hypothesis 3). Considering service leaders normally believe that good leaders must be of high moral quality [22], this study hypothesized that SLA would be positively associated with MSC (Hypothesis 4). Considering service leaders should have a positive attitude toward a commitment to continuous improvement in service leadership [22] and that positive attitude is positively correlated with self-efficacy [15], it was hypothesized that SLA would be positively associated with LEF (Hypothesis 5). As service leaders should have multiple intrapersonal and interpersonal competencies [22], so SLA would be expected to be positively correlated with IRI (Hypothesis 6). Besides, as service leaders are expected to exhibit care to peers and subordinates, and empathic concern is an important prerequisite to exhibit care [35], SLA would be expected to be positively correlated with EC (Hypothesis 7). Considering service leadership model posits that service quality should be judged by service receivers and the service provided based on the needs of service receivers is more likely to lead to their satisfaction [36], SLA would also be expected to be positively correlated with PT (Hypothesis 8).

WHAT WE FOUND

A total of 4,555 completed questionnaires were received by the research team. After excluding those declining to participate ($n = 6$), multiple participation ($n = 33$), ineligible responses ($n = 30$), the final sample consisted of 4,486 undergraduate students. Around 500 students were affiliated to each university except for The Hong Kong Polytechnic University, whose sample was doubled to around 1,000. Among the 4,486 respondents (i.e., Mean age = 20.47; SD = 1.67), 1,517 (33.8%) were male and 2,969 (66.2%) were female. The full data set was randomly split into two sets: Set A contained 2,246 respondents, whereas Set B was composed of 2,240 respondents.

Factor Structure

After checking the item-total correlation coefficients, 9 items with values less than 0.25 were deleted from the original 73-item scale. To avoid double loading and to derive a conceptually meaningful picture, a seven-factor solution was tested. The solution could explain for 53.67% of the whole variance. The factor loading of all items was over 0.30.

Table 1 reports the factor loadings of all items. Seven factors identified were Vision and Competence (18 items), Social Competence (8 items), Caring Disposition (13 items), People Orientation (11 items), Self-Reflection and Self-Understanding (5 items), Positive Views about Human Beings (3 items), and Ethical Role Models (6 items). Based on this finalized factor structure, the coefficient of congruence across two subsamples was 0.97 and the coefficient of congruence of each subscale ranged from 0.96 to 0.98 (see Table 2), indicating that the seven-factor structure across two subsamples was almost the same [33]. After removing 18 items with the factor loading less than 0.50 to keep a more robust factor solution, the finalized 7-factor scale contained 46 items (SLA-SF-46E). In another paper under preparation, CFA was further conducted to look at the factor structure of the scale.

Table 1. Factorial structural of Service Leadership Attitude Scale (SLA-SF-73) using varimax rotation (N = 2,246)

	Factor loading of component						
	1	2	3	4	5	6	7
Vision and Competence							
SL22	<u>0.64</u>	0.05	0.19	0.26	0.14	0.07	0.17
SL27	<u>0.61</u>	0.24	0.17	0.13	0.19	0.10	0.10
SL23	<u>0.60</u>	-0.01	0.16	0.14	0.10	0.06	0.25
SL21	<u>0.59</u>	0.16	0.17	0.32	0.17	0.11	0.15
SL26	<u>0.59</u>	0.21	0.16	0.22	0.22	0.02	0.13
SL15	<u>0.58</u>	0.02	0.16	0.37	0.11	-0.04	0.12
SL28	<u>0.58</u>	0.36	0.12	0.20	0.19	0.12	0.07
SL20	<u>0.58</u>	0.19	0.11	0.31	0.17	0.02	0.11
SL33	<u>0.55</u>	0.25	0.24	0.13	0.13	0.07	0.19
SL14	<u>0.52</u>	0.11	0.08	0.39	0.20	0.00	0.06
SL24	<u>0.51</u>	0.21	0.18	0.34	0.12	0.07	0.14
SL30	<u>0.49</u>	0.16	0.23	0.15	0.08	0.10	0.30
SL36	<u>0.48</u>	0.41	0.14	0.18	0.15	0.04	0.13
SL16	<u>0.48</u>	0.17	0.18	0.39	0.19	-0.08	0.06
SL19	<u>0.47</u>	0.20	0.17	0.34	0.13	-0.04	0.18
SL34	<u>0.47</u>	0.40	0.23	0.22	0.18	0.08	0.12
SL25	<u>0.45</u>	0.31	0.12	0.29	0.23	0.11	0.07
SL31	<u>0.44</u>	0.44	0.13	0.33	0.16	0.09	0.07
Social Competence							
SL37	0.38	<u>0.57</u>	0.17	0.31	0.16	0.10	0.08
SL35	0.39	<u>0.54</u>	0.17	0.29	0.22	0.06	0.08
SL38	0.39	<u>0.52</u>	0.16	0.27	0.15	0.06	0.12
SL41	0.37	<u>0.50</u>	0.21	0.29	0.26	0.05	0.11
SL40	0.30	<u>0.43</u>	0.23	0.21	0.21	0.11	0.22
SL49	0.14	<u>0.42</u>	0.35	0.36	0.15	-0.10	0.31
SL42	0.15	<u>0.41</u>	0.32	0.16	0.10	0.14	0.34
SL29	0.26	<u>0.37</u>	0.17	0.16	-0.04	0.18	0.32
Caring Disposition							
SL56	0.12	0.13	<u>0.64</u>	0.16	0.11	0.18	0.30
SL57	0.26	0.11	<u>0.63</u>	0.17	0.19	0.10	0.14
SL58	0.31	0.06	<u>0.60</u>	0.16	0.21	0.05	0.08
SL59	0.37	-0.02	<u>0.59</u>	0.10	0.23	0.04	0.14
SL55	0.12	0.15	<u>0.56</u>	0.04	0.08	0.20	0.25
SL53	0.12	0.25	<u>0.56</u>	0.19	0.05	0.10	0.38
SL54	0.07	0.18	<u>0.55</u>	0.17	0.06	0.23	0.36
SL60	0.34	0.09	<u>0.51</u>	0.21	0.29	0.03	0.10
SL52	0.18	0.28	<u>0.51</u>	0.23	0.12	0.08	0.31
SL51	0.16	0.36	<u>0.48</u>	0.36	0.14	0.03	0.29
SL50	0.15	0.34	<u>0.47</u>	0.31	0.13	-0.09	0.32

Table 1. (Continued)

	Factor loading of component						
	1	2	3	4	5	6	7
SL48	0.13	0.31	0.38	0.30	0.19	0.02	0.32
SL32	0.21	0.10	0.35	-0.01	-0.14	0.34	0.27
People Orientation							
SL11	0.30	0.28	0.12	0.62	0.19	0.14	0.05
SL08	0.35	0.17	0.09	0.60	0.25	0.15	0.06
SL09	0.36	0.10	0.17	0.59	0.20	0.15	0.08
SL10	0.35	0.10	0.10	0.58	0.21	0.18	0.09
SL12	0.24	0.18	0.25	0.58	0.00	0.03	0.14
SL07	0.27	0.18	0.12	0.56	0.19	0.17	0.10
SL02	0.18	0.06	0.11	0.54	0.09	0.27	0.22
SL17	0.25	0.21	0.34	0.54	-0.02	-0.06	0.16
SL01	0.20	0.20	0.08	0.53	0.08	0.25	0.19
SL13	0.39	0.16	0.15	0.53	0.13	0.06	0.04
SL18	0.32	0.14	0.34	0.49	0.00	-0.11	0.25
Self-Reflection and Self-Understanding							
SL68	0.30	0.23	0.08	0.26	0.61	-0.01	0.13
SL66	0.27	0.27	0.17	0.19	0.68	0.03	0.11
SL65	0.21	0.16	0.14	0.14	0.68	0.05	0.21
SL67	0.26	0.19	0.21	0.18	0.64	-0.01	0.15
SL64	0.20	-0.05	0.19	0.06	0.53	0.02	0.14
Positive Views About Human Being							
SL04	0.02	0.06	0.09	0.14	0.03	0.73	0.13
SL03	0.04	0.05	0.16	0.21	-0.04	0.71	0.13
SL73	0.14	0.08	0.30	0.10	0.19	0.33	0.03
Ethical Role Model							
SL44	0.18	0.11	0.22	0.13	0.16	0.05	0.74
SL46	0.13	0.05	0.23	0.10	0.08	0.15	0.70
SL47	0.08	0.05	0.28	0.11	0.15	0.16	0.67
SL45	0.24	0.10	0.18	0.13	0.18	0.02	0.66
SL43	0.28	0.14	0.16	0.14	0.15	0.04	0.62
SL39	0.02	0.33	0.30	0.07	0.05	0.30	0.40

Table 2. Coefficients of congruence across two subsamples (N = 4,486)

	Between two random sub-samples
Service Leadership Attitude Scale (SLA-SF-73)	0.97
SLA-SF-73 - Vision and Competence	0.98
SLA-SF-73 - Social Competence	0.97
SLA-SF-73 - Caring Disposition	0.98
SLA-SF-73 - People Orientation	0.97
SLA-SF-73 - Self-Reflection and Self-Understanding	0.97
SLA-SF-73 - Positive Views About Human Being	0.96
SLA-SF-73 - Ethical Role Model	0.97

Internal Consistency and Convergent Validity

Full SLA-SF-46E and its seven subscales demonstrated high internal consistency. The Cronbach's value of full SLA-SF-46E scale was 0.96 and those of subscales were between 0.70 and 0.91 (see Table 3), showing good internal consistency. As expected, the scores of SLA-SF-46E and seven subscales were all positively correlated with those of SLK-SF-40, SLB-SF-38, RSLP, MSC, LEF, IRI, EC, and PT (see Table 4). Consistently, the scores of

SLA-SF-46E and seven subscales were found positively associated with the scores of each subscale of SLB-SF-38 (see Table 5). The findings supported all hypotheses, establishing the convergent validity of SLA-SF-46E and seven subscales among Hong Kong undergraduate students.

Table 3. Internal consistency of Service Leadership Attitude Scale (SLA-SF-46E) and external criterions scales (N = 2,246)

	α	Mean Inter-item correlations
Service Leadership Attitude Scale (SLA-SF-46E)	0.96	0.36
SLA-SF-46E - Vision and Competence	0.91	0.46
SLA-SF-46E - Social Competence	0.84	0.56
SLA-SF-46E - Caring Disposition	0.89	0.47
SLA-SF-46E - People Orientation	0.89	0.46
SLA-SF-46E - Self-Reflection and Self-Understanding	0.82	0.49
SLA-SF-46E - Positive Views About Human Being	0.70	0.54
SLA-SF-46E - Ethical Role Model	0.85	0.53
Service Leadership Knowledge Scale (SLK-SF-40)	0.93	0.21
Service Leadership Behavioral Scale (SLB-SF-38)	0.96	0.38
SLB-SF-38 - Self-Improvement and Self-Reflection	0.91	0.53
SLB-SF-38 - People and Principles Orientation	0.87	0.42
SLB-SF-38 - Resilience	0.87	0.50
SLB-SF-38 - Social Competence	0.86	0.55
SLB-SF-38 - Problem-Solving	0.87	0.56
SLB-SF-38 - Mentorship	0.85	0.65
Revised Servant Leadership Scale (RSLP)	0.94	0.46
Moral Self-Concept Scale (MSC)	0.83	0.44
Leadership Efficacy Scale (LEF)	0.72	0.25
Interpersonal Reactivity Index (IRI)	0.74	0.17
IRI - Empathic Concern	0.62	0.19
IRI - Perspective Taking	0.59	0.19

Table 4. Correlation coefficients with external criterion scales and other Service Leadership scales (N = 2,246)

	SLK-SF-40	SLB-SF-38	RSLP	MSC	LEF	IRI	EC	PT
SLA-SF-46E	0.29	0.58	0.59	0.55	0.24	0.40	0.33	0.37
SLA-SF-46E-F1	0.37	0.46	0.46	0.50	0.18	0.38	0.33	0.34
SLA-SF-46E-F2	0.17	0.50	0.53	0.45	0.20	0.33	0.28	0.30
SLA-SF-46E-F3	0.17	0.50	0.53	0.45	0.20	0.33	0.28	0.30
SLA-SF-46E-F4	0.33	0.47	0.50	0.49	0.20	0.37	0.32	0.34
SLA-SF-46E-F5	0.24	0.47	0.44	0.44	0.19	0.29	0.22	0.29
SLA-SF-46E-F6	0.04	0.26	0.29	0.21	0.13	0.13	0.11	0.11
SLA-SF-46E-F7	0.04	0.42	0.45	0.36	0.16	0.25	0.20	0.23

Note. SLK-SF-40: One-factor Service Leadership Knowledge Scale (40 items); SLB-SF-38: Six-factor Service Leadership Behavior Scale (38 items); RSLP: Revised Servant Leadership Profile; MSC: Moral Self-Concept; LEF: Leadership Efficacy; IRI: Interpersonal Reactivity Index; EC: IRI- Empathic Concern; PT: IRI- Perspective Taking. SLA-SF-46E-F1: Vision and Competence; SLA-SF-46E-F2: Social Competence; SLA-SF-46E-F3: Caring Disposition; SLA-SF-46E-F4: People Orientation; SLA-SF-46E-F5: Self-Understanding and Reflection; SLA-SF-46E-F6: Positive View About Human Beings; SLA-SF-46E-F7: Ethical Role Model. All correlations are significant at the level of 0.01(two-tailed).

Table 5. Correlation coefficients with subscales of SLB-SF-38

	SLB-SF-38-F1	SLB-SF-38-F2	SLB-SF-38-F3	SLB-SF-38-F4	SLB-SF-38-F5	SLB-SF-38-F6
SLA-SF-46E	0.52	0.62	0.38	0.50	0.36	0.35
SLA-SF-46E-F1	0.48	0.55	0.33	0.45	0.36	0.25
SLA-SF-46E-F2	0.43	0.53	0.27	0.44	0.29	0.19
SLA-SF-46E-F3	0.43	0.53	0.34	0.42	0.28	0.39
SLA-SF-46E-F4	0.43	0.54	0.29	0.44	0.28	0.23
SLA-SF-46E-F5	0.44	0.47	0.30	0.40	0.33	0.24
SLA-SF-46E-F6	0.36	0.42	0.31	0.31	0.22	0.38
SLA-SF-46E-F7	0.21	0.26	0.21	0.22	0.13	0.24

Note. SLB-SF-38-F1: Self-Improvement and Self-Reflection; SLB-SF-38-F2: People and Principles Orientation; SLB-SF-38-F3: Resilience; SLB-SF-38-F4: Social Competence; SLB-SF-38-F5: Problem-Solving; SLB-SF-38-F6: Mentorship. SLA-SF-46E-F1: Vision and Competence; SLA-SF-46E-F2: Social Competence; SLA-SF-46E-F3: Caring Disposition; SLA-SF-46E-F4: People Orientation; SLA-SF-46E-F5: Self-Understanding and Reflection; SLA-SF-46E-F6: Positive View About Human Beings; SLA-SF-46E-F7: Ethical Role Model. All correlations are significant at the level of 0.01(two-tailed).

DISCUSSION

This study reported the shortening of the SLA-LF-73 from 73 items to 46 items after factor analyses based on 4,468 college students in Hong Kong, and tested the reliability, convergent validity and factorial validity of the 46-item scale. Exploratory factors analyses showed that seven factor emerged from the scale and this seven-factor structure was stable across two sub-samples of Hong Kong college students. Based on the cut-offs of inter-item correlation and factor loading, 73 items were further shortened into 46 items. The findings suggested that both the full scale and seven sub-scales demonstrated excellent reliability status. In addition, both the 46-item scale and all seven sub-scales demonstrated convergent validity, which is proven by their significant correlations with SLK-SF-40, SLB-SF-38 (and sub-scales), RSLP, MSC, LEF, IRI, EC, and PT.

As expected, there were positive correlations between SLA-SF-46E and SLK-SF-40, echoing to a series of previous findings that knowledge and information establish the understanding of importance of a subject, shaping positive attitudes toward it at the next stage [33, 37]. SLA-SF-46E was found positively correlated with SLB-SF-38 and its subscales, which is consistent with the theory of planned behavior that positive attitude is able to shape positive behavior through behavioral intentions [15]. There were positive correlations detected between SLA-SF-46E and RSLP, echoing the common philosophy and practices of both service leadership and servant leadership that enrich the lives of individuals and create a caring environment [27]. Besides, SLA-SF-46E was positively correlated with MSC, which is consistent with the core philosophy of service leadership that service leaders should possess moral character and practice following the principles of integrity, fairness, and humanity [22]. For service leaders, the strong motivation of being ethical role models make them take efforts to shape their moral character and improve their moral self-concept, causing the strong positive correlations between SLA-SF-46E and MSC. As expected, SLA-SF-46E was positively correlated with LEF as confidence is normally generated from the behavior and experience and positive attitude always drives positive behaviors [38]. SLA-SF-46E was found positively correlated with IRI, echoing the core belief of service leadership that service

leaders should demonstrate interpersonal and intrapersonal competencies in terms of the willingness of collaborating with peers, the capacity of addressing conflicts within a team, and capabilities in constructing communication channels to promote information exchange [22]. More specific, the positive correlations between SLA-SF-46E and EC are consistent with the literature that empathic concern increases the likelihood of exhibiting care, which is believed to be one of the core practices of service leaders [35]. The positive correlations between SLA-SF-46E and PT echo the literature that thinking from the perspective of service receivers is positively associated with their satisfaction on the service received [36].

This study helps to develop a briefer and focused measure of service leadership attitude for Hong Kong undergraduate students. The SLA-SF-46E is important to local universities in view of the need to objectively evaluate service leadership programs, which has long-term impacts on the healthy operation of the Hong Kong's service economy.

Although current study makes a sound contribution, some limitations should be noted. First, the study examined service leadership attitude and behavior by directly asking students only without checking the accuracy of their answers by comparing with the assessment from the perspective of teachers and peers. Similar to other self-report measures, it is noteworthy that social desirability may cloud the findings. Comparatively, their attitudes and behavior may be more accurately recognized by teachers and peers, suggesting future studies should invite teachers and peers to rate the same items. Second, the data in this study are from eight publically funded universities only. It is noteworthy that there are a number of undergraduate students studying in the self-funded tertiary institutions. Future studies might consider extending the sample of this study to cover students in self-funded tertiary institutions. Third, as the sample adopted in this study is essentially a convenient sample, there is a problem of generalizability of the findings, which should be addressed in future studies.

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Chapter 141

CONVERGENT AND FACTORIAL VALIDATION OF THE SERVICE LEADERSHIP BEHAVIOR SCALE

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ABSTRACT

Utilizing a sample of 4,486 Hong Kong undergraduates recruited from eight government-funded universities, this chapter reports the findings of a cross-institution validation study on the Service Leadership Behavior Scale (Short-Form) with 65 items (SLB-SF-65). Specifically, we examined the internal consistency, convergent validity, as well as the dimensionality of the SLB-SF-65. Results of the exploratory factor analysis indicated that six factors could be extracted with 48 items retained in the trimmed version

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of the scale (SLB-SF-48) with a stable factor structure. Besides, the overall scale showed excellent internal consistency and was positively correlated to a myriad of theoretically relevant constructs. In short, the present findings underscored the adequacy of the trimmed Service Leadership Behavior Scale (SLB-SF-48) as an objective assessment to gauge whether one possesses the behavioral qualities of a Service Leader.

INTRODUCTION

As an emergent leadership paradigm in advanced economies [1, 2], the Service Leadership paradigm, contrary to the traditional elitist leadership models, contends that leadership success should extend beyond discipline-oriented knowledge or task-specific competencies (i.e., the “hard (or *product*) skills”) to cover “soft (or *process*) skills” including interpersonal communication and intrapersonal qualities [3, 4]. As Shek and colleagues [5] remarked, such a paradigm which “calls for leaders with qualities to serve others” (p. 164) and inspires a revamp in leadership initiative, informs education and research which are instrumental to Hong Kong where service takes up a whopping 92.2% of GDP [6]. As such, Po Chung, Chairman of the Hong Kong Service Leadership and Management Limited (HKI-SLAM), initiated the notion of Service Leadership education targeting university students of Hong Kong (i.e., SLAM framework).

With the financial support of the Victor and William Fung Foundation and the collaborative effort of the HKI-SLAM and the government, a multi-year project entitled the “Fung Service Leadership Education Initiative” was implemented in eight government-funded universities. On the basis of the SLAM framework, each participating institution would design her own curriculum aimed to promote students’ Service Leadership attributes (see 7). Specifically, Po Chung highlighted Competence (i.e., “Doing things right”), Moral character (i.e., “Doing the right things”), and Caring disposition (i.e., “Serving with unselfish intent”) as the three defining attributes in building a leader’s legitimacy and thereby contributing to leadership success [8, 9]. Hence, the formula “E (Effective leadership) = M (Moral character) C² (Competence * Caring)” laid the conceptual foundation for the model of Service Leadership education [10].

To objectively assess qualities of effective Service Leaders [11], the research team at The Hong Kong Polytechnic University (PolyU) initiated a project entitled “Development and validation of measures based on the Service Leadership Model (“The Project” hereafter)” [5]. Via developing and validating three scales on attitude, behavior, and knowledge corresponding to the three dimensions argued to define the educational success of Service Leadership [12], Shek and colleagues [5] endeavored to develop reliable and valid assessment tools to judge whether an individual is a good Service Leader. In this chapter, findings of a large-scale validation study of the Short-Form of Service Leadership Behavior Scale (SLB-SF-65) are reported.

The long-form Service Leadership Behavior Scale (SLB-LF-97) was developed to measure the “behavioral qualities a Service leader should demonstrate” [5, p. 165]. Operating on a six-point Likert Scale (1: very dissimilar; 6: very similar), the SLB-LF-97 includes 97 items developed based on the SLAM framework, 25 principles of Service Leadership [8], and the leadership literature [e.g., 13-15]. These 97 items cover four main dimensions, including

i) service provision, ii) principle “ $E=MC^2$,” iii) commitment to continuous improvement, and iv) distributed leadership.

As part of “The Project” [see 5], a validation study involving 231 PolyU undergraduates was conducted in November 2016 to examine the psychometric properties and factorial structures of the 97-item SLB-LF-97. The results highlighted the excellent reliability of the SLB-LF-97 ($\alpha = 0.97$) and its moderate to strong correlations (r s ranging from 0.51 to 0.81) with several theoretically relevant constructs including Servant Leadership [16], empathy [17], moral self-concept [18], and leadership efficacy [19, 20]. Meanwhile, findings of the exploratory factor analysis (EFA) suggested the removal of 32 items due to the double-loading [21] and insufficient-loading issues (i.e., loadings less than 0.40) [see 22]. Ultimately, 65 items were retained to form the Short-Form of the Service Leadership Behavior Scale (SLB-SF-65).

While the above unpublished study pioneered the convergent validation and the analysis of the dimensionality of the initial behavior scale (i.e., SLB-LF-97), there is a need to replicate the psychometric soundness and to re-examine the dimensionality of the trimmed scale using on a larger sample. As the main body of “The Project,” the present study utilized a sample of 4,486 undergraduates to examine the item homogeneity, convergent and factorial validity of the 65-item SLB-SF-65. Specifically, this chapter is mainly focused on reporting the results of the EFA, in addition to analyses of the internal consistency and convergent validity of the SLB-SF-65.

OUR STUDY

Utilizing an e-platform, a total of 4,486 undergraduates (mean age: 20.47 years; SD: 1.67) from eight government-funded universities participated in the Service Leadership Scales validation study. Amongst the 4,486 respondents, 1,517 (33.8%) were males and 2,969 (66.2%) were females. An overwhelming proportion of the participants were aged 20 to 24 years (68.4%), had neither received any credit-bearing (74.3%) nor non-credit-bearing (82.0%) training in Service Leadership, despite the fact that 64.4% had formerly served as a leader (such as being the chairperson of a student association). Furthermore, 77.1% sat the Hong Kong Diploma of Secondary Education Examination (HKDSE). Details regarding other demographic information of the present working sample are addressed in another chapter in this book.

Procedures

The data collection, which commenced in March 2017, was implemented via the mySurvey@PolyU electronic survey system. The research objectives, instructions on how to complete the present self-administered survey, participants’ rights to voluntarily participate and withdraw, and the principle of data confidentiality were highlighted in the invitation documents and on the survey webpage. Participants were also informed that 45 to 60 minutes would be warranted to conscientiously complete the entire questionnaire. Students’ informed

consent was obtained at the start of the e-survey. Upon the completion of the study, each participant was entitled to a supermarket cash coupon valued at HK\$100 (US\$12.80).

Participants’ completed responses were downloaded as an EXCEL file for a data-cleaning process before the conversion to an SPSS file for statistical analyses. Details on the various steps taken and criteria as regards the eligibility of the responses were reported in another chapter in this book. Ultimately, 4,486 cases were considered eligible for further analyses.

Instruments

The present e-survey was composed of items from the Short-Forms of the Service Leadership scales, including i) the Service Leadership Attitude Scale (SLA-SF-73; 73 items), ii) the Service Leadership Behavior Scale (SLB-SF-65; 65 items), and iii) the Service Leadership Knowledge Scale (SLK-SF-50; 50 items). The present chapter is primarily concerned with the validation of the 65-item Service Leadership Behavior Scale (SLB-SF-65).

Developed based on the SLAM framework, 25 principles of Service Leadership [8], and other published works on *leadership* [e.g., 15, 23], the 97-item Service Leadership Behavior Scale (i.e., SLB-LF-97) was constructed to examine the extent to which an individual demonstrates behaviors that are representative of a Service Leader. Sixty-five items were ultimately retained to form the SLB-SF-65, following an unpublished validation study involving 231 PolyU undergraduates as part of the project “Development and validation of measures based on the Service Leadership Model” [see 5]. The SLB-SF-65, which is in English with a six-point Likert Scale (1: very dissimilar; 6: very similar), describes some leaders’ behaviors whereby participants rate how each description resembles their behaviors if they are in a position to lead. Table 1 features four sample items of the SLB-SF-65.

Table 1. Four sample items of the SLB-SF-65

Items	Very Dissimilar to Me	Moderately Dissimilar to Me	Slightly Dissimilar to Me	Slightly Similar to Me	Moderately Similar to Me	Very Similar To Me
15. I trust myself in tackling difficulties in my life.	1	2	3	4	5	6
36. I have no problem letting others know my shortcomings.	1	2	3	4	5	6
49. I can motivate myself to achieve any goals I set.	1	2	3	4	5	6
64. I impose total control over duties assigned to other individuals. (Reverse-item)	1	2	3	4	5	6

Note. All sample items were slightly re-worded due to copyright issues.

Four other validated scales as listed below from the leadership and personality literature were also administered, with the aim of ascertaining the convergent validity of the SLA-SF-73, the SLB-SF-65, and the SLK-SF-50. These validated external inventories included the 20-item Revised Servant Leadership Profile (RSLP), the 8-item Leadership Efficacy Scale

(LEF), the 8-item Moral Self-Concept Scale (MSC), plus 14 items selected from Interpersonal Reactivity Index (IRI). There were also forced-choice and open-ended items aimed to measure the respondents' demographics.

1. **Revised Servant Leadership Profile (RSLP):** The RSLP was developed by Wong and Page [24] to assess the multidimensional construct *Servant Leadership*. In this study, 20 items from five dimensions deemed relevant to the SLAM curriculum—including, i) *Empowering and developing others* (five items), ii) *Serving others* (seven items), iii) *Open, participatory leadership* (two items), iv) *Inspiring leadership* (two items), and v) *Integrity and authenticity* (four items)—were included. The RSLP operates on a seven-point Likert scale. A higher score indicates higher likelihood to behave like a *Servant Leader*. Reliability analyses underscored the high item homogeneity of RSLP ($\alpha = 0.94$; mean inter-item correlations = 0.45).
2. **Leadership Efficacy Scale (LEF):** Developed by Murphy [20], the LEF comprises eight items designed to tap into people's "confidence in their general leadership ability" [19, p. 270]. Items were rated on a five-point Likert scale, with a higher score symbolizing one's perceived capability to take on a leadership role. Reliability analyses demonstrated an acceptable internal consistency amongst the eight items ($\alpha = 0.73$; mean inter-item correlations = 0.27).
3. **Moral Self-Concept (MSC):** Developed and validated by Cheng [18] as a subscale under the Chinese Adolescent Self-Esteem Scales (CASES), the MSC, which consists of eight items, examines youngsters' self-appraisal on dimensions pertaining to i) *Conduct and virtues*, ii) *Self-control and discipline*, and iii) *Altruism*. Items were rated on a seven-point Likert scale, with a higher score indicative of one's value of *morality* to him/herself, which is a cornerstone of effective leadership based on the SLAM curriculum [25]. In this study, we adopted the English-translated and slightly amended version of the MSC. Reliability assessment indicated a good internal consistency of the MSC on the current sample ($\alpha = 0.83$; mean inter-item correlations = 0.44).
4. **Interpersonal Reactivity Index (IRI):** Developed by Davis [17] and tested across nations and languages [see 26-28], the IRI is the most widely utilized inventory in assessing empathy as a multidimensional construct [29]. The 14 items utilized in the present study were from subscales *Perspective Taking* (PT; seven items) and *Empathic Concern* (EC; seven items). All items were rated on a five-point Likert scale. A higher score, according to Shek and Yu [30], denotes a higher level of empathy which is crucial for effective leadership. Besides computing the component scores for both subscales, a composite IRI score was also calculated. Cronbach's alpha for subscales PT and EC and the composite IRI score were 0.59, 0.62, and 0.74, respectively.

We performed both exploratory (EFA) and confirmatory factor analyses (CFA) in the present validation study. SPSS statistics version 24.0 (IBM) was used to perform the EFA, descriptive analyses, and measurement of internal consistency and convergent validity. AMOS 24.0 (IBM) statistical package was utilized to perform the CFA. The present chapter is primarily concerned about reporting the findings of the PCA, the internal consistency and

convergent validity of the 65-item SLB-SF-65. Details regarding the CFA and the final version of the behavior scale with 38 items will be addressed in another paper under preparation.

To explore the factorial structure of SLB-SF-65, we administered the EFA using the principal component analysis (PCA) with varimax rotation. The aggregate dataset (N= 4,486) was split into two random subsets, namely subset A (N= 2,246) and subset B (N= 2,240). The PCA was performed on subset A to explore the dimensionality of SLB-SF-65, whereby CFA was administered on subset B with the purpose of finalizing a factorial structure of the SLB-SF-65. Meanwhile, to establish the stability of the factorial structure, we performed the identical PCAs on subsets A and B. The Tucker’s coefficients of congruence (r_c) were then computed to gauge the resemblance of factor structures across subsets A and B [31, 32].

Cronbach’s alpha values and item-total correlations were computed to assess the internal consistency of the scale and the individual factor (i.e., subscale) derived. Regarding the assessment of convergent validity, the composite scores—computed via averaging respondents’ ratings—of both the scale and the subscales were correlated with the four external criterion measures adopted at present. Since the SLAM curriculum which preaches the behavioral prerequisites of a Service Leader covers domains in *Servant Leadership*, *leadership efficacy*, *morality* and *empathy*, it is logical to hypothesize a positive and significant correlation between the behavior scale (and the subscales) and the i) RSLP, ii) LEF, iii) MSC, and iv) IRI (including subscales EC and PT). Correlational analyses with other Service Leadership scales under validation were also performed. Considering that all these scales were designed to tap into different dimensions (i.e., *knowledge*, *attitude*, and *behavior*) of Service Leadership, there is no reason not to expect significant positive correlations amongst the behavior scale (with the subscales) and the validated versions of the SLK-SF-50 and the SLA-SF-73 (and the subscales).

FINDINGS

Table 2. Eigenvalues and total variance explained for the analyses on subset A and B

	Subset A (N= 2,246)		Subset B (N= 2,240)	
Factors	Eigenvalues	Total Variance Explained (%)	Eigenvalues	Total Variance Explained (%)
1	23.85	36.69	23.90	36.77
2	2.96	41.25	3.01	41.40
3	2.56	45.18	2.51	45.26
4	2.12	48.44	2.28	48.77
5	1.77	51.17	1.70	51.38
6	1.57	53.58	1.63	53.88
7	1.46	55.82	1.44	56.10
8	1.24	57.73	1.26	58.03
9	1.14	59.48	1.07	59.67
10	1.02	61.05	1.01	61.22
11	0.99	62.58	0.99	62.74

Note. Eigenvalues for the remaining factors are all below unity.

Table 3. Factor loadings of the SLB-SF-65 (N= 2,246)

	M	SD	Component											Retained for CFA?	Retained after CFA?
			1	2	3	4	5	6	ITC						
SLB-01	4.35	0.95	0.020	0.501	0.154	0.118	0.149	0.277	0.49	Yes	Yes	Yes	Yes	Yes	Yes
SLB-02	4.15	1.02	-0.036	0.388	0.206	0.091	0.113	0.403	0.44	No	No	No	No	No	No
SLB-03	4.46	0.88	0.146	0.434	0.131	0.233	0.228	0.232	0.56	No	No	No	No	No	No
SLB-04	4.39	0.99	0.233	0.168	0.207	0.134	0.666	0.110	0.57	Yes	Yes	Yes	Yes	Yes	Yes
SLB-05	4.21	1.01	0.204	0.066	0.253	0.139	0.658	0.225	0.56	Yes	Yes	Yes	Yes	Yes	Yes
SLB-06	4.55	0.98	0.237	0.170	0.231	0.110	0.711	0.055	0.58	Yes	Yes	Yes	Yes	Yes	Yes
SLB-07	4.52	0.98	0.235	0.181	0.200	0.090	0.765	0.051	0.58	Yes	Yes	Yes	Yes	Yes	Yes
SLB-08	4.50	0.99	0.194	0.165	0.148	0.139	0.741	0.083	0.55	Yes	Yes	Yes	Yes	Yes	Yes
SLB-09	4.39	0.97	0.184	0.135	0.166	0.216	0.704	0.155	0.57	Yes	Yes	Yes	Yes	No	No
SLB-10	4.58	0.99	0.241	0.290	0.340	0.228	0.226	-0.079	0.52	No	No	No	No	No	No
SLB-11	4.13	1.12	0.056	0.120	0.691	0.200	0.131	0.165	0.51	Yes	Yes	Yes	Yes	No	No
SLB-12	4.13	1.07	0.066	0.116	0.702	0.138	0.215	0.155	0.52	Yes	Yes	Yes	Yes	Yes	Yes
SLB-13	4.29	1.04	0.231	0.130	0.563	0.159	0.207	0.213	0.58	Yes	Yes	Yes	Yes	Yes	Yes
SLB-14	4.29	0.94	0.240	0.226	0.457	0.048	0.219	0.097	0.52	No	No	No	No	No	No
SLB-15	4.40	0.97	0.302	0.241	0.529	0.145	0.245	0.099	0.63	Yes	Yes	Yes	Yes	Yes	Yes
SLB-16	4.48	0.94	0.365	0.215	0.525	0.181	0.257	0.092	0.66	Yes	Yes	Yes	Yes	Yes	Yes
SLB-17	4.41	0.96	0.372	0.182	0.532	0.158	0.202	0.101	0.62	Yes	Yes	Yes	Yes	Yes	Yes
SLB-18	4.24	1.04	0.148	0.112	0.652	0.134	0.144	0.165	0.52	Yes	Yes	Yes	Yes	Yes	Yes
SLB-19	4.21	1.09	0.157	0.106	0.670	0.190	0.076	0.216	0.54	Yes	Yes	Yes	Yes	Yes	Yes
SLB-20	4.61	0.91	0.234	0.316	0.371	0.564	0.043	0.030	0.63	Yes	Yes	Yes	Yes	Yes	Yes
SLB-21	4.63	0.89	0.228	0.376	0.281	0.611	0.062	-0.017	0.64	Yes	Yes	Yes	Yes	Yes	Yes
SLB-22	4.66	0.90	0.230	0.391	0.212	0.620	0.052	-0.047	0.61	Yes	Yes	Yes	Yes	Yes	Yes
SLB-23	4.69	0.92	0.173	0.476	0.101	0.465	0.141	0.014	0.57	No	No	No	No	No	No
SLB-24	4.48	0.94	0.145	0.283	0.234	0.642	0.120	0.190	0.62	Yes	Yes	Yes	Yes	Yes	Yes
SLB-25	4.35	1.00	0.146	0.134	0.193	0.661	0.255	0.292	0.62	Yes	Yes	Yes	Yes	No	No
SLB-26	4.38	0.96	0.214	0.082	0.186	0.545	0.375	0.275	0.61	Yes	Yes	Yes	Yes	No	No
SLB-27	4.48	0.95	0.210	0.205	0.145	0.557	0.292	0.142	0.59	Yes	Yes	Yes	Yes	Yes	Yes
SLB-28	4.38	0.97	0.236	0.218	0.234	0.336	0.247	0.299	0.60	No	No	No	No	No	No
SLB-29	4.69	0.93	0.279	0.371	0.161	0.347	0.212	0.108	0.60	No	No	No	No	No	No
SLB-30	4.69	0.94	0.222	0.461	0.159	0.273	0.113	0.124	0.57	No	No	No	No	No	No
SLB-31	4.70	0.91	0.331	0.379	0.142	0.400	0.189	0.126	0.64	No	No	No	No	No	No
SLB-32	4.53	0.94	0.225	0.503	0.157	0.232	0.118	0.205	0.60	Yes	Yes	Yes	Yes	Yes	Yes
SLB-33	4.23	0.98	0.111	0.419	0.355	0.070	0.057	0.406	0.56	No	No	No	No	No	No
SLB-34	4.49	0.90	0.222	0.437	0.295	0.109	0.217	0.288	0.63	No	No	No	No	No	No
SLB-35	4.25	1.03	0.085	0.385	0.302	0.074	0.068	0.450	0.53	No	No	No	No	No	No
SLB-36	4.13	1.13	0.062	0.312	0.181	0.086	-0.018	0.420	0.40	No	No	No	No	No	No
SLB-37	4.71	0.88	0.366	0.553	0.150	0.175	0.114	0.053	0.62	Yes	Yes	Yes	Yes	Yes	Yes
SLB-38	4.77	0.89	0.250	0.623	0.042	0.286	0.125	0.053	0.60	Yes	Yes	Yes	Yes	Yes	Yes
SLB-39	4.76	0.93	0.248	0.620	0.017	0.273	0.069	0.106	0.58	Yes	Yes	Yes	Yes	No	No
SLB-40	4.49	1.00	0.132	0.533	0.037	0.247	0.049	0.379	0.56	Yes	Yes	Yes	Yes	Yes	Yes
SLB-41	4.68	0.89	0.258	0.569	0.026	0.306	0.065	0.272	0.63	Yes	Yes	Yes	Yes	No	No

Table 3. (Continued)

	M	SD	Component			3	4	5	6	ITC	Retained for CFA?	Retained after CFA?
			1	2							Yes	Yes
SLB-42	4.68	0.86	0.271	0.534		-0.029	0.310	0.080	0.340	0.62	Yes	Yes
SLB-43	4.36	0.98	0.279	0.240		0.102	0.248	0.209	0.578	0.63	Yes	Yes
SLB-44	4.20	1.05	0.201	0.250		0.113	0.153	0.121	0.711	0.57	Yes	Yes
SLB-45	4.17	1.04	0.223	0.224		0.125	0.130	0.127	0.723	0.57	Yes	Yes
SLB-46	4.32	1.10	0.455	0.002		0.262	0.221	0.070	0.369	0.53	No	No
SLB-47	4.54	0.99	0.615	0.058		0.186	0.254	0.112	0.295	0.61	Yes	No
SLB-48	4.61	0.94	0.615	0.302		0.153	0.150	0.122	0.165	0.65	Yes	Yes
SLB-49	4.48	0.98	0.625	0.040		0.225	0.245	0.136	0.323	0.64	Yes	Yes
SLB-50	4.39	1.03	0.607	0.057		0.236	0.210	0.146	0.324	0.63	Yes	Yes
SLB-51	4.67	0.89	0.660	0.296		0.115	0.171	0.223	0.081	0.67	Yes	Yes
SLB-52	4.65	0.95	0.660	0.303		0.089	0.103	0.167	0.035	0.60	Yes	Yes
SLB-53	4.60	0.92	0.655	0.277		0.091	0.113	0.232	0.094	0.63	Yes	No
SLB-54	4.56	0.96	0.637	0.250		0.104	0.103	0.172	0.116	0.60	Yes	Yes
SLB-55	4.68	0.92	0.637	0.315		0.150	0.122	0.216	0.041	0.65	Yes	Yes
SLB-56	4.72	0.89	0.675	0.306		0.162	0.139	0.175	0.087	0.67	Yes	Yes
SLB-57	4.61	0.92	0.594	0.340		0.178	0.161	0.150	0.113	0.66	Yes	No
SLB-58	4.58	0.95	0.612	0.312		0.193	0.097	0.160	0.125	0.65	Yes	Yes
SLB-59	4.46	0.92	0.445	0.342		0.199	0.146	0.148	0.297	0.65	No	No
SLB-60	4.72	0.89	0.393	0.556		0.185	0.113	0.147	0.067	0.64	Yes	Yes
SLB-61	4.56	0.92	0.315	0.538		0.258	0.037	0.171	0.132	0.62	Yes	No
SLB-62	4.62	0.87	0.278	0.584		0.221	0.048	0.110	0.067	0.58	Yes	Yes
SLB-63	4.43	0.93	0.226	0.462		0.226	0.002	0.149	0.262	0.54	No	No
SLB-64	3.23	1.27	-0.131	0.027		-0.153	0.066	-0.085	-0.543	-0.28	No	No
SLB-65	4.82	0.85	0.362	0.581		0.168	0.101	0.110	0.004	0.59	Yes	Yes
Eigenvalues			23.85	2.96		2.56	2.12	1.78	1.57			
Variance explained (%)			36.69	4.55		3.93	3.26	2.73	2.41			
Total variance (%)									53.58			
S1	4.59	0.71										
S2	4.64	0.63	0.72									
S3	4.29	0.76	0.61	0.56								
S4	4.51	0.72	0.63	0.68		0.63						
S5	4.43	0.80	0.59	0.50		0.60	0.55					
S6	4.44	0.90	0.56	0.60		0.51	0.52	0.44				
SLB-SF-65	4.46	0.57	0.87	0.87		0.80	0.82	0.72	0.69			
SLB-SF-48	4.50	0.60	0.88	0.86		0.80	0.82	0.74	0.69			

Note. N = 2,246; M: mean scores; SD: standard deviation. Bold and underlined values are the highest loadings by a variable among the factors which are over 0.50. ITC: item-total correlation. Forty-eight items were retained for the CFA in which 38 items were retained to form the finalized version of the scale. SLB-SF-65: 65-item Short-Form Service Leadership Behavior Scale; SLB-SF-48: the six-factor, 48-item solution to be subjected to CFA. S1: Subscale 1 (12 items, *Self-improvement and Self-reflection*); S2: Subscale 2 (12 items, *People and Principles Orientation*); S3: Subscale 3 (8 items, *Resilience*); S4: Subscale 4 (7 items, *Social Competence*); S5: Subscale 5 (6 items, *Problem-Solving*); S6: Subscale 6 (3 items, *Mentorship*). All correlation coefficients are statistically significant at $p < .001$ (two-tailed).

While ten factors were shown to have eigenvalues over unity across the two subsets (see Table 2), visual inspection of both scree plots and consideration of interpretability of the factor solution suggested that six factors which accounted for 53.58% of the total variance could be retained. Accordingly, the PCA was rerun on subset A specifying the extraction of six factors. The factor loadings of each item, eigenvalues, the percentage of variance explained by each factor, and the correlations amongst the factors and the entire scale are detailed in Table 3.

To assess the stability of this six-factor solution, we computed the coefficients of congruence (r_c) across subsets A ($N=2,246$) and B ($N=2,240$). As illustrated in Table 4, the value of r_c of SLB-SF-65 across subsets is 0.99, indicating that the six-factor structure was essentially identical across the two subsets [32]. Additionally, the r_c of the six factors across these two random subsamples are all above 0.98 (see Table 4). In short, these findings corroborate the stability of the factors derived [33].

With the objective to simplify and thereby lead to a more stringent interpretability of the factorial structure, 17 items with loadings below 0.50 were removed [34, 35]. The resultant 48-item, six-factor solution (SLB-SF-48) was then subjected to a confirmatory factor analysis (CFA), which will be discussed in detail in another paper under preparation. The six factors, each of which forms a subscale, were accordingly named “Self-improvement and Self-reflection” (items 47 to 58), “People and Principles Orientation” (items 1, 32, 37 to 42, 60 to 62, and 65), “Resilience” (items 11 to 13, 15 to 19), “Social Competence” (items 20 to 22, 24 to 27), “Problem-Solving” (items 4 to 9), and “Mentorship” (items 43 to 45).

Table 4. Coefficient of congruence across two subsamples

	Between two random subsamples (subset A: $N=2,246$; subset B: $N=2,240$)
Short-Form Service Leadership Behavior Scale (SLB-SF-65)	0.991
1: <i>Self-improvement and Self-reflection</i>	0.996
2: <i>People and Principles Orientation</i>	0.996
3: <i>Resilience</i>	0.989
4: <i>Social Competence</i>	0.982
5: <i>Problem-Solving</i>	0.993
6: <i>Mentorship</i>	0.988

Reliability of the Measures

As detailed in Table 5a, the total scale (SLB-SF-65), trimmed scale (SLB-SF-48) and the subscales all demonstrated at least meritorious internal consistency (i.e., all α values $>.80$, mean inter-item correlations $>.30$) across subsets. Similar findings (i.e., all α values $>.80$, mean inter-item correlations $>.30$) emerged (see Table 5b) even when we further split the two subsamples based on the respondents' gender. All items, except for item 64 which was subsequently excluded from SLB-SF-48, had a corrected item-total correlation of at least 0.40 (see Table 4). Taken together, the present findings supported the high reliability of the SLB-SF-48 and its subscales.

Table 5a. Internal consistencies of SLB-SF-65, SLB-SF-48, and subscales across subsamples

	Entire Sample (N= 4,486)		Subset A (N= 2,246)		Subset B (N= 2,240)	
	α	Mean Inter-item correlations	α	Mean Inter-item correlations	α	Mean Inter-item correlations
SLB-SF-65	0.97	0.34	0.97	0.34	0.97	0.34
SLB-SF-48	0.97	0.38	0.97	0.37	0.97	0.38
1: <i>Self-improvement and Self-reflection</i>	0.93	0.53	0.93	0.53	0.93	0.53
2: <i>People and Principles Orientation</i>	0.90	0.44	0.90	0.44	0.91	0.45
3: <i>Resilience</i>	0.88	0.49	0.88	0.48	0.89	0.50
4: <i>Social Competence</i>	0.89	0.54	0.89	0.53	0.90	0.56
5: <i>Problem-Solving</i>	0.89	0.56	0.89	0.59	0.88	0.54
6: <i>Mentorship</i>	0.85	0.65	0.85	0.66	0.85	0.65

Note. α = Cronbach's alpha value. SLB-SF-65: 65-item Short-Form Service Leadership Behavior Scale; SLB-SF-48: the six-factor, 48-item solution to be subjected to CFA.

Table 5b. Internal consistencies of SLB-SF-65, SLB-SF-48, and subscales across gender

	Subset A (N= 2,246)				Subset B (N= 2,240)			
	Males (N= 775)		Females (N= 1,471)		Males (N= 742)		Females (N= 1,498)	
	α	Mean Inter-item correlations	α	Mean Inter-item correlations	α	Mean Inter-item correlations	α	Mean Inter-item correlations
SLB-SF-65	0.97	0.38	0.97	0.32	0.97	0.37	0.97	0.33
SLB-SF-48	0.97	0.42	0.96	0.35	0.97	0.40	0.96	0.36
Subscale 1	0.94	0.56	0.92	0.51	0.93	0.52	0.93	0.53
Subscale 2	0.91	0.45	0.90	0.43	0.92	0.48	0.89	0.41
Subscale 3	0.88	0.48	0.88	0.48	0.88	0.49	0.89	0.51
Subscale 4	0.90	0.55	0.88	0.52	0.90	0.56	0.89	0.55
Subscale 5	0.89	0.57	0.90	0.59	0.87	0.54	0.88	0.54
Subscale 6	0.83	0.62	0.87	0.68	0.84	0.63	0.85	0.66

Note. α = Cronbach's alpha value. SLB-SF-65: 65-item Short-Form Service Leadership Behavior Scale; SLB-SF-48: the six-factor, 48-item solution to be subjected to CFA. Subscale 1: *Self-improvement and Self-reflection*; Subscale 2: *People and Principles Orientation*; Subscale 3: *Resilience*; Subscale 4: *Social competence*; Subscale 5: *Problem-Solving*; Subscale 6: *Mentorship*.

Validity Analyses: Correlation with External Criterion Scales (and Subscales)

Consistent with our hypotheses, correlational findings (see Table 6a) revealed that the SLB-SF-48 scores (and the six subscales) correlated significantly (all $ps < .001$) and positively with all external criterion measures. Using the software package *cocor* [36] which permits comparisons of magnitude between two pairs of correlation coefficients [e.g., Steiger's [37] computation of z-score using average correlations), the findings (see Table 6b) revealed that amongst all significant correlations, the SLB-SF-48 correlated most robustly with the *Revised Servant Leadership Profile* ($r = 0.790$) and noticeably more modest with the *Interpersonal Reactivity Index* ($r = 0.412$). In summary, these findings shed light on the convergent validity

of the SLB-SF-48, which was demonstrated to be positively linked with constructs (e.g., a Servant Leadership mindset and one's inner urge to uphold morality) theorized to delineate the behavioral prerequisites for a Service Leader [8, 9].

Table 6a. Correlations with external criterion scales (and subscales)

	External criterion scales					
	RSLP	MSC	LEF	IRI	IRI-EC	IRI-PT
SLB-SF-65	0.80	0.66	0.51	0.42	0.30	0.45
SLB-SF-48	0.79	0.65	0.53	0.41	0.29	0.43
1: <i>Self-improvement and Self-reflection</i>	0.69	0.59	0.42	0.35	0.24	0.39
2: <i>People and Principles Orientation</i>	0.78	0.69	0.37	0.54	0.44	0.51
3: <i>Resilience</i>	0.58	0.41	0.45	0.20	0.10	0.27
4: <i>Social Competence</i>	0.65	0.56	0.52	0.36	0.29	0.34
5: <i>Problem-Solving</i>	0.49	0.37	0.47	0.19	0.10	0.23
6: <i>Mentorship</i>	0.62	0.42	0.40	0.24	0.16	0.27

Note. N= 2,246. All correlation coefficients are statistically significant at $p < .001$ (two-tailed). SLB-SF-65: 65-item Short-Form Service Leadership Behavior Scale; SLB-SF-48: the six-factor, 48-item solution to be subjected to CFA. RSLP: Revised Servant Leadership Profile; MSC: Moral Self-Concept; LEF: Leadership Efficacy; IRI: Interpersonal Reactivity Index; IRI-EC: Subscale "Empathic Concern"; IRI-PT: Subscale "Perspective Taking."

Table 6b. Comparison of strength of correlations between SLB-SF-48 with the criterion scales

Correlations with the external criterion scales (and subscales)			Z-scores of difference between r_s [36, 37] with SLB-SF-48:				
	α (MITC)	r	MSC	LEF	IRI	IRI-EC	IRI-PT
1. RSLP	0.94 (0.45)	0.790***	14.88***	18.45***	25.32***	29.16***	24.02***
2. MSC	0.83 (0.44)	0.648***	—	7.15***	15.28***	20.14***	13.28***
3. LEF	0.73 (0.27)	0.526***	—	—	5.41***	10.12***	4.44***
4. IRI	0.74 (0.17)	0.412***	—	—	—	12.67***	-2.15*
4a. IRI- EC	0.62 (0.19)	0.293***	—	—	—	—	-7.46***
4b. IRI- PT	0.59 (0.19)	0.433***	—	—	—	—	—

Note. N= 2,246. * $p < .05$ (two-tailed). *** $p < .001$ (two-tailed). α = Cronbach's alpha value. MITC: Mean inter-item correlations. RSLP: Revised Servant Leadership Profile; MSC: Moral Self-Concept; LEF: Leadership Efficacy; IRI: Interpersonal Reactivity Index; IRI-EC: Subscale "Empathic Concern"; IRI-PT: Subscale "Perspective Taking."

Validity Analyses: Correlation with Other Service Leadership Scales under Validation

As Table 7a shows, the SLB-SF-48 correlated significantly and positively with both the composite scores of the single-factor, 40-item Service Leadership Knowledge (i.e., SLK-SF-40) scale ($r = 0.170$), and the eight-factor, 46-item Service Leadership Attitude (i.e., SLA-SF-46) scale ($r = 0.565$). Details about the validation of SLK-SF-40 and SLA-SF-46 are addressed in two separate chapters in this book. The SLB-SF-48 also correlated positively with most of the subscales of SLA-SF-46. Regarding the six subscales of SLB-SF-48, they are mostly correlated positively and significantly with both the SLK-SF-40 and SLA-SF-46 (including the subscales), despite occasional non-significant or unexpected findings (see Table 7a).

Table 7a. Correlations with other Service Leadership scales (and subscales) under validation

	SLK-SF-40	SLA-SF-46-F1	SLA-SF-46-F2	SLA-SF-46-F3	SLA-SF-46-F4	SLA-SF-46-F5	SLA-SF-46-F6	SLA-SF-46-F7	SLA-SF-46-F8	SLA-SF-46-Total
SLB-SF-65	0.17	0.52	0.48	0.51	0.43	0.47	0.48	0.27	-0.08	0.57
SLB-SF-48	0.17	0.52	0.47	0.50	0.42	0.47	0.47	0.26	-0.07	0.56
1: Self-improvement and Self-reflection	0.20	0.48	0.43	0.44	0.37	0.44	0.45	0.21	-0.03	0.52
2: People and Principles orientation	0.26	0.55	0.55	0.53	0.42	0.54	0.47	0.26	-0.01	0.62
3: Resilience	0.02 ^{n.s.}	0.31	0.27	0.33	0.30	0.26	0.29	0.21	-0.13	0.34
4: Social Competence	0.16	0.43	0.41	0.41	0.32	0.41	0.39	0.22	-0.03 ^{n.s.}	0.47
5: Problem-Solving	0.11	0.36	0.29	0.29	0.23	0.30	0.33	0.13	-0.05*	0.35
6: Mentorship	-0.12	0.24	0.22	0.38	0.38	0.19	0.24	0.24	-0.19	0.30

Note. N= 2,246. * $p < .05$ (two-tailed). "n.s." denotes statistical non-significance. Unless otherwise specified, all correlation coefficients are significant at $p < .001$ (two-tailed). SLB-SF-65: 65-item Short-Form Service Leadership Behavior Scale; SLB-SF-48: the six-factor, 48-item solution to be subjected to CFA. SLK-SF-40: Scale score of the single-factor, 40-item Service Leadership Knowledge Scale; SLA-SF-46-Total: Scale score of the eight-factor, 46-item Service Leadership Attitude (SLA) Scale; SLA-SF-46-F1: SLA Factor 1 "Vision and competence"; SLA-SF-46-F2: SLA Factor 2 "People orientation"; SLA-SF-46-F3: SLA Factor 3 "Caring disposition"; SLA-SF-46-F4: SLA Factor 4 "Ethical role model"; SLA-SF-46-F5: SLA Factor 5 "Social competence"; SLA-SF-46-F6: SLA Factor 6 "Self-understanding and reflection"; SLA-SF-46-F7: SLA Factor 7 "Positive view about human beings"; SLA-SF-46-F8: SLA Factor 8 "Unchangeable and dark human nature."

Table 7b. Comparison of strength of correlations between SLB-SF-48 and other Service Leadership scales under validation

Correlations with the external criterion scales (and subscales)			Z-scores of difference between r_s [36, 37] with SLB-SF-48 ^a								
	α (MITC)	r	SLA-SF-46-F1	SLA-SF-46-F2	SLA-SF-46-F3	SLA-SF-46-F4	SLA-SF-46-F5	SLA-SF-46-F6	SLA-SF-46-F7	SLA-SF-46-F8	SLA-SF-46-Total
1. SLK-SF-40	0.94 (0.28)	0.170***	-15.56	-13.63	-13.40	-9.21	-13.61	-12.58	-3.23	10.53	-18.99
2. SLA-SF-46-F1	0.90 (0.46)	0.515***	—	3.46	1.08 ^{n.s.}	5.47	3.86	3.02	11.07	20.88	-5.68
3. SLA-SF-46-F2	0.87 (0.47)	0.474***	—	—	-1.60 ^{n.s.}	2.93	0.50 ^{n.s.}	0.23 ^{n.s.}	9.60	19.57	-9.65
4. SLA-SF-46-F3	0.86 (0.46)	0.499***	—	—	—	5.39	2.04	1.74 ^{n.s.}	10.96	19.33	-5.98
5. SLA-SF-46-F4	0.85 (0.53)	0.419***	—	—	—	—	-2.57	-2.69	6.91	15.53	-10.23
6. SLA-SF-46-F5	0.84 (0.57)	0.467***	—	—	—	—	—	-0.17 ^{n.s.}	8.83	19.50	-9.50
7. SLA-SF-46-F6	0.82 (0.49)	0.470***	—	—	—	—	—	—	8.50	18.10	-7.13
8. SLA-SF-46-F7	0.70 (0.54)	0.261***	—	—	—	—	—	—	—	11.47	-15.37
9. SLA-SF-46-F8	0.78 (0.41)	-0.068**	—	—	—	—	—	—	—	—	-25.12
10. SLA-SF-46-Total	0.94 (0.28)	0.565***	—	—	—	—	—	—	—	—	—

Note. N= 2,246. *** $p < .001$ (two-tailed). α = Cronbach's alpha value. MITC: Mean inter-item correlations. ^aUnless otherwise specified by the superscript "n.s." which denotes statistical non-significance, all other Z-scores of difference were significant at $p < .05$ (two-tailed) (i.e., $|Z\text{-score}| > 1.96$). SLK-SF-40: Scale score of the single-factor, 40-item Service Leadership Knowledge Scale; SLA-SF-46-Total: Scale score of the eight-factor, 46-item Service Leadership Attitude (SLA) Scale; SLA-SF-46-F1: SLA Factor 1 "Vision and competence"; SLA-SF-46-F2: SLA Factor 2 "People orientation"; SLA-SF-46-F3: SLA Factor 3 "Caring disposition"; SLA-SF-46-F4: SLA Factor 4 "Ethical role model"; SLA-SF-46-F5: SLA Factor 5 "Social competence"; SLA-SF-46-F6: SLA Factor 6 "Self-understanding and reflection"; SLA-SF-46-F7: SLA Factor 7 "Positive view about human beings"; SLA-SF-46-F8: SLA Factor 8 "Unchangeable and dark human nature."

Additionally, comparison of the strengths of correlation (see Table 7b) revealed that the strengths of associations between SLB-SF-48 and SLA-SF-46 (including the subscales) were, in general, significantly greater ($ps < .05$) than that of SLB-SF-48 and SLK-SF-40. These results indicated that the display of Service Leadership behaviors would be linked more to whether someone is prone to think or feel (i.e., attitude) like a Service Leader than him/her being more “book-smart” (i.e., knowledge) in the SLAM curriculum.

DISCUSSION

Utilizing a large sample of Hong Kong undergraduates, the present study attempted to validate the Short-Form Service Leadership Behavior Scale. The findings underlined the excellent reliability amongst the items. Results of the EFA suggested a six-factor solution which was demonstrated to be stable across sub-samples, hence providing support for the factorial validity of the 48-item Service Leadership Behavior Scale (SLB-SF-48). Besides, the six subscales were found to correlate significantly and positively with all external criterion measures. The SLB-SF-48 and subscales, which recorded excellent internal consistencies, were also demonstrated to correlate positively and significantly with the two other Serviced Leadership scales. These results provide support for the convergent validity of SLB-SF-48. Taken together, the present analyses lend support to the legitimacy of SLB-SF-48 as a valid and reliable rubric to judge whether someone demonstrated qualities characteristic of a good Service Leader.

There are several contributions of the present chapter. First, in view of the lack of leadership assessment tools in the Chinese context, this is an important addition to the literature. As Chinese people constitute roughly one-fifth of the world's population, objective leadership scales for Chinese people need to be developed. Second, the present findings are important for the Service Leadership literature. As the ever-expanding global economy becomes more service-oriented, this is a timely effort to develop objective tools in this area. Third, the scale permits an objective assessment of Service Leadership behavior which is important for personnel decisions. Employers may wish to employ workers capable of exhibiting Service Leadership behaviors. Fourth, the scale can be used by researchers to evaluate the effectiveness of Service Leadership training programs. Basically, if a training program works, the trainees should show positive changes after completion of the program. Finally, the scale can enable an individual to understand oneself more regarding his/her attributes in Service Leadership.

While the current chapter may have underscored the psychometric soundness and factorial stability of SLB-SF-48, there are still aspects which warrant addressing. First, this chapter focuses only on the exploratory side of the dimensionality assessment of the behavior scale. While an interpretable and stable initial factorial solution has been established, to further quantify and accordingly, ascertain the absolute and relative agreement (i.e., the fit indices) of this six-factor solution with the response data, it is imperative that a confirmatory factor analysis (CFA) be administered [38]. Due to the limitation of word count in this book, the present article is unable to also report the CFA which had been conducted as part of this large-scale validation study. As reiterated throughout this chapter, the findings of the CFA would be detailedly discussed in another paper under preparation.

Second, the *Knowledge-Behavior* link ($r = 0.17$) was noticeably weaker compared to the *Attitude-Behavior* association ($r = 0.56$), implying a disconnect between one's *understanding* and propensity to *practice* in relation to the SLAM curriculum. This may be attributable to the varying nature of different Service Leadership surveys. Unlike the knowledge scale which has a "correct" answer for every item, the behavior and attitude scales are more like an opinion poll. It is, therefore, conceivable that respondents in behavior and attitude scales may respond according to their *personal* or *normative theory* rather than their *genuine stances* on the matter [39]. Social desirability responding may also come into the equation [40]. In other words, instead of indicating whether he/she had previously demonstrated a certain behavioral quality of a Service Leader, a participant may have responded based on what he/she believes a Service Leader *should* do in this situation, or alternatively, he/she may have tried to rate in a particular fashion that presents him/her in a favorable light [41].

In spite of all these shortcomings, this chapter does not only evidence the internal consistency and convergent validity of the SLB-SF-65, but also informs the "rightsizing" of the scale (accordingly forming the SLB-SF-48) which has been well-documented to promote response rate and minimize response burden [see 42 for a review]. As systematic evaluation research in the context of Service Leadership education remains scanty [7, 12], the present chapter constitutes a valuable addition to the literature by presenting a pioneer assessment tool in behavioral qualities of Service Leadership which was demonstrated to be valid and reliable.

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Chapter 142

THE SERVICE LEADERSHIP KNOWLEDGE SCALE: NORMS AND PSYCHOLOGICAL CORRELATES

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ABSTRACT

Guided by the Service Leadership Theory, substantial effort has been devoted to service leadership education in Hong Kong. In contrast, scientific instruments that assess the basic concepts of service leadership are non-existent. As such, we developed three scales pertinent to the notion of service leadership, including knowledge, attitude, and behavior scales. The present study reported the development of norms and psychological correlates of the Service Leadership Knowledge Scale consisting of 40 multiple-choice questions (i.e., SLK-SF-40). Based on a large and representative sample (N = 4,486) of university students recruited from the eight University Grants Committee (UGC)-funded universities in Hong Kong, the results showed that the female students had a significantly higher level of service leadership knowledge than did the male students, resulting in the

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separate norms for the two groups. While age did not show significant influence on the students' knowledge score, the students' grade point average (GPA), leadership training experience, and experience of taking leadership roles in university organizations were all positively associated with their service leadership knowledge scores, but the effect size was small. The percentile norms of this knowledge scale developed in this study provide a useful tool for designing, implementing, and evaluating service leadership education programs.

INTRODUCTION

With the growing globalization and rapid technology development which have intensified international economic competition, skilled human capital is deemed vital to sustaining a nation's competitiveness and long-term prosperity [1, 2]. Regarding the list of desirable attributes, leadership is among the most frequently cited ones. As Ewing, Bruce and Ricketts [3] stated, "the future success of local communities, states, and the country is tied to the development of quality leaders" (p. 119).

The increasing need for leadership qualities comes with a great emphasis on leadership education. In particular, higher education institutions have incorporated leadership into their mission statements and included leadership as one of the important student learning outcomes [4-6]. To cultivate leadership qualities among the university students, a vast number of leadership programs in different forms (e.g., curriculum, course, workshop and outdoor training) have been offered to them [7-9]. For instance, with the financial support of the Victor and William Fung Foundation, a large-scale leadership project was launched in eight public universities funded by the University Grants Committee (UGC) in Hong Kong to satisfy the needs of predominant service economy by nurturing "service leaders" [10].

Despite the divergent patterns, common themes of learning goals can be identified for these leadership programs, such as improving leadership knowledge and nurturing a diverse range of leadership attributes [11, 12]. From the perspective of evidence-based practice [13], it is essential to carry out systematic evaluation studies to examine whether these intended learning outcomes are achieved and whether the related leadership education is effective. Unfortunately, rigorously designed evaluation research for leadership education is scarce, particularly in the Chinese culture. One possible reason has to do with the severe lack of valid tools to assess Chinese people's leadership attributes in the dimensions of leadership knowledge, attitudes and behavior.

Service Leadership Education and Evaluation in Hong Kong

With specific reference to Hong Kong, the economic structure has shifted from the manufacturing economy to the service economy which calls for leaders with a service mindset [14]. To facilitate leadership education in the service era, Chung [15] proposed the Service Leadership Theory which defines service leadership as to "satisfy needs by consistently providing quality personal service to everyone one comes into contact with, including one's self, others, groups, communities, systems, and environments" (p. 5). To elaborate, service leadership highlights service orientation and manifest itself in three

realms—self, others, and systems [15, 16]. Furthermore, it is believed that effective service leadership is determined by three key elements: leadership competency including intra- and inter-personal competencies, moral character, and caring disposition [15].

Guided by the Service Leadership Theory and with the financial support of the Victor and William Fung Foundation, the eight UGC-funded universities in Hong Kong have designed and implemented their own service leadership programs, which incorporate knowledge and beliefs of service leadership and aim to nurture critical service leadership qualities (i.e., leadership competency, caring disposition, and moral character) in the university students [10]. For instance, at The Hong Kong Polytechnic University (PolyU), both credit-bearing service leadership subjects embedded in the general education curriculum and the non-credit bearing programs have been offered to the students since the 2012/2013 academic year [17]. In addition, PolyU and other universities in mainland China jointly organized several intensive service leadership training programs for their students. While evaluation findings have consistently shown that the participants were highly satisfied with these service leadership education programs and they showed improvements in self-perceived service leadership attributes [18-20], the participants' actual gain in service leadership knowledge remains unknown.

Evaluation on Knowledge Gain and Service Leadership Knowledge Scale

Acquisition and application of leadership knowledge are among the desirable outcomes of leadership education [12, 17]. This learning outcome can be regarded as the foundation of service leadership education, which endeavors to promote a new leadership philosophy. To illustrate, without mastering service leadership knowledge, for example, what does service leadership emphasize and what qualities an effective service leader should develop, it is quite difficult, if not impossible, for the participants to adapt for the leadership beliefs and optimize their leadership practice. In this sense, it is indispensable to evaluate the participants' knowledge gained through a service leadership program so as to portray a full picture of the program effectiveness.

In leadership education, it is not uncommon to examine what the participants have learned from the program. However, due to the dearth of validated leadership knowledge scales, most studies examined self-perceived knowledge instead of objectively assessed knowledge. For instance, in an evaluation study conducted by Stedman, Rutherford, Rosser, and Elbert [21], the participants were asked to evaluate their own capacity in defining authentic leadership, character, relationship building stages, and other related knowledge points after a 5-day leadership conference. While measuring self-perceived knowledge seems to have advantages (e.g., easy and efficient), this approach has potential shortcomings. For example, the participants may overestimate their own knowledge level due to social desirability bias [22]. Besides, the trainees' self-ratings are likely to be affected by their subjective experience in the training. As argued by Sitzmann, Ely, Brown, and Bauer [23], "self-assessed knowledge is generally more useful as an indicator of how learners feel about a course than as an indicator of how much they learned from it" (p. 180).

Concerning these potential issues of measuring subjective leadership knowledge, it can be argued that a validated objective knowledge scale is a prerequisite for rigorously assessing

the participants' improvement of knowledge in a leadership program. Unfortunately, such objective leadership knowledge assessment tools are virtually non-existent in the Chinese communities. To fill this research gap as well as facilitating the evaluation of service leadership education in Hong Kong, we have developed a 200-item long-form Service Leadership Knowledge Scale (SLK-LF-200), which is able to assess individuals' actual understanding of service leadership. The scale primarily covered the knowledge points of the aforementioned Service Leadership Theory and associated publications of Chung, Shek and collaborators [e.g., 24, 25]. The details of the content of the SLK-LF-200 have been reported elsewhere [26].

The SLK-LF-200's content-validity and criterion-related validity were found to be good [26, 27]. More specifically, the criterion-related validation study compared an experimental group (i.e., 67 students who took the "Service Leadership" subject at PolyU) with a control group (i.e., 94 students who had never received any service leadership education) regarding their scores on the SLK-LF-200. In the study, 63 out of the initial 200 items were identified as being able to significantly differentiate the two groups [27]. A further item screening procedure was conducted and another 13 items were discarded concerning face validity or item duplication issues. As a result, a 50-item short-form Service Leadership Knowledge Scale (SLK-SF-50) was formed, constituting a fundamental assessment tool for evaluating service leadership education.

Norms and Correlates of the Knowledge Scale

While the content validity and criteria-related validity of the long-form Service Leadership Knowledge Scale (i.e., SLK-LF-200) have been supported, psychometric properties such as the convergent and divergent validity of the 50-item scale (i.e., SLK-SF-50) are unknown. Besides, the norms, as well as the potential correlates of the knowledge scale, are also important issues to be considered. As such, the eight UGC-funded universities in Hong Kong jointly organized a large-scale online survey to validate and finalize the service leadership assessment tools including the knowledge scale. Using the SLK-SF-50, the validation study yielded a final version of the Service Leadership Knowledge Scale which consists of 40 items (i.e., SLK-SF-40). While the procedure of obtaining the SLK-SF-40 as well as the scale's convergent and construct validity is reported in another article of this issue, the norms and the possible psychological correlates of university students' scores on SLK-SF-40 are the foci of the current chapter.

The norms of the service leadership knowledge are important because it serves as a benchmark to assist educators and researchers in developing, implementing, and evaluating effective service leadership programs for the purpose of helping students become knowledgeable service leaders. First, the established norms can be used to identify the standing of the target group's knowledge level in the normative population, based on which training needs can be determined and tailored training programs can be designed. Second, with the norms, participants' progress during training can be monitored by examining changes of their rank in the normative population. Likewise, the norms can be applied to evaluate the training effectiveness.

Normative data can be presented in terms of means and standard deviations of the raw score [28]. In using this type of normative data, one's standing on the assessment can be estimated through using a standardized score (i.e., *z* score), which can be further referred to a table of areas under the normal curve. While this method assumes normative data to be normally distributed, the reality is that normative data will often depart significantly from a normal distribution. Under this circumstance, an alternative, maybe a better choice is percentile norms, which may consist of a full presentation of the percentile rank for each raw score, or it may simply present some of the raw scores corresponding to several landmark percentiles (e.g., the 1st, 5th, 10th, 50th percentile etc.). Various examples of the use of percentile norms can be found in the extant literature [29-31].

Apart from its usefulness when normative data are not normally distributed, a further advantage of percentile norms is simplicity. While a standardized score needs to be interpreted by mapping it on to percentile rank through a look-up table developed by the researcher or an external conversion table [28], the percentile norms can tell us directly the relative position of an individual's test score in the normative population. Percentile norms are easy to understand even for lay people, as the meaning of percentiles is apparently unequivocal [32]. In view of the above positive features of percentile norms, the current study utilized this method to develop norms for the Service Leadership Knowledge Scale using university students in Hong Kong as the normative population.

To determine whether there is a need to develop separate norms for sub-groups, the present study considered two demographic characteristics: gender and age. For gender, in the previous studies, women were found to be more cooperative, relational, empathetic and caring as compared with men [33-37]. Possessing these characteristics which are related to service leadership qualities, women may be more aware of the demands of service leaders in today's service economy and have a better understanding of the philosophy and concepts of service leadership. Therefore, we expected that female students would have a higher level of service leadership knowledge as compared to male students (Hypothesis 1). For the influence of age, very little evidence can be identified in the existing literature. Besides, for the target population (i.e., university students) in the present study, variability in age is generally very small. Thus, we did not expect a significant influence of age on the participants' service leadership knowledge score.

The current study also considered the participants' academic achievement indexed by grade point average (i.e., GPA), the experience of receiving leadership training and experience of being a leader as another three potential correlates of service leadership knowledge score. A high GPA generally indicates an individual's success in course assignments thus could in part represent one's cognitive ability [38]. Based on the prior studies which consistently showed a positive relationship between leadership and intelligence observers including GPA [38, 39], we expected a positive association between GPA and service leadership knowledge (Hypothesis 2).

Although leadership training received by university students may not be directly related to the notion of service leadership, some overlapped knowledge points might be covered, such as the required leadership competency (e.g., problem solving and emotional competence). As a result, it is quite reasonable to expect that one's leadership training experience, regardless of its form and content, will be positively associated with one's service leadership knowledge score (Hypothesis 3). For student leadership experience, we argue that being a leader in a student organization will allow a student to understand what is demanded

by such a position and how he or she can better serve other students. Indeed, previous research found that years of being in a leadership role increased a leader's servant leader behaviors such as altruistic and empathetic behaviors [35]. As such, we hypothesized that the experience of being a leader would positively correlate with service leadership knowledge score as well (Hypothesis 4).

The Present Study

In March 2017, an online-survey project was initiated in the eight UGC-funded institutions in Hong Kong to validate measures assessing the qualities of service leaders as outlined by the Service Leadership Theory. The eight universities include The Hong Kong Polytechnic University (PolyU), The Chinese University of Hong Kong, The Education University of Hong Kong, Hong Kong Baptist University, City University of Hong Kong, Lingnan University, The University of Hong Kong, and Hong Kong University of Science and Technology. Ethics approval for the validation study was obtained from the Human Subjects Ethics Sub-committee of PolyU, which served as the lead institution of the project. The project aimed at validating three scales including knowledge, attitude, and behavior scales, among which the knowledge scale was the focus of the present study. Specifically, the present study outlined the norms and psychological correlates of the final version of the Service Leadership Knowledge Scale (i.e., SLK-SF-40).

OUR STUDY

The online survey was launched simultaneously in eight higher education institutions in Hong Kong. While the research team at PolyU prepared the questionnaire and set up the online survey, each participating university recruited their undergraduate students as participants by distributing the link of the online survey. The participants were well informed the principles of voluntary, anonymity, and freedom to withdraw from the study at any time. The students' consent was sought and each was given a supermarket voucher of 100 Hong Kong dollars as a token of appreciation upon completion of the survey.

Table 1. Demographic characteristics of the sample

University	1	2	3	4	5	6	7	8	Total
No. of participants	1,000	505	500	517	464	500	500	500	4,486
Percentage	22.29%	11.26%	11.15%	11.52%	10.34%	11.15%	11.15%	11.15%	100%
Age range	18-27	17-29	17-34	15-28	18-34	18-29	17-28	16-28	15-34
Age (Mean/SD)	20.46/1.65	20.08/1.55	21.05/1.75	20.79/1.67	20.63/1.77	20.54/1.55	20.38/1.67	19.85/1.50	20.47/1.67
Age group (15-19) (n/%)	297/29.70	193/38.22	95/19.00	117/22.63	112/24.14	133/26.60	173/34.60	224/44.80	1,344/29.96
Age group (≥ 20) (n/%)	703/70.30	312/61.78	405/81.00	400/77.37	352/75.86	367/73.40	327/65.40	276/55.2	3,142/70.04
Male students (n/%)	409/40.90	130/25.74	98/19.60	122/23.60	128/27.59	148/29.60	151/30.20	331/66.20	1,517/33.82
Female students (n/%)	591/59.10	375/74.26	402/80.40	395/76.40	336/72.41	352/70.40	349/69.80	169/33.80	2,969/66.18

The data collection lasted for approximately four months from March to June in 2017. Cases having at least one of the following issues were excluded from further analyses: 1) the participants did not provide consent as indicated by their selection of the option “I decline” on the consent form page, 2) the case was identified as repeated completion due to its same student ID as that of another case, and 3) the participants who claimed to be postgraduate students by themselves. After removing these invalid cases ($n = 69$), the final sample consisted of 4,486 participants, among whom 1,517 (33.82%) were male and 2,969 (66.18%) were female. The participating students’ age range was between 15 to 34 years ($M = 20.47$, $SD = 1.67$), with 1,344 (29.96%) aged between 15 to 19 years and 3,142 (70.04%) aged 20 years or above. Table 1 summarizes the demographic characteristics of the participants in each university based on age and gender.

Measures

The validation project included a wide array of measurements including the three service leadership scales, external criterion scales such as Moral Self Concept, demographic measures, and potential correlates. The present study focused on the Service Leadership Knowledge Scale, and its demographic and other potential correlates.

Service Leadership Knowledge Scale

The knowledge scale (i.e., SLK-SF-50) administrated in the present project consisted of 50 multiple-choice questions generated based on the Service Leadership Theory proposed by Chung [15]. The scale had a holistic coverage of the service leadership knowledge points pertaining to different domains such as the general description and the three realms of service leadership, service leadership competency, moral character, caring disposition, the core belief “everyone can be a leader,” and so on. Detail description of each knowledge domain has been reported elsewhere [26].

In the present study, 10 items in the SLK-SF-50 were discarded due to their low item-total correlations (i.e., below .30; see another chapter in this book). The retained 40 items formed the final scale (i.e., SLK-SF-40) which covered the same knowledge domains as did the original scale. The final scale possessed a one-factor structure with good overall goodness-of-fit indices (e.g., $\chi^2_{(740)} = 3,492.44$, $p < .001$; CFI = .98; TLI = .99; RMSEA = .03). The validation procedure and related validation indicators of the SLK-SF-40 are reported in another article in this issue. The present study was based on the final 40-item scale, which showed good internal reliability (i.e., Cronbach Alpha = .94). Each participant’s answer on each item was coded as “1” or “0” to indicate a correct or incorrect answer, respectively. A total score across the 40 items was computed as the service leadership knowledge score for each participant. In the present study, the participants’ knowledge score ranged from 2 to 40 ($M = 22.55$, $SD = 10.46$).

Demographic and Other Potential Correlates

The demographic characteristics concerned in the present study included age and gender. Other potential correlates included grade point average (i.e., GPA), the experience of leadership training and experience of being in a leadership role.

For GPA, while four participating universities adopted a system with 4.00 as the maximum score, other three universities had different maximum GPA scores (e.g., 4.5). Thus, for participants coming from these three universities, their raw GPA scores were converted to new scores using the formula: new GPA score = raw GPA score $\times$ 4/the maximum GPA score in the university. After this adjustment, the participants' GPA ranged between 0 and 4 ($M = 2.89$, $SD = .45$).

Furthermore, the participants reported whether they had ever taken any leadership course or training including that related to service leadership (0 = No, 1 = Yes), and whether they had served in any leadership position in an organization such as student association (0 = No, 1 = Yes).

Data Analyses

First, a multiple regression analysis was performed to examine whether gender (1 = Male, 2 = Female) and age significantly influenced participants' knowledge score. The results were used to decide whether there was a need to create separate norms for sub-groups. For example, if male students' knowledge scores significantly differ from that of their female counterparts, norms will be constructed separately for male and female students.

Second, we run normality tests to see whether knowledge scores are normally distributed. If the data are normally distributed, we will calculate standardized scores as well as percentile norms, and percentiles will be constructed only if the data are not normally distributed.

When constructing percentile norms, we first mapped raw scores to each percentile from 1 to 100. As several students gained the same knowledge score, one raw score can have several percentile rank scores, which may cause difficulties in interpreting the norms. Therefore, we further calculated a unique percentile for each raw score. As strongly recommend by Crawford et al. [28], we defined the unique percentile of raw scores as the percentage including those fall below as well as half of those obtaining the score of interest. This calculation method can be presented by the formula below:

$$\text{Percentile rank of a given raw score} = 100 \times (m + 0.5k)/N,$$

where m means the number of participants scoring below the given raw score, k is the number of participants obtaining the given score, and N represents the overall size of the normative sample considered. This method is adopted as it takes the discrepancy between a test score and the real-valued score into account [28]. After this calculation procedure, we further rounded off the figures to present the integer values.

Third, correlational analyses were utilized to investigate associations between other potential correlates (e.g., GPA and leadership training experience) and the participants' knowledge score.

OUR FINDINGS

While age did not show significant predicting effect on the knowledge score ($\beta = -.0003$, $p = .99$), gender significantly predicted the participants' knowledge score ($\beta = .17$, $p < .001$; Cohen's $f^2 = .03$), with female students ($M = 23.85$, $SD = 10.10$) having significantly higher

knowledge scores than male students ($M = 20.02$, $SD = 10.70$). Thus, Hypothesis 1 was supported.

Table 2. Percentiles and related raw scores for Service Leadership Knowledge Scale (SLK-SF-40) by gender

Percentile (1-50)	Raw Score			Percentile (51-99)	Raw Score		
	Male ($N = 1,517$)	Female ($N = 2,969$)	Total sample ($N = 4,486$)		Male ($N = 1,517$)	Female ($N = 2,969$)	Total sample ($N = 4,486$)
1	≤ 4.00	≤ 5.00	≤ 5.00	51	18.00	27.00	24.00
2	5.00	6.00	6.00	52	19.00	27.00	25.00
3	6.00	7.00	6.00	53	19.00	27.00	25.00
4	6.00	7.00	6.00	54	20.00	28.00	26.00
5	6.00	7.00	7.00	55	20.00	28.00	26.00
6	6.00	8.00	7.00	56	21.00	28.00	27.00
7	7.00	8.00	7.00	57	22.00	29.00	27.00
8	7.00	9.00	8.00	58	23.00	29.00	28.00
9	7.00	9.00	8.00	59	23.00	29.00	28.00
10	7.00	9.00	8.00	60	24.00	30.00	28.00
11	7.00	10.00	9.00	61	24.00	30.00	29.00
12	8.00	10.00	9.00	62	25.00	30.00	29.00
13	8.00	10.00	9.00	63	26.00	30.00	29.00
14	8.00	10.00	9.00	64	26.00	31.00	30.00
15	8.00	11.00	10.00	65	27.00	31.00	30.00
16	8.00	11.00	10.00	66	27.00	31.00	30.00
17	9.00	11.00	10.00	67	28.00	31.00	30.00
18	9.00	12.00	10.00	68	28.00	31.00	31.00
19	9.00	12.00	11.00	69	28.42	32.00	31.00
20	9.00	12.00	11.00	70	29.00	32.00	31.00
21	9.00	13.00	11.00	71	29.00	32.00	31.00
22	9.96	13.00	12.00	72	30.00	32.00	32.00
23	10.00	13.00	12.00	73	30.00	32.00	32.00
24	10.00	14.00	12.00	74	30.00	33.00	32.00
25	10.00	14.00	12.00	75	31.00	33.00	32.00
26	10.00	14.00	13.00	76	31.00	33.00	33.00
27	10.00	15.00	13.00	77	31.00	33.00	33.00
28	11.00	15.00	13.00	78	32.00	33.60	33.00
29	11.00	16.00	14.00	79	32.00	34.00	33.00
30	11.00	16.00	14.00	80	32.00	34.00	33.00
31	12.00	17.00	14.00	81	32.00	34.00	34.00
32	12.00	17.00	15.00	82	33.00	34.00	34.00
33	12.00	18.00	15.00	83	33.00	34.00	34.00
34	12.00	18.00	15.00	84	33.00	35.00	34.00
35	13.00	19.00	16.00	85	34.00	35.00	35.00
36	13.00	19.00	16.00	86	34.00	35.00	35.00
37	13.00	20.00	17.00	87	34.00	35.00	35.00
38	13.00	20.00	17.00	88	35.00	35.00	35.00
39	13.00	21.00	18.00	89	35.00	36.00	35.00
40	14.00	21.00	18.00	90	35.00	36.00	36.00
41	14.00	22.00	19.00	91	35.00	36.00	36.00
42	14.00	23.00	19.00	92	36.00	36.00	36.00
43	15.00	23.00	20.00	93	36.00	36.00	36.00
44	15.00	23.00	20.00	94	36.00	37.00	36.00
45	15.00	24.00	21.00	95	36.00	37.00	37.00
46	16.00	24.00	22.00	96	37.00	37.00	37.00
47	16.00	25.00	22.00	97	37.00	38.00	37.00
48	16.64	25.00	23.00	98	38.00	38.00	38.00
49	17.00	26.00	23.00	99	38.82	39.00	39.00
50	17.00	26.00	24.00	100	39.00	40.00	40.00

Then we performed normality tests for female and male groups separately. A Shapiro-Wilk’s test ($p < .001$) [40, 41] showed that the knowledge scores were not normally distributed for both males and females, with a skewness of .22 ($SE = .06$, $z\text{-value} = 3.67$, $p < .001$) and a kurtosis of -1.43 ($SE = .13$, $z\text{-value} = -11$, $p < .001$) for the male participants, and a skewness of $-.30$ ($SE = .04$, $z\text{-value} = -7.5$, $p < .001$) and a kurtosis of -1.31 ($SE = .09$, $z\text{-value} = -14.56$, $p < .001$) for the female group [42-44]. A further visual inspection of their histograms revealed a bimodal distribution for both groups. As such, only percentile norms were built separately for both male and female students. (see Table 2 and Table 3).

Table 3. Raw scores and related percentiles for Service Leadership Knowledge Scale (SLK-SF-40)

Raw score	Percentiles		
	Male ($N = 1,517$)	Female ($N = 2,969$)	Total sample ($N = 4,486$)
1	0.0	0.0	0.0
2	0.0	0.0	0.0
3	0.0	0.0	0.0
4	1.0	0.0	0.0
5	2.0	1.0	1.0
6	5.0	2.0	3.0
7	9.0	4.0	6.0
8	14.0	6.0	9.0
9	19.0	9.0	12.0
10	25.0	12.0	17.0
11	29.0	16.0	20.0
12	33.0	19.0	24.0
13	37.0	22.0	27.0
14	41.0	25.0	30.0
15	44.0	27.0	33.0
16	47.0	30.0	35.0
17	49.0	32.0	38.0
18	51.0	34.0	40.0
19	53.0	36.0	41.0
20	55.0	37.0	43.0
21	56.0	39.0	45.0
22	57.0	41.0	47.0
23	59.0	43.0	48.0
24	60.0	45.0	50.0
25	62.0	48.0	52.0
26	64.0	50.0	54.0
27	66.0	52.0	57.0
28	68.0	55.0	59.0
29	70.0	58.0	62.0
30	73.0	62.0	66.0
31	76.0	66.0	70.0
32	80.0	71.0	74.0
33	83.0	76.0	78.0
34	86.0	81.0	83.0
35	90.0	86.0	87.0
36	94.0	91.0	92.0
37	97.0	95.0	96.0
38	98.0	98.0	98.0
39	100.0	99.0	99.0
40	100.0	100.0	100.0

Correlates of Knowledge Score

Results of correlational analysis showed that the participants' service leadership score was significantly correlated with their GPA ($r = .20, p < .001; r^2 = .04$), experience of taking leadership course or training ($r = .07, p < .001; r^2 = .005$), and experience of being a leader ($r = .12, p < .001; r^2 = .014$), meaning that students with higher GPA, having experience of taking leadership course or training, or having experience of being a leader before were likely to have a better understanding of service leadership knowledge. Hence, Hypotheses 2 to 4 were also supported. However, it is noteworthy that the effect size involved was small.

DISCUSSION

The present study outlined percentile norms and potential psychological correlates of the Service Leadership Knowledge Scale (SLK-SF-40). As a pioneering attempt to develop and validate objective knowledge scale pertinent to service leadership, the present study is a timely response to the lack of assessment tools measuring individuals' leadership knowledge in the Chinese context. Concerning the fact that substantial effort has been taken on promoting service leadership education in Hong Kong while little research has articulated the effectiveness, the present study also makes an important progress in addressing the issue of evaluation. In particular, the established norms will serve as a useful instrument not only to assess individuals' standing in a normative population regarding the fundamental knowledge of service leadership but also to track the improvement of the participants' relative standing during and after receiving service leadership education.

Noteworthy, the current study has two methodological strengths. First, we developed the norms based on a large and representative sample of university students coming from multiple higher education institutions in Hong Kong. Therefore, we believe that the generalizability of the findings is good. Second, we used an objective knowledge scale where the items were derived from a solid leadership framework. In addition, the validity and other psychometric properties of the scale have been proved to be good. Thus, the norms can be regarded as reliable and valid in delineating university students' service leadership knowledge level.

Apart from the norms, our study adds to the extant literature on the potential correlates of university students' comprehension of service leadership. Three notable observations from the present findings could be highlighted. First, as expected, the university students' service leadership knowledge scores were not significantly associated with their age. This result indicates that the students will not gain a better understanding of the service leadership concepts automatically as time goes by. Instead, leadership training could be an effective means for knowledge acquisition. Indeed, previous studies suggest that leadership development among youth is closely related to their involvement in leadership training programs [45, 46]. The present study also found that overall leadership training experience was positively correlated to service leadership knowledge score, supporting the utility of conducting leadership training for youth. Nevertheless, the effect size of the correlation between leadership training experience and service leadership knowledge was not large. This may be because we did not specify the focus of leadership training. Although leadership

training programs, regardless of their focus, may cover some common knowledge points which are also useful for increasing the understanding of service leadership, those training programs specifically focusing on service leadership may be more effective.

Second, also in line with our hypothesis, the female students demonstrated a higher knowledge level than did the male students. This is understandable because women are more service-oriented than men in nature, as evidenced by research findings showing that women tended to be more caring, relationship-oriented and empathetic than men [34-36]. These qualities fit the demands of the service economy at the first place and help women better understand the service leadership concepts than men. Given this gender difference, two separate norms were established for female and male students. One practical implication of this finding is that gender effect should be considered when implementing and evaluating service leadership education programs.

Third, the participants' GPA was positively correlated with their service leadership knowledge score. For GPA, a better score usually indicates a student's better cognitive ability such as reasoning and problem solving skills [38], which may better enable them to infer what kind of leadership qualities can fulfill the needs of service economy. Fourth, we found that the experience of being a leader in a student organization was associated with a higher service leadership knowledge score. This result also echoes the previous findings which suggested that serving in leadership roles in university exerts positive impacts on diverse student learning outcomes such as leadership efficacy [47]. It is believed that student leadership in college embody a wide range of elements such as helping people, building relationship and working as a team [48], all of which are related to service leadership concepts, directly or indirectly.

Although the present study represents a pioneering effort to construct percentile norms and identify potential psychological correlates for service leadership knowledge, it has three limitations. First, we only investigated university students which may limit the generalizability of the findings to other populations. Future research will certainly benefit from employing a more heterogeneous sample of potential service leaders including employees in different economic sectors and constructing norms of service leadership knowledge accordingly. Second, we did not collect data in other Chinese communities. As service economy grows rapidly as well in mainland China where there is also a need to launch service leadership education programs, it is also necessary to build norms among mainland Chinese people for evaluation purpose. Thus, future research could go further by collecting data and comparing knowledge levels in different Chinese communities. The final limitation is related to the limited number of potential correlates considered in the present study. For example, we did not examine the influence of students' undergraduate major. As some of the knowledge points are not unique to service leadership, it is thus possible that students in certain majors can learn the knowledge from their own major subjects such as social work or psychology. Future studies could include students' major and other individual traits such as personality to examine and compare the relationships between these factors and service leadership knowledge level.

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Chapter 143

THE SERVICE LEADERSHIP ATTITUDE SCALE: NORMATIVE DATA AND PERSONAL CORRELATES IN CHINESE UNIVERSITY STUDENTS

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ABSTRACT

As there are few validated measures of service leadership in the Chinese contexts, there is a need to develop and validate scientific instruments to assess service leadership attitudes and beliefs of Hong Kong university students. In this chapter, we present normative findings for the 46-item Service Leadership Attitude Scale (SLA-SF-46) and explore the potential personal correlates in a large university sample (N = 4,486) recruited from eight universities in Hong Kong. Results showed that while female

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students scored significantly higher on the SLA-SF-46 compared to male students, no age-related differences were observed. Hence, separate norm tables for both gender groups were constructed. With regard to the potential personal correlates, students' grade point average (GPA), previous leadership training, and experiences of being a leader were all positively correlated with their SLA-SF-46 scores, although the effect sizes were not large. The creation of the percentile norms helps educators and practitioners to understand the service leadership attributes of individuals.

INTRODUCTION

Hong Kong has experienced a drastic reform of the economic system from an industrial era to a post-industrial era since the 1970s. The service sector, represented by traditional key industrials (such as trading, tourism, and financial services) and emerging industries (such as medical services, education services, and creative industries), has replaced manufacturing and become the engine of economic development in Hong Kong. The core assets of the modern society are intangible human capitals (e.g., knowledge, intelligence, and skills) beyond tangible physical assets (e.g., the real estate or the machinery). Leadership, as a core determinant for the operation of contemporary business enterprises, has different meanings in every era and every society [1]. For the traditional manufacturing economy, top-down and bureaucratic paradigms of leadership models are notably effective as they are product-oriented and task-focused. However, those paradigms are no longer well suited for the modern service-oriented and knowledge-based economy [2]. As commented by Manville and Ober in the "Harvard Business Review," "we're in a knowledge economy, but our managerial and governance systems are stuck in the Industrial Era. It's time for a whole new model" [3]. Unfortunately, we find very few explicit discussions of leadership models for the knowledge era with regard to Hong Kong. Against this background, Chung [4] advocated the notion of service leadership and refined the idea with the Service Leadership and Management (SLAM) model. According to him, service leadership "is about satisfying needs by consistently providing quality personal service to everyone one comes into contact with, including one's self, others, groups, communities, systems, and environments" [4].

Classic leadership models proposed that leaders shall possess specific genetic traits, which was much based on the belief that leaders are born and not made [5]. In contrast, service leadership theory begins with the basic assumption that leadership could be learned and everyone can be a leader [6]. Therefore, the call for leadership is for everyone. Particularly, for students in tertiary institutions, leadership development is viewed as one of the most prominent themes and objectives as they will become pillars of the society in the foreseeable future [7]. Although there are leadership courses and programs targeting young people, several limitations merit attention. First, most of the existing leadership development programs in the business world are usually expensive and still aim for "elitists" solely [8]. Second, only "hard" skills (such as knowledge and management skills) of a leader are emphasized in most leadership development programs [9], whereas "soft" skills (such as interpersonal and intrapersonal competences) are overlooked. Third, there is a lack of systematic evaluation of leadership training programs [9].

Service Leadership Education in Hong Kong

Effective leadership courses or programs designed for university students are rare in Hong Kong. As such, with the theoretical groundwork of the Hong Kong Institute of Service Leadership and Management (HKI-SLAM) and financial support of the Victor and William Fung Foundation, the Fung Service Leadership Initiative was launched in 2012 and a series of service leadership projects were subsequently conducted in eight institutions that funded by the University Grants Committee (UGC). These projects included both credit-bearing subjects and non-credit bearing programs aiming to nurture leaders with the fundamental service leadership qualities, including competences, characters, and caring dispositions [4]. To date, findings from many evaluation studies suggested that service leadership training had received favorable responses from different stakeholders. Taking The Hong Kong Polytechnic University (PolyU) as an example, participants indicated their satisfaction with the service leadership programs and showed great improvements in service leadership attributes (such as intrapersonal competences) based on multiple evaluation strategies [10-12].

One important dimension of leadership training is leadership attitudes and beliefs such as whether a leader believes the followers are changeable. It is not rare to measure leadership attitudes and beliefs with respect to a particular leadership model. For instance, Fleishman [13] developed the Leadership Opinion Questionnaire (LOQ) to assess leadership attitudes in the industry setting from the perspective of the Leadership Skills Model that mainly focused on the competences of leaders, such as problem-solving skills and social judgment skills. Wielkiewicz [14] also developed a Leadership Attitudes and Beliefs Scale (LABS) based on the assumption that leadership could be understood through organizational success rather than individual actions. Unfortunately, none of the extant leadership attitude scales is suitable for examining individuals' understanding of the service leadership theory. In contrast to these existing theories, Service Leadership theory adopts a more systematic and comprehensive approach. As service leadership training programs have been designed and organized in different institutions, it is imperative for researchers and educators to have a standardized tool assessing service leadership attitude.

Under this premise, the Research Team at PolyU endeavored to develop and validate scales on service leadership knowledge, attitude, and behavior. With regard to the Service Leadership Attitude Scale (SLA), a 132-item long form (i.e., SLA-LF-132), was initially developed on the grounds of the SLAM framework [4] with relevant publications authored by Chung, Shek, and collaborators [15-17]. The previous study demonstrated that SLA-LF-132 had good content validity [18]. Results of an initial exploratory factor analysis (EFA) based on 200 sets of questionnaires suggested a 5-factor solution with 73 items (i.e., SLA-SF-73), which showed good reliability and significant correlation with the 50-item short-form Service Leadership Knowledge Scale (i.e., SLK-SF-50). Based on the SLA-SF-73, further EFA and confirmatory factor analysis (CFA) based on larger samples ($N = 2,246$ and $2,240$, respectively) informed a finalized solution with 46 items (i.e., SLA-SF-46), which demonstrated good fit indices ($CFI = 0.93$; $NNFI = 0.92$; $RMSEA = 0.041$). Results showed that the SLA-SF-46 covered dimensions of vision and competence, people orientation, caring disposition, ethical role model, social competence, self-understanding and reflection, positive view about human beings, and unchangeable and dark human nature. The findings are reported in a chapter in this book. In the current study, all the results were based on the final version Service Leadership Attitude Scale (i.e., SLA-SF-46).

Normative Data for the Service Leadership Attitude Scale

Normative data for the Service Leadership Attitude Scale is fundamental to the development and implementation of the service leadership education. The use of normative data is common in psychological assessment. In the field of leadership study, there has been relatively little research concerning the norms of leadership [19], not to mention in different Chinese contexts. Accordingly, the development of normative data for SLA-SF-46 is an important addition to the literature. First, normative data provides a yardstick to measure, rank, and compare individuals' level of service leadership attitudes and beliefs. Second, with the help of normative data, educators could detect students' current beliefs and blind spots on service leadership. Then targeted curriculum and teaching could be offered and developed. Third, a straightforward and convenient norm table provides a very useful research tool that could objectively assess program effectiveness.

The Literature on normative data suggested different ways of explaining the means and standard deviations of raw scores [20]. For normative distributions, standardized Z scores could be calculated for estimation. The normal curve could indicate the corresponding area with the given Z score. However, the distributions in real life are usually non-normal. In such situations, another alternative but complementary approach to describe normative data is percentile norms [21], which provides a full and concise picture of the correspondence between a raw score and its percentile rank. Furthermore, percentile norm is convenient to use, even for non-professionals. As such, the overarching objective of this chapter was to provide the estimates of percentile ranks corresponding to raw scores on the SLA-SF-46.

Personal Correlates of Service Leadership Attitude

For sub-groups of a population, separate norms would be needed if they demonstrate notable differences. Gender and age were the principal demographic factors covered in the current study. Societies always have discrepant gender role expectations, which influence individuals' leadership attitudes and beliefs. Across cultures, females are still underrepresented in leadership positions in comparison to males [22]. In previous literature, there was an incongruity in the association of gender and leadership attitude. According to Wielkiewicz et al. [23], a greater percentage of male first-year college students was located in the Low Hierarchical/Low Systemic category of leadership beliefs, which was associated with effective ecological leadership. Based on this finding, it was hypothesized that male college students in Hong Kong would possess a higher level of service leadership attitude than female college students (Hypothesis 1a). Nevertheless, multiple empirical studies demonstrated that women leaders were better at emotional balance and control, more expressive, and cooperative than men [24, 25]. Hence, it could also be assumed that female college students in Hong Kong would possess a higher level of service leadership attitude compared with male college students (Hypothesis 1b). The primary goal of this study was to test these two competing hypotheses, and preliminarily explore the gender differences issue in service leadership.

Although a body of research has tried to shed light on the age-related differences in leadership over the last decades, there is no solid conclusion [26]. Existing findings on age-

leadership linkages are scarce and contradictory. For example, Barbuto et al. [27] found that age positively predicted transformational leadership and individualized consideration. Other studies, in contrast, observed that older leaders demonstrated less mastery of teamwork knowledge [28], less delegating and considerate behaviors [29]. Besides, other studies have reported non-significant relationships between leaders' age and their task-oriented behaviors [27, 30] or leadership styles [31]. Considering the inconclusive findings of the relationship between age and leadership, and the narrow span in age for the targeted population (i.e., university students), we did not put up any specific hypothesis on the relationship between age and service leadership attitude.

Other personal factors were assumed to be associated with service leadership attitude in the current study, which included participants' grade point average (i.e., GPA), their leadership training experience, and the previous experience of being a leader. GPA has been regarded as a good predictor of the performance of solving complex tasks, which was closely associated with favorable leadership attributes [32]. Besides, studies have observed that university students' GPA was positively correlated with their life-long learning attitude, self-rated leadership abilities, and disagreement with hierarchical leadership thinking [33]. Therefore, the current study attempted to examine this GPA-leadership linkage and expected a positive correlation between participants' GPA and service leadership attitude (Hypothesis 2).

Multifarious leadership training programs in and out of campus are not uncommon for university students. Empirical studies have investigated the benefits of such education efforts. According to a longitudinal study that assessed the outcomes of 31 leadership development programs in ten institutions in the United States [34], participation in leadership programs had a positive impact on college students' personal development, multi-cultural awareness, and values understanding ability. Although the philosophy and concepts of other leadership programs would not perfectly match service leadership theory, some could share the similar attitudes or beliefs. As inspired by previous studies, it was expected that one's leadership training experiences would be positively related to the service leadership attitude (Hypothesis 3).

Apart from the leadership training experiences, college students nowadays have abundant opportunities to serve as a leader. Qualitative findings showed that college students' practices in leadership roles brought about positive experiences in the aspects of skills-building and interacting personality [35]. Accordingly, it was expected that being a leader previously would be positively associated with service leadership attitude (Hypothesis 4).

OUR RESEARCH

An online survey was adopted in the present study. A total of 4,555 university students were recruited using snowball sampling from the eight UGC-funded universities in Hong Kong, including The Hong Kong Polytechnic University (PolyU), The University of Hong Kong (HKU), The Chinese University of Hong Kong (CUHK), Hong Kong Baptist University (HKBU), City University of Hong Kong (CityU), The Education University of Hong Kong (EdUHK), Lingnan University (LU), and Hong Kong University of Science and Technology (HKUST). Each institution recruited at least 500 full-time undergraduate students

to complete the survey via the PolyU “mySurvey” online survey platform (<https://www.polyu.edu.hk/mysurvey/>).

Table 1. Socio-demographic profiles of participants (N = 4486)

	N (%)
Gender	
Male	1,517 (33.82%)
Female	2,969 (66.18%)
Age	
15-19 years	1,344 (29.96%)
20-24 years	3,070 (68.44%)
25-29 years	69 (1.54%)
30 years or above	3 (0.07%)
University	
PolyU	1,000 (22.29%)
CUHK	505 (11.26%)
EdUHK	500 (11.15%)
HKBU	517 (11.52%)
CityU	464 (10.34%)
LU	500 (11.15%)
HKU	500 (11.15%)
HKUST	500 (11.15%)

Note. PolyU = The Hong Kong Polytechnic University; CUHK = The Chinese University of Hong Kong; EdUHK = The Education University of Hong Kong; HKBU = Hong Kong Baptist University; CityU = City University of Hong Kong; LU = Lingnan University; HKU = The University of Hong Kong; HKUST = Hong Kong University of Science and Technology.

Website link of the survey was provided for interested participants, where they were able to electronically sign a consent form before the survey started. Students were informed about the confidentiality of their responses and the rights to withdraw from this study at any time. Each participant would be given \$HK100 as a token of appreciation upon completion of the survey. The online survey hosted at each university with links between March to June 2017. Among all the 4,555 respondents, six students were excluded as they declined to complete the questionnaire. In the next step, thirty-three cases who completed the questionnaire for multiple times were also removed. Other thirty more cases were deleted due to the ineligibility of participants (e.g., mismatching in the institution and the questionnaire version, as well as those postgraduate students who accidentally completed the questionnaire). In the end, the sample of this study consisted of 4,486 university students between the age of 15 and 34 years ($M_{age} = 20.47$, $SD_{age} = 1.67$), including 1,517 (33.82%) males and 2,969 (66.18%) females. Table 1 summarizes the socio-demographic characteristics of the participants.

Instruments

The online survey consisted of demographics, the composite Service Leadership Scale, and several well-validated leadership or personality measurements (e.g., Leadership Efficacy Scale; Interpersonal Reactivity Index) [36-38] serving as external criteria. The composite Service Leadership Scales measured Service Leadership Attitude, Service Leadership

Knowledge, and Service Leadership Behavior. This chapter only focused on Service Leadership Attitude Scale and its potential personal correlates.

Service Leadership Attitude Scale

The 46-item final version SLA-SF-46 was developed and validated by the first author of the current study [18] on the basis of the SLAM framework and relevant literature on service leadership theory [9, 39]. Details for the scale validation procedure shall be documented in another article in this book.

The scale aims to assess individuals' views and beliefs about the role of leader or desirable leadership practices/qualities. Scores for each item range from 1 (very dissimilar to me) to 6 (very similar to me). Eight subscales are incorporated in the SLA-SF-46, including vision and competence (10 items), people orientation (8 items), caring disposition (7 items), ethical role model (5 items), social competence (4 items), self-understanding and reflection (5 items), positive view about human beings (2 items), and unchangeable and dark human nature (5 items). A raw score of SLA is yielded by summing scores of all 46 items. The SLA-SF-46 was found to be internally consistent in this study ($\alpha = .94$ for the full scale; $\alpha = .70$ to $.90$ for all subscales).

Personal Correlates

The demographic profile in the survey covered participants' age ($M_{\text{age}} = 20.47$, $SD = 1.67$) and gender (0 = Female, 1 = Male). Other potential correlates concerned their learning experiences in leadership-related courses/programs, leadership experience, and grade point average (GPA) in University. Specifically, participating students reported whether they had ever taken any leadership (including but not limited to service leadership) course or program (0 = No, 1 = Yes), whether they had ever served in any leadership position in an organization (0 = No, 1 = Yes), and their recent GPA (ranged between 0 and 4 after standardization).

Data Analyses

All statistical analyses were performed using SPSS for Windows, version 23.0 (IBM-SPSS Inc, Chicago, Illinois, USA). First of all, to decide if there was a need to create separate SLA-SF-46 norms for different sub-groups, differences originated from gender and age were firstly assessed utilizing a multiple regression analysis.

Before creating the percentile norms, we ran normality tests to make sure whether SLA-SF-46 total scores were normally distributed or not. If the test scores of the sample are normally distributed, the raw scores should be standardized to Z scores based on the means and SDs. Then a parametric method [40] could be adopted to provide an interval estimate of the percentile rank. If not normally distributed, the interval cannot be estimated and only the percentiles for raw scores would be constructed.

To sketch the percentile norms, we listed all raw scores to each percentile from 1 to 100. Because of the granularity of raw scores, a given raw score could match more than one percentile. As suggested in the article of Crawford, Garthwaite, and Slick [20], in such situations, if the number of test items is modest, the user would be suggested to calculate the unique percentile rank for each raw score based on the standard formula [41]: *Percentile Rank*

$= (m + 0.5k)/N \times 100$. Among which, m stands for the number of individuals who scored lower than that specific raw score, k means the number of individuals who scored that specific raw score, while N indicates the total number of the norm sample. The calculated percentile ranks were then rounded to integers from 1st to 99th percentiles.

Last, correlational analyses were carried out to assess other potential correlates (i.e., training experience in leadership courses/programs; experiences of being a leader; and GPA).

FINDINGS

Multiple regression analysis (Cohen's $f^2 = .02$) showed that age did not significantly contribute to the variances of participants' SLA-SF-46 score ($\beta = -.01$, $p = .41$). Generally speaking, gender significantly predicted participants' SLA-SF-46 score ($\beta = -.14$, $p < .001$), with higher SLA-SF-46 total scores for female students ($M = 217.29$, $SD = 19.49$) compared with male students ($M = 210.79$, $SD = 24.07$). Univariate analysis showed gender differences for all dimensions of SLA, with female students obtaining higher scores than male students ($F = 14.60 \sim 96.39$, $ps < .001$, $\eta^2 = .005 \sim .021$). Therefore, Hypothesis 1b was supported while Hypothesis 1a rejected. Separate norm tables were subsequently created for different genders.

The normality tests showed that the SLA-SF-46 scores for both female and male groups were negatively skewed with a skewness of $-.67$ for females and -1.07 for males, and a kurtosis of 3.58 for females and 3.90 for males. Kolmogorov-Smirnov tests confirmed that the distributions deviated highly significantly from a normal distribution ($D = .071$ and $.076$ respectively for female and male groups, $ps < .001$). Hence, percentiles for raw scores, instead of standardized Z scores, were calculated due to the non-normalized distributions. The tabulation method was adopted to display the corresponding raw score for each percentile rank (Table 2). Meanwhile, another lookup table demonstrated the corresponding percentile for each raw score (Table 3). The normative data were stratified by gender as gender influenced SLA-SF-46 scores appreciably.

Correlational analyses showed that the participants' SLA-SF-46 scores were significantly correlated with their leadership training experience ($r = .09$, $p < .001$; $r^2 = .008$), leadership position experience ($r = .09$, $p < .001$; $r^2 = .008$), and GPA ($r = .15$, $p < .001$; $r^2 = .02$). As such, Hypotheses 2 to 4 were all supported. However, the findings should be interpreted with caution, as the effect sizes were limited.

DISCUSSION

To address the issue of evaluation and assess objective changes in attitudes and beliefs in Service Leadership education program, a validated measurement is indispensable. To fill this gap, the current study presents findings on the percentile norms and personal correlates of the Service Leadership Attitude Scale with a large university sample ($N = 4,486$) in a Chinese context. The constructed norms shall serve as a reference to rank and compare individuals' service leadership attitude among a particular population, as well as a useful resource for educators and practitioners to detect the changes before and after receiving service leadership courses or programs.

Table 2. Percentiles and related raw scores for Service Leadership Attitude Scale (SLA-SF-46) by gender

Percentile (1-50)	Raw Score				Percentile (51-99)	Raw Score		
	Male (N = 1,517)	Female (N = 2,969)	Total sample (N = 4,486)			Male (N = 1,517)	Female (N = 2,969)	Total sample (N = 4,486)
1	≤ 136.36	≤ 163.70	≤ 155.00		51	214.00	218.00	216.37
2	155.00	173.40	165.74		52	214.00	218.00	217.00
3	161.54	179.00	172.00		53	215.00	219.00	217.00
4	167.00	182.00	176.48		54	215.00	219.00	218.00
5	172.00	185.00	179.00		55	215.00	219.00	218.00
6	174.00	187.00	182.00		56	215.00	220.00	218.00
7	176.00	190.00	184.00		57	216.00	220.00	219.00
8	178.00	191.00	186.00		58	216.00	220.00	219.00
9	179.00	193.00	188.00		59	217.00	221.00	220.00
10	181.00	194.00	190.00		60	217.00	221.00	220.00
11	182.00	195.70	191.00		61	218.00	221.00	220.00
12	184.00	197.00	192.00		62	218.00	222.00	221.00
13	186.00	198.00	194.00		63	219.00	222.00	221.00
14	187.00	199.00	195.00		64	219.00	223.00	222.00
15	188.00	200.00	196.00		65	220.00	223.00	222.00
16	190.00	201.00	197.00		66	220.00	224.00	222.00
17	191.00	202.00	198.00		67	221.00	224.00	223.00
18	192.00	203.00	199.00		68	221.00	225.00	223.00
19	193.00	203.00	200.00		69	222.00	225.00	224.00
20	194.00	204.00	201.00		70	222.00	226.00	224.00
21	195.00	205.00	202.00		71	223.00	226.00	225.00
22	196.00	206.00	203.00		72	223.00	227.00	226.00
23	197.00	207.00	203.00		73	224.00	227.00	226.00
24	197.32	207.00	204.00		74	224.00	228.00	227.00
25	198.00	207.00	205.00		75	225.00	228.00	227.00
26	199.00	208.00	205.00		76	226.00	229.00	228.00
27	200.00	209.00	206.00		77	226.00	229.00	228.00
28	201.00	209.00	207.00		78	227.00	230.00	229.00
29	202.00	210.00	207.00		79	228.00	231.00	230.00
30	203.00	210.00	208.00		80	228.00	231.00	230.00
31	203.00	210.00	209.00		81	229.00	232.00	231.00
32	204.00	211.00	209.00		82	229.00	233.00	232.00
33	204.00	211.00	209.00		83	230.00	233.00	232.00
34	205.00	212.00	210.00		84	231.00	234.00	233.00
35	206.00	212.00	210.45		85	232.00	235.00	234.00
36	206.00	213.00	211.00		86	234.00	236.00	235.00
37	207.00	213.00	211.00		87	235.00	237.00	236.00
38	207.00	213.00	212.00		88	236.00	239.00	237.56
39	208.00	214.00	212.00		89	237.00	240.00	239.00
40	209.00	214.00	213.00		90	238.00	242.00	240.00
41	209.00	214.00	213.00		91	239.00	243.70	242.00
42	210.00	215.00	213.00		92	241.00	246.00	244.00
43	211.00	215.00	214.00		93	243.00	247.00	246.00
44	211.00	215.00	214.00		94	245.00	248.80	248.00
45	212.00	215.00	214.00		95	247.10	250.00	249.00
46	212.00	216.00	215.00		96	251.00	252.00	251.00
47	212.00	216.00	215.00		97	252.00	254.00	253.00
48	213.00	217.00	215.00		98	255.00	257.00	256.00
49	213.00	217.00	216.00		99	259.00	261.00	261.00
50	214.00	217.00	216.00		100	≥ 271.00	≥ 272.00	≥ 272.00

Table 3. Raw scores and related percentiles for Service Leadership Attitude Scale (SLA-SF-46)

Raw score	Percentiles		
	Male (N = 1517)	Female (N = 2969)	Total sample (N = 4486)
≤ 136	1.0	1.0	1.0
137	2.0	1.0	1.0
138	2.0	1.0	1.0
139	2.0	1.0	1.0
140	2.0	1.0	1.0
141	2.0	1.0	1.0
142	2.0	1.0	1.0
143	2.0	1.0	1.0
144	2.0	1.0	1.0
145	2.0	1.0	1.0
146	2.0	1.0	1.0
147	2.0	1.0	1.0
148	2.0	1.0	1.0
149	2.0	1.0	1.0
150	2.0	1.0	1.0
151	2.0	1.0	1.0
152	2.0	1.0	1.0
153	2.0	1.0	1.0
154	2.0	1.0	1.0
155	2.0	1.0	1.0
156	3.0	1.0	2.0
157	3.0	1.0	2.0
158	3.0	1.0	2.0
159	3.0	1.0	2.0
160	3.0	1.0	2.0
161	3.0	1.0	2.0
162	4.0	1.0	2.0
163	4.0	1.0	2.0
164	4.0	1.0	2.0
165	4.0	2.0	2.0
166	4.0	2.0	2.0
167	4.0	2.0	3.0
168	5.0	2.0	3.0
169	5.0	2.0	3.0
170	5.0	2.0	3.0
171	5.0	2.0	3.0
172	5.0	2.0	3.0
173	6.0	2.0	4.0
174	6.0	3.0	4.0
175	7.0	3.0	4.0
176	7.0	3.0	4.0
177	8.0	3.0	5.0
178	8.0	3.0	5.0
179	9.0	3.0	5.0
180	10.0	4.0	6.0
181	10.0	4.0	6.0
182	11.0	4.0	6.0
183	12.0	5.0	7.0
184	12.0	5.0	7.0
185	13.0	5.0	8.0
186	13.0	6.0	8.0

Raw score	Percentiles		
	Male (N = 1517)	Female (N = 2969)	Total sample (N = 4486)
187	14.0	6.0	9.0
188	15.0	7.0	9.0
189	16.0	7.0	10.0
190	16.0	7.0	10.0
191	17.0	8.0	11.0
192	18.0	9.0	12.0
193	19.0	9.0	13.0
194	20.0	10.0	13.0
195	21.0	11.0	14.0
196	22.0	11.0	15.0
197	24.0	12.0	16.0
198	25.0	13.0	17.0
199	26.0	14.0	18.0
200	27.0	15.0	19.0
201	28.0	16.0	20.0
202	29.0	17.0	21.0
203	31.0	19.0	23.0
204	33.0	20.0	24.0
205	34.0	21.0	26.0
206	36.0	22.0	27.0
207	38.0	24.0	29.0
208	39.0	26.0	30.0
209	41.0	28.0	32.0
210	42.0	30.0	35.0
211	44.0	33.0	37.0
212	46.0	35.0	39.0
213	49.0	37.0	41.0
214	51.0	40.0	44.0
215	55.0	44.0	47.0
216	58.0	47.0	50.0
217	60.0	49.0	53.0
218	62.0	52.0	55.0
219	64.0	54.0	58.0
220	66.0	57.0	60.0
221	68.0	60.0	63.0
222	70.0	63.0	65.0
223	72.0	65.0	68.0
224	74.0	67.0	70.0
225	75.0	69.0	71.0
226	77.0	71.0	73.0
227	78.0	73.0	75.0
228	80.0	75.0	77.0
229	82.0	77.0	78.0
230	83.0	78.0	80.0
231	84.0	80.0	81.0
232	85.0	81.0	83.0
233	86.0	83.0	84.0
234	86.0	84.0	85.0
235	87.0	85.0	86.0
236	88.0	86.0	87.0
237	89.0	87.0	88.0
238	90.0	88.0	88.0
239	91.0	88.0	89.0
240	92.0	89.0	90.0
241	92.0	90.0	91.0

Table 3. (Continued)

Raw score	Percentiles		
	Male (N = 1517)	Female (N = 2969)	Total sample (N = 4486)
242	93.0	90.0	91.0
243	93.0	91.0	92.0
244	94.0	91.0	92.0
245	94.0	92.0	93.0
246	95.0	92.0	93.0
247	95.0	93.0	94.0
248	96.0	94.0	94.0
249	96.0	94.0	95.0
250	96.0	95.0	96.0
251	96.0	96.0	96.0
252	97.0	96.0	97.0
253	98.0	97.0	97.0
254	98.0	97.0	98.0
255	98.0	98.0	98.0
256	99.0	98.0	98.0
257	99.0	98.0	99.0
258	99.0	99.0	99.0
259	99.0	99.0	99.0
260	99.0	99.0	99.0
261	99.0	99.0	99.0
262	99.0	99.0	99.0
263	99.0	99.0	99.0
264	99.0	99.0	99.0
265	99.0	99.0	99.0
266	99.0	99.0	99.0
267	99.0	99.0	99.0
268	99.0	99.0	99.0
269	99.0	99.0	99.0
270	99.0	99.0	99.0
271	100.0	99.0	100.0
272	100.0	100.0	100.0
273	100.0	100.0	100.0
274	100.0	100.0	100.0
275	100.0	100.0	100.0
276	100.0	100.0	100.0

The present study contributes to the future service leadership research and practices in two ways. First, a multi-institutional sample of Hong Kong university students helps to develop the normative profile, which can assist the interpretations of the raw scores. Second, the scale that originated from the SLAM framework provides some insight into the content of the service leadership theory.

Beyond the norms, the examination of individual differences and potential personal correlates broadens researchers and educational practitioners' understanding of university students' attitudes and beliefs towards service leadership. First, the current study revealed that female college students in Hong Kong possessed a higher level of service leadership attitude compared with male students. Although leadership has been traditionally viewed as a masculine activity [42], some studies have identified females' strengths being as leaders [23-25]. One factor that contributes to gender differences in service leadership attitude owes to the features of service leaders. A service-oriented economy requires service leaders to be

caring and interpersonal-oriented, which have been viewed as the unique features of femininity.

Second, no age-related difference was observed in the service leadership attitude, echoing prior scholars' arguments that non-significant relationship exists between leaders' age and their leadership behaviors [27, 30]. Meanwhile, leadership training experiences turned out to be positively associated with the service leadership attitude in the current study. The findings imply the importance of service leadership education that one's service leadership attitudes and beliefs could be acquired through training and learning.

Third, participants' service leadership attitude scores were positively associated with their GPA, leadership training experiences, and the experience of being a leader. These findings can be attributed to the fact that students with higher GPA usually perform better in solving cognitively complex tasks [32], which may promote their understanding of service leadership attitude. On the other hand, experiences of receiving leadership training and opportunities being a leader were believed to positively impact university students' service leadership attitude. It is consistent with previous studies [43] that student leadership in universities creates positive impacts on building their skills and characters.

Although our study is pioneering in the field of leadership, it is not without limitations. First, the sample recruited in the current study was limited to Hong Kong university students. Hence, it restricts the generalizability of the findings to other populations or the same population in other regions. To follow up the pioneering work of this study, future research shall employ other heterogeneous populations to create corresponding norm tables, as well as test the possible personal correlates. To this end, the service leadership theory should be tested in various professions and industries. The second limitation pertains to the investigation of possible personal correlates. On the one hand, although the correlations were significant, the effect sizes were not large. A possible explanation for this might be the undetected intermediate effects, which should be further explored in the future. Hence, future studies should take possible correlates, such as students' majors and personalities, into account. Despite these limitations, this study constitutes a good progress for the area of service leadership measurement.

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Chapter 144

THE SERVICE LEADERSHIP BEHAVIOR SCALE: NORMS AND PERSONAL CORRELATES

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ABSTRACT

The shift from industrial society to service society calls for effective service leaders who can unite and motive people to work together effectively. However, valid scales assessing important leadership qualities required by service economy are rare. To fill this gap, three scales were developed based on the Service Leadership Theory to measure leadership qualities. In this chapter we present findings on the norms and personal correlates of the Service Leadership Behavior Scale using data collected from an online questionnaire administered to 4,486 students from eight University Grants Committee (UGC) funded universities in Hong Kong. As significant gender differences were found, two norms were developed separately for female and male participants. No significant influence of age on leadership behaviors was noted. For other personal correlates, students' grade point average (GPA), experience in leadership training, and experience of

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being a leader were associated with the leadership behavior scores, though the effect size was small. Limitations and implications of the present findings are discussed.

INTRODUCTION

The economic growth in the twenty-first century is shown by the transition from the manufacturing economy into service economy [1]. This transition, characterized by the provision of service rather than goods, has transformed global economies on a massive scale. As service is essentially delivered through people to people, strong service leadership that helps people work together effectively has become the key to organization success.

The era of service economy calls for effective leaders. Growing leadership training programs in higher education sectors have been developed to improve university students' leadership qualities, which can better prepare them for the challenges in the service economy. For example, supported by the Victor and William Fung Foundation, a leadership program entitled "Fung Service Leadership Initiative" was developed and launched in eight public universities funded by the University Grants Committee (UGC) in Hong Kong, aiming at nurturing students' development in leadership knowledge, attitude and behavior [2].

To improve program effectiveness, objective outcome evaluation is essential as it provides evidence of the program's contribution to students' leadership development and the knowledge base. However, scales specifically designed to measure leadership qualities required by service economy are rare. In the following sections, the "Fung Service Leadership Initiative" in Hong Kong and the development of the Service Leadership Behavior Scale are described.

Service Leadership Education and Evaluation in Hong Kong

The economy of Hong Kong is very service-oriented [3]. The share of the service sector has almost reached 93% of the Gross Domestic Product (GDP) in Hong Kong in 2007, and remained around that level in the recent decade [4]. Chung has thoroughly discussed the contemporary service society in Hong Kong and proposed the Service Leadership Theory [5–7]. According to Chung [8], service leadership is to "satisfy needs by consistently providing quality personal service to everyone one comes into contact with, including one's self, others, groups, communities, systems, and environments". Service Leadership Theory highlights three essential qualities underlying effective service leadership, which include competence, character and care. All of these three qualities are indispensable to effective leadership. In other words, a lack of any of three fundamental characteristics may lead to ineffectiveness, dysfunction, and even the dark side of leadership [9].

The Service Leadership Theory serves as the cornerstone of the leadership education program of eight UGC-funded universities in Hong Kong. Supported by the Victor and William Fung Foundation, these universities have developed service leadership education programs to enrich students' knowledge about service leadership, shaping their attitude of being service leaders, and improving their leadership behavior in practice [2]. For example, in The Hong Kong Polytechnic University (PolyU), education programs have been provided in

different forms, including credit-bearing and non-credit-bearing courses, as well as short-term workshops [10]. These programs have been carefully designed to help students improve the three fundamental service leadership qualities, namely competence, character and care. Previous studies have showed that students reported a high level of satisfaction towards the programs, and the programs were perceived to be effective [11–13].

Development of the Service Leadership Behavior Scale (SLBS)

Many leadership theories have focused on behavior of leaders [14]. A number of leadership models have been developed in the postindustrial era to understand the role of leadership behavior in employees' engagement and organization effectiveness [15]. Recent leadership literature has increasingly moved the focus from highlighting leaders' competences (e.g., charismatic leadership) towards an emphasis on shared, ethical, people-centered leadership styles (e.g., servant leadership and ethical leadership) [16, 17]. For example, servant leadership highlights the personal growth of followers [16]. Ethical leadership focus on normatively appropriate conduct demonstrated by leaders [17].

The above-mentioned models capture many key elements of leadership skills and behaviors, but are not sufficient to measure service leadership behavior in specific cultural contexts. First, most models solely measure leadership competences, and only a few theories specifically focus on leaders' character and care. However, almost none of these theories has considered competence, character and care three indispensable elements of effective service leadership [18]. In other words, a model integrating these three leadership qualities required by service economy is missing. Second, though it is widely agreed that culture and local contexts are important leadership research, assessment tools of leadership behavior seldom take cultural contexts into accounts. As Tsui advocated, to develop contextual measurement to deepen leadership research in China is "not only desirable, but essential" [19].

To fill the above gaps, the research team at The Hong Kong Polytechnic University (PolyU) designed a long-form Service Leadership Behavior Scale (SLB-LF-97) guided by the Service Leadership Theory. The SLB-LF-97 contains 97 items, aiming to measure the behavioral characteristics of a service leader [20]. The initial validation of SLB-LF-97 was conducted in a study involving 231 PolyU undergraduate students as part of the "Development and validation of measures based on the Service Leadership Model" project. The reliability of the SLB-LF-97 was excellent ($\alpha = 0.97$). Exploratory factor analysis (EFA) suggested the removal of 32 items with multiple or low loadings. A short-form of the Service Leadership Behavior Scale (SLB-SF-65) containing 65 items was formed. The results of the initial validation of the SLB-LF-97 were reported in another article prepared by Shek, Ma and Lin in this book. Generally speaking, the refined scale (i.e., SLB-SF-65) reflected good internal consistency and convergent validity. The SLB-SF-65 was further validated in a large-scale project, which resulted in the final version of the scale including 38 items (SLB-SF-38). Details can be seen in another chapter prepared by Shek and Ma in this book as well as in the User Manual.

Norms and Correlates of the Service Leadership Behavior Scale

The present study aims to provide norm data of the Service Leadership Behavior Scale to better interpret students' leadership behavior scores. Besides, potential personal correlates between gender, age, academic achievement, experience in leadership training, experience of being a leader and students' service leadership behavior scores were examined.

Norm data of a scale provide the necessary frame of reference to aid test administrators, educators and researchers to interpret the scores of individuals. For the test data that are normally distributed, standardized scores are commonly used to represent an individual's performance level [21]. For the non-normative sample, however, percentile rank is often used as an alternative option. Compared with standardized score, percentile rank provides the ranking position of individual's score among the population, and directly shows the intrinsic meaning which the standardized scores do not [22]. The norms can consist the tables including all percentile ranks for each raw score, or only including some landmark percentiles and the corresponding raw scores [22]. The norms are useful source that helps improve the effectiveness of leadership educational programs. On one hand, identifying the benchmarks of behavior performance for different populations helps better design these programs for populations with specific needs. On the other hand, change in percentile rank for an individual can be tracked, implying that the effectiveness of the leadership program at the individual level can be evaluated.

As the norm data may differ among populations, gender and age are two important demographic characteristics that were taken into account in the present study. Several reviews have thoroughly discussed gender difference in leadership styles and behaviors [23-25]. For example, Mandell and Pherwani [24] examined gender difference in emotional intelligence and transformational leadership style. The results suggested that female leaders managed their own and others' emotions better than their counterparts did. In addition, using 40 data sets drawn from 28 studies in research of gender and instructional leadership, Hallinger and his colleagues [23] concluded that compared with male principals, female principals tended to engage in more active instructional leadership. However, gender difference in leadership behavior remains inconclusive. For example, Oshabemi and Gill [25] collected data from leaders in UK and found no significant gender difference in leadership styles.

Despite the different results drawn from statistical comparison, many studies have suggested that female leadership are often characterized by strong interactive, transformational and cooperative management. Rosener [26] pointed out that women tend to adopt a transformational style through providing care to others. This argument was supported by Carless [27], who argued that women were naturally socialized towards skills in participative leadership, collaborative group management, and quality interpersonal relations. Therefore, in the present study, we hypothesized that female participants' service leadership behavior scores would be higher than those of male participants (Hypothesis 1). As to age, some studies have suggested that the elder leaders may present stronger leadership as both their leadership experience and social relationship would be developed as time goes on [28], but the associations were often found to be weak [29]. In addition, given that the participants were all university students in this study, the variation in age was small. Therefore, we included age as a demographic characteristic in the analysis, but did not anticipate that age would significantly influence service leadership behavior scores.

The present study also took participants' academic achievement, experience of receiving leadership training and experience of being a leader into account. Grade Point Average (GPA) has been commonly used to define participants' academic achievement. Though the direct relationship between university students' GPA and their leadership remains unclear [30], many studies have revealed that GPA is closely related to some important abilities that can strongly predict leadership. For example, Kellett, Humphrey and Sleeth [31] found that GPA was a strong predictor to complex task choice, and these two factors showed a combined positive influence on leadership perceptions. In addition, studies in the Chinese context also observed similar correlations [32]. As such, we hypothesized that there would be a positive correlation between GPA and leadership behavior scores (Hypothesis 2).

As to the potential correlation between leadership training experience and behavior, research has highlighted the benefits of service and experiential learning to students' leadership development [33]. Many leadership programs often provide a variety of activities to construct the connection between students' own experience and reflection, which can effectively engage students in learning process. We hypothesized that leadership training experience would be positively related to students' service leadership behavior (Hypothesis 3).

Regarding the experience of being a leader, it is argued that students with relevant experience may have a deeper understanding of how to lead, motivate, unite people, and serve others [28]. Therefore, we hypothesized that the experience of being a leader would show positive correlation with service leadership behavior (Hypothesis 4).

OUR STUDY

The data were collected from an online questionnaire administered to undergraduate students from eight UGC-funded universities in Hong Kong in March 2016, which included The Hong Kong Polytechnic University (PolyU), The Chinese University of Hong Kong (CUHK), The Education University of Hong Kong (EdUHK), Hong Kong Baptist University (HKBU), City University of Hong Kong (CityU), Lingnan University (LU), The University of Hong Kong (HKU), and Hong Kong University of Science and Technology (HKUST). The research team in PolyU developed the questionnaire and set up the online survey. The local researchers in each university distributed the link to students. The participants were informed of the purpose of the study, and were assured that the data would be analyzed anonymously, and all information would be kept confidential. In addition, they were encouraged to response honestly based on their knowledge and impression about themselves. Each participant received a supermarket voucher of HK\$100 as a token of appreciation for completing the survey.

Data collection lasted for around four months from March till June 2017. A total of 4,555 participants completed the survey. Sixty-nine responses were excluded from the following analyses due to a denial of consent form, duplicated responses, and the responses completed by non-targeted group (e.g., graduates). After removing the invalid responses, the final sample consisted of 4,486 participants, including 2,969 females (66.2%) and 1,517 males (33.8%). The age of the participants ranged from 15 to 34 years old ($M = 20.47$, $SD = 1.67$). The demographic characteristics of the participants are showed in Table 1.

Table 1. Demographic characteristics of the participants

University	PolyU	CUHK	EdUHK	HKBU	CityU	LU	HKU	HKUST	Total
Participants (n/%)	1000/22.29	505/11.26	500/11.15	517/11.52	464/10.34	500/11.15	500/11.15	500/11.15	4486/100
Age range	18-27	17-29	17-34	15-28	18-34	18-29	17-28	16-28	15-34
Age (Mean/SD)	20.46/1.65	20.08/1.55	21.05/1.75	20.79/1.67	20.63/1.77	20.54/1.55	20.38/1.67	19.85/1.50	20.47/1.67
15-19 (n/%)	297/29.70	193/38.22	95/19.00	117/22.63	112/24.14	133/26.60	173/34.60	224/44.80	1,344/29.96
≥ 20 (n/%)	703/70.30	312/61.78	405/81.00	400/77.37	352/75.86	367/73.40	327/65.40	276/55.2	3,142/70.04
Males (n/%)	409/40.90	130/25.74	98/19.60	122/23.60	128/27.59	148/29.60	151/30.20	331/66.20	1,517/33.82
Females (n/%)	591/59.10	375/74.26	402/80.40	395/76.40	336/72.41	352/70.40	349/69.80	169/33.80	2,969/66.18

Note. PolyU = The Hong Kong Polytechnic University; CUHK = The Chinese University of Hong Kong; EdUHK = The Education University of Hong Kong; HKBU = Hong Kong Baptist University; CityU = City University of Hong Kong; LU = Lingnan University; HKU = The University of Hong Kong; HKUST = Hong Kong University of Science and Technology.

Measures

Based on the literature on the service leadership, the Service Leadership Behavior Scale was developed to measure the extent to which the participants demonstrate behaviors that are representative of a service leader. The SLB-SF-65 is measured on a 6-point Likert scale (1 = strongly disagree; 2 = disagree; 3 = slightly disagree; 4 = slightly agree; 5 = agree; 6 = strongly agree). Some sample items include: “I constantly seek to improve my personality,” “I strive to take care of other people regardless of their positions,” “when there is a problem, I can solve it quickly,” and “I am able to develop positive relationships with my friends.”

In the large-scale validation study, the SLB-SF-65 was refined based on exploratory factor analysis (EFA) and confirmatory factor analysis (CFA). Two subsets were randomly generated from the entire dataset (N subset A = 2,246; N subset B = 2,240). EFA was conducted on subset A to examine the factorial structure of the SLB-SF-65 by applying the principal component analysis. A trimmed scale (SLB-SF-48) containing 48 items was formed. Six factors were extracted, including self-improvement and self-reflection, people and principles orientation, resilience, social competence, problem-solving and mentorship. Details of the formation of SLB-SF-48 based on the EFA can be found in another article prepared by Shek and Ma in this book. CFA was performed on subset B using Maximum Likelihood estimation to evaluate the factorial structure. After removing ten items reflecting unsatisfactory factor loadings, and allowing the residual covariance for three pairs of parameters, we observed a significant improvement in goodness-of-fit. The resultant 38-item scale (SLB-SF-38) reflected a good fit (CFI = .92; NNFI = .91; RMSEA = .055), which met the benchmarks suggested by Hu and Bentler [34]. The SLB-SF-38 reflected the same factorial structure and labeling as the SLB-SF-48 did. In addition, the SLB-SF-38 showed good internal reliability (Cronbach Alpha = .96). The detailed information of CFA and indicators of the SLB-SF-38 are reported in another article submitted for the consideration of publication as well as in the User Manual. In the present study, the final data generated by CFA were used to develop norm tables and personal correlates.

Demographic Characteristics and Personal Correlates

Age and gender were two important demographic characteristics included in the present study. In addition, students' academic achievement, experiences of participating leadership training program, and being a leader were taken into account. Following previous research, we also used GPA to represent participants' academic achievement. The GPA systems in eight universities were adjusted and the GPA scores were standardized. Students were asked to report their recent GPA (ranging from 0-4), whether they have ever participated any leadership course or program (0 = No, 1 = Yes), and whether they have served in any leadership position in any organization (0 = No, 1 = Yes).

Data Analyses

We performed multiple regression analyses to examine the influence of gender and age on participants' behavior scores with SPSS version 23. If the behavior scores were

significantly predicted by gender, separate percentiles norms should be provided for female and male groups.

Normality tests were conducted for selecting the way to present norms. If the sample was normatively distributed, both the standardized scores and percentile norms would be presented. If the sample is non-normatively distributed, only the percentile norms would be provided.

When producing the norm data, we first presented the raw scores corresponding to the percentiles from 0 to 100. Second, the full tables presenting the percentiles for each raw score were provided. By doing so, the individual's score can be positioned precisely, which is useful for proper interpretation of the results. Crawford and colleagues [22] have suggested that though the behavior score is discrete, the underlying leadership ability is considered a continuous index. Thus, a given score x is actually a point estimate of the real valued behavior ability ranging from $x - 0.5$ (inclusive) to $x + 0.5$ (exclusive). In other words, given that the population distribution is unknown, the best estimation would be that the ability of half of the participants scoring x is actually below x and half above [22]. Thus, we followed Crawford et.al' suggestion on the definition of a percentile rank: the percentage of scores that fall below the score of interest and half of those obtaining the score of interest [22]. The calculation formula is showed as follows:

$$\text{Percentile rank} = \left(\frac{m + .5k}{N} \right) \times 100$$

In this formula, m refers to the number of participants scoring below a given raw score, k represents the number of participants that obtain a given raw score, and N means the entire normative sample size. The percentile ranks were calculated and rounded to integer.

For GPA, experience of leadership training and experience of being a leader, correlation analyses were applied to examine the potential relations between these factors and students' behavior scores with SPSS 23.

FINDINGS

The results of multiple regression analyses suggested that students' behavior scores were significantly predicted by gender, though the effect size was small ($\beta = .049$, $p < .001$; Cohen's $f^2 = .002$). In particular, female students obtained higher behavior scores ($Mean = 172.02$, $SD = 21.49$) than male students did ($Mean = 169.69$, $SD = 25.15$). Hypothesis 1 was supported. The influence of age on behavior scores was not statistically significant.

Tests for normality were conducted separately on female and male groups. The results of Shapiro-Wilk's test indicated that the distribution of behavior scores was non-normative for both female and male groups ($p < .001$) [35]. Field has suggested that the Shapiro-Wilk's test for large samples can be significant though the scores are only slightly different from a normal distribution [35]. Therefore, we also checked the histograms and the values of skew and kurtosis. The histograms showed a left-skewed and leptokurtic distribution for both

Table 2. Percentiles and corresponding raw scores of Service Leadership Behavior Scale (SLB-SF-38) by gender

Percentile (1-50)	Raw Score			Percentile (51-99)	Raw Score		
	Male (N = 1,517)	Female (N = 2,969)	Total sample (N = 4,486)		Male (N = 1,517)	Female (N = 2,969)	Total sample (N = 4,486)
1	≤ 94.36	≤ 112.70	≤ 107.00	51	173.00	174.00	174.00
2	112.36	123.00	119.74	52	173.00	175.00	174.00
3	121.00	131.00	128.00	53	174.00	175.00	175.00
4	126.00	135.00	131.00	54	175.00	176.00	175.00
5	129.00	137.00	134.00	55	175.00	176.00	176.00
6	131.00	139.00	136.00	56	176.00	177.00	177.00
7	133.00	142.00	138.00	57	177.00	177.00	177.00
8	135.00	143.00	141.00	58	177.00	178.00	178.00
9	137.00	145.00	142.00	59	178.00	178.00	178.00
10	139.00	146.00	144.00	60	178.00	179.00	179.00
11	141.00	147.00	145.00	61	179.00	179.00	179.00
12	142.00	148.00	146.00	62	180.00	180.00	180.00
13	143.00	149.00	147.00	63	180.34	180.00	180.00
14	144.00	150.00	148.00	64	181.00	181.00	181.00
15	146.00	151.00	149.00	65	182.00	181.00	181.00
16	147.00	152.00	150.00	66	182.00	182.00	182.00
17	148.00	152.00	151.00	67	183.00	182.00	183.00
18	149.00	152.60	152.00	68	183.00	183.00	183.00
19	150.00	154.00	152.00	69	184.00	183.00	183.00
20	151.00	154.00	153.00	70	184.00	184.00	184.00
21	152.00	155.00	154.00	71	185.00	184.00	185.00
22	152.00	156.00	154.00	72	186.00	185.00	185.00
23	152.00	156.00	155.00	73	186.00	185.00	186.00
24	153.00	157.00	156.00	74	187.00	186.00	186.00
25	154.00	158.00	157.00	75	188.00	186.00	187.00
26	155.00	159.00	157.00	76	188.00	187.00	187.00
27	155.00	160.00	158.00	77	189.00	187.00	188.00
28	156.00	160.00	159.00	78	190.00	188.00	188.00
29	157.00	161.00	160.00	79	190.00	188.00	189.00
30	158.00	162.00	160.10	80	190.00	189.00	189.00
31	158.00	162.70	161.00	81	190.00	189.00	190.00
32	159.00	163.00	162.00	82	191.00	190.00	190.00
33	160.00	164.00	163.00	83	191.00	190.00	191.00
34	161.00	165.00	163.00	84	192.00	191.00	191.00
35	162.00	165.00	164.00	85	193.00	191.50	192.00
36	162.00	166.00	165.00	86	194.00	192.00	193.00
37	163.00	167.00	165.00	87	195.00	193.00	194.00
38	164.00	167.00	166.00	88	196.00	194.00	195.00
39	164.00	168.00	167.00	89	197.00	195.00	196.00
40	165.00	168.00	167.00	90	198.00	197.00	197.00
41	165.00	169.00	168.00	91	199.00	198.00	199.00
42	166.00	169.00	168.00	92	201.00	200.00	200.00
43	167.00	170.00	169.00	93	202.00	201.00	201.00
44	167.00	171.00	170.00	94	204.00	202.00	203.00
45	168.00	171.00	170.00	95	207.00	205.00	205.00
46	169.00	172.00	171.00	96	208.00	207.20	208.00
47	169.00	172.00	171.00	97	212.00	211.00	212.00
48	171.00	173.00	172.00	98	217.00	215.00	216.00
49	171.00	173.00	173.00	99	222.82	221.30	222.00
50	172.00	174.00	173.00	100	≥ 228.00	≥ 228.00	≥ 228.00

female and male groups. In particular, the behavior scores yielded a skewness of -0.78 for male participants ($SE = .06$, $z\text{-value} = -12.37$, $p < .001$) and a skewness of -0.54 for female participants ($SE = .04$, $z\text{-value} = -11.99$, $p < .001$). In terms of kurtosis, the results showed a peaked distribution with positive kurtosis for both male (kurtosis = 2.23, $SE = .13$, $z\text{-value} = 17.79$, $p < .001$) and female groups (kurtosis = 1.76, $SE = .09$, $z\text{-value} = -19.61$, $p < .001$) [35]. According to the results of multiple regression and normality tests, we presented

Personal Correlates of Service Leadership Behavior Score

The results of correlation analysis suggested that the behavior scores were significantly correlated with GPA ($r = .10$, $p < .001$; $r^2 = .01$), experience of taking leadership course or training ($r = .13$, $p < .001$; $r^2 = .036$), and experience of being a leader ($r = .14$, $p < .001$; $r^2 = .028$). Students achieving higher GPA, having experience of taking leadership course or training, or having experience of being a leader were likely to have a better understanding of service leadership behavior. The results supported Hypotheses 2, 3 and 4, though the effect size of the correlates was low.

Table 3. Raw scores and corresponding percentiles of Service Leadership Behavior Scale (SLB-SF-38)

Raw score	Percentiles		
	Male ($N = 1,517$)	Female ($N = 2,969$)	Total sample ($N = 4,486$)
≤ 78	0.0	0.0	0.0
79	1.0	0.0	0.0
80	1.0	0.0	0.0
81	1.0	0.0	0.0
82	1.0	0.0	0.0
83	1.0	0.0	0.0
84	1.0	0.0	0.0
85	1.0	0.0	0.0
86	1.0	0.0	0.0
87	1.0	0.0	0.0
88	1.0	0.0	0.0
89	1.0	0.0	0.0
90	1.0	0.0	0.0
91	1.0	0.0	0.0
92	1.0	0.0	0.0
93	1.0	0.0	1.0
94	1.0	0.0	1.0
95	1.0	0.0	1.0
96	1.0	0.0	1.0
97	1.0	0.0	1.0
98	1.0	0.0	1.0
99	1.0	0.0	1.0
100	1.0	0.0	1.0
101	1.0	0.0	1.0
102	1.0	0.0	1.0
103	1.0	1.0	1.0
104	1.0	1.0	1.0
105	1.0	1.0	1.0
106	1.0	1.0	1.0

Raw score	Percentiles		
	Male (N = 1,517)	Female (N = 2,969)	Total sample (N = 4,486)
107	1.0	1.0	1.0
108	2.0	1.0	1.0
109	2.0	1.0	1.0
110	2.0	1.0	1.0
111	2.0	1.0	1.0
112	2.0	1.0	1.0
113	2.0	1.0	1.0
114	2.0	1.0	1.0
115	2.0	1.0	2.0
116	2.0	1.0	2.0
117	2.0	1.0	2.0
118	2.0	1.0	2.0
119	3.0	1.0	2.0
120	3.0	2.0	2.0
121	3.0	2.0	2.0
122	3.0	2.0	2.0
123	3.0	2.0	2.0
124	4.0	2.0	3.0
125	4.0	2.0	3.0
126	4.0	2.0	3.0
127	4.0	2.0	3.0
128	4.0	2.0	3.0
129	5.0	2.0	3.0
130	5.0	3.0	4.0
131	6.0	3.0	4.0
132	6.0	3.0	4.0
133	7.0	3.0	5.0
134	7.0	4.0	5.0
135	8.0	4.0	5.0
136	8.0	5.0	6.0
137	9.0	5.0	6.0
138	9.0	5.0	7.0
139	10.0	6.0	7.0
140	10.0	6.0	8.0
141	11.0	7.0	8.0
142	12.0	7.0	9.0
143	13.0	8.0	9.0
144	14.0	8.0	10.0
145	14.0	9.0	11.0
146	15.0	10.0	12.0
147	16.0	11.0	13.0
148	17.0	12.0	14.0
149	18.0	13.0	15.0
150	19.0	14.0	16.0
151	20.0	15.0	17.0
152	22.0	17.0	19.0
153	24.0	18.0	20.0
154	25.0	20.0	22.0
155	26.0	21.0	23.0
156	28.0	22.0	24.0
157	29.0	24.0	25.0
158	30.0	25.0	27.0
159	32.0	26.0	28.0
160	33.0	27.0	29.0

Table 3. (Continued)

Raw score	Percentiles		
	Male (<i>N</i> = 1,517)	Female (<i>N</i> = 2,969)	Total sample (<i>N</i> = 4,486)
161	34.0	29.0	31.0
162	35.0	30.0	32.0
163	37.0	32.0	34.0
164	38.0	33.0	35.0
165	40.0	35.0	37.0
166	42.0	36.0	38.0
167	44.0	38.0	40.0
168	45.0	39.0	41.0
169	46.0	41.0	43.0
170	47.0	43.0	45.0
171	49.0	45.0	46.0
172	50.0	47.0	48.0
173	52.0	49.0	50.0
174	53.0	51.0	51.0
175	55.0	53.0	53.0
176	56.0	55.0	55.0
177	58.0	57.0	57.0
178	59.0	59.0	59.0
179	61.0	61.0	61.0
180	62.0	62.0	62.0
181	64.0	64.0	64.0
182	66.0	66.0	66.0
183	67.0	68.0	68.0
184	69.0	70.0	70.0
185	71.0	72.0	72.0
186	73.0	74.0	74.0
187	74.0	76.0	76.0
188	76.0	78.0	77.0
189	77.0	80.0	79.0
190	80.0	82.0	82.0
191	83.0	84.0	84.0
192	84.0	86.0	85.0
193	85.0	87.0	86.0
194	86.0	88.0	87.0
195	87.0	89.0	88.0
196	88.0	89.0	89.0
197	89.0	90.0	90.0
198	90.0	91.0	91.0
199	91.0	92.0	91.0
200	92.0	92.0	92.0
201	92.0	93.0	93.0
202	93.0	94.0	93.0
203	94.0	94.0	94.0
204	94.0	95.0	95.0
205	94.0	95.0	95.0
206	95.0	96.0	95.0
207	95.0	96.0	96.0
208	96.0	96.0	96.0
209	96.0	96.0	96.0
210	96.0	97.0	97.0
211	97.0	97.0	97.0
212	97.0	97.0	97.0

Raw score	Percentiles		
	Male (<i>N</i> = 1,517)	Female (<i>N</i> = 2,969)	Total sample (<i>N</i> = 4,486)
213	97.0	97.0	97.0
214	97.0	98.0	98.0
215	98.0	98.0	98.0
216	98.0	98.0	98.0
217	98.0	98.0	98.0
218	98.0	99.0	98.0
219	98.0	99.0	99.0
220	99.0	99.0	99.0
221	99.0	99.0	99.0
222	99.0	99.0	99.0
223	99.0	99.0	99.0
224	99.0	99.0	99.0
225	99.0	99.0	99.0
226	99.0	99.0	99.0
227	100.0	99.0	100.0
228	100.0	100.0	100.0

DISCUSSION

Using data collected through a survey carried out in eight UGC-funded universities in Hong Kong (*N* = 4,486), the present study examined percentile norms and important correlates of the service leadership behavior scores. This study responded the call for valid assessment tool evaluating university students' leadership behavior in a Chinese context.

Results showed that female students achieved higher behavior scores than male students did, which was in line with previous research [27, 29]. Though men are often perceived as having more leadership qualifications [36], females were found to perform better in building relationship with others, showing care and empathy, and leading in a transformational way. The development of service economy provides females more opportunities in professional development, which will improve gender equity in organizational leadership roles.

Our results also indicated that students who have attended leadership training course or have acted as a leader tended to perceive themselves having a higher level of leadership behavior. This implies the value of training programs in improving students' leadership, as the related training may enrich their knowledge and provide opportunities from them to reflect and practice leadership behavior. Similarly, acting as a leader directly provides specific task and contexts that students need to make decisions, coordinate, solve problems, and even handle conflicts, which will reinforce their leadership development. In addition, students' GPA was also positively correlated with their leadership behavior score. As GPA has been often used as an indicator of cognitive ability, students achieving high GPA may know how to choose learning strategies and possess the ability to work well with others in group projects, which will facilitate their learning process in relation to leadership development.

There are several theoretical, methodological, and practical implications. As stated earlier, numerous programs have been developed to respond the call for effective leaders in service economies. However, valid measurements are limited. This study tried to contribute to the literature by presenting the norms and correlates of service leadership scores. A main

methodological strength of this study is the development and validation of a measurement based on large sample size and confirmatory factor analyses. The findings also clarify the conceptual dimensions underlying the concept of service leadership behavior, which include self-improvement and self-reflection, people and principles orientation, resilience, social competence, problem-solving and mentorship dimensions revealed by the scale. This study also provides some practical implications for practitioners. The gender difference in service leadership behavior scores implies that more efforts should be made to improve male students' leadership performance.

Although we believe that our study has an addition to the Service Leadership Theory literature and leadership program evaluation, some limitations should be noted. More research variables can be included in the analysis to better understand the leadership behavior scores and variance. For example, students' Majors can have an influence on their service leadership behavior scores. It is possible that students majoring in helping professions, such as nursing, psychological counseling, education and social work, may possess a higher level of service leadership skills. As to the research sample, the present study was conducted solely in eight universities in Hong Kong, implying that some results may be difficult to be generalized to other contexts. For example, some idiosyncratic characteristics of Hong Kong, such as its long-standing service economy, can have an influence on the norm data. In addition, as one of our research aims was to evaluate leadership programs in higher education, only university students were involved in our study. Special attention should be paid to this issue when using the Service Leadership Behavior Scale in other populations. Despite these limitations, the present study contributes to the current literature by providing norm data of Service Leadership Behavior Scale to evaluate individual's leadership behavior and monitor their improvements.

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Chapter 145

A USER MANUAL FOR THE SERVICE LEADERSHIP KNOWLEDGE SCALE

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ABSTRACT

With a strong evidence base linking leadership knowledge to leadership practices, the Service Leadership Knowledge Scale was developed as an objective assessment tool to assess an individual's knowledge pertaining to Service Leadership based on the Service Leadership Theory. With an initial item pool of 200 items, the final Service Leadership Knowledge Scale consists of 40 items which demonstrated robust psychometric properties. In this chapter, a brief introduction of the development of the Service Leadership Knowledge Scale as well as its conceptual framework is attempted. The validation process, norm statistics, administration notes, and guidelines for scale score interpretation are also discussed.

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INTRODUCTION

Owing to the transformation in economic composition amongst capitalist societies across the globe, Hong Kong, as a cosmopolitan Asian financial hub, has transitioned from the once manufacturing-dominant economy to a service-driven economy [1-3]. According to the Information Services Department [4], nearly 90% of jobs in Hong Kong are currently service-oriented. This shift in the economic structure has huge implications on what constitutes good leadership practices in this age [2, 5]. Po Chung, the co-founder of DHL International and the incumbent chairperson of the Hong Kong Institute of Service Leadership and Management Limited (HKI-SLAM), asserted that a corresponding evolution to a service mentality, which stresses nurturance of human assets, autonomy, and innovation [2], is the key to leadership success in this Service era [6].

Obviously, such an evolution cannot be taken for granted. As stated by Shek et al. [3], there is still a noticeable incompatibility between what is valued amongst the potential employers vis-à-vis the graduates or the employees in certain service sectors. Such a discrepancy does not only engender mismatch in recruitment and under-utilization of talents [8] but also deterioration in employees’ job satisfaction as well as mental and physical well-being [9]. In view of such a backdrop, the Service Leadership and Management (SLAM) framework was put forth by HKI-SLAM, with the vision to educate a new generation of service leaders who can thrive in the contemporary service economy by possessing task-specific competences, a caring disposition, and capability to make morally correct decisions [3, 10].

According to the SLAM framework, effective leadership is conceptualized as a “service aimed at ethically satisfying the needs of self, others, groups, communities, systems, and environments” [11, p. 233]. To put this in the context of leadership education, Chung and Bell [12] proposed 25 defining principles of effective Service Leadership which are subsumed under seven Core Beliefs (see Table 1).

Table 1. The seven core beliefs of the SLAM framework (HKI-SLAM, n.d.)

Core Beliefs (CB)
CB1: Leadership is a service aimed at ethically satisfying the needs of self, others, groups, communities, systems, and environments.
CB2: Everyday, every human occupies a position of leadership and possesses the potential to improve his or her leadership quality and effectiveness.
CB3: Leadership effectiveness and service satisfaction are dependent on a leader or service provider possessing relevant situational task <i>competences</i> plus being judged by superiors, peers, and subordinates as possessing <i>character</i> and exhibiting <i>care</i> .
CB4: Service includes self-development efforts aimed at ethically improving one’s competences, abilities, and willingness to help satisfy the needs of others.
CB5: Service Leadership is about creating appropriate personal service prepositions in real time and constantly striving to provide the highest quality service one afford to everyone one comes into contact with and whose lives are affected by one's actions or leadership.
CB6: Service Leadership is the world’s oldest, most competitive, and longest surviving business model.
CB7: Now and in the future, high-paying, high-status positions and management promotions will go to people who have domain-specific knowledge and skills plus Service Leadership competences, appropriate character strengths and a caring social disposition.

Note. Adapted from Shek and Lin (2015).

Furthermore, Chung and Elfassy [6] highlighted 12 areas of personal qualities instrumental to Service Leadership. These include Expertise, Character, Compassion, Relationship, Daily Management, Happiness, Intellectual, Inspirational, Health, Security, Follower, and Maturation dimensions. As Chung and colleagues [12, 13] astutely pointed out, these 12 dimensions boil down to three core features of an effective Service Leader, which are Competence (i.e., “doing things right”), Character (i.e., “doing the right things”), and Caring (i.e., “serving with an unselfish intent”). In a nutshell, both the seven core beliefs and the 3-Cs of Service Leadership outline the theoretical foundation of the model of Service Leadership education [i.e., 14, 15].

With the objective of nurturing and developing future leader with service mindset and key Service Leadership qualities the Victor and William Fung Foundation financed the “Fung Service Leadership Initiative” (FSI) in eight government-funded Hong Kong universities from 2012 to 2015. To assess one’s attitude, knowledge, and behavior in an objective manner, three assessment tools were developed and subsequently validated [3].

This manual outlines the development and validation of the Service Leadership Knowledge Scale (SLK-SF-40), including its conceptual framework, item development, psychometric properties, and potential use. Validity and reliability of the finalized scale are provided to corroborate its effectiveness on measuring knowledge of Service Leadership. Administration guidelines and interpretation on raw scores are also included for scale users to have a better understanding when using the scale.

CONCEPTUAL FRAMEWORK

On the basis of the SLAM framework [10], 25 Principles of Service Leadership [12], the 12 Dimensions of a Service Leader [6], and related literature [e.g., 16, 17], the initial item pool containing a total of 200 multiple-choice items was developed covering seven crucial domains of knowledge points pertaining to the Service Leadership paradigm. These included a) General description of Service Leadership, b) Three realms of Service Leadership, c) Principle “E (Effective Leadership) = 3Cs (i.e., Competence, Caring Disposition, and Moral Character)”, d) Manufacturing vs. service economies and current societal status, e) Distinction of Service Leadership and other leadership theories, and f) other knowledge points in SLAM framework. Table 1 provides an overview of all the above-mentioned domains and the coverage for each of them. Detailed description regarding each domain are documented in the previously published work [e.g., 3, 7].

DIFFERENT STAGES OF THE VALIDATION PROCESS

The Long-Form Service Leadership Knowledge Scale (i.e., SLK-LF-200) including 200 English items was developed by Shek et al. [3] with the primary purpose of examining the “essential knowledge points of Service Leadership in the format of multiple-choice questions” [3, p.164].

Following the initial development of the item pool, the knowledge scale was subjected to multiple stages of the validation process. The following steps below summarizes the three validation studies which ultimately led to the trimming of the initial 200-item knowledge scale to the final version that contained roughly one-fifth of the items in the initial item pool:

Stage 1: A content validation study was conducted to exam the 200-item SLK-LF-200. A group of experts who were previously involved in the development of the SLAM curriculum evaluated the 200 items based on three criteria, including relevance, clarity, and representativeness. The analyses revealed that the SLK-LF-200 demonstrated meritorious content validity on both the individual item and the scale levels [3, 7].

Stage 2: The SLK-LF-200 was administered to 160 PolyU students in a criterion-related validation study. Amongst them, 67 took a three-credit course “Service Leadership” before served as the experimental group, while the remaining 93 students who had not taken the course served as the control group. Analyses revealed that the experimental group performed significantly better in all component scores as well as the composite score for the SLK-LF-200, indicating good criterion validity of the scale. Additionally, analyses on the individual item revealed that the experimental group outperformed the control group on 63 items. These 63 items were subjected to further screening, resulting in the removal of 13 items based on item duplication and face validity concern [18]. Eventually, these 50 items constituted the Short-Form Service Leadership Knowledge Scale (i.e., SLK-SF-50) which were utilized in a large-scale validation study involving 4,486 university students [18, 19].

Stage 3: The SLK-SF-50 was administered to 4,486 undergraduates from eight government-funded universities in Hong Kong. Initial inspection of reliability informed the deletion of ten items due to low item-total correlations (i.e., < 0.30). Consequently, a single-factor, 40-item factorial solution (i.e., SLK-SF-40) was subjected to confirmatory factor analysis (CFA) using the robust weighted least squares (WLSMV) estimation [18].

Overall, the goodness-of-fit statistics, which were detailed in Section 5 of the present manual, underscored the factorial validity of the proposed SLK-SF-40. Aside from recording good internal consistency, the SLK-SF-40 also exhibited robust convergent validity as evidenced by its significant correlations with different constructs theorized to be relevant to the SLAM curriculum.

DESIGN AND USE OF THE SCALE

As above mentioned, the original item pool of the SLK-LF-200 was developed based on the SLAM framework and other related publications from the Service Leadership literature. These items, written in English and taking the form of multiple-choice questions, were created with the objective to measure respondents’ “understanding of the fundamental knowledge points that a Service Leader is expected to obtain” [3, p. 166]. The final version of the scale (i.e., SLK-SF-40) is comprised of 40 items (see Table 2 for three sample items)

assessing mastery of key knowledge points in Service Leadership as a unidimensional construct [see 18]. For each item, there is a correct answer, where “1” (“0”) point is scored for each correct (incorrect) answer. A higher total score (out of 40) is indicative of the acquisition of more key knowledge points of Service Leadership [3, 18]. The final 40-item version of the Service Leadership Knowledge Scale (SLK-SF-40) was revised based on findings from the psychometric analyses.

Table 2. Three sample items of the SLK-SF-40

Items	Options	Model Answers
6. A manager under the service economy plans to hire someone. Based on the Service Leadership model, which of the following advice would you give him/her?	A. Hire for qualifications, train for character B. Hire for character, train for skills C. Hire for attitude, train for character D. Hire for efficiency, train for mindset	B
28. Which of the below attributes constitutes one of the three key components of Caring Disposition according to the Service Leadership and Management (SLAM) model?	A. Responsibility B. Conscientiousness C. Empathy D. Warmth	C
39. According to the 25 Principles of Service Leadership, which of the below statements is most appropriate?	A. It is not the Service Leaders' responsibility to predict and avoid errors that are costly to one's service reputation. B. Service Leaders should hide the errors that are costly to one's service reputation. C. Service Leaders can easily make amends for errors detrimental to one's service reputation. D. Service Leaders have to try to predict and avoid errors that are costly to one's service reputation.	D

Note. These sample items were slightly re-worded to minimize familiarity effect.

Target Respondents

The SLK-SF-40 was targeted at the undergraduate and adult population in Hong Kong and other Chinese communities (i.e., Taiwan and mainland China). Norms based on other populations may be needed when the scale is used elsewhere because the normative data reported in this manual were based on university students in Hong Kong.

Instructions

The SLK-SF-40 is administered in a self-report manner in English. A standardized set of instructions is provided as illustrated in Figure 1, while slight modifications in wordings may be acceptable. A cover page including a) the objective of the survey, b) the emphasis on

voluntary participation and data confidentiality, c) compensation (in terms of credit or pecuniary interest if applicable), d) contact details of the administrators or the researchers, and e) options for potential respondents to agree or refuse to join the study should be included. While no time limit is explicitly specified, the normal completion time for SLK-SF-40 is around 30 minutes.

Information on the personal particulars of respondents may be sought (see Figure 2). Additional items may be included depending on the test administrators’ needs (e.g., whether a repeated/pretest/posttest design is utilized) as well as the characteristics of the target sample (e.g., an undergraduate sample or a group of adult trainees signed up to certain training course in Service Leadership).

Please read each question carefully and select the best option to your understanding about leadership. The following questions are about Service Leadership and Management (SLAM) Model. No matter whether or not you have learned anything about this model, please respond to the questions based on what you know as of this moment.

Figure 1. A sample introductory note.

The below contains questions on personal particulars of yours. Please select or write down your answers in the space provided.

*Please delete as appropriate

1. Your 8-digit student ID:
2. Your Gender: *Male/Female
3. Age:
4. Have you taken any of the following credit-bearing Service Leadership courses (You may select multiple answers)?
5. Have you ever participated in any of the below non-credit bearing Service Leadership programs organized by your university (You may select multiple answers)?
6. Have you ever taken any other leadership training (e.g., any extra-curricular activities that warrant applications of your leadership competence)? *Yes/No
7. How much do you think you know about “Service Leadership”? *No Knowledge/Little Knowledge/Some Knowledge/A Lot of Knowledge/All the Knowledge
8. Have you worked before (You may select multiple answers)? *No Work Experience (single choice only)/Full-Time Work/Part-Time Work/Internship

Figure 2. Sample questions on respondents’ personal information.

Administration Guidelines

While users are at liberty to customize the cover page, introductory notes, the personal information sheet as well as the mode of administration (i.e., electronic or paper-based) according to their needs, the following points should be strictly observed:

1. The full title of the test “Service Leadership Knowledge Scale” should not appear or be explicitly announced anywhere in the introductory note.
2. Even though the SLK-SF-40 was constructed as a knowledge test pertaining to the SLAM curriculum, it can still be utilized to gauge the individual’s “baseline”

knowledge concerning Service Leadership before the start of any training programs or workshops. Specifically, upon administration to respondents who are untrained in Service Leadership, the users may remind the respondents to just respond to the items based on their current knowledge.

3. The scale must be completed by the participant on his/her own. No discussion or collaboration with fellow participants should be permitted. Furthermore, the scale must be administered in a closed-book fashion, meaning that participants are not allowed to search for answers from the Internet, lecture notes and/or other relevant materials (e.g., books or journal articles) throughout the test. The test administrator, however, may offer explanations for certain specific terms (e.g., decentralized, formalized, etc.) when participants express difficulties in comprehending those terminologies. While no specific time limit is stipulated, the normal time of completion of the SLK-SF-40 is approximately 30 minutes.
4. It is advisable that the SLK-SF-40 be administered by trained personnel including, but not limited to teachers, psychologists or social workers, or self-administered in the presence of such qualified users on an individual or a group basis. Under normal circumstances, the scale should be completed in ONE setting. Should the paper-based version be utilized, the questionnaire ought to be collected by the test administrators immediately upon completion.

RELIABILITY AND VALIDITY

Normative sample in this manual was derived through a large-scale validation study involving 4,486 university students in Hong Kong. All analyses presented in this chapter are based on the normative sample data.

Internal Consistency

Analyses revealed that the SLK-SF-40 possesses excellent internal consistency, with the Kuder-Richardson 20 (KR-20) coefficient = 0.94. To inspect the internal consistency of the SLK-SF-40 across gender and various age groups, KR-20 coefficients and mean inter-item correlations were also computed for each gender and age group (see Tables 3 and 4, respectively). The KR-20 coefficients, as shown in tables 3 and 4, were over 0.90 across gender and different age groups. Additionally, the mean inter-item correlations for all four sub-groups were within the optimal range (i.e., 0.20 to 0.40) defined by Briggs and Cheek [20]. Taken together, the SLK-SF-40 demonstrates excellent internal consistency in the present sample.

Table 3. Reliability indices by gender

Reliability indices	Male (N = 1,517)	Female (N = 2,969)	Total (N = 4,486)
Kuder-Richardson 20	0.94	0.94	0.94
Mean inter-item correlations	0.28	0.27	0.28

Table 4. Internal consistency Kuder-Richardson 20 coefficients by age groups

Reliability indices	15-19 (N = 1,344)	≥ 20 (N = 3,142)	Total (N = 4,486)
Kuder-Richardson 20	0.94	0.94	0.94
Mean inter-item correlations	0.28	0.28	0.28

Table 5. Correlations between SLK-SF-40 and the adopted external criterion scales

Correlations with the external criterion scales (and subscales)	Z-scores of difference between <i>rs</i> with SLK-SF-40:						
	α (MITC)	<i>r</i>	MSC	LEF	IRI	IRI-EC	IRI-PT
1. RSLP	0.94 (0.46)	0.200***	-16.17***	4.83***	-16.92***	-14.15***	-10.09***
2. MSC	0.83 (0.44)	0.361***	—	15.11***	-6.25***	-4.31***	1.12
3. LEF	0.72 (0.25)	0.125***	—	—	-18.83***	-16.76***	-13.09***
4. IRI	0.74 (0.17)	0.438***	—	—	—	2.97**	12.91***
4a. IRI- EC	0.62 (0.19)	0.419***	—	—	—	—	5.64***
4b. IRI- PT	0.58 (0.19)	0.346***	—	—	—	—	—

Note. ** $p < .01$ (two-tailed). *** $p < .001$ (two-tailed). MITC: Mean inter-item correlations. RSLP: Revised Servant Leadership Profile; MSC: Moral Self-Concept; LEF: Leadership Efficacy; IRI: Interpersonal Reactivity Index; IRI-EC: Subscale “Empathic Concern”; IRI: PT: Subscale “Perspective Taking”.

Concurrent Validity

Aside from the strong internal consistency, the SLK-SF-40 was demonstrated to be valid as it was associated with various measures of theoretically-relevant constructs, including empathy and servant leadership. As detailed in Table 5, the composite score of SLK-SF-40, which was calculated via summing each participant’s correct response to every item, was positively and significantly (all $ps < .001$, two-tailed) correlated to well-established external measures of Servant Leadership ($r = 0.20$), Moral Self-Concept ($r = 0.36$), Leadership Efficacy ($r = 0.13$), and Empathy (i.e., Interpersonal Reactivity Index, $r_{\text{composite}} = 0.44$, $r_{\text{empathic concern}} = 0.42$, and $r_{\text{perspective taking}} = 0.35$). Notably, comparisons [21, 22] revealed that the SLK-SF-40 was correlated most strongly with the empathy measure while least correlated with the leadership efficacy measure (see Table 6).

The concurrent validity of the SLK-SF-40 was further supported by its correlations with the final versions of the two other measures of Service Leadership. As demonstrated in Table 6, the SLK-SF-40 was positively and significantly correlated with both the 38-item Service Leadership Behavior Scale (SLB-SF-38, $r = 0.18$) as well as the 46-item Service Leadership Attitude Scale (SLA-SF-46, $r = 0.38$). The SLK-SF-40 was also positively and significantly correlated with most of the subscales of the SLB-SF-38 and SLA-SF-46 (see Table 6). Additionally, comparison of the strengths of correlation [21, 22] revealed that the SLK-SF-40 was significantly more strongly linked to the SLA-SF-46 than to the SLB-SF-38 (see Table 6).

Table 6. Correlations between SLK-SF-40 and other Service Leadership scales (and subscales) under validation

Correlations with other Service Leadership Scales under validation		Z-scores of difference between <i>r</i> s with SLK-SF-40 ^a															
	<i>r</i> (MITC)	SLB-SF-38-F2	SLB-SF-38-F3	SLB-SF-38-F4	SLB-SF-38-F5	SLB-SF-38-F6	SLB-SF-38-Total	SLA-SF-46-F1	SLA-SF-46-F2	SLA-SF-46-F3	SLA-SF-46-F4	SLA-SF-46-F5	SLA-SF-46-F6	SLA-SF-46-F7	SLA-SF-46-F8	SLA-SF-46-Total	
1.SLB-SF-38-F1	0.91 (0.53)	0.203***	-5.93	12.03	-0.20 ^{n.s.}	6.39	21.47	3.32	-7.57	-8.78	3.06	8.76	-11.35	-2.05	8.91	-10.53	-12.44
2.SLB-SF-38-F2	0.87 (0.42)	0.269***	—	16.39	5.56	10.44	26.85	11.54	-3.36	-5.08	8.01	13.51	-7.81	2.31	13.37	-7.42	-8.87
3.SLB-SF-38-F3	0.87 (0.50)	0.047**	—	—	-12.57	-5.26	9.64	-14.88	-16.03	-17.07	-6.42	-0.48 ^{n.s.}	-18.95	-10.93	0.53 ^{n.s.}	-17.40	-20.59
4.SLB-SF-38-F4	0.86 (0.55)	0.205***	—	—	—	6.06	20.81	2.92	-7.19	-8.71	3.18	8.77	-11.25	-1.82 ^{n.s.}	9.17	-10.59	-12.14
5.SLB-SF-38-F5	0.87 (0.56)	0.117***	—	—	—	—	13.36	-5.80	-12.20	-13.09	-2.22	3.35	-15.34	-7.05	4.06	-14.54	-16.32
6.SLB-SF-38-F6	0.85 (0.65)	-0.097***	—	—	—	—	—	-25.32	-23.05	-24.12	-15.34	-9.03	-25.78	-18.11	-7.35	-23.05	-28.03
7.SLB-SF-38-Total	0.96 (0.37)	0.178***	—	—	—	—	—	—	-9.59	-10.91	1.61 ^{n.s.}	7.67	-13.46	-3.74	7.92	-11.54	-15.12
8.SLA-SF-46-F1	0.90 (0.46)	0.315***	—	—	—	—	—	—	—	-2.35	12.83	18.20	-5.98	6.73	15.51	-4.97	-8.93
9.SLA-SF-46-F2	0.87 (0.47)	0.337***	—	—	—	—	—	—	—	—	14.30	18.90	-3.52	7.80	17.93	-3.96	-5.44
10.SLA-SF-46-F3	0.86 (0.47)	0.155***	—	—	—	—	—	—	—	—	—	8.28	-17.20	-5.85	7.01	-12.12	-24.59
11.SLA-SF-46-F4	0.85 (0.53)	0.055***	—	—	—	—	—	—	—	—	—	—	-21.46	-11.92	1.05 ^{n.s.}	-16.15	-27.97
12.SLA-SF-46-F5	0.83 (0.56)	0.373***	—	—	—	—	—	—	—	—	—	—	—	11.05	19.00	-2.09	-0.54 ^{n.s.}
13.SLA-SF-46-F6	0.82 (0.49)	0.235***	—	—	—	—	—	—	—	—	—	—	—	—	10.41	-8.53	-13.48
14.SLA-SF-46-F7	0.70 (0.54)	0.037***	—	—	—	—	—	—	—	—	—	—	—	—	—	-18.97	-22.18
15.SLA-SF-46-F8	0.79 (0.42)	0.411***	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1.92 ^{n.s.}
16.SLA-SF-46-Total	0.93 (0.28)	0.377***	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Total																	

Note. ^aUnless otherwise specified by the superscript “n.s.” which denotes statistical non-significance, all other Z-scores of difference were significant at $p < .05$ (two-tailed) (i.e., $|Z\text{-score}| > 1.96$). ** $p < .01$ (two-tailed). *** $p < .001$ (two-tailed). MITC: Mean inter-item correlations. SLB-SF-38-Total: Scale score of the six-factor, 38-item Service Leadership Behavior (SLB) Scale; SLA-SF-46-Total: Scale score of the eight-factor, 46-item Service Leadership Attitude (SLA) Scale; SLB-SF-38-F1: SLB Factor 1 “Self-improvement and self-reflection”; SLB-SF-38-F2: SLB Factor 2 “People and principles orientation”; SLB-SF-38-F3: SLB Factor 3 “Resilience”; SLB-SF-38-F4: SLB Factor 4 “Social competence”; SLB-SF-38-F5: SLB Factor 5 “Problem-solving”; SLB-SF-38-F6: SLB Factor 6 “Mentorship”; SLA-SF-46-F1: SLA Factor 1 “Vision and competence”; SLA-SF-46-F2: SLA Factor 2 “People orientation”; SLA-SF-46-F3: SLA Factor 3 “Caring disposition”; SLA-SF-46-F4: SLA Factor 4 “Ethical role model”; SLA-SF-46-F5: SLA Factor 5 “Social competence”; SLA-SF-46-F6: SLA Factor 6 “Self-understanding and reflection”; SLA-SF-46-F7: SLA Factor 7 “Positive view about human beings”; SLA-SF-46-F8: SLA Factor 8 “Unchangeable and dark human nature”.

In short, findings from the correlational analyses provided a solid convergent evidence base for the construct validity of SLK-SF-38. Besides recording significant and positive correlations with constructs theorized to underpin the SLAM curriculum [10], the SLK-SF-40 also demonstrated significant correlation with the two separate objective assessment tools of Service Leadership.

Factorial Validity

We subjected the proposed one-factor structure of the SLK-SF-40 to a Confirmatory Factor Analysis (CFA) using Mplus version 6.12 [23]. Overall, the goodness-of-fit statistics (e.g., CFI, NNFI, and RMSEA) strongly supported the unidimensional structure of the SLK-SF-40 (see Table 7). Almost all indices, with the exception of WRMR, met the well-established criteria of adequate fit according to the literature [24]. Besides, as indicated in Table 8, the standardized factor loadings of all 40 items ranged from moderate to strong (i.e., 0.32 to 0.90) and were statistically significant ($p < .001$, two-tailed). In short, the present study supports the unidimensionality of the SLK-SF-40 [18].

Table 7. Model fit indices of the one-factor SLK-SF-40

Model Tested	χ^2	df	WRMR	NNFI	CFI	RMSEA (pclose)	RMSEA (90% CI)
One-factor	3,492.44	740	1.725	0.985	0.984	0.029 (1.00)	0.028/0.030
Criterion for goodness-of-fit	-	-	≤ 0.90	≥ 0.95	≥ 0.95	≤ 0.05	≤ 0.08

Note. WRMR = weighted root-mean-square residual; NNFI = Bentler-Bonett Nonnormed Fit Index; CFI = comparative fit index; RMSEA = root mean square error of approximation; pclose = probability of RMSEA ≤ 0.05 ; 90% CI = 90% Confidence Intervals (lower value/upper value).

NORMS

Student participants in this normative sample were recruited from the undergraduate programs of eight government-funded universities in Hong Kong. As the lead institution, the research team at the Hong Kong Polytechnic University utilized the “mySurvey@PolyU” electronic survey system to prepare the online survey and shared the link to the coordinators of all other participating institutions. The coordinators then sent the prepared online survey link to students who were interested in taking part. All prospective respondents were well informed about the principles of voluntary participation, anonymity, and rights to withdraw from the study at any time prior to the start. As a token of appreciation, each respondent was entitled to a local supermarket voucher valued at HK\$100 upon completion.

The data collection lasted from late March to early June in 2017. After excluding invalid cases such as repeated participation and participant ineligibility, a total of 4,486 sets of responses were included in the final sample for normative analysis. The participants were aged between 15 and 34 years ($M = 20.47$, $SD = 1.67$), comprised of 2,969 (66.18%) female students and 1,517 (33.82%) male students.

Table 8. Confirmatory Factor Analysis Loadings

Items	Mean ^a (Standard Deviation)	Accuracy Rate ^b	Standardized factor loadings	R- squared	Residual variance	Corrected Item-total Correlations
SLK-01	0.391 (0.488)	39.12%	0.528	0.279	0.721	0.396
SLK-02	0.751 (0.433)	75.06%	0.545	0.297	0.703	0.396
SLK-03	0.830 (0.376)	83.01%	0.646	0.417	0.583	0.433
SLK-05	0.742 (0.438)	74.19%	0.537	0.289	0.711	0.391
SLK-06	0.439 (0.496)	43.87%	0.419	0.175	0.825	0.316
SLK-08	0.612 (0.487)	61.21%	0.570	0.325	0.675	0.444
SLK-10	0.447 (0.497)	44.72%	0.597	0.356	0.644	0.461
SLK-11	0.523 (0.500)	52.25%	0.522	0.272	0.728	0.399
SLK-12	0.607 (0.489)	60.65%	0.535	0.287	0.713	0.415
SLK-13	0.740 (0.439)	73.99%	0.831	0.690	0.310	0.621
SLK-14	0.592 (0.492)	59.16%	0.718	0.515	0.485	0.565
SLK-15	0.396 (0.489)	39.59%	0.676	0.456	0.544	0.509
SLK-16	0.604 (0.489)	60.43%	0.878	0.770	0.230	0.699
SLK-17	0.673 (0.469)	67.32%	0.869	0.755	0.245	0.682
SLK-18	0.597 (0.490)	59.74%	0.901	0.813	0.187	0.726
SLK-19	0.673 (0.469)	67.32%	0.558	0.311	0.689	0.422
SLK-20	0.624 (0.484)	62.44%	0.838	0.703	0.297	0.667
SLK-21	0.675 (0.468)	67.50%	0.570	0.324	0.676	0.433
SLK-22	0.685 (0.465)	68.46%	0.760	0.578	0.422	0.577
SLK-23	0.619 (0.486)	61.93%	0.819	0.672	0.328	0.652
SLK-24	0.542 (0.498)	54.19%	0.603	0.363	0.637	0.469
SLK-25	0.568 (0.495)	56.82%	0.755	0.570	0.430	0.598
SLK-26	0.594 (0.491)	59.38%	0.748	0.559	0.441	0.583
SLK-28	0.664 (0.472)	66.41%	0.316	0.100	0.900	0.653
SLK-30	0.672 (0.469)	67.23%	0.833	0.693	0.307	0.568
SLK-31	0.536 (0.499)	53.63%	0.731	0.534	0.466	0.573
SLK-32	0.552 (0.497)	55.19%	0.739	0.546	0.454	0.522
SLK-33	0.399 (0.490)	39.88%	0.662	0.438	0.562	0.494
SLK-34	0.536 (0.499)	53.59%	0.651	0.424	0.576	0.665
SLK-36	0.375 (0.484)	37.47%	0.820	0.673	0.327	0.462
SLK-38	0.429 (0.495)	42.93%	0.617	0.381	0.619	0.478
SLK-39	0.358 (0.480)	35.84%	0.618	0.382	0.618	0.318
SLK-41	0.608 (0.488)	60.81%	0.430	0.185	0.815	0.616
SLK-42	0.514 (0.500)	51.38%	0.772	0.596	0.404	0.580
SLK-44	0.343 (0.475)	34.26%	0.731	0.534	0.466	0.366
SLK-45	0.526 (0.499)	52.56%	0.497	0.247	0.753	0.591
SLK-46	0.649 (0.477)	64.87%	0.757	0.572	0.428	0.437
SLK-47	0.539 (0.499)	53.92%	0.563	0.317	0.683	0.343
SLK-48	0.363 (0.481)	36.31%	0.442	0.196	0.804	0.314
SLK-50	0.566 (0.496)	56.58%	0.421	0.177	0.823	0.575

Note. ^a Each correct (incorrect) response was coded “1” (“0”). ^b Accuracy Rate = (Number of correct responses)/(Total responses, i.e., 4,486) *100%. All standardized factor loadings and R² metrics were statistically significant at $p < .001$ (two-tailed).

Table 9. Percentiles and related raw scores for Service Leadership Knowledge Scale (SLK-SF-40) by gender

Percentile (1-50)	Raw Score			Percentile (51-99)	Raw Score		
	Male (N = 1,517)	Female (N = 2,969)	Total sample (N = 4,486)		Male (N = 1,517)	Female (N = 2,969)	Total sample (N = 4,486)
1	≤ 4.00	≤ 5.00	≤ 5.00	51	18.00	27.00	24.00
2	5.00	6.00	6.00	52	19.00	27.00	25.00
3	6.00	7.00	6.00	53	19.00	27.00	25.00
4	6.00	7.00	6.00	54	20.00	28.00	26.00
5	6.00	7.00	7.00	55	20.00	28.00	26.00
6	6.00	8.00	7.00	56	21.00	28.00	27.00
7	7.00	8.00	7.00	57	22.00	29.00	27.00
8	7.00	9.00	8.00	58	23.00	29.00	28.00
9	7.00	9.00	8.00	59	23.00	29.00	28.00
10	7.00	9.00	8.00	60	24.00	30.00	28.00
11	7.00	10.00	9.00	61	24.00	30.00	29.00
12	8.00	10.00	9.00	62	25.00	30.00	29.00
13	8.00	10.00	9.00	63	26.00	30.00	29.00
14	8.00	10.00	9.00	64	26.00	31.00	30.00
15	8.00	11.00	10.00	65	27.00	31.00	30.00
16	8.00	11.00	10.00	66	27.00	31.00	30.00
17	9.00	11.00	10.00	67	28.00	31.00	30.00
18	9.00	12.00	10.00	68	28.00	31.00	31.00
19	9.00	12.00	11.00	69	28.42	32.00	31.00
20	9.00	12.00	11.00	70	29.00	32.00	31.00
21	9.00	13.00	11.00	71	29.00	32.00	31.00
22	9.96	13.00	12.00	72	30.00	32.00	32.00
23	10.00	13.00	12.00	73	30.00	32.00	32.00
24	10.00	14.00	12.00	74	30.00	33.00	32.00
25	10.00	14.00	12.00	75	31.00	33.00	32.00
26	10.00	14.00	13.00	76	31.00	33.00	33.00
27	10.00	15.00	13.00	77	31.00	33.00	33.00
28	11.00	15.00	13.00	78	32.00	33.60	33.00
29	11.00	16.00	14.00	79	32.00	34.00	33.00
30	11.00	16.00	14.00	80	32.00	34.00	33.00
31	12.00	17.00	14.00	81	32.00	34.00	34.00
32	12.00	17.00	15.00	82	33.00	34.00	34.00
33	12.00	18.00	15.00	83	33.00	34.00	34.00
34	12.00	18.00	15.00	84	33.00	35.00	34.00
35	13.00	19.00	16.00	85	34.00	35.00	35.00
36	13.00	19.00	16.00	86	34.00	35.00	35.00
37	13.00	20.00	17.00	87	34.00	35.00	35.00
38	13.00	20.00	17.00	88	35.00	35.00	35.00
39	13.00	21.00	18.00	89	35.00	36.00	35.00
40	14.00	21.00	18.00	90	35.00	36.00	36.00
41	14.00	22.00	19.00	91	35.00	36.00	36.00
42	14.00	23.00	19.00	92	36.00	36.00	36.00
43	15.00	23.00	20.00	93	36.00	36.00	36.00
44	15.00	23.00	20.00	94	36.00	37.00	36.00
45	15.00	24.00	21.00	95	36.00	37.00	37.00
46	16.00	24.00	22.00	96	37.00	37.00	37.00
47	16.00	25.00	22.00	97	37.00	38.00	37.00
48	16.64	25.00	23.00	98	38.00	38.00	38.00
49	17.00	26.00	23.00	99	38.82	39.00	39.00
50	17.00	26.00	24.00	100	39.00	40.00	40.00

Normative Statistics

As the raw scores in the full normative sample and sub-groups (i.e., male and female groups) did not follow a normal distribution, instead of using z scores, percentile ranks were

calculated. Norms of the total score of the full normative sample and sub-groups are presented in Table 9 (percentile ranks and corresponding raw scores) and Table 10 (raw scores and equivalent percentile ranks).

Table 10. Raw scores and related percentiles for Service Leadership Knowledge Scale (SLK-SF-40)

Raw score	Percentiles		
	Male (<i>N</i> = 1517)	Female (<i>N</i> = 2969)	Total sample (<i>N</i> = 4486)
1	0.0	0.0	0.0
2	0.0	0.0	0.0
3	0.0	0.0	0.0
4	1.0	0.0	0.0
5	2.0	1.0	1.0
6	5.0	2.0	3.0
7	9.0	4.0	6.0
8	14.0	6.0	9.0
9	19.0	9.0	12.0
10	25.0	12.0	17.0
11	29.0	16.0	20.0
12	33.0	19.0	24.0
13	37.0	22.0	27.0
14	41.0	25.0	30.0
15	44.0	27.0	33.0
16	47.0	30.0	35.0
17	49.0	32.0	38.0
18	51.0	34.0	40.0
19	53.0	36.0	41.0
20	55.0	37.0	43.0
21	56.0	39.0	45.0
22	57.0	41.0	47.0
23	59.0	43.0	48.0
24	60.0	45.0	50.0
25	62.0	48.0	52.0
26	64.0	50.0	54.0
27	66.0	52.0	57.0
28	68.0	55.0	59.0
29	70.0	58.0	62.0
30	73.0	62.0	66.0
31	76.0	66.0	70.0
32	80.0	71.0	74.0
33	83.0	76.0	78.0
34	86.0	81.0	83.0
35	90.0	86.0	87.0
36	94.0	91.0	92.0
37	97.0	95.0	96.0
38	98.0	98.0	98.0
39	100.0	99.0	99.0
40	100.0	100.0	100.0

SCORING AND INTERPRETATION

The SLK-SF-40 is consisted of 40 items, and each has a correct answer. Each participant's answer on each item was coded as "1" or "0" to indicate a correct or incorrect answer, respectively. A total score across the 40 items is computed as the Service Leadership knowledge score, with a maximum score of 40.

Handling Missing Items

Completion of all items in the present scale is important to ensure satisfactory reliability of the scale. Results have to be interpreted cautiously in the event of missing responses. The responses with missing value(s) should be excluded from data analysis or be imputed with appropriate method prior to further analysis.

Interpretation of Test Scores

The objective of SLK-SF-40 is to measure participants' mastery of key knowledge points in Service Leadership. Interpretation of SLK-SF-40 test score is based on the full scale. A higher total score (out of 40) is indicative of the acquisition of more key knowledge points a Service Leader is expected to have.

Table 9 shows percentile norms for the scores of SLK-SF-40. Percentile rank of a specific raw score represents the percentage of people in the normative sample whose score is the same or lower than the specific raw score for a particular measure. In other words, the percentile rank of an individual shows his/her standing in the relevant group. Taking a female student who gets score of 30 as an example, her received score has made her surpassed more than half (60%) of all female students.

As mentioned in earlier section, a higher total score indicates one has more understanding of key knowledge points on Service Leadership. There is no specific cut-off value to segregate "rich" from "inadequate" knowledge on Service Leadership. When interpreting test scores, scale users (i.e., researchers or program evaluators) are recommended to locate the score of the participant from the norm tables to gauge his/her relative position regarding Service Leadership knowledge. Scale users may utilize expressions such as "less as compared to the normative sample", "similar to the normative sample", or "more as compared to the normative sample" to describe participants' different levels on Service Leadership knowledge.

To evaluate the effectiveness of Service Leadership training program, it is recommended that the scale be administered by the program evaluators prior to and after completion of the program. Evaluators can compare participants' received score in pre and post-test, which means scores can be used without referring to the norm table.

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Chapter 146

A USER MANUAL FOR SERVICE LEADERSHIP ATTITUDE SCALE

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ABSTRACT

As there are few objective measures of attitudes to leadership in the service economies, The Service Leadership Attitude Scale was developed to assess an individual's attitudes towards leadership and effective leadership in the service economies. The scale was based on the Service Leadership Theory proposed by Po Chung. With an initial item pool of 132 items, the final scale comprises 46 items which showed very good psychometric properties. In this chapter, the background of the development of this scale, validation process and the psychometric properties of the scale are presented. Reminders for administration of the scale and guides for interpretation of the scales are also outlined.

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INTRODUCTION

Hong Kong has an economy heavily depending on traditional and creative service industries which contribute 92.2% to the total Gross Domestic Product (GDP) and 92.7% to the employment [1]. To sustain the competitive advantage of Hong Kong's service industries in the Asian Pacific region and even in the whole world market, service leaders are expected to be people-oriented and care about individual human needs including not only one's own but also others' needs as well as wellness of group, environment and the society. To this end, Po Chung proposed a new concept of Service Leadership Theory, which regards leadership as "a service aims at ethically satisfying the needs of self, others, groups, communities, systems, and environments" and stresses on humanistic values, moral ethics, and care of a service leader [2].

Guided by the Service Leadership Theory, and financially supported by the Victor and William Fung Foundation, the "Fung Service Leadership Initiative" (FSI) was implemented in the eight government-funded universities in Hong Kong from 2012 to 2015, with an aim of spotting and nurturing future leaders with service mindset and key service leadership qualities. To evaluate service leadership attributes and the effectiveness of service leadership education, it is imperative to have validated assessment tools specifically designed based on Service Leadership Theory. Thus, three assessment tools including knowledge, attitude, and behavior scales were developed and validated. While this manual focuses on the attitude scale and its finalized 46-item version (i.e., SLA-SF-46), the other two scales are introduced in respective user manuals.

This manual was written for potential users of the SLA-SF-46, including university teachers, program evaluators, human resources trainers, and employers. There are five purposes of this manual. First, it provides the scale users a brief description of the conceptual framework of Service Leadership Attitude Scale. Second, it introduces how the different versions of the scale were developed. Third, it presents statistical evidence documenting the reliability and validity of the finalized scale as an effective measure of service leadership attitude. Fourth, the manual presents normative statistics for interpretation of raw scores. Finally, the manual provides users with other information they need to administer the test and interpret the results.

CONCEPTUAL FRAMEWORK

Service Leadership Theory is characterized by several unique features, such as the seven core beliefs (e.g., everyone can be a leader and three realms of leadership) [3] and the strong emphasis on service orientation and self-leadership [4, 5]. Based on these propositions, attitude toward service leadership was conceptualized as one's beliefs and perceptions about the nature of leadership process and role of a leader with reference to the eight domains. These domains are briefly outlined below, and detailed elaborations can be found elsewhere [6].

The first domain pertains to service orientation. Service leaders should see leadership as a service rather than a tool merely for generating profits. Modern service leaders are expected to believe in the importance of contributing to improving service ecology without instant

economic returns, which enhances wellbeing at the societal level and benefits all market participants in the long run.

The second domain is pertinent to the belief that “everyone can be (and is) a leader.” It has been shown that leadership in the service sectors is a learned behavior rather than a natural gift [7, 8]. When leaders establish the sense that leadership qualities are not innate but learned, they can better recognize and nurture followers’ potential and maximize followers’ personal contribution.

The third domain is seeing distributed leadership as a desirable leadership practice. Distributed leadership allows employees to extend their roles in implementing service improvement by initiating changes from the bottom [9]. This process of shared decision making and empowerment entails employees to see themselves as part of the organization which increase job performance and commitment.

Fourth, service leaders believe that service leadership increases employability. Service leadership is built upon professional competence, moral character and caring disposition, which are fundamental leadership qualities demanded in modern service industries. Thus, belief is expected to be established among service leaders that service leadership increases the likelihood of being employed and being a service leader will enjoy monetary and spiritual benefits [3].

The fifth domain has to do with the belief of providing personalized service and being sensitive to people’s diversified needs. With the rapid development of technologies, traditional notion of delivering “one-size-fits-all” service to customers is no longer an optimal choice in the modern service era [3]. Instead, how to provide customized service that fits each individual’s needs has become the key area of competition [11].

Sixth, service leaders believe that providing service is intrinsically enjoyable to the service providers. High-quality service provision is more likely to be invigorated in the organizations with enjoyable atmosphere, where leaders and followers are not motivated only by external rewards such as economic returns. Service leaders believe in the importance of service passion and cultivate service enthusiasm among subordinates.

Seventh, service leaders believe that good leaders should demonstrate competence, character, and care (3Cs). For competence, it is important to possess multiple intrapersonal and interpersonal skills, so as to fulfill one’s duties. For character, service leaders must be aware of the importance of “doing the right thing” in right ways. Regarding the importance of care, it is well known that caring behaviors of a leader as a service-provider will breed trust, loyalty and commitment in the followers and service recipients [3].

The eighth domain is about commitment to continuous improvement. In addition to serving others, service leaders are also expected to realize the need of serving oneself by continuously improving oneself, in order to accumulate resources and capacities to serve and lead others more effectively.

DIFFERENT STAGES OF THE VALIDATION STUDY

To further support the development of service leadership education in Hong Kong, the Victor and William Fung Foundation provided additional funding for the eight universities which collaborated in developing and validating scales on the service leadership knowledge,

attitude and behavior in 2015. As far as the development of the attitude scale is concerned, several stages were involved as follows:

Stage 1: With reference to the conceptual framework mentioned before, the original long-form Service Leadership Attitude Scale including 132 items (i.e., SLA-LF-132) was developed.

Stage 2: The SLA-LF-132 was initially validated through a content validation study involving three experts [6] and a quasi-experimental study. Based on the results of an exploratory factor analysis (EFA) which utilized the pre-test data collected in the quasi-experimental study, 73 items with a 5-factor structure were retained to form a short-form attitude scale (SLA-SF-73). The SLA-SF-73 demonstrated good reliability.

Stage 3: The SLA-SF-73 was subject to a large-scale validation study involving 4,468 undergraduates recruited from the eight public universities in Hong Kong. Based on EFA using a sub-sample ($N = 2,246$), 46 items with a 7-factor structure were retained to form a new short-form scale (i.e., SLA-SF-46E). The SLA-SF-46E showed excellent internal consistency and strong convergent validity [11].

Stage 4: The SLA-SF-46E was subject to confirmatory factor analysis (CFA) based on another sub-sample ($N = 2,240$), which informed a finalized 46-item scale with an 8-factor structure (i.e., SLA-SF-46). The finalized scale and its eight subscales showed good reliability and convergent validity, which will be reported in Section 5 of this manual.

DESIGN AND USE OF THE SCALE

The item contents of the attitude scale were derived from two sources. First, some items were modified from existing measures on attitude [12-14]. Second, some items were specifically constructed with reference to the conceptual framework and related service leadership curriculum. In the finalized scale (i.e., SLA-SF-46), 46 items were structured into 8 factors. The names and sample items of these factors are listed below:

- Factor 1: Vision and competence (10 items). A hypothetical sample item is “good leaders do not give in easily when facing challenges.”
- Factor 2: People orientation (8 items). A hypothetical sample item is “good leaders encourage subordinates to contribute their ideas.”
- Factor 3: Caring disposition (7 items). A hypothetical sample item is “good leaders help followers develop their talents.”
- Factor 4: Ethical role model (5 items). A hypothetical sample item is “leadership effectiveness is largely dependent on ethical beliefs of the leader.”
- Factor 5: Social competence (4 items). A hypothetical sample item is “good leaders have good interpersonal skills.”
- Factor 6: Self-understanding and self-reflection (5 items). A hypothetical sample item is “good leaders have much self-reflection.”

- Factor 7: Positive views about human beings (2 items). A hypothetical sample item is “everyone has what it takes to be a leader.”
- Factor 8: Unchangeable and dark human nature (5 items, reversed). A hypothetical sample item is “We have to closely monitor subordinates’ work to make sure that they are not lazy” (reverse-item).

Target Respondents

The SLA-SF-46 was designed for university students and employees who may receive training on service leadership. In principle, its target population is Chinese people who are or will be taking a leading role in service sectors in Hong Kong and other Chinese communities such as mainland China and Taiwan. When using the scale outside Hong Kong, it is necessary to construct local norms as the normative sample included in this manual was based on university students in Hong Kong.

Instructions

The SLA-SF-46 is administered in English. The questionnaire is normally completed in the self-administered manner. The scale should not be issued to respondents before they give formal consent to complete the scale. Before responding to scale items, participants should read through the instructions presented at the beginning of the questionnaire.

There is no specific time limit for respondents to complete the whole questionnaire. Generally speaking, the scale can be completed within 20-30 minutes. In principle, the questionnaire should be completed and collected in the administration venue and must not be taken away by the respondents.

Administration Notes

Different users may adapt the instructions and response format by complying with the following principles:

- 1) The questionnaire should be completed by respondents alone. Participants are not allowed to discuss with each other about the items.
- 2) Field administrators may explain grammatical and expression issues raised by respondents who have difficulties in understanding the meaning of any specific words or phrases. However, respondents should respond to the items according to their own interpretations.
- 3) The scale can be adopted in terms of full scale or individual subscales. However, the items included in a specific subscale should be fully utilized without any deletion.
- 4) SLA-SF-46 uses a 6-point Likert scale ranging from 1 (Strongly disagree) to 6 (Strongly agree). Testers should use the same rating scale.

- 5) SLA-SF-46 can be administered in paper-and-pencil or computerized formats. If the questionnaire is completed in the paper-and-pencil form, the completed questionnaires must be submitted to field administrators immediately. The questionnaires are not allowed to be retained or taken away by participants.

RELIABILITY AND VALIDITY

The normative sample was obtained in the large-scale validation study mentioned above. The psychometric properties of SLA-SF-46 were examined based on the normative sample and following sections briefly describe related findings.

Internal Consistency/Reliability

Results showed that SLA-SF-46 and its eight factors demonstrated good internal consistency, as reflected by Cronbach’s alphas ranging from .70 to .93 and mean inter-item correlations ranging between .28 and .56 (see Table 1).

Table 1. Internal consistency of SLA-SF-46 and its subscales

Scale/subscale	No. of items	Cronbach’s alpha	Mean Inter-Item Correlations
Vision and competence	10	.90	.46
People orientation	8	.87	.47
Caring disposition	7	.86	.47
Ethical role model	5	.85	.53
Social competence	4	.83	.56
Self-understanding and self-reflection	5	.82	.49
Positive view about human beings	2	.70	.54
Unchangeable and dark human nature	5	.79	.42
Full scale	46	.93	.28

Convergent Validity

The convergent validity of SLA-SF-46 was supported by the correlations among its subscales (see Table 2) and their correlations with external criterion constructs (see Table 3), including service leadership knowledge, service leadership behavior, servant leadership, moral self-concept, leadership efficacy, interpersonal reactivity index, empathic concern, and perspective thinking.

Factorial Validity

The 8-factor structure was shown to be the best solution fitting for the finalized 46-item attitude scale (i.e., SLA-SF-46). CFA based on the full normative sample (*N* = 4,486) yielded

good fit indices of the 8-factor structure, with CFI = .92, TLI = .91, RMSEA = .044 (90% CI = [.043, .045]). As shown in Table 4, majority of factor loadings were above .60.

Table 2. Inter-factor correlations of finalized attitude scale/subscales

	F1	F2	F3	F4	F5	F6	F7	F8
F1: Vision and competence	--							
F2: People orientation	.77***	--						
F3: Caring disposition	.63***	.61***	--					
F4: Ethical role model	.52***	.47***	.67***	--				
F5: Social competence	.76***	.73***	.60***	.47***	--			
F6: Self-understanding and reflection	.65***	.57***	.57***	.48***	.60***	--		
F7: Positive view about human beings	.24***	.33***	.35***	.31***	.24***	.16***	--	
F8: Unchangeable and dark human nature	-.05**	.02	-.16***	-.22***	.04**	-.15***	.03*	--
Full scale	.87***	.86***	.80***	.68***	.83***	.72***	.43***	.12**

Note. F1 = Factor 1, F2 = Factor 2, F3 = Factor 3, F4 = Factor 4, F5 = Factor 5, F6 = Factor 6, F7 = Factor 7, F8 = Factor 8. * $p < .05$, ** $p < .01$, *** $p < .001$.

Table 3. Correlations between finalized attitude scale/subscales and external criterion constructs

	SLK-SF-40	SLB-SF-38	RSLP	MSC	LEF	IRI	IRI-EC	IRI-PT
SLA-SF-46	.38***	.57***	.57***	.57***	.25***	.46***	.39***	.42***
SLA-SF-46-F1	.32***	.51***	.49***	.49***	.20***	.36***	.29***	.34***
SLA-SF-46-F2	.34***	.48***	.48***	.50***	.21***	.39***	.33***	.36***
SLA-SF-46-F3	.16***	.50***	.52***	.44***	.19***	.33***	.26***	.31***
SLA-SF-46-F4	.06***	.41***	.45***	.36***	.17***	.24***	.19***	.24***
SLA-SF-46-F5	.37***	.48***	.47***	.50***	.18***	.40***	.34***	.37***
SLA-SF-46-F6	.24***	.47***	.42***	.42***	.18***	.29***	.22***	.29***
SLA-SF-46-F7	.04*	.27***	.29***	.23***	.14***	.15***	.12***	.15***
SLA-SF-46-F8	.41***	-.06***	-.07***	.10***	.07***	.25***	.27***	.16***

Note. SLK-SF-40: Finalized Service Leadership Knowledge Scale (40 items); SLB-SF-38: Finalized Service Leadership Behavior Scale (38 items); SLA-SF-46: Finalized Service Leadership Attitude Scale (46 items); RSLP: Revised Servant Leadership Profile; MSC: Moral Self-Concept; LEF: Leadership Efficacy; IRI: Interpersonal Reactivity Index; EC: IRI- Empathic Concern; PT: IRI- Perspective Taking. SLA-SF-46-F1: Vision and competence; SLA-SF-46-F2: People orientation; SLA-SF-46-F3: Caring disposition; SLA-SF-46-F4: Ethical role model; SLA-SF-46-F5: Social competence; SLA-SF-46-F6: Self-Understanding and reflection; SLA-SF-46-F7: Positive view about human beings; SLA-SF-46-F8: Unchangeable and dark human nature. * $p < .05$, *** $p < .001$.

The related findings for the different validation studies can be seen in publications about background and development of the scale [15], content validation study [6], psychometric properties of the SLA-SF-46E obtained based on EFA [11], and a manuscript under preparation which aims to present findings of CFA using the normative sample and psychometric properties of the SLA-SF-46. In addition, norms and personal correlates of attitude to service leadership with reference to the full scale of SLA-SF-46 have also been reported by Shek and colleagues [16]. Section below will further present norms of SLA-SF-46 based on its full scale and subscales as well.

NORMS

The snowball sampling approach was adopted to recruit undergraduate students from eight publically-funded universities in Hong Kong, including The Hong Kong Polytechnic University (PolyU), The University of Hong Kong (HKU), The Chinese University of Hong Kong (CUHK), Hong Kong Baptist University (HKBU), City University of Hong Kong (CityU), The Education University of Hong Kong (EdUHK), Lingnan University (LU), and Hong Kong University of Science and Technology (HKUST). With the assistance offered by the coordinator in each university, the link of online survey was issued to students who had shown willingness to join the study. Students were well informed of the principles of confidentiality and their rights to withdraw from this study at any time. A local supermarket voucher worth \$HK100 dollars was offered to each participant who completed the whole survey as an incentive.

Table 4. Confirmatory factor analysis loadings

Item	Factor loading	Item	Factor loading
Vision and competence 1	.67	Caring disposition 6	.67
Vision and competence 2	.66	Caring disposition 7	.69
Vision and competence 3	.70	Ethical role model 1	.71
Vision and competence 4	.74	Ethical role model 2	.80
Vision and competence 5	.74	Ethical role model 3	.76
Vision and competence 6	.62	Ethical role model 4	.67
Vision and competence 7	.67	Ethical role model 5	.66
Vision and competence 8	.72	Social competence 1	.73
Vision and competence 9	.68	Social competence 2	.74
Vision and competence 10	.61	Social competence 3	.76
People orientation 1	.61	Social competence 4	.73
People orientation 2	.63	Self-Understanding and reflection 1	.50
People orientation 3	.72	Self-Understanding and reflection 2	.71
People orientation 4	.69	Self-Understanding and reflection 3	.79
People orientation 5	.75	Self-Understanding and reflection 4	.76
People orientation 6	.68	Self-Understanding and reflection 5	.73
People orientation 7	.71	Positive view about human beings 1	.76
People orientation 8	.63	Positive view about human beings 2	.71
Caring disposition 1	.70	Unchangeable and dark human nature 1	.76
Caring disposition 2	.71	Unchangeable and dark human nature 2	.85
Caring disposition 3	.60	Unchangeable and dark human nature 3	.67
Caring disposition 4	.72	Unchangeable and dark human nature 4	.35
Caring disposition 5	.72	Unchangeable and dark human nature 5	.50

The data were collected between late March and early June 2017. After excluding 6 students who refused to give a formal consent, 33 students who had a record of completing the survey for multiple times, and 30 students who reported they were postgraduates, the final sample consisted of 4,486 undergraduates whose data were used to perform normative analyses. The normative sample was aged between 15 and 34 years old ($M = 20.47$, $SD = 1.67$), comprised of 2,969 (66.18%) female students and 1,517 (33.82%) male students.

Table 5. Percentiles and related raw scores for SLA-SF-46 (full scale) by gender

Percentile (1-50)	Raw Score				Percentile (51-99)	Raw Score		
	Male	Female	Full sample			Male	Female	Full sample
1	≤ 136.00	≤ 164.00	≤ 155.00		51	214.00	218.00	216.37
2	155.00	173.40	165.74		52	214.00	218.00	217.00
3	161.54	179.00	172.00		53	215.00	219.00	217.00
4	167.00	182.00	176.48		54	215.00	219.00	218.00
5	172.00	185.00	179.00		55	215.00	219.00	218.00
6	174.00	187.00	182.00		56	215.00	220.00	218.00
7	176.00	190.00	184.00		57	216.00	220.00	219.00
8	178.00	191.00	186.00		58	216.00	220.00	219.00
9	179.00	193.00	188.00		59	217.00	221.00	220.00
10	181.00	194.00	190.00		60	217.00	221.00	220.00
11	182.00	195.70	191.00		61	218.00	221.00	220.00
12	184.00	197.00	192.00		62	218.00	222.00	221.00
13	186.00	198.00	194.00		63	219.00	222.00	221.00
14	187.00	199.00	195.00		64	219.00	223.00	222.00
15	188.00	200.00	196.00		65	220.00	223.00	222.00
16	190.00	201.00	197.00		66	220.00	224.00	222.00
17	191.00	202.00	198.00		67	221.00	224.00	223.00
18	192.00	203.00	199.00		68	221.00	225.00	223.00
19	193.00	203.00	200.00		69	222.00	225.00	224.00
20	194.00	204.00	201.00		70	222.00	226.00	224.00
21	195.00	205.00	202.00		71	223.00	226.00	225.00
22	196.00	206.00	203.00		72	223.00	227.00	226.00
23	197.00	207.00	203.00		73	224.00	227.00	226.00
24	197.32	207.00	204.00		74	224.00	228.00	227.00
25	198.00	207.00	205.00		75	225.00	228.00	227.00
26	199.00	208.00	205.00		76	226.00	229.00	228.00
27	200.00	209.00	206.00		77	226.00	229.00	228.00
28	201.00	209.00	207.00		78	227.00	230.00	229.00
29	202.00	210.00	207.00		79	228.00	231.00	230.00
30	203.00	210.00	208.00		80	228.00	231.00	230.00
31	203.00	210.00	209.00		81	229.00	232.00	231.00
32	204.00	211.00	209.00		82	229.00	233.00	232.00
33	204.00	211.00	209.00		83	230.00	233.00	232.00
34	205.00	212.00	210.00		84	231.00	234.00	233.00
35	206.00	212.00	210.45		85	232.00	235.00	234.00
36	206.00	213.00	211.00		86	234.00	236.00	235.00
37	207.00	213.00	211.00		87	235.00	237.00	236.00
38	207.00	213.00	212.00		88	236.00	239.00	237.56
39	208.00	214.00	212.00		89	237.00	240.00	239.00
40	209.00	214.00	213.00		90	238.00	242.00	240.00
41	209.00	214.00	213.00		91	239.00	243.70	242.00
42	210.00	215.00	213.00		92	241.00	246.00	244.00
43	211.00	215.00	214.00		93	243.00	247.00	246.00
44	211.00	215.00	214.00		94	245.00	248.80	248.00
45	212.00	215.00	214.00		95	247.10	250.00	249.00
46	212.00	216.00	215.00		96	251.00	252.00	251.00
47	212.00	216.00	215.00		97	252.00	254.00	253.00
48	213.00	217.00	215.00		98	255.00	257.00	256.00
49	213.00	217.00	216.00		99	259.00	261.00	261.00
50	214.00	217.00	216.00		100	≥ 271.00	≥ 272.00	≥ 272.00

Note. $N = 1,517$ for male sample, $N = 2,969$ for female sample, $N = 4,486$ for full sample.

Table 6. Raw scores and related percentiles for SLA-SF-46 (full scale) by gender

Raw score (≤ 182)	Percentiles			Raw score (183-229)	Percentiles			Raw score (230-276)	Percentiles		
	Male	Female	Full sample		Male	Female	Full sample		Male	Female	Full sample
≤ 136	1.0	1.0	1.0	183	12.0	5.0	7.0	230	83.0	78.0	80.0
137	2.0	1.0	1.0	184	12.0	5.0	7.0	231	84.0	80.0	81.0
138	2.0	1.0	1.0	185	13.0	5.0	8.0	232	85.0	81.0	83.0
139	2.0	1.0	1.0	186	13.0	6.0	8.0	233	86.0	83.0	84.0
140	2.0	1.0	1.0	187	14.0	6.0	9.0	234	86.0	84.0	85.0
141	2.0	1.0	1.0	188	15.0	7.0	9.0	235	87.0	85.0	86.0
142	2.0	1.0	1.0	189	16.0	7.0	10.0	236	88.0	86.0	87.0
143	2.0	1.0	1.0	190	16.0	7.0	10.0	237	89.0	87.0	88.0
144	2.0	1.0	1.0	191	17.0	8.0	11.0	238	90.0	88.0	88.0
145	2.0	1.0	1.0	192	18.0	9.0	12.0	239	91.0	88.0	89.0
146	2.0	1.0	1.0	193	19.0	9.0	13.0	240	92.0	89.0	90.0
147	2.0	1.0	1.0	194	20.0	10.0	13.0	241	92.0	90.0	91.0
148	2.0	1.0	1.0	195	21.0	11.0	14.0	242	93.0	90.0	91.0
149	2.0	1.0	1.0	196	22.0	11.0	15.0	243	93.0	91.0	92.0
150	2.0	1.0	1.0	197	24.0	12.0	16.0	244	94.0	91.0	92.0
151	2.0	1.0	1.0	198	25.0	13.0	17.0	245	94.0	92.0	93.0
152	2.0	1.0	1.0	199	26.0	14.0	18.0	246	95.0	92.0	93.0
153	2.0	1.0	1.0	200	27.0	15.0	19.0	247	95.0	93.0	94.0
154	2.0	1.0	1.0	201	28.0	16.0	20.0	248	96.0	94.0	94.0
155	2.0	1.0	1.0	202	29.0	17.0	21.0	249	96.0	94.0	95.0
156	3.0	1.0	2.0	203	31.0	19.0	23.0	250	96.0	95.0	96.0
157	3.0	1.0	2.0	204	33.0	20.0	24.0	251	96.0	96.0	96.0
158	3.0	1.0	2.0	205	34.0	21.0	26.0	252	97.0	96.0	97.0
159	3.0	1.0	2.0	206	36.0	22.0	27.0	253	98.0	97.0	97.0
160	3.0	1.0	2.0	207	38.0	24.0	29.0	254	98.0	97.0	98.0
161	3.0	1.0	2.0	208	39.0	26.0	30.0	255	98.0	98.0	98.0
162	4.0	1.0	2.0	209	41.0	28.0	32.0	256	99.0	98.0	98.0
163	4.0	1.0	2.0	210	42.0	30.0	35.0	257	99.0	98.0	99.0
164	4.0	1.0	2.0	211	44.0	33.0	37.0	258	99.0	99.0	99.0
165	4.0	2.0	2.0	212	46.0	35.0	39.0	259	99.0	99.0	99.0
166	4.0	2.0	2.0	213	49.0	37.0	41.0	260	99.0	99.0	99.0
167	4.0	2.0	3.0	214	51.0	40.0	44.0	261	99.0	99.0	99.0
168	5.0	2.0	3.0	215	55.0	44.0	47.0	262	99.0	99.0	99.0
169	5.0	2.0	3.0	216	58.0	47.0	50.0	263	99.0	99.0	99.0
170	5.0	2.0	3.0	217	60.0	49.0	53.0	264	99.0	99.0	99.0
171	5.0	2.0	3.0	218	62.0	52.0	55.0	265	99.0	99.0	99.0
172	5.0	2.0	3.0	219	64.0	54.0	58.0	266	99.0	99.0	99.0
173	6.0	2.0	4.0	220	66.0	57.0	60.0	267	99.0	99.0	99.0
174	6.0	3.0	4.0	221	68.0	60.0	63.0	268	99.0	99.0	99.0
175	7.0	3.0	4.0	222	70.0	63.0	65.0	269	99.0	99.0	99.0
176	7.0	3.0	4.0	223	72.0	65.0	68.0	270	99.0	99.0	99.0
177	8.0	3.0	5.0	224	74.0	67.0	70.0	271	100.0	99.0	100.0
178	8.0	3.0	5.0	225	75.0	69.0	71.0	272	100.0	100.0	100.0
179	9.0	3.0	5.0	226	77.0	71.0	73.0	273	100.0	100.0	100.0
180	10.0	4.0	6.0	227	78.0	73.0	75.0	274	100.0	100.0	100.0
181	10.0	4.0	6.0	228	80.0	75.0	77.0	275	100.0	100.0	100.0
182	11.0	4.0	6.0	229	82.0	77.0	78.0	276	100.0	100.0	100.0

Note. $N = 1,517$ for male sample, $N = 2,969$ for female sample, $N = 4,486$ for full sample.

Table 7. Raw scores and related percentiles for SLA-SF-46 (Factor 1) by gender

Percentile (1-50)	Raw Score				Percentile (51-100)	Raw Score		
	Male	Female	Full sample			Male	Female	Full sample
1	≤ 26.00	≤ 35.00	≤ 31.00		51	50.00	50.00	50.00
2	31.00	38.00	36.00		52	50.00	50.00	50.00
3	35.00	40.00	38.00		53	50.00	50.00	50.00
4	36.00	40.00	39.00		54	50.00	50.00	50.00
5	37.00	41.00	40.00		55	50.00	50.00	50.00
6	38.00	42.00	40.00		56	50.00	50.00	50.00
7	39.00	43.00	41.00		57	50.00	51.00	50.00
8	40.00	43.00	42.00		58	50.00	51.00	50.46
9	40.00	44.00	42.00		59	50.00	51.00	51.00
10	40.00	44.00	43.00		60	50.00	51.00	51.00
11	41.00	45.00	43.00		61	51.00	51.00	51.00
12	41.00	45.00	44.00		62	51.00	51.00	51.00
13	42.00	45.00	44.00		63	51.00	51.00	51.00
14	42.00	46.00	45.00		64	51.00	51.00	51.00
15	43.00	46.00	45.00		65	51.00	52.00	51.00
16	43.00	46.00	45.00		66	51.00	52.00	52.00
17	44.00	46.00	46.00		67	51.00	52.00	52.00
18	44.00	47.00	46.00		68	51.00	52.00	52.00
19	44.00	47.00	46.00		69	52.00	52.00	52.00
20	44.00	47.00	46.00		70	52.00	52.00	52.00
21	45.00	47.00	46.00		71	52.00	52.00	52.00
22	45.00	47.00	47.00		72	52.00	53.00	52.00
23	45.00	48.00	47.00		73	52.00	53.00	53.00
24	45.00	48.00	47.00		74	52.00	53.00	53.00
25	46.00	48.00	47.00		75	53.00	53.00	53.00
26	46.00	48.00	47.00		76	53.00	53.00	53.00
27	46.00	48.00	48.00		77	53.00	53.00	53.00
28	46.00	48.00	48.00		78	53.00	54.00	53.00
29	47.00	48.00	48.00		79	53.00	54.00	54.00
30	47.00	49.00	48.00		80	53.00	54.00	54.00
31	47.00	49.00	48.00		81	54.00	54.00	54.00
32	47.00	49.00	48.00		82	54.00	54.00	54.00
33	47.00	49.00	48.00		83	54.00	55.00	54.00
34	48.00	49.00	49.00		84	54.00	55.00	55.00
35	48.00	49.00	49.00		85	55.00	55.00	55.00
36	48.00	49.00	49.00		86	55.00	56.00	55.00
37	48.00	49.00	49.00		87	55.00	56.00	56.00
38	48.00	49.00	49.00		88	56.00	56.00	56.00
39	48.00	49.00	49.00		89	56.00	56.00	56.00
40	48.00	50.00	49.00		90	56.00	57.00	57.00
41	48.00	50.00	49.00		91	57.00	57.00	57.00
42	49.00	50.00	50.00		92	57.00	58.00	57.00
43	49.00	50.00	50.00		93	57.00	58.00	58.00
44	49.00	50.00	50.00		94	58.00	58.00	58.00
45	49.00	50.00	50.00		95	59.00	59.00	59.00
46	49.00	50.00	50.00		96	59.00	59.00	59.00
47	49.00	50.00	50.00		97	60.00	60.00	60.00
48	50.00	50.00	50.00		98	60.00	60.00	60.00
49	50.00	50.00	50.00		99	60.00	60.00	60.00
50	50.00	50.00	50.00		100	60.00	60.00	60.00

Note. $N = 1,517$ for male sample, $N = 2,969$ for female sample, $N = 4,486$ for full sample.

Table 8. Raw scores and related percentiles for SLA-SF-46 (Factor 1) by gender

Raw score (≤ 37)	Percentiles			Raw score (38-49)	Percentiles			Raw score (50-60)	Percentiles		
	Male	Female	Full sample		Male	Female	Full sample		Male	Female	Full sample
≤ 26	1.0	1.0	1.0	38	6.0	2.0	3.0	50	54.0	48.0	50.0
27	2.0	1.0	1.0	39	7.0	4.0	4.0	51	65.0	61.0	62.0
28	2.0	1.0	1.0	40	9.0	4.0	6.0	52	72.0	68.0	69.0
29	2.0	1.0	1.0	41	12.0	5.0	7.0	53	78.0	75.0	76.0
30	2.0	1.0	1.0	42	14.0	6.0	9.0	54	83.0	80.0	81.0
31	2.0	1.0	1.0	43	16.0	8.0	11.0	55	86.0	84.0	85.0
32	3.0	1.0	2.0	44	19.0	10.0	13.0	56	89.0	88.0	88.0
33	3.0	1.0	2.0	45	23.0	12.0	15.0	57	92.0	91.0	91.0
34	3.0	1.0	2.0	46	27.0	16.0	19.0	58	94.0	93.0	94.0
35	3.0	1.0	2.0	47	31.0	20.0	24.0	59	96.0	96.0	96.0
36	4.0	2.0	2.0	48	38.0	26.0	30.0	60	100.0	100.0	100.0
37	5.0	2.0	3.0	49	45.0	35.0	38.0				

Note. N = 1,517 for male sample, N = 2,969 for female sample, N = 4,486 for full sample.

Table 9. Raw scores and related percentiles for SLA-SF-46 (Factor 2) by gender

Percentile (1-50)	Raw Score				Percentile (51-100)	Raw Score		
	Male	Female	Full sample			Male	Female	Full sample
1	≤ 20	≤ 28.00	≤ 25.00		51	40.00	40.00	40.00
2	25.00	30.00	28.00		52	40.00	40.00	40.00
3	27.00	31.00	29.00		53	40.00	40.00	40.00
4	28.00	32.00	31.00		54	40.00	41.00	41.00
5	29.00	32.00	32.00		55	40.00	41.00	41.00
6	30.00	33.00	32.00		56	40.00	41.00	41.00
7	30.00	34.00	32.00		57	40.00	41.00	41.00
8	31.00	34.00	33.00		58	40.00	41.00	41.00
9	32.00	35.00	33.00		59	40.00	41.00	41.00
10	32.00	35.00	34.00		60	40.00	41.00	41.00
11	32.00	36.00	34.00		61	40.00	41.00	41.00
12	33.00	36.00	35.00		62	41.00	41.00	41.00
13	33.00	36.00	35.00		63	41.00	41.00	41.00
14	34.00	36.00	35.00		64	41.00	42.00	42.00
15	34.00	37.00	36.00		65	41.00	42.00	42.00
16	34.00	37.00	36.00		66	41.00	42.00	42.00
17	35.00	37.00	36.00		67	41.00	42.00	42.00
18	35.00	37.00	36.00		68	41.00	42.00	42.00
19	35.00	38.00	37.00		69	41.00	42.00	42.00
20	35.00	38.00	37.00		70	41.00	42.00	42.00
21	36.00	38.00	37.00		71	42.00	42.00	42.00
22	36.00	38.00	37.00		72	42.00	42.00	42.00
23	36.00	38.00	38.00		73	42.00	43.00	43.00
24	36.00	38.00	38.00		74	42.00	43.00	43.00
25	36.00	39.00	38.00		75	42.00	43.00	43.00
26	37.00	39.00	38.00		76	42.00	43.00	43.00
27	37.00	39.00	38.00		77	42.00	43.00	43.00
28	37.00	39.00	38.00		78	43.00	43.00	43.00
29	37.00	39.00	39.00		79	43.00	43.00	43.00
30	37.00	39.00	39.00		80	43.00	44.00	44.00
31	38.00	39.00	39.00		81	43.00	44.00	44.00
32	38.00	39.00	39.00		82	43.00	44.00	44.00

Percentile (1-50)	Raw Score				Percentile (51-100)	Raw Score		
	Male	Female	Full sample			Male	Female	Full sample
33	38.00	39.00	39.00		83	43.00	44.00	44.00
34	38.00	39.00	39.00		84	44.00	44.00	44.00
35	38.00	40.00	39.00		85	44.00	45.00	45.00
36	38.00	40.00	39.00		86	44.00	45.00	45.00
37	38.00	40.00	39.00		87	44.00	45.00	45.00
38	39.00	40.00	39.00		88	44.00	45.00	45.00
39	39.00	40.00	40.00		89	45.00	46.00	46.00
40	39.00	40.00	40.00		90	45.00	46.00	46.00
41	39.00	40.00	40.00		91	45.00	46.00	46.00
42	39.00	40.00	40.00		92	46.00	46.00	46.00
43	39.00	40.00	40.00		93	46.00	47.00	47.00
44	39.00	40.00	40.00		94	46.00	47.00	47.00
45	39.00	40.00	40.00		95	47.00	47.00	47.00
46	39.00	40.00	40.00		96	47.00	48.00	48.00
47	40.00	40.00	40.00		97	48.00	48.00	48.00
48	40.00	40.00	40.00		98	48.00	48.00	48.00
49	40.00	40.00	40.00		99	48.00	48.00	48.00
50	40.00	40.00	40.00		100	48.00	48.00	48.00

Note. $N = 1,517$ for male sample, $N = 2,969$ for female sample, $N = 4,486$ for full sample.

Table 10. Raw scores and related percentiles for SLA-SF-46 (Factor 2) by gender

Raw score (≤ 29)	Percentiles			Raw score (30-39)	Percentiles			Raw score (40-48)	Percentiles		
	Male	Female	Full sample		Male	Female	Full sample		Male	Female	Full sample
≤ 20	1.0	1.0	1.0	30	7.0	2.0	4.0	40	54.0	44.0	46.0
21	2.0	1.0	1.0	31	8.0	3.0	4.0	41	66.0	59.0	59.0
22	2.0	1.0	1.0	32	10.0	5.0	5.0	42	74.0	68.0	68.0
23	2.0	1.0	1.0	33	13.0	6.0	9.0	43	81.0	76.0	76.0
24	2.0	1.0	1.0	34	15.0	8.0	11.0	44	86.0	82.0	83.0
25	2.0	1.0	1.0	35	19.0	10.0	13.0	45	90.0	87.0	87.0
26	3.0	1.0	2.0	36	23.0	13.0	17.0	46	93.0	91.0	91.0
27	3.0	1.0	2.0	37	28.0	17.0	21.0	47	96.0	94.0	94.0
28	4.0	1.0	2.0	38	34.0	22.0	26.0	48	100.0	100.0	100.0
29	5.0	2.0	3.0	39	42.0	30.0	34.0				

Note. $N = 1,517$ for male sample, $N = 2,969$ for female sample, $N = 4,486$ for full sample.

Table 11. Raw scores and related percentiles for SLA-SF-46 (Factor 3) by gender

Percentile (1-50)	Raw Score				Percentile (51-100)	Raw Score		
	Male	Female	Full sample			Male	Female	Full sample
1	≤ 18.00	≤ 22.00	≤ 20.00		51	34.00	34.00	34.00
2	21.00	24.00	22.74		52	34.00	34.00	34.00
3	22.00	24.10	24.00		53	34.00	34.00	34.00
4	23.00	25.00	24.00		54	34.00	34.00	34.00
5	24.00	26.00	25.00		55	34.00	34.00	34.00
6	24.08	26.00	26.00		56	34.00	35.00	34.00
7	25.00	27.00	26.00		57	34.00	35.00	34.00
8	26.00	27.00	27.00		58	34.00	35.00	35.00
9	26.00	28.00	27.00		59	34.00	35.00	35.00
10	26.00	28.00	27.00		60	34.00	35.00	35.00
11	27.00	28.00	28.00		61	34.98	35.00	35.00
12	27.00	28.00	28.00		62	35.00	35.00	35.00
13	27.00	29.00	28.00		63	35.00	35.00	35.00
14	27.00	29.00	28.00		64	35.00	35.00	35.00

Table 11. (Continued)

Percentile (1-50)	Raw Score				Percentile (51-100)	Raw Score		
	Male	Female	Full sample			Male	Female	Full sample
15	28.00	29.00	28.00		65	35.00	35.00	35.00
16	28.00	29.00	29.00		66	35.00	35.00	35.00
17	28.00	29.00	29.00		67	35.00	35.00	35.00
18	28.00	30.00	29.00		68	35.00	35.00	35.00
19	28.00	30.00	30.00		69	35.00	35.00	35.00
20	29.00	30.00	30.00		70	35.00	35.00	35.00
21	29.00	30.00	30.00		71	35.00	35.00	35.00
22	29.00	30.00	30.00		72	35.00	35.00	35.00
23	30.00	31.00	30.00		73	35.00	35.00	35.00
24	30.00	31.00	30.00		74	35.00	35.00	35.00
25	30.00	31.00	31.00		75	35.00	36.00	36.00
26	30.00	31.00	31.00		76	36.00	36.00	36.00
27	30.00	31.00	31.00		77	36.00	36.00	36.00
28	30.00	31.00	31.00		78	36.00	36.00	36.00
29	31.00	32.00	31.00		79	36.00	36.00	36.00
30	31.00	32.00	31.00		80	36.00	36.00	36.00
31	31.00	32.00	32.00		81	36.00	36.00	36.00
32	31.00	32.00	32.00		82	37.00	37.00	37.00
33	31.00	32.00	32.00		83	37.00	37.00	37.00
34	31.00	32.00	32.00		84	37.00	37.00	37.00
35	32.00	32.00	32.00		85	37.00	37.00	37.00
36	32.00	33.00	32.00		86	37.00	38.00	37.00
37	32.00	33.00	32.00		87	38.00	38.00	38.00
38	32.00	33.00	33.00		88	38.00	38.00	38.00
39	32.00	33.00	33.00		89	38.00	38.00	38.00
40	32.00	33.00	33.00		90	38.20	38.00	38.00
41	32.00	33.00	33.00		91	39.00	39.00	39.00
42	33.00	33.00	33.00		92	39.00	39.00	39.00
43	33.00	33.00	33.00		93	39.00	40.00	40.00
44	33.00	33.00	33.00		94	40.00	40.00	40.00
45	33.00	34.00	33.00		95	41.00	41.00	41.00
46	33.00	34.00	33.00		96	41.00	41.00	41.00
47	33.00	34.00	34.00		97	42.00	42.00	42.00
48	33.00	34.00	34.00		98	42.00	42.00	42.00
49	33.00	34.00	34.00		99	42.00	42.00	42.00
50	33.00	34.00	34.00		100	42.00	42.00	42.00

Note. N = 1,517 for male sample, N = 2,969 for female sample, N = 4,486 for full sample.

Table 12. Raw scores and related percentiles for SLA-SF-46 (Factor 3) by gender

Raw score (≤ 26)	Percentiles			Raw score (27-35)	Percentiles			Raw score (36-42)	Percentiles		
	Male	Female	Full sample		Male	Female	Full sample		Male	Female	Full sample
≤ 18	1.0	1.0	1.0	27	13.0	8.0	9.0	36	79.0	78.0	78.0
19	2.0	1.0	1.0	28	17.0	11.0	13.0	37	84.0	84.0	84.0
20	2.0	1.0	1.0	29	21.0	15.0	17.0	38	89.0	88.0	89.0
21	2.0	1.0	1.0	30	26.0	20.0	22.0	39	92.0	92.0	92.0
22	3.0	1.0	1.0	31	32.0	26.0	28.0	40	94.0	94.0	94.0
23	4.0	2.0	2.0	32	38.0	32.0	34.0	41	96.0	96.0	96.0
24	6.0	2.0	4.0	33	46.0	40.0	42.0	42	100.0	100.0	100.0
25	7.0	4.0	5.0	34	56.0	50.0	52.0				
26	9.0	6.0	7.0	35	68.0	65.0	66.0				

Note. N = 1,517 for male sample, N = 2,969 for female sample, N = 4,486 for full sample.

Table 13. Raw scores and related percentiles for SLA-SF-46 (Factor 4) by gender

Percentile (1-50)	Raw Score				Percentile (51-100)	Raw Score		
	Male	Female	Full sample			Male	Female	Full sample
1	≤ 10.00	≤ 12.00	≤ 11.00		51	24.00	24.00	24.00
2	12.00	14.00	13.00		52	24.00	24.00	24.00
3	14.00	15.00	15.00		53	24.00	24.00	24.00
4	15.00	16.00	16.00		54	24.00	24.00	24.00
5	16.00	16.00	16.00		55	24.00	24.00	24.00
6	16.00	17.00	17.00		56	24.00	25.00	24.00
7	17.00	18.00	17.00		57	24.00	25.00	24.00
8	17.00	18.00	18.00		58	24.00	25.00	25.00
9	18.00	18.00	18.00		59	24.00	25.00	25.00
10	18.00	19.00	18.00		60	24.00	25.00	25.00
11	18.00	19.00	19.00		61	24.00	25.00	25.00
12	18.00	19.00	19.00		62	25.00	25.00	25.00
13	19.00	19.00	19.00		63	25.00	25.00	25.00
14	19.00	20.00	19.00		64	25.00	25.00	25.00
15	19.00	20.00	20.00		65	25.00	25.00	25.00
16	19.00	20.00	20.00		66	25.00	25.00	25.00
17	19.00	20.00	20.00		67	25.00	25.00	25.00
18	20.00	20.00	20.00		68	25.00	25.00	25.00
19	20.00	20.00	20.00		69	25.00	25.00	25.00
20	20.00	21.00	20.00		70	25.00	25.00	25.00
21	20.00	21.00	20.00		71	25.00	25.00	25.00
22	20.00	21.00	21.00		72	25.00	25.00	25.00
23	20.00	21.00	21.00		73	25.00	25.00	25.00
24	20.00	21.00	21.00		74	25.00	25.00	25.00
25	21.00	21.00	21.00		75	25.00	25.00	25.00
26	21.00	22.00	21.00		76	25.00	25.00	25.00
27	21.00	22.00	21.00		77	25.00	26.00	25.00
28	21.00	22.00	21.00		78	25.00	26.00	26.00
29	21.00	22.00	22.00		79	26.00	26.00	26.00
30	21.00	22.00	22.00		80	26.00	26.00	26.00
31	21.00	22.00	22.00		81	26.00	26.00	26.00
32	21.00	22.00	22.00		82	26.00	26.00	26.00
33	21.00	22.00	22.00		83	26.00	26.00	26.00
34	22.00	23.00	22.00		84	26.00	27.00	26.00
35	22.00	23.00	22.00		85	26.00	27.00	27.00
36	22.00	23.00	22.00		86	27.00	27.00	27.00
37	22.00	23.00	23.00		87	27.00	27.00	27.00
38	22.00	23.00	23.00		88	27.00	27.00	27.00
39	22.00	23.00	23.00		89	27.00	28.00	28.00
40	22.00	23.00	23.00		90	28.00	28.00	28.00
41	22.00	23.00	23.00		91	28.00	28.00	28.00
42	23.00	23.00	23.00		92	28.00	28.00	28.00
43	23.00	23.00	23.00		93	28.00	29.00	29.00
44	23.00	23.00	23.00		94	29.00	29.00	29.00
45	23.00	24.00	23.00		95	29.00	29.00	29.00
46	23.00	24.00	23.00		96	30.00	30.00	30.00
47	23.00	24.00	24.00		97	30.00	30.00	30.00
48	23.00	24.00	24.00		98	30.00	30.00	30.00
49	23.00	24.00	24.00		99	30.00	30.00	30.00
50	23.00	24.00	24.00		100	30.00	30.00	30.00

Note. $N = 1,517$ for male sample, $N = 2,969$ for female sample, $N = 4,486$ for full sample.

Table 14. Raw scores and related percentiles for SLA-SF-46 (Factor 4) by gender

Raw score (≤ 17)	Percentiles			Raw score (18-25)	Percentiles			Raw score (26-30)	Percentiles		
	Male	Female	Full sample		Male	Female	Full sample		Male	Female	Full sample
10	1.0	1.0	1.0	18	11.0	8.0	9.0	26	82.0	80.0	81.0
11	2.0	1.0	1.0	19	15.0	12.0	13.0	27	88.0	86.0	87.0
12	2.0	1.0	2.0	20	21.0	17.0	18.0	28	92.0	91.0	91.0
13	3.0	2.0	2.0	21	29.0	23.0	25.0	29	95.0	94.0	94.0
14	3.0	2.0	3.0	22	38.0	30.0	33.0	30	100.0	100.0	100.0
15	4.0	3.0	3.0	23	46.0	39.0	42.0				
16	6.0	5.0	5.0	24	56.0	50.0	52.0				
17	8.0	6.0	7.0	25	70.0	66.0	68.0				

Note. N = 1,517 for male sample, N = 2,969 for female sample, N = 4,486 for full sample.

Table 15. Raw scores and related percentiles for SLA-SF-46 (Factor 5) by gender

Percentile (1-50)	Raw Score				Percentile (51-100)	Raw Score		
	Male	Female	Full sample			Male	Female	Full sample
1	≤ 10.00	≤ 13.00	≤ 12.00		51	20.00	21.00	20.00
2	12.00	15.00	14.00		52	20.00	21.00	20.00
3	13.00	16.00	15.00		53	20.00	21.00	20.00
4	14.00	16.00	16.00		54	20.00	21.00	20.00
5	15.00	16.00	16.00		55	20.00	21.00	21.00
6	15.00	17.00	16.00		56	20.00	21.00	21.00
7	16.00	17.00	16.00		57	20.00	21.00	21.00
8	16.00	17.00	17.00		58	20.00	21.00	21.00
9	16.00	17.00	17.00		59	20.00	21.00	21.00
10	16.00	18.00	17.00		60	20.80	21.00	21.00
11	16.00	18.00	17.00		61	21.00	21.00	21.00
12	17.00	18.00	18.00		62	21.00	21.00	21.00
13	17.00	18.00	18.00		63	21.00	21.00	21.00
14	17.00	19.00	18.00		64	21.00	21.00	21.00
15	17.00	19.00	18.00		65	21.00	22.00	21.00
16	17.00	19.00	18.00		66	21.00	22.00	21.00
17	18.00	19.00	18.00		67	21.00	22.00	21.00
18	18.00	19.00	19.00		68	21.00	22.00	22.00
19	18.00	19.00	19.00		69	21.00	22.00	22.00
20	18.00	19.00	19.00		70	21.00	22.00	22.00
21	18.00	20.00	19.00		71	21.00	22.00	22.00
22	18.00	20.00	19.00		72	22.00	22.00	22.00
23	18.00	20.00	19.00		73	22.00	22.00	22.00
24	18.00	20.00	19.00		74	22.00	22.00	22.00
25	19.00	20.00	19.00		75	22.00	22.00	22.00
26	19.00	20.00	20.00		76	22.00	22.00	22.00
27	19.00	20.00	20.00		77	22.00	23.00	22.00
28	19.00	20.00	20.00		78	22.00	23.00	22.00
29	19.00	20.00	20.00		79	22.00	23.00	23.00
30	19.00	20.00	20.00		80	22.00	23.00	23.00
31	19.00	20.00	20.00		81	22.00	23.00	23.00
32	19.00	20.00	20.00		82	22.00	23.00	23.00
33	19.00	20.00	20.00		83	23.00	23.00	23.00
34	19.00	20.00	20.00		84	23.00	23.00	23.00
35	19.00	20.00	20.00		85	23.00	23.00	23.00
36	20.00	20.00	20.00		86	23.00	23.00	23.00
37	20.00	20.00	20.00		87	23.00	23.00	23.00

Percentile (1-50)	Raw Score				Percentile (51-100)	Raw Score		
	Male	Female	Full sample			Male	Female	Full sample
38	20.00	20.00	20.00		88	23.00	24.00	23.00
39	20.00	20.00	20.00		89	23.00	24.00	24.00
40	20.00	20.00	20.00		90	23.00	24.00	24.00
41	20.00	20.00	20.00		91	24.00	24.00	24.00
42	20.00	20.00	20.00		92	24.00	24.00	24.00
43	20.00	20.00	20.00		93	24.00	24.00	24.00
44	20.00	20.00	20.00		94	24.00	24.00	24.00
45	20.00	20.00	20.00		95	24.00	24.00	24.00
46	20.00	20.00	20.00		96	24.00	24.00	24.00
47	20.00	20.00	20.00		97	24.00	24.00	24.00
48	20.00	20.00	20.00		98	24.00	24.00	24.00
49	20.00	20.00	20.00		99	24.00	24.00	24.00
50	20.00	20.00	20.00		100	24.00	24.00	24.00

Note. $N = 1,517$ for male sample, $N = 2,969$ for female sample, $N = 4,486$ for full sample.

Normative Statistics

Norms for full sample and subgroups (i.e., male and female groups) were calculated. Due to non-normalized distribution of the raw scores in the full sample and sub-groups, percentile ranks instead of standardized Z scores were provided. A total of 18 norm tables (Tables 5-22) are presented in the manual. While Tables 5 and 6 demonstrate norms of total score of the full scale, Tables 7-22 are norm tables for the eight sub-scales. For both full sale and sub-scales, percentile ranks and corresponding raw scores (Tables 5, 7, 9, 11, 13, 15, 17, 19, 21) as well as each raw score and its equivalent percentile rank (Tables 6, 8, 10, 12, 14, 16, 18, 20, 22) are presented, for the full sample and the two sub-groups.

Table 16. Raw scores and related percentiles for SLA-SF-46 (Factor 5) by gender

Raw score (≤ 15)	Percentiles			Raw score (16-21)	Percentiles			Raw score (22-24)	Percentiles		
	Male	Female	Full sample		Male	Female	Full sample		Male	Female	Full sample
10	1.0	1.0	1.0	16	9.0	4.0	6.0	22	77.0	71.0	73.0
11	2.0	1.0	1.0	17	14.0	8.0	10.0	23	87.0	82.0	84.0
12	2.0	1.0	1.0	18	21.0	12.0	15.0	24	100.0	100.0	100.0
13	3.0	1.0	2.0	19	30.0	17.0	22.0				
14	4.0	2.0	2.0	20	47.0	36.0	40.0				
15	6.0	2.0	3.0	21	66.0	58.0	61.0				

Note. $N = 1,517$ for male sample, $N = 2,969$ for female sample, $N = 4,486$ for full sample.

Table 17. Raw scores and related percentiles for SLA-SF-46 (Factor 6) by gender

Percentile (1-50)	Raw Score				Percentile (51-100)	Raw Score		
	Male	Female	Full sample			Male	Female	Full sample
1	≤ 12.00	≤ 16.00	≤ 14.00		51	25.00	25.00	25.00
2	15.36	17.40	17.00		52	25.00	25.00	25.00
3	17.00	18.00	18.00		53	25.00	25.00	25.00
4	18.00	19.00	18.00		54	25.00	25.00	25.00
5	18.00	19.00	19.00		55	25.00	25.00	25.00
6	19.00	20.00	19.00		56	25.00	25.00	25.00

Table 17. (Continued)

Percentile (1-50)	Raw Score				Percentile (51-100)	Raw Score		
	Male	Female	Full sample			Male	Female	Full sample
7	19.00	20.00	20.00		57	25.00	25.00	25.00
8	19.00	20.00	20.00		58	25.00	25.00	25.00
9	20.00	20.00	20.00		59	25.00	25.00	25.00
10	20.00	21.00	20.00		60	25.00	25.00	25.00
11	20.00	21.00	20.00		61	25.00	25.00	25.00
12	20.00	21.00	21.00		62	25.00	25.00	25.00
13	20.00	21.00	21.00		63	25.00	25.00	25.00
14	20.00	21.00	21.00		64	25.00	25.00	25.00
15	20.00	22.00	21.00		65	25.00	25.00	25.00
16	21.00	22.00	21.00		66	25.00	25.00	25.00
17	21.00	22.00	22.00		67	25.00	25.00	25.00
18	21.00	22.00	22.00		68	25.00	25.60	25.00
19	21.00	22.00	22.00		69	25.00	26.00	26.00
20	21.00	22.00	22.00		70	26.00	26.00	26.00
21	22.00	23.00	22.00		71	26.00	26.00	26.00
22	22.00	23.00	22.00		72	26.00	26.00	26.00
23	22.00	23.00	23.00		73	26.00	26.00	26.00
24	22.00	23.00	23.00		74	26.00	26.00	26.00
25	22.00	23.00	23.00		75	26.00	26.00	26.00
26	22.00	23.00	23.00		76	26.00	26.00	26.00
27	22.00	23.00	23.00		77	26.00	26.00	26.00
28	23.00	23.00	23.00		78	26.00	27.00	26.00
29	23.00	23.00	23.00		79	26.00	27.00	27.00
30	23.00	23.00	23.00		80	27.00	27.00	27.00
31	23.00	24.00	23.00		81	27.00	27.00	27.00
32	23.00	24.00	23.00		82	27.00	27.00	27.00
33	23.00	24.00	24.00		83	27.00	27.00	27.00
34	23.00	24.00	24.00		84	27.00	27.00	27.00
35	23.00	24.00	24.00		85	27.00	28.00	27.00
36	23.00	24.00	24.00		86	27.00	28.00	28.00
37	24.00	24.00	24.00		87	28.00	28.00	28.00
38	24.00	24.00	24.00		88	28.00	28.00	28.00
39	24.00	24.00	24.00		89	28.00	28.00	28.00
40	24.00	24.00	24.00		90	28.00	28.00	28.00
41	24.00	24.00	24.00		91	28.00	29.00	28.00
42	24.00	24.00	24.00		92	29.00	29.00	29.00
43	24.00	24.00	24.00		93	29.00	29.00	29.00
44	24.00	24.00	24.00		94	29.00	29.00	29.00
45	24.00	24.50	24.00		95	29.00	29.00	29.00
46	24.00	25.00	24.00		96	30.00	30.00	30.00
47	24.00	25.00	25.00		97	30.00	30.00	30.00
48	24.00	25.00	25.00		98	30.00	30.00	30.00
49	24.00	25.00	25.00		99	30.00	30.00	30.00
50	25.00	25.00	25.00		100	30.00	30.00	30.00

Note. *N* = 1,517 for male sample, *N* = 2,969 for female sample, *N* = 4,486 for full sample.

Table 18. Raw scores and related percentiles for SLA-SF-46 (Factor 6) by gender

Raw score (≤ 18)	Percentiles			Raw score (19-25)	Percentiles			Raw score (26-30)	Percentiles		
	Male	Female	Full sample		Male	Female	Full sample		Male	Female	Full sample
12	1.0	1.0	1.0	19	7.0	5.0	6.0	26	75.0	73.0	74.0
13	2.0	1.0	1.0	20	12.0	8.0	9.0	27	83.0	81.0	82.0
14	2.0	1.0	1.0	21	18.0	12.0	14.0	28	89.0	88.0	89.0
15	2.0	1.0	2.0	22	24.0	18.0	20.0	29	94.0	93.0	94.0
16	3.0	1.0	2.0	23	32.0	26.0	28.0	30	100.0	100.0	100.0
17	3.0	2.0	2.0	24	44.0	38.0	40.0				
18	5.0	3.0	4.0	25	60.0	56.0	58.0				

Note. $N = 1,517$ for male sample, $N = 2,969$ for female sample, $N = 4,486$ for full sample.

Table 19. Raw scores and related percentiles for SLA-SF-46 (Factor 7) by gender

Percentile (1-50)	Raw Score				Percentile (51-100)	Raw Score		
	Male	Female	Full sample			Male	Female	Full sample
1	≤ 2.00	≤ 3.00	≤ 3.00		51	9.00	9.00	9.00
2	3.00	4.00	4.00		52	9.00	9.00	9.00
3	3.00	4.10	4.00		53	9.00	9.00	9.00
4	4.00	5.00	4.00		54	9.00	9.00	9.00
5	4.00	5.00	5.00		55	9.00	9.00	9.00
6	4.00	5.00	5.00		56	9.00	9.00	9.00
7	4.00	6.00	5.00		57	9.00	9.00	9.00
8	5.00	6.00	5.00		58	9.00	10.00	9.00
9	5.00	6.00	6.00		59	9.00	10.00	9.00
10	5.00	6.00	6.00		60	9.00	10.00	10.00
11	5.00	6.00	6.00		61	9.00	10.00	10.00
12	6.00	6.00	6.00		62	9.00	10.00	10.00
13	6.00	6.00	6.00		63	9.00	10.00	10.00
14	6.00	6.00	6.00		64	10.00	10.00	10.00
15	6.00	7.00	6.00		65	10.00	10.00	10.00
16	6.00	7.00	6.00		66	10.00	10.00	10.00
17	6.00	7.00	7.00		67	10.00	10.00	10.00
18	6.00	7.00	7.00		68	10.00	10.00	10.00
19	6.00	7.00	7.00		69	10.00	10.00	10.00
20	7.00	7.00	7.00		70	10.00	10.00	10.00
21	7.00	7.00	7.00		71	10.00	10.00	10.00
22	7.00	7.00	7.00		72	10.00	10.00	10.00
23	7.00	7.00	7.00		73	10.00	10.00	10.00
24	7.00	7.00	7.00		74	10.00	10.00	10.00
25	7.00	8.00	7.00		75	10.00	10.00	10.00
26	7.00	8.00	7.00		76	10.00	10.00	10.00
27	7.00	8.00	8.00		77	10.00	10.00	10.00
28	7.00	8.00	8.00		78	10.00	10.00	10.00
29	7.00	8.00	8.00		79	10.00	10.00	10.00
30	8.00	8.00	8.00		80	10.00	10.00	10.00
31	8.00	8.00	8.00		81	10.00	10.00	10.00
32	8.00	8.00	8.00		82	10.00	10.00	10.00
33	8.00	8.00	8.00		83	10.00	10.00	10.00
34	8.00	8.00	8.00		84	10.00	11.00	10.00
35	8.00	8.00	8.00		85	10.00	11.00	11.00
36	8.00	8.00	8.00		86	10.00	11.00	11.00
37	8.00	8.00	8.00		87	11.00	11.00	11.00
38	8.00	8.00	8.00		88	11.00	11.00	11.00

Table 19. (Continued)

Percentile (1-50)	Raw Score				Percentile (51-100)	Raw Score		
	Male	Female	Full sample			Male	Female	Full sample
1	≤ 2.00	≤ 3.00	≤ 3.00		51	9.00	9.00	9.00
39	8.00	8.00	8.00		89	11.00	11.00	11.00
40	8.00	8.00	8.00		90	11.00	11.00	11.00
41	8.00	8.00	8.00		91	11.00	11.00	11.00
42	8.00	9.00	8.00		92	11.00	11.00	11.00
43	8.00	9.00	8.00		93	11.00	12.00	12.00
44	8.00	9.00	9.00		94	12.00	12.00	12.00
45	8.00	9.00	9.00		95	12.00	12.00	12.00
46	8.00	9.00	9.00		96	12.00	12.00	12.00
47	8.00	9.00	9.00		97	12.00	12.00	12.00
48	9.00	9.00	9.00		98	12.00	12.00	12.00
49	9.00	9.00	9.00		99	12.00	12.00	12.00
50	9.00	9.00	9.00		100	12.00	12.00	12.00

Note. *N* = 1,517 for male sample, *N* = 2,969 for female sample, *N* = 4,486 for full sample.

Table 20. Raw scores and related percentiles for SLA-SF-46 (Factor 7) by gender

Raw score (≤ 5)	Percentiles			Raw score (6-9)	Percentiles			Raw score (10-12)	Percentiles		
	Male	Female	Full sample		Male	Female	Full sample		Male	Female	Full sample
2	1.0	1.0	1.0	6	16.0	11.0	13.0	10	75.0	71.0	72.0
3	3.0	1.0	1.0	7	25.0	20.0	22.0	11	90.0	88.0	89.0
4	6.0	3.0	3.0	8	39.0	33.0	35.0	12	100.0	100.0	100.0
5	10.0	5.0	7.0	9	56.0	50.0	52.0				

Note. *N* = 1,517 for male sample, *N* = 2,969 for female sample, *N* = 4,486 for full sample.

Table 21. Raw scores and related percentiles for SLA-SF-46 (Factor 8) by gender

Percentile (1-50)	Raw Score				Percentile (51-100)	Raw Score		
	Male	Female	Full sample			Male	Female	Full sample
1	≤ 5.00	≤ 6.00	≤ 6.00		51	16.00	16.00	16.00
2	7.00	8.00	7.00		52	16.00	16.00	16.00
3	8.00	9.00	8.00		53	16.00	16.00	16.00
4	8.00	9.00	9.00		54	16.00	17.00	16.00
5	9.00	9.00	9.00		55	16.00	17.00	16.00
6	9.00	10.00	9.00		56	16.00	17.00	17.00
7	9.00	10.00	10.00		57	16.00	17.00	17.00
8	9.00	10.00	10.00		58	17.00	17.00	17.00
9	10.00	10.00	10.00		59	17.00	17.00	17.00
10	10.00	10.00	10.00		60	17.00	17.00	17.00
11	10.00	10.00	10.00		61	17.00	18.00	17.00
12	10.00	10.00	10.00		62	17.00	18.00	17.00
13	10.00	11.00	10.00		63	17.00	18.00	18.00
14	10.00	11.00	11.00		64	17.00	18.00	18.00
15	10.00	11.00	11.00		65	18.00	18.00	18.00
16	10.00	11.00	11.00		66	18.00	18.00	18.00
17	11.00	11.00	11.00		67	18.00	18.00	18.00
18	11.00	11.00	11.00		68	18.00	18.00	18.00
19	11.00	12.00	11.00		69	18.00	19.00	18.00
20	11.00	12.00	12.00		70	18.00	19.00	19.00
21	11.00	12.00	12.00		71	18.00	19.00	19.00

Percentile (1-50)	Raw Score				Percentile (51-100)	Raw Score		
	Male	Female	Full sample			Male	Female	Full sample
22	11.00	12.00	12.00		72	19.00	19.00	19.00
23	11.00	12.00	12.00		73	19.00	19.00	19.00
24	12.00	13.00	12.00		74	19.00	19.00	19.00
25	12.00	13.00	12.00		75	19.00	19.00	19.00
26	12.00	13.00	13.00		76	19.00	20.00	19.00
27	12.00	13.00	13.00		77	19.00	20.00	20.00
28	12.00	13.00	13.00		78	19.00	20.00	20.00
29	12.00	13.00	13.00		79	20.00	20.00	20.00
30	12.40	13.00	13.00		80	20.00	20.00	20.00
31	13.00	14.00	13.00		81	20.00	20.00	20.00
32	13.00	14.00	13.00		82	20.00	21.00	20.00
33	13.00	14.00	14.00		83	20.00	21.00	21.00
34	13.00	14.00	14.00		84	20.00	21.00	21.00
35	13.30	14.00	14.00		85	21.00	21.00	21.00
36	14.00	14.00	14.00		86	21.00	21.00	21.00
37	14.00	14.00	14.00		87	21.00	21.00	21.00
38	14.00	15.00	14.00		88	21.00	22.00	21.56
39	14.00	15.00	14.00		89	21.00	22.00	22.00
40	14.00	15.00	15.00		90	22.00	22.00	22.00
41	14.00	15.00	15.00		91	22.00	22.00	22.00
42	15.00	15.00	15.00		92	22.00	23.00	23.00
43	15.00	15.00	15.00		93	22.74	23.00	23.00
44	15.00	15.00	15.00		94	23.00	23.00	23.00
45	15.00	15.00	15.00		95	24.00	24.00	24.00
46	15.00	15.00	15.00		96	24.00	24.00	24.00
47	15.00	16.00	15.00		97	25.00	25.00	25.00
48	15.00	16.00	16.00		98	25.00	25.00	25.00
49	15.00	16.00	16.00		99	27.00	26.00	27.00
50	15.00	16.00	16.00		100	30.00	30.00	30.00

Note. $N = 1,517$ for male sample, $N = 2,969$ for female sample, $N = 4,486$ for full sample.

Table 22. Raw scores and related percentiles for SLA-SF-46 (Factor 8) by gender

Raw score (≤ 13)	Percentiles			Raw score (14-22)	Percentiles			Raw score (23-30)	Percentiles		
	Male	Female	Full sample		Male	Female	Full sample		Male	Female	Full sample
5	1.0	1.0	1.0	14	39.0	34.0	36.0	23	94.0	93.0	93.0
6	2.0	1.0	1.0	15	46.0	42.0	44.0	24	96.0	96.0	96.0
7	2.0	2.0	2.0	16	54.0	50.0	52.0	25	98.0	98.0	98.0
8	4.0	2.0	3.0	17	61.0	57.0	59.0	26	99.0	99.0	99.0
9	7.0	4.0	5.0	18	68.0	65.0	66.0	27	99.0	99.0	99.0
10	13.0	9.0	10.0	19	75.0	72.0	73.0	28	99.0	99.0	99.0
11	20.0	16.0	17.0	20	82.0	79.0	80.0	29	99.0	99.0	99.0
12	27.0	21.0	23.0	21	87.0	85.0	85.0	30	100.0	100.0	100.0
13	33.0	28.0	29.0	22	91.0	90.0	90.0				

Note. $N = 1,517$ for male sample, $N = 2,969$ for female sample, $N = 4,486$ for full sample.

SCORING AND INTERPRETATION

The SLA-SF-46 has 46 items operating on eight content specific subscales. The score of each subscale is calculated by summing up the scores of respective items. The total score of

service leadership attitude is calculated by summing up the scores of all eight subscales. It has the property of having a minimum score of 46 and a maximum score of 276.

Handling of Missing Items

The satisfactory internal consistency is conditioned on that all items in a subscale or full scale have been completed. When there are missing values in any subscale, the responses should be interpreted with caution. The responses with missing value(s) should not be adopted for analysis or appropriate methods should be used for computing missing value(s) before doing further analyses.

Interpretation of Test Scores

Interpretation of SLA-SF-46 test scores can be based on the score of full scale or each subscale. The score of full scale shows how favorable the core value of contemporary service leadership is viewed by participant, while the score of each subscale reflects his/her perception of specific service leadership quality. For example, a high score of “ethical role model” subscale indicates a strong belief that a service leader must take a leading role in setting ethical standards.

As mentioned before, Tables 5-22 present percentile norms for the score of full scale and each subscale. Percentile rank scores represent the percentage of people in the normative sample (full sample or sub-samples) who scored at or below a particular raw score for a particular measure (full scale or subscales). In other words, a percentile rank score informs the relative position of one’s score in relation to his/her relevant group. For example, if a male college student wants to surpass 20% of his male peers in developing positive service leadership attitude, he needs to get at least 194 points (see Table 5). Likewise, if a male college student gets 214 points for full scale, he has already surpassed half of all male students (see Table 6).

When interpreting test scores, we do not intend to define a cut-off value for determining positive versus negative attitude toward service leadership. Thus, “positive attitude” and “negative attitude” are not suggested to be adopted to differentiate people with different attitude. Researchers or program evaluators may locate the score of a student into the norm tables to determine his/her comparative position regarding service leadership attitude, and use “less positive than the normative sample,” “similar to the normative sample,” or “more positive than the normative sample” to conclude different levels of service leadership attitude. Furthermore, when evaluating the effectiveness of a specific service leadership education program, evaluators are suggested to compare participants’ attitude scores obtained before and after they receive the program. In this case, mean scores could be used without making reference to the norm tables.

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Chapter 147

A USER MANUAL FOR THE SERVICE LEADERSHIP BEHAVIOR SCALE

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ABSTRACT

The rapid development of service economies calls for validated tools measuring service leadership qualities. In view of the dearth of measures of leadership behaviors in the service economies, the Service Leadership Behavior Scale was developed to assess service leaders' leadership skills and practices based on the Service Leadership Theory, which defines effective leadership behavior in service economies. With an initial item pool of 97 items, the final scale was trimmed to 38 items after several validation studies, which demonstrated very good psychometric properties. In this chapter, we briefly introduce the background of the development of the Service Leadership Behavior Scale and its related conceptual framework. In addition, validation process, reliability and validity of the scale, norm statistics, and guidelines for administering the scale and interpreting scores are outlined as well.

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INTRODUCTION

In recent decades, there is rapid development of the service sector in industrialized economies worldwide [1]. Service economy has become the leading contributor to local GDP in many countries and areas. For example, Hong Kong is regarded as a highly developed service economy with a significant portion of service sector contributing to the local economic development. It is argued that the prosperity of Hong Kong fundamentally relies on the success of the service sector [2].

The growth of service economy calls for strong leadership to adjust organization to respond to turbulent and complex environments. Among the various leadership models, service leadership has attracted increasing attention in response to a call for more ethical and people-focused leadership style associated with the rise of the service economy. According to Service Leadership Theory proposed by Po Chung [3], service leadership is about “satisfying needs by consistently providing quality personal service to everyone one comes into contact with, including one’s self, others, groups, communities, systems, and environments.” Service Leadership Theory is unique because it integrates three key attributes of effective leadership required by service economy: competence, moral character, and caring disposition.

To develop future leaders and citizens with service mindset and attributes qualities, the Victor and William Fung Foundation funded the Service Leadership Initiative in eight government-funded universities in Hong Kong from 2012 to 2015. To strengthen the assessment component of the service leadership education initiative, assessment tools have subsequently been developed and validated to evaluate service leadership attributes and the impact of service leadership education. In particular, three scales were developed to evaluate the attitude, knowledge, and behavior of students’ service leadership.

This manual introduces the development, validation, and usage of the finalized 38-item version of behavior scale (i.e., SLB-SF-38). It is useful for academics, practitioners, and researchers who are concerned about the evaluation of leadership behavior and the effectiveness of training programme aiming at promoting desired leadership behavior. This manual also provides evidence showing that the Service Leadership Behavior Scale is a reliable and valid tool. Normative data can be used for interpreting raw scores and group comparison. Some suggestions and directions of interpretation of the results are also discussed.

CONCEPTUAL FRAMEWORK

Based on the Service Leadership Theory and its unique propositions such as the emphasis on character and caring behaviors (i.e., not just leadership skills), the Service Leadership Behavior Scale was developed with reference to four fundamental areas as briefly outlined in the following paragraphs. Detailed elaborations can be found elsewhere [4, 5].

The first area is “service provision” describing an individual’s people- and service-oriented mindset of providing high-quality and personalized services. Effective service leaders are expected to be sensitive to others’ needs and be willing to transcend one’s own interests to satisfy the needs of others and society.

The second area is pertinent to key skills intrinsic for an effective service leader. In particular, effective service leaders possess not only “competence” but also “character” and “care” (i.e., the 3Cs). Competence includes both intrapersonal and interpersonal competence [6, 7]. Intrapersonal competence covers a wide range of human intellectual abilities related to processing information and understanding and managing oneself and others. Shek and Lin [6] highlighted four types of intelligence particularly reflecting intrapersonal competence, which include intelligence quotient (IQ), emotional quotient (EQ), adversity quotient (AQ), and spiritual quotient (SQ). In addition to intrapersonal competence, effective service leaders should also be capable of forming and maintaining positive relationships, collaborating and communicating effectively with people, and being assertive and solving conflicts in a constructive way. All these skills are considered interpersonal competence. Regarding the second C (i.e., character), a good service leader is expected to lead oneself and others with moral values that are universally upheld, such as integrity, humility, and fairness [8]. For the third C (i.e., care), it is argued that a good service leader should be a caring leader who cares about others’ interests and wellness in terms of showing empathy and compassion, loving others, being supportive, and helping others to have better development [9].

The third area is related to continuous improvement. Service Leadership Theory stresses that one should continuously improve oneself for better providing services to others and systems. To improve one’s competence and willingness to serve, an effective service leader should promote self-leadership through active self-reflection and life-long learning.

The last area highlights the importance of distributed leadership. First, a good service leader maintains shared decision-making by encouraging every teammate to voice out and take initiatives. Second, a quality service leader also respects their followers’ views and recognizes their contributions. Third, a good service leader is expected to trust his or her followers’ abilities and help them to maximize their potentials and grow to good service leaders as well.

DIFFERENT STAGES OF THE VALIDATION PROCESS

The Service Leadership Behavior Scale is one of the three assessment tools evaluating service leadership education and related leadership qualities. With the financial support from the Victor and William Fung Foundation, The Hong Kong Polytechnic University (PolyU) led the collaboration with other seven government-funded universities in Hong Kong for carrying out validation studies on the attitude, knowledge, and behavior scales of service leadership. To develop the behavior scale, several stages were involved in the process:

Stage 1: The original 97-item Long-Form Service Leadership Behavior Scale (SLB-LF-97) was developed with reference to the conceptual framework of the Service Leadership Theory.

Stage 2: A study investigating the content validity of SLB-LF-97 was first conducted [4]. Ratings from three experts suggested that the SLB-LF-97 has good content validity indexed by clarity, relevance, and representativeness of each item.

Stage 3: The SLB-LF-97 was further validated and streamlined through an initial validation study involving 231 university students [10]. According to the results of

exploratory factor analysis (EFA), 65 of the original 97 items were retained to form a short-form behavior scale (i.e., SLB-SF-65), which had a 12-dimension structure. The SLB-SF-65 demonstrated good reliability and convergent validity.

Stage 4: To further refine the behavior scale, a large-scale validation study ($N = 4,486$) was jointly carried out in the eight government-funded universities in Hong Kong. EFA based on a half-dataset ($N = 2,246$) suggested a new 48-item short form (SLB-SF-48) which consisted of six subscales [11].

Stage 5: Based on the other half-dataset ($N = 2,240$), a confirmatory factor analysis (CFA) was used to finalize the SLB-SF-48. Informed by CFA, 38 items were kept in the finalized behavior scale (SLB-SF-38), which also possessed a 6-factor structure. This finalized behavior scale and its six subscales showed good internal consistency and convergent validity. Detailed information is summarized in Section 5 of this manual.

DESIGN AND USE OF THE SCALE

Some items of the Service Leadership Behavior Scale were modified from existing scale items related to leadership behaviors [12, 13]. Other items were developed by the research team based on the conceptual framework and propositions related to Service Leadership Theory [14]. The six factors of the finalized behavior scale (i.e., SLB-SF-38) are described below:

- Factor 1: Self-improvement and self-reflection (9 items). A hypothetical sample item is “I have a habit of reflecting my work and life.”
- Factor 2: People and principles orientation (9 items). A hypothetical sample item is “I allow others to decide how to get things done.”
- Factor 3: Resilience (7 items). A hypothetical sample item is “I usually become stronger instead of weaker when facing adversity such as failures and setbacks.”
- Factor 4: Social competence (5 items). A hypothetical sample item is “I can maintain positive relationships with others.”
- Factor 5: Problem-solving (5 items). A hypothetical sample item is “I am good at independent thinking.”
- Factor 6: Mentorship (3 items). A hypothetical sample item is “I can facilitate other’s growth by mentoring them.”

Target Respondents

The SLB-SF-38 can be used to assess the service leadership behavior of university students or employees in different Chinese communities (e.g., Hong Kong, Taiwan, and mainland China). Noteworthy, local norms need to be constructed when the scale is used in a context other than Hong Kong, because the normative data reported in this manual were derived from a university student sample in Hong Kong.

Instructions

The SLB-SF-38 is administrated in a self-report manual in English. Formal written consent should be obtained from respondents. Instructions are outlined at the beginning of the questionnaire for participants to follow.

In general, respondents can complete the whole questionnaire without a specific time limit. On average, a respondent can complete the scale within 15-20 minutes. In principle, participants should return the completed questionnaire to test administrator. Taking the questionnaire out of the administration venue is not normally allowed.

Administration Guidelines

The test administrator should observe the following principles:

- 1) Respondents should complete the questionnaire independently. Discussion and communication on scale items among participants are not allowed.
- 2) Field administrators can give explanations on grammars or meaning of scale items if respondents have difficulties in understanding any specific words or phrases. However, respondents need to complete all times based on their own understanding.
- 3) In addition to full-scale, subscale(s) can be used independently if all items of the subscale(s) are included without any omission.
- 4) The same rating scale (i.e., 6-point Likert scale) should be used.
- 5) SLB-SF-38 can be administered using paper-and-pencil or online questionnaire. If paper-and-pencil administration is applied, the completed questionnaire should be collected by testers on-site in a confidential manner.

RELIABILITY AND VALIDITY

The reliability and validity of SLB-SF-38 were investigated in the aforementioned large-scale validation study using a normative sample ($N = 4,486$) [11, 15]. Related findings are briefly outlined below.

Internal Consistency/Reliability

SLB-SF-38 and its six subscales demonstrated good internal consistency. Cronbach's alphas of the full-scale and subscales ranged from .85 to .96. The mean inter-item correlations across scale/subscales ranged between .38 and .65 (see Table 1).

Table 1. Internal consistency of SLB-SF-38 and its subscales

Scale/subscale	No. of items	Cronbach's alpha	Mean Inter-Item Correlations
Self-improvement and self-reflection	9	.91	.53
People and principles orientation	9	.87	.42
Resilience	7	.87	.50
Social competence	5	.86	.55
Problem-solving	5	.87	.56
Mentorship	3	.85	.65
Full scale	38	.96	.38

Convergent Validity

SLB-SF-38 showed good convergent validity. First, the full-scale and its six subscales significantly correlated with each other (see Table 2). Second, as shown in Table 3, there were significant correlations between full-scale/subscales and the eight external criterion scales (e.g., the knowledge and attitude to service leadership, moral self-concept, and leadership efficacy).

Table 2. Inter-factor correlations of finalized behavior scale/subscales

	F1	F2	F3	F4	F5	F6
F1: Self-improvement and self-reflection	--					
F2: People and principles orientation	.70***	--				
F3: Resilience	.61***	.57***	--			
F4: Social competence	.61***	.69***	.62***	--		
F5: Problem-solving	.58***	.50***	.60***	.50***	--	
F6: Mentorship	.56***	.58***	.50***	.48***	.43***	--
Full scale	.87***	.86***	.82***	.80***	.74***	.70***

Note. F1 = Factor 1, F2 = Factor 2, F3 = Factor 3, F4 = Factor 4, F5 = Factor 5, F6 = Factor 6.

*** $p < .001$.

Table 3. Correlations between finalized behavior scale/subscales and external criterion constructs

	SLK-SF-40	SLA-SF-46	RSLP	MSC	LEF	IRI	IRI-EC	IRI-PT
SLB-SF-38	.18***	.57***	.79***	.65***	.52***	.42***	.30***	.45***
SLB-SF-38-F1	.23***	.51***	.69***	.58***	.43***	.37***	.26***	.39***
SLB-SF-38-F2	.27***	.62***	.77***	.69***	.37***	.54***	.43***	.52***
SLB-SF-38-F3	.05**	.37***	.57***	.43***	.44***	.22***	.11***	.29***
SLB-SF-38-F4	.21***	.50***	.63***	.59***	.46***	.41***	.32***	.40***
SLB-SF-38-F5	.12***	.37***	.49***	.37***	.45***	.19***	.10***	.25***
SLB-SF-38-F6	-.10***	.32***	.63***	.43***	.40***	.25***	.16***	.28***

Note. SLK-SF-40: Finalized Service Leadership Knowledge Scale (40 items); SLB-SF-38: Finalized Service Leadership Behavior Scale (38 items); SLA-SF-46: Finalized Service Leadership Attitude Scale (46 items). RSLP: Revised Servant Leadership Profile; MSC: Moral Self-Concept; LEF: Leadership Efficacy; IRI: Interpersonal Reactivity Index; EC: IRI- Empathic Concern; PT: IRI- Perspective Taking. SLB-38-F1: Self-improvement and self-reflection; SLB-38-F2: People and principles orientation; SLB-38-F3: Resilience; SLB-38-F4: Social competence; SLB-38-F5: Problem-solving; SLB-38-F6: Mentorship. ** $p < .01$, *** $p < .001$.

Factorial Validity

Results of CFA based on the normative sample ($N = 4,486$) suggested a good fit of the 6-factor structure of SLB-SF-38 ($CFI = .91$, $TLI = .90$, $RMSEA = .055$, $90\% CI = [.054, .056]$). As shown in Table 4, factor loadings were between .51 and .86.

More detailed findings of different validation studies aforementioned can be found in publications on the background and conceptual model of the scale [5], content valuation [4], the initial validation study [10], factorial and convergent validity of SLB-SF-48 based on EFA [11] and a manuscript in preparation which attempts to report findings of CFA and psychometric properties of the finalized behavior scale (SLB-SF-38). Additionally, percentile norms and personal correlates of service leadership behavior regarding the full scale of SLB-SF-38 have also been presented by Shek and collaborators [15]. Norms of SLB-SF-38 with reference to the full scale and its subscales will be outlined in the following section.

Table 4. Confirmatory Factor Analysis loadings

Item	Factor loading	Item	Factor loading
Self-improvement and self-reflection 1	.73	Resilience 2	.71
Self-improvement and self-reflection 2	.67	Resilience 3	.76
Self-improvement and self-reflection 3	.65	Resilience 4	.77
Self-improvement and self-reflection 4	.76	Resilience 5	.78
Self-improvement and self-reflection 5	.75	Resilience 6	.69
Self-improvement and self-reflection 6	.73	Resilience 7	.69
Self-improvement and self-reflection 7	.75	Social competence 1	.79
Self-improvement and self-reflection 8	.80	Social competence 2	.83
Self-improvement and self-reflection 9	.71	Social competence 3	.81
People and principles orientation 1	.51	Social competence 4	.72
People and principles orientation 2	.71	Social competence 5	.64
People and principles orientation 3	.73	Problem-solving 1	.70
People and principles orientation 4	.62	Problem-solving 2	.70
People and principles orientation 5	.63	Problem-solving 3	.77
People and principles orientation 6	.70	Problem-solving 4	.77
People and principles orientation 7	.69	Problem-solving 5	.73
People and principles orientation 8	.63	Mentorship 1	.75
People and principles orientation 9	.65	Mentorship 2	.86
Resilience 1	.62	Mentorship 3	.82

NORMS

The normative sample involved in this manual was obtained through a snowball sampling strategy in the aforementioned large-scale validation study. First, PolyU initially set up an online survey and distributed the link to the coordinators in other seven participating universities in Hong Kong. Second, the coordinator in each university invited undergraduate students to respond to the online survey. Student participants were well informed of several important principles, such as confidentiality, anonymity, and freedom to withdraw. After completing the questionnaire, each participant was given a local supermarket voucher worth HK\$100 as an incentive.

The final normative sample of 4,486 undergraduate students was recruited from late March to early June 2017. The age of participants ranged between 15 and 34 years ($M = 20.47$, $SD = 1.67$). Among these participants, 2,969 (66.18%) were female students and 1,517 (33.82%) were male students.

Normative Statistics

The raw scores of full-scale and sub-scales obtained from full sample and gender-specific samples were non-normative. Therefore, norms of percentile rank of the score of full- and sub-scales instead of standardized Z scores were calculated for full sample and gender-specific samples. Related norm tables are presented in Tables 5-18. While Tables 5 and 6 show norms of total score, Tables 7-18 demonstrate norms of the six subscales in SLB-SF-38. For both total score and scores of subscales, percentile ranks (1-100) and corresponding raw scores are summarized in Tables 5, 7, 9, 11, 13, 15, and 17. Raw scores and related equivalent percentile ranks are outlined in Tables 6, 8, 10, 12, 14, 16, and 18.

Table 5. Percentiles and corresponding raw scores of Service Leadership Behavior Scale (SLB-SF-38) by gender

Percentile (1-50)	Raw Score			Percentile (51-99)	Raw Score		
	Male (N = 1,517)	Female (N = 2,969)	Total sample (N = 4,486)		Male (N = 1,517)	Female (N = 2,969)	Total sample (N = 4,486)
1	≤ 94.36	≤ 112.70	≤ 107.00	51	173.00	174.00	174.00
2	112.36	123.00	119.74	52	173.00	175.00	174.00
3	121.00	131.00	128.00	53	174.00	175.00	175.00
4	126.00	135.00	131.00	54	175.00	176.00	175.00
5	129.00	137.00	134.00	55	175.00	176.00	176.00
6	131.00	139.00	136.00	56	176.00	177.00	177.00
7	133.00	142.00	138.00	57	177.00	177.00	177.00
8	135.00	143.00	141.00	58	177.00	178.00	178.00
9	137.00	145.00	142.00	59	178.00	178.00	178.00
10	139.00	146.00	144.00	60	178.00	179.00	179.00
11	141.00	147.00	145.00	61	179.00	179.00	179.00
12	142.00	148.00	146.00	62	180.00	180.00	180.00
13	143.00	149.00	147.00	63	180.34	180.00	180.00
14	144.00	150.00	148.00	64	181.00	181.00	181.00
15	146.00	151.00	149.00	65	182.00	181.00	181.00
16	147.00	152.00	150.00	66	182.00	182.00	182.00
17	148.00	152.00	151.00	67	183.00	182.00	183.00
18	149.00	152.60	152.00	68	183.00	183.00	183.00
19	150.00	154.00	152.00	69	184.00	183.00	183.00
20	151.00	154.00	153.00	70	184.00	184.00	184.00
21	152.00	155.00	154.00	71	185.00	184.00	185.00
22	152.00	156.00	154.00	72	186.00	185.00	185.00
23	152.00	156.00	155.00	73	186.00	185.00	186.00
24	153.00	157.00	156.00	74	187.00	186.00	186.00
25	154.00	158.00	157.00	75	188.00	186.00	187.00
26	155.00	159.00	157.00	76	188.00	187.00	187.00
27	155.00	160.00	158.00	77	189.00	187.00	188.00
28	156.00	160.00	159.00	78	190.00	188.00	188.00
29	157.00	161.00	160.00	79	190.00	188.00	189.00

Percentile (1-50)	Raw Score			Percentile (51-99)	Raw Score		
	Male (N = 1,517)	Female (N = 2,969)	Total sample (N = 4,486)		Male (N = 1,517)	Female (N = 2,969)	Total sample (N = 4,486)
30	158.00	162.00	160.10	80	190.00	189.00	189.00
31	158.00	162.70	161.00	81	190.00	189.00	190.00
32	159.00	163.00	162.00	82	191.00	190.00	190.00
33	160.00	164.00	163.00	83	191.00	190.00	191.00
34	161.00	165.00	163.00	84	192.00	191.00	191.00
35	162.00	165.00	164.00	85	193.00	191.50	192.00
36	162.00	166.00	165.00	86	194.00	192.00	193.00
37	163.00	167.00	165.00	87	195.00	193.00	194.00
38	164.00	167.00	166.00	88	196.00	194.00	195.00
39	164.00	168.00	167.00	89	197.00	195.00	196.00
40	165.00	168.00	167.00	90	198.00	197.00	197.00
41	165.00	169.00	168.00	91	199.00	198.00	199.00
42	166.00	169.00	168.00	92	201.00	200.00	200.00
43	167.00	170.00	169.00	93	202.00	201.00	201.00
44	167.00	171.00	170.00	94	204.00	202.00	203.00
45	168.00	171.00	170.00	95	207.00	205.00	205.00
46	169.00	172.00	171.00	96	208.00	207.20	208.00
47	169.00	172.00	171.00	97	212.00	211.00	212.00
48	171.00	173.00	172.00	98	217.00	215.00	216.00
49	171.00	173.00	173.00	99	222.82	221.30	222.00
50	172.00	174.00	173.00	100	≥ 228.00	≥ 228.00	≥ 228.00

Table 6. Raw scores and corresponding percentiles of Service Leadership Behavior Scale (SLB-SF-38)

Raw score	Percentiles			Raw score	Percentiles			Raw score	Percentiles		
	Male	Female	Total sample		Male	Female	Total sample		Male	Female	Total sample
≤ 94	1.0	1.0	1.0	134	8.0	4.0	5.0	174	53.0	51.0	52.0
95	2.0	1.0	1.0	135	8.0	4.0	6.0	175	54.0	53.0	54.0
96	2.0	1.0	1.0	136	9.0	5.0	6.0	176	56.0	55.0	55.0
97	2.0	1.0	1.0	137	9.0	5.0	7.0	177	58.0	57.0	57.0
98	2.0	1.0	1.0	138	10.0	6.0	7.0	178	60.0	59.0	59.0
99	2.0	1.0	1.0	139	10.0	6.0	8.0	179	61.0	61.0	61.0
100	2.0	1.0	1.0	140	11.0	7.0	8.0	180	62.0	63.0	63.0
101	2.0	1.0	1.0	141	11.0	7.0	8.0	181	64.0	65.0	65.0
102	2.0	1.0	1.0	142	12.0	7.0	9.0	182	66.0	67.0	66.0
103	2.0	1.0	1.0	143	13.0	8.0	10.0	183	68.0	69.0	68.0
104	2.0	1.0	1.0	144	14.0	9.0	10.0	184	70.0	71.0	70.0
105	2.0	1.0	1.0	145	15.0	9.0	11.0	185	71.0	73.0	72.0
106	2.0	1.0	1.0	146	15.0	10.0	12.0	186	73.0	75.0	74.0
107	2.0	1.0	1.0	147	16.0	11.0	13.0	187	74.0	77.0	76.0
108	2.0	1.0	2.0	148	17.0	12.0	14.0	188	76.0	79.0	78.0
109	2.0	1.0	2.0	149	18.0	13.0	15.0	189	77.0	81.0	80.0
110	2.0	1.0	2.0	150	19.0	14.0	16.0	190	80.0	83.0	82.0
111	2.0	1.0	2.0	151	20.0	15.0	17.0	191	83.0	84.0	84.0
112	2.0	1.0	2.0	152	22.0	17.0	19.0	192	84.0	86.0	85.0
113	3.0	2.0	2.0	153	24.0	19.0	20.0	193	85.0	87.0	86.0
114	3.0	2.0	2.0	154	25.0	20.0	22.0	194	86.0	88.0	87.0
115	3.0	2.0	2.0	155	27.0	21.0	23.0	195	87.0	89.0	88.0
116	3.0	2.0	2.0	156	28.0	23.0	24.0	196	88.0	90.0	89.0
117	3.0	2.0	2.0	157	29.0	24.0	26.0	197	89.0	90.0	90.0
118	3.0	2.0	2.0	158	31.0	25.0	27.0	198	90.0	91.0	91.0

Table 6. (Continued)

Raw score	Percentiles			Raw score	Percentiles			Raw score	Percentiles		
	Male	Female	Total sample		Male	Female	Total sample		Male	Female	Total sample
119	3.0	2.0	2.0	159	32.0	26.0	28.0	199	91.0	92.0	91.0
120	3.0	2.0	3.0	160	33.0	28.0	29.0	200	92.0	92.0	92.0
121	3.0	2.0	3.0	161	34.0	29.0	31.0	201	92.0	93.0	93.0
122	4.0	2.0	3.0	162	36.0	30.0	32.0	202	93.0	94.0	94.0
123	4.0	2.0	3.0	163	37.0	32.0	34.0	203	94.0	95.0	94.0
124	4.0	3.0	3.0	164	39.0	33.0	35.0	204	94.0	95.0	95.0
125	4.0	3.0	3.0	165	41.0	35.0	37.0	205	95.0	95.0	95.0
126	4.0	3.0	3.0	166	42.0	36.0	38.0	206	95.0	96.0	96.0
127	5.0	3.0	3.0	167	44.0	38.0	40.0	207	95.0	96.0	96.0
128	5.0	3.0	3.0	168	45.0	40.0	42.0	208	96.0	97.0	96.0
129	5.0	3.0	4.0	169	47.0	42.0	43.0	209	96.0	97.0	97.0
130	5.0	3.0	4.0	170	48.0	43.0	45.0	210	96.0	97.0	97.0
131	6.0	3.0	4.0	171	49.0	45.0	47.0	211	96.0	97.0	97.0
132	7.0	4.0	5.0	172	50.0	47.0	48.0	212	97.0	98.0	97.0
133	7.0	4.0	5.0	173	52.0	49.0	49.0	213	98.0	98.0	98.0
214	98.0	98.0	98.0	219	99.0	99.0	99.0	224	100.0	100.0	100.0
215	98.0	98.0	98.0	220	100.0	99.0	99.0	225	100.0	100.0	100.0
216	98.0	99.0	98.0	221	100.0	99.0	99.0	226	100.0	100.0	100.0
217	98.0	99.0	99.0	222	100.0	100.0	99.0	227	100.0	100.0	100.0
218	99.0	99.0	99.0	223	100.0	100.0	100.0	228	100.0	100.0	100.0

Note. *N* = 1,517 for male sample, *N* = 2,969 for female sample, *N* = 4,486 for full sample.

Table 7. Percentiles and corresponding raw scores of Service Leadership Behavior Scale (Factor 1) by gender

Percentile (1-50)	Raw Score			Percentile (51-99)	Raw Score		
	Male	Female	Total sample		Male	Female	Total sample
1	≤ 20.00	≤ 24.00	≤ 22.00	51	42.00	43.00	42.00
2	24.00	27.40	27.00	52	42.00	43.00	43.00
3	27.00	29.00	28.00	53	42.00	43.00	43.00
4	28.00	30.00	30.00	54	42.00	43.00	43.00
5	29.00	31.00	30.00	55	42.90	43.00	43.00
6	30.00	32.00	31.00	56	43.00	43.00	43.00
7	30.00	33.00	32.00	57	43.00	44.00	43.00
8	31.00	33.00	32.00	58	43.00	44.00	43.00
9	31.00	33.00	33.00	59	43.00	44.00	44.00
10	32.00	34.00	33.00	60	43.00	44.00	44.00
11	32.00	34.00	34.00	61	43.00	44.00	44.00
12	33.00	35.00	34.00	62	44.00	44.00	44.00
13	33.00	35.00	34.00	63	44.00	44.00	44.00
14	34.00	35.00	35.00	64	44.00	44.00	44.00
15	34.00	36.00	35.00	65	44.00	45.00	44.00
16	34.00	36.00	35.00	66	44.00	45.00	45.00
17	35.00	36.00	36.00	67	44.00	45.00	45.00
18	35.00	36.00	36.00	68	45.00	45.00	45.00
19	35.00	36.00	36.00	69	45.00	45.00	45.00
20	36.00	36.00	36.00	70	45.00	45.00	45.00
21	36.00	36.00	36.00	71	45.00	45.00	45.00
22	36.00	37.00	36.00	72	45.00	45.00	45.00
23	36.00	37.00	37.00	73	45.00	45.00	45.00

Percentile (1-50)	Raw Score			Percentile (51-99)	Raw Score		
	Male	Female	Total sample		Male	Female	Total sample
24	36.00	37.00	37.00	74	45.00	45.00	45.00
25	36.00	38.00	37.00	75	45.00	45.00	45.00
26	36.00	38.00	37.00	76	45.00	45.00	45.00
27	37.00	38.00	38.00	77	46.00	46.00	46.00
28	37.00	38.00	38.00	78	46.00	46.00	46.00
29	37.00	39.00	38.00	79	46.00	46.00	46.00
30	37.00	39.00	38.00	80	46.00	46.00	46.00
31	37.58	39.00	39.00	81	47.00	47.00	47.00
32	38.00	39.00	39.00	82	47.00	47.00	47.00
33	38.00	39.00	39.00	83	47.00	47.00	47.00
34	38.00	40.00	39.00	84	47.00	47.00	47.00
35	39.00	40.00	39.00	85	48.00	48.00	48.00
36	39.00	40.00	40.00	86	48.00	48.00	48.00
37	39.00	40.00	40.00	87	48.00	48.00	48.00
38	39.00	40.00	40.00	88	48.00	48.60	48.00
39	40.00	41.00	40.00	89	49.00	49.00	49.00
40	40.00	41.00	40.00	90	49.00	49.00	49.00
41	40.00	41.00	41.00	91	50.00	50.00	50.00
42	40.00	41.00	41.00	92	50.00	50.00	50.00
43	40.00	41.00	41.00	93	50.00	51.00	51.00
44	41.00	42.00	41.00	94	51.00	51.00	51.00
45	41.00	42.00	41.00	95	52.00	52.00	52.00
46	41.00	42.00	42.00	96	52.28	53.00	53.00
47	41.00	42.00	42.00	97	53.00	53.00	53.00
48	41.00	42.00	42.00	98	54.00	54.00	54.00
49	41.00	42.00	42.00	99	54.00	54.00	54.00
50	42.00	42.00	42.00	100	54.00	54.00	54.00

Note. $N = 1,517$ for male sample, $N = 2,969$ for female sample, $N = 4,486$ for full sample.

Table 8. Raw scores and corresponding percentiles of Service Leadership Behavior Scale (Factor 1)

Raw score	Percentiles			Raw score	Percentiles			Raw score	Percentiles		
	Male	Female	Total sample		Male	Female	Total sample		Male	Female	Total sample
20	1.0	1.0	1.0	32	11.0	6.0	8.0	44	65.0	61.0	62.0
21	2.0	1.0	1.0	33	13.0	8.0	10.0	45	72.0	71.0	71.0
22	2.0	1.0	1.0	34	16.0	11.0	12.0	46	79.0	79.0	79.0
23	2.0	1.0	2.0	35	18.0	13.0	15.0	47	83.0	83.0	83.0
24	2.0	1.0	2.0	36	23.0	18.0	20.0	48	87.0	86.0	87.0
25	3.0	2.0	2.0	37	29.0	23.0	25.0	49	90.0	90.0	90.0
26	3.0	2.0	2.0	38	33.0	27.0	29.0	50	92.0	92.0	92.0
27	3.0	2.0	2.0	39	37.0	31.0	33.0	51	94.0	94.0	94.0
28	4.0	3.0	3.0	40	41.0	36.0	38.0	52	95.0	95.0	95.0
29	5.0	3.0	4.0	41	47.0	41.0	43.0	53	97.0	97.0	97.0
30	7.0	4.0	5.0	42	52.0	47.0	49.0	54	100.0	100.0	100.0
31	9.0	5.0	6.0	43	59.0	54.0	55.0				

Note. $N = 1,517$ for male sample, $N = 2,969$ for female sample, $N = 4,486$ for full sample.

Table 9. Percentiles and corresponding raw scores of Service Leadership Behavior Scale (Factor 2) by gender

Percentile (1-50)	Raw Score				Percentile (51-99)	Raw Score		
	Male	Female	Total sample			Male	Female	Total sample
1	≤ 22.00	≤ 27.00	≤ 25.00		51	42.00	43.00	42.00
2	25.00	30.00	29.00		52	42.00	43.00	43.00
3	28.54	32.00	31.00		53	42.00	43.00	43.00
4	30.00	33.00	32.00		54	42.00	43.00	43.00
5	31.00	34.00	32.00		55	42.00	43.00	43.00
6	31.00	34.00	33.00		56	42.00	44.00	43.00
7	32.00	35.00	34.00		57	42.00	44.00	43.00
8	32.00	35.00	34.00		58	42.00	44.00	43.00
9	33.00	36.00	34.00		59	43.00	44.00	44.00
10	33.00	36.00	35.00		60	43.00	44.00	44.00
11	33.00	36.00	35.00		61	43.00	44.00	44.00
12	34.00	36.00	36.00		62	43.00	44.00	44.00
13	34.00	36.00	36.00		63	43.00	44.00	44.00
14	35.00	36.00	36.00		64	43.00	44.00	44.00
15	35.00	37.00	36.00		65	44.00	44.00	44.00
16	35.00	37.00	36.00		66	44.00	45.00	44.00
17	35.00	37.00	36.00		67	44.00	45.00	44.00
18	36.00	37.00	37.00		68	44.00	45.00	45.00
19	36.00	38.00	37.00		69	44.00	45.00	45.00
20	36.00	38.00	37.00		70	44.00	45.00	45.00
21	36.00	38.00	37.00		71	44.00	45.00	45.00
22	36.00	38.00	38.00		72	45.00	45.00	45.00
23	36.00	39.00	38.00		73	45.00	45.00	45.00
24	36.00	39.00	38.00		74	45.00	45.00	45.00
25	37.00	39.00	38.00		75	45.00	45.00	45.00
26	37.00	39.00	38.00		76	45.00	45.00	45.00
27	37.00	39.00	39.00		77	45.00	46.00	45.00
28	37.00	39.00	39.00		78	45.00	46.00	46.00
29	38.00	40.00	39.00		79	45.22	46.00	46.00
30	38.00	40.00	39.00		80	46.00	46.00	46.00
31	38.00	40.00	39.00		81	46.00	46.00	46.00
32	38.00	40.00	40.00		82	46.00	47.00	46.00
33	38.00	40.00	40.00		83	46.00	47.00	47.00
34	39.00	41.00	40.00		84	47.00	47.00	47.00
35	39.00	41.00	40.00		85	47.00	47.00	47.00
36	39.00	41.00	40.00		86	47.00	47.00	47.00
37	39.00	41.00	41.00		87	47.00	48.00	48.00
38	39.00	41.00	41.00		88	47.00	48.00	48.00
39	40.00	41.00	41.00		89	48.00	48.00	48.00
40	40.00	41.00	41.00		90	48.00	49.00	48.00
41	40.00	42.00	41.00		91	49.00	49.00	49.00
42	40.00	42.00	41.00		92	49.00	49.00	49.00
43	40.00	42.00	41.00		93	49.00	50.00	49.00
44	41.00	42.00	42.00		94	50.00	50.00	50.00
45	41.00	42.00	42.00		95	50.00	50.00	50.00
46	41.00	42.00	42.00		96	51.00	51.00	51.00
47	41.00	42.00	42.00		97	52.00	52.00	52.00
48	41.00	43.00	42.00		98	53.00	52.00	53.00
49	41.00	43.00	42.00		99	53.82	54.00	54.00
50	41.00	43.00	42.00		100	54.00	54.00	54.00

Note. *N* = 1,517 for male sample, *N* = 2,969 for female sample, *N* = 4,486 for full sample.

Table 10. Raw scores and corresponding percentiles of Service Leadership Behavior Scale (Factor 2)

Raw score	Percentiles			Raw score	Percentiles			Raw score	Percentiles		
	Male	Female	Total sample		Male	Female	Total sample		Male	Female	Total sample
22	1.0	1.0	1.0	34	13.0	6.0	8.0	46	82.0	79.0	80.0
23	2.0	1.0	1.0	35	16.0	8.0	11.0	47	86.0	84.0	85.0
24	2.0	1.0	1.0	36	21.0	12.0	15.0	48	90.0	88.0	89.0
25	2.0	1.0	1.0	37	27.0	17.0	20.0	49	92.0	91.0	92.0
26	3.0	1.0	2.0	38	31.0	21.0	24.0	50	95.0	94.0	95.0
27	3.0	1.0	2.0	39	36.0	26.0	29.0	51	96.0	96.0	96.0
28	3.0	2.0	2.0	40	41.0	31.0	34.0	52	97.0	99.0	97.0
29	4.0	2.0	2.0	41	47.0	37.0	40.0	53	98.0	99.0	98.0
30	4.0	2.0	3.0	42	55.0	44.0	48.0	54	100.0	100.0	100.0
31	6.0	3.0	3.0	43	62.0	52.0	55.0				
32	8.0	3.0	5.0	44	68.0	61.0	63.0				
33	10.0	4.0	6.0	45	75.0	71.0	73.0				

Note. $N = 1,517$ for male sample, $N = 2,969$ for female sample, $N = 4,486$ for full sample.

Table 11. Percentiles and corresponding raw scores of Service Leadership Behavior Scale (Factor 3) by gender

Percentile (1-50)	Raw Score				Percentile (51-99)	Raw Score		
	Male	Female	Total sample			Male	Female	Total sample
1	≤ 15.00	≤ 15.00	≤ 15.00		51	31.00	30.00	31.00
2	18.00	18.00	18.00		52	31.00	31.00	31.00
3	19.00	19.00	19.00		53	32.00	31.00	31.00
4	20.00	20.00	20.00		54	32.00	31.00	31.00
5	21.00	21.00	21.00		55	32.00	31.00	31.00
6	21.00	22.00	22.00		56	32.00	31.00	32.00
7	22.00	22.00	22.00		57	32.00	31.00	32.00
8	22.00	23.00	23.00		58	32.00	32.00	32.00
9	23.00	23.00	23.00		59	32.00	32.00	32.00
10	23.00	23.00	23.00		60	32.00	32.00	32.00
11	24.00	24.00	24.00		61	33.00	32.00	32.00
12	24.00	24.00	24.00		62	33.00	32.00	32.00
13	25.00	24.00	24.00		63	33.00	32.00	33.00
14	25.00	25.00	25.00		64	33.00	33.00	33.00
15	25.00	25.00	25.00		65	33.00	33.00	33.00
16	25.00	25.00	25.00		66	33.00	33.00	33.00
17	26.00	25.00	25.79		67	33.00	33.00	33.00
18	26.00	26.00	26.00		68	34.00	33.00	33.00
19	26.00	26.00	26.00		69	34.00	33.00	33.00
20	26.00	26.00	26.00		70	34.00	33.00	34.00
21	26.00	26.00	26.00		71	34.00	34.00	34.00
22	27.00	26.00	26.00		72	34.00	34.00	34.00
23	27.00	27.00	27.00		73	34.00	34.00	34.00
24	27.00	27.00	27.00		74	35.00	34.00	34.00
25	27.00	27.00	27.00		75	35.00	34.00	34.00
26	27.00	27.00	27.00		76	35.00	34.00	34.00
27	27.00	27.00	27.00		77	35.00	34.00	35.00
28	28.00	27.00	27.36		78	35.00	35.00	35.00
29	28.00	28.00	28.00		79	35.00	35.00	35.00
30	28.00	28.00	28.00		80	35.00	35.00	35.00

Table 11. (Continued)

Percentile (1-50)	Raw Score				Percentile (51-99)	Raw Score		
	Male	Female	Total sample			Male	Female	Total sample
31	28.00	28.00	28.00		81	35.00	35.00	35.00
32	28.00	28.00	28.00		82	35.00	35.00	35.00
33	28.00	28.00	28.00		83	35.00	35.00	35.00
34	28.00	28.00	28.00		84	35.00	35.00	35.00
35	28.00	28.00	28.00		85	36.00	35.00	35.00
36	28.00	28.00	28.00		86	36.00	35.00	35.00
37	29.00	28.00	28.00		87	36.00	35.00	36.00
38	29.00	28.60	29.00		88	36.00	36.00	36.00
39	29.00	29.00	29.00		89	36.02	36.00	36.00
40	29.00	29.00	29.00		90	37.00	36.00	37.00
41	29.00	29.00	29.00		91	37.00	37.00	37.00
42	30.00	29.00	29.00		92	38.00	37.00	37.00
43	30.00	29.00	29.00		93	38.00	37.00	38.00
44	30.00	29.00	30.00		94	38.00	38.00	38.00
45	30.00	30.00	30.00		95	39.00	38.00	38.00
46	30.00	30.00	30.00		96	39.00	39.00	39.00
47	30.00	30.00	30.00		97	40.00	39.90	40.00
48	31.00	30.00	30.00		98	41.00	40.00	41.00
49	31.00	30.00	30.00		99	42.00	42.00	42.00
50	31.00	30.00	31.00		100	42.00	42.00	42.00

Note. $N = 1,517$ for male sample, $N = 2,969$ for female sample, $N = 4,486$ for full sample.

Table 12. Raw scores and corresponding percentiles of Service Leadership Behavior Scale (Factor 3)

Raw score	Percentiles			Raw score	Percentiles			Raw score	Percentiles		
	Male	Female	Total sample		Male	Female	Total sample		Male	Female	Total sample
15	1.0	1.0	1.0	25	15.0	16.0	15.0	35	79.0	83.0	82.0
16	2.0	2.0	2.0	26	19.0	20.0	20.0	36	87.0	89.0	88.0
17	2.0	2.0	2.0	27	25.0	26.0	25.0	37	91.0	92.0	91.0
18	2.0	2.0	2.0	28	32.0	33.0	33.0	38	93.0	95.0	94.0
19	3.0	3.0	3.0	29	39.0	42.0	41.0	39	96.0	96.0	96.0
20	4.0	4.0	4.0	30	45.0	48.0	47.0	40	97.0	98.0	97.0
21	6.0	5.0	5.0	31	50.0	55.0	53.0	41	98.0	99.0	98.0
22	8.0	7.0	7.0	32	57.0	61.0	59.0	42	100.0	100.0	100.0
23	10.0	9.0	9.0	33	64.0	67.0	66.0				
24	12.0	12.0	12.0	34	71.0	74.0	73.0				

Note. $N = 1,517$ for male sample, $N = 2,969$ for female sample, $N = 4,486$ for full sample.

Table 13. Percentiles and corresponding raw scores of Service Leadership Behavior Scale (Factor 4) by gender

Percentile (1-50)	Raw Score				Percentile (51-99)	Raw Score		
	Male	Female	Total sample			Male	Female	Total sample
1	≤ 10.00	≤ 13.00	≤ 12.00		51	23.00	24.00	24.00
2	13.00	15.00	14.00		52	23.00	24.00	24.00
3	14.00	16.00	15.00		53	23.00	24.00	24.00
4	15.00	17.00	16.00		54	23.00	24.00	24.00
5	15.00	17.00	17.00		55	23.00	24.00	24.00
6	16.00	18.00	17.00		56	23.00	24.00	24.00
7	17.00	18.00	18.00		57	23.00	24.00	24.00
8	17.00	18.00	18.00		58	24.00	24.00	24.00

Percentile (1-50)	Raw Score				Percentile (51-99)	Raw Score		
	Male	Female	Total sample			Male	Female	Total sample
9	17.00	19.00	18.00		59	24.00	24.00	24.00
10	18.00	19.00	18.00		60	24.00	25.00	24.00
11	18.00	19.00	19.00		61	24.00	25.00	24.00
12	18.00	19.00	19.00		62	24.00	25.00	24.00
13	18.00	20.00	19.00		63	24.00	25.00	25.00
14	18.00	20.00	19.00		64	24.00	25.00	25.00
15	19.00	20.00	20.00		65	24.00	25.00	25.00
16	19.00	20.00	20.00		66	24.00	25.00	25.00
17	19.00	20.00	20.00		67	24.00	25.00	25.00
18	19.00	20.00	20.00		68	25.00	25.00	25.00
19	19.00	20.00	20.00		69	25.00	25.00	25.00
20	19.60	20.00	20.00		70	25.00	25.00	25.00
21	20.00	20.00	20.00		71	25.00	25.00	25.00
22	20.00	21.00	20.00		72	25.00	25.00	25.00
23	20.00	21.00	20.00		73	25.00	25.00	25.00
24	20.00	21.00	20.00		74	25.00	25.00	25.00
25	20.00	21.00	21.00		75	25.00	25.00	25.00
26	20.00	21.00	21.00		76	25.00	25.00	25.00
27	20.00	21.00	21.00		77	25.00	25.00	25.00
28	20.00	21.00	21.00		78	25.00	25.00	25.00
29	20.00	21.00	21.00		79	25.00	26.00	25.00
30	20.00	22.00	21.00		80	25.00	26.00	26.00
31	20.00	22.00	21.00		81	25.00	26.00	26.00
32	21.00	22.00	21.00		82	25.00	26.00	26.00
33	21.00	22.00	22.00		83	26.00	26.00	26.00
34	21.00	22.00	22.00		84	26.00	26.00	26.00
35	21.00	22.00	22.00		85	26.00	26.00	26.00
36	21.00	22.00	22.00		86	26.00	27.00	26.00
37	21.00	23.00	22.00		87	26.00	27.00	27.00
38	21.00	23.00	22.00		88	27.00	27.00	27.00
39	21.00	23.00	22.00		89	27.00	27.00	27.00
40	21.00	23.00	22.00		90	27.00	28.00	27.00
41	22.00	23.00	23.00		91	27.00	28.00	28.00
42	22.00	23.00	23.00		92	28.00	28.00	28.00
43	22.00	23.00	23.00		93	28.00	28.00	28.00
44	22.00	23.00	23.00		94	28.00	28.80	28.00
45	22.00	23.00	23.00		95	29.00	29.00	29.00
46	22.00	23.00	23.00		96	29.00	29.00	29.00
47	22.00	24.00	23.00		97	30.00	29.90	30.00
48	22.00	24.00	23.00		98	30.00	30.00	30.00
49	23.00	24.00	23.00		99	30.00	30.00	30.00
50	23.00	24.00	23.50		100	30.00	30.00	30.00

Note. N = 1,517 for male sample, N = 2,969 for female sample, N = 4,486 for full sample.

Table 14. Raw scores and corresponding percentiles of Service Leadership Behavior Scale (Factor 4)

Raw score	Percentiles			Raw score	Percentiles			Raw score	Percentiles		
	Male	Female	Total sample		Male	Female	Total sample		Male	Female	Total sample
10	1.0	1.0	1.0	17	8.0	5.0	6.0	24	63.0	53.0	57.0
11	2.0	1.0	1.0	18	12.0	7.0	9.0	25	75.0	69.0	71.0
12	2.0	1.0	1.0	19	17.0	11.0	13.0	26	85.0	82.0	83.0
13	2.0	1.0	2.0	20	26.0	17.0	20.0	27	90.0	88.0	89.0
14	3.0	2.0	2.0	21	36.0	26.0	29.0	28	93.0	92.0	93.0
15	5.0	2.0	3.0	22	45.0	33.0	37.0	29	96.0	96.0	96.0
16	6.0	3.0	4.0	23	53.0	42.0	45.0	30	100.0	100.0	100.0

Note. N = 1,517 for male sample, N = 2,969 for female sample, N = 4,486 for full sample.

Table 15. Percentiles and corresponding raw scores of Service Leadership Behavior Scale (Factor 5) by gender

Percentile (1-50)	Raw Score				Percentile (51-99)	Raw Score		
	Male	Female	Total sample			Male	Female	Total sample
1	≤ 11.00	≤ 11.00	≤ 11.00		51	23.00	22.00	23.00
2	13.00	13.00	13.00		52	23.00	22.00	23.00
3	14.00	14.00	14.00		53	23.00	23.00	23.00
4	15.00	15.00	15.00		54	23.00	23.00	23.00
5	16.00	15.00	15.00		55	24.00	23.00	23.00
6	16.00	16.00	16.00		56	24.00	23.00	23.00
7	17.00	16.00	16.00		57	24.00	23.00	23.00
8	17.00	17.00	17.00		58	24.00	23.00	23.00
9	17.00	17.00	17.00		59	24.00	23.00	23.00
10	18.00	17.00	17.00		60	24.00	23.00	24.00
11	18.00	17.00	18.00		61	24.00	23.00	24.00
12	18.00	18.00	18.00		62	24.00	24.00	24.00
13	18.00	18.00	18.00		63	24.00	24.00	24.00
14	19.00	18.00	18.00		64	24.00	24.00	24.00
15	19.00	18.00	18.00		65	24.00	24.00	24.00
16	19.00	18.00	19.00		66	25.00	24.00	24.00
17	19.00	18.00	19.00		67	25.00	24.00	24.00
18	19.00	19.00	19.00		68	25.00	24.00	24.00
19	19.00	19.00	19.00		69	25.00	24.00	24.00
20	20.00	19.00	19.00		70	25.00	24.00	25.00
21	20.00	19.00	19.00		71	25.00	24.00	25.00
22	20.00	19.00	19.00		72	25.00	25.00	25.00
23	20.00	19.00	20.00		73	25.00	25.00	25.00
24	20.00	20.00	20.00		74	25.00	25.00	25.00
25	20.00	20.00	20.00		75	25.00	25.00	25.00
26	20.00	20.00	20.00		76	25.00	25.00	25.00
27	20.00	20.00	20.00		77	25.00	25.00	25.00
28	20.00	20.00	20.00		78	25.00	25.00	25.00
29	20.00	20.00	20.00		79	25.00	25.00	25.00
30	20.00	20.00	20.00		80	26.00	25.00	25.00
31	21.00	20.00	20.00		81	26.00	25.00	25.00
32	21.00	20.00	20.00		82	26.00	25.00	25.00
33	21.00	20.00	20.00		83	26.00	25.00	25.00
34	21.00	20.00	21.00		84	26.00	25.00	26.00
35	21.00	21.00	21.00		85	27.00	25.00	26.00
36	21.00	21.00	21.00		86	27.00	26.00	26.00
37	21.00	21.00	21.00		87	27.00	26.00	26.00
38	22.00	21.00	21.00		88	27.00	26.00	26.56
39	22.00	21.00	21.00		89	28.00	26.00	27.00
40	22.00	21.00	21.00		90	28.00	27.00	27.00
41	22.00	21.00	21.00		91	28.00	27.00	27.00
42	22.00	21.00	22.00		92	28.00	27.00	28.00
43	22.00	21.00	22.00		93	28.00	27.00	28.00
44	22.00	22.00	22.00		94	29.00	28.00	28.00
45	23.00	22.00	22.00		95	29.00	28.00	29.00
46	23.00	22.00	22.00		96	29.00	29.00	29.00
47	23.00	22.00	22.00		97	30.00	29.00	29.00
48	23.00	22.00	22.00		98	30.00	30.00	30.00
49	23.00	22.00	22.00		99	30.00	30.00	30.00
50	23.00	22.00	23.00		100	30.00	30.00	30.00

Note. N = 1,517 for male sample, N = 2,969 for female sample, N = 4,486 for full sample.

Table 16. Raw scores and corresponding percentiles of Service Leadership Behavior Scale (Factor 5)

Raw score	Percentiles			Raw score	Percentiles			Raw score	Percentiles		
	Male	Female	Total sample		Male	Female	Total sample		Male	Female	Total sample
11	1.0	1.0	1.0	18	12.0	15.0	13.0	25	73.0	79.0	77.0
12	2.0	2.0	2.0	19	17.0	21.0	19.0	26	82.0	88.0	86.0
13	2.0	2.0	2.0	20	25.0	29.0	28.0	27	87.0	92.0	90.0
14	3.0	3.0	3.0	21	34.0	39.0	38.0	28	91.0	95.0	93.0
15	4.0	5.0	5.0	22	41.0	48.0	46.0	29	95.0	97.0	96.0
16	6.0	7.0	7.0	23	50.0	57.0	55.0	30	100.0	100.0	100.0
17	8.0	10.0	9.0	24	60.0	67.0	65.0				

Note. $N = 1,517$ for male sample, $N = 2,969$ for female sample, $N = 4,486$ for full sample.

Table 17. Percentiles and corresponding raw scores of Service Leadership Behavior Scale (Factor 6) by gender

Percentile (1-50)	Raw Score				Percentile (51-99)	Raw Score		
	Male	Female	Total sample			Male	Female	Total sample
1	≤ 5.00	≤ 6.00	≤ 6.00		51	13.00	13.00	13.00
2	6.00	6.00	6.00		52	13.00	13.00	13.00
3	7.00	7.00	7.00		53	13.00	13.00	13.00
4	7.00	7.00	7.00		54	13.00	13.00	13.00
5	8.00	8.00	8.00		55	13.00	13.00	13.00
6	8.00	8.00	8.00		56	13.00	13.00	13.00
7	9.00	9.00	9.00		57	13.00	13.00	13.00
8	9.00	9.00	9.00		58	14.00	13.00	13.00
9	9.00	9.00	9.00		59	14.00	14.00	14.00
10	9.00	9.00	9.00		60	14.00	14.00	14.00
11	9.00	9.00	9.00		61	14.00	14.00	14.00
12	9.00	9.00	9.00		62	14.00	14.00	14.00
13	10.00	10.00	10.00		63	14.00	14.00	14.00
14	10.00	10.00	10.00		64	14.00	14.00	14.00
15	10.00	10.00	10.00		65	14.00	14.00	14.00
16	10.00	10.00	10.00		66	14.00	14.00	14.00
17	10.00	10.00	10.00		67	14.00	14.00	14.00
18	10.00	10.00	10.00		68	14.00	14.00	14.00
19	10.00	11.00	10.00		69	14.00	14.00	14.00
20	11.00	11.00	11.00		70	15.00	14.00	14.00
21	11.00	11.00	11.00		71	15.00	15.00	15.00
22	11.00	11.00	11.00		72	15.00	15.00	15.00
23	11.00	11.00	11.00		73	15.00	15.00	15.00
24	11.00	11.00	11.00		74	15.00	15.00	15.00
25	11.00	11.00	11.00		75	15.00	15.00	15.00
26	11.00	11.00	11.00		76	15.00	15.00	15.00
27	11.00	12.00	11.00		77	15.00	15.00	15.00
28	11.00	12.00	12.00		78	15.00	15.00	15.00
29	12.00	12.00	12.00		79	15.00	15.00	15.00
30	12.00	12.00	12.00		80	15.00	15.00	15.00
31	12.00	12.00	12.00		81	15.00	15.00	15.00
32	12.00	12.00	12.00		82	15.00	15.00	15.00
33	12.00	12.00	12.00		83	15.00	15.00	15.00
34	12.00	12.00	12.00		84	15.00	15.00	15.00
35	12.00	12.00	12.00		85	15.00	15.00	15.00

Table 17. (Continued)

Percentile (1-50)	Raw Score				Percentile (51-99)	Raw Score		
	Male	Female	Total sample			Male	Female	Total sample
36	12.00	12.00	12.00		86	15.00	15.00	15.00
37	12.00	12.00	12.00		87	15.00	15.00	15.00
38	12.00	12.00	12.00		88	16.00	15.00	15.00
39	12.00	12.00	12.00		89	16.00	15.00	15.00
40	12.00	12.00	12.00		90	16.00	16.00	16.00
41	12.00	12.00	12.00		91	16.00	16.00	16.00
42	12.00	12.00	12.00		92	16.00	16.00	16.00
43	12.00	12.00	12.00		93	16.00	16.00	16.00
44	12.00	12.00	12.00		94	17.00	17.00	17.00
45	12.00	12.00	12.00		95	17.00	17.00	17.00
46	13.00	13.00	13.00		96	17.00	17.00	17.00
47	13.00	13.00	13.00		97	18.00	18.00	18.00
48	13.00	13.00	13.00		98	18.00	18.00	18.00
49	13.00	13.00	13.00		99	18.00	18.00	18.00
50	13.00	13.00	13.00		100	18.00	18.00	18.00

Note. $N = 1,517$ for male sample, $N = 2,969$ for female sample, $N = 4,486$ for full sample.

Table 18. Raw scores and corresponding percentiles of Service Leadership Behavior Scale (Factor 5)

Raw score	Percentiles			Raw score	Percentiles			Raw score	Percentiles		
	Male	Female	Total sample		Male	Female	Total sample		Male	Female	Total sample
5	1.0	1.0	1.0	10	16.0	16.0	16.0	15	79.0	80.0	80.0
6	2.0	1.0	2.0	11	24.0	23.0	24.0	16	91.0	92.0	92.0
7	4.0	4.0	4.0	12	37.0	36.0	37.0	17	95.0	95.0	95.0
8	6.0	6.0	6.0	13	52.0	52.0	52.0	18	100.0	100.0	99.0
9	10.0	10.0	10.0	14	64.0	65.0	65.0				

Note. $N = 1,517$ for male sample, $N = 2,969$ for female sample, $N = 4,486$ for full sample.

SCORING AND INTERPRETATION

The SLB-SF-38 includes 38 items grouped into six subscales. The score of each subscale is calculated on the sum of each item of the subscale. The total score of service leadership behavior is calculated by adding up the scores of all 38 items. Theoretically, the total score ranges between 38 and 228.

Handling of Missing Items

Satisfactory reliability of the scale/subscales largely depends on participants’ responses to all items included in the scale/subscales. If there is missing value in any item, the results should be interpreted with cautions. Cases with missing value(s) should be excluded from data analysis or handled by appropriate missing value imputation methods before conducting data analysis.

Interpretation of Test Scores

Test scores of SLB-SF-38 can be interpreted in terms of a total score of full scale or test score(s) of subscale(s). The total score represents an individual's overall behavioral characteristics with reference to service leadership. The score of an individual subscale shows one's leadership practice and related skills in one specific area. For example, a high score of "Resilience" reflects one's capability of using effective strategies to overcome adversity and bounce back.

Tables 5-18 show norms of percentile ranks for the scores of full scale and the subscales. The percentile rank of a particular raw score represents the percentage of people in the normative sample scored no higher than this raw score. In other words, a percentile rank can be interpreted as one's relative standing in the relevant group according to the score. For instance, if a female university student wishes to surpass 50% of her female peers in demonstrating resilience, she has to get at least 30 points (see Table 11). Similarly, if a university student, regardless of gender, gets 31 points for subscale of resilience (i.e., Subscale 3), he/she has already surpassed 53% of all university students (see Table 12).

There is no specific cut-off value to define effective/good versus ineffective/bad service leadership behaviors. Therefore, testers are not recommended to describe people with different service leadership behaviors using objectives such as "effective," "good," "ineffective" or "bad," although norm-referenced descriptors may be used. For instance, scale users are suggested to locate a participant's test score in the norm tables to determine his/her relative position regarding service leadership behavior. Descriptions like "less effective than the normative sample," "similar to the normative sample," or "more effective than the normative sample" can be adopted to differentiate people with different service leadership behaviors.

In addition, when using the scale/subscales to examine the effectiveness of service leadership training programmes, evaluators are suggested to monitor the improvement through the comparison between pre- and post-test. In this case, using mean scores provides more meaningful information than referring to the norm tables does.

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Chapter 148

ORIGIN, DEVELOPMENT AND ASSERTIONS OF SERVICE LEADERSHIP THEORY

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ABSTRACT

In response to the emergence of service economy in different societies, there is a need to rethink what effective leadership is in this changing landscape. With his expertise and success in courier service, Po Chung (the former CEO of DHL International) proposed the Service Leadership Theory (SLT) which posits that successful leadership in the era of service economy is governed by 3Cs – competencies, character and care. Through a qualitative study via analyses of the written work of Po Chung and personal interviews with him as well as his former colleagues, we document the chronology of the development of the Service Leadership Theory with reference to a) why he proposed the theory; b) the major milestones in the development of the SLT; and c) emphases of the SLT. The findings are discussed with reference to the leadership models and research in the scientific literature.

INTRODUCTION

Over the past few decades, the service sectors across the world have shown dynamic and fast growth, propped by the rise of a variety of service industries such as IT, e-commerce, communications, wholesale and retail trade, consultancy, and education [1]. In Hong Kong, the service sector has taken up as much as 92% of its GDP in 2017 [2]. The decline of manufacturing industry and the expansion of service industry have brought about far-reaching

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impact on employment, division of labor and social relations. A manufacturing economy is characterized by the transformation and utilization of materials, with mechanized production of commodities [1]. Those commodities are very often tangible and standardized. In addition, workers in the production line are expected to operate machines and equipment to perform their specific tasks routinely without much input from their own (i.e., doing things right). The production processes, therefore, can be easily automated to ensure a higher level of productivity and efficiency [3, 4]. In contrast, service industries involve the provision and production of intangible goods, such as knowledge, information, advice, and experience, which are not mass-produced and must be tailored to customers' needs with the input from the service providers [1, 5]. Employees in the new era are thereby expected to be more skilled, knowledgeable, innovative and autonomous, and can gain intrinsic satisfaction from their work [3, 6]. Besides, providing quality service is much related to the moral standards and care of the service providers (i.e., doing the right things).

Due to the structural transformation of the societies, the demands of leadership have also been changed [7]. Characteristics of leadership in manufacturing industry include a clear-defined hierarchy, top-down management, centralized authority, bureaucracy and regulations [8, 9]. However, organizations and companies that over-emphasize leadership competencies and management skills would lose sight of the importance of moral character and caring dispositions [8]. On the other hand, due to the dynamics and complexity in service economies, employees are now yearning for flexibility and autonomy at work, and leaders play a vital role in empowering and motivating followers to develop capacity and achieve personal growth [3]. Accordingly, leaders are no longer assumed at the central position. Instead, the new vision of leadership emphasizes mutual influence between leaders and followers, with the decision-making process becoming a collaborative and shared process [6, 9]. Besides, in view of the mental problems faced by young people [10], there is a need to strengthen the psychosocial competence and inner strengths of service leaders.

The pivotal role that higher education plays in preparing future leaders for a society has been recognized by many researchers [11, 12]. In university leadership programs, there has been a growing quest for leadership competencies, such as communication and negotiation skills [13], critical thinking ability [14], global vision [15], etc. However, the current university leadership education has been criticized for its inadequate impact in nurturing future leaders that the coverage in cultivating service mindset and civic awareness is limited [12, 16-18]. The weight placed on skills development by many university leadership programs reflects that they still espouse beliefs of an industrial paradigm [19]. Therefore, university leadership programs need to revise the curriculum so as to meet the demands of the postindustrial era that emphasize service mindset, relationships, trust, ethics, etc. [19, 20].

As a service-oriented society, Hong Kong also calls for a transformation in leadership education [8]. In response to this development, the Hong Kong Institute of Service Leadership and Management (HKI-SLAM) was established in 2011. Headed by Po Chung, the founder of DHL International (Hong Kong) Ltd, this institute represents an effort to promote the principles and values of service leadership and facilitate practices in education, business and government sectors in Hong Kong. With financial support from the Victor and William Fung Foundation, HKI-SLAM launched the Li and Fung Service Leadership Initiative (SLI) to support service leadership education in the eight UGC-funded universities in Hong Kong [21]. The eight universities financed by UGC have all developed service leadership programs and incorporated them into the curriculum.

Obviously, the development and implementation of universities' leadership programs give rise to the need for evaluation of its effectiveness in developing leadership. [22]. Against this background, Shek and his colleagues carried out a series of large-scale quantitative studies that drew on validated assessment tools to measure the effectiveness of the service leadership programs [8, 23-24]. For example, in Lin and Shek's [23] pretest-posttest quasi-experimental study, researchers used measures that had been validated in their previous studies, such as the Chinese Positive Youth Development Scale [24, 25], to examine the effectiveness of a service leadership program in Hong Kong. They found that students who took the service leadership course (experimental group) showed greater improvements in terms of leadership knowledge, attitude and life satisfaction than students who did not take the course (control group). The findings also showed that students' leadership development contributed to their well-being.

Alternatively, a few studies turned to qualitative evaluation which examined students' subjective perspectives and views towards the service leadership courses [20, 26]. Most findings demonstrated that students perceived the courses positively and considered the participation conducive to their holistic development. For example, Shek and Lin [20] conducted a qualitative evaluation on a non-credit-bearing service leadership program in Hong Kong. Participating students were invited to describe their perception of their experiences by using three descriptors and one metaphor. Results indicated that over 90% of both the descriptors and the metaphors were positive in nature. In general, both quantitative and qualitative evaluation studies provided compelling and consistent evidence that participation in those programs contributed to service leadership development, which also confirmed that service leadership could be nurtured in tertiary education.

With much research concentrating on evaluating program effectiveness, several questions concerning the Service Leadership Theory proposed by Po Chung remain unanswered. For example, what prompted Po Chung to conceive a leadership model in the first place? What are the milestones in the development of the model? How do the major changes intertwine with each other against a broader background of social and economic transformation? To answer these questions, we seek to explore the chronology of this theory, as a study of chronology unfolds the causes and effects of events in the process and deepens our understanding of the interdependence and interconnections of the events in the topic under focus [27]. To be specific, the present study attempted to contribute to the knowledge about the development of the SLT by looking into the chronology of the theory and milestones in the process with reference to three guiding questions:

- a. How has the SLT evolved (i.e., chronology)? What are the major milestones in developing the SLT?
- b. Why did Po propose the SLT?
- c. What are the key propositions of the SLT?

OUR STUDY

Given the nature of the above-mentioned research questions, a qualitative approach was considered more appropriate for the current study, as it allows for a deep understanding of the

complex social world and attends to the intricacy in people's lives [28-29]. Situated in qualitative approach, narrative inquiry is a methodology that pays close attention to people's life stories over time, where researchers gather valuable information through people's storytelling [30]. It allows researchers an opportunity to make an in-depth inquiry into people's voices, thoughts and behaviors, as well as how they make sense of their world [31]. In addition, narrative inquiry can work with a variety of data collection methods to elicit data of the subjective experiences such as autobiographical writing, journal writing, interviews and observation [32]. As stated previously, the present study intended to probe into Chung's personal journeys and his colleagues' experiences to explore the chronology of the SLT and the critical steps in the process.

In the current study, autobiographical writing and semi-structured narrative interviews were adopted as the major inquiry tools. The data were collected between October 2019 and May 2020, which involved Chung's autobiographical writing, followed by five interviews with Po Chung and two group interviews with Chung's colleagues. The autobiographical writing provides an initial inquiry into Chung's personal journey and a context for the ensuing interviews. Chung was invited to write about his experiences based on the prompts we sent to him beforehand. The autobiographical writing was about Chung's stories related to the origin and development of the SLT.

Regarding the following interviews, the open-ended nature of the semi-structured interviews allows for some flexibility during interviews whereby the researchers can further probe for details while it also enables the interviewees to express themselves freely [33]. Individual interviews were conducted to elicit data on the evolvement of the SLT, the milestones of the theory such as competence, character, care and self-leadership, as well as the future of service leadership. Each interview was based upon the previous one in order to get a deeper understanding of the topic. For example, Chung mentioned in the first interview that he had developed the initial sense of leadership from the elementary school education, which contributed to the construct of the SLT in his later stages of life. In the second interview, we followed up on how his family imbued him with leadership awareness in his childhood in order to obtain a more in-depth understanding of how his family upbringing contributed to the development of SLT.

Based on Chung's recommendations, we contacted his colleagues to invite participants for the group interviews. Two colleagues voluntarily participated in the two group interviews. The focus of the group interviews was to elicit the informants' experiences of how DHL incorporated the SLT into practices and how the development of the theory was reflected in its management. Each of the seven interviews lasted for approximately one hour.

Data Analysis

All interviews were recorded and transcribed. As some interviews were conducted in Cantonese, the transcripts were translated into English before the analysis. Thematic analysis was used in the data analysis as it plays a critical role in categorizing data, identifying themes and facilitating high-order thinking in qualitative research [34]. We first singled out the meaningful parts relevant to each of our three research questions, and identified codes and preliminary themes. Following a cyclical process, those codes and preliminary themes were

revisited, reworked and refined in alignment with the research foci and questions. The codes were then peer checked by two other researchers to maintain the credibility of the data analyses and conclusions drawn. After the revision and finalization of codes, the coding files were then sent to the informants for the purpose of member checking.

Drawing upon the evaluation of a database of qualitative evaluation studies, Shek and his colleagues [35] identified several principles that qualitative researchers should have awareness concerning the issue of quality. We applied the principles in examining the quality of the present study. First, they [35] argued many qualitative studies used the term *qualitative* in a vague manner and failed to specify the qualitative approach. In response, the present study focused on narrative inquiry as to the methodology. Second, we also upheld the principle of auditability in which sufficient details of data collection procedures were provided as above, including that we adopted continuous interviews for data collection. Third, in order to increase the overall “reliability and validity” they called for, the present study adopted peer checking and member checking to assess accuracy and adequacy of the data, and allowed alternative interpretations in the analysis.

THE CHRONOLOGY OF SLT

The chronology is summarized in Figure 1 based on the collected data and writings of Po Chung [3, 21, 36-39].

Initial Sense of Leadership Developed in Childhood

It was made clear from Chung’s autobiographical writing that his initial sense of leadership was shaped by the joint effort of both family and school education. His father who worked for a tobacco company as a manager and led hundreds of coworkers was his role model. Explicitly or implicitly, his father inculcated the values of leadership in him, such as altruism, caring and respecting others. As Chung recalled in the first interview, his father constantly reminded him that being a good person and leader “you have to take care of colleagues. So, don’t do things that are only selfish, but (those you) really have to do.” Later, Chung and his family moved to Macau, and they lived with the subordinates of his father. Although lives were hard, they looked after and took care of each other from the heart. The experience made him understand the importance of building human relationships and networks.

Chung received his elementary education at St Stephen’s College, and the setting of “perfect” in school inspired him in the development of SLT. In Hong Kong schools, some well-behaved senior students with excellent performance in academics or sports would be selected by teachers as “perfect” and were treated as role models for other students to learn from. By observing the behavior of the prefects, Chung found self-management not just critical to personal growth and self-improvement, but it also helps in earning trust and respect from others. He shared in the interview:

“So St. Stephen is a Christian boarding school... In this boarding school, we had things called ‘prefect’... So in the old school, the senior class, we had six people that are chosen to be models of other students...This is where we learned how to behave as ourselves...After you learn how to behave, you have the values. You have the behavior. Then you get the respect and the trust of the rest of your schoolmates...And that’s where we learned self-management, and self-management became part of self-leadership...” (The first interview with Chung)

Chung accounted his early schooling and family upbringing with Christian values provided a positive context to him in developing the initial sense of leadership qualities, such as self-management, selflessness, care, respect, trust, etc.

Leadership Values Practiced at DHL

As a co-founder of DHL International, Chung brought those leadership qualities with him along the way and ingrained them into the managerial philosophy of the organization. For example, he highlighted mutual trust and respect between employees and the company:

“We know that if other people who work for us, there’s no trust or there’s no respect, and if we don’t give them the dignity of being a human being, they would not trust us, they would not respect us.” (The first interview with Chung)

The interview narratives from the DHL colleagues echoed Chung’s vision on trust and how it served as the cornerstone in maintaining global business:

“What has been established in DHL culture since a long time ago is trust, the unbelievable trust between colleagues...When I have received an urgent parcel in Hong Kong, I will trust my colleagues in the US to deliver it to (US)... I won’t worry about it because he will get this right, and vice versa...Trust was deeply rooted in our mindset...When I promise others, no matter this task is from the US or Taiwan, as long as I take the request and make the promise, I will try my best. I won’t let you down.” (The second interview with DHL staff)

Based on the belief of trust, DHL used a “master and apprentice” system to impart skills and wisdom that is similar to the “perfect system. In this system, employees demonstrate their self-management ability, and they are encouraged to observe and learn from the supervisor and continuously improve themselves. At the same time, they were also granted autonomy to make decisions, carry out those decisions, and learn from their mistakes. Chung explained:

“We use a ‘master and apprentice’ system. And when we finish teaching them the master skills, they become masters...So what we teach them is autonomy, being able to make the best decision, being the best version of himself as a courier, (the) best version of himself as a supervisor, best version of himself as an assistant manager. That’s what we try to do.” (The first interview with Chung)

“Push decision to the lowest level... A courier goes on a street. Every street is different. Every country is different. Every city is different. So, if you don’t let him make decisions, he will never learn. He will do the minimum because he does not dare to do anything creative.” (The second interview with Chung)

Theory Development (5 Dynamics of Entrepreneurship Model)

After the retirement from DHL, Chung began teaching entrepreneurship at universities in Hong Kong, which started his journey of “collecting, researching, deconstructing and explaining what (he) experienced as an entrepreneur” (Chung’s autobiographical writing). This experience prompted him to think about the defects of the present leadership education and models and why they failed to address the needs of our service-oriented economy (This part will be elaborated in the next section, i.e., “Why Chung proposed SLT”). Chung then worked with a group of entrepreneurs to conceptualize entrepreneurship and developed the “5 Dynamics of Entrepreneurship” framework (5D Model). It represented his initial attempt to develop a leadership model:

“One major stage for advancement happened from 2004-2005, when Saimond Ip, Leonard Lane, Thomas Osgood and I designed the 5 Dynamics of Entrepreneurship model. This began the formal articulation of a character-driven leader at the heart of a start-up.” (Chung’s autobiographical writing)

The center of the 5D Model is the entrepreneur’s personal operating system (POS) which stated the qualities of entrepreneur to get the startup off the ground in an uncertain and competitive environment [37]. Notably, the value of character strengths is articulated and underscored in this model. Chung also held the belief that the five entrepreneurial dynamics could be taught [37].

Establishment of Hong Kong Institute of Service Leadership and Management (HKI-SLAM) and Theory Development

Both the writing and interview narratives revealed Chung’s vision of promoting more service-centric leadership to meet the demands of our service-oriented society. This vision, together with his educational and career trajectory, guided him in taking the lead in the establishment of HKI-SLAM in 2010. According to Chung’s autobiographical writing, he worked with Ran Elfassy from 2012 to 2013, during the period they identified the 12 dimensions concerning the desirable traits of a service leader [38]. The 12 dimensions are grouped into four facets, i.e., doing, being, thinking and growing [38]. Through what Chung called “pattern recognition,” SLT was further developed into a 3Cs model where competence, character and care were recognized as the three major principles in establishing effective service leadership:

“I seem to have ability to look at a whole group of things and then group them together. So, this one and this one (are in) one group; this and this in one group; and this is another group. So, that’s pattern recognition.” (The second interview with Chung)

This service leadership model was then fully developed by HKI-SLAM to boost service leadership education and practices [36]. In this model, service leadership was clearly defined as “a service aimed at ethically satisfying the needs of one’s self, others, groups, communities, systems, and environments” and conceptualized with 7 core beliefs [21].

Fung Service Leadership Initiative for Eight UGC-Funded Universities in Hong Kong

Sponsored by the Victor and William Fung Foundation, the Fung Service Leadership Initiative was launched in 2012 to promote sustainable service leadership education at the higher education levels in Hong Kong. From Chung's perspective, university education was gatekeepers of legitimate knowledge and values, and hence could serve as an incubator for cultivating future leaders. This perspective was also embraced by many previous educators [11, 12] who recognized the mission of Higher Education Institutions (HEIs) to inspire future leaders.

Despite the initial skepticism, the eight UGC-funded universities gradually endorsed service leadership philosophies and embraced the idea of incorporating the SLT in their curriculum:

"We went to (the) eight universities and we faced a lot of skepticism in the beginning, but now it's mostly accepted by all eight universities. Why we went to (the) eight universities? Why we went to universities? Because those are the gatekeepers of values or gatekeepers of knowledge...But now, nobody resists it anymore. EdU does it. PolyU is teaching it. BU is teaching it, and Lingnan is; all of them are doing it." (The second interview with Chung)

The promotion of service leadership education involves two non-mutually exclusive strands: One is to acquire the concepts and philosophies in the SLT, and the other is to engage students in experiential learning where students can practice their leadership and achieve personal development. With the support from the Fung Service Leadership Initiative, PolyU was among the first batch that introduced to its undergraduates a credit-bearing course entitled "Service Leadership" in 2012/13 academic year:

"We can see two sides of leadership service; one is called service learning or service doing. That's more like the lab, the practical. It's like teaching chemistry - there is a theory side, and this is what we are...and there's a practice side that we organize students to go out and do the service. Before, some universities only have the lab. We gave the theory and now they are merging it together. EdU is definitely doing that. You guys are doing it. PolyU is doing it because there is another team that goes out and says, 'You go to Cambodia. You go to Vietnam.'" (The second interview with Chung)

WHY CHUNG PROPOSED THE SLT?

Gaps between What the Schools Teach and What Societies Need

From the above excerpts and illustration of the chronology of the SLT, we can see that Chung's leadership awareness was nurtured by the upbringing and reinforced by the successful implementation at DHL. However, it was his experiences of teaching university students entrepreneurship that motivated him to think about conceptualizing leadership and promoting leadership education that meets the demands of the time. In his opinion, our society has undergone a tremendous shift from manufacturing-oriented to service-oriented economy. The former society was characterized by industrial production of tangible goods

while the latter is featured by business or customer orientations and the production of intangible values:

“So, we were shifting from manufacturing to service...There were no factories anymore and put people out of work. Because there were no more factories, we had to train (and) retrain 200 thousand people from manufacturing to service, and I was one of them.” (The second interview with Chung)

“Then, we have to move on to the post-industrial age. We are in the post-industrial age because the making of things is over, because AI is coming, and we have to be more human to lead other humans. So we are changing from making things to motivating humans to do better things so that humans can become better.” (The first interview with Chung)

However, his university lecturing experiences made him realize the gap between what schools were teaching and what the current society needed. From his keen observation and research, schools stressed and valued students’ skills and knowledge rather than their character and caring disposition, which largely aligned with an industrial manufacturing mindset:

“MBA is all about skills. It’s all about skills. It’s all about knowledge, but very little on character and care.” (The second interview with Chung)

“(After lecturing at universities,) it was clear that there was a gap in mindset between what the schools were teaching and what companies needed. After my team and I surveyed what was being taught at the MBA schools, it dawned on us that the ideology was driven from an industrial manufacturing mindset. That was fine for overseeing production lines, but service was completely different!” (Chung’s autobiographical writing)

Chung further explained the rationale behind the over-emphasis of one C (competence) and neglect of the other two Cs (character and care), and he pointed out the setting is a sign of the times:

“One C (Competence) was logical. Many business schools in the US were sponsored by manufacturers, so they concentrated on getting more people who can do things right, but neglected (we should) do the right thing with the right heart.” (The third interview with Chung)

In contrast, a service-oriented economy underlines creating values for customers and the society while achieving self-fulfillment:

“To summarize, I clearly showed how management was designed for industrial manufacturing and making sure things are done well. This is crucial when a production line must produce millions of identical objects. High-level services, on the other hand, are complex exchanges between people that help one another thrive, be more fulfilled, and reach their whole self-actualization.” (Chung’s autobiographical writing)

Existing Leadership Models Fail to Address What the Societies Need

The weight casted on leadership skills and competencies was also mirrored in leadership theories and models. Many traditional leadership models entail a top-down notion, evidenced by the highlight of regulation, hierarchy, managerial skills and efficiency in the output [36]. Service leadership, as Chung argued, would be a complement to existing leadership models by giving considerable attention to the principles of character and care:

“All leadership models have their own advantages. Any leader who wants to succeed must keep learning and absorbing the essence in all areas. Rather than displacing other models, service leadership is a complement to other models that any leader should bear in mind if they really want to succeed and should put it in (the) first order.” (Chung’s autobiographical writing)

“Specifically, leadership programs and models are overly weighted on addressing the competencies, EQ and related facets of a leader. The Service Leadership model I designed, on the other hand, is most interested in helping a leader to improve their character through self-knowledge, self-governance and commitment to continuous learning and development. To put it another way, the ultimate goal in self-actualization of a leader is helping everyone in his or her network meet all their needs, including their self-actualization.” (Chung’s autobiographical writing)

It can be drawn from the above quotes that Chung’s service leadership is also contrasted with several other models which may also adopt a follower-centric vision. For example, the transformational leadership proposed by Kouzes and Posner [40] also lays stress on collective interest and personal devotion as a leader. However, it fails to address the importance of continuous self-improvement as well as a balanced development of oneself and the collective [36].

In summary, the premise of service leadership was prompted by Chung’s understanding of the gaps between what schools taught as well as what existing leadership models addressed and what societies needed. This understanding was gained from collecting, deconstructing and scrutinizing his business and teaching experiences. The pivotal part of service leadership, as Chung succinctly put it in a statement, “it’s not only that you do things right. It’s you have to do the right things with the right heart” (The second interview with Chung).

WHAT ARE THE KEY PROPOSITIONS OF THE SLT?

Service Centric

Regarding the major differences that distinguish the SLT from other existing models of leadership, Chung condensed them into three dimensions in his autobiographical writing: a service-centric vision, highlighting character strengths in leadership, and the separation of management from leadership.

A service-centric vision places a premium on serving, motivating and empowering followers as well as oneself, reflecting the requirements of a service-oriented society:

“The largest difference is that we make a clear distinction that our model is service centric, one that is separated from industrial manufacturing. We see this blurring of operational aims (i.e., confusing a manufacturing operation as being similar to a high-value service one) as being of critical importance. This blind spot is one we are trying to address and correct.” (Chun’s autobiographical writing)

Notably, the SLT sets itself apart from Greenleaf’s [41] servant leadership which also upholds the belief that a leader is to serve. The SLT was not established on the premise that the needs of others outweigh the needs of self. Instead, it accents a concerted effort to address the needs of oneself, others and system [36, 42]. In addition, it underscores the value of self-leadership where one should continuously reflect on and motivate oneself, and improve his or her competence, care and character.

Emphasis on a Person's Character in Leadership

Character has been recognized as one of the key attributes of service leadership, along with care and competence. Chung believed that good characters are morally valued traits that steer people in the right direction and bind people together. Empirical studies have also provided evidence that good characters are robustly associated with school achievements, altruism, resilience and life satisfaction, etc. [43, 44]. Moreover, character strengths can be cultivated and promoted through school education [45]. However, as argued by Chung, the cultivation of character strengths was in a subordinate role in existing leadership models and leadership education:

“We have found a gross lack of training, discussion or investigation in the leader's character. We have noted how universities skimp on character education, and this oversight has created many problems on leaders that we would describe as ‘toxic.’ To put it using our 3-Cs of Service Leadership, other models are great for covering Competence and even Care, but Character has gone ignored for too long ... There are many examples of leaders who did very well or got far ahead with only one strong C. More importantly, there are many examples of bad or toxic leaders in history who lead followers on a wrong track or use corrupt practice for getting advancement and achievement.” (Chung's autobiographical writing)

“A good character is character that attracts people. Bad character is a character that repels people. And you find them repulsive. We call it repulsive.” (The first interview with Chung)

Separate Management from Leadership

SLT does not equate leadership with management. Management, in Chung's opinion, is attentive to top-down regulation, control and hierarchy in operation, and efficiency in the output. Those tenets are conceived as typical indicators for a manufacturing setting [46]. In a service economy, however, it is vital for leaders to adapt their leadership to service contexts. Service leadership, in particular, values the possession of character strength and caring dispositions [42]. Chung explicated that a service leader earned respect and trust from the followers by committing to their needs and helping them thrive:

“Our model carefully separates management from leadership. Management is all about operational efficiency, stability and excellence – in short, doing things ‘right’ or well. In our view, leadership is more about doing the right things with good intentions. This is about ensuring that what a company does is aligned with human values and needs, resulting in the greatest good for communities and stakeholders.” (Chung's autobiographical writing)

“Leadership is different from management, so a leader is different from managers. Management is more like top-down because the company pays the employee, so the employee has the obligation, and the employees feel that they would listen to their manager because they report to the manager. But leadership is different because your position makes you a manager, but it's your followers that make you a leader. So it's a kind of human-relationship instead of employment, he follows you because he can get something from you. So what's the reason for me to follow you? You are not paying me to follow you. I am voluntary, it is my will to follow you. So it's a human relation instead of an employment relation... So these are pulling forces.” (The first interview with Chung)

DISCUSSION

On reflection, we highlighted several unique features of the current study. First, this is a pioneering study documenting the development of the SLT from its infancy to the present development. Second, the analysis of its development was not decontextualized. On the contrary, we examined how the model developed from an embryonic status to its prosperity with particular reference to the service economy of Hong Kong. Third, the understanding of the topic is derived from an integration of the collected data and literature. For example, in order to gain a more comprehensive understanding of Chung's views of the defects of existing leadership models, we revisited relevant literature of other models such as the servant leadership [41] and transformational leadership [40]. This integration facilitates our understanding of how the SLT distinguishes itself from others.

On a theoretical level, this study adds to the literature by showing how the milestones of the SLT interweave with the trajectory of Chung as well as the social and economic transformation. It reveals the ways the SLT responds to the demands of Hong Kong, a service-oriented economy. By doing this, the present study demonstrates that the values and principles of the SLT can be both an epitome and impetus for a service society. Practically, this study reinforces the previous arguments [23, 47] that it is necessary for universities to shift the focus of leadership education from training competencies and skills to cultivating students' characters, disposition and moral senses. It also echoes the viewpoints that HEIs can work as an incubator for cultivating future leaders [11-12, 48]. Finally, it provides insights into the efforts that have been undertaken to promote this leadership model and incorporate it into university curriculum in Hong Kong, providing practical implications to wider contexts.

While this paper outlines the chronology underlying the development of the SLT, it has several limitations. First, the focus on Chung's autobiographical writing and interviews as the methodological techniques relies on his ability to honestly and accurately recall his previous experiences and behaviors, which could raise the issue of reliability and validity of the study [49]. Second, it would have elicited richer data if additional interviewees had been involved. For example, our understanding of the DHL practices in relation to the SLT values could have been deepened if more DHL colleagues had been included. Another possible limitation of the current study is a biased interpretation which is inherent to qualitative research [50]. This limitation should draw our particular attention, as our researchers are practitioners in the related field, and thereby the interpretations could be influenced by their own perspectives and compromise the objectivity of the research. In response, participating researchers conducted a series of procedures, including disciplined data collection, disciplined data analyses, peer checking and member checking to minimize the bias in the analysis and interpretation. In conclusion, we probed into the chronology of the SLT against the background of social and economic transformations. More research can be conducted to explore the future development of service leadership and the limitations of this model. For example, with the development of validated measures on service leadership and behavior [51, 52], we can further examine the impact of service leadership on the well-being of the leaders, followers, service recipients and the community [53].

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Chapter 149

HUMANISTIC LEADERSHIP IN SERVICE ECONOMY

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ABSTRACT

Humanity is an essential component of effective leadership in service economy because human interactions play an indispensable role in providing high-quality services. Several theories highlighting the importance of satisfying human needs provide theoretical support for humanistic leadership in service economy. Based on interviews with Dr. Po Chung and his colleagues in DHL International, the present paper explores how the notion of humanity is put into leadership practice in the workplace and the outcomes associated with humanistic leadership practices. The qualitative findings were also integrated with previous empirical findings in the leadership literature. Both the narratives and leadership research strongly suggest that the element of humanity can be put into leadership practice in terms of developing followers, satisfying their needs, and empowering them, which further lead to positive outcomes at both individual and organizational levels.

INTRODUCTION

Along with the worldwide shift from manufacturing economy to service economy, more human interactions are involved during the inseparable processes of service provision and consumption. On the one hand, service values are co-created through effective interactions between customers and other partners, including employers and employees, as well as leaders and followers [1-3]. As such, satisfying customers' needs becomes one of the leadership goals. At the same time, employees are increasingly valued as "human assets" who are

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capable to store and share knowledge in order to provide high-quality services and contribute to organizational success. Therefore, fulfilling followers' needs through motivating, engaging, and empowering them constitutes another important dimension of leadership behavior in service economy. Taken together, "humanity" or "fulfilling human needs" is the core of leadership practice in the service era (i.e., "Service leadership," SL) in terms of people orientation and service orientation [4].

SL represents a new paradigm that highlights empowerment and distributed leadership that values everyone's contribution in complicated decision-making processes involving different stakeholders, including customers, leaders, followers, and other agencies acquiring resources [5, 6]. SL also highlights a culture that entails organizations to achieve their promises, design their process, and engage their "human assets" in a proactive pursuit of service advantage [7]. In SL, capable leaders emphasize the satisfaction of followers' needs, cultivation of their internal motivation, and promotion of their personal development so as to maximize individual and team capacity and the attainment of organizational and even societal goals [8, 9].

These people-oriented and service-oriented beliefs about SL underscore the uniqueness of leadership in the service economy, suggesting that leadership practice is in fact a service provision process that can be performed by everyone and satisfy the needs of not only customers but also followers. However, existing leadership theories have not systematically incorporated these elements to guide leadership practice, education, and research in the service era. Against this background, Dr. Po Chung, co-founder of DHL International, established the "Hong Kong Institute of Service Leadership and Management" (HKI-SLAM) after his retirement and proposed the "Service Leadership Theory" (SLT) to promote service leadership practice and education in Hong Kong and abroad. Noteworthy, SL was defined as "satisfying needs by consistently providing quality personal service to everyone one comes into contact with, including one's self, others, groups, communities, systems, and environments" [10].

The definition of service leadership itself reflects a strong emphasis on humanity by highlighting fulfillment of a wide range of needs, including one's own needs, such as self-serving efforts that improve individual competencies and willingness to provide high-quality services. Besides, SLT proposed that "3Cs" ("competence," "character," and "care") determine effective leadership in the service economy [11]. Competence refers to a service leader's skills and abilities to accomplish the job tasks, and more importantly, to inspire the followers to do the job well and help them improve. Character means that service leaders should demonstrate good morality so that they can ethically satisfy the needs of self, others, and society. Care refers to a leader's concern and respect for the benefits of others in leading people and providing services. These effective leadership qualities summarized by the 3Cs also highlight the importance of "humanity" (e.g., satisfying followers' needs by developing and respecting them) in service leadership practice.

The importance of humanity highlighted in the SLT is in line with different theoretical assertions addressing the importance of satisfying human needs, including the "self-determination theory" (SDT), "Maslow's hierarchy of needs" and the notion of "flourishing" in positive psychology. First, according to SDT that investigates intrinsic motivation and internal needs that drive people's behaviors, there are three inherent psychological needs, including autonomy, relatedness and competence [12, 13]. Satisfaction of these innate needs has been found to be closely related to positive outcome indicators such as vitality,

satisfaction of life and work, persistent performance, and secure attachment [14-16]. According to the SDT, effective service leaders are expected to satisfy followers' intrinsic needs in the workplace by enhancing their development, empowering them, and recognizing their contributions.

The second related theory is Maslow's hierarchy of needs, which conceptualizes human needs as a 5-tier hierarchy that includes physical needs (e.g., safety) at the basement two levels and psychological needs (e.g., love or sense of belonging, self-esteem, and self-actualization) at three higher levels [17]. These needs, especially psychological needs, play a crucial role in motivating people and securing positive development. Previous findings revealed that people might develop social anxiety or withdrawal from a group if they are not accepted or respected (i.e., lower self-esteem) or fail to form a sense of belonging [18]. Studies also showed that self-actualization reflects a good understanding of oneself and the development of one's potential, which enables one to acquire self-respect that others cannot take away [18]. Referring to the Maslow's hierarchy of needs, effective service leadership emphasizes the importance of satisfying human needs in the upper hierarchy in terms of fulfilling the needs of belongingness, self-esteem, and self-actualization of the followers.

The third psychological theory that provides support for the SLT is the concept of "flourishing" in positive psychology, which refers to "thrive, prosper, be in a period of the highest productivity or influences" [19]. This concept points to individuals' pursuit of well-being as a final goal [20]. To reach flourishing, there are five essential pursuits, including "positive emotion," "engagement," "relationships," "meanings" and "accomplishment" [20]. Once these psychological pursuits are fulfilled, flourishing and other positive outcomes, such as hopefulness, gratitude, empathy, and character strength, can be achieved [21]. Indeed, empirical evidence shows that these five aspects are positively linked to multiple indicators of well-being such as happiness, physical health, job satisfaction and life satisfaction [22, 23]. Therefore, from the perspective of flourishing, effective service leaders should help followers satisfy those key pursuits in order to achieve flourishing, which echoes the attributes of "3Cs" in effective service leaders. This also presents an approach to actualize humanity in service leadership.

According to the above-mentioned theories, satisfying followers' higher needs is of paramount importance in the workplace. As Jansen [24] stated: "work is no longer about completing tasks to make money for a company and its shareholders...It is also about you as an individual needing and wanting choices, meaning, rewards, motivation, and success in your work" (p. 236). Humanistic values and principles have also been discussed in existing leadership models. For example, Pirson and Lawrence [25] proposed a humanistic paradigm of leadership that emphasizes leaders' relational traits (e.g., viewing followers as individual human beings instead of merely resources to achieve intended outcomes). According to their paradigm, transformational leadership fits well the value of humanism as transformational leaders inspire, stimulate, develop, and engage followers and facilitate long-term relationships and commitment to the organization [26]. Hayat and Suliman [27] also differentiated between transformational leadership and transactional leadership with reference to humanistic values. While transactional leadership is based on a relationship of exchange between a leader and followers where only lower needs of followers (e.g., getting money) will be met, transformational leadership satisfies followers' higher needs by identifying their potential and converting them into leaders as well. In servant leadership [28], leaders also treat the followers and service recipients with humanistic principles.

Based on these theories, it can be argued that the emphasis on humanity in “Service Leadership Theory” has a solid theoretical basis. However, how “humanity” is practiced in actual leadership behavior and what the consequences are remain under-researched. To fill this knowledge gap, the present study attempted to uncover key practices in service leadership that reflect humanity and explore the outcomes of such humanistic practices. To achieve these two research objectives, the present study integrated previous empirical findings with data collected from interviews with Dr. Po Chung (Chairman of HKI-SLAM) and his two colleagues in DHL International.

INTERVIEWS WITH DR. PO CHUNG AND HIS COLLEAGUES

In order to have an in-depth and comprehensive understanding of humanistic practices in the workplace and associated consequences, a qualitative methodology was applied in the present study. Qualitative approaches have been widely employed in social science research as they allow people to express in-depth personal experiences and subjective feelings, so that researchers can have a better understanding of emotions, attitudes, behaviors, and experiences of humans [29, 30]. Among different qualitative methods, narrative inquiry focuses on participants’ stories and events that happened, from which researchers can have an in-depth investigation on participants’ voices, thoughts, and behaviors in a specific context as well as look into how the participants interpret their world and reality [31, 32]. Narrative research also provides a unique and contextual-based evaluation that reveals the occurrence of changes through a personal perspective [33]. Furthermore, narrative inquiry is workable with subjective data collected from different approaches such as autobiographical writing, storytelling, journal record, observation, and interviews [34].

In the present study, we attempted to understand humanistic leadership practices and consequences based on an integration of empirical evidence and individual experience of the key informants. Dr. Po Chung was the first key informant in the present study. The SLT emerged from leadership practices in DHL International, of which Dr. Po Chung was a co-founder. Besides, he is the Chairman of HKI-SLAM established to develop and promote SLT and leadership education. Considering the critical leading role of Dr. Po Chung in DHL International and HKI-SLAM, he is arguably the most important informant to provide insights into how the SLT is developed and how service leadership has been practiced in the workplace. In addition, Dr. Po Chung’s two colleagues (A and B), who had been under his leadership in DHL International for more than 25 years, were also invited to join the present study to provide more details on humanistic service leadership practices and consequences from employees’ perspectives.

Narrative inquiry was conducted by examining Dr. Po Chung’s writings and data collected from semi-structured interviews to underscore Dr. Po Chung’s and his colleagues’ personal views. Interview is a commonly used qualitative tool that can yield “insights into people’s perceptions, understandings and experiences of a given phenomenon and can contribute to in-depth data collection” [35]. Semi-structured interview with open-ended questions is a flexible approach that allows for deep discussion on planned topics as well as follow-up for unexpected answers or issues emerged during the discussion [36].

Data were collected between October 2019 and May 2020 from Dr. Po Chung's writing texts, five individual interviews with Dr. Po Chung and two group interviews with his colleagues. During the interviews, they were invited to share their observations and personal experiences toward different concepts and practices related to SLT, such as how the notions of humanity and 3Cs incorporated in SLT had been put into practice in DHL International and what the influences of these practices were with reference to the service economy. The humanistic practices and related influences in service leadership are the foci of the present study.

Upon Dr. Po Chung's and his colleagues' consent, all the interviews were audiotaped. A well-trained research assistant documented all interviews. Since Cantonese was the medium in some interviews, the transcripts were translated into English by the research team. The informants checked and confirmed the transcripts. All transcripts were analyzed through thematic analysis that is helpful in identifying and analyzing patterns and themes emerged from qualitative data [37]. Data analysis included five steps in the present study. First, an experienced researcher reviewed all data carefully and categorized informants' sharing into condensed summaries on the topic of "humanity." Second, the researcher further identified themes emerged from condensed summaries and merged conceptually similar themes into a broad thematic concept. Third, peer check for the coding was performed by two other experienced researchers in order to ensure the credibility of data analysis and conclusion eventually drawn [38]. Fourth, the responsible researcher further refined the structure and description of the themes based on peer check comments. Finally, the coding was sent to the informants for member checking. After this thematic analytic procedure, four themes related to "humanity" were confirmed. Details of each of them are outlined below.

THEME 1: LEADING PEOPLE IN SERVICE ECONOMY IS TO MOTIVATE AND DEVELOP THEM

In the industrial age where the operation system manifests itself as manufacturing tangible products, leadership mainly focuses on the management of production lines and processes, machines, and operation workers. In contrast, in the post-industrial age (i.e., service era), service provision involves more knowledge, skills, and human interactions. Thus, workers instead of machines serve as imperative assets of a service organization. Just as Chung [39] put it: "In manufacturing, people function as living robots. In service, in contrast, people are engaged to be, to think, and to feel like a person with the agency (the capacity of individuals to act independently and make free choices)." As a result, in service economy, motivating people and facilitating them to have a better achievement become an important agenda for service leaders in leading people. As Dr. Po Chung and his colleagues shared:

"We are in the post-industrial age because the making of things is over, because AI is coming, and we have to be more human to lead other humans. So, we are changing from making things to motivating humans to do better so that humans can become better. And what we are organizing in our, we would have to call it, our set of knowledge, is to become better humans and make humans work better." (From Dr. Po Chung's autobiographical writing).

"We will form groups where middle-level supervisors or bottom-level workers, but not managers, suggest some tactics for improving. And we will organize some sharing sessions after improvement...During the process, all can learn how to be mutually inclusive, help each other, give feedback to each other, and coach each

other...Through the process, each team can learn something within the team and also form other teams. Besides, all members involved can obtain much recognition..." (Colleague A's sharing in the interview).

"We have many line trainers. But how can we identify line trainers from employees? First of all, he or she should be enthusiastic about the work so that he or she can serve as a role model. Then, we will train his or her training skills. Generally speaking, after one employee is certified as a line trainer, he or she will conduct training workshops with all managers as trainees. In fact, we did not expect the benefits associated with the 'line trainer' concept at the very beginning. However, this practice has brought about substantial positive outcomes regarding people development...It fosters the development of communications skills, facilitation skills, and presentation skills among those line trainers. The managers also realize that their followers have the potentials to become 'stars'." (Colleague A's sharing in the interview).

Based on these narratives, it can be argued that one aspect of humanistic leadership in the workplace is motivating and developing followers. This kind of practice has been shown to be beneficial in previous empirical studies as well. For example, Ojokuku, Odetayo and Sajuyigbe [40] found that leadership focusing on developing followers and satisfying their needs was positively associated with organizational performance. Recently, Zheng, Graham, Epitropaki and Snape [41] reported that service leadership in terms of valuing high-quality service and supporting followers was positively associated with followers' work engagement, which further promoted their service performance. These findings suggest that leaders' humanistic practice can effectively motivate followers and enhance their performance.

THEME 2: LEADERS SHOULD BE PEOPLE-ORIENTED AND HELP FOLLOWERS TO FLOURISH

In the service economy, it is desirable to have self-motivated and proactive employees who are engaged and willing to provide high-quality services. Thus, it is also important for leaders to take care of the needs of their followers in order to motivate them and engage them in collaboratively providing services to others and system. As such, Dr. Po Chung strongly advocated people-oriented leadership in service economy. Particularly, in his writings as well as in the present interviews, Dr. Po Chung highlighted the importance and benefits of satisfying employees' psychological needs in terms of the five pursuits of flourish. He treated such needs satisfaction as having psychic income in addition to material benefits. Some narratives are outlined as follows:

"We realize that we have to lead the staff instead of managing them. We have to let them work happily, feel pleasant when they come back to workplace. We also have to take care of their needs if we want them to feel joyful and work diligently" (Dr. Po Chung's sharing in the interview).

"The DHL leaders showed our people how to get joy and fulfillment through service and how to build their psychic income every day. These tenets became quite easy to practice once our people knew what to do and how to do it. Humility is an organic, intuitive behavior in the people we sought to hire" (Dr. Po Chung's writing in the book) [39].

"DHL discovered that motivating, developing, and enculturating a group of couriers to teach them how to gain positive emotional energy or income every chance they could was one key to our success...DHL leaders modeled the practice of saying thank you, smiling, and putting that psychic income into their emotional wallets...Saving these instances of appreciation allows you to deposit this psychic income into your psychic bank account and build stronger, more self-confident, and healthier self-esteem. It's positive emotion: know how to recognize what it is, how to accumulate it, and how to use the psychic income to your benefit. Service generates positive emotion and generates psychic income. It's good for your body, mind, and soul. We thrive on it, live on it, and that's why we all are born wanting to serve others: it's a psychic reward system" (Dr. Po Chung's writing in the book) [39].

“At DHL, we reduced the transactional costs by paying attention to PERMA –a model of psychological well-being and happiness comprising five core elements...Positive emotion, engagement, relationship, meaning, and achievement. The PERMA formula leads to a happy person and creates groups of happy people – and joyful people in a people-service industry naturally deliver and provide better results” (Dr. Po Chung’s writing in the book) [39].

Notably, empirical studies also supported the beneficial influences of people-oriented leadership (e.g., satisfying the five pursuits related to flourishing) on followers’ well-being. For example, Schultz et al. [42] found that employees in service sectors (e.g., finance, health care, marketing, etc.) were more likely to have higher work engagement and a more positive working attitude if their leaders were able to fulfill their pursuit of meaning and accomplishment. Similarly, Slemp, Kern, Patrick and Ryan [43] revealed that leadership with humanistic features (i.e., a focus on communication instead of controlling, respect for employees’ perspectives, encouragement for self-initiation) was positively associated with satisfaction of employees’ needs in being connected and building a positive relationship with others, which in turn resulted in employees’ higher levels of intrinsic motivation and work engagement. In the Service-Leadership education programmes, there are also findings showing that SL attributes such as caring are related to personal well-being [44, 45]. Thus, empirical findings echo the present narrative findings that effective service leaders should enable followers to have psychic income such as a sense of meaning and relatedness, which can further benefit both employees and the organization in the light of higher internal motivation and work engagement as well as positive work attitude.

THEME 3: A BELIEF OF “EVERYONE CAN BE A LEADER”

For humanity in leadership, empowerment is also an important element. In SLT, it is maintained that “everyone can be, or has potential to be a leader” [46]. Dr. Po Chung and his colleagues in DHL International all believed that empowering leadership could bring positive outcomes to both employees and the organization, such as a sense of ownership and better custom relationships. Related narratives are listed below:

“DHL has bottom-up leadership. What we are doing is delivery of service with people orientation instead of managing production lines...They (couriers) keep making decisions and making improvements. We also let them know that their contributions are key to the success of the company, to the success of customers, and also the success of themselves... Therefore, these are psychic income and joyfulness of carrying the job.” (Dr. Po Chung’s sharing in the interview).

“When management pushed decisions to the lowest level, each courier, acting as the CEO of their own route, could design, create, operate, and upgrade their route to the best of their ability in accordance with the situation in their particular city and get psychic reward as a result.” (Dr. Po Chung’s writing in the book) [39].

“...across the company, everyone understands that decision-making is part of the job. This creates the feeling of ownership, responsibility and contribution among everyone, be they a courier, supervisor, city manager, or anyone else...This signals to each employee that they are trusted and that at any given moment they are empowered to take control and take charge...At the corporate level, this brings joyfulness, engagement, contribution and a deep sense of meaning to everyone, no matter where they are in the company...The result is that our people keep building their sense of achievement, self-esteem, and importance, for themselves and for the global network.” (Dr. Po Chung’s writing in the book) [39].

“... like the “Can Do Spirit,” we always highlight in our unspoken culture, which means that you are determined or self-motivated to accomplish the mission, no matter what difficulties you encounter. I think this “Can Do Spirit” is very pervasive. For example, although you are working in DHL in France, if you receive and respond to a request from your colleague in Hong Kong to help deliver a package, you still have to take the

ownership of the task. You cannot say ‘I don’t know as I am on leave’... Instead, you will pay full attention to the progress and try many methods to accomplish the task.’ (Colleague B’s sharing in the interview).

Traditionally, leadership is seen as a means of exerting influence on a group of followers and making them strive for a common goal [47, 48]. Thus, a leader usually is considered inborn, and only those who are “great men and women” can take a leading role [49]. In contrast, the leading role in service economy is not necessarily occupied by those who are already in a higher position (i.e., top-down leadership). Instead, anyone can contribute to decision-making. Particularly, leadership practices exist in everyone’s daily life, ranging from self-improvement efforts to complex leadership acts such as managing a company. In fact, studies showed that leadership qualities can be nurtured and promoted among the general university student population through well-designed leadership education [44, 50].

In addition, as service economy is characterized by complex human interactions, distributed leadership featured with shared decision-making processes is preferred to enable effective communication between service providers and service receipts [6]. Indeed, empirical studies have demonstrated positive outcomes associated with distributed and empowering leadership. For instance, Ghafoor, Qureshi, Khan and Hijazi [51] found that leaders’ empowerment of employees to take control and make decisions was positively linked with employees’ sense of belonging and self-identity in the organization. The findings implied that empowerment gives employees a sense of ownership and makes them psychologically connected to the organization, which in turn increases their commitment and loyalty. Apart from employees’ belongingness, empowerment can also enhance customer satisfaction and relationship. Ahearne, Mathieu and Rapp [52] conducted a research on salespersons from pharmaceutical sector to examine how leadership empowerment behavior influenced the customer satisfaction and relationship. Results showed that leaders’ empowerment exhibited a significant positive influence on employees’ adaptability, which further resulted in a higher level of customer satisfaction.

To sum up, the belief of “everyone can be a leader” enables leaders to empower their followers in the decision-making process as well as to recognize followers’ strengths and contributions. As a humanistic approach in service leadership, empowerment can enhance the employees’ sense of ownership and eventually increase employees’ determination in achieving better performance and providing better services, which benefit all stakeholders involved, including employees, organizations, and customers.

THEME 4: POSITIVE ORGANIZATIONAL OUTCOMES OF PEOPLE-ORIENTED CULTURE

The last theme emerged from the present interview narratives is the positive organizational outcomes of people-oriented culture in service sectors. Given the transformation from the manufacturing era to the service era, a people-oriented organizational culture has to be fostered in response to the complex environment and challenges in service economy. In Dr. Po Chung’s writings and sharing in the interviews, several organizational positive outcomes were acknowledged as a result of the people-oriented culture in DHL International, such as loyalty and commitment to the company. Dr. Po Chung’s colleagues

also indicated in the interviews that an organization with people-oriented culture can make its employees recognize the value and culture of the organization and automatically adapt to such a culture, even if there was no extra effort made to promote the culture. Related narratives are presented below:

“In the competition, judges were confused. Why did this company get such high scores rated by employees on aspects such as loyalty to the company, cultural recognition, and brand recognition? After all, compared with other organizations which had five or more employee programmes such as ‘Women and Family Friendly’ and others, this company only had one programme of ‘Employee of the Year Award’. After I knew the company is DHL, I realize that it is all about those unspoken things and what I can feel instead of those different programmes. In fact, we do not have that kind of programmes. In the best of time in our days, we actually do many fundamental training and projects, and pass the things down to others.” (Colleague A’s sharing in the interview).

“DHL began to formulate clear and reliable guidelines...Pushing decisions to the lowest level...Establish company values that are an extension of family values...These practices generate employee loyalty which, in turn, results in low turnover, institutional memory, and institutional partner relationships. Maintaining a continual sea of familiar, friendly, smiling faces enabled DHL to facilitate ease in inspiring the people to find daily positive energy from making contributions to the company. (Dr. Po Chung’s writing in the book) [39].

In addition to the present qualitative findings, previous empirical research also revealed that a people-oriented organizational culture leads to positive organizational outcomes. For example, Liu, Zhang and Xiong [53] investigated how organizational culture impacted employees’ commitment to the organization. They found that a people-oriented organizational culture and climate (e.g., openness to the employees) exerted a significant positive influence on employees’ affective and normative commitment to their organizations. Similarly, Suharti and Suliyanto [54] identified a positive association between the people-oriented organizational culture and employees’ loyalty. Their study highlighted that a people-oriented organizational culture characterized by the supportive attitude to employees, open climate, and the focus on satisfying employees’ needs was able to cultivate more engaged employees who showed high loyalty and strong intention to stay in the organization.

A possible explanation of the above observation is that a supportive and people-oriented organizational culture is arguably conducive to employees to achieve human needs satisfaction in the organizational context, which in turn promotes employees’ commitment to the organization. Under a positive and people-oriented organizational culture, employees are more engaged, feel proud to work and psychologically safe, which could maintain their loyalty to the organizations. To conclude, both the present findings related to the fourth theme and previous empirical evidence suggest the benefits of building a people-oriented organizational culture in service economy.

DISCUSSION

Using a qualitative research inquiry, the present study attempted to integrate the humanity notion advocated in the “Service leadership theory” (SLT) with existing psychological theories and empirical findings. The present study has several unique features. First, it links qualitative experience toward humanistic leadership practices in the workplace with theoretical models and empirical research findings. Second, the qualitative data were obtained from key informants, including the person (i.e., Dr. Po Chung) who developed the

SLT and two employees who worked under Dr. Po Chung's leadership for over 25 years in the organization (i.e., DHL International) where SLT has been put into practice since its establishment. Thus, all three informants can provide first-hand information about the humanistic leadership practices and related consequences in a service sector. Third, the qualitative data collected in the present was interpreted with reference to the existing empirical literature, which advances our understanding of the importance and influence of humanistic leadership in service economy.

Three important observations in the present study could be highlighted. First, humanistic leadership includes a wide range of practices, such as taking care of employees' needs, developing their skills, empowering them to take initiations and make decisions, and recognizing their values and contributions. Generally speaking, these humanistic practices can be classified into two major groups: one is the facilitation of employees' development and the other is empowering them to take a leading role under certain situations. These two aspects in fact reflect efforts to fulfill employees' needs at different levels. For example, promotion of employees' development is a means of satisfying needs of competence and self-esteem highlighted in "self-determination theory" (SDT) and "Maslow's hierarchy of needs." Leaders' empowerment to followers to make decisions and take a leading role in certain circumstances help fulfill the needs of autonomy, relationship, sense of belonging, self-actualization, meaning, accomplishment, etc. All these humanistic features reflect a basic principle that "human assets" are fundamental to secure service advantages in a service era [4].

Second, among the above-mentioned elements in humanistic leadership, the belief and practice of "everyone can be a leader" deserves emphasis. This notion reflects a sharp contrast to the traditional perspective that leadership is owned by elites or powerful people at a high position. SLT believes that leadership qualities can be nurtured. The present qualitative findings suggest that such a notion has been put into practice in the business world. Future research should further investigate the universality of the practice in service economy. In addition, such a belief is also applicable in leadership education so that every student can be nurtured to become an effective leader [55]. In fact, several universities in Hong Kong have implemented service leadership curricula or training programmes for university students who wish to develop and improve their leadership qualities [11, 56, 57]. Evaluation findings also showed that such leadership education is effective in promoting students' service leadership attributes as well as well-being [44, 58]. Future efforts should be devoted to expanding humanistic leadership education [59].

The third observation is that humanity in leadership is not only beneficial to the leader and followers, but also leads to better organizational outcomes. The qualitative narratives in the present study revealed that people-orientation in leadership practices in DHL International resulted in employees' strong sense of ownership, loyalty, commitment, and better custom relationships. The experiences shared by Dr. Po Chung and his colleagues are congruent with previous quantitative findings showing positive linkages between humanistic leadership characteristics and positive outcomes at both individual and organizational levels [51, 54]. There is also theoretical discussion on the influences of humanistic leadership on organizational culture and external parties' satisfaction [60]. While most of the previous studies we referred to in the present study were conducted in the Western context, the present qualitative findings obtained in a Chinese community further suggest that the benefits of humanistic leadership could be universal. This speculation calls for further investigation.

The present paper has several limitations. First, an inherent limitation of the present qualitative study is that there might be bias in data interpretation. For example, the interpretations could be influenced by the researcher's own experience and perspectives, thus affecting the reliability of the research findings. To reduce such possibility, several measures were applied in data analysis and interpretation processes to minimize potential bias, including peer as well as member checking for the coding [38]. Nevertheless, further studies could utilize both qualitative and quantitative methods to triangulate the related findings. Second, qualitative data were collected from three key informants. Although they were experienced with reference to service leadership practice, additional interviewees could be involved to yield richer data from different perspectives. For instance, sharing from front-line couriers in DHL International could help us understand the influence of humanistic leadership from the bottom. It is quite possible that empowering not only gives employees chances to make the decision and actualize potentials but also puts challenges and pressures on them. Finally, the present paper mainly focuses on how humanistic leadership has been practiced and the associated influences, future research will benefit from further examining the antecedents of humanistic leadership in both East and West contexts.

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Chapter 150

MORAL CHARACTER IN THE SERVICE LEADERSHIP THEORY

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ABSTRACT

Human interaction is fundamental in a service economy where service providers provide service to service recipients. As such, whether service is provided in an ethical way is of paramount importance. In the Service Leadership Theory (SLT) proposed by Dr. Po Chung, Co-Founder of DHL International, moral character is regarded as a vital component of successful service leadership. Through the interviews with Dr. Po Chung and his colleagues and an examination of the published work in SLT, we attempted to answer three questions in this paper: a) why is moral character important in the service economy? b) how is moral character conceived in the SLT? c) how is moral character manifested in the organizational culture of DHL International? We also reviewed the concept of moral character in the existing leadership models and research with reference to the SLT. It is concluded that moral character is an important element of successful leadership in the Western and Chinese contexts.

INTRODUCTION

Moral character has been drawing scholarly attention from different researchers because it influences individual, family, and organizational development. As an essential branch of philosophy, moral character has generally been conceptualized as what is good or bad, right or wrong, virtue or vice, and fair or unfair. It relates to values that people attribute to a system of beliefs [1, 2]. Morality, morals, and ethics are often regarded as synonyms sharing similar

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meanings with slight differences: morality referring to the patterns of thought, action and decision operative in everyday life; moral values (honesty and integrity) attributing to a system of beliefs; and ethics about actions and decisions [2].

The high relevance of ethical concerns in organizations has led to the emergence of a growing body of literature on moral character in leadership and business. According to Giacalone and Thompson [3], moral character plays a critical role in influencing people's way of thinking and decision-making. According to Joyner and Payne [4], good ethics could positively impact the economic performance of companies in the service economy, supporting the idea that "good ethics is good business." In addition, research revealed that a better match between personal and organizational ethics could lead to higher levels of employees' commitment and job satisfaction, and lower levels of turnover intent [5]. According to Bedi, Alpaslan and Green [6], ethical leadership is positively related to followers' perception of leaders' interactional fairness and transformational leadership, as well as followers' ethical behaviors. On the contrary, immoral behaviors in organizations, such as corruption and abusive leadership, will erode consumer confidence and hinder organizational development [7]. Thus, moral character may be invisible in daily operations but crucial for the long-lasting development of an organization.

A Service Era

The world is moving to a service economy. According to the statistics of The World Bank, service sectors have contributed over 60% to the world's total Gross Domestic Product (GDP) since the year of 2000 [8]. The service economy in developed countries occupies a high percentage of the total GDP, such as Israel (69.8%), Japan (69.1%), and Canada (66.7%) in 2018 [8]. Famous for its finance, trade, law, and other services, Hong Kong is undoubtedly a service economy. The service sectors in Hong Kong accounted for 92.2% to the total GDP in 2008, and for 93.1% in 2017 [9]. More than 87% of the total working population in Hong Kong are employed in the service sectors [9]. Besides, many developing countries have witnessed a big rise in the size of the service economy in recent years. For example, China has made great efforts to transform from a manufacturing economy to a service economy. A considerable amount of work and resources have been devoted to service sectors, such as scientific services, high-technology services, and other higher-end services [10]. The size of service sectors in China has doubled in the last two decades to account for 52.2% of the total GDP in 2018 [11]. In line with the trend, the service economy emphasizes quality humanistic service and sets new requirements for leadership qualities, which calls for a new leadership theory to better understand the key to effective service organizations.

The Service Leadership Theory

Dr. Po Chung, the Co-Founder of DHL International and Chairman of Hong Kong Institute of Service Leadership & Management (HKI-SLAM), has proposed the Service Leadership Theory (SLT) in the context of a service economy [12]. Unlike traditional leadership concepts, the SLT fits the needs of the service economy by reflecting a service

mind through principles such as “to serve to lead” and “for the benefits of others”, instead of a sole focus on the interests of the leaders or goal completion [13]. According to the SLT, service leaders should “do the right things” rather than only “do the things right.” The SLT aims to answer the question: What type of leaders or leadership does the service economy need? According to the SLT, effective service leaders should possess Competence, Character, and Care (the 3Cs). In other words, service leaders are those who have proper soft skills and abilities, personal growth, and moral standards, but not necessarily the ones associating with certain positions [14]. Numerous studies have evinced that the SLT is a useful framework in guiding personnel development programs to promote soft skills and well-being [15].

In an interview, Dr. Chung expressed his ideas on leadership and leaders referring to his career at DHL International that trust, the 3Cs (especially character) and the mindset of serving clients at a humanistic level are the qualities that service leaders should possess [16]. In his leadership, DHL International is a company that practices service leadership, aiming at promoting people’s lives through providing green logistics [17]. Shouldering the social responsibilities, DHL International displays a good company moral character in the processes of meeting the needs of its clients and the natural environment. Therefore, by taking DHL International as an example, this paper attempted to explore the moral practices in a service-oriented company in the service economy era.

Based on the above literature review, three research questions were framed in the present study:

1. Why is moral character essential in the service economy?
2. How is moral character conceived in the SLT?
3. How is moral character manifested in the organizational culture of DHL International?

OUR STUDY

A qualitative approach was used in the present study to understand moral character as well as DHL International’s moral practices in the framework of the SLT. Compared to quantitative research, which often focuses on “searching for truth”, qualitative research aims to “bring meaning to a situation” [18]. In the present study, the data were collected through Dr. Chung’s autobiographical writings, individual interviews with Dr. Chung, and group interviews with Dr. Chung’s colleagues. One of the main advantages of autobiographical writings is that this method allows the author to recall memories and give sense and meanings. It also allows the researchers to have a higher level of interpretation through the author’s reflection. Interviews give the interviewee(s) opportunities to express views verbally, allow the interviewer(s) to improvise follow-up questions based on the responses, and foster reciprocity between the interviewer(s) and interviewee(s) [19]. In addition, group interviews provide information about ideas and perceptions that a group of individuals have on certain issues. Group interviews illuminate the similarities and differences between the perspectives of a group of individuals [18] which can serve as a strategy for triangulation.

Data Collection

The data were collected between October 2019 and May 2020, which included Dr. Chung’s autographical writing texts, five individual interviews with Dr. Chung, and two group interviews with two of Dr. Chung’s former DHL International colleagues.

Dr. Chung was firstly invited to write about his experiences related to the origin and development of the SLT. The autobiographical writings provided contextual information for researchers to make an initial inquiry for interviews. Based on Dr. Chung’s writing texts, his publications on the SLT and its application in DHL International, and a review of the existing academic literature, the initial interview questions were developed. Three researchers reviewed the questions and provided feedback and comments regarding the relevance and appropriateness of the questions. The questions were then revisited and refined accordingly, resulting in a semi-structured interview protocol. Interviews with Dr. Chung aimed to understand moral character as a desired leadership quality within the framework of the SLT. Interviews with Dr. Chung’s two former colleagues focused on their perceptions of the organizational environment and the practices promoting moral character in DHL International. The interview questions with Dr. Chung and his colleagues are listed in table 1 and table 2, respectively.

Table 1. Interview questions with Dr. Chung

1	What is the role of moral character in effective service leadership?
2	What types of character do you believe are crucial in establishing effective leadership in DHL International? Can you give us some examples of those most important ones?
3	Do you think adopting traditional Confucian values in leadership practice can help promote moral character? Can you give us some examples based on your experiences?
4	How does DHL International build a healthy culture or habitat to recruit, retain, and promote employers with characters? Could you share some examples with us?
5	Do you think it is difficult to keep a balance between moral character, well-being, and profit in a context where profit is still highly valued by the market? Why?

Table 2. Interview questions with Dr. Chung’s two former colleagues

1	Service Leadership Model upholds the 3Cs (Competence, Character and Care). What are your views on this model?
2	One of the Cs is character. What are your views on the Service Leadership Theory?
3	What character attributes do you believe are crucial in establishing effective leadership in DHL International? How does DHL International incorporate these character attributes in leadership practices? Could you give us some examples?
4	In your opinion, what are the challenges/difficulties of applying Service Leadership Theory (e.g., 3Cs)? Any examples in DHL International? And what strategies did DHL International use to deal with these challenges/difficulties?
5	Do you practice the Service Leadership Model? Any personal reflections?

The interviews were conducted by two researchers who were familiar with the SLT and made Dr. Chung’s acquaintance prior to the interview. Based on Dr. Chung’s recommendations, two of his former DHL International colleagues, Mr. A and Ms. T, were invited to participate in the group interviews. Both of them were senior staff with more than 25 years of working experience at DHL International. In total, five interviews were conducted with Dr. Chung, and two group interviews were conducted with Mr. A and Ms. T. Before

each interview, the researchers obtained permission from the interviewee(s) to record the interview.

Data Analysis

All interviews were transcribed verbatim. Thematic analysis was used in the data analysis to develop a coding scheme [20]. In the process of data analysis, the research objectives were explicitly communicated to three researchers. Firstly, a researcher reviewed the transcripts to gain a general and holistic sense of the data and independently selected the contents relevant to research questions and preliminarily identified themes. Secondly, the researcher revisited the scripts and revised the codes and themes to improve the alignment between themes and research questions. New themes were added as they emerged. Thirdly, the codes and themes were peer-checked by another researcher. The two researchers had several rounds of discussion to determine the level of connectedness and improve coding reliability. Fourthly, the revised codes and themes were again peer-checked by a third researcher who was experienced in qualitative research and had good knowledge of the SLT to maintain the credibility of the data analyses [21]. Adjustments were further made in coding and themes based on the feedback. All the autobiographical writings and interview transcripts were analyzed with RQDA (an R package for qualitative analysis) [22].

OUR FINDINGS

Dr. Chung underscored the indispensability of moral character in the SLT from different perspectives, including the requirements of the service economy, the positive outcomes that moral character drives, and the negative outcomes brought by a lack of moral character.

The Requirement of a Service Economy

In Dr. Chung's book entitled "The 12 Dimensions of a Service Leader", moral character has been argued as the most critical element of one's personal brand. Dr. Chung suggested that the shift from a manufacturing economy to a service economy has made people, instead of machines, the key to successful business development, which calls for a new set of leadership qualities that are different from what has been desired in a manufacturing economy:

"One of the aims of Service Leadership training is to highlight the crucial role that a leader's character for success in a service organization. Service isn't necessarily customer service, by the way, but across a network of people who are united by a vision and positive energy. Therefore, a person's character is of the kind that is free from the toxic behaviors and qualities that erode trust across those in the group" (Dr. Chung's autobiographical writing)

More specifically, in a manufacturing economy, leaders who have strong managerial skills are considered effective in improving collective productivity and efficiency. Meanwhile, moral character does not often gain particular emphasis in the manufacturing economy, and

sometimes can be even downplayed when potential conflicts between ethical standards and economic efficiency may occur. In contrast, the service economy highly demands for people skills to attract, maintain, and develop followers, to build and promote trustful relationships in the internal and external environments of organizations. Dr. Chung explicitly differentiated leading from managing in the two types of economies:

“Management is all about operational efficiency, stability, and excellence – in short, doing things ‘right’ or well. In our view, leadership is more about doing the right things with the right heart. This is about ensuring that what a company does is aligned with human values and needs, resulting in the greatest good for communities and stakeholders” (Dr. Chung’s autobiographical writing)

In Dr. Chung’s opinion, the economic transformation from a manufacturing economy to a service economy reshapes the relationship between leaders and subordinates. Leaders are those who attract and keep followers, but not necessarily the ones occupying managerial positions:

“It is the position that defines the relationship between managers and subordinates. However, for leaders, the relationship is defined by followers. You need to be followed by someone before you can be called a leader” (Dr. Chung’s autobiographical writing)

“It’s a human-relationship thing instead of an employment thing. The follower follows you because he finds things that he can get from you. So what is in it for me to follow you? You are not paying me to follow you. It is volunteering, a will to follow you. So it’s a human relation instead of an employment relation” (The first interview with Dr. Chung)

In this regard, if leaders have flaws in their character, they are not able to maintain followers in the long run or build a healthy organizational climate:

“The most important thing in a follower following you is after they ask the question to themselves - not necessarily asking you - that ‘what’s in it for me? What benefit will I get if I follow you?’ So usually there are three things to consider: I can learn things from you, I find there are qualities that I can trust and respect you, and at least you don’t have the qualities that push me away. So these are the pulling forces” (The first interview with Dr. Chung)

One important belief of the SLT is that service leaders need to provide quality service to everyone that one interacts with, including oneself, others, groups, communities, systems, and environments [23]. In Dr. Chung’s opinion, leaders in the service economy should provide quality service to followers, such as effective mentoring, to promote followers’ competence and character building. In this regard, leaders’ moral character is essentially required by the service economy to attract and keep followers:

“The Service Leadership model I designed, on the other hand, is most interested in helping a leader improve their character through careful self-knowledge, self-governance and commitment to continuous learning and development. To put it another way, that a leader’s greatest self-actualization comes by helping everyone in his or her network meet all their needs, including each person’s individual self-actualization” (Dr. Chung’s autobiographical writing).

The Positive Outcomes of Moral Character

As discussed earlier, existing research has linked leaders' moral character to various outcomes at both the individual and organizational levels, such as leaders' and followers' job satisfaction, organizational commitment, cohesion, collaboration, and work performance [24, 25]. Promoting ethical codes will also improve the leader-follower relationship within a company [26]. Dr. Chung also joined the agreement that solid ethical codes of a company promote its competitiveness, particularly through building trust in both internal and external relationships. In Chung's opinion, leaders with good moral characters can attract the best people and motivate them to give full play to their potential in work. Dr. Chung particularly challenged the mindset that "if you want to make more profits, you have to give up care, or give up character." He holds the belief that if a leader pays a lot of attention to character and care, and learns the competences of leading and motivating followers, the leader can get both:

"It's not an 'either/or' question. Yes, if you keep your eyes only on money, which is profit, you think that you don't have to pay attention to the other things. In a manufacturing economy, it can be true because when facing a production line, you'll improve the management and knows how to manage the robots. But people hold that belief forget that humans are not robots. If you can lead them better with a heart while doing the right thing, people would work faster, work better. On the production line, everybody controls other people's speed. But on the service line, it's not. It's whether you put your heart into, and your smile, and take what you learn from being a leader and take it home, and treat your spouse better, your children better, your in-laws better, your cousins better. The whole tribe benefit...it is not only the balance but what you do as a priority. If you put character as a priority, what you would do is make good people stay with you longer, so that you don't have a turnover" (The first interview with Dr. Chung)

As to the external relationship with customers and the public, Dr. Chung argued that treating customers with good character behaviors such as respect, courtesy and fairness will result in a trustful relationship between customers and companies. When customers are well-treated, they tend to establish a long-term business relationship [27]. Moreover, ethics can be a powerful marketing advantage for a company because the service relationship depends on these hidden qualities that are often unspoken and unwritten [27].

Negative Outcomes When There is a Lack of Moral Character

Dr. Chung applies the Anna Karenina principle to demonstrate the negative outcomes due to a lack of character. Adapted from the opening sentence of Leo Tolstoy's novel *Anna Karenina* that "all happy families are alike; each unhappy family is unhappy in its own way," the Anna Karenina principle states that a deficiency in any factor required for success dooms an endeavor to failure. In other words, a successful endeavor should be free of any possible deficiencies. Dr. Chung applies this principle in understanding the importance of moral character:

"A lack of character can get you in all kinds of troubles, and there are thousands of ways of having bad character... Followers will follow leaders as long as they can learn things from leaders. However, if there are values in leaders' behavior that push followers away, the followers will leave after learned what they wanted to learn" (The first interview with Dr. Chung)

Dr. Chung discussed different negative consequences caused by a lack of good moral character. A lack of good character immediately impairs interpersonal relationships and threatens the company culture. Even if the unethical person has not cheated others, the knowledge that one may act unethically toward others stops people from maintaining the relationship and encourages them to establish collaboration with morally sound people:

“There are leaders who think that as long as I have all the competence, it would be okay. But, if you have all the competence, but no character and no care, you cannot keep people’s loyalty and their heart and their stay. They will look for somebody that has the same competence but also has the character and the care. This is how it operates in an open environment; in a closed environment, there’s nowhere you can go, then people just live under fear and control” (The fifth interview with Dr. Chung)

Dr. Chung’s colleagues shared the same view that a leader’s character is essential in attracting committed followers. One colleague pointed out that:

“Leaders are all the time being observed by others around them. People will evaluate your competence - which is very basic - and people will also evaluate leaders as a person. Leaders need to be fair and just. Otherwise, no one will follow them” (The first interview with Dr. Chung’s colleagues)

In Dr. Chung’s opinion, in a service economy where people are the key to successful service, a high turnover rate essentially means a significant threat to a company’s competitiveness:

“When the best ones left, you could not keep the best team. So, if you want to maintain competitiveness, recruit the best people, maintain the best people, and keep them for a long time” (The third interview with Dr. Chung)

“If your best people keep on leaving because you have no character, your competitor will get your people. So you may be started as the best company, but every eight months, one of your best people joins your competitor, then two years later, you won’t be the best company in providing a service” (The first interview with Dr. Chung)

When the flaws in character further develop and leaders turn a blind eye toward immoral practices, a lack of moral character can cause a serious public relations crisis. There have been cases involving companies that abuse customer profiles. These moral crises also cost companies much to enforce internal ethics codes and to restore public trust. Although no companies will include respect, courtesy, fairness and the trust results from these qualities in any contract, lacking these qualities can “prove empty and sterile to both the customer and to the service provider” [27]. Dr. Chung argued that leaders lacking essential moral character can cause dysfunction of the team and even the entire organization:

“If you have somebody lacking character but taking managerial positions, the team will not work. A lack of character will make it go wrong. For example, if people at the middle level involve a “MeToo” issue, your entire organization will not work” (The third interview with Dr. Chung)

Dr. Chung’s colleagues raised an interesting point concerned with the changing dynamics of the company culture, which reflect the reciprocal influence between workplace values and personal values. A leader with moral characters will attract followers sharing the same values, which in turn strengthens the moral climate of a company. In contrast, a leader lacking moral qualities or tolerating other’s immoral behaviors will expel followers, which will consequently undermine the ethical foundation of a company:

“Although we all know the saying that ‘don’t think any vice trivial, and so practice it; don’t think any virtue trivial, and so neglect it,’ sometimes people feel that ‘it doesn’t matter and nobody knows what we did.’ Then this value will be slowly instilled and integrated as one’s own belief. This belief will affect our behavior and even change our life trajectory. If a company prioritizes performance and considers money everything, it is not a service-mind company, but a business-target-driven company. In fact, in such a company, human nature will be distorted” (The second interview with Dr. Chung’s colleagues)

“People who are evaluated by others as “not satisfactory” normally don’t last very long, as they don’t feel comfortable staying here and they had a hard time. Once I had a superior who was competent but often gave comments that made me felt being despised. That person could not fit in our culture and both he and the people around him felt stressed. He left DHL after half a year. In such a short time period, he quitted due to a mismatch with the culture in DHL” (The second interview with Dr. Chung’s colleagues)

This idea actually reflects the notion of person-organization fit, which means the compatibility between individuals and organizations [28]. Person-organization fit can be based on goals and values. Research indicated that organizational ethical values were positively linked to organizational commitment and person-organization fit. In addition, literature also supports that the exchange between individuals and organizations, and the expectations about reciprocity can influence individuals’ adjustment to the organizational culture [28, 29]. It is suggested that companies should adopt ethical policies that increase individual perceptions of an ethical company environment [30].

The Conceptualization of Moral Character in the SLT

As mentioned above, moral character is listed as one of the core 3Cs in the SLT. Different from most leadership models that primarily highlight the existence of specific virtues and conducts when conceptualizing moral character, Dr. Chung adopts the “opposite” perspective emphasizing the avoidance of a lack of any critical virtues. According to Dr. Chung, each tradition has a variant of the Golden Rule, which advises doing unto others as one would have done unto oneself. The reverse can be called the Silver Rule, which is an inversion of the Golden Rule, advising people to avoid the behaviors that one would not want to be done unto oneself. More specifically, the Golden Rule highlights the proactive gold standards instructing one’s behaviors. In other words, it tells people how to behave altruistically. The Silver Rule, in contrast, is not against the existence of self-interest, but against asocial self-interest or egoism [31]. It tells people to “first do no harm.” The Silver Rule provides demanding standards for one’s behaviors and requires people to view behaviors from others’ perspectives [32].

Dr. Chung found it challenging to communicate about the Golden Rule to students because people understand morality differently and adopt diverse personal codes of ethics. However, identifying immoral behaviors is far less controversial than defining moral behaviors [33]. Dr. Chung believed that it could be an easy and straightforward way to define moral character by using “double negative” notions:

“If our humanity is looking for a leader, we need to find out if they have a deficit in these places. It is a very succinct and simple way to explain what character means. Character means that you don’t do immoral things” (The third interview with Dr. Chung)

Table 3. Thirteen Confucian virtues and the adapted “negative” virtues

Confucian virtues (The Golden Rule)	Adapted Confucian “negative” virtues (The Silver Rule)
Kindness	Don’t be unkind.
Righteousness	Don’t be unfair.
Respect	Don’t be rude.
Wisdom	Don’t be foolish.
Trustworthiness	Don’t be untrustworthy.
Loyalty	Don’t be disloyal.
Courage	Don’t be cowardly.
Uncorrupted	Don’t be corruptible.
Shame	Don’t be shameless.
Care for the old	Don’t abuse the old.
Care for the young	Don’t abuse the young.
Self-correction	Don’t refuse to correct when you are wrong.
Forgiveness	Don’t hold a grudge.

In Asian societies where Confucianism dominates social life and values, there are sayings reflecting the Silver Rule. Table 3 outlines the opposite notions of 13 Confucius values [33].

In Dr. Chung’s opinion, people who take leadership roles need to go a step further than only adopting the Silver Rule as personal codes of ethics. To keep the best followers sharing the same values, leaders also need to protect the whole team by showing zero tolerance towards others’ immoral behaviors in the workplace:

“When you are the leader, not steal, not cheat, and not lie are not enough because when you are the leader, these rules are a little bit short. You have to say, ‘I would not cheat, I would not lie, I would not steal, and I would not tolerate those people who do.’ Then people around you, your friends, your relatives, and people who follow you or your peers will feel that you are looking after each other” (The first interview with Dr. Chung)

Dr. Chung’s incorporation of Confucian values into leadership practices has been supported by the literature. Ip [34] reviewed the application of the core elements of Confucianism in modern business and proposed a notion of “Confucian firm” with idiosyncratic concepts of the moral person (Junzi), benign social structure (He), relationships (guanxi), and core human morality (ren, yi, li). It was concluded that Confucian values, such as familial collectivism, have implications for business in Chinese societies. According to Spitzer [35], the Silver Rule can be restated in a functional language as “avoid harming others.” Leadership adopting the Silver Rule provides the first and fundamental rule of ethics for people to live out.

The Emphasis of Moral Character in the Organization Culture of DHL International

Moral character has been highly valued in DHL International culture. According to Dr. Chung, although family education and early experiences play critical roles in forming one’s personal codes of ethics, the source of one’s moral standards involves both nature and nurture [27]. Many practices in DHL International have been designed and implemented to identify and promote vital moral qualities valued by the company.

Practices Identifying One's Character in the Personnel Decision-Making Process

According to Dr. Chung, one's personal ethics and a set of character attributes will be brought to the job. In DHL International, the selection mantra, "Hire for character, train for skills," has been adopted in the hiring process [27]. Dr. Chung stresses the importance of well-designed hiring processes and well-trained interviewers to reveal character traits and tendencies of the candidates [27]. In addition, character is a critical item to consider when making a promotion decision. In DHL International's practices, the character of a candidate for a leadership position is evaluated by the people around him/her. The senior staff also serve as gatekeepers:

"If you would like to know one's moral character, you ask other people. For example, when promoting somebody, we talk to people around this person and ask, 'we are promoting one of the supervisors to be the assistant manager. Other than yourself, who do you think should be that person? Don't pick the most popular one just because that one can tell jokes. But remember, you have to work for this person after he got promoted.' Then people will find somebody who is fair, who thinks correctly, and who understands the vision of the company" (The first interview with Dr. Chung's colleagues)

Besides, when a person has flaws in competence, moral character and care, the person will be assessed and subject to dismissal. Besides, the person having flaws in character will not be promoted:

"After three or four times being passed over for promotion, they will tend to leave the company. They either blame the company for not promoting them or they realize that something about them is the reason not being promoted after our coaching" (The fourth interview with Dr. Chung)

Practices Promoting Moral Knowledge and Climate

In DHL International, moral knowledge and practices are promoted through company codes of ethics and through on-the-job mentoring. Personnel development programs are designed to equip staff with a service mindset, people skills, and other abilities and knowledge to better align personal values to workplace values. According to Dr. Chung's colleagues, many of the DHL International personnel developmental programs gave sufficient attention to character-building:

"It is not possible to teach all couriers all contingent solutions to all situations. The only possible way is to teach them how to be a good person. If they go back home and behave the same, it means that they are touched" (The first interview with Dr. Chung's colleagues)

In practice, the development programs refreshed participants' mindsets about service and helped them become more competent in leading themselves and others. One colleague highly acknowledged the benefits of these development programs:

"When I look back, I realize that our training program is helpful to build character rather than solely teaching skills — although we also teach skills, such as customer service skills, telephone skills and complaint handling skills, the foundation is character building. We all know that one should lead by modeling and should take the initiative to make things better. The training helped me to reflect on myself instead of criticizing,

condemning, or complaining. With good character, you will treat colleagues and costumers nicely. It even benefits my family life, as I am now happy to be the one taking proactive steps and initiating change” (The first interview with Dr. Chung’s colleagues)

In addition to in-house training programs that communicate company ethics codes, DHL International also employs on-the-job mentoring to cultivate core values. In other words, leaders in DHL International are encouraged to lead by example. As a colleague of Dr. Chung mentioned:

“You cannot finish setting rules, but instead, you can lead by example and let people know what is acceptable and what is not” (The second interview with Dr. Chung’s colleagues)

In this regard, Dr. Chung emphasized the importance of self-leadership and the awareness of one’s responsibility to others. In particular, senior staff taking the leading positions need to consistently reflect on and improve themselves:

“In the beginning, I’m just a courier; then I become a supervisor; then I become a manager. So every time I go up, I realize that I have to do certain things in this position: when I am a courier, I have to take care of document collection and show a warm smile to my customers; when I deal with the airline and the customers, I have to build the relationship and do business; when I supervise followers, I have to behave. In every step and during times when something comes up, I behave appropriately, and I learn. I’m still learning now, today. It could be I’m still learning here because I have done all there” (The first interview with Dr. Chung)

DISCUSSION AND CONCLUSION

In the study, we addressed the rationale of including moral character as one of the core 3Cs in the SLT, reviewed the conceptualization of moral character rooted in the traditional Chinese values, and explored the manifestation of moral character in the organizational culture of DHL International.

Based on Dr. Chung’s autobiographical writings and the interviews with Dr. Chung and his former DHL International colleagues, we found moral character indispensable for leaders who want to attract the best followers and maintain organizational competitiveness in a service economy. The conceptualization of moral character in the SLT has incorporated traditional Chinese values and philosophies. This integration is in line with the call for interpreting organizational ethical codes and practices in the contexts of social values and culture in recent research [36]. Besides, the application of the Silver Rule can be a straightforward and practical way to communicate the basics of moral character [35].

Our findings also evince the positive impacts that moral leaders and culture can bring, including an increase in the congruence of person-organization fit, followers’ character-building, and organizational commitment. These positive impacts also echo the existing research, which has consistently revealed the positive influence of moral character on both individual and organizational development [25, 37].

Besides, this study discussed ways to promote moral character by exploring the practices in DHL International. Firstly, moral character can be cultivated through well-designed personnel development programs. We suggest that the personnel development programs should pay sufficient attention to cultivating the inner qualities of the staff rather than narrowly focusing on improving their skills. In other words, both the “Being” and the “Doing”

aspects of human qualities should be incorporated in the development programs. Besides on-the-job training, the preparation for university students to appreciate the importance of Service Leadership qualities is also important [15]. Secondly, the cultivation of character will trigger positive changes in employees' ethical mindset and behaviors in the workplace and even in personal life [38, 39]. Also, the interaction between individual and organizational values results in changing dynamics of organizational ethics, which yields important insights for promoting the ethical culture of organizations in the long run.

While this study highlights the importance of moral character based on the analyses of the published work of Dr. Po Chung and interviews with him and his colleagues, this study has some limitations. First, our analyses were based on Dr. Chung's autobiographical writings and interviews with Dr. Chung and two senior colleagues. It would be more interesting to invite some junior staff to share their perceptions of the manifestation of moral character in DHL International. Second, other data sources, such as field observations and text analysis of company documentation, can be informative to evaluate the applications to promote moral character in DHL International. Third, quantitative data could be collected from employees of DHL International to triangulate the qualitative findings of the present study.

Despite the limitations, this study provides insights into the moral character literature by exploring moral character in the framework of the SLT. We also reviewed the concept of moral character in the existing leadership models and research concerning SLT. We can draw the conclusion that moral character is considered critical leadership quality in different leadership models in both Western and Chinese contexts.

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Chapter 151

THE DARK SIDE OF LEADERSHIP IN THE SERVICE LEADERSHIP THEORY

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ABSTRACT

The dark side of leadership is not uncommon in the business world. It is often driven by a pursuit of short-term personal interests at the cost of others and organizations. Existing literature has revealed its negative influences on individual and organizational outcomes, such as employee motivation, interpersonal relationship, and organizational effectiveness. In the service economy, the dark side of leadership may bring even greater destructive outcomes to individuals and organizations as it undermines the quality of service and people relationships that are highly valued in the service economy. As such, to prevent the dark side of leadership is of paramount importance. According to the service leadership theory (SLT) proposed by Dr. Po Chung, Co-Founder of DHL International, the dark side of leadership occurs when leaders lack Competence, Character, or Care. Through interviews with Dr. Po Chung and his former colleagues in DHL, as well as an exploration on Dr. Po Chung's autobiographical writings, we tried to understand the dark side of leadership in the service economy under the framework of the SLT, and the practices adopted by DHL International to prevent it. Results indicate that the conceptualization and destructive impacts of the dark side of leadership in the SLT echo existing academic research. In addition, results also highlight practices and strategies adopted by DHL International to prevent the dark side of leadership.

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INTRODUCTION

The dark side of leadership in business contexts is not uncommon. We watch news media demonstrating how “dark” leaders tarnish a company’s reputation, damage its market value and even make people suffer. The dark side of leadership has gained scholarly attention in recent decades and has become one popular research topic in the field of management [1]. Different terms are used in the literature to depict the characteristics of the dark side of leadership, such as undermining, destructive, unethical, negative, tyrannical, abusive, toxic, and derailed leadership [1, 2].

Existing research has provided different definitions of the dark side of leadership. McIntosh and Rima [3] defined it as the inner urges, compulsions, and dysfunctions of leaders’ personalities. Bass and Steidlmeier [4] indicated that the dark side of leadership occurs when leaders serve with bad faith. Similarly, Aasland et al. [5] argued that the concept of the dark side of leadership is broad and involves different behaviors. In their overarching definition, destructive leaders refer to those who repeatedly violate the interest, goals, and resources of organizations, and obstruct motivation, job satisfaction, and effectiveness of followers [6]. According to Eisenbeiß and Brodbeck [7], unethical leadership refers to leaders’ behaviors that violate the moral standards and promote unethical conducts in organizations [8]. Schilling summarized the characteristics of negative leadership, which include insincerity, despot, exploitation, restriction, failure, laissez-faire, and passive leadership [9]. Furthermore, Aryee et al. [10] and Whitman et al. [11] suggested that the dark side of leadership is reflected in uncaring and humiliating behaviors towards subordinates. For example, leaders using abusive supervision tend to yell at subordinates, which increases their stress level and threatens their security and career development. Besides, supervisors’ undermining behavior means unfavorable treatment of the followers aiming to prevent them from achieving individuals’ goals [12]. According to Duffy et al. [13], supervisors’ undermining behaviors include repressing followers when they raise questions, belittling their ideas, talking down to them, subverting their efforts, and making them feel incompetent. Also, derailed leadership displays uncaring or unethical behaviors towards followers, such as bullying or harassment [6]. McCall and Lombardo [14] indicated that derailed leaders have poor management skills and are insensitive to followers when demonstrating intimidating and humiliating style.

Apart from different definitions and conceptualizations of the dark side of leadership, scholars have also explored its negative influences on individuals and organizations. For individuals, the negative impacts can be work-related or life-related [2]. In the workplace, Tepper and his colleagues [15] pointed out that abusive supervision in leadership would increase followers’ resistance to the leaders and lower the level of job satisfaction [16, 17]. In addition, Aryee and his colleagues [10] pointed out that followers who perceived their leaders as destructive were less likely to dedicate to their job. Similarly, Liu and his colleagues [18] found that abusive supervision in leadership led to a cascade of followers’ creativity as it undermined followers’ intrinsic motivation. For the life-related aspect, empirical findings have suggested a close relationship between abusive supervision and more significant work-family conflicts based on employee’s perceptions. For example, Tepper [18] reported that the followers who experienced higher levels of abusive supervision reported a more significant negative spillover from their work to their family life, as they perceived oppression and

injustice in their work. Hoobler and Brass [19] argued that an abusive leader could extend the subversion to the subordinates' family members, such as their parents and spouse.

The dark side of leadership also harms organizational relationship, climate, and effectiveness [2]. Li and Zhu [20] found that destructive leadership provokes followers' negative emotions and undermines organizational cohesion, interpersonal harmony, and task collaboration among employees [16, 21-23]. Tepper [16] found that subordinates who worked under abusive supervision perceived greater work conflicts and worse relationships with their leaders. Mitchell and Ambrose [24] reported that followers might show "displaced deviance" towards the organization, which was related to retaliation, resistance, and negative behaviors. Ashforth [25] indicated that tyrannical leadership would create work alienation, make followers treat the organization negatively, and increase their turnover intention. Besides, Zhang and Liao [26] also found that abusive supervision brought negative effects to organizational performance through counterproductive interactions and exchanges between subordinates and leaders [27, 28]. Therefore, subordinates were more likely to respond to abusive supervision by being resisting and slack at work. Hence, the dark side of leadership not only erodes personal development but also negatively affects organizational climate and effectiveness.

According to the Service Leader Theory (SLT) proposed by Dr. Po Chung, the Co-Founder of DHL International, Competence, Character, and Care (3Cs) are the three fundamental and indispensable characteristics for an effective service leader [29]. When there is a lack of any of the 3Cs, the dark side of the leadership occurs. Without competence, the leaders are unable to attract and retain high-quality followers in a competitive circumstance. Without a competent leader, the whole team or the organization will lose a clear direction for the long-term development and hardly maintain its competitiveness in an open marketplace [30]. Besides competence, care and character are also vital elements of successful leadership that are strongly emphasized in the SLT. According to Chung [30], people may follow those leaders who are competent but uncaring only for a short period. When followers acquired what they have been longing for, such as leaders' competences or resources, they will leave and follow another leader who has competence, character, and care. A lack of care will shake followers' confidence in leaders and lower their willingness to stay. The deficits in character of leaders threaten interpersonal relationships in organizations, undermine the trust among people, and increase employees' turnover rates. Moreover, leaders without good character will lead the whole organization in the wrong direction by endorsing immoral behaviors, bullying subordinates, and chasing for personal interests at the cost of followers, companies, customers, and even the society. According to the SLT, a lack of any of the 3Cs can cause leadership failure and severe damage to persons and organizations, especially when the destructive leader takes a high position in an organization [2]. This article aims to explore the dark side of leadership under the framework of the SLT based on interviews and autobiographical writings. Three research questions were framed:

1. Why do we need to prevent the dark side of leadership in the service economy?
2. What is the dark side of leadership according to the SLT?
3. How does DHL International prevent the dark side of leadership in practices?

OUR STUDY

As demonstrated above, these constructed research questions seek to enhance our understanding of the dark side of leadership in theory and practice by exploring the perspectives, life stories, and experiences of others. With this epistemological underpinning, a qualitative approach was used as it provides great depth and details when inquiring into human interactions and life events [31]. The qualitative research approach focuses on idiosyncratic meanings created, extended, and expanded by people, and thus highlights openness and invites multiple realities in data collection [31]. Among the methods that embrace a qualitative nature, narrative inquiry is a powerful tool to probe into the complexities of individual life stories through storytelling and personal narratives, and it requires collaboration between the narrator and the narrative researcher to construct the meaning [32]. It aligns well with our research purpose of making in-depth meaning of people's stories and experiences, and therefore it is suitable for the present study. To be specific, the study draws on the methods of autobiographical writing, individual interviews, and group interviews to collect narrative stories from the informants.

The narrative data were collected from October 2019 to May 2020. We first invited Dr. Po Chung as the key informant. He was first asked to complete a piece of autobiographical writing on general topics in the SLT, such as the origin of the SLT and his views on existing leadership models. Based on his autobiographical writing, we conducted five semi-structured interviews with him to follow up on several focused areas including the dark side of leadership. Two of his former colleagues who had worked in DHL International for more than 25 years were also invited for two group interviews. These interviews revolved around their career experiences in DHL and the connection to the SLT, especially how the SLT was applied in daily practice. Informed consent was obtained from the three informants before the data collection.

A well-trained research assistant performed data transcription. The data that were conducted and responded in Cantonese were translated into English. Thematic analysis was employed to generate patterns and themes from the data. First, the chunks of data related to the dark side of leadership were pinned down by three researchers. Second, one researcher identified patterns that occurred, and combined them to themes. Two peers then reviewed the themes and corresponding narrative chunks for the credibility of the data analysis. The initial researcher would revise them based on the feedback. Finally, the refined themes were sent to informants for participant validation.

OUR FINDINGS

RQ1: Why Do We Prevent the Dark Side of Leadership in the Service Economy?

Unlike standardized products in an industrial economy, services in the service economy bear the features of intangibility and heterogeneity, leading to a higher degree of variability, customization, and uncertainty of service products [33, 34]. Furthermore, the production and consumption of service products are simultaneously and inseparable, and thus the quality of

services largely and crucially depends on the competencies of service providers [33]. These dynamic features in the new era set a higher bar for employees, making it essential for them to be innovative, autonomous, professional, adaptable, and intrinsically motivated [33, 35]. The service economy also requires leaders to embrace qualities such as empathy, caring, sincerity, flexibility, and trustworthiness [36]. The two former DHL colleagues, based on their career experiences in service sectors, shared their perspectives on the consequences that the dark side of leadership could incur for organizations as well as for individuals.

Destructive Interpersonal Skills of a Leader Repel Colleagues and Undermine Organizational Effectiveness

According to the interviewees' accounts, interpersonal competence of a service leader played a critical role in team collaboration and employee satisfaction in the workplace. Failing to foster a good relationship with subordinates often led to miscommunication and low employee recognition, which adversely affected organizational productivity and effectiveness. The recount of their experiences corresponds to the perspective that "hard skills" (professional knowledge and skills) do not suffice for career success in the service economy [37, 38]. Equipment of both strong hard and soft skills, including the interpersonal skills, enables one to navigate the complexity in a career and maintain an efficient workflow:

"We fired some of our employees not because of their incompetence in the professional field, but because they were stepping on others. This behavior amounts to incompetence because it is important to collaborate with others, across the teams or within the teams. If a person is capable of completing the tasks, but always steps on others and unable to effectively handover a task to or takeover a task from others, it means he or she is incompetent... If a person upsets colleagues every time he or she engages in a task, and makes a lot of troubles which would, in turn, delay things, it means this person is incompetent... Fulfilling a task includes competencies in communication and relationship-building, which are as important as the tasks themselves... You have to have good interpersonal skills—not to say you have to make friends, but at least you have to maintain that relationships." (The second interview with the colleagues)

"In fact, he was a person with ability, a good man, but he couldn't communicate in our DHL environment. He carried out things in the way he believed to be right and ended up with not getting along with the peer group and the employees." (The second interview with the colleagues)

Self-Centered Leadership Erodes Team Morale and Sabotages Supportive Working Environment

One distinguishing feature of the SLT is that its systems orientation which includes "self, follower, habitat, and larger system," and it is the service leader's responsibility to maintain a healthy habitat for the team [36, 39]. It is premised on that self is only one orientation in the systems, and service leaders should not focus on excessive self-interest. Instead, they need to inspire and empower the team to grow and pay due attention to shared decision-making [36]. This premise makes the SLT markedly different from heroic leadership, such as charismatic leadership, where only the leaders are always under the spotlight [40]. In the interviews, the former DHL colleagues cast doubts on the effectiveness of self-centered, heroic leadership to navigate the complexity in a service industry based on their experiences. Explicit in their accounts is that this type of leadership would erode team morale and give rise to a hostile working environment:

"It is more obvious for service leadership, because you can't lead people like this. You will never be a true leader, because you are the only hero in the team. On a certain level, being a hero is okay if you want to lead a team or have a winning team, but you can't be the single hero all the time... A service often requires joint efforts,

so as a leader you need to break through the barrier. Don't be too self-centered. You need to be considerate of other colleagues." (The second interview with the colleagues)

"(The problem with this type of leader is) he can't duplicate the task because he is the only one who can manage it. Maybe he has no idea of how to teach others, or he's reluctant to do so because if he teaches others, he will become less worthy, so he will hide those skills..." (The second interview with the colleagues)

"I realized culture could influence interpersonal relationship. We wouldn't be so supportive, because it was not necessary. I could just mind my own business. I wouldn't remind others of their mistakes because it was none of my business." (The second interview with the colleagues)

The Dark Side of Leadership Restricts Personal Career Development

As discussed earlier, existing literature focuses on the negative outcomes brought about by the dark side of leadership for subordinates such as discontent, anxiety and depression [16, 18]. In the same vein, narratives of the DHL colleagues showed that the dark side also brought about negative outcomes for leaders themselves. The dark side, such as excessive self-interest or the lack of crucial soft skills, would lead to an obnoxious and unhealthy environment, which in turn undermined the team performance and restricted personal development of the leaders:

"For some colleagues, being a supervisor or a team leader will be the end of the road for them. It will cause problems if they continue, not because they lack seniority, loyalty, or competence, but because they don't have the coaching or communication skills, or the leadership skills to carry a team." (The second interview with the colleagues)

"It gave me a deep impression that one guy, a very talented and experienced guy who worked in the DHL for a short time. He was self-defeated. To be around him was painstaking. The colleagues would not judge him directly, but you can tell people did not want a lot of interactions with him. He was difficult to communicate with. He also found it pains-taking to work here, so he left." (The second interview with the colleagues)

"Some people are skillful, but they may think it takes much effort to teach others, so they could just do it all by themselves. On these occasions, the company often promotes them to a middle-level leadership position because they are capable, but then they will create problems because he is the only one who is capable in the team." (The second interview with the colleagues)

RQ 2: What is the Dark Side of Leadership According to the SLT?

It is a Narrow Road to Eschew Dark Leadership Constructs

To reveal how the dark side of leadership is conceived in the SLT, Dr. Po Chung and Bell in their publications [39] and our interviews reiterated a well-known quote from Anna Karenina Principle, namely, "Happy families are all alike; every unhappy family is unhappy in its own way." It shows an essential notion in the SLT — it is a narrow road to become an effective service leader and to eschew the dark leadership constructs. As demonstrated in the Introduction and Dr. Po Chung's studies elsewhere [2, 39] that the absence of any of the 3Cs, such as incompetence, ill moral standards and lack of caring disposition, would have detrimental impacts on organizational performance and preclude successful leadership. Dr. Po Chung articulated this perspective again in his autobiographical writing:

"There are many examples of leaders who did very well or got far ahead with only one strong C. Crucially, there are many examples of bad or toxic leaders who managed to get many people down the wrong path of history or at least the path towards great human advancement and achievement but with corrupt, if not outright evil or toxic ends." (The autobiographical writing of Dr. Po Chung)

Many Dark Leadership Constructs are the Antithesis of Confucian Virtues

The SLT is deeply influenced by Confucian ideology and ethics [30]. Chung listed 13 doctrinal ideas from Confucianism that were crucial for service leadership ethics — “Kindness (‘ren’, 仁), righteousness (‘yi’, 义), propriety (‘li’, 礼), wisdom (‘zhi’, 智), trustworthiness (‘xin’, 信), loyalty (‘zhong’, 忠), courageousness (‘yong’, 勇), incorruptibility (‘lian’, 廉), having a sense of shame (‘chi’, 耻), filial piety (‘xiao’, 孝), brotherly love (‘ti’, 悌), self-correction (‘gai’, 改), and forgiveness (‘shu’, 恕)” [2]. Accordingly, the virus or the dark side of leadership is the antithesis of these virtues. In one of the interviews, he shared a broader spectrum of viral values or behaviors reflected in Chinese traditional philosophies on which leaders should keep alert:

“掛羊頭賣狗肉 (‘gua yang tou mai gou rou,’ sail under false colors), 睜眼說瞎話 (‘zheng yan shuo xia hua,’ lie through one’s teeth), 指鹿為馬 (‘zhu lu wei ma,’ deliberately misrepresenting something), 生安白造 (‘sheng an bai zao,’ deliberately provocative), 過河拆橋 (‘guo he chai qiao,’ ungrateful and leave one’s benefactor in the lurch), 大石砸死蟹 (‘da shi za si xie,’ surrender to power), 秋後算賬 (‘qiu hou suan zhang,’ people bide time to take revenge), 借刀殺人 (‘jie dao sha ren,’ make use of another person to get rid of an adversary), 死不認錯 (‘si bu ren cuo,’ stubborn to admit mistakes), 面子大過天 (‘mian zi da guo tian,’ false sense of pride), 打完齋不要和尚 (‘da wan zhai bu yao he shang,’ ungrateful and leave one’s benefactor in the lurch), 講一套做一套 (‘shuo yi tao zuo yi tao,’ one’s words are not matched by deeds), 惡人先告狀 (‘e ren xian gao zhuang,’ The guilty party files the suit first), 借屍還魂 (‘jie shi huan hun,’ something revives in a new guise), 反口覆舌 (‘fan kou fu she,’ break one’s promise), 瞞天過海 (‘man tian guo hai,’ being deceptive), 趁火打劫 (‘chen huo da jie,’ loot a burning house), 殺人放火 (‘sha ren fang huo,’ being vicious), 無中生有 (‘wu zhong sheng you,’ deliberately provocative), 笑裏藏刀 (‘xiao li cang dao,’ nice-nasty), 釜底抽薪 (‘fu di chou xin,’ sabotage other’s efforts), 渾水摸魚 (‘hun shui mo yu,’ take advantage of a crisis), 關門打狗 (‘guan men da gou,’ control and then destroy someone), 遠交近攻 (‘yuan jiao jin gong,’ manipulate powers), 偷天換日 (‘tou tian huan ri,’ cheat), 指桑罵槐 (‘zhi sang ma huai,’ make groundless accusations), 假癡不癲 (‘jia chi bu dian,’ being deceptive), 反客為主 (‘fan ke wei zhu,’ a guest supplanting the host), 美人計 (‘mei ren ji,’ badger game), 反間計 (‘fan jian ji,’ sow discord), 苦肉計 (‘ku rou ji,’ play weak or innocent), 金錢計 (‘jin qian ji,’ corruptive).” (The fifth interview with Dr. Po Chung)

RQ 3: How Does DHL Prevent the Dark Side of Leadership in Practices?

As demonstrated in the data and research [2], any absence of the 3Cs can lead to mismanagement and counterproductive performance, contaminating a supportive working environment and burning out enthusiasm and job satisfaction of the employees. It can be seen from the excerpted examples below that in order to prevent toxic leadership, the DHL International had been committed to different systems that encouraged continuous self-improvement in competence, moral standard, and caring disposition to establish a virtuous circle:

“... All department heads or above would have no other option [of whether to organize programs/workshops or not] but be nominated as trainer automatically. You would be trained as a trainer first, and as a trainer or facilitator, you need to lead your colleagues from your department and other departments too... We also had other regular courses (for the trainers) such as the management course, where the trainers would sign up, being trained by the training consultants and evaluated of their strengths... DHL built a culture like this. You would be assimilated by this environment, even you were not the type of manager or executive before.” (The second interview with colleagues)

“... Many leaders won’t teach you. They would say, “You could just follow me.” It was like this before, but fortunately we changed because DHL used ISO system, which required supervisors to prepare a process document for subordinates and ask them if the document made sense to them. If yes, the subordinates could go on with their works, otherwise it meant that there were some problems with the process document, and it needed revision. This solved the challenges that some of the supervisors lacked team spirit and were reluctant to share his unique skills.” (The second interview with the colleagues)

“In DHL we had Employee of the Year, as many companies did. Normally the selection criteria gave the most attention to business performance. In many companies, Employee of the Year meant best business performance. However, in DHL, business performance was only one of the measurement criteria, and the criteria were not absolute... If we focus on creativity for employees from a department dealing with creative business, it meant the colleagues in the IT Department could never be selected for this honor, because they couldn’t create any new business. But what could they create? They could create a good technical service environment... So in DHL, you could see colleagues in different departments engaging in different jobs all had the opportunity to be nominated as Employee of the Year, including many jobs we easily took for granted such as the cleaning lady.” (The second interview with the colleagues)

DISCUSSION

This paper aims to understand the dark side of leadership in the era of service economy by reviewing the autobiographical writings of Dr. Po Chung and interviewing him and his two former colleagues in DHL International. Results summarize the conceptualization of the dark side of leadership in the SLT, its negative impacts, and ways to prevent in organizations. In general, the outcomes extracted from Dr. Po Chung’s autobiographical writings and the sharing from the Dr. Po Chung’s and his two colleagues’ interviews echoed the existing literature, which highlighted the indispensability of the 3Cs and destructive influences of the dark side of leadership on individuals and organizations [2, 16, 18, 20].

Three observations are highlighted in the study. Firstly, the dark side of leadership involves a lack of any of the 3Cs. According to the SLT, competence, character, and care are the fundamental features of an effective service leader. To maintain competitiveness in the service economy, leaders need to be not only competent but also supportive, empathetic, sincere, and trustworthy [36]. In particular, the importance of care and character of leaders and the destructive outcomes of a lack of care or character were clearly illustrated by Dr. Po Chung and his colleagues. For leaders who lack a caring disposition, the followers tend to have a lower level of attachment with their leaders, which also increases their willingness to leave [2]. Shek, Chung, and Dou [2] suggested that a lack of character may destroy trustful relationships between followers and leaders, and thus increase the turnover rate. In short, a lack of any of the 3Cs covered in the SLT results in the dark side of leadership.

Secondly, the dark side of leadership can bring destructive influences on leaders, followers, and organizations in the service economy, which is consistent with the literature. For example, Li and Zhu [20] proposed that a destructive leadership model can bring negative emotions to followers and influence their mental health, and thus affect the cohesion of the organization. Besides, literature also suggests that the dark side of leadership can hinder one’s development [2], which is reflected in Dr. Po Chung and his colleagues’ sharing. Liu, Liao, and Loi [18] claimed that abusive leadership erodes followers’ creativity and undermines followers’ intrinsic motivation in career development.

Thirdly, some approaches have been suggested to prevent the dark side of leadership. It is important for leaders to be aware of the negative impact of destructive behaviors and committed to creating organizational mechanisms to prevent destructive behaviors. Besides,

well-designed human resource management systems and policies are needed to encourage continuous self-improvement in competence, character, and care. These systems will promote a positive organizational culture, which can prevent the working practice of “command and control” in organizations and the dark side of leadership. Besides, time and collective efforts are also needed to promote positive changes in leadership and organizational culture. Lastly, the dark side of leadership reflects the antithesis of Confucian virtues. Companies do not work in a vacuum, and organizational culture is greatly influenced by its interaction with social environments and values. Results also indicate that the dark side of leadership is undesirable in both Western and Eastern values.

Although this paper clarifies the nature of the dark side of leadership and ways to prevent it, this paper has several limitations. First, this study only involved qualitative data, as the source of information mainly came from the three interviewees. Quantitative data can be collected to have a holistic and accurate picture. Secondly, social desirability bias can exist as the respondents may tend to fulfill the favor of society when answering questions, especially for those questions regarding the dark side of leadership. Considering the potential bias, we need to interpret the results with caution.

Despite the limitations, the present paper contributes to the ongoing discussion on the dark side of leadership by examining the nature, and the negative outcomes of the dark side of leadership through the lens of the SLT and ways to prevent it based on the practices of DHL International.

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Chapter 152

CARING LEADERSHIP IN SERVICE ECONOMY

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ABSTRACT

Care is one of the three key elements of effective leadership in the service era, according to the service leadership theory. Existing literature has highlighted the contribution of caring behaviors to personal growth, interpersonal relationships, and leadership effectiveness. The present chapter analyzed the qualitative data based on Dr. Po Chung's autobiographical writings and interviews with him and his two colleagues in DHL International. This study also integrated findings with the existing literature regarding the influence of leaders' caring behaviors. The present narrative findings suggest that caring leadership can be put into practice in terms of allowing followers to make and learn from non-moral mistakes as well as the "*Master and apprentice*" approach. Consistent with the previous evidence, the present findings suggest that caring leadership benefits the leader, followers, and the whole organization.

INTRODUCTION

Since the emergence of the service economy in the post-industrial era, the world has been emphasizing knowledge, service, and human capital [1]. In this context, the concept of caring leadership highlighting leaders' caring disposition has drawn much attention. The word "caring" is derived from the Latin word "cura" (i.e., "cure of the soul"), which is a multi-faceted concept that includes managing, devotion and healing, etc. [2]. In modern times, caring indicates having others in one's considerations, other-oriented, a state of helping other people grow with support and encouragement [3]. Caring also means always answering a call

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for help, being there for the “other”, and immediately responding to others’ needs [4]. These recent conceptualizations of caring echo Kahn’s [5] earlier identification of eight dimensions in caregiving, namely “accessibility”, “inquiry”, “attention”, “validation”, “empathy”, “support”, “compassion”, and “consistency”.

While other-orientation and taking care of others’ needs can be regarded as the key elements of caring, there are also other unique features of conceptualization of caring in specific professions. For example, within the teaching context, besides orientation towards others, caring disposition is also seen as commitment, relatedness, physical care, expressing, affection, parenting, and mothering [6]. In nursing, caring disposition is closely related to clinical leadership and is seen as an integral part of the nursing profession [4]. Furthermore, the common components of caring have been identified, including empathy, communication, devotion, healing, and attention with empathy [3, 7, 8]. According to Houghton et al [3], caring is displayed by involving and engaging others, including deep listening, entering into another’s world and being entirely accessible or emotionally engaged. For example, Louis, Murphy, and Smylie [9] highlighted that “caring is often defined by its broad purposes: promoting the general development, welfare, and well-being of others; addressing particular needs of others; and developing the capacity for caring among self and others” [9]. Stephens and Carmeli [10] remarked that organizational caring refers to “a set of values and principles that focus on fulfilling employee needs” while felt care refers to “the experience of feeling that one’s co-workers consider, support, and show concern for one’s needs” [10]. All these theoretical emphases on caring are in line with Maslow’s hierarchy of needs, where the needs of love represent a higher level of human needs [11].

Caring is beneficial for personal growth, leading to high morality, self-regulation, self-significance, and self-esteem [3, 12, 13]. Morality, as Wren [14] argued, is linked to caring dispositions such as kindness and fidelity. Therefore, developing caring dispositions in children is an important part in developing morality and self-regulation [13]. Hunzicker et al [12] found that teachers working in a school environment with a higher level of support and mutually caring relationships were more likely to enhance their self-esteem and self-efficacy.

Caring can also benefit interpersonal relationships [15]. For example, Hargreaves [16] found that teachers’ caring disposition influenced their relationships with students, parents, and colleagues. The teacher preparation program at Larmer University emphasized trust and caring relationship between master teachers and student teachers because a good interpersonal relationship contributes to teachers’ positive transformation and professional development [15].

Caring is also of paramount importance for leadership effectiveness. For example, in educational institutions, leadership strategies that fail to embrace caring orientation undermine teachers’ practices and self-efficacy, hence leading to powerlessness and incompetence in leadership [16]. In the healthcare system, leadership with a caring disposition does not only benefit nursing practices, but also contributes to organizational effectiveness and professional satisfaction of the employees [17]. Spears [18] argued that servant leadership was strongly based on leaders’ caring behaviors, which may also improve mutual caring among group members. In line with this notion, caring disposition was found to be helpful in achieving servant leadership goals such as personal growth, shared decision-making and teamwork building [17]. A caring servant leader can listen attentively to the messages sent by employees, show genuine empathy to them, have the ability to heal relationships and commit to employees’ personal growth [17]. Likewise, Houghton et al. [3]

asserted that shared leadership served as a primary driver for the development of group-level caring, which was in turn conducive to better group performance and team spirit.

In addition, caring disposition is among the three key components of effective service leadership. Service leadership is a concept that emerges along with the rapid development of service economy [19]. Different from traditional leadership theories which emphasize more on leaders' "hard skills" and "doing" (e.g., giving commands and managing people), service leadership theory (SLT) focuses more on "soft skills" and "being" (e.g., whole-person development) with the purpose of nurturing a younger generation of leaders to satisfy the diversified needs of oneself, others, groups, communities, and the whole society [20]. SLT proposes that three "Cs", namely, "competence," "character," and "care", are key to effective leadership practice in the service economy [19]. According to SLT, on top of professional and leadership competencies, a good service leader should be caring in serving others with good character qualities. The relationship between caring disposition and service leadership has been specifically stated and analyzed from different perspectives. Shek and Li [21] stated that caring disposition is the first priority for a service leader as it contributes to the growth of followers, organizational effectiveness, the leader's maintenance of authority, power, and career success. Shek and Li [21] also emphasized the importance of nurturing university students into caring leaders as care represents a core value of effective leadership in the contemporary service era.

In order to fulfill the demands of effective service leaders in Hong Kong, where service economy contributes more than 90% to total GDP [22], the SLT has also been adopted to guide different leadership programs in local universities to nurture tomorrow's service leaders. These programs have been evaluated and proven to be effective in promoting students' well-being, leadership qualities and values related to service leadership [23, 24]. While the importance of nurturing caring service leaders has been emphasized and the STL has been shown to be an effective framework in youth leadership training, how caring leadership is conceived and practiced in service sectors that endorse service leadership remains under-researched. Practically speaking, it is also necessary to outline the benefits of caring leadership in an organization to further promote SLT in the service economy. As such, the present study endeavored to address these two research questions by integrating existing empirical evidence with interviews on leadership practice in DHL International, where service leadership refers to the practices aiming at promoting employers' well-being and customers' lives through providing high-quality services [25]. While the importance of nurturing caring service leaders has been emphasized and the STL has been shown to be an effective framework in youth leadership training, how caring leadership is conceived and practiced in service sectors that endorse service leadership remains under-researched. Practically speaking, it is also necessary to outline the benefits of caring leadership in an organization to further promote SLT in the service economy. As such, the present study endeavored to address these two research questions by integrating existing empirical evidence with interviews on leadership practice in DHL International, where service leadership refers to the practices aiming at promoting employers' well-being and customers' lives through providing high-quality services [25].

OUR STUDY

In order to have a deeper and more thorough understanding of data provided by interviewees, a qualitative methodology was adopted in the present study. Compared to quantitative approaches, qualitative approaches are more beneficial in revealing rich information and in-depth meanings behind words and numbers, such as personal experiences, emotions, attitudes, etc., with a subjective perspective through an interviewee's words and an objective perspective through observations and analyses [26]. Being widely used in social sciences, qualitative approaches include many research methods with different foci, among which narrative inquiry emphasizes interviewees' life stories and experiences [27]. With narrative inquiry, researchers can gain a deep understanding of the interviewee's thoughts and feelings, and how he or she sees the world based on the data collected via autobiographical writings, journal writings, interviews, and observations that provide rich data and information. Thus, the present study employed narrative inquiry by collecting data from D. Po Chung's autobiographical writings, individual interviews with him, and group interviews with his two former colleagues in DHL International.

Data Collection

By adopting a qualitative methodology, the authors interviewed Dr. Po Chung, the Co-Founder of DHL International, and two of his former colleagues in DHL International, A and B, in order to have a clearer picture of how the caring disposition and SLT are applied and practiced in the company and the outcomes of such practice. As the key informant, Dr. Po Chung was interviewed five times from October 2019 to May 2020. During the same time period, Dr. Po Chung's colleagues, A and B, previous senior managers with over 25 years of working experience in DHL International, were invited to share their interpretations of SLT and views toward the practice of caring leadership in the workplace in two group interviews. The interviews were semi-structured with open-ended questions for flexible and in-depth responses on theoretically driven topics. Before the interviews started, well-informed consent was obtained from Dr. Po Chung and his colleagues for the interviews being audio-taped and further analyzed.

Data Analysis

All the interviews were conducted by two well-trained researchers, and some of the scripts were translated from Cantonese into English by the research team as interviewees shared some views in Cantonese. The interview transcriptions were checked and confirmed by the interviewees. Thematic analysis was used to identify and interpret the patterns and themes emerging from the data collected in this study. Data analysis in this study was performed by three experienced and qualified researchers. After the interview transcriptions were confirmed, the data were reviewed and categorized into condensed summaries concerning the topic of "caring disposition" by an experienced researcher. The researcher then further identified the themes from the condensed summaries and grouped similar

conceptual themes into a broad thematic concept. After this step, the other two researchers reviewed and checked condensed summaries, themes, and the broad thematic concepts for peer checking on the credibility of the data analysis. Based on the peer checking comments, the first researcher refined the theme structure. Member checking of the finalized codes was then conducted by involving the informants.

FINDINGS

Theme 1: Caring is to Allow Followers to Make Mistakes and Learn From Mistakes, and Caring Leadership is Practiced through the Master-Apprentice Approach

In the industrial age where the leadership was highly autocratic and had minimal communication with followers, only satisfying the needs of manufacturers was the major concern in leadership practice [1]. In contrast, the leaders in the service economy emphasize the importance of care as one of the elements in the three 3Cs principles in SLT, which means showing sincerity and empathy in providing services and caring for others' needs [1]. According to Dr. Po Chung's and his colleagues' viewpoints, there are two important aspects of caring leadership in the service economy. First, leaders need to allow employees to make mistakes and let employees learn from their own and other colleagues' mistakes so that they will not make the same mistakes in the future. Another aspect of being a caring leader is to serve as a role model who treats employees as human assets rather than "machines". This is called the "Master and Apprentice" approach in DHL International, through which employees can learn from leaders in an open and inclusive environment. As Dr. Po Chung and his colleagues shared:

"We allow colleagues to make mistakes. It is impossible that every task can be done by the most experienced person. Therefore, it is unavoidable to have some newcomers do the tasks without related training and experience. Then he will make mistakes. How should we treat such mistakes? Do we need to lay him off? Of course, we can lay him off if there is no other solution. However, can we take this mistake as a good lesson to learn from and share the experience with others so that other people will not make the same mistake? The situation is simply like falling into a hole. You have to fill the hole after you come out so that others will not fall into the same hole. Here we have an example. A boy drove a van to deliver customers' files. He forgot to close the window of the van when delivering files. Finally, an entire bag full of cheques was stolen. After that incident, his supervisor did not dismiss him. Instead, his supervisor told me that the young boy would be one of the best couriers. It is because he will not make the same mistake in future. Besides, he will share this experience with other colleagues if we keep him and others would not make the same mistake either. I think this approach is incredible. This is one of the first lessons both in life and leadership that I learned from this story." (Colleague A's sharing in the interview)

"The permissive culture of allowing non-moral mistakes was huge because anyone and everyone were allowed to screw up – including the boss – and no one lost face by making mistakes. This was especially important in cultures such as China, Japan, and Korea that heavily emphasized personal responsibility in a way that could bring too much pressure to bear and ultimately be counterproductive. With the "some mistakes are okay" tenet, nobody felt the need to dig in to defend mistakes. The value of this was that the learning from a specific mistake was adopted quickly and shared with the entire network through the channels of communication we had established." (Dr. Po Chung's writing in the book) [28].

"One thing we incorporate is that we teach leaders how to be masters. We use a 'Master and Apprentice' system. And when we finish teaching leaders the master skills, they become masters and train others. They do and transfer their skills to followers. They do, and followers watch. Followers learn from leaders by watching.

So more than just saying, leaders have to behave. Then, followers start doing, and leaders supervise them.” (Dr. Po Chung’s sharing in the interview)

“Apprenticeship is an age-old approach to training. At DHL, we harnessed its wisdom to pass on vital knowledge and skills... DHL used the ‘Master and Apprentice Method’ as the most efficient method for passing on key guidelines and rules in a one-to-one situation. Since DHL could only add couriers on a regular basis but never in large groups, the Master and Apprentice Method has remained the best method for the company when it comes to passing on operational and people-skills training. This method is how DHL built a large team of people with high Competence, Character, and Care... This technique was very much like big brothers taking care of younger brothers, organically teaching them the skills, values, and behaviors as they demonstrated that it took Competence, Character, and Care to run a successful global network company.” (Dr. Po Chung’s writing in the book) [28].

From the above narratives, it can be seen that one method to practice caring leadership is to accept and allow non-moral mistakes made by employees and let them learn from the mistakes. Relating this practice to academic findings, Cheng et al [29] pointed out that leadership with forgiveness, openness, and acceptance had a positive effect on the gratitude of subordinates and repayment to the leaders. Besides, the Master and Apprentice approach, where the master teaches and cares for the apprentice and the apprentice learns from the master at the same time, is considered as an effective strategy of caring leadership to nurture competent, caring, and moral employees in the company. This kind of approach has been found to be beneficial in the empirical research. For example, Wati, Dwiantoro and Juanamasta [30] found that caring leadership mentoring was effective in enhancing nurses’ ability to apply caring leadership and making them feel confident and supportive when they deliver services.

Theme 2: Caring for Others Can Be Beneficial for Oneself

Effective service leadership in service economy is a result of caring disposition, character, and leadership competencies of the leaders. Thus, it is important that leaders are ready to exhibit care and support to the employees. In fact, caring leadership practices bring benefits not only to others and organizations, but also to the one who shows caring to others. One of Dr. Po Chung’s colleagues highlighted how caring for others could be self-beneficial in the interviews. Dr. Po Chung also stressed the benefits to oneself of being caring to others in terms of attracting followers. Related narratives are listed below:

“We always pass the related documents to the girl in the telex room after completing job duties at the airport. She will convert the files into digital format for filing. In general, it is the girl’s job duty to do this work. However, I think she is exhausted. She stays at the office to do the paperwork every day. She is supposed to work from 9 am to 5 pm. Yet, we have to complete delivery tasks at the airport, and we do not know how long it will take as we do not know how many other people are at the airport. In this case, it is uncertain that when we will come back to the office, which may keep the girl waiting for a long time. I told my supervisor and said, ‘we do not need her to wait and do the paperwork. I can type efficiently as well.’ In fact, I did not consider that this is not my job duty. I just proposed a better solution to finish the work without wasting too much time and resources or causing inconvenience to others. Why not, right? Typing is a simple thing for me, and I only spent minimal effort. Probably, my boss noticed my spontaneous ‘kind behavior’ even though I did not know about it. Eventually, I was promoted after this change.” (Colleague B’s sharing in the interview)

“‘What’s in it for me to follow you?’ This fundamental question has Care at its root. Care is again human relations. It is a mixture of empathy, love, and feelings between two human beings... to lead others, you must have charisma that appeals to them. Yet, charisma on its own isn’t enough to help build a thriving global network. Caring for others is an important part of charisma because charisma without care is seen as fake or

forced. Just as a smile without feeling is a fake smile, a person without genuine feeling behind the person's behavior comes across as inauthentic" (Dr. Po Chung's sharing in the interviews and writing in the book) [28].

Particularly, some empirical studies have reported the beneficial influence of caring on oneself. For example, Gentry, Weber and Sadri [31] revealed that leaders who showed more caring and empathy were more likely to be viewed as having better performance in fulfilling their job duties. Caring and understanding followers' feelings, in fact, can be seen as a leader's skill, which contributes to competent management and effective leadership. Similarly, Young et al [32] found that a leader's caring and empathy towards employees was positively related to the leader's opportunity to be promoted. Hence, echoing these empirical findings, the present narrative findings suggest that caring for others can benefit oneself, such as having a higher chance to get promoted in the organization and being admired and regarded as a good leader to follow.

Theme 3: Caring Leadership Increases Employees' Loyalty and Fosters a Better Team

In the service economy, caring leadership is very important as it maintains employees' loyalty, decreases the turnover rate and retains the best team for the organizations. Pellegrini and Scandura [33] stated that leaders who can exhibit care for followers' professional development and personal livelihood would win followers' loyalty and compliance. Dr. Po Chung believed that a leader with care makes employees follow the leader willingly for a long time, and a caring leader can retain the best employees in the team, sustaining competitiveness of the team. Related narratives are presented below:

"And also, when I learn all his competences, and I know his characters are not bad, but if he doesn't care about me, I would rather look for somebody else who has the same competences, the same characters, and cares about me to follow. If he cares about me, I care about him. Then I'll stay with him for a long, long time. If a leader wishes to keep the best followers and maintain good relationships with them, the leader must be caring...So, you want to recruit the best people, maintain the best people, and keep them for a long time. In this way, you can also sustain the competitiveness of your service." (Dr. Po Chung's sharing in the interview)

"While competency is doing things right, character is doing the right things, and care is doing it with the right heart. The person who does things with heart will out-compete the one who does not. Therefore, make sure to treat people right, and usually you'll find that they give 100% or 120% in return. Let's say you have 20 people, and each gives you 25%, then you have a total of five people working for you. Naturally, this can work in reverse. With 20 people giving 120%, then you have 24 people working for you – that is what they call a good return on heart count" (Dr. Po Chung's writing in the book) [28].

Indeed, empirical studies have revealed a positive relationship between employees' loyalty and caring leadership. For example, Wu, Hu and Jiang [34] found that followers' loyalty to a supervisor was positively associated with the supervisor's benevolent leadership. Farr-Wharton, Shacklock and Brunetto [35] reported that nurses were more willing to stay if the supervisor-subordinate relationship has trust, support, care, and respect. Recently, Rupp [36] also showed that caring leadership practice was positively correlated with the intention and willingness to stay among nurses. The finding implied that caring leadership could promote job satisfaction among nurses, and thus increased their intention to stay in their position. To sum up, in conjunction with previous findings, the present qualitative findings suggest that caring leadership with support and trust can retain the best followers with high

loyalty and positive leader-follow relationships, which are fundamental to foster a better team and maintain organizational competitiveness.

Theme 4: Caring Leadership Brings Benefits to Employees and the Organization

The present interview narratives also revealed that caring leadership leads to positive outcomes for the organization. In the interviews, Dr. Po Chung's colleagues shared their views toward positive impacts on employees and the organization as a result of caring leadership practices in DHL International, such as a sense of belonging, commitment to the organization, and high-quality services provided to customers. Below are the related narratives:

"DHL has introduced Service Excellence Programme, putting service into mind. What does 'service excellence' mean? It means that we have to consider serving others in any aspect. We have internal customers in our company. With this concept in mind, the question is how I can help you and make you happy, and vice versa, you also treat me in the same way. Then, you will always think about what you should do, what you should not do, and whether you can take one step forward and do extra things. Simply like what I did for the girl at that time (help the girl in the telex room to document the files). I can help the girl so that she did not have to stay while the company also did not have to pay for her overtime work. Actually, I think that girl did not want to work over-time, not knowing the time to go home every night. In addition, it may cause inconvenience for the girl to get off work late. Therefore, what I did can make the girl happier. At the same time, she would not complain about colleagues from the Operation Department, like saying 'I cannot get off because of you guys.' By considering and caring about others' needs, the relationship among colleagues will be more harmonious and happier. (Colleague B's sharing in the interview)

"Care refers to care for the needs of your followers as they have many needs. You also have to motivate the 'heart' of other people because leading people is leading their 'hearts'. They can do anything for you if you can persuade their 'hearts'. Why are there people who wish to get things done even you do not ask them to do so, or become adaptive? It is because they treat it as their own responsibility, and they have ownership as well. How can we make people have ownership? You have to persuade their "hearts". Like we all have an emotional bank account. For example, sometimes your leader may yell at you. However, in the long run, the colleague may think in this way 'he yelled at me today, but he cares about me in daily work. He allowed me to take leave so that I can travel together with my child. He also helped me with other things.' In fact, everyone has an emotional bank account. If you deposit more into your follower's account in daily life, you can have a better chance to get his forgiveness for yelling at him. I feel that there is a great sense of ownership among colleagues. One really thinks that it is his responsibility to get things done. For example, we are in a team with four people. I will remind you if you do not do well. It is because it is our team's failure, not only your failure, if I do not offer you help. I think we all do not expect to get promoted by beating others down, but to be promoted together. Colleagues always say that 'it is not enough if only you do well or feel good.' Service excellence means only happy employees can provide good services to customers. There is customer satisfaction only if there is employee satisfaction. (Colleague B's sharing in the interview)

"This is the change of mindset, if you pay a lot of attention to character and care and learn all the competence of how to lead people, motivate people, you can have higher productivity. If you can lead people better with a heart while doing the right thing, then they would work faster, work better" (Mr Po Chung's sharing in the interview)

Previous empirical research also showed that caring leadership leads to positive outcomes for employees and organizations as well. Fu and Deshpande [37] investigated the relationship between caring leadership and employees' commitment to the organization. They found that caring leadership exerted a significant positive impact on the employees' organizational commitment. Similarly, Chen et al [38] identified a positive association between leadership with caring and employees' in-role and extra-role performance. A possible explanation for

these findings is that when a leader shows care and concern for employees' personal and job-related well-being, the employees tend to have warm and pleasant feelings and gratitude toward the leader, which could further help establish a reciprocal emotional bond and positive relationships between the leader and the employees. Consequently, caring leadership may help motivate employees to engage in their work by putting in more effort. To conclude, the present findings are consistent with previous research findings, supporting the beneficial influences of caring leaderships on employees and organizations in service economy.

DISCUSSION

With reference to the development of service leadership theory (SLT) and previous empirical studies on caring leadership, this paper explores the practice of caring leadership in DHL International and its significance in the service era by reviewing Dr. Po Chung's autobiographical writings and interviewing Dr. Po Chung and his two former colleagues. Based on interviewees' own first-hand life stories and experiences in the workplace, the present study revealed the two most important elements of caring leadership in DHL International and how leaders, followers, team, and the organization have benefited from caring service leadership. Generally speaking, the findings obtained from Dr. Po Chung's writings and the present individual, as well as group interviews, are in line with the existing literature, which demonstrates that caring disposition plays an important role in service leadership in terms of enhancing personal growth for both leaders and followers, improving team and organization development, and leader-follower relationships [3, 4]. This paper is unique because it does not only explain the importance of caring disposition in service leadership based on theoretical and empirical findings, but also decodes the practical applications of caring leadership and demonstrates the benefits of the theoretical proposal in SLT.

Three observations can be highlighted from the present study. Firstly, caring leadership can be exercised through allowing followers to make non-moral mistakes and learn from the mistakes as outlined in Theme 1. In the workplace, mistakes usually mean loss of profits, so employees are always required to try their best to avoid mistakes, though mistakes are unavoidable. The fear of making mistakes in the workplace might hinder work efficiency, while a culture of learning from mistakes may instead lead to higher productivity. A study conducted by Lorenzet et al [39] showed that trainees receiving guidance about common mistakes and support during error correction displayed a higher level of self-efficacy than error-free trainees. Self-efficacy, in turn, was positively related to the accuracy and working speed (efficiency) of those trainees. Accordingly, instead of demanding no mistakes from followers, a caring leader expects his or her followers to turn a non-moral mistake into a valuable lesson, which would benefit not only the one who has made it but also whoever is witnessing the mistake. In this way, similar mistakes can be avoided, and work efficiency will be promoted while the cost of making mistakes is in fact minimized.

Secondly, in the service economy, when mentioning caring, one may usually think of the benefits that clients or followers receive from being served. However, the leaders who display care to their clients and followers can enjoy benefits from the caring behaviors as well, as suggested by the sharing of one of the interviewees in Theme 2. Harris et al [15] proposed

that caring dispositions can help improve one's interpersonal relationships with others and intrapersonal well-being. Therefore, when applying caring leadership in the workplace, the leader-follower and organization-client relationships will be more successful, from which leaders may also benefit to some extent. In fact, strengthened followers' loyalty to the leader and the best work team retained as a result of the leader's care, as suggested in Theme 3, can also be regarded as bringing about benefits to the leader.

Thirdly, organizations advocating caring leadership can be more competitive in the service economy. McAllister and Bigley [7] concluded that caring organizations that fulfill their employees' best interests and needs make employees demonstrate higher levels of organization-based self-esteem. In the nursing field, a caring disposition is also regarded as an important part of the nursing profession and in the work of nurse middle managers [4]. The present findings also indicate that caring service leadership leads to positive outcomes, such as a lower turnover rate, higher organizational commitment and better leader-follower relationships, all of which will subsequently sustain organizational competitiveness. On the one hand, with strengthened loyalty of followers and their better relationships with colleagues as well as better teamwork brought forth by caring leadership practice, the leaders' leading role and authorities will be better recognized and respected, which establishes a solid foundation for the development of efficient and cooperative teamwork and cultivates a caring organizational culture in the long run. On the other hand, followers can improve their capabilities, efficiency, and self-efficacy by observing and imitating what and how leaders do as apprentices. In addition, followers are not afraid of making mistakes but can improve from making mistakes in a caring organization as they are allowed to learn lessons from their mistakes and avoid making similar mistakes in the future. As a result, operation and leadership processes in an organization are expected to be more smooth and organizational caring cultures will be constantly developing with the growing development of human resources.

Although the present paper instills the concept of caring disposition in SLT and links it to the scientific literature, it has several limitations. First, as the present study only involved three informants, future research should include more people from different levels in different service organizations, such as junior managers or grassroots employees. In this way, a more general picture of caring leadership will be uncovered from multiple angles. Second, this study is a cross-sectional qualitative study. A longitudinal study can be considered as it can help reveal changes in caring leadership and how it may influence leaders, followers, and the whole organization over time. Third, this paper adopted a qualitative methodology based on the analyses of interviews and documents. However, if quantitative materials can be included in the paper, a clearer and more convincing picture can be drawn with greater power in generalization.

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Chapter 153

THE ROLE OF TRUST IN THE SERVICE ECONOMY

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ABSTRACT

Although existing literature has revealed the importance of trust in leadership effectiveness and organizational success, limited research has explored the nature, determinants, and outcomes of trust in the service economy. According to the Service Leadership Theory (SLT) proposed by Dr. Po Chung (co-founder of DHL International), the role of trust in leadership effectiveness becomes increasingly important in the contemporary service economy. Based on Dr. Chung's autobiographic writings, interviews with him and his former colleagues in DHL, and existing literature on trust, this study examined the meanings, determinants, and outcomes of trust in the SLT. Results underscore the importance of trust in the service economy. In addition, results show that service leaders should develop competence, character, and care to build up trust with followers and service recipients.

INTRODUCTION

Trust is the foundation of the leader-follower relationship. Along with the worldwide transformation from a manufacturing economy to a service economy, the importance of trust in leadership effectiveness has been particularly highlighted. In the service economy, human assets are vital as the production and provision of high-quality service rely on knowledge, attitudes, skills, capacities, creativity, and quality of employees [1]. Therefore, building strong relationships with employees, motivating, empowering them, and promoting their competences becomes a leader's central task [1, 2]. As trust is "the building block of social exchange and role relationship" [3], a high level of trust between leaders and followers is

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essential for relationship building. Although existing literature has highlighted the importance of trust in achieving organizational success, limited research has examined the meaning and role of trust in the service economy. Therefore, this paper attempts to fill the gap by analyzing the literature on trust, autobiographic writings by Dr. Po Chung (co-founder of DHL International and advocator of the Service Leadership Theory in Hong Kong), and in-depth interviews with him and his former colleagues in DHL.

Definition and Nature of Trust in the Leadership Literature

The concept of trust has been defined in various ways in the literature on interpersonal relationships and leadership. Rousseau et al. [4] defined trust as “a psychological state comprising a willingness to accept vulnerability based on positive expectations about the intentions or behavior of another.” In other words, trusting another person means putting oneself in a vulnerable position and taking risks because one believes that the person to be trusted would not harm him or her [5]. Trust was also defined as an individual’s belief and confidence about a set of characteristics of another person, such as competence, morality, and care [3, 6]. Bligh [7] defined trust as “an expectation or belief that one can rely on another person’s actions and words and that the person has good intentions toward oneself.” Based on a literature review, Burke et al. [8] argued that trust was conceived differently in the literature. In some studies, trust was regarded as an inborn personal trait or a propensity, which is hard to be influenced by environments. In some other studies, trust was defined as “cognitive, motivational, or affective states” and “a function of contextual factors” [8].

Scholars also identified two types of trust in leadership literature: cognitive trust and affective trust [9]. Cognitive trust refers to the confidence of an individual’s rational assessment or judgment of key characteristics, such as competence, responsibility, or reliability of a leader [10, 11]. In other words, cognitive trust demonstrates subordinates’ confidence in their leaders’ capacities, qualities, character, and abilities [11]. Affective trust refers to the confidence built on emotional connections between leaders and subordinates and their reciprocal exhibition of care and concern [6, 12].

Nature of Trust in Leadership Styles

Literature suggests that trust is not only an outcome of leadership but also an important underlying mechanism through which different leadership styles exert influence on employees and organizations. First, leadership literature suggests that different leadership styles would lead to different levels of trust. In general, positive leadership styles such as benevolent and moral leadership, transformational leadership, authentic leadership, and servant leadership would promote trust of followers in leaders [3, 13-15]. These leadership styles contain certain common elements, such as showing competence, benevolence, care, and integrity to followers, which would foster followers’ trust-building. On the contrary, some unfavorable leadership styles, such as authoritarian leadership or passive leadership, would lead to a decreased level of trust of employees in their leaders [14, 16].

Besides, leadership literature suggests that trust is an important underlying mechanism on the influence of different leadership styles on subordinate outcomes. For example, trust mediated the positive impact of ethical leadership, authentic leadership, and transformational leadership on individual and organizational outcomes, such as organizational citizenship behavior, work engagement, lower emotional exhaustion, job satisfaction, acceptance of change, and knowledge sharing [17-22]. These studies strongly suggest the important role of trust in performing these leadership styles. As Bligh [7] argued, trust is an important process or foundation in transformational, ethical, authentic, and servant leadership. These leadership styles mainly exert influence on followers through strong relationships, which are based on leaders' trust-related morality, such as integrity, trustworthiness, and credibility. The importance of trust in different leadership styles could also be explained by the leader-member exchange (LMX) theory [23]. High-quality LMX is manifested by the high-quality exchange of information and emotions and high levels of trust, respect, and obligation between leaders and followers [23, 24]. However, there is a lack of theoretical and empirical work based on qualitative data to discuss the concept of trust in the service economy in the SLT.

Determinants of Trust in Leadership

Besides the meaning and nature of trust, existing literature has also identified the important factors determining or shaping trust in leadership or organization. For example, Butler Jr [25] identified ten conditions for the development of trust in a manager, including "availability, competence, consistency, discreetness, fairness, integrity, loyalty, openness, promise fulfillment, and receptivity" [25]. Mishra [26] proposed that subordinates would develop trust in their leaders if their leaders demonstrate competence, openness/honesty, concern, and reliability. However, Butler and Mishra did not provide detailed explanations of each quality. Mayer and Davis [27] also proposed that the three key determinants of trust in an organization are ability, benevolence, and integrity. Ability means strong domain-specific expertise, competence, or skills in completing domain-specific tasks. Benevolence refers to care about the needs and interests of others. A person demonstrating all three qualities would be perceived as "quite trustworthy." However, this model has limitations. First, Mayer and Davis's explanation of each quality is unclear. For example, they regarded benevolence as "concerning others' needs and interests" and "loyalty and honesty," which are more related to moral character. Also, they only highlighted the integrity aspect but did not mention other moral character attributes. Furthermore, this model mainly focuses on the interpersonal and organizational trust-building in general, but not specifically on the trust-building between leaders and followers. Bligh [7] extended Mayer and Davis's model by arguing that competence should include not only domain-specific competence but also generic competence such as interpersonal competence to shape subordinates' trust in leaders.

Impact and Outcomes of Trust in Leadership

A body of literature showed that trust could lead to many positive outcomes at the individual and team levels. First, existing research showed that trust in leaders was positively related to employees' psychological well-being [28]. Besides, high levels of trust led to increased work engagement, job satisfaction, self-efficacy, knowledge sharing, and organizational commitment in workers [3, 12, 29-31]. Research also found that affective trust predicted "in-role" and "out-role" performance of employees [32].

Limitation of the Existing Literature

Several limitations could be identified from the existing leadership literature on trust. First, most studies were based on quantitative research methods, such as questionnaire survey. There have been no research studies conducted by adopting qualitative research methods with particular reference to the service economy. Second, most existing studies were conducted in Western contexts. Given the cultural differences, it is questionable whether the meaning of trust in leadership in Western cultures also applies to Chinese contexts. Third, limited studies explored trust in the SLT, which is an important leadership theory in the contemporary service economy.

Service Leadership Theory Proposed by Dr. Chung

Hong Kong has long been the business and financial center in Asia and a key meeting place for Chinese and Western cultures [33]. Since the end of the twentieth century, Hong Kong's economy has shifted from manufacturing to service orientation. In the 1990s, around 80% of Hong Kong's GDP was contributed by service sectors [34], while this number had risen to around 93% in 2014 [35]. The economic transformation has raised significant challenges to management and leadership in Hong Kong, requiring robust leadership qualities in young people.

As the co-founder of DHL International and the Chairman of the Hong Kong Institute of Service Leadership and Management (HKI-SLAM), Dr. Chung defined service leadership as "satisfying needs by consistently providing quality personal service to everyone one comes into contact with, including one's self, others, groups, communities, systems, and environments" [36]. Effective service leadership requires three key leadership qualities: competence, character, and care. First, generic leadership competencies such as task-related competence, leadership competence, and service competence are vital to an effective service leader. These competences enable a leader to have adequate domain-specific knowledge and skills, be able to lead oneself and others appropriately, and have the willingness and attitudes to serve. Effective service leaders should also possess moral characters such as integrity, fairness, and trustworthiness. According to Dr. Chung [36], people with character strengths are considered as friendly and trustworthy. Furthermore, effective service leaders should have care, which means concerns about the mind, body, and spirit of oneself, others, groups, and the whole system. Lack of any of the three qualities would lead to a failure of service

leadership. Compared to other leadership styles (e.g., ethical leadership), service leadership also stresses leaders' morality but upholds higher requirements for effective and successful leaders in the service economy [37, 38].

As trust is vital to successful leadership, the present paper investigates the idea and concept of trust in service leadership based on the interviews with Dr. Chung and his former colleagues, his autobiographic writing, and the scientific literature. The paper was developed based on a research project on the SLT conducted in 2019. As the co-founder of DHL International, Dr. Chung successfully led DHL to become a global service company. During this process, he developed and practiced the concept and theory of service leadership. After retiring from DHL, he has committed himself to the promotion of the SLT in Hong Kong. He has published several books about service leadership, such as *The 12 dimensions of a service leader* [39].

This study adopted in-depth interviews and document analyses. Both interviews and document analyses belong to qualitative research methodology, which is interpretive in nature and focuses on meaning exploration [40, 41]. Qualitative methods could help gain an in-depth understanding of a phenomenon within its real-life contexts [42]. We conducted five in-depth individual interviews with Dr. Chung and two group interviews with his two former colleagues who have over 25 years of working experience in DHL.

OUR STUDY

Interview is an important and commonly used qualitative data collection method. It is valuable in "gaining insights into people's perceptions, understandings, and experiences of a given phenomenon and can contribute to in-depth data collection" [41]. In this study, we used semi-structured interviews. Through open-ended questions, semi-structured interviews allow for unexpected answers, which could lead to a more in-depth discussion on the topics [41]. For the interview with Dr. Chung, the interview questions mainly focused on (a) definition and meaning of trust, (b) key elements of trust, (c) determinants of trust, and (d) the importance of trust to effective leadership. About the interview with his former colleagues, the interview questions mainly focused on how concepts and theories of service leadership (including trust) have been practiced in DHL. All the interviews were conducted from October 2019 to May 2020, which lasted from about 1.5 hours to 2 hours. During each interview, two researchers having rich experience in qualitative research were present as the interviewer and the observer. The process of each interview was audio-recorded and transcribed into full texts by trained research assistants. Besides, Dr. Chung's written materials and published books and articles were also collected.

Analyses of Interview Data and Written Texts

Thematic data analyses were employed to analyze the qualitative data conducted from Dr. Chung's written documents and interviews with him and his former colleagues in DHL. Thematic analysis is a commonly used method in qualitative data analyses, which identifies, analyzes, and reports themes (patterns) within data [43]. This paper adopted a combination of

“deductive” and “inductive” approaches in the process of data analyses [43]. First, a deductive approach was adopted in which the authors of the paper carefully read through all transcripts of interviews with Dr. Chung and his written documents, and categorized the materials based on different themes related to the topic of “trust” in the interview questions. Second, under each broad question, the authors further used an inductive approach to code data into different patterns/themes. Third, the authors merged certain themes to form the final pattern/theme structure. To ensure the reliability and validity, the completed coding was checked by two other researchers and further adjusted based on the peer check feedback.

FINDINGS

Four essential themes emerged based on the interviews with Dr. Chung and his colleagues in DHL as well as Dr. Chung’s written work. These themes are 1) definition and nature of trust; 2) determinants of trust; 3) importance of trust in service economy and 4) consequence of trust.

Theme 1: Definition and Nature of Trust

According to Dr. Chung, trust is a fundamental quality of being a “human being.” Confucius asked rhetorically that “how can one be acceptable without being trustworthy in words (*ren er wu xin, bu zhi qi ke ye*)?” Based on this fundamental idea, Dr. Chung believes that a leader should try his or her best to do things that can build trust with his/her followers. He argued that “the first thing we should do is to avoid doing anything that could destroy trust. And then think of all the things that can help increase trust.”

In general, Dr. Chung defined trust as “a feeling between two individuals,” which contains several levels and different types. At a lower level, trust refers to a feeling that the other person will not harm oneself. At a higher level, trust can be further categorized into morality-based trust and competence-based trust. Morality-based trust refers to the confidence developed based on the moral character of the person. On the other hand, competence-based trust is derived from the confidence in strong competence demonstrated by the person. For example, Dr. Chung said in the interview:

As for trust, I think it is a feeling between two individuals, which can be established at several levels. First, [you trust a person because] he will not hurt you. This is the lowest level of trust. Then there are several kinds of trust. One is the morality-based trust; the other is the competence-based trust. It is very simple to understand them. For example, you trust your brother, right? However, if your brother always does something wrong, you will not trust him in doing things, but you will still trust that he will not hurt you.

By integrating the idea of trust with the SLT, Dr. Chung further argued that trust could actually include three different types: competence-based trust, character-based trust, and care-based trust. For the competence-based trust, it refers to trusting someone because of his/her “reliability” in “doing things” or “accomplishing tasks.” In other words, trusting someone could do things well because the person has a high standard of doing things. The character-based or morality-based trust refers to trusting someone because of his/her high morality or strong character strengths such as honesty and integrity. The third type is the care-based trust,

which refers to trusting someone because of his/her caring for the welfare of others or benevolence. This can be illustrated by Dr. Chung's narratives in the interview:

We can link trust to the three Cs [Competence, Character, and Care]. The first one is the competence-based trust: whether a person is reliable or not [in doing things]; whether a person has a high standard of doing things or not. The second one is morality-based trust or character-based trust: whether a person will cheat others, does he lie, does he steal things? The third one is that you trust a person based on whether he would put his heart in doing things; if you work together with him, whether he cares about you and cares about the work to be done will also influence your judgement of whether he is trustworthy or not.

Furthermore, Dr. Chung proposed that trust is a system. That is, people need to employ a systemic approach to understand trust. The above-mentioned different types of trust are the interrelated elements in the whole system of a person's trust in another person. Therefore, one person's overall trust in another person is not determined by individual elements but by the interactions of different types of trust as a whole. In other words, different types of trust and their inter-relationship/interaction would finally produce a system affecting a person's trust in another person. Dr. Chung has explained this in the interview:

A lot of work is done in a system approach. The system must include different elements. These elements are interconnected, forming the purpose of the system. Trust is the function of the system as a whole. This is system thinking, which is different from linear thinking. Linear thinking is like making a tea ceremony because you need to go from the first step to the next step. System thinking is like viewing a painting. You can view the painting as a whole and also go to some details if you want.

Theme 2: Determinants of Trust

Based on Dr. Chung's definition, the development of trust could be determined by competence, moral character, and care, which are the three elements of effective service leadership. An individual's competence determines whether other people could trust him/her in accomplishing a task professionally. The competence-based trust not only applies to the leader-follower relationship but also relationships between organizations or between the organization and customers. If an organization cannot show competence in its services to customers, the customers would not develop trust in the organization. For example, Dr. Chung argued that one major reason that DHL has gained trust from customers worldwide is that DHL people always deliver goods or packages on time. Therefore, trust is established based on the strong competence of DHL in delivery services. For example, in his book entitled *Designed to win: What every business needs to know to go truly global* [44], Dr. Chung wrote:

"The Founders started a company that people trusted enough to give their most important documents to – they were trusted by individuals, banks, shipping companies, and trading companies. That trust was built on two things – speed and accuracy – as well as DHL's growing positive reputation. The best sales referrals always come from somebody in the same chain. For example, if DHL was courting a banker, we would suggest that the banker checks with the CEO of American Express for a recommendation of DHL's services. When the banker asked the Amex CEO – 'What do you think of DHL?' – they would hear that Amex had been using us for a reasonable amount of time. DHL was highly recommended due to our speed, reliability, and professionalism. At that time, DHL didn't realize that the reliability, not just of delivering on time, but also picking up at the same time every day, using the same courier, was so important to our customers. In fact, it defined us and differentiated us from all other transportation services."

The second factor influencing the development of trust is the moral character of the person. According to Dr. Chung, moral character of a service leader is the key determinant of trust between the leaders and the followers. For example, he claimed: “people trust you because you behave correctly and appropriately.” The moral character and behavior of a leader could develop in others a strong sense of trust, which helps leaders attract and retain high-quality followers. According to Dr. Chung, Chinese and Western cultural foundations share some moral principles and standards. Leaders who behave based on these moral standards and principles would develop trust in relationships with their followers. As argued by Dr. Chung in the interview:

[Among] the ten commandments, the first three are talking about God; the fourth to the tenth regulate how people have to behave or not behave if they want to live together as a community, for example, “don’t steal, don’t lie, and don’t cheat,” ...And now we compare it with Confucianism. We can see Confucian moral principles as the positive ones “*xiao, ti, zhong, xin, li, yi, lian, chi, zhi, ren, yong, shu*” (“filial piety, brotherly love, loyalty, truthfulness, propriety, righteousness, integrity, shamefulness, wisdom, benevolence, courage, forgiveness”). I talk about the ten commandments when I talk about ethics and characters, saying that you should not do these. These are the things, if you do, people will move away from you. And if people hear enough about these behaviors and there is a pattern, then you have a bad reputation. People don’t trust you, they don’t do business with you, and you stop being a leader.

Dr. Chung used a personal operating system to explain the importance of an individual’s moral character. The personal operating system comprises a person’s beliefs, values, and all other factors that shape the person’s character. A person’s moral character guides his/her behaviors. Dr. Chung believed that one person’s trust in another person is because he/she believes that another person would not do immoral things that hurt him/her.

The third influencing factor to trust-building is care. Besides competence and moral character, Dr. Chung also argued that leaders’ care could build trust between leaders and followers. All in all, he perceived that trust-building is determined by the three Cs of service leadership altogether but not by one single factor. As illustrated in his book entitled *12 dimensions of a service leader* [39]:

The key ingredients behind a great service leader are his or her 3Cs of Competence, Character, and Care. By making each one as strong as possible, the intersection of the 3Cs is our leadership potential. This is also the building block for establishing and maintaining our level of trustworthiness. Let’s also narrow things a bit and look at the tribe of the classroom, an environment where someone wants to emerge as a leader. Again, this leadership is a service you would be delivering to fellow students through a healthy blend of Competence, Character, and Care. In exercising this over time, the classmates will reinforce their acceptance and trust, which build self-esteem in the leader.

Theme 3: Importance of Trust in the Service Economy

Dr. Chung’s written work and interviews highlighted the importance of trust in leadership in the service economy. First, trust differentiates “a leader” from “a manager.” The manager’s function is mainly based on job duties, payment, and positions. This “functional” relationship is ineffective in gaining followers’ long-term loyalty and commitment and empowering followers to perform at their best or even beyond expectation. Therefore, a leader needs to build trust with followers, thus promoting stronger and closer bonds with followers. For example, Dr. Chung said in the interview:

The definition of a leader is separable from that of a manager. If I am a manager and you are my employee, you have no choice but to work for me because I pay your salary. However, if I am a leader and you are my follower, our relationship is not defined or shaped by money. If there is no trust, followers can leave and find somebody they can trust to follow. I believe that if you want to do something well, you need good followers. If you have many followers, but their service standards are not acceptable, your whole team performs poorly.

Second, trust between leaders and followers plays a vital role in delivering the best services in the service economy. Dr. Chung mentioned that to deliver the best services, frontline employees need to have strong initiative and autonomy to make on-the-spot decisions, which requires leaders' trust in employees. Dr. Chung explains this in his book [44]:

As we have discussed above, trust is fundamental to service network leadership. Your followers have to trust you if they're going to exercise autonomy and take the initiative – which they have to do, given the distributed, decentralized nature of the operation. And you need to trust your followers to do this, given that a service network can only work through such decentralization.

Theme 4: Outcomes of Trust

Two outcomes of trust were identified based on the interview data in the SLT. The first outcome is the employees' sense of fellowship and ownership, which would further maximize their work performance and service quality. This was articulated by one of Dr. Chung's colleagues in the interview:

Trust has been an important element of the culture of DHL. When I received an urgent delivery task in Hong Kong [and needed to deliver the package to the United States], I trusted my colleague in the United States who would deliver it to the customer. If I had any special request, I would tell him by telex or long-distance phone. I did not need to be worried about whether he would do it well for me because he would. And vice versa, if I receive his request, I will do everything to ensure that I can fulfill my commitment to him. He does not need to be worried either. I will tell him after completing the task. This is normal practice in DHL. The trust was built at a very early stage and then gradually became DHL's unique culture. When I promised our customers and told our overseas DHL colleagues, I could rest assured. When traveling overseas, we were very relieved as long as there were DHL offices. No matter what happened, we could always seek support from the local DHL office. This kind of trust is built in our hearts, and we also will perform this trust ourselves. (Colleague A)

The second outcome of trust is the followers' strong organizational commitment. An organization with a strong culture of trust would gain business success and followers' commitment because it appeals to human values. To trust and to be trusted are fundamental human values that sustain and shape social behaviors. Therefore, establishing a "trust" culture among the whole organization is vital for enhancing followers' commitment, loyalty, and identification to with organization. This was also illustrated by the interview with Dr. Chung's former colleagues in DHL:

Company culture must appeal to some personal values because we all want others to trust us and respect us. This is very fundamental. If you could repeat these things in your company's environment, people would naturally feel comfortable there. Otherwise, you are against some of their values. (Colleague A)

DISCUSSION

In this study, we attempted to obtain an in-depth understanding of the concept and idea of trust in service leadership based on in-depth interviews with Dr. Chung and his former DHL colleagues, Chung's written work, and the existing leadership literature. The paper has some features. First, the paper is pioneering in using an integrative approach combining qualitative data and literature review to explore the concept of trust in the service economy. One unique feature of qualitative research is its "richness" in describing and interpreting a phenomenon [45]. Second, this paper explores the meaning of trust in the SLT. Although the existing literature has investigated trust in different positive leadership theories, limited research has investigated the role of trust in the SLT. Third, this paper explores trust in the Chinese context, which enriches our current understanding of trust in leadership across different cultures.

Definition and Nature of Trust

Both interview data and literature regard "showing vulnerability" as a key element of trust. It is based on the belief that another person will not do harmful things to him or her. Therefore, trust is not regarded as an inborn trait, but a psychological state influenced by environmental factors. The literature suggested two types of trust, which are cognitive and affective oriented [6, 11]. Cognitive trust is developed based on rational assessment of the leader's competence and moral character. Affective trust is built on leader-follower emotional connections. Among the three types of trust proposed by Dr. Chung, competence-based and character-based trust could correspond to cognitive trust, and care-based trust could correspond to affective trust. Besides, according to Dr. Chung, trust is a system determined by the interactions between different determining factors.

Determinants of Trust

In line with the existing research, results demonstrated the importance of leaders' qualities in building trust between leaders and followers. These qualities include competence, moral character, and care, promoting different types of trust. First, domain-specific competence of leaders promotes trust between followers and leaders. Competence-based trust could be established when one person perceives another person capable of performing a task professionally. Dr. Chung also considered the company's strong competence in delivery service a key reason for DHL being trusted by customers. In the literature, Mishra [26] listed leader competence, such as the capability to make sound and professional decisions, as an important factor of followers' trust in their leaders. Besides, literature also suggests that trust could be built on leaders' generic competence, such as interpersonal competence [7]. Therefore, both domain-specific and generic competence could help to promote trust.

The second determinant of trust is moral character. In line with the existing literature, this paper highlights the importance of moral character of leaders in building trust between leaders and followers. Leaders with moral characters would treat their subordinates fairly,

communicate with them openly and honestly, care about their welfare and interests, and promote their higher levels of trust in leaders [19]. Besides, moral character such as integrity and behavioral consistency could provide a certain level of predictability, which helps subordinates cope with uncertainty [46]. Although the existing literature suggests the important role of moral character of leaders in shaping trust, it mainly focuses on specific moral character attributes such as integrity, honesty, or loyalty [25-27]. Dr. Chung's ideas add value to the existing literature by arguing that leaders' moral character as a whole determines followers' trust in leaders.

The third determinant of trust is the care of a leader. Scholars have proposed that benevolence is an important determinant of trust in leadership, which refers to leaders' concern for the needs, interests, and well-being of followers [7, 27]. This corresponds with Dr. Chung's idea that trust could also be established based on followers' perceived care and love of leaders. Finally, Dr. Chung's perception of determinants of trust goes beyond the existing literature. He states that trust development is a system in which the three determinants interact and shape the followers' trust in a leader.

Outcomes of Trust

One outcome of trust in service leadership is the development of employees' sense of fellowship and ownership. As pointed out by McCulloch [47], fellowship has elements such as identification, cohesion, sense of membership and responsibility. The sense of fellowship is vital for individuals and organizations. It manifests the values and responsibility shared by members of a group [47], which are vital for organizational success in the service economy. Besides, employees possessing a strong sense of ownership would do their best in their positions or even perform beyond their job requirements to best satisfy the needs of customers [48, 49]. Furthermore, this paper illustrates that trust-building is fundamental because it pertains to "human values." Followers having a strong trust in leaders would demonstrate strong organizational loyalty and commitment, which contribute to higher performance and long-term success. This is in line with the existing literature, which shows that high levels of trust would benefit a wide range of individual and organizational outcomes [3, 29].

Although this paper adds value to literature by focusing on the importance of trust in a service-oriented economy, there are limitations of this study. First, this study only involved Dr. Chung and two senior colleagues in DHL as three key informants. Multiple informants in DHL, such as leaders, employees, and other stakeholders, should be recruited to understand trust in the service economy. Besides, interviewing successful service leaders in other service companies would enhance the richness and validity of the findings. Second, as this paper only employed interview and document analyses as the major data-collection tools, other data-collection tools in qualitative methodology such as field observations can also be employed to further validate the findings of the paper.

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Chapter 154

SELF-LEADERSHIP IN THE SERVICE LEADERSHIP THEORY

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ABSTRACT

The economy in many countries has been transforming from a manufacturing economy to a service economy. The service economy requires service providers to have strong self-leadership to direct and improve oneself and make on-the-spot decisions independently before leading others. Although existing research has demonstrated the importance of self-leadership to both individuals and organizations, there is a need to examine self-leadership in the service economy based on the service leadership theory (SLT) proposed by Dr. Po Chung (co-founder of DHL International). With reference to the existing literature on self-leadership and the SLT and interviews with Dr. Chung and his former colleagues in DHL, we examined the nature and outcomes of self-leadership in the service economy according to the SLT. Besides, we explored strategies to improve self-leadership based on DHL practices. This study emphasizes the significance of cultivating and practicing self-leadership in the service economy and highlights practices adopted by DHL International to improve self-leadership in organizations.

INTRODUCTION

Self-leadership can be regarded as a starting point for fostering work performance, improving personal well-being, and achieving personal development [1, 2]. One needs to constructively improve self-leadership before successfully leading others [3]. The concept of self-leadership can be understood in terms of behaviorism [4] and social learning theory [5].

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In this way, self-leadership is regarded as a set of learned behavior skills, which can be trained and improved [6]. Despite of the positive influence of self-leadership on individuals and organizations, most extant leadership models focus on leading others rather than leading oneself [5].

Conceptualization of Self-Leadership

The concept of self-leadership has been defined in varied ways. Self-leadership is grounded in several self-influence theories, including self-regulation [7], self-management [8], intrinsic motivation theory [9], and social cognitive theory [5]. However, the concepts of self-leadership, self-regulation, and self-management are different. On the bottom of self-influence is self-regulation, consisting of self-observation, self-evaluation, and self-reaction [10]. The concepts of self-regulation and self-management mainly focus on managing behaviors to meet external standards. On the contrary, self-leadership adopts a broader perspective, stresses intrinsic values and motivational potentials, and acknowledges the external rewards associated with performing tasks. Thus self-leadership includes the concepts of self-regulation and self-management [11]. As defined by Manz [11], self-leadership refers to “a comprehensive self-influence perspective that concerns leading oneself toward the performance of naturally motivating tasks as well as managing oneself to do work that must be done but is not naturally motivating” [11].

Neck, Stewart and Manz [12] regarded self-leadership as a process, including self-motivation and self-direction to effectively complete tasks. Self-leadership strategies include three types of strategies [13]. First, behavior-focused strategies emphasize behavioral change through self-regulation and attention, such as self-observation, goal setting, punishment, and reward. By cultivating desirable behaviors and prohibiting undesirable behaviors, these strategies are specifically useful in managing behaviors to complete unpleasant but necessary tasks. Second, natural reward strategies include creating enjoyable and delightful features into tasks and shaping one's feelings of the tasks [14]. These strategies would enable individuals to accomplish tasks based on intrinsic motivation. People are rewarded by completing tasks and would feel gratified during the process. The strategies would increase perceived self-determination and competence, which are the two fundamental elements of intrinsic motivation [15]. Third, constructive thought pattern strategies concentrate on setting up thought patterns in desirable ways. These strategies include analyzing and improving belief systems, managing self-dialogue, mentally imagining possible results of behavior to be taken, and using positive scripts to replay the ineffective ones [16, 17]. Constructive thought pattern strategies are effective mechanisms to enhance the thinking process and behaviors for goal-setting and goal-accomplishing [18].

Besides the three self-leadership strategies, scholars also identified specific personal factors or qualities that could promote self-leadership, such as self-directed learning readiness [19] and reflexivity [20]. In addition, Rose [21] argued that the process of self-leadership includes a positively reinforcing cycle, including self-esteem, self-concept, self-confidence, positive attitude, self-motivation, and positive behavior. Starting from self-esteem and self-concept, each element in the process would strengthen the following element. Therefore, in this self-leadership model, self-esteem, self-confidence, and self-concept are contributors and consequences of self-leadership.

Self-Leadership, Psychological and Physical Health, and Job Performance

Self-leadership can foster self-motivation and self-direction through different behavior- and cognitive-focused strategies [13]. Existing literature suggests that self-leadership would benefit individual development, including psychological health, physical health, and work-related positive outcomes. First, research has shown that stronger self-leadership would promote individuals' psychological health. Several experimental studies revealed that self-leadership training could promote individuals' self-efficacy and positive affect [17, 22]. Dolbier, Soderstrom and Steinhardt's [23] research showed that self-leadership was positively associated with employees' psychological functioning, psychological well-being, and physical well-being. Research also found that self-leadership would increase self-efficacy and positive affect, consequently strengthening stress-coping abilities and reducing stress [24, 25]. Furthermore, Rose [21] argued that self-leaders would possess self-esteem and self-confidence. Godwin, Neck and D'Intino [26] proposed that self-leadership strategies could enhance one's spirituality.

Previous research also revealed the positive impact of self-leadership on work-related outcomes, such as employees' job satisfaction, commitment, and work performance. For example, Bailey, Barber and Justice [27] found that self-leadership predicted a 4% increase in job performance at the individual and organizational levels. Similarly, Hauschildt and Konradt's study [12] revealed that strong self-leadership could promote individual and team proficiency. Besides, studies conducted in different fields, such as nursing and education, have consistently shown that self-leadership is associated with higher job satisfaction and lower turnover intention [28]. Lovelace, Manz and Alves [29] suggested that introducing self-leadership into the working environment can facilitate healthy regeneration and engagement, leading to a greater feeling of control and a more active working environment.

Besides bringing positive work-related outcomes, self-leadership can help reduce stress and improve coping skills. Individuals with self-leadership can analyze the stress situation based on their available resources and capabilities and figure out solutions. Houghton and colleagues [30] argued that self-leadership strategies could help individuals effectively cope with stress in life and working environments. Wang, Xie and Cui [31] found that all three self-leadership strategies were positively associated with positive stress coping.

Self-Leadership and Leadership Development

Although different theories have discussed definitions and strategies of self-leadership, little research has focused on the role of self-leadership in leadership development. Only limited studies have revealed that self-leadership is the foundation for the development of positive leadership capabilities. For example, Cunha et al. [20] argued that self-leadership is a prerequisite for leaders to lead and influence others. Besides, self-leadership was found to predict positive leadership styles, such as transformational leadership, but negatively predict undesirable leadership styles, such as laissez-faire leadership [32]. Another study also found that self-leadership based on behavioral-focused strategies positively predicted transformational leadership [33]. Also, research showed that leaders using behavioral-focused self-leadership strategies would demonstrate more positive leadership behaviors [34].

Research Gaps

The existing literature on self-leadership has mainly focused on the theoretical discussion and expansion of self-leadership strategies. Besides, self-leadership is often regarded as a process but not a personal quality. The theoretical discussion and empirical exploration of the role of self-leadership in different leadership paradigms are also scarce. Notably, the service economy calls for new leadership paradigms, such as service leadership. However, questions such as how self-leadership is related to service leadership and what roles self-leadership plays in the service leadership process remain unanswered.

The emergence of service leadership responds to the increasing dominance of the service economy in many countries and areas. For example, the service sector's contribution to Hong Kong GDP was 92.2% of GDP in 2009 and reached 93.1% in 2018 [35]. Hong Kong's economy has been dominated by service industries, including banking services, international trades, real estate services, tourism, convention, and exhibition services. The service economy sets new requirements for service providers. Knowledge and skills become the input of production, and service is the "product." The service process involves human interactions between service providers and service recipients. Service providers' knowledge, attitudes, characters, and intrapersonal and interpersonal competences become the key to high-quality service. Leaders are required to have high quality and strong soft skills to motivate and inspire followers. Given this leadership paradigm change, Dr. Chung, the co-founder of DHL International and the Chairman of HKI-SLAM (Hong Kong Institute of Service Leadership and Management), proposed the "Service Leadership Theory (SLT)." Based on Dr. Chung [36], service leadership refers to "satisfying needs by consistently providing quality personal service to everyone one comes into contact with, including one's self, others, groups, communities, systems, and environments." Effective service leadership is determined by three qualities of service leaders: competence, character and care [37]. The service leadership paradigm emphasizes both the "being" and "doing" of leaders. In particular, the "being" of leaders is vital as human assets become essential in a service economy. Attracting, motivating, and retaining high-quality employees become the core of leadership tasks. The service leadership paradigm holds several beliefs [37]. First, leadership effectiveness is not solely determined by possessing generic leadership competence but also by demonstrating character and care. Second, leadership is a "service," as leaders need to continuously improve their competence, character, and care to provide high-quality service to both themselves and others.

Research Questions

Based on the SLT, self-leadership quality is essential to service leadership's success. However, limited literature has discussed self-leadership in a service economy. Remarkably, no literature has systematically discussed the role and essence of self-leadership in the SLT. The present study aims to fill in the research gaps by discussing self-leadership in the service economy according to the SLT. This study tries to answer the following two research questions:

- 1) What are the conception and essence of self-leadership in the leadership context?
- 2) What role does self-leadership play in service leadership in the service economy?

OUR STUDY

The present study constitutes a part of a larger project on the SLT and service leadership education. The present study adopted a qualitative approach. The primary reason is that the qualitative approach, compared to the quantitative approach, allows more significant details into subjective meaning [38, 39]. Among different qualitative approaches, narrative inquiry enables researchers to systematically analyze and present people's voices and life stories through structured inquiry such as autobiographical writing and structured interviews [40, 41]. Given the nature and the objective of the study, we considered narrative inquiry an appropriate method.

Data Collection

Centering on the concept of self-leadership in the SLT, the present study inquired into the experiences and life stories of Dr. Chung and two of his former colleagues who had over 25-year working experience in DHL. As the founder of SLT, Dr. Chung was invited to share his stories regarding the establishment and development of the SLT and his interpretation of different dimensions of the theory via autobiographic writing and interviews. His colleagues were invited to attend two group interviews to unfold their service leadership experiences, including how self-leadership was structured and mediated in DHL practices. The interviews were designed to be semi-structured to provide greater space for informants to express and thus maintain the depth and flexibility of the data [42].

All the data were collected during October 2019 and May 2020. Informed consent to collect the informant's autobiographic writing, interview, and audio-record was obtained from each informant. Each interview lasted between one hour and two. Four out of seven interviews were conducted in Cantonese or with code-switching between English and Cantonese.

Data Analysis

The interviews were transcribed and cross-checked by a team of research assistants. The interviews conducted in Cantonese were translated into English. Thematic analysis was employed to generate patterns and identify themes. An initial round of data analysis was performed by three experienced researchers to identify the pieces of text that matched the focus of the study. One researcher carefully went through the text, generated initial codes and patterns, and further reviewed the codes and patterns to generate themes. The identified themes were sent to the other two researchers for peer-checking and then to the corresponding informants for member-checking. Based on feedback, the researcher revises, refined, and finalized the themes. This conduct was to improve the accuracy and credibility of the

analysis. Notably, the data analysis was also complemented by a review of works in the related field.

FINDINGS

Theme 1: Self-Leadership is an Indispensable Type of Service in the SLT

A distinguishing characteristic in the SLT is that it sheds light on the indispensable relationship between self-leadership, service leadership, and self-actualization [3, 43]. Core in this belief is that self-serving is a crucial type of service. Long-term self-management and self-improvement is the foundation and prerequisite for providing quality service in other service realms, i.e., the realms of others and systems [37, 44]. This core belief contrasts with many existing leadership models, such as charismatic leadership [45] and servant leadership [46], which do not show much concern for self-leadership. Some other leadership models, such as transformational leadership [47], allude to the notion of self-transformation and self-improvement but only conceive it as a pathway to effectively lead followers and overlook the service orientation towards the leaders per se. On the contrary, the SLT conceptualizes services as an integral system of different service orientations, in which self-serving is a crucial part:

“Leadership is a service aimed at ethically satisfying the needs of self, others, groups, communities, systems, and environments” [36]

“Service includes self-development efforts aimed at ethically improving one’s competencies, abilities, and willingness to help satisfy the needs of others” [36]

“A leader’s greatest self-actualization comes by helping everyone in his or her network to meet all their needs, including each person’s individual self-actualization” (Chung’s autobiographic writing)

“If you don’t take care of yourself, then everyone else who comes into contact with you won’t be happy or enriched by the experience of receiving your personal service” [48]

Reiterated in both the collected data and Dr. Chung’s publications is that service leaders should pay due attention to the balanced needs and development of others and themselves. It is a critical process during which individuals can realize their self-actualization.

Theme 2: Constant Practice of Self-Leadership Contributes to the Development of Service Leadership Attributes

The SLT is structured as a 3C model that incorporates the components of competence, character, and caring disposition in building up effective service leadership [49]. The theory perceives service leadership attributes related to the three components as trainable and malleable. Service leaders can develop those attributes through self-empowerment and self-improvement and by constantly aligning personal strengths with goals [3, 37]. These all point to the importance of self-leadership in service leadership development:

“The other thing is that care is trainable. It is like your muscle. You can train your muscle, and you can train your care. One way of care for training would be “awareness”. Awareness is very important. Being aware of it and then being aware that you can train your compassion and your care. I can give you a link, particularly about positive meditation. First, you have to care about yourself, so you close your eyes, you meditate, and then you feel that you care about yourself and then care about everybody around, in the room or in the family. And then if you do that, practice that for a while, then you feel that you are really contributing to the university, to Hong Kong, and to the universe eventually” (The fourth interview with Chung)

“You need to cultivate your morality, as Confucius said...you can’t be a person of disloyalty or a person who shows no righteousness or trustworthiness... I check myself every day. I check if I am loyal to my friends or if I practice what I have learned, right? This is self-serving. By doing this, you are doing your leadership. Most importantly, being a leader means cultivating your morality” (The fifth interview with Chung)

“There are many emotions that may be driving us, and depending on your personal make-up, you may need to focus on the management of specific emotions within you” [48]

“The thing that I can think of being directly connected to competence is continuous improvement...What is my observation? Those (capable) persons keep learning...” (The second interview with DHL staff)

The positive association between one’s self-managing/self-development (key components in self-leadership) and competence development has been identified and documented in many empirical studies [27, 50]. Notably, the excerpts above and Chung’s publications elsewhere make it explicit that the application of self-leadership should be extended from the “doing” dimension (i.e., leadership skills/competence) to the “being” (i.e., moral character).

Theme 3: Development of Self-Leadership Requires Self-Reflection and A Life-Long Learning Mindset

Practicing self-reflection allows one to give serious thought to his or her behavior and mentality, bringing clarity to the strengths and weaknesses of oneself [51]. The importance of introspection emphasized in the SLT resonates with Kanfer and Ackerman’s argument that self-observation, self-evaluation, and self-reaction underpin self-influence [10]. The importance of constant self-reflection and self-awareness to self-leadership is shown in the following excerpts:

“Becoming a better leader means developing your competence, character, and care, and for that to happen, you need to be self-aware. By being aware of the importance, ingredients, and paths to leadership, and are committed to improving, then this awareness followed up with action is a great recipe for improvement” [48]

“I involve in a lot of things every day. If I do not check my self-leadership every day, I will be sluggish” (The fifth interview with Chung)

Fostering a Life-Long Learning Mindset

It is highlighted in the SLT that the concept of self-leadership transcends self-management or self-regulation, which accents the influence of external rewards or recognition [3]. According to Dr. Chung and his formal colleagues, it is important for service leaders to be psychologically and mentally engaged in committing themselves to be life-long learners. In other words, they should be intrinsically motivated to pursue self-improvement and self-perfection [3, 11]. The transformation of mentality requires embracement of many qualities such as humility and curiosity, exemplified in the quotes below:

“In terms of being leaders, it is important for them to be equipped with curiosity and engage in continuous learning because you need to set examples for your followers. Only through continuous improvement, you can keep your credibility and professionalism as a leader” (The second interview with DHL staff)

“(After a business from Beijing) This experience really broadened my horizon...I told Agnes, ‘I realized there are so many things I don’t know’. I thought I was quite good before that, but when I was there, I found many lecturers and tutors were at the master level, using their own books or publications to teach us. I opened my eyes and realized I was not as good as I thought... But I was happy because it came to me that I was not that capable. After this, I would not say I was quite good. I learned to be humble” (The first interview with DHL staff)

“When it comes to how to strengthen and improve your mental dimension, the greatest single piece of advice I can think of is to commit yourself to the path of lifelong learning” [48]

Theme 4: Organizations Should Highlight a Culture That Cultivates Self-Leadership

An organization with a high level of autonomy and a strong sense of ownership creates a culture of accountability, flexibility, and empowerment [52]. In such a culture, employees have the propensity to make a positive transformation and achieve personal accomplishments [3]. To create this culture, employees should be encouraged to make their own choices and take ownership of their actions, and accordingly, leaders need to put trust in employees’ competence and minimize intervention to the delegated tasks. Second, leaders should allow employees to take risks and make mistakes and guide them to learn from the mistakes and treat mistakes as a pathway to self-improvement [53]. Based on the career trajectories as well as DHL practices, Dr. Chung and his former colleagues shared their views of the importance to boost such a culture for nurturing self-leadership:

“Make sure that the only mistake that they cannot make is a moral mistake, otherwise let them make a mistake...because when a courier is on the street, collecting documents and delivering documents, they are on their own. We did not have mobile phones at that time. They cannot call their supervisors and say: ‘what should I do?’ Also, if the supervisor has six people to supervise. If everybody calls the supervisor one phone call per day, the supervisor has six phone calls. And six supervisors, which means the manager has 36 phone calls per day. You cannot. So, what we teach them is autonomy, being able to make the best decision, being the best version of himself as a courier, best version of himself as a supervisor, best version of himself as an assistant manager. That’s what we try to do. Assistant manager should learn from all the mistakes from the courier, the supervisor and himself” (The first interview with Chung)

“...You have to explore the culture and values widely accepted by all, and then you build up them and make them flourish. For employees, this move can lead to a sense of ‘I find part of me in this environment’, which initiates their transformation. They will feel that they are not required to do work, but to do it out of their own choice...If they feel they are granted autonomy to make their own choices, they will be much happier and develop more sense of ownership. By making them feel a part of the work, you can bring about their transformation” (The second interview with DHL staff)

“The permissive culture of allowing non-moral mistakes was huge because anyone and everyone were allowed to screw up – including the boss – and no one lost face by making mistakes...With the ‘some mistakes are okay’ tenet, nobody felt the need to dig in to defend mistakes. The value of this was that learning from a specific mistake was adopted quickly and shared with the entire network through the channels of communication we had established” [53].

“(DHL) gave me many opportunities. Most senior staff wouldn’t run the whole show. For one thing, that would be too much to take, and second, you would leave others enough opportunities to develop. I found we were very confident because you believed in your confidence. Even for those things out of our league, your boss believed in your competence even more than you did. Imagine this” (The first interview with DHL staff)

Theme 5: Organizations Should Provide Wide Access to Learning and Development Opportunities

The DHL colleagues' narratives illustrated three ways of how DHL is committed to promoting life-long learning and development: First, DHL cultivated a self-leadership mindset by creating an environment where everyone engaged in skill-building, professional learning, and potential expansion through regular training courses. The courses were not designed for junior staff only, but also managers and executives. As trainers, the senior staff would need to learn how to teach and share better, update knowledge, and set examples for followers. Second, DHL also financed formal education to encourage systematic learning alongside work. Third, employees were rotated among various positions or departments to broaden their skill sets.

"...All department heads or above would have no other option but be nominated as trainer automatically. You would be trained as a trainer first, and as a trainer or facilitator, you need to lead your colleagues from your department and other departments too...We also had other regular courses (for the trainers) such as the management course, where the trainers would sign up, being trained by the training consultants, and evaluated their strengths...DHL built a culture like this. You would be assimilated by this environment, and even you were not the type of manager or executive before" (The second interview with DHL staff)

"In DHL, many would apply for further study because you would have a clear vision that if you hope to be a manager, you'd better have a degree. You should start from getting a degree if you couldn't do anything else (to improve yourself). Many of us did not graduate from high school, but they ended up getting a certificate, diploma, degree, and master's degree. Many, like Chan (pseudonym), she was our colleague. She was so diligent... She got one degree and two master's degrees here... She first started working after Year Six, but because of this environment (of DHL), she was encouraged to keep learning" (The first interview with DHL staff)

"DHL was a small company then. The bad news is you had to do everything on your own, but the good news is you could learn everything because of the blurred boundary. I remember we had to take calls, arrange the routes, and pick up mails... If we received a bill from the account, we would give it to the corresponding customer and ask for the payment. We would also do packing if got back early..." (The first interview with DHL staff)

DISCUSSION AND CONCLUSION

The present study explored self-leadership in the service economy based on the existing literature, Dr. Chung's autobiographic writing, and interviews with Dr. Chung and his two former colleagues in DHL. Some observations can be drawn from the results.

First, self-leadership is essentially a type of service that one provides to oneself for self-improvement and self-direction. Many leadership theories have mainly focused on the influence of leadership on employees' development but not leaders' own developmental and psychological needs, thus neglecting the importance of self-leadership. Based on the SLT, leadership is a "service" that one can provide to others as well as to "one's self." The notion of self-leadership in the SLT transcends the concepts of self-regulation and self-management, representing a broader perspective of the self-influence theories. As revealed in Chung's narratives, self-leadership is essential for service leaders to achieve "self-actualization." Dr. Chung also stressed the importance of self-reflection and lifelong learning in achieving self-leadership. Individuals with self-leadership can regulate their behaviors and intrinsically

pursue self-improvement [11]. Specifically, self-leadership will direct one's behavior to conform to social norms and requirements. Meanwhile, it will cultivate self-motivation to guarantee sustainability [13]. A service leader should devote to be a life-long learner [3]. Self-leadership can facilitate service leaders to maintain their credibility and advance their profession with the times.

Second, results indicate that strong self-leadership helps service leaders continuously improve their competence, moral character, and caring disposition, which are the three determinants of effective service leadership. Existing literature has mainly focused on the competence aspect of self-leadership in terms of managing one's behavior and thoughts to achieve specific tasks [11, 18]. However, as revealed in the results, the meaning and essence of self-leadership in the SLT go far beyond the traditional meaning of self-leadership. According to the SLT, self-leadership refers to a more comprehensive self-improvement or self-perfection process integrating the "doing" aspect (i.e., competence) as well as the "being" aspect (i.e., characters and care) of a person [37, 43]. Leaders with strong self-leadership tend to have a healthy body, strong minds, spirits, and the ability to satisfy others' needs. In other words, self-leadership does not solely aim to complete specific tasks but to achieve self-perfection and become a role model to influence others.

Third, although self-leadership is a self-serving endeavor, it does not only improve leaders' own leadership attributes but also benefits others and the system [37, 43]. Through self-improvement, service leaders can align their strengths and purposes with collective goals, use different strategies to improve themselves, and strive for excellence, which can further benefit organizations' function and performance. Shek and Lin [37] stated that individuals need to put great efforts to continually improve themselves before they can fully engage in serving the public. Constant self-leadership practice can enhance organizations' creativity, vitality, and team commitment [49]. Through self-leadership practice, positive interaction between co-workers and between leaders and followers can be established and enhanced, leading to an increase in individuals' belongings and organizations' development.

Fourth, results highlight some practices to improve self-leadership in organizations. The service economy requires service providers to possess high levels of independence, self-initiative, on-the-spot decision-making, and problem-solving skills. Service providers need to become "self-leaders" who could motivate themselves and make sound decisions independently. Thus, it is important to cultivate employees' self-leadership in organizations by establishing a supportive organizational environment. For example, grant a certain level of autonomy could develop employees' intrinsic motivation and self-leadership to achieve success in work performance. As mentioned in the interviews, when DHL frontline couriers have autonomy and the ability to use autonomy properly, they can make the best contingent decision on the spot. This experience will increase their self-worth, self-determination, and motivation. As more autonomy often leads to higher responsibility and accountability, employees may feel reluctant to use their autonomy or innovate. Thus, organizations may support employees' self-leadership practices by allowing their mistakes. For individuals, mistakes are the pathways to achieve self-improvement. Neck et al. [13] stated that self-leadership could boost self-motivation and self-direction in coping with behavior, affect, and cognition. Individuals with strong self-leadership can transform mistakes into precious experiences and improve himself or herself through this lesson. The effectiveness of self-leadership depends on the level of organizations' autonomy and the sense of ownership. To what extent individuals can achieve self-improvement is closely related to how leaders allow

individuals to take action on their behalf and make mistakes [52]. For organizations, allowing employees to make mistakes shows leaders' care at the situation, which would enhance relationships between leaders and followers and drive a harmonious organizational atmosphere [54].

Although this study integrates the writings of Dr. Chung and interview data collected from Dr. Chung and his colleagues, there are some limitations to this study. First, we only adopted qualitative methods in this study. It would be informative if quantitative data could also be collected and included in the analyses. Second, the information source was limited, as only three informants were involved. Involving more DHL staff at different organizational levels would help present a more comprehensive picture. Third, more empirical studies should be conducted to examine the impacts of self-leadership on individual and organizational outcomes in the Chinese context.

Despite the limitations, this study outlines the critical role of self-leadership in the service economy under the SLT. In line with previous studies, self-leadership is closely associated with positive employee outcomes in the service economy. These positive outcomes would motivate employees to provide high-quality services to themselves, co-workers, customers, and organizations, thus achieving individual and organizational success in the service economy. A supportive organizational environment, including personal training and policy, would promote employees' self-leadership.

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Chapter 155

THE FUNG SERVICE LEADERSHIP INITIATIVE IN HONG KONG

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ABSTRACT

Although there are leadership programs in the higher education sector, most of them are elitist leadership models and rigorous evaluation is not common. With reference to the emerging leadership needs in the service economy, the Victor and William Fung Foundation initiated a program to support the universities funded by the Hong Kong SAR Government to develop Service Leadership education programs and curricula materials. In this paper, we introduce the background and nature of the “Fung Service Leadership Initiative” and the “Hong Kong Institute of Service Leadership and Management (HKI-SLAM).” We also present the work done by the eight universities. With particular reference to The Hong Kong Polytechnic University, we examined the evaluation findings supporting the Service Leadership education initiative. Finally, the contributions of the Fung Service Leadership Initiative and future challenges are described.

INTRODUCTION

In the last decade, the services sector has expanded tremendously in Hong Kong, contributing over 90% to the local GDP [1]. The variety of service industries in Hong Kong ranges from import/export, finance and insurance, public administration, and tourism to information and communication [1]. Labor in a service economy is no longer perceived as mere input, but as an interactive learning, development, and transaction process [2]. As a result, this service-oriented economic environment of Hong Kong constitutes a novel ecology for local graduates who are now expected to be armed with both the hard skills (e.g.,

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specialized knowledge and professional skills), soft skills (e.g., intrapersonal skills), and good character (e.g., work ethics, trustworthiness) [3]. Researchers and educators have also developed a consensus that leaders with a service mindset are highly demanded in the contemporary Hong Kong society [4, 5]. However, the leadership programs in tertiary education in Hong Kong are often trait-based, overvaluing the leadership competencies and skills at the cost of adequately cultivating students' character, caring disposition, and service mindset [6, 7]. Besides, existing leadership programs in the higher education sector are mostly elitist leadership programs, assuming that leaders can only be generated from the "cream of the cream." This mode of leadership training actually reinforces the Hong Kong culture that only those who achieve academic excellence can serve as leaders. As Chung and Bell [8] argued, "our educational institutions and company training programs put so little planning, effort, or resources into teaching people how to succeed in the service economy" (p. 115-116).

Li & Fung Service Leadership Initiative (SLI) and the Hong Kong Institute of Service Leadership and Management (HKI-SLAM)

In response to the urgent call for a shift of focus on leadership education and practices in Hong Kong, Po Chung founded the HKI-SLAM in 2011 [9]. The mission of this institute is to join hands with interested communities, agencies, companies, and institutions to develop and strengthen service leadership learning and practices [9]. As highlighted in the conference booklet of the International Conference on Service Leadership Education in Service Economies (ICSLE) [10], service economy requires a new concept of leadership:

"The primary paradigm shifts embrace new ways of thinking about service, leadership, and service leadership. They are:

- Leadership is a service aimed at ethically satisfying the needs of self, others, groups and communities.
- Every day, people experience service and leadership opportunities. Everyone also possesses the potential to improve his or her leadership effectiveness and service satisfaction.
- The server is the service. Judgments about leadership effectiveness and service satisfaction are influenced by followers and customer experiences and judgments made about the competency, character, and caring social disposition of a leader or service provider.
- Service Leadership is about creating new personal service propositions and consistently striving to provide high quality caring service to everyone who one comes into contact with, including oneself" (p.4).

Before the establishment of HKI-SLAM, Po Chung had already embarked on conceptualizing a leadership model that allows a good alignment with the demands of a service age while incorporates traditional Chinese culture and values, where he assembled, reconstructed, and refined his 40-year experiences in the field of leadership and entrepreneurship [11]. In collaboration with other colleagues, Po Chung identified 12 dimensions of the attributes of an effective service leader [12]. His proposed model provides a theoretical framework for service leadership education. Notably, this leadership model does not only apply to the conventional service industries such as tourism and catering, but a

variety of modern service industries such as information and technology, education and financing [13].

The initial collaboration between the HKI-SLAM and the Victor and William Fung Foundation began as early as in 2011. This Foundation is a local-registered charity, which commits to promoting leadership development and thought leadership, as well as nurturing future leaders for the society. The collaborative effort was made to exchange ideas about how to promote service leadership through university courses and programs. In January 2012, the Victor and William Fung Foundation earmarked a grant of HK\$40 million to officially fund the Li and Fung Service Leadership Initiative (SLI) [14]. In the announcement on 15 January 2012, it is stated that:

“Hong Kong derives more than 90% of its GDP from the services sector, said Dr. Victor Fung, Chairman of the Board of the Foundation. ‘For Hong Kong to maintain its competitiveness in the prevailing trend of globalisation, we must maintain leadership in the Services Sector. In this regard, I believe our young people will benefit greatly from an education which will provide them with a good framework and hands-on experience to make a long-term commitment to Service Leadership.’ Dr. Fung also stressed that Hong Kong’s next phase of development, in the context of China’s latest 12th 5-year Plan, emphasises the development of the services sector.”

The Fung SLI represents a partnership between HKI-SLAM, the Foundation, and the eight public universities in Hong Kong, with all of them sharing the same vision of developing a curriculum to cultivate undergraduates into effective service leaders and maintain Hong Kong’s position as a global social leader [9, 14]. Each university was totally autonomous and could develop its own research-supported curriculum and materials as well as creating experiential learning opportunities for its students, which can include credit-bearing academic courses, non-credit-bearing programs, and extra-curricular activities. The curriculum should generally address the guiding principles and the values of the Service Leadership Theory (SLT), such as the 3Cs (competence, character, and care) of leadership, the belief that everyone possesses the potential to be a service leader, and the values of being a life-long learner [11]. Pedagogies that facilitate learners in applying, assessing, and questioning the values and beliefs in the SLT were encouraged [11].

As mentioned in the ICSLE [10], the collaboration amongst HKI-SLAM, Fung SLI and the universities is as follows:

“HKI-SLAM provides its SLAM curriculum framework and serves as the secretariat of the Fung Service Leadership Initiative. The Victor and William Fung Foundation provides catalyst funding and intellectual support. Each university provides a principle investigator and other supporting colleagues who participate in regular exchange of research findings about service leadership and in sharing ideas about how university education might help sustain Hong Kong’s reputation as a global service leader. This collaboration provides a unique curriculum development research platform for the universities. Each participating university is empowered to autonomously develop its own research-supported curriculum that is reasonably aligned with the SLAM framework and the unique needs of its students, the institution, and the communities the university serves.” [10]

ACHIEVEMENTS OF THE FUNG SLI

With the support of the HKI-SLAM and Fung SLI, the eight universities developed their own curriculum materials and projects with the aim of promoting service leadership education

(SLE) in the emerging global service economic ecology. While the focus is on service leadership, each university has complete academic freedom to develop its own education program and material. The current section presents the deliverables of the SLE in the respective universities based on their presentations in the 2016 ICSLE.

City University of Hong Kong (CityU)

The SLE program at CityU started from a small initiative which gradually developed into an expanded project entitled “*Project flame*” that involved 18 academic departments across the university, with the spirit of fostering social innovation and entrepreneurship [15]. “*Project flame*” offered a wide range of courses and extra-curriculum activities via four areas: “1) academic and professional education, 2) student service leadership, 3) incubation of social innovation, and 4) research and knowledge transfer” [16].

The academic and professional education aimed to combine traditional lecturing with innovative, practice-oriented teaching approaches such as study tours, seminars, and internships. Students were offered a variety of purposefully designed Gateway Education courses such as “*Make a difference: The challenge of social entrepreneurship in a globalized world*,” and “*Social innovation and entrepreneurial venture exploration*,” where their service leadership values and skills were expected to be fostered. Notably, CityU has also initiated the first Minor Program in Social Entrepreneurship in Hong Kong [15]. The second area, student service leadership, exposed students to direct experiences in service settings such as agency visits, and local and international internship programs. Students were expected to participate, observe, and have a critical reflection on social entrepreneurship via these activities. The area of “social innovation” incubation highlighted the development of students’ innovative ideas and practices. The last area of “research and knowledge transfer” underscored the sharing and application of ideas with the aim of laying groundwork for its future agenda in the field of SLE [16].

Hong Kong Baptist University (HKBU)

The SLE programs at HKBU had been implemented through the curricular and extra-curricular approaches [17]. The curricular approach mainly engaged students in a number of general education (GE) courses that emphasized interdisciplinary learning opportunities and dynamic interactions where students could learn from and for the community [18]. Between 2012 and 2015, HKBU had offered seven SLE GE courses to its students. A few examples of the GE courses are “*Service leadership and emotional intelligence*” offered by the Department of Social Work and Office of Student Affairs, “*Paths to service leadership in health services*” offered by Department of Religion and Philosophy and School of Chinese Medicine, and “*From responsible citizenship to service leadership*” offered by the Department of Religion and Philosophy. The GE office was also in close collaboration with other units at HKBU to launch service activities and events, such as sponsoring service trips and exchange programs [17]. Abundant extra-curricular activities were also provided to students as a supplement to the GE courses. For example, the “Be eager to learn, to care, to

lead” Series was a huge success. In 2015, this activity attracted 450 students to participate [17].

Lingnan University (LU)

The SLE at LU comprised six integral components. The first component was embedding service-learning projects in SLE. Since 2012, LU had developed seven credit-bearing service leadership courses that incorporated service-learning projects, namely, “*Corporate social responsibility, strategic management, leadership and teamwork, introduction to business, service leadership, social marketing, and services marketing*” [19]. By 2015, more than 600 students had taken part in the service-learning projects of the seven courses. The second component was comprehensive project infrastructure. Each project was operated by the following three phases for the sake of quality assurance, i.e., “the preparatory phase, the service phase, and the review phase” [19]. The third component was using self-report templates to guide students in completing self-review of their practices and attributes. The fourth aspect was formative evaluation studies. Drawing on the self-report data, LU had developed an eight-faceted model that attempted to promote students’ participation and ensure effective progress. The fifth component was extra-curricular service leadership practicums. The Office of Service Learning (OSL) provided students with internship opportunities and hands-on community engagement in NGOs, government organizations, social enterprises, etc. The final aspect was “discipline-based studies of service leadership in the commercial field” [19]. Both quantitative and qualitative discipline-based research had been carried out to examine the impact of the services on service recipients.

The Chinese University of Hong Kong (CUHK)

The SLE at CUHK had been undertaken in four areas [20]. First, a 14-week, credit-bearing GE course entitled “*Service leadership in an uncertain era*” was introduced to students. It contained four weeks of theory acquisition, eight weeks of showing examples of leaders from different spheres, and two weeks of synthesis. Second, the SLE team produced a series of video-assisted cases as a supplement to the traditional lecture-based teaching approach. Third, an SLE module was delivered through the “*I-CARE NGO internship program*,” where more than 20 undergraduates were offered overseas internship opportunities to practice services in NGOs and social enterprises each year. In this program, students could directly participate in addressing many social issues such as poverty and environmental protection. Finally, a social website was developed as a digital platform for the service leadership learning community to promote communication [20, 21].

The Hong Kong Institute of Education (HKIEd) Which was Renamed “Education University of Hong Kong” in 2016

In order to promote SLE, the Student Affairs Office (SAO) in the HKIEd launched the Project “*Achiever*” in 2012. As a co-curricular project, “*Achiever*” had attracted more than

1,000 student participants and accumulated more than 70,000 hours of learning between the duration of 2012 to 2015. It was consisted of a three-phase training structure. Students were first guided through a progressive learning process of building up fundamental concepts and knowledge (Phase One). Then students were encouraged to strengthen self-understanding by reflecting on their personal qualities (Phase Two). At the final stage, students were exposed to abundant experiential learning activities where they could apply knowledge and skills to improve service leadership and solve problems in a real-life context (Phase Three). A few examples of the experiential activities were “Intergeneration Learning and Elderly Service Academy,” “Leadership Enhancement and Development (LEAD) Programme,” and “Service Exposure for Global Awareness (SEGA) Programme.” Over 90% students reported positive perception of the learning experiences and enhanced leadership qualities [22, 23].

The Hong Kong University of Science and Technology (HKUST)

HKUST established a Service Learning Community (SLC) of three types of platforms, namely, platforms for service leadership apprentices, service leadership practitioners, and service leaders. The community was designed to meet the needs of students of different levels in terms of service leadership learning. The apprentice platform served as a starting line for beginners to increase their exposure to service leadership knowledge and values by displaying publications and videos and holding regular forums (e.g., EnG Chitchat). The platform also established customized workshops and activities to encourage students to learn. For the second level, the SLC developed a peer monitoring program (PMP) where senior students were offered the opportunity to become mentors to freshman after rigorous training and to practice their service leadership in the process. For the third level, several service leadership courses had been developed for students including a general course of “*Community service project: The way to success*,” and more technical courses such as “*Community service project: The mobile app development for hearing impaired children*.” These courses employed an interactive, multifaceted teaching approach that engaged students in actively serving local underprivileged communities [24, 25].

The University of Hong Kong (HKU)

In 2012, the HKU launched a credit-bearing Service Leadership Internship Program to promote SLE. It was initially designed for students in the Faculty of Social Sciences in the first three years, with more than 400 students participating in this project. Before embarking on the internship, students were required to attend several mandatory workshops to equip themselves with necessary knowledge and skills. Students then teamed up (groups of three to five) and worked in collaboration with community partners of HKU such as NGOs and social enterprises. During this process, student interns needed to commit as shared leaders as well as reflective learners, offering innovative solutions to real problems. Evaluation studies had also been conducted in order to assess students’ learning outcomes and program effectiveness. Results showed that students found their experiences in this program rewarding [26]. Since 2015, this program has been open to all faculties, with the objective to create a multi-

disciplinary setting, build up a synergy between students from different backgrounds, and adopt a team-based approach [26].

The Hong Kong Polytechnic University (PolyU)

With the support from the Fung SLI, PolyU had committed to nurturing service leaders by developing both credit-bearing subjects and non-credit-bearing programs since 2012. Two credit-bearing subjects were offered to students with different orientations in the design. For the subject entitled “*Service leadership (APSS1A21)*,” it aimed to equip students with the core values and concepts of the SLT, and guide them to the critical evaluation of existing leadership models. Concerning the subject entitled “*Service leadership through serving children and families with special needs (APSS2S09)*,” it integrated both classroom lecturing and the powerful pedagogy of experiential learning, providing services to underprivileged groups in different community settings. Besides the credit-bearing subjects, the SLE in PolyU went beyond the borders of Hong Kong to explore partnership with other higher education institutions and develop non-credit-bearing programs. For example, in 2015, 50 students joined the “Silk Road Youth Leadership Program,” which was co-organized by PolyU, Xi’an Jiaotong University, and Peking University to facilitate communication, hone leadership skills, and enhance social awareness [27]. In the next section, we will present the achievements of PolyU, including the subjects and programs developed as well as evaluation studies.

WHAT POLYU HAS ACHIEVED IN FUNG SERVICE LEARNING INITIATIVE?

The 3-credit subject entitled “*Service leadership*” has been offered in different delivery modes (e.g., APSS1A21 with classroom teaching mode, and APSS1A21U/V with blended learning mode that integrates e-learning and classroom teaching sessions). This subject aims to guide students through a variety of leadership models with special attention given to the SLT. It was designed to nurture students’ service leadership qualities and enhance the application in real life. With regard to the pedagogy, “*Service leadership*” highlights the innovative teaching approaches that include “reflective learning, experiential learning, and collaborative learning” [28]. Students are offered many opportunities to participate in structured experiential learning activities in class such as debate, drawing, role play and group presentation, building up an interactive environment where students can practice their leadership attributes. Students are also encouraged to demonstrate self-reflection on their leadership qualities in class exercise and written assignment to gain a deeper understanding of the theory as well as themselves [27]. The following learning outcomes are expected from students upon completion:

- a) “Understand the contemporary models of leadership with reference to the service sector, including their assertions, strengths and weaknesses;

- b) Demonstrate understanding of the basic leadership attributes intrinsic to effective service leaders;
- c) Reflect upon the need for developing the qualities of effective service leaders and their own leadership qualities;
- d) Appreciate the potential application of knowledge on effective service leadership gained in this subject to oneself' [28].

The Leadership and Intrapersonal Development (LIPD) Team, which designed and developed this subject, also actively pursue partnership with Peking University and Xi'an Jiaotong University in mainland China to promote SLE through curricular and extra-curricular leadership programs. In 2019 summer, the PolyU and Xi'an Jiaotong University jointly organized Service Leadership Summer School. During the two weeks, students from both universities completed the course tasks, acquired knowledge of the SLT and improved their service leadership qualities, while engaging in global perspectives and cultural diversity. We have also provided intensive training programs for students joining the leadership programs offered by the Global Youth Leadership Institute. In 2016, this subject was awarded the Bronze Award (Ethical Leadership category) in the Wharton-QS Stars Reimagine Education Awards [29].

The other subject entitled "*Service leadership through serving children and families with special needs*" (APSS2S09) is a 3-credit service-learning subject. It integrates classroom-based learning and community-based service learning, which were designed to facilitate students to obtain in-depth knowledge of the SLT, reflect on their leadership qualities, apply the core attributes during the service learning process, and enhance empathy and social awareness. Students taking the subject have served clients in NGOs, providing services for children and adolescents with behavioral and emotional problems, preschool kids with developmental problems, substance abusers and students experiencing social deprivation and disadvantage. In mainland China, PolyU students have also served migrant children and disadvantaged kids in Chengdu and Xi'an. In 2016, it won the Bronze Award for the category of social enterprise in the Wharton-QS Stars Reimagine Education Awards [30]. In 2018, together with three other subjects, this subject was awarded the UGC Teaching Award, which is the most prestigious teaching award in all public universities in Hong Kong.

This Service-Learning subject consists of three types of teaching and learning approaches: 1) Students are asked to complete the 10-hour learning modules online, 2) Students are required to attend the purposefully designed lectures, workshops, and seminars in person and 3) Students should team up and provide well-planned services as a group in one of the community partners. The intended learning outcomes are as follows:

- 1) "Address the needs of the service recipients through service delivery;
- 2) Link their service experiences with academic course materials;
- 3) Appreciate and respect people from diverse background;
- 4) Integrate academic learning (e.g., knowledge on service leadership) into the service experience and activities;
- 5) Demonstrate empathy and care by providing community service;
- 6) Apply the skills (e.g., active listening) and knowledge (e.g., moral character and competencies) they have acquired in university education to deal with complex issues in the service setting;

- 7) Reflect on their service leadership qualities through service learning;
- 8) Work effectively with different parties (e.g., students, teachers, families, and community partners) when preparing and delivering service” [31].

The community partners in which students can choose to serve include Society of Boys' Centres (serving students with emotional and behavioral problems), Christian Zheng Sheng College (serving clients with substance abuse and behavioral problems), Wharf's Project WeCan (serving students with social deprivation) [32]. In Project WeCan, for example, PolyU students provided customized activities to meet the learning needs of local secondary school students from disadvantaged backgrounds. Between 2017/18 academic year, 8,571 secondary students benefited from this program [33, 34]. In Christian Zheng Sheng College, a local drug rehabilitation school for youth, PolyU students engaged in daily routines as Zheng Sheng students did, and they also shared their life experiences with each other. By doing so, this service learning experience aimed to improve PolyU students' empathy and caring disposition [35]. The philosophy underpins the design is that service learning is an effective vehicle to strengthening service leadership qualities [33].

In order to assess the effectiveness of the service leadership subjects, systematic evaluation studies adopting both quantitative and qualitative evaluation methods have been undertaken to measure different dimensions of the program quality. Generally speaking, three evaluation strategies have been used to examine the impact of SLE, such as the knowledge, attitudes and behavior of the students taking the academic subjects or participating in the non-credit-bearing service leadership programs. First, objective outcome evaluation studies have been conducted to examine whether there are positive changes in the students after joining the program. Several studies have shown that students showed positive changes in their service leadership knowledge, attitudes and behavior as well as psychological well-being after receiving the service leadership education. In a study utilizing a quasi-experimental research strategy, research findings showed that students in the experimental group showed improvements in the leadership outcomes as compared to the control participants [36]. The second approach is subjective outcome evaluation. Several studies have shown that students joining the service leadership education initiatives had a very positive subjective evaluation of the service leadership subjects and programs, teachers and workers, as well as benefits of the program. Finally, qualitative evaluation based on focus groups, individual interviews, and written reflections of the students have also revealed the positive outcomes of the related subjects and non-credit-bearing programs. Generally speaking, the evaluation studies have provided ample empirical evidence that students perceived the service leadership subjects positively and were able to achieve positive changes in service leadership qualities and positive youth development qualities. Tables 1 and 2 present the data collected between the academic year 2012/13 and 2018/19 as well as the publications arising from SLE at PolyU.

One important observation based on the evaluation findings is that the Service Leadership education programs can promote the well-being of the program participants, including life satisfaction and psychosocial competencies. In a study adopting cross-lagged analyses involving 114 students [37], students' knowledge, attitude, and behavior on service leadership, life satisfaction and positive youth development attributes were found to be higher after taking the subject. Besides, cross-lagged analyses showed that positive changes in student well-being were significantly related to positive changes in students' service leadership attitudes and behaviors. This finding underscores the developmental impact of SLE

on the holistic development of students. This finding is important because there are views showing that there are worrying trends in the mental health issues of university students in Hong Kong [38, 39]. Obviously, Service Leadership education is a promising approach to promote holistic development of university students, including their psychological well-being.

Table 1. Data collected for Service Leadership subject/program between 2012/13-2018/19 by PolyU

Methodology	Measures	Data Collected
Objective Outcome Evaluation (Pretest-posttest Evaluation)	Well-being	Positive youth development (PYD) (31 items)
		Life satisfaction (5 items)
	Service leadership qualities	Self-leadership (5 items)
		Caring disposition (8 items)
		Character strength (15 items)
	Beliefs of service leadership	Beliefs of service leadership (6 items)
	Service leadership knowledge	Service leadership knowledge (10-50 items)
	Service leadership attitude	Service leadership attitude (20-132 items)
	Service leadership behavior	Service leadership behavior (19-20 items)
Subjective Outcome Evaluation	Students' perception of the subject/program	Perceived program qualities (10 items)
		Instructor qualities (10 items)
		Perceived benefits of the program (18 items)
Process Evaluation	Quality of program delivery	Quality of program delivery (13 items)
	Program adherence	Observers' ratings
	Program fidelity	Observers' ratings
Qualitative Evaluation	Students' perspectives towards the subject/program	Students used descriptors and metaphors to describe the subject/program
Focus Group	Students' experiences in the subject/program	Observational data

Table 2. Evaluation Research of Service Leadership Initiative at PolyU

Course and Program	Methodology	Status
2-credit subject Service Leadership 2012-13 2 nd semester	Objective outcome evaluation	Shek, D. T. L., Yu, L., & Ma, C. M. S. (2014). The students were happy, but did they change positively? Yes, they did. <i>International Journal on Disability and Human Development</i> , 13(4), 505-511. DOI: 10.1515/ijdh-2014-0348
	Subjective outcome evaluation	Shek, D. T. L., Lin, L., & Liu, T. T. (2014). Service leadership education for university students in Hong Kong: Subjective outcome evaluation. <i>International Journal on Disability and Human Development</i> , 13(4), 513-521. DOI: 10.1515/ijdh-2014-0349
	Process evaluation	Shek, D. T. L., Lin, L., Liu, T. T., & Law, M. Y. M. (2014a). Process evaluation of a pilot subject on service leadership for university students in Hong Kong. <i>International Journal on Disability and Human Development</i> , 13(4), 531-540. DOI: 10.1515/ijdh-2014-0351
	Qualitative evaluation	Shek, D. T. L., Lin, L., Liu, T. T., & Law, M. Y. M. (2014b). Service leadership education for university students in Hong Kong: Qualitative evaluation. <i>International Journal on Disability and Human Development</i> , 13(4), 523-529. DOI: 10.1515/ijdh-2014-0350

Course and Program	Methodology	Status
	Focus group	Shek, D. T. L., Law, M. Y. M., & Liu, T. T. (2015). Focus group evaluation of a service leadership subject in Hong Kong. <i>International Journal on Disability and Human Development</i> , 14(4), 371-376.
2-credit subject Service Leadership 2013-14 1 st semester	Objective outcome evaluation	Shek, D. T. L., Lin, L., & Leung, H. (2018). Objective outcome evaluation of service leadership education for university students in Hong Kong. <i>International Journal on Disability and Human Development</i> , 17(1), 119-124.
	Subjective outcome evaluation	Shek, D. T. L., & Liang, J. (2015). Subjective outcome evaluation of a university subject on service leadership. <i>International Journal on Disability and Human Development</i> , 14(4), 385-392.
	Process evaluation	Shek, D. T. L., Liang, J., & Law, M. Y. M. (2016). Process evaluation of a university subject on service leadership in Hong Kong. <i>International Journal of Child and Adolescent Health</i> , 9(2), 253-261.
	Qualitative evaluation	Shek, D. T. L., Lin, L., & Xie, Q. (2016). Service leadership education for university students in Hong Kong: A qualitative evaluation study. <i>International Journal of Child and Adolescent Health</i> , 9(2), 235-243.
	Focus group	Shek, D. T. L., Xie, Q., Lin, L., & Law, M. Y. M. (in press). Evaluation of a service leadership subject in Chinese university students in Hong Kong using focus groups. <i>International Journal on Disability and Human Development</i> .
2-credit subject Service Leadership 2013-14 2 nd semester	Objective outcome evaluation	Shek, D. T. L., Lin, L., & Leung, H. (2018). Objective outcome evaluation of service leadership education for university students in Hong Kong. <i>International Journal on Disability and Human Development</i> , 17(1), 119-124.
	Subjective outcome evaluation	Shek, D.T.L., Liang, J., & Zhu, X. (2016). Subjective outcome evaluation of a service leadership subject for university students in Hong Kong. <i>International Journal of Child Health and Human Development</i> , 9(2), 225-232.
3-credit Cluster-Area Requirement (CAR) subject Service Leadership 2014-15 1 st semester	Objective outcome evaluation	Shek, D. T. L., Lin, L., & Leung, H. (2018). Objective outcome evaluation of service leadership education for university students in Hong Kong. <i>International Journal on Disability and Human Development</i> , 17(1), 119-124.
	Subjective outcome evaluation	Shek, D. T. L., Chi, X., & Lin, L. (2017). Subjective outcome evaluation of a service leadership subject for university students in Hong Kong. <i>International Journal of Child and Adolescent Health</i> , 10(2), 213-221.
	Qualitative evaluation	Shek, D. T. L., Wu, J., Lin, L., & Pu, E. X. P. (2017). Qualitative evaluation of a service leadership subject in a Chinese context. <i>International Journal on Disability and Human Development</i> , 16(4), 433-441. DOI: 10.1515/ijdh-2017-7012
3-credit CAR subject Service Leadership 2014-15 2 nd semester	Objective outcome evaluation	Shek, D. T. L., Lin, L., & Leung, H. (2018). Objective outcome evaluation of service leadership education for university students in Hong Kong. <i>International Journal on Disability and Human Development</i> , 17(1), 119-124.
	Subjective outcome evaluation	Shek, D. T. L., Chi, X., & Lin, L. (2017). Subjective outcome evaluation of a service leadership subject for university students in Hong Kong. <i>International Journal of Child and Adolescent Health</i> , 10(2), 213-221.
	Qualitative evaluation	Shek, D. T. L., Wu, J., Lin, L., & Pu, E. X. P. (2017). Qualitative evaluation of a service leadership subject in a Chinese context. <i>International Journal on Disability and Human Development</i> , 16(4), 433-441. DOI: 10.1515/ijdh-2017-7012

Table 2. (Continued)

Course and Program	Methodology	Status
3-credit subject Service Leadership 2015-16 1 st semester	Objective outcome evaluation	Chai, W., Shek, D. T. L., Lee, B., & Xie, M. (2020). Impact of Service Leadership Education on University Students in Hong Kong. <i>International Journal of Child and Adolescent Health</i> , 13(2), 113-123.
	Subjective outcome evaluation	Shek, D. T. L., Kwok, R. K. H., & Low, S. S. (2020). Promotion of Service Leadership in University Students: Views of University Students. <i>International Journal of Child and Adolescent Health</i> , 13(2), 153-166.
3-credit subject Service Leadership 2015-16 3 rd semester	Objective outcome evaluation	Chai, W., Shek, D. T. L., Lee, B., & Xie, M. (2020). Impact of Service Leadership Education on University Students in Hong Kong. <i>International Journal of Child and Adolescent Health</i> , 13(2), 113-123.
	Subjective outcome evaluation	Shek, D. T. L., Kwok, R. K. H., & Low, S. S. (2020). Promotion of Service Leadership in University Students: Views of University Students. <i>International Journal of Child and Adolescent Health</i> , 13(2), 153-166.
3-credit subject Service Leadership 2016-17 1 st semester	Objective outcome evaluation	Lin, L., & Shek, D.T.L. (2019). Does service leadership education contribute to student well-being? A quasi-experimental study based on Hong Kong university students. <i>Applied Research Quality of Life</i> , 14, 1147–1163. DOI: 10.1007/s11482-018-9644-x
	Subjective outcome evaluation	Leung, J. T. Y., & Shek, D. T. L. (2019). Subjective outcome evaluation of a service leadership subject: Findings based on university students in Hong Kong. <i>International Journal of Child Health and Human Development</i> , 12(3), 247-257.
3-credit subject Service Leadership 2016-17 1 st semester	Qualitative evaluation	Yang, Z., Shek, D. T. L., & Zhang, J. (2020). The effectiveness of a service leadership subject in Hong Kong: A qualitative evaluation study. <i>International Journal of Child and Adolescent Health</i> , 13(2), 181-194.
	Subjective outcome evaluation	Leung, J. T. Y., & Shek, D. T. L. (2019). Subjective outcome evaluation of a service leadership subject: Findings based on university students in Hong Kong. <i>International Journal of Child Health and Human Development</i> , 12(3), 247-257.
	Qualitative evaluation	Yang, Z., Shek, D. T. L., & Zhang, J. (2020). The effectiveness of a service leadership subject in Hong Kong: A qualitative evaluation study. <i>International Journal of Child and Adolescent Health</i> , 13(2), 181-194.
	Qualitative evaluation	Yang, Z., Shek, D. T. L., & Zhang, J. (2020). The effectiveness of a service leadership subject in Hong Kong: A qualitative evaluation study. <i>International Journal of Child and Adolescent Health</i> , 13(2), 181-194.
3-credit subject Service Leadership 2017-18 1 st semester	Objective outcome evaluation	Zhu, X., Shek, D. T. L., Zhu, Z., & Zhao, P. (2020). Promotion of Well-being and Leadership Qualities among University Students after Taking a Credit-bearing Service Leadership Subject. <i>International Journal of Child and Adolescent Health</i> , 13(2), 125-135.
	Qualitative evaluation	Yang, Z., Shek, D. T. L., & Zhang, J. (2020). A Qualitative Evaluation of a Service Leadership Subject in a Higher Educational Institution in Hong Kong. <i>International Journal of Child and Adolescent Health</i> , 13(2), 195-208.

Course and Program	Methodology	Status
3-credit subject Service Leadership 2017-18 3 rd semester PolyU course	Objective outcome evaluation	Zhu, X. & Shek, D. T. L. (2021). Promoting service leadership qualities and well-being among university students: Evaluation findings in Hong Kong. <i>Applied Research in Quality of Life</i> . DOI: 10.1007/s11482-021-09922-w
	Qualitative evaluation	Yang, Z., Shek, D. T. L., & Zhang, J. (2020). A Qualitative Evaluation of a Service Leadership Subject in a Higher Educational Institution in Hong Kong. <i>International Journal of Child and Adolescent Health</i> , 13(2), 195-208.
3-credit subject Service Leadership 2017-18 3 rd semester Cambodia course	Objective outcome evaluation	Zhu, X. & Shek, D. T. L. (2021). Promoting service leadership qualities and well-being among university students: Evaluation findings in Hong Kong. <i>Applied Research in Quality of Life</i> . DOI: 10.1007/s11482-021-09922-w
	Qualitative evaluation	Yang, Z., Shek, D. T. L., & Zhang, J. (2020). A Qualitative Evaluation of a Service Leadership Subject in a Higher Educational Institution in Hong Kong. <i>International Journal of Child and Adolescent Health</i> , 13(2), 195-208.
3-credit subject Service Leadership 2018-19 2 nd semester Blended course	Objective outcome evaluation (pre- and post-tests)	Zhu, X., Shek, D. T. L., Dou, D., & Chai, W. (2020). Development and Evaluation of a Service Leadership Subject in a Blended Learning Mode. <i>International Journal of Child and Adolescent Health</i> , 13(2), 209-221.
	Subjective outcome evaluation	
	Qualitative evaluation (descriptors and metaphors)	

CONCLUSION

Several points can be summarized to describe the development of the Fung Service Leadership Education Initiative. First, as service economy is emerging in the globe including Hong Kong, there is a need to nurture leadership in service economies. Second, the 3Cs (competence, character, and care) in SLT are qualities that should be possessed by effective service leaders. Third, to help Hong Kong develop service leadership education, Victor and William Fung Foundation provided funding for the Fung SLI with the participation of eight UGC-funded tertiary institutions. Fourth, each university has full autonomy to develop its own service leadership education programs and curricula. As a result, the principle of “let the hundred flowers bloom” was fully maintained in the process. Fifth, great works have been developed in different universities which have promoted the development of SLE in Hong Kong. Sixth, with reference to PolyU, evaluation studies using different approaches showed that Service Leadership subjects could promote the service leadership qualities and well-being of the students. Seventh, Fung Service Leadership Education Initiative is an excellent vehicle to promote the leadership and holistic development of undergraduates.

Overall speaking, the Fung Service Leadership Education is an overwhelming success. Looking into the future, there are several challenges in the field of service leadership education. First, policymakers and educators must appreciate the transformation of the global economy and the need to have a new type of leadership who can play well in an “infinite game” [40]. Second, stakeholders have to change their mindset that every student can be a leader (i.e., believing that every young person has leadership potentials) which focuses on the

strengths and potentials of young people. Third, reflection on the teaching pedagogies should be promoted. In particular, emphases on experiential, reflective and collaborative learning should be promoted. Finally, there is a need to accumulate evaluation findings to further support the utility of service leadership education.

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Chapter 156

CAN WE NURTURE UNIVERSITY STUDENTS TO BECOME THE LEADERS OF TOMORROW?

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ABSTRACT

Since we think university students are the “cream of the cream”, it is important to ask whether they thrive well. To what extent can university students in Hong Kong develop in a holistic manner? How should we nurture university students to become the leaders and talents of tomorrow? As part of the general university requirements in Hong Kong is the leadership and intrapersonal development requirement, students must take one 3-credit subject on leadership and intrapersonal development. To meet this requirement, a subject entitled “tomorrow’s leaders” was developed and piloted twice in 2010-2012, and was offered to more than 2,100 students annually in 2012-2014. The design of the subject, curriculum materials, reflection of teachers and evaluation findings in connection with this subject are presented in this book.

INTRODUCTION

University students are commonly regarded as leaders of tomorrow and pillars of the society. In many societies, investment in higher education is a priority policy area. With the emergence of knowledge-based economies in the global contexts, the proportion of young people who can receive university education has increased tremendously in the past few decades, particularly in Asia.

With particular reference to Hong Kong, university students have been historically regarded as the “cream of the cream” in the society. Under the influence of the Chinese belief that academic excellence is the key to upward social mobility, Chinese parents place heavy emphasis on examination results and academic attainment of their children. Furthermore, as only 18% of high school leavers can enjoy subsidized university places provided by the Government, competition in public examinations is very intense in Hong Kong. Generally speaking, only those with good public examinations results can get a subsidized university place in the eight universities in Hong Kong funded by the University Grants Committee.

As university students are the “cream of the cream”, it is important to ask whether they thrive well. To what extent can university students in Hong Kong develop in a holistic manner? How should we nurture university students? Shek [1] pointed out there were several developmental issues in university students, such as mental health problems, political apathy and lack of psychosocial competencies. Shek and Wong [2] further argued that as adolescent developmental issues would not disappear overnight, it is important to address such issues and promote holistic development in university students. In a recent review of developmental issues in university students, Shek and Cheung [3] highlighted several developmental issues in university students. These included behavioral and lifestyle problems (e.g., addictive behavior, problematic sleep pattern and interpersonal violence), mental health issues (e.g., suicidal ideation and depression), lack of personal goals, materialism, and egocentrism. Some recent incidents also suggest that there is a need to consider how holistic development in university students can be promoted: university students who were anxious about their academic achievement set fire in the street after drinking; probably under the influence of mental disorder, a university student ran in the street without any clothes; shoplifting behavior in university students are not uncommon in Hong Kong.

Although curricular, co-curricular and extra-curricular activities can help to promote the development of university students, the use of formal curriculum to help university students is attractive for three reasons. First, if the subjects are to be taken by all students, it is consistent with the philosophy that “no student is left behind”. In fact, while allowing students to take personal growth subjects may give more flexibility to students, the needy students may not choose the related subjects. Second, credit bearing subjects can give students an impression that the subjects are important. Actually, students are usually required to take subjects which are considered to be significant by the university. Third, the provision of credits can motivate students to pay more effort in the learning process. If the subject is just a requirement without credits, students may be unmotivated to do well in the process. Unfortunately, credit bearing subjects on leadership and holistic youth development for university students are not widespread.

Modeled after the British model, the duration of undergraduate degree programs in Hong Kong had been three years until 2012. In line with the education reform in secondary schools, duration of the new undergraduate program became four years for the 2012/13 cohort of students taking the Hong Kong Diploma of Secondary Education Examination. Generally speaking, it was expected that the extra one year would be devoted to broadening the horizon of the students through General Education studies. In the new 4-year undergraduate degree program at The Hong Kong Polytechnic University, students are required to fulfill 120 credits for graduation. Amongst these 120 credits, 30 credits are within the area of General University Requirements (GUR) which attempt to promote critical thinking, communication, innovative problem solving, ethical leadership and lifelong learning attributes in the students.

One component in the general university requirements is the leadership and intrapersonal development requirement, where students must take one 3-credit subject on leadership and intrapersonal development. To meet this requirement, a subject entitled “tomorrow’s leaders” was developed and piloted twice in 2010/11 and 2011/12 school years (4-12). In 2012/13 and 2013/14 school years, the subject was offered to more than 2,100 students annually. The design of the subject, curriculum materials, reflection of the teachers and evaluation findings in connection with this subject are presented in this book.

“Tomorrow’s leaders” has several unique features. First, positive youth development approach is used as the conceptual framework. According to the positive youth development approach, it is important to develop the resources (particularly psychosocial competencies) of young people. Second, a wide range of positive youth development constructs including resilience, cognitive competence, social competence, moral competence, spirituality, interpersonal relationship, and self-leadership are covered in the subject. Third, instead of using traditional didactic lecture style, experiential learning activities with active student involvement are used. Fourth, reflective learning is strongly emphasized and there are many self-reflection opportunities for students. Fifth, collaborative learning is emphasized in the learning process. This provides a good opportunity for interpersonal communication and learning by discussing with others. Sixth, besides academic content, the subject also focuses on practical application of the concepts learned in the subject. Finally, through a series of studies using both quantitative and qualitative methods, evaluation findings consistently showed that students had positive views of the subject and they perceived the subject to be beneficial to their development.

With this book we earnestly hope that colleagues who are passionate about the holistic development of university students can understand and give further thoughts on how the

positive youth development approach can be utilized to promote the leadership and intrapersonal development of university students in Hong Kong. The attempt is valuable because there are few related subjects in different Chinese societies.

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Chapter 157

EMOTIONAL COMPETENCE

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ABSTRACT

In the leadership literature, emotional competence is commonly regarded as an important quality of an effective leader. In this chapter, the basic concepts and theories of emotional competence are introduced. The role of emotional competence in positive youth development and effective leadership is described. To help students appreciate the importance of emotional competence, a lecture on emotional competence was developed in a subject entitled "Tomorrow's Leaders" at The Hong Kong Polytechnic University. The objectives, intended learning outcomes, lecture outline and lecture materials are presented in this chapter. Issues regarding the teaching of emotional competence are discussed.

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INTRODUCTION

Nowadays, employers have high expectations for potential employees. While professional and technical skills are important, employers place more emphasis on the “soft skills” of graduates. For example, employers are concerned about how well the graduates are able to communicate effectively, be innovative and think critically in the face of complex and competitive environments [1]. College students are not only expected to possess knowledge within their discipline, but also to understand what business values in order to improve their employment opportunities and request for higher wages. Indeed, top rated skills including collaboration, work ethics, communication, and critical thinking are suggested for entry-level employment [2-3]. With the emergence of service economies, university graduates are also expected to possess leadership skills cherished in the service sectors, such as intrapersonal and interpersonal skills.

Although employers stress the importance of non-technical skills, evidence shows a gap between the skills students possess and what employers need [4]. For example, employers value analytical skills and technical skills, which were rated significantly lower in terms of perceived importance by students [5]. Besides, college students often underestimate the importance of social and emotional skills and assume that mastery of their professional knowledge is sufficient when they enter the workforce [6]. This is supported by a recent study which showed that among the six top desired skills as rated by the employers, only team work was listed as the most important skill as perceived by a sample of college students [7]. According to Hodge and Lear [7], “this lack of preparation may be related to three factors including not listening to professors and advisors, lack of participation in class exercise, and an inability to transfer meaning from their experiences into choices that will impact their future” (p. 29). Instead of solely focusing on the intellectual development of students, more effort is warranted to provide and sustain initiatives for career preparation. In 2011/12 academic year, about 12,246 (81.4%) university graduates entered the job market [8]. Although the unemployment rate (1.8%) was low, it is important to help them understand the value of career-related skills that facilitates their long-term career success. These skills are critical to meet the demands for cognitive, emotional, and physical resources in a dynamic and complex environment and to make the right decision or choice in this ever-pacing world. A good example is the experience of a graduate student with an advanced academic degree (i.e., a master’s degree) who had very good academic results. He sent more than 200 application letters but even so did not succeed in finding a job and eventually had to rely on social security to meet his living expenses [9]. As university students studying in UGC-funded places represent only approximately 18% of the relevant cohort in Hong Kong, they can be regarded as leaders for the future of Hong Kong. What leadership qualities do tertiary institutions need to nurture? In the literature on positive youth development, there are views suggesting that psychosocial competence is very important for the optimal functioning of adolescents. By adopting the strength-based approach, young adults are considered as a community resource rather than problems which could be nurtured through their developmental assets [10-12]. For instance, the National Research Council and Institute of Medicine argued that personal and social assets in four areas (i.e., physical, cognitive, social and emotional/psychological) are important for successful youth development [13]. Similarly, Catalano and colleagues [14] highlighted 15 constructs that are vital to positive youth

development programs in order to help youths become thriving and successful adults. These constructs are resilience, behavioral competence, cognitive competence, emotional competence, self-determination, self-efficacy, prosocial norms, prosocial involvement, beliefs in the future, bonding, spirituality, clear and identity, moral competence, recognition for positive behavior and social competence. In general, the concept of positive youth development is aimed at providing opportunities for fostering positive developmental qualities in adolescents before they enter healthy and productive adulthood.

Emotional Competence as a Leadership Quality

Amongst the different psychosocial competencies emphasized in the positive youth development literature, emotional competence is an important attribute commonly mentioned by different researchers. Emotional competence refers to individual's ability to recognize, identify, and manage one's own personal and others' emotions [15-16]. Evidence shows that high emotion competence is associated with effective leadership, higher job satisfaction and greater customer satisfaction [17-19]. Students with high emotional competence were more adaptable to changes and reported greater satisfaction [19-20]. Students who are more social integrated are likely to have a better academic performance to receive social support, and have a higher level of psychological wellbeing [21]. This is particularly significant among females [22-23].

"Emotion is one of the most central and pervasive aspects of human experience" [24, p. 3]. Emotional intelligence, also known as emotional competence, includes the ability to perceive accurately through understanding and regulating one's emotions and to promote emotional and intellectual development [25]. House and Aditya [26] noted that emotional competence is an important trait for a successful leader. This is supported by Kemper [27] who posited that "for those in leadership position, emotional intelligence skills account for close to 90% of what distinguishes outstanding leaders from those judged as average" (p. 16). Interestingly, emotional expression is not an easy task for the human being. As pointed out by Ernest Hemingway, "a cat has absolute emotional honesty: human beings, for one reason or another, may hide their feelings, but a cat does not". Hence, how to hide one's feeling yet express it in a healthy manner is an important lesson to be learned.

"Tomorrow's Leaders" at The Hong Kong Polytechnic University

Recent educational trends focus on the holistic development of college students [28]. Educators argue the need to develop a wide range of intrapersonal and interpersonal skills among college students [29-30]. According to Hodge and Lear [7], "recognizing that students do not necessarily understand the importance of skills that are important to 21st century employers is a key indicator for faculty members...who are in charge of curriculum and the content of their classes... may be able to guide students through experiential learning exercise to value the skills employers value" (p. 39). Indeed, such skills need to be developed through collaborative learning rather than simply "talking about" it. This learning experience changes the paradigm by "putting a high responsibility on the student, viewing education as something

one engages in rather than something one obtains” [5, p. 10]. Given the importance of nurturing students to meet the needs of the society and acquire self-awareness skills, all students under the 4-year undergraduate degree program at The Hong Kong Polytechnic University were required to enroll a 3-credit bearing subject entitled “Tomorrow’s Leaders”. This subject was designed to develop students’ leadership capacities through introducing the qualities of effective leadership and providing structured learning experiences. The purpose of this paper was to briefly describe the design of a lecture that aimed at promoting students’ emotional competence. First, the rationale and intended learning outcomes were discussed. Then, different class activities were presented.

With the importance of emotional competence in the effectiveness of leadership, this lecture provides students with an overview of this concept and suggests ways to enhance that competence in meeting their daily challenges. In the first part of the lecture, Goleman’s [31] major components of emotional competence are presented. These include a) self-awareness: identifying and observing one’s own emotions; b) self-management: managing and regulating one’s own emotions; c) motivation: intention to achieve one’s own goal by monitoring his/her motion; d) social skills: the ability to adapt and interact proactively in social contexts, and e) empathy: the ability to take other’s perspective. In the second part of the lecture, the importance of emotional competence in personal and professional development is discussed. Lastly, various ways to promote emotional competence are suggested.

Lecture Content

The objectives of this lecture were to: 1) introduce concepts and theories of emotional competence; 2) help students understand the antecedents and consequences of emotional competence; 3) enhance students’ awareness of emotional competence; 4) examine the relationship between emotional competence and leadership; 5) provide ways to promote emotional competence, and 6) understand issues intrinsic to the relationship between emotional competence and leadership.

After taking this lecture, it is expected that students will be able to: 1) understand concepts and theories of emotional competence; 2) explain the antecedents and consequences of emotional competence; 3) reflect students’ own awareness of emotional competence; 4) examine the relationship between emotional competence and leadership; 5) generate ways to promote emotional competence, and 6) review issues intrinsic to the relationship between emotional competence and leadership.

The teaching methods of this lecture are varied, including lecture, group discussion, role play, and self-reflection. The lesson plan consists of four parts which are illustrated as follows:

- Part 1: Definitions and theories of emotional competence
 - Warm-up activity: “How do you feel today?”
- Part 2: Framework for emotional competence
 - Class activity: “Guess emotions”
- Part 3: Emotional competence and leadership
 - Class activity: “Expression emotions”

- Part 4: Conclusion
 - Self-reflection exercise: “Make a wish”

In Part 1, a warm-up activity is introduced first before the lecture begins. The purpose of this activity is to raise students’ awareness of their own feelings and emotions. Students receive a set of colored dots and they need to pick the dots with the color that best represents their emotion and stick them on their faces or hands (e.g., Red: Happy; Blue: Bored; Green: Sad; Yellow: others). Then, students are invited to share their feelings or thoughts with each other. The teacher debriefs the activity by raising students’ awareness of their own and others’ emotions. For example, “*Instead of using the colored dots, are you able to identify others’ emotions accurately?*” “*In what ways do you usually express your own feelings?*”

In Part 2, the Saarni’s [32] framework of emotional competence is introduced. According to Saarni [32], there are eight skills in emotional competence. These include: a) the awareness of one’s own emotions; b) the ability to be aware of and understand others’ emotions; c) the ability to take others’ perspective to understand others’ emotions (i.e., empathic involvement); d) the ability to use different words to express emotions (i.e., emotional vocabulary); e) the ability to cope with aversive emotions and life distress; f) the ability to control one’s emotions (i.e., emotional efficacy); g) the ability to communicate emotions within interpersonal relationship; and h) the ability to differentiate internal and external emotions.

To facilitate students’ understanding of theories, another class activity “Guessing emotions” is implemented. The purpose of this activity is to see how well the students can express and interpret emotions accurately. The teacher then distributes emotional cards to students (Appendix 1). Each group is asked to act out a given emotion without using verbal cues (i.e., different facial expressions, body gestures and postures). The rest of the students will try to guess the feeling being acted out. The teacher debriefs the activity by asking students whether they are able to identify other people’s emotions and to express one’s own feelings effectively and accurately. For example, “*Which emotion(s) is/are easy and difficult to guess? Why?*” “*How do you feel when you are being misinterpreted?*”

In Part 3, Goleman’s [31, 33] proposed emotional skills are discussed. In the model, it is argued that there are five domains of emotional competence. These include self-awareness (knowing one’s emotions), self-management (dealing with one’s emotions), self-motivation (driving oneself to achieve one’s desired goals), relationship management (interacting with others in a positive and ethical manner), and social awareness (recognizing feelings and emotions of others).

The teacher explains the relationship between emotional competence and effective leadership. According to Goleman [31, 33], there are five areas of emotional competence skills for effective leadership. These include self-regulation (conscientiousness, trustworthiness and adaptability), self-awareness (emotional awareness, self-confidence and accurate self-image), self-motivation (initiative, commitment and optimism), empathy (showing consideration to others, seeing others more important than others, and developing others) and social skills (helping followers develop positive affect and confidence, encouraging followers to express and generate new ideas, and managing conflict).

To improve students’ emotional literacy, another activity is introduced. In this activity (Appendix 2), students are asked to write down a list of words related to different emotions and draw the corresponding faces. At the end of the activity, the teacher conducts a poll and

examines how much emotions the students know. The teacher debriefs the activity by explaining the importance of emotional learning in our daily life. For example, “*How well do you manage your emotions when facing sudden changes?*” “*How do you respond when facing conflict with others?*”

In Part 4, the teacher discusses the importance of emotional skills in today’s complex and competitive world and suggests several ways for promoting emotional competence. The possible strategies include:

- Keep a journal to record things that make you angry and upset.
- Listen to your inner voice and understand your emotional as well as social needs.
- Be aware of signs, people and places that make you feel good and those that do not.
- Talk to your friends. Listen to their points of view on issues to see how they respond and react when facing similar situations. (What strategies would they habitually use when they experience strong emotions?)
- Use “self-talk” to regulate your emotions before the emotion is further triggered.
- Practice emotion regulation strategies that help decrease expressive behaviors (e.g., reappraisal, turns one’s attention to other things).

This lecture ends with asking students to review their own strengths and weaknesses based on Goleman’s five emotional skills. To encourage students to continuously improve their emotional skills in the future, they are asked to set up a goal for themselves by completing a worksheet (Appendix 3).

Theoretical and Practical Issues

There are several theoretical issues that the teacher can further discuss with the students. Primarily, while emotional expression is highly valued in the Western contexts, emotional inhibition is strongly emphasized in the Chinese culture (e.g., Confucianism, Buddhism and Taoism). In particular, forbearance and patience are emphasized in Chinese thoughts. Hence, how to integrate the notion of emotional expression in the cross-cultural context is an important task for theorists on emotional competence. Second, ecological factors influencing emotional competence should be further examined. In particular, how family upbringing affects one’s emotional competence is an important issue to be addressed. Third, as the emotional expression may lead to interpersonal conflicts, there is a need to explore the optimal form of emotional expression and how interpersonal conflict can be minimized with maximum emotional expression.

Practically, as Chinese people have difficulty in expressing emotions publicly, the teacher may consider different ways to encourage students to share their emotional responses. First, instead of class sharing, group sharing would be helpful. The teacher may also form dyads amongst the students to share their emotions. Second, self-disclosure of the teachers can encourage students to share their emotional experiences. Third, inviting students to write down their emotions and share amongst the students is another strategy to engaging the students. Finally, sharing of stories with emotional content would be helpful to students.

Apart from helping students understand their emotions, it is also important to help them develop skills to nurture their emotional health. Students should be helped to understand the factors influencing emotional health and how emotional health can be nurtured. Furthermore, when students share their emotions, they may be disturbed by such re-connection and disclosure. Hence, the teacher should provide suitable counseling if necessary.

From our teaching experience, it would be helpful to use novels to help students understand the different issues surrounding emotional competence. We have used “Tuesdays with Morrie” [34] to encourage students to think about how Morrie felt when he was ill. The following quotations were used to help students reflect:

“I give myself a good cry if I need it. But then I concentrate on all the good things still in my life...I don’t allow myself any more self-pity than that.” (p. 57)

“When I have people and friends here, I’m very up. The loving relationships maintain me...But there are days when I am depressed...I see certain things going and I feel a sense of dread.” (p. 70)

“What I’m doing now, is detaching myself from the experience....If you hold back on the emotions--if you don’t allow yourself to go all the way through them--you can never get to being detached, you’re too busy being afraid. You’re afraid of the pain, you’re afraid of the grief. You’re afraid of the vulnerability that loving entails. But by throwing yourself into these emotions, by allowing yourself to dive in, all the way, over your head even, you experience them fully and completely.” (p. 103-104)

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APPENDIX 1.

“Emotion Cards”

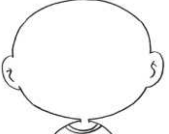
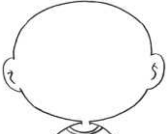
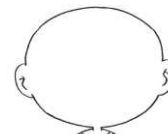
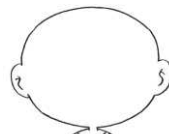
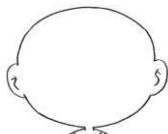
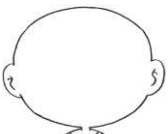
**Without using words, please use facial expressions,
body postures or gestures to represent the following emotions**

Disappointed	Anxious
Excited	Angry
Embarrassed	Grateful
Guilty	Shame
Contented	Shocked

APPENDIX 2.

“Expressing Emotions”

Please write down an emotion word and draw the corresponding facial expression on each character’s face. Try to draw as many faces as possible

 <i>Sample:</i> HAPPY			
			
			

APPENDIX 3.

“Make A Wish”

1. Are you emotionally stable? What things or events would make you feel irritable or agitated? Please give an example or scenario based on your personal experience.

2. State one type of emotional competence skills that you hope to improve in the future. How can you achieve this? Write it down and *make a wish!* Share your wish with other group members.

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Chapter 158

COGNITIVE COMPETENCE

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ABSTRACT

Cognitive competence is an important quality for effective leaders. To help university students understand the importance of cognitive competence and develop this quality, a lecture on cognitive competence is designed and incorporated in a general education subject entitled "Tomorrow's Leaders." In this chapter we review the basic concepts and theories of cognitive competence and outlines its linkages with positive youth development and effective leadership. The objectives, intended learning outcomes for students, lecture outline and related materials of the lecture on cognitive competence are introduced. Some teaching and learning issues in relation to this lecture are also discussed.

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INTRODUCTION

Cognitive competence is a basic survival skill and it has become more so in contemporary society which is characterized by rapid change and knowledge explosion in different fields. In recent decades, cognitive competence has attracted much attention from researchers [1]. With particular reference to the field of youth development, many studies have shown that cognitive competence significantly promotes adolescent physical health and psychological well-being [2]. In addition, youth risk behaviors, including substance abuse, Internet addiction, delinquent behaviors, and emotional problems (such as depression and anxiety) are negatively related to cognitive competence [3-6].

With specific reference to organizational behavior, cognitive competence is one of the most critical factors that determine one's working performance, job satisfaction, and leadership [7]. As such, how to nurture cognitive competence in young people and arouse their awareness of the importance of cognitive competence has become an urgent question for researchers and educators. Unfortunately, despite the fact that intellectual abilities are highly emphasized in both primary and secondary school education, relatively limited efforts are made for university students, few attempts have been systematically carried out to promote cognitive competence in young people [8].

This chapter introduces one lecture on cognitive competence development for university students in Hong Kong which is embedded in an interpersonal and intra-personal development subject entitled "Tomorrow's Leaders" at The Hong Kong Polytechnic University of Hong Kong. There are several parts in this paper. First, the definitions and concepts of cognitive competence are outlined. In the second section, a brief review of empirical studies that investigated the relationship between cognitive competence and other psychological constructs is presented. The third section of the paper provides an overview of the lecture on cognitive competence that is currently implemented in teaching for university students. Both the major content and activities designed for the lecture will be introduced. Finally, students' feedbacks and the instructor's reflections on teaching this lecture are discussed.

Concepts and Theories on Cognitive Competence

The term cognitive competence has been used interchangeably with intelligence by many researchers, while the former is considered more generic [9] as it avoids "prejudgment about the organization or generality of cognitive abilities" related to intelligence (p. 336). A survey of the scientific literature shows that there are a wide range of definitions for cognitive competence. A simple definition given in The American Heritage Dictionary [10] is the "capacity to acquire and apply knowledge" (p. 910). Similarly, in the Oxford English Dictionary [11], cognitive competence means "the ability to acquire and apply knowledge and skills." According to Merriam-Webster Online Dictionary [12], intelligence (cognitive competence) refers to "the ability to learn or understand or to deal with new or trying situations...the skilled use of reason...the ability to apply knowledge to manipulate one's environment or to think abstractly as measured by objective criteria." Basically, all the definitions of cognitive competence highlight the ability of individuals to acquire knowledge

and skills and the ability to transfer them to solve problems, i.e., the process of learning and application.

In addition to the definitions in the dictionaries, psychologists have proposed a variety of theoretical models to conceptualize the construct of cognitive competence [1]. In a broad sense, Catalano et al. [13] conceptualized cognitive competence as having two major components. The first one is “the ability to develop and apply the cognitive skills of self-talk, the reading and interpretation of social cues, using steps for problem-solving and decision-making, understanding the perspective of others, understanding behavioral norms, a positive attitude toward life, and self-awareness” [14]. The second component focuses on the ability to use logical and analytic thinking, and abstract reasoning which directly contribute to academic and intellectual achievement. In another popular model proposed by Fry [15], cognitive competence has three elements, including cognitive structure, cognitive processes, and overt behaviors, among which cognitive process is referred to as one’s metacognition, self-regulation, and cognitive skills of thinking, reasoning, analyzing problems, where information processing plays a critical role. Cognitive process affects not only one’s overt behaviors such as the real performance in solving problems and decision making, but one’s cognitive structure, like pattern of thoughts and knowledge structure [15]. According to Fry, cognitive competence is the ability to internalize, self-regulate, and transfer appropriate cognitive skills to construct knowledge and interpret the environment [15].

Another group of scholars considered the high-level ability that enables one to further develop and use one’s cognitive skills, what people called “metacognitive” skills or “metacognition,” as the key component of cognitive competence. According to Sternberg [16], metacognitive skills are higher-order executive processes used in planning, monitoring, and evaluating one’s problem solving. Similarly, Geiwitz [17] defined metacognitive skills as the capacities to monitor and guide the application of cognitive skills so as to obtain the greatest possible success. He further proposed several functions of metacognitive process: to facilitate an understanding of the problem and its parameters, to promote the search for effective solutions, to monitor the process of problem solving based on which to generate feedback, and to devise solutions for changing condition. While cognitive skills is involved in doing, metacognition is involved in choosing and planning what to do and monitoring what is being done [18, 19]. As such, it is believed that metacognitive skills determine the level of one’s cognitive competence as they guide the problem-solving process and improve the efficiency of goal-oriented behavior [20].

When the above models are integrated, cognitive competence can be regarded as having three basic elements: a) existing knowledge acquired through formal and informal learning; b) cognitive skills which together with knowledge help individuals to perform a specific cognitive task; and c) metacognitive skills, the high-level ability that enables one to further develop and use one’s cognitive skills to perform the task better. Borrowing Winter’s taxonomy of knowledge [21], cognitive competence may be best represented by a triarchic model: know what (knowledge), know how (cognitive skills), and know why (metacognitive skills).

Importance of Cognitive Competence for Young People

Good cognitive competence empowers young people in their educational, professional, and personal lives. Nowadays, one major purpose of high education is to train innovative thinkers in the ever-changing world. As such, cognitive competence is considered more important than ever [22]. One's capacity to think and solve problems in diverse contexts is vital for obtaining knowledge, developing understanding, and achieving quality performance. According to a recent report in Australia, employers in enterprises considered cognitive competence, particularly problem solving skills, an essential factor to success in their respective organizations, such as finding out creative solutions, showing independence and initiative in problem identification and solving, testing assumptions taking data and circumstances into account, and resolving customer concerns in relation to complex project issues [23]. In university education, it is necessary to provide students with various opportunities to engage in complex and authentic problem solving, encourage them to use knowledge in innovative and creative ways, and promote deep understanding.

In the literature, numerous studies have demonstrated that adolescents who were cognitively more competent had better developmental outcomes in various aspects. First, a high level of cognitive competence has been consistently found a significant and powerful predictor of school performance and academic achievement in different populations [24, 25]. Second, there is a positive relationship between good problem solving skills and one's physical health [26]. Third, researchers have reported that cognitive competence serves as an important protective factor for youth development. Cognitive competence has been associated with fewer problem behaviors, such as bullying and violence [27], unhealthy externalization and internalization problems, substance use, and delinquent behaviors [3]. Fourth, the development of cognitive competence leads to a reduction of emotional problems, including depression and anxiety [28]. Finally, studies have also shown that cognitive ability was the best predictor of leadership effectiveness [29, 30]. In the context of Hong Kong, there are research findings showing that higher cognitive competence was related to better positive youth development [31] and lower levels of adolescent problem behavior [32, 33].

A Lecture on Cognitive Competence for University Students

In view of the developmental issues in university students in Hong Kong [34], Shek has developed a subject entitled "Tomorrow's Leaders" at The Hong Kong Polytechnic University based on the premise of universal prevention in the public health approach and the literature on positive youth development [35]. The subject aims at promoting leadership and intrapersonal competencies in university students. The subject was successfully piloted twice in the 2010/11 and 2011/12 school years. Utilizing multiple evaluation strategies including objective outcome evaluation, subjective outcome evaluation, qualitative evaluation and process evaluation, it was found that the subject was able to promote the holistic development of university students in Hong Kong [36-39]. Specifically, ten key positive youth development constructs are introduced in a total of 14 lectures for undergraduate students, with one lecture focusing on cognitive competence. The outline, content, and related activities of this lecture are presented in the following sections.

Overview of the Lecture Structure

To help students acquire an in-depth understanding of cognitive competence and its relationship with effective leadership, this lecture has five major parts. In the first part, the basic concepts and theories related to cognitive competence are introduced. Second, important factors affecting the development of cognitive competence and its consequences are summarized. The third part focuses on the relationship between cognitive competence and leadership with particular focus on metacognitive skills. In the fourth paper, different methods that promote the development of cognitive competence in students are introduced and they are encouraged to explore their own ways to facilitate cognitive development. Finally, a few reflective questions regarding cognitive competence are presented to help students reflect on their own cognitive competence and appreciate issues surrounding this topic.

Major Content and Activities

Before the start of the lecture, a warm-up activity is conducted to elicit students' interests in the topic. A series of interesting questions regarding different aspects of cognitive competence such as reasoning skills and creativity are presented to students and ask for their answers. For example, one question asks "how many animals of each species Moses took with him in the Ark?" This question actually tests not only one's previous knowledge about Bible, but also the ability to pay attention to details (i.e., it was Noah who took animals to the Ark instead of Moses), both of which relate to one's cognitive competence. Through this activity, students start to develop interests in the content of the lecture and become aware that cognitive competence is used in solving different problems.

The concepts and theoretical models of cognitive competence are introduced in the first part of the lecture. Based on numerous definitions proposed by researchers, cognitive competence was conceptualized as the capacity to acquire knowledge and skills and to transfer them when solving problems. In this definition, two cognitive processes including learning and application are highlighted. To further explain the construct of cognitive competence, a three-factor model comprising "know what," "know how," and "know why" is introduced. "Know what" refers to the knowledge acquisition, which include both the "Jump start" knowledge base acquired through intensive period of formal education in the earlier stage of life, such as literacy, basic mathematics, language, etc., and the refined wisdom gained through informal learning and experience, professional knowledge, as well as the process of knowledge integration. The second factor is "know how" which represents cognitive skills that are used for information gathering, building understanding, and productive thinking [40]. Examples that are closely related to students' lives are given to help them better understand the concept. For instance, people have different styles such as visual or sensing, sequential or holistic in learning; there are various skills in memorizing information like working with patterns and rules or developing meanings. The third factor is "know why" which is "metacognition." In the lecture, metacognition is explained as the process that people regulate and monitor the application of cognitive skills in problem solving, i.e., "thinking of thinking." Three steps involved in metacognitive process are also introduced to students with explicit examples: 1) understand the problem and its parameters; 2) search

for and specify effective solutions; and 3) monitor solution implementation, generate feedback, and make adjustment in the face of changing conditions. To facilitate students' understanding, a metaphor of constructing a house is used. While "know what" can be compared to the construction materials, "know how" is the construction workers who put bricks and cement together with their techniques to build the house, and "know why" is like the architect who makes the blueprint of the building, monitors the whole process of constructing, and makes sure the house can be built up with high quality. In real teaching, this metaphor works quite well in explaining the three-factor model of cognitive competence.

After this part of lecture, students are invited to participate in a group activity entitled "Survival in the wilderness." The purpose of this activity is to enhance students' understanding of how different components of cognitive competence play a role in problem solving. In this game, students are asked to imagine that they just survived in a crash of a small plane. Both the pilot and co-pilot were killed in the crash. It is winter in Canada and the crash site is in a forest area 20 miles away from the nearest downtown. They are all dressed in city clothes appropriate for a business meeting. Then 12 items are provided to students and they are asked to pick up five most important items in order to save themselves. In groups, students are also required to list the reasons why they choose the five items on a worksheet (Appendix 1) and then share in class. After students' sharing, the teacher will show the recommended answers by a military survival trainer and share the reasons. Using one or more items as example, such as the multiple uses of a can of Tuna, the role of the three components of cognitive competence ("know what," "know how," and know why" in the decision-making process will be further explained.

In the second part of the lecture, factors affecting cognitive competence and its consequences in different aspects of individuals' life are highlighted. From an ecological perspective, two groups of influential factors that determine one's cognitive competence are discussed: biological factor and environmental factors at various ecological levels. Particularly, the interaction between biological and environmental factors on the actual level of cognitive competence is discussed. In addition, the role of attention in perception and problem solving process is explained supported by a few interesting examples, such as illusive pictures and videos.

The third part focuses on the relationship between cognitive competence and leadership. Students are provided with research findings that investigated the effect of cognitive competence on different leadership qualities. More importantly, the functions of metacognitive skills in effective leadership are emphasized in terms of several aspects: 1) choose and plan what to do and monitor what is being done [18]; 2) guide the problem-solving process and improve the efficiency of goal-oriented behavior [20]; 3) define the nature of the problem to be solved; 4) specify the most appropriate solution; 5) implement the chosen solution; and 6) monitor and evaluate the solution and its consequences [19]. Specifically, two thinking styles/strategies that help people to find out the best solutions to a problem including divergent thinking and convergent thinking are also introduced.

Two activities are then implemented to help students further understand what divergent thinking and convergent thinking are. The first activity is called "Guess what I have." Five different objectives are printed on five cards (Appendix 2). Five students are invited to come out as the respondents and each respondent is assigned one card. The task for other students is to guess the correct object on the respondent's card by asking "Yes" or "No" questions (e.g., "is it eatable?"). In each round, there are one respondent and two competing groups to guess

the answer. The two groups take turns to ask one question and the respondent can only answer “Yes” or “No.” The group which first calls out the correct answer wins the competition. After this activity, the concept of convergent thinking, i.e., to draw a conclusion / to find an answer by summarizing different pieces of information will be recapped. For the second activity, students are required to work in groups to think of as many uses of a paper clip as possible in a limited time. When time is up, each group will report in class the number of uses they have figured out. The group which names most uses of a paper clip wins the game. The teacher will then show students a webpage on which more than 150 uses of a paper clip are listed and wrap up the activity by reviewing the concept of divergent thinking. It is expected that students can better understand the two thinking styles for metacognition introduced in the lecturing part.

The fourth part proposes several methods for students to promote their cognitive competence development. Echoing the three components of cognitive competence, different strategies are suggested by the teacher. For example, to develop metacognitive skills (“Know why”), a four-step reflective writing practice is introduced. First, simply describe the experience happened. Second, try to list at least three reasons to explain why this happened. Third, write down pros and cons of this event particularly what meaning I can find in this experience. Finally, figure out what can be done to change the situation for the better [41]. The teacher will use personal examples to demonstrate the process of reflective writing. Students will also be encouraged to do a brief reflective writing in class to experience how reflective writing as a way to promote one’s metacognition and help one to face negative experience as well as to solve problems.

In the last section of the lecture, there is a review of the whole lecture, including the conceptual model, influential factors and consequences of cognitive competence, its relationship with leadership, and ways to improve cognitive competence. Furthermore, a list of reflective questions is provided in order to help students reflect on their own cognitive development, consider possible methods they can use/have used to promote cognitive development effectively, and link the topic to their real lives.

Student Feedbacks and Teacher Reflection

In the 2012/13 school year, nearly 2,100 Year 1 students in The Hong Kong Polytechnic University took the subject “Tomorrow’s Leaders” and the lecture on cognitive competence introduced above was well received by students and is considered one of the most welcome lectures in this subject. Students expressed very favorable opinions toward this lecture in various aspects. Students perceived the lecture content as informative and the activities really helped them to understand the concept [42]. Particularly, through experiential learning, they have become more aware of the importance of cognitive competence for university students as “tomorrow’s leaders” and are getting more interested in this topic. Students also perceived the teaching staff as effective in conveying useful knowledge and skills related to cognitive competence to students. Meanwhile, they also realized that cognitive development requires life-long learning and continuous efforts.

As a teacher, the authors have several observations in the class and reflection regarding the teaching experiences. First, a well-designed warm-up activity at the beginning of a lecture is very useful. In this lecture, the warm up successfully raised students’ interests in the topic

and their energy level, which set the tone for the whole lecture. From the beginning, students generally had a favorable attitude toward the lecture and were able to concentrate. Second, interactive teaching approach greatly promotes students' active learning and helps the teacher quickly assess the extent to which students have mastered the knowledge. In this lecture, various interactive teaching techniques were used, such as video watching, group project on problem solving, whole-class discussion, etc. The interactions between teacher and students as well as among students themselves effectively facilitated students' engagement in thinking about the related concepts and theories and applying the knowledge in real problem solving tasks. There were also opportunities to challenge students' understanding of the knowledge and help identify their misconceptions.

Third, students' diverse background and needs must be considered in arranging different teaching activities. As a general education subject, this lecture was delivered to students from different departments with various characteristics. For the same teaching materials, students' ability to comprehend the knowledge and their reflective skills were quite different. For example, students from humanistic disciplines (such as social work, language, physiotherapy, etc.) generally showed higher levels of self-reflective ability and were more expressive than students from science background (e.g., engineering, physics, etc.). Therefore, more time and facilitation shall be given to the latter group of students. Fourth, students' awareness of the importance of cognitive competence has been strengthened in the lecture. Particularly, students were more aware of the role of metacognitive competence in problem solving and decision-making. They realized that cognitive development requires a life-long learning and they were more willing to make efforts to actively develop themselves in this area. Finally, it is important to help students to understand how the concept of cognitive competence is related to their real life experiences.

CONCLUSION

In contemporary society, the society looks for university graduates with a whole range of skills, particularly people who are able to solve problems. To nurture university students who will become the pillar of our society in the future, more effort shall be paid to the development of students' cognitive competence, which includes not only professional knowledge but the ability of problem solving, decision making, and innovative thinking. The lecture on cognitive competence introduced in this paper was well implemented in The Hong Kong Polytechnic University. Students from different disciplines generally had positive perceptions about the lecture and perceived that this lecture effectively aroused their awareness on the importance of cognitive competence and provided good opportunities for them to practice critical thinking and problem solving. This indicates that credit-bearing course that targets at nurturing university students' cognitive development could be quite effective. With regard to the lack of such curriculum-based programs in university settings, this is an important addition to the scientific literature on leadership and positive youth development in the university context.

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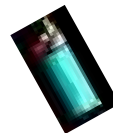
APPENDIX 1.

Worksheet for class activity: Survival in the wilderness

You and your group mates are on your way to Canada by air in January. Unfortunately, the plane crashed into a mountain near the forest. The crash site is 20 miles away from the nearest downtown. There is snow on the ground, and the countryside is wooded with several creeks crisscrossing the area (溪流的交叉地带). You and your group mates are the only survivors in the crash. Your group managed to salvage the following items:



A ball of steel wool
 A small ax
 A loaded 45-caliber pistol
 A can of tuna
 Newspapers (one per person)
 A cigarette lighter (without fluid)
 Extra shirt and pants for each survivor
 A 20 x 20 ft. piece of heavy-duty canvas
 A sectional air map made of plastic
 One quart of 100-proof whiskey
 A compass
 Several family-size chocolate bars
 (one per person)



Discuss with your group members. Select five items from the above list and rank them from 1 to 5 (1-the most important and 5- the least important).

Your group needs to come to a consensus to pick 5 items from the list for survival.

Items for your survival	Reasons
1.	
2.	
3.	
4.	
5.	

Correct Answer (for teacher's use)

Order	Items
1	Cigarette lighter (without fluid) The gravest danger facing the group is exposure to cold. The greatest need is for a source of warmth and the second greatest need is for signaling devices. This makes building a fire the first order of business. Without matches, something is needed to produce sparks, and even without fluid, a cigarette lighter can do that.
2	A ball of steel wool To make a fire, the survivors need a means of catching the sparks made by the cigarette lighter. This is the best substance for catching a spark and supporting a flame, even if the steel wool is a little wet.
3	Extra shirts and pants for each survivor Besides adding warmth to the body, clothes can also be used for shelter, signaling, bedding, bandages, string (when unraveled) and fuel for the fire.
4	A can of tuna This has many uses. A mirror-like signaling device can be made from the lid. After shining the lid with steel wool, it will reflect sunlight and generate 5 to 7 million candlepower. This is bright enough to be seen beyond the horizon. While this could be limited somewhat by the trees, a member of the group could climb a tree and use the mirrored lid to signal search planes. If they had no other means of signaling than this, they would have a better than 80% chance of being rescued within the first day. The empty can is useful in melting snow for drinking water. It is much safer to drink warmed water than to eat snow, since warm water will help retain body heat. Water is important because dehydration will affect decision-making. The can is also useful as a cup.
5	A 20 x 20 ft. piece of heavy-duty canvas The cold makes shelter necessary, and canvas would protect against wind and snow (canvas is used in making tents). Spread on a frame made of trees, it could be used as a tent or a wind screen. It might also be used as a ground cover to keep the survivors dry. Its shape, when contrasted with the surrounding terrain, makes it a signaling device.
6	A small ax Survivors need a constant supply of wood in order to maintain the fire. The ax could be used for this as well as for clearing a sheltered campsite, cutting tree branches for ground insulation, and constructing a frame for the canvas tent.
7	Several family-size chocolate bars (one per person) Chocolate will provide some food energy. Since it contains mostly carbohydrates, it supplies the energy without making digestive demands on the body.
8	Newspapers (one per person) These are useful in starting a fire. They can also be used as insulation under clothing when rolled up and placed around a person's arms and legs. A newspaper can also be used as a verbal signaling device when rolled up in a megaphone-shape. It could also provide reading material for recreation.
9	A loaded .45-caliber pistol The pistol provides a sound-signaling device. The international distress signal is 3 shots fired in rapid succession. There have been numerous cases of survivors going undetected because they were too weak to make a loud enough noise to attract attention. The butt of the pistol could be used as a hammer, and the powder from the shells will assist in fire building. By placing a small bit of cloth in a cartridge emptied of its bullet, one can start a fire by firing the gun at dry wood on the ground. The pistol also has some serious disadvantages. Anger, frustration, impatience, irritability, and lapses of rationality may increase as the group awaits rescue. The availability of a lethal weapon is a danger to the group under these conditions. Although a pistol could be used in hunting, it would take an expert marksman to kill an animal with it. Then the animal would have to be transported to the crash site, which could prove difficult to impossible depending on its size.

Order	Items
10	One Quart of 100 proof whiskey The only uses of whiskey are as an aid in fire building and as a fuel for a torch (made by soaking a piece of clothing in the whiskey and attaching it to a tree branch). The empty bottle could be used for storing water. The danger of whiskey is that someone might drink it, thinking it would bring warmth. Alcohol takes on the temperature it is exposed to, and a drink of minus 30 degrees whiskey would freeze a person's esophagus and stomach. Alcohol also dilates the blood vessels in the skin, resulting in chilled blood being carried back to the heart, resulting in a rapid loss of body heat. Thus, a drunk person is more likely to get hypothermia than a sober person is.
11	A compass Because a compass might encourage someone to try to walk to the nearest town, it is a dangerous item. Its only redeeming feature is that it could be used as a reflector of sunlight (due to its glass top).
12	A sectional air map made of plastic This is also among the least desirable of the items because it will encourage individuals to try to walk to the nearest town. Its only useful feature is as a ground cover to keep someone dry.

(Source: <http://wilderdom.com/games/descriptions/SurvivalScenarios.html>).

APPENDIX 2.

Worksheet for class activity on convergent thinking: Five cards

An Octopus card



A basketball



A pair of earrings



A paper clip



A pack of ketchup



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Chapter 159

DEVELOPMENT OF A CLEAR AND POSITIVE IDENTITY

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ABSTRACT

In many adolescent developmental models, it is proposed that having a clear and positive identity is an important developmental task for adolescents. In this chapter, the conception of positive and healthy identity and the related theories are outlined and the determinants and effects of having a positive and healthy identity are presented. The relationship between healthy and positive identity and leadership is then explored. Finally, the question to know how positive and healthy identity can be promoted is examined. Issues surrounding the ways of how to teach students to develop the attribute of having a clear and positive identity as a leader are discussed.

INTRODUCTION

For many decades, many studies have explored the nature and development of identity across different disciplines. In different theories, personal identity has been regarded as an

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essential concept to understand the development of oneself [1-4]. According to Sharma and Sharma [5], identity “is an umbrella term used throughout the social sciences to describe an individual’s comprehension of him or herself as a discrete, separate entity” [5]. Identity formation is a dynamic and evolving developmental process that could be structured meaningfully into the general, physical, psychological, social and spiritual domains [4]. In the Western societies, there has been a strong urge for individuals to search for their own unique identity by understanding their own characteristics and choosing from a large variety of socially-formulated alternatives [6]. Although the identity for the traditional Chinese was quite “static” and closely related to the class or hierarchy in which they were born, the quest for identity is still an essential issue for the Chinese in searching for “Who am I” and “Who I really am?” [4].

Within the field of psychology, the notion of “identity” is closely related to the concept of “self”, with examples of related concepts like “self-concept” and “self-identity” which are closely related to the belief that personal development is a process of acquiring and achieving different “selves.” Generally speaking, the formation of identity is by individual’s collection of self-understanding, self-conceptions and self-images [6, 7]. The “self” plays a crucial role in defining and formulating one’s own identity. Through the dynamic process of comprehending different concepts about self, an “identity” is evolved and an individual might have a better understanding of how his or her past and present experiences help formulate the identity as he or she understands now. This is an active and creative process of making sense of the personal experiences to formulate one’s own identity, which increases the awareness of “self” to help one recognize and examine one’s identity.

During the process of making sense of one’s experiences and his or her idea of “self”, the understanding of different “selves”, including “real self”, “ideal self” and “ought self” assists an individual to identify whether an individual has achieved his or her identity. “Real self” is the self as the individual *experiences*; “ideal self” is the self that the individual *wishes or desires* to be; and “ought self” is the self that an individual *should* be. The development of a person could be seen as a process of acquiring and achieving these different selves. The extent to which these three selves overlap determines whether a person’s identity is well defined or not [1]. However, some scholars reiterated that the functions of self-knowledge focus only on the factual idea of “self” at present which might limit a person’s understanding on how their own expectations and the social reality influence their process of identity formation [3]. The self-knowledge should be extended to exploring the “possible selves,” which is the understanding of how an individual think about their potential and future. Although the possible selves share similarities with the “ideal self” such as representing what an individual would like to be in the future, it also explores the self that we could become and fear to become. The possible selves are more individualized and personalized with the comprehension of the hopes, dreams and fears of the past-, present- and future- selves [3, 8].

Apart from looking inwardly at one’s own identity formation and the possible selves, the perceptions of others, social contexts and the environment also contribute to one’s identity formation [9]. Traditionally, “identity” was believed to be a fairly uniform concept but with massive structure comprising some number of physical features and psychological structures [3]. A review of the recent literature showed that identity is now portrayed as an “ever-changing” process through which an individual can formulate his or her identity by understanding his or her own perceptions of self, the experiences throughout the life span and others’ perceptions and views on the individual [3, 7]. The construction of “self” is seen as a

result of comparisons in which the individual's own thoughts, feelings, characteristics and behaviors are compared with those of others. The reflections from and the understanding of other people or the generalized community might also help give another perspective to individuals to formulate their own identity.

Regarding the discussion of identity, Erik Erikson's theory is the most prominent theory addressing the nature and the development of adolescent identity. He proposed the eight-stage human development framework with a particular emphasis on the identity formation in the stage of adolescence [6]. Erikson [1] conceptualized the ego identity both as "conscious" comprehension of one's uniqueness and "unconscious" striving of one's experiences. An "identity crisis" might occur when adolescents seriously start questioning their "conscious" and "unconscious" selves, the perceptions of themselves, and how others view them. "Identity crisis" represents a psychosocial task and constitutes a challenging turning point for adolescents to achieve a healthy adult identity. The adolescents might move toward either "identity achievement" or "identity confusion" statuses [1].

Marcia's [2] identity status paradigm is the most popular elaboration of Erikson's views on identity formation [4, 6]. Marcia [2] identified two important elements (i.e., exploration and commitment). "Exploration" refers to the active questioning and inquiring of different roles, values, beliefs or goals to offer an individual various identity alternatives. "Commitment" refers to the firm choice made regarding aspects such as vocation, political ideology, religion and social roles, and the strategies geared toward those desired paths and outcomes. Four identity statuses are derived from the interaction between exploration and commitment, which are "identity diffusion," "moratorium," "foreclosure," and "identity achievement." In identity diffusion, there is no pro-active interaction between the exploration and commitment and no commitment has been made for any identity domain. Moratorium refers to an individual who has explored actively various identity alternatives yet with no commitment to them while foreclosure denotes the status that commitment has been made with little exploration. For identity achievement, an individual actively explore different identity alternatives thoroughly and make a commitment to the choice in a specific identity domain.

In recent decades, the focus of investigating the identity statuses has shifted from focusing exclusively on the outcomes to focusing on the process of identity formation and development. As the author of the four identity statuses, Marcia [10] recognized the importance of exploring the process of identity formation rather than the outcomes. Building upon Marcia's work on the identity statuses, recent research has explored the newly developed identity models like "commitment," "in-depth exploration" and "reconsideration of the commitment" [6]. "Commitment" denotes similar view as Marcia's model yet the individual's self-confidence in committing to the choices is elicited in the process more explicitly. For "in-depth exploration," the individual would reflect upon the choices made, explore additional information about the choices an individual is making or going to make, and discuss with significant others about the choices and the reflections. "Reconsideration of the commitment" refers to an individual's re-consideration of the present alternatives and strives for the best commitment as the present one is no longer satisfactory. The newly developed orientation in exploring the process of identity formation sheds light on enriching the exploration and investigation of identity development.

It is our belief that before one leads others, one must have a clear and positive identity. Before exerting influence on others as a leader, it is essential for an individual to search and

discover “who he or she is,” what they value and for them to build a clear understanding of “self.” In the leadership process, clear understanding of self and the identity, known as the “authentic leadership,” provides a firm anchor for decisions and actions and offers positive modelling to the development of followers’ self-awareness of their values, identity, emotions and motives [11]. This clear self-understanding and sense of identity is achieved through the unbiased collection and interpretation of self-related information of the leader without distortion and exaggeration. The heightened levels of self-awareness of a leader help him or her be more engaged with their role as a leader and develop a distinct “leader identity”. The individual with this distinctive leader identity would become the “prototypical member” [11] who views himself or herself as the role model who could be trusted and respected and exerts influence, and hence leadership, on the rest of the group.

The self-understanding of an individual does not only consist in contributing to its own individual well-being but also to the organizational or collective good. The clear identification of the leader and follower not only serve as distinguishing social relationships, but it also helps build social identities as individuals would define themselves as being members of the organization or the community. The collective identification implies the “psychological merging” of self and the group that the individuals identify themselves with as they see themselves as similar to members of the group [12]. When the definition of “self” is extended to the collective terms, collective interest becomes self-interest and the individuals would be motivated to contribute to the collective good and move towards the collective goals of the community or the organization. In their studies, Kark, Shamir and Chen [13] found that the social identification has mediated the positive relationship between transformational leadership and aspects of self-concept such as self-efficacy, collective efficacy and organization-based self-esteem.

Lecture Content

The development of a clear and positive identity involves “building self-worth and self-esteem, facilitating exploration of and commitment to self-definition, reducing self-discrepancies, and further fostering role formation and achievement” [4]. Successful leaders not only have a clear and positive identity, but they also motivate followers to search for their own identities [12]. In this lecture, the concepts of self and identity are discussed. Strategies for facilitating the development of self-conception (i.e., self-concept, self-identity) are also presented.

As far as the intended learning outcomes are concerned, it is expected that the students should be able to master the following concepts and skills after the completion of this lecture: a) understand the basic concepts and theories related to positive identity and related concepts; b) articulate the antecedents and consequences of having positive and healthy identity; c) discuss the role of positive and healthy identity in leadership; and d) explore ways to promote the development of positive and healthy identity. The teaching methods in this subject include lecture, group discussion, in-class interactive activities (such as drawings), and self-reflection.

There are five parts in this lecture. In Part 1, the basic concepts and theories of self-identity are outlined. In this part, a warm-up activity (“How do I view myself?”), class discussion on “Living Funeral” and a self-reflection exercise (“Can I (You) see the REAL

ME?") are involved. In Part 2, the antecedents and consequences of self-identity and self-concept are introduced. A class activity entitled "The Image of a Successful Leader" is conducted. In Part 3, theories and research findings on the relationship between positive identity and leadership are presented. In Part 4, ways to promote positive and healthy identity are discussed. In particular, teachers will share their experience in this area. In Part 5, conclusion and reflections are carried out. A self-reflection exercise on "A Memorandum to Myself" will be introduced.

In Part 1, the lecture commences with a warm-up activity named "How do I view myself" with the purpose of helping students reflect on how well they describe themselves. "Identity" is well understood as "an umbrella term" [5] and adolescents might find it difficult to conceptualize their own identities without concrete vivid aids. When the question "who am I" is asked, it is difficult for an individual to formulate concretely who he or she is throughout the life process. With the aid of the images of animals projected on screen and printed on a worksheet for easy reference, students are asked to choose an animal (or they could propose other animals not on the list) which could best represent themselves in different contexts (e.g., when they are studying or when they are with friends/family members). This might help the university students visualize their self-images through familiar animals or objects. After choosing the image of an animal, students are encouraged to share their choices in pairs or within their own groups in order to have a preliminary understanding yet multi-angled conception of their own identities. This warm-up activity is wrapped up by stating the rationales of the activity, which can facilitate the students' exploration of self-definition and understand how these self-definitions might influence the identity formation in their lives [4].

After the warm-up exercise, a model of self-concept and a theory of identity statuses are introduced to help students address the core questions when exploring the development of identity. The introduction of "the hierarchical model of self-concept" advocated by Shavelson, Hubner and Stanton [14] aids students to explore and understand the development of self-concepts in different domains in respect of academic, social, emotional and physical domains. Through evaluating self-perception of experiences in different domains, the students could gain some basic understanding of "self-concept" in each area and as a result could better understand the overall concept of self. Teachers conclude these domain-specific evaluations by asking students to examine how these evaluations influence their overall self-worth and the perceptions of themselves in relation to their environment. Marcia's [2] theory of "four identity statuses" (i.e., identity diffusion, foreclosure, moratorium and identity achievement) is presented afterwards to enhance students' understanding of the structure and dynamics of identity development. Examples in daily life are given against each status to assist students in understanding the interactions of "exploration" and "commitment." An example of "Your religious commitment," drawn from Marcia's [2] article is given to illustrate the typical answers on the four statuses and help students understand how these statuses influence one's decision-making and identity-formation. This part is concluded by articulating the essence of identity-formation, which refers to the integration of different roles into an identity that helps one to answer the question "Who am I" more thoroughly.

In order to have a more in-depth exploration of self-identity, the antecedents and consequences of self-identity and self-concept are illustrated in Part 2. This part starts off with a self-reflection exercise and a group sharing on an excerpt "living funeral" of a book "Tuesdays with Morrie" [15]. This excerpt is about Professor Morrie, who suffered from the Amyotrophic lateral sclerosis (ALS) and his life was going to end soon, so he prepared a

“living funeral” to hear about the words and comments of his loved ones on himself. This extracted piece is arranged to help students reflect on how one’s own and others’ (especially the significant others) perceptions and past experiences influence one’s identity development. The self-reflection is further deepened by the “Can I (You) see the real me?” exercise. The purpose of this worksheet is to help students better understand their different selves by articulating the three most important actual (“actual self”) and ideal (“ideal self”) attributes that the students and their parents or good friends perceive them to have. The students are invited to think about the reasons for the discrepancies between the “actual self” and the “ideal self” and further reflect on how these discrepancies influence their own identity formation.

By specifying the perceptions of the “actual self” and the “ideal self,” the students could grasp the preliminary ideas of the factors affecting the development of their identities. Then the factors influencing the identity formation derived from the literature are introduced to students. The factors are introduced at both levels – the individual level (e.g., visible physical disabilities; body image dissatisfaction and gender) and the social level (e.g., peer relationship; family and socio-cultural norm), which echo the “dynamic” nature of identities of Marcia’s model introduced in Part 1. The consequences (self-monitoring; psychological well-being and academic adjustment) are also presented in this session to help students understand the importance of having a positive and healthy identity. The students’ understanding of the concept of identity is further reinforced by inviting the students to draw an image of a successful leader. A list of successful leader’s attributes is distributed to students. The students discuss among their groups and choose the three most important attributes (or more) that might contribute to the success of a leader. Then the students are asked to draw the image on a poster-size paper and are invited to share the reasons for choosing these attributes. This activity helps students to recognize and visualize the attributes that might help them develop their ideal leadership attributes and have a concrete image of a successful leader. This might help make the students aware of the potentials they possess and understand the “possible selves” that they might wish to achieve.

In Part 3, the focus is put on the relationship between positive identity and leadership. In the traditional approach to leadership, leadership is viewed as transactional: the leaders would set a task goal with rewards and ask the followers to work towards completing the task in exchange of rewards. The leadership is exerted through the exchange relationship between the leader and the follower. However, transformational leadership has been advocated in recent decades as the leader is treated as a changing agent empowering the followers to understand their own self-conceptions, identities and potentials. This constitutes a relationship of mutual stimulation and elevates the followers to be leaders [11]. With the introduction of the differences between transactional and transformational leadership, students can understand that the types of leadership depend on how you define the identity of a leader.

The ways to promote positive and healthy identity are introduced in Part 4 as a summary session for summarizing the ideas about identity formation discussed in the previous parts. Five ways of promoting positive and healthy identity are depicted to show students how to consolidate the key learning points in the previous parts. Firstly, the “self-evaluation” is intended to guide us to re-think about the standards we are using to evaluate ourselves. This evaluation is not depicting one’s weaknesses but aims to help people lead a purpose-driven life instead. Secondly, it is important to cultivate one’s self-efficacy (i.e., our ability to perform and achieve a goal). Focusing on what an individual is able to do can help him or her

to be persistent in his or her goal-directed behaviors and help them succeed in pursuing these goals.

To have self-acceptance is the third way to construct one's identity. It is thought that self-acceptance is a crucial step to cultivate a positive and healthy identity by overcoming the "trigger events" and to assist an individual in shaping his or her identity development [11]. "Authentic living" and "positive thinking" are the last two ways to be introduced. Students are encouraged to behave and express their emotions and views according to their true selves, which is to live authentically, and to think positively to accentuate their strengths. The teachers' sharing is strongly encouraged in this part to act as an example for students to understand how to develop a positive and healthy identity in a real life situation. The teachers' self-disclosure is one of the crucial teaching pedagogies in the subject "Tomorrow's Leaders." It is believed that a self-disclosing atmosphere inside the classroom could act a catalyst to facilitate students' sharing and personal reflection and thus encourage the openness of students [16]. In addition, through sharing the success or failure of building a positive and healthy identity by teachers, students could integrate the theories learnt in the previous parts with their own personal reflections or experiences. Learning is thus enhanced through the interpersonal dynamics between teachers and students.

The lecture ends with a self-reflection exercise consisting in writing "A memorandum to myself." The students are asked to evaluate the "now-me" in relation to the three most salient positive and negative characteristics that they perceive about themselves. The students are then invited to foresee the three most salient characteristics in their self-image when they graduate and think of the ways to build up these characteristics in their self-concept. The students are strongly advised to keep this memorandum until they graduate so that they can witness their own personal growth. Finally, a few reflective questions (for example, "How does the Chinese culture shape your self-concept?"; "How does your family influence your self-concept?") are raised to help students consolidate what they have learnt in the lecture and widen and deepen the horizons of students' reflections on identity-formation.

There are several issues that a teacher should be aware of when teaching the topic on positive and healthy self-identity. First, Chinese adolescents in Hong Kong are not encouraged to reflect on their self-identity in the socialization process. Actually, adolescent children are encouraged to develop a "foreclosure" identity such as getting good academic results and studying in a program with "good career prospect." Therefore, it is a frightening and challenging experience for Chinese adolescents to face their "real" self instead of their "ought" self. Second, there are two tendencies generally followed by Chinese people when describing themselves openly. On the one hand, they may respond in a "socially desirable" manner by not disclosing one's weaknesses. On the other hand, with the emphasis on humility and interpersonal harmony, Chinese people tend to describe themselves in a reserved manner. Hence, teachers should be alert to these Chinese characteristics in self-description. Third, within a collectivistic culture, as Chinese people tend to focus more on the "ought" self (i.e., what other people want you to be) instead of the "ideal" self (i.e., what one wants oneself to be), more coaching and directions are needed.

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Chapter 160

RESILIENCE, LEADERSHIP AND INTRAPERSONAL DEVELOPMENT

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ABSTRACT

Resilience is an important construct in the positive youth development literature. In this chapter, the definition and concept of resilience are introduced. The relationships between resilience and adolescent development as well as leadership are also addressed. To help students develop qualities on resilience, a lecture on resilience is developed in a subject entitled "Tomorrow's Leaders." The objectives, intended learning outcomes, lecture outline, and lecture materials are presented in this chapter. Some issues surrounding the teaching of this lecture are discussed.

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INTRODUCTION

Adolescents are confronted with multitude of challenges, resulting from developmental changes, as well as threats present in their external environment, such as problems with interpersonal relationships, conflicts with parents, close friends, and romantic partners [1], emerging identity confusions [2], and heightened competitiveness in the job market [3]. While some adolescents are able to successfully weather through these storms, others may engage in health-compromising behaviors to drown their worries. Researchers recognize the need to investigate factors critical for increasing the likelihood of adolescents to remain on healthy and productive trajectories to adulthood, in spite of the ebb and flow in life. Resilience has been identified as a buffering factor against the adverse impact of oscillations, enabling positive outcomes.

Although university students are generally perceived to be a privileged group of adolescents, this does not imply that they are immune to stress and mental disorders [4]. Studies found that university students suffered from psychological problems including personality disorders and depression [5]. Some students even reported that they felt so depressed it was difficult to function [6]. Increasing trends in problem behaviors, such as illicit drug use, alcohol abuse, and self-injury were also noted in this population [7]. With the heightening prevalence of mental disorders and developmental problem behaviors among adolescents worldwide, researchers and practitioners begin to question why certain adolescents when confronted with life's hardships, snap; while others are able to snap back? [8]. "Resilience" is one of the answers.

Concept of Resilience

Various metaphors for resilience have been elicited by researchers to elucidate the concept:

"Resilient leaders are like rubber bands; they bounce back from adversities stronger and faster, learn from experiences, gain more self-confidence in the process and develop new skills." [9]

"A cast iron is hard, brittle, and breaks easily (not resilient), whereas wrought iron is soft, malleable, and bends without breaking (resilient). This metaphor can be carried over to psychological resilience, which entails a similar resistance to the psychological strain associated with negative experiences." [10]

According to Greene and Conrad [11], resilience refers to an individual's capacity to cope successfully when confronted with changes, risks, and adversities. Effective coping involves the ability to bounce back from adversities [10], to operate above the norm in spite of stress [12], and to move forward from a catastrophe with greater vigor and experience a positive change [13]. It has also been conceptualized as a buffer mechanism that helps ameliorate a person's reaction to an adverse situation that in ordinary circumstances may negatively impact on one's life [14]. Pulley [15] outlined several characteristics of resilient individuals, including engagement in life-long learning, having high-levels of self-efficacy, possession of a sense of meaning, engagement in continuous improvisation, are less occupied with monetary attainment and definition of identity and success by their internal values and standards.

Traditionally, resilience has been conceptualized as a trait-like construct, implying a fixed or an all-or-none nature [16]. Empirical evidence has since demonstrated that there are methods through which resilience can be enhanced. Tugade and Fredrickson [10] showed that individuals can make use of positive emotions to build resilience. High-resilient individuals are able to experience positive emotions even amidst stress. Survivors of the 911 terrorist attack reported experiencing negative affects including fear and anger, but also that of positive emotions, such as gratitude and love, which helped them get through the traumatic event [17]. Fostering self-enhancement has shown to be effective in strengthening resilience [18]. The effectiveness of the above measures in building resilience suggest on its malleable nature.

Resilience and Adolescent Development

In contrast to risk factors, different categories of protective factors have also been identified to positively impact on one's resilience. These include individual factors (e.g., healthy attribution style, hope) or dispositional attributes (e.g., emotional stability, openness, agreeableness) [19, 20], relational factors (e.g., social support, supportive family environment), and community factors (e.g., good school, community assets). It has been speculated that one of the reasons for the occurrences of mental health issues and problem behaviors in adolescents is their lack of resilience -their inability to apply productive strategies to cope with stress [21] and their incapability to effectively deploy their emotional, cognitive, and social resources in troubling times [22-24]. Low levels of resilience have been associated with an array of developmental problems, including alcohol use [25], school failure, adolescent pregnancy, and delinquency [26]. On the other hand, adolescents who possess high levels of resilience are able to develop healthily in different areas. Resilience has been associated with lower levels of academic stress [27], higher levels of self-esteem, and effective use of problem-solving coping strategies when facing difficulties [28].

Resilience and Leadership

Resilient leaders are equipped with psychosocial and behavioral competencies that enable them to bounce back from inevitable setbacks and failures. On an intrapersonal level, resilient leaders often have high levels of emotional stability [29]. Emotional intelligence facilitates individuals' adaptation to change, through receptivity (i.e., one's willingness to consider change), mobilization (i.e., concrete steps individuals take in times of change), and active learning from the outcome of changes [30]. Cognitive abilities to perceive experiences positively and tolerate uncertainty [31] have also been associated with information seeking, making sense of, and ascribing meaning to changes and risks, which are critical for resilience. On an interpersonal level, followers observe resilience from their leaders which operates on a "cascade and contagion" mechanism; the witness of resilient leaders' success enables followers to build on such efficacy and develop their own resiliency to recover from subsequent setbacks [32] and to provide intellectual stimulation for followers [33].

Resilience in leadership literature is often considered as a construct under the umbrella of positive organizational behaviors and a type of psychological capital (PsyCap). PsyCap is defined as “an individual’s positive state of development” [34] marked by individuals’ (i) self-efficacy (i.e., being confident that one is able to take on challenges and achieve organizational goals), (ii) optimism (i.e., making positive attributions about succeeding in the present, as well as the future), (iii) hope (i.e., persevering in challenging times and redirecting paths when necessary), and (iv) resilience (i.e., bouncing back and performing beyond norms to attain success). Resilience in this context is conceptualized as a reactive process, where the presence of risk factors activates the resiliency process. Although PsyCap was initially developed in the organizational arena from the West, Luthans et al. [35] emphasize the imperative need to develop and manage “this untapped positivity” in Chinese societies. Riolli and colleagues [14] also suggested its applicability to the academic setting by arguing that students experience many difficulties which are common to those found within a business setting. This is supported by their findings which demonstrate that students’ PsyCap levels were positively correlated to their psychological well-being, life satisfaction, and health symptoms.

PsyCap also acted as a buffer against the impact of stress on negative outcomes. Riolli and colleagues [14] believed that it was likely that students with higher levels of PsyCap make use of optimistic explanatory styles when perturbed. The findings from their study yield “implications for university educators to include a focus on aspects of psychological capital within the academic curriculum. Psychological capital may be as, or even more, valuable as a resource for students than is traditional academic content, since PsyCap helps students persevere in their studies in a psychologically and physically healthier manner” [14]. Stoltz [36] asserted that “resilient individuals, teams, and organizations consistently outlast, outmaneuver, and outperform their less resilient competitors - making resilience training one of the most important emerging trends in learning” [36]. King and Rothstein [37] concur that “while exceptional leaders are considered to be highly resilient, resilience is not a characteristic of exceptional people,” which implies that resilience is an attribute that can potentially be learned.

Identity status change during adolescence and young adulthood: a meta- nurtured in all students. The above converge to bring forth the need to develop a curriculum that will incorporate the skills for enhancing resilience among university students. In fact, resilience is not merely a competency; it is also an attitude, “a reflex, a way of facing and understanding the world, that is deeply etched into a person’s mind and soul” [8], a life-long attitude that we aim to nurture in leaders of tomorrow.

Lecture on Resilience in “Tomorrow’s Leaders”

Riolli and colleagues [14] claimed that “the impact of those stressors on student well-being can have a variety of negative psychological, health, and behavioral effects that may reduce student effectiveness, cause high levels of distress, and in the long run deprive the economy and the nation of valuable, educated contributors” [14]. Given the far-reaching impact of resilience on individual and societal development, researchers argued for the need to develop campus-wide programs to build resilience factors in the student population [25].

However, the majority of the existing positive youth development interventions aimed at promoting holistic development (including resilience) in adolescents have been developed and investigated in a Western context. Few programs have been comprehensively and systematically implemented in an Asian context (with the exception of Project P.A.T.H.S. in Hong Kong) [38]. There are arguments that a curricular-based approach adopting the positive youth development model [39], that includes resilience and other protective factors, would be helpful to nurture university students. In addition, culture specific factors influencing the development of resilience have also been identified and must be considered in preventive programs. Therefore, the teaching aims of the present lecture on resilience are to introduce the basic theories and concepts related to resilience, highlight its importance to adolescent development, and outline the protective factors that contribute to the development of resilience, and encourage students to make use of these factors and resources when encountering setbacks.

The lecture on resilience introduces the concepts and theories of resilience and highlights the importance of resilience in effective leadership. Practical skills and strategies for strengthening one's resilience are also presented. Regarding the intended learning outcomes, it is expected that students should be able to: a) define the basic concepts and theories related to resilience; b) identify the antecedents and consequences of resilience; c) recognize the relationship between resilience and leadership; d) list a variety of ways to promote resilience; and e) critically discuss issues related to resilience. The teaching methods include lecturing, video playing, experiential learning activities, group discussions, and self-reflection.

As far as the lecture organization is concerned, there are four parts of the lecture. In Part 1, the definitions and theories of resilience are presented via three activities: warm-up activity ("Armless piano performance by Liu Wei"), experiential learning activity ("mission possible") and self-reflection activity ("are you resilient?"). In Part 2, the relationship between resilience and leadership is addressed and the video clip on "the stories of Steve Jobs" is shown. In Part 3, ways to promote resilience are discussed. The lecture ends by showing a video clip of "Nick Vujicic." In different parts of the lecture, students are challenged to critically discuss and share their ideas on controversial issues related to resilience.

The lecture begins with a video clip aimed at introducing the concept of resilience. A touching piano performance by an armless pianist, Liu Wei, on a China music talent show is played. Twenty-six years-old Liu Wei had both his arms amputated at the age of 10 years shares in the video, the hardships he has undergone and how he is able to overcome adversities and persist to achieve his dreams of being a pianist. Students are then invited to share their thoughts and feelings after watching the clip. Many students admired Liu's will to live a fruitful life in spite of his circumstances. The lecturer then concludes by highlighting the importance of perseverance in overturning adverse situations in life.

The purpose of the first part of the lecture is to introduce the concept of resilience. First, various definitions of resilience will be given and the core essence of the concept will be highlighted. Second, components of resilience will be outlined; specifically, the different intrapersonal and interpersonal factors (e.g., dispositional attributes, familial factors, social support systems) that have impacts on the development of resilience will be discussed. Third, the importance of resilience on positive development will be illustrated with the use of research showing the positive impacts of high resilience and adverse effects of lacking thereof. Students are guided to consider about the nature-nurture debate pertaining to

resilience, i.e., whether they believe that resilience is a malleable asset and to perpend on factors influencing individuals' resilience.

Subsequent to the lecturing section, the first experiential learning activity will be conducted. The activity entitled "mission possible" aims to provide students with a first-hand experience, both physically and emotionally, how it feels to be confronted with an obstacle, given limitations. The activity stresses the importance of creativity, determination, and social support in overcoming challenges. The activity is divided into two stages. In the first stage, students are asked to work alone to complete the task. Without using their palms, they are to creatively devise methods in which they could effectively copy a quote, as well as a simple picture (shown to them on the PowerPoint) to a piece of paper, within an assigned timeframe. Some interesting methods students came up with include using their mouths, wrists, or attaching pens to their watches to complete the challenge. In the second stage of the activity, students are asked to work collaboratively with their group mates. A pile of small candies are distributed evenly on a table, similar to stage one, without using their palms, students are instructed to think of ways in which they could work together to pick up as many candies as possible. Students often made use of their arms, or other tools such as their jackets to facilitate the process. Upon completion of the two stages, students are invited to share how they felt during the two challenges, how the two stages differ from each other, and reflect on how the activities are related to resilience. Students frequently reported feeling frustrated in the beginning, but a sense of efficacy upon devising creative methods to solve the task. They also realized the importance of social support and collaboration, making the second stage easier than the first to complete. Students are then invited to critically discuss how social factors (e.g., family, peers, community, etc.) may influence individual's levels of resilience. Students are steered to consider the development of resilience as an ongoing process across one's lifespan and how external factors can impact the process. Teachers conclude this activity by relating back to the theories of resilience, reiterating the essence of the concept and stressing the components and factors that contribute to resilience.

Following the activity, a self-reflection activity entitled "are you resilient?" will be conducted where students complete the 10-item Resilience Assessment Questionnaire [40] aimed at providing them with a better understanding of their degree of resilience, and increasing their awareness of areas in which they can work on to increase their resilience. Students indicate on a 5-point Likert scale the extent to which they agree, ranging from 1 (strongly disagree) to 5 (strongly agree), to statements such as, "I view change as an opportunity." and "I regularly participate with friends in social activities where I can relax." Students are asked to reflect on their strengths and weaknesses with relevance to resilience. Teachers also share the scores they obtained from the Resilience Assessment Questionnaires and areas in which they need improvements on. Following the sharing of the results, teachers also share personal stories of hardships experienced in the past, and how resilience has helped them overcome the obstacles.

In the second part of the lecture, the relationship between resilience and leadership is emphasized. In small groups, students are first asked to brainstorm and make a list of attributes that they think resilient leaders should possess and share their ideas with the class. Teachers then highlight the fact that being a resilient leader requires a diverse set of psychosocial competencies. Research findings on qualities (e.g., emotional stability, strategic problem solving skills in times of stress, intellectual stimulation) inherent to resilient leaders are shared. The concept of psychological capital and its relevance to resilient leadership will

also be introduced. Subsequently, teachers will ask students whether they think that Steve Jobs is an effective leader and reveal that in fact, Jobs also faced numerous obstacles on his path to success. Students are shown a video clip of the commencement speech that Jobs delivered to university students at the Stanford University in 2005 [41]. In his speech, he shared three stories from his life. First, the hardships he faced growing up as an adoptee and the challenges he encountered during his quest for a meaning of life as a college student. Second, the journey of finding what he was passionate about in life and his career, as well as the obstacles he encountered when setting up his first company. Third, Jobs talked about his diagnosis of cancer, how he recovered from it, and his realizations as a result of this adversity.

After hearing Jobs' commencement speech, students are invited to choose one of the three resilient stories that was most inspiring to them and reasons for supporting their choice. Students choose different stories for various reasons. Some felt that they can relate to the first story most; being a university student faced with increasing demands and expectations posed on them. They were trying to adapt to their role as a university student while simultaneously searching for their identities and reasons for choosing their majors. Some students felt that the second story was most inspiring; it related to finding what one is passionate about and how this love enables perseverance in times of tribulations. Students shared how they experienced failure from obtaining poor results in their public examination, but their ambition to enter university to pursue their ultimate career goals reminded them not to give up and to work even harder toward their dreams despite the setback. Lastly, some students shared stories of experiencing death of family members, close friends, or personal illnesses and how they overcame the period of hardship and what they have realized about the meaning of life. Teachers thanked students for their sharing and concluded this section by highlighting that adversities are inevitable in different stages and domains in one's life, and even successful leaders experience obstacles. However, the outcomes of these misfortunes are determined by whether individuals are resilient and able to turn these challenges into opportunities and how determination, perseverance, passion for what you do, and love for those around you help transcend suffering in turbulent times.

In the third section of the lecture, practical methods in which students can strengthen their resilience is introduced. According to the American Psychological Association [42] ten ways to build resilience include: (i) maintain positive relationships with family members and friends, students are reminded that in times of adversity, they need not feel shy to seek help from family and friends and that social support is an effective way that can help one get through tough times. Providing help and being a good listener to others' problems can also help strengthen one's own resilience; (ii) avoid perceiving stressful events as insurmountable problems, highlighting individuals' free-will and active role in interpreting inevitable events; (iii) accept circumstances that cannot be changed by accurately assessing the attainability of goals against the changing environment and making alterations when called for; (iv) develop realistic goals and work towards them; (v) take decisive actions in adverse situations rather than engaging in avoidance coping; (vi) develop self-confidence; (vii) search for opportunities of self-discovery after struggles and losses; (viii) keep a long-term perspective and consider stressors in a broader context; (ix) maintain a hopeful outlook and visualize what you want or desire; and (x) take good care of one's mind and body by exercising regularly and maintaining a balanced life.

As one of the intended learning outcomes of this lecture is for students to critically discuss issues related to resilience, students are further challenged to contemplate on and discuss controversial topics pertaining to resilience. These include, (i) Whether resilience is merely an active coping process as conceptualized by Western theories and models or whether passive coping strategies are also effective in overcoming adversities? Particularly, students are invited to consider (ii) How cultural beliefs impact on resilience; e.g., traditional Confucius teachings suggest that sufferings should be accepted as an inevitable part of human life, and (iii) teachers introduce the Chinese proverb “Hardship increases stature” which underscores the functional value of failures and adversities to human development and maturity. Based on the above ideologies, students are invited to comment and discuss their views and to reflect on their personal beliefs of resilience based on one’s own cultural values.

To conclude the lecture, a final video clip of Nick Vujicic is shown to students as a wrap-up of the lecture and to encourage them to be resilient. A brief biography of Vujicic, who suffers from a rare disorder characterized by the absence of all four limbs, is outlined in the video. Photographs and videos of how he accepted his circumstances and overcame his disability and strived to live a fruitful life are presented. Segments of Vujicic’s motivational speeches addressed to high school students are also shown.

Teachers finish off by reminding students that with faith and determination, everyone can be a resilient leader.

To what extent is the subject “Tomorrow’s Leaders” able to promote positive development in the students? In a series of evaluation studies using different methods (including objective outcome evaluation, subjective outcome evaluation, and process evaluation), findings showed that the subject is able to promote the psychosocial competencies in students [43-48].

For this lecture, post-lecture evaluation with the collection of quantitative and qualitative evaluation data reported previously demonstrated that students appreciated the lecture and felt that the lecture was able to promote their resilience.

“I really like today’s lecture. Thanks for giving us so many videos to watch and they are very meaningful, touching, and inspiring... In today’s lecture, I learnt that ... resilience is not only the most important attribute in becoming a leader but also for own life’s attitude.”

“I learnt how to be resilient and make a sense that ‘nothing is impossible.’”

“I think though I may not need some of them (the theories or skills introduced in the lectures) now, sooner, like Steve Jobs once said, ‘The dots will somehow connect in your future.’”

“Even if we fail or we’re frustrated, we can still prove our values, our uniqueness by fighting back fiercely. The rainbow exists where the storm ends.”

Resilience is considered as a multidimensional construct that includes intrapersonal attributes (e.g., self-concepts, emotional competence, problem-solving skills, and spirituality), interpersonal competencies, and external protective factors (e.g., supportive family and social environment). This lecture provides students with theories, underpinnings, and importance of resilience and presents a comprehensive view of how different attributes (i.e., topics in the curriculum) contribute to individuals’ development of resilience as effective leaders.

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Chapter 161

DEVELOPING SELF-LEADERSHIP AND RESPONSIBILITY

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ABSTRACT

To lead others, successful leaders must first be able to lead themselves. Hence, self-leadership is an important element of leadership development for university students. In this chapter, the definitions of self-leadership and responsibility are introduced. Their impacts on effective leadership are also addressed. In addition, the concept of egocentrism as a barrier to effective leadership and adolescent development is highlighted. To facilitate the development of self-leadership and responsibility in adolescents, a lecture on self-leadership, responsibility, and egocentrism is designed in the curriculum of a university subject entitled "Tomorrow's Leaders." The objectives, intended learning outcomes, lecture outline and materials are presented in this chapter. Issues surrounding this lecture are discussed.

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INTRODUCTION

“To govern the country and bring peace and harmony to the world, one should first be able to regulate one's family; to orderly regulate one's family; one should first learn to cultivate oneself.” - Confucius from *The Analects* [1]

Manz [2] conceptualized self-leadership as “a comprehensive self-influence perspective that concerns leading oneself toward performance of naturally motivating tasks as well as managing oneself to do work that must be done but is not naturally motivating” (p. 589). Interestingly, the notion of self-leadership has long existed before Manz's [2] theoretical conceptualization. Traditional Confucian philosophy suggests precisely the idea that before one could successfully lead others, one must first be able to manage themselves. Because of its importance, the concept of self-leadership or self-cultivation is covered in the subject entitled “Tomorrow's Leaders” offered at The Hong Kong Polytechnic University. In addition, most existing leadership courses offered in university settings present students with theories and applications based on traditional leadership models which focus narrowly on “hard skills,” such as situational, task, manufacturing and management competencies that result in tangible outcomes (e.g., team performance). This in capacious focus, however, has been critiqued. For instance, Brass and Krackhardt [3] acutely observed that “largely ignored in leadership is an approach that focuses on the structure of interpersonal relationships” (p. 181), supported by Crosbie [4] who acknowledges the enduring value of “soft skills” and intangible outcomes of leadership.

Self-leadership refers to a process where individuals manage, influence, and lead oneself to establish self-direction and self-motivation to reach goals and perform effectively. The theory distinguishes itself from previous notions of self-management by addressing higher level standards of self-influence (e.g., intrinsic motivation of goal attainment and self-regulation) and suggests specific behavioral and cognitive strategies that enables individuals to exercise self-leadership [1]. Self-leadership strategies are divided into three broad categories. First, behavioral focused strategies facilitate self-awareness, enabling one to better manage their behaviors necessary to maintain performance standards. They include self-observation (i.e., being aware of reasons why one has to accomplish certain tasks), self-goal setting (i.e., setting challenging but attainable and specific goals), self-reward and self-punishment (i.e., being able to use appropriate rewards, such as commending oneself, when one demonstrates favorable goal-attaining behaviors, and use self-punishment, for instance, introspective examination of failure, when one is not performing up to standard), and self-cueing (i.e., providing environmental cues, such as to-do-lists and motivational posters, to encourage and prompt desirable behaviors). Second, natural reward strategies focus on making difficult tasks appealing and intrinsically rewarding. This can be achieved by making assignments inherently interesting by building enjoyable elements to tasks (e.g., decorating and personalizing one's workspace), or de-emphasizing unpleasant aspects of a task and focusing attention on the rewarding aspects instead. The last category is the use of constructive thought patterns, such as identifying dysfunctional beliefs and attitudes and replacing them with optimistic beliefs, positive self-talk or using mental imagery by visualizing success [5]. As reviewed by Neck and Houghton [6], self-leadership has been found to positively impact on individual and organizational outcomes, as evidenced by increases in commitment, job satisfaction, creativity, and positive affect. The positive

association between self-leadership and favorable performance outcomes may be mediated by psychological empowerment, and self-efficacy. Specifically, self-leadership creates a sense of competence, self-control, meaningfulness, or task responsibility [7]. Self-leadership enables one to take on increasing amounts of responsibility internally [8], which serves as a drive towards goal-attainment, as supported by findings of positive association between personal responsibility and motivational achievement [9].

Alongside with self-leadership, sense of responsibility is also important for an effective leader. Sense of responsibility is defined as “one’s positive attitude and obligations toward the fulfillment of tasks directly or indirectly assigned to him or her” [10, p. 74]. The notion was developed based on Adlerian’s school of Individual Psychology which emphasizes the need for humans to nurture abilities to meet five important life tasks, including, work, friendship, love, spirituality and universal values, and responsibility towards self [11]. Indeed, individuals engage in self-management by taking responsibility for ones’ decisions and outcomes, while feeling personally accountable for their performances and behaviors [12]. Various leadership models stress the importance of responsibility in effective leadership. Servant leadership entails the mission of responsibility to others, where servant leaders are accountable for the service they provide to their followers [13]. Transformational leaders take responsibility for the development of their followers [14], and accountability is an important dimension of ethical leadership [15]. Although most research investigating the relation between sense of responsibility and leadership were conducted in the West; values such as authority, order, and sense of responsibility are in fact, also inherent in the Chinese culture [16]. These deeply rooted ideologies and expectations of responsibility in adolescents persevere in spite of modernization and industrialization, as evidenced by Hong Kong parents who continue to believe that an ideal child should be able to fulfill their responsibilities within the family and in their studies [17].

Egocentrism is another important factor influencing leadership. Findings from studies investigating the relationship between self-leadership and personality traits often identify positive associations between self-leadership and socially desirable traits, such as, conscientiousness and extraversion [6]. Yet more recently, Furtner and colleagues [18] found narcissism to be associated with self-leadership. Narcissism is characterized by traits such as arrogance, excessive self-focus, self-absorption, and self-admiration. The authors explained that both self-leaders and narcissists possess high levels of need for achievement, which acts as a motivation for their persistence in the pursuing of goals. However, they differ in that narcissists focus on the outcomes of goal-achievement, whereas self-leaders focus on the process of achieving it. Self-leaders are driven by the intrinsic motivation from the tasks itself, while narcissists aim to obtain personal glory, self-enhancement, and admiration from others. Narcissistic leaders engage in self-promotion, self-nomination, deception, and manipulation [19, 20]. Self-preoccupational traits of egocentrism, greed, low levels of compassion and integrity are barriers to effective leadership [21]. More prominently, Shek and colleagues [22] investigated the egocentric phenomena in Hong Kong adolescents and found that over half of the respondents held egocentric beliefs that their own opinions were superior to others, and that fortune was always on their sides. The authors warned school psychologists and educators to pay close attention to this tendency that may bring deleterious influences to the healthy development of young people. As such, it is critical that while promoting self-leadership and responsibility in adolescents, educators should also warn students not to fall prey to the “dark side” of self-leadership [18].

Self-Leadership, Responsibility, Egocentrism and Adolescents

As self-leadership originated from organizational psychology literature, few studies directly explore the impact of self-leadership on adolescent behaviors and developmental outcomes. However, the role of self-management has been well-researched in both adolescent and student populations. Adolescents with high levels of self-regulation are less likely to engage in problem behaviors, including risky drinking, sexual behaviors [23], tobacco, alcohol, and marijuana use [24]. Non-delinquent adolescents perceive academic and career goals more important than delinquent youths and regulate energy to productive goal-attainment [25]. Furthermore, adolescents who made use of self-regulating cognitions (e.g., goal commitment, efficacy, and ownership) were more likely to engage in healthy eating habits [26]. The impact of fearfulness and frustration on both internalizing and externalizing problems were also attenuated by effortful control of attention and inhibiting behaviors among adolescents [27]. Shek [28] also found a negative relation between students' levels of mastery (i.e., perceived sense of control) and problem behaviors, supporting the self-efficacy model [29]. Academically, students who have higher levels of self-regulation were less prone to procrastination [30]. These adolescents monitor and evaluate progress, and regulate attention and effort to improve learning [31]. Adolescents' self-discipline was even found to be more predictive of academic success than intelligence [32]. The aforementioned findings support Manz's [2] model suggesting that self-leadership strategies function to enhance self-efficacy perceptions, which in turn results in higher levels of performance.

In terms of responsibility, most existing studies on adolescents focus on investigating family and social responsibilities. Findings suggest that adolescents with greater sense of responsibility to their families reported lower levels of depression, more intimate relationships with their parents, higher self-esteem [33], and higher academic motivation [34]. Adolescents' levels of social responsibility have been associated with civic engagement. Socially responsible youths were more likely to consider public interest as an important life goal and aim to improve their society and help their country [35]. In addition, social responsibility was positively associated with motivation achievement, as it facilitates learning and classroom performance, through increased positive interactions with teachers and peers [36]. In contrast to socially responsible adolescents' orientation toward collective-interest, self-interested, egocentric adolescents have trouble differentiating others' thoughts and their own mental preoccupations and self-obsessions. During social interactions, these adolescents anticipate others' reactions to be synonymous to theirs [37]. Egocentrism in adolescents have been associated with drunk driving [38], drug use, delinquency [39] and aggression [40].

Lecture on Self-Leadership, Responsibility and Egocentrism in "Tomorrow's Leaders"

Adolescents nowadays (born from 1980 to present) are coined as the Me Generation or Millennials, notorious for their egocentric tendencies. A recent article in the Time Magazine entitled "The me me me generation" [41] reported increasing prevalence of narcissism, as found in a nationwide study where 58% more college students scored higher on a narcissism scale in 2009 than in 1982. In addition, youngsters nowadays have unrealistic expectations on

job promotions (e.g., another study revealed that 40% of adolescents believe they should be promoted every two years, regardless of their work performance), and few of them want jobs with greater responsibility. Although most of the above studies were conducted with Millennials in America, in his article, Stein [41] claims that “even in China, where family history is more important than any individual, the Internet, urbanization and the one-child policy have created a generation as overconfident and self-involved as the Western one.” (p. 30). In a comprehensive review of adolescent developmental issues, Shek and Wong [42] identified mental health and problem behaviors, including depression, suicide, drug abuse, smoking and drinking among university students reared in the West, as well as Hong Kong adolescents [43]. Youths’ engagement in risky health-compromising behaviors has been attributed to their sense of egocentrism and the misperception of subjective invulnerability (i.e., the belief of indestructibility) [39], and possibly, their low sense of responsibility. Academically, students today are less mature and not ready for the responsibility that both being in college and young adults require of them [44]. Instead of using self-leadership strategies to reach academic goals, some adolescents procrastinate, and practice self-handicapping strategies by playing the evening before a test, deliberately allowing their peers to keep them from paying attention during class, and make external attributions for failure [45].

Although Stein [41] reported grave trends among the Millennials, he ended his article on a positive note, “a generation’s greatness isn’t determined by data; it’s determined by how they react to the challenges that befall them. And, just as important, by how we react to them.” (p. 35) Shek and colleagues [43] shared the same optimistic view on adolescence and suggested ways in which universities can respond to these emerging developmental adolescent issues. To tackle these problems, the authors proposed a curricular-based approach adopting the positive youth development model, including the promotion of constructs such as, emotional management (e.g., delaying gratification), cognitive competence (e.g., self-talk, decision-making), cultivation of self-determination, promotion of positive beliefs in the future, which are inherent to the nurturance of self-leadership, sense of responsibility, and holistic development in university students. Grow [46] also argued that “the goal of the educational process is to produce self-directed, lifelong learners. Many current educational practices in ... universities, however, do more to perpetuate dependency than to create self-direction” (p. 127). Lerner and colleagues [47] stress that “self-regulation processes must be integrated across childhood and adolescence for adaptive developmental regulations to exist and for the developing person to thrive” (p. 1). Hazard [48] further contended that training for university student success and achievement must go beyond traditional academic teachings in reading, writing, searching and organizing information, to incorporate the cultivating of “habits of minds.” One of the most important habits that college students should develop is taking responsibility.

Against this background, the teaching aims of this lecture on self-leadership, responsibility, and egocentrism are to introduce the respective concepts and theories and highlight the importance of self-leadership and responsibility in effective leadership. Students are also alerted of the detrimental effects of egocentrism on leadership and development. Regarding the intended learning outcomes, upon the completion of this lecture, it is expected that students should be able to: (a) introduce the concepts and theories of self-leadership, responsibility, and egocentrism; (b) recognize the relationship between self-leadership, responsibility, and egocentrism and leadership; (c) reflect on one’s own self-leadership, sense

of responsibility, and levels of egocentrism; (d) list various methods to enhance self-leadership. The teaching methods include lecture, group discussion, and self-reflection.

The lecture is organized into three main parts. In Part 1, the definitions and theories of self-leadership, responsibility, and egocentrism are presented. A warm-up activity (“Your Unique Peanut”) and a self-reflection exercise (“My Responsibility”) are conducted. In Part 2, the positive effects of self-leadership and responsibility, and the negative impacts of egocentrism on effective leadership will be discussed. A self-reflection activity (“How Well Do You Lead Yourself?”) is conducted. In the Final Part, strategies to promote self-leadership are introduced.

Warm-Up Activity

As lectures of “Tomorrow’s Leaders” are held on a weekly basis, in preparation for the current lecture on self-leadership, a week earlier, teachers distributed to each student a peanut and asked them to bring the peanut back in the following week. The lecture commenced with a warm-up activity, aimed to highlight the importance of self-leadership and responsibility and enable students to engage in self-reflection on their own self-leadership skills and ability to take responsibility of their behaviors in their daily lives. Teachers invited students to take out the peanuts that were distributed to them the week before. While the majority of the students remembered to bring their assigned peanuts back to class, some were unable to do so. Students were instructed to reflect on why they were or were not able to complete the task. Subsequently, teachers walked around the classroom and invited those who brought back their peanuts to share reasons behind the successful completion of the task. Different reasons were given by students; some claimed that they had put it in a safe place ensuring that the peanut would be untouched and intact, while others refrained from eating the peanut by reminding themselves about the instructions of the assignment. Teachers concluded the warm-up activity by leading the class to a round of applause to congratulate those who remembered to bring back their peanuts, as they demonstrated the important essence of self-leadership having effectively managed themselves in order to achieve a goal, and showed a sense of responsibility.

Part 1 of the Lecture

The first part of the lecture is dedicated to introducing the concepts and theories related to self-leadership, responsibility, and egocentrism. First, the definition of self-leadership is presented, and underlying processes including self-understanding and self-management are introduced. The notion of self-understanding was covered in an earlier lecture of the curriculum. Therefore, teachers invite students to recall the definition of self-understanding and to discuss in small groups. The discussion questions include “Why self-understanding is important for effective self-leadership?” and “What components of one’s ‘self’ do we need to better understand?” Teachers highlight the importance of being aware of one’s strengths, weaknesses, values, and directions in relevance to self-leadership.

Regarding self-management, students are reminded to accept and embrace their own uniqueness (self-acceptance), and to set personal standards (i.e., targets or goals), and devise strategies to control, monitor, and motivate oneself toward achieving personal goals (self-control). Second, the notion of responsibility is presented as “response-ability” (i.e., one’s ability to choose their response). Students are reminded of the conscious choice behind every decision they make and action they take in their lives, as guided by their inherent values.

Given this consciousness and free-will, individuals must therefore, take responsibility for their behaviors. Teachers then emphasize the fact that, as university students, we can fulfill our responsibilities in different domains: (i) to our self (e.g., exercising regularly, refraining from engaging in health-compromising behaviors, maintaining a healthy sleep schedule), (ii) to our family and friends (e.g., being good role models for our siblings, doing chores at home, being filial to our parents, supporting our friends), (iii) to our university (e.g., joining clubs and societies, attending lectures punctually, participating in class), (iv) to our society (e.g., engaging in voluntary work, being sensitive to current affairs), and (v) to our world (e.g., being environmentally friendly).

In order to facilitate students' self-reflection on their sense of responsibility, they are asked to complete a worksheet entitled "My Responsibility" (see Appendix 1). As students complete the worksheet, teachers engage in self-disclosure by sharing their own responses to the respective questions. To begin, students are asked to nominate an area of their life that they would like to improve on and to briefly elaborate on their wish. For instance, some students write about how they aspire to be more responsible students, specifically, be able to procrastinate less in their studies, while some reflect on their roles as sons and daughters, and how they want to communicate more with their parents to better understand them. Then, students rate on a scale of 0 (no responsibility) to 9 (full responsibility) how much responsibility they are currently exerting in their suggested area for improvement. Teachers highlight the fact that, even as adults, there are also areas in their lives that they wish to improve their sense of responsibility in. Lastly, students are asked to think of two things they can do differently to make a one-point increment on their score on the previous scale. Some examples of behavioral changes students proposed including setting goals, refusing classmates' invitation to go out until they complete their assignments, and trying to go home for dinner each night to spend more time with their parents. Teachers invite several students to share with the class their responses and suggestions. Students are reminded that sometimes we may find it difficult to act responsibly because we fail to see the consequences, especially negative ones, our actions may bring to ourselves or others around us. The concept of egocentrism and its characteristics are outlined, including one's inability to perceive the world in others' perspectives, the incomplete differentiation of the self and the outside world, over-preoccupation with one's own beliefs, and the assumption that others must share identical thoughts and feelings. Teachers conclude this section by stressing the importance of being responsible and avoiding egocentrism by considering others' feelings along with the impacts of our actions, as we take on different roles, and reiterate that everyone can improve on their sense of responsibilities with determination and motivation, as we are all self-leaders.

Part 2 of the Lecture

In Part 2, the importance of self-leadership and responsibility to effective leadership is highlighted. Students are reminded of their abilities to master their minds and Manz and Sims' [49] notion that "if you want to lead somebody, the first critical step is to lead yourself" (p. 25) is reiterated. Positive outcomes of responsible leadership are introduced. These include the ability to build trust among followers, gain support and respect from others, likelihood of becoming role models, particularly via ethical leaders' commitment to self-examination and accountability for ethical decision-making and behaviors. Lastly, egocentrism as a barrier to effective leadership is underscored.

In order to allow students to evaluate their own self-leadership, students are asked to complete the 35-item Revised Self-Leadership Questionnaire [50], consisting on subscales representing the three primary self-leadership dimensions. Regarding the behavior-focused dimension, subscales include self-goal setting, self-reward, self-punishment, self-observation, and self-cueing. The natural reward strategies dimension is measured with a subscale assessing individuals' ability to focus their thoughts on natural rewards, and lastly, constructive thought dimension is represented by subscales including, visualizing successful performance, self-talk, and evaluating beliefs and assumptions. Teachers introduce each of the self-leadership strategies and students are guided to calculate their scores for each of the subscales and to identify their strengths and weaknesses in the usages of the respective self-leadership strategies and to spot out which aspects they need to improve on.

Final Part of the Lecture

In the last section of the lecture, various strategies to enhance self-leadership with reference to the three self-leadership dimensions are introduced. First, students are encouraged to make use of behavioral-focused strategies, such as goal-setting, self-monitoring, and self-cueing strategies in achieving goals. Students are guided to set goals that are SMART (i.e., Specific, Measurable, Attainable, Relevant, and Time-bound). Second, students are encouraged to make use of natural reward strategies, by creating situations or environments that will enable them to be intrinsically interested in completing the tasks. For instance, photographs from the Google office in Zurich are shown to students. The office is creatively designed, with different themes and vibrant colors to allow employees to feel enthusiastic and inspired when they attend work. Students are persuaded to focus on the positive elements of a task and create reinforcing environments in order to turn mundane or challenging tasks to become more interesting. Lastly, constructive thought pattern strategies are outlined. The relationship between ones' thoughts and behaviors are highlighted, thus, students are encouraged to try to perceive events as positive, and use optimistic self-talk, rather than negative destructive self-talk, especially in times of set-back. Teachers conclude the lecture by reminding students that leadership is not confined to leading others, in fact, everyone can be a leader by leading themselves. In order to become effective self-leaders, though, one must be responsible to oneself and those surrounding them, and avoid being egocentric.

EVALUATION AND RELATED ISSUES

To what extent is the subject "Tomorrow's Leaders" able to promote positive development in the students? In a series of evaluation studies using different methods, including objective outcome evaluation, subjective outcome evaluation, and process evaluation, findings showed that the subject is able to promote psychosocial competencies in students [51-56]. For this lecture, post-lecture evaluation with the collection of quantitative and qualitative evaluation data reported previously demonstrated that students appreciated the lecture and felt that the lecture was able to promote their self-leadership and heighten their sense of responsibility:

- “This lecture is not about teaching me to lead others, but most important is myself. We are all leaders of our lives.”
- “It (this lecture) teaches us not to be egocentric and before being a leader of others, we must first manage ourselves. Those who know how to manage themselves will succeed in all that they do.”
- “We are responsible not only for ourselves, but also our family, friends, and the world.”
- “Be confident and strict to ourselves. Be caring, kind, and helpful to others. This is what I learned from this subject.”

Most educators or scholars would agree that there is no “cookie cutter” path to successful leadership [57]. Students are unique and each possesses their own potentials and weaknesses. What teachers can do, however, is to equip them with the necessary leadership and developmental competencies (i.e., the different topics in this curriculum) and more importantly, is to encourage students to take responsibility to lead themselves on this life-long journey. After all, as Lao Tzu once said “A journey of a thousand miles begins with a single (self-initiated!) step.”

Several conceptual and methodological issues should be taken into account when teaching self-leadership, sense of responsibility and egocentrism in a subject on leadership. First, conceptual integration of the leadership literature and adolescent development studies can be further attempted. For example, how self-reflection might shape leadership and adolescent development is an interesting theoretical question to ask. Second, it would be theoretically stimulating to integrate Western and Confucian literature on self-cultivation and fulfillment of one’s responsibilities. Third, while there are Western measures of self-leadership, no related scale has been developed in the Chinese context. Hence, more research is needed in this area. Practically, providing more opportunities for students to practice self-leadership and responsibilities is a desirable direction. Credit-bearing subjects like service learning are important vehicles for students to practice what they have learned in the leadership subject [58, 59].

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APPENDIX 1. WORKSHEET (SAMPLE)

My Responsibility

- 1. I would like things to be different in the following area of my life (e.g., study ...).
Elaborate on your wish.**

- 2. How responsible am I in this area of my life? ()**

No responsibility 0-----1-----2-----3-----4-----5-----6-----7-----8-----9 Full responsibility

- 3. What can I do differently to move my level of responsibility up by just one point on the scale?**

1.

2.

Chapter 162

DEVELOPING SOCIAL COMPETENCE

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ABSTRACT

Social competence is an important positive youth development attribute for adolescent development and effective leadership. In this chapter, the definitions and approaches of social competence are introduced. The antecedents and consequences of social competence are highlighted. Moreover, the relationships between social competence and effective leadership, as well as adolescent development are also addressed. In particular, egocentrism as the barrier of social competence is discussed. To enhance social competence of university students, a lecture on social competence is designed in the curriculum of a university subject entitled "Tomorrow's Leaders". The objectives, intended learning outcomes, lecture content and special features of the lecture are presented in this chapter.

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INTRODUCTION

University students are regarded as “tian ji jiao zi” (the favored son of the Heaven), and they are the skeleton of the future society. However, this generation has been commented as “Generation ME”, having portrayed as egocentric, narcissistic, depressed and not empathetic [1]. It is alarming that there was a big increase of the narcissism scores of contemporary university students when compared with the students in the nineties [2, 3]. Furthermore, in a meta-analysis of changes of dispositional empathy in American college students over the period of 1999 to 2009, Konrath et al [4] found that there was a sharp decline of empathic concern and perspective-taking of college students from after 2000. In Hong Kong, the adolescents were labeled as the “spoilt generation” who showed signs of narcissist traits [5]. Sadly to say, “Hong Kong Kid Syndrome” has been used to describe Hong Kong adolescents as “highly self-centered, short-sighted, over-reliant and unwilling to shoulder responsibility” [6]. Social competence, as one of the components of positive youth development, has become more and more important for adolescents to acquire in this era. As such, the attribute of social competence is covered in the subject entitled “Tomorrow’s Leaders” offered in The Hong Kong Polytechnic University.

DEFINITIONS AND APPROACHES OF SOCIAL COMPETENCE

Social competence is not a well-defined, unitary concept and its terminology interplays with “communication competence”, “interpersonal competence”, “social skills”, “relational competence” etc., reflecting the different conceptual and operational variations of the construct [7]. The variations bring the difficulties and complexity in defining and conceptualizing social competence.

Social competence has been defined as “the ability to achieve personal goals in social interaction while simultaneously maintaining positive relationships with others over time and across settings” [8, p. 285]. Other definitions include “an ability to build positive interpersonal relationships and to resolve interpersonal conflicts” [9, p. 380], the ability to ‘read’ and understand different situations, knowledge of social roles, and norms [10, 11], the ability to maintain favorable interpersonal relationships through cooperation, responsiveness, assuming responsibility, and behaving in friendly, warm, and other positive ways [12]. Under these definitions, three important elements should be noted. First, social competence is an ability of an individual. Second, interactions with others are focused. Third, positive interpersonal relationships are the expected outcomes.

In understanding how social competence works, different approaches are highlighted. The approaches provide different lenses for social scientists and researchers to examine the attribute. While peer status approach understands social competence based on how popular an individual is among his/her peers, the relationship approach assesses one’s social competence by the ability of an individual to develop positive interpersonal relationship [13]. The former emphasizes the popularity of an individual in his/her social circle, whereas the latter focuses on the quality of relationship built among partners. Both peer status approach and relationship approach are considered as the outcome-based approaches that emphasize social competence as the outcome attribute. The social skills approach, in contrast, is skill-based approach that

conceptualizes social competence to be the acquisition of the skills. Under social skills approach, social competence entails a set of desirable skills and behaviors that are effective in social interactions, including assertiveness, empathy, listening, defining problems, evaluating solutions, negotiation, expression of justified emotions, and realization of one's mistakes [13].

Last but not least, the functional approach suggests that social competence is context-specific and concerns with the identification of social goals. According to the information processing models of social skills [14], social behaviors are resulted from a multistep social-cognitive process that includes selection of social goals, monitoring the environment, formulation, selection and implementation of strategies, evaluation of outcomes, and finally the decision of an appropriate solution. Thus, social competence is regarded as the ability to make the process be an effective and functional one [13].

ANTECEDENTS AND CONSEQUENCES OF SOCIAL COMPETENCE

Similar to the other attributes, the antecedents of social competence are prone to nature-nurture debates. From a survey of literature, there are three factors contributing to social competence: temperament, attachment and parenting style [15].

Temperament is defined as “the characteristic phenomena of an individual's emotional nature including his susceptibility to emotional stimulation, his customary strength and speed of response, the quality of his prevailing mood, and all the peculiarities of fluctuation and intensity of mood” [16, p. 54]. It describes one's biological responses to the environment [17] that are related to activity, reactivity, emotionality and sociability of an individual [18]. Williamson and Dorman [15] suggested that there are four ways of which temperament may influence child's social competence: temperament may influence (a) child's exposure to potentially stressful situations; (b) child's range of sensitivity to stress; (c) patterns of child's social behaviors and emotional expressions; and (d) readiness of parents and others to engage the child.

Attachment refers to “a long-lasting relationship characterized by a strong emotional bond between two individuals” [15, p. 19]. Attachment provides a secure foundation for social experiences. Attachment helps to satisfy the physical survival needs as well as social emotional needs of the child, provide them with chance for learning the rules of interactions, and help to shape beliefs and expectations on social engagement [15]. Zeanah et al [19] identified four patterns of attachment: secure, avoidant, ambivalent and disorganized/disoriented. It was found that the secure pattern of attachment was related to social competence. Children growing up with secure attachment were generally more cooperative, sociable and competent than with the other attachments.

Finally, the socialization practice of parents influences social and emotional development from infancy stage to adolescence. Maccoby and Martin [20] classified parenting style into two-dimensional framework: parental demandingness and parental responsiveness. While parental demandingness expects parents to be more restrictive and firm in monitoring and supervision of their children, parental responsiveness entails qualities of sensitivity, warmth, encouragement and closeness through responding to the needs of the children [21]. Four types of parenting styles (authoritarian, authoritative, permissive, and neglected) are emerged [21] from the categorizations. It was found that authoritative parenting style (high levels of

parental demandingness and responsiveness) influences social competence of children and adolescents [22, 23].

Undoubtedly, social competence is very important for adolescent positive development and psychosocial wellbeing. In a longitudinal study of social functioning of 261 Chinese adolescents, Chen et al [24] identified that sociability-leadership and shyness-sensitivity in childhood influenced leadership, academic achievement, and self-perceptions in adolescence, whereas aggression in childhood predicted externalizing problems (e.g. delinquent behaviors) and negatively influenced academic achievement in adolescence. Luthar [25] in a longitudinal study further found that social competence was associated with depression in inter-city teenagers. Echoing with the results, Burt et al [26] also identified the robust negative path of social competence in predicting the internalizing problems (anxiety, depression, withdrawal and somatization) from childhood to adolescence. As a summary, high social competence may result in good leadership, academic achievement and high self-esteem of adolescents, whereas low social competence may result in psychopathological problems and delinquent behaviors.

SOCIAL COMPETENCE AND LEADERSHIP

Social competence has been regarded an essential competence for leadership excellence [27]. It forms the basis for a spectrum of favorable developmental outcomes, including self-esteem, achievement, responsibility, and leadership qualities [24]. Generally speaking, there are four aspects of social competence that are important for effective leadership: self-awareness, self-management, social awareness and relationship management [28]. Self-awareness is the accurate self-assessment of one's strengths, limitations, values and motives. One needs to be honest to oneself, realistic and self-reflective. Self-management consists of the attributes of emotional self-control, transparency, adaptability, achievement, initiative and optimism. They manage their emotions, maintain clear mindset, and provide energy for action. Social awareness is the sensitivity to understand how others feel, think and action. This included empathy (understanding others and taking active interests of their concern), organizational awareness (perceiving the political relationships within the organization) and service orientation (recognizing and meeting others' needs). Last but not least, relationship management is the ability of handling relationships and moving people to the right direction. This involves influencing, developing others, change management, conflict management, building bonds and teamwork.

In respect of social skills approach, Riggio and Reichard [29] classified three components of social competence: Social expressiveness, social sensitivity and social control. Social expressiveness is the skill in verbal expression and the ability to engage others in the social interactions. It is essential for a leader in public speaking, persuasion and coaching. Social sensitivity consists of the ability and skills to read and interpret the verbal and non-verbal messages of others, understand the social situations, norms and rules, be aware of others' needs and feelings, and respond to them appropriately. Active listening, regulation of the social behaviors are necessary for a leader. Social control addresses the issue of knowing what should be done in social interactions. This involves the skills in role-playing and social

self-presentation, which are essential for a leader to develop emotional control, sense of confidence and self-efficacy in social situations.

SOCIAL COMPETENCE, EGOCENTRISM AND ADOLESCENT DEVELOPMENT

During the past two decades, the advancement of information technology that stretched all spheres of our daily life [30], the globalization in economic, political and cultural arenas [31], as well as the high levels of parental involvement and care [32] have helped to “generate” the next generation into the “Generation ME” [1], or “Generation Y” [33], who are regarded as egocentric, narcissistic, cynical, depressed and not empathetic [1]. Shek and Wong [34] termed the “dark-side attributes” to describe some of the negative attributes that affect the healthy development of the adolescents. Egocentrism, in particular, is the cognitive barrier for the promotion of social competence.

Egocentrism is “a descriptive concept of a state of undifferentiation between the self and the nonself, as the individual is confined to a highly personalized point of view while ignorant of the uniqueness of others’ perspectives” [35, p. 208]. It is characterized by the state that an individual has a preoccupation with one’s own internal world, and an incomplete differentiation between the self and the world. He/she may assume that others have the same thoughts and feelings as his/her. As a result, the individual tends to perceive, understand and interpret the world in terms of the self, without taking others’ perspectives into considerations.

Egocentrism originally refers to an early cognitive developmental stage that exhibits over-emphasis of self and a lack of differentiation in areas of subject-object interaction [36, 37]. Elkind [38, 39] suggested that egocentrism re-emerges at the transitions of each cognitive developmental stage. In early adolescence, egocentrism is characterized by manifestations of the imaginary audience and the personal fable. Imaginary audience describes to the situation that adolescents believe that there is some audience who is overly interested in their deeds. Personal fable refers to the situations that adolescents perceive that they are always unique in feeling, thinking and actions [40]. Normally, adolescent egocentrism will diminish in late adolescence and adulthood, when formal operational thought is consolidated [38]. However, more and more studies identified that egocentric tendencies have extended to late adolescence and early adulthood [41-43].

As suggested by Goleman [28], “self-absorption in all its forms kills empathy, let alone compassion. When we focus on ourselves, our world contracts as our problems and preoccupations loom large. But when we focus on others, our world expands. Our own problems drift to the periphery of the mind and so seem smaller, and we increase our capacity for connection - or compassionate action” (p. 54). Egocentrism is the enemy of social competence. There is empirical evidence that egocentric lifestyle and behaviors hamper the development of empathy and social competence [44-46].

WAYS TO PROMOTE SOCIAL COMPETENCE

Social competence has been regarded as a “relative competence” [47] that can be developed and refined through practice. There are some ways for promoting social competence. First, self-awareness and determination is essential in understanding one’s own capacities and recognizing other’s. Being aware of the norms, cues and patterns in social interactions may help one to interact with others smoothly and harmoniously. Second, observation and modeling of the behaviors of others who have high social competence may help to improve one’s social skills. Genuine feedback from others is always the medicine to improve oneself. Third, positive body language is critical in non-verbal communication. The SOFTEN technique (smile, open posture, forward lean, touch, eye contact and nod) [48] is simple, practical and useful in improving one’s non-verbal communicative skills. Fourth, effective conflict management strategies (forcing, accommodating, avoiding, compromising and collaborating) [49] are important in resolving conflicts that may inevitably happen in social interactions. Fifth, empathy is the milestone to understand and respond to the needs and situations of others. Empathy is more than a social skill, it is the capacity of an individual to understand and react with others through observed experience [50]. Thus, empathic listening and responses are essential in social interactions. Last but not least, social skills are developed and refined over time through implementation [47]. Hence, patience and practice are the keys for promoting social competence.

LECTURE ON SOCIAL COMPETENCE IN “TOMORROW’S LEADERS”

The lecture aims at enhancing the knowledge, understanding, and skills of social competence to the students. In this lecture, the definitions and concepts of social competence are introduced to the students. The antecedents and consequences of social competence, and the relationships between social competence and leaderships as well as adolescent development are highlighted. Finally, the strategies and skills to promote social competence are also presented. Regarding the intended learning outcomes, upon the completion of this lecture, it is expected that students should be able to: (a) understand the definitions, theories and concepts of social competence; (b) identify the antecedents and consequences of social competence; (c) realize the relationship between social competence and leadership; and (d) be familiar with the ways of promoting social competence. The teaching methods include lecture, reflection exercises, video sharing, experiential learning activities, role-play, group discussions and self-reflections.

There are four important features in the teaching content and methods in this lecture. First, self-reflections are the important tools for the students to critically examine their social competence as well as the relationships with others, including the peers, friends, and family members. Thus, in each part of the lecture, students are requested to reflect on their attitudes, perceptions, and capacity of social competence and critically discuss the related controversial issues. Second, students may perceive that social competence is an in-born attribute guided by the introversive-versus-extroversive personality. In fact, it is a relative competence that can be learned and developed through practice [47]. Hence, it is essential to clarify the misconception and encourage the students to enhance their social competence through

practice. Third, social competence not only involves theories and concepts, it also involves an array of social skills. Thus, the practice of social skills is highlighted throughout this lecture. Fourth, the class can serve as a platform for students to practice social competence through interactions. As such, interactive activities are provided in this lecture so to facilitate interactions among students and between teacher and students.

The lecture covers four parts based on the intended learning outcomes. The first part presents the definitions and concepts of social competence. The second part highlights the antecedents and consequences of social competence. A self-reflection exercise is performed to encourage students to reflect on how family life and relationships with family members affect their social competence. The third part discusses the relationship between social competence and leadership. A video clip of “Story of a master’s degree holder” is presented and students are requested to reflect on the problems of egocentrism to adolescent development. The fourth part suggests the ways and strategies to promote social competence. A group activity of “collaging the tips of social competence” is introduced to allow the students to brainstorm the practical and useful methods in promoting social competence. Furthermore, empathy, as an important attitude and skill in social competence, is emphasized for the students to acquire and practice. Two cases are given for the students to practice empathic listening and responses. Students are invited to role-play the scenarios. Finally, more reflective questions are suggested for the students to reflect on their own perspectives on social competence.

In the first part of the lecture, the definitions and concepts of social competence are introduced. As a warm-up activity, some pictures and photos related to social competence (such as the smiling face, the “Like” icon in Facebook) are shown. Students are invited to share their associations of the pictures with their impression of social competence. After that, the concepts and approaches are introduced to the students. In each approach, students are encouraged to self-reflect on their social competencies.

In the second part, the antecedents and consequences of social competence are presented. Social competence is a socially learned construct that one experiences and learns through the socialization process in life [7]. Family, as a vital system of socialization where social competence is nurtured, is worthwhile for the students to examine their relationships with their own family members as well as the impacts to their social competence. Hence, apart from the lecture, there is a self-reflection exercise entitled “My family dining table” to help the students to do their reflections. A worksheet (see appendix 1) is distributed to the students. Each student is requested to draw a simple floor plan of his/her family dining table and indicate the seating arrangements of the family members. A facial emotional expression for each family member is drawn on the worksheet. Finally the interactional patterns among the family members are indicated. In their reflections, the three antecedents of temperament, attachment and parental styles are highlighted to examine their impacts to the development of social competence. The teacher will use his/her own “family dining table” to illustrate the requirements of the exercise, and share with the students on how family relationships influence his/her social competence. Group sharing on their reflections is encouraged, and some students are invited to share their reflections in class. As the sharing might be sensitive and personal when touching their relationships with the family members, it is advised that the teachers should be sensitive to the readiness as well as the emotions of students.

The third part introduces the relationship between social competence and leadership. The components of social competence (social expressiveness, social sensitivity and social control)

suggested by Riggio and Reichard [29] are presented. Subsequent to the lecture, a video of “The story of a master’s degree holder” is presented to the students. The video presents the story of a Master’s degree holder who was graduated from an international university in Hong Kong but failed to obtain a job from the job market after attending more than 200 job interviews. He finally had to depend on social welfare assistance to support his life for three years. The video presents his perceptions and justifications of his joblessness, as well as his performance in a mock job-interview offered by a human resources consultant. From the sharing of the video, while most of the students could spot out the lack of social skills possessed by the master’s degree holder, but only a few could point out the heart of his problem was due to his egocentric characters. After the sharing, it is more important to invite the students to reflect on their own social competence, in relations to the egocentric lifestyle and behaviors that become salient nowadays. Following the reflections, the four aspects of social competence for effective leadership (self-awareness, self-management, social awareness and relationship management) suggested by Goleman et al [51] are introduced.

The fourth part suggests the methods and strategies in promoting social competence. As social competence is a relative competence that can be learned through practice [47], it is essential for students to explore useful and practical ways in promoting their social competence. A group activity on “Collaging the Tips of Social Competence” is conducted. In the activity, each group is given some magazines. Students are required to select the wordings, pictures, photos and whatever they find simulating in representing and enhancing social competence and cut them out from the magazines. They then design a poster comprising the “meaningful” materials that they have cut out from the magazines, and discuss how these materials promote social competence. Finally, they are requested to share the ideas of the posters in class. In the activity, it is interesting to observe that the students concentrated on their own piece of work initially, without communicating with others. However, after selection of a pool of materials, they started to communicate on the themes and ideas of the poster. They practiced the social skills of listening, assertiveness, negotiation, conflict management etc. and came out with the themes of the poster. Then students re-examined the magazines again according to the themes. But during this time, they would ask the opinions of the other group members. The representatives introduced the posters systematically, and they understood that the poster is the group’s masterpiece. The materials and themes they selected were also very thoughtful, such as “thankfulness”, “walk in other’s shoes” (empathy), “free from prejudice and discrimination”, etc. The posters and presentations not only suggested the possible ways in promoting social competence, they also represented their desires and aspiration in friendship and interacting in the social world. After the activity, the teacher will debrief the activity based on his/her observations and introduce the tips for developing social competence.

As empathy is the milestone on promoting social competence and there is evidence that students are getting less empathic nowadays [4], practice on empathic listening and response is provided during the lecture. After the introduction of the concept of empathy, two scenarios are provided to the students (see appendix 2). The first scenario is that a friend’s father had been jobless for three months, and the friend seemed stressful and depressed when sharing the financial hardship of the family. The second scenario is that a good friend was pregnant and she was extremely anxious and stressed because she was not prepared to have a baby. The students are invited to role-play the scenarios in pairs, one will act as the character of the scenario and the other will practice the empathic listening and response. The teacher further

invites one pair to role-play the scenarios in front of the class. This is another valuable experience of the students, as most students would keep on giving advice and suggestions to the characters after knowing the information, without addressing to the emotions of the characters. The genuine sharing of the students (the characters) after the role-play is definitely a challenge to the students on their ways to understand and help others. This would help them reflect more on their previous experiences when sharing with friends and significant ones in times of sorrows and adversities. Teacher will soon demonstrate the skills and techniques of empathic responses to the students based on the scenarios.

Finally, the teacher will round up the lecture by encouraging the students to self-reflect their social competence, as well as emphasizing that social competence can be learned and developed through practice.

To what extent is the lecture beneficial to promote the social competence of the students? The quantitative and qualitative data of post-lecture evaluation reported that students appreciated this lecture very much, especially on the usefulness and practicability of the lecture content. There are some qualitative feedbacks from the students:

- “This lesson is really useful to us as social competence is essential to our daily lives. I’ve learnt how to comfort people from this lecture.”
- “It is a good time to think about my friendship. Good lecture!”
- “Never think of saying words of empathy =) more powerful than the others.”
- “The lesson is gonna be very interesting and funny. Rather than cramming theories in our mind, but teach something useful. I love this lesson!”
- “I had learnt how to help my friends.”
- “It makes me understand the importance of dealing with social competence by sincere & trust.”
- “The tutor asked students to do role-play, this made learning more two-sided and interactive.”
- “I learn some social skills which help me easier to communicate/ connect to others.”

There is an inspirational quote from Albert Camus [52]: “Human relationships always help us to carry on because they always presuppose further developments, a future -and also because we live as if our only task was precisely to have relationships with other people”. Social competence, as the bridge of human relationships, should be nurtured and developed as a curriculum in the universities.

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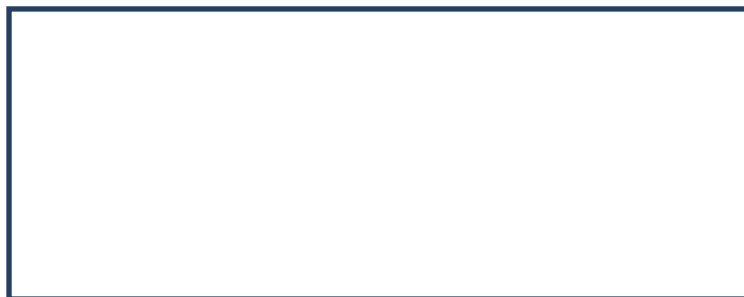
APPENDIX 1.

**The Hong Kong Polytechnic University
Department of applied social sciences**

**APSS1L01Tomorrow's Leaders
Lecture Nine: Social Competence**

MY FAMILY DINING TABLE

4. Draw a simple floor plan of your family dining table.
5. Indicate the seating arrangements which should include all your family members.
6. Draw a face with emotional expression for each family member and indicate the interactional patterns of your family.



Reflective Question

*How does your family life affect your present
social competence?*

APPENDIX 2.

**The Hong Kong Polytechnic University
Department of Applied Social Sciences**

**APSS1L01Tomorrow's Leaders
Lecture Nine: Social Competence**

Scenario A

Your friend, Mike, just told you that his father lost his job 3 months ago. Mike seemed stressed and depressed. When he talked about the financial hardship of his family, he burst into tears in front of you.

How Would You Respond?

Think about three sentences and one action that might help the person feel better.

Scenario B

Your best friend, Jenny, just told you that she got pregnant. As a first year university student, she was not prepared to have a baby. She told you that she felt extremely anxious and stressed.

How Would You Respond?

Think about three sentences and one action that might help the person feel better.

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Chapter 163

SPIRITUALITY

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ABSTRACT

The curriculum of a lecture about spirituality in the course entitled “Tomorrow’s Leaders” developed by The Hong Kong Polytechnic University is introduced in this chapter. With reference to the basic tenets of outcome-based learning, the intended learning outcomes and the curriculum structure are illustrated. The following topics related to the construct of spirituality are included in this paper: definition and basic concepts of spirituality, theories of spirituality, antecedents of spirituality, spirituality and adolescent developmental outcomes, spirituality and leadership, and ways to promote spiritual leadership. Topics for reflections are also presented at the end of the chapter.

Keywords: spirituality; life meaning, leadership subject, curriculum development

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INTRODUCTION

Although religion has been regarded as an important influence in the lives of people, there is no agreed upon definition of spirituality. Scott [1] examined 31 definitions of religiousness and 40 definitions of spirituality. It was concluded that these conceptions could be subsumed under nine content areas, including connectedness or relationship, processes contributing to higher level of connectedness, reactions to sacred or secular things, beliefs or thoughts, traditional institutional structures, pleasurable existence, beliefs in the sacred or higher being, personal transcendence, and existential issues and concerns. Markow and Klenke [2] similarly suggested that there were more than 70 definitions of spirituality in the context of work. According to Myers, Sweeney and Witmer [3], spirituality can be defined as “personal and private beliefs that transcend the material aspects of life and give a deep sense of wholeness, connectedness, and openness to the infinite” (p. 265). Along this line of thought, meaning and purpose of life, hope and optimism, love and compassion, moral and ethical guidelines, related thoughts, feelings, and behaviors are essential elements in spirituality.

While spirituality is always associated with religion, there are some distinguishing features between spirituality and religion. First, religion is the search for significance in ways related to the sacred whereas spirituality is the search for the sacred. As such, religion is finding the means to reach the end while spirituality is a more general feeling of closeness and connectedness to the sacred. Second, religion is about the adherence to a belief system and practices associated with a tradition in which there is agreement about what is believed and practiced. However, the sacred in spirituality is often a socially influenced perception of either (a) a divine being or object or (b) a sense of ultimate reality or truth.

According to Worthington et al. [4], there are four types of spirituality, namely humanistic spirituality, nature spirituality, religious spirituality, and cosmos spirituality. First, humanistic spirituality refers to the closeness and connection to mankind. Second, nature spirituality refers to the closeness and connection to nature. Third, religious spirituality refers to the closeness and connection to the sacred defined by religion. Fourth, cosmos spirituality refers to the closeness and connection to the whole of creation.

While Worthington categorized the four types of spirituality in a macroscopic view, Lau [5] contextualized spirituality in a narrow way to show that there are three key elements on the spirituality of Chinese, namely connectedness to others, personal beliefs and values, and meaning of life. The first element, “connectedness to others” refers to a two-dimensional model to illustrate a person’s transcendent relationship with the higher being (vertical dimension) and the relationship one shares with himself/herself, others and the environment in connectedness (horizontal dimension). The second element, “personal beliefs and values” means that different types of spirituality provide a variety of beliefs and values that guide our behaviors and/or answer some essential questions surrounding life and death issues [6]. Lastly, “meaning of life” is contributed by three sources that a career to which a person commits oneself (creation), some beautiful things or love of others appear to a person (experience), and the active choice of a person’s attitudes (attitude) [7].

ANTECEDENTS AND CONSEQUENCES OF SPIRITUALITY

There are many factors influencing the development of spirituality. Adopting an ecological model, factors on different levels shape the development of adolescent spirituality [8-10]. For example, in a longitudinal study to examine the factors influencing adolescent spirituality, Regnerus, Smith and Smith [11] found that parents and friends had strong impact on the development of adolescent's religious spirituality while country-level influences seemed to be minimal. Parents' religious behavior and expectation shape the spirituality in adolescents and young adults strongly. Besides, peer influence, maternal communication, and paternal affection exert strong impact as well.

In fact, developing adolescent spirituality is essential due to the fact that it will promote adolescents' physical health, psychological well-being, and at the same time reduce the effect of psychopathology and stress and turnover. Based on the theory of logo therapy proposed by Victor Frankl [12], existential vacuum (i.e., loss of meaning in life) is a precursor of mental problems and adjustment problems. According to Emmons [13], religion provides goals and value system that shape life meaning which would eventually promote quality of life. Powell, Shahabi and Thoresen [14] also provided evidence suggesting the positive relationship of religion on health outcomes. In the context of the workplace, adolescent spirituality not only reduces the possibility of employee absenteeism, but also increases employees' productivity, ethicality, and health [7, 15-17].

SPIRITUALITY AND LEADERSHIP

After considering the basic nature of spirituality, it is important to examine the relationship between spirituality and leadership. Spiritual leadership refers to the intrinsic motivation towards oneself and others. Based on this definition, a person perceives work as a calling in a sense that spirituality as the source of their motivation. Besides, a person who helps other scares about their own development of their body, minds heart and spirit. Nonetheless, spiritual leadership intrinsically motivates oneself and others through developing inspiring vision and mission statements that foster a spirit of cooperation, trust, mutual caring, and a commitment to organizational effectiveness. Last but not the least, a spiritual leader should be competent to gain followers' acceptance in terms of credibility, teaching, trust, inspiration, and to be knowledgeable about the group's work.

According to Greenleaf [18], the concept of servant-leader based on the assumption that servant-leader is a servant first. It begins with the natural feeling that one wants to serve, and then conscious choice brings one to aspire to lead. Servant-leaders give priority attention to the needs of their colleagues and those they serve. As such, servant-leadership consists of the following characteristics: listening, empathy, healing, awareness, persuasion, conceptualization, foresight, stewardship, commitment to the growth of people, and building community.

The characteristics of servant-leadership suggested by Greenleaf are closely related to six spiritual practices for leadership effectiveness. First, demonstrating respect for others' values is essential in leadership effectiveness. A leader respects values of followers, creates empowerment rather than dependency, and promotes sustainability rather than short-term

success. Also, a value-based leader's behavior has powerful effects on followers' motivation and work performance. Second, treating others fairly is also an important practice for an effective leader. In fact, justice and fairness are values important to spirituality. Therefore, treating others fairly is a natural consequence of viewing them with respect. In contrast, treating others unfairly indicates a lack of respect, compassion, and integrity. Third, effective leadership will express care and concern. The leader will emphasize individualized consideration, such as coaching followers, listening, and attending to individual needs and desires. The leader will also place people over strategy since that he/she values person-person interaction more on relational quality rather than functional quality. Along this line of thought on relationship building, the leader will express care and concern goes beyond the organization to make a commitment to the community. Fourth, an effective leader would listen responsively. He/she acknowledges the concerns of employees, and at the same time recognizes and respects good ideas. Fifth, an effective leader will appreciate the contribution of others. The appreciation of others serves as worthy of respect and praise to others. When leaders recognize employees' contributions, employees feel a stronger sense of belonging to the community, more likely to stay with the organization and continue to contribute. Lastly, an effective leader will engage in reflective practice. He/she will take time for individual self-examination and/or communication with God [19]. Some common practices include prayer, journaling, meditation, and spiritual reading.

WAYS TO PROMOTE SPIRITUALITY

Several strategies can be used to help students develop their spirituality. For example, Shek [8] suggested that understanding different forms of religions and spirituality via different media can foster the development of spirituality. He further suggested that active reflection on spiritual questions is effective to deepen adolescents' spirituality. For example, "why do we exist?", "where are we going?", "is there any life after death?", and "what should we do when we are still conscious?" are inspirable questions for adolescents to reflect on personal growth and the life goals of this world and of the metacognitive world. In fact, these are important spiritual questions demanding conscious reflection. Similarly, Bruce and Cockreham [20] suggested that adolescents could gain more spiritual experiences through joining religious groups, church activities, spiritually related gatherings, and meditation.

Meditation is another strategy that can help students to develop their spirituality and reflection. The word "meditation" is derived from two Latin words—*Meditari* and *Mederi*. *Meditari* means to think, to dwell upon and to exercise the mind where *Mederi* means to heal. Based on this understanding, mediation is defined as an art of stilling the mind that helps an individual overcome negative emotions. Besides, meditation is a technique to reduce stress and gives you a peaceful mind. According to Benson, Beary and Carol [21], there are four steps in meditation. First, it is necessary to have a quiet environment. Then, a mental device is needed so that the meditator can focus his/her attention on a constant stimulus. In order to calmly redirect attention to meditator's mental device, a passive attitude is required. Lastly, the meditator should have a comfortable position by simply sitting up. After introduced the definition and the steps of meditation, it is always helpful that an activity is assigned to students for them to apply the knowledge acquired.

OVERVIEW OF THE LECTURE

Catalano et al. [22] highlighted 14 positive youth development constructs that are essential to the all-rounded development of adolescents. Utilizing some of the related constructs, a credit-bearing subject entitled “Tomorrows’ Leaders” was developed and implemented at The Hong Kong Polytechnic University to promote the intrapersonal and interpersonal skills of the students. Aligning with the major aims of the course, the lecture about spirituality has the following objectives: a) to theorize the definitions and basic concepts related to spirituality; b) to summarize the antecedents and consequences of spirituality; c) to explain the relationship between spirituality and leadership; d) to explore ways to promote spirituality; and e) to appreciate the conceptual and practical issues surrounding spirituality. As far as learning outcomes are concerned, through engaging students in an active learning environment, it is expected that students will be able to understand a) the definitions, basic concepts, and theories related to spirituality; b) the antecedents and consequences of spirituality; and c) the relationship between spirituality and leadership. Besides, they will be able to apply the knowledge through participating in individual and group activities in order to experience ways to promote spirituality for themselves. Finally, the lecture will illustrate some conceptual and practical issues surrounding spirituality for students to generate new ideas about the spirituality construct.

THE OVERALL STRUCTURE OF CURRICULUM

The curriculum is designed to put emphasis in facilitating students’ understanding about spirituality in terms of theories and practices. While theories are used to build up the conceptual framework for students to understand spirituality, practices during the lecture are used to deepen students’ understanding through having application and/or synthesis of new ideas about spirituality. The lecture is started with playing a song to raise students’ awareness of thinking the meaning of life. Some issues/questions are raised, such as: *Why are we here? What’s life all about? What is life? What is our fate?* Then, the lecture is structured in five sections, including definitions and theories of spirituality, antecedents and consequences of spirituality, spirituality and leadership, spiritual practices for leadership success, and ways to promote spirituality. The topics are arranged from the understanding of spirituality towards the relationship between spirituality and leadership, and ultimately lead to a practical side on the qualities of spiritual leadership. To conclude the lecture, several reflective questions and issues related to spirituality are being raised for students to think after class: What is the meaning of spirituality in your life? How are individual, family, and social factors related to adolescent spirituality? It is expected that these questions can promote the learning experience extending after the lecture. The lecture outline for the students can be seen in appendix A.

REFLECTIONS AND CONCLUSION

Teaching spirituality cannot be done solely by transferring knowledge theoretically. Indeed, spirituality is an experiential knowledge that requires students to practice as well. The

design of this curriculum to teach spirituality has been well structured in order to make a well balance of the two. On one hand, theories about spirituality can be delivered to provide basic understanding about the conceptual framework of spirituality in the earlier part of the lecture. On the other hands, students have the opportunity to practice and therefore be able to re-enter into their personal experience which turns to become a re-visit of their lives as spiritual journeys at the latter part of the lecture. Having said that, there is room to further enhance the constructive alignment between the intended learning outcomes, teaching and learning activities and the assessment tasks of this lecture in order to enriching students' learning experience in this subject matter.

In fact, knowledge and skills are inter-related. According to Chan [23], students can learn best with daily-life examples in problem-based learning. Besides, as Franklin [24] mentioned that, spirituality is "a spiritual awareness needs to be impressed on students to effect a positive influence in their life; it is a way of thinking, being and living" (p. 2). In view of the current curriculum, although there are two activities to engage students in personal reflection, there is a gap to demonstrate spirituality as an experiential knowledge to students. One way to fill in this gap is to provide a real case for students to associate with the conceptual framework of spirituality acquired in the first part of lecture. The teacher can provide a real case by either sharing his/her personal testimony or writing up a case scenario based on the real case of others or the public. Following the case scenario shared with students, reflective questions will be given for students to think of the situation. At this point, the questions should be set in order to allow students to apply their understanding of the concepts about spirituality, and therefore synthesize new ideas about the topic. Below is an example of a case scenario which can be used to enhance the learning experience of students:

CASE SCENARIO

This case scenario is based on the personal testimony of the second author:

"When I was pursuing for my first degree in Vancouver, Canada, I joined the count-down activity with my friends in my church fellowship in the last night of December every year. One night, after we had finished the count down in one of our friends' home, I drove my friends back home as usual in mid night. At that time, the temperature was low (nearly zero degree Celsius), the wind blew and no one on the street. Suddenly, a car was coming very fast and then had a head-on collision towards the left hand side of my car. Without any notice and in a split of second, I felt that my car was spinning for several rounds. After the car had come to stop, I found that all the windows were broken, and by natural instinct, I climbed up from the side window and then got out of the car. The first person I saw was one of my friends. He was lying on the icy street a meter away from my car while his hands were shaking. Then, I looked back and I found that one of passengers were hanging on the side window and the other one's head was bending down and felt unconscious.

Within few minutes' time, nine ambulances arrived and brought all the patients from the two cars to hospitals nearby. While I was not having serious injury, I stayed in a police car to keep warm. At that time, I felt that I was so weak and could not do anything for my friends but just sitting there to wait for my homestay parent to come. My anxiety climbed so high and

I blamed myself so much that I was the person to make this accident happened. As my homestay parent came, I took on his car and we went to visit my friends in the hospitals. Also, I needed to phone the relatives of my friends about the accident. As a visa student, it was hard for me to speak up to tell their relatives that I was the one to induce this accident and asked them to go to hospital at the same time. In the journey, my homestay parent and I did not talk so much. The silence in the car echoed with the dark night outside. At that time, I felt mysterious. Suddenly, he held my hand and said, "The end of man is the beginning of God". Immediately, my tears came out after I heard this. In fact, after the accident happened, I did not cry at all not because I was brave enough, but I just suppressed my emotion that I didn't know how to cry. Indeed, his phrase did give me insight and hope, which granted me strength to carry through.

At last, my friends came out from the hospitals and we all had no major damage on our health. Also, the court judged that the driver of the other car had the 100% responsibility in this accident. By that time, I was relieved."

With reference to this case, reflective questions are being set to deepen students' understanding about spirituality and the application on spiritual leadership. The level of questioning is starting from a surface level to a deeper level that higher order thinking is required for students to provide in-depth feedback. Depending on the availability of time, the reflective questions can be discussed in the group or open class discussion contexts.

1. The author came to an intersection of life and death. How would you feel if you were in the same circumstance that your friends were injured after the accident was happened? Will life and death be an issue to you by that time? Why or why not?
2. The author came to an emotional break down after the accident. He seemed to be disconnected to his friends or even himself in the police car. Do you think you will behave similarly or you will do something in order to stabilize your emotion? How?
3. Do you agree that "the end of men is the beginning of God"? How do you perceive if there is any supernatural power in this universe?
4. If you were the boss of this author, how would you write him a letter to encourage him from recovering from this bad experience? Try to integrate the characteristics of a spiritual leader (listening, empathy, healing, awareness, persuasion, conceptualization, foresight, stewardship, commitment to the growth of people, building community) in your letter.

In all, teaching spirituality is not an easy task since there is no absolute answer to individual's life which is intrinsic and intrapersonal [24]. Perhaps asking students to write their personal reflection would be a good assessment task for and of their learning so that students can be able to re-visit their past experience and then come up with insights to live fruitfully. In future, some issues are worth to explore. For example, the contextualization of the theories of spirituality in local Hong Kong context, and the integration of spirituality and spiritual leadership in students' lives are the essential for the sustainable development of adolescence. Based on the successful experience of developing and implementing positive youth development programs like the Project P.A.T.H.S. in Hong Kong [25, 26], it would be an attractive option to develop curricula-based spirituality promotion program in the university context. The subject "Tomorrow's Leaders" is a pioneer example in different Chinese contexts.

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APPENDIX A: OVERVIEW OF THE LECTURE (HANDOUT TO STUDENTS)

Spirituality can be defined as “an awareness of being or force that transcends the material aspects of life and gives a sense of wholeness or connectedness to the universe”. The growth in spirituality is an inner developmental process that helps a person to change and to connect with the universe. Researchers have found that spirituality has significant effects on different aspects of youth development and contributes to adolescents’ active participation in social activities. Thus, it is important for our university students, tomorrow’s leaders, to gain a clear understanding of spirituality and how it relates to the concept of leadership in both a broad and narrow sense. This lecture gives a brief introduction on the concepts and theories of spirituality. Students are guided to reflect on their own spiritual values and how these values can be further developed and embodied in one’s leadership.

Intended Learning Outcomes

After taking this lecture, students should be able to:

7. introduce the definitions, basic concepts, and theories related to spirituality;
8. summarize the antecedents and consequences of spirituality;
9. examine the relationship between spirituality and leadership;
10. explore ways to promote spirituality;
11. appreciate the conceptual and practical issues surrounding spirituality.

Teaching methods

- Lecture
- Video viewing
- Experiential learning activity
- Group discussion
- Meditation
- Self-reflection

Lecture Plan

Part 1: Definitions and theories of spirituality

- Warm-up activity: “The meaning of life”

- Group discussion: “Tuesdays with Morrie”
- Self-reflection activity: “My treasure box”

Part 2: Antecedents and consequences of spirituality

Part 3: Spirituality and leadership: Spiritual practices for leadership success

- Video clip: “A spiritual leader”
- Group discussion: “Spiritual practices of Mandela”

Part 4: Ways to promote spirituality

- Meditation: “Let’s meditate”

Part 5: Conclusion and student reflection

Required Reading

Shek DTL. Spirituality as a positive youth development construct: A conceptual review. *Scientific World Journal* 2012. doi:10.1100/2012/ 458953.

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Chapter 164

MORAL COMPETENCE

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ABSTRACT

Moral competence is an important dimension in healthy adolescent development and effective leadership. In this chapter, a lecture attempting to nurture the moral competence of university students in Hong Kong is described. There are several parts in this lecture. In the first part, moral dilemmas in real life and hypothetical situations are introduced. Second, conceptual frameworks on moral judgment are outlined. In the third part, the relationship between morality and leadership is addressed. In the next part, strategies to promote moral development are discussed. Finally, conclusions and reflections by the students are carried out. In the lecture, students are invited to have personal reflections on their moral competence and integrity in relation to their real life context.

Keywords: moral competence; ethics; moral development; personal reflections; integrity

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INTRODUCTION

“Morality” is “*moralis*” in Latin which means customs or manners. In fact, the original meaning of morality is closely related to the term “ethics” which means “character” in Greek “*ethos*”. Perle [1] stated that morality pertains to the individual character of a person, while ethics focuses on the relationships among humans. Modern usage of morality refers to “conduct” itself and ethics (or moral philosophy) is defined as the study of “moral conduct”. Some researchers [2, 3] believed that “morality” is the judgment of our conduct or behavior. In other words, it is as a matter of fact that whether it is right or wrong. For example, it is understood that murder is wrong and honesty is right. Also, “ethics” is a set of principles used to decide what is right or wrong, which are the standards of conduct in different disciplines and institutions. For example, integrity, respect, and social responsibility are listed in the code of ethics. In all, the terms “morality” and “ethics” are closely related to their original meanings and can be used interchangeably [2, 3]. Albrecht [4] stated ten universal values for ethical behavior, including honesty, promise-keeping, accountability, fidelity, responsible citizenship, pursuit of excellence, caring, integrity, fairness, and respect for others.

Philosophers in different cultures have different conceptions about the essence of morality. With specific reference to the Chinese culture, the Confucian idiom of “look at nothing in defiance of ritual, to listen to nothing in defiance of ritual, to speak of nothing in defiance of ritual, never to stir hand or foot in defiance of ritual” (fēilǐwùshì, wùtīng, wùyán, wùdòng) underscores the importance of propriety (lǐ) in the traditional Chinese culture. Confucius also emphasized that the virtues of kindness (rén) and righteousness (yì) as “a superior person” (Junzi). Similarly, Socrates in the Western world also stated that “virtue is not given by money, but that from virtue comes money”. In fact, both the western and eastern moral philosophies illustrate that a moral sage or leader should have self-cultivation and be able to transform others and the social environment [5].

Why morality and ethics are important? First, ethical values serve as the foundation for an orderly society. Besides, Smith, Smith and Mulig [6] suggested that trust instead of greed energizes the economy. Lastly, truly ethical professionals will keep their conduct well above the minimum. In other words, ethics and morality are not only essential to intrapersonal development, they are also the corner stone to healthy social development.

Closely related to the concepts of morality, ethics is the construct of integrity, which means a person’s behavior is consistent with espoused values and that the person is honest and trustworthy [7]. Integrity is the reputation for truthfulness and honesty of the trusted person, which involves an individual’s commitment to principles [8, 9]. As Rand [10] suggested that, integrity means loyalty to rational principles (general truths) and values, and the integration of outward virtuous actions with inner virtuous values. Integrity plays an important role in interpersonal relationship. Without integrity, a person will not be trusted.

CONCEPTUAL FRAMEWORKS FOR MORAL JUDGMENT

Among the different models on morality, the theory proposed by Lawrence Kohlberg is a popular one [11]. According to Kohlberg’s moral judgment competence, the way we make moral decisions in our daily lives is shaped by the socialization process. He proposed a theory

of moral development with three levels. The first level is called “pre-conventional level” which focuses on concrete and physical consequences. The second level is called “conventional level” where moral judgment is guided by social norms. The third level is the “post-conventional level” where morality is determined by universal ethical principles.

All the stages of moral development are related to moral behaviors [11]. Dolgin [12] stated that Kohlberg’s levels and stages of moral development consist of conscious and rational reasoning processes. First, there are two stages in Level I (Pre-conventional Moral Reasoning) which is focusing on oneself. The reasoning starts with “punishment orientation” in Stage 1 and then moves on to “instrumental hedonism orientation” in Stage 2. Upon the completion of Level I, the focus of reasoning will shift from personal to interpersonal in Level II (Conventional Moral Reasoning). On this level, “good boy and nice girl orientation” is evolved in Stage 3 and then moves on to “law and order orientation” in Stage 4. Upon the completion in Level II, the reasoning process goes up the to the last stages of 5 and 6 in Level III (Post-conventional Moral Reasoning). On this level, moral reasoning is further advanced from concerning others to caring about each other. The orientation is changing from “social contract orientation” in Stage 5 to “universal principle orientation” in Stage 6.

Moral dilemmas are commonly used to assess morality in individuals. The most famous one is “Heinz’s dilemma”. In the story, Heinz’s wife was diagnosed to have cancer and there was a newly developed drug that can save her. Unfortunately, Heinz did not have enough money to buy the drug because the druggist was charging much higher than the cost. The questions posed to the students are: what will you do if you were Heinz? Would you steal the drug? Why? In fact, moral dilemma is a good tool to reflect the moral development of a person.

MORALITY AND ADOLESCENT DEVELOPMENT

Adolescents’ level of morality is often discussed in the context of adolescent moral competence. It is defined as “a youth’s ability to assess and respond to the ethical, affective, or social-justice dimensions of a situation” [13]. According to Piaget [14, 15], adolescent moral maturity is indicated by both a respect for rules and a sense of social justice. Morality has long been considered a necessary part of adolescent social competences, which is often linked to their prosocial behaviors and other positive performance [16]. In the Chinese culture that particularly values interpersonal harmony, moral values, and prosocial norms, morality of young people is a topic of high significance [17].

Morality is closely related to adolescent behavior, such as empathy and egocentrism. First, social cognitive theory holds that one’s adoption of values, standards, and attitudes is governed by a much broader and more dynamic social reality. The process of internalizing moral values and principles entails a perspective-taking skill that is necessary for an individual to concentrate on others’ needs instead of one’s own and thus defined as empathetic reaction [18]. Empirical evidence is also available to show that people who make mature moral judgments tend to be empathic and autonomous [19]. Also, from the social-cognitive perspective, human’s long-term goal, such as moral striving, is chronically accessible to a person and guide one’s behavior automatically [20]. Poor development in morality would thus make one to give up ethical rules easily and become susceptible to

unhealthy environmental influences. Hence, adolescents who have lower morality are more likely to develop materialistic thoughts and behaviors in the consumer society today, to concentrate on themselves and to ignore others' interests, given a social culture that increasingly values individualism.

How about morality in university students? Despite the fact that the number of universities throughout the world is increasing, there is a concern regarding the morality of university students. First, research findings showed that narcissism levels have gradually increased over the past 25 years [21], which is an attribute of pre-conventional morality. Second, Loeb [22] observed and conversed with college students across thirty states in the US throughout late 1970s and early 1990s, and noted that they were "pathologically selfish, greedy, apathetic, and unconcerned with higher ideals" (p. 2). Again, these characteristics suggest a pre-conventional morality.

MORALITY AND LEADERSHIP

Brown, Trevino, and Harrison [23] defined that ethical leadership as "...the demonstration of normatively appropriate conduct through personal actions and interpersonal relationships, and the promotion of such conduct to followers through two-way communication, reinforcement, and decision-making" (p. 120). Ethical leaders should consist of the characters such as trustworthiness, fairness, and respect. Also, the influence of ethical leaders would be altruistic, focusing on organizational success rather than their own. Based on these characteristics of ethical leadership, researchers claimed that leaders' influence strategies should be framed actions in ethical terms which can motivate others to follow a shared vision [24, 25].

If leadership is the art of influencing and motivating others to their maximum performance to accomplish any task, objective, or project, then integrity is a critical characteristic of authentic leadership. In other words, a leader will never be able to have the strength to impact others if his/her life is fragmented or lacking wholeness. Moreover, great leadership comes from the identity and integrity of the leader. After all, leaders must always display the highest standards of integrity. Following this line of thought, Smith et al. [6] stated that "what we do determines who we are, and whether we made the world better or worse".

Moral competence is also strongly emphasized in other leadership models. One example is service leadership [26]. According to the Hong Kong Institute of Service Leadership and Management [26], service leadership "is about satisfying needs by consistently providing quality personal service to everyone one comes into contact with, including one's self, others, communities, systems, and environments" (p. 5), whereas a service leader is "an on-the-spot entrepreneur who possesses relevant task competencies and is judged by superiors, peers, subordinates, and followers as having character and exhibiting care in action situations" (p. 5). Besides relevant situational task competencies, moral character and caring disposition are fundamental attributes of an effective service leader.

Another example is servant leadership which emphasizes the importance of moral values and integrity. A servant-leader is a servant first. Servant leadership begins with the natural feeling that one wants to serve, and then conscious choice brings one to aspire to lead. The

servant leader will give priority attention to the needs of their colleagues and those they serve. According to Greenleaf [27], servant leadership is “a model which puts serving others as the number one priority. Servant-leadership emphasizes increased service to others; a holistic approach to work; promoting a sense of community; and the sharing of power in decision-making” (p. 33). Greenleaf upholds the moral values and integrity of being a leader whom should consist of the following moral attributes: listening, empathy, healing, awareness, persuasion, conceptualization, foresight, stewardship, commitment to the growth of people, building community. Joseph and Winston [28] suggested that these ten moral attributes as essential to servant leadership.

WAYS TO PROMOTE MORAL DEVELOPMENT

In order to foster the moral development of students, three practical ways can be introduced. First, students are encouraged to discuss moral dilemmas with others. This can help clarify what the intention and motive are in the reasoning process. Second, students can use dramatic play and role playing to show the authentic cases of real dilemmas. Through role playing, students can deepen their thoughts by having more reflections at different angles. Lastly, self-reflection can be recommended for students to ask themselves before making an ethical decision. During the self-reflection, Smith et al. suggested some questions for ethical decision making [6]: 1) Is it legal? 2) Is it fair? 3) Who would be affected by this? 4) Does it comply with the organization’s values? 5) What will others think of me if they knew about my decision? 6) How will my decision look in the newspaper? 7) How will it make you feel about yourself? Young people should be reminded that when facing moral dilemmas, leaders should focus on “doing the right thing” and that everyone can make a difference in doing the right thing.

CURRICULUM OVERVIEW OF THE LECTURE

Based on the above understanding of morality and ethics, the attribute of moral competence is introduced in the credit-bearing course, entitled “Tomorrow’s Leaders” in The Hong Kong Polytechnic University. This course is being offered to introduce the 14 competences which are essential to leadership based on the positive youth development constructs stated by Catalano et al. [13]. Aligning with the major aims of the course, the lecture about morality construct has the following intended learning outcomes which help students: a) understand the concepts and theories related to morality and integrity; b) identify the antecedents and consequences of morality; c) explain the relationship between morality and leadership; d) generate ways to promote moral development; and e) explain causes of a series of moral dilemmas and related issues.

Corresponding to the intended learning outcomes in developing intrapersonal competence, the curriculum is designed to provide opportunities for students to have substantial personal reflections and integration of personal experience to the theories in their contexts. For example, the concept of integrity is illustrated by contextualizing the term in relation to the issue of academic integrity. Students were being asked to comment on the statement given by

Steven Davis, a psychology professor quoted in *The Wall Street Journal* that “students say cheating in high school is for grades, cheating in college is for a career.” Two common academic dishonesty issues were raised to further support the seriousness of cheating in higher education. Bowers [29] stated that there were over 75% of college students had cheated which were about 5,000 college students. Few decades later, McCabe [30] indicated that there were 50,000 undergraduate students had cheated which was covering 70% of the population in higher education. In addition to cheating, plagiarism is another major issue related to dishonesty. Sheard et al. [31] suggested that it was easy for students to copy and paste from the web to complete their assignments. In fact, research stated that academic dishonesty, especially cheating would lead to deviant behaviors such as substance abuse and illegal behaviors [32, 33]. Moreover, work performance of employees will be affected if they have unethical behaviors or low scores in integrity tests [34, 35].

Apart from reflection exercises, the teaching and learning environment is designed to provide more group discussion time for students to have collaborative learning in comparing with other lectures of similar class size. For example, a group activity, “The Golden Virtues of Confucius” is designed to raise students’ awareness about the qualities or virtues of a leader in the Chinese context. The 13 golden virtues of Confucius are highlighted to students; they are: kindness, righteousness, respectfulness, having a sense of shame, courageousness, incorruptibility, forgiveness, loyalty, trustworthiness, filial piety, brotherly love, self-correction, and wisdom. Each group of students was given a bag of Legos representing the 13 golden virtues of Confucius. Students in the groups were asked to make a model with the Legos given to represent their idea about the golden virtues of Confucius. Their image of the selected virtue(s) was then reflected physically as an object. Students were required to explain about the idea and the meaning of the object in relation to the virtue(s). Group discussion and reflection are embedded in this activity. A brainstorming question was raised to ask students what kinds of qualities or virtues a leader should possess. To debrief, a quote from Dwight D Eisenhower (1890-1969), who was a five-star general in the United States Army and the 34th President of the United States was used to state that, “the supreme quality for leadership is unquestionably integrity. Without it, no real success is possible, no matter whether it is on a football field, in an army, or in an office.”

CONCLUSION

Overall speaking, the lecture content is useful to introduce the conceptual framework of morality with resourceful and convincing information. The linkage between morality and leadership is also stressed to signify the importance of morality as one of the essential competences of leadership. In terms of the teaching effectiveness, collaborating learning strategy enables students participating in group learning. The depth of group discussion depends on the facilitation skills of individual subject teachers. The issue of deep learning can be explored further in future research to enhance the learning experience of students. Furthermore, the successful experience in connection with the development and implementation of positive youth development programs such as the Project P.A.T.H.S. [36, 37] can help to design curriculum materials for university students as well.

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APPENDIX 1: LECTURE OUTLINE GIVEN TO STUDENTS

Moral behavior is the result of the interaction between individual (e.g., cognitive moral development, gender, self-esteem) and situational factors (e.g., ethical codes and culture) (Kohlberg, 1981; Rest, 1986). Ethical leadership is an important component for promoting an organizational functioning and maintaining social orders (Smith, Smith, & Mulig, 2005). Ethical leaders can influence the followers' values, beliefs and behaviors by demonstrating normatively appropriate behaviors (Brown, Treviño, & Harrison, 2005). In this lecture, we will discuss the process of moral judgment and moral reasoning, and how students incorporate various effective ethical decision-making methods in their perceptions of ethical dilemmas in the real world. [Dear Dr. Shek, I don't have the lecture outline in hand. Please put the references at the end of the Appendix]

After taking this lecture, students should be able to:

1. understand the concepts and theories related to morality and integrity;
2. identify the antecedents and consequences of morality;
3. explain the relationship between morality and leadership;
4. generate ways to promote moral development;
5. explain causes of a series of moral dilemmas and related issues.

Teaching Methods

- Lecture
- Video Viewing
- Experiential Learning Activity
- Group Discussion
- Self-Reflection

Lecture Plan

Warm-up activity: "What Will You Do?"

- To introduce the lecture topic by presenting several scenarios to the students.

Part 1: Understanding Morality

- Group Discussion: "What Should Heinz Do?"

Part 2: Frameworks for Moral Judgment

Part 3: Morality and Leadership

- Class Activity: “The Golden Virtues of Confucius”

Part 4: Ways to Promote Moral Development

- Video viewing and sharing: “The Story of Star-Fish”

Part 5: Conclusion

Required Reading:

- Dalton J, Crosby P. Being and having: Shouldn't excellence in higher education (and people) be a measure of what one does rather than what one has? *J Coll Character* 2007;9(1):1-5.
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Chapter 165

REFLECTIVE TEACHING AND HOLISTIC PERSONAL DEVELOPMENT

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ABSTRACT

Research shows that reflective practice plays an important role in promoting teaching performance and facilitating a positive learning atmosphere. This chapter provides a case study on teacher's reflection in a university course. The author discusses the difficulties she encountered and the strategies she used when teaching a leadership course. Students' post-lecture qualitative evaluation is used as illustration to show how these feedbacks guide the teacher when reflecting and evaluating her teaching performance. Implications are discussed to highlight the importance of reflective practice in university contexts.

INTRODUCTION

In the field of teacher education, reflective practice refers to the involvement of questioning individuals' assumptions, values and beliefs of teaching [1]. Given the increased popularity on student-centeredness in education, teachers no longer just feed the students. They need to strengthen their role as learners to foster a meaningful development for themselves. Indeed, reflection is critical for teachers' learning and development [2]. It highlights the importance on learning through critically examining and questioning on their own performance [3]. It is also known as experiential learning process, which involves four stages of learning: concrete experience, reflective observation, abstract conceptualization and active experimentation [4].

Through this cycle, effective learners are able to 1) use their experience to identify problem, 2) review and reflect on the experience, 3) transform the experience into new idea and new concept and 4) engage in new behavior to test the hypothesis. Once this cycle is

completed, another cycle begins. In general, professional development is a continuous learning process [5]. Teachers “collect data about their teaching, examine their attitudes, beliefs, assumptions, and teaching practices, and use the information obtained as a basis for critical reflection about teaching” [6]. This method is considered as a way to promote professional development [7] and has been used in various areas of teaching, such as classroom format and teaching context [8-10]. However, little is known in the university context, particularly when teaching a holistic education course.

Universities have been suggested to help students better prepare themselves when they enter to the society. During college, students need to make a lot of important decisions and to face changes in various aspects of life, such as family, friends, intimate relationship and career. “It is a time of ‘soul searching’ where students actively develop a sense of who they are, who they want to be and what roles they will play in life” [11]. Apart from nurturing intellectual ability and knowledge, a broader development of human and education performance, including critical thinking, content and process is suggested. Recently, a holistic education approach receives increasingly attention regarding its nature and importance [12, 13].

“Holistic education incorporates the insights, knowledge, and skills necessary for ‘learning how to learn’ as a lifelong process” [14]. “To nurture our students to be critical thinkers, effective communicators, innovative problem solvers, lifelong learners and ethical leaders”, The Hong Kong Polytechnic University developed a 3-credit bearing course titled “Tomorrow’s Leaders.” This course aims at promoting students’ intra- and inter-personal qualities of effective leadership and developing self-reflection skills in their daily lives. Previous results generally showed the positive development of psychosocial competencies among students after enrolling in this course [15-19]. However, prior studies in the field of holistic education mainly focus on students’ perception; little is known from teachers’ perspective. For example, what were the barriers and effective strategies when teaching a course on holistic personal development? The purpose of this article is to provide a case study on teacher reflection in a university course. In this paper, I share my experience when teaching a holistic leadership course. Some examples included a) what were the difficulties I faced when teaching this course; b) what strategies I used when facing these difficulties; and c) how effective of these strategies in addressing the aforementioned problems. Students’ post-lecture qualitative evaluation was used as illustration to show how these feedbacks guide teacher in reflecting and improving her performance when teaching the course.

COURSE DESCRIPTION

All full-time students from multidiscipline (e.g., humanities, engineering, health care professional, sciences, social sciences, and design) were required to take a 3-credit bearing course titled “Tomorrow’s Leaders” in their freshman year. Students met three hours a week for 14 weeks (a total 42 hours). At the end of each lecture, students are asked to complete a subjective outcome evaluation form including 12 items and one open-ended question regarding the content and process of the lecture [details in Shek, 15]. In the present paper, focus was put on the findings based on the qualitative data (i.e., an open-ended question).

Teacher's Background

Being a coach and teacher for more than 10 years, I love working with adolescents and young people and like getting in touch with students. I often think they have a lot of potentials. What they need is how we, as an active social agent, provide opportunities for them to find their identity, to reach their goal and to experience their full potential. I hope I can help them become their best. These beliefs are aligned with the rationale of the course "Tomorrow's Leaders". This course adopts a positive youth development approach, which focuses on nurturing what is the best in individual's life and developing individuals' strengths [20]. It is a place to help the college students to be well prepared, search for identity and pursue their personal growth goal. It is my hope that students can achieve optimal functioning and develop a strong sense of direction before they enter the next step in their adult life. When teaching this course, students' needs and learning processes are my major concerns. However, these concerns might not be easily addressed due to the following challenges:

Traditional Passive Learning Behavior

When I knew I was assigned to teach "Tomorrow's Leaders," I felt quite nervous. On one hand, unlike other discipline-based courses, this course is focused on personal growth and development, which is quite different from what I used to teach. Perceiving myself as the change agent, I began to question my teaching, seek alternatives to meet the students' needs and engage in systematic reflection about my teaching. On the other hand, I perceived this as a great experience to understand and empower our students. I asked myself a series of questions: *"What do I want my students to learn?"*, *"How to raise their awareness of their inner self and to transform their knowledge into different contexts?"*

In particular, the biggest challenge was how to motivate students to actively engage in the class. Hong Kong Chinese students were used to sit in the classroom, take notes, and answer questions as teacher requested. In general, under this "spoon-fed" learning environment, they were very passive in classrooms. For me, this is the greatest challenge to elicit their active involvement and participation, which is essential for holistic education [21]. Furthermore, students, especially freshmen, might suffer from stress and anxiety. They need time to adapt, to search a new identity, and to achieve a successful integration into the new one when facing the transition from high school to college [22]. This is also reflected from the qualitative lecture evaluation:

"The teaching method is totally different from that in secondary school and I really need more time to get used to it..."

"Have a good chance to interact with my classmates from diverse cultural backgrounds! A new experience."

Multitasking and Media Saturated World

Another challenge was how to maintain students' attention in a media saturated world. Nowadays, multitasking is becoming more common in our young generation. They are grown up in a highly-connected world and are immersed in digital stimuli. They are glued to various digital devices, such as laptop, tablets and smartphone. Studies show that the use of these digital technology hampered university students' attention to focus and comprehend complex concepts [23, 24]. In particular, university students are not good at time management. Very often, they suffer from sleep deprivation, problem of concentration, irritable moods, poor diet and unhealthy lifestyle [25, 26]. With the increased availability of new portable digital technologies, it is very difficult for them to concentrate in a class, especially for a three-hour lecture. It is not uncommon that students engage in active texting, sending email or surfing the internet during class. Facing this ubiquity of digital technology, I asked myself "*How to deal with this problem?*", "*How to keep my students focus on the class and less distracted by their digital devices?*"

Abstract-Oriented Holistic Education

During class, I observed students, especially from science and engineering disciplines, expressed their difficulties in understanding the qualities of effective leadership. In fact, this perhaps relates to an abstract conceptualization nature of holistic education [14]. When examining the effectiveness of holistic education, Benander and Lightner [27] noted that students might not be able to recall what they had just learned, to transform the abstract conceptualization into a meaningful way, and to apply this holistic knowledge later in other contexts. Therefore, more real-life stories and concrete examples would be helpful for students' to understand the lecture materials. This is reflected from the qualitative lecture evaluation:

"Can have more inspirational and life stories of the influential leaders e.g., Barack Obama, Steve Jobs, etc. This would help us better understand the theory."

"Teacher can share her own experience with us."

"Lecturers can share their personal past experiences."

Regarding to the aforementioned challenges, I reflected my previous teaching experiences, searched for alternatives, and tried trying out new strategies to meet the students' needs and the course goals.

Strategies

To help students develop a sense of belonging and elicit their participation in the new learning environment, several methods, such as calling students' names, adopting their ideas, telling jokes, joining the group discussions and praising desired behavior, were used. These strategies not only provide a safe and welcoming learning atmosphere, but also motivate

students to participate and share their thoughts in the class [28]. As reflected from the qualitative lecture evaluation:

“Today’s lecture is surrounded by a very comfortable and positive atmosphere. I enjoy the exchanges I had with my group mates. Things are getting better around me.”

This friendly and relaxed learning environment ensures productive sessions by encouraging students to interact with others and build their confidence [29].

“In this lecture, I achieved my first goal. That is, I volunteered to answer the question in front of the whole class. Next time, I’ll try to be more active when interacting with the international students. It might not be easy, but I will try.”

“Thank you for remembering my name! Every time I participate in the class, I receive positive energy and have a clear sense of direction.”

Use of Cooperative Teaching Strategies

Another way to elicit students’ active participation was to provide a cooperative learning context. Cooperative learning is considered as essential part of the collegial experience [30]. Under the cooperative learning atmosphere, students were asked to respect others’ views, work together to create new ideas, take an active role for their learning, and thereby enriching learning process [31].

During the first week of the semester, students were divided into small groups (6-8 students per group) and were assigned with different roles (i.e., leader, coordinator, time keeper, recorder and reporter) in order to promote their function in leading small groups. They were asked to complete a task, to share and to reflect their thoughts with their neighbors or on their own. Sometimes, they were invited to report their views in the class. This is particularly effective when class size is large (above 80 students).

Similar to the findings in the field of cooperative learning research [14, 31, 32], this approach deepens students’ learning process by giving them an opportunity to review what they just learned and discussed with their classmates in small groups. It also motivates students to work together and realize the importance of intergroup relations. They are encouraged to work in a mixed-ability group, to learn the importance of interdependence and to foster an appreciation for differences in terms of ability, race, and background. This learning approach allows students to become more active in learning by cultivating students’ mental openness, taking responsibility of their own learning and appreciating the influence of others on shaping their personal growth [31] and this is aligned with the objectives of the course [16]. This is reflected in the post-lecture qualitative evaluation.

“From this lesson. I make friends from different cultural backgrounds.”

“It’s really nice to divide us into small groups. It provides us a good chance to build our friendship.”

“The class activities give us an opportunity to communicate with group members.”

“The games are very funny. I enjoy interacting with my group mates!”

“I really like the games in this lesson. I learn the cooperation skills.”

“The class activity enhances our communication and teamwork skills.”

Furthermore, by using the clarification pauses technique, the lecture was divided into several mini-lectures (around 20-25 minutes) [33]. As suggested by Hamer [9], this mini-lecture keeps students actively engaging in the class. This is especially important as nowadays the average of attention span of students is generally short and often distracted by the ubiquity of digital technology. This is also reflected from the qualitative lecture evaluation:

“Two breaks are good; it makes us stay awake in class.”
 “It is a good idea to have short breaks.”

The Use of Self-Disclosure

To help students transform the knowledge and apply it into other contexts, an effective instructional tool—self-disclosure was used. Self-disclosure refers to “the act of making yourself manifest, showing yourself so others can perceived you” [34]. This process focuses on facilitating students’ learning by making one’s own and other’s experiences meaningful [3]. For me, each lecture provides a good opportunity to review my life experiences and explores ways to enrich the course materials. Similar to the findings in self-disclosure research, students perceived the teacher positively by incorporating social and affective elements in the students-teachers relationship [32, 35, 36]. After listening to my unique stories and experience (e.g., the failure in public examination, an identity crisis story in my freshman year of university), students perceived their teacher to be friendly and approachable. This reduces the distance of teacher-student relationship and fosters the establishment of a warm and supportive environment [37], thereby enhancing students’ understanding of the teaching materials [38-40]. The above influences are reflected in the qualitative post lecture evaluation:

“A very important lecture. Your personal experience is important. It let us know that we are not alone.”
 “It is great to hear the lecturer’s own story because it is so real and encouraging.”
 “Your sharing is very important as it helps us better understand the topic. Every lesson is a chance to build a relationship with you. Enjoy your lesson!”
 “I really love to listen to your sharing...just like listening some meaningful stories. I enjoy this lesson very much!”

GENERAL OUTCOMES ON STUDENTS LEARNING

By using the above strategies, students’ learning process was enhanced by raising their self-awareness. For example, through the in-class self-reflection exercises, students were encouraged to reflect their thoughts and to take an active role in constructing their understanding. They become more self-aware by evaluating their strengths and weaknesses. This is aligned with the holistic education by assisting students to develop a reflection practice as a life-long process [41]. This is reflected from the qualitative evaluation:

“This lesson helps me reflect on my own values and find meaning in my life.”
 “I know more about my personality. I need to be more active and less fear to express myself openly.”
 “Every lesson is a good chance to know more about myself. It encourages me to face my future. I want to achieve something after graduation.”
 “I learnt something new today. The lecturer told us that there is no reason that we put ourselves down. I should be more confident.”

Encouraging Students to Reflect on Their Own Experience and Promote Their Profession Development

Through the cooperative learning, students were asked to work together and held accountable for their learning. This promotes cognitive changes in their thinking and learning [32]. Furthermore, through the use of teachers' self-disclosure, the process of transforming abstract conceptualization ideas into a concrete experience was improved. Students were able to perceive the connection between the lectures and real-life experiences and to apply the knowledge in other contexts. They were motivated to reflect on their own strength and weakness and to achieve personal goals in the future. This is reflected from the qualitative evaluation:

"It is a meaningful lecture as it gives us a chance to reflect on our emotions. Emotion management is very important but people often ignore it in our daily lives."

"Today, I learnt some emotional management skills, which are essential in my career."

"After this lesson, I learnt that controlling bad temper is really important. I decided to write my own journal to capture my emotion. I hope I can see sunshine every day."

"I love the part that you share your own story. It is interesting and inspiring. I believe that everyone is special and his/her story is unique. Listening is an important skill in hospitality industry. And it is my interest."

"The reflective activity helps me to recall my past experiences, which makes me have a clear view about my life in the future."

The above qualitative evaluation states showed the cognitive changes in the process of learning, which is important to the development of higher-order of thinking [42]. Students were encouraged to connect the lecture materials to their past personal experience or major life events related turning points in their life. They became more actively reflect on their own learning experience and focused on their personal and profession development. They were able to make the content they learned in the class in a meaningful way and to use it later in other contexts.

BENEFITS TO THE TEACHER

In the field of teacher education, there is an increasingly emphasis on the integration of teaching and reflection in practice. Through this continuous self-evaluation process, I reconstruct my teaching practice and searched for new solutions to meet the needs of the students [43]. I deliberately searched for a mindful solution once problem is identified, thereby leading to ongoing and deeper understanding of teaching [44]. It involves self-directed thinking and ongoing critical inquiry of my practice and helps me better understand how my thinking, beliefs and values affect my behaviors [45].

As noted by Loughran [10], both "seeing" and "action" are essential elements of effective reflective practice. Using my experience, intuition and values during teaching, I tried out new strategies relating to my profession and reflecting upon students learning processes [46, 47]. I became more sensitive to students' response and searched for solutions and other instruction tools to meet their needs and to promote their learning.

"When self-disclosing, gathering feedback from your students is one way to gauge the effectiveness of the amount you disclose" [29]. When reading their post-lecture evaluation

feedbacks, I gained feelings of social intimacy from the students. It ensures my disclosure is well received and suitable to the lecture topics. It also helps me reduce anxiety and uncertainty about the appropriateness of my self-disclosure. It also provides a trust environment for the students to disclose themselves through the written feedbacks [39]. This motivates me to search for another new solution to address this new facing problem.

This reflective practice encourages me to reflect upon my previous experiences in order to improve my teaching. This method is also used during out-of-class communication (e.g., chatting with teachers after class). It provides me another effective instructional tool to produce a positive learning environment that is conducive to student and teacher learning. This supports the notion of the inclusion of social and affective development between students and between teachers and students through cooperative learning [14, 31, 32].

CONCLUSION

With the overemphasis on academic and vocational training, more effort is needed to promote the personal development and learning [48]. Holistic-oriented course is important to nurture an individuals' potential in terms of the cultural, moral, spiritual and interpersonal aspects of their lives. Under this learning atmosphere, students are asked to take an active role and engage in the learning process in order to expand the concepts in an interactive and creative manner [49]. They are asked to integrate what they learned in the class to real-life situation and apply to everyday life. This experiential practice challenges traditional educational practices, which rely heavily on lecture as the only method of class instruction, and deepens students' learning by building the connectedness of materials and transforming later in other contexts to other various aspects including moral, social, emotional, and physical of learning [27, 31].

With the assumption of lecturing equals learning [50], the traditional lecture format, which is characterized by students' passive note-taking behavior, challenges my view of teaching by encouraging me to reframe and seek alternative ways of approach to my teaching practice. It enhances a greater sense of understanding of the given situation by reshaping my approach on teaching practice. I become more willing to listen to other's opinions and views, to take responsibility to change and to explore ways to meet students' needs. These changes improve the development of my attitudes and profession [51].

In line with Farrell [43], through the reflective teaching, I continuously recalled and evaluated my teaching experiences in order to improve my performance in the future. As reflective practitioner, effective teachers emphasis on improving teaching through questioning and evaluating their teaching practice. The importance of reflective teaching has been examined, particularly with the emphasis on student learning outcomes [52]. Little is known its beneficial effects on teachers. The present study provides a case study on demonstrating how a teacher utilizing reflective capabilities (e.g., identifying problems, gathering information, searching and experimenting solutions) when teaching a holistic leadership program. It highlights the role of reflective practice on teacher professional development.

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Chapter 166

REFLECTION OF A TEACHER

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ABSTRACT

“Tomorrow’s leaders” is a general education subject aiming at promoting holistic development of undergraduate students in The Hong Kong Polytechnic University. In this chapter, the author presents her views and reflections on teaching this subject during a two years period. Successful experiences and lessons learned in terms of the curriculum design, ways of building relationship with students, and the application of experiential learning in this subject were shared. It is highlighted that teacher’s reflective practices are fundamental for promoting students’ effective learning and teacher’s personal development.

INTRODUCTION

For a two years period, I have been teaching a leadership subject, “Tomorrow’s leaders,” for first-year undergraduate students at The Hong Kong Polytechnic University. As a general education subject, “Tomorrow’s leaders” attempts to promote leadership and intrapersonal competencies in university students in Hong Kong [1]. While this subject was piloted twice and multiple evaluative strategies have suggested its desirable learning outcomes in terms of the holistic development of university students [2-7], it puts a few challenges to me. First of all, starting from 2012/13 school year, “Tomorrow’s Leaders” became a compulsory course. All freshmen at The Hong Kong Polytechnic University are required to take this subject, which, like other compulsory subjects, inevitably results in reluctance in the students to attend the course, particularly for those who major in “hard science.” Second, this subject is featured by the incorporation of various class activities based on the theory of experiential learning.

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Students are provided with different opportunities to understand, practice and reflect on the knowledge and skills learned in lectures. It is very important for the teachers to find out methods to actively engage students in these activities so as to have desirable learning outcomes. Third, the aim of the subject is to promote students' all-round development in different domains of one's life which makes one's in-depth personal reflection a precondition to learn well in this subject. This is quite different from the subjects I taught before. Basically, self-reflection is the capacity to introspect originated from the willingness to learn more about oneself. How could I force the students to reflect on themselves if they do not have strong self-motivation? At that time, all these challenges created much anxiety in me.

The teaching period passed quickly and I found myself growing with my students in the process of teaching this subject. It does not only promote the development of my students, but help me to become a more mature and reflective teacher. In this chapter, I would like to share a few experiences and reflections in three aspects in my teaching, curriculum of the subject, building relationship with students, and the application of experiential learning. With these reflections, my understanding about teaching has been deepened and meanwhile I gained more confidence in my abilities as a teacher.

CURRICULUM OF THE SUBJECT

The primary objectives of the subject "Tomorrow's leaders" are to train students to develop and reflect on their intra-personal and interpersonal qualities and promote students' active pursuit of knowledge for becoming a responsible and contributing citizen [1]. Guided by these objectives, an integrated curriculum was designed which comprised 12 interrelated topics focusing on different aspects of positive development in university students, including self-understanding and personality, cognitive competence, emotional competence, resilience, spirituality, morality, positive and healthy identity, social competence, interpersonal communication and conflict management, relationship building and team building, mental health, and self-leadership. Utilizing various evaluation strategies including objective outcome evaluation, subjective outcome evaluation, qualitative evaluation and process evaluation, it was found that the subject was able to promote the holistic development of university students in Hong Kong and that students generally like this subject and have positive perceptions about the curriculum [2-8]. These findings suggest that overall the curriculum is successful in arousing students' interests and helping to achieve the learning objectives of the subject.

While I was teaching "Tomorrow's leaders," one of my observations was that students were quite attentive and participative in most classes but once in a while some students showed boredom and uninvolved. Apart from students' personal reasons (e.g., physical discomfort, tiredness, etc.), one factor that may lead to this phenomenon is that the teacher failed to make meaningful connections between the curriculum and students' lives.

Students are always attracted by cases and examples that are directly related to their own lives. Like Peterson stated [9], "a teacher cannot build a community of learners unless the voices and lives of the students are an integral part of the curriculum." (p. 30). One of the most welcomed topics in this subject is "social competence" and the related lecture really links the topic to the lives of university students well. After an introduction about a theoretical

model of social competence (i.e., three basic components of social competence), a real case was shared with students about a master's degree holder who failed to find a job in three years after graduation from a famous university in Hong Kong. Students watched a video clip and then were asked to discuss the reasons why this person with high IQ could not secure a job using the model learned in the lecture. They were also encouraged to reflect on themselves in terms of their own social competence. Students showed strong interests in this case as it is so close to their present lives. They might have to face the same problem when they graduate. The group discussion on this topic was very hot and many students were able to analyze the case from different perspectives. They also reflected that they became more aware of the importance of one's social competence than before. Some shared that they shall try the methods learned in this subject to develop their own social competence in daily lives. As such, this case study successfully helped students understand the concept of social competence, its importance, and promoted students' active pursuit of knowledge.

Another experience is about teaching the lecture on spirituality. At first, the concept of spirituality was introduced in terms of its key elements, i.e., connectedness, personal beliefs and values, and meaning of life. Many examples were given to facilitate students' understanding about each element of spirituality and the teacher also shared her own spirituality in different aspects. However, students still appeared to be confused and bored about this topic as it seemed to be too far away from their lives. Quite a few students had never thought about these "philosophical questions," such as "the meaning of life." I have to confess that in the first semester teaching this topic was a "disaster": students looked sleepy, tired, and non-responsive though I'd tried all means to "warm them up." I was also exhausted after the teaching. This experience motivated me to ponder: in what way could I concretize this abstract concept and make it more relevant to students' lives? Working together, my colleagues and I designed a new activity called "an auction of dreams" by which we attempted to illustrate the concept of spirituality in an easy-to-understand way and also give students time to reflect. In this activity, students were provided with opportunities to bid for one or more dreams from a series of ten items (e.g., "a flat," "a stable job," "an outstanding talent," and "a position in the Government that can influence the education policies," etc.) with a limited number of "magic bars." They were first asked to choose three dreams they wanted to achieve most and list the reasons. When the auction game started, students bid for their favorite dreams and the person who gave the highest price (most magic bars) would get the dream. As the quota for each item is limited, students have to strategize about how they can successfully get the item. After the auction, several reflective questions would be further proposed for students. For example, "what are the things that you value the most in your real life and why are they important," "how do you invest for your dreams," "are you satisfied with the dreams you've got? Why and why not," etc. By reflecting on these questions, students realized that there is always something they value behind their dreams; it could be the connectedness with people or the high being; it could be the meaning and purposes of one's life, or one's personal beliefs, etc. And all these constitute one's spirituality. In this way, students obtained a better understanding about the topic and also a deeper self-understanding.

In addition to making the curriculum relevant to students' lives, more efforts could be made in connecting the subject content to the current world. Showing students the relevance of what they have learned in the subject to the society broadens students' horizon and further motivates them to pursuit and apply the knowledge. This shall also be the responsibility of a

teacher. In my classes, I found that students are particularly interested in discussion on current social issues in Hong Kong and the International society as well. For example, in teaching morality and ethics, we had a fierce group debate on a classic case of moral dilemma, Heinz's story, in which students showed great participation. Despite of this, students expressed that although the lecture was very intriguing, they wish to have more discussion on controversial issues that currently exist in our society, for example, the genetically modified food. I tried to bring this topic for group discussion in another class and not surprisingly students demonstrated diverse perspectives based on their understanding of morality and ethics; they also shared that they really enjoyed the discussion and have more interests to self-study morality and ethical issues. In fact, every topic of "Tomorrow's Leaders" could be readily connected to the current world and university students' lives. Teachers shall strive to make such connections as much as possible, and this will greatly contribute to effective teaching and learning.

BUILD RELATIONSHIPS WITH STUDENTS

The importance of positive teacher-student relationship for students' academic achievement and personal development has been stressed in numerous studies [10-13]. Researchers suggested that teachers who have personal involvement with students show them that they are respected, valued and cared [14, 15]. These feelings motivate and engage students toward improved academic performance and positive development [16, 17]. According to Payne [18], most children do not fail because of their cognitive abilities but because they feel unwelcome, detached, or alienated from significant others in the educational environment. The relationship between a teacher and a student serves as the foundation for the student's learning and largely determines the student's successes or failures in the subject. There is no exception in teaching "Tomorrow's Leaders" although we are facing "successful" and "mature" university students. In my classes, students appeared to more willing or happier to learn, to share, and to express different opinions when they felt comfortable and safe in the learning environment, which depends largely on a good teacher-student relationship.

Get to Know Students

Getting to know students is the first step for building positive teacher-student relationship. From the beginning of a semester, I try to remember every student's name. Calling a student by his or her name gives the student the feelings of being valued and important. Like one student from the Department of Physiotherapy shared:

"What impressed me most is that the teacher could remember all of our names which I did not think any university lecturer is able to do so. This makes me feel respected and pleased when she is able to call my name... Attending lectures of 'Tomorrow's Leaders' therefore becomes one of the things I look forward to every week."

However, it is not easy to recognize every face in the classroom especially when you have several classes with each consisted of more than 60 students. There is one activity which

I found helpful. Usually in the first lecture, I asked every student to write down three words to describe oneself (such as a hobby, one's appearance, or personality traits). Then students would take a group picture in which one must show at least one characteristic that he or she just described him/herself. In a self-introduction session, students would introduce to their group members how this picture showed one's unique characteristic(s). A group coordinator would then send me their group photo with all members' names as well as their respective descriptors being marked out on the picture. With these materials and a few times of practices in class, I would be able to recognize every face of my students and also create a short student information sheet which tells me at least one aspect of each student. In the following lectures, I would try to talk to different students as much as possible. Every time when we have self-reflection exercises, or individual work, I would add the materials to the information sheet. These exercises help me gradually know my students and develop interests in their individual lives.

Show Care and Respect to Every Student

Simply knowing students is not enough. What's more important for teachers to build a true bond with students is to show them care and respect [19]. In my own teaching, I also found that it was not until I genuinely show my care and concerns to the students that they started to trust and depend on me. Interestingly, when students feel the care and respect from the teacher, they also learn to respect and care about each other. This, to a large extent, contributes to cultivating a secure and positive learning environment where students are comfortable to answer or ask questions, to participate in various activities, to share their views and feelings in front of the whole class without being worried about that someone may laugh at them. The mutual respect between students and the teacher also serves as a foundation for good classroom management. Students would more readily accept disciplinary actions when they violate the classroom rules, for example, the deduction of participation score due to lateness or absence. Like Jones put it [20], "if the students like you, they will go along with almost anything" (p. 191).

Admittedly, every teacher has challenging students in class, who are more difficult to make connection with. In teaching "Tomorrow's Leaders," one problem that I have to face is that some students are "required" to take this compulsory subject although they have no personal interests. Most of them would show passive aggression, for example, come late for class; keep silent in group discussion; do other assignments in lecture time, and take a casual attitude towards class activities, etc. These students' behaviors usually change after a few lectures, when they start to experience the benefits of the subject, such as a friendly atmosphere of learning, the care of the teacher, interesting knowledge that can be readily applied in their daily lives. However, there may still be a small number of students who remain the same, if not worse. Even I have gone out of my way to show the students that they are liked and valued; it seems that they just don't buy it, which made me really frustrated. For many times, I asked myself whether I had done anything wrong with the students; where my problem was; why these students didn't recognize my efforts and hard work; how I could make the students like me, etc. The obsession with these self-doubt questions and the negative feelings disturbed my teaching by slowing down the pace of the whole class, shifting my

attention away from the majority, and so forth. At the same time, the grudges I hold prevented me from developing truly positive relationships with the challenging students.

In my reflection, I was inspired by Tauber [21] who pointed out that teachers shall not take a student's negative behaviors personally because the problem is with the student, not the teacher. This is a good reminder for me. Instead of focusing on finding faults in my teaching, I shall make more efforts to understand the students. I found that when I dropped all grudges, took a personal interest in the students and genuinely cared about them despite their inappropriate behaviors, the connections between the students and me were gradually established. They started to show a less negative view towards the subject and become more and more participative in lectures. Meanwhile, the established connections with the teacher and other students supported the challenging students to reflect on their past experiences as well as their current behavioral patterns. Like one student from Faculty of Engineering shared in his reflection,

"To be honest, when I first enrolled in this course, I hate it...I really didn't think that the lectures are useful for me or my career...it's just a waste of time... my views gradually changed as time passed by...the teacher is very caring and patient to all students...though sometimes my behaviors may disappoint her, she always forgive me...after today's lecture, for the first time I started to think about the person who I really am... my arrogance...my relationships with others..."

Borba [22] said that people "all need to feel a sense of connectedness to another human being—particularly to those whom we consider to be important and significant" (p. 163). In classroom, teacher-student relationship can make the greatest difference. It is gratifying to see this miracle happens in my class.

EXPERIENTIAL LEARNING

Experiential learning represents a pioneering pedagogical approach based on the central principle that people learn knowledge by constructing the knowledge themselves [23]. It is believed that if the students do not participate in an active learning process, i.e., their brains do not process the things that their teachers delivered, the learning results would be limited [24]. In "Tomorrow's Leaders," a highly interactive teaching and learning methodology is adopted to facilitate students' experiential learning. For every lecture, various types of games and activities were incorporated into the curriculum. There are video watching and discussion, news sharing, self-reflective writing, team debates, role plays, group projects such as collage and poster making, as well as individual and group presentations. Students are provided with abundant opportunities to discuss and report their views toward various issues, to role play different scenarios, and to reflect on and share one's feelings and experiences. For example, in the lecture about resilience, a video clip of Steve Jobs' speech at Stanford University was played in which three stories about Jobs were told. Students were asked to pick up their favorite story and explain what insights about resilience they obtained from the story that can be applied to their current lives. A few students would be invited to share their opinions in class. In such an activity, students have to link the concept of resilience to the experiences of Steve Jobs based on their own understanding and actively explore the importance of resilience to their own lives. They also have to organize these views and reflections in order to give a short presentation. As such, students construct the knowledge by

themselves instead of passively receiving the information from the teacher or the lecture notes. This has also trained students' critical thinking, effective communication, and problem solving abilities, all of which are regarded ideal attributes of university graduates [25].

Motivate Students' Participation with Praise and Support

Unquestionably, this highly interactive teaching and learning approach requires students' active participation, while for first-year undergraduate students, particularly those who just graduated from secondary schools where the medium of instruction is Chinese, speaking in front of the whole class in English is intimidating, not to mention discussing or sharing one's inner feelings. In my own teaching, students' participation has been greatly improved by providing them enough praise and unconditional support.

Recognizing student's effort in learning is one effective way to improve students' motivation to learn [26]. When students failed to perform well, support from the teacher motivates them to keep trying without being defeated; while if students perform well the teacher's sincere praises encourage their further learning. In my class, it is not uncommon to see that students cannot express clearly about their opinions when answering a question or reporting the results of group discussion. Providing timely assistance (e.g., further clarify the students' points of view) is important to support the students to complete the task successfully. This also helps regain other students' attention. One of my common practices is to always highlight a few good points in the students' performance and invite other students to give the presenters a big hand. This communicates the teacher's confidence in the presenting students' ability and also nurtures a culture of mutual-respect and appreciation in the classroom. Following this further, after every lesson, I would write an email to the whole class to summarize the content of the lecture, appreciate the participation of every student, highlight the performance of a few students/groups, and invite them to ask questions related to the topic. This practice further enhances the teacher's recognition for students' active participation and helps to maintain a good teacher-student relationship.

Another reflection on inviting students' participation in class activities is that all students shall be called on impartially. Often, we tend to call on a small number of students who are active and responsive while allow few chances for students whom we have low expectation for. This may cause some students lose self-confidence in their ability and interests in the subject because they believe that the teacher doesn't expect them to be able to answer the questions or perform well. To monitor myself in providing all students with equal opportunities, I often put a check on the name of the student or group I call on during class discussion. Such a record helps me to notice those students whom I gave less attention to so that I will call on them in the next discussion. Over time, some passive students in my class actually become active students, like one student from Broad Discipline of Computing shared with me in her email,

"For many students like me, we are so afraid of speaking in front of many people. We feel scared that we would say some inappropriate words or make funny mistakes and be laughed at by others...I used to keep silent in class or avoid eye contact with the teacher when she invites students to answer questions. However, in Tomorrow's Leaders' class, every student has a lot of chances to talk in front of the class...when I have the chance to speak...I can practice more...and I build up my self-confidence when the teacher and my classmates applauded for me. I found myself less scared and more enjoyed about representing my group to report in class."

Teachers' Self-Disclosure

The role of the teacher is no longer the knowledge transmitter but the facilitator in experiential learning [27]. While the topics taught in “Tomorrow’s Leaders” are all interpersonal and intra-personal qualities which everyone encounters almost every day, the teacher’s self-disclosure can go a long way facilitate students’ learning. By talking about oneself and sharing personal feelings and beliefs, the teacher demonstrates how he or she understands a particular issue and how personal insights could be gained from reflective practices.

In my own teaching, I found self-disclosure a powerful tool, when used appropriately. It deepens students’ understanding, increases their trust in the teacher, motivates them to share more about themselves and take a more active and serious attitude towards learning. Many students expressed that the clarity of the knowledge points is improved when I use personal experiences as examples. For instance, while I was teaching Marcia’s identity development theory [28], I shared with students how I achieved my own identity as a student majoring in psychology using the model: how I explored different possibilities in regard to my career when I was a undergraduate and finally make my commitment. Students felt much easier to understand the theory after listening to my case. They were also more readily to apply the theory in analyzing the process of their own identity formation and find out their problems which shall be further resolved. Sometimes I am not just disclosing myself, but talking about my family, experiences of previous students, my friends, their lives and personal problems. The various topics increase students’ interests and motivation. Many times after my self-disclosure, students shared that they gained insights about their own lives and wished to have more such cases in other lectures, like one of my students from the Institute of Textiles and Clothing wrote in her reflection:

“I really appreciate the teacher’s sharing about her own experiences and the stories of her previous students. This helped me to understand the topic well and gave me the courage to reflect on myself...Knowing that I am not the only person who has the struggles makes me feel less lonely...it’s fine to have problems and to make mistakes... I wish to hear more such stories in the next lecture.”

On the other hand, when teacher’s self-disclosure is not well planned / prepared, it may not be effective in facilitating students’ learning, and sometimes may cause negative perceptions of the teacher by students. In teaching the lecture “emotional competence,” we designed an activity called “life line,” in which students were invited to recall their memories on one happiest and one saddest events in the past and reflect on how these events affected their present lives. To demonstrate how this activity can be conducted, I shared one of my saddest experiences, the passing away of my grandma. Without being fully prepared, I burst into tears in front of the whole class while talking about this traumatic event and it took me quite a while to recover and continue the lesson. This obviously affected students’ participation in the activity because their attention was shifted from the activity to the teacher’s emotion. One lesson obtained from this experience is that teachers shall consider to what degree and how much personal experiences they can disclose to students when preparing for class. Although a teacher’s self-disclosure could be a very effective method to facilitate students’ experiential learning, we should do this appropriately with good preparation.

CONCLUSION

The experience in teaching “Tomorrow’s Leaders” has also changed me both as a teacher, and as a person. First and foremost, my views about teaching have been transformed. Trained in traditional teacher-centered educational environment, I used to believe that a good teacher’s job is to clearly disseminate knowledge and students have the responsibilities to absorb the knowledge if I have done my job. I was able to deliver a lecture with clarity, explain a concept/theory with many examples, answer students’ questions effectively, but I didn’t have much know-how on students’ active learning and teacher-student interaction. With the well-designed interactive curriculum of the subject, frequent discussions with colleagues, constant practices of different methods, and most importantly, many times of reflections on my teaching in each lecture, I have gradually understood the essence of student-centered approach to teaching and learning, i.e., to “produce learning through student discovery and construction of knowledge” [29]. In this process, I’ve also learned a few methods to actively interact with my students; for instance, using different types of questions (e.g., survey the class, rhetorical questions, brainstorming, etc.) to stimulate students’ thinking and interest. By shifting the focus from teacher’s teaching to learner’ learning and taking into account each student’s interest and individual style, the teacher can actively involve students in the learning process and desirable learning outcomes can be then achieved.

Secondly, reflection on teaching the subject deepened my self-understanding and made me a more mature person. One insight I have gained is about my fear for interactive teaching. In the beginning of the first semester when I taught this subject, I had a million reasons not engaging in interactive lectures: games and activities are too childish for university students, I was trained in research not teaching, sacrificing important content for interaction is not worthwhile, etc. Deeply inside, however, it was the fear of losing control when conducting this type of teaching that disturbed me. I cannot accept myself losing control of the students or the class. I was afraid of not being able to deliver all of the important content in time, not knowing how to respond to some “unexpected” questions students may ask, getting no response from students when asking a question, or being dominated by a certain student group in class, etc. With reflection, I realized that all of these hypothesized situations are in fact acceptable in teaching and I don’t have to be perfect in order to become a good teacher. To conquer the fear, the first step may be to learn how to fully accept myself without any condition, i.e., I can make mistakes and this would not change the fact that I could still be a good person. This helps! When I let go of my anxiety and fear, when I be the true person who I am on the stage, I start to enjoy the interaction with my students, and I can tell from the students’ faces that they also like me in this status.

Last but not least, in preparing for my teaching on numerous issues to be discussed in this subject, I have been reminded of my responsibility as a social scientist when I have to spend time in searching for educative issues in our society and trying to analyze them from different perspectives. As a researcher, I used to focus too much on my personal interests when selecting a research topic, while take little concerns about social influence into account. Teaching the subject makes me being further aware of the implication of scientific research to the society. By performing rigorously designed studies on important social issues, and disseminating the findings, we are able to educate the public, influence policy making, and

eventually make the world a better place. The discussions with my students in class also inspired me to explore more on current issues in Hong Kong society, for example, views about morality, democracy, the general election, the Hong Kong mainland conflicts, etc. This has largely broadened my research interests and areas.

In one of the seminal books on teaching and learning written by John Biggs [30], it is said that for teachers “learning new teaching techniques is like the fish that provides a meal for today,” while “reflective practice is the net that provides the meal for the rest of one’s life” (p. 7). Similarly, Grant and Zeichner [31] argued that as a teacher “you may be able to get by, by putting little thought into your work, but if you want to strive to be the best teacher that you possibly can, there is in reality no alternative to reflective teaching” (p. 110). Reflection on teaching “Tomorrow’s Leaders” helps me to understand my students, their behaviors, needs and concerns and use this understanding to consciously guide my teaching; it also enables me to make sense of myself, what I have done in a classroom and the reasons behind, and to explore the potential impact of my action on students and myself. Moreover, if we aim to educate our students to be thoughtful about their life and eventually become an active participant with independent mind in nowadays society, the place to begin is with us and reflection plays an integral role in this process [31].

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Chapter 167

REFLECTIONS ABOUT “KNOWING THYSELF”

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ABSTRACT

This chapter aims to provide insights gained from teaching a subject on leadership and intrapersonal development in the university setting. The teacher reflects upon how her previous working experience influenced the teaching of the subject and the development of professionalism in the university setting. It is concluded that a teacher has to first understand and know oneself and this self-awareness benefits student learning.

INTRODUCTION

“Know thyself” Socrates (469-399BCE)

This quote appears in the first lecture of “Tomorrow’s Leaders”, the subject on leadership and intrapersonal development in the Hong Kong Polytechnic University (PolyU), to share with students about the importance of self-understanding in developing one’s own potentials and aspiration in leadership. This quote also serves as a reflective remark of my teaching of the subject “Tomorrow’s Leaders” in the past two years. To “know myself” is not only to understand my role of and reflect on the teaching this Subject, but also to understand the personal growth throughout the process and accept who I really am while I am facing genuinely with my limitations and strengths in teaching this subject. Students are invited fervently to have reflections throughout the learning journey in this Subject. It is essential, too, for me as a teacher to reflect on the teaching and the personal growth in teaching the subject “Tomorrow’s Leaders”.

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In responding to the drastic change of the academic structure in Hong Kong, the eight public Universities have formally transformed the structure of the undergraduate education from three years to four years starting from the academic year 2012-2013. This change urges the universities to think how to better cater the needs of the “younger” university students and thus the students would better adapt to the university environment. As such, all eight universities in Hong Kong developed new general education curriculum in each of the new four-year undergraduate curriculum. PolyU is of no exception. “Tomorrow’s Leaders” is one of the subjects in the general university requirements (the general education curriculum in PolyU) under the component “leadership and intrapersonal development”. Although there have been certain levels of leadership training in the secondary school, there is an increasing demand for the universities to nurture future leaders, especially leaders with personal qualities. What makes the subject “Tomorrow’s Leaders” unique is our belief in strengthening the “within” of the students and sharpening their awareness of their potentials and competencies to be the self-leader first and then to lead others. “Tomorrow’s Leaders” is the universal subject for all freshmen in PolyU and teachers would be meeting students from all the disciplines. This poses challenges, at the same time opening up opportunities, for the teachers to review their teaching methodologies, pedagogical arrangements and delivery of the subject and student-teacher relationships under this arrangement.

In view of professional development, teachers’ reflection on their teaching practices and experiences is crucial for the development of expertise. Coombs [1] denoted that “teachers need consciously to think about their experiences if they are to learn from them” (p. 63). Reflections help teachers to have new awareness of their teaching routines and thus to make analytical and adaptive plans to improve the teaching quality. To have a systematic yet insightful reflection, teachers could have “reflections-in-action”, “reflection-on-action” [2] and “reflection-for-action” [3]. “Reflection-in-action” refers to an individual’s ability to think about what is happening during the course of teaching. Teachers reflect upon “on the spot” situations and make immediate responses to react proactively in class. For “reflection-on-action”, it refers to the intentional revisit of the episodes or critical events happened in class for reflection. And the third type of reflection, “reflection-on-action” is the process on past actions and decisions as a means to guide future practices. In my personal experience in teaching the subject “Tomorrow’s leaders”, these three dimensions of reflection assist me in “the process of becoming” [4]—becoming more sensitive to the students’ needs; becoming more professional in delivering the subject contents; and becoming more sensible in understanding the roles of a university teacher and a researcher. This piece of reflection is not only reflecting on the teaching of a single subject, but also reflecting upon the role of a university lecturer and the meaning of quality teaching.

GETTING BEHIND THE MASK

Rogers [4] suggested in his book “On becoming a person” that there were several “steps” to let an individual understand his or her own growth pathway, which are (a) getting behind the masks; (b) openness to experience; (c) willingness to be a process; and (d) internal locus of evaluation. This piece of reflection is adopted these few steps as the framework of reflecting my own identity as a university teacher and an academia in the university setting.

Understanding the “masks”—the well-understood practices or beliefs—behind is the first step that facilitates an individual’s discovery of something more basic and something more truly in his or her life. I have been teaching in the secondary school setting in local context for ten years. This experience has equipped me with both knowledge of pedagogy and practice wisdom in educating adolescents. The experience marked an end with another start—teaching “Tomorrow’s Leaders” in the PolyU. This transition urges me to think of my role here as a teacher in the university setting. The initiation to reflect on well-established beliefs suggested by Rogers is applicable to me in such sense. As being engaged in teaching in secondary school for quite a long time, a set of educational principles, beliefs and values for adolescents has been developed in my career. On one hand, these convictions serve as the consolidation of previous teaching experience and let me have a better personal teaching efficacy [5]. On the other hand, these well-established thoughts might blind me from being aware of the growth—as I might have a thought of “have grown already”—and getting in touch of the real inner self. It is crucial for me to revisit these well-established convictions and search for their meanings on my present career.

“Florence is willing to care for each student, no one in this class feel ignored during lessons. She shared a lot of experiences that she had and help us know more about the application of the skills to the daily life.” (Student Feedback Questionnaire, APSS1L01, 2012)

“Florence is really kind and helpful, which I could feel her unconditional support towards students’ responses.” (Student Feedback Questionnaire, APSS1L01, 2012)

The interpersonal context, especially in the higher educational setting, has been often overlooked as lecturers’ expertise and “satisfied content or curriculum delivery” are determinants for effective teaching [6]. University lecturers are driving greater emphasis on the content delivery with incorporation of research findings and being less engaged in establishing relationships with students. In addition, getting too close to students and revealing self in lectures is perceived as “unprofessional” and “emotional” in university teaching [7]. However, research in recent decade finds that teachers’ self-disclosure positively affected the cognitive learning of students and there is no change in students’ perceptions of competence of teachers who frequently self-disclosed in higher educational setting [8]. Teachers’ self-disclosure is encouraged in teaching Tomorrow’s Leaders and this teaching methodology helps foster students’ capacity for self-awareness and teachers’ empathic understanding of students’ sharing. The disclosure should be an arranged one with considerations of relevancy to the subject materials, motives of sharing and teachers’ credibility. The teachers’ self-disclosure should not be a mere personal sharing of thoughts and feelings [9]. This comment from the Student Feedback Questionnaire (SFQ) recognized the help of my personal revelation of experiences on his or her daily life and my self-disclosure is shown to increase student perception of the relevancy of the subject materials.

Despite the encouraging comment of the help of self-disclosure to the students, the word “care” triggers me to go beyond the mask and reflect on my teaching style and the student-teacher relationships in the university setting. Providing caring and warm learning environment is the major task of elementary and secondary schools. The caring and warm environment provided is to cater the developmental needs, especially development of different life skills in aspects of personal, social, career aspiration and academic development of children and adolescents. A parent-like or mentor-like teacher with caring attitudes is

crucial for nurturing personal assets and strengths for children and adolescent in their primary and secondary schooling [10]. As a secondary school teacher, I was used to “taking care” the students in or outside classroom and was acting like a “parent-like” or “mentor-like” school teacher. The affective learning environment facilitates and benefits students’ growth and teachers’ professional development in nurturing youngsters in the frontline educational field [9].

However, in facing the young adults in the higher educational setting, the meaning of “care” has to be revisited. Most of the university teaching focuses on acquiring knowledge and learning theories. Teaching excellence in higher education is defined as the demonstration of lecturers’ or professors’ expertise and teaching students at an appropriate level [6, 7]. Caring about students is seldom addressed in university teaching as liberty and self-discipline is emphasized in higher educational setting. There is scant literature in exploring the issue of establishing a caring and supportive classroom or class milieu in higher education setting. Student’s comment about the care I have given in class urged me to doubt if students’ personal growth is undermined with my caring attitude and question if I am just performing as a secondary school teacher rather than a university lecturer. There was a fear of not catering the genuine needs of the students. However, students’ assurance of my care to every student, or as McCroskey and Taven [11] suggested the “perceived caring”, is seen as goodwill that opened the communication channel more widely in the classroom. Acknowledging students’ needs by providing care and the openness for communication is especially crucial in teaching “Tomorrow’s leaders”. These would provide a trustworthy and safe environment to help increase students’ motivation of sharing and reflecting upon themselves. Teachers’ care and expressiveness can contribute the teaching effectiveness by maintaining student interest [12]. And I believe that quality teaching in any of the level in the education system is not primarily an accomplishment in appropriate planning, excellent teaching technique and thoughtful pedagogical moves, but “as a lived accomplishment that is intimately linked to the way” students live their lives [13].

The reflection upon the “care” also sheds light in understanding the student-teacher relationships in university setting. Student-focused approach, for example devising teaching plan focusing on changing and developing students’ understanding; teaching at an appropriate student level; and thinking from students’ perspectives, is highly appreciated in educational setting across primary, secondary and tertiary levels [14]. The focus on students’ needs in planning the pedagogical arrangements definitely helps develop students’ conceptions and understanding of the subject matter and foster self-initiated learning [7]. Besides the pedagogical arrangements, student-focused approach to teaching also caters the developmental needs of the students, despite the level in educational system. The students enrolled in the subject “Tomorrow’s leaders” are all freshmen and “Tomorrow’s Leaders” might perhaps be the first university course they have attended in their brand new university lives. The frustrations and anxieties aroused from the adaptation to new environment might need someone to listen to. With the self-disclosing and trustworthy classroom atmosphere in the class of “Tomorrow’s leaders”, students might have shared their worries and frustrations verbally or non-verbally. There was a student sharing in the lecture “resilience” that his happiest and saddest incident is “entering the university”. I understood how this mixed feeling frustrated him and responded verbally in class of this complex feeling. At the same time I noticed some other students’ non-verbal cues, such as nodding and raising their eye brows when listening to this sharing. During the time for group sharing, I went into those groups and

listened to the students’ sharing of the issue or other related concerns. The personal authenticity in which teacher’s real human presence encouraged students to look inwardly to what their genuine needs are. Being a teacher, I have to be aware of how to understand the students’ concerns, empathize students’ views and accept them as valid views, and react to students’ communicative attempts in class accurately and quickly. The relational exchange and the understanding of their feelings connected the teacher and the student and this sense of “togetherness” nurtured a trustworthy student-teacher relationship. This might be echoing with the student’s comment of “unconditional support towards students’ responses”.

OPENNESS TO EXPERIENCE

As a teacher receiving traditional subject-based pedagogical training, my training in the educational field has limited relevance to the teaching delivery in higher educational contexts. Fortunately, some sessional and part-time university teaching has enabled me to continually improve my teaching delivery in university settings and the research conducted in my doctoral degree in relation to Positive Youth Development has enriched me with theoretical understanding of psychosocial competence in some extent. However, teaching leadership attributes with reference to the positive youth development and other related psychology theories and models [15] is still a challenge to me, especially in the time of both career and workplace transitions. Being open to the experience is another step to understand an individual’s growth and changes and challenges inspire teachers to be emerged from one’s inwardness and thus search for the best in teaching and learning [16]. Having substantial preparation both cognitively in understanding the concepts and knowledge of the subject and psychologically in facing challenge is the start. The lecture materials for “Tomorrow’s Leaders” were well-developed by the curriculum team and the lecture notes were ready-for-use for lectures. Novice teachers in higher educational settings found difficulties in planning an overall framework of a subject or a course and the unpreparedness for assuming the role of planning might bring the novice university teachers “praxis shock”—the inadequacy of executing what should be performed in the teaching environment [17]. The ready-for-use lecture materials in “Tomorrow’s Leaders” provide the lecturers a clear framework of the lecture contents and theoretical grounds of the subject, which in turns lessen our burden in planning for the whole subject and grant us capacity in refining and enriching the contents with reference of the suggested theoretical grounds and frameworks. It is gratifying to have such preparation in times of commencing the teaching career in university settings.

“Good teachers”, however, “possess the capacity for connectedness” [16]. Teachers should be able to weave the meaningful web of connections among themselves, the subject contents and their students and thus the students could learn how to weave a web of integrated knowledge and attitudes learnt in class. It is therefore essential for us to make meaning of the ready-for-use lecture materials of each lecture with reference to different constructs and link each lecture with our own understanding in relation to the theories and models presented, and the rationale of the whole subject–self-leadership. The meaning-making process of the lecture notes is not limited to revising the lecture materials to fit in our teaching styles. It is the interaction between teachers’ own frame of reference and the perception of the students’ needs resulting in the personal interpretation of the lecture materials [18]. Even if there is a

designed-rationale in the ready-for-use lecture materials, teachers could still devise a personal attempt to create new information into existing knowledge system in the meaning-making process. In addition, the sense of ownership of the lecture materials and the whole Subject assists to make the teacher a continuation of the refinement and change processes in the future, even if other extrinsic motivation is no longer present. The sense of ownership leads us to feel the urge or necessity to change, which is the motivation to improve teaching quality by consistently evaluating if we have achieved expected objectives or standards [18]. According to Pierce et al. [19], “people use ownership for the purpose of defining themselves, expressing their self-identity to others, and ensuring the continuity across time”. The well-prepared and standardized lecture materials will make less sense if there is no teacher’s identity within them. With the sense of ownership, teachers would instill their own self—my belief in promoting self-leadership; my understanding of the theories and models of leadership; my eagerness in knowing better the young adults; my passion in teaching—into the subject matter and thus to liven up the lecture materials. It is encouraging to see students understanding and echoing with my instilled “self” in the process of learning in class: “She can always make some knowledge interesting” and “The teacher’s detailed explanations for the topics with appropriate examples, as well as her enthusiasm in teaching” (Student Feedback Questionnaire, APSS1L01, 2012).

The teaching in the university setting is leaving the academic staff “isolated professionally” [17]. This isolation will often become personal isolation as well as university teaching is quite individualized that each academic staff would be responsible of his or her own courses only. The individualized nature of this teaching style prevents academic staff from sharing and examining each other’s teaching practice and reflecting upon the underlying assumptions [20]. As the lecture materials of “Tomorrow’s Leaders” are consistent throughout every class, we shared about the challenges and difficulties quite often before or after lectures. A collegial professional community in the context of teaching is gradually developed in which we can interdepend in reflecting, exploring and improving our teaching practice [21]. The sharing about the difficulties and challenges might reveal our “perceived inadequacy” in delivering the lecture materials or even if challenge our professionalism in the teaching field. However, the collaborative and supportive culture with evolutionary relationships of openness, trust and support among us grant us autonomy to define and develop our own rationale of the Subject and individualized curriculum [22]. Within the research-intensive environment in the university, exchange of research ideas or methodologies becomes the dominant trend and teaching effectiveness might not be fervently discussed, though quality teaching should have to be upheld [23]. This professional yet supportive exchange of teaching wisdom has strengthened my professional confidence in times of career change and granted the autonomy in initiating a culture of professionalism in our team.

WILLINGNESS TO BE A PROCESS

Rogers [4] stated that the individual seems to become more content to be a *process* rather than a *product*. In delivering lectures of “tomorrow’s leaders”, I am not seeing myself only as a “fixed entity” of achieving the goals and outcomes set in times of preparation. Instead, I

intend to accept a more satisfying realization of entering “the process of becoming” [4] to let myself be into the class. Besides investigating the inwardness, that is teacher’s “self” towards teaching, it is equally important to examine how the beliefs and rationale delivered to the students, that is the “process” that Rogers emphasized. In “Tomorrow’s Leaders”, students are arranged into groups in order to facilitate the interactive activities such as group discussions and role-playing. Arranging students in groups is a common pedagogical practice across different levels of education. Compared to large-class settings, the interaction among students in groups is often more cooperative and collaborative, in which to help students acquire teamwork and collaboration skills, and develop interpersonal skills [24]. Although the advantages of arranging students in groups are acknowledged, the pre-assigned random groupings have once frustrated me. Chapman and colleagues [25] suggested that students’ self-selected groups are probably better than assignment and the arrangement of the pre-assigned groups is rather teacher-focused which might contradict with my belief in student-focused teaching approach [7]. Some students might find it difficult to join in the group as they do not know each other well in times of the pre-assignment of the groups. When I let myself enter the “process”, however, I discovered that the pre-assigned random groupings have an appropriate mixture of different talents, characteristics and skills that could facilitate the students to learn from each other within the groups. As a facilitator in class, I should remind myself to maintain as space to support solitude (those who might be a bit detached from the group at the beginning) yet surrounding it with sources of other students as a community. This respectful environment would help each other remove the impediments and discernments, which in turn nourished a multi-perspective yet with respect learning environment in the “Tomorrow’s Leaders” subject.

Over-sized class in higher educational settings is one of the traditional beginning teacher horror stories. Novice teachers find their incapacity to engage students and inadequacy in managing the class in right pace and momentum [17, 23]. The conventional belief of the benefits of small class size persists in higher educational settings. Interestingly, Stes, Gijbels and Van Petegem [26] have evidence that effective teaching approaches are not related to the context itself, including the class size. I agree with Stes and his colleagues [26] that it is not the objective measures of the class size that matters but teachers’ experience or perception of the teaching and learning context that is important. Despite the large number of students in class, teachers’ cautious arrangements of both intellectual and interactive in-class activities would facilitate student learning as well. Concerning the management of the class, there is limited literature exploring the issue of classroom management in higher education setting as the setting in university goes beyond the conventional understanding of a “class”. In addition, the misbehaviors or chaos aroused in university setting are not as obvious and problematic as in primary or secondary school settings. Some university teachers found “relieved” as they have not to deal with behavioral problems and are able to connect with students more effectively [17]. There might be a mythical assumption that there should not be any classroom management in university with its liberal environment and young adults in university are free to choose the way they are. Kounin [27], however, stated that managing a class is achieving a quality lesson, despite the level of education. I believe that to manage a class is to have an appropriate pace and momentum, and smooth transition of learning activities, but not posing control on the students’ choices or learning space. What makes a class sometimes a “chaotic void” is that the teaching and learning space is without boundaries. The space should be bounded and open. Palmer [16] stated that “[i]f boundaries remind us that our journey has a

destination, openness reminds us that there are many ways to reach that end” (p. 77). A class should be with boundaries created by relevant pedagogical arrangements that keep the teacher and students focused on the subject yet students are free to speak with relevance to the topic.

INTERNAL LOCUS OF EVALUATION

Teaching effectiveness is generally defined as the “degree to which one has facilitated student achievement of educational goals” [28]. The most apparent criterion for teaching effectiveness is student learning and thus student feedback questionnaires are administered in many universities worldwide and constitute the most widely used form of teaching evaluation in higher education [29]. It serves as a means for quality management in higher education and helps students reflect upon their learning. In my previous teaching experience in secondary school, there is rare or even no such evaluation system to help teachers review their teaching performance and effectiveness. The evaluation of teaching effectiveness depends quite much on teachers’ self-reflection and relies much on teachers’ own integrity and personal and practical experience [30]. In the university setting, student feedback questionnaire is frequently used to evaluate and analyze the outcomes and impacts of these subjects on student learning and teachers’ professional development. In “Tomorrow’s Leaders”, there was a post-lecture evaluation, in both quantitative and qualitative, administered to evaluate teaching effectiveness and the achievement of learning outcomes after each lecture [31]. It was at first quite “stunning” to learn that my teaching performance would be evaluated after each lecture, though I have been quite used to review my teaching effectiveness by self-reflection when serving as a secondary school teacher. The stunning feeling was not generated because of the scores from the evaluation. It was the mirroring of self-seeing and understanding my teaching identity and teaching passion transparently—that urged me to review what benefit the student and excel my teaching most. Student feedback questionnaire, with a number of students’ genuine perception on the teaching effectiveness and teachers’ performance, did provide a platform for teachers to reflect upon their own teaching effectiveness. This might lead teachers to look to students for approval or disapproval and for standards to teach in class as well. Prosser [7], however, advised university academics “[go] beyond student evaluation of teaching and learning score to improve teaching” and Rogers [4] further posited that the locus of evaluation should lie within an individual himself or herself. “Good teaching cannot be reduced to technique; good teaching comes from the identity and integrity of the teacher” [16]. It might be more satisfying if teachers recognize the choices or decisions made for the teaching rest within him- or herself.

CONCLUDING REFLECTIONS

“...the biggest defect we human beings have is our shortsightedness. We don’t see what we could be. We should be looking at our potential, stretching ourselves into everything we can become” [32].

Being an academia in the university setting is a journey fraught with self-doubt and anxiety. My school experience, however, is invaluable in assisting in the shift to academia.

The pedagogical insights with integration of the teachers’ training and front-line experiences equipped me in facing the career change and nurtured my teaching efficacy. However, research and teaching is seen as the integral part of the academic lives and both are viewed as the functions of academia’s intellectual passion [6]. Research is stressed and publication is a must for an academia. Faced with this novice responsibility and challenge, it is easy for me to place my faith on the “known”—by focusing on my teaching. Sufficient teaching experience before joining as a role of academia would contribute to increasing professional credibility and overcoming some initial difficulties [17]. In hindsight, I am more comfortable with my teacher identity more than the researcher. Obviously, the inability of translating former expertise has led me initially suffer from “imposter syndrome”, which is referring to “individuals’ feelings of not being as capable or adequate as other perceive or evaluate them to be” [33]. This “shortsightedness”, as Morrie refers [32], might hinder my development as an academia. Nevertheless, with growing understanding of the difference of practice field and research field, and growing awareness of the genuine university setting, I saw the need to increase my research ability concurrently with learning to teach at the university. Being immersed in research while in the educational context will enable experienced school teachers to overcome major challenges faced by many novice university academics [34]. In addition, research and teaching are reciprocally inspiring each other in creating new knowledge to facilitate students’ learning in the higher educational settings [23]. Thus, it is essential for me step out my comfort zone and search for the opportunities to “stretch myself into everything I can become”.

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Chapter 168

LEVELS OF REFLECTION

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ABSTRACT

To promote holistic development in Chinese university students in Hong Kong, a general education subject entitled “Tomorrow’s Leaders” was developed and has been fully implemented in the new four-year university curriculum since 2012. In this chapter, the Onion model is used as a framework for conducting systematic teacher reflection to enhance professional development. Challenges and issues central to the environment, behavior, competencies, beliefs, identity, and mission, as experienced and observed by a teacher of a leadership and positive youth development subject in Hong Kong are discussed. Issues include the Hong Kong education environment, the impact of reinforcement and the role of culture in teaching and learning, as well as postulations on leadership and human development. The chapter concludes with implications of the core reflection on my personal development.

INTRODUCTION

Over a century ago, Hall [1, 2] described adolescence as a developmental period of “stress and storm,” marked by mood disruptions, conflicts with parents, and risk behaviors [3]. The vicissitudes of autonomy, status, material resources, are met with increased expectations and responsibilities. The myriad of cognitive, psychological, physiological and social changes further add to result in stress experienced by these budding young adults [4]. In fact, long before Hall’s [2] delineation, Rosseau [5] had described adolescence using the metaphor of a storm:

“As the roaring of waves precedes the tempest, so the murmur of rising passions announces the tumultuous change... Keep your hand upon the helm,” he advised parents, “or all is lost.”

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Rousseau's forewarning should not be confined to parents, but also to researchers and educators. In light of the emergent developmental issues (e.g., mental health problems, substance abuse, and egocentric tendencies) observed in adolescents of Hong Kong [6] and attempts to "keep our hands upon the helm," a university subject entitled "Tomorrow's Leaders" (TL) at The Hong Kong Polytechnic University was developed by Shek [7]. The objective of the subject goes beyond the mere avoidance of "losing it all" or salvaging the remnants of the storm, but rather, to help these university students to weather through the turbulence by nurturing positive youth development and promoting leadership qualities in them.

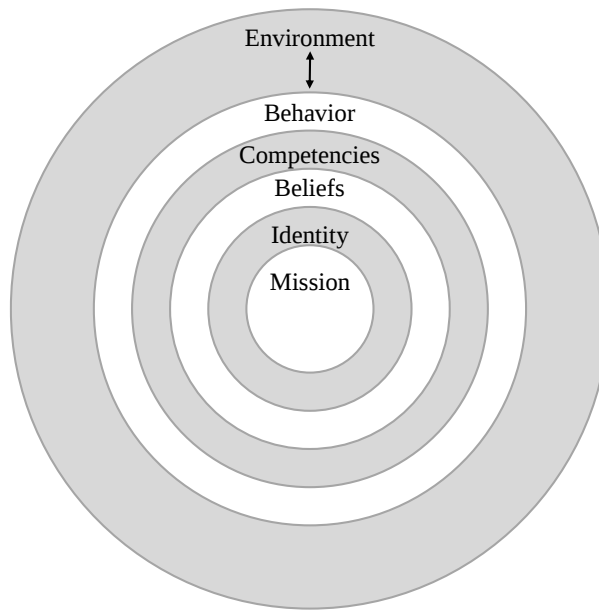


Figure 1. The Onion model with the six levels of reflection [1].

The subject was piloted twice in the second term of the 2010/11 academic year, and subsequently, in the first term of 2011/12. With the inception of the new 4-Year undergraduate curriculum commencing in the 2012/13 school year, a 3-credit curriculum for TL was developed and all undergraduate Year 1 students are required to enroll in this subject. As such, my journey as a teacher (or a co-storm rider, as I perceive myself) of TL began. Evaluation studies on the subject have been conducted using different quantitative methodologies, including post-course objective outcome evaluations [8], post-lecture [9, 10] and -course subjective outcome evaluations [11], and qualitative methodologies such as reflective journals [12], and focus groups from students [13]. Findings have consistently demonstrated that the subject impacted students positively. After having taught the subject for three semesters, in the present article, I aim to share my reflection and observations from the perspective of a teacher, with the use of Korthagen and Vasolos' [1] model for systematic core reflection.

THEORETICAL MODEL FOR CORE REFLECTION

Teacher reflection is a common practice in educational settings for professional development, yet, Korthagen and Vasolos [14] warn that not all reflection can result in optimal or sustainable outcomes and professional growth, as many instances of reflection focus on identifying problems and devising solutions for specific problems in a superficial manner. Specifically, when practitioners reflect, many are prone to “focus on finding a “quick fix” - a rapid solution for a practical problem - rather than shedding light on the underlying issues determining the situation at hand.” [14]. This type of problem-based reflection seems to overlook the fact that individuals’ behaviors are guided and influenced by ones’ inherent beliefs and attitudes. Therefore, if the goal of reflective practice is to bring about prolonged professional development in a teacher, reflection must be conducted in a deeper manner to delve upon the teacher’s personal values which naturally influences (and are simultaneously influenced by) one’s interaction with students. To enable systematic core reflection, the Onion model was developed by Korthagen and Vasolos’ [1] as depicted in figure 1. The model presents different levels (i.e., content) on which reflection can center on. The underlying notion is that the inner levels of the model determine individual’s behaviors in the outer levels, and vice versa. The authors of the Onion Model warn that reflections conducted without a systematic model may remain too superficial by being narrowly confined to reflecting on behaviors, competencies, or beliefs alone. The strengths of the model lie in its abilities to help practitioners raise their self-awareness by conducting deeper core reflections at all levels, help teachers identify particularly, at which level their strengths and weaknesses are in, and highlight processes which can be deepened or broadened [1].

ENVIRONMENT

The outermost layer of the Onion model is the environment, which includes the class, the students, and the university. One of the fundamental challenges of teaching TL pertains to the nature of the subject. Higher education in Hong Kong has undergone great reform, moving from a three-year undergraduate curriculum that favors early disciplinary specialization to a four-year curriculum that aims to encourage interdisciplinary exchanges by incorporating broad-based general education components to complement discipline-specific studies; TL being one of them at The Hong Kong Polytechnic University. The implementation of effective general education, however, is challenged by the deeply-rooted traditional cultural values of utilitarianism [15]. I would like to elaborate on the above using an in-class exercise I have conducted.

In order to gain a better understanding of my students and to gauge their expectations, during the first lecture of the semester, prior to the introduction of the course content, I would distribute a small piece of paper and them to answer the following question, “What do you expect to gain after taking “Tomorrow’s Leaders”? I would then collect the sheets, which are anonymous, and share some of them with the whole class. During one semester, I received the following two responses:

“Nothing.”

“Gain credits.”

I was not surprised to receive these comments which provide support for the fact that Hong Kong is indeed a pragmatic society pre-occupied by utilitarian cultural values, which unfortunately, poses as a challenge for the general education reform. Our society emphasizes on “what works rather than philosophical debates and perspectives... Educationally, this pragmatism has also been expressed in narrow, technical specialization.” [15]. Chinese students adopt a pragmatic approach to education and expect to gain skills and social mobility through education [16]; attending university is perceived as an investment [17]. Hong Kong university students when compared with those from the Mainland were even more pragmatic and instrumental. They were preoccupied with trying to get distinctions in school, as compared with China University students who were more concerned with the quality of content included in their course materials. The authors concluded that while Hong Kong students were exam-oriented, their Chinese counterparts perceived university education as a means to equip themselves for dealing with future challenges in the changing economic environment [17]. This is also reflected through the Hong Kong education system which is highly competitive and strongly oriented toward students’ academic achievement [18]. It is not surprising that students who are brought up in such an environment would not expect to gain anything from a general education subject aimed at encouraging critical thinking, creativity, self-leadership, and reflection; these are all abstract conceptualizations to many.

While students attempt to deal with the confronted changes to the higher education system logistically, they are also trying hard to understand the educational philosophy behind the reform. To implement general education subjects effectively, I believe that as a teacher, it is pivotal to guide students to first appreciate the importance of equipping oneself with competencies beyond those taught in their own disciplines. The goal of education must move beyond the traditional training of graduates for employment confined to one’s trained discipline or Hong Kong. Instead, graduates should be trained to reach broad employment goals. This can only be achieved “by creating lifelong learners who can change careers by learning to learn... (and creating) global citizens, adults who can contribute to society and the good of the whole.” [15].

Referring back to the short exercise, I began by sharing with the class the two aforementioned comments and told them that it is understandable why some students may feel this way, and that it is alright if one is unsure of what to expect; but I go on to ask them to think about whether it is acceptable to hope to gain nothing from a subject, given how hard they have strived to enter university. I subsequently highlight the experiential and reflective nature of TL and how reflection in itself is invaluable, and whether one can gain from any experience depends on one’s willingness, openness, and motivation to immerse oneself in the experience. I then show the expectations of other students who yearn to develop themselves through TL, and reassure the class that the subject is designed to meet these expectations,

“To realize ourselves.”

“Developing skills of (being a) lifelong leader.”

“To know myself deeply.”

“Find what I want and (am) looking for, like what is meaningful to me.”

“To be brave.”

“Observation, cooperation, and communication skills.”

To conclude the activity, I shared two last responses and emphasized that TL is unique from other discipline-specific subjects in which we are not merely teaching theories and hard knowledge; but rather, we equip them with competencies that will help them find,

“The way to be ourselves. And do it well.” and
“To become an adult in the society.”

BEHAVIOR

The second layer of the Onion model is behavior, as defined by observable actions of a teacher in class (e.g., how does one deal with problems).

TL is a subject that encourages students to take initiative and responsibility in different spheres of their lives and to liberally share their ideas in class. This however, becomes a challenge due to the highly collectivistic nature of Hong Kong society [19], where students will only speak up in class when appointed by the teacher, individual initiatives are often discouraged, and students opt to conform [20]. Various reasons account for these behaviors, including the fear of losing face (*mian zi*) [21], or harsh self-evaluations subsequent to failures [18]. Recognizing positive behavior seems to be one of the solutions to overcome this challenge. According to Law and colleagues [22], providing appropriate responses of the social environment to desirable behaviors can encourage adolescents to continue to these behaviors. Positive behavior recognition strategies may involve positive reinforcement, observational learning (e.g., modeling), and unconditional positive regard. In terms of positive reinforcement, in Hong Kong it is not only parents who seldom praise or make use of positive reinforcements to motivate their children [23]; many teachers are not trained to practice these strategies either. Research has been conducted universally to identify qualities of successful teachers. Cheung and colleagues [24] interviewed outstanding teachers in Hong Kong and came up with a list of elements of personal and professional qualities that a successful teacher should have (e.g., care for students, enthusiasm, subject knowledge, classroom management, etc.). Majority of the elements from Cheung and colleagues' [24] study are in line with those proposed by Tamblyn [25] whose study was conducted in the West. However, one noticeable quality that was not mentioned by Hong Kong teachers was “the skill in the science and art of motivation through positive reinforcement.” I concur that the use of positive reinforcement is indeed a science, multitude of studies show the positive impact of reinforcement on learning, but at the same time, an art, which I am still trying to master.

Positive Reinforcements inside the Classroom

In my TL classes, I try to motivate my students using different strategies, both inside and outside of the classrooms. During lectures, every time a student shares their ideas to the class, I would verbally thank and commend them for their sharing. To model, I would also lead the class to give the student a round of applause to show their appreciation to his/her classmates' efforts and contributions to the class' discussion. In gradual time, even in the absence of my lead, students would automatically clap whenever their classmates share. This creation of a

supportive environment has resulted in significant improvements throughout the semester; students who were shy to speak up in the beginning became more willing to take initiative to share their thoughts and demonstrated higher levels of confidence while doing so. This supports “the notion of supportive learning communities (which) reflects what we have learned about the nature of individual minds operating in an enabling culture” [26]. This is in line with unconditional positive regard proposed by Rogers [27], where individuals maintain a positive attitude towards others, enabling the receiver to experience a sense of self-worth. Positive behavior recognition may be demonstrated by means of personal warmth through providing supportive verbal or nonverbal gestures [22] (e.g., thanking students for their sharing or clapping). Highly functioning communities are characterized by trust and mutual support, which is pivotal for effective pedagogy and the sustaining of productive discourse [26]. In addition, students in TL are assigned to small groups, in which they are to conduct in-class activities, discussions, and a group presentation collaboratively. This arrangement also introduces reinforcement contingencies such as, immediate consequences from peers, as well as increased interaction between students and teachers or teaching-assistants; given that our role as facilitators during these activities is to rotate to different groups to facilitate and answer questions that students may raise [28].

Positive Reinforcements outside the Classroom

Teaching TL has trained me to be more observant and sensitive to the needs of individual students. I remember there was a student in one of my classes; he was never very enthusiastic about participating in any group activities, and was sometimes late for class. I had tried different motivation strategies during class, but somehow it never really succeeded. Until suddenly one week, I observed that he had made the slightest improvement in one of the activities that day. I recall that the activity required students to exercise their creativity and aesthetic skills to express qualities of a successful leader. So after class, I emailed him to acknowledge his efforts in taking responsibility for his learning, and complimented him for his creative input in that activity. To my surprise, he began to be more participative in our in-class activities and showed increasing interest and enthusiasm in subsequent lectures throughout the semester. In TL, we always encourage students to reflect and identify their own potentials, but as a teacher of TL, it is of equal importance to be sensitive to each student’s unique interests and potentials. It is often in these eureka moments that we are able to provide the positive recognition needed for their healthy development. In addition to sending individual emails to certain students, after each lecture, I also post weekly announcements on Blackboard to thank the class for their active participation, and highlight one or two episodes from that particular lecture to compliment them on. I find that students appreciate this form of encouragement, as evidenced by qualitative comments from student feedback questionnaires and reflections on the subject,

“I appreciate the lecturer’s attitude very much. She sent us emails after the lectures and motivated us to participate in the lectures, which encourages students to respect the class much more.”

“I would like to thank the teacher for her passion in teaching and encouragement; emailing us after each lecture and uploading photos from class. The feeling is that of a teacher and friend. Thank you for their dedication.” (Comment translated from Chinese)

Echoing the idea of motivation through positive reinforcement being an art, Picasso once said, “Some painters transform the sun into a yellow spot, others transform the yellow spot into the sun.” I vie to be the latter by motivating and reassuring my students that they all have the potential to shed light and be radiant.

Positive Self-Reinforcement

Self-reinforcement refers to the administration of rewards to oneself in the absence of external control. Self-reinforcement plays an important role in positive development, as it acts as a link between one’s self-concept and overt behaviors. For instance, positive self-evaluation statements function as positive reinforcements for future behaviors [29]. In fact, recognition of one’s positive behaviors and strengths can facilitate adolescents’ development of a positive and healthy identity and also serves as a protective factor [22]. In the lecture of positive and healthy identity, students are invited early in the lecture to make reflections on their real and ideal selves. An initial observation is that they are quick to write negative descriptions about their real selves (e.g., lazy, pessimistic, and even, ugly); as aforementioned, this may be influenced by their upbringing where Chinese parents seldom praise them for their achievements. However, as the lecture progresses, students are then guided to reflect particularly, on their strengths in different domains of their lives (e.g., at school, home, in sports teams, among their peers, etc.), and to write down practical behaviors/achievable goals they can reach in order to realize their ideal selves. At the end of the lecture, students are asked to stand up and verbally reaffirm themselves of their strengths and abilities to reach their set goals. The self-reinforcement strategies applied in this lecture, and similarly throughout the semester, have helped students develop a more positive identity, as shown by their comments:

“Sometimes we do not like ourselves, but this lecture reminds me that actually I am beautiful just the way I am and I should love myself more.”

“It is difficult to be an ideal self. But I will try my best from now on.”

Modeling

Modeling is demonstrated in numerous educational settings; it refers to teachers’ demonstrations of concepts to students. Research has shown that individuals learn naturally by observing others, and thus effective modeling for student imitation is a useful tool in classrooms [30]. For instance, this subject requires students to engage in self-reflection and to share their experiences with their classmates. However, students are often shy and reluctant to do so. One of the most effective ways to encourage student sharing is for teachers to model the act of sharing through self-disclosure (i.e., the revelation of past experiences, stories, genuine feelings and thoughts with students). Appropriate use of self-disclosure has been shown to be effective for student learning and strengthening of teacher-student relationships [31]. Indeed, students in TL are more comfortable to talk about their experiences and feelings subsequent to listening to my sharing as a teacher. While mathematics lecturers may demonstrate how to do calculations to arithmetic problems, or teachers in nursing may show

students how to draw blood from a patient; what a teacher in TL “models” is not confined to discipline-specific task competencies, but also one’s attitude as a leader. Within a classroom setting, the teacher is the leader that students will first look up to in attempts to identify leadership qualities to imitate; as such, leadership behaviors/attributes exhibited by a teacher in class becomes critical. This will be further elaborated in the following level of reflection.

COMPETENCIES

The third layer of the Onion model is competencies, which refers to teacher’s integrated knowledge, skills, and attitudes [32]. Lowman [33] observed that “college classrooms are dramatic arenas first and intellectual arenas second.” He does not imply that teachers should put up a facade, but rather, to make use of the classroom environment as a stage to create an emotional effect on students. Many of the topics in TL, such as resilience, morality and integrity, positive identity, and spirituality require teachers to set an emotional tone to facilitate deep reflections prior to changes. Any of us who have watched a moving performance would agree on its lasting impact. Similarly, Lowman further asserts that “Good lectures are difficult to ignore.” A competent teacher is someone who is able to put on a stimulating performance students will not forget. Such performance is one where play becomes so real that its distinction from reality is difficult. In order to achieve this, actors have to be “in character.” This is similar to the notion of presence in teachers; the idea of “being-while-teaching.” Teaching presence means that teachers are “wide awake to one’s self, to one’s students and to their learning in such a way that that learning is served through skillful and compassionate analysis and access to both subject matter knowledge and pedagogical strategies” [34]. In order to achieve this, there must be a harmonious connection between one’s professional knowledge and beliefs with one’s behaviors. It is to teach with integrity; - to “walk the walk.”

As a teacher of TL, one discusses many topics such as emotional competence, resilience, morality, sense of responsibility, and effective leadership, which are all competencies and values reflected in every word we say, or action we make in class. During my first semester of teaching TL, I remember being very disappointed after my lecture on Spirituality. The content of this lecture, particularly, spoke to me in great depths, as it gave me a chance to reflect on my meaning in life and role as a teacher. I held high expectations that the lecture would impact on my students the way it had on me. Unfortunately, many students found the concept to be abstract and difficult to relate to. I was upset and for the first time in my teaching career, I cried in front of my class as I shared how I felt. Of course, it did not occur to me at that moment that any student would take this incident to heart. This was until after the semester had ended, when I received an email from a student;

“Thank you for this semester’s Tomorrow’s Leaders! To make a long story short, I love the feeling of struggling, and to find this feeling on you as well. We all know there are quantities of difficulties during the process of this course, while you still stick to teaching us seeking for the best effects.

I still remember the time that you teared, because I am always moved by myself to cry as well, and others can be surprised by us...”

In TL, we teach students the importance of being resilient even in face of obstacles and difficulties. I feel it is important as a teacher to demonstrate this kind of courage and persistence. As alike with other constructs we teach, it is crucial that we act as role models, to be present and practice what we preach at all times.

BELIEFS

The fourth layer of the Onion model is beliefs. Before teaching TL, one of the subjects I have been teaching is industrial and organizational behavior, which of course, is a subject that includes a wide range of leadership theories and models. Therefore, I would say that the greatest “belief assimilation” I have had to undergo is that related to notions of leadership. First, most traditional leadership theories and models focus on investigating situational and task competencies of leaders, i.e., “hard” skills that are likely to result in positive organizational outcomes. Few theories are concerned with the “soft,” intrapersonal and intrapersonal competencies of effective leaders, of which we now know, are equally important for positive outcomes of leadership [35]. Second, trait theorists argue that certain individual traits differentiate leaders from non-leaders and assume that leaders are “born” [36]. Over the summer, some of my students attended an exchange program in China, where they had the opportunity to visit large multinational corporations and to engage in dialogues with “leaders” of these corporations. A (rather confused) student returned and shared that one of the leaders boldly claimed that “Leaders are born! Some people are born to be leaders, while others are not.” Some firm believers of trait theories are unable to appreciate the situational influences on leadership and the malleable nature of personality. But as a teacher of TL, this fixation becomes detrimental. It is important for a teacher to challenge the underlying assumption proposed by trait theorists and more importantly to clearly convey to students, the belief that “Everyone can be a leader.” If not, all else will be in vain. The second belief about leadership which lays foundation for the subject’s endeavors is the concept of self-leadership. Most existing leadership theories are about leading others, but in fact, before one can lead others, one must first be able to lead one self. As a teacher of TL, it is crucial to highlight the fact that as individuals, we have the free-will to make decisions and our behaviors are determined by the choices we make. As such, the subject aims to nurture students who are able to effectively lead themselves to make wise and moral decisions in life.

IDENTITY

The fifth layer of the Onion model is identity, which refers to how one defines oneself, specifically, how a teacher sees his or her professional identity. Reflection at this level pertain to questions such as “Who am I?” or “What kind of teacher do I want to be?.” It is agreed among scholars that teacher identity is dynamic [37], and can be impacted by factors such as one’s emotions, life experiences, and teaching contexts [38, 39]. The process of self-evaluation enables one’s identity to be “continually informed, formed, and reformed” [40]. On reflection, teaching TL has not only resulted in a reformation of my professional identity

as a teacher, but also reinforced my self-identity as a Chinese. I would use Yin and Yang to describe my experience in TL on this level of reflection.

The Yin: “Who Am I?”

Having been educated abroad and teaching and researching on psychology and leadership theories and models developed predominantly in the West, it has seldom occurred to me the strong relation between my heritage and what I teach. As I teach the subject, I learned to appreciate the traditional Confucian teachings and came to the realization that in fact, many of the theories that I have been teaching and researching on for years have been notions and ideologies that have long existed in traditional Chinese culture. The TL curriculum has been carefully designed to maintain elements that have been shown to be effective in the development of positive youth development programs, such as the importance of incorporating relevant theoretical models and research findings from both the Western and Chinese context, the inclusion of cultural elements, and considerations of cross cultural differences in the program [41]. TL is a subject that requires and facilitates students to exercise and nurture the habit of self-reflection, to gain a higher level of self-awareness and to identify one’s potentials and weaknesses. Introspection was advocated by Confucius as found in his teachings in “The Analects” [42], “Every day, I look inside my own soul to find if I have done anything that betrays myself.” It is thought that through introspection, one is able to continuously improve oneself in order to reach higher standards of achievement [43]. In addition, many of the constructs that are covered across the weeks in the curriculum share core Confucian ideologies. For instance, a lecture on self-leadership discusses how individuals manage, influence, and lead oneself to establish self-direction and motivation to attain goals [44]. This resonates Confucian culture’s emphasis on self-cultivation, where one’s continuous effort to build one’s character is perceived as a moral value itself [42]. The importance of developing a sense of responsibility to one’s self, family, and the community is also highlighted in TL, which are tantamount to the fulfillment of obligations as advocated by traditional Chinese doctrines.

The Yang: “What Kind of Teacher Do I Want to Be?”

In TL, students are encouraged to be creative and to freely share their thoughts and ideas with other classmates. Teacher-student dialogues and self-disclosure of teachers are highly valued. These individualistic behaviors seem to contrast with the collectivistic society of Hong Kong. I find Hofstede’s [45] cultural dimension of power-distance to be particularly relevant to my teaching of TL. Power distance refers to the extent which authorities (i.e., more powerful members) of an organization should have control over their subordinates (i.e., less powerful members). Hong Kong is a society relatively high in power-distance [19]. Students in these cultures are dependent on teachers for their learning, communication in class is one-sided and initiated by the teacher, and teachers are perceived as “gurus” who transmit knowledge and personal wisdom and truths to students [46]. Having been accustomed to traditional forms of “one-way” lecturing, I find that one of the challenges I had

was to lower my position as the teacher or authority figure who “knows it all,” to more of a facilitator to observe and stimulate students’ learning. This shift from a teacher-centered approach to a student-centered classroom encourages students to take responsibility of their learning and to perceive me as more of an equal to them. A psychological hurdle that I encountered was that I had to first accept the fact that I really did not always have the “right” answers to every question. When conducting lectures in the past, I was confident that I was familiar with the theories being taught and was able to cite studies and figures that supported what I was teaching; to a great extent, I was convinced that I had the “right” answers to many questions raised in class. Teaching TL is a different story; the subject is not about transferring truths to students, many of the discussions, for instance, on morality and integrity, and spirituality, do not require an absolute answer. I would share my views or what I would do under different circumstances with my students, but by no means were they considered as truths. My role instead, is to act as a facilitator to help students find their own stance on these issues. Without undertaking the role of the “guru,” the power-distance between my students and I were greatly reduced, we were no longer unequals, but equals with shared leadership [47] roles of both teaching and learning. This notion of shared leadership, in fact, is not so much in contradiction to traditional Taoist’s teachings of selflessness and Confucian’s notion of providing service or even sacrificing the “little me” (*xiao wo*) (i.e., one self) for the benefits of the “big me” (*da wo*) (i.e., the community in which one is embedded in).

In TL, we hope that students are able to develop healthy selves, but more importantly, to help them find their contributive roles in the bigger Self. I quote John Maxwell in my lecture; “Leaders must be close enough to relate to others, but far enough ahead to motivate them.” which I feel coincides with how I see my leadership role in TL. In terms of my professional identity as a teacher, I believe that it is about striking a balance between the dualities of Chinese and Western teachings and orientations, on both a theoretical and pedagogical level.

MISSION

The inner most layer of the Onion model is mission, concerned with “highly personal questions as to what end the teacher wants to do his or her work, or even what he or she sees as his or her personal calling in the world” [48]. The analogy of the teacher being a planter of seeds is familiar to many. As educators, we aim to plant seeds of knowledge in our students, and hope that they will flourish in time as they develop. I believe that my role as a teacher is to provide students with a supportive environment that encourages self-reflection and discoveries of personal strengths. Especially given the fact that many of these students grow up in a culture where upward comparison is common and positive reinforcement is rare. It is only with self-confidence and awareness of one’s potentials can one truly thrive and excel. More so than that, adolescents nowadays are confronted with aversive temptations which can easily lead them astray. Shek and colleagues [49] reported observations of increasing instances of problem behaviors in Hong Kong adolescents, including substance abuse, internet addiction, premarital sex, and overemphasis on money and material possessions. In this harsh climate, it is not any type of seeds that teachers plant, but rather, seeds that will be able to survive in all kinds of “dirt” and to transcend hardships to blossom in the toughest weathers. Shek [50] shared that the Chinese term for leaders (*ling xiu*) comprises of two

characters, meaning; collar and sleeves, which can easily get filthy when one finds him/herself in hard work. Inevitably, our leaders of tomorrow will face moral dilemmas, and as a teacher of TL, I believe that my role is to accentuate the importance of self-cultivation in the upholding of moral beliefs as a life-long pursuit.

PERSONAL DEVELOPMENT

TL has helped me develop professionally in that it has changed my perception of what a teacher should aim to achieve. Teachers easily fall into the trap of being overly outcome-oriented; after all, teaching effectiveness have traditionally been measured by the achievement of learning outcomes mainly reflected by students' scores in examinations. Admittedly, before I actually started teaching TL, I was primarily concerned with observing whether my students would be able to demonstrate the attributes I was about to teach in class each week. Yet paradoxically, I was not sure as to how much to expect regarding the impact of a general education subject on students. This was probably due to the fact that I have never taught, nor taken any subjects alike during my undergraduate or postgraduate training. So frankly, I came into teaching TL with a high degree of openness accompanied with a sense of curiosity as to the extent that TL would impact on my students. I started teaching TL with the feeling that it is like driving on a highway with no streetlights at night; you can only see what is in front of you and know that you are getting closer and closer to where you want to be, but exactly how far you are away from your destination is not always clear. In reality, the impact of the subject soon became apparent. With only a few weeks into the semester, students had already demonstrated significant changes in their behaviors. Improvements in learning attitude (e.g. punctuality, attentiveness, and openness) were clearly evident, and by the end of the semester, majority of students had demonstrated development and showed maturity in many aspects. However, I gradually came to another realization that in fact, I must not try to reach a destination; there is no such thing as an ultimate destination, since all students internalize, learn and develop at their own pace, and each student has their own destination. My belief now is that the value of TL (or teaching TL) is more of a means to an end rather than an end itself. Leadership is a lifelong journey and not a destination in my students that I should "drive" towards, but more important is the ride itself.

Making the ride worthwhile has two meanings for me; professionally, it is about fine-tuning my teaching skills through evaluations, self-reflection, training and practice. Personally, it is on finding inspiration and joy in teaching and in life. Each semester, I show a video of the commencement speech that Steve Jobs gave at the Stanford University [51], although I have watched it for several times, every time I am inspired differently. Jobs said,

"Your work is going to fill a large part of your life, and the only way to be truly satisfied is to do what you believe is great work. And the only way to do great work is to love what you do. If you haven't found it yet, keep looking. Don't settle."

In my students, I see inquisitiveness, wonder, openness and critical minds. I remind myself that I ought to be like them, I must find something to learn, to love, and be inspired about in every lecture I teach or everything I do, no matter how many times it has been done before.

It is easy to succumb to mundane in life; it is the safe thing to do. Some university lecturers are critiqued for repeating the same PowerPoint slides (and even jokes!) year after year, it is indeed tempting to do so. I believe that as a teacher who will teach this subject repeatedly, it is important to be sensitive to the needs of different student populations across semesters. Students in different disciplines may need more specific examples to illustrate certain theories or concepts which may be foreign to the training they are used to. For instance, if I were to teach engineering students again, I may allocate more time on demonstrating empathy and interpersonal skills to this group of students. When I teach design or nursing students, I may provide more opportunities for them to exercise their cognitive skills in systematic problem-solving. Effective teachers are like parents who must be sensitive and responsive to the needs of their child. Thus, I would like to conclude my reflection with excerpts from the poem “On children” by Khalil Gibran [52] which happens to be how I perceive myself as a teacher of TL,

“... You may give them your love but not your thoughts.
For they have their own thoughts.
You may house their bodies but not their souls,
For their souls dwell in the house of tomorrow,
which you cannot visit, not even in your dreams...”

You are the bows from which your children as living arrows are sent forth.
The archer sees the mark upon the path of the infinite,
and He bends you with His might that His arrows may go swift and far.
Let your bending in the archer's hand be for gladness;
For even as He loves the arrow that flies,
so He loves also the bow that is stable.”

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Chapter 169

RIDING ON A ROLLER COASTER

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ABSTRACT

A university subject on leadership and intrapersonal development was delivered during the academic year of 2012-2013 to the first-year university students. The teacher taught four classes of totally 268 undergraduate students coming from four different disciplines. The teacher shared her experience in teaching the subject with reference to the stages of forming, storming, norming and performing that the students had gone through. Personal reflections on teaching the subject as well as perceived benefits to the students were also highlighted. The teacher deeply reflected the essence of university education in the cultivation of the leadership and intrapersonal attributes of the students. In facing the growing trend of “McDonaldization” and commercialization of university education, a general education subject that emphasizes the intrapersonal and interpersonal qualities of the students, and fosters the holistic development of the students is essential in university education.

INTRODUCTION

During the academic year of 2012-2013, I taught a university subject on leadership and intrapersonal development named “Tomorrow’s leaders” for the first-year students in The Hong Kong Polytechnic University. I taught four classes of students coming from four different disciplines, including applied science, humanities, building and construction, and nursing. The class sizes were 56, 43, 86, and 83 respectively.

During the last lesson of “Tomorrow’s leaders,” each student was invited to share a metaphor that could best describe the subject. They then discussed in their groups and selected the most representative metaphor that would be shared in front of whole class. One

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group from the nursing discipline drew a shoe-shaped roller coaster to represent the subject (see appendix 1). The students explained their journey of “Tomorrow’s leaders” as a roller coaster ride that had involved four stages: (i) Initial stage: this stage was filled with “uncertainties.” They were wondering about the nature and the content of the subject, reasons for studying leadership and intrapersonal qualities in the university, and the assessment of the subject (students were keen to respond to assessment as they had gone through various examinations before entering university). (ii) Enjoyable stage: students were getting familiar with the “task” and “people” of the subject. They were acquainted to the format of “teaching,” which included experiential games, reflective exercises, sharing etc., and became more interactive with their classmates (they were first-year students who were not familiar with each other before) and lecturers. There were funs and thrills when riding over the peaks, but there were boring moments when waiting for the next peak. (iii) Advancing stage: this was the stage that the students needed to do their group presentation. They became more active in the participation. This was the real stage to examine their different competencies and courage, and they experienced more group cohesion and conflicts. (iv) Ending stage: The various moments of the journey brought an unforgettable memory in their university life, and finally, they were unwilling to leave the roller coaster! The shoe-shaped roller coaster represented that they have to learn how to “walk” in their own lives. I was thrilled by their thoughtful idea and earnest sharing. Their learning experiences inspired me to think over my teaching experience of the subject. And I echoed with them. I also have had a memorable journey on a roller coaster ride.

In the lecture of team building, the stages of team development suggested by Tuckman [1] were introduced. There are four stages of team building: forming, storming, norming and performing [1]. Echoing with the stages, Whittaker [2] also identified five stages of group development which was widely used in social group work: pre-affiliation, power and control, intimacy, differentiation and termination. Though a class of over 50 students would never be equivalent to a group, the stage development models give us a useful skeleton to understand the learning progress of students, the interactions between teachers and students, as well as the reflections on teaching the subject. Hence, in this paper, I would share my teaching experience of the subject of Tomorrow’s Leaders in three aspects: the different stages of the subject implementation, personal reflections, and perceived benefits to the students.

AN ADVENTURE, A CHALLENGE, AND A MOVE

Adolescents nowadays are growing up from a rather prosperous and protective environment. On one hand they receive better care and nurture from their families and schools, which may facilitate them to become special, confident and achieving individuals [3]. But on the other hand they are sheltered and protected, which may foster the egocentric, narcissistic and cynical characters [4].

Growing up from a “4-2-1 indulgence” culture (i.e., four grandparents and two parents spoiling one child) [5], as well as the popularity of having the maids to do housework, Hong Kong adolescents have become the “little emperors” in their families. The adolescents today are labeled as the “spoilt generation” who show signs of narcissist traits [6], and as “Hong

Kong Kid” who are “unable to look after themselves, have low emotional quotients and even lower adversity quotients.” [7].

The university students belong to this generation. There was evidence showing that university students were vulnerable to narcissism [8]. Against this background, a three-credit-bearing subject entitled “tomorrow’s leaders” that focused on leadership and holistic development was developed and implemented in the Hong Kong Polytechnic University. The subject lasted for 14 weeks and covered different topics, including personality, cognitive competence, resilience, emotional competence, moral competence, spirituality, positive and healthy identity, social competence, interpersonal communication, team building and self-development.

Before teaching in the university, I had been a social worker for 20 years, mainly responsible for youth, family and community services. When I was a frontline social worker, I used to help the adolescents understand and develop themselves through guidance work and socialization programs. The experiences were rewarding when the adolescents shared their joys and sorrows, recognized their potentials and searched for their purposes of life. They were empowered. Gratefully, I witnessed the positive changes and development of the adolescents in their walks of life, and these have been some of the sweetest memories in my professional life. As adolescence is a critical stage for the adolescents to search for roles and identity [9, 10], a good adjustment during this stage would help adolescents to smoothly transit between the stages of childhood and adulthood, and build up their role commitment to themselves, their families and the society they belong. As suggested by Astin and Sax [11], the “affective outcomes such as self-understanding, tolerance, honesty, citizenship, and social responsibility” (p. 587) are important elements for university students. “Tomorrow’s leaders,” a general university education that focuses on leadership and intrapersonal qualities, may provide university students with insights on their intra-personal and interpersonal development. The subject was attractive to me – a chance to accompany with students in their journeys of self-understanding and holistic development. Under these considerations, I decided to make a move to teach this subject.

EXPERIENCES OF THE RIDE: TEACHING THE SUBJECT OF “TOMORROW’S LEADERS”

There were mixed feelings before teaching “Tomorrow’s leaders,” which was similar to the moment waiting for a roller coaster ride. On one hand, it was exciting, thrilling, and aspiring, as this was a refreshing experience to teach leadership and intrapersonal qualities in the university, and accompany with the students in joys, sorrows, struggles, insights, challenges and breakthroughs. But on the other hand, I was anxious and worried. The subject went beyond knowledge transfer. It touched upon the personal development of the students. Thus, it was more demanding for the teacher, and the steps were not easy. In order to have a better psychological preparation for the teaching, there are some tips:

- Be familiar with the concepts of the positive youth development attributes and the teaching materials;

- Collect some daily-life materials related to the positive youth development attributes, such as video clippings of resilient stories; newspaper clippings about integrity concern etc.;
- Cognitive and real rehearsal of lecturing.

The Forming Stage

“Unfamiliarity” is the word used to describe the psychological state of the students. Being the freshmen of the university, students were unfamiliar with the new subject, the learning patterns, the lecture hall, their classmates, and the teacher. Besides, leadership and intrapersonal qualities as a teaching subject was uncommon among the students’ learning experiences in their secondary school lives. Furthermore, with the rise of specialization and professionalism in the competitive world, the outcomes in tertiary education focused much on the technical and occupational domains, with holistic development of young people being ignored [12]. University students became more instrumental and functional in perceiving their needs and the purpose of education. Thus, the students showed approach-avoidance behaviors in the first few sessions. While majority of the students tried to comply with the rules and regulations and tuned into the learning environment, there were always some students who were uninvolved and non-attentive. Some students had biases and preoccupations that the subject was unpractical for their professional qualifications, and some had never thought to become leaders. Besides, as the students were unfamiliar with their group-mates, they were hesitant to disclose themselves in the sharing. More warm-ups and encouragements were needed in the group sharing. Another observation was that the students were not getting used to self-reflections, as this approach was not a common way of learning in their primary and secondary school lives. Acknowledgement of the subject’s objectives as well as familiarity with the environment was the primary emphasis in this stage. Three key attitudes and actions are crucial: openness, respect and encouragement. Openness is the key to access of knowledge, respect is the bridge between the teacher and the students, and encouragement is the direct engagement of the students. With respect to teaching, there are some suggestions that may help to build up familiarity of the students with the subject and the learning environment:

- Engage the students and build up rapport with them;
- Clarify any uncertainties, preoccupations, biases and queries;
- Establish the class norms;
- Allow students to foresee what would happen in the lectures;
- Build up patterns of collaborative learning and mutual sharing;
- Emphasize the importance of both conceptual and experiential learning;
- Build up a supportive learning environment such as introducing the useful resources to the students.

The Interplay of Storming and Norming Stages

At this stage, the students were getting familiar with the learning patterns of the subject, the classmates and the teachers. They participated more openly and naturally in class. The teaching content of intrapersonal qualities of resilience, moral competence, spirituality, healthy and positive identity, as well as interpersonal qualities of social competence and interpersonal communication required them to have active sharing and genuine reflections. Some topics were seldom touched upon by the students (such as spirituality), some were relatively personal (such as healthy and positive identity), and some were very interactive (such as social competence). Nevertheless, they were fundamental attributes for the students to understand themselves, to interact with others, and to stand firm and honest in the society.

When students got familiar with the learning environment, more commonness as well as diversity was experienced in the class. Unlike group development that has clearer stages of development, the class of “Tomorrow’s leaders” undertook the interplay between “storming” and “norming” stages. While students established group norms and interactional patterns within their groups and the class as a whole (norming), there were conflicts and diversities in their interactions that might affect their relationships (storming). Informal group leaders were identified, but at the same time subgroups were formed. On a roller coaster ride, this is the stage with ups and downs. Sometimes, the teacher was thrilled by the students’ active participation. The insightful ideas, personal reflections, genuine sharing, creativity of students were positive triggers. But sometimes, the teacher was frustrated with the apathy of the students.

Another critical process during this stage was the preparation of the students’ group presentations. As freshmen who might not have prior experience of conducting academic presentation, this task drew the students together to work for a common goal, but at the same time brought them to resolve conflicts, polarities and animosities that might arise. It was found that positive leadership was critical at this stage to build up group cohesion, boost the group-mates to participate, coordinate the preparatory task, and set up the standard of their performance. This would enhance the “norming” of the group and facilitate the transformation to the “performing” stage [1]. On the contrary, if positive leadership among the group was absent, the group was disorganized and the group members were disengaged. They might experience a loss of direction and cohesion, and the students easily got frustrated with the presentation task. As a result, the “storming” stage was prolonged. Hence, we did not only “teach” leadership in “Tomorrow’s leaders,” we encouraged the students to practice leadership in reality. I have heard a comment from a student:

“We used to do presentation in every subject. In other subjects, we simply divided the task into several pieces and each prepared his/her own part. But in this subject, we gathered together several times, brainstormed the presentation content and activity. And we shared the materials together, including the books, articles and video clips from the Web. We boost one another up at late night. We worked as a group!” (A student from the Faculty of Building and Construction)

Frankly speaking, not all the groups experienced this positive group process. Some were very instrumental and just wanted to get the task done, some had conflictual views and later burst into hot arguments, and some had free-riders and those who were hard-working had to share others’ burdens. To facilitate the positive learning experience of the students, there are some tips that are worth-noting:

- Illustrate the concepts with daily life examples so that the students could grasp the concepts easily;
- Have clear expectations and guidelines on students' presentation, and share with the students during the lectures;
- Conduct preparatory discussion with the groups and support them to make academic presentations;
- Identify the group leaders, be sensitive to the group dynamics and respond appropriately to their needs;
- Encourage the students to search for their unique features in their presentations, such as narrowing down their presentation topics, relating the topic with their major program, making self-reflections etc.

The Performing Stage

I always refer group presentation as the time of the harvest – Students consolidate and crystalize what they have learned and perform a group presentation in front of the whole class. The presentations reflect the students' understanding of the concepts, their creativity and motivation to excel, and their group's effort and cohesion. Students turn from a relatively passive role to an active role during the presentation. This is always a rewarding experience for a teacher, when we witness the students to acquire, digest, apply and reflect on what they had learned. I still remembered clearly how a group of students majoring in Building and Construction produced their own video to illustrate the concepts of social competence, and a group of Applied Science students made a splendid presentation on the sophisticated theories of utilitarianism and libertarianism in relations to morality. There was a group of students in Humanities who led an impressive reflection on how materialism eroded one's spirituality, and a group from School of Nursing shared an inspiring video emphasizing the importance of empathy to patients. The students always surprised me on their creativity and originality in their presentation, and kept reminding me that they did have views and opinions on the topics they presented – they are the masters of their own lives.

On a roller coaster ride, this is the stage when you appreciate the beautiful scenery at the top of the peak, and share the exciting moments with the participants on the ride. You are amazed with what you have seen, and enjoy the moments of what you have experienced.

To make the ride a facilitating learning experience, a constructive feedback on the students' presentation is essential. The learning experience can go beyond the positive youth attributes that the groups has presented, and let the students reflect and cherish the learning process that they have gone through. Appendix 2 is an example of my feedback on a group presentation.

The Termination Stage

Mixed feelings were experienced in this stage, just as when you get off from the roller coaster ride. A sense of achievement and excitement filled with unforgettable memories was experienced, accompanied with a sense of weariness after the fourteen weeks of intense

involvement. During the last lecture, we shared the process with the students, and evaluated the perceived effectiveness of the subject. Many students expressed that they treasured the experience and enjoyed the “ride,” but still there were some who did not appreciate the journey. I have learned to accept the fact, we cannot force every student to love to reflect and make changes, but we do have a simple belief that once the seed is sown, life starts. When the harvest would be is just a matter of time.

Perhaps we may find some answers from their term papers. Students were requested to write a paper covering two parts: critically discuss the concept of a positive youth development attribute and make self-reflections on the possession of the attribute. From their papers, we could share the students’ stories and struggles in facing their own weaknesses. At the same time, we could hear their triumphs when they discovered their strengths. There were many touching self-reflections showing the students’ passion towards their lives. For instance, a student shared her experiences of loss of direction in her secondary school life, and finally discovered her future goals that she decided to commit. Another student shared her resilient story when her father passed away, and how she recovered from the loss.... Simultaneously, we realized that the seeds that we had sown would germinate and grow.

As a subject on holistic development, we expect that the students could keep on searching their life goals and reflect on their life experiences. The roller coaster ride has a terminus, but life is a continuous track filled with experiences. Attitude is latitude! It is important to help the students consolidate the experience and transform them into motives. There are some tips that may be useful:

- Recall the memories of the lectures, group sharing, preparation and performance of group presentations, and appreciate the effort that they have made in their learning process;
- Guide the students to pick up the changes that they have gone through, and celebrate for the positive changes;
- Have clear expectations and guidelines on writing the term papers, and share with the students during the lectures;
- Invite the students to integrate the theories into life practice; and do personal reflections in the term papers;
- Give constructive feedback on their term papers, and give encouragement to them in their reflections.

REFLECTIONS ON TEACHING “TOMORROW’S LEADERS”

Being an experienced social worker but a green teacher in the university, teaching “Tomorrow’s leaders” brought many reflections to me. We are born in a “fast-food” culture, and the emerging “fast-food” attitude has penetrated in every part of our lives. We ask for immediate returns, and perform the cost-benefit analysis to calculate the worth of an action. Ritzer [13] used the term “McDonaldization” to characterize the overwhelming emphases of “efficiency,” “calculability,” “predictability” and “control” in different spheres of life. McDonaldization of the university (or McUniversity) has become the growing trend in higher education, where university serves as a means of consumption for the students to “consume”

knowledge [14]. Knowledge has been reduced to a “commodity.” Another challenge that we have to face is that university has been regarded as a factory production line to “manufacture” the technocrats and professionals that fit the labor market demand [13], and as a “tertiary-level industry” to build up national and international standing so to attract international students [15, 16]. The “commercialization” and “industrialization” of the academy seems inevitable in the changing world where specialization, professionalism and competitiveness are stressed. University has become a vehicle to serve the market, instead of being a platform to nurture the holistic development of the students, and cultivate their civic responsibility to contribute to the society. Chickering [17] strongly commented that universities “have generally ignored outcomes related to moral and ethical development as well as other dimensions of personal development” (p. 1) and “have failed to graduate citizens who can function at the level of cognitive and moral, intellectual, and ethical development that our complex national and global problems require” (p. 3).

The impacts of McUniversity were penetrative, when the students queried about the need to study leadership and intrapersonal development in the university, or when they asked the relevance of leadership attributes to their professional qualifications. Students become more instrumental in selecting the subjects, and their perceptions on “usefulness” of the subjects are often constrained to the grades, qualifications and ease of employment that the subjects would bring to them. However, Jasper [18] reminded us that the principle of the university is to “furnish all the tools and offer all possibilities in the province of the *intellect*, to direct the individual to the *frontiers*, to refer the learner *back to himself* for all his decisions, to his own *sense of responsibility*” (p. 66). There were two twin visions that a university should possess: knowledge of self and knowledge of the boundaries of life outside self [19]. “Tomorrow’s Leaders,” for me, is a restatement of the importance of holistic development in the tertiary education, though it is becoming more challenging to be fulfilled in this era. In responding to the queries of the students on “why” they have to study leadership and intrapersonal development, or when facing the apathy of some students in their reflections and participation, frustrations and despair might arise. The roller coaster journey may not always be a pleasant experience – we may have a dizzy moment. There are three tablets there are very useful: (i) Emotional competence – this is the moment of self-awareness, self-management, self-motivation, relationship management and social awareness [20, 21]. These are the elements that we have taught to the students. (ii) Patience – The students may also be frustrated. Allow some time for the students to get through from the experience. Saleebey [22] reminded us that our brains are filled with plasticity that provides “marvelous capacity to alter, extend, and reshape behavior, feeling, and cognition” (p. 11). Students may change their views when they gain more experience and learning. (iii) Have a little faith – A simple belief of “sowing the seeds” works. Against the trend of McUniversity, we may need to pay more effort, but it is worthy!

For me, the experience of teaching “Tomorrow’s leaders” was very precious not only in my pursuit to be a teacher, but also on my understanding of the needs and ideas of the students. This subject opens the door for me to share the aspirations and despair, ups and downs, strengths and weaknesses of the students, which required mutual trust, acceptance and recognition. Engagement of the students, self-disclosure, high but reasonable expectations of the students’ performance, encouragement and acknowledgement of students’ potential are essential keys to break the ice and build up the trust with the students. Though I had been a social worker before who needed to engage well with my clients in the helping process,

engaging the students in the classroom and accompanying with them in their learning was really a refreshing and treasurable experience to me.

Another reflection of teaching “Tomorrow’s leaders” is the personal growth that I have experienced. The theories, activities and videos prepared for every lecture inspired me to have deeper understanding about myself. The resilience of Steve Jobs (1955-2011) in face of hardship, the persistent motive of Nelson Mandela (1918-2013) in building up one nation of different colors, the serving heart of Mother Teresa (1910-1997) for the poor and the neglected etc. not only inspired the students to have a better understanding about themselves, those “great teachers” also encouraged me to be reflective and persistent towards our life goals. Furthermore, during the lecture, I used to share my stories and experiences with the students, on one hand to make the concepts more down-to-earth and related to their daily life, and on the other hand to stimulate the students to reflect more on their own experiences and views. The self-disclosure process involved my consolidation of the past experiences, as well as my self-understanding of my personalities, strengths, weaknesses and competencies. It is not an easy task, but it is essential and valuable for a new teacher.

PERCEIVED BENEFITS OF THE SUBJECT TO THE STUDENTS

Rome was not built in a day. What I expect the students to get from the subject is to start off their search for their purposes of life, and equip themselves towards their goals with competencies, integrity and strengths. The subject employed different evaluative methods to assess the benefits of the students [23-31]. I would like to share some metaphors that my classes have used to describe the subject, as these metaphors represented the meanings of the subject in respect to their learning. Besides the “roller coaster ride” that I have mentioned in the introduction, there were other interesting and “encouraging” metaphors with the students’ explanations:

- Compass – It gives us direction to improve our thinking, and leads us not just be a good leader, but also a good person.
- Rice – I get the “energy” in my leadership! I become stronger and powerful when leading people in the future.
- Painting – It represents different interesting and colorful points of life and displayed its most amazing part.
- Map – The course shows the different roads to me and helps me to identify the ways which I should go.
- Philosopher – The course directs me how to behave in daily life.
- Mirror – The course can let me know more about myself and make myself a better person.
- Rain in Spring and snow in Winter – It moistures the creatures in silence [written in Chinese].
- Pusher – The course pushes us to think, to learn how to be a leader. That’s a good learn[ing] experience and means a lot in my life.
- Coffee – We have gone through some challenging (bitter) times to do our project, but it is a good experience (taste of social science subject).

- Light at the end of the tunnel – It directs my future.
- Water – We are like a seed and need water to help us grow.
- An electric bulb – The course gradually enlightens my awareness of self-understanding. My harvest is the warmth left on it.
- A coffee shop – I feel relaxed and I am free to express what we have learned. We are also free to share our experience with each other.

I was thrilled by the students' creative ideas as well as positive feedback of the subject. From their descriptions, the subject of leadership and intrapersonal qualities has special meanings to the students in four aspects. First, the subject provides insights and directions for the students to search for their life goals. This is especially important for university students as they are the skeleton of the society in the future. Their motivation for further development, as well as the core values (such as moral standards, honesty, integrity) they possess are their "maps" and "compasses" for the attainment of life goals. Second, the subject enhances their self-understanding and self-awareness through reflections. The "mirror" helps them reflect on their strengths and weaknesses and accept themselves as what they are and what they hope to be. Third, the subject provides different learning opportunities for the students to enhance their competencies, like the "rice" to keep them strong and "paintings" that are filled with colors. Last but not least, the subject gives the students a free and secure environment to share their views and ideas, and facilitate mutual learning through collaborations. The "coffee shop" serves as a platform for them to develop their interpersonal competence.

CONCLUSION

Teaching "Tomorrow's leaders" was an exciting and fruitful experience for me, just like having a roller coaster ride. On one hand I needed to equip the students with knowledge on leadership and intrapersonal competence. On the other hand I was a facilitator who sculpted a learning environment for the students to experience and breakthrough. The students went through the different stages of forming, storming, norming and performing. Some gained a wonderful experience and started to search for their life goals, some identified their own strengths and weaknesses and had a better self-understanding, some developed friendship during the team work process and enhanced their social competence, though some remained queried about the need to study leadership in the university. The students may have diverse experiences during the ride.

In facing the growing trend of "McDonaldization" and commercialization of university education, we sometimes may get misted over the missions and objectives of higher education. Tomorrow's Leaders, as a general education subject that emphasizes on the intrapersonal and interpersonal qualities of the students, is a restatement of the importance of holistic development in university education. I am grateful to be one of the participants in the movement. Lastly, I would like to use the verse of Mother Teresa to express my wish of the subject:

“We ourselves feel that what we are doing is just a drop in the ocean...But the ocean would be less because of the missing drop.”

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APPENDIX 1. THE METAPHOR DRAWN BY A GROUP OF STUDENTS STUDYING “TOMORROW’S LEADERS”



APPENDIX 2. A SAMPLE OF FEEDBACK TO STUDENTS ON THEIR PRESENTATION

Dear Students,

Thank you very much for your presentation. Your presentation demonstrated your teamwork. We are pleased for the effort that you have made. There are six areas that are commendable:

- 1) Rich content – You gave us many important ingredients in understanding social competence. You have clear description of the tri-component model and further highlighted the model and ways of enhancing social competence with examples. You have done comprehensive literature review and your presentation showed your ability to understand the concepts. Well done!
- 2) Systematic presentation – You presented the definitions, concepts, models, importance and ways of strengthening social competence systematically. Your presentation has a smooth flow and covered as much as you could. A good attempt!
- 3) Use of different means in the presentation – You attempted to use different means to arouse the interests of the students, such as video clippings of Ah Yuen and Obama. This showed your meticulous design of the presentation.

- 4) Good management in the preparation – Your group handed in the work (outline and powerpoint) on time, and you worked independently and effectively in the preparation.
- 5) Effort you have made – You have done good review of the topic and made good slides for the presentation. I believe that your group spent much time in the presentation.
- 6) Group cohesion – It is not easy to work effectively in a group, as everyone is unique and has his/her strengths and weaknesses. Your group performed well and members have had high morale. We observe the group cohesion among the members, and no one has been left out. Keep it up! Friendship is precious.

As a learning process, there are three points that you can improve in the future:

- 1) Engage your classmates – It is important to engage the audience and have some interactions with them. Presentation is a part of communication: You convey the message and at the same time, you need to ask feedback from classmates. What makes the difference from information and message is that whether the respondents capture the essence of it.
- 2) More reflections – Try to include your unique thoughts, feelings and reflections in the presentation. Make the experience a fruitful one with personal reflections.
- 3) Better time management in presentation - I could share the worry to make a good presentation in 30 minutes, with such a rich content. Try to allocate the time more efficiently and be more concise in the presentation in the future.

Sincerely speaking, we are impressed by your intellectual ability and effort, as demonstrated in your presentation. Share the “fruit” of learning together!

Add oil!

Best regards,
Janet

Chapter 170

EVALUATION OF A SERVICE LEADERSHIP PROJECT

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ABSTRACT

University students (N = 32) responded to a 45-item subjective outcome evaluation scale after taking a credit-bearing elective subject titled "Service Leadership" at The Hong Kong Polytechnic University in the second semester of the 2013-14 academic year. Both quantitative and qualitative responses were analyzed to give a comprehensive picture on the students' perceptions of the course. Consistent with previous studies, results showed that students generally had positive perceptions of the subject quality, teaching quality as well as the benefits they gained from the program. There was support for the reliability and validity of the subjective outcome evaluation scale. As predicted, quality of program, instructor and program effectiveness were significantly correlated amongst themselves.

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INTRODUCTION

“Serve to learn, learn to serve” is a well-known motto of today’s university education. In the new era of post-industrial and service-driven global economic development, it is necessary to nurture our university students into service leaders beyond the restriction of textbooks—with the mindset and commitment to serving oneself, others and the communities in an ethical manner [1, 2]. In addition, university social responsibility has been an emergent international agenda, which was highlighted in The Second Summit on University Social Responsibility held by The Hong Kong Polytechnic University in November 2014 [3]. The rising demand for qualified young leaders in the service sector provides a good opportunity for universities to promote leadership education through classroom learning and extra-curricular practice as a means to achieve their social responsibility.

A review on the university courses on leadership in different places shows that validated and effective programs are limited, and there are few subjects with the strong focus to promote university students’ understanding, integration and application of the theories, research and concepts of service leadership. Against this background, the Hong Kong Institute of Service Leadership and Management has been pioneering the development of the curriculum of service leadership and management (the SLAM model) in the eight universities in Hong Kong [2]. The aim of the project is to bring a paradigm shift in services and leadership education in Hong Kong and even worldwide [4]. The teaching pedagogy of SLAM grounds on the belief of “the server is the service” as well as the focus on nurturing the character, skills and caring attitude of future service leaders through experiential learning [1].

The classical physics equation “ $E=MC^2$ ” can be used as a metaphor to highlight the three core perspectives of SLAM — an Effective service leader should embrace: a) Moral character, b) generic leadership Competence and c) Caring disposition [2]. $E=MC^2$ is not merely outcome-oriented but also congruent with the process of developing self-understanding, self-leadership and leadership skills of serving and satisfying the needs of oneself, others and society. Moral character refers to one’s sense of morality and development of different character strengths, such as integrity, humanity and traditional Confucian virtues. Generic leadership competence refers to relevant intrapersonal and interpersonal qualities for a successful service leader, such as independent and critical thinking, emotional management, communication skills, conflict resolution and problem solving. Sense of care is also important, which includes respect, loving other people, active listening and empathy for other people.

The Hong Kong Polytechnic University takes a proactive role in adopting the SLAM framework, as well as implementing and evaluating the service leadership courses designed for undergraduate students. “Service Leadership” is an elective credit-bearing subject that has been implemented for four consecutive semesters. The paramount objective of this subject is to promote the service leadership qualities of the students [5]. There are several unique features of the subject. First, instead of following the traditional business-management perspective, the subject emphasizes reflection and promotion of students’ moral character, leadership attributes and caring disposition. Second, experiential learning and interaction between the students and teachers are the major components of the lectures. Students are encouraged to achieve the learning outcomes of understanding, integrating and applying

theories and knowledge of service leadership through group discussion, sharing, project presentation and individual reflective essay. Third, the course serves as an introductory course which provides a good foundation for the students to take another practical service learning course (i.e., Service Leadership through Serving Children and Families with Special Needs) at The Hong Kong Polytechnic University, which is a pioneering attempt in different undergraduate programs [6]. Finally, this subject is characterized by continuous and systematic program evaluation (i.e., objective outcome, subjective outcome evaluation, focus group and qualitative assessments) [5].

Subjective outcome evaluation is an important approach to examine the satisfaction of the students taking the subject as well as the perceived effectiveness of the program [7]. Previous subjective outcome evaluation studies have been conducted to evaluate this subject. Results showed that students were generally satisfied with the subject, implementers and benefits of the program. Besides, the subjective outcome evaluation scale had sound reliability and validity. Perceived program quality and perceived quality of instructors were also significantly associated with program effectiveness and overall satisfaction [8, 9]. As replication is a gold standard in science, there is a need to replicate the positive findings reported previously. As such, this study examined subjective outcome evaluation findings in a new cohort of students.

OUR STUDY

The participants (N=32) were students from different disciplines (i.e., engineering, nursing, design) who took “Service Leadership” in the second semester of the 2013-14 academic year. Students were invited to complete a post-course evaluation questionnaire in the last lecture. Their written consent was all obtained. Enough time was provided for them to answer the questions in a self-administered manner. All the questionnaires were collected and kept strictly confidential. Data cleaning and analyses were conducted by a well-trained post-doctoral fellow.

Instruments

A modified Subjective Outcome Evaluation Scale (SOES) was used in the evaluation. Previous studies showed that this scale possessed adequate psychometric properties [7-9]. The form has five consecutive parts:

1. The Program Content (PC) indicates the perceived quality of the subject in 10 items, such as the objectives of the curriculum, lecture organization, design and implementation of the class activities, and the students’ overall evaluation on the course content (a1 to a10 in Table 1).
2. Program Implementers (PI) includes 10 items as well, which assess the teaching quality (i.e., mastery of the course, preparation, professional attitudes, involvement and caring to the students) perceived by the students (b1 to b10 in Table 2).

3. Program Effectiveness (PE) covers 18 items (c1 to c18 in Table 3), including how students perceive their benefits gained from the course (i.e., development of intrapersonal and interpersonal competencies, improvement in terms of character strengths and caring disposition).
4. Overall Satisfaction (OS) with the program includes 3 items (d1 to d3 in Table 4): a) the extent the students will recommend their friends to take the course; b) their intention to participate in another leadership course; and c) the global satisfaction with the program.
5. Students are also invited to share their additional comments on four open-ended questions (e1 to e4 in Table 5): a) the important things learned from the course; b) the most appreciated things of the course; c) opinions on the lecturers; and d) suggestions for the course development.

To get a comprehensive picture on the students' subjective feelings and perceptions on the subject, all quantitative and qualitative data were analyzed and discussed in this paper.

All data analyses were performed by the statistical package of SPSS 21 (IBM Corp., Armonk, NY, USA). First, the psychometric properties of the SOES were examined in terms of its reliability. Second, as it was expected that different facets of the scale should be inter-related, composite measures of the sub-scales (PC, PI, PE and OS) were created to further test the inter-relationships amongst these variables. Pearson correlation was used to indicate the correlation coefficients amongst the variables. Third, percentages of students' positive rating on each item of the sub-scale as well as their written comments on the overall perceptions of the subject were discussed.

FINDINGS

First, analyses of the sample data showed that the SOES scale had good reliability (see Table 6). Results showed that internal consistency of each sub-scale was all acceptable (above .80): Program Content (Cronbach's alphas = .93; Inter-item correlations = .58), Program Implementers (Cronbach's alphas = .93; Inter-item correlations = .60), Program Effectiveness (Cronbach's alphas = .95; Inter-item correlations = .51), Overall Satisfaction (Cronbach's alphas = .83; Inter-item correlations = .67). As the overall scale and sub-scales were internally consistent, related composite variables were formed.

Second, as predicted, there were significant associations amongst the sub-scales (see Table 7). Pearson correlation analyses showed that there were strong correlations amongst the variables: Program Content and Program Implementers ($r = .87, p < .01$), Program Content and Program Effectiveness ($r = .71, p < .01$), Program Content and Overall Satisfaction ($r = .69, p < .01$), Program Implementers and Program Effectiveness ($r = .68, p < .01$), Program Implementers and Overall Satisfaction ($r = .60, p < .01$), Program Effectiveness and Overall Satisfaction ($r = .63, p < .01$). This observation gives support to the convergent validity of the SOES scale.

Third, the mean scores of different sub-scales could be considered as high: PC (4.12), PI (4.29), PE (3.98) and OS (4.06) which were supported by the percentage findings. In terms of students' perception on the subject (PC, in Table 1), a majority of them enjoyed the experiential and interactive approach of learning, 97% of them appreciated the adequate peer

interaction during the lectures, 91% of them were satisfied with the well-designed activities, and 91% of the students appreciated the overall quality of the course. Regarding the qualitative feedback on the course, students shared that they learned much new knowledge on service leadership. In Table 5, nine out of the 26 positive responses (e1) were related to gaining knowledge in care or caring. Students particularly enjoyed the good interaction with peers and teachers, with 16 out of 27 positive responses (e2) being related to appreciation of good interaction, interactive atmosphere in the class.

Amongst the 10 items of students' perceived quality of instructors, positive responses were over 90% in nine items (PI, in Table 2): 97% of the students appreciated the professional attitude, caring, encouragement and support of the teachers, 94% of them had positive evaluation of the well preparation and teaching skills of the teachers. Linking to the written comments (e3, in Table 5) of the instructors, all valid responses (20 out of 32) were positive. For instance, students wrote, "the lecturers paid so much effort in lessons," "they are well prepared," "keep up the good work, good examples and elaborations," and "giving insights to students."

Besides positive perceptions on quality of the subject and teachers, Table 3 and Table 4 show the percentages of perceived effectiveness of the program (PE) and overall satisfaction (OS), respectively. Roughly 91% of the students agreed that their social competence and self-leadership quality were improved after the course, 88% of them found the course helpful to discover the importance of the proposed framework ($E=MC^2$) of an effective service leader, and 97% of the students had positive evaluations on learning the theories, research and concepts covered in the course. With their positive experiences, 75% of the students indicated their interest to participate in similar leadership courses in the future, and 91% of them would recommend the course to their peers. Overall, 91% of them were satisfied with the course. They also provided many constructive comments on the course (e4, in Table 5), such as providing more practical suggestions for improving leadership skills and using a smaller classroom to facilitate the peer discussion.

DISCUSSION

The study examined the psychometric properties of SOES as well as the effectiveness of "Service Leadership" as a pioneer university subject. In line with the previous studies, the findings of this study demonstrated that SOES had good reliability and validity. As predicted, the total scale and sub-scales were internally consistent and its sub-scales (PC, PI, PE and OS) were significantly associated. As the sample was too small ($N=32$), multiple regression analyses were not performed.

The present findings also showed that a high proportion of the participants had positive evaluations of the course, teachers and perceived benefits to their interpersonal and leadership development. The findings echoed our previous multi-dimensional evaluations on the same subject [10-13]. It is noteworthy that many students gained good knowledge on caring disposition, which is one of the three core elements ($E=MC^2$) in the SLAM model of service leadership. Students learned the importance of caring attitude and providing authentic care to others. In addition, students were satisfied and appreciated the interactive learning and teaching approach, which is one of the uniqueness of the subject—to promote students' self-understanding and acquisition of service leadership knowledge through experiential learning.

Table 1. Summary of the evaluation of the subject (N = 32)

	1		2		3		4		5		Positive response (options 4-5)	
	Strongly disagree		Disagree		Neutral		Agree		Strongly agree			
	N	%	N	%	N	%	N	%	N	%	N	%
a1. The objectives of the curriculum are very clear.	0	0	0	0	5	15.6	21	65.6	6	18.8	27	84
a2. The content design of the curriculum is very good.	0	0	1	3.1	3	9.4	19	59.4	9	28.1	28	88
a3. The activities were carefully arranged.	0	0	0	0	3	9.4	20	62.5	9	28.1	29	91
a4. The classroom atmosphere was very pleasant.	0	0	0	0	5	15.6	17	53.1	10	31.3	27	84
a5. There was much peer interaction amongst the students.	0	0	0	0	1	3.1	17	53.1	14	43.8	31	97
a6. I participated in the class activities actively (including discussions, sharing and games, etc.).	0	0	1	3.1	7	21.9	14	43.8	10	31.3	24	75
a7. I was encouraged to do my best.	0	0	0	0	7	21.9	18	56.3	7	21.9	25	78
a8. The learning experience enhanced my interests towards the course.	0	0	2	6.3	7	21.9	15	46.9	8	25.0	23	72
a9. Overall speaking, I have a very positive evaluation on the course.	0	0	0	0	4	12.5	20	62.5	8	25.0	28	88
a10. On the whole, I like this course very much.	0	0	1	3.1	2	6.3	17	53.1	12	37.5	29	91

Table 2. Summary of the evaluation of the instructors (N = 32)

	1		2		3		4		5		Positive response (options 4-5)	
	Strongly disagree		Disagree		Neutral		Agree		Strongly agree			
	N	%	N	%	N	%	N	%	N	%	N	%
b1. The instructor(s) had a good mastery of the course.	0	0	0	0	3	9.4	18	56.3	11	34.4	29	91
b2. The instructor(s) was (were) well prepared for the lessons.	0	0	0	0	2	6.3	19	59.4	11	34.4	30	94
b3. The teaching skills of the instructor(s) were good.	0	0	0	0	2	6.3	20	62.5	10	31.3	30	94
b4. The instructor(s) showed good professional attitudes.	0	0	0	0	1	3.1	19	59.4	12	37.5	31	97
b5. The instructor(s) was (were) very involved.	0	0	0	0	1	3.1	20	62.5	11	34.4	31	97
b6. The instructor(s) encouraged students to participate in the activities.	0	0	0	0	1	3.1	17	53.1	14	43.8	31	97
b7. The instructor(s) cared for the students.	0	0	0	0	5	15.6	16	50.0	11	34.4	27	84
b8. The instructor(s) was (were) ready to offer help to students when needed.	0	0	0	0	1	3.1	19	59.4	12	37.5	31	97
b9. The instructor(s) had much interaction with the students.	0	0	1	3.1	2	6.3	15	46.9	14	43.8	29	91
b10. Overall speaking, I have a very positive evaluation on the instructor(s).	0	0	0	0	3	9.4	18	56.3	11	34.4	29	91

Table 3. Summary of the evaluation of the perceived benefits (N = 32)

	1	2		3		4		5	Positive response (options 4-5)			
	Strongly disagree	Disagree		Neutral		Agree		Strongly agree	Strongly agree			
		N	%	N	%	N	%		N	%		
c1. It has enhanced my social competence.	0	0	0	0	3	9.4	23	71.9	6	18.8	29	91
c2. It has improved my ability in expressing and handling my emotions.	0	0	0	0	8	25	22	68.8	2	6.3	24	75
c3. It has enhanced my critical thinking.	0	0	1	3.1	8	25	21	65.6	2	6.3	23	72
c4. It has increased my competence in making sensible and wise choices.	0	0	1	3.1	6	18.8	19	59.4	6	18.8	25	78
c5. It has helped me make ethical decisions.	0	0	0	0	8	25	16	50	8	25	24	75
c6. It has strengthened my resilience in adverse conditions.	0	0	1	3.1	7	21.9	16	50	8	25	24	75
c7. It has strengthened my self-confidence.	0	0	1	3.1	7	21.9	15	46.9	9	28.1	24	75
c8. It has helped me face the future with a positive attitude.	0	0	2	6.3	4	12.5	20	62.5	6	18.8	26	81
c9. It has enhanced my love for life.	0	0	2	6.3	10	31.3	15	46.9	5	15.6	20	63
c10. It has helped me explore the meaning of life.	0	0	2	6.3	5	15.6	18	56.3	7	21.9	25	78
c11. It has enhanced my ability of self-leadership.	0	0	0	0	3	9.4	22	68.8	7	21.9	29	91
c12. It has helped me cultivate compassion and care for others.	0	0	0	0	7	21.9	19	59.4	6	18.8	25	78
c13. It has helped me enhance my character strengths comprehensively.	0	0	0	0	5	15.6	21	65.6	6	18.8	27	84
c14. It has enabled me to understand the importance of situational task competencies, character strengths and caring disposition in successful leadership.	0	0	0	0	4	12.5	18	56.3	10	31.3	28	88
c15. It has promoted my sense of responsibility in serving the society.	0	0	2	6.3	9	28.1	14	43.8	7	21.9	21	66
c16. It has promoted my overall development.	0	0	0	0	7	21.9	17	53.1	8	25	25	78
c17. The theories, research and concepts covered in the course have enabled me to understand the characteristics of successful service leaders.	0	0	0	0	1	3.1	27	84.4	4	12.5	31	97
c18. The theories, research and concepts covered in the course have helped me synthesize the characteristics of successful service leaders.	0	0	1	3.1	2	6.3	20	62.5	9	28.1	29	91

Table 4. Students' overall satisfaction with the course (N = 32)

	Positive response (options 4-5)	
	N	%
d1. Will you suggest your friends to take this course? ^a	29	91
d2. Will you participate in similar courses again in the future? ^a	24	75
d3. On the whole, are you satisfied with this course? ^b	29	91

Note: ^a 1= Definitely will not, 2 = Will not, 3 = Not sure, 4 = Will, 5 = Definitely will.

^b 1= Very dissatisfied, 2 = Moderately dissatisfied, 3 = Neutral, 4 = Satisfied, 5 = Very satisfied.

Table 5. Summary of students' written comments on the course (N=32)

	Positive responses	Total responses	Percentage	Highlights
e1. The most important thing(s) learned in the course	26	32	81.3%	-"How to take care of others and the importance to take care of others and yourself. Need to give support to others." -"Caring and sharing. Teachers and partners shared their feelings and experiences, then we would give feedback and appreciation to support." -"I learnt that to serve is better than to be served." -"Group interactions and reflection." -"Lots of interaction between students and lecturers." -"Lots of interaction and activities in the lectures." -"Interactive teaching and learning." -"Interactive activities, recap video, music, video, sharing." -"Lots of interaction, demonstrate our knowledge by doing presentation and assignments which is the most effective."
e2. The things that appreciated most in the course	27	32	84.4%	-"The lecturers paid so much effort in lessons (e.g., preparing a gift in the first lesson and a very detailed Power point)." -"They are well prepared." -"Keep up the good work, good examples and elaborations." -"Giving insights to students."
e3. Comments on the lecturer(s)	20	32	62.5%	-"Find another lecture hall, may be a smaller one that would help to discuss with classmates." -"Focus too much on theories, may allow students to practice more." -"Give more suggestions for improving leadership skills. Not only emphasize the importance of service leadership."
e4. Areas for improvement	11	32	34.4%	

Table 6. Means, standard deviations, Cronbach's alphas, and mean inter-item correlations amongst the variables

	Mean	Standard deviation	Cronbach's alpha	Mean inter-item correlations
1. Program Content (PC: 10 items)	4.12	0.54	0.93	0.58
2. Program Implementers (PI: 10 items)	4.29	0.48	0.93	0.60
3. Program Effectiveness (PE: 18 items)	3.98	0.50	0.95	0.51
4. Total Effectiveness (TE: 38 items)	4.10	0.46	0.97	0.47
5. Overall Satisfaction (OS: 3 items)	4.06	0.60	0.83	0.67

Table 7. Correlation coefficients amongst the variables

Variable	1	2	3	4
Program Content (10 items)	-			
Program Implementers (10 items)	.87**	-		
Program Effectiveness (18 items)	.71**	.68**	-	
Total Effectiveness (38 items)	.91**	.89**	.92**	-
Overall Satisfaction (3 items)	.69**	.60**	.63**	.70**

Note: ** $p < .01$.

Overall, the study could make a contribution to the scholarship of service leadership and the leadership programs in the higher education.

Although the present findings are positive, some areas should be further improved in the future studies. First, the sample size of this study was quite small. As such, factor analysis could not be conducted to further explore the dimensionality of the main factors and multiple regression analyses could not be meaningfully conducted. Second, comparison of different findings by using different evaluation methods is preferred. It is necessary to further explore students' critical reflections and narratives on their learning experiences. It is also helpful to integrate evaluation of objective outcome (pre-test and post-test of students' intrapersonal and leadership development) and subjective outcome to enrich the understanding of the overall effectiveness of the subject. Last but not least, with positive feedback on interactive and mutual learning, it will be meaningful to expand the outcome-based evaluation to observe the teacher-student interaction and the exchange and discussion of some new ideas on service leadership throughout the subject.

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Chapter 171

QUALITATIVE EVALUATION OF LEADERSHIP

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ABSTRACT

A subject entitled "Tomorrow's Leaders" aiming at promoting the holistic development of university students was offered to students at The Hong Kong Polytechnic University. Toward the end of the term, students were invited to give descriptors and metaphors about the subject. Based on the written narratives of 1,029 students, it was observed that most students used positive descriptors to describe the subject. Concerning the metaphors that could stand for the subject, most of the metaphors are positive in nature. Reliability analyses based on randomly selected coded responses showed that intra- and inter-rater reliabilities were high. In conjunction with other

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evaluation findings, the present study suggests that this subject was able to promote the holistic development in Chinese university students in Hong Kong.

INTRODUCTION

The quantitative-qualitative methodology debate appears to be everlasting in the field of evaluation [1-10]. On the one hand, some researchers argued that quantitative and qualitative evaluation methods cannot be combined because they have different axiological and paradigmatic considerations [11, 12]. According to Denzin and Lincoln [11], “[c]ommensurability is an issue only when researchers want to ‘pick and choose’ among the axioms of positivist and interpretivist models, because the axioms are contradictory and mutually exclusive” (p. 117). On the other hand, there are theorists arguing that both quantitative and qualitative methods are compatible for any evaluation research with reference to specific conditions of practice [13-16]. Besides, the concept “methodological appropriateness” has been coined [13, 14, 17, 18]. According to Patton [17], methodological appropriateness was defined as “matching the evaluation design to the evaluation situation taking into account the priority questions and intended uses of primary intended users, the costs and benefits of alternative designs, the decisions that are to be made, the level of evidence necessary to support those decisions, ethical considerations, and utility” (p. 460). Patton [17] further proposed eight developments contributing to the feasibility of methodological appropriateness. For example, there is a growing consensus on interdisciplinary and multi-method approaches to evaluation.

With specific reference to the recent discussions of paradigms in the field evaluation, there are three main paradigms. They are post-positivism, constructivism and related perspectives, and pragmatism [17, 19-21]. For example, Alkin [19] pointed out that the goal of post-positivistic research is trying to measure universal truth and its causal relationships amongst variables, although a perfect understanding of the truth cannot be achieved because of various observational errors. Constructionists, however, do not believe in one single truth; there are many truths that are relative to one’s cultural and historical experiences. Relationships are also interdependent and thus no linear causal relationship can be found. Hence, observational biases need not be controlled but acknowledged. Moreover, the pursuit of local relevant findings is more appreciated than searching for universal truth. Pragmatists, like constructionists, also believe in no one single truth but one explanation of reality can be regarded “truer” than the other at a given timeframe; they also believe in causal relationships, like post-positivists, but in a more sophisticated manner [21, 22].

Besides the choice of paradigm in evaluation, it is also important to consider which method is suitable to be used under what conditions. In fact, a review of literature in educational evaluation has also shown that many approaches and models are available for various uses. First, House [23] proposed various evaluation models such as the utilitarian and intuitionist/pluralist perspectives. Second, Worthen and Sanders [24] classified six alternative approaches to educational evaluation. They are objectives-oriented, management-oriented, consumer-oriented, expertise-oriented, adversary-oriented, as well as naturalistic and participant-oriented approaches. Third, Scriven [25] suggested another six types of evaluation approaches, including strong decision support view, weak decision support view, relativistic view, rich description approach, social process school, and constructivist approach. Fourth,

Stufflebeam, Madaus, and Kellaghan [26] analyzed twenty-two program evaluation approaches to identify which approach is the worthiest one to be applied under certain conditions. Fifth, Cousins and Ryan [27] suggested four ongoing issues for educational evaluation, including evidence-based policy and programming, performance measurement, auditing and monitoring, learning and discovery-oriented evaluation, and values-oriented evaluation.

In the context of higher education, many approaches have similarly been used to assess the effectiveness of courses and programs. Amongst the various approaches that have been adopted, it is common to conduct mandatory course evaluation (i.e., subjective outcome evaluation) at the end of the semester [28]. As a means of obtaining information about the strengths and weaknesses of a course and to make instructional and administrative decision [29], course evaluation usually takes the form of a series of ubiquitous Likert scales [28, 30, 31]. Although course evaluation is an efficient way to gauge the views of the students, it might not be able to reflect the complexity of the subjective learning experiences [32]. Starr-Glass [28] regarded course evaluation based on the questionnaire approach “fail[ing] to capture the quintessential dimensions of learning engagement” (p. 198). Parlett and Hamilton [33] commented that many formal evaluations present “an emaciated and artificial picture of real education life” (p. 16). In order to address these criticisms, it is argued that qualitative evaluation methods could give some additional information on the merits and effectiveness of a course.

There are many qualitative evaluation approaches and methods [13, 14, 34, 35], such as focus groups, interviews and written reflections. In this study, qualitative data in the form of written descriptors and metaphors were collected to understand the perceived benefits of a subject. The concept of metaphor has been emphasized in the field of educational evaluation [14, 36-39]. Metaphors are used in everyday communication and they can be regarded as good representations of realities [40]. Metaphor has been conceived as a fundamental vehicle that people use to understand, express, construct and organize their world [39-42]. It provides insights for new perspectives and innovation [39], helps people to explain unknown experiences by known one [42], serves as a convenient way to communicate a complex idea [43], describes important features of a complex array variables in a simple form [44], transmits a complete story using simple images [45], and offers dynamic and dramatic views beyond the surface of things and reveals their deeper significance [46].

In terms of conceptualization of metaphor as an analogy, metaphor is defined as an analogy that imaginatively identifies one object with another [47] and as an analog device that serves as a means for framing and defining experiences [48]. Yob [49] further explained that metaphor is employed when one wants to explore and understand something esoteric, abstract, novel or highly speculative.

In the domain of education research, Martinez, Saulea and Huber [50] argued that teaching and learning could be addressed from three major perspectives. The first one is the behaviorist/empiricist perspective. This perspective regards the learner as passive and knowledge is developed by forming associations and by subdivision of learning tasks into small and logically sequenced components. Under this perspective, teachers may be treated as transmitters of information whereas learners as passive recipients in metaphors. The second one is the cognitive/constructivist perspective. This perspective regards development of knowledge as actively constructed by the learner through transforming the old schema into a new one. Under this perspective, teachers may be treated as facilitators of information

whereas learners as active agents of the learning process in metaphors. The third one is the situational/socio-historical perspective. Under this perspective, learning is situated in the social context in which it is constructed. Knowledge is a by-product of the activity, context, and culture in which it is used. Classifying metaphors of teaching and learning into three major dimensions provides a basic conceptual framework to understand the educational beliefs of the teachers and students.

Concerning the meaning of metaphor in the field of education evaluation, Madaus and Kellaghan [51] argued that metaphors “influence the way we understand and talk about education; they create mind-sets and influence behavior toward school and teachers; they also influence the kinds of questions we ask about educational programs”. Results of related research indicate that metaphor is able to illustrate diversified and authentic understanding of the respondents [28, 32, 52, 53]. Alvesson [54] further suggested that a sophisticated use of metaphor can “facilitates offering various comprehensive images of research, thus reducing the risk of latching on to a one-sided and favourite conception”. However, Alvesson [54] also stated that “we can think in contradiction to our favored metaphors and not just deviate from the thinking they encourage in those exceptional cases where they clearly don’t work”. This reminder of using metaphor is also shared by other scholars [55, 56].

Nevertheless, the use of metaphor in education contexts does contain drawbacks [57]. First, metaphors have a constrained conceptual framework because the assumptions and predispositions reflected by the metaphors can only related to the phenomena the author intends to cover [56]. Second, metaphors may create distortions because metaphors create “a way of seeing” and “ways of not seeing” at the same time [55]. Despite these limitations, research shows that there are several merits of using metaphors in education contexts [57]. First, metaphors provide coherent and internal consistent information that gives insights into implicit ideas. Second, metaphors are evocative and stimulating for people to tease out connections that might not be made use of by direct questions [57]. Third, metaphors synthesize a large amount of knowledge about teachers, learners and teaching methods [58]. Fourth, metaphors serve as tools for teachers to gain distances from their own practices and to act as external observers reviewing their teaching. Fifth, metaphors make implicit knowledge explicit through reflection on and representation of the concepts. Sixth, metaphors give a language that can connect theory and practices. Seventh, metaphors empower teachers to examine their own assumptions and to explore hidden intellectual avenues [59]. Finally, metaphors reflect upon alternative teaching practices and theoretical frameworks [57].

Given the fact that metaphors and related concepts like descriptors have many strengths, metaphors play a central role in conceptualizing and reflecting upon the nature of teaching and learning [57] and they have been used as tools to evaluate education programs. For instance, to evaluate a distance-learning course in business and economics at the undergraduate level, Starr-Glass [28] asked the students to provide semantic indicators and metaphors and found that the course was promoting independent thoughts, consideration and reflection. In addition, with the use of semantic indicators and metaphors, Starr-Glass [28] identified “a great of ostensibly significant and authentic emotional engagement with the course” (p. 205). Thomas and Beauchamp [32] used metaphors in semi-structured interviews to explore the learning experiences of newly graduated teachers in terms of their professional identity. Newly graduated teachers were interviewed immediately after graduation of their teacher education programs and after their first year of teaching. The participants were asked

to create their own metaphors on teaching experiences. The metaphors were coded using NVivo. The findings indicated that the new teachers struggled to develop their professional identity during their first year, and that this development process was gradual, complex and often problematic. Research also examined how metaphors revealed changes of pre-service elementary teachers' beliefs about learning and teaching. The factors contributing to the changes of pre-service elementary teachers' beliefs were also examined [57].

Finally, Levin and Wagner [52] also used metaphors to explore eighth grade students' views on writing in science classrooms. They divided 97 eighth graders into intervention classes and comparative classes. In the intervention classes, students were assigned to complete informal reflective writing tasks whereas the students in comparative classes were not required to write anything. At the end of the teaching units, all students were required to submit two final reflective writings. Levin and Wagner [52] analyzed the students' writing and found that the students in the intervention group expressed emotional dimension less than the students in the comparative group. The students in the intervention group expressed the social dimension more than the students in the comparative group. Levin and Wagner [52] further analyzed the contents of the reflective writing. The results showed that the writing-to-learn task, feedback and reflective writing greatly influenced students' views on writing.

Although research utilizing metaphors and related descriptors is available in education evaluation research, studies focusing on learning experiences from students' perspective at university education setting were limited. A computer search of PsycINFO in March 2014 using the search terms of "metaphor", "university education" and "evaluation" showed that there were 52 citations. A similar survey of Social Sciences Citation Index using the same search terms only located 3 citations. If adding "descriptor" as a search term, no citation was found. These figures imply that there are only few studies using metaphors and descriptors to understand the subjective learning experiences from students' perspectives, especially in the Chinese context [60]. To fill this research gap, the present study intended to explore the views of university students on a subject on leadership and intrapersonal development using metaphors and descriptors.

To promote holistic development of university students and address community concern about young people [61], a general university requirements subject titled "Tomorrow's Leaders" was offered at The Hong Kong Polytechnic University to cultivate various intra- and inter-personal competences of students. Through lectures, experiential learning, group presentation and individual assignments, students were nurtured on their self-understanding, personality, emotional competence, cognitive competence, resilience, spirituality, social competence, moral competence, positive identity, interpersonal communication, conflict resolution, team-building, and relationship-building.

In the pilot phase, research indicated the effectiveness of the course by several evaluation strategies. These included: a) pretest/post-test questionnaires using the Chinese Positive Youth Development Scale to examine changes in intra- and inter-personal qualities in students [62], b) subjective outcome evaluation at the end of each lecture, c) post-course subjective outcome evaluation conducted at the end of the whole course [63], d) process evaluation via systematic observation [64], e) focus group interview for students' views on their learning experiences [65], and f) descriptors and metaphors about the students' feelings and perception of the course in a reflection sheet. Based on the data collected in the formal

implementation phase, the objective of this study was to evaluate the subject based on the descriptors and metaphors written by the students.

OUR STUDY

Sixteen classes of students took this course, with a total enrollment of 1,029 students (57 in Class A, 52 in Class B, 58 in Class C, 70 in Class D, 59 in Class E, 55 in Class F, 83 in Class G, 66 in Class H, 84 in Class I, 73 in Class J, 91 in Class K, 72 in Class L, 56 in Class M, 58 in Class N, 52 in Class O and 43 in Class P). At the end of the course, the personal reflection forms were given to the students in which they were invited to fill in two parts. In the first part, students were invited to use three words or phrases to describe their feelings, perceptions and experiences about taking this subject (i.e., descriptors of this course). In the second part, students were invited to think about a metaphor which could stand for the course and give some explanations about the meaning of the metaphor. The metaphor may be an object, an event or a state (e.g., a wonderful journey, a seed or a book).

Data Analyses

A total of 633 personal reflection forms were collected from the students. Their responses in the reflection form were entered in the computer for analyses. Four researchers were involved in the data analysis process. Two research assistants were responsible for the “descriptor” part and the other two were responsible for the “metaphor” part. A meaningful unit was used as the basic unit of analysis. For instance, the statement that a course was “wonderful and relaxing” was broken into two meaningful units, namely “wonderful” and “relaxing”. On the other hand, descriptions with the same meaning (e.g., “relaxed” and “relaxing”) were grouped into the same attribute category. Regarding the positivity of the codes, four possible codes were involved, including positive codes, negative codes, neutral codes and undecided codes. A total of 1,881 descriptors and 613 metaphors were coded and analyzed.

According to Miles and Huberman [66], check-coding facilitated definitional clarity and it also served as a good reliability check. Check-coding becomes sharper when two researchers code the same data set and discuss their initial difficulties. To enhance the reliability of the coding on the positivity nature of the raw codes, both intra- and inter-rater reliabilities were conducted. Regarding the first part (i.e., descriptors), 40 randomly selected descriptors were re-coded among the two researchers to check for the intra-rater reliability. Regarding the inter-rater reliability, 40 randomly selected descriptors were also re-coded among the other two researchers who did not involve in the initial coding process.

Regarding the second part (i.e., metaphors), 40 randomly selected metaphors were re-coded among the two researchers to check for the intra-rater reliability. With a view to check for the inter-rater reliability, 40 randomly selected metaphors were also recoded among the two researchers who were not involved in the initial coding process. The raw data files and

steps involved in the development of coding system were properly documented and systematically organized.

Table 1. Categorization of descriptors to describe the course

Descriptors	Nature of the responses				Total
	Positive	Neutral	Negative	Undecided	
Comprehensive	44				44
Creative	13				13
Enjoyable	63				63
Funny	70				70
Good	51				51
Happy	44				44
Inspiring	204				204
Interactive	58				58
Interesting	237				237
Knowledgeable	9				9
Leadership	7				7
Meaningful	142				142
Positive	19				19
Practical	4				4
Reflective	92				92
Relaxing	140				140
Self-understanding	15				15
Touching	7				7
Unique	4				4
Useful	286				286
Warm	14				14
Well-organized	4				4
Co-operation	23				23
Self-improvement	17				17
Teaching staff attributes	20				20
Other positive descriptors	158				158
(e.g., I'm loving it, time flies when you enjoy yourself)					
Memorable		19			19
Other neutral descriptors		27			27
(e.g., games, new experience to me)					
Abstract			3		3
Boring			17		17
Demanding			10		10
Long lesson			6		6
Useless			5		5
Other negative descriptors (e.g., confused, tired)			26		26
Academic				14	14
Creative				1	1
Unexpected				8	8
Total count, n	1745	46	67	23	1881
Total count, %	92.77	2.45	3.56	1.22	100

Table 2. Descriptors coded as negative responses

Negative descriptors	n
Boring	17
Demanding	10
Long lesson	6
Useless	5
Abstract	3
Other negative descriptors	26
Total	67

Table 3. Categorization of the metaphors to describe the program

Metaphors	Nature of metaphors					Number of codes derived from the metaphors and its nature				
	Positive	Neutral	Negative	Undecided	Total	Positive	Neutral	Negative	Undecided	Total
Air and earth	5				5	6				6
Apple	6				6	11				11
Beacon	7	2			9	12				12
Book	18				18	21	1	2		24
Box	1			1	2	1			1	2
Buffet	9			1	10	11	1	1		13
Chinese medicine	4				4	6		2		8
Compass	30				30	39				39
Cooperation	1			1	2	1			1	2
Dictionary and wikipedia	4	1			5	4	1			5
Garden	5				5	5			1	6
Journey	30	1	1		32	45	3	2		50
Lego	4				4	4				4
Library	4				4	7	1			8
Light	29				29	46				46
Map	7				7	11				11
Microscope	7				7	9				9
Mirror	36				36	50				50
Pizza	4				4	7				7
Planting	6				6	5				5
Rainbow	9				9	13				13
Sea and sky	5				5	5				5
Seed	7	1			8	8	1			9
Snow ball	4				4	5	1			6
Star	4			1	5	4			1	5
Sweets	15	1		1	17	24		3	1	28
Tree	6				6	13				13
Water and sun	25	1			26	45	2			47
Annoying orange				1	1				1	1
Rain in spring and snow in winter				1	1				1	1
Other metaphors	277	20	9		306	437	28	31	2	498
Total count, n	569	27	10	7	613	855	39	41	9	944
Total count, %	92.82	4.4	1.63	1.14	100	90.57	4.13	4.34	0.95	100

FINDINGS

Qualitative findings on two areas are presented as follows: (a) descriptors that were used by the participants to describe the program; and (b) metaphors (objects, occasions, feelings) that were used by the participants to portray the program. The descriptors that the participants used to describe the program are presented in Table 1. There were 1,881 raw descriptors in total, which could be further classified into different classifications.

Table 4. Illustrations of metaphors coded as negative

1.	Boring
2.	Bitter
3.	Process is hard
4.	Theories are not attractive
5.	Boring and dull
6.	Bitter at first
7.	Demanding workload
8.	Don't find my way in the first lecture
9.	Intangible
10.	Annoying
11.	Appearance is not attractive
12.	Boring lectures
13.	It is not yummy
14.	Difficult in project part
15.	Difficult to apply in daily life
16.	Do not want to do it at the beginning
17.	I did not learn anything
18.	It is not an interesting subject
19.	Long lecture hour
20.	Many concepts but they are difficult to understand
21.	Mysterious
22.	Not attractive
23.	It is not easy to learn those concepts and search for the eggs
24.	It is not helpful to me
25.	It is not useful to me
26.	Quite confusing
27.	I can't understand the concepts
28.	It takes short time to master them
29.	Students have chances to do reflection in class but they simply don't have the initiative to do so
30.	The subject on the whole is quite time-consuming as well as its assignment and projects
31.	Topics are not connected
32.	Useless

Among all of the descriptors, 1,745 (92.8%) of them were positive responses, 67 (3.6%) of them were negative responses (see Table 2), 46 (2.5%) of them were classified as neutral responses and 23 (1.2%) of them were undecided. It was found that the participants used "boring", "demanding", "long lesson", "useless", "abstract" to describe most of the negative responses, while the remaining responses were classified as other negative responses. Eighty raw descriptors were randomly selected for the calculation of the reliability tests. The intra-rater reliability was 100% whilst the inter-rater reliability was 95%.

The categorization of metaphors written by the participants is shown in Table 3. There were 613 raw metaphors which could be further categorized into different categories. Among the responses, 569 (92.8%) of them were positive responses while 10 (1.6%) of them were negative responses. The description for the negative responses can be seen in Table 4. Results revealed that participants used different expressions to describe the program, with most using “mirror” as the metaphor. Some participants used “journey”, “compass”, “light” and “water and sun” to describe the program. Eighty raw metaphors were randomly selected for the calculation of intra- and inter-rater reliabilities of the coding. The related values were 95% and 92.5%, respectively.

DISCUSSION

Based on the qualitative data on the descriptors and metaphors collected from students, the present study investigated perceptions of students of “Tomorrow’s Leaders”, a credit-bearing course enhancing holistic development of the students at The Hong Kong Polytechnic University, in the full implementation stage. There were several distinctive features of the present study. First, the present study provided a qualitative evaluation on the subjective learning experiences of the students based on metaphors and descriptors. As there are few related studies in this area, this study fills the research gap in this area. Second, this study demonstrated how qualitative data of the metaphors and descriptors from students supplemented quantitative course evaluation using ubiquitous Likert scales. Unlike numbers and statistics, the metaphors and descriptors showed complexity of the subjective learning experiences of the students [32]. Third, a large sample was used in this study. This is unique because the sample size in qualitative studies is usually small.

This study provided evidence supporting the positive impacts and effectiveness of “Tomorrow’s Leaders” based on qualitative data on the subjective experiences of the students. Two salient conclusions can be drawn from the present study. First, students perceived the course positively. Roughly nine-tenth of the responses in the descriptors and metaphors were positive (see Tables 1 and 3). For example, the students described the course as “interesting”, “inspiring” and “useful” according to the descriptors collected (see Table 3). Most of the negative responses were related to the views that the course was boring and academically demanding. Although the negative responses accounted for only 3.6% of the responses, this information was useful for further improvement of the course. Another observation was that some negative responses were contradictory in nature. For instance, some students reported that the lecture time was too long whereas some regarded that the lecture was too short for them to master the knowledge.

The positive feedback obtained in this study is consistent with other evaluation studies based on different methods [60, 62-65, 67-73]. For instance, objective outcome evaluation findings showed that students had positive changes in intra- and inter-personal competences after taking the course [62]. In addition, both subjective outcome evaluation at the end of each lecture and post-course subjective outcome evaluation showed that students had positive perception of the program, implementers and effectiveness [63, 71]. Process evaluation via systematic observation also showed that the program had high program adherence [68]. In

sum, research findings in different studies suggested that the course brought positive impacts on students for their holistic development and students had positive views on the course.

Nevertheless, although positive feedback was documented among focus groups, alternative explanations should be acknowledged [74]. First, positive responses from students might be due to demand characteristics. However, this explanation was not plausible because students freely gave their responses and negative comments were noted. In addition, the identity of the students was not revealed in their submission. Second, favorable results might be explained by researchers' preoccupations about positive evaluation outcomes. However, intra- and inter-rater reliabilities as well as disciplined data analyses were performed to reduce possible biases in data collection and analyses.

While the findings are positive, it should be noted that the present study faced several limitations. First, metaphors and descriptors from students were collected toward the end of the course. It would be illuminating if data could be collected at different time points (e.g., mid-term evaluation). Second, in addition to metaphors and descriptors, in-depth individual interviews of both students and teachers could be attempted. This can allow researchers to understand the subjective experiences in different stakeholders. Finally, due to practical and time constraints, peer-checking and member checking were not carried out. It would be desirable to add such feedback mechanisms in future. Despite these limitations, the present study provides qualitative findings to support the positive features and effectiveness of the course "Tomorrow's Leaders" and its effectiveness from the perspective of the students.

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Chapter 172

FOCUS GROUP EVALUATION

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ABSTRACT

In this chapter, five focus groups involving 30 students were conducted to evaluate a subject entitled "Tomorrow's Leaders", which was designed to promote the leadership and intrapersonal competence of university students under the new four-year undergraduate curriculum at The Hong Kong Polytechnic University. Four major themes could be highlighted from the narratives of the participants. First, the students generally had positive perceptions of the subject and the learning process, and positive features of the subject and related experiences were also identified. Second, the students pointed out that they had personal gains and positive changes after taking this subject. Third, the students generally felt that there was a need for this subject. Finally, the students mentioned some negative aspects of the subject and they proposed some suggestions for the refinement of the subject. Overall speaking, the qualitative findings suggest that the students had positive views about the subject and they experienced the benefits of taking this subject.

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INTRODUCTION

In the field of evaluation, many different approaches have been proposed. For those who believe in the natural science models, experimental evaluation strategies such as clinical trials and quasi-experimental studies have been used. Actually, findings based on randomized controlled trials are usually regarded as the “gold standard”. However, experimental and quantitative approaches to evaluation have been criticized as superficial which cannot give any in-depth inquisition of the experiences of the program participants in the process. Hence, in contrast to the quantitative and experimental approaches, researchers have argued for the use of qualitative evaluation methods to examine the meaning of a program to its participants and the related program effects. Patton [1] pointed out that qualitative evaluation would be desirable if the evaluator wishes to look at individualized outcomes and internal processes of a program. Besides, the quest for in-depth and descriptive information, diverse and unique views of the stakeholders, and new insights from human interactions would motivate one to adopt qualitative evaluation methods. Finally, if an evaluator wishes to be humanistic and personal and these are the ideological principles to be maintained, qualitative evaluation should be used. The qualitative research is therefore attempting to “make sense of, or interpret, phenomena in terms of the meanings people bring to them” [2].

There are different strategies and data collection methods in qualitative research, such as interviews, observations, and textual analyses [2]. Amongst these methods, focus groups are commonly used in the context of evaluation. Focus group interview is a qualitative research method which assesses clients’ opinions and program quality in different fields, including mass communication and public opinion [3], education and psychology [4], and health settings [5]. According to Kamberelis and Dimitriadis [6], “focus group research is a key site where pedagogy, politics, and inquiry intersect and interanimate each other. Because of their synergistic potentials, focus groups often produce data that are seldom produced through individual interviewing and observation and thus yield particularly powerful knowledge and insights” (p. 559).

The advantages of adopting focus group interviews include cost-effectiveness in data collection [7, 8], allowing interactions among group participants that stimulate a fruitful exchange of ideas [4, 9], and enhancing data quality by checks and balances of the ideas shared by one another [10]. A wide range of perspectives on the research issues could be sought and some cultural-specific or community-specific norms or practices could also be identified in the group environment. Despite the advantages of using focus group interviews in exploring the depth of the research issues, various experienced qualitative researchers highlighted some methodological issues in doing qualitative research [2, 7, 10, 11]. First, the response time available for each participant is limited because of the presence of other members in the group. Second, a skillful moderator is required to facilitate a fair and free-eliciting communication environment. Third, issue of confidentiality can hardly be guaranteed in focus group settings because of the involvement of many people. Fourth, the focus group interviews are conducted in an arranged setting and thus the interactions among participants may not be as natural as usual.

Despite the wide use of focus group interviews in social science research, there are few studies using this method as an evaluation method in higher education settings [12-14]. Only 22 citations were found based on a survey of PsycINFO in March 2014 when “focus group”,

“university education” or “college students” were used as keywords. A similar search of Social Sciences Citation Index using the same keywords only located 37 citations. These two searches also indicated that there were limited focus group evaluation studies in Chinese populations [14]. Recently, there are views suggesting that evaluators should use more focus groups in higher education contexts [15-22]. With specific reference to Hong Kong, Shek and Sun [14] used focus group interviews as an evaluation methodology for a general education course. The use of focus group interviews aids the researchers to obtain a community-specific (i.e., the students who have attended the general education course) perceptions of the course contents, lecturers, and the learning process. The results showed that there were personal gains and positive changes in students after taking the course. The students also voiced out the urgent need for similar courses in university settings.

Concerning university students in Hong Kong, Shek and Wong [23] identified several problems, including high level of mental distress, low social responsibility, drop in empathy, rising narcissistic personalities, and lower level of maturity. To respond to the needs of Hong Kong university students utilizing a holistic development approach, the first author developed and offered a subject entitled “Tomorrow’s Leaders” to cultivate various intra- and interpersonal competences of students under the General University Requirements at The Hong Kong Polytechnic University. Concepts of self-understanding, personality, emotional competence, cognitive competence, resilience, spirituality, social competence, moral competence, positive identity, interpersonal communication, conflict resolution, team-building, and relationship-building are covered in this course. It is expected that students can learn these concepts through lectures, experiential learning, group presentation, and individual assignment, and apply them in their daily life.

There are several studies showing the effectiveness of this course in the pilot stage. These studies used several evaluation strategies including a) a pre-test/post-test design using the Chinese Positive Youth Development Scale to examine changes in intra- and interpersonal qualities in students, b) subjective outcome evaluation at the end of each lecture, c) post-course subjective outcome evaluation at the end of the whole course, d) process evaluation via systematic observation, e) focus group interviews for gathering students’ view on their learning experiences, f) descriptors and metaphors from students about their feelings toward the course, and g) students’ perception of the course written on a reflection sheet [14, 24-37]. Taken as a whole, the evaluation findings were very positive, suggesting that the subject was well-received by the students and students generally felt that they benefitted from the course. Bloor et al. [38] suggested that the findings of focus group interviews can be mixed with that of other evaluation methods which can generate a triangulated picture. The triangulated picture generated from the existing evaluation studies generally showed that the subject could promote the holistic development of the students. To further understand the impacts of the subject on the students, this paper reports evaluation findings of the course “Tomorrow’s Leaders” in its full implementation stage based on focus group data. Translated excerpts (originally in Cantonese and Putonghua) of the focus group interviews would also be presented to support the findings.

OUR STUDY

Sixteen classes of students took this course, with a total enrolment of 1,029 students (57 in Class A, 52 in Class B, 58 in Class C, 70 in Class D, 59 in Class E, 55 in Class F, 83 in Class G, 66 in Class H, 84 in Class I, 73 in Class J, 91 in Class K, 72 in Class L, 56 in Class M, 58 in Class N, 52 in Class O, and 43 in Class P). After the completion of the subject, local and non-local students were asked to participate in focus group interviews. Five focus groups were conducted as follows: Group 1 (8 local students), Group 2 (4 local students), Group 3 (7 local students), Group 4 (6 local students), and Group 5 (5 non-local students). All of the interviews were audio-taped, transcribed, and then checked for accuracy in transcription.

Instruments

To conduct the focus group interviews, a semi-structured interview guide based on the CIPP evaluation model (Context, Input, Process, Product) developed by Stufflebeam [39] was used. The CIPP model provides a systematic way of looking at different aspects of the curriculum development process as well as outcomes. Based on the CIPP model [39], questions about the context, input, process and product were asked. About context evaluation, questions on the difference between “Tomorrow’s Leaders” and other courses, and whether the students thought the existing university education was able to help them develop in a holistic manner were asked. For input evaluation, questions on whether the subject matter was difficult and how much time the students put into the course were asked. For process evaluation, questions on their views of the subject and the teaching/learning process were asked. Finally students were asked about the changes they had after taking this course.

Based on these questions, the data were collected and analyzed with reference to the following domains: (a) positive comments about the subject, class, and the lecturers; (b) benefits that students thought the subject had brought to them; (c) negative comments about the subject; (d) whether there was a need to have this subject; and (e) suggestions for future improvement. For the data analyses, broad themes related to the above domains were extracted to give a general picture of the process and outcomes of the evaluation. The analyses were discussed and reviewed by the researchers.

FINDINGS

Based on the results of thematic analyses, four major conclusions could be drawn from the focus group interview data.

Conclusion 1: Students Had Positive Perceptions of the Subject, Learning Process, Features of the Subject and Related Learning Experiences

Generally speaking, students had positive perceptions toward the nature, content, and lecturers of the subject. The students liked the experiential learning activities. They thought

the activities did help them gain the knowledge and understand themselves better, as shown in the following narratives.

- “It (“Tomorrow’s Leaders”) provided varied activities that enhanced discussions among group mates with the relevant topics. Comparing with other lectures that conducted in merely lecturing, this subject allowed students to interact more.”
- “Playing this game allowed us to discover our own ‘blind spots’ in interpersonal communication. The use of activities could help us understand the theories better than reading papers by ourselves which is quite time-consuming.”
- “I think the contents were good because the leadership skills focused in this subject were related to the self-level, like self-awareness and self-improvement. These were excellent contents.”
- “This subject related to our daily life and future career much, like teaching us the ways to cope with life challenges. ‘Tomorrow’s Leaders’ was an all-rounded subject.”

The students also showed their appreciation of the lecturers. They were impressed by the flexible and unique teaching methods of the lecturers. Some narratives are as follows:

- “We could not understand the content well at first. The lecturer then tried to change her teaching style by adding more daily examples. This fostered our understanding of the theories.”
- “Sometimes it was boring when the lecturer was talking about the theories. However, the lecturer would walk around the lecture hall to ensure the learning progress of the students, which also attracted our attention to the lectures.”
- “Our lecturer would conduct her lecture in a research format that helped explaining the related issues to students.”
- “What our lecturer did very well was that she would go to every group to see if we were on the right track and gave us suggestions. She would share our ideas to the class and we could gain insights from different views. One more thing was that she could remember all of our names. She was awesome.”

Furthermore, students thought they had more in-depth reflection and gained a higher level of self-awareness from the learning process in this subject.

- “I thought leadership is just a kind of entrepreneurship or virtues at first. Never could I imagine that leadership can be related to different issues before the lecturer linked them up together. This linkage helps me to think comprehensively and deepens my memories.”
- “This subject really made me reflect on myself. The videos (one of the teaching tools) triggered me to have self-reflection and think of ways to equip myself to be a better person.”
- “I was so impressed by the activity about resilience. We had to write a sentence, draw a picture, and grab the candies on the table without using our hands. I suddenly

realized that we would have restrictions without our hands. It was a good experience for us to practice alternative solutions when encountering obstacles.”

- “The subject provided us with lots of opportunities for self-detection, and we can understand ourselves better.”

Conclusion 2: Students Had Personal Gains and Positive Changes after Taking the Subject

Students perceived the subject was able to facilitate their reflection on themselves, thinking about the meaning of life, and thus enhancing their self-understanding and thinking in a more positive way.

- “I think the subject facilitated my in-depth thinking through an academic perspective, which is different from the understanding only based on common sense.”
- “This subject reminds us of a very important thing: in addition to study, it is also important to nurture our own qualities.”
- “When there is a problem or a moment of feeling bad, I learned how to relieve myself.”
- “The subject provides a learning process in which we are able to reflect about ourselves seriously. For example, by writing the term paper, we could recall and reorganize our life experiences seriously. This is not imagination but self-reflection. Therefore, I think the term paper is useful for us!”
- “It makes me being even more attentive to my social skills, such as communication skills I will, throughout the entire [life] process, reflect myself constantly.”
- “I also think ‘Tomorrow’s Leaders’ is a subject different from the other subjects. Other subjects focus on instilling academic information into students. ‘Tomorrow’s Leaders’, however, provides us with many opportunities for self-reflection, which makes students understand themselves more. In my opinion, studying in the university is not only for the pursuit of academic knowledge, but also for self-understanding.”
- “I always carried out many reflections about myself on the way home after classes of ‘Tomorrow’s Leaders’. Therefore, this subject provides a very strong message to me, and that is reflection.”

Some students further stated that the subject has cultivated their competences, such as cognitive competence.

- “After the game had finished, I felt enlightened—the original idea [in head] did not work in fact. This was a very memorable experience for me!”
- “This subject is very useful for me, which changed my mode of thinking. I am now able to think with reference to situational needs.”
- “We now have a different approach to deal with various issues in life.”

Besides, students mentioned that the subject has provided an opportunity for them to learn how to work together.

- “‘Tomorrow’s Leaders’ provided many opportunities for us to make friends with classmates. As such, students were able to get to know one another through the class activities. Hence, the subject can encourage us to be more involved in those class activities, and we thus actively participated in the entire process.”
- “There was much interaction during classes. Apart from making friends with classmates, I also understood the importance of listening to others’ ideas. No one can always be right. I have also recognized the ways of effective collaboration.”
- “This subject can help us understand how our personality can be developed, or how to get a job done better. This is also a subject about team-building. So I agree that, in most of the situations, the contents covered in this subject should be very useful to our daily life.”
- “This subject is useful to a certain extent. I have learned some communication skills. As there are many group projects throughout the university learning life, the experiences in this subject [of doing projects] can act as a reference for communicating with others in a better way, especially in dealing of interpersonal issues.”

Conclusion 3: Student Felt That There Was a Need for This Subject

Generally speaking, the students perceived the subject to be essential to their transition to the university life.

- “I think this subject is suitable for freshmen in their first semester. There was full of interactions in the subject, which allowed students within the same faculty interacting with each other. The students in the same group knew each other quite well and would take care of one another. I believe all these experiences are helpful to our learning in future.”
- “The subjects I am studying [in the university] are mostly science courses. I think the provision of subjects by the University like ‘Tomorrow’s Leaders’ is good for the holistic development of students. It does not only broaden the horizon of the students, but also facilitates their intrapersonal development.”
- “I think it is fine to keep the subject that provides a bridge [with others] for those who are passive in their university life.”
- “I think it is like a ‘bridging class’ for freshmen if they could enroll the subject in the first semester as the university or even Hong Kong might be a totally new environment for freshmen. There is a need of adaptation. The subject does play a role in this adaptation process.”

Moreover, the students stated that the subject was able to prepare them for a better performance now and in the future.

- “I think the rationale of this subject is very good to include the topics of emotional management, self-awareness issues, self-reflection, and self-improvement. I think these ideas are very good and necessary.”
- “I think the subject is helpful. As I said earlier, although you learned some theories, you may not be aware of how the theories, such as team building and personality, can be utilized in the daily life. The subject is thus able to facilitate students' self-understanding, enhance their self-confidence, and even change their lifestyle.”
- “I think one of learning outcomes of the subject is to facilitate your competence of interpersonal communication, which should be a must for undergraduates.”
- “The subject is necessary for our preparation for entering the society. It is because we need to deal with people with different background, which requires a better self-understanding, emotional control, and even being empathetic to others.”

Conclusion 4: Students Mentioned Some Negative Aspects of the Subject and Proposed Suggestions to Overcome Them

Apart from the positive comments and personal benefits, there are narratives on the negative aspects of the subject. First, some students remarked that there were too many theories in the course and the theories were quite difficult to understand. One student remarked, “Most of the theories are related to psychology but I am not from the social sciences stream. So it is quite hard for me to understand the concepts.” Another student said, “I found that the theories were quite difficult for me to understand even though I have read through the journals from the required readings.” A student suggested that more practical opportunities should be given, “There should be more opportunities for us to practice what we have learned about leadership in real life situations.”

Second, some students found that the class started too early in the morning. A student remarked, “The class started at 8:30 am. Even though the activities were very interesting, we were too sleepy to participate much in the activities.”

In addition, other negative comments were heard. These included: (a) some group members were not involved; (b) there were difficulties in the group presentations and individual assignment; (c) there was a comparatively heavy workload; (d) the lecture time was long (three hours lecture).

With respect to the above negative aspects of the subject, there were several suggestions for improvement from the students. Some narratives are illustrated as follows:

- “The lecturers could use more real life examples or conduct more in-class activities to illustrate those abstract and difficult concepts.”
- “There are too many students from different disciplines in a group. There were seven students in my group. The number of students should be set at four to five in each group.”
- “There could be more breaks because the lecture began too early in the morning and the duration of the lecture was too long.”

- “The guidelines for the group presentation and the individual paper could be explained more clearly so that we know the expectations from the teachers.”
- “I know that there are many teachers teaching the subject ‘Tomorrow’s Leaders’. It would be fruitful if they could share their teaching methods and experiences with each other.”
- “The teachers could give us more time for in-class discussions. This could provide more chances for us to interact with our team members and develop group cohesion.”

DISCUSSION

Based on the data collected from several focus groups, the present study investigated the views of students taking “Tomorrow’s Leaders,” a credit-bearing course on intrapersonal and interpersonal development at The Hong Kong Polytechnic University. There are several distinct features of this study. First, the present study was one of the few empirical studies documenting the views and perceptions of university students of a credit-bearing course on intrapersonal and interpersonal development. Second, different students from different faculties were recruited so that perspectives of students with different backgrounds were examined. Third, based on the CIPP model [39], content, input, process and product of the course were covered in the focus group interviews.

Based on the themes derived from the focus group discussions, several conclusions could be highlighted from the qualitative findings. First, students from different faculties had positive views and experiences on the subjects, including content of the subjects (e.g., different intrapersonal and interpersonal competences were covered), teaching methods (e.g., group discussion, interactive teaching methods, and various in-class activities were used), teachers (e.g., caring and flexible) and benefits (e.g., better self-understanding after taking the course). The participants underwent a journey of growth throughout the learning experiences in the subject “Tomorrow’s Leaders.” The subject provided them with opportunities to explore themselves in a safe and supportive environment, especially with the lecturers’ provision of “caring” and “flexible” milieu. In addition, the arrangement of sitting in groups in the subject allowed the participants to have better interactions with their fellow classmates, which might be rare in other university subjects. This setting aids the passive students to start building relationships with their classmates through collaboration in the in-class activities and communication in the group discussions during lectures. The participants thus gradually developed the “rapport community” in their own discipline. These could also be shown as students reported positive changes in intrapersonal and interpersonal competences in the interviews. For instances, some students felt that they became more resilient and sensitive in interpersonal contexts after taking the course. Given some real life examples and personal sharing (among group-mates or with lecturers) in lectures, the participants agreed that they could practice how to communicate with group-mates more effectively and appropriately. As one of the participants recalled, “It makes me being even more attentive to my social skills... I will, throughout my entire [life] process, reflect on myself constantly.” Moreover, students regarded this course to be vital and important for university students. Some students claimed that this course could help freshmen adapt to university by developing good inter-personal communication, being more active in learning and enriching the students in holistic

development. These findings are consistent with the results obtained in the pilot stage [14] and with findings based on different evaluation methods [27-37]. Besides the present qualitative findings, other findings based on post-lecture and post-course evaluation as well as qualitative data based on metaphors suggested that students generally had positive views and perceptions on the contents and implementation of the course.

Although most of the students had positive views about the program, some negative comments were reported in the focus groups. First, some students felt that the course was too theoretical and contained too many theories. Although some participants asserted that learning theories or concepts was essential in the university life, it was still difficult for freshmen to grasp the abstract and refined concepts of the theories during their secondary school-university transition. It took time for the students to prepare themselves academically. While this comment was well-acknowledged, it would not be easy to balance the demand for academic excellence (as "Tomorrow's Leaders" is a credit-bearing course) and personal development of the students. One possibility is to give more real life examples to students to make them understand the theories.

Second, some students mentioned that they experienced difficulty in group presentation and assignments. The participants had mentioned that there were "too many" group members in each group. They might have to take time to understand and communicate with each other, though some of the participants found that the groupings in Tomorrow's Leaders helped nurture their social competence ("I also understood the importance of listening to others' ideas"; "This is also a subject about team-building"). In their secondary school-university transition, the students needed time to learn how to present and write their ideas academically. It is understandable for the participants found it difficult to accomplish the term paper and presentation of the subject. To address this issue, workshops on group presentation and term papers were provided. Individual consultations were available upon students' requests. The lecturers tended to be more open to give room for students' originality and let them grow and learn in the process of uncertainty and self-exploration. In fact, most of students performed well in group presentation and assignments and they treasured the opportunity for self-learning.

Finally, a few students complained early class-time. In fact, the earliest class begins at 8:30 am which was more or less the same as the class time in secondary schools. Some of the participants admitted that it was their sleeping habit affecting their perception of "early lecture". To address this issue, various class activities and breaks were offered to refresh students' energy level. Students were also invited to re-think about their lifestyle and sleeping patterns.

Although the positive feedbacks documented can be interpreted as support for the effectiveness of this subject, alternative explanations should be well-acknowledged. First, students might give positive comments on the course because they wished to act as "good students" (i.e., demand characteristics). However, this explanation was not plausible because students were invited to voice out their views honestly and their identities were kept confidential. The other explanation is that only students with positive comments joined in the focus groups. This possibility is low because participants were recruited from different faculties and the researchers did not have prior knowledge about students' perceptions of the course. Third, favorable results might be the results of researchers' biases and preoccupations (i.e., researchers influenced the data collection and analyses processes to "create" this positive picture unconsciously). As the researchers were not directly involved in the data collection

and analyses processes, and there was discussion amongst the authors on the results, this possibility is not high.

Although there is a growing trend in using focus group interviews as the research tool to investigate the in-depth meaning of the “conversational process” of the participants, there is a lack of literature analyzing the limitations of the processes and structures involved [40]. It is thus essential to realize the methodological limitations of focus group interviews in the present study. Firstly, focus groups have been described as particularly useful at an early stage of research as a means for eliciting issues which participants think are relevant [40]. This might help collect large volume of information yet the depth of the data has to be acquired or investigated by administering individual in-depth interviews. To fully reveal the in-depth inferences in dialogues can be very time intensive [41]. Secondly, the moderators of the focus group interviews are the teachers or tutors of “Tomorrow’s Leaders.” Having the moderators from the same background might help facilitate the discussion in putting the participants at their ease [40]. The issues addressed were ensured to be the “same” issues across all the focus groups. However, Hurd and McIntyre [42] reminded the researchers about the “seduction in sameness” between the researchers and the participants that might hinder critical reflexive research. The moderators should be highly aware of the heterogeneity of the discussions in the focus groups and their potential biases in directing the participants to disclose what the moderators desire. Thirdly, during the process of focus group interviews, there might be some confusions of treating the dominant voice as the collective voice of the groups. Smithson [40] asserted that the voice of each focus group interview should be the collective and consensus procedures. The opinions of the participants should not be viewed as static or previously formed. The opinions are constructed in social situations and are the discourses emerged from the context. The researchers thus should be well-aware of the subtleties which are emerged in focus group discussions.

In this chapter we documented the perceived attributes and benefits of a credit-bearing course on leadership and intrapersonal development at The Hong Kong Polytechnic University. The current findings concurred with other studies using various evaluation methods [27-37] that the subject was well-received by the students and the subject was perceived to be beneficial to the development of the students. However, like other studies, the present study has several limitations. First, as the participants were not recruited using random sampling, generalization of the findings should be cautious. Second, due to practical considerations and time constraint, interpretations of results were not counter-checked by participants (i.e., member checking). Third, the inner subjective experiences of students during taking the course were not investigated. Obviously, other qualitative studies, such as in-depth interviews or using students’ daily dairies could be employed in the future studies. Despite these limitations, the present study provided qualitative data to support the positive features of the course “Tomorrow’s Leaders” from students’ perspectives.

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Chapter 173

EVALUATION OF A LEADERSHIP AND INTRAPERSONAL DEVELOPMENT PROGRAM

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ABSTRACT

Qualitative evaluation was conducted for students taking a subject on leadership and intrapersonal development ("Tomorrow's Leaders") at The Hong Kong Polytechnic University. A total of 1,029 students completed a reflection worksheet to describe their experiences about the subject through the use of descriptors and metaphors. Reliability analyses showed that the coding of responses was consistent across raters. Regarding the descriptors used to describe the program, most of the descriptors were positive and around 3% were negative responses. Concerning the metaphors used to represent the program, 93% of the responses were positive in nature, with 12 themes emerging from the responses. Consistent with the findings reported previously, the present chapter suggests that "Tomorrow's Leaders" was well received by the students and they regarded the subject to be beneficial to their own development.

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INTRODUCTION

Evaluation serves as an assessment tool for helping program implementers to understand the impact and effectiveness of a program [1]. It allows the implementers to improve the quality of the program by carrying out continuous evaluations throughout the implementation process [2]. Two main approaches, quantitative and qualitative approaches, are often used in conducting evaluation. The quantitative approach relies on numerical data to assess how the participants perceive a program at different time points [3]. Qualitative approach focuses on the evaluation of comprehensive and in-depth thoughts as well as experience of the participants [4]. As qualitative approach can generate data which can capture the experiences of the program participants, a qualitative approach was adopted in this study to evaluate a subject on leadership and intrapersonal development developed for university students in Hong Kong.

In the field of program evaluation, metaphor analysis is one of the major types of qualitative research. It not only serves as a key for people to communicate some abstract thinking and experience [5], it also makes the complex information more structured and clearer [6]. There are several metaphor theories, including salience-imbalance theory [7], domains-interaction theory [8], class-inclusion theory [9] and conceptual metaphor theory [10]. Among these theories, conceptual metaphor theory is the most popular method in educational and psychology research.

Conceptual metaphor theory, also known as cognitive metaphor theory, is often used to understand the abstract concepts and reasoning in our daily life [10]. A conceptual metaphor not only shapes our communication but also influences the way we think and act. According to Lakoff and Johnson [10], “communication is based on the same conceptual system that we use in thinking and acting, language is an important source of evidence for what the system is like” (p. 3). In other words, it is not only a property of language (i.e., a linguistic phenomenon), but also a property of thought (i.e., a cognitive phenomenon) [10, 11].

A conceptual metaphor consists of two domains; they are the target (also named as “topic” or “tenor”) and the source (also referred to as “vehicle”) [10]. The target domain is the conceptual domain that we try to comprehend while the source domain is the conceptual domain from which we use metaphorical expression to understand another conceptual domain. The metaphor can be understood as a mapping from a source domain, that is, sets of conceptual correspondences [10]. For example, “life” (the source) is a “journey” (target). According to Lakoff [12], the life as journey mapping is “a set of ontological correspondences that characterize epistemic correspondence by mapping knowledge about journeys onto knowledge about life” (p. 207). These correspondences allow us to reason about life using the knowledge we use to reason about journeys.

Despite the common use of conceptual metaphor analysis [13-15], little is known whether it can be employed in assessing the extent to which a program achieves the learning outcomes in tertiary education contexts. In particular, it would be helpful to understand how university students perceive a course by using this method. With reference to the Chinese contexts, metaphors have been used in different education contexts. For example, Shek and colleagues used this method to understand students’ perception toward a positive youth development program [4, 16] and two university leadership courses [17-19].

There are several advantages of using metaphors to evaluate the effectiveness of a course. First, more novel ideas and inspirations on how students perceived the course could be obtained by mapping between the metaphors and their learning process [20, 21]. Second, it provides an alternative way to understand the subjects which emphasize holistic personal growth and development. By using conceptual metaphors, students could reflect on their learning and past experience, which in turn yields a more genuine perception with less embellishing thoughts toward the course. Researchers, therefore, can have a better understanding of the reality by providing an “emic, idiographic, case-based position that directs attention to the specifics of particular cases” [22]. Shek and Wu [23] noted that “a thick description would be formulated by revealing the multilayered understanding of students’ learning experience and meaning-making process” (p. 474). This provides a better picture on how the students perceived a course, which especially focused on promoting self-reflection and holistic development of the students.

Given the aforementioned advantages of conceptual metaphors, this study assessed the effectiveness of a university leadership subject “Tomorrow’s Leaders.” Students were asked to write a personal reflection on their experience, perceptions and feelings of the course via the use of conceptual metaphor.

A Subject on Leadership and Intrapersonal Development

“Tomorrow’s Leaders” is a 3-credit subject developed at The Hong Kong Polytechnic University to promote the leadership and intrapersonal competence of the students taking this subject. This course aims at helping students understand the constructs in positive youth development, including cognitive competence, emotional competence, resilience, moral competence, self-understanding, personality, positive and healthy identity, spirituality, social competence, relationship and team building, conflict management, as well as interpersonal communication. Various teaching methods, including lectures, experiential learning activities, group project presentation and individual written assignments, are used in this course to nurture both the interpersonal and intrapersonal competencies of the students.

There are several objectives of this course: a) to enable students to learn and integrate theories, research and concepts of effective leadership qualities (particularly intrapersonal and interpersonal qualities) of effective leaders; b) to develop students’ intrapersonal and interpersonal qualities of effective leaders; and c) to increase students’ awareness of the importance of lifelong learning.

OUR STUDY

A total of 1,029 students enrolled in the subject “Tomorrow’s Leaders” in the second semester of the 2012/2013 academic year. By using a reflection worksheet, students were asked to choose three phrases or words to describe their feelings toward the course. Also, they were invited to write a metaphor which best described the course and to give explanations about the metaphor. A total of 885 worksheets were collected at the end of the course.

Students were informed that their participation was voluntary and the data were used for educational and research purposes.

For each descriptor, four types of codes (i.e., positive codes, negative codes, neutral codes and undecided codes) were adopted. Moreover, to analyze the metaphors, thematic analysis was performed as Miles and Huberman [24] contended that this method is “a way of grouping those summaries into a small number of sets, themes or constructs... it’s an analogue to the cluster-analytic and factor-analytic devices used in statistical analysis” (p. 69).

To enhance the coding reliability, intra-rater and inter-rater reliability tests were carried out. Twenty raw descriptors and twenty metaphors were randomly selected for the intra- and inter-rater reliability tests. Two researchers, who did not participate in the coding analysis, were recruited to perform the inter-rater reliability test. One of them has a master’s degree in Educational Psychology and another has a bachelor’s degree in Social Sciences and is currently studying a master’s degree. All researchers completed the task independently without discussion.

FINDINGS

A total of 2,642 descriptors were received and categorized into 25 areas. In Table 1, there were 2,548 (96.4%) positive descriptors and 74 (2.8%) negative descriptors. In Table 2, negative descriptors were found, such as “difficult,” “boring,” “time-consuming,” “tiring,” “noisy,” “not environmentally friendly” and “not helpful.” Lastly, there were 8 (0.3%) neutral and 12 (0.5%) undecided descriptors.

Table 1. Categorization of descriptors used by the participants to describe the course

Descriptions	Nature of the responses				Total
	Positive	Neutral	Negative	Undecided	
applicable	21				21
educational	156				156
energetic	9				9
guidance	5				5
helpful	521				521
innovation	15				15
Interacting	188				188
Interesting	656				656
meaningful	508				508
reflective	183				183
relaxing	166				166
personal development	64				64
valuable	46				46
teacher is good	4				4
challenging		4			4
difficult			21		21
boring			16		16
time-consuming			14		14
tiring			10		10
not helpful			6		6
cold			2		2
other negative descriptors (e.g., noisy)			5		5
other undecided descriptors (e.g., OMG, rain)				12	12
other positive descriptors (e.g., big, born)	6				6
other neutral descriptors (e.g., pluralistic, metaphors)		4			4
Total count, n	2548	8	74	12	2642
Total count, %	96.44	0.30	2.80	0.45	100.00

Table 3. (Continued)

Metaphors	Nature of the responses					Nature of the responses (Coding)				
	Positive	Neutral	Negative	Undecided	Total	Positive	Neutral	Negative	Undecided	Total
Paper		8				10	8	2		20
periodic table				1		4				4
swallow's nest				1		2				2
tea table				1		2				2
Gift	35				35	61	9	6		76
magic box	1					1	1			2
surprise	3					3	1			4
sweet	19					36	4	6		46
treasure	12					21	3			24
Guidance	157			1	158	250	10	6		266
manual	2					3		1		4
guide	93					148	8	2		158
light	62					98	2	3		103
lantern fish				1		1				1
Hope	20				20	40	2	2		44
dream	7					14	1	1		16
heaven	3					7	1			8
newborn baby	1					2		1		3
rainbow	9					17				17
Interactive	12				12	23	1			24
friend	5					10				10
group cooperation	7					13	1			14
Knowledge	77	2			79	122	14	11	1	148
encyclopedia	13					22	2			24
elderly	4					7		1	1	9
leaflet	8					11				11
lesson	11					16	4			20
dictionary	9					18	5	5		28
book	32					45	3	3		51
assignment		2				3		2		5
Meaningful	7	1			8	11				11
meaningful movie	2					3				3
meaningful tour	5					7				7
abstract painting		1				1				1

Metaphors	Nature of the responses					Nature of the responses (Coding)				
	Positive	Neutral	Negative	Undecided	Total	Positive	Neutral	Negative	Undecided	Total
Multi-dimension	33				33	53	4			57
canteen	1					2				2
various fruits	6					10				10
supermarket	3					4				4
buffet	23					37	4			41
Necessity	125	4			129	224	20	32	4	280
human	4					7	1	1		9
fresh air	4					7	1	2		10
ocean	10					19	2	5	1	27
home	4					5	2			7
nutrients	27					44	2	5		51
sun	18					40				40
tree	40	3				72	5	13	2	92
water	18					30	6	6	1	43
toilet		1					1			1
Reflection	70	1		1	72	115	5	2		122
chicken soup	2					5				5
diary	3					3				3
photo album	3	1				7				7
mirror	62			1		100	5	2		107
Others	42	17	3	5	67	106	7	24	3	140
other positive metaphors (e.g., snowball, special, additional products)	42					73	3	13	1	90
other neutral metaphors (e.g., America, lemon, pig)		17				24	1	8	2	35
other negative metaphors (e.g., white elephant, compulsory military trip)			3			1		3		4
other undecided metaphors (e.g., ant, coke)				5		8	3			11
Total Count, n	813	48	3	10	874	1462	119	105	8	1694
Total Count, %	93.02	5.49	0.34	1.14	100.00	86.30	7.02	6.20	0.47	100.00

For the metaphors, a total of 874 raw data, which involved 1,694 codes, were obtained (Table 3). Results showed that 813 were positive metaphors (93.0%), such as “*journey*,” “*guide*,” “*light*,” “*book*,” “*buffet*,” “*tree*” and “*mirror*.” Moreover, 48 metaphors (5.5%) were regarded as neutral. Some neutral metaphors were “*games*,” “*rope*” and “*paper*.” Based on the 874 metaphors, 12 themes were categorized, including “entertainment/relaxing,” “functional,” “gift,” “guidance,” “hope,” “interactive,” “knowledge,” “meaningful,” “multi-dimension,” “necessity,” “reflection” and “others.” The results of intra- and inter-rater reliability tests are good (intra-rater reliability tests: 85%, 90% and 100%; inter-rater reliability tests: 82%, 85% and 85%).

DISCUSSION

The purpose of the present study was to assess the students’ perception of a leadership course “Tomorrow’s Leaders” by using a qualitative approach. There are several strengths of this paper. First, by using descriptors and metaphors, students can use their own words to conceptualize their learning experiences and impact of the course. Second, a large sample size, which is rare in the field of qualitative evaluation research, was obtained. Third, the results of inter-rater and intra-rater reliability tests were good.

In general, students perceived the course positively. First, based on the results of the descriptors, about 96% of the students perceived the course was helpful, meaningful, reflective, interesting and relaxing. In fact, one of the characteristics of the subject “Tomorrow’s Leaders” is to provide an opportunity to students to participate in a variety of in-class activities and the reflective exercises related to the concepts and theories of leadership qualities (e.g., cognitive competence, emotional competence, resilience, moral competence, self-understanding, personality, positive and healthy identity, spirituality, social competence, relationship and team building, conflict management and interpersonal communication). With the adoption of experiential learning approach, students were asked to participate in different interactive activities and found these activities interesting and inspiring as reflected from the positive descriptors. Through the diversified learning experience, students were more aware of their intra- and interpersonal competencies. This explains why the students used the positive descriptors, such as *helpful*, *meaningful* and *reflective*, to describe the course.

Second, based on the results of metaphor analyses, the majority of the students (above 90%) perceived the course positively as reflected by the metaphors, such as *a meaningful tour*, *nutrients*, *guide*, *light*, *book*, *buffet*, *rainbow*, *treasure*, *tree* and *mirror*. In addition, the present study extends prior studies [18, 25, 26] by grouping the metaphors into themes. In this study, all metaphors were categorized into twelve themes, which demonstrated the extent to which the intended learning outcomes of the course were achieved from the students’ perspective.

Some metaphors were coded under the themes, such as “*entertaining*,” “*relaxing*” and “*gift*,” indicating that the students enjoyed the course and would take a similar course in the future. Some were categorized into “*functional*,” “*knowledge*,” “*multi-dimension*” and “*necessity*,” showing that students understood different qualities of effective leaders and recognized the importance of these attributes. Other themes, such as “*hope*” and “*guidance*,”

demonstrated that students were inspired by the course content and perceived positively toward the future. The findings of the present study showed that the intended learning outcomes of the course have been achieved from the students' perspective.

While the findings based on descriptors and metaphors are generally positive, there are plausible alternative explanations for the findings. First, it can be argued that the students might please the teachers by giving positive responses (i.e., demand characteristics). However, this possibility is not high because the students were encouraged to give their honest responses and negative responses. Second, the students gave positive responses because they were afraid to be punished. This possibility is also not high because the students were not required to write down their names on the reflection sheets.

Several limitations of the study should be taken into account. First, the data were collected at one single point of time (i.e., at the end of the semester). This cross-sectional design may limit the understanding of the long-term effects of the course on students' personal growth and development. Second, the students were asked to complete a worksheet. Some students, especially those who were not good at writing, may not be able to express their innermost feelings and thoughts freely by using this paper-and-pencil format. In particular, the students may prefer to have a quiet place with no limit on the time frame to reflect on their learning experience. This may be difficult as the students were asked to submit the worksheets at a particular amount of time (i.e., 5-10 minutes). This might hinder the students to do an in-depth reflection during the class. Finally, the worksheet format also limits the depth of information that can be gathered.

In order to have a more comprehensive understanding of students' perception and thoughts about this course, future studies may consider the use of mixed-method approach. By using both quantitative and qualitative methods, a more comprehensive picture of the effectiveness of the course can be obtained. Also, other qualitative methods like focus-group interviews and weekly diaries could be used in the future. Therefore, students can express the innermost feelings comfortably and freely without hesitation. This can help researchers capture a better picture of the impact and effectiveness of a holistic youth development university course. Despite the above limitations, students generally perceived the subject positively and beneficial to their academic and personal lives. It is important as university students is a sizable part of population and will be leaders in different fields and disciplines. The current study sheds light on promoting holistic development of students in the university context.

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Chapter 174

A NEW 4-YEAR UNDERGRADUATE PROGRAM IN HONG KONG

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ABSTRACT

Have universities forgotten their educational role and guiding students to grow up?
With specific reference to Hong Kong, the university structure was a three-year program

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before 2012/13 academic year, which was modeled after the British system, but with the introduction of the higher education reform, university structure was changed to four years, with the additional year devoted to general education. At The Hong Kong Polytechnic University (PolyU), the General University Requirements (GUR) were designed to promote the holistic development of the students. In this book we summarize the evaluation findings and answer the question of how well the desired graduate attributes were achieved. It is our modest wish that through this book, we will have a better understanding of the implementation of the general education program in Hong Kong.

INTRODUCTION

What are the attributes of a “good” university? With respect to this question, many people would say that a good university should have a good ranking based on international ranking systems such as the QS World University Rankings, the Times Higher Education World University Rankings, and Center for World University Rankings. Unfortunately, while ranking figures may give some snapshots about universities based on quantitative figures, they do not give any idea about the quality of education received by the students, particularly with respect to the question of how the undergraduate program promotes the holistic development of students. In fact, in most ranking schemes, we do not look at what subjects are offered and the impact of the undergraduate program on students. Most important of all, many ranking systems simply do not answer the question of how the undergraduate curriculum may meet the diverse needs of university students.

Actually, contemporary universities have been criticized for failing to achieve the ultimate aim of education (i.e., helping students to develop in a holistic manner). Harry Lewis [1] provocatively commented that “universities have forgotten their larger educational role for college students, namely to succeed, better than ever, as creators and repositories of knowledge. But they have forgotten the fundamental job any undergraduate education is to turn eighteen- and nineteen-year-olds into twenty-one- and twenty-two-year-olds, to help them grow up, to learn who they are, to search for a large purpose of their lives, and to leave the college as better human beings [1, p.xii].” He also remarked that “over the decades I have heard many academic discussions about teaching, about the curriculum, about grading, about athletics, and about responding to student misdeeds. I have almost never heard discussions among professors about making students better people” [1]. Obviously, the comments of Lewis motivate us to think about what should be the essence of undergraduate curriculum.

From a youth developmental perspective, we have to seriously re-consider the needs of university students and ask how the undergraduate curriculum can meet their needs. A few centuries ago, university education was fundamentally “scholarly” in nature, nurturing students in the “ivory tower.” In the past decades, university education became more vocationally oriented, which addressed the needs of occupational needs of the students. However, with the growing complexities of the society and emergence of the knowledge-based economy, we have to ask what sort of development university students should have. There is a growing voice arguing that besides “hard skills” in the disciplinary training, students should also acquire “soft skills” to respond to the needs of the changing world. There are two main areas of “soft skills” that university students should acquire. The first is on

intrapersonal development. Some of the qualities include psychosocial competence (cognitive, emotional, social and moral competence), communication skills, resilience, positive identity, spirituality. Obviously, qualities such as resilience and emotional intelligence are very important for young people in the knowledge-based economy. On the other hand, university students should have good interpersonal skills, including relationship building, relationship maintenance, team building and conflict resolution. Most important of all, moral character is an important desired graduate attribute under the service economy. For example, having excellent skills in finance is good, but if such skills are used to issue junk bonds, it would not be desirable. Essentially, graduates should do the “right” things in a world full of moral confusion. Besides, addressing the “soft skills” of university students is also important because there are growing developmental issues (e.g., depression, suicidal and alcoholism) in university students.

With specific reference to Hong Kong, the university structure was a three-year program before 2012/13 academic year, which was modeled after the British system. With the introduction of higher education reform, university structure was changed to four years, with the additional year devoted to general education. At The Hong Kong Polytechnic University (PolyU), the General University Requirements (GUR) were designed to promote the holistic development of the students. There are several components of the GUR, including a) Language and communication requirements (9 credits); b) Freshmen seminar (3 credits); c) Cluster areas requirements (12 credits); d) Leadership and intrapersonal development (3 credits); e) Service-learning (3 credits); and f) Healthy lifestyle (non-credit bearing). Through the new 4-year undergraduate curriculum, it is expected that the graduate would develop holistically, with the attributes of critical thinking, innovative problem solving, effective communication, ethical leadership and lifelong learning.

Obviously, having a set of desired graduate attributes and an elegant 4-year new undergraduate program are not enough. We have to conduct evaluation studies to examine the impact of the new 4-year curriculum. To understand the effectiveness of the 4-year new undergraduate program, we started collecting evaluation data starting from the 2012/13 academic year. There are several components in the evaluation study. First, we conducted objective outcome evaluation with three sub-studies: a) we tracked a random sample of students over four years; b) we compared the third-year students of the PolyU 4-year program with the third-year students of the PolyU 3-year program, and c) we compared the third-year students of PolyU 4-year program with the third-year students in a comparable university in Hong Kong. Second, we conducted qualitative studies including focus group studies involving students and teachers. A longitudinal case study was also carried out. Third, we conducted secondary data analyses looking at the student feedbacks through student feedback questionnaires. Fourth, changes in the students were examined using the repertory grid test.

We have already published papers on the effectiveness of the 4-year program [2-5]. In this book, we have included papers published in the *International Journal of Adolescent Medicine and Health* in 2017 (volume 29, number 1) and *International Journal of Child and Adolescent Health* to be published in 2019 (volume 12, number 1). It is our modest wish that through these papers, we will have a better understanding of the implementation of the general education program in Hong Kong.

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Chapter 175

LEADERSHIP QUALITIES AS A FOUNDATION OF SERVICE LEARNING

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ABSTRACT

In many adolescent developmental models, serving others is regarded as an important attribute of healthy development of adolescents and young adults. Besides, programs promoting university students' service to the community, such as service learning subjects/programs, are developed. In this paper, it is argued that to facilitate community service competence of university students, there is a need to cultivate their basic leadership competencies, including intrapersonal and interpersonal competencies. At The Hong Kong Polytechnic University, a 3-credit subject entitled "Tomorrow's leaders" was developed to promote leadership competencies in students. In the past five years, different evaluation strategies have been used to examine the impact of the subject. Evaluation findings consistently showed that this subject was able to promote psychosocial competencies and ethical leadership qualities after students took this subject, which forms a solid foundation for students to undertake their service learning projects.

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INTRODUCTION

Serving others is an important vehicle through which healthy development of adolescents and young adults can be promoted. For example, Benson [1] proposed 40 adolescent developmental assets. Amongst these assets, caring (i.e., a young person places a strong emphasis on helping other people) is an important developmental asset conducive to healthy adolescent development. In the positive youth development literature, serving others is intimately related to six “C”s of optimal youth development - competence, character, confidence, connectedness, caring, compassion, and contribution [2].

With particular reference to Hong Kong, involvement of young people in community service has undergone much transformation throughout the history of Hong Kong. Hong Kong was a British colony before 1997. The mission of university education in Colonial Hong Kong was to nurture elites for Hong Kong and Britain who were submissive to the British. As such, students were not encouraged to have much community participation. To set a clear and non-political goal for young people that could consume their energy, the education system was very examination-oriented. Although Hong Kong has become part of China since July 1997, the education system is still very examination-oriented where young people are encouraged to strive for academic excellence. While there is greater emphasis on voluntary service in high school students in the recent education reform, the motive of the students in community engagement is still quite instrumental, such as using voluntary activities to “enrich” their curriculum vitae.

Service Learning in the University Context: Promise and Challenge

For university students in Hong Kong, opportunities for community service have increased in the past decade, although the service learning movement is still in its infancy. There are two key questions we should ask. The first question is whether academic work on service learning is adequately covered in the scientific literature. The second question is whether university students are adequately prepared for service learning. Regarding the former question, computer search shows that there is not much academic work on service learning in Hong Kong. From the statistics, it can be concluded that scientific literature on service learning is still very inadequate. While Chinese young people constitutes roughly one-fifth of the world’s youth population, less than 1% of the published work is based on Chinese people.

To promote service learning in undergraduate students, every undergraduate student at The Hong Kong Polytechnic University (PolyU) has to fulfill the Service Learning Requirement by taking a 3-credit Service Learning course since the 2012/13 academic year. This initiative is a pioneer in two aspects. First, PolyU is the first university in Hong Kong (and probably in China) that includes Service Learning Requirement as a graduation requirement. Second, to give due recognition to students and teachers, three credits are given to the Service Learning Requirement. This ensures that there would be a universal coverage for all the undergraduate students. Besides the pilot projects developed before the 2012/13 academic year, a 10-hour e-learning package for the students [3] and a 3-hour e-learning package for the teachers [4] have been developed.

However, while we endorse the service learning initiative at PolyU, we have to ask a more fundamental question - are undergraduate students ready and well-equipped to serve other people? This question should be asked because there is research evidence suggesting that there are developmental issues in contemporary university students [5], such as growing mental health problems, decline in empathy, and growing egocentrism in university students. Shek and Cheung [6] further reported developmental problems in university students, such as lifestyle and Internet addiction problems. As pointed out by Bips [7], "students now are less mature and often not ready for the responsibility of being in college ...many students today lack the resilience and are unable to summon strategies to cope ...many students are often not prepared to be young 'adults' with all the responsibilities of life" (p. 1).

Because of the above observations, it would be an ideal strategy to equip students with competence before they take up challenges in service learning. In the literature of positive youth development, it is asserted that it is important to nurture the psychosocial competence of young people [8, 9]. For instance, Weissberg and O'Brien [10] suggested that social-emotional competencies such as self-awareness, social awareness, and responsible actions are basic to youth development. Besides, character development is regarded as an ideal developmental goal [2].

Park, Peterson and Seligman [11] pointed out that there are 24 character strengths, which can be subsumed under six broad categories of virtue, including wisdom and knowledge (such as love of learning), courage (such as honesty), humanity (such as love and social intelligence), justice (such as fairness), temperance (such as forgiveness and modesty), and transcendence (such as gratitude and hope). Interestingly, although character education is covered in primary and high schools, focus on morality is less emphasized in higher education. Probably it is assumed that university students should have attained moral maturity.

Crosby [12] asked an interesting and important question –what is the most important subject in the university? Crosby [12] argued that "some would say that it is a course in economics or business, since that is what most jobs, at bottom, seem to be about. Others might want to argue that it is a course in mathematics or computer science, since so many of the jobs in our world are becoming scientific and technological. Still others might claim that it is a course in English composition, critical thinking, or speech, since clear and effective communication is so essential in any job. But the most important course at the university is none of the above. It is 'the course of each student's own life' "(p. 1). In fact, Crosby [12] argued that character development is of paramount importance and that "proper development of a student's character can enable that student to see beyond education merely as certification and preparation for a job to the critical importance and value of a life that is lived well in all of its dimensions, a life that continues throughout its course to develop and sustain a sense of purpose and fulfillment in oneself and the satisfaction of contributing responsibly and effectively to the wellbeing of others" (p. 1). Hence, while we promote service learning in undergraduate students, it is equally important to nurture their character and psychosocial competencies [13].

Promotion of Leadership Competencies in University Students

Starting from the 2012/13 academic year, the undergraduate curriculum in universities in Hong Kong has changed from three years to four years. At The Hong Kong Polytechnic University, undergraduate students are required to complete a requirement on leadership and intrapersonal development. As such, a subject entitled “Tomorrow’s leaders” was developed to help the students fulfill this requirement with the following content, which is intended to nurture their psychosocial competencies and character:

- Role of self-understanding and interpersonal relationship qualities in effective leadership
- Self-understanding: personality characteristics leading to effective leadership
- Emotional competence: understanding the emotions of oneself and others; role of EQ in effective leadership
- Cognitive competence: different components of cognitive competence, such as IQ; creative, logical and critical thinking, cognitive competence in effective leadership
- Resilience: life adversities and challenges; coping with life stresses; role of resilience quotient (AQ) in effective leadership
- Spirituality: meaning in life; spirituality and well-being; role of spiritual quotient (SQ) in effective leadership; servant leadership
- Ethics and morality: moral competence; ethical issues and leadership; morality in effective leadership
- Social competence: skills basic to social interaction; positive human relationship; social skills in effective leadership; egocentrism in university students
- Clear and positive identity: role of self-identity in human development; self-evaluation and self-worth; self-discrepancies; role of positive self-concept in leadership effectiveness
- Interpersonal communication: concepts and skills; effective interpersonal communication; communication skills and effective leadership
- Interpersonal conflict; dealing with conflict; conflict resolution and leadership; team building; relationship quality and effective leadership
- Personal integrity and sense of responsibility in effective leaders; egocentrism in university students
- Self-leadership: leading one’s own life; self-leadership initiatives

There are two stages on the development and implementation of this subject. In the pilot stage, a 2-credit course was offered to 268 and 195 students in the 2010/11 and 2011/12 school years, respectively [14]. Since the 2012/13 academic year, the subject has been implemented on a full implementation basis (i.e., full implementation stage). In the 2012/13 to the 2015/16 school year, the course was offered to 2,000+ students per year.

EVALUATION OF THE SUBJECT

To understand the impact of the subject, different evaluation methods were used [14]. These include objective outcome evaluation, post-lecture subjective outcome evaluation, subjective outcome evaluation (post-lecture and post-course student satisfaction survey), process evaluation, and qualitative evaluation based on written narratives and focus groups were carried out. These methods and the related findings are presented in the following sections.

Objective Outcome Evaluation

Objective outcome evaluation typically examines changes in program participants after they join a program such as a credit-bearing course. To examine changes in students after taking “Tomorrow’s leaders”, two main research designs have been used. First, a one- group pretest-posttest design has been used to evaluate changes in several cohorts of students. Second, a non-equivalent control group design was used. For the outcome measures, 13 measures based on the Chinese Positive Youth Development Scale were used, including indicators in the domains of resilience, psychosocial competence (social, emotional, cognitive, behavioral and moral), self-determination, self-efficacy, positive identity, belief in the future, spirituality, prosocial norms and prosocial involvement. Several composite measures based on the indicators in the subscales were also used.

The findings based on the one group pretest-posttest design are generally positive. In the pilot stage, evaluation findings showed that the participants displayed positive changes in some of the domains (e.g., emotional competence and positive identity) and composite measures [15]. In the full implementation stage, based on the responses of 1,029 students, Shek and Ma [16] showed that although students showed positive changes in self-determination, thriving, and life satisfaction, their scores on some of the domains declined over time. Further analyses suggest that the impact of the course might differ for students in different programs.

Besides the one-group pretest-posttest design, a quasi-experimental study was conducted in the pilot stage with an experimental group ($n=195$) and a control group ($n=71$), with similar socio-demographic characteristics in the two groups. After controlling the pretest scores, analyses showed that the students in the experimental group showed a higher level of psychosocial competence indexed by resilience, emotional competence, and beliefs in the future. The study suggests that this course is able to promote psychosocial competence and ethical leadership in Chinese university students in Hong Kong [17].

Subjective Outcome Evaluation (Post-Lecture Evaluation)

To provide feedback to teachers, a post-lecture questionnaire was used after each lecture in the pilot stage. Based on the data collected by 2,039 post-lecture subjective outcome evaluation forms, Shek [18] showed that the students perceived the subject, class, and teacher attributes in a favorable light, with 93% and 90% of the respondents having positive views of

the teachers and subject, respectively. In another study in the pilot stage, Shek and Sun [19] showed that the client satisfaction findings on the subject, class, and teacher attributes were very positive, with over nine-tenths of the respondents showing positive evaluation of the subject and the teacher. In short, post-lecture evaluation findings suggest that the lectures were well-received by the students.

In the full implementation stage, Shek and Leung [20] conducted post-lecture evaluation assessing student perception of the subject, instructor and effectiveness among 1,029 students. The findings generally revealed that the students had a very positive evaluation of the lectures. As predicted, the findings supported a three-factor structure, and global evaluation of the lectures and the teacher was predicted by the perceived subject, lecture and teacher attributes. In another study based on 1,070 students, Yu, Shek and Leung [21] carried out a post-lecture evaluation of the modified version of the course. The results showed that the students generally held positive views about the lectures and teachers. The findings also supported the hypothesis that the perceived subject, teacher and lecture attributes predicted overall evaluation of the teachers and the lectures.

Subjective Outcome Evaluation (Post-Subject Evaluation)

Besides the post-lecture evaluation, a post-course subjective evaluation using a validated client satisfaction scale (comprising perceived program quality, perceived implementers quality, and perceived program effectiveness) was conducted to examine the views of the students after taking the course. Based on the responses of 189 students, Shek and Sun [22] reported that over 90% of the students had positive views of the subject and the course was effective in helping the students to thrive. Shek and Sun [23] similarly showed that the client satisfaction findings were very positive from 195 students measured by the same subjective outcome evaluation scale, with high proportion of students agreeing that the subject had helped them develop in a holistic manner. In the full implementation stage, post-course subjective outcome evaluation studies were also conducted. Researchers showed that the students had a positive evaluation of the subject, the instructor as well as the perceived benefits of the subject [24, 25].

Process Evaluation

A process evaluation was conducted to understand the implementation quality of the course in the pilot stage. In the first process evaluation study, Shek and Sun [26] showed that the mean program adherence across the lectures (i.e., 85.71%) and the implementation quality (such as reflection opportunity and preparation quality) were high. In the second piloting exercise, Shek and Sun [27] showed that the mean program adherence and the quality of implementation were generally high. In both studies, qualities of the program implementation were predictive of the overall quality and the success of the program.

Qualitative Evaluation (Individual Reflection)

Several qualitative evaluation strategies involving individual reflection have been used to evaluate the impact of the subject. In the first strategy, we asked students to use descriptors and metaphors to portray their experiences. In the pilot stage, Shek and Sun [28] reported that students generally used positive descriptors (e.g., “meaningful” and “enlightening”) and positive metaphors (such as “meaningful tours” and “compass”) to describe the subject. In the full implementation stage, Shek and Law [29] also showed that the students ($N = 143$) gave positive responses, with 94.4% and 92.7% of positive responses for descriptors and metaphors, respectively.

The second evaluation strategy was to invite the students to write personal reflections on the course. Shek [30] reported some personal reflections as follows:

“This course, Tomorrow’s Leaders, was very different from what I have taken in my major, Marketing. In my major, there are only lectures and tutorials. After the lecturers finished what they wanted to say, they left. Interactions were seldom seen. But in Tomorrow’s Leaders, there were many interactions which shocked me at the very beginning. Nearly everyone has to share what he/she thinks and feels during the lesson. ...This is something I can never encounter if I haven’t taken this course. Also, the most interesting part was the worksheet. First, I think the worksheet is just like work in primary school. A bit wired. But later I find that these few pieces of paper can help me find my truth and know more about myself. I have the deepest feeling when I was filling the worksheet about my strengths, weaknesses and ideal-self. I thought a lot. I would like to find out the answers. Fortunately, I found it, more than the worksheet required.”

“It is a valuable experience to study this subject. In the course of this subject, different activities, writings, and drawings enhanced my understanding about myself, including my strengths and weaknesses, which helped me improve my interpersonal skills. The topics taught in this subject are important to our daily living. For instance, we need emotional competence when our feeling is fluctuating; we need resilience when we are in a deadlock. Good interpersonal skill is a must for all of us nowadays when almost every one of us is holding a bachelor degree. Our personality and how we deal with problems are more important than what we know.”

Finally, to motivate the students, students with outstanding performance were awarded the Wofoo Foundation Scholarship and they were invited to write personal reflections on the subject. The scholarship recipients generally felt that there was a strong need to have this subject and shared that there were many benefits of the subject. Besides, they saw that there were many attractive features in the subject and the lectures were interesting and interactive. These attributes can be seen in the reflection of one scholarship recipient report by Shek and Wu [31] as follows:

“The subject facilitates me to be more confident in taking up a leader’s role in my social work profession. The course introduced 13 elements that a successful leader should possess. I have heard some of them before but some of them were new to me. One new element has inspired me a lot and provided me insight to be a leader is “spirituality.” A spiritual leadership style should include spiritual values such as integrity, honesty, and humility. By showing us a movie called “Invictus,” the teacher used Nelson Mandela as an example to demonstrate these elements. During the movie, I was impressed by the decision made by Mandela. He provided meaning (i.e., unity of one nation) for every political decision even though such decision would be at the expense of his political capital. He could create ethical influence and climate that would influence the others. His belief in unity and caring for his original enemies guided him to be the President. This element inspired me that as a social worker, despite facing difficulties and structural constraints, there are some human values that I have to uphold – that is honest communication with self and others and at the same time be respectful and caring to every human, even the one you hate or originally is your enemy. Of course, this type of leadership quality sounds hard to achieve. It is difficult to love the one you hate. However, such leadership practice is attractive to me and I think I am willing to learn to be a spiritual leader in order to make ethical influence to my followers.”

Similar positive reflections can be seen in the reflections of the scholarship holders reported by Shek, Wu and Law [32]:

“Concerning how this subject assisted my personal development, it changed my belief in leadership. I used to think that leadership is innate. The idea had been consolidated during my secondary school life when only the best students were nominated to join leadership camps and workshops. Such students had been academically outstanding in primary school. Later, they became the president of the student union or held other important student posts in school. Nevertheless, the subject provided an alternative perspective for me. The materials suggest that leadership attributes can be developed. Everyone can be a leader. It gives me a new hope.”

Qualitative Evaluation (Focus Group Interviews)

In the pilot stage, Shek and Sun [33] reported findings of a study using focus groups to examine the views of the students on the course. Generally speaking, the students were positive about the interesting course content, the interactive class atmosphere, and the useful guidance of the teachers. Most important of all, the students felt that the subject could promote their reflection and self-understanding. Some of the benefits of the subject were as follows:

- “I have changed to another person with at least some changes – I will think more about different possibilities of a matter so that it may change from unsuccessful to successful outcomes. This would promote my competitiveness.”
- “One of the changes I have after taking this subject is that I have my own views. That is, I have more courage to say ‘yes’ or ‘no’.”
- “I think this subject is not primarily concerned about IQ but EQ. Actually, EQ is very important in our study and after our graduation. There are many opportunities where we have to use our EQ. I feel that it is very useful. After we heard the lectures, we realized that we neglected something important and we pay attention to them again.”
- “I felt that after taking this course, I realized something which I had neglected before such as understanding myself.”
- “I had more understanding about my identity. After reading journal papers and doing my assignment, I understand that there are different ways of attaining ideal positive identity. When I do things now, I will think more and think about other people.”
- “I feel that it is helpful to my self-confidence. When you know your strengths and weaknesses, you know how to appreciate yourself.”
- “We learned how to do a group project. If you are a leader, you have to deal with some emergencies and how to relate to the professor. These would be helpful to our academic performance.”

In the focus group study, the students also highlighted the need for this subject:

- “I absolutely agree that we need this course. Maybe you have grown up in a very protective family and you will offend other people ...We have to learn how to evaluate oneself and then change some of the ‘bad things’ and reintegrate in the

society. I think this understanding is not just unique to university students. It is vital to everybody.”

- “When I communicate with secondary school students, I find that they have difficulty to express themselves and manage their matters. Therefore, having this course to help them reflect is a good method.”
- “This is a very good subject which is helpful for future. University education relies heavily on self-autonomy and interpersonal relationships.”

5-Year Longitudinal Study

“Tomorrow’s Leaders” was developed to enable students to satisfy the Leadership and Intrapersonal Development requirement of the General University Requirements (GUR) under the new 4-year undergraduate program. To understand students’ experiences of the GUR, a 5-year longitudinal study has been conducted [34]. We have conducted focus groups as well as secondary data analyses of the data collected by the Student Feedback Questionnaire to understand student feedback on “Tomorrow’s Leaders”. For example, based on the secondary data analyses of the data collected via the Student Feedback Questionnaire, the results showed that the students were satisfied with the subject and teaching of the instructor [35].

DISCUSSION

In this chapter, we outlined the development of a subject entitled “Tomorrow’s Leaders” for students to fulfill the Leadership and Intrapersonal Development requirement in the 4-year undergraduate program at The Hong Kong Polytechnic University (PolyU). The subject was piloted in the 2010-2012 academic years and it has been fully implemented since the 2012/13 academic year. Through several evaluation mechanisms, we have examined the impact of the subject on the psychosocial competencies and ethical leadership of the students. Overall speaking, the evaluation findings are overwhelmingly positive [14]. The findings are promising because we have used multiple evaluation methods to collect multiple types of data from multiple stakeholders.

According to Shek and Wong [36], adolescent developmental issues would not “disappear overnight”. With reference to this warning, there is a need to strengthen the psychosocial competencies and character strengths of students before they undertake any Service Learning projects. Interestingly, although there are numerous positive youth development programs designed for high school students [37], there are comparatively fewer programs developed for university students. In the present context, the evaluation findings demonstrate the usefulness of designing credit-bearing subjects using principles of the positive youth development approach. In fact, the evaluation findings accumulated in the past six years clearly point out that promotion of psychosocial competence in university students via credit bearing subjects is a promising approach to promote holistic development of university students.

Actually, the evaluation findings related to “Tomorrow’s Leaders” strongly complement the evaluation findings based on a project entitled “P.A.T.H.S. to Adulthood: A Jockey Club Youth Enhancement Scheme” (Project P.A.T.H.S.), which was designed to promote holistic development in junior secondary school students. The Project P.A.T.H.S. was launched more than one decade ago, serving more than 280,000 secondary school students (600,000+ man-times) involving more than 280 secondary schools in Hong Kong with an earmarked grant of HK\$750 million. Multiple evaluation findings showed that the program was effective in promoting holistic development and reducing risk behaviors in young people in Hong Kong [38]. Taken as a whole, the evaluation findings collected from the high school and tertiary education settings suggested that it is possible to promote psychosocial competence and character development in young people using the curriculum-based approach.

Palmer [39] maintained that it is important to help students understand themselves. As he argued, “our colleges and universities help student examine many dimensions of the external world - history, politics, economics, physical reality; yet we rarely turn the lens inward to help students examine their own lives. This lack of critical inquiry into these personal dimensions of students’ lives reflects a multi-leveled fear on the part of academics – the fear of venturing into ‘subjective territory’, saying, ‘I don’t want to go there because I’m not a psychotherapist’. But faculty and staff need to find ways of inviting students to examine these inner drivers and dynamics within the classroom and co-curricular activities that lead to greater self-understanding, without which one cannot be said to be well-educated” (p. 4). Obviously, “Tomorrow’s Leaders” is a constructive response to this comment.

Astin [40] also pointed out that “although we argued that institutions needed to focus more on student outcomes, we avoided specifying what any of these outcomes should be, arguing instead that this task should be left largely to the individual institution. In retrospect, I think this was a mistake. If we had been more forthcoming about our own values with respect to some of the most important student outcomes, we certainly would have generated more controversy, but I think the controversy would have been healthy. More specifically, I wish we had spoken more directly about the importance of so-called affective outcomes such as self-understanding, tolerance, honesty, citizenship, and social responsibility” (p. 587). Obviously, “Tomorrow’s Leaders” can strengthen the affective outcomes of student development which provides a solid foundation for service learning activities. We earnestly hope that the subject can provide the necessary foundation through which the Service Learning projects can be competently executed by the university students in Hong Kong.

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Chapter 176

SERVICE-LEARNING AS A MANDATORY CREDIT-BEARING SUBJECT

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ABSTRACT

Many universities have integrated community engagement in their undergraduate programs. At The Hong Kong Polytechnic University, it is compulsory for all students to take at least one 3-credit subject on service-learning (SL). In each SL subject, there are purpose-designed academic teaching, rigorous service and structured assessment components. At full implementation, roughly 4,500 undergraduate students would enroll in around 70 subjects offered by a wide range of departments and faculties across the university. The subjects cover a diverse range of topics, such as digital divide, learning difficulties, engineering design, healthy living environments, orthotics, and eco-tourism. The target beneficiaries are equally diverse, including slum dwellers, disabled people,

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children with HIV, villagers without water nor electricity, new immigrants, mentally ill patients, ethnic minorities, and children of migrant workers. To date, students have served different groups of clients in Hong Kong, Chinese Mainland, Cambodia, Vietnam, Indonesia, Myanmar, and Rwanda. This chapter outlines the pedagogical design of the program, challenges and strategies for implementation, and the experiences gained so far.

INTRODUCTION

In 2012, the undergraduate degree education structure in Hong Kong moved from three years to four years. One of the intended outcomes of the change is to ensure that “the higher education institutions will be in a better position to provide a balanced education to their students, through an integrated 4-year undergraduate programme, that allows for a broader knowledge base to support specialised learning” [1]. Internationally, increasing emphasis has been put on the role of universities in educating students into socially responsible citizens with a heart to serve the community [2-5].

At The Hong Kong Polytechnic University (PolyU), one of the strategic goals is to nurture all-round graduates with social and national responsibility. To this end, PolyU has successfully encouraged many students to engage with society through community service, mostly in the form of non-credit-bearing, co-curricular activities both local and offshore even before the inception of the four-year curriculum [6]. With the development of the 4-year undergraduate degree structure, all students are required to complete a 3-credit subject with an approved SL component in order to qualify for graduation. Given the size of the student body, this is a mammoth task with several major challenges. First, there is a need to design a rigorous academic structure for the development, offering, and quality control of SL subjects. Second, it is necessary to cultivate long-term service projects and collaborative relationships with external collaborators such as non-government organizations. Third, we have to build a critical mass of academic staff with the passion and expertise to offer SL subjects. Finally, there is a need to develop robust mechanisms for funding SL subjects and associated projects.

This chapter examines the major challenges and the institutional strategies in meeting the above challenges. In the development of the institutional strategy for SL, we have carefully studied and reviewed experiences at many institutions, including the University of San Francisco, University of Pennsylvania, Tufts University, Purdue University, among others, as well as the consolidated information at Campus Compact. Consequently, we have adopted many of their good practices.

ACADEMIC STRUCTURE

As an important type of experiential learning, SL integrates community service with instruction and reflection to enrich students’ learning experience in order to achieve intended institutional or program learning outcomes. It enhances students’ sense of civic responsibility and engagement as well as benefits the community at large on the other [7].

Background of Service-Learning at PolyU

Prior to the curriculum changes in 2012, approximately 1,000 students and staffs at PolyU had engaged in various voluntary community service projects each year. Many such projects were organized under the Community Service Learning Program (CSLP) managed by the Student Affairs Office. One exemplary project was the Assistive Technology Development Initiative where a team of students from the Electronic and Information Engineering Department designed and developed a range of assistive devices to help handicapped students in a special school to use computers, including enlarged buttons for students with difficulties in making precise motions with their hands and fingers. In another project, a team of students from different health care departments in the Faculty of Health and Social Sciences jointly organized with the Xinyang Vocational Technical College an integrated health promotion activity in rural Henan province in central China. It provided environmental, health and nutritional assessment for more than 100 primary school students.

Each year CSLP gave awards to exemplary projects to recognize their efforts, and to encourage students and staff to engage even more in the community. However, while the program encouraged quite a large number of students to engage in a variety of projects, there were nevertheless a number of issues encountered. For example, students often lost enthusiasm and failed to maintain momentum when they encountered other opportunities or when they were under academic pressure, such as approaching deadlines of assignments and at times of examinations. In addition, students were generally more interested in the action of providing service than the planning and preparation for the project, or reflecting on their experiences or following-up with needed support.

Under the new undergraduate academic structure, students stay in the university for four years. During the first year, students may not be ready to engage heavily in services. During the final year, they may focus on graduation and looking for jobs or graduate schools. Hence, there is only a 2-year window when students are available for services. Besides, every year is a transitional year for new teachers and leaders in service-learning. Given these constraints, it may be difficult to maintain consistency and develop long-term projects and collaborative relationships with partners and communities.

Credit-Bearing Service-Learning Subjects

Service-learning has certain similarities with, but is not the same as, volunteer work. While volunteer work stresses service without compensation or reward, service-learning calls for a balanced approach integrating community service with learning, and emphasizes learning through participation in services [8]. Hence, students' self-reflection and assessment are critical elements of service-learning [9].

At PolyU, a relatively broad definition of service-learning is adopted. It primarily focuses on activities that serve people directly, but it also covers indirect service activities relating to civic responsibility and engagement. It can include direct service activities such as tutoring children in poverty, construction for remote villages, and health education for under-developed communities as well as indirect services such as field research on sustainable

development and advocacy for social justice. Both local and offshore activities are included. The students' achievement of academic objectives is then revealed by academic credits.

PolyU is a comprehensive university with a wide range of disciplines. Each academic program is typically composed of Discipline-Specific Requirements (DSR) and General University Requirements (GUR). GUR includes languages and general education subjects, with 30 credits. As part of GUR, any academic department can design a 3-credit Service-Learning subject. It may target general issues such as poverty relief or assisting the elderly. It may target more specific issues such as assistive devices for the handicapped, housing problems, or dyslexia. It may require generic skills such as communication in English and Chinese, or it may require discipline-specific skills such as bridge-building, accounting, nursing or graphic design. In short, an academic subject qualifies as a SL subject if it has clear academic objectives and expected outcomes for the students, which may be generic, discipline-specific, or both.

There are four common learning outcomes for SL subjects. These include application of knowledge and skills they have acquired in the service setting, reflection on their role and responsibilities both as a professional in their chosen discipline and as a responsible citizen, demonstrating empathy for people in need, and an understanding of the linkage between the academic content of the subject and the needs of society. For each SL subject, we expect students to undertake a SL project of at least 40 hours under supervision and to conduct rigorous student reflections on the linkage of their studies to the needs of the community and the services, their personal role and growth, and the impact of their services.

Categories of SL Subjects

Based on literature and the experiences of other universities, we can achieve the common SL learning outcomes in many different ways. Each subject may differ in the background of the students, the associated academic discipline, the type of services involved, the type of clients served, the location, etc. By 2016, four years after the policy came into effect, 25 out of 29 academic departments at the university are offering at least one SL subject. Table 1 shows some examples of subjects designed for students with different backgrounds.

Broadly speaking, there are two major types of SL subjects. There are "general education" types (referred to as General University Requirement, GUR) subjects. They attempt to enhance students' general knowledge. They do not require specific pre-requisite subjects or knowledge beyond what an average undergraduate student should know. Hence, many GUR subjects are open to all undergraduate students without pre-requisites. However, there are some GUR SL subjects designed for students with certain backgrounds, such as engineering, health-related disciplines, and business. We expect these subjects contribute to the general education of students of that particular background. On the other hand, there are other subjects designed for students in a specific discipline, such as Optometry, English, Biomedical Engineering... etc. In these subjects, we expect students specializing in professional disciplines to use their specialist knowledge to serve and enhance their professional expertise. Students in their senior (i.e. third or fourth year) typically take such subjects.

All SL subjects, including those that are open to all students, are expected to have strong academic objectives and learning outcomes. Students are given rigorous training in the academic elements and relevant skills prior to engaging in the prescribed community service projects. Besides, they are rigorously assessed in the achievement of the expected learning outcomes. For example, the “Technology Beyond Borders” subject is focused on information technology. One of the main topics of study is the “digital divide” between communities with advanced IT technologies and those who are without. Students learn about the digital divide, appropriate technologies and methods for bridging it, and then participate in service projects applying those technologies and methods.

The wide range of SL subjects on offer can counteract the negative consequence of the compulsory nature of the SL requirement. Some students object being required to take a subject they may not be interested in fulfilling the SL requirement. Even among those who are positive about community service, some may still resent being compelled to “do something good”. Obviously, the wide range of subject contents, locales, service types available provides students options and a sense of control.

Table 1. Examples of service-learning subjects

Sample service-learning subjects	
GUR subjects open to all students	• Building green communities with environmental NGOs • Engaging fashion as a communication media for the needy • Growing resilience of children in post-disaster areas • Preserving Cultural Heritage for Ethnic Minorities in Contemporary China • Promotion of Children and Adolescent Development • Serving the Community through Teaching English • Social Justice in Private Housing Redevelopment • Technology beyond borders: service-learning across cultural, ethnic and community lines
GUR subjects for students with certain backgrounds	• Built Environment Enhancement for Underprivileged Communities • Community Psychology • Comprehending and Overcoming Learning Hurdles in STEM for Local Schools • Financial literacy for low-income youths • Helping Primary Students with Specific Reading Difficulties • Promotion of Healthy Ageing in the Community • Serving people with special needs through assistive technology
Discipline-specific subjects	• Accounting and Internal Control in the Elderly Centre through Service Learning • Community Tourism: Tour, Training, Operator, and Event from and for the Community • Enabling occupation in home and community practice • Indoor Environment for Serving the Elderly • Public health optometry • Teaching Chinese as a second language • Teaching English as a Service Learning Experience

Class Size of SL Subjects

The first strategic decision regarding service-learning was to make it credit-bearing. The second was to make it compulsory for all undergraduates. There are two major arguments for the decision. Firstly, the learning objectives of civic responsibility, social justice and ethics are critical components of all-round education, and hence should be required of all students. Secondly, the requirement provides an opportunity for those who would not volunteer for community service.

Table 2. Complementary roles of sub-committee on Service-Learning Subjects (SCSLs) and the Office of Service-Learning (OSL)

Sub-committee on SL Subjects	Office of Service-Learning
Vetting of subject proposals	Assisting in development of proposals
Formulating of policies and procedures	Administration of policies and procedures
(developing) Quality Control	Assisting in the teaching of SL, execution of service projects, and other support activities

These two decisions create a need for large numbers of SL subjects and places for students. At many colleges and universities, service-learning is carried out in the form of small classes with around 20 students. Usually the students select the SL subject or project voluntarily. They are highly motivated. Hence, the subjects may not be very structured, allowing a high degree of autonomy for the students in designing and carrying out their projects. Many of the SL subjects at PolyU fit this pattern. However, the offering of service-learning subjects to large classes (e.g., over 100 students) is a unique feature of SL at PolyU. This is a result of both necessity and design. Primarily, as there is a need to provide thousands of places each year for the students who are required to take SL subjects, there is a need for large classes. Besides, some of these students may not be as highly motivated even though they can choose a subject from a wide variety of SL subjects. Hence, there are some SL subjects in which the service projects are highly structured, which can also accommodate a large number of students.

For example, we take BME2S01 (Scientific Literacy for Low-Performing Students) as an example, which enrolls 100 students annually. The arrangement is to send 50 PolyU students to one secondary school, with 10 PolyU students in one classroom for 50 secondary students to help the secondary students carry out pre-designed science projects. Another 50 PolyU students will go to another secondary school doing similar projects. Within this structure, there is a lot of room for autonomy and self-initiative. PolyU students are given a general topic for the science project (e.g., Grade 8 physics using the Arduino platform), and they develop the project details, procure the materials, write the lesson plans and worksheets, etc. This arrangement is a balance between providing the structure and discipline to support a large number of students, while at the same time providing sufficient room for the students to learn to be independent and innovative in problem solving.

Quality Assurance and Control

With such a broad diversity of subjects and staff, it is important to have a process for assuring the quality of the student learning experience. To this end, we formed a committee on service-learning subjects with the objective to oversee the offering of SL subjects at the university. The committee is composed of faculty members from diverse faculties and departments, who are experienced in SL and general academic matters. The composition of the committee ensures representation of a broad spectrum of disciplines and departments and presence of balanced academic viewpoints. The committee invites proposals for new subjects, vets the proposals and finally recommends them for implementation.

The committee works closely with the Office of Service-Learning (OSL), which is the operational arm of the support structure. The OSL assists departments in developing subject proposals, projects, and student supervision. Table 2 shows the roles of the committee and OSL.

The decision to make SL credit-bearing and compulsory was made in December 2010, with the decision applicable to the first cohort of students entering in 2012. Since 2011, the main goal of the committee and OSL was to promote and develop SL subjects. In each year, the University approved approximately 15-20 new subjects. By December 2015, there were 58 approved subjects from 25 academic departments. While the University will continue to develop new subjects, the focus will also shift to evaluation, consolidation, and research on evidence-based SL.

The fact that multiple departments offer SL subjects poses particular challenges in quality control. The existing practice is that departments are responsible for quality control of the subjects that they offer. However, as most departments offer only a few SL subjects, there is an on-going discussion on whether it is preferable to have a centralized unit to oversee the operation of SL subjects across campus and to ensure parity across the multiple subjects. There is also an on-going teaching development project on the evaluation of SL subjects, which will provide research-based input to the development of a rigorous academic quality control process for SL.

OPERATIONAL SUPPORT

When the SL requirement became reality in 2012, a few departments were already experienced in SL mainly because of the nature of their discipline. Most of these departments are in the health sciences, such as social work, nursing and rehabilitation sciences. Some other departments, such as computing and biomedical engineering, had acquired some experience because of their own initiatives. Most of the other departments and their staff, however, were relatively inexperienced. Therefore, it is important for the University to provide needed support for developing subject syllabi, teaching methods, and service projects, etc. This need is also evident from studying practices at many leading universities. Hence, the University established the Office of Service-Learning to provide central support and coordination.

Office of Service-Learning (OSL)

The OSL advises departments and academic staffs on various matters related to OSL. These include development of subjects and projects, liaison with non-government organizations to find suitable projects for the teachers, liaison with funding agencies and donors to support projects, offering of staff development workshops and courses, and organization of exploratory projects.

Working closely with the committee in charge of vetting subject proposals, the OSL also developed an eLearning module for students, which covers basic concepts of service-learning that can be used as a core part of a SL subject. The module lasts for 10 hours and it has been integrated into many SL subjects. It reduces the teaching load of the teaching staff, ensures some consistency in teaching, and promotes the implementation of service-learning.

Collaboration with External Partners

In most cases, we carry out service projects in collaboration with external organizations, such as non-profit organizations, primary schools, secondary schools, and other universities. In some cases, PolyU staffs are responsible for designing and planning the majority of the project, while the external partner contributes little. For example, in some projects aiming at reducing the “scientific divide,” the collaborating schools are responsible for selecting the participating students and scheduling the sessions and venue. The PolyU staffs are in charge of the service projects, including designing the projects, providing the project material and notes and transportation for the students.

In some other projects, the external partner may play a much more significant role. This is particularly true for offshore projects in the Chinese mainland or overseas. For example, one of our projects in rural development collaborates with a university in Indonesia. Our partner institution has a strong service-learning program of their own as well as good connections to the local government and many villages around Yogyakarta, and their students speak the local language. In this particular case, the local partner takes many initiatives in the planning of the services, selection of villages, logistics, accommodation in village homes, interpretation, etc. Our faculty members work closely with the local university, and retain full control in supervising and assessing our students in the execution of the service projects. The middle part of Figure 1 shows this arrangement.

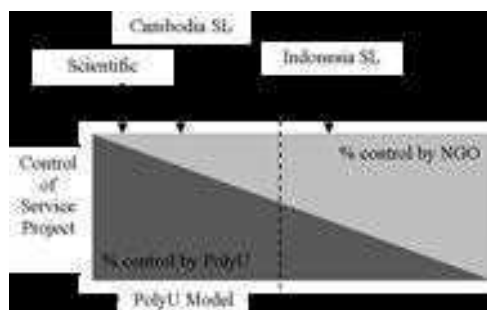


Figure 1. Collaborative relationship between university and service-learning partner.

Many of the projects are in between the “scientific divide” case (i.e., PolyU has practically full control) and the “Indonesia” case (i.e., our partner doing much of the planning and logistics) in Figure 1. For example, we have sent teams to Cambodia since 2010 and have built up many good contacts and a good understanding of the local transportation and accommodation. Hence, we are able to control a lot of the planning, selection of projects, logistics, etc., although we still have to rely on our local partners for liaising with the target community and interpretation. At the same time, we are helping some of our partners to build up their service-learning capacity and experience. This case is positioned about 25% from the left edge of the diagram in Figure 1.

We discourage and we have never approved service-learning projects that give complete control to our external partners. Given that service-learning is a core requirement of the University, it is imperative for the learning outcomes and the learning experience of our students that the design of the project is an integral part of the subject, which makes outsourcing to external partners inappropriate. Hence, the range of collaborative relationships supported in the PolyU model covers generally the left half of the diagram in Figure 1.

Staff Development

Prior to the implementation of academic credit-bearing SL in 2011, there were few faculty members who had significant experience in developing, delivering and assessing credit-bearing service-learning. At full implementation, we probably need around 100 teachers to teach around 60 SL subjects, some of which may need two or more teachers to co-teach because of the large class size, heavy supervisory duties, or the multi-disciplinary nature of the subject or services. Hence, staff development is critical [10]. In the past years, we have developed several initiatives on staff development.

Workshops and Seminars

From the start, workshops and seminars were heavily used to promote the concept of service-learning as well as to educate staff on different aspects of teaching an SL subject. These seminars were organized on a monthly basis on a broad range of topics, including policy on service-learning, how to write a syllabus, how to assess students’ performance, etc. At the beginning, outside speakers were invited. As colleagues gained more experience, speakers experienced in various aspects of SL within PolyU are leading these workshops.

E-Learning

An eLearning short course for staff was developed and implemented in September 2012. It takes 3 hours to complete and covers the basic concepts, advantages, myths, subject and project development guidelines, samples of SL subject syllabi and projects [11]. More than 50 staff members have since taken the eLearning course. An evaluation survey found that overall satisfaction with the eLearning short course was around good (4 points out of a maximum of

5 points). Many who have taken the course have gone on to propose and teaching SL subjects. We have also shared the e-learning module with colleagues from other institutions.

In addition, we have developed an eLearning module covering basic concepts of SL. It takes 10 hours for the student to complete. Many SL subjects incorporate the eLearning module in the curriculum where students will take this at the beginning of the term. The module has two major purposes. First, it reduces the workload of the subject lecturer. Second, it ensures that there is a consistent coverage of the core concepts of SL across SL subjects. Many subject lecturers apply the inverted classroom method with the eLearning module: after the students complete the eLearning module, teachers hold a face-to-face classroom discussion to discuss the concepts introduced in the eLearning module, in more depth.

Practical Experience and Training

Colleagues who are interested in SL are given opportunities to participate in service projects to acquire hands-on experience. Starting in 2011, we have invited a small number of colleagues to participate in some of our more “mature” projects as observers or assistants, such as the Cambodia off-shore service-learning project. A practical experience short course was offered for the first time in summer 2013, and repeated in 2014. Several colleagues who participated have come back to become strong advocates and supporters with SL subjects of their own.

In 2016, 17 staff members from both academic and non-academic departments participated in a staff project in Cambodia. They visited a number of student projects to observe the students’ service and carried out their own projects on helping to set up a community learning center. Some of the colleagues were already involved in teaching SL subjects in Hong Kong or proposing new subjects. They found the experience valuable in understanding what it takes to operate an overseas SL project. Staff with administrative responsibilities found it valuable in understanding SL and helpful in promoting and supporting SL from their own posts, such as in publicity, fundraising, and in general supporting the operations of SL subjects in academic departments. Overall, it is an important step towards staff participation in service-learning and embedding SL as a core value of the university.

Community of Practice

A community of practice has been nurtured as a platform for staff to share experiences, collaborate in exploratory projects and research, and to promote the practice of service-learning. As mentioned earlier, SL subjects exist in a wide range of departments, with some departments having relatively few colleagues engaging in SL. To provide support to our SL faculty members, we have created an institution-wide community of practice. The community has a modest budget for supporting small-scale projects, attendance at conferences, etc. Regular gatherings encourage colleagues to share experiences and information on writing proposals for new subjects, seeking funding, and assessing student performance. Such gatherings are usually well-attended, testifying to their usefulness. Members of the

community have proposed SL subjects and projects, participated in the organization of conferences, and become the prime movers of SL across the university.

FUNDING SUPPORT

One of the core strategies of credit-bearing service-learning is that SL subjects are offered and funded like other academic subjects. In addition, it is recognized that service-learning involves a significant amount of activities conducted outside the classroom. Hence, there may be a need for additional resources for supporting the subject delivery, such as field supervision, travelling and equipment. Because of the special nature of SL subjects, the total funding of SL subjects is approximately 30% higher than other GUR (general education) subjects.

Project and Travel Expenses

While around 80% of our students participate in service-learning projects in Hong Kong, an increasing number are serving in offshore projects beyond Hong Kong. These include sites in the Chinese mainland, as well as foreign countries such as Cambodia, Indonesia, Vietnam, Myanmar and Rwanda. These projects serve multiple purposes in addition to learning through service. To begin with, Hong Kong is geographically very small and relatively racially homogeneous. In addition, many of our students are from working-class backgrounds without any travel experience outside Hong Kong. This means that many of them have not previously had experience interacting with peers from a different race or culture for an extended period. Offshore projects therefore afford students an additional learning experience from interacting with people from different cultures and races. For projects that involve appropriate technology, they also afford students the opportunity to work in a low-resource environment.

Offshore service-learning projects necessarily incur additional costs beyond that of a conventional academic subject, and even beyond that of local service-learning subjects. While the University is expecting the students to cover part of their own costs to ensure ownership and accountability, it also raises funds to subsidize the students' expenses. It is encouraging to witness that many donors, both individuals and institutions, are quite willing to donate generously to fund SL projects. Since 2011, donations of more than US\$3 million to support service-learning projects have been received.

INTERNATIONAL SERVICE LEARNING

Hong Kong is a small and relatively homogenous society. Internationalization of our SL projects is important for many reasons, not the least for broadening the students' experience and benchmarking. In 2012, while the University was making a major effort in developing SL subjects, the University organized the first University Social Responsibility Summit, with the participation of senior administrators from a number of prestigious universities active in the field. In 2014, the second submit was organized, in conjunction with the first international

conference on service-learning organized by the University. In 2015, the USR Network was formally launched, with 14 founding members. By then, SL has been firmly established as a major component of the social responsibility initiative of the University.

In summer 2016, USR Network member universities sent nine students to participate in PolyU's SL projects. Eight of them (from Washington University in St Louis from the USA, Haifa University from Israel and Sichuan University from China) participated in the Cambodia project organized by the Department of Computing. They joined 30 students from PolyU and another around 30 students from two institutions in Cambodia. Supported by around 10 colleagues, the team went through a week of training at a local university and then carried out a range of technology-based projects, including installation of four solar power stations where they used solar panels to charge car batteries. Besides, they wired up 15 households where car batteries charged at the charging stations were used to power LED lights and phone chargers and maintained six charging stations and around 30 households set up in 2015. In addition, they installed two used containers as a community learning center. In the learning center, they installed solar-powered electrical fans, LED lighting, and a rain-collection system. They also made furniture, set up computers and Internet access via SIM cards. Throughout the week, the whole team stayed in village homes in a home-stay program. The project enabled the 80 students from seven educational institutions from Hong Kong, China, the USA, Israel and Cambodia to bond with each other through an intense serving and learning experience. This project serves as the prototype of an international summer institute of SL and leadership that we are planning to start in summer 2017.

In addition, there are also a number of other initiatives in internationalization of SL. The Biomedical Engineering team has long been collaborating with the Washington University in St Louis and the University of Pennsylvania on a project serving handicapped people in southern China. The Department of Computing launched a joint SL subject with the University of Maryland, combining technology-based services with community need assessment in Rwanda. The Office of Service-Learning launched a SL journalist project with a team composed of students from Brown University and the PolyU as a new initiative in development communications.

SELECTED CASE STUDIES

The previous sections describe the background of the service-learning initiative at The Hong Kong Polytechnic University. In this section, we will describe some representative projects.

Technology Beyond Borders: Addressing the Digital Divide

This is one of the first credit-bearing SL subjects as well as one of the most ambitious ones. The subject aims to enable students from across the university to learn about the impact of (actually the lack of) information technology on communities and how technology can be used to empower developing and underprivileged communities. The students start with the eLearning module on basic concepts of service-learning. Then they learn the various aspects

of the digital divide in several lectures: hardware, software, access to the Internet, education, ethical issues, use of appropriate technology to tackle problems in the developing world, addressing the needs of underprivileged communities such as those who are disabled.

The subject is open to all students with an enrollment of 100-150 students every year. The students come from disciplines such as engineering, science, language, finance, nursing, design, etc. The students then form project teams based on their preference as well as the needs of the project. In 2015-16, there are projects with different communities in five locations. These include assistive devices for handicapped children in special schools in Hong Kong, solar power and a community learning center for villagers without electricity and water in Cambodia, technology-based projects for a secondary school in rural Myanmar, solar power and a community learning center in villages without electricity and running water in Rwanda, and technology-based projects for schools in Kyrgyzstan. Then the students attend specific lectures and workshops about the target communities of their projects. These workshops cover the historical and cultural background of the target community as well as the technical contents of the project. For Cambodia and Rwanda, we discuss the genocidal civil wars and their impact on the country.

After the training, students are then ready for the service-project. These typically take place in May and June after the end of the second semester, with supervision and support from the teaching team consisting of professors and teaching assistants/SL officers. We hold debriefing and sharing sessions throughout the service period to assist the students in reflecting on their experience, making observations, asking probing questions and making adjustments in their service projects. The students write journals and reports individually and collectively. Teachers assess the three aspects of the project (preparations, execution, and reflections) as part of the overall grading.

This subject has been running since 2011. In the process, we have developed strong collaboration relationships with a number of collaborating organizations and universities in the various locales. These relationships have led to long-term projects. It has also facilitated the setting up of other projects in these locales, by departments such as Optometry, Hotel and Tourism Management, Nursing, and English Learning Center. It has also led to several international collaboration projects with foreign universities mentioned above.

Engaging Fashion as a Communication Media for the Needy

This is a subject offered by the Institute of Textile and Clothing. It is open to students from all disciplines. After studying the core concepts of SL through e-Learning, students learn a number of fashion design concepts such as trends, sourcing, taking measurements, basic garment patterns, fitting and sewing. They also learn fashion creativity as communication media, social perception and social influence of fashion on community. Students then form teams to plan, co-ordinate, teach and conduct small workshops for elderly, disabled or ex-mental patients on fashion design and styling as well as garment making, and assist the service recipients to create and style an outfit. The teachers and students will then showcase the creative works derived from this project in an exhibition within the PolyU campus and/or a mini fashion show at a public venue or within the university. Professional photographers engage in photography sessions to create portfolios for the clients. Finally,

students write reflective journals and reports to link their service-learning experiences with the academic focus/discipline-specific content of the subject, reflect on their service-learning experience to identify their learning gains as well as areas for future improvements, and reflect on their roles and social responsibilities.

The project approaches fashion creativity as a form of caring tool and help service recipients build inner confidence in utilizing their personal creativity to create a fashion outfit and enhance their personal fashion image. The project has been running for several years and receives very good feedback from students, clients, partner NGOs funding agencies and the government.

EVALUATION BASED ON THE FIRST FOUR YEARS

Initially, we estimated that an average SL subject could accommodate 50 students. As such, we need to offer around 60 subjects each year to accommodate all the 2,800 students in full-time 4-year undergraduate degree programs needing to take a SL subject, when the initiative is in full implementation. Since then, the University has decided that the requirement also applies to the “senior year” students who enter these 4-year programs with advanced standing, typically after completing an associate degree at a community college. This raises the total number of students who have to take a SL subject to around 4,500 each year.

Since spring of 2011 until May 2016, we had developed and approved 60 subjects (see Figure 2). Not surprisingly, many departments in health and social science offer the related subjects. However, it is also encouraging to see departments in engineering as well as construction and environment offer SL subjects. In fact, all faculties and schools are now active in offering service-learning.

Impact on Students

In the academic year 2015-16, around 3,790 students enrolled in SL subjects. Amongst them, 75% of them participated in projects in Hong Kong, about 18% of them served in projects in the Chinese mainland, and 7% served in overseas countries, mostly in South-East Asia, and a few as far as in Kyrgyzstan in Central Asia and Rwanda in East Africa (see Figure 3). Students completed a questionnaire before and after they had taken their SL subjects. At the time when we wrote this chapter, we had collected data from around 2,000 students who had completed one of 55 credit-bearing SL subjects, and the preliminary results are quite encouraging (see Figure 4).

One distinguishing characteristic of the SL requirement at PolyU is that it is mandatory for all undergraduate students. To understand the impact of the mandatory requirement on the students, we have also conducted a 2-part study. Part 1 is a quantitative study of the correlation between the students’ response to an online survey of their learning experience and the students’ subject grade. Part 2 is an in-depth individual interview with 46 students randomly selected. The conclusion from the analysis indicated that students as a whole did learn quite a lot from the mandatory SL requirement. Interestingly, the “less-inclined”

students learned almost as much as those who were “more-inclined”. Results also showed that quality of learning experience, and to a less extent, their interest in the subject, had a much stronger impact than their initial inclination on their learning and development from SL. Finally, most students, particularly those who adopted a negative or “passive acceptance” stance, reported a very positive change in their views on SL after taking the subject (see Figure 5).

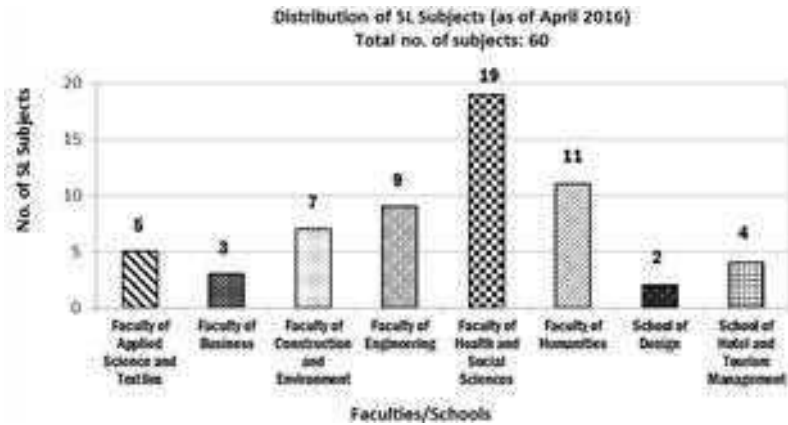


Figure 2. Number of SL subjects approved, offered by each faculty/school.

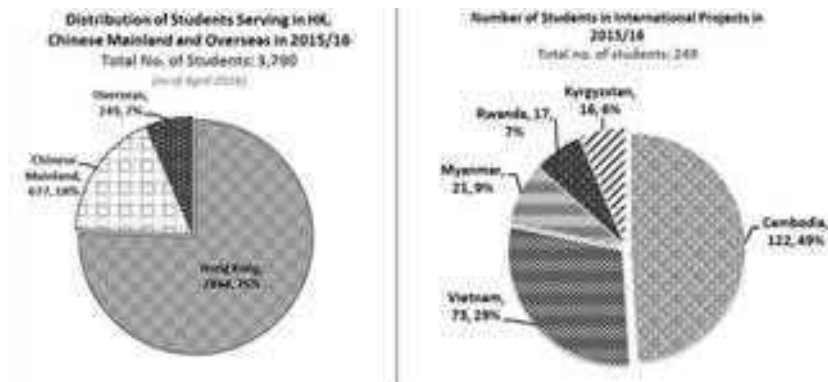


Figure 3. Distribution of students by (left) service location and (right) international projects.

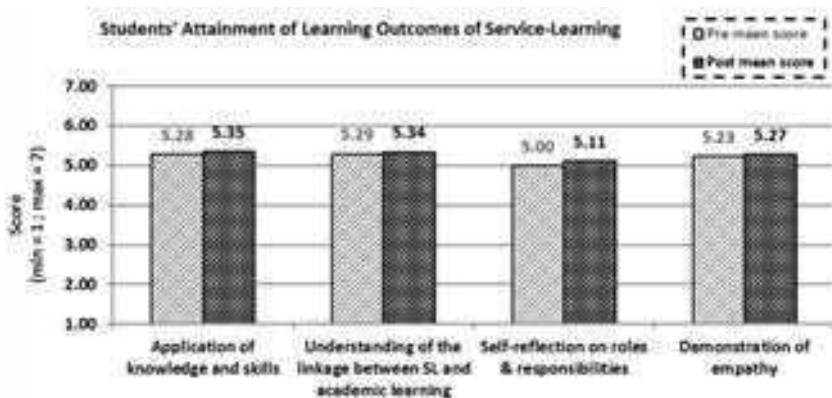


Figure 4. Students' self-evaluation of generic skills before and after taking SL.

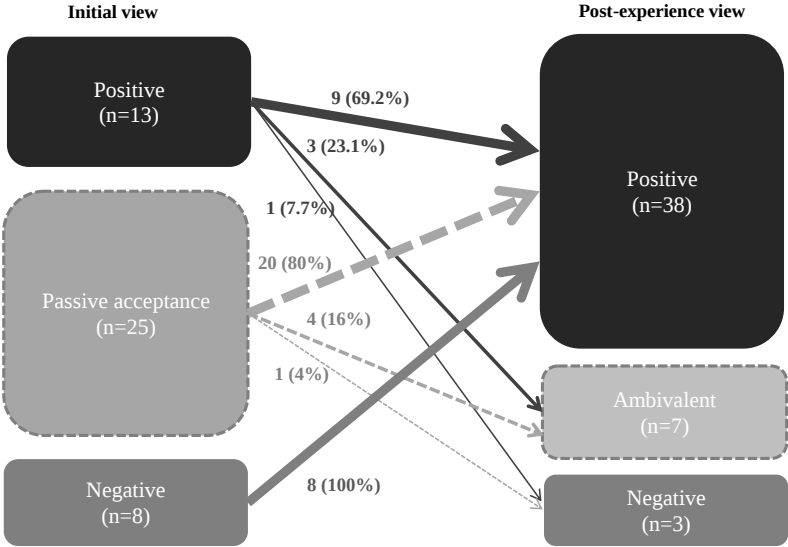


Figure 5. Changes in students’ view about SL after taking SL subject.

The objective of the SL initiative at PolyU is not only for students to take a SL subject. Instead, it attempts to cultivate a culture of civic engagement and social responsibility at the University. It is encouraging to observe that some of the students who have taken a SL subject have returned to participate in service projects as student assistants and leaders, organized their own service projects, and even developed their own organizations in community service. The University is developing a number of mechanisms, including scholarships, internship opportunities, and participation in SL-related conferences, to encourage and support students in furthering their involvement in service-learning. A student SL Network has been set up as an umbrella organization for a number of student clubs on a variety of themes in SL, such as Cambodia, Technology for Development, Drones for STEM, Rehabilitation Services in Rural China, and Volunteer Teaching in China.

Impact on Staff and the University

When the SL initiative was proposed, there were many doubters and sceptics. Fortunately, in the past several years, there are encouraging signs that more staff members are actively involved. There is now a Community of Practice on SL with 50+ core members. Starting with just a handful of staff, we have now around 150 academic staff involved in the teaching of 60+ subjects annually. We also see an increasing interest from alumni, individuals and organizations external to the university, which is concretely reflected in the increasing amount of donations dedicated to service-learning. The amount of funds needed to send the 900+ students to mainland China and overseas is estimated to be approximately 10 million Hong Kong dollars per year, financed mainly by donations, government funds and the students’ own contributions.

CONCLUSION AND FUTURE WORK

Starting from scratch in 2011, the SL initiative has been largely progressing on schedule. This is the result of adopting best practices from leading universities, determination and strong support from the senior management, clear and balanced policies, the effort of a number of enthusiastic advocates, and most importantly, support from a broad spectrum of staff and students from across the university.

Nevertheless, from the experience in the past three years, we have identified a number of issues requiring attention. The first issue is on quality assurance. There is a need to ensure that the subjects offered are genuine SL subjects and teachers teach the subject according to its design, and the assessment is consistent across subjects. Second, there is a need for funding support. Many subjects, particularly those involving travelling and equipment incur significant expenses. We need to ensure stability of funding for long-term operation of the program. Third, we should further explore appropriate pedagogy to develop appropriate teaching methods for different types of SL subjects, particularly for students who do not necessarily participate voluntarily. In the past years, we have learned a few lessons. However, we have to ensure that the students derive maximum benefits from the SL requirement.

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Chapter 177

UNIVERSITY SOCIAL RESPONSIBILITY AND PROMOTION OF THE QUALITY OF LIFE

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ABSTRACT

There are many issues confronting the contemporary world that adversely affect the quality of life of human beings, living creatures and the environment. With reference to these problems and the notion of “corporate social responsibility,” it is argued that universities have to develop the culture of “university social responsibility” (USR) to tackle these problems to promote the quality of life. In this chapter, it is argued that universities should engage in USR activities through teaching, research and services. Issues surrounding the role of USR in the promotion of the quality of life are discussed.

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INTRODUCTION

The traditional image of a university is to generate advanced knowledge of complex nature. The term “higher” education clearly describes this point. Hence, the traditional image of a university is also an “ivory tower” where there is a wide abyss between “ordinary” people and “learned” intellectuals in the university. However, there are more people including academics arguing that the role of the university and academic pursuits is not just conducting intellectual exercises, such as asking the question of what “truth” is. The community is asking how academic knowledge can promote the quality of life for human beings, living organisms, communities, countries, regions, and the global world.

In the good old days when few people studied at universities, getting “good jobs” after graduation was not a problem. However, with more young people going to university and competition for jobs becoming more intense, some universities have changed to vocational training “factories” to equip students with vocational skills. While there is nothing wrong with this approach, over-emphasis on job preparation would necessarily constrain the mindset of students to form a narrow conception about the social responsibilities of university students. Besides, university students might become more egocentric focusing on tangible outcomes of university education. Hence, there are views arguing against such over-emphasis on the job preparation function of universities.

It is not uncommon to see that universities focus on the promotion of the quality of life as a vision and/or mission of universities. As shown in Table 1, many universities throughout the world attach great importance to the promotion of the quality of life as part of the duty of a university. While these are noble statements, how can universities promote the quality of life of human beings, living creatures and the environment? In this chapter, we will discuss how universities can possibly promote the quality of life through teaching, research and service. We will also identify issues surrounding university’s role in the promotion of the quality of life. According to Shek and Lee [1], the quality of life (QOL) is a multidimensional approach incorporating material well-being (e.g., income, living quality), physical well-being (e.g., health, fitness, personal safety), social well-being (e.g., personal relationships, community engagement), emotional well-being (e.g., mental health, life satisfaction, self-esteem), and productive well-being (e.g., competence, productivity).

Problems Confronting the World

There are many problems confronting the world which adversely affect the quality of life for human beings, living creatures and the environment. Based on an extensive review of the literature [2-6], there are ten key global challenges which are faced by the human race. The first challenge is abrupt climate change. There is a growing body of evidence that human activity since the industrial revolution has significantly increased the production of greenhouse gasses [7] which has led to a warmer Earth. Extreme high temperature does not only kill people, it also adversely affects agriculture and infrastructure [8]. The second global challenge is food security which occurs as a result of the rise in population size and catastrophic climate change. Searchinger et al. [9] pointed out that food production needs to be increased by 50-100% in order to meet the demand. According to the Food and

Agricultural Organization [10] of the United Nations, there are still 795 million people undernourished, although the prevalence rate of undernourishment has decreased globally from 18.6% in 1990-92 to 10.9% in 2014-16. The third global challenge is related to water and sanitation which are recognized as a basic human right by the United Nations General Assembly [11]. Around 9% of the global population does not have access to an improved source of drinking water [12]. Regarding sanitation, around 50% of people in rural areas lack improved sanitation facilities, while only 18% of people in urban areas lack them.

Table 1. Promotion of quality of life focus in the vision and mission statements in different universities

University		Promotion of quality of life focus
1	California Institute of Technology	"to expand human knowledge and benefit society through research integrated with education" (http://www.caltech.edu/content/caltech-glance)
2	University of Oxford	"We seek to do this in ways which benefit society on a national and a global scale." (https://www.ox.ac.uk/about/organisation/strategic-plan?wssl=1)
3	University of Cambridge	"to contribute to society through the pursuit of education, learning, and research at the highest international levels of excellence." (https://www.cam.ac.uk/about-the-university/how-the-university-and-colleges-work/the-universitys-mission-and-core-values)
4	Massachusetts Institute of Technology	"to advance knowledge and educate students in science, technology, and other areas of scholarship that will best serve the nation and the world in the 21st century." (http://web.mit.edu/facts/mission.html)
5	Harvard University	"to educate the citizens and citizen-leaders for our society" (https://college.harvard.edu/about/history)
6	Princeton University	"with a pervasive commitment to serve the nation and the world" (https://www.princeton.edu/main/about/mission/)
7	Yale University	"to improving the world today and for future generations" (http://www.yale.edu/about-yale/mission-statement)
8	University College London	"to transform how the world is understood, how knowledge is created and shared and the way that global problems are solved" (http://www.ucl.ac.uk/ucl-2034)
9	Columbia University	"to support research and teaching on global issues" (http://www.columbia.edu/content/mission-statement.html)
10	University of California, Los Angeles	"the creation, dissemination, preservation and application of knowledge for the betterment of our global society" (http://www.ucla.edu/about/mission-and-values)
11	University of Toronto	"with vigilant protection for individual human rights, and a resolute commitment to the principles of equal opportunity, equity and justice" (https://www.utoronto.ca/about-u-of-t/mission)
12	Duke University	"to contribute in diverse ways to the local community, the state, the nation and the world" (https://trustees.duke.edu/governing-documents/mission-statement)
13	University of Edinburgh	"make a significant, sustainable and socially responsible contribution to Scotland, the UK and the world, promoting health and economic and cultural wellbeing." (http://www.ed.ac.uk/about/mission-governance/mission)
14	University of Melbourne	"contributing to society in ways that enrich and transform lives" (http://about.unimelb.edu.au/__data/assets/pdf_file/0006/1462065/11364-GROWING-ESTEEM-2015-FA-WEB.pdf)
15	University of British Columbia	"supports outstanding research to serve the people of British Columbia, Canada and the world." (http://strategicplan.ubc.ca/the-plan/vision-statement/)

Table 1. (Continued)

University		Promotion of quality of life focus
16	The University of Tokyo	"aims to expand the boundaries of human knowledge in partnership with society." (http://www.u-tokyo.ac.jp/en/about/mission.html)
17	The University of Hong Kong	"to attract and nurture outstanding scholars from around the world through excellence and innovation in teaching and learning, research and knowledge exchange, contributing to the advancement of society" (http://www.hku.hk/about/vision.html)
18	Washington University in St. Louis	"strive to enhance the lives and livelihoods of students, the people of the greater St. Louis community, the country and the world." (https://wustl.edu/about/mission-statement/)
19	Brown University	"to serve the community, the nation, and the world by discovering, communicating, and preserving knowledge" (https://www.brown.edu/about/mission)
20	University of Sydney	"leading to improve the world around us" (http://sydney.edu.au/about-us/vision-and-values.html)
21	Hong Kong University of Science and Technology	"to contribute to the economic and social development of the nation as a leading University in China" (http://www.ust.hk/about-hkust/hkust-at-a-glance/mission-vision/)
22	University of Southern California	"the development of human beings and society as a whole through the cultivation and enrichment of the human mind and spirit" (https://about.usc.edu/files/2011/07/USCRole_and_Mission_Statement_1993.pdf)
23	University of Glasgow	"We should use our work to benefit and enhance Glasgow, the West of Scotland and the global community wherever possible." (http://www.gla.ac.uk/about/strategy/visionandmission/values/)
24	Kyoto University	"to sustain and develop its historical commitment to academic freedom and to pursue harmonious coexistence within the human and ecological community on this planet" (http://www.kyoto-u.ac.jp/en/about/profile/ideals/mission.html)
25	University of Wisconsin-Madison	"transmit the knowledge, wisdom and values that will help ensure the survival of this and future generations and improve the quality of life for all" (http://www.wisc.edu/about/mission/)
26	Tsinghua University	"dedicated to the well-being of Chinese society and to world development." (http://www.tsinghua.edu.cn/publish/newthuen/newthuen_cnt/about-th/about-1.html)
27	University of Texas at Austin	"to transform lives for the benefit of society" (http://www.utexas.edu/about/mission-and-values)
28	Boston University	"committed to generating new knowledge to benefit society" (http://www.bu.edu/info/about/mission-statement/)
29	University of Minnesota	"to engage our students, faculty, and staff in addressing society's most pressing issues" (https://twin-cities.umn.edu/about-us)
30	The Hong Kong Polytechnic University	"To learn and to apply, for the benefit of mankind." (http://www.polyu.edu.hk/web/en/about_polyu/motto_vision_mission/ind ex.html)

The fourth global challenge is population growth and aging. According to the Department of Economic and Social Affairs of the United Nations [13], the global population reached 7.3 billion in mid-2015, and will reach 9 billion by 2043 and 10 billion by 2083. Obviously, population growth imposes high demands on the Earth's resources. In addition, because of low mortality and low fertility rate, the global share of older people aged 60 years or older has already increased from 9.2% in 1990 to 11.7% in 2013. The rate is expected to grow continuously and reach 21.2% by 2050 [14]. This continuous growth of the general population and the aging population give tremendous pressure to the social and economic

system. The high dependency ratio will create a huge pressure on social security as well as health care demands.

The fifth global challenge is gender inequality. Despite the increased awareness of gender equality and the related effort to improve the status of women in recent decades, a huge gender gap in economic participation, political empowerment, health access and educational attainment still exist across the world [15]. It is estimated that the gap in economic opportunity between women and men will only close until 2133, which will take 118 years to complete. Besides economic inequality between men and women, violence against women is a serious problem globally [16]. Furthermore, according to United Nations Children's Fund [17], in 2050 more than 700 million females were still married as children and they were often vulnerable to early pregnancy and sexually transmitted diseases.

The sixth global challenge is inequalities in economic growth. Despite the existence of poverty reduction [18], there is a rise in income inequality around the world. As shown in the report published by Credit Suisse [19], the richest 1% of people have accumulated more wealth than the rest of the people of the world altogether. The Oxfam also found that the inequality has been getting worse in the recent years [20]. Obviously, the widening of income inequality leads to many serious economic and social problems [21]. The seventh global issue is unemployment. Actually, since the financial tsunami in 2008, the world economy has not fully recovered. According to Horne and colleagues [22], the global employment outlook will decline in the next five years. In 2015, over 197 million people were unemployed around the world, 27 million more than the pre-crisis level. In particular, unemployment is very serious among young people. In 2015, there were around 74 million young job seekers in the world. Finally, poor job quality remains as a global challenge. Workers in vulnerable employment have increased by more than 27 million since 2012 and reached 1.5 billion people worldwide.

The eighth global issue is new emerging diseases, such as H5N1 avian influenza. Since 2003, 584 confirmed cases of H5N1 avian influenza have led to 345 deaths [23]. If H5N1 would transmit easily between humans, the estimated death toll of an H5N1 pandemic could reach 1.7 billion fatalities [2]. Recently, Ebola and Zika viruses have also created a great challenge for the world. The ninth global challenge is war and conflict. While emergent diseases are typically beyond human control, war and regional conflicts are largely man-made. According to the Global Peace Index (GPI) by the Institute for Economics and Peace [24], the world has become less peaceful since 2008, in 2015, there were only ten countries in the whole world which could be considered free from conflicts. Besides, terrorism has grown over the past years. The recent incidents in Western Europe have created much psychological trauma for people around the world. Finally, wars and regional conflicts have created the tenth global challenge – refugees. According to the United Nations [12], every day, 42,000 people are displaced and forced to seek protection due to conflicts [12]. Among all the displaced people, 21.3 million people were recognized as refugees. As a result of the prolonged nature of conflicts, many of them have been exiled for decades and have little hope of returning home.

Promotion of the Quality of Life through Teaching

Primarily, university education should focus on nurturing students who have a sense of social responsibility to promote the quality of life among human beings, living creatures, and the environment. Nevertheless, there are growing criticisms about the mission of universities. Sax [25] commented that “higher education was not effectively meeting the challenge of nurturing students’ sense of civic responsibility.” Bringle and Hatcher [26] remarked that Boyer challenges higher education “to reconsider its mission to be that of educating students for a life as responsible citizens, rather than educating students solely for a career.” Similarly, Lewis [27] stated that “over the decades I have heard many academic discussions about teaching, about the curriculum, about grading, about athletics, and about responding to student misdeeds. I have almost never heard discussions among professors about making students better people.” Finally, Lewis [28] also maintained that universities “will not have fulfilled their public obligations simply by adding to the national stock of human capital, no matter how well they achieve that goal. They must recognize a direct responsibility for the civic learning of their students, spread across the curriculum.”

How can we nurture a sense of social responsibility and the importance of promoting the quality of life in students? Basically, there are three ways of doing this. First, messages about the needs of people, living organisms, and the world are directly taught in the formal curriculum. For example, students learn about global warming, inequality, vulnerable groups, conservation issues and even animal rights in their major study and general education exposure. Some subjects such as Service-Learning are vehicles to promote social responsibility and related awareness in students. Second, through co-curricular activities such as community service and conservation projects, students know more about the needs of people and the environment. Third, besides directly teaching students about social issues and indirectly exposing students to the needs of the world, universities should also nurture students’ moral values (e.g., not greedy) and a sense of care for other people.

Indeed, cultivating caring beliefs and moral values of students are very important. Crosby [29] asked, “What is the most important course in the university?” He argued that while economics, business, mathematics, computer sciences and English were important, the course about “each student’s own life” is the most important course. As he argued, “development of moral character in students is not an appendage, afterthought, or mere by-product of the process of liberal education, but something that lies at its very heart. Proper development of a student’s character can enable that student to see beyond education merely as certification and preparation for a job to the critical awareness of the importance and value of a life that is lived well in all of its dimensions, a life that continues throughout its course to develop and sustain a sense of purpose and fulfillment in oneself and the satisfaction of contributing responsibly and effectively to the well-being of others” (p. 1). However, focus on the moral character of the students is more a lip service than reality in the higher education sector.

In response to the comment of Chickering [30] that universities “have generally ignored outcomes related to moral and ethical development as well as other dimensions of personal development” and “have failed to graduate citizens who can function at the levels of cognitive and moral, intellectual, and ethical development that our complex national and global problems require,” universities should reflect on how we can nurture students’ passion and

compassion about people, and sensitivity about issues surrounding how university students and graduates can promote the quality of life.

Promotion of the Quality of Life through Research

Besides teaching, generation of knowledge through research is another basic duty of universities. Fundamentally, universities generate knowledge which changes our conceptions of many issues, which eventually promote the quality of life of human beings, living creatures, and the world. For example, through gender studies, we understand that women are oppressed in many parts of the world. Based on poverty studies, we understand that people tend to blame poor people for their laziness and ignore how exploitation and lack of opportunities may contribute to poverty. In addition, conservation studies tell us that resources on the planets will be depleted if the consumption culture continues. Finally, studies on animals change our views on animal rights and protection of animals. In short, university research generates new knowledge, which changes our views of many things, which would eventually promote the quality of life not just in human beings, but also living things as well as the environment.

Besides transforming our views about things, research in the university also generates practical solutions to human problems that promote the quality of life in people. For example, biomedical research is conducted to investigate the causes of diseases and has made tremendous contributions to generate new ways to improve human health and extend human lives [31, 32]. Advances in biomedical research allow doctors to have a better understanding of the genetic basis of many diseases [33], such as how different combinations of mutated cancer genes could be identified [34]. Research attempting to identify genes of new intellectual disability has also been conducted, which can help to identify developmental disorders as early as possible [35]. Using genetic engineering techniques, bacteria that produce human insulin could be made [36]. Besides, using functional magnetic resonance imaging has decreased the risk for diseases in some heritable disorders [37].

In the areas of engineering and applied sciences (such as applied biology, civil engineering, information engineering), there are numerous examples on how related research can promote the quality of life. For example, the use of optical fiber communication has improved human communication and transport safety through the use of sensors [38, 39]. The application of nanotechnology has produced better clothing and medical treatment procedures [40]. Regarding renewable energy, engineering research has produced solar panels, the wind electricity generators and hydroelectric power generators [41]. Engineering research can also lead to a better irrigation system and crop harvest technology. Finally, urban renewal research has helped policymakers to identify the needs of the community and provide pointers to the details of the renewal process.

In the field of education, research showed that education could promote economic growth in Africa [42] and reduce poverty in Uganda and Costa Rica [43, 44]. Besides, education promotes emotional well-being by improving psychosocial competence such as resilience, self-efficacy, and emotional competence. For instance, the Head Start Program in the United States demonstrated that participants had improved in the cognitive, health, and behavioral functioning [45]. In Hong Kong, multiple evaluation results revealed that Project P.A.T.H.S.

could enhance the well-being of adolescents by reducing risk-taking behavior and other negative outcomes [46].

Social science research also has substantial contributions to the quality of life in human beings. For example, social science research helps to understand the effectiveness of a specific program or policy. Social science research can give sound evidence for a positive psychology intervention to be judged viable [47]. Graham [48] remarked that happiness studies can be an effective tool for tracking the quality of life, welfare, and other well-being measures. Furthermore, research findings can influence the policy-making of government as a useful reference. For example, the concepts of the quality of life are regarded as the backbone policies in Association of Southeast Asian Nations (ASEAN) and the UN Millennium Development Goals. In ASEAN's [49] regional action plan on Healthy ASEAN Lifestyles, it establishes the quality of life in the key policies, such as the 'promotion of social participation,' 'minimizing of discrimination,' and 'enhancement of economic opportunities.' The plan was further incorporated into the ASEAN Socio-Cultural Community Blueprint [50], which means that subjective quality of life has been increased.

Finally, research in humanities (such as history, literature, music) also promotes the quality of life in human beings. For example, some novels (e.g., *Men search for meaning* by Victor Frankl) have provided hope for people in distress. Some literature also helps us appreciate human potentials and strengths (e.g., *Chicken soup for the soul* series) are also empowering. Some musical pieces are composed to empower people or celebrate human achievement. People can also change through music therapy [51]. Through historical research, we can learn the good practices from different cultures and countries, which would eventually promote the quality of life [52]. Finally, arts also promote the quality of life [53].

Promotion of the Quality of Life through Service

Obviously, one direct way to promote the quality of life of other people is to serve them. In many universities, there are community service projects serving the needy driven by volunteerism and support from the university administration. Besides students, employees and alumni are also involved. In this book, there are many outstanding projects undertaken by colleagues in different universities, such as those undertaken by the University of Manchester and University of New South Wales.

In fact, having service to promote the quality of life of others is just an outcome. What is more important is the serving mindset. First, similar to the notion of "corporate social responsibility" (CSR), academics should also emphasize the importance of "university social responsibility" (USR). In fact, academics must see that serving others and promotion of the quality of others as their duties. Without such a paradigm shift, it would be difficult to talk about university social responsibility. Second, we must have a service culture which is treasured by members within the university community.

Issues for Consideration

There are several issues we have to resolve when we propose that promotion of the quality of life is one of the core businesses of universities. Primarily, we have to reconsider the vision and mission of universities. Obviously, universities should not be “ivory towers” or “job training places.” While searching for answers to very academic issues and training students to get better jobs are legitimate, university education without consideration of the needs of the living creatures and the environment is a serious missing.

The second issue is how we should incorporate concepts of USR and QOL in the formal curriculum. Obviously, these concepts are foreign to many teachers with a PhD degree where they conduct in-depth study in their disciplines without really making reference to the promotion of quality of life in people. Hence, there is a need to develop curriculum on how such elements can be incorporated into the formal curriculum, particularly in an indirect way. Innovative pedagogies should also be explored. Regarding intended learning outcomes, it is not just improvement in knowledge about social issues in the world but also the development of positive attitudes towards serving and readiness to promoting the quality of life through serving and contributing to the society.

The third issue is to research on the role of research in the promotion of the quality of life. While it is perfectly legitimate to conduct research for pure academic interests, it is equally important to conduct research that has applied relevance to the quality of life. When universities are driven by ranking, academics may produce work that has no direct relevance to ordinary people in reality. Hence, when we look at “impact factor,” we should seriously look at “social impact factor” as well – how the research may promote the quality of life of other people, living creatures, and the environment. Furthermore, while research leads to enhanced understanding of certain phenomena, we should also realize the “dark side” of research. For example, while the Internet promotes human communication, it also adversely affects work-life balance. Similarly, the technological advance may lead to more comfortable life but such developments may also bring about pollution and conservation crises.

Finally, when we attempt to promote the quality of life through service, service culture is again another issue we should consider. For example, are colleagues aware of the significance of university social responsibility? Are related initiatives authentic attempts or just window-dressing in nature? Is such work incentivized? Do we have enough funding to support the related attempts? Are human resources processes linked to the related services? These are some of the critical issues that should be considered when we attempt to promote the quality of life through service related to USR.

CONCLUSION

As a corporation, the notion of “corporate social responsibility” is relevant to a university. However, as intellectuals who are usually regarded as the “social conscience” of the society, universities can be regarded as a special type of organizations which have “university social responsibility.” It is argued that universities can carry out university social responsibility through the promotion of the quality of life via teaching, research, and service, although there are related issues that should be addressed.

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Chapter 178

WHAT SHOULD BE THE DESIRED ATTRIBUTES OF YOUTH LEADERS?

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ABSTRACT

Although there are many existing models on leadership, they have two problems. First, prevailing models focus more on the competencies (i.e., “doing”) instead of personal qualities (i.e., “being”) of leaders. Second, most of the models are developed with reference to adults in the business settings instead of young people who are not working. Drawing on the literature on positive youth development and the experiences gained from The Hong Kong Polytechnic University, it is argued that a holistic youth leadership framework should focus on several attributes, including: a) social responsibility (passion about the needy and motivation to serve); b) excellence (excel in different areas, particularly in the domains of intrapersonal and interpersonal development); c) reflection (ability to honestly assess one's strengths, weaknesses and behavior); d) visionary (youth leaders should have visions particularly with reference to

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the needs and problems of the society and the world); and e) ethical leadership (moral character is the foundation of leaders). Using the first letter in these attributes, a “SERVE” model is proposed to guide youth leadership programs.

INTRODUCTION

Leadership is an important dimension in organizations. Without a good leader, organizations do not thrive and the directions of development are blurred. Hence, leadership development forms an important dimension in organizational behavior, particularly in the business field. Conceptually speaking, many leadership models focusing on the competencies of leaders (particularly management skills) have been proposed. In the management field, most of the leadership skills focus on management skills and efficiency enhancement. Practically speaking, many leadership programs have been developed by many management consulting companies which pledge to nurture leaders who will promote efficiency and profit maximization in organizations. For some famous programs, the fee is enormously high.

Unfortunately, there are two basic problems of the existing models on leadership, particularly those evolved from the business sector. First, most of the existing leadership models are developed for adults [1]. As the developmental tasks of adults are different from those of adolescents, there is a need to develop leadership models with particular reference to the developmental needs and challenges of young people. Second, youth leadership programs commonly lack developmental focus [2], focusing too much on competence but not values [3]. Besides, evaluation studies on youth leadership programs are severely lacking in the field [4]. Against this background, there is a need to highlight the desired leadership qualities in young people which will guide leadership programs.

The positive youth development approach forms an important anchor for the development of youth leadership program. According to the positive youth development approach, there are strengths and talents in every young person [5]. Hence, it is maintained that every young person can be (and is) a leader [6]. This view is in sharp contrast to the notion of “elitist leadership” which upholds that only the “cream of the cream” can be leaders. Consistent with such views, there are views asserting that leadership knowledge, attitude, values, and behavior can be trained through well-designed leadership programs [7]. In other words, given appropriate opportunities, young people can develop leadership qualities. This view is in sharp contrast to the view that leaders are inborn and there is little room for the nurturance of leadership development. Furthermore, developmental psychologists and youth workers also argue that we should expect young people to strive for excellence in different domains (i.e., aiming high and trying to excel) so that they can have self-actualization [8].

There are several points we have to consider when we design leadership models for young people. First, many theorists suggest that training of management skills is fundamental to leadership training programs [7]. However, there are also views arguing that while leadership skills (i.e., “doing”) such as resilience (adversity quotient, AQ) and emotional competence (emotional quotient, EQ) are necessary for leadership effectiveness, development of intrapersonal qualities (i.e., “being”), such as spirituality (spiritual quotient, SQ) and moral character are equally important [9-11]. Besides, there are also views maintaining that reflection and self-leadership [12] are important attributes of successful leadership.

Regarding intrapersonal qualities, two attributes deserve particular attention. The first is reflection. Reflection basically means stepping back and pondering about the reality. For a mature leader, he/she will think about whether his/her leadership is desirable or not and how the related leadership can be improved. Another attribute that is very important for successful leadership is ethical leadership. A mature leader cherishes moral values such as fairness, justice, and concern about other people. It can be argued that without ethics, a leader with excellent skills would do more harms than good. For example, a very skillful leader may have excellent strategies to earn money from the customers by producing harmful products.

A successful leader never lives in a vacuum. Besides nurturing one's inner qualities, a successful leader leads the followers. Hence, a leader should have good interpersonal relationship qualities, such as relationship building, collaboration, team building, conflict resolution and building consensus. Most important of all, successful leaders should gain respect and trust from the followers and co-workers [13]. With reference to the growing egocentrism and drop of empathy in young people, interpersonal competence is very important for young leaders.

Besides leadership skills, young leaders have to re-think about one's relationship with the society. As young people are pillars of the society in future, young people are also expected to have visions about the community, society, nation and the world they live in. In particular, young leaders should be sensitive to the needs of the society and go beyond self-serving interests to serve and contribute to the needs of others [14].

Finally, as leadership programs are human service programs, it is important to evaluate the effectiveness and impact of the programs [15]. As systematic evaluation studies on leadership are sparse, it is important to conduct systematic evaluation so that evidence-based leadership programs can be developed.

Based on the above discussion, several principles should be emphasized when we design leadership subjects or programs for young people. These include:

- Principle 1: In contrast to the notion of “elitist leadership,” we should believe that every student is (and can be) a leader.
- Principle 2: Leadership knowledge, attitude, values and behavior can be trained through well-designed leadership programs. That is, leadership qualities can be nurtured.
- Principle 3: Before one can lead others, one must lead oneself. In other words, self-leadership is important.
- Principle 4: Besides generic leadership competence such as management skills, intrapersonal and interpersonal development (i.e., “being”) of the leader determines the quality of leadership behavior (i.e., “doing”).
- Principle 5: Interpersonal relationship qualities are essential for a successful leader.
- Principle 6: Leaders should be sensitive to the needs of the society. Hence, leadership goes beyond self-serving interests to serve and contribute to the needs of the needy.
- Principle 7: Evidence-based leadership programs are necessary. Hence, evaluation plays a key role in the development of effective leadership programs.

LEADERSHIP DEVELOPMENT AT THE HONG KONG POLYTECHNIC UNIVERSITY

The above core beliefs are translated into actual leadership courses and programs at The Hong Kong Polytechnic University (PolyU). Since the inception of the 4-year undergraduate program, both credit-bearing leadership subjects and non-credit-bearing leadership programs have been developed. With particular reference to the credit bearing subjects, three subjects deserve particular attention.

Leadership Subject 1 (Tomorrow's Leaders)

There are many developmental issues in university students, such as mental health issues and rising in egocentrism. Although universities should promote holistic development in students, there are criticisms that universities have failed to perform this duty [16]. As pointed out by Harry Lewis [17], "over the decades I have heard many academic discussions about teaching, about the curriculum, about grading, about athletics, and about responding to student misdeeds. I have almost never heard discussions among professors about making students better people" (p. xv). Dalton and Crosby [18] similarly argued that university education fails to help students to "make internal connections to the defining beliefs and purposes in their lives ... since they do not reach that part of students' lives where things really matter" (p. 1).

Against the above background, we have developed a subject entitled "Tomorrow's Leaders" at The Hong Kong Polytechnic University based on the positive youth development (PYD) approach. According to the PYD approach, psychosocial competencies are vital to student development. The PYD approach is widely adopted in youth enhancement programs. In this subject, there is an integration of theories and research on PYD and leadership. Through curricula-based program and experiential learning activities, students learn and reflect on their intrapersonal and leadership competencies.

The subject is truly innovative and integrative in terms of curriculum design. Several features are intrinsic to the curriculum design: a) emphasis on both academic knowledge and personal development; b) expectation of high level of teacher-student and student-student interactions; c) learning from experience (experiential learning); d) learning through reflection (reflective learning); e) learning in group (collaborative learning); f) creation of enjoyable learning experiences for the students; g) high expectations of student participation and responsive teaching style; and h) use of peer assessment for class participation. There are several core beliefs in this subject as follows:

- 1) Every student is (and can be) a leader, although most students may not be aware of their potential and abilities.
- 2) Self-understanding and intrapersonal competence are very important to effective leadership. Through the structured and systematic curriculum, self-understanding, interpersonal communication and ethical leadership in students will be enhanced.

- 3) Experiential learning is an important vehicle to help students understand themselves. As such, individual, group, and class experiential learning activities with high interaction among the students are developed.
- 4) Individual reflection is the key to student development and learning.
- 5) Collaborative learning can help students develop intrapersonal and interpersonal competence. Learning through group sharing, discussion, evaluation and presentation is important.
- 6) There is an equal emphasis on the academic knowledge of positive youth development and leadership as well as on the application of knowledge in real life. Students are encouraged to consciously apply what they have learned to their lives.
- 7) Systematic evaluation utilizing different evaluation mechanisms is crucial to understanding the effectiveness of the subject developed.

Before the subject was formally implemented in 2012/13 school year, it was piloted in 2010/11 and 2011/12 school years, with 463 students taking the subject. From 2012/13 school year onwards, the subject was offered to more than 2,000 students per year. To date, the subject has been taken by almost 10,000 students. Multiple evaluation strategies were adopted to understand the impact of the subject:

- 1) Objective outcome evaluation: One group pretest-posttest design was used to assess the impact of the subject using a validated instrument. For the pilot subjects, results revealed that there was a significant increase in scores in different domains, such as emotional competence and social competence. For the subjects implemented in the full implementation phase, there were also findings suggesting that students changed in the positive direction in different measures.
- 2) Subjective outcome evaluation: Subjective outcome evaluation data were collected after each lecture and after completion of the subject using validated instruments. In the pilot and full implementation stages, findings showed that students had a positive perception of the subject and instructors, and they perceived that the subject was beneficial to their development.
- 3) Process evaluation: Process evaluation was conducted using a validated instrument assessing the program implementation quality and program adherence. The findings suggest that program adherence as well as quality of program implementation were high.
- 4) Qualitative evaluation: Qualitative evaluation was conducted through written reflective journals from students and focus groups. In the pilot and full implementation stages, findings showed that there were positive perceptions of the students regarding the subject, instructors, and benefits of the subject.

In addition, the multiple studies on the effectiveness of General University Requirements (GUR) curricula – general education that aims at promoting holistic development of students, also suggested that this subject was successfully implemented and well-received by the students (see the list of publications in Appendix 1). This subject was shortlisted for the QS STARS 2015 Reimagine Education Awards which had more than 500 entries in the competition.

Leadership Subject 2 (Service Leadership)

With the industrial transformation and globalization, Hong Kong has shifted its economic structure from manufacturing to service-oriented economy with approximately 95% of GDP coming from service industries. The success of service economy demands a paradigm shift in leadership, particularly from an industrial orientation focusing on control, efficiency, and financial interest to a postindustrial orientation emphasizing relationship between the service provider and service recipient, integrity, and care [19]. Hence, universities should take the responsibility to nurture their students to be effective leaders who meet such demands. However, higher education in Hong Kong fails to develop leaders in a holistic manner [20]. Leadership qualities such as care and moral character are often overlooked.

Against the above background, we have developed a credit-bearing subject entitled “Service Leadership” at The Hong Kong Polytechnic University based on the Service Leadership and Management (SLAM) curriculum framework proposed by Dr. Po Chung, the Co-founder of DHL International (Asia Pacific). Chung [21] defined service leadership as “satisfying needs by consistently providing quality personal service to everyone one comes into contact with, including one’s self, others, groups, communities, systems, and environments.” SLAM proposes that the effectiveness of leadership (E) is a function of three fundamental factors, including competencies (C) of the leaders, caring disposition (C) and moral character (M) of the leaders perceived by superiors, subordinates and peers, which can be summarized as $E=MC^2$. Therefore, in addition to competencies, strong emphasis is placed on cultivating students’ caring disposition and moral character in this subject.

Therefore, we offered a 3-credit subject entitled “Service Leadership” at The Hong Kong Polytechnic University. This subject is open to all the university students with an overarching goal to nurture effective service leaders. First, this subject intends to bring a paradigm shift in the students’ mindset about leadership and cultivate their understanding of the basic qualities of service leaders. Next, this subject aims to help students reflect on and develop their competencies (including intrapersonal competencies and interpersonal competencies), caring disposition (listening, empathy and love) and moral character (character strengths and Chinese virtues). Finally, this subject intends to help students understand the importance of service leadership to the quality of life of individuals, other people, and the society.

The Service Leadership and Management (SLAM) framework proposes that effective service leadership is not only determined by how competent the leader is, but also by how much the leader possesses moral character and a caring disposition. Therefore, the subject includes topics on the basic service leadership theory (i.e., seven core beliefs and three realms of service leadership) and three essential leadership qualities (i.e., competencies, caring disposition and moral character). The teaching/learning methodology includes lectures, experiential classroom activities, reflective exercises, a group project presentation and an individual paper. Our teaching philosophy for this subject is outlined below:

- 1) Every student is (and can be) a leader. Teachers should encourage every student to develop his/her leadership and appreciate the merits of every student.
- 2) Self-understanding and self-reflection are very important for effective service leadership. Individual self-reflection exercises should be conducted, which allows students to enhance their self-understanding.

- 3) Experiential learning is an effective approach to enhance student learning. Individual, group and class experiential learning activities should be conducted, in which students can work individually or collaboratively to experience the knowledge learned.
- 4) Collaborative learning can help students develop competencies, caring disposition and moral character. Learning will be facilitated through group sharing, discussion, evaluation and presentation.
- 5) Critical thinking is encouraged throughout the learning process. As such, debates and critical appraisal on the SLAM framework can be conducted, which allows students to think from multiple perspectives.
- 6) Equal emphasis is placed on the theoretical knowledge of service leadership and on the application of that knowledge in real life. Teachers should highlight the link between theoretical knowledge and students' lives and future careers. Students are encouraged to consciously apply the knowledge to their lives.
- 7) Systematic evaluation utilizing different evaluation approaches is critical to understanding the effectiveness of the course developed.

This subject was offered in 2012/13 academic year as a 2-credit General Education subject to students under the 3-year undergraduate program. A total of 190 students took this subject. In 2014/15 academic year, this subject was modified and enriched to be a 3-credit subject for students under the 4-year undergraduate program. A total of 207 students took this subject. Multiple evaluation approaches have been carried out to understand the effectiveness of the subject:

- 1) Objective outcome evaluation: One group pretest-posttest design was used to assess the outcome of the subject using a validated instrument. The results of all classes revealed that students in the 3-year program and 4-year program showed positive changes in measures of positive youth development, service leadership qualities and beliefs, and life satisfaction.
- 2) Subjective outcome evaluation: Subjective outcome evaluation data were collected after completion of the course using a validated instrument. The findings showed positive client satisfaction findings in the domains of subject design and implementation, instructor(s), and the gains from this subject.
- 3) Process evaluation: Two raters were typically involved to observe and assess program implementation quality and program adherence. The findings showed that program adherence and the implementation quality were high.
- 4) Qualitative evaluation: Qualitative evaluation was conducted through written reflective sheets and focus groups. The findings showed that students generally had positive perceptions of the subject, instructor(s), and the gains from this subject.

To date, the evaluation results have been published in refereed journals and in a book series entitled "Quality of Life in Asia" and two special issues in "International Journal on Disability and Human Development." The achievement of Service Leadership project will be also documented in a forthcoming special issue in "International Journal of Adolescent Medicine and Health" edited by Shek, Chung, Lin and Merrick. The publication list is

outlined in Appendix 2. This subject was awarded the Bronze Award under the “Ethical Leadership” category in the QS STARS 2016 Reimagine Education Awards.

Leadership Subject 3 (Service Leadership through Serving Children and Families with Special Needs)

In view of the need to promote service leadership for the post-industrial societies, a 3-credit Service-Learning course entitled “Service Leadership through Serving Children and Families with Special Needs” has been implementing in The Hong Kong Polytechnic University (PolyU) since the 2013/14 academic year. The course is a 2-semester course, which aims to develop service leadership of students through delivering high-quality services based on the framework of Service-Learning pedagogy. Service-Learning is an experiential learning pedagogy that aims to deepen students’ learning experiences through integrating community service with academic study and reflection. The authentic scenarios provide challenging and conflict-filled situations for students to handle. In Service-Learning, students are envisaged not only to provide service but also to foster their learning in the process. Besides, Service-Learning benefits both the students and the service recipients. Through engaging in serving the service targets, students are expected to promote their psychosocial development, cognitive development, and civic engagement.

The curriculum of this course was based on the Service Leadership and Management Model (SLAM) [21]. Seven core beliefs are intrinsic to the frame of reference in service leadership education, which was included in the subject as the overarching framework of the curriculum. Within the framework, the importance of generic leadership competencies, moral character and caring disposition are addressed. Besides intrapersonal competencies, interpersonal competencies are also addressed in the course. According to the course outline, this course is designed “to enable students to:

- a) understand the core attributes of a service leader;
- b) apply the core components of service leadership through the engagement of community-based service activities;
- c) develop self-awareness of sharing and empathy to others and the community; and
- d) reflect on their service leadership qualities, particularly intrapersonal and interpersonal competencies.”

The pedagogy used is based on Kolb’s [22] four-stage learning cycle, which emphasizes the importance of experiential learning. To benefit the most from the experience, the students systematically went through the four stages of the experiential learning cycle: concrete experience (“do” or “act” stage), reflective observation (“reflection” stage), abstract conceptualization (“thinking” stage), and active experimentation (“application” stage).

Students first attended lectures to acquire the basic understanding of the definitions, theories, and concepts about service leadership. Workshops were subsequently provided for students to develop their service proposals. Students applied knowledge that they learned on Service Leadership through activities in several service sites, including special schools, social welfare service units for preschool children with developmental problems, a drug

rehabilitation agency, and schools admitting students with social and economic deprivation. For example, we served students in Project WeCan which provides support for schools admitting students with academic and family needs.

To academically engage our students, the teaching and learning activities on this subject were designed to include 1) 10-hour e-learning to acquire knowledge about the concepts of Service-Learning; 2) lectures on service leadership; 3) small group discussions to prepare for the service project; 4) service provided to service targets. In terms of assessment for learning, reflective journal writings were given to allow students to deepen their learning experience. Feedback was provided by teachers to improve students' learning. In terms of assessment of learning, group presentations were done by individual groups to consolidate the learning experience of the groups as a whole by the end of the subject.

When the course was first launched in the 2013-14 academic year, there were 145 students enrolled in this course, which aimed at providing quality services in two non-government organizations, namely Society of Boys' Centres and Heep Hong Society. Up to the academic year of 2015/16, 476 students have enrolled in this course. Moreover, the number of service sites has also expanded to Christian Zheng Sheng College and over 10 participating schools/centers from Project WeCan, which located in different parts of Hong Kong. The increased number of the service sites denotes the increased impact of our project and demand from the participating schools and organizations. Moreover, the services delivered were not only beneficial to the service targets but also fostered the development of well-being of the PolyU students.

First, the agencies were highly satisfied with the students in terms of their positive service attitudes, caring disposition, service leadership towards service targets, problem-solving skills and reflective attitude in delivering services. Second, the PolyU students provided highly positive responses about the course. In a quantitative evaluation, over 90% of the respondents rated positively on the professional quality of teaching staff, effectiveness to promote service leadership, and holistic personal development. Students were also praised for their generic competences such as emotional competence, critical thinking, social competence and sense of responsibility.

Qualitatively speaking, students shared their learning gains through writing reflective journals in terms of leadership competences, moral competence, demonstrating care and empathy, active listening, roles and responsibilities during services, and the usefulness of the subject to prepare for their future. In addition to writing reflective journals, students who served in Christian Zheng Sheng College reflected that their service experience during the reflection time in service camp at nights. The students were also asked to write three descriptions and one metaphor to reflect their service learning experiences of the day. The students experienced the service as enjoyable and meaningful. One student even thought that the service changed his worldview. Overall speaking, the findings support the integration effects of service leadership and service learning to foster the development of well-being of PolyU students and the benefits towards the schools/NGOs in the community. This subject was awarded the Bronze Award under the "Ethical Leadership" category in the QS STARS 2016 Reimagine Education Awards.

Besides credit-bearing subjects, Service Leadership education is embedded in non-credit-bearing programs, including Wofoo Leaders' Network and leadership programs organized by the Global Youth Leadership Institute. For example, an intensive 3.5-day to 4-day programs on Service Leadership have been included in the related programs.

TOWARDS AN INTEGRATIVE AND HOLISTIC MODEL OF YOUTH LEADERSHIP DEVELOPMENT

Our experience in these credit-bearing subjects as well as non-credit-bearing subjects re-affirm the importance of the principles set out earlier in the paper. Based on our experience and a conceptual integration of the available models, there are several cardinal qualities to be nurtured in university students, which is represented by the acronym of SERVE – social responsibility, excellence, reflection, vision and ethical leadership. The conceptual model is presented in Table 1. This leadership model is consistent with the motto of PolyU of “to learn and to apply, for the benefit of mankind.” It is also in line with the vision of the Global Youth Leadership Institute “to nurture students to be leaders to be reflective and ethical leaders who are sensitive to the social needs in the local and global contexts.”

Table 1. Conceptual model on the leadership development model at PolyU

Leadership qualities	Expectation about the leaders	Definition
Social responsibility	Socially responsible	Having passion and compassion about other living beings; sensitive to the needs of the society; development of responsible citizenship
Excellence	Excel in different domains, particularly in intrapersonal and interpersonal development	Strive for excellence in different domains. In particular, striving for excellence in intrapersonal competence (such as AQ, EQ, and SQ) and interpersonal competence (such as respect for others and empathy)
Reflection	Reflective	Awareness of one’s leadership behavior particularly its impact on other people, self-evaluation, self-critical stand
Vision	Visionary	Having high expectations about oneself, others, society, and the world; actively developing ideas about ways to create a better world
Ethics	Ethical leadership	Development of moral character and virtues conducive to effective leadership

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APPENDIX 1: PUBLICATION LIST FOR TOMORROW'S LEADERS

Pilot Stage (2010/11 – 2011/12)

Conference

1. Shek D. T. L., Chui, Y. H., Lit, S. W., Yuen, W., Chung, Y. Y. H., & Ngai, S. W. (2011, July). *Preparing university students for adulthood and the labor force: Role of positive youth development*. Invited Paper presented at the International Conference on Transitioning to Adulthood in Asia: Courtship, Marriage, Fertility, and Labour Force Participation organized by the Asia Research Institute and the Family, Children and Youth Cluster, Faculty of Arts and Social Sciences, NUS, together with the Ministry of Community Development, Youth and Sports.
2. Shek, D. T. L. (2012, June). *Promotion of holistic development of university students via the formal curriculum*. Paper presented at the General Education and University Curriculum Reform: An International Conference in Hong Kong organized by City University of Hong Kong and the Hong Kong America Centre.
3. Shek, D. T. L. (2012, November). *Nurturing social responsibility in university students; The Hong Kong experience*. Paper presented at the Summit on University Social Responsibility in an Era of Globalization organized by The Hong Kong Polytechnic University and China Institute of Education Policy.
4. Shek, D. T. L., & Sun, R. C. F. (2012, May). *Nurturing university students to be tomorrow's leaders: The role of positive youth development*. Paper presented at the International Conference on Youth Development in the Global Context: Emergent Issues and Responses organized by the Project P.A.T.H.S., School of Social Work of University of Washington, U.S.A. and University of Kentucky College of Medicine, U.S.A.

Publications

1. Dorcas, A. (2014). Teaching a subject on leadership and intrapersonal development: Some personal reflections. *International Journal on Disability and Human Development*, 13(4), 413-422.
2. Shek, D. T. L. (2012). Development of a positive youth development subject in a university context in Hong Kong. *International Journal on Disability and Human Development*, 11(3), 173-179.
3. Shek, D. T. L. (2012). Postlecture evaluation of a positive youth development subject for university students in Hong Kong. *The Scientific World Journal*. Article ID 934679, 8 pages, doi:10.1100/2012/934679
4. Shek, D. T. L. (2013). Promotion of holistic development in university students: A credit-bearing course on leadership and intrapersonal development. *Best Practices in Mental Health*, 9(1), 47-61.
5. Shek, D. T. L., & Sun, R. C. F. (2013). Process evaluation of a leadership and

- intrapersonal development subject for university students. *International Journal on Disability and Human Development*, 12(2), 203-211.
6. Shek, D. T. L., & Sun, R. C. F. (2012). Promoting leadership and intrapersonal competence in university students: What can we learn from Hong Kong? *International Journal on Disability and Human Development*, 11(3), 221-228.
 7. Shek, D. T. L., & Sun, R. C. F. (2012). Process evaluation of a positive youth development course in a university setting in Hong Kong. *International Journal on Disability and Human Development*, 11(3), 235-241.
 8. Shek, D. T. L., & Sun, R. C. F. (2012). Promoting psychosocial competencies in university students: Evaluation based on a one-group pre-test/post-test design. *International Journal on Disability and Human Development*, 11(3), 229-234.
 9. Shek, D. T. L., & Sun, R. C. F. (2012). Focus group evaluation of a positive youth development course in a university in Hong Kong. *International Journal on Disability and Human Development*, 11(3), 249-254.
 10. Shek, D. T. L., & Sun, R. C. F. (2012). Qualitative evaluation of a positive youth development course in a university setting in Hong Kong. *International Journal on Disability and Human Development*, 11(3), 243-248.
 11. Shek, D. T. L., Sun, R. C. F., Chui, Y. H., Lit, S. W., Yuen, W. W., Chung, Y. Y. H., & Ngai, S. W. (2012). Development and evaluation of a positive youth development course for university students in Hong Kong. *The Scientific World Journal*. Article ID 263731, 8 pages, doi:10.1100/2012/263731
 12. Shek, D. T. L., Sun, R. C. F., & Merrick, J. (2012). How to promote holistic development in university students? *International Journal on Disability and Human Development*, 11(3), 171-172.
 13. Shek, D. T. L., Sun, R. C. F., Tsien-Wong, T. B. K., Cheng, C. T., & Yan, H. R. (2013). Objective outcome evaluation of a leadership and intrapersonal development subject for university students. *International Journal on Disability and Human Development*, 12(2), 221-227.
 14. Shek, D. T. L., Sun, R. C. F., Yuen, W. W. H., Chui, Y. H., Dorcas, A., Ma, C. M. S., Yu, L., Chak, Y. L. Y., Law, M. Y. M., Chung, Y. Y. H., & Tsui, P. F. (2013). Second piloting of a leadership and intrapersonal development subject at The Hong Kong Polytechnic University. *International Journal on Disability and Human Development*, 12(2), 107-114.
 15. Shek, D. T. L. & Wu, F. K. Y. (2012). Reflective journals of students taking a positive youth-development course in a university context in Hong Kong. *The Scientific World Journal*. Article ID 131560, 8 pages. doi:10.1100/2012/131560.

Book Chapter

1. Shek, D. T. L. (2013). Development of a positive youth development subject in a university context in Hong Kong. In D. T. L. Shek, R. C. F. Sun, & J. Merrick (Eds.), *University and college students: Health and development issues for the leaders of tomorrow* (pp. 179-191). New York: Nova Science Publishers.
2. Shek, D. T. L., & Sun, R. C. F. (2012). Process evaluation of a positive youth development course in a university setting in Hong Kong. In D. T. L. Shek, R. C. F. Sun, & J. Merrick (Eds.), *University and college students: Health and development issues for the leaders of tomorrow* (pp. 221-231). New York: Nova Science Publishers.

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5. Shek, D. T. L., & Sun, R. C. F. (2013). Qualitative evaluation of a positive youth development course in a university setting in Hong Kong. In D. T. L. Shek, R. C. F. Sun, & J. Merrick (Eds.), *University and college students: Health and development issues for the leaders of tomorrow* (pp. 233-243). New York: Nova Science Publishers.
6. Shek, D. T. L., & Sun, R. C. F. (2013). Focus group evaluation of a positive youth development course in a university setting in Hong Kong. In D. T. L. Shek, R. C. F. Sun, & J. Merrick (Eds.), *University and college students: Health and development issues for the leaders of tomorrow* (pp. 245-255). New York: Nova Science Publishers.
7. Shek, D. T. L., Sun, R. C. F., & Merrick, J. (Eds.). (2013). *University and college students: Health and development issues for the leaders of tomorrow*. New York: Nova Science Publishers.

Full Implementation Stage (2012/13, 2013/14, 2014/15)

Publications

1. Leung, H. (2016). Levels of reflection on teaching a leadership and positive youth development subject. *International Journal on Disability and Human Development* 15(2), 211-220.
2. Leung, H., Shek, D. T. L., & Mok, B. P. W. (2016). Post-lecture subjective outcome evaluation of a university subject on leadership and intrapersonal development. *International Journal of Child and Adolescence Health*, 9(2), 223-234.
3. Leung, J. T. Y. (2016). Riding on a roller coaster: Personal reflections of teaching a subject on leadership and intrapersonal development. *International Journal on Disability and Human Development*, 15(2), 221-229.
4. Ma, C. M. S. (2016). Reflective teaching in a holistic personal development course for Chinese university students: A case study. *International Journal on Disability and Human Development*, 15(2), 187-193.
5. Ma, C. M. S., Shek, D. T. L., Li, P. P. K., Mok, B. P. W. & Leung, E. Y. K. (2016). Qualitative evaluation of a leadership and intrapersonal development subject for university students in Hong Kong. *International Journal of Child Health and Human Development*, 9(2), 217-224.
6. Shek, D. T. L. (2013). Reflections of Chinese students on a university subject on leadership and intrapersonal development. *International Journal on Disability and Human Development*, 12(2), 213-219.
7. Shek, D. T. L., Fok, H. K., Leung, C. T. L., & Li, P. P. K. (2016). Qualitative evaluation of a credit-bearing leadership subject in Hong Kong. *International Journal*

of *Child Health and Human Development*, 9(2), 173-183.

8. Shek, D. T. L., & Ho, W. W. L. (2016). Nurturing moral competence in university students via a credit-bearing subject. *International Journal on Disability and Human Development*, 15(2), 181-186.
9. Shek, D. T. L., & Ho, W. W. L. (2016). Spirituality as a key positive youth development construct for university students. *International Journal on Disability and Human Development*, 15(2), 175-180.
10. Shek, D. T. L., & Law, M. Y. M. (2014). Evaluation of a subject on leadership and intrapersonal development: Views of the students based on qualitative evaluation. *International Journal on Disability and Human Development*, 13(4), 435-441.
11. Shek, D. T. L., & Leung, H. (2014). Post-lecture subjective outcome evaluation of a university subject on leadership and positive youth development in Hong Kong. *International Journal on Disability and Human Development*, 13(4), 465-472.
12. Shek, D. T. L., & Leung, H. (2016). Developing self-leadership and responsibility and moving away from egocentrism. *International Journal on Disability and Human Development*, 15(2), 157-164.
13. Shek, D. T. L., & Leung, H. (2016). Resilience as a focus of a subject on leadership and intrapersonal development. *International Journal on Disability and Human Development*, 15(2), 149-155.
14. Shek, D. T. L., & Leung, J. T. Y. (2016). Developing social competence in a subject on leadership and intrapersonal development. *International Journal on Disability and Human Development*, 15(2), 165-173.
15. Shek, D. T. L., & Leung, J. T. Y. (2014). Perceived benefits of a university subject on leadership and intrapersonal development. *International Journal on Disability and Human Development*, 13(4), 481-488.
16. Shek, D. T. L., Liang, J. Q., & Law, M. Y. M. (2016). Subjective outcome evaluation of a university subject on leadership and intrapersonal development. *International Journal on Disability and Human Development*, 15(2), 231-239.
17. Shek, D. T. L., & Ma, C. M. S. (2014). Do university students change after taking a subject on leadership and intrapersonal development? *International Journal on Disability and Human Development*, 13(4), 451-456.
18. Shek, D. T. L., & Ma, C. M. S. (2016). Emotional competence: A key leadership competence for university students. *International Journal on Disability and Human Development*, 15(2), 127-134.
19. Shek, D. T. L., & Sun, R. C. F. (2013). Post-course subjective outcome evaluation of a course promoting leadership and intrapersonal development in university students in Hong Kong. *International Journal on Disability and Human Development*, 12(2), 193-201.
20. Shek, D. T. L., & Sun, R. C. F. (2013). Post-lecture evaluation of a university course on leadership and intrapersonal development. *International Journal on Disability and Human Development*, 12(2), 185-191.
21. Shek, D. T. L., & Wu, F. K. Y. (2014). The role of teachers in youth development: Reflections of students. *International Journal on Disability and Human Development*, 13(4), 473-480.
22. Shek, D. T. L., Wu, F. K. Y. & Law, M. Y. M. (2014). Perceptions of a university

- subject on leadership and intrapersonal development: Reflections of the scholarship recipients. *International Journal on Disability and Human Development*, 13(4), 435-450.
23. Shek, D. T. L., Wu, F. K. Y., Leung, C. T. L., Fok, H. K., & Li, P. P. K. (2016). Focus group evaluation of a subject on leadership and intrapersonal development in Hong Kong. *International Journal of Child and Adolescent Health*, 9(2), 185-194.
 24. Shek, D. T. L., & Wu, F. K. Y. (2016). Clear and positive identity as an attribute of an effective leader. *International Journal on Disability and Human Development*, 15(2), 143-148.
 25. Shek, D. T. L., & Yu, L. (2014). Post-course subjective outcome evaluation of a subject on leadership and intrapersonal development for university students in Hong Kong. *International Journal on Disability and Human Development*, 13(4), 457-464.
 26. Shek, D. T. L., & Yu, L. (2016). Student feedback on a subject on leadership and intrapersonal development for university students in Hong Kong. *International Journal on Disability and Human Development*, 15(3), 339-345.
 27. Shek, D. T. L., & Yu, L. (2016). Cognitive competence: A key positive youth development construct for university students. *International Journal on Disability and Human Development*, 15(2), 135-142.
 28. Shek, D. T. L., & Yu, L. (2017). An evaluation study on a university general education subject in Hong Kong. *International Journal of Adolescent Medicine and Health*, 29(1), 103-109.
 29. Shek, D. T. L., Yu, L., Wu, F. K. Y., & Merrick, J. (2017). Evaluation of positive youth development and leadership programs in Hong Kong. *International Journal of Adolescent Medicine and Health*, 29(1), 1-3.
 30. Shek, D. T. L., Yu, L., & Xie, Q. Z., (2017). Student feedback on a pioneer subject on leadership and intrapersonal development in Hong Kong. *International Journal of Adolescent Medicine and Health*, 29(1), 83-89.
 31. Wu, F. K. Y. (2016). "Know thyself": Some personal reflections in teaching a subject on leadership and intrapersonal development. *International Journal on Disability and Human Development*, 15(2), 203-209.
 32. Yu, L. (2016). A teacher's reflection on teaching "Tomorrow's Leaders" in university students in Hong Kong. *International Journal on Disability and Human Development*, 15(2), 195-202.
 33. Yu, L., Shek, D. T. L., & Leung, E. Y. K. (2016). Post-lecture evaluation of a university subject on leadership and intrapersonal development. *International Journal of Child and Adolescent Health*, 9(2), 155-164.

Special Issue (Editorial)

1. Shek, D. T. L., Ma, C. M. S., & Merrick, J. (2016). Nurturing university students to be Tomorrow's Leaders [Special issue]. *International Journal of Adolescent Medicine and Health*, 15(2), 125-126.
2. Shek, D. T. L., Ma, C. M. S., & Merrick, J. (2016). Promoting leadership and intrapersonal development in university students [Special issue]. *International Journal on Disability and Human Development*.
3. Shek, D. T. L., Wu, F. K. Y., & Merrick, J. (2016). Developmental issues in children and adolescents: Promotion of positive youth development [Special issue]. *International Journal of Child and Adolescent*.

APPENDIX 2: “SERVICE LEADERSHIP” PUBLICATION LIST

A. Curriculum Development and Theories

Journal Articles

1. Leung, H., Ma, C. M. S., Shek, D. T. L., & Law, M. Y. M. (2016). Nurturing service leaders through service learning for university students. *International Journal of Child and Adolescent Health*, 9(2), 211-221.
2. Shek, D. T. L., Chung, P. P. Y., & Leung, H. (2015). How unique is the service leadership model? A comparison with contemporary leadership approaches. *International Journal on Disability and Human Development*, 14(3), 217-231.
3. Shek, D. T. L., Chung, P. P. Y., & Leung, H. (2015). Manufacturing economy vs. service economy: Implications for service leadership. *International Journal on Disability and Human Development*, 14(3), 205-215.
4. Shek, D. T. L., Chung, P. P. Y., Yu, L., & Merrick, J. (2015). Editorial: Service leadership curriculum and higher education reform in Hong Kong. *International Journal on Disability and Human Development*, 14(4), 297-298.
5. Shek, D. T. L., Chung, P. P. Y., Yu, L., & Merrick, J. (2015). Editorial: Service leadership education for university students: The Hong Kong experience. *International Journal on Disability and Human Development*, 14(3), 203-204.
6. Shek, D. T. L., & Li, X. (2015). Nurturing students to be caring service leaders. *International Journal on Disability and Human Development*, 14(4), 361-369.
7. Shek, D. T. L., & Li, X. (2015). The role of a caring disposition in service leadership. *International Journal on Disability and Human Development*, 14(4), 319-332.
8. Shek, D. T. L., & Lin, L. (2015). Core beliefs in the service leadership model proposed by the Hong Kong Institute of Service Leadership and Management. *International Journal on Disability and Human Development*, 14(3), 233-242.
9. Shek, D. T. L., & Lin, L. (2015). Factors leading to the creation, development and maintenance of positive social relationship. *International Journal on Disability and Human Development*, 14(4), 333-342.
10. Shek, D. T. L., & Lin, L. (2015). Intrapersonal competencies and service leadership. *International Journal on Disability and Human Development*, 14(3), 255-263.
11. Shek, D. T. L., & Lin, L. (2015). Leadership and mentorship: Service leaders as mentors of the followers. *International Journal on Disability and Human Development*, 14(4), 351-359.
12. Shek, D. T. L., & Lin, L. (2015). Nurturing university students to be social entrepreneurs: Relevance of service leadership education. *International Journal on Disability and Human Development*, 14(3), 285-293.
13. Shek, D. T. L., Ma, C. M. S., & Liu, T. T. (2015). Adolescent developmental assets and service leadership. *International Journal on Disability and Human Development*, 14(3), 275-283.
14. Shek, D. T. L., Ma, C. M. S., Liu, T. T., & Siu, A. M. H. (2015). The role of self-leadership in service leadership. *International Journal on Disability and Human Development*, 14(4), 343-350.
15. Shek, D. T. L., Sun, R. C. F., & Liu, T. T. (2015). Character strengths in Chinese

philosophies: Relevance to service leadership. *International Journal on Disability and Human Development*, 14(4), 309-318.

16. Shek, D. T. L., Sun, R. C. F., & Liu, T. T. (2015). Evolution and realms of service leadership and leadership models. *International Journal on Disability and Human Development*, 14(3), 243-254.
17. Shek, D. T. L., & Yu, L. (2015). Character strengths and service leadership. *International Journal on Disability and Human Development*, 14(4), 299-307.
18. Shek, D. T. L., Yu, L., & Fu, X. (2013). Confucian virtues and Chinese adolescent development: A conceptual review. *International Journal of Adolescent Medicine and Health*, 25(4), 335-344. DOI: 10.1515/ijamh-2013-0031.
19. Shek, D. T. L., Yu, L., Ma, C. M. S., Sun, R. C. F., & Liu, T. T. (2013). Development of a credit-bearing service leadership subject for university students in Hong Kong. *International Journal of Adolescent Medicine and Health*, 25(4), 353-361. DOI: 10.1515/ijamh-2013-0033.
20. Shek, D. T. L., Yu, L., & Siu, A. M. H. (2015). Interpersonal competence and service leadership. *International Journal on Disability and Human Development*, 14(3), 265-274.

Book Chapters

1. Shek, D. T. L., & Chung, P. P. Y. (2015). Service leadership education for university students: Seven unfinished tasks. In D. T. L. Shek & P. P. Y. Chung (Eds.), *Promoting service leadership qualities in university students: The case of Hong Kong. Quality of life in Asia*, vol. 6 (pp. 225-232). Singapore: Springer.
2. Shek, D. T. L., & Leung, H. (2015). Service leadership qualities in university students through the lens of student well-being. In D. T. L. Shek & P. P. Y. Chung (Eds.), *Promoting service leadership qualities in university students: The case of Hong Kong. Quality of life in Asia*, vol. 6 (pp. 1-16). Singapore: Springer.
3. Leung, H., Ma, C. M. S., Shek, D. T. L., & Law, M. Y. M. (2015). Nurturing service leaders [Reprint]. In D. T. L. Shek, F. K. Y. Wu, & J. Merrick (Eds.), *Leadership and service learning education: Holistic development for Chinese university students* (pp.55-74). New York: Nova Sciences Publisher.
4. Leung, H., Shek, D. T. L., & Xie, Q. (2015). Service leadership education evaluation by university students in Hong Kong [Reprint]. In D. T. L. Shek, F. K. Y. Wu, & J. Merrick (Eds.), *Leadership and service learning education: Holistic development for Chinese university students* (pp.95-110). New York: Nova Sciences Publisher.
5. Leung, J. T. Y., & Shek, D. T. L. (2015). To serve and to learn [Reprint]. In D. T. L. Shek, F. K. Y. Wu, & J. Merrick (Eds.), *Leadership and service learning education: Holistic development for Chinese university students* (pp.23-40). New York: Nova Sciences Publisher.
6. Shek, D. T. L., & Liang, J. (2015). How can we know a program is effective? [Reprint]. In D. T. L. Shek, F. K. Y. Wu, & J. Merrick (Eds.), *Leadership and service learning education: Holistic development for Chinese university students* (pp.125-140). New York: Nova Sciences Publisher.
7. Shek, D. T. L., Chung, P. P. Y., & Leung, H. (2016). Implications of the shift from manufacturing economy to service economy [Reprint]. In D. T. L. Shek, C. M. S. Ma, L. Lin & J. Merrick (Eds.), *Education in Hong Kong: Service leadership for university*

- students (pp. 9-25). New York: Nova Science Publishers.
8. Shek, D. T. L., Chung, P. P. Y., & Leung, H. (2016). The service leadership model [Reprint]. In D. T. L. Shek, C. M. S. Ma, L. Lin & J. Merrick (Eds.), *Education in Hong Kong: Service leadership for university students* (pp. 27-48). New York: Nova Science Publishers.
 9. Shek, D. T. L., Chung, P. P. Y., Yu, L., & Merrick, J. (2016). Leadership and management education for university students [Reprint]. In D. T. L. Shek, C. M. S. Ma, L. Lin & J. Merrick (Eds.), *Education in Hong Kong: Service leadership for university students* (pp. 3-6). New York: Nova Science Publishers.
 10. Shek, D. T. L., & Lin, L. (2016). Core beliefs and the service leadership model [Reprint]. In D. T. L. Shek, C. M. S. Ma, L. Lin & J. Merrick (Eds.), *Education in Hong Kong: Service leadership for university students* (pp.49-62). New York: Nova Science Publishers.
 11. Shek, D. T. L., & Lin, L. (2016). Different forms of intrapersonal competence [Reprint]. In D. T. L. Shek, C. M. S. Ma, L. Lin & J. Merrick (Eds.), *Education in Hong Kong: Service leadership for university students* (pp. 81-93). New York: Nova Science Publishers.
 12. Shek, D. T. L., & Lin, L. (2016). University students as social entrepreneurs [Reprint]. In D. T. L. Shek, C. M. S. Ma, L. Lin & J. Merrick (Eds.), *Education in Hong Kong: Service leadership for university students* (pp. 121-133). New York: Nova Science Publishers.
 13. Shek, D. T. L., Ma, C. M. S., & Liu, T. T. (2016). Human development assets and leadership [Reprint]. In D. T. L. Shek, C. M. S. Ma, L. Lin & J. Merrick (Eds.), *Education in Hong Kong: Service leadership for university students* (pp. 109-120). New York: Nova Science Publishers.
 14. Shek, D. T. L., Sun, R. C. F., & Liu, T. T. (2016). History and evolutionary origin of leadership [Reprint]. In D. T. L. Shek, C. M. S. Ma, L. Lin & J. Merrick (Eds.), *Education in Hong Kong: Service leadership for university students* (pp. 63-79). New York: Nova Science Publishers.
 15. Shek, D. T. L., Yu, L., & Siu, A. M. H. (2016). Promotion of interpersonal competence [Reprint]. In D. T. L. Shek, C. M. S. Ma, L. Lin & J. Merrick (Eds.), *Education in Hong Kong: Service leadership for university students* (pp. 95-108). New York: Nova Science Publishers.
 16. Shek, D. T. L., Yuen-Tsang, A. W. K., & Ng, E. C. W. (2016). Global Youth Leadership Institute [Reprint]. In D. T. L. Shek, C. M. S. Ma, L. Lin & J. Merrick (Eds.), *Education in Hong Kong: Service leadership for university students* (pp. 147-155). New York: Nova Science Publishers.
 17. Shek, D. T. L., Chung, P. P. Y., Yu, L. & Merrick, J. (2016). Higher education reform and development of leaders in Hong Kong [Reprint]. In D. T. L. Shek, A. M. H. Siu, H. Leung, & J. Merrick (Eds.), *Higher education in Hong Kong: Nurturing students to be caring service leaders* (pp. 3-6). New York: Nova Sciences Publisher.
 18. Shek, D. T. L., Ma, C. M. S., Liu, T. T., & Siu A. M. H. (2016). The nature of self-leadership [Reprint]. In D. T. L. Shek, A. M. H. Siu, H. Leung, & J. Merrick (Eds.), *Higher education in Hong Kong: Nurturing students to be caring service leaders* (pp. 71-82). New York: Nova Sciences Publisher.
 19. Shek, D. T. L., & Li, X. (2016). Caring disposition: Awareness, love and nurturing

- [Reprint]. In D. T. L. Shek, A. M. H. Siu, H. Leung, & J. Merrick (Eds.), *Higher education in Hong Kong: Nurturing students to be caring service leaders* (pp. 37-53). New York: Nova Sciences Publisher.
20. Shek, D. T. L., & Li, X. (2016). Nurturing Students [Reprint]. In D. T. L. Shek, A. M. H. Siu, H. Leung, & J. Merrick (Eds.), *Higher education in Hong Kong: Nurturing students to be caring service leaders* (pp. 97-110). New York: Nova Sciences Publisher.
 21. Shek, D. T. L., & Lin, L. (2016). Creation, development and maintenance of social relationship [Reprint]. In D. T. L. Shek, A. M. H. Siu, H. Leung, & J. Merrick (Eds.), *Higher education in Hong Kong: Nurturing students to be caring service leaders* (pp. 55-70). New York: Nova Sciences Publisher.
 22. Shek, D. T. L., & Lin, L. (2016). Mentorship [Reprint]. In D. T. L. Shek, A. M. H. Siu, H. Leung, & J. Merrick (Eds.), *Higher education in Hong Kong: Nurturing students to be caring service leaders* (pp. 83-96). New York: Nova Sciences Publisher.
 23. Shek, D. T. L., Sun, R. C. F., & Liu, T. T. (2016). Chinese philosophy and character strength [Reprint]. In D. T. L. Shek, A. M. H. Siu, H. Leung, & J. Merrick (Eds.), *Higher education in Hong Kong: Nurturing students to be caring service leaders* (pp. 23-36). New York: Nova Sciences Publisher.
 24. Shek, D. T. L., & Yu, L. (2016). How to foster character strengths [Reprint]. In D. T. L. Shek, A. M. H. Siu, H. Leung, & J. Merrick (Eds.), *Higher education in Hong Kong: Nurturing students to be caring service leaders* (pp. 9-21). New York: Nova Sciences Publisher.

Conference Presentations

1. Ma, C. M. S., Shek, D. T. L., & Liu, T. T. (2012, December). Caring dispositions and positive youth development: Relevance to service leadership in university students. *Paper presented at the The Gerry Schwartz and Heather Reisman 3rd International Conference on Paediatric Chronic Diseases, Disability and Human Development*, Jerusalem, Israel organized by Cincinnati Children's Hospital Medical Centre, Hadassah-Hebrew University Medical Centre, and National Institute of Child Health and Human Development, Israel.
2. Shek, D. T. L., Sun, R. C. F., Yu, L., Ma, C. M. S., & Siu, A. M. H. (2012, December). Promotion of holistic development of university students in Hong Kong: Development of a service leadership course. *Paper presented at the The Gerry Schwartz and Heather Reisman 3rd International Conference on Paediatric Chronic Diseases, Disability and Human Development*, Jerusalem, Israel organized by Cincinnati Children's Hospital Medical Centre, Hadassah-Hebrew University Medical Centre, and National Institute of Child Health and Human Development, Israel.
3. Yu, L., & Shek, D. T. L. (2012, December). Confucian virtues and positive youth development: Insights for service leadership. *Paper presented at the The Gerry Schwartz and Heather Reisman 3rd International Conference on Paediatric Chronic Diseases, Disability and Human Development*, Jerusalem, Israel organized by Cincinnati Children's Hospital Medical Centre, Hadassah-Hebrew University Medical Centre, and National Institute of Child Health and Human Development, Israel.
4. Shek, D. T. L., & Law, M. Y. M., & (2013, March). Development of a non-credit-bearing service leadership program for university students in Hong Kong: Some initial

- experience. *Paper presented at the International Roundtable on "Service Leadership", The Hong Kong Polytechnic University, Hong Kong.*
5. Leung, H., & Shek, D. T. L. (2013, March). The development of service leadership models and its implications for university education in Hong Kong. *Paper presented at the International Roundtable on "Service Leadership", The Hong Kong Polytechnic University, Hong Kong.*
 6. Lin, L., & Shek, D. T. L. (2013, March). A good service leader, a good mentor. *Paper presented at the International Roundtable on "Service Leadership", The Hong Kong Polytechnic University, Hong Kong.*
 7. Liu, T. T., & Shek, D. T. L. (2013, March). Developmental assets of service leaders. *Paper presented at the International Roundtable on "Service Leadership", The Hong Kong Polytechnic University, Hong Kong.*
 8. Ma, C. M. S., & Shek, D. T. L. (2013, March). Caring disposition and service leadership among Hong Kong university students. *Paper presented at the International Roundtable on "Service Leadership", The Hong Kong Polytechnic University, Hong Kong.*
 9. Shek, D. T. L., Sun, R. C. F., & Siu, A. M. H. (2013, March). Helping university students to thrive: The service leadership initiative at The Hong Kong Polytechnic University. *Keynote speech presented at the International Roundtable on "Service Leadership", The Hong Kong Polytechnic University, Hong Kong.*
 10. Yu, L., & Shek, D. T. L. (2013, March). Character strengths in Chinese philosophies: Confucian virtues and service leadership. *Paper presented at the International Roundtable on "Service Leadership", The Hong Kong Polytechnic University, Hong Kong.*
 11. Shek, D. T. L., Sun, R. C. F., Yu, L., Ma, C. M. S., Siu, A. M. H., Lin, L., Leung, H., & Law, M. Y. M. (2014, May). Service leadership education and research at The Hong Kong Polytechnic University: An overview. *Paper presented at the International Conference on Service Leadership Education for University Students: Experience in Hong Kong, Hong Kong.*
 12. Shek, D. T. L., Sun, R. C. F., Lin, L., Leung, H., Yu, L., Ma, C. M. S., Siu, A. M. H., & Law, M. Y. M. (2016, January). Service Leadership Education at The Hong Kong Polytechnic University. *Paper presented at the International Conference on Service Leadership Education in Service Economies, Hong Kong.*

Other Articles

1. 石丹理、鍾普洋、林立、黎翔. (2014). 如何培育香港大學生的領袖素質？
紫荊論壇, 5-6 月號第 15 期, 86-94.
2. 石丹理. (2014). 香港如何培育人才？*紫荊論壇*, 11-12 月號第 18 期, 27-35.

B. Evaluation (Credit-Bearing Subjects):

Journal Articles

1. Shek, D. T. L., Yu, L., & Ma, C. M. S. (2014). The students were happy but did they change positively? *International Journal on Disability and Human Development*, 13(4), 505-511.

2. Shek, D. T. L., Lin, L., & Liu, T. T. (2014). Service leadership education for university students in Hong Kong: Subjective outcome evaluation. *International Journal on Disability and Human Development*, 13(4), 513-521.
3. Shek, D. T. L., Lin, L., Liu, T. T., & Law, M. Y. M. (2014). Service leadership education for university students in Hong Kong: Qualitative evaluation. *International Journal on Disability and Human Development*, 13(4), 523-529.
4. Shek, D. T. L., Lin, L., Liu, T. T., & Law, M. Y. M. (2014). Process evaluation of a pilot subject on service leadership for university students in Hong Kong. *International Journal on Disability and Human Development*, 13(4), 531-540.
5. Shek, D. T. L., Law, M. Y. M., & Liu, T. T. (2015). Focus group evaluation of a service leadership subject in Hong Kong. *International Journal on Disability and Human Development*, 14(4), 371-376.
6. Shek, D. T. L., & Liang, J. (2015). Subjective outcome evaluation of a university subject on service leadership. *International Journal on Disability and Human Development*, 14(4), 385-392.
7. Shek, D.T.L., Liang, J., & Law, M.Y.M. (2016). Process evaluation of a university subject on service leadership in Hong Kong. *International Journal of Child and Adolescent Health*, 9(2), 253-261.
8. Shek, D.T.L., Liang, J., & Zhu, X. (2016). Subjective outcome evaluation of a service leadership subject for university students in Hong Kong. *International Journal of Child Health and Human Development*, 9(2), 225-232.
9. Shek, D. T. L., Lin, L., & Xie, Q. (2016). Service leadership education for university students in Hong Kong: A qualitative evaluation study. *International Journal of Child and Adolescent Health*, 9(2), 235-243.
10. Shek, D. T. L., Xie, Q., Lin, L., Law, M. Y. M. (in press). Evaluation of a service leadership subject in Chinese university students in Hong Kong using focus groups. *International Journal on Disability and Human Development*.
11. Shek, D. T. L., & Lin, L. (in press). Objective outcome evaluation of Service Leadership Education at The Hong Kong Polytechnic University. *International Journal on Disability and Human Development*.

Book Chapters

1. Shek, D. T. L., Yu, L., & Ma, C. M. S. (2015). The students were happy, but did they change positively? [Reprint]. In D. T. L. Shek, A. M. H. Siu, & J. Merrick. (Eds). *Tomorrow's leaders: Service leadership and holistic development in Chinese university students* (pp. 157-168). New York: Nova Sciences Publisher.
2. Shek, D. T. L., Lin L., & Liu, T. T. (2015). Service leadership education for university students in Hong Kong: Subjective outcome evaluation [Reprint]. In D. T. L. Shek, A. M. H. Siu, & J. Merrick. (Eds). *Tomorrow's leaders: Service leadership and holistic development in Chinese university students*, (pp. 169-180). New York: Nova Sciences Publisher.
3. Shek, D. T. L., Lin L., Liu, T. T., & Law, M. Y. M. (2015). Service leadership education for university students in Hong Kong: Qualitative evaluation [Reprint]. In D. T. L. Shek, A. M. H. Siu, & J. Merrick. (Eds). *Tomorrow's leaders: Service leadership and holistic development in Chinese university students*, (pp. 181-192). New York: Nova Sciences Publisher.

4. Shek, D. T. L., Lin L., Liu, T. T., & Law, M. Y. M. (2015). Process evaluation of a pilot subject on service leadership for university students in Hong Kong. In D. T. L. Shek, A. M. H. Siu, & J. Merrick. (Eds). *Tomorrow's leaders: Service leadership and holistic development in Chinese university students*, (pp. 193-204). New York: Nova Sciences Publisher. (Reprint)
5. Shek, D. T. L., & Lin, L. (2015). Evaluating service leadership programs with multiple strategies. In D. T. L. Shek & P. P. Y. Chung (Eds.), *Promoting service leadership qualities in university students: The case of Hong Kong. Quality of life in Asia*, vol. 6 (pp. 197-211). Singapore: Springer.
6. Shek, D. T. L., Chi, X., & Lin, L. (2016). Student service leadership program: Subjective outcome evaluation [Reprint]. In D. T. L. Shek, F. K. Y. Wu, J. T. Y. Leung, & J. Merrick (Eds.), *Adolescence: Positive youth development programs in Chinese communities* (pp. 125-136). New York: Nova Sciences Publisher.
7. Shek, D. T. L., Law, M. Y. M., & Liu, T. T. (2016). Focus group evaluation of service leadership [Reprint]. In D. T. L. Shek, A. M. H. Siu, H. Leung, & J. Merrick (Eds.), *Higher education in Hong Kong: Nurturing students to be caring service leaders* (pp. 111-122). New York: Nova Sciences Publisher.
8. Shek, D. T. L., & Liang, L. (2016). Student evaluation of a university subject on service leadership [Reprint]. In D. T. L. Shek, A. M. H. Siu, H. Leung, & J. Merrick (Eds.), *Higher education in Hong Kong: Nurturing students to be caring service leaders* (pp. 137-150). New York: Nova Sciences Publisher.

Conference Presentations

1. Shek, D. T. L., Lin, L., Leung, H., Law, M. Y. M., & Li, X. (2014, May). Evaluation of service leadership programs using multiple evaluation methods. *Paper presented at the International Conference on Service Leadership Education for University Students: Experience in Hong Kong*, Hong Kong.
2. Shek, D. T. L., Lin, L., & Leung, H. (2016, January). Objective Outcome Evaluation of Service Leadership Education at The Hong Kong Polytechnic University. *Paper presented at the International Conference on Service Leadership Education in Service Economies, Hong Kong*.

C. Evaluation (Non-Credit-Bearing Programs)

Journal Articles

1. Shek, D. T. L., & Li, X. (2015). Evaluation of an innovative leadership training program for Chinese students: Subjective outcome evaluation. *International Journal on Disability and Human Development*, 14(4), 393-400.
2. Shek, D.T.L., & Lin, L. (2016). Service leadership education in the global youth leadership programme: A qualitative evaluation. *International Journal of Child and Adolescent Health*, 9(2), 245-252.
3. Shek, D. T. L., & Lin, L. (2016). Changes in university students after joining a service leadership program in China. *Journal of Leadership Education*, 15(1), 96-109.
4. Shek, D. T. L., Zhu, X., & Lin, L. (in press). Evaluation of an intensive service leadership course in mainland China. *International Journal of Child and Adolescent*

Health.

5. Shek, D. T. L., Lin, L., Leung, H. & Zhu, X. (2017). The impact of an intensive service leadership course in Mainland China: Objective outcome evaluation. *International Journal of Child and Adolescent Health*, 10(1), 63-71.
6. Leung, H., Shek, D. T. L., Lin, L. (in press). Promotion of service leadership qualities in Chinese university students: Objective outcome evaluation based on six waves of data. *The International Journal of Child and Adolescent Health*.

Book Chapters

1. Shek, D. T. L., & Lin, L. (2015). "Global Youth Leadership Programme" and its evaluation [Reprint]. In D. T. L. Shek, F. K. Y. Wu, & J. Merrick (Eds.), *Leadership and service learning education: Holistic development for Chinese university students* (pp. 111-124). New York: Nova Sciences Publisher.
2. Shek, D. T. L., & Li, X. (2016). Evaluation of a leadership training program for Chinese students [Reprint]. In D. T. L. Shek, A. M. H. Siu, H. Leung, & J. Merrick (Eds.), *Higher education in Hong Kong: Nurturing students to be caring service leaders* (pp. 151-164). New York: Nova Sciences Publisher.
3. Shek, D. T. L., Lin, L., Leung, H., & Zhu, X. (2016). Impact of an intensive service leadership course in mainland China [Reprint]. In D. T. L. Shek, C. M. S. Ma, L. Lin & J. Merrick (Eds.), *Education in Hong Kong: Service leadership for university students* (pp. 135-145). New York: Nova Science Publishers.
4. Shek, D. T. L., Zhu, X., & Lin, L. (2016). Service leadership course in mainland China: An evaluation [Reprint]. In D. T. L. Shek, F. K. Y. Wu, J. T. Y. Leung, & J. Merrick (Eds.), *Adolescence: Positive youth development programs in Chinese communities* (pp. 137-148). New York: Nova Sciences Publisher.

Conference Presentations

1. Leung, H., Shek, D. T. L., Lin, L. (2016, August). Promotion of service leadership qualities in Chinese university students: An evaluation based on six waves of data. *Paper presented at The 2016 International Society for Quality of Life Studies Annual Conference – "Bridging Quality-of-Life Experiences From East to West," Seoul, South Korea.*

D. Assessment Tools*Journal Articles*

1. Shek, D. T. L., & Lin, L. (in press). Criterion-related Validation of the Service Leadership Knowledge Scale. *International Journal on Disability and Human Development*.
2. Shek, D. T. L., Lin, L., Leung, H., Yu, L. Ma, C. M. S., & Li, X. (in press). Development and validation of the Service Leadership Knowledge Scale in a Chinese context. *International Journal on Disability and Human Development*.
3. Shek, D. T. L., Lin, L., Leung, H., Yu, L. Ma, C. M. S., & Li, X. (in press). Content validation of the Service Leadership Attitudes Scale. *International Journal on Disability and Human Development*.

E. Books and Special Issues

Special Issues

1. Shek, D. T. L., Siu, A. M. H., & Merrick, J. (Eds.). (2014). A tale of two innovative leadership programs in Hong Kong, China [Special issue]. *International Journal on Disability and Human Development*, 13(4), 409-543.
2. Shek, D. T. L., Chung, P. P. Y., Yu, L., & Merrick, J. (Eds.) (2015). Service leadership education for university students: The Hong Kong experience [Special issue]. *International Journal on Disability and Human Development*, 14(3), 203-293.
3. Shek, D. T. L., Chung, P. P. Y., Yu, L., & Merrick, J. (Eds.). (2015). Service leadership curriculum and higher education reform in Hong Kong [Special issue]. *International Journal on Disability and Human Development*, 14(4), 297-406.
4. Shek, D. T. L., Ma, C. M. S., & Merrick, J. (Eds.) (2016). Promoting leadership and intrapersonal development in university students [Special issue]. *International Journal on Disability and Human Development*, 15(2), 125-239.
5. Shek, D. T. L., Chung, P., Lin, L. & Merrick, J. (Eds.) (in press). Service Leadership Education for University Students [Special issue]. *International Journal on Disability and Human Development*.

Books

1. Shek, D. T. L., & Chung, P. P. Y. (Eds.). (2015). Promoting service leadership qualities in university students: The Case of Hong Kong. *Quality of life in Asia*, vol. 6. Singapore: Springer.
2. Shek, D. T. L., Siu, A. M. H., & Merrick, J. (Eds.). (2015). *Tomorrow's leaders: Service leadership and holistic development in Chinese university students*. New York: Nova Sciences Publisher.
3. Shek, D. T. L., Wu, F. K. Y., & Merrick, J. (Eds.). (2015). *Leadership and service learning education: Holistic development for Chinese university students*. New York: Nova Sciences Publisher.
4. Shek, D. T. L., Ma, C. M. S., Lin, L., & Merrick, J. (Eds.). (2016). *Education in Hong Kong: Service leadership for university students*. New York: Nova Sciences Publisher.
5. Shek, D. T. L., Siu, A. M. H., Leung, H., & Merrick, J. (Eds.). (2016). *Higher education in Hong Kong: Nurturing students to be caring service leaders*. New York: Nova Sciences Publisher.

Conferences (Organized by PolyU):

1. *International Roundtable on "Service Leadership"* held on March 22, 2013 at The Hong Kong Polytechnic University, Hong Kong.
2. *International Conference on Service Leadership Education for University Students: Experience in Hong Kong*, held on May 14-15, 2014 at The Hong Kong Polytechnic University, Hong Kong.
3. *International Conference on Service Leadership Education in Service Economies* held on January 6-7, 2016 at The Hong Kong Polytechnic University, Hong Kong.

Chapter 179

GENERAL EDUCATION AT THE HONG KONG POLYTECHNIC UNIVERSITY

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ABSTRACT

The present chapter evaluated the implementation and impact of the “General University Requirements” (GUR) at The Hong Kong Polytechnic University (PolyU) using both quantitative and qualitative methods. Quantitative methods included a four-year longitudinal online survey, Collegiate Learning Assessment Plus (CLA+), and secondary analyses of student feedback data in different years. Qualitative methods included focus groups and qualitative evaluation forms involving students and teachers as well as a longitudinal case study. Results showed that students displayed positive development based on different developmental indicators of the five desired graduate attributes of PolyU in their study of the four-year program. Both students and teachers also generally showed positive perceptions of the GUR, with reference to its subject

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content, teaching and learning, and benefits. Several major concerns regarding the GUR were also identified.

INTRODUCTION

In a fast-changing and increasingly uncertain society, general education has become more important. General education was defined by the Association of American Colleges and Universities (AAC&U) [1] as “that part of a liberal education curriculum that is shared by all students. It provides broad exposure to multiple disciplines and forms the basis for developing essential intellectual, civic, and practical capacities.” In the 21st century and an increasingly globalized age, company structure becomes flatter and company composition becomes more international; employees have more empowering, diverse and unstable work environment and professional life, which require them to be more flexible and diverse and to have strong social and cognitive skills such as communication, problem-solving, critical and integrative thinking, interpersonal relationship building, and cultural awareness [2, 3]. These social changes challenged higher education. General education is regarded as a crucial instrument to help students to form a foundation of knowledge and develop valuable skills such as communication, quantitative reasoning, and integrative and critical thinking to become lifelong learners and global citizens in a fast-changing and an interconnected world [4]. For example, in a report named *Higher education in developing countries: Peril and promise* published by the Task Force on Higher Education and Society (convened by the World Bank and UNESCO) in 2000 [5], it was stated that “a general education is an excellent form of preparation for the flexible knowledge-based careers that increasingly dominate the upper tiers of the modern labor force” [5, p. 83] and it can “promote responsible citizenship, ethical behavior, educational ambition, professional development in a broad range of fields, and even global integration” [5, p. 88].

Against the above backdrop, many countries have incorporated or are exploring different approaches of general education in their higher education curriculum to strengthen their students’ college learning experience. In this exploration, the models that were widely adopted or referred to were the models of general education in American higher education, in which students normally study a set of general education courses in their first and second college years and then gradually move to their specialized study in later years. Nowadays, the American mode of general education has been transplanted to the higher education systems in many countries and districts, including Japan, mainland China, Hong Kong, Taiwan, and other places [6, 7].

While the “American” models were widely adopted, there were different stages in their development. In the early days, the general education curriculum inherited the tradition of liberal education in some traditional famous English universities such as University of Oxford and University of Cambridge, which was manifested by a unified curriculum focusing on classical studies to develop lawyers, doctors and ministers for the upper class of a preindustrial society [8]. Since the late nineteenth century, the curriculum was challenged by the rapid industrialization and science development of American society and was replaced by a free elective system firstly proposed by Charles Eliot, the prior president of Harvard University, which offered students full freedom to choose subjects that fulfilled their individualized learning needs and interests [9, 10]. The free elective system was then replaced

by a “distributional requirement” due to the criticism that it lacked unification and integration in students’ learning [11]. The distributional requirement required students to take courses from each of a broad scope of disciplines with certain freedom which could balance the common requirements and students’ personalized interests [8]. In recent decades, some new curricular or course models were developed to meet with challenges of current social changes, including Freshman Experience program, interdisciplinary subjects, and service learning activities [8]. In a survey conducted by AAC&U in 2009 [1], 58% of AAC&U member institutions had developed First Year Experience programs in their general education curriculum preparing for their students’ first-year transition. Also, 39% institutions developed service learning programs in their general education curriculum and the percentage was still increasing. These developments showed the longstanding nature of general education and the new curricular models developed in it in coping with constant social changes.

Nevertheless, the implementation of general education is always a hard task and obstacles are bound to happen. Hence, constant evaluation and revision work need to be done to maintain healthy functioning and facilitate further improvement of general education programs and initiatives. In a report released by the Carnegie Foundation for the Advancement of Teaching in 1977 [12], general education in American universities was depicted as “a disaster area” and was blamed for its incoherence in programs. Challenged by these evaluation results, many universities and colleges reviewed and strengthened their general education programs in the 1980s [13]. Subsequently, from the 1990s to 2000s, the priority of general education has increased, more reforms were conducted and new models such as thematic programs were developed [14]. Also, more higher education institutions conducted formal review and assessment of their general education programs and even incorporated assessment as a routine practice in their program implementations [15].

With particular reference to Hong Kong, higher education in Hong Kong has experienced a comprehensive reform in the past few years, marking a shift from previous British-style to American-style undergraduate education. The previous undergraduate education in Hong Kong was based on a three-year curriculum, which highly emphasized early specialization and disciplinary concentration of students’ studies [16]. However, starting from the academic year of 2012-2013, all Hong Kong public universities extended their undergraduate curricula from three years to four years. At the same time, each university introduced a significant general education component in its new four-year undergraduate program which attempted to develop manpower with a broad knowledge scope, an innovative and integrated vision, positive attitudes and important generic and transferable skills to cope with the challenges of Hong Kong’s construction of a globally competitive and value-added service economy in the 21st century [16, 17] and development of a civil society as a Special Administrative Region of China [18].

However, there were very few evaluation studies to systematically evaluate these reform initiatives in Hong Kong universities. This research gap needs to be filled because evaluation can tell us how well the four-year undergraduate curricula and the new general education programs in different universities function, how effective they are, and what kind of promoting and hindering factors are existent in the functioning of these programs. Against this background, a comprehensive evaluation study was conducted to evaluate the new four-year curriculum and general education at The Hong Kong Polytechnic University (PolyU). In the 2012-2013 academic year, PolyU introduced a new general education structure into its new four-year curriculum framework. This general education structure is named “General

University Requirements” (GUR), which includes six major components. With this comprehensive structure, the GUR aims to develop PolyU students in five desired graduate attributes, including effective communication, critical thinking, innovative problem-solving, lifelong learning, and ethical leadership.

Freshman Seminar (FS)

FS is the first component of GUR. It is a three-credit mandatory subject offered by each faculty/school of PolyU to all its first-year students. FS aims to cultivate students’ understanding of their professions and broad disciplines and to develop their entrepreneurship and self-learning ability.

Leadership and Intrapersonal Development (LIPD)

LIPD component is intended to develop students’ understanding of intrapersonal and interpersonal skills that are needed for successful and ethical leaders. The component consists of two three-credit subjects. One is “Tomorrow’s Leaders” (TL) that is offered to all first-year students except for students of the Faculty of Business (FB), who are instead offered another subject named “Tango! Managing Self & Leading Others” (Tango!).

Language and Communication Requirements (LCR)

This component attempts to enhance students’ Chinese and English communication skills. The component requires students to take one Chinese and two English subjects according to their different language proficiencies.

Cluster Area Requirements (CAR)

This component requires students to take one three-credit subject in each of the four learning areas in addition to meeting three additional requirements, namely China studies requirements (CSR), English writing and reading requirements (EW/ER), and Chinese writing and reading requirements (CW/CR). The four learning areas are “Human Nature, Relations and Development” (CAR-A), “Community, Organization and Globalization” (CAR-B), “History, Culture and World Views” (CAR-C), and “Science, Technology, and Environment” (CAR-D). CAR aims to expand students’ intellectual potential and cultivate their understanding of the Chinese culture and their Chinese and English writing skills.

Service Learning (SL)

Each student needs to take a three-credit SL subject that includes a significant service component. This component aims to cultivate students' sense of social responsibility, empathy, and application of professional knowledge.

Healthy Lifestyle (HLS)

The HLS component is non-credit-bearing, whereby students are required to take a series of courses including introductory lecture, sports training, e-learning, and wrap-up lecture. The purpose of this component is to cultivate students' understanding of a healthy lifestyle and their mastery of related knowledge and skills.

To evaluate the implementation and effectiveness of the GUR, a five-year evaluation research was conducted. The research attempted to answer two basic evaluation questions: a) What are the changes in the students in their undergraduate study particularly with reference to the five desired graduate attributes of PolyU? b) What are the views of students and teachers on the GUR, especially in terms of content, teaching, implementation, and effects? To investigate these questions, different evaluation components were incorporated in the research, including:

- a) A four-year longitudinal online survey to track the development of students in a set of developmental indicators during their four-year study of the undergraduate curriculum and the GUR at PolyU
- b) Collegiate Learning Assessment Plus (CLA+) for assessing students' development in problem-solving, communication, and critical thinking in their study of the four-year curriculum
- c) Secondary data analyses of the Student Feedback Questionnaire (SFQ) data that was used to measure students' subjective outcome evaluation of GUR
- d) Student focus group interviews and qualitative evaluation based on evaluation forms used to understand students' perceptions of different subjects of GUR, especially the contents, teaching methods, implementation, and effects
- e) Teacher focus group interviews and qualitative evaluation based on evaluation forms, which was used to understand the teachers' view of the GUR curriculum, with reference to the curricular idea, teaching and learning, and curricular effects
- f) Longitudinal case study used to track the long-term development of students in the study of the four-year curriculum, and
- g) Repertory grid test to study the development of students after studying the four-year curriculum and the GUR.

A summary of different evaluation mechanisms and their major findings are presented in the sections below.

LONGITUDINAL ONLINE SURVEY

The longitudinal online survey attempted to investigate the changes of students under the new four-year undergraduate curriculum and the GUR at PolyU, with reference to the five desired graduate attributes (i.e., effective communication, critical thinking, innovative problem-solving, lifelong learning, and ethical leadership). This evaluation component included three sub-studies. Sub-Study 1 investigated the changes of PolyU four-year curriculum students in a set of developmental indicators in the four academic years from 2012-2013 to 2015-2016. Sub-Study 2 compared the performance of PolyU four-year curriculum students (Experimental Group) with those of PolyU three-year curriculum students (Control Group 1) in the 2014-2015 academic year (i.e., third-year students in the 3-year program and the 4-year program). Sub-Study 3 compared the performance of Experimental Group with those of four-year curriculum students in a comparable local university (Control Group 2) in the 2014-2015 academic year (i.e., third-year students in the 4-year program). Below is a summary of the three sub-studies.

Sub-Study 1

In the 2012-2013 academic year, 677 out of a random stratified sample of 1,000 first-year students enrolled in the new four-year curriculum of PolyU responded to an online questionnaire of GUR longitudinal online survey (Wave 1). These students were further invited to complete the same questionnaire annually in the following three academic years, i.e., 2013-2014 (Wave 2), 2014-2015 (Wave 3), and 2015-2016 (Wave 4) academic years. Of the 677 students initially invited, 434 had completed all four waves of the questionnaire.

The survey questionnaire was comprised of four validated instruments, including Chinese Interpersonal Reactivity Index (C-IRI), Chinese Positive Youth Development Scale (CPYDS), Index of Learning Style (ILS), and National Survey of Student Engagement (NSSE). The C-IRI comprises three subscales, including Personal Distress, Fantasy and Empathy, to measure empathy in Chinese people [19]. The CPYDS measures positive characteristics in Chinese adolescents [20]. A shortened version of CPYDS was adopted in the present longitudinal survey, which comprises 14 subscales including Cognitive Competence, Emotional Competence, Behavioral Competence, Problem Solving, Social Competence, Critical Thinking, Self-Determination, Self-Efficacy, Resilience, Moral Competence, Ethical Leadership, Self-Leadership, Life Satisfaction, and Lifelong Learning. The ILS measures students' individual learning preferences in terms of four dimensions: Active versus Reflective, Sensing versus Intuitive, Verbal versus Visual, and Global versus Sequential [21]. The NSSE measures students' engagement in learning and other university experiences, which consists of 11 subscales including Collaborative Learning, Reflective and Integrative Learning, Student Faculty Interaction, Higher Order Learning, Effective Teaching Practice, Quantitative Reasoning, Discuss with Diverse Other, Learning Strategies, High Impact Practice, Quality of Interaction, and Supportive Environment.

Repeated measures ANOVAs and Bonferroni post hoc tests were performed to compare the performance of the participants in indices of desired graduate attributes tested by survey instruments in the four academic years from 2012-2013 to 2015-2016. Results showed the

participants' increased ratings on the majority of indicators in their junior and senior years than in their freshman and sophomore years including problem-solving, collaborative learning, discuss with diverse other, higher order learning, reflective and integrative learning, and quantitative reasoning. Participants' ratings in the academic years of 2014-2015 and 2015-2016 were significantly higher than those in 2012-2013 and 2013-2014. The participants' ratings of critical thinking in the academic year of 2015-2016 were also higher than those in the academic years of 2012-2013 and 2013-2014. Their ratings of ethical leadership, self-leadership, and lifelong learning were also significantly higher in the academic year of 2015-2016 than in 2013-2014. Their ratings of learning strategies in 2015-2016 were higher than in 2013-2014, and their ratings in 2014-2015 were also higher than those in 2012-2013 and 2013-2014. The participants' ratings of social competence remained stable over the four academic years, and their empathy scores decreased in the academic year of 2013-2014 when compared to those in the year of 2012-2013. The findings for the changes in the students over time have been published [22].

Sub-Study 2 and Sub-Study 3

The sub-studies 2 and 3 were added to the whole study of the longitudinal survey in the 2014-2015 academic year (i.e., Year 3 of the cohort). While Sub-study 2 involved a control group consisting of 300 students enrolled in the old three-year undergraduate curriculum of PolyU (Control Group 1), Sub-study 3 involved a control group consisting of 300 students enrolled in a new four-year curriculum in a comparable local university (Control Group 2). Results of independent samples t-tests showed that the Experimental Group performed significantly better than Control Group 1 on critical thinking, ethical leadership, collaborative learning, discuss with diverse other, higher order learning, reflective and integrative learning, learning strategies and empathy, while the two groups had no differences in their performances on problem-solving, self-leadership, lifelong learning, and quantitative reasoning. The Experimental Group also performed significantly better than Control Group 2 on problem-solving, emotional competence, cognitive competence, behavioral competence, moral competence, life satisfaction, learning strategies, and quality of interaction. In short, the findings are consistent with the hypotheses of the study and they have been published elsewhere [23, 24].

COLLEGIATE LEARNING ASSESSMENT PLUS (CLA+)

The second quantitative method employed in the comprehensive evaluation research of the GUR was the Collegiate Learning Assessment Plus (CLA+). The CLA+ is a norm-referenced and standardized online test developed by the U.S. Council for Aid to Education (CAE). It assesses the contribution of an institution to the development of its students in competencies including analysis and problem-solving, writing effectiveness, writing mechanics, scientific and quantitative reasoning, critical reading and evaluation, and critique an argument [25]. These competencies are basically aligned with three desired graduate attributes of PolyU, namely, problem-solving, critical thinking, and effective communication.

Before the start and near the end of the 2013-2014 and 2015-2016 academic years, respectively, four rounds of CLA+ tests were performed with four groups of 150 randomly selected students who studied in the PolyU four-year curriculum. Group 1 consisted of 150 first-year students who conducted the test before the start of the 2013-2014 academic year. Group 2 was comprised of 150 second-year students participating in the test in Semester 2 of the 2013-2014 academic year. The 150 students were randomly selected from the participant pool of the longitudinal survey. Group 3 included 150 first-year students who completed the test before the start of the 2015-2016 academic year. Group 4 comprised 150 senior-year students participating in Semester 2 of the 2015-2016 academic year. Among the 150 participants in group 4, 127 were participants from Group 2.

Paired samples t-test comparing the performance of the 127 participants in both Group 2 and Group 4 showed that Group 4 scored significantly higher than Group 2 in almost all the variables of CLA+, including analyses and problem-solving, writing mechanics, scientific and quantitative reasoning, critical reading and evaluation, and critique an argument except for writing effectiveness on which the two groups had no differences in performance. Secondly, the independent samples t-test comparing the performance of Group 1 and Group 4 showed that Group 4 performed significantly better than Group 1 in all CLA+ subscales, except for writing mechanics on which the two groups performed comparable to each other. All the results indicated students' improvements in problem solving (measured by analyses & problem-solving), effective communication (measured by writing mechanics and writing Effectiveness) and critical thinking (assessed by scientific & quantitative reasoning, critical reading and evaluation, and critique an argument) in senior year than in freshmen and sophomore years under their study of the PolyU four-year curriculum and the GUR. A paper reporting the findings is under preparation [26].

SECONDARY DATA ANALYSES OF DATA FROM STUDENT FEEDBACK QUESTIONNAIRES (SFQ)

Secondary data analyses of the SFQ data were conducted to investigate students' subjective views of GUR subjects in terms of subject attributes and teacher attributes. In the academic years of 2012-2013, 2013-2014, 2014-2015 and 2015-2016, 16,909, 19,242, 24,902 and 24,360 SFQ on GUR subjects were collected, respectively, by the Educational Development Centre (EDC) of PolyU. The SFQ was a faculty/school-based questionnaire developed by EDC to assess perceptions of students on university subjects in each semester in terms of students' learning experiences and perceived teaching of staff. The present study gathered data from six standardized items in SFQ for GUR subjects for further analyses. The six items include four items concerning students' learning experiences in GUR subjects and two items on students' views of the teaching staff.

Results showed higher mean scores of students' ratings of all six SFQ items in all the four years. All the mean scores were above (or equal to) 4.00 out of a maximum of five, except for two ratings being 3.90. Results of the one-way ANOVA and post hoc comparison showed that students' ratings of almost all the items in the academic years of 2014-2015 and 2015-2016 were significantly higher than in academic years 2012-2013 and 2013-2014. The SFQ ratings for different GUR components were also positive. For LCR-English and LCR-

Chinese components, the mean scores of all items in all the four years were above (or equal to) 4.00, except for the score of one item in LCR-Chinese being 3.90. The mean scores for CAR, LIPD and SL were all above (or equal to) 3.70. Only the mean scores for FS were slightly lower, ranging from 3.40 to 4.10. Result based on one-way ANOVA and post hoc comparisons showed that on most of the SFQ items, students' ratings in FS, LCR, and CAR components had increased in the academic year of 2015-2016 compared to their ratings in 2012-2013. For LIPD, students' ratings of all items in the academic year of 2014-2015 were higher than those in 2013-2014, and their ratings of some items in 2014-2015 were also higher than those in 2012-2013. Students' SFQ ratings in SL component remained stable across the four academic years. These results indicated that students' evaluation of different GUR components were generally positive in the four years. These findings are published in different journals [27-29].

STUDENT FOCUS GROUPS AND QUALITATIVE EVALUATION BASED ON EVALUATION FORM

Student focus groups and qualitative evaluation based on evaluation form were conducted to understand students' subjective perceptions of the GUR subjects, especially their contents, teaching methods, implementation, and impacts. In each academic year, students were randomly selected from different faculties/schools to participate in focus group interviews. In the four academic years from 2012-2013 to 2015-2016, thirteen ($n = 62$), eighteen ($n = 74$), eight ($n = 73$), and eight ($n = 70$) student focus groups were conducted, respectively. In addition, in the academic years of 2013-2014 and 2014-2015, 320 and 480 randomly selected students studying in the four-year curriculum were invited to complete a qualitative evaluation form on their views of the GUR, respectively. A total of 163 evaluation forms from 2013-2014 and 332 from 2014-2015 academic years were collected from these students.

All focus groups were guided by a focus group protocol developed by the authors. The protocol consisted of several groups of questions to solicit the interviewees' views on rationales, teaching and learning, implementation and impacts of the GUR. The evaluation form was comprised of several open-ended questions to ask students to describe their general impressions of the GUR by using descriptors or short phrases, and to ask students about their unforgettable experiences, difficulties and personal achievements in their study of the GUR subjects. Thematic analyses were adopted to analyze the qualitative data collected.

The findings suggested that students' views of different GUR components were generally positive. The data collected from the qualitative evaluation form in different years indicated students' positive impressions and feelings of different GUR subjects. Different qualitative evaluation data also suggested that students perceived different GUR subjects positively with specific reference to content, teaching, implementation, and benefits. Students positively commented on the subject content of several components, such as LIPD, LCR-English, and CAR. Students perceived the topics in TL and CAR subjects as interesting and attractive and they perceived the contents of CAR and LCR-English subjects as practical and applicable to their lives and study. Students also liked the stratified teaching methods in LCR component and the design of CAR component that gave them freedom in selecting their interested subjects. Students had positive views of the active, interactive, and experiential teaching and

learning methods as well as the authentic assessment methods adopted in many GUR subjects. They perceived these methods as engaging, conducive to deep learning, and helpful to their achievement of the intended learning outcomes of different subjects. The findings are reported in a series of journal articles [30-33].

TEACHER FOCUS GROUPS AND QUALITATIVE EVALUATION BASED ON EVALUATION FORM

In each academic year from 2012-2013 to 2015-2016, a sample of teachers teaching different GUR subjects were invited to participate in focus group interviews based on nomination of program leaders and key teachers. In total, four ($n = 20$) focus groups in 2012-2013, eight ($n = 49$) in 2013-2014, eight ($n = 52$) in 2014-2015, and eight ($n = 50$) in 2015-2016 were conducted. Also, in the academic years of 2013-2014 and 2014-2015, 99 and 128 teachers teaching different GUR subjects were invited to complete a qualitative evaluation form, respectively. A total of 75 forms in 2013-2014 and 78 forms in 2014-2015 academic years were collected from the teachers.

All teacher focus groups were guided by a focus group protocol developed by the authors. The protocol included five groups of questions asking teachers to share their views on different aspects of the GUR subjects they taught, including rationale, impact on students, workable and unworkable subject components, and challenges to teaching. Teacher evaluation form included questions asking about teachers' general impression of the GUR subjects they taught, their perceived benefits of GUR, and the challenges in their teaching. Thematic analyses were used to analyze teacher focus group data and teacher evaluation form data.

Results showed that the teachers' views of the GUR were also generally positive. Teachers teaching different GUR subjects had positive impressions about the subjects they taught, which was evidenced by the high percentage of positive descriptors given by teachers in different GUR components in different academic years. Teachers in different GUR components positively perceived different aspects of the subjects they taught, including the general rationale, teaching methods, and impacts on students. Some teachers, particularly those teaching CAR subjects, displayed a deeper understanding of the rationale of the GUR and general education and gave highly positive support to GUR subjects. Many teachers perceived the active and interactive teaching and learning methods in their subjects as welcomed by students and engaged students in learning. The teachers also perceived a basic alignment of their subjects with the intended learning outcomes. Challenges were also noted, including teaching big classes in some GUR subjects and teaching FS subjects in some faculties composed by more diversified disciplines. The related findings are published in different papers [34-37].

LONGITUDINAL CASE STUDY

In the academic year of 2012-2013, 57 students participating in the student focus groups and additional 14 first-year students enrolled in the four-year curriculum of PolyU were

invited to participate in a four-year longitudinal case study to follow up the personal growth of these students under the study of the new curriculum and the GUR. In the academic year of 2013-2014, 42 active student cases were retained and the 29 inactive cases were removed from the study. The 42 cases were then followed up in the following three academic years from 2013-2014 to 2015-2016. At the end of each academic year, each student was invited to attend an individual interview to understand their personal growth and views of the four-year curriculum and the GUR in that year. The numbers of students who participated in interviews in each academic year were 71 in 2012-2013 (including the 14 newly recruited students participating in the individual interviews and the 57 focus group students), 31 in 2013-2014, 20 in 2014-2015, and 23 in 2015-2016. All the individual interviews were guided by an interview protocol developed by the research team. The data of 2014-2015 and 2015-2016 were still in analyses. The results of 2012-2013 and 2013-2014 have been published [38, 39].

REPERTORY GRID TEST

To assess the change in the undergraduate students with reference to the desired graduate attributes, a repertory grid test was adopted. In the second semester of the 2015-2016 academic year, a random stratified sample of 100 fourth-year students from the GUR longitudinal online survey cohort completed the repertory grid test. Basically, students perceived themselves as developing in a positive direction based on different indicators of self-identity. The findings provide support for the claim that GUR was able to promote positive development in undergraduate students over time. The analyses of data and paper writing are underway.

DISCUSSION AND CONCLUSION

This paper presented a five-year longitudinal and multi-method evaluation study on the implementation and impact of a new general education program entitled General University Requirements (GUR) in the new four-year undergraduate curriculum at The Hong Kong Polytechnic University (PolyU). Basically, whether students had changed in their study and how different stakeholders looked at the program were examined.

For the four-year longitudinal online survey (which also included a quasi-experimental design involving two control groups in one academic year, i.e., 2014-2015), the results indicated that the students had improved in almost all the five attributes. Besides, the CLA+ was used in the present study to assess students' changes in problem-solving, written communication, and critical thinking abilities after their study in the four-year curriculum and the GUR. The results also indicated students' significant improvements in these attributes.

These quantitative findings are further supported by the qualitative evaluation findings. In student and teacher focus groups, both students and teachers pointed out that the GUR structure facilitated students' holistic development. The qualitative data also suggested that good subject design, such as attractiveness and practicality of subject topics, and the design of teaching approaches to better deliver the topics and facilitate students' learning determined how well students could be benefited by the GUR subjects. This was in line with the literature

suggesting that a good subject design, such as those that could promote transferability and practicality of knowledge [40], together with active teaching and learning methods, such as collaborative learning and experiential learning, could increase student satisfaction with the general education subjects and could facilitate the goal-achievement of different general education programs [41, 42].

Regarding the question of how different stakeholders viewed the GUR, four methods were used, including Student Feedback Questionnaires (SFQ), student focus group and qualitative evaluation, teacher focus group and qualitative evaluation, and longitudinal case study. The SFQ results suggested that students had positive experiences of GUR subjects in terms of different aspects, and had positive evaluation of teaching staff. Particularly, for LCR component, students had highly positive evaluation and the evaluation had also increased over the four academic years. This observation was supported by the student and teacher focus group and qualitative evaluation findings. There are several explanations for this result. First, the LCR component was mainly designed to train students' English and Chinese writing and expression skills. In particular, the English LCR subjects trained students a lot on basic referencing and paper-writing skills and these skills could be directly applied by students in their study of other academic subjects involving essays-writing tasks. Secondly, with regard to LCR component (particularly the English LCR subjects), many subjects adopted a pedagogy that combined small-class teaching with a workshop style of instruction, which highly promoted student interaction with their teachers and enhanced student satisfaction with the subjects. The positive results of small-class and workshop style teaching were also supported by the existing literature [43, 44]. Thirdly, in English LCR, many subject teachers had overseas education experience and some were foreigners. These teachers' teaching styles might be more open, democratic and more welcomed by the students.

Besides, SFQ results suggested students' highly positive evaluation of teaching staff of LIPD component. There are two explanations for this. Firstly, since the LIPD component (particularly the TL subject) required teachers to show care, self-disclose, and provide assistance to their students, and stressed highly the teacher-student relationship, some teachers who could do this would receive high appreciation and recognition from their students. This was supported by the findings from student and teacher focus groups in the present study. Secondly, although the content of LIPD subjects, such as the content of TL subject, included many theories and concepts, excellent teachers who could better integrate these theories with appropriate teaching approaches and with their personal experiences could promote deeper learning in students and increase student satisfaction. This was supported by the previous studies on TL subjects [45, 46].

Nevertheless, this evaluation study highlighted some issues on the implementation of the GUR and in general education programs. One problem was teaching large class general education subjects. Nowadays, due to the restriction of university resources and classroom settings, large class teaching has become a trend. Therefore, how to implement effective teaching in big class, particularly how to better integrate traditional lecturing method and active teaching methods in large classes to promote students' learning has become a critical issue faced by many general education programs, including the GUR. Extant literature suggested that adding some active teaching methods such as in-class group discussion, short class presentation, poster sharing, and out of class reading tasks in traditional lecturing could effectively promote students' learning [47, 48]. Particularly, a study conducted by Morgan, Whorton and Gunsalus [49] even revealed that a combination of traditional lecture method

with group discussion resulted in better learning effects of students than totally using cooperative and active learning methods. These studies indicated a great potential to better design and utilize big class teaching to promote students' effective learning and provided directions for the further refinements of some GUR subjects.

Another problem was the challenge in teaching interdisciplinary subjects. This was manifested by both students' and teachers' concerns about FS subject implementation in the present study. One deeper reason for this was overspecialization of and strong boundary between knowledge disciplines in modern society, which made it increasingly harder for teachers in one discipline to understand the interconnections of their discipline with other disciplines. Without qualified teachers, the implementation of interdisciplinary subjects would be in vain. Studies suggested that more student-centered teaching and learning approaches, such as problem-based learning, enquiry-based learning, and learning communities, could help to facilitate student learning and engagement in interdisciplinary subjects [50, 51]. This was also supported by the findings of this study in that some FS subjects adopting more active learning approaches such as hands-on workshops led to much better learning among the students.

Two limitations of the present study should be noted. Firstly, some learning effects, particularly some long-term impacts or influence of the GUR, may not be identified in a short period. Therefore, it would be better to also investigate students' development and perceptions of the impact of GUR after their graduation. Secondly, although students and teachers are two important groups of stakeholders of the GUR, university administrators and policymakers were also important stakeholders of the GUR and their views should also be investigated. Despite of these limitations, the present study provides a comprehensive picture about the implementation and impact of the GUR at PolyU, which contributes to the existing literature on evaluation of general education.

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Chapter 180

THE ACHIEVEMENT OF DESIRED UNIVERSITY GRADUATE ATTRIBUTES

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ABSTRACT

In this chapter, we investigated how the new 4-year undergraduate program, particularly the “General University Requirements” (GUR) at The Hong Kong Polytechnic University (PolyU) contributed to the development of five desired graduate attributes amongst students of PolyU, including critical thinking, effective communication, innovative problem solving, lifelong learning and ethical leadership. The findings based on different evaluation methods, including longitudinal survey studies, Collegiate Learning Assessment Plus, secondary analyses of Student Feedback Questionnaire data, qualitative evaluation studies, longitudinal case study and repertory grid test evaluation are first summarized. Based on the findings, the question of whether the 4-year program contributed to the development of desired graduate attributes was explored. Integration of the available evaluation findings suggests that the GUR has

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helped the undergraduate students to develop the graduate attributes and the new 4-year undergraduate programme can promote the holistic development of the students.

INTRODUCTION

Key generic competences such as effective communication, higher-order thinking, and problem-solving skills are becoming critically important in knowledge-based economy. There is no doubt that these competences were also stressed in previous times. However, in the previous era based on a manufacturing economy, the focus was mainly on the capital assets rather than the human assets [1]. Instead, in the current era dominated by a globalized knowledge economy and a service-based economy, the human assets play a key role in economic development [1]. Therefore, The Association of American Colleges and Universities issued a report named “*College learning for the new global century*” in 2007 [2]. The report proposed that the American university and college education should develop in students a set of core learning outcomes including knowledge of human cultures as well as physical and natural world, intellectual and practical skills, social responsibility, and integrative learning. Particularly, under the category of intellectual and practical skills, several key skills were stressed, including critical and creative thinking, written and oral communication, teamwork and problem solving. In addition, in order for developing these skills, the report called for a strengthening of general education programs in different American higher education institutions to foster “cross-disciplinary inquiry, analysis, and application” [2].

The review of goals of college education in the new century and its related curricular reforms have also been rigorously carried out in different places in Asia. In Mainland China, from the 1990s to the early 2000s, there had been a heated discussion on and rigorous implementation of quality education and general education in Chinese higher education institutions. Accompanying this was a deep reflection on what quality of manpower should be developed by Chinese higher education in the 21st century. Although various views emerged, their common threads were to develop high-quality graduates with strong flexibility, broad knowledge base, moral character and strong generic skills [3, 4]. Based on this consensus, many Chinese top universities have revised their Soviet-style overspecialized undergraduate curriculum by adding American elements of general education program [3, 5]. In Taiwan, the programs of general education had been introduced into higher education institutions since the 1950s and had undergone a rigorous and institutionalized development since the 1990s [6]. Up to the 2000s, almost all higher education institutions in Taiwan have implemented a formal general education program in their undergraduate curriculum [6]. Similarly, in Japan, general education programs had been introduced into Japanese higher education system since the 1950s and achieved a rigorous development in the 1960s. Although there was a decline in formal general education programs since the 1990s, the spirit of general education has been integrated into specialized education and achieved by various innovative pedagogy and curricula in different universities [7]. These different practices in different Asian areas illustrated that general education has become an important strategy for different areas to enhance their higher education quality and to develop more rounded manpower to rise up to the challenges of a more globalized society.

Besides actual practices in the undergraduate programs, theories of general education also suggested that it was a very important strategy to develop students' generic competences. Earlier in the 1820s, one famous report of Yale University [8, p.7] defended liberal education which is the predecessor of the current concept of general education, claiming that the core purpose of a liberal education was "discipline and furniture of the mind; expanding its powers, and storing it with knowledge." The Harvard report on general education entitled "*General education in a free society*" published in 1945 [9] also maintained that the essential aim of general education was to train students in four traits of mind, including "to think effectively, to communicate thought, to make relevant judgments, to discriminate among values." In addition, the previous President of Chicago University, Robert Maynard Hutchins, a famous advocator of general education and the founder of the classic books model of general education program in Chicago University in the 1930s and the 1940s, also stressed that the goal of general education was to "draw out the elements of our common human nature" [10]. These elements of common human nature were manifested in important intellectual virtues, such as the five intellectual virtues stressed in ancient times including the habits of induction, demonstration, philosophical wisdom, art, and prudence. These theoretical arguments and propositions further support the view that general education is an important curricular mean for students' development in important generic competences.

Among general education initiatives in Asian societies, Hong Kong can be regarded as a "late starter." Under the old British rule, there was not much room for the development of general education. Since the 2012-2013 academic year, mandated by the University Grants Committee, the higher education in Hong Kong has implemented a comprehensive reform on its undergraduate education program. Specifically, all the eight public universities in Hong Kong extended the length of their undergraduate degree programs from three years to four years. In addition, they introduced a significant general education structure in their new four-year undergraduate curricula. The reform was targeted to nurture a more flexible and rounded manpower to cope with challenges of Hong Kong's transformation from a manufacture-based to a service-based economy and its increasing integration into a globalized knowledge economy [11, 12].

Among all these reforms, the one at The Hong Kong Polytechnic University (PolyU) was unique. In the 2012-2013 academic year, PolyU transformed its undergraduate curriculum from three to four years in length. In the new four-year curriculum, a new general education framework entitled "General University Requirements" (GUR) was introduced. A major objective of the GUR was to nurture PolyU students in five desired graduate attributes, including effective communication, critical thinking, innovative problem solving, lifelong learning, and ethical leadership. These five attributes are regarded as key to PolyU students for their development to be locally and internationally competitive professionals and citizens.

The GUR is comprised of six major components, including freshman seminar (FS), leadership and intrapersonal development (LIPD), language and communication requirements (LCR), cluster area requirements (CAR), service learning (SL) and healthy lifestyle (HLS). Detailed introduction of these components can be seen in reference [13]. An alignment of different components with the five desired graduate attributes of PolyU is shown in Table 1.

Table 1. Alignment of GUR components with five desired graduate attributes of PolyU

	Professional competence	Critical thinker	Effective communicator	Innovative problem solver	Lifelong learner	Ethical leader
Freshman Seminar	○	○	○	○	○	
Language and Communication Requirements			●		○	
Leadership and Intrapersonal Development		○	○	○	●	●
Service Learning	○	●	○	●	○	●
Cluster Area Requirement		●	●		●	
Healthy Lifestyle Requirement					●	○

Note: ●: Target to make a significant contribution to the attribute; ○: Only some of the subjects/activities target to make a significant contribution to the attribute.

To gauge the effectiveness of the 4-year program and to understand the changes in the students, a longitudinal study was carried out from the academic years of 2012-2013 to 2015-2016. Seven evaluation components based on different methods were included in the project, including (a) a four-year longitudinal online survey, (b) Collegiate Learning Assessment Plus (CLA⁺), (c) secondary data analyses of the Student Feedback Questionnaire (SFQ) data for GUR subjects, (d) student focus groups and written qualitative evaluation, (e) teacher focus groups and written qualitative evaluation, (f) longitudinal case study, and (g) repertory grid test. This evaluation project has several distinctive features and strengths. Firstly, it adopted a mixed-method approach including both quantitative and qualitative methods. This is valuable since the different methodologies could help to evaluate a program from different approaches and could help to answer different evaluation questions. Their results could also be integrated and triangulated to form a deeper understanding of an evaluation question [14]. Second, even within either the quantitative or qualitative methodologies, different specific methods were adopted. For example, within quantitative methodology, both direct-approach evaluation (CLA⁺) and indirect-approach evaluation (longitudinal survey) were adopted to increase the validity of the research. Within the qualitative approach, focus groups with different stakeholders (students and teachers) were conducted to form a deeper understanding of the program from different stakeholders' perspectives.

How might the evaluation findings tell us whether the five desired graduate attributes have been attained? In this paper, the major findings based on the different evaluation strategies are presented and summarized. The findings are then integrated to answer the question of whether the desired graduate attributes have been successfully achieved.

Different Evaluation Studies in the Longitudinal Evaluation

The longitudinal online survey assessed the longitudinal development of students in the five desired graduate attributes of PolyU in their study of the new four-year curriculum and the GUR. Four hundred and thirty-four participants completed the questionnaire of all four academic years. Two control groups were added in the third academic year, comprising 300 students studying in previous three-year curriculum of PolyU and 300 students studying in a four-year curriculum in a comparable local university based on quota sampling. Four validated instruments were included in the survey, including measures of empathy, positive youth development, learning styles and student engagement [15, 16]. An alignment of different instruments with the five desired graduate attributes of PolyU is presented in Table 2. Findings revealed students' positive changes in four academic years in study of the PolyU four-year curriculum, particularly in the five desired graduate attributes of PolyU. PolyU four-year curriculum participants also performed better when compared to PolyU three-year curriculum participants and participants in four-year curriculum in a comparable local university [17-20].

Table 2. Alignments between longitudinal online survey scales and desired graduate attributes of PolyU

Desired Graduate Attributes	Instruments	Index
Problem Solving	CPYDS	Problem Solving
Critical Thinking	CPYDS	Critical Thinking
Lifelong Learning	CPYDS	Life-long Learning
	NSSE	Higher Order Learning
		Reflective and Integrative Learning
		Learning Strategies
		Quantitative Reasoning
Ethical Leadership	C-IRI	Empathy
	CPYDS	Ethical Leadership
		Self-leadership
Effective Communication	CPYDS	Social Competence
	NSSE	Collaborative Learning
		Discuss with Diverse Other

Note: CPYDS = Chinese Positive Youth Development Scale; C-IRI = Chinese Interpersonal Reactivity Index; NSSE = National Survey of Student Engagement.

Collegiate Learning Assessment Plus (CLA⁺)

Four rounds of CLA⁺ were conducted with four groups of students enrolled in the PolyU four-year curriculum, respectively, in four time points (i.e., before the start and near the end of the 2013-2014 and 2015-2016 academic years) [21]. The CLA⁺ is a standardized online test developed by U.S. Council for Aid to Education measuring an institution's contribution to students' development of problem solving, critical thinking and written communication skills [21]. Findings revealed that students in senior-year group performed significantly better than students in freshman-year and sophomore-year groups in almost all the competences tested by CLA⁺. A paper is under drafting on the findings [22].

Secondary Data Analyses of the Student Feedback Questionnaire (SFQ) Data

Students' subjective outcome evaluation of GUR was conducted through secondary analyses of Student Feedback Questionnaire data obtained in the four academic years. Results revealed that across the four academic years from 2012-2013 to 2015-2016, students had positive evaluation of the GUR subjects based on the general and specific indicators. Students' positive evaluation of some components such as LCR-English has even increased over the four academic years. Findings of some specific academic years have been published [23-28].

Student Focus Groups and Written Qualitative Evaluation

Qualitative evaluation based on student focus groups and written evaluation form was also conducted [29-33]. The focus groups were guided by a protocol asking about students' views about the rationale, teaching methods, implementation and benefits of the GUR. The qualitative evaluation form included students' descriptors to describe the GUR, and their memorable experiences and perceived benefits. Results based on thematic analyses suggested that students in different years had positive views of the GUR, with specific reference to its subject contents, teaching methods, implementation and perceived benefits.

Teacher Focus Groups and Written Qualitative Evaluation

Teachers teaching different GUR subjects were invited to participate in focus groups in four academic years from 2012-2013 to 2015-2016, and in written qualitative evaluation in 2013-2014 and 2014-2015 [34-38]. The teacher focus groups were guided by a protocol inquiring teachers' views of the rationale, subject content, pedagogy, and benefits of GUR subjects. The written qualitative evaluation form included teachers' descriptors of the GUR, and their perceived implementation, challenges, and benefits of the GUR. Results suggested teachers' generally positive perceptions of the GUR, with specific reference to its rationale, teaching and learning, and impacts on students, although few concerns were noted.

Other Evaluation Methods Incorporated (Longitudinal Individual Case Study and Repertory Grid Tests)

The longitudinal case study and repertory grid test were also incorporated in the study. The former traced 42 students' longitudinal development during their study of the four-year curriculum (including the GUR) from freshman to senior year. The latter assessed 100 stratified random sample of senior-year students in terms of their change in indicators of self-identity after the study of four-year curriculum. The longitudinal case study data indicated students' positive personal growth and development of PolyU desired graduate attributes after studying the GUR [39, 40]. The results of repertory grid test also suggested students' positive changes based on different indicators of self-identity. The related data analyses and paper writing are under way. Table 3 summarizes the papers in References section that have been published or under preparation for each evaluation component.

Integration of Findings with Reference to the Desired Graduate Attributes

This part presents the findings related to the development of students under the new four-year curriculum and the GUR at PolyU, with particular reference to the five desired graduate attributes (i.e., critical thinking, innovative problem solving, effective communication, ethical leadership and lifelong learning). For each attribute, results from different evaluation approaches were presented and integrated. Table 4 shows how different evaluation mechanisms provide evidence for the achievement of the five desired graduate attributes.

Table 3. Summary of papers published on the longitudinal evaluation project of the general university requirements (GUR) at PolyU

GUR evaluation component	Paper published (in reference section)
Four-year longitudinal online survey	16,17,18,19,20
Collegiate Learning Assessment Plus (CLA+)	21,22
Secondary analyses of Student Feedback Questionnaire (SFQ) data	23,24,25,26,27,28
Student focus group and qualitative evaluation	13,29,30,31,32
Teacher focus group and qualitative evaluation	34,35,36,37
Longitudinal case study	39,40
Overall evaluation	15,33,38

Table 4. Alignment of findings of different evaluation components with students' development in the five desired graduate attributes of PolyU

Evaluation Component	Critical Thinking	Innovative Problem Solving	Effective Communication	Ethical Leadership	Lifelong Learning
Four-year longitudinal survey	√	√	√	√	√
Collegiate Learning Assessment Plus (CLA+)	√	√	√		
Secondary analyses of Student Feedback Questionnaire (SFQ) data					
Student focus group and qualitative evaluation	√	√	√	√	√
Teacher focus group and qualitative evaluation	√	√	√	√	√
Longitudinal case study	√	√	√	√	√
Repertory grid test	√	√		√	

Critical Thinking

In the longitudinal online survey, students' ability in critical thinking was assessed by the Critical Thinking subscale of CPYDS. Results showed students' significantly higher ratings of Critical Thinking subscale in the academic year of 2015-2016 than in 2012-2013 and 2013-2014 [17]. Compared with control group 1, i.e., the students studying PolyU three-year curriculum, the experimental group (i.e., the students of PolyU four-year curriculum) scored significantly higher in critical thinking subscale [18], although no significant difference was found between experimental group and control group 2 (i.e., the students in the four-year curriculum in a comparable local university) [19]. Students' critical thinking ability was also

assessed by three subscales of CLA⁺, including scientific and quantitative reasoning, critical reading and evaluation, and critique an argument. Results revealed that senior-year group of students performed significantly better than sophomore-year group of students in all the three subscales indicating critical thinking [22]. Results also showed that the senior-year group of students scored significantly higher in all three subscales than the freshman group of students [22].

The qualitative data based on different methods including student and teacher focus groups, written qualitative evaluation, and longitudinal case study also consistently indicated students' improvements in critical thinking skills through studying different subjects in GUR in different years [13, 31, 32, 34, 35]. Qualitative data also indicated the important role of the interactive teaching and learning methods played in students' critical thinking development. Particularly, group projects and discussion contributed greatly to students' development of critical thinking through confronting them with different viewpoints of their peers [32, 35].

Innovative Problem Solving

Different evaluation data suggested students' improvements of problem solving ability after studying the four-year curriculum and the GUR at PolyU. Students' problem solving in the longitudinal survey was assessed by the Problem Solving subscale of CPYDS. Results demonstrated that students had higher ratings of Problem Solving subscale in their junior and senior years when compared with their freshmen and sophomore years [17]. Although the students of PolyU four-year curriculum performed similar to the students in the four-year curriculum of a comparable local university on problem solving subscale [19], they performed significantly better than the students in PolyU three-year curriculum [18]. Students' ability of problem solving was also measured by the analysis and problem solving subscale of CLA⁺, with the senior-year student group scoring significantly higher than both the sophomore and the freshman groups on analysis and problem solving subscale [22].

Focus group results suggested the positive impacts of the GUR to students' development of problem solving ability [34, 35, 39]. Particularly, the Service Learning subjects were perceived as much helpful to students' innovative problem solving, which provided students with opportunities to solve problems in natural social circumstance through a 40-hour community service practice. Both teachers and students perceived that many unexpected events occurring in service practices promoted students' ability to solve problems innovatively [35]. Some other teaching approaches in GUR such as hands-on workshop in freshman seminar subjects and field work in cluster area requirement subjects also trained students in problem solving ability [39].

Effective Communication

The GUR and the four-year curriculum successfully promoted students' effective communication competencies. Students' effective communication was firstly measured in the longitudinal survey by three subscales, including the Social Competence subscale of CPYDS, and the Collaborative Learning and Discuss with Diverse Other subscales of NSSE. Comparing students' performances in the four academic years, students' ratings of Collaborative Learning and Discuss with Diverse Other subscales in the academic years of 2014-2015 and 2015-2016 were significantly higher than those in 2012-2013 and 2013-2014, although their ratings of Social Competence subscale remained stable [17]. The PolyU four-year curriculum students also performed better than the PolyU three-year curriculum students

in collaborative learning and discuss with diverse other subscales, while no significant difference was found between their performance of social competence subscale [18]. The PolyU four-year curriculum students performed comparable to the students studying four-year curriculum in a comparable local university on all three subscales [19]. Students' competence in effective communication, particularly written communication, was also measured by two subscales of CLA⁺ (writing effectiveness and writing mechanics). Comparison of students' ratings between different groups showed that the senior-year group performed better than the sophomore group in writing mechanisms and the two groups had no significant difference in their ratings of writing effectiveness [22]. The senior-year group also performed better than the freshmen group in writing effectiveness, while the two groups performed similar in writing mechanisms [22].

Besides, focus group and written qualitative evaluation results in different academic years suggested that the students' development in written communication skills were effectively strengthened by students' study in language and communication requirements, particularly English-LCR subjects [30, 32, 34-36, 39]. Through English-LCR subjects, students were effectively taught how to integrate and critique different sources and viewpoints in writing academic essays, and how to structure academic articles and cite references [35, 36]. Some cluster area requirement subjects with English reading and writing requirements also effectively trained students' ability in effective written communication [36]. Some students perceived the cluster area requirement subjects with reading and writing requirements as highly useful because these subjects offered them opportunities to get individualized instructions from English tutors about their academic writing assignments [30, 32]. Besides, students' oral communication and public expression skills were promoted through studying in different group projects and group presentation tasks, which built up students' confidence in oral communication and increased their ability to communicate with people from different backgrounds and disciplines through group projects [30, 32, 35, 39].

Ethical Leadership

Students' ethical leadership was measured in the longitudinal survey by three subscales: Empathy subscale of C-IRI, and Ethical Leadership and Self-Leadership subscales of CPYDS. Results showed that students' rating of empathy in their sophomore year decreased when compared with their rating in freshmen year; their ratings of ethical leadership decreased in sophomore year but rebounded in senior year; and their rating of self-leadership in senior year was higher than in sophomore year [17]. The PolyU four-year curriculum students, i.e., experimental group, scored significantly higher in empathy and ethical leadership than the PolyU three-year curriculum students (i.e., control group 1), although the two groups performed comparable in self-leadership [18]. The experimental group and control group 2 (i.e., the students studying four-year curriculum in a comparable local university) performed similar in empathy, ethical leadership and self-leadership [19]. Qualitative evaluation results indicated students' improved understanding of leadership concepts and development of leadership skills through studying GUR subjects, particularly the leadership and intrapersonal development subjects. First, the leadership and intrapersonal development subjects, particularly the tomorrow's leaders subject, promoted students' understanding of leadership attributes, particularly concept of self-leadership [35, 36, 39]. Some students could be able to apply the leadership attributes learned in leadership subjects in their daily life in interpersonal relationship building [13, 39]. Besides the leadership

subjects, the service learning subjects cultivated some students' empathy and social responsibility, which are important components of ethical leadership [34-36]. Furthermore, different group project works in different GUR subjects created good platforms for students to practice their leadership skills [32].

Lifelong Learning

Different evaluation studies also suggested students' improvements in lifelong learning ability. Students' ability of lifelong learning was assessed by the lifelong learning subscale of CPYDS, and four subscales of NSSE, including higher-order learning, reflective and integrative learning, learning strategies, and quantitative reasoning in the longitudinal survey. Results showed that students' ratings of higher-order learning, reflective and integrative learning and quantitative reasoning in the academic years of 2013-2014 and 2014-2015 were significantly higher than their ratings in 2012-2013 and 2013-2014 [17]. Students' ratings of learning strategies in 2014-2015 and 2015-2016 were significantly higher than that in 2013-2014 [17]. The experimental group scored higher than the control group 1 on higher-order learning, reflective and integrative learning and learning strategies, while the two groups had no difference in their ratings of lifelong learning and quantitative reasoning [18]. The experimental group also performed better than control group 2 on learning strategies, while the two groups performed similar on lifelong learning, higher-order learning, reflective and integrative learning and quantitative reasoning [19]. These results generally suggested students' improvements in lifelong learning ability over their four-year study, particularly in higher-order learning, reflective and integrative learning, learning strategies and quantitative reasoning.

Qualitative evaluation findings were also positive, suggesting that the GUR was conducive to students' development in lifelong learning capacity. Perceived by students, some cluster area requirement subjects promoted their interests in learning some topics beyond their fields of specialized studies [30]. These students had intention to further study these topics if there were opportunities. The sports-training courses in HLS component also nurtured some students' interests in further learning and doing these sports, and developed in these students a notion of pursuing healthy lifestyle. In addition, some assessment methods such as written assignments adopted in many GUR subjects promoted students' ability of lifelong learning through facilitating students to search literature and accomplish their writing tasks independently [32].

DISCUSSION

This paper reported findings of a five-year longitudinal evaluation project on how the new four-year undergraduate curriculum and the "General University Requirements" (GUR) contributed to students' development on the five desired graduate attributes of The Hong Kong Polytechnic University (PolyU). Results from different evaluation mechanisms, including longitudinal online survey, collegiate learning assessment plus (CLA⁺), Student Feedback Questionnaires (SFQ), focus groups with students and teachers, written qualitative evaluation, and longitudinal case study, consistently suggested that the four-year curriculum

and the GUR were effective in promoting students' development in the five desired graduate attributes.

These findings have two general implications. Firstly, although the curriculum reform and the introduction of general education in higher education of Hong Kong are significant, fewer studies have been conducted to evaluate the effectiveness of these reform initiatives. Since general education was mainly a heritage of Western, especially American higher education, whether its curricular models adapt to Hong Kong context with a Chinese cultural heritage and a heritage of British model of higher education should be investigated. Actually, some scholars raised their worries about the adaptation of general education to the context of Hong Kong [11, 41]. They doubted the effects the new curriculum with a significant component of general education in Hong Kong higher education. The findings of the present evaluation study challenged these doubts by showing the effectiveness of the GUR curriculum and the new four-year curriculum of PolyU in cultivating students' desired graduate attributes of PolyU.

Secondly, findings of the present study indicated that teaching and learning design plays an important role in aligning general education with desired graduate attributes. Literature also suggested that active learning strategies such as group-based learning with authentic tasks, game-based learning, and written assignments are highly helpful in helping students to develop desired graduate attributes such as critical thinking and effective communication [42-44]. Scholars promoting general education movements in American higher education also advocated that general education reform should pay more attention to teaching and learning methods than focusing solely on curricular content of general education [45]. The findings of the present study are in line with the existing literature by showing that the active pedagogy adopted in GUR subjects was highly effective in promoting students' development of the desired graduate attributes.

The present study has several limitations. First, the longitudinal survey only included the control groups in one academic year (i.e., 2014-2015), which could not compare group effects over time. Second, since participants in control group 2 also studied a general education program in a comparable local university which might have similar effects as the GUR, the effects of PolyU new four-year curriculum comparing to the old three-year curriculum could not be fully tested by comparing the experimental group and control group 2. Third, the four groups of participants participating in four rounds of CLA⁺ were not the same participants, which also limited the interpretation of the results. Despite of these limitations, this present comprehensive evaluation research is pioneering in Hong Kong in evaluating the effectiveness of the new four-year curriculum and general education program of PolyU in promoting students' development in the five desired graduate attributes.

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Chapter 181

THE PERCEPTIONS OF TEACHERS OF THE NEW GENERAL EDUCATION CURRICULUM IN HONG KONG

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ABSTRACT

Through focus group interview, this chapter explored teachers' perceptions and experiences of the general university requirements (GUR) in the new four-year undergraduate degree program of The Hong Kong Polytechnic University in Hong Kong. A total of 52 colleagues involved in teaching and coordination work participated in focus group interviews. Eight focus group sessions were formed to understand the views of teachers on the eight GUR curriculum components. Results showed that teachers generally had positive views of subject content as well as student learning and engagement. Teachers also demonstrated deeper understanding of teaching with active involvement. Teachers also had gained multidisciplinary working experience through

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teaching GUR subjects. Teachers perceived their subjects and related teaching as beneficial to students' all-round development, particularly in communication, critical thinking, confidence and self-esteem.

INTRODUCTION

Teachers play a vital role in educational activities. Some scholars [1] depicted teachers as "change agents" of curriculum reforms. Gaff [2] argued that even the well-designed curriculum could not ensure student learning if there were no effective teachers. Empirical studies consistently suggested that teachers' attitudes and beliefs had significant influence on curriculum implementation. For example, teachers' positive attitudes towards curriculum content could facilitate curriculum implementation, and their beliefs about teaching could influence their teaching practices as well as student learning, motivation and achievement [3-5]. In addition, actual implementation of education reforms and effects of such reforms depend heavily on teachers since different teachers may interpret new policies differently due to different beliefs and experiences, student characteristics and working contexts [6].

With regard to general education in higher education, the role of teachers is particularly critical. In reviewing general education status in American higher education and advocating further reforms, Gaff [7] proposed that in addition to curriculum content, the teachers as one critical element had to be considered. Particularly, Gaff [7] suggested that it was imperative to examine general education teachers' motivation, barriers to their teaching, and their strategies for successful implementation of general education curriculum. French [8] argued that the role of teachers was particularly important in general education than in specialized education since students' motivation was lower in general education than in specialized education. Hence, teachers' art of teaching, their understanding of student needs and adoption of teaching strategies would be very important for engaging students in general education learning process.

Although the significant role of teachers in general education was recognized, there were fewer empirical studies conducted in this area. Gaff [9] observed that "when the revival of interest in general education began, attention focused almost exclusively on content" and "little attention was given to the teacher and strategies for teaching." A review of existing literature found that teachers' experience and views were only mentioned in a marginalized place in many reports and studies on general education reforms. Even within this limited literature, there were inconsistent findings. For example, Tobolowsky, Cox and Wagner [10] examined faculty's perceptions of freshmen seminar in a university in the United States. The freshmen seminar was designed to foster freshmen transition to university life. The content included time management, study strategies, academic integrity, university understanding, and career planning, etc. The survey found that through teaching the seminar, the majority of teachers perceived that they were more enjoying and engaged in teaching, understood more about student needs, and met more colleagues outside their own disciplines.

However, many other studies reported teachers' negative attitudes towards and experiences of general education courses and their frustrations in teaching these courses. For example, a study [11] on undergraduate curriculum reform in a renowned Chinese university to promote general education showed reluctance of faculty in teaching general education subjects. Many faculty members perceived teaching general education subjects as challenging

and time-consuming because they had less experience in teaching these subjects and the teaching was not helpful to their own research and promotion. Similarly, in many American universities, teaching staff of general education subjects was normally “borrowed” from specialized departments [12]. Therefore, these staff had low loyalty to and little concern about general education subjects and was unaccustomed to teaching these subjects [2, 12].

Similar observation was also reported by some scholars on recent curriculum reform in higher education in Hong Kong that transferred its three-year to four-year curriculum and developed a significant component of general education in new curriculum. For example, Hoshmand [13] argued that some academic staff in universities in Hong Kong perceived teaching general education subjects as time-consuming and worthless since they were more research-oriented and their promotion depended more on their research achievements. Also, since many faculty members were educated under the previous three-year specialized structure of undergraduate education in Hong Kong, they might have less understanding of general education and its related teaching. For example, Hoshmand [13] argued:

“the faculty (in Hong Kong higher education) has not experienced General Education in their undergraduate studies and has difficulty stepping out of their comfort zone to offer the courses that integrate knowledge across the disciplines. They also have a wrong assumption about the nature of the General Education courses. Often they think that a GE course is similar to an introductory course in a discipline. This alone is a major barrier to change.”

The above literature sheds light on how teachers perceive and experience general education. However, there are few empirical studies in this area. Also, although some studies explored teachers’ positive or negative perceptions, they did not reveal why teachers had related perceptions and what factors contributed to their perceptions. Furthermore, there were fewer studies that explored teachers’ perceptions and experiences in general education in a comprehensive manner. Finally, no study has to date been conducted to understand the views of teachers of general education within the context of an education reform.

Against the above background, the present study examined teachers’ perceptions and experiences of a new general education program, “General University Requirements” (GUR), in the new four-year undergraduate curriculum of Hong Kong Polytechnic University (PolyU) in Hong Kong. Since the 2012-2013 academic year, PolyU transformed its undergraduate degree program from three to four years. As an integrated part of the reform, the GUR was introduced as a significant general education component of the new four-year curriculum of PolyU. The GUR attempts to develop students in the five desired graduate attributes, including effective communication, critical thinking, innovative problem solving, lifelong learning, and ethical leadership. The GUR was formally implemented in the 2012-2013 academic year. It adopted a more active and interactive pedagogy. The curriculum had six major components, as introduced below.

- *Freshman seminar (FS: 3 credits)*: A FS subject is offered by each faculty/school to all freshmen enrolled in the faculty/school. FS introduces freshmen to their disciplines and potential majors. It also develops students’ entrepreneurship, higher-order thinking, and self-directed learning.
- *Leadership and intrapersonal development (LIPD: 3 credits)*: Two subjects are offered in LIPD component. They are “Tango! Managing self and others” (“Tango!”) for students in Faculty of Business, and “Tomorrow’s leaders” (TL) for students in

other faculties/schools. LIPD nurtures students' understanding of theories on inter- and intrapersonal qualities of leadership and develops their self-awareness and self-reflection skills.

- *Language and communication requirements (LCR: 9 credits)*: LCR includes English LCR (6 credits) and Chinese LCR (3 credits). LCR attempts to cultivate students' language and communication proficiencies in both Chinese and English.
- *Cluster area requirements (CAR: 12 credits)*: In CAR, each student is required to study at least four subjects, with each subject being selected from each of four cluster areas, namely "CAR A: Human nature, relations and development," "CAR B: Community, organization and globalization," "CAR C: History, culture and world views," and "CAR D: Science, technology and environment." Among the four subjects studied, three additional requirements should also be fulfilled. They are China studies requirements (CSR), English writing and reading requirements (EW/ER) and Chinese writing and reading requirements (CW/CR). CAR attempts to expand intellectual capacities of students beyond their majors and develop their written communication proficiencies in English and Chinese as well as understanding about China.
- *Service learning (SL: 3 credits)*: Each student is required to take one SL subject with a significant service component. SL attempts to help students apply academic knowledge into practice, help them reflect on their roles as professionals and citizens, and develop their empathy for people in need.
- *Healthy lifestyle (HLS: non-credit-bearing)*: In HLS, students need to complete four components of courses including introductory lecture, sports training/participation, e-learning, and wrap-up lecture. HLS attempts to help students to master important knowledge and skills contributing to healthy living and wellbeing.

In view of the important role of teachers in general education and the fact that there are few studies in this area, this study attempted to explore teachers' perceptions and experiences of the GUR subjects at PolyU. The study is meaningful not only for gaining knowledge of implementation of the GUR and its future improvement, but also for shedding light on teacher views of general education in the broad literature. The present study belongs to a comprehensive evaluation project of the GUR starting from the 2012-2013 academic year. Different evaluation components were implemented in the project, including objective outcome evaluation, subjective outcome evaluation, and qualitative evaluation. In qualitative evaluation, teacher focus groups and student focus groups were conducted in each academic year. This study is based on the teacher focus groups conducted in the 2014-2015 academic year.

OUR STUDY

Participants were 52 staff members who were involved in subject teaching or coordination in different components of the GUR curriculum in the 2014-2015 academic year. These staff members were recruited based on purposeful sampling through the nomination of program leaders or key teachers in different GUR components. These staff members participated in a focus group interview at the end of the second semester of the 2014-2015

academic year. Eight focus group sessions were conducted based on eight GUR curricular areas. These sessions included FS (n = 7), LIPD-TL (n = 8), LIPD-“Tango!” (n = 1), English LCR (n = 8), Chinese LCR (n = 8), CAR (n = 8), SL (n = 6), and HLS (n = 6). Since the subject “Tango!” only had two teaching staff, and one staff member was on leave during the focus group period, this session only had one participant. Each session was conducted by two experienced researchers. One served as the moderator and the other served as the observer. All the sessions lasted for one to two hours.

Focus Group Protocol

A focus group protocol was developed by the authors to guide the focus group interview. It included a set of guideline questions aiming to explore teachers’ perceptions and experiences of the GUR subjects they taught. The key questions included:

- What is your understanding about the GUR and its significance to PolyU students?
- Please describe the changes you have witnessed from the students attending your GUR subject.
- Could you suggest any particular component(s) of your GUR subject that is associated with the positive/negative feedback from your students?
- How would you comment the support, communication channel, and collaboration from your counterpart? To promote the effectiveness, what kinds of support would you suggest?
- In your perspective, what are the major challenges in the implementation and goal-alignment of the GUR curriculum?
- What is your perception of the alignment of your component of GUR subject with PolyU desired graduate attributes, and with intended learning outcomes of your GUR component?

All the focus group sessions were audiotaped and all audio files were fully transcribed into the texts. Method of framework analysis [14] in qualitative data analyses was adopted. Firstly, one researcher quickly read all the transcripts for twice to familiarize herself with the data and identify key ideas and important themes. The key ideas and major themes were then organized to form a thematic framework for further coding. Secondly, the researcher read all transcripts again to carefully code all data in detail under the thematic framework. During the coding process, the thematic framework was also revised based on the researcher’s enriched understanding of the data. Based on the coding, interpretations and explanations about the data were formed.

FINDINGS

Teachers generally developed a deep recognition and appreciation of the rationale underneath the design of different components of the GUR. For example, for the design of LCR component that offered different language subjects to students with different levels of

language proficiencies, LCR teachers developed deep understanding and recognition of the rationale of the design. This can be illustrated by one ELCR teacher's narratives below:

"One important difference is that ELC (English Language Center of PolyU which is responsible for offering the English LCR subjects) is now streaming students based on their DSE (The Hong Kong Diploma of Secondary Education) results. I teach one of the high-level (ELCR) courses to students with the DSE English exam score above grade 'five.' And I am totally impressed by their standard of English, sort of their native speakers' standard. So, I'm not actually teaching them English in terms of grammar. I'm teaching them 'persuasive communication,' which is the name of the course they haven't done before. So I think it is good to let higher level students to get something specially designed for them, which they didn't get in the old curriculum."

In some components such as CAR where teachers might have more freedom in designing their subjects, some teachers explored how to design their subjects to cater for the learning needs of students from other disciplines. For example, a teacher teaching a subject in science area of CAR component expressed:

"The subject I taught is *Chemistry in Everyday Living*. In case students had weak mathematical and physics knowledge backgrounds, I taught my subject in a simpler way, mainly focusing on developing students' appreciation of chemistry. ...The subject also had experimental classes. The students were very excited in these classes."

Some teachers consciously arranged their subject teaching around "hot topics or themes in real world" or themes that had immediate concern to students' life. Through this, the teachers intended to have students relate the knowledge they learned from the class closely with the outside world, as a teacher teaching a Chinese LCR subject expressed in the following way:

"For our Chinese LCR subjects, we base our teaching on some contexts that are related closely to the critical issues in current society. Some critical issues include issues related to Hong Kong medical insurance system and environmental protection. Based on these issues, we conduct some language training. In such a way, students would not only gain knowledge about Chinese language, but also relate the knowledge to the real world."

In some components, teachers developed a much richer understanding of the functions of their components than those set by the University. Teachers also wove their understanding into their subject design and teaching. For example, according to the guideline of the University, the aim of the Chinese LCR component was to enhance students' language proficiency in Chinese. However, the CLCR teachers understood the function of CLCR at a richer level. They perceived that Chinese subjects, if designed well, could not only foster students' language and communication competence but also cultivate their ability of critical thinking and problem solving. These teachers implemented this understanding in the subject design and implementation of CLCR. This can be illustrated by two CLCR teachers' narratives below:

"Actually our assessment methods are also diversified. We are not developing one approach of thinking but hope to have students to think issues from multiple perspectives. So we incorporate role play in assessment of our subjects. During the role play activity, students learn to deal with some problems. This would be helpful to students' critical thinking and problem solving."

“Many people may think the training of Chinese is not important in the university level. Actually, Chinese is most students’ first language. When these students are thinking, they are using Chinese. Hence, while the University set the goal of this component (CLCR) as language skill training, we think these subjects could achieve more outcomes, including communication, problem solving and critical thinking. Therefore, it seems that we are doing language training on the surface but in fact we are doing more. This is also the value of our subjects.”

Teachers’ narratives also indicated that for teachers in certain disciplines such as Chinese language, the GUR or general education served as an opportunity for them to re-claim the value and legitimacy of their disciplines in university community and in contemporary society.

Opportunities and Challenges in Teaching Interdisciplinary Subjects

Although teachers generally had positive views about rationale of GUR and its subject design, their views on Freshman seminar which incorporates knowledge from multiple disciplines and team-based teaching were diversified or even bi-polar.

For a few teachers, FS subject served as an opportunity for them to explore interdisciplinary teaching that they seldom experienced before. For example, in one faculty, in order to engage students who came from different disciplines of the faculty and develop students’ interdisciplinary understanding, the staff members of the faculty designed the FS subject content to center on common issues in real world to solve which multidisciplinary knowledge should be utilized. The staff members also incorporated innovative teaching and learning methods in the subject. This was mentioned by one teacher as below:

“Sometimes it’s a bit hard to pick a topic that of interest to every student because we have four departments [in our faculty] and we have a lot of students with different natures. So that’s why we try to pick a theme on environmental protection that is an issue and challenge that students will face when they finish their study and work as professionals. So that’s why in the first lecture what I do is to give them a general message about what is the environmental problem we encounter in construction industry. And then we have another three lecturers from other departments to talk about different things.”

Another staff member who was involved in designing the same FS subject in the same faculty talked about the incorporation of site visit as another important approach in the subject to engage students in interdisciplinary learning. He said:

“But the site visit is very good, right? Because like Disney, we can go there, and it can explain the construction from civil engineering, building management, and there are many hotels in the Disney, and then building services, LSGIS (land surveying and geo-informatics), and some sorts of very small parts. So by doing site visit, they...the students...even they come from different disciplines, understand what they will be and how they will be collaborating after graduation.”

However, for staff members from some other faculties, they designed and delivered the FS subjects in their faculties in a different approach that mainly invited teachers from each discipline to give introductory speeches on their respective disciplines. These staff members encountered a failure in the design and implementation. They observed lower engagement of students in their FS subjects because many students did not have much interest in understanding knowledge of other disciplines and could not perceive the linkage between other disciplines and their own disciplines. Defeated by this effect, staff members from these

faculties perceived that the University should fine-tune FS subject to make it more department-based rather than faculty-based.

Teaching Promoting Active Learning and Student Engagement

Teachers commonly viewed that students liked many active teaching and learning methods adopted in different GUR components, including group project, fieldtrip, and experiential learning. The reason perceived by teachers was that through these methods students learned more interactively and diversely. Students also gained “autonomy” and “initiative” in planning and directing their own learning. These all promoted students’ motivation in learning. For example, two teachers shared in the focus group respectively:

“So I think, interview they (students) like it, site visit they like it. I think group project they like it. You know, they are interacting with a different group, and many times they are not from homogenous group. [This is] quite different. [Students come from disciplines of] business, technology and designs. So they work together. ... I have to say [the learning is] more like a play, learning from a play.”

“(when the teacher was asked about whether students enjoyed the group work on interviewing successful people in different industries in the ‘Tango!’ subject) Yes, they do, because they are actually getting their full freedom, you know, of choosing their own topic, of choosing the person to interview, of choosing the business they interview. So we suggest them that for example if you study logistics and maritime, maybe [it] would be good to interview someone from this area, from this business you want to enter anyways. You know, if you want to be this person, we might want to know what it takes to take this position. And so I think some of them put this assignment through seriously, then they benefit a lot from that.”

Some other teachers teaching SL subjects observed their students’ attitude changed from “not enjoyed” to “enjoyed” in studying SL subjects. They thought that SL subjects made students feel that they were capable of “doing something to the society” and developed students’ “sense of achievement and sense of meaning” through learning. For example, a teacher teaching a SL subject shared:

“Based on our observations of students, we all agree that students enjoy very much the service process. However, at the very beginning of the subject, a number of students were having great reluctance. They probably felt ‘I was forced to come’... Then when it came to the later stage of the subject, they might feel ‘well, I could make some change.’ So they were enjoying. I think we could all feel that in the later stage students might have realized what they were doing, such as ‘I have helped people’, even though they were much unwilling at the very beginning. So we changed their minds and made them enjoy.”

In addition to teachers’ perceptions of the impact of active teaching and learning on students, a few GUR teachers were going deeper to have talked about their deep teaching philosophy and how they implemented this philosophy in teaching practice. In these teachers’ philosophy, teachers and students were equal in the learning process and they worked together to construct students’ learning. Therefore, these teachers supported very much the active learning approach and implemented this approach in their teaching. This can be illustrated by the following two narratives:

“Um, I hope that they (students) become overall much more open, because I noticed many students... because we especially have most first year and second year students...they come in right from secondary schools and have the attitude that teacher is the big hierarchical figure that they cannot question; and they can just sit there silently listening and looking, [but] not disturbing. And I am trying to break through this [kind of]

thinking, because I am telling them that, ‘You know, we are on the same level. If I say something that you don’t agree with, you need to tell me. You know, you need to ask questions.’”

“In each term, I would bring students out to do field work. Sometimes we went to museums. Sometimes I watched movies and chatted with students. From their feedbacks, students said the fieldwork made them learn a lot, read more books, and know more things. ... Even in the class, I would also ask them questions every ten or fifteen minutes. This contact with teacher is very important. Through this, I want to have them be more confident. Many students thought that they could find answers through the Internet. However, the interaction between students and between students and teachers would be something beneficial to their whole life.”

While teachers commonly observed students’ deep engagement and active learning in GUR curriculum, they also expressed that there were two factors hindering students’ engagement. The first factor was students’ utilitarian attitudes towards their university study, as elaborated by one teacher that “For some students, they were very ‘strategic’ in their university study. When they saw that their four-year curriculum had so many requirements, they only wanted to take, take, take, and to get these subjects done as fast as possible.” Students’ less serious or indifferent attitudes towards their GUR study had defeated some teachers’ passion to teach GUR subjects.

The other factor was that students were “too busy” under the new four-year curriculum structure. This made some students had no time and energy to study their GUR subjects carefully and attentively, as expressed by one teacher in the following way:

“The situation I have seen was this: for these students enrolled in the new four-year curriculum ... the thirteen-week long semester course would be very harsh and they also need to take CAR subjects. So they made themselves very busy. So they had no choice but to cope with these subjects hastily. So instead, I feel that I sympathize with them.”

Challenging but Joyful Inter- and Intra-Disciplinary Collaboration

The teaching in the GUR provided opportunities and joyful experiences for multiple kinds and levels of collaboration among teachers, in a disciplinary and interdisciplinary manner. This was generally valued and appreciated by teachers for providing opportunities for them to extend their horizons. For example, in coordinating FS subject teaching in some faculties, the academic staff developed feelings that although coordinating staff members from different disciplines to collectively teach FS subject was quite a challenging task, the process gave them valuable and joyful interdisciplinary work opportunities and experiences. This was shared by one staff member below:

“I am a coordinator. I don’t teach the Freshmen Seminar. I coordinate all the tutors, all the departmental representatives (teaching FS subject). I think this kind of Freshmen Seminar is quite, in the very beginning is very challenging because it is quite diverse. We have to cooperate among different departments, and chase after everybody on proposing [teaching] project and schedule, whatever. But then it turns out that it is quite joyful experience, because I have the chance to mix with other departments’ colleagues. Otherwise I would never work with them, even in the same faculty. I know more people at least.”

In addition to gaining interdisciplinary working experience, the teaching in the same GUR component promoted some teachers’ interaction and mutual learning with their fellow colleagues within the same department. For example, one teacher in ELCR and another teacher in LIPD component noted respectively:

“There is one good thing about all (ELCR) subjects actually. [It] is that, um, like I taught PEUS (one ELCR subject) and you taught AEUS (another ELCR subject), and then, there is an area we call it the ‘teacher area’ where we have lots of notes and supplementary materials that we can use. And they are developed and contributed by colleagues voluntarily and then they are all good stuff.”

“(One LIPD subject teacher was talking about another senior colleague teaching the same LIPD subject) Oh, it is really great, really great. She is a great professor. So what we are doing is that we are so responsible for the lectures. But she is always asking me for some inputs or having any comments or suggestions. She is always willing to actually incorporate them in the whole material. And for the tutorials, actually she gives me ‘green light’ to do almost anything. Actually in the seven semesters what we did was that I was more or less developing the contents and then she would just follow my suit. So I found it very very very good.”

Positive but Belated Effects on Students’ Development of Competences

Teachers perceived that their teaching in GUR has promoted students’ positive development in different skills and competences. The first competence was effective communication. For example, some teachers from CAR, ELCR and LIPD components perceived that through their subject teaching and paper writing assessment, they observed their students’ increased confidence and self-esteem in English writing skills, as well as a strong sense of achievement in academic writing. This can be illustrated by the following two narratives:

“For the writing requirement, we do see improvements in confidence, and that was what students told us during the focus group meetings. So I can’t comment on the improvement in language but I think they are more confident to tackle a bigger piece of writing. So, I think that is quite important.”

“Term paper writing is a very good training. Particularly for students in some disciplines, which did not have much writing tasks, they said ‘wow, this is the first time that I have written so many things.’ Particularly for some students upgraded from Associate Degrees, they directly felt ‘it is so good to do this.’ After doing this, they even did not care about their grades. They felt ‘oh, I have achieved something.’ Their self-esteem has been improved a lot and they would not be afraid of writing.”

In addition, there were teachers who consciously promoted frequent group discussions or free expressions of their students in classes. They observed students’ improved confidence in presenting ideas in public through these methods. This can be illustrated by the following narrative of a teacher:

“After this course, I collected some feedbacks from our students. They commonly reflected that they had become bolder in public expression because of the many discussions in tutorial sessions. Maybe in some faculties such as business, there were constant group discussions or presentations. However, for students in department of engineering or other disciplines, it might be hard for them to express their ideas in public. At the very beginning of this subject when they did not know each other, they were unwilling to speak. But I used a lot of methods to evoke their expression, which made them feel that they became more confident in public speaking after they completed this subject.”

Apart from the above-mentioned skills, teachers perceived that some of their students gained improvements in their higher-order thinking ability, also through the active learning practices. For example, one teacher teaching a LIPD subject perceived that her subject promoted students’ multi-perspective and critical thinking through peer influence fostered by group discussion and peer sharing in the classes:

“One point I want to add is that students developed multi-perspectives, because when they were doing some sharing, they found that their peers had different stories. Then they would refer to the experiences of their peers, whose effect was bigger than what we have told them. So the peer influence is more significant, which made them have more multi-perspectives and critical thinking such as ‘what is it exactly? In the moment, am I inside the box? Or could I think out of the box?’ So they gained many experiences from peer learning.”

Furthermore, some teachers believed that the impacts of individual GUR subject existed but might not be visible in a short time. They believed that each GUR subject served as a piece of an integrated whole to contribute to students’ holistic development. Some teachers depicted the function of the GUR as “sowing a seed,” while others perceived that all GUR subjects, together with students’ other educational experiences such as internship, and students’ life experience, served as a whole to shape students’ all-round development at PolyU.

DISCUSSION

The present study is among the few to explore teachers’ views and experiences about general education curriculum in higher education settings, particularly in contexts of Hong Kong. In view of important roles that teachers play in general education, this study could add significant contribution to the existing limited literature on teachers’ perspectives of general education.

Several major observations could be generated from the findings. First, teachers teaching different subjects in GUR generally supported the rationale and subject design of their respective GUR components. Some teachers even consciously designed their subject contents and teaching to be around important issues in contemporary society, to promote interdisciplinary learning, and to meet student needs better. This demonstrated teachers’ deep understanding of and engagement in general education teaching. This observation challenged part of the existing literature that suggested teachers’ lower engagement in general education teaching [13, 15]. This might be explained by the application- and practice-oriented culture of PolyU. Newton [15] argued that in institutions that had a more entrepreneurial-oriented culture and whose mission was more sensitive to outside needs, faculties and general education courses might be more responsive to students’ needs and more influenced by students’ aspirations. A practical-oriented culture in PolyU might have made teachers more sensitive to changing requirements of the society and student needs; and therefore more devoted to general education teaching and subject design that were deemed important for contemporary society. The finding was also in line with the previous studies based on teacher focus groups and qualitative evaluation, which showed that teachers of different GUR subjects generally understood and supported the rationales of the GUR [16, 17].

Secondly, teachers commonly perceived that the GUR subjects with a variety of active teaching and learning methods such as service learning, group project, and writing assignment were effective to engage students in deep and active learning. Not only this, some teachers consciously designed their subject content and teaching based on their educational philosophy to promote students’ active, interactive, and interdisciplinary learning. The views and actions of teachers also indicated GUR teachers’ deeper understanding of general education and active participation in teaching and learning, which challenged the current mainstream of

literature suggesting that most teachers were lack of experience and enthusiasm in general education [2, 11-13].

Thirdly, some teachers gained quite valuable interdisciplinary working experiences from teaching the GUR subjects. The GUR teaching and subject coordination in some subjects offered teachers new opportunities to work with fellow colleagues outside of their own disciplines. The finding suggested that teachers appreciated and valued these “fence-breaking” experiences. This finding supported the current limited literature suggesting that some general education subjects such as first-year seminar promoted professional partnership among teaching staff across different disciplines [18].

Fourthly, teachers perceived positive impacts of the GUR on the holistic development of students. These impacts included the development of students’ sense of achievements, confidence and their increased self-esteem. They also included students’ improvements in oral and written communication, and critical thinking skills. Teachers perceived that one major factor contributing to students’ positive change was the active teaching and learning methods adopted. This was supported by the literature that teachers’ instructions promoting active and interactive learning could foster students’ growth in important competences such as thinking, communication, problem solving, cognitive skills, etc. [19, 20]. These views are also consistent with the findings of other evaluation studies of the GUR [21, 22].

Furthermore, challenges in teachers’ teaching of the GUR subjects were also identified. One major challenge was the design and teaching of subjects with an interdisciplinary nature such as FS subject. One major reason was that many staff members were educated under the previous British structure of higher education that stressed early specialization and strict division of academic disciplines. They may get less chance to experience interdisciplinary teaching and learning [13]. Meanwhile, teaching interdisciplinary subjects were also a world-wide challenge in general education since the over-division of knowledge and disciplines in modern universities greatly hindered this kind of teaching and it was more and more difficult to find interconnections and common understanding among different disciplines. Another challenge was some students’ unserious and utilitarian attitude towards their study in GUR. This phenomenon has also been noted by the literature [15, 23], which suggested that some students viewed general education requirements as obstacles to overcome since they wanted to focus more on their major studies. Findings from the present study further enriched the existing literature by showing that students’ utilitarian attitudes towards their GUR study might be partly caused by their increasingly packing undergraduate study in contemporary society.

Despite the challenges, the present study in general suggested teachers’ overall positive perceptions and experiences of the general education program in the new four-year curriculum of PolyU. The findings are also consistent with the existing literature [24-26]. In view of the shortage of scientific literature in this area, the present study contributed significantly to literature on teachers’ views and experiences of general education in Hong Kong contexts.

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Chapter 182

THE WELL-BEING OF UNIVERSITY STUDENTS IN HONG KONG

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ABSTRACT

The general university requirements (GUR) at The Hong Kong Polytechnic University (PolyU) is an integral part of the new 4-year undergraduate curriculum. To evaluate GUR, a longitudinal case study involving 42 cases from different faculties/schools was conducted, with several interviews conducted with the informants over time. The present article is to report the findings of the second year evaluation. Three major observations on students' views about the effectiveness of GUR study were generated from the study, including 1) broadened horizons; 2) increased awareness of the connection between GUR study and all-round development and 3) urge of linking GUR components with one's profession. The longitudinal case study findings suggest that students generally had fruitful learning experiences in GUR study. This study helps to paint a more complete picture of students' views toward GUR and their personal development.

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INTRODUCTION

University students' lives are becoming increasingly pressurized due to higher parental and societal expectations as well as rigorous educational changes or reforms in Western and Asian countries [1-3]. The major stresses for university students are commonly related to academic, relationship and financial difficulties [4]. The onset of psychological distress often upsets the fulfillment of different developmental and educational needs. The growing of psychological disturbance amongst students in higher education has called for concern of the scholars and healthcare professionals and a body of research investigating university students' psychological well-being has increased in recent decades [1, 2, 4]. Although there is an increasing concern for university students' development in the higher education fields, one under-researched area is to examine the major transition from their high school to higher education and how the well-being of university students' changes throughout the years in the university [2, 4]. Hence, studies on how universities assist students to adapt to the higher education and longitudinal research on the temporal changes of students' holistic development and their well-being are indispensable.

Given the challenges of globalization and international competitions in the new century, numerous educational reforms and initiatives have been carried out in the Asia-Pacific Region [5] including Hong Kong. In the past two decades, there have been "large-scale changes in nearly every key aspect" of the education system in Hong Kong [5, p.7]. One notable change is to change the senior secondary education and higher education system from the existing British system (3 years of junior secondary +2 years of senior secondary +2 years of matriculation +3 years of university) [3 + 2 + 2 + 3] to a new academic structure (3 years of junior secondary +3 years of senior secondary +4 years of university) [3 + 3 + 4], known as the "3-3-4 reforms". The "3-3-4 reforms" are intended to promote the future competitiveness of Hong Kong university graduates in the global knowledge economy and align "Hong Kong's educational pipeline with those in the Chinese mainland, the United States and the European Union" [3]. However, entry to university "one year younger" in the new academic structure has aroused concerns regarding students' transition from secondary school to the higher education and institutions have focused their efforts on designing the first-year curriculum to assist students to have a smoother transition [6].

Although the 3-3-4 reforms imposed much pressure on teachers and students of the secondary schools, the reforms were perceived as "an opportunity to grow" with numerous new educational initiatives in the higher education in Hong Kong [3]. The previous three-year undergraduate degree program exclusively focusing on disciplinary-specific training is changed to a four-year undergraduate degree program with the addition of a substantial component of nonspecialized or general education. The introduction of the new academic structure with the one-year expansion of higher education leads university administrators, teachers and scholars to explore the reinvention of undergraduate education in Hong Kong [3]. This reinvention is not limited to the curricular redevelopment. In fact, holistic development, including the expansion of different learning experiences such as out-of-classroom learning experiences and service-learning opportunities, is emphasized as well. The University Grants Committee [7] asserted in their official webpage that having an additional undergraduate year will "enable students to have more time and space to build a broader knowledge base and a more solid foundation for whole-person development" (paragraph 2).

This openness challenges the long-held belief of “academic excellence surpasses other things” initiates the establishment of general education in Hong Kong [8].

The advocacy of general education in the higher education setting echoes with the emphasis on students’ “lifelong learning” and “all-round development” in the education reforms [8]. In addition, the establishment of general education in higher education setting strikes a right balance between the breadth and depth of different programs and help students “develop a sense of integrity, positive attitude, a broad vision and important generic skills” [9]. Most importantly, general education could provide the freshmen opportunity to map out their own study paths to suit their interests and aspirations. This flexible and student-centered education helps nurture students’ whole-person development, enrich their undergraduate learning experience and foster their well-being in general.

Echoing the comprehensive curriculum reform carrying out in higher education in Hong Kong, the eight public higher education institutions in Hong Kong have all extended their undergraduate degree program from three years to four years, mandated by the University Grants Committee (UGC) since the 2012-13 academic year. With this implementation, each institution developed its new four-year curriculum by adding a significant general education component. Among these universities, one remarkable case was The Hong Kong Polytechnic University (PolyU). Since 2012-2013, PolyU implemented a new general education curriculum, named “general university requirements” (GUR) as an integral and significant part of its new four-year undergraduate degree program. The objective of GUR is, in combination with students’ specialized education, to provide an all-round education to all PolyU students, with a particular focus on nurturing them on five desired graduate attributes, including effective communication, critical thinking, problem-solving, lifelong learning and ethical leadership. The nurturance of these attributes is facilitated by different GUR requirements including leadership and intrapersonal development requirement, cluster area requirements, freshman seminar, service-learning requirement, language and Communication requirements, and healthy lifestyle.

To evaluate the effectiveness of the GUR, a five-year longitudinal evaluation project has been conducted since the inception of the new 4-year undergraduate curriculum in the academic year 2012-2013. Different quantitative and qualitative evaluative components have been carried out in evaluating the implementation and effectiveness of the GUR. One of the examples is the longitudinal study with 4 waves of data to investigate how the university students grow with the assistance of the GUR in the researched university [10]. The study has revealed significant changes in most well-being indicators over time.

Although quantitative studies are helpful, they may not capture the inner experiences of the students. The present study is one of the qualitative evaluation studies of the project. This study attempted to investigate the effects of general education on student development in the Hong Kong context. It helps to broaden readers’ understanding of the association between general education and freshmen development, and factors contributing to this association. A longitudinal case study was adopted as one of the evaluative methods in the present project. Case study is one of the most common research methodologies employed in educational research [11, 12]. Most of the scholars reached the consensus that a “case” should be the phenomena happening in the “bounded system” where researcher’s concern, interests and hypotheses might rest upon [12]. With such bounded systems, researcher aims to “uncover the interaction of significant factors characteristic of the phenomenon” [13]. “Case study” is specifically appropriate for the present study where the researchers attempted to study a

single case (The Hong Kong Polytechnic University) and the newly implemented general education curriculum named “GUR requirements”. In addition, how freshmen perceive the assistance of GUR in their transitional stage from secondary schooling to the university life is what Shaw [14, p.2] suggested that researchers should focus on “particular groups of people confront[ing] specific problems”. Although the researchers are from the researched university, the employment of case study allows the researchers to examine the relationship between “what was known” and “what previous unknown” and leads to a “rethinking of the phenomenon” [15]. Concrete and contextual insights could be drawn from this case study with researchers’ resonations with their own experiences rooted in the researched university.

Regarding utilizing case study as an evaluation method in research, Guba and Lincoln [16] have concluded that case study is the best reporting form for evaluations. Case study can at its best in providing thick and grounded description and is “holistic and lifelike” [17]. The case study not only allows the researchers to revisit the contexts they have been situating, but also enables readers to bring in their own experiences and understanding which lead to “generalization when new data for the case are added to old data” to thicken the description of the understanding [15]. As the participants are freshmen of the researched university, the students can add on their own experiences while the researchers were conducting the interviews. This addition has facilitated researchers to investigate the differences of views and suggest how these influences have influenced the understanding and perception of the assistance of GUR.

In the present study, a group of students (“cases”) were followed up by researchers on their personal growth starting from the freshman to graduation year. This would help trace the changes and development of individual students throughout their university lives and further understand students’ voiced views on their GUR study in greater details. The present study denotes some of the general observations based on researchers’ first-year following up with the freshmen.

OUR STUDY

Purposive sampling was adopted in the case selections. A total of 71 cases from different faculties or schools were recruited from participants of student focus groups held in the academic year of 2012-2013. The students shared their general impressions on their first-semester experience of taking some of the GUR subjects in the focused group interview. These students were invited to participate in the present study of having the longitudinal case study in the form of in-depth interviews. In the present study, the authors report the findings of the second-year longitudinal case study. After the initial contacts in the first year (71 cases), 42 actively engaged cases (59.2%) who maintained regular contacts with the researchers and 10 re-activated cases who had one or two meetings with the researchers during the past year. The remaining 19 student cases (26.8%) showed no interests in joining the study and did not respond to the several rounds of invitations by the researchers. These cases have now been deleted from the longitudinal study. At the beginning and the end of the 2013-2014 academic year, researchers conducted individual interviews for those 42 actively engaged cases using an interview guide developed by the research team. In addition to the two individual interviews each year, informal meetings with the student participants were

held by the researchers in each semester. Students were invited to share their university experiences, challenges encountered, and personal gains during the semester with the researchers in a more relaxing milieu.

Regarding the recruitment of researchers, eight researchers from the Department of Applied Social Sciences of the researched university started to follow the student cases commencing on the 2013-14 academic year. Most of the researchers had experience in teaching the GUR subjects. This shared experience constituted the common language between the researchers and the students. This “common language” assists the researchers to better understand students’ sharing during the interviews and such an empathic understanding will hence foster the students’ trust in sharing their own experiences in the interviews reciprocally. The trusting relationship between the students and researchers reinforces the process of thickening the data [11]. Each researcher was responsible for seven to eight cases. The constant encounters between the researcher and students assist the researchers to better capture the deep meaning of experiences in students’ own words in the form of individual in-depth interviews [18]. The researchers act as the “miners” and “travelers” in the interviewing process to unearth the meanings initiated by the students and wander together with the students to “the unknown terrain” and co-construct the “new knowledge” with more interactive involvements in the interviewing process [19, p. 48]. With the mining and traveling between the researchers and students, the substance of the interchanges is constructed and thus the meaning-making process could be thickened.

Instrument

A semi-structured interview guide developed by the authors was adopted in the study to explore students’ views and experiences about the GUR and their university study in general. The interview guide comprised two major categories: students’ experiences in GUR in relation to personal growth and the development of five graduate attributes of PolyU (including critical thinker; effective communicator; life-long learner; problem-solver and ethical leader), and students’ perceptions and expectations of their university lives. The inclusion of students from different faculties and schools was intended to gauge students’ perceptions on GUR with reference to their professional disciplinary training. This arrangement could help facilitate the students to have some “debates” between their established internal frame of reference upon disciplinary professionalism and their perceptions on the GUR. These debates could further facilitate the establishment of a “framework for discussion” in relating their experiences in learning the GUR during the interviews [11].

The researchers were allowed to change the sequence or wording of these questions during their interview process. The questions in the interview guide were listed as below:

1. Apart from the knowledge in your major (disciplinary specific study), what do you think an undergraduate student should learn in his/her undergraduate years? What qualities should a university student develop during their undergraduate study?
2. Do you know the five desirable attributes (critical thinking, effective communication, innovative problem solving, lifelong learning, and ethical leadership) of a PolyU

graduate? What is your understanding of these attributes (e.g., perceptions and importance)?

3. Do you feel that you have grown or become more mature in terms of the desirable attributes in the past semester/academic year? If yes, please let us know more about the experiences?
4. In retrospect, do you think the GUR subjects have helped you to develop the ideal PolyU attributes? Have you applied what you have learned in GUR subjects in your life?
5. Do you have any plans/goals for the rest of your university life? How may any GUR subjects or other resources the university provides help you achieve your goals?

The audio recordings of all the interviews were fully transcribed into texts. The method of thematic analysis was used to analyze and code the data to better understand the complexity and richness of the case. Two part-time research assistants with Master degrees and one postgraduate student pursuing a Master degree coded different parts of the data into different themes under the careful instructions and supervisions of the authors. During the coding process, the authors met with all coders twice to provide feedbacks on the coders' partial coding work. After the coding, all the codes were combined together.

Based on the interviews, each interviewer was invited to write a one-page summary based on their observations during the interviews and the informal meetings with students. These summaries are served as "complementary sources" to understand the researchers' views on their comprehension of students' sharing in the interviews. The use of researchers' summaries helps gauge the "factors normally hidden" and "idiosyncratic variables" that interviews might not reach [20]. The "hidden" elements revealed in the researchers' summaries could help thicken the interpretations of data obtained in the interviews. The summaries were read through and analyzed by researchers from the research team.

DISCUSSION

Several general observations were derived from the researchers' summaries on student development and their views towards GUR study based on the transcriptions. First, most researchers mentioned that they have developed trusting and reciprocal relationships with their case students which were beneficial to students' self-disclosure of their views on GUR study and university life. Second, three major observations on students' views about the effectiveness of GUR study were generated. These included 1) broadened horizons, 2) increased awareness of the connection between GUR study and all-round development, and 3) urge for linking GUR Components with one's profession.

Trusting and Reciprocal Relationships

Researchers have agreed that trusting and reciprocal relationships had been established through the constant encounters or informal meetings with the students. It is believed that the relationship helps college students better adapt to the life as a freshman, and most

importantly, the researchers' understanding and self-disclosure in the process support its beneficial role on students' learning outcomes [21]. One of the researchers stated the impact of empathic understanding and self-disclosure on her student case in her summary:

From the interviews, I witnessed the personal growth of my students after taking these experiential and diversified courses. I felt their enthusiasm and excitement on learning. Meanwhile, a closeness relationship was established between us. When listening to their sharing and thoughts (e.g., memorable service learning experience, academic study difficulties and personal issues), I also shared my thoughts and feelings with them (e.g., difficulties and challenges that I faced in my freshman years of college).

College students' level of strain was generally highest during Semester 1 in their freshman year. This period is predominately an anxiety-provoking time for college students [2]. Although the researchers approached a limited number of students compared to the entire student population, the timely support and empathic understanding from the researchers led students to their awareness of "personal growth" and helped lighten their anxiety in their first year of study in the university. In addition, this connection between the researchers and the students fostered human spirituality. Spirituality has been demonstrated to be uniquely and meaningfully associated with university students' psychological health [1].

Broadened Horizons

Students acknowledged that GUR subjects provided them with opportunities to understand knowledge beyond their own disciplines. Quite a number of researchers reported that the students were exposed to domains that "they have never seen" or "they seldom have experienced before". Learning experiences in GUR study also promoted students' "openness" to new things and challenged their preoccupations. For example, while some students initially perceived GUR subjects as simply "mandatory" to fulfill for graduation or "not as useful as the major subjects", these misunderstandings and preoccupations were quashed after the students had immersed themselves in learning these subjects. Students in different interviews noted that they were "more aware of the importance of service and learning" after taking the SL subjects; they also understood that "leadership actually relates to personal qualities and individual development" after studying LIPD subjects.

For the course "Tomorrow's Leaders", it is not about how to lead others but leading oneself, that is "self-leadership". That is why we have to behave well and be the role-model of others.

I am a passive person and usually listen to others' commands. I am not an in-born leader. I love to be in the supporting role...this is my personality and I might not be that brave to be the leader.... But I would like to learn more about the concepts and skills in the course to see if I could try later in my life.

Most students also reported that CAR subjects "exposed them to a new world". These experiences encouraged students to view things from different perspectives and be aware of one's preoccupations. From the researchers' reports, students have developed a more reflective attitude toward their lives through multiple reflective activities in GUR classes (e.g., LIPD subjects like "Tomorrow's Leaders" and SL subjects). Similar point of views is found in students' interviews.

When a decision is made, I will think of the reasons of making that decision and its applicability on the problems. When I am willing to reflect upon what has happened, I have learnt a lot from a newer perspective.

I will always ask myself “why did I fail this time?” and the disappointment generated will be lingered on for a while. But I think time is usually too short for happiness. Sufferings make one grow. I will reflect upon the sufferings and think of ways to improve.

Students’ responses also assured the importance of experiential learning adopted in most GUR subjects. The focus of the experiential learning is not just the experience itself but the reflections on the experiences which are instrumental to personal growth. The interview process has granted students’ opportunities to reflect upon their first-year learning experiences as well. Some students have expressed their appreciations for the researchers to have offered them a chance to “talk over” and “explore” their ways of thinking and understanding of their new academic lives, with the assistance of the general education GUR in the university setting.

Increased Awareness of Connection between GUR Study and All-Round Development

Students’ awareness of the importance of GUR study in helping their personal development has increased. Researchers learned from the cases that students enjoyed the interactive and collaborative learning activities conducted in most GUR subjects and perceived such teaching and learning methods to have helped them step out of their comfort zone and polish their social and interpersonal skills. The strengthening of students’ sense of connectedness and thus their optimism has enhanced students’ well-being and “feelings of relief, happiness, perceived social support, and [thus] quality of life” [1]. Other skills such as critical thinking, problem-solving, and leadership were also taught and practiced in GUR study, which echoed the desirable graduate attributes defined by PolyU. Students believed that these skills were indispensable for their all-round development thus enabling them to become competent professionals in the future.

Usually most of us would only encounter friends from our own discipline. Certainly, knowing friends from our own discipline will help me build a future network and gain some help for the professional examination. But we should extend our social circle. Studying GUR could help extend my social circle and have my social network extended.

We should know more than our own disciplinary knowledge. We should learn knowledge from other disciplines. And the learning should not be limited to the “present moment”. It is life-long learning that we could learn after graduation.

On the other hand, researchers reported that several students knew less of how the “desired graduate attributes” of PolyU could be developed through the general education course, although these attributes were yet subtly and progressively developed through their learning experiences. This indicates that more efforts are warranted to help students know more explicitly what the expectations of the University are and the importance of holistic development in terms of how these expectations relate to one’s professional and personal growth.

Urge for Linking GUR Components with One's Profession

Researchers reported that although the students in the present study agreed that the GUR components have provided them with new learning experiences, they were not able to clearly identify the linkage of different GUR components with their disciplines and profession. The aim of providing general education in higher education settings is to offer students another platform for exploring and developing students' various competencies and skills, and to have "major transformation of both faculty and student orientations toward the learning process" [22]. PolyU has her own strong tradition in making knowledge into practice and it is understandable for the students' urge for linking up what they have learned in the University to their professions. Judging from the students' responses, there seems to be a gap between University's rationale for general education and students' understanding of the aim of general education.

At first, what I understand of GUR is to choose [the subjects] we like or are interested in. This is to equip ourselves with different talents and thus to develop ourselves. But it seems that not every university student understands the importance of GUR. I think this is a problem. The design of the GUR is nice and helpful for our growth. It is sad to know that we do not understand its rationale well.

The students were aware of the "problem" of not understanding the rationale of the general education offered. They felt "sad" about not being able to understand how the general education assists their personal discovery and growth in their freshman year. With such gap and insufficient understanding of the purpose of general education, such "urge" might hinder students' integration of their learning experience with their personal growth. While it takes time for students to understand the meaning and importance of general education to their professional development, more opportunities for reflecting upon the purposes and meaning of learning the GUR components should be given to students during their learning experiences in the GUR. Even though the case students may have accomplished their freshman year, they are still experiencing the initial stage of university life. With maturity in their professional and personal growth to be expected in later years, the relevance of what they have learned in their disciplines and the GUR components to their own life development may be gradually seen.

There are several strengths of utilizing case study as the major research methodology in the present study. First, the focus on freshmen perspective could assist the researchers to focus on freshmen's perceptions upon how the GUR could have been maximized in the fixed period of time available in case study [23]. Second, the present study gave the students an avenue to share their perceptions and understanding of the general education implemented in the researched university. This inclusion is a "highly significant part of the story" [24] that has facilitated the exploration of the meanings of GUR in freshmen perspective and thus thickened the understanding. Third, case study is known as a triangulated research strategy [12, 25]. The present study is one of the evaluative components of the longitudinal research project. The findings of the present study could be used to ensure accuracy and alternative explanations of other evaluative components in the project.

Despite the strengths of the present study, some limitations are noteworthy as well. First, the cost-effectiveness of collecting and analyzing the data is doubted. Scholars have commented that both the data collection and analyses pertaining to case study are time-

consuming [12, 25]. Second, the data collected in the present study may not be generalizable in the conventional sense. The sample in the present study focuses on the freshmen of a single university that the sample may be idiosyncratic. It would be difficult to establish the likelihood that the data are representative of some larger population of other universities in the Hong Kong context [24].

Overall speaking, researchers' reports and students' interviews on the first year longitudinal case study suggest that students generally had fruitful learning experiences in GUR study. While students became more aware of the benefits of GUR study, the linkage between different GUR components and students' professional development could be further highlighted. Longitudinal follow-up studies would help to form a clearer picture of students' views toward GUR and their personal development.

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Chapter 183

THE DEVELOPMENT OF UNDERGRADUATE UNIVERSITY STUDENTS

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ABSTRACT

Using a longitudinal case study approach, this study investigated students' development in their undergraduate years and perceptions of the "General University Requirements" (GUR) in the new four-year undergraduate curriculum of The Hong Kong Polytechnic University (PolyU). Forty-two students enrolled in the new curriculum were invited to participate in yearly interviews, with 42, 31, 20, 23 students finally completed the yearly interviews from Year 1 to Year 4, respectively. Students' views in different academic years systematically indicated that the GUR program helped to promote

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students' development in a holistic manner, particularly with reference to the development of PolyU desired graduate attributes, knowledge broadening, and mental health promotion. Students' views towards different GUR subjects and the overall university education were also positive. Meanwhile, some challenges mentioned by students were noted for further improvement.

INTRODUCTION

General education, once an important legacy of American higher education, is now being widely adopted in higher education institutions all over the world [1]. A recent report showed that at least 58 countries have included in their higher education curricula some general education elements, of which Asian countries constituted a major part [1]. There are both factors outside and inside the university for the growing adoption of general education ideas and programs. With regard to factors outside the university, the rapid economic and workplace changes and the fast obsolescence changed the nature of work and study. Many university graduates may need to change their jobs several times over their entire career life [2]; more and more working people return to university for a second major or retraining; and many university students might not do jobs relating to their original specialized field of studies in university [3]. The fast-changing, increasingly interconnected, and globally competitive world also reshaped the manpower requirements of workforce.

Beyond professional knowledge, employers expect their employees to have strong transferable skills, critical thinking, effective communication, innovative problem-solving skills, as well as a sense of ethics and responsibility to not only adapt to the fast-changing environments but also help with enhancing the international competitiveness of the nation [2, 4-6]. A report of Association of American Colleges & Universities (AAC&U) [7] claimed that more than 70% of employers expected university education to put more emphasis on developing generic competences such as teamwork skills, oral and written communication, critical thinking, analytic reasoning, innovative problem-solving and global awareness. Therefore, a narrow undergraduate education is unable to equip students with these required competences for a changing world. David Kearns, the former CEO of the Xerox Corporation said:

"The only education that prepares us for change is a liberal education. In periods of change, narrow specialization condemns us to inflexibility-precisely what we do not need. We need the flexible intellectual tools to be problem solvers, to be able to continue learning over time." [8, p. 2]

For the need within the university, the changing profiles of current university students and their increasing psychological and behavioral problems also raised concerns of university administrators, teachers, and scholars. Research consistently showed that there was an increasing high prevalence of mental health problems among university students [9, 10]. Challenged by a double transition from adolescence to adulthood and from high school to university stage, university students were much vulnerable to mental health problems [11]. Some common mental health problems included depression, anxiety, and stress [11, 12]. Also, university students reported higher levels of emotional problems, suicidal ideation, and psychotic disorders compared with their normal generation [11]. Therefore, both the outside challenges and inside needs suggest that more strong educational initiatives or interventions

should be provided to university students to help them adapt to critical transition and develop better to thrive to be competitive professionals and citizens in society. General education, with its outmost aim as developing holistic person, is an important mean to help university fulfill this task. This is as claimed by Louis [13, p. 31] that “general education has been perceived as a medicine to cure many ills, including overspecialization and vocationalism, to incite much virtue in areas as civic responsibility, and to prepare individuals for full self-realization.” Also, the value and meaning of a general/liberal education in contemporary age was claimed by AAC&U [7] as:

“Liberal education is an approach to learning that empowers individuals and prepares them to deal with complexity, diversity, and change. It provides students with broad knowledge of the wider world (e.g., science, culture, and society) as well as in-depth study in a specific area of interest. A liberal education helps students develop a sense of social responsibility, as well as strong and transferable intellectual and practical skills such as communication, analytical and problem-solving skills, and a demonstrated ability to apply knowledge and skills in real-world settings.”

Propelled by the above-mentioned internal and external factors, there have been movements in different places of the world to enhance general education component or introduce new general education programs in undergraduate curriculum of higher education. Meanwhile, the emphasis of general education implementation has changed from focusing on its curricular content to innovative and engaging teaching and learning approaches that promote “modes of learning that are collaborative, experiential, service, and integrative” [14]. Based on this shifted conception, different innovative and engaging curricular modes and pedagogy were developed, which included freshman-year seminars, learning communities, service learning, collaborative assignments, capstone courses, and writing-intensive courses, and other engaging courses [14, 15]. The underlying rationale of these new initiatives, as claimed by Schneider [15, p. 34], reflected a philosophy of general education that:

“It emphasizes an approach to learning rather than course categories, and gives primary attention to the habits of mind, breadth of perspective, and capabilities the student is developing. The ability of students to apply their knowledge to real problems is one indicator of their achievement level.”

In line with the worldwide trends, there was a new general education initiative in higher education in Hong Kong in recent years. Since the 2012-2013 academic year, the eight public universities in Hong Kong extended their three-year early-specialization-oriented undergraduate degree programs to a four-year length. In the new four-year curricular structure, a significant general education component was introduced. This curricular transformation is a systematic response of Hong Kong higher education to the ongoing social and economic changes of Hong Kong society in an increasingly globalized age [16, 17]. Among different new general education programs, a notable one was the “General University Requirements” (GUR) developed and implemented in the new four-year undergraduate degree program at The Hong Kong Polytechnic University (PolyU). In addition to arming students with a broad knowledge base and learning experience, the GUR at PolyU is also intended to nurture PolyU students in five desired graduate attributes, including effective communication, critical thinking, innovative problem solving, lifelong learning and ethical leadership. To achieve these goals, the GUR is comprised of six major learning components, including Freshman Seminar, Leadership and Intra-Personal Development Component, Language and Communication Requirements, Cluster Area Requirement, Service Learning,

and Healthy Lifestyle program. Across these different components, the GUR framework adopted new pedagogies such as hands-on workshop, service learning, group projects, writing assignments, in-class activities and other approaches to engage students in a more in-depth, collaborative and experiential-based learning. The objectives and characteristics of each GUR component are briefly introduced below:

- Freshman Seminar (FS): a three-credit subject in each broad discipline designed to broaden students' understanding of their chosen discipline and nurture their entrepreneurship and university-preferred learning styles.
- Leadership and Intra-Personal Development (LIPD): includes two alternative leadership subjects: "Tomorrow's leaders" and "Tango! Managing self and leading others" to nurture students' knowledge and skills pertaining to successful and ethical leadership.
- Language and Communication Requirements (LCR): includes both English and Chinese subjects to develop students' oral and written language proficiencies in English and Chinese.
- Cluster Area Requirement (CAR): to choose four subjects respectively from four cluster areas to expand students' intellectual capacity and develop their reading and writing skills as well as an understanding of China.
- Service Learning (SL): subjects with significant service components where students need to take one to apply academic knowledge in practice and develop civic responsibility.
- Healthy Lifestyle (HLS): includes a series of learning including online tutorial and sports-doing classes to help students establish healthy lifestyle.

While the program of GUR was carefully designed and innovative teaching and learning methods were incorporated, how well this program works and how effective it promotes students' all-round development were less studied. In view of this, a five-year longitudinal evaluation project with multiple evaluative approaches has been conducted since the 2012-2013 academic year. The project was intended to understand the effectiveness of the GUR in promoting students' all-round development, particularly their development in the five desired graduate attributes of PolyU. The project was comprised of five major evaluative components: (a) longitudinal online survey; (b) Collegiate Learning Assessment Plus (CLA+); (c) secondary analyses of Student Feedback Questionnaire data; (d) student and teacher focus groups and written qualitative evaluation; and (e) longitudinal case study. For the first four components, they have generated rich and solid results. For example, the longitudinal online survey and CLA+ found that students had better performances in a set of developmental indicators in their junior and senior years than in their freshman and sophomore years [18, 19] and PolyU students performed better than did control group students [20, 21]. Student and teacher focus group results indicated that in different years, both students and teachers perceived that different GUR subjects helped with their holistic development in different aspects [22-24].

However, there is still a need to conduct longitudinal individual case studies. Different from focus groups based on different students in different years, longitudinal case study follows the same group of students over the four academic years. Thus, students'

development over time could be more systematically identified. Also, longitudinal case study was based on individual interviews, which could help probe individual students' perceptions in deeper and richer approach. Moreover, data from longitudinal case study could help further triangulate with or interpret data from the objective outcome evaluation such as longitudinal online survey and CLA+ and other qualitative evaluation such as focus groups. Against the above background, this paper reports the methods and findings generated from the longitudinal case study component of the GUR evaluation project. It helped to answer the research question that how students perceived the GUR and how they develop under the GUR program over the four academic years.

OUR STUDY

In the 2012-2013 academic year, 71 first-year students enrolled in the four-year program of PolyU were recruited based on purposeful sampling. These students were invited to participate in a longitudinal case study in the GUR evaluation project. They had been followed up by a group of scholars about their development and perceptions of the GUR over their four-year study since the 2012-2013 academic year. In each academic year, each student would be invited to attend an individual interview conducted by their respective scholars. Since during the 2012-2013 academic year, only 42 students performed actively in the study and the other 29 students acted inactively, the 29 inactive students were removed from the study. The 42 active participants were further invited to participate in the yearly interviews in the following three academic years (from 2013-2014 to 2015-2016). The number of students who finally attended the interviews in each academic year was 31 for 2013-2014, 20 for 2014-2015, and 23 for 2015-2016. All interviews were conducted around the end of the different academic years, with a length from 0.5 to 2 hours. All interviews were audio recorded. After each interview, the student was given a supermarket coupon as an incentive.

An interview guide with a set of semi-structured questions was developed by the authors to guide the individual interviews of the study in each academic year. The questions focused on (a) students' perceptions of different GUR subjects, (b) their personal growth during each academic year and previous years, (c) the contribution of GUR to their personal development, and (d) students' overall views of their four-year university study.

After the interviews of each academic year, all audio records of individual interviews were transcribed into full transcripts with the help of a group of trained student helpers. Then these transcripts were divided into three parts to be given to three trained research assistants for coding. These research assistants coded these transcripts based on method of thematic analyses and generated themes under supervision of a senior researcher who had solid experiences in qualitative study and data analyses. In the middle and at the end of the coding work, meetings were held and different research assistants' coding work was compared with each other and cross-checked, based on which relevant revisions were made to keep consistency of the coding. After the fourth-year data collection and coding work, a senior researcher combined the codes of all four years together and generated a comprehensive coding scheme of the study.

FINDINGS

The data collected over four years revealed that students generally had positive perceptions of the GUR program, particularly with reference to its subject content, teaching and learning methods, and quality of teachers. Students generally perceived the contents of different GUR subjects as useful, attractive and important. They commended highly the engaging pedagogies adopted in different subjects and the high quality of subject teachers. These views of students were presented in detail as below.

Attractive and Useful contents

One theme emerging from students' four-year narratives was students' positive views of the contents of different GUR subjects. Students generally perceived the GUR subject contents as rich, attractive, important and useful. For example, some students perceived the content and knowledge covered in the "Tomorrow's Leaders" subject as very important to their development. They said: "it ('Tomorrow's Leaders' subject) taught you something useful and let you know that to be a leader you need to have a lot of different abilities. This is very important." Students also appreciated that the freshman seminar subjects provided them opportunities to understand different professions in their broad disciplines and their interconnections. Furthermore, students commented that CAR subject contents were "very interesting" and "very rich" and fulfilled their desire to study their interested subjects beyond their own majors. In one interview, one student expressed that "the CAR subjects let us study based on our own interests" and "we have never expected that the University could offer these subjects to us such as the subject on 'logics and reasoning'." More narratives were provided below to illustrate students' views.

"I found this (CAR) subject very interesting. It conveyed to us something about human nature, some social phenomenon and some other issues that science fiction films would like to convey to the public."

"I have strong interests in Chinese culture and China. Therefore, I want to learn more through this (CAR) subject. Meanwhile, I am also interested in religion. This subject just taught the Buddhism and Chinese culture. It taught us different religions in Chinese culture and their influences to ancient, modern and contemporary Chinese societies."

EXPERIENTIAL AND INTERACTIVE LEARNING AND QUALITY TEACHING

Over the four academic years, students also had general positive perceptions of the teaching and learning in different GUR subjects. This was manifested in different aspects. Commonly shared by students, one major characteristic of the GUR was its "experiential learning" components incorporated in many different subjects, which included hands-on workshop in Freshman Seminar subjects, fieldwork in CAR subjects, and service project in Service Learning subjects. These "experiential learning" components gave students a vastly different learning experiences that cannot be gained through traditional subjects, which greatly engaged students in learning and was highly welcomed by students. Besides, lots of

students favorably commented on Tomorrow's Leaders' (one leadership subject) for its delicately and carefully designed in-class activities and in-class games to facilitate students' learning and apprehension of leadership concepts. Some games were icebreaking games to help students get familiar with their group members. Some games were classical leadership-promotion games to help students practice leadership skills such as teamwork or cooperation. Students viewed these activities and games very positively, perceiving these activities as helpful not only to their understanding of leadership concepts but also to creating an active and relaxing class atmosphere to engage and facilitate their learning. Students' positive views of different innovative and engaging pedagogies were illustrated by narratives below.

"I liked the Solar-Car-Making project (in Freshman Seminar subject)! I had never done this kind of hands-on projects in my high school. In this project, we needed to complete all the design work by ourselves and the subject teacher only provided us raw materials. This is really good and fun because we really 'made' something out. The sense of achievements from this project was much greater than that from studying textbooks."

"There were many interactive elements in the 'Tomorrow's Leaders' subject, or many so called 'small games'. We might not know our groupmates at the very beginning of the course. But we got to know each other better and united our team members quickly through playing these games. Meanwhile, we could comprehend something behind each small in-class game."

"I remembered in one class (of 'Tomorrow's Leaders' subject) we did an activity to draw superman figures. We put a lot of efforts to draw and then presented to others how our drawing illustrated the advantages and disadvantages of teamwork. Our group was very united in doing this and felt very happy."

Students in different years also commented positively on the good teaching skills of some teachers, particularly the CAR subject teachers and teachers in "Tomorrow's Leaders" subject. Students perceived some teachers could teach "beyond the content of PPT" and could use methods such as "story telling" or "case sharing" to illustrate the content of lectures. This can be illustrated by the following two narratives.

"She gave us a lot of examples. Also, in every class, she did not just teach new knowledge but helped us review the previous knowledge. For example, she would remind us of the linkage between topics in current lecture and the previous lectures, which made us know that different topics were not isolated."

"This topic ('Spirituality' in Tomorrow's Leaders subject) is difficult. Nevertheless, in our lectures, Amy (alias of the subject teacher) worked very hard to explain this concept to us. Then when we are doing our group projects, Amy and Alice (alias of the tutor) provided a lot of support to us, which helped us to understand this concept."

Students' Development under the GUR

Multiple aspects of development and benefits were perceived by the students who have studied the GUR subjects across the four academic years. These developments and benefits included a broadened knowledge base and horizon, effective communication, effective and ethical leadership, critical thinking and innovative problem-solving skills, as well as other positive developments. Students also indicated their capability of applying certain knowledge and skills into practice. These different aspects of development were presented in detail as below.

BROADENED KNOWLEDGE BASE AND HORIZON

One important benefit of the GUR was that it helped to broaden students' knowledge base and horizons. Students over the four years consistently perceived this benefit. Meanwhile, along with progression of university study, students increasingly realized the importance of having a broad knowledge base and horizon to their future development. Students found that Freshman Seminar subjects shaped their understanding of knowledge in different specialized fields of studies covered by a broad discipline and helped them meet students from different disciplines. Students perceived in different years that CAR subjects broadened their horizons as they had met students from different disciplines and even from different academic years. Students benefited a lot from communicating with these different peers. Besides, across different years, students shared that service learning subjects also helped broaden their horizons. These subjects, particularly for those offering overseas service experiences, provided students with opportunities to experience and learn different cultures and people living in different conditions. Through these experiences, students' horizons were broadened and their understanding of society was enriched. Students' positive views of these benefits can be illustrated by narratives below.

"If there have been no these subjects, we might have developed to be narrow professionals. But we have had these subjects. They could stimulate our multi-perspective thinking and let us try different things. For example, in Healthy Lifestyle program, besides badminton, I also took a hip-hop course. Although I like hip-hop very much, I had no opportunity to study it before. But the University provided me this opportunity and I would like to have a try. This really could broaden our horizons."

"These (CAR) subjects are very useful to facilitate our interpersonal communication and broaden our horizons. You see, we could study Psychology, Biology, or Map Reading. These subjects could help broaden our knowledge base beyond the engineering field (the student's major)."

"To see society and culture of a different place will broaden our horizon largely. Before my service learning trip, I only focused on what happened in Hong Kong and only knew that Cambodia was an underdeveloped country from the TV. But this understanding was very shallow. When I finished my Cambodia project and experienced life there, I was deeply shocked and felt that 'actually there are so many people in the world who are less fortunate than me!' The experience made me to do a lot of reflections."

Effective Communication

Communication competency was another major aspect of development of students through studying GUR subjects. Two approaches contributed to students' effective communication. First, students' effective communication was promoted by English and Chinese Language and Communication subjects offered in different years. These subjects enhanced students' writing skills through specifically teaching these skills and practical writing practices in assignments. Some students reflected that they could apply these learned writing skills to the writing assignments in their major subjects. Besides, students reported that these Language and Communication subjects trained their different oral communication skills, such as discussion skills, class-presentation skills, and interview-presentation skills. This was through different innovative and engaging teaching methods such as group discussion tasks, in-class presentation and role-play activities. The benefits of language and communication subjects to students' effective communication were illustrated by two narratives below.

“These subjects (English and Chinese) included mock interview parts. Therefore, they trained our expression skills in job interview. Meanwhile, they taught us how to write letters, which is very useful.”

“My year one study built a good foundation for me. I find very interesting because at the very beginning of my study, the English subjects taught me how to find materials and how to write an essay. These helped with my major subjects because we had a lot of writing tasks in our major subjects.”

Across different academic years, students’ effective communication skills were also enhanced through engaging in different interactive learning activities in different GUR subjects such as attending different group-based learning activities and performing different writing assignments. For example, some students claimed that the hands-on group project work incorporated in most Freshman Seminar subjects trained their skills of discussion and negotiation through group members working together to make out one product. Students also commented that “Tomorrow’s Leaders” subject trained their presentation skills through class teaching and in-class group presentation tasks. Moreover, students’ effective communication was also promoted by Service Learning subjects that provided students opportunities to work ingroup to design and implement a service project. This kind of group work facilitated intensive and in-depth communication between group members and large amount of communication between students and service clients. During the group work process, lots of students perceived an improvement of their skills to communicate ideas in groups and with people outside of the campus. For example, students expressed below:

“Students needed to communicate with others (in the service project) no matter what majors they came from. When going to a place, no matter in a local or non-local service project, we need to communicate with others. When doing some activities, some students who were not good at communicating with others were pushed to communicate. To have opportunities to practice our communication skills is a good thing.”

“In Year 1, I am not good at communication. I was very stubborn in communicating with others and would stick to what I think is right. I also communicated with others in this way in my Service Learning subject. Although I only wanted to speak out my own thoughts, the others thought I was objecting to their views. Therefore, I tried to improve my ways of communication from then on, and tried to be softer in communication with others.”

Effective and Ethical Leadership

Students’ leadership awareness has demonstrated an increase along with their four-year university study. For example, in the third and fourth years, more students perceived the leadership development as important to their personal and future development. For example, one student clearly claimed in the third-year interview that one of his future goals was to “strengthen leadership and learn how to become an ethical leader.”, while he did not demonstrate this idea in the first and second year interviews. Students’ leadership attributes have been nurtured by different GUR subjects in different years. Firstly, the “Tomorrow’s Leaders” subject provided an important platform for students to learn and understand leadership knowledge and concepts. Students in interviews in different years all expressed that the subject was useful, which enhanced their understanding of the quality of a good leader, improved their self-understanding and understanding of “self-leadership”, helped them to reflect on their leadership skills in practice. For example, one student said “I always remember what Iris (alias of the subject teacher) said that we not only need to lead others but also need to lead ourselves. So, ‘Tomorrow’s Leaders’ subject really helped us in leadership development.” In another example, a student talked about his understanding of the concept of

“spirituality” and its impact on his personal life. The student said “based on my understanding, spirituality means we should have a firm belief” and “based on this, I began to feel that I should not waste time in the four-year university period and I should have faith to study hard on my own major.” Furthermore, a student talked about how he applied the leadership knowledge learned from the “Tomorrow’s Leaders” subject in his leadership practices:

“One lecture (of ‘Tomorrow’s Leaders’ subject) taught us different leadership styles, such as the difference between the leader ordering his subordinates to do things and the leader joining in the teamwork and leading and instructing his team members to do something. I prefer the latter one. For example, when I was in charge of some activities, I normally joined to work together with the whole team and then told my team members how they should do about the task. Under these circumstances, I feel that I am applying leadership theories learned in practice.”

Besides the “Tomorrow’s Leaders” subject, across the four years, students also gained a lot of different chances to practice leadership skills through different group project work experiences in different GUR subjects, such as freshman seminar and service learning subjects. Particularly, through group projects in service learning subjects, students learned how to collaborate with other students from different departments and how to collaborate with different people outside of the University to perform better services to the community.

“Service Learning helped my leadership development. When my group was to do a service, I had chances to take the leadership role to lead our group to accomplish the service project. I also learned how to get along with people and how to communicate with groupmates about the project.”

Social and civic responsibility was important component in students’ development of ethical leadership. Students generally perceived that Service Learning subjects nurtured their social responsibility and civic awareness. For example, through helping underprivileged people in different places in their service learning projects, some students developed a strong sense of social responsibility to help underprivileged people in future and also reflected on their life values. Service Learning subjects also helped some students understand the social roles of their professions and helped them review their intentions in studying their professions. This influence was profound and even lasted to students’ senior-year period. For example, two students shared the influence of service learning experiences to their social responsibilities in their senior-year interviews, respectively:

“I think the most important thing is the (Service Learning) subject changed my attitude toward my profession. It made me remember why I choose to study physiotherapy in university. The major reason is that when I was very young, I have seen some doctors in *Doctors Without Borders*. They are so good and so great. So I also hope that I could use my profession to help others.”

“We went to a village to teach students in a school. I felt that although those students lived in poor families and could only study half-day class, they cherished their learning opportunities very much. You could see their big differences from Hong Kong students, in terms of their learning attitudes and respect to their teachers. This made me reflect that I have wasted a lot of time through skipping classes or wondering in the campus when I have so good opportunity to go to study in university. This reflection changed my mind that I should try my best in my university study.”

Critical Thinking and Problem-Solving Skills

GUR subjects offered in different years all helped to promote the development of students' critical thinking. Based on students' narratives in different years, teachers in different GUR subjects such as Freshman Seminar did not merely teach subject knowledge but tried to inspire students' critical thinking consciously. For example, in an interview of the 2014-2015 academic year (i.e., students' third-year study), a student still clearly remembered how his first-year Freshman Seminar subject teacher inspired his critical thinking: "I still remembered that my teacher said 'the chair you are now sitting on is not just a chair.' He taught us in this approach in almost every class, to try to promote our thinking." Other subjects also promoted students' development of critical thinking. For example, the study of CAR subjects in different knowledge areas helped students to understand intellectual approaches of different disciplines. Students find that "Tomorrow's Leaders" subject not only covered sufficient theories but also allowed students to think critically. Besides, Service Learning subjects also helped students to develop critical and multi-perspective thinking. Some students shared that in planning and conducting a service project, they learned to consider one issue from different perspectives. For example, a student having joined a Service Learning subject on cultural conservation in an oversea district reflected:

"From the cultural aspect, our service project was only a cultural conservation project. However, it is also linked to the economic aspect since the local government had an urgent need to develop the local economy and too much emphasis on economic development might do harm to the local culture."

Besides, students' narratives indicating that some GUR subjects also promoted the development of students' problem-solving skills. Particularly, students' consistently agreed that the hands-on projects in Freshman Seminar subjects and service experiences in Service Learning subjects were conducive to their problem-solving skills. The common aspect of these subjects was that they provided complex real-problem contexts for students to solve problems effectively and innovatively, which is as one student said: "Service Learning subject helped me a lot. There were many unexpected situations that we need to modify our plan. This actually is problem-solving." In another case, another student also said:

"We finally went to Cambodia to develop a map for local people based on testing local soil and water. I think we practiced innovative problem-solving through this project. This is because that we needed to use some test instruments in doing the project, while we could not find these instruments in local place and also could not bring these instruments from our University to Cambodia. Under this circumstance we have to find some solutions to this problem, to think of some innovative ideas."

Other Aspects of Student Development

Besides the above developments, students' narratives in different years also revealed that the GUR program helped with development of mental and physical health, self-efficacy, and friendship and social network of different students. Some students consistently claimed that "Tomorrow's Leaders" helped to improve their mental health and self-efficacy. For example, one student shared that "my mental health has improved. Throughout 'Tomorrow's Leaders' subject, I realized actually we should hold positive attitudes towards everything and should

not be too negative.” “Tomorrow’s Leaders” subject also helped students to build their inner powers and increased their self-efficacy in general and in pursuing their academic study. For example, several students said that the subject taught them “how to cope with and bounce back to adversities” and how to “change” themselves for a better personal development, which made them “more positive to study their majors” because “I have realized that I should strive hard to study in the four years”. Furthermore, among all GUR subjects, with their general-education-based course nature, involved different students in the class and learning, which greatly increased students’ social interaction with peers from other departments and knowledge backgrounds. This helped many students to broaden their social networks and were perceived as useful for students’ future development. For example, one student said:

“My groupmates in ‘Tomorrow’s Leaders’ subject helped me a lot not just in this subject. For example, some male groupmates’ mathematics is very good. They helped me a lot on calculus. In turn, for some who take the CAR subjects that I have already studied in the last semester, I could give some advice to them.”

Application to Life and Helpful to Future Development

Across the four years, a number of students perceived that the knowledge, skills, or learning experiences they have gained from different GUR subjects could be applied in their daily life or could be helpful to their future development. For example, students perceived that their group work experiences in GUR subjects in early university years prepared for their group work in major studies in later university years. Also, students from non-business disciplines perceived that the business planning knowledge they learned in Freshman Seminar subjects were helpful to their future career development since their professions had interconnection with business fields. For example, one student from engineering discipline expressed that the business plan gave him “a good foundation” because “our engineering profession would have some relationships with business sectors, we can use this knowledge (business plan) if we would like to run business in engineering field in future.” Students also commonly perceived that the academic writing skills such as referencing skills learned from English language and communication subjects were very useful to their writing tasks in major subjects. Furthermore, there were students who benefited from “Tomorrow’s Leaders” subject, perceiving the subject helped their leadership in reality and self-reflection. In an interview, a student expressed that leadership knowledge was very important to him because he took several leadership roles in student societies and church work. He expected to learn leadership knowledge and skills from “Tomorrow’s Leaders” subject and then “Finally, it turned out that through the subject I really learned a lot, comprehend a lot, and reflected a lot. This facilitated my development.”

Students’ General Impressions of Their University Study

Students were also asked about their general impressions of their university study in interviews of longitudinal evaluation study. Overall speaking, students’ views were highly positive. The majority of the students perceived their university study as “fulfilling”, “enriching”, and “rewarding”. Some also used “busy but happy”, “changing”, “exploring”,

and “enjoying” to describe their four-year university life. Some students perceived that the four-year university study, with different subjects including GUR and major subjects, helped them to pursue their personal and professional goals. Many students commended that the University provided them many different learning opportunities such as service learning and oversea exchange and different activities to enrich their life and build their multiple abilities, which helped shape their future competitiveness in society. Some students also perceived that during their four-year university study, they had chances to meet and communicate with students from different backgrounds. Students’ positive views can be illustrated by the following Chinese narratives translated in English:

“I think the university is a place that helps you to realize or get close to your dreams. As I have said earlier, since I want to help people, I chose physiotherapy as my major. Then the service learning project in Cambodia made me realize more about the meaning of my Major. So the four-year university life made me closer to my dream and developed my different abilities such as communication, leadership and problem-solving. These were very useful to my future profession.”

“I feel hard but rewarding. This rewarding is not only on the grade but also on how to get along with people and dealing with things. These interpersonal experiences are so treasurable, which cannot be gained elsewhere. But the University provided these opportunities to us, for us to train ourselves. Therefore we could arm ourselves better to compete with others in future.”

“Very enriching! Almost in every year, I could be able to use the opportunities provided by the University to go to exchange in different places and to join different activities. I have been to Japan, Taiwan and Cambodia. Every time I could learn different things. This helped to prepare for our future career because we will not feel so challenging in doing different things in our workplace in future if we have already tried so many different things. So my four-year university life was very enriching and I have explored different things in this life.”

“Before enrolling in the University, I was not clear about my future goals. But after the four-year study, I find that I have not only got more understanding about my profession but also a clearer conception about my future directions. Also, I have learned and improved a lot in interpersonal skills in the University.”

“My university study was enjoyable and worthwhile. I was not just sitting in the classroom to read the textbooks every day. The GUR subjects, such as the Service Learning subject, provided me a lot of different experiences to apply our knowledge into helping the community. This made me feel that I have the ability to contribute to the society and to help people living in different conditions. I feel that my horizons have been broadened and my knowledge learned is applicable. These life experiences are so good and valuable to me.”

Challenges

Although students over the four academic years generally had positive views of the GUR and perceived the GUR program as effective in promoting students’ all-round development, they indicated challenges in studying GUR subjects. Three major challenges were noted by the students. First, although students perceived that many GUR subjects incorporated innovative and engaging pedagogy, they noted that there were still few courses adopting a big-class and mere-lecturing teaching method, which made their learning process boring and ineffective. For example, one student expressed in an interview “when I came in the class, the classroom was very dark and there were so many students there. Only one teacher stood far away speaking.” Another student also shared in another interview that “the content (of lectures of a CAR subjects) was very introductory. There was a far distance between the lecturer and us, and the lecturer was just speaking for himself, regardless of whether we listened to him or not.” Second, a number of students indicated that they could not register their interested CAR subjects because a large part of their timetables was occupied by their major subjects and most of their interested CAR subjects had timetable conflicts with their pre-assigned major subjects. Third, some students in their early university years showed an

unclear understanding and unfamiliarity with the course objectives and rationales of the GUR, which hindered their active participation and learning in these subjects. They expected to be given clearer information about the rationales and objectives of the GUR and its different subjects at the very start of their learning.

DISCUSSION

This study investigated students' perceptions of the General University Requirements (GUR) at The Hong Kong Polytechnic University (PolyU) and their developments under this new general education framework over the four academic years. This study was one component of a five-year longitudinal evaluation project to evaluate the effectiveness of the GUR at PolyU. Results showed that students improved in different aspects of developments under the GUR and held positive views of different aspects of GUR program. These results were consistent with the other quantitative and qualitative findings gained from other evaluation components of the project [18-24], which suggests a general effectiveness of the GUR in promoting students' holistic development and the development in the five desired graduate attributes of PolyU.

The findings of the present study have broad implications to the general education implementation and effectiveness in different higher education institutions. Particularly, broad literature on general education suggests that although general education was perceived as important by many educators, scholars, philosophers, and university administrators for centuries for developing all-round persons and broad-based professionals for a changing society, its implementation in higher education encounters increasing challenges in an age marked by over-proliferation and over-division of knowledge, science and university disciplines [25-27]. Against this, the reform and implementation of the GUR at PolyU provided experiences and references for other higher education institutions about implementation of general education in undergraduate education.

Several important observations can be gained from the findings of the present study. Firstly, results of the present study indicated that the GUR at PolyU incorporated large amount of elements of innovative and engaging teaching, and interactive and experiential learning. These new course modes and pedagogies were shown as the key determinants to students' engaged learning in the GUR and their development of important competencies through GUR subjects. Instead, the fewer courses adopting mere-lecture teaching method were criticized by students as less engaging and less effective in GUR. This observation is consistent with the general literature, which suggested that some engaging pedagogy or high impact practices in general education or liberal arts education such as service learning, capstone courses, first-year seminar, and collaborative learning and others had highly positive impacts on students' learning and development of desired learning outcomes [28-30]. In conjunction with the existing literature, the present study further supports the idea that the teaching and learning modes rather than the knowledge were key factor to successful general education program. Thus, university administrators and curricular reformers should focus more on how to develop innovative and engaging teaching and learning modes than on debating what and how many knowledge should be included in a general education program

[31, 32]. The recent reform trends on general education in different higher education institutions have further strengthened this argument [33-35].

Secondly, the present study indicated that students' clear knowledge about the objectives of the GUR and the subject registration mechanisms were also important factors impacting their learning motivations and effects in the general education. Students' unclear knowledge about the course rationale would hinder their active participation in learning. University administrators and general education subject teachers should pay more attention to how to clearly deliver the messages of their course objectives to their students before their learning. Students' failing to register their interested subjects would also greatly diminish their learning motivation and interests. However, there was not much literature concerning how to design selection mechanisms of elective subjects in general education to maximize students' course selection effects. More research is needed in this area for promoting a better functioning of different general education programs.

Thirdly, students' overall experiences about their four-year university education were very positive. One major contribution to this was the multiple learning experiences provided by the GUR program, such as the overseas service learning experiences. This was also in line with some literature suggesting that although students perceived their specialized studies highly, they valued a good and valuable general education as well and expected university provide broader and diversified learning experiences [36-38]. In conjunction with these existing findings, the findings of this study not only help to support the success of the GUR at PolyU, but also further indicate the importance and value of general education in modern universities.

Although the current study is pioneer in nature, limitations of the present study should be noted. Although the four-year longitudinal case study gained rich results about how students develop and perceive the GUR during their four-year university study, its data were subjective and still need to be combined with results from objective outcome evaluation such as objective survey and competency tests to determine the effectiveness of the GUR. Also, the present study only followed the first cohort of students enrolled in PolyU new curriculum, the views of students enrolled in later academic years should also be investigated. Despite the limitations, the present study explored students' development under the general education program in a longitudinal case study approach, which was pioneering in its methodology in field of evaluating effectiveness of general education.

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Chapter 184

GENERAL UNIVERSITY REQUIREMENTS AND HOLISTIC DEVELOPMENT IN UNIVERSITY STUDENTS

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ABSTRACT

The General University Requirements (GUR) at The Hong Kong Polytechnic University (PolyU) is an integral part of the new 4-year undergraduate curriculum which attempts to promote holistic student development. To evaluate the effectiveness of the GUR, a study adopting a static group comparison design was adopted, with a sample of Year 3 PolyU students studied in the 4-year undergraduate degree program (N = 566) compared with a control Year 3 sample recruited from a comparable university in Hong Kong (N = 285). The students in both samples responded to measures on empathy, positive youth development, and engagement in university study. Results showed that although both groups basically did not differ in the major background demographic variables, PolyU students performed better than did the students of the control group on measures of holistic development. Bearing in mind the intrinsic problems of the static comparison group design, the present findings provide support for the effectiveness of the GUR at PolyU.

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INTRODUCTION

Nowadays, the society has strong expectation for the higher education sector to nurture students the ability of solving real-world issues and meeting the needs in our community through instruction, research, or community partnership [1]. With the changing economic structure from manufacturing economies to knowledge-based economies, university graduates are expected not to just have narrow professional knowledge, but also general education, creativity, and problem-solving skills. In fact, many employers would regard soft skills (such as emotional management and cooperation) as more important than professional skills in university graduates. As argued by Baker, university education should be “much more than a production line for work-ready graduates” [2]. Similar view was held by Lewis who proposed that the core business of undergraduate training is to “... help them [students] grow up, to learn who they are, to search for a larger purpose for their lives, and to leave college as better human beings” [3].

How can we nurture university students in terms of general education and soft skills? In the North American university systems, it is commonly achieved through general education programs where students are exposed to knowledge of different disciplines, including humanities and social sciences. It is assumed through such “general exposure,” students can develop a broader and more flexible mind-set. Typically, general education may include language enhancement subjects, freshman seminars, and subjects in different disciplines such as human development, social development, globalization, history and philosophies, and science and technology. For some universities, they may have other requirements such as service learning, leadership programs and healthy lifestyle programs. As commented by the Task Force on Higher Education and Society [4], general education is “an excellent form of preparation for the flexible, knowledge-based careers that increasingly dominate the upper tiers of the modern labor force. With knowledge growing at unprecedented rates, higher education systems must equip students with the ability to manage and assimilate greatly expanded quantities of information.”

With specific reference to Hong Kong, the structure of the undergraduate university education has been changed from a 3-year to 4-year one since 2012-13 academic year. Before July 1, 1997, as Hong Kong was a British Colony, its education system was modelled after the British model, with five years of secondary school education, two years of matriculation education, and three years of university education. As there were many criticisms against the old education system modelled after the British system and propositions for aligning the system with the higher education system in China and North American, the old British system was changed in 2006 with three years of junior secondary school education, three years of senior secondary school education, and four years of university education. For the four year undergraduate university education, it began in 2012-13 academic year.

This education reform is regarded as “an important watershed for Hong Kong education as well as a unique opportunity for universities to move from a specialized focus to a more holistic student-oriented approach to undergraduate education” [5]. As advocated by the University Grants Committee (UGC), “having an additional undergraduate year will enable students to have more time and space to build a broader knowledge base and a more solid foundation for whole-person development. This will be conducive to the nurturing of capable talents to underpin the development of a knowledge-based economy as well as to meet the

rapid-changing needs of the society” [6]. According to UGC, “the rationale of the new curriculum is to provide students with greater flexibility, more broad-based and student-centered learning experience. Institutions have put in extraordinary efforts to ensure that the four-year undergraduate programme, which comprise the core, major and elective courses with an emphasis on general education and exposure to both academic and non-academic skills and knowledge, will be coherent, and the additional year is not simply an add-on to the current three-year undergraduate programme.” [7]

To achieve the above expectations, The Hong Kong Polytechnic University has formulated a General University Requirements (GUR) initiative which formed an integral part of the new 4-year undergraduate curriculum commencing from 2012-13 academic year. In the new 4-year curriculum, GUR study of the students includes Freshman Seminar (3 credits), Language and Communication Requirements (9 credits), Cluster Area Requirements (12 credits), Leadership and Intrapersonal Development (3 credits), Service Learning (3 credits), and Healthy Lifestyle (0 credit). By doing this, PolyU graduates are expected to not only attain professional competence in their areas of professional training, but also develop core competence of employability and civility to be responsible and contributing members of our society. The University has refined the general student learning outcomes and arrived at six major desired attributes for graduates. In addition to professional competence, five other attributes are highlighted including critical thinking, effective communication, problem-solving, lifelong learning, and ethical leadership. It is expected that the GUR can contribute to the development of these five qualities in the students.

Although the design of the GUR is conceptually elegant and noble, there is a need to understand whether and how the GUR works well. To investigate the changes in the undergraduate students with respect to the above desired attributes under the 4-year undergraduate curriculum, the University awarded a Teaching Development Grant to a Research Team of colleagues to review and evaluate the GUR study in 2012-13 academic year, with the first author as the principal investigator and the second author as the co-principal investigator. The research adopts a five-year longitudinal mixed-method design. Quantitative methods included online surveys addressing student-level developmental indicators (objective outcome evaluation), students’ feedback questionnaires on GUR subjects (subjective outcome evaluation), and the Collegiate Learning Assessment (CLA+) (objective outcome evaluation). Qualitative methods included document analysis and focus group interviews with different stakeholders (review of the offering and implementation of the GUR and qualitative evaluation).

Is the GUR effective in promoting the holistic development of the students? To date, some evaluation findings showed that students had positive evaluation of the GUR components and its perceived benefits. Shek, Yu, Wu and Ng [8] examined the implementation and impact of GUR components. Evaluation based on different approaches revealed that students had favorable evaluation of the subjects, teachers and benefits of the GUR. Besides, students generally held the view that GUR subjects could promote the problem-solving, critical thinking, effective communication, ethical leadership and lifelong learning attributes in students (i.e., desired PolyU graduate attributes). Shek, Yu and Ngai [9] examined students’ feedback using the Student Feedback Questionnaires. The subjective outcome evaluation findings generally showed that the students had positive views of the GUR subjects, teachers and the benefits. Furthermore, Shek, Yu, Wu and Chai [10] conducted focus group interviews to collect views of 62 students on GUR subjects. It was found that the

GUR (subjects, teachers and benefits) component of the 4-year curriculum was well-received by the students. The students also appreciated the interactive teaching and learning methods used in GUR subjects.

Obviously, although the existing evaluation findings are positive, they are based primarily on subjective outcome evaluation and qualitative evaluation. Hence, it would be desirable to look at the effectiveness using objective outcome evaluation data. As such, a study based on a static group comparison design was carried out. A static group comparison design is a pre-experimental design which is commonly used in social sciences research. In this design, there is a treatment group as well as a control group without baseline assessment. The differences between the two groups are then compared at some subsequent time. There are several advantages of this design. First, it can be used in a convenient manner in many contexts where data on a large number of variables and subjects are collected. Second, in contrast to classical experimental designs, the related procedures in the static group comparison design are simple. For a treatment group, what is needed is a control group possibly through matching the background socio-demographic attributes. Third, in cases where randomization is not possible, static group comparison can help to generate hypotheses and serve a good purpose as an exploratory research.

On the other hand, there are several disadvantages of a static group comparison design. First, as it is a cross-sectional study, it does not permit the researchers to look at changes across time. Second, as there is no real “control” of the experimental condition, it is not possible to establish the cause-effect relationship. Third, there are rival explanations for the differences between the experimental group and control group. For example, it can be argued that the differences between the two groups are due to differences in socio-demographic factors. Although such differences in confounding can be dealt with through statistical analyses, there are always the logical possibility that the two groups are different in terms of other factors not included in the study [11].

Researchers in many fields have used the static group comparison design for program evaluation. Odundo, Anjuri and Odhiambo [12] used a static group comparison design to examine the influence of peer education on behavior change in secondary education and HIV/AIDs. The basic research design was to compare those who joined peer education club and those who did not in terms of their sexual behavior and HIV testing. While acknowledging the limitations of the study design such as confounding factors, the authors concluded that the intervention promoted abstinence in sex, faithfulness to a partner, use of condom and testing for HIV. Another example is from the work of Moodley, Kritzinger, and Vinck [13] who investigated the effect of play-based versus formal instruction on English language proficiency using a static two-group comparison design. The researchers showed that the formal approach had better effect than the play-based approach on the English test scores.

In this study, the impact of GUR on student development was examined via a two-group static group comparison method. For the “treatment” group, Year 3 students studying in the 4-year undergraduate degree program were recruited. For the “control” group, Year 3 students studying in a 4-year undergraduate degree program in a comparable university in Hong Kong were invited to participate in the study.

OUR STUDY

The participants of the “treatment” group (i.e., PolyU group) were Year 3 students under the 4-year curriculum who had participated in a longitudinal evaluative project on GUR at PolyU. Based on stratified random sampling method, 643 students were initially selected from eight faculties and schools at PolyU in 2012-13 in terms of the faculty-based proportions of First Year First Degree (FYFD) intake in that year. These students were invited for the third time to respond to the GUR online survey in November of 2014. A total of 566 students (response rate = 88.02%) completed the survey via the electronic system.

Table 1. Comparison of background variables between PolyU and ControlU participants

		PolyU	ControlU	Comparison	Effect size
Gender ^a	Male	235(41.5%)	106(37.2%)	$\chi^2 = 1.67$, $df = 2$, $p = .43$	-
	Female	327(57.8%)	176(61.8%)		
	Not indicated	4(0.7%)	3(1.0%)		
Parental marital status ^a	Divorced	53(9.4%)	20(7.0%)	$\chi^2 = 4.07$, $df = 4$, $p = .40$	-
	Separated	8(1.4%)	5(1.8%)		
	Married (First marriage)	473(83.6%)	238(83.5%)		
	Married (second marriage)	12(2.1%)	5(1.8%)		
	Others	20(3.5%)	17(6.0%)		
Family economic status ^a	CSSA recipient	45(8.0%)	19(6.7%)	$\chi^2 = 0.48$, $df = 2$, $p = .79$	-
	Non-CSSA recipient	492(86.9%)	252(88.4%)		
	Not indicated	29(5.1%)	14(4.9%)		
Academic Field ^a	Business	136(24.0%)	75(26.3%)	$\chi^2 = 6.88$, $df = 3$, $p = .08$	-
	Art & Social Science	155(27.4%)	55(19.3%)		
	Science & Engineering	258(45.6%)	147(51.6%)		
	Design & Media	17(3.0%)	8(2.8%)		
Perceived family life satisfaction ^b		3.77(0.88)	3.80(0.83)	$t = -.42$, $df = 849$, $p = .68$	-
HKDSEE results ^b		Omnibus Multivariate Test: $F(4, 699) = 10.12$, Wilk's Lambda = 0.97, $p < .01$			
	Chinese	4.23(0.93)	3.98(0.80)	$F = 11.93$, $df = 1, 702$, $p = .01$	$\eta^2 = .02$
	English	4.01(0.83)	4.10(0.73)	$F = 1.76$, $df = 1, 702$, $p = .19$	-
	Mathematics	4.46(0.90)	4.13(0.69)	$F = 23.01$, $df = 1, 702$, $p < .01$	$\eta^2 = .03$
	Liberal Studies	4.17(0.81)	4.15(0.86)	$F = 0.06$, $df = 1, 702$, $p = .81$	-
Age ^b		20.12(0.57)	20.28(0.90)	$t = -3.10$, $df = 848$, $p < .01$	Cohen's $d = 0.21$

Note:

^aCategorical variables: values outside parenthesis were numbers of participants and values in parenthesis were the related within-group percentages.

^bContinuous variables: values outside parenthesis were means and values in parenthesis were standard deviations.

CSSA denotes CSSA denotes Comprehensive Social Security Assistance Scheme.

For the participants of the “control” group, quota sampling was adopted to select students of the same cohort from a comparable university in Hong Kong, based on the proportion of students from each faculty/school. Considering the difference in the institutional structure of the two universities, the eight faculties of PolyU were re-grouped into four academic fields for better alignment, namely Business, Arts and Social Science, Science and Engineering, Design and Media. In total, 290 Year 3 students under the 4-year curriculum in the comparable university (named as “ControlU” in this paper) were selected and invited to complete the GUR online survey at the same time period. Two hundred and eighty five participants completed the questionnaire on time (response rate = 98.28%).

Basic demographic information for the experimental group (N = 566) and the control group (N = 285) is shown in Table 1. In total, 341 participants were male and 503 participants were female. The majority of the respondents were 20 years old (N = 626; 74%), living with parents of first marriage (N = 461; 85%), and from a family with an average income (N = 711; 84%). Statistical analyses were conducted to compare the background variables between the two groups and the results generally showed that the two groups were generally equivalent, except their scores on the university entrance examination and age (see Table 1).

Written consent was obtained from the students before they responded to the questionnaire. Participating students were administered the GUR online survey through the MySurvey@PolyU electronic survey system in November of 2014. Students could choose to complete the survey at home or in a preserved computer room at PolyU. Research purposes and detailed instructions about how to complete the questionnaire were explained to students by several rounds of email and further announced on the survey webpage. It took around 40 minutes to complete the whole questionnaire. Respondents’ electronic answers were directly downloaded as a SPSS file for statistical analysis.

The questionnaire included several validated scales and a few items on participants’ demographic information. The present study would focus on three major scales including the Chinese Interpersonal Reactivity Index (C-IRI), Chinese Positive Youth Development Scale (CPYDS), and National Survey of Student Engagement (NSSE). The three scales and their subscales measure students’ developmental outcomes in relation to five desired university graduate attributes (i.e., problem-solving, critical thinking, lifelong learning, ethical leadership, and effective communication). The alignment between the three scales and the attributes was shown in Table 2.

- *Chinese Interpersonal Reactivity Index (C-IRI)*: It is a self-reported questionnaire designed to assess different components of empathy in Chinese population validated by Siu and Shek [14] based on Davis’s [15] work. The C-IRI comprises 22 items which further constitute three subscales: Empathy (11 items), Fantasy (4 items), and Personal Distress (7 items). Using a four-point Likert scale, scores for each domain are expressed in terms of average domain items scores. High C-IRI score represents for high level of empathy which is an essential quality of ethical leadership and effective communication. In the present study, the three composite scores of C-IRI were calculated and compared between the two groups. Cronbach’s alpha coefficients for the C-IRI on the experimental group and control group were 0.80 and 0.82, respectively.
- *Chinese Positive Youth Developmental Scale (CPYDS)*: It was developed by Shek, Siu, and Lee [16] to measure positive characteristics and developmental assets in

Chinese adolescents. In the present study, a selection of 14 major subscales from the CPYDS were adopted to measure participants' development, including Problem-solving (3 items), Resilience (3 items), Social Competence (3 items), Emotional Competence (3 items), Cognitive Competence (4 items), Behavioral Competence (2 items), Moral Competence (3 items), Self Determination (2 items), Life-Long Learning (2 items), Self-Efficacy (2 items), Ethical Leadership (15 items), Critical Thinking (3 items), Self-Leadership (5 items) and Life-Satisfaction (5 items). Items of Self-Leadership subscale were rated on a five-point Likert scale while all other items were rated on a six-point Likert scale. Subscale scores were expressed in terms of average domain items scores. Higher scores mean higher level of positive youth development. The 14 subscale scores (composite scores) of CPYDS were computed and compared across the two groups in the present study. Cronbach's alpha coefficients of the CPYDS for the experimental group and control group were 0.95 and 0.96, respectively.

- *National Survey of Student Engagement (NSSE)*: Students' engagement in learning and other university experience was assessed with a locally adapted version of the National Survey of Student Engagement (NSSE) [17]. The NSSE has been administered and validated in both the United States [18] and mainland China [19, 20] with good psychometric properties. The NSSE evaluates students' university experiences in terms of 11 major indexes: Collaborative Learning (4 items), Reflective and Integrative Learning (7 items), Student-Faculty Interactions (4 items), Higher-Order Learning (4 items), Effective Teaching Practices (5 items), Quantitative Reasoning (3 items), Discussions with Diverse Others (4 items), Learning Strategies (3 items), High-Impact Practices (6 items), Quality of Interactions (5 items), and Supportive Environment (8 items). Responses on the adapted NSSE were measured based on a four-point Likert scale except items of Quality of Interactions (7-point Likert scale). Composite scores for each NSSE domain were expressed in terms of average index items scores. The present study compared the 11 composite scores across the two groups. Cronbach's alpha coefficients of the adapted NSSE for the experimental group and control group were 0.86 and 0.91, respectively.

Table 2. Relationships between instruments and desired university graduate attributes

Desired Attributes	Instruments		
	C-IRI	CPYDS	NSSE
Problem-solving		√	
Critical thinking		√	
Life-long learning		√	√
Ethical leadership	√	√	
Effective communication	√	√	√

Note:

C-IRI = Chinese Interpersonal Reactivity Index;

CPYDS = Chinese Positive Youth Development Scale;

NSSE = National Survey of Student Engagement.

FINDINGS

Background variables of the two groups were first compared before the comparison on key developmental indicators was made. For categorical variables including gender, family economic status, and parental marital status, a series of chi-square tests were conducted. For continuous variables including age and perceived family life satisfaction, t-tests were performed to examine the group differences. In addition, to examine whether the two groups were differ in their academic performance when they first entered into University, grades in four major areas in HKDSEE (the Hong Kong Diploma of Secondary Education Examination) were compared by employing MANOVA.

As shown in Table 1, the results showed that there were no significant group differences in participants' gender ratio ($\chi^2 = 1.67$, $p = .43$), parental marital status ($\chi^2 = 4.07$, $p = .40$), family economic status ($\chi^2 = 0.48$, $p = .79$), and perceived family life satisfaction ($t = -.42$, $p = .68$). In other words, for these demographic variables, the two groups of students can be regarded as equivalent.

As for the university entry grade, PolyU students scored higher than ControlU students in Chinese and Mathematics, and no significant differences were identified in English and Liberal studies. Partial eta squares were further calculated for the two variables with significant differences and the results (see Table 1) suggested small effect sizes based on the criterion given by Miles and Shevlin [21]. This indicates that participants from the two universities had similar level of academic performance when they first entered into University. The only significant difference in demographic variables between PolyU and ControlU participants was found in students' age ($t = -3.10$, $p < .01$, Cohen's $d = 0.21$). PolyU students (mean age = 20.12, standard deviation = 0.57) were slightly younger than students of ControlU (mean age = 20.28, standard deviation = 0.90). According to the rule of thumb proposed by Cohen [22], the effect size could be regarded as small. Given that all participants were sampled from the same cohort/grade, and that the minor difference in age is unlikely to influence students' development in their University study, age would not be controlled in the following analyses.

Group Comparison in Developmental Indicators

To compare the development of students from the two universities in different areas, a series of t-tests were conducted on participants' scores of the three scales and their subscales. Table 3 presented the means and standard deviations of participants' scores for PolyU group and ControlU group as well as the statistical results of t-tests. As can be seen in the table, the two-tailed tests showed that nine variables displayed significant group differences including Cognitive-Behavior Competence, $t(566) = 2.44$, $p < .05$, Problem-solving, $t(566) = 2.10$, $p < .05$, Emotional Competence, $t(566) = 2.94$, $p < .05$, Cognitive Competence, $t(566) = 2.44$, $p < .05$, Behavioral Competence, $t(566) = 2.04$, $p < .05$, Moral Competence, $t(566) = 2.07$, $p < .05$, Life Satisfaction, $t(566) = 2.58$, $p < .05$, Learning Strategies, $t(566) = 2.99$, $p < .05$, and Quality of Interactions, $t(566) = 3.02$, $p < .05$. PolyU students performed better than ControlU students in all the nine indicators.

Table 3. Results of independent-samples t-tests comparing PolyU and ControlU participants

	PolyU			ControlU					
	N	M	SD	N	M	SD	t	df	p
C-IRI									
Empathy	566	2.91	0.36	285	2.91	0.39	.18	849.00	.86
Fantasy	566	2.72	0.57	285	2.72	0.58	.11	849.00	.91
Personal Distress	566	2.46	0.52	285	2.49	0.56	-.72	849.00	.47
CPYDS									
Problem-solving*	566	4.44	0.65	285	4.33	0.78	2.10	489.83	.04
Resilience	566	4.61	0.78	285	4.52	0.81	1.48	849.00	.14
Social Competence	566	4.60	0.75	285	4.59	0.79	0.16	849.00	.87
Emotional Competence*	566	4.34	0.71	285	4.19	0.77	2.94	849.00	.00
Cognitive Competence*	566	4.56	0.62	285	4.44	0.72	2.44	501.54	.02
Behavioral Competence*	566	4.52	0.70	285	4.40	0.81	2.04	501.00	.04
Moral Competence*	566	4.77	0.68	285	4.66	0.77	2.07	849.00	.04
Self Determination ^a	566	4.49	0.77	285	4.39	0.84	1.77	849.00	.08
Lifelong Learning	566	4.62	0.73	285	4.58	0.79	0.67	849.00	.50
Self-Efficacy	566	4.49	0.76	285	4.42	0.78	1.18	849.00	.24
Ethical Leadership	566	4.62	0.50	285	4.60	0.54	0.61	849.00	.54
Critical Thinking	566	4.65	0.69	285	4.58	0.81	1.27	496.91	.21
Self-Leadership	566	3.85	0.57	285	3.79	0.61	1.32	849.00	.19
Life Satisfaction*	566	3.86	0.95	285	3.69	0.95	2.58	849.00	.01
Total CPYDS Score	566	4.58	0.49	285	4.51	0.54	1.86	849.00	.63
Cognitive-Behavioral Competence*	566	4.53	0.59	285	4.41	0.68	2.44	503.45	.02
NSSE									
Collaborative Learning	566	2.59	0.55	285	2.60	0.55	-0.13	849.00	.90
Reflective and Integrative Learning	566	2.62	0.52	285	2.63	0.56	-0.11	849.00	.91
Student-Faculty Interactions ^a	566	1.96	0.67	285	2.04	0.72	-1.67	849.00	.10
Higher-Order Learning	566	2.75	0.58	285	2.69	0.59	1.36	849.00	.17
Effective Teaching Practices	566	2.70	0.53	285	2.65	0.55	1.31	849.00	.19
Quantitative Reasoning	566	2.41	0.62	285	2.42	0.69	-0.07	517.32	.94
Discussions With Diverse Others	566	2.46	0.59	285	2.46	0.56	0.05	849.00	.96
Learning Strategies*	566	2.59	0.61	285	2.45	0.59	2.99	849.00	.00
High-Impact Practices ^a	566	2.57	0.49	285	2.64	0.49	-1.91	849.00	.06
Quality of Interactions*	566	4.63	0.86	285	4.44	0.97	3.02	849.00	.00
Supportive Environment	566	2.52	0.57	285	2.47	0.55	1.21	849.00	.23

Note: * means $p \leq .05$ (two-tailed); ^ameans $p \leq .05$ (one-tailed); ns means non-significant.

Total CPYDS Score = Total score of the Chinese Positive Youth Development Scale; Cognitive-Behavioral Competence = the composite score of a second-order factor based on subscales of Cognitive Competence, Behavioral Competence, and Self-Determination.

By adopting a one-tailed test of significance, it was further found that PolyU participants also scored higher than ControlU students on Self Determination, $t(566) = 1.77$, $p = .08$; while ControlU participants scored higher than PolyU participants on Student-Faculty Interactions, $t(566) = -1.67$, $p < .05$, and High-Impact Practices, $t(566) = -1.91$, $p < .05$. These findings suggest that PolyU participants showed higher levels of cognitive-behavioral competence, emotional competence, moral competence, problem-solving ability, life satisfaction, and self-determination than did their ControlU peers. In terms of university engagement, PolyU students also reported more positive interpersonal relations in university environment and

more effective learning strategies than did ControlU students. Meanwhile, PolyU students rated their degree of interaction with faculty members and participation in practices designated as having higher impact on their development slightly lower than ControlU students. These findings overall suggest a better developmental outcome in PolyU participants as compared to ControlU students in the same cohort after two-year University study.

DISCUSSION

The primary objective of this study was to examine the effectiveness of the 4-year undergraduate curriculum implemented at PolyU by comparing the Year 3 PolyU students and Year 3 students of a comparable university in Hong Kong. Several strengths of this study are noted. First, this is the first known scientific study examining the effectiveness of the general education component of the 4-year undergraduate program using objective outcome evaluation. Second, a static group comparison design was used to compare the Year 3 PolyU students and a control group. Third, validated measures of empathy, positive youth development and university engagement were employed. Finally, the findings give support to the original hypotheses.

Consistent with the general hypothesis, the present findings show that students in the treatment group performed better than did students in the control group. Generally speaking, PolyU students did better than the control group students on several indicators on positive youth development and student engagement. These findings are consistent with the other evaluation findings based on student feedback questionnaires and qualitative evaluation strategies that GUR was able to promote the holistic development of university students. In particular, psychosocial competence in PolyU students was higher than that of the control group students. As soft skills are of paramount importance in knowledge-based economies, the finding that PolyU students had higher cognitive, emotional, behavioral and moral competence is encouraging. Besides, the higher level of life satisfaction in PolyU students is a sign suggesting that quality of life in PolyU students was relatively favorable.

While the findings are positive and they give support to the original hypotheses, several limitations of the study should be realized. First, the study can only give some clues to the cross-sectional differences between the two groups. As such, longitudinal data reflecting changes in the students should be collected in future. Second, as the sample in the control group was recruited through quota sampling, the generalizability of the findings may be questionable. Third, as the two groups slightly differed in age and university entrance examination results, further matching work could be carried out to ensure that the two samples are equivalent. Of course, by doing this, the tradeoff is reduction in the sample size. Besides, as the control group students were relatively older than the treatment group students, their differences in terms of maturation is not a viable explanation. In short, despite the intrinsic problems of a static group comparison design, the present study provides some support to the claim that the GUR component at The Hong Kong Polytechnic University is beneficial to the holistic development of the students studying in the new 4-year undergraduate program.

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Chapter 185

THE IMPACT OF THREE-YEAR AND FOUR-YEAR UNDERGRADUATE PROGRAMS ON UNIVERSITY STUDENTS

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ABSTRACT

The undergraduate curriculum structure in Hong Kong was changed from three years to four years starting from 2012-13 school year, with the extra year of study primarily devoted to general education study. At The Hong Kong Polytechnic University (PolyU), the General University Requirements (GUR) has been designed in response to this change. In this study, the question of whether the development of students in the 4-year program was better than that of the 3-year program was examined via a static group comparison design. The treatment group was third-year students of the 4-year undergraduate degree program (N = 566) whereas the control group was comprised of third-year students of the 3-year degree program (N = 290). Measures on empathy,

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positive youth development, and student engagement were used as indicators of student holistic development. While the mean age of students in the 3-year program was higher than that of the 4-year program, students in the 4-year program performed better than did the students of the 3-year program on several indicators of desired graduate attributes. Bearing in mind the limitations of the static comparison group design, the present study provides support for the positive impact of GUR at PolyU on students of the 4-year undergraduate curriculum.

INTRODUCTION

There are different types of undergraduate degree programs in different parts of the world. In the British and Commonwealth systems, three-year undergraduate degree programs are common. For example, in the case of United Kingdom, secondary school students are required to study for five years before taking the General Certificate of Secondary Education (GCSE). After that, they need to take two years of advanced level education before entering university, which normally offers three-year undergraduate program. On the other hand, the undergraduate degree program in North America is typically under a four-year structure. The general framework is three years of junior secondary school education, three years of senior secondary school education, and four years of undergraduate degree education.

With particular reference to Hong Kong, the education system was modeled after the British model before the handover of Hong Kong back to China in 1997. Secondary school students took five years of secondary school education before taking the Hong Kong Certificate of Education Examination. After that, they were required to take two years of matriculation education before taking the Advanced Level Examination. For university education, it was a three-year program except for some professional programs such as medicine. Although the education system at the Colonial time was quite successful to nurture elites for Hong Kong, the system had been severely criticized, such as morbid emphasis on academic excellence and creation of excessively high examination stress for the students. Hence, there was a call for education reform in Hong Kong after its handover in 1997. Eventually, there was a change in the education system starting from 2006. In the new academic structure, there are three years of junior secondary school education, three years of senior secondary school education, and four years of university education. The 4-year undergraduate curriculum has been formally implemented since 2012-13 academic year. The background and rationales of the education reform and the 4-year undergraduate curriculum can be seen from the reports of the Education Commission (EC) and the University Grants Committee (UGC). Some of the relevant quotes can be seen below:

- “Internationally, the academic structure and length of study in higher education have been evolving continuously to cater for the needs for life-long learning in a knowledge-based society. The common trend is to broaden the scope of learning in the universities and to defer the process of specialization. ... For many years, teaching staff of the higher education sector have been calling for a change to the academic structure of university education in the hope that students will be allowed more room to build up a broader knowledge base. This is in line with the trend mentioned above. This does not mean that the EC would like to see all first-degree

programmes adopting the same duration. A 3-year senior secondary academic structure does not necessarily require first degree programmes to be 4 years. However, if the students can enter university one year earlier, the universities will have more room in providing higher education” [1].

- “Universities are recommended to review the functions, contents, focuses and modes of teaching of their first-degree programmes, so as to strike the right balance between the breadth and the depth of such programmes. This would, in addition to helping students master the necessary knowledge and skills for specific professions/disciplines, give them exposure to other learning areas and help them develop a sense of integrity, positive attitude, a broad vision and important generic skills” [1].
- “The UGC strongly believes that all students stand to benefit significantly from the move to six years of secondary schooling and a normative four-year undergraduate programme as it will provide a more balanced, all-round and fulfilling learning experience that suits their different needs, aptitudes, abilities and interests. Having an additional undergraduate year will enable students to have more time and space to build a broader knowledge base and a more solid foundation for whole-person development. This will be conducive to the nurturing of capable talents to underpin the development of a knowledge-based economy as well as to meet the rapid changing needs of the society” [2].
- “The rationale of the new curriculum is to provide students with greater flexibility, more broad-based and student-centered learning experience. Institutions have put in extraordinary efforts to ensure that the four-year undergraduate programme, which comprise the core, major and elective courses with an emphasis on general education and exposure to both academic and non-academic skills and knowledge, will be coherent, and the additional year is not simply an add-on to the current three-year undergraduate programme” [3].

For the extra year under the 4-year curriculum, it was argued in the education reform process that general education would be beneficial to the holistic development of the students. On top of the Government views reflected in the reports by the Education Commission and University Grants Committee, there are arguments advanced by academics which are reflected in the following quotes:

- “Higher education has two dimensions – breadth and depth. Institutions are expected to instill both a breadth and depth of knowledge to insure that students will function effectively in their adult roles. The general education component is the breadth dimension and is usually defined on an institutional-wide basis, involving study in the several subject areas cited above” [4].
- “It is beyond all reasonable doubt that the universities have their share of responsibility for the well-being of the community. It is exactly because they have to face this responsibility, and because they do not run away from it, that they have to insist on the importance of a more general education. Life is more than technology, economics and commerce; life is even more than mere survival, and to learn the art of living has to be part of the education offered by the university” [5].

- “Undergraduate students are typically exposed to a wide range of subjects in their early college years. This gives them some conception of the foundations and forms of knowledge available to them. Then we require them to choose an area of concentration, a major subject, believing that the organized pursuit of knowledge brings special benefits. This approach differs from that of the dilettante by positing intriguing relationships among the different parts of a particular form of human understanding and demonstrating confidence that pursuing these relationships with sustained persistence bears its own fruit” [6].
- “We believe that the aim of education is not to teach students a vocation, because the vocations of the present will become obsolescent in the future; nor will the aim of education be merely to acquire knowledge, a futile enterprise when our knowledge and our knowledge base double virtually every decade. We believe in an education that involves training out students to think for themselves, to use what we know of the past to prepare them for the future, and to develop those skills and habits of insight and of imagination to solve problems and to resolve questions which are scarcely imaginable today. And those best equipped for the future will be self-sufficient and self-motivated individuals who can construct new solutions to old problems. And this is particularly true in the ‘new economy’” [7].

As a university funded by the University Grants Committee, the undergraduate program at The Hong Kong Polytechnic University (PolyU) was changed in 2012-13 school year. With reference to the 120-credit minimum graduation requirement, 30 credits are devoted to General University Requirements (GUR) which includes Language and Communication Requirements (9 credits), Freshman Seminar (3 credits), Cluster Area Requirements (12 credits), Leadership and Intrapersonal Development (3 credits), Service Learning (3 credits), and Healthy Lifestyle (0 credit). It is expected that the General University Requirements can promote the holistic development of undergraduate students, including effective communication, innovative problem solving, critical thinking, ethical leadership, and lifelong learning.

To what extent the four-year program contributes to the developmental outcomes of PolyU students? As it is not possible to randomly assign students to the three-year and four-year programs in the Hong Kong context, we might rely on pre-experimental designs. One possible design is to use a static group comparison design to compare students in the 3-year program with students in the 4-year undergraduate program. In this study, differences between students in the 3-year and 4-year programs at PolyU were investigated using a two-group static group comparison design. While the subjects in the “experimental” group were third-year students studying in the 4-year undergraduate degree program, subjects in the “control” group were consisted of third-year students (i.e., graduating students) studying in the 3-year undergraduate degree program at PolyU.

OUR STUDY

The current study adopted a static group comparison design. Participants included 566 third-year PolyU undergraduate students enrolling in the 4-year degree program

(experimental group) and 290 third-year students under the 3-year degree program at the same university (control group). The experimental group participants came from the 643 participants who were originally selected to participate in a five-year longitudinal evaluation research on the GUR from eight faculties/schools of PolyU in the 2012-13 academic year based on stratified random sampling. In the 2014-15 academic year, all 643 participants were invited to respond to the online survey for the third time. A total of 566 students (response rate = 88.02%) finally completed the survey. The control group participants were selected from third-year undergraduate students studying 3-year degree program in the 2014-15 academic year using quota sampling based on the basic characteristics (faculty and gender) of the experimental group participants. Out of 300 students being selected, 290 control group participants completed the online survey (response rate = 96.67%).

The demographic information of the participants is reported in Table 1. For the whole sample, there were 349 male students and 501 female students. The mean age of the participants was 21 years (age = 20.74 ± 1.16). The majority of them came from Non-CSSA recipient families ($N = 753$; 88.0%), and lived with parents in their first marriage ($N = 702$; 82.0%).

Written consent was obtained from the students before they responded to the questionnaire. Participants were administered the GUR online survey through the MySurvey@PolyU electronic survey system in November of 2014. Students could choose to complete the survey at home or in a preserved computer room at PolyU. Detailed explanations on the study and the rights of the participants (including withdrawal at any time they wished) were explained to students in the invitation e-mails and the survey webpage. Generally speaking, the participants took around 40 minutes to complete the questionnaire.

The students responded to different measures on the Internet. In the e-questionnaire, measures of empathy, positive youth development, student engagement, and socio-demographic characteristics were used. The scales adopted in this study included:

- *Chinese Interpersonal Reactivity Index (C-IRI)*: Based on the work of Davis [8], Siu and Shek [9] developed the Chinese version of the Interpersonal Reactivity Index. There are 22 items in C-IRI, including 11 items on empathy, 4 items on fantasy, and 7 items on personal distress, which are all rated on a four-point Likert scale. A higher C-IRI score represents a higher level of empathy. Reliability analyses showed that the total scale was reliable for both the experimental group and the control group ($\alpha = .80$ and $.82$, respectively).
- *Positive Youth Development Attributes*: To assess positive youth development in Chinese adolescents, Shek, Siu, and Lee [10] designed the Chinese Positive Youth Development Scale (CPYDS). Some of the subscales and items were included in this study. Besides, items assessing the desired graduate attributes were also included. The final scale included 3 items on problem solving, 3 items on resilience, 3 items on social competence, 3 items on emotional competence, 4 items on cognitive competence, 2 items on behavioral competence, 3 items on moral competence, 2 items on self-determination, 2 items on life-long learning, 2 items on self-efficacy, 15 items on ethical leadership, 3 items on critical thinking, 5 items on self-leadership, and 5 items on life satisfaction. The items were averaged to form subscale and total scale scores, with higher scores indicating higher level of positive youth development. Two composite scores of the CPYDS were also calculated and

compared, including the scale score of the CPYDS and the score of a second-order factor, cognitive-behavioral competence. Cronbach's alpha coefficients of the CPYDS were .95 and .96 for experimental group and control group, respectively, suggesting good internal consistency of the scale.

- *National Survey of Student Engagement (NSSE)*: The Chinese version of the National Survey of Student Engagement [11] was used to assess student engagement and learning in university education. Research findings showed good psychometric properties of NSSE in the United States [11] and China mainland [12, 13]. There are 11 major domains in NSSE, including Collaborative Learning (4 items), Reflective and Integrative Learning (7 items), Student-Faculty Interaction (4 items), Higher-Order Learning (4 items), Effective Teaching Practices (5 items), Quantitative Reasoning (3 items), Discussions with Diverse Others (4 items), Learning Strategies (3 items), High-Impact Practices (6 items), Quality of Interactions (5 items), and Supportive Environment (8 items). Results showed that the instrument in these two groups was internal consistent (alpha = .86 and .91 for experimental group and control group, respectively).

FINDINGS

The experimental group and control group were first compared on their demographic characteristics. Chi-square tests were carried out to examine group differences on gender ratio, family economic status, parental marital status, and faculty-based student proportion (see Table 1). Findings revealed that the two groups did not differ significantly in gender ratio ($\chi^2 = 0.39$, $p = .82$), family economic status ($\chi^2 = 0.11$, $p = .74$), parental marital status ($\chi^2 = 2.75$, $p = .10$), and the proportions of students from different faculties ($\chi^2 = 0.81$, $p = 1.00$).

Independent-samples t-tests were also performed to compare the two groups on age and perceived family life satisfaction (see Table 1). Results showed that the two groups did not differ significantly on their perceived family life satisfaction ($t = 0.29$, $p = .77$), while differed significantly on age, $t = -26.54$, $p < 0.01$, Cohen's $d = -2.09$. Control group participants (age = 21.94 ± 1.09) were older than the experimental group participants (age = 20.12 ± 0.57), which was expected. These results generally indicated that the experimental group sample and the control group sample were similar in their background characteristics.

Group Differences on Developmental Indicators

Independent-samples t-tests were carried out to compare the differences between the experimental group and control group on scores of the three scales and their subscales (see Table 2). Findings revealed that compared with the control group, participants in the experimental group scored significantly higher on two variables of the C-IRI including Empathy ($t = 2.84$, $p < .05$) and Fantasy ($t = 3.03$, $p < .05$), and eight variables of the measures of positive youth development, including Resilience ($t = 2.30$, $p < .05$), Emotional

Table 1. Comparison of background variables between PolyU third-year participants under 4-year and 3-year programs

		Total	PolyU 4YD	PolyU 3YD	Comparison	Effect size
Gender ^d	Male	349(40.8%)	235(41.5%)	114(39.3%)	$\chi^2 = 0.39$, $df = 2$, $p = .82$	-
	Female	501(58.5%)	327(57.8%)	174(60.0%)		
Parental marital status ^{a,c}	Not indicated	6(0.7%)	4(0.7%)	2(0.7%)	$\chi^2 = 2.75$, $df = 1$, $p = .10$	
	Intact family	702(82.0%)	473(83.6%)	229(79.0%)		-
	Non-intact family	154(18.0%)	93 (16.4%)	61(21.0%)		
Family economic status ^{ad}	CSSA recipient	71(8.3%)	45(8.0%)	26(9.0%)	$\chi^2 = 0.11$, $df = 1$, $p = .74$	-
	Non-CSSA recipient	753(88.0%)	492(86.9%)	261(90.0%)		
	Not indicated	32(3.7%)	29(5.1%)	3(1.0%)		
Academic Field ^a	FAST	69(8.1%)	46(8.1%)	23 (7.9%)	$\chi^2 = 0.81$, $df = 7$, $p = 1.00$	-
	FB	168(19.6%)	112(19.8%)	56(19.3%)		
	FCE	56(6.5%)	38(6.7%)	18(6.2%)		
	FENG	268(31.3%)	174(30.7%)	94(32.4%)		
	FH	47(5.5%)	32(5.7%)	15(5.2%)		
	FHSS	184(21.5%)	123(21.7%)	61(21.0%)		
	SD	25(2.9%)	17(3.0%)	8(2.8%)		
	SHTM	39(4.6%)	24(4.2%)	15(5.2%)		
Perceived family life satisfaction ^b		3.77(0.88)	3.77(0.88)	3.76(0.90)	$t = 0.29$, $df = 854$, $p = .77$	-
	Age ^b	20.74(1.16)	20.12(0.57)	21.94(1.09)	$t = -26.54$, $df = 368.57$, $p < .01$	Cohen's $d = -2.09$

Note: PolyU 4YD = PolyU third-year participants under the 4-year program; PolyU 3YD = PolyU Year3 participants under the 3-year program.

^a Categorical variables: values outside parenthesis were numbers of participants and values in parenthesis were the related within-group percentages.

^b Continuous variables: values outside parenthesis were means and values in parenthesis were standard deviations.

^c Intact family = parents are married in their first marriage; Non-Intact family = parents are divorced/ separated/ married in their second marriage/ others.

^d Comparison was made on the ratio of CSSA recipient to Non-CSSA recipient between the two groups.

CSSA denotes Comprehensive Social Security Assistance Scheme.

FAST = Faculty of Applied Science & Textiles, FB = Faculty of Business, FCE = Faculty of Construction & Environment, FENG = Faculty of Engineering, FH = Faculty of Humanities,

FHSS = Faculty of Health & Social Sciences, SD = School of Design, SHTM = School of Hotel & Tourism Management.

Competence ($t = 4.11, p < .05$), Cognitive Competence ($t = 2.15, p < .05$), Behavioral Competence ($t = 2.28, p < .05$), Self Determination ($t = 2.04, p < .05$), Critical Thinking ($t = 1.63, p < .05$, one-tailed), Ethical Leadership ($t = 2.26, p < .05$), and Life Satisfaction ($t = 2.41, p < .05$). Besides, the experimental group performed better than the control group on seven variables of the NSSE including Collaborative Learning ($t = 2.15, p < .05$), Higher-Order Learning ($t = 1.99, p < .05$), Effective Teaching Practices ($t = 2.47, p < .05$), Learning Strategies ($t = 4.54, p < .05$), and Supportive Environment ($t = 2.14, p < .05$), Reflective and Integrative Learning ($t = 1.87, p < .05$, one-tailed), and Discussions with Diverse Others ($t = 1.77, p < .05$, one-tailed). Moreover, two composite scores of CPYDS, the CPYDS total score and Cognitive-Behavioral Competence score also showed that the experimental group performed better than the control group. However, control group had higher scores on High-Impact Practices ($t = -1.90, p < .05$, one-tailed) than the experimental group.

Table 2. Results of independent-samples t-tests comparing developmental outcomes of PolyU 4YD and 3YD participants

	PolyU 4YD			PolyU 3YD			t	df	p
	N	M	SD	N	M	SD			
Empathy*	566	2.91	0.36	290	2.84	0.38	2.84	854.00	.00
Fantasy*	566	2.72	0.57	290	2.59	0.63	3.03	534.67	.00
Personal Distress	566	2.46	0.52	290	2.41	0.54	1.24	854.00	.21
CPYDS Total Score*	566	4.58	0.49	290	4.48	0.55	2.60	854.00	.01
Cognitive-Behavioral Competence*	566	4.53	0.59	290	4.42	0.68	2.48	515.67	.01
Problem Solving	566	4.44	0.65	290	4.42	0.71	0.45	854.00	.66
Resilience*	566	4.61	0.78	290	4.48	0.83	2.30	854.00	.02
Social Competence	566	4.60	0.75	290	4.51	0.78	1.62	854.00	.11
Emotional Competence*	566	4.34	0.71	290	4.11	0.80	4.11	525.76	.00
Cognitive Competence*	566	4.56	0.62	290	4.45	0.72	2.15	511.86	.03
Behavioral Competence*	566	4.52	0.70	290	4.39	0.81	2.28	515.22	.02
Moral Competence	566	4.77	0.68	290	4.71	0.75	1.15	854.00	.25
Self Determination*	566	4.49	0.77	290	4.37	0.88	2.04	519.79	.04
Life-long Learning	566	4.62	0.73	290	4.56	0.81	1.05	854.00	.30
Self-Efficacy	566	4.49	0.76	290	4.44	0.85	0.73	854.00	.46
Ethical Leadership*	566	4.62	0.50	290	4.53	0.58	2.26	516.79	.02
Critical Thinking ^a	566	4.65	0.69	290	4.57	0.76	1.63	854.00	.10
Self-Leadership	566	3.85	0.57	290	3.79	0.60	1.36	854.00	.17
Life Satisfaction*	566	3.86	0.95	290	3.70	1.02	2.41	854.00	.02
Collaborative Learning*	566	2.59	0.55	290	2.50	0.60	2.15	854.00	.03
Reflective and Integrative Learning ^a	566	2.62	0.52	290	2.55	0.54	1.87	854.00	.06
Student-Faculty Interaction	566	1.96	0.67	290	1.90	0.75	1.13	528.58	.26
Higher-Order Learning*	566	2.75	0.58	290	2.67	0.60	1.99	854.00	.05
Effective Teaching Practices*	566	2.70	0.53	290	2.61	0.55	2.47	854.00	.01
Quantitative Reasoning	566	2.41	0.62	290	2.37	0.65	0.87	854.00	.39
Discussions With Diverse Others ^a	566	2.46	0.59	290	2.39	0.59	1.77	854.00	.08
Learning Strategies*	566	2.59	0.61	290	2.38	0.63	4.54	854.00	.00
High-Impact Practices ^a	566	2.57	0.49	290	2.64	0.54	-1.90	854.00	.06
Quality of Interactions	566	4.63	0.86	290	4.54	0.97	1.46	854.00	.14
Supportive Environment*	566	2.52	0.57	290	2.43	0.55	2.14	854.00	.03

Note: PolyU 4YD = PolyU third-year participants under the 4-year program; PolyU 3YD = PolyU third-year participants under the 3-year program.

*means that $p \leq .05$ (two-tailed); ^a means that $p \leq .05$ (one-tailed); Total CPYDS Score = Total score of the Chinese Positive Youth Development Scale; Cognitive-Behavioral Competence = the composite score of a second-order factor based on subscales of Cognitive Competence, Behavioral Competence, and Self-Determination.

DISCUSSION

This study was conducted to investigate the impact of the 4-year undergraduate curriculum on PolyU students by comparing the developmental outcomes in third-year students in the 4-year program and third-year students in the 3-year program. Several unique features are intrinsic to this study. First, this is the first known scientific study which compared the 4-year degree program and 3-year degree program in the context of education reform in Hong Kong. Second, the study adopted a static group comparison design where third-year PolyU students in the 3-year degree program formed the control group. Third, the measures used in this study possessed good psychometric properties. Finally, the findings are overwhelmingly supportive of the original hypotheses.

In line with the original hypothesis, students in the experimental group performed better than did students in the control group. Compared with students in PolyU 3-year undergraduate degree program, participants in PolyU 4-year undergraduate degree program had higher levels of interpersonal competence (such as empathy and fantasy), and higher levels of intrapersonal development, including resilience, emotional competence, cognitive competence, behavioral competence, self-determination, ethical leadership, life satisfaction, and critical thinking. Besides, students under the 4-year program also showed more effective engagement in university life than did students studying the 3-year program. Specifically, 4-year program students engaged more in collaborative learning, reflective and integrative learning, higher-order learning, and learning activities involving discussion with students with diversified backgrounds. These findings are consistent with the available evaluation findings that the 4-year undergraduate degree program was beneficial to the holistic development of the students [14-18].

Although the findings provided support for the original hypothesis and they were overwhelmingly positive, there are several limitations of the present findings. First, the findings showed that students in the two cohorts were different in their third year (i.e., cross-sectional differences). As cross-sectional comparison can only show differences between the two groups at a particular time point, longitudinal data are needed to give a more complete picture of the differences between the two groups over time. Second, as quota sampling was used, the sample might not be representative of the two groups in the general population. Third, as expected, students in the 3-year program were older than students in the 4-year program because they had one more year of secondary school education. As such, the differences may be explained in terms of age effect. However, this alternative explanation does not make sense because control group students performed poorer than experimental group students, despite the fact that they were older. One possible solution to this problem is to match the two samples further so that there would not be age differences between the two groups. However, by doing this, the sample size would be reduced.

In conclusion, using the static group comparison design, this pioneer study showed that students in the 4-year undergraduate degree program did better than students in the 3-year degree program, which suggests that the GUR component has possible impact on the development of the 4-year degree program students. Nevertheless, one should bear in mind the limitations of the static group comparison design while interpreting the findings.

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Chapter 186

THE VIEW OF THE TEACHER IN A NEW GENERAL EDUCATION PROGRAM IN HONG KONG

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ABSTRACT

Under the new education reform in Hong Kong, The Hong Kong Polytechnic University (PolyU) has expanded its undergraduate education from three to four years since the 2012-2013 academic year. Along with the transition, the General University Requirements (GUR) has been developed as an integral part on general education of the new four-year undergraduate curriculum of PolyU. The present chapter examined the implementation quality and effectiveness of the GUR in the 2012-2013 academic year based on focus group interviews with teachers. Twenty teachers who taught GUR subjects were interviewed for their perceptions and experiences about the GUR. Results revealed that the teachers generally had positive perceptions of the GUR in terms of its rationales, teaching and learning modes, and implementation quality. GUR subjects were also considered effective in helping students to develop in a holistic manner. The findings suggest that the first-year implementation of the GUR at PolyU was basically successful.

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INTRODUCTION

In recent decades, the society of Hong Kong has been experiencing drastic changes. Primarily, Hong Kong has established itself as an emerging knowledge-based economy. In addition, the political and economic blueprint of Hong Kong has been reshaped by its transition from a British colony to a Special Administrative Region of China. Furthermore, the fast development of information technology has transferred Hong Kong people's lives and exposed them to unexpected new domains [1]. Facing these changes, education was deemed vital for developing people with strong character, emotional attributes, adaptability, creativity, and independent learning to underpin Hong Kong's development to be a diverse, democratic, and civilized cosmopolitan city [1]. However, the education system in Hong Kong was criticized for its early narrowing and "streamlining" in students' study [2]. In particular, the three-year undergraduate education under the British system has been criticized for its disciplinary concentration upon students' enrollment and its inadequacy of helping students to develop in a holistic manner. Moreover, pedagogy in both secondary and higher education was criticized for examination-driven, emphasis on passive learning, and inability to provide holistic learning experiences [1].

As a result, there was a strong need to reform the secondary and higher education system of Hong Kong to reinforce general education and promote students' all-round development. In 2000, the Hong Kong Education Commission issued a report named "Learning for Life, Learning through Life: Reform Proposals for the Education System in Hong Kong". The report proposed a comprehensive reform on secondary and higher education in aspects of academic structure, curricula and assessment to foster lifelong learning and all-round education. With regard to higher education, its aim was proposed as:

"to develop students' independent and critical thinking, creativity and ability to learn independently and to explore, in preparation for the mastering of knowledge in a certain discipline; to foster in students an aspiration for self-improvement, a positive attitude towards life and a commitment to their families, their society and their country; and to enhance students' ability to learn, live and work in a diverse social and cross-cultural environment" [1].

To this end, the undergraduate education in Hong Kong was suggested to be reformed from three to four years and to "strengthen general education and multi-disciplinary learning" [1].

Against the above background, the University Grants Committee (UGC) mandated the eight UGC-funded universities in Hong Kong to formally change the structure of their undergraduate education from three to four years in the academic year of 2012-2013. Although the UGC did not directly mandate a formal general education curriculum, it required the new four-year undergraduate curriculum to strike a right balance between the breadth and depth of students' study, and proposed the additional year should "enable students to have more time and space to build a broader knowledge base and a solidier foundation for whole-person development" [1]. The new curriculum was expected to contribute to the development of qualified talents to sustain the development of a knowledge-based economy and fast-changing society in Hong Kong [3]. As a response, all the eight universities officially implemented their new four-year undergraduate programmes in 2012-2013 academic year, with the incorporation of a general education curriculum in each

programme [4]. These universities developed a set of intended learning outcomes for their GE curricula which centered on multidisciplinary knowledge, critical thinking, communication, problem solving, lifelong learning, civic responsibility, morality and global outlook [4, 5]. The GE curricula normally consisted of two components: a core curriculum mandated to all students and a distributional requirements system requiring students to take subjects selectively within several broad knowledge areas [4-6]. Furthermore, a more engaging and active pedagogy and “more authentic forms of assessment” [2] were encouraged in the new GE curricula, which was believed as contributing to “a major transformation of both faculty and student orientations toward the learning process consistent with the stated objectives of the reform” [2].

As one of the eight UGC-funded universities, The Hong Kong Polytechnic University (PolyU) officially launched its new four-year undergraduate curriculum in 2012-2013 academic year. It developed a set of desired graduate attributes for its new curriculum including effective communication, critical thinking, problem solving, lifelong learning, ethical leadership, and professional competence [7]. To cultivate these attributes in students, a unique GE system entitled the General University Requirements (GUR) was developed as a fundamental part of the new four-year curriculum. The GUR consisted of six components [8]: Freshman Seminar (FS, 3 credits), Leadership and Intrapersonal Development (LIPD, 3 credits), Language and Communication Requirements (LCR, 9 credits), Cluster Area Requirements (CAR, 12 credits), Service Learning (SL, 3 credits) and Healthy Lifestyle (HL, non-credit-bearing). Each student who studies in the four-year undergraduate program starting from 2012-2013 academic year is required to complete 30 credits in his or her GUR study which is one fourth of the minimal total credits (120 credits) for graduation. The rationale and purpose of each GUR component are briefly described below:

- FS aims to introduce students to their broad disciplines through offering one mandatory FS subject to all students in each broad discipline.
- LIPD aims to cultivate intrapersonal and interpersonal knowledge and skills that are conducive to effective leadership in students. It consists of two subjects: “Tango! Management Self and Leading Others” (for students in Faculty of Business), and “Tomorrow’s Leaders” (TL) (for students in all other faculties).
- LCR aims to enhance students’ language proficiencies in both English and Chinese. It consists of two sub-components: LCR-Chinese and LCR-English.
- CAR aims to expand students’ intellectual capacity and enquiry methods, and develop students’ reading and writing skills. Each student needs to take at least one subject from each of the four cluster areas of learning: “CAR A–Human Nature, Relations and Development”, “CAR B–Community, Organization and Globalization”, “CAR C–History, Culture and World Views”, and “CAR D–Science, Technology and Environment”. The CAR subjects that each student completed also need to cover three requirements: China Studies Requirements, English Writing and Reading Requirements (EW/ER), and Chinese Writing and Reading Requirements (CW/CR).
- SL aims to develop the awareness and competence to serve others in students through requiring each student to take one subject with significant service component.

- HL aims to help students acquire knowledge and skills for maintaining a healthy lifestyle through requiring each student to take a non-credit-bearing subject in HL.

Most GUR subjects have incorporated a more active and engaging pedagogy in their teaching and learning strategies, including group project, hands-on workshop, field work and real case demonstration. More authentic forms of assessments like individual/group project and peer assessment were also incorporated to effectively evaluate students' meaningful application of essential knowledge [9]. In 2012-2013 academic year, 107 GUR subjects were offered to all first-year students enrolled in the four-year undergraduate programme.

While the reform in higher education was rigorous in Hong Kong, little evaluation research has been conducted. With reference to PolyU, there is a need to examine whether the GUR ran smoothly and how effective it was in promoting students' all-round development. To this end, a five-year comprehensive evaluation project was conducted since 2012-2013 academic year. Different evaluation components were incorporated in the project, including objective outcome evaluation based on a longitudinal survey on students' changes under the new four-year curriculum and the GUR and on Collegiate Learning Assessment Plus (CLA+), subjective outcome evaluation based on secondary data analyses of the PolyU Student Feedback Questionnaire (SFQ), qualitative evaluation based on yearly student and teacher focus groups, and longitudinal case study. Teacher focus group is one component of qualitative evaluation, aiming to investigate teachers' views on the GUR with reference to its teaching and learning, implementation, and perceived benefits and challenges.

Qualitative evaluation was incorporated in the current evaluation project for several reasons. First, as commonly used methods in evaluation research, qualitative methods help researchers explore in-depth human experiences and perspectives, which could not be obtained by quantitative methods [10-12]. Second, qualitative evaluation is characterized by its intensity, subtlety, depth and detail in data collection [13, 14], which was contributed by the nature of qualitative data collection that "not constrained by predetermined categories of analysis" [13]. Third, qualitative evaluation helps researchers identify "the factors that contribute to successful or unsuccessful delivery" [11]. It also helps explore the program outcomes and how these outcomes are brought into being.

Focus group interview is a widely used qualitative method which collects data through interviewing a group of people on their perceptions, experiences, and attitudes toward a defined topic [15-17]. It was adopted as a method in qualitative evaluation in this study for the following reasons. First, focus group is more efficient than observation and individual interview in terms of the time and energy required [16]. Second, focus group is useful for investigating participants' attitudes and perspectives which are hard to be obtained from observations [16]. Third, compared with individual interview, focus group provides an opportunity for researchers to identify the similarities and differences between participants' views through group discussion so that further explorations can be carried out [16, 18]. Furthermore, focus group is advantageous for gaining "richer and more well-thought-out ideas"[19] and "providing some in-the-moment triangulation as interviewee elaborate, explain, and correct information as it is provided" [20]. Focus group method has been widely used in educational settings for educational planning and assessment [21-24]. In the specific context of Hong Kong, focus group method was used to evaluate subjects promoting holistic development and leadership in university students [25, 26].

In this study, focus group method was adopted to explore the views of subject teachers on the GUR with reference to its teaching and learning, implementation, perceived benefits and challenges in the first-year implementation. Teachers teaching GUR subjects are important stakeholders of the GUR because they are directly involved in activities of class teaching and obtain first-hand information of course delivery and students' changes. Comparing to students, teachers would look at the issues from an adult, teacher, and professional perspective. As teachers are directly involved in the development of GUR subjects, and are more familiar with the policy of the GUR, their understanding would offer an alternative perspective different from those of other stakeholders such as students. Teachers' views could also be balanced by and integrated with students' views to gain a more comprehensive understanding of the implementation status of the GUR. Against this background, the present study attempted to investigate the implementation and effectiveness of the GUR at PolyU in its' first-year implementation (2012-2013 academic year) based on focus group interviews with teachers. As a qualitative evaluation research, the principles suggested by Shek, Tang and Han [27] were adhered to as far as possible. A general qualitative orientation was adopted in this study.

OUR STUDY

The participants were teachers involved in the teaching of GUR subjects in 2012-2013 academic year. These teachers were recruited in May of 2013 through the nomination of program leaders and invitation of key teachers in different GUR components. In late May and early June, four teacher focus groups were formed and conducted, with each focus group corresponding to one specific GUR area. The four focus groups were: TL, CAR, LCR-English and LCR-Chinese. A total of 20 teachers participated in the focus groups. The numbers of participants in each focus group were: TL ($n = 6$), CAR ($n = 4$), LCR-English ($n = 4$), LCR-Chinese ($n = 6$). There was no focus group interview being conducted for SL, HL and FS. As SL subjects were not offered to Year 1 students in Semester 1 and Semester 2, there was no need to collect data for this area. For FS, as the senior management met with teachers of FS at the end of 2012-2013 academic year, this component was not assessed. Since HL subject refers to a systematically stepwise training within two years which starts from lecture to fitness and sports skill training, there were only lectures of health and sports knowledge offered but no substantial training conducted in the first academic year. Therefore, the focus group of HL was also not conducted.

The length of the focus group interviews ranged from one to two hours. The whole process of each focus group was audio-recorded. A focus group protocol was developed by the research team to guide the interview. The protocol was comprised of four major categories of questions including: (a) teachers' understanding and perceived significance of the GUR; (b) teachers' views on the teaching and learning of GUR subjects; (c) teachers' observed and perceived changes from students in studying GUR subjects, and (d) teachers' perceptions of the challenges in the implementation of the GUR.

All the focus group records were transcribed into full texts. All the transcripts were imported in NVivo Software (Version 10) for analyses. Each transcript was carefully read for at least twice and coded in the software into different categories/themes based on the

transcript itself and the focus group protocol. After the initial coding, all the codes were read again for further organization. Inter-rater reliability on the coding was also calculated. A research assistant who was not involved in the coding process re-coded 20 randomly selected narratives without knowing the original codes generated. The inter-rater agreement percentage calculated on the generated themes from the coding was 90%.

OUR FINDING

At the very beginning of the focus group interviews, teachers were asked to express their understanding and perceived significance of the GUR. Basically, the majority of teachers indicated their basic understanding of and agreement with the rationale of the GUR. Some selected narratives were provided below to show teachers' understanding:

"We agree with the idea of the GUR which tries to broaden students' horizons. GUR actually has a broad coverage. It includes broadening subjects, subjects related to students' health and students' leadership development, and so on. This is good and this is what we agree with."

"To my understanding, GUR subjects are to provide students with a general education in addition to their development in their major studies. These are general topics for all the students regardless of their major studies. I agree with the idea of the GUR because it is very important to students' all-round development."

A few teachers' elaboration was richer and more profound than the original rationale of the GUR, which reflected their in-depth understanding of the philosophy of general education. For example, a teacher in the focus group of CAR said:

"Based on my understanding, GE (GUR) has three aims. The first [aim] is to train students' critical thinking and communication skills, and other generic transferable skills. The second aim is to develop in students a basic and overall understanding of human, society and the world, and capacity to make value judgments. The third aim is to develop in students a sense of responsibility based on their understanding of the critical issues in the world."

With reference to teachers' perceived significance of the GUR, majority of teachers perceived the GUR as important and valuable for the development of students beyond their major studies. For example, in the focus group of CAR, another teacher said:

"I perceive these [GUR] subjects as very important because they would not focus on one discipline but provide students with opportunities to learn knowledge in other disciplines and promote students' interdisciplinary development. This is very important for students because they are usually absorbed in the study in their own disciplines. Nevertheless, when they enter into the society, they would face a very broad world. Therefore, the GUR provides them with opportunities to learn different aspects of the world and to develop in multiple ways."

Teachers' Perceptions of the Teaching and Learning of GUR Subjects

Teachers in focus groups were asked to express their views on the teaching and learning (T&L) of the GUR subjects. Teachers' perceptions were generally highly positive. They perceived the adoption of active and engaging teaching and learning methods in their subjects as effective in promoting students' active engagement in learning and their development of

important generic skills. For example, teachers whose subjects involving group work expressed that group work greatly facilitated peer learning and peer interaction, and developed students' interpersonal skills. In the focus group of CAR, one teacher said:

"I think they (students) quite like group work. ...we have created some activities in my subject. Students enjoyed it a lot. ... At the beginning of this term, I grouped students into four different groups and students complained you know 'I want to be a group with Catherine when I am doing this'. But at the end, they were grateful that they were not with their friends because they learn[ed] so much better with some other people. And they can actually exchange ideas better."

A few teachers mentioned that at the very beginning, group work might not be very appealing to students but be more challenging to them. However, after completing group work tasks, students treasured their learning experiences very much since the process provided them with authentic opportunities to interact with their peers. One teacher in the focus group of TL expressed:

"The group project and presentation must not be called 'appealing' to the students. But it is a very important task for them because they need to present their group tasks in front of all the students in the class. But for many groups of students in my class, it was in this moment that they felt this subject had impact on them very much....One interesting aspect is that through students' final reflections, I found that they treasured their learning in group work and presentation very much. And through group work and presentation, they were experiencing the process of interaction with others, learning to do group projects better, and learning to listen to others better."

Teachers also remarked that the experiential learning component in their GUR subjects offered students profound learning experiences through learning by doing and from real-life experience. This T&L mode was regarded as highly conducive to the development of students' problem solving ability. In the focus group of CAR, a teacher who taught one subject on dealing with disasters said:

"I asked students to go to community to do assessment. So they came to know a lot about their surroundings because in the past they did not pay much attention to. I was asking them to take note of everything that was not perfect and they took pictures and then they would have to offer me how to improve their surroundings so that you know we reduce the risks of disasters. ...We have also had big exhibitions that our students could participate by going into the exhibition and they could ask people questions why these are important and how am I going to use this. They learned in a real life environment and I think that will make things different for them and by doing so they picked up cues from the environment. You know each point would be a learning point for them and I think that is important. You don't actually need to open a book and read in order to learn because learning from life experiences is one way of learning so that sharpens students' observational skills and also they learned how to improvise things."

Other engaging teaching and learning methods have also gained teachers' positive comments, such as case demonstration and visualized methods. Teachers commented that visualized methods such as video-playing were much welcomed by students and engaged students in learning because they helped to demonstrate the abstract subject contents in a vivid approach to facilitate students' understanding.

Meanwhile, teachers perceived that some traditional methods such as mere lecturing in a large lecture hall were less conducive to students' active learning and students' interaction with their peers and teachers, and were less appealing to students.

Teachers' Perceived Changes from Students after Studying GUR Subjects

Teachers in focus groups were also asked to describe their perceived changes in the students after taking their GUR subjects. The responses were very positive. Majority of teachers responded that they perceived positive changes in their students after attending their classes. The most obviously perceived change was improvement of students' communication skills in both Chinese and English. Teachers in the focus group of LCR-Chinese expressed that, after fourteen weeks' teaching, they observed obvious improvement in their students' discussion and expression skills. For example, one teacher said:

"Students do have changes. For example, in the discussion session in my first class, I found that many students' discussion was very 'standardized' or 'mechanical'. They would prepare in advance who speaks first and who second. This was very obvious. However, in the later classes, I saw their improvements. Some students began to try to make summaries or conclusions of others' points. Some would try to lead the discussion back to the topic if the discussion was going off the track. In the final stage, some students' progress was very obvious, especially in their listening and inquiry skills."

Teachers in the focus groups of LCR-English and CAR also perceived improvement of their students' English written communication skills through the training of academic writing in these subjects. For example, teachers in the focus group of LCR-English expressed that their students' writing skills were improved through the process of integrating and criticizing different sources in their writing. Teachers in the focus group of CAR expressed that CAR subjects with English reading and writing requirements greatly facilitated the development of students' English writing skills through a collaborative effort of CAR subject teachers and teachers in English Language Centre (ELC) in instructing and supervising students' writing tasks. This benefit of the GUR could be illustrated by the following selected narratives:

"At the very beginning, students felt their [LCR-English] subjects could be just like other English subjects in their secondary school and they could handle them quite easily. Then later on by having done the course, they realized that these subjects were not exactly the same, because that kind of depth of research and the ability to produce or put all the ideas together and to show that they are able to critique... All these elements are something that students really appreciated."

"Because my subject had reading and writing requirement, students needed to see teachers in ELC. Here I especially want to express my gratitude to ELC teachers for their support, inspiration, and help to my students. During my teaching of this subject, comparing to the same year students' writing assignments in other subjects, I found that the assignments of my students were much easier for marking. For example, in the past I usually needed to read students' writings for several times to understand what they were saying. Now I don't find this barrier anymore."

Another change from students perceived by teachers was the deepening of students' understanding of interpersonal and intrapersonal attributes after students had studied the TL subjects. Viewed by teachers in the focus group of TL, students were changing from not perceiving the relevance and importance of the leadership theories to increasingly being aware of the value and importance of the intrapersonal and interpersonal attributes to their lives. For example, one teacher in the focus group of TL expressed:

"I feel that they (students) changed gradually from not knowing what the subject was teaching in the first semester to thinking these [interpersonal and intrapersonal] attributes important and needed to be learned in the second semester. ... I think that the impact [of the subject] is that they gradually understood what roles these attributes would play in their lives."

TL teachers also perceived the deepening of students' understanding of "leadership" after attending the TL courses. They said that many students perceived leadership as just "an inborn trait to lead others" or had other misunderstandings such as "I don't want to become a leadership so I don't think it is necessary for me to take this subject", etc. at the very beginning of the classes. However, many of these students changed their mind-sets at the later stage of the subject. For example, some students realized that leadership also meant "self-leadership" and "to take responsibility for one's own life". One teacher said in the focus group:

"One point I want to highlight is that students' understanding of the concept of leadership has changed a lot. At the very beginning of the class, many students thought this subject had no relationship with them because they thought many leaders were 'inborn'. Some students thought they could never become a leader because they did not have the inborn traits of a leader. However, after completing this subject, many students thought that actually every person could become a leader. Most importantly, they knew that they should 'take responsibility for their life' which meant they knew the importance of self-leadership."

Furthermore, some teachers indicated the development of students' self-reflection and self-awareness through writing reflective journals. Students' critical thinking and problem solving skills were also perceived as improved through knowledge study, experiential learning, and writing assignments in different GUR subjects.

Although positive changes from students were perceived, some teachers cautioned that the development of some attributes such as critical thinking and ethical leadership might need a longer time and might not be obviously perceived by teachers. Nevertheless, teachers believed that their subjects would serve as a foundation in facilitating students' development in these important attributes, as was said by one teacher in the focus group of TL:

"Actually I think growth needs time. That means some students might possibly be enlightened by the subject after ten years later. But that doesn't matter. I hope the impact is 'sowing the seeds' and actually these seeds were not firstly sowed by us. Some people have sowed them in an earlier stage. What we do is to continue to give water and nutrition to them to keep them growing."

Teachers' Perceived Challenges in the Implementation of the GUR

In the focus groups, teachers were also asked to express their perceived challenges in the implementation of the GUR. One major challenge noted by the teachers was CAR subject registration. Teachers in the focus group of CAR noted that many students encountered difficulties in registering CAR subjects because students in different departments were assigned different timeslots to register CAR subjects. Those whose departments were assigned a later timeslot would find few places left in the registration system for them. One teacher in School of Nursing who also taught CAR subjects expressed this "inequality" of CAR subject registration system:

"At the very beginning, some of the students from my department indicated that they would really like to join my subject (a CAR subject). The problem is none of them could get on to it because within the first hour [of subject registration], all the places were gone. Because they arrange different departments to register [CAR subjects] in different time zones, my students usually have a later time zone because they think my students have five years [of undergraduate programme] and they could do it (CAR) later on. But later on, my student will need to go to hospital [to do clinical placement]."

Another challenge noted by the teachers was some teachers' heavier workload in teaching and marking students' assignments. A few teachers in focus groups indicated that they felt stressful in teaching large classes and marking hundred pieces of students' writing assignments. These teachers expressed expectations for more manpower assistance in their teaching and paper marking tasks.

DISCUSSION

This study attempted to evaluate the implementation and effectiveness of the GUR at PolyU in its first-year implementation based on teachers' perspectives collected from focus group interviews. This study has several strengths. First, in view of the paucity of evaluation studies of the new four-year curriculum in Hong Kong, this is a pioneer study. Second, teachers were recruited in this study because we believed that teachers were major stakeholder of the study. This practice is in line with the standards of evaluation in the major evaluation societies on evaluation [28]. Third, as there are few evaluation studies on general education programs in the Chinese context, this is an additional unique feature of this study.

The present findings suggested the GUR subjects were successfully and smoothly implemented and they contributed to the development of desired graduate attributes in undergraduate students at PolyU. As key stakeholders of the GUR implementation, teachers generally understood and agreed with the rationale of the GUR. They perceived the GUR as important for students' development. Teachers' agreement with the rationale of the GUR is vital to the successful implementation and continuing development of the GUR. Reform on GE was not only a curricular but also a cultural change [29] and one critical obstacle to it is the apathetic or "not buy-in" attitudes of academic staff towards the new GE curriculum [30]. For example, research showed that faculty' resistance to the reform of general education could result in the turning down of reform proposals, drawn out of the reform process, and the unachievable reform goals [31, 32]. Therefore, development of shared educational values and philosophy is a key to the implementation of GE [33], and significant effort should be made to ensure teachers' internalization of rationale of GE [34].

Teachers' views also indicated a basic alignment of the GUR with the desired graduate attributes of PolyU. The factors that contributed most to this alignment were active and engaging T&L methods that were widely adopted in different GUR components, including group project, field trip, case demonstration and visual methods, etc. The adoption of an active pedagogy facilitated students' understanding and digestion of subject contents, engaged students in learning, and promoted students' development in some important attributes such as communication, interpersonal relationship, self-reflection, critical thinking and problem solving. As shown in the literature, the group work and experiential learning could provide students with profound experiences in learning, develop in them important competencies, and connect their learning to practices [35-37]. The recent reform on GE also showed a changed focus from content to teaching modes and methods [38], and a transition from traditional to more engaging and student-centered T&L methods such as group project, case study, experiential learning, etc. [39]. These methods were shown to have stimulated students in learning and to be more conducive to students' all-round development than some traditional methods [40-42].

Finally, challenges were identified from the present findings, which was important for improving the implementation of the GUR. Students' difficulty in CAR subject registration indicated the limitations of CAR subject registration system and the inadequacy of CAR subjects on offer, which might be a risk for future successful implementation of the GUR. In view of these findings, the registration system was enhanced and refined in 2013-2014 academic year.

The present findings are basically in line with the findings of student focus groups conducted by Shek et al. [43] on the implementation of GUR in 2012-2013 academic year. The focus group findings showed that students gave highly positive comments on the active and engaging teaching and learning mode of the GUR, and perceived the GUR as beneficial to their development in all-round way in terms of the important attributes of communication, problem solving, lifelong learning and leadership. With particular focus on TL, the findings are consistent with the findings of the quantitative evaluation conducted by Shek and Leung [44], Shek and Ma [45], Shek and Yu [46] which indicated that the TL subject was beneficial to the holistic development of the students.

Several limitations of the study should be noted. First, although focus group interview is good at collecting constructed ideas and perspectives from different participants, its conclusion is limited when making generalization or representativeness to a larger population [47]. Second, since teacher is the only one kind of stakeholders, their views might not represent the views of other stakeholders such as students or administrators. The experiences of other stakeholders need to be voiced. Furthermore, the current findings need to be triangulated by findings from other stakeholders. For example, a combination of teachers' views with those of students could help gain a better understanding of the "merits" and "flaws" of the GUR and of students' development. Furthermore, to gain a more comprehensive understanding of the implementation of the GUR, findings based on other evaluation methods need to be incorporated, such as objective outcome evaluation and longitudinal case studies on students. Despite the above-mentioned limitations, the current study provides evidence on the effectiveness of the GUR as a unique GE curriculum in promoting all-round development in undergraduate students in PolyU. In conjunction with the findings of other evaluation methods, the GUR at PolyU can be regarded as successful in promoting the holistic development of the students. Given the limited literature on the evaluation of GE in Hong Kong, the present study could be considered an important contribution to the field.

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Chapter 187

A FOCUS GROUP EVALUATION OF TEACHERS’ VIEWS CONCERNING A NEW GENERAL EDUCATION PROGRAM

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ABSTRACT

Using teachers’ focus group interviews (n = 40), this study examined the impact of the General University Requirements (GUR) implemented at The Hong Kong Polytechnic University (PolyU). Results showed that teachers were generally satisfied with the GUR subjects and its implementation in its second year. Teachers regarded the design of GUR subjects was good and the students generally welcomed the subjects. Interactive teaching and learning methods adopted in GUR subjects such as fieldwork, hands-on project, and team debate were highly appreciated by the respondents. Teachers also reflected that the GUR had promoted the intrapersonal and interpersonal development of the students. However, several challenges were also reported by teachers,

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including the difficulty level of Freshman Seminar subjects and lack of interaction in some GUR subjects, which suggested directions for further improvements.

INTRODUCTION

Program effectiveness can be assessed by different methods and the view of program implementers is one of the key areas for evaluation. There are several reasons why program evaluation should include the view of program implementers. First, since program implementers are important stakeholders in program development, their ideas should be identified and taken into account [1-3]. Second, from a practical perspective, a more holistic view about the program effect can be obtained from program implementers and thereby improves the quality of program implementation. Specifically, program implementers can provide opinions regarding the feedback from the program participants. At the same time, program workers would gain a sense of equality and respect when their voices are heard, which may further promote their work enthusiasm and engagement. Third, program implementers play a particular role in providing their opinions concerning the activities being implemented and suggestions on how the program can be improved. For instance, in adolescent prevention programs, it is common to interview the program workers (e.g., social workers and teachers) regarding their perceptions of the program design, objectives, and rationales [4, 5]. In such contexts, program implementers are believed to have more relevant experiences in making professional judgment about the quality of the program.

With reference to school/university-based programs, teachers are essential implementers and their perceptions about the program provide important information on the effectiveness of the program implementation [6-8]. First, as teachers are the primary deliverers of the program, their feelings, comments, and suggestions are crucial for quality program implementation in school/university settings [5]. As noted by Flannery and Torquati [9], “teachers who are not satisfied with a program are less likely to use the program materials, regardless of whether their principal or district administration is supportive of the program” [9]. Second, teachers with professional training and experience can usually view the program in a deep and professional way and thus are in a good position to assess the effectiveness of the program. Third, teachers who are directly engaged in class teaching can gain valuable information (i.e., students’ changes and teaching problems) which program managers, developers, and researchers could not obtain directly. Therefore, in evaluating university-based programs, it is necessary to take into account the views of teachers. Despite the merits of teachers’ views on school/university-based program, evaluation research based on teachers’ views is grossly inadequate in different Chinese contexts. In this study, we examined the effectiveness of a university-based general education program in Hong Kong from the perspectives of teachers.

At The Hong Kong Polytechnic University (PolyU), a new general education program entitled “General University Requirements (GUR)” has been developed and implemented since 2012/13 as an integral part of the four-year undergraduate curriculum. The purposes of the GUR are to promote the development of five core attributes in PolyU undergraduate students, including effective communication, innovative problem solving, critical thinking, ethical leadership, and lifelong learning. There are six areas in GUR as follows:

- 1) *Freshman Seminar (FS)*: Introduce student to the professional world of a broad discipline, cultivate higher order thinking skills, encourage entrepreneurship and learn to engage in self-directed and autonomous study.
- 2) *Language and Communication Requirements (LCR)*: Help students to develop language competence for academic and professional needs in both Chinese and English.
- 3) *Leadership and Intra-Personal Development (LIPD)*: Help students to develop self-awareness and acquire interpersonal and self-reflection skills essential for an effective leader.
- 4) *Cluster Area Requirements (CAR)*: Expand intellectual capacity beyond disciplinary domain.
- 5) *Service-Learning (SL)*: Apply the knowledge and skills from university learning to meet community needs.
- 6) *Healthy Lifestyle (HL)*: Acquire the basic knowledge and skills to maintain a healthy lifestyle and quality of life.

To evaluate the effectiveness of GUR, a five-year longitudinal project has been conducted since the inception of the new four-year undergraduate curriculum in 2012/2013 academic year. The project adopts a mixed-method design including the collection of qualitative and quantitative data. Qualitative methods include document analyses and focus group interviews with different stakeholders (e.g., teachers and students). Quantitative methods include objective outcome evaluation addressing student-level developmental indicators and subjective outcome evaluation on students' feedback on GUR subjects.

Using such a mixed-method design, previous evaluation research on initial implementation of GUR demonstrated favorable findings. For example, in a study based on student focus groups ($n = 62$), it was found that participants generally had positive perceptions of GUR subjects, the teachers, and the benefits of the subjects in 2012/2013 [10]. Another study based on teacher focus groups ($n = 20$) in the same academic year revealed similar findings that the subject contents, teaching quality, and the effectiveness of GUR subjects were perceived in a positive manner by the teachers [11]. A more recent study based on student feedback questionnaire showed that students generally held positive perceptions of GUR subjects in terms of their learning experiences and the quality of staff teaching in 2012/2013 [12]. These findings consistently suggest that the initial implementation of the GUR was successful.

Despite the success of the GUR in its first-year implementation, it is unknown whether the program implementation in its second year would also be smooth and effective. In 2013/2014 academic year, the GUR implementation had two new features. First, there were modifications in the curricula of a few GUR subjects. In particular, LCR subjects' arrangement and policies were refined in 2013/2014. For example, in 2012/2013, students with low levels of English and Chinese language proficiency were required to take remedial courses to enhance their basic skills before they could take advanced courses. However, such remedial courses were cancelled in 2013/14 based on the feedback of students and teachers. Another example is Freshman Seminars. With the experience in first year, the content and delivery mode of Freshman Seminars were fine-tuned in 2013/14 school year. Second, the number of students enrolled in 2013/2014 increased largely ($n = 32,339$) as compared to 2012/13 academic year ($n = 21,080$). Thus, class size, teaching strategies, and resources were

refined accordingly. It is imperative to find out whether these factors may affect GUR implementation.

Against this background, the present study attempted to examine teachers’ views on GUR subjects and its implementation in 2013/2014 via focus groups approach. Specifically, teachers who taught GUR subjects in this academic year were invited to participate in focus group interviews regarding their views on the contents, teaching and learning methods, perceived benefits on students, as well as perceived challenges of the GUR subjects they taught. It is expected that findings of the present study would constitute an important addition to literature about the evaluation and improvement of general education program in university contexts.

THE FOCUS GROUP

A total of 40 teachers who taught GUR subjects in 2013/14 participated in the focus groups. These teachers were mostly nominated by leaders of the relevant subjects. Seven teacher focus groups were formed, with each group corresponding to one specific GUR area including FS, CAR, SL, LCR-Chinese, LCR-English, LIPD-“Tango! Managing Self and Leading Others” (Tango!), and LIPD-“Tomorrow’s Leaders” (TL). The number of participants in each focus group ranged from three to nine and the related information is presented in Table 1. One teacher who taught in two GUR areas was invited to participate in two focus groups.

Table 1. Number of participants in each session of teacher focus group interviews

Teacher Focus Group Interviews	No. of Participants
Session 1 (LCR-Chinese)	9
Session 2 (FS)	4
Session 3 (CAR)	6
Session 4 (SL)	6
Session 5 (LCR-English)	6
Session 6 (Tango!)	3
Session 7 (TL)	7
Total	40

Note. One teacher taught in two different GUR areas were invited to participate in the focus groups in these two areas. Therefore, the sum of numbers of participants in each focus group was 41 and the actual total number of the participants was 40. “Tango!” and “TL” belong to LIPD component.

All focus groups were conducted at the end of the second semester of 2013/2014 academic year. For each interview session, one researcher was present served as the moderator hosting the whole interview. The moderators were all academic staffs in the project with rich experience in qualitative research. The length of the interviews ranged from one to two hours. The group interviews in all six focus groups were audio-recorded. The process of one focus group was recorded by taking notes since one participant refused the audio-recording. All six audio records were transcribed into full texts. Each transcription text was further checked by a research assistant of the project and a student helper with basic research training to ensure accuracy and consistency.

A teacher focus group protocol was developed by the research team to guide the interviews with teachers. The protocol included the following basic categories: (a) teachers' views on the contents of the GUR subjects, (b) teachers' views on teaching and learning of the GUR subjects, (c) teachers' perceived benefits of the GUR subjects on students, (d) teachers' views on the evaluation system of the GUR subjects, and (e) major challenges perceived by teachers in GUR implementation.

The six transcripts based on audio tapes and one written summary for one focus group interview were imported into NVivo Software (Version 10) for coding, which coded the raw data into different themes and categories based on both the transcription text and the interview protocol. Specifically, by using NVivo software, a researcher coded each transcript for at least twice. After the initial coding, all the codes were further read and organized by the researcher. During this process, only one researcher was involved. Doubtful codes were resolved through discussion amongst the researchers. The inter-rater reliability was also examined. After the initial coding, another researcher who did not know the initial codes recoded 20 randomly selected narratives. The inter-rater agreement percentage on the selected narratives was 90%. Common themes and categories were generated in five aspects: contents, teaching and learning, perceived benefits, evaluation system, and major challenges in GUR implementation.

WHAT WE FOUND

At the very beginning, teachers were asked to express their views on the contents of the GUR subjects they taught. The majority of the teachers perceived the subject contents as inspirational and highly welcomed by students. For example, a teacher in the focus group of LCR-English subjects said:

"In the first chapter, we started to talk about styles, and they (students) have to start to understand better, and know what kind of words can be used in academic writing and what kind of words cannot be used. And they (students) actually seemed to be quite interested in this one; they felt like, 'oh, I've never thought about this one...you know, like these (words) [students showing to me] should not be used in academic writing.'"

Besides, most teachers perceived that the GUR subject content was beneficial, interesting, rich, and concrete since they were closely related to students' practices and real life issues. Several related narratives were provided below:

"I think the design of course is not only for text examination, but also for promoting students' capability for dealing with difficulties in life. We asked students to design Chinese version of leaflets and advertising narrations. The students liked it and thought the skills were very useful in the commercial society." (One teacher in LCR-Chinese)

"I am collecting students' reflective journal these days. By reading their writings, I feel the course is really interesting. Many students treat the course very positively. Because they think the course really let them broaden their horizon and attracts them. Science students think the content talking about culture in the course is very interesting." (One teacher in CAR)

"I think this is very important. ... I don't know how others teach leadership. Within the community, students in the leadership courses typically play with 'paper tower exercise'. That is traditional teaching. They (teachers) don't teach some concrete knowledge. These (the contents in TL subjects) are really some research-based evidence. ... I think the content was very rich and could also be transferred to different disciplines." (One teacher in TL)

On the other hand, teachers in some subjects, especially FS subjects, expressed concerns on their subject content. They were worried that some FS subjects were a bit too difficult for freshmen to study. Teachers also perceived the contents of a few GUR subjects as not directly related to students' own disciplines which had probably reduced the students' learning motivation. Meanwhile, promising suggestions were also raised by teachers accordingly to address these issues. Two teachers in the focus group of FS subjects said, respectively:

"FS seminars in APSS required students to finish the project work assignment. I think the scope of assignment, particularly quantitative data analysis, might exceed students' ability at the time of the subject offered. It might be very hard for freshmen to obtain such knowledge."

"Ur, our students (in FS subjects) complained: 'Why am I learning things that I don't need to use at work?' I think students might need to find motivation to learn from other's stream as some might express contempt towards streams other than their own. I suggest maybe making lecture captivating, multimedia, and interesting could be a way out to resolve the students' disinterest in exposure to broad discipline in their own field."

Teachers' Views on Teaching and Learning of GUR

Teachers were also asked to verbalize their views on teaching and learning of the GUR subjects. Teachers generally held positive perceptions. They perceived that the adopted teaching and learning methods can help students develop self-learning ability, facilitate students' understanding of the subject content, promote students' engagement in learning, as well as provide students with profound learning experiences. Among different teaching and learning methods, interactive approaches based on experiential learning were highly appreciated by the teachers. Specifically, the majority of the teachers consistently noted that field work was effective and greatly favored by students. For example, two teachers in the focus groups of CAR and SL illustrated, respectively:

"I think field work is very useful for our students' learning. For example, many students in my class (CAR) told me they treasured the home visit opportunity very much. I observed they did not know how to get along with older people at first. They were very nervous and had no confidence. They did not know how to communicate with the older people. In the end of field work project, they could easily talk with the older people and actively asked what they can help. Through getting along with old persons, I think students can truly feel and understand what the outside world looks like and really hope they can do something to help people in need."

"I have two groups of students in my class (SL). One group of students went to Sichuan (a province in China) to experience life there. I felt the experience (going to Sichuan) greatly impacted them (students). Now, they have started to learn to think about self and life, think about ideal and reality, and think about what they can do for the society."

In addition to field work, teachers perceived that hands-on project in assignment as another effective and welcomed method. For example, in the focus group of CAR, one teacher expressed:

"I feel students really like and devote to complete the video assignment. The quality of the assignment is quite good. I am surprised they spent much time on doing the thing, especially in examination period, but everyone submitted it. They were also happy and enjoyable in the process of critiquing videos."

A number of teachers also expressed that team debate was favored and welcomed by students. They perceived that this method promoted students' cognitive ability. For example, one teacher in focus group of LCR said:

"For Persuasive Communication, um, I think the students enjoy the debate part of the course. The course ends with the teams' debate. I find that there are big intellectual challenges for them (students) because they have to predict what the other team is going to say and prepare their arguments against it, etc. and think on their feet and reply to the arguments. Um..."

Apart from the aforementioned teaching and learning strategies, considerable teachers also mentioned that in-class group discussion was very beneficial to students' active learning. Through interacting with others, group discussion provided students profound learning experiences, such as collaborative learning, critical thinking, and communication skills, etc. Moreover, a number of teachers commented that utilizing visual aids such as video-demonstration was highly favoured by students and successfully engaged students in learning. On the other hand, teachers reflected a few sessions of GUR subjects delivered by renowned speakers were not well-received by students due to a lack of interactions. Improvements on the designs of these subjects are needed to further motivate students' learning and participation.

Teachers' Perceived Benefits of the GUR

When being asked about the benefits of GUR subjects, teachers expressed very positive views. They considered the benefits of GUR subjects comprehensive which covered different areas. Teachers observed several direct positive changes in students after taking GUR subjects. The first was students' improved communication competence in both oral and written skills, though such changes were usually not immediate. Several selected narratives were provided below to show teachers' positive comments:

"In fact, the course (TL) provides a platform for students to meet different people who might come from different countries or be with different backgrounds. They (students) need to overcome language obstacle and egocentrism, and self-disclose to talk with different people. After taking the subject, many students told me that it (the course) was a very good learning experience. I think effective communication is reached." (One teacher in TL)

"In my opinion, the subject (SL) is very useful for communication. Because students would meet different people and deal with different real-life situations and problems. Of course, they (students) do not only learn verbal communication, but learn how to use different ways to creatively communicate with other." (One teacher in SL)

"The improvement is not immediate, it takes 2 to 6 credits of LCR to... and they are still learning how to... you can see the difference from when they entered university at the very beginning... more like secondary school students' writing style. When they finished the subjects, they are more on their way to be able to write academic essays. Sometimes, I would like to use 'turn bad into good' to describe many students' achievement in academic writing in end of course. I am very happy to see this." (One teacher in LCR)

Teachers perceived the second most obvious improvement among students was their competence in ethical leadership. Teachers reflected that after attending GUR subjects, students' capacities of self-leadership and reflection, empathy to people in need, and social responsibilities were developed. Several selected narratives were provided below to show teachers' perspectives:

"I strongly agree students learn self-reflection and self-management by taking the subject (TL). Some students once felt it's difficult for them to wake up in the morning. Even washing face and coming to school to attend morning classes were very difficult things. Now, they have self-reflection on these life styles and some of them started to make plans and write diary. I think this is a very important improvement." (One teacher in TL)

"I feel a lot of students take many things for granted most of time. After taking the subject (of CAR), they realize happiness is not taken for granted. They also realize their behaviors influence others and should usually consider from others' angle." (One teacher in CAR)

"They (students) wrote something about visiting older people in their reflective journal. From their writing, I find they start to have social responsibility. They want to help older people, but they feel their ability is limited. But I think at least they think about how to help them (the older people). The subjects (in SL) offered such opportunities for them (students). I think the subjects are very useful for my students." (One teacher in SL)

The third positive change described by teachers was the improvement in students' problem solving ability as shown in their group projects. For example, one teacher in the focus group of SL stated:

"When I talked to students about group assignment, I feel they are quite daunted by it at the very beginning. But then that's why I say that they really grew in confidence and improve ability in solving problems. Because in order to complete the task, they have to think how can they possibly do for this assignment, and how do they find someone to interview, how do they interview them, etc. Then, you see, they figured it out in the end."

A few teachers also mentioned that GUR subjects promoted students' capacities of critical thinking by encouraging students to think from different perspectives and asking them to write persuasive essays and to do comparison. For example, two teachers described as below:

"In EUS (a course in advanced LCR-English subject), they (students) cannot simply describe a view; they actually have to either defend it or criticize it. It requires slightly higher cognitive skills." (One teacher in LCR-English)

"In this course, we did a lot of critical comparisons. We asked students to read texts and literature, as well as, um, like movies, or adapted plays, and we asked them to do a comparison of the two. Then, they really have to use, you know, use their brains to talk about the literary creation and the ways by which things are handled in the two different media." (Another teacher in LCR-English)

Furthermore, a few teachers indicated that students' capacities of lifelong learning, global outlook, and resilience were also developed as reflected in their group work, presentation, and reflective writing in GUR subjects.

Teachers' Views on the Evaluation System of GUR

Regarding views on the evaluation system of GUR subjects, teachers generally had positive comments on the current assessment mechanism. For example, teachers in the focus group of TL expressed that the evaluation system is quite effective because it employed comprehensive evaluative methods to examine both objective and subjective outcomes of the subject. For example, there are objective outcome evaluation which measures students' development in different positive attributes before and after taking the subject; qualitative evaluation in which students are asked to use three metaphors to describe their general impression about the subjects, and student feedback questionnaires which gauge their subject views on learning experiences and teachers' effectiveness in this subject. Such an evaluation

system provides the teachers with important information in understanding the effectiveness of the subject from different aspects. In particular, teachers of TL mentioned that a post-lecture evaluation effectively helped them understand students' comments and suggestions after each lecture. Based on students' feedbacks, teachers can make immediate improvements in the following classes. For example, one teacher in the focus group of TL said:

"Actually, I think post-lecture evaluation really helped me to know my teaching effectiveness. Particularly from open-ended questions, I can receive their (students') ideas and feedbacks. Then I can respond to those students quickly in the next lecture. They (students) are also impressed that what they wrote can be really paid attention to by the teacher. They became more willing and active to share their opinions. I think this is a positive circle."

Besides, teachers in LCR-Chinese subjects perceived that the frequent formal meetings among subject teachers and written reviews on the evaluation of the subjects effectively helped them further improve the subjects, as shared by one teacher as below:

"From teachers' perspective, I think the evaluation system is very exquisite. We had regular meetings for each GUR component subject. We discussed these courses and wrote reflective reviews. In meeting, every teacher reported what were problems of their courses; what were students' and teachers' feedbacks? For example, there is one subject of LCR-Chinese. We had many meetings to discuss how we could teach better. We did many revisions about teaching design. As a result, I find students much liked and enjoyed the course. I am also satisfied with the quality of the course. I think meeting is very useful."

Teachers' Perceived Challenges in GUR Implementation

Near the end of each focus group interview, teachers were invited to describe their perceived challenges in delivering the GUR subjects. Several issues arose that deserve attention. First, students' instrumental orientation and indifferent attitude towards general education potentially undermined their active participation and engagement in GUR subjects. Teachers believed that it would take time to change students' mindset and improve their learning attitudes. For example, one teacher in focus group of LCR-Chinese said:

"I think the most difficult thing is that they (students) asked what this (course) has to do with me. Why do they need take the course? For example, science students asked why I need to take Chinese subject. It is really hard to explain to them. ...But they would understand the importance. I think it needs time."

Second, some teachers expressed that marking writing assignments and group work in large classes brought them heavy workload, as one teacher in the focus group of "Tango!" claimed:

"Group and individual assessment in large classes in FS and LIPD in fact, is regarded as one of the major challenge in the evaluation. For example, we have only 3 or 4 teachers. But we have a lot of students. It's really a hassle when we have such a large group presenting and we are trying to, you know, trying to give a mark to every group in terms of the performance and see how everybody got on board. It is really huge work."

Third, it was observed that Mainland students generally had more difficulties in LCR-English subjects than local students, as most Mainland students were not well trained in oral and written English skills in their secondary schools. For example, one teacher in the focus group of LCR-English said:

"I think the students from Mainland China come here in a stream line according to their university entrance examination. It may not be a very good predictor of their language proficiency. Their speaking and writing productive skills are really really not trained. In Mainland China, basic speaking is not tested in their university entrance examination, so lots of Mainland students come here, rather than get into EUS, um... there are very good students but you can see them struggling..."

Besides, teachers teaching SL subjects expressed that the SL trips could not get funds from the Finance Office of the University in advance. Teachers and students needed to pay everything by themselves first and the following reimbursement procedure was very complicated, which may negatively influence students' learning motivation and engagement.

DISCUSSION

This paper presents the qualitative evaluation findings of the General University Requirements (GUR) at The Hong Kong Polytechnic University in 2013/2014 academic year based on data collected from teachers' focus groups. The findings indicated that the GUR was evaluated positively by teachers in its second year implementation. Primarily, the GUR subject content was perceived by teachers as beneficial and interesting. According to Ranaweera [13] and Gibbs et al. [14], the content of general education in universities should not only meet diverse and changing needs of students and society, but also arouse teachers' interest and enthusiasm and form their positive attitude toward general education. Teachers' positive attitude and involvement would positively and significantly impact the effectiveness of general education curriculum delivery. Teachers' general positive perceptions on the GUR subject content revealed in the present study may further motivate them to teach the subjects with passion and thus further promote the effectiveness of the program. Meanwhile, some concerns expressed by teachers on the level of difficulty in FS subjects, such as statistical analyses, must be addressed. Lecture contents of these subjects should be modified to better address the needs of first-year university students.

Several teaching and learning methods adopted in GUR subjects were highly praised by teachers in focus groups, including field work, hands-on project, and team debate. These methods are common in their interactive nature and the use of experiential learning. Students learned effectively by discussing, reflecting on, and applying the theoretical knowledge in solving real problems. These interactive learning approaches were also welcomed by students and successfully facilitated students' active participation in these subjects. In the present study, teachers reflected that students' positive feedbacks further encouraged them to adopt more interactive/participative methods based on experiential learning in their GUR classes. This would result in more favorable learning outcomes.

On the other hand, teachers noted that lectures lacking interactions were not well-received by students even they were delivered by famous speakers. Lucas [15] suggested that teachers may feel reluctant to use interactive methods due to their teacher-centered pedagogical philosophy. However, there has been an increasing consensus that students' active learning is much more effective than passively receiving the instructions by teachers, along with which the mode of education has been changed from teacher-centered to learner-centered [16, 17]. The present finding provides further support to the benefits of learner-centered interactive methods in teaching general education subjects.

Teachers generally perceived that GUR subjects have brought comprehensive benefits to students. This finding is consistent with previous findings based on teachers' and students' focus groups in 2012/2013 academic year [11, 12]. At the intrapersonal level, the teachers observed that GUR subjects strengthened students' self-reflection, self-regulation, critical thinking, lifelong learning, and problem solving skills. On the interpersonal level, teachers reported that the subjects enhanced students' oral and written communication competence, ethical leadership, particularly social responsibility and empathy. These findings indicate that the GUR program has effectively promoted students' development in the five desired university student attributes and facilitated their all-round development.

With reference to the evaluation system of different GUR subjects, teachers generally considered the current mechanism effective and useful. For example, post-lecture evaluation and formal regular meetings were perceived by subject teachers as helpful for them to maintain and improve the quality of subject implementation in a timely manner. The findings also echo previous reports showing effective evaluation mechanism of a subject could serve as a useful strategy that enables teachers to quickly understand their teaching effectiveness [18-20]. Before subjective and objective outcomes on the effectiveness of GUR program can be observed, the evaluation system of each subject would provide immediate information on the subjects which is important for teachers to make timely adjustment on the subjects.

Despite the aforementioned positive findings, several challenges expressed by teachers should be noted, which implies directions for further improvements of the GUR implementation. First, relatively low learning motivation toward GUR subjects in some students were noted by several teachers, which could potentially affect the learning outcomes of the GUR [21]. To tackle the problem, it is important to help students understand the rationale of implementing general education and the importance of whole-person development for university students. Related GUR orientation workshops can be conducted upon students' enrollment to convey these messages. Second, although most teachers held positive views on the implementation of GUR subjects, a few teachers responded that marking written assignment and group projects in large classes created heavy workload. This may be related to the increased number of students enrolled in 2013/2014 as compared to 2012/2013, which has led to larger class sizes particularly in GUR subjects. The University may consider how to reduce the workload of these teachers, such as hiring more tutors to share the work. Third, it was noted that Mainland students showed difficulties in their first-year English learning. Special assistance in improving first-year Mainland students' English proficiency may be needed. In addition to the English Department, different organizations in the University may also provide workshops to help Mainland students better adapt to the new learning environment. Fourth, teachers in SL subjects complained about the complicated funding application and reimbursement procedure. More supportive services shall be provided to staff and students by the University to facilitate a smooth and efficient implementation of SL subjects.

The current study has several strengths. First, congruent with previous research findings [10, 20, 22], the present study provides further evidence for the effectiveness of university general education curriculum in promoting student whole-person development based on teachers' perspectives. Second, the study affirms an overall successful and smooth implementation of the GUR at The Hong Kong Polytechnic University, a pioneering general education project in universities in Hong Kong. Third, the study demonstrates the strengths of obtaining teachers' views in program evaluation. The personal feelings and experiences

shared by the teachers provided deep insights on different aspects of the program implementation and outcomes, which can guide further improvement of the program in the future and triangulate findings obtained from other evaluation research.

Nevertheless, several limitations of the study shall be acknowledged. First, although most focus groups had an ideal number of participants in the present study [23], two groups (“Tango!” and “FS”) only had three or four participants. The small sample sizes may influence the representativeness of the information collected. Future studies could try to recruit more teachers for these two groups to obtain more diversified views of teachers. Second, while focus groups have many methodological benefits in program evaluation, they cannot be used in isolation due to some inherent disadvantages. For example, respondents may feel peer pressure to give similar answers to the interview questions, and the moderator’s skills may affect the responses from the participants. Therefore, other research methods such as quantitative evaluation based on a more representative sample and in-depth individual interviews focusing on individual teachers’ perspectives shall be conducted to further evaluate the implementation process and effectiveness of the GUR. Third, while the present study investigated the perspectives of teachers who are important stakeholders of the GUR program, other stakeholders’ opinions shall not be overlooked. Future research should examine the views of students, administrative staff, and other stakeholders on the implementation of the GUR to gain a more comprehensive picture.

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Chapter 188

WHAT DID THE STUDENTS SAY?

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ABSTRACT

The General University Requirements (GUR) is the core general education component of the new four-year undergraduate curriculum at The Hong Kong Polytechnic University (PolyU) commencing from 2012/13 academic year. The major objective of the GUR is to widen students' horizons and promote their holistic development in their undergraduate years. To evaluate the perceived effectiveness of the GUR in its second year implementation, 18 focus group interviews (n = 74 students) were conducted in 2013/14 academic year. Findings showed that subjects under the GUR framework were overall welcomed by students for the well-designed subject contents, dedicated teaching staff, and collaborative and experiential learning methods. Students perceived that the GUR was beneficial to their development ineffective communication, critical thinking, problem solving, lifelong learning, and ethical leadership. Some challenges encountered by students were noted to further revamp the GUR curriculum in the future.

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INTRODUCTION

The Hong Kong Polytechnic University (PolyU) is one of the eight public universities in Hong Kong under the funding of the University Grants Committee (UGC). In 2012/13 academic year, PolyU formally transformed its undergraduate programme from three years to four years. A core general education structure named “General University Requirements” (GUR) was developed as a foundational part of the new four-year curriculum. In combining with students’ disciplinary studies, the GUR at PolyU aims to nurture students with a broad knowledge base, and capacities of effective communication, critical thinking, innovative problem solving, lifelong learning and ethical leadership, defined by PolyU as the five desired graduate attributes under the new four-year curriculum. Credits assigned to GUR subjects account for one quarter of the total credits of university study required for graduation. GUR has become a major vehicle to achieve PolyU’s new mission to deliver a more “balanced and well-rounded education” [1].

The curriculum reform at PolyU as well as in other universities in Hong Kong was shaped by the drastic social changes. Hong Kong’s economy has been altered from a manufacture-based to a service-based one. Nowadays, “98% of Hong Kong’s GDP is based on services” [2], which raises challenges for nurturing high quality manpower with flexibility and generic skills. The globalized knowledge economy, rapid outdated of knowledge, and increased societal instability in Hong Kong also confronted tertiary education with the need to cultivate graduates with adaptability, self-directed learning, effective communication, intrapersonal attributes, and knowledge transferable skills [3, 4]. Furthermore, the change of Hong Kong from a British colony to a special administrative region of China raised demands for social leaders who could actively engage in the construction of Hong Kong’s new political identity and civil society [2]. Despite the above challenges, government and business sectors complained that local university graduates lacked creativity and innovative ability although they were good at examination skills [2]. These graduates were also regarded as not adept at “making thoughtful decisions in the workplace” [3]. The Hong Kong education system is criticized for being examination-driven, giving insufficient attention to lifelong learning, and lacking “comprehensive learning experiences” [4].

Specifically, the three-year British-style higher education system was blamed for early streamlining students’ learning [4] and early vocationalization [2]. This system was incompatible with the international trend stressing a broadened learning in higher education [4]. To address these challenges and problems, a systematic and comprehensive education reform was initiated after the handover to Hong Kong in 1997. Starting from 2006/07 academic year, senior secondary education in Hong Kong has been changed into a 3-year structure in order to provide a coherent and diversified learning experience to secondary school students and to equip students with a solid foundation for lifelong learning [4]. Along with the senior secondary education reform, all eight public universities in Hong Kong formally extended their undergraduate education programmes from three years to four years starting from 2012/13 academic year. Students under the new four-year undergraduate programme are provided with more room for their whole-person development. In the new undergraduate education framework, each university developed its respective general education curriculum as an embedded component. General education, a curricular tradition in

American higher education, was revitalized in Hong Kong to make higher education to be “the inspiration for institutional and pedagogical transformation” [5].

The GUR at PolyU has several unique features. First, the GUR curriculum is comprised of six distinct components, with each having its characteristic design and specific learning outcomes, as briefed below:

- Freshman Seminar (FS) (3 credits). FS is a mandatory subject offered to students from each broad discipline in their first year of study.
- Leadership & Intrapersonal Development (LIPD) (3 credits). LIPD aims to introduce theories/concepts of leadership to students to prepare them to be leaders in their profession.
- Language and Communication Requirements (LCR) (9 credits). LCR aims to develop competences of effective communication in both Chinese and English in students. LCR comprises two components: LCR-English (6 credits) and LCR-Chinese (3 credits).
- Cluster Area Requirements (CAR) (12 credits). CAR aims to expand intellectual capacity and develop multiple disciplinary perspectives of students. It comprises four cluster areas of learning. Each student needs to take at least one subject from each area. Also, the subjects taken by each student need to cover three requirements: “China Studies”, “English Writing and Reading” and “Chinese Writing and Reading”.
- Service Learning (SL) (3 credits). Each student needs to take a subject with a significant service component to apply academic knowledge into practices, and develop sense of civic responsibility.
- Healthy Lifestyle (HL) (non-credit-bearing). HL aims to develop knowledge and skills for maintaining a healthy lifestyle.

Second, the GUR stresses students’ active and participative learning as reflected in its interactive pedagogy. For example, Tomorrow’s Leaders (TL), one LIPD subject offered to around 2,000 PolyU freshmen every year, adopts a pedagogy combining lectures, experiential classroom activities, group project presentation, and written assignments to promote students’ reflective, experiential and collaborative learning [6].

Third, strong administrative mechanisms were established to ensure a quality implementation of the GUR [7]. Special assistants to Vice President were appointed for the GUR development and quality assurance. A university-wide Task Force was formed to facilitate the GUR development and implementation. Subjects in different components were piloted and refined before their formal implementation.

Last but not least, various evaluative studies have been conducted to evaluate the GUR implementation since its launch [8-10]. Multiple evaluation methods were adopted in this longitudinal research, including objective and subjective outcome evaluation, qualitative evaluation based on open-ended questions, longitudinal case study, and focus groups with different stakeholders [11].

Wright and Hendershott [12] suggested that the evaluation in one time point might give “partial truths”. Although the evaluative findings in the first year of GUR implementation are encouraging, it is necessary to investigate the effectiveness and implementation quality of the GUR in subsequent years. The present paper reports findings obtained from student focus

groups in 2013/14 academic year, i.e., the second year of implementation. Focus group, defined by Krueger and Casey [13], was “a carefully planned series of discussions designed to obtain perceptions on a defined area of interest in a permissive, nonthreatening environment.” It collects rich data on participants’ perceptions in a more cost-effective way [13], and helps achieve a deeper understanding of the topic during group interaction [14]. In this paper, students’ views on the GUR were examined via focus groups.

OUR STUDENTS

The participants were 74 Year Two students enrolled in the new four-year undergraduate curriculum in 2012/13 academic year at PolyU. At the end of the first semester of 2013/14 academic year, 320 students were randomly selected from all Year Two students, with 40 students being selected from each faculty/school. A total of 18 student focus groups were conducted before the end of the 2013/14 academic year. All the focus groups were faculty/school-based. The numbers of focus groups for each faculty/school were: FAST (n = 2), FB (n = 2), FCE (n = 3), FENG (n = 2), FH (n = 2), FHSS (n = 2), SD (n = 2), and SHTM (n = 3). The number of participants in each group ranged from two to six (Table 1). There were two sessions (one in FCE and one in FHSS) with only two participants. For these two sessions, four students had formerly agreed to participate while only two finally attended as the absentees were engaged with some emergency issues. The length of the interviews ranged from one hour to one and a half hours. For each interview, one researcher was presented to serve as the moderator. The whole process of each focus group was audio-recorded with students’ consents.

Table 1. Number of participants in each session of student focus group interviews

Student Focus Group Interviews	No. of Participants
Session 1 (FB)	6
Session 2 (SD)	3
Session 3 (FENG)	4
Session 4 (FCE)	3
Session 5 (SHTM)	3
Session 6 (FAST)	4
Session 7 (FENG)	4
Session 8 (FHSS)	4
Session 9 (FAST)	6
Session 10 (SD)	5
Session 11 (FH)	3
Session 12 (SHTM)	6
Session 13 (FHSS)	2
Session 14 (SHTM)	5
Session 15 (FCE)	2
Session 16 (FB)	5
Session 17 (FCE)	4
Session 18 (FH)	5
Total	74

Note. FB: Faculty of Business. SD: School of Design. FENG: Faculty of Engineering. FCE: Faculty of Construction and Environment. SHTM: School of Hotel and Tourism Management. FAST: Faculty of Applied Science and Textiles. FHSS: Faculty of Health and Social Sciences. FH: Faculty of Humanities.

A focus group protocol developed by the research team in 2012/13 academic year was revised and used in the present study to guide the interview. The protocol is comprised of four major categories of questions: [1] students' general impression about the GUR; [2] students' views on the GUR subjects (including contents and teaching); [3] students' perceived benefits of the GUR; and [4] students' comments about the implementation of the GUR.

All the records of the 18 focus groups were transcribed by student helpers into full texts. To ensure the accuracy and consistency of the transcription, four researchers further checked the 18 transcripts and made minor amendments. The transcripts were then imported into NVivo Software (Version 10) for coding and analyses. Each text was coded for at least twice. The common themes and categories were initially generated based on coding of the texts. After the initial coding, the common themes/categories were further read, organized and confirmed by one researcher. To test the inter-rater reliability, another researcher who did not know the original coding recoded 20 randomly selected narratives from the transcripts. The agreement percentage of the recoding and the original coding was 85%.

FINDINGS

Five major themes emerged from the data, including 1) well-designed subject contents, 2) caring and devoted teachers, 3) collaborative and experiential learning-based pedagogy, 4) benefits of the GUR subjects, and 5) smooth implementation. These themes are further elaborated below.

Well-Designed Subject Contents

The GUR was appreciated by students for its "well-designed" course structure and contents. Students in focus groups expressed that this design had provided them with valuable opportunities to learn their interested subjects. In fact, many students were eager to learn and understand the world beyond their own disciplines and thus they appreciated rich content of the well-designed curriculum of GUR subjects which successfully evoked their inner learning motivation. One merit of the CAR component summarized by students was that many interesting materials in different knowledge areas were incorporated in the subject content and students were given "some degree of freedom" to choose their favorite subjects to fulfill their personal interests:

I like to study history. However, in my high school, I had no opportunity to study arts subjects as I enrolled in the science stream. The University helped me fulfill my desire; I have studied [the subject on] the History of Hong Kong [in CAR].

Students also highly praised the course design of service learning subjects. They appreciated the reasonable proportion of class-teaching and service practices, and the matching of knowledge taught in the classroom with direct service activities. Some SL subjects were perceived by students as having concise, clear, and logical content:

I think my service learning subject is very good. The subject is related to doing service in Shanghai. I think the proportion of the theory and practice parts [in the subject] is perfect. For the theory part, we had three lectures and each lecture taught us three things. The content was very concise and insightful. It is because this concise and insightful content that we could easily link the knowledge with our service practices.

One concern noted by students was the design and level of difficulty of subjects in CAR-D (“Science, Technology and Environment”). Students without science background (e.g., majoring in social sciences and humanities disciplines) expressed that the contents of CAR-D subjects were too advanced and specialized for them, which made them feel frustrated:

I haven’t studied science subjects in my high school. Then [in the university] I selected one subject [in CAR-D] the title of which looked interesting to me; it was about electronic music. Later on, however, I found myself “fell into an ambush” since the subject offered very “professional” science knowledge to students, such as those of “waves in physics”.

On the other hand, another group of students from Faculty of Humanities viewed their selected CAR-D subjects as well-designed with interesting contents. These subjects enabled the students to appreciate the beauty of science:

I am now taking a subject in CAR-D named “Science behind Crime Scene Investigation (CSI)”. ... So far I think this subject is very good, because it actually depends on how the professor designs the course and its purpose. ... The professor uses very simple ways to teach us how to discern in a crime scene where several holes exited in a window hit by a hammer which hole was hit first.

Caring and Devoted Teachers

A number of students noted that they loved their GUR subjects because their subject teachers were dedicated and enthusiastic. The teachers’ passion, knowledge, and personal characters demonstrated in teaching altogether provided students with profound and unforgettable learning experiences:

One of the CAR-C subjects I studied was taught by a very brilliant and passionate lecturer... I think through this subject it is the first time that I felt having learned something. ... She was very brilliant! She spoke a lot of interesting things. We never felt the class boring. She also had a lot of interactions with us during the class. Although the class was held in a very big lecture hall, there were a lot of students attending the class every week. Almost all seats were occupied [in each class].

Students were also impressed by the warmth and care given by their teachers. For example, a few students expressed that their teachers showed great concerns on their learning experiences and always tried to make improvement based on students’ feedbacks. Some students mentioned that their teachers could remember their names even in the first few weeks, which made them feeling being respected:

I have very good and deep impression of the teacher of my service learning subject. ... Our teacher was very dedicated to attend each class in different times to oversee and provide assistance to us. So I think my teacher is very good.

Furthermore, a few students complimented their subject teachers on their detailed guidance in their learning process which greatly facilitated their learning:

[In Service Learning] ... Our teacher gave us very clear criteria and guidance and provided us with the good and bad examples for making the storybooks. Then in the following service, we could really use these books to teach.

Meanwhile, students believed that less engaged and dedicated teachers had negative impact on students' interests in the subjects. In fact, as noted by several students, their participation in GUR subjects largely depended on the "lecturer". For subjects with "half-hearted" teachers, students said that the number of students attending the lectures decreased significantly week by week:

One student: In certain subjects, the lecturers did not want to teach and engage us. Then we had no interests and did not want to learn in a serious manner. The lecturers also felt very hard teaching us.

Another student: It really depends on the lecturer...

The first student: It did! One lecture I encountered is like that. In his first class, the lecture hall was almost full; however, in his second and later classes, the lecture hall was almost empty...

Collaborative and Experiential Learning-Based Pedagogy

GUR subjects were also praised by students for the interactive pedagogy that focused on collaborative learning and experiential learning, including group work, field trip, hands-on workshop, real case demonstration, multimedia methods, etc. Students gave very positive comments to these teaching and learning methods. One beneficial outcome of collaborative learning raised by students was their broadened social network. Students felt "happy" to "know people from other disciplines" through group work. Different group projects also promoted students' development in communication and leadership skills, just as a student from Mainland China expressed in the focus group:

The GUR subjects [in PolyU], such as CAR subjects, would arrange group work [to us]. Different students, no matter from Mainland [China] or Hong Kong or no matter from one discipline or multiple disciplines, would have more chances of communicating with each other; learning many things from one another; knowing how to communicate and discuss with others. I think this [mode of learning] is very meaningful.

A number of students used "interesting", "attractive", and "happy" to describe the experiential learning components in their GUR subjects such as field trip, laboratory work, in-class experiment, etc. Students perceived that the experiential learning helped them better comprehend the knowledge and apply the knowledge in their daily lives:

I think some CAR subjects were intriguing. For example, I have studied one on food science which taught food quality and smell. ... The most favorable part was that it had a lab for us to DIY food, e.g., making molecular ice-creams. I think this format could really make students learn more things ... as well as develop a better understanding about the knowledge which could be used in their daily lives.

Furthermore, students gave highly positive comments to their service learning experiences. They perceived service learning as happy, hands-on, and "meaningful". Some students shared that they gained multicultural learning experiences in their field trip and were provided with opportunities to "really help people". Such experiences successfully fulfilled students' inner desire to serve and help others.

I think service learning will teach you the reality ... My service learning subject was related to the community tourism. You could really see what the clients want, and you planned for catering their needs, e.g., doing a real conference.

Benefits of the GUR Subjects

During the focus group discussions, benefits of the GUR subjects constantly emerged. Two general categories of benefits were identified by the participants, i.e., broadened learning experience and personal development in different desired graduate attributes defined by PolyU. First, the majority of students perceived that their GUR study broadened their knowledge base, horizons and experiences. Different GUR components such as CAR, SL, and HL exposed students to different knowledge domains beyond their disciplines. Through GUR study, students gained more opportunities to interact and communicate with their peers from other disciplines, which enriched their views about the world. Several narratives were provided below to illustrate these benefits:

In studying CAR I have gained exposure to different subjects in other disciplines, although the learning experience was painful sometimes. For example, in semester one I have studied one subject on China's reform and opening-up. Although I hate to study history all along, I think this subject offered me some different perspectives and helped me understand more about China.

My most impressive experience was to visit and talk with people lived in the "rippled room". This experience really let me know more. For example, I asked them where they go in their daily life and how they apply the subsidy, etc. Then I came to understand the huge gap between the rich and the poor, and how a poorest person could be.

In my SL subject, I went to Cambodia. Since we depended on the local students as our language translators, we had more communication with them and learned their cultural and historical background, as well as the local life.

Second, students generally viewed their GUR study as conducive to their personal development in different areas particularly the five desired graduate attributes. Students expressed that GUR study helped them develop oral and written communication skills. The group projects in many GUR subjects effectively trained students in communication with their peers from different disciplines with distinctive thinking styles. The experiences gained in group presentation also greatly enhanced students' confidence and ability in public speaking:

I think I have developed more confidence through doing a variety of tasks such as group works and individual projects [in GUR study]. In my first several group projects, I often felt that I had less contribution to the projects, and did not dare to express my views. Then, after experiencing so many group projects, I feel that the group project is not so scary, and I am able to express what I am thinking now.

Students also perceived the CAR subjects with reading and writing requirements as much helpful in improving their skills of academic writing in English. Students appreciated the close collaboration between CAR subject teacher and teachers from English Language Center (ELC), by which students obtained continuous guidance from ELC teachers while completing their writing assignments in CAR subjects:

I think that the CAR subject with [English] reading and writing requirements that I enrolled in was very useful. The subject required us to write an essay. In the middle of the semester, we met with the tutor (ELC teachers) and he discussed with us the problems in our essays. I felt this part very useful.

GUR study also promoted students' motivation and skills for lifelong learning. As mentioned, students commonly perceived that CAR subjects had aroused their interests in learning knowledge of other disciplines. The writing tasks in certain GUR subjects also trained students' independent learning such as literature search and review on particular topics.

Some students mentioned that their leadership competences were promoted through their GUR study, such as team-building skills, habit of self-reflection, and a strong sense of responsibility. All these were important ingredients in ethical leadership:

[After studying the GUR subjects,] my abilities in thinking and reflection were improved. I really did more self-reflections on some ethical issues, and on my own performance and cooperation with others in doing things.

Smooth Implementation

Most students expressed that their GUR study went smoothly. However, a small number of students had relatively slow progress in GUR study which was mainly due to personal issues. Meanwhile, students also shared their concerns on the course registration system for the CAR and HL subjects. Some students commented that it became more difficult for them to select their preferred CAR and HL subjects in 2013/14 academic year than the previous year because in this year, there were two cohorts of students compete for the limited quota of each subject. For some popular subjects, the competition was fierce:

I think the registration of HL subjects was a very troublesome issue. I am not able to register HL subjects. So troublesome!

DISCUSSION

This study investigated students' views on the perceived implementation and effectiveness of the General University Requirement at The Hong Kong Polytechnic University in 2013/14 academic year through focus group interviews. The findings indicated an overall success of the GUR in its second year of implementation. Students perceived the GUR as effective in promoting their holistic development and the implementation of GUR was smooth.

Several observations could be highlighted. First, students viewed the content of the GUR curriculum as well-designed and interesting. While LCR, LIPD, and FS basically adopt the "core requirement" mode in which students have to take the subjects in a compulsory manner, CAR, SL, and HL have more "distributional requirements" which give students more freedom to select their own preferred subjects [15]. Such design well balanced the "prescription" of the University and students' "personal interests" in general education and provided students with comprehensive learning experiences.

Second, students had very positive perceptions about the teachers of GUR subjects. In particular, the teachers were described as “caring” and “dedicated”. The knowledge, attitude and passion in these teachers greatly motivated students’ active learning in GUR study. This finding is in line with the literature which suggests that teacher plays a key role in high quality general education [16-18]. For example, Gaff [19] argued that “courses, even well-designed ones, are insufficient without effective teachers who can stimulate students and assist them in learning.” In Wright and Hendershott’s [12] study, students’ satisfaction about a course was found closely related to the enthusiasm of the course teacher demonstrated in teaching. Apart from this, Noddings [20] also stressed that “caring is the very bedrock of all successful education.” It is believed that caring teachers are able to establish close bonds with their students by believing in and affirming their students’ efforts, potential and talents, place their students at the center of the educational process, and engage their students in learning, which is “essential for learning to be fun, meaningful, and enduring” [21]. Given the fact that most research on the role of teachers in effective teaching and learning was based on primary or secondary school settings and few studies had been conducted in the context of university general education, the present finding could be regarded as an interesting contribution to the literature.

Third, students favored the interactive pedagogy adopted in GUR subjects based on collaborative learning and experiential learning. Researchers pointed out that the adoption of pedagogy emphasizing active learning had become one of the most important trends in general education reform in American universities [22-24]. There are literature supporting the significant impact of such pedagogy on students’ learning outcomes [25, 26] through promoting students’ direct interaction with subject contents [27], and placing “the onus of learning on learners” [28]. This could not be achieved by traditional lecture method which focused on knowledge instilling and memorization [28]. The present findings further suggest that the interactive pedagogy was well-received by students. Since the goal of general education is to develop students’ qualities, attitudes, and generic capacities instead of static knowledge, interactive pedagogy seems to be vital for the success of general education programs and should be promoted in teaching GUR subjects. Even in classes with large size where lecturing is inevitable [29, 30], teachers may try to adopt more active teaching methods such as small-group work, class discussion, short writing activity, or student presentations during the lecture sessions [26, 30].

Fourth, students perceived the GUR as beneficial to their development, especially in broadening their learning experiences and fostering their personal qualities in the five desired graduate attributes. For example, CAR subjects were perceived as having greatly improved students’ skills in the areas of effective communication, critical thinking and lifelong learning. SL subjects challenged students to be problem-solvers and ethical leaders when providing services in the community. This finding also echoed previous findings based on different evaluative studies that suggested the effectiveness of the GUR in promoting university students’ holistic development.

In conclusion, based on students’ views shared in focus group interviews, the implementation of GUR in 2013-14 academic year can be regarded as smooth and successful. The findings also provide further evidence for the effectiveness of the GUR in developing important qualities and competences in students at PolyU. Meanwhile, there are several limitations of this study. First, although students are important stakeholders of the GUR program, the viewpoints of other stakeholders such as teachers need to be collected to provide

a more comprehensive picture about the effectiveness and implementation of the GUR as well as to triangulate students' views [28]. Second, while the method of focus group interview is advantageous in collecting rich and in-depth data, generalization of the findings should proceed in caution. Quantitative evaluation methods based on a larger sample of students shall be used to further evaluate the GUR. Despite the limitations, due to the limited evaluation research on the new general education and the new four-year undergraduate curricula in Hong Kong, the present study constitutes an important contribution to the field.

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Chapter 189

STUDENT FEEDBACK ON A PIONEER SUBJECT ON LEADERSHIP AND INTRAPERSONAL DEVELOPMENT

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ABSTRACT

To promote leadership and intrapersonal development in university students, a subject entitled "Tomorrow's Leaders" was developed and offered at The Hong Kong Polytechnic University. To assess the perceived effectiveness of this subject, 647 students completed the Student Feedback Questionnaire. Results showed that the feedback questionnaire had very good psychometric properties, including internal consistency reliability and construct validity. Regarding students' views of the subject, results showed that students generally had good evaluation of the content of the subject, teaching quality, and perceived benefits of the subject. The present findings have implications for the teaching of general education regarding leadership development.

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INTRODUCTION

In the global world of today, the economy in many places such as Hong Kong has gradually transformed from product orientation to service orientation. Product-oriented economy emphasizes logistics and products, and thus often requires obedience of followers to leaders' demands [1, 2]. In contrast, service-oriented economy emphasizes on services as well as the benefits of all participating parties in the economic exchange. Several leadership concepts, such as Servant Leadership [3, 4] and Service Leadership [5], have been put forward to address the important leadership issues in the service-oriented economy. These leadership concepts emphasize the importance of shared leadership and leadership qualities involving a variety of interpersonal and intrapersonal competences [4, 5]. To cultivate qualified graduates who will become the pillar of tomorrow's society, universities have an urgent need to develop validated program/subject that can foster leadership qualities in students.

Globalization also brings other changes to the society, which requires the development of new thinking and new skills. For example, the economy in China has been growing sharply and the Chinese market has become increasingly important for business in the world. In such context, more and more Hong Kong people may work for mainland China's market and they will encounter the challenges of mastering Mandarin Chinese language [6]. Facing such changes, life-long learning should be emphasized for university students where they need to enhance self-learning along with the acquisition of more knowledge [6].

In the context of Hong Kong, Shek pointed out that because of limited tertiary education resources admission to Government funded universities is highly competitive. As a result, students and schools tend to pay great attention to the academic performance of the students [6]. As higher education in Hong Kong tends to be utilitarian with a strong emphasis on employment after graduation, sense of purpose and self-fulfilment are largely neglected. As a result, although the development of intellectual competence may be rather successful in Hong Kong, other competences of university graduates such as social, emotional, and interpersonal competences are largely ignored by both educators and students themselves [6]. Over-emphasis on examinations and the related demands also create much stress for the students. Indeed, several studies suggested that there were psychological problems in Hong Kong students. For instance, Wong, Cheung, Chan, Ma, and Tang [7] found that above 20% university students displayed depression problems and over 40% university students displayed anxiety symptoms. Besides, around 10% students at The Hong Kong Polytechnic University showed psychological problems deserving further attention [8].

It is important to promote university students' holistic development, especially their psychosocial competences [6]. A few scholars argued that courses that facilitate students' character development are pivotal to their life [9, 10]. Building on the above-mentioned background, a subject entitled "Tomorrow's Leaders" (TL) was offered to the 4-year students in 2012/13 academic year at The Hong Kong Polytechnic University. The main goal of TL was to promote student all-round development. Specifically, the subject attempted to "enable students to learn and integrate theories and research of basic personal qualities (particularly intrapersonal and interpersonal qualities) of effective leaders; to train students to develop and reflect on their intrapersonal and interpersonal qualities, and to promote the development of

an active pursuit of knowledge on personal qualities in leadership amongst students” [11, p. 108].

TL was designed as a credit-bearing course typically offered to Year 1 students based on the rationale that the subject is beneficial for the personal development of the students in their four-year university life. Various teaching approaches were used to enhance student learning experiences in this course, including lectures, experiential learning session, group project presentation, and written assignment [6]. Before this course was officially offered in 2012/13 school year, it was piloted in four classes ($n = 268$) in the 2010/12 academic years to understand the implementation process and the effectiveness of this course on students’ development [12]. Multiple evaluation strategies including process evaluation, objective evaluation, subjective outcome evaluation, and qualitative evaluation were conducted. Results generally showed that students were interested in this course and they also evaluated the course content, course design, and the teaching quality in a positive manner [13-15]. Moreover, students perceived that the course facilitated student general development (especially their development in psychosocial competences) and increased their potential to be qualified future leaders [16-18].

In most universities in Hong Kong, student feedback survey is commonly conducted at the end of each semester to evaluate the effectiveness of different subjects. Such evaluation by students (also known as client satisfaction approach or subjective outcome evaluation) is important for keeping teaching staff as well as course and curriculum designers informed of students’ perception of effectiveness of the course and qualities of teaching. This can help teachers to be aware of whether a course is well received by students as well as how to improve this course. Although some scholars questioned that subjective outcome evaluation may not truly reflect the situation [19-21], a number of studies did demonstrate that clients’ satisfaction of a program was associated with their objective changes [22-24].

At PolyU, student feedback survey has been adopted as a way to evaluate different subjects for a long time [25]. Due to the changed undergraduate curriculum in 2012/13 academic year, several rounds of revisions were made on the student feedback questionnaire. To evaluate the subject “Tomorrow’s Leaders”, the Student Feedback Questionnaire (SFQ) was further revised to make the items be more aligned with the characteristics of the subject and its specific learning outcomes [26]. This custom version of SFQ for TL has been used since 2012/13 academic year to provide student subject outcome evaluation on this course. In the first semester of 2012/13, results showed that students had positive perceptions about the subject in terms of their perceived learning experiences, achievement of learning objectives, and teaching of the staff members [27]. While the findings based on the revised SFQ provided important evidence for the effectiveness of TL from students’ perspectives, the psychometric properties of the questionnaire were not thoroughly examined. Although previous researchers have reported good reliability evidence of this questionnaire, its construct validity has not been investigated.

The current study had two main purposes. The first purpose was to investigate the psychometric properties of the SFQ by examining its internal consistency reliability and construct validity. The second purpose was to further investigate students’ evaluations of the subject “Tomorrow’s Leaders” (TL) offered in the second semester of 2012/13 academic year in terms of both the subject and the teaching staff.

CONTACT WITH ALL THE STUDENTS

One week before the completion of the course, an email was sent by the Educational Development Centre (EDC) of PolyU to all students who took TL inviting them to voluntarily complete the SFQ online for this subject by the week after the course was finished. In the second semester of 2012/13 academic year, 1,002 students were enrolled in this subject, among whom 393 males and 254 females ($n = 647$) completed the SFQ online. The students were all in the first year of their university study. Students' answers were automatically saved by the online system. The data were preliminarily processed by EDC and all personal information (such as faculty, student ID, etc.) was removed from the dataset before it was used for research purposes to ensure the anonymity and confidentiality.

The SFQ for TL was revised by the Research Team of the subject based on an original version developed by the Educational Development Centre of The Hong Kong Polytechnic University [28]. The revised questionnaire has two sections. The first section is about students' perceptions about the subject which includes three scales: perceived learning experience (4 items), achievement of learning objectives (5 items), and perceived benefits of the subject in promoting one's personal development (5 items). The second section is related to students' perception of the teaching of the staff member (12 items) which measures teaching quality and attitude of the subject teacher. A 5-point Likert scale was used (1 = strongly disagree and 5 = strongly agree). A high score indicates good quality of the subject.

OUR FINDINGS

Table 1 reports the internal consistency of the SFQ. Cronbach's alpha coefficients for the three subscales regarding the first section of the SFQ (perceived learning experience, achievement of learning objectives, and perceived benefits of the subject in promoting one's personal development) were on the high side (.91, .94, and .94 respectively). The teaching of staff member subscale was also found to be internally consistent (Cronbach's $\alpha = .97$).

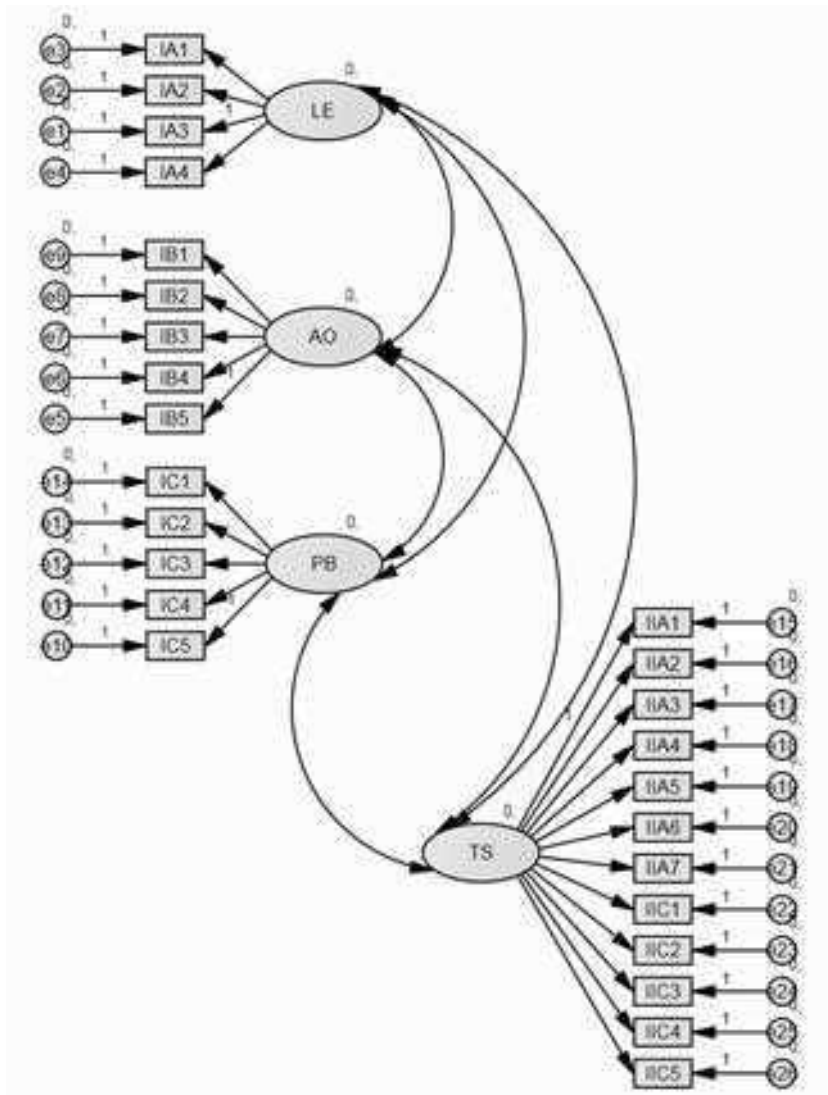
To examine the construct validity of the SFQ, confirmatory factor analysis (CFA) was conducted using Amos 22.0. The four scales (namely, perceived learning experience, achievement of learning objectives, perceived benefits of the subject, and perception of teaching staff) were treated as latent factors in the CFA model, and their corresponding items were the observed variables (indicators). Full information maximum likelihood analysis was used to impute for missing data, and the correlations between the latent factors were considered. Figure 1 shows the hypothesized model. The results indicate that the model fitted the data quite well: $\chi^2(df = 293) = 1300.68$, RMSEA = .07 (95% CI from .069 to .077), CFI = .94, TLI = .93. The standardized path coefficients (from the latent factors to the corresponding items) ranged from .79 to .90, and all these paths were significant ($p < .001$). The correlation coefficients among the four latent factors ranged from .71 to .94, $p < .001$ (Figure 2). These findings provide sound evidence for the construct validity of the revised SFQ.

Regarding the responses of the students to the questionnaire, descriptive statistics of students' responses to the SFQ are summarized in Table 1. The mean scores on the three scales of students' perceptions about the subject were all above 3.73, and for students'

perceptions about the teaching staff the mean scale score was 4.14, which suggest that students generally had positive evaluation on the subject and the teacher.

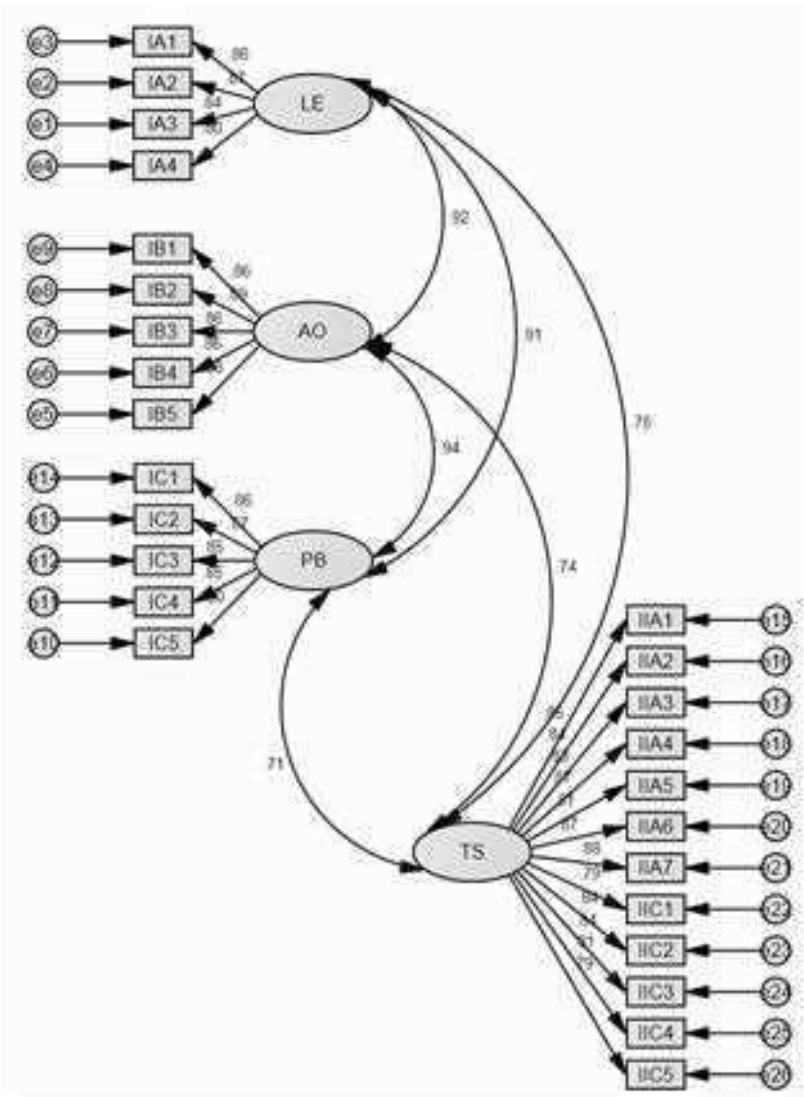
Table 1. Descriptive statistics and internal consistency of the SFQ for TL

Scale	No. of items	Cronbach's α	Mean	SD
Perceived learning experience	4	.91	3.82	.70
Achievement of learning objectives	5	.94	3.82	.71
Perceived benefits of the subject	5	.94	3.73	.72
Teaching of the staff member	12	.97	4.14	.62



Note. LE = perceived learning experience; AO = achievement of learning objectives; PB = perceived benefits of the subject; TS = perceived teaching of the staff member. The rectangles indicate observable variables, and the circles indicate latent variables. The observable variables on the left are the items on the corresponding scales. Standardized path coefficients are reported.

Figure 1. Hypothesized construct model of the student feedback questionnaire for TL.



Note. LE = perceived learning experience; AO = achievement of learning objectives; PB = perceived benefits of the subject; TS = perceived teaching of the staff member. The rectangles indicate observable variables, and the circles indicate latent variables. The observable variables on the left are the items on the corresponding scales. Standardized path coefficients are reported.

Figure 2. CFA results on the student feedback questionnaire for TL.

DISCUSSION

The first purpose of this study was to explore the psychometric properties of the Student Feedback Questionnaire for this course. Royse argued that good psychometric properties of subjective outcome evaluation surveys are necessary for obtaining valid evaluation results [29]. Hence, exploring the reliability and validity of this questionnaire is important for us to know whether student evaluation measured by this questionnaire is objective or not. Results

showed that the Cronbach alpha coefficients for each scale were very high, suggesting that this questionnaire has very good internal consistency reliability. Furthermore, the results of confirmatory factor analysis indicated good construct validity of this questionnaire. Specifically, the absolute and comparative fit indices (RMSEA, CFI, and TLI) suggest that the CFA model fitted the data well. In addition, all the items loaded significantly on their corresponding scales. To summarize, these results indicate that the SFQ for TL used in the current study has good psychometric properties. Methodologically speaking, the findings suggest that the information collected is reliable and valid.

The second purpose of the current study is to investigate the quality and effectiveness of the subject “Tomorrow’s Leaders”. As a large sample of students who took this course in the second semester of 2012/13 academic year completed the SFQ online anonymously, and confidentiality was emphasized during the survey, it is likely that the students might respond to the questionnaire in a genuine way. The high mean score of each scale of the SFQ indicates that students perceived the course as effective and having high teaching quality. Students clearly understood the teaching goals of this course; the subject design was perceived as effective in helping them achieve the learning objectives, and students agreed that this subject has promoted their development of different interpersonal and intrapersonal competences (such as critical thinking, problem solving, moral competence, etc.) which are necessary for leadership and one’s personal growth. These findings support the effectiveness of the subject in its first-year implementation. By enhancing students’ personal development in these important generic skills and leadership qualities, this subject is likely to prepare students to better adapt to the ever changing society, help them become more abled people, and increase their chances to be qualified leaders in today’s world. Moreover, results showed that students evaluated highly on teaching quality of the subject teacher and perceived the workload as appropriate. These results are consistent with students’ evaluations at the initial pilot stage of this subject as an elective subject [13] and suggest that “Tomorrow’s Leaders” was well designed and implemented successfully in its’ first-year implementation.

This study has several practical implications. First, it suggests the effectiveness and necessity of offering leadership and intrapersonal development courses like “Tomorrow’s Leaders” to students in university settings. Character and competence are critical in numerous aspects of one’s life [9]. While programs focusing on moral education and positive youth development are primarily implemented in primary and secondary school periods, the current findings demonstrated a successful example of offering such programs to university students. As reflected in the evaluation finding, students perceived that their overall development was promoted after attending the lecture. The successful experiences of “Tomorrow’s Leaders” could inspire teachers and researchers in other universities to design and implement similar curriculum-based programs for their students. Second, our study provides evidence for the good psychometrical properties of the SFQ for TL. Researchers could be more confident to use this validated instrument to measure the quality and effectiveness of the course in future and make good use of the findings based on the questionnaire to triangulate evaluation results obtained from other methods.

At the same time, this study has several limitations. First, the evaluation of the course in this study was only based on students’ reports. Therefore, these evaluations may not be objective enough. To gain a deeper understanding of the course quality, evaluation of this course based on the views of experienced professionals is needed. Longitudinal studies that examine student changes in leadership qualities and intrapersonal competences before and

after taking this course based on objective measures should be further conducted. Second, as no in-depth information can be generated from e-course evaluation surveys, qualitative studies should be done to supplement the present study which primarily yielded quantitative data. However, it is noteworthy that qualitative studies conducted previously have demonstrated the usefulness of the subject in promoting holistic development in the students [30-32].

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Chapter 190

QUALITATIVE EVALUATION OF THE GENERAL UNIVERSITY REQUIREMENTS

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ABSTRACT

Following the North American model, the length of undergraduate programme in Hong Kong has been extended from three to four years since 2012. To maximize the impact of the additional year, The Hong Kong Polytechnic University (PolyU) has implemented a new general education framework entitled “General University Requirements (GUR)” aiming to cultivate students in a holistic manner. This study explored students’ impressions of the GUR subjects using a survey collecting primarily qualitative data. Results from 163 students of eight faculties showed that students perceived the GUR subjects favorably. Having opportunities to make new friends from other departments and the teaching and learning methods, particularly experiential learning stimulated students’ interest and enriched their learning experiences which were reportedly unforgettable. Some of the obstacles encountered by students in several

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subjects were identified. The beneficial effects of the GUR subjects in different domains were voiced by the students.

INTRODUCTION

Traditionally, universities are solely training grounds for vocational and professional skills. With the impact of globalization and increased competition in society, universities have come with more responsibilities to nurture students with both professional knowledge and “the ‘key’, ‘core’, ‘transferable’ and/or ‘generic’ skills needed in many types of high-level employment” [1]. Similarly, Shafie and Nayan [2] highlighted that employers today are concerned about finding employees who not only possess basic academic skills such as reading, writing, listening, science, mathematics, and oral communication, but also higher order thinking skills (i.e., learning, reasoning, thinking creatively, decision making and problem solving). These skills are believed to be teachable that can be taught in both schools and employment settings [3]. Universities are therefore obliged to equip students with not only professional knowledge but also different desired interpersonal and intrapersonal attributes. On the other hand, increasing emphasis has been placed on student satisfaction which is an optimal indicator of quality [4]. Hence, obtaining student feedback on courses, lecturers, and their university experiences becomes increasingly important in higher education.

Many performance indicators are based on the quantitative data from student feedback surveys. While quantitative surveys are the primary means of obtaining student feedback, Grebennikov and Shah [5] argued that qualitative data received relatively less attention. Likewise, Richardson [6] pointed out that qualitative research on student feedback is extremely sparse. Williams, Coyle, and Healy [7] contended that the drawbacks of quantitative study involve the closed-ended questions which would restrict the respondents to express their negative experiences completely. Additionally, high satisfaction ratings do not necessarily mean that respondents “have had good experiences in relation to the services; rather, expressions of satisfaction may more often reflect attitudes such as ‘they are doing the best they can’, or ‘it’s not really their job to do ...’” [7].

Grebennikov and Shah [5] argued that systematic collection and analyses of qualitative data can be utilized as an effective institutional performance indicator and help improve students’ learning experience. Scott and colleagues [8] stressed that qualitative data are indeed “a lot richer than expected” [5]. For instance, Kabanoff, Richardson, and Brown [9] reported that there were recurring themes regarding different aspects of the course that were not tapped in existing quantitative evaluations of university experience. Studies examining students’ use of online faculty rating sites have found that students considered qualitative comments to be more informative than quantitative rankings [10, 11]. Therefore, the value of qualitative feedback is to “map the scope and strength of issues deemed important by students or graduates” [6]. Scott et al. [8] further suggested that “universities [should] focus more on what students have to say in their own words and incorporate such feedback into their priorities” and “the quantitative and qualitative data should complement each other as together they cover a broader range of student views on their university experience” [8].

Ragin [12] highlighted one of the differences between quantitative and qualitative approaches: “most quantitative data techniques are data condensers. They condense data in

order to see the big picture. Qualitative methods, by contrast, are best understood as data enhancers. When data are enhanced, it is possible to see key aspects of cases more clearly” (p. 93). These two research approaches are commonly used in the field of evaluation. Qualitative evaluation can allow the participants to voice their experiences [13] and enable researchers to gain insights into the processes and outcomes of programs through exploring into participants’ experiences and stories [14]. Royse [15] emphasized that using open-ended questions can allow the researchers to know the problems they never anticipate. More importantly, qualitative study may address some concerns about quantitative surveys that result in inflated satisfaction scores. “Clients often are more critical when qualitative methodologies are utilized, and are free to express their concerns about all aspects of care in a way that is not possible with many surveys. For new and innovative programs seeking to mold their programming around the needs of their clients, it is especially important that their client satisfaction reports be as accurate as possible, not inflated through the use of a poorly crafted survey” [16]. Qualitative evaluation is therefore an appropriate strategy to elicit feedback on newly implemented program.

With a shift from a three-year to a four-year undergraduate education structure since 2012, the curriculum of higher education in Hong Kong had undergone “significant and monumental change” [17]. One of the changes is the inclusion of General Education (GE) in the undergraduate curriculum. Ample literature indicates that numerous universities worldwide have incorporated GE into their undergraduate curriculum as a vital strategy to increase their students’ international competitiveness. In sharp contrast to pure professional and vocational training, GE focuses on the whole development of an individual which includes the development of a wide array of skills, such as language and communication skills, quantitative and analytical skills, planning and investigative skills, critical thinking, and problem solving skills [18] which are highly valued nowadays. Baker [19] argued that higher education should be “much more than a production line for work-ready graduates”. The fundamental job of undergraduate education is to “... help them [students] grow up, to learn who they are, to search for a larger purpose for their lives, and to leave college as better human beings” [20].

The Hong Kong Polytechnic University (PolyU) has developed a new General Education framework entitled “General University Requirements” (GUR) which aims to cultivate five desirable graduate attributes (i.e., critical thinking, effective communication, problem solving, lifelong learning, and ethical leadership). The GUR curriculum includes six major components: Freshman Seminar (FS) (3 credits), Language and Communication Requirements (LCR) (9 credits), Cluster Area Requirements (CAR) (12 credits), Leadership and Intra-personal Development (LIPD) (3 credits), Service Learning (SL) (3 credits), and Healthy Lifestyle (HL) (0 credit). To evaluate the effectiveness of the GUR, a five-year longitudinal project has been conducted since the first introduction of the new four-year undergraduate curriculum in 2012-2013 academic year. While the evaluative findings of the first-year implementation of the GUR were very encouraging [21, 22], it would be helpful if consistent findings can be found for 2013-2014 academic year based on different evaluation strategies. In the present paper, based on the qualitative evaluation sheet, qualitative data were collected to address the following research questions:

1. What were students' overall impressions of the GUR subjects?
2. What were students' most unforgettable experiences while they studied the GUR subjects?
3. What were the difficulties encountered by students while studying the GUR subjects?
4. What were students' perceived benefits of studying the GUR subjects?

OUR STUDY

In late December 2013 (i.e., end of the first semester of 2013-2014 academic year), 320 students were randomly selected from all Year 2 students enrolling in the four-year curriculum of PolyU in the 2012-2013 academic year. Forty students were randomly selected from each faculty/school. Emails and phone calls were sent to students to invite them to participate in the GUR qualitative evaluation. Students were asked to fill in a qualitative evaluation sheet attached to the invitation email. Before the commencement of the second semester of 2013-2014 academic year, 163 students returned the completed evaluation sheet (response rate = 50.94%). The number of participants who completed the qualitative evaluation sheets in each faculty was: Faculty of Applied Science and Textiles (FAST) (n = 18), Faculty of Business (FB) (n = 20), Faculty of Construction and Environment (FCE) (n = 21), Faculty of Engineering (FENG) (n = 20), Faculty of Humanities (FH) (n = 20), Faculty of Health and Social Sciences (FHSS) (n = 22), School of Design (SD) (n = 22), and School of Hotel and Tourism Management (SHTM) (n = 20).

A qualitative evaluation sheet developed by the research team was used to examine students' views on the GUR subjects that they enrolled in semester one of 2013-2014 academic year. The qualitative evaluation sheet consists of the following parts:

- Three descriptors/short phrases that were used by students to describe their general impressions and feelings towards the GUR subjects;
- Students' unforgettable experiences in studying the GUR subjects;
- Difficulties/challenges encountered by students in studying the GUR subjects;
- Students' perceptions of the benefits of the GUR subjects to themselves.

All the responses in the qualitative evaluative sheets were entered in the computer for analyses. The unit of analysis was a meaningful unit instead of a statement [23]. For instance, a comment on one's general impression about GUR subjects, "interesting and relaxing" would be broken down into two meaningful units, i.e., "interesting" and "relaxing". Meanwhile, descriptions with the same meaning would be grouped into the same attribute category. After initial coding, all units were further categorized into four categories: "positive", "negative", "neutral", and "undecided". To enhance the reliability of the coding, both inter-rater and intra-rater reliabilities were examined. For the inter-rater reliability, a research assistant with a Master degree who did not know the original coding recoded 20 randomly selected responses from students after the completion of the raw coding. The inter-rater agreement for these responses was 90%. For the intra-rater reliability, a post-doctoral fellow who coded the raw data recoded the above 20 randomly selected students' responses. The intra-rater agreement percentage for the responses was 90%.

FINDINGS

Since the majority of students had completed the FS and LIPD in the first year, the findings reported focused primarily on students' perspectives on subjects of LCR-English and LCR-Chinese, CAR, SL, and HL which they enrolled in 2013-2014 academic year. First, most students used positive descriptors to describe their general impressions and feelings towards the GUR subjects. The categorizations of descriptors are shown in Tables 1-5. The total number of descriptors for each GUR component was: LCR-English ($n = 96$), LCR-Chinese ($n = 58$), CAR ($n = 232$), SL ($n = 70$), and HL ($n = 185$). Among the descriptors for each GUR component, the number and percentage of positive responses were: LCR-English ($n = 70$, 72.92%), LCR-Chinese ($n = 35$, 60.34%), CAR ($n = 129$, 55.60%), SL ($n = 49$, 70.00%), and HL ($n = 144$, 77.84%). Some common positive descriptors across the GUR subjects included "interesting", "practical", "useful", "helpful to development" and "have increased knowledge" whereas the negative responses were "heavy workload" and "boring".

Table 1. Categorization of the descriptors about the LCR-English subjects

Descriptors	Nature of the descriptor				Total
	Positive	Neutral	Negative	Undecided	
Improvement in English	5				5
Improvement in English reading	2				2
Improvement in English writing	3				3
Interesting	9				9
Helpful to my development	5				5
Interactive	2				2
Useful	9				9
Ok	3				3
Inspiring	4				4
Practical	6				6
Appropriate amount of assignment	2				2
Very useful	2				2
Helpful	4				4
Other positive descriptors (e.g., enjoyable, communication skill improvement)	14				14
Want to know more grading criteria		1			1
Could shorten class time		1			1
Hope to teach reflection- or report-writing instead of essay-writing		1			1
Heavy workload			3		3
Difficult			2		2
Other negative descriptors (e.g., boring, troublesome)			13		13
Challenging				2	2
American style is better than British style				1	1
Academic-oriented				1	1
Easy to get a bad grade				1	1
Total count	70	3	18	5	96
(Percentage)	(72.92%)	(3.13%)	(18.75%)	(5.21%)	(100%)

Regarding students' unforgettable experiences in studying the GUR subjects in semester one of 2013-2014 academic year, 84 meaningful responses were extracted from the raw data which were further categorized into 30 categories. Among these meaningful responses, 64 (76.19%) were regarded as positive responses, 7 responses (8.33%) were categorized as

neutral and 13 responses (15.48%) were counted as negative responses (see Table 6). Specifically, responses pertaining to students' unforgettable experiences were related to two domains: teaching and learning as well as perceived benefits of the GUR subjects. Regarding the realm of teaching and learning, experiential learning experience in Service Learning subjects, having been taught by a good teacher, and studying subjects not related to the major discipline were reported by the greatest number of students as unforgettable. In addition, having opportunities to learn different kinds of interesting sports and making new friends from other faculties were often cited as unforgettable experiences by students. Nevertheless, some negative experiences were also reported, including the difficulty to enroll in one's desired GUR subjects, long lecture time and heavy workload in some subjects, and having free-rider in group work.

Table 2. Categorization of the descriptors about the LCR-Chinese subjects

Descriptors	Nature of the descriptor				Total
	Positive	Neutral	Negative	Undecided	
Improvement in Chinese writing	4				4
Improvement in Putonghua	3				3
Interesting	6				6
Relaxing	2				2
Helpful to my development	5				5
Useful	2				2
Improvement in communication skill	2				2
Other positive descriptors(e.g., knowledge broadening, inspiring)	11				11
Content not very difficult		1			1
Can be more interesting		1			1
Neutral		1			1
Boring			2		2
Not very useful			2		2
Too many tests			2		2
Other negative descriptors (e.g., Heavy workload, Dreary)			9		9
Not many assignments				1	1
Challenging				1	1
Easy to get a bad grade				1	1
Should not teach Putonghua				1	1
Total count	35	3	15	4	57
(Percentage)	(60.34%)	(5.26%)	(25.86%)	(6.90%)	(100%)

Table 3. Categorization of the descriptors about the CAR subjects

Descriptors	Nature of the descriptor				Total
	Positive	Neutral	Negative	Undecided	
Knowledge broadening	15				15
Interesting	30				30
Improve critical thinking	4				4
Relaxing	3				3
Know more students and friends from other departments	4				4
Helpful to my development	7				7
Inspiring	9				9
Diversified learning	8				8
Practical	4				4
Deeper understanding of society	2				2

Descriptors	Nature of the descriptor				Total
	Positive	Neutral	Negative	Undecided	
Meaningful	2				2
View/Horizons broadening	8				8
Helpful to self-understanding	2				2
Strengthen knowledge in other disciplines	7				7
Other learning experiences	2				2
Beneficial	3				3
Broaden thinking	2				2
Other positive descriptors	17				17
(e.g., unforgettable, collaborative)					
Somehow interesting		3			3
Other neutral descriptors		9			9
(e.g., content not very difficult)					
Boring			7		7
No use			8		8
Heavy workload			11		11
Difficult			4		4
Waste time			2		2
Bad teaching			2		2
Not interested			4		4
Other negative descriptors			34		34
(e.g., inadequate quotas, messy)					
Challenging				2	2
Not related to majors				2	2
Other undecided descriptors(e.g., unfamiliar with historical knowledge)				15	15
Total count	129	12	72	19	232
(Percentage)	(55.60%)	(5.17%)	(31.03%)	(8.19%)	(100%)

Table 4. Categorization of the descriptors about the SL subjects

Descriptors	Nature of the descriptors				Total
	Positive	Neutral	Negative	Undecided	
Interesting	6				6
Interactive	2				2
Collaborative	2				2
Volunteering opportunity	2				2
Unforgettable	3				3
Deeper understanding of society	2				2
Meaningful	5				5
Improvement in communication skill	2				2
Rewarding	2				2
Other positive descriptors (e.g., relaxing, enjoyable)	23				23
Heavy workload			1		1
Boring			2		2
No use			2		2
Troublesome			2		2
Long service hour			2		2
Other negative descriptors(e.g., messy, unclear marking scheme)			8		8
Challenging				1	1
Need time to prepare				1	1
Need self-initiative				1	1
Many different kinds of work in different SL subjects				1	1
Total count	49	0	17	4	70
(Percentage)	(70.00%)	(0.00%)	(24.29%)	(5.71%)	(100%)

For obstacles or challenges encountered by the students, 101 meaningful responses were extracted from the raw data (see table 7). These responses were further categorized into 24 types of difficulties or challenges within eight broad categories: language, time management, group work, assignment and assessment, teaching and learning, lengthy and timetable of class, subject registration and fulfillment of requirements. The challenges that gained relatively higher frequency of responses included: CAR subjects enrolled with little knowledge of the background (16.83%), heavy workload (11.88%), and time management (10.89%). More specifically, the contents of some CAR subjects were perceived by students to be abstract and difficult. Students expressed that they had heavy academic workloads, and poor time management was another challenge to students.

Table 5. Categorization of the descriptors about the HL subjects

Descriptors	Nature of the descriptors				Total
	Positive	Neutral	Negative	Undecided	
Interesting	29				29
Relaxing	14				14
Funny	7				7
Helpful to my development	3				3
Helpful to my health	12				12
Encourage physical activity doing	7				7
Ok	2				2
Inspiring	2				2
Healthy	11				11
Joyful	7				7
Practical	3				3
Enjoyable	5				5
Increasing interests in doing exercise	2				2
Exciting	3				3
Increase awareness of doing exercise	5				5
Very helpful	2				2
Learnt some new sports skills	6				6
Very good	2				2
Reduce pressure	2				2
Other positive descriptors (e.g., fulfilling, enthusiastic teacher)	20				20
Want to do other exercises		1			1
Interesting for some sports items		1			1
Easy		1			1
Should provide more sessions for sports skill training		1			1
Too many stages			5		5
Not very effective			2		2
Boring			4		4
Inadequate quotas			5		5
Secondary school subject/not applicable to university students			2		2
Time wasting			2		2
Hard to register			2		2
Other negative descriptors (e.g., complicated, bad timetabling)			11		11
Challenging				2	2
Sporty				1	1
Extra activities				1	1
Total count	144	4	33	4	185
(Percentage)	(77.84%)	(2.16%)	(17.84%)	(2.16%)	(100%)

Table 6. Categorization of students' unforgettable experiences in GUR study

Unforgettable Experiences	Nature of the response				Total
	Positive	Neutral	Negative	Undecided	
General experience					
Difficulty in registering CAR subjects			2		2
Difficulty in registering SL subjects			1		1
Difficulty in registering HL subjects			1		1
Heavy workload in CAR subjects			1		1
Long lecture			2		2
Bad teaching			1		1
Dissatisfied with Putonghua as the major assessment language in LCR-C			1		1
Difficulty in communicating with group mates when doing group work			1		1
Met irresponsible students in group work in CAR subjects			1		1
Attended CAR lectures and tutorial at night			1		1
Boring and too theoretical oriented teaching			1		1
				Subtotal	13
Teaching and learning					
Experienced good and interesting teaching	5				5
Encountered interesting and enthusiastic teacher	6				6
Used Putonghua to communicate in class in study LCR-C	1				1
Experienced innovative way of teaching and learning in LIPD and CAR subjects	4				4
Experiential learning experience in SL subjects	7				7
Did volunteering work to help and understand the underprivileged people	5				5
Studied interested subjects outside one’s major discipline	6				6
Participated in exchange program	1				1
Did novel and interesting forms of assignment	2				2
				Subtotal	37
Benefits					
Made improvements in language learning	1				1
Met friends from other majors and enlarged social circle	7				7
Made achievements from hard study	1				1
Praised by teacher for good work	1				1
Inspired communication with teacher	1				1
Learned from peers in group work	1				1
Increased multicultural understanding through service activity	1				1
Felt interesting, funny, and relaxing in study HL	4				4
Learned different kinds of interesting sports	10				10
				Subtotal	27
No particular experiences					
		7			7
				Subtotal	7
Total count	64	7	13	0	84
(Percentage)	(76.19%)	(8.33%)	(15.48%)	(0.00%)	(100%)

A total of 163 meaningful responses related to the students' perceived benefits derived from GUR study were extracted from the raw data. Among the 163 meaningful responses, 156 (95.71%) were regarded as positive responses which were further categorized into "five desired graduate attributes", "other competences", "character", "health", "learning and knowledge", and "others" domains (see Table 8). Among the five desired graduate attributes, many students reported that they have improved their communication skills, developed their

critical thinking skills, and ethical leadership skills. Additionally, students expressed that their knowledge has been broadened.

These benefits can be seen in the narratives below excerpted from students' responses:

"Most GUR subjects required us to work with other classmates on some projects and presentations. It helped my personal development through enhancing my communication skills and teaching me how to cooperate with others and accomplish some goals with them."

Table 7. Categorization of students' difficulties/challenges in GUR study

Difficulties / Challenges	N	%
Language		
Difficulty in catching up with language courses due to inadequate language foundation	3	2.97
Difficulty in catching up with courses taught in English due to inadequate language foundation	5	4.95
Difficulty in practicing English and Chinese in LCR subjects	1	0.99
Subtotal	9	8.91
Time Management and Self-Discipline		
Time management	11	10.89
Subtotal	11	10.89
Group Work		
Met free riders in doing group work	4	3.96
Challenge to communicate and collaborate with different group members in doing group work	3	2.97
Subtotal	7	6.93
Assignment and Assessment		
Writing long English paper or report	4	3.96
Unclear guidance about assessment and assignment	5	4.95
Subtotal	9	8.91
Teaching and Learning		
Difficult to understand too abstract contents in some subjects	3	2.97
Hard to learn something from bad teaching and knowledge organization	2	1.98
The level of science subject in CAR is much deep for students who do not have science foundation	8	7.92
It is challenging for students to study CAR subjects which they have no or little knowledge	17	16.83
Heavy workload	12	11.88
Lack of experiences in doing service learning projects	4	3.96
Interview industry managers	1	0.99
Subtotal	47	46.53
Lengthy and Timetable of Class		
Felt hard to concentrate in three hours' CAR class	1	0.99
Longer length of healthy lifestyle subjects	2	1.98
Attended CAR classes at night	1	0.99
Subtotal	4	3.96
Subject Registration		
Difficulty in registering CAR subjects due to later registration timeslot assigned	3	2.97
Difficulty in registering CAR subjects due to time clashes between CAR subjects and students' other pre-assigned subjects	4	3.96
Difficulty in registering HL subjects	4	3.96
Difficulty in registering SL subjects	2	1.98
Subtotal	13	12.87
Requirements Fulfilling		
Felt challenge to fulfill the complicated GUR requirements within four years' time	1	0.99
Subtotal	1	0.99
Total count	101	100

"Most importantly, my critical thinking has been improved. Previously, I used to blindly believe what the books and teachers told us with little critical thinking. Now, I start to have my own thinking."

"Through LIPD subjects, I developed a deeper understanding of leadership, particularly in its theoretical aspects. Also, my self-understanding and self-reflection were deepened."

Table 8. Categorization of students' perceived benefits of GUR subjects

Perceived Benefits	Nature of the response				Total
	Positive	Neutral	Negative	Undecided	
Critical Thinking					
Improved critical and independent thinking	10				10
Improved creative thinking	1				1
Broadened thinking	1				1
Effective Communication					
Improved communication skills	23				23
Problem Solving					
Improved problem solving skills	7				7
Improved analyzing ability	1				1
Lifelong Learning					
Improved independent learning	2				2
Improved lifelong learning	1				1
Ethical Leadership Skills					
Leadership development	12				12
Other Competences					
Improved interpersonal skills	5				5
Improved time management skills	6				6
Improved team work skills	7				7
Improved judgment	2				2
Improved organizing ability	1				1
Character					
Self-reflection and self-understanding	3				3
Development of empathy	2				2
Development of self-examination	1				1
Improved resilience	4				4
Perseverance	1				1
Improved independence	1				1
Health					
Improved mental health	4				4
Improved physical health	6				6
Increased awareness of keeping healthy lifestyle	4				4
Learning and Knowledge					
Broadened horizons	8				8
Improved active learning	1				1
Enriched and broadened learning and knowledge out of majors	14				14
Enhanced understanding of majors	1				1
Gained knowledge on health and exercise	1				1
Had chance to learn knowledge and put in practice	1				1
Others					
Expanding social networks across disciplines	4				4
All-round training	1				1
Improved skills in doing research	1				1
Enriched life experience	2				2
Deepen understanding of society	3				3
Beneficial to future career	3				3
Learned different kinds of sports skills	7				7
Peer learning and peer understanding through team work	1				1
Not much help			7		7
Total count	156	0	7	0	163
(Percentage)	(95.71%)	(0.00%)	(4.29%)	(0.00%)	(100%)

DISCUSSION

Due to a paucity of research findings on the effectiveness of GE in Hong Kong, this study attempted to fill the knowledge gap and to evaluate the effectiveness of the GUR program at PolyU in the 2013-2014 academic year based on a qualitative evaluation of students. The present study is an important contribution to the field as systematic qualitative evaluation studies involving a large sample is lacking in the field. There are several unique features of the study. First, this is the first known qualitative study examining the 4-year curriculum in Hong Kong. Second, a large sample of students from different faculties was recruited. Third, both quantitative and qualitative analyses were carried out. Finally, inter and intra-rater reliability checks were conducted for analyses.

Concerning the students' impressions of the GUR program, the results showed that students generally had positive perceptions of different GUR subjects, with the positive responses ranging from 55.60% to 77.84% across components. The majority of students perceived the contents of GUR subjects as interesting and conducive to learning additional knowledge and skills beyond their majors. The active and engaging teaching and learning (T&L) methods used in different GUR components helped enhance students' learning experiences that augment the learning outcomes. There were also less favorable views expressed by students such as heavy workload and relatively boring content, which suggest the need to further examine the syllabus and teaching in some GUR subjects.

Regarding unforgettable experiences in studying the GUR subjects, approximately 76.19% were positive responses, suggesting that students had remarkable, positive learning experiences. As mentioned above, students expressed appreciation of the T&L methods, in particular the experiential learning and collaborative learning (e.g., group project) adopted in many GUR subjects. Numerous studies have found that experiential learning can develop students' competences, link their learning to practice, and provide students with profound learning experiences [24, 25]. Group work helps promote work-related skills, develop deeper understanding of complex tasks, and manage time-consuming tasks [26]. The UK Quality Assurance Agency for Higher Education guidelines for economics considers group work as vital because it provides "active and deep learning opportunities for students' learning" [27, p1]. Experiential learning, group work, and other student-centered T&L methods actively engage students, improve the T&L experience, and offer fruitful and satisfying learning experiences to students so they found their learning unforgettable. In addition, having been taught by good and enthusiastic teachers made students' learning experiences unforgettable.

On the other hand, some undesirable experiences were also noted. First, one of the negative experiences was the difficulty to enroll in students' interested CAR subjects through the current subject registration system. In fact, this issue has been reported in the first year of GUR implementation [22] and administrative strategies have been conducted to address the problem, such as adjusting the timetable of CAR subjects so that students would have more flexibility in subject selection. The current finding seems to suggest that more strategies shall be attempted to further resolve this problem. Another negative experience reported by students was the free-riding problem in group work. According to Morris and Hayes [28], the free-riding problem refers to "the problem of the non-performing group member who reaps the benefits of the accomplishments of the remaining group members with little or no cost to him/herself" [28]. Free-riding behavior of a student can demotivate diligent students in the

same group. Therefore, teachers should provide close monitoring to students and are encouraged to adopt strategies such as identifying individual contribution by group members in the process of evaluating the project work [29]. This method has been used in one of the GUR LIPD subjects, “Tomorrow’s Leaders”, which effectively reduces the free-riding problem in group work.

Several obstacles or challenges students encountered in their GUR study are noted. First, the contents of CAR subjects were perceived too advanced for some students. These results were congruent with those of Shek et al. [22] who found that students from humanities and social sciences backgrounds expressed difficulty in studying science-based CAR subjects as these students had little or no background knowledge. Morgan and Tam [30] found that difficult content was one of the barriers often cited by non-persisting university students who subsequently dropped out from the course. The implication is that GUR teachers shall reflect on the level of difficulty of the subjects they offered and make adjustment on the lecture content to cater to the needs of students at different knowledge levels.

Second, students reported that the workload of some GUR subjects was heavy. Gardner and Parkinson [31] found that university students who reported having heavy subjective workloads were more stressed. Kember [32] noted that excessive perceived workload encourages surface approaches to learning because students tend to resort to undesirable study approaches to deal with the work demand. Teachers should help identify those students in need of additional assistance for their homework and simultaneously, set appropriate workload which was found to be significantly related to a deep approach to learning in students [33]. The promotion of effective communication between students and teachers is also recommended as it can help teachers set some reasonable expectations from students. Another problem was poor time management which, coupled with perceived excessive homework and poor time management skills, can be an important source of stress for students.

Lastly, an obstacle reported by students was the difficulty in writing long English paper or report for the GUR subjects and the guidance from teachers to complete the assignment was not clear. Similar results were reported by Lee and Tajino [34] who found that the first-year Japanese university students perceived difficulty in writing English. They explained that a possible reason for expressing a higher perception of difficulty in writing English paper or report was students’ perception of their low English ability. A local Education Commission report in Hong Kong on language proficiency in the mid-1990s has already noted that “... many of our upper secondary schools do not have the English proficiency required by tertiary education institutions or the vocational sector” [35]. To address this need, the Office of General University Requirement (OGUR) has organized a series of workshops for students to learn how to write reflective papers and prepare group presentation starting from 2013-2014 academic year. Students participated in the workshops expressed satisfaction and gained more self-efficacy in handling such assignments. Other methods, such as peer-partner learning may be further attempted.

Students perceived that the GUR subjects had beneficial effects on their development, with 95.93% of the responses coded as positive. Students considered the GUR subjects were able to increase their knowledge, different competence, character, and health (i.e., both physical and mental health). Evidently, the GUR components were perceived as conducive to the development of generic attributes in students, especially of the five desired graduate

attributes of PolyU as revealed in the narratives of the students. These findings are generally consistent with the findings based on the first year findings of the GUR longitudinal study.

Nevertheless, several limitations of the study should be noted. First, although the qualitative evaluation is the optimal strategy to collect different participants' perspectives, its conclusion is limited when making generalization or representativeness to a larger population [36]. Second, this study only focused on the students' perspectives on the GUR subjects, while the views of other stakeholders such as teachers should also be examined in order to obtain a more comprehensive picture. In addition, other evaluative methods such as objective outcome evaluation and longitudinal case study on students should be adopted to triangulate the findings from the current study. Despite these limitations, the present study provides valuable qualitative evaluation findings which support the effectiveness of the GUR in developing the desired graduate attributes among university students in Hong Kong.

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Chapter 191

AN EVALUATION STUDY ON A UNIVERSITY GENERAL EDUCATION SUBJECT IN HONG KONG

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ABSTRACT

This chapter evaluated a university general education subject on leadership and intrapersonal development ("Tomorrow's Leaders") offered at The Hong Kong Polytechnic University based on an online survey using the Student Feedback Questionnaire (SFQ). At the end of the first semester of 2013/14 academic year, 725 year-one students completed the online questionnaire. Results showed that the students generally had positive ratings on both the subject attributes and the qualities of teachers. The majority of the participants perceived the subject as beneficial to their holistic development and leadership competencies. Students from Faculty of Health and Social Sciences and Faculty of Applied Science and Textiles had more favorable evaluation of the subject than did students in Faculty of Construction and Environment. Students'

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perceived benefit of the subject was significantly predicted by the subject attributes and teacher attributes. Implications of the findings are discussed.

INTRODUCTION

There is a growing concern about the mental health of university students nowadays and their competencies to successfully integrate into future workforce after graduation. In particular, as a Special Administrative Region (SAR) of China and a major financial and service center, the changing economy of Hong Kong has placed high demands and challenges to university students. Empirical studies have revealed high rates of emotional and anxiety problems in first-year university students in Hong Kong [1]. According to the results of a recent survey, more than 80% of the local business leaders considered today's university graduates as having insufficient personal and interpersonal abilities to adapt to the rapidly changing market [2]. To better prepare students to meet the demands and challenges, the Education Commission of Hong Kong Government had launched a university education reform starting from 2012/13 academic year which extended the traditional three-year undergraduate programme to four years [3]. With the one extra year, universities are expected to provide a series of General Education subjects for students to promote their personal growth and holistic development.

As one of the eight public universities in Hong Kong, The Hong Kong Polytechnic University (PolyU) has designed and implemented a general education framework (the General University Requirement, GUR) for all students enrolled in the new four-year undergraduate curriculum [4]. Under the GUR framework, one important area is the "Leadership and Intra-personal Development" (LIPD), which aims to promote students' holistic development and leadership qualities based on experiential learning. The LIPD component of the GUR consists of two subjects: "Tango! Managing Self and Leading Others" (Tango) and "Tomorrow's Leaders" (TL). While Tango was designed by the Faculty of Business and offered to their own students, TL is offered to all first-year undergraduate students as a compulsory course since the launch of the new 4-year undergraduate programme in 2012/13 [1].

Specifically, TL has adopted multiple teaching and learning approaches, such as lectures, group discussion and debates, reflective writing, and role play, to achieve the intended learning outcomes of the LIPD component. As the subject is offered in a large scale (more than 2,000 students enrolled every year), it is important to understand how well the subject has been implemented and to what extent it has promoted students' personal development. Since 2012/13, systematic evaluation studies have been conducted to examine the implementation and effectiveness of TL, including pre- and post-test survey based on objective outcome indicators, focus group interviews with students and teachers, post-lecture evaluation, post-course evaluation, and students' reflective journals [6-9]. The findings converged to suggest an overall success of the subject in promoting students' holistic development. For example, findings on students' reflective journals ($n = 62$) in 2012/13 revealed that students perceived the subject as beneficial in improving their self-understanding, self-management, communication skills, and ethical leadership. Adopting a one group pretest-posttest design, Shek and Ma reported that students showed positive changes in self-determination, thriving, and life satisfaction after completing the subject

based on objective outcome measures in 2012/13 [7]. Based on student feedback questionnaire, it was found that students had positive perceptions about the subject content, quality of the teaching staffs, and overall effectiveness of the subject [9].

Although TL can be regarded as successful in its first-year implementation, the teaching environment and conditions are always changing. In fact, several factors changed in the second year which might influence the implementation of the subject. First, to meet the needs of the large number of students, new academic staff was recruited to teach this subject. Second, the average class size in 2013/14 was larger than that in 2012/13 which resulted in some changes in teaching strategies. For example, in classes with more than 90 students, some of the originally designed interactive activities cannot be implemented thoroughly. Third, the curriculum was refined based on the post-lecture feedback collected from students in 2012/13. Under these new conditions, it is necessary to know whether the subject remained to be effective and well-received by students.

An interesting observation based on previous findings is that students from Faculty of Engineering (FENG) and Faculty of Applied Science and Textiles (FAST) had more positive views about the subject than students of other disciplines [9]. This is inconsistent with the general findings that students majoring in social sciences or “soft” disciplines (e.g., arts and humanities) often reported more favorable attitudes toward general education subjects than did students majoring in sciences [10, 11]. It was speculated that both the good quality of teaching demonstrated by teachers who delivered the subject to students of these two faculties and the unique characteristics of the subject contributed to students’ positive evaluation result. In 2013/14, as all teaching staff were randomly assigned to teach different classes, it would be interesting to further examine whether the evaluation by students from different faculties would still be different following the same pattern revealed in the previous academic year.

Moreover, while empirical studies have suggested program attributes (e.g., plan, design and delivery approaches) and program implementer characteristics (e.g., personal experience and attitudes) were crucial factors to the success of a program [12-14], there is little research focusing on curriculum-based program in university settings, particularly in Hong Kong. Based on student feedback collected in 2012/13 about TL, Shek and Yu [9] reported that only students perceived qualities of teaching staff (but not subject attributes) significantly predicted students’ final grade in the subject. One limitation of the study was that students’ final grade might not fully reflect their learning outcomes as some personal development such as self-reflective skills or interpersonal competences may not be immediately shown in one’s term paper or presentation. As such, it would be informative to investigate the factors that contribute to students’ perceived benefits of the subject.

Against the above background, the current study was intended to address the following three research questions: [1] how did students evaluate the subject “Tomorrow’s Leaders” (TL) in 2013/14 based on the validated Student Feedback Questionnaire (SFQ)? [2] Would students’ SFQ ratings on TL vary across faculties? [3] How would students’ perceived subject attributes and teacher qualities predict students’ perceived benefits of TL?

OUR STUDY

In total, 1,070 year-one students from 17 classes took TL in the first semester of 2013/14 academic year. Near the end of the semester, all students were invited to participate in the online SFQ survey through an email sent by the Educational Developmental Centre (EDC) of the University. Purpose of the survey, confidentiality of participation, and the link to the online questionnaire were highlighted in the email. Clear instructions on how to answer the questions were provided at the beginning part of the questionnaire. After students completed and submitted the questionnaire, their data were saved in the database of Information and Technology Services Office (ITS) in an automatic way. To assure the confidentiality, the database was only accessed by research staff in EDC who provided the data for the present study.

Seven hundred and twenty-five students agreed to participate and completed the questionnaire, indicating a good response rate of 67.8%. Among the 725 students, there were 72 students from Faculty of Humanities (FH); 47 from Faculty of Construction and Environment (FCE); 261 from Faculty of Engineering (FENG); 97 from School of Hotel and Tourism Management (SHTM); 100 from Faculty of Health and Social Sciences (FHSS), and 148 from Faculty of Applied Science and Textiles (FAST). Students from Faculty of Business (FB) and School of Design (SD) did not evaluate the subject, as FB students took another LIPD subject (Tango) and SD students would take the subject in the second semester of 2013/14. The survey was administered anonymously online without asking students to report any identifiable individual information. Therefore, the characteristics of the participants were unknown.

The Student Feedback Questionnaire (SFQ) developed by EDC was used in this study [15-16] which examines students' evaluations about the subject on two dimensions: the "subject attributes" (learning experience and achievement of learning objectives) and the "teacher attributes" (qualities of teachers) [16]. To evaluate TL, two subscales with extra questions were added: perceived benefits of the subject (5 items) and other qualities of the teaching staff (5 items). The modified version of SFQ for TL thus constitutes three dimensions: "subject attributes", "teacher attributes (including both the original items and the newly added items on other qualities of the teaching staff)", and "perceived benefits of the subject" (5 items). Cronbach's alphas of the modified SFQ and its subscales ranged from .92 to .98, which indicated sound reliability of the questionnaire based on the present sample. All items of the scale were scored on a 5-point Likert scale (5 = *strongly agree*, 4 = *agree*, 3 = *no strong view*, 2 = *disagree*, 1 = *strongly disagree*). Scale score and subscale scores were calculated by averaging the related item scores, with higher score representing for a more positive evaluation.

First, to examine students' general evaluation about the subject, descriptive statistical analyses were conducted including numbers and percentages of students with different responses on each item. Means and standard deviations of different subscale scores and the SFQ scale score were also calculated. Second, to investigate whether students from different faculties had different perceptions toward the subject, MANOVA was conducted to compare students' SFQ ratings across faculties. Faculties were considered as the independent variables and students' SFQ scores on subject and teacher attributes as well as perceived subject benefits were regarded as the dependent variables. One-way ANOVA was also carried out to

examine faculty differences in students' overall SFQ score, with faculty being treated as the independent variable and students' overall SFQ score as the dependent variable. Third, to investigate the predictive effects of students' evaluation on subject attributes and teacher attributes on their perceived benefits of the subject, multiple regression analyses were performed. Students' SFQ scores on subject attributes and teacher attributes were treated as the independent variables and perceived benefits of the subject was considered as the dependent variable. All the analyses were performed using the statistical package of SPSS 20.0.

FINDINGS

Descriptive results were presented in Table 1 and Table 2. Several observations can be highlighted from the findings. First, in terms of subject attributes, the majority of students had favorable learning experiences and perceived that the subject has helped them achieved the learning objectives. For example, 77.6% of the participants agreed that the assessments require them to demonstrate their knowledge, skills and understanding of the subject, and most of the participants believed that the subject has enabled them to develop a good understanding of the qualities of effective leaders (77.0%) as well as a better self-understanding (75.0%). Second, students gave high ratings on the qualities of the teaching staff. More than 90% of the students considered the subject teachers as well prepared for the lessons and being willing to provide help when necessary. A large proportion of students believed that the staff member had good teaching skills (83.5%) and professional attitudes (88.7%). Students also appreciated teachers' interactions with students (87.0%), logical and clear subject content organization (86.1%), and timely class feedback (84.2%). Overall, the majority of the students (84.7%) indicated that the teaching staff was an effective teacher, who provided them with a valuable learning experience (82.4%). Third, students generally perceived the subject as beneficial to their holistic development, including understanding of ethical leadership (74.2%), critical thinking (65.4%), communication skills (71.0%), problem-solving skills (59.8%), and personal growth (75.7%). Fourth, the mean scores of SFQ scale and subscales were all above 3.79 out of a maximum of 5 (Table 2). All these findings suggest that students were satisfied with the subject and the teaching staff. They also perceived the subject as having a positive influence on their personal development.

Means and standard deviations of SFQ subscale and scale scores rated by students from different faculties were summarized in Table 3. Results of MANOVA showed that SFQ subscale scores differed significantly across faculties, Wilk's $\Lambda = .95$, $F(10, 1288) = 3.25$, $\eta^2 = .03$, $p < .001$. Post-hoc comparisons using Bonferroni procedure revealed that students of FENG, FHSS, and FAST rated subject attributes significantly higher than did students of FCE ($ps < 0.05$); students from FHSS and FAST also gave higher ratings on teacher attributes than did students from FH and FCE ($ps < 0.001$). Regarding perceived benefits of the subject, FHSS and FAST students showed more positive ratings than did students of FCE. SFQ ratings among other faculties were not significantly different. Similar results were obtained when comparing the overall SFQ scale score across faculties based on ANOVA, $F(5, 645) = 3.46$, $\eta^2 = .03$, $p < .001$. The total scale scores of SFQ given by students of FHSS and FAST were significantly higher than the scores given by students of FCE. Overall, the comparison

findings indicated that students in FHSS and FAST had more positive perceptions about the subject while students in FCE showed less favorable evaluation.

The inter-correlations among different subscale scores and scale score of SFQ were reported in Table 5. All SFQ subscale scores were positively correlated with each other. Results of multiple regression analyses (Table 6) showed that both subject attributes ($\beta = .47$, $p < .001$) and teacher attributes ($\beta = .46$, $p < .001$) significantly predicted students' perceived benefits of the subject. The two predictors together explained 84% of the variance of the dependent variable.

DISCUSSION

This study evaluated the subject "Tomorrow's leaders" based on student feedback in its second-year implementation at The Hong Kong Polytechnic University. Results showed that students generally held positive perceptions on the subject in terms of subject attributes, teacher attributes and perceived subject benefits. The majority of students rated their learning experiences and the achievement of learning outcomes in the subject positively. The qualities of teaching staff were considered high. Students also believed that the subject effectively promoted their personal development in different interpersonal and intrapersonal domains. These findings are generally consistent with the results based on other evaluative studies as well as findings obtained in the first-year implementation of the subject [6-9]. In conjunction with previous reports, the present study provides further evidence for the effectiveness of the subject and suggests that the subject remained well-received by students in 2013/14 academic year.

Students from Faculty of Health and Social Sciences (FHSS) and Faculty of Applied Science and Textiles (FAST) expressed more favorable evaluation than did students from Faculty of Construction and Environment (FCE) in almost every dimensions of SFQ. The pattern is similar to the findings reported by Shek and Yu [9] based on data collected in 2012/13 academic year. While FAST students remained to have more favorable attitudes towards TL, FCE students continuously showed less positive perceptions about the subject. As mentioned, the teaching staff was randomly assigned to students of different faculties in each year, and therefore, it is unlikely that the faculty-based difference in SFQ ratings was due to the qualities of teaching by different staff members. Researchers have suggested that students' motivation in studying a subject would contribute to their ratings of the subject [17]. It is possible that FAST and FHSS students had higher motivation than did students of FCE in studying TL, which led to their different ratings on the subject. This speculation needs to be further investigated by examining students' learning motivation in this subject and controlling this factor when comparing SFQ ratings across faculties. Other possible factors may include the preferred learning styles of students in different majors and their respective academic goals in relation to the subject. Such student characteristics and their influences on SFQ ratings could be interesting topics of future research. Meanwhile, given the relatively low ratings of FCE students, teachers and subject designers of TL need to consider how to further improve the motivation of these students and adjust the teaching mode to better cater the needs and learning styles of FCE students.

Table 1. Numbers and percentages of students with different responses to the SFQ

Items	1		2		3		4		5		-	
	Strongly Disagree		Disagree		No Strong View		Agree		Strongly Agree		Positive Response	
	%	n	%	n	%	n	%	n	%	n	%	n
Subject attributes												
<i>Learning experience of the subject (Items in the original SFQ)</i>												
I11 I have a clear understanding of what I am expected to learn from this subject.	2.4	17	3.9	28	17.3	125	57.6	415	18.9	136	76.5	551
I12 The teaching and learning activities have helped me to achieve the subject learning outcomes.	2.2	16	3.8	27	16.0	115	54.7	394	23.3	168	78.0	562
I13 The assessments require me to demonstrate my knowledge, skills and understanding of the subject.	2.3	17	2.5	18	17.5	125	55.4	397	22.2	159	77.6	556
I14 I understand the criteria according to which I will be graded.	1.4	10	3.9	28	21.6	154	54.5	389	18.6	133	73.1	522
<i>Achievement of learning objectives (Items in the original SFQ)</i>												
I15 This subject has enabled me to develop a good understanding of the qualities of effective leaders.	2.4	17	2.9	21	17.8	128	55.7	401	21.3	153	77.0	554
I16 This subject has enabled me to develop a better understanding of myself.	2.1	15	3.3	24	19.5	140	53.3	383	21.7	156	75.0	539
I17 I have acquired interpersonal skills essential for functioning as an effective leader.	2.5	18	4.7	34	23.6	170	49.2	354	20.0	144	69.2	498
I18 I have learned self-reflection skills in this subject.	2.1	15	3.8	27	19.7	141	52.1	373	22.3	160	74.4	533
I19 I have learned to become more active and self-motivated in pursuing knowledge on self-understanding and interpersonal relationship.	2.4	17	4.4	31	23.8	169	49.6	353	19.8	141	69.4	494
Teacher attributes												
<i>Qualities of the teacher (Items in the original SFQ)</i>												
I111 The teacher has been willing to provide help when necessary.	0.7	5	0.7	5	8.4	61	50.8	367	39.3	284	90.1	651
I112 The teacher has motivated me to learn.	1.1	8	1.8	13	17.5	126	49.0	352	30.5	219	79.5	571
I113 The teacher has given me/the class feedback for improvement.	1.0	7	1.5	11	13.3	96	48.3	349	35.9	259	84.2	608
I114 The teacher has organized the subject contents logically and clearly.	0.6	4	1.1	8	12.2	88	50.5	363	35.6	256	86.1	619
I115 The teacher has enabled me to relate the knowledge taught to my professional/intended career.	1.0	7	3.0	21	19.0	135	47.5	337	29.5	209	77.0	546
I116 The teaching of the staff member has provided me with a valuable learning experience.	1.3	9	1.9	14	14.3	103	50.6	364	31.8	229	82.4	593
I117 Overall, I think that the staff member is an effective teacher.	0.7	5	1.0	7	13.6	97	49.2	351	35.5	253	84.7	604
<i>Other qualities of the teacher (New items in the e-SFQ)</i>												
I118 The teacher was well prepared for the lessons.	0.4	3	0.4	3	8.0	58	42.8	310	48.4	351	91.2	661
I119 The teaching skills of the teacher were good.	0.8	6	3.3	24	12.3	89	45.6	330	37.9	274	83.5	604
I1110 The teacher showed good professional attitudes.	0.7	5	1.2	9	9.4	68	44.5	321	44.2	319	88.7	640
I1111 The teacher encouraged me/the class to participate in the activities.	0.4	3	1.2	9	10.9	79	44.0	318	43.4	313	87.4	631
I1112 The teacher had much interaction with me/the class.	0.1	1	1.5	11	11.4	82	44.9	324	42.1	304	87.0	628

Table 1. (Continued)

Items	1		2		3		4		5		-	
	Strongly Disagree		Disagree		No Strong View		Agree		Strongly Agree		Positive Response	
	%	n	%	n	%	n	%	n	%	n	%	n
Perceived benefits of the subject (New items in the e-SFQ)												
I10 This subject has strengthened my problem-solving skills.	2.2	16	5.7	41	32.3	233	44.0	317	15.8	114	59.8	431
I11 This subject has enhanced my critical thinking.	2.4	17	5.1	37	26.1	188	49.3	355	17.1	123	65.4	488
I12 This subject has promoted my understanding of ethical leadership.	1.7	12	4.6	33	19.5	140	52.4	376	21.8	156	74.2	532
I13 This subject has improved my communication skills.	2.4	17	4.3	31	22.3	160	52.9	380	18.1	130	71.0	510
I14 This subject has promoted my personal growth.	2.2	16	3.8	27	18.4	132	54.4	391	21.3	153	75.7	554

Note: Positive response = students' responded as agree or strongly agree.

Table 2. Means and stand deviations of SFQ scores and Cronbach's alpha coefficients

Items	M	SD	Cronbach's alpha	Mean inter-item correlations
Subject attributes	3.84	0.75	.96	.74
Teacher attributes	4.20	0.65	.97	.70
Perceived benefits of the subject	3.79	0.78	.94	.76
Overall SFQ score	4.01	0.65	.98	.61

Note: ^aSubject attributes = mean score of I1-I9; ^bteacher attributes = mean score of I11-I12; ^cperceived benefits of the subject = mean score of I10-I14.

Table 3. Means and standard deviations of SFQ scores across faculties

	FH		FCE		FENG		SHTM		FHSS		FAST	
	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD
Subject attributes	3.83	.69	3.44	.87	3.85	.74	3.83	.83	3.91	.70	3.88	.71
Teacher attributes	4.01	.57	3.94	.82	4.16	.68	4.23	.62	4.33	.59	4.31	.63
Perceived benefits of the subject	3.74	.69	3.38	.89	3.81	.80	3.76	.84	3.89	.72	3.85	.72
Overall SFQ score	3.92	.60	3.69	.74	4.01	.67	4.03	.62	4.12	.60	4.10	.62

Note: ^aSubject attributes = mean score of I1-I9; ^bteacher attributes = mean score of I11-I12; ^cperceived benefits of the subject = mean score of I10-I14.

FH: Faculty of Humanities; FCE: Faculty of Constructing and Environment;

FENG: Faculty of Engineering; SHTM: School of Hotel and Tourism Management;

FHSS: Faculty of Health and Social Sciences; FAST: Faculty of Applied Science and Textiles.

Table 4. Results of MANOVA and ANOVA comparing SFQ scores across faculties

DV (MANOVA)	<i>df</i>	<i>df</i> error	<i>F</i>	η^2	Faculties
Subject attributes	5	645	2.66*	.02	FENG, FHSS, FAST > FCE
Teacher attributes	5	645	4.13**	.03	FHSS, FAST > FCE, FH
Perceived benefits of the subject	5	645	2.34*	.02	FHSS, FAST > FCE
DV (ANOVA)	<i>df</i>	<i>df</i> error	<i>F</i>	η^2	Faculties
Overall SFQ score	5	645	3.46**	.03	FHSS, FAST > FCE

Note: ^aSubject attributes = mean score of I1-I9; ^bteacher attributes = mean score of II1-II12; ^cperceived benefits of the subject = mean score of I10-I14.

* $p < .05$; ** $p < .01$.

Table 5. Correlation coefficients among SFQ scores

Variables	1	2	3
Subject attributes ^a	-	-	-
Teacher attributes ^b	.93	-	-
Perceived benefits of the subject ^c	.90	.90	-
Overall SFQ score	.98	.94	.96

Note: ^aSubject attributes = mean score of I1-I9; ^bteacher attributes = mean score of II1-II12; ^cperceived benefits of the subject = mean score of I10-I14.

All correlation coefficients in the table were significant, $p < .001$.

Table 6. Multiple regression analyses predicting students' perceived benefits of the subject

Predictors	B	SE	β	R ²
Subject attributes	.49	.05	.47***	
Teacher attributes	.56	.05	.46***	.84***

Note: ^aSubject attributes = mean score of I1-I9; ^bteacher attributes = mean score of II1-II12; ^cperceived benefits of the subject = mean score of I10-I14.

*** $p < .001$.

Both subject attributes and teacher attributes significantly predicted students' perceived benefits of the subject. This finding concurred with the results of previous studies that V showed students' learning outcomes were largely influenced by the qualities of the subject and students' perceptions about the instructor [14, 18-20]. In other words, both the subject itself and the person who delivered the subject play an important role in helping students to achieve the intended learning objectives. It should be noted that compared to teacher attributes, the effect of subject attributes was relatively higher, which is different from the findings reported by Shek and Yu [9] that when students' final grade was used as the indicator of students' learning outcomes, only teacher attributes showed significant predictive effects. This may be due to the fact that students' score in the subject can only partially reflect students' learning outcomes. As a subject focusing on students' interpersonal and intrapersonal development, both short-term and long-term effect shall be considered when evaluating the effectiveness of TL. If students perceive the subject as effective, they would be more willing and likely to apply the knowledge and skills acquired in the subject in their future life, i.e., long-term effects. Therefore, when evaluating students' learning outcomes, both objective indicators (such as students' final grade) and subjective indicators (e.g., perceived benefits of the subject) must be taken into account. Overall, the current findings

indicate that both the good design of TL and highly qualified teachers promoted students' effective learning in this subject [21].

The present study has several limitations. First, when evaluating the implementation and effectiveness of the subject, although students' perceptions are important, views of other stakeholders cannot be overlooked. To comprehensively understand the effectiveness and implementation of the subject, future studies may collect views from the subject teachers and other staff from different faculties who may witness the changes of their students (such as the academic advisors). Second, the present study based on quantitative design was unable to provide a detailed narrative of participants' perceptions toward the subject and the reasons behind [22]. Qualitative evaluation is necessary for the researchers to further understand the current findings, such as the reasons why FCE students held relative less favorable attitudes than did students of FAST and FHSS. Third, due to anonymity of the data, no student individual characteristics were included in the analyses. It would be interesting to look at how these factors may affect students' learning experience and outcomes in this subject in the future.

Despite these limitations, the study affirmed the overall smooth and effective implementation of the general education subject, "Tomorrow's Leaders", in 2013/14 academic year based on student feedback. Both subject attributes and teacher attributes significantly predicted students' perceived benefits of the subject. Given the limited evaluative research on curriculum-based interpersonal and intrapersonal programs in university settings, the present study is an important addition to the literature.

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Chapter 192

HISTORY AND BACKGROUND OF VASCULITIS

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ABSTRACT

The descriptions of previous poorly understood and obscure diseases by early workers, and their insights and discoveries that followed have formed many of the foundations of modern medicine. The original descriptions of inflammatory vascular diseases in particular shaped the cultural context of medical science and provided the catalysts and inspirations that fueled later clinical investigation. The transition from the so-called *romantic era* to the *scientific era* of medicine in turn mirrored advances in the pathogenesis, treatment and classification of the vasculitides. The stories of the early contributions from Hippocrates to Kussmaul will forever guide clinicians in the fundamental humanity of this discipline.

Keywords: vasculitis, history

INTRODUCTION

The study of the history of vasculitis provides insights into the evolution of clinical thinking and the pathophysiologic that guided the evolution of concepts integral to the modern appreciation of this fascinating group of diseases. Forms of idiopathic vasculitis were identified as early as the nineteenth century, moreover accounts of idiopathic vasculitis in the form of what is presently termed Behçet disease can be found in the writings of Hippocrates [1] as can those related to giant cell arteritis by the oculist Ali ibn Isa in Baghdad in 1000 AD [2].

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VASCULITIS IN HISTORICAL CONTEXT

The introduction of scientific methodology in the nineteenth replaced brought to a close the romantic era of medicine and ushered in the scientific era, promoted by the advent of university-based systematized anatomic pathology and technical developments notably microscopic anatomy. Such advances were critical to the development of theories of the cellular basis of disease embraced by Rudolf Virchow and others between 1848 and 1858 [3, 4].

Yet even in 1554, Antoine Saporta [5] provided the classical description of non-traumatic macrovascular disease related to infectious disease due in the occurrence of syphilitic aneurysms in an affected patient. Over time, anatomic pathologists frequently noted inflamed vessels. By the early nineteenth century, infection was accepted as a cause of vasculitis [6, 7] and other forms of vascular disease were more clearly delineated including atherosclerotic disease and developmental arterial disease of the arteries [8]. The first clear description of non-infectious vascular inflammation was likely by Joseph Hodgson in 1815 [9] in his inspection of large arteries at postmortem examination and the recognition of arterial intimal inflammation suggesting that such changes could result from high intravascular pressure, trauma, and a systemic inflammatory state. Moreover, vascular inflammation previously related only to syphilitic infection, could also be associated with other diseases [9]. During the same era, John Hunter [10] described inflammation of the veins.

The advent of microscopy enabled further investigation of the nature of vascular inflammation and its origins. The anatomic pathologist Karl von Rokitansky, who viewed arteritis as having its origin in the adventitia, was unlike Virchow who employed careful microscopic studies of his anatomic specimens and postulated that inflammation instead began in the intima and media [3, 11].

Polyarteritis Nodosa

Adolf Kussmaul and Rudolf Maier described the first clearly recognizable patient with idiopathic vasculitis of the polyarteritis nodosa type (PAN) in 1865 [12] in a 27-year-old journeyman, the findings of whom influenced and systematized later observations. The patient, Carl Seufarth had improved from a prior infectious illness one month earlier when he was arrested in destitute circumstances after wandering into the city of Freiburg, in the Black Forest of Germany during the summer of 1865, and taken to the municipal jail where the officers recognized his poor medical state. He was later transferred to the University of Freiburg Internal Medicine Clinic where he was and was able to walk up the two flights of stairs to Dr. Kussmaul's office, where he examined him, and thereafter hospitalized. Over the ensuing months, Seufarth developed fever, generalized muscle aching, mononeuritis multiplex of the arms and legs, abdominal pain, and proteinuria. He died on May 30, 1865 and an English account of his case was later published [13]. Working closely together with Kussmaul, the anatomic pathologist Rudolf Maier, at the University of Freiburg performed detailed postmortem microscopic examination and described the findings under the rubric of periarteritis nodosa, and later PAN. In their words, there was a "peculiar, mostly nodular thickening of countless arteries of and below the caliber of the liver artery and the major

branches of the coronary arteries of the heart, principally in the bowel, stomach, kidneys, spleen, heart, and voluntary muscles and, to a lesser extent, also in the liver, subcutaneous cell tissue, and in the bronchial and phrenic arteries” [12]. The nodular thickened vessels revealed inflammatory changes in the media and adventitia. The kidneys had changes of “acute Bright’s disease.” Maier wrote, *“The change affects the intralobular arteries, which have glomeruli at their bifurcations, and extends into these branches and even into the glomeruli”* [12].

Kussmaul and Maier ascribed the pathological alterations in the arteries to “inflammation of the arteries affecting principally the perivascular sheath, in which the media also had a part, at least in its outer layers,” recognizing that the inflammatory changes “often attacked neighboring tissues in the opposite direction, for example, the renal parenchyma, connective and muscle tissues.” The investigators initially considered the disease to be a result of infectious causes including a worm infestation, both because of the peculiar nature of the pea-size nodules, which appeared in the tissue below the epidermis of Seufarth’s abdomen, and the thickened fibrotic nature of the affected vessels. Indeed, an abstract cited their patient as an example of nematode aneurysmal disease before Maier [14] conducted a later thorough microscopic evaluation.

There may even have been earlier cases of PAN, but none was so recognized in the medical literature. Karl von Rokitansky provided a very brief clinical description of a patient seen in 1852 at the University of Vienna found to have fatal aneurysmal coronary and mesenteric arterial changes [15] believed to be an early example of PAN. However, Rokitansky did not undertake microscopic examination of the tissue, and it was not until his student Hans Eppinger later examined the specimens microscopically that it was clear that the patient had PAN [16]. Kussmaul did not consult Rokitansky about his earlier patient because of his unfavorable experience as a visiting clinician in Rokitansky’s Institute of Anatomic Pathology institute at about 1840. Instead, he collaborated with Virchow who affirmed that while he might have seen a similar patient but did not understand its fundamental nature [12, 17]. Attesting to the rarity of the disorder, only about 30 additional cases were described in Europe and the United States in the ensuing four decades [17-19], and into the twentieth century.

Necrotizing Vasculitis

The first cases of vasculitis were macroscopically apparent and could be assessed with the naked eye. A clear understanding of microscopic necrotizing vasculitis did not emerge until well into the twentieth century. Davson in 1948, and Wainwright in 1950, provided the first English language accounts of microscopic PAN or polyangiitis that affected small arterial capillaries and venules, particularly in the kidney and lungs, often associated with necrotizing glomerulonephritis [20, 21]. The neuropathologist Friedrich Wohlwill of Hamburg provided the first coherent description of microscopic necrotizing vasculitis, coining the term microscopic PAN in a description of two reported patients in 1923 [22]. Both patients described by Wohlwill [22] had antecedent illnesses characterized by weight loss, fevers, clinical evidence of nephritis, widespread muscle pain, and paresis consistent with mononeuritis multiplex. At postmortem examination, there was evidence of glomerulonephritis, and widespread inflammation of small vessels on microscopic

examination. He also described inflammatory involvement with marked polymorphonuclear cell infiltration of arterioles, capillaries and venules [22]. Wohlwill [22] conceived of a direct relationship to the disease described by Kussmaul and Maier, drawing upon his findings of systemic vascular inflammation and “a well characterized and uniform disease, which practically demand the assumption of a unified etiology [22].

In 1931, Heinz Klinger described a patient with necrotizing granulomatous vasculitis with glomerulonephritis that he considered a form of periarteritis nodosa [23]. He also described a second patient with similar findings and hemoptysis on presentation postulating a possible infectious etiopathogenesis [23]. Friedrich Wegener reported further patients which were interpreted as forms of periarteritis nodosa, however, it was clear that he viewed the disease course and related pathology as unique and anatomically distinctive particularly the invasive granulomatous process, which he believed to be due to an infectious agent [24, 25], and the granulomatous vasculitis as a form of rheumatoid or rheumatic disease [26].

In 1949, Churg and Strauss [27] described an eosinophilic form of granulomatous polyangiitis with the constellation of “allergic granulomatosis, allergic angiitis, and periarteritis nodosa. This combination of findings was previously reported by Ophüls [28] in 1923 in a patient who with granulomatous nodules, particularly of the pericardium and peritoneum with eosinophilic infiltration of the bronchi and pulmonary tissue, and concomitant arteritis, capillaritis, venulitis, and nephritis. Otani [29] also described a variant of periarteritis nodosa in 1924 in the description of a 35-year-old woman with asthma and eosinophilia. Churg and Strauss [30] provided more clinical information and systemization to the disease that eventually bore his name in a subsequent analysis of 13 patients, all of whom had asthma and granulomatous lesions in small arteries of parenchymal organs including the epicardium. These investigators [30] considered the disease to be essentially a “malignant expression” of allergic granulomatosis in contrast to other more benign forms of allergic granulomatosis such as Loeffler syndrome.

In the decades that followed, investigators provided additional clinical observations, anatomic correlations, and pathophysiologic connections between various forms of necrotizing vasculitis employing antineutrophil cytoplasmic antibodies (ANCA) that contrasted with other forms of necrotizing vasculitis. First detected in 1982 in the sera of patients with Ross River Arbovirus infection and idiopathic segmental necrotizing glomerulonephritis [31], ANCA have advanced concepts of the immunopathogenesis of necrotizing vasculitis. Subsequently detected in the sera of patients with GPA and MPA and to a lesser extent, in eosinophilic GPA (eGPA) [20], further elucidation of the role of these antibodies led to considerable advances in the understanding of the pathogenesis of systemic vasculitis [32].

Large Vessel Vasculitis

Patients with large vessel vasculitis or *pulseless disease* have been described for the past 3000 years [8]. Early descriptions of the condition were initially related to trauma while those in the late eighteenth and nineteenth centuries were causally associated with arterial sclerosis [4, 33, 34]. The formidable anatomic pathologist Morgnani [35] described an approximately 40-year-old woman with absent radial pulses for at least six years prior to her death in which

postmortem examination showed ectasia of the proximal aorta with stenosis of the lower portion, and histologically normal radial artery vessels.

In 1839, Davy [36] described two patients with likely large vessel vasculitis including a 55-year-old male who presented with weak arm pulses and later vertigo. The physical findings were of “a throbbing pulse at the upper part of the sternum, and a slight prominence of the bone there to some little extent”. Davy [36] suspected an aortic arch aneurysm, which was indeed found one and one-half years later at postmortem examination. So stated, a large aneurysm of the aortic arch was found and “all the great vessels arising from the arch were completely closed up at their origin”. Davy [36] described absent arm pulses in a 36-year-old man who like the first patient, was a soldier in the British Army. Postmortem examination in the second patient showed aortic arch dilatation and occlusion of the left subclavian and carotid arteries.

A further description from this era was given by Savory [37] in 1854 of a 22-year-old woman who was ill for five years with pulseless arteries of the arms and neck, and blindness over the ensuing year. Postmortem examination in that patient showed marked stenosis of the aortic arch and its branches, without aneurysms. Savory [37] was probably aware of the previous descriptions by Rokitsansky [15], and further differentiated his patient by ascribing the observed inflammation to an origin in the intima and media, rather than the adventitia.

It has been speculated that Ali ibn Isa [2] may have described a patient with temporal arteritis at about 1000 AD when reporting, “one treats not only migraine and headache in those patients that are subject to chronic eye disease but also acute, sharp, catarrhal affections, including those showing heat in and inflammation of the temporal muscles. These disease conditions may terminate in loss of eyesight; frequently, they are attended by a considerable degree of chemosis.” While it remains unclear whether this actually represents a case of giant cell arteritis, there is no doubt that in 1890, Hutchinson [38] provided the first clinical description of what is truly regarded as contemporary temporal arteritis when he reported a “peculiar form of Thrombotic Arteritis of the aged, which is sometimes productive of Gangrene,” in an 80-years-old man. His patient, a servant named Rumbold, presented with headache and “red streaks on his head, which were painful and prevented him from wearing his hat.” Hutchinson [38] recounted that the patient lived for several years without “any other manifestation of arterial disease.”

The clinical syndrome and histological aspects of giant cell arteritis was clearly delineated by Horton, Magath, and Brown [39] at the Mayo Clinic in 1932. Indeed, they obtained the first biopsies of the affected temporal arteries in living patients and described the typical findings including “peculiar circumscribed areas of what appear to be granulation tissue...in the adventitia of the blood vessels, which suggested granulomas,” stating further that “this represented the most characteristic lesion present.” Like Hutchinson [38], of whose work they apparently were not aware, these investigators [39] initially regarded the disease as benign, as “complete recovery occurred in each case,” however on further follow-up, they observed that two of their first patients died within two years of what they termed “unrelated conditions.” By 1938, visual loss was associated with giant cell arteritis by Jennings [40]. The association of headache with occasional jaw claudication prompted the term “cranial arteritis” in 1946 by Kilbourne and Wolffe [41].

Much earlier in 1908, Takayasu [42] described a young woman with peculiar retinal artery changes and “wreath-like anastomosis surrounding the optic disc at a distance of 2 or 3 mm, and surrounding this was another circular anastomosis”. Takayasu [42] described

“lumps” in the surrounding vessels that were seen to “move from day-to-day.” These findings were discussed at the 12th Annual Meeting of the Japanese Society of Ophthalmology whereupon other discussants noted the relation of pulseless radial arteries to the retinal artery changes in their own patients, an association that Takayasu had not appreciated [42]. By 1925, Beneke [43] reported the first comprehensive histopathologic analysis of affected large vessels in patients with pulseless disease of Takayasu arteritis type. There was virtually complete medial necrosis, intimal sclerosis, adventitial scarring and thickening of large arteries at postmortem examination in affected patients. More importantly, Beneke [43] described giant cells which he related instead atheromatous changes and white blood cell infiltrates of greater importance to the disease pathogenesis.

Other Forms of Idiopathic Vasculitis

Henoch-Schönlein Purpura

The disease known as Henoch-Schönlein purpura (HSP) likely first appeared in a report by William Heberden [44] in 1801 in the account of a 4-year-old with purpuric lesions of the leg, buttock, and scrotum; as well as in a 5-year-old with similar lesions and abdominal pain. Ollivier [4] described a youngster with purpura and abdominal pain in 1827, but the distinct disease awaited the description of “peliosis rheumatica” by Schönlein in 1837. In 1874, Henoch [46] reported four affected children with joint pain, purpuric rash, abdominal pain, and diarrhea recognizing the potentially fatal aspect of the disease. The cause of the disease has been ascribed to infection, although a specific infectious agent has yet to be definitively identified. In 1915, Frank [47] postulated an allergic cause so termed “anaphylactoid purpura”. Glanzmann [48] postulated that the combination of infection and hypersensitivity culminated in the observed findings of purpura, nephritis and abdominal pain, although a potentially causative antigen was not identified.

Behçet Disease

Oral and genital mucosal ulcers and eye inflammation of Behçet disease may have been recognized by Hippocrates but was certainly described by Blüthe [49] in 1908, Planner and Remenovskiy [50] in 1922, Shigeta [51] in 1924, and Whitwell in 1934 [52]. One of latter described patients [52], a 29-year-old woman, with oral and genital ulcers, likely erythema nodosa, and venous emboli of the leg, had the cardinal features of so-called Adamantiades-Behçet. Adamantiades [53] described a 22-year-old soldier patient with oral and genital ulcerations who experienced recurrent iritis and hypopyon, and was thought to have syphilis based on a positive Wassermann reaction. Treatment for syphilis was unsuccessful. In his initial description, Behçet [54] described two patients, a 34-year-old woman and 40-year-old man with recurrent oral and genital aphthous ulcerations, uveitis and hypopyon. Behçet [54] speculated an infectious viral cause, undertaking a detailed examination for the presence of viral products whereas a vasculitic etiopathogenesis was not contemplated.

Kawasaki Disease

In 1961, childhood febrile mucocutaneous lymph node syndrome was first described by Kawasaki [55] in Tokyo. The suspected causes included allergic, infectious, and autoimmune

mechanisms. In a subsequent report in 1974 based on more than 6000 patients seen in Japan, Kawasaki [56] indicated he noted “infantile periarteritis nodosa-like arteritis of the coronary artery accompanied by thrombosis and aneurysm...” Kawasaki disease is increasingly regarded as an infantile/juvenile form of PAN.

Single Organ Vasculitis

A multitude of single organ vasculitides has been recognized in the past several decades. Diaz-Perez and Winkelmann [57] at Mayo Clinic described a cutaneous form of PAN in 1974. A nonsystemic vasculitic neuropathy (NSVN) was described by Dyck and coworkers at the Mayo Clinic in 1986 [58]. Granulomatous angiitis (GANS), isolated angiitis of the central nervous system (IACNS) and primary angiitis of the CNS (PACNS) are equivalent terms for a potentially lethal adult CNS vasculitis, clinically and pathologically characterized beginning with the description by Cravatio and Fegin in 1959 [20, 59]. An equivalent disease affects children although curiously without granulomatous pathology. The occurrence of idiopathic vasculitis in isolated organs which has become increasingly recognized, and on occasional may evolve to affect other organs, was included in the 2012 Revised Chapel Hill Consensus Conference (CHCC) Nomenclature of Vasculitides [60]. Since the initial description by Kussmaul and Maier [14], secondary forms of vasculitis due to hypersensitivity, infection, and vasculitis occurring in the context of other autoimmune rheumatic diseases such as rheumatoid arthritis and systemic lupus erythematosus have also been described. Vasculitis has also been related to the presence of systemic cancer. Indeed, in 1958, Guichard [61] introduced the term “paraneoplastic” to describe the latter occurrence.

VASCULITIS CLASSIFICATION, NOMENCLATURE, MANAGEMENT GUIDELINE DEVELOPMENT AND RECENT ADVANCES

Early attempts to categorize the vascular diseases were based upon the likeliest etiological postulates to explain a given gross anatomical feature. Indeed, Rokitsky's [11] nineteenth century classification of aneurysms included those arising as a result of increased blood pressure and aging, non-atheromatous muscularis inflammation, trauma, pseudomembranous intimal proliferation of the intima or adventitial weakness of the intima at the site of atheroma. In 1952, Zeek [62, 6]) offered the first modern classification system of vasculitis, dividing them simplistically into hypersensitivity and angiitis, allergic granulomatous angiitis, rheumatic arteritis, periarteritis nodosa, and temporal arteritis; granulomatosis and polyangiitis and Takayasu arteritis were not included.

In 1990, the classification of vasculitis by the American College of Rheumatology (ACR) distinguished one form another based on review of nearly 1200 cases of vasculitis [64]. The 1994 [60] and 2013 Revised CHCC [65] provided better systematization and nosology, recognizing both primary idiopathic vasculitis and secondary vasculitis including those associated with hepatitis C viral infection, while foregoing the category of hypersensitivity vasculitis.

Classification criteria continue to be reexamined and revised. A major effort in this regard is the prospective enrollment of now nearly 6000 patients into the Diagnostic and Classification Criteria in Vasculitis (DCVAS) study headquartered at Oxford University and

cosponsored by the American College of Rheumatology and the European League Against Rheumatism [66]. DCVAS is a multinational, observational study that aims to develop diagnostic criteria and update classification criteria in vasculitis. DCVAS investigators have recruited over 6000 patients from 133 sites in 32 countries who have vasculitis, and vasculitis mimics.

A number of more recent contributions have made recent advances in the management of vasculitis possible and certainly will be seen in their historical context. Development of investigator cooperatives including the Vasculitis Clinical Research Consortium, the European Vasculitis Study Group, and others has greatly enhanced the ability to pursue investigation into the pathogenesis and genetics of vasculitis, as well pursuit of multicenter treatment studies. These include the advent of large scale, formal randomized trials such as the Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis (RAVE), tocilizumab in patients with Giant Cell Arteritis (GACTA), CYClophosphamide or AZathioprine As a REMission therapy for vasculitis (CYCAZAREM), and many others at the national and international level has been a major reason for improvement in vasculitis care [67, 68]. An important result of the more systematic and collaborative efforts in developing outcome measures such as the Birmingham Vasculitis Activity Score and its variants among many others [68, 69]. These approaches have are improving outcomes and lowering drug toxicity rates in patients suffering from these diseases.

Pursuit of these therapeutic studies by the various work groups has resulted in insights about how long to use cyclophosphamide, how and when to use methotrexate, azathioprine and more recently mycophenolate mofetil and other drugs in various forms of vasculitis. The studies of rituximab and other biological therapies in ANCA associated vasculitis (AAV) such as mepolizumab that targeted eosinophilic granulomatosis with polyangiitis were groundbreaking, as were later trials of biological therapy for other forms of vasculitis. These included abatacept and tocilizumab for giant cell arteritis (GCA). Such efforts led to the approval of rituximab by the Food and Drug Administration (FDA) for AAV; and tocilizumab for GCA, the latter as the first non-glucocorticoid agents ever approved by the FDA for treatment of any form of vasculitis.

Just as investigator networks have advanced the knowledge and therapeutics of vasculitis, support groups, partnerships and networks have emerged worldwide over the past three decades including, the Vasculitis Foundation in the United States, Vasculitis United Kingdom (UK), and the Arbeits-Kreis Vaskulitis in Germany. History favorably record their unique contributions in brining patients' voices to the forefront of vasculitis care and research, at the same time educating patients, families, physicians and allied healthcare providers about vasculitis.

New tests such as the ANCA (anti-neutrophil cytoplasmic autoantibodies) that came into routine use in the late 1980's and early 1990's, have been supplemented by other new tests developed in the last 30 years to more precisely image involved blood vessels and organs. These include highly sensitive magnetic resonance imaging (hsMRI); MRI and computed tomographic angiography (MRA and CTA), 2-deoxy-2-[fluorine-18]fluoro- D-glucose integrated with CT (¹⁸F-FDG PET/CT), and vascular ultrasonography techniques.

While many of the systemic vasculitides described as "idiopathic," have been discovered, some cases of PAN are also recognized to be a result of concomitant infections with hepatitis B and C virus (HBV and HCV). Likewise, a number of genes contribute to the risk for AAV and GCA and determine in part, how the diseases will affect patients [70].

CONCLUSION

The contributions of early workers in vasculitis had a profound impact in forming our modern concepts of vasculitis. They reflect careful clinical observation, the application of emerging technologies, and advances in therapy, which form the basis for our understanding of these disease entities. They are the product of an ongoing tradition of investigation, which is alive and well today. Our current knowledge of vasculitis is the result of a both long and recent history of applied clinical observation and basic science investigation. Better recognition of vasculitis in clinical practice, development of research networks and patient involvement in vasculitis care, improved imaging modalities, outcome measure development, and application of novel therapeutics based upon better understanding of disease pathogenesis have also led to better effective treatment of vasculitis.

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Chapter 193

OVERVIEW OF PRIMARY AND SECONDARY VASCULITIDES

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ABSTRACT

The systemic vasculitides are heterogeneous clinicopathologic disorders that share the common feature of vascular inflammation. The resulting disorder can vary depending upon involvement of specific organs, caliber of blood vessels, the underlying inflammatory process, and individual host factors. The cumulative result is diminished blood flow, vascular alterations and eventual occlusion with variable ischemia, necrosis and tissue damage. An international revised nomenclature system based on the current state of knowledge provides clinicians and investigators alike with the necessary nosology and findings relevant to classify each of the vasculitides. This chapter is an introduction and overview of the clinical presentation, differential diagnosis, laboratory evaluation, and treatment of systemic and nervous system vasculitides.

INTRODUCTION

The term vasculitides refers to heterogeneous disorders characterized by vascular inflammation affecting vessels of different sizes from large arteries to capillaries or tiny venules. This leads to diminished blood flow or vessel occlusion resulting in ischemia,

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necrosis and subsequent tissue damage. Blood vessels themselves can also be damaged in vasculitis resulting in permanent stenosis, aneurysmal change or rupture.

CLASSIFICATION AND NOSOLOGY

The 2012 Revised Chapel Hill Consensus Conference (CHCC) [1] serves as a guide for the categorization of diverse forms of vasculitis based upon the vessels involved (Table 1).

Large vessel vasculitis (LVV) including giant cell arteritis (GCA) and Takayasu arteritis (TAK) affects the aorta, its major branches and analogous veins. Medium vessel vasculitis (MVV) inclusive of polyarteritis nodosa (PAN) and Kawasaki disease (KD) involves main visceral arteries and veins and initial branches. Small vessel vasculitic (SVV) involvement affects intraparenchymal arteries, arterioles, capillaries, veins and venules, with a disease mechanisms related to anti-neutrophil cytoplasmic antibody (ANCA) or immune complexes.

Table 1. Classification of vasculitides

Large Vessel Vasculitis
Giant cell arteritis
Takayasu arteritis
Medium Vessel Vasculitis
Polyarteritis nodosa
Kawasaki disease
Small Vessel Vasculitis
<i>ANCA-Associated Vasculitis</i>
Microscopic polyangiitis
Granulomatosis with polyangiitis (Wegener)
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)
<i>Immune-Complex Vasculitis</i>
Cryoglobulinemia
IgA vasculitis (Henoch-Schönlein)
Hypocomplementemic urticarial vasculitis (anti-C1q)
Variable Vessel Vasculitis
Behçet disease
Cogan syndrome
Single Organ Vasculitis
Primary Angiitis of the CNS
Nonsystemic peripheral nerve vasculitis
Idiopathic aortitis (IgG4)
Vasculitis Associated with Systemic Collagen Vascular Disease
Systemic lupus erythematosus
Rheumatoid arthritis vasculitis
Vasculitis Associated with Infection
Acute bacterial meningitis
Tuberculous meningitis
Spirochete disease
Neurosyphilis
Lyme neuroborreliosis
Varicella zoster virus
HIV/AIDS

Adapted from [1].

The category of ANCA-associated vasculitis (AAV) includes granulomatosis with polyangiitis (GPA) (Wegener granulomatosis [WG type]), eosinophilic granulomatosis with polyangiitis (EGPA) (Churg-Strauss syndrome [CSS]), and microscopic polyangiitis (MPA) (microscopic polyarteritis), while vasculitic disorders associated with immune complexes (IC) includes IgA vasculitis (IgAV) (Henoch-Schönlein purpura [HSP]), cryoglobulinemic vasculitis (CV), and Hypocomplementemic urticarial vasculitis (HUV) associated with C1q antibodies. Vasculitis without a predominant vessel size and caliber, respectively from small to large, involving arteries, veins and capillaries, comprises the category of variable vessel vasculitis (VSV), characteristic of Behçet disease (BD) and Cogan syndrome. Vascular inflammation confirmed to a single organ system such as vasculitis restricted to the central nervous system (CNS) and peripheral nervous system (PNS), and IgG4 related aortitis (IgG4-related disease [RD]), are collectively referred to as single organ vasculitides (SOV).

There is a separate category for vasculitis associated with systemic disease notably for connective tissue disorders such as rheumatoid arthritis vasculitis (RAV) and systemic lupus erythematosus (SLE); and another for vasculitis associated with a probable specific etiology, such as substance abuse and infection designated by the specific vasculitic disorder with a prefix to denote the causative agent.

In 2008, the Pediatric Rheumatology European Society (PRES) and the European League against Rheumatism (EULAR) and the Pediatric Rheumatology International Trials Organization (PRINTO) reported methodology and overall clinical, laboratory and radiographic characteristics for several childhood systemic vasculitides [2] followed by a final validated classification [3] based upon vessel size, similar to the CHCC nomenclature [1].

Insight into effective therapies of systemic vasculitides have been guided by collaborative evidence-based randomized clinical trials (RCT) or observational cohorts by the French Vasculitis Study Group (FVSG) database, United States-Canadian Vasculitis Clinical Research Consortium (VCRC), European Vasculitis Study Society (EUVAS), the European League Against Rheumatism (EULAR), The French Vasculitis Cohort of Patients with Primary Vasculitis of the Central Nervous System (COVAC), Diagnostic and Classification Criteria in Vasculitis Study (DCVAS), the Pediatric Vasculitis Initiative (PedVas), the Diagnostic and Classification Criteria in Vasculitis Study (DCVAS), and the web-based network BrainWorks.

Despite disparities in vessel involvement and end-organ damage, it is usually possible to reach a presumptive diagnosis of primary and secondary vasculitides in the majority of patients based upon the combination of presenting symptoms and signs, disease-specific serological studies, and visceral and neurovascular imaging studies, while awaiting the results of tissue histopathology.

This chapter is an overview of primary and secondary vasculitides in adults and children for clinicians treating such patients. Five major challenges encountered in clinical practice will be addressed and emphasized as follows.

First, clinical, pathological, and serological differentiation and diagnosis of the primary vasculitides including LSV (GCA, TAK), MVS (PAN, KD), SVS (AAV [MPA, GPA, EGPA] and IC-mediated types [IgAV and anti-C1q]); and VSV (BD and Cogan syndrome), all of which share demonstrable histopathological evidence of systemic vasculitis.

Second, recognition of secondary vasculitides associated with an underlying primary systemic illness, in which some but not all patients will demonstrate evidence of vasculitis

including, CV, RA vasculitis (RAV), and CNS vasculitis associated with SLE, syphilis, Lyme neuroborreliosis (LNB); bacterial meningitis, tuberculosis (TB), varicella zoster virus (VZV), and human immunodeficiency virus type 1 (HIV) and acquired immune deficiency syndrome (AIDS).

Third, the identification of the SOV, PCNSA, NSPNV, and IgG4-RD.

Fourth, a recommended laboratory approach to the diagnosis of vasculitides.

Fifth and last, evidence-based treatment options for each of the vasculitides. Interested readers are recommended to another in-depth overview [4].

DIFFERENTIATION OF PRIMARY VASCULITIDES

Large Vessel Vasculitides

The concepts of GCA and TAK have evolved over a century, with considerable advances in the past decade that have translated into more improved diagnosis and management.

Giant Cell Arteritis

First named temporal arteritis for the site of granulomatous giant cell inflammation and vessel involvement [5], those with associated blindness due to vasculitic involvement of ophthalmic and posterior ciliary vessels were subsequently classified as cranial arteritis [6], and later generalized GCA [7] when giant cell lesions were discerned along the aorta, its branches, and in other medium- and large-sized arteries at postmortem examination. There are five discriminatory features of GCA including, age >50 years at onset, new localized headache, temporal artery tenderness or decreased temporal artery pulse, ESR >50 mm/hour, and biopsy of an artery showing necrotizing arteritis and a predominance of mononuclear cells or granulomatous process with multinucleated giant cells (Figure 1), that collectively serve as useful guideposts in recognizing GCA.

Unrecognized and therefore untreated or inadequately treated, there is a high likelihood of large artery complication. Nuenninghoff and coworkers [8] reported patients with large-artery complications representing 27% of 168 patients in a GCA cohort at the Mayo Clinic between 1950 and 1999 that included aortic aneurysm or dissection in 18%, large artery stenosis in 13%, cervical artery stenosis in 9%; and subclavian, axillary or brachial artery stenosis in 4%.

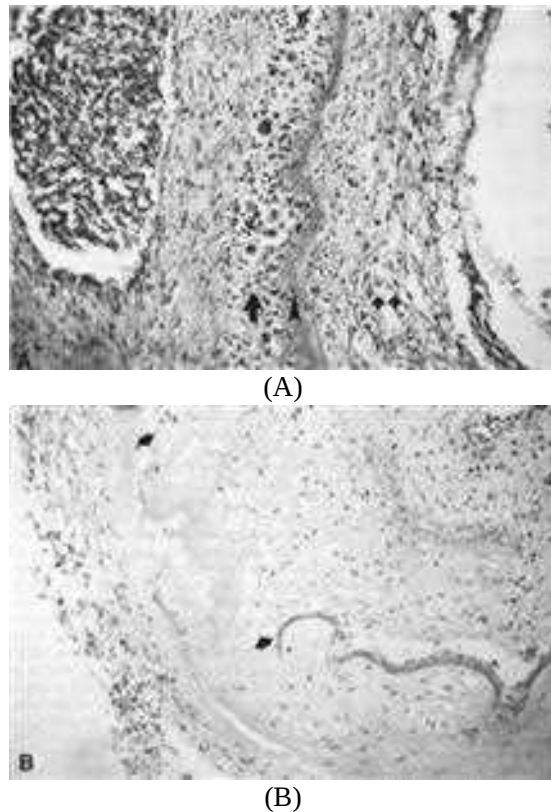
Temporal artery biopsy is the only sure way of establishing the diagnosis however false negative findings on the contemplated affected side may be due to inadvertent sampling of a vasculitic-free length of vessel. The pathological heterogeneity of GCA was further exemplified by the occasional finding of intracranial lesions in several patients who also qualified for the diagnosis of granulomatous angiitis of the nervous system (GANS) [9]; however PNS involvement in GCA remains exceedingly uncommon [10].

Takayasu Arteritis

Contemporaneously, another LVV was described in the Japanese literature as unusual changes of the central vessels of the retina in the absence of peripheral arterial pulses in women [11]. Patients with so called pulseless disease [12], occlusive thromboangiopathy [13]

or TAK [14], manifested constitutional complaints of malaise, fever, stiffness of the shoulders, nausea, vomiting, night sweats, anorexia, weight loss, and irregularity of menstrual periods weeks to months before the local signs of vasculitis were recognized in up to two-thirds of patients. TAK is the commonest large vessel vasculitis among Asian women.

The non-invasive assessment of LVV includes performance of color-Doppler sonography (CDS), contrast enhanced high-resolution magnetic resonance imaging (MRI) combined with MRA, and contrast-enhanced computed tomography (CT) combined with CTA to visualize the vessel wall and the lumen of large vessels. The signs of early inflammation that include vessel wall thickening and mural inflammation, as well as the late complications of stenosis and aneurysms, can be ascertained.



Source: Reproduced from reference [4], with permission.

Figure 1. Giant cell arteritis. (A) An early lesion of a large muscular artery, necrosis, inflammation, and giant cell formation (single arrow) can be seen immediately adjacent to the internal elastic lamina (arrowhead), which is undergoing degenerative changes, and there is some intimal proliferation (double arrows) (stain, hematoxylin and eosin; original magnification, $\times 100$). (B) This more advanced lesion has complete segmental destruction of the internal elastic lamina and virtually the entire media (arrows). Marked intimal proliferation has nearly occluded the lumen, and few inflammatory cells remain (stain, hematoxylin and eosin; original magnification, $\times 50$).

^{18}F - Fluorodeoxyglucose (FDG) positron emission tomography (PET) detects increased FDG uptake by metabolically active cells, including inflammatory cells infiltrating the vessel wall in vasculitis, while digital subtraction angiography (DSA) is a useful modality to

demonstrate luminal changes. Moreover, such studies can assist the surgeon in centering on an involved segment of vessel. Performance of CDS is better suited to study superficial vessels such as the internal and external carotid artery and its branches, while MR and CT are best suited for deep vessels. When performed together, they can be used to monitor disease extent and severity through the demonstration of early vascular changes in wall thickness and mural inflammation, to which PET can be added to ascertain active inflammation in vessels affected by GCA and TAK. Since the early reports of a salutary effect of corticosteroids on GCA in 1950 [15], corticosteroids have remained the standard of care because of their ability to reduce disease-related morbidity, mortality, and symptoms that negatively impact on quality of life. However they are not curative, do not prevent relapses, and are associated with significant toxicity. Disease-related morbidity in GCA which largely results from cranial ischemic events or LVV, leads to visual loss in up to 20% of patients.

The risk factors for GCA-related ischemic events include visual loss, prior ischemic events, marked intimal hyperplasia on temporal artery biopsy, elevated inflammatory markers, older age at diagnosis, hypertension, ischemic heart disease, and absence of systemic manifestations [16]. While there is no treatment to date that has been found to completely reverse blindness in GCA once it has occurred, there is strong evidence to suggest that once corticosteroids have been started the risk of visual loss is low [17]. For this reason, corticosteroids should be started while the diagnostic evaluation is in progress and continued for up to one year before tapering to the lowest maintenance levels.

Ohigashi and colleagues [18] ascertained an improved prognosis among 106 consecutive patients with TAK in those with onset before 1999 compared to those diagnosed after 2000 (4.2% versus 0%) that was attributed to reduction in the time from onset to diagnosis, replacement of digital subtraction angiography (79% versus 9%) with ultrasound (6% versus 34%), CTA (24% versus 77%), MRA (21% versus 57%), and ¹⁸F-FDG PET (0% versus 20%); less frequent complications of moderate or severe aortic regurgitation, and not surprisingly, an increase in the use and maximal dose of corticosteroids (70% versus 97%); and the use of first and second-line immunosuppressant agents (7% versus 42%). Surgical treatment of TKA was similar between those with onset before 1999 and after 2000 (22.5% versus 22.8%).

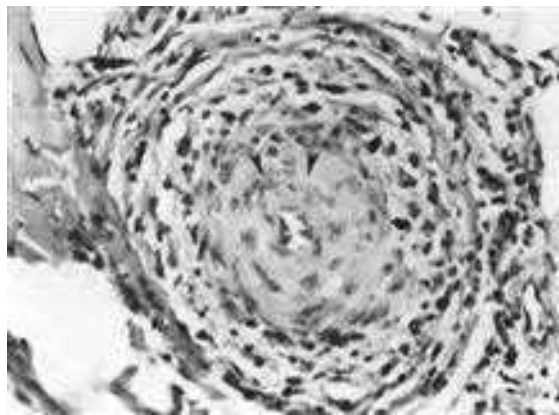
Medium Vessel Vasculitides

Polyarteritis Nodosa and Kawasaki Disease

Kernohan and Woltman [19] summarized the clinicopathological aspects of adult PAN at postmortem examination, while Krahulik and colleagues [20] described fulminant childhood PAN (cPAN), three decades after the first description of the first American patient by Longcope in 1908 [21]. The dominant clinicopathological syndrome was peripheral neuritis that occurred in one-half of patients early in the illness with a predilection for the legs. The combination of acute and chronic lesions correlated with known exacerbations. Arteritic lesions along nutrient arteries of the peripheral nerves were characterized by invasion of the intima, media and adventitia by polymorphonuclear, plasma cells, eosinophils, and lymphocytes associated with swelling of the media, fibrinoid necrosis, and fragmentation of the internal elastic lamina (Figure 2). So impressed was Dr. Harry Lee Parker by the

frequency of arteritic lesions in the PNS, that he conceptualized nerve and muscle biopsy as a useful mode for the diagnosis in life during a discussion of the paper by Kernohan and Woltman [19]. Variants of cPAN were contemporaneously recognized in infants and young children under the rubric of mucocutaneous lymph node syndrome, infantile PAN before arrival at the preferred term KD [22-25] for the childhood syndrome affecting children of all ages and races, with worldwide occurrence.

A retrospective study of 348 adult patients registered in the French Vasculitis Study Group (FVSG) [26] who satisfied criteria for the diagnosis of PAN between 1963 and 2005 noted constitutional findings included fever, weight loss, myalgia, and arthralgia at presentation in 93% of patients. PNS involvement included peripheral neuropathy and mononeuritis multiplex in nearly equal proportion in 79%, and cutaneous involvement notably, purpura, skin nodules, and livedo reticularis were noted in 50% of patients; CNS involvement was noted in 5% of patients.



Source: Reproduced from reference [4], with permission.

Figure 2. This small muscular artery from muscle is from a patient with polyarteritis nodosa. In the third, or proliferative, phase illustrated here, chronic inflammatory cells replace the neutrophils of the second phase; there is evidence of necrosis of the media (arrows), early intimal proliferation (arrowheads), and fibrosis. The lumen is almost completely occluded. Ultimately, in the healing phase, this process is replaced by dense, organized connective tissue (stain, hematoxylin and eosin; original magnification, $\times 250$).

The classification criteria for cPAN requires histological evidence of necrotizing vasculitis in medium-or small-sized arteries or angiographic abnormalities demonstrating aneurysm formation or vascular occlusions, as a mandatory criterion, plus two of five features among them myalgia, skin involvement, hypertension, neuropathy, or abnormal urinalysis or impaired renal function [6], with disease manifestations ranging from a benign cutaneous form with clinical, laboratory and molecular characteristics of Familial Mediterranean Fever [27, 28] to severe disseminated multisystem disease. Ozen and colleagues [29] studied 110 children of mean age 9 years, from twenty-one pediatric centers worldwide diagnosed with cPAN dividing them into four groups including systemic PAN (57%), cutaneous PAN (30%), and classic PAN with hepatitis B surface antigen (HBsAg) (4.6%). Children with serological and microbiologic evidence of preceding streptococcal infection have also been described [30]. The FVSG study [26] allowed for a comparison of diagnostic modalities in adult PAN.

Only 6 of 47 sera so tested manifested a positive ANCA finding by immunofluorescent testing (IFT) and enzyme linked immunosorbant assay (ELISA) techniques, rendering it helpful in support of PAN especially when negative to differentiate it from AAV and MPA. Cutaneous nerve biopsy performed in 129 patients, including 108 with peripheral neuropathy and 21 without peripheral neuropathy, showed typical vasculitic lesions respectively in 83% and 81%, compared to muscle biopsy that revealed vasculitis respectively in 68% and 60% of patients. Angiography showed renal and gastrointestinal microaneurysms or stenosis respectively in 66% and 57% of patients. Patients with HB virus (HBV)-related PAN had more frequent peripheral neuropathy, abdominal pain, cardiomyopathy, orchitis, and hypertension than those with non-HBV-related PAN, with respective five-year relapse-free survival rates of 59% and 67% in scheduled therapeutic regimens depending upon involvement in clinical trials, or according to the standard of care at the time of diagnosis, among them glucocorticoids and cyclophosphamide [31, 32]. The predictors of a poor prognosis were age >65 years, hypertension, and gastrointestinal involvement, and cutaneous manifestations or non-HBV-related PAN had higher rates of relapse.

Henegar and colleagues [33] identified three positive predictive parameters including HBV antigen and DNA in serum, arteriographic anomalies, and mononeuropathy or polyneuropathy; and five negative predictive parameters including detection of ANCA; asthma, ear, nose and throat signs; glomerulopathy; and cryoglobulinemia, that yielded a 70.6% sensitivity for control vasculitides and 92.3% specificity for all controls.

Small Vessel Vasculitides

ANCA-Associated Vasculitis

Microscopic Polyangiitis

Wohlwill [34], Davson and colleagues [35] and Wainwright and Davson [36] recognized that fever, arthralgia, purpura, hemoptysis, pulmonary hemorrhage, abdominal pain, and gastrointestinal bleeding preceded the explosive phase of systemic necrotizing vasculitis in some patients with a disorder other than PAN that affected the kidney and lungs, with rapidly progressive glomerulonephritis and pulmonary capillaritis. Such patients with selective involvement of small microscopic arteries, arterioles, capillaries and venules including glomerular and pulmonary alveolar capillaries were deemed to have microscopic PAN. Among thirty-four such patients described by Savage and colleagues [37] the clinical symptoms and signs at presentation were constitutional (67%), arthralgia (65%), purpura (44%), hemoptysis in (32%), abdominal pain (32%), mouth ulcers (21%), sensory peripheral neuropathy (18%), and CNS (headache, seizures) (18%). Eighty-five additional patients studied by Guillevin and colleagues [38] with MPA so termed, had renal involvement (79%), weight loss (73%), skin involvement (purpura, livedo, nodules, urticarial) (62%), mononeuritis multiplex neuropathy (57%), fever (55%), arthralgia (50%), myalgia (48%), vascular manifestations [hypertension, cardiac failure, pericarditis] 50%, lung involvement (alveolar hemorrhage, pneumonitis, pleurisies) (24%), and CNS involvement (12%). Ahn and colleagues [39] noted pANCA or anti-MPO antibody positivity in 69% of Korean MPA patients, compared to 74.5% of positive ANCA in European patients, of whom 87% had a

pANCA staining pattern. Antibodies to PR3 were present in 8% of patients compared to MPO in 61% of those as determined by ELISA. Childhood MPA (cMPA) appears to be very uncommon and the criteria for diagnosis require three of the following features to be present: abnormal urinalysis, granulomatous inflammation on tissue biopsy, nasal sinus inflammation; subglottic, tracheal, or endobronchial stenosis; abnormal chest radiograph or chest CT scan, and PR3 ANCA or cANCA staining [3]. Those with cMPA accounted for four of the first 32 children in the United States/Canadian ARChiVe registry [40].

Eosinophilic Granulomatosis with Polyangiitis

Contemporaneous with the description of MPA, the first patient with EGPA was probably Case 1 of Lamb [41] reported in 1914 also under the heading of PAN. That patient, a 26-year-old man with two years of worsening asthma, developed fever, palpable purpura, nodular skin lesions, hemoptysis, vomiting, urinary difficulty and granular urinary casts. He died one month later and postmortem examination showed necrotizing arteritis of small arteries, with dense collections of extravascular eosinophils and tissue eosinophilia in the heart, stomach, and kidney. Decades later, Churg and Strauss [42] described the clinical and postmortem findings of thirteen patients with asthma, fever, and hypereosinophilia, accompanied by eosinophilic exudation, fibrinoid change, and granulomatous proliferation or the so called allergic granuloma. The latter was found within vessels walls and in extravascular connective tissue of major organ systems, leading to cardiac, pulmonary, gastrointestinal, skin, PNS and CNS manifestations. In 1990, the American College of Rheumatology (ACR) [43] developed criteria for the classification of EGPA that included ascertainment of four or more of the following: asthma, eosinophilia of >10%, mononeuropathy or polyneuropathy, non-fixed pulmonary infiltrates on chest radiograph, paranasal sinus abnormality, and extravascular eosinophils on tissue biopsy that included an artery, arteriole or venule. These criteria were inadequate since a patient with asthma and paranasal sinusitis could also fit the designation of EGPA. The 1994 CHCC [1] characterized EGPA as an eosinophil-rich and granulomatous inflammatory process that involved the respiratory tract, with necrotizing vasculitis that affected small to medium-sized vessels such as capillaries, venules, arterioles and arteries, with associated asthma and eosinophilia. Among 383 patients enrolled in the FVSG Cohort [44] who satisfied the ACR criteria [43] or in 1994 CHCC definition for EGPA [45], the mean age at presentation was 50 years without sex predominance. Clinical manifestations at presentation included asthma (91%), peripheral neuropathy (51%), weight loss (49%), ear, nose and throat signs (48%), non-erosive sinusitis and polyposis (41%), skin lesions (39%), purpuric rash (22%), lung infiltrates (38%), gastrointestinal involvement (23%), renal manifestations (22%), cardiomyopathy (16%), CNS (5%), and cranial nerve involvement (3%). A total of 108 (31%) patients tested positive for ANCA with significantly more frequent ear, nose and throat, peripheral nerve and renal involvement, but less frequent cardiac manifestations. Small numbers of children have been included in large studies of EGPA sufficient to allow comparisons to adults. Among 133 vasculitic patients in the ARChiVe registry, only two were reported to be of the EGPA type [46].

Granulomatosis with Polyangiitis

Godman and Churg [47] described the syndrome of GPA that included granuloma in the nasopharynx, sinuses and lower respiratory tract with focal segmental glomerulonephritis and

disseminated small vessel vasculitis. In a landmark article, Godman and Churg [47] concluded that MPA, EGRA and GPA were related to one another yet distinct from PAN. This astute conclusion was based mainly on pathological features was later substantiated by their common association with ANCA, but not so for PAN [48]. Fauci and colleagues [49] and Hoffman and colleagues [50] at the National Institutes of Health (NIH), respectively reported a prospective series of eighty-five patients with GPA, and a retrospective assessment of 180 patients followed for 6 months to 24 years. The presenting signs included pulmonary infiltrates (71%), sinusitis (67%), arthritis and arthralgia (44%), fever (34%), cough (34%), otitis (25%), and hemoptysis (22%), with an overall predominance of organ system involvement in the lung (94%), paranasal sinuses (91%), kidney (85%), joints (67%), and nasopharynx and nose (64%). Fauci and colleagues [49] established the efficacy of cyclophosphamide and prednisone in achieving complete remissions in 93% of patients, as well as, the tendency of patients to relapse and accrue additive mortality from both disease and treatment. The characteristic histopathology is a necrotizing granulomatous vasculitis which may be found in lung and renal biopsy tissue although the latter is less common. Instead, a focal, segmental glomerulonephritis is often seen. Other inflammatory or vasculitic phenomenon can be encountered such as leukocytoclastic vasculitis in skin lesions, and acute and chronic inflammation in sinus, retro-orbital, and tracheal tissues. A limited form of GPA without glomerulonephritis was described [51] that was a long-term disease stage or phenotype accounting for about 5% of all patients characterized by destructive and space-consuming lesions associated with relapse rates of 46% and local damage [52].

The 1990 ACR criteria for the classification of GPA [53] which preceded routine ANCA testing, included the presence of two or more from criteria from among four including nasal or oral inflammation (painful or painless oral ulcers or purulent or bloody nasal discharge); abnormal chest radiograph (showing nodules, fixed infiltrates or cavities); urinary sediment (showing microhematuria >5 red blood cells per high power field, or red cell casts in urinary sediment); and granulomatous inflammation on biopsy tissue (within the wall of an artery or in the perivascular or extravascular area of an artery or arteriole).

A proposed classification tree substituted hemoptysis for granulomatous inflammation on a tissue biopsy if the latter was not available. Baseline serum samples for 180 participants in the WG Etanercept Trial Research Group (WGET) found that when IF, direct and capture ELISA ANCA testing were performed at baseline, 166 (92%) were seropositive, including 96% with severe disease and 83% with limited disease.

Holle and colleagues [54] who prospectively compared a highly sensitivity (hs)PR3-ANCA ELISA to the IFT noting an excellent performance of the hsPR3-ANCA ELISA in identifying GPA and other AAV disorders associated with PR3-ANCA suggesting that the former by used as screening test. Since the early observations of ANCA provided by van der Woude and colleagues in 1985 [55], and Falk and Jennette [56] and Goldschmeding and colleagues [57], and ensuing progress in the differentiation and understanding of ANCA subtypes [58], the past quarter century has witnessed a renaissance in the understanding of primary systemic vasculitis with convincing clinical evidence to support an important role for ANCA in the development of AAV. An AAV classification appears to better recognize ANCA disease and predict prognosis than other any existing clinical classification systems [59].

However as with other autoimmune disorders, the etiology and pathogenesis appears to be multifactorial, involving the interplay of initiating and predisposing environment and

genetic factors [60-62]. Induction with corticosteroids and either cyclophosphamide followed by maintenance with rituximab [63-68] or azathioprine [69-71] is recommended treatment. Among 197 ANCA-positive patients with GPA or MPA in nine centers participating in the Rituximab in ANCA-Associated Vasculitis-Immune Tolerance Network (RAVE-ITN), a randomized, double-blind, double-dummy, non-inferiority trial [72] comparing rituximab 375 mg per square meter (m²) body-surface area (BSA) per week for 4 weeks to cyclophosphamide 2 mg per kilogram of body weight per day controls for severe AAV, 67% of study patients compared to 42% of controls achieved the primary end point of remission of disease without use of prednisone at six months.

Treatment and efficacy and safety data in children with AAV continue to be largely derived from adult GPA studies, however as described in ARChive, pediatric patients in the United States and Canada are being offered pulse methylprednisolone for 3 to 5 days, followed by oral prednisone, and cyclophosphamide orally or with one of two intravenous regimens, followed by maintenance therapy, most frequently with methotrexate [40].

Early outcome results last year for the treatment of childhood AAV, in particular GPA, reported by Morishita and colleagues on behalf of ARChive Investigators Network and the Pediatric Vasculitis (PedVas) Initiative [73] was somewhat unencouraging. Among 105 children with AAV, mainly GPA, who received corticosteroids, cyclophosphamide, methotrexate, or rituximab for remission-induction, and plasma exchange in conjunction with cyclophosphamide and/or rituximab, 42% achieved remission at 12 months (Pediatric Vasculitis Activity Score [PVAS] of 0, CS dose < 0.2 mg/kg/day), 21 (48%) of whom discontinued CS by 12 months; all but 3 remaining on maintenance treatment at 12 months receiving azathioprine, methotrexate, rituximab, mycophenolate mofetil, and cyclophosphamide. However, up to 63% had a (Pediatric Vasculitis Damage Index [PVDI]) score of 1 or more by 12 months, with the presence of renal, ear, nose and throat, or pulmonary damage; moreover, 41% of children reported hospitalizations. Thus, a significant proportion of patients were not in remission at 12 months, and more than one-half of the patient cohort experienced damage early in the disease course. The 12-month remission rate of 42% in the cohort was significantly lower than Sacri and colleagues [74] who reported 73% remission at post-induction and 90% overall remission rate (including secondary remissions after a median time of 6.7 months).

Immune Complex Vasculitis

The foundations for IC-mediated or hypersensitivity vasculitis were conceptualized in the mid-twentieth century, as an immunologic response to antigenic material associated with clinically evident purpura, and small vessel inflammation affecting arterioles, capillaries, and post-capillary venules. It was likened by Zeek [75] to the anaphylactoid Arthus reaction produced by the experimental injection of horse serum into rabbits [76].

IgA Vasculitis (Henoch-Schönlein Purpura)

Children with HSP were described by Gairdner [77] with anaphylactoid purpura including one who developed rash, colic, melanotic stools, intussusception, and hematuria following by a typical exanthema and fatal convulsion. Postmortem examination showed

scattered cortical hemorrhages associated with cerebral necrotizing arteriolitis. Levitt and Burbank [78] described the clinicopathological findings in two previously non-allergic patients with recurrent fatal attacks of HSP after injection of penicillin and ingestion of strawberries respectively that included glomerulonephritis alone or with systemic arteriolitis. The findings of IgA deposits in cutaneous blood vessel walls and in glomerular mesangial biopsies of patients with HSP and IgA nephropathy (IgAN) [79, 80] were circumstantially convincing enough to substitute the term IgAV for HSP. IgAV/HSP is the commonest vasculitis in children. The 1990 ACR criteria [81] for the identification of HSP included age less than or equal to 20 years at disease onset, palpable purpura, acute abdominal pain, and tissue biopsy showing granulocytes in the walls of small arteries or venules. The presence of any two or more of these criteria distinguished 85 patients who were diagnosed as having HSP by physicians who submitted cases for the vasculitis criteria compared to 722 patients diagnosed with other forms of vasculitis, arriving at sensitivity of 87.1% and specificity of 87.7%. The addition of gastrointestinal bleeding in a classification tree format respectively increased sensitivity to 89.4% and specificity to 88.1%. The EULAR/PRINTO/PReS classification criteria [3] which recognizes the contribution of IgA deposits, differs in the mandatory finding of purpura with predominance in the legs, and the presence of one of the four following features: diffuse abdominal pain, arthralgia or arthritis; a biopsy showing predominant IgA deposits, and renal involvement including proteinuria and hematuria. Derived from the analysis of 827 patients in the database, the calculated sensitivity, specificity for the clinical and laboratory findings in between the consensus panel and specific definition were respectively 100% and 87%. Peru and colleagues [82] studied 254 children with IgAV/HSP between 2003 and 2006 with a distribution of skin, joint, GI and renal manifestations respectively of 100%, 66%, 56% and 30%. The disorder commences with fever and palpable purpura, although early lesions can be urticarial. Arthralgia and abdominal pain precede, accompany or follow the rash. Melena is common as are signs of peritonitis. Proteinuria and hematuria are of variably severity and renal pathology may be of a mild glomerulitis to necrotizing or proliferative glomerulonephritis. Ozen and coworkers [3] noted palpable purpura, commonly in crops with lower limb predominance in 89% of patients, arthritis or arthralgia in 78%, diffuse abdominal pain in 60%, proteinuria and hematuria combined in 33%; and IgA deposition in 10% of children. The treatment of IgAV/HSP remains empiric and largely supportive, with conflicting conclusions in retrospective and uncontrolled case series of immune suppression in severe HSP nephritis [46]. Extrarenal manifestations can be managed by symptomatic treatment.

A meta-analysis of 15 studies based on a comprehensive review of the literature in the Medline database from 1956 to 2007, and Cochrane Controlled Trials Registry among 15 studies and over 1300 patients [46] found that early treatment conferred a protective effect on developing persistent renal disease (odds ratio [OR] .43) and the likelihood of surgical intervention for abdominal pain (OR .75), as well as a statistically significant positive effect on shortening the duration of abdominal symptoms (OR 5.42).

C1q (Hypocomplementemic Urticarial) Vasculitis

McDuffe and colleagues [83] later described several patients with recurrent attacks of erythematous, urticarial, and hemorrhagic skin lesions that lasted 24 hours at a time, associated with recurrent attacks of fever, joint swelling, abdominal distress, and depressed serum complement. When tested by immunodiffusion against purified preparations RF and

human C1q, several patients reacted strongly with purified C1q. Skin biopsies showed leukocytoclasia, characteristic of necrotizing vasculitis, anaphylactoid purpura, or mild nonspecific perivascular infiltration. Immunofluorescence of skin specimens showed fixation of Ig in the patient with necrotizing vasculitis. Renal biopsy showed mild to moderate glomerulonephritis indistinguishable for those seen in other forms of chronic membranoproliferative glomerulonephritis. The differences from SLE included more urticarial and purpuric skin lesions, with relatively mild renal or absent and other visceral involvement in the patients with HUV. An etiopathogenesis related to chronic vascular inflammation resulting from deposits of immune complexes in small vessel walls seemed likely. Zeiss and colleagues [84] characterized C1q IgG precipitins from HUV sera that precipitated C1q in agarose gel among four additional patients. Wisnieski and Naff [85] later showed C1q binding activity in IgG from HUV sera. Buck and colleagues [86] defined the HUV syndrome as the presence of UV with multi-organ involvement notably arthralgia or arthritis, angioedema, pulmonary, ocular, renal, and pericardial. However, anti-C1q antibodies are elevated and the serum low C1q levels are reduced in virtually all children so studied. Antihistamines are the drug of choice with cutaneous lesions to control itching, but they may be insufficient in controlling the formation of immune complexes when given late in the inflammatory cascade. There is yet a consensus on the most effective therapeutic regimen; however plasmapheresis and intravenous immune globulin (IVIg) are alternative immunosuppressant modalities.

Variable Vessel Vasculitis

Behçet Disease

Behçet [87] described the clinicopathological findings of a 28-year-old Turkish patient with relapsing oral, genital and oral eruptions over 4 years, accompanied by severe headache, memory loss, dizziness, lethargy, fatal seizures and coma. Postmortem examination showed perivascular inflammatory cell infiltration of the meninges, brain, and central retinal artery and optic nerve with necrotic cerebral lesions. The first well-documented American patient with nervous system involvement of BD was described by Wolf and coworkers [88], namely a 22-year-old woman with a five year history of recurrent oral and genital ulceration, and a two year course of progressive visual loss, headache, hemiparesis, ataxia, tremor, dysarthria, cranial nerve palsy, cerebellar and corticospinal tract disease, and mental deterioration, which responded to prednisone therapy. The most widely used diagnostic criteria of BD were formulated by the International Study Group (ISG) [89] that included recurrent oral ulcerations plus any two of genital ulceration, typical defined eye lesions, typical skin lesions, or a positive pathergy. Recurrent oral ulcerations were categorized as minor aphthous, major aphthous, and herpetiform ulcerations that recurred at least three times in a 12-month period. Recurrent genital ulcerations were defined as aphthous ulceration and scarring. Eye lesions were defined as anterior uveitis, posterior uveitis or cells in the vitreous on slit lamp examination; and retinal vasculitis. Compatible skin lesions included erythema nodosum, pseudofolliculitis, papulopustular lesions, and acneiform nodules in post-adolescent patients not receiving corticosteroids. A positive pathergy test of cutaneous hypersensitivity was defined as positive when a sterile pustule developed after twenty four to forty-eight hours at

the site of a needle prick to the skin [90]. Although the usual onset of BD is in the third or fourth decade of life, pediatric-onset patients have been described [91]. The neuropathological findings in BD in brain biopsies and postmortem examination have been remarkably consistent among patients over the past several decades evidencing perivascular cuffing of small meningovascular and parenchymal arteries and veins, rarely medium-sized arteries displaying fibrinoid degeneration and recanalization, and examples of venous thrombosis. Cortical venous sinus thrombosis (CVST) [92] in BD presents with subacute or chronic onset of symptoms of isolated intracranial hypertension accompanied by headache, blurred vision, and diplopia [93], and underlying necrotizing vasculitis. Venous infarcts occur in up to 63% of those with CVST of other causes, but in only 6% of patients with BD. The inflammatory cell infiltrates are generally comprised of lymphocytes, both T-, and B-cells, macrophages, rarely plasma cells and eosinophils, with reactive astrocytosis and microscopic gliosis in neighboring cerebral, cerebellar and brainstem white matter. Matsumoto and colleagues [94] noted large vessel lesions in seven of eight patients age 31 to 56 years with BD, including saccular aneurysms of the sinus of Valsalva or aortic arch, thoracic and abdominal aorta, pulmonary, femoral, and iliac arteries, and thrombotic occlusions in the pulmonary vein and superior and inferior vena. Aortitis was noted histologically in six of the eight patients that was active in one, scarred in six, and intermixed in another. Active aortitis was characterized by intense infiltration of inflammatory cells in the media and adventitia more frequently than in the interim with occasional giant cell formation. Although anticoagulation would not be recommended for BD-related CVST, it might be considered in association with arterial occlusions, with both venous and arterial occlusive episodes warranting prompt consideration of corticosteroids alone or in association with another immunosuppressant agent.

Cogan Syndrome

The first patient with Cogan syndrome of non-syphilitic interstitial keratitis (IK) was reported by Mogan and Baumgartner [95], that of a 26-year-old man with recurrent pain, spasm and redness of the left eye with photophobia, excessive tearing, and marked conjunctival injection, followed by severe attack of dizziness, tinnitus, vertigo, nausea, vomiting, ringing in the ears, profuse perspiration, and deafness. A diagnosis of recurrent interstitial keratitis and explosive Menière disease was made. Vestibuloauditory symptoms were later described by Cogan [96]. Haynes and colleagues [97] set forth diagnostic criteria for typical Cogan syndrome according to the definitions established in a review of 30 patients seen at the National Eye Institute of the NIH by Cogan [96, 98, 99]. Symptoms of IK developed abruptly and gradually resolved, associated with photophobia, lacrimation, and eye pain which was unilateral or bilateral. Such symptoms tended to recur periodically for years before becoming quiescent. Vestibuloauditory dysfunction was manifested by sudden onset of Menière-like attacks of nausea, vomiting, tinnitus, vertigo, and frequently progressive hearing loss that characteristically occurred before or after the onset of IK. However within one to six months of the onset of eye symptoms, auditory symptoms progressed to deafness over a period of one to three months, certainly no longer than two years. With less than 100 reported patients with this rare childhood and young adult disorder, the majority of reported patients with typical Cogan syndrome have appeared as single case reports or patient series, often without pathological confirmation or evidence of systemic vasculitis in a biopsy or at postmortem examination. Early recognition of the diagnosis of childhood Cogan syndrome is

important in instituting corticosteroid therapy to preserve hearing especially when hearing loss is a later occurrence. A combination of oral and intravenous corticosteroids may be considered in children who partly but not fully improve. Most patients with Cogan syndrome (58%) treated with corticosteroids derived a favorable response in both vestibuloauditory and ophthalmologic manifestations, with the remainder demonstrating only ophthalmologic (23%) or vestibuloauditory improvement (19%) alone [100]. Other therapies include methotrexate (23%), cyclophosphamide (10%), azathioprine (5%), entanercept (3%), hydroxchloroquine (2%), and IVIg (2%). Surgical cochlear implantation can lead to objective and subjective benefits with improved hearing.

RECOGNITION OF SECONDARY VASCULITIDES

Cryoglobulinemic Vasculitis

The presence in the serum of one or more immunoglobulins (Ig) that precipitate below core body temperatures and redissolve on rewarming is termed cryoglobulinemia [100, 101]. Wintrobue and Buell [102] described the first patient with cryoglobulinemia, that of a 56-year-old woman who presented with progressive frontal headache, left face and eye pain; and right shoulder, neck and lumbar discomfort after a bout of shingles. This was followed by Raynaud symptoms, recurrent nosebleeds, exertional dyspnea and palpitation, and changes in the eye ground attributed to central vein thrombosis. Postmortem examination showed infiltrating myeloma of the humerus and lumbar vertebra, and splenic enlargement. A unique plasma protein was detected that spontaneously precipitated with cold temperature and solubilized at high temperature that differed from Bence-Jones proteinuria of other myeloma patients. Brouet and coworkers [103] provided modern classifications of cryoglobulinemia among 86 patients that included type 1, composed of a single monoclonal Ig; and types II and III as mixed cryoglobulinemia (MC), composed of different Ig, with a monoclonal component in type II, and polyclonal Ig in type III. In the absence of well-defined disease the presence of MC was termed “essential”. Since recognition of hepatitis C virus (HCV) infection in patients with MC [104, 105], and the recognition of the high rate of false-negative serological tests in type II MC [106], it became evident that HCV was associated in most patients with MC. Cryoglobulinemic vasculitis is characterized by the classical triad of purpura, weakness and arthralgia, frequent multiple organ involvement, and infrequent late lymphatic and hepatic malignancies. The commonest clinical manifestations of HCV- negative MC vasculitis in the CryoVas survey [107] included purpura (75%), peripheral neuropathy (52%), arthralgia or arthritis (44%), glomerulonephritis (36%), cutaneous ulcers (16%), and cutaneous necrosis (14%). A connective tissue disease was diagnosed in 30% of patients, and B-cell non-Hodgkin lymphoma (B-NHL) was noted in 22% of patients, whereas MCV was considered essential in 48% of patients. There was a greater frequency of joint involvement (53% versus 40%), peripheral neuropathy (74% versus 52%), CNS involvement (9% versus 2%) in those with HCV-MC compared to those with HCV-negative MC [108], with an equal frequency of purpura (71% versus 75%) and renal involvement (34% versus 35%). Cacoub and colleagues [109] noted five high prevalent extrahepatic manifestations in chronic HCV infection including, arthralgia (23%), paresthesia (17%), myalgia (15%), pruritus (15%), and sicca

syndrome (11%), and a 40% prevalence of cryoglobulins. These findings suggest the possibility of an independent role of HCV infection in the clinicopathological manifestations of MC and MCV. Among 114 patients including 18 children and 96 adults with cryoglobulinemia between 2000 and 2012, children had more frequent prolonged fever (17% versus 3%), petechiae and purpura (27% versus 15%), arthralgia and arthritis (66% versus 16%), and cutaneous involvement (77% versus 50%, than adults [110]. Aggressive optimal therapy of HCV-related CV with PEGylated (PEG)-INF alpha to improve the pharmacologic properties, and ribavirin with a protease inhibitor in the instance of HCV genotype 1 infection, should be considered as induction therapy for CV and administered for forty-eight weeks for all HCV genotypes [108]. An induction phase of immunosuppression such as rituximab plus antivirals is recommended in patients with more severe HCV-related CV exemplified by worsening renal function, mononeuritis multiplex, extensive skin disease including ulcers and distal necrosis [111].

Terrier and colleagues [107] showed a greater therapeutic efficacy of rituximab and corticosteroids compared with corticosteroids alone and alkylating agents with corticosteroids in achieving complete clinical, renal, and immunologic responses and a prednisone dosage of < 10 mg per day at six months. However, this regimen was associated with severe infections, particularly when high doses of corticosteroids were employed.

Plasmapheresis combined with immunosuppression can be useful in fulminant HCV-related CV to engender an immediate effect but should be continued to avoid post-pheresis rebound worsening. Rituximab, fludarabine, and cyclophosphamide treatment is effective treatment for refractory CryoVas associated with lymphoma. One-year, 2-year, 5-year, 10-year survival rates of 91%, 89%, 79% and 65% respectively, have been reported in patients with CV [108] with fatalities related to serious infection and disease flares of CV.

Systemic Lupus Erythematosus

Although distinctly uncommon, two collagen-vascular disorders, SLE and RA can be associated with vasculitis of the nervous system. The early concepts of the collagen-vascular disorders introduced by Klemperer [112, 113] stemmed from the appreciation of fibrinoid necrosis using collagen staining in patients with SLE. As collagen swells and fragments, it dissolves to form a homogeneous hyaline and granular periodic acid-Schiff (PAS)-positive material. The latter fibrinoid material contains immunoglobulins, antigen-antibody complexes, complement, and fibrinogen. The organ-specific responses to this fibrinoid material, especially of the CNS, leads to recognizable clinical sequela due to vascular and parenchymal damage.

The ACR delineated criteria for the diagnosis of SLE [114]. The recognition of neuropsychiatric lupus (NPSLE) was noted in 6.4% of a cohort of 1,253 SLE patients defined by the ACR [115]. According to Tomic-Lucic and colleagues [116] those with late-onset SLE due to development of disease after age 50 year, had a frequency of NPSLE of 6.6% compared to 36.6% in early-onset disease despite less major organ involvement and more benign course. Once thought to be an important cause of CNS or cerebral lupus, true vasculitis was present in only 12% of postmortem examinations in the series of Johnson and colleagues [117], and in 26.7% of late-onset SLE patients compared to 16.6% of those with

early-onset SLE. A comparison of the cumulative incidence of clinical manifestations in the two latter groups showed that seizures were more common in early-onset patients compared to later-onset patients (6.6% versus 0%), similarly for multiple cerebrovascular attacks (23.3% versus 3.3%), cranial and peripheral neuropathy (6.6% versus 3.3%). Nonetheless, there was no mention of CNS vasculitis among 150 patients with SLE described by Estes and Christian [118], despite the finding of neurological complications in 30% of patients that included focal deficits, seizures, dementia, stupor, and coma. Devinsky and colleagues [119] noted a prevalence of 3.5% of psychiatric involvement that included organic affective, delusional and hallucinatory syndromes in a cohort of 50 patients with SLE, one-half of whom had CNS lesions. Feinglass and colleagues [120] noted neuropsychiatric manifestations at onset of SLE among 3% of 140 patients compared to 37% in the course of the illness; however headache was not specifically tabulated. Cerebral dysfunction in SLE can be caused by large vessel or small vessel involvement or both. In the series by Feinglass and colleagues [120] vasculitis was noted overall in 28% of patients, as well as in 46% of those with neuropsychiatric involvement compared to 17% of patient lacking neuropsychiatric involvement. Postmortem examination of the CNS in ten of nineteen fatalities showed two cases of multiple large and small infarcts, which in one of them, demonstrated inflammatory cells infiltrates in the walls of medium-sized vessels, and perivascular infiltrates around small arterioles. Although active CNS vasculitis was absent in the brain and spinal tissue of all fifty patients reported by Devinsky and colleagues [119], two had evidence of inactive healed CNS vasculitis so suggested by focal disruption of the elastic lamina and mild intimal proliferation of a single medium-sized artery, one of which had active systemic vasculitis of the PAN type, both of whom evidenced Libman-Sacks endocarditis and embolic brain infarcts. Focal angiitis of the CNS with cyst-like formation around affected blood vessels was noted at postmortem in the patient described by Mintz and Fraga [121] with typical SLE rash, cutaneous vasculitis, and active neuropsychiatric involvement. Trevor and colleagues [122] summarized the literature of large named cerebral vessel occlusions from 1958 to 1965 noting one patient with a middle cerebral artery (MCA) stenosis progressing to occlusion and three others with angiographic internal carotid artery (ICA) occlusions, adding three new patients and suggesting a relation of the occurrence to cerebral arteritis. Two women, one age 21 and the other age 42 years, presented with headache followed by focal neurological symptoms attributed respectively to lesions along the left MCA followed by right ICA occlusions, and a right MCA stenosis progressing to occlusion in four months. A third patient had a left ICA occlusion without mention of headache. Among the four literature patients, one had angiographic occlusion of the MCA, and three others had occlusion of the ICA.

Johnson and colleagues [117] attributed the vasculitic nature of this process histopathologically to cerebral vasculitis mediated by acute inflammation and necrosis. Younger and colleagues [123] reported large named cerebral vessel occlusion attributed to circulating anticardiolipin antibodies in a young man in whom a vasculitic mechanism was not evoked. A number of fluorescent antibody tests provide serological support of SLE. The antinuclear antibody (ANA) screen produces a homogenous pattern in the majority of patients, with antibodies to native double-stranded DNA (anti-dsDNA) and reactivity to the smith (Sm) and ribonucleoprotein (RNP) antigens, the combination of which constitutes the extractable nuclear antigen (ENA). Circulating IgG and IgM antibodies with an affinity for charged phospholipids, antiphospholipid antibodies (APA), some of which have procoagulant activity such as the lupus anticoagulant (LAC) and the generic anticardiolipin (aCL) antibody

assay using cardiolipin as the antigen probe for APA are all important determinants of prothrombotic events, especially in the CNS wherein there is a propensity for occlusive microangiopathy. Circulating SLE-related antibodies can impact the CNS by affecting both vascular mechanisms and brain tissue directly. Immune complex mediated vasculitis probably affecting small vessels is thought to account for much of the damage in CNS lupus in light of spite of the paucity of cerebral vasculitis evident in the form of inflammatory infiltrates in vessel walls at postmortem examination. In those with discrete vascular infarcts, there is a known association with the presence of circulating pathogenic antibodies which predisposes some individuals to a high risk of stroke due to both small and large vessel occlusion [123, 124]. Lupus cerebritis and meningoencephalitis are two neurological disturbances that can be associated with preceding headache. So noted in up to 75% of patients with SLE depending upon criteria [125], an etiopathogenesis related to antibody-mediated neuronal dysfunction is likely given the lack of correlation of symptoms of NPSLE and CNS lesions at postmortem examination, together with the transient nature of the disturbance. Patients with SLE are also predisposed to infectious episodes including those yet treated due to impaired B-cell function and humoral immunity, in addition to others receiving immunosuppressant medication rendered impaired in T-cell function and cell mediated immunity [125]. The treatment of CNS Lupus should be guided by the tempo of the presenting neurological features, duration of disease activity, results of serological studies, comorbid disorders, and the presence of true vasculitis, with most patients receiving corticosteroids and those with true vasculitis of the brain considered for concomitant immunosuppressant therapy. Despite less major organ involvement and decreased incidence of neurological complications overall, late-onset SLE has a poor prognosis because of the higher frequency of comorbid conditions, longer exposure to classical vascular risk factors, both the less likelihood of treatment with higher doses of corticosteroids and the concomitantly higher rate of complications to cyclophosphamide when administered [116].

Rheumatoid Arthritis Vasculitis

A joint working group from the ACR and the European League Against Rheumatism (EULAR) published the 2010 classification criteria for RA [126]. Extra-articular RA (ExRA) occurrence is associated with increased comorbidity and mortality [127]. Criteria for severe ExRA were proposed in 2004 [128]. Active RA with high disease activity is associated with increased risk of severe ExRA manifestations. Major cutaneous vasculitis and vasculitis involving other organs are two such ExRA occurrences.

The diagnosis of RAV has generally been ascertained according to the criteria of Scott and Bacon [129] according to the presence of one or more of the following: 1) mononeuritis multiplex; 2) peripheral gangrene; 3) biopsy evidence of acute necrotizing arteritis plus fever and weight loss; and 4) deep cutaneous ulcers or active ExRA disease if associated with typical digital infarcts or biopsy evidence of vasculitis. Watts and colleagues [130] reported an annual incidence of RAV of 11.6 per million inhabitants between 1988 and 1992 in the Norfolk area of the United Kingdom, and a rate of 3.6 per million between 1998 and 2002. Myasoedova and coworkers [131] reported a ten-year cumulative incidence of 50% of any ExRA, including cutaneous and other organ-specific RAV in a retrospective population-based

cohort study of 463 RA patients in Olmsted County, Minnesota from 1995 to 2007. The ten-year cumulative incidence of RAV, but not other ExRA, was significantly lower in the 1995-2007 cohort (0.6%) compared to the 1985 to 1994 cohort (3.6%). The markers of RA severity including RA positivity, erosion and joint destructive changes (21% among those in the 1985 to 1994 cohort, compared to 29% in 1995 to 2007), use of methotrexate, other disease-modifying anti-rheumatic drugs, and systemic corticosteroids were significantly associated with ExRA development between 1995 and 2007. Vollerstein and colleagues [132] studied 52 patients with RAV at the Mayo Clinic from 1974 to 1981, who developed clinical vasculitis evidenced by classic ischemic skin lesions, mononeuritis multiplex, or a positive tissue biopsy in comparison to population controls. The initial manifestation of vasculitis was seen in skin (26 patients), nerve (20 patients) or both (3 patients), and mononeuritis multiplex presented in one (2 patients), two (9 patients), three (5 patients) or four nerves (4 patients). More than 90% of tissue biopsy specimens revealed vascular necrosis and inflammation. At diagnosis, 80% of patients began therapy with aspirin and other non-steroidal anti-inflammatory drugs however three-fourths continued or began corticosteroid therapy. Sixteen of the original 52 patients eventually received cytotoxic immunosuppressive therapy. Compared to the general population, those with RAV had decreased survival that was immediately evident and continued for six years. Compared with a previously reported incidence cohort [133] and adjusted for referral bias, survival of RAV was not different from classic RA. The factors that predicted decreased survival in RAV in a univariate proportional-HR model included older age, failure to receive previous non-steroidal anti-inflammatory drugs, previous administration of cytotoxic immunosuppressive agents, a higher dose of corticosteroids at diagnosis, decision to continue or initiate corticosteroids, and abnormal urinary sediment. Ouyang and coworkers [134] estimated CNS involvement in RA to be extremely uncommon, and other authors [135, 136] found CNS vasculitis to be decidedly rare. Puéchal and colleagues [137] found vasculitic involvement of vasa nervorum of both small- and medium-sized arteries indistinguishable from PAN in 64% of patients, with a mortality ranging from 28 to 44% according to the length of follow-up. Epineurial and perineurial vasculitis was observed with the same frequency among those with primary sensory neuropathy as others with predominant motor involvement, respectively 67% versus 64%. A greater extent of the neuropathy and motor involvement tended to predict decreased survival, however mononeuritis multiplex was not associated with a poor five-year survival rate (57%) than was distal symmetrical sensory or sensorimotor neuropathy (55%). Scott and Bacon [129] reported that five patients (24%) died in the group receiving methylprednisolone and cyclophosphamide, postmortem examination in four of whom failed to demonstrate active vasculitis.

By comparison, seven patients (29%) died receiving other treatments, of which one so studied at postmortem examination showed active vasculitis. Three forms of vasculitis classically occur in RA affecting all calibers of blood vessels from dermal postcapillary venules to the aorta, usually in association with circulating IgM and IgG rheumatoid factor as measured by the latex fixation test, decreased complement levels, and a positive ANA. The first is a proliferative endarteritis of a few organs, notably the heart, skeletal muscle, and nerves characterized by inflammatory infiltration of all layers of small arteries and arterioles, with intimal proliferation, necrosis, and thrombosis. The second is fulminant vasculitis indistinguishable from PAN with less severe leukocytosis, myalgia, renal and gastrointestinal involvement, and bowel perforation. The third type takes the form of palpable purpura,

arthritis, cryoglobulinemia, and low complement levels. The literature contains references to RAV with involvement of the CNS at postmortem examination in only nine patients. Detailed postmortem findings evidencing CNS vasculitis has been reported in only nine patients [134-136, 138-142] with accompanying clinical neurological findings including, delirium, confusion, seizures, hemiparesis, Gerstman-like syndrome, blindness, and peripheral neuropathy. Postmortem examination has shown widespread systemic vasculitis, single major cerebral artery involvement, generalized PAN-like changes in the CNS, isolated CNS vasculitis affecting the temporal lobes and brainstem with diffuse infiltrative thickening of the pia arachnoid, rheumatoid nodular formation, and inflammatory cell infiltration of leptomeningeal vessels in subjacent brain tissue including the midbrain, medulla, and upper cervical cord; and chronic perivasculitis and transmural chronic inflammatory cell infiltration with severe fibrinoid necrosis of the media of small leptomeningeal vessels and cortical arterioles.

Despite development of new and potent drugs for RA, there are no available evidence-based recommendations for treatment of systemic rheumatoid vasculitis [143]. Complete remission of systemic rheumatoid vasculitis occurred in nearly three-fourths treated with rituximab, with a significant decrease in daily prednisone dosage and an acceptable toxicity profile, making it a suitable therapeutic option to induce remission but maintenance therapy was necessary. Bartels and Bridges [144] recommended prednisone therapy to initially decrease systemic inflammation with a dose dependent upon the degree of systemic inflammation and level of organ system involvement. The presence of CNS involvement mandated intravenous corticosteroid therapy and consideration of cytotoxic or biologic agents from among them methotrexate, azathioprine, cyclophosphamide, anti-TNF agents and rituximab. Bartolucci and colleagues [145] reported the successful induction of a prompt symptomatic response in ten patients with systemic vasculitis not responsive to conventional treatment, including two with RA and associated vasculitis. Puéchal and colleagues [146] demonstrated evidence of efficacy of adjunctive anti-TNF therapy and corticosteroids for treatment of active refractory systemic RAV with remission achieved in two-thirds of patients, and a significant decrease in prednisone dose, with a higher risk of infection in the most severely ill patients.

Bacterial Meningitis

The category of secondary vasculitides related to infection includes acute bacterial and mycobacterial meningitis, spirochete organisms notably neurosyphilis, LNB, and viral agents notably VZV, and HIV/AIDS.

The relationship between vascular and parenchymatous cerebral changes including vasculitis, and acute and chronic neurological symptoms and signs was studied extensively in 9 infants and 5 children by Adam and colleagues [147] with *Hemophilus (H.) influenzae* meningitis. Fever, stiff neck, and alteration of consciousness followed a respiratory infection, with subsequent enlargement of the head and separation of the fontanelles, followed later by lethargy, coma and death despite sulfadiazine antibiotics and antiserum in the earliest stages of meningitis lasting one to two weeks (7 patients), moderate stages of two to four weeks (4 patients) or late in the stage of meningitis of more than four weeks (three patients). Vascular

inflammation by neutrophilic cells so noted in five patients (36%) was typified by inflammation of meningeal veins (2 patients) or meningeal arteries (1 patient) among those with early stage meningitis involvement; with involvement of meningeal arteries in the moderate stage patient, and in subarachnoid arteries of the patient in late stage meningitis. Vascular inflammation was absent in nine patients (63%), four of whom manifested vascular endothelial hyperplasia of meningeal vessels, while the remaining five were reported to have no vascular alterations. Based upon the clinicopathological findings, the authors [147] proposed that from the earliest stages of meningitis, pathological changes could be found in small and medium sized subarachnoid arteries and veins comprised of neutrophilic cellular inflammation accompanied by endothelial cell swelling, multiplication and crowding of lumina, a reaction that ensued over 48 to 72 hours. This was followed by infiltration of adventitial connection by neutrophilic cells, and in the intima of arteries accompanied by lymphocytes forming a conspicuous layer. Foci of vascular necrosis occurred in some cases. Vascular inflammation of the adventitia of subarachnoid vessels was believed to be due to involvement of the arachnoid membrane which formed the adventitia of the subarachnoid vessels, thus in a sense, the vessel wall was affected from the very beginning by the inflammatory process arising within itself. Subintimal inflammation was believed to have an origin in the foci of necrosis with spread beneath the intima along the line of least resistance. Spinal and cranial nerves surrounded by purulent exudates from the beginning of the infectious process at the base of the brain, were infiltrated by inflammatory cells only after several days, and not very pronounced in comparison to meningeal and cortical vessels, with comparatively more lymphocytes. Among 34 other infants and children reported by Smith and Landing [148] with *H. influenzae* meningitis of 2 to 42 days, six postmortem studied patients showed involvement of arterial vessels and venous lesions in 10 cases, three of whom had cortical necrosis and concomitant arteritis, and five had phlebitis. However in only one patient, a 10-week-old infant who died the evening of admission was arteritis believed to be responsible for brain damage. In this subject, postmortem examination disclosed acute inflammation of the walls of several veins and small arteries in the polymorphonuclear meningeal exudate overlying the cortical surface and extending into the superficial cortex, with narrowing of the lumina by endothelial proliferation and fibrin thrombi, associated with extensive early cortical necrosis.

Tuberculosis

Although the different forms of bacterial purulent meningitis was possible only after development of modern bacteriologic methods and the introduction of the lumbar puncture as a diagnostic measure by Quinke in 1891, TB meningitis was the first type of meningitis to be described clinically as dropsy of the brain in 1768, and subsequently shown to be inflammatory when meningeal tubercles and visceral tubercles were found to be identical in 1830. The tuberculoma, once the commonest intracranial tumor, is now exceptionally rare. The chief neurological signs and symptoms of tuberculous meningitis reflecting meningeal irritation are neck stiffness and positive Kernig sign; and raised intracranial pressure notably headache and vomiting with mental changes, seizures, and focal neurological signs. According to Smith and Daniel [149], arteritis is the rule in the vicinity of tuberculous

lesions, wherein vessel walls are invaded by mononuclear cells, with the adventitia more heavily involved than the media. The subintimal and intimal regions form a layer of homogenous fibrinoid material that later involves the media, and the vessel lumen is reduced by inflammatory cell exudation beneath the fibrinoid material, the end results of which are reduction or complete obliteration of the lumen, proliferative endarteritis, and cerebral infarction. The vessels most heavily involved are those at the base of the brain and others in the Sylvian fissure.

Pathologically-proven TB-associated CNS vasculitis was described in five heterogeneous patients [149-151]. The first patient described by Smith and Daniel [149] was an 18-year-old girl with fever, confusion, right hemiplegia, back and neck pain for several days followed by incontinence, complete flaccid paraplegia, delirium dementia, generalized spasticity and death. Postmortem examination showed advanced tuberculous meningitis with dense basal adhesions, hydrocephalus, and obliteration of the spinal subarachnoid space by adhesions, hemorrhagic infarction, and widespread arteritis with acute fibrinoid necrosis, without tuberculomas. The second case was Patient 4 of Greitz [150], a 4-year-old girl with fever, left arm weakness and increasing disorientation that rapidly progressed to coma, nuchal rigidity, and spasticity of the legs. Vertebral angiography showed local widening of a branch of the left posterior cerebral artery and a posterior fossa mass. The patient died soon afterward and at postmortem examination there was tuberculous meningitis with typical tuberculous vasculitis consisting of inflammatory changes in arteries at the base of the brain, notably in small vessels with intimal swelling leading to concentric narrowing of vessel lumina. Headache was a presenting symptom in one of three patients described by Leher [151], none of whom had a prior history of tuberculosis, and all of whom had diagnostic angiographic abnormalities and histopathologic evidence of tuberculous arteritis. A third pathologically-proven case of TB-associated CNS vasculitis was Patient 1 of Leher [151], a 33-year-old man with anorexia and insomnia. Carotid angiography showed narrowing of the supraclinoid ICA as well as narrowing of two convexity vessels in the Sylvian fissure. At postmortem examination there was marked eccentric left fronto-parietal region arterial narrowing due to fibroblastic proliferation of the intima with large numbers of inflammatory cells below the elastica. Headache was not mentioned in two other histopathologically confirmed patients with tuberculous vasculitis. The fourth case was Patient 2 of Leher [151], a 33-year-old man presented with fever and stiff neck. Cerebral angiography demonstrated irregularity of the supraclinoid ICA and reduction in the caliber of the convexity MCA vessels. He died shortly thereafter and postmortem examination disclosed tuberculous leptomenigitis and arteritis of the ICA and MCA with thickened vessel walls and narrowed lumina. The fifth case was Patient 4 of Leher [151], a 39-year-old man who presented with confusion and stupor, was found to have indentation of the lateral aspect of the ICA as it entered the subarachnoid space above the anterior clinoid on cerebral angiography. Ventriculography showed a block at the aqueduct of Sylvius. He died shortly thereafter and postmortem examination showed widely distributed systemic tuberculosis with binding of vessels at the base of the brain that showed arteritis, accompanied by infarction of the basal ganglia and brainstem.

Kopsachilis and colleagues [152] described a 39-year-old man without known tuberculosis, who developed sudden visual loss in one eye. Fluorescein angiography showed an infero-temporal branch retinal vein occlusion consisting of blockage with areas of hemorrhage, exudation, and late leakage. This was followed by optic disc swelling and headache. Biopsy of an enlarged cervical and submandibular lymph node revealed caseating

epithelioid ant cells confirming tuberculosis. Treatment with antituberculous treatment leads to improved visual acuity.

Syphilis

Meningovascular syphilis comprises 39 to 61% of all symptomatic cases of neurosyphilis and tends to occur more frequently in patients with concurrently infected HIV/AIDS. It is characterized by obliterative endarteritis that affects blood vessels of the brain, spinal cord and leptomeninges precipitating substantial ischemic injury.

Often referred to as Heubner arteritis, it involves medium-sized to large arteries with lymphoplasmacytic intimal inflammation and fibrosis however there is a variant form termed Nissl-Alzheimer arteritis that characteristically affects small vessels and produces both adventitial and intimal thickening. Both types can lead to vascular thrombotic occlusions and cerebral infarction, with preferential involvement of the MCA.

The search for the cause of stroke in young adults should include meningovascular syphilis as a potential etiology. Sudden acute severe headache heralded onset of occlusion of bilateral vertebral and proximal basilar artery documented by MRA [153] in a 35-year-old African man. He responded to thrombectomy with restoration of blood flow but succumbed to fatal pontine and subarachnoid hemorrhages. Postmortem examination revealed reactive plasma reagin (RPR) and a positive Venereal Disease Research Laboratory (VDRL) test in CSF with CNS vasculitis characterized by mural thrombi along the vertebrobasilar arteries with well-defined lines of Zahn of alternating layers of fibrin, platelet and red blood cell aggregates, and inflammatory cell infiltration of the arterial walls particularly in the adventitia. Headache of two to three weeks in duration were the presenting features of two other patients with stroke syndromes [27] one of whom had narrowing of bilateral M1 segments of the MCA, reactive CSF VDRL positive *Treponema pallidum* hemagglutinin-assay and fluorescent treponemal antibody-absorption (FTA-Abs) staining in the CSF, similar to second patient who instead presented with a stroke in the territory of the posterior cerebral artery (PCA) without focal changes on cerebral angiography, neither of whom were studied pathologically for true vasculitis.

One patient with abrupt onset of confusion, aphasia, and hemiparesis had carotid angiography that documented normal named cerebral vessels except for smaller than average caliber, with an abnormal complement fixation test of the blood and CSF, positive colloidal gold curve test, and leptomeningeal biopsy that showed lymphocytic infiltration, focal fibrosis, and chronic perivasculitis consistent with meningovascular syphilis [154].

Neither headache nor confirmatory pathological evidence of CNS vasculitis was mentioned in a patient with basilar artery stenosis and serologically confirmed syphilis in the CSF presumed to be due to meningovascular syphilis [155] so suggested by a positive string sign of the mid-basilar artery at cerebral angiography.

Lyme Neuroborreliosis

The term Lyme neuroborreliosis was introduced by Veenendaal-Hilbers and colleagues [156] in 1988 to emphasize that CNS involvement due to *B. burgdorferi* infection, the causative agent of Lyme disease. Among 20 patients described in the literature with neurovascular clinical syndromes ascribed to CNS vasculitis in which detailed information was available including documentation of positive CSF Lyme serology, two patients [157, 158] who presented with headache were ultimately noted to have histopathologically confirmed vasculitis on brain biopsy. Patient 3 of Oksi and colleagues [157] was an 11-year-old boy with headache and hyperactivity syndrome who developed gait difficulty concomitantly with a stroke visualized on brain MRI. Subsequent craniotomy and biopsy of the area of enhancement disclosed lymphocytic vasculitis of small vessels without fibrinoid necrosis, and CSF *B. burgdorferi* serology was positive. Headache and the MRI improved with intravenous antimicrobial therapy. Patient 2 of Topakian and coworkers [158] presented with headache, fatigue, malaise, nausea and vomiting first considered migrainous then psychosomatic until subsequent MRI disclosed ischemic brain infarctions, MRA was compatible with diffuse vasculitis, and CSF showed lymphocytic pleocytosis with positive oligoclonal bands, and diagnostic CSF and serum *B. burgdorferi* serology. Brain biopsy showed vasculitis involving leptomeningeal arteries comprised of lymphoplasmacytic vessel wall infiltration with focal necrosis. Epithelioid cells were beaded in multiple granuloma-like formations in the leptomeninges. There was symptomatic improvement after a course of intravenous antimicrobial therapy. A third patient reported by Miklosy and colleagues [159], a 50-year-old man with leg spasticity and CSF pleocytosis for 15 months who progressed to hemiparesis and ventilatory support, was later found to have diagnostic *B. burgdorferi* serology in serum and CSF. Postmortem examination showed perivascular lymphocytic inflammation of leptomeningeal vessels, some of which displayed infiltration of the vessel walls, duplication of the elastic lamina, narrowing of lumina, and complete obstruction of some leptomeningeal vessels by organized thrombi. Seventeen other patients with presumed CNS vasculitis due to *B. burgdorferi* infection of the CNS were reported, so suggested by complaints of headache [27, 28, 156, 162-164], while unmentioned in the case report of eight others [165-168], none of whom had histologically-proven CNS vasculitis.

Varicella Zoster Virus Infection

VZV is the cause of childhood chickenpox and most children manifest only mild neurologic sequela. However, after it resolves, the virus becomes latent in neurons of cranial and spinal ganglia of nearly all individuals, and has the propensity to reactivate in elderly adults and immunocompromised individuals to produce shingles. An uncommon but serious complication of virus reactivation is ischemic and hemorrhagic stroke. VZV vasculopathy affects both immunocompetent and immunocompromised individuals typically presenting with headache and mental status changes with or without focal neurological deficits and a spectrum of vascular damage from vasculopathy to vasculitis with stroke [169, 170]. Both large and small vessels can be involved and MRI shows multifocal ischemic lesions,

commonly at gray-white matter junctions. The diagnosis of VZV can be missed when symptoms and signs occur months after zoster, or in the absence of a typical zoster rash.

Fourteen patients with VZV-related vasculopathy with detailed clinicopathologic data have been described in the literature. One patient presented with headache, fever, mental status change, focal neurological deficits, and focal narrowing of the ICA, anterior cerebral artery (ACA) and MCA, with CSF antibodies to VZV, but without a rash [171]. VZV DNA and VZV-specific antigen were found in three of five cerebral arteries examined with histologically-confirmed CNS vasculitis involving the circle of Willis. Patient 1 of Eidelberg and colleagues [172] who presented with headache and herpes zoster ophthalmicus (HZO) rash was deemed to have CNS vasculitis based upon complete occlusion of the MCA and so treated, however postmortem examination showed no evidence of vasculitis. Headache was not mentioned in five other patients despite histologically-proven widespread small vessel granulomatous angiitis associated with lymphoma in two patients [173] and basilar branch vessel involvement of granulomatous angiitis in another [174]. One patient with contralateral hemiplegia one month after HZO was found at postmortem examination to have endarteritis of unilateral ACA, MCA and PCA [175] with VZV DNA from the involved vessels. One patient with AIDS, unilateral weakness and garbled speech due to ischemic infarction in association with lumbosacral zoster rash, was found to have CNS vasculitis of vessels of the circle of Willis with VZV DNA without herpetic inclusions at postmortem examination. Finally, neither headache nor supporting histopathology was present in seven other patients with VZV-vasculopathy including five patients with HZO and contralateral hemiparesis [176], and two patients with HZO and contralateral delayed hemiparesis [177].

Nagel and colleagues [178] analyzed virus-infected cerebral and temporal arteries from three patients with VZV vasculopathy. Several characteristic were noted in all VZV-infected arteries so studied including, disrupted internal elastic lamina, hyperplastic intima composed of cells expressing α -smooth muscle actin and smooth muscle myosin heavy chain but not endothelial cells expressing CD31, and decreased medial smooth muscle cells. The location of VZV antigen, degree of neointimal thickening and disruption of the media were related to the duration of disease. The presence of VZV primarily in adventitia early in infection and later in the media and intima supported the hypothesis that after reactivation from ganglia, VZV spread transaxonally to the arterial adventitia followed by transmural spread of virus. Stroke in VZV vasculopathy appears to result from changes in arterial caliber and contractility produced in part by abnormal accumulation of smooth muscle cells and myofibroblasts in thickened neointimal and disruption of the media [178]. Nagel and colleagues [178] also studied the immune characteristics of virus-infected temporal artery three days after onset of ischemic optic neuropathy, and after ten months of protracted CNS disease in the MCA. In both early and later VZV vasculopathy, T-cells, activated macrophages, and rare B-cells were found in adventitia and intima, whereas neutrophils and VZV antigen were abundant along with a thickened intima associated with inflammatory cells in vasa vasorum. Viral antigen but not leukocytes were found in the media in late VZV vasculopathy [179].

HIV/AIDS

Early in the HIV/AIDS epidemic, it was clear that a significant proportion of infected persons were intravenous drug users. Their associated risk behavior exposed them to infection through sharing of contaminated needles thereby increasing the risk of spread of HIV and other blood borne infections. The two postulated periods in the neurobiology of HIV when autoimmune disease manifestations and cerebral vasculitis can occur are shortly after seroconversion and before the spread of productive infection, and after initiation of highly active antiretroviral therapy (HAART) in association with the immune reconstitution inflammatory syndrome (IRIS) [180]. The timing of early HIV invasion has been difficult to ascertain based on the presence of one or well-recognized clinicopathological HIV/AIDS syndromes including HIV encephalitis, HIV-associated dementia and AIDS-dementia complex [181-183], all of which are indicative of symptomatic infection. Headache associated with irritation and confusion was the presenting feature of a 42-year-old homosexual man without evidence of immunodeficiency who developed cerebral granulomatous angiitis in association with human-T-lymphotropic virus type II (HTLV-III). At postmortem examination there was evidence of fibrous intimal scarring and marked luminal narrowing of the ACA, MCA and PCA and their proximal branches, with mononuclear cell infiltration of the vessel walls and numerous multinucleated giant cells near the internal elastic lamina. Six presymptomatic HIV-seropositive drug abusers by Gray and colleagues [160] had non-necrotizing cerebral vasculitis at postmortem examination.

IDENTIFICATION OF SINGLE ORGAN VASCULITIDES

Primary Angiitis of the Central Nervous System

Adult and childhood isolated angiitis or vasculitis are prototypical primary vasculitic disorders restricted to the CNS. Childhood and adult isolated CNS angiitis (IACNS), primary angiitis of the CNS (PACNS), granulomatous angiitis of the brain (GAB) and GANS, and adult and childhood PACNS (cPACNS) are all equivalent terms for a prototypical primary vasculitic disorder restricted to the CNS [184-188]. The diagnosis of PACNS [184], like IACNS [185] originally relied upon classic angiographic (Figure 3) or histopathologic features of angiitis within the CNS in the absence of systemic vasculitis or another cause for the observed findings. The typical patient with PACNS presented with headache of gradual onset often accompanied by the signs and symptoms of dementia, while only later developing focal neurological symptoms and signs. The clinical course might be rapidly progressive over days to weeks, or at times insidiously over many months with seemingly prolonged periods of stabilization. Those with GAB or GANS [186] presented with headache, mental change, and elevated CSF protein content with or without pleocytosis. Hemiparesis, quadriparesis, and lethargy were associated with a poor prognosis and mandated the need for combined meningeal and brain biopsy to establish the diagnosis with certainty. Granulomatous giant cell and epithelioid cell infiltration in the walls of arteries of various caliber, from named cerebral vessels to small arteries and veins, were noted at postmortem examination.



Source: Reproduced from reference [4], with permission.

Figure 3. Radiographic features of cerebral vasculitis. Ectasia and beading in the M1 segment and lack of flow in the A1 segment of the right anterior cerebral artery (arrow).

A recent retrospective cohort of PCNSV from the Mayo Clinic [187] and a multicenter prospective cohort of PACNS from the French Vasculitis Study Group, French NeuroVascular Society and the French Internal Medicine Society [189] have stratified cases of based upon clinical, neuro-radiographic and histopathologic laboratory features, offering additional insights into the management of CNS vasculitis.

Between 2004 and 2011, Salvarani and collaborators [187] enrolled 105 patients, of whom (64%) met inclusion criteria for the diagnosis of probable CNS vasculitis based upon cerebral angiography manifesting areas of smooth-wall segmental narrowing or dilatation, and occlusions that affected multiple cerebral arteries without the proximal vessel changes of atherosclerosis or other causes); and 58 patients (36%) who met the definite diagnosis based upon a CNS tissue biopsy showing transmural vascular inflammation involving leptomeningeal or parenchymal vessels. The latter histopathology was granulomatous in 35 (60.3 %), lymphocytic in 13 (22.4 %), and necrotizing alone in 10 (17.2 %). These histological patterns appeared to identify subsets of disease rather than different stages of the same process since no individual patient had histological evidence of more than one pattern. A favorable response to therapy including corticosteroids (prednisone) alone or in association with cyclophosphamide was observed in 85% of patients. Three patients treated with biological agents including rituximab (1 patient) and a tumor necrosis factor- α inhibitor (2 patients) for treatment of refractory disease, were also improved. Relapses were observed in 27% of patients, and 25% of patients had discontinued therapy by the time of the last follow-up visit. While response to treatment was not associated with any histological pattern of the biopsy specimen, treatment with corticosteroids alone was associated with more frequent relapses (OR, 2.90), while large named vessel involvement (OR 6.14) and cerebral infarcts at the time of diagnosis (OR, 3.32) were associated with a poor response to treatment. Among the patients diagnosed exclusively by angiography alone, relapses were more frequent when there was large-vessel involvement (30%) than only small-vessel changes (9%), with an

increased mortality rate due to fatal neurovascular problems caused by PCNSV. Subsets of patients with PCNSV showed equally interesting insights.

An associated poor prognosis of GANS was noted by Molloy and colleagues [190] who described granulomatous vasculitis changes in CNS tissue biopsies of 10 of 13 (77%) patients with amyloid-beta-related angiitis (ABRA). Salvarani and coworkers [191] noted granulomatous vasculitis in all 8 (100%) cerebral biopsies of patients with lymphoma and PCNSV, two of whom had concomitant cerebral amyloid angiopathy. Among 131 consecutive patients with PCNSV, 11 (8.4%) had a rapidly progressive course that was resistant to immunosuppressive therapy resulting in severe disability or death. Such patients had bilateral cortical and subcortical infarction on initial brain MRI and LVV on cerebral angiography with granulomatous and necrotizing vasculitis in brain tissue biopsies. All 11 patients failed to respond to aggressive immunosuppressive therapy, only one of whom survived with major fixed neurological deficits.

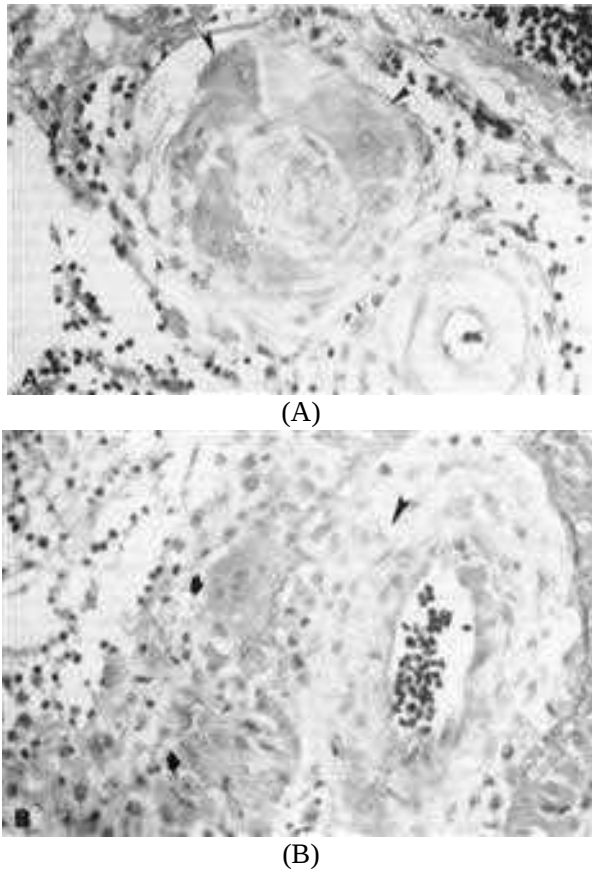
In 2018, De Boysson and colleagues [189] described the treatment and long-term outcomes of an observational cohort of 112 patients with PCNSV derived from three main networks: the French Vasculitis Study Group, French Neurovascular Society, and the French Internal Medicine Society. The three main criteria inclusion were (1) involvement of CNS vessels evidenced by biopsy or based on imaging (on digital subtraction angiography or MRA), showing intracranial arterial stenoses, occlusions, or fusiform dilations); (2) a complete workup performed, including infectious and immunologic serologies (HIV, hepatitis B virus, hepatitis C virus, syphilis, tuberculosis, antinuclear and ANCA, echocardiography and whole body imaging, to exclude other alternative conditions affecting CNS vessels; and (3) a >6 months follow-up (unless the patient died before 6 months of a biopsy-proven PCNSV) to prevent the inclusion of other vasculopathies, such as reversible cerebral vasoconstriction syndrome (RVCS) where vascular lesions reverse within the first months [192]. The rate of prolonged remission was defined by the absence of relapse at ≥ 12 months after diagnosis; as was the functional status at last follow-up in accordance with three main groups of treatments administered: CS (group 1); induction treatment with CS and an immunosuppressant, but no maintenance (group 2); and combined treatment with CS and an immunosuppressant for induction followed by maintenance therapy (group 3). Good functional status was defined as a modified Rankin Scale score ≤ 2 at the last follow-up.

Among the 112 patients reported by De Boysson and colleagues [189], 33 (29%) patients were included with a diagnostic CNS tissue biopsy, and 68 (61%) and 11 (10%) respectively had digital subtraction angiography or MR angiography consistent with PCNSV. Remission was achieved with the initial induction treatment in 106 (95%) of the 112 patients. Prolonged remission without relapse was observed in 70 (66%) patients after a mean of 57 months (range 12-198) of follow-up. A good functional status at last follow-up (i.e., modified Rankin Scale score ≤ 2) was observed in 63 (56%) patients. The overall mortality was 8%. More prolonged remissions ($P=0.003$) and a better functional status at the last follow-up ($P=0.0004$) were observed in group 3. In multivariate analysis, the use of maintenance therapy was associated with prolonged remission (OR, 4.32 [1.67-12.19]; $P=0.002$) and better functional status (OR, 8.09 [3.24-22.38]; $P<0.0001$). These findings suggest that maintenance therapy with an immunosuppressant combined with corticosteroids leads to the best long-term clinical and functional outcomes in patients with PCNSV after having achieved remission with either corticosteroids alone or in combination with another immunosuppressant. In that regards, cyclophosphamide in combination with corticosteroids for induction, and azathioprine for

maintenance were the two main immunosuppressants used in this registry. Whether other combinations or sequences can achieve better results remained to be ascertained.

The past decade has also revealed insights into childhood PACNS (cPACNS) [193], one of the many childhood inflammatory brain diseases that affect small and large vessels. So called angiographically-negative small-vessel cPACNS (SVcPACNS) is associated with persistent headache, cognitive decline, mood disorder, focal seizures and abnormal brain neuroimaging in children. Brain biopsy findings include inflammatory cell infiltrates in intramural arterioles, capillaries, or venules consisting predominantly of a mixture of lymphocytes and macrophages, with occasional plasma cells, polymorphonuclear cells, and eosinophils. Granulomatous inflammation and multinucleated giant cells are generally absent. Awaiting the results of The PedVas Initiative, a Canadian and United Kingdom collaborative study (ARChiVe Investigators Network within the PedVas Initiative [ARChiVe registry], BrainWorks, and DCVAS) of pediatric and adult cases of AAV (GPA) and PACNS (NIH identifier, NCT02006134), there is yet satisfactory prevalence and incidence data or evidence-based guidelines to treat cPACNS. The PedVas Initiative has been prospectively collecting clinical and biobank data in January 2013 of registered cases, within 12 months of study entry. The approach to diagnosis and management has been to first differentiate cPACNS and SVcPACNS respectively from angiography-positive, and angiography-negative, brain biopsy-positive mimickers. However, it has been difficult to reconcile the early outcome results of the PedVas Initiative employing corticosteroids, cyclophosphamide, methotrexate, or rituximab for remission-induction of childhood GPA [73] for the analogous therapy of cPACNS using similar protocols for AAV, due to the disappointing rate of remission status (42%) and visceral organ damage (63%) in its study cohort.

The aim of treatment in cPACNS has nonetheless been to rapidly control the underlying inflammatory response and stabilize the blood-brain barrier while protecting the brain from further insults. Methylprednisolone has been the first-line agent administered intravenously at a dose of 30 mg/kg/day to a maximum of 1 gram per day for 3 to 5 days followed by 1 to 2 mg/kg/day of oral CS to a maximum of 60 mg/day of prednisone. After stabilization, immunosuppressive treatment is directed at the likeliest inflammatory pathways involved in the primary vasculitic process. Induction therapy with corticosteroids and pulse cyclophosphamide followed by maintenance therapy with azathioprine or mycophenolate mofetil has been recommended in cPACNS. Children with SV-cPACNS were treated in an open-label study [194] with cyclophosphamide in doses of 500 to 750 mg/m² monthly infusions for six months, and followed with maintenance therapy of azathioprine of 1 mg/kg/day and a target dose of 2 to 3 mg/kg/day, and mycophenolate mofetil at titrated doses of 800 to 1200 mg/m²/day followed for up to 24 months employing pediatric stroke outcome measures (PSOM). Among 19 such patients, 13 completed 24 months of follow-up, of whom 9 had a good neurological outcome by PSOM scoring, 8 experienced disease flares, and 4 achieved remission of disease; and mycophenolate mofetil was more effective than azathioprine. One retrospective analysis [188] found that cyclophosphamide conferred little benefit over azathioprine in patients with GAB so treated and in fact, increased the risk for potentially fatal side effects.



Source: Reproduced from reference [4], with permission.

Figure 4. Central nervous system vasculitis. (A) The media and adventitia of this small leptomeningeal artery have been almost completely replaced by multinucleated giant cells (arrowheads). There is intimal proliferation with obliteration of the vascular lumen, and a dense, perivascular, mononuclear inflammatory infiltrate can be seen (stain, hematoxylin and eosin; original magnification, $\times 250$).

(B) A somewhat larger leptomeningeal vessel shows necrosis of the media and internal elastic lamina with multinucleated giant cell formation (arrows), intimal proliferation (arrowhead), and lymphocytic infiltration of the adventitia and neighboring meninges (stain, hematoxylin and eosin; original magnification, $\times 250$).

The approach to the patient with presumed PACNS begins with exclusion of disorders that can mimic primary CNS vasculitis including RVCS. The evaluation is incomplete without sampling of the CSF which often demonstrates elevation of the protein content and lymphocytic pleocytosis [188]. Cerebral angiography, high-resolution MRA and CTA, all provide complementary information however a small vessel vasculitis may escape detection, making it necessary to contemplate combined brain and meningeal biopsy for tissue confirmation (Figure 4).

Idiopathic Aortitis-IgG4-Related Disorders

In 1972, an unusual form of inflammatory aortic disease or aortitis came to light in the surgical literature with far-reaching implications for concepts of autoimmunity. Walker and colleagues [193] noted that 10% of 217 patients presenting with abdominal aneurysms at Manchester Royal Infirmary between 1958 and 1969 for resection showed excessive thickening of aneurysm walls and perianeurysmal adhesions at operation. Subsequent histological examination of the walls of the aneurysms showed extensive active chronic inflammatory changes including plasma-cell infiltration.

The clinical features of patients with inflammatory aneurysms differed from those with atherosclerotic disease due to generally younger age by a decade, lower incidence of rupture, lack of claudication of intermittent the limbs and presence of peripheral pulses, less likelihood of unusual presenting features, elevated ESR, and lack of calcification on preoperative abdominal Rojo-Leyva and colleagues [196] noted idiopathic aortitis in 43% of 1,204 aortic specimens gathered over a period of 20 years. In 96% of the patients with idiopathic aortitis patients and aneurysm formation, aortitis was present only in the thoracic aorta. In 2001, Hamano and colleagues [197] noted a high concentrations of IgG4 associated with sclerosing pancreatitis characterized by obstructive jaundice, infrequent attacks of abdominal pain, irregular narrowing of the pancreatic duct, sonolucent swelling of the parenchyma, lymphoplasmacytic infiltration, fibrosis, and a favorable response to corticosteroid treatment. One year later, Hamano and coworkers [198] noted the association of sclerosing pancreatitis with raised concentrations of IgG4 among those with concomitant hydronephrosis that caused ureteral masses later diagnosed as retroperitoneal fibrosis (RPF).

Histologic examination of ureteral and pancreatic tissues revealed abundant tissue infiltration by IgG4-bearing plasma cells. In the same year, 2008, three important observations were made. First, Sakata and colleagues [199] concluded that inflammatory abdominal aortic aneurysm (IAAA) was related to IgG4 sclerosing disease. Second, Kasashima and colleagues [200] concluded that IAAA was an IgG-RD together with RPF. Third, Ito and colleagues [201] described a patient with IAAA, hydronephrosis caused by RPF and high levels of IgG4, in whom treatment with corticosteroids led to clinical improvement and reduction in IgG4 levels. Histological inspection of the aortic wall specimen showed lymphocytoplasmacytic infiltration. Immunohistochemical analysis of the tissue showed IgG4 positive plasma cells. The findings suggested that IAAA had an etiopathogenesis similar to autoimmune pancreatitis and that some cases of IAAA and RPF could be aortic and periaortic lesions of an IgG4-RD. One year later in 2009, Khosroshahi and colleagues [202] described thoracic aortitis due to IgG4-RD with marked elevation of the serum IgG4 levels with progression to autoimmune pancreatitis, and Stone and coworkers [203] described IgG4-related thoracic aortitis with a media-predominant pattern of aortic wall infiltration and marked elevation of serum IgG4 levels, unequivocally linking IgG4-RD with thoracic lymphoplasmacytic aortitis.

Color-Doppler sonography, MRI combined with MRA and CTA, which adequately visualize the aortic wall and lumen, combined with FDG PET to detect increased uptake by metabolically active cells including inflammatory cells infiltrating the vessel wall, are essential in the assessment of the extent and severity of the various forms of aortitis including

IgG4 types. The histopathologic analysis of biopsy specimens has been the cornerstone of the diagnosis of IgG4-RD.

A 2012 consensus statement on the pathology of IgG4-RD by Deshpande and colleagues [204] proposed a terminology scheme for the diagnosis of IgG4-RD based upon the morphological appearance and tissue IgG4+ plasma cell counts in biopsy tissue. Three histopathological features associated with IgG4-RD included a dense lymphoplasmacytic infiltrate, fibrosis arranged at least focally in a storiform pattern, and obliterative phlebitis in morphological specimens. The majority of cells were T-cell with scattered B-cells, and an essential component of plasma cells with occasional eosinophils and macrophages. The level IgG4 antibody, which represents less than 5% of the total IgG in healthy individuals is tightly regulated and has a unique structure and functional property. It undergoes half antibody exchange *in vivo* resulting in recombined antibodies composed of two different binding specificities. Their production is driven in part by Th2 cytokines that mediate allergic reactions and IgE production. It does not activate complement pathways and has reduced effector function relative to other IgG subtypes. It remains unclear as to whether IgG4 directly mediates the disease process or reflects a protective response induced by anti-inflammatory cytokines, making it simply a valuable biological marker of IgG4-RD.

A Japanese consensus management guideline [205] suggested the initiation of oral prednisolone for induction of remission at a dose of 0.6 mg per kilogram per day for 2 to 4 weeks, with tapering by 5 mg every 1 to 2 weeks based on clinical manifestations, biochemical blood tests, and repeated imaging, to a maintenance dose of 2.5 to 5 mg per day for up to 3 months. Re-administration of corticosteroids is advised for treating relapses. Treatment with azathioprine, mycophenolate mofetil and methotrexate can be used as corticosteroid sparing agents or as remission-maintenance drugs after corticosteroid-induced remissions. Patients with recurrent or refractory disease and B-cell depletion may be considered for rituximab [206].

Nonsystemic Peripheral Nerve Vasculitis

The vasculitic neuropathies are heterogeneous disorders that present in the setting of systemic vasculitis or in the absence thereof where necrotizing arteritis may remain clinically and pathologically restricted to the peripheral nerves as a SOV. The Peripheral Nerve Society [207] established guidelines for the classification, diagnosis, investigation, and treatment of NSVN. Pathologically-definite vasculitic neuropathy is defined by active or chronic peripheral nerve and muscle tissue lesions that show cellular invasion of the walls of blood vessels with accompanying acute vascular damage (fibrinoid necrosis, endothelial loss/disruption, internal lamina loss/fragmentation, smooth muscle media loss/fragmentation/separation, acute thrombosis, vascular/perivascular hemorrhage or leukocytoclasia) or chronic vascular damage (intimal hyperplasia, fibrosis of media, adventitial/periadventitial fibrosis or chronic thrombosis chronic thrombosis with recanalization), without evidence of another primary disease process that could mimic vasculitis pathologically such as lymphoma, lymphomatoid granulomatosis or amyloidosis.

Patients with NSVN lack symptoms, signs, or laboratory evidence of involvement of other organs (demonstrable by laboratory evidence of PR3-, MPO-ANA, mixed cyro-

globulins, SSA, SSB, Sm, RNP, Scl-70, centromere, dsDNA, CCP serology; ESR >100 mm per hour, or tissue biopsy evidence of vasculitis in another organ other than muscle; serologic, PCR or culture evidence of a specific infection associate with vasculitis), and no predisposing factors (other than diabetes) of a connective tissue disease, sarcoidosis, inflammatory bowel disease, active malignancy, HUV, cutaneous PAN, or exposure to drugs likely to cause vasculitis. Inflammation of microvessels less than 40 to 70 μ m in diameter without vascular damage are broadly referred to as MV.

The management of NPNV has remained uncertain because of the very concept presumes that the vasculitic disease process is widespread within the nerves and not present elsewhere in the body. This assumption has been called into question by four lines of evidence.

First, the definition of NPNV allows for the finding of vasculitic lesions in muscle tissue, [207] perhaps making the syndrome more appropriately termed peripheral nervous system vasculitis or “PNSV”. Moreover, the detection of vasculitis in cutaneous nerve and muscle tissue specimens has been incorporated into the FVSG database to establish the diagnosis of systemic vasculitis. Among 129 patients with PAN [208] who underwent nerve biopsy with (108 patients) or without (21 patients) peripheral neuropathy, vasculitic lesions were noted in cutaneous nerve tissue in 83% and 81% of patients respectively, compared to 68% and 60% of cases where muscle biopsy tissue was examined.

Second, the lack of long-term follow-up in most cases series ranging from 6 months to 22 years [209].

Third, the report of only two proposed cases, both with foci of vasculitis outside the PNS in a visceral organ [19] or the temporal artery [210]. Patient 1 in the series of pathologically confirmed cases of PAN by Kernohan and Woltman [19] was a 54-year-old man with five years of progressive generalized painful peripheral neuropathy that was so severe before death that he was partially paralyzed, and unable to speak or swallow. Postmortem examination showed PAN limited to the nerve trunks of the arms and legs. The brain, cranial nerves, and spinal cord were normal except for early acute changes without evidence of vasculitis. Examination of all other organs failed to reveal a single vascular lesion, except one small artery in the capsule of the prostate gland. Torvik and Berntzen [210] described a 76-year-old woman with diffuse fever, pain, and central scotoma of the eye that improved with corticosteroids. A biopsy of the temporal artery and pectoralis muscle disclosed necrotizing arteries of small arteries and arterioles in small adventitial vessels of the temporal artery without frank temporal arteritis. However, postmortem examination evidence of healed vasculitis in numerous small arteries and arterioles of muscle and nerve tissue measuring 50 to 200 microns in diameter without vasculitis in visceral organ or the CNS. .

Fourth, the inclusion of patients with diabetes according to the 2010 guidelines [210] may be introducing selection bias. Over the years, there has been increasing support for the contribution of autoimmune mechanism in the pathogenesis of diabetic neuropathy. Diabetes itself appears to be caused by autoimmune mechanisms directed at insulin-producing pancreatic beta cells, and a variety of autoantibodies have been detected in patients with type-1 diabetes (T1D) or insulin dependent (IDDM), including anti-islet cell cytoplasmic antibodies, present in up to 80% of newly diagnosed patients and glutamic acid decarboxylase (GAD) antibodies, also present in patients with autoimmune stiff person syndrome. Younger and colleagues [211] reported the clinicopathologic and immunohistochemical findings of sural nerve biopsy tissues in a cohort of 20 patients with heterogeneous forms of diabetic neuropathy. That series was continued to a total of 107 patients [212], of which 3 (3%)

showed MV, and 3 (3%) showed necrotizing arteritis. Although diabetes has not been considered a predisposing factor in PNV, the presence or absence of diabetes became a defining feature of patients with LSRPN [213, 214]. In the only postmortem case of LSRPN described by Younger [215], sural nerve biopsy showed mononuclear inflammatory cells surrounding a small epineurial artery with extension into the vascular wall, with reactive luminal connective tissue suggesting recanalization of a thrombus. An adjacent nerve fascicle showed marked loss of myelinated nerve fibers. The patient was treated for painful diabetic lumbosacral plexopathy (DLSRPN) and peripheral nerve vasculitis according to prevailing standards with 2 g/kg intravenous immunoglobulin for 5 days, followed by 750 mg of intravenous cyclophosphamide and 1,000 mg of methylprednisolone intravenously for 3 additional days. Acute tubular necrosis, increasing lethargy, unresponsiveness, and aspiration pneumonia supervened and the patient expired 4 weeks after admission. General autopsy showed no evidence of systemic or peripheral nerve vasculitis. The brain showed diffuse loss of neurons in all sampled cortical areas, including the cerebellum, consistent with anoxia secondary to cardiac arrest. Sections of extradural lumbar plexus, sciatic, and femoral nerve tissue showed perivascular epineurial inflammation with infiltration of adjacent endoneurium. This case exemplifies the restricted nature of LSRPN as an example of a true NSVN.

There have far more studies of living cohorts with NSPNV. Kissel and colleagues [216] reported that 4.5% of 350 consecutive nerve biopsies performed at a single institution evidenced peripheral neuropathy secondary to necrotizing angiopathy. Six patients manifested a distal symmetrical sensorimotor polyneuropathy, while ten had a mononeuritis multiplex presentation, eight of whom had overlapping involvement of peripheral nerves that obscured the picture of mononeuritis. In three-quarters (12 patients), a specific underlying collagen vascular disease was not diagnosed despite extensive clinical, radiologic, and serological evaluation. Said and colleagues [217] studied 100 patients with necrotizing arteritis in muscle or nerve biopsy tissue that occurred in the context of a connective tissue disorder in fifty-five patients and in association with a disorder unrelated to connective tissue pathology in thirteen others. The commonest complaints at presentation in this cohort were specific cutaneous manifestation of vasculitis, including livedo, cutaneous necrosis, and nodules in one-third. Thirty-two patients had neuropathy only and necrotizing arteritis, the most common complaints at of which were spontaneous pain of neurogenic or muscle origin (48%).

More recently, Collins and colleagues [218] described forty-eight patients with NSPNV, 85% of whom had extensive, overlapping involvement of multiple nerves. Peroneal nerve and peroneal muscle tissue biopsy was 58% diagnostically sensitive compared to 47% for sural nerve biopsy for the diagnosis of vasculitis. Combination therapy with corticosteroids and cytotoxic agents was more effective than corticosteroids monotherapy for inducing remission and improving disability, with trends toward reduced relapses and chronic pain. Overall, ten patients died (21%) over the period of 63 months follow-up, five (10%) of whom were related to the disease or treatment, including two patients who succumbed to pulmonary emboli as a result of limited mobility of the legs or myocardial infarction in another; and two patients, one of whom had fatal sepsis and another metastatic bladder cancer as a consequence of cyclophosphamide toxicity.

There are no ongoing observational cohort studies to guide the treatment of NPNV. Recommendations for the treatment of NSPNV [210] include prednisone monotherapy unless there is rapidly progressive neuropathy at the dose of 1 mg per kilogram per day, with tapering over one year to a low dose. Combination therapy employing cytotoxic drugs

including cyclophosphamide, methotrexate, and azathioprine may be employed with adjuvant plasma exchange or IVIg. However, IVIg showed efficacy in a multicenter RCT of the treatment of small-to-medium systemic vasculitis due to EGPA with persistent disease activity [219].

This suggests that IVIg may be appropriate, first-line therapeutic modality in NSPNV. Moreover, the benefit of IVIg may be achieved without the risk of potentially fatal cytotoxic side-effects. However there has not been a prospective RCT of IVIg in NSPNV. A variety of mechanisms have been thought to be responsible for the beneficial effects of IVIg in NSPNV and other systemic vasculitides including neutralization of autoantibodies, inhibition of complement pathways, alteration of Fc receptor expression, and alteration of cytokine profiles [220]. Careful monitoring should be performed to observe desired therapeutic responses and to avoid potentially serious drug side effects.

CONCLUSION

In no other disorder have there been so many triumphs as in the diagnosis and treatment of primary systemic vasculitis. Physicians in a variety of subspecialties including neurology, rheumatology, immunology/allergy, dermatology and clinical pathologist, all working side-by-side, aided by subspecialties of public health, epidemiology, genetics, and clinical trial specialists, have benefited the outlook for individual patients and population cohorts around the globe. Yet it starts with clinical acumen typically of the general practitioner. This chapter on clinical approach was written with such diverse backgrounds in mind, from generalist to subspecialist with the hope that it will bring the field up to date and to the present.

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Chapter 194

EPIDEMIOLOGY OF PRIMARY SYSTEMIC VASCULITIS

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ABSTRACT

The epidemiology of the vasculitides has been extensively studied over the past the years, yet despite this, there remain a number of areas where there is a deficit of data. The first problem is that the vasculitides are generally rare conditions and this makes conducting accurate epidemiological studies difficult. The second is the lack for some conditions, as for example, the anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) of a reliable and validated classification system. Overall, the vasculitides are diseases of the age spectrum, with Kawasaki disease and IgA vasculitis being conditions of childhood, and giant cell arteritis occurring in those age 60 years or more. The AAV also occur more commonly with increased age. The occurrence of the vasculitides in different ancestries has been less well studied, primarily because there are many health care systems in which it is not possible to derive epidemiological data. Kawasaki disease is much more common in far Eastern populations than Europeans, while IgA vasculitis is more common in Asians. Giant cell arteritis occurs in those of northern European ancestry. The AAV have an overall uniform occurrence, but granulomatosis with polyangiitis is more common than microscopic polyangiitis in Europeans, whereas the reverse is true in the Far East. Improving classification systems and health care systems will hopefully mean that some of the gaps in our knowledge will be filled over the next few years.

Keywords: epidemiology, primary systemic vasculitis, vasculitides

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INTRODUCTION

The epidemiology of systemic vasculitis has been increasingly well described over the past 30 years; however, there remain formidable challenges and gaps in our knowledge.

Obtaining accurate epidemiological data is important for several reasons. Knowledge of the occurrence and pattern of disease in a given population is important for planning health services; identification of patterns of occurrence such as epidemics or seasonality may provide clues to the causes of disease both infectious and environmental. Comparison of disease occurrence between populations also provides clues as causation and also possible permit exploration of genetic risk factors.

The challenges fundamentally relate to the difficulty of conducting high quality epidemiology research in rare diseases. Accurate epidemiology requires a discrete population from within a well-defined geographical boundary. Universal health care systems with registration of patients receiving inpatient or ambulatory care are ideal for this type of research, in many parts of the world such universal health care systems do not exist and it is therefore much more difficult if not impossible to obtain reliable data. To collect a sufficiently large number of patients for reliable data from a rare disease either takes a long time or requires a large population, both of which make it harder to conduct high quality epidemiology research. A further requirement is a reliable classification system. The American College of Rheumatology (ACR) (1990) system for the classification of vasculitis is widely used, but has several major deficiencies in particular the absence of microscopic polyangiitis (MPA) and the results of ANCA testing. New classification systems are being developed as part of the Diagnosis and Classification of Vasculitis (DCVAS) project and will be available within the next 2 to 3 years. With increasing interest in the occurrence of disease in different populations accurate determination of ancestry is important, populations have become multi-ethnic with genetic admixture occurring. Such studies can be conducted either in a single population of multi-ancestry or by direct comparison of population in geographically dispersed areas, for example in the United Kingdom (UK) versus Japan. When comparing populations from different ancestries, it is important to ensure that the age structure of the studied population is the same. This is especially important for vasculitis, in which several types show a marked age tropism, as with IgA vasculitis (IgAV) and Kawasaki disease (KD) and giant cell arteritis (GCA) at opposite ends of the age spectrum.

Two main approaches have been used in studying the epidemiology of the vasculitides. The first is active surveillance with development of a complete cohort from a well-defined geographical area often based around a single referral center, examples being Norwich in the UK, Skane in Sweden, and Olmsted County in the United States (US) (Watts et al. 2012; Mossberg et al. 2018; Chandran et al. 2015). The second is passive surveillance using administrative databases, for example the UK Clinical Research Practice Database (UKCPRD) (Pearce et al. 2017). The former method has the major advantage that it is often possible to examine the individual patient case records to confirm the diagnosis and formally classify the individual patient. Because of the difficulties of collecting a complete cohort, such studies tend to have relatively small denominator populations, and total numbers of patients. The use of administrative databases has the advantage of automatic data collection, large populations and hence large numbers of patients. The downside is that it is usually impossible or impracticable to confirm the diagnosis and classification of any individual.

Algorithms are being developed which have been validated to extract information from administrative databases. (Sreih et al. 2016).

More recently, large-scale genetic epidemiology data has been published for many of the vasculitides. Again, there are formidable challenges to these studies, not least being the large number of well-characterized patients required for genome-wide association studies (GWAS). High quality data is now available for the large vessel vasculitides, Kawasaki disease and the AAV. This chapter focuses on the descriptive epidemiology of the vasculitides.

LARGE VESSEL VASCULITIS

The two main types of large vessel vasculitis (LVV), Takayasu arteritis (TAK) and GCA, are clinically considered to be the ends of a spectrum (Grayson et al. 2012). Recent genetic data, however, suggests that the two conditions are distinct (Carmona et al. 2017). It is well known that GCA occurs in the older patient age > 50 years whereas Takayasu arteritis (TAK) occurs predominately in those age < 40 years. This has left patients presenting with a large vessel vasculitis in their 40s essentially unclassifiable, and it is unclear whether they have late onset TAK or early onset GCA.

Takayasu Arteritis

Takayasu arteritis occurs in those age <40 years and presents with large LVV involving the aorta and its branches. For the purpose of epidemiological studies, the case definition has generally followed the ACR 1990 criteria for the classification of TAK (Arend et al. 1990).

There remains relatively little epidemiological data on TAK. The available data is summarized in Figures 1 and 2. Takayasu arteritis was first described in Japan and there has long been a view that it occurs more frequently in non-European populations. Most studies suggest there is a female predominance. In populations of European ancestry the annual incidence is 0.4 to 3.4/million, whilst it is 2.2/million in Kuwait/Arabia and 2.6/million in USA (Saritas et al. 2016; Dreyer et al.; Moriwaki et al. 1997). A recent Norwegian study observed an overall increase in the incidence over the last decade and a 3.5 to 5-fold difference in prevalence when comparing populations of north European ancestry to those of Asian and African ancestry respectively (Gudbrandsson et al. 2016). Although the incidence remains at similar levels in Japan, TAK is far more common in Japan with an estimated prevalence of 43/million with a strong female predominance (83.8%) and median age at onset at age 35 years, which was significantly lower in women (34 years) than males (43.5 years) ($P < 0.001$) (Watanabe et al. 2015).

Giant Cell Arteritis

Giant cell arteritis remains the commonest form of systemic vasculitis in those aged > 50 years. GCA is usually classified for epidemiology studies using the ACR 1990 criteria. Not all studies required a temporal artery biopsy to confirm the diagnosis, this can make it

difficult to compare studies. The incidence is highest in populations of northern European ancestry with the highest incidences and prevalence being recorded in Scandinavian populations, and in Olmsted County Minnesota, a population that is predominately of Scandinavian ancestry. The available data is presented in Figure 3. Some studies have suggested an increasing incidence but it is not always clear that this does not reflect better case identification and awareness of the disease. GCA is much less common in non-European populations especially from Asia. The prevalence in Japan appears to be 100-fold less than in Olmsted County. GCA is rarely observed in African ancestry populations (Kobayashi et al. 2003; Chandran et al. 2015). Some studies have suggested an increasing incidence over time, but it is not always clear that this does not reflect better case identification, changing rates of temporal artery biopsy and awareness of the disease. A recent Scandinavian study described a rise in reported incidence from 1972 to 1992 but no further increase up to 2012 (Brekke et al. 2017).

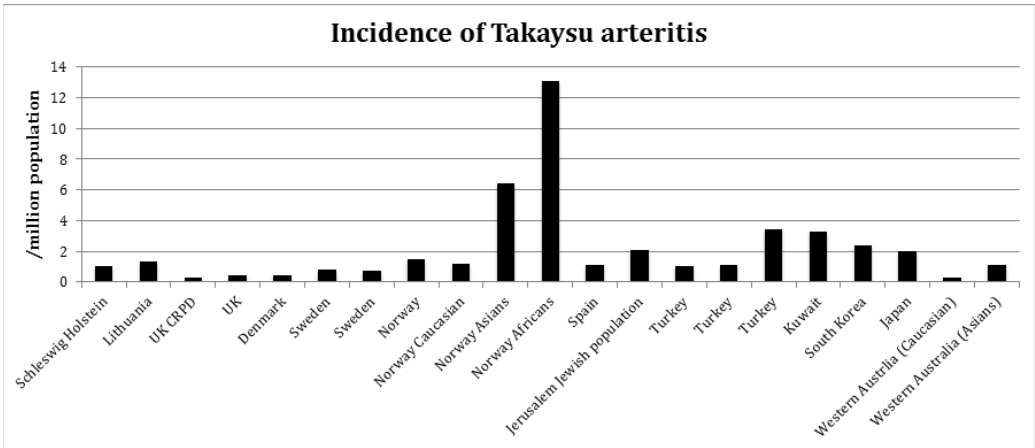


Figure 1. Global incidence of Takayasu arteritis.

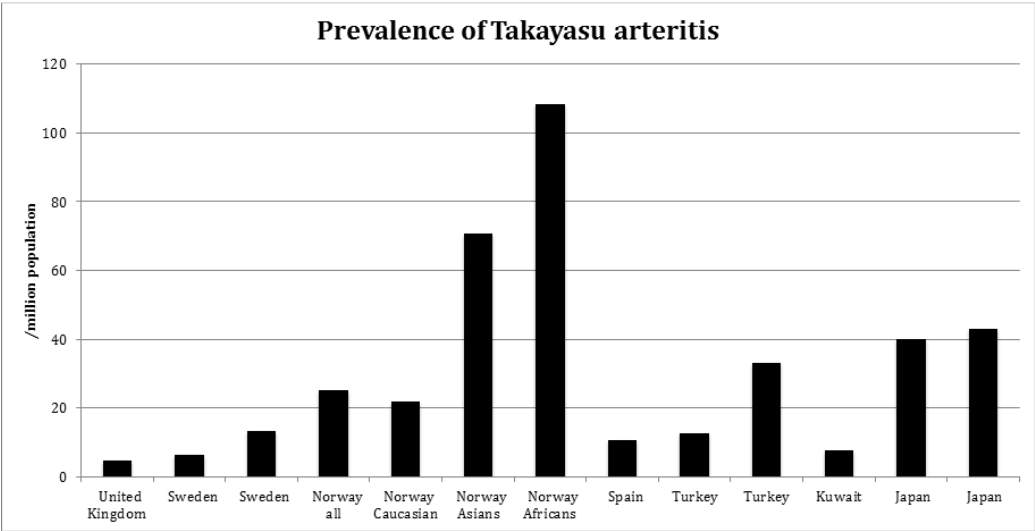
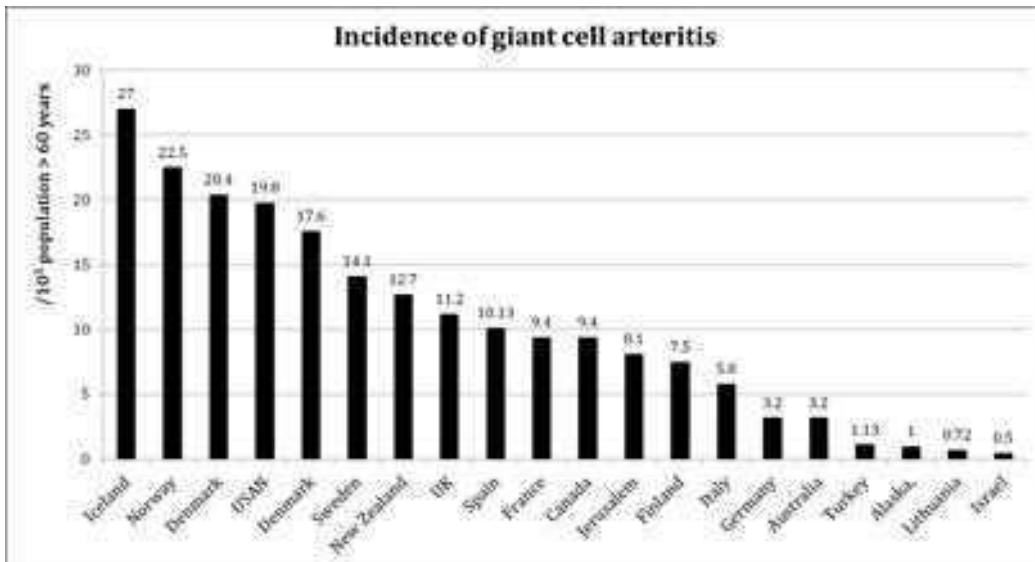


Figure 2. Global prevalence of Takayasu arteritis.



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Figure 3. Annual incidence of giant cell arteritis.

Environmental factors have long been thought to be important in the etiopathogenesis of GCA. There is an inconsistent relation with season of onset, some studies reporting a summer time preponderance but this has not been confirmed. Infection has also been suspected but no clear link has emerged.

Genetic epidemiology studies have shown that HLA-DRB1*04 is the strongest risk factor for GCA, and it has been suggested that variation in population HLA-DRB1*04 frequency may partly explain variations in GCA incidence, with the incidence being higher in populations with the greatest frequency of HLA-DRB1*04 (Mackie et al. 2015).

In conclusion there is still no good explanation for the striking age tropism shown by GCA, immune senescence combined with a strong genetic background is the most likely explanation.

MEDIUM VESSEL VASCULITIS

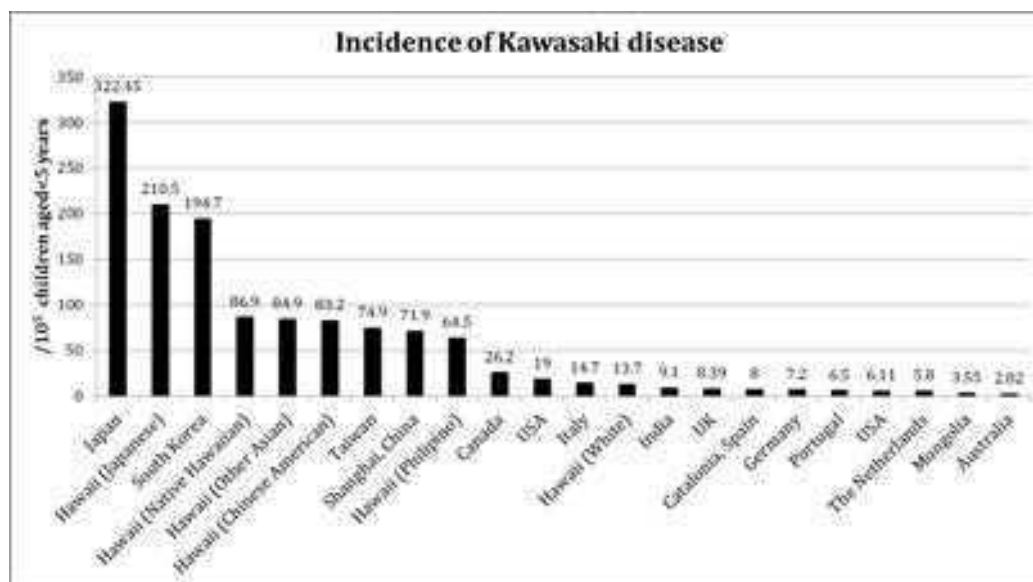
Kawasaki Disease

Kawasaki disease is a medium sized vasculitis which predominately affects children age < 5 years, and is the predominant cause of childhood-acquired heart disease in the developed world (Burns & Glode 2004). It was originally described by Kawasaki in Japan in the 1960 but has been recognized as occurring in most populations, there are however, marked differences in occurrence between populations. Populations of Asian ancestry have the highest incidence of KD. The incidence of KD continues to increase in Japan in 2012, where the annual incidence rates were 243.1/100,000 population aged 0 to 4 years in 2011 and 264.8 in 2012/100,000 (Makino et al. 2015a). In Japan, the cumulative incidence now means that by

the age of 10 years 1.5/100 boys and 1.2/100 girls have been affected by KD (Nakamura et al. 2017). By contrast, recent data from Italy suggests that the incidence rate was 5.7/100,000 children 0 to 14 years old, and 14.7 years among children < 5 years (Cimaz et al. 2017). The present epidemiological data is summarized in Figure 4. Most studies suggest that it is more common in boys. In Japan, there have been several epidemics of KD but none since 1986, raising the possibility of an infectious etiology, however so far no single infectious agent has been identified.

Several countries have reported distinct seasonality in KD, but there is no overall pattern even allowing for differences in latitude and longitude. Japan reports two seasonal peaks of KD incidence in January and July, with a nadir in October (Makino et al. 2015a). Korea, at approximately similar latitude, has similar peaks in June/July and December/January. (Kim et al. 2017) Taiwan has peaks in May/June and the lowest incidence is reported from November to January (Huang et al. 2009). Seasonality data from China are more variable (Uehara & Belay 2012). In Chandigarh (India), a consistent peak in October with a nadir in February is observed. KD has been reported to occur more commonly in the winter months in mainland US, Canada and Europe, and in the more temperate regions of Australia.

In Europe, the USA and Australia, the previously observed increase in incidence appears to have plateaued. Whereas, in North-East Asian countries (so as Japan and Korea) (Makino et al. 2015b; Kim et al. 2014; Huang et al. 2009) report an incidence 10 to 20 times higher than the US and Europe, and the incidence is continuing to increase. The current incidence in Japan is 265/100 000 in those < 5 years of age (Makino et al. 2015a). China and India, the two most populous countries, from where only more recent and less complete epidemiological data are available, the incidence also appears to be increasing, mirroring rapid industrialization and economic growth.



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Figure 4. Annual incidence of Kawasaki disease.

Polyarteritis Nodosa

Polyarteritis nodosa (PAN) is a rare vasculitis of medium vessels associated with development of aneurysms. Following the introduction of modern classification systems especially the 1994 Chapel Hill Consensus definition it has become increasingly uncommon (Jennette et al. 1994). It should be remembered that up until the 1990s the term PAN was used to cover several types of vasculitis, which would now be considered to be AAV. PAN is one of the few types of vasculitis for which a clear infectious cause has been recognized, Hepatitis B (HBV) infection is well-recognized cause of PAN. However, polyarteritis nodosa associated with HBV infection has become very uncommon since the introduction of vaccination programs and effective screening of blood donations. Before vaccination against HBV was available, more than one-third of adults with PAN were infected by HBV. Currently, less than 5% of patients with PAN are HBV positive.

The annual incidence of PAN currently ranges from 0 to 1.6 cases/million inhabitants in European countries. There is not a clear ethnic variation. There is a 1.5:1 male preponderance, and it occurs rarely in children (Figure 5).

SMALL VESSEL VASCULITIS

ANCA-Associated Vasculitis

The AAV (granulomatosis with polyangiitis [GPA], microscopic polyangiitis [MPA], eosinophilic granulomatosis with polyangiitis [EGPA]) have all been extensively studied over the past 20 years resulting in a large amount of available epidemiologic data. However, the field has been hindered by inadequate and poorly performing classification criteria, which has meant that it can be difficult to compare studies from different populations. Although widely used, the ACR (1990) criteria do not include MPA or ANCA testing, while the Chapel Hill Consensus Definitions from 1994 and 2012 were not intended to be used as classification criteria. These issues led to overlapping classification and inconsistency in their application. Results from the forthcoming DCVAS study may help to clarify this situation.

The overall incidence rates of AAV in Europe are reported to be in the range of 13 to 20/million (Figure 6), and the incidence of GPA has increased since the 1980s. The combined annual incidence of GPA and MPA in the UK was reported to be 1.5/million in the beginnings of the 1980s, and subsequently increased to 6.1/million at the end of the 1980s (Andrews et al. 1990). Similarly, during the same time period, the incidence of GPA increased in Sweden from 3 to 8/million (Knight et al. 2006). This increase could be due to several factors including: i) increased awareness among physicians, ii) the introduction of routine ANCA testing, and, iii) a genuine increase in incidence rates. However, the incidence has been stable since the early 2000s, suggesting that the likely explanation was increasing physician awareness following the introduction of routine ANCA testing. Geographical factors may also play a role. A comparison study from three regions in Europe showed overall incidence rates of all AAV to be quite similar; about 19/million (Watts et al. 2001). There were, however, differences in the incidence of GPA and MPA between northern and southern Europe; with GPA more common in the north, and MPA more common in southern Europe.

(Watts et al. 2001). However, the north-south gradient was not evident in southern Sweden which had an incidence rate of MPA more comparable to that of southern Europe (Mohammad et al. 2009). A recent Norwegian study reported higher rates of MPA than previously noted, suggesting that the north-south gradient might not be as pronounced as previously thought, or that there were changing environmental factors. Studies from New Zealand and Australia showed quite similar incidence rates for GPA comparable with those of northern Norway (Ormerod & Cook 2008; Gibson et al. 2006). By contrast, the proposed latitudinal gradient was observed in New Zealand (O'Donnell et al. 2007). Using the International Classification of Disease, patients coded as GPA were more frequent in southern New Zealand latitudes. Patients with EGPA were previously studied in the PAN group. The highest incidence rate for EGPA, 2.7/million (Watts et al. 2000) was reported from Norwich (UK); and recently 2.3/million (Ormerod & Cook 2008) from Australia.

The gender distribution of AAV is fairly similar in most studies with a slight increased ratio of men to women. The age-specific incidence for the whole group of AAV shows a clear increase with age. However, some variation has been reported between studies; the peak incidence in the age group of 55 to 64 years (Gonzalez-Gay et al. 2003), 65 to 74 years (Watts et al. 2000), and others $\geq$ age 75 years (Mohammad et al. 2009).

There is a need for studies in other regions and in other ancestries. There is only one study from central and Latin America as opposed to Europe and more recently Asia and Oceania. In a Peruvian population, MPA was more frequent than GPA (Sánchez Torres et al. 2005).

There are relatively few prevalence estimates compared with incidence studies of AAV. The prevalence of AAV is estimated to be 46 to 184/million (Ormerod & Cook 2008; Reinhold-Keller et al. 2000). The prevalence of AAV has generally increased over the last 20 years, reflecting improved patient survival and increased case identification, as shown by multiple retrieval sources.

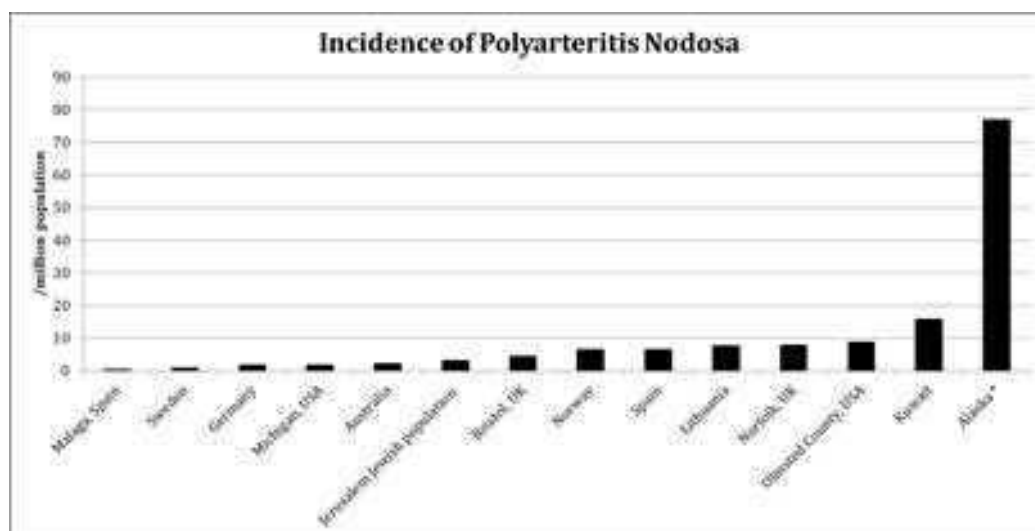
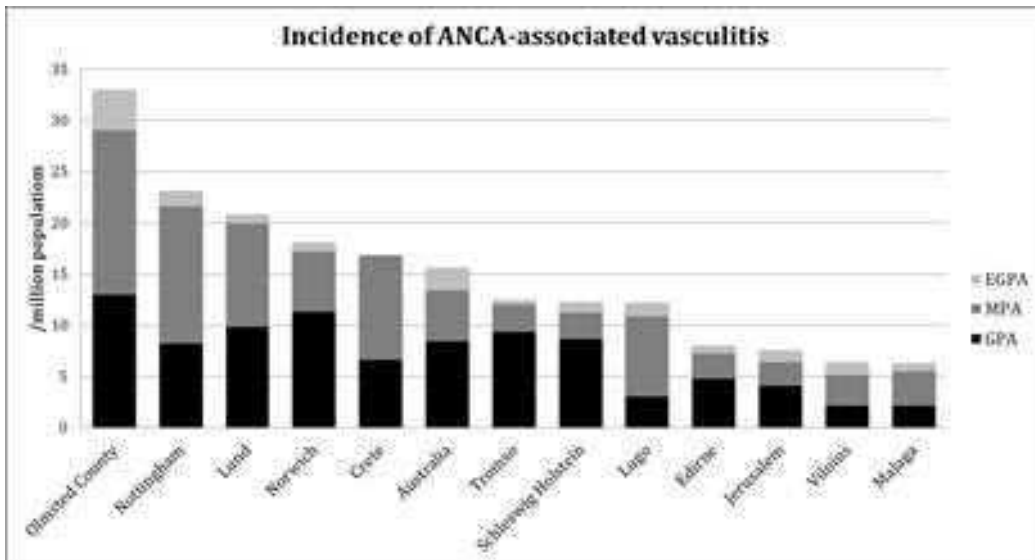


Figure 5. Incidence of polyarteritis nodosa.



Source: Reproduced from Watts and Robson *Best Practice & Research Clinical Rheumatology* 2018, with permission.

Figure 6. Annual incidence of ANCA-associated vasculitis.

The prevalence of GPA doubled in northern Germany from 58/million in 1994, to 98/million in 2006 (Herlyn et al. 2014). A study from an urban multi-ethnic population of Paris showed a low prevalence of GPA of 23.7/million (Mahr et al. 2004). In Northern Europe, the prevalence of GPA in Norway increased from 30.4/million in 1988, to 95.1/million in 1998 (Koldingsnes & Nossent 2000), and was 160/million in Sweden in 2003 (A. J. Mohammad et al. 2007). The prevalence of GPA in the southern hemisphere was estimated at 112/million in New Zealand and 95/million in Australia (Ormerod & Cook 2008; Gibson et al. 2006).

There is a paucity of data on the prevalence of MPA which varies from 25.1/million to 94/million. (Figure 7). As expected, the prevalence of EGPA is much lower than either GPA or MPA, with the highest estimate being 45.7/million.

Genetic factors are clearly important as it has long been observed anecdotally that cases of AAV are relatively rare in non-Caucasian populations. The first study to show differences in the occurrence of AAV in different ethnic groups was reported from Paris, so suggesting that GPA was less common in people of non-European ancestry than MPA (Mahr et al. 2004). A study directly comparing two ethnically different populations, white UK Caucasian and the Japanese showed that the overall similar incidence rate for AAV, but GPA and PR3-ANCA vasculitis were much less common in Japan than in Europe (Fujimoto et al. 2011); whereas in Japan, MPA and MPO-vasculitis were the dominant form of AAV compared to Latin America (Peru) wherein MPA was more common than GPA (Sánchez Torres et al. 2005). In New Zealand, GPA was twice as common in Europeans than Maoris or Asians (O'Donnell et al. 2007). Large case series from China suggest that MPA is more common than GPA (Liu et al. 2008). A multi ethnic series from Chapel Hill, US found that GPA was relatively uncommon in African Americans (Cao et al. 2011). These differences may reflect global variation in the frequency of the allele HLA DPB1*0401, which has been associated

with GPA (Watts et al. 2014). The north-south gradient in Europe may also reflect genetic differences between northern and southern Europeans (Tian et al. 2009). The clinical phenotype of systemic lupus erythematosus (SLE) has been shown to differ between northern and southern Europeans (Chung et al. 2009) accounting for the different clinical phenotypes of AAV in northern and southern European populations commensurate with their different genetic background.

A recent study of the UKCPRD that investigated the role of preceding illness in the cause of GPA found a 5-fold (odd ratio [OR] 5.1 95% CI 2.7 - 9.4, $p < 0.0001$) increased risk of diagnosis of bronchiectasis in the 5 years preceding the diagnosis of GPA (Pearce et al. 2018). Patients with GPA were 2 to 3 times more likely than controls to have a previous diagnoses of an autoimmune disease and chronic renal impairment, and these effects also remained stable more than 5 years prior to diagnosis. People with GPA were more likely to have a diagnosis of pulmonary fibrosis (OR 5.7, 95% confidence interval [CI] 1.7 - 19.5, $p = 0.01$) and sinus infections (OR 2.7, 95% CI 1.8 - 4.2, $p < 0.0001$) recorded in the 3 years before diagnosis, but not before. A history of smoking, and a higher socio-economic status were significantly, but less strongly associated factors.

In an attempt to unravel the link between disease and latitudinal gradient, an ecological study was undertaken to examine the relationship between ambient ultra-violet radiation (UVR) and incident data from several international epidemiological studies. Ambient UVR was obtained from satellite data using the longitude and latitude of the largest urban center in any given area. The crude incidence rates of both EGPA and GPA increased with latitude, although only GPA achieved statistical significance. Using a negative binomial regression there was a modest increase in the incidence of both EGPA (3.4%) and GPA (3.5%) per higher degree of latitude. MPA showed no association in either analysis (Gatenby et al. 2009). Although UVR has local effects on the immune system in the skin (Ponsonby et al. 2005), and is of particular importance in SLE, the most plausible explanation for these findings is the effect on vitamin D synthesis, a hormone that has profound effects on the immune system, a finding observed in a wide range of inflammatory rheumatologic conditions. (Gatenby et al. 2013) There is however no population data on vitamin D from the cohorts for which we have AAV incident data and no series measuring vitamin D in patients and matched controls (Gatenby 2013).

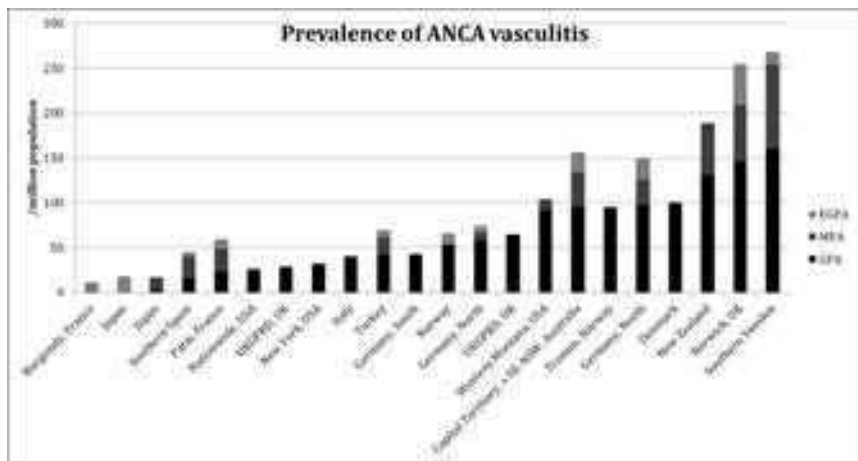


Figure 7. Prevalence of ANCA-associated vasculitis.

Silica appears to be a consistently identified risk factor among existing case-control studies for both GPA and MPA. This is not surprising given its known association with a number of other autoimmune syndromes (Steenland 2005). Commonly inhaled, the association with AAV is observed even in the absence of respiratory tract disease so suggesting an impact beyond the immediately exposed airways. Environmental dust was likely proposed as an important determinant with an association to silica (Gómez-Puerta et al. 2013). Studies in Japan after two large earthquakes suggested an increased incidence in the years immediately after earthquake (Yashiro et al. 2000; Takeuchi et al. 2017). However, an increased incidence was not seen after the Twin Towers attack in New York (Webber et al. 2015).

IMMUNE COMPLEX SMALL VESSEL VASCULITIS

IgA Vasculitis

IgA vasculitis or Henoch-Schönlein purpura, is an immune complex vasculitis that predominantly affecting small vessels (Jennette et al. 2013). This common childhood systemic vasculitis has the clinical characteristics of cutaneous palpable purpura, arthralgia/arthritis, bowel angina, and hematuria/proteinuria. The annual incidence which ranges from 3.5 to 27.6/100,000 in children, is highest between the ages of 4 and 6 years (70/100,000) (Gardner-Medwin et al. 2002). Two recent European studies reported similar incidences; a suburban area of Paris described an annual incidence of 18.6/100 000 (13.6 - 24.5) children, and 17.5/100,000 (16 - 19.1) in Sweden (Piram et al. 2017; Mossberg et al. 2018). In the French study the annual distribution of diagnoses consistently showed a trough in summer months; 72% of children had infectious symptoms (mainly upper respiratory tract) a few days before the onset of IgAV; and 23% had a North African background (Piram et al. 2017). The outcome of IgAV in children is generally good with a low rate of development of renal failure.

IgA vasculitis is much less common in adults. Recent studies from Finland and Spain suggest an incidence of about 1.4 to 1.5/million adults, whereas earlier studies from the UK and Spain suggested an incidence up to 10-fold higher. It is not certain whether this represents different case capture approaches or classification. Adult onset IgAV is more common in males (63%) and has a mean age of onset of 50 years (Audemard-Verger et al. 2017).

Anti-Glomerular Basement Membrane Disease

Anti-glomerular basement membrane (GBM) disease or Goodpasture syndrome, is a vasculitis affecting glomerular capillaries, pulmonary capillaries, or both, with basement membrane deposition of anti-basement membrane autoantibodies. Lung involvement causes pulmonary hemorrhage, and renal involvement causes glomerulonephritis with necrosis and crescents. This autoimmune disorder presents mainly with rapidly progressive glomerulonephritis and pulmonary hemorrhage in conjunction with increased serum levels of anti-GBM antibodies. The target “Goodpasture antigen” is the non-collagenous (NC1) region

of the $\alpha 3$ chain of type IV collagen. Some patients also have ANCA present, leading to the suggestion of an overlap with AAV. Authorities debate whether the disorder represents a true vasculitis or a vasculopathy. An Irish study calculated the national incidence at 1.64/million per year during the 11-year period of 2003 to 2014) (Canney et al. 2016).

Cryoglobulinemic Vasculitis

Cryoglobulinemic vasculitis (CV) is a rare form of immune complex vasculitis in which circulating cryoglobulins are demonstrated in serum or tissue. There is an association with myeloproliferative disorders, connective tissue diseases, in particular hepatitis C virus (HCV) infection. The incidence and prevalence of CV vasculitis is unknown. The outcome is dependent on the underlying condition. Modern antiviral therapies for HCV are highly effective in curing the infection and consequently improving the prognosis of affected individuals.

Hypocomplementemic Urticarial Vasculitis

There is very little data on the epidemiology of hypocomplementemic urticarial vasculitis (HUVS). A study from Sweden reported on 16 patients (14 women) all of whom were anti-C1Q antibody positive during the years 2000 to 2015 and derived from a well-defined population of 1,474,105. The annual incidence was 0.7/million with a point prevalence on 31 December 2015 of 9.5/million. There was no detectable age variation. The median age of onset was 51 years. The 5-year survival was 92%, with a 10-year survival of 83% (Sjöwall et al. 2018).

OTHER VASCULITIDES

Behçet Disease

The epidemiology of Behçet disease (BD) is characterized by a striking geographic variation with a greater incidence in an area spanning from China to the eastern Mediterranean Sea, leading to the descriptive term, *Silk Road disease*. The majority of studies in BD have been prevalence rather than incidence studies including many from countries where the health care system is challenged to obtain accurate incidence figures. Two main methods have been used: census surveys and sample surveys.

A recent meta-analysis of 45 population based surveys confirmed the geospatial variation in the prevalence of BD (Maldini et al. 2018). The global overall prevalence was 10.3/100,000 inhabitants. In Turkey the pooled prevalence was 119.8/100,000 inhabitants, 31.8/100,000 in the Middle East, 4.5/100,000 for Asia and 3.3/100,000 for Europe (Maldini et al. 2018). In Europe, there was a north-south increase in prevalence, suggesting that BD in those of Northern European ancestry. The case finding methodology has also strongly influenced the reported figures, with sample surveys giving generally higher estimated of the

population prevalence compared census surveys; notwithstanding, the method employed to classify cases probably does not influence prevalence estimates (Maldini et al. 2017).

The geospatial distribution of BD is strongly related to expression levels of HLA-B*51, with prevalence being highest in Europe and the Middle and Far East, where HLA-B*51 is found in > 15% of individuals, and the prevalence being lowest in Africa (Wallace 2014).

SECONDARY VASCULITIS

Rheumatoid Vasculitis

Rheumatoid vasculitis (RV) first became widely recognized and reported in the 1960s. In the UK, the first estimate of the incidence was from Bath/Bristol in the 1970s and suggested an incidence of 6/million (Scott et al. 1981). In Spain, the annual incidence of biopsy proven RV during 1988–1997 was 6.4/million (González-Gay & García-Porrúa 1999). A detailed study conducted in Norfolk, UK, between 1988 and 2010, compared the incidence of RV between 1988 and 2000 with the period 2001 to 2010 (Ntatsaki et al. 2014). The annual incidence decreased from 9.1/million to 3.9/million. This decline occurred predominately during the late 1990s. The incidence in the Norfolk study was equal in both males and females. The decline in RV has been attributed to better disease control especially with the much wider use of methotrexate during the 1990s, and predates the common use of biologic drugs.

Several US studies have supported this decline in RV; a population based study of the incidence of extra-articular RA reported a reduction in the 10 year cumulative incidence of RV from 3.6% in 1985-1994 to 0.6% between 1995 and 2007 (Myasoedova et al. 2011). The reduction of the prevalence of RV was also reported in a serial cross-sectional study of both hospitalised and ambulatory patients from the US veteran population seen between 1985 and 2006, comprising a similar duration of cohort observation with our study of 22 years (Bartels et al. 2009). There has also been a decline in hospitalisation in California of SRV patients between 1980 and 2001 (Ward 2004).

CONCLUSION

The epidemiology of the vasculitides is much better understood now than was the case 20 - 30 years ago, however much of the data comes from populations of European descent. The main exceptions to this are KD and BD, which have very clear variations in geographical occurrence, for most other types of vasculitis it remains unclear how much geographical variation occurs. These variations give clues to possible genetic differences. There is still relatively little data from much of Asia especially the Indian subcontinent, Africa and Latin America. Knowledge of environmental risk factors is also sparse for most of the vasculitides.

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Chapter 195

HEALTH RELATED QUALITY OF LIFE AND ITS MEASUREMENT IN THE VASCULITIDES

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ABSTRACT

Patient reported outcomes (PRO) using mainly the generic Short-Form 36 have been studied in diverse systemic vasculitides, in particular in patients with anti neutrophil cytoplasmic antibody-associated vasculitis (AAV), who report significant impairment in their health-related quality of life (HRQOL). Patients report different priorities regarding disease assessment compared with their physicians and this should be captured in clinical studies. The Outcome Measures in Rheumatology (OMERACT) Vasculitis Working Group, has gained endorsement by OMERACT for use of a disease-specific PRO, the AAV-PRO and generic Patient Reported Outcome Measurement Information System (PROMIS) instruments in clinical trials of vasculitis. Generic and disease-specific instruments are complimentary to each other and require further study to assess their utility in longitudinal settings, including their ability to distinguish between treatments of varying efficacy in randomized clinical trials (RCTs). This chapter reviews HRQOL measures in systemic vasculitis further separable by the caliber of vessels involved.

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INTRODUCTION

Systemic vasculitis can be organ and life-threatening [1-3]. International randomized controlled trials with standardized outcome measurement have revolutionized their treatment [4-6]. Irreversible damage, ongoing disease activity and adverse effects of medications can all impact on Health-related quality of life (HRQoL) scores [7-9]. This chapter describes HRQoL and its measurement in systemic vasculitis.

CLASSIFICATION OF VASCULITIDES

The Revised 2012 International Chapel Hill Consensus Conference established distinct categories for the classification of vasculitis based upon the caliber vessels involved [10]. Large vessel vasculitis (LVV) including giant cell arteritis (GCA) and Takayasu arteritis (TAK) affects the aorta, its major branches and analogous veins. Medium vessel vasculitis (MVV) inclusive of polyarteritis nodosa (PAN) and Kawasaki disease (KD), involves main visceral arteries and veins and initial branches. Small vessel vasculitis (SVV) involvement affects intraparenchymal arteries, arterioles, capillaries, veins and venules, with disease mechanisms related to anti-neutrophil cytoplasmic antibody (ANCA) or immune complexes. The group of AAV includes granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA). The subgroup of variable vessel vasculitis (VVV) includes Behçet disease (BD).

BACKGROUND

Measurement of HRQoL scores in systemic vasculitis has historically been based on generic patient reported outcomes (PROs), mainly the Short-Form 36 (SF-36) [11]. The benefits of the SF-36 is that it is a well-recognized and validated outcome measure [11] and allows comparison between patients with systemic vasculitis and other conditions. Limitations in the use of generic PROs can include a reduction in face and content validity, as they have not been designed to capture areas of most interest to patients with that specific disease [12]. This lack of specificity reduces the ability to detect differences in state between patients and in the same patient over time [12]. In GCA, the SF-36 does not detect differences between patients with and without visual loss or systemic involvement for example [13]. Trials in AAV fail to show difference in SF-36 scores between arms, despite use of less toxic medications such as cyclophosphamide versus rituximab [14]. Whether this is a lack of sensitivity with the SF-36 or due to glucocorticoid effects in the arms remains unanswered. The difference in HRQoL scores as measured by the SF-36 in a randomized controlled trial (RCT) of tocilizumab in GCA, which may be attributable to the reduction in glucocorticoid-related adverse effects in the tocilizumab only arm [15], requires further analysis.

The Outcome Measurement in Rheumatology (OMERACT) initiative is an international collaboration to define core sets of outcome measurements for use in RCTs [16]. Working groups include researchers, clinicians, patient partners, and methodologists; other stakeholders including the Food and Drug Administration (FDA) and representatives from

pharmaceutical companies participate in the workshops [16]. The Vasculitis Working Group published a core set of domains and outcome measures for use in clinical trials in AAV in 2011 [17], and LVV in 2017 [18] and a core-set of domains for BD at OMERACT 2018. Due to the appreciation that patients and their physicians commonly rank aspects of their disease in different orders [19], groups have recently been focused on the patient perspective in systemic vasculitis. This has included the development of a new disease-specific PRO, the AAV-PRO [20], underpinning qualitative work in TAK and BD [21, 22] and evaluation of alternative generic PROs such as the Patient Reported Outcome Measurement Information System (PROMIS) [23].

Disease-specific PROs developed with patient involvement at every stage are in line with guidance from the FDA on the development of PROs [24]. They should be based on underpinning qualitative research with patients and the specific disease to identify the full range of impacts of the disease and its treatment, ensuring good face and content validity [25]. Themes rewritten as candidate questionnaire items, including stems and response categories, and corresponding questionnaire items are then piloted and tested within cognitive interviews to check readability and understanding [26]. Large scale testing within a survey is then performed, using statistical analyses such as Exploratory Factor analysis [27] and Rasch analysis [28] to confirm the ideal structure of the PROM and validate its measurement properties [20, 29].

Generic and disease-specific PROs are complimentary [30] and can be used together, and adapted to the specific context of the study. The growing recognition of the importance of PROs in the assessment of vasculitis, and the availability of validated instruments to capture PROs in vasculitis, will likely mean patients' perspectives will also be incorporated into composite outcome measures in future trials.

SMALL VESSEL VASCULITIS

ANCA-Associated Vasculitis

Vasculitic involvement in the subgroup of AAV variably effects the kidneys, lungs, nervous system, skin, ears nose and throat, and eyes, resulting in intrusive symptoms, and irreversible damage and impact on HRQoL [2, 31].

The generic SF-36 has been used in clinical studies of patients with AAV and is a core outcome measure listed within the 2010 OMERACT core set [17]. Data from four European RCTs of newly diagnosed patients with AAV demonstrated impairment in HRQoL at entry [32]. Physical functioning scores were the most affected, particularly in those with neurological involvement and of older age [33]. A Scottish case-control study demonstrated that patients with AAV were twice as likely to have fatigue than matched controls, with levels of fatigue strongly associated with impairment in physical function [34]. Survey data suggests that AAV-related fatigue is multifactorial, with associations seen with increasing levels of pain, sleep disturbance and inflammation [35]. Fatigue was ranked by patients as being of greatest importance to their HRQoL, in contrast to physicians, who ranked being dialysis or oxygen dependent as more important [19].

The OMERACT Vasculitis Group has identified the lack of a disease-specific PRO for AAV [36]. An international collaboration of researchers and patients has overseen the development of a new PRO to fulfill this unmet need. Qualitative interviews with 50 patients with AAV from the United Kingdom (UK), United States (US) and Canada identified the following domains of interest: symptom severity, and the impact of problems and limitations imposed by patients' ANCA-associated vasculitis and treatment on their work and domestic roles, family and social interactions, including activities and interests outside the home; and psychological state [31]. Themes used as underpinning data to develop candidate items for the new PRO and tested using cognitive interviewing and psychometric evaluation to create the final validated PRO [20].

The AAV-PRO 29-item questionnaire has six subscales/domains: "Organ-Specific Symptoms," "Systemic Symptoms," "Treatment Side Effects," "Social and Emotional Impact," "Concerns about the Future," and "Physical Function." The domains offer a comprehensive profile of the impact of AAV and its treatment on patients' everyday life [20].

AAV-PRO domain scores distinguish between patients who self-report active disease versus disease in remission, and therefore can be used as an outcome measure to define treatment success from the patient's perspective [20]. Scores for each separate domain are examined separately to provide a profile of the overall impact of the disease and its treatment on HRQoL. A greater focus is placed on pre-specified domains depending on the aims of the trial. For example, in a non-inferiority trial of a glucocorticoid-sparing agent, the treatment domain of the AAV-PRO might be key, but other investigators may instead wish to collect and analyze all domain scores to examine any differences across the symptoms and HRQoL domains. Further work is necessary to determine whether summary component scores are applicable to AAV-PRO.

Women scores are higher (i.e., worse) on all six subscales of the AAV-PRO [20] and in other conditions [37, 38]. Such trends in women were previously been reported in AAV [32]. Younger people (<65) scored higher (worse) on the Social and Emotional Impact subscale of the AAV-PRO, a trend also seen in other chronic diseases in this age group, potentially due to feeling different to peers, being unable to achieve ambitions and uncertainty at key stages of usual transition into adulthood [37, 39]. Younger age is a possible risk factor for negative illness perceptions in AAV, and increased levels of fatigue [40].

The PROMIS, which is a collection of generic item banks of self-reported health drawn originally from different diseases, in relation to fatigue and physical function, has been examined in patients with GCA, and appears feasible, with scores correlating with relevant SF-36 domain scores [23]. Further testing of different PROMIS item banks across other HRQoL domains within the systemic vasculitides is ongoing.

LARGE VESSEL VASCULITIS

Takayasu Arteritis

The symptoms of TAK are attributable to involvement of the aorta, its major branches, and the pulmonary arteries [41]. Constitutional symptoms related to systemic disease include

weight loss, fever and fatigue; while those associated with vascular inflammation and occlusion lead to pain, claudication and tissue loss [41].

Health-related quality of life examined in Turkish patients via generic SF-36 showed worse scores in patients with TAK than healthy controls, in line with scores from patients with ankylosing spondylitis and rheumatoid arthritis [42]. A patient survey in the US identified an association between use of immunosuppressant medications and worse HRQoL probably due to severity of disease, while younger patients and those in remission had better HRQoL [7]. Patients with TAK have higher levels of anxiety and depression than healthy controls as well as physical limitations [43].

A review by the OMERACT Large Vessel Vasculitis Working Group identified the lack of a disease-specific PRO for TAK [44]. Qualitative research, including individual interviews and focus groups in the US and Turkey have identified domains of importance to patients with TAK [21]. Salient themes include, “Pain and Discomfort,” “Fatigue and Low Energy Levels” and “Emotional Effects,” that could underpin the future development of a disease-specific PRO [21].

Giant Cell Arteritis

Giant cell arteritis is associated with inflammation of cranial and neck vessels [45] and is a medical emergency due to the risk of blindness in 20% [46, 47]. Prompt treatment with high dose glucocorticoids (GC) is needed to protect vision [48, 49]. Presenting features include vice-like headache, jaw claudication, flu-like symptoms and inflammatory pain and stiffness in the shoulders and hips (polymyalgia rheumatica, present in 50%) [47]. For 60 years GC alone have been the mainstay of treatment, but patients are concerned about the risks [50-53]. Patient report the psychological impact of weighing up the necessity of treatment with GCs to prevent blindness, versus fears about adverse effects [50]. The use of novel biologic medications such as tocilizumab versus standard GC regimens, does appear to benefit patients in terms of their HRQoL at one year [15], and this should be examined further.

Qualitative research in the UK has revealed the impact of GCA on patients' lives is due to their symptoms (e.g., pain, visual disturbance and musculoskeletal symptoms), adverse effects of glucocorticoids, and the disruption to normal life [54]. Patients fear blindness and have concerns about delay in diagnosis [54]. Patients with GCA ranked “losing sight in both eyes permanently,” “having intense or severe pain” and “feeling weak, tired or exhausted” as the most important domains of health-related quality of life [55].

The OMERACT Vasculitis Working Group has highlighted the development of a disease-specific PROM for GCA as one of the next steps in their research agenda [18, 56]. Generic PROs alone may not be specific enough for use in GCA. SF-36 scores in patients with GCA do not correlate with visual loss or systemic complications, so may be unable to differentiate between clinically important groups [13, 57].

Underpinning qualitative work with patients in the UK and Australia was presented, revealing themes including: “Anxieties around getting a diagnosis of GCA,” “Description of symptoms related to GCA and its treatment,” “Lack of bodily strength, stability and stamina; difficulties with completing daily tasks,” “Difficulties with participating in social activities, work and caring roles,” “Not feeling normal and impact on general perception of health,”

“Anxiety and fear of the future” [58]. Themes are being developed further into candidate questionnaire items for a disease specific PRO for GCA.

VARIABLE VESSEL VASCULITIS

Behçet Disease

Behçet disease is a variable vessel vasculitis affecting veins and arteries of different sizes [10]. Male and female patients present in young adulthood with a spectrum of different disease manifestations [59]. Organ involvement can include mucocutaneous (such as oral and genital ulcers, nodular and papulopustular skin lesions), ophthalmological (panuveitis), musculoskeletal (usually monoarthritis or arthralgia), neurological (from parenchymal stroke-like syndromes, to cerebral venous thrombosis [60]) and/or gastro-intestinal involvement (which can present in a similar to inflammatory bowel disease) [59].

Patients with BD have worse SF-36 scores compared with healthy controls, particularly in women and those with high disease activity [61]. Mucocutaneous (oral and genital ulcers), central nervous system, musculoskeletal and ocular involvement are all independent predictors of worse HRQoL [61]. Physical functioning is most impaired in panuveitis compared with other ocular presentations [61]. Sexual function can be impaired in men and women [62]. Patients reporting high activity in relation to their joints, oral ulcers and fatigue, scored highly on the physical domains of the Nottingham Health Profile (NHP); joint and oral ulcer activity was also correlated with high psychosocial subscale NHP scores [8].

A systematic review of outcome measures used in BD by the OMERACT Vasculitis Working Group revealed a lack of standardization and large variability in terms of outcomes used across trials [63].

There is a validated disease specific HRQoL measure, namely, the BD-QoL scale [29, 64-66] which has undergone cross-cultural adaptation and validation in Korean and Arabic [64, 67]. Item development was based on underpinning qualitative work with patients with BD in the UK, and included the following salient themes: “Relationships,” “Emotions,” “Limitations in Day to Day Activities” and “Self-Image” [29].

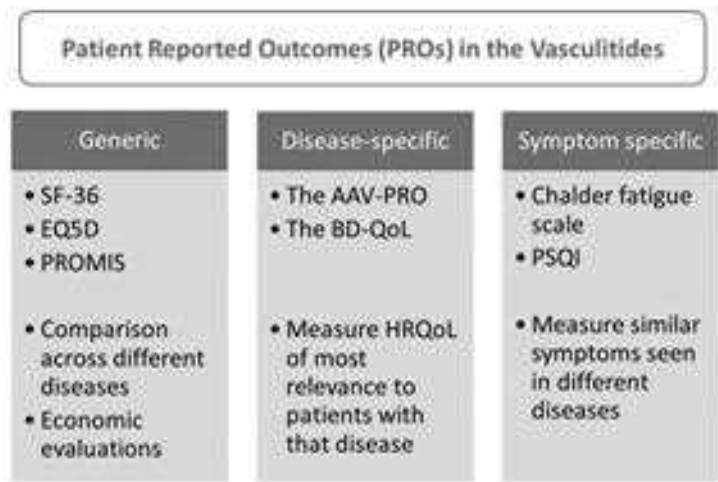
Generic measures to evaluate HRQoL in trials in BD have largely been the SF-36 [68] and the EQ-5D [63]. A range of different symptom-specific tools have been used, including the Oral Health and Related Quality of Life scale, which has been validated in Turkey and the UK in BD [69]. Symptoms specific tools to measure impact on Sexual Function (e.g., the Arizona Sexual Experience Scale [62] and Sleep (e.g., the Pittsburgh Sleep Quality Index [70]) have also been used, but not in a systematic way across trials [63]. Psychological impact has most commonly been measured within trials of BD using the Beck Depression Index [71] and Beck Anxiety Scale [66, 72].

The OMERACT Vasculitis Working Group continues to work towards standardized assessment of BD within clinical trials [22]. A new core set of outcome domains for BD, including HRQoL as a core domain, was ratified at OMERACT 2018. The core domain set will be published this year; next steps within the OMERACT process will be to evaluate and recommend appropriate tools with which to measure these domains, including HRQoL [73].

Use of generic, disease-specific and symptom specific tools may be appropriate depending on context, i.e., whether the trial is focused on a specific organ manifestation.

CONCLUSION

The impact of symptoms and side effects of treatment in systemic vasculitis can affect all aspects of HRQoL, depending on stage of life. Systemic vasculitis affects people of working age [74], those planning a family [75] or active retirement [54]. Patients also face the situation of having a rare autoimmune rheumatic disease [76] which can be isolating, results in delays to get a diagnosis and treatment, and difficulties in navigating health care systems between different specialists [76].



Key. SF-36: The Short Form 36; EQ5D: The EuroQOL five dimensions questionnaire; PROMIS: Patient Reported Outcome Measurement Information System; AAV-PRO: Disease specific PRO for ANCA-associated vasculitis; BD-QoL: Disease specific PRO for Behcet’s Disease; PSQI: Pittsburgh Sleep Quality Index.

Figure 1. Patient Reported Outcomes (PROs) in the Vasculitides.

Patients have different perspectives on their disease and its impact than their clinicians and it is important to capture this within clinical studies using validated outcome measures.

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Chapter 196

NEUTROPHILIC CELL PATHOBIOLOGY IN THE VASCULITIDES

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ABSTRACT

Neutrophils play a critical role in the pathogenesis of vasculitides, especially in anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). ANCA cooperates with pro-inflammatory cytokines in activating neutrophils. Activated neutrophils contribute to the development of small vessel vasculitis. The ANCA-cytokine sequence is pivotal to the understanding the pathogenesis of AAV. Recent studies reveal that neutrophil extracellular traps (NETs) extruded from activated neutrophils are implicated in vascular endothelial cell (VEC) injury. NETs are also implicated in the mechanism of ANCA production. These findings suggest that the NETs-ANCA vicious cycle is involved in the pathogenesis of AAV. This chapter updates the literature relating to ANCA-cytokine sequence theory.

Keywords: ANCA-associated vasculitis, ANCA-cytokine sequence, NETs-ANCA vicious cycle, NETs-ANCA-cytokine sequence

INTRODUCTION

Neutrophils play critical roles in the pathogenesis of vasculitides, especially in anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). They are primed by pro-inflammatory cytokines, such as TNF- α , and express myeloperoxidase (MPO) and proteinase 3 (PR3) on the cell surface. ANCA binds to the antigen and simultaneously bridges the antigen and bystander Fc γ receptor on the cell, which activates neutrophils. Consequently, the activated neutrophil releases reactive oxygen species (ROS) and lytic enzymes, in turn

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contributing to the development of small vessel vasculitis (SVV). This ANCA-cytokine sequence therapy is pivotal for the understanding of AAV [1]. Recent studies have revealed that neutrophil extracellular traps (NETs) extruded from the activated neutrophils are also implicated in vascular endothelial cell (VEC) injury [2, 3]. Recent reports suggest involvement of NETs in the mechanism of ANCA production [4-6], as well as in ANCA-mediated cytotoxicity.

This chapter focuses on NETosis and the neutrophilic cell metamorphosis of NET formation in AAV.

Discovery of NETs

In 2004, Brinkmann and coworkers [7] reported that phorbol myristate acetate (PMA)-stimulated neutrophils extrude decondensed DNA that form extracellular web-like structure decorated with bactericidal proteins, such as MPO and PR3. These substances, termed NETs, bind to, and kill bacteria. NET formation is regarded as an important event of innate immunity.

Patients with chronic granulomatous diseases (CGD) who fail to generate NETs are susceptible to diverse bacterial and fungal infections. However, restoration of NET formation in CGD results in resistance to such infections [8]. NETs appear to be an innate response that binds microorganisms, prevents them from spreading, and ensures a high local concentration of antimicrobial activity derived from neutrophils [9].

Process of NET Formation

PMA-stimulated neutrophils undergo cell death with NET formation [10]. Since the characteristics of cell death resembles neither typical necrosis nor apoptosis, Steinberg and colleagues [11] coin NETosis for neutrophilic cell death with NET formation. NETosis induction by PMA requires activation of the Raf-MEK-ERK pathway, with NADPH oxidase-dependent production of ROS, and RIPK1-RIPK3-MLKL signaling [12, 13]. In this pathway, peptidylarginine deiminase 4 (PAD4)-dependent citrullination of histones induces decondensation of DNA resulting in a mixture of DNA and bactericidal proteins, contained originally in intracytoplasmic granules [14]. Thereafter, these substances extrude from the ruptured plasma membranes of neutrophils.

NETs in AAV

Kessenbrock and coworkers [4] first showed that ANCA derived from AAV induces NETs from TNF- α -primed neutrophils obtained from healthy donors. They also demonstrated co-localization of extracellular DNA, neutrophilic enzymes, and histones. NET formation was evident in crescents of glomeruli affected by AAV.

Subsequent investigations noted similar findings using citrullinated histones as a specific marker of NETs [15-17].

Vascular Endothelial Cell Toxicity of NETs

Carmona-Rivera and coinvestigators [18] demonstrated that direct incubation of VEC lines with NETs promoted VEC death. The cytotoxicity of NETs is mediated by matrix metalloproteinase (MMP)-9, which is externalized from neutrophils. NET formation and activation of MMP-2 in VECs culminates in cell death. The neutralization of MMP-9 prevents MMP-2 activation in VECs leading to a decrease in NET-mediated cytotoxicity.

Thrombosis Induced by NETs

Patients with AAV are predisposed to deep vein thrombosis (DVT), especially during the active stage of the disease [19]. As ANCA induces NET from the primed neutrophils, NETs are critically associated with DVT as histones within NETs bind platelets and coagulate blood [20, 21]. Such findings are consistent with an abundance of NETs detected in DVTs of patients with AAV [15, 17]. The collective findings suggest a link between AAV, accelerated thrombosis and DVT via NETs.

Degradation of NETs

NETs play an essential role in the innate immune system with excessive formation and persistence of NETs, a consequence of which is the heightened risk of adverse events. Notwithstanding, NETs are strictly regulated *in vivo*. The most important NET degradation factor is serum DNase I [22].

Propylthiouracil Induces DNase I-Resistant NETs

Propylthiouracil (PTU) is an anti-thyroid drug used for the treatment of hyperthyroidism. Approximately 30% of patients administered with PTU produce MPO-ANCA, some of whom develop MPO-AAV. The majority of PTU is metabolized in the liver. However, MPO in neutrophils also modifies PTU [23]. We hypothesize that PTU influences the formation or regulation of NETs and induces MPO-ANCA, and subsequently MPO-AAV [5]. We examined whether the addition of PTU created an impact on the formation or regulation of NETs *in vitro*. Widely extended DNA fibers studded with MPO are observed when human neutrophils are treated with PMA alone. To the contrary, treatment with PMA with PTU leads to a rounded-shape distribution of DNA fibers. The ensuing NETs surround dead neutrophils. Although DNase completely digests PMA-induced normal NETs, abnormal NETs induced by PMA with PTU is barely digested by DNase I. These findings clearly indicate that PTU influences NET formation and degradation by DNase I.

DNase I-Resistant NETs Cause ANCA Production

Next, we examined whether the DNase I-resistant NETs induced the production of MPO-ANCA *in vivo*. For this purpose, we generated rodent models. WKY rats and BALB/c mice are given oral PTU with intra-peritoneal injection of PMA [5, 24]. Contrary to the finding that widely extended NETs are observed in the peritoneal tissues of the PMA-injected models without PTU administration (PMA-treated models), NETs in the PMA-injected models with PTU administration (PTU/PMA-treated models) do not extend outward. Those in peritoneal tissues of PTU/PMA-treated models are significantly larger than NETs of PMA-treated models. These findings correspond to *in vitro* data indicating an abnormal conformation and impairment of NETs degradation induced by PMA with PTU. As expected, MPO-ANCA is produced in the PTU/PMA-treated models [5, 24]. Moreover, the amount of NETs in the peritoneal tissues and the titer of MPO-ANCA are significantly decreased when PTU/PMA-treated mice are administered the PAD inhibitor, Cl-amidine [24]. The collective findings clearly indicate that PTU induces the NETs disorder and the subsequent production of MPO-ANCA.

Implications of Disordered NETs in the Pathogenesis of AAV

Although most patients with MPO-AAV are not administered PTU, undetermined environmental factors that act like PTU, such as infectious exposures may induce the disorder of NETs and trigger the MPO-ANCA production resulting in the development of MPO-AAV [25].

NETs-ANCA Vicious Cycle in AAV

Hakkim and colleagues [22] demonstrated that a subgroup of systemic lupus erythematosus (SLE) patients hardly digested NETs because of the low activity of serum DNase I. Similar to SLE patients, serum DNase I activity in AAV is significantly lower than healthy controls [26]. These findings suggest that involvement of the NETs-ANCA vicious cycle in the pathogenesis of AAV (Figure 1).

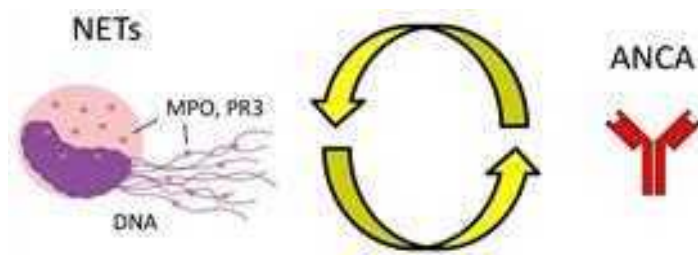


Figure 1. NETs-ANCA vicious cycle in the pathogenesis of AAV. An excessive formation and/or persistence of NETs under low degradation condition can cause ANCA production. Simultaneously, ANCA can induce further NET formation from primed neutrophils.

The Formation of the Pauci-Immune Lesion in AAV

AAV is characterized by necrotizing crescentic glomerulonephritis and SVV. Although the pathogenic role of ANCA in the formation of necrotizing lesions can be demonstrated, there is little deposition of immunoglobulins (Ig) in affected tissues. This histological feature is termed, “pauci-immune”. Futamata and colleagues [27] reported the release of elastase from NET-forming neutrophils, digesting Ig, including ANCA, in pauci-immune lesions in AAV.

CONCLUSION

Neutrophils play a critical role in the pathogenesis of vasculitides, especially AAV. The ANCA-cytokine sequence is pivotal to the etiopathogenesis of AAV. There is an increasing literature supporting the role for an NETs-ANCA vicious cycle in AAV and the related contribution of NETs-ANCA-cytokine sequence theory.

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Chapter 197

COMPLEMENT FACTORS IN ANCA-ASSOCIATED VASCULITIS

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ABSTRACT

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) are potentially life-threatening autoimmune diseases. The histopathological hallmark is a “pauci-immune” necrotizing crescentic glomerulonephritis. It has been assumed that the complement system is not involved in the development of AAV, however, new evidence suggests that the complement system is crucial in the pathogenesis of AAV. This article reviews updated information on clinical, *in vivo* and *in vitro* evidence for the role of complement activation in the development of AAV. Activation of the alternative pathway is crucial for the development of AAV, and the complement activation product C5a plays a central role. Activation of the alternative pathway of complement, at least in part *via* activated neutrophils, results in the generation of C5a, which is a strong chemoattractant for neutrophils. C5a is also effective in neutrophil priming, a process leading to increased membrane expression of the ANCA antigens, enabling neutrophils to be further activated by ANCA. Blocking complement, especially C5, is a potentially promising approach in the treatment of AAV.

Keywords: ANCA, complement, renal, vasculitides

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INTRODUCTION

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) are life-threatening systemic autoimmune diseases, comprising granulomatosis with polyangiitis [GPA, previously named Wegener's granulomatosis (WG)], microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA) [1]. ANCA are serological markers for the abovementioned vasculitides, predominantly IgG class autoantibodies against primary granule constituents of neutrophils and lysosomes of monocytes. By indirect immunofluorescence (IIF) on ethanol-fixed neutrophils, two fluorescence patterns of ANCA are distinguished, a cytoplasmic staining pattern (cANCA) and a perinuclear staining pattern (pANCA). Most patients with a cANCA pattern have ANCA directed against proteinase-3 (PR3) while pANCA is associated with several antigens, in particular, myeloperoxidase (MPO) [2].

Renal involvement occurs frequently in AAV and is histopathologically characterized by pauci-immune necrotizing crescentic glomerulonephritis (NCGN), characterized by little or no glomerular staining for immunoglobulins or complement. It was previously assumed that the complement system was not involved in the development of AAV, however, emerging evidence has suggests that activation of the complement system plays a significant role in the pathogenesis of AAV. This article reviews updated information on clinical, *in vivo* and *in vitro* evidence for the role of complement system in the development of AAV.

THE COMPLEMENT SYSTEM

At the turn of the nineteenth century, the complement system was already considered a major part of the innate immune system and is one of the main effector mechanisms of antibody-mediated immunity. A wide range of its biological activity is due to the cooperation of more than 30 plasma proteins [3, 4]. In humans, the complement can be activated *via* the three pathways: classical pathway, alternative pathway and lectin pathway.

The classical pathway is initialized when C1q binds to antibody attached to antigen, activating C1r and C1s, which cleave C4 and C2. The lectin pathway is activated when mannose-binding lectin (MBL) encounters conserved pathogenic carbohydrate motifs, activating the MBL-associated serine proteases (MASPs) and cleaving C4 and C2 the cleavage products of which form the classical and lectin pathway C3 convertase, including C4bC2a, which cleaves C3 into C3b and C3a. The latter is a chemo-attractant factor while sufficient C3b associates with C4bC2a to form the C5 convertase of the classical and lectin pathways, including C4bC2aC3b.

The alternative pathway is activated when C3 undergoes spontaneous hydrolysis and forms the initial alternative pathway C3 convertase, including C3(H₂O)Bb, in the presence of factors B and D, leading to additional C3 cleavage and eventual formation of both alternative pathway components C3 (C3bBb) and C5 convertase (C3bBbC3b). Properdin facilitates alternative pathway activation by stabilizing alternative pathway convertases.

All three pathways culminate in the formation of the convertases, which in turn generate the major effectors of the complement system that includes among others, anaphylatoxins C4a/C3a/C5a, membrane attack complex (MAC) and the opsonin C3b. Anaphylatoxins are

potent proinflammatory molecules derived from the cleavage of C4, C3, and C5. MAC is the terminal assembly of complement components C5b through C9, which directly lyse targeted surfaces. C3b induces phagocytosis of opsonized targets and also serves to amplify complement activation through the alternative pathway.

Due to the destructive potential of complement activation, especially in light of the potent feedback amplification ability of the alternative pathway, complement activities need to be confined to appropriate pathogenic surfaces. The generation of potent effectors needs to be tightly regulated to prevent collateral damage to healthy host tissues. Several steps are involved in complement activation checked by inhibitors so that the final system represents an intricate, homeostatic balance between the efficient detection and destruction of pathogens and the minimization of bystander tissue damage. Among them, complement factor H (CFH) is a key regulatory component of the alternative complement pathway. CFH impedes the formation of alternative pathway C3 convertases (C3bBb) by competing with factor B for binding to C3b, and accelerates the decay of C3bBb. CFH acts as a co-factor for the factor I-mediated proteolytic inactivation of C3b.

CD46, CD55 and CD59 are major membrane-associated regulators of complement in human cells. CD46 (membrane cofactor protein), is a ubiquitously expressed type 1 transmembrane glycoprotein that acts as a cofactor for factor I mediated cleavage of C3b and C4b, preventing formation of the classical and alternative C3 convertase. CD46 also regulates the amplification loop of the alternative pathway of activation of complement [5]. CD55 (decay accelerating factor) is a glycosylphosphatidylinositol (GPI) anchored protein, which serves to inhibit assembly of new C3 convertases and shorten the half-life of preformed convertases, thereby limiting their ability to participate in further complement activation [6]. CD59 (protectin) is a naturally occurring inhibitor of MAC found tethered to the membranes of cells via a GPI anchor [7].

Additional complement regulators include the above mentioned factor I, which mediates cleavage of C3b and C4b, preventing formation of active convertases; in addition to cofactor activity and surface-expressed complement receptor 1 (CR1). The latter exhibits decay accelerating activity and cofactor activity for factor I. C1 inhibitor, a serine protease that irreversibly binds to and inactivates C1r, C1s, MASP-1, and MASP-2, limits classical and lectin pathway activation, as well as C4-binding protein (C4BP) [8].

CROSS-TALK BETWEEN COMPLEMENT AND OTHER SYSTEMS

Cross-Talk between Complement and the Coagulation System

The complement and coagulation systems have a number of common characteristics and many potential implications for health and diseases. Activation of both systems lead to conversion of zymogens and assembly of proteolytic complexes that are mainly serine protease-mediated activation steps. Recent evidence indicates that some serine proteases, in particular, plasmin and thrombin from the coagulation cascade, directly activate C3 and C5, independent of the traditional C3/C5 convertase, generating biologically active C3a and C5a [9, 10].

The interaction between platelets and complement has important implications for innate immunity especially when the latter is in an activated form [11]. Platelets may express the receptors of C3a and C5a (C3aR and C5aR) [12], while C5b-9 may induce platelets to release α -granules and microparticles [13]. Del Conde and co-workers [14] found that activated platelets activate the complement system which in turn increases C3a generation, C3b deposition, and C5b-9 formation. For detailed information of the interaction between complement and platelets, see the comprehensive review by Speth and colleagues [15].

Cross-Talk between Complement and Pattern Recognition Receptors

Pattern recognition receptors (PRRs) are essential components in the innate immunity, recognizing pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs) [16]. PRRs include Toll-like receptors (TLRs), leucine-rich repeat-containing receptors (NLRPs), nucleotide-binding oligomerization domain (NOD)-like receptors, RIG-I-like receptors, and C-type lectin receptors [17]. Examples of PAMPs include endotoxin or lipopolysaccharide (LPS) of gram-negative bacteria, lipoteichoic acid of gram-positive bacteria, and β -glucan of fungi [18]. The crosstalk starts when MBL binds to common carbohydrate PAMPs on gram-positive and gram-negative bacteria and yeast, as well as viruses and parasites, activating the lectin pathway through the abovementioned chain reaction [19].

Furthermore, substantial studies have revealed more intense interactions between complement and TLRs as well as NLRPs in a variety of inflammatory diseases. For example, Raby and co-workers [20] demonstrated *in vitro* activation of TLRs that mediated the down-regulation of C5a-like receptor 2 (C5L2), thus enhancing C5a-induced inflammatory responses. In a mouse model of polymicrobial sepsis, factor B, which is the unique component of the alternative pathway, acts as a downstream effector of TLR signaling [21].

Cross-Talk between Complement and Adaptive Immunity

The complement system provides a link between innate and adaptive immunity. Complement depletion can impair antibody production, as there might well be a requirement for functional C3 in the induction of thymus-dependent, but not thymus-independent antibody production [22]. The deeper mechanism might involve antigen-bound C3dg, and iC3b cleavage product binding to B-cell-expressed CR2 (CD21), which facilitates antigen presentation to B-cells, lowering the threshold for its activation [23].

There are other unexpected roles for complement as a regulator of T-cell immunity. Immune cells, including T-cells and antigen-presenting cells (APCs), produce alternative pathway complement components during cognate interactions [24]. The subsequent local complement activation yields production of the anaphylatoxins C3a and C5a, which bind to C3aR and C5aR respectively on both partners to augment effector T-cell proliferation and survival, while simultaneously inhibiting regulatory T-cell induction and function [25]. CFH, as an immunological brake, may directly affect the function of adaptive immunity by decreasing the production of key proinflammatory Th1-cytokines, including interleukin (IL)-

12, interferon (IFN)- γ , IL-6 and IL-8, from dendritic cells, while promoting the production of immunomodulatory mediators (IL-10 and transforming growth factor [TGF]- β), impairing effector CD4 (+) T cell alloproliferation and conversely, inducing Foxp3 (+) regulatory T-cells (Tregs) [26]. Figure 1 shows an overview of the complement system and the interactions with other systems.

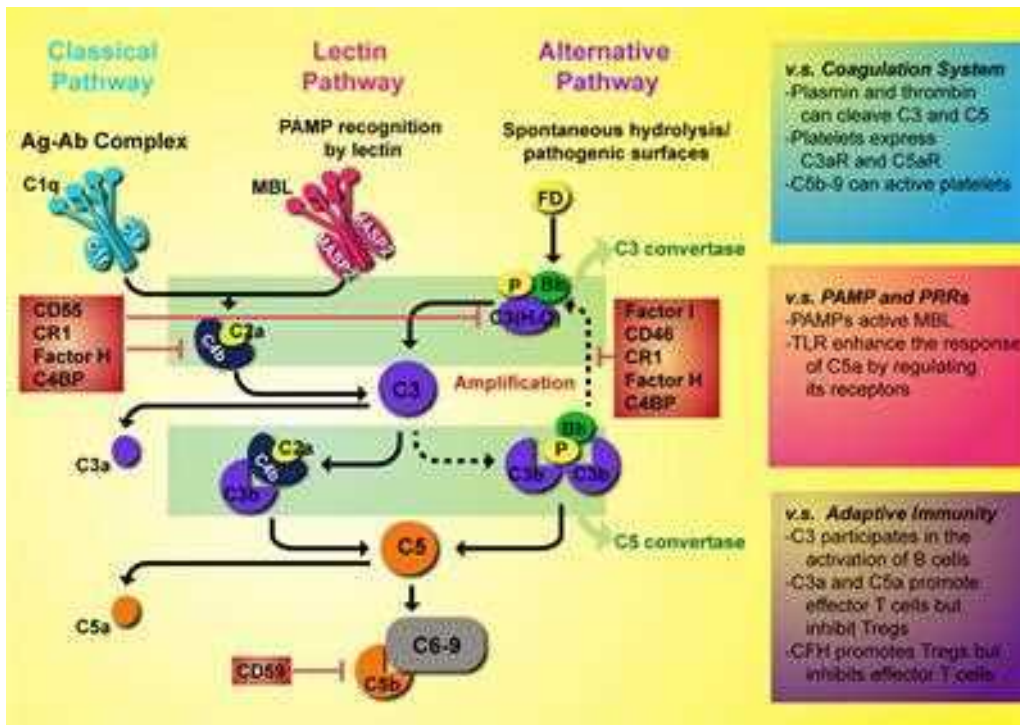


Figure 1. The three pathways of complement activation: the classical, lectin and alternative pathways. There are three pathways of complement activation: the classical, lectin and alternative complement pathways. Activation of the classical pathway begins with the binding of immune complexes to C1q leads to the activation of its C1r and C1s serine protease subunits. Then, C1s activates C4 and C2 and subsequently results in the formation of the classical pathway C3 convertase, C4bC2a. The alternative pathway is initiated by hydrolysis of C3. Factor D cleaves the C3b-bound factor B, resulting in the formation of C3bBb, the C3 convertase. The lectin pathway is activated through the binding of MBL and MASP. MASP can cleave and activate C4 and C2 to form C4bC2a. Activation of any abovementioned pathway leads to activation of C3. Activation of C3 generates C3b and C3a, a chemo-attractant factor. Sufficient activation of C3 leads to the activation of C5. C5 activation leads to the formation of C5a and C5b-9. There are also crosstalk between the complement system and coagulation system, pattern recognition receptors and adaptive immunity.

PATHOGENIC ROLE OF ANCA AND NEUTROPHILS IN AAV

The pathogenesis of AAV is complex as can be appreciated in ANCA-mediated glomerulonephritis, which is attributed to possible infectious mediation and a multistep process that includes recruitment and priming of neutrophils to glomeruli. There, recruited ANCAs initiate injury by activation of primed and adherent neutrophils directly leading to

endothelial injury. ANCA-induced neutrophil activation also causes an inflammatory amplification loop leading to complement activation and generation of C5a that might in turn exert its role the development of AAV [27].

ANCA IN THE PATHOGENESIS OF AAV

The most convincing evidence for the pathogenic role of ANCA comes from animal studies. Xiao and co-workers [28] immunized MPO^{-/-} mice with mouse MPO and obtained MPO-ANCA IgGs or MPO-reacting splenocytes. MPO-ANCA IgGs or MPO-reacting splenocytes were injected into recipient mice. All the mice that received MPO-ANCA IgGs developed pauci-immune crescentic glomerulonephritis. The mice that received high doses of MPO-reacting splenocytes developed severe NCGN with systemic necrotizing vasculitis. Schreiber and co-workers [29] reported a modified mouse model of anti-MPO induced disease, further documenting the pathogenic potential of ANCA. MPO knockout (MPO^{-/-}) mice were immunized with mouse MPO and exposed to irradiation and transplanted bone marrow (BM) cells from either MPO^{-/-} or MPO^{+/+} wild type mice. Transfer of MPO^{+/+} BM cells into irradiated MPO^{-/-} mice led to disease development, while transfer of MPO^{-/-} BM cells into irradiated MPO^{+/+} mice did not, demonstrating that MPO^{+/+} BM-derived cells were pathogenic targets for anti-MPO IgG in the cause of disease. Little and co-workers [30] immunized rats with human MPO, inducing the generation of antibodies against human MPO, cross-reacting with rat neutrophils. Almost all the recipient rats developed pauci-immune glomerulonephritis and pulmonary capillaritis, indicating a direct pathogenic role of ANCA *in vivo*.

In vitro studies have verified the pathogenic role of ANCAs. Neutrophils stimulated by pro-inflammatory factors, especially TNF- α or C5a, target antigens of ANCAs, MPO and PR3, move from the cytoplasm to the cell membrane in a process termed priming. ANCAs combined with their target antigens, and cross-linked with Fc receptors on neutrophils, are induced to undergo a respiratory burst and degranulate, playing a direct pathogenic role in the development of systemic vasculitis [31]. A randomized controlled trial by the European Vasculitis Study Group (EUVAS) [32, 33] showed superiority of plasma exchange (PEX) over intravenous methylprednisolone in restoring renal function, thus supporting a pathogenic role for circulating ANCA in renal vasculitis.

NEUTROPHILS IN THE PATHOGENESIS OF AAV

Investigators [28] reported the development of NCGN in an experimental mouse model of accompanied by glomerular accumulation of neutrophils and macrophages providing direct evidence that neutrophils played a major role in the pathogenesis of anti-MPO-induced NCGN in this animal model and implicated neutrophils in the induction of human ANCA disease. Later studies [34] showed that neutrophil depletion prevented disease development in recipient mice. While pro-inflammatory mediators could prime neutrophils by inducing translocation of more ANCA antigens from the cytoplasm to the cell surface *in vitro*; ANCAs

further activate primed neutrophils to undergo respiratory burst and degranulation, suggesting the pathogenic role of neutrophils in AAV.

One other important mechanism of neutrophil effector function in the development of AAV was reported by Kessenbrock and colleagues [35] who found that ANCA-mediated neutrophil activation induced the formation of neutrophil extracellular traps (NETs), which are fibrous networks containing DNA, histones, and neutrophil granule proteins, triggering vasculitis and promoting the autoimmune response against neutrophil components. Excessive NETs formation was further found to be related to active clinical disease in patients with AAV [36]. NETs could enhance the uptake of ANCA antigens PR3 and MPO by myeloid dendritic cells [37], and activate autoreactive B-cells and ultimately the induction of ANCA [38].

EMERGING ROLE OF THE COMPLEMENT SYSTEM IN THE PATHOGENESIS OF AAV

ANCA-associated glomerulonephritis, characterized by pauci-immune NCGN histopathologically, showed little, if any, immunoglobulin and complement deposition in the glomeruli of AAV patients leading to the initial assumption that the complement system might not be involved in the development of AAV. However, observations in animal models and human disease, as well as increasingly sophisticated mechanism studies *in vitro* and in rodent models *in vivo*, have allowed a more nuanced understanding of complement system in the pathogenesis of AAV.

Evidence from the Animal Studies

Pre-treatment of mice with cobra venom factor to deplete complement, and C5 deficient mice fail to develop glomerulonephritis and vasculitis whereas disease development was comparable to wild type mice in C4-deficient mice, and C5- or factor B-deficient mice were completely protected from the disease [39]. This suggests that complement activation via the alternative pathway of complement system is critical to the development of AAV. The importance of inflammatory cell activation by C5a in amplifying the anti-MPO IgG-induced inflammatory response, was later appreciated. Huugen and colleagues [40] found that pretreatment with anti-C5 inhibiting monoclonal antibody prevented or strongly attenuated the development of ANCA-associated glomerulonephritis in mice. Schreiber and co-workers [41] investigated the role of the C5aR (CD88) in a model of ANCA-induced NCGN noting that C5aR-deficient mice were protected from developing NCGN. Xiao and investigators [42] further elucidated the role of C5a and its receptors in a mouse model of anti-MPO-induced NCGN, noting that CD88 deficiency ameliorated the disease, while C5L2 deficiency resulted in more severe disease. This indicated that CD88 enhances, while C5L2 suppresses, the inflammatory reactions. A recent study by Dick and co-workers [43] delineated the a role of CD88 in the generation of anti-MPO autoimmunity, and effector responses that resulted in renal injury by employing an experimental active autoimmunity to MPO by an anti-GBM

globulin trigger model, however the pathological changes were prevented by CD88 inhibition.

Evidence from Human Studies

Several studies found a certain degree of immune complex and complement C3c deposition, which correlated with poorer renal function [44, 45]. Chen and colleagues [46] analysed renal biopsies in 112 patients with ANCA-associated pauci-immune glomerulonephritis noting that C3c could be detected in glomeruli of a third of specimens. However, the intensity of C3c deposition was mild to moderate, and patients with C3c deposition had more severe lesions in the kidneys than those without C3c deposition, along with higher levels of proteinuria, poorer renal function at presentation, higher percentage of crescents and more severe tubulointerstitial lesions.

Scaglioni and co-workers [47] found that 26.4% of patients with ANCA-associated glomerulonephritis were actually not pauci-immune, and immune deposits were associated with higher proteinuria. Researchers investigated various components of complement in kidney specimens of patient. Xing and coinvestigators [48] found that C5b-9, C3d, and factor B, but not C4d, could be detected in the renal specimens; while C3d and factor B co-localized with C5b-9 in active glomerular lesions. The deposition of Bb, a marker of the alternative complement pathway activation in glomeruli of AAV patients correlated positively with the proportion of crescents, the extent of interstitial infiltrates, interstitial fibrosis and tubular atrophy; and negatively with the proportion of normal glomeruli [49]. Similar results were found in a study by Hilhorst and colleagues [50] who analyzed 187 renal biopsies of ANCA-associated pauci-immune glomerulonephritis detecting C3c, C3d, C4d and C5b-9 in the majority of tissue specimens. C3d and properdin staining were particularly associated with the proportion of cellular crescents, and presence of properdin correlated with the level of proteinuria. The staining of the two receptors of C5a, including CD88 and C5L2, were noted mainly on infiltrating neutrophils and macrophages in kidney specimens of patients with AAV. The staining of CD88 was down-regulated, while the staining of C5L2 was up-regulated, and that of CD88 was associated with initial renal function and the extent of interstitial fibrosis [51]. Given that CD88 can be rapidly internalized after the interaction with C5a [52], the down-regulation of CD88 in renal biopsies of AAV might be a result of C5a-mediated internalization and contribute to the self-protection mechanism to alleviate the C5a-mediated inflammation [51].

Besides the components of complement deposited in kidneys, Gou and co-workers [49] studied urinary levels of various components of complement in AAV patients noting that urinary levels of Bb, C3a, C5a and C5b-9 in active stage of AAV were higher than those in remission. In particular, correlation analysis showed that in patients with active AAV, urinary levels of Bb correlated with disease severity, including initial serum creatinine and the proportion of normal glomeruli in renal specimens. Circulating levels of various components of complement in AAV were also detected and similar circumstances were found in the circulation of AAV patients. Plasma levels of C3a, C5a, soluble C5b-9 and Bb were also elevated, while plasma levels of properdin were lower in active AAV compared to the remission phase. Plasma levels of C4d did not significantly differ between the active and

remission stages. Disease activity was related to plasma levels of Bb, the proportion of crescents in the renal specimen, erythrocyte sedimentation rate (ESR), and the Birmingham Vasculitis Activity Score (BVAS) [53].

Other studies [54-57] examined serum C3 and C4 levels in those with hypocomplementemia at diagnosis of AAV, noting a worse prognosis when present. A study by Manenti and colleagues [58] that included 46 patients with AAV, observing that 8 out of 30 renal biopsies had evidence of a thrombotic microangiopathy (TMA), similar to a large-Chinese cohort [59]. Manenti and colleagues [58] also noted that 35% of patients had a decreased C3 level in the circulation, and a low C3 level was associated with decreased renal survival and the presence of TMA.

Using proteomic analysis by mass spectrometry, Sethi and co-workers [60] found amounts of C3 and moderate amounts of C9, implicating activation of the alternate and terminal pathway of complement in pauci-immune NCGN with negative ANCA serology, suggesting that its cause may be promoted by a genetic or acquired defect in the alternative complement pathway.

CFH, which is a key regulator of the alternative complement pathway, inhibits amplification of the complement cascade both in the fluid phase and on host cell surfaces. Quantitative deficiency or impaired function of CFH, resulting in dysregulation of the alternative complement pathway, is involved in the pathogenesis of several autoimmune diseases, including TMA and C3 glomerulopathy [61-63]. Chen and colleagues [64] found that plasma CFH levels in active AAV patients were lower than those in remission, and related to parameters of disease activity, including BVAS, initial serum creatinine, and proportion of crescents in renal specimens. In multivariate survival analysis, plasma CFH levels were independently associated with the composite outcome of end stage renal disease (ESRD) and death. The functional activities of CFH including its interaction with, and the regulation of C3b; binding to mCRP and endothelial cells, and rendering of protection of host cells against complement attack, are all impaired in AAV patients [65].

Cheng and colleagues [66] reported that the expression levels of CD46, CD55 and CD59, the three major membrane associated regulators, were dysregulated in kidneys of patients with AAV, and associated with the severity of renal injury of AAV patients.

Evidence from *In vitro* Studies

Among the various components of the complement system, C5a plays a central role in the pathogenesis of AAV. Schreiber and co-workers [41] found that recombinant C5a dose-dependently primed neutrophils for an ANCA-induced respiratory burst. At the cellular level, activation of p38 mitogen-activated protein kinase (p38MAPK), extracellular signal-regulated kinase (ERK), phosphoinositol 3-kinase (PI3K) and protein kinase C (PKC) pathways were all indispensable steps in the translocation of ANCA antigens and activation of neutrophils by ANCA [67, 68].

Among the two receptors of C5a, CD88 contributes to the initiation of acute inflammatory responses, such as the respiratory burst and chemotaxis, while the function of C5L2 remains more controversial. C5L2 may function as a “default” or “scavenger” receptor, by competing with CD88 for binding of C5a [69, 70]; and a proinflammatory role for C5L2

has been suggested [71, 72]. By blocking C5L2 with neutralized antibodies, Hao and co-workers [73] found that C5a primed neutrophils could be mitigated, as well as the ANCA-induced C5a-primed neutrophils respiratory burst and degranulation, suggesting C5L2 might also play a pro-inflammatory role in C5a-primed neutrophils in ANCA-induced activation. However, that premise was inconsistent with the findings of Xiao and colleagues [42] who demonstrated that knockout of C5L2 was associated with more severe disease.

The reason for discrepancies in the function of C5L2 in AAV is not well understood but may be related to different *in vitro* and *in vivo* experimental environments, and differences in human and murine models of disease. Moreover, the function of C5L2 may be different in various cells, species, and disease contexts [74]. Whether C5L2 plays a pro- or anti-inflammatory role in the development of AAV will require further investigation.

Two key down-stream molecules, sphingosine-1-phosphate (S1P) and high mobility group box 1 (HMGB1), appear to play important roles in the cellular and molecular mechanisms of neutrophil activation by C5a. As a potent bioactive sphingolipid metabolite, S1P can regulate a number of cellular processes in autoimmune disorder [75-77], and participates in the regulation of the balance between expression of CD88 and C5L2 in endotoxin-induced lung inflammation [78]. According to Hao, and Sun and colleagues [79, 80] plasma levels of S1P are elevated in the active stage of AAV; and S1P is released from neutrophils in an autocrine or paracrine manner upon the C5a-priming process, which further activates neutrophils and injure glomerular endothelial. S1P may up-regulate the expression of CD88 on the surface of neutrophils, and blocking S1P receptors could attenuate activation of C5a-primed neutrophils by ANCAs and exert a protective effect in endothelial injury.

HMGB1 exists within the nucleus ubiquitously, but it becomes a pro-inflammatory mediator when released extracellularly [81]. Circulating and urinary levels of HMGB1 are associated with disease activity in AAV [82, 83], and HMGB1 could prime neutrophils by increasing translocation of the ANCA antigens PR3 and MPO. These primed neutrophils may be further activated by ANCAs, resulting in the respiratory burst and degranulation of neutrophils, and the formation of NETs [84, 85]. During the process of C5a priming, HMGB1 may be released from the neutrophil cytoplasm into the extracellular space, further enhancing the effects of C5a on neutrophil activation. Blocking HMGB1 could mitigate C5a-mediated translocation of ANCA antigens, and ANCA-induced respiratory burst and degranulation of C5a-primed neutrophils [86]. HMGB1 could exert its direct or indirect role on the endothelial injury in the presence of ANCAs [87, 88]. Hence the interactions between S1P and C5a, as well as HMGB1 and C5a, play a notable role in neutrophils for ANCA-mediated activation.

Complement activation could lead to the activation of neutrophils and further activate the complement system especially via the alternative pathway. In the study by Xiao and co-workers [39] supernatant from human neutrophils stimulated with ANCAs activated complement in normal human sera, a finding indicating that ANCA-activated neutrophils may release certain substances that subsequently activate the complement system. Camous and colleagues [89] demonstrated that activated neutrophils could further activate the alternative complement pathway via their cell membranes and microparticles.

Leffler and colleagues [90] discovered that NETs could activate the complement system via the classical pathway by the interaction with C1q. Wang and co-workers [91] noted that NETs released from ANCA-activated neutrophils could activate the complement system via the alternative pathway. Schreiber and colleagues [92] observed that NETs provided a scaffold for alternative pathway activation that in turn contributed to endothelial cells

damage. They further established the *in vivo* relevance of NETs and the requirement of RIPK1/3/MLKL-dependent necroptosis for disease induction using both murine AAV models and in human kidney biopsies.

An *in vitro* study by Chen and coinvestigators [93] revealed pathophysiological mechanisms of CFH in the pathogenesis of AAV. On one hand, CFH inhibited ANCA-induced neutrophil activation by interacting with neutrophils and protected against glomerular endothelial injury, indicating a deficient function of CFH from patients with active AAV in their ability to bind neutrophils and inhibit neutrophil activation by ANCAs. On the other hand, MPO, which could be released from ANCA-stimulated neutrophils, influenced the complement regulatory activity of CFH [94]. Those would contribute to better understanding of complement system in the pathogenesis of AAV.

EVIDENCE OF CROSS-TALK BETWEEN COMPLEMENT AND OTHER SYSTEMS IN AAV

Cross-Talk between Complement and Coagulation System in AAV

The complement and coagulation systems have a number of common characteristics and have many potential implications for health and diseases.

Several studies have reported that patients with AAV are in a hypercoagulable state, with an increased risk of developing venous thromboembolic events (VTEs) [95-97], indicating the involvement of coagulation system in AAV. C5a was found to induce expression of tissue factor (TF) on neutrophils and endothelial cells, thus triggering the extrinsic coagulation system [98, 99]. Huang and colleagues [100] found that stimulation of neutrophils with C5a and ANCAs not only resulted in the respiratory burst and degranulation, but also led to release of TF bearing microparticles and NETs; and subsequently activated the coagulation system and thrombin generation.

Platelet counts are usually elevated in patients with active AAV. Willeke and co-workers [101] found that platelet counts correlated with disease activity in AAV, while Miao and colleagues [102] demonstrated that platelets were activated in AAV via thrombin-PARs pathway, and could activate the alternative pathway of complement, further enlightening the connection between the complement system and platelets.

Cross-Talk between Complement and TLRs in AAV

In an animal model of MPO-AAV mediated by passive transfer of anti-MPO antibodies, LPS can aggravate the disease via a TLR4 dependent manner [103]. Wang and colleagues [104] investigated the renal expression of TLRs in kidneys of patients with AAV by immunohistochemistry noting that expression of TLR2 and TLR4 was up-regulated in AAV, while that of glomerular TLR4 was inversely related to baseline serum creatinine and the proportion of crescents. HMGB1 is a typical ligand of TLR2 and TLR4. The interaction of HMGB1 and C5a likely plays an important role in ANCA-induced neutrophil activation [86]

like that of both complement and TLRs in AAV. The role of PRRs other than TLRs have received little attention in AAV.

Cross-Talk between Complement and Adaptive Immunity in AAV

The study by Dick and colleagues [43] revealed the genetic absence or pharmacological inhibition of CD88 resulting in reduced autoimmunity to MPO, with an attenuated Th1 response, increased Tregs, and reduced generation of MPO-ANCA.

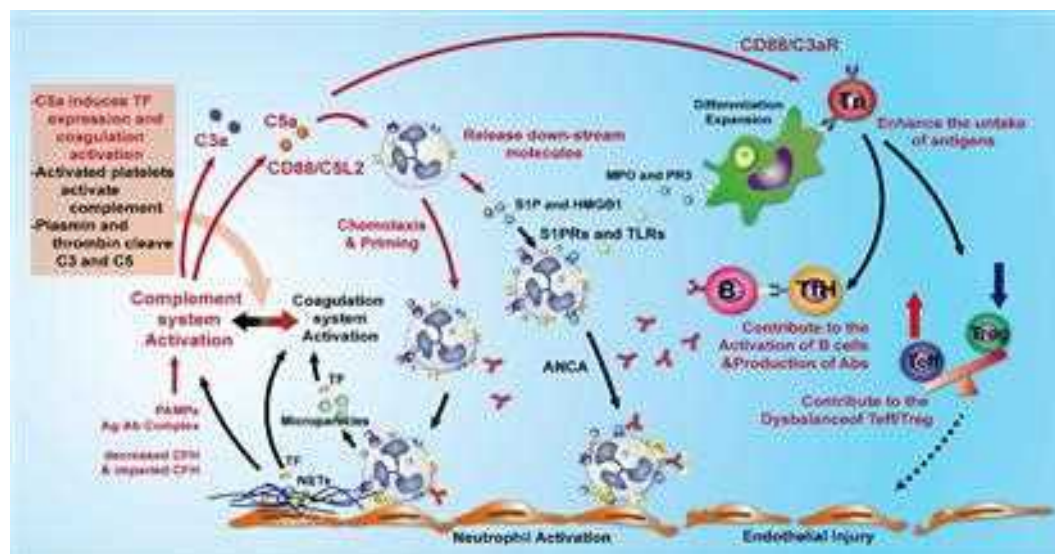


Figure 2. The roles of complement system in a proposed working model showing the pathogenic events of ANCA-associated vasculitis.

One other study using murine models of MPO-AAV by the same author [105] found that C3aR did not alter histological disease severity. However, it promoted macrophage recruitment to the inflamed glomerulus and inhibited the generation of MPO-ANCA while not influencing T cell autoimmunity. Thus, complement activation, especially via the alternative pathway, plays an important role in the pathogenesis of human AAV, indicating potent and promising intervention targets for management of patients with AAV and ameliorating the course of ANCA-mediated disorders. Figure 2 shows the pathogenic role of complement in the pathogenesis of AAV.

IMPLICATIONS FOR MANAGEMENT OF PATIENTS WITH AAV

As progress is made in understanding the molecular pathogenesis of this disease, new targets will be found for potential therapeutic attack, including targeting C5, C5a/C5aR, C1 and C3. Eculizumab, the first available anti-complement treatment, is a fully humanized recombinant monoclonal antibody that binds C5 with high affinity. Eculizumab efficiently blocks C5 cleavage and prevents the formation of C5a and C5b-9 [106]. Several well-

designed studies have demonstrated the therapeutic efficacy of eculizumab in paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic-uremic syndrome (aHUS) [107-109], leading to approval of eculizumab for these indications by the FDA. Subsequent small-scale studies and case reports have studied eculizumab in other renal diseases, including C3 glomerulopathy, IgA nephropathy, resistant lupus nephritis and anti-phospholipid antibody syndrome [110-113], but not in cases of AAV.

Castellano and colleagues investigated C1 inhibition in renal ischemia-reperfusion injury using a swine model [114]. The infusion of C1-inhibitor led to reduced deposition of various complement activation products in glomerular and peritubular capillaries, and reduced the number of infiltrating inflammatory cells. Several clinical trials of C1 inhibition in renal transplantation are ongoing [(NCT01147302, NCT01134510 and NCT02134314)].

Paixão-Cavalcante and colleagues [115] reported a humanized monoclonal antibody binding to C3 that inhibited C3 cleavage by the nephritic factor-stabilized convertase. Zhang and co-workers [116] employed soluble CR1 therapy in C3 glomerulopathy noting that it prevented the dysregulation of the alternative pathway C3 convertase.

Blocking of C5aR has been regarded as a novel therapeutic target for the treatment of patients with AAV. A multicenter phase 2 randomized, double-blinded placebo-controlled trial led by the EUVAS evaluated the efficacy and safety of CCX168 (avacopan), a small molecule that blocks CD88 (ClinicalTrials.gov Identifier: NCT01363388) among 67 patients randomly divided into three arms: (1) prednisone 60 mg/day; standard of care control, (2) CCX168 30 mg twice a day plus prednisone 20 mg/day; and (3) CCX168 30 mg twice a day without prednisone. All patients received intravenous cyclophosphamide (15 mg/kg per 2 to 4 wks) or rituximab (375 mg/m² intravenous weekly for 4 weeks). The primary end point at 12 weeks was reached in 70% of patients in the control group, 86% of patients in the reduced-steroid group, and 81% of patients in the avacopan plus placebo group, demonstrating noninferiority for both avacopan groups. There were no apparent differences in the response rates with respect to disease category or ANCA type. However, assessment of the change in BVAS and urinary albumin to creatinine ratio suggested that patients in the avacopan groups had a more rapid and consistent improvement in the study parameters by 4 weeks. Quality-of-life indicators were improved with the steroid-free protocol. The incidence of total and serious adverse events was similar in the three arms suggesting that C5a receptor inhibition with avacopan was effective in replacing high-dose glucocorticoids in treating vasculitis [117]. A phase 3 randomized trial was launched (ClinicalTrials.gov Identifier: NCT02994927) to include patients with AAV and eGFR $\geq$ 15 ml/min/1.73 m² with sustained remission as an end-point.

Other agents that target complement include TP10, which is a C3 soluble complement receptor; and two inhibitory peptides of C3: AMY-101 and compstatin; and small molecule factor D inhibitors to block complement activation. Although there are trials of the treatment of C3 glomerulopathy, TMA and IgA nephropathy, there are none so far in AAV [118].

CONCLUSION

In conclusion, activation of the complement system, especially the alternative pathway, plays a central role in the development of AAV. Among various components of the

complement system, C5a plays a central role priming neutrophils to undergo the respiratory burst with degranulation and release of NETs in the presence of ANCAs, and contributing to the development of systemic vasculitic lesions. The stimulation of neutrophils with C5a in conjunction with ANCAs leads to the release of TF-bearing microparticles and NETs that subsequently activate the coagulation system and generate thrombin. Neutrophils, ANCA and complement system form a positive feedback loop and lead to the development of AAV. The inhibition of complement, especially C5a, is a promising approach for remission induction in AAV. However, whether the same mechanism can also maintain long term remission through control of neutrophil activation remains to be explored.

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Chapter 198

EXPERIMENTAL AUTOIMMUNE VASCULITIS: INSIGHTS INTO HUMAN VASCULITIS USING ANIMAL MODELS

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ABSTRACT

Over the last decade several different experimental models have been described that try to recapitulate the clinical features of ANCA associated vasculitis. Although all are limited to some extent in their ability to mirror human disease, together they have provided important and sometimes unexpected insights into disease pathogenesis, as well as new avenues for therapeutic innovation.

Rodent models of both MPO-, and more recently, PR3-ANCA associated vasculitis have replicated some of the clinical features found in affected patients with ANCA-associated vasculitis (AAV), notably with pulmonary and renal involvement. The vast majority of successful work in this field has concerned MPO-AAV, yet there remains the need for a better model for aspects of PR3-AAV, including the granulomatous lesions found in granulomatosis with polyangiitis, and the relapsing nature of the illness. By virtue of the means by which they are induced and their time course, such experimental animal models have not replicated the complex and varied human disease AAV phenotype. However, the effector pathways and the final organ damage appear very similar to those found clinically, allowing many conclusions to be drawn regarding disease etiology. This chapter reviews the salient experimental animal models that replicate the vasculitic lesions in human AAV. Further refinement of these models may yield the full spectrum of the human condition, providing insight regarding organ tropism and therapeutic targets for disease subtypes.

Keywords: vasculitis, ANCA, animal, models

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INTRODUCTION

Anti-neutrophil cytoplasm antibodies (ANCA) are associated with diseases characterized by relapsing necrotising vasculitis of small calibre blood vessels, frequently involving the kidneys and lungs respectively leading to pauci-immune glomerulonephritis and pulmonary capillaritis.

Many organs may be affected and, as a result, the conditions cause significant morbidity and mortality. The precise disease triggers are not known, but clinical associations with infection have been reported, with experimental data implicating altered responses to microorganisms as potentially important initiators of autoimmune responses.

ANCA are directed towards two autoantigen, proteinase 3 (PR3) and myeloperoxidase (MPO), found in neutrophil granules and monocyte lysosomes that are involved in innate immune responses to infection, while the clinical significance of other proposed ANCA targets, including lysosome associated membrane protein (LAMP)-2 [1] and moesin [2] remain to be completely characterised. The ANCA-associated vasculitides (AAV) are more common in older age and although they can be treated with immunosuppressive therapies, the disease relapses in up to 50% of treated patients and with re-treatment, there is the increased likelihood of treatment related adverse events.

Animal models of experimental autoimmune vasculitis (EAV) have been developed to dissect the pathological basis of disease, to understand the role of ANCA in the etiopathogenesis of AAV, and to replicate the clinical features. The use of murine models has been favoured because they allow the use of genetically altered animals so that key molecules and pathways involved in pathogenicity can be investigated.

The most novel insight gained from such an approach was the discovery the importance of the alternate complement pathway employing passive anti-MPO antibody transfer in C5 and factor B deficient animals [3], a finding that later prompted a therapeutic trial targeting complement C5a receptor as adjunctive therapy in patients with AAV and renal disease.

Development of adequate models has taken considerable time, with many attempts and refinements over the years. There remain major deficiencies in modelling granulomatous PR3-AAV, relapsing disease overlap syndromes and non-pulmonary-renal involvement such as cardiac, neurological and gastrointestinal disease.

Moreover, the impact of age and immune senescence, infectious triggers, and latent viral infections on disease susceptibility and initiation need further exploration. The inability to model PR3-AAV in mice is in part due to differences between human and rodent neutrophil PR3 expression.

These important omissions and differences should lend some caution to translating the findings from one animal model to all forms of human AAV. PR3-and MPO-AAV may have certain common features, such as the occurrence of pauci-immune glomerulonephritis and pulmonary capillaritis, but they also display many diverse characteristics that translate into important differences in disease phenotype and outcome.

These in turn influence the long-term clinical management. Moreover, genetic studies that demonstrate the differing molecular associations of PR3- and MPO highlight the necessity of considering the two entities separately.

MODELS OF MPO-AAV

There have been many historical attempts at developing models of MPO-AAV, but most have failed to mirror the clinical findings, as they were associated with significant immune complex deposition, a major deviation from the pauci-immune characteristics of clinical disease. Spontaneous models of crescentic nephritis and vasculitis characterised by the presence of circulating MPO-ANCA have been reported, for example the spontaneous crescentic glomerulonephritis/Kinjoh (SCG/Kinjoh) mice. However, they are not pauci-immune and have an array of other autoantibodies besides MPO-ANCA [4]. Significant advances were made in this field through use of knockout and genetically manipulated mice strains, in particular rat strains inherently susceptible to glomerulonephritis. Those strategies included the passive transfer of pathogenic antibody, which proved useful in modelling the acute vascular injury response, and active immunization with MPO that resulted in activation of both humoral and cellular immune elements, consequently providing more insight into the adaptive autoimmune response and potential responses to novel therapies.

Murine Models

Xiao and colleagues [5] developed an acute passive transfer model using purified antibody or splenocytes taken from MPO-deficient mice immunized with purified murine MPO. This took advantage of the allo-immune response to MPO in MPO-deficient mice, generating antibodies and lymphocyte responses that were sufficiently potent to induce disease. Anti-MPO antibodies injected into wild type or RAG-deficient recipient mice led to development of necrotizing pauci-immune glomerulonephritis, and in some cases, pulmonary capillaritis over 6 to 13 days. It was further noted that splenocytes transfer recipients developed glomerular immune deposits, whereas antibody transfer recipients remained pauci-immune. Virtually all subsequent work was conducted with the model that used a passive transfer strategy even though the degree of induced disease was much milder.

The development of glomerulonephritis using cell transfer was dependent on B-cells rather than T-cells, and required the presence of neutrophils [6]. This model was replicated at other centres and further refined to produce augmented disease through the addition of lipopolysaccharide (LPS) [7], mimicking the effects of infection, and exacerbating autoimmunity via toll like receptor (TLR) activation and up-regulation of tumour necrosis factor- α . Further investigation of the model using different mouse strains, demonstrated that the genetic background of the mice had a profound effect on the severity of the model, with 129S6 mice developing worse crescentic disease than C57BL/6 mice in which the model was first generated [8], and with augmented pulmonary-renal disease in the absence of the inhibitory Fc γ -II receptors [9]. That model demonstrated a critical role for alternative, but not classical, complement components in disease induction [3], which was surprising given the lack of clinical evidence of complement consumption in AAV. Since the available small molecule inhibitors of C5a receptor were only active against the human form of the receptor, Xiao and colleagues [10] adapted the murine anti-MPO transfer model by generating mice transgenic for the human C5a receptor allowing them to test the inhibitor in the murine model and demonstrate its efficacy in reducing renal disease.

A subsequent human trial using this C5a receptor antagonist in treatment of AAV was initiated [11]. Further modifications of this model used a bone marrow transplant approach in which immunization of MPO-deficient mice with murine MPO, were subjected to lethal irradiation followed by transfer of either MPO-expressing or MPO-deficient bone marrow.

MPO expression on hematopoietic cells was necessary for disease induction [12], as only transfer of MPO-sufficient cells resulted in disease manifested as necrotizing glomerulonephritis. With various refinements, this model [5] revolutionised the understanding of the mechanisms of acute anti-MPO induced vascular injury. However, all of the model variations had limitations, as these were not autoimmune in nature, but relied instead on alloimmune responses to MPO. Comparisons of the avidity of alloimmune anti-MPO antibodies and other autoimmune ones formed by immunizing WT mice with MPO have not been reported, although it is suspected that there would be significant differences reflecting the propensity for disease induction with this model compared to previous failed attempts by direct MPO immunization. Furthermore, as with all induced models, they begin downstream of the break in clinical immune tolerance with a pre-formed anti-MPO antibody, restricting some of the potential insights into clinical disease initiation. A slightly different strategy for modelling MPO autoimmunity was adopted by Ruth and co-workers [13]. The investigators [13] immunized C57BL/6 mice with MPO in adjuvant, both human and murine, generating cellular and humoral anti-MPO responses, followed by low dose sub-nephritogenic nephrotoxic serum to induce a local renal immune response within glomeruli. In contrast to the passive MPO model, this technique depended upon T-cell and not B-cell immunity. Effector CD4⁺ cell depletion attenuated crescentic glomerulonephritis and effector cell influx without altering ANCA titers. However, B cell-deficient mice, with no ANCA, still developed severe crescentic glomerulonephritis with accumulation of effector cells [13]. The proposed explanation of the model was that it relied upon deposition of MPO in the glomerular circulation following neutrophil migration and de-granulation in response to deposited nephrotoxic serum. There was in turn a subsequent adaptive cellular immune response towards the deposited MPO already induced by the prior immunization of MPO in adjuvant. This model was used by Gan and colleagues [14] to illustrate the importance of the key Th17 effector cytokine IL-17A. To test whether IL-17A also drives autoimmune delayed-type hypersensitivity in the kidney, the investigators [14] injected MPO into the kidneys of MPO-sensitized mice noting that IL-17A deficiency reduced accumulation of renal macrophages and renal CCL5 mRNA expression, lending support to the clinical findings of elevated IL-17 levels in patients with acute and more severe disease in AAV [15]. This model also demonstrated the importance of innate immune pathway stimulation as a co-stimulus for disease induction as well as the pathogenic role of TLR in initiating autoimmune AAV in a series of experiments in which TLR-2 induced Th17 CD4 cells while TLR-9 directed vasculitis by enhanced Th1 autoimmunity [16]. These observations were likely due in part to the mimicking influence of infection and TLR signalling on development of ANCA autoimmunity and organ related disease leading to glomerulonephritis.

Rat Models

A model of MPO-AAV was developed by immunization of a susceptible Wistar-Kyoto (WKY) rat strain with human MPO, in Complete Freund's adjuvant (CFA).

This approach resulted in generation of MPO-ANCA and MPO-reactive T-cells [17] with development of a crescentic, pauci-immune glomerulonephritis, and pulmonary capillaritis in a proportion of treated animals (Figure 1) [18]. The induced anti-human MPO antibodies cross-reacted with rat MPO, displaying significant homology to the human molecule.

Although ANCA-IgG was not found to transfer disease in this model, it did increase leukocyte-endothelial interaction [19], and clearly showed that the composition of the adjuvant providing the innate immune stimulation and the genetic background of the rat were critical to the determination of severity and disease susceptibility. Lewis rats, which share the same MHC Rt1 locus as the WKY strain, do not develop vasculitis or glomerulonephritis despite achieving similar levels of anti-MPO antibodies, demonstrating that non-MHC genes are important in mediating the pathogenic potential of MPO-ANCA.

The significant genetic differences conferring susceptibility to other forms of glomerulonephritis including nephrotoxic nephritis and anti-glomerular basement membrane disease, in these rats has been described, largely related to differences in macrophage reactivity and Fc receptor activation [20].

The role of certain genetic loci as susceptibility factors in the MPO-AAV model and resulting disease severity was examined using congenic Lewis/WKY animals demonstrating the critical role of chromosome 13 and 16 susceptibility loci in the development of experimental autoimmune vasculitis [21].

While the murine T-cell mediated model implicates deposited MPO directing a delayed type hypersensitivity response within the kidney, it does not appear to be the main mechanism in the rat MPO autoimmune model [18] as there is no evidence of deposited MPO.

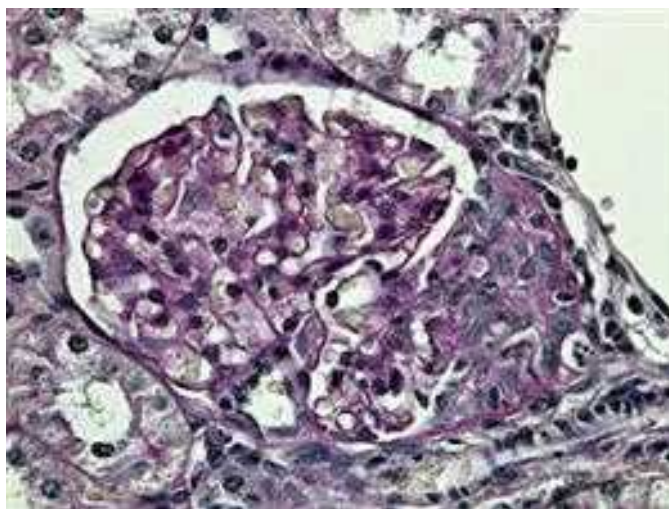


Figure 1. Photomicrograph of a single glomerulus from a rat with experimental autoimmune vasculitis demonstrating crescentic change (PAS x400).

Experimental animal models of vasculitis that may be contrived or manipulated to produce the desired phenotype do not necessarily have to be mediated through identical pathways. MPO-ANCA induced in MPO deficient animals by an alloimmune anti-MPO response may be very different from the autoimmune anti-MPO response.

Indeed, it is now appreciated that there is significant heterogeneity in anti-MPO antibodies found in patients with different epitope reactivity and with interference of immune reactive sites under certain circumstances [22]. It would therefore be of interest to investigate the differences between induced anti-MPO antibodies from different rodent models. Epitope differences may contribute to why the model cannot be transferred with anti-MPO T-cells. This may relate in part to the short duration of follow up in comparison to the immunized rat model, which takes four or more weeks to develop similar glomerular lesions.

In the combined anti-MPO/nephrotoxic nephritis model, the anti-MPO response is a recall response in a previously immunized animal.

When considered together, the rodent models demonstrate that vasculitis, as manifested by pulmonary and renal disease, may be induced when a sufficient anti-MPO immunity threshold is achieved. Patients rarely display an exclusively T- or B-cell response, or a uniquely innate or adaptive immune response.

Rather, the observed disease represents the sum of these different pathways. Reductionist models can provide critical insights into individual mechanisms or pathways of disease induction, even though they may be incapable of defining them all. In particular, none of the models currently explains why or how immune tolerance to self-antigens is broken in the first instance, with later destructive anti MPO reactivity.

RODENT MODELS OF PR3-AAV

There have been no spontaneous experimental models in rodents of glomerulonephritis or vasculitis in association with anti-PR3 antibodies, nor PR3-ANCA in association with other autoantibodies. This is likely related to differences between humans and rodents in PR3 and its cellular expression. Despite immunizing rats and mice with combinations of human or murine PR3, chimeric molecules, and demonstrating induction of PR3-ANCA, van der Geld and colleagues [23] were unable to experimentally generate vasculitis. Pfister and colleagues [24] immunized PR3- and neutrophil elastase-deficient mice with murine PR3, transferred the resultant antibodies into LPS-primed mice, and did not observe significant renal or pulmonary pathology. There was a mild increase in panniculitis following intradermal TNF injection and PR3-ANCA transfer compared to controls. Primo and colleagues [25] described the successful transfer of PR3-ANCA producing splenocytes isolated from recombinant murine PR3-immunized autoimmune-prone non-obese diabetic (NOD) mice into naïve NOD-severe combined immunodeficient (SCID) recipients lacking endogenous T-cells and B-cells.

The immunized NOD mice developed PR3-ANCA without apparent disease despite prolonged follow up while the NOD-SCID mice that received PR3-reactive splenocytes rapidly developed signs of disease with vasculitis and necrotizing crescentic glomerulonephritis. Moreover, there were no granulomata observed despite significant anti-PR3 immune reactivity; and C57BL/6-RAG mouse recipients of the same splenocytes did not develop disease.

These findings suggested that there were protective mechanisms operating in immunized NOD mice mediated by regulatory lymphocyte populations, while the genetic background and degree of immunodeficiency appeared to play an important role in disease susceptibility. In the successful anti-MPO splenocyte transfer model of Xiao et al. [5], the recipient strain was C57BL/6-RAG2^{-/-} further underscoring the difference between MPO and PR3 immunity. The presence of glomerular immune deposits was not discussed in the report by Primo and colleagues [25]. Their results were of limited applicability to human anti-PR3 associated AAV. Relle and colleagues [26] successfully created transgenic FVB mice that expressed human PR3 into which they infused monoclonal anti-PR3 antibodies.

However, expression of PR3 was under the control of the promoter meaning that protein was expressed only in glomeruli. Not surprisingly, they [26] did not detect any pathological features of vasculitis as the current AAV paradigm for pathogenesis proposes interaction of the antibody with PR3 on neutrophils and monocytes, not glomerular cells, with resultant activation of these cells and bystander microvascular injury.

One hallmark of ANCA vasculitis is that the glomerular lesions are pauci-immune, meaning that there is little or no local glomerular immune complex formation. One wonders whether different results would have been obtained if human PR3 had been expressed on the surface of myeloid cells, although it is likely that one would need to link it to other membrane bound proteins such as CD177 to see the intracellular effect of ANCA binding.

Little and co-workers [27] recently described the use of humanized immunodeficient NOD SCID IL2-receptor knockout mice, which received human hematopoietic stem cells and developed a human-mouse chimeric immune system. These mice developed mild glomerulonephritis and lung hemorrhage without evidence of granulomata following passive transfer of PR3-ANCA containing IgG derived from patients with severe systemic vasculitis.

These exciting developments open the way for further investigation of pathogenic mechanisms and definition of immune requirements for the induction of anti-PR3 associated vasculitis.

CONCLUSION

By inducing an abnormal immune response to MPO, investigators have succeeded in generating pathological changes in mice and rats that mimic human MPO-ANCA-AV, although most models exhibit much milder disease than that usually seen in patients. Passive transfer of pathogenic antibody has proven a useful tool for investigating the molecular mechanisms underlying acute vascular injury, and supports the concept that anti-MPO antibodies, in conjunction with neutrophils, are capable of inducing such injury.

This provides a rationale in support of therapeutic strategies that aim to remove these antibodies, such as plasma exchange and rituximab.

Active immunization of mice and rats with MPO has provided a more accurate model of an immune response that involves both cellular and humoral immunity allowing investigation of the role of T-cells, specifically those of the Th17 axis that have been implicated in autoimmune disease. Such active immunization strategies are well suited to long-term therapeutic trials of novel agents, although for this to be truly useful, the disease phenotypes of the particular models will need to be more severe.

Table 1. Models of MPO- and PR3-ANCA associated vasculitis and glomerulonephritis

Model	Induction protocol	Proposed Mechanism	Organs affected	Severity	Comments/Reference
Passive anti-MPO Ab transfer	Anti-MPO-Ab induced in MPO-deficient mice and transferred into LPS primed recipients	ANCA induced neutrophil degranulation, dependent on B-cells and alternative complement activation	Lungs, kidneys	Mild crescentic GN, more severe in 129 strain	Noticeable strain effect
MPO-ANCA DTH model	MPO-immune response induced by immunization of MPO in CFA, followed by subnephritogenic dose of nephrotoxic serum in C57BL/6 mice	Delayed type hypersensitivity response to planted nephrotoxic antigen, allowing neutrophil degranulation and deposition of MPO target. T-cell, but not B-cell dependent.	Kidney only	Mild crescentic GN	Dosing and timing of nephrotoxic serum critical
Experimental autoimmune vasculitis	Immunization of WKY rats with human MPO in CFA	Induction of anti-MPO Ab and T- cells.	Lungs, Kidney	Mild crescentic GN	Dose dependent effect of MPO on disease severity
PR3-ANCA vasculitis in NOD mice	Immunization of NOD mice with recombinant PR3 in CFA and passive transfer of splenocytes into NOD-SCID mice	Development of PR3-ANCA and presumably PR-3 specific B-cells. No comment on T-cell reactivity	Lungs, kidneys	Crescentic GN	NOD-RAG recipients did not develop disease while NOD-SCID did, suggesting that significant other factors apart from PR3 reactive splenocytes play a role.
PR3-ANCA vasculitis in humanized mice	Generation of chimeric human-mouse immune system by transfer of human CD34+stem cells to NOD SCID IL2-receptor KO mice followed by passive transfer of human PR3-ANCA	Generation of myeloid and lymphoid chimerism providing human neutrophil and monocyte targets for PR3-ANCA	Lungs, kidneys	Mild proliferative GN	

Modelling of anti-PR3 associated disease in animals is significantly less advanced and, by virtue of the differences in PR3 structure and expression between mice and men, will probably rely in the future on the use of humanized and transgenic *in vivo* systems. The generation of an animal model incorporating both anti-PR3 associated vasculitis and granuloma formation, as well as, relapsing disease, cardiac, gastrointestinal and neurologic disease remains a major challenge for the next decade.

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Chapter 199

GENETIC ASPECTS OF VASCULITIS

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ABSTRACT

The generation of large-scale genotyping data is substantially increasing the understanding of human diseases with a complex genetic component. Such data analysis has been applied to the vasculitides, which are characterized by inflammatory damage of the blood vessels. They show a very complex etiology in which both environmental and genetic factors seem to contribute to the predisposition and clinical phenotype of the disease. During the last decade, a large number of genetic studies, genome-wide association studies in some cases, have been performed on vasculitides and, strikingly, most of the identified risk loci shared susceptibility factors amongst them. This reinforces the idea that some immunological pathways are key players in the major hallmarks of these diseases.

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However, since the current knowledge of the genetic basis of the vasculitides is often based on studies performed in reduced populations, further collaborative studies on larger cohorts are required to provide the last pieces of the genetic puzzle underlying vasculitides, giving us a better perspective of their etiopathogenesis and allowing novel approaches for the development of more effective therapies.

INTRODUCTION

Vasculitides present a complex etiology in which both environmental and genetic factors appear to influence the development and progression of disease. The genetic component of these disorders is supported by the identification of an increased risk among first-degree relatives of affected patients and monozygotic twins. For most vasculitides familial aggregation has been described in case reports or small series without quantification. In the absence of family studies, differing prevalence of these diseases in different ethnic groups supports the existence of important genetic components.

Two main approaches, candidate gene studies and high-throughput genotyping, including genome-wide association studies (GWAS), have been used to identify disease-associated genes in complex diseases both of which involve genotyping of genetic variations, mainly the single-nucleotide polymorphisms (SNP) in cases and controls. Until recently, all genetic studies in vasculitides were designed as candidate gene studies, examining a SNP or a set of polymorphisms within certain *loci* with a potential role in a particular phenotype or disease. In these studies, the selection of a candidate gene or genomic region was based on its biological function or its location in a region implicated by previous associations or linkage studies. In contrast to candidate gene studies, the GWAS approach, in which millions of polymorphisms are analyzed across the whole genome, is unbiased and it does not require prior hypotheses about the type of genes or polymorphisms most likely to be associated with the phenotypes of interest. The recent publication of GWAS in vasculitides has increased the understanding of potential underlying genetic mechanisms. Moreover, the two methodologies have shown that the human leukocyte antigen (HLA) region harbors the strongest genetic contribution to the pathophysiology of vasculitides. This genomic region occupies a large segment of DNA extending about 3.6 megabases on the short arm of chromosome 6, and containing hundreds of genes involved in immune function.

This chapter summarizes the genetic aspects of vasculitides giving an overview of the recent progress in the elucidation of their genetic component. Two Chapel Hill Consensus Conference (CHCC) nomenclatures, one in 1994 and a Revised version in 2012 [1, 2], provided consensus on nosology and definitions for the commonest forms of vasculitis in adults based upon the caliber of vessels involved. The Pediatric Rheumatology European Society (PRES), European League against Rheumatism (EULAR), and the Pediatric Rheumatology International Trials Organization (PRINTO) proposed specific classification criteria, as well as, clinical, laboratory and radiographic characteristics for the commonest childhood vasculitis syndromes, based upon vessel size [3, 4], similar to the 2012 Revised CHCC nomenclature [2]. These overlapping nomenclatures form the basis for the definition of most recent cohorts of vasculitides to which reference is made in this chapter.

LARGE VESSEL VASCULITIS

Giant Cell Arteritis

Increasing knowledge suggests that giant cell arteritis (GCA) has an important genetic basis [5]. Familial aggregation with sharing of HLA alleles has been reported for GCA from several decades ago [6-13].

However, until recently most studies were performed in unreplicated Spanish and Italian populations [14] usually with small sample sizes. Despite these initial limitations, GCA was always considered as one of the best examples of vasculitis in which a genetic influence has been implicated in both disease susceptibility and severity. As discussed below, the establishment of international collaborative groups and the recent large scale genetic studies performed in this type of vasculitis have represented a turning point in the elucidation of its pathogenic mechanisms [15, 16].

HLA Association

Early candidate gene studies identified HLA class II region as the most consistent susceptibility *locus* for GCA. Carriage of HLA-DRB1*04 alleles (specifically DRB1*0401 and DRB1*0404) was proposed as the main contributor of the GCA genetic component [17-29]. An increased predisposition for the development of visual manifestations as well as resistance to corticosteroid treatment in GCA patients was related to the presence of HLA-DRB1*04 allele [26, 30, 31], which gave an idea of the crucial role that this allele may have in GCA pathophysiology. On the other hand, associations between GCA and alleles of the HLA class I region, including HLA-B*15, HLA-A*31, HLA-B*8, HLA-Cw3 and HLA-Cw6, as well as the nearby gene MHC class I polypeptide-related sequence A (*MICA*), encoding a stress-inducible transmembrane molecule, were also reported [17, 32-34], although not as consistent as those of the class II region.

The publication of the first large scale genetic study of GCA in 2015 definitively represented a considerable leap in the understanding of the genetic contribution of the HLA system to the susceptibility of this form of vasculitis. In collaboration with the UKGCA Consortium, the Vasculitis Clinical Research Consortium (VCRC), and many other research groups and hospitals from Europe, our group carried out a dense fine-mapping of immune-related *loci* using the Immunochip platform, a custom high-density genotyping array designed for immunogenetics studies [35]. One of the advantages of this chip is the presence of a high SNP coverage in the HLA region, which allows imputation of two- and four-digit classical HLA alleles as well as polymorphic amino acids using reference panels [36, 37]. We performed a comprehensive interrogation of the HLA region at the amino acid level using this bioinformatics approach in a total of 1,651 GCA patients and 15,306 unaffected controls. Our results highlighted the class II molecules as the main contributors to GCA risk, specifically HLA-DR β 1 and HLA-DQ α 1. The class I gene *HLA-B* was also associated, but with a considerable lower statistical significance. We proposed a model of 3 amino acid positions that explained most of the HLA association with GCA, which included positions 13 and 56 of HLA-DR β 1 and HLA-DQ α 1, respectively, as well as 45 of HLA-B. All three positions were located at the binding pocket of the protein, suggesting a possible involvement in antigen recognition. The top signal corresponded to presence of histidine at position 13 of HLA-

DRβ1, consistent with the previous associations between GCA and HLA-DRB1*04 classical alleles, as His13 is one of the amino acids that define them [16].

Non-HLA Association

The protein tyrosine phosphatase nonreceptor type 22 (*PTPN22*) gene encodes a tyrosine phosphatase known as LYP that it is expressed mainly in lymphoid tissues and is involved in several signaling pathways associated with the immune response, including the T-cell receptor (TCR) pathway in which LYP plays a central role in its negative control, but also the humoral activity of B-cells. A functional *PTPN22* variant (rs2476601/R620W) has been associated with several autoimmune diseases, representing the clearest example of a common genetic risk factor in autoimmunity [38]. *PTPN22* R620W represented the strongest non-HLA association signal in the Immunochip of GCA [16], which confirmed previously reported observations through the candidate gene approach [39]. This association was initially identified in a large discovery cohort from Spain and subsequently replicated in three European replication cohorts from the United Kingdom (UK), Germany and Norway. It has been demonstrated that the R620W change interferes with the ability of LYP to bind its partner c-src tyrosine kinase (CSK) [40] which prevents the formation of the complex between both proteins and the suppression of the T-cell activation.

The first GWAS performed in GCA was published on 2017. The involvement of the European Vasculitis Genetics Consortium (EVGC) allowed the recruitment of three additional cohorts to the first case/control set of the Immunochip, comprising a total of 2,134 GCA patients and 9,125 controls from 11 populations of European origin (Spain, Italy, UK, USA, Canada, France, Germany, Norway, The Netherlands, Ireland and Switzerland) [15]. The analysis of a total of 1,844,133 genetic markers across the whole genome led to the identification of two genes involved in angiogenesis and vascular remodeling as the most relevant non-HLA genetic factors of GCA, i.e., plasminogen (*PLG*) and prolyl 4-hydroxylase subunit alpha 2 (*P4HA2*). The first one encodes a precursor of both plasmin and angiotatin proteins [41]. The GCA-associated *PLG* variants were predicted to affect their gene expression, which could unbalance the plasminogen/plasmin system favoring a pro-inflammatory environment [15]. On the other hand, *P4HA2* encodes the α subunit of the collagen prolyl 4-hydroxylase, a hypoxia responsive enzyme involved in collagen biosynthesis [42]. Some of the *P4HA2* alleles that conferred risk to GCA were predicted to alter *P4HA2* expression in lymphoblastoid cells and the aorta [15].

Different lines of evidence clearly suggest that Th17 cells are crucial players in GCA development. They include both presence of this cell type and increased levels of IL17 in the vascular lesions of GCA patients. Interestingly, corticosteroid therapy seems to be more effective on Th17 cells than on Th1 cells under a GCA background [43-45]. Consistent with these observations, associations between GCA and *IL17A* gene polymorphisms were described in a candidate gene study performed on 2014 [46].

The NLR family pyrin domain containing 1 (*NLRP1*) gene, another autoimmune disease-associated locus, was also confirmed as a GCA susceptibility gene in a study on Spanish and Italian populations [47]. This gene encodes a cytoplasmic protein involved in the assembly of the inflammasome that activates caspases 1 and 5 which results in the activation of proinflammatory cytokines. As expected, considering its inflammatory nature, different cytokines have been implicated in GCA pathogenesis. Amongst them, the interleukin 10 (*IL10*) gene represents the most consistent association [48, 49]. This gene encodes an anti-

inflammatory Th2 cytokine with pleiotropic effects in the immune system, including the negative control of Th1 cytokines such as interferon gamma (IFN- γ), the regulation of the B cell function, and the repression of nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) activity. Two independent studies in Italian [48] and Spanish [49] populations indicated that variation of the *IL10* promoter region may be involved in the pathogenic mechanisms leading to GCA.

Other genes encoding cytokine or cytokine receptors that have been suggested as possible genetic risk factors for GCA: *IL33*, encoding an IL-1 family member with strong immunomodulatory functions; *IL4*, encoding a protein that acts reciprocally with IFN- γ inducing the Th2 immune response; *IL6*, with pleiotropic effects that may exert both pro-inflammatory and anti-inflammatory functions; *IL18*, encoding a pro-inflammatory cytokine with cytotoxic T-cell functions; monocyte chemotactic protein-1 (*MCP1*), encoding a chemoattractant protein for mononuclear cells to the sites of inflammation; regulated and normal T-cell expressed and secreted (*RANTES*), encoding a potent chemotactic factor for immune cells; the *IL2/IL21* region of cytokines important in the correct function of the immune system; IL12 receptor beta 2 (*IL12RB2*), a key player in the inflammatory response; tumor necrosis factor (TNF), encoding a proinflammatory cytokine involved in the regulation of immune cells; and *IFNG*, encoding a key cytokine involved in innate and adaptive immunity against intracellular pathogens and tumor control [50-59].

The possible role of a number of important molecules for the endothelial function in GCA predisposition and severity has been also explored. Although most of the studies were low-powered and without replication, evidence of association was observed for intercellular adhesion molecule 1 (*ICAM1*), encoding a cell surface glycoprotein involved in the interactions between immune and endothelial cells during inflammation; vascular endothelial growth factor (*VEGF*), encoding an important vasculogenic mediator; cytokine-inducible and endothelial nitric oxide synthases (*NOS2A* and *NOS3*), involved in the regulation of the oxidative stress; and matrix metalloproteinase 9 (*MMP9*), encoding an enzyme with proteolytic activity on the extracellular matrix [52, 60-66].

Finally, genes of the innate immunity may also have a role in GCA pathogenesis. Significant associations have been reported for toll-like receptor 4 (*TLR4*), implicated in signal transduction events induced by lipopolysaccharide from Gram-negative bacteria; Fc gamma receptor 2A and 3A (*FCGR2A* and *FCGR3A*), encoding cell-surface proteins of the immunoglobulin superfamily; and myeloperoxidase (*MPO*), an important gene in the neutrophil function [67-69]. However, all these associations require confirmation in larger and independent cohorts.

Takayasu Arteritis

A few candidate gene studies exploring the possible role of genetic polymorphisms in Takayasu arteritis (TAK) were performed before the publication of three recent large scale analyses, i.e., a genome scanning of exonic regions in a Japanese cohort [70], an Immunochip in Turkish and North Americans [71], and an unbiased GWAS also in Turkish and North Americans [72].

HLA Association

Different genetic studies showed that *HLA-B* alleles are involved in the disease susceptibility. Specifically, *HLA-B*5201* was associated with TAK in multiple cohorts of diverse ethnicities including different populations from Asia and Mexico [73-78], which was confirmed in the GWAS of Japanese [70]. However, this association was not observed in North American and Arab populations [79, 80]. In the former [79], a positive correlation of *HLA-DR4/MB3* and a strongly negative association of *HLA-DR1* with TAK were reported, whereas in Arab patients [80] the association with this region was narrowed down to *HLA-A2*, *HLA-A9*, *HLA-Bw35* and *HLA-DR7* alleles.

Studies on polymorphisms of the gene encoding the human complement factor 4 (C4), located at the class III region of the HLA, showed a significantly high frequency of C4A2 and C4BQ0 allotypes in strong association with *HLA-Bw52* [81]. Furthermore, the analysis of *MICA*, situated between the class I and class III regions, revealed an association between the *MICA-1.2* allele and TAK, even in the absence of *HLA-B52* [82].

A subsequent study [83] in which five microsatellites, C1-2-A, MIB, C1-4-1, C1-2-5 and C1-3-1, around the *HLA-B* and *MICA* genes were analyzed in Japanese TAK patients, suggested two different disease-susceptibility loci for TAK, one that mapped near the C1-2-A locus, and another closely linked to the *HLA-B* gene. Very recently, the *MICA* and the *HLA-DQB1/HLA-DRB1* regions were also described as TAK risk factors in the Immunochip study on Turkish and American cohorts [71].

Non-HLA Association

The most consistent associations with TAK outside the HLA region rely on *IL6*, the leukocyte immunoglobulin like receptor B3 (*LILRB3*) region, *IL12B* and the *FCGR2A/FCGR3A* loci. The two first loci were identified in the GWAS on 2015 [72]. *IL6* was previously suggested as a TAK locus by candidate gene studies [84]. This gene encodes an important cytokine with key roles in different aspects of the immune response, including the differentiation of Th17 cells and regulatory T-cells (Treg). Consistent with this association, an altered production of several cytokines, including IL-6, IL-2 and IL-12, were detected in TAK patients. Increased levels of IL-6 and IL-12 and a lower number of CD3+ T cells producing IL-2 in the active phase of the disease were described [85-87]. Polymorphisms of the genes encoding these cytokines were correlated with altered protein levels [84, 88-93]. Regarding the second non-HLA signal of the GWAS, *LILRB3* is located in an immune-regulatory gene rich region on chromosome 19q13.4, which contains genes encoding for killer immunoglobulin-like receptors (KIR), leucocyte immunoglobulin-like receptors (LILR), and leucocyte-associated immunoglobulin-like receptors (LAIR). Remarkably, the top marker within the associated region was related to reduced transcription levels of multiple genes including *LILRB3* [72]. On the other hand, *IL12B* showed a high association peak in both the exome screening study and the Immunochip, whereas *FCGR2A/FCGR3A* was identified as a susceptibility region for TAK in the Immunochip [70, 71].

Two genes encoding members of the IL-1 cytokine family, *IL1B* encoding IL-1 β , and IL-1 receptor antagonist (*IL1RN*) encoding IL1-Ra, were involved in TAK predisposition [94]. IL-1 may mediate the inflammatory response occurring in the vascular wall by activating monocytes and expression of adhesion molecules on endothelial cells, inducing secretion of

other inflammatory mediators. IL-1Ra inhibits the activities of IL-1 α and IL-1 β , and modulates a variety of IL-1 related immune and inflammatory responses.

Functional and genetic studies [95-97] have reported an implication of both genes in cardiovascular disease, a common feature in TAK patients. In addition, different polymorphisms of *IL1B* and *IL1RN* were associated with TAK in the Mexican population [94], which suggests a crucial role of IL-1 in the vasculitis lesions of TAK.

Genes encoding cardiovascular-related molecules may also play a role in TAK development [98, 99]. For instance, paraoxonase 1 (*PON1*), a high density lipoprotein (HDL)-associated enzyme involved in prevention of lipid peroxidation, was diminished in activity in TAK patients suggesting a possible role of these lipoproteins in TAK vascular dysfunction [98]. A recent study in the Mexican population [99] suggested that variation within *PON1* may be involved in TAK susceptibility by influencing development and progression of arterial damage.

MEDIUM VESSEL VASCULITIS

Kawasaki Disease

A large number of genetic studies have been conducted in order to unravel the genetic component of Kawasaki disease (KD) [100] focused mainly on candidate genes implicated in the immune response. In addition, since the most serious complication of KD is the development of coronary artery lesions (CAL), the role of cardiovascular-related *loci* has been extensively studied. However, sample sizes have often been insufficient and only a few associations have been replicated in subsequent studies [100].

In the last years, six GWAS on KD have been published [101-106]. This approach has represented an important step forwards to the understanding of the genetic basis of this vasculitis.

HLA Association

The involvement of the HLA region in KD is controversial. Association between KD and HLA class I molecules was evidenced [107-111], but the results were inconsistent. Early studies reported an association between HLA-Bw22 now called Bw54, and KD in the Japanese population [107, 108], whereas the HLA-Bw51 and HLA-B44 alleles were predominantly associated with the disease in Caucasians [109-111]. On the contrary, in a recent GWAS [105], a significant association of HLA class II region with Japanese KD patients was identified. Specifically, the strongest association signal was observed at the intergenic region between HLA-DQB2 and HLA-DOB (rs2857151). This association was replicated in a subsequent Han Chinese study [112]. A suggestive association signal was also observed in the HLA class III region (rs2516390), close to the nuclear factor of kappa light polypeptide gene enhancer in the B-cell inhibitor-like 1 (*NFKBIL1*) and lymphotoxin alpha (*LTA*) genes.

However, no significant associations of HLA alleles were documented in other published GWAS. Thus, a consistent allele or haplotype of HLA conferring KD susceptibility has not yet been identified.

Non-HLA Association

Several genes have been suggested to play a role in KD susceptibility through candidate gene studies [113-125]. Susceptibility *loci* include 1) cytokines and their receptors, such as *IL4*, *TNF*, the chemokine (C-C motif) receptor 2-3-5 (*CCR2-CCR3-CCR5*) gene cluster which encodes three receptors of different chemokines that play a critical role in the selective accumulation and activation of inflammatory cells in affected tissues; 2) genes encoding cardiovascular-related molecules, including *VEGF* implicated in the predisposition to this vasculitis and CALs development in different populations, and *MMP3*, 9, 13 also associated with CAL; and 3) genes involved in innate immunity, like mannose binding lectin 2 (*MBL2*) involved in complement activation and associated with an increased risk of CAL, and *NLRP1* involved in the inflammasome assembly.

Potential *loci* implicated in KD susceptibility in Japanese families include the 19q32.2 and 4q35 regions. Subsequent fine-scale studies [126] of the 19q32.2 region have led to the identification of functional polymorphisms of the inositol 1,4,5-triphosphate 3-kinase C (*ITPKC*) gene significantly associated with the susceptibility to KD, with particular risk of developing CAL in both Japanese and Caucasian patients. This gene encodes one of the three isoenzymes that phosphorylate inositol 1, 4,5-trisphosphate (IP3) acting as an important molecule in the regulation of T-cell activation.

Regarding the 4q35 linkage region, several immune genes have been mapped around the peak of linkage, including the IFN regulatory factor 2 (*IRF2*), *TLR3* and caspase 3 (*CASP3*) that play central roles in apoptosis. A subsequent positional candidate gene study [127] in Japanese and Americans of European ancestry subjects identified a functional *CASP3* variant that altered the gene expression in immune effector cells. This SNP was shown to influence KD susceptibility. Both the *ITPKC* and *CASP3* associations with KD were replicated in the Taiwanese population [128, 129].

More recently, based on previously published suggestive linkage signals at chromosome 12q24 [125], a missense SNP located within exon 2 of the calcium release-activated calcium modulator 1 (*ORAI1*) gene was described as a risk factor for KD in the Japanese population. This gene encodes a membrane calcium selective ion channel involved in T-cell activation through the Ca^{2+} /NFAT pathway. Strikingly, the frequency of the risk allele is more than 20 times higher in Japanese compared to that in Europeans, suggesting that *ORAI1* may be related to the differential KD incidence between populations of Asian and European descent [130].

In 2009, the first GWAS performed on KD Caucasian patients [101] led to the identification of eight putative novel susceptibility *loci*. Five of these genes, calcium/calmodulin-dependent protein kinase II delta (*CAMK2D*), CUB and Sushi multiple domains 1 (*CSMD1*), ligand of numb-protein X1 (*LNK1*), N-acetylated alpha-linked acidic dipeptidase-like 2 (*NAALADL2*), and t-complex 1 (*TCP1*), formed a functionally close network of 35 genes defined in the Ingenuity database (Ingenuity Systems, Redwood City, CA, www.ingenuity.com). This gene network suggests possible mechanisms by which one or more infectious triggers may lead to deregulated inflammation and apoptosis, and cardiovascular pathology.

In 2011, another GWAS [103] was conducted in a Korean population, and two novel susceptibility signals were identified: a SNP close to the Dab reelin signal transducer homolog 1 (*DAB1*) gene associated with KD predisposition, and an intronic variant of pellino E3 ubiquitin protein ligase 1 (*PELI1*) gene which is involved in the TLR pathway associated

with CAL development. The first GWAS in the Han Chinese population [106] identified several putative genetic variants associated with KD susceptibility, although none of them reached GWAS statistical significance due to a limited sample size.

The highest peaks included three SNP close to coatomer protein complex beta-2 subunit (*COPB2*) gene, one located within the intronic region of endoplasmic reticulum amino peptidase 1 (*ERAP1*), and six clustered in an area containing immunoglobulin heavy chain variable region (*IGHV*) genes.

A well-powered GWAS [102] in KD patients from different populations of European ancestry (Australia, UK, Netherlands and US) identified two *loci* that exceeded the threshold for GWAS significance. One of them was *ITPKC*, confirming this gene as a risk factor for KD, and a functional polymorphism (H131R, rs1801274) of *FCGR2A*. Finally, both Taiwanese [104] and Japanese [105] groups independently reported GWAS results in 2012 [104, 105]. In both studies, significant associations were observed in the B-lymphoid tyrosine kinase (BLK) region. The most strongly associated polymorphism in the Taiwanese study [104] was in high linkage disequilibrium (LD) with a genetic variant associated with systemic levels of BLK and increased risk of systemic lupus erythematosus (SLE). SNP around cluster domain 40 (*CD40*, a member of the *TNFR* superfamily that potentially contributes to inflammation and autoimmune disease processes through the selection of autoreactive T cells in the thymus and the activation of B- and T- cells) were also associated with KD at GWAS level in both studies. Interestingly, increased cell surface expression of CD40L, the ligand of CD40, and elevated serum levels of soluble CD40L have been detected in KD. On the other hand, the Japanese study also replicated the association of the previously identified *FCGR2A* functional SNP.

On 2016, Shimizu and colleagues [131] performed a pathway-based analysis followed by gene stability selection using the previously published GWAS data of individuals of European ancestry [102]. They identified variants associated with both susceptibility to KD and aneurysm formation within the solute carrier family 8 member A1 (*SLC8A1*) gene, which encoded protein contributes to the regulation of calcium flux and calcium-dependent cellular processes. The results were further replicated in an independent cohort of Japanese origin [131].

Finally, a recent whole genome screening of a 6-member African American family with two affected KD children identified rare compound heterozygous variants in another TLR member, *TLR6*, shared between both affected siblings [132].

Small Vessel ANCA-Associated Vasculitis

Early genetic studies in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), which comprises granulomatosis with polyangiitis (GPA) [Wegener type], microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA) (Churg-Strauss type), focused on self-evident candidate genes encoding respective ANCA target antigens, proteinase 3 (PR3) and myeloperoxidase (MPO).

Subsequent studies reported a clear familial aggregation of GPA, with a relative risk of 1.56 for first-degree relatives, which indicated the importance of the genetic component for this disease [133]. In 2012, the 'European Vasculitis Study Group' (EUVAS) conducted the

first GWAS in AAV [134] (including a large cohort of GPA and MPA patients), reporting more consistent associations with the disease, and suggesting genetic distinctions between the clinical entities of AAV that may be associated with ANCA specificity. Subsequently, two additional GWAS were performed by the VCRC (one only in patients diagnosed with GPA and another in a cohort including GPA and MPA cases) [135, 136]. Those studies definitively helped to increase the knowledge on AAV genetics.

HLA Association

Several early low-power studies [137-139] suggested that different HLA class I and class II *loci* might be involved in the predisposition to GPA including HLA-DQw7, HLA-DR3, HLA-DR1, HLA-DR9 and HLA-B50. However, only the HLA DPB1*0401 allele was firmly associated with GPA, although other neighboring *loci* such as ring finger protein 1 (*RING1*), a transcriptional repressor, and retinoid X receptor beta (*RXRβ*), involved in mediating the effects of retinoic acid, may have independent effects [140,141].

HLA-DP also showed the highest association signals in the three AAV GWAS [134-136], with HLA-DPB1*04 as main contributor of GPA risk [135]. Interestingly, the main associations in the HLA region were observed in the subgroup of patients with presence of anti-PR3 antibodies, although there were also associations in the cohort of AAV patients positive for anti-MPO [134]. Hence, it is likely that HLA-DP alleles are a key factor for autoantibody production in AAV, particularly for anti-PR3.

An increased prevalence of HLA-DR4 was also associated with AAV in general, and more specifically with GPA. One study [142] performed in a Dutch population showed that the three subtypes of AAV had a similar HLA antigen distribution, except for HLA-DR1, which was more prevalent in GPA patients, and HLA-DR8, which showed a decreased frequency in EGPA patients in comparison with the other two subtypes. Other evidences suggested that HLA-DRB4 could represent a risk factor specific for EGPA [143].

Non-HLA Association

PRTN3 and *MPO* encode the two major ANCA autoantigens PR3 and MPO respectively. PR3 is a neutrophil intracellular protease that can be also located on the plasma membrane.

It has been proposed that elevated membrane expression of PR3 is involved in progression of chronic inflammatory diseases, including AAV, and that this fact is likely to be genetically determined.

More than one decade ago, the entire coding and promoter sequences of *PRTN3* were analyzed to identify polymorphisms that could influence the pathophysiology of GPA. The genetic variations described in that study [144] included seven SNPs, one amino acid change (Val119Ile), one 84 base pair insertion/deletion (INDEL), and a microsatellite.

Among them, only one SNP affecting a putative transcription factor-binding site (rs62132295, A-564G) was associated with GPA. In the AAV GWAS [134], this *PRTN3* variant was not associated at GWAS level, although a suggestive P-value with GPA but not with MPA was yielded. However, a stronger size effect was observed when the GPA patients were stratified accordingly with the type of autoantibody production instead of the clinically defined syndromes.

Patients positive for anti-PR3 show a stronger association with *PRTN3* rs62132295 than those positive for anti-MPO, when compared with cohort controls. Additionally, the allele frequencies of this SNP also differed considerably between both subsets of patients. Similar

results were observed for the serpin A1 (*SERPINA1*) gene [134], which encodes a serine protease inhibitor known as α 1-antitrypsin whose targets include PR3 that protects tissues against enzymes from inflammatory cells like neutrophils. The Z (null) allele seems to be specifically associated with anti-PR3 presence rather than with the clinical subtypes, since the most significant P-value was obtained when the AAV patients showing this autoantibody were compared against controls. *SERPINA1* was the only *locus* outside the HLA region that reached GWAS significance. The association between this gene and ANCA positivity has been confirmed in many candidate gene studies [145-150]. The autoimmune disease-associated *PTPN22* functional variant R620W was also reported to confer risk to AAV through candidate gene studies [151,152]. Specifically, it was first implicated in the susceptibility to develop GPA [152], and this association was further confirmed in a higher cohort in which both GPA and MPA patients were included [151].

The second GWAS was performed in North American GPA patients of European descent. The study reported semaphorin 6A (*SEMA6A*), on chromosome 5, as a novel susceptibility marker for GPA. Although the role of semaphorins remains unclear, they seem to control axon guidance, vasculogenesis, cardiogenesis, osteoclastogenesis, tumor metastasis, and immune regulation [135]. The same consortium conducted another GWAS in GPA and MPA patients from European origin on 2017, and confirmed *PRTN3*, *SERPINA1* and *PTPN22* as the strongest non-HLA susceptibility genes for this forms of vasculitis [136].

Another gene that has been associated with AAV predisposition is cytotoxic T-lymphocyte associated antigen 4 (*CTLA4*), which encodes a central regulatory molecule expressed on T- cells that inhibits T-cell function and peripheral tolerance. It has been reported that elevated levels of CTLA4 are expressed in GPA patients [153].

In concordance, many studies have described associations of different *CTLA4* polymorphisms with AAV [154-159], thus supporting the idea that *CTLA4* represents another common susceptibility factor in autoimmunity.

There are other genes of the immune system that showed less consistent evidence of association with AAV, and confirmation in independent cohorts is still required [160]. These include, *IL10*, *CD226*, an adhesion molecule expressed on the surface of natural killer cells, platelets, monocytes and T cells; IL2 receptor alpha (*IL2RA*), an important Treg marker; leukocyte immunoglobulin-like receptor A2 (*LILRA2*), an immunoreceptor expressed in immune cells; integrin, beta 2 complement component 3 receptor 3 and 4 subunit (*ITGB2*), which participates in cell adhesion as well as cell-surface mediated signaling; and *FCGR2A/3B* members of IgG receptor family. Except for *SERPINA1*, *PRTN3*, *CTLA4* and *CD226*, none of the above described genetic associations have been confirmed at the 95% significance level in the AAV GWAS [134].

Small Vessel Immune Complex Vasculitis

IgA Vasculitis/Henoch-Schönlein Purpura

Similar to the other vasculitides, the understanding of the genetic background of IgA vasculitis/Henoch-Schönlein purpura (IgAV/HSP) remains elusive, and further research on well-powered cohorts is still needed to unravel the genetic basis and pathogenic mechanisms leading to this vasculitis.

Until the publication of the first GWAS of IgAV/HSP in 2017, the current knowledge of the genetic component of IgAV/HSP was based exclusively on candidate gene studies including genes mainly involved in the immune and inflammatory responses, but also in endothelial function, mechanisms of complement system activation, coagulation and fibrinolysis, and antioxidation [161].

HLA Association

There is a limited number of studies on the HLA region in IgAV/HSP, all of which have been performed in Spanish, Italian and Turkish populations [161, 162]. In relation to the HLA class II region, an association of the HLA-DRB1*01, HLA-DRB1*07, and HLA-DRB1*11 alleles with IgAV/HSP was first reported in Italy [163] and subsequently confirmed in independent cohorts from Spain [164, 165] and Turkish [166]. The HLA alleles DRB1*01 and DRB1*11 increase the risk for the disease onset, whereas DRB1*07 confer a protective effect to the disease. Also, a protective effect against IgAV/HSP development was described in patients carrying the HLA-DRB1*03 haplotype [165].

The publication of the first GWAS of IgAV/HSP confirmed the HLA class II region as the major susceptibility locus for IgAV/HSP. The authors also used the imputation method described in the GCA section to narrow down the HLA association to a region between *HLA-DQA1* and *HLA-DQB1*. As observed in GCA, positions 13 and 11 of the HLA-DR β 1 carried the strongest disease risk [167].

Other HLA class II alleles have been associated with specific IgAV/HSP clinical characteristics in Turkish cohorts [166] including HLA-DRB1*14, significantly reduced in IgAV/HSP patients with joint involvement, and HLA-DRB1*13, increased in IgAV/HSP patients with nephrotic proteinuria. An association between HLA class I alleles and IgAV/HSP have been also reported, although they remain controversial.

In relation to the class I region, HLA-B35 was first described as a susceptibility factor for nephritis development in IgAV/HSP patients from Spain [168], whereas this allele was subsequently associated with increased risk of the overall disease in a Turkish cohort [169]. The study on IgAV/HSP patients from Turkey [169] also suggested that the presence of the antigens HLA-A2, HLA-A11, and the absence of HLA-A1, HLA-B49, and HLA-B50, influenced IgAV/HSP predisposition. In a recent study, López-Mejías and collaborators [170] reported an association between HLA-B*41:02 and predisposition to IgAV/HSP in Spaniards irrespective of the HLA-DRB1 status.

In addition, HLA-A3 and HLA-B44 were associated with joint involvement, and HLA-A1, HLA-B56, and HLA-B58 were associated with disease severity.

Regarding class III, there is evidence of association between the *C4* locus (involved in the clearance of immune complexes) and IgAV/HSP [171, 172].

Non-HLA Association

In relation to genes involved in inflammatory pathways, polymorphisms of *IL1RN*, *IL8* and *IL1B* have been shown to influence renal involvement in IgAV/HSP patients of European origin [173-176]. Interestingly, a SNP of *IL1B* has been recently described as a potential marker of severe renal manifestations and renal sequelae in patients with IgAV/HSP from Spain [177]. On the other hand, a promoter polymorphism of the *TGFB1* gene and a non-synonymous variant of the Mediterranean fever gene (*MEFV*) has been also associated with susceptibility and severity of IgAV/HSP in Chinese children [178, 179]. Regarding *MEFV*,

this gene encodes a protein known as pyrin that is an important modulator of innate immunity. The name of the gene is based on the fact that variations within this *locus* are related to the phenotype of the Mediterranean fever (a hereditary periodic fever syndrome). Interestingly, a connection between *MEFV* mutations and IgAV/HSP has been suggested [179-181].

Molecules involved in the endothelial function could be also important players in IgAV/HSP. Several studies [182-186] have explored the role of an INDEL polymorphism in the angiotensin I converting enzyme (*ACE*) gene, which is involved in the control of the blood pressure, with contradictory results. Some of them [182-184] suggested that the presence of the deletion may increase the predisposition to IgAV/HSP, while others did not find evidence of association with the disease [185, 186].

Another member of the rennin–angiotensin system, the angiotensinogen (*AGT*) gene has been also suggested to be involved in HPS pathophysiology [184].

On the other hand, a CCTTT repeat polymorphism within *NOS2A*, involved in the metabolism of nitric oxide as indicated before, was associated with IgAV/HSP predisposition and nephritis presence in a cohort from northwest Spain [187]. Similarly, genetic polymorphisms of the *VEGF* gene have been suggested to have a potential implication in the development of nephritis in patients with IgAV/HSP [188, 189].

Other *loci* involved in IgAV/HSP susceptibility or nephritis development include *CTLA4* and *PON1* (which inhibits T cell function and regulates the formation of oxidized lipoproteins, respectively, as indicated before in this chapter) [166, 190].

VARIABLE VESSEL VASCULITIS

Behçet Disease

Although the pathogenesis of Behçet disease (BD) is still poorly understood, major contributors of BD genetics have been identified mainly due to the publication of three GWAS conducted in Turkish, Japanese, Korean and Italian populations [191-193], a follow-up study of one of them [194], and a Immunochip in Spaniards [195].

HLA Association

As observed in most autoimmune diseases, the HLA region harbors the highest susceptibility *loci* for BD, specifically the HLA class I region. In this sense, HLA-B51 (in particular HLA-B51*01 and HLA-51*08) represents the most robust genetic association with BD. This association has been confirmed in populations of different ancestry groups since it was first described in the early eighties [191-193, 196, 197]. Subsequently, the HLA-A26 allele was also reported to have an independent contribution to disease predisposition [198]. In the Immunochip study HLA-B51 also represented the primary-association marker for BD, but two independent susceptibility signals, HLA-B*57 and HLA-A*03, were also described. Besides, the authors proposed an amino acid model comprising the position 97 of HLA-B and the position 66 of HLA-A which accounted for most of the genetic risk of the HLA region [195].

However, a recently published analysis of imputed GWAS data from a Turkish cohort [194] evidenced that the HLA-B51 association with BD is explained by a SNP located between the *HLA-B* and *MICA* loci (rs116799036). The authors also identified three additional independent signals within the extended HLA region located at the psoriasis susceptibility 1 candidate 1 (*PSORS1C1*) gene, HLA-F antisense RNA 1 (*HLA-F-AS1*), and HLA-Cw*1602.

Non-HLA Association

The three GWAS and the Immunochip performed in BD [191-193, 195] represented a turning point in the understanding of the genetic contribution of the non-HLA loci to the disease.

One of the most significant associations with BD described to date is *IL10*. This gene was previously suggested as a genetic factor for BD in candidate gene studies [199, 200], and confirmed by the GWAS data on the Turkish [191] and Japanese [192] populations. However, the recent GWAS on Koreans [193] failed to reproduce this finding. As indicated previously in this chapter, this genetic association is shared with GCA and AAV, but also with other autoimmune diseases such as ulcerative colitis, type 1 diabetes or SLE [197].

Another genomic region associated with BD at GWAS level is *IL23R/IL12RB2* [191, 192, 201]. As stated before, the latter gene encodes a subunit of the IL-12 receptor whose expression is regulated by IFN- γ .

This pathway is crucial in the Th1 and Th17 cell differentiation and it is involved in the inflammatory response. On the other hand, IL-23 is another important immunoregulatory cytokine that also promote Th17 function associated with the active intraocular inflammation in BD patients. Shortly before the publication of the two first BD GWASs [191, 192], an association between *IL23R* and BD was reported in the Han Chinese population [201]. Moreover, this gene harbored the strongest non-HLA signal in the Immunochip [195]. Similarly to *IL10*, the association was confirmed using the GWAS methodology in Turkish and Japanese [191, 192], but not in Koreans [193].

In 2013, the GWAS on Koreans [193], which had a lower statistical power than those on Turkish [191] and Japanese [192] cohorts, identified the GTPase IMAP family member (*GIMAP*) cluster, whose members play an important role in T cell function as well as T cell development and selection, as a novel genetic factor for BD. The peak signal outside the HLA region was observed in *GIMAP4*.

Functional studies performed by the authors evidenced that the minor allele of the associated polymorphism led to lower protein activity than the major allele, and that BD patients showed a lower *GIMAP4* expression in CD4 T cells.

Regarding the Immunochip, besides *IL23R*, two additional non-HLA risk loci for BD were established at the genome-wide level of significance, *IL12A* (which encodes a subunit of the heterodimeric cytokines IL-12 and IL-35) and the jerky like (*JRKL*)/contactin 5 (*CNTN5*) region. The function of *JRKL* is unknown, and *CTCN5* encodes a member of the immunoglobulin superfamily involved in the control of cell surface interactions during the development of the nervous system [195].

A large number of additional genetic associations with BD have been suggested through candidate gene studies, although most of them do not rely on consistent results. For example, associated variants have been identified in 1) genes encoding cytokines/chemokines, such as transforming growth factor beta 1 (*TGFB1*), *TNF*, *IFNG*, *IL1A*, *IL1B*, *IL2*, *IL4*, *IL6*, *IL8*,

IL17A, *IL18*, and *MCP1* amongst others [200, 202-217]; 2) genes involved in the endothelial function, including *VEGF*, *ICAM1*, *MMP9*, *NOS3*, and glutathione S-transferase (*GST*) [218-225]; 3) important immunomodulatory genes, like *NFKB*, *IRF1*, *CTLA4*, *STAT4*, and *CD40* [226-232]; and 4) genes encoding receptors of the innate immunity, as *TLR2*, *TLR4*, *TLR9*, TNF receptor superfamily 1A (*TNFRSF1A*), *FCGR2A*, *FCGR3A* and *FCGR3B* [233-238]. Interestingly, an epistatic interaction between the KD-associated *ERAP1* gene and *HLA-B* was proposed to influence BD predisposition in the Spanish population [239]. Nevertheless, studies on well-powered cohorts are required to definitively confirm or discard these associations.

SHARED GENETIC COMPONENT IN VASCULITIS

A large number of the known susceptibility loci described across this chapter are shared amongst different vasculitides (Figure 1), which supports the hypothesis of common molecular pathways influencing the development of autoimmune diseases in general and vasculitides in particular [240]. In this regard, the Immunochip platform is a valuable tool that allows comparison of the genetic landscape between different immune-mediated conditions, as it contains a large panel of SNPs covering most immune genes and in all cases the markers analyzed are the same [241]. In order to obtain genetic insights into the common immunopathological pathways involved in vasculitis development, our group carried out two cross-phenotype meta-analyses of Immunochip data from different forms of vasculitis in collaboration with several consortia [242, 243].

In the first of them, the previously published Immunochip studies of GCA and TAK [16, 71] were combined to evaluate the shared genetic component of large vessel vasculitis (LVV). As expected, no genetic pleiotropy was observed within the HLA, consistent with the fact that GCA and TAK are archetypal HLA class II and class I diseases, respectively. However, a significant genetic correlation was detected outside the HLA region, with *IL12B* representing the strongest shared susceptibility factor for both forms of LVV. This common association is in agreement with the key role proposed for Th1 and Th17 cells in the granuloma formation of LVV, as its encoded protein is the P40 subunit of both IL-12 and IL-23 (involved in Th1 and Th17 cell differentiation, respectively) [244]. Other genes that showed suggestive signals of common association were *NOS2A*, *ERAP1*, *REL* and *PRKQC* [242].

The second inter disease analysis was aimed at deciphering the shared genetic component of all forms of vasculitis. Hence, Immunochip data from GCA, TAK, AAV, and IgAV/HSP were combined and meta-analyzed. The pooled cohort included a total of 2,465 patients diagnosed with any of these four types of vasculitis and 4,632 unaffected controls. Interestingly, a common signal was identified within the lysine demethylase 4C (*KDM4C*) gene, which encodes a histone demethylase involved in epigenetic mechanisms. The shared association was confirmed in an additional cohort that included a subset of BD patients [243].

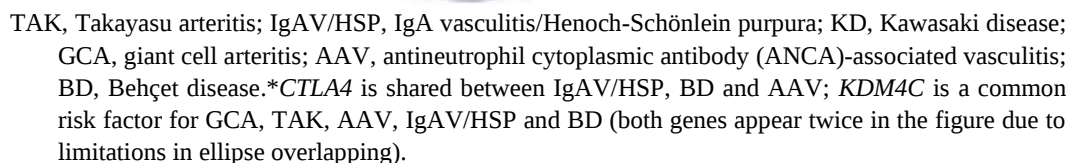


Figure 1. Shared genetic risk factors in vasculitides.

Despite the recent advances in the identification of the risk factors underlying vasculitides predisposition, there is still a long road ahead before completing the big picture of their genetic landscape.

In most studies, the limited statistical power and the lack of replication in independent cohorts have made difficult the identification of consistent genetic association signals. However, the establishment of big consortia has represented an important step forward that has facilitated the collection of cohorts large enough to perform adequately powered studies. These international collaborative efforts will definitively help to identify novel risk factors and to confirm previously reported genetic associations.

The use of high throughput genotyping has been also of great help, and data mining of the generated large-scale genetic data is producing valuable insights into the specific and common immunopathological pathways that lead to the development of the different forms of vasculitis.

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Chapter 200

NOMENCLATURE AND PATHOLOGIC FEATURES OF VASCULITIDES

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ABSTRACT

The goal of this chapter is to establish a general framework for categorizing vasculitis, which also serves as a framework for diagnosing vasculitis. The basis for the names and definitions used in this chapter is the 2012 Chapel Hill consensus conference nomenclature system for vasculitides. The major subdivisions are large vessel vasculitis, medium vessel vasculitis, small vessel vasculitis, variable vessel vasculitis, single-organ vasculitis, vasculitis associated with systemic disease, and vasculitis associated with a probable etiology. Although the names of the first four categories imply that vessel diameter is a defining feature of many forms of vasculitis, the different functional and structural characteristic of vessels are more important than the diameter of the vessel in determining their involvement in different forms of vasculitis, as well as the nature of the pathogenic events that are inducing the inflammation. Vasculitides that will be defined in this chapter include Takayasu arteritis, giant cell arteritis, polyarteritis nodosa, Kawasaki disease, microscopic polyangiitis, granulomatosis with polyangiitis (Wegener), eosinophilic granulomatosis with polyangiitis (Churg-Strauss), anti-glomerular basement membrane disease, cryoglobulinemic vasculitis, IgA vasculitis (Henoch-Schönlein), hypo-complementemic urticarial vasculitis (anti-C1q vasculitis), Behçet disease and Cogan syndrome. Many factors must be taken into consideration to make an accurate and precise clinical diagnosis of vasculitis. These include the type of vessels affected, as for example arteries versus venules; the histopathologic features of the inflammatory process such as leukocytoclastic inflammation or granulomatous inflammation; the immunopathologic features that may include IgA-dominant deposits or a paucity of

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immunoglobulin in vessel walls; the serologic findings such as cryoglobulins or anti-neutrophil cytoplasmic autoantibodies; any significantly associated systemic diseases such as rheumatoid arthritis or systemic lupus erythematosus; and associated etiologies such as hepatitis C virus infection or propylthiouracil exposure; the organ system distribution such as lung versus brain; accompanying extravascular lesions such as necrotizing granulomatosis or aphthous ulcers; or other possible factors. In a given patient, the goal of the clinician is to make a diagnosis, namely, assign a disease name that specifies the nature of the root disease process in the patient, and correctly assigns the particular form of vascular inflammation to the observed signs and symptoms that comprise the clinical criteria of that disorder, while providing useful predictions about disease outcome and appropriate treatment.

Keywords: nomenclature, pathology, vasculitides, Chapel Hill Consensus Conference 2012, ANCA

INTRODUCTION

Vasculitis is inflammation in vessel walls. The categorization and diagnosis of vasculitis is based on the nature of the inflammatory injury in vessels, including the etiology, pathogenesis, pathologic features and associated organ system dysfunction. The diagnosis of vasculitis is based on signs and symptoms of the disease or diagnostic criteria that allow a conclusion about the nature of the inflammatory injury in vessels, including the etiology, pathogenesis and pathologic features. Criteria that lead to a diagnosis in a specific patient may or may not involve direct microscopic visualization of inflammation or its sequela, such as vascular scarring in a tissue sample. However, to make a diagnosis of vasculitis, a conclusion must be reached that vasculitis with certain characteristic pathologic changes is occurring or has occurred in the patient. Thus, the underlying basis for the diagnosis of all patients with vasculitis is the nature of the pathologic inflammatory process that caused the vasculitis, although this does not mean that the pathologic lesions must be directly visualized histologically to make an actionable diagnosis.

This chapter reviews the pathology of many forms of vasculitis and presents an approach to nomenclature, classification and diagnosis that derives from these pathologic lesions. The 2012 Chapel Hill consensus conference nomenclature system (2012 CHCC) will be emphasized [1], since it modified and extended the 1994 CHCC nomenclature [2]. Disease nomenclature is a system of names used to identify and categorize diseases; and as for all words, each name has a definition.

The primary underlying defining characteristics of vasculitis in a patient are the cause and the nature of the vascular inflammation including the type of inflammation and the vascular distribution of inflammation. A diagnosis that refers only to cause or only to clinical/pathologic phenotype is problematic since 1) One cause can produce more than one pattern of injury, for example myeloperoxidase-specific anti-neutrophil cytoplasmic autoantibodies (MPO-ANCA) causing either microscopic polyangiitis (MPA) or granulomatosis with polyangiitis (GPA); and 2) One type of vasculitis can be induced by multiple causes, for example MPA caused by MPO-ANCA or proteinase 3-specific ANCA (PR3-ANCA). When possible, the definition of a vasculitis should include a reference not only to the nature of the inflammatory vascular injury but also the likeliest cause if known.

For example, the name IgA vasculitis (IgAV) emphasizes that the vasculitis is caused by IgA1-dominant immune deposits in the walls of small vessels. The alternative name, Henoch-Schönlein purpura (HSP) was originally based on a set of clinical manifestations that can be caused by multiple etiologies. Use of the term IgAV emphasizes the need to carefully consider the specific cause of the clinical manifestations. However, in a clinical setting, as with other pathologic features, there may be diagnostic criteria that warrant a confident diagnosis of IgA vasculitis in the absence direct observation of IgA in vessel walls by immunohistology. The conclusion that a patient has IgAV predicts clinically important clinical characteristics that guide prognosis and therapy. In patients with similar initial clinical manifestation of purpura, arthralgia and glomerulonephritis, the prognosis and appropriate treatment is very different depending on whether or not the clinical findings, including laboratory testing and pathologic observations are indicative of IgAV, cryoglobulinemic vasculitis, lupus vasculitis, MPO-ANCA MPA or PR3-ANCA GPA. However, the etiology and precise pathogenesis of some forms of vasculitis remains unknown, for example in Kawasaki disease (KD) and Takayasu arteritis (TAK). In this circumstance, the only defining features are the nature of the vasculitis and associated clinical features with no indication in the name about the cause.

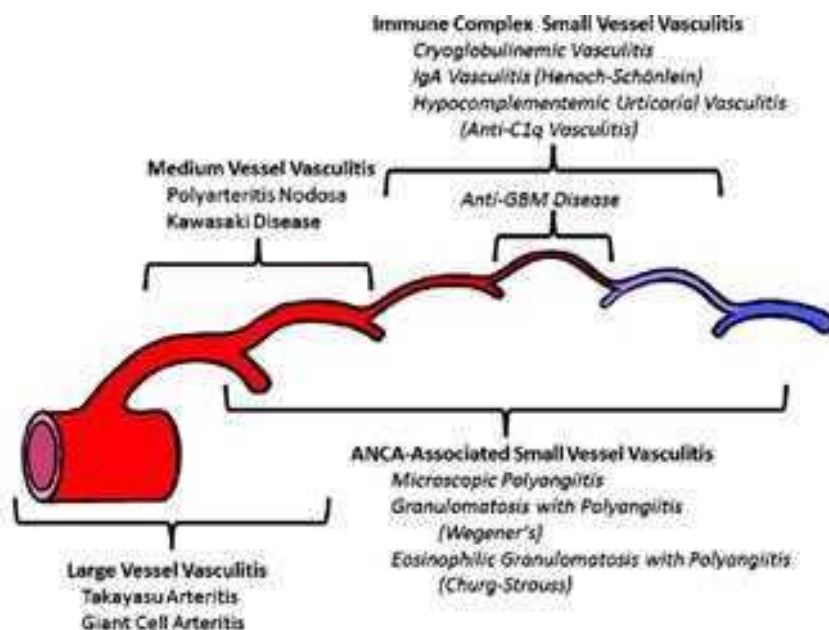
The CHCC 2012 provides names and definitions for many forms of vasculitis, but does not provide specific diagnostic criteria or classification criteria [1]. Specific observations that can practicably be made in a patient for clinical management purposes comprise diagnostic criteria. Specific observations that can be made in a patient for inclusion in a cohort of patients for a clinical trial or other research project comprise classification criteria. Although definitions may remain unchanged, diagnostic criteria and classification criteria evolve over time as modalities for evaluating patients develop, for example in improved imaging methods and more sensitive and specific laboratory tests become available.

A widely used first level of categorization of vasculitides divides vasculitides into large vessel vasculitis (LVV), medium vessel vasculitis (MVV) and small vessel vasculitis (SVV) (Figure 1) (Table 1) [1, 2]. This is somewhat problematic because it implies that the size or diameter of the involved vessel alone is the major defining feature for these categories and the major basis for susceptibility to different forms of vasculitis, however this is definitely not the case. The different functional and structural characteristic of these categories of vessels are more important than the diameter of the vessel in determining their involvement in the different forms of vasculitis. The relative size of vessels is merely a convenient characteristic that facilitates reference to these biologically different types of vessels. Another source of confusion is the fact that there is overlap in the types of vessels that can be involved in different forms of vasculitis. In particular, medium and small arteries can be involved by LVV, MVV and SVV.

LARGE VESSEL VASCULITIS (LVV)

CHCC 2012 [1] defines LVV as vasculitis affecting large arteries more often than other vasculitides, and defines large arteries as the aorta and its major branches. However, the point is made that any size artery may be affected. Importantly, the definition states that LVV affects large vessels “more often than other vasculitides” rather than LVV has more large

vessels affected since in a given patients with LVV, there may be, and often are numerically more involved medium and small vessels than large ones.



Reproduced from reference [1] with permission.

Figure 1. Diagram showing the predominant distribution of vessels affected by large vessel vasculitis, medium vessel vasculitis, and small vessel vasculitis. All categories of vasculitis can affect all types of arteries, but large vessel vasculitis most often affects large arteries. Medium arteries are most often affected by medium vessel vasculitis but large and small arteries may be affected. Small vessel vasculitis preferentially affects venules and capillaries, although arteries and veins may be affected. ANCA (antineutrophil cytoplasmic antibody) associated vasculitis affects a broad spectrum of vessels, whereas immune complex vasculitis usually affects capillaries or venules or both.

For example, a patient with giant cell arteritis may have involvement of the aorta, a carotid artery and several major branches of the carotid artery all of which are considered large arteries; however, many more medium and small arteries extending into the scalp, tongue, orbit and eye also may be involved. Thus, in a given patient with a LVV, there may be numerically more medium and small arteries affected. These same arteries can be affected by SVV, but SVV rarely affects the aorta and its main branches. Large vessel, including the aorta, can also be affected by variable vessel vasculitis (VSV) including Behçet disease (BD) and Cogan syndrome (CS); and by infectious vasculitis (e.g., aortitis caused by tertiary syphilis) and lymphoplasmacytic disease, for example aortitis as a component of IgG4-related disease [3]. Inflammation of large vessels with histopathologic features of Takayasu arteritis (TAK) and GCA may occur as isolated single organ vasculitides (SOV), such as isolated aortitis or isolated GCA along visceral arteries. Whether these represents limited expressions of TAK or GCA, or a distinct form of SOV has not been definitively determined.

In addition to the vascular distribution, LVV is characterized pathologically by a predominance of monocytes, macrophages, sometimes including multinucleated giant cells and lymphocytes even in the acute phase of vascular inflammation [3-5].

Table 1. Names for vasculitides adopted by the 2012 International Chapel Hill Consensus Conference on the Nomenclature of Vasculitides

<i>Large vessel vasculitis (LVV)</i>
Takayasu arteritis (TAK)
Giant cell arteritis (GCA)
<i>Medium vessel vasculitis (MVV)</i>
Polyarteritis nodosa (PAN)
Kawasaki disease (KD)
<i>Small vessel vasculitis (SVV)</i>
Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV)
Microscopic polyangiitis (MPA)
Granulomatosis with polyangiitis (Wegener's) (GPA)
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA)
Immune complex SVV
Anti-glomerular basement membrane (anti-GBM) disease
Cryoglobulinemic vasculitis (CV)
IgA vasculitis (Henoch-Schönlein) (IgAV)
Hypocomplementemic urticarial vasculitis (HUV) (anti-C1q vasculitis)
<i>Variable vessel vasculitis (VVV)</i>
Behçet disease (BD)
Cogan's syndrome (CS)
<i>Single-Organ vasculitis (SOV)</i>
Cutaneous leukocytoclastic angiitis
Cutaneous arteritis
Primary central nervous system vasculitis Isolated aortitis
Others
<i>Vasculitis associated with systemic disease</i>
Lupus vasculitis
Rheumatoid vasculitis
Sarcoid vasculitis
Others
<i>Vasculitis associated with probable etiology</i>
Hepatitis C virus-associated cryoglobulinemic vasculitis
Hepatitis B virus-associated vasculitis
Syphilis-associated aortitis
Drug-associated immune complex vasculitis
Drug-associated ANCA-associated vasculitis
Cancer-associated (paraneoplastic) vasculitis
Others

In addition, overt fibrinoid necrosis of the vessel wall is absent or a minor feature of LVV lesions, whereas in the acute phase of MVV and SVV there often is a predominance of neutrophils and conspicuous fibrinoid necrosis. LVV may have focal areas of medial coagulative necrosis, possible caused by occlusion of vasa vasorum. It is important to realize that within a week or two of the inception of a focus of acute inflammation in MVV and SVV, the inflammation at that site evolves into chronic inflammation with replacement of neutrophils and necrosis by mononuclear leukocytes and scarring that can be indistinguishable pathologically from chronic LVV. However, many forms of MVV and especially SVV have multiple sites of inflammation arising at different times so that there may be at least some diagnostic acute lesion in a tissue specimen even if there are many less specific chronic lesions.

The two major categories of LVV are TAK and GCA. Although on average there are some pathological and clinical features that differ between these two categories of disease, the

most objective difference is that the onset of TAK is primarily before 50 years old while that of GCA is typically after age 50 years. Thus, CHCC 2012 defines Takayasu arteritis (TAK) as arteritis, often granulomatous, predominantly affecting the aorta and/or its major branches with an onset usually in patients younger than 50 [1]. GCA is defined as arteritis, often granulomatous, usually affecting the aorta and/or its major branches, with a predilection for the branches of the carotid and vertebral arteries, often involves the temporal artery, and with onset usually in patients older than 50 and often associated with polymyalgia rheumatica (PMR) [1].

In the past, the term temporal arteritis was used as synonymous with GCA but this is not an acceptable approach because not all GCA involves the temporal arteritis and not all vasculitis affecting the temporal arteries is GCA. For example, the temporal arteries can be affected by polyarteritis nodosa (PAN), MPA, and GPA [6-8].

Active aortitis and arteritis of TAK and GCA is characterized by transmural inflammation with influx of monocytes, macrophages and lymphocytes (predominantly T lymphocytes) [3-5]. Multinucleated giant cells, formed by the fusion of monocytes into syncytial cells, often are identifiable but are not required for a pathologic diagnosis (Figure 2). Weakening and dilation of vessel walls results in aneurysm formation, and scarring and fibrotic intimal thickening result in narrowing of lumens and ischemia in downstream tissues. In arteries with an elastic media, such as the aorta and its initial branches, special stains for elastic fibers demonstrate a moth eaten appearance with irregular zones of lysis of the multi-laminated elastic media. In non-elastic arteries, there is focal fragmentation of the internal elastic lamina at the junction between the media and the intima. Fibrinoid necrosis is uncommon and when present is usually a minor feature of the overall injury. The presence of extensive fibrinoid necrosis should raise the possibility of some form of MVV or SVV [6-8].

MEDIUM VESSEL VASCULITIS (MVV)

CHCC 2012 [1] defines MVV as vasculitis predominantly affecting medium arteries defined as the main visceral arteries and their branches. Any size artery may be affected and inflammatory aneurysms and stenoses are common. In the acute phase, the inflammation typically is accompanied necrosis, which may result of spillage of plasma constituents into the vessel wall and perivascular tissues where the constituent coagulation cascade contacts thrombogenic stimuli, including tissue factor, resulting in the formation of fibrin. This irregular accumulation of fibrin in areas of necrosis is called fibrinoid necrosis and is deeply eosinophilic in hematoxylin and eosin (H&E) stained sections (Figure 3), and red (fuchsinophilic) in Masson trichrome stained sections (Figure 4A).

Within a week or two, foci of fibrinoid necrosis are replaced by collagenous matrix as the site of acute necrosis transforms into chronic scar. The initial infiltrating inflammatory cells are neutrophils, especially in polyarteritis nodosa; and monocytes, especially in Kawasaki disease. As the acute phase of inflammation transforms into the chronic phase of inflammation and sclerosis, macrophages and T lymphocytes become the predominant inflammatory cells.

The two major categories of MVV are PAN and KD. CHCC 2012 [1] defines PAN as necrotizing arteritis of medium or small arteries without glomerulonephritis or vasculitis in

arterioles, capillaries, or venules; and not associated with ANCA or mucocutaneous lymph node syndrome. The absence of ANCA helps distinguish the necrotizing arteritis of PAN from the histopathologically indistinguishable necrotizing arteritis of ANCA-associated vasculitis (AAV) [9, 10]. The absence of mucocutaneous lymph node syndrome distinguishes PAN from the necrotizing arteritis of KD [1]. Further, necrotizing arteritis that is indistinguishable from PAN also can secondarily occur in systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and other systemic autoimmune and autoinflammatory conditions; secondary to infection notably with the hepatitis B virus (HBV); and as a component of variable vessel vasculitis (VVV) in BD and CD; or as a SOV such as cutaneous arteritis.

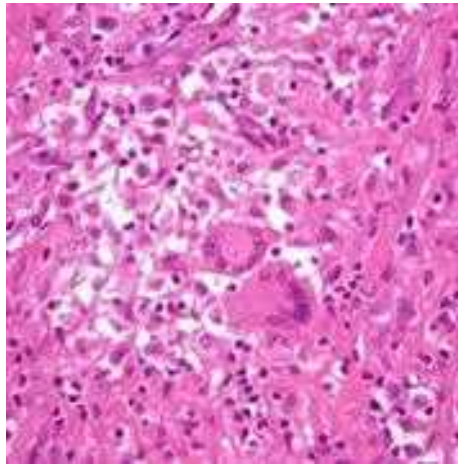


Figure 2. Multinucleated giant cells in the inflamed media of the aorta (aortitis) in a patient with giant cell arteritis (H&E stain).

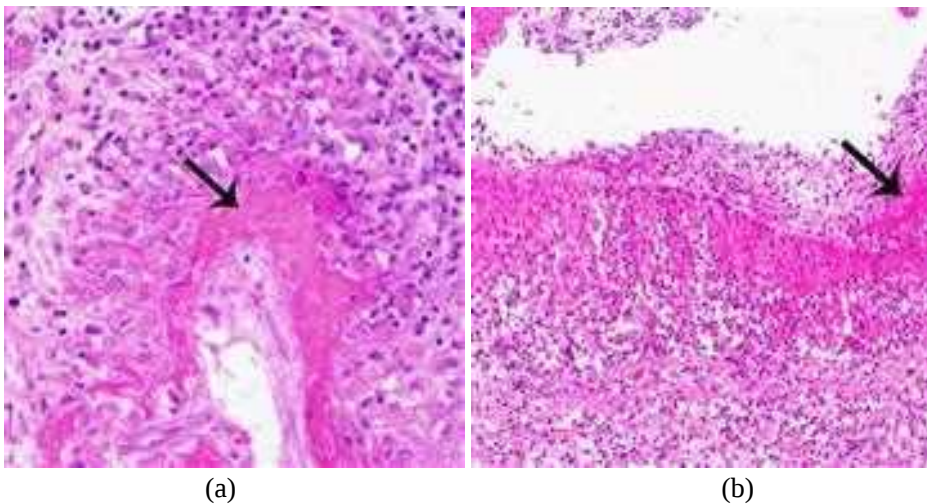


Figure 3. (a) (left): Irregular accumulation of eosinophilic fibrin in areas of fibrinoid necrosis with adjacent neutrophil-rich leukocyte infiltration in a medium artery in a patient with polyarteritis nodosa. (b) (right): Renal interlobar artery in a patient with Kawasaki disease with transmural inflammation including intimal arteritis, medial inflammation with dehiscence of medial cells, adventitial inflammation and a small focus of intimal fibrinoid necrosis (arrow).

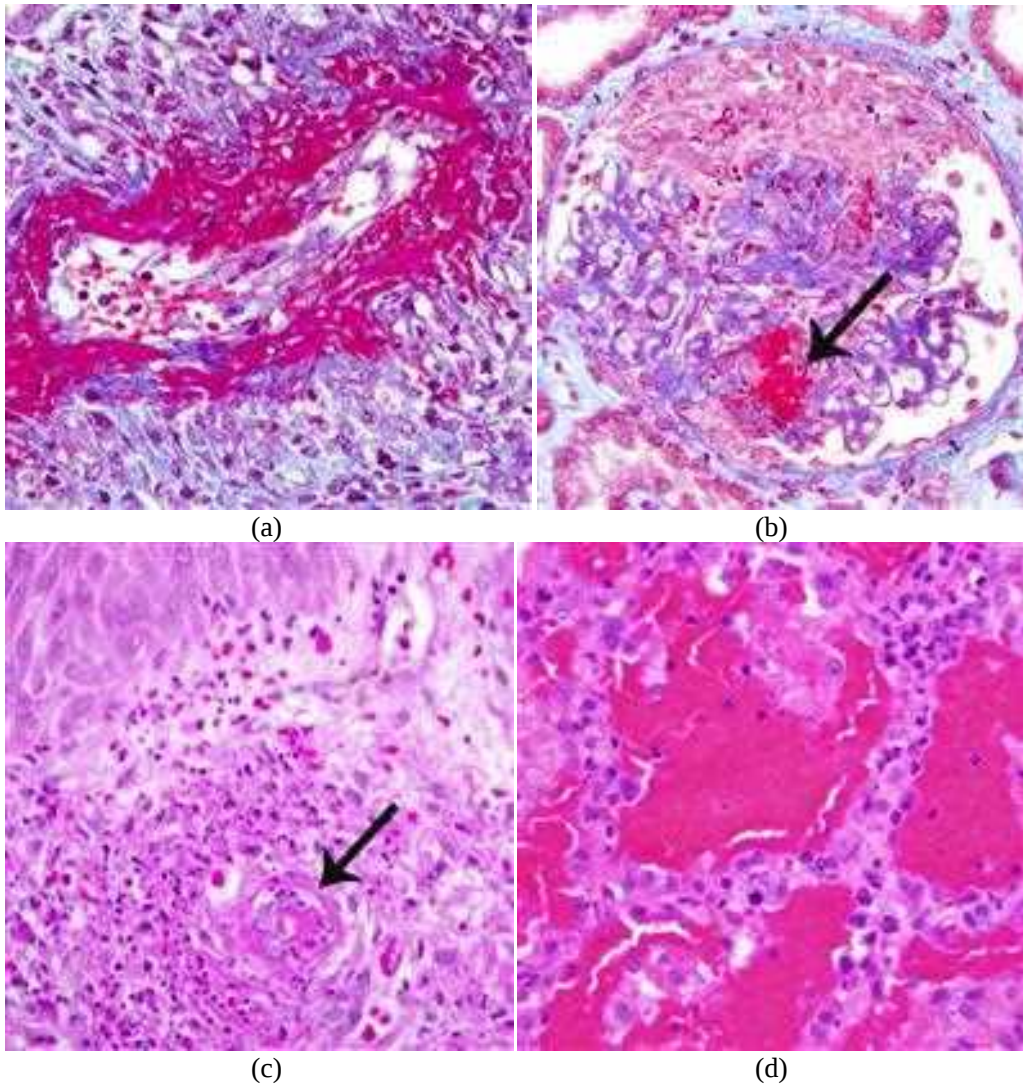


Figure 4. ANCA associated vasculitis with (a) necrotizing arteritis with extensive fibrinoid necrosis that stains red with a Masson trichrome stain, (b) glomerulonephritis with segmental fibrinoid necrosis (arrow) that is red with the Masson trichrome staining and a cellular crescent overlying the top of the tuft, (c) dermal leukocytoclastic angitis affecting a venule (arrow) with adjacent hemorrhage and leukocyte infiltration with numerous neutrophils and leukocyte nuclear fragmentation (leukocytoclasia), (d) hemorrhagic alveolar capillaritis with neutrophils in the alveolar septa and hemorrhage in the alveolar air spaces.

Thus, a diagnosis of PAN is a diagnosis of exclusion, that is, all other forms of vasculitis that can cause necrotizing arteritis must be excluded before a diagnosis of PAN is appropriate. In a clinical setting, this can be difficult and may require that a patient initially have a generic diagnosis of necrotizing arteries until a more specific diagnosis is warranted.

KD is defined as arteritis associated with the mucocutaneous lymph node syndrome and predominantly affecting medium and small arteries [1]. Coronary arteries are often involved although the aorta and other large arteries may be involved. KD usually occurs in infants and young children, with onset after 5 years old very uncommon. The acute necrotizing arteritis of

KD can resemble the acute lesion of PAN, which is why this disease was once called infantile PAN by some investigators. However, in general, compared to PAN the acute arteritis of KD has more monocytes, less neutrophils, and more vessel wall edema (medial cell dehiscence) and less fibrinoid necrosis (Figure 3B). Coronary arteritis can occur anywhere along the course of coronary arteries in the epicardium and myocardium, but occurs most often in the origin of the coronary arteries adjacent to the aorta. Inflammatory aneurysms form at the sites of inflammation and necrosis, and may induce thrombosis resulting in myocardial infarction, which is the major cause for mortality in KD.

SMALL VESSEL VASCULITIS (SVV)

CHCC 2012 [1] defines SVV as vasculitis predominantly affecting small vessels, defined as small intraparenchymal arteries, arterioles, capillaries and venules. Medium arteries and veins may be affected. As noted already, LVV and MVV also can affect arteries, and MVV can cause acute necrotizing inflammatory lesions in arteries that are indistinguishable from the lesions of SVV necrotizing arteritis. Both MVV and LVV cause necrotizing arteritis with conspicuous fibrinoid necrosis (Figure 3A and 4A). Thus, identifying arteritis does not distinguish between MVV and SVV. Whether or not arterioles are involved also is not an effective means of distinguishing between MVV and SVV because identifying arterioles versus small arteries is problematic. The most workable definition of arterioles is “the smallest branches of arteries.” Definitions of arterioles based on structural features such as layers of muscle cells in the media and absence on internal elastica; do not consistently identify a distinct vessel type.

Thus using arteriolar involvement is not a reliable approach to distinguishing between MVV and SVV. The best approach for identifying a SVV is to identify involvement of venules and capillaries, for example dermal venulitis (Figure 4C), glomerular capillaritis (glomerulonephritis) (Figure 4B) or pulmonary alveolar capillaritis (Figure 4D).

According to CHCC 2012 [1], SVV is further subcategorized on the basis of immunopathologic findings into AAV or immune complex SVV (Table 1) (Figure 1). AAV has few or no deposits of immunoglobulin or complement in affected vessel walls, whereas immune complex SVV has moderate to marked vessel wall deposits of immunoglobulin and/or complement components (Figure 5).

This paucity of immunostaining for immunoglobulins in involved vessels in patients with AAV is the basis for the pathologic term “pauci-immune” to distinguish AAV and glomerulonephritis from immune complex vasculitis and glomerulonephritis.

This subcategorization is warranted in part because there is compelling evidence that the ANCA and the vessel wall immune deposits are not only useful biomarkers for diagnosis but also are prime movers in the pathogenesis of the vascular inflammation [13].

ANTINEUTROPHIL CYTOPLASMIC ANTIBODY-ASSOCIATED VASCULITIS

CHCC 2012 [1] defines AAV as necrotizing vasculitis with few or no immune deposits, predominantly affecting small vessels including capillaries, venules, arterioles and small arteries, and association with MPO-ANCA or PR3-ANCA. However, not all patients have ANCA. A prefix should be added to the name indicating the ANCA reactivity, for example PR3-ANCA, MPO-ANCA, or ANCA-negative [1, 15].

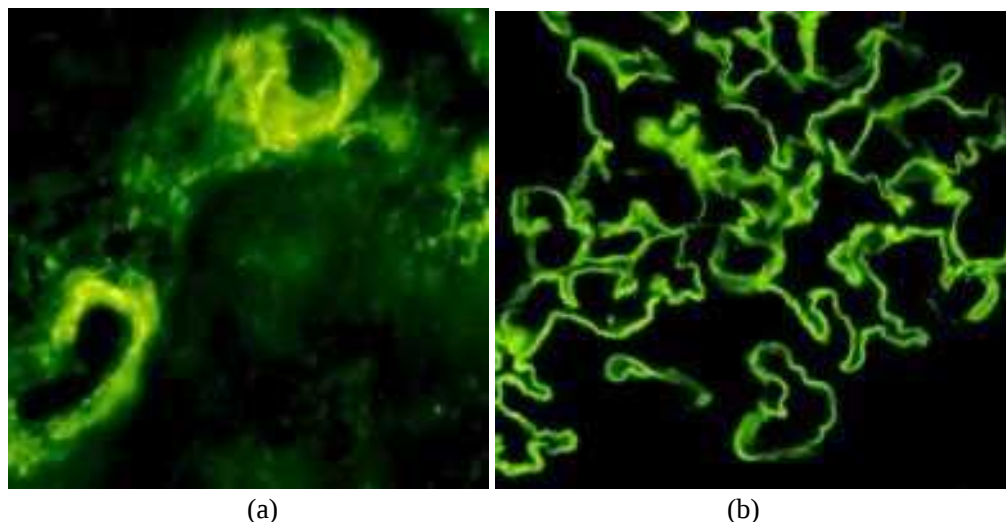
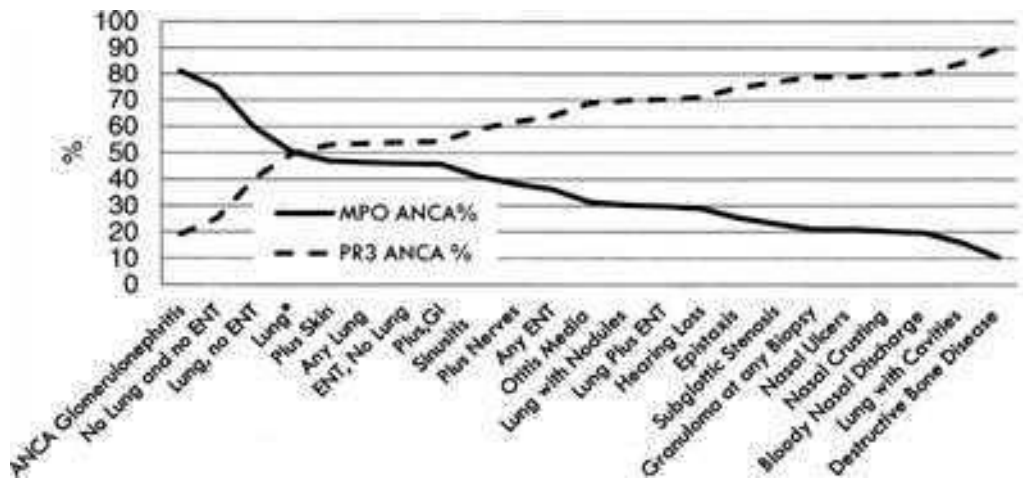


Figure 5. (a) Dermal venules with granular vessel wall staining for IgA in a patient with IgA vasculitis (Henoch-Schönlein purpura) (Fluoresceinated anti-IgA stain). (b) Glomerular capillary basement membranes with linear staining for IgG in a patient with anti-GBM disease (Fluoresceinated anti-IgG stain).

AAV are further categorized as MPA, GPA and EGPA [1]. Thus, when adequate information is available, an optimum AAV diagnosis based on CHCC 2012 includes both the ANCA serotype and the clinicopathologic phenotype, such as MPO-ANCA MPA, PR3-ANCA MPA, MPO-ANCA GPA, PR3-ANCA GPA, ANCA-negative GPA, and MPO-ANCA-EGPA. In a clinical setting, the serotype alone predicts some disease characteristics (Figure 6) and outcomes as for example the frequency of recurrence after induction of remission; while the clinicopathologic variant alone also predicts some disease characteristics and outcomes. However, the two together give a more complete picture about the patient and expected treatment [14, 15]. Thus, from a practical perspective, the available information may require that a more generic diagnosis be made initially, as for example MPO-ANCA AAV, and then refined after more thorough evaluation or as clinical manifestations evolve such as the emergence of compelling evidence for GPA rather than MPA.

MPA is defined as necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels such as capillaries, venules, and arterioles [1].



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Abbreviations: No Lung and No ENT (ear, nose and throat involvement): Vasculitis in any organ except the lungs and the ENT system; Lung no ENT: Vasculitis localized in the lungs but not in the ENT system; Lung: Vasculitis localized in the lungs without indicative markers such as nodules or cavities, or histological proof such as granulomas indicative of granulomatous inflammation; Plus Gastrointestinal (GI involvement): Vasculitis localized at any organ plus involvement of the gastrointestinal tract; Plus Skin: Vasculitis localized at any organ plus dermal involvement; Plus Nerves: Vasculitis localized at any organ plus involvement of the nerves; Any Lung: Any type of pulmonary vasculitis such as pulmonary hemorrhage, infiltrates, nodules, cavities, granulomas, or respiratory arrest; ENT, no Lung: Vasculitis localized to the ENT system but not in the lungs; Any ENT: Any type of vasculitic manifestation of the ENT system; Lung with nodules: Vasculitis localized at the lungs with radiographic proof of nodules; Lung plus ENT: Any type of pulmonary vasculitis plus any type of vasculitic manifestation of the ENT system.

Figure 6. Frequency of PR3- and MPO-ANCA specificity correlated with clinical manifestations of AAV disease. Organ groupings are not mutually exclusive.

Necrotizing arteritis involving small and medium arteries may be present (Figure 4A). Necrotizing glomerulonephritis is very common (Figure 4B). Pulmonary capillaritis often occurs (Figure 4D). Granulomatous inflammation is absent.

All of the lesions observed in MPA can occur in patients with GPA and EGPA. Thus, among patients with AAV, a diagnosis of MPA is a diagnosis of exclusion, once GPA and EGPA are ruled out. Of course, in a clinical setting this is never unequivocal, because a patient thought to have MPA may in fact have an occult focus of necrotizing granulomatosis. This may not be a major problem because the presentation at that time may be primarily as MPA, and if the GPA features become overt, the working diagnosis would change to GPA.

The histopathologic lesions of immune complex SVV can be indistinguishable from those of AAV. For example, leukocytoclastic angiitis or vasculitis (LCV) (Figure 4C) in the skin can be caused by any of the systemic variants of AAV including MPA, GPA, and EGPA, as well as, most if not all forms of immune complex SVV, including but not limited to IgAV, cryoglobulinemic vasculitis (CV) and serum sickness.

Light microscopy alone is not sufficient to identify the cause of LCV. Additional data are required, such as serologic findings and tissue immunostaining.

GPA is defined as necrotizing granulomatous inflammation usually involving the upper and lower respiratory tract, and necrotizing vasculitis affecting predominantly small to medium vessels such as capillaries, venules, arterioles, arteries and veins [1]. Necrotizing glomerulonephritis is common. The defining granulomatosis of GPA is a very destructive lesion that in the acute phase resembles an abscess (Figure 7A) more than a typical granuloma. In the acute phase, neutrophils predominate at the sites of granulomatosis, and a few scattered multinucleated giant cells are the only histologic features justifying a designation of granulomatosis.

However, as the lesions evolve, the neutrophils in the central zone of necrosis lyse and are replaced by amorphous necrotic debris, and epithelioid macrophages form palisades that wall of the zone of necrosis in a typical granulomatous pattern (Figure 7B).

EGPA is defined as eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small to medium vessels, and associated with asthma and eosinophilia. ANCA is more frequent when glomerulonephritis is present. The asthma that precedes EGPA typically is late onset, and affected patients often have a prodromal phase of eosinophil rich inflammatory disease for example eosinophilic pneumonia or eosinophilic gastroenteritis, prior to the onset of definitive manifestations for vasculitis or glomerulonephritis [15]. Eosinophils are conspicuous at sites of tissue inflammation, including sites of vasculitis (Figure 8).

However, similar prominence of eosinophils can be observed in lesion of MPA and GPA, thus this is not diagnostic in the absence of the asthma and blood eosinophilia.

With sensitive clinical assays, 90% or more of patients with active untreated MPA and GPA are ANCA positive, with PR3-ANCA more frequent in GPA and MPA in Europe and North America [16].

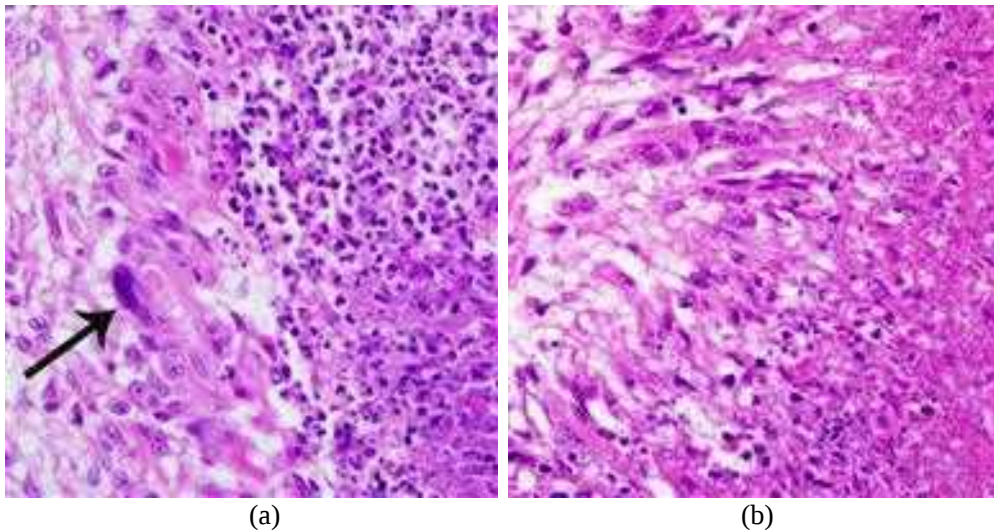


Figure 7. Lung tissue from a patient with granulomatosis with polyangiitis (Wegener's) showing (a) an early lesion with an intense infiltrate of neutrophils on the right and an adjacent accumulation of macrophages including a multinucleated giant cell (arrow), (b) more advanced granulomatosis with an amorphous zone of necrosis on the right and an adjacent zone of palisading epithelioid macrophages (Hematoxylin and eosin [H&E] stain).

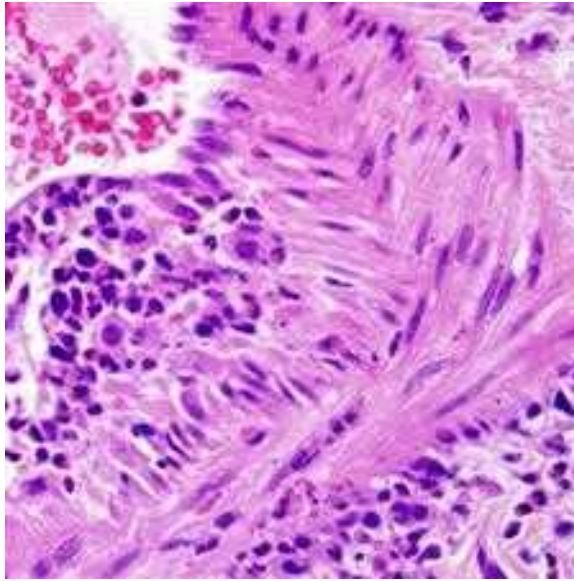


Figure 8. Arteritis in a patient with eosinophilic granulomatosis with polyangiitis (Churg-Strauss) showing intimal arteritis with numerous eosinophils in an expanded intima (left), scattered eosinophils in the media, and numerous eosinophils in the adventitia (right) (H&E stain).

However, <50% of patients with EGPA are positive for ANCA, almost always MPO-ANCA [16]. Interestingly, more than 75% of EGPA patients with renal disease are ANCA-positive compared to approximately 25% of EGPA patients with no clinical evidence for kidney disease [17].

Organ limited expressions of AAV occur, for example isolated cutaneous vasculitis, lung capillaritis, upper respiratory tract granulomatosis, or pauci-immune necrotizing and crescentic glomerulonephritis also called renal-limited vasculitis. In some but not all patients, multisystem involvement is identified later. Isolated granulomatosis often is considered a limited form of GPA and isolated vasculitis as a limited form of MPA if the lesions otherwise are identical to those observed in systemic AAV.

IMMUNE COMPLEX SMALL VESSEL VASCULITIS

CHCC 2012 [1] defines immune complex SVV as vasculitis with moderate to marked vessel wall deposits of immunoglobulin and/or complement components predominantly affecting small vessels such as capillaries, venules, arterioles and small arteries; glomerulonephritis is frequent.

Immune complex SVV differs immunopathologically from AAV with respect to the extent of immunoglobulin deposited in vessel walls. This most likely is a reflection of the different etiologies and pathogenic mechanisms. Immune complex vasculitis appears to result from initial extensive localization of immune complexes in vessel walls followed by complement activation and mediation of inflammation. The immunoglobulin is diffusely distributed in the walls of affected small vessels. In contrast, AAV appears to be mediated by more direct interaction of ANCA with neutrophils and monocytes resulting in activation that

in turn releases factors that activate the alternative complement pathway, which amplifies the inflammation to cause the severe necrotizing lesions of AAV [13].

There are many forms of immune complex SVV caused by immune complexes of different compositions. The antigens in pathogenic immune complexes can be derived from heterologous sources such as infectious pathogens or drugs, or from endogenous sources such as autoantigens. CHCC 2012 only defines several of these many variants: anti-glomerular basement membrane (anti-GBM) disease, CV, IgAV, and hypocomplementemic urticarial vasculitis (HUV) (anti-C1q vasculitis).

Anti-GBM disease is defined as vasculitis affecting glomerular capillaries, pulmonary capillaries, or both, with basement membrane deposition of anti-basement membrane autoantibodies. Lung involvement causes pulmonary hemorrhage, and renal involvement causes glomerulonephritis with necrosis and crescents.

From an immunopathologic perspective, anti-GBM disease is somewhat distinct from many other forms of immune complex vasculitis and glomerulonephritis because immunostaining of involved capillaries shows linear staining rather than granular staining (Figure 5B). This is because the target autoantigen is a diffusely distributed constituent component of the glomerular and alveolar capillary basement membranes, type IV collagen. Thus, immune complexes containing anti-GBM antibodies and type IV collagen form in situ diffusely along these basement membranes resulting in the linear staining. By contrast, other types of immune complexes gather stochastically and irregularly within vessels walls producing the granular pattern of immunostaining. The inflammatory vascular injury of anti-GBM disease affects glomerular capillaries, pulmonary capillaries, or both, with focal rupture of capillary walls and hemorrhage into the urinary space or alveolar air spaces.

By routine light microscopy, neutrophils often are not conspicuous at sites of necrosis, probably because they are destroyed in the process of activation and necrosis. However, in some lung specimens, more overt pulmonary capillaritis with influx of neutrophils is observed [18]. Approximately a third of patients with anti-GBM disease also have ANCA, usually MPO-ANCA [19]. They have an initial renal outcome more like anti-GBM disease than AAV with a higher rate of progression to end stage [19]. Renal biopsy specimens from patients with concurrent anti-GBM and ANCA may reveal necrotizing arteritis as well as glomerulonephritis.

Cryoglobulinemic vasculitis (CV) is defined as vasculitis with cryoglobulin immune deposits affecting small vessels (predominantly capillaries, venules, or arterioles) and associated with cryoglobulins in serum [1]. Skin, glomeruli and peripheral nerves are often involved. Localization of cryoglobulins in vessel walls incites inflammation (vasculitis) by complement activation [20, 21]. Monoclonal cryoglobulins (type I) are not as effective at activating inflammatory mediator systems as are mixed cryoglobulins (types II and III), which are immune complexes composed of anti-antibodies or rheumatoid factors (RF) bound to target antibodies. An important cause for cryoglobulinemia is hepatitis C virus (HCV) infection [21]. Acute CV affecting venules, arterioles and small arteries typically has neutrophilic infiltration with leukocytoclasia (Figure 9). The inflammation may be accompanied by luminal or vessel wall deposits of PAS-positive hyaline material composed of coagula of cryoglobulins (Figure 9). Cryoglobulinemic glomerulonephritis occurs as a renal limited process and as a component of systemic CV. Cryoglobulinemic glomerulonephritis usually has a membranoproliferative pattern but may have other patterns

of proliferative glomerulonephritis. A frequent finding is hyaline material in glomerular capillary lumens (“hyaline thrombi”) that are coagula of cryoglobulins.

Although glomerulonephritis is a frequent component of many forms of immune complex SVV, the glomerular lesions, including immunopathologic features, are very helpful in distinguishing among them, for example, CV with membranoproliferative lesions and IgG/IgM deposits, IgAV with IgA-dominant deposits, anti-GBM disease with necrosis and linear IgG, and AAV vasculitis with necrosis and a paucity of immunoglobulin deposits.

IgAV is defined as vasculitis, with IgA1-dominant immune deposits, predominantly affecting small vessels such as capillaries, venules, and arterioles (Figure 5A) [1]. IgAV often involves skin and gastrointestinal tract, and frequently causes arthritis. Glomerulonephritis indistinguishable from IgA nephropathy may occur. The shift in terminology to IgA vasculitis is prompted in part by mounting evidence that abnormally reduced glycosylation of the O-linked glycans in the hinge region of IgA1 molecules play a pivotal pathogenic role in IgA vasculitis and IgA nephropathy [22, 23].

In patients with these diseases, serum IgA1 has reduced terminal galactosylation and sialylation, resulting in increased exposure of N-acetylgalactosamine at the ends of the hinge region glycans. There also is evidence that patients have autoantibodies that recognize these abnormally glycosylated IgA1 hinge regions, which could result in immune complex formation. In addition to forming pathogenic immune complexes, abnormal glycosylation of the glycans in the hinge region of IgA1 molecules could play a pathogenic role through a variety of other mechanisms, such as reduced clearance from the circulation because of lack of receptor engagement by the abnormal IgA, increased aggregation of IgA in the circulation resulting in mesangial trapping, and increased affinity of the abnormal IgA for mesangial matrix.

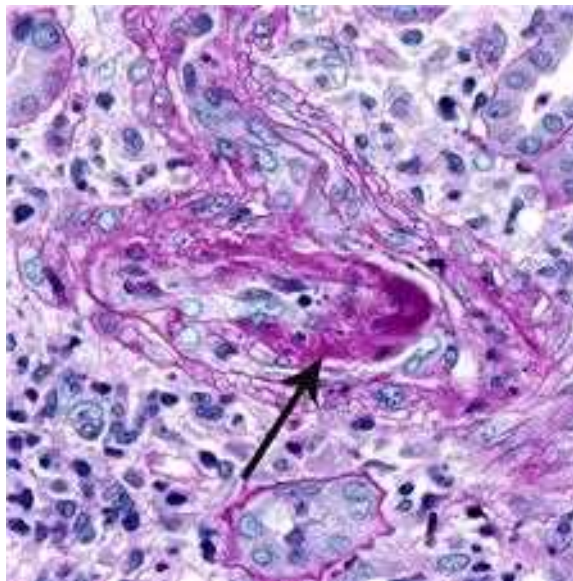


Figure 9. Inflammation of a small interlobular renal artery in a patient with cryoglobulinemic vasculitis. The arrow points to some hyaline material in the lumen that may be aggregated cryoglobulins. Some of the vessel wall leukocytes are undergoing leukocytoclasia (PAS stain).

Purpura hematuria and proteinuria are frequent clinical manifestations of IgA vasculitis that also are shared by other forms of SVV, including AAV and cryoglobulinemic vasculitis [24]. Demographic, clinical, laboratory and pathology observations all help resolve the differential diagnosis. For example, IgAV is most frequent in children, especially children under 10 years old, whereas AAV and CV are more common in older patients. However, all can occur at any age. Useful disease markers include immunohistologic findings such as IgA1 deposits, cryoglobulin deposits, and a paucity of deposits; and serologic tests under glycosylated IgA1, RF and ANCA.

The glomerular lesions in the kidney are indistinguishable from those of IgA nephropathy although necrosis, crescents and capillary wall deposits are somewhat more frequent in IgA vasculitis patients who undergo renal biopsy. In addition to the glomeruli, IgA1-dominant immune deposits occur in renal arterioles and peritubular capillaries in <20% of patients. IgA1-dominant immune deposits also can be identified in small vessels of the skin and gut; however, this is not of value in differentiating IgA vasculitis from IgA nephropathy because many IgA nephropathy patients also have IgA in dermal venules.

HUV is accompanied by urticaria and hypocomplementemia affects small vessels such as capillaries, venules, and arterioles, and is associated with anti-C1q antibodies [1]; glomerulonephritis, arthritis, obstructive pulmonary disease, and ocular inflammation are common.

HUV is characterized by recurrent episodes of urticaria with underlying leukocytoclastic vasculitis that causes hemorrhage into the lesions [24]. Skin manifestations include painful, tender, burning or pruritic lesions that persist for greater than 24 hours, often with central or diffuse areas of hemorrhage. HUV can be isolated or associated with autoimmune diseases (including lupus), infections, drug reactions, or neoplasms. Proteinuria and hematuria occur in 20-30% of patients and the underlying glomerular lesion usually has a membranoproliferative pattern, but other proliferative and focal necrotizing lesions may occur. Glomeruli and dermal vessels have granular deposits of IgG, IgA, IgM, C3 and C1q, which resembles the “full house” immunostaining seen in SLE.

IgG autoantibodies to the collagen-like region of C1q (anti-C1q) are usually present and may play a role in pathogenesis [25]. The hypocomplementemia appears to be secondary to classical pathway activation with reduced C1, C2, C4, and C3. The marked localized edema (urticarial) may be a manifestation of enhanced complement mediated vascular permeability resulting from an effect of anti-C1q antibodies on complement activation.

VARIABLE VESSEL VASCULITIS

VVV is a category of vasculitis that was not included in the CHCC 1994 nomenclature system [2]. The CHCC 2012 defines VVV as vasculitis with can affect vessels of any size (small, medium, and large) and type (arteries, veins, and capillaries). Two protean vasculitides are included, Behçet disease (BD) and Cogan’s syndrome (CS) [1]. Although these disease are rare and vasculitis caused by them is even rarer, they were included for completeness and so that they will be considered in the differential diagnosis of patients with vasculitis.

BD is clinically characterized by recurrent oral and/or genital aphthous ulcers accompanied by cutaneous, ocular, articular, gastrointestinal, and central nervous system (CNS) inflammatory lesions. Small vessel vasculitis, thromboangiitis, thrombosis, arteritis and arterial aneurysms may occur. The associated vasculitis can involve both arteries and veins of all sizes for example the aorta and large arteries to small mucosal and cutaneous veins, venules, arterioles and arteries (Figure 10) [24, 27-29]. The aorta and other large arteries such as the pulmonary arteries may demonstrate transmural neutrophil-rich inflammation resulting in aneurysm formation, and small vessels have leukocytoclastic angiitis. Aortitis and arteritis can result in aneurysm formation, vascular stenoses and occlusions. Arterial complications are less common than venous lesions, which include phlebitis and thrombosis. A variant called ‘vasculo-Beçet disease’ has prominent vascular complications including vasculitis, thrombosis, stenoses, occlusions, and aneurysms.

CS is clinically characterized by ocular inflammatory lesions, including interstitial keratitis, uveitis, and episcleritis, and inner ear disease, including sensorineural hearing loss and vestibular dysfunction [30-32]. The associated vasculitis which occurs in approximately 15% of affected patients, includes arteritis of small, medium or large arteries; aortitis, aortic aneurysms, and aortic and mitral valvulitis [1]. Involved vessels can have transmural infiltration of neutrophils in the acute phase.

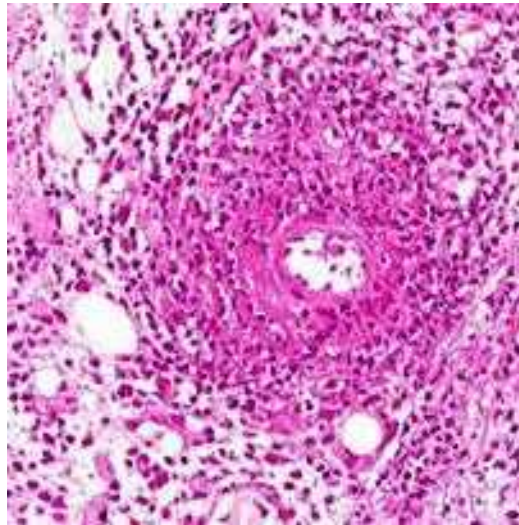


Figure 10. Leukocytoclastic angiitis affecting a small subcutaneous artery in a patient with Behçet's disease (H&E stain).

The differential diagnosis of a patient with CS includes GPA, EGPA, RV, and relapsing polychondritis, all of which may be complicated by inflammatory eye disease and, less commonly, sensorineural hearing loss [30].

SINGLE-ORGAN VASCULITIS

CHCC 2012 defines SOV as vasculitis in arteries or veins of any size in a single organ that has no features that indicate that it is a limited expression of a systemic vasculitis [1]. The

involved organ and vessel type should be included in the name, for example cutaneous small vessel vasculitis, testicular arteritis, and CNS vasculitis. Vasculitis distribution may be unifocal, multifocal or diffuse within an organ. Some patients originally diagnosed with SOV will develop additional disease manifestations that warrant redefining the case as one of the systemic vasculitides, as for example cutaneous arteritis later developing into systemic polyarteritis nodosa. A diagnosis of SOV always requires careful exclusion of systemic vasculitis.

Many forms of SOV have been reported, for example cutaneous LCV [24], cutaneous arteritis or cutaneous polyarteritis [24, 33, 34], primary angiitis of the CNS (PACNS) [35] or the equivalent term primary CNS vasculitis (PCNSV) [36]; isolated aortitis, and others [37]. The histopathologic pattern of injury can resemble any of the recognized forms of systemic vasculitis, although necrotizing arteries and granulomatous arteritis are most frequent.

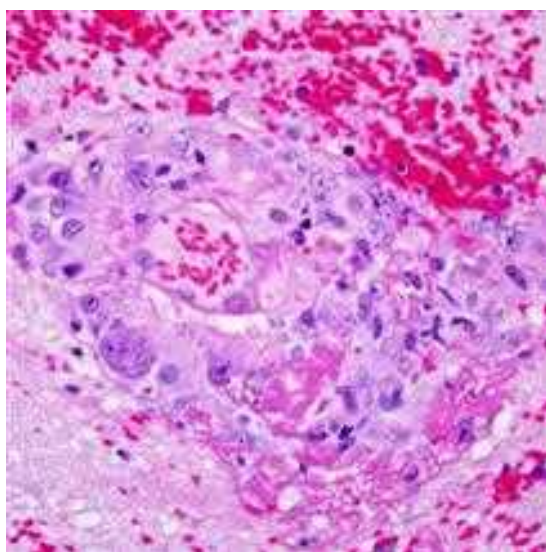


Figure 11. Primary central nervous system vasculitis (CNS single organ vasculitis) affecting a small intracerebral artery with granulomatous inflammation resulting in perivascular hemorrhage (H and E stain).

An extended period of surveillance is recommended to substantiate the accuracy of the diagnosis of SOV and that excision of the affected site provides a cure [37]. Moreover, CHCC 2012 recommends that the term SOV not be used for organ-limited expressions of vasculitides that usually have multisystem involvement, for example GPA confined to the lungs also known as lung-limited GPA; or ANCA-positive pauci-immune necrotizing glomerulonephritis without systemic vasculitis also known as renal-limited-AAV.

VASCULITIS ASSOCIATED WITH SYSTEMIC DISEASE

CHCC 2012 acknowledges that vasculitis can be associated with different systemic diseases, which may be causing the vasculitis [1]. Therefore the name or diagnosis should include a prefix term specifying the systemic disease such as rheumatoid vasculitis, lupus

vasculitis and sarcoid vasculitis (Figure 12). There is a subjective distinction between vasculitis secondary to a systemic inflammatory disease and vasculitis that is characteristic of a systemic inflammatory disease. In some instances, it may be a relatively infrequent feature of a systemic disease as for example vasculitis in rheumatoid arthritis, or a frequent feature and therefore characteristic component of the systemic disease, such as in GPA; however in CS, vasculitis falls into a gray zone. The important concept is that whenever a vasculitis is identified, the possibility of vasculitis secondary to a systemic disease should be considered.

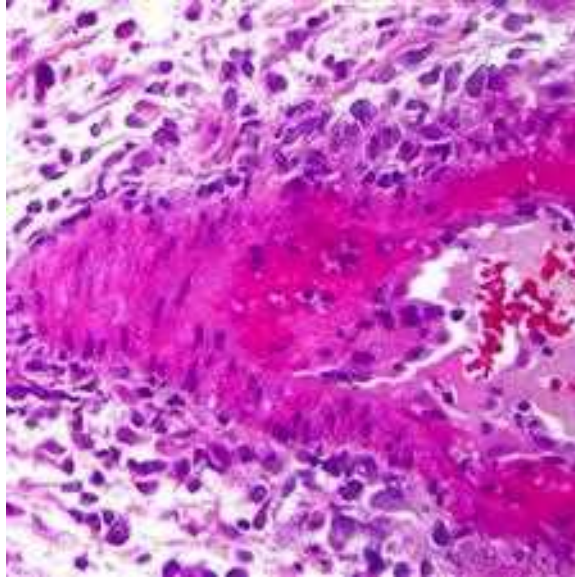


Figure 12. Necrotizing arteritis in the perirenal adipose tissue of a patient with systemic lupus erythematosus showing focal fibrinoid necrosis and leukocyte infiltration (H and E stain).

VASCULITIS ASSOCIATED WITH PROBABLE ETIOLOGY

CHCC 2012 acknowledges that vasculitis may be associated with a probable specific etiology [1]. In this case, the name or diagnosis should have a prefix term specifying the association, for example hydralazine-associated microscopic polyangiitis, HBV-associated vasculitis and HCV-associated CV, minocycline-associated vasculitis, and paraneoplastic vasculitis.

The likelihood that an association with a probable etiology is because of a causal relationship depends on the credibility of the supporting data. Some etiologic relationships are reflected in the names of major categories and others designate categorical subsets. For example, propylthiouracil-associated MPO-ANCA and HCV-associated CV are designations that each refer to two different etiologies that act in sequence to cause vasculitis, highlighting the importance of using diagnostic terms that provide information about likely or definite causes of vasculitis in a given patient.

Emerging data from genomic, proteomic and metabolomic studies are demonstrating previously unrecognized probable etiologies and pathogenic mechanisms [38]. Monogenic mutations have been discovered associated with various patterns of vasculitis. For example,

Deficiency of Adenosine deaminase 2 (DADA2) resulting from mutations in the CECR1 gene can cause a necrotizing vasculopathy that resembles PAN pathologically and clinically. However, DADA differs clinically from typical PAN because the onset usually is in childhood [39].

CONCLUSION

Many factors must be taken into consideration in rendering an accurate and precise clinical diagnosis of vasculitis in a given patient, such as the clinical signs and symptoms, results of laboratory tests, and the observed histopathology of involved organ tissue. Important parameters include the types of vessels affected, as for example arteries or venules; the pathologic features of the inflammatory process such as leukocytoclastic inflammation versus granulomatous inflammation; immunopathologic features such as IgA-dominant deposits or paucity of immunoglobulin in vessel walls; serologic findings such as cryoglobulins or ANCA; associated systemic disease such as RA or SLE; proximate etiologies such as HCV and propylthiouracil; the distribution of lesions to affected organ systems such as the lungs versus the gut; and any accompanying extravascular lesions such as necrotizing granulomatosis or aphthous ulcers, and other factors.

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Chapter 201

CLASSIFICATION OF PEDIATRIC VASCULITIDES

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ABSTRACT

The primary systemic vasculitides in childhood are quite uncommon with the exception of Ig A vasculitis (Henoch-Schönlein purpura) and Kawasaki disease. Although children and adults share many characteristics in vasculitis, they also differ in certain aspects of different vasculitic diseases. The criteria of the 2012 Chapel Hill Consensus nomenclature and the validated Ankara 2008 classification for childhood vasculitides can be applied to pediatric practice. Advances in the understanding and diagnosis of childhood primary systemic vasculitis will continue to shape classification criteria in the future.

Keywords: pediatric, vasculitis, classification

INTRODUCTION

Vasculitis is characterized by the inflammation of the blood vessels leading to vascular stenosis, occlusion, aneurysm, or rupture [1]. The vasculitides have specific vessel involvements, specific organ system choices and sometimes age selections. In fact, the types of vasculitis and their course differ in childhood. With an overall estimated incidence of childhood vasculitis of about 50 cases per 100,000 children per year [2], the most frequent vasculitic disorders are IgA Vasculitis (Henoch Schonlein purpura) (IgAV (HSP)) and Kawasaki disease (KD) [2]. The prevalence of childhood HSP and KD range from 13.5/100,000 for IgAV (HSP) [3, 4], and 135 to 200/100,000 IgAV/for KD in Japan to 9 to 17/100,000 in Caucasians [5]. This compares with the lower prevalence of adult vasculitides

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wherein the estimated annual incidence for IgAV (HSP) is 0.8 to 1.8/100 000 [6], and around 10/million total population for both granulomatosis with polyangiitis (GPA) (Wegener granulomatosis) and microscopic polyangiitis (MPA) [7, 8].

The 2012 revised definitions of the Chapel Hill consensus conference vastly improved the understanding of the vasculitides [9]. The new nomenclature is reviewed elsewhere in this volume, however neither are they intended to be classification or diagnostic criteria.

Many vasculitides affect both children and adults. However, some, like KD, occur exclusively in childhood, while others such as temporal arteritis rarely if ever occur in childhood. Children and adults also differ in the etiology, relative frequency of some clinical manifestations, and prognostic characteristics of different vasculitides [9, 10]. This may be due to immune system differences between adults and children. With aging, certain changes occur in the immune system. With aging, there is progressive thymic involution that decreases the number of naïve and regulatory T-cells. There is continuous reshaping of the immune repertoire by persistent antigenic challenges as well as, reduced production of naïve B cells and dysregulation of toll-like receptors that have major roles in innate immunity [11]. These changes may have direct linkages with different autoimmune disease susceptibility.

Disease classification systems are based on arbitrary combinations of different disease characteristics with the purpose of differentiation of closely related syndromes [12]. The primary objective of classification criteria is to define homogenous patient populations mainly for research purposes and epidemiological data; not to diagnose disease in individuals [13]. A diagnosis is made by considering all clinical features of the patient, not only the classification criteria [14]. However, classification criteria are used for diagnosis in practice, albeit with a low sensitivity [14]. In 1990, the American College of Rheumatology (ACR) proposed classification criteria for adult patients with vasculitides [16-20]. However, it had a number of shortcomings. For example, ACR criteria excluded MPA as a disease category, and there was no reference to antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitides (AAV) or KD [16-20]. In as much as the ACR criteria were not validated in children, they were not suitable for childhood vasculitis. With this background, in 2005, the vasculitis-working group of the Pediatric Rheumatology European Society (PRES) proposed preliminary classification criteria for some of the commonest childhood vasculitides: HSP/IgAV, childhood polyarteritis nodosa (PAN), GPA, childhood Takayasu arteritis (TA) and KD [21]. These criteria were validated and took the final form at the 2008 Ankara Consensus Conference with support from the European League Against Rheumatism (EULAR) and the Pediatric Rheumatology International Trials Organization (PRINTO) [22, 23]. In a recent study [24], the Ankara 2008 criteria performed better in a large cohort of North American GPA patients.

IGA VASCULITIS / HENOC-SCHÖNLEIN PURPURA

HSP/IgAV is the most common form of childhood vasculitis with an incidence of at least 135 per 1 million children [3, 4]. About 90% of IgAV/HSP patients are younger than 10 years of age [25]. The disease is less severe in children than in adults [26]. To fulfill ACR classification criteria for HSP/IgAV, two of the following are required: age < 20 years, palpable purpura, abdominal pain, and vessel wall granulocytes on biopsy [17].

During the revision process for children, the major change was to make palpable purpura a mandatory criterion [23]. The biopsy criterion was also revised as presence of IgA deposition in any biopsy to increase the specificity of the criteria in children. In addition, it is important to define IgA deposits as “predominant” to differentiate HSP/IgAV from other diseases with IgA deposits [22-24].

It was agreed to use the United Nations/UNICEF definition of a “child” as 18 years or less [27]. Thus, the age criterion in IgAV/HSP was deleted [21]. As the joint involvement is more common in children, it was added to the group of criteria [23]. Renal involvement is the main because of late morbidity and mortality in pediatric IgAV/HSP patients and approximately 40% of children with IgAV/HSP develop nephritis within six weeks of presentation [28]. Renal involvement was also considered as a new criterion to underline its importance in long-term prognosis [23].

In its final form, for IgAV/HSP classification, the Ankara 2008 criteria required the presence of palpable purpura with lower limb predominance plus one of the following four features: diffuse abdominal pain, any biopsy showing predominant IgA deposition, arthritis or arthralgia, and renal involvement (any hematuria and/or proteinuria). If purpura has an atypical distribution, the demonstration of IgA deposits in a biopsy is required [23]. The sensitivity and specificity of these criteria were found as 100% and 87% respectively in children [23].

KAWASAKI DISEASE

KD is an acute, self-limited systemic vasculitis of medium- and small-sized vessels predominantly occurring in children aged 6 months to 5 years [29]. It is the second most common childhood vasculitis and the leading cause of acquired heart disease in children in developed countries [30]. The distribution is worldwide. However, among children younger than 5 years of age, the incidence in Japan (135 to 200 per 100,000) is 10 to 15 times greater than the Caucasian incidence (9 to 17 per 100,000) [5].

KD classification was based on either Japanese or American classification criteria [31, 32]. The Japanese classification criteria for KD requires the presence of five of the following six features: characteristic fever, bilateral conjunctivitis, changes in lips and oral cavity, polymorphous exanthema, changes of peripheral extremities, and cervical lymphadenopathy [32]. The American classification required fever plus four of the remaining five criteria [31].

The major complication of KD is damage to coronary arteries; and while 25% of untreated KD patients suffer from coronary artery aneurysm, this decreases to 4% with proper treatment [33]. In the aforementioned 2006 criteria, it was agreed that a child with typical echocardiographic changes could be classified as KD without fulfilling four of the remaining criteria [21]. The second modification was the addition of perianal desquamation to the criterion describing the changes in extremities [21]. After these modifications, the classification criteria for KD included fever persisting for at least five days (mandatory criterion) plus four of five additional features: changes in the peripheral extremities or perianal area, polymorphous exanthema, bilateral conjunctival injection, changes of lips and oral cavity and/or injection of oral and pharyngeal mucosa, and cervical lymphadenopathy. In the case of fever and coronary artery disease detected by echocardiography, fever than four of

the remaining five criteria are enough to classify a patient as having KD [21]. The American Heart Association recently published suggestions for the diagnosis and management of KD [33].

POLYARTERITIS NODOSA

PAN is a necrotizing vasculitis characterized by aneurysmal nodules along the walls of predominantly medium-sized arteries and multi-organ involvement that affects individuals of all ages [30]. The estimated annual incidence is 2 to 9/million in adults in Europe and the United States [34]. The epidemiologic data are scarce in childhood. However, it is the third most common vasculitis after HSP and KD in children [10, 35].

The ACR requires at least three of the following 10 criteria for the diagnosis of PAN: granulocytic or mixed leukocytic infiltrates in a biopsy of an arterial wall, arteriographic abnormalities, livedo reticularis, myalgia, diastolic blood pressure >90 mmHg, mono or polyneuropathy, elevated blood urea nitrogen or creatinine, testicular pain/tenderness, hepatitis B reactants, and weight loss >4 kg [19].

Modified forms of ACR criteria were being used for PAN classification in childhood [36, 37], however, they were found insufficient, and so, all criteria were revised again.

As hepatitis B serology positivity is unusual in childhood PAN probably due to the vaccination protocols [10], this criterion was removed. Furthermore, according to the 2012 Chapel Hill nomenclature, if the vasculitis is related to hepatitis B infection, it should be classified under “vasculitis associated with probable etiology” [9]. Monogenic diseases may mimic common vasculitic disorders such that deficiency of adenosine deaminase2 mimics PAN with similar histopathological features [38].

The childhood PAN criteria designates the typical histopathology or angiographic abnormalities as a mandatory criterion [23]. In the final validation, the criteria for the signs and symptoms of vasculitis in specific organ systems and testicular pain and tenderness were removed [23]. With all these modifications, the criteria had a sensitivity of 89.6% and a specificity of 99.6% [23].

The Ankara 2008 classification for childhood PAN requires histologic evidence of necrotizing vasculitis in medium- or small-sized arteries or angiographic abnormalities (conventional angiography if magnetic resonance angiography is negative) as a mandatory criterion, plus one of the following five: skin involvement, myalgia or muscle tenderness, hypertension, peripheral neuropathy, and renal involvement [23]. Renal involvement is specified as involvement of medium to small size arteries excluding glomeruli.

CUTANEOUS PAN

CPAN is a form of PAN affecting small- and medium-sized vessels limited to the skin [39]. It constitutes a large group in pediatric practice. In an international survey of childhood vasculitis, approximately one-third of the children with PAN were categorized as CPAN [10]. Although there are no formal classification criteria for CPAN, in 2005, it was defined as cutaneous polyarteritis characterized by the presence of subcutaneous nodular, painful, non-purpuric lesions with or without livedo reticularis, and with no systemic involvement (except

for myalgia, arthralgia, and non-erosive arthritis) [22]. The other defined characteristic features were skin biopsy demonstrating necrotizing non-granulomatous vasculitis, negative tests for ANCA and association with evidence of streptococcal infection [22].

MICROSCOPIC POLYANGIITIS

MPA is a pauci-immune necrotizing small vessel vasculitis. Necrotizing glomerulonephritis occurs in most of the patients with MPA [40]. There are no specific classification criteria for MPA. However, it is described in the 2012 Chapel Hill Consensus Conference (CHCC) [9].

GRANULOMATOSIS WITH POLYANGIITIS (GPA) (WEGENER GRANULOMATOSIS)

GPA is a necrotizing ANCA-associated vasculitis affecting small- to medium-sized vessels [40]. AAV are rare in childhood with an incidence of 0.24/100,000 children annually with GPA as the most frequently diagnosed form [41].

For classification of GPA, the ACR criteria require two of the following four features: nasal-oral inflammation, abnormal chest X ray, abnormal urinalysis, and granulomatous inflammation on biopsy [20].

Approximately 90% of GPA patients are ANCA (mostly classical ANCA) positive [42]. So, any ANCA positivity was added as a new criterion. Most features of GPA are similar in children and adults. However, subglottic stenosis has been reported to be more common in pediatric patients [43, 44]. Based on these data, the presence of subglottic, tracheal, or endobronchial stenosis was added to the group of criteria [23]. Another minor modification was the addition of chest computed tomography (CT) scan results to the definitions based on radiological imaging [23].

According to the final classification, childhood GPA requires at least three of the following six criteria: granulomatous inflammation on biopsy, upper airway involvement, laryngo-trachea-bronchial stenosis, pulmonary involvement (chest radiograph or CT), any ANCA positivity, and renal involvement [23]. It had a sensitivity and specificity of 93.3% and 89.2% respectively, in the validation cohort [23]. In a study on 100 children with GPA, the Ankara 2008 criteria was significantly more sensitive than the ACR 1990 criteria in classifying these patients [24].

TAKAYASU ARTERITIS

TA is a granulomatous large vessel vasculitis involving the aorta and its main branches leading to stenosis and aneurysms [40]. The mean prevalence of TA was 4.7/million in adults [45]; however, pediatric incidence data for TA are not available. It is predominantly the disease of the third decade, but it can occur in children, as well [46]. In fact, 20% of all TA

patients are younger than 19 years of age at disease onset [47] and it has been suggested that age at onset younger than 15 years was associated with a probability of delay in diagnosis [48]. Thus, it is important for pediatricians to suspect and classify children with TA.

The ACR criteria for TA requires the presence of three of the following six criteria: age < 40 years, claudication of the extremities, decreased brachial pulse, and blood pressure difference >10 mmHg between arms, bruit over subclavian arteries or aorta, and arteriographic abnormalities [18].

During the process of revising these criteria for children, the age criterion was deleted and the “angiographic abnormalities” was made a mandatory criterion and modified with imaging modalities such as CT and magnetic resonance imaging (MRI) [23]. Hypertension may be the only symptom in children with TA at presentation, so it was included as a new criterion [21]. The increased acute phase reactants were also included in the criteria as this was an important finding before the onset of complications and could help with the differential diagnosis. With all these modifications, the criteria had a sensitivity of 100% and a specificity of 99% in children [23].

The final classification criteria for childhood TA are angiographic abnormalities of the aorta and its main branches and pulmonary arteries showing aneurysm/dilatation (mandatory criterion) plus one of the five as follows: pulse deficit or claudication, four-limb blood pressure discrepancy, bruits, hypertension, and elevation of acute phase reactants [23].

Finally yet importantly, a group of pediatricians has suggested new classification criteria for childhood Behçet diseases based on a large cohort of cases [49].

CONCLUSION

Primary systemic vasculitides are relatively uncommon in children as compared to adults. However, certain vasculitides such as KD do occur almost exclusively in childhood. Although children and adults may share many common characteristics in vasculitis, they differ in certain aspects such as the etiology, the frequency of some clinical manifestations, and prognosis. As most of the pediatric vasculitides are rare diseases, collaborative multicenter studies are needed to improve these criteria contemporaneously with advances in the diagnostic approach and improved etiopathogenic understanding of these disorders. The pediatric community is also awaiting the classification task led by the adult rheumatologists, which will surely affect our practice as well.

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Chapter 202

DETECTION TECHNIQUES AND CLINICAL RELEVANCE OF ANCA TESTING

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ABSTRACT

Antineutrophil cytoplasmic antibodies (ANCA) testing is an established diagnostic tool in the necrotizing small vessel vasculitis and their presence define ANCA-associated vasculitides (AAV) including granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic GPA (EGPA). These autoantibodies are also detected in a wide range of inflammatory and infectious diseases leading to a critical reappraisal in the diagnostic significance. The diagnostic utility of ANCA depends on the type of assay performed and the clinical setting. Methods of ANCA detection have been standardized in large multicenter studies. Classically, laboratories screen for ANCA by indirect immunofluorescence (IIF) on ethanol-fixed neutrophils, and positive IIF samples are further analyzed for antibodies to proteinase 3 (PR3) or myeloperoxidase (MPO) by immunoassay. Such diagnostic algorithm is based on an international consensus statement on testing and reporting of ANCA published in 1999. Novel methods for PR3- and MPO-ANCA detection have been developed to improve the performance of traditional ANCA-specific assays and new high quality immunoassays have been shown to have superior diagnostic performance compared to IFT. The 2017 revised consensus recommendations on ANCA testing state that high quality antigen-specific immunoassays are the preferred screening methodology for the diagnosis of ANCA-associated vasculitis. ANCA subtype (PR3-ANCA and MPO-ANCA) are associated with different epidemiological, genetic and clinical features. The remaining challenges in routine clinical practice include the methodological aspects of test performance by antigen-specific immunoassays, the application of testing in clinical settings with low pretest probability of vasculitis, and the value of serial testing in the prediction of disease relapse.

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Keywords: ANCA, proteinase 3, myeloperoxidase, ANCA-associated vasculitides

INTRODUCTION

In 1982, Davies and colleagues [2] discovered the association of the antineutrophil antibody in segmental necrotizing glomerulonephritis, and three years later, Van der Woude and coworkers [3] characterized their presence as a diagnostic tool and marker of disease in Wegener's granulomatosis. The spectrum of diseases associated with antineutrophil cytoplasmic antibodies (ANCA) has since increased. Two ANCA are highly associated markers for ANCA-associated vasculitides (AAV), the latter of which includes granulomatosis with polyangiitis (GPA, [Wegener's]), microscopic polyangiitis (MPA), eosinophil granulomatosis with polyangiitis (EGPA), and primary pauci-immune crescentic glomerulonephritis, namely C-ANCA synonymous with cytoplasmic fluorescence and specificity for proteinase 3 (PR3-ANCA) and P-ANCA with perinuclear fluorescence and specificity for myeloperoxidase (MPO-ANCA).

However, ANCA can be demonstrated in patients with inflammatory disease due to irritable bowel disease (IBD), autoimmune liver disease, rheumatoid arthritis (RA), drug-induced vasculitides and infections, often with multiple antigen specificities and unclear clinical significance. Accurate identification of all patients with AAV and the avoidance of misdiagnosis can be achieved by use a "gating policy" based on clinical information given to the laboratory at the time of request. This policy limits requests for ANCA testing exclusively to clinical scenarios that may suggest a diagnosis of necrotizing vasculitis.

The clinical utility of serial ANCA measurements for predicting and assessing clinical relapses is under discussion, but may be informative in subsets of patients, such as patients with renal involvement or alveolar hemorrhage and in patients treated with rituximab.

The new testing strategy for ANCA in vasculitis directly identifies the ANCA target antigen (PR3- and MPO-ANCA) and has a particular value for the AAV sub classification. Indeed, new studies have shown that AAV can be classified based on ANCA serotype, since PR3- and MPO-ANCA- diseases are strongly associated with distinguishable genetic alleles, different clinical and histological features. ANCA presence and the antigen specificity also may have important value as a prognostic factor and may serve as a guide for immunosuppressive therapy. This chapter considers current data on ANCA testing, the application of particular ANCA assays, and how such testing can be used in the management of patients with small-vessel vasculitis.

ANCA TESTING IN SMALL-VESSEL VASCULITIS

According to the international consensus statement of 1999 [5], ANCA testing by IFT for screening followed by mandatory antigen-specific ELISA for positive IFT tests [5, 6] has become the standard in many laboratories. The three major patterns demonstrated with IFT (Figure 1). The first is granular cytoplasmic neutrophil fluorescence with central interlobular accentuation ("C-ANCA") so noted overall in 90% of patients, in particular in active generalized GPA. The second is perinuclear neutrophil staining often with nuclear extension

(“P-ANCA”) so noted in those with MPA and EGPA. So-called “atypical” patterns are infrequent, comprising a mix of cytoplasmic and perinuclear fluorescence, with multiple antigen specificities such as in association with drug exposure, IBD and RA, most often in the absence of vasculitis [4]. However, the interpretation of IFT patterns can be tricky even for experienced laboratories, and studies have shown that misinterpretation can happen frequently. IFT is also a time consuming method, followed by ELISA as a two-step process even more so.

The alternative to conventional IFT is *image analysis*, which quantifies fluorescence in a single dilution of a patient sample in comparison with the intensity of standardized calibrators. Evaluation of the image analysis for the potential to detect ANCA in a cohort a consecutive PR3-ANCA positive GPA patients [10] revealed detectable ANCA levels in 75% of patients at the time of renal relapse, indicating a lower diagnostic sensitivity as compared with IFT and capture ELISA (100%). Quantitative image analysis predicted disease relapse somewhat better than IFT, but was comparable to direct ELISA [9].

Due to significant differences in sensitivity, specificity and predictive value among commercially available ANCA ELISA kits the combined method of IFT and ELISA have been shown to provide the highest diagnostic performance in a meta-analysis [22]. In recent years, many new developments for ANCA testing have become available. New solid phase methods like chemiluminescent immunoassays (CLIA), addressable laser bead immunoassays, fluorescent-enzyme immunoassays (FEIA) and line or dot immunoassays as well as IFT assays have become commercially available.

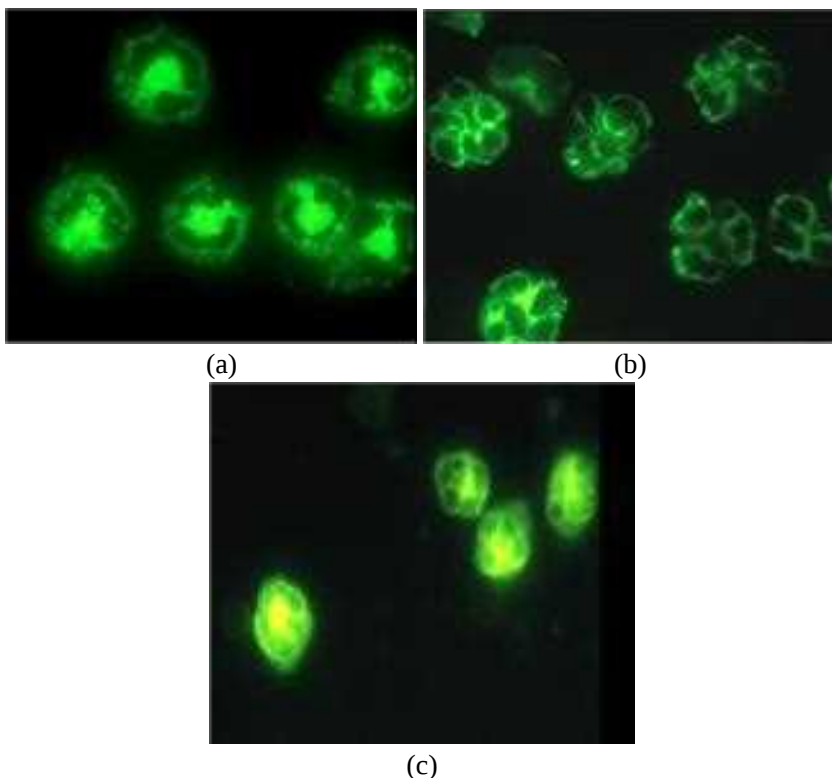


Figure 1. ANCA immunofluorescence patterns on ethanol-fixed neutrophils. (a) C-ANCA; (b) P-ANCA; and (c) A-ANCA.

A *multiplex* technology offers the unique opportunity to detect the presence of multiple autoantibodies at the same time and in the same sample. This new automated immunoassay builds on a synthesis of bead-based multiplex assays and flow cytometry. Trevisin and colleagues [11] compared the performance of a flow cytometric immunoassay for PR3 and MPO-ANCA with IFT and ELISAs in active and treated vasculitis and inflammatory bowel disease and found a specificity of 88% compared with 96% and 94% respectively for IFT and both ELISA. The PR3- and MPO-ANCA immunoassay was almost as sensitive as IFT, and more sensitive than, but just as specific as most ELISA in detecting ANCA in active and treated vasculitis [11]. A major advantage of this assay is the ability to screen simultaneously for a panel of autoantibodies relevant to vasculitis, however, prospective studies are needed this automated method in the initial screening of patients with suspected vasculitis.

With the emergence of new detection technologies, a comparative study to challenge current recommendations seemed required. In 2016 a multicenter study [21] led by the European Vasculitis Society (EUVAS) compared sensitivity and specificity of various antigen specific immunoassays and IFT. The results showed no significant difference for several classical ELISA, automated FEIA, chemiluminescence assay, multiplexed flow immunoassay and multiplexed microbead IFT assay. Furthermore, the study showed a significant difference and high variability in the performance of IFT at two expert laboratories. Differences between automated multiparameter IFT devices were also observed. Thus, the diagnostic value of immunoassays is at least as high as, if not better than IFT [21].

In 2017, a revised international consensus on ANCA detection has been published [1]. Screening for ANCA by high-quality immunoassays is recommended as the preferred method. IFT adds little value to ANCA screening, especially if the pre-test probability for AAV is high. If test results for both PR3-ANCA and MPO-ANCA are negative, yet the clinical likelihood of small-vessel vasculitis is high, then using another immunoassay or IFT, or referral to an experienced laboratory is recommended.

DIAGNOSTIC SIGNIFICANCE OF ANCA

Whereas PR3- and MPO-ANCA have been shown to be highly specific for AAV, the diagnostic value of such testing in other non-vasculitic conditions is very limited. An overestimation of the diagnostic relevance of a positive ANCA test may erroneously misdirect clinicians and delay adequate treatment. ANCA-positivity has been noted in diverse autoimmune disorders. Among them the connective tissue diseases systemic lupus erythematosus, RA, and Felty syndrome; the gastrointestinal disorders including ulcerative colitis, Crohn disease, and autoimmune hepatitis; infectious disorders including tuberculosis, leprosy, and subacute bacterial endocarditis; malignancy, and in association with the drugs propylthiouracil, hydralazine, and illicit cocaine use. Since the diagnostic accuracy of ANCA testing in vasculitis should be improved by an increased pretest probability, it makes sense that such testing should be guided by the likelihood of AAV. According to the consensus statement [1], adherence to clinical ordering guidelines for ANCA, testing can reduce the number of false-positive tests by 27% without missing a single patient with AAV [12]. A symptom related gating policy for ANCA testing could reduce the total number of ANCA tests performed by more than 20% with appreciably increased efficiency and cost saving.

Arnold and colleagues [13] investigated the impact of a gating policy at a single regional center in the year prior to and following the consensus guidelines [5] to ensure appropriate usage by auditing clinical outcomes in patients in whom ANCA testing was declined and documenting the absence of either GPA or MPA in all so studied. Their findings demonstrated that adherence to gating policy for ANCA testing coupled with close liaison between clinician and laboratory does not result in either a missed or delayed diagnosis of a small-vessel vasculitis belonging to the GPA-MPA spectrum.

ANCA LEVELS AND DISEASE ACTIVITY

The clinical usefulness of measuring ANCA levels in relation to disease activity and in guiding therapy is still controversial. Although ANCA titers are typically high at presentation and predictably relate to disease activity [14], there are potential confounders of the relationship between ANCA levels and disease activity including, publication bias against negative results, definition of relapse, intensity of clinical screening for disease activity, intervals of follow-up visit, and variable methods and intervals employed in sequential ANCA detection. A rise in serial ANCA measurements in patients with AAV presumably in remission status can be a clue to the prediction of disease relapse. However ANCA levels should not be used alone to guide treatment. Notwithstanding, a significant increase in ANCA levels or the reappearance of ANCA in the proper clinical and histopathological context, may suggest the need for more attentive management.

PR3- AND MPO-ANCA-SUBTYPES

Of all the possible known ANCA target antigens, only two, PR3 and MPO are closely associated with small-vessel vasculitis. Extra renal manifestations, granuloma formation and relapse were more frequent in patients with PR3-ANCA than in those with MPO-ANCA [15, 16]. Among 173 patients screened at the time of diagnosis with renal biopsy tissue, both active and chronic renal lesions were more common in MPO-ANCA-positive than PR3-ANCA-positive [17]. Despite substantial overlap, there were clinical and pathologic differences between patients with PR3-ANCA and MPO-ANCA that may reflect different pathogenic interactions between ANCA, their target antigens, and organ involvement at the molecular level. A genome-wide association study [18] confirmed a genetic component in the pathogenesis of AAV revealing distinctions between GPA and MPA that were associated with ANCA specificity, suggesting that the response against PR3-ANCA was a central pathogenic feature of PR3-ANCA associated vasculitis. Moreover, the strongest genetic associations were with antigenic specificity of ANCA, not the clinical syndrome. *HLA-DP* and the genes encoding α_1 -antitrypsin (*SERPINA1*), proteinase 3 (*PRTN3*) were associated with PR3-ANCA specificity, whereas MPO-ANCA was associated with *HLA-DQ*.

About 10% of patients with GPA do not have demonstrable ANCA by IFT or antigen specific assays and are likely to have localized disease. Moreover, ANCA-negative patients and generalized GPA tend to be younger in age, more likely to be of female gender, with less

lung and kidney involvement, lower rate of relapse, and improved outcome compared to those ANCA-positive patients.

Since ANCA specificity seems to affect the phenotype of small vessel vasculitis, the initial response to remission-inducing drug therapy, long-term prognosis and relapse risk more than the clinical diagnosis, it has been suggested that classification of AAV by ANCA specificity could provide more useful information than clinical diagnosis [19].

CONCLUSION

ANCA serology and the associated clinical manifestation of AAV continue to attract the attention of clinicians and investigators alike. In addition, to be providing a useful diagnostic tool for small vessel vasculitis, ANCA testing may be useful in predicting relapses and in guiding therapy. Worldwide, most laboratories currently perform IFT to screen for ANCA positivity patients with small-vessel vasculitis, with later confirmation employing PR3- and MPO-ANCA immunoassays. However, in recent studies new high-quality antigen-specific immuno-assays have been shown to have equal or better diagnostic performance than IFT. Therefore, the new international consensus of 2016 recommends screening for ANCA with immunoassays primarily since there is no apparent benefit of combining it with IFT. Notwithstanding, any testing strategy applicable to vasculitis should be able to identify relevant ANCA target antigens since these correlate best with the clinicopathological aspects, disease activity, and propensity for relapse. The solution to problems regarding ANCA-diagnosis lies in focusing upon the implementation of high-quality immunoassay testing according to the revised international consensus, and restriction of such tests to those with the highest pretest probability of AAV.

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Chapter 203

CLASSIFICATION AND PATHOGENICITY OF ANCA-ASSOCIATED VASCULITIS

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ABSTRACT

Anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitides (AAV) include several distinct multi-systemic disorders, the diagnoses of which rely on recognition of a compatible clinical syndrome supported by radiological, immunological and histological laboratory findings. If unrecognized, there may be significant delays in treatment culminating in multi-organ morbidity. The pathogenesis of AAV is complex, involving both innate and adaptive immune systems, with loss of tolerance to autoantigens leading to the production of antibodies that activate cytokine-primed neutrophils. The factors leading to production of ANCA are incompletely understood, but may involve cross-reactivity to bacterial antigens and the expression of complementary peptides. T-cells appear to play a role in both loss of self-tolerance and in the cause of tissue injury. Moreover, peripheral blood T-cells show evidence of persistent activation driven partly by cytomegalovirus infection. Activation of the alternative complement pathway has recently emerged as a significant pathogenic mechanism in the development of glomerulonephritis in AAV.

Keywords: ANCA, vasculitides, classification, pathogenesis, pathogenicity

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INTRODUCTION

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are a group of rare life-threatening autoimmune disorders that includes microscopic polyangiitis (MPA) and its renal limited variant (RLV), granulomatosis with polyangiitis (GPA, previously known as Wegner’s granulomatosis), and eosinophilic granulomatosis with polyangiitis (EGPA; previously known as Churg-Strauss syndrome (CSS)). Although these diseases can manifest in many different ways, there is significant overlap between GPA, MPA and RLV in clinical features, presentation, pathogenesis and treatment. This article reviews the current understanding of classification and pathogenesis of MPA, RLV and GPA.

EPIDEMIOLOGY

AAV are rare diseases with an annual incidence of <10 per million population [1, 2] and peak age of onset in the seventh and eight decades [3]. They form a highly heterogeneous group, both in terms of severity and organ involvement, and thus manifest in a wide variety of clinical presentations.

NOMENCLATURE AND CLASSIFICATION

Although there are no diagnostic criteria, the Chapel Hill Consensus Conference (CHCC) (Table 1) [4] provided useful nomenclature and definitions for the classification of the vasculitides, classifying AAV as small-vessel vasculitides (SVV) according to the caliber of the vessels involved and associated clinicopathological features. Subsequently, the European Medicines Agency (EMA) algorithm was developed to accurately classify patients with AAV for epidemiological studies [5, 6]. This algorithm employs clinical, serological, histological and radiological criteria to minimize the problem of patients being unclassified or assigned to overlapping categories. Table 2 shows an extent and severity categorization of AAV utilized by the European Vasculitis Study Group [7]. Revised classification criteria and validated diagnostic criteria are currently under development.

Table 1. Chapel Hill Consensus Conference on the nomenclature of systemic vasculitis: definitions [4]*

Granulomatosis with polyangiitis (Wegener’s) (GPA)	Granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small to medium-sized vessels (e.g., capillaries, venules, arterioles, and arteries). Necrotizing glomerulonephritis is common.
Microscopic polyangiitis (MPA)	Necrotizing vasculitis, with few or no immune deposits, affecting small vessels (i.e., capillaries, venules, or arterioles). Necrotizing arteritis involving small and medium-sized arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs.
Renal limited vasculitis (RLV)	Pauci-immune necrotizing glomerulonephritis with no apparent extra-renal features at presentations.

*Adapted from reference 4.

Table 2. European Vasculitis Study Group disease extent and severity categorization for antineutrophil cytoplasmic antibody-associated vasculitides [7]*

Category	Definition
Localized	Upper and/or respiratory tract disease with systemic involvement or constitutional symptoms
Early systemic	Any, but without any imminent organ-threatening or life-threatening disease
Generalized	Renal or other organ-threatening disease with serum creatinine <500µmol/L (5.6mg/dL)
Severe	Renal or other vital organ failure with serum creatinine >500µmol/L (5.6mg/dL)
Refractory	Progressive disease unresponsive to glucocorticoids and cyclophosphamide

*Adapted from reference 5.

CLINICAL PRESENTATION

The clinical presentation can be divided into systemic symptoms and organ-specific symptoms, the former commonly including fever, night sweats, malaise, weight loss, arthralgia and myalgia which may occur multiply and wax and wane over several months [8]. About 96% of patients with GPA and 88% of those with MPA have systemic symptoms at presentation [9]. Due to the highly variable presentation and lack of diagnostic criteria there may be significant delay in establishing the diagnosis in GPA and MPA, with respective median times from symptom onset to diagnosis of 4.5 and 6 months [9]. The single most notable difference between GPA and MPA or RLV is the presence of granulomata in GPA which are not seen in MPA or RLV.

Ophthalmic

AAV may cause inflammation of various structures of the eye including the lids and nasolacrimal system. Lane and colleagues [9] described ophthalmic involvement in 40% of patients with GPA at the time of presentation compared to 4% of those with MPA; and in 48% of patients with GPA at some point during the disease. Such involvement ranges from mild inflammation to severe sight-threatening inflammation with episcleritis, conjunctivitis, scleritis, keratitis, uveitis, and retinal vasculitis [10]. Eye redness may be painless or severely painful, and proptosis, diplopia and visual loss may occur secondary to retrobulbar orbital pseudotumor [11]. Intra-ocular granulomata may also develop and need to be differentiated from tumors. Nasolacrimal duct obstruction occurs in approximately 10% of patients with GPA and results in chronic epiphora and places patients at increased risk of chronic infection [10]. Fibro-vascularization of the palpebral surface of the eyelids may result in entropion and trichiasis [12, 13]. Optic nerve ischemia may also occur [8].

Ear, Nose and Throat (ENT)

Up to 77% of patients with GPA will have upper respiratory tract symptoms at presentation compared to 29% of those with MPA [9]. Nasal disease is more common than

deafness and middle ear involvement in both GPA and MPA. More than 90% of patients with GPA develop ear and upper airway disease [14, 15]. Typical nasal symptoms of GPA include rhinitis, nasal stuffiness and pain, epistaxis, and brown or bloody crusting. The characteristic “saddle-nose deformity” is secondary to septal erosion due to chronic nasal inflammation. Patients with GPA are at increased risk of nasal and sinus infections due to chronic damage which increases the difficulty in differentiating secondary infection from disease activity.

Middle ear involvement in GPA presents as conductive hearing loss with the commonest cause being Eustachian tube dysfunction secondary to nasopharyngeal disease [16, 17]. Sensorineural hearing loss is due to inner ear disease which may also be associated with vestibular dysfunction with some patients presenting with vertigo and balance disturbance [17, 18]. The mechanism of inner ear involvement in GPA is poorly understood when compared to middle ear involvement [19].

Involvement of the trachea may present with pain, cough, hoarseness, wheezing or stridor, however it is often asymptomatic at onset. The development of subglottic or bronchial stenosis can lead to severe dyspnea requiring tracheostomy or reconstruction [11].

Pulmonary

Pulmonary involvement occurred at presentation in 63% of patients with GPA compared to 29% of those with MPA [9]. Pulmonary manifestations range from new-onset asthma and ‘antibiotic-resistant’ pneumonia to life-threatening alveolar hemorrhage. In those with GPA the symptoms may be due to single or multiple lung nodules and granulomata, and may be misdiagnosed as cavitating infectious or neoplastic lesions; mediastinal and hilar lymphadenopathy may also occur [20]. Pulmonary capillaritis is responsible for lung hemorrhage and rapidly changing alveolar infiltrates and should be suspected in patients with falling hemoglobin levels in conjunction with hemoptysis and dyspnea. Those with MPA may also develop pulmonary interstitial fibrosis [21]. Other indicators of pulmonary involvement include wheezing, productive or non-productive cough, and exertional dyspnea. [8].

Renal

This is often a severe manifestation of AAV [3] that affects an estimated 77% of patients with GPA and 92% of those with MPA at presentation [9]. Renal vasculitis presents with proteinuria, hematuria, and red cell casts due to focal necrotizing glomerulonephritis [22]. It can lead to rapid deterioration of renal function with eventual dialysis dependency. Hematuria may be visible or non-visible, while proteinuria is usually insufficient to cause nephrotic syndrome [8]. Renal biopsy is the most appropriate method of identifying and prognosticating glomerulonephritis in AAV [23, 24].

Nervous System

AAV can affect the peripheral (PNS) and central nervous system (CNS), as observed in 19% of patients with GPA and 17% of those with MPA at presentation [9]. Involvement of

the PNS usually manifests as motor or sensory deficits in a mononeuritis multiplex or distal sensory polyneuropathy distribution. While typically painless in the acute stage, pain syndromes commonly develop as a result of neuro-regeneration. Involvement of the CNS occurs in 8% of patients with AAV at presentation [15], presenting with weakness, dysphagia, blindness or other CNS disturbances [25]. Three distinct patterns of CNS involvement have been identified: during the generalized phase the small and medium sized vessels of the CNS can become inflamed; secondly, localized granulomatous masses from the upper respiratory tract may invade the CNS; thirdly, granulomata may develop within CNS structures [26].

Cutaneous

Cutaneous involvement occurs in 42% of GPA and 25% of MPA patients at diagnosis [9]. A wide range of signs are seen that include purpura, papules, urticaria, infiltrative erythema, infarction and splinter hemorrhage, ulcerated nodules, livedo reticularis, and digital gangrene [27]. The type of lesion is determined by the size of the blood vessel affected. The most common manifestation is a palpable purpuric rash beginning along the lower extremities that may become ulcerated or vesicular. The urticarial rash seen in vasculitis can be differentiated from allergic non-vasculitic urticaria by the fact that it will usually last for more than one day and may progress to purpuric lesions [28].

Cardiac

Direct cardiac involvement is uncommon in either GPA or MPA however the former may be associated with coronary arteritis, pericarditis and valvular disease. Endocarditis can occur as a result of aortic valvular lesions [29]. MPA may be associated with pericarditis, heart failure and hypertension however the incidence is very low [30].

Gastrointestinal

Gastrointestinal involvement occurs at presentation in up to 30% of patients with AAV [14, 31-33]. Gastrointestinal involvement may present with ischemic or vasculitic colitis, bloody diarrhea, pain and progression to ulceration, perforation and infarction [11, 34]. 30-56% of patients with MPA have been found to have GI involvement [35, 36], the commonest presenting symptom of which was pain, noted in 97% of patients, followed by nausea, vomiting, diarrhea, melena, and hematemesis [37]. Rarely, other intra-abdominal organs can be involved such as the gallbladder and pancreas [34].

ETIOPATHOGENESIS

There is evidence for a pathogenic role of ANCA in the etiopathogenesis of inflammation and organ damage mediated by immune mechanisms. With regards to the innate immune

system, neutrophils play a pivotal role in the effector phase causing organ and tissue damage. Complement activation, particularly the alternative pathway, seems to be important in glomerulonephritis. The adaptive immune system is important in the development of autoimmunity with the production of autoantibodies against proteinase 3 or myeloperoxidase by B-cells and there is increasing evidence for a pathogenic role for T-cells. Genetic susceptibility factors are encoded by certain human leukocyte antigen (HLA) haplotypes [38], notably *HLA-DPB1*0401* alleles are associated with an increased risk for development of GPA [39], while *HLA-DRB1*0901* is associated with MPA [40]. In addition, the *DRB1*15* haplotype was associated with anti-PR3 AAV in African American patients [41]. Polymorphisms of genes involved in the control of the immune system and associated with increased risk of vasculitis include *CD226*, *PTPN22* protein, *CTLA-4*, *IL-10*, and *TLR9* [42-47], although none are specific for AAV. A recent genome-wide association study correlated single-nucleotide polymorphisms in *HLA-DPB1* and *PRTN3* with frequency of autoreactive T-cells and neutrophil expression of PR3 [48], thus providing a functional link between genetic risk factors and the immunopathology of AAV.

Copy number variation of *FcγR3b* and human β -defensin (*DEFB4*) may represent further important mechanisms in AAV susceptibility [42, 49]. Genes expressed by memory T-cells as well as a *CD8+* T-cell transcription signature have been described in both systemic lupus erythematosus and AAV with associated poorer outcome. This signature is thought to comprise enriching genes involved in the *IL-7* receptor and T-cell receptor signaling pathway [50].

Recent work by Yang and colleagues [51] has addressed the contribution of epigenetic mechanisms to AAV pathogenesis. Chromatin immunoprecipitation (ChIP) performed on peripheral blood neutrophils demonstrated an association between specific histone modifications at the *MPO* and *PRTN3* loci and active AAV. However, it is unclear whether these histone modifications in themselves play a pathogenic role.

Carriage of the dysfunctional *z* allele of the α -1-antitrypsin (*A1AT*) gene is associated with an increased risk of developing AAV and predicts more severe outcomes [52-57]. Patients carrying the *z* allele not only have an increased risk of AAV but also have increased concentrations of circulating *A1AT* polymers capable of priming circulating neutrophils for ANCA-induced activation [58].

Environmental factors may also have a role in disease development. Provocation of an immune response and inflammation is thought to occur after exposure to silica dust with 22-46% of patients with AAV having documented exposure to silica prior to disease development. It is proposed that exposure results in accelerated apoptosis of macrophages and polymorphonuclear leukocytes, thereby triggering disease development [59, 60].

Infectious triggers have also been implicated in the etiopathogenesis of AAV. A contributory role of low-grade *Staphylococcus aureus* infection in the etiopathogenesis of AAV has been suggested based on the observation that 63% of patients with GPA had chronic nasal carriage when compared with 20% of control individuals [61]. Moreover, nasal carriage has been associated with disease relapse [61, 62], and patients who received maintenance co-trimoxazole treatment were observed to have fewer relapses [63]. A study of bronchioalveolar lavage fluid (BALF) in GPA patients identified increased levels of infection compared to controls and demonstrated that BALF was permissive for bacterial growth [64].

Molecular mimicry may also underlie the development of necrotizing and crescentic glomerulonephritis (NCGN) through infection with fimbriated bacteria, such as *Escherichia*

coli and *Klebsiella pneumonia* [65]. The bacterial adhesion protein FimH was found to be homologous to a major epitope of LAMP-2 which is in turn recognized by anti-LAMP-2 antibodies in pauci-immune NCGN [66, 67] although these results have not been replicated by other researchers [68].

The development of AAV has been linked to several drug exposures, most commonly propylthiouracil with a prevalence of ANCA expression ranging from 4% to 46% [69, 70]. D-penicillamine, hydralazine and minocycline have also been associated with disease. Sulphasalazine, and other similar drugs, may increase autoantibody production as they induce apoptosis which in turn increases expression of ANCA antigen targets on the surface of apoptotic neutrophils [71, 72].

ANCA PATHOGENICITY

Since the discovery of ANCA there has been considerable debate as to whether or not it has a direct pathogenic role with most authors now accepting that anti-myeloperoxidase (MPO) antibodies are pathogenic based on the results of clinical, laboratory and animal studies. Proteinase 3 (PR3) was found to be the target antigen of the cytoplasmic-ANCA indirect immunofluorescence pattern while MPO is the target antigen of the perinuclear-ANCA pattern, with the specificity of PR3-ANCA and MPO-ANCA for AAV as high as 98% [73, 74].

Clinical Evidence for ANCA Pathogenicity

The most striking clinical evidence for the pathogenicity of ANCA was the report of a neonate developing pulmonary hemorrhage and glomerulonephritis caused by transplacental transfer of ANCA IgG from the mother who had anti-MPO antibody positive MPA [75]. There has, however, been a lack of clear consistent evidence of a relationship between the serum ANCA titer and disease activity [76-79]. A meta-analysis of studies investigating the association between ANCA and disease activity found a rise in the serum ANCA titer and persistent presence of ANCA was only modestly predictive of future disease relapse, suggesting that serial ANCA measurements had a limited utility in guiding treatment decisions in individual patients [80]. It is possible that there are subtle changes in ANCA such as glycosylation state or change in the predominant subclass that are related to disease activity and undetected by routine assays [81-84].

Animal Models of AAV

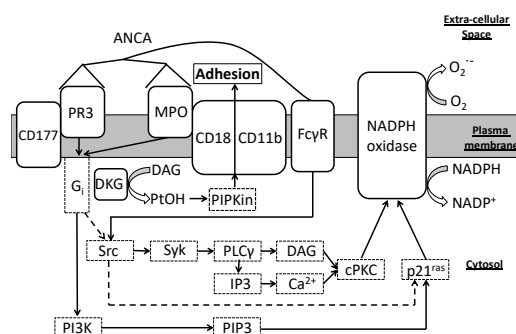
Several murine and rat models of anti-MPO AAV have been created; unfortunately to date there has not been a suitable animal model for anti-PR3 [85-87]. Xiao and colleagues [88] immunized MPO-/- mice with purified MPO to generate high avidity anti-MPO antibodies. Granulomatous inflammation, necrotizing and crescentic glomerulonephritis, and systemic necrotizing vasculitis developed when mouse splenocytes were transferred to Rag2-

/- mice or when anti-MPO containing IgG was transferred to wild-type mice. Levels of tumor necrosis alpha (TNF- α) were increased and renal injury enhanced when lipopolysaccharide (LPS) was added. The importance of cytokines in the pathogenic process was emphasized by the finding that these effects could be ameliorated by addition of anti-TNF- α antibodies [88]. Prominent macrophage and neutrophil invasion was found at sites of glomerular injury which, along with the observation that crescentic glomerulonephritis did not develop in neutrophil-depleted mice, supports the important role of neutrophils in the pathogenesis of AAV [89].

Leukocyte adhesion and transmigration were shown by intravital microscopy to be enhanced by anti-MPO IgG in wild-type mice pre-treated with cytokines. β 2-integrins (CD18) and Fc γ receptors were shown to be necessary as recruitment was not seen following the co-administration of anti-CD18 antibodies or in Fc receptor γ chain-/- mice [90]. Kuligowski and colleagues [91] found that high-dose anti-MPO induced β -integrin dependent adhesion in the absence of LPS, while LPS was necessary to induce adhesion at low doses of anti-MPO.

***In vitro* Activation of Neutrophils by ANCA**

In vitro work on the effect of patient-derived IgG containing ANCA demonstrated ANCA-activation of cytokine primed neutrophils. During the priming process, MPO and PR3 were translocated to the plasma membrane of neutrophils where they can interact with ANCA [92-94]. In addition to increasing surface expression of ANCA, interleukin (IL)-18, TNF α and granulocyte macrophage colony stimulating factor lead to mobilization of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex components necessary for superoxide generation [94-97]. Subsequent crosslinking between ANCA and Fc γ receptors and ANCA antigens results in degranulation, production of pro-inflammatory cytokines, adhesion to endothelium and generation of superoxide with multiple signaling pathways implicated [98-103] (Figure 1). Neutrophil gene expression is also induced by binding of both intact ANCA and F(ab')₂ portions [104].



Abbreviations: Cbl, Casitas b-lymphoma protein; cPKC, protein kinase C; DAG, diacylglycerol; DGK, diacylglycerol kinase; G_i, G protein; IP3, inositol 1, 4, 5-triphosphate; PI3K, phosphatidylinositol 3-kinase; PIP3, phosphatidylinositol 3, 4, 5-triphosphate; PIPKin, phosphatidylinositol-4-phosphate-5-kinase; PLC γ , phospholipase C γ ; PtoH, phosphatidic acid; Src, tyrosine kinase; Syk, spleen tyrosine kinase.

Figure 1. Summary of the neutrophil intracellular signaling pathways activated by ANCA cross ligation of MPO or PR3 and Fc γ receptors. This activation results in superoxide production, degranulation and adhesion to the endothelium. Separate pathways are activated by either interaction with the ANCA antigens or Fc γ receptors. Signaling must be induced via both pathways for full neutrophil activation, which is highlighted by the protection to development of vasculitis demonstrated in mice lacking phosphatidylinositol-3 kinase γ .

Effect of ANCA on Neutrophil-Endothelium Adhesion

Endothelial necrosis is a histological feature of small vessel disease in AAV, with exposure of the basement membrane leading to platelet aggregation, thrombosis and occlusion [105]. Swelling, necrosis and dehiscence of endothelial cells is an early histological feature and thought to be mediated by ANCA activation of cytokine-primed circulating neutrophils. This results in neutrophil adhesion to and transmigration through endothelium, associated with neutrophil degranulation and production of superoxide. Adhesion and transmigration of leukocytes is promoted by the release of chemoattractant proteins by endothelial cells and upregulation of adhesion molecules. The serum concentrations of soluble factors associated with this process include vascular endothelial growth factor (VEGF), inter-cellular adhesion molecule (ICAM)-3, P-selectin, thrombomodulin, angiopoietin-2, matrix metalloproteases 1, 3, and 9; endothelial microparticles and stem cells [106-112].

In vitro studies showed that ANCA stabilized adhesion and promoted transmigration of neutrophils flowing over endothelial cells [113]. In shear stress models employing human endothelial cells and healthy donor neutrophils, this interaction depended on the interaction between neutrophil-expressed CXCR1 and CXCR2, and CD18/CD11b and their ligands on endothelial cells, [113-115]. An MPO-/- animal model demonstrated stimulation of neutrophil-endothelial adhesion dependent on the action of CD18 [90].

In activated neutrophils, intracellular F-actin polymerizes making the neutrophil more rigid and less deformable. This may lead to retention of neutrophils in small diameter capillaries and increased contact with endothelium, promoting damage leading to cell detachment and lysis [116, 117]. One study demonstrated reduced CXCR1 and CXCR2 expression on neutrophils from AAV patients, even those in remission where expression showed an inverse relationship with serum IL-8 concentrations. Reduced chemokine receptor expression impaired endothelial transmigration but not adhesion, which may increase contact with endothelium and promote intra-vascular retention of activated neutrophils [118]. The actions of endothelial cells inhibit the neutrophil production of superoxide, implying that granule content release may be a more important pathogenic mechanism in AAV [89-91].

ANCA and Neutrophil Cell Death

Neutrophil apoptosis does not normally result in the release of the intracellular contents, thus preventing inflammation. ANCA-activated neutrophils were shown to undergo dysregulated and accelerated apoptosis which may lead to increased inflammation associated with the release of granule contents, increased surface expression of MPO and PR3, and macrophage-mediated uptake of ANCA opsonized neutrophils [71, 119, 120].

More recently, there has been increasing focus on the relationship between ANCA and neutrophil extracellular trap (NET) formation. NETs are reticular structures released by activated neutrophils, composed of decondensed chromatin and associated antimicrobial proteins [121]. Since the first description of their structure in 2004, NETs have been implicated in the pathogenesis of a range of inflammatory and autoimmune disorders [122].

Kessenbrock and colleagues first demonstrated the presence of NETs in glomeruli from AAV patients [123], suggesting a potential role in mediating tissue damage. Since then, NETs were shown to be more prevalent in nerve tissue from patients with MPA neuropathy than other types of neuropathy [124], and circulating levels of NET remnants were found to be increased in AAV patients compared to healthy controls [125]. Individual case reports identified NETs in cutaneous lesions [126] and thrombus [127] from AAV patients. Taken together, these findings suggest that NETs could play a role in mediating autoimmune damage in multiple organ systems. Notably, ANCA-induced NETs associate with alternative complement pathway components C3b and C5b-9 in human serum, with subsequent activation of the alternative complement pathway *in vitro* [128]. This provides a possible link between NETosis and mechanisms of complement-mediated damage in AAV.

Kessenbrock and colleagues also showed that ANCA could stimulate neutrophils to release NETs [123]. Interestingly, independent work found that neutrophils from AAV patients exhibited increased NET production compared to neutrophils from healthy controls when stimulated with ANCA [129]. MPO-ANCA affinity but not titer correlated with increased levels of NETs in AAV patients [40], and the pro-inflammatory mediator high-mobility group box 1 (HMGB1) was identified as an additional factor that potentiates ANCA-induced NET release *in vitro* [130]. In addition, there is evidence that NET degradation is impaired in serum from MPA patients [131], which could contribute to both NET-induced tissue damage and immunogenicity.

Since NETs represent a source of autoantigens PR3 and MPO, it is possible that disordered NETosis plays a role in the induction of autoimmunity. Sangaletti and colleagues loaded myeloid dendritic cells (mDCs) with NET components and transferred them into naïve mice [132]. This induced circulating PR3- and MPO-ANCA and resulted in pulmonary-renal vasculitis. In contrast, injection of mDCs co-cultured with apoptotic neutrophils resulted in autoantibody production in the absence of this disease phenotype. This study demonstrated that NET components are able to induce ANCA-like disease in a murine model, implying that NETs represent a potential source of autoantigens in AAV. Therefore, NETosis may contribute to a positive feedback loop in which ANCA induce both NET-mediated tissue damage and the exposure of NET-derived autoantigens. However, this model does not explain how tolerance to these autoantigens is broken, and thus far there is limited evidence that this process plays a pathogenic role in humans.

Cell-Mediated Immunity

Both B- and T-cells have important roles in the pathogenesis of AAV and are important in the induction of autoimmunity and the development of tissue inflammation. The production of autoantibodies, implying a loss of self-tolerance to PR3, MPO and possibly LAMP-2, could occur via several possible mechanisms. The presence of low levels of specific autoantibodies (SAA) to MPO and PR3 in the healthy population has led to the theory that ANCA form part of the natural repertoire [133]. One explanation for the non-pathogenic nature of SAA is that compared to MPO-ANCA derived from patients with AAV, significantly lower titers of SAA MPO are found with lower avidity suggesting that high affinity autoantibodies underlying the autoimmune pathology of AAV may result from

dysregulation of SAA-producing B-cells. However, the precise mechanism remains unknown and larger cohort studies are required [133]. One intriguing suggestion has been the role of complementary peptides in the production of anti-PR3 ANCA. These peptides are produced by the transcription and translation of the DNA complementary to the PR3 gene. The peptides so produced generate an anti-complementary PR3 (cPR3) response which leads to an anti-idiotypic response producing anti-PR3 antibodies [134]. It has also been suggested that cPR3 shows homology with proteins from staphylococcal bacteria. T-cells specific for cPR3 have also been identified in AAV patients [135].

T-cells are required to allow IgG subclass switching, a process which has been shown to be essential in the pathogenesis of AAV [136]. The importance of T-cells in the disease process is further supported by the presence of high levels of soluble IL-2 receptors and activated CD4⁺ cells in patient blood and sera, as well as soluble CD4 and CD8 [137]. MPO and PR3 have been shown to promote the proliferation of autoreactive T-cells [138-140].

Regulatory CD4⁺ T-cells (Treg) important in the maintenance of self-tolerance have functional defects in patients with GPA in remission [141, 142]. The percentage of Treg cells was found to be inversely related to the disease relapse rate in patients with GPA and was associated with both functional and numerical defects in PR3-specific Treg cells [143].

There has been increasing interest in the role of IL-17 producing helper T-cells (Th17) in autoimmune disease in which higher proportions of Th17 cells were found in the peripheral blood of AAV patients compare to controls [144]. Furthermore, in patients with GPA there was expansion of the effector Th17 population and increased IL-17A production by T-cells stimulated with aCD3/aCD28 *in vitro* [145]. MPO-specific Th17 cells were identified in AAV patients with MPO-ANCA, suggesting a pathogenic role [146]. Mice deficient in IL-17A were almost completely protected from developing GN in an anti-MPO model of vasculitis [147].

T-cells are prominent at sites of inflammation in AAV particularly in the kidney where they are the predominant infiltrating cell type [148]. Four major subtypes, Th1, Th2, Th17 and Treg, were identified in inflamed AAV tissue [149-152]. The presence of interstitial Foxp3-positive Treg predicted renal survival in patients with MPO ANCA-associated glomerulonephritis, suggesting a beneficial role in suppression of inflammation [153].

Large populations of T-cells and macrophages have been found in the granulomatous and vasculitic lesions in AAV and studies have demonstrated the involvement of CD4⁺ T cells in AAV disease manifestation, particularly effector memory T cells (T_{EM}) [154]. The theory that CD4⁺ cells migrate to sites of inflammation in AAV was supported by the observation of decreased levels of peripheral blood CD4 T_{EM} in patients with GPA with active disease compared to those in remission [154]. Moreover, the observation that T-cell depletion is effective in controlling disease in therapy-resistant patients supports their role in inflammation [155]. GPA patients in remission were found to have a significantly increased circulating proportion of Th17 effector memory cells and decreased proportion of Th1 effector memory cells compared to healthy controls [156]. The degree of this aberrant distribution of T_{EM} subsets was associated with tendency to relapse and multi-organ disease involvement, providing further evidence for the pathogenic importance of the Th17 response in AAV.

One particularly interesting population of Th cells in AAV is the frequently reported expanded population of CD4⁺CD28⁻ cells which has been associated with increased disease severity [154, 157-161]. CD4⁺CD28⁻ cells have potent effector functions and are a major

source of Th-1 type cytokine secretion, predominantly IFN γ and TNF α and express perforin and granzyme B [162]. The expansion of this cell population is driven by cytomegalovirus infection in AAV, and was no difference between AAV patients and controls matched for CMV-specific IgG seropositivity. Recent evidence showed that prior infection with both Epstein-Barr virus (EBV) and CMV was associated with increased percentage of peripheral CD4+CD28- cells compared to either infection alone in the context of GPA [163]. The expansion of this population in AAV patients was associated with a reduced number of naïve helper T-cells and an increased risk of infection and mortality [164].

B-cells are responsible for the production of ANCA and are thus vital in the pathogenesis of AAV. Tissues affected by GPA, such as nasal lesions, contain B-cells [148, 165] and the proportion of activated B cells is increased in active GPA [158]. That treatment with the B-cell depleting anti-CD20 monoclonal antibody rituximab has been shown to induce disease remission and reduce ANCA titers in AAV supports a role for B-cells in the pathogenesis of the disease [166, 167]. Such B-cells appear to be able to evade the regulatory processes that ensure tolerance to self-proteins. For example, autoreactive B-cells may persist due to low surface expression of CD19, resulting in decreased signaling strength and thus allowing them to evade normal tolerance mechanisms [168].

Further work has examined the role of regulatory B-cells (Breg) in AAV [169], although this is made challenging by the absence of a definitive Breg phenotype [170]. The CD19+CD24(hi)CD38(hi) B-cell is one subset that has been demonstrated to possess regulatory potential [171]. AAV patients with active disease were observed to have significantly lower proportions of CD19+CD24(hi)CD38(hi) B-cells than healthy controls, and B-cells from such patients produced less IL-10 when stimulated *in vitro* [169]. Both the CD19+CD24(hi)CD38(hi) and IL-10+ B-cell populations increased as patients transitioned from active disease to remission [169]. Taken together, these findings suggest that active AAV is associated with deficits in regulatory B-cells.

The selection and maturation of B cells that produce anti-PR3 ANCA may occur in sites of early granulomatous inflammation as histological examination of granulomata in GPA show B-cell clusters closely associated with numerous PR3-positive cells [165]. The proteasome inhibitor bortezomib was studied in a murine model of AAV, noting that bortezomib treatment was associated with MPO-specific plasma cell depletion, reduced anti-MPO titers, and prevention of crescentic GN [172]. One case of refractory MPA successfully treated with bortezomib was recently reported [173]. However, further investigation into timing of treatment and adverse effect profile is needed before bortezomib can be recommended as a routine treatment for refractory AAV.

Complement-Mediated Mechanisms

The presence of immune complex deposits in skin tissue of patients with cutaneous vasculitic lesions, and in renal biopsy tissue in those with ANCA-associated crescentic glomerulonephritis, suggests a role for complement-mediated immune mechanisms in development of inflammation and glomerular damage in AAV [174]. Chen and colleagues [175] demonstrated that approximately 33% of renal biopsy samples from patients with ANCA-associated NCGN demonstrated C3c expression. Membrane attack complex (MAC),

along with C3d and factors B and P were found in glomeruli and microvasculature of human renal biopsy tissue [176]. Xiao and colleagues [177] employed renal biopsy samples from patients with MPO-ANCA-associated pauci-immune NCGN to study the various complement components. All biopsy samples showed MAC, factor B and C3d. Diseased glomeruli were found to express C3d and factor B that co-localized with expression of MAC. This, coupled with the observation that C4d was not detected in either frozen renal sections or paraffin-fixed sections, strongly suggested that the renal damage associated with AAV was secondary to the alternative pathway of the complement system [176]. In addition, complement deposition has been associated with more severe renal disease [175].

Multiple retrospective studies have demonstrated an association between hypo-complementemia at AAV onset, likely reflecting systemic activation of the complement cascade, and poor outcomes [178-180]. In the largest of these studies, low serum C3 at disease onset was an independent predictor of end-stage renal disease and death [179].

In vitro studies indicate that C5a, acting via the neutrophil C5a receptor (C5aR), plays a role in priming neutrophils for ANCA activation via the alternative pathway [181]. This suggests that an amplification loop, comprising C5a and neutrophil C5aR, might mediate ANCA-induced neutrophil activation [181, 182].

Additionally, there is evidence that regulation of the alternative pathway is impaired in AAV. Complement factor H, a negative regulator of the alternative pathway, was detected at significantly lower levels in patients with active MPO-AAV compared to patients in remission and healthy controls [183]. Furthermore, patients with active AAV exhibited deficient factor H function, shown by reduced regulation of C3b and impaired protection of erythrocytes against plasma-mediated lysis [184]. These data reinforce the role of the alternative pathway in AAV, and suggest that impaired negative regulation of this pathway could play a role in its pathogenesis. It is not yet understood what mechanisms underlie this dysregulation.

Perhaps the most convincing evidence of the role of the complement comes from animal models where the development of vasculitis is completely blocked by complement depletion [185]. Xiao and co-workers [182] studied the role of specific complement activation pathways in the development of NCGN and vasculitis using wild type and knockout mice for the common pathway component C5, the classic and lectin binding pathway component C4, and the alternative pathway component Factor B. They showed that C5^{-/-} and Factor B^{-/-} mice, but not C4^{-/-} mice, were protected from disease development after injection of anti-MPO IgG. Their findings suggested that stimulation of neutrophils by ANCA caused release of factors that activate complement via the alternative pathway, initiating an inflammatory amplification loop that mediated severe necrotizing inflammation. Inhibition of complement factor C5 protected against anti-MPO IgG-mediated NCGN, with an 80% reduction in glomerular crescent formation when anti-C5 monoclonal antibodies were administered one day after disease induction [185].

The use of C5 inhibition to treat AAV has also been tested in patients. In a recent randomized controlled trial, C5a receptor inhibitor avacopan was non-inferior to high-dose prednisolone in achieving clinical response in active vasculitis treated with cyclophosphamide or rituximab [186]. In addition to providing a possible means of reducing glucocorticoid exposure, this trial provides further evidence for the role of complement in AAV.

CONCLUSION

The AAV comprising GPA, MPA and RLV are life-threatening diseases affecting small to medium sized vessels with significant overlap in their non-organ specific and organ specific features. Current diagnosis of AAV relies on recognition of a clinical picture and supporting evidence from radiological, immunological and histological investigations. Their highly variable clinical presentation and absence of diagnostic criteria often leads to a delay in diagnosis and initiation of effective therapy. The pathogenesis of AAV is complex, involving both the innate and adaptive immune systems. Significant advances have been made in understanding the AAV over the past few decades, notably with development of animal models. Future development of effective treatment approaches and preventative strategies will be targeted based on improving understanding of pathogenic mechanisms in AAV.

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Chapter 204

CRYOGLOBULINEMIC VASCULITIS

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ABSTRACT

Cryoglobulinemic vasculitis, also termed mixed cryoglobulinemia syndrome, is a rare systemic small vessel vasculitis due to the vessel deposition of immune-complexes, mainly mixed IgG-IgM cryoglobulins. In the majority of cases, it is associated with the hepatitis C virus infection, immunological, and neoplastic diseases. Cryoglobulinemic vasculitis is characterized by the classical triad of purpura, weakness, and arthralgia, frequent multiple organ involvement, and with infrequent late lymphatic and hepatic malignancies. The etiopathogenesis of cryoglobulinemic vasculitis is not completely understood. However, hepatitis C viral infection and associated lymphotropism, genetic, and environmental factors play important roles in B-lymphocyte expansion and cryoglobulin and immune-complex production. The diagnosis is suggested by clinical evidence of purpura, circulating mixed cryoglobulinemia and low C4 levels, and pathologically evident leukocytoclastic vasculitis in skin biopsy lesions. The prognosis is poor in patients with renal disease, liver failure, malignancy, and/or widespread vasculitis with multiple organ involvement. Treatment is directed toward eradicating hepatitis C infection employing the new direct-acting antivirals, immunomodulatory, and immunosuppressant medications as warranted by the level of clinical severity.

INTRODUCTION

Cryoglobulinemic vasculitis (CV) is a small vessel vasculitis (SVV) due to the vascular deposition of cryoprecipitable and/or non-cryoprecipitable immune-complexes (IC) and complement [1]. Cryoglobulinemia and cryoimmunoglobulinemia are interchangeable terms

that refer to the presence in the serum of one (monoclonal cryoglobulinemia) or more immunoglobulins (Ig) or mixed cryoglobulinemia (MC), which precipitate at temperatures below 37°C and re-dissolve on rewarming [1].

NOSOLOGY AND CLASSIFICATION

Cryoglobulinemia is classified into three categories according to the Ig composition [1]. Type I cryoglobulinemia consists of singular isotypes or subclass of Ig, whereas types II and III MC contain ICs composed respectively of polyclonal IgG autoantigens and monoclonal or polyclonal IgM autoantibodies, the latter of which contain rheumatoid factor (RF) activity. Type II MC shows a microheterogeneous composition with immunoblotting and two-dimensional polyacrylamide gel electrophoresis of oligoclonal IgM or a mixture of polyclonal and monoclonal IgM [1-4]. This serological subset represents an intermediate evolutionary state between type III and type II MC, so termed type II-III MC. These findings are in agreement with molecular studies that show the presence of oligoclonal B-lymphocyte proliferation in liver and bone marrow tissue from patients with MC [1-6]. Whereas cryoglobulinemia type I is often asymptomatic and usually associated with well-known hematological disorders [1-6], MC occurs in diverse infectious and systemic disorders and frequently presents as an isolated laboratory finding without clinical significance. Mixed cryoglobulinemia syndrome (MCs) and CV are interchangeable terms for the resultant distinctive SVV related to cryoglobulinemia [1-6].

EPIDEMIOLOGY

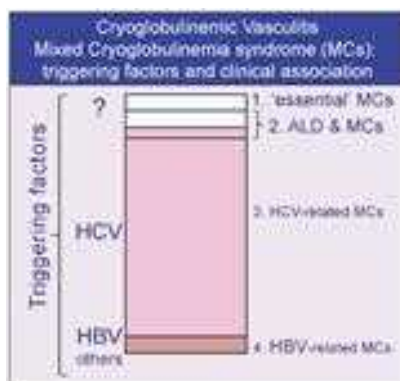
Cryoglobulinemic vasculitis is a rare disorder of yet certain prevalence with marked heterogeneity in its geographical distribution, and increased prevalence in Southern more than Northern Europe or Northern America. The male to female ratio is 3:1, with the most common age at onset of disease in the fourth to fifth decades and in older age [1-5]. Because of the clinical polymorphisms of CV the prevalence of single manifestation such as skin vasculitis, nephritis, chronic hepatitis, and peripheral neuropathy vary largely among cohorts. The relationship between hepatitis C virus (HCV) with cryoglobulinemia and CV has been examined in numerous cohorts [1, 4, 5]. Low levels of circulating MC are detectable in more than 50% of patients while overt CV develops in approximately 5% of HCV-infected individuals [1, 8]. Considering the high prevalence of HCV infection worldwide, an increasing number of patients with HCV-related CV and extrahepatic manifestations are expected to occur particularly in underdeveloped countries where HCV prevalence is increased relative to the general population [1, 4]. Essential MCs (EMCs) and CV, so defined as the absence of a recognized triggering factor that underlie a systemic infectious or specific neoplastic disorder, occur less frequently in individuals of Southern European descent and in selected geographic areas where there is a higher prevalence of HCV infection and CV [1, 4].

ETIOPATHOGENESIS

The triggering factors and etiopathogenesis of CV and MCs are depicted in Figures 1 and 2. Vascular deposition of circulating IC, cryoglobulins and complement mediated by humoral and local factors, affects small vessels, predominantly arterioles, capillaries, and venules similar to Henoch-Schonlein purpura, another IC type of SVV, with variable systemic organ involvement [1-5]. Mild to moderate chronic hepatitis is related in up to two-thirds of affected patients with CV suggesting a pathogenic role for hepatotropic viruses [1-4, 9].

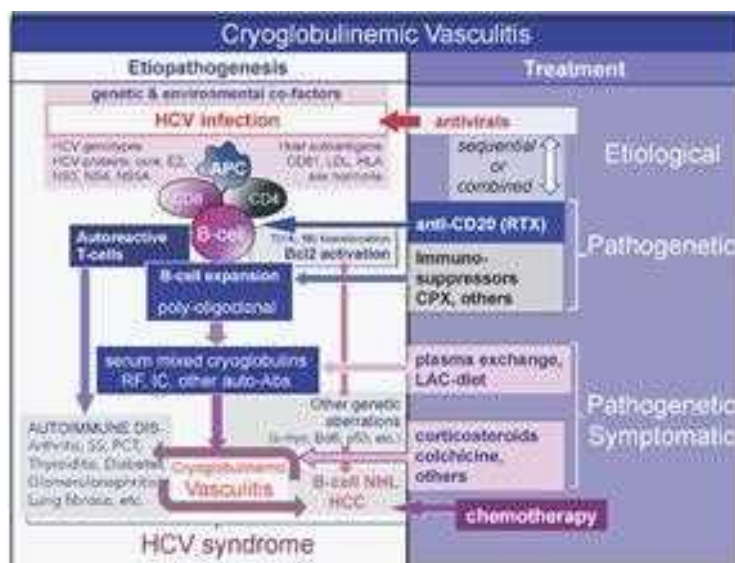
Hepatitis B virus (HBV) is a possible causative factor in <5% of patients, while HCV is considered the main pathogenic agent in CV [1, 4, 5]. First proposed by two independent groups who recognized the increased prevalence of serum anti-HCV antibodies in CV patients relative to the general population [10, 11], the causative link between HCV and CV was later established when the presence of HCV RNA was detected by polymerase chain reaction (PCR) in 86% of patients with CV [7]. The causative role of HCV in CV is apparent in up to 95% of patients among cohorts of diverse geographical derivation [1, 4-6, 9]. In consideration of the striking association of HCV with CV, EMC occurs in a minority of patients [1, 4]. The clinical features and prognosis of CV are linked to the natural history of chronic HCV infection with different CV phenotypes believed to be the result of contributory genetic and environmental cofactors which hitherto remain unknown [1, 4, 12]. The role of HCV in autoimmunity has been ascribed to viral lymphotropism [1, 4, 5, 12] wherein the HCV, which lacks the ability to integrate into the host genome due to absence of reverse transcriptase activity, chronically stimulates the immune system leading to autoimmune phenomena. The proposed etiopathogenesis (Figure 2) is connected to HCV-related epitopes, autoantigens, and molecular mimicry-related mechanisms such as the association with the anti-GOR autoantibody, as well as the binding of HCV to host low-density lipoprotein (LDL), specific antiviral IgG and IgM, RF and cryoglobulins, and monoclonal RF bearing B-cells that express the WA cross-idiotype. Collectively, these immunological phenomena are the cause and the consequence of chronic stimulation of B-lymphocytes with expansion of B-cell subpopulations. HCV-related lymphomagenesis represents an important model of virus-driven malignancy, similarly to that observed for mucosa-associated lymphoid tissue (MALT) lymphoma of the stomach related to gastrointestinal *Helicobacter (H.) pylori* infection [1, 4, 12], two malignancies characterized by an analogous multistep and multifactorial etiopathogenesis.

The interaction between the HCV E2 envelope protein and CD81 molecule, a ubiquitous tetraspannin present on the surface of B cells, likely represents an important pathogenic step in the development of HCV-related autoimmune and lymphoproliferative disorders that results in potent sustained polyclonal stimulation of the B-lymphocytes [1, 4, 12]. The occurrence of HCV-related autoimmune-lymphoproliferative disorders may also be related to t(14;18) translocations found in B-cells of HCV-infected patients leading to increased expression of the Bcl-2 protein, with inhibition of apoptosis and abnormally prolonged B-cell survival [1, 4, 12, 13]. Apart from cryoglobulin production with or without overt CV, HCV-driven lymphoproliferation could explain the pathogenic role of HCV infection in idiopathic B cell lymphoma [1, 4]. Since the first description in 1994 [14], epidemiological and laboratory studies have confirmed this association in geographical areas where both HCV-associated CV and lymphoproliferative disorders occur [1, 4, 12].



Abbreviations: MC, mixed cryoglobulinemia; MCs, mixed cryoglobulinemia syndrome; ALD, autoimmune-lymphoproliferative disorders, HCV, hepatitis C virus; HBV, hepatitis B virus.

Figure 1. The different clinical and virological subsets of MCs can be schematically summarized as follows: (1) Essential MC; (2) Essential MC and HCV-related MC as an overlapping syndrome (lymphoproliferative disorders, Sjögren syndrome, rheumatoid arthritis, autoimmune hepatitis, and B-cell lymphomas); (3) Subsets of HCV-associated MC; and (4) MC associated with other infectious agents notably hepatitis-B virus.



Abbreviations: HCV, hepatitis C virus; RF, rheumatoid factor; IC, immune-complex; pSS, primary Sjögren syndrome; SS, sicca syndrome; PCT, porphyria cutanea tarda; HCC, hepatocellular carcinoma; B-NHL, B-cell non-Hodgkin lymphoma; CPX, cyclophosphamide; RTX, rituximab; LAC, low antigen-content.

Figure 2. Left: CV is the most frequent extrahepatic manifestation of the so-called HCV syndrome. CV represents a crossing road between benign and malignant HCV-related complications. Given its biological characteristics, HCV may be involved in a wide number of autoimmune and lymphoproliferative disorders. This figure summarizes the main causative factors including, infection, toxics, genetic and environmental causes potentially involved in the pathogenesis of the complex HCV syndrome, in particular of CV. These factors, alone or in combination, may trigger two nonexclusive multistep pathogenic processes, notably the production of benign poly-oligoclonal B-cell proliferation responsible for organ- and non-organ-specific autoimmune disorders including IC-mediated CV; and another characterized by different oncogenic alterations, which ultimately leads to malignant complications. Right: Therapeutic strategies in patients with HCV-related CV and other autoimmune lymphoproliferative disorders. Following the multistep pathological process leading from HCV infection to overt CV, etiologic, pathogenic and symptomatic treatments are instituted at different levels.

The etiopathogenesis of HCV-negative CV [15] remains a challenge to explain apart from concurrent infectious processes including HBV and concomitant autoimmune rheumatologic and lymphoproliferative disorders (Figure 1). Patients with human immunodeficiency virus (HIV) type I infection may also have HCV co-infection. HIV may exert continuous antigenic stimulation of B-cells leading to MC type III production early in its course, followed by monoclonal type II MC, and the typical manifestations of CV [1-4, 12].

CLINICAL MANIFESTATIONS

The demographic, clinical-serologic and virologic findings of 270 patients with CV at our institution are shown in Table 1. The triad of purpura, weakness and arthralgia, the clinical hallmark of CV and MCs, were frequent seen in addition to chronic hepatitis, type 1 membranoproliferative glomerulonephritis (MPGN), peripheral neuropathy, skin ulcers, diffuse vasculitis, and in some instances, malignant B-cell non-Hodgkin lymphoma (B-NHL) and hepatocellular carcinoma [1-5, 9, 12]. Although the prevalence of singular clinical-serological features of CV in our cohort was comparable among those with type II and III MC, the reported clinical variability may relate to bias of ascertainment from renal or rheumatology clinics, and cohorts of geographically diverse origin [1-5, 8].

There are different presenting clinical-serological patterns that vary from mild arthralgia and sporadic purpura in those with MC alone, to more severe cutaneous and systemic involvement of classical MCs [1-4]. In all such patients, the disease combines MC with RF activity, low C4 levels, and the clinical-pathological features of orthostatic purpura due to leukocytoclastic vasculitis (LCV) with variable multi-organ involvement. Patients chronically infected with HCV demonstrate asymptomatic serum MC that may precede the clinical onset of disease by years to decades [1, 4]. Conversely, some patients show typical cryoglobulinemic manifestations without serum cryoglobulins. The absence of this serological hallmark is not surprising since cryoglobulins represent only a portion of IC that cryoprecipitate, which may be transient and vary both among patients and during follow-up in individual patients [1, 4]. Most experts agree that repeated cryoglobulin determinations are necessary for a definite diagnosis in such patients.

Cutaneous manifestations are the most common clinical feature of CV, with orthostatic purpura, the pathognomonic feature, varying largely in dimension and diffusion to sporadic isolated petechiae and severe vasculitic lesions, and complicated by torpid ulcers of the legs and malleoli [16]. Repeated episodes of purpura lead to stable, sock-like ochraceous discoloration of the legs [1, 4]. Humoral cofactors and vascular disturbances stemming from increased cryocrit levels, chronic venous insufficiency and physical stress all contribute to vasculitic alterations. More intense purpuric manifestations may occur in the afternoon with prolonged standing and when cryocrit levels are highest, especially in muggy weather conditions. Arthralgia, non-erosive oligoarthritis, and less frequently frank arthritis may also be noted. When CV occurs in association with the sicca syndrome, there was mild xerostomia and xerophthalmia in up to one-half of patients [1, 4].

Table 1. Cryoglobulinemic vasculitis: Demographic, clinicoserological, and virological findings at a single institution*

Total Number of Patients	270
Mean age at disease-onset ($\pm$ SD), years (range)	55 ($\pm$ 14) (29-74)
Female/Male ratio	3:1
Disease duration, mean $\pm$ SD years (range)	14 ($\pm$ 11) (2-42)
Purpura	98%
Weakness	98%
Arthralgia	93%
Non-erosive arthritis	9%
Raynauds phenomenon	32%
Sicca syndrome	51%
Peripheral neuropathy	81%
Renal involvement	32%
Liver involvement	73%
B-cell non-Hodgkin lymphoma	12%
Hepatocellular carcinoma	3%
Mean cryocrit% ($\pm$ SD)	4.1 ($\pm$ 14)
Type II/type III mixed cryoglobulins	2/1
Mean C3 ($\pm$ SD) in mg/dl (normal 60-130)	91 ($\pm$ 35)
Mean C4 ($\pm$ SD) in mg/dl (normal 20-55)	10 ($\pm$ 14)
Antinuclear antibodies	31%
Antimitochondrial antibodies	9%
Anti-smooth muscle antibodies	15%
Anti-extractable nuclear antigen antibodies	9%
Anti-HCV RNA	92%
Anti-HBV antibodies	30%
HBsAg	1%

*Evaluated at the end of the patient follow-up period.

Peripheral nervous system involvement that includes small fiber neuropathy of the legs with painful, burning paresthesia that worsens at night is often resistant to treatment. A minority of patients develop large fiber sensorimotor involvement, but when present, most often occurs with abrupt asymmetric onset of mononeuritis. Peripheral neuropathy may also be triggered or exacerbated during the first several weeks of treatment with interferon-alpha (IFN- α) in patients so disposed [1, 4]. Central nervous system vasculitis, albeit rare, presents with focal deficits such as dysarthria and hemiplegia, which may be difficult to distinguish from more common atherosclerotic vascular sequela.

Systemic liver involvement is rarely observed in other systemic vasculitides, but is present in CV, and generally preceded by mild to moderate chronic hepatitis that is apparent at presentation or develops in two-thirds of patients particularly those with HCV-related CV [1, 4]. Clinically overt liver cirrhosis occurs in one-quarter of patients, while life-threatening hepatorenal syndrome occurs in association with progressive CV [9]. The overall outcome of CV-associated chronic hepatitis seems to be more favorable than HCV-related hepatitis without MCs, whereas hepatocellular carcinoma is less frequently observed in HCV-related CV compared to the overall population of HCV-infected individuals. Such differences are difficult to fully explain, however, the relatively low prevalence of the 1b HCV genotype in those that develop CV, along with a lower median consumption of alcohol might predict a

more benign clinical course of liver involvement [1, 4]. Immune complex-mediated glomerulonephritis, most often seen in type 1 MPGN, affects the prognosis and survival of patients with CV due to hypothesized immune mechanisms [1, 4]. Intestinal vasculitis presents with severe life-threatening acute abdominal pain necessitating prompt diagnosis and aggressive treatment [1, 4].

Interstitial lung disease characterized by subclinical alveolitis has been described in those with CV and in association with isolated HCV infection [1, 4]. When present, interstitial lung disease can be a predisposing condition to pulmonary infections, and in rare instances, to clinically manifest interstitial lung fibrosis. Capillaritis complicated by severe cough and hemoptysis, are other rare manifestations of CV-related lung involvement, as well as overt hyperviscosity syndrome are due to high levels of serum cryoglobulins [1, 4].

A low or undetectable C4 level with a normal C3 fraction occurs in patients with CV regardless of disease activity. *In vitro* consumption of hemolytic complement is due to the anti-complement activity of cryo-Ig [1, 4]. A sudden increase in C4 from low to abnormally high levels can precede the development of B-NHL [1]. The absence of a clear-cut correlation between the severity/activity of CV clinical manifestations and the observed cryocrit levels may be related to the large variability of cryo- and non-cryoprecipitable IC ratio and/or the intrinsic ability of IC to activate complement, as well as the possible *in situ* formation of IC [1].

Endocrine disorders occur more frequently in CV than in the general population including thyroid disturbances, type II diabetes mellitus, and gonadal dysfunction [1, 12, 17]. The former include autoimmune thyroiditis, subclinical hypothyroidism, and rarely thyroid cancer. Reversible hyperthyroidism occurs as a complication of IFN- α treatment [1].

B-NHL, the most common malignancy in association with CV, is often seen late in the course of MCs [1, 4, 12]. The development of B-NHL may be a consequence of peripheral B-cell expansion of lymphoid infiltrates in the liver and bone marrow. Such lymphoid infiltrates, which are considered to be early indolent lymphomas, are indistinguishable from more advanced B-cell cancers that include chronic lymphocytic leukemia, small lymphocytic lymphoma, and immunocytoma [1, 4, 12]. While the majority of affected patients remain stable for years, overt B-NHL is observed in approximately 10% of affected patients most often late in the course of CV [1, 4-6, 12]. Other neoplastic manifestations, including hepatocellular carcinoma and papillary thyroid cancer occur in the natural progression of CV [1, 4, 12]. Accordingly, MC may be considered, in part, a pre-neoplastic disorder in which careful clinical monitoring is recommended even when the severity of MCs is mild.

DIAGNOSIS

There are no standardized methodologies for the measurement of cryoglobulin levels [1, 4] nor have the diagnostic criteria for CV been prospectively validated. In 1966, Meltzer and Franklin [2] described EMCs in patients with the triad of purpura, weakness, and arthralgia, circulating MC, low C4 levels, LCV of arterioles, capillaries and venules, and multiorgan involvement without discernible infectious, autoimmune, or systemic involvement [1-6]. Recent classification criteria for CV were developed by a cooperative multicenter study using a standardized methodology [18]. Successively validated in MC patients referred to experts

from a larger number of countries, these criteria may be usefully employed in epidemiological and clinical-pathogenic studies, and prospective therapeutic trials [19]. Evidence of MC in the serum of patients with suspected CV is necessary for a definite classification of the disease [18, 19], taking into account the above-mentioned variability of IC cryoprecipitation needing repeated cryoglobulin determinations [1].

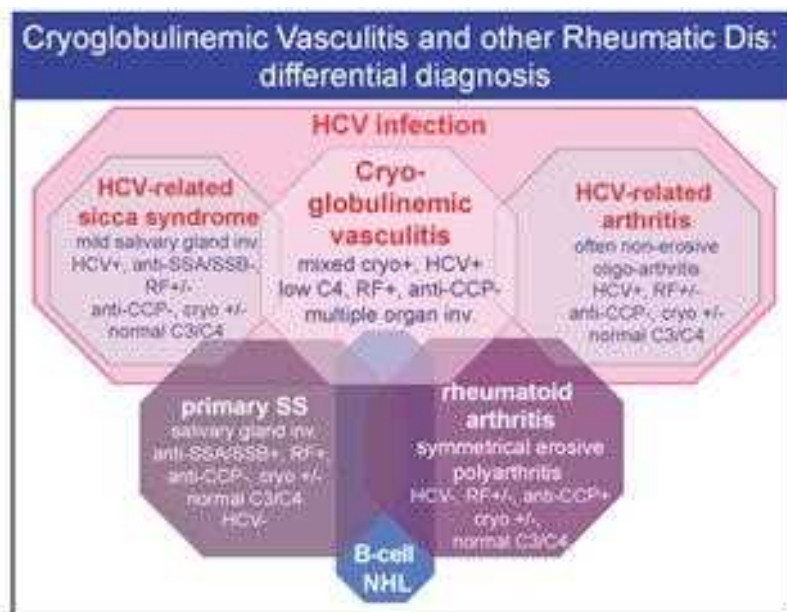
DIFFERENTIAL DIAGNOSIS

Figure 3 describes aspects of the differential diagnosis of CV which shares a number of etiopathogenic events with both HCV-related and idiopathic disorders, namely sicca syndrome, primary Sjögren syndrome (pSS), polyarthritis, classical rheumatoid arthritis, autoimmune hepatitis, and B-NHL [1, 4, 12]. Therefore, a differential diagnosis with regard to the presence or absence of HCV infection should be carefully made in all patients with cryoglobulinemia and/or some autoimmune/neoplastic manifestations; a correct disease classification may decisively affect the overall clinical therapeutic approach and outcome. The presence of HCV in the large majority of individuals with CV may nonetheless lead to difficulty in the differentiation of CV from HCV-infected patients with other extrahepatic manifestations that characterize the HCV syndrome [12, 20]. Such patients develop slow progression from mild HCV-associated hepatitis to various extrahepatic manifestations including arthralgia, RF-positive arthritis, sicca syndrome, Raynaud's phenomenon, and others to clinically overt cryoglobulinemic syndrome (Figure 2). Of note, a minority of patients with long-lasting CV develop a clinically relevant malignancy [1, 20].

Patients with mild CV complain of arthralgia often without synovitis [1, 4, 21, 27] while those with HCV-associated CV and symmetrical erosive polyarthritis are more likely to have the syndrome of overlapping CV-rheumatoid arthritis further definable by serum anti-cyclic citrullinated peptide (anti-CCP) IgG antibodies and RF serology (Figure 3). Sicca syndrome occurs in up to one-half of patients with CV; however, formal criteria are satisfied in only a minority of patients [1, 4, 12, 21]. Patients with pSS shares various symptoms with CV including purpura, xerostomia, xerophthalmia, arthralgia, and laboratory evidence of RF seropositivity, cryoglobulinemia, and the associated complication of B-cell lymphoma [21]. Histopathological alteration of the salivary glands and the specific autoantibody pattern (anti-Ro/SSA-La/SSB) of pSS are rarely found in patients with MCs. Moreover, pSS is rarely complicated by chronic hepatitis, glomerulonephritis, or concomitant HCV infection. In this regard, HCV infection should be considered an exclusionary criterion for pSS [21]. In rare cases, and often in subjects without HCV infection, the differential diagnosis may be challenging. In those instances, it may be more appropriate to classify such patients as CV-pSS overlap syndrome [1, 4, 12, 21]. This clinical condition shows a rather severe clinical progression, less frequent Ro/SSA and La/SSB seropositivity, high levels of serum MC, hypocomplementemia, with frequent autoimmune-vasculitic manifestations, and a higher risk of lymphoma [4, 21, 27].

Autoimmune hepatitis may be associated with HCV infection in the same geographic areas that HCV-associated CV occur. The differential diagnosis between CV and autoimmune hepatitis may be difficult due to the presence of hepatic and extrahepatic autoimmune phenomena in both entities [1, 4, 12]. The presence of the typical features of CV including

LCV, hypocomplementemia, glomerulonephritis, but generally mild hepatitis may collectively be a clue in differentiating CV from classical autoimmune hepatitis [1, 4, 12].



Abbreviations: CV, cryoglobulinemic vasculitis; RF, rheumatoid factor; CCP, cyclic citrullinated peptide; pSS, primary Sjogren syndrome; LCV, leukocytoclastic vasculitis; B-NHL, B-cell non-Hodgkin's lymphoma; RA, rheumatoid arthritis.

Figure 3. Differential diagnosis of CV and other rheumatic diseases. In clinical practice, it is possible to observe some clinical overlap syndromes involving CV and other autoimmune lymphoproliferative disorders. In particular, pSS and RA may share some clinico-pathological features with CV, including a possible association with HCV infection. However, a correct differential diagnosis may be done based on some considerations: pSS shows a typical histopathological pattern of salivary gland involvement and specific autoantibodies anti-Ro (SSA) and La (SSB), which are rarely found in patients with CV. Conversely, cutaneous LCV, visceral organ involvement including glomerulonephritis, hepatitis, low C4 and HCV infection, are typically found in CV. On the other hand, erosive symmetrical polyarthritis and serum anti-CCP characterize classic RA. Moreover, B-NHL may complicate CV, pSS, and RA. B-NHL may be suspected after careful clinical-serological monitoring. Finally, incomplete variants of both pSS and RA, namely isolated sicca syndrome and arthritis, can be associated to CV in the setting of chronic HCV infection, but they do not generally present typical clinical-serological and pathological features of pSS or RA.

PROGNOSIS

The overall 10-year survival of CV is estimated to be about 50% [9]. The clinical course and prognosis of CV relates mainly to disease manifestations, response to treatments and comorbid disorders, as well as, complications accrued to CV and its treatment [9]. Those with renal disease, liver failure, lymphoproliferative and other malignancies demonstrate the least favorable outcome [1, 4, 9, 12]. Careful monitoring of patients to avoid life-threatening complications of CV, including nephropathy, widespread systemic vasculitis, hepatitis, and malignancy, favor a better prognosis.

TREATMENT

Figure 4 summarizes the therapeutic approach to CV. Taking into account three important aspects of disease pathogenesis, the treatment can be aimed at chronic immune stimulation by eradicating HCV infection, attenuating the resultant T- and B-cell activation, and attenuating the production of cryoglobulins and IC, as well as, the identification and treatment of B-cell lymphoproliferation to avert the development of B-NHL. This multistep, multifactorial etiopathogenesis-oriented approach to therapy targets HCV infection, B-cell proliferation, and the resultant CV inflammatory involvement. The recent introduction of direct acting antivirals (DAAs) led to sustained clearance of HCV in the large majority of patients so treated [4, 22-27], without the frequent side-effects previously observed with IFN- α treatment, such as peripheral neuropathy, thyroiditis, and rheumatoid-like polyarthritis [1, 4, 12]. Preliminary studies suggest a role for DAAs in the treatment and eradication of HCV, whereby elevated its tolerability and efficacy, offers new hope in the management of severe complications [22-27]. However, the variable and unpredictable CV response to the antiviral therapy observed in some patients, including the paradoxical response with disease exacerbation or new symptom appearance, indicates that DAAs effect on CV needs to be further evaluated. The immune system of a single patient may be decisive in the clinical outcome following antiviral treatment. There is a point of no return in a viral-driven lymphoproliferative disorder that may affect the overall clinical response after HCV eradication. Like *H. pylori*-associated gastric lymphomas [1, 4], HCV-associated CV is more responsive to biologically based treatment of the underlying infection, early in the he early phase of the illness.

Therapeutic Strategies of Cryoglobulinemic Vasculitis (CV)		
Activity Levels	Treatment Strategies	Symptom Combination & Treatments
asymptomatic	monitoring (DAAs for HCV eradication)	CV with severe-active manifestations GN, SU, s-m neuropathy, diffuse vasculitis
mild-moderate purpura, weakness, arthralgia, mild sensory neuropathy	low-medium dose CS +/- LAC- β et +/- other symptomatic DAAs	
moderate-severe active chronic hepatitis, glomerulonephritis, skin vasculitis	DAAs low-medium dose CS +/- RTX	CV with active chronic hepatitis + minor MCs symptoms
severe-rapidly progressive GN, s-m neuropathy, Diffuse vasculitis	PE, CS, and CPX (or RTX) DAAs	sequential (or combined) treatment DAAs $\rightarrow$ Rituximab

Abbreviations: HCV, hepatitis C virus; CS, corticosteroids; LAC, low-antigen-content; DAAs: direct-acting antivirals; CPX, cyclophosphamide; RTX, rituximab; MCs, mixed cryoglobulinemic syndrome; GN: glomerulonephritis; s-m-neuropathy: sensory-motor neuropathy; SU: skin ulcers

Figure 4. Therapeutic strategy of cryoglobulinemic vasculitis according to the activity and severity of the disease or symptom combination. Asymptomatic generally require careful monitoring. Those with mild manifestations such as transient purpuric lesions of the legs may be monitored and offered therapy to eradicate HCV infection. Individuals with moderate to severe manifestations, mainly active chronic hepatitis are treated with new direct-acting antiviral therapies. Patients with severe, rapidly progressive disease complications or a partial response to traditional therapy receive aggressive treatment regimens similar to other systemic vasculitides; employing, sequential or combined treatment schedules.

Physicians must choose from among available therapies for CV including low-antigen-content (LAC) diets, plasma exchange (PE), and immunosuppressant regimens employing corticosteroids, rituximab, and cyclophosphamide alone or in combination depending upon the severity and activity of the illness and clinical manifestations [1, 4, 17]. A LAC-diet improves the clearance of circulating IC by restoring the activity of the reticuloendothelial system, which becomes overloaded, by circulating cryoglobulins [1, 4, 21]. It reduces the input of alimentary macromolecules crossing the mucosal barrier of the gut as some foods such as dairy products and eggs present a potential antigenic activity and might otherwise be pathogenic. Reduction of the alimentary input of macromolecules directed to mononuclear phagocytic system improves its function in conditions characterized by abnormal endogenous hyperproduction of IC responsible for organ damage such as MCs. Combined LAC-diet and 2 to 4 mg per day of 6-methyl-prednisolone may be sufficient to ameliorate mild manifestations of CV such as sporadic purpura and arthralgia. The limitations of an LAC-diet treatment include poor patient compliance, which can be improved by tailoring the treatment duration, for example 7 to 14 days of restricted diet followed by 14 to 28 days of free diet. Those with mild-moderate symptoms including palpable purpura may be particularly sensitive to the small variations in daily steroid dosage of 1 to 2 mg, and derive benefit from dietary therapy.

Cyclophosphamide and in particular, rituximab are each first-line therapies for EMCs [1, 4, 21, 22]. Rituximab is first-choice treatment based on the results of observational and controlled studies in seronegative and seropositive HCV patients with CV [1, 4, 21, 22, 27-31]. Traditional and double-filtration PE can reduce the levels of circulating IC and cryoglobulins [1, 4, 21]. Oral cyclophosphamide at the dose of 50 to 100 mg per day for 2 to 6 weeks during the tapering of PE sessions, as well as rituximab, reinforces the beneficial effects of PE. Moreover, the latter can also potentiate the effect of cyclophosphamide [9], and is beneficial in the treatment of fulminant manifestations of CV such as widespread vasculitis and/or rapidly progressive MPGN [9].

The treatment of CV should be tailored to individual patients according to the severity of clinical symptoms, with the most severe vasculitic manifestations treated promptly with combination corticosteroids, PE, and cyclophosphamide or rituximab [1, 4, 9, 21]. Pilot studies suggest that sequential or combined antiviral and immunosuppressive treatment is a useful strategy [4, 27, 30, 31] especially in those with major clinical manifestations and partial or transitory remission after antiviral therapy (Figure 4). Clinically asymptomatic patients may be monitored without treatment even in the presence of elevated cryocrit levels; in these patients, an attempt to HCV eradication should be always considered. Careful clinical monitoring of the disease is mandatory in all cases with particular attention to neoplastic transformation [1, 4].

CONCLUSION

Cryoglobulinemic vasculitis is an important model for the study of autoimmune and lymphoproliferative diseases mediated by viral infections. Recent advancements in the understanding of the underlying multifactorial and multistep processes in the etiopathogenesis of CV have translated into more effective etiological treatment modalities including antiviral treatments directed at eradication of HCV infection as both a triggering factor and contributor

to the self-perpetuating mechanism of autoimmune disease. In addition, pathogenetic therapies may be employed to target the variably severe consequences of LCV, systemic SVV, multiorgan involvement, and malignancies. Future challenges in CV include improvements in the differential diagnosis with some overlapping disorders, as well as the improvement in therapeutic strategies tailored to different CV clinical variants in selected patients.

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Chapter 205

AORTITIS AND PERIAORTITIS

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ABSTRACT

Aortitis and periaortitis are inflammatory diseases of the aorta and its branches. They differ in the extension of inflammation, which is confined to the aortic wall in aortitis and extends in the periaortic space in periaortitis. Although aortitis occurs as either an infectious or a non-infectious process, the latter suggests an etiology related to large-vessel vasculitis. Periaortitis and aortitis are recognizable fibro-inflammatory systemic disorders, categorized under the rubric of IgG4-related diseases. This chapter reviews the nosology, pathogenesis, histopathology and clinical phenotype of the different forms of aortitis and periaortitis, and discusses their diagnosis and management.

Keywords: aortitis, periaortitis, IgG4-related disease, fibrosis, vasculitis, giant cell arteritis, Takayasu arteritis

ABBREVIATIONS

¹⁸ F-FDG-PET	¹⁸ F-fluorodeoxyglucose positron emission tomography;
AAV	ANCA associated vasculitis;
ANCA	anti-neutrophil cytoplasm antibody;
CRP	C-reactive protein;
CT	computed tomography;
CTL	cytotoxic T lymphocyte;
ECD	Erdheim Chester disease;
ESR	erythrocyte sedimentation rate;

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GCA	giant cell arteritis;
HLA	human leucocyte antigen;
IAAA	inflammatory abdominal aortic aneurysm;
IgG4-RD:	IgG4-related disease;
IL	interleukin;
LVV	large vessel vasculitis;
MRI	magnetic resonance imaging;
NK	Natural killer;
PDGF	platelet-derived growth factor;
RPF	retroperitoneal fibrosis;
SLE	systemic lupus erythematosus;
SUV	standardized uptake value;
TA	Takayasu arteritis;
TLR:	toll-like receptor;
US	ultrasonography.

INTRODUCTION

Aortitis and periaortitis are in the spectrum of systemic inflammatory disorders characterized by chronic inflammation that may be limited to the aortic wall or to the adjacent periaortic space. Both conditions may arise in the context of a recently recognized clinical-pathological entity known as an IgG4-related disease (IgG4-RD), characterized by marked fibrosis and T-lymphocyte and IgG4-positive plasma cell infiltration of various organs.

In 2015, a standardized classification for inflammatory diseases of the aorta was proposed as a part of a consensus statement issued by the Society for Cardiovascular Pathology and the Association for European Cardiovascular Pathology [1]. The committee identified three general categories of inflammatory aortic disease: (a) atherosclerosis, (b) atherosclerosis with excessive inflammation and (c) aortitis/periaortitis.

Atherosclerosis is a degenerative inflammatory process that starts from the intimal layer of arteries. It is classified as mild, moderate, or severe based on the medial destruction and the presence of extracellular lipid deposition with fibrosis. In some cases, the inflammatory reaction is unusually intense but always due to atherosclerosis. Two major examples of this phenomenon are atherosclerosis with excessive neutrophilic inflammation and inflammatory abdominal aortic aneurysms (IAAA).

The terms aortitis and periaortitis are reserved for inflammatory aortic conditions unattributed to atherosclerosis alone. Aortitis is a pathological term that describes an extensive inflammatory process that involves the media and/or the intima of the aortic wall.² The inflammatory response affects the aorta at any level and extends to its major branches and other large vessels. Aortitis can be the presenting feature of large vessel vasculitides (LLV), but may also occur in the absence of clinical symptoms or signs of systemic vasculitis making it an incidental diagnosis on imaging studies or in histologically studied specimens of surgically resected aortic tissue [1]. Aortitis rarely develops in association with concomitant rheumatologic disorders or in the presence of an infectious illness.

It is recommended to apply the term periaortitis to an inflammatory process that arises from the adventitia of the aortic wall and extends into the surrounding periaortic space. The ensuing pathological lesion consists of a fibrous component and a chronic inflammatory infiltrate. Periaortitis typically involves mainly the lower abdominal aorta and the common iliac arteries and can arise around either a dilated or non-dilated aorta. The tissue infiltrating the retroperitoneum frequently encases adjacent structures such as the ureters and the inferior vena cava [3]. Originally, periaortitis was thought to be confined to the abdominal aorta, although histopathologic studies provided evidence of simultaneous involvement of other vascular districts [4]. Computed tomography (CT), magnetic resonance imaging (MRI) and especially ^{18}F -fluorodeoxyglucose positron emission tomography (^{18}F -FDG-PET) imaging identify vascular inflammation in virtually all large arteries. The thoracic aorta and the epiaortic arteries are involved in about a third of patients suffering from abdominal periaortitis wherein the condition is typically asymptomatic [5]. The coronary, renal, mesenteric and coeliac arteries may rarely be involved. While diverse causes of periaortitis and aortitis may be clearly distinguishable, the differential diagnosis is often challenging when an affected patient presents with nonspecific systemic symptoms or fever of unknown origin, and the inflammatory process diffusely involves the aorta.

In 2001, Hamano and colleagues [6] first described IgG4-RD noting an association between sclerosing pancreatitis and high serum levels of IgG4+. The recognition of other involved sites led to the concept of a fibro-inflammatory systemic disease. Large vessels involved by IgG4-RD [7] present clinically as aortitis or periaortitis. Notwithstanding, the corresponding lesions are similar throughout the different affected sites.⁸

CLASSIFICATION AND NOSOLOGY

Aortitis is classified into two main groups, according to the presence or absence of an infectious source. While infectious aortitis is now rare in developing countries as a result of the introduction of antibiotics, it nevertheless remains important to differentiate the infectious and non-infectious entities since the therapeutic strategies significantly differ [2].

Infectious aortitis develops in the course of septicemia or embolization of a septic embolus as a complication of infective endocarditis [1]. Pre-existing aortic wall damage in the form of arteriosclerotic lesions or vascular dilatation facilitates infection. Elderly men and immune compromised patients are populations at the greatest risk for the most common associated organisms, namely, gram-positive bacteria including *Staphylococcus* spp, *Enterococcus* spp and *Streptococcus pneumoniae* that typically involve the thoracic aorta; and gram-negative bacteria, notably *Salmonella* spp, that affect the abdominal aorta. Syphilitic aortitis develops in the setting of tertiary syphilis, typically involving the ascending aorta. *Treponema pallidum* preselects the *vasa vasorum* of the aortic wall leading to ischemic injury of the medial layer, with secondary aneurysmal dilatation. Tuberculous aortitis should be suspected in those with pulmonary and extrapulmonary tuberculosis in the course of miliary spread or direct extension of the infectious process from adjacent tissues, such as infected lymph nodes or lung lesions [2]. In those cases, the thoracic and abdominal aorta are affected with comparable frequency [1]. Fungal infection-related aortitis occurs in immune-compromised patients or in others chronically exposed to broad-spectrum antibiotics [1].

Table 1. Aortitis and periaortitis: Classification and etiologic basis

Infectious aortitis	Non-infectious aortitis	Idiopathic/IgG4 related periaortitis	Other diseases with periaortic infiltration
Bacterial (<i>Staphylococcus</i> spp, <i>Streptococcus pneumoniae</i> , <i>Salmonella</i> spp, <i>Escherichia</i> spp, <i>Treponema pallidum</i> , etc.)	Large-vessel vasculitides (Giant cell arteritis, Takayasu arteritis)	Idiopathic retroperitoneal fibrosis	Infections (Actinomycosis, Tuberculosis, Histoplasmosis)
<i>Mycobacterium tuberculosis</i>	ANCA associated vasculitides	Inflammatory abdominal aortic aneurysm	
Fungi (Candida, Aspergillus, Cryptococcus, Paracoccidioidomycosis)	Other vasculitides (Behçet Disease's, Cogan syndrome)	Perianeurysmal retroperitoneal fibrosis	Drugs (Ergot-alkaloid derived drugs, Methyldopa, Beta-adrenergic blockers, Phenacetin, Paracetamol, Aspirin, Hydralazine, Carboplatin, Methotrexate, Etanercept, Infliximab)
	Idiopathic/IgG4 related Isolated Aortitis	Thoracic periaortitis without aneurysm	
	Connective tissue diseases (Systemic lupus erythematosus, Relapsing polychondritis, Sarcoidosis)	Thoracic aorta aneurysm without periaortitis	Malignancies (Metastases of carcinomas: breast, lung, pancreas, stomach, colon, rectum, kidney, bladder, prostate, ovary and cervix; Carcinoid tumors, Hodgkin and non-Hodgkin lymphomas)
		Periaortitis with thoracic aorta aneurysm	
	Inflammatory arthritides (Rheumatoid arthritis, Ankylosing spondylitis)	Diffuse thoraco-abdominal periaortitis	Others (radiation therapy, abdominal trauma and surgery, Erdheim–Chester disease)

Non-infectious aortitis associated with LVV, including giant cell arteritis (GCA) and Takayasu arteritis (TA) represents two large groups of cases [2]. Aortic involvement occurs in systemic rheumatic disorders. Rheumatoid arthritis vasculitis (RAV), in which aortitis is an uncommon extra-articular manifestation, may be associated with vascular involvement of vessels of any size and may appear in any phase of the illness, although typically in the later stages [9]. The aortic root, the ascending aorta [10] and the branches of the aortic arch [11] can be involved in ankylosing spondylitis. Aortitis is also described in cases of systemic lupus erythematosus (SLE), most often manifesting as an aortic aneurysm or dissection [12, 13]; and in rare cases of relapsing polychondritis [14].

Large vessel involvement occurs in several small vessel vasculitides (SVV). In anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitides (AAV), aortitis may present with stenosing arteritis, aneurysmal disease and aortic dissection [15]. Vasculitis involvement of the *vasa vasorum* affecting the aortic root is associated with valvular dysfunction in some cases of Behçet disease [16]. Aortitis also occurs in a minority of patients with Cogan syndrome [17] with severe incipient complications thereof [18]. Aortitis is unusual in sarcoidosis [19]. Cryptic isolated aortitis involving the ascending aorta may be detected in clinically asymptomatic patients, without evidence of a coexisting rheumatic disease [1].

Periaortitis has to be distinguished from aortitis not only for classification purposes, but also for its clinical and therapeutic implications. Periaortitis usually affects the infra-renal portion of the abdominal aorta and the iliac arteries. The aorta is undilated in idiopathic retroperitoneal fibrosis (RPF) while IAAA and perianeurysmal retroperitoneal fibrosis are the perianeurysmal forms [3]. Abdominal periaortitis must be differentiated from other diseases leading to periaortic retroperitoneal infiltration, particularly malignancies, granulomatous infections, drug-related and radiotherapy-induced conditions, and Erdheim-Chester disease [20]. In some patients, an idiopathic form of periaortitis involves the thoracic aorta with three possible patterns: thoracic periaortitis without aneurysm, thoracic aorta aneurysm without periaortitis, and periaortitis surrounding a thoracic aorta aneurysm.

Both aortitis and periaortitis can arise in the context of IgG4-RD signaling involvement as a multifocal disease; and in other cases, isolated to the thoracic tract. IgG4-related aortitis accounts for 75% of thoracic aortitis with a lymphoplasmacytic pattern [21]. Periaortitis is a common manifestation of IgG4-RD, responsible for up to 50% of periaortitis cases [22]. Table 1 summarizes the main etiologies of aortitis and periaortitis.

MAIN HISTOLOGIC PATTERNS

Aortitis may exhibit four different histological patterns of inflammation, namely granulomatosis/giant cell, lymphoplasmacytic, mixed inflammatory and suppurative, each related to different etiologies [1].

The *granulomatosis/giant cell pattern* is the most common pattern of inflammation in aortitis. It is characterized by the presence of large activated epithelioid macrophages with or without giant cells and compact granulomas. An accompanying lymphoplasmacytic infiltrate is often present. This pattern occurs in GCA- and TA-related aortitis, isolated aortitis, and aortitis associated with rheumatoid arthritis, ANCA associated vasculitides (AAVs), sarcoidosis, mycobacterial and fungal infections.

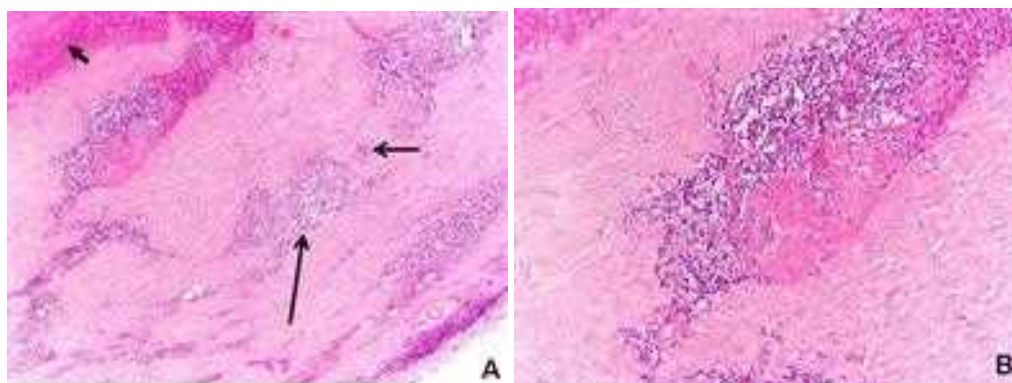


Figure 1. Histopathological findings in a case of IgG4-related aortitis. (A) (Hematoxylin and eosin, original magnification x4) shows inflammation and fibrosis involving the aortic adventitia and the periaortic soft tissue. Nodular lymphoplasmacytic infiltrates (long arrow) are seen in the context of abundant adventitial and periadventitial fibrosis. Fibrosis has an irregular pattern and is often organized around small adventitial and periadventitial vessels (short arrow). The arrowhead indicates the aortic media. (B) (Hematoxylin and eosin, original magnification x10) shows a detail of the image shown in (A) where a cluster of inflammatory mononuclear cells can be observed in the context of irregular fibrosis. Immunohistochemistry performed in this case (not shown) demonstrated an IgG4⁺/IgG⁺ plasma cell ratio of 50%.

The *lymphoplasmacytic pattern* consists of lymphocytes and plasma cells without a granulomatous/giant cell component. It is seen in IgG4-RD, SLE and syphilitic aortitis (Figure 1).

The *mixed inflammatory pattern* is relatively uncommon. The inflammatory infiltrate is composed of almost all inflammatory cell types: macrophages, lymphocytes, plasma cells, eosinophils, mast cells and neutrophils without a granulomatous component. It is associated with aortitis in Cogan's syndrome, Behçet disease and relapsing polychondritis.

The *suppurative pattern* is characterized by a marked neutrophilic infiltrate and extensive necrosis. This pattern occurs in some forms of infectious aortitis such as infections with Gram-positive cocci, *Salmonella*, *Pseudomonas* and fungi.

Idiopathic periaortitis (either IgG4-related or unrelated) histologically shows two components: a fibrous tissue and a chronic inflammatory infiltrate. The fibrous component includes an extracellular matrix of type I collagen fibers and a population of fibroblasts and myofibroblasts. The inflammatory infiltrate displays a *lymphoplasmacytic pattern*. It consists of B and T lymphocytes, macrophages, plasma cells and rare eosinophils [20].

The histopathological appearance of IgG4-related forms of aortitis and periaortitis is comparable to that of their IgG4-unrelated counterparts; however, the IgG4-related forms more frequently show a storiform pattern of fibrosis, lymphoid aggregates with germinal centers, tissue eosinophilia, and obliterative phlebitis, and by definition, a higher proportion of IgG4⁺ plasma cells. The diagnosis of IgG4-related forms requires a ratio of IgG4⁺/total IgG⁺ plasma cells > 40% [23].

CLINICAL PHENOTYPES

Herein, we describe the clinical phenotype of the most common aortitis and periaortitis syndromes, with particular emphasis on non-infectious forms, and we highlight the characteristics of these two conditions in the course of IgG4-RD.

Giant Cell Arteritis

This medium- and large-vessel vasculitis usually affects the aorta and its major branches with a predilection for the branches of the carotid and vertebral arteries [24]. Defined in the past as “temporal arteritis,” the term is inadequate to describe GCA because not all patients have temporal artery involvement and other categories of vasculitis can affect the temporal arteries. GCA is the most common type of non-infectious arteritis in North America and Western Europe. It occurs primarily in elderly individuals older than 50 years. Women are affected two to three times more commonly than men [25].

The typical histological pattern of GCA is a granulomatous inflammatory infiltrate composed of lymphocytes, macrophages and in 50% of the cases, multinucleated giant cells.²⁵ Inflammation has a focal nature, with “skip” lesions, wherein non-affected arterial segments intermingle with inflamed tracts. It is located mainly in the intima-media junction of the vessel wall but it can be present throughout the artery. At the beginning of the disease process, the intimal layer appears thickened by the inflammatory infiltrate and edema, at later stages by myofibroblast migration. The media remains well preserved, although focal smooth muscle necrosis may occur. The adventitia is inflamed in a moderate proportion of cases [26].

The pathogenesis of GCA has not been fully explained but dysregulated interactions between the vessel wall and the immune system are key to disease development [27]. The allelic variant of human leucocyte antigen (HLA)-DRB1*04 is the most common genetic association with GCA. The involvement of class II HLA molecules implies antigen-presentation to CD4⁺ T cells which then triggers the vasculitic lesion [28]. The involved antigens are still unknown, both infectious agents and autoantigens have been suspected.

Vascular dendritic cells located at the adventitia-media border of the artery have a critical role in the initiation of disease. Dendritic cells become activated once their toll-like receptors (TLRs) are engaged by microbial products and turn into non-tolerogenic cells able to present potential auto-antigens to T cells; their ability to produce chemokines is thus enhanced, thus leading to recruitment of T cells and macrophages into the vascular wall through the *vasa vasorum* [28]. The activated dendritic cells express CD86, a co-receptor required to trigger T-cell activation, and produce cytokines, such as interleukin (IL)-6 and IL-12 that guide the differentiation of T cells into selected functional lineages [27].

IL-6 is a pleiotropic cytokine released also by endothelial cells, vascular smooth muscle cells, lymphocytes and macrophages and implicated in the production of acute-phase proteins. IL-6 shifts T-cell differentiation towards the Th17 lineage and blocks the anti-inflammatory T regulatory cell expansion. Th17 cells produce a plethora of cytokines (IL-17, IL-21, and IL-22) that recruit macrophages and neutrophils and activate vascular smooth muscle cells, fibroblasts and endothelial cells.

The IL-6/IL-17 cytokine cluster seems to play an important role in early GCA, while the IL-12/IFN- γ cytokine cluster appears to drive the tissue remodeling during chronic disease [27]. IL-12 promotes the differentiation of the Th1 lineage, which releases IFN- γ into the microenvironment. IFN- γ amplifies T-cell responses and stimulates macrophage activation. Macrophages have the potential to induce arterial wall injury through multiple pathways. They release reactive oxygen intermediates and metalloproteinases that lead to the fragmentation of the internal elastic lamina. Macrophages produce also platelet-derived growth factor (PDGF) and vascular endothelial growth factor that are critically involved in intimal layer proliferation. Myofibroblasts, stimulated by IFN- γ and PDGF migrate in the intima where they replicate and secrete extracellular matrix leading to concentric intima hyperplasia [28]. Outgrowth of the intima is consistently associated with marked neoangiogenesis. The end result is a vascular occlusion caused by the vessel wall thickening or the formation of arterial aneurysm (particularly thoracic aorta aneurysm) caused by destruction of the arterial wall [28].

Medium-sized arteries, such as the branches of external and internal carotid arteries and the vertebral arteries respond with occlusion of the lumen and, consequently, ischemic organ damage. Clinical symptoms reflect end organ ischemia.

The classic manifestations are headache, scalp tenderness, jaw claudication, blindness, stroke, transient ischemic attacks and vertigo. Similarly, involvement of the subclavian, axillary, and proximal brachial arteries leads to arm claudication and absent or asymmetric pulses [28]. Compared to patients with cranial symptoms, those with aortic arch syndrome tend to be younger at diagnosis and have a longer duration of symptoms prior to diagnosis [29].

Instead of forming stenotic lesions, the aorta responds with wall destruction. Aortitis most often occurs in the thoracic aorta while involvement of the branches of the abdominal aorta and lower extremity arteries is less common. It may produce chest or back pain but it is more frequently asymptomatic until complications arise. These complications are aneurysm formation and rupture, dissection and aortic valve insufficiency (Figure 2). In early studies, the prevalence of aortic involvement in patients with GCA was based on the rate of aneurysm diagnosed fortuitously or after acute events and autopsy data, remaining under-estimated. Recently, the large use of imaging techniques (essentially CT, MRI or PET) in the diagnosis and follow-up of LVVs showed that aortic involvement may be more prevalent than previously reported, with a frequency ranging from 33%³⁰ to 50% [31-33]. The risk of aortic structural damage significantly increases in the first 5 years from diagnosis and progresses slowly afterwards, suggesting that chronic inflammation of the vascular wall is the major determinant of aortic damage [34].

In almost all patients with GCA, a syndrome of systemic inflammation accompanies vascular manifestations and presents with nonspecific symptoms including malaise, anorexia, weight loss, fever and depression. Around 40% of patients with GCA also have polymyalgia rheumatica, characterized by aching and morning stiffness involving the neck, shoulder and pelvic girdles [25].

Takayasu Arteritis

This disease predominantly affects the aorta and its major branches, along with pulmonary arteries. In accordance with the Chapel Hill consensus conference nomenclature, TA is a granulomatous vasculitis that usually occurs before the age of 50 years [24]. It is a rare disease with few reports regarding prevalence and incidence. Nonetheless, the highest prevalence has been described in Japan with 40 cases/million [35], but incidence rates seem to be similar in different countries worldwide [36]. It affects predominantly young women, with a peak incidence around the second and third decade [36].

The inflammatory process is a panarteritis affecting all the three layers of the vessels, with a focal distribution, which results in narrowing of the lumen due to the fibrosis with stenosis and occlusion, or aneurysmal formation in cases where the process is more rapid [26, 37].

In the acute phase, *vasa vasorum* of the adventitia appear inflamed with granulomatous inflammatory infiltrates involving the media, too. The most abundant cells are T and B cells, along with granulocytes and eosinophils. Giant cells are present as in GCA and this feature may account for the difficulties in differentiating the two vasculitides. Neovascularization and proliferation of the smooth cells and fibroblasts lead to derangement of the intima. In chronic stages of the disease fibrosis and dense scarring lead to a thickening of the adventitia and the intima appears as a “tree bark,” a characteristic common to other aortitides. The disruption of the elastic fibers may lead to aneurysm formation (Figure 2) [1, 37].

The pathogenesis of TA is not well understood. Various antigens have been explored but the exact triggers and involved immunologic pathways remain obscure. Current evidences suggest an autoimmune mechanism with a prominent cell-mediated immunity, along with genetic predisposition mediated by HLA alleles. In particular a strong association was reported between class I HLA alleles and TA [38].

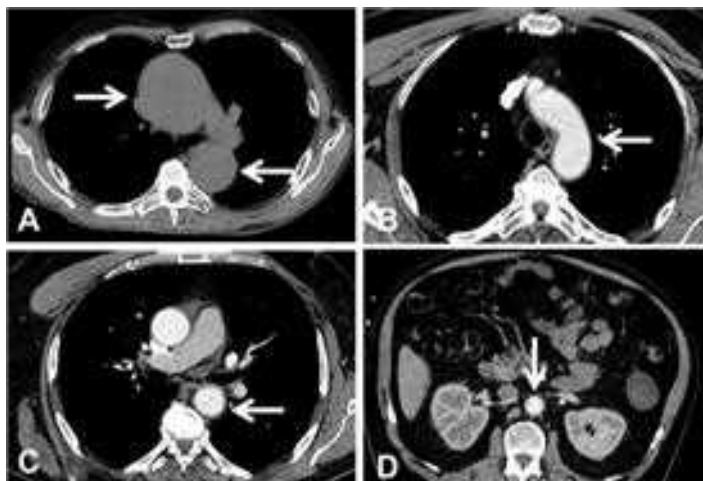


Figure 2. Computed tomographic (CT) findings in aortitis. The images A-C show the CT appearance of thoracic aortitis: (A) aneurysms of ascending (upper arrow) and descending aorta (lower arrow); (B, C): wall thickening of the aortic arch (B, arrow) and of the descending aorta (C, arrow). CT appearance of abdominal aortitis (D, arrow).

Natural killer (NK) cells and $\gamma\delta$ T lymphocytes appear to have a role in inducing apoptosis of the vascular cells by releasing perforin. These cells are activated by 65-kDa heat shock protein (HSP) which is overexpressed in aortic samples of patients affected by TA [39]. Similar to GCA, CD4⁺ T cells have a leading role particularly in the formation of granulomas. Both Th1 and Th17 pathways are expanded and correlate with disease activity [40].

The clinical manifestations are variable during the early stages of the disease with anorexia, fever and malaise. In fibrotic stages (also known as pulseless stages) symptoms are related to vascular stenosis and aneurysms [41]. Most typical clinical features include: diminished or absent pulses with limb claudication and discrepancies in blood pressure, multiple vascular bruits, renovascular hypertension and retinopathy [37]. Complications are related to organ ischemia and congestive heart failure due to hypertension and valve regurgitation when thoracic aneurysms are present.

Isolated Aortitis

Isolated aortitis is a single-organ vasculitis found primarily in the ascending part of the thoracic aorta [24]. This condition is not a component of a systemic vasculitis like GCA and TA, or associated with a systemic disease such as SLE or sarcoidosis. The disorder emerged with the advent of aortic surgery and histopathologic examination of the aortic surgical specimens. The introduction of new imaging techniques facilitated recognition of the disease before development of structural aortic abnormalities requiring surgery.

The epidemiology of isolated aortitis has not been clearly established, but its prevalence is probably underestimated, as the disease may remain undiagnosed for a long time. The incidence of isolated aortitis in the population of patients undergoing thoracic aortic surgery is between 3.8% and 4.4% [42-44]. Some studies show a higher incidence in women [42, 43] others in men [44, 45]. The mean age of patients at diagnosis ranges from 63 to 72 years [42-44]. Unlike those with TA and GCA, patients with isolated aortitis do not have symptoms related to systemic illness or extra-aortic arteritis [43].

Most cases of isolated aortitis show a granulomatous/giant cell pattern of inflammation localized in the medial layer. The inflammatory infiltrate comprises macrophages, giant cells, lymphocytes, plasma cells and well-formed granulomas replacing irregular areas of medial destruction. Adventitial inflammation contains minimal mononuclear cell infiltration without granuloma formation.

Isolated aortitis is identified incidentally during radiological exams or in the repair of the complications of aortic surgery [46]. Isolated aortitis can lead to thoracic aortic aneurysms, aortic dissection and aortic valve regurgitation. The aortic aneurysm is certainly the most frequent complication, so noted in 95% of patients with isolated aortitis and is usually localized in the ascending tract [42, 43].

Recent studies have evaluated the rate of new aortic events in patients with the diagnosis of isolated aortitis [47, 48]. Follow-up data indicate that patients with isolated aortitis are at increased risk for subsequent aortic events, such as new aneurysms and dissections also involving the descending thoracic aorta or the abdominal aorta. Even in the absence of signs of systemic vasculitis, aortitis identified in the ascending aorta is associated with an increased frequency of distal aortic events during long-term follow-up. Patients with isolated aortitis should be monitored with periodic aortic imaging.

Though the studies are limited, there is an increasing evidence that patients with aortitis isolated to aortic ascending segment have actually a smoldering systemic vasculitis that is subclinical in other districts at the time of presentation and fully manifests at a later time [46].

IgG4-Related Aortitis

Since the first description of IgG4-RD, diverse clinical entities without clear nosology have been categorized in the spectrum of this systemic fibro-inflammatory disease, including cases of aortitis, once considered isolated or idiopathic.

IgG4-related aortitis preferentially affects the thoracic aorta and particularly the aortic arch [21, 49]. It presents with a lymphoplasmacytic pattern and accounts for a significant proportion of non-infectious thoracic aortitis cases, and about 75% of cases of lymphoplasmacytic thoracic aortitis [21, 50]. The vasculitic process can also involve the abdominal aorta, along with medium-sized vessels originating from the aorta, such as the carotid and coronary arteries [7, 51]. Small vessel involvement has also been described, thus supporting the idea that IgG4-RD may be included in the category of vasculitis of vessels of variable size [52].

IgG4-related aortitis occurs among elderly men aged 60 years or older, in keeping with the epidemiology of the systemic and other organ-limited forms of IgG4-RD [50].

The inflammatory infiltrate affects predominantly the adventitia with a lesser involvement of the media (Figure 1), in contrast with other LVV.¹ Histological findings are typical and are the same throughout different lesions, regardless of the involved site. The main features are storiform fibrosis, obliterative phlebitis, moderate eosinophilia and dense lymphoplasmacytic infiltrates, with a predominance of T and B cells that occasionally organize into germinal centers [23]. IgG4-immune staining of the affected tissue is mandatory to have a “definite” diagnosis of IgG4-related aortitis. However, in cases not undergoing surgery or when the pathological specimen is unavailable, evidence of aortitis on imaging studies, along with increased serum IgG4 levels, supports a “possible” diagnosis of this condition [49].

The pathogenesis of IgG4-RD, and consequently of IgG4-related aortitis, remains unclear although significant advances have been made: IgG4 antibodies does not seem to have a central role, and their anti-inflammatory characteristics lead to consider them as an attempt to dampen a primary inflammatory process [53]. The immune mechanisms are probably cell-mediated. A subpopulation of CD4⁺ T cells with a cytotoxic phenotype (CTLs) has been found in IgG4-RD lesions and clonally expanded in the circulation, which appears to orchestrate the pathogenic mechanisms activated by antigen-presenting B cells [54]. The latter have a pivotal role in initiating and maintaining the disease, as shown by the efficacy of B cell-depleting therapies, such as rituximab. The antigens that trigger the immune response are unknown.

IgG4-related aortitis occurs sub-acutely and is often asymptomatic. It may be diagnosed after an incidental finding on CT (Figure 2) or after pathological examination of surgical specimens. It can also present with symptoms related to the presence of aneurysms, whereas end organ ischemia is far less common and appear when medium-size vessels such as the main aortic branches are also involved [7]. Acute pain may indicate dissection, which has also

been described as a complication of IgG4-related aortitis [55]. Involvement of other organs may be absent at onset and appear only during follow-up with a metachronous pattern [56], leading to difficulties in promptly recognizing IgG4-RD. The most frequent clinical pictures of IgG4-RD include sclerosing pancreatitis (type 1 autoimmune pancreatitis), Mikulicz disease and RPF, but several other conditions may be found such as diffuse lymphadenopathy, sclerosing cholangitis, pseudotumor of the orbit, and tubulo-interstitial nephritis.

Periaortitis

Periaortitis is a fibroinflammatory disorder characterized by the presence of fibrosis accompanied by a variable number of chronic inflammatory cells that extend from the adventitia of the aortic wall into the surrounding periaortic space [57]. The term “chronic periaortitis,” proposed by Mitchison in 1980 underlines the nature of the inflammatory infiltrate and has traditionally been applied to describe this condition.

Periaortitis includes three main entities: idiopathic RPF, inflammatory abdominal aortic aneurysms (IAAAs) and perianeurysmal RPF. In idiopathic RPF, the aorta is undilated and the retroperitoneal fibroinflammatory tissue frequently entraps neighboring structures such as the ureters and the inferior vena cava (Figure 3); in IAAAs, the mass develops around a dilated aorta without involving adjacent organs (Figure 3). Perianeurysmal RPF represents a combination of these two diseases, the aorta is dilated and the periaortic tissue causes obstruction of other structures.

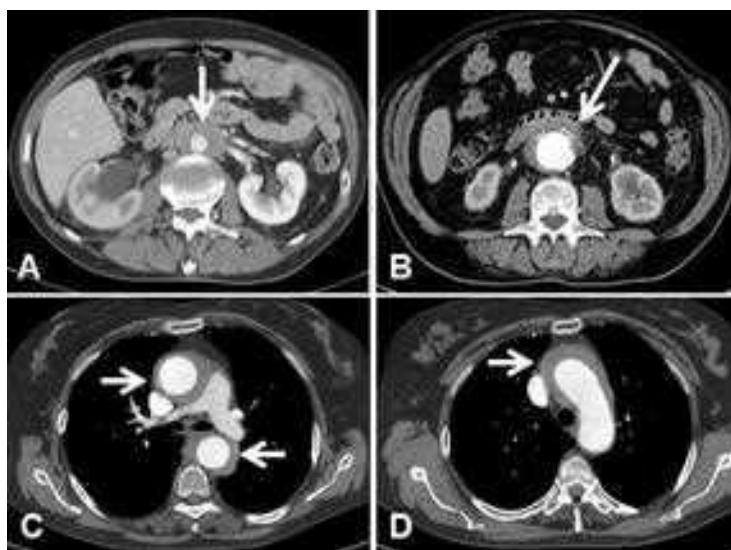


Figure 3. CT findings in periaortitis. The images show the CT appearance of periaortitis with typical localization (A), where the soft-tissue mass (arrow) surrounds the anterior and lateral sides of the abdominal aorta, spreads to the right ureter and causes hydronephrosis. CT appearance of perianeurysmal periaortitis (B): the fibro-inflammatory tissue encircles a dilated abdominal aorta (arrow). CT appearance of thoracic periaortitis (C, D). The perivascular tissue surrounds the ascending thoracic aorta (C, upper arrow), the aortic arch (D, arrow) and the descending thoracic aorta (C, lower arrow).

Periaortitis is a rare disease and data about its epidemiology are limited to idiopathic RPF and IAAAs. The incidence of idiopathic RPF is 0.1-1.3 per 100,000 person-years and its prevalence 1.4/100,000 inhabitants [58, 59]. IAAAs represent 4-10% of all abdominal aortic aneurysms [60]. The mean age at onset is 50-60 years [61], although rarely cases have been reported in pediatric patients [62]. Men are affected two to three times more often than women and this ratio is higher in the aneurysmal forms [58].

Pathologic changes in periaortitis involve both the aortic wall and the surrounding soft tissues. The typical macroscopic appearance of periaortitis is that of a greyish mass infiltrating the retroperitoneal tissue surrounding the abdominal aorta, the iliac arteries and, in most cases, the inferior vena cava and the ureters [63]. The mass usually develops between the origin of the renal arteries and the pelvic brim. In some instances, periaortitis shows atypical localizations, which might be peri-duodenal, peri-pancreatic, pelvic, presacral, peri-ureteral or peri-renal and not characterized by involvement of the periaortic space. These cases are thought to have a different pathogenesis.

Microscopic examination reveals the presence of two components: a fibrous tissue and an inflammatory infiltrate [20]. The fibrous component comprises fibroblasts that show signs of activation and transition into myofibroblasts (α -smooth muscle actin expression) and produce an extracellular matrix composed of type I collagen fibers organized in thick irregular bundles. The inflammatory infiltrate consists of numerous lymphocytes, plasma cells, macrophages and scattered eosinophils. The inflammatory cells are interspersed within the collagen bundles (diffuse pattern), but also organized in nodular aggregates, usually around small vessels (perivascular nodular pattern). These aggregates have a B-cell core surrounded by T cells, which are predominantly CD4⁺. In some cases, these lymphoid follicles have the structure of germinal centers, which is a sign of ectopic lymphoneogenesis, thus proving the presence of a highly structured immune-mediated/autoimmune response.

The aortic wall shows intimal atherosclerosis, medial thinning and adventitial inflammation and fibrosis. The composition of the inflammatory infiltrate in the aortic adventitia is similar to that of the retroperitoneal one. When the pattern is arranged in nodular aggregates, these are usually centered on the adventitial *vasa vasorum* which can show signs of vasculitis [64].

The pathogenesis of periaortitis is still unclear. The theory proposed by Parums and Mitchinson suggests that it is due to a local inflammatory reaction against antigens localized in the atherosclerotic plaques of the aorta such as oxidized low-density lipoproteins or ceroid [65, 66]. These antigens would be presented by plaque macrophages to B and T lymphocytes residing in the adventitia, where they would elicit a fibro-inflammatory response inducing lymphocyte activation and immunoglobulin production. This theory, however, cannot explain the presence of constitutional symptoms and the increase in acute phase reactant levels in patients with periaortitis, and the frequent associations with autoimmune or fibro-inflammatory diseases involving other organs. Additionally, periaortitis may affect patients without atherosclerotic lesions and involve vascular territories/segments spared by atherosclerosis [67]. Recently, it has been proposed that periaortitis may actually be a systemic autoimmune disease rather than the result of a local inflammatory reaction [64]. This theory is supported by similarities to systemic LLV, such as GCA and TA: the inflammatory process starts in the adventitial layer leading to perivascular infiltrates surrounding aortic *vasa vasorum*. Thus, it cannot be excluded that periaortitis originates as a primary aortitis which subsequently induces a fibro-inflammatory reaction into the periaortic space [3].

The pathogenesis of the disease is probably multifactorial, recognizing genetic, environmental and immune-mediated determinants. The role of genetic factors is demonstrated by the association between periaortitis and the HLA class II allele HLA-DRB1*03, a marker of autoimmune diseases such as SLE, type 1 diabetes, autoimmune thyroiditis and myasthenia gravis [68].

A more recent study also describes an increased susceptibility to the aneurysmal forms of periaortitis in patients carrying the $\Delta 32$ polymorphism of the *CCR5* gene [69]. *CCR5* is expressed on many immune cells, particularly Th1 cells, and acts by binding to different chemokines, including RANTES, MIP-1a and MIP-1b. The *CCR5* $\Delta 32$ polymorphism creates a truncated, nonfunctional receptor and probably shifts the immune response toward a Th2 pattern.

Among environmental agents, cigarette smoking and asbestos exposure are significantly associated with an increased risk of developing the disease. Interestingly, smoking and asbestos had a multiplicative effect on disease risk, with an odds ratio of 12.04 (95% confidence interval, 4.32 to 38.28) in co-exposed subjects [70]. The role of other environmental or infectious agents remains elusive.

The immunopathogenic model of periaortitis is based on the hypothesis that the disease is antigen-driven, although the triggering antigens are still unknown. Based on the available experimental evidence, it can be postulated that antigen-presenting cells present such hypothetical antigens to CD4⁺ T cells within the aortic wall, probably in the adventitia. CD4⁺ T cells expand, secrete IL-6 [71], which enhances the production of acute-phase proteins and promotes the activation of B cells and fibroblasts. CD4⁺ T cells also secrete Th2 cytokines such as IL-4, IL-10 and IL-13, which induce B-cell expansion and maturation into plasma cells producing, in a fraction of cases, IgG4. Lymphoid cells also release eotaxin-1 (also known as CCL11), which drives tissue infiltration by eosinophils and mast cells, whose products induce fibroblast activation [72]. Once activated, fibroblasts mature into myofibroblasts and secrete collagen, promoting fibrosis. The pathogenic importance of IL-6 and of B cells was confirmed *in vivo* by the efficacy of therapies targeting selectively the IL-6 receptor (tocilizumab) and the B-cell marker CD20 (rituximab) [71, 73].

The clinical presentation of periaortitis includes two types of manifestations: localized, due to the compressive effects of the retroperitoneal mass, and systemic, related to the inflammatory nature of the disease. The more frequent localized symptom, present in about 80% of the patients, is side, back or abdominal pain. It is usually described as persistent and dull, not exacerbated by movement or palpation; it transiently responds to nonsteroidal anti-inflammatory drugs and, in cases of ureteral involvement, it can be colic-like [3]. Ureteral involvement is the most frequent complication and can be unilateral or bilateral. In cases with unilateral involvement, ureteral obstruction can also be asymptomatic for a long time and, at diagnosis, these patients present with renal hypoplasia/atrophy, whose frequency is estimated to be up to 30%. However, most cases are symptomatic and bilateral involvement usually leads to acute renal failure. Other urologic manifestations are frequent: they range from testicular pain, often accompanied by hydrocele and/or varicocele due to spermatic vein encasement by periaortitis, to retrograde ejaculation and erectile dysfunction [20]. The extrinsic compression of retroperitoneal lymphatic vessels and veins can be the cause of lower extremity edema and deep vein thrombosis. Claudication and intestinal ischemia are

less common. Systemic symptoms include fatigue, weight loss, anorexia, sleep disturbances and low-grade fever [3].

Periaortitis can affect not only the lower abdominal aorta and the iliac arteries but also other vascular segments. This may suggest that in such cases, periaortitis actually represents a primary, diffuse inflammatory disease of the aorta and its major branches (Figure 3) [5]. In 1970, Mitchinson described for the first time the presence of mild inflammation and fibrosis in the adventitial layer of the thoracic aorta in autopsy studies performed on patients with abdominal periaortitis [4]. Subsequent reports have also documented the involvement of coronary arteries [57], renal arteries [74], and celiac axis, superior and inferior mesenteric arteries [75].

A recent study performed in a large cohort of patients showed that, in one third of cases, periaortitis might also affect the thoracic aorta and the epiaortic arteries [5]. The perivascular tissue may develop around the ascending aorta, the aortic arch, the descending aorta and the origin of epiaortic arteries. Three main patterns can be observed: periaortitis with thoracic aorta aneurysm, thoracic periaortitis without aneurysm and thoracic aorta aneurysm without periaortitis [5]. Histology of the thoracic tissue is definitely similar to that found in abdominal periaortitis. The pathological lesions involve the adventitia and the periadventitial tissue and consist of a fibrous component and a chronic inflammatory infiltrate comprising lymphocytes, histiocytes, plasma cells, and eosinophils.

The observation that the thoracic aorta is usually spared by atherosclerosis strongly supports the hypothesis that, when periaortitis develops, it is a primary immune-mediated process [76]. The clinical presentation of thoracic involvement in periaortitis includes specific symptoms such as laryngeal nerve paralysis, dry cough, upper limb claudication and paresthesias; however, in about 85% of cases it is asymptomatic. Interestingly, the comparison of demographic and clinical characteristics of patients with and without thoracic involvement revealed that these subgroups were different. Patients with thoracic involvement had a significantly higher female prevalence, a greater age at disease onset, a higher prevalence of systemic symptoms and of back or abdominal pain [5].

The female prevalence and the advanced age in patients with thoracic aorta involvement is a feature shared by GCA, which often affects not only the epiaortic tree but also the thoracic aorta. Indeed, GCA is characterized by only mild periaortic thickening does not cause obstructive uropathy, while periaortitis, on the other hand, does not lead to typical GCA-related cranial symptoms. However, the differential diagnosis between GCA and periaortitis may become more challenging when patients present with non-specific systemic symptoms, including fever of unknown origin, and lack clinical manifestations specific for either disease.

Periaortitis may be associated with a large variety of autoimmune conditions. This observation underlines the relevance of autoimmune mechanisms in the pathogenesis of the disease. Hashimoto's thyroiditis is the most commonly associated autoimmune disorder; it may arise together with periaortitis, but it can also precede or follow periaortitis diagnosis. Overall, it has been reported that 25% of patients with periaortitis develop hypothyroidism after a median follow-up of 45 months [77]. Other associated conditions are AAV, particularly granulomatosis with polyangiitis, membranous nephropathy, SLE, rheumatoid arthritis, uveitis and psoriasis [3].

IgG4-Related Periaortitis

Periaortitis may also be a manifestation of IgG4-RD. Histological examination is mandatory to differentiate IgG4-related and -unrelated forms. However, the coexistence of other clinical conditions belonging to the spectrum of IgG4-RD may help classify periaortitis as IgG4-related [78].

Periaortitis (particularly the abdominal form) is reported among the most frequent manifestations of IgG4-RD in different studies, even if its prevalence remains quite variable, ranging from 11% to 30% [79-82]. It appears that environmental factors influence the different organ involvements, since periaortitis is more frequent in Western cohorts, whereas in Asian countries extra-vascular lesions are more common [82].

IgG4-related periaortitis may differ from IgG4-unrelated forms in terms of microscopic findings, whereas the macroscopic ones are very similar. In particular, there were no significant differences in disease localization and characteristics when CT or MRI findings were compared [83, 84]. IgG4-related IAAAs (which are considered perianeurysmal forms of periaortitis) are frequently saccular, as the IgG4-unrelated ones, but the former show a more prominent thickening of the wall due to the fibrotic tissue which is also adherent to neighboring structures, leading to an apparently lower risk of rupture [85]. IgG4-related periaortitis is distinguishable from its IgG4-unrelated counterpart especially for the organization of the fibrotic tissue, which is storiform in the former, resembling the spokes of a cartwheel. IgG4-unrelated forms usually do not show obliterative phlebitis, and the inflammatory infiltrate is less dense and not markedly enriched with IgG4⁺ plasma cells and eosinophils [83]. However, these differences may be only slight, and it must be emphasized that the background histologic appearance of IgG4-related and -unrelated forms is often very similar, thus leading to the concept that these two entities may represent different ends of the same spectrum.

From a clinical standpoint, there are no substantial differences, except for a male predominance in IgG4-related forms [86]. The clinical manifestations of both IgG4-related and -unrelated periaortitis are comparable, with flank and abdominal pain being the most common presenting symptom. However, it must always be remembered that IgG4-related forms are more commonly associated with extra-retroperitoneal manifestations of IgG4-RD; this may help clarify the clinical picture of the disease.

DIAGNOSIS

The differential diagnosis among different forms of inflammatory aortitis and periaortitis is challenging, and histological examination is often required to have a clear definition of the disease. The particular site of inflammation makes it difficult to perform biopsies, unless aortic or retroperitoneal/ureteral surgery is required. Therefore, in most cases the diagnosis is based on laboratory tests and imaging studies, along with clinical presentation.

Aortitis in Large-Vessel Vasculitides

Both GCA and TA often manifest with typical symptoms, which render them more easily recognizable than other cases of apparently idiopathic aortitis. Cranial symptoms (e.g., jaw claudication, scalp tenderness and visual alterations) usually occur in GCA, whereas TA may manifest with signs and symptoms related to vascular stenosis (e.g., absence of pulses, bruits, limb claudication) [87]. Acute-phase reactants, namely C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are high in most cases of GCA whereas they are frequently normal in TA, which is in line with the clinical presentation of TA, whose clinical manifestations often arise in a late, “fibrotic” stage.

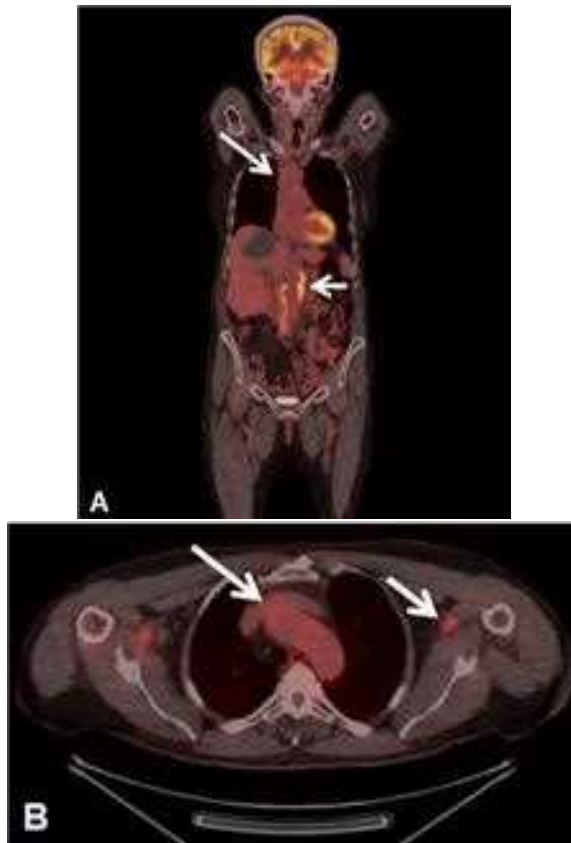


Figure 4. ^{18}F -fluorodeoxyglucose (FDG) positron emission tomography (PET) findings in patients with periaortitis and/or aortitis. (A) ^{18}F -FDG PET findings in a patient with abdominal periaortitis and thoracic aortitis. The scans show intense FDG uptake at the level of the thoracic aorta (long arrow) and of the abdominal aorta (short arrow). (B) ^{18}F -FDG PET findings in a patient with giant cell arteritis. The scans show intense FDG uptake at the level of the aortic arch (long arrow) and of the axillary arteries (short arrow).

Imaging studies, such as ultrasonography (US), angio-CT and angio-MRI have become crucial for the diagnosis of GCA and TA: mural thickening and enhancement are typical findings [88]. CT and MRI also show some disease-related aspects that are essential for the differential diagnosis between aortitis and periaortitis, since aortitis (also that occurring in

GCA or TA) does not have the thick periaortic cuff that characterizes CP and does not lead to encasement of neighboring structures such as ureters and inferior vena cava [76]. Over the last few years, ^{18}F -FDG PET (Figure 4) has become part of the diagnostic armamentarium of LVVs, and has allowed detection of aortic involvement. The advantage of PET is that it is a whole-body imaging study, able to reveal other FDG-avid lesions, and that it provides a measurable degree of FDG uptake by means of the maximal standardized uptake value (SUVmax) that can be useful to monitor vascular inflammation. Despite its widespread use in patients with LVV, ^{18}F -FDG PET still has an uncertain role as predictor of response or as disease-monitoring tool [88].

In patients with GCA, temporal artery biopsy remains the principal diagnostic examination; however, it must be recognized that a fraction of GCA patients may lack temporal artery involvement, and this is particularly the case of those with diffuse involvement of large arteries including the aorta. In sum, the diagnosis of GCA and TA, and consequently of aortic involvement in these conditions, relies on the integration of clinical examination, laboratory tests, imaging studies and, particularly in the case of GCA, vascular (temporal artery) biopsy.

Isolated Aortitis

Isolated aortitis is by definition a vasculitis confined to the aorta, in the absence of symptoms related to other systemic diseases [24]. It tends to affect mostly the thoracic aorta in its ascending part and usually presents as a thoracic aortic aneurysm [42]. It is often an incidental finding that can be diagnosed in two distinct settings. Traditionally and most commonly, the disorder is diagnosed pathologically following surgical resection of an aortic segment for aneurysm or dissection, and the patient is clinically found to have no other signs or symptoms of vasculitis. Isolated aortitis can also be identified radiologically, most often by CT or MRI, as an isolated aneurysm or as wall thickening limited to one segment of the aorta [46]. The absence of a diffuse atherosclerotic disease or of common risk factors for atherosclerosis should heighten suspicion of isolated aortitis in patients showing the above abnormalities on CT or MRI.

Once imaging studies disclose an apparently isolated aortitis, and the patient has no associated rheumatologic diseases, it is mandatory to exclude infectious causes (Table 1); laboratory tests can be useful in this setting to rule out particularly syphilis and tuberculosis and, in patients with systemic infections or in immunocompromised subjects, fungal and bacterial etiologies. Finally, the diagnostic work-up of an isolated aortitis should also consider the exclusion of IgG4-RD, of which aortitis can also be the sole manifestation. Therefore, in the absence of a biopsy, testing serum IgG4 levels and searching for other sites potentially involved by the disease is recommended (see below).

Periaortitis

The diagnosis of periaortitis is usually based on imaging studies and requires histological confirmation only in a small proportion of patients. Indeed, the clinical signs and symptoms

at disease presentation, as well as the laboratory tests are quite non-specific. Ultrasound is usually performed at onset and may detect both aneurysmal aortic dilatation and periaortitis as a hypoechoic periaortic halo. It also allows the detection of hydronephrosis; such US findings are crucial both at diagnosis and during the follow-up.

On CT, periaortitis appears as a homogeneous, plaque-like tissue, isodense to muscle, which develops around the anterolateral sides of the abdominal aorta. In the retroperitoneum, it may encase the ureters, drawing them medially, and also cause inferior vena cava compression [67]. On MRI, the inflammatory aortic/periaortic thickening and the tissue surrounding the vessels are seen as hypointense on T1-weighted images, while they are hyperintense on T2-weighted images during active disease phases, due to the presence of edema and hypercellularity. Contrast-enhancement, both on CT and MRI, is more pronounced during the early disease stages [89].

^{18}F -FDG PET is increasingly used for the diagnosis of periaortitis, although its specificity is low given that forms of periaortitis secondary to infections or neoplasms may also be FDG-avid. However, ^{18}F -FDG PET has the advantage of being able to provide whole-body imaging of metabolically active lesions, thus allowing both the detection of other vascular segments (Figure 4) involved by periaortitis and of occult neoplastic or infectious foci. In patients with multifocal fibroinflammatory conditions (e.g., periaortitis and mediastinal fibrosis), ^{18}F -FDG PET can be positive at different sites [90]. Interestingly, ^{18}F -FDG PET recently proved able to predict response to therapy, since metabolically inactive periaortitis is less likely to respond to glucocorticoid treatment than totally inactive lesions. However, no significant differences in response to treatment were detected among patients with different degrees of FDG uptake [91].

Periaortic retroperitoneal biopsy is recommended in all cases of difficult interpretation, especially when there is suspicion of infections or malignancies, and in patients not responsive to treatment. Patients with atypical presentations usually undergo diagnostic biopsies.

Aortitis and Periaortitis in IgG4-Related Disease

As reported above, aortitis and periaortitis may arise in the context of IgG4-RD. In 2008, criteria were proposed for the diagnosis of IgG4-RD [92]. They include: i) typical organ involvement (pseudotumoral lesions) with organ swelling and/or dysfunction; ii) histologically compatible features and immunohistochemical evidence of IgG4⁺/IgG⁺ plasma cells >40% together with IgG4⁺ plasma cells >10/hpf; iii) serum IgG4 level >135 mg/dl. The diagnosis is considered to be “definite” when all three criteria are fulfilled, “probable” when i) and ii) are met, and “possible” when i) and iii) are met and histopathology is either unavailable or non-diagnostic. These criteria are widely used, even if their specificity and sensitivity still warrant validation.

It has been reported that in aortic and periaortic tissue, immune staining findings might be inconsistent with a diagnosis of IgG4-RD, even on a background where the three main characteristics (storiform fibrosis, obliterative phlebitis and lymphoplasmacytic infiltrate) are represented [93]. In these cases the diagnosis of IgG4-RD relied upon morphological findings, along with clinical and imaging data.

Laboratory abnormalities that can be found in IgG4-RD include elevation of acute-phase reactants, especially in cases with multifocal involvement, and polyclonal hypergammaglobulinemia. Peripheral eosinophilia and serum IgE increase may be encountered in about a third of cases. Positive ANCA with specificity for either myeloperoxidase or proteinase 3 may also occur, indeed overlap forms of IgG4-RD and AAV have recently been described [94].

The same imaging studies used for the diagnosis and follow-up of aortitis and periaortitis not associated with other IgG4-related lesions are employed for cases arising in the context of IgG4-RD. Thus, US, CT or MRI and ^{18}F -FDG PET may all be helpful both at diagnosis and during the follow-up to detect the major involved sites and to assess their metabolic activity, although the FDG-avidity of the different IgG4-related lesions varies widely. Typical findings are tumor-like lesions, which may be diffuse, leading to an enlargement of the involved organ, or focal. These aspects make IgG4-RD a mimicker of malignancies: in these cases biopsy is the only way to differentiate them.

Other Diseases with Periaortic Involvement

Periaortic infiltration may be observed in other disorders (Table 1) that should be excluded before arriving at the diagnosis of periaortitis, whether IgG4-related or not. Unfortunately, an increase in serum IgG4 has little value in the differential diagnosis between IgG4-related cases and secondary forms.

Malignancies may resemble periaortitis [95] and in these cases imaging studies play a fundamental role. Indeed, on CT and MRI neoplastic forms appear to be inhomogeneous and lobulated, more adherent to surrounding organs with no clear cleavage site, and often extend above the origin of the renal arteries, unlike typical periaortitis [96, 97]. In addition, periaortitis is usually located anterolateral to the aorta, whereas neoplastic masses are also anterior to the spine and tend to displace the aorta anteriorly.^{96,97} Moreover, malignancies may also infiltrate muscles and erode bones [98].

One large retrospective study evaluated the utility of ^{18}F -FDG PET in differentiating neoplastic forms from idiopathic/IgG4-related ones [99]. It was reported that malignancies could have a greater FDG avidity; moreover, PET allows detection of all neoplastic sites, if the neoplasm itself is FDG-avid.

A rare cause of aortic wall and periaortic involvement is ECD, a non-Langerhans cell histiocytosis with predilection for long bones, cardiovascular system, central nervous system, and endocrine glands [100]. Interestingly, ECD can involve both the thoracic and abdominal aorta, giving rise to an aspect usually reported as “coated aorta.” On imaging ECD should be suspected when the fibrous tissue surrounds the kidneys, showing the typical finding of “hairy kidneys” [101]. In these cases, a biopsy is recommended, indeed morphological and immune staining features are very different in ECD versus idiopathic periaortitis. Typical findings in ECD include tissue infiltration by CD68⁺ CD1a⁻ “foamy” histiocytes, along with diffuse lymphoplasmacytic infiltrates and abundant fibrosis [102].

The conditions (Table 1) that can result in secondary forms of periaortic disease include drugs, surgical procedures, radiotherapy and trauma [98, 103], that may be excluded by a careful review of the patient’s medical history.

PRINCIPLES OF TREATMENT

A detailed review of the treatment of all causes of aortitis and periaortitis is beyond the scope of the present chapter. However, it is important to outline some aspects. The exclusion of neoplastic, infectious and other proliferative (e.g., ECD) causes of aortic disease have obvious therapeutic implications since most of the idiopathic forms of aortitis and periaortitis are treated with glucocorticoid and immunosuppressive therapies. It is also important to carefully differentiate aortitis/periaortitis occurring in the setting either of LVV, systemic connective tissue or small-vessel vasculitic syndromes, or fibro-inflammatory disorders including IgG4-RD. LVVs are treated with glucocorticoids and or other conventional immunosuppressants, and only recently biologic therapies (particularly the anti-IL6 receptor antibody tocilizumab) have been introduced for the management of GCA [104]. The treatment of aortitis associated with systemic connective tissue diseases as well as systemic small-vessel vasculitis varies depending on the underlying condition; generally, the occurrence of aortitis is considered a severe complication, requiring aggressive immunosuppression. Idiopathic aortitis and periaortitis, whether isolated or in the context of IgG4-RD, are generally corticosteroid-sensitive, and therefore corticosteroids should be considered first-line treatment. In relapsing or difficult-to-treat cases, rituximab has recently proved effective [73, 105]. Aortitis and periaortitis may lead to aneurysmal dilatation of both the abdominal and thoracic aorta that requires evaluation by vascular surgeons as prompt treatment using endovascular or surgical techniques may prevent life-threatening complications.

CONCLUSION

Inflammatory aortitis and periaortitis are inflammatory diseases of varying etiology, and recognition of them is critical for optimal management. Imaging studies such as CT, MRI, and ¹⁸F-FDG-PET are widely used for their management and follow-up. Diagnostic biopsies are required in a fraction of cases, with histological patterns that may range from lymphoplasmacytic to granulomatous and suppurative presentations. The treatment will differ depending on the cause, with isolated cases and those suffering from systemic immune-mediated conditions, managed with a combinations of corticosteroids and immunosuppressive drugs. Surgical evaluation may be required in cases presenting with significant aneurysmal dilatation, or with less common complications such as dissection and rupture.

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Chapter 206

SYSTEMIC VASCULITIS AND THE LUNG

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ABSTRACT

The lungs are affected by systemic vasculitides with differing frequency, characteristics, and severity, depending on the specific vasculitis syndrome. Alveolar hemorrhage, nodules, interstitial disease and airway stenoses are the most common lung manifestations of antineutrophil cytoplasm antibody-associated vasculitides. Pulmonary vascular involvement occurs in Behçet disease and Takayasu arteritis, where it manifests as pulmonary artery aneurysm, thrombosis and stenosis. Lung involvement can occur along with other systemic features of vasculitis syndromes but can also be isolated, which leads to diagnostic and therapeutic challenges. Lung infection, pulmonary edema due to cardiac failure or renal impairment, cancer, and drug-induced lung toxicity are potential mimickers of pulmonary involvement in vasculitis. Once a diagnosis has been made, the management of lung disease in patients with vasculitis includes systemic and local therapies.

Keywords: vasculitis, lung, ANCA, AAV

INTRODUCTION

The lungs are affected by systemic vasculitides with differing frequency, characteristics and severity, which vary by type of vasculitis. There can be involvement of the airways, lung parenchyma, intra-parenchymal proximal pulmonary arteries and veins, capillary vessels or

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pleura. These manifestations can be clinically silent or life-threatening, as with diffuse alveolar hemorrhage. They can occur with other systemic manifestations of vasculitis or, less commonly, in isolation, which creates diagnostic challenges. Treatment should be tailored to the type and severity of the underlying vasculitic process and may combine systemic and local therapies. Lung infection, pulmonary edema due to cardiac failure or renal failure, cancer, and drug-induced lung toxicity can occur in patients with vasculitis.

This chapter focuses on the lung manifestations of systemic vasculitides, as defined by the Chapel Hill Consensus Conference (CHCC) [1], and prophylactic measures to limit the risk of secondary complications.

MAIN LUNG MANIFESTATIONS IN SYSTEMIC VASCULITIS

A broad spectrum of lung manifestations may occur with systemic vasculitis and include alveolar haemorrhage, lung nodules, interstitial disease, airway stenoses, fibrosis, pleural effusion and pneumothorax. These may occur in small-vessel (SVV) antineutrophil cytoplasm antibody (ANCA)-associated vasculitides (AAV) (granulomatosis with polyangiitis [GPA], eosinophilic granulomatosis with polyangiitis [EGPA] and microscopic polyangiitis [MPA]). Lung vessel involvement manifests as pulmonary artery aneurysms, thrombosis and stenoses in the variable vessel vasculitis (VVV) Behçet disease (BD) and the large-vessel vasculitis (LVV) Takayasu arteritis (TAK). The risk of pulmonary embolism increases during disease flares in AAV.

Airway Disease

Nasal, sinus, mouth, throat and the upper airways are commonly involved in GPA leading to chronic erosive sinusitis, crusting rhinitis, nasal septum perforation and subglottic stenosis. Allergic rhinosinusitis, nasal polyposis, lower large- and small-airway disease (asthma) are manifestations associated with EGPA. Tracheo-bronchial stenosis is more characteristic of GPA but can also occur in EGPA.

Tracheo-Bronchial Stenosis

Tracheal and bronchial involvement occurs in up to 70% of patients with GPA. Stenoses of the main bronchus, seen more often the left along the first branches, are observed in less than 10% of patients [2-5]. Subglottic stenosis is the classic large airway lesion and occurs in 7% to 15% of patients with GPA [6-8]. It may cause dysphonia. Like subglottic stenosis, tracheal and bronchial stenoses cause dyspnea, with or without stridor and wheezing. Large airway obstruction occasionally requires emergency dilatation, often combined with local injections of corticosteroids, or tracheostomy. Complete bronchial occlusion can cause partial or complete collapse of the lung distally. Endobronchial lesions can cause hemoptysis if there is mucosal ulceration and erosion of an underlying vessel. Such tracheal and bronchial lesions are best studied with a combination of chest computed tomography (CT) (Figure 1) and direct visualization with fiber-optic bronchoscopy because of possible multifocal involvement with strictures, ulceration and granulomatous endobronchial lesions. These airway lesions can

parallel extra-respiratory manifestations of GPA or may progress despite adequate control of the systemic vasculitis.



Figure 1. Left main bronchial stenosis, visible on bronchoscopy (left image), with beading appearance on axial CT scan (right image).

Asthma

Asthma is a defining feature of EGPA [9, 10] and usually develops before the onset of systemic manifestations of vasculitis. 90% of affected patients have asthma at EGPA diagnosis, but it rarely develops after the initial diagnosis. The interval between onset of asthma and EGPA diagnosis is about 9 years, on average, with a mean age at onset of asthma of 32 years, which emphasizes its relatively late-onset compared to usual asthma. Asthma typically increases in severity in the months to years before the onset of systemic manifestations of vasculitis and persists when the initial vasculitic manifestations occur, even after adequate control of the underlying vasculitis. Many patients require long-term, low-dose prednisone and inhaled corticosteroids for control of airway symptoms despite remission of the systemic vasculitis. Whether the characteristics of vasculitis-associated asthma differ from idiopathic and allergic asthma is not well understood [11]. Spirometric evaluation reveals an obstructive pattern, but no clinical findings or functional tests distinguish among these various causes of asthma. As a rule, late-onset asthma, especially if it is difficult to control and increasing blood eosinophilia should prompt consideration of EGPA.

Parenchymal Disease

Vasculitis-related parenchymal lung disease is common in GPA, MPA, EGPA, and anti-glomerular basement membrane (anti-GBM) disease but also occurs in the LVV giant cell arteritis (GCA) and the SVV immune complex (IC) disorder, Henoch-Schonlein purpura/IgA vasculitis (HSP/IgAV) [12].

Alveolar Hemorrhage

Diffuse alveolar hemorrhage (DAH) is a classical manifestation of AAV and occurs in 12% to 32% of patients with MPA and in 8% to 30% of those with GPA, 60% to 80% of

those with anti-GBM disease (or Goodpasture syndrome), and in less than 10% and 2% with EGPA and IgAV, respectively. The extent and severity of pulmonary capillaritis varies from clinically silent to shortness of breath and subacute to acute fulminant hemoptysis and respiratory distress syndrome. Hemoptysis is absent in up to one third of patients with alveolar hemorrhage, which then is diagnosed by the presence of anemia, patchy ground-glass opacities on chest CT (Figure 2), and persistently bloody returns on broncho-alveolar lavage. In addition to ground-glass opacities, chest CT may reveal alveolar consolidation and localized rather than diffuse or patchy infiltrates. CO diffusion capacity is usually increased when there is blood in the alveoli, but pulmonary function testing (PFT) is rarely indicated or performed in patients with frank alveolar hemorrhage. DAH is frequently associated with renal disease in GPA, MPA and anti-GBM disease and may be part of a pulmonary–renal syndrome. When alveolar hemorrhage occurs as an isolated event or is associated with non-specific constitutional symptoms, diagnoses other than vasculitis should be considered (Table 1) [13, 14]. Hemoptysis from lung capillaritis should be differentiated from other vasculitic causes of bleeding such as submucosal vessel rupture in patients with endobronchial GPA mucosal ulceration or rupture of larger-vessel aneurysms in patients with TAK and BD.

Table 1. Main causes of alveolar hemorrhage

Disease or disease group		Comments
Lung parenchymal disease/inflammation		
<i>Small vessel vasculitis</i>	ANCA associated vasculitis	Mainly GPA and MPA (rarely EGPA)
	Anti-GBM disease	
	Immune-complex mediated vasculitides	Rarely IgA vasculitis (exceptionally, cryoglobulinemic vasculitis)
	Isolated (idiopathic) lung capillaritis	
<i>Other systemic diseases</i>	Systemic lupus erythematosus	
	Antiphospholipid syndrome	
	Rheumatoid arthritis	Through lung disease and/or associated vasculitis
	Systemic scleroderma	Through lung disease and/or associated vasculitis and/or veno-occlusive disease
	Polymyositis/dermatomyositis	
	Sarcoidosis	
<i>Drug-related lung toxicity</i>	Propylthiouracil, diphenylhydantoin, amiodarone, mitomycin, D-penicillamine, methotrexate, gold, haloperidol, nitrofurantoin all-trans-retinoic acid, bleomycin	Most can cause interstitial lung infiltrates rather than diffuse alveolar hemorrhage
<i>Toxic and irritant inhalation</i>	Trimellitic anhydride, isocyanates, crack cocaine, pesticides, detergents	
<i>Miscellaneous</i>	Lung-graft rejection	
<i>Infections</i>	Human immunodeficiency virus infection, infective endocarditis, cytomegalovirus infection, herpes simplex virus infection, hantavirus infection, invasive aspergillosis, legionellosis, mycoplasmosis, leptospirosis, other bacterial pneumoniae	

Disease or disease group		Comments
Not primarily due to lung parenchymal disease/inflammation		
<i>Lung vessel and/or aneurysm rupture</i>	Multiple causes: traumas, vascular malformation or fibrodysplasia, vasculitis-related aneurysms (Takayasu arteritis, Behcet's disease), lung abscess/cavity or bronchial lesions eroding nearby vessels, etc.	
<i>Hemostasis disorders</i>	Thrombotic thrombocytopenic purpura and idiopathic thrombocytopenic purpura, anticoagulants, antiplatelet agents, thrombolytics; disseminated intravascular coagulation	Usually associated with another and underlying lung condition when causing diffuse alveolar hemorrhage
<i>Mitral stenosis and mitral regurgitation</i>		
<i>Pulmonary veno-occlusive disease</i>		
<i>Idiopathic pulmonary hemosiderosis</i>		
<i>Pulmonary embolism</i>		
<i>Malignant conditions</i>	Lung cancer, pulmonary angiosarcoma, Kaposi sarcoma, multiple myeloma, acute promyelocytic leukemia	
<i>Other conditions/ miscellaneous</i>	High-altitude pulmonary edema, barotrauma	
	Lymphangioleiomyomatosis	
	Pulmonary capillary hemangiomatosis	
	Lymphangiography	
	Tuberous sclerosis	

ANCA: antineutrophil cytoplasm antibody; EGPA: eosinophilic granulomatosis with polyangiitis; GBM: glomerular basement membrane; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis.

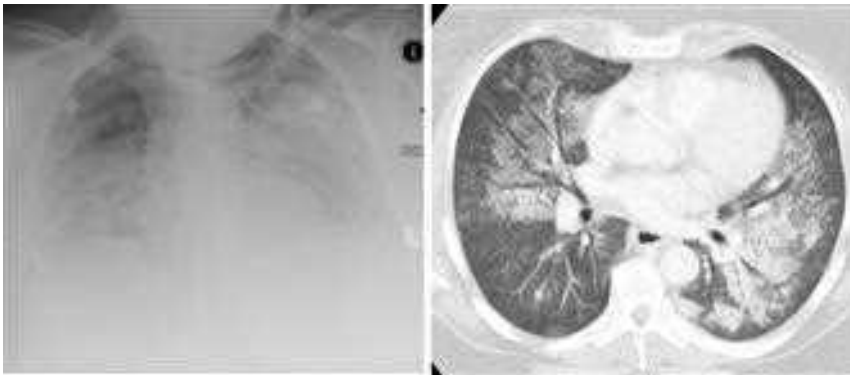


Figure 2. Diffuse alveolar hemorrhage in a patient with granulomatosis with polyangiitis (left: chest X-ray with diffuse infiltrate; right: diffuse ground-glass opacities and infiltrates on axial CT scan).

Nodules

Lung nodules are a classical feature of GPA but can also occur in EGPA [15]. They can be cavitated, single or multiple, and vary in size and location (Figures 3 and 4). No specific characteristics on chest CT differentiate them from malignancy; tuberculous, nocardial or *Burkholderia* species infections; or lymphomatoid granulomatosis and sarcoidosis (Table 2). Supra-infection of cavitating nodules, notably by *Aspergillus* species, can occur. Surgical tissue biopsy, wedge-resection and CT-guided needle aspiration of nodules in GPA may reveal non-caseating granulomatous and necrotizing inflammation [16-19]. Plain nodules can

become cavitated as a result of central necrosis and evolve into nodular scars that persist beyond remission of vasculitis. They have been inconsistently associated with risks of relapse: over a follow-up of 8.8 years, the presence of cavitary nodules at diagnosis was identified as an independent predictor factor with 53% rate of relapse [20]. Non-active nodules at remission are more often plain than cavitated and smaller, measuring <15 mm in diameter [21].

Table 2. Main differential diagnoses of granulomatosis with polyangiitis with lung nodules

Other vasculitides		Comments
Primary	Eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome)	Lung nodules can occasionally occur
	Microscopic polyangiitis	Anecdotal cases with lung nodules
	Giant cell arteritis (temporal arteritis)	Anecdotal cases with lung nodules
	Henoch–Schonlein purpura	Anecdotal cases with lung nodules
Secondary	Relapsing polychondritis	Few cases with lung nodules (possible overlapping diagnosis with GPA)
	Drug-induced (and/or hypersensitivity) vasculitis	Anecdotal cases with lung nodules
	Rheumatoid arthritis	Lung nodules can occasionally occur, with or without associated vasculitis
	Inflammatory bowel disease, systemic lupus erythematosus, systemic sclerosis, primary Sjogren syndrome, etc.	Rare cases with lung nodules
Granulomatous diseases		
	Lymphomatoid granulomatosis (Liebow)	Rare systemic angiodestructive lymphoproliferative disease, usually associated with chronic Epstein-Barr virus infection
	Nasal NK-cell lymphoma	
	Sarcoidosis	
	Berylliosis	
	Inflammatory bowel disease	Rare cases with lung nodules
Infections (not limiting list)		
	Tuberculosis	
	Histoplasmosis	
	Atypical mycobacterial infections	
	Blastomycosis, coccidioidomycosis, actinomycosis, cryptococcosis	
	Nocardiosis, Burkholderia cepacia infection	
	Secondary syphilis	
	Parasitic helminth infections (ascariasis, alveolar echinococcosis, paragonimiasis, Schistosoma mansoni, pulmonary dirofilariasis, larva migrans - toxocarosis)	Can cause lung cysts, potentially mimicking lung nodules
Cancers and hemopathies (not limiting list)		
	Lymphomas	
	Plasmacytoma	
	Carcinoid tumors	
	Lung cancer (all types)	
	Lung metastases	
Other/miscellaneous		
	Pulmonary amyloidosis	Anecdotal cases with lung nodules
	Pulmonary pyoderma gangrenosum	
	Mineral oil (lipoid) pneumonia	
	Benign tumors Fibroma, hamartoma, neurofibroma, blastoma, bronchial adenoma	
	Bronchogenic cysts	Can present like nodules
	Atelectasis (post-infection or -surgery)	Can present like nodules
	Anthracoilicosis	Lung nodules are usually small but can reach 1 cm in diameter and be coalescent in severe cases

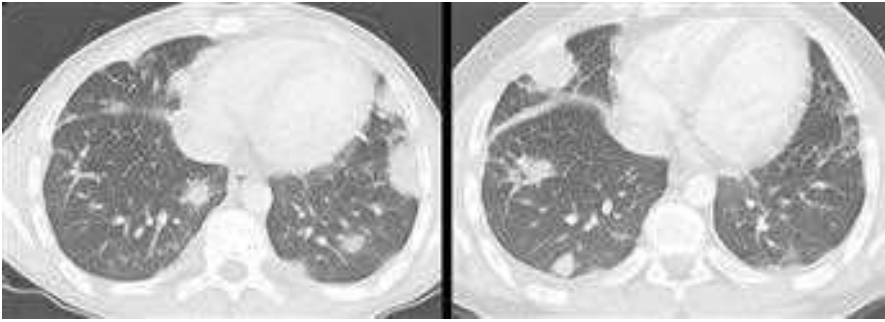


Figure 3. Multiple plain lung nodules in a patient with granulomatosis with polyangiitis (axial CT images).



Figure 4. Large cavitation nodule in a patient with granulomatosis with polyangiitis (left: chest X-ray showing hydro-aeric cavity; right: same nodule on frontal CT scan, upper and aeric part of the nodule).

Eosinophilic Lung Infiltrates

Lung infiltrates, corresponding to eosinophilic pulmonary inflammation, occur in up to three quarters of patients with EGPA. On chest CT, they appear as patchy, multifocal, with peripheral ground-glass attenuation; uni-, or bilateral and symmetrical or asymmetrical; and sometimes as transient or migratory areas of consolidation (Figure 5). They may be associated with pleural effusions mimicking chronic eosinophilic pneumonia, although the latter presents most often with homogeneous and peripheral lung infiltrates. Broncho-alveolar lavage or thoracentesis can demonstrate the predominant eosinophilic nature of the abnormality, typical of EGPA, and exclude other diagnoses such as infection and alveolar hemorrhage [22].

Fibrosis

Fibrosis is increasingly recognized complication of AAV, mainly anti-MPO AAV. Most often the interstitial pneumonitis and fibrosis preferentially involves the lung bases (Figure 6). Interstitial lung disease (ILD) can either occur after onset or precede the onset of full vasculitis by years [23-25]. The pathogenic mechanism of ILD is not well understood but may relate to oxidative bursts of inflammatory cells triggered by ANCA, along with damage resulting from recurrent or chronic alveolar hemorrhage [26-28]. Usual interstitial pneumonia (UIP) is the most common radiologic pattern [25]. The mortality rate of pulmonary fibrosis with anti-MPO P-ANCA, mainly related to respiratory failure, is similar to that of idiopathic

pulmonary fibrosis and worse than ILD occurring with collagen vascular diseases without anti-MPO ANCA [24, 29].

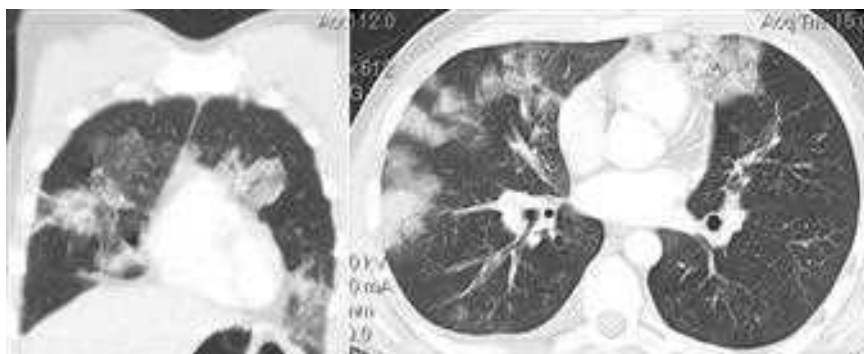


Figure 5. Patchy lung alveolar interstitial infiltrates in a patient with eosinophilic granulomatosis with polyangiitis (frontal and axial CT images).

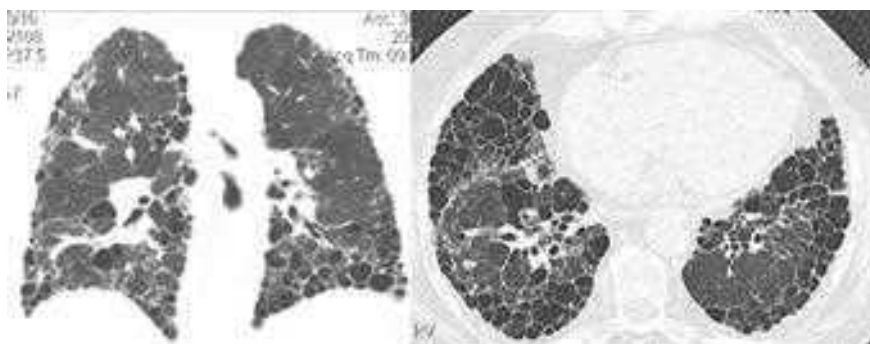


Figure 6. Massive lung fibrosis in a patient with anti-MPO-ANCA vasculitis in remission (frontal and axial CT images), with honeycombing appearance.

Non-Specific Pulmonary Consolidation

Pulmonary consolidation and infiltrates mimicking infectious pneumonia can be observed in GPA, MPA and EGPA. Diffuse interstitial lung infiltrates can be seen in GCA, TAK, IgAV, BD and cryoglobulinemic vasculitis (CV) [12, 30, 31]. ILD and alveolar hemorrhage due to pulmonary capillaritis can also occur in rheumatoid-associated vasculitis (RAV), or with systemic lupus erythematosus (SLE).

Pleural Effusion and Pneumothorax

Pleural effusions are common in EGPA and polyarteritis nodosa (PAN). They can be inflammatory or related to cardiac or renal failure. They may also be due to pulmonary embolism, which is more frequent during disease flares. Pneumo- and hydro-pneumothoraces can be caused by the outward progression of peripheral lung nodules that involve the pleura and cavitate, leading to development of bronchopleural fistula [32, 33].

Pulmonary Embolism

Patients with AAV and to a lesser extent, medium-vessel vasculitis (MVV) such as PAN, are at increased risk of venous thromboembolic events, including pulmonary embolism, during the active phase of the vasculitic disease [34, 35]. In BD, pulmonary embolism can be due to right ventricular thrombi related to increased tissue-factor expression, neutrophilic extracellular traps and neutrophil-derived micro-particles [36]. Anti-PR3-ANCA antibodies with dual reactivity to plasminogen and complementary PR3 may be pathogenic in thrombosis in GPA [37].

Pulmonary Artery Stenosis and Aneurysms

The pulmonary arteries are involved by the vasculitic process in LVV and BD and exceptionally in other vasculitides [38]. Stenoses and aneurysms of the main pulmonary arteries can occur (Figure 7). Dilations of single, multiple, unilateral and bilateral pulmonary and bronchial arteries occur in less than 5% of patients with BD referred to as Hughes-Stovin syndrome [39]. Affected patients are typically men with a history of thrombophlebitis. Pulmonary and bronchial artery aneurysms can rupture, thus leading to hemoptysis and internal haemorrhage, or demonstrate progressive occlusion with thrombosis.

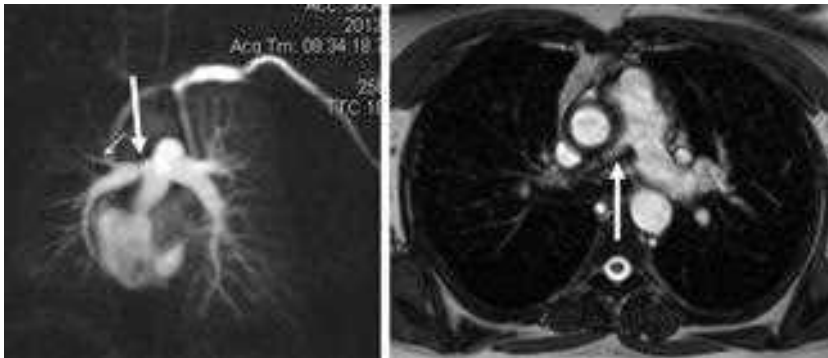


Figure 7. Main right pulmonary artery stenosis in a patient with Takayasu arteritis (CT-angiography, frontal reconstruction and axial image).

Pulmonary Hypertension

There are anecdotal reports [40, 41] of pulmonary hypertension in patients with TAK, PAN and AAV. Secondary pulmonary hypertension can result from pulmonary artery involvement, constrictive pericarditis, restrictive cardiomyopathy, or lung fibrosis [42]. Chronic thrombo-embolism can lead to pulmonary hypertension and should be actively considered as it is treatable.

Phrenic Palsy

Unilateral phrenic palsy due to mono-neuritis multiplex can occur in GPA and EGPA [43, 44]. However, it can be co-incidental, related to pre-existing conditions including trauma, or due to an unknown and unrelated cause.

LARGE-VESSEL VASCULITIDES

Parenchymal lung manifestations occur so rarely in LVV that when present, should prompt review of the diagnosis of vasculitis or consideration of a co-existing condition. However, involvement of pulmonary arteries can be an expected feature of LVV, especially in TAK.

Giant Cell Arteritis

One-quarter of patients with GCA have a dry, non-productive cough. Less common manifestations include alveolar hemorrhage, T-CD4⁺ lymphocytic alveolitis, pleural effusion and thickening, multiple pulmonary infarctions, lung nodules and ILD [45-48].

Takayasu Arteritis

TAK can involve the pulmonary arteries, although less frequently than the aorta or other arteries with stenoses, with or without dilations (Figure 7). The involvement can be associated pulmonary hypertension, lung infarction, arterial rupture and hemorrhage, regional hypoperfusion, and lung ventilation and perfusion mismatching suggestive of pulmonary embolism. There may be lung nodules, parenchymal consolidation, sub-pleural reticulo-linear changes, pleural effusion and thickening, pulmonary-renal syndrome, and ILD [49-56].

MEDIUM-VESSEL VASCULITIDES

Pulmonary artery and less often parenchymal involvement can occur in MVV.

Polyarteritis Nodosa

The lung parenchyma is not typically affected in PAN and the occurrence of capillaritis with alveolar hemorrhage should raise doubt about the diagnosis of PAN or question the possibility of an underlying genetic disease such as STING-associated vasculopathy [57]. Prior to the 1994 CHCC [58], patients presenting purpura, hemoptysis, and pulmonary hemorrhage that preceded the explosive phase of systemic necrotizing vasculitis affecting the

kidney and lungs with rapidly progressive glomerulonephritis and pulmonary capillaritis were considered to have a microscopic form of PAN. This condition was later considered a separate category of SVV, termed MPA [59]. Pulmonary edema and pleural effusion in PAN are usually due to renal and/or cardiac insufficiency. Patients with PAN can present with interstitial pneumonia, lung nodules and cavitary lesions. Although clinical and angiographic bronchial artery involvement is considered uncommon, seven of ten patients were found to have bronchial arteritis on post-mortem examination [60-62], so this manifestation of vasculitis may be under-recognized.

Kawasaki Disease

Children with Kawasaki disease (KD) often develop respiratory symptoms due to upper-respiratory tract inflammation. Affected children may present with pneumonia, and up to 15% show lung consolidation on chest radiography within 10 days of illness onset. Other radiographic abnormalities include peri-bronchial cuffing, pleural effusion, atelectasis and air trapping [63]. The incidence of coronary artery lesions is greater in patients with abnormal chest radiographs. Interstitial micro-nodular infiltrates and larger inflammatory pulmonary nodules can occur [64-68].

SMALL-VESSEL VASCULITIDES

Parenchymal and airway disease occur more commonly in SVV than MVV and LVV. Alveolar hemorrhage is the hallmark of GPA, MPA and EGPA; lung nodules and bronchial stenosis are more characteristic of GPA, and asthma is most consistent with EGPA [69].

Granulomatosis with Polyangiitis

Overall, 70% to 100% of patients with GPA show lung involvement, with clinical manifestations ranging from mild cough, dyspnea, chest pain, and intermittent hemoptysis to acute respiratory distress syndrome and massive alveolar hemorrhage. In 6% of patients, lung involvement remains asymptomatic, especially with lung nodules. Tracheobronchial involvement, including subglottic stenosis, ulcerating tracheo-bronchitis and sometimes endobronchial stenoses, can be seen in 17% of patients [70]. Subglottic involvement seems to be more common in the pediatric-onset GPA compared with the adult population, occurring in up to 41% of cases [71]. Although not specific, lung nodules are among the most characteristic involvement, and are present in 40% to 66% of patients with GPA, occurring as ≤ 10 in number, unilateral, bilateral, and single or multiple lesions [20]. Half of them may cavitate, especially when larger than 2 cm [72]. The differential diagnosis of lung nodules remains wide, and should include primary and metastatic tumors, sarcoidosis, tuberculosis and fungal infections (Table 2). Alveolar hemorrhage, the most feared manifestation, is usually secondary to capillaritis and is noted in 18% to 30% of patients with GPA. It can occur at disease onset or later in the course signaling relapse of the disease [20, 73]. It may

appear as ground-glass opacities surrounding pulmonary nodules. In all, 30% to 50% of patients show other pulmonary infiltrates or lung consolidations, and 9% to 28% show pleural effusion. Spontaneous pneumothorax and empyema can occur, sometimes related to nodule cavitation and rupture. Pulmonary embolism may indicate active GPA and systemic inflammation. All patients with acute presentation of GPA should undergo chest CT/HRCT, because small nodules, alveolar hemorrhage and other lesions may be missed on chest radiography. Even when the diagnosis of GPA is clinically apparent, broncho-alveolar lavage should be considered to exclude concurrent infection and clinically silent alveolar hemorrhage. Surgical lung biopsies, targeting nodules and consolidated lesions, have a diagnostic yield of 76% to 91% [3, 74]. Transbronchial biopsies are seldom positive, unless performed on a macroscopically abnormal lesion. Transbronchial cryobiopsy and video-assisted thoracoscopic biopsy are other possible diagnostic options [75].

Microscopic Polyangiitis

Alveolar hemorrhage and pulmonary–renal syndrome can be observed in MPA [59, 76, 77]. Arteritis with intimal thickening and focal destruction of the internal elastic lamina and sub-intimal fibrous scarring of the media are typical histological features in diagnostic tissue biopsy specimens. Diffuse alveolar damage and pulmonary fibrosis (Figure 6) can complicate MPA, mainly in patients with anti-MPO P-ANCA MPA. In patients with established idiopathic pulmonary fibrosis, MPO-ANCA positivity may be present in up to 5%. Seroconversion from negative to positive anti-MPO during follow up can be found in up to 15% of patients [78, 79]. The risk of developing systemic vasculitis over time is greater in MPO-ANCA positive patients than those with negative ANCA, and can be as high as 22% [78]. Additionally, pulmonary fibrosis and vasculitis may have independent outcomes, with progression of the fibrosis despite treatment and sustained good control of the vasculitis [24–26, 29]. There is little data on the role of immune suppressing therapies and anti-fibrotic therapies such as pirfenidone and nintedanib in MPO-positive IPF and MPA with pulmonary fibrosis.

Eosinophilic Granulomatosis with Polyangiitis

This rare pulmonary and systemic SVV with an annual incidence of 0.5 to 6.8 per million and a prevalence of 10.7 to 14 per million, develops through three prototypical successive phases. The prodromal phase begins with asthma and allergic manifestations, followed by tissue eosinophilia affecting visceral organs such as the lung and myocardium, and later development of vasculitic features primarily affecting the skin and peripheral nerves. The preponderance of Th2 lymphocytes and eosinophils suggests their participation in the pathogenesis of EGPA. However, ANCA production is noted in up to 40% of patients, which suggests a role in amplifying or facilitating the development of vasculitic lesions. Asthma is a predominant feature in EGPA, present in up to 91% of cases at diagnosis [9]. Lung infiltrates were reported in 39% of patients in the largest series (and up to 72% in a smaller previous series) [9, 80], presenting as multifocal peripheral consolidation in two-thirds of patients, with

unilateral or bilateral, and symmetrical or asymmetrical appearance [81]. A centri-lobular perivascular dense pattern with scattered centri-lobular nodules measuring 5 mm within ground-glass opacities is often found. Multiple large nodules may occur, with occasional cavitation; however, alveolar haemorrhage is rare in EGPA, occurring in less than 5%. Non-compressive mediastinal or hilar adenopathy may also be detected on chest CT. Pleural effusions are present in 9% to 30% of patients and are typically exudative and rich in eosinophils [9].

Anti–Glomerular Basement Membrane Disease

Anti-GBM disease, which was included in the revised 2012 CHCC [1] under the SVV category of IC diseases, typically affects young people, aged 15 to 35 years. Isolated glomerulonephritis occurs in 20% to 40% of patients and is combined with alveolar hemorrhage in 60% to 70% of patients. Isolated alveolar hemorrhage is a rare but described presenting feature of anti-GBM. Alveolar hemorrhage is strongly associated with smoking [82, 83]. Up to one third of patients with anti-GBM disease become ANCA positive at some time during their illness. Such patients have intermediate prognosis with worse renal prognosis than those with isolated AAV.

Other Small-Vessel Vasculitides

Alveolar hemorrhage occurs in less than 5% of patients with IgAV [30] and mixed CV. Other lung manifestations may be due to co-incident human immunodeficiency virus (HIV) or hepatitis C virus (HCV) infection, or a lymphoproliferative disorder.

VARIABLE VESSEL VASCULITIDES

Behçet Disease

Lung manifestations occur in less than 10% of patients with BD [84-89]. Pulmonary artery involvement is most common after aortic involvement in young men with aneurysms and thrombosis, with or without associated aneurysm or vascular stenosis [90, 91]. Clinically, it can remain silent, or present with hemoptysis. Other symptoms of pulmonary artery involvement are cough, fever, pleuritic chest pain and dyspnea [86]. Patients should be systematically screened for aneurysms, which can be seen on chest radiographs, but are best visualized by chest CT and magnetic resonance imaging (MRI). They can be multiple, unilateral or bilateral, with varying diameter, usually 1 to 7 cm. Pulmonary artery involvement is associated with poor prognosis, with mortality exceeding 25% after 7 years of follow-up. Aneurysms can rupture, causing catastrophic hemorrhage or lead to thrombosis with later pulmonary hypertension and lung infarction. Most patients have concomitant extra-pulmonary venous thrombi and thrombophlebitis (Hughes-Stovin Syndrome). A pulmonary aneurysm justifies treating with cyclophosphamide and high-dose corticosteroids. Consensus

is lacking on the role of anticoagulant and antiplatelet therapies as they may be associated with massive hemorrhage and mortality risk. Surgery, embolization, and endovascular procedures should be considered in combination with systemic therapy because of the complications associated with active vasculitis. Atelectasis, nodular, or reticular opacities and cavities can occur, corresponding to foci of pulmonary hemorrhage, infarction, and diffuse alveolar hemorrhage due to SVV. Secondary organizing pneumonia, pleural nodules or effusions resulting from vasculitis of the pleura or thrombosis of the superior vena cava, ulcerative lesions of the trachea and/or proximal bronchia as well as mediastinal lymphadenopathy can also occur. Pulmonary embolism in BD is rare and most often due to local pulmonary artery thrombosis rather than embolic peripheral venous thrombosis.

Other Vasculitides

Lung manifestations occur in patients with lupus vasculitis, RAV, sarcoidosis, systemic scleroderma, HCV infection, and illicit use of substances such as cocaine [92-96]. Alveolar hemorrhage due to capillaritis in SLE is similar to what is observed in MPA. Different pathogenic mechanisms may be involved in the development of ILD and lung nodules in RAV. Cocaine and levamisole-tainted cocaine induce lung complications including a GPA-like syndrome with skin, nasal sinus involvement and lung-nodules rather than alveolar hemorrhage. ANCA-seropositivity can be present as well as ELISA findings of specificity to PR3 and various patterns on indirect immunofluorescence [97, 98].

TREATMENT AND PROGNOSIS

Before initiating therapy for pulmonary manifestations, the treating physician should be certain that other conditions, especially infections, cancers, and drug toxicity, are not mimicking pulmonary vasculitis. These conditions may co-exist with active vasculitis, such as supra- or opportunistic infection of a lung cavity with *Mycobacteria* and *Aspergillus* species or cancer leading to paraneoplastic syndrome [99, 100]. Treatment should be individualized to the vasculitis identified, its severity and the type of organ involvement. Although lung manifestations in AAV do not necessarily confer poorer prognosis, alveolar hemorrhage and tracheo-bronchial stenoses warrant aggressive management to avert excess morbidity and mortality. It has been demonstrated that rituximab was as effective for induction therapy as cyclophosphamide in diffuse alveolar hemorrhage in the rituximab in ANCA-Associated Vasculitis (RAVE) trial, although patients requiring mechanical ventilation were excluded from this trial [101]. Conversely, the preliminary results of the large, controlled PEXIVAS study [102] suggested that plasma exchange did not improve survival in patients with severe diffuse alveolar hemorrhage, as opposed to reports from a few small case series or case-control studies [103]. Systemic treatment is often disappointing in subglottic and bronchial stenoses. Endoscopic dilations with bougies, balloons and repeated local injection of corticosteroids with or without mitomycin application may be effective. Tracheal stents and surgery should be considered only in refractory disease. Patients with GPA and lung nodules, without any other threatening systemic manifestations or major organ

involvement, can be managed with less toxic drugs such as methotrexate. The optimal treatment strategy for lung fibrosis and ILD remains to be determined.

Consensus is lacking on the optimal clinical and laboratory monitoring of patients with vasculitis and lung manifestations, but repeated chest radiographs and PFTs at 3 to 6-month intervals earlier in the disease seem reasonable. Repeat CT, because of radiation concerns, should be reserved to resolve uncertainties or to evaluate response to treatment, complications or new manifestations of disease. The intensity of follow-up would vary, depending on the severity of the lung lesions and the impairment of function as well as the presence of subglottic and bronchial stenotic lesions which require direct visualization at bronchoscopy.

CONCLUSION

Lung manifestations are common in several vasculitides and can present various features, some of them potentially life-threatening. After exclusion of conditions mimicking vasculitis, treatment with systemic and local therapies can be initiated with the expectation of improvement. In the longer term, complications of treatment can be as troublesome as complications of the disease. Identification of effective, less toxic and optimal combinations of therapies for the most severely affected patients, and those with chronic lung complications such as anti-MPO-ANCA-associated pulmonary fibrosis, and others with AAV will be clarified by emerging evidence from clinical trials.

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Chapter 207

SYSTEMIC VASCULITIS AND THE KIDNEY: ANCA-ASSOCIATED VASCULITIS AND GLOMERULONEPHRITIS

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ABSTRACT

Systemic vasculitides affecting small- and medium-sized vessels are particularly likely to involve the kidneys. These vasculitides include microscopic polyangiitis, granulomatosis with polyangiitis, and eosinophilic granulomatosis with polyangiitis, IgA vasculitis, polyarteritis nodosa, and cryoglobulinemic vasculitis. The most common culprits of kidney injury in adults are microscopic polyangiitis, granulomatosis with polyangiitis, and eosinophilic granulomatosis with polyangiitis, which predominantly affect small vessels and are typically associated with the presence of anti-neutrophil cytoplasmic autoantibodies. For this reason, we focus here on anti-neutrophil cytoplasmic autoantibody-associated vasculitides. Over the past three decades, tremendous progress has been made through investigative efforts to understand etiologic, pathogenetic and clinical underpinnings of these disorders. We highlight notable findings that represent key breakthroughs in the field and proceed to the clinical presentation, diagnosis, and an up-to-date discussion of studies related to clinical management for inducing and maintaining remission. Finally, we review key prognostic indicators of renal outcomes and predictors of treatment resistance and relapse. Although these diseases have been transformed from ones that were usually fatal to ones that are now chronic with potential

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for long-term and symptom-free remission, many challenges remain to decrease diagnostic delays, increase our understanding of molecular mechanisms of genetic and environmental risk factors for disease, and further refine and personalize treatment strategies that maintain remission and minimize treatment-related morbidity.

Keywords: ANCA, vasculitis, kidney

INTRODUCTION

Many forms of systemic vasculitis directly affect the kidneys, and resultant injury can lead to chronic kidney disease and even end-stage kidney disease. Vasculitides affecting small- and medium-sized vessels are particularly likely to involve the kidneys. They include polyarteritis nodosa (PAN), IgA vasculitis (IgAV, formerly Henoch-Schönlein purpura), microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA, formerly Wegener granulomatosis), eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss syndrome), and cryoglobulinemic vasculitis. The most common causes of kidney injury among this group are IgAV in children; and MPA, GPA, and EGPA in adults. MPA, GPA, and EGPA affect predominantly small vessels, and are often, although not always, associated with the presence of antineutrophil cytoplasmic autoantibodies (ANCA). Given their predilection for kidney involvement, further discussion in this chapter will focus primarily on these ANCA-associated vasculitides (AAV).

EPIDEMIOLOGY

Most data on the incidence and prevalence of AAV derive from studies in Caucasian populations of European descent, although there are also emerging data from Asia and parts of the Middle East. Disproportionate reporting in Caucasians may reflect case ascertainment bias, availability of diagnostic resources, or high prevalence of competing diagnoses, for example, tuberculosis in the case of granulomatous disease, rather than true difference. However, data from multi-ethnic populations suggest that there are true differences in disease incidence based on geographical location, ethnicity, or race, or a combination thereof. As an example, a study of a multi-ethnic population in a Paris suburb, 28% of who were of non-European ancestry, found that the overall prevalence of AAV, as well as PAN, in Europeans was twice that observed in non-Europeans [1]. Similar ethnic differences are seen in New Zealand, where Europeans appear to have a much higher annual incidence of AAV of 60.2 cases per million individuals than the indigenous Māori population with 34.2 cases per million individuals [2]. The annual incidence in Pacific Peoples in New Zealand of 17.26 cases per million individuals was also lower than that of Europeans.

The average incidence of AAV in Japan appears to be similar to that in the United Kingdom (UK), with 22.6 and 21.8 cases per million individuals annually, respectively, [3] however, with notable differences. In Japan, the vast majority (83%) of patients has MPA and is MPO-ANCA positive. Conversely, 66% of patients in the UK have GPA, and a similar number are proteinase 3 (PR3)-ANCA positive. Interestingly, kidney involvement was noted

to be less common in patients with GPA in Japan than in the UK. AAV is also recognized in China [4] and India [5], as well as regions of the Middle East [6], but there are no data regarding incidence and prevalence in these areas. In a study on distribution of ANCA types, MPO-ANCA was more common than PR3-ANCA in the Chinese patients (OR 6.8, CI 2.6-17.8) [7]. Though AAV is uncommon in Africans, there are rare case reports of AAV from Africa [8]. African Americans are more often MPO-ANCA positive (71% vs. 54%, $p = 0.01$) and younger at diagnosis (52 versus 57 years), when compared to Caucasians [9]. However, treatment response, ESRD, renal relapse, and death were similar between the two groups [9]. It is important to note that while PAN, a medium-vessel vasculitis, is not classified as an AAV; it has historically been included in most of these data. Collectively, there is believed to be an overall incidence of approximately 10 to 20 cases per million individuals annually in Caucasian patients of European descent [10]. The prevalence of AAV is approximately 46 to 184 cases per million individuals [11].

Strikingly, multiple examples exist of differences in incidence of AAV that appear to be dependent upon geographic milieu. For example, in northern Saskatchewan, Canada, a 2.69 odds ratio (OR) of developing AAV was reported in a rural versus urban setting [12]. A study from the Australian Capital Territory of New South Wales found the annual incidence of MPA to be significantly higher in rural versus urban areas (13.9 vs 1.6 cases per million individuals), with a similar trend seen in the incidence of GPA [13].

There are also multiple reports that demonstrate differences in incidence relative to latitude. A north-to-south positive gradient was observed in the Southern Hemisphere, and a south-to-north positive gradient is seen in the Northern Hemisphere. In other words, incidence of AAV appears to correlate with latitudinal equatorial proximity. This association was apparent in one study from New Zealand [2], located in the Southern Hemisphere, where an increase in incidence of GPA was noted moving from north to south. A second study comparing incidence of AAV in two regions of Europe, including Norwich, UK, latitude 52°N; and Lugo, Spain, 43°N, both in the Northern Hemisphere, found a higher incidence of GPA in Norwich, the more northerly latitude, than in Lugo, even though the overall incidence of AAV was nearly identical [14]. Interestingly, no such difference has been noted in MPA or EGPA. Similar observations regarding incidence relative to latitude have been reported elsewhere [15]. The incidence of AAV is similar in males and females, and the average age of disease-onset varies somewhat within populations, but occurs predominantly in the sixth and seventh decades of life. The relationship of disease to this demographic may be somewhat skewed since, when evaluated retrospectively, a number of patients arguably had evidence of disease years prior to diagnosis. Diagnostic delays are well-substantiated in the literature [16, 17]. Furthermore, most studies of disease do not include pediatric patients, and it is important to remain cognizant that AAV can occur at any age [18-20].

PATHOGENESIS

Since the initial discovery of AAV and glomerulonephritis [21], incredible strides have been made in understanding the etiology and pathogenesis of these diseases. From a fundamental point of view, for autoimmunity to occur, there needs to be a break in self-tolerance to autoantigens. The three major phases of autoimmunity in a susceptible individual

include initiation, propagation and resolution [22]. Genetic susceptibility and environmental factors including many infections are common initial triggers. Molecular mimicry and autoantigen complementary to a bacterial peptide are some of the mechanisms responsible for origination of ANCA production. HLA can bind peptides, from self- or non-self-antigens and present it to T cells for initiation of immune activation. Among other genetics associations, a strong link has been found between HLA genetic regions and AAV [24].

Along with continuous antigen exposure, a defect in regulatory machinery of immune response, T regulatory cells (Tregs) and B regulatory cells results in propagation of the disease process. Although the mechanism still needs to be defined, multiple studies have shown involvement of persistently activated T cell effector arm of the adaptive immune system [23]. A balance between Tregs/effector cells is essential to prevent autoimmunity. FOXP3 is a major transcriptional factor for CD4⁺ Tregs; in active AAV, these Tregs, due to use of a splice variant of FOXP3, are unable to suppress effector CD4⁺ T cells, thus playing an important role in the propagation of autoimmunity [25]. Also, B cells with regulatory function (with high CD5 expression) are decreased in active AAV and increased during remission [26].

Various *in vitro* observations have established that ANCA can bind to cytokine-primed neutrophils, resulting in its degranulation, respiratory burst and efflux of the proteinases. In addition, upon activation, neutrophils can release proinflammatory cytokines, resulting in augmentation of inflammatory cascade. Both MPO and PR3 are cytoplasmic antigens, priming with cytokine results in its expression on cell surfaces. ANCA bind to FcγR expressed on neutrophil and F(ab')₂ segment binds to MPO/PR3 antigen on the cell surface leading to neutrophil activation [27-29].

The pathogenicity of IgG ANCA comes from different observations, clinical, *in vitro* and from animal models. The majority of patients with pauciimmune necrotizing crescentic glomerulonephritis have positive ANCA serology, but its titer does not always correlate with disease severity, remission or relapse. The first true clinical record depicting the pathogenicity comes from a case of transplacental passive transfer of anti-MPO IgG from a mother with MPA to her neonate, resulting in pulmonary hemorrhage and renal dysfunction [30]. Both clinical hints and *in vitro* results are only suggestive, but to prove the pathogenicity of IgG ANCA, one strives to fulfill Koch's postulates as established by our group in an animal model: (1) immunization of MPO knockout mice MPO^{-/-} with purified mouse MPO in complete Freund's adjuvant resulting in development of anti-MPO antibody; (2) anti-MPO splenocytes containing B and T lymphocytes; (3) injection anti-MPO IgG causes pauci-immune crescentic glomerulonephritis in immune deficient Rag2^{-/-} mice and also wild type mice; and (4) adoptive transfer of anti-MPO splenocytes into Rag2^{-/-} resulted in a severe phenotype of vasculitis in a dose-dependent manner [31]. This demonstrates that anti-MPO antibody itself is sufficient to cause disease, but the severe phenotype seen in the adoptive transfer model is possibly due to synergistic effects of anti-MPO T lymphocytes. Studies on bone marrow transplantation approach showed that bone marrow-derived cells, neutrophils and monocytes were necessary and sufficient for induction of disease by anti-MPO antibody [32]. Systemic administration of bacterial LPS in an animal model caused enhanced circulating TNF-α resulting in severe phenotype of crescentic glomerulonephritis induced by IgG MPO [33]. In addition, due to unknown factors, there is evidence of activation of alternate complement pathway, priming of neutrophils by C5a by binding to C5aR results in

augmentation of inflammatory pathways [34]. The observations from *in vivo* and *in vitro* studies stems the therapeutic tree in AAV, from use of cyclophosphamide, which suppresses both B cell and T cell effector function, to more specific B cell therapy with anti-CD20 monoclonal antibody.

Silica

Noted geographical differences in incidence may imply that environmental and other geo-local triggers play a role in disease development. Silica has been implicated as one such trigger. The first account of a possible association of silica with autoimmune disease was a 1914 report of systemic sclerosis occurring in Scottish stonemasons [35]. There have since been a number of studies correlating silica exposure with the development of other autoimmune diseases, particularly rheumatoid arthritis (RA) [36], but also systemic lupus erythematosus (SLE) [37-39]. Data regarding the latter are conflicting [40], but differences in results may reflect dissimilarities in study methodology and patient characteristics. Data on the contribution of silica to the development of AAV have been inconsistent. A study of 2,288 patients from Sweden found no statistically significant association between an occupation and development of GPA, although borderline associations were seen in miners, paper workers, bakers, and animal keepers [41]. However, a meta-analysis of six case-control studies examining silica exposure and risk of AAV found an overall significant summary effect of silica exposure (summary OR 2.56; 95% confidence interval [CI] 1.51-4.36) with development of AAV [42]. This summary OR was similar to the OR seen in studies looking exclusively at either MPA (OR 3.95, 95% CI 1.89-8.24) or GPA (OR 3.56, 95% CI 1.85-8.82).

Difficulties in comparing studies like these have been due largely to study heterogeneity, with studies using different methods for ascertaining silica exposure. Negative studies have been quite large numbering up to 2,288 patients, whereas positive studies have generally been small, ranging from 16 to 129 patients, with variable inclusion criteria. For example, one study included only men [43], while others differed in the age range of patients included. All but one study [44] included only patients with glomerulonephritis, with or without other organ system involvement. Determination of ANCA seropositivity by immunofluorescence (IF) enzyme-linked immunosorbant assay (ELISA) or a combination thereof varies in the literature with one study including 3 patients who were ANCA seronegative [45]. The duration of exposure to potential silica-containing compounds, as well as the time from exposure to clinically-evident disease has varied. However, the degree of silica exposure, which included both duration and intensity of exposure, was found to be significant in a case control study of biopsy proven glomerulonephritis caused by AAV [46]. High lifetime silica exposure was associated with development of AAV when compared to none (OR 1.9, 95% CI 1.0-3.5, $P = 0.05$). No study of silica exposure included patients with pulmonary- or otolaryngologic-limited disease, even though exposure is likely through inhalation of crystalline particulates. However, in terms of exposure risk, the study by Hogan and coworkers [40] did not find significant differences in patients with and without pulmonary involvement. The geographical region of either study could have contributed to the variable results.

Despite data inconsistencies, silica is generally accepted as having a potential role in the development and perpetuation of AAV. Mechanisms by which silica may promote autoimmunity have not yet been fully elucidated. One study of silica-exposed workers in Brazil [47] found increased levels of soluble interleukin-2 receptor (sIL-2R), thought to reflect increased immune activation in these individuals. However, investigators did not specifically consider the role of silica in autoimmunity. Another study of slate miners demonstrated increased and chronic T-cell activation in patients with silicosis either with or without autoimmune disease, including one with pauci-immune glomerulonephritis [48], and found proliferation of peripheral blood mononuclear cells (PBMC) to be 45% higher in cell cultures of silica-exposed patients than in healthy controls. Patients had elevated levels of both pro-inflammatory (interleukin [IL]-1 β , IL-6, tumor necrosis factor [TNF]- α , interferon [IFN]- γ) and anti-inflammatory (IL-10, tumor growth factor [TGF]- γ) cytokines. Chronic T-cell activation was observed in cultured PBMC of silicosis patients in Japan [49]. In particular, activation of T responder cells (Tresp) resulted in later entry into the peripheral CD4+25+ population, whereas activation of FoxP3+ regulatory T-cells (Treg) led to more rapid and higher levels of apoptosis. The net effect was reduced inhibitory function. Silica may also contribute to immune dysregulation by increasing oxidative stress, as suggested by a study of denim sandblasting workers with silicosis in Turkey [50]. Patients had a 1.4-fold higher level of superoxide dismutase (SOD), a possible marker for increased reactive oxygen species generation in these patients [50]. Another study showed decreased L-selectin expression in workers with >16 years of occupational silica exposure, and associations with inflammatory and oxidative stress biomarkers [51]. More recently, neutrophil extracellular traps (NETs) have been implicated in the pathogenesis of AAV [52, 53]. These NETs are involved in trapping silica and have been postulated to trigger autoantibody production by exposing neoantigens [54].

Taken together, these data suggest a somewhat generalized disruption in immune homeostasis in silica-exposed individuals. However, studies to date have not specifically addressed the mechanisms by which silica may cause or promote disease in AAV. By extrapolation, silica is more likely to have an adjuvant effect in patients with predisposition to AAV rather than to be a primary trigger.

Infection

Wegener considered infection as a potential factor in the cause of GPA in the first half of the 20th century [55]. Since then *Staphylococcus (S.) aureus* has received particular attention. The first study comparing the rates of GPA relapse with carriage of *S. aureus* found that 36 of 57 (63%) patients were chronic carriers of *S. aureus*, and analysis demonstrated an adjusted relative risk (RR) for relapse of 7.16 (95% CI 1.63-31.50) independent of other factors [56]. A 2008 study of Polish patients with limited disease [57] found that 17 of 28 (60%) patients were chronic nasal carriers of *S. aureus*, independently conferring a relative hazard risk (HR) for relapse of 4.56 (CI 2.45-7.65). A third study compared nasal carriage of *S. aureus* in patients with GPA to those with rheumatoid arthritis (RA) and chronic rhinosinusitis with nasal polyps (CRS), as well as to hospital staff and subjects without regular exposure to a hospital environment, noting that 72% of patients with GPA had *S. aureus* nasal colonization,

versus 28% of those with CRS, and 25% of patients without regular hospital exposure [58]. Patients with RA and hospital workers had *S. aureus* carriage rates of 46% and 58% respectively, but the differences were statistically insignificant. Colonized GPA patients had significantly higher rates of endoscopically-proven endonasal activity, with more frequent upper respiratory tract involvement at first presentation, and with significantly higher relapse rates compared to uncolonized patients. The use of prophylactic antibiotics, such as prophylactic trimethoprim/sulfamethoxazole, to reduce the relapse risk by decreasing carrier rates is controversial [59-61]. In a 2017 study of AAV [59], the relapse rates for GPA were higher for chronic nasal carriers of *S. aureus*, and prophylactic trimethoprim/sulfamethoxazole reduced the number of carriers (OR 0.19, 95% CI 0.04-0.91, $P = 0.04$). However, in this study, prophylactic trimethoprim/sulfamethoxazole itself did not reduce the relapse risk (OR 0.71, 95% CI 0.36-1.41, $P = 0.33$).

The mechanism(s) by which infection may incite disease has not been fully elucidated, but early investigations have yielded intriguing possibilities. Molecular mimicry, which leads to cross-reactivity of antibodies to both pathogen-derived and self-antigens with substantial structural homology, has been implicated as one of the etiopathogenic factors in AAV. Such cross-reactivity has been observed in several other diseases; streptococcal M proteins and cardiac myosin, as well as other proteins, cross-react in rheumatic fever [62, 63]; *Campylobacter jejuni* epitopes and peripheral gangliosides cross-react in Guillain-Barré syndrome [64]; and Epstein Barr virus epitopes and *Mycobacterium avium paratuberculosis* cross-react with myelin basic protein in multiple sclerosis [65]. A peptide or protein homologous to complementary PR3 (cPR3), transcribed and translated from the antisense strand of *PRTN3* DNA, is thought to be an inciting antigen in a subset of patients with PR3-ANCA disease. In those who are predisposed, antibodies are generated to cPR3. Anti-idiotypic antibodies, or antibodies to anti-cPR3 antibodies, are then produced that are reactive to PR3 [66, 67]. Complementary PR3 shows homology with proteins of multiple microorganisms, including two proteins found in *S. aureus*, thus suggesting a role for molecular mimicry in the pathogenesis of AAV. While PR3-ANCA and MPO-ANCA patients may have the same type of *S. aureus* as the general population, they do have different distributions of clonal complexes [68]. Given recent reports of *S. aureus* proteins binding MPO and/or PR3 antigens, it is postulated [61, 69] that this bacterial protein-autoantigen complex is then internalized and processed by B-cells and then presented to T-cells. This could account for antibody production by B-cells and role of T-cells in ANCA.

Although it remains highly controversial, lysosome-associated membrane protein 2 (LAMP-2) has been identified as a possible antigenic target in patients with AAV [70]. The P₄₁₋₄₉ epitope of LAMP-2 reportedly has significant homology with an epitope of FimH, having in common 8 of 9 amino acids [71], but these findings were not subsequently confirmed [72].

Illicit and Prescription Drugs

Both illicit and prescription drugs have been implicated in the cause of AAV, but the etiopathogenic mechanisms are not well understood. The ant-helminthic agent levamisole, sometimes found in cocaine, is the most recognized drug cause of vasculitis. Affected patients

[73, 74] are typically MPO-ANCA positive, but may have dual positivity with MPO- and PR3-ANCA [73, 74], and typically present with cutaneous disease. While cutaneous disease in idiopathic AAV typically manifests as recurring crops of purpuric lower extremity lesions, the lesions associated with levamisole are more widespread and variable in character, with necrotic lesions involving the ears, and bullous purpura in any location. Full-thickness, large necrotic lesions are suggestive of levamisole exposure. Affected patients can have arthralgia, particularly of the large joints, and constitutional symptoms. Severe disease with isolated glomerulonephritis and pulmonary-renal syndrome occurs. Patients with signs and symptoms of AAV should be questioned regarding illicit drug use, particularly when dual MPO-ANCA and PR3-ANCA serology is present, and urine toxicology screen for the presence of cocaine and levamisole should be obtained.

The commonest prescription drug offenders include hydralazine and propylthiouracil (PTU), although penicillamine, minocycline, sulfasalazine, allopurinol, carbimazole, methimazole, and gold have all been implicated [75, 76]. Unlike levamisole-induced disease, the presentation of other drug-induced forms of disease mirrors idiopathic disease, with rapidly progressive glomerulonephritis being especially common. Serologically, patients generally have MPO antibodies at high titers, and dual positivity to MPO and PR3 is rare. Affected patients tend to be positive for other autoantibodies, including antinuclear antibody (ANA), anti-double-stranded DNA (anti-dsDNA), anti-histone, anti-lactoferrin antibodies, and other forms of ANCA, specifically anti-human neutrophil elastase (HNE). Propylthiouracil typically causes a pauci-immune necrotizing and crescentic glomerulonephritis, but other organ systems may be involved. While patients with PTU-induced disease tend to have high titers of MPO-ANCA, the ANA is not usually positive. In both illicit and prescription drug-induced AAV, cessation of the causative agent is imperative, and management is similar to that of the idiopathic forms of disease, employing immunosuppressive medication, as well as plasmapheresis and hemodialysis as indicated by disease severity.

Genetic Associations

The ability to sequence DNA from humans is becoming more and more facile, and investigators have taken full advantage of this to understand the genetic underpinnings of AAV, uncovering disease associations with both MHC and non-MHC genes [24]. Genome-wide association studies (GWAS) of patients and healthy controls of European descent revealed an association of PR3-ANCA positive AAV with *HLA-DP*, *SERPINA1* (encoding α -1 antitrypsin), and *PRTN3* (encoding PR3), whereas MPO-ANCA positive disease was associated with *HLA-DQ* [77, 78]. The largest risk was seen with single-nucleotide polymorphism (SNP) variants rs141530233 and rs1042169 at the *HLA-DPB1* locus [78]. Among non-MHC genes, an association were demonstrated with *CTLA4*, which encodes a T-cell surface molecule (CTLA-4) that down-regulates T-cell activation [77]. Two *CTLA4* single nucleotide polymorphisms (SNP), +49 G [51-53] and CT60 [77, 79, 80], have been implicated in several studies. All of the studies identifying disease association with the *CTLA4* SNP were performed in European cohorts comprising only Caucasian patients. No such association with *CTLA4* was found in Japanese patients with AAV [81]. The SNP

rs3087243 of the *CTLA4* gene [80], which encodes an inhibitory regulator of T-cell activation, and rs2476601 of the *PTPN22* gene [80, 82, 83], which encodes a regulator of cytoplasmic tyrosine kinase and T-cell function, are both associated with AAV in Caucasian European cohorts [80, 81, 83]. Mutations in these genes have been implicated in other autoimmune diseases, suggesting a predisposition to general immune dysregulation [80, 82].

Racial and geographic variability may reflect differences in genetic predisposition. AAV has been rarely described in Africa [8], and it is notably rare in African Americans. An association of the *HLA-DRB1*15* alleles with PR3-ANCA positive disease has been found, conferring a 73.3-fold higher risk in African American patients than in community-based controls [84]. These alleles were also associated with PR3-ANCA positive disease in Caucasians, but with an odds ratio of only 2.2. The *DRB1*1501* allelic variant, which is of Caucasian descent, was found in 50% of African American patients, whereas the *DRB1*1503*, of African descent, was under-represented in this group. Only the *DRB1*1501* allele was found in Caucasian patients. A significant association was found with *DRB1*16* in African American patients with MPO-ANCA positive disease. No allele has been so significantly associated with MPO-positive disease in Caucasians. In Chinese patients, the allelic variants *DRB1*1101* and *DRB1*1202* were observed significantly more often in patients with MPO-ANCA and PR3-ANCA-associated disease, respectively, than in healthy controls [85]. The finding in PR3-ANCA positive disease is difficult to interpret given the overall high prevalence of this allele in the Han population. This may reflect a particular AAV-associated haplotype. In Chinese Han population, variant rs3117242 of *HLA-DPB1* was found to be associated with GPA [86]. In a Japanese cohort, *HLA-DRB1*0901* was significantly associated with MPO-ANCA positive disease [81]. Collectively, these findings lend credence to the concept that MPO- and PR3-AAV are genetically distinct diseases with phenotypic overlap. This genetic difference between PR3- and MPO-AAV was also noted in a meta-analysis demonstrating stronger association by ANCA serotype than clinical phenotype [87].

CLINICAL PRESENTATION

The most commonly recognized presentation of AAV is pulmonary-renal syndrome, with alveolar hemorrhage and kidney injury that typically manifests as a rapidly progressive glomerulonephritis. However, presentation can be influenced to some extent by the type of disease be it GPA or MPA, as well as, duration of disease prior to presentation. In terms of kidney involvement, both GPA and MPA can present with severe kidney failure, at times requiring dialysis. EGPA less commonly involves the kidneys, and when it does, kidney disease tends to be less severe than in GPA or MPA. Dysmorphic hematuria with or without red blood cell casts, proteinuria, and an elevated creatinine are all clues to the diagnosis. Proteinuria is typically within the nephritic range (<3g/day), but nephrotic-range proteinuria does not exclude the diagnosis. Kidney disease can occur absent other clinical manifestations.

LABORATORY DIAGNOSIS

Any testing for AAV begins with clinical suspicion of disease. This typically prompts non-specific studies, such as blood tests and urine microscopy, to look for elevated creatinine and dysmorphic hematuria with or without red blood cell casts, respectively, as evidence of kidney involvement. Similarly, chest radiograph or computed tomography (CT) may be used to screen for pathological changes if present. In those with otolaryngologic symptoms, endoscopic examination with biopsy is preferred, followed by more specific avenues of investigation if necessary. Tissue biopsy is the gold standard for diagnosis of AAV. In the acute setting, the lesion common to all affected tissues is segmental inflammation with fibrinoid necrosis (Figure 1), often with accompanying neutrophil infiltration initially, followed in quick succession by mononuclear leukocyte infiltration [88, 89]. As disease progresses, the lesions become sclerotic. The finding of pauci-immune necrotizing crescentic glomerulonephritis strongly supports a diagnosis of AAV. However, lesions can be detected at various stages of development, so mild segmental fibrinoid necrosis with or without an adjacent crescent is common (Figure 1). If the acute lesion is severe, the glomerular tuft may have global necrosis with a circumferential crescent. In patients with granulomatous disease, GPA and EGPA, granulomatous inflammation most often affects the respiratory tract, including the lungs, rather than the kidneys, and is present concomitantly with small-vessel vasculitis. Lesions appear histologically as necrotic zones with surrounding mixed cellular infiltrate of neutrophils, lymphocytes, monocytes, macrophages, and often multinucleated giant cells. Eosinophils may also be present, but are more obvious, although not pathognomonic, in EGPA.

Anti-neutrophil cytoplasmic autoantibodies, first described by Davies and colleagues [90], have become routine in the diagnostic armamentarium of AAV. Treatment should not be delayed while awaiting results. A serologically-negative form of AAV is recognized in which current clinical assays do not detect MPO-ANCA or PR3-ANCA. By using highly sensitive epitope excision with mass spectrometry, Roth and coworkers identified a single small linear MPO epitope with high pathogenicity that was undetectable by usual assays due to obfuscation in serum by ceruloplasmin, the endogenous inhibitor of myeloperoxidase activity [91].

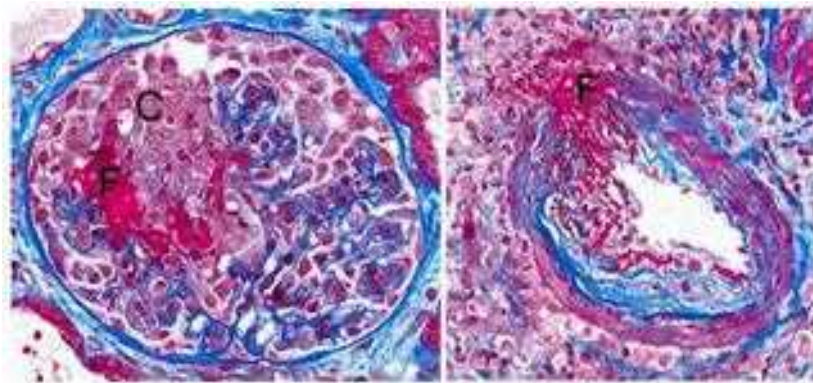


Figure 1. Photomicrographs of a kidney biopsy specimen from a patient with MPA showing a glomerulus (left panel) with segmental fibrinoid necrosis (F) and a cellular crescent (C), and an interlobular artery (right panel) with segmental fibrinoid necrosis (F). (Masson trichrome stain, X400).

Patients presenting with clinical signs and symptoms consistent with disease, but who are serologically negative, may have this or another as yet unidentified epitope that is not readily detected by currently available means. There are ANCA that occur in healthy individuals in very low titer that are not detected by routine serologic assays [92]. These are considered natural autoantibodies. Thus, while ANCA can be used to rule in disease in the appropriate clinical setting, neither their presence nor absence alone can be used to determine if disease is present. Additionally, some patients have persistently elevated autoantibody titers even in the absence of any clinical evidence of disease, thereby limiting their utility in diagnosing disease flares [93].

MANAGEMENT

Treatment of AAV can be considered in three phases: remission induction, remission maintenance, and treatment of relapse. Over the past decade, there has been an explosion of investigation into identifying ideal induction and maintenance strategies for patients with AAV.

Cyclophosphamide with corticosteroids has been used historically as induction therapy for AAV. Cyclophosphamide, an oxazaphosphorine that is chemically related to the nitrogen mustard family of alkylating agents [94], is the mainstay of AAV treatment. Multiple animal models have demonstrated its immunosuppressant activity apart from its antimetabolic or cytotoxic characteristic [95, 96].

Although there is no randomized trial studying the optimum dose with glucocorticoids, the question of oral versus pulse intravenous (IV) cyclophosphamide to reduce the cumulative exposure to cyclophosphamide has been looked at. The CYCLOPS trial compared pulse iv versus daily oral cyclophosphamide in 149 patients with AAV and found no difference in time to remission, but a lower rate of leukopenia in the pulse group (HR 0.41, CI 0.23-0.71) [97]. Though the relapse rate was higher in the IV group in a long term follow up study, the mortality and renal function was similar [98]. The cumulative dose of cyclophosphamide should be kept in mind when choosing a regimen.

More recently, great strides have been made using rituximab-induced B-cell depletion for induction of remission. Rituximab, a chimeric murine/human monoclonal antibody that depletes B-cells by binding CD20 and inducing antibody-dependent cellular cytotoxicity (ADCC), was reported to be non-inferior to cyclophosphamide for induction therapy in GPA and MPA in short- [99, 100] and long-term [101] follow-up. Rituximab is approved by the Food and Drug Administration and European Medicines Agency for induction therapy in patients with GPA and MPA.

Plasmapheresis has been used in AAV patients with diffuse alveolar hemorrhage and severe renal disease [102, 103]. The MEPEx trial randomized 137 patients with AAV and serum creatinine > 5.8 mg/dL to receive plasma exchange or intravenous prednisolone, in addition to cyclophosphamide and oral prednisolone. Plasma exchange reduced risk of end stage kidney disease at 3 and 12 months [103]. A randomized controlled trial (PEXIVAS) of plasma exchange and glucocorticoid dosing was conducted in 704 AAV by Walsh and colleagues, the preliminary unpublished results of which were presented at the 2018 meeting of the European Renal Association – European Dialysis and Transplant Association (ERA-

EDTA) suggesting that plasma exchange was not beneficial in preventing death or progression to ESRD.

B-cell depletion to durably maintain remission is a logical next step, and there are numerous case reports, case series, and retrospective studies that suggest efficacy of this strategy [104-106]. The Maintenance of Remission using Rituximab in Systemic ANCA-associated Vasculitis trial (MAINRITSAN), compared low dose rituximab with azathioprine for remission maintenance in 115 AAV patients. Although rituximab was superior to azathioprine in preventing relapse, azathioprine was tapered and stopped earlier, which limits the results of the study [107]. Currently, the RITAZAREM trial (NCT01697267) in the United States is underway to also address this question of remission maintenance.

Complete depletion of peripheral B-cells cannot continue indefinitely if toxicities associated with immunosuppression are to be avoided. Targeted depletion of only B-cells with the future capacity to produce pathogenic ANCA would be ideal. To this end, there are data suggesting that patients with active disease have a lower percentage of CD5+ B-cells compared to patients in remission, and that rituximab-exposed patients who have a robust reconstitution of CD5+ B-cells after therapy require less immunosuppression [108].

Novel treatment strategies aimed at other components of the inflammatory process, such as alternative complement pathway activation, are also needed. Alternative complement activation pathway products in kidney tissue (Bb) and urine (Bb, C3a, C5a, and soluble C5b-9) of patients with active disease correlate with severity of kidney injury [109]. In the mouse model of MPO-ANCA glomerulonephritis, blockade of the C5a receptor (C5aR) using an oral antagonist ameliorates disease in mice expressing human C5aR [110]. At present, a randomized phase 3 clinical trial (ADVOCATE) is underway to evaluate the safety and efficacy of C5aR blockade to induce remission in patients with ANCA vasculitis treated concomitantly with rituximab or cyclophosphamide/azathioprine (NCT02994927).

Mepolizumab is an anti-interleukin-5 monoclonal antibody that reduces eosinophilic inflammation, and has been successfully used to prevent exacerbations of eosinophilic asthma [111]. In a study of 136 relapsing or refractory EGPA, patients were treated with mepolizumab versus placebo [112]. Mepolizumab treatment was associated with a higher rate of remission (OR 16.74, CI 3.61-77.56) at 36 and 48 weeks. The Food and Drug Administration recently approved Mepolizumab for the treatment of EGPA in 2017.

There are several alternative drug options for maintenance immunosuppression, including azathioprine, mycophenolate mofetil, methotrexate, and leflunomide. Controlled trials of these various options are limited. A meta-analysis looking at the comparative efficacy of azathioprine, mycophenolate mofetil, methotrexate, and leflunomide found a 55% probability that leflunomide is superior to the other three agents for remission maintenance [113]. However, true head-to-head comparisons are lacking. Therefore, provider preference, patient tolerance, cost, and risk of drug-specific adverse effects all play a role in which medication is selected.

OUTCOMES

Although AAV is associated with high mortality, the introduction of immunosuppressive medications has improved the survival over time [114]. The objective now is to prevent relapse and preserve organ function.

The presence of kidney disease and its severity at presentation have long been recognized as important prognostic indicators of renal outcomes in patients with ANCA-associated vasculitis [115, 116]. A recent study investigating predictors of patient and renal survival in a Dutch cohort of 273 consecutive patients with ANCA vasculitis followed for almost twenty years [117] found that overall survival was better in patients without kidney involvement (hazard ratio [HR] 0.55, CI 0.33-0.92, $P = 0.02$). Renal survival was worse in MPO-ANCA positive patients (HR 2.1, CI 1.11-3.8, $P = 0.01$).

A study of 350 patients with AAV evaluated predictors of treatment resistance and relapse [118]. Altogether, 88% of those enrolled had kidney involvement at or near the time of diagnosis and followed longitudinally for a median of 49 months. Female or black patients and those with severe kidney disease appeared to be more resistant to initial therapy. Increased relapse risk was associated with the presence of lung (HR 1.71, CI 1.04-2.81) or upper airway disease (HR 1.73, CI 1.04-2.88) and PR3-ANCA positivity (HR 1.87, CI 1.11-3.14). Most importantly, however, severity of histopathologic findings at diagnosis does not predict patients for whom treatment would be futile [119]. While the presence of kidney disease is associated with poor renal outcomes [115, 116], lack of renal involvement is associated with increased risk of relapse [114]. More recently, a high neutrophil to lymphocyte ratio ($NLR > 5.9$) has been shown to predict more frequent relapse in AAV during follow-up [120].

Another controversy is routine monitoring of serum autoantibodies to predict relapses. Presence of PR3-ANCA at the time of remission maintenance has been associated with high rates of relapse [121]. In a recent study of 181 MPO-ANCA positive Japanese patients, the reappearance of MPO-ANCA, after negative conversion, was associated with relapse (OR 26.2, CI 8.2-101) [122]. However, 12-29% patients do not relapse despite reappearance of MPO-ANCA [93, 122, 123]. Thus, serial monitoring of ANCA may predict relapse, but given the high proportion of patients that do not relapse, it should not be used to guide therapy.

CONCLUSION

Upon hearing the first case reports of patients with GPA [55], Ludwig Aschoff, a renowned German pathologist, described the disease as “a new and very special disease” [124]. Over the past three decades, tremendous progress, more than could have been imagined as recently as the late 20th century, has been made through investigative efforts to understand the etiologies, pathogenesis and clinical management of AAV and glomerulonephritis. They have been transformed from diseases that were usually fatal to diseases that are chronic and manageable, with the potential for long-term, symptom-free remission. Nevertheless, many challenges remain. Ideally, investigations will focus on increasing the understanding of molecular mechanisms of genetic and environmental risk factors for disease, decreasing diagnostic delays to lessen the impact of disease on patient’s health, and further defining and personalizing treatment strategies that will induce and maintain remission while minimizing occurrence of relapse. Future pursuits, built upon the foundation of discoveries to date, may well lead to a cure.

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Chapter 208

ANTI-GLOMERULAR BASEMENT MEMBRANE DISEASE

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ABSTRACT

Anti-glomerular basement membrane (anti-GBM) disease is a rare small vessel vasculitis that typically presents with rapidly progressive glomerulonephritis, often in combination with diffuse alveolar haemorrhage. It is characterised by the presence of directly pathogenic autoantibodies directed against antigens expressed in type IV collagen in glomerular and alveolar basement membranes. Treatment aims to rapidly remove these antibodies, and to suppress ongoing antibody production, with a combination of plasmapheresis, cyclophosphamide and prednisolone. When started promptly, the majority of patients respond successfully to treatment, though recovery from severe renal dysfunction presenting with a requirement for dialysis is uncommon. In contrast to other forms of glomerulonephritis and vasculitis, relapse in anti-GBM disease is exceedingly rare, as is recurrent disease after renal transplantation. Despite its rarity, anti-GBM has been extensively studied and now serves as model autoimmune disorder, with recent studies describing novel mechanisms of HLA-associated immune susceptibility, epidemiologic clustering of disease suggesting the importance of environmental exposures, and a potential role for injurious T cell responses in inciting disease

Keywords: ANCA-associated vasculitis, basement membrane, antibodies

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INTRODUCTION

Anti-glomerular basement membrane (GBM) disease is a rare small vessel vasculitis that usually presents with rapidly progressive glomerulonephritis, diffuse alveolar hemorrhage, or both. It is typified by the presence of autoantibodies directed against antigens intrinsic to the glomerular and alveolar basement membranes, which can be detected in serum or deposited in tissue, and it is therefore classified an immune-complex small vessel vasculitis in the Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides [1]. The Consensus acknowledges the relative misnomer of anti-*glomerular* basement membrane disease, given the frequent involvement of alveolar basement membranes, though recognizes the widely accepted use of anti-GBM disease to describe this condition regardless of lung involvement. The Consensus also recognizes the phasing out of eponymous terminology in the classification of vasculitides, though the term ‘Goodpasture Disease’ is still often used to describe this condition, a reference dating back to a case of necrotizing glomerulonephritis and lung hemorrhage in 1919, that was at the time attributed to atypical influenza infection [2]. It was not until the 1970s, however, and the explosion in immunological laboratory methods, that the disease was fully described [3], following the demonstration of deposited anti-GBM antibodies in renal tissue [4], their detection in circulation [5], and ultimately their pathogenic potential upon passive transfer to non-human primates [6]. Treatment with plasmapheresis and immunosuppression, to rapidly remove these pathogenic autoantibodies and to prevent their ongoing production, was introduced a few years later [7], and remains the mainstay of current treatment approaches, though novel agents are under investigation. Despite its rarity, anti-GBM disease has served as a model for the study of autoimmunity, and it is often regarded as a prototypic antibody-mediated disease. However, the recent recognition of a role for cellular immune effectors in experimental models, studies of the molecular basis of genetic susceptibility to disease, and the description of atypical clinical presentations, highlight that the immuno-pathogenic mechanisms underlying anti-GBM are not yet fully understood, and require further investigation to improve treatment strategies and clinical outcomes.

EPIDEMIOLOGY

Anti-GBM disease is rare, with an estimated incidence of 1-2 per million population (pmp)/year (yr) in European populations, based on single-center biopsy- or serology-based series. A recent study from Ireland was the first to define a nationwide disease incidence, by identifying all cases over a decade via reference immunology laboratories and a national pathology database, reporting a rate of 1.64 pmp/yr [8]. The disease is well recognized in Asian populations [9-12], though is thought to be rarer in African populations [13].

Single-center series suggest that 15-20% of pulmonary-renal syndromes are caused by anti-GBM disease [14-16], and large renal biopsy series show that it accounts for 10-15% of all cases of crescentic glomerulonephritis [17], though it appears to be a rare cause of end-stage renal disease (ESRD) in both adults and children [18, 19]. Anti-GBM disease has a bimodal age distribution, with a peak incidences in the 3rd decade, where a slight male

preponderance and presentation with both kidney and lung disease are observed, and in the 6-7th decades, where presentation with isolated kidney disease is more common [20-22].

GENETIC ASSOCIATIONS

The precise etiology of anti-GBM disease remains obscure, though it is likely that environmental triggers act in genetically susceptible individuals to induce disease onset. Anti-GBM disease has strong HLA-gene associations, with approximately 80% of patients inheriting an HLA-DR2 haplotype [23]. A hierarchy of associations with particular *DRB1* alleles has been identified, some positively associated with disease, such as *DRB1*1501*, an observation that has been replicated in both Caucasian and Asian populations [23-25], and some conferring a dominant-negative protective effect (e.g., *DRB1*01*). It has previously been suggested that the dominant-negative effect might be attributed to the higher affinity of the latter allele for binding peptides from the target autoantigen (thus preventing their favorable presentation on MHC molecules) [23], though a recent series of studies using mice transgenic for human HLA molecules (and lacking murine MHC Class II) suggest novel mechanisms of HLA-disease association. These experiments confirmed epidemiologic observations in humans: *HLA-DR15* transgenic mice are susceptible to the induction of experimental anti-GBM disease, whereas mice expressing either *HLA-DR1* or both *HLA-DR15* and *-DR1* are resistant [26, 27]. These studies suggest that presentation of the immunodominant T-cell epitope in the distinct binding registries of *HLA-DR15* and *-DR1* can differentially induce conventional and tolerogenic T cell responses, respectively, thus accounting for the dominant protective effect of *HLA-DR1* via induction of antigen-specific regulatory T cells, even when co-inherited with the *HLA-DR15* susceptibility allele.

In contrast to other antibody, associated glomerular diseases, such as anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis and membranous nephropathy, where genome-wide association studies have identified polymorphisms in the target autoantigen associated with disease susceptibility, a small study did not identify any polymorphisms in *COL4A3*, the gene encoding the anti-GBM disease autoantigen, related to disease predisposition [28]. This observation may require validation in a larger cohort of patients, however, before polymorphisms in *COL4A3*, or other collagen genes, can be definitively excluded from playing a role in disease pathogenesis.

ENVIRONMENTAL ASSOCIATIONS

Goodpasture's original description of pulmonary-renal syndrome occurred during an influenza outbreak in 1919, and other small series of anti-GBM disease have likewise been described in association with influenza infection [29, 30]. Other reports have described seasonal variation and 'outbreaks' of anti-GBM disease [20, 21], and a recent Chinese study identified a high proportion of patients with prodromal respiratory tract infection at the time of anti-GBM disease diagnosis [31]. These observations suggest that those environmental triggers such as infection may contribute to disease onset, a hypothesis that is further supported by the formal identification of both spatial and temporal clustering of cases in the

recent Irish study [8]. A number of mechanisms may account for this association with infection – studies in experimental animal models, for example, suggest auto-reactivity to basement membrane antigens may arise through a process of ‘molecular mimicry’ or idiotype anti-idiotype interactions following a primary response to microbial or other foreign peptides [32, 33]. Of note, excess reactivity to microbial peptides has been described in patients with anti-GBM disease [34]. It is also possible that usually quiescent autoreactive lymphocytes undergo ‘bystander activation’ because of systemic inflammatory responses, or that pulmonary inflammation at times of infection may release usually sequestered alveolar basement membrane antigens to immune detection.

The release of sequestered antigens may also account for the association of pulmonary irritant exposure and the development of lung hemorrhage in anti-GBM disease, which occurs in nearly all patients who smoke but less frequently in non-smokers [35]. Hydrocarbon exposure has likewise been implicated in disease onset [36, 37], and there are case reports of anti-GBM disease after use of inhaled recreational drugs including cocaine and amphetamine [38-40]. It has been suggested that pulmonary irritants may increase capillary permeability, thus predisposing to alveolar bleeding, or that they may modify or expose sequestered basement membrane antigens to immune detection, resulting in disease enhancement.

IMMUNOPATHOGENESIS

The Autoantigen

The collagen IV family consists of six genetically distinct α -chains ($\alpha 1$ -6) that trimerize with each other to make specific triple-helical protomers: $\alpha 1\alpha 1\alpha 2$, $\alpha 3\alpha 4\alpha 5$, and $\alpha 5\alpha 5\alpha 6$. The expression of the $\alpha 3\alpha 4\alpha 5$ protomer is almost exclusively restricted to the glomerular and alveolar basement membranes (with the $\alpha 1\alpha 1\alpha 2$ protomer being most abundantly expressed elsewhere), and the clinical pattern of renal-pulmonary disease thus reflects the restricted expression of this antigen to these locations. In the GBM, these $\alpha 3\alpha 4\alpha 5$ protomers polymerize end-to-end via their C-terminal non-collagenous domains (NC1) to form hexameric NC1 structures. Specialized sulfilimine bonds cross-linking opposing trimeric NC1 domains reinforce the quaternary structure of this hexamer. It has recently been shown that the generation of these crosslinks, between methionine and lysine residues in the non-collagenous domains, is dependent on the activity of peroxidasin, a peroxidase enzyme that generates hydrobromous acid, a critical intermediate for crosslink formation [41, 42]. The $\alpha 3\alpha 4\alpha 5$ protomers likewise associate via their N-terminal 7S domains to complete a lattice-like network that is essential for glomerular structure and function. The primary target of the autoimmune response in anti-GBM disease was first identified as a 27kDa protein in collagenase-solubilized GBM preparations, and subsequently shown to be the non-collagenase domain of the $\alpha 3$ chain: $\alpha 3(\text{IV})\text{NC1}$ [43, 44]. Immunization with either collagenase-solubilized or recombinant forms of this protein from various species induces disease in a number of animal models, confirming the universal antigenicity of this protein.

HUMORAL IMMUNITY

Anti-GBM disease is regarded as a prototypic antibody-mediated condition, following the seminal observation of disease induction following passive transfer of autoantibody from humans to Squirrel monkeys [6]. All patients with typical anti-GBM disease have antibodies reactive to $\alpha 3(\text{IV})\text{NC1}$, and a proportion also demonstrate reactivity to $\alpha 4$ or $\alpha 5$ chains, identified either in serum or upon elution from kidney tissue, which may arise secondarily due to a process of ‘epitope-spreading’ within the collagen IV network [45]. Studies in animal models suggest that anti- $\alpha 5$ antibodies also have direct pathogenic potential, and their detection is associated with worse prognosis, though reports of human disease in the native kidney caused by anti- $\alpha 5(\text{IV})\text{NC1}$ antibodies (without concurrent anti- $\alpha 3(\text{IV})\text{NC1}$ antibodies) are exceptionally rare [46].

Two key B-cell epitopes within $\alpha 3(\text{IV})\text{NC1}$ are recognized, designated E_A (incorporating residues 17–31 toward the amino terminus) and E_B (residues 127–141 toward the carboxy terminus) [47]. In disease, antibodies tend to be of the IgG1 and IgG3 subclass, and their titer and avidity have been associated with disease severity [48–51]. Once bound in the kidney, these antibodies can initiate a local inflammatory response *via* both complement- and FcR-dependent mechanisms. It is notable, however, that low-level natural autoantibodies that recognize the same epitopes can be identified in healthy individuals, though they tend to be of different subclass (Ig2 and IgG4 dominant) [52]. In addition, the presence of circulating anti-GBM antibodies can predate the onset of clinical disease by several months [53]. These observations suggest that additional factors contribute to disease pathogenesis.

CELLULAR IMMUNITY

The strong HLA association, the detection of high-affinity, class-switched autoantibody, and the phenomenon of ‘epitope spreading,’ indicates a requirement for T cell help in the generation of anti-GBM antibodies. Indeed, peripheral CD4⁺ cells from patients have been shown to proliferate in response to $\alpha 3(\text{IV})\text{NC1}$ (as do cells from healthy individuals, but at much lower frequency), and the frequency of autoreactive CD4⁺ T cells has been shown to correlate with disease activity [54, 55].

Studies in experimental models of anti-GBM disease also suggest that directly nephrogenic T-cell responses may contribute to disease pathogenesis. In early avian models, mononuclear cells could transfer disease to bursectomised birds [56], and B cell deficient mice develop glomerular injury following immunization with $\alpha 3(\text{IV})\text{NC1}$ [57]. Disease has also been transferred by CD4⁺ T-cells from nephritic rats, expanded *in vitro* by stimulation with $\alpha 3(\text{IV})\text{NC1}$, without detectable antibody responses, suggesting directly injurious responses by cellular effectors [58]. In a series of experiments using HLA transgenic mice, Ooi et al identified an immunodominant T-cell epitope within $\alpha 3(\text{IV})\text{NC1}$ that can induce both autoantibody production and glomerulonephritis in mice expressing the human *DRB1*1501* susceptibility allele (but not in mice expressing the protective *DRB1*01* allele) [26]. In addition, CD4⁺ T-cell clones generated from *DRB1*1501* transgenic mice and specific for the immunodominant T-cell epitope transferred disease to naïve animals. In a rat model, immunization with an immunodominant T-cell epitope resulted in glomerular injury,

followed by the expansion of B cell responses to distinct $\alpha 3(\text{IV})\text{NC1}$ epitopes in renal draining lymph nodes [59]. It has thus been suggested that T-cell mediated glomerular injury may be the inciting event in anti-GBM disease, that then triggers *de novo* 'internal' immunization to B-cell epitopes released from damaged GBM, and subsequent autoantibody production required for full expression of disease. Direct evidence of this phenomenon in humans is lacking, though historical case reports of patients who developed glomerulonephritis prior to the deposition of anti-GBM antibodies, and the detection of an early T-cell infiltrate in pathology studies [60, 61], suggests that cell-mediated injury may occur in at least a subset of patients.

TOLERANCE AND AUTOIMMUNITY

$\alpha 3(\text{IV})\text{NC1}$ is expressed in human thymus [55, 62], though the finding of natural autoantibodies and autoreactive T cells in healthy individuals suggests central tolerance to the antigen is incomplete. However, additional immune 'check-points' must be broken for disease to develop. Of note, the B cell epitopes within native $\alpha 3(\text{IV})\text{NC1}$ are cryptic, being sequestered within the quaternary structure of the hexameric NC1 structure stabilized by sulfilamine cross-links, such that they remain protected from immune surveillance in normal circumstances [63]. It has been shown that patient-derived anti-GBM antibodies do not bind cross-linked $\alpha 3\alpha 4\alpha 5$ hexamers until they are dissociated, and it is proposed that the resistance of some mouse strains to experimental anti-GBM disease is due to extensive cross-linking in murine GBM [64]. Thus a process of 'conformational transformation' of the cross-linked $\alpha 3\alpha 4\alpha 5$ hexamer is thought to be critical to disease pathogenesis, by exposing hidden epitopes to immune detection, and allowing the binding of pathogenic autoantibodies [45]. This may explain the association of anti-GBM disease with other pathologies that physically disrupt or modify the structure of the glomerular (e.g., ANCA vasculitis, lithotripsy) or alveolar (e.g., smoking) basement membranes, and of the induction of humoral responses following T cell mediated glomerular injury.

Relapses are rare in anti-GBM disease, suggesting that immune tolerance can be reinstated as disease resolves. This is supported by the finding of an expanding population of CD25+ antigen-specific T cells in patients after their acute presentation, that may suppress responses to $\alpha 3(\text{IV})\text{NC1}$ [65].

CLINICAL PRESENTATION AND DIAGNOSIS

The majority of patients present with rapidly progressive glomerulonephritis (RPGN). As such, a short prodrome of non-specific constitutional symptoms is typical, culminating with overt features of oliguria, fluid overload and uremia. Approximately half of patients require hemodialysis at the point of initial presentation [22]. Loin pain, attributable to distension of the renal capsule, and visible hematuria are recognized. Urine microscopy may identify dysmorphic erythrocytes or red blood cells casts. Proteinuria is usually in the sub-nephrotic range ($<3\text{g/day}$), perhaps reflecting a severe reduction in glomerular blood flow that limits the rate at which protein filtration can occur.

Approximately 40-60% of patients have concurrent alveolar hemorrhage, which is more common in young male patients, and in current smokers [35]. It may present with cough, dyspnea, and hemoptysis, or be apparent radiographically. A disproportionately severe iron-deficient anemia should also alert to the possibility of covert underlying alveolar bleeding. A small proportion of patients (<10%) may present with isolated pulmonary disease in the absence of renal involvement. In one small series, it was found that 11% of patients with lung hemorrhage required artificial ventilation during their treatment for anti-GBM disease [66].

The presence of extra-renal/pulmonary manifestations is uncommon in anti-GBM disease, and may suggest an alternative cause of pulmonary-renal syndrome, or that the patient has co-existing ANCA positivity.

Central to the diagnosis of anti-GBM disease either is the identification of anti-GBM antibodies, in serum or deposited in tissue, along with pathological features of crescentic glomerulonephritis, with or without evidence of alveolar hemorrhage.

SEROLOGIC TESTING

Circulating anti-GBM antibodies were first described using indirect immunofluorescence techniques on normal human or primate kidney [5]. In current practice, a variety of commercial immunoassays is available, which are accepted to have high sensitivity and specificity [67]. These may use native human or animal GBM isolates, or more commonly recombinant $\alpha 3(\text{IV})\text{NC1}$ preparations. It is recognized that between 5-10% of patients with demonstrable anti-GBM antibody on renal biopsy are negative by conventional serum assays. As summarized in a recent commentary by Glasscock [68], this may be due to:

- Intrinsic sensitivity of the chosen assay
- Isotope or subclass of antibody not being detectable (e.g., for example, rare cases of IgA or IgG4 mediated anti-GBM disease are described)
- Antibody disappearance prior to clinical resolution
- The ‘immunological sink’ – high affinity antibodies rapidly bind tissue and are removed from circulation, with only low affinity antibodies remaining,
- Absence of relevant epitopes in antigens used in the detection assay
- T-lymphocyte, complement or other mediators causing tissue damage rather than a predominantly antibody mediated process

A proportion of patients who have demonstrable deposition of IgG on the GBM by immunofluorescence, but who are negative for circulating antibodies by these conventional techniques, may be positive when tested by highly sensitive biosensor assay [69]. These cases demonstrate that serological tests, though useful for rapid diagnoses, should not be the sole means of excluding a diagnosis of anti-GBM disease, and reinforces the importance of performing a renal biopsy when possible.

DEPOSITED ANTIBODY

Direct immunofluorescence for immunoglobulin on frozen kidney tissue has high sensitivity for detecting deposited antibodies, and is the gold standard for diagnosis of anti-GBM disease, typically showing a strong linear ribbon-like appearance (Figure 1A). Other causes of linear fluorescence should be excluded (including diabetes, monoclonal paraproteinemia, lupus nephritis, and rarely fibrillary glomerulonephritis). In addition, it should be noted that fluorescence might be negative or unclear in cases with severe glomerular inflammation, where the underlying architecture is so disrupted that the linear pattern may not be recognized. In typical anti-GBM disease, these deposits are polyclonal and do not show light-chain restriction. Immunoperoxidase techniques using paraffin-embedded tissue may also be used, but may be less sensitive. In our experience, immunofluorescence on lung tissue is rarely informative.

Conventional direct immunofluorescence techniques will identify all IgG subclasses, though will not differentiate the antigenic target of the kidney-bound antibody, and so may detect anti- $\alpha 3$ (IV) NC1, anti- $\alpha 5$ (IV)NC1, or other antibodies recognizing GBM components. Antibodies to non-collagen chain antigens, such as nidogen (entactin), have been identified in historical case series [70, 71], though their significance is not well characterized. In addition to detecting deposited anti-GBM antibody, immunofluorescence may demonstrate the presence of complement components, in particular C3 and C1q, along the GBM [21]. A proportion of patients may also demonstrate immunoglobulin or complement deposition along tubular basement membranes.

RENAL BIOPSY FINDINGS

Almost all patients with anti-GBM disease will have evidence of crescent formation on kidney biopsy (Figure 1B), and in 80% of patients more than 50% of glomeruli will be affected. The average proportion of affected glomeruli is approximately 75% [17, 72]. The proportion of crescents observed in the biopsy correlates strongly with the degree of renal impairment at presentation [21, 22]. These crescents will typically be of uniform age (Figure 1C), in contrast to other causes of RPGN, where a mixture of cellular, fibrocellular and fibrous crescents may be seen. Asynchronous crescent formation, or the presence of necrotizing vasculitis in larger blood vessels on renal biopsy, should thus alert to the possibility of a concomitant ANCA-mediated process. Given the acuity of disease onset, interstitial fibrosis and tubular atrophy are uncommon in anti-GBM disease (unless there is pre-existing kidney pathology) though interstitial inflammation may be observed. Electron-dense deposits are not seen in isolated anti-GBM disease, though electron microscopy is necessary to exclude concomitant glomerular pathologies, such as membranous glomerulonephritis, and may identify other diseases that may cause linear fluorescence (such as fibrillary GN and diabetic GBM thickening).

DIAGNOSIS OF ALVEOLAR HEMORRHAGE

There are no uniform diagnostic criteria for the diagnosis of diffuse alveolar hemorrhage, and diagnosis is often made on a combination of clinical, radiological and laboratory findings. This may account for the variable frequency of lung hemorrhage described in clinical series of anti-GBM disease.

Plain chest radiography may demonstrate non-specific diffuse opacification patterns with occasional predilection for the midzones and apical and costophrenic sparing [73]. High-resolution computed tomography may show ground-glass opacifications due to alveolar filling with blood, which may progress to frank consolidation, again with peripheral sparing. As hemorrhage is resorbed in the pulmonary interstitium, later imaging may show reticular or nodular appearances [74].

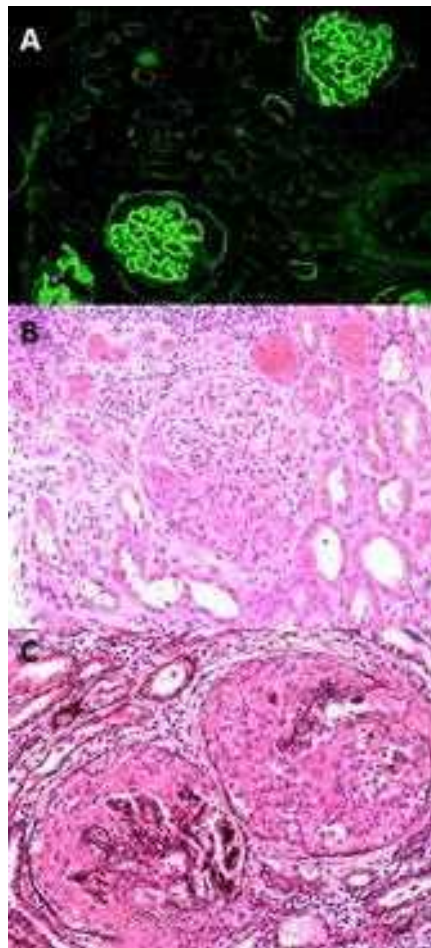


Figure 1. Renal biopsy findings in anti-GBM disease. (A) Immunofluorescence for IgG in anti-GBM disease, showing bright linear deposits along glomerular (and to a lesser extent, tubular) basement membranes. (B) Hematoxylin and eosin staining in anti-GBM disease, showing a circumscribed glomerular crescent with compression of the underlying tuft. Red blood cells casts are present in tubular lumens. (C) Jones methenamine staining in anti-GBM disease, clearing delineating glomerular basement membranes, large circumferential and synchronous crescent formation in adjacent glomeruli, with associated rupture of Bowman's capsule.

Acute alveolar hemorrhage may be indicated by the finding of hemorrhagic broncho-alveolar lavage fluid, classically with increasing blood content on successive washes. After 2-3 days, alveolar macrophages convert hemoglobin to hemosiderin, and these hemosiderin-laden cells may persist in the lung for several weeks, being evident on Perls staining of broncho-alveolar samples [75]. Threshold proportions of 20-30% hemosiderin-laden cells of the total macrophage count have been suggested to be strongly indicative of diffuse alveolar hemorrhage.

An increase in diffusing capacity of the lung for carbon monoxide (KCO) has been reported in alveolar hemorrhage in anti-GBM disease, being attributed to increased CO uptake by intra-alveolar erythrocytes [76]. However, this finding may not be present in all cases [66], perhaps due to ventilation-perfusion mismatch in a proportion, such that measurement of KCO may have useful positive, but not negative, predictive value.

Lung biopsy is rarely performed in cases of alveolar hemorrhage in anti-GBM disease. When undertaken, it is likely to show alveolar lumens filled with erythrocytes and hemosiderin-laden cells. Pulmonary capillaritis may be present, with features of fibrinoid necrosis of capillary walls and inflammation and edema of the alveolar interstitium [77].

TREATMENT

The combination of immunosuppression and plasmapheresis to treat anti-GBM disease was first described in 1976 [7], and it remains the core recommendation of the latest KDIGO guideline for treating anti-GBM GN [78]. We have reproduced a recommended treatment schedule (Table 1).

Plasmapheresis aims to rapidly remove directly pathogenic anti-GBM antibodies from the circulation, and its use is supported by observational studies that suggest improved renal and patient survival compared to historical or contemporaneous cohorts treated with immunosuppression alone [22, 79, 80], and one small randomized trial [81]. The American Society for Apheresis (ASFA) includes anti-GBM disease in its recommendations for therapeutic plasmapheresis (Grade 1B, 1C) [82]. Immunoabsorption is an alternative form of extra-corporeal therapy that may be more efficient than plasma exchange for the removal of pathogenic autoantibody (though conversely it may not remove pro-inflammatory or pro-coagulant factors). In small series, it appears to have comparable outcomes to plasma exchange therapy [83, 84].

In addition to plasma exchange therapy, immunosuppression and corticosteroid treatment are required to prevent ongoing autoantibody production to reduce renal and pulmonary inflammation. Daily oral cyclophosphamide and oral prednisolone are the most commonly used agents, forming the basis of nearly all published experience in anti-GBM disease. An uncontrolled retrospective analysis suggests that daily oral cyclophosphamide may be superior to pulsed intravenous treatment [85], in contrast to AAV. The use of other immunosuppressive therapies is less well described [86-88]. Rituximab is an effective treatment for a number of other autoantibody associated glomerular diseases, though published experience in anti-GBM disease is limited to approximately 20 cases [89-98], where it has most commonly been used as adjunctive or second-line therapy in resistant disease. It appears to be associated with immunological response, though clinical outcomes

are variable. At present, there is insufficient evidence to recommend its use first-line in the treatment of anti-GBM disease; however, it may be considered where there are compelling contra-indications to cyclophosphamide therapy or as adjunctive treatment in severe disease. Rituximab may also be considered for expediting antibody clearance in patients awaiting renal transplantation who remain seropositive.

Table 1. Initial treatment of Anti-GBM disease (adapted from references [13, 140])

Agent	Details and Duration	Cautions
Plasma exchange	Daily 4 L exchange for 5% human albumin solution. Add fresh human plasma (300-600 mL) within 3 days of invasive procedure (e.g., kidney biopsy) or in patients with alveolar hemorrhage. Continue for 14 days or until antibody levels are fully suppressed. Monitor antibody levels regularly after cessation of treatment as plasma exchange may require reinstatement if antibody levels rebound.	Monitor and correct as required: platelet count; aim $>70 \times 10^9/L$; fibrinogen; aim >1 g/L (may require cryoprecipitate supplementation to support PEX); hemoglobin, aim for >90 g/L; corrected calcium, aim to keep in normal range
Cyclophosphamide	2 mg/kg/day given orally for 2–3 months. Reduce dose to 2 mg/kg in patients >55 years.	Stop if leukocyte count falls to $<4 \times 10^9/L$ and restart at reduced dose when recovered. Insufficient evidence to recommend use of IV cyclophosphamide.
Corticosteroids	Prednisolone 1 mg/kg/day (maximum 60 mg) given orally. Reduce dose weekly to 20mg by 6 weeks, then gradually taper until complete discontinuation at 6–9 mo.	There is no evidence to support the use of methylprednisolone, and it may increase the risk of infection
Prophylactic treatments	Prophylaxis against oropharyngeal fungal infection (e.g., nystatin, amphotericin, or fluconazole) while on high-dose steroids. Peptic ulcer prophylaxis (e.g., with PPI) while on high-dose steroid treatment. Prophylaxis against PCP (e.g., cotrimoxazole) while receiving high-dose corticosteroids and cyclophosphamide. Consider acyclovir for CMV prophylaxis. Consider prophylaxis against HBV reactivation (e.g., lamivudine) in patients who have evidence of previous infection (HBV cAb positive).	H ₂ receptor antagonists in those who are intolerant of PPI. Cotrimoxazole may contribute to leukopenia; monitor leukocyte count. Alternatives include nebulized pentamidine.

Abbreviations: cAb = core antibody; CMV = cytomegalovirus; GBM = glomerular basement membrane; HBV = hepatitis B virus; IV = intravenous; PCP = *Pneumocystis jiroveci* pneumonia; PEX = plasma exchange; PPI = proton pump inhibitor. Table adapted from reference [13].

Novel therapies undergoing evaluation in anti-GBM disease include IdeS (IgG-degrading enzyme of *S. pyogenes*), a streptococcal enzyme that is able to cleave both circulating and membrane-bound immunoglobulin [99]. IdeS was safe and tolerable in early phase human studies, and was shown to be effective for the removal of anti-HLA antibodies in patients undergoing renal transplantation [100]. A clinical study in severe anti-GBM disease, where it may promote rapid clearance of pathogenic autoantibody, is ongoing (EudraCT number: 2016-004082-39). We have recently shown that treatment with fostamatinib, a spleen tyrosine kinase (SYK) inhibitor, effectively reverses crescent formation in rodent models of anti-GBM disease [101, 102] (and that intra-glomerular SYK can be detected in patient kidney biopsies [103]) so it would be of interest to explore the use of this agent in advanced clinical disease.

OUTCOME AND PROGNOSIS

Diffuse alveolar hemorrhage secondary to anti-GBM disease appears to be highly responsive to treatment, with 90-100% of cases responding to immunosuppression and plasmapheresis [22, 66]. Data on long-term respiratory outcomes, however, are scarce. One small study suggested that patients who had lung hemorrhage have significantly reduced KCO compared to controls without lung involvement [104]. However, a subsequent larger series suggested that long-term respiratory sequela after lung hemorrhage in anti-GBM disease are not common [66]. This is in contrast to AAV, where interstitial lung disease is increasingly recognized as an important long-term complication, especially in patients positive for MPO-ANCA, suggesting that distinct mechanisms of pulmonary injury in these diseases [105, 106].

Renal outcomes in anti-GBM disease may be more variable. Long-term follow up of the largest cohort of patients ($n = 71$) all treated with the combination of plasma exchange, cyclophosphamide and corticosteroids, suggests that this approach is effective in preserving independent kidney function in the majority of patients, including those who present with severe kidney dysfunction, provided they do not require dialysis at presentation [22]. In patients presenting with creatinine values $<500\mu\text{mol/L}$, renal survival was 95% and 94% at 1- and 5- years respectively. In patients presenting with creatinine $>500\mu\text{mol/L}$, but not requiring immediate dialysis, renal survival was 82% and 50% at the same respective time-points. In patients presenting with an initial requirement for dialysis, however, renal recovery occurred in only 8% at 1 year. Other reports have described similarly low levels of renal recovery in patients presenting with dialysis-dependent kidney failure, with the highest rate of approximately 20% recovery in one series [107].

Predictors of poor renal outcome include severe renal dysfunction at diagnosis, the proportion of glomeruli affected by crescents, and oliguria at presentation [21, 22, 108]. A recent worldwide, multi-center study recruited 123 cases of renal biopsy-proven anti-GBM glomerulonephritis, making it the largest histopathological study in anti-GBM disease to date [109]. It confirmed previous observations of more favorable outcomes in patients presenting with creatinine of $<500\mu\text{mol/L}$. Independent predictors of ESRD were dialysis-requirement at presentation, reduced proportion of normal glomeruli, and increased interstitial infiltrate on kidney biopsy. Of note, no patient with 100% crescents or $>50\%$ sclerotic glomeruli recovered renal function, and so withholding treatment may be considered in these cases if lung hemorrhage is not present. Rare cases of renal recovery despite adverse pathologic findings [110, 111], however, highlights the need to consider all cases for treatment, with specific attention to other features that might predict renal recovery on biopsy (such as concomitant acute tubular injury). A short trial of early treatment may be considered, and rapidly tapered if there is no evidence of renal recovery within 2-4 weeks. In addition, the potential benefit of a period of immunosuppression to expedite autoantibody clearance, thus allowing earlier kidney transplantation, should be considered in suitable patients.

Relapse is rare in anti-GBM disease, occurring in fewer than 3% of patients [22]. It is usually associated with ongoing exposure to pulmonary irritants such as cigarette smoke or hydrocarbons [112, 113], and avoidance of these precipitants is an essential part of long-term management of these cases. We recommend repeat kidney biopsy in cases of relapse with kidney involvement, in order to secure an accurate diagnosis and to exclude concomitant

pathologies such as AAV and membranous nephropathy. In confirmed cases, standard re-treatment with cytotoxic medications and corticosteroids is usually indicated.

The long-term outcome of patients who progress to ESRD due to anti-GBM GN appears to be comparable to patients with ESRD of other causes, whether they remain on dialysis or undergo kidney transplantation [18, 114]. It should be noted, however, that kidney transplantation performed in the presence of anti-GBM antibodies results in a high likelihood of disease recurrence in the allograft, at frequencies of up to 50% in historical series [115], and that a period of at least six months sustained seronegativity is advised prior to undertaking transplantation in patients who have reached ESRD due to anti-GBM disease [78]. Under these circumstances, and with current immunosuppressive regimens, recurrent disease is rare [18].

VARIANT PRESENTATIONS OF ANTI-GBM DISEASE

Double-Positive Anti-GBM and ANCA-Associated GN

In some series, almost half of patients with anti-GBM disease have detectable ANCA (usually recognizing myeloperoxidase, MPO), and up to 10% of patients with ANCA have circulating anti-GBM antibodies [116-118]. This phenomenon was first reported within a few years of the first description of ANCA [116, 119], and while it is clear that the autoantibodies are antigenically distinct [120], the mechanism of this association is not understood. It has been shown that ANCA may be detected before the onset of anti-GBM disease, suggesting that ANCA-induced glomerular inflammation may be a trigger for the development of an anti-GBM response, perhaps by modifying or exposing usually sequestered disease epitopes in GBM [53].

These 'double-positive' patients appear to have a hybrid clinical phenotype, experiencing the early morbidity and mortality of anti-GBM disease, with severe kidney and lung disease at presentation, requiring aggressive immunosuppressive therapy and plasma exchange [121]. There is a suggestion they may be more responsive to treatment, with increased rates of recovery from dialysis. During long-term follow-up, however, they relapse at a frequency comparable to patients with AAV, suggesting they warrant more careful long-term follow up and maintenance immunosuppression, unlike patients with single-positive anti-GBM disease.

Anti-GBM Disease Associated with Membranous Nephropathy

There are several reports of anti-GBM disease associated with membranous nephropathy, occurring as a preceding, simultaneous, or succeeding diagnosis [122, 123]. As with the ANCA-association, it is postulated that disruption of glomerular architecture by one disease reveals hidden epitopes that allow the second process to occur. A rapid decline in kidney function in a patient with known membranous nephropathy should raise suspicion of the development of superimposed crescentic nephritis or anti-GBM disease, and re-biopsy is recommended. We suggest that such cases are treated initially as for anti-GBM disease, though how they should be managed in the long-term is not clear. The authors of a recent case

report suggest that rituximab may be a useful agent to treat both pathologies simultaneously [92].

Post-Transplant Anti-GBM Disease in Alport Syndrome

After kidney transplantation for Alport syndrome, recipients may develop anti-GBM antibodies as an alloimmune response to the neo-antigens contained in ‘normal’ $\alpha 3$, $\alpha 4$ or $\alpha 5$ chains expressed in the kidney allograft. In classical X-linked Alport syndrome (caused by mutations in the *COL4A5* gene encoding the $\alpha 5$ collagen chain) these antibodies do not recognize the individual E_A and E_B epitopes of the $\alpha 3$ chain recognized by sera from typical Goodpasture patients, but rather a distinct, composite epitope on the $\alpha 5$ chain, that is not sequestered within the native hexamer of the Goodpasture antigen [45]. It should be noted that commercially available anti-GBM assays, which are optimized to detect reactivity to the $\alpha 3(IV)NC1$ antigen, might fail to detect circulating antibodies in this setting. Anti-GBM antibodies may be detected in 5-10% of Alport patients following transplantation, though the development of overt glomerulonephritis in the allograft is less frequent (perhaps owing to the effects of maintenance immunosuppression). When glomerulonephritis develops, however, it usually occurs early and carries a high risk of graft loss [124, 125]. Repeated transplantation in this setting almost invariably leads to more aggressive disease recurrence and rapid graft loss, and is undertaken at very high risk [126]. Individuals with large *COL4A5* gene deletions are at increased risk of post-transplant anti-GBM disease, and recent guidelines encourage the use of genetic testing to inform discussions regarding the risk of *de novo* anti-GBM disease after transplantation [127].

‘ATYPICAL’ ANTI-GBM DISEASE

‘Atypical Anti-GBM disease’ is a term that has been used variably to describe cases with classical linear IgG staining on renal biopsy, but uncharacteristic clinicopathologic features. A large series ($n = 20$) of ‘atypical’ cases was recently reported by Nasr and colleagues – all had bright linear GBM staining for immunoglobulin on kidney biopsy, though none had detectable $\alpha 3(IV)NC1$ antibodies by commercial ELISA, and none had lung hemorrhage [128]. Most had had only mild renal insufficiency, though all had proliferative glomerular changes on renal biopsy, but without diffuse crescent formation. Treatment was with heterogeneous immunosuppression (and generally did not include plasma exchange), and both patient and renal survival at one year were favorable, at 93% and 85%, respectively. Of note, GBM staining was IgM dominant in two cases, and IgA dominant in another. In addition, half of the patients had restriction for either kappa or lambda lights on immunofluorescence testing, though none had glomerular capillary wall deposits on electron microscopy (that would be expected in proliferative GN with monoclonal immunoglobulin deposits; PGNMID), nor did they have identified features of an underlying plasma cell dyscrasia. A number of other case reports and small series have similarly described ‘atypical’ cases, with similarly indolent renal disease and seronegativity by conventional assay. One recent report describes a case of florid anti-GBM disease with kappa-light chain restriction on

GBM staining in association with a circulating paraprotein [129], thus suggesting that anti-GBM disease may occur within the spectrum of ‘monoclonal gammopathy of renal significance.’ A number of mechanisms for the unusual pattern of renal injury in these cases have been proposed, including differences in antibody isotype or subclasses, varied antigenic targets, and differential pathogenicity in antibodies related to their ability to fix complement or recruit inflammatory cells [130].

ANTI-GBM DISEASE AFTER ALEMTUZUMAB THERAPY

Secondary autoimmune phenomena after alemtuzumab, an anti-CD52 lymphocyte depleting treatment for relapsing-remitting multiple sclerosis (MS), are common [131]. Autoimmune thyroid disease occurred in up to 30% of patients in controlled trials, and there are case reports of both membranous nephropathy and anti-GBM disease following treatment [132, 133]. It has been proposed that T-cell reconstitution after alemtuzumab is driven largely by homeostatic expansion of cells that have escaped deletion (rather than by thymopoiesis), resulting in a T-cell pool that is enriched for autoreactive cells [134]. Anti-GBM disease has not been reported when alemtuzumab is used for other indications other than MS (e.g., renal transplantation), perhaps due to the use of maintenance immunosuppression, or due to the shared HLA susceptibilities in MS and anti-GBM disease. Careful monitoring of patients for renal pathology after treatment with alemtuzumab is needed in order to facilitate early detection and treatment [135]. We suggest conventional treatment for anti-GBM disease occurring in this setting.

ISOLATED PULMONARY INVOLVEMENT IN ANTI-GBM DISEASE

Presentation with isolated or predominant pulmonary involvement in anti-GBM disease is recognized, though uncommon, being estimated to occur in <10% of patients in larger series. Such cases are not extensively characterized, perhaps reflecting publication bias from renal centers, though there are small case series [136, 137]. Some patients may have mild urinary abnormalities and minor proliferative changes on renal biopsy, but with preserved excretory renal function, while others may have no clinical or histological evidence of renal inflammation. Renal biopsy, however, may still reveal linear deposits of immunoglobulin, including in those patients who are negative by serological assay. A small series from Sweden recently described four young female patients who presented with severe alveolar hemorrhage and favorable renal outcome, who were seronegative for circulating anti-GBM antibodies by conventional assay [138]. They were, however, found to have circulating IgG4 anti-GBM antibodies by dedicated ELISA, and this was confirmed on kidney biopsy. Together, these findings suggest that clinical presentation in anti-GBM disease may be influenced by differences in antibody subclass or antigen target, and highlight the need to consider variant anti-GBM disease in cases of ‘idiopathic’ pulmonary hemorrhage.

CONCLUSION

Despite its rarity, anti-GBM disease has been extensively studied, and it now serves as a model autoimmune disorder: it has a well-characterized autoantigen with defined epitopes; it demonstrates the directly pathogenic potential of specific autoantibodies; T-cell responses contribute to disease pathogenesis, both as orchestrators of the immune response and as effectors of tissue injury; and recent work sheds light on the molecular mechanisms via which HLA inheritance may confer autoimmune susceptibility. However, variant and atypical presentations demonstrate that anti-GBM disease cannot be regarded as a 'one-dimensional' entity [139], and that the mechanisms which induce the aberrant adaptive immune response directed to self-antigen are not fully understood and may not be common to all patients. Further insights into these inciting events and, given the extreme rarity of relapses, the mechanisms via which immune tolerance is reinstated as disease resolves, may have important therapeutic implications not just in anti-GBM disease, but also for a spectrum of autoimmune disorders in future. The abrupt clinical presentation of life-threatening lung hemorrhage and rapidly progressively glomerulonephritis, however, renders the disease of equal import to physicians as to immunologists, as early recognition and prompt initiation of immunosuppression and plasmapheresis is necessary to preserve kidney function and prevent mortality. Current treatment strategies, when introduced early enough, appear to be effective, though improved prognostic and therapeutic approaches are required for those presenting with advanced renal failure.

CONFLICT OF INTEREST

The authors have nothing to disclose.

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Chapter 209

SYSTEMIC VASCULITIS OF THE GASTROINTESTINAL TRACT

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ABSTRACT

Systemic vasculitides are a cause of vascular inflammation throughout the body including the gastrointestinal tract. The nature of gastrointestinal (GI) involvement depends on the size and location of the affected vessels. Involvement of large vessels typically leads to downstream ischemia and tissue infarction. Medium vessel involvement can cause hemorrhage from ruptured aneurysms, downstream ischemia and tissue infarction. Small vessel involvement typically leads to ulceration, patchy infarction and bleeding. Severe GI involvement in systemic vasculitis confers a worse prognosis. Management of the underlying vasculitic process includes some form of immunosuppression however surgical intervention to manage intra-abdominal pathology caused by the vasculitic process may also be necessary. Revascularization procedures may be needed to manage aneurysm formation and to rescue ischemic tissue. This chapter reviews GI involvement in primary and secondary vasculitic diseases and outlines their management. Consideration will be given to GI tract complications due to immunosuppressive therapy for systemic vasculitis.

Keywords: systemic, vasculitis, gastrointestinal, autoimmunity

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INTRODUCTION

The hallmark of vasculitis is inflammation in the blood vessels seen histologically as fibrinoid necrosis or in some cases granulomatous inflammation. Inflammation and occlusion of the vessel lumen of muscular arteries leads to downstream tissue ischemia and necrosis while focal involvement of the vessel wall can result in aneurysm formation and vessel rupture with catastrophic bleeding [1]. Vasculitis affects any part of the body depending on the blood vessel or vascular bed involved. In some vasculitides, gastrointestinal tract (GIT) involvement is common. In considering how different vasculitides can affect the GIT it is important to revisit the classification of vasculitis.

Vasculitis can be classified as primary or secondary in nature, and localized or systemic in its distribution and organ involvement. The 2012 Chapel Hill Consensus Conference (CHCC) [2] provides a useful nosology and definitions of the vasculitides based upon the caliber of the vessel involved and the associated clinicopathological features (Table 1). Primary systemic vasculitides occur as a primary process, whereas secondary vasculitides are secondarily associated with another underlying condition such as connective tissue disease, hypersensitivity reactions to drugs or infection. Localized or single organ vasculitides manifest symptoms confined to a single organ or to the skin whereas systemic vasculitides are characterized by constitutional symptoms and multiorgan involvement.

Overall, the extent and distribution of GIT involvement by the underlying vasculitic process, whether primary or secondary, depends mainly upon the size and location of affected vessels. A vasculitic cause for a given GIT disturbance should be suspected when unusual sites such as the stomach, duodenum, and rectum are involved by mesenteric ischemia along with systemic features or multi-organ involvement, particularly in young patients [3]. In a recent series reporting endoscopically confirmed upper GI involvement amongst 148 patients with vasculitis, IgA vasculitis was the most prevalent underlying vasculitic process (57%) followed by Takayasu arteritis (TA) (14%), microscopic polyangiitis (MPA) (10%) and polyarteritis nodosa (PAN) (7%) [4]. Notably, patients with Bechet disease (BD) were excluded from this study.

Table 1. Classification of vasculitis*

	Primary	Secondary
Large vessel	Giant cell arteritis	
	Takayasu arteritis	
Medium vessel	Polyarteritis nodosa	
	Kawasaki disease	
Small vessel	Henoch-Schonlein purpura	Systemic lupus erythematosus
	Granulomatosis with polyangiitis	Rheumatoid vasculitis
	Microscopic polyangiitis	Cryoglobulinemia
	Eosinophilic granulomatosis with polyangiitis	Other (drugs, infections, malignancy)

*Adapted from reference 13.

Acute mesenteric ischemia and tissue infarction secondary to vasculitis are well recognized [5-10]. Although relatively rare, vasculitic GIT involvement leading to acute abdominal pathology is potentially catastrophic and it is therefore important to promptly diagnose it in the appropriate clinical setting. Mesenteric vasculitis accounts for less than 5%

of all patients with chronic mesenteric ischemia [11], while other GIT manifestations of vasculitis include ulceration, submucosal oedema, hemorrhage, paralytic ileus, bowel obstruction and perforation [12].

This chapter will consider both primary and secondary vasculitides first giving a brief outline of the diseases followed by specific GIT involvement with consideration of the investigations, management and prognostic implications of GIT involvement. Treatment-related GIT morbidity will also be considered.

PRIMARY SYSTEMIC VASCULITIS

Large Vessel Vasculitides

Vasculitic involvement of large vessels leads to symptoms similar to mesenteric ischemia and may be difficult to differentiate from atherosclerotic disease when systemic features are absent or not apparent.

Takayasu Arteritis

Epidemiology

Takayasu arteritis involves large arteries and is pathologically characterized by granulomatous inflammation of the aorta and its major branches [13]. The disease, which has a female preponderance with a predominant age at onset of 10 to 40 years [14, 15], is rare but has an increased incidence in Asian, Mexican and Japanese populations [16].

Classification and Diagnostic Criteria

In 1990 the American College of Rheumatology (ACR) published criteria for the classification of TA [15], while other useful classification and diagnostic criteria were published in 1988 by Ishikawa [17], and later modified by Sharma and colleagues [18], both of which are shown in Tables 2 and 3.

Table 2. The American College of Rheumatology 1990 criteria for the classification of Takayasu arteritis*

Criteria	Definition
Age at disease onset <40 years	Development of symptoms or findings related to Takayasu arteritis at age <40 years
Claudication of extremities	Development and worsening of fatigue and discomfort in muscles of one or more extremity while in use, especially the upper extremities
Decreased brachial artery pulse	Decreased pulsation of one or both of brachial arteries
BP difference >10mmHg	Difference of >10mmHg in systolic blood pressure between arms
Bruit over subclavian arteries or aorta	Bruit audible on auscultation over one or both subclavian arteries or abdominal aorta
Arteriogram abnormality	Arteriographic narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper or lower extremities, not due to arteriosclerosis, fibromuscular dysplasia or similar causes; changes usually focal or segmental

For purposes of classification, a patient shall be said to have Takayasu arteritis if at least three of these six criteria are present. The presence of any three or more criteria yields a sensitivity of 90.5% and a specificity of 97.8%.

*Adapted from reference 15.

Table 3. Ishikawa criteria for diagnosis of Takayasu arteritis*

Criteria	Definition
Three Major Criteria	
1. Left mid subclavian artery lesion	The most severe stenosis or occlusion present in the mid portion from the point 1 cm proximal to the vertebral artery orifice up to that 3 cm distal to the orifice determined by angiography
2. Right mid subclavian artery lesion	The most severe stenosis or occlusion present in the mid portion from the right vertebral artery orifice to the point 3 cm distal to the orifice determined by angiography
3. Characteristic signs and symptoms of at least 1 month duration	These include limb claudication, pulselessness or pulse differences in the limbs, an unobtainable or significant blood pressure difference (> 10 mmHg systolic blood pressure difference in limb), fever, neck pain, transient amaurosis, blurred vision, syncope, dyspnea or palpitations
Ten Minor Criteria	
1. High ESR	Unexplained persistent high ESR >20 mm/hour (Westergren) at diagnosis or presence of the evidence in patient's history
2. Carotid artery tenderness	Unilateral or bilateral tenderness of common carotid arteries on palpation. Neck muscle tenderness is unacceptable
3. Hypertension	Persistent blood pressure >140/90 mmHg brachial or >160/90 mmHg popliteal
4. Aortic regurgitation or annuloaortic ectasia	By auscultation, angiography or Doppler echocardiography. By angiography or two-dimensional echocardiography
5. Pulmonary artery lesion	Lobar or segmental arterial occlusion or equivalent determined by angiography or perfusion scintigraphy, or presence of stenosis, aneurysm, luminal irregularity or any combination in pulmonary trunk or in unilateral or in bilateral pulmonary arteries determined by angiography
6. Left mid common carotid lesion	Presence of the most severe stenosis or occlusion in the mid portion of 5 cm in length from the point 2 cm distal to its orifice determined by angiography
7. Distal brachiocephalic trunk lesion	Presence of the most severe stenosis or occlusion in the distal third determined by angiography
8. Descending thoracic aorta lesion	Narrowing, dilatation or aneurysm, luminal irregularity or any combination determined by angiography. Tortuosity alone is not acceptable
9. Abdominal aorta lesion	Narrowing, dilatation or aneurysm, luminal irregularity or aneurysm combination
10. Coronary artery lesion	Documented on angiography below the age of 30 years in the absence of risk factors like hyperlipidemia or diabetes mellitus

The presence of two major, one major and three minor, or four minor criteria suggests a high probability of TA.

*Adapted from reference 18.

Clinical Features

Constitutional symptoms including fatigue, weight loss, arthralgia and fever are common in TA particularly in the early stages of the disease. Specific symptoms such as claudication of extremities, headaches, presyncope, syncope, and angina depend on the affected vessels involved [19] (Tables 2 and 3).

Imaging

Conventional angiography is the gold standard for vascular assessment in TA with common sites of involvement located along the middle and proximal parts of the left subclavian and carotid arteries [19]. A study of 60 patients with TA found the abdominal aorta to be involved in 47% of patients employing conventional angiography, with the vast majority of abnormalities due to stenotic rather than aneurysmal vascular changes [19]. Involvement of the abdominal aorta occurs in the descending aortic syndrome that can lead to mesenteric vasculitis in TA. Mesenteric vessel involvement is seen in up to 18% of patients with TA studied by conventional angiography [3, 16, 19]. Although mesenteric vascular involvement of TA is relatively common on radiological assessment, symptomatic GIT

involvement on presentation is rare with one study looking at TA in children reporting only 9% presenting with abdominal symptoms [20].

Due to the invasive nature of conventional angiography, computed tomographic angiography (CTA), magnetic resonance angiography (MRA), and positron emission tomography (PET) have been employed in the evaluation of TA, particularly when therapeutic intervention is not anticipated. CTA averts the risk of arterial puncture, accurately depicts luminal changes, and provides useful information on mural changes such as arterial wall thickening and mural thrombi that might otherwise not be appreciated on conventional angiography [20]. MRA avoids the risks of radiation and the need for intravenous injection of iodinated contrast, while providing a generalized arterial survey similar to that of CTA. PET may have a role in differentiating between active lesions and scar formation along areas of vascular wall thickening [21]. A recent meta-analysis found PET to have a sensitivity of 87% and specificity of 73% for assessing TA disease activity [22].

Gastrointestinal Involvement

GI involvement is manifested by mesenteric artery ischemia presenting mainly as postprandial mesenteric angina that may require revascularization. Diarrhea and GI haemorrhage commonly occur due to mesenteric vessel involvement. Rarely this may culminate in acute intestinal infarction which is catastrophic when it occurs [16, 19]. There is a single case report of TA initially presenting as intestinal gangrene secondary to intestinal infarction [23]. Aneurysmal dilatation is a recognized complication of TA particularly along the descending thoracic and abdominal aorta [18]. There is a single report of a patient with TA manifesting as primary aortic-esophageal fistula formation associated with a saccular aneurysm of the proximal descending aorta [24].

Treatment

Treatment in TA can be divided into pharmacological therapy aimed at suppressing inflammation, and revascularization. Corticosteroids are the mainstay of pharmacotherapy although methotrexate, azathioprine, anti-tumor necrosis factor (TNF) therapy, and cyclophosphamide have all been used in patients with TA refractory to corticosteroids [25-27].

Revascularization treatment in TA is delivered by open conventional bypass grafting or endovascular means including, percutaneous transluminal angioplasty with or without stent insertion [28]. Advances in interventional radiology have led to more widespread use of endovascular techniques in the management of high-risk patients. There are several patient reports and case series of TA in the literature describing the successful outcome of endovascular repair of challenging stenotic and aneurysmal lesions [29-33]. Comparisons of the surgical versus endovascular management of lesions of the abdominal aorta in TA shows that the risk of complication, especially restenosis, is higher with endovascular than surgical intervention [34, 35]. A multicenter retrospective study found that over a median follow up of 6.5 years the risk of complications following endovascular repair was 50% compared to 37.5% after surgical repair [35]. Multivariable analysis revealed that patients with TA and evidence of systemic inflammation at the time of revascularisation, as defined by an erythrocyte sedimentation rate (ESR) > 30 mm/hour and C-reactive protein (CRP) level > 6 mg/L, were 7-fold more likely to develop post-procedural complications including restenosis.

Giant Cell Arteritis

Epidemiology and Classification

Giant cell arteritis (GCA) is characterized by granulomatous inflammation that predominantly affects the thoracic aorta and its branches. The age of onset is greater than 50 years with an increased incidence in those 70 to 80 years of age, and a higher incidence in Northern Europeans and North Americans of Scandinavian descent compared to other ethnic groups [36]. The 1990 ACR criteria are shown in Table 4. It should be noted that these criteria were intended for the classification not the diagnosis of GCA [37].

Table 4. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis*

Criteria	Definition
Age at disease onset >50 years	Development of symptoms beginning at age 50 years or older
New headache	New onset of or new type of localized pain in the head
Temporal artery abnormality	Temporal artery tenderness on palpation or decreased pulsation, unrelated to arteriosclerosis of cervical arteries
Elevated ESR	ESR > 50mm in the 1st hour by the Westergren method
Abnormal artery biopsy	Biopsy specimen with artery showing vasculitis characterized by a predominance of mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cells

For the purposes of classification at least 3 criteria must be fulfilled; sensitivity 93.5%, specificity 91.2%.

*Adapted from reference 37.

Clinical Features

The commonest manifestation of GCA is headache followed by scalp tenderness, jaw claudication and visual disturbances; constitutional symptoms such as fever, fatigue and weight loss are also prominent [5, 36]. Approximately 20% of patients with GCA develop clinical manifestations reflecting large vessel involvement including aneurysmal and stenotic lesions of the abdominal aorta which in turn can lead to GI sequelae [36].

Gastrointestinal Involvement

GCA can affect both the liver and the bowel. Asymptomatic involvement of the liver, as manifested by elevated serum alkaline phosphatase and transaminase levels, is reported in up to 50% of patients with GCA [38]. The mechanism leading to liver enzyme derangement is not fully understood however when liver biopsy has been conducted in cases of symptomatic liver involvement, this has demonstrated granulomatous inflammation of medium-sized arterioles within the portal tracts [39]. Whilst clinically evident mesenteric involvement is uncommon, occult radiographic manifestations are noted on arteriography in 18% of patients with GCA [5, 40, 41].

In total there have been 11 reported cases of GCA with bowel involvement, mainly in the form of mesenteric ischemia. Of 11 patients with bowel involvement in GCA, nine were biopsy-proven [5, 8, 42-49], of whom four presented with abdominal symptoms in the absence of symptoms of temporal arteritis. Temporal artery biopsy was positive in only two of the four patients suggesting a negative temporal artery biopsy may not be able to reliably exclude GCA involving the mesenteric vasculature [5].

Treatment

The mainstay of treatment in GCA is high dose corticosteroids to induce remission. Methotrexate is recommended as an adjunctive therapy, while TNF- α and interleukin (IL)-6 inhibitors may have a role in the treatment of relapsing or refractory disease [36, 50-52]. The IL-6 inhibitor tocilizumab has shown particular promise with a recent phase three randomized controlled trial demonstrating significant improvement in sustained remission rates and steroid sparing effects in both newly diagnosed and relapsing GCA [52]. For occlusive disease surgical revascularization is indicated. Comparison of the outcomes of 15 patients undergoing open revascularization for occlusive mesenteric vasculitis secondary to TA, PAN, GCA and indeterminate vasculitis compared to 163 patients undergoing open operations for atherosclerotic disease [11] showed that both groups had similar freedom from mesenteric symptoms and primary graft patency. In this study 8 of the 15 patients with vasculitic disease had active inflammation at the time of intervention and by the end of follow up (mean follow-up 41 months) 14 of 15 patients remained asymptomatic suggesting that surgical revascularization even during active disease is an effective treatment for occlusive mesenteric vasculitis.

MEDIUM VESSEL VASCULITIDES

Ischemia and infarction in dependent organs associated with bleeding in the GIT and within the abdominal cavity, and aneurysm formation occurs in the context of vasculitic involvement affecting medium size vessels typified by polyarteritis nodosa (PAN) and Kawasaki disease (KD).

Polyarteritis Nodosa

Epidemiology

This systemic necrotizing vasculitis is characterized by fibrinoid necrosis that typically involves medium sized arteries [53]. It typically affects middle-age and older individuals with a peak onset in the 6th decade of life. Hepatitis B virus (HBV) infection is associated in up to one third of patients with PAN and is an important consideration with regards to treatment and prognosis [54].

Classification and Diagnosis

Diagnosis of PAN entails the integration of clinical, angiographic and biopsy findings (table 5). Angiographic evaluation is very helpful in the diagnosis and management of PAN. The gold standard is conventional arteriography, with increasing utilization of both CTA and MRA. The typical findings are multiple aneurysms less than 1 cm in diameter that are most often found in the distribution of the renal and mesenteric arteries, the superior mesenteric artery being the commonest vessel involved in some series [16, 55]. The lesions classically affect branch points and the bifurcation of arteries due to segmental erosion and inflammation that weakens the arterial wall [3]. These aneurysms are not pathognomonic for the condition

as they can be found in granulomatosis with polyangiitis (GPA) as well as in systemic lupus erythematosus (SLE) [56].

Table 5. The American College of Rheumatology 1990 criteria for the classification of polyarteritis nodosa*

Otherwise unexplained weight loss of > 4 kg
Presence of livedo reticularis
Testicular pain or tenderness
Myalgia (excluding that of the shoulder hip and girdle) or weakness
Mononeuropathy or polyneuropathy
New onset rise in diastolic blood pressure >90 mmHg
Elevated levels of serum blood urea nitrogen (>40 mg/dL or >14.3 mmol/L) or creatinine (>1.5 mg/dL or >132 µmol/L)
Evidence of hepatitis B virus infection via serum antibody or antigen serology
Characteristic arteriographic abnormalities not resulting from non-inflammatory disease processes
A biopsy of medium or small sized artery containing polymorphonuclear cells

For the purposes of classification at least 3 criteria must be fulfilled; sensitivity 82%, specificity 87%.

*Adapted from reference 53.

Clinical Features

Clinical features of PAN include constitutional symptoms such as malaise, weight loss and fever as well as specific symptoms and signs reflecting the extent of multi-system involvement [57] (Table 6).

Table 6. Clinical features of polyarteritis nodosa*

Manifestation	Specific Problems	Frequency (%)
Systemic symptoms	Fever, malaise, weight loss	80
Neuropathy	Mononeuritis multiplex, polyneuropathy	75
Arthralgia and/or myalgia	Articular and/or diffuse extremity pain	60
Cutaneous	Livedo reticularis, purpura, ulcers	50
Renal disease	Elevated creatinine, hematuria, glomerulonephritis	50
Gastrointestinal symptoms	Abdominal pain, rectal bleeding	40
Hypertension	New onset	35
Respiratory manifestations	Infiltrates, nodules, cavities	25
Central nervous system disease	Stroke, confusion	20
Orchitis	Testicular pain, swelling	20
Cardiac involvement	Cardiomyopathy, pericarditis	10
Peripheral vascular disease	Claudication, ischemia, necrosis	10

*Adapted from reference 57.

Gastrointestinal Involvement

GI involvement occurs in 14 to 65% of patients with PAN affecting both the bowel and hepatobiliary system [55]. Abdominal pain is the most commonly reported GI symptom in PAN. Bowel manifestations of PAN include ulceration, obstruction, infarction, and perforation and hemorrhage that can affect the stomach, small and large bowel and the appendix with the small bowel being most commonly affected [56-58]. Bowel involvement can arise from stenotic lesions that lead to bowel wall ischemia and aneurysm formation that results in hemorrhage. Necrosis of the bowel wall with the potential for subsequent perforation can develop if systemic inflammation gives rise to transmural ischemia and

confers a poor prognosis [55]. Liver involvement occurs in 16 to 56% of patients and can manifest as fibrinoid necrosis of the liver, hepatic artery aneurysms, liver infarction or hepatolithiasis [55, 59, 60]. Small vessel vasculitis of the arteries that supply the bile ducts and gall bladder can lead to intrahepatic sclerosing cholangitis, bile duct stricture, cholecystitis, and hemobilia. Pancreatic involvement can also occur in the form of pancreatitis, pseudocysts and pancreatic insufficiency [55]. Hepatobiliary involvement is potentially life threatening with death due to rupture of the hepatic artery reported [61].

A retrospective analysis of 54 patients with PAN reported GI involvement in 24 (44%) with two-thirds noting abdominal pain at presentation, while all others had abdominal pain at some point in their illness. Of the 24 patients with GIT involvement at presentation 13 (54%) developed an acute abdomen secondary to bowel infarction, perforation, acute cholecystitis, gall bladder infarction, aneurysmal rupture of hepatic, splenic or renal arteries, or bleeding from perforated gastric ulcers [62]. Multiple aneurysm formation is a defining feature of PAN and is noted in 50 to 70% of those with involvement of the GIT with the hepatic artery affected in 50 to 60%; splenic artery in 45%; and pancreatic artery in 25 to 35% [62-64]. Massive internal hemorrhage due to rupture of an aneurysm within the intestine is rare but nonetheless carries a high mortality of up to 75% [64-67].

Treatment

The mainstay of treatment for mild PAN is corticosteroids. However GI involvement constitutes severe disease, which has been shown to have a better outcome when treated with a combination of cyclophosphamide and corticosteroids [68]. PAN secondary to HBV infection is treated with two weeks of corticosteroids followed by antiviral treatment combined with plasma exchange. Those so treated with antiviral therapy do not experience HBV relapses once viral replication has stopped and seroconversion has been achieved [54].

Occlusive mesenteric disease can be managed successfully with open revascularization [11]. Percutaneous endovascular trans-catheter embolization is increasing used to deal with ruptured visceral artery aneurysms associated with PAN [69]. If tissue necrosis or gangrene occurs due to infarction then definitive surgical management in the form of resection is indicated [70].

Kawasaki Disease

Epidemiology and Clinical Features

Kawasaki disease (KD) is one of the commonest childhood vasculitides with a particularly high incidence and prevalence in East Asia. Most patients have disease onset before 5 years of age with a peak incidence at 30 months [71]. The diagnosis is confirmed by the presence of fever for more than five days, and the presence of four of the following five diagnostic criteria: bilateral conjunctival injection; changes of the mucous membranes of the upper respiratory tract including injected pharynx, fissured lips or strawberry tongue; polymorphous rash; limb changes including peripheral edema, erythema, or periungual desquamation; and cervical adenopathy. Untreated KD is a self-limiting disease that lasts for 10 to 12 days; however, coronary artery aneurysms develop in 20% to 25% of patients with significant associated morbidity and mortality [71].

Gastrointestinal Involvement

GI involvement is relatively uncommon but tends to involve the gallbladder and the liver leading to acute non-calculous distension of the gallbladder (gallbladder hydrops), hepatic dysfunction with elevated serum transaminase concentrations and febrile cholestatic jaundice [73-72]. Presentation with an acute abdomen was reported in 4.6% of children with KD [73] due to vasculitic appendicitis, paralytic ileus, or hemorrhagic duodenitis. KD may be an important cause of febrile cholestatic jaundice with up to 21% of febrile cholestatic cases overall being attributed to KD in a recent series [74]. A high index of suspicion for KD should therefore be maintained for children presenting with febrile cholestatic jaundice.

Treatment

Treatment of KD with aspirin and intravenous immunoglobulin (IVIg) reduces the incidence of coronary artery complications compared with aspirin alone [75]. There are no studies that have investigated the GI outcomes or GI response to treatment in KD. Interestingly, elevated bilirubin and gamma-glutamyl transpeptidase (γ GT) have been associated with non-responsiveness, defined by persistent fever, to IVIg treatment [76].

SMALL VESSEL VASCULITIDES

Involvement of small vessels by vasculitis can lead to ulceration, erosions, strictures and occasionally perforation.

IgA Vasculitis/Henoch-Schönlein Purpura

Epidemiology and Clinical Features

IgA vasculitis/Henoch-Schönlein purpura (IgAV/HSP) is a small vessel vasculitis characterized by a leukocytoclastic vasculitis and deposition of IgA-containing immune complexes. It is the commonest form of systemic vasculitis in children with a peak incidence at four to six years of age, although adult patients have been described [77]. It is usually self-limiting and characterized by the tetrad of palpable purpura in the absence of thrombocytopenia or coagulopathy; arthritis or arthralgia; abdominal pain; and renal involvement. The disease follows a more severe course when it presents in adults with a higher incidence of renal impairment and end-stage renal disease [78].

Diagnosis

Although childhood IgAV/HSP is typically clinically diagnosed, adults generally undergo skin or renal biopsy for tissue confirmation. Imaging can be helpful in assessing the GI manifestations of IgAV/HSP especially ultrasonography for the detection of increased bowel wall thickness, hematomas, and intussusception [79].

Gastrointestinal Involvement

GI involvement occurs in 50% of children with IgAV/HSP and can affect the hepatobiliary system or the bowel in a number of ways [16]. Bowel manifestations include;

intussusception [80, 81], intestinal ischemia and infarction, intestinal perforation, gastrointestinal hemorrhage and purpura [82-88] esophageal necrosis [89], ileitis and ileal stricture [90], fistulae formation and acute appendicitis [91]. Hepatobiliary features include; pancreatitis [92] and hydrops of the gallbladder [93]. Functional GIT disorders such as irritable bowel syndrome are reported to have a higher prevalence in children with IgAV/HSP despite resolution of acute flares and are associated with increased steroid use [94]. GI symptoms tend to occur within eight days of the appearance of the rash although they may precede the rash. Abdominal pain is seen in 60-70% of children with IgAV/HSP and is thought to be caused by submucosal bleeding and oedema [95]. A 2001 Spanish study [96] noted that 16.7% of affected children presented with abdominal pain as the solitary symptom; 7.6% presented with abdominal pain and a rash, and 2.6% with abdominal pain, rash and joint pains. Altogether, 70.5% of patients progressed to mesenteric ischemia, and 30.8% had evidence of GI bleeding. The commonest GI manifestation in childhood IgAV/HSP was intussusception. Although the prognosis of IgAV/HSP in children is good, adult onset IgAV/HSP often has a less favorable outcome [78]. In adults severe GI involvement, manifested by abdominal pain and bleeding [97-99], can be associated with a fatal outcome [100-102].

Predictive Markers in Gastrointestinal IgAV/HSP

Due to the high frequency of GI complications in IgAV/HSP and its potentially serious complications predictive markers have been sought. Serum amyloid A and faecal calprotectin have both been demonstrated to be significantly increased in GIT IgAV/HSP compared to non GIT IgAV/HSP [103, 104]. In a study of 70 patients with IgAV/HSP compared to controls serum amyloid A levels were significantly increased in cases of IgAV/HSP with GIT involvement but were not increased in renal or joint involvement [103]. Faecal calprotectin is a heterodimer of calcium binding proteins and elevated stool levels are associated with GI inflammation [105]. Faecal calprotectin is a useful screening tool in the diagnostic workup of inflammatory bowel disease [106]. In a study of 66 children with IgAV/HSP faecal calprotectin levels were found to be significantly different between groups with and without GIT involvement as well as being significantly different between groups with and without renal involvement [104].

Hematological ratios such as neutrophil-lymphocyte ratio and platelet-lymphocyte ratio have been associated with GIT IgAV/HSP and have been suggested as screening tools for GI involvement [107, 108].

Personalised medicine and genomics may be another approach to risk stratification of GIT IgAV/HSP. A Chinese study has reported an association between platelet-activating factor acetyl-hydrolase gene polymorphisms and GI bleeding [109]. None of these predictive markers are in routine use and further prospective studies with larger numbers are needed to confirm these findings before they could be used in routine clinical practice.

Treatment

Management of IgAV/HSP is largely supportive with administration of non-steroidal anti-inflammatory drugs and corticosteroids for severe abdominal pain and joint involvement.

There is no convincing evidence to suggest that early use of corticosteroids reduces the risk of renal involvement or acute GI complications [110]. Plasma exchange, IVIg, mycophenolate mofetil (MMF) and single dose cyclophosphamide have all been reported in the management of GIT IgAV/HSP [111-114]. In one case series of eight children with severe GIT IgAV/HSP involvement six responded to IVIg with two having a further relapse both of which responded to a second dose of IVIg [113]. Plasma exchange has also been reported to improve disease control in a case series [111]. The management of intussusception in children with IgAV/HSP often requires surgical correction [115].

ANCA-Associated Vasculitis

Epidemiology and Classification

The antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are a group of autoimmune inflammatory conditions comprising GPA, microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA) that predominantly affect small- to medium-sized blood vessels.

The individual annual incidence of the AAV is 10 to 20 per million population with a peak age of onset in the seventh and eighth decades [118]. Table 7 lists classification criteria for the AAV [13].

Clinical Features

The clinical features of AAV include constitutional symptoms including malaise, joint pains and weight loss, and other symptoms and signs depending on the extent of systemic involvement. The upper and lower airways, skin, peripheral and central nervous system, as well as the kidneys, are typically involved organ systems [119].

Table 7. Chapel Hill consensus conference on the nomenclature of systemic vasculitis: Definitions

Granulomatosis with polyangiitis (Wegener’s) (GPA)	Granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small to medium-sized vessels (e.g., capillaries, venules, arterioles, and arteries). Necrotizing glomerulonephritis is common
Microscopic polyangiitis (MPA)	Necrotizing vasculitis, with few or no immune deposits, affecting small vessels (i.e., capillaries, venules, or arterioles). Necrotizing arteritis involving small and medium sized arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs
Eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome) (EGPA)	Eosinophil-rich and granulomatous inflammation involving the respiratory tract, necrotizing vasculitis affecting small to medium-sized vessels, and associated with asthma and eosinophilia

*Adapted from reference 13.

Gastrointestinal Involvement

Abdominal pain and diarrhea in EGPA results from eosinophilic gastroenteritis and mesenteric vasculitis leading to bowel ulceration, ischemia, and perforation [12]. Up to one third of patients with EGPA manifest GI involvement with severe involvement associated with increased mortality [120]. The potential for GI involvement is varied and can include

upper or lower GI bleeding, perforation of the esophagus, stomach, small and large intestine, bowel ischemia, bowel obstruction secondary to stenosis, colitis and cholecystitis; the commonest manifestation is abdominal pain [16, 116].

GI involvement in GPA is reported in 0-26% of patients [117-122]. Seventy-one percent of GPA patients who ever have GIT involvement will have it at presentation [123]. Abdominal pain, diarrhea and blood loss are the commonest findings. More severe GI involvement can lead to ulceration, massive hemorrhage, ischemia of the small and large intestine or bowel perforation [3, 117, 124-128]. Isolated granulomatous pancreatic lesions, presenting with painless jaundice, pancreatitis and abdominal pain, have been reported in GPA, often being misdiagnosed radiologically as adenocarcinoma [129-131].

GI involvement is uncommon in MPA but can include hemorrhage, ulceration, and intestinal ischemia, in some cases as the presenting feature of disease [132-135]. Life-threatening gallbladder bleeding secondary to vasculitic involvement of the gallbladder has been reported [136].

The French Vasculitis Study Group (FVSG) developed a Five Factor Score (FFS; Table 8) to predict outcomes in patients with PAN and EGPA. The presence of one or more factors predicted a higher mortality [137]. In a retrospective analysis of 1108 consecutive patients with PAN, MPA, EGPA and GPA registered in the FVSG database; age >65 years, cardiac symptoms, gastrointestinal involvement and renal insufficiency, which were all independently associated with a higher five year mortality [138]. More recently, GIT involvement in EGPA was associated with more frequent relapses of disease but had no association with overall survival [139].

Treatment

Management of AAV entails induction of disease remission followed by maintenance treatment and therapy directed at disease relapses. Different immunosuppressive agents can be used depending on disease severity ranging from methotrexate for localized and early systemic disease, to a combination of high dose corticosteroids, plasma exchange and cyclophosphamide or rituximab in severe life-threatening disease [140]. Where GI involvement has been complicated by large GI hemorrhage definitive intervention in the form of transarterial embolization or surgical intervention has been successful [128, 141].

Table 8. The five factor score*

	Factor	Definition
1	Renal involvement	Proteinuria >1g/24 hours
2	Renal impairment	Serum creatinine >1.582 mg/dl
3	Gastrointestinal involvement	Presence of any of the following: bleeding, perforation, infarction pancreatitis
4	Central nervous system involvement	
5	Cardiac involvement	Presence of cardiomyopathy

*Adapted from reference 138.

SECONDARY VASCULITIDES

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a systemic autoimmune condition that can affect any part of the body and GIT. SLE can cause lupus mesenteric vasculitis which can affect any part of the GIT but shows a predilection for the superior mesenteric artery [3]. Mesenteric vasculitis is reported in 0.2-9.7% of patients with SLE and affects around 60% of SLE patients presenting with abdominal pain [142]. The underlying pathogenesis arises from complement activation, immune complex deposition and thrombotic processes [142]. Ultimately this leads to ulceration, bleeding, stricture formation, and perforation resulting from tissue ischemia and infarction [143-146]. Rarely mesenteric vasculitis can be the presenting feature of SLE [145, 146]. GI involvement in SLE is generally associated with increased mortality, in some case series being as high as 50% [147]. Mesenteric vasculitis is generally treated initially with high dose intravenous methylprednisolone then with a tapering regime of oral corticosteroid [148]. Cyclophosphamide has also been reported to be effective [149].

VARIABLE VESSEL VASCULITIS

Behçet Disease

Behçet disease is a non-specific necrotizing vasculitis that affects multiple organs and blood vessels of all sizes. It is classically characterized by oro-genital ulceration, ocular disease, skin lesions and a positive pathergy test. BD has a prevalence of between 3.8-420 per 100000 population, and is most prevalent in countries along the old Silk Road such as Turkey [150]. GI involvement occurs in 2.8 to 60% of patients [150]. GIT involvement frequently mimics inflammatory bowel disease with features such as diarrhea, abdominal pain, rectal bleeding and endoscopic findings including mucosal ulceration with a preference for the ileocecal region and esophagus [12]. The GIT features of BD arise from large vessel vasculitis resulting in ischemia and infarction or from neutrophilic phlebitis leading to mucosal ulceration [151, 152]. Ulceration is often deep and can penetrate through the bowel wall leading to perforation, hemorrhage and fistula formation [153-155]. The most common hepatic manifestation of BD is Budd-Chiari syndrome, seen in 1.3-3.2% of patients, which can result in portal hypertension, ascites, varices and liver failure [150]. It is associated with significant mortality, one study reporting a mean survival of 10.4 months [156]. Other rare GIT complications of BD include carotid-esophageal fistula, aortic pseudoaneurysm rupture into the colon and pancreatitis [157-159].

Disease Monitoring

Intestinal BD can be monitored clinically with the Disease Activity Index for Intestinal BD (DAIBD), categorizing activity as quiescent, mild, moderate and severe [160]. Fecal Calprotectin has been shown to be raised in intestinal BD and correlate with disease severity; this could potentially become a predictive marker for intestinal BD [161].

Treatment

There is no universally accepted treatment regime, however 5-ASA and sulfasalazine have been the mainstay of treatment for mild to moderate disease and corticosteroids for severe disease or to induce remission [162, 163]. Azathioprine, anti-TNF therapy, thalidomide and methotrexate have also been used successfully in intestinal BD [164-166]. For Budd-Chiari Syndrome the mainstay of management is cyclophosphamide and corticosteroids whilst anticoagulation remains controversial [167]. Surgical intervention is generally used for uncontrolled GI bleeding and perforation [168]. Endoscopic intervention has been used for ulcer related GI bleeding [169]. Large vessel involvement can be treated via open surgical techniques or via the endovascular approach [170].

Other Secondary Vasculitides

GI complications occur in other autoimmune conditions such as rheumatoid arthritis (RA) and mixed connective tissue disease (MCTD) due to secondary vasculitis. In patients with RA vasculitis, up to 38% of cases have involvement of the mesenteric vessels leading rarely to ischemic ulceration and bowel perforation [171]. Secondary vasculitis leading to GI involvement in MCTD is rare and occurs in the form of small and large bowel ulceration and perforation [172, 173] as well as fatal hemorrhage [174]. Vasculitic GI manifestations occur in patients with Hepatitis C virus infection, as well as non-infectious mixed cryoglobulinemic vasculitis, ranging from abdominal pain to GI bleeding, infarction, duodenitis, hepatic and mesenteric vasculitis and perforation. GI perforation is associated with increased mortality [175-177]. In addition, GI involvement has been described in vasculitis secondary to the drugs propylthiouracil [178], hydroxyurea [179] and cocaine [180], or infection associated with cytomegalovirus (CMV) [181].

Urticarial vasculitis (UV) is a rare small vessel vasculitis thought to be secondary to immune complex deposition into the blood vessel wall. Clinical features include urticarial rash, angioedema and tissue ischemia. The etiology of UV is usually idiopathic however; it can also be secondary to autoimmune disease, paraneoplastic disease, drug reactions and infections [182]. UV secondary to infection has been reported to present as circumferential duodenitis and ulceration secondary to duodenal ischemia [183].

Treatment-Related GI Side Effects

As the treatment of vasculitis often involves immunosuppression with drugs such as corticosteroids, cyclophosphamide, azathioprine, methotrexate and biological therapies such as rituximab, treatment-related morbidity of the GI tract must be considered. Reactivation of CMV can lead to GI inflammation in the context of immunosuppression. Symptoms of abdominal pain, diarrhea and bleeding, as well as endoscopic signs of erythema, nodules and ulceration, are non-specific but similar to those of vasculitis [12]. It is very important to secure the diagnosis with biopsy specimens and peripheral blood CMV viral load. CMV disease usually responds to anti-viral therapy. Candida involvement of the oral cavity and the esophagus is a recognized complication of high-dose corticosteroid treatment. British Society

of Rheumatology Guidelines for the management of ANCA-associated vasculitis recommend that anti-fungal prophylaxis should be considered in patients receiving immunosuppressive therapy [140, 179]. However, according to a recent meta-analysis there is no clear evidence that the use of topical anti-fungal preparations such as nystatin is effective in preventing fungal colonization and infection in immunosuppressed patients [184]. Finally, corticosteroids and NSAID can lead to gastroduodenal ulceration as well as small and large intestine enteropathy [12].

CONCLUSION

GI involvement in vasculitis largely reflects the size of the blood vessel involved. Large vessel involvement may lead to stenotic lesions manifesting as ischemia or infarction of large, but often unusual segments of the GI tract. Medium vessel involvement is typified by aneurysmal as well as stenotic disease that can produce ischemia or infarction and bleeding whilst small vessel disease can present with abdominal pain, patchy ulceration, infarction and bleeding as well as intestinal perforation. Hepatobiliary and pancreatic involvement can occur and represent common GIT manifestations in some vasculitides. Treatment is aimed at controlling the underlying vasculitic process with immunosuppression although open surgical or endovascular therapy is important in the management of mesenteric vasculitis. Severe gastrointestinal involvement in vasculitis is associated with a higher mortality.

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Chapter 210

RHEUMATOID ARTHRITIS VASCULITIS

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ABSTRACT

Rheumatoid arthritis is a systemic autoimmune disease characterized by inflammatory synovitis. The presence of fever, weight loss, digital infarcts, deep cutaneous ulcers, mononeuritis multiplex, peripheral gangrene, and other extra-articular complications suggest rheumatoid vasculitis. It is confirmed by the presence of necrotizing arteritis in a biopsy of involved skin, nerve or muscle tissue. Accurately recognized and properly treated with immunosuppressant and biological therapies, the morbidity and damage related to rheumatoid vasculitis can be mitigated. Thus, it is important to consider the diagnosis in any patient with RA in whom features emerge that could suggest the presence of arteritis. This chapter considers the epidemiology, clinical and laboratory manifestations, histopathology, and management of rheumatoid vasculitis.

Keywords: rheumatoid, vasculitis, classification, clinical, pathology, treatment

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by inflammatory synovitis. An estimated 1,293,000 adults ≥ 18 year of age in the United States have RA representing about 0.6% of the adult population. Rheumatoid vasculitis (RV) is suggested by the presence of fever, weight loss, digital infarcts, deep cutaneous ulcers, mononeuritis multiplex, peripheral gangrene, and other extra-articular complications extra-articular (ExRA) complications, including necrotizing vasculitis, the initial histopathologic manifestations of which are generally found in a biopsy of skin, nerve and muscle tissue in

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the majority of affected patients. While not strikingly different from classical or definite RA, those with RV have a reduced survival compared to the general population that is immediately evident and continues for up to six years [1, 2]. Vasculitis is a particularly significant ExRA manifestation, as it typically requires an escalation of immunosuppressive therapy at a time when patients may have already accrued significant disease-related tissue damage and therapy-related complications. It is important to consider RV because unrecognized and therefore untreated, the morbidity of this RA feature is substantial. This chapter discusses the epidemiology, clinical manifestations, histopathology, and treatment of RV.

HISTORICAL ASPECTS

The earliest reported patients with RA were children described in 1951 by Pirani and Bennett [3] with particularly severe RA progressing from childhood. The first patient was ill for four decades with numerous exacerbations and rare remissions with progressive limitation of the joints and a diagnosis of Still's disease that emerged into chronic disseminated RA before he died. Postmortem examination was notable for severe deforming RA and ankylosis, with left cerebellar hemorrhage, atrophy of bone, skin and muscle; healed glomerulonephritis and marked inflammatory spinal arachnoiditis with splenic follicular necrosis. The second patient presented at age 22 years after many years of disability unable to walk bedridden when he died. Postmortem examination was notable for severe deforming RA and ankylosis with widespread polyarteritis nodosa (PAN). A third patient developed progressive joint deformities from age 17 months before fatal pneumonia. Postmortem examination was notable for RA involving all joints and chronic aortitis. In the same year, Sokoloff and colleagues [4] reported arteritis in small muscular arteries of muscle biopsy tissue in 5 of 57 (10%) adults with RA, the histopathology of which included, mononuclear and polymorphonuclear cell adventitial infiltration, slight necrosis, endothelial cell injury, and secondary elastic involvement without vascular thrombosis or aneurysm formation, and frequent cardiac complication manifesting as pericarditis. The incidence of arteritis is estimated to occur overall in about 8.8% of patients with RA. These observations were followed by 10 additional patient descriptions in 1957 by Sokoloff and Bunim [5] of arteritis in patients with RA. The age range was 30 to 65 years (mean 47 years), at presentation, with a duration of arthritis of 6 months to 30 years (mean 9 years). The diagnosis of RV was established at postmortem examination in five patients and by biopsy of muscle, subcutaneous nodules, and synovial tissue antemortem in five patients. Postmortem examination showed widespread arteritis in three patients, with isolated involvement of the testis in one patient, and the sciatic nerve and coronary artery in another patient. Among the five patients who were diagnosed antemortem, arteritis was detected in muscle biopsy tissue in two patients, in early subcutaneous nodules in two others, and in synovial tissue of another patient. In contrast to the earlier study conducted by the same author of vasculitic muscle biopsy lesions in RA [4], the pathological features of the subsequent 10 patients [5] resembled PAN. Two additional patients with RV were mentioned after publication of the latter study by the same authors [5], both with necrotizing arteritis, in which one was associated with arteritis of the pancreas, and another with isolated peripheral nerve vasculitis (PNV).

TERMINOLOGY AND NOSOLOGY

In 2010, the American College of Rheumatology (ACR), and the European League Against Rheumatism Collaborative Initiative jointly published RA classification criteria [6] that replaced the 1987 Revised ACR criteria for RA [7], defining definite RA by the presence of synovitis in at least one joint, the absence of a better alternative diagnosis, and achievement of a threshold score from the individual scores in four domains in involved joints, in addition to a compatible symptom duration, serological abnormalities, and increased acute-phase responses. This represented a focus upon features associated with earlier disease that was associated with persistent and erosive disease rather than late-stage features thereof. The Revised 2012 Chapel Hill Consensus Conference (CHCC) [8] provides a useful nosology for the vasculitides, categorizing RV as a vasculitis associated with systemic disease. Scott and Bacon [9] described the response to early treatment with intravenous cyclophosphamide and methylprednisolone compared to conventional drug regimens, defining eligible patients as those meeting one or more criteria of the following criteria including, MNM, peripheral gangrene, biopsy evidence of acute necrotizing arteritis plus systemic disease manifested by fever and weight loss; and deep cutaneous ulcers or active ExRA disease if associated with typical digital infarcts or biopsy tissue evidence of vasculitis (Table 1). Overall, the combination of intravenous cyclophosphamide and methylprednisolone resulted in more frequent healing of vasculitic lesions including leg ulcers and neuropathy, and a lower mortality than did other conventional treatments.

Table 1. Scott and Bacon criteria for RV [9]

Mononeuritis multiplex or peripheral neuropathy
Peripheral gangrene
Biopsy evidence of acute necrotizing arteritis plus systemic illness such as fever or weight loss
Deep cutaneous ulcers or active extra-articular disease (pleurisy, pericarditis, scleritis) if associated with typical digital infarcts or biopsy evidence of vasculitis

EPIDEMIOLOGY

In a population-based study of patients living within the Norwich Health Authority in the United Kingdom from 1988 to 1994, the overall annual incidence rate of RV was 12.5 per million (95% CI 8.5 to 17.7) [10]. In a retrospective cohort study of hospitalized RA patients in Malmo, Sweden, from 1990 to 1994, the annual incidence rate of RV was calculated to be 7.1 per million (95% CI 2.7 to 16.1) [11]. This annual incidence rate may underestimate the true incidence rate, as not all patients with RV are hospitalized. There are conflicting data as to whether the incidence of RV has changed or remained stable over recent decades. However, the preponderance of data does suggest that the incidence of RV may in fact be decreasing, perhaps due to improvements in therapy for RA. In an incident RA cohort in Olmsted County, Minnesota, from 1955 to 1994 [12], the 10-year cumulative incidence rate of severe RV, defined as major cutaneous vasculitis and neuropathy due to vasculitis, remained stable by decade of RA diagnosis (2.1% for 1955-1964, 3.5% for 1965-1974, 2.5% for 1975-1984, 4.3% for 1985-1994, p -value = 0.72). However, looking at more recent data

from Olmsted County, Minnesota [13], the 10-year cumulative incidence of RV decreased from 3.6% in the 1985-1994 RA cohort to 0.6% in the 1995-2007 RA cohort on ($p = 0.011$). In a retrospective study of the prevalence of RV among US veterans [14], the prevalence of RV decreased significantly between 2000 and 2001 for both inpatient and outpatient US veterans. The prevalence decreased by 31% (41/1000 RA cases to 28/1000 RA cases, $p < 0.003$) among ambulatory US veterans and by 53% (32/1000 RA cases to 15/1000 RA cases, $p < 0.001$) among hospitalized US veterans. Moreover, an extension of the Norwich Health Authority studies from 1988 to 1994 [10] to 2002 showed a decline in the annual incidence rate of RV over the period 1988 to 2002 [15]. The annual incidence rate of RV in 1988-1992 was 11.6 per million (95% confidence interval [CI] 7.4 to 17.0); in 1993-1997 it was 8.9 per million (95% CI 5.3 to 13.6); and in 1998-2002 it was 3.6 per million (95% CI 1.6 to 7.1) [15]. The overall annual incidence rate of RV during the time period 1988 to 2002 in the former Norwich Health Authority in the UK was 7.9 per million (95% CI 5.9 to 10.4) [15]. Data from a population-based database of hospitalizations in California compiled by the California Office of Statewide Health Planning and Development indicated that the risk of hospitalization for RV was 33% lower in the period 1998 to 2001 than 1983 to 1987 (adjusted rate ratio 0.67, 95% CI 0.61–0.74; $p = \text{value} < 0.0001$). Adjusting for age, sex, and ethnicity, the rate decreased from 170 per 100,000 persons with RA in 1983 to 99 per 100,000 persons with RA in 2001 [16]. A plausible explanation for the declining incidence of RV include more aggressive early therapy and improved therapeutic armamentarium including the use of biologics for treating RA in general. Conversely, there have been rare case reports of vasculitis occurring in the context of therapy with TNF inhibitors, although the magnitude of that complication of anti-TNF therapy in patients with RA is very low [17–21].

Patients who develop RV typically have longer-standing RA lasting 10 years or more [22, 23]. In a retrospective study of 50 patients with RV, the mean duration of RA prior to the onset of RV was 13.6 years [24]. Although RA more frequently affects women than men [22], men are more likely to develop RV than women with RA [10, 23]. In a population-based study of patients living within the Norwich Health Authority in the United Kingdom from 1988 to 1994, the annual incidence rate of RV in men was 15.8 per million (95% CI 9.5 to 24.7) compared to 9.4 per million (95% CI 4.8 to 16.4) in women [10]. Patients with erosive, seropositive disease are also more likely to develop RV than those without destructive disease who are seronegative [23, 25]. Moreover, the presence of certain other extra-articular manifestations of RA, such as rheumatoid nodules and Felty syndrome, has been associated with the development of RV [23, 25, 26]. Smoking is a major risk factor for later development of both RA in general and RV in particular [27–29]. In a case-control study of 45 RA patients with RV and 211 RA patients without RV, a significantly greater percentage of RV patients were current smokers ($p\text{-value} < 0.02$) [28]. In a case-control study of patients with severe RA with and without ExRA from the Mayo Clinic in Rochester, Minnesota, and 3 RA cohorts in Sweden, smoking was an independent predictor of RV in a multivariate mode [29].

An intriguing observation from a large case-controlled study of RV reported from the Mayo clinic suggested that hydroxychloroquine and low dose aspirin use in patients with RA might be protective against the development of RV, perhaps related to the benefits of those interventions with regard to vasculopathy and atherosclerosis [30].

Genetic factors likely also contribute to the development of RV. In a meta-analysis of individual patient data from 1,568 patients with RA, 129 of whom had RV, those with RV

were significantly more likely than others without RV to have a “double dose” of the shared epitope: HLA-DRB1*0401/*0401 (OR 6.2, 95% CI 1.01–37.9), *0401/*0404 (odds ratio [OR] 4.1, 95% CI 1.1–16.2), and *0101/*0401 (OR 4.0, 95% CI 1.4–11.6) [31]. In a case-control study of 46 patients with RV and 178 RA without ExRA from the Mayo Clinic and Sweden, the HLA-C3 allele was positively associated with RV (allele frequency 0.411 in RV patients versus 0.199 in RA controls without ExRA (p-value < 0.001) [29].

CLINICAL PRESENTATION

As mentioned, RV often presents relatively late in the course of the disease and can occur at a time when articular disease activity is not high. Rheumatoid vasculitis can manifest in a variety of ways including, deep cutaneous ulcers [32], digital gangrene [33], nail fold infarcts [34], MNM [35], and scleritis [36, 37]. Systemic vasculitis commonly extends beyond the peripheral nervous system (PNS) and skin, to internal organs including, the stomach, heart, intestine, pancreas, kidney, and gallbladder [22, 38–40]. A postmortem series of 81 Japanese patients with RA showed histologically evident necrotizing arteritis in 25 (30.8%) patients; however, there was no mention of frequency of clinically significant antemortem vasculitic disease. Therefore, the true prevalence of clinically significant arteritis in this cohort might have been significantly less than the 30.8% stated.

Scott and colleagues [24] reported the clinical features of 50 patients with RV based clinically on the development of deep cutaneous ulceration, acute peripheral neuropathy, mononeuritis or MNM; peripheral gangrene or severe systemic disease in the presence of typical digital or nail fold infarcts. So defined, the clinical manifestations of RV in the 50 patients included cutaneous features of digit infarcts, ulcerations, purpura, and gangrene noted in 44 (88%) patients; rheumatoid nodules in 43 (86%); systemic features of weight loss, hepatomegaly and splenomegaly in 41 (82%); sensory or motor neuropathy in 21 (42%); and cardiac involvement. This included pericarditis, arrhythmia, aortic incompetence, and myocardial infarction in 17 (34%); pulmonary involvement including fibrosing alveolitis, pleurisy, effusions and lung nodules in 17 (34%); renal involvement due to amyloid, chronic renal failure, proteinuria and hematuria in 12 (24%); ophthalmic manifestations of scleritis in seven (14%); and gastrointestinal features in five (10%). An open study by Scott and Bacon⁹ of 45 RV patients analyzed treatment with intravenous cyclophosphamide plus methylprednisolone given (21 patients) versus conventional drug regimens including oral azathioprine, prednisolone, D-penicillamine, chlorambucil, oral cyclophosphamide, prostaglandin infusion, and intramuscular methotrexate, in whom the diagnosis of vasculitis was noted in 57% of the former group versus 46% of the latter. In this cohort of severe RV receiving intermittent bolus intravenous cyclophosphamide plus methylprednisolone versus other modalities, rheumatoid nodules were seen respectively in 90% and 71% of patients, nail infarcts in 78% and 70% of cases, neuropathy in 52% and 25%, leg ulcers in 43% and 33%, cardiac involvement in 34% and 18%, peripheral gangrene in 14% and 8%, and ophthalmic manifestations in 14% and 12%. There was more severe initial disease, a higher incidence of neuropathy, and frequent evidence of necrotizing arteritis on biopsy in the former group compared to the latter.

Puéchal and colleagues [41] studied RV among 32 patients defined by the RA and histologically proven necrotizing vasculitis in cutaneous nerve or muscle biopsy tissue specimens respectively in 4 (14%) and 10 (36%) of patients, and together in 14 (50%). The clinical presentation of their patients included 5 (14%) patients with mononeuritis, 18 (51%) patients with MNM, and 12 (34%) patients with distal symmetrical sensory or sensorimotor neuropathy. Cutaneous lesions were seen in 12 (38%) patients including, purpura in nine, ulcers in six, nail-edge infarcts in four, livedo in four, gangrene in two, and one patient each with maculopapular rash or bullous rash. Cardiac involvement was evidenced in four (12.5%) patients including, pericarditis, and fatal rupture of a small mitral valve, congestive heart failure, and myocardial infarction. Eye involvement was noted in two (6%) patients including scleritis and scleromalacia. Life threatening gastrointestinal involvement was noted in 2 (6%) patients due to small bowel perforation and necrosis by endarteritis, accompanied by acute abdomen with sepsis and gangrenous toes and cutaneous ulcers, despite treatment with high-dose corticosteroids and cyclophosphamide therapy,. Altogether, among the 32 patients, all had evidence of PNV that was accompanied by cutaneous vasculitic involvement in 12 patients, 4 of whom had cardiac involvement, and 2 with concomitant vasculitic involvements of nerve, skin, and eye. Four patients had PNV and kidney involvement, and two others had lung involvement.

Vollerstein and colleagues [1] studied 52 patients with RV at the Mayo Clinic from 1974 to 1981 who developed clinical vasculitis evidenced by classic ischemic skin lesions, MNM, or a positive tissue biopsy in comparison to population controls. The initial manifestation of vasculitis was seen in skin in 26 (50%) patients; nerve in 20 (38%) patients, or both in 3 (6%) patients. Serositis, pulmonary or renal manifestations were present each in six patients (12%); and three patients (6%) had eye findings. Mononeuritis presented in 2 (4%) patients; while mononeuritis multiplex involved two nerves in 9 (12%) patients; three nerves in 5 (10%) patients, and four nerves altogether in four (13%) patients. More than 90% of tissue biopsy specimens revealed vascular necrosis and inflammation.

Despite advances in therapy of RA in general, the morbidity and even mortality of RV remains high. A study from the UK reported a mortality rate as high as 60% at 5 years in patients diagnosed with RV despite aggressive therapy usually with cyclophosphamide and high dose corticosteroids. Organ damage and infection were the leading causes of death in this cohort [42].

SEROLOGICAL STUDIES

Among 50 patients with RV described by Scott and colleagues [24], IgM rheumatoid factor (RF) was positive in 94% of patients, the C1q assay was abnormal in 65% of patients, serum antinuclear antibody (ANA) titers were raised in 59% of patients; immune complex assay was positive in 50% of patients overall; with abnormally reduced serum C3 and C4 complement levels respectively in only 0.73% and 0.2% of patients. Serological findings were not mentioned in a report by Scott and Bacon [9] of 45 patients with RV treated with cyclophosphamide and methylprednisolone or other regimens.

In the series of 32 patients with RV described by Puéchal and colleagues [41], in whom vasculitis was obtained in cutaneous nerve or muscle biopsy tissue specimens, articular

erosions were noted in all patients, RF seropositivity was demonstrated in 97% of patients, ANA antibody elevation was noted in 27%, decreased C4 complement titers in 62%, circulating immune complexes in 66%, and cryoglobulins in 13% of patients so studied. At onset of the disease, the erythrocyte sedimentation rate (ESR) was a mean of 80 mm/hour. Hepatitis B surface antigen was not detected in any of the 25 sera so studied, however one patient tested positive for hepatitis B surface antibody; there was no data available for hepatitis C seropositivity.

In the series of 52 patients with RV summarized by Vollerstein and colleagues [1], the ESR was elevated in 44 of 51 (86%) patients; low titers of ANA were noted in 15 of 43 (35%) patients; cryoglobulins in 1 of 28 (4%) patients; immune complexes in 3 of 8 (38%) patients; and C3 and C4 complement was abnormally reduced in 1 of 31 (3%) and 7 of 29 (24%) patients so studied. There is no data on the serological evaluation of the subjects reported by Scott and Bacon [9].

Anti-cyclic citrullinated peptide autoantibodies (anti-CCP) are commonly found at high titers in those with RV, but their absence does not preclude the diagnosis [43]. Anti-neutrophil cytoplasmic antibodies (ANCA) are detectable in greater than a third of patients, generally in a perinuclear (pANCA) pattern. More specific enzyme immunoassays however typically do not reveal the presence of anti-proteinase 3 (PR3) or anti-myeloperoxidase (MPO) antibodies [30, 44].

HISTOPATHOLOGY

RV primarily affects small- and medium-sized vessels [23, 45]. Small-vessel disease may histologically resemble a hypersensitivity vasculitis, whereas medium-vessel disease typically resembles PAN [46]. A given patient with RV may have demonstrable vasculitic involvement of both small- and medium-vessels, with histopathological features of vascular necrosis, occlusion, and tissue ischemia. In a series of 50 patients described by Scott and colleagues [24], vasculitis was noted in 28 patients including leukocytoclastic vasculitis (LCV) of dermal and sub-dermal capillaries was seen in 16 of 19 skin biopsies performed for cutaneous rashes; and necrotizing vasculitis involving small arteries was noted from rectal biopsy tissue in 8 patients, renal biopsy tissue in 2 patients, ovarian and appendix specimens in one patient, and in the coronary artery at postmortem examination in another patient.

Among fifteen patients who died with RV, postmortem examination in seven patients showed active vasculitis in five, three of which showed systemic vasculitis; and one each with vasculitis limited to the coronary arteries, peripheral nerves and muscle, or skin; and inactive vasculitis in another patient. One remaining patient failed to show vasculitis at postmortem examination. In the later series by Scott and Bacon [9], the clinical diagnosis of RV was confirmed histologically in 57% of the patients treated with cyclophosphamide and methylprednisolone compared to 46% of those treated with other conventional therapies. Biopsy tissue specimens of 10 skin rashes showed LCV capillaritis among four patient receiving cyclophosphamide and methylprednisolone, as did six patients receiving other treatments. Deep rectal biopsy showed necrotizing arteritis in nine of 18 (50%), patients who received cyclophosphamide and methylprednisolone compared to four of 17 (24%) patients in the group receiving other treatments.

In the series of 32 patients with RV and PNS, vasculitis described by Puéchal [41], vasculitis was found in nerve biopsy tissue with the same frequency among those with sensory or predominantly sensory neuropathy as among others with predominantly motor findings (67% versus 64%). However, vasculitic nerve lesions were no more frequent in the patients with MNM than those with distal symmetrical sensory or sensorimotor neuropathy (59% versus 78%). Among 44 nerve fascicles from 28 nerve specimens, Wallerian degeneration was noted in three-quarters of fibers compared to segmental demyelination in 1% of fascicles. There was a close correlation between the severity of the clinical neuropathy and degree of axonal loss or fiber degeneration.

Vollerstein and colleagues [1] summarized a series of 52 patients with RV defined by classical ischemic skin lesions including ulceration, gangrene, purpura or petechiae, in the absence of significant atherosclerosis; MNM, or a positive biopsy tissue specimen. Altogether, 26 patients underwent biopsies of skin, nerve or other tissues that showed vascular necrosis and inflammation in more than 90% of specimens. Vasculitis was noted in 17 of 25 (68%) skin biopsy tissues, and in 5 of 25 (25%) nerve biopsy tissues specimens, in addition to one patient each with histologic evidence of vasculitis of the kidney, gastrointestinal tract, and muscle tissues; rectal biopsy tissue specimens were not sampled for vasculitis.

PROGNOSIS

Using actuarial methods and then current ARA criteria for RA [47], Vollerstein and colleagues¹ noted decreased survival of patients with RV when compared to age- and sex-matched Upper Middle Western general population. The clinical factors that predict decreased survival in RV using an univariate proportional-hazards model in older patients includes failure to receive previous non-steroidal anti-inflammatory drug (NSAID) therapy, previous administration of cytotoxic immunosuppressive agents, a higher dosage of corticosteroids at diagnosis, the decision to continue or initiate corticosteroids, and an abnormal urinary sediment ($p < 0.05$). Increasing referral distance, concomitant comorbid disease, hypogammaglobinemia, and hypoalbuminemia also confer a trend toward decreased survival. The authors did not demonstrate a statistically significant association between decreased survival and sex, type of skin lesion, MNM or number of extremities involved, a positive biopsy, initial manifestation of vasculitis, duration of RA, activity of RA, ExRA manifestations or subcutaneous nodules, previous treatment, presence of concentration of RF, C3 and C4 levels, anemia, thrombocytosis, ESR, and abnormal chest radiograph.

Voskuyl and colleagues [48] studied the mortality of 61 RV patients in comparison to 244 RA controls. The unadjusted risk of death (HR) in RV patients compared with RA controls was 1.65 (95% CI 1.05-2.58). After adjustment for prognostic factors, the HR was reduced to 1.26 (95% CI 0.79-2.01), mainly due to removal of the effects of age and sex. There was no excess mortality seen in RV patients with severe organ involvement when compared with RV patients without severe organ involvement, although the former patients were treated more often with cytostatic and immunosuppressive drugs. Infection was the main cause of death in RV patients and cardiovascular disease in the RA controls. Vasculitis was reported as the cause of death in only one RV patient. After allowance for general risk factors

such as age and sex, there remained only a slight excess mortality in RV patients compared with RA controls.

TREATMENT

Isolated nail fold lesions tend to be benign and typically do not require an escalation of immunosuppressive therapy [34].

Cyclophosphamide

Cyclophosphamide in combination with high dose corticosteroids is the mainstay of therapy for RV [49]. An open label study compared intravenous cyclophosphamide plus intravenous methylprednisolone in 21 patients, with a variety of other treating modalities including azathioprine, prednisolone, D-penicillamine, chlorambucil, oral cyclophosphamide, prostaglandin infusion and intramuscular methotrexate in 24 patients, noting that those receiving intravenous cyclophosphamide plus intravenous methylprednisolone were more likely to experience healing or significant improvement in nail infarcts, leg ulcers, sensory neuropathy, and mononeuritis [9]. Patients receiving intravenous cyclophosphamide plus intravenous methylprednisolone were also less likely to have relapses of their RV or to suffer serious complications such as limb amputation or death. Patients receiving intravenous cyclophosphamide plus intravenous methylprednisolone did better than those receiving the other medications despite more serious disease at baseline. In a case series of 16 RA patients with necrotizing scleritis or peripheral ulcerative keratitis refractory to aggressive therapy with topical and systemic steroids and NSAID, 8 (50%) patients ultimately responded to cyclophosphamide, 6 (38%) eventually responded to methotrexate, and 1 (6%) patient eventually responded to cyclosporine A [37]. In addition to medical therapy, 9 (56%) patients with peripheral ulcerative keratitis also required surgical therapy, including ulcer debridement, conjunctival resection, application of cyanoacrylate tissue adhesive, and tarsorrhaphy. Abel and colleagues [50] reported a series of 5 patients with RV who clinically improved following treatment with oral cyclophosphamide. There are patients in whom cyclophosphamide was ineffective and those with contraindications to this particular therapy. In such instances, treatment with other medications, such as tumor necrosis factor (TNF) inhibitors [45, 51] and rituximab [52, 53], has been attempted. However, evidence to date is limited to case reports and case series.

Rituximab

Given its proven efficacy of rituximab in the treatment RA and diverse small vessel vasculitides (SVV) including ANCA associated vasculitis and cryoglobulinemic vasculitis, rituximab is an appealing candidate biologic for the treatment of RV. A retrospective study of 17 patients with RV from the Autoimmunity and Rituximab Registry reported that 12 (71%) patients who achieved a complete response, while 4 (23%) patients showed a partial response

after six months of treatment with rituximab [54]. Twelve months after therapy, 14 (82%) patients achieved sustained complete responses. Hellmann and colleagues [52] report two patients with RV-associated cutaneous ulcers refractory to corticosteroids and disease modifying anti-rheumatic drug therapy but successfully treated with rituximab. Maher and Wilson [53] reported a patient with RV-associated foot drop and sural nerve necrotizing vasculitis in who foot drop improved following multiple courses of rituximab therapy.

Tumor Necrosis Factor Inhibitors

Unger and colleagues [51] reported three patients with RV who developed treatment-limiting adverse effects or a poor clinical response to cyclophosphamide and a later beneficial response to infliximab. Puéchal and colleagues [45] performed a retrospective study of nine patients with RV treated with etanercept or infliximab after failing to respond to treatment with a mean cumulative dose of 8.4 g (range 4 to 15 g) of cyclophosphamide over a mean of 6.2 months (range 3 to 10 months) and high dose corticosteroids. Of the nine patients, 5 developed a complete remission and experienced partial remission after a mean of 28.6 weeks of therapy. Two patients withdrew due to adverse effects and one patient never achieved remission. Two of the patients who responded to TNF inhibitory therapy developed four cutaneous relapses. In 2 patients with RV studied in an open-label pilot study of infliximab [55], both of whom were previously refractory to cyclophosphamide, one demonstrated complete responsiveness to infliximab and another showed a partial response. Garcia-Porrúa and Gonzalez-Gay [56] reported a patient with refractory RV-associated MNM and sural nerve biopsy tissue specimen that revealed necrotizing vasculitis with fibrinoid necrosis in whom foot drop improved after treatment with methotrexate and infliximab. Van der Bijl and colleagues [57] described a patient with RV characterized by fibular mononeuropathy in who foot drop improved following the addition of infliximab to the regimen of methotrexate.

Azathioprine

Azathioprine was evaluated in RV in a small randomized, double blind, placebo-controlled study of 15 patients. No differences between the azathioprine-treated and the placebo-treated groups at a mean duration of 27 weeks of therapy [58] were recognized. In a randomized non-blinded trial in 19 patients with RV limited to cutaneous involvement eight patients were treated with azathioprine and prednisone versus continuation of the existing therapeutic regimen in 11 patients, all taking non-steroidal anti-inflammatory drugs including hydroxychloroquine (one patient), aurothioglucose or gold thioglucose, (two patients) and one each of penicillamine, and one sulfasalazine. Although patients treated with azathioprine and prednisone show greater improvement at 3 months, there appeared to be no significant difference in clinical or laboratory parameters between the two groups at 18 months, [50, 59].

Other Biologics

There are case reports suggesting that tocilizumab, an anti-interleukin (IL)-6 strategy proven effective in giant cell arteritis (GCA), a large vessel vasculitis may be of value in patients with refractory RV [60–62]. Successful treatment of RV with abatacept, a co-stimulatory molecule blocker has been described, and abatacept has been of interest in the treatment of granulomatosis with polyangiitis (GPA), another SVV. Not surprisingly however, given the rarity of the condition and the more common use of cyclophosphamide and now rituximab in patients with severe disease, our understanding of the role of some of these newer biologics in the treatment of RV remains limited.

CONFLICTS OF INTEREST

The Authors have not conflicts of interest to report.

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Chapter 211

DERMATOLOGIC ASPECTS OF SYSTEMIC VASCULITIS

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ABSTRACT

Systemic and localized vasculitis affects the skin and subcutis due to their large vascular bed, as well as, hemodynamic factors such as stasis in lower extremities, and environmental influences as occurs in cold exposure. The initial cutaneous manifestations of vasculitides include diverse and dynamic patterns of discoloration, swelling, hemorrhage, and necrosis. One-half of affected patients present with localized, self-limited disease to the skin without any known trigger or associated systemic disease, known as idiopathic cutaneous leukocytoclastic vasculitis. Cutaneous vasculitis manifests as urticaria, erythema, petechiae, purpura, purpuric papules, hemorrhagic vesicles and bullae, nodules, livedo racemosa, deep punched-out ulcers and digital gangrene. Skin biopsy and dermatopathology contribute relevant information however; they require correlation with the clinical history, physical exam and laboratory findings in order to reach an accurate diagnosis in a given affected patient.

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INTRODUCTION

Systemic and localized vasculitis affects the skin and subcutis due to their large vascular bed, as well as hemodynamic factors such as stasis in lower extremities, and environmental influences as occurs in cold exposure. The initial cutaneous manifestations of vasculitides include diverse and dynamic patterns of discoloration, swelling, hemorrhage, and necrosis. One-half of affected patients present with localized, self-limited disease to the skin without any trigger or associated systemic disease, known as idiopathic cutaneous leukocytoclastic vasculitis (LCV) [1]. Cutaneous vasculitis manifests as urticaria, erythema, petechiae, purpura, purpuric papules, hemorrhagic vesicles and bullae, nodules, livedo racemosa, deep punched-out ulcers and digital gangrene [2]. Skin biopsy and dermatopathology contribute relevant information however; they require correlation with the clinical history, physical exam and laboratory findings in order to reach an accurate diagnosis in a given affected patient. The vasculitides that present primarily and within their course with cutaneous manifestations are summarized in Table 1. This chapter is a comprehensive overview of the clinical dermatologic aspects of primary and secondary vasculitides.

GENERAL CONCEPTS AND NOSOLOGY

The skin receives its blood supply from penetrating vessels from within the underlying subcutaneous fat, which contains medium sized vessels [3]. Branches of medium-sized vessels give rise to two vascular plexuses that intercommunicate, the deep vascular plexus lying at the interface between the dermis and subcutaneous fat, and the superficial plexus located in the superficial aspects of the reticular dermis. Further, distally, they supply the papillary dermis by forming capillary loops. These loops are composed of terminal arteriole, capillaries (arterial and venous), and post-capillary venules (Figure 1). The type of cutaneous lesions closely correlates with the size of vessel affected by vasculitis. For example, in cutaneous LCV, immune complexes (IC) deposition and inflammation mainly target post-capillary venules giving rise to small palpable purpura (Figure 2). Inflammation that targets arterioles and arteries results in large purpuric lesions with irregular borders (Figure 3) since these vessels supply multiple dermal papillae. Ulcers, nodules, pitted scars, and livedo reticularis are associated with arterial muscular vessel involvement, which is localized to the dermal-subcutis interface or within the subcutis [4]. Table 2 reviews the size of vessel affected with corresponding clinical presentation. The 2012 Revised Chapel Hill Consensus Conference (CHCC) [5] and most recent dermatological addendum for the 2012 CHCC [6] serves as a guide for the nosology and categorization of diverse forms of vasculitis based upon the vessels involved. The Pediatric Rheumatology European Society (PRES) and the European League against Rheumatism (EULAR) and the Pediatric Rheumatology International Trials Organization (PRINTO) proposed nosology and classification for several of the primary pediatric vasculitides based upon vessel size [7, 8] similar to the CHCC nomenclature [5]. The clinicopathological aspects of primary and secondary vasculitides are extensively reviewed in Chapter 2 of this text.

Table 1. Percentage of patients with systemic vasculitis presenting primarily and within their course of disease with cutaneous manifestations

Type of Vasculitis	Cutaneous manifestation as first clinical presentation	Cutaneous manifestations during their course of disease	Most common cutaneous manifestation
Microscopic polyangiitis	4 - 14%	44 - 62.4%	Purpura
Granulomatosis with polyangiitis	< 1-21%	10 - 40%	Purpura
Eosinophilic granulomatosis with polyangiitis	14%	40 - 81%	Purpura
Polyarteritis nodosa	11%	25 - 60%	Purpura
Connective tissue diseases	-	12%	Purpura*
Giant cell arteritis	< 1%	-	Scalp tenderness/blanching
Levamisole-induced vasculitis	-	60%	Purpura involving the ears
Henoch-Schönlein Purpura	-	100%	Purpura
Cryoglobulinemic vasculitis	-	100%	Purpura

* Except for Lupus Vasculitis which most commonly presents as erythematous punctate lesions of the fingertips.

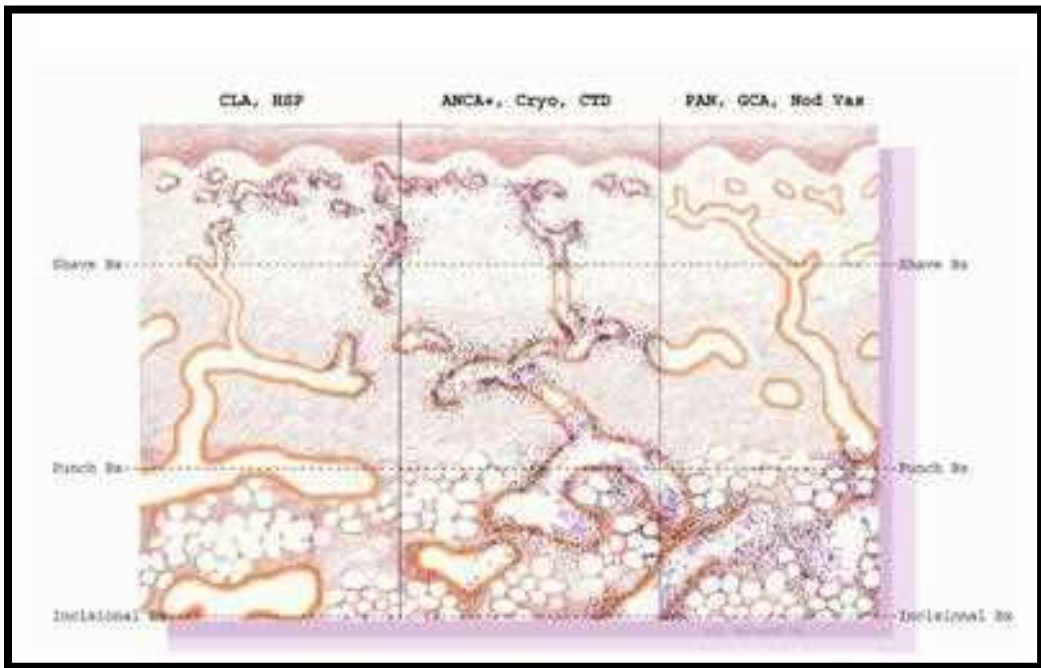


Figure 1. The size of vessel involvement is one histologic feature coupled with the predominant inflammatory cell that allow for classification of most common forms of cutaneous vasculitis. In general, HSP/IgAV cutaneous leukocytoclastic vasculitis affects superficial skin vessels whereas polyarteritis nodosa, nodular vasculitis and giant cell arteritis affect deep muscular vessels found at the dermal-subcutis interface and within the subcutis. Most other forms of vasculitis such as cryoglobulinemic vasculitis and ANCA-associated vasculitis that affect multiple visceral organs more diffusely affect the vascular tree. The depth and type of skin biopsy greatly influences the diagnostic yield.



Figure 2. Typical palpable purpura, some with central necrosis in a patient with idiopathic cutaneous vasculitis of the legs.



Figure 3. Large purpuric lesions with irregular borders affecting the left wrist of a patient with idiopathic systemic vasculitis.

Table 2. Clinical manifestations of vasculitis based on vessel size affected

Large vessel	Medium vessel	Small vessel
Limb claudication	Subcutaneous nodules Nodular erythema	Purpura, infiltrated/elevated erythema
Asymmetric blood pressure	Ulcers	Urticaria
Absence of pulses	Livedo reticularis	Vesiculobullous lesions
Aortic dilation	Pitted palmar/digital scars	Splinter Hemorrhages
Bruits	Digital Gangrene	Scleritis, episcleritis, uveitis
	Mononeuritis	Palisaded neutrophilic granulomatous dermatitis*
	Aneurysms	Glomerulonephritis
	Infarct	Gastric colic
	Hypertension (renal artery)	Pulmonary hemorrhage

Constitutional symptoms: fever, weight loss, malaise, arthralgias and arthritis are common to vasculitic syndromes of all vessel sizes

* Extravascular necrotizing granuloma. Small vessel neutrophilic vasculitis is frequently seen in the vicinity of granulomas and necrosis

Table adapted from Carlson et al. [15].

EPIDEMIOLOGY

The incidence of cutaneous vasculitis ranges from 15.4 to 29.7 cases per million per year, affecting adults more than children of all ages, with slight female predominance, and up to 90% of children diagnosed with Henoch–Schönlein purpura (HSP/ IgA vasculitis [IgAV]) [1]. The mean age at presentation of adult vasculitis is 47 years, while amongst children the mean age at onset is 7 years [1, 4]. The onset of vasculitis after exposure to a trigger such as a drug or infection is 7 to 10 days. A mean interval of 6 months occurs between the onset of symptoms and signs of systemic disease and the onset of secondary cutaneous vasculitis. Almost one-half of patients presenting with cutaneous vasculitis have disease localized to the skin without an attributable cause, trigger or associated systemic disease, referred to as idiopathic LCV [1]. The remainder of localized cutaneous vasculitis cases are attributed to recent infection and drug ingestion. LCV that results from drugs or infection is termed hypersensitivity or allergic vasculitis. The antinuclear cytoplasmic antibody (ANCA)-associated vasculitides (AAV) vasculitis syndromes include eosinophilic granulomatosis with polyangiitis (EGPA) (previously known as Churg-Strauss Syndrome [CSS]), microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA) (previously known as Wegner granulomatosis [WG]) may first present with cutaneous vasculitis [9]. The onset of cutaneous vasculitis may be an indication of secondary vasculitis in association with connective tissue disease (CTD) such as systemic lupus erythematosus (SLE) vasculitis (LV) [10], and rheumatoid arthritis (RA) related vasculitis (RAV) [11].

The evolution of cutaneous vasculitis occurs in three phases, (a) single acute, self-limited episode that resolve in ≤ 6 months in association with drug exposure or an infectious trigger so noted in 60% of patients; (b) relapsing disease with symptom-free periods usually found in patients with HSP/IgAV and cryoglobulinemic vasculitis (CV) so noted in 20% of patients; and (c) a chronic, unremitting disease most often associated with primary systemic vasculitides and secondary vasculitides in association with CTD, CV, or malignancy altogether in about 20% of patients [1]. The duration of vasculitis ranges from 1 week to 318 months, with mean and median durations of 28 months and 3.7 months, respectively. Less than 20% of cutaneous vasculitis cases have extracutaneous or visceral vasculitis. Fatal disease occurs in less than 7% of patients [1, 12].

ETIOPATHOGENESIS

A variety of injurious processes can lead to identical responses in the vessel wall resulting in the activation of neutrophils, abnormal neutrophil diapedesis and fibrinoid necrosis, the hallmarks of the vasculitides [1, 13]. Other morphological patterns of vasculitis include lymphocytic endarteritis and endarteritis obliterans of transplant vascular rejection, which are not generally associated with abundant fibrin deposits and destruction of the vessel wall with loss of the elastic lamina [14, 15]. Adding to the difficulties in the histological evaluation of vasculitides are that the characteristics of the initial insult may be lost during the process of repair leading to the transformation from active, acute inflammatory lesions into older, often sclerotic lesions wherein T-cells and macrophages predominate and neovascularization transpire to compensate for the ischemic insult. Nonetheless, the type of

inflammatory cell mediating vessel damage and vessel size affected roughly correlates with pathogenic mechanisms. Ascertaining the optimal time for obtaining the skin biopsy offers relevant preserved data of the skin lesion. An estimated time of a lesion within 24 to 48 hours of its onset is ideal for the biopsy, and for immunofluorescence between 8 to 24 hours [16].

CLINICAL PRESENTATION

Systemic symptoms of fever, malaise, weight loss, arthritis, and arthralgia accompany most cutaneous vasculitides. Vasculitic lesions may affect dependent sites of the legs especially under tight fitting clothes, less so along the arms, trunk, head and neck signifying more severe disease or coexisting systemic vasculitis [17]. Cutaneous vasculitis commonly manifests as palpable purpura and infiltrated erythema indicating dermal small vessel vasculitis (SVV), less frequently as nodular erythema, livedo racemosa, punched-out ulcers, or digital gangrene due to muscular-vessel vasculitis. The type of cutaneous lesions closely correlates with the size of vessel affected by vasculitis. Sparse superficial perivascular neutrophilic infiltrates associated with nuclear debris and extravasated red blood cells result in urticarial papules and plaques, which last > 24 h, burn rather than itch, and resolve with residual pigmentation (Figure 4). A predominant small vessel vasculitis (SVV) results in purpuric macules and infiltrated erythema, whereas deeper dermal SVV correlate with palpable purpura and vesiculobullous lesions. Ulcers, nodules, pitted scars, or livedo reticularis are associated with arterial muscular vessel involvement, which will be located at the dermal–subcutis interface or within the subcutis [4].

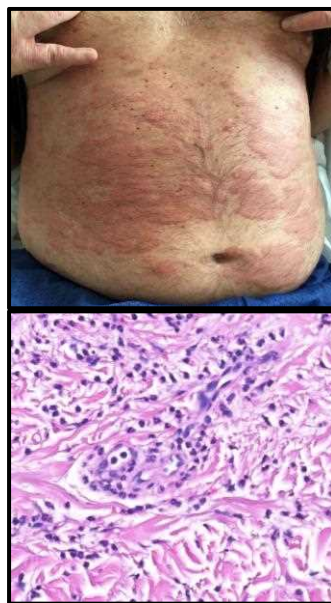


Figure 4. Urticarial vasculitis (UV): patient with hypocomplementemia presenting with an urticarial rash that lasts for more than 24 hours in fixed locations which subsequently slowly resolves spontaneously. They can possibly resolve leaving ecchymosis and hyperpigmentation. Histologically, the features (as in most cases of UV) show perivascular neutrophilic infiltrate with red blood cell extravasation but no fibrin deposition.

LABORATORY EVALUATION

Histopathologic Studies

Table 3 shows the histologic criteria for the diagnosis of cutaneous vasculitis. The diagnosis of cutaneous vasculitis of small- and medium-sized muscular vessels is established by biopsy and examination of hematoxylin and eosin (H& E)-stained sections followed by direct immunofluorescent (DIF) studies. Fibrinoid necrosis is comprised of fibrin deposition within and around the vessel wall and is a feature of nearly all early vasculitic lesions. It results from the accumulation of plasma proteins, including coagulation factors that are converted to fibrin along sites of vessel wall destruction. Inflammatory infiltrates within and around the walls of vessels accompanied by fibrin deposition (Figure 5) may be accompanied by endothelial damage in the form of endothelial swelling and shrinkage due to apoptosis and sloughing (Figure 6). The finding of inflammatory cells infiltrating the adventitia and media and disrupting the endothelium or endothelialitis, is a *de facto* sign of vasculitis (Figure 7). Secondary changes that infer underlying vasculitis include extravasation of red blood cells causing purpura, necrosis leading to infarction, and ulceration secondary to the ischemia and vessel obstruction. The type of inflammatory cells mediating vessel damage and the caliber of the vessels affected roughly correlate with pathogenic mechanisms listed in Table 4. Circumstantial evidence of vessel wall damage includes lamination of the adventitia, media and/or intima of vessels or so-called onion skinning (Figure 8); perivascular nuclear dust or leukocytoclasia (Figure 9) without fibrin deposits such as in early evolving LCV; sharply defined loss of the elastic lamina associated with acellular scar tissue in the healed stage of muscular vessel vasculitis; and sub endothelial, intramuscular, and adventitial inflammatory cells. Neovascularization of the adventitia (Figure 10) and the formation of small capillaries are prominent features of mature and older lesions in chronic localized SVV such as erythema elevatum diutinum, medium vessel vasculitides (MVV) such as polyarteritis nodosa (PAN), and large vessel vasculitides (LVV) such as giant cell arteritis (GCA), Luminal obliteration or endarteritis obliterans, the ischemic consequence of lymphocytic and granulomatous vasculitides, affects small- to medium-sized arteries. Endarteritis obliterans occur in several stages. First, lymphocytic endothelialitis or endarteritis is followed by formation of a sponge-like plug composed of mononuclear cells, fibrin, and red blood cells resulting in partial to complete obstruction. Perivascular lymphohistiocytic, non-neutrophilic, inflammatory infiltrates develop around affected arteries, followed by formation of dilated capillaries in the adventitia of obstructed vessels. Smooth muscle cells immigrate and proliferate in the subendothelial zone, organizing the occluding plug during the intermediate stage. The final stage is fibrosis, shrinkage, and atrophy of the occluded artery (Figure 11). Healed lesions may be associated with luminal stenosis and aneurysm formation. Persistence of vessel wall inflammation, either medial or intimal, can eventually lead to luminal obliteration or aneurysm rupture.

Immunofluorescence analysis of a tissue biopsy of involved skin lesions is indispensable. The commonest immunoreaction found in vessels by DIF is C3, followed by IgM, IgA and IgG, and fibrin deposits [1, 4]. The type of Ig and pattern of deposits in DIF will be of additional diagnostic value. For example, predominance of IgA in HSP/IgAV (Figure 12) will direct attention to renal involvement. Basement membrane zone or keratinocyte nuclear or *in*

vivo ANA and IgG immunoreactions are found in vasculitides associated with CTD such as LV. The finding of basement membrane zone immunoreactions occurs in those with HUV/C1q and CTD. In addition, IgM deposition in blood vessels, circulating RF and monoclonal production of IgM are readily seen in patients with CV and RAV.

Table 3. Histologic diagnostic criteria for cutaneous vasculitis and associated histology¹

Histologic signs of acute (active) vasculitis
<i>Dermal small vessels (venules and arterioles) (2 of 3* criteria needed)</i>
*Angiocentric(†) and/or angio-invasive inflammatory infiltrates
*Disruption and/or destruction of vessel wall by inflammatory infiltrate
*Intramural and/or intraluminal fibrin deposition (“fibrinoid necrosis”)
<i>Dermal-Subcutaneous muscular vessels (small arteries and veins)</i>
*Infiltration of muscular vessel wall by inflammatory cells
*Intramural and/or intraluminal fibrin deposition (“fibrinoid necrosis”) [§]
<i>†Secondary changes of active vasculitis (suggestive of, but not diagnostic of vasculitis)</i>
RBC extravasation (petechiae, purpura, hematoma)
Nuclear dust, perivascular (leukocytoclasia)
Endothelial swelling, sloughing or necrosis
Eccrine gland necrosis (or regeneration with basal cell hyperplasia)
Ulceration
Necrosis/infarction
Histologic sequelae of vasculitis (chronic signs and healed lesions of vasculitis)
†Lamination (onion-skinning) of vessel wall constituents
†Luminal obliteration (endarteritis obliterans)
*Segmental or complete loss of elastic lamina in medium and large vessels associated with acellular scar tissue
†Reactive angioendotheliomatosis
Neo-vascularization of adventitia

*: Required for diagnosis of vasculitis.

[§]: Intraluminal fibrin deposition can be found in non-vasculitic arterial lesions such as malignant hypertension and anti-phospholipid antibody syndrome.

†: Other types of vessel injury (pseudovasculitis [91]) can cause same pattern

¹ Adapted from Carlson et al. [1].

Table 4. Pathogenic mechanisms of vasculitis and their clinical diagnostic and histologic correlates¹

Pathogenic Mechanism	Vasculitic Syndrome	Vasculitis Pattern
Type I (Anaphylactic)	Eosinophilic vasculitis	Eosinophilic small-vessel vasculitis
Type II (Cytotoxic-cytolytic antibody)	EGPA GPA MPA	Eosinophilic small- and medium vessel vasculitis Neutrophilic mostly small- and medium vessel vasculitis Neutrophilic mostly small- and medium vessel vasculitis
Type III (Immune complex)	HSP CLA CV PAN	Neutrophilic small-vessel vasculitis Neutrophilic small-vessel vasculitis Neutrophilic mostly small- and medium vessel vasculitis Neutrophilic medium-vessel vasculitis
Type IV (Delayed hypersensitivity)	GCA Chronic GVHD	Granulomatous medium-vessel vasculitis Lymphocytic small-vessel vasculitis

CLA = Cutaneous leukocytoclastic angiitis; CV = Cryoglobulinemic vasculitis; EGPA = Eosinophilic granulomatosis with polyangiitis; GCA = Giant cell arteritis; GPA = Granulomatosis with polyangiitis; GVHD = Graft-versus-host disease; HSP = Henoch-Schönlein purpura; MPA=Microscopic polyangiitis, PAN = Polyarteritis nodosa

¹ Adapted from Carlson et al. [1].

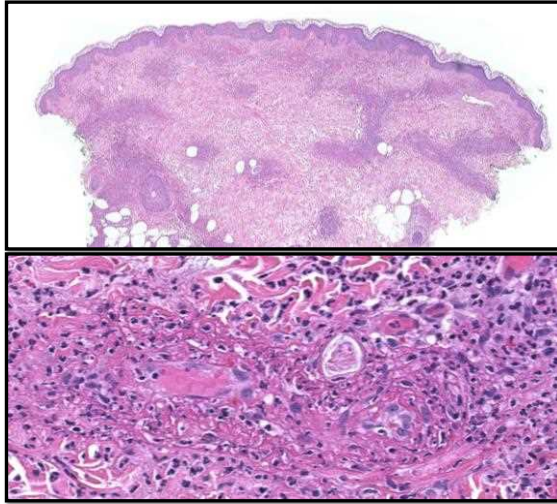


Figure 5. Inflammatory infiltrates within and around the walls of vessels accompanied by fibrin deposition indicative of vasculitis.

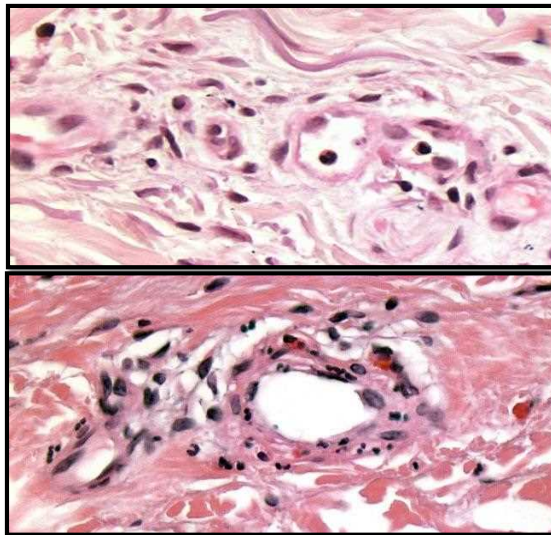


Figure 6. Endothelial swelling, shrinkage, apoptosis, and sloughing seen in early and mature lesions of urticarial vasculitis occurring in association with hepatitis C virus infection.

Further laboratory evaluation of patients with cutaneous vasculitis should be guided by the history and physical examination as to the possibility of preexisting or concomitant systemic illness, including relevant drug and infectious exposures [1, 18]. Clues to the presence of underlying systemic illness include night sweats, weight loss, dry eyes and mucous membranes, photosensitivity, facial cutaneous eruption, oral lesions, muscle weakness, mononeuritis multiplex, arthralgia, myalgia, fever, hemoptysis, shortness of breath, cough, wheezing, eye or ear symptoms, sinusitis, hoarseness, numbness or paresthesia, abdominal or testicular pain, melena, and hematuria [1, 18]. Patients with suspected of a primary vasculitides should undergo baseline complete blood cell count (CBC) with differential, blood

urea nitrogen (BUN), creatinine, liver function panel, urinalysis, stool guaiac, hepatitis B (HBV) and C virus (HCV) serology, antinuclear antibody (ANA), cryoglobulins, and ANCA testing. Other studies include blood cultures and echocardiography when fever or heart murmurs are present, anti-streptolysin O titers in children and adults with a history of cardiac septal defect; cytokines IL-6, TNF α , C-reactive protein (CRP), activated coagulation marker complex thrombin–antithrombin III, functional endothelial markers endothelial microparticles and thrombomodulin; and ANCA serology when SVV (MPA, EGPA, GPA) is suspected. Perinuclear pattern of ANCA (pANCA) with myeloperoxidase (MPO) antibodies as well as lactoferrin and cathepsin, which occurs most often in MPA and EGPA. Cytoplasmic (cANCA) with proteinase-3 (PR3) is strongly associated with GPA.

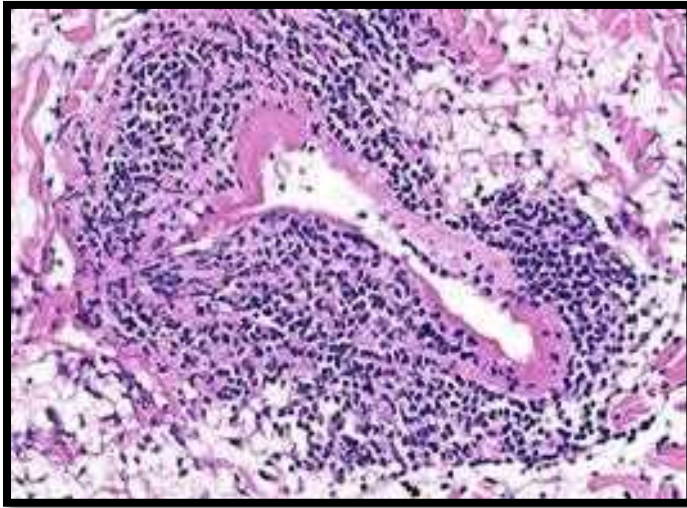


Figure 7. Lymphocytes infiltrate the adventitia and media of a small vein and the intima shows extensive fibrin deposits.

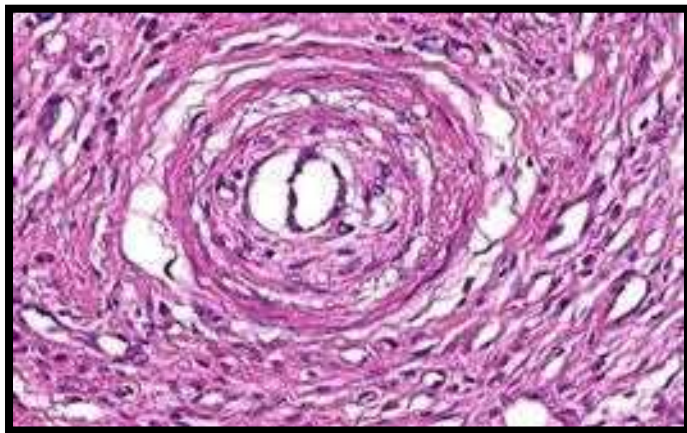


Figure 8. Erythema elevatum diutinum- chronic localized fibrosing leukocytoclastic vasculitis. Concentric rings of collagen surround this small vessel due to recurrent leukocytoclastic vasculitis. There is a cycle of vasculitis → vessel damage → and granulation tissue formation.

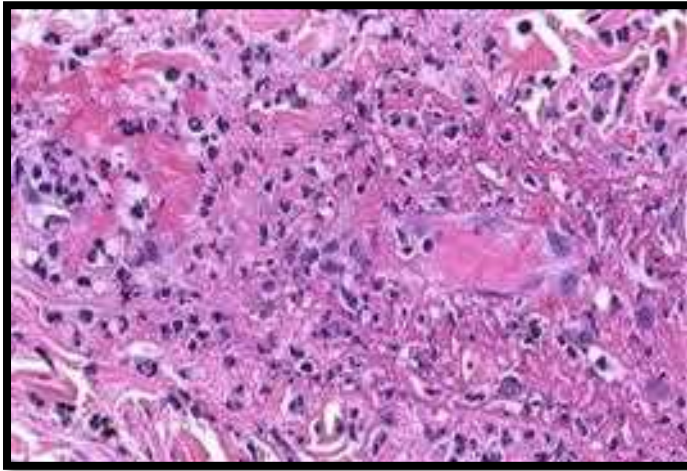


Figure 9. Deposition of neutrophilic nuclear debris or leukocytoclasia. Note the disruption of the small thin wall vessel by fibrin and numerous degenerated adventitial apoptotic neutrophilic nuclei.

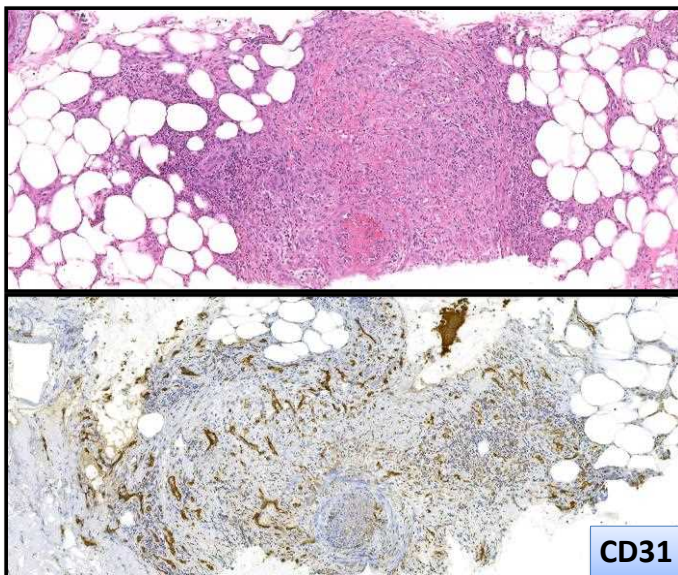


Figure 10. Neovascularization in cutaneous polyarteritis nodosa. CD31 staining marks the vasculature and as demonstrated in this image, reveals multiple newly formed vessels surrounding the affected vessel.

The presence of ANCA is not diagnostic of systemic vasculitis since up to 60% of patients with cutaneous LCV can be ANCA-positive with disease limited to the skin. Positive ANCA serology so noted in diverse systemic inflammatory and pulmonary disorders that mimic vasculitis [19] usually demonstrates atypical indirect immunofluorescent patterns with negative antibodies to PR-3 and MPO by antigen specific enzyme-linked immunosorbent assays (ELISA). The absence of IC and the presence of minimal IgG and C3, so-called pauci-immune vasculitis, are expected findings in GPA, EGPA and MPA. These three vasculitides can present with negative serology and exploring other antigen targets for such situations may

be of diagnostic utility. Kain and colleagues found the serum anti-human lysosomal-associated membrane protein-2 (hLAMP-2) to be positive in different assays in > 80% of untreated 122 AVV patients. Levels dropped to almost becoming undetectable once the immunosuppression therapy started, raising the possibility to be used as a biomarker and contrasting with MPO and PR3 antibodies, which do not correlate well with the disease activity due to different kinetics. Moreover, in the same study, positive anti-hLAMP-2 antibodies were found in 7 out of 8 ANCA, PR3 and MPO negative patients [20]. Inadequacies of current assay techniques limit hLAMP-2 antibody kits to be commercially available; even they have shown to have a high sensitivity and clinical correlation, but poor specificity for cutaneous AAV, as they were also detected in HSP and cutaneous polyarteritis nodosa [21].

Patients with suspected secondary vasculitis and biopsy-proven cutaneous vasculitis in association with a serologically specific CTD, so suggested by dry eyes and mouth, arthritis, sclerosis, or photosensitivity, should be further screened for antinuclear antibody (ANA), rheumatoid factor (RF), anti-phospholipid (aPL), Ro (SSA), La (SSB), ribonucleoprotein (RNP) and Sm (Smith) antibodies [1, 22, 23]. The secondary vasculitides in association with CTD typically involve multiple organs and vessels of variable caliber. Extravascular histologic findings can provide a clue to diagnosis of associated CTD. Examples include interface dermatitis with dermal mucin deposition so noted in SLE and dermatomyositis; dermal or subcutaneous sclerosis in scleroderma; as well as, palisading neutrophilic and granulomatous dermatitis in RA and SLE, and tissue neutrophilia, rather than a neutrophilic dermatosis, in SLE and Sjögren syndrome [2].

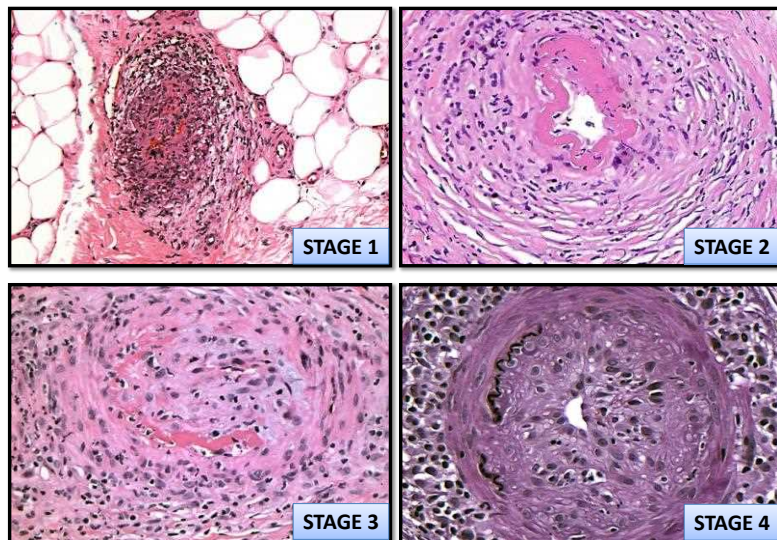


Figure 11. The four morphologic stages of cutaneous polyarteritis nodosa with end-stage healed arteritis or endarteritis nodosa. The acute stage is characterized by endothelial loss and fibrin thrombi with neutrophil infiltration without obvious internal elastic lamina disruption and medial fibrinoid necrosis. The subacute stage shows mixed cellular infiltration and unique intimal target-like fibrinoid necrosis and leakage extending through the disrupted internal elastic lamina sites to the media. The reparative stage shows intimal fibroblastic proliferation and perivascular neovascularization with predominant histiocyte and lymphocyte infiltration. The healed stage reveals minimal cellular inflammation and occlusive intimal thickening.

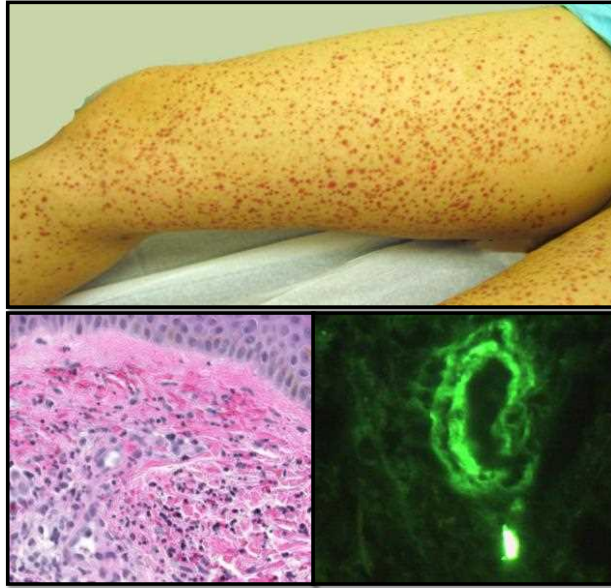


Figure 12. Petechial leg eruption in HSP/IgAV. Skin biopsy shows neutrophilic small vessel vasculitis restricted to the superficial dermis. Direct immunofluorescence demonstrates IgA vascular deposits.

PRIMARY SMALL VESSEL VASCULITIDES

ANCA-Associated Vasculitides

Microscopic Polyangiitis

This neutrophilic necrotizing SVV characteristically involves arterioles, capillaries, and venules, and occasionally small and medium arteries of the kidney and lung resulting in pulmonary capillaritis and necrotizing glomerulonephritis. It typically affects patients > 50 years of age, with a male: female ratio of 1:1.5, and a greater prevalence in Asians [24]. The largest cohorts ascertained in departments of medicine or nephrology render a bias toward certain spectrums of the disease [25] and may underestimate the true incidence of cutaneous manifestations [26]. Agard and coworkers [27] found skin lesions, primarily purpura, at presentation in 14% of 36 patients, compared to 4% by Cupps and Fauci [28]. Kluger and colleagues [29] ascertained skin manifestation in 44% of 162 patients comprised of palpable purpura of the legs in 26%, livedo racemosa in 12%, nodular lesions in 10%, ulcer/necrosis in 6%, urticaria in 1.2%, oral and genital ulcers each in 0.6%; arthralgia, mononeuritis multiplex and ocular symptoms occurred more often as well. Guillevin and coworkers [30] observed cutaneous involvement, primarily purpura, in 62.4% of 85 patients.

The French Vasculitis Study Group (FVSG) [31], a multicenter nationwide study, that retrospectively analyzed 1553 AAV patients, noted cutaneous manifestations (CM) overall in 51.9%, typically at a younger age (57.5 years) with features of segmentary edema (19.5%) and livedo reticularis (12.4%), as compared to those with GPA and EGPA. In addition, myalgia, arthralgia, gastrointestinal hemorrhage and peripheral neuropathy were all

significantly more frequently in association with CM, with less frequently impaired renal function [31].

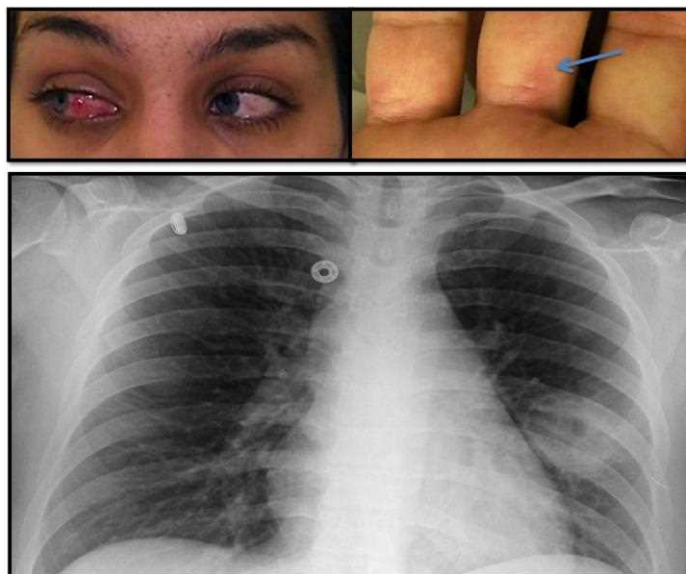


Figure 13. Granulomatosis with polyangiitis. This young 22-year old female presented with progressive ocular (episcleritis), ear, and lung symptoms and history of tuberculosis. Chest radiograph showed left lung nodule cavitation. Cutaneous exam revealed painful papules some of which were vesicular over the volar aspects of the proximal phalanges. Punch biopsy was diagnostic of granulomatosis with polyangiitis.

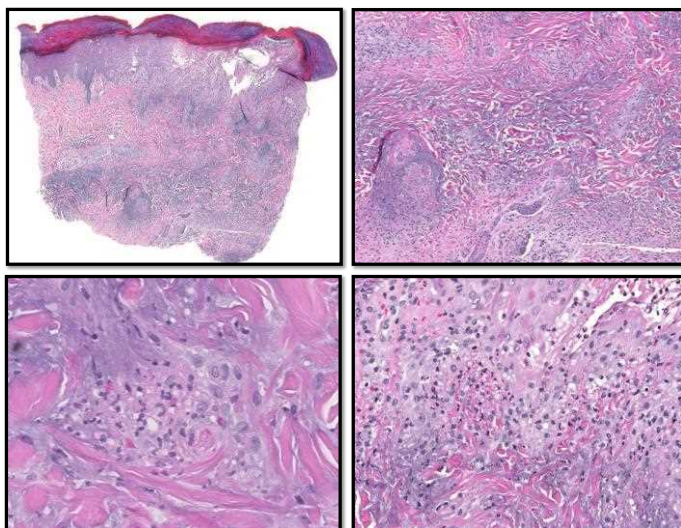


Figure 14. Punch biopsy of the patient in Figure 13 that shows regional epidermal necrosis overlying a pandermal infiltrate characterized by neutrophilic small vessel vasculitis (bottom left panel), and surrounding, palisading granulomatous inflammation associated with basophilic debris or blue collagenolytic granuloma.

Granulomatosis with Polyangiitis

The clinicopathological features of GPA include granulomatous inflammation of the upper and lower respiratory tracts (Figures 13, 14) and necrotizing granulomatous inflammation of the kidneys leading to glomerulonephritis [23]. The disease is not evenly distributed among geographic areas, time intervals or ethnic populations [32]. The diagnosis rests upon a positive biopsy demonstrating surrogate markers of granulomatous inflammation of the respiratory tract and kidney and the presence of systemic necrotizing vasculitis of small-to medium-sized vessels, and positive c-ANCA specifically targeting intra-granular, anti-proteinase-3 (PR3), but without blood or biopsy tissue eosinophilia. About 10% to 50% of patients with GPA develop cutaneous disease during the course of disease [33-36] that takes one of many forms including, palpable and non-palpable purpura due to small vessel neutrophilic vasculitis; subcutaneous nodules, ulcers and digital infarcts with gangrene due to medium vessel vasculitis (Figure 15). Polymorphic lesions consist of necrotic rheumatoid papules and nodules along extensor surfaces particularly the elbows; and pyoderma gangrenosum-like ulcers and gingival hyperplasia with strawberry gingivitis.



Figure 15. Digital gangrene in a patient with muscular-vessel vasculitis and radial artery thrombosis, status post thrombectomy. The patient was diagnosed subsequently as granulomatosis with polyangiitis.

Among 40 patients with the diagnosis of GPA described by Patten and colleagues [33], 16 (40%) had cutaneous and oral mucosal disease, 12 of whom had a skin alone, most commonly palpable purpura; and 2 each had oral mucosal disease or both skin and mucosal disease leading to oral ulcers, with a single example of gingival hyperplasia. Among 766 ANCA-positive patients with GPA, Comfere and colleagues [34] noted skin manifestations in about 10% of patients, several of whom underwent skin biopsy evidencing concomitant cutaneous and systemic involvement, isolated cutaneous disease several weeks to 8 years after diagnosis of systemic GPA, and others in whom the cutaneous eruptions preceded systemic involvement by one to seven years. Among 66 patients with GPA Zycinska and coworkers [35] discerned skin involvement in 21 (32%) patients, 14 (21%) of whom had skin involvement as an initial clinical presentation. The histologic identification of isolated LCV,

cutaneous GPA, and positive c-ANCA/PR3-ANCA serologic test results should raise clinical suspicion for later systemic involvement.

In the AAV cohort of the FVSG, CM noted in 36.7% of cases, manifested frequent oral ulceration (4.6%) and two distinctive lesions: pyoderma gangrenosum (1.1%) and gingival hyperplasia (0.9%). There was frequent alveolar hemorrhage, arthralgia, peripheral neuropathy, renal, cardiovascular and gastrointestinal involvement. Patient with GPA and CM had more frequent vasculitis than the granulomatous phenotype and poorer relapse-free and overall survival. Patients with GPA and predominant granulomatous features manifesting lung nodules and pachymeningitis had infrequent CM [31]. The histopathology of GPA is a LCV with fibrinoid necrosis mostly affecting small vessels and preferentially the dermis. Fewer cases show deeper tissue inflammation. Other presentations include purpura, nodules, papules, urticaria and granulomatous vasculitis. Neutrophils prevailed in almost all the specimens. Among 52 pediatric GPA cases [37], CM noted in 36.5% of cases, was a presenting feature in 7.7%. Nineteen patients had specific findings related to the disease presenting as palpable purpura, folliculitis, pyoderma gangrenosum-like and nodules, with histopathologic findings of leukocytoclastic vasculitis, granulomatous inflammation, granulomatous vasculitis and palisading granulomas. Acneiform papules and pustules with perifollicular inflammation are unique to this age group [37].

Eosinophilic-Granulomatosis with Polyangiitis

Patients with EGPA present clinically with adult-onset of asthma and allergic rhinitis, and pathologically with necrotizing granulomatous inflammation, peripheral blood and tissue eosinophilia, and systemic vasculitis [23] in adults age 30 to 60 years without gender differences [38]. There is frequent renal disease and more frequent peripheral nerve, cutaneous, and cardiac involvement compared to GPA. ANCA-positive patients are more likely to have cutaneous vasculitis, alveolar hemorrhage, mononeuritis multiplex and renal disease [39]. In contrast to GPA and MPA, 40% of EGPA cases are ANCA-positive, with most manifesting p-ANCA and MPO specificity (in 30% - 40%) [40], and fewer cases presenting with c-ANCA and PR3 seropositivity. Following a prodromic initial phase of asthma and allergic rhinosinusitis, a second phase ensues with peripheral blood and tissue eosinophilia demonstrable in the lungs, heart and other organs; followed by a third phase of frank vasculitis. Cutaneous manifestations were the presenting feature of EGPA patients in about 14% of cases [41], so noted in 40% to 80% of cases [42].

The lesions of EGPA were first described in 1951 as erythematous maculopapular lesions resembling erythema multiforme; also include petechiae, palpable purpura, urticarial papules; and cutaneous and subcutaneous nodules [43]. In a recent cohort, the skin manifestations of EGPA at initial onset included palpable purpura, petechiae, ecchymosis and hemorrhagic bullae in $\leq 50\%$ of patients; dermal and subcutaneous papules and nodules on the scalp or symmetrically distributed over the extremities (Figure 16) in about 30%; and urticaria and erythematous macules in $\leq 25\%$ of patients, with others manifesting livedo reticularis. In the FVSG cohort, among 436 EGPA cases, 53% presented with CM along with more frequent fever (50.9%), arthralgia (44.1%), ocular involvement (12.5%), alveolar hemorrhage (7.8%) and gastrointestinal involvement (29.5%), without cardiovascular, neurological or renal involvement [31].



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Figure 16. Dermal and subcutaneous papules around the elbows and hemorrhagic bullous purpuric macules and papules over the lower extremities in a patient with eosinophilic granulomatosis with polyangiitis.

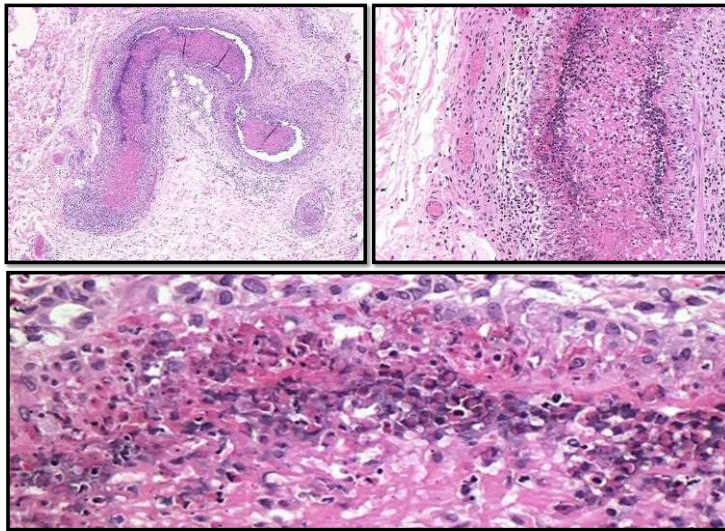


Figure 17. Eosinophilic arteritis with thrombophlebitis in a patient with eosinophilic granulomatosis with polyangiitis.

Cutaneous biopsy reveals three histopathologic changes, alone or together, including 1) eosinophil-rich neutrophilic SVV affecting dermal venules and arterioles, less commonly an eosinophil-rich muscular arteritis (Figure 17) or granulomatous histiocyte-rich arteritis of the dermal subcutaneous junction or subcutis; dermal eosinophilia; 2) palisading neutrophilic and granulomatous dermatitis with neutrophilic debris among basophilic degenerated collagen bundles, so called blue granuloma (Figure 14) or abundant eosinophils and eosinophilic granules and debris that coat degenerated collagen bundles or red granulomas (Figure 18) [23, 44, 45]; and less often, 3) granulomatous arteritis [45].

Immune Complex Vasculitides

Henoch Schönlein Purpura/IgAV

Comprising about 10% of all cases of cutaneous vasculitis and about 90% cases of primary childhood vasculitis [1, 23], HSP/IgAV is characterized by retiform or patterned purpura preceded by an upper respiratory tract infection in about one-half of children and a recent drug exposure in a minority. Isolated or predominate IgA vascular deposits, and two or more of the following support the diagnosis: age ≤ 20 years, colicky gastrointestinal pain or hematochezia, an upper respiratory tract infection prodrome, hematuria, and renal biopsy showing mesangioproliferative glomerulonephritis with or without IgA deposits. Renal disease is found in HSP patients with a history of recent infection, fever, lesions above the waist or spread of purpura to the trunk, and papillary dermal edema and perivascular C3 on DIF histopathology [46, 47]. Long term follow-up is necessary in children with abnormal baseline urinalysis [48] since up to 20% develop chronic renal failure compared to those with a normal baseline urinalysis in which no person developed later renal impairment [48, 49]. Patients with fever, purpura above the waist, and elevated erythrocyte sedimentation (ESR) rate are more likely to develop IgA glomerulonephritis. In addition, in the pediatric population, serum pentraxin3 levels predicts future renal disease [50]. Furthermore, the lesions above the waist and edema on the exam are associated with gastrointestinal involvement [47]. Skin biopsy in patients with HSP/IgAV demonstrates neutrophilic SVV restricted to the superficial dermis (Figure 12), although the whole dermis may eventually become involved [51]. Patients older than age 40 years with HSP/IgAV with absent eosinophils on histologic examination of skin tissue had a three-fold increased risk of renal involvement compared to those younger than age 40 with tissue eosinophilia [52]. The IgA and IgM deposits in the skin by DIF also predicts renal disease [50].

The link of HSP and familial Mediterranean fever (FMF) has been well known since recognition that the classical features of the former, including purpura, gastrointestinal tract bleeding hematuria, localized edema, arthritis and positive skin biopsies; overlapped with periodic fever and abdominal pain lasting for 1 to 3 days, of the latter [53]. Pathophysiological inflammatory mechanism include complement consumption and circulating immune complexes [54]. Features unique to HSP include the absence of classical cutaneous IgA deposits on DIF, and recurrent, dispersed purpuric lesions of atypical areas along the face and trunk [54]. Serum anti-LAMP-2 antibodies were significantly higher in 36 HSP patients versus 51 healthy controls [55].

Cryoglobulinemic Vasculitis

Cryoglobulins are cold-precipitating immunoglobulins that persist in the serum and solubilize when rewarmed. There are three types, type I, monoclonal cryoglobulins that comprise 10% to 15% of all cases and produce non-inflammatory small vessel hyaline thrombi; type II or mixed monoclonal IgM with RF activity and polyclonal IgG cryoglobulins which comprise 50% to 60% of cases; and type III or mixed polyclonal IgM with RF activity and IgG cryoglobulins comprising 30% to 40% of cases. The oligoclonal type consists in the composite of oligoclonal IgM (several monoclonal) against polyclonal IgGs with RF activity and is described as a transitional form type or IIa, [56]. Type II and III mixed cryoglobulinemia are associated with CTD, hematologic malignancies and HCV infection.

Greater than 50% of HCV-seropositive patients have mixed cryoglobulins, and a lesser frequency of vasculitis. Persistence of CV immunological features was reported in 52% of effectively treated patients with HCV after 12 weeks of anti-viral therapy who potentially may remain clinically active [57].

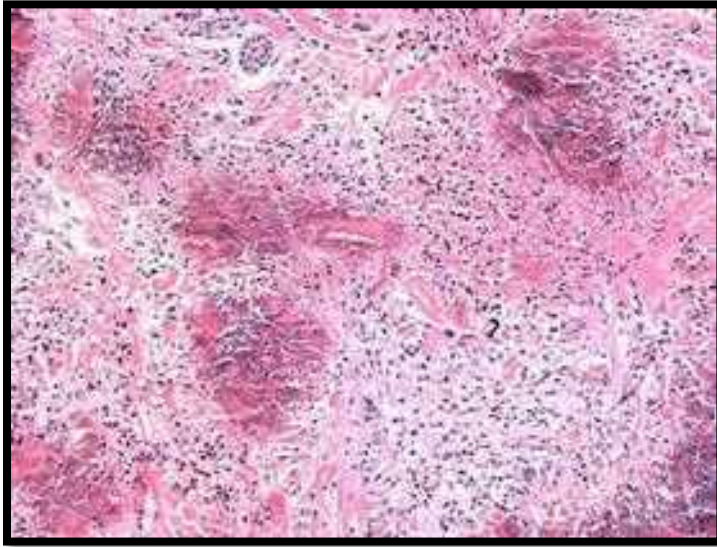


Figure 18. Multiple red collagen lytic granulomas in a patient with eosinophilic granulomatosis with polyangiitis.



Reproduced courtesy of Henry Foong, MD, Ipoh, Malaysia).

Figure 19. Severe cutaneous polyarteritis nodosa with secondary livedoid vasculopathy.

Cryoglobulinemic vasculitis is characterized by Meltzer's clinical triad of purpura triggered by cold exposure or prolonged standing, arthralgia, and weakness in association with mixed cryoglobulinemia. Other cutaneous manifestations include PAN-like lesions,

ulcers, splinter hemorrhages, palmar erythema and even digital gangrene if digital vessels become obliterated, this later, especially whenever the cryocrit is elevated. Systemic disease in CV includes glomerulonephritis, neuropathy, and pulmonary involvement with high titers of RF and low levels of C4. Most patients demonstrate neutrophilic SVV that equally affects vessels of the superficial dermis and subcutis on skin biopsy with vascular IgM and complement deposits on DIF; a minority of patients displays PAN-like histopathology [23].

PRIMARY MEDIUM VESSEL VASCULITIS

Polyarteritis Nodosa

This less frequently seen MVV affects men and women age 40 to 60 years without sexual preference; a childhood form of PAN (cPAN) is well recognized [58] and in some familial clusters associated with recessive loss-of-function mutations in the gene encoding adenosine deaminase 2 [59]. Most of PAN cases have no known etiology and are labeled as idiopathic PAN. Secondary PAN associates with HBV, HCV infection, human immunodeficiency virus (HIV), cytomegalovirus, parvovirus B19, and human T-lymphotropic virus (HTLV). The frequency of PAN-associated with HBV has dropped in cases from 36% to less than 5% in developed countries due to effected vaccination programs [60], whereas HIV-associated PAN prevails in developed countries [61]. Other than the PAN-associated HBV subgroup, cutaneous PAN and single-organ PAN constitute other acknowledged subgroups (62).

Constitutional symptoms, fever and weight loss and myalgia are almost universal (> 90%), followed by neurologic (75%) and cutaneous manifestations (60%) (Figure 19). It affects almost any other system/organ, like the gastrointestinal (40 - 50%), renal (50%) with renovascular hypertension in < 80%, testicular (20%), musculoskeletal (arthritis in < 75%), ophthalmologic (8%), vascular (claudication, ischemia, necrosis) in 6%, cardiac (cardiomyopathy, pericarditis in 5% and heart failure in $\leq$ 30%, central nervous system (stroke, confusion) in 5% and respiratory (lung infiltrates and pleural effusions) in 3% [58, 63-65] implying multi-organ involvement.

Tissue biopsy of muscle, sural nerve, kidney, liver, testis, and rectum shows segmental neutrophilic muscular vessel vasculitis affecting medium- and small-sized arteries. Even the pathogenic role of immune complexes is considered to play a central role, for unknown reasons PAN does not affect arterioles, capillaries or venules sparing vital organs (absence of capillaritis in lungs and no glomerulonephritis) which together with the negative serology for ANCA differentiates PAN from any other AAV [62]. Active vasculitic lesions are frequently associated with chronic reparative changes that show endarteritis obliterans. Skin lesions are observed in 25 to 60% of patients [66] the commonest of which palpable purpura and erythema of the legs [67]. Subcutaneous leg nodules ranging from 0.5 to 2 cm occur in proximity to blood vessels in 20% of patients. 49.7% of the cases, more often in non-HBV-related PAN (57.8 vs. 35 %). Purpura was the most common type of lesion in patients with PAN with or without an associated HBV infection. Cutaneous vasculitis was found overall in about one-half of their 348-patient cohort of Pagnoux and coworkers with PAN [65], including 57.8% of 225 HBV-seronegative and in 35% of those HBV-seropositive. Interestingly, they also found on multivariate analysis that the presence of cutaneous manifestations at diagnosis, especially nodules, was associated with a higher risk of relapse.

Agard and colleagues [27] reported cutaneous involvement as the initial finding in 11% of 36 patients with MPA and PAN.



Figure 20. Giant Cell Arteritis in a patient who underwent the temporal artery biopsy (seen at the lower arterial tract) and atrophy of surrounding soft tissue. Note the irregularity of the arterial surface.

Cutaneous PAN (CPAN), an indolent form of PAN confined to the skin, is suggested by tender nodules, livedo vasculopathy, livedo racemosa, ulcers, acral gangrene and neuropathy [1, 4, 68]. Deep punch and incisional biopsy demonstrates neutrophilic muscular vessel vasculitis at arterial branch points located at the dermal-subcutis junction or within the subcutis. Macular arteritis [69-72] and lymphocytic thrombophilic arteritis [73] are related variants of CPAN that represent latent or late evolutionary stages of the disease and manifest lymphocytic vasculitis [69, 74]. Nodular vasculitis or erythema induratum of Bazin, a lobular panniculitis and vasculitis of venules and septal veins [75] can be mistaken for CPAN [1, 4, 68]. Their differentiation is possible by considering the relative silhouette and patterns of elastic tissue distribution [76, 77] such that in contrast to the rounded contour of arteries, venous vessels have oval silhouettes with few or no elastic fibers.

LARGE VESSEL VASCULITIS

Giant Cell Arteritis

This disorder occurs in fair-skinned Caucasian individuals of older age females presents with headache, jaw claudication, visual and neurological disturbances resulting from ischemic endarteritis obliterans, and systemic features of malaise, weight loss, and fever due to release of inflammatory cytokines. The cutaneous signs consist of scalp tenderness; blanching, decreased or loss of temporal artery pulses, and cord-like temporal artery thickening (Figure 20) and occasionally distal cutaneous ulceration in the scalp secondary to obliterative

endarteritis. Accurate and timely diagnosis is important because serious morbidity especially loss of vision if the correct treatment with corticosteroids are delayed. Skin biopsies that include muscular vessels of the subcutis and temporal artery biopsies are diagnostic key elements but not necessary for treatment onset if GCA is a highly suspected cases. Areas of normal pathology between lesions, or “skip lesions” may drive to conclude false-negative tissue readings for which the artery biopsy should be at least of 20 mm and analysis should contemplate serial cross-sectioning with an additional 1 - 5% diagnostic yield improvement if a bilateral biopsy is performed [78]. Histopathologically, lesions show granulomatous vasculitis with giant-cell-containing inflammatory infiltrates, while the essential diagnostic features of temporal artery biopsy include segmental inflammation with disruption of media and intima, and fragmentation of the internal elastic lamina.

VARIABLE VESSEL VASCULITIS

Behçet Syndrome

Behçet syndrome is a systemic vasculitis sharing with Cogan syndrome the category of variable vessel vasculitis. It is a chronic relapsing inflammatory disease with high prevalence in the Silk Road countries and of unknown etiology. The clinical features are the recurrent painful oral (aphthous) and genital ulcerations, variable types of ocular inflammation with predominant choroido-retinitis and a plethora of cutaneous manifestations ranging from acneiform lesions, papulopustulosis, pseudofolliculitis, erythema nodosum-like, erythema elevatum diutinum, pyoderma gangrenosum-type lesions, Sweet’s syndrome-like lesions and hyperreactivity to small injuries [79]. This later phenomenon known as the pathergy test is used routinely in the clinical practice as is one of the diagnostic criteria for Behçet syndrome. The pustule-like lesion or papule follows a skin prick by a 20-gauge needle 48 hours later and may be evident during vascular procedures. Behçet syndrome may affect any organ, including the CNS, gastrointestinal system and lungs among others. The histopathology shows variable features like classic leukocytoclastic vasculitis, perivascular inflammation and interstitial infiltrates. In the acne lesions of Behçet LCV and lymphocytic vasculitis was found in 48% of patients compared to acne of patients without Behçet and controls [80]. Other findings may show superficial thrombophlebitis and in the erythema nodosum-like lesions, septal panniculitis with medium vessel vasculitis in up to half of these lesions [81].

SECONDARY VASULITIDES

Connective Tissue Diseases

Lupus Vasculitis

Ramos-Casals and colleagues [10] noted cutaneous vasculitis in 76% of 670 patients with SLE. The commonest cutaneous lesions were erythematous punctate lesions of the fingertips and palms, followed by purpura. Female SLE patients, anti-Ro seropositive, had a 1.63 greater risk of develop cutaneous vasculitis [82]. Compared with SLE controls, those with

cutaneous LV had a higher likelihood of Raynaud phenomenon and ribosomal P protein antibodies, but not greater frequency of kidney or nervous system involvement [83]. Patients with LV typically present with livedo reticularis, anemia, high ESR, and anti-La/SS-B antibodies than SLE patients without vasculitis. Additionally, they are younger, tend to have a higher SLEDAI/SLICC/ACR DI scores with musculoskeletal symptoms and hypocomplementemia, this later with a high sensitivity to detect LV. Lupus nephritis, cardiovascular features and comorbid Sjogren syndrome are significantly linked with the development of LV [84]. Arterioles and post-capillary venules are the most commonly affected by vasculitis, manifested as purpura, vesiculobullous lesions, urticaria, and splinter hemorrhages. Cutaneous ulcers, nodules, digital gangrene, necrotizing livedo reticularis, punctate acral scars, and pyoderma gangrenosum (PG)-like lesions (Figure 21), suggest arterial vessel involvement and multiorgan involvement. There may be p-ANCA and less often c-ANCA-seropositivity. Skin biopsy shows neutrophilic vasculitis with lesions that can resemble either typical LCV or PAN, or coexistence of both small and muscular vessel vasculitis in the same biopsy specimen.



Figure 21. Cutaneous Lupus vasculitis. A young woman with longstanding systemic lupus erythematosus and multiorgan involvement with nodules, pyodermatous ulcers, painful erythematous palmar macules and punctate scars.

Rheumatoid Vasculitis

The extra-articular (ExRA) manifestation of clinically evident RAV were noted in 2% of patients [22] compared to 15% to 31% in postmortem studied cases of RA [85]. The onset occurs in longstanding RA, averaging 10 - 14 years after the outset [86]. Cutaneous RAV is the most common vasculitic type within RA, typically affecting small- and medium size blood vessels. . It should be thought that patients with ‘burned-out’ arthritis with no or very few articular symptoms of disease activity may manifest with RAV in the context of other extra-articular features, like the lungs (pulmonary fibrosis), scleritis, Felty syndrome or co-morbid peripheral vascular disease [87]. Moreover, the odds for developing RAV are the

coexistent peripheral vascular disease, cerebrovascular disease, severe RA (with presence of severe deformities requiring surgery, radiographic evidence of erosions, nodulosis) and use of biologic therapy. Despite the advanced knowledge in the pathogenesis and the introduction of effective biologic therapies, RAV is still associated with increased premature mortality after 5 years of the diagnosis, with mortality of 25% in the 2000's that dropped from a 40% in the 90's. The significant morbidity, in about 36% of patients with RAV, relates to the systemic vessel involvement, in which the devastating inflammatory process, if untreated, leads to the recurrence or further progression in other target organs, while the excessive cytotoxic immune suppression may bring a burden of equal or more morbidity or predispose worse lethal consequences [88]. and is associated with increased premature mortality with mortality in 40 % of patients by 5 years as well as significant morbidity due to both organ damage from vasculitis and consequences of the cytotoxic treatment [89]. Two drugs have proven to decrease the odds for the development of RAV, hydroxychloroquine and aspirin. The former drug, hydroxychloroquine, relies its protective properties as it has protean immunomodulatory action by several mechanisms of action, like the Toll-like receptor inhibition, anti-thrombotic and antilipemic action [90], and the by contributory anticoagulation effects of aspirin. Cutaneous manifestations of RAV are graded mild, moderate, and severe.



Figure 22. Arteritis and small vessel vasculitis leading to geographic ulceration in rheumatoid arthritis vasculitis.

Mild cutaneous RAV presents with nail fold and palmar telangiectasia, thrombosis, minute digital ulceration, petechiae, and livedo reticularis. A well-known presentation are Bywater lesions consisting in periungual infarctions in long-term RA carrying without systemic implications requiring no escalate in the immune suppression [91]. Moderate cases manifest palpable purpura. Severely affected patients present with digital gangrene, nail-fold infarcts, and large cutaneous ulcers (Figure 22). The histopathology of RAV mimics that of polyarteritis nodosa without forming microaneurysms [92]. To define the vasculitic process, three layers of vessel need to be involved, distinguishing this from perivascular infiltrates

without invasive features commonly seen in RA. Neutrophilic proliferation as well as, lymphocytic, and plasmacytic cells infiltrate all layers of the small arteries [93]. Patients with RA and cutaneous LCV alone without RAV, have a better prognosis than those with other ExRA involvement [22]. High acute phase reactants in a RA patient with established disease are the only proving biomarkers contrasting with the rheumatoid factor and anti-citrullinated cyclic peptide antibodies which titers are minimally or not clinically meaningful in RAV. Conversely, the absence of RF and anti-CCP antibodies have an excellent negative predictive value for RAV [94]. Some patients may express a positive anti-nuclear antibody or an anti-perinuclear antibody (atypical), other than then PR3 or MPO antigens suggestive of the underlying vasculitic process targeting other antigens in neutrophil granules. Anti-lactoferrin antibodies have been reported in the latter circumstance [95]. Minocycline-induced cutaneous PAN was reported and associated with the chronic treatment for acne treatment improving after discontinuation of the drug [96].

Drug-Induced Cutaneous Vasculitis

Hypersensitivity vasculitis due to adverse drug reactions manifests as superficial dermal neutrophilic or lymphocytic SVV on skin biopsy, and represents about 20% of cases of cutaneous vasculitis [1, 4, 68, 97]. Tissue eosinophilia is an indicator of drug-induced cutaneous SVV [98].

Tumor Necrosis Factor- α

Tumor necrosis factor- α (TNF- α) inhibitors employed in the treatment of autoimmune and rheumatic diseases [99] were the reported cause of cutaneous vasculitis in 8 patients so treated for 2 to 72 months [100], including four patients with RA, three patients with ulcerative colitis, and one patient with Crohn disease. The commonest presenting manifestation of the patients was palpable purpura, followed by ulcerated lesions, erythematous macules and blisters. After discontinuation of anti-TNF- α , none had recurrent vasculitis. Appearance of ANCA titers in patients under anti-TNF- α therapy should prompt excluding AAV overlap, for which anti-TNF- α is not efficacious, and that requires switching to disease specific therapy [101].

Levamisole

Levamisole was originally introduced as an anthelmintic agent and later employed in Behçet disease and rheumatoid arthritis for immunosuppression. It has been employed in colon cancer enhancing the immunity by potentiating the T-cell mediated immune response. More recently, Levamisole was added to cocaine to potentiate the stimulant effects as it has dopamine agonistic effects provoking a synergistic effect with cocaine [102]. Affected patients have constitutional symptoms, arthralgia, leukopenia, agranulocytosis and cutaneous vasculitis [103, 104] with purpuric lesions of the ears, nose, cheeks, and extremities. The lesions have bright-red borders with central necrosis (Figure 23). Despite the severe and dramatic clinical appearance of these lesions, they usually resolve spontaneously within a few weeks of drug discontinuation but can recur with subsequent contaminated cocaine abuse. Subsequently, clinicians need to differentiate this presentation from other forms of vasculitis,

particularly with GPA, as the degree of immune suppression will differ between both. The degree of skin necrosis has been as severe and large as to require skin grafting, and by removing the offender combined with a short course of corticosteroids will suffice to control the disease, contrasting with the management for GPA, which requires more aggressive immune suppression [105]. One-half of affected patients each demonstrated positive anti-MPO or positive anti-PR3 antibodies [103]. In addition, cocaine contaminated with levamisole by unclear mechanisms, is the mediator of ANCA-mediated vasculitis. The target, differing from AAV, was found to be the neutrophil elastase within the granules eliciting an atypical ANCA positive antibody response. Furthermore, elastase a constituent of neutrophil extracellular traps (NETs) is a target of patients exposed to cocaine/levamisole. It has been suggested that the programmed-cell death of neutrophils by NETs release, which is the extrusion of nuclear (chromosomal material) and mitochondrial DNA containing pro-inflammatory and thrombogenic peptides, is potentiated by cocaine/levamisole. This combination of drugs induces the release of highly immunogenic NETs containing high concentrations of elastase [106]. Other targets have also been reported, like the antiphospholipid antibodies found in 63% of patients [104], and anti-C1q antibodies [107].



Figure 23. Levamisole-induced vasculitis shows histologic signs of a vaso-occlusive disorder and vasculitis.

AUTOINFLAMMATORY DISEASES

Autoinflammatory diseases (AD) comprise a heterogeneous group of diseases in which inflammation is triggered spontaneously and periodically with activation of the innate immune system. Most of them follow a well-defined Mendelian pattern of inheritance while others do not. The common onset of AD starts at early ages and in others, the onset is not seen until early or full adulthood. Although in most of the AD, the prevailing cutaneous expression reveals the group of neutrophilic dermatoses or urticarial presentation, few cases and series report true vasculitic processes, revealing the heterogeneity of disease phenotype and perhaps expressing a process outside the main pathogenesis.

Most notably of this group, Hyper-IgD syndrome has revealed true vasculitis. Hyper-IgD syndrome is characterized by periodic fever flares of 3 - 7 days, in infants and accompanied by arthralgia, abdominal pain, splenomegaly, cervical lymphadenopathy aphthous ulcers and maculopapular rash, annular erythema, palpable purpura and urticarial lesions [108]. The histopathology revealed perivascular infiltrates of variable numbers of lymphocytes and polymorphonuclear neutrophils fibrin deposits and red blood cell extravasation in a case report and analog findings in 7 out of 17 cases [109].

In cryopyrin-associated periodic syndromes (CAPS), which is a continuum of three disorders with the mutations in the NLRP3/CIAS1 gene, familial cold autoinflammatory syndrome (FCAS), Muckle Wells syndrome (MWS) and neonatal onset multisystem inflammatory disease/chronic infantile neurological cutaneous articular syndrome (NOMID/CINCA), neutrophils urticarial dermatoses is the classical feature. Predominant perivascular and peri-ecrine and interstitial neutrophil infiltration is seen and very few lymphocytes/eosinophils. The deep dermis has also engorged vessels also filled with neutrophils [110]. Cases of cutaneous vasculitis were reported in MWS and CINCA/NOMID syndrome in which other organs are also compromised [111].

TNF receptor-associated periodic syndrome (TRAPS) is an autosomal dominant disorder consisting of periodic fever episodes lasting from 3 to 21 days, and in which manifestations show pleuritic chest pain, abdominal pain, conjunctivitis, periorbital edema, monoarthritis, testicular pain, myalgia, papulomacular and urticarial rash. A report revealed small vessel vasculitis and panniculitis in a 66-year old patient diagnosed with TRAPS with migratory macular erythematous rash and with positive ANCA against elastase, successfully treated with etanercept [112].

IGG4 RELATED DISEASE

The analogy in the histopathology of two small vessel vasculitides granuloma faciale (GF) and erythema elevatum diutinum (EED) with IgG4-related disease suggests that they might belong to the same spectrum. The two vasculitides, considered as a single disease with different presentations, share two distinctive features: small vasculitic lesions and concentric fibrotic processing. Granuloma faciale affects preferentially the face with one or multiple erythematous purplish plaques, and with lesions showing dense inflammatory infiltrate with neutrophils, eosinophils, lymphocytes and plasma cells and formation of perivascular concentric fibrosis.

Similarly, erythema elevatum diutinum presents with plaques nodular lesions preferring the trunk and lower extremities and with predominant neutrophils in the infiltrate. GF has been linked with eosinophilic angiocentric fibrosis, an eosinophil-rich infiltrate with perivascular fibrosis characteristically present in the upper respiratory tract. This latter has also been proposed being an expression of IgG4-related disease and the hypothetical link between both surmounts to the functional role of IgG4 with allergic responses and the production of IL-5 attracting eosinophils with subsequent fibrosing process formation. IgG4-related disease is a systemic illness causing mass lesions in different organs, like the pancreas, exocrine glands, lymph nodes peribiliary infiltrates, interstitial nephritis and other tissues, and associated with a predominant lymphoplasmacytic cell infiltrate producing excessive IgG4,

eosinophils, storiform fibrosis and obliterative thrombophlebitis. The quantity of lymphoplasmacytic infiltrates, serum IgG4 levels, the IgG4/IgG ratio are diagnostic criteria [113] and to test whether EED and GF fulfilled these, tissues of 32 patients (GF, n = 25; EED, n = 7) were analyzed with Immunohistochemistry. However, results failed to provide confirmatory evidence in the two vasculitides attributable to the stringent diagnostic criteria and to the retrospective nature of the study [114]. In another report, however, the results in tissues of GF and EED, 7 (22.6%) out of 31 patients fulfilled criteria for IgG-related disease (IgG4/IgG ratio > 40% and > 50 cells with IgG4 IHC per high power field), but none in the EED patients. Curiously all patients were males and with recurrent multiple lesions without other organ involvement suggestive of a localized form of IgG4-related disease might be expressed as GF in some subpopulations [115]. Further prospective and larger multicentric studies are required supporting this concept.

Table 5. Clinical, pathologic, and laboratory findings indicating a high probability of systemic disease¹

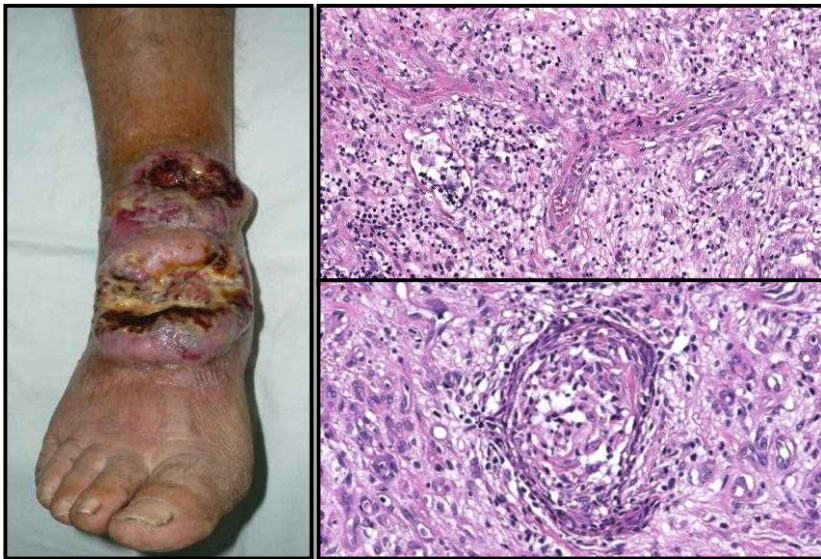
Clinical signs or symptoms	Suspected Systemic Vasculitis Syndrome
High fever	Infection, systemic inflammatory disorders
Paresthesias, foot drop	EGPA, PAN
Abdominal pain	HSP, EGPA, MPA, PAN, RV, LV, BD
Frank arthritis	RV, infection, PAN, systemic inflammatory disorder
Hypertension	PAN
Purpura above waist, upper extremities	HSP, MPA, GPA, EGPA
> 1 type of vasculitic lesion*	HSP, MPA, GPA, EGPA, RV, LV, BD
Punctate palmar lesions	LV
Laboratory evaluation	Suspected Systemic Vasculitis Syndrome
ESR > 40mm/hr	Infection, hematologic malignancies, systemic inflammatory disorders
Elevated RF, cryoglobulins and low complement	CV
Chest x-ray: infiltrates or cavities	GPA (fixed infiltrates), EGPA (non-fixed infiltrates), MPA, malignancy
Hematuria and/or proteinuria and/or abnormal creatinine	Dermal-renal vasculitis syndrome: GPA, MPA, HSP, SLE
Hypocomplementemia	UV associated with SLE, RV, CV, infective endocarditis
Abnormal blood count	Infection, hematologic malignancy, systemic inflammatory disorders
cANCA (PR3)	GPA
pANCA (MPO)	MPA, EGPA
Eosinophilia, elevated IgE, elevated RF	EGPA
Histologic Examination	Suspected Systemic Vasculitis Syndrome
Deep dermal and/or subcutaneous small and/or muscular vessel vasculitis	Systemic vasculitis syndrome (GPA, EGPA, MPA, CV, BD, RV, LV, septic vasculitis), malignancy associated
Palisaded neutrophilic (extravascular) granulomatous dermatitis	GPA, EGPA, LV, RV
Tissue neutrophilia	SLE, infection
Tissue eosinophilia	EGPA and drug induced vasculitis
Direct immunofluorescence	Suspected Systemic Vasculitis Syndrome
Isolated or predominate IgA vascular deposits	HSP
Lupus band (IgG, IgM, and/or C3 at the BMZ)	LV, UV associated with SLE

BD = Behcet disease; BMZ = basement membrane zone; c-ANCA = cytoplasmic anti-neutrophil cytoplasmic antibody; CV = cryoglobulinemic vasculitis; EGPA = Eosinophilic granulomatosis with polyangiitis; ESR = erythrocyte sedimentation rate; GPA = Granulomatosis with polyangiitis; HSP = Henoch-Schonlein purpura; LV = lupus vasculitis; MPA = microscopic polyangiitis; MPO = myeloperoxidase; PAN = polyarteritis nodosa; p-ANCA = perinuclear pattern of anti-neutrophil cytoplasmic antibody; PR-3 = antiproteinase-3; RF = rheumatoid factor; RV = rheumatoid vasculitis; SLE = systemic lupus erythematosus; UV = urticarial vasculitis

¹Adapted from Chen and Carlson et al. [4].

SYSTEMIC MALIGNANCY

Lymphoproliferative, myeloproliferative, and carcinomatous tumors comprise < 5% of paraneoplastic cutaneous vasculitis (Figure 24), a diagnosis that may be considered in patients with recurrent purpura, hematologic abnormalities including cytopenia, monoclonal gammopathy, immature blood cells; hematuria, abnormal tissue or nodal masses on imaging studies, and refractory responses to immune therapies. There are three such categories of patients including, those with true paraneoplastic vasculitic syndromes wherein the vasculitis improves with extirpation or treatment of the tumor; vasculitis masquerading as malignancy such as lung masses in GPA; and malignancy masquerading as vasculitides as in emboli from an atrial myxoma and superficial migratory thrombophlebitis with pancreatic cancer. Most paraneoplastic cutaneous vasculitic syndromes are the result of a paraproteinemia secondary to lymphoproliferative disorders, including cryoglobulinemia in association with lymphocytic lymphoma and Waldenström macroglobulinemia.



Courtesy of Juan Carlos Graces, MD, Guayaquil, Ecuador).

Figure 24. Myelodysplastic syndrome presenting as erythema elevatum diutinum. A large ulcerative tumor shows localized fibrosing leukocytoclastic vasculitis.

PROGNOSIS

There are clinical and histologic predictors for the prognosis of cutaneous vasculitis that suggest the likelihood of concomitant or later systemic vasculitis [1, 18, 116] as shown in Table 5. The distinction between localized cutaneous and systemic vasculitis is important since the former carries a relatively favorable outcome, while the latter conveys the likelihood of permanent organ damage, increased morbidity and mortality. About 20% to 40% of patient with cutaneous vasculitis have concomitant limited systemic vasculitis notably kidney such as so called renal-dermal vasculitis while the likelihood of chronicity and systemic progression

is enhanced when there is coexisting CTD, cryoglobulinemia, frank ulceration [117], arthralgia [19], more than one form of cutaneous vasculitic lesion such as ulceration and palpable purpura, putative muscular and SVV, normal serum IgA levels [17], paresthesia, fever, painless lesions [19] and cutaneous necrosis [118]. Histologically, the severity of vessel injury in cutaneous vasculitis correlates with the clinical severity and course [117, 119]. Others have noted histopathological changes of LCV were not predictive of extracutaneous involvement [120]. Lesional IgA deposits by DIF predict proteinuria and subsequent renal involvement [121]. Up to 60% of patients presenting with cutaneous vasculitis on skin biopsy have SVV restricted to the dermis while the remainder have deep dermal and pannicular SVV and muscular vessel involvement [122].

THERAPY

Therapy depends upon the nature and severity of the vasculitis. Mild hypersensitivity due to drug reactions should be treated with discontinuation of the offending agents, antihistamines for urticaria-associated pruritus, and a short course of corticosteroids in more severe cases. Simple observation may be adequate for mild cases and transient lesions of HSP/IgAV-related purpura. Non-steroidal anti-inflammatory agents, colchicine, antihistamines, and dapsone may be employed in chronic cutaneous vasculitis without recognizable cause and in selected patients prior to administration of corticosteroids and cytotoxic drugs. Rituximab has equivalent remission-induction efficacy as cyclophosphamide in AAV each in conjunction with corticosteroids [123]. Morphologic alternations of the vessel wall lumina and perivascular areas may be useful in treatment strategy. Healed arteritis with intimal thickening due to luminal occlusion should suggest the need for anticoagulation and vascular dilating agents, whereas pathologically confirmed acute and subacute arteritis generally warrants combination immunosuppressive therapy to suppress ongoing vascular inflammation and tissue damage.

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Chapter 212

THE CLINICAL APPROACH TO PATIENTS WITH VASCULITIS

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ABSTRACT

The systemic vasculitides are a heterogeneous group of disorders. Pathologically defined by the presence of vascular inflammatory infiltrate, primary vasculitides occur in the absence of a known cause or associated disease state, while secondary vasculitides occur in association with known underlying disorders and disease triggers. The vasculitic process is often systemic however vascular inflammation may be confined to an isolated organ system such as the kidney or even central nervous system. This chapter provides an overview of the approach to patients with systemic vasculitis including the clinical presentation, differential diagnosis, imaging and histopathologic evaluation, and short- and long-term treatment-related complications.

INTRODUCTION

The primary systemic vasculitides are a diverse group of multisystem syndromes characterized according to the size of the blood vessels involved and the organ systems affected. Inflammation in the blood vessels can lead to diminished blood flow or vessel occlusion resulting in ischemia, necrosis and subsequent tissue damage. The blood vessels themselves can be damaged in vasculitis resulting in permanent stenosis, aneurysmal change and vessel rupture. Any combination of vessels from large arteries to tiny venules and

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capillaries may be involved in the inflammatory process. The 2012 Revised Chapel Hill Consensus Conference (CHCC) [1] provides useful nosology for the primary vasculitides based upon the caliber of the vessels, both arteries and veins, involves. Small vessel vasculitis (SVV) includes granulomatosis with polyangiitis (GPA) (Wegener type)], microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA) (Churg-Strauss syndrome [CSS]), known collectively as anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV).

Vasculitic disorders associated with immune complexes (IC) include IgA vasculitis (IgAV) (Henoch-Schönlein purpura [HSP]), cryoglobulinemic vasculitis (CV), and hypocomplementemic urticarial vasculitis (HUV) associated with C1q antibodies. Vasculitis without a predominant vessel size and caliber, respectively from small to large, involving arteries, veins and capillaries, comprises the category of variable vessel vasculitis (VVV), characteristic of Behçet disease (BD) and Cogan syndrome. Medium vessel vasculitides (MVV), exemplified by polyarteritis nodosa (PAN) also includes Kawasaki disease (KD) in children. Large vessel vasculitides (LVV) are represented by giant cell arteritis (GCA), and Takayasu arteritis (TAK). Vascular inflammation confirmed to a single organ system such as the kidney, peripheral nerves, brain or vessel such as IgG4 related aortitis, are deemed single organ vasculitides (SOV).

In 2008, the Pediatric Rheumatology European Society (PRES) and the European League against Rheumatism (EULAR) and the Pediatric Rheumatology International Trials Organization (PRINTO) reported methodology and overall clinical, laboratory and radiographic characteristics for several childhood systemic vasculitides [2] followed by a final validated classification [3] based upon vessel size, similar to the CHCC nomenclature [1].

This chapter provides an overview of the clinical approach and management of patients with primary systemic vasculitis including aspects of the clinical presentation, differential diagnosis, imaging, histopathologic evaluation, and short- and long-term treatment-related complications.

HISTORY AND EXAMINATION

Clinical acumen combined with a thorough history and physical exam is essential to making the diagnosis and defining the correct testing to complete the diagnosis and assess the extent of disease. Thus, while it may seem obvious, the first challenge in the diagnosis of primary systemic vasculitis is in fact considering it as a possible diagnosis. The diagnosis is often delayed as more common causes of multi-system disease like infections and malignancies are investigated. One population-based study reported a median time interval between the onset of symptoms and diagnosis of 11 months (range, 1 to 50 months) in TAK [4]. The past decade has witnessed a decrease in the time to diagnosis of AAV from a mean of 17 months to 4 months; however delays in diagnosis occur in subgroups of patients with flu-like prodromal and upper respiratory symptoms [5]. Failure to make a timely diagnosis can have devastating consequences such as blindness due to unrecognized GCA, renal failure caused by untreated AAV, and death due to a rupture of an unrecognized mesenteric aneurysm caused by PAN.

Despite significant overlap, vasculitic disorders generally manifest characteristic patterns of organ involvement. Fever, weight loss, fatigue, arthritis, skin rash, peripheral (PNS) and central nervous (CNS) manifestations are common symptoms and signs of systemic vasculitides. In spite of expected disparities in vessel involvement and resultant end-organ damage, in one cohort of 800 patients with AAV, PAN, GCA, and TAK [6], greater than 30% of those with LVV, and more than 70% of patients with SVV and MVV experienced constitutional symptoms at the time of diagnosis. Certain clinical presentations should prompt swift evaluation for systemic vasculitis such as mononeuritis multiplex, pulmonary-renal syndrome with a rapidly progressive glomerulonephritis, alveolar hemorrhage and infarction in multiple vascular beds.

The presence of concomitant infection should be sought in suspected patients. Both hepatitis B (HBV) and C virus (HCV) infections are associated with concomitant IC-mediated vasculitis, and there are recognized relationships between HBV and PAN, and HCV contributes to the pathogenesis of mixed cryoglobulinemic vasculitis. Although effective vaccine programs in the developed world may already have dramatically reduced the rate of acute HBV infection, large cohort studies have found an association between HBV and PAN in up to a third of patients [7]. Hepatitis B surface antigen (HBsAg) and antibody (HBsAb), and core antibody (HBcAb), and HCV should thus all be included in the routine evaluation of such patients. Human immunodeficiency virus-type 1 (HIV-1) is an associated cause of vascular inflammation predominating in SVV [8]; and in the absence of systemic vasculitis, patients with HIV may demonstrate ANCA-seropositivity. HIV-infected patients become susceptible to opportunistic infection including cytomegalovirus (CMV). The latter may be associated with true vasculitis with discernible CMV inclusions in the inflammatory infiltrate, especially in those with established acquired immune deficiency syndrome (AIDS), and skin, gastrointestinal, pulmonary, and CNS involvement. Other opportunistic infections that cause vasculitis in the immunocompromised hosts include *Pneumocystis jirovecii* and *Toxoplasma gondii*. Endovascular infection by bacterial or fungal agents in the course of endocarditis and mycotic aneurysms can mimic systemic vasculitis. Koenig and colleagues [9] identified a *Burkholderia*-like gram-negative bacterial strain in the temporal arteries of subjects with GCA. Two other pathogens, *Treponema pallidum*, the spirochete pathogen of tertiary syphilis, and *Mycobacterium tuberculosis* (TB), both contribute to the development of aortitis and LVV, with histologically evident chronic granulomatous in endemic areas where the prevalence of TAK is highest.

A knowledge of potentially offending medications or known drug abuse may give valuable clues to the origin of vasculitis in susceptible patients. There is an ever-growing list of medications associated with hypersensitivity vasculitis, the clinical presentation of which is usually self-limited and resolves once the causative agent has been identified and removed. The prescription drugs hydralazine and propylthiouracil are both associated with ANCA-seropositivity but not true vasculitis. One important distinction in the diagnosis of drug-induced AAV is that unlike idiopathic AAV, those associated with drug-induced ANCA-seropositivity often have antibodies against more than one antigen [10]. The acute onset of headache and focal neurological deficit in a known cocaine abuser should lead to consideration of cocaine-induced vasospasm with cerebral hemorrhage. Such patients will often have midline destructive nasal sinus lesions. Cocaine-induced midline destructive lesions (CIMDL) may also resemble GPA, further complicating the distinction between CIMDL and AAV is often present ANCA-seropositivity. Cocaine-induced CIMDL can be

associated with p-ANCA, c-ANCA or both. The most common autoantibody in CIMDL, occurring in 84% of patients in one study, was atypical p-ANCA directed against human neutrophil elastase (HNE) [11]. Requesting specific ANCA serology by the immunofluorescence technique (IFT), and not just the ANCA pattern, avoids misdiagnosis between CIMDL and sino-nasal GPA.

Fever, purpuric rash, acute renal failure, and neurologic involvement may also be the clue to SVV. While prothrombotic disorders may mimic systemic vasculitis, the manifestations of anti-phospholipid syndrome (APS) can overlap with systemic vasculitis. Affected patients with catastrophic APS can present with pulmonary-renal syndrome, and unlike those with SVV, such patients require anti-coagulation. The non-criterion manifestations of APS-like skin ulcers and emboli from verrucous valvular heart disease can appear grossly similar to vasculitic lesions however skin biopsy which instead shows *in situ* thrombi instead of vascular inflammation distinguishes the two entities.

Ischemic limb pain and claudication may well be the presenting manifestations of MVV and LVV in older patients with diabetes, hyperlipidemia, hypertension and tobacco use that is due to atherosclerosis. Moreover, both vasculitis and atherosclerosis may reveal abnormalities on non-invasive vascular imaging and contrast angiography studies. While the suspicion of primary systemic vasculitis should generally be reserved for younger patients and older individuals lacking traditional cardiovascular risk factors, the exception occurs in cholesterol crystal embolism [12]. Such patients manifest distal embolization of atherosclerotic plaques leading to livedo skin rash, digital ischemic, visual and renal manifestations. Arteriolar cholesterol clefts are demonstrable in tissue biopsy of skin, muscle, and cutaneous nerve specimens.

A history of malignancy or the suspicion of cancer may be indispensable and life-saving. The majority of malignancy-associated vasculitides occur in conjunction with hematologic malignancies and myelodysplastic syndromes. A reported 4.5% to 8% of patients with lymphoproliferative disease developed primary systemic vasculitis with renal, cerebral, pulmonary, and cutaneous involvement [13]. There are reports of homology between the genetic sequences of serine proteinase-3, the antigenic target in GPA, and myeloblastin a protein found in certain human leukemic cells, explaining in part the association between hematologic malignancy and systemic vasculitis [14]. Hairy cell leukemia may be the proximate cause of necrotizing systemic vasculitis. Other tumors can cause constitutional symptoms mimicking vasculitis and embolic phenomena including atrial myxoma, so noted in more than 30% of patients that manifested fever, arthralgia and weight loss in association with laboratory features of acute inflammation [15]. These benign tumors express increased levels of IL-6, a pro-inflammatory cytokine implicated in the pathogenesis of LVV such as GCA. A history of thyroid endocrinopathy may lead to consideration of autoimmune thyroid disease and Hashimoto thyroiditis and encephalopathy.

Although very rare, the literature describes cases of Hashimoto encephalopathy attesting to its occurrence [16]. Affected patients present with seizures, stroke-like episodes, transient focal and global neurological deficits, and a variety of neuropsychiatric disturbance from dementia to hallucinations and psychosis. The encephalopathy evolves with concomitantly elevated anti-thyroid peroxidase antibodies, independent from hormonal thyroid function setting it apart from thyrotoxicosis and myxedema. Albeit rare, such cases may be indistinguishable from CNS vasculitis and share an autoimmune vasculitic etiopathogenesis.

The autoimmune encephalitides [17], so suggested by cognitive, neuropsychiatric complaints and seizures, are clinically and histopathologically associated with serum and intrathecal antibodies to intracellular and surface neuronal antigens, and constituents of the limbic system neuropil. This has led to a reconsideration of a number of neuropsychiatric and neurocognitive disorders as having shared mechanisms of origin. While there are no convincing cases of vasculitis autoimmune encephalitis, there may be difficulty in clinically distinguishing them from primary CNS vasculitis.

A detailed genetic pedigree may not be practical in all cases, but knowledge of a familial disorders or genetic syndromes affecting the vasculature resembling vasculitides may signal the need for associated targeted genetic testing in given patients. At least three congenital disorders, Ehlers-Danlos syndrome, type-4 Loeys-Dietz and Marfan syndrome [18-20], all enter in to the differential diagnosis of LVV and idiopathic aortitis, also a component of the IgG4-related disorders (IgG4-RD); and a fourth disorder termed Grange syndrome that resembles PAN.

LABORATORY EVALUATION

Accurate diagnosis depends upon familiarity with the myriad of clinical features of the various vasculitides together with results of carefully selected laboratory studies including screening metabolic, autoimmune and infectious serology, followed by appropriate vascular imaging studies, and appropriate tissue biopsies or sampling of body fluids.

Blood studies will often reflect the severity and type of immunological storm due to underlying primary vasculitis in analysis of a complete blood count (CBC) and differential, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), antinuclear antibody (ANA), basic metabolic panel, ANCA by IFT and enzyme-linked immunosorbent antibody (ELISA) serology specific for proteinase-3 (PR3) and myeloperoxidase (MPO); T- and B-cell subset quantitation; C1q binding and Raji cell circulating immune complexes and C3, C4, and CH50 complement protein levels; quantitative immunoglobulins, subsets, and immunofixation (IFE); with rheumatoid factor (RF) titers, cryoglobulins, serologic analysis for HBV, HCV, HIV, lupus and anticardiolipin antibodies, acute and convalescent *Borrelia* and coinfectious serology; and human leukocyte antibody (HLA) alleles appropriate for different types of primary vasculitides.

Urine should be obtained for spot analysis and 24-hour collection for chemical and cellular microscopic constituents to screen for renal impairment.

The *radiologic evaluation* of patients with primary vasculitis should include color-Doppler sonography (CDS), and 3-Tesla (T) magnetic resonance imaging (MRI) combined with angiography (MRA) or CT angiography (CTA) to assess the temporal arteries and great vessels. Digital subtraction angiography (DSA) of individual vascular organ beds can be employed to visualize the vessel walls and luminal changes. Mural changes with vessel wall thickening correlate with early inflammation while vascular luminal stenoses and aneurysm formation indicate late vasculitic complications. ¹⁸Fluorodeoxyglucose positron emission tomography (PET) detects metabolically active inflammatory cells infiltrating vessel walls in affected patients especially in large vessels. However, the extent of disease and monitoring of luminal changes is best appreciated by employing a combination of PET and DSA techniques.

Likewise the combination of nuclear medicine cerebral perfusion with single photon emission CT (SPECT) and PET fused with MRI provides a unique estimation of perfusion across the blood-brain barrier in relation to cerebral regional metabolism.

Cerebrospinal fluid (CSF) obtained in patients with presumed CNS involvement, should be obtained atraumatically and sampled for an extensive panel of constituents with an extra tube placed in a negative 80 degree Celsius freezer for future analysis or to replace specimens lost in transport. This includes analysis of CSF total protein and glucose levels, white blood cell and red blood cell counts, IgG and albumin levels, oligoclonal bands, cytology, bacterial gram stain, latex agglutination of meningitis-associated bacterial antigens related to *Group B strep*, *Strep pneumoniae*, *Haemophilus influenza* (Type b), *Neisseria meningitidis* (Groups A,B,C,Y & W135) and *E. coli* K1 infection; India ink preparation, cryptococcal antigen, acid-fast stains; bacterial, fungal, parasitic, and TB cultures. New York State has a viral encephalitis panel that includes Adenovirus, West Nile virus, HSV 1 and 2, CMV,VZV, EBV, and HHV6 DNA viruses, as well as Eastern Equine Encephalitis, Saint Louis Encephalitis and Enterovirus RNA viruses, all analyzed by real-time polymerase-chain reaction (PCR). Patients suspected of *Borrelia burgdorferi* infection undergo paired serologic and PCR analysis of CSF and serum to demonstrate intrathecal production of *Borrelia*-specific antibodies [21]. A commercially available panel of CNS antibodies for patients with autoimmune or paraneoplastic dementia with or without sensory and motor neuronopathy or dysautonomia includes N-methyl-D-aspartate receptor (NMDA-R), voltage-gated potassium channel (VGKC)-complex, glutamic acid decarboxylase (GAD) 65, gamma-amino butyric acid beta receptor (GABA-R), anti- α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA), anti-neuronal nuclear antibody (ANNA)-1, -2, -3; anti-glial nuclear antibody (AGNA)-1; Purkinje cell cytoplasmic antibody (PCA) types 2 and Tr; amphiphysin, N and P/Q-type calcium channels, ganglionic neuronal and muscle acetyl choline receptors (AChR), and collapsin response-mediated protein-5-(CRMP-5-IgG).

Tissue biopsy is important in defining the type, extent and character of the inflammatory process and categorizing the underlying systemic vasculitic disorder. In AAV, histologic evidence of necrotizing SVV with accompanying granulomatous inflammation noted in GPA can be used to support the diagnosis in conjunction with clinical and serologic information. Although nasal, sinus and upper airway involvement in GPA may be noted overall in 92% of patients at onset of disease [22], tissue biopsy of these regions is associated with vasculitis and necrosis in only 23% of upper airway biopsy specimens; vasculitis and granulomatous inflammation in 21%; and vasculitis together with necrosis and granulomatous inflammation in only 16%. The small amount of tissue available in biopsy specimens from areas of the head and neck make it surprisingly difficult or impossible to identify the classical pathological features of GPA in some patients. By comparison, renal biopsy in patients with GPA show varying degrees of segmental necrotizing glomerulonephritis in 80% of tissue. In the absence of renal involvement, targeted biopsy of radiographically abnormal lung parenchyma via a thorascopic or open lung biopsy technique showed granulomatous changes in 22% and capillaritis in 31% of those so studied [20] compared to the efficacy of transbronchial biopsy in establishing the diagnosis of pulmonary vasculitis in 10% of suspected tissues [23].

The finding of focal, segmental necrotizing vasculitis in medium-sized arteries confirms the diagnosis of PAN in suspected patients. Angiographic demonstration of microaneurysm formation is an acceptable surrogate to the histopathologic confirmation when tissue cannot be readily obtained [24]. Histologically-proven PAN is ascertained in 70% of patients by

nerve, muscle or skin tissue biopsy in one large cohort [25]. Of 129 patients underwent nerve biopsy including 108 with peripheral neuropathy and 21 without peripheral neuropathy, vasculitic lesions were noted respectively in 83% and 81% of patients compared to muscle biopsy which showed vasculitis respectively in 68% and 60%. Angiography showed renal and gastrointestinal microaneurysms or stenosis respectively in 66% and 57% of patients. While PAN frequently involves the gastrointestinal tract especially the small intestine, biopsy of visually apparent lesions on luminal exam rarely provide histopathologic confirmation of vasculitis [26]. Renal biopsy may be negative even in patients with frank organ involvement due to sampling error. Unlike AAV, where the histopathologic renal lesion is the kidney glomerulus, microaneurysm formation due to PAN increases the risk of bleeding associated with renal biopsy.

Histopathologic evidence of vascular wall infiltration by giant cells at the junction of the intima and media, leading to thrombosis, intimal hyperplasia, and fibrosis [27] is the gold standard method of GCA diagnosis. Accordingly, temporal artery biopsy is recommended for all patients with suspected GCA [28]. The sensitivity of temporal artery biopsy in GCA has been estimated to be 85% [29]. Evidence in support of unilateral as compared to bilateral temporal artery biopsy is lacking, leaving it up to the judgment of the treating physician. Temporal artery ultrasonography can be used to guide the surgeon to the arterial segment with the clearest halo sign in performance of temporal artery biopsy [30], however the discontinuous nature of inflammation in GCA leading to skip lesions may still lead to unforeseen false-negative results when the tissue specimen is of insufficient length and multiple sections are not examined. Certain clinical features, such as the presence of jaw claudication can increase the positivity predictive value of a temporal artery biopsy. Arteritis can be observed histologically even after several weeks of high dose corticosteroid therapy [31]. Notwithstanding, the heightened risk of ischemic complications culminating in irreversible visual loss in early untreated GCA has led to the recommendations for prompt administration of high-dose corticosteroid therapy while awaiting tissue biopsy results.

Skin biopsy can be performed for IF analysis of vessel walls to search for microscopic analysis for leukocytoclasia, Ig and complement deposition. Two 3 mm punch skin biopsies of along the distal calf and proximal thigh fixed in anti-protein-gene-product 9.5 (PGP 9.5) solution will discern epidermal nerve fiber depletion useful in the designation of small and large fiber neuropathy, and in the selection of patient who should undergo surgical biopsy of the sural nerve or branch of the superficial fibular sensory nerve and corresponding soleus and peroneus brevis muscle to search for vasculitic lesions and confirm the neuropathic or myopathic changes found on electrodiagnostic studies. Adults and children with CNS involvement whether clinically, by MRI, SPECT, PET imaging of the brain, cerebral angiography, or CSF examination, especially in the setting of acute mental change, new focal neurological deficit, CSF protein content >100 mg/dL or pleocytosis, may be candidates for empiric therapy for primary CNS angiitis [32] or combined leptomeningeal and brain biopsy to diagnose granulomatous or non-granulomatous necrotizing arteritis [33-34].

TREATMENT

Most experts concur with the following three principles to guide management of patients. First, vasculitis is a potentially serious disorder with a propensity for permanent disability owing to tissue ischemia and infarction. Second, undiagnosed and untreated, the outcome of vasculitis is potentially fatal. Third, a favorable response to an empiric course of immunosuppressive and immunomodulating therapy should not be considered a substitute for the histopathologic confirmation of vasculitis. Physicians treating vasculitides must choose the sequence and combination of available immunosuppressant and immunomodulating therapies to induce and sustain remission and treat relapses, recognizing the possible beneficial and adverse effects. Recommended treatment options for the different categories of vasculitis are summarized in Table 1.

The standard of care for the treatment of vasculitides, notably AAV, has been evolving in response to many factors [35]:

First, the steady influx of data from multicenter, national and international collaborative, evidence-based randomized clinical trials (RCT) and observational cohorts in adult vasculitides, notably from the French Vasculitis Study Group (FVSG) database, United States-Canadian Vasculitis Clinical Research Consortium (VCRC), European Vasculitis Study Society (EUVAS), the European League Against Rheumatism (EULAR), The French Vasculitis Cohort of Patients with Primary Vasculitis of the Central Nervous System (COVAC), and the Diagnostic and Classification Criteria in Vasculitis Study (DCVAS). Childhood vasculitides have been represented by the Pediatric Vasculitis Initiative (PedVas), a Canadian and United Kingdom collaborative study of ARChiVe Investigators Network within the PedVas Initiative and ARChiVe registry, including BrainWorks and DCVAS, of pediatric and adult cases of AAV (GPA) and PACNS (NIH identifier, NCT02006134). PedVas has been prospectively collecting clinical and biobank data of registered cases within 12 months of study entry since 2013.

Second, while many vasculitides still lack well-validated measures of disease activity or state for use in clinical trials, there have nonetheless been advances in standardized approaches to conducting clinical trials as advocated by the EULAR and its collaborators worldwide [36]. Moreover, the Vasculitis Working Group of the Outcome Measures in Rheumatology (OMERACT) initiative is actively pursuing projects to advance development of valid measures in the vasculitides [37-39], such as disease-specific self-reported patient-related outcomes (PRO) applicable to AAV to distinguish treatments of varying efficacy, included among them, Health Related Quality of Life (HRQoL) measures, that are further separable by the caliber of vessels involved [40, 41]. Children's self-reported HRQoL measured by the Pediatric Quality of Life Inventory Version 4.0 (PedsQL) Generic Scores Scales, repeatedly measured over time in pediatric inflammatory brain disease (IBrainD) [42], including cPACNS, shows poor HRQoL scores in >50% of patients at that associates with cognitive dysfunction as the most presenting symptom, as well as, small vessel cPACNS (SV-cPACNS) [43].

Third, the influence of gene-wide association studies (GWAS) and biobank data such as the UK Biobank to elucidate risk gene loci, single nucleotide polymorphism (SNP) and human HLA polymorphisms in disease clusters and population cohorts [44]. Such inherited and environmental factors, gene-gene interactions, epigenetic factors, and other influences

upon the immunopathogenesis of vasculitides have had important theoretical importance for the performance of RCTs in vasculitides subtypes, as well as, relevance for screening studies and timing of therapy.

Fourth, historically, the introduction of effective therapy for AAV, beginning with corticosteroids in 1948, and cyclophosphamide two decades later, together with adjunctive therapies, transformed the outcome of AAV with five-year rates approaching 80% [45]. The AAVs were thus transformed into chronic relapsing disorders with progressive organ damage and disability. Hope for a better treatment was heralded by the effectiveness of a daily oral regimen of 2 mg/kg/day of oral cyclophosphamide and prednisone in GPA that served as a template for the treatment of virtually all types of systemic vasculitis for decades. However, almost all patients had serious morbidity from irreversible features of their disease or side effects of treatment, including the cumulative exposure to corticosteroids leading to osteoporosis and bone fractures; and cytotoxic therapy-related chronic myelosuppression, infection, urothelial malignancy, and infertility [46, 47]. Three later adjustments in the use of cyclophosphamide in AAV were instructive. One was the sequential replacement of cyclophosphamide by azathioprine [48]. A second was the replacement of cyclophosphamide by methotrexate by for early systemic disease without critical organ manifestations in the NORAM study [49]. A third was pulsed intravenous cyclophosphamide with a dose reduction in patients >60 years of age and renal impairment rather than daily oral cyclophosphamide as in the CYCLOPS study [50], enabling a cumulative dose reduction of approximately one-half. Follow-up analyses [51], however showed that reduced cyclophosphamide dose was associated with a higher risk of relapse, while methotrexate was associated with less effective disease control than with cyclophosphamide induction [52]; neither with increased long-term morbidity or mortality.

Fourth, the licensing of rituximab for the treatment of AAV was the most significant recent achievement but the optimal treatment strategy after rituximab induction-remission awaits delineation. Rituximab is a chimeric monoclonal anti-CD20 antibody that selectively depletes B-cells, but not plasma cells. The Rituximab in ANCA-Associated Vasculitis (RAVE) Study [53] found that rituximab was not inferior to daily cyclophosphamide treatment for induction of remission in severe AAV and possibly superior in relapsing disease. The Rituximab Versus Cyclophosphamide in ANCA-Associated Vasculitis (RITUXVAS) [54] demonstrated non-superiority of rituximab to standard intravenous cyclophosphamide for severe AAV with high-sustained remission rates in both groups. Rituximab-based therapy was not associated with reductions in early adverse events. However, rates of cardiovascular disease and malignancy in AAV increased, as well as, underlying patterns of disease such as accelerated atherosclerosis [55] raising other concerns that there might be non-traditional risk factors such as endothelial activation and excessive vascular remodeling [56]. Early outcome results for the treatment of childhood AAV, in particular GPA, reported by Morishita and colleagues on behalf of ARCHiVe Investigators Network and the PedVas [57] have been less encouraging than in adults. Among 105 children with AAV, mainly GPA, who received CS, CYC, MTX, or RTX for remission-induction, and PE in conjunction with CYC and/or RTX, 42% achieved remission at 12 months (Pediatric Vasculitis Activity Score [PVAS] of 0, CS dose < 0.2 mg/kg/day), 21 (48%) of whom discontinued corticosteroids by 12 months; all but 3 remaining on maintenance treatment at 12 months receiving azathioprine, methotrexate, rituximab, mycophenolate mofetil, and cyclophosphamide. However, up to 63% had a Pediatric Vasculitis Damage Index [PVDI]

score of 1 or more by 12 months, with the presence of renal, ear, nose and throat, or pulmonary damage; and 41% of children reported hospitalizations. Thus, a significant proportion of patients were not in remission at 12 months, and more than one-half of the patient cohort experienced damage early in the disease course. The 12-month remission rate of 42% in the cohort was significantly lower than Sacri and colleagues [58], who reported 73% remission at post-induction and 90% overall remission rate (including secondary remissions after a median time of 6.7 months). Disappointing early outcomes in the PedVas treatment study for GPA [57] serve as a cautionary note in the treatment of IBrainD and cPACNS with similar immunosuppressive regimens.

Fifth, animal models of AAV [59] have enabled the transfer of murine MPO-ANCA IgG without functioning B-, or T-cells, resulting in pauci-immune, necrotizing crescentic glomerulonephritis similar to human AAV [60, 61], while other lines of evidence link infection to ANCA-related autoimmunity through molecular mimicry [62]. Using experimental material from patients with inflammatory vascular disease caused by ANCA and specificity for PR-3, autoimmunity can be initiated through an immune response against a peptide, antisense or complementary to the autoantigen, which then induces anti-idiotypic antibodies cross-reactive with the autoantigen [63].

Table 1. Recommendations for the treatment of vasculitides

<i>Large Vessel Vasculitis</i> GCA, TAK: CS, AZA, RTX, infliximab, anti-TNF α , anti-IL-6R, tocilizumab, and MM. Adjunctive therapy: ASA and AC.
<i>Medium Vessel Vasculitis</i> PAN, KD: CS and CYC; MM.
<i>Small Vessel Vasculitis-AAV Type</i> GPA, EGPA, MPA: Induction with CS + CYC; CS + RTX; or CS + MM and maintenance RTX, AZA or MM.
<i>Small Vessel Vasculitis- IC Type</i> CV: MM; INF-alpha and PegINF-alpha plus ribovarin or RTX in HCV-associated MC. IgAV: CS and/or MM; and supportive care.
<i>Hypocomplementic-C1q</i> : Antihistamines, IVIg, PE.
<i>Variable Vessel Vasculitis</i> Cogan Syndrome: CS. BD: CS, MM; colchicine or anti-TNF α .
<i>Single Organ Vasculitis-Isolated Aortitis, PACNS</i> Isolated Aortitis: CS, AZA, MM, MTX. cPACNS: Induction with CS, CS +CYC or RTX, followed by maintenance with AZA, MTX or MM PCNSV: Induction with CS, CS +CYC or RTX, followed by maintenance with AZA, MTX or MM
<i>Vasculitis Associated With Systemic Collagen Vascular Disease-SLE, RAV</i> SLE: CS, MM; and AC. RAV: CS, RTX, infliximab and AZA or MTX
<i>Vasculitis Associated with Illicit Substance Abuse</i> Avoid illicit substance.
<i>Vasculitis Associated with Infection</i> Antimicrobial agents chosen specifically to treat a given etiologic organism.

Abbreviations: AC, anticoagulation; ASA, aspirin; AZA, azathioprine; BD, Behçet disease; CS, corticosteroids, CV, cryoglobulinemic vasculitis; CYC, cyclophosphamide; EGPA, eosinophilic granulomatosis with polyangiitis; GCA, giant cell arteritis; GPA, granulomatosis with polyangiitis; HCV, hepatitis C virus; IC, Immune complex; IgAV, IgA vasculitis; INF, interferon; IL, interleukin; IVIg, intravenous immune globulin; KD, Kawasaki disease; MC, mixed cryoglobulinemia; MM, mycophenolate mofetil; MPA, microscopic polyangiitis; MTX, methotrexate; cPACNS, childhood primary angiitis of the central nervous system; PCNSV, primary central nervous system vasculitis; PAN, polyarteritis nodosa; PE, plasma exchange; RAV, rheumatoid arthritis vasculitis; RTX, rituximab; SLE, systemic lupus erythematosus; TAK, Takayasu arteritis; TNF, tumor necrosis factor.

Sixth, there is increasing evidence for the role of both humoral-mediated and cell-mediated immunity in AAV, with involvement of complement activation in the renal damage of human ANCA-associated pauci-immune vasculitis [64]. Cell-mediated immunity is exemplified by activation of circulating T-cells and B-cells, with infiltration of plasmoblasts into affected tissues [65] are co-stimulated by the secretion of pro-inflammatory cytokines including IL-6 and TNF α . While T-cells contribute an important role in the pathogenesis of AAV [66], B-cells are still the main therapeutic target as precursors of ANCA-secreting plasma cells.

CONCLUSION

The heterogeneous nature of the systemic vasculitides expresses itself in the diversity of clinical presentations. The diagnosis rests upon first considering it as a possibility based upon the history and physical examination and supportive findings thereof on laboratory studies. Accurately diagnosed and so treated, the outcome can be favorable.

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Chapter 213

POLYARTERITIS NODOSA

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ABSTRACT

Polyarteritis nodosa is an exemplary multi-systemic medium-sized, primary systemic vasculitis of adults and children. Once the most frequent vasculitis, it has become progressively less common notably in developed countries due to eradication of hepatitis B virus infection, one of its most frequent causes. The evolution of clinical manifestations commences with the acute phase of neutrophilic and variable lymphocytic and eosinophilic inflammation of arterial vessel walls with medial necrosis, followed by aneurysm formation, and later by the healing of lesions that entrains fibrotic endarteritis and vascular occlusions. The coexistence of necrotizing vasculitis, healed lesions and normal arteries in different tissues or portions of the same tissue is a pathognomonic feature of the disease. Effective treatment of polyarteritis nodosa, which includes consideration of corticosteroids and cyclophosphamide depending upon the presence of favorable or unfavorable prognostic factors, and an antiviral agent if complicated by hepatitis B infection, have improved the 5-year survival of patients. This chapter considers aspects of the classification criteria, epidemiology, etiopathogenesis, main clinicopathologic features, treatment and outcome of PAN.

Keywords: polyarteritis nodosa, vasculitis, CNS, PNS, systemic vasculitis

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INTRODUCTION

In 1852, Carl von Rokitansky, Professor of Pathology at the University of Vienna described polyarteritis nodosa (PAN) in a 23-year-old man with a 5-day history of fever and diarrhea [1]; Küssmaul and Maier [2] rediscovered the disorder in 1866. Within decades, PAN was one of the most frequent vasculitides which became progressively less common in developed countries as a consequence of the eradication and treatment of one of its most frequent causes [3], hepatitis B virus (HBV) infection. This chapter reviews the classification criteria, epidemiology, etiopathogenesis, main clinicopathologic features, treatment and outcome of PAN.

CLASSIFICATION AND DIAGNOSTIC CRITERIA

In 1990, the American College of Rheumatology (ACR) (Table 1) established criteria for the classification of PAN [4], and although frequently cited, it did not distinguish between PAN and microscopic polyangiitis (MPA). These two disorders were initially considered different forms of the same disease because of similar main clinical manifestations. However, the two entities were clearly distinguished by the 2012 Revised Chapel Hill Consensus Conference (CHCC) Nomenclature [5], defining PAN as a necrotizing arteritis of medium- or small-sized arteries without glomerulonephritis, vasculitis in arterioles, capillaries or venules; and absent anti-neutrophil cytoplasm antibodies (ANCA). While both disorders involve the kidneys such as glomerulonephritis in MPA and vascular nephropathy in PAN, the former is associated with lung capillaritis while the latter has at most subclinical lung involvement. Moreover, the two disorders may be difficult to discern when nephropathy and lung capillaritis are absent, and especially when tissue biopsy does not distinguish involved vessel types or size. The 2012 Revised CHCC Nomenclature classifies PAN in the category of medium-sized vessel vasculitis (MVV), and vasculitis associated with a probable etiology when associated with HBV infection. ANCA serology, so noted in the majority of patients with MPA and other small-sized-vessel vasculitides (SVV) including granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA), is virtually never detected in PAN. Accordingly, a positive ANCA serology excludes the diagnosis in a given patient. It is important to emphasize that the Chapel Hill Consensus defined the nosology of vasculitides, but not the diagnostic criteria. Given that the 1990 ACR criteria are misleading, internationally recognized criteria are needed. Table 2 lists criteria useful in the diagnosis of PAN [6].

EPIDEMIOLOGY

PAN affects all racial and ethnic groups with an estimated annual incidence in the general population from 4.6 per 1,000,000 inhabitants in England [7], to 9.0 per 1,000,000 inhabitants in Olmsted County, Minnesota, to 77 per 1,000,000 inhabitants in a hepatitis B-hyperendemic Alaskan Eskimo population [8]. In a German study [9], the incidence of PAN was 0.3 to 0.4 per 1,000,000 inhabitants depending on the year and part of the country. A comparison of the

incidence of PAN among two European areas of Lugo, Spain, and Norwich, United Kingdom (UK) found insignificant incidence differences of 6.2 and 9.7 and 1,000,000 inhabitants [10, 11]. In France, the prevalence of PAN was 34 per 1,000,000 inhabitants in Seine–Saint-Denis, a northern suburb of Paris [12].

Table 1. 1990 ACR criteria for the classification of polyarteritis nodosa*

Criterion	Definition**
1. Weight loss >4 kg	Loss of ≥ 4 kg of body weight since illness began, not due to dieting or other factors
2. Livedo reticularis	Mottled reticular pattern over the skin of portions of the extremities or torso
3. Testicular pain or tenderness	Pain or tenderness of the testicles, not due to infection, trauma or other causes
4. Myalgia, weakness, or leg tenderness	Diffuse myalgia (excluding shoulder and hip girdles), or weakness of muscles or tenderness of leg muscles
5. Mononeuropathy or polyneuropathy	Development of mononeuropathy, mononeuropathy multiplex, or polyneuropathy
6. Diastolic BP > 90 mm Hg	Development of hypertension with the diastolic BP > 90 mm Hg
7. Elevated BUN or creatinine	Elevation of BUN > 40 mg/dL (14.3 mmol/L) or creatinine >1.5 mg/dL (132 μ mol/L), not due to dehydration or obstruction
8. Hepatitis B virus	Presence of hepatitis B surface antigen or antibodies in serum
9. Arteriographic abnormality	Arteriogram showing microaneurysms or occlusions of the visceral arteries, not due to arteriosclerosis, fibromuscular dysplasia or non-inflammatory causes
10. Biopsy of small- or medium-sized artery containing neutrophils	Histological changes showing the presence of granulocytes or granulocytes and mononuclear leukocytes in the artery wall

* Adapted from, reference [4].

** For classification purposes, a patient with vasculitis shall be said to have PAN if at least 3 of these 10 criteria are present. The presence of any 3 or more criteria yields a sensitivity of 82.2% and a specificity of 86.6%.

Abbreviations: ACR, American College of Rheumatology; BP, blood pressure; BUN, blood urea nitrogen; kg, kilogram; mmHg, millimeters of mercury.

Table 2. Diagnostic criteria for adult-onset polyarteritis nodosa*

Criteria**	OR	95% CI	R ²
Positive for PAN			
HBV infection	16.85	6.30–45.08	0.320
Myalgia	1.93	1.06–3.53	0.517
Mononeuropathy or polyneuropathy	3.36	1.93–5.86	0.619
Arteriographic abnormalities	20.40	7.30–56.99	0.640
Testicular pain or tenderness	5.27	1.98–28.26	0.661
Negative (exclusion) for PAN			
ANCA-positivity	0.11	0.05–0.23	0.668
Glomerulonephritis	0.07	0.02–0.29	0.674
Recent asthma onset	0.01	0.01–0.06	0.433

* Adapted from reference [6].

**Based on the analysis of 582 systemic vasculitis patients with all data available in the French Vasculitis Study Group's database: 194 PAN (among whom 117 had HBV-related PAN) and 388 other systemic vasculitides (GPA, n = 144; EGPA, n = 115; MPA, n = 101; cryoglobulinemia, n = 28). Abbreviations: OR, odds ratio; CI, confidence interval; R, coefficient of determination.

The incidence of PAN has dramatically declined in parallel with HBV infection [3], and is now very rare indeed. Public health measures including vaccine prophylaxis, blood-transfusion safety and other prophylactic measures against infectious exposure have resulted in the sharp drop in the annual number of PAN cases, suggesting a contributory infectious etiopathogenesis. Although HBV infection is a known cause of PAN, other infectious agents including viruses may be implicated in its onset. Although incidence of PAN has significantly decreased, paralleling HBV infection control, the incidence of PAN not related to HBV seems to increase again in France.

PATHOGENESIS

The immunopathogenic mechanisms leading to vascular injury in PAN are likely heterogeneous and remain largely unexplained. Vascular inflammation is the consequence of immune-complex (IC) mediated lesions [13–15]. When HBV infection causes PAN, evidence supports IC disease with HBV surface antigen (HBsAg) as the triggering factor [16, 17]. Almost all patients with HBV-related-PAN are associated with wild-type HBV, HBe antigenemia and high HBV replication, bolstering the concept that lesions could result from the deposition of soluble HBV antigen–antibody complexes in antigen excess, possibly involving HBeAg. Immune complexes could activate the complement cascade, the activated components of which could in turn attract and stimulate neutrophils. Circulating HBV-related antigens, distinct from HBeAg may be involved, as could direct endothelial cell injury due to viral replication [18]. Anti-endothelial cell autoantibodies (AECA), directed against antigens expressed on the endothelial cell surface, have been implicated as a pathogenic factor participating in vasculitis [19] leading to direct endothelial damage. There is yet little known of the possible vasculitic target autoantigens and whether AECA are of pathogenic significance. However, the sera of some patients with PAN and AECA recognize a 60-kDa heat-shock protein [20, 21]. Markedly increased interferon (IFN)- α and interleukin (IL)-2 levels, and moderately elevated tumor necrosis factor (TNF)- α and IL-1 β levels were detected in the sera of patients with PAN [22]. Inflammatory infiltrates, mainly macrophages and T-cells, particularly of CD8⁺ subset, were observed in perineural and muscle vessels of patients with PAN [23]. T-cell-mediated immune mechanisms likely play a role in the development and perpetuation of PAN lesions however to date there have been no experimental animal models. A PAN-like disorder in *cynomolgus* macaques [24, 25] very similar to the human disease sporadically occurs.

ETIOLOGY AND PRECIPITATING FACTORS

Relation to HBV Infection

Trepo and colleagues [16, 26] described the close relation between PAN and HBs antigenemia. In 1987 Guillevin and colleagues [3] reported one of the first addict patients who were proven to be contaminated by intravenous drugs. Intravenous drug abuse and sexual transmission of HBV to at risk, non-vaccinated individuals are the major causes of

HBV-related PAN. The development and distribution of anti-HBV vaccines to at-risk individuals explains the dramatic decrease in the number of new cases since 1989. Over the past few years, the frequency of HBV-related PAN has progressively declined and almost disappeared. Indeed, for the last 5 years, fewer than five cases have been identified annually throughout France.

Other Etiologies

In spite of occasional anecdotal cases [27], neither hepatitis C (HCV) nor GB virus, the latter phylogenetically related to the former were considered etiologically important in the development of PAN. Although there were several reported patients with parvovirus B19-infection [28], systematic testing of PAN patients did not find their occurrence to be statistically significant compared to controls [29]. Calabrese [30], and Gisselbrecht and colleagues [31] suggested a role for human immunodeficiency virus type 1 (HIV1) in the development of vasculitis. A close relation between hairy-cell leukemia and PAN was suggested by Elkon and colleagues [32, 33], but the relation to other malignancies has not been apparent. A Cleveland Clinic Foundation retrospective study by Hutson and coworkers [34] reported 69 patients with systemic vasculitis and malignancy, twelve of whom had both diseases occurring in same twelve months period, including two with PAN.

In 2014 a new monogenic autoinflammatory disease has been characterized, with many clinical and pathological features corresponding to hallmarks of PAN [35, 36]. The newly named DADA2 (Deficiency in Adenosine DeAminase 2) corresponds to a loss-of-function mutation in the CECR1 gene (Cat Eye syndrome Chromosome region 1). Although the role of ADA2 protein as a growth and differentiation factor for monocytes is known, the underlying pathophysiological mechanisms of the disease remain unclear. Children may present with necrotizing vasculitis, mimicking PAN, with strokes and hypogammaglobulinemia. Nevertheless, adult-onset cases have been reported and clinicians should be aware of this misleading disease for which new mutations have been described recently [37, 38]. DADA2 could be considered as a differential diagnosis for patients diagnosed as PAN if they have a family history of vasculitides, early stroke, an immune deficiency, or fail to respond to conventional therapy. Indeed, conventional immunosuppression is frequently ineffective while TNF- α blockers show interesting results [37, 39, 40].

We recommend CECR1 screening for unaffected siblings of index cases, cases of familial vasculitis, and cases of PAN that is resistant to standard treatment. Indeed, ADA2 deficiency could be a differential diagnosis of PAN or one of its cause. The phenotypic expression of PAN is common to infectious or non-infectious disease and shows that PAN could be a heterogeneous disease, due to different etiologies or pathogenic mechanisms. It may be that the individualization of ADA2 deficiency is one of the steps in deciphering PAN.

PATHOLOGY

PAN lesions can occur in any artery, but involvement of the aorta, other large elastic arteries and the pulmonary vasculature have rarely been described. The acute phase of arterial

wall inflammation is characterized by fibrinoid necrosis of the media and intense pleomorphic cell infiltration, with predominant neutrophil and variable lymphocytic and eosinophilic inflammatory cells. The normal architecture of the vessel wall, including the elastic lamina, is completely destroyed and replaced by a band of amorphous eosinophilic material that resembles fibrin when appropriately stained. Arterial aneurysms and thromboses can occur at lesion sites. Arterial healing is characterized by fibrotic endarteritis that can lead to aneurysm regression or when too abundant, vascular occlusion. A characteristic histological feature of PAN is the coexistence of necrotizing vasculitis and healed lesions or normal arteries in different tissues or in portions of the same tissue sample. Indeed, the lesions are usually segmental with presence of damages of different ages.

SPECIFIC ORGAN SYSTEM MANIFESTATIONS

Clinical Features

Table 3 shows the main clinical manifestations of PAN. This disorder occurs in patients of all ages, including children and the elderly, albeit most often between the ages of 40 and 60 years, without sexual predominance. A poor general condition is common, with two-thirds of patients experiencing weight loss and fever. Non-specific symptoms which occur early in the course of disease may be present at onset or even the singular manifestation. Although PAN is most often diagnosed after systemic manifestations appear, it is important to consider the diagnosis among individuals with unexplained or prolonged poor general health.

Table 3. Main organ or system involvement and clinical manifestations of polyarteritis nodosa in the literature

Reference	Patients (n)	Mean age	Organ/system involved or manifestation (%)						
			Heart	Hypertension	Skin	CNS	PNS	Kidney	GI
Pagnoux et al. [41]	348	51	22	35	50	5	74	51	38
Günel et al. [42]	15 (children)	10	67	20	20	0	0	13	47
Travers et al. [43]*	17	41	89	29 (mild) 41 (severe)	65	41	59	77	65
Schrader et al. [44]*	36	—	61	72	—	—	—	76	—
Fortin et al. [45]	45	54	18	—	44	24	51	44	53
Cohen et al. [46]*	53	54	4	14	58	—	60	66	25
Leib et al [47]*	64	47	30	25	28	25	72	63	42
Frohnert et al. [48]*	130	—	10	—	58	3	52	8	14
Guillevin et al. [49]	165	48	23	31	46	17	67	29	31
Ludici et al. [50]	21 (children)	11	10	14	81	—	38	24	19

*These older studies may have included PAN patients who would now be diagnosed as having MPA. Abbreviations: CNS, central nervous system; GI, gastrointestinal; PNS, peripheral nervous system.

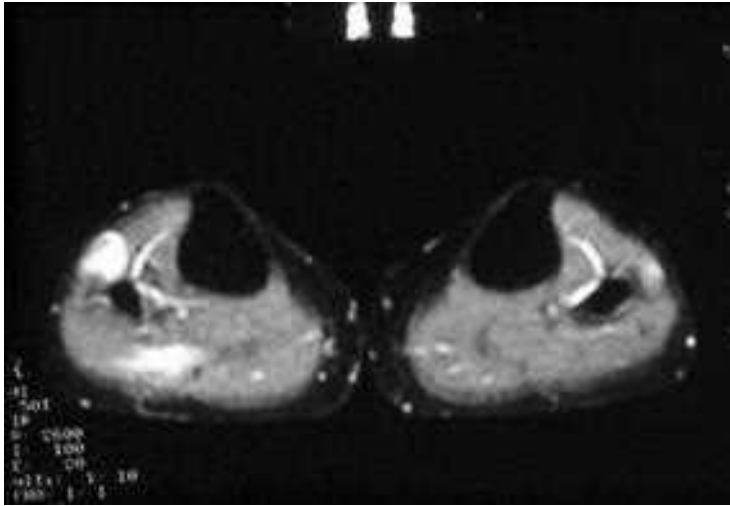


Figure 1. Peroneus muscle hyperintense signals on T₂-weighted MRI in a PAN patient with skeletal muscle involvement.

Myalgia and Arthralgia

Up to one-half of patients have variably intense, diffuse and spontaneous myalgia, with normal or slightly elevated muscle enzyme levels. Amyotrophy may be marked reflecting weight loss sometimes exceeding 20 kilograms (kg), or underlying peripheral neuropathy. Affected patients may be bedridden due to pain severity and amyotrophy. Magnetic resonance imaging (MRI) of painful muscles can show hyperintense signal intensities on T₂-weighted enhanced images after administration of gadolinium (Figure 1) due to inflammatory lesions. Skeletal muscle MRI, which correlates poorly with the presence of vasculitis, is not recommended in the selection of the site for muscle biopsy. Rather, the biopsy should be performed distally in an affected limb especially in painful areas to maximize pathogenic vasculitic lesions which may be in differing stages of evolution. Arthralgia occurs in the knees, ankles, elbows and wrists, rather in the shoulders or hips; arthritis is typically absent and joint deformities do not occur.

NERVOUS SYSTEM INVOLVEMENT

Peripheral Neuropathy

Peripheral neuropathy is the most common peripheral nervous system (PNS) manifestation, so noted in up to 75% of affected patients [41, 48], and may be the earliest symptom in up to a third. Segmental edema precedes the development of cranial nerve palsy reflecting capillary-permeability dysfunction. Hypo- and hyperesthesia, dysesthesia and frank pain, resulting from sensory nerve involvement, are prominent and earliest presenting complaints. Motor deficits typically affect the legs often preceding sensory involvement, commencing suddenly with involvement of one nerve at a time, termed mononeuritis or

mononeuropathy multiplex, in one-half to two-thirds of patients [41, 51]. The peripheral neuropathy is typically distal and asymmetric, preferentially affecting the fibular, sural, radial, ulnar, and median nerves. A symmetrical process may be observed due to the coalescence of nerve lesions. Cerebrospinal fluid (CSF) findings are typically normal and electromyography (EMG) and nerve conduction studies (NCS) are compatible with an axonopathy process evidenced by reduced compound muscle action potential (CMAP) amplitudes with normal or near normal conduction velocities. Rare patients are encountered with brachial plexus neuropathy [52] and peripheral motor conduction block [53] indicative of a demyelinating process similar to Guillain–Barré syndrome or other acquired demyelinating neuropathies, and peripheral nerve entrapment [54]. Isolated sensory neuropathy is a rare complication of PAN and may be the consequence of isolated small fiber involvement vasculitis [55]. Mononeuropathy multiplex regresses slowly and improves to a variable degree in over 12 to 18 months following effective therapy without residual lesions, however paresthesia can persist longer or indefinitely.

Isolated peripheral nerve vasculitis, categorized as a single organ vasculitis (SOV) [56] by the 2012 Revised CHCC Nomenclature [5], differs from the isolated phenotypic expression of PAN that often conveys a more benign and chronic outcome.

Central Nervous System Manifestations

Central nervous system (CNS) involvement was observed in 4.6% of patients with PAN [41]. Affected patients with encephalopathy have altered cognitive function with disorientation, psychosis, hallucinations. There can be focal or multifocal neurological disturbances leading to seizures, strokes or subarachnoid hemorrhages [57] resulting from focal cerebral arteritis leading to cerebral artery-aneurysm rupture and hematoma, alternatively due to malignant hypertension. Distal occlusion of spinal vessels engenders sphincter dysfunction [58]. MRI of the brain typically shows non-specific T₂-weighted white matter subcortical hyperintensities, while MR angiography (MRA) and conventional cerebral angiography may be normal.

Cranial Nerve Manifestations

Albeit rare, involvement of the oculomotor, trochlear, abducens, facial, and vestibulocochlear nerves are most often affected in PAN [59]. Effective treatment can lead to partial or full recovery, which is less likely in the vestibulocochlear nerve [60]. There may be vasculitis of the optic nerve, optic chiasm or occipital cortex. Cerebrospinal fluid is typically normal.

Dermatologic Manifestations

Despite involvement of medium-sized vessels, one-half of patients with systemic PAN have cutaneous lesions [41] including cutaneous and subcutaneous nodules, and palpable

purpura, which can be bullous or necrotic (Figure 2). Skin nodules occur in clusters along the trajectories of superficial arteries, often disappearing spontaneously over a few days prior to new lesions. Palpable nodules can reach a size of 20 mm. Skin ulcerations and livedo reticularis occur less frequently [47]. The latter is typically localized to the legs, the backs of the arms, and sometimes the trunk with a fish net reticular pattern of infiltrated areas. Painful distal ulcerations may be associated with ischemia of the fingers and toes, and distal gangrene. Digital ischemia should lead to consideration of cholesterol and atherosclerotic emboli. Angiography demonstrates vascular stenosis or microaneurysm formation [61].



Figure 2. Necrotic purpura in the legs and ankles of a patient with PAN.

PAN may be limited to the skin for decades before development of systemic vasculitis, without systemic involvement, abnormal biological markers of inflammation or circulating autoantibodies [62, 63]. Skin relapses are not uncommon.

Renal Manifestations

Renal manifestations result from medium-sized-vessel involvement leading to renal infarcts and microaneurysm formation. Malignant arterial hypertension [64], which occurs in 6.9% of patients [41], reflects vascular ischemic nephropathy. Renal insufficiency is an overall poor prognostic factor [65]. Angiography shows renal parenchymal infarction (Figure 3), with characteristic multiple stenosis and microaneurysms of branches of celiac, mesenteric and renal arteries (Figure 4). Microaneurysms can spontaneously rupture notably after renal biopsy, the latter of which is strongly contraindicated when microaneurysms are present. Renal hematoma can be extensive requiring embolization [66] or nephrectomy [67]. Acute renal insufficiency can occur soon after onset or following a disease flare. Plasma exchanges may be required initially however renal function is unpredictable. Some patients develop end-stage renal failure decades after the first PAN flare.



Figure 3. Renal infarcts reflecting vascular nephropathy.

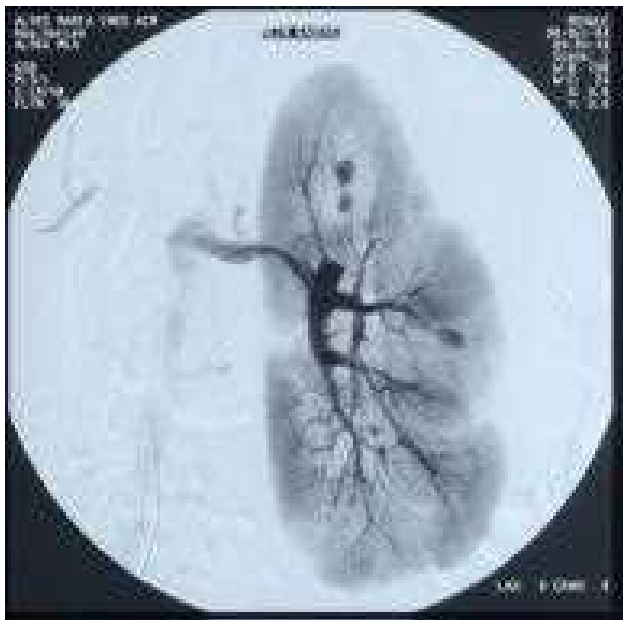


Figure 4. Multiple renal artery microaneurysms.

Cardiac Manifestations

Cardiac involvement was mentioned in the first publication of PAN [2] that described a patient with “nodular coronaritis”. Clinical cardiac involvement occurs in 10% of patients with clinical expression of PAN [48], with an increase to 40% after recognition of radiologic and electrocardiographic abnormalities, and in 78% of those studied histopathologically [68]. Although one recent series [41] found cardiac involvement in 22.4% of patients with PAN, this frequency may have underestimated the true occurrence since newer laboratory investigations were not employed to gauge cardiac involvement. Congestive heart failure, the main clinical manifestation of cardiac involvement, reflects both vasculitis of the coronary arteries and its branches with myocardial arteriolar infarcts, and end-organ renovascular or hypertensive disease.

Cardiomyopathy occurs 3 to 4 months after onset of PAN onset. Despite coronary artery vasculitis, angina and myocardial infarctions are uncommon. Among 66 postmortem studied patients, 41 had features of myocardial infarction, of whom three had clinical cardiac symptoms, and three had coronary atherosclerosis [68]. Coronary angiography and CT of the coronary arteries demonstrate coronary involvement in most affected patients with clinical signs of myocardial infarction, and in some, the latter be a result of small coronary artery vessel vasculitis or vasospasm [69]. Coronary artery aneurysm, notably in children, suggests Kawasaki disease (KD), however rupture of them is uncommon but severe, because it can cause a hemopericardium.

There are no current guidelines for the evaluation of coronary artery involvement in PAN, however cardiac MRI may be promising. Heart murmurs are generally due to anemia and not endocardial involvement, the latter of which is infrequent in PAN such that its presence should lead to an alternative diagnosis. Even less common non-specific pericardial manifestations reflect secondary myocardial involvement so noted in up to 5% of patients with PAN [70]; a frequency that increased to one-third in postmortem series [68]. Supraventricular cardiac arrhythmia and conduction disorders occur in 2 to 19% of PAN patients [68, 71] due to arteritis of the sinus node and neighboring nerve fibers.

Aortic Dissection and Peripheral Vascular Manifestations

These authors have not observed a case of PAN-related aortic dissection, a rare complication that is attributed to diffuse vasculitis of the vasa vasorum which manifested in one such case as fatal tamponade [72]. Dissection of proximal aortic branches and Raynaud phenomenon when present may be complicated by vasonecrosis. Cryoglobulinemia may be found in patients with cardiac disease and HBV-related PAN.

Gastrointestinal Manifestations

Gastrointestinal manifestations are among the most severe in PAN, affecting 38% of patients [41], most often associated with HBV infection, so noted respectively in 50.4% versus 31.1% of patients. While generally reflective of systemic involvement, they may also

be the initial findings of PAN [3]. Gastrointestinal complications are a major cause of death in the first year of disease ranking third after infection and cardiac disease [73]. Abdominal pain was the most common symptom, so noted in 30 to 40% of patients with PAN and overall in 97% of those with gastrointestinal involvement. The intensity and persistence of abdominal pain despite corticosteroids treatment, suggests a vascular cause and confer a less favorable prognosis [74]. Hemorrhage and small intestine perforation are the most feared manifestations with respective reported frequencies of 20% to 50% and 2% to 40% (mean, 5%) [75]. When present, ischemic vasculitis affects the small bowel and more rarely the colon and stomach. Perforation of the esophagus is unusual; and vasculitis of the gallbladder occurs in 2% to 17% of patients [75–77].

Vasculitic appendicitis may be the first manifestation of PAN or a localized form thereof. Patients with isolated and histologically-proven vasculitic appendicitis progress to systemic PAN within five years. The prognosis of closely monitored and surgically treated necrotizing vasculitis of the gallbladder or appendix is generally favorable without immunosuppressant treatment. Acute necrotizing and chronic pancreatitis, the latter often accompanied by pseudocyst formation, were diagnosed in 3.7% of patients [41], however the prognosis is extremely dismal because of the frequent association with small intestinal ischemia and perforation. Exploratory surgery should be performed in such patients to detect underdiagnosed bowel perforation. Digestive malabsorption and exudative enteropathy rarely occurs. The liver and spleen can be involved with or without hematoma formation [78] that may be clinically silent. One patient with fibrinoid necrosis of the splenic artery and later splenic rupture was described [45]. When abdominal pain is present, computed tomography (CT) and MRI of the abdomen can be useful to detect organ infarction and pancreatitis. Gastric and colonic endoscopy can detect areas of ischemia and ulceration that precede perforation. Of note, despite increasing resolution performance of CT and MRI imaging, angiography remains the gold standard to detect microaneurysms.

Angiography, which images areas of organ infarction, hematoma and microaneurysm formation measuring 5 mm in diameter, identifies suggestive areas of arterial stenosis in up to 90% of patients with PAN. Angiography also depicts vascular lesions in renal, celiac, and mesenteric vessels respectively in 54%, 24%, and 14% of patients, although even more often in hepatic and splenic arteries [41, 79] without prognostic significance. While not rapidly fatal, intraperitoneal ruptures of such aneurysms are treatable with selective arterial embolization. Gastrointestinal tissue biopsy, i.e., during GI tract endoscopy or liver fine needle biopsy, rarely detects vasculitis and may be life-threatening with a risk of aneurysm rupture. However, histologic examination of whole organ after surgery is of outmost importance as it regularly confirms diagnosis.

Severe GI manifestations, like bowel perforations and ischemia, peritonitis and intestinal occlusion, confer a poor prognosis [65]. Effective treatment combines prompt surgical intervention and medical therapy with corticosteroid and immunosuppressive treatment.

Testicular Manifestations

Unilateral orchitis and testicular tenderness due to testicular artery ischemia were common findings in PAN, so noted in 17% of patients, although rarely the first manifestation of disease [41, 80]. Indeed, orchitis was included in the 1990 ACR classification criteria of

PAN [4]; and although it typically improves with a prompt course of corticosteroids, however in some instances it can be irreversible. We noted orchitis in association with HBV-related PAN however an etiologic relation between viral infection and testicular manifestations was not discerned [3]. Fertility is usually preserved.

Ureteral and Urogenital Manifestations

Ureteral manifestations are rare and ureteral stenoses are specific of small-sized-vessel vasculitis SVV. Urodynamic and electrophysiological studies may demonstrate detrusor hypoactivity in patients with voiding difficulty when the cause is vasculitis of vasa nervorum supplying the bladder. It is unusual to discern a vasculitic spinal cord etiology for bladder disturbances.

Pulmonary Manifestations

Unlike MPA, GPA and EGPA, pulmonary involvement in PAN is either asymptomatic or subclinical, even when histopathologic involvement is found at postmortem examination. Size of involved vessels in PAN explains the absence of lung manifestations as only bronchial arteries are medium-sized vessels and parenchymal vessels are exclusively small-sized arterioles, capillaries and venules.

Bone Manifestations

Periosteal involvement resulting from pan develops mainly in the legs (Figure 5) with associated pain and localized edema, tissue biopsy of which may reveal underlying necrotizing vasculitis [81, 82].



Figure 5. Fibula periostitis during PAN illustrated on X-rays radiograph and nuclear imaging, adapted from [82].

Ophthalmologic Manifestations

Ocular manifestations of necrotizing vasculitis were noted in 42/393 (10.7%) of patients with PAN [83] the most common features of which included blurred vision in 31%, sudden visual loss in 19%, retinal vasculitis in 16.7%, and uveitis in 11.9% of patients. Conversely to AAV, scleritis, episcleritis and other manifestations are rarely observed.

HBV-RELATED MANIFESTATIONS

An onset before age 40 years, concomitant malignant hypertension, renal infarction, orchi-epididymitis, gastrointestinal manifestations, and surgical emergencies were all more frequent in HBV-associated infection. Sergent and coworkers [84] noted that two of the three deaths among nine patients were attributed to colon vasculitis. Ischemia was responsible for gastrointestinal and renal manifestations that were due to microaneurysm formation and infarction noted on visceral angiography. Effectively treated, microaneurysms regress on serial angiography [85] that may result from microaneurysmal thrombosis with evolution to fibrosis. Hepatic cytolysis is usually moderate and cholestasis is minor or absent. Liver biopsy pathology exhibits signs of chronic hepatitis even when PAN becomes manifest a few months after HBV infection. HBV-related PAN is acute and initially severe but the outcome is excellent for most patients when adequate treatment is associated with seroconversion. The sequela of vascular nephropathy is similarly favorable in those patients able to obtain substantial recovery with little residual functional renal impairment.

CHILDHOOD PAN

PAN is the most common systemic necrotizing vasculitis in children after KD and IgA vasculitis (Henoch–Schönlein purpura or HSP) [86]. Neither the ACR criteria [4] nor the 2012 Revised CHCC Nomenclature [5] were validated for children. The European League against Rheumatism/Pediatric Rheumatology European Society (EULAR/PReS) proposed specific classification criteria for juvenile vasculitides [87].

The EULAR/PReS criteria [87] were based mainly on a literature review and a consensus-based process. The primary objective of the 2008 Ankara Consensus Conference was to validate the EULAR criteria for pediatric vasculitides. The final EULAR/PRINTO/PReS childhood PAN (cPAN) classification criteria achieved a sensitivity of 89.6% and a specificity of 99.6% and are indicated in Table 4 [88]. Since their setting, several case-series used these criteria [50, 89]. In the work from the French Vasculitis Study Group's database, among 21 cPAN patients 86% met the criteria [50].

The mean age at diagnosis of childhood PAN is age 9 ± 4 years, with an equal ratio of boys and girls. Clinical manifestations fall within the same spectrum as for adults, except for more frequent cutaneous involvement in children. Indeed, 80% of affected children manifest skin involvement, with a limited cutaneous form accounting for one-third of cases. Prognosis is more favorable for children than adults with an overall mortality rate of 1% to 16%. Relapses are more frequent and occur only many years following diagnosis, sometimes

preceded by ear, nose and throat infections. Penicillin can contribute to a cure by effectively lowering the relapse rate when *Streptococci* are involved as the cause or target factor [90]; however, the optimal antibiotic regimen is unknown. Relapses have been described up to 20 years after the first episode.

Table 4. EULAR/PRINTO/PReS proposed classification criteria for childhood polyarteritis nodosa*

A systemic inflammatory illness characterized by the presence of
-At least 1 mandatory criterion:
1. Biopsy showing small- and medium-sized artery necrotizing vasculitis
2. Angiographic abnormalities on medium or small-sized arteries: aneurysms, stenoses or occlusions [†]
-Plus 1 among the 5 clinical criteria:
1. Skin involvement: livedo reticularis, skin nodules, superficial or deep skin infarctions
2. Myalgia or muscle tenderness
3. Systemic hypertension, greater than 95 th percentile for the age
4. Peripheral neuropathy: mononeuropathy or polyneuropathy
5. Renal involvement: abnormal urine analysis (proteinuria >0.3 g/24h or hematuria) and/or impaired renal function with GFR < 50% of normal

* Adapted from reference [88] [†]Should include angiography if MR angiography is negative. Abbreviations: EULAR/PRINTO/PReS, European League against Rheumatism/Pediatric Rheumatology Inter National Trials Organization/Pediatric Rheumatology European Society; GFR, glomerular filtration rate.

LABORATORY EVALUATION

Inflammation markers are found in the majority of patients. A one-hour erythrocyte sedimentation rate (ESR) >60 mm is noted in three-quarters of patients; and an elevated C-reactive protein, α -2 globulin levels and white blood-cell counts in one-half to three-quarters of patients. Eosinophilia >1,500/mm³ and normochromic anemia can occur. HBsAg and ANCA serology should be routinely tested.

As previously described, the DADA2 syndrome can mimic PAN, therefore genetic testing should be performed for the following: childhood-PAN-like presentation with familial history of vasculitis or early stroke for the patient, unresponsiveness to standard therapy protocols.

IMAGING

Bron and coworkers [91] showed the diagnostic value of angiography in visualizing saccular or fusiform microaneurysms measuring 1 to 5 mm in diameter, and stenosis in medium-sized vessels. Although not pathognomonic for PAN, they are predominantly seen in the kidneys, mesentery and liver. Angiography is a useful tool when other diagnostic examinations are negative, especially when abdominal pain and nephropathy are present. As cited for HBV-related PAN, the microaneurysms may disappear after several months with the resolution of the causative agent [85].

Of note, despite increasing resolution performance of CT and MRI imaging, angiography remains the gold standard to detect microaneurysms as these technics currently fail to detect

such aneurysms in all cases [92]. Nonetheless, it is likely that in the future invasive angiography is abandoned thanks to imaging progress.

Unlike large-vessel vasculitides, PET/CT scan usage as a diagnosis tool appears limited in PAN, mainly due to the smaller size of affected vessel. Nonetheless its positivity has seldom been reported as localized [93] or diffuse [94] 18-FDG uptake. Therefore PET/CT is not routinely recommended for PAN diagnosis or follow-up.

PROGNOSIS AND OUTCOMES

Untreated, 12% of patients with PAN survived [48]. However, with effective therapy the overall survival rate exceeded 80% [95] for PAN alone, and 70% in those with associated HBV infection [3]. A systematic retrospective study of 348 patients with PAN registered in the French Vasculitis Study Group (FVSG) database [41] satisfying ACR [4] and CHCC Nomenclature [5], and followed for 68.3 months showed relapses in 76 (21.8%) and deaths in 86 (24.7%). Mortality and relapse rate were significantly different between PAN groups with and without HBV infection. HBV infection appears associated to higher mortality but lower relapses rates. Indeed, 44 patients died (19.6%) with PAN alone versus 42 (34.1%) with associated HBV infection ($P = 0.003$). Regarding relapses, 63 (28%) relapsed with PAN alone versus 13 (10.6%) with associated HBV infection ($P < 0.001$) and the 5-year relapse-free survival rate for PAN was 59.4% (95% confidence interval [CI] 52.6–67.0) versus 67.0% (95% CI 58.5–76.8) with HBV-associated infection.

Age is another important prognosis factor. As previously detailed for cPAN, early-onset of the disease is associated with lower mortality, although higher relapse rates. This has been further confirmed in pediatric case-series [89, 96] and with direct comparison between adult- and childhood-onset PAN [97]. Of note, age is part of the prognostic FFS score detailed further.

Fulminating vasculitis, which may manifest gastrointestinal involvement, renal failure, pulmonary hemorrhage and rarely, cerebral involvement, may be unresponsive to treatment resulting in excessive mortality and morbidity in the first few months following diagnosis.

Relapse

In contrast to GPA and MPA, remission once obtained, disease tends to recur less frequently during first years in PAN. The outcome is even better during HBV-related PAN: in one large cohort [95] 8% of the HBV infection-associated PAN and 19% of the HBV-free PAN demonstrated a first relapse at 37 months and 29 months from disease onset respectively. In another cohort study, only 10% with HBV-related PAN relapsed [3]. Relapses associated with HBV infection occur in those with persistent active virus replication after treatment. A stepwise multivariate analysis [41] calculated hazard ratios (HR) and CI for independent predictors of relapse that included, HBV-related PAN (2.27 [95% CI 1.11–4.63]) and cutaneous manifestations at diagnosis (HR 1.85 [95% CI 1.08–3.23]), especially when only nodules were considered (HR 2.21 [95% CI 1.30–3.78]) Although the severity of relapses was unpredictable, rash and arthralgia conferred a more favorable prognosis for a

less severe disease status compared to the initial clinical presentation. Long-term follow-up studies until 8 to 10 years from disease onset indicated relapses rate of approximately 50% [98, 99].

Table 5. Causes of Death in Polyarteritis Nodosa*

	Gayraud et al. [95]	Cruz et al. [102]	Cacoub et al. [104]	Leib et al. [47]	Cohen et al. [46]	Guillevin et al. [3]	Pagnoux et al. [41]
Number of patients	278	26	165	64	53	115	348
Type of vasculitis (n)	HBV-related PAN (63), PAN (93), MPA (58) and CSS (64)	Patients admitted to ICU, PAN (5), MPA (4), CSS (7) and others (10)	PAN	PAN	PAN	HBV-related PAN	PAN
Deaths, n (%)	85 (31)	2/5 PAN (20)	61 (37) [†]	32 (50)	22 (42)	41 (36)	86 (24.7)
Progressive vasculitis	22 (26)	0	21 (43) [†]	20 (63)	–	11 (27)	29 (33.7)
Bowel infarction	10	–	8	–	6 (27)	7	
Cardiac failure	5	–	4	–	–	1	
Multi-visceral involvement	3	–	2	–	–		
Renal failure	3	–	5	–	6 (27)		
Stroke	1	–	2	–	–		6 (7)
Infectious treatment side effects	11 (13)	2 (100)	13 (27)	2 (6)	–	4 (10)	
Bacterial pneumonia	5	1	11	–	–	–	
Septicemia	6	1	6/11	–	–	3/4	10 (11.6)
Sudden deaths	9 (11)	0	3 (6)	–	–	1 (2)	12 (14)
Heart disease	8 (9)	0	6(12) [‡]	5 (16)	8 (36) [‡]	5 (12) [‡]	
Cancer	13 (15)	0	5 (10)	1 (3)	1 (5)	3 (7)	5 (5.8)
Pulmonary embolism	3 (3.5)	0	2 (4)	–	–		
Chronic respiratory disease	3 (3.5)	0	–	–	–		
End-stage renal disease	–	–	–	3 (9)	–		
Fulminant viral hepatitis	2 (2)	0	–	–	–	1 (2)	
Miscellaneous	14 (17)	0	2 (4)	1 (3)	1 (5)	16 (39)	24 (27.9)

* Including HBV-associated PAN. [†]Some patients may have died for example from heart disease due to vasculitis alone, treatments or other associated conditions, not always specified; hence, the total of listed causes exceeds 100%.

[‡]Includes cerebrovascular and cardiovascular complications. Abbreviations: ICU, intensive care unit; n, number.

Mortality

The major causes of mortality in PAN are shown in Table 5. Mortality can be divided into two types: those attributed to the vasculitic process involving major organ and others due to severe treatment-related side effects. While a few patients may die during the first few months of the disease due to unresponsiveness to treatment [73], the majority occur with

longer durations of multi-organ involvement associated with fever and rapid weight loss, especially those with gastrointestinal involvement. Mortality related to treatment side effects generally occur in the years following treatment for controlled or uncontrolled vasculitis with infections representing the primary cause of death due to intense initial therapy with corticosteroids and cytotoxic agents. Viral infections, notably *Pneumocystis jirovecii*, occur later in the course associated with profound drug-induced immunosuppression [100, 101]. A small number of patients suffer die within the first weeks or months following the diagnosis of PAN despite adequate treatment. Bourgarit and colleagues [73] showed that 38/309 (12%) patients died during the first year predominantly due to vasculitis (58%), while other deaths were related to treatment side effects or factors independent of vasculitis. The primary cause of early mortality in PAN is severe gastrointestinal involvement with associated perforation and hemorrhage, so noted by the FFS [65]; however, HBV infection was not a factor of severity. Among patients hospitalized in intensive care units (ICU), the main prognostic factor for early mortality was predicted by the Acute Physiology and Chronic Health Evaluation (APACHE) [102] which was not specifically devised for vasculitis. Neither the vasculitis-specific Birmingham Vasculitis Activity Score (BVAS) [103] nor the FFS scoring system [65], predicted ICU mortality [102].

TREATMENT

The FFS [105] is a useful guide to treatment, the associated features of which predicted increased mortality: proteinuria >1 g/day, renal insufficiency (serum creatinine >140 $\mu\text{mol/L}$ or 1.6 mg/dL), specific cardiomyopathy, gastrointestinal and CNS involvement. Although treatment should not be overly influenced by FFS criteria [105], they may be considered in deciding the therapeutic strategy. Accordingly, patients lacking the poorest prognostic symptoms (FFS = 0) may be treated with corticosteroids alone to reduce the number and severity of treatment related side effects. This strategy is effective with a few minor relapses necessitating transient dose intensification and addition of an immunosuppressant agent. The 1996 FFS for systemic necrotizing vasculitides was revisited [65]. The following factors were significantly associated with increased 5-year mortality: age >65 years, cardiac symptoms, GI involvement, and renal insufficiency (stabilized peak urinary creatinine ≥ 150 $\mu\text{mol/L}$ or 1.7 mg/dL) with each accorded +1 point; while ear, nose and throat manifestations were scored – 1 point, as they were associated with better outcomes. The 5-year mortality rates for FFS of zero, one, and ≥ 2 , were respectively 9%, 21% and 40%. The same strategy previously described for the 1996 FFS [105] has been applied to patients with PAN. Since then it has been shown that even if patients with FFS = 0 at diagnosis had good overall survival rate, relapses could occur up to 50%, particularly when mononeuropathy multiplex is present at diagnosis [106]. Moreover, these patients were frequently treated with immune-suppressant therapy as a consequence of GC resistance.

BVAS is another tool frequently used during SNVs to assess severity and prognosis. Comparisons between FFS and BVAS showed conflicting results regarding which one would be the best scoring system for PAN [73, 95, 107]. However, the two scores frequently parallel and FFS is very simple and readily usable in daily clinical practice.

Supportive care represents an important part of the therapeutic regimen for patients with potentially fatal disease. Pain control, prevention of pressure sores and physical therapy may be needed, especially for symptomatic mononeuritis multiplex. Angiotensin-converting-enzyme inhibitors are effective antihypertensive agents in those with renal vasculitis due to the beneficial effect on renal function. Persistent abdominal pain should lead to consideration of exploratory laparotomy to identify treatable bowel perforation; such patients may require medication via intravenous route to circumvent impairment of orally administered drugs. Rapid and severe weight loss due to severe gastrointestinal involvement can be counterbalanced with parenteral nutrition. Although weight loss is not a proven poor prognostic factor [65] common sense dictates the importance of optimizing all factors, notwithstanding optimal weight, that might mitigate increased susceptibility to infection rate with cytotoxic agents. Atherosclerosis is a potentially treatable comorbid factor that can worsen prognosis. The Vasculitis Damage Index (VDI) [108] is a useful measure of the cumulative impact of scars and sequela caused by the disease and its therapy. Since maximal immunosuppression is given at disease onset, antibiotic prophylaxis of opportunistic infections is often necessary but decided on an individual basis.

Immunosuppressant Medication

The introduction of corticosteroids, which led to an improvement in the untreated 5-year survival rate of 10% of the preceding two decades to 55% by mid-to-late 1970s [47, 48], further increased to 82% by the addition of cyclophosphamide and azathioprine [47, 109].

Corticosteroids

Corticosteroids are administered for only a few days in those with HBV infection, but is given as a prolonged course lasting up to one year in the presence of life-threatening organ involvement or the extension phase of mononeuritis multiplex, commencing with pulse methylprednisolone dose of 7.5 to 15 mg/kg IV over 60 min, repeated at 24-h intervals for 1–3 days. The side effects of an empiric dose of pulse-methylprednisolone dose <1000 mg are usually mild and transient in the short term. However, severe side effects which are fortunately rare include sudden death, cardiac arrhythmia, myocardial infarction, gastrointestinal bleeding, and seizures. This is followed by prednisone in doses of 1 mg/kg/day or the equivalent dose of methylprednisolone for two to three weeks after which tapering can begin. The FVSG trial [110] which tapered the corticosteroid dose by one-half to 20 to 30 mg per day by three months, aimed for a dose of 10 mg by six months, and 5 mg by one year. This gradual reduction had the advantage of limiting side effects. The results of a prospective trial devoted to treatment of vasculitides in the elderly ≥ 65 (CORTAGE) noted that the dose of corticosteroids could be even lower and still retain disease-free survival benefits [111].

Cyclophosphamide

Cyclophosphamide can be administered in combination with corticosteroids at a dose of up to 2 mg/kg/day oral route for three to six months. However, it is associated with major side effects including, hemorrhagic cystitis, bladder fibrosis, bone-marrow suppression, ovarian failure, bladder cancer, and hematological malignancy [112]. In addition, life-threatening infection can supervene when given in conjunction with high dose corticosteroids [73, 95]. Protocols employing intermittent treatment with higher dose of cyclophosphamide to limit the associated morbidity of daily doses were developed for the treatment of PAN [113]. Intravenous pulse cyclophosphamide is preferable to oral cyclophosphamide in the treatment of systemic necrotizing vasculitis. The FVSG protocol employs a dose of 0.6 g/m² given every two weeks for three pulses, followed by a schedule of every three weeks for a total of six treatments. The analysis of 2 cyclophosphamide regimen strategies, 6 vs 12 months treatment, during PAN and GPA was performed after a 10-year follow-up period of the CHUSPAN trial [99]. None of the strategies was superior, indicating 6 months may be a sufficient duration for cyclophosphamide. After initial cyclophosphamide regimen, a maintenance therapy with azathioprine or methotrexate, as recommended in the treatment of AAV [114, 115], is an acceptable yet invalidated approach in PAN. For patients over 65 years, the CORTAGE study indicated that low-dose of cyclophosphamide, i.e., maximum of 6 pulses of 500 mg each, was similar to classical FSVG protocol in terms of remission, but with a lower rate of severe adverse events [111].

For pediatric PAN, treatment is currently based on adult recommendations as no controlled trial has been performed specifically in this population. The MYPAN study in childhood PAN aims at comparing cyclophosphamide and mycophenolate mofetil as experts in the field judge this drug could be a good alternative [116].

It is the authors' opinion that cyclophosphamide should be given judiciously based upon the anatomical location and severity of PAN involvement, rather than to all PAN patients. Oral low-dose cyclophosphamide was successfully employed to control disease activity and relapses within the first six months of treatment in patients with systemic vasculitis who failed to respond to pulse intravenous high-dose regimen [117]. Patients with PAN and associated poor-prognostic factors should be treated with combination corticosteroids and cyclophosphamide for six months, followed by a corticosteroid agent and less toxic immunosuppressant such as azathioprine or methotrexate. Patients without such poor prognostic factors can be treated safely with corticosteroids alone and adjuvant immunosuppression introduced only in cases of treatment failure for disease control [118]. This is confirmed by the CHUSPAN2 randomized controlled trial that compared standard corticosteroid therapy to adjunction of azathioprine in SNVs and PAN without poor prognosis factors. After 12-months treatment period, the main end-points at 24 months were not significantly different between two groups for relapses rate, mortality, adverse events [119].

Other Cytotoxic Agents

Azathioprine, methotrexate and other cytotoxic agents are all reserved for patients with contraindications to the initial or continued use of cyclophosphamide, and as maintenance therapy for up to eighteen months.

Plasma Exchange

There is little support for the use of plasma exchange in PAN in the absence of HBV infection [120], including those with poor-prognosis factors [121]. Plasma exchange is a second-line treatment of PAN refractory to conventional therapy. Its use in patients with AAV is to limit renal disease sequela.

Rituximab

At present, and contrarily to AAV, there is no suitable pathogenic mechanism, published finding, or ongoing study of the use of rituximab in the treatment of PAN. The authors have used rituximab in rare patients with PAN following failure of other treatments.

HBV-Related PAN

Patients treated with conventional regimens of corticosteroids and cyclophosphamide allows HBV to replicate, facilitating the development of chronic hepatitis and liver cirrhosis. Therefore, a preferred initial treatment commences with plasma exchange combined with vidarabine or interferon- $\alpha 2b$, and corticosteroids. This controls the most common life-threatening manifestations of PAN during the first few weeks of disease. Afterward, corticosteroid agent is safely discontinued enhancing the immunological clearance of HBV-infected hepatocytes favoring anti-HBeAb seroconversion. This strategy [122, 123] which is preferred over conventional regimens, was confirmed among 41 patients, 23 (56.1%) of whom no longer exhibited serological evidence of replication, and an overall cure rate of 80.5% [124]. The antiviral agent lamivudine [3], which increases the seroconversion rate from 56.1% to 60%, did not confer additional improvement in the survival rate at 18 months. Those treated with conventional corticosteroids with or without cyclophosphamide and no antiviral drugs demonstrated a mortality rate of 27.5% at 18 months compared to 17.5% when combined antiviral therapy was offered ($P = 0.46$). The benefits of adjunctive antiviral therapy appear after prolonged follow-up, since these drugs lower the risk of cirrhosis or liver failure. In 2017, treatment protocol guidelines for classical HBV infection (without PAN) highlight the need for long-term administration of nucleoside analogues limiting viral resistance such as tenofovir or entecavir [125]. This strategy has not yet been proven useful in HBV-associated-PAN.

Localized PAN

Localized forms of PAN without poor-prognostic factors can be treated initially without immunosuppression, awaiting refractory or relapsing disease. Isolated appendix or gallbladder involvement is associated with a favorable prognosis after surgical removal [126]. Cutaneous PAN, particularly in childhood forms, can be successfully treated with colchicine or dapsone in combination with topical corticosteroids. Colchicine and dapsone are both effective against PAN restricted to skeletal muscles.

CONCLUSION

Polyarteritis nodosa is an exemplary multi-systemic medium-sized, primary systemic vasculitis of adults and children. Once the most frequent vasculitis, it has become progressively less common notably in developed countries due to eradication of hepatitis B virus infection. Effective treatment of polyarteritis nodosa which includes consideration of corticosteroids and cyclophosphamide depending upon the presence of favorable or unfavorable prognostic factors, and an antiviral regimen when complicated by hepatitis B infection, has improved the 5-year survival of patients.

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Chapter 214

GIANT CELL ARTERITIS

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ABSTRACT

Giant cell arteritis (GCA) or large-vessel GCA (LV-GCA) is a chronic, idiopathic, granulomatous vasculitis of medium and large arteries comprising overlapping phenotypes of cranial arteritis and extra-cranial GCA. Vascular complications associated are generally due delay in diagnosis and initiation of effective treatment. Advancements in magnetic resonance imaging (MRI) and MR angiography (MRA), computed tomography angiography (CTA), ¹⁸fluoro-deoxyglucose/positron emission tomography (FDG/PET) and color duplex ultrasonography, have led to improved diagnosis of GCA. Corticosteroids are the mainstay of therapy in GCA. However, their use is associated with predictable and occasionally serious side effects. Biological agents including tocilizumab are effective and safe corticosteroid-sparing agents in treating GCA.

Keywords: giant cell arteritis, vasculitis, temporal artery biopsy, temporal artery ultrasound

INTRODUCTION

In the 10th century, Ali ibn Isâ described a man with heat and inflammation of the temporalis muscle and loss of sight [1]. In 1890, Hutchinson [2] described painful inflamed temporal arteries that prevented a man from wearing his hat. Giant cell arteritis (GCA) also known as large vessel (LV)-GCA, which was characterized as a distinct entity by Horton in

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1932 [3], is now recognized as the most common primary systemic vasculitis of the Western world in those aged over 50. The 2012 Revised Chapel Hill Consensus Conference (CHCC) Nomenclature [4] categorizes GCA as a large vessel vasculitis (LVV) prompting use of the equivalent term, large vessel (LV)-GCA. The spectrum of morphological changes have been described [5, 6]. This chapter reviews the epidemiologic, clinicopathologic features, diagnosis and treatment of giant cell arteritis.

OVERVIEW

The clinical symptoms in GCA are usually due to inflammation of the medium sized extra-cranial branches of the carotid artery, particularly the superficial temporal division [7]. About one-half the time, GCA is accompanied by aching and stiffness of the shoulder and hip girdles typical of polymyalgia rheumatica (PMR). Unfortunately neither the classical clinical presentation nor the combinations of clinical symptoms and signs predictive of a definite diagnosis of GCA occur commonly [8]. Visual loss in one or both eyes can be averted by early diagnosis and prompt treatment [9]. Temporal artery biopsy (TAB) is the gold standard of diagnosis, perhaps guided by non-invasive temporal artery ultrasound (TAUS). Glucocorticoids or corticosteroids (CS) remain the best treatment for GCA with similar long-term survival rates as age-matched population controls [10]. There are no randomized clinical trial (RCT) data in GCA to decide the correct CS dose regimen. Recent international guidelines [11, 12] provide assistance in diagnosis and treatment although the evidence base is weak and the guidance is at best advisory. The introduction of GCA care pathways may improve patient outcome [13, 14].

EPIDEMIOLOGY

The lifetime risk of developing GCA is estimated at 1% for women and 0.5% for men [15]. The disease rarely occurs in individuals under the age of 50 years and peaks in the eighth decade of life. It more commonly affects Scandinavians and North Americans of Scandinavian descent than Southern Europeans [16], and occurs rarely in Black and Asian populations [17-20]. Such racial patterns together with familial aggregation [21] point to a genetic predisposition to the disease. There is an association with the *HLA-DRB1*04* allele [7, 22].

The geographical variation and seasonal fluctuation of GCA in turn suggests a contribution from environmental and infectious factors [23] although definite links to particular microorganisms or vaccinations [24-26] have not been established. Moreover, there is no evidence that GCA occurs with increased prevalence in association with malignancy or as a paraneoplastic syndrome [27]. GCA is likely a polygenic disease wherein multiple environmental and genetic factors influence susceptibility and severity [28].

PATHOLOGY

The classical histological changes of GCA include arterial wall inflammation, internal elastic lamina fragmentation and intimal thickening (Figure 1). Although GCA derives its name from the presence of multinucleated giant cells, the latter are seen in only about one-half of positive TAB, albeit in association with a granulomatous inflammatory infiltrate composed of CD4⁺ T-cells and macrophages located at the intima-media junction near fragments of the internal elastic lamina. Other TAB specimens manifest lymphomononuclear-predominant panarteritis with occasional neutrophils and eosinophils without giant cells [29].

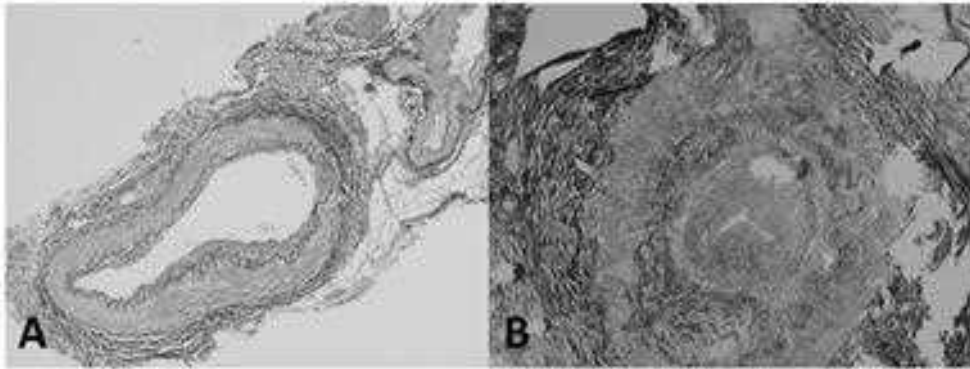


Figure 1. Temporal artery biopsies. (A) Normal (B) Typical GSA showing inflammation of the arterial wall, fragmentation of the internal elastic lamina, intimal thickening and luminal occlusion.

In a small minority of TAB, inflammation may only be seen in peri-adventitial vessels external to the adventitia or the vasa vasorum in a network of small blood vessels that supply larger ones [30]. There is considerable variation in histopathology between patients as well as within a given TAB tissue sample [29]. Arteritic involvement of a given artery may be focal and segmental leading to skip lesions [7]. There may be healed arteritis suggested by intimal thickening, fragmented elastic lamina and scarred media, although these may in part be age related changes [31]. Arterial wall thickening can lead to partial or complete occlusion of the lumen and ischemic complications such as anterior ischemic optic neuropathy (AION) [23]. One subset of patients has small-vessel vasculitis surrounding non-inflamed temporal artery segments in TAB tissue specimens [30, 32], but there is no indication that such patients should be considered any differently than typical GCA. Arteritis of the temporal artery is not entirely specific for GCA, and can be encountered with polyarteritis nodosa (PAN), anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), malignancy, and atypical PMR [33-37].

IMMUNOPATHOGENESIS

Inappropriate activation, maturation and retention of antigen presenting adventitial dendritic cells are early steps in the pathogenesis of GCA [24, 38]. These cells sample the

surrounding environment for viral and bacterial pathogens through the action of toll-like receptors (TLR) wherein particular TLR profiles appear to be vessel specific [39] which may explain why some blood vessels are more prone to be targeted by GCA than others. Mouse models [40] show that activated vessel wall-embedded dendritic cells release chemokines that recruit CD4⁺ T-cells and macrophages. Moreover the pattern of arterial inflammation corresponds to TLR specificity such that TLR4 stimulation induces panarteritis and TLR5 stimulates perivasculitis [41].

At least six observations support a T-cell mediated etiopathogenesis of GCA according to Borchers and colleagues [23]. First, the inflammatory cell infiltrate in GCA is comprised mainly of T-cells and macrophages with few or no B-cells and polymorphonuclear cells notably neutrophils are often absent. Second, the formation of granulomas depends upon T-cells, particularly the CD4⁺ subset. Third, infiltrating T-cells in GCA lesions demonstrate main histocompatibility class II and IL-2 receptor expression with selective T-cell clonal expansion in TAB tissue specimens. Fourth, GCA is associated with specific human leukocyte antigen (HLA) alleles. Fifth, there is attenuation of vascular inflammation after depletion of T-cells in experimental models of GCA. Lastly, two types of T-cells that play important roles in GCA, Th1 and Th17, express high levels of interferon (IFN)- γ mRNA compared in TAB specimens compared to control samples without arteritis [23]. The balance between Th1 and Th17 may contribute to the clinical presentation of GCA since T-cell derived IFN γ correlates with visual symptoms and jaw claudication in a manner that those with high levels demonstrate more intense intimal hyperplasia in tissue samples [42]. In addition, T-cell derived IFN γ expression may contribute to CS resistance leading to a more chronic course, as well as the heightened expression of giant cells, ischemic complications, and neo-angiogenesis [23] and constitutional symptoms of GCA [38, 43]. The pro-inflammatory cytokine interleukin (IL)-6 appears to be a good target molecule to induce remission in GCA as serum levels mirror disease activity and IL-6 is up-regulated in the inflamed vessels of patients with GCA [44]. Macrophages are thought to be the effector cells in GCA as they are the major source of many cytokines and other drivers of the inflammatory process such as IL-1 β , IL-6, TNF, TGF β , IL-32, matrix metallo-proteins and platelet derived growth factors that are over expressed in TAB, however their precise role remains to be elucidated [23]. IL-6 concentrations correlate with a strong inflammatory response in GCA but appear to be inversely related to GCA related ischemic events. IL-6 is also a potent inducer of angiogenesis leading to the hypothesis that collateral vessel formation in the presence of high levels of IL-6 may be protective [45].

CLINICAL FEATURES

The onset of GCA tends to be insidious over weeks to months, and abrupt in up to 20% of patients [28], with a spectrum of initial disease manifestations attributable to the localized effects of vascular and systemic inflammation [46, 47] including new-onset headache, scalp tenderness, jaw claudication, fever, fatigue, malaise, anorexia, weight loss polymyalgia, and visual loss [48]. The artificial separation of cranial and extracranial features either localized to the head or owing respectively to large vessel involvement is misleading as postmortem studies show that the intracranial arteries are largely spared in GCA [49].

Headache

Although headache is a prominent feature, it is not universal [46, 50-52]. Classically it tends to be a constant ache of sudden onset in the temporal region and is usually severe enough to disturb sleep [51, 53]. It can vary greatly in intensity and location, be constant or intermittent, and assume virtually any form mimicking tension-type headache, thunderclap, migraine and even cluster headaches [1]. It may become progressively worse, or wax and wane, temporarily subsiding in the absence of treatment [54]. A key feature is that it typically differs from any other previously experienced headache, and for this reason, the patient may deny headache, instead calling the symptom head pain [55]. The headache may be associated with scalp tenderness especially on hair brushing and combing or wearing glasses [47]. When severe, even the slightest pressure on resting the head on a pillow may be intolerable. Pain is usually localized to one or both temporal regions, the forehead or occiput. However, the pain may be generalized, spare the scalp altogether or affect the eye, ear; face, jaw or neck [55]. Tenderness, prominence and decreased temporal artery pulsation (Figure 2) increase the likelihood of GCA [46], although one-third of TAB-proven GCA patients have normal temporal arteries on clinical examination.



Figure 2. Prominence of the temporal artery in GCA.

Jaw Claudication

Although the most specific feature of GCA, jaw claudication, or pain and fatigue in the masseter muscles on protracted or vigorous chewing that eases with rest, is present only in about one-half of patients, it can also have an abrupt trismus-like symptom [54] and remain intermittent for weeks or months [55]. Jaw claudication should not be confused with temporomandibular joint (TMJ), tooth or gum disease. Tongue claudication is less common.

Constitutional Findings

With the widespread availability of CS in the empiric treatment of GCA, constitutional symptoms such as fever, fatigue, malaise, anorexia and weight loss are less often encountered at the formal diagnosis of affected patients [55]. Fever which occurs in about one-half of patients is usually low grade. A small number of TAB-proven patients with GCA present with only symptoms of systemic inflammation without localizing vascular symptoms [29, 51, 56].

Ophthalmologic Involvement

An estimated 15% of patients with GCA experience ophthalmologic complications [57], notably ischemic optic neuropathy (AION) due to arteritic involvement of the short posterior ciliary arteries supplying the optic nerve head [58, 59], with the remainder comprised mainly of retinal blindness due to central retinal artery involvement [58, 59]. Visual loss is painless, partial or complete, and unilateral or bilateral; and once established it is usually irreversible [38]. It may be preceded by fleeting visual blurring with exercise, amaurosis fugax or diplopia, but commonly occurs without warning and may be the presenting symptom [46, 60]. Ophthalmoplegia is usually due to a partial or complete oculomotor or abducens nerve palsy, and is a recognized complication of ischemia affecting the extra-ocular muscles, cranial nerves or brainstem [14].

Other ischemic complications of GCA include transient ischemic attack (TIA) and stroke which may occur due to thrombosis, microembolism or a combination of intimal hyperplasia and distal thrombosis [55]. Although the vertebral arteries are inflamed in the large majority of patients at postmortem examination [49], clinically significant vertebrobasilar insufficiency is uncommon [55]; scalp and tongue necrosis are rare [61].

Polymyalgia Rheumatica

Although up to one-half of patients with GCA develop inflammatory shoulder and hip girdle pain and stiffness [62], only about 5% of patients with frank PMR ever develop GCA [7].

Large Vessel Involvement

Aortic inflammation can be observed in surgical biopsies or at postmortem examination in GCA [5, 63] however the true frequency is difficult to ascertain. Computed tomography angiography (CTA) [6] and helical aortic computed tomodensitometry [64] discern aortic involvement in 45 to 65% of patients with GCA, with the thoracic aorta most often affected. The relationship between aortitis and subsequent aortic aneurysm remains unclear [65]. In the first year of the disease, aortitis confers a small significant risk of dissection or rupture even in the absence of aortic aneurysm with resultant high mortality. Long term dilatation or aneurysm formation can occur with an increased risk of rupture [66, 67]. Retrospective

studies note aortic aneurysm and dissection in 3% to 18% of patients with GCA [66-70]. In a cross-sectional study employing CT, 12/54 (22.2%) patients with GCA developed aortic aneurysms after 4 to 10.5 years [63] with relative risks (RR) ranging from 3 to 17.3 [66, 71]. Distal stenotic lesions of the subclavian, axillary and brachial arteries occur in 3% to 15% of patients [51, 67, 72, 73]. Lower extremity arteries are infrequently affected [67], however the identification of claudication and vascular bruits is important to ascertain before initiation of empiric CS because such findings, which add weight to the formal diagnosis of GCA, may resolve with effective treatment [70, 74]. The management of peripheral arterial involvement rarely requires surgical intervention [55, 70, 75].

DIAGNOSIS

Classification Criteria

The American College of Rheumatology (ACR) 1990 criteria for the classification of GCA [76] required the presence of three or more of the following including, age >50 years, new onset localized headache, temporal artery tenderness or decreased pulsation, erythrocyte sedimentation rate (ESR) >50 mm/hr, and abnormal TAB, yielding a sensitivity of 93.5% and specificity of 91.2% to discern GCA from other vasculitides.

Table 1. Positive predictive value of clinical features of GCA*

Clinical Features Associated With a positive TAB	PPV Positive Predictive Value	Percentage of Patients
New headache	46%	49%
Scalp tenderness	61%	18%
Jaw claudication	78%	17%
Double vision	65%	10%
Jaw claudication + Scalp tenderness + New headache	90%	6%
Jaw claudication + Double vision or decreased vision	100%	0.7%

*Adapted from [8]. Abbreviations: GCA, giant cell arteritis; PPV, positive predictive value; TAB, temporal artery biopsy.

In the absence of consensus with regard to diagnostic criteria for GCA, the ACR criteria [76], jaw claudication, diplopia, temporal artery beading, prominence and tenderness increased the likelihood of positive TAB [46]. Jaw claudication in association with diplopia or decreased vision, or scalp tenderness and new headache were likewise predictive of GCA (Table 1). The insensitivity of the ACR Classification criteria is exemplified by the potential enigma of an 85-year-old man with headache, jaw claudication, loss of vision, temporal artery pain, and a clinically abnormal temporal artery who might only have a pre-TAB probability of GCA of 68% [77] emphasizing the difficulty in ascertaining a conclusive histopathologic diagnosis even when the clinical features are highly suggestive.

Laboratory Studies

Blood Studies

Acute phase markers of inflammation are often significantly elevated, and a normocytic normochromic anemia and thrombocytosis may be present [78], as may elevation of liver transaminase levels [79], while the serum albumin level may be depressed. The presence of rheumatoid factor, antinuclear (ANA) and other autoantibodies are not present in greater frequency than in the general population; however ascertainment of serum ANCA may help to differentiate GCA from other forms of vasculitis. Although the ESR has historically been the acute phase measure of choice in the diagnosis of GCA, up to a quarter of patients may have a normal value [47, 80-82] and elevation of the C-reactive protein (CRP) is a better predictor of obtaining a diagnostic TAB [9, 81, 83, 84]; the combination of an elevated CRP and positive TAB render the highest sensitivity and specificity for the diagnosis of GCA. Only 1 in 119 (.8%) patients to 7 in 177 (4%) patients [81, 84] with GCA presented with both normal ESR and CRP levels, however such findings may be subject to selection and referral bias. We routinely measure the CRP and plasma viscosity in all patients with suspected GCA since the latter has the advantage of paralleling the ESR, uninfluenced by age, gender, hematocrit or time to analysis.

Temporal Artery Biopsy

Temporal artery biopsy has been the gold standard test representing definitive pathological diagnosis [7, 13, 14, 38, 46, 55]. Performed correctly, TAB carries a low procedural risk of significant complications [77], and a positive result removes later doubts about diagnosis, particularly if treatment causes complications [85, 86] or if the patient fails to respond promptly to therapy [87], whereas a negative biopsy is important in averting long term risk of empiric CS [88]. Up to one-third of clinicians surveyed did not recommend TAB for the diagnosis of GCA [89] possibly because it did not alter the perceived necessity of empiric therapy when the result was inconclusive or negative [90-92]. The true sensitivity of unilateral TAB was 87% employing Bayesian analysis [93] with a variation in sensitivity of 24% to 94% in clinical cohorts [87]. The likelihood of a false-negative TAB may be influenced by the length of the specimen, the duration of prior CS therapy, pathological sectioning techniques and the presence of predominantly non-cranial disease. Retrospective reviews suggest a post-fixation biopsy length of 1 to 2 centimeters (cm) is adequate [94-97], but a length of greater than 2 cm was also recommended [97- 100]. A length of artery nearer to 3 cm probably allows for post fixation shrinkage [99]. Whether bilateral biopsies should be performed depends on the rate of discordance, which in a pooled analysis of four studies looking at 439 synchronous bilateral biopsies was 5.9% [93], although the range in individual studies was 1.4% to 12.7% (101). If the selected artery is negative for arteritis, some investigators [29, 88] advocate biopsy of the temporal artery on the contralateral side while others [12] consider the additional burden on the patient not justified for the small increase in diagnostic yield particularly if an adequate length of unilateral specimen can be ascertained and reviewed by an experienced pathologist in TAB analysis [55, 99]. The side selected for TAB should be the one, if present, with lateralizing symptoms or signs [102].

Temporal Artery Ultrasound

Temporal artery ultrasound studies (TAUS), which are cost-effective, non-invasive and lack significant complications, take about five minutes to perform, and render an image of the inflamed temporal artery characterized by edematous wall swelling. The latter conforms to a dark hypoechoic circumferential halo sign that represents continuous or segmental wall thickening (Figure 3).

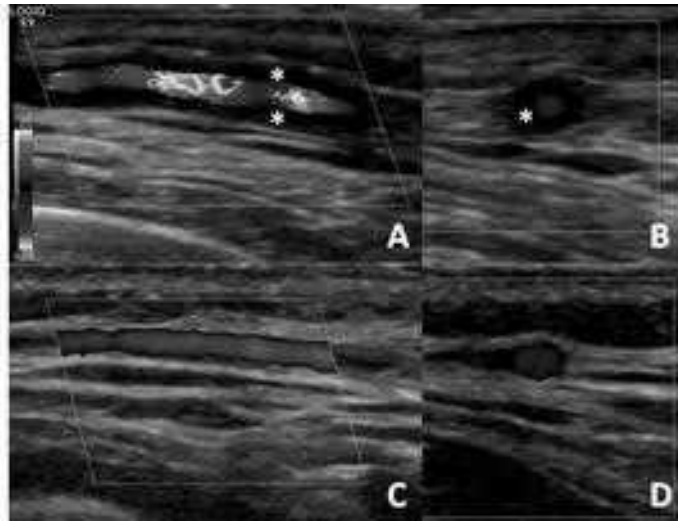
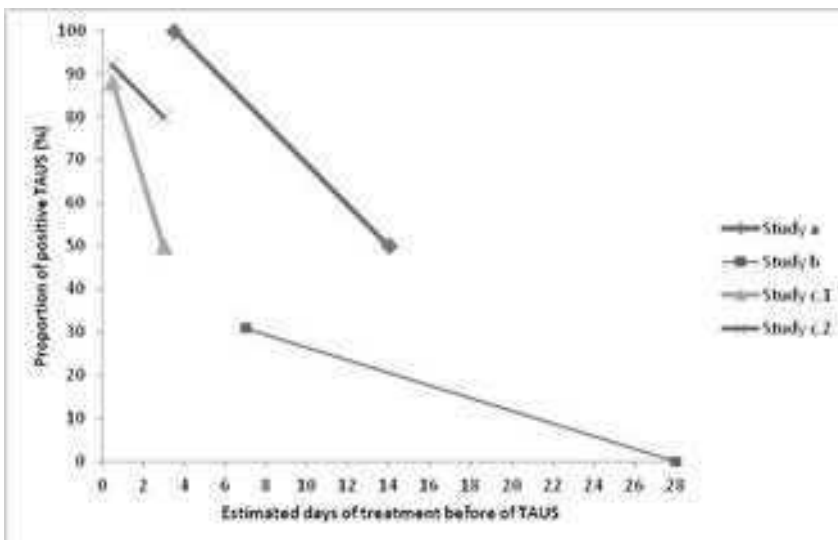


Figure 3. Temporal artery ultrasound (TAUS). The hypoechoic “halo” sign (asterisks) on (A) longitudinal and (B) transverse section. (C) and (D) normal artery.



References: Study a (174); Study b (104); Study c (116). Abbreviations: TAUS, temporal artery ultrasound.

Figure 4. Proportion of positive temporal artery ultrasounds as a function of days on treatment with corticosteroids. An estimate of the mean length of treatment at two time points was made from each study listed below and plotted on the chart. The thickness of the lines represents the number of subjects reported in the study. Study c allowed two such estimates.

Stenosis and occlusion common in elderly patients due to atherosclerosis, neither of which are specific or sensitive for GCA, may also be noted [103, 104]. Three meta-analyses [105-107], which demonstrated the usefulness of the halo sign in the diagnosis of GCA with a sensitivity of 68% and specificity of 91% for a unilateral halo sign, showed 100% specificity for the bilateral halo sign. However, the findings may be influenced by CS use; moreover there is a presumed limited window of opportunity wherein which to correctly ascertain the diagnosis [65]. One-half of positive TAUS findings may be missed within seven days of treatment initiation (Figure 4), implying that in order to avert the low sensitivity of TAUS in those with suspected GCA, the study should be performed as soon as possible, preferably before or on the first day of treatment. Some [108] argue that it is never too late to perform TAUS because even if the sensitivity is diminished, the specificity remains. Therefore there is a rationale for its use as it has the potential to avert the need for TAB when a halo sign is noted. Furthermore, it can increase the diagnostic yield of TAB by directing the incision site to the most affected area of artery [104, 109].

Other Imaging Studies

Whereas non-invasive vascular imaging may be useful when there is atypical extracranial large vessel involvement or limb claudication and persistent acute phase reactants or fever of unknown origin [110], conventional angiography has little if any role unless a surgical intervention is contemplated [111]. Ultrasound of the thoracic aorta is generally inadequate but it may provide useful information in proximal upper limb arteries to increase the diagnostic yield of GCA [112]. Both magnetic resonance imaging (MRI), MR angiography (MRA), and contrast-enhanced computerized tomographic angiography (CTA) provide useful images of mural and luminal changes suggestive of large vessel vasculitis in GCA [6, 64, 113, 114] that include circumferential wall swelling, smoothly tapered luminal narrowing of aortic branches and aortic aneurysm formation [111]. Moreover, MRI and MRA which do not lead to radiation exposure are favored over CTA by some specialists [38, 101].

Bright mural enhancement of the temporal artery on contrast-enhanced high-resolution MRI had comparable sensitivity and specificity to TAUS in the diagnosis of GCA in one retrospective single-center analysis [115], the latter of which decreased in sensitivity over the first few days of CS treatment (85% after 0-1 days, 64% after 2-4 days, 56% after >4 days) [116].

Whole body ¹⁸Fluorodeoxyglucose (FDG)-positron emission tomography (PET) increased the overall diagnostic accuracy of large vessel involvement in GCA from 54% to 70% [117]. One meta-analysis [118] found that the absence of FDG uptake conferred a negative predictive value of 88% of GCA, whereas thoracic vascular uptake was highly suggestive of GCA. However there have not been properly designed trials to assess the sensitivity and specificity of ¹⁸F-FDG PET in GCA, nor does it reliably distinguish between atherosclerosis and vasculitis [119]. The radiographic features of large-vessel involvement so noted in CTA and PET imaging decrease rapidly after the initiation of CS treatment; features of large-vessel vasculitis including concentric wall thickening were significantly more frequent in treatment naïve patients compared to patients treated with corticosteroids for 1-3 days (77% versus 29%, $p = 0.005$) [6]. The diagnostic accuracy of PET in detecting large-vessel involvement was significantly higher in patients not receiving immunosuppressive therapy (93.3% vs 64.5%) [117].

Rapid Diagnostic Pathway

The authors advocate a clinical review of patients within 24 hours of suspected GCA, including access to specialty assessment for the performance of necessary blood tests, followed by TAUS, and TAB within seven days [13, 14, 55]. The threshold is kept low for the performance of TAUS or TAB in all patients suspected of GCA awaiting the findings before commencement of CS in the absence of visual disturbances and jaw claudication [8]. The risk of blindness in other patients with typical GCA while awaiting results of laboratory studies is carefully weighed against the risk of potentially serious medication side effects associated with empiric CS treatment. The cost effectiveness of such pathways in secondary care has yet to be calculated, but visual loss particularly in the elderly, has major consequences for quality of life [14]. While those with monocular vision loss would trade one in three of their remaining years for unimpaired vision, this rose to two in three in those with binocular vision [120].

PROGNOSIS

Clinical studies have not validated the relation of existent classification criteria for GCA [76] to clinical and laboratory measures to prognosticate relapse likelihood and outcome. Common features of clinical relapse include recurrent headache, scalp pain and PMR-like symptoms associated with a raised acute phase response reactants [121-124]. Clinical symptoms and changes in the acute phase response can occur independently [125]. Acute phase responses can take several weeks to return to normal after initiating treatment while symptoms improve over several days [126, 127]. It can be argued that maintaining the lowest level of acute phase response achieved for each individual patient is an important goal of therapy [128] but pursuing a normal acute phase response might lead to overtreatment and unacceptably high rates of CS-related adverse events. Up to 20% of patients with a significant asymptomatic rise in ESR failed to relapse clinically [122] although clinicians may be overly concerned that improved control of the acute phase response may be protective against late atherosclerosis [129]. It seems reasonable to consider a return to higher dose treatment to improve prognosis in patients experiencing a returning headache, PMR-like symptoms, jaw claudication and visual symptoms. Since the advent of CS for GCA, the long term outcome and survival rates have been similar to age matched population [27, 130] including those with large vessel complications [131], although prior to CS estimated mortality was 12.5% [132]. The presence of clinical or subclinical aortitis could infer a poorer prognosis [6, 68] but this requires further corroboration. It is uncertain to what degree aortic involvement so noted on imaging studies resolves with standard GCA therapy, or whether it predicts a more chronic and relapsing GCA course requiring continued or more aggressive treatment [64, 68, 133]. Standard chest radiography, echocardiogram, CT, MRI and PET imaging have all been used to screen for emerging thoracic aortic dilatation [12, 38, 63, 67, 131, 134]. However there are no prospective studies comparing the sensitivity of these studies separately or together in discerning thoracic aortic aneurysm formation. Mackie and Pease [55] advocate tight control of blood pressure without regular imaging.

TREATMENT AND OUTCOME

Most experts including the British Society of Rheumatology (BSR) and European League Against Rheumatism (EULAR) recommend early initiation of high-dose CS therapy before TAB, although the evidence for this approach is weak with a level of evidence equal to 3 and strength of recommendation equal to C [11, 12]. The case can be made for early intervention with empiric treatment in patients with visual loss since untreated, the other eye is at heightened similar risk in up to one-third of cases for the ensuing three weeks [121], moreover partial visual improvement in vision is more likely if treatment commences within the first day of visual loss [135]. A similar approach may be advocated in those with features of impending visual loss such as amaurosis fugax, diplopia and jaw claudication. However, if the likelihood of GCA is low to moderate, withholding treatment and awaiting TAB that later returns negative would avoid unnecessary treatment. Figure 5, which show the proportion of positive TAB biopsies in relation to the number of weeks taking corticosteroids among several reported cohorts [8, 87, 136-138], suggests a 5% to 10% loss of TAB positivity for each week of treatment. While those with initially high likelihood of GCA pretreatment will have persistently high rates of TAB positivity weeks later, the latter would not likely influence therapeutic decisions unless such patients suffer later relapse or manifest treatment related side effects that questioned need for continued therapy. A bilateral TAB length of > 3cm so noted in one-half of specimens, predicted the subsequent need for corticosteroid therapy in 94% of patients [139], whereas a negative TAB measuring >2 cm performed before six days of starting prednisolone led to cessation of therapy without later visual loss [140].

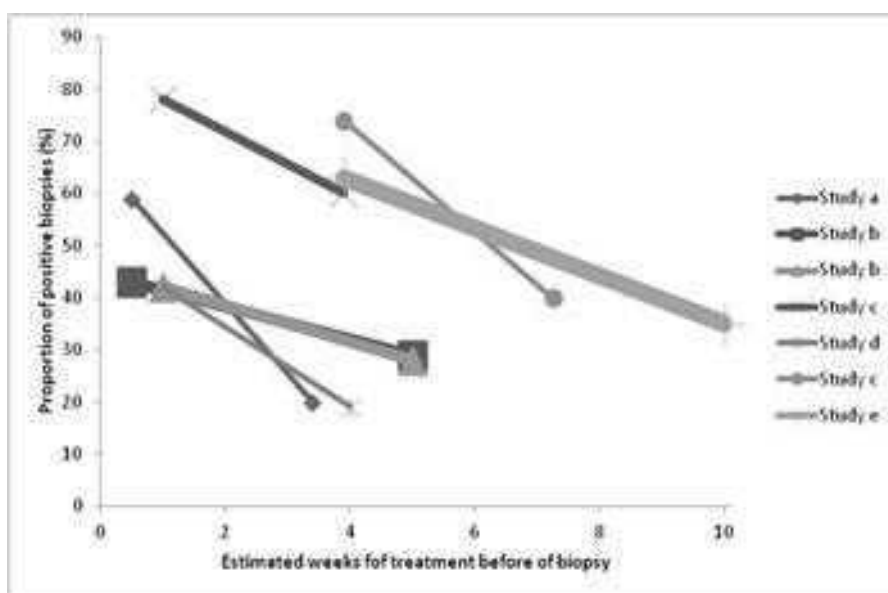


Figure 5. Proportion of positive TAB biopsy specimens as a function of weeks on treatment with glucocorticoids. An estimate of the mean length of treatment at two time points was made from each study report listed below and plotted on the chart wherein the thickness of the lines represented the number of subjects reported in the study. References: Study a: (136); Study b: (137); Study c: (87); Study d: (138); Study e: (8). Abbreviation: TAB, temporal artery biopsy.

Although there are no RCT of the use of CS in GCA [11, 12], most experts agree with daily morning treatment of prednisone at doses of 40 mg to 60 mg until symptoms and laboratory abnormalities resolve [7, 11, 12, 122]. Alternate daily CS were not as effective as a daily regimen, alone or in association with adjuvant methotrexate for GCA [122, 141]. In fact, the symptomatic response that follows CS treatment is so striking and rapid in GCA, that it is a diagnostic criterion of the disease [122]. Patients with PMR experience improvement in symptoms related to systemic inflammation over two to three days while symptoms related to impaired blood flow such as jaw claudication and visual disturbance generally take longer to respond and resolve [142]. Although sustained visual loss may be permanent and unresponsive to therapy [143], the risk of further progression is low [144]. Although prednisone in the dose range of 10 mg to 40 mg per day was effective in several cohorts [90, 145, 146], the results were not considered conclusive due to small sample sizes and apparent selection bias [86, 147]. Pulsed intravenous methylprednisolone was advocated in patients with GCA and visual disturbances [11, 12], however one observational study [128] and another RCT [148] failed to demonstrate improved efficacy in preventing visual loss compared to high-dose oral therapy. Moreover, intravenous pulsed methylprednisolone, which demonstrated no significant long term CS-sparing effects in the treatment of simple forms of GCA, was reserved for complicated forms of GCA.

The concern for CS resistance in patients with GCA has its origin in the ophthalmology community where visual loss in GCA is more prevalent [128]. One small RCT [149] that administered three consecutive days of one gram of intravenous pulsed methylprednisolone induction, followed by oral CS found higher rates of remission, less relapses, and more rapid tapering compared to patients treated with oral high-dose CS.

The apparent corticosteroid-sparing benefit of pulsed intravenous methylprednisolone [149] may not have been clinically significant since the criteria for disease relapses included instances of raised acute phase responses without clinical flares; moreover there were no differences in CS-related side effects [129]. The CS dose can be gradually tapered in the first month after the resolution of reversible clinical symptoms and the levels of acute phase reactants falls by 50% [11, 12]. Although other tapering regimens have been employed [122, 142], the available evidence [90, 142, 146, 150, 151] suggests that treatment should be continued for at least two years, with most patients weaned off of medication by four to five years. A minority of them may need continued low-dose CS [85, 121]. Among several GCA treatment trials conducted between 1988 and 2003 [90, 121-123, 142, 145, 146], the median duration of treatment of GCA ranged from 24 to 191 weeks, with an equivalent cumulative dose of prednisone that ranged from 5,275 mg to 9,194 mg. Such broad differences in the duration and dosage of administered CS would be expected to translate into a spectrum of relapse rates so noted in 27% to 84.2% of patients, with increased rates among those receiving the highest initial CS doses with more rapid tapering.

A meta-analysis of the use of adjuvant treatment with methotrexate [152] calculated the time-to-event outcomes in three randomized, placebo-controlled trials of patients with newly diagnosed GCA treated with initial high-dose CS and randomly assigned to 7.5 mg to 15 mg per week of oral methotrexate therapy or placebo [122, 123, 153]. There was a reduction in the cumulative equivalent dose of prednisone by 842 mg in 48 weeks ($P < 0.001$), but prednisone only treatment was reduced rapidly, and the rate of relapse in this group was 80% and it did not reflect current treatment practice. Current guidelines [12] of a recommended CS tapering regimen were loosely based on clinical experience at the Mayo Clinic [142] with the

consensus of a group of international clinicians. Some clinicians prefer slower dose reduction regimens with a lower anticipated rate of relapse [13], while others [126, 128, 154] favor individualized dose reduction schedules based on regular clinical review. The main drive to keep the CS dose to a minimum is the fear of adverse CS effects, particularly cardiovascular and bone fractures. Several cohort studies [90, 142, 146, 155, 156] suggested the clear association between the cumulative dose of steroids and the rate of CS complications other than cardiovascular and bone fracture, whereas others [67, 68, 71] were variably confounded by patients with differing severe disease requiring more aggressive treatment. The meta-analysis by Mahr and colleagues [152] noted adverse events in two-thirds of patients treated with CS alone, with methotrexate or placebo that included infection, abnormal liver function tests, fractures, diabetes, malignancy, thrombocytopenia, and leukopenia in descending order of frequency.

There is evidence from single case reports and small patient series of a clinical benefit in GCA employing the pyrimidine inhibitor leflunomide [157], and the immunosuppressants mycophenolate mofetil [158] and cyclophosphamide [159], however their efficacy has not yet been confirmed in RCT. Cyclosporin showed no additional CS-sparing effect in GCA [160].

Therapy with the anti-tumor necrosis factors (TNF) infliximab and etanercept [161-163] was of no benefit and potentially harmful in newly diagnosed GCA. Tocilizumab, an IL-6 receptor alpha inhibitor, induced remission and reduce glucocorticoid requirements in patients with refractory GCA [44, 164-167]. A multicenter RCT underway at the time of the writing of this chapter in 2015 has been concluded [168]. Tocilizumab, received weekly or every other week, combined with a 26-week prednisone taper, was superior to either 26-week or 52-week prednisone tapering plus placebo with regard to sustained CS-free remission in patients with GCA. Longer follow-up is necessary to determine the durability of remission and safety of tocilizumab. Sustained remission at week 52 occurred in 56% of the patients treated with tocilizumab weekly and in 53% of those treated with tocilizumab every other week, as compared with 14% of those in the placebo group that underwent the 26-week prednisone taper and 18% of those in the placebo group that underwent the 52-week prednisone taper ($P < 0.001$ for the comparisons of either active treatment with placebo). The cumulative median prednisone dose over the 52-week period was 1862 mg in each tocilizumab group, as compared with 3296 mg in the placebo group that underwent the 26-week taper ($P < 0.001$ for both comparisons) and 3818 mg in the placebo group that underwent the 52-week taper ($P < 0.001$ for both comparisons). Serious adverse events occurred in 15% of the patients in the group that received tocilizumab weekly, 14% of those in the group that received tocilizumab every other week, 22% of those in the placebo group that underwent the 26-week taper, and 25% of those in the placebo group that underwent the 52-week taper.

The impact of aspirin use on ischemic cranial complications was demonstrated in GCA as a basis for management of GCA [169, 170], however an impact was not shown in retrospective cohorts [171-173].

CONCLUSION

GCA is a common, serious and treatable vasculitis that affects older adults. Rapid access and management care pathways ensure the early referral of untreated suspected patients for

readily available TAB especially warranted in those with low to moderate probability of disease, and appropriate primary and secondary care to prevent excess morbidity and mortality associated with empiric and often unwarranted high-dose CS therapy. Published guidelines for GCA diagnosis and management need to be rigorously examined to assess the impact of CRP, TAUS signs, large vessel imaging, and TAB in any given patient, especially those who warrant empiric high dose CS due to impending visual loss. Moreover, guidelines need to reflect a unified definition of clinical relapse. Studies assessing the link between clinical symptoms, inflammatory markers, imaging techniques and mimicking conditions will be very valuable. Finally, long-term vascular complications are increasingly recognized in GCA, and this is blurring the margin between atherosclerosis and vasculitis, which may improve our understanding of both these conditions [65]. Biological agents including tocilizumab are emerging as effective and safe CS-sparing therapy in treating GCA

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Chapter 215

OPHTHALMOLOGIC AND NEURO-OPHTHALMOLOGIC ASPECTS OF VASCULITIDES

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ABSTRACT

There have been significant advances in the understanding of the vasculitides in the past several years leading to more precise classification and nosology. Ophthalmologic manifestations may be the presenting feature of and a clue to the diagnosis of vasculitis, or develop in the course of the illness due to a common disease mechanism. Precise diagnosis and prompt treatment prevents short and long-terms ophthalmologic sequela.

Keywords: neuro-ophthalmology, ophthalmology, vasculitis, CNS

INTRODUCTION

Vasculitis is a term used to characterize a spectrum of diseases associated with vascular inflammation. Ophthalmologic manifestations may be the presenting features of primary and secondary systemic vasculitis and a clue to early diagnosis to prevent ischemic vascular sequela. Unrecognized and therefore untreated, the ophthalmologic and neuro-ophthalmologic features can be catastrophic with irreversible loss of function particularly when visual involvement coincides with vasculitic brain infarction, hemorrhage, and aneurysm formation or ischemic involvement of the optic nerve or surrounding orbital structures. This chapter

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considers the ophthalmologic aspects of primary systemic vasculitis and primary central nervous system vasculitis (PCNSV) in children and adults. Galetta [1] has reviewed the neuro-ophthalmologic aspects of vasculitides.

CLASSIFICATION OF VASCULITIS

Two Chapel Hill Consensus Conferences (CHCC), one in 1994, and the other revised in 2012 [2, 3], provided consensus on nosology and definitions for the commonest forms of vasculitis in adults based upon the caliber of vessels involved. The Pediatric Rheumatology European Society (PRES) and the European League against Rheumatism (EULAR) proposed specific classification criteria for the commonest childhood vasculitis syndrome [4] based upon vessel size similar to the CHCC nomenclature [3]. The EULAR, PRES, and the Pediatric Rheumatology International Trials Organization (PRINTO) defined the clinical, laboratory and radiographic characteristics for several childhood systemic vasculitides in a validated classification of pediatric vasculitis [5]. There is a continuum of vasculitic disorders with some occurring exclusively in childhood or in older adults, and others across the age spectrum although with differing epidemiology, clinical and laboratory manifestations, and response to treatment. Large vessel vasculitis (LVV) includes giant cell arteritis (GCA) and Takayasu arteritis (TAK) affects the aorta, its major branches and analogous veins. Medium vessel vasculitis (MVV) includes polyarteritis nodosa (PAN) and Kawasaki disease (KD) with typical involvement of main visceral arteries and veins and initial branches. Small vessel vasculitis (SVV) comprises disorders with vasculitis of intraparenchymal arteries, arterioles, capillaries, veins and venules, and disease pathogenesis related to anti-neutrophil cytoplasmic antibody (ANCA) production, or the formation of immune complexes (IC). The category of ANCA-associated vasculitis (AAV) includes granulomatosis with polyangiitis (GPA) (Wegener granulomatosis type), eosinophilic granulomatosis with polyangiitis (EGPA) (Churg-Strauss syndrome type), and microscopic polyangiitis (MPA) (microscopic polyarteritis), while vasculitic disorders associated with IC include hypocomplementemia urticarial vasculitis (C1q), cryoglobulinemic vasculitis (CV), and IgA vasculitis (IgAV) (formerly Henoch-Schönlein purpura [HSP]). Vasculitis without a predominant vessel size and caliber, respectively from small to large, involving arteries, veins and capillaries, comprises the category of variable vessel vasculitis (VVV), characteristic of Behçet disease (BD) and Cogan syndrome (CS). The category of single-organ vasculitis (SOV), that involves arteries or veins of any size in a single organ without features to indicate that it is a limited expression of a systemic vasculitis, is typified by central nervous system (CNS) vasculitis.

LARGE VESSEL VASCULITIS

Giant Cell Arteritis

This granulomatous LVV involves cranial branches of the arteries arising from the arch of the aorta. It occurs exclusively in individuals older than age 50 years, with an annual incidence of 15-25 persons per 100,000, with higher rates in Caucasian individuals compared

to African Americans, and among women compared to men in a ratio of 2 to 3:1 [6-9]. The ACR 1990 criteria for the classification of GCA [10], designed for use in investigative studies to help distinguish GCA from other types of vasculitides, are not useful for making the diagnosis in individual patients [11]. Five criteria were selected by the ACR [10] from which three or more in a given patient was associated with a sensitivity of 93.5% and a specificity of 91.2%, from among the following: age equal to or greater than 50 years at disease onset, new localized headache, temporal artery tenderness or decreased temporal artery pulse, elevated erythrocyte sedimentation rate (ESR) to 50 mm/hour or more, and vascular tissue biopsy sample showing necrotizing arteritis with predominance of mononuclear cells infiltration or granulomatous multinucleated giant cell inflammation. The histopathology of biopsy-positive GCA is typified by vessel wall infiltration by mononuclear cells, CD4+ T-cells, activated macrophages and multinucleated giant cells, that latter of which form granulomas close to the internal elastic lamina of involved vessels in up to one-half of specimens [12].

Visual loss due to anterior ischemic optic neuropathy (AION), which results from occlusion of short posterior ciliary arteries that supply the optic nerve head, is the commonest ocular symptom in GCA with a frequency that varies from 10% to 60%. Other causes of visual loss include vasculitic involvement of the choroid, posterior optic nerve and retina [13]. Visual loss may be partial, complete, or permanent, and is preceded by amaurosis fugax in 44% of patients [9]. A prospective study of 170 patients with biopsy-confirmed GCA [14] noted ocular involvement in 85 (50%) patients, including visual loss present in 83 (97.7%), amaurosis fugax in 26 (30.6%), eye pain in seven (8.2%), and diplopia in 5 (5.9%). Ocular ischemic lesions consisted of arteritic AION in 69 (81.2%), central retinal artery and cilioretinal occlusions each in 12 (14.1%), the latter after satisfactory fundus fluorescein angiography (FFA); as well as, posterior ischemic optic neuropathy in 6 (7.1%), and ocular ischemia in 1(1.2%) patient. Those with ocular involvement were significantly older than the patients without ocular involvement, and surprisingly less likely to have prominent constitutional and systemic symptomatology. Among 42 other patients from Olmsted County Minnesota studied by Huston and coworkers [15], visual symptoms preceded the clinical and histopathologic diagnosis of GCA in 15 (40%) patient, of which blurred vision was most common so noted in 6 (19%) of patients, followed by diplopia in 5 (12%), transient vision loss in 5 (12%), permanent partial loss in 4 (10%), and permanent complete loss in 3 (10%) patients. A followup Olmsted County cohort twenty-five years later totaling 168 patients with GCA by Nuenninghoff and colleagues (16) found visual disturbances overall at presentation in 16 (9.5%) patients, and at the time of diagnosis in 37 (22%) patients, of whom 14 (8.3%) patients had transient vision loss, 18 (10.7%) had permanent vision loss, and 14 (8.3%) had diplopia.

Of 18 patients with varying visual loss and occult GCA [17], amaurosis fugax was noted in 6 (33.3%), diplopia in 2 (11.1%), and eye pain in 1 (5.6%) patient. Ocular ischemic lesions included AION in 17 (94.4%) patients, and central retinal artery occlusion and cilioretinal artery occlusions each in 2 (11.1%) after FFA. The authors [17] concluded a high index of suspicion for GCA for patients older than 50 who develop amaurosis fugax, visual loss, or AION in the absence of constitutional and systemic symptoms (Figure 1).

Ocular involvement was more common in patients with GCA without large vessel vasculitic involvement according to Prieto-González and colleagues [18] who studied 40 patients with newly diagnosed biopsy-proven GCA by computed tomographic (CT) imaging to define LVV involvement of the aorta and its tributaries. Ocular involvement was noted

more often in those with LVV aortic involvement than without (15% versus 54%). Conversely, ischemic events were more common in those without than with evidence of LVV aortic involvement by CT-imaging (54% vs. 22%). The authors postulated a spectrum of GCA disease with cranial arteritis manifested by ocular symptoms, headache, and jaw claudication at one end and predominant LVV at the other.



Figure 1. Patient with giant cell arteritis and brainstem stroke demonstrating left gaze paresis.

The incidence and severity of visual loss and ocular involvement appears to depend upon the promptness of diagnosis and treatment. Although AION is the commonest cause of visual loss in GCA, only 5.7% of patients with AION will have GCA making it critical to distinguish arteritic from non-arteritic AION in suspected patients [19]; FFA are a critical tool in this distinction. The appearance of posterior ciliary artery occlusion is diagnostic of arteritic AION, while non-arteritic AION is almost always due to a fall in perfusion pressure in the peripapillary choroid and not from primary ciliary artery occlusion (20). One other finding that supports the diagnosis of arteritic AION in up to one-half of affected patients presenting with visual symptoms is chalky-white optic disc swelling [21]. A small disc and cup may be associated with both arteritis and non-arteritic AION, while a normal or large cup is highly suggestive of an underlying arteritic process [22]. Color Doppler imaging of the central retinal and short posterior ciliary arteries is helpful in distinguishing GCA from non-arteritic AION. Ho and colleagues [23] compared color Doppler flow imaging in patients with GCA to matched control subjects revealing reduced central retinal and short posterior arterial mean flow velocities and increased vascular resistance.

The mainstay of treatment for GCA is corticosteroids however the exact dosing regimen and mode of administration depends upon the presence of visual involvement at the time of diagnosis. Patients with unilateral complete loss, evidence of fellow eye involvement, and amaurosis fugax are treated with 1 gram of intravenous corticosteroids every 6 to 8 hours followed by the oral prednisone. Salvarani and colleagues [24] employed 40 mg to 60 mg oral prednisone for GCA, and intravenous methylprednisolone 1g per day for 3 day for those with recent or impending visual loss. The addition of low dose aspirin to corticosteroid therapy was beneficial in preventing cranial ischemic complications including acute visual loss and cerebrovascular complications of GCA than steroids alone. Patients treated with aspirin and

corticosteroids are five-fold less likely to experience cranial ischemic complications than those who received corticosteroids alone [25]. Aiello and colleagues [26] noted visual improvement in 15% of eyes after commencing therapy for GCA and estimated a probability of further visual loss developing of 1% in the absence of a defined visual deficit, compared to 13% when an established deficit was ascertained. Danesh-Meyer and colleagues [27] evaluated the incidence and extent of visual recovery of 34 patients with biopsy-proven GCA treated with high dose systemic corticosteroids noting that 27% of eyes suffered loss of visual acuity by two or more lines within one week of starting corticosteroid treatment, while 15% of eyes so treated showed an improved visual acuity of 2 or more lines. Of the 15% of eyes that showed an improvement in visual acuity, none showed further improvement in visual fields or color vision, leading the authors [27] to conclude that the improvement in visual acuity may reflect learning to view eccentrically. Liu and colleagues [28] investigated 45 patients with biopsy-proven GCA, 25 of whom were treated with intravenous methylprednisolone, and 20 treated with oral prednisolone. Visual loss remained unchanged in 49% so treated, worsened in 17%, and improved in 34%, defined as visual acuity improvement of two or more lines and final acuity greater than 20/80. Fellow eye involvement more often occurred in patients receiving oral corticosteroid therapy compared to those receiving intravenous therapy. Similarly, visual acuity was more likely to improve after a course of intravenous treatment than oral therapy (39% versus 28%).

Takayasu Arteritis

This systemic necrotizing LVV is characterized by thrombosis of the vessels arising from the aortic arch. TAK predominantly occurs in young Japanese females, typically arising before the age of 40, in a 9:1 female to male ratio [29-31]. The incidence of TAK is estimated to be between 0.4 to 2.2 per million people, [32, 33] with higher rates in South East Asia, Africa and South America [34, 35].

The ACR [36] selected six criteria for the classification of TAK, from which three or more in a given patient were associated with a sensitivity of 90.5% and a specificity of 97.8%, from among the following: age less than or equal to 40 years, claudication of an extremity, decreased brachial artery pulse, greater than 10 mmHg difference in systolic blood pressure between arms, a bruit over the subclavian arteries or the aorta, and arteriographic evidence of narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper or lower extremities. Although the histopathology of TAK is not included as part of the ACR criteria [36], it may aid in the diagnosis, and it is characterized by an acute periarteritis with extensive cellular infiltration, necrosis of the media, and intra-arterial thrombosis [37]. Ocular features not formally part of the criteria of TAK occur in 35% to 68% of patients [38-40], typically due to ischemia and hypoperfusion resulting from occlusive arteritis of the aortic arch branches, while those arising in the setting of hypertension result from vasculitic renal artery involvement.

The commonest ischemic ocular manifestation of TAK is retinopathy, first described by Takayasu [41] who noted peculiar fundus changes consisting of dilated vessels around the optic disc due to arteriovenous (AV) anastomoses in female patients without a palpable radial pulse. Less common ocular ischemic manifestations include anterior ischemic optic

neuropathy (AION), central retinal artery occlusion, and ocular ischemic syndrome [29, 42]. The retinal changes in TAK vary in symptomatology and severity depending on the location of carotid artery involvement, the rate and duration of ocular vascular hypoperfusion, and the presence of collateral blood supply to the eye [38].

Uyama and Asayama [30] studied 80 patients with TAK noting that 38 (48%) of patients had involvement of the aortic arch and stenosis or occlusion of its proximal branches denoting type I TAK; 25 (31%) patients had type II TAK characterized by involvement of the whole aorta and its branches, and 16 (20%) had type III TAK characterized by involvement of the descending thoracic and abdominal aorta and its branches. Altogether, 38 (100%) of patients with type I TAK had retinopathy. Uyama and Asayama (30) classified retinopathy into stages 1 to 4 wherein 20 (53%) patients with stage 1 had dilations of small vessels; 12 (32%) patients with stage 2 disease had microaneurysm formation; 3 (8%) patients each with either stage 3 or 4 disease, respectively manifested AV anastomoses or ocular complications of vitreous hemorrhages, proliferative retinopathy and vision loss. The authors attributed the retinal vascular changes to decreasing blood flow in the retinal vasculature noting decreased intraocular pressure with disease progression. In contrast to type I TAK, hypertensive fundal changes predominated in patients with type III disease with 12 (86%) demonstrating hypertensive changes occurring in the fundus, and 2 (14%) manifesting hypertensive retinopathy.

Chun and colleagues [38], who reviewed medical records and FFA of 156 eyes from 78 patients with TAK, noted that the commonest ocular symptoms were subjective decrease of vision in 23 (29.5%) patients; amaurosis fugax in 20 (25.6%) patients; ocular pain in 9 (11.5%) patients; and metamorphopsia in 3 (4%) patients. Among 13 cases of retinopathy, 69% occurred in patients with TAK involving primarily the aortic arch and its branches, and among 25 patients with hypertensive retinopathy, 18 (72%) patients had involvement of the thoraco-abdominal aorta, its branches, and the aortic arch. Thus, patients with retinopathy were more likely to have carotid artery or aortic arch involvement, while those with hypertensive retinopathy were more likely to have involvement of the descending aorta.

The importance of staging retinopathy was highlighted by Chun and coworkers [38] who demonstrated that visual acuity (VA) dramatically worsened as patients progressed from stage 3 to stage 4 retinopathy. The best corrected VA in patients with Stage 1 to Stage 3 retinopathy ranged from 20/15 to 20/30, while those with stage 4 disease had VA ranging from 20/200 to hand motion alone. Causes of impaired VA in such patients included total cataract in 4 patients, neovascular glaucoma in 2 patients, vitreous hemorrhages in 1 patient, tractional retinal detachment in 3 patients, optic atrophy in 3 patients, and AION in 1 patient. Peter and coworkers [29] demonstrated an association between VA and retinopathy, noting a causal relation between uncorrected refractive error among 18 patients that was due to a cataract in 6 (33%) patients, grade 4 retinopathy in 4 (22%) patients, optic atrophy in 2 (11%) patients, hypertension with retinal detachment, longstanding papilledema, and retinal pigment changes of the fovea, and a posterior capsular opacity each in 1 (6%) patient. Although there was no correlation of patient age, duration of symptoms, history of limb claudication, presence of a carotid bruit, hemiplegia, or increased ESR or C-reactive protein (CRP) levels with the development of retinopathy, retinopathy was more frequent in those with significantly lower blood pressures and non-recordable right upper limb blood pressures than in patients without retinopathy.

Ocular symptoms are typically a late manifestation of disease, with ophthalmic evaluation occurring on average 55 ± 69 months after disease onset. [29]. An ocular ischemic syndrome was the initial disease manifestation of TAK in three reported patients ranging in age from 14 to 42 years, of subacute or chronic progressive onset (43-45) , in whom vascular imaging was crucial in the etiological diagnosis.

FFA is an important tool in determining the extent of ocular involvement in TAK [46], and when compared with indirect ophthalmoscopy in 31 eyes with TAK showed no additional changes in ten eyes without retinal vein dilation on indirect ophthalmoscopy. However, of 7 eyes with dilated retinal veins, FFA revealed additional abnormal findings such as microaneurysms, arteriovenous shunts, retinal neovascularization, and avascular areas important in grading the stages of retinopathy. Chun and colleagues (38) noted prolongation of arm-to-retina circulation time in all 21 (100%) eyes with retinopathy while 14 (67%) patients had delayed arteriovenous filling time. Similarly Uyama and Asayama [30] noted that arm to retinal time was delayed by 20 seconds on FFA in patients with retinopathy.

Kerr and colleagues [31] noted a 60% response rate to corticosteroids alone among 60 patients with TAK with an estimated time to remission of 22 months. In the steroid resistant patients, cytotoxic therapy employing methotrexate and cyclophosphamide induced remission in another 40% of patients. Jales-Neto and coworkers [47] found that combination corticosteroid and immunosuppressive therapy led to disease remission in 55% of adult patients, and in 24% of patients less than age 18 years. Among four patients with TAK treated with corticosteroids described by Ishikawa [48], one improved from stage 3 to stage 2 TAK, while another patient developed unilateral blindness, and two others, were stable. Pan-retinal photocoagulation is an adjunctive therapy used to treat cases of severe retinal ischemia [38], whereas antiplatelet agents reduced the frequency of arterial ischemic events in patients with TAK [49]. So noted and treated promptly with corticosteroids, the inflammatory process underlying ocular manifestations may lead to improvement, however arterial stenoses may require bypass surgery [50, 51].

MEDIUM VESSEL VASCULITIS

Polyarteritis Nodosa

This systemic necrotizing vasculitis predominantly affects medium-sized arteries with an estimated annual incidence of 1.1 cases per 1,000,000 people in Australia [52] to 31 per 1,000,000 people in Sweden [53], and 77 per 1,000,000 people in the hepatitis-B virus (HBV) endemic area of Alaskan Eskimos [54]. The disorder is slightly more prevalent in males, with a male-to-female ratio of 1.7 to 1.9:1, and most predominant in patients 40 to 60 years of age, with an average age at onset of 47 years [55, 56]. The 2012 Revised CHCC [3] distinguished PAN from MPA, distinguishing it as a necrotizing arteritis of medium or small sized arteries without glomerulonephritis, or vasculitis in arterioles, capillaries or venules, and unassociated with antineutrophil cytoplasm antibodies (ANCA). The pathologic findings of PAN include hyaline-like necrosis in the media which rapidly spreads to the adventitia and intima, and infiltration by neutrophils, eosinophils, lymphocytes and plasma cells. This is followed later by proliferation of fibroblasts that can thicken the intima and occlude vascular lumina [57].

Although ocular manifestations are not a part of the diagnostic criteria for PAN, they occur in 10% to 20 per cent of patients [58] either due to the direct effects of arteritis that results in vascular ischemia, or as a secondary effect of renovascular hypertension with subsequent retinal edema, transudates, hemorrhages and cystoid body formation [59]. The most common arteries affected are the posterior ciliary arteries and choroidal vessels, which can result in choroidal infarcts and exudative retinal detachments [59]. Conjunctival and anterior uveal involvement has also been reported [60]. Orbital involvement may result in exophthalmos, optic nerve involvement in visual loss, ocular vessel involvement in episcleritis, necrotizing scleritis, and corneal and scleral ulcers [61]. In an analysis of 393 patients with PAN [62], 42 (10.7%) patients had ophthalmologic manifestations of which blurred vision was the most common so noted in 13 of 42 (31%) patients, followed by conjunctivitis in 8 (19%) patients, retinal exudates in 8 (19%) patients, and retinal vasculitis in 7 (17%) patients. Other less common manifestations included uveitis in 5 (12%) patients, episcleritis in 4 (10%) patients, thrombosis in 4 (10%) patients, keratitis and optic neuropathy each in 3 (7.1%) patients, retinal hemorrhages in 2 (5%) patients, and oculomotor nerve palsy in 1 (2%) patient. A study on 348 patients with PAN [63] noted ophthalmologic manifestations in 30 (8.6%) patients, consisting of retinal vasculitis, retinal exudates, or both in 15 (4.3%) patients; conjunctivitis or keratitis in 12 (3.4%) patients, uveitis in 3 (0.8%) patients, and blurred vision in 2 (0.6%) patients. There was little difference in the frequency of ophthalmologic manifestations in those with or without HBV-related PAN, so noted respectively in 10% versus 7% of patients. Moreover, visual symptoms were the presenting manifestation of PAN in several reported patients, including one with thrombocytosis and acute blindness secondary to central retinal vein thrombosis [64], others with visual loss due to retinal vasculitis [59] and bilateral choroidal vasculitis [65], and another patient with dacryoadenopathy [66].

Reports of fundoscopic examination findings in patients with PAN are varied and include papilledema, macular star formation, cotton-wool spots, retinal or subhyaloid hemorrhages, retinal exudates, vascular occlusion of the central retinal artery, and irregularity of the retinal arteries with or without aneurysm formation [59]. Retinal fluorescein angiography may also be particularly helpful in the diagnosis and management of PAN. Acute multifocal choroidal ischemia is a common feature seen on fluorescein angiography in patients with PAN, yet very rare in the general population, presumably because the degree of vasculitis is sufficiently severe to affect the choroid [67]. Other common features on fluorescein angiography in PAN include retinal vasculitis with multiple arteriolar and capillary occlusions [67].

Although there are few studies of the effect of corticosteroid treatment on the ocular manifestations of PAN, Nanjiani [58] reported treatment of bilateral optic neuritis, and circumscribed posterior choroiditis with serous retinal detachment with corticosteroids that improved systemic but not ocular manifestations. Akova and colleagues [68] described responsiveness of a spectrum of ocular findings including scleritis, peripheral ulcerative keratitis, nongranulomatous uveitis, retinal vasculitis, pseudotumor of the orbit, and central retinal artery occlusion in five patients, four of whom responded to combination corticosteroid and cyclophosphamide or azathioprine therapy.

Kawasaki Disease

This medium vessel vasculitis is one of commonest vasculitides in children with incidence rates varying from 8.39 per 100,000 children under age 5 per year in England [69] to 218.6 per 100,000 children under age 5 in Japan [70]. The disease occurs more often in males, with a male to female ratio of 1.3-1.6:1 [71, 72]. KD typically occurs in patients under 5 years of age, with a peak age of onset ranging from 9 to 11 months in Japan [70], and over 12 months in Canada and Britain [73, 74]. There are six diagnostic features of KD, five of which are needed for the diagnosis. They include fever of unknown origin lasting five days or more not responding to antibiotics; bilateral conjunctival hyperemia and indurated edema that spares the limbal region; orolabial lesions; redness and edema of palms and soles followed by fingertip desquamation; an erythematous polymorphous rash; and cervical lymph node enlargement [71].

Ocular involvement in KD is typified by bilateral conjunctival hyperemia and indurated edema that spares the limbal region; and conjunctivitis that occurs in 83% to 92% of patients [74]. The conjunctival lesion typically develops within a day or two of fever-onset and lasts up to several months [75]. Other ocular findings included bilateral injection of the bulbar conjunctiva so noted in up to 89% of patients, bilateral iridocyclitis in 78% of patients, superficial punctate keratitis in 22%, vitreous opacities and papilledema each in 11%, and subconjunctival hemorrhage in 6% of patients. Bulbar conjunctival injection typically occurs first, followed by acute iridocyclitis identified by inflammatory cells in the anterior chamber that reaches a maximum between the fifth and eighth day, thereafter diminishing after one month. Acute bilateral iridocyclitis is more common in children 4 years and older however the severity of iridocyclitis is generally independent of age [76]. Burke and co-workers [77] noted that anterior uveitis was a predominant finding during the acute phase of illness. Other less common ocular findings in KD include disciform keratitis, so noted in a 10-year-old [78] and 11-year-old reported children [79], the latter of who presented with diffuse bilateral non-purulent conjunctival congestion, VA of 6/6 in the right eye and 6/5 in the left eye, and later developed cloudy vision. Ophthalmologic examination revealed that his vision was reduced to less than 6/60 in both eyes and that he had bilateral central stroma edema with localized keratic precipitates. However, fundoscopy showed bilateral disc swelling without evidence of posterior segment inflammation. The latter, also rare, was similarly documented in several patients, including.

Posterior segment involvement in KD was documented in two patients with bilateral vitreous opacities and bilateral optic disc swelling [76], unilateral retinal exudates, macular and disc edema with severe visual loss [80] and in a patient with bilateral inner retinal ischemia diagnosed at postmortem examination [81]. Retinal vasculitis occurs rarely in KD due to selective inflammation of the blood-ocular barrier [76]. Several reported patients underwent FFA for retinal vasculitis, including one with retinal exudation, macular edema, and temporal disc swelling that showed no leakage [82], and another with bilateral acute anterior uveitis, in whom FFA showed disc edema and leakage with localized areas of perivascular sheathing suggestive of periphlebitis and vasculitis [83].

First line therapy for KD includes intravenous immune globulin (IVIg) therapy and aspirin. However corticosteroids and tumor necrosis factor (TNF) inhibitors may be beneficial those who fail to respond to IVIg therapy [84, 85]. A few small series and case reports

showed a favorable response of conjunctivitis and anterior uveitis respond to treatment with corticosteroids and mydriatics [80], IVIg therapy and aspirin [83]. One other patient with disciform keratitis and bilateral disc swelling, without signs of posterior segment inflammation, treated with topical steroids every 2 hours, cyclopentolate 1% twice a day and oral acyclovir 200 mg five times a day, experienced rapid resolution of ocular signs and symptoms. His VA improved from 6/60 bilaterally to his baseline of 6/6 in the right eye and 6/5 in the left eye after three weeks of therapy [86]. However, since anterior uveitis can be self-limiting in 2 to 8 weeks, it can be difficult at times to ascertain the true impact of treatment on symptom resolution. Rennebohm [87] described six children with KD, five of whom developed anterior uveitis during the acute phase of KD. Both children treated with corticosteroids and cycloplegic drugs improved, as did the other three untreated children. Similarly, Puglise [75] described a 4-year-old child with KD who presented with bilateral swelling and hyperemia of the conjunctiva unresponsive to intense topical steroid therapy; however there was a reduction in conjunctival inflammation within one week of 30mg/kg of aspirin therapy and complete resolution in four weeks.

SMALL VESSEL VASCULITIS

ANCA-ASSOCIATED

Granulomatosis with Polyangiitis

This systemic necrotizing SVV is characterized by granulomatous inflammation of the upper and lower respiratory tract, with focal necrotizing glomerulonephritis. The disease shows a strong predominance for Caucasians, particularly those of northern European ancestry with a prevalence ranging from 23.7 cases per 1,000,000 people in France [88], to 63 cases per 1,000,000 people in the United Kingdom [89], and 95 cases per 1,000,000 people in Northern Norway [90]. It is slightly more common in men than in women with a 1.3 to 1.7:1 male to female ratio [62, 91], and typically occurs in the fourth and fifth decades of life [62, 88, 91]. The disease is rare in children, but when it occurs, it is four times more common in girls than boys [92]. The histopathology of GPA is characterized by a triad of multinucleated giant cell granulomatous inflammation, vasculitis, and necrosis [93].

The ACR [91] identified four diagnostic criteria for GPA, two of which must be present in order to make the diagnosis from among the following including, nasal or oral inflammation, an abnormal chest radiographic showing nodules, fixed infiltrates, or cavities, urinary sediment showing microhematuria or red cell casts, and granulomatous inflammation on biopsy. The presence of two or more criteria imparted a sensitivity of 88.2% and specificity of 92.0% for the diagnosis of GPA. Although serum ANCA level is not part of the ACR criteria, GPA is associated with ANCA, particularly c-ANCA, the presence of which had 99% specificity and 96% sensitivity for generalized GPA, and 67% sensitivity for the limited form [94]. Ocular findings are not part of the diagnostic criteria for GPA; however among patients with vasculitis [91], ocular inflammation, so noted as scleritis, episcleritis, and proptosis, had a sensitivity of 27.4% and a specificity of 96.9% for the diagnosis of GPA.

Ocular manifestations occur overall in 30% to 60% of patients with GPA [95-97], and are the presenting features in up to 16% of patients [97]. Ocular symptoms can be due to primary inflammation or focal vasculitis that affects the anterior and posterior segments of the eye causing conjunctivitis, episcleritis, and keratitis, and optic nerve vasculitis; or as a result of the contiguous spread of longstanding granulomatous sinusitis leading to proptosis, orbital pseudotumor and nasolacrimal duct obstruction. Vascular complications such as retinal artery occlusion can occur [98]. Frequent symptoms of orbital disease included ocular pain, epiphora and injection although proptosis, vision loss, diplopia and ophthalmoplegia [99, 100]. Rothschild and colleagues [62] noted ocular manifestations in 117 (34%) of 343 patients with GPA, exceeding the expected frequency of 11% for EGPA and 9% for MPA. Conjunctivitis was noted in 61 (51.2%) patients, followed by episcleritis in 46 (39.3%) patients, and orbital inflammatory disease in 23 (19.7%) patients. Other ocular manifestations also included blurred vision in 18 (15.4%) patients, uveitis in 9 (7.7%) patients, oculomotor nerve palsy in 5 (4.3%) patients, and sudden visual loss in 4 (3.4%) patients. Less common ocular manifestations were adnexal inflammation, scleritis, blepharitis, keratitis, optic neuropathy, retinal exudates and hemorrhages.

Hoffman and colleagues [96] noted ocular manifestations of GPA among 15% of 158 patients at presentation, and in 52% of those in the course of the illness. Conjunctivitis and dacrocystitis each occurred in 20% of patients; however, they were considered nonspecific features. Painful proptosis, often associated with visual loss due to optic nerve ischemia, and diplopia resulting from extraocular muscle entrapments, so noted in up to 2% of patients at onset of disease and in 15% throughout the course of illness, was a useful diagnostic feature typically caused by retro-orbital pseudotumor. Fauci and co-workers [97] identified proptosis in 15 of 49 (31%) patients with ocular involvement associated with GPA due to retro-orbital mass lesions.

Akikusa and co-workers [92] found eye involvement in 13 of 25 (52%) children with GPA at presentation and in 15 (60%) children over the course of their illness. Similar to adults, the commonest ocular manifestations were conjunctivitis in 14 (56%) patients, scleritis or episcleritis in 3 (12%) patients, and proptosis in 2 (8%) patients. Cabral and colleagues [101] reviewed the presenting clinical features of pediatric patients with GPA in three single-center cohorts and one multicenter cohort, noting ocular manifestations as common presenting features of GPA in children, with conjunctivitis occurring in up to 44% at presentation.

GPA is classified into classic and limited forms, the latter specifically excluding renal disease with a more favorable prognosis. Although both forms can have ocular manifestations of disease, Stavrou and colleagues [102] noted sight-threatening manifestations more often in 16 patients with classic GPA than 15 patients with limited GPA, further noting ocular manifestations in 13 (87%) limited GPA patients compared to 14 (89%) classic GPA patients. Moreover, 4 (27%) patients in the limited group experienced sight-threatening complications compared to 8 (50%) patients in the classical group.

Magnetic resonance imaging depicts mucosal inflammation and ulceration in the sinuses, nasal cavity and orbits in GPA with greater sensitivity than computed tomography (CT) and can aid in the determination of ocular involvement [103]. The serum ANCA test is useful in tracking patient responsiveness to systemic therapy. Shiuey and Foster [94] recognized that patients with GPA and non-normalizing serum ANCA levels after treatment often developed recurrent ocular despite apparent clinical remission. ANCA serology was further helpful in

determining disease severity and future complications in patients who present with episcleritis [104], moreover those with positive ANCA serology were more likely to have ocular complications including keratopathy, visual acuity (VA) less than 20/50, and vascular pannus.

Fauci and colleagues [97] recommended remission induction treatment of GPA with 2mg/kg/day of oral cyclophosphamide and 1mg/kg/day of prednisone, followed by tapering of prednisone to an alternate day administration, achieving complete remission rates of 93% for a mean duration of 48.2 months. Chan and colleagues [98] reported a patient with bilateral corneal ulcers and a VA reduced to 20/200 in the right eye and 20/70 in the left eye that was treated with 2 mg/kg/day of oral cyclophosphamide and 1mg/kg/d of prednisone. Two years later the VA in both eyes returned to 20/40, and the peripheral corneal ulcers healed although shallow peripheral corneal thinning remained. Foster and colleagues [105] studied a patient with GPA and progressive blurred vision, diplopia and increased supraorbital pressure, who was found to have a VA of 20/200 in the right eye, 20/40 in the left eye, 90% ophthalmoplegia in the left eye, and normal fundoscopic exam. The patient was treated with oral cyclophosphamide and prednisone, and one month later VA improved to 20/40 with complete resolution of ophthalmoplegia. Vischio and McCrary [106] who reported a 70-year-old man with left eye visual change, third nerve palsy and orbital mass compressing the optic nerve that was biopsied with proven GPA. The patient was treated with prednisone 40mg twice daily and cyclophosphamide 125mg daily, without visual improvement eleven weeks later. There is substantial ocular morbidity associated with GPA despite efficacious immunosuppressant therapy so noted in three enucleations among 140 patients [95]. Sadiq and colleagues [100] identified a subgroup of patients with GPA and orbital involvement with a poor prognosis evidenced by permanent visual loss in 43% of the patients.

Some patients with episcleritis, conjunctivitis, and anterior uveitis respond to topical therapy, but they should not be used because of secondary corneal thinning and perforation [107]. Although the surgical intervention is generally reserved for the performance of tissue biopsies, dacryocystorhinostomy was effective therapy for nasolacrimal duct obstruction, achieving symptomatic relief in 13 of 14 (93%) of patients [108].

Eosinophilic Granulomatosis with Polyangiitis

This systemic necrotizing small vessel vasculitis involves multiple organ systems, typically causing chronic rhinosinusitis, asthma, and eosinophilia. It is a rare disorder with an estimated annual incidence of 2.7 cases per 1,000,000 people and a period prevalence rate of 6.8 per million in those taking anti-asthma drugs [89, 109]. With most patients developing the disease in the fourth decade of life between age 14 and 74 years, EGPA has no gender predominance [62, 88, 110].

The ACR 1990 diagnostic criteria for EGPA [111] included six criteria, four of which were necessary from the following including, asthma, eosinophilia greater than 10%, neuropathy, pulmonary infiltrates, paranasal sinus abnormality, and extravascular eosinophils. The presence of four or more criteria yielded a sensitivity of 85% and a specificity of 99.7% for the diagnosis of EGPA. Although ANCA positivity is not part of the ACR's diagnostic criteria, it can be helpful in making the diagnosis in up to 70% of patients [88]. The characteristic changes of EGPA histopathology include necrotizing vasculitis and extra-

vascular necrotizing granulomas with eosinophilic infiltrates; however, early cases may be characterized by tissue infiltration by eosinophils without overt vasculitis [112].

Ocular features of EGPA can involve all parts of the eye and orbit. Takanashi and co-workers [113] classified the ocular manifestations into two types, pseudotumor or orbital inflammatory and ischemic vasculitis types. Patients with the pseudotumor type typically present with a chronically red eye, dacryoadenitis, myositis, periscleritis, perineuritis, conjunctival granuloma, episcleritis, orbital abnormalities on imaging, and ANCA seronegativity. Those with the ischemic vasculitis present with sudden visual loss, amaurosis fugax, anterior ischemic optic neuropathy, central retinal artery or branch retinal artery occlusion, normal orbital imaging, and ANCA seropositivity.

Among 270 patients with EGPA [62] 30 (11%) patients had ocular manifestations of which conjunctivitis was the most common so noted in 13 (43.3%) patients followed by blurred vision in 9 (30%) patients, oculomotor nerve palsy and sudden visual loss each in 4 (13.3%) patients. retinal vasculitis in 3 (12%) patients; orbital inflammatory disease, and retinal exudates each in 2 (6.7%) patients; and episcleritis, keratitis, uveitis, retinal thrombosis, and retinal exudates present each in 1 (3.3%) patient. Androudi and colleagues [114] described a patient with a 20 year history of severe steroid-dependent asthma, hematuria, pleuritis and sinusitis, who later developed uveitis and bilateral scleritis. Anterior ischemic optic neuropathy was reported by Lee and colleagues [115] in a 54- year-old man with bronchial asthma, allergic rhinitis, and sinusitis who presented with a sudden decrease in VA. Central retinal artery occlusion, another complication of EGPA, leading to sudden visual loss, was described among several other patients. Skrapari and colleagues [116] described a 50-year-old woman with left foot drop and painless visual loss in whom fundoscopy revealed central retinal artery occlusion. Kumano and co-workers [117] reported a 54-year-old woman with sudden loss of vision after tapering prednisolone from 30 mg to 10 mg per day, in whom central retinal artery occlusion was noted on FFA that showed delayed filling of the retinal and cilioretinal arteries, without leakage secondary to vasculitis. Hamann and Johansen [118] reported severe visual loss in association with central retinal artery occlusion evidenced by retinal whitening, macular cherry-red spot, combined with central retinal vein occlusion so noted by papilledema, retinal hemorrhages, and dilated and tortuous veins on Fundoscopy; fluorescein angiography revealed an absence of retinal filling.

Among 96 patients with EGPA described by Guillevin and colleagues [110] 3 (3.1%) patients presented with ophthalmic involvement. 2 had episcleritis, and 1 had bilateral exophthalmos. Koenig and co-workers [119] reported a patient with monocular blindness due to central retinal artery occlusion as the presenting feature of EGPA. McNab [120] described a 66-year-old woman with diplopia, foreign body sensation, redness and proptosis of the left eye, in whom orbital CT scan revealing increased density of the left orbital fat. In addition, Jordan and co-workers [121] reported two cases of EGPA who presented with dacryoadenitis and diffuse orbital inflammation. Takanashi and colleagues [113] recommended enhanced orbital imaging to look for inflammatory lesions. Fundoscopy is useful in identifying patients with central retinal artery occlusion.

The treatment of EGPA typically consists of corticosteroids and cyclophosphamide [122]; however plasma exchange can be added to treat patients with advanced renal disease, with expected survival rates approaching 90% [123]. There are no randomized, controlled studies of the efficacy of treatment on the ocular manifestations of EGPA. McNab [120] described a 66-year-old woman with orbital inflammation who responded rapidly and

completely to an oral prednisolone taper starting at 50 mg. A patient with anterior ischemic optic neuropathy responded to treatment with 24 mg of methylprednisolone daily however after one month, VA improved from 20/50 to 20/25 in addition to improved respiratory symptoms. Followup fundoscopy revealed subsiding papilledema and splinter hemorrhages but Goldmann perimetry showed residual central visual field defect [115]. Central retinal artery occlusion generally carries a less favorable prognosis.

Microscopic Polyangiitis

This necrotizing small vessel vasculitis typically affects the kidney causing a pauci-immune focal necrotizing crescentic glomerulonephritis, and the lungs causing pulmonary capillaritis. Its annual incidence is 3.6 cases per million people [124], with a mean age of onset over 50 years, and slightly male predominance with a male to female ratio varying from 1 to 1.2:1 [62, 125]. The histopathology of MPA is similar to GPA and EGPA in that there is a necrotizing vasculitis; however, the absence of granulomatous inflammation distinguishes MPA from GPA, as does absence of asthma and eosinophilia from EGPA [126].

In 1990 the ACR developed criteria for diagnosing the systemic vasculitides, but it did not distinguish MPA from PAN. However, the 2012 revised CHCC distinguished the two defining MPA as a necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels, often associated with necrotizing glomerulonephritis and pulmonary capillaritis; granulomatous inflammation is absent [3]. Although the presence of ANCA is not part of the diagnostic criteria, up to 65% of patients are positive for pANCA [125, 127].

Ocular findings are not part of the diagnostic criteria for MPA, and are much less common in MPA than in other AAV. Nevertheless, ocular involvement can occur in up to 24% of patients with MPA most often presenting as episcleritis or conjunctivitis [128]. A study by Rothschild and colleagues [62] in 280 patients with MPA found that 25 (9%) had ocular manifestations. Of those with ocular manifestations, the most common was conjunctivitis occurring in 7 (28%), episcleritis occurring in 5 (20%), and blurred vision occurring in 4 (16%). Other less frequent ocular manifestations included retinal vasculitis in 3 (12%), retinal exudates, optic neuropathy, sudden visual loss and oculomotor nerve palsy in 2 (8%) patients each, and scleritis, keratitis, uveitis, retinal hemorrhage in 1 patient (4%) each. Other studies report less frequent ocular manifestations of disease, so noted in a study by Guillevin and colleagues [125] in a study of 85 patients that found only 1 patient (1.2%) with ocular involvement.

Although ocular signs and symptoms are rarely presenting features of MPA, there are patients who initially present with ocular involvement. Hara and colleagues [127] described a patient who presented with hyperemia and photophobia of the eyes and found to have limbal infiltration, iritis and scleritis due to MPA. Altaie and co-workers [129] reported an 80-year-old woman with MPA who presented with painless vision loss in the right eye, and was found to have optic neuritis. Darlington and co-workers [130] described a 16-year-old woman with the initial presentation of peripheral keratitis.

Episcleritis and conjunctivitis are the commonest ocular manifestations of MPA, and it is critical to distinguish between the two since episcleritis generally implies a worse prognosis. Alrashidi and colleagues [131] demonstrated the importance of recognizing anterior scleritis

in the description of a patient with MPA with recurrent episodes of pain and redness for 7 years thought to be due to conjunctivitis. Eventually, the patient was diagnosed with episcleritis when she presented with severe ocular inflammation and vision loss, and slit lamp evaluation that demonstrated episcleritis. Thus, the authors suggest that a slit lamp evaluation should be done on patients with MPA to aid in the evaluation of the patient and determine appropriate treatment.

MPA is typically treated with corticosteroids and cyclophosphamide, and in severe cases plasmapheresis and IVIG have shown to be beneficial. If renal function is preserved, methotrexate may be added to induce remission. Maintenance therapy is recommended with azathioprine [132]. A favorable response to treatment occurs in up to 79% of patients with 5-year survival rates ranging from 65% to 80% [128, 133].

Since ocular features in MPA are rare, the effects of treatment on ocular disease have been documented through single patient reports or small series. Mihara and co-workers [134] described two patients, one of whom had hypopyon iridocyclitis in the right eye, and ophthalmoscopy with retinal cotton-wool spots in the left eye, both of which responded to oral prednisolone, topical instillation of 1% atropine sulfate and subconjunctival injections of betamethasone.

The patient with bilateral scleritis and corneal infiltration responded to the betamethasone treatment. Altaei and co-workers [129] described a patient with initial VA of hand movement only in the right eye that improved to 6/9 in the right eye after 4 months of pulsed 100 mg/day of methylprednisolone followed by 60 mg/day of oral prednisolone and 100 mg/day of azathioprine.

IMMUNE COMPLEX MEDIATED

Hypocomplementemia Urticarial Vasculitis

HUV is a rare severe systemic form of urticarial vasculitis characterized by chronic non-pruritic urticarial lesions, angioedema, ocular inflammation, arthritis or arthralgia, obstructive lung disease, and glomerulonephritis. Its exact incidence is unknown, but it is twice more common in women than in men, and its peak incidence is seen in the fifth decade of life [135]. The histopathology of HUV is characterized by an interstitial neutrophilic infiltrate of the dermis, and a necrotizing vasculitis with immunoglobulin or C3 deposits in the blood vessels on immunofluorescence [136].

The diagnostic criteria for HUV were first described by Schwartz and colleagues [137]. The major criteria are urticaria for more than 6 months duration and hypocomplementemia. The minor criteria, two of which are required for diagnosis, were dermal venulitis on biopsy, arthralgia or arthritis, uveitis or episcleritis, mild glomerulonephritis, recurrent abdominal pain, and a positive C1q precipitin test by immunodiffusion, with reduced circulating C1q levels. Exclusion criteria included significant cryoglobulinemia, elevated anti-DNA antibody titer, high titer of antinuclear antibody (ANA), hepatitis B virus (HBV) antigenemia, decreased C-esterase inhibitor levels, and inherited complement deficiency. HUV and SLE share many clinical features, thus it is important to note that COPD and uveitis are typically found in HUV, but not SLE [138].

Ocular manifestations of HUV are found in up to 60% of patients. A study by Wisnieski and colleagues [138] in 18 patients with HUV found that 11 (61%) patients had ocular manifestations, 8 (44%) had conjunctivitis, episcleritis, and/or inflammation of the uveal tract, while 3 (16.6%) had scleral inflammation and photophobia. Davis and colleagues [139] found that 21% of patients had episcleritis or uveitis, while none with normocomplementemic urticarial vasculitis had ocular manifestations. Iridocyclitis, so noted in two patients by Corwin and Baum [140] was postulated to result from immune complex deposits. Thorne and colleagues [141] described a 67-year-old-man with eye pain, redness, rash, arthralgia and malaise later noted to have bilateral anterior scleritis without evidence of keratitis or uveitis, and diagnosed with HUV. Mosawi and Hermi [142] described an 8-year-old boy with conjunctivitis who later developed episcleritis. The diagnosis of HUV is ultimately based on clinical presentation, laboratory findings, and tissue biopsy; however since ocular manifestations of disease are so pervasive, Wisnieski and co-workers [138] suggested that suspected patients should be screened for ocular inflammation with a slit lamp exam.

The treatment of HUV consists of dapsone and systemic corticosteroids, and nonsteroidal anti-inflammatory medication (NSAID) for symptomatic arthralgia and arthritis, and plasmapheresis in severe cases [135, 139]. Wisnieski and colleagues [138] studied 8 patients with C1q/HUV with conjunctivitis, episcleritis, and inflammation of the uveal tract, identifying three patients with scleral inflammation and noting that none developed chronic or irreversible ocular injury. All responded to prednisone and ophthalmic steroids. Thorne and colleagues [141] documented the response of scleritis to treatment in a 67 year-old-man with bilateral scleritis, who responded to 1 mg/kg/day of prednisone 1 mg/kg daily and 30 mg/kg/day of mycophenolate mofetil in six months. The response of iridocyclitis to cycloplegic and topical corticosteroids was shown by Corwin and Baum [140].

Cryoglobulinemic Vasculitis

Cryoglobulinemic vasculitis is a small vessel vasculitis involving the skin, joints, peripheral nervous system and kidneys. The disease is more common in Southern Europe than in Northern Europe or Northern America, and the prevalence of essential mixed cryoglobulinemia is reported to be approximately 1 case per 100,000 people [143]. The mean age of onset of CV is in the fifth to sixth decade of life, with an age at onset of 27 to 78 years, and a female to male ratio of 1.3 to 3:1 [144-146]. The histopathology of CV is characterized by a leukocytoclastic vasculitis, B-lymphocyte expansion and tissue B-cell infiltrates [146].

The 2012 Revised CHCC defined CV as a vasculitis with cryoglobulin immune deposits affecting small vessels associated with serum cryoglobulins. Skin, glomeruli, and peripheral nerves are often involved [3]. Ocular signs and symptoms are neither part of the diagnostic criteria for CV, nor are they very common.

The first ocular manifestation of CV was likely described by Wintrobe and Buell [147] in a patient suffering from multiple myeloma that had bilateral thrombosis of the central retinal veins and visual impairment. Other ocular manifestations included anterior uveitis, scleritis, and peripheral ulcerative keratitis. Ryan and colleagues [148] described a 42-year-old woman with CV who had attacks of acute arthritis and urticarial lesions with painful red eyes and photophobia, later found to have 4+ cellular infiltrates and flare on slit-lamp examination

consistent with anterior uveitis. Anterior uveitis was documented by Nicholson and Sobrin [149] in the description of a 40-year-old man with severe anterior uveitis associated with type II essential cryoglobulinemia. Scleritis and peripheral ulcerative keratitis were other manifestations so noted by Kedhar and co-workers [150] in a 49-year-old woman with necrotizing scleritis and peripheral ulcerative keratitis associated with Hepatitis C virus (HCV) infection.

Myers and colleagues [151] described in a 44-year-old man with chronic HCV-associated CV who developed sudden loss of vision in his left eye and abdominal pain. Fundoscopy revealed peripapillary cotton-wool spots and superficial retinal whitening in the macula. FFA revealed retinal vascular non-perfusion in the left macular and peripapillary region, but not in the periphery, consistent with Purtscher retinopathy. The authors proposed that the retinopathy developed as a result of complement-mediated microembolism leading to vaso-occlusion. Sauer and co-workers [152] documented a patient with Purtscher-like retinopathy associated with HCV-associated CV with complaints of visual loss. Purtscher retinopathy and hypertensive retinopathy were described by Gorevic and colleagues [153] among 22 patients with CV, 14 (63.6%) of whom had hypertension, and 8 (36.4%) with hypertensive retinopathy; the latter likely resulted from CV-mediated, renovascular hypertension.

Central serous chorioretinopathy is another ocular complication of CV. Cohen and colleagues [154] reported two patients with CV who presented with serous retinal and retinal pigment epithelial detachments resembling central serous chorioretinopathy. The authors postulated that the increased protein content of the choroid in patients with CV caused an abnormal excess of interstitial fluid to accumulate in the subretinal pigment epithelium or subretinal space resulting in retinal pigment epithelial detachment.

The treatment of CV consists of corticosteroids plus an alkylating agent which is associated with induction of remission in up to 62% of patients. Rituximab plus corticosteroids has more recently been found to be beneficial producing induction of remission in up to 64% of patients. Though the combination of rituximab and corticosteroids is the most effective treatment for CV, it is associated with infection in 42% [145] of patient so treated. In those with HCV-associated CV, treatment of HCV with pegylated IFN and ribavirin in addition to rituximab is the optimal treatment for most [155]. Nicholson and Sobrin [149] described a patient with CV who presented with severe anterior uveitis who did not respond to corticosteroids but improved with plasmapheresis and rituximab. Kedhar and co-workers [150] found that necrotizing scleritis and peripheral ulcerative keratitis due to CV improved with high-dose prednisone, pegylated interferon, ribavirin, and cyclophosphamide. Myers and colleagues [151] described successful treatment of Purtscher retinopathy with plasmapheresis, prednisone and cyclophosphamide leading to improvement in left eye VA from 1/200 to 20/200, and resolution of retinal whitening, cotton-wool spots and retinal hemorrhages observed on fundoscopy in six months.

Central serous chorioretinopathy, another ocular manifestation of CV, responded to treatment with laser photocoagulation so noted by Cohen and colleagues [154] in two patients who achieved near normal VA in both eyes.

IgA Vasculitis

This small vessel vasculitis is characterized by IgA IC deposition, in addition to nonthrombocytopenic palpable purpura, abdominal pain and arthritis. It is one of the most common vasculitides in children, with an annual incidence rate between 10-18 per 100,000 children per year [156, 157]. IgAV has a peak incidence in those under age 6, is slightly more common in males, and more frequent during winter months [156-158]. The pathology of IgAV is characterized by infiltration of small blood vessels with polymorphonuclear leukocytes, and the presence of leukocytoclasia [156].

The ACR diagnostic criteria have found that the presence of two or more of the following criteria were 89.4% diagnostically sensitive and 88.1% specific for IgAV including, age at onset before 20 years, palpable purpura, acute abdominal pain, and biopsy showing granulocytes around arterioles or venules [159].

Ocular manifestations of IgAV are rare, but case reports have documented a range of ophthalmologic complications. Recurrent episcleritis was one of the first ocular complications of IgAV in a 14-year-old girl who developed photophobia and intermittent ocular pain 5 weeks after the onset of joint symptoms [160], ophthalmologic evaluation of whom revealed episcleritis and engorgement of the episcleral vessels.

The association between anterior uveitis and IgAV was first reported by Yamabe and colleagues [161] in the description of a patient with nephritis, anterior uveitis and keratitis later. Muqit and co-workers [162] described a 42-year-old man with HSP complicated by keratitis and granulomatous anterior uveitis. Erer and co-workers [163] reported a 39-year-old man with IgAV who presented with three episodes of anterior uveitis, one of which was bilateral, and unilateral episodes of each eye. Kaur and colleagues [164] documented bilateral anterior uveitis associated with IgAV in an 11-year-old boy with a 4 year history of eye pain and photosensitivity. Uveitis in IgAV is thought to be due to circulating IC, which reach the eye and deposit in uveal tissues. IC can deposit in vascular endothelial cells, pigmented epithelial cells, and corneal endothelial cells, expressing adhesion molecules that allows leukocytes to migrate to the uveal tissue and cornea causing injury [165].

Although IgAV is not typically associated with frank bleeding, bilateral subperiosteal orbital hematomas are a recognized complication so noted by Ma'luf and colleagues [166] in a 5- year-old-boy who presented with bilateral exophthalmos and bilateral upper eyelid ecchymosis.

Wu and colleagues [167] reported a 6-year-old girl who developed sudden vision loss, and later found on fundoscopy to have a cherry red spot with severe retinal edema of the macula and peripallary area of the eyes, with disc edema and venous engorgement consistent with bilateral central retinal artery occlusion. Central retinal vein occlusion was reported in a 12-year-old boy with IgAV [168].

Other rare ocular manifestations include AION [169] and acute visual loss due to bilateral cystoid macular edema and cotton wool spots [170].

The treatment of IgAV varies with disease severity with milder cases responsive to supportive therapy and self-resolve in 6 to 16 weeks, and more severe involvement requiring systemic corticosteroids and IVIg [171]. Ocular manifestations of IgAV resolve with a combination of systemic and topical corticosteroids. A patient with episcleritis due to IgAV responded to corticosteroids, but had exacerbations of episcleritis whenever the alternate day

prednisone dose was tapered to less than 30 mg (160). Erer and co-workers [163] described a patient with anterior uveitis who had three recurrent episodes of anterior uveitis, each which resolved within days of treatment with topical corticosteroids. Kaur and colleagues [164] reported on an 11-year-old male with anterior uveitis that responded to systemic prednisolone, topical steroids and homatropine eye drops.

AION-associated IgAV responds moderately well to corticosteroid treatment as noted by Chuah and Meaney (169) in the care of a 54-year-old man with AION whose VA improved from counting fingers to 6/36 with 4 mg of daily prednisolone. Cystoid macular edema and cotton wool spots were noted to respond to 60 mg of oral prednisone with resolution of the macular edema in two days [170].

VARIABLE VESSEL VASCULITIS

Behçet Disease

This disorder is characterized by relapsing aphthous ulcers of the mouth, eye and genitalia [172]. The most widely used diagnostic criteria of BD were formulated by the International Study Group (ISG) [173] that include recurrent oral ulcerations plus any two of genital ulceration, typical defined eye lesions, typical skin lesions, or a positive pathergy. Recurrent oral ulcerations are categorized as minor aphthous, major aphthous, and herpetiform ulcerations that recurred at least three times in a 12-month period. Recurrent genital ulcerations are defined as aphthous ulceration and scarring. Eye lesions were defined as anterior uveitis, posterior uveitis or cells in the vitreous on slit lamp examination; and retinal vasculitis. Compatible skin lesions included erythema nodosum, pseudofolliculitis, papulopustular lesions, and acneiform nodules in post-adolescent patients not receiving corticosteroids. A positive pathergy test of cutaneous hypersensitivity was defined as positive when a sterile pustule developed after twenty four to forty-eight hours at the site of a needle prick to the skin [174]. Although the usual onset of BD is in the third or fourth decade of life, pediatric-onset cases have been described [175, 176]. Uluduz and colleagues [175] studied two large Istanbul BD cohorts totaling 728 patients, ascertaining and comparing pediatric-onset (26 patients) and adult adult-onset (702 patients)-neurological (NBD) that differed in male predominance and more frequent dural venous sinus thrombosis in pediatric patients compared to parenchymal neurological involvement in adults. Citirik and colleagues [176] described ocular findings in 34 pediatric patients that included panuveitis, posterior and anterior uveitis respectively in 53%, 32% and 15% of patients. Other ocular findings included cataracts in 59%, posterior synechiae in 24%, postoperative capsular opacification 24%, vitreous condensation after vitritis in 50%, optic atrophy in 30%, cystoid macular edema 15%, narrowed or occluded retinal vessels after retinal phlebitis and branched retinal occlusions in 6%, neovascularization of the disk and phthisis bulbi each in 3% of patients. Arai and colleagues [177] described the postmortem findings in a young man with BD with relapsing unilateral uveitis, sensorineural hearing loss, slight fever, and progressive CNS and autonomic nervous system involvement that included multifocal brainstem and cerebellar necrotic foci, perivascular neutrophilic inflammation, and perivasculitis.

Cortical venous sinus thrombosis (CVST) in BD most commonly presents with symptoms and signs of increased intracranial pressure with a rarity of venous infarcts. Prothrombosis when present, is presumed to commence as an endothelial disturbance. The treatment of BD-related CVST includes consideration of anticoagulation and corticosteroids alone or in association with another immunosuppressant agent.

Cogan Syndrome

Morgan and Baumgartner [178] described a 26-year-old man with recurrent pain, spasm and redness of the left eye with photophobia, excessive tearing, and marked conjunctival injection, followed by severe attack of dizziness, tinnitus, vertigo, nausea, vomiting, ringing in the ears, profuse perspiration, and deafness. A diagnosis of recurrent interstitial keratitis and explosive Menière disease was made however in retrospect this patient may have been the first reported case of CS associated with nonsyphilitic interstitial keratitis (IK). Vestibuloauditory symptoms were later described by Cogan [179]. Haynes and colleagues [180] set forth diagnostic criteria for typical CS according to the definitions established by Cogan [179] in a review of 30 patients seen at the National Eye Institute of the National Institutes of Health (NIH) by Cogan [179, 181] with symptoms of IK that developed abruptly and gradually resolved, associated with photophobia, lacrimation, and unilateral or bilateral eye pain. Such symptoms tended to recur periodically for years before becoming quiescent. Vestibuloauditory dysfunction was manifested by sudden onset of Menière-like attacks of nausea, vomiting, tinnitus, vertigo, and frequently progressive hearing loss that characteristically occurred before or after the onset of IK. However within one to six months of the onset of eye symptoms, auditory symptoms progressed to deafness over a period of one to three months, certainly no longer than two years.

Gluth [182] reviewed a cohort of CS seen at the Mayo Clinic between 1940 and 2002. The commonest symptoms at presentation were sudden hearing loss in 50%, balance disturbance in 40%, ocular irritation in 32%, photophobia in 23%, tinnitus in 13%, and blurred vision in 10%. Specifically noted inflammatory eye findings that occurred in the course of disease included interstitial keratitis in 77%, iritis or uveitis in 37%, oscillopsia in 25%, scleritis or episcleritis in 23%, and conjunctivitis in 10%.

Most patients with CS (58%) were treated with corticosteroids with an overall favorable response in both vestibuloauditory and ophthalmologic manifestations, with the remainder demonstrating only ophthalmologic (23%) or vestibuloauditory improvement (19%) alone (98). Other therapies included methotrexate, cyclophosphamide, azathioprine, entanercept, hydroxchloroquine, and IVIg therapy. Surgical cochlear implantation can lead to objective and subjective benefits with improved hearing recognition.

SINGLE ORGAN VASCULITIS

Primary CNS Vasculitis

Adult [183] and childhood isolated CNS angiitis [184], primary angiitis of the CNS [185], adult [186] and childhood PCNSV [187]; granulomatous angiitis of the brain (GAB)

(188) and granulomatous angiitis of the nervous system (GANS) [189], are equivalent terms for a prototypical primary vasculitic disorder restricted to the CNS of diverse cause and clinicopathologic expression.

The diagnosis of PACNS [185], like IACNS [183] relies upon the presence of the classic angiographic features of beading in cerebral angiographic studies or the histopathologic features of angiitis in brain and meningeal vessels in the absence of systemic vasculitis or another cause for the observed findings. Affected patients with PACNS present with headache of gradual onset accompanied by either focal neurological signs or diffuse cognitive changes, so noted respectively in those with involvement of either large named arteries or small meningeal and distal terminal cortical vessels. The clinical course can be rapidly progressive over days to weeks, or insidiously over weeks to months, with seemingly prolonged periods of stabilization.

Younger and colleagues [188] described symptoms and signs in four patients with GAB alone or in association with concomitant neurosarcoidosis, varicella zoster virus (VZV) infection, and Hodgkin lymphoma, and reviewed the clinical and laboratory findings in 74 additionally-proven cases. Mental change, headache, fever, focal weakness, and visual changes, were the commonest symptoms and signs at onset respectively in 58%, 54%, 21%, 15%, 9% at presentation, and in 78%, 54%, 21%, 42%, and 12% during the course of the illness. Visual symptoms included diplopia, amaurosis fugax, blurring of vision, and contiguous involvement of the eye in those with V1 dermatomal VZV lesions. Hemiparesis, quadriparesis, and lethargy were associated with a poor prognosis and mandated the need for combined meningeal and brain biopsy to establish the diagnosis followed by combination chemotherapy employing corticosteroids and cyclophosphamide.

Cupps and colleagues [183] noted neuro-ophthalmological involvement in two of four patients with IACNS. Patient 1 had transient hemifield visual loss accompanied by headaches before the angiographic diagnosis of IACNS with involvement of named cerebral vessels, followed several months later after commencement of combination immunosuppressant therapy by a one-week period of altered VA. Patient 3 had a unilateral fundus Roth spot, with markedly decreased VA and normal pupillary response before diagnostic cerebral angiography of IACNS showed narrowing of named cerebral vessels, followed months later after commencement of combination immunosuppressant therapy by occipital headaches, transient decreased visual acuity and a starburst image in the central visual field.

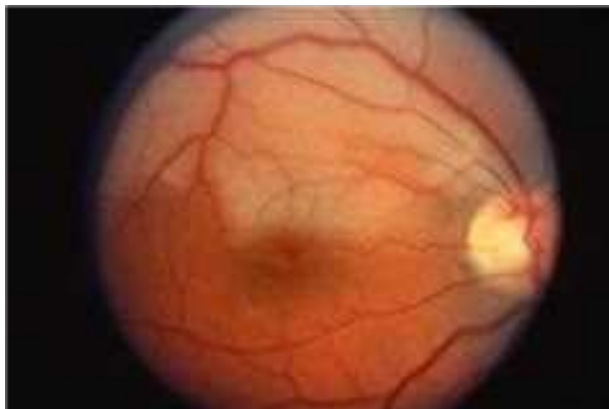


Figure 2. Branch retinal artery occlusion in a patient with isolated CNS vasculitis.

Calabrese and Mallek [185] reported eye signs in 15% of literature cases with angiographically or pathologically defined PACNS but in none of 8 Cleveland Clinic patients. Among 70 patients with angiographically-defined and 31 patients with pathologically-verified PCNSV described by Salvarani and colleagues [186], hemiparesis, unilateral numbness, blurred vision and decreased acuity were most common in those with angiographically-defined PCNSV, although persistent neurological deficit or stroke and headache were the commonest initial findings overall in 68% of patients. A granulomatous pattern of inflammation was seen most often in those with altered cognition and at an older age. Lanthier and coworkers [184], who described histologically-proven IACNS in two children, had one child (Case 2) with bilateral optic disk swelling and persistent conjugated gaze-evoked nystagmus at presentation. Among four children with angiographically-negative childhood PACNS described by Benseler and colleagues [187] one child (Patient 3) was noted to have gaze-evoked nystagmus. (Figure 2)

CONCLUSION

Ophthalmologic and neuro-ophthalmologic manifestations of primary systemic and isolated CNS vasculitis typically arise in association with ischemic vascular disease of the CNS. Although uncommon, such manifestations may be the first clue to underlying ischemic disease due to primary or secondary involvement of visual and eye movement pathways warranting further evaluation for CNS vasculitis.

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Chapter 216

THE BLOOD-BRAIN BARRIER

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ABSTRACT

There has been extraordinary research in the blood-brain barrier over the past decade. Once considered a static anatomical barrier to the traffic of molecules in and out of the central nervous system when fully developed in adults, and otherwise irrelevant to neuroscience and disease, the blood-brain barrier is now known not only to be fully functional in development, but vital in cerebrovascular angiogenesis. The cellular components and other molecular constituents of the blood-brain barrier, contained in a neurovascular unit, protect the central nervous system from injury and disease by limiting the passage of toxins, pathogens, and inflammatory effectors of the immune system. Blood-brain barrier breakdown has been recognized as an important factor in a variety of primary neurological diseases however such disturbances while common to primary and vasculitis of the central nervous system, has yet to be critically analyzed. The chapter provides a comprehensive review of the blood-brain barrier in health and disease, with special consideration to the pathogenesis of central nervous system vasculitis. This chapter reviews the history, neurodevelopment, ultrastructure, function, and clinicopathologic correlation and relevance to central nervous system vasculitis.

Keywords: blood-brain barrier, blood-nerve barrier, systemic vasculitis

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INTRODUCTION

The past decade has witnessed an expansion of knowledge in the properties possessed by the blood-brain barrier (BBB) in health and disease as summarized in several excellent recent reviews [1-5]. In essence, the neurovascular unit of the BBB is comprised of capillary vascular and neural cells, extracellular matrix components, and a variety of immune cells that mediate local immunity. The schematized and electron microscopic (EM) appearance of cerebral capillaries in the BBB shown in Figures 1 and 2, demonstrate layers of pericytes adherent to the abluminal or parenchymal surface of endothelial cells, together surrounded by a layer of basal lamina comprised of extracellular matrix protein molecules. The end feet of neighboring astrocyte processes ensheath the blood vessels. Monolayers of adjacent endothelial cells that form tight junctions (TJ) strands shown in Figure 1, connecting adjacent endothelial cells by adhesions of transmembrane occludin, claudin, and junctional associated molecules [JAM] across the intercellular space while cytoplasmic scaffolding and regulatory proteins such as zona occludens type 1 and 2 [ZO-1, ZO-2] provide linkage to the actin cytoskeleton and initiate several signaling mechanisms via protein-protein interactions. Endothelia BBB cells are also linked by adherens junctions composed of vascular endothelial (VE)-cadherin, which mediates cell-cell adhesion interactions, linking adherens junctions to the actin cytoskeleton via catenins [2, 3]. Perivascular macrophages that reside between astrocyte endfeet and the vessel wall, mast cells associated with specific regions of the CNS; resident microglia that act as antigen presenting cells (APC), and circulating leukocytes that can penetrate the intact BBB via interactions with endothelial adhesion molecules (CAM) to mediate bidirectional crosstalk between immune cells and endothelium for normal surveillance, constitute the extended neurovascular unit (NVU) [2].

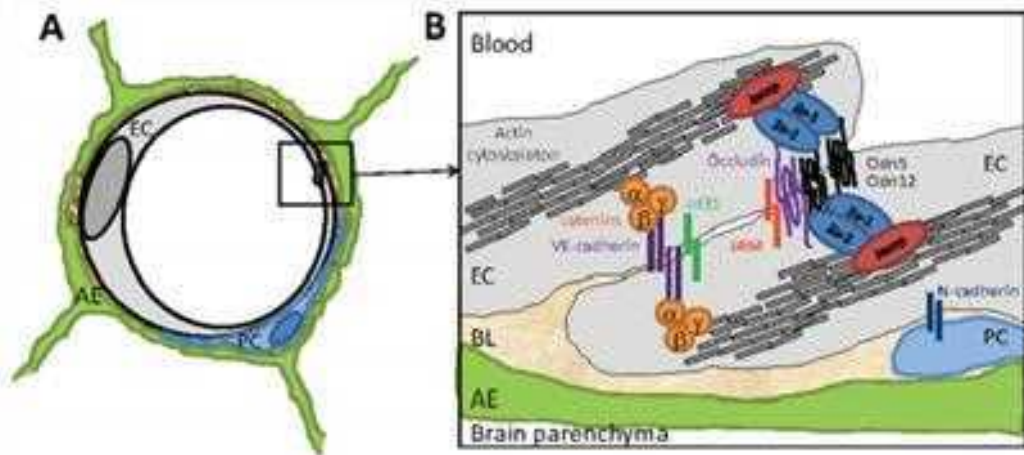


Figure 1. A. Cross-section schematic representation of a capillary in the human blood-brain barrier over an endothelial tight junction. B. The insert shows the molecular composition of tight and adherens junctions. See text for details. Reproduced from [1], with permission of the publisher.

Breakdown or disruption of the BBB accompanies a variety of inflammatory and autoimmune, neoplastic, infectious, and neurodegenerative central nervous system (CNS) disorders, notably stroke, multiple sclerosis, brain trauma, human immune virus, infection,

and Alzheimer disease. These disorders are associated with the abnormal entry of plasma components, immune molecules and cellular elements that leads to further neural dysfunction and varying degrees of irreversible neural degeneration. Although there is little known about the role of BBB breakdown in primary and secondary CNS vasculitis, future progress could lead to improved understanding of primary and secondary forms of CNS vasculitis [6] with the prospect of even improving the outcome two potentially devastating disorders, childhood and adult primary angiitis of the CNS (PACNS) [7-9]. According to Weiss and colleagues [10] further understanding of the BBB could envision the use of new therapeutic strategies that bypass it, taking advantage of the selective expression of membrane bound proteins expressed by brain endothelia cells or circulating leukocytes to target new drugs, as well as improve the effectiveness of conventional systemic immunosuppression. This chapter reviews the history, neurodevelopment, ultrastructure, function, and clinicopathologic correlation and relevance to CNS vasculitis.

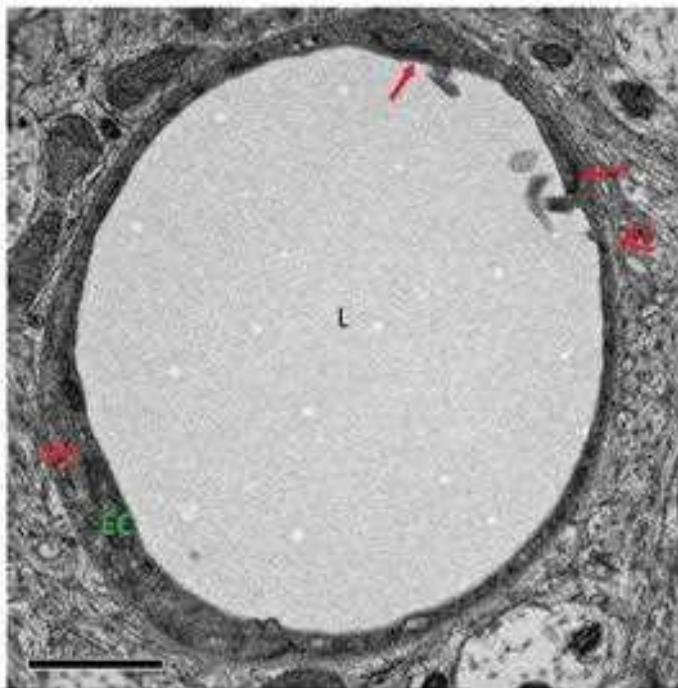


Figure 2. Electron micrograph of a capillary in the adult murine blood-brain barrier. Endothelial cells are held together by tight junctions (red arrow). Reproduced from [1], with permission of the publisher.

HISTORICAL BACKGROUND

In 1885, Ehrlich [11] provided the first suggestion of the presence of a barrier when a parenteral injection of vital dye into the bloodstream of mice penetrated practically every systemic organ except the brain turning them dark purplish-blue, leaving the brain and spinal cord pale white-yellow. Ehrlich himself thought that this difference was due to a low binding affinity. The existence of a barrier at the level of the cerebral vessels was postulated by Bield

and Kraus [12] and later by Goldman [13] and Lewandowsky [14] at the turn of the twentieth century, who jointly interpreted their experience in favor of a true BBB, later termed *Blut-Hirn-Schranke*. In 1967, Reese and Karnovsky [15] demonstrated a structural barrier to an intravenous injection of horseradish peroxidase (HRP) demonstrating exogenous peroxidase to the lumina of blood vessels and in some micropinocytotic vesicles within endothelial cells, but none beyond the vascular endothelium. The relatively scarce number of vesicles was a morphological feature of a functioning BBB. Their findings localized at a fine structural level a barrier composed of the plasma membrane and the cell body of endothelial cells and TJ between adjacent cells of the cerebral cortex. In 1969, EM studies by Brightman and Reese [16] in the mouse conclusively demonstrated endothelial and epithelial TJ that occluded the interspaces between blood and parenchyma or cerebral ventricles, constituting the ultrastructural basis for the blood-brain and blood-cerebrospinal fluid barriers. Feder [17] noted active exclusion of the small electron-dense tracer microperoxidase by intact TJ after parenteral injection supplementing the findings of Reese and Karnovsky [15]. Nagy and colleagues [18] examined fracture faces of cerebral endothelium in normal and hyperosmolar mannitol-treated rat brains to elucidate the organization of TJ in various segments of the cerebral vascular bed and the structural basis of BBB opening in hyperosmotic conditions. Their findings provided no direct evidence for the structural basis of BBB opening in hyperosmolar mannitol-treated rat brains noting extended TJ regions in capillaries and postcapillary venules. Shivers and coworkers [19] studied isolated rat brain capillaries employing freeze-fracture images of interendothelial ZO revealing complex arrays of intramembrane ridges and grooves characteristic of TJ. The ZO of these capillary endothelial cells were considered very tight.

NEURODEVELOPMENT

In contrast to the neuronal development, the vascular system undergoes blood vessel formation through the two distinct processes, vasculogenesis and angiogenesis. The former commences with endothelial differentiation from angioblasts to vascular plexuses, while the latter is associated with sprouting of new vessels from existing ones. Both vasculogenesis and angiogenesis are influenced by vascular endothelial growth factor (VEGF), a major attractive molecule for extending blood vessels especially endothelial tip cells [20], as well as by other molecules, blood flow and contact with surrounding tissues. Found at the growing end of extending vessels, the shaft of extending endothelial tip cells is composed of an endothelial cell chain made of stalk cells similar to the axon growth cone and its associated axonal shaft. *In vivo* imaging employing green fluorescent protein (GFP) depicts the advancing endothelial tip cell navigating the environment and sprouting from existing vasculature [21]

Several experimental observations have suggested the importance of the neurodevelopment of the BBB [5]. First, there are shared molecular and cellular mechanisms in both neurogenesis and angiogenesis [22, 23]. Four major families of axon guidance ligand-receptor pairs include Slit/Robo, semaphoring/plexin/neuropilin, Netrin/Unc5/DCC, and Ephrin/Eph, together mediating complex cellular navigational programs within axons as both chemoattractants and repellents, and directing the angiogenic tip cells toward its final destination.

Neuropilin-1 is necessary for endothelial tip cell guidance in the developing central nervous system [24]. Moreover, axonal terminal arborization parallels vessel sprouting. Similar to hypoxic tissue that secretes VEGF via hypoxia-inducible factor (HIF), a transcription factor that promotes cell survival through the downstream activation of numerous genes including *VEGF* [25]. Axonal terminals devoid of synaptic input secrete nerve growth factor (NGF), the expression of which is down-regulated when innervation occurs.

Second, there is co-regulation of these two systems in developing embryonic and adult brains [22, 26; 27]. Stubbs and colleagues [26] found that blood vessels provided a supporting niche in regions of adult neurogenesis. The investigators [26] employed Tbr2-GFP transgenic mice that served as a correlate for the expression of the intermediate progenitor cell (IPC) T-box transcription factor Tbr2, to examine the proximity of dividing cells in the subventricular (SVZ) and ventricular zone (VZ) of the shaking rat Kawasaki and reeler mutant mouse in relation to blood vessels throughout neurogenesis. Their findings which included the extension of neuritis toward and along labeled blood vessels supported the notion of vascular-neuronal interactions in development. Javaherian and coworkers [27], who likewise studied IPC in the SVZ of embryonic Swiss Webster mouse cortices, employed confocal microscopy to image the vast network of capillaries in the SV and SVZ. The authors [27] noted that Tbr2 cells divided near vascular branch-points suggesting endothelial tip cells contributed to the neurogenic niche for IPC, with ectopic overexpression of VEGF-A in a pattern that followed that of blood vessel development. These findings indicated that the developing cortical vasculature provided a microenvironment within the SVZ in which IPC accumulated and divided during neurogenesis.

Third, a structural and functional BBB complete with TJ appear as soon as cerebral vessels penetrate the CNS parenchyma [28, 29]. Johansson and colleagues [28] explained that the widely held view that the BBB was immature during development stemmed from teleological interpretations and experimental observations of high cerebrospinal fluid (CSF) protein levels in fetal CSF and the apparent passive passage of biomarkers during development. Instead, the blood-CSF barrier, like the BBB is functionally and morphologically mature from very early in development. The authors maintain that inconsistent terminology used in the literature such as leaky, immature, and developing, used to describe the barrier gives a connotation of TJ that are more permeable than their adult counterparts without evidence to support this concept. Mølgård and Saunders [30] noted well-formed complex TJ across cerebral endothelial cells in human embryos and fetuses by freeze fracture and thin section EM by 8 weeks of age, commensurate with the differentiation of brain capillaries. Efflux transporters are likewise expressed in cerebral endothelial and choroid plexus epithelial cells early in the fetal and postnatal rats [31]. Ballabh and colleagues [32] studied the expression and quantification of endothelial TJ molecules including claudin-5, occluding, and JAM by immunohistochemistry and Western blot analysis in blood vessels of germinal matrix, cortex, and white matter of fetuses and premature infants gestational age 16 to 40 weeks. The authors [32] noted no significant decrease in the expression of the endothelial TJ molecules claudin-5, occludin, and JAM-1 as a function of gestational age in germinal matrix compared with cortex and white matter suggesting that they were unlikely to be responsible for germinal matrix fragility and vulnerability to hemorrhage in premature infants. These findings are consistent with the concept that TJ molecules develop and perhaps mature early during human gestation. Ballabh and colleagues [33] observed that a paucity of

TJ or pericytes coupled with incomplete coverage of blood vessels by astrocyte end-feet, could instead account for the observed fragility of blood vessels in the germinal matrix of premature infants. Braun and colleagues [34] found that pericytes coverage and density that was less in the germinal matrix vasculature than in the cortex or white matter in human fetuses, premature infants, and premature rabbit pups. Although VEGF suppression significantly enhanced pericyte coverage in germinal matrix, it remained less than in other brain regions.

NEUROBIOLOGY AND CELLULAR INTERACTIONS

Endothelial Cell Interactions

The existence of the endothelial cell was first surmised by William Harvey, and first observed by Marcello Malpighi in blood capillaries using compound microscopy in the nineteenth century, and later by EM in the mid-twentieth century, revealing the presence of plasmalemmal vesicles or caveolae. The ability to culture EC later permitted even more detailed investigation of their activation and function *in vivo*. Derived from mesoderm via the differentiation of hemangioblasts and angioblasts, there are a few protein/mRNA marker candidates including platelet/endothelial cell adhesion molecule (PECAM)-1 in monocytes and VE-cadherin in fetal stem cells. Endothelial cells of the BBB not only provide a physical barrier between the systemic circulation and the brain, but assure the selective inward passage of ions, nutrients, and neuropeptides via specialized transport mechanisms. Sodium, potassium, chloride, hydrogen, bicarbonate and calcium ions are transported across the BBB via transporters located mainly along the luminal surface of endothelial cells including, the sodium and potassium adenosine triphosphate (ATP)- dependent transport pump, the sodium-potassium-chloride cotransporter (NKCC), sodium-proton, chloride-bicarbonate, and sodium calcium exchanges that assure optimal levels of brain electrolyte levels and intracellular pH. The transport of essential nutrients is assured by members of the soluble carriers (SLC) superfamily, located variably along the luminal and abluminal membrane including, glucose transporter-1 (GLUT1), monocarboxylic acid-1 (MCT-1); excitatory, organic acid (OAT), cation (OAC), amine and choline transporters (CTL1), respectively to transport lactate and ketone bodies as alternative energy neuronal sources, and sodium-independent or dependent removal of glutamate, aspartate, glutamine, histidine, and asparagine from the interstitial compartment of the brain. Other specific carrier-mediated transporters mediate the passage of transferrin, low-density lipoproteins, leptin, immunoglobulin G (IgG), insulin, and growth factors via receptor-mediated transcytosis via binding of the protein to specific receptors on the endothelial cell surface following by endocytosis of the ligand-receptor complex with passage across the cytoplasm and exocytosis at the opposite side of the cell [35] and via the formation of caveolae or vesicle formation for the transport of macromolecules [36]. Transmigration of cellular elements across endothelial cells of the BBB during inflammation including leukocytes, neoplastic cells, and pathogenic viruses, bacteria and yeasts, investigated in experimental animal models utilizing HRP, highlighted the role of caveolae as mini-transporters of the CNS [36]. Unique systems of modified caveolae that fuse together forming transendothelial cell channels and later vesiculo-canalicular or vesiculo-tubular

structures (VTS) or vesiculo-vacuolar organelles (VVO), appear to be an important gateway to the CNS in damaged endothelial cell populations [36]. Transportation of potentially toxic endogenous or xenobiotic lipid-soluble nonpolar molecules from the brain to the blood are accomplished by transporters located along the luminal membrane such as the ATP binding cassette (ABC) transporter P-glycoprotein 1 (P-gp or Pgp) (multidrug resistance protein 1 [MDR1] or ATP-binding cassette sub-family B member 1 [ABCB1]) respectively important in the distribution of CNS tumor drug therapy [37] and the active efflux of the anti-human immunodeficiency virus type 1 (HIV1) nucleoside drug abacavir at the BBB [38-40]; and breast-cancer resistance protein (BCRP) and multidrug resistance related protein (MRP) 1, 2, 4 and 5 efflux transporter pumps that serve as defense mechanisms and determinate bioavailability and concentration of many CNS drugs important in the treatment of CNS cancers [41] such as the novel tyrosine kinase inhibitor dasatinib [42], and the efflux transportation of the protease inhibitor lopinavir that contributes to its poor oral bioavailability in the treatment of HIV1 [43]. The neuroinflammation and progression of damage associated with focal cerebral ischemia appears to be modulated by upregulation of other MRP protein molecules that activate Toll-like receptor (TLR) signaling contributing to neuroinflammation and progression of ischemic cerebral damage [44].

Transendothelial migration of circulating leukocytes involves a multistep process. Leukocyte adhesion molecules (LAM) expressed on the surface of EC initiate binding of leukocytes as a beginning step in the in their entry in brain tissue which later includes rolling adhesion to EC, firm adhesion, and transmigration. Although less well understood, the molecular mechanism is believed to involve endothelial CAM including CD99, platelet ECAM (PECAM-1)/CD31, vascular CAM-1 (VCAM-1) (important in firm adhesion); junctional adhesion molecule-1; expression of leukocyte adhesion molecules E- and P-selectin (rolling adhesion); cytokine responsiveness so noted *in situ* and in cell culture [45, 46] and expression of the integrins alpha4- and beta-2. Inflamed capillary endothelia support transmigration of different subsets of leukocytes. There are two routes for leukocytes to pass through endothelial cell, the so called paracellular route, or through the endothelial cell itself or transcellular route. The BBB with its abundance of TJ complexes relies primarily on the transcellular route as it does for solute and fluid transport. Neutrophil recruitment is partially dependent ICAM-1, and expresses L-selectin and lymphocyte function-associated antigen (LFA)-1 but not chemokine C motif receptor 7 (CCR7), which may explain why granulocytes roll but do not arrest for transmigrate in high endothelial venules (HEV).

Pericyte Interactions

Brain endothelial cells are exposed to a myriad of pericyte interactions [47] in the regulation of brain angiogenesis, endothelial cell TJ formation, as well as the differentiation, microvascular vasodynamic capacity, structural stability, and neuroimmunologic network operations of the intact BBB [48]. Rouget [49] first ascribed capillary contractility to pericytes but Zimmermann [50] named the cell and described its morphologic aspects. The presence of smooth muscle cells in association with pericytes and the absence of a smooth muscle layer from capillaries and postcapillary venues influenced early views ascribing contractile properties to narrow capillaries hence regulate microvascular flow even though a

number of subsequent experimental studies failed to substantiate it [51, 52]. Smooth muscle actin was conclusively demonstrated in pericytes by immunocytochemistry employing smooth muscle α -actin isoform specific antibodies and immunogold labelling in conjunction with EM noting that smooth muscle α -actin expression in capillaries was limited exclusively to pericytes and not present in endothelial cells [53]. Since the histochemical localization of smooth muscle α -actin is demonstrated in precapillaries and not in midcapillaries, it has been suggested that smooth muscle α -actin containing capillaries are involved in contractility and the control of capillary blood flow in the BBB [54].

Unlike other perivascular cells, they lie within the microvessel basal lamina and contribute to its formation. Typical CNS pericytes are flattened or elongated, stellate-shaped solitary cell with multiple cytoplasmic processes encircling the capillary endothelium and contacting a large abluminal vessel area. Brain pericytes are characterized by granular deposits present in lysosomes that strongly react with acid phosphatase, a finding that led to consideration of a phagocytic role [55]. They rapidly phagocytose an intravenous injection of HRP which can be employed as a pericytes histochemical stain. The number of granular lysosomes in brain pericytes increases with disruption of the BBB. Several other markers have been employed in the identification of pericytes including, smooth muscle α -actin (SMA), desmin, polydendrocytes (NG2 cells), platelet-derived growth factor receptor (PDGFR)- β , aminopeptidase A and N, regulator of G-protein signaling 5 (RGS5) and the promoter trap transgene *XlacZ4* [56].

An active role of pericytes in the BBB was inferred from the localization of γ -glutamyl transpeptidase (GGTP) in brain capillary endothelial cells and pericytes, both *in vivo* and *in vitro* [57]. This heterodimeric glycoprotein distributed on the external surface of the cell catalyzes the transfer of γ -glutamyl from glutathione to accept peptides and functionally appears to be concerned with transport of large neutral amino acids across the BBB. Detectable amounts of GGTP are found in other regions of the brain with an intact BBB but not in those that lack one such as the median eminence. Abnormal platelet derived growth factor (PDGF)-B and PDGF- β signaling plays a critical role in the recruitment of pericytes to newly formed vessels, and when deficient, as in knockout of *pdgfb* and *pdbfrb*, leads to perinatal death due to vascular dysfunction with associated vascular leakage and hemorrhage.

Pericyte-endothelial cell signaling factors have been identified. Sphingosine-1-phosphate (SIP) signaling triggers cytoskeletal, adhesive, and junctional changes, affecting cell migration, proliferation, and survival [58]. Angiopoietin-Tie2 signaling in the vascular wall involved in reciprocal communication between endothelial cell and pericytes, such as may be seen in *ang1*- or *tie2*-null mice deficient in Ang1, leads to defective angiogenesis and poorly organized BM, with reduced coverage and detachment of pericytes. Conversely, overexpression of Ang1 leads to expanded and stabilized, leakage resistant microvasculature [59, 60].

The importance of CNS pericytes has been underscored by their proposed role in neuroimmunological networks associated with BBB function. First, CNS pericytes may be actively involved in the regulation of leukocyte transmigration, antigen presentation, and T-cell activation. They constitutively express low levels of VCAM-1 and ICAM-1, which have costimulatory activity in main histocompatibility cell (MHC)-class II dependent antigen presentation; leukocytes cluster on pericytes in culture [48] suggesting a role in inflammation. Smooth muscle pericytes present antigen *in vivo* and differentially activate Th1 and Th2

CD4-T cells. Moreover, CNS pericytes produce a number of immunoregulatory cytokines including interleukin (IL) 1 β , IL-6, and granulocyte-macrophage colony stimulatory factor (GM-CSF) [61]. Transforming growth factor (TGF)- β produced in an active form in pericytes/endothelial cocultures, may function as an endogenous immunoregulator at the BBB [62]. It is therefore of interest that TGF- β 1 inhibits cytokine-induced CNS endothelial cell activation in isolated rat CNS microvessels [63]. To further emphasize the importance of pericyte interactions in association with endothelial cells, there are no known genetic human diseases due to pericyte deficiency.

Astrocyte Interactions

The intimate relationship of astrocytes and blood vessels was appreciated by Cajal [64] and Golgi [65] in the late nineteenth century. Since then, ultrastructural studies have shown that astrocytic endfeet in the perivascular astroglial sheath leads to a complete covering of brain microvessels [66]. Signaling at the gliovascular interface is facilitated by astrocyte-specific proteins and channels in astrocyte endfeet including, aquaporin-4, connexin 43, purinergic receptors, and potassium channels [67]. Moreover, ultrastructural studies have demonstrated that processes of vasoactive neurons for the regulation of cerebrovascular tone, in particular those expressing noradrenaline, synapse onto astrocytes rather than directly onto blood vessels [68]. Altogether, these findings support the observation that astrocytes one of the more numerous cells in the CNS, are important determinants of the intact BBB and crucial as well for ionic homeostasis, neurotransmitter uptake, synapse formation, and neurodevelopment. Zhang and Barres [69] have reviewed the differences in astrocyte morphology, developmental origin, gene expression profile, physiological properties, function and response to injury and disease. Two essential roles of astrocytes, in neurovascular coupling and the regulation of lymphocyte trafficking across the BBB have been extensively studied.

All signaling molecules targeted to the cerebral vasculature must first act on, or pass through astrocytes in order to reach smooth muscle cells in the vessel wall. It is now recognized that neurotransmitter-mediated signaling has a key role in regulating cerebral blood flow, and that much of this control is mediated by astrocytes [70]. Moreover, cerebral blood flow may be controlled by capillaries as well as by arterioles. The glial and neuronal control of cerebral blood flow has been studied in brain slices [71]. Koehler and colleagues [72] demonstrated that electrical field stimulations in brain slices led to an increase in intracellular calcium in astrocyte cell bodies, which when transmitted to perivascular endfeet, was followed by a decrease in vascular smooth muscle calcium oscillations and arteriolar dilation.

The increase in astrocyte calcium after neuronal activation was in part mediated by activation of metabotropic glutamate receptors. Calcium signaling *in vitro* was influenced by adenosine acting on A2B receptors and by epoxyeicosatrienoic acids (EET) shown to be synthesized in astrocytes. Moreover, prostaglandins, EET, arachidonic acid, and potassium ions are candidate mediators of communication between astrocyte endfeet and vascular smooth muscle. Astrocytes appear to be capable of transmitting signals to pial arterioles on the brain surface to ensure adequate blood flow to feeding arterioles. Therefore these cells

play an important role in the coupling of dynamic changes in cerebral blood flow in association with neuronal activity.

Koehler and colleagues [72] provided insight into the morphological aspects of neurovascular coupling at the capillary level of the BBB. At least one astrocyte endfoot process contacts a blood vessel and those abutting capillaries and larger vessels express connexin-43 and purinergic P2Y receptors, which together permit Ca^{2+} increases to be transmitted 60 μm or more along the abluminal side of the vessel wall. Astrocytic cells are therefore in a unique position for sensing neuronal activity, integrating that information, and communicating with blood vessels in brain parenchyma. While neurons do not directly innervate intraparenchymal vascular smooth muscle, subpopulations of GABAergic interneurons come into close contact with astrocyte foot processes and elicit vasodilation. Such neurons might modulate vascular function through stimulation of nitric oxide (NO) synthase (NOS) activity, release of vasoactive peptides, or an astrocyte signaling mechanism.

Hudson and coworkers [73] studied trafficking of peripheral blood mononuclear cells (PBMC) across feline brain endothelial cells (FBEC) in cell culture system after the addition of combinations of different configurations of astrocytes and microglia in a model of feline immunodeficiency virus.

The addition of astrocytes to FBEC significantly increased the adherence of PBMC which was suppressed by the addition of microglia, whereas the latter alone had no effect on PBMC adherence. Whereas all PBMC showed some level of trafficking across FBEC, monocytes and B cells were significantly increased if astrocytes were present. The exposure of astrocytes notably increased the percentage of trafficking CD8 T-cells from 24% to 64%, while microglia led to a significant reversal in the preferential trafficking of CD8 cells in the presence of astrocytes. Astrocytes are capable of secreting various cytokines and chemokines in the upregulation of adhesion molecules and T-cell ligands in intact endothelial cells such as ICAM, VCAM, E-selectin, and PECAM. Human cocultured human endothelial cells and astrocytes increase the expression of ICAM-1 due to inflammatory activation by hypoxia *in vitro* [74].

Other studies have demonstrated that astrocytes are a source of IL-6, TNF- α , and MCP-1 which contribute to the CNS inflammatory response [75]. Trafficking of PBMC along the endothelial cell of the BBB is a complex mechanism that involves major subsets of immune cells and relies heavily on astrocyte, microglia and endothelial cell interactions, moreover, astrocytes appear to be an active factor in the recruitment of immune cells, while microglia appear to curtail this activity.

IMPLICATIONS FOR CEREBRAL VASCULITIS

There is an extensive literature of BBB biology in health and in widely differing neurological disorders including stroke [76], epilepsy [77], multiple sclerosis [78], Alzheimer disease [79], motor neuron disease [80], Parkinson disease [81], trauma [82], glioblastoma [83], HIV encephalitis [84] and systemic lupus erythematosus (SLE) [85]. Between 40 and 70% of patients with SLE have involvement of the central nervous system (CNS) [86], yet unlike systemic and primary CNS vasculitides, the role of the BBB in CNS lupus has been the subject of intense study employing animal models and human clinical data.

The BBB is crucial because it maintains the brain internal milieu constant, allowing optimal neuronal function. Loss of BBB integrity leads to influx of inflammatory cells, and molecules such as autoantibodies causing brain injury. Earlier studies using the well-established MRL/*lpr* mouse model that reflects the events that occur in human CNS lupus, revealed loss of BBB integrity with worsening disease [87, 88] due to chronic activation of the complement cascade with the generation of the anaphylatoxins, C3a and C5a, and aggravated C5a/C5aR signaling. In cell culture, C5a causes neuronal cells to become apoptotic, and binds to two receptors, the G-coupled, C5aR1 and the alternate receptor, C5aR2 [89]. C5a/C5aR1 signaling mediates a number of biological processes, including chemotaxis and degranulation of mast cells, basophils, neutrophils and eosinophils. It increases vascular permeability, generation of reactive oxygen species, and enhances production of cytokines from monocytes and macrophages. Whether C5a/C5aR signaling is protective or neurotoxic depends upon the setting with increases in circulating C5a leading to poor outcomes in CNS lupus [89].

Hopkins and colleagues [90] measured levels of complement anaphylatoxin split products, C3a and C5a, in the circulation of patients with SLE who were followed serially. Means complement levels were significantly higher during periods of lupus flare compared to those during a stable period, with the highest levels seen in patients with CNS involvement. Pathologic specimens from two cases who died during an acute lupus flare revealed neutrophils occluding the cerebral and systemic intestinal vessels.

C5a also contributes to cellular apoptosis in lupus [91] wherein treatment with the C5aRant, inhibiting C5a/C5aR signaling results in significant and substantial decreases in brain pathology in MRL/*lpr* mice, leaving upstream potentially protective complement activation events intact. There was evidence for a relationship between complement activation, inflammation and neuronal viability in lupus brain tissue. C5aR1 is present predominantly on blood myeloid cells, but is also constitutively expressed on several brain cell types including endothelial cells, which contribute to BBB integrity. Such studies shows the possible neuroprotective role for C5aR antagonists in MRL/*lpr* mice, and indicates a potential future avenues of research for systemic and primary CNS vasculitides.

CONCLUSION

There has been extraordinary research in the blood-brain barrier over the past decade. Once considered a static anatomical barrier to the traffic of molecules in and out of the CNS, the BBB of children and adults is now recognized to be fully functional and vital to both cerebrovascular angiogenesis and normal homeostatic maintenance. The cellular components and other molecular constituents of the blood-brain barrier, contained in the NVU protect the CNS from injury and disease by limiting the passage of toxins, pathogens, and inflammatory effectors of the immune system. The implications of BBB disruption in cerebral vasculitis have yet to be appreciated, however comparisons to CNS lupus may lead to a better understanding of the neural mechanisms involved in disease pathogenesis and BBB integrity, and efficacious neuroprotective treatment strategies.

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Chapter 217

NEUROIMAGING OF CNS VASCULITIS

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INTRODUCTION

Vasculitis is a term used to describe a diverse spectrum of diseases characterized by inflammation of the blood vessels that may progress to ischemic injury of the central nervous system (CNS) resulting in a myriad of focal and generalized neurologic symptoms. The injury is usually secondary to mural changes resulting in vessel stenosis or occlusion. Endothelial inflammation promotes intraluminal coagulation and thrombosis [1]. Perivascular inflammatory changes and edema contribute to the pathologic picture. Arterial and venous components may be involved separately or together and dural sinuses may be affected. Generalized inflammatory processes may produce a secondary encephalitis or myelitis. Although the CNS vasculitides can have a wide range of clinical, radiographic and pathologic manifestations, they also resemble more common non-inflammatory and occlusive vascular and connective tissue diseases. The radiological aspects of CNS vasculitis have evolved in the past decade [2]. No one single imaging modality is sufficient or preeminent. A combination of studies is typically required for a confident diagnosis of CNS vasculitis.

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OVERVIEW AND CLASSIFICATION

With an estimated worldwide incidence of 20 per million for eosinophilic granulomatosis with polyangiitis (EGPA) also known as Churg-Strauss syndrome, 10 per million for granulomatosis with polyangiitis (GPA), 2.6 per million for Takayasu arteritis (TAK), and 0.9 per million for polyarteritis nodosa (PAN) [3, 4], and only a fraction of patients presenting with CNS involvement, it is important for clinicians to be familiar with clinical and neuroradiologic presentation of vasculitis. This is especially important in young and middle aged adults where the prevalence of atherosclerotic disease is low [5, 6].

The historical aspects of the classification of the vasculitides are reviewed elsewhere [7, 8]. Early classification schemes were based upon pathological parameters such as large, medium, or small vessels size; location of the vessel such as the aortic arch, pulmonary, abdominal, or skin; caliber of vessels including muscular artery, arteriole, venule, vein or combination thereof; histopathological characteristic of the inflammatory cell infiltrate whether polymorphonuclear, mononuclear, eosinophilic, giant cell or epithelioid cell types; location of the vascular inflammation such as intimal, media, elastic lamina, adventitial, or panarteritis; and the presence of immune complexes.

Cupps and Fauci [9] summarized the advances of the preceding decades recognizing several clinicopathologic categories for the vasculitides. The PAN group of systemic necrotizing vasculitis comprised classic PAN and the small vessel vasculitis EGPA. Hypersensitivity vasculitis comprised serum sickness, Henoch-Schönlein purpura, now termed IgA vasculitis (IgAV), and cryoglobulinemic vasculitis. GPA was separated from PAN and EGPA. The giant cell arteritis (GCA) category comprised temporal arteritis, now termed GCA, and TAK, recognized more for the unique location of vasculitic involvement and inflammatory giant cell composition.

To illustrate the clinical importance placed on the angiographic manifestations of the PAN group of primary systemic vasculitides, Citron and colleagues [10] described multi-organ arteritis including the CNS in a highly publicized report of fourteen Los Angeles multidrug abusers. The drug closest to a common denominator was intravenous use of methamphetamine by all but two patients and exclusively by one. Acute vessel lesions of fibrinoid necrosis of the media and intima with infiltration by polymorphonuclear cells, eosinophils, lymphocytes and histiocytes, followed by vascular elastic and vascular smooth muscle destruction resulting in lesions considered typical for PAN. However substantiation of necrotizing arteritis was present in only four of the fourteen patients. Citron and Peters [11] responded to the criticism from Baden [12] that he had not observed a causal relation between drug abuse and necrotizing arteritis at the Office of Chief Medical Examiner of New York City for the past one-half century among thousands of autopsied drug abusers, with the countering opinion that evidence of aneurysms, noted in thirteen of the fourteen patients, was ample proof of arteritis.

The contribution of angiography to CNS vasculitis commenced with the identification of angiographic beading and a sausage-like appearance of cerebral vessels at sites of presumed arteritis, first described in GCA by Hinck and coworkers [13] in 1964. Cupps and Fauci [14] established the utility of cerebral angiography in the diagnosis of histologically-proven isolated angiitis of the CNS or primary angiitis of the CNS (PACNS) in 1983. As giant cells

and epithelioid cells, usually found at postmortem examination in such patients were an inconsistent finding in a meningeal and brain biopsy and therefore considered unnecessary for antemortem diagnosis, Moore and colleagues [15] considered angiography necessary for diagnosis noting that normal cerebral angiograms had shown postmortem evidence of CNS vasculitis affecting only small vessels. This prevailing opinion was shared by Calabrese and Mallek [16] who proposed criteria for the diagnosis of primary angiitis of the central nervous system (PACNS), and Hajj-Ali and Calabrese who later separated PACNS from the reversible cerebral vasoconstrictive syndrome (RCVS), characterized instead by transient nonvasculitic narrowing of intracranial vessels [17].

By 1990, Hunder and colleagues [18] on behalf of the American College of Rheumatology (ACR) noted that the goal in classification was to identify sets of sensitive criteria that recognized a high proportion of patients with a particular form of vasculitis, while specifically excluding a high proportion of those with other diseases. Although highly specific and sensitive classification criteria might prove useful in the depiction of patients for epidemiologic studies and therapeutic trials, such criteria might not necessarily include the full spectrum of manifestations of a particular vasculitic disease, which was instead the role of formal diagnostic criteria. Lie [19] noted that while a definitive diagnosis of vasculitis almost invariably required histological documentation, the interpretation of a diagnostic tissue sample was subject to variables as diverse as the pathologist's experience, tissue selection, sample size, chronological age of the disease, and any prior treatment at the time of the biopsy. The angiographic appearance of aneurysms or occlusions of visceral arteries not due to arteriosclerosis, fibromuscular dysplasia or other non-inflammatory causes, were useful in the classification of PAN [20] with a sensitivity of 73.5% and specificity of 89.2%. The angiographic features of narrowing, aneurysm, or occlusion of the aorta or its primary branches, were employed in the classification of TAK [21] with sensitivities and specificities of 85.5% and 81.2%, 20.3% and 95.9%, and 51.6% and 86.1%, respectively. In the same 1990 volume of the journal, *Arthritis and Rheumatism*, the ACR Subcommittee on Classification of Vasculitis noted no diagnostic features of angiography useful in the classification criteria of EGPA [22], GPA [23], hypersensitivity vasculitis [24], IgAV [25], or GCA [26].

Jennette and colleagues [27, 28] held two Chapel Hill Consensus Conferences (CHCC) beginning in 1994 [27] and again in 2012 [28], establishing the nomenclature or nosology of systemic vasculitides. However, different from the ACR Subcommittee on Classification of Vasculitis [18], Jennette and colleagues [27, 28] incorporated prevailing knowledge about etiology, pathogenesis, pathology, demographics, and clinical manifestations, and employed a model of the predominant caliber of involved vessel that delineated the three major categories of systemic vasculitis including large size vessel vasculitis (LVV), medium size vessel vasculitis (MVV), and small sized vessel vasculitis (SVV) types, adding further distinctions as to the structural and functional characteristics of particular vascular beds, as well as the known biochemical and functional properties that rendered them susceptible to vasculitic injury. With about twenty-six recognized vasculitides in the 2012 revised CHCC, many of which demonstrate overlap in affected involved arteries, coupled with advances in the neuroradiologic techniques for discerning CNS involvement, there has been heightened interest in imaging the cerebral vasculature.

Küker [29] differentiated the entities of extracranial LVV, and intracranial MVV and SVV noting that vasculitic involvement of the internal carotid (ICA), common carotid (CCA),

M1 and A1 segments of the middle (MCA) and anterior cerebral arteries (ACA), intracranial vertebral and basilar arteries, and P1 segment of the posterior cerebral artery (PCA), generally regarded as intracranial LVV, would instead be considered systemic MVV by 2012 Revised CHCC nomenclature [28].

Moreover, vasculitic involvement along arterial vessels distal to the MCA bifurcation as well as communicating vessels such as the anterior (AComm) and posterior communicating (PComm) arteries, were still considered MVV systemically although intracranial. They may not be demonstrable along with intracranial LVV by magnetic resonance imaging (MRI), magnetic resonance angiography (MRA) or computed tomographic angiography (CTA), and may require conventional angiography (CA) for luminal irregularity to be visualized.

The smallest muscular arteries and arterioles within the brain parenchyma, as well as, the capillaries and proximal venules, all considered intracranial SVV by their lumen size corresponding to a caliber of 200 to 500 microns or less [30, 31], and considered beneath the resolution of invasive and non-invasive neuroimaging, require tissue biopsy to diagnose vasculitic involvement. The radiologic findings of CNS vasculitis may be similar to nonvasculitic inflammatory vasculopathies such as systemic lupus erythematosus (SLE), and other non-inflammatory vasculopathies such as atherosclerosis and spontaneous dissection in association with connective tissue disease and infection.

Examples of the neuroradiographic imaging of systemic LVV due to TAK and GCA (Figures 1-3), MVV in association with PAN (Figure 4), SVV related to EGPA (Figure 5), SLE (Figure 6), Behçet disease (BD) (Figure 7), PACNS (Figures 8-11), human immunodeficiency virus (HIV) (Figure 12), and RCVS (Figure 13) are all shown at the end of the chapter.

NEURORADIOLOGIC APPROACH TO CNS VASCULITIS

Küker [29] described three steps in the diagnostic evaluation of CNS vasculitis beginning with the demonstration of brain lesions by T₂- and diffusion and perfusion-weighted MRI, followed by the delineation of underlying vascular pathology by 1.5 Tesla (T) MRA to study the entire course of the carotid and vertebral arteries, as well as the circle of Willis. Time-of-flight (TOF) MRA sequences permits detection of more subtle stenoses and improves spatial resolution, as well as mural thickness in basal brain arteries with MRA source images; moreover, MRI may discern mural enhancement. Conventional angiography with digital subtraction (DSA) is employed to evaluate medium-sized and small-sized brain vessels, the status of cerebral hemodynamics, and assess brain perfusion.

Gomes [32] divided available neuroimaging studies into three groups including those that investigated the brain parenchyma, vessel lumen and vessel wall. Parenchymal findings, while least specific, were necessary to detect the presence of disease as well as to follow progression and remission status. Vessel lumen abnormalities, while highly suggestive for systemic vasculitis when present, were considered nonspecific and insensitive in the diagnosis of intracranial SVV.

Parenchymal Imaging

The MRI findings of CNS vasculitis have been previously described [33-36], the commonest of which are T₂/fluid attenuation inversion recovery (FLAIR) hyperintense lesions secondary to ischemia distributed throughout subcortical and deep white matter, the deep grey nuclei and the cortices. The MCA territory was the commonest involved in CNS vasculitis [37, 38]. Diffusion weighted imaging (DWI) helps to distinguish acute, subacute and chronic ischemia and is thus mandatory. Lesions are frequently bilateral and of differing ages. Involvement of multiple vascular territories or lesions within a frankly non-vascular territorial distribution may be clues to the diagnosis of CNS vasculitis although they can also be seen in association with thrombophilic and cardiogenic multiple embolic process that produce ischemia. Ischemic lesions were present in up to one-half of patients with PACNS [35]. Nonspecific white matter changes, which may be the only finding in symptomatic patients [39, 40], would be unlikely findings of atherosclerotic hypertensive disease in young patients, yet sometimes difficult to distinguish from CNS demyelinating disease.

Intraparenchymal and subarachnoid hemorrhages may be presenting or associated radiographic features of CNS vasculitis [41] although they occur less commonly than ischemic lesions so noted in up to 40% of patients with PACNS as compared to hemorrhage that occurred in only 4% to 12% of patients [42-44]. There is uncertainty regarding the significance of microscopic hemorrhage in patients with CNS vasculitis. T₂-weighted gradient-echo MRI, which depicts chronic blood or hemosiderin products as regions with marked signal intensity loss (susceptibility effect), was useful in demonstrating multiple silent petechial hemorrhages scattered throughout both cerebral hemispheres located in cortical-subcortical regions in a patient with stereotypic tingling spells in the right hand followed by acute mutism due to histological-proven PACNS. Brain CT showed a small hematoma in the left parietal lobe and 1.5 T T₁-weighted, turbo spin-echo T₂-weighted, and fluid-attenuated inversion recovery brain MRI demonstrated acute hemorrhage in the left parietal lobe as well as subacute hemorrhage in the right frontal lobe [42]. However, T₂-weighted gradient-echo images showed multiple small hemorrhages scattered throughout the cerebral hemispheres located in the cortical-subcortical regions sparing the basal ganglia, thalamus, and brain stem. Conversely, neither large nor small silent cortical hemorrhages were found among 25 patients with intracranial vasculitis employing T₂*-weighted MRI [45].

Leptomeningeal enhancement by MRI was noted in up to 9% of patients with PACNS [34, 44] often in association with cognitive disturbances, normal MRA and catheter angiography (CA), granulomatous angiitis histopathology and small vessel involvement [44].

Delayed perfusion and reduced cerebral blood volume may be seen on brain CT and MRI in patients with cerebral vasculitis [34, 45, 46]. Magnetic resonance spectroscopy (MRS) reveals elevated glutamate and glutamine levels and reduced N-acetyl aspartate content in cerebral vasculitis [46, 47], and absence of a choline peak [46-47].

High Resolution Magnetic Resonance Imaging

High resolution MRI (hrMRI) employing gadolinium enhanced fat-saturation T₁ spin echo techniques provides useful information of possible inflammatory changes in those with

suspected systemic LVV. More recently the use of vessel wall imaging has increased due to the multiple applications in vivo such as the differentiation between atherosclerosis and vasculitis, the visualization of intracranial dissection and to determine which aneurysm has ruptured in patients with acute subarachnoid hemorrhage and multiple aneurysms. The arterial wall enhancement in patients with vasculitis is probably related to contrast leakage from the lumen into the arterial wall given the increased permeability of the endothelium; it is also possible that the presence of dilated neovessels in the wall is responsible for the increased contrast enhancement. It is important to keep in mind that there may be a discordance between the MRI findings and the clinical vasculitis activity [48]. In 26 patients with TAK and 16 healthy subjects so studied [49], contrast-enhanced T₁-weighted spin echo MRI using small fields of view and thin slices showed enhancement of thickened aortic wall compared with myocardium suggested active TAK. The degree of disease activity was concordant with laboratory measures of disease activity in 88.5% of patients, including erythrocyte sedimentation rates and C-reactive protein. The measured signal intensity of the aortic wall relative to that of myocardium during the early phase of contrast-enhanced MRI, which was significantly correlated with serological markers of inflammation, provided a useful assessment of disease activity in TAK. Notably T₂-weighted signal intensity changes were less sensitive than enhanced images. In sixty-four consecutive patients with suspected GCA, Bley and colleagues [50a] assessed mural thickness, lumen diameter, and mural contrast-enhancement scores by T₁-weighted spin-echo images with sub-millimeter in-plane spatial resolution. Their findings demonstrated that evaluation of the mural inflammatory MRI signs for diagnosing vasculitis resulted in a sensitivity of 80.6% and a specificity of 97%, in comparison to histologic results alone which demonstrated a sensitivity of 77.8% and specificity of 100%. Some positive MRI results were associated with biopsy-negative histopathology for GCA presumably due to sampling errors with skip lesions predominating in the tissue biopsy. Among GCA patients who received treatment with corticosteroids <10 days, sensitivity of hrMRI ranged from 81% to 85% while others receiving corticosteroids >10 days demonstrated a sensitivity of 33%. Notwithstanding, hrMRI still should provide sensitive and specific information when neuroimaging is performed within days following the initiation of immunosuppressive treatment. Additionally, in GCA, Geiger et al. demonstrated how mural contrast enhancement of the ophthalmic arteries can be demonstrated using a 3 T MRI examination and they showed that it is a common finding in patients with GCA with suspicious ophthalmic arteries involvement.

High-resolution MRI findings of intracranial vasculitis include concentric and asymmetric vessel wall thickening, an eccentric or narrowed vessel lumen and vessel wall enhancement. Enhancement may be limited to the vessel wall or extend to adjacent leptomeninges. Kuker and colleagues [50b] reported that 25 of 27 (92.5%) children and adults patients with a diagnosis of cerebral vasculitis affecting large brain vessels secondary to various etiologies demonstrated mural thickening, 23 of whom had abnormal mural enhancement confirmed in more than one plane of imaging. The authors contended that for intracranial large vessel disease, direct vascular wall inflammatory wall changes provided greater specificity than indirect luminal imaging findings and perhaps exceeded that of tissue biopsy. Obusez and coworkers ([50c] suggested that the degree and persistence of vessel wall enhancement helped to differentiate PACNS and RCVS in a cohort of 26 patients with respectively confirmed diagnoses. Whereas mural enhancement was less prominent in RCVS and resolved in nearly all patients restudied at mean followup of 3.5 months, those with

PACNS demonstrated an increased degree of vessel wall enhancement with persisted over a mean followup of 13.5 months.

An additional role of wall imaging MRI is to help selecting the appropriate target for biopsy in cases of suspected vasculitis [48].

Indirect Vessel Imaging Techniques

Indirect imaging techniques that characterize changes in the vessel lumen leading to ischemia, infarction and hemorrhage in cerebral vasculitis can be obtained by MRA, CTA and CA, however these do not provide direct evidence of the associated underlying mural and perivascular inflammation. Catheter angiography provides up to 0.2 mm of spatial resolution and 0.5 to 0.25 seconds of temporal resolution in a typical study, exceeding MRA and CTA [30]. The spatial resolution of multi-detector CTA, which is dependent on detector row thickness, is approximately 0.4 to 0.75 mm. CA provides detailed information regarding hemodynamics that is generally absent from both CTA and MRA. Dynamic 320-section CTA provides limited hemodynamic information with a temporal resolution of 1 second and a spatial resolution of 0.5mm [51]. Indices for MRA spatial resolution are even less precise than these other techniques.

Magnetic Resonance Angiography

This non-invasive non-ionizing indirect vessel wall imaging study does not require intravenous contrast administration for the assessment of intracranial stenoses and vascular occlusions in suspected CNS vasculitis. MRA may overestimate vascular stenosis secondary to diminished signal intensity from vessel tortuosity and slow flow. The more subtle finding of intracranial vessel irregularity is more difficult to assess due to lower spatial resolution. Among nine arteries from 14 young patients with clinical and radiological suspicion of cerebral vasculitis, the sensitivity for detecting a stenosis by three-dimension (3D) TOF MRA or DSA varied from 62% to 79% for MRA, and 76% to 94% for DSA. The specificity for detecting a stenosis varied from 83% to 87% for MRA, and 83% to 97% for DSA. Using the criterion of >2 stenoses in two or more separate vascular distributions as a true positive criterion for cerebral vasculitis, the false positive rate for MRA and DSA were comparable [52]. When more than two stenoses were noted on MRA, DSA is unlikely to add further diagnostic precision in a given patient with suspected cerebral vasculitis, but yet might be useful when MRA was normal or disclosed <3 stenoses [52].

Computed Tomography Angiography

Indirect vessel wall imaging employing CTA has been used in TAK, GCA, PAN and CNS vasculitis. The efficacy of CTA in TAK, a chronic idiopathic LVV that primarily affects large vessels such as the aorta and its major branches, as well as the pulmonary and coronary arteries, is well established [53]. Non-specific inflammation of involved vessels leads to concentric wall thickening, fibrosis and thrombus formation. These produce the characteristic neuroradiologic findings of focal stenosis, occlusion, dilatation and luminal irregularity with a characteristic distribution and severity of involvement. The relative sensitivity and specificity of CTA for TAK was respectively 93% to 95% and 98% to 100% [54]. The salient CTA

features of TAK include mural thickening, luminal changes, collateral vessels, and other findings usually with respect to the pulmonary and coronary arteries. In the early stages of TAK mural inflammatory changes may precede luminal contour changes, an important advantage of CTA as compared with DSA.

CTA is useful in patients with GCA in whom LVV occurs in 25% of patients [55], especially in those with confirmed biopsy pathology to screen for the presence of stenosis, dissection, and aneurysms, as well as to assess the extent of arterial involvement and to monitor vascular lesions for signs of progression [56]. Intramural leaky microvessels which give rise to delayed enhancement of the arterial wall are consistent with, but not specific for inflammatory vasculopathy. Moreover, generally irreversible wall thickening and increased intra-wall blood pooling despite immunosuppressant treatment should not be employed to assess the inflammatory burden or disease activity [56]. Aneurysm formation along gastrointestinal, renal arteries and other systemic medium sized vessels so noted on CTA, particularly in the absence of aortic involvement, are useful neuroradiologic signs of PAN in the differential diagnosis of GCA [57, 58].

An entity considered by some to be part of the GCA spectrum, and often diagnosed with a CTA of the neck, is carotidynia, a clinical entity described first in 1927, which manifests with tenderness and pain at the neck at the level of the carotid bifurcation. The two clinical signs of carotidynia are not specific, and other causes of neck pain can have the same clinical presentation. This entity is thought to be caused by perivascular inflammation as proved by the common coexistence of increase of the erythrocyte sedimentation rate or C-reactive protein as well as ipsilateral lymph node enlargement and pharyngeal or laryngeal inflammation, as well as biologic findings, with a mild increase of the erythrocyte sedimentation rate or C-reactive protein. The findings on CT are presence of a perivascular infiltration, defined as soft amorphous tissue replacing the fat surrounding the carotid artery.

A relationship with GCA has not been demonstrated but in a series of 47 patients, 8 patients had an autoimmune disease such as rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylarthritis, Graves disease, Sjögren syndrome, or Hashimoto thyroiditis, often presenting during clinical relapse of the primary autoimmune disease [59]. A new name for the condition was recently proposed, Transient Perivascular Inflammation of the Carotid artery (TIPIC) syndrome [59].

CTA also provides useful assessment of stenotic, dilated and focally occluded vessels of the circle of Willis in the 2nd and 3rd order branches of the ACA, MCA and PCA involved by CNS vasculitis. However the resolution of luminal irregularity is less well appreciated on CTA compared with CA, since the former modality which is less dynamic, and requires the inference of collateral flow and angio-architecture from opacified vessels. The radiation dose penalty, which is slightly greater than a routine head CT, makes CTA suitable as an initial screening modality for CNS vasculitis in adults, but less desirable in children and young adults. CT readily identifies abnormal mural thickening as defined by thickness >1 mm in 93% of patients with clinical evidence of TAK along the ascending aorta, aortic arch, and descending thoracic aorta [53]. Up to 73% of patients with TAK so studied demonstrated changes within the cervicocerebral vessels, most commonly the arch and descending thoracic aorta, brachiocephalic artery and common carotid artery where wall thickening varied from 1 mm to 10 mm. Once considered the gold standard for detecting abnormal vasculature, CA may be falsely negative in the early stages of TAK [47, 53]. This is an important consideration as the disease is most effectively treated with immunosuppressive therapy during the earliest phase of the illness; a time when CA may be non-diagnostic. CTA is an

excellent option in these circumstances as it provides not only information regarding luminal abnormalities, including stenosis, occlusion, aneurysmal dilatation and contour irregularities similar to CA, but direct diagnostic findings including wall thickening, calcification and abnormal enhancement [47, 53]. While nonspecific to the cerebrovascular circulation, Yamada and colleagues [54] demonstrated a sensitivity and specificity of 95% and 100% respectively, for CTA in the diagnosis of TAK, with claims of positive correlation of vessel wall changes to the histopathologic findings [47]. Heterogeneous mural enhancement and an inner concentric low attenuation ring that enhanced at delayed imaging likewise demonstrated a positive correlation with the acute phase of histopathologic findings of vascularization and intimal swelling in the tunica media.

Catheter Angiography

Although CA has been the gold standard for diagnosis of cerebral vasculitis, it occupies a less important role compared to MRA and CTA in the initial evaluation of suspected patients. The classical angiographic features of CNS vasculitis are multifocal luminal narrowing, vascular contour irregularity and vascular dilatations with the appearance of a string of beads often along multiple vessels and in differing vascular territories, although ectasia and normal luminal diameter may also occur. The affected vessel may demonstrate a smooth or irregular luminal contour and vascular stenosis which is classically a discrete short segment or elongated. The size of the vessels affected and the distribution of lesions within each of the vessels varies with the vasculitic etiology and may be a clue to the proximate cause. Extracranial large vessel narrowing and undulation of long segments with variable luminal angiographic involvement occurs in GCA, while variable intracranial skull based and medium cortical vessel involvement occurs in anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV), SLE and PACNS. There is no predilection for vessel branch points in PACNS in contrast to atherosclerosis and hypertensive disease [59]. Luminal narrowing along vascular regions of laminar flow disruption and high shear stress in the ICA bulb, petro-cavernous junction and cavernous segments suggests atherosclerosis. However, multifocal stenosis and luminal irregularity within the same vessel segment with intervening normal vessel contours, and isolated stenosis within separate vascular territories and otherwise normal vessel contours favors vasculitis. Multiple emboli generally present with more obstructive than stenotic lesions, and tends not to occur as discretely along multiple vascular territories or in tandem along the same vessel in contrast to CNS vasculitis. Angiographic features that favor medium vessel vasculitic involvement due to systemic vasculitis and autoimmune disease in contrast to PACNS include abrupt vascular truncation, occlusion and microaneurysm formation [60]. The collateral circulation should be investigated and quantified by CT and MR perfusion imaging in patients with severe luminal narrowing and vascular occlusion of medium and large vessels as should abnormal cerebral hemodynamics typified by slow anterograde flow, diminished distal luminal size, and prolonged circulation time. Vascular dissection which rarely occurs in intracranial vasculitis is much more common in the extracranial vasculature in GCA.

The sensitivity of CA for PACNS is reportedly 40% to 100% [34, 35, 38, 40, 59-63] and the specificity no higher than 37% for CA in the diagnosis of PACNS [64]; however they may vary depending upon the particular clinical, radiographic and histopathologic definitions employed. Vasculitic small vessel involvement is typically beneath the resolution of CA. Children with so-called angiography negative, biopsy positive, small vessel (SV)-childhood

PACNS (cPACNS) [65] who present with negative angiography and a positive MRI, are generally considered to be candidates for cerebral and leptomeningeal biopsy to confirm the presence of vasculitis.

There is a poor correlation between neuroradiologic findings on MRI and CA in PACNS [38, 60]. Whereas two-thirds of lesions detected by MRI showed a CA lesional correlate, only 44% of those detected by CA were conversely identified by MRI. Furthermore, the correlation of 41 territories involved by MRI subsequently studied by CA was 15%, whereas among 50 vascular territories involved by CA, a correlate was found in 34% of MRI studies.

The risk of transient neurological injury is 10% and permanent morbidity occurs in about 1% of patients undergoing CA for the evaluation of CNS vasculitis [66]. Intravenous corticosteroids administered prior to CA may ameliorate the risk of injury and reduce complications.

NUCLEAR MEDICINE IMAGING MODALITIES

Positron Emission Tomography

Nuclear Medicine evaluation of neurovasculitis remains promising but problematic. Conceptually the ability to monitor metabolic activity within the vessel wall should be a good indicator of inflammatory activity. ¹⁸fluorodeoxyglucose positron emission tomography (FDG-PET) has been the best studied radionuclide for this indication, particularly in systemic LVV. One meta-analysis [67] demonstrated a wide variability of diagnostic sensitivity for TAK ranging from 28% to 100% while the range of specificity was 50% to 100%. Fused PET and CT images provide superior anatomic localization and improved sensitivity and specificity of 91% and 89% for TAK. A greater diagnostic sensitivity of 80% and specificity of 89% in those studied by FDG-PET were noted for GCA [68]. Nonetheless, the specificity of FDG-PET is degraded by the presence of atherosclerosis as active inflammatory plaques may produce false positive findings [69]. The utility of FDG-PET for monitoring disease activity in these patients may be problematic. Some patients with TAK deemed inactive by clinical criteria may in fact demonstrate biopsy-proven active inflammation [70]. Studies indicate that FDG-PET is a sensitive and helpful diagnostic study for identifying patients with subclinical active disease, with 83% of biopsy-proven GCA patients demonstrating positive or concordant lesions by FDG-PET imaging [71]. The sensitivity and specificity of FDG-PET in the identification of active vasculitic disease compared with clinical signs and laboratory criteria led to respective rates of 100% and 89% [72].

Single Photon Emission Computed Tomography

Single photon emission computed tomography (SPECT) employs multiplanar nuclear medicine imaging for the investigation of regional CNS perfusion abnormalities. It provides direct information about the pathophysiology and cerebral metabolism in cerebral vasculitides at the level of capillary endothelium in the blood-brain barrier (BBB) microcirculation beyond the resolution of MRA, CTA, and CA [73, 74].

There are claims of the utility of brain SPECT imaging in the clinical diagnosis and management of cerebral vasculitis associated with SLE [75, 76], Kawasaki disease [77], IgAV [78], neurological BD [79], GPA [80], and brain irradiation [81, 82]. Apart from the direct impact of vascular narrowing and occlusion resulting from necrotizing arteritis and vascular infiltration, other explanations for an abnormal brain SPECT include circulating immune complexes on the BBB [83], and neurotoxic effects of antibodies and brain antigenic targets [81], glial cell interactions [82], and pathogenic hypersensitivity responses to brain antigens released during vascular-mediated tissue necrosis [82].

The results of brain SPECT imaging were described in one patient with histologically-verified cerebral vasculitis [84]. This 71-year-old man with later-proven granulomatous angiitis of the brain underwent Tc-99m hexamethylpropyleneamine oxime (HMPAO) brain SPECT three weeks after onset of CNS disease. There was irregular radiotracer uptake throughout both cerebral hemispheres with scattered multiple areas of hypoperfusion, further demonstrated in surface volumetric images. Postmortem examination showed fibrinoid necrosis, inflammatory cells, mainly lymphocytes, histiocytes and a few multinucleated giant cells involving medium-to-small meningeal and parenchymal vessels with intramural vascular deposits of amyloid, without systemic vasculitis. Although there was no specific mention of the correlation of the SPECT findings with anticipated BBB involvement, the authors [88] attributed the observed cortical hypoperfusion to focal narrowing and occlusion of small- and medium-sized cerebral arteries.

Color Doppler Ultrasonography

Color Doppler ultrasonography (CDU) and color duplex imaging provide direct imaging and evaluation of superficial arteries and their vessel walls. They have been most extensively studied in systemic LVV such as GCA and TAK. This non-invasive methodology which lacks exposure to ionizing radiation can be easily administered and repeated to monitor disease activity and response to treatment. It provides a high resolution imaging of the walls of deep-seated vessels as compared with MRI, detecting wall thickness and edema the latter of which produces a hypoechoic signal on CDU as a halo sign. In a meta-analysis of 998 patients with 17 studies, the sensitivity of the halo sign for biopsy-proven GCA was only 75%, but specificity was 83%. Concentric homogeneous mural thickening, stenosis and occlusion of the aorta and brachiocephalic branches are typical CDU features of GCA and TAK [69, 85, 86], which may be differentiated from atherosclerotic disease by the absence of plaque formation, concentric long segment involvement and location. Ultrasonography revealed subtle mural changes characterized by a homogenous, circumferential mid-echoic wall thickening within the subclavian and carotid arteries in the early stages of TAK preceding abnormalities detected by CA [87], with overall greater wall thickness of the CCA and ICA in the vasculitic vessels compared to controls. The CCA intima to medial thickness ratio was increased in patients with TAK compared with normal control [88] yielding respective sensitivity and specificity rates of 82% and 70%.

The wall diameters of common, frontal and parietal division of the superficial temporal artery were significantly greater in patients with GCA than in symptomatic patients without the disease as well as asymptomatic age-matched controls [89]. A hypoechoic halo

surrounding a patent vessel lumen was found in 73% of biopsy proven vasculitis patients but not in symptomatic patients without GCA and asymptomatic controls. The histopathologic finding of mural cellular infiltration did not correlate with a hypoechoic halo albeit attributed to edema. The halo disappeared at a mean of 16 days following effective treatment. Similar findings are present in the occipital arteries [90] although the sensitivity is less when compared with the superficial temporal arteries. The halo examination is a useful exam for symptomatic patients presenting with nuchal pain, occipital headache or occipital scalp tenderness, especially when occipital artery involvement may be the only imaging manifestation of the disease.

CONCLUSION

The neuroimaging evaluation of vasculitis may seem complex and nonspecific, particularly for PACNS and the primary systemic autoimmune vasculitides. When all imaging modalities including those that provide parenchymal, luminal and mural evaluation are brought to bear on a given patient with suspected vasculitis, the entire constellation of findings typically brings clarity to the situation. The largest single series of PACNS [35] demonstrated that 77% of CT, 97% of MRI, 59% of MRA and 90% of CA studies were ultimately positive in comparison to 62% of positive brain biopsies. While each individual modality may be nonspecific, combining CNS parenchymal and peripheral vascular radiological studies with serological and histopathologic studies in clinically suspected patients, should assure the accurate diagnosis of systemic and nervous system vasculitis in virtually all true cases.

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Chapter 218

ADULT PRIMARY ANGIITIS OF THE CENTRAL NERVOUS SYSTEM AND RELATED SYNDROMES

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ABSTRACT

Primary angiitis of the central nervous system is one of the most complex and serious forms of central nervous system vasculitis. Adding to the challenge of diagnosis and recognition in the absence of predictive non-invasive laboratory tests, research into this disorder is limited by the scarcity of human pathological material and absence of an animal model. Nonetheless, there have been significant advances in the recognition of the clinical heterogeneity of the disorder and the differentiation from those that may mimic it. This chapter reviews the epidemiological, clinicopathologic, diagnostic laboratory and therapeutic aspects of primary angiitis of the central nervous system.

INTRODUCTION

Primary angiitis of the central nervous system (PACNS) is a vasculitic disorder confined to the brain, spinal cord, and its coverings. It is differentiated from secondary forms of CNS vasculitis most often due to concomitant or undying infection, connective tissue disease, or primary systemic vasculitis, and other disorders that may mimic it. Adult [1] and childhood PACNS (cPACNS) [2], primary CNS vasculitis (PCNSV) [3], granulomatous angiitis of the brain (GAB) [4], CNS (GACNS) or nervous system (GANS) [5], and isolated angiitis of the CNS (IACNS) [6], are roughly equivalent terms for a prototypical primary vasculitic disorder restricted to the CNS of diverse cause and clinicopathologic expression.

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The past decade has witnessed renewed interest in PACNS since the first description of PACNS by Calabrese and Mallek [7] of eight patients from the Cleveland Clinic Foundation patients, two of which included children age 10 and 12 years. Selection criteria for the definite diagnosis of PACNS [7] included a history of clinical findings of an acquired neurological deficit that remained unexplained after a thorough initial basic evaluation, and demonstration of classic angiographic or histopathologic features of CNS angiitis without evidence of systemic vasculitis or another disorder to explain the observed laboratory findings. These criteria were expanded by Benseler and colleagues [8] to include children age 18 years or less with neurological or psychiatric involvement, emphasizing their unique neuropsychiatric and cognitive presentations. At least three reasons account for the renewed interest in PACNS. First, the recognition that cPACNS fit into the larger designation of inflammatory brain disease (IBD) [8, 9]; moreover, PACNS was the most frequently diagnosed IBD at the Hospital for Sick Children in Toronto between 1990 and 2012. Second, the inclusion of PACNS as a prototypical single organ vasculitis (SOV) in the 2012 Revised Chapel Hill Consensus Conference [10] so defined as vasculitic involvement of arteries or veins of a single organ without features to indicate the limited expression of a systemic vasculitis. Third, the formation of the French COVAC' Cohort, a collaboration of the French Vasculitis Study Group and French NeuroVascular and Internal Medicine Societies [11] of antemortem diagnosed PACNS cases available for prospective analysis.

This chapter reviews the epidemiological, clinicopathologic, diagnostic laboratory and therapeutic aspects of adult PACNS. This topic has been recently reviewed by the present authors [12].

BACKGROUND

Primary CNS vasculitis was first described by Harbitz in 1922 [13] in two patients, one with worsening headaches, mental change, and ataxia culminating in stupor, spastic paraparesis, coma and death in 2 years; and a second patient with hallucinations and confusion progressing to gait difficulty, stupor, coma and death in nine months. Granulomatous vasculitis of the meninges comprised of lymphocytes, multinucleated giant cells and epithelioid cells with vessel necrosis and extension into the brain along involved veins and arteries of varying caliber. Over the ensuing quarter century, additional patients were reported under the rubric of allergic angiitis and granulomatosis [14], giant cell arteritis [15] and even sarcoidosis [16]. Cravioto and Fegin [17] delineated the clinicopathologic syndrome of non-infectious granulomatous angiitis of the CNS, and for two more decades, rare affected patients were identified in life. The identification of angiographic beading of cerebral vessels at sites of presumed arteritis was first noted by Hinck and coworkers [18] in cases of giant cell arteritis (GCA), and later by Cupps and Fauci in IACNS [6]. In the same year, 1988, that Calabrese and Mallek [7] proposed unifying criteria for the antemortem diagnosis of PACNS, Younger and colleagues [4] described clinicopathologic heterogeneity of postmortem proven cases.

Calabrese and colleagues [19] and later Singhal [20] separated PACNS from the most common mimickers of PACNS, the angiographically-defined variants of reversible cerebral angiopathy including benign angiopathy of the CNS. By 2007, these reversible syndromes

were combined into a separate nosology termed the reversible cerebral vasoconstriction syndromes (RCVS) [21], the diagnosis of which was clinically suggested by sudden, severe thunderclap-like headache with or without associated neurological deficits, and reversible angiographic findings not due to true vasculitis. In the same year, Salvarani and colleagues [3] reported a large cohort of more than 100 patients with primary CNS vasculitis (PCNSV) from a single center based upon the criteria of Calabrese and Mallek for PACNS [7], delineating clinicopathological subsets of heterogeneous disease. The importance of the accurate definition of disease employing the criteria of Calabrese and Mallek [7] was apparent in two forms of cPACNS, one with a predilection for small meningeal and penetrating cerebral vessels and unobvious cerebral angiographic features [9, 22], and another that affected medium-to-large named cerebral vessels in which angiographic features were readily apparent [8, 22, 23].

CLINICAL FEATURES

PACNS

PACNS affects patients of all ages with a peak at about 50 years of age and a more frequent occurrence among men than women. A retrospective analysis of 101 cases [3] revealed an average annual incidence of 2.4 cases per 1,000,000 million person-years. Although underdiagnosed in the setting of an evaluation for dementia, CNS vasculitis was found to be one of the common misdiagnoses of patients with presumed sporadic Jakob-Creutzfeldt disease [24]. The clinical signs and symptoms of PACNS are non-specific reflecting the diffuse and often patchy nature of the pathological process with a clinical course that varies from hyperacute to chronic and insidious. The most common presenting symptoms are headache followed by progressive focal neurologic deficits. The headache may vary in description, intensity and pattern, but is most often chronic and insidious. Thunderclap headache virtually never occurs in true PACNS and its presence should lead to a suspicion of RCVS [21]. Other symptoms including cognitive impairment, stroke and transient ischemic attacks, occurred in 30% to 50% of patients [3, 25]. Strokes are frequently multiple and vary in age and anatomic distribution, affecting both grey and white matter. Cranial nerve palsies occur rarely as may myelopathy, seizures, and ataxia. Constitutional symptoms and signs such as weight loss and specific organ-related disease are atypical in PACNS and when present suggests a systemic inflammatory process. PACNS should be strongly considered when there are multiple areas of cerebral ischemia affecting different vascular territories in association with an inflammatory cerebrospinal fluid (CSF) profile; and subacute or chronic headache with cognitive impairment or chronic aseptic meningitis, especially after exclusion of infectious and neoplastic disorders.

GACNS

With less than a handful of such patients seen at our center per year, the epidemiology of the disease is poorly understood, but appears to be a male-predominant disorder that occurs at

virtually any age with a median of 50 years [25, 26]. Four patients with GACNS [4] were defined by the presence of granulomatous giant cell and epithelioid cell infiltration in the walls of arteries of various calibers from named cerebral vessels to small arteries and veins at postmortem examination. Whereas the typical patient with PACNS might present with headache of gradual onset accompanied by focal signs and symptoms, or rapidly progressive neurological deficits evolving over days, weeks, or months with seemingly prolonged periods of stabilization, those with GACNS present with headache, mental change, and elevated CSF protein content with or without pleocytosis. Headache was noted at onset in all four patients of one series of GACNS [4] and in 57% of literature patients, as well as, in the course of the disease in 78% of patients overall. Neuroimaging employing magnetic resonance imaging (MRI) typically shows multiple bilateral ischemic foci. The combination of a normal MRI and normal CSF examination carries a high negative predictive value for the diagnosis of GACNS whereas hemiparesis, quadriparesis, progressive lethargy and impending coma were associated with a poor prognosis and mandated the need for combined meningeal and brain biopsy to establish the diagnosis with certainty.

Salvarani and colleagues [3] diagnosed primary PCNSV in 31 patients by histopathology and 70 patients by angiography, in whom 18 had a granulomatous inflammatory pattern, 8 a lymphocytic pattern, and 5 an acute necrotizing pattern. Headache was the most common symptoms noted overall in 63% of patients, followed by abnormal cognition, hemiparesis and persistent neurological deficit. A granulomatous pattern of inflammation was seen most often in those with altered cognition and at an older age.

The diagnosis of GACNS is generally established by pathologic examination of the brain and leptomeninges that shows granulomatous giant cell and epithelioid cell vasculitis of the walls of arteries of various calibers from named cerebral vessels to small arteries and veins. Examination of antemortem leptomeningeal and brain tissue is vital to the exclusion of infectious, malignant, and other etiologies that may lead to a similar neuropathology. Although false-negative biopsy can occur in 25% to 50% of cases [27], the yield is enhanced when a radiographically abnormal area is targeted, and the specimen includes leptomeningeal tissue in addition to the brain parenchyma. The size of the vessels affected in GACNS is beyond the spatial resolution of cerebral angiography, which is typically normal in these patients.

Younger and colleagues [4] noted one patient each with non-Hodgkin lymphoma, sarcoidosis, Varicella-zoster virus (VZV) infection, and no associated disorder in their four cases. In a subsequent review of the cumulative literature up to 1997, the same authors [5] reported a new case of GACNS and described the clinicopathologic features of 136 published cases, 51 of which had concomitant lymphoproliferative diseases, VZV infection, amyloidosis, sarcoidosis, systemic lupus erythematosus, GCA, and human immunodeficiency virus type 1(HIV1) without the acquired immunodeficiency syndrome (AIDS). Whether such cases are equivalent to GACNS occurring *de novo* is unknown, but this analysis remains the basis of much of the clinical appreciation for this relatively rare disorder.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of PACNS and hence GACNS (Table 1) comprises primary and secondary arteriopathies that mimic the clinical and angiographic presentation of

PACNS. One category includes primary systemic vasculitis notably polyarteritis nodosa, anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, Behçet disease, Cogan syndrome; and diverse connective tissue disorders such as systemic lupus erythematosus, Sjogren syndrome, and lymphomatoid granulomatosis, that can mimic PACNS, as may viral, bacterial, fungal and *Rickettsia* infections.

Malignant disorders such as primary CNS lymphoma, malignant angioimmuno-proliferative, carcinomatous and gliomatous brain tumors; and coagulopathies resulting from thrombotic thrombocytopenic purpura, subacute bacterial endocarditis, cardiac myxoma and embolism, can lead to confusion with PACNS, as may atherosclerotic diabetic, dyslipidemic and hypertensive cerebral arteriopathy, moyamoya disease, intracranial dissection, and fibromuscular dysplasia. Genetically inherited disorders including Susac syndrome, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and the autosomal recessive variant CARASIL, retinal vasculopathy with cerebral leukoencephalopathy (RVCL), may also have a clinical presentation similar to PACNS.

Table 1. Differential diagnosis of PACNS

Primary Systemic Disorders
<i>Vasculitis</i> : PAN, MPA, GPA, EGPA, BD, CS
<i>Connective Tissue Disease</i> : SLE, Sjogren syndrome, sarcoidosis, lymphomatoid granulomatosis
Infection
Viral, bacterial, fungal, <i>Rickettsia</i>
Malignancy
Angioimmunoproliferative disorders, carcinomatous meningitis, infiltrating glioma, malignant angioendotheliomatosis, PCNSL
Arterial Vasospasm
Primary: RCVS
Secondary: Pheochromocytoma, aneurysmal subarachnoid hemorrhage
Hypercoagulation
Thrombotic thrombocytopenic purpura, embolism, subacute bacterial endocarditis, cardiac myxoma, paradoxical emboli; APL
Other Cerebral Arteriopathies
Moyamoya disease, cerebrovascular atherosclerosis, arterial dissection, fibromuscular dysplasia
Demyelination
Demyelinating disease
Radiation
Radiation vasculopathy
Genetically Inherited
RVCL, Susac syndrome, NF, MELAS, CADASIL, CARASIL

Abbreviations: PAN, Polyarteritis nodosa; MPA, Microscopic polyangiitis; GPA, Granulomatosis with polyangiitis; EGPA, Eosinophilic granulomatosis with polyangiitis; BD, Behçet disease; CS, Cogan syndrome; SLE, Systemic lupus erythematosus; PCNSL, Primary CNS lymphoma; RCVS, Reversible cerebral vasoconstriction syndrome; APL, Antiphospholipid syndrome; RVCL, retinal vasculopathy with cerebral leukodystrophy; Susac syndrome, Encephalopathy, branch retinal artery occlusions and sensorineural hearing loss; NF, neurofibromatosis; APMPE, Acute posterior placoid pigment epitheliopathy and cerebral vasculitis; MELAS, Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes; CADASIL, Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CARASIL, Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy.

Table 2. Essential elements for RCVS

1. Thunderclap headache with or without other neurological signs and symptoms
2. No evidence of aneurysmal subarachnoid hemorrhage
3. Normal or near normal cerebrospinal fluid analysis
4. Reversible cerebral segmental vasoconstriction involving arteries of Circle of Willis documented by serial angiography, CTA, MRA or a flow-related vascular study such as TCD within 12 weeks of onset

Abbreviations: RCVS, Reversible cerebral vasoconstriction syndrome; CTA, Computed tomography angiography; MRA, Magnetic resonance angiography; TCD, Transcranial Doppler.

However, RCVS [21, 28-31], and related disorders sharing a similar clinical phenotype of reversible cerebral artery vasoconstriction, may be indistinguishable from PACNS arteritis. The diagnostic criteria of RCVS (Table 2) include: 1) thunderclap headache with or without other neurological signs and symptoms, 2) absence of aneurysmal subarachnoid hemorrhage, normal or near-normal CSF profile, 3) reversible segmental vasoconstriction involving arteries of Circle of Willis documented by serial angiography, CTA, MRA or a flow-related vascular study within twelve weeks of onset of the presentation, and 4) resolution in 60 days. Subarachnoid and intracerebral hemorrhages were usually encountered in the first week of onset respectively in 34% and 20% of cases, and typically along the cerebral convexity. Ischemic infarction ensues in 39 % of patients with RCVS during the second week from onset of symptoms along watershed areas between the anterior and posterior circulations, so noted as multiple, bilateral and symmetrical lesions with or without associated cerebral edema [29, 30]. Clues to the differentiation of RCVS and PACNS include a history of vasoconstrictive drug exposure or recent childbirth and thunderclap rather than insidious or chronic headache in the former, with normal or near-normal CSF however both may demonstrate seizure, strokes, and abnormal cerebrovascular imaging. Neuroimaging is rarely normal in PACNS and infarcts tend to be ischemic, infrequently hemorrhagic, while RCVS manifests severe vasoconstriction without parenchymal lesions, alternatively lobar and cortical surface subarachnoid hemorrhages or reversible edematous lesions characteristic of the ‘posterior reversible leukoencephalopathy syndrome.’ The angiographic abnormalities in RCVS are typically more dynamic, severe, and resolve over weeks to 3 months. High-resolution MRI holds promise in differentiating RCVS from CNS vasculitis based upon the presence and the pattern of concentric and eccentric vessel wall contrast enhancement [32]. Nonetheless, differentiation of the two disorders may remain uncertain when other studies supporting PACNS including brain biopsy are falsely negative.

LABORATORY EVALUATION

Blood Studies

The diagnostic workup in PACNS, which may be extensive, covers a wide range of modalities reflective of the intrinsic lack of test specificity for this diagnosis. Peripheral blood counts, chemistries, acute phase reactants and inflammatory markers such as the C- reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are expectedly normal but useful to obtain to exclude an underlying or concomitant systemic inflammatory process. Although there are no specific serologic markers for PACNS it is useful to obtain antinuclear antibody

(ANA), ANCA, serum complement levels, antiphospholipid (APL), baseline coagulation studies, as well as acute and convalescent infectious antibody titers as may be suggested by epidemiological, host immune factors and exposure history.

Cerebrospinal Fluid

It is imperative to perform a lumbar puncture to analyze the CSF unless otherwise contraindicated especially to exclude infection and malignancy; and in GACNS, the majority of affected patients will demonstrate elevation of the protein level and lymphocytic pleocytosis, however in either disorder, neither the white blood cell count nor protein level will respectively exceed 250 cells/mm³ or 500 mg/dL [25, 33, 34]. Emerging molecular techniques with next generation sequence applied to CSF provide an unbiased approach to identify infectious etiologies in patients with possible CNS vasculitis [35].

Magnetic Resonance Imaging

The reported sensitivity of MRI in PACNS, which has been 75% and approaching 100% [1] in the detection of cautive lesions, may not be reliable due to the erroneous inclusion of patients with RCVS. Cerebral infarction, the most common lesion seen on MRI, was noted overall in 53% of patients with PACNS [1], and often multiple, affecting the cortical and subcortical parenchyma; with nonspecific high-intensity T₂-weighted white matter FLAIR lesions [1]. Mass lesions occur in up to 5% of affected patients as do intracranial hemorrhage in 8% of patients. Collectively, abnormalities of CSF and MRI are noted in close to 100% of those with GACNS which then when normal, generates a high negative predictive probability for the diagnosis of GACNS [36].

Cerebral Angiography

The expected cerebral angiographic findings of PACNS are alternating areas of stenosis and dilatation that resemble beads on a string, which may be smooth or irregular in appearance, bilateral or involve single named vessels [37]. Other angiographic findings include tapering of the vessel lumen of a single vessel or multiple vessels. However, these angiographic findings are non-specific and can be observed in nonvasculitic atherosclerosis, radiation vasculopathy, fibromuscular dysplasia, infection, and especially RCVS. Moreover, the reported specificity of 30% of cerebral angiography in the diagnosis of PACNS suggests the need for further work-up to rule out other mimicking conditions when the typical angiographic features for vasculitis are not observed [37]. The sensitivity of direct cerebral angiography exceeds that of brain MRA, however the spatial resolution falls in vessels <500 μm in diameter. Accordingly, higher false negative results should be expected in the setting of known small vessel vasculitic pathology such as GACNS and angiography-negative small vessel cPACNS. High-resolution vessel wall MRI, which provides detail of vessel lumina and

wall structure, has the capacity to increase the test specificity of non-invasive vascular neuroimaging in CNS vasculopathy [32].

Brain Biopsy

Pathologic examination of the brain is still the gold standard for the diagnosis of PACNS because of its ability to confirm the diagnosis of PACNS and more importantly exclude PACNS mimics [38]. Special stains are useful to examine for malignancy and as are tissues culture for infectious etiologies of secondary CNS vasculitis. A non-diagnostic or negative biopsy does not rule out PACNS, and false-negative biopsy results, that can be as high as 25% of autopsy-documented cases [38] are due to patchy vasculitic involvement and potential inaccuracy of a non-lesional biopsy sample. The microscopic appearance of GACNS includes segmental necrotizing multinucleated giant cell and epithelioid granulomatous vasculitic involvement of small to medium-sized arteries in the leptomeninges and cortex, with involvement of veins in about one-half of cases. Not all of these features are present in all patients, and the distribution of lesions may be patchy in the CNS. Although loosely formed granulomatous giant cell lesions may be encountered, well-formed granulomas are more commonly observed, with up to 20% of cases demonstrating lymphocytic inflammation of vessel walls without prominent granulomas [38]. Tissue biopsy should ideally be performed through open craniotomy with sampling of both leptomeningeal and parenchymal brain tissue at abnormal sites suggested by neuroimaging, and if inaccessible, along the temporal tip of the non-dominant hemisphere [38].

TREATMENT AND PROGNOSIS

Rheumatologists and neurologists treating adult patients with PACNS must choose their treatment from among available immunosuppressant and biological agents without the benefit of randomized-controlled clinical trials however the literature does provide some guidance. The historical basis for the use of aggressive immunosuppressant therapy for CNS vasculitis commenced with the reports of the efficacy of combination immunosuppressant therapy employing oral corticosteroids and intravenous cyclophosphamide by Cupps and coworkers [6, 27], and later Moore [40] who ascertained the diagnosis of CNS vasculitis based upon the clinical criteria of a clinical pattern of headache, multifocal neurological deficits and cerebral angiography demonstrating segmental arterial narrowing, with exclusion of systemic inflammation and infection and proof of vascular inflammation in a leptomeningeal or parenchymal biopsy tissue. Empiric therapy with corticosteroids and cyclophosphamide was advocated at doses similar to that employed for granulomatosis with polyangiitis [41] in all five patients in the series by Moore [40] even though brain or leptomeningeal biopsy showed unequivocal evidence of cerebral vasculitis in only two patients, and non-diagnostic perivascular inflammation in three others. The author's explanation was that while useful in diagnosis and management, antemortem biopsy could be less striking and inconsistent. Prednisone alone appeared to have either a transient or no effect on the course of the disease process.

It has been suggested that historical surveys of PACNS might be misleading because of the bias of ascertainment, favoring the larger number of postmortem cases that proved fatal without treatment [5]. A meta-analysis of 54 literature patients comprising 30 patients diagnosed antemortem and 24 patients treated before postmortem confirmation [5] found equally satisfactory outcomes in those treated with corticosteroids alone or with oral cyclophosphamide, with overall improvement in 24 of 34 (70%) so treated. Three patients treated with corticosteroids and oral cyclophosphamide died due to serious sequela of the latter treatment. Although the findings appeared to challenge the imperative of aggressive empiric treatment, there is still agreement among experts [5] that cyclophosphamide can be safely employed in histologically-confirmed patients, especially those who continued to progress while on corticosteroids and can be closely monitored for medication related side effects.

Hutchinson and colleagues [42] described the treatment of small vessel PACNS in a single-center open-label childhood cohort. They employed cyclophosphamide at doses of 500 to 750 mg/m² monthly infusions for six months, followed by maintenance therapy of azathioprine 1 mg/kg/day and a target dose of 2 to 3 mg/kg/day, with mycophenolate mofetil titrated at dosages of 800 to 1200 mg/m²/day for up to 24 months. Outcome was rated using a pediatric stroke outcome measures (PSOM). Among 13 who completed the treatment regimen, nine had a good neurological outcome by PSOM scoring and four achieved remission of disease. Therapeutic guidelines remain informal, based upon expert opinions and historical bias suggesting that PACNS is progressive and uniformly fatal if left untreated [25].

In our experience, the majority of patients with documented GACNS should be treated with combination corticosteroid and cyclophosphamide therapy similar to systemic small vessel vasculitis algorithms [42, 43] to control the disease, implementing maintenance therapy with mycophenolate mofetil or azathioprine [1], and monitoring the activity of disease clinically and with serial MRI. All patients should receive prophylaxis for *Pneumocystis jirovecii* infection and followed for infections, osteoporosis, and other treatment-related complications [1], and followed by a team of health care professionals in rheumatology, neurology, neuroradiology, and physical therapy to ensure optimal care.

CONCLUSION

Adult PACNS is one of the most challenging and complex vasculitic disorders to diagnose and treat. Moreover, research into this disorder has been limited by the scarcity of human pathological material and absence of an animal model. There have been significant advances in the recognition of the clinical heterogeneity of the disorder and the differentiation from less fatal disorders that may mimic it.

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Chapter 219

PRIMARY CNS VASCULITIS: PATHOPHYSIOLOGICAL DIVERSITY*

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INTRODUCTION

Primary central nervous system vasculitis (PCNSV) is a rare vasculitis that affects the brain and occasionally the spinal cord of adults and children [1]. Extensive progress has been achieved in the recognition of clinicopathological subsets that has translated into useful nosology reflective of the natural history and response to immunosuppressant treatment.

HISTORICAL BACKGROUND OF PRIMARY CNS VASCULITIS

The first case of PCNSV was described in 1952 by Newman and Wolf [2] and subsequently by Cravioto and Feigin [3] in 1959. The latter authors designated the disease as granulomatous angiitis of the nervous system (GANS) or granulomatous angiitis of the central nervous system (GACNS), because of the histologic granulomatous vasculitic changes

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they observed. Cupps and Fauci [4], influenced by their advances in the classification, diagnosis, and treatment of systemic vasculitides at the National Institute of Health (NIH) [5], named the disorder isolated angiitis of the central nervous system (IACNS). Over the ensuing decades, PCNSV was relegated to the penumbra of vasculitis [6]. In 1988, Younger and colleagues [7] recognized the diversity in etiology due to association of some cases with neurosarcoidosis, non-Hodgkin lymphoma, or varicella zoster virus infection as well as the varied pathological expression which included arteries and veins of variable caliber both intracerebral and more distal leptomeningeal vessels. In the same year of 1988, Mallek and Calabrese [8] described the clinicopathological aspects, findings in diagnostic studies, and response to therapy in 8 Cleveland Clinic Foundation cases and a review of 40 patients in the literature. Headache was noted in 58% of entire group followed by hemiparesis in 35% of patients, mental impairment in 27%, dysphasia in 15%, seizures in 13% and ocular signs in 13%. Cerebrospinal fluid (CSF) was abnormal in 81% of patients. Two-thirds of patients who underwent conventional cerebral angiography manifested vascular changes consistent with cerebral vasculitis. Histopathologic confirmation of CNS vasculitis was available in 26 of 37 (74%) patients examined at postmortem examination, and in 10 of 14 (71%) of patients by antemortem brain biopsy with or without leptomeninges. Of the four patients with negative antemortem brain biopsy, one specifically did not include leptomeninges, and three others had demonstrable vasculitis of meningeal vessels at postmortem examination emphasizing the importance of obtaining combined brain and leptomeningeal tissue. Mortality was noted in 28 of 46 (61%) patients, however among the Cleveland Clinic Foundation patients, full resolution was achieved in six treated with combination corticosteroid and cyclophosphamide therapy, as well as in one patient each treated with high dose prednisone and another patient with only angiographic validation of vasculitis, who was untreated. These observations suggested an improved prognosis with an aggressive therapeutic approach as was previously proposed by Cupps and colleagues [4] and Fauci and colleagues [5]. Although not so stated, there was an obvious admixture of benign angiopathy in the patient who fully resolved without treatment. Calabrese and Mallek [8] proposed formal diagnostic criteria requiring fulfillment of three conditions: a history or presence of an acquired neurological deficit, histological or angiographic evidence of vasculitis, and lack of evidence of a systemic vasculitis or other conditions to which the angiographic or pathologic features could be attributed. The interchangeable term primary CNS angiitis (PACNS) like PCNSV, underscored the restricted nature of the illness, and like IACNS, emphasized the primary and often idiopathic nature of the disorder [9, 10] rather than the granulomatous pathology. The rationale was that giant cells and epithelioid cells, usually found at postmortem examination were inconstant findings in meningeal and brain biopsy tissue and therefore not necessary for antemortem diagnosis [11].

Later observations by Salvarani and colleagues in adults [12] would begin to unravel the clinicopathological dichotomy of granulomatous and non-granulomatous histology in adults beyond the simplistic assumption that granulomatous pathology was simply more lethal and found most often at postmortem examination than less fatal non-granulomatous changes so seen antemortem. Contemporaneously, PCNSV was described in two children with acute presentation of headache and focal neurological signs diagnosed by combined leptomeningeal and brain biopsy demonstrating non-granulomatous, non-necrotizing lymphocytic vasculitis predominantly affecting leptomeningeal arterioles, capillaries and venules [13]; and three others with acute headache and focal neurological deficits who died. In the latter three,

postmortem examination showed involvement of large named vessels by necrotizing granulomatous vasculitis including the distal vertebral [14], basilar [15], and middle cerebral artery [16] arteries. The clinicopathologic dichotomy of PCNSV in children was later summarized by Benseler and colleagues [17]. Angiographic large CNS vessel stenoses or occlusions in affected children caused strokes with manifestations of hemiparesis, hemifacial weakness, and hemisensory loss due to decreased perfusion in the area of the stenotic vessel and ischemia of the dependent brain territory. In contrast, distal CNS vasculitic and adjacent parenchymal inflammation led to diffuse neurologic deficits including headache, seizures, and subtle or overt cognitive, behavioral and personality changes. Those with both small- and large-vessel inflammatory vasculitic involvement might present with overlapping clinical deficits. Yet, in contrast to fatal adult PCNSV and the few fatal childhood cases [14-16], brain and meningeal biopsy performed in children at one center [18] with suspected vasculitis but negative angiograms revealed non-granulomatous, lymphocytic vasculitis of small vessels. This subset in children appears to be the fastest growing group of children with primary vasculitis at most centers [17].

SPECTRUM OF PRIMARY CNS VASCULITIS

The achievements of the 1980s proved to be the lessons for the 1990s. Although the acceptance and application of diagnostic criteria for PCNSV facilitated research and clinical studies alike, as the number of recognized patients increased, it became clear that PCNSV was more heterogeneous than previously thought. Moreover, enthusiasm for the empiric treatment of cerebral vasculitis waned as it became evident that cerebral angiography alone was insufficient for the diagnosis of PCNSV. This was noted in Case 3 of Calabrese and Mallek's 1987 paper [8] with angiographically diagnosed CNS vasculitis and full resolution without treatment. In later publications, Calabrese and colleagues [19-21] displayed the increasing awareness that patients who they earlier called "benign angiopathy of the CNS" (BACNS), represented a reversible cerebral vasoconstriction syndrome (RCVS) [21] and might be intermixed with angiographically-proven PCNSV due to common clinical and angiographic findings as shown in Table 1. By 1997, with 136 published cases of histologically-defined granulomatous CNS vasculitis alone [22] and the recognition that the criteria were performing poorly in discriminating PCNSV from RCVS, Calabrese and coworkers [21] proposed formal criteria for RCVS, the five critical elements of which included, transfemoral cerebral angiography or indirect computerized tomography angiography (CTA) or magnetic resonance angiography (MRA) documenting multifocal segmental cerebral artery vasoconstriction; lack of evidence for aneurysmal subarachnoid hemorrhage; normal or near-normal CSF with protein content <80 mg%, normal glucose content, and <10 mm³ leukocytes; development of acute severe headache with or without additional neurologic signs or symptoms; and reversibility of angiographic abnormalities within 12 weeks of onset. If death occurred before the followup studies were completed, postmortem examination should exclude vasculitis, intracranial atherosclerosis and aneurysmal subarachnoid hemorrhage, which might also manifest with headache and stroke similar to RCVS. The accuracy of cerebral angiography alone for detecting vasculitis was

estimated to be 50% to 90%, citing Salvarani and colleagues [12], when beading and interposed regions of ectasia of normal luminal architecture were present.

Magnetic resonance imaging (MRI) is also helpful in the evaluation of CNS vasculitis. MRI abnormalities were observed in 90% or more of affected cases, the most common of which were subcortical white matter lesions followed by deep gray matter, deep white matter, and cerebral cortical lesions [23]. Cerebrospinal fluid studies have demonstrated one or more abnormal findings in 88% of confirmed cases, most often elevated protein concentration (median, 98mg/dL) and leukocyte pleocytosis (median, 17 cells/ml) or both citing Salvarani and colleagues [12].

Birnbaum and Hellmann [24] proposed changes to the criteria of Calabrese and Mallek [8]. The proposed criterion for “definite” CNS vasculitis was a positive CNS biopsy. Patients classified as “probable” CNS vasculitis should have CNS angiograms showing changes suggesting vasculitis, concordant MRI abnormalities, and CSF findings consistent with CNS vasculitis but without biopsy confirmation.

Further, discriminatory clinical features of PCNSV and RVCS which might help suggest RVCS in patients with high-probability findings on cerebral angiography and a normal CSF, were female sex, acuteness and severity of the headache, focality of neurological deficits at onset, history of provocative vasospastic syndromes, dynamic improvement after three months, and amelioration with non-cytotoxic therapy [24].

Table 1. Characteristics of PCNSV and RCVS¹

	PCNSV	RCVS
Precipitating factor	None	Post-partum onset or onset after exposure to vasoactive substances
Onset	More insidious, progressive course	Acute onset followed by a monophasic course
Headaches	Chronic and progressive	Acute, thunderclap type
CSF findings	Abnormal (leucocytosis and high total protein concentrations)	Normal to near normal
MRI	Abnormal in almost all patients	Normal in 70% of patients
Angiography	Possibly normal, otherwise, diffuse abnormalities are often indistinguishable from RCVS; irregular and asymmetrical arterial stenoses or multiple occlusions are more suggestive of PCNSV; abnormalities might be irreversible	Always abnormal, strings of beads appearance of cerebral arteries; abnormalities reversible within 5-12 weeks
Cerebral biopsy	Vasculitis	No vasculitic changes
Drug treatment	Prednisone with or without cytotoxic agents	Nimodipine

PCNSV=primary CNS vasculitis; RCVS=reversible cerebral vasoconstriction syndrome; CSF=cerebrospinal fluid

¹Reproduced from Salvarani C, Brown RD, Jr., Hunder GG Adult primary central nervous system vasculitis. *Lancet* 2012; 380:767-777, with permission.

SUBSETS OF PRIMARY CNS VASCULITIS

Further evidence of the heterogeneous nature of PCNSV was appreciated in a review of 101 patients seen at the Mayo Clinic over a 21-year period from 1983 to 2003 [12]. Diagnostic criteria similar to those of Calabrese and Mallek [8] were used. Diagnostic histopathological features were transmural vascular inflammation involving leptomeningeal or parenchymal vessels. Angiographic changes indicating a high probability of vasculitis included areas of smooth-wall segmental narrowing or dilatation and occlusions that affected multiple cerebral arteries without the proximal vessel changes of atherosclerosis or other

causes. Those with single vessel abnormalities in multiple arteries or multiple abnormalities in a single artery were excluded from the analysis. Cases with other conditions that might mimic PCNSV, such as hypercoagulability, varicella zoster virus and other infectious vasculitides, were excluded. There were 58 women and 43 men with a median age at diagnosis of 47 years. The diagnosis of PCNSV was ascertained by cerebral angiography in 70 patients and by CNS tissue in 31 patients. The clinical features of the patients are detailed in Table 2. Patients with large-artery involvement, characterized by multiple, large brain lesions on MRI and diffuse stenoses on angiograms, had more severe neurological disease and worse outcomes. Conversely, those with PCNSV that predominantly affected small leptomeningeal and cerebral arteries, characterized by prominent enhancement of lesions or meninges on MRI after intravenous administration of gadolinium, had less disability and a lower risk of mortality. Moreover, three histological patterns were observed, granulomatous (in 58%), lymphocytic (in 28%), and necrotizing (in 14%) of histologically-proven cases. β -amyloid vascular deposits were noted in 8 specimens, all of which showed granulomatous inflammation. Granulomatous changes were also more frequently encountered in older-onset patients, and in those with altered cognition. These histological patterns appeared to identify subsets of disease rather than different stages of the same process since no individual patient had histological evidence of more than one pattern. Underscoring this hypothesis, were findings in seven patients in whom two biopsy specimens were obtained at different times. In four such patients both specimens were positive for vasculitis and each pair of specimens showed the same inflammatory pattern.

In 2011, Salvarani and colleagues [25] extended the previous cohort of PCNSV [12] to include the period 2004 to 2007, yielding a total of 131 cases, to assess the clinical characteristics of similarly defined patients with PCNSV. Several subgroups were identified. Using a modified Rankin scale [26] to assess outcomes, a subgroup with rapidly progressive PCNSV was distinguished. Among 131 consecutive patients in the updated cohort, 11 (8.4%) had a rapidly progressive course resulting in severe disability or death, (Rankin 5 and 6). Such patients had more frequent paraparesis or quadriparesis at presentation, cerebral angiographic evidence of bilateral, large vessel vasculitis, and MRI evidence of cerebral infarctions. The latter lesions were usually multiple and bilateral, involving both cortex and subcortical regions on initial MRI. Of three open CNS tissue biopsies, one each showed granulomatous changes, necrotizing vasculitis, or both. All 11 patients failed to respond to aggressive immunosuppressant therapy, culminating in stroke as the cause of death in eight and fatal aspiration pneumonia in two patients. One patient who was alive at followup had fixed major neurological impairment.

Eight patients (8%) with biopsy positive-cerebral angiography-negative PCNSV were identified from 101 consecutive patients in the original cohort of Salvarani and colleagues [12, 27]. In comparison to 76 patients with cerebral angiography-positive PCNSV, the former more commonly manifested a cognitive disorder, elevated CSF protein level and leukocyte pleocytosis, and enhancement of meningeal or parenchymal lesions on MRI after administration of intravenous gadolinium. All patients responded to treatment and none died. A similar favorable outcome was reported in children with cerebral angiography-negative PCNSV [18].

Eight (26%) of the 101 patients in the same cohort [12, 28] with positive biopsies also had cerebrovascular amyloid deposits (cerebrovascular amyloid angiopathy or CAA). Compared to PCNSV without CAA, such patients (Figure 1) were comparatively older at

diagnosis, predominantly male, had a more acute onset of PCNSV, with greater frequency of cognitive dysfunction, and prominent enhancement of leptomeningeal lesions by brain MRI after intravenous administration of gadolinium. The presence of vascular amyloid in this group raised the suggestion that the deposits may somehow be an inciting factor in the vascular inflammation. Six of the eight patients responded promptly to therapy, similar to the others in the cohort.

Table 2. Clinical features at presentation in PCNSV¹

Characteristics	All Patients (N = 101), n (%)	Patients Diagnosed by Biopsy (n = 31), n (%)	Patients Diagnosed by Angiography (n = 70), n (%)
Headache	64 (63)	16 (52)	48 (69)
Altered cognition	50 (50)	22 (71)	28 (40)
Hemiparesis	44 (44)	6 (19)	38 (54)
Persistent neurological deficit or stroke	40 (40)	8 (26)	32 (46)
Aphasia	28 (28)	11 (36)	17 (24)
Transient ischemic attack	28 (28)	5 (16)	23 (33)
Ataxia	19 (19)	5 (16)	14 (20)
Seizure	16 (16)	2 (7)	14 (20)
Visual symptoms (any kind)	42 (42)	9 (29)	33 (47)
Visual field defect	21 (21)	5 (16)	16 (23)
Diplopia (persistent or transient)	16 (16)	5 (16)	11 (16)
Blurred vision or decreased visual acuity	11 (11)	0 (0)	11 (16)
Monocular visual symptoms or amaurosis fugax	1 (1)	0 (0)	1 (1)
Papilledema	5 (5)	2 (7)	3 (4)
Intracranial hemorrhage	8 (8)	2 (7)	6 (9)
Amnesic syndrome	9 (9)	4 (13)	5 (7)
Paraparesis or quadripareisis	7 (7)	4 (13)	3 (4)
Parkinsonism or extrapyramidal signs	1 (1)	0 (0)	1 (1)
Prominent constitutional symptoms	9 (9)	4 (13)	5 (7)
Fever	9 (9)	4 (13)	5 (7)
Nausea or vomiting	25 (25)	6 (19)	19 (27)
Vertigo or dizziness	9 (9)	3 (10)	6 (9)
Dysarthria	15 (15)	2 (7)	13 (19)
Unilateral numbness	13 (13)	0 (0)	13 (19)

¹Reproduced from Salvarani C, Brown RD, Jr., Calamia KT et al. Primary central nervous system vasculitis: analysis of 101 patients. *Ann Neurol* 2007; 62:442-51 with permission.

The clinical findings, response to therapy, and outcomes of patients with cerebral vascular β -amyloid deposition with and without inflammatory vascular infiltration were evaluated in 2013 by Salvarani and coworkers in 78 consecutive patients with cerebral vascular β -amyloid deposition [29]. Compared to 118 consecutive patients with PCNSV without β -amyloid deposition, the 28 patients with granulomatous vasculitis (A β -related angiitis or ABRA) had similar results of treatment and outcomes, confirming that ABRA represents a distinct subset of PCNSV.

Sixteen patients (12%) with evidence of intracranial hemorrhage at or near the time of diagnosis of PCNSV were identified from 131 consecutive patient with PCNSV [25], and

reanalyzed further by Salvarani and colleagues [30]. Twelve patients had intracerebral hemorrhages, and four were subarachnoid in location. Twelve were diagnosed by findings on cerebral angiography and four by findings on CNS tissue biopsy. Compared to the 115 patients without intracranial hemorrhage, the 16 affected patients were more frequently women, altogether had less alteration of cognition, persistence of the neurological deficit, stroke at presentation, MRI evidence of cerebral infarction, or needed therapy at last followup visit. Among the four patients with evidence of hemorrhage on CNS tissue biopsy, three showed necrotizing histopathologic pattern of vasculitis. None of the patients with intracranial hemorrhage had evidence of lymphoproliferative disorders, in contrast to one-third in the series described by Calabrese and colleagues [20]. These findings indicate that while intracranial hemorrhage does not occur in the majority of patients with early PCNSV, it nonetheless needs to be considered in the differential diagnosis.

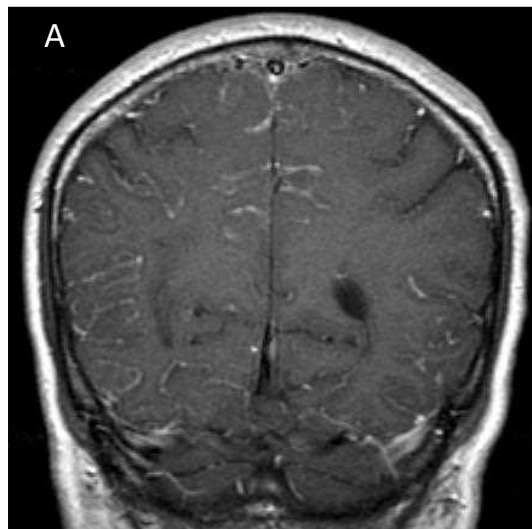


Figure 1. Brain MRI and histopathological features of a PCNSV patient with leptomeningeal vasculitis and amyloid angiopathy. A. MRI at onset of symptoms shows prominent leptomeningeal enhancement after intravenous administration of gadolinium. B. Histopathological findings shows destructive vasculitis with well-formed granulomata in leptomeningeal vessels and wall thickening with eosinophilic material (*) (Hematoxylin and eosin stain X100). The right-hand image shows amyloid- β deposits in all vessels (immunoperoxidase stain for β A4 amyloid X100).

Five patients (5%) with spinal cord involvement were identified from 101 consecutive patients with PCNSV [12, 31]. Five others in the cohort had spinal symptoms but no objective findings and were therefore not included in the spinal group [31]. In the five so studied, the median time from onset of symptoms was 26 days that included leg weakness or paralysis, numbness, and urinary incontinence in all patients, in addition to cerebral symptoms. Symptoms of spinal cord involvement developed before cerebral symptoms in one patient, simultaneously in two patients, and after cerebral disease in two others. Spinal cord vasculitis was the only manifestation in one patient preceding symptomatic brain involvement by 10 months. Spinal cord MRI showed enhancement of thoracic lesions after administration of intravenous gadolinium in all five patients. Cerebral angiography performed in four of the patients were normal. CNS tissue biopsy showed necrotizing vasculitis in three patients and

granulomatous histology in two specimens. Although the small number of patients with spinal cord involvement precluded statistical comparison, there were no significant differences in the clinical and laboratory studies other than symptoms of myelopathy, which occurred exclusively in those with thoracic lesions. Notwithstanding, cerebral angiography showed evidence of vasculitis more frequently in those without spinal cord involvement, while the patients with spinal cord involvement had CNS tissue biopsy findings more often consistent with vasculitis perhaps indicating more widespread disease. Overall, four of the five patients responded to therapy that included corticosteroids alone in one, and combined in the others with cytotoxic agents including cyclophosphamide, azathioprine or mycophenolate mofetil for a median duration of 19 months. Four patients recovered with slight or moderate deficits and disability; however, all sustained at least one relapse or recurrence.

Molloy and colleagues [32] described tumor-like mass lesions (ML) in 38 patients with PCNSV including seven patients from the case records of the Cleveland Clinic, and 31 patients of 535 (5.6%) with PCNSV from the English language medical literature. Patients were included only if they presented with a solitary cerebral ML and histological proof of vasculitis; 13 of 45 (29%) cases of amyloid- β related angiitis (ABRA) reported in the literature were included. The commonest symptoms of PCNSV with a ML were headache (74%), focal neurological deficit (64%), diffuse neurological deficit (50%), and seizures (47%), prompted affected patients to present typically one month after onset compared to patients with PCNSV without a ML who typically presented on average 6 months afterward. Neuroimaging, which detected the ML employing MRI in all 24 patients so studied, and by computed tomography (CT) in 29 of 30 patients, showed edema, contrast enhancement, and hemorrhage in association with the ML respectively in 17, 15, and five patients. Cerebrospinal fluid showed an elevation of the protein content and pleocytosis in two-thirds of patients so studied; and cerebral angiography performed in 14 patients, showed mass effect but no suggestion of vasculitis in eight patients, and angiographic evidence of small vessel vasculitis in the other six. The diagnosis of PCNSV was confirmed by CNS tissue in all 38 patients with granulomatous changes in 20 (53%) and lymphocytic vasculitis in 18 (47%); positive staining for amyloid was found in 13 of 38 CNS tissue biopsies (34%), accompanied by granulomatous vasculitis in 10 of 13 (77%). Overall, 26 of 38 (68%) entered remission status defined as regression of the lesion and resolution or stabilization of neurological symptoms. Six patients died during followup, five of whom were ABRA-positive. Moderate or severe residual deficits were noted in three-quarters of patients, occurred more often in those treated with corticosteroids alone as compared with those administered combination therapy with corticosteroids and cyclophosphamide.

A recent study from Mayo Clinic evaluated the clinical findings, response to therapy, and course of patients with PCNSV associated with lymphoma [33]. Ten patients were identified (6 with Hodgkin lymphoma – HL – and 4 with non-HL) and their findings compared with those from 158 patients with PCNSV without lymphoma seen at Mayo Clinic over 29 years. In 7 patients, lymphoma and PCNSV were diagnosed simultaneously, suggesting an immunologic paraneoplastic mechanism. A granulomatous vasculitis was found in all 8 patients with cerebral biopsies, associated with CAA in 2.

Patients with lymphoma had more neurologic disability at last follow-up and their survival was reduced compared to patients without lymphoma, appearing to have a more severe form of vasculitis.

CONCLUSION

Primary CNS vasculitis is a multifaceted disease with diverse clinicopathological subsets. Affected patients with small-artery vasculitis characterized by positive histology, negative cerebral angiography and prominent leptomeningeal enhancement on MRI after intravenous gadolinium administration have a milder disease course and more favorable outcome compared to those with large-artery PCNSV with multiple large-artery stenoses on cerebral angiography and extensive lesions on MRI. Subsets of patients presenting with rapidly progressive PCNSV, solitary ML, association with lymphoma and vascular amyloid deposits have the worst prognosis.

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Chapter 220

STROKE DUE TO VASCULITIS IN ADULTS

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ABSTRACT

The vasculitides are diseases characterized by inflammation of blood vessels and inflammatory leukocytes in vessel walls. There is an increased propensity for ischemic stroke due to the compromise in vessel lumina and distal tissue ischemia, with hemorrhagic stroke and aneurysmal bleeding due to loss of vessel integrity.

INTRODUCTION

The vasculitides are diseases characterized by inflammation of blood vessels and inflammatory leukocytes in their walls. There is an increased propensity for ischemic stroke due to the loss of vascular integrity with stenosis of vessel lumina and distal tissue ischemia; and hemorrhagic stroke and aneurysmal bleeding due to loss of vessel integrity. The 2012 Revised Chapel Hill Consensus Conference (CHCC) [1] nomenclature provides systemic nosology and a categorization of primary and secondary vasculitides. Central nervous system (CNS) involvement and stroke both occur in the single-organ vasculitic (SOV) syndrome primary CNS vasculitis (PCNSV) [2], as well as, due to limited or multiorgan manifestations of primary systemic vasculitides [1].

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PRIMARY CNS VASCULITIS

With several proposed diagnostic schemes for PCNSV over the years [3-5], the combination of clinical and histopathological findings derived from cerebral angiography and leptomeningeal and brain biopsy remains the recommended method of definite diagnosis [6]. This approach facilitates the identification of clinicopathologic subtypes with persistent focal deficits and stroke [2] or intracranial hemorrhage [7] from those with reversible cerebral vasoconstriction syndrome (RCVS) [8] that may mimic true vasculitis, but do not require cytotoxic therapy.

Torres and colleagues [9] did not find a significant correlation between brain and leptomeningeal tissue, and the results of cerebrospinal fluid (CSF), neuroimaging, surgical technique, biopsy characteristics, or preoperative immunosuppressive therapy in 9/79 (11%) patients with suspected CNS vasculitis studied between 2005 and 2013. Yet in nearly three-fold (30%) of patients undergoing biopsy, the investigators noted alternative diagnoses of cerebral amyloid angiopathy, encephalitis, demyelination, and lymphoma. Postoperative complications occurred in 16%, 4% of which were serious. The authors concluded that while brain biopsy remains an important diagnostic tool, however further studies are needed to establish the clinical variables associated with a positive yield, as well as the surgical techniques that are most likely to provide diagnostic results with the lowest complication risk.

Historically, Younger and colleagues [3] described four patients with granulomatous angiitis of the brain histopathologically manifesting necrotizing vasculitis of arteries and veins of varying caliber in conjunction with giant cells and epithelioid cells. These authors [3] noted non-focal symptoms of headache and mental change, followed by focal weakness, seizures, and fatal coma in all four patients. Focal weakness with a stroke onset was noted in two (Patient 1 and 3) of the four patients, Patient 1 had onset of lethargy, focal ptosis and hemiparesis had predominant anterior (ACA), middle (MCA), posterior cerebral artery (PCA) and basilar artery involvement at postmortem examination. Patient 3, who presented with hemiparesis, ataxia, and dysarthria, and found to have predominant small leptomeningeal artery and vein involvement. Altogether, 15% of 78 patients overall had focal weakness with stroke onset compared to 42% who presented with focal deficits during the course of the illness.

In the same year, 1988, Calabrese and Mallek [4] described eight patients with classic angiographic or histopathologic features of PCNSV or so called primary angiitis of the CNS (PACNS), and reviewed the literature of 40 literature cases. Patient 2 [9] who presented with the clinical diagnosis of isolated angiitis of the CNS (IACNS) defined by classical angiographic features, had a clinical onset of transient weakness that progressed to fixed hemiparesis, nonfluent aphasia, alexia, and agraphia with later stabilization after combination prednisone and cyclophosphamide therapy.

Birnbaum and colleagues [5] proposed changes to the criteria of Calabrese and Mallek [4] to include a definite diagnosis of PCNSV only after tissue biopsy confirmation, noting strokes or persistent deficits in less than 20% of patients at onset, and with only about 28% of symptoms overall related to large cerebral vessel involvement. Salvarani and co-workers [2] noted that persistent neurological deficit or stroke and headache were the commonest initial symptoms affecting 68% of 101 patients so studied with PCNSV defined by diagnostic criteria similar to those suggested earlier [4]. Cerebral infarction noted on magnetic resonance

imaging (MRI) of the brain in 53% of patients, were multiple in appearances in 85%, bilateral in 83%, and involved the cortex and subcortex in 63%. Overall, their appearance suggested large-artery, branch-artery or small-artery distributions. Intracranial hemorrhage was noted in 8% of patients, and gadolinium enhancement was found in a third of patients, a quarter of whom demonstrated gadolinium enhancement of the meninges.

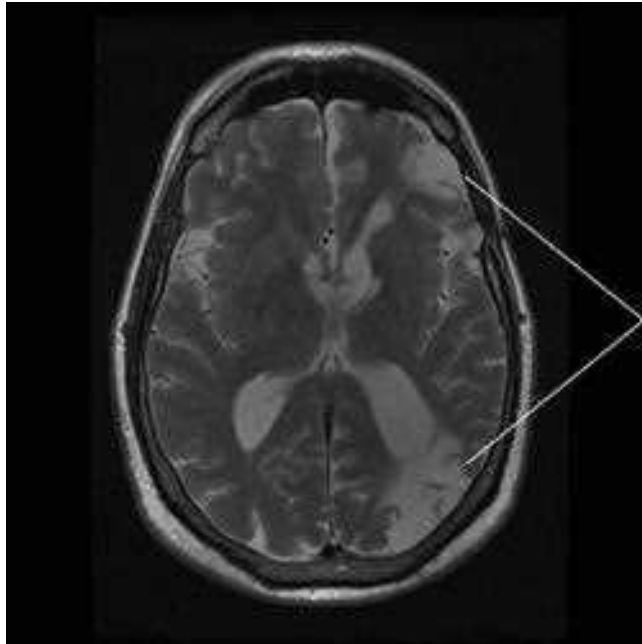


Figure 1. Primary CNS vasculitis. T₂-weighted MRI of the brain demonstrates left frontal and parieto-occipital lobe areas of infarction. Reproduced with permission from [10].

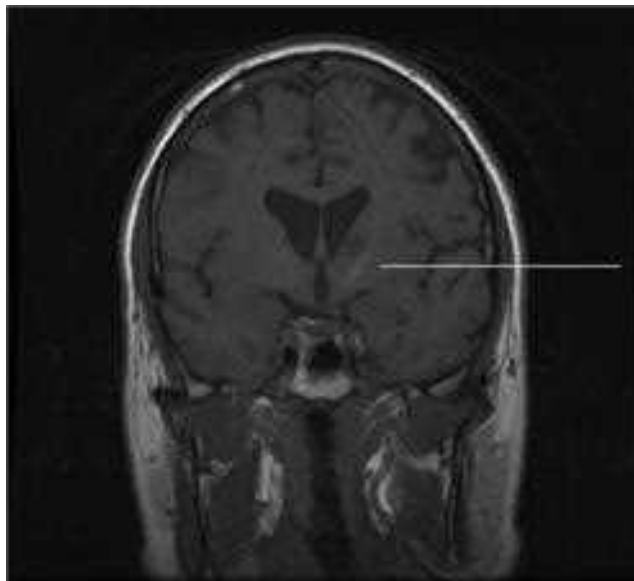


Figure 2. Primary CNS vasculitis. T₁-weighted MRI of the brain showed left basal ganglia hemorrhage. Reproduced with permission from [10].

Montefort and co-workers [10] described a 57-year-old man with brain-biopsy confirmed PCNSV and a 2-month history of right arm weakness and numbness superimposed on a history of left-sided headache and intermittent visual field loss. Brain MRI showed evidence of cortical infarction across more than one vascular territory with signal changes consistent with hemorrhage in the left basal ganglia and parieto-occipital lobe. There was angiographic evidence of irregular narrowing and aneurysmal dilatation of the left terminal carotid artery that stabilized without new areas of new infarction after treatment with intravenous pulsed cyclophosphamide and corticosteroids followed by azathioprine. The neuroimaging features of this patient are shown in Figures 1 to 4, as well as, in a similarly affected patient in Figures 5 and 6.

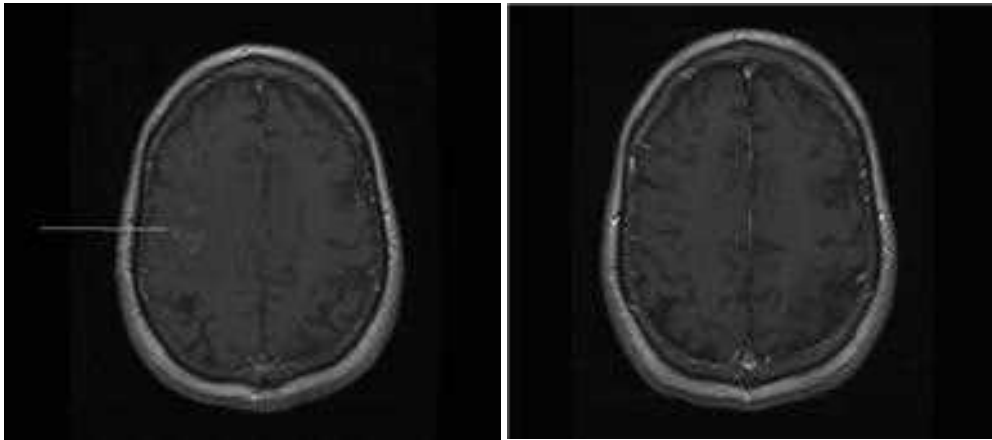


Figure 3. Primary CNS vasculitis. T₁-weighted MRI of the brain demonstrates gyral enhancement after intravenous administration of gadolinium before treatment (A), that resolves after immunosuppressant therapy (B). Reproduced with permission from [10].

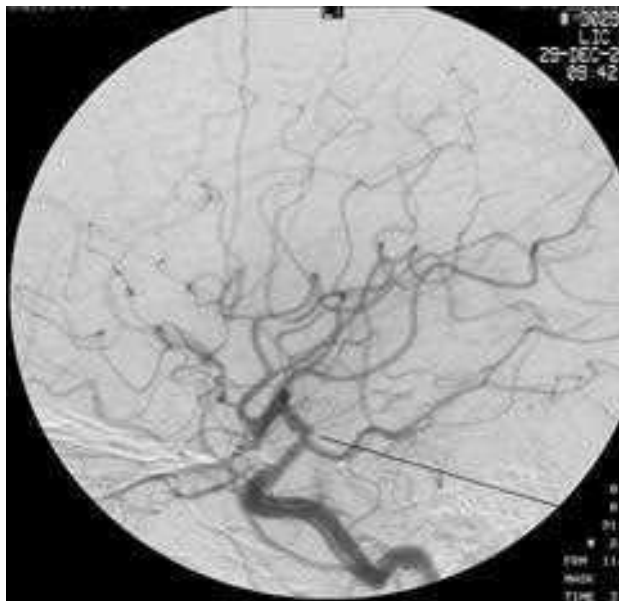


Figure 4. Primary CNS vasculitis. Cerebral angiography shows a sessile internal carotid artery aneurysm. Reproduced with permission from reference 10.

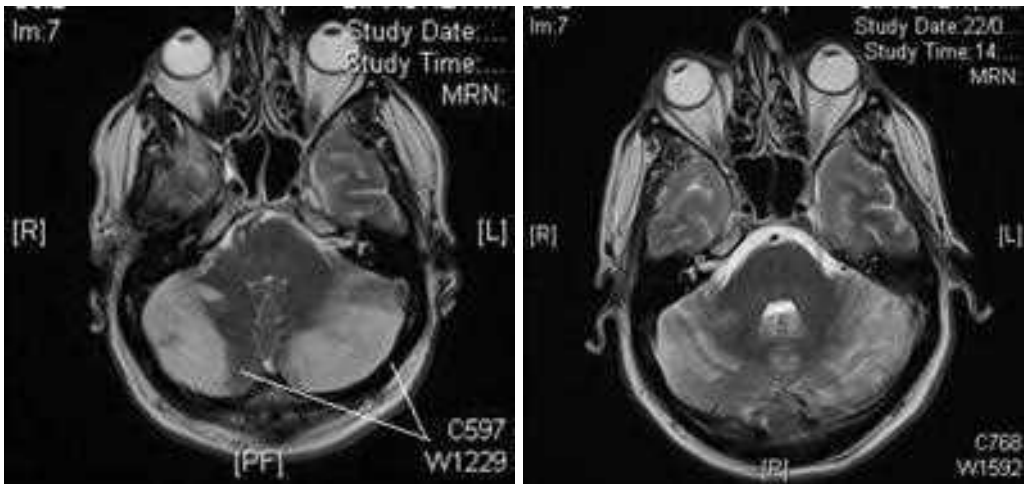


Figure 5. Primary CNS vasculitis. T₂-weighted MRI of the brain shows bilateral cerebellar hemispheric infarcts and abnormal signal hyperintensities before treatment (A) that resolve after immunosuppressant.

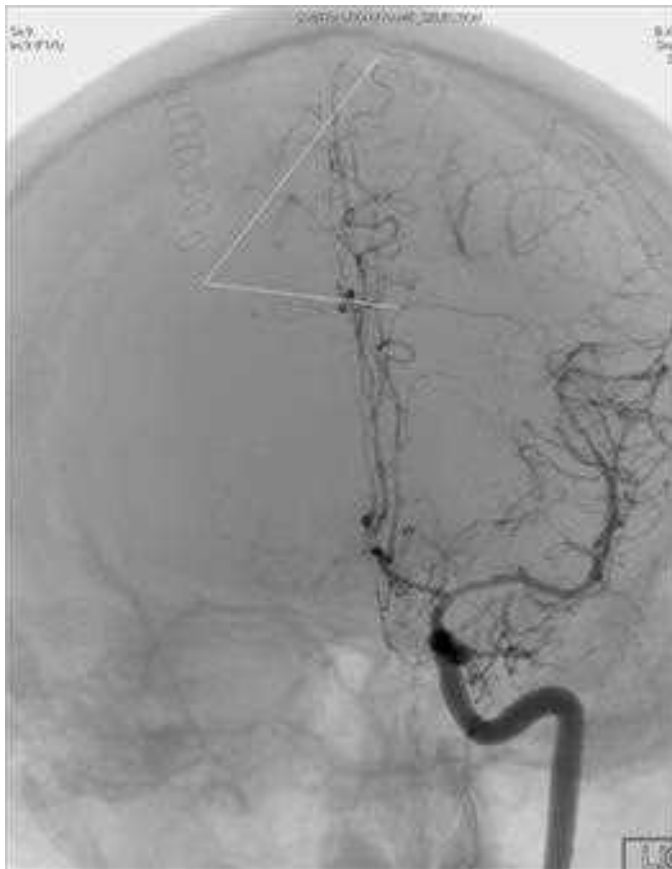


Figure 6. Primary CNS vasculitis. Cerebral angiography shows widespread vessel irregularity and beading.

PRIMARY LARGE VESSEL VASCULITIS

Giant cell arteritis (GCA) and Takayasu arteritis (TAK) are prototypical large vessel granulomatous vasculitides (LVV). They involve the aorta and its major branches however any size artery can be affected [1]. Imaging studies and fluorescein angiography studies have shown that ocular involvement in GCA can affect not only ophthalmic, but also medium caliber retinal arteries and multiple ciliary arteries and their smaller branches; blindness may result from not only LVV but also injury to smaller ophthalmic branches [1]. Whereas GCA has a predilection for branches of the carotid and vertebral arteries and an age of onset older than 50 years, there is often polymyalgia rheumatic. TAK involves proximal subclavian and carotid arteries with an onset of 40 years or less. Neuroimaging studies employing ultrasonography, high-resolution MRI, and ¹⁸fluorodeoxyglucose-positron emission tomography (FDG-PET) imaging are useful modalities to depict superficial cranial and extracranial vessels, and large vessel subclavian and aortic involvement in GCA and TAK [11].

CNS involvement in GCA, which results from thrombosis of the carotid and vertebral arteries rather intracranial arteritis, affects vessels that contain elastin, more specifically the internal elastic lamina that is absent from intracranial vessels more than 5 millimeters beyond the point of dural perforation. Reich, colleagues [12], Gonzalez-Gay, and co-workers [13] summarized the literature pertaining to stroke and GCA. Reports of CNS involvement have erroneously attributed to intracranial GCA rather than PCNSV [14-16]. Hellenhorset and colleagues [17] noted CNS events including stroke in 7.4% of 175 patients with confirmed GCA, as well as, and one patient with massive cerebral hemorrhage, two with stroke, and six with occlusive disease of the aortic arch. Caselli and colleagues [18] noted transient ischemic attacks or stroke in 7% of 166 patients with biopsy-proven GCA, among whom four had events in the vertebrobasilar systemic, and eight affected the carotid arterial system. With approximately 30% of patients manifesting neurological findings, the commonest of which were neuropathies of the arms and legs according to Caselli and colleagues [18], Salvarani and colleagues [19] observed that transient ischemic attacks or stroke in the territory of the carotid or vertebrobasilar arteries were less common neurological findings.

Gonzalez-Gay and co-workers [13] ascertained the frequency of cerebrovascular accidents (CVA) in association with GCA among 239 patients in a multicenter retrospective analysis to assess the features, therapeutic response, and predictors of visual loss and CVA. Eight patients (3%) developed CVA, equally divided between the vertebrobasilar and carotid territories. Symptoms of vascular ischemia preceded onset of arteritis by a median of 1.5 months, and were more frequent in those with visual involvement, especially permanent visual loss. Two patients with vertebrobasilar stroke died within one month despite aggressive corticosteroid therapy. Stepwise logistical regression analysis revealed visual loss and jaw claudication as the predictors of CVA.

Kerr and colleagues [20] summarized the clinical, laboratory and treatment responses of 60 patients with TAK based upon the presence of symptoms and signs of ischemic, inflammatory large-vessel disease as well as supportive arteriographic findings, noting ten (17%) patients with either transient ischemic attacks or CVA, and carotid or vertebral artery disease, eight of whom corresponded to the neurological deficit. One of the remaining two had hypertension, whereas the other patient had isolated stenosis of the innominate artery.

Riehl [21], and Riehl and Brown [22] reported the clinical and pathological features of six patients with TAK noting widespread arteritis that not only involved the aortic arch and its tributaries by clinical and angiographic studies, but many other medium-, and large-sizes vessels. One patient with TAK manifested clinical and histopathological evidence of CNS involvement. That patient, a 43-year-old woman who presented with rapidly disappearing blood pressure and complained of spells of progressively worsening dizziness and dimness of vision, died of severe congestive heart failure. At postmortem examination, there was severe stenosis of the distal aorta, thrombosis of an aortic arch graft with nearly complete obstruction of all the great vessels by granulomatous panarteritis, as well as vasculitic involvement of the proximal portion of the left MCA, both PCA arteries, and anterior third of the basilar artery. There was massive infarction of the left temporoparietal region, the left half of the midbrain, brain stem, and cerebellum.

PRIMARY MEDIUM VESSEL VASCULITIS

Polyarteritis nodosa (PAN) and Kawasaki disease (KD) are prototypical medium vessel vasculitides (MVV). Although any size of artery is affected in this category, PAN is associated with necrotizing arteritis of medium or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules; however, it is not associated with anti-neutrophilic cytoplasmic antibodies (ANCA) [1]. By contrast, KD is an infantile or childhood disorder that is associated with the mucocutaneous lymph node syndrome, predominantly affecting medium and small arteries, occasionally coronary, the aorta, and other large arteries [1].

Among early postmortem series of PAN, Middleton and McCarter [23] noted CNS involvement due to arteritic lesions in one (Patient 1) that consisted of an occasional small artery. Brain tissue was not examined in one patient (Patient 2) and was not mentioned in another (Patient 3). Kernohan and Woltman [24] summarized the clinicopathological aspects of adult PAN in six patients studied at postmortem examination, estimating CNS involvement associated with stroke in about 8% of cases, and a combination of acute and chronic lesions that correlated with known exacerbations. In three patients, the peripheral nervous system (PNS) was widely involved at onset and at postmortem examination in addition to systemic involvement typically sparing the CNS, while in one patient, the PNS and CNS was involved alone. That patient was a 32-year-old man with onset of left arm and leg hemisensory loss and headache that progressed to paralysis. At postmortem examination, there was marked thickening and near complete obliteration of the right MCA, less so on the left side, and obstruction of the right PCA by a recent thrombus, with a normal PCA on the left. Microscopic analysis showed subacute and chronic lesions of PAN.

According to Guillevin and co-workers [25], CNS involvement is rare but motor deficiencies, stroke and brain hemorrhages can occur as well as cognitive disturbances associated with abrupt memory loss and scattered T₂-weighted hyperintensities on brain MRI suggestive of cerebral vasculitis. CNS involvement including stroke was noted in 9.6% of 115 patients in the FVSG [26] with hepatitis B virus (HBV)-PAN between 1972 and 2002. The FVSG treatment protocol for HBV-PAN generally included cyclophosphamide, corticosteroids and plasma exchange (PE), alone or together, followed by vidarabine,

interferon-alpha (INF- α), or lamivudine, depending upon the time of diagnosis and different treatment protocols available [27-29]. So treated, nine patients (9.7%) who achieved remission subsequently relapsed, one of whom died of stroke, although the relationship between PAN and stroke was not clearly established. A retrospective study of 348 adult patients registered in the FVSG [30] who satisfied criteria for the diagnosis of PAN between 1963 and 2005 noted CNS involvement including stroke in 4.6% of patients overall, with a relatively equivalent frequency among patients with and without HBV-related illness.

PRIMARY SMALL VESSEL VASCULITIS

Small vessel vasculitis affects intraparenchymal arteries, arterioles, capillaries, and venules, however medium-sized vessels and veins are also be involved [1]. Two major categories of SVV include ANCA-associated vasculitis (AAV) characterized by necrotizing vasculitis with few or no immune complex (IC) deposits predominantly affecting small arteries, arterioles, capillaries, and venules associated with myeloperoxidase (MPO) ANCA or proteinase 3 (PR3). Marked vessel wall deposits of immunoglobulin (Ig) and complement characterize immune complex vasculitides. Granulomatosis with polyangiitis (GPA) (Wegener granulomatosis [WG] type), eosinophilic granulomatosis with polyangiitis (EGPA) [Churg-Strauss syndrome [CSS]], and microscopic polyangiitis (MPA) (microscopic polyarteritis) are prototypical AAV, while cryoglobulinemic vasculitis (CV), IgA vasculitis/Henoch-Schönlein purpura (IgAV/HSP), and hypocomplementemia urticarial vasculitis (HUV) associated with C1q antibodies comprise the IC vasculitides; HSP/IgAV is predominantly a disorder of childhood.

ANCA-ASSOCIATED VASCULITIS

Granulomatosis with Polyangiitis

GPA leads to necrotizing granulomatous inflammation of the upper and lower respiratory tracts associated with necrotizing vasculitis of small to medium arteries, arterioles, capillaries, veins, and venules together with glomerulonephritis [1]. Drachman [31] described a patient with one month of headache that awakened him from sleep followed by rhinitis, nasal obstruction, epistaxis, mononeuropathy multiplex, confusion and hypertension. Active arteritis and necrotizing granulomata were found in the brain but not in peripheral nerves. Based upon the observations in a single postmortem studied patient, cerebral involvement according to Drachman [31], depended upon a combination of four separate entities, 1) Frank vasculitis of larger arterial branches particularly over the surface of the brain as demonstrated in his patient report; 2) Ischemia in portions of the territory supplied by the affected vessels; 3) Subarachnoid hemorrhage and hypertensive encephalopathy evidenced by microscopic infarcts in close relation to arteries with fibrinoid impregnation of their walls; and 4) Meningeal infiltration by mononuclear cells. Nishino and colleagues [32] described neurological involvement in 34% of 324 consecutive patients with GPA at the Mayo Clinic between 1973 and 1991 classified according to the American College of Rheumatology

(ACR) [33] that included peripheral neuropathy in 16% compared to cerebrovascular events in 4% at some time in the course of illness, however rarely if ever at presentation. Of five patients with presumed clinical vasculitis, cerebral angiography was negative in two. Of twelve patients studied at postmortem examination, findings of vasculitis were found in only two. Fauci and colleagues [34] noted nervous system involvement in 22% of 85 patients, 10 patients (12%) of whom had CNS involvement including strokes at some point in the illness although not specifically mentioned at presentation. Moore and co-workers [35] estimated the frequency of neurological abnormalities of GPA at 23% to 50%, citing possible mechanisms of neural dysfunction due to inflammation from primary sites, remote granuloma formation, and vasculitis. Drachman [31] opinioned that contiguous extension of necrotizing granulomas might account for 24% of all neurological complications including those of the CNS.

Extensive cerebral infarction in the territory of the bilateral ACA was ascertained in a 67-year-old man with frontal headache that preceded detection of a large midline frontal mass lesion on computed tomography (CT), and known biopsy-proven GPA and granulomatous vasculitis of the nasal cavity, liver and kidney. Postmortem examination showed cerebral infarction in the areas supplied by A2 branches of both ACA, with occlusion of large sized ACA vessels by organized mural thrombi, and fibrinoid necrosis in the arterial branches. There was similar vasculitis with multinucleated giant cells involving small arteries and veins diffusely in the frontal region of the brain suggesting contiguous spread from granulomatous nasal cavity lesions. Hoffman and colleagues [36] retrospectively assessed 180 patients with GPA for 6 months to 24 years noting nervous system involvement in 23% of patients, including CNS involvement and stroke in 8% of patients. A prospective analysis of clinical, electrophysiologic, radiologic, and serologic data of 128 GPA patients over 19 months [37] noted CNS involvement in 7%, the latter including granulomatous infiltration of frontobasal cortex arising from adjacent paranasal sinus granulomas, cerebral vasculitis, stroke, vascular myelopathy, and meningeal granulomatosis.

Microscopic Polyangiitis

Microscopic polyangiitis is a necrotizing AAV vasculitis with few or no IC deposits and commonly associated glomerulonephritis without granulomatous inflammation [1]. Davson and colleagues [38] separated fourteen postmortem studied patients from 1934 to 1947 with MPA into two groups based upon the presence of severe widespread glomerular damage. Wainwright and Davson [39] described MPA among six post-mortem studied patients from 1947 to 1948, mentioned CNS involvement. However, neither paper [38, 39] recorded stroke or histopathologic evidence of brain involvement. Nor was there mention of patients with CNS involvement by Adu and co-workers [40] among 43 patients with renal histologic evidence of MPA. Savage and co-workers [41], who studied 34 patients with MPA, all of whom presented with clinical evidence of a systemic SVV predominantly affecting the skin and musculoskeletal system associated with focal necrotizing glomerulonephritis, cited CNS involvement at presentation in 18% of patients without specific mention of stroke. Serra and colleagues [42], who reported the presentation, histopathology and long-term outcome of 53 patients with MPO from 1965 to 1981, cited CNS involvement at presentation in 15% of patients, the findings of which included stroke, convulsions, headache, confusion and

drowsiness. Guillevin and co-workers [43] who reported the clinical and laboratory findings in 85 patients from the FVSG with MPA from 1969 to 1995, noted CNS involvement in 11.8% of patients at presentation and in 3% of 29 patients who experienced a relapse; however, there was no specific mention of stroke. Gayraud and co-workers [44] analyzed four prospective trials that included 278 patients with PAN, MPA and EGPA from 1980 to 1993, that reported stroke occurrence that accounted for 85 deaths. Villiger and Guillevin [45], who reviewed several retrospective European patient cohorts [40-43, 46], cited CNS involvement that included subarachnoid hemorrhage, cerebrovascular disease, meningitis and diffuse brain injury. Ben Sassi and colleagues [47] described intracerebral hemorrhage secondary to necrotizing vasculitis that similarly involved the nerves and muscles, citing three additional patients with hemorrhagic stroke due to MPA [48-50]. Ahn and colleagues [51] studied 55 patients with MPA, 69% of whom demonstrated perinuclear ANCA by immunofluorescence (IF) or MPO ANCA-seropositivity, noting CNS involvement in 5 (9.1%), none of whom developed end-stage renal disease. and one of whom died at follow-up without known autopsy.

Eosinophilic Granulomatosis with Polyangiitis

EGPA is a necrotizing vasculitis involving small to medium vessels that differs from GPA by the presence of eosinophil-rich necrotizing granulomatous inflammation of the respiratory tract in association with asthma and eosinophilia, and ANCA seropositivity when glomerulonephritis is present [1]. Churg and Strauss [52] described the clinical and postmortem findings of thirteen patients with asthma, fever, and hypereosinophilia. This was accompanied by eosinophilic exudation, fibrinoid change, and granulomatous proliferation that constituted the so called allergic granuloma. The latter were found within vessels walls and extravascular connective tissue of major organ systems. CNS organ manifestations were described in 8 (61.5%) of patients, and the cause of death in 3 patients who sustained cerebral hemorrhage or subarachnoid hemorrhage. Chumbley and co-workers [53] described 30 asthmatic patients from the Mayo Clinic over the period from 1950 to 1974 with necrotizing vasculitis of small arteries and veins, extravascular granulomas and infiltration of vessels and perivascular tissue eosinophilia. Lanham and colleagues [54], who emphasized that the combination of necrotizing vasculitis, tissue infiltration by eosinophils and extravascular granulomas suggested by Churg and Strauss [52] occurred contemporaneously in only a minority of patients, and that such histological findings could be encountered in other granulomatous, vasculitic and eosinophilic disorders in the absence of clinical asthma, allergic rhinitis, sinusitis, pulmonary infiltrates, and cardiac involvement pathognomonic of EGPA, noted CNS involvement in 25% of cases. Cerebral hemorrhage and infarction as a consequence of vasculitis or hypertension was a major cause of morbidity and mortality, accounting for 16% of deaths.

Sehgal and colleagues [55] noted neurological involvement among 14 patients with the clinical diagnosis of EGPA, three of whom had cerebral infarction two to fifteen years after initial diagnosis. The first patient was a 68-year-old woman with a stroke involving the territory of the MCA manifested as hemiparesis and aphasia. The second patient was a 34-year-old man with a right parietal lobe infarction pursuant to embolization of a left ventricular

thrombus, manifested incoordination and hemisensory loss of the arm. The third patient was a 62-year-old woman with a thalamic infarction who manifested hemibody sensory loss. Guillemin and co-workers [56] studied 96 patients with EGPA between 1963 and 1995, noting ischemic stroke onset in 6 (6%) by brain computed tomography (CT). Mouthon and colleagues [57], reported 38 patients with EGPA from 1978 to 1998, citing CNS involvement in 3 elderly patients (7.9%) in whom CNS vasculitis was suggested by MRI of the brain in only one patient. Among 383 patients with EGPA enrolled in the FVSG Cohort [58] employing the definition of the ACR [59], CNS involvement was noted in 20 (5.2%) of patients at onset, with two-fold greater frequency of ANCA-seropositive serology than those ANCA-seronegative, but no specific mention of stroke frequency.

IMMUNE COMPLEX VASCULITIS

Cryoglobulinemic Vasculitis

Cryoglobulinemic vasculitis (CV) or CryoVas is typified by cryoglobulinemic IC deposited along small vessels predominantly arterioles, capillaries, veins, and venules in association with serum cryoglobulins. In mixed cryoglobulinemia (MC), the immune complex is composed of IgM and polyclonal IgG with rheumatoid factor activity often in association with hepatitis C virus (HCV) infection. Disease manifestations of cryoglobulinemia was noted in 206 of 443 (47%) patients [60] that included palpable purpura, 12 (6%) of whom had CNS involvement; HCV Infection was the main etiologic factor noted overall in 75% of the 443 patients. A concomitant autoimmune disorder was noted in 24%, hematologic disease in 7%, and essential cryoglobulinemia in 11% of the patients overall. The original patient described by Lerner [61], a 56-year-old man who presented with chest pain, purpuric rash and a cold precipitating serum protein, did not have symptoms or postmortem findings referable to the nervous system. Marshall [62] noted widespread cerebral purpura with hemorrhage ascribed to occlusion of small blood vessels by eosinophilic protein precipitates that correlated with the clinical presentation of progressively fatal coma.

Abramsky and Slavin [63] described three patients with MC and CNS involvement. The first was a 55-year-old woman with anarthria, hyperreflexia, bilateral Babinski signs and progressively fatal coma, who was later found at postmortem to have multiple thrombotic occlusions of small intracerebral blood vessels with adjacent foci of ischemia and marked demyelination. The second patient was a 50-year-old woman, who presented with a Wallenberg syndrome and was found to have MC with occlusion of the left posterior inferior artery at angiography. The third patient, a 50-year-old woman who presented with right hemiparesis and pyramidal signs, was found to have a cryoprecipitate and occlusion of the left MCA.

Gorevic and colleagues [64] summarized the clinical aspects of long-term followup of 40 patients with MC noting incidental CNS involvement at postmortem examination and a fatal stroke in another patient. Petty and co-workers [65] described a 35-year-old woman with type II cryoglobulinemia, headache, purpura, and seizures who was found to have multiple areas of T₂ and proton density signal abnormalities in the cerebral and cerebellar hemispheres, with a

gyral pattern of enhancement in the cerebral cortex, a nodular pattern of enhancement in the cerebellum, and early cortical infarction on right frontal brain biopsy without vasculitis; cerebral angiography was normal. HCV RNA was detected by polymerase chain reaction (PCR). Ince and colleagues [66] described a patient with paranoid psychosis and MC who was found to have right basal ganglia hemorrhage and multifocal small vessel occlusions by amorphous bland protein plugs and abundant Russell bodies present in arterioles and venules with relative sparing of capillaries.

Stroke was the presenting feature of CNS involvement in MC among two patients with lacunar infarcts and associated subcortical white matter changes on brain MRI [67, 68], and in one patient with a temporal arteritis-like syndrome with associated ischemic cerebral infarction [69]. Cacoub and co-workers [70] compared the features of patients with HCV examined for systemic vasculitis manifestations of PAN or MC noting two patients with cerebral vasculitis in the former versus none in the latter. Cacoub and colleagues [68] described CNS involvement in three patients with HCV infection and MC, one of whom was found to have a hemorrhagic lesion of the external capsule in association with pontine T₂ hyperintensities and parietal lobe infarcts. A second patient had a hemorrhagic occipital lobe lesion in association with cerebellar infarction and abnormal periventricular hyperintensities. A third patient had abnormal white matter hyperintensities.

Ferri and colleagues [71] studied the demographic, clinical, serologic features and survival of 231 patients with MC seen between 1972 and 2001, noting widespread vasculitis involving small- to medium-sized arteries, capillaries and venules with two or more visceral organs including the kidney, gut, and lung, noting no CNS manifestations of MC with exception of focal dystonia during interferon treatment in one patient [71]. Filipini and colleagues [72] reported a 63-year-old woman with acute severe encephalopathy HCV-related MC, dysarthria and hemiplegia. Fragoso and co-workers [73] reported a 35-year-old woman with dysarthria, left facial and left limb hemiparesis and hemisensory loss with MC in whom MRI showed ischemic lesions in the tail of the right caudate nucleus, corona radiata and posteromedial putamen. Casato and co-workers [74] reported the CNS findings in 40 patients with HCV-related CV in a multicenter, case-control study using MRI and neuropsychological testing. Although none evidenced cerebral infarction, small white matter lesions were found in all HCV-related MC subjects, a higher mean number of white matter intensities compared to HCV and healthy controls.

Terrier and co-workers [75] analyzed the data of 242 patients registered in the CryoVas survey ascertaining CNS involvement in 5 (2%) patients without specifying whether stroke was encountered. Terrier and Cacoub [76] reviewed CNS findings in HCV-seronegative and seropositive MC in CryoVas noting 2 (0.7%) patients among the former with CNS involvement, compared to 9 (5%) patients in the latter group evidencing CNS involvement but without further mention as to presence of stroke in any of the patients.

Hypocomplementemic Urticarial Vasculitis/C1q

Hypocomplementemic urticarial vasculitis/C1q presents with recurrent attacks of erythematous, urticarial and hemorrhagic skin lesions lasting up to 24 hours at a time, associated with recurrent attacks of fever, joint swelling, and variable abdominal distress.

Circulating hypocomplementemia and C1q antibodies are associated with necrotizing SVV in skin biopsy tissue affecting arterioles, capillaries, and venules [1]. Apart from orbital pseudotumor with ptosis, diplopia, and headache in one patient with HUV syndrome, there was no mention of CNS involvement or stroke in a review of 18 patients with HUV/C1q [77]. Nor was stroke mentioned in a review of four patients studied at postmortem examination with HUV/C1q [78]. Buck and colleagues [79] cited rare CNS manifestations in HUV/C1q including aseptic meningitis, pseudotumor cerebri, transverse myelitis but no mention of stroke or cerebral vasculitis. Grotz and colleagues [80] did not mention stroke or CNS vasculitis in a case report and review of the literature of HUV/C1q. In a review of HUV/C1q, Davies and Brewer [81] cited CNS involvement as “very rare”, attributing development of pseudotumor cerebri to vasculitis of the venous sinus system. Ludivico and colleagues [82] suggested that chronic pseudotumor cerebri in their patients was a diagnosis of exclusion and possibly related to chronic corticosteroid use, but did not cite patients with cerebral vasculitis or stroke.

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Chapter 221

CENTRAL NERVOUS SYSTEM VASCULITIS DUE TO INFECTION

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ABSTRACT

A number of pathogens have the propensity to involve blood vessels during central nervous system infection which can lead to cerebrovascular complications. Infection is a recognized cause of secondary central nervous system vasculitis. It is very important not to miss the diagnosis of infection-related central nervous system vasculitis since specific antimicrobial therapy may be necessary; this chapter reviews the major implicated organisms.

INTRODUCTION

Vasculitis or angitis is defined as inflammation of blood vessels. Vasculitic involvement of large, medium and small caliber vessels respectively leads to arteritis, venulitis and capillaritis alone or in combination. Central nervous system (CNS) vasculitis typically affects blood vessels within the brain and rarely the spinal cord. It can also lead to a range of complications including ischemic infarction, intracerebral or subarachnoid hemorrhage,

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mycotic aneurysms, venous thrombosis, and transient ischemic attacks (TIA). Three suggestive clinical patterns are shown in Table 1 [1].

Table 1. Suggestive clinical presentations for CNS vasculitis*

● Encephalopathy with headache ● Intracranial mass lesion with headache and other abnormalities ● Atypical relapsing multiple sclerosis picture (with headache, seizures, encephalopathy, stroke-like features)

*Adapted from reference [1].

Infection is a recognized cause of secondary CNS vasculitis. In a series of 16 patients with CNS vasculitis not due to primary CNS angiitis, 12.5% of cases were attributed to infection [2]. The 2012 Revised Chapel Hill Consensus Conference (CHCC) Nomenclature considered infectious vasculitis as vasculitis associated with a probable etiology [3]. Infection can injure blood vessels in different ways. The pathogen may bind to or actually infect endothelium, or may trigger an adjacent immune or toxic response that indirectly affects vasculature. Blood vessel injury may reflect the sequela of direct infection, compressive inflammatory exudate, septic emboli, or formation of mycotic aneurysms. The infectious agents associated with CNS blood vessel disease are shown in Table 2.

BACTERIAL PATHOGENS

Acute Septic Meningitis

Acute septic bacterial meningitis is associated with vascular complications in 15% to 20% of patients [4]. Vascular complications typically occur early including days to weeks following initiation of antibiotic therapy. Invasive pneumococcal disease (IPD) is defined as a proven isolation of *Streptococcus (S.) pneumoniae* bacteria from normally sterile sites such as blood or cerebrospinal fluid. It remains a major cause of morbidity and mortality worldwide despite the availability of antibiotic therapy and vaccines. Host as well as bacterial factors contribute to IPD pathogenicity. Ethnicity, extremes of age, comorbidities and alcoholism are well-known host risk factors associated with increased susceptibility and higher mortality. Pneumococcal meningitis remains a potentially devastating disease with high mortality rate and neurological damage among those who survive. Focal neurological findings may be present during the acute phase of bacterial meningitis, but more often occur after a few days as immunological complication of meningitis. Case death rates and risk of sequelae following meningitis are higher for *S. pneumoniae* than *Neisseria meningitidis* or *Haemophilus influenza* infection.

The ensuing proinflammatory cascade triggered by *S. pneumoniae* and self-perpetuated by a dysregulated host inflammatory response, triggers mediators with vascular toxicity resulting in seizures, diffuse brain swelling, hydrocephalus, hearing loss and ischemic or hemorrhagic stroke. Arteries are involved more often than veins, and show narrowing on ultrasonography [5]. Ischemic complications result from vasculitis, vasospasm, associated endocarditis, or intra-arterial thrombosis [5].

Among 87 consecutive adult patients with pneumococcal meningitis, mortality was 24.1% [6]. Cerebrovascular arterial complications were seen in 21.8%, and venous complications in 10.3% of cases. Bacterial meningitis produces a subarachnoid inflammatory exudate that worsens over time, encasing large vessels at the base of the brain. Invasion of blood vessel walls by inflammatory cells leads to edema, focal stenosis and dilation, and intimal thickening. Large and medium vessels are typically involved in the Circle of Willis and along the terminal internal carotid artery (ICA), but the process can spread to involve smaller vessels as well. While vasculitis and vasospasm lead to cerebral ischemia and infarction however, disseminated intravascular coagulation may also supervene in the setting of septic meningitis and hypercoagulability, with activation of antifibrinolytic, proinflammatory, and procoagulant pathways. Pneumococcal meningitis was associated with cerebral venous thrombosis and carotid and vertebral artery dissection in one reported patient [7]. There are reports of late stroke with pneumococcal meningitis involving small penetrating arterioles [8].

Table 2. Infectious agents associated with CNS blood vessel disease

Bacterial Pathogens: ● Agents of Acute Septic Meningitis: <i>S. pneumoniae</i>, <i>N. meningitidis</i>, etc. ● Infective Endocarditis ● <i>Mycobacterium tuberculosis</i> ● Spirochetal Infections: <i>T. pallidum</i>, <i>B. burgdorferi</i>, and <i>Leptospiriosis</i> ● <i>Mycoplasma pneumonia</i> ● <i>Bartonella</i> ● <i>Tropheryma whippelii</i>
Viral Pathogens: ● Herpes Pathogens: VZV, CMV, HSV 1 and 2; EBV ● Retroviruses (HIV, HTLV-1) ● Hepatitis Agents: HBV, HCV ● Parvovirus B19 ● West Nile Virus ● Rare cases: Adenovirus, Echo/Coxsackie, Parainfluenza, Rubella
Fungal Pathogens: ● <i>Aspergillus</i> ● <i>Candida</i> ● <i>Coccidioides</i> ● <i>Cryptococcus</i> ● <i>Exserohilum rostratum</i> ● <i>Histoplasma capsulatum</i> ● <i>Mucormycosis</i>
Parasitic Pathogens: ● <i>Taenia solium</i> (Neurocysticercosis) ● <i>Plasmodium falciparum</i> (Malaria) ● <i>Schistosoma mansoni</i> ● <i>Toxoplasma gondii</i>
Rickettsial Pathogens: ● <i>Rickettsia rickettsiae</i> (RMSF) ● Scrub typhus

Abbreviations: VZV, Varicella zoster virus; CMV, cytomegalovirus; HSV, herpes simplex virus; EBV, Epstein Barr virus; HIV, human immunodeficiency virus; HTLV-1, human lymphotropic virus type 1; HBV, hepatitis B virus; HCV, hepatitis C virus; RMSF, Rocky Mountain Spotted Fever.

There can be delayed or chronic vasculopathy and progressive arterial stenosis consistent with late immune-mediated mechanisms, the hypercoagulable state, or rebound inflammatory effects [4, 8, 9]. Such patients are exceptional but may respond to corticosteroid therapy.

Infective Endocarditis

Infection of the endocardial inner lining of the heart can involve heart valves, mural endocardium, and septal defects [10]; valvular heart disease is a predisposing factor for infective endocarditis. The commonest site of valvular infection is the mitral followed by the aortic valve; the pulmonic valve is the least frequently involved. Mitral valve carries the highest risk for CNS emboli as noted in Table 2. Both sterile and infected emboli may occur as a result of endocarditis. CNS vasculitis is a concern in the setting of subacute rather than acute endocarditis. Both isolated angiitis of the central nervous system (IAN) and bacterial endocarditis may present with similar clinical and auxiliary findings.

Endocarditis is generally due to bacterial infection, although fungi, *Rickettsiae* and viruses are occasional agents [11]. The microorganisms most commonly implicated are *Staphylococcus (S.) aureus*, followed by *Streptococcus viridans*, coagulase-negative *Staphylococci*, other streptococci, and gram negative rod organisms [12]; *S. aureus* in particular infects endothelial cells. *Streptococcus bovis* is a rare cause of infective endocarditis in association with occult gastrointestinal tumors in up to 56% of cases [10]. Bacteremia associated with gingivitis due to *Haemophilus*, *Actinobacillus*, *Cardiobacterium*, *Eikenella* and *Kingella* (HACEK) organism with pneumonia or pyelonephritis, can infect sterile fibrin-platelet vegetation. Infection occurs with trivial everyday activities such as brushing of teeth, bowel movements, and invasive procedures such as dental extraction, prostate removal, endoscopy or colonoscopy, barium enema, and trans-esophageal echocardiography. Intravenous (IV) drug use is a risk factor for infectious-related endocarditis. Indwelling lines can be a source of bacteremia. Internal jugular lines are more likely to become infected than subclavian lines. Subacute endocarditis is not only associated with embolism, but it promotes the formation circulating immune complexes, cryoglobulins, agglutinating and complement-fixing bactericidal antibodies.

CNS complications occur in 20% to 40% of patients with infective endocarditis, the commonest of which is stroke due to septic embolism [11, 13, 14]. Clinically diagnosed intracranial mycotic aneurysms complicate 2% to 3% of infective endocarditis cases, although the postmortem rate is in the range of 5% to 10%. About 2% to 6% of all intracranial aneurysms are due to infection, tending to affect distal portions of secondary and tertiary branches of the middle cerebral artery (MCA).

The clinical features of neurologic involvement in endocarditis may initially be very subtle with nonspecific fever; headache, fatigue, and malaise are common. Abnormalities on physical examination suggestive of embolism include Janeway lesions, splinter hemorrhages, and Roth spots; multiple ischemic strokes may also be present. Rupture of resultant mycotic aneurysm can lead to acute catastrophic hemorrhage, the symptoms of which depend upon the location. Multiple microscopic emboli can lead to non-focal encephalopathy.

A recent analysis of neurologically asymptomatic patients with infective endocarditis [13] found that 71.5% of cases manifested occult brain magnetic resonance imaging (MRI)

abnormalities consisting mainly of multiple small infarcts in a watershed distribution, and cerebral microscopic hemorrhages within cortical regions.

Most affected patients demonstrate leukocytosis, elevated acute phase reactants, and positive blood cultures. Diffusion-weighted and gradient-echo MRI sequences are recommended to image the commonest findings in affected patients that include ischemia and hemorrhage. While brain computed tomographic angiography (CTA) and MR angiography (MRA) detect mycotic aneurysms measuring 3 mm to 4 mm or larger in size, digital subtraction angiography (DSA) remains the gold standard, but can be associated with serious complications.

The differentiation of infective endocarditis and primary cerebral vasculitis is extremely important [15]. Therapy of infective endocarditis includes both supportive care and medical interventions whereas cerebral vasculitis requires immunosuppression. Failure to accurately distinguish the two can result treatment failures and heightened morbidity and mortality. A comparison of the findings of six patients with biopsy-proven CNS vasculitis with the data of six patients with infective endocarditis showed that the former were generally younger (27-62 years) and presented with multiple strokes ($n = 4$), intracerebral hemorrhage ($n = 1$), epileptic seizures ($n = 2$), or encephalopathy ($n = 1$). All had pathologic cerebrospinal fluid (CSF) findings including pleocytosis ($n = 5$), protein elevation ($n = 4$), and angiography revealed multilobar stenoses in two cases while digital subtraction angiography was normal in four. Those with infective endocarditis were generally older (32-77 years) and presented with multiple ($n = 3$) or single ischemic strokes ($n = 2$) or encephalopathy and headache ($n = 2$). While all patients showed inflammatory serum findings (C-reactive protein $n = 6$, leukocytosis $n = 4$), CSF-pleocytosis was present in two cases only. Angiography revealed a vasculitic pattern in two patients. The diagnosis of BE was established based on transesophageal echocardiography and blood cultures. Leptomeningeal and brain biopsies performed in two cases were normal. Patients with either cerebral vasculitis or infective endocarditis may present with multiple strokes and encephalopathy. The frequency of a vasculitic pattern in angiography is similar in both conditions. While inflammatory serum findings are the rule in infective endocarditis, pathologic CSF findings were present in all of those with cerebral vasculitis. Transesophageal echocardiography and blood cultures should be performed in order to diagnose or exclude infective endocarditis in those at higher risk. Notwithstanding, immunosuppressive therapy may be dangerous in suspected cases of cerebral vasculitis without a confirmatory brain and leptomeningeal biopsy.

Mycobacteria

Mycobacterium (M.) tuberculosis (TB) meningitis was the first type of meningitis to be described clinically as *dropsy* of the brain in 1768, and subsequently shown to be inflammatory when meningeal tubercles and visceral tubercles were found to be identical in 1830. The tuberculoma, once the commonest intracranial tumor, is now exceptionally rare. The chief neurological signs and symptoms of tuberculous meningitis reflecting meningeal irritation are neck stiffness and positive Kernig sign; and raised intracranial pressure notably headache and vomiting with mental changes, seizures, and focal neurological signs. Arteritis is the rule in the vicinity of tuberculous lesions, wherein vessel walls are invaded by

mononuclear cells, with the adventitia more heavily involved than the media [16]. The subintimal and intimal regions form a layer of homogenous fibrinoid material that later involves the media, and the vessel lumen is reduced by inflammatory cell exudation beneath the fibrinoid material, the end results of which are reduction or complete obliteration of the lumen, proliferative endarteritis, and cerebral infarction. The vessels most heavily involved are those at the base of the brain and others in the Sylvian fissure. CNS involvement, which occurs in only 1% of TB infections, has the greatest mortality of any organ involvement], with fatality or severe residual mortality noted in up to one-half of cases of resultant TB meningitis [17]. Children and human immunodeficiency virus (HIV)-infected individuals are at special risk for developing CNS involvement. Polymorphisms in genes involved in the innate immune response such as the toll-like receptor 2 gene may influence dissemination and development of TB meningitis [17]. The pathogenesis of infection is usually due to rupture of a previously seeded meningeal, subpial, or subependymal focus. Chronic meningitis produces a thick, gelatinous inflammatory exudate that results in intimal thickening with obliterative vasculitis involving vessels at the base of the brain. Stroke occurs in 15% to 60% of affected patients and may be more common in HIV-infected individuals [4, 18]. Cerebral Infarction can be clinically silent, overshadowed by the meningeal features, or insidious in development. TB-related strokes show a predilection for the anterior rather than posterior circulation. The basilar exudates produce inflammatory vascular changes within the Circle of Willis. Distal ICA, proximal MCA and its perforating branches are particularly affected [17]. More severe meningitis carries a greater risk for vascular involvement. Vasospasm impacts strokes in the early period while proliferative intimal disease is a factor in later outcome. The immune reconstitution inflammatory syndrome (IRIS) can supervene during treatment for extraneural TB, unmasking latent TB meningitis and presenting with neurologic features including stroke. Hydrocephalus is a common sequela with often associated meningeal enhancement particularly along basal brain regions. Contrast-enhanced MRA is more sensitive in the detection of small vessel involvement. Pathologically-proven TB-associated CNS vasculitis has been described in five heterogeneous patients to date [16].

The diagnosis is confirmed by detection of TB bacilli in CSF using a Ziehl-Neelsen stain and culture, as well as a positive polymerase chain reaction (PCR). A positive yield is increased with large sample volumes, and ventricular CSF demonstrating an even higher yield than lumbar CSF. Interferon (INF)- γ releasing assays and TB antigen analysis can be studied in CSF [20]. Neuroimaging features of basilar exudate and hydrocephalus are suggestive.

Treatment involves induction therapy for two months with isoniazid, rifampin, pyrazinamide, and a fourth drug either streptomycin or ethambutol, followed by maintenance therapy with two drugs for an additional seven to ten months, typically isoniazid and rifampin. Fluoroquinolones are used in multidrug resistant cases. Adjunctive corticosteroids may be warranted in the first six to eight weeks. Aspirin is potentially useful in reducing stroke and mortality [20].

Spirochetal Agents

Spirochetes, which have a propensity to cause vasculopathy, can be associated with CNS vascular disease.

Syphilis

Syphilis is a spirochetal infection due to *Treponema (T.) pallidum*. Infection is acquired or congenital, with an estimated worldwide annual incidence of 12 million new adult cases [21]. About 4% to 10% of untreated patients develop CNS involvement. Symptomatic neurosyphilis presents with meningitis and meningovascular syndromes. Meningitis occurs in the first year of infection, producing basilar meningitis often culminating in stroke and vasculitis. Meningovascular syphilis comprises 39 to 61% of all symptomatic cases of neurosyphilis. It is characterized by obliterative endarteritis that affects blood vessels of the brain, spinal cord and leptomeninges, precipitating substantial ischemic injury. Often referred to as Heubner arteritis, it involves medium-sized to large arteries with lymphoplasmacytic intimal inflammation and fibrosis however there is a variant form termed Nissl-Alzheimer arteritis that characteristically affects small vessels and produces both adventitial and intimal thickening. Both types can lead to vascular thrombotic occlusions and cerebral infarction, with preferential involvement of the MCA

Meningovascular syphilis occurs months to years later associated with perivascular inflammatory endarteritis that leads to luminal narrowing and rarely dilatation. It typically involves large and medium-sized intracranial vessels, in particular the MCA, as may small intracranial vessels, altogether comprising 15% to 23% of cases [4].

Patients may experience prodromal symptoms of headache, vertigo, insomnia, and behavioral changes. Stroke symptoms developed in a subacute progressive pattern in one-quarter of patients. A recent Australian series [21] noted a prevalence of 4% for stroke or TIA among those with seropositive meningovascular syphilis.

The affected supraclinoid ICA and proximal vessels of the Circle of Willis show smooth or beaded segmental narrowing on neuroimaging, without common or cavernous ICA involvement atypical for atherosclerotic disease. Amorphous proteinaceous firm masses with a necrotic center surrounded by inflammatory tissue termed gumma are noted in the brain of patients with tertiary syphilis and meningovascular disease.

The fluorescent *Treponemal* antibody (FTA-Abs), which detects specific *T. pallidum* antibodies later in the course of the disease, can be used to confirm the results of plasma reagin (RPR) and Venereal Disease Research Laboratory (VDRL) tests which register reactivity to cardiolipin-lecithin-cholesterol antigen elaborated early in the course of syphilis exposure. The CSF in affected patients with neurosyphilis demonstrates pleocytosis, reactive VDRL, and increased intrathecal *T. pallidum* antibody index. All patients should be checked for HIV infection. Treatment of neurosyphilis is IV penicillin for 10 to 14 days with CSF monitoring in HIV-positive individuals to document normalization. Aspirin 81mg daily can be added for stroke prophylaxis.

The search for the cause of stroke in young adults should include meningovascular syphilis as a potential etiology. Sudden acute severe headache heralded onset of occlusion of bilateral vertebral and proximal basilar artery documented by MRA was noted in an African man who responded to thrombectomy with restoration of blood flow but succumbed to fatal pontine and subarachnoid hemorrhages [22]. Postmortem examination revealed RPR and a positive VDRL test in CSF with CNS vasculitis characterized by mural thrombi along the vertebrobasilar arteries with well-defined lines of Zahn of alternating layers of fibrin, platelet and red blood cell aggregates, and inflammatory cell infiltration of the arterial walls particularly in the adventitia. Another patient with abrupt onset of confusion, aphasia, and hemiparesis had carotid angiography that documented normal named cerebral vessels except

for smaller than average caliber, with an abnormal complement fixation test of the blood and CSF, positive colloidal gold curve test, and leptomeningeal biopsy that showed lymphocytic infiltration, focal fibrosis, and chronic perivascularitis consistent with meningovascular syphilis [23].

Lyme Neuroborreliosis

The term Lyme neuroborreliosis was introduced by Veenendaal-Hilbers and colleagues [24] in 1988 to emphasize that CNS involvement due to Lyme disease. *Borrelia (B.) burgdorferi sensu lato* is the spirochete responsible for Lyme disease. *B. burgdorferi sensu stricto*, hereafter referred to as *B. burgdorferi*, is the species agent that causes Lyme disease and its neurological complications in North America; *B. garinii* and *afzelii* species predominate outside of North America. Virtually all cases result from an infected *Ixodes* tick bite. Lyme disease is a systemic infection with most patients manifesting the prototypical expanding skin lesion at the bite site termed erythema migrans. Both the CNS and peripheral nervous system (PNS) are targeted body organs. CNS vasculitis while exceedingly uncommon, probably accounted for less than 1% of all Lyme disease cases in endemic area. Patients with Lyme neuroborreliosis may present with cerebral infarction, intracerebral or subarachnoid hemorrhage, and TIA [25-30].

Only three patients reported in the literature with neurovascular clinical syndromes ascribed to CNS vasculitis in which detailed information was available including documentation of positive CSF Lyme serology, were ultimately found to have verifiable vasculitis [28-30]. Two patients [28] presented with headache were ultimately noted to have histopathologically confirmed vasculitis on brain biopsy. Patient 3 of Oksi and colleagues [28] was an 11-year-old boy with headache and hyperactivity syndrome who developed gait difficulty concomitantly with a stroke visualized on brain MRI. Subsequent craniotomy and biopsy of the area of enhancement disclosed lymphocytic vasculitis of small vessels without fibrinoid necrosis, and CSF *B. burgdorferi* serology was positive. Headache and the MRI improved with intravenous antimicrobial therapy. Patient 2 of Topakian and coworkers [29] presented with headache, fatigue, malaise, nausea and vomiting first considered migrainous then psychosomatic until subsequent MRI disclosed ischemic brain infarctions, MRA was compatible with diffuse vasculitis, and CSF showed lymphocytic pleocytosis with positive oligoclonal bands, and diagnostic CSF and serum *B. burgdorferi* serology. Brain biopsy showed vasculitis involving leptomeningeal arteries comprised of lymphoplasmacytic vessel wall infiltration with focal necrosis. Epithelioid cells were beaded in multiple granuloma-like formations in the leptomeninges. There was symptomatic improvement after a course of intravenous antimicrobial therapy. The third patient reported by Miklossy and colleagues [30], a 50-year-old man with leg spasticity and CSF pleocytosis for 15 months who progressed to hemiparesis and ventilatory support, was later found to have diagnostic *B. burgdorferi* serology in serum and CSF. Postmortem examination showed perivascular lymphocytic inflammation of leptomeningeal vessels, some of which displayed infiltration of the vessel walls, duplication of the elastic lamina, narrowing of lumina, and complete obstruction of some leptomeningeal vessels by organized thrombi.

There are rare instances of cerebral venous sinus thrombosis. *B. burgdorferi* infection in the CNS may be associated with lymphocytic cerebral vasculitis [31] preceding clues of which include, headache, arthralgia, myalgia, peripheral facial nerve palsy, and flu-like illness during the summer months. Laboratory evaluation may demonstrate meningeal enhancement

on brain MRI although there appears to be a propensity of vasculitis to involve the posterior circulation. Lumbar CSF analysis typically reveals pleocytosis, increased protein, and intrathecal Lyme antibody production. CNS vasculitis due to Lyme neuroborreliosis should be treated with IV ceftriaxone 2 grams daily for four weeks via midline or permanent intravenous catheter (PIC) line with daily acidophilus to lower risk of *Clostridium difficile* colitis.

Leptospirosis

Leptospirosis is a worldwide zoonotic infection due to a spirochete from the genus *Leptospira*. It is transmitted by the urine of infected animals, and to people exposed to the pathogenic organism through contact with contaminated water, blood or soil. Infection is biphasic, with flu-like symptoms, followed by a second immune phase that can involve meningitis, jaundice with liver injury, and renal failure. Infection can be asymptomatic. About 90% of symptomatic infections manifest a benign biphasic febrile illness with 10% involving icteric Weil disease, and a fatality rate of 10%. Spirochetes are found in blood and CSF early in the course of the illness, and in the urine later in the disease. Leptospirosis more commonly causes meningitis or meningoencephalitis. Clinically apparent CNS vascular involvement is unusual but can result in stroke, hemorrhage and venous sinus thrombosis [32-34]. Diagnostic tests include screening serology via enzyme linked immunosorbant assay (ELISA), microscopic agglutination test, and polymerase chain reaction (PCR). Vasculitis is a recognized feature of this infection involving capillaries, with consequent edema, necrosis, and lymphocytic infiltration. Therapy involves primarily doxycycline however other effective antibiotics include cefotaxime, penicillin, ampicillin, and amoxicillin.

Relapsing Fever

Relapsing fever is spread by tick or lice bites. Louse-borne relapsing fever is due to *Borrelia recurrentis*. Tick-borne relapsing fever is due to at least 15 different *Borrelia* species. Clinical illness is characterized by febrile episodes accompanied by prominent headache and myalgia. Neurologic involvement is characterized by meningitis, facial palsy, myelitis, radiculitis, and focal or diffuse CNS dysfunction [35]. Neuropathologic changes involve edema, subarachnoid, and parenchymal hemorrhage, with perivascular mononuclear infiltrates. Spirochetes can be found in the cerebral microvasculature and interstitial spaces. Diagnosis is based on culture and stain. Treatment includes administration of doxycycline, oxytetracycline, or cephalosporin.

Other Bacterial Agents

Mycoplasma

Mycoplasmas are very small bacteria that have a plasma membrane boundary, but lack a cell wall. The nervous system is a major extrapulmonary target, and neurologic disease can occur after primary atypical pneumonia or *de novo* [36]. Mycoplasma encephalitis reflects direct brain invasion or an immune-mediated syndrome. There is evidence for vascular injury and microthrombi, with endothelial cell infection [36, 37]. Stroke occurs in both children and adults [38]. Diagnosis is based on serology and PCR when positive. Therapy involves a

course of macrolide antibiotics, although neurologic involvement may be post-infectious and immune-mediated. Anticoagulation can be considered for thrombotic disease [].

Rosales and colleagues [38] described isolation of *Mycoplasma gallisepticum* and *synoviae* from the brains of poultry showing meningeal vasculitis and encephalitis, postulating a role for invasive mycoplasma species in human across the blood-brain barrier (BBB).

Bartonella

Bartonella are facultative gram negative intracellular bacteria that cause human and zoonotic disease. *Bartonella henselae* causes cat scratch disease. Several *Bartonella* species are associated with neuroretinitis, a retinal vasculitis. Immunocompromised hosts are vulnerable to more severe infections. *Bartonella* species can produce cutaneous and systemic vasoproliferative lesions [39]. *Bartonella henselae* is known to invade and colonize vascular endothelial cells, among others. Among a broad neurologic spectrum, there are rare cases of ischemic stroke and cerebral arteritis. Diagnosis is based on serology and PCR. Therapy involves doxycycline, or azithromycin.

Balakrishnan and colleagues [40] described isolation of *Bartonella henselae* DNA by PCR from a 12 year old's brain and blood with headaches, visual and auditory hallucinations, anxiety, vision loss, bouts of paralysis, facial palsy, chronic insomnia, seizures, dizziness, cognitive dysfunction, and memory loss resulting in cerebral infarction so noted on brain biopsy tissue, postulating cerebral vasculitis, however frank vasculitic lesions were not observed.

Tropheryma whippelii

Tropheryma (T.) whippelii, a member of gram positive Actinobacteria family, is the etiologic agent of Whipple disease is the soil-borne gram positive bacillus. CNS involvement, which occurs in up to 43% of cases, may be the initial presentation of infection in 5% of cases [41]. CNS involvement occurs in the setting of active Whipple disease, as well as in those relapsing previously treated disease, and isolated CNS involvement [42]. Stroke presentation, while very rare, has been described [43] and should be in the differential diagnosis of CNS vasculitis. Stroke also occurs with leptomenigeal arterial fibrosis and thrombosis, or associated with endocarditis [41]. Clues to diagnosis are extraneural disease including weight loss, fever, polyarthritis, diarrhea, and uveitis. Oculomasticatory myorhythmia and supranuclear gaze palsy are characteristic neurologic features. The diagnosis can be confirmed with PCR and tissue biopsy that reveals macrophages that stain positive for glycogen with the Periodic Acid Schiff (PAS) assay, or the identification of the causative organism by immunoreactive antigen. Effective treatment includes administration third generation cephalosporins followed by long-term, on average two years of trimethoprim-sulfamethoxazole (TMP-SMZ) and doxycycline.

Famularo and colleagues [44] identified arterial and arteriolar fibrosis, thrombosis, and thickening associated with inflammation of adjacent brain parenchyma and leptomeninges and cerebral vasculitis in a patient with cerebral Whipple's disease and stroke syndrome of without gastrointestinal involvement due to hematogenous spread of *Tropheryma whippelii*.

VIRAL PATHOGENS

Herpes Viruses

Herpes viruses are a large family of enveloped DNA viruses. Nine distinct agents affect humans, and all result in lifelong latent infection.

Varicella Zoster Virus

Varicella zoster virus (VZV) is the cause of childhood chickenpox and most children manifest only mild neurologic sequela, and an important infectious agent of associated blood vessel disease. After the infection resolves, the virus becomes latent in neurons of cranial and spinal ganglia of nearly all individuals, and has the propensity to reactivate in elderly adults and immunocompromised individuals to produce shingles. An uncommon but serious complication of virus reactivation is ischemic and hemorrhagic stroke. VZV vasculopathy affects both immunocompetent and immunocompromised individuals typically presenting with headache and mental status changes with or without focal neurological deficits and a spectrum of vascular damage from vasculopathy to vasculitis with stroke. Both large and small vessels can be involved and MRI shows multifocal ischemic lesions, commonly at gray-white matter junctions. The diagnosis of VZV can be missed when symptoms and signs occur months after zoster, or in the absence of a typical zoster rash.

It is the only virus documented to replicate in human arteries, and is a recognized risk factor for ischemic stroke in children, and stroke and TIA in adults under age 40 [45, 46]. It is latent in cranial nerve, dorsal root, and autonomic nervous system ganglia. VZV but when reactivated, spreads to arteries of the brain and spinal cord to produce a large and small vessel vasculopathy. Cerebral blood vessels show multinucleated giant cells, Cowdry type A inclusion bodies with viral particles, and detectable VZV antigens and DNA, consistent with direct infection. In one series of 30 patients [7], 50% had both large and small vessel involvement; 37% showed small artery involvement and 13% manifested large artery invasion [47]. Clinical sequela includes infarction, aneurysm, hemorrhage, and ICA dissection [48]. Recently, VZV vasculopathy was recognized as an etiologic agent in patients presenting with giant cell arteritis (GCA) in spite of non-informative temporal artery biopsy. Vascular involvement can be unifocal or multifocal. Both immunocompetent and immunocompromised hosts are affected, although more commonly it is the immunocompromised patient. Infarctions can be superficial or deep. Gray-white matter junction lesions are suggestive. With regard to primary infection, there are unusual cases of cerebral infarction or hemorrhage in children. With regard to reactivated infection, vasculopathy can occur up to 6 months after a zoster outbreak. Herpes zoster ophthalmicus (HZO) can be followed weeks later by delayed contralateral hemiparesis, with segmental carotid siphon arteritis, typically in immunocompetent individuals.

Small vessel involvement may lead to central retinal or posterior ciliary artery involvement, with monocular vision loss. Neuroimaging in these VZV cases is typically abnormal. CSF is often abnormal with an increase in WBC and RBC, raised CSF protein content and present oligoclonal bands. The CSF VZV IgG antibody should be measured along with a sample for PCR analysis however the former is more likely to be informative in true cases. CNS VZV vasculopathy often presents with headache and progressive neurologic

deficits without a history of zoster rash; rarely is VZV associated with spinal cord infarction. Treatment involves antiviral therapy with IV acyclovir however oral valcyclovir can be employed to extend the length of treatment in more profoundly affected or refractory cases due to concomitant HIV-infection.

Thirteen patients with VZV-related vasculopathy with detailed clinicopathologic data including histological findings of vasculitis have been described in the literature. VZV DNA and VZV-specific antigen were found in three of five cerebral arteries examined with histologically-confirmed CNS vasculitis involving the circle of Willis. Patient 1 of Eidelberg and colleagues [49] who presented with headache and herpes zoster ophthalmicus (HZO) rash was deemed to have CNS vasculitis based upon complete occlusion of the MCA and so treated, however postmortem examination showed no evidence of vasculitis. One patient with contralateral hemiplegia one month after HZO was found at postmortem examination to have endarteritis of unilateral ACA, MCA and PCA [50] with VZV DNA from the involved vessels.

Cytomegalovirus

Cytomegalovirus (CMV) replicates in leukocytes and vascular endothelial cells during primary infection with single patient reports of CMV associated with vasculitis. Venous involvement can be found in addition to occlusive arteritis. Affected individuals are usually HIV-positive or an immunocompromised host [51]. Diagnosis involves serological studies, PCR, culture, and histopathological tissue analysis for the causative organism. Therapy includes IV ganciclovir, foscarnet, or a combination of both. One recently described elderly woman with CMV encephalitis [52] later developed a post-infectious primary CNS vasculitis.

Koeppen and coworkers [53] described rapidly progressive CNS and peripheral nervous system (PNS) deterioration two years after chemotherapy for small cell undifferentiated lymphoma in whom postmortem examination demonstrated occlusive arteritis in gray and white matter with involvement of veins indicative of vasculitis, in addition to Cowdry A inclusions and chorioretinitis.

Herpes Simplex and Epstein-Barr Virus

Herpes simplex virus (HSV), types 1 and 2, and *Epstein Barr virus* (EBV) have been associated with CNS vasculitis [54, 55], however vessel wall contrast enhancement may be a clue in suspected patients [55] and a positive findings in CSF PCR is adequate to justify antiviral therapy. However, in contrast to VZV where reactivation is the mechanism of causation, CNS vasculitis may be problematic due to latency of infection. Kano and colleagues [56] described EBV-associated CNS vasculitis in brain biopsy tissue of a patient with rapid CNS deterioration and positive EBV DNA in CSF.

Retroviruses

Human Immunodeficiency Virus

Approximately 1% to 5% of individuals infected with human immunodeficiency virus (HIV) are at risk of developing a stroke due to opportunistic infections, coagulopathy, cardioembolism, HIV-associated vasculopathy and frank vasculitis [57]. Moreover, HIV-

associated arterial vasculitis is believed to account for 13% to 28% of ischemic strokes. CNS vasculitis which is estimated to occur in less than 1% of cases of HIV infection is a diagnosis of exclusion. Typically patients are in an advanced stage of the infection. HIV can be associated with a granulomatous inflammation involving small arteries and veins within the brain and leptomeninges. HIV patients with vasculitis should be assessed for cryoglobulins and accompanying infection especially TB, syphilis, CMV, VZV, hepatitis B and C virus (HBV and HCV), or a drug induced vasculitis. Therapy typically involves highly active antiretroviral therapy (HAART), with corticosteroids reserved for refractory cases due to vasculitis.

Early in the HIV and the acquired immune deficiency syndrome (AIDS) epidemic, it was clear that a significant proportion of infected persons were intravenous drug users. Their associated risk behavior exposed them to infection through sharing of contaminated needles thereby increasing the risk of spread of HIV and other blood borne infections. The two postulated periods in the neurobiology of HIV when autoimmune disease manifestations and cerebral vasculitis can occur are shortly after seroconversion and before the spread of productive infection, and after initiation of HAART in association with the immune reconstitution inflammatory syndrome (IRIS). The timing of early HIV invasion has been difficult to ascertain based on the presence of one or well-recognized clinicopathological HIV/AIDS syndromes including HIV encephalitis, HIV-associated dementia and AIDS-dementia complex, all of which are indicative of symptomatic infection. Six presymptomatic HIV-seropositive drug abusers by Gray and colleagues [58] had non-necrotizing cerebral vasculitis at postmortem examination.

HTLV-1

Human T-cell lymphotropic virus-type 1 (HTLV-1) was the first described human retrovirus. It causes adult T-cell leukemia and lymphoma, as well as a progressive myelopathy referred to as tropical spastic paraparesis-HTLV-1 associated myelopathy in less than 1% of infections. Neurological syndromes associated with HTLV-1 infection appear to be due to active and selective expansion of retrovirus infected T-cells that harbor provirus that selectively express HTLV-1 proteins such as Tax. In particular, activated cytotoxic CD8⁺ T cells are increased. Perivascular inflammation is a frequent histopathological feature. The laboratory diagnosis of HTLV-1 infection is based on serological and PCR studies. There is no proven antiviral therapy. Ma and coworkers [59] reported vasculitis in brain biopsy tissue of a patient with HTLV-1 infection.

Hepatitis Agents

Hepatitis C is estimated to affect 170 million people worldwide with extrahepatic involvement that occurs in 38% to 74% of cases. Hepatitis C is associated with cryoglobulinemia, arthritis, and palpable purpura. There is an immune response to the Fc portion of immunoglobulin, characterized by the Wa idiotype. The resulting immune complex which contains virus, idiotypic antibody, and antibody precipitates in the cold and produces a small vessel vasculitis. HCV can cause CNS vasculitis independent of cryoglobulinemia, and CNS vasculitis may be the first clinical manifestation of hepatitis C infection.

Affected patients present with progressive headache, multiple strokes, and typical angiographic patterns. Therapy includes the antiviral agents interferon (IFN), ribavirin, sofosbuvir, protease inhibitors, and corticosteroids. Both HBV and HCV have been associated with polyarteritis nodosa (PAN) [60] that typically involves the peripheral nervous system (PNS), but unusual cases may involve the CNS. In such cases antiviral therapy is added to corticosteroids, and cyclophosphamide in more severe cases. This might involve the virostatic agent lamivudine or INF-alpha for HBV and ribavirin for HCV [61]. Plasma exchange and rituximab can be added in specific cases as needed.

Parvovirus B19

Parvovirus B19 is a small non-enveloped DNA virus that only infects humans. It causes erythema infectiosum also known as fifth disease, a benign childhood condition characterized by a classic slapped-cheek appearance. It can cause anemia with pre-existing disease as well as arthritis. The cellular receptor for parvovirus B19 is an antigen of the P blood group present on endothelial cells and erythroid progenitor cells. Rare patients with CNS vasculitis have been reported in association with Parvovirus B19 infection [62]. The diagnosis is based on serological studies and PCR testing. There is no specific antiviral therapy for Parvovirus B19 infection; however both intravenous immune globulin (IVIG) and corticosteroids have been used therapeutically.

West Nile Virus

West Nile virus is a flavivirus typically transmitted by the bite of infected culex mosquitos. Less than 1% of patients develop invasive neurological disease that includes meningitis, encephalitis, and resultant flaccid paralysis, with rarely reported cases of ischemic infarction and CNS vasculitis [63-65] and occlusive retinal artery vasculitis. Patients with a history of diabetes and alcohol abuse, and older individuals are at increased risk for ischemic complications. Diagnosis is based on IgM antibody and viral RNA detection, as well as virus isolation. There is no antiviral therapy, but IVIG has been beneficial in individual patients.

Zika Virus

Zika virus is an arbovirus belonging to the *Flaviviridae* family. Younger has reviewed the epidemiology of Zika virus [66]. Originally isolated in Uganda, known to cause mild clinical symptoms similar to those of dengue and chikungunya, Zika is transmitted by different species of *Aedes* mosquitoes. Non-human primates and possibly rodents play a role as reservoir. Direct interhuman transmission has been reported to occur perinatal, through blood transfusion and sexually. The first human cases were reported in Africa and, but recent outbreaks in several regions of the world including including Brazil, highlighted the needs of the scientific and public health community to consider it as an emerging global threat.

Its clinical profile is that of a dengue-like febrile illness but recently associated Guillain-Barre syndrome and microcephaly have appeared. There is neither a vaccine nor prophylactic medications available to prevent Zika virus infection so current public health recommendation advise pregnant women to postpone travel to areas with Zika viral infection is epidemic, and if not, to follow steps to avoid mosquito bites to avert fetal brain injury associated with intrauterine infection. Viral RNA indicating Zika virus, Chikungunya virus, and Dengue infection can be pathogenically isolated from the CSF of adults with neurological symptoms with meningitis or encephalitis, Guillain-Barré Syndrome, and CNS vasculitis.

FUNGAL PATHOGENS

Aspergillus

Aspergillosis is the most common invasive mold infection worldwide. It typically causes disease in immunocompromised hosts, although CNS vasculitis and stroke occur in immunocompetent patients [67, 68]. The major human pathogens are from the *Aspergillus fumigatus*, *niger* and *flavus* species. Patients with hematologic malignancies and a history of bone marrow transplantation can have fulminant CNS courses with mortality rates of 85% to 99% [4].

The *Aspergillus* organisms invade blood vessels with resultant production of proteases that weaken the vessel wall leading to aneurysm formation [69]. The course can be more chronic and insidious in those with lesser degrees of immune compromise, such as due to diabetes mellitus. Spread to the CNS occurs via hematogenous routes from the lung, or by direct extension through the paranasal sinuses and orbits. CNS involvement which occurs in 10% to 50% of systemic infections includes meningoencephalitis and intracerebral hemorrhage, as well as, vasculopathy, and mycotic aneurysm formation leading respectively to stroke and potentially fatal subarachnoid hemorrhage with greater involvement of penetrating than larger named vessels.

Aspergillus infection should be considered in immunocompromised hosts with pulmonary disease and either ischemic or hemorrhagic stroke. The diagnosis can be difficult since CSF cultures are positive in less than 50% of cases, and PCR is investigational. Two antigen assays, each for biomarkers including galactomannan and beta-D-glucan, have not been standardized in the CSF. Tissue biopsy can be confirmatory. Brain neuroimaging may demonstrate ring-enhancing lesions, meningeal enhancement, and ischemic or hemorrhagic stroke. Therapy involves oral voriconazole and surgical resection of focal cerebral and extraneural sites of involvement.

Candida

Candida species are part of normal human flora and thus typically are not pathogenic unless there is mitigating systemic immune compromise. Neutropenia is a major risk factor for invasive disease. *Candida* is considered a yeast infection with *Candida albicans* the most common agent in humans. It invades small blood vessels and can be associated with

thrombosis and infarction. Neurologic involvement most often takes the form of meningitis that may predispose to basilar artery thrombosis [70]. One affected patient with HIV/acquired immune deficiency virus syndrome (AIDS) and subacute meningitis who was treated empirically for tuberculosis and initiated on HAART therapy developed fatal worsening due to postmortem-proven basilar *Candida* meningitis and cerebral vasculitis characterized by CD8+ T-cell infiltration and microinfarcts, consistent with IRIS [77]. The diagnosis of *Candida* infection is based on a positive culture and informative PCR, and suggestive findings on antigen assays to mannan and beta-D glucan albeit not routinely performed. Effective treatment depends upon the age and severity of infection with lipid formulations of amphotericin, fluconazole, or echinocandin.

Lipton and colleagues [71] described CNS vasculitis at postmortem examination in 48% of 29 patients with systemic candidiasis, only 21% of whom had suspected antemortem involvement noting that immunosuppression represent a risk factor for both systemic and cerebral mycoses.

Coccidioides immitis

Coccidioides immitis is a soil based fungus endemic to the arid Southwest and Latin America. Infection may be asymptomatic or the cause of mild pulmonary issues such as occurs in valley fever. About one-half of disseminating cases involve the CNS resulting in basilar meningitis with a local vasculitis of small and medium arteries, and occasionally larger ones that is more likely to occur in immunocompromised hosts [72]. Cerebral infarction complicates about 40% of patients with *coccidioides* meningitis leading to alteration of mental status and emergency of focal deficits [4]. Stroke can occur years later following the initial infection [72]. In general, acute infectious related injury can predispose to vasculitic changes that include transmural inflammation with thrombosis and fibrinoid necrosis, while chronic injury leads to intimal thickening, proliferation, and narrowing of the lumen with little or no inflammation.

CSF culture is positive in 33% of cases, often in association with eosinophilic pleocytosis. Complement fixation is positive in about 40% of serum and CSF specimens, but seroconversion can take up to 12 weeks. Treatment involves high-dose fluconazole followed by maintenance therapy. Voriconazole is a second line agent. A self-limited course of corticosteroids can be given in the setting of cerebral infarction to reduce inflammation.

Eron and colleagues [73] described vasculitis and encephalitic as a complications of *Coccidioides immitis* infection of the CNS in six cases of apparent, and four cases of histologically proven vasculitis, including one with vasculitis and encephalitis associated with coccidioidal meningitis. Vasculitic complications includes mental status changes, aphasia, hemianopia, and hemiparesis.

Cryptococcus neoformans

The yeast form, *Cryptococcus neoformans* is the commonest cause of fungal meningitis [4]. Vessels of the circle of Willis are most affected by the resultant basilar exudate. Vascular involvement occurs early or late in 4% to 32% of cases. Diagnosis is made by the presence of CSF cryptococcal antigen, India ink stain, and culture. Treatment involves induction therapy with intravenous amphotericin and flucytosine for 2 weeks followed by consolidation with fluconazole once CSF cultures are negative. Corticosteroids may offer a benefit in the setting of stroke [74].

Exserohilum rostratum

Exserohilum rostratum is a dematiaceous fungus and black mold that does not typically cause human disease. It is a major contaminant in iatrogenic infections due to mold contamination of methylprednisolone acetate. There was one fatal case of meningitis and CNS vasculitis in an immunocompetent host who received a cervical epidural steroid injection for chronic neck pain [80]. The diagnosis is based on culture and PCR of CSF. Recommended therapy is liposomal amphotericin B and voriconazole, with monitoring of drug levels [75].

Lyons and colleagues [76] described angioinvasive septate fungal hyphae associated with diffuse vasculitis at postmortem examination in the brainstem of a patient with fatal *Exserohilum* meningitis following cervical epidural methylprednisolone injection for new occipital headaches.

Histoplasma capsulatum

Histoplasma capsulatum is a dimorphic fungus that is endemic in the Ohio and Mississippi River Valley, as well as parts of Latin America, Asia, and Africa [4, 77]. Although infection in immunocompetent hosts may remain asymptomatic or lead to mild lower respiratory tract illness, others can experience disseminated infection with CNS involvement in up to 20% of cases. The latter most commonly manifests meningitis however strokes may accompany associated infective *histoplasma* endocarditis or associated meningovascular disease with ensuing mortality of 11% to 100%. CSF culture and antigen studies which show evidence of CNS infection can be supported by anti-histoplasma antibodies. Treatment includes liposomal amphotericin followed by itraconazole or fluconazole for at least one year.

Mucormycosis

Mucormycosis is due to infection by filamentous fungi of the order *Mucorales* and class *Zygomycetes*. They are ubiquitous organisms in bread mold, soil, manure, and decaying vegetation, and the second commonest invasive mold infection [78, 79]. *Rhizopus*, *Mucor*, and *Lichtheimia* are the most common genera to cause mucormycosis. Immunocompromised hosts are at particular risk. Underlying conditions include diabetes mellitus, hematologic malignancy, trauma, solid cancers, and solid organ transplants.

Sites of infection include lung, skin, gastrointestinal tract, and the rhino-orbito-cerebral region. Iron is an important component in this infection. These fungi contain spore coat homolog proteins that are unique, and required for angioinvasion. The result of this blood vessel invasion is vessel thrombosis and tissue necrosis. The rhino-orbito-cerebral form may produce suggestive necrotic nasal or sinus eschars. Patients may experience carotid or basilar artery thrombosis, cavernous sinus thrombosis, or intracerebral hemorrhage [80, 81].

Diagnosis is based on clinical suspicion confirmed by biopsy, scraping, or culture. PCR is being evaluated. Treatment involves a combination of surgery and systemic therapy. Liposomal amphotericin B is favored therapy however thiazoles and posaconazole antibiotics have been used in selected individuals.

PARASITIC PATHOGENS

Taenia solium

Cysticercosis due to infection with the larval stage of the pork cestode tapeworm *Taenia solium* is the commonest CNS parasite accounting for 10% of stroke cases in endemic areas, and a major cause of headache and seizures. Lenticular striate lacunar infarcts are more common than large artery stroke, however TIA and intracranial hemorrhages also occur [4, 82-84]. Among 28 patients with subarachnoid cysticercosis, 15 (53%) had angiographic evidence of cerebral arteritis, 12 (80%) of whom had a stroke syndrome ($P=0.02$). Eight of the 15 patients (53%) with cerebral arteritis had evidence of cerebral infarction on MRI, whereas only one patient without cerebral arteritis had cerebral infarction ($P=0.05$). The most commonly involved vessels were the MCA and posterior cerebral artery (PCA). Small vessels are preferentially affected, with superficial cortical vessel thrombosis, occlusive endarteritis, and focal arteritis. Larger circle of Willis vessels are involved when severe arachnoiditis is present. Diagnosis involves antibody testing and suggestive findings on neuroimaging; however antigen testing is not routinely used. Anti-helminthic therapies include the benzimidazole drug albendazole and the anti-helminthic drug praziquante with corticosteroids.

Plasmodium falciparum

Plasmodium falciparum is a unicellular parasitic protozoan that infects humans causing more severe forms of malaria. The disease is typically transmitted by the bite of an infected female *Anopheles mosquito*. Inoculated sporozoites infect and multiply in liver cells, then differentiate into merozoites that are released and invade red blood cells. Infection leads to expression of adhesive surface proteins that cause the red cells to stick to the walls of small blood vessels. Intercellular adhesion molecule (ICAM)-1 is a major host binding site.

Falciparum malaria is a leading cause of morbidity and mortality in tropical countries. Cerebral malaria is the most severe neurologic manifestation]. It is defined by coma that is not due to seizures, hypoglycemia, or any other identifiable cause, and that is associated with a positive blood smear for parasitized red blood cells.

Pathophysiology is believed to be due to parasitic sequestration in cerebral microvessels. As infected red cells adhere to the endothelium, they cause further erythrocyte agglutination along with platelet clumping. There is endothelial activation, and direct cytotoxic injury. Perfusion is abnormal, and tissue oxygenation is compromised. There may also be injury mediated by soluble factors including various chemokines, cytokines, nitric oxide, and quinolinic acid. Diagnosis is based on blood smear, and antigen-based rapid diagnostic tests. Patients diagnosed with uncomplicated malaria can be effectively treated with the oral antimalarial drug chloroquine phosphate (Aralen™) or hydroxychloroquine (Plaquenil™). Patients who are considered to have severe disease should be treated aggressively with parenteral antimalarial therapy. Treatment of severe malaria involves parenteral quinidine gluconate given by continuous infusion for at least 24 hours in an intensive care setting plus

one of the following: doxycycline, tetracycline or clindamycin orally or IV followed by oral administration for a full course of seven days.

There is an investigational new drug protocol that can be obtained by contacting the Centers for Disease Control and Prevention (CDC) that employs artesunate followed by one of the following: atovaquone-proguanil (MalaroneTM), doxycycline (clindamycin in pregnant women), or mefloquine (LariamTM).

Schistosoma mansoni

This Trematoda infection which involves a flatworm is endemic to sub-Saharan Africa and South America. There is percutaneous penetration of cercariae in the invasive stage followed by mating worms that inhabit the inferior mesenteric veins where they excrete eggs in the adult stage. Neurologic involvement occurs in later stages of infection wherein adult worms can be found in spinal meningeal veins and the intracranial venous system [94]. Ectopic eggs migrate to the brain provoking granuloma formation. Cerebrovascular lesions are found in 20% of patients from postmortem series.

CNS vasculitis occurs in both early and later stages of *Schistosoma* infection [85, 86] associated with multiple infarctions, marked eosinophilia, and a corticosteroid response reflective of eosinophil-mediated injury. Presumptive diagnosis is suggested by a known travel history and compatible clinical presentation combined with serological testing and documentation of eggs in the stool. Treatment involves praziquantel.

Toxoplasma gondii

Toxoplasma gondii is an obligate intracellular protozoan that causes toxoplasmosis. During the initial acute phase of the infection, rapidly dividing tachyzoites spread throughout the host. The development of an effective cellular immune response suppresses the replication of tachyzoites and eradicates most of them, ending the acute phase of the infection. In the brain, the parasites undergo conversion to bradyzoites, which remain viable in the form of cysts because of the low levels of class I MHC and, in addition, the parasites within the cyst are surrounded by the parasitophorous vacuole that is enclosed by a cyst wall, thus little antigen escape into the cytoplasm of the cyst-containing host cell. The organisms reproduce slowly throughout the life of the host and can remain viable within intact nerve cells. Cyst rupture occurs rarely and, in immunocompetent individuals, a rapid immune response leading eventually to microglial nodule formation limits the damage to small inflammatory foci. However, in immunocompromised hosts, cyst rupture may reactivate the infection, leading to the conversion of bradyzoites to the active and rapidly replicating tachyzoites and development of severe tissue injury. Therefore, the CNS may be affected in congenital toxoplasmosis, as a primary infection in immunocompetent individuals, or as an opportunistic infection in immunosuppressed individuals. Thus, most CNS infections represent reactivation of old lesions and hematogenous spread from prior infections instead of primary infection.

The resulting disease is widely distributed worldwide among domestic animals and humans. The oocyst form is excreted in cat feces and can be the source of infection. Eating

infected raw or undercooked meat is another source of infection. Most infections are asymptomatic however immunocompromised hosts are particularly vulnerable to clinical disease. Toxoplasmosis is the leading cause of focal CNS disease in patients with HIV/AIDS and low CD4+ T-cell counts.

Congenital toxoplasmosis causes the characteristic eye lesion termed chorioretinitis, cerebral calcifications, hydrocephalus, and CSF pleocytosis. The pathological features include periventricular microglial nodules surrounded by lymphocytic vasculitis and necrotic foci. Toxoplasma encephalitis shows well circumscribed areas of hemorrhage and necrosis, with vascular thrombosis and present tachyzoites. The resulting clinical presentation is usually headache with constitutional symptoms that progress to encephalopathy and focal neurological deficits.

Toxoplasmosis as an opportunistic infection in immunosuppressed individuals has been reviewed by Pittella [87]. In HIV-infected patients, the disorder presents as a mass lesion, usually multiple, with the basal ganglia, thalamus, and the cerebral gray and white matter junctions being the preferred sites. The lesions consist of well-defined areas of coagulative necrosis, with or without hemorrhage, containing karyorrhectic debris. Blood vessel changes are common, characterized by necrosis, vasculitis, and thrombosis. Mononuclear inflammatory cells and reactive astrocytes in variable numbers are seen surrounding the necrosis. Bradyzoites and tachyzoites are present in large numbers, the former at the periphery of the lesion and the latter within the necrosis. The immunohistochemical identification of tachyzoites is especially useful when bradyzoites are not seen. In more chronic lesions, macrophages may surround the necrosis associated or not with calcification and parasites are reduced in number. In treated patients, the lesions undergo cystic change and are surrounded by macrophages, scanty inflammatory infiltrate, and astrocytosis.

Serological testing is generally positive, but may not be so in immunocompromised patients. Parasites can sometimes be observed in biopsy-stained tissues and CSF however a positive CSF PCR is helpful. Culture is typically too time-consuming to perform. Compatible features of the disorder on brain MRI include single or multiple lesions in the basal ganglia and white matter, with mass effect and homogeneous or ring enhancing lesions. However, brain neuroimaging may also be normal when there is diffuse CNS involvement.

Treatment includes pyrimethamine, sulfadiazine, and folinic acid administered for six weeks and treatment of any underlying immunocompromised condition. Alternative therapy includes trimethoprim-sulfamethoxazole and clindamycin for patients allergic to sulfa medication.

RICKETTSIAL PATHOGENS

Rickettsiae (R.) are obligate intracellular gram negative coccobacillary agents that multiply in eukaryotic cells. Phylogenetically they fall between bacteria and viruses. Both mammals and arthropods are natural hosts. Within the genus *rickettsiae*, there are three biogroups that cause illness: the spotted fever group, the typhus group, and the scrub typhus biogroup. *Rickettsiae* adhere to, and invade endothelium with increased vascular permeability, leakage, edema, and hypotension. They are capable of eliciting a generalized vasculitic response in the CNS.

Rickettsia rickettsiae

R. rickettsia cause Rocky Mountain spotted fever (RMSF). More than 90% of infections in the United States occur from April through September via tick bite. The tick vectors are larger soft ticks including *Dermacentor andersoni* and *variabilis*; and *Amblyomma americanum*. Within the CNS the vasculitis provokes a damaging immune response that is predominantly cell-mediated. The overall associated mortality rate is about 4%.

Symptomatic infection involves severe headache, abdominal pain, persistent fever, peripheral macular centripetal rash, confusion and myalgia. The classic triad is fever, headache, and rash. Conjunctivitis may also be noted. Neurologic involvement includes meningoencephalitis, focal deficits, and coma. Suggestive laboratory abnormalities are thrombocytopenia, hyponatremia, and elevated liver enzymes. A deficiency of glucose -6-phosphate dehydrogenase enzyme is associated with more severe infection.

Diagnosis is made on clinical grounds, confirmed by positive serology. Therapy involves doxycycline for 7 to 14 days.

Kumar and Pramod [88] described a young Indian male with high fever and severe acute headache followed by mental change who developed facial weakness, hyperreflexia and right posterior cerebral and bilateral thalamopeduncular infarcts on computerized tomography (CT) of the brain, with filling defects in the origin in the P1 segment of the right PCA on CTA. CSF showed lymphocytic pleocytosis and a positive Weil-Felix test for the proteus antigen OX19. The patient was diagnosed with cerebral vasculitis, however confirmatory histopathology was not obtained.

Scrub Typhus

Scrub typhus (Tsutsugamushi disease) involves infection with different species of *Orientia tsutsugamushi*. Most cases occur in the southwest Pacific and Southeast Asia. Infection occurs with the bite of the larval form of trombiculid mites or chiggers, resulting in small vessel perivasculitis. The ensuing illness is typically mild and self-limited, but can progress to life-threatening neurological illness [89-91] including meningoencephalitis. Suggestive features of the disorder include necrotic eschar at the site of the mite bite so noted in 50% of case; generalized lymphadenopathy, and mild truncal rash. CSF shows a pattern of aseptic meningitis. Serologic testing is available, and therapy involves doxycycline or another tetracycline.

CONCLUSION

Underlying infections are important to consider in patients with CNS vasculitis and when seriously suspected warrant prompt and thorough investigation. Selected antimicrobial therapy combined with supportive care can be life-saving however a self-limited course of corticosteroids can lead to prompt reduction in associated inflammation and preservation of neurological integrity.

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Chapter 222

PERIPHERAL NERVE VASCULITIS: CLASSIFICATION AND DISEASE ASSOCIATIONS

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ABSTRACT

The vasculitides are diverse disorders characterized by inflammation of vessel walls resulting in damage to the mural structures and ischemic injury. Necrotizing vasculitic lesions of peripheral nerve microvessels measuring 75 to 300 microns in diameter impact small arteries, large arterioles, and variably smaller vessels in the majority of primary and secondary systemic vasculitis. Microvasculitis is distinguished by transmural non-necrotizing inflammatory lesions affecting the smallest arterioles typically less than 40 microns, impacting smaller arterioles, endoneurial capillaries, and venules. These histopathological features are characteristic of several primary and secondary disorders, including nonsystemic vasculitic neuropathy and the interrelated disorders of diabetic and non-diabetic lumbosacral radiculoplexus neuropathy, diabetic cervical radiculoplexus neuropathy, and painless diabetic motor neuropathy. The resultant clinical features in each of these vasculitic entities depend on the size of the vessels involved, the severity of the inflammatory process, and the location and cumulative extent of the lesions along the peripheral nerve.

In light of these observations, we favor a simplified binary clinicopathological classification of vasculitic neuropathy based upon the size of the affected vessels, and the separation into the broad categories of nerve large arteriole vasculitis and microvasculitis. Such categorization informs prognosis and the approach to treatment. This chapter

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reviews the essential aspects of the nosology and classification, clinicopathologic aspects, prognosis and selected management of the representative vasculitides.

Keywords: primary, secondary, vasculitic, systemic, non-systemic, radiculoplexus, diabetic, painless, motor, lumbosacral, microvasculitis

INTRODUCTION

Vasculitis of the peripheral nerves occurs when the walls of arteriae nervorum and other nerve microvessels are infiltrated and damaged by inflammatory cells with secondary ischemic injury [1]. Vasculitic processes may be systemic or restricted to the nerves. Systemic vasculitis is primary or secondary to other disorders such as a connective tissue disease, infectious process, paraneoplastic syndrome, or drugs [2, 3]. This chapter examines the classification, diagnosis, clinical features, and treatment of common primary and secondary systemic vasculitic neuropathy (SVN), non-systemic vasculitic neuropathy (NSVN), and other recently described radiculoplexus neuropathies, including diabetic lumbosacral radiculoplexus neuropathy (DLRPN) and non-diabetic LRPN, diabetic cervical radiculoplexus neuropathy (DCRPN), and painless diabetic motor neuropathy (PDMN).

Classification

There are several accepted classification schemes for systemic vasculitic neuropathy based on the clinical characteristics, histopathological features and underlying mechanisms. Over the last several decades the classification schemes have become gradually more complex due to the increasing number of disorders considered to be vasculitic [4–9]. Additional studies to further define the optimal classification scheme are ongoing [10].

In 2010, the Peripheral Nerve Society Task Force [4] proposed a classification scheme that categorized SVN into primary and secondary forms, NSVN, and other localized presentations (Table 1). In this classification pathologically-definite vasculitic neuropathy must meet the pathological criteria for an active or chronic lesion. The former required demonstration of cellular invasion of the walls of blood vessels and one or more signs of active vascular damage, including fibrinoid necrosis, endothelial loss/disruption, internal lamina loss/fragmentation, smooth muscle media loss/fragmentation/separation, acute thrombosis, vascular/perivascular hemorrhage or leukocytoclasia (Figure 1). Chronic vasculitic lesions require demonstration of chronic vascular damage with repair, including intimal hyperplasia, fibrosis of media, adventitial/periadventitial fibrosis or chronic thrombosis with recanalization. Non-systemic vasculitic neuropathy require pathology to be isolated to the peripheral nerves. The Peripheral Nerve Society guideline group adopted two new exclusionary criteria for NSVN, both with >95% specificity for SVN, namely antineutrophil cytoplasmic antibodies (ANCA) and erythrocyte sedimentation rate (ESR) >/100 mm/h [4].

Table 1. Classification of peripheral neuropathy-associated vasculitides

I. Primary systemic vasculitides
1. Predominantly small vessel vasculitis
a. Microscopic polyangiitis
b. Eosinophilic granulomatosis with polyangiitis
c. Granulomatosis with polyangiitis
d. Essential mixed cryoglobulinemia (non-HCV)
e. IgA vasculitis
2. Predominantly medium vessel vasculitis
a. Polyarteritis nodosa
3. Predominantly large vessel vasculitis
a. Giant cell arteritis
II. Secondary systemic vasculitides associated with one of the following
1. Connective tissue diseases
a. Rheumatoid arthritis
b. Systemic lupus erythematosus
c. Sjögren syndrome
d. Systemic sclerosis
e. Dermatomyositis
f. Mixed connective tissue disease
2. Sarcoidosis
3. Behcet disease
4. Infection due to HBV, HCV, HIV, CMV, leprosy, Lyme disease, and HTLV-I
5. Drugs
6. Malignancy
7. Inflammatory bowel disease
8. Hypocomplementemic urticarial vasculitis syndrome
III. Non-systemic/localized vasculitis
1. Non-systemic vasculitic neuropathy, including non-diabetic radiculoplexus neuropathy and some cases of Wartenberg migrant sensory neuritis
2. Diabetic radiculoplexus neuropathy
a. Diabetic lumbosacral radiculoplexus neuropathy
b. Diabetic cervical radiculoplexus neuropathy
c. Diabetic thoracic radiculopathy
d. Painless diabetic motor neuropathy
3. Localized cutaneous/neuropathic vasculitis
a. Cutaneous polyarteritis nodosa
b. Others

Abbreviations: ANCA, anti-neutrophil cytoplasmic antibody; CMV, cytomegalovirus; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HTLV, human T-lymphotropic virus.

The Revised 2012 Chapel Hill Consensus Conference (CHCC) [5], which categorized the diverse forms of primary and secondary systemic vasculitis based upon the caliber of the vessels involved and the associated clinicopathologic features, did not directly consider NSVN. However, under their nosology [5], NSVN would be designated a single-organ vasculitis (SOV) of the peripheral nervous system (PNS), analogous to primary central nervous system (PCNS) vasculitis. Peripheral nerve involvement is distinctly uncommon in large vessel vasculitis that affects the aorta, its major branches and analogous veins. It is more prevalent in polyarteritis nodosa (PAN) which involves medium and small caliber vessels, notably visceral arteries and veins and their initial branches and small vessel vasculitis in

association with ANCA and immune complexes, with involvement of intraparenchymal arteries, arterioles, capillaries, veins and venules. The category of ANCA-associated vasculitis (AAV) includes granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA) and microscopic polyangiitis (MPA), while vasculitic disorders associated with immune complexes include IgA vasculitis, cryoglobulinemic vasculitis, and hypo-complementemia urticarial vasculitis associated with C1q antibodies. There were in addition, separate categories for vasculitis associated with specific systemic connective tissue disorders such as rheumatoid arthritis and Sjögren syndrome, and disorders associated with a known systemic disorder such as might occur in paraneoplastic and infection-related vasculitis. Drug-related vasculitic neuropathies comprise a separate secondary systemic vasculitic neuropathy category.

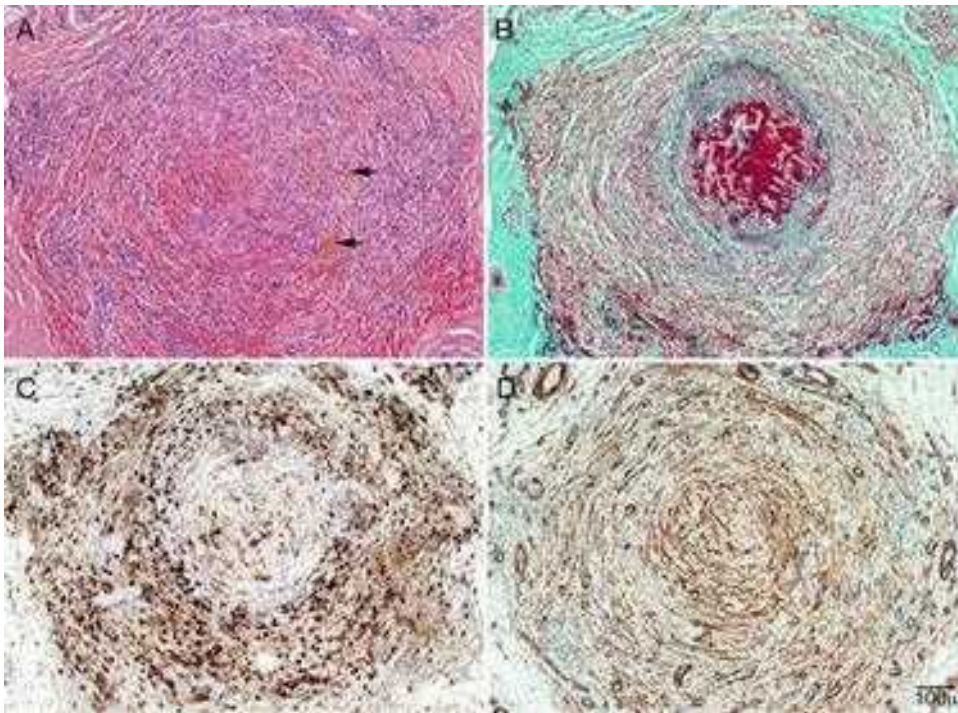


Figure 1. Serial transverse paraffin sections of a sural nerve biopsy showing larger arteriole necrotizing vasculitis: Panel A (H&E) and B (Mason's trichrome) shows fibrinoid necrosis of the mural elements with inflammatory infiltration, orange discoloration (arrows), luminal occlusion and vessel wall destruction. Panel C (CD45) confirms the leukocyte infiltration and panel D (smooth muscle actin) shows the fragmentation and destruction of muscle layers with loss of normal architecture.

We favor a simplified binary classification of vasculitic neuropathies based on the size of the affected vessels into nerve large arteriole vasculitides and microvasculitis. This classification scheme is valuable as the prognosis and treatment approach differs between these two groups. The former category, which affects vessels ranging from 75 to 300 microns in diameter, involves small arteries, large arterioles and variably smaller vessels. As virtually all peripheral nerve vessels, even the largest intraneural arteries, can in a general sense be considered small vessels, it is possible to group most patients with PAN, AAV, and secondary vasculitis associated with connective tissue disease, infection and paraneoplasia in nerve large

arteriole vasculitis [7]. By comparison, nerve microvasculitis, which includes DLRPN, LRPN, DCRPN and PDMN, involves small arterioles, endoneurial microvessels, capillaries and venules all measuring less than 40 microns. Nerve large arteriole vasculitis typically demonstrates fibrinoid necrosis, whereas microvasculitis is differentiated by inflammation in the vessel wall with fragmentation and necrosis of the tunica media (Figure 2). Common features to both forms of vasculitis include multifocal fiber loss, perineurial thickening, hemosiderin-laden macrophages, active Wallerian degeneration, neovascularization, and immune deposits of IgM, complement proteins, and fibrinogen in the epineurial vessel walls. The overlap of vessel size in NSVN was anticipated in the Revised 2012 CHCC (5), nonetheless most cases of NSVN fit better into the microvasculitis than the nerve large arteriole vasculitis category.

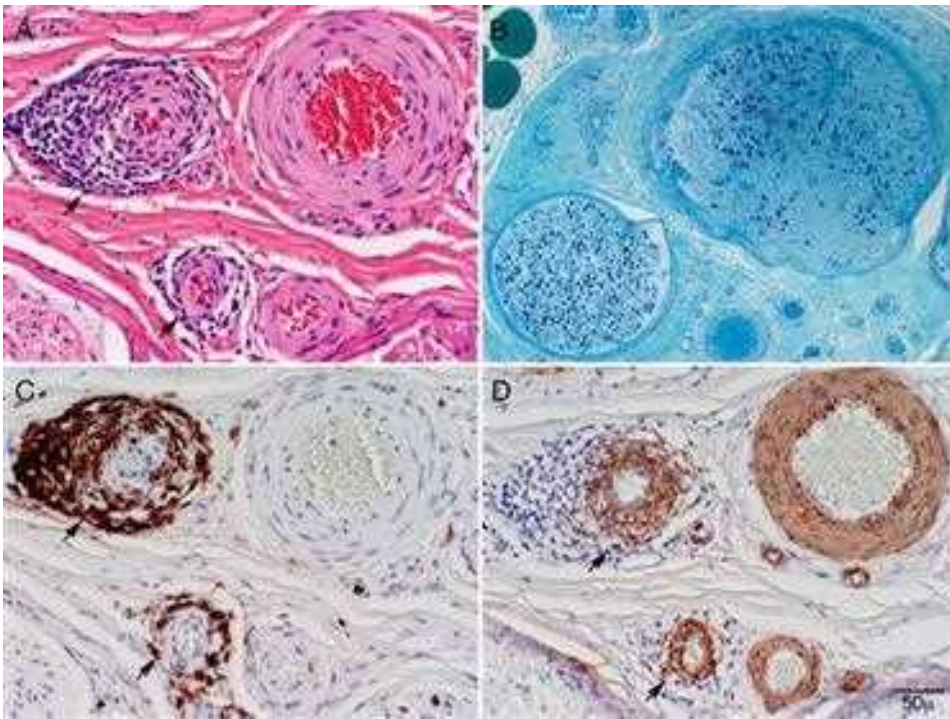


Figure 2. Serial transverse paraffin sections (panels A, C, and D) and an epoxy section (panel B) of a sural nerve showing nerve microvasculitis: Panel A (H&E) shows inflammation surrounding and involving two vessel walls (arrows), panel B (methylene blue) shows multifocal fiber loss with the upper right fascicle showing fiber degeneration and loss (typical ischemic injury) that can result from both large arteriole necrotizing vasculitis and microvasculitis, panel C (CD45) shows the transmurial inflammation is mostly leukocytes (lymphocytes [arrows]), and panel D (smooth muscle actin) shows fragmentation and disruption of the muscular layers of vessel walls (arrows).

Clinical Features

The clinical presentation of a vasculitic neuropathy depends on the distribution and severity of blood vessel involvement. Patients with primary and secondary systemic vasculitis typically manifest severe multiorgan symptoms that can overshadow the peripheral nervous

system involvement. However, one-quarter of patients with PAN and AAV may have neuropathy as a heralding feature [11]. Patients typically display constitutional symptoms including weight loss, fatigue, fever, rash or night sweats. Other organs may also be involved with evidence of respiratory symptoms, skin manifestations, gastrointestinal symptoms, and hematuria [12–15]. In contrast, NSVN is not accompanied by extraneural involvement, although constitutional symptoms such as fatigue, weight loss, arthralgia, and myalgia occur in up to one-third of patients [4, 9].

Patients with both SVN and NSVN will typically present with acute to subacute onset of painful sensory or sensorimotor mononeuropathies followed by stepwise involvement of other nerves resulting in mononeuropathy multiplex (otherwise known as multiple mononeuropathy). Some patients have a fulminant presentation, whereas others have a more slowly progressive form and may go undiagnosed for up to a decade or longer, especially those reported with NSVN [16, 17]. Although vasculitic neuropathies are classically associated with a multiple mononeuropathy presentation, a given patient may demonstrate overlapping mononeuropathies that instead resemble distal predominant symmetrical or asymmetrical polyneuropathy [2, 13]. The pattern frequencies are multifocal neuropathy, 45%; asymmetric neuropathy, 35%; and distal symmetric polyneuropathy, 20% (4,18). One-third of patients present with slowly progressive neuropathy that does not develop in a stepwise fashion [19–21]. Vasculitis has a predilection for particular nerves including the common fibular mixed nerve, the fibular division of the sciatic nerve in the legs, and the ulnar nerve in the arm [22, 23]. Cranial neuropathy, which occurs infrequently in NSVN, may be seen in those with EGPA [24] and less often in GPA [25, 26].

NERVE LARGE ARTERIOLES VASCULITIS

Primary Systemic Vasculitis

Polyarteritis Nodosa

This multisystem disorder affects both small and medium-sized arteries and is the commonest type of primary vasculitic neuropathy so noted in up to 70% of patients [27, 28]. The skin and peripheral nervous system are the two organs most commonly involved (27). Renal arteritis, hepatitis B virus (HBV) infection and antigenemia, and visceral microaneurysms can all fall in the clinical spectrum of PAN [27, 29]. In contrast to AAV, PAN spares the lungs [30].

ANCA-Associated Vasculitis

Microscopic Polyangiitis

This AAV affects large arterioles and is associated with p-ANCA (or myeloperoxidase [MPO]-ANCA) in 50 to 70% of patients, and c-ANCA (or proteinase 3 [PR3]-ANCA) in 20 to 30% [31]. This disorder is differentiated from other AAV by the absence of granulomas. The incidence of MPA in Europe ranges from 3 to 10 per million [32] with a usual age at diagnosis of 60 to 70 years [33, 34]. Most patients have constitutional symptoms at the time

of diagnosis. Renal involvement, notably progressive glomerulonephritis occurs in 80% of patients, while peripheral neuropathy occurs in about 50% of patients [18, 35, 36]. Estimates of pulmonary involvement vary widely ranging from 25-92% [37, 38]. Alveolar hemorrhage caused by pulmonary capillaritis is the classic manifestation and is reported in up to 55% of patients [39, 40]. Skin lesions such as palpable purpura and gastrointestinal symptoms such as abdominal pain occur nearly 50% of the time (Greco 2015).

Eosinophilic Granulomatosis with Polyangiitis

This category of AAV affects small-sized vessels and large arterioles. The Lanham clinical diagnostic criteria required asthma, eosinophilia of greater than 1500/mm³, and vasculitis involving two or more non-pulmonary sites, not uncommonly in association with sinusitis [41]. The American College of Rheumatology 1990 Criteria requires 4 out of 6 of the following: asthma, eosinophilia, history of allergy, pulmonary infiltrates, paranasal sinus abnormalities, and extravascular eosinophils [42]. The disorder affects younger people with a mean age at diagnosis of 48 to 52 years [12, 43–46]. Neuropathy occurs in 60 to 70% of patients with infrequent cranial nerve involvement [12, 36, 41, 44, 45, 47, 48]. About 30 to 40% of patients display ANCA-seropositivity, typically p-ANCA [12, 41, 49]. ANCA-positive patients are more likely to have peripheral nerve involvement and glomerular nephritis whereas cardiomyopathy is more common in ANCA-negative patients [12, 44, 50].

Granulomatosis with Polyangiitis

Granulomatosis with polyangiitis primarily affects the lungs and kidneys [51–53], though the skin, heart and GI tract may also be involved [54]. The disease presents in two stages, first with localized granulomatous inflammation of the respiratory tracts resulting in nasal ulceration, nasoseptal perforation, sinusitis, conductive hearing loss and otitis media. The next stage is generalized vasculitis heralded by constitutional symptoms and vasculitic involvement of the upper respiratory tract, lungs, kidneys and eyes [18, 52]. Neuropathy occurs in approximately 25% of patients [55]. With cranial involvement in between 15% to 33% of patients with GPA [14, 25, 56, 57]. GPA has an estimated relapse rate of 50% [51, 58].

Secondary Systemic Vasculitis

Rheumatoid Vasculitis

Rheumatoid vasculitis (RV) typically affects small to medium-sized arteries, including smaller arterioles, capillaries and venules [59], and is typically a late manifestation of severe seropositive RA. Vasculitic neuropathy occurs in 40 to 50% of patients with RV and in about 10% of patients with RA [47, 60]. Smoking, vascular disease and severity of RA are risk factors for RV [61]. Despite aggressive treatment, mortality rates remain high at approximately 25% over 5 years [61]. Central fascicular fiber degeneration distal to the site of ischemia with multifocal fiber loss and axonal degeneration was found among more than 15,000 serial skip sections in tissue sections of the roots, lumbosacral plexus, fibular and tibial nerves at postmortem examination of a patient with RV and peripheral neuropathy [18]. In spite of necrotizing vasculitis of small arteries and large arterioles, there was no evidence

of ischemic nerve injury until the mid-sciatic vascular watershed zone, the latter of which is now regarded as the initial site of nerve infarction in many forms of vasculitic neuropathy.

Sjögren Syndrome

Estimates of peripheral nerve involvement in Sjögren syndrome vary from 2 to 64% [62] with presentation of trigeminal sensory neuropathy, distal sensorimotor neuropathy, small or large fiber sensory neuronopathy, autonomic neuropathy, and multiple mononeuropathy [47, 63, 64]. The latter neuropathy was encountered in 3 to 12% of patients as a manifestation of vasculitic neuropathy [47, 64]. Sjögren syndrome may be associated with either nerve large arteriole or microvasculitis with perivascular cellular invasion as the most common histological feature in one series [64].

Viral Infection

Certain viral infections which persist in the body for long periods of time, such as HBV, hepatitis C virus (HCV), human immunodeficiency virus (HIV), and Parvovirus B19, demonstrate good associations with vasculitis and vasculitic neuropathies [65–67]. Those with HBV infection who also go on to develop PAN typically do so within the first 9 months of the acute hepatitis [68]. Moreover, circulating HBV surface antigenemia, so noted in 10 to 50% of patients with PAN, does not distinguish the 1 to 5% who go on to develop PAN (69). Hepatitis is often undiagnosed prior to the onset of PAN when clinically latent. Although clinical symptoms may be similar, peripheral neuropathy was more common in HBV-related PAN than those without concomitant HBV infection, so noted by Pagnoux and colleagues [27] in 85% of patients with HBV-related PAN.

Chronic HCV infection is a determinant of cryoglobulinemic vasculitis (CV) [70], with up to 65% of patients with HCV-related CV developing clinically significant peripheral neuropathy. Affected patients present with palpable purpura, glomerulonephritis, leg ulcers, arthritis, and sicca syndrome. Tissue damage in CV results from complement-dependent immune complex mediated inflammation of small blood vessels [71] with 85% of patients manifesting overtly abnormal electrodiagnostic findings [72]. In one relatively large series of patients, CV neuropathy comprised of only 8% of 71 patients with cryoglobulinemic neuropathy [73]. Patients with HCV-associated PAN similarly also develop vasculitic neuropathy in the absence of cryoglobulinemia [74]. In contrast to HCV-associated CV, HCV-associated PAN patients had a higher incidence of constitutional symptoms, multiple mononeuropathy, livedo, hypertension and GI tract involvement [74].

Paraneoplastic Vasculitis

Paraneoplastic vasculitic neuropathy occurs in the setting of hematologic tumors, thymoma, and small cell lung cancer with lesions confined to the peripheral nerves and muscles in biopsy and postmortem tissue sections [75, 76]. Anti-Hu or serum antineuronal nuclear antigen-2 (ANNA-2) autoantibodies are associated with paraneoplastic vasculitic peripheral neuropathies [77]. In contrast to paraneoplastic vasculitis, solid tumors are more often associated with paraneoplastic vasculitic neuropathies than hematological malignancies [78]. Sensory ataxia and autonomic dysfunction may occur in patients who harbor anti-Hu antibodies.

Drug-Induced Vasculitis

Several drugs have recently been associated with vasculitic neuropathies. Minocycline, which is a tetracycline derivative used for acne vulgaris, has been reported to trigger a vasculitic neuropathy in several patients [79, 80]. The time course from time of initiation of the minocycline to development of peripheral nerve vasculitis is variable. Discontinuation of minocycline and initiation of corticosteroids and other immunosuppressant drugs results in improvement. Minocycline has interestingly also been associated with CNS vasculitis [81].

Cocaine has been implicated as a trigger in AAV [82]. Cocaine may actually spark a pseudovasculitis rather than the true vasculitis seen in systemic AAV [83]. Patients will have sinus involvement, a vasculitic purpuric rash, inflammatory arthritis and peripheral neuropathy. ANCA positivity may be c-ANCA or p-ANCA [82]. Corticosteroids and steroid sparing agents may be used.

Anti-programmed death 1 (PD-1) antibodies, such as pembrolizumab or nivolumab, are used in the treatment of solid-organ tumors and hematological cancers [84]. These immune checkpoint inhibitors have been associated with various autoimmune complications including two cases of vasculitic neuropathy [84, 85]. In addition to discontinuation of the antibody treatment, additional immunotherapy may be necessary [84].

MICROVASCULITIS

Non-Systemic Vasculitic Neuropathy

NSVN differs from SVN in its restriction to the nerves secondarily affecting muscle, the slow progression, and non-fatal outcome [47]. There are typically less severe constitutional symptoms or less markedly abnormal laboratory studies. Approximately one-third of patients report a weight loss and 10 to 13% note fever [9]. As a result of slow, progressive development of asymmetric and multifocal neurological deficits, there is often a longer delay, in some reports up to 14 years, to diagnosis than systemic vasculitic neuropathy [16, 17, 86, 87]. Overall, 45% have an asymmetric neuropathy, 33% multifocal neuropathy and 23% symmetric polyneuropathy [9]. Patients with NSVN typically present with pain and weakness that commences unilaterally and spreads to the contralateral side in 80 to 90% of patients. Twenty percent of patients will have no pain [9]. Affected patients classically manifest sensorimotor symptoms and signs, with 15% of patients presenting a sensory-predominant syndrome depending upon both the precise location and extent of the vasculitic lesion in the mixed nerve and selective involvement of sensory branches [18]. Continued monitoring is recommended for those with NSVN since 10% of affected patients may evolve into SVN. Most patients continue to be ambulatory and independent in activities of daily living [9]. Sugiura and colleagues [88] considered NSVN, noting the clinicopathologic similarity to MPA, in spite of restriction of relapses to the PNS, the absence of ANCA-seropositivity, and overall improved prognosis of the former. Takahashi and colleagues, however, demonstrated a distinct pathogenesis in NSVN and MPA [89]. In both ANCA-positive and ANCA-negative MPA, neutrophils attach to vascular endothelial cells, whereas complement plays more integral role in NSVN with C3d deposition in epineurial small vessels. The antigens most often identified in the inflammatory lymphocytic infiltrates in NSVN include CD52, BAFF,

and CD49d which were expressed in the epineurial, perivascular and intramural lymphocytes in all 20 treatment-naïve sural nerve biopsies in one series [90].

Diabetic Lumbosacral Radiculoplexus Neuropathy

Dyck and coworkers [91] described monophasic severe lower leg pain and weakness that commenced unilaterally, with delayed involvement of the other leg in an asymmetrical pattern affecting both the proximal and distal lower extremities in middle to later age type 2 diabetics with relatively good glycemic control. The onset of pain and weakness is often heralded by significant weight loss, a median of 30 pounds in the Dyck study [91]. There is generally a lack of correlation between developing DLRPN and a greater duration or severity of diabetes mellitus, as opposed to cases of typical diabetic polyneuropathy. Sharp, lancinating allodynic pain and burning sensations along the legs are typical presenting features. Sensory impairments become overshadowed by leg weakness, which is the most disabling feature, prompting use of ambulatory aids including wheelchairs in one-half of patients [91]. The non-diabetic form "LRPN" has an identical presentation of monophasic severe lower leg pain and weakness [92, 93]. Unlike other forms of vasculitic neuropathy, multiple leg and thigh nerves, lumbosacral plexus and nerve roots are affected. Electrodiagnostic studies reveal active axonal features and acute spontaneous activity in multiple proximal and distal lower leg muscles and in lumbosacral paraspinal muscles, and motor unit potential changes consistent with a radiculoplexus (involving root, plexus and peripheral nerve) neuropathy as the term LRPN implies. Autonomic nervous system (ANS) involvement occurs in approximately one-half of patients. There may be associated thoracic radiculopathy and mononeuropathy of the arms, and less commonly cervical radiculoplexus neuropathy [91]. An etiopathogenesis attributed to microvasculitis-induced ischemic injury was postulated in a series of 33 prospectively studied patients with DLRPN [91] in whom biopsy of a distal cutaneous nerve revealed neovascularization, injury neuroma, perineurial thickening, multifocal fiber loss and abnormal amounts of inflammation, one-half of the biopsied nerves showed findings diagnostic or suggestive of microvasculitis. Further in support of a vasculitic ischemic etiopathogenesis, was the finding of necrotizing arteritis in biopsy tissue of the superficial fibular cutaneous nerve of a patient with clinically apparent DLRPN [94] in whom postmortem examination also showed epineurial perivascular inflammation of the femoral nerve, lumbar plexus and roots. Although spontaneous improvement is expected, recovery is often incomplete with foot drop being the most common long-term sequela.

Diabetic Cervical Radiculoplexus Neuropathy

Massie and colleagues [95] reported a series of 85 patients with DCRPN, most of whom were type 2 diabetics, with a mean age of 62 years. The commonest presenting symptoms were pain noted in 69 (81%), and numbness in 56 (66%) of patients, which were overshadowed by weakness noted in all but one patient. In contrast to DLRPN, the presentation was more acute and clinical deficits peaked in the first week. Moreover, unlike brachial plexus neuritis, which typically manifests upper trunk involvement, the upper, middle and lower plexuses are equally affected in DCRPN, with about 30% of patients demonstrating pan-plexus involvement. Electrodiagnostic studies showed axonal neuropathy in all 80 patients studied, with evidence of paraspinal denervation in 32%, with abnormal ANS testing (evaluating cardiovagal, cardioadrenergic, and post-ganglionic sudomotor

function) in 96%, and abnormal quantitative sensory testing in 77%. Altogether, 44 (52%) patients had one or more additional body regions affected including 30 contralateral cervical, 20 lumbosacral, and 16 thoracic regions. Evidence of ischemic nerve injury was the predominant feature in cutaneous nerve biopsy tissues, within which epineurial perivascular inflammation was seen in all 22 specimens, microvasculitis in 5 (23%), multifocal nerve fiber loss in 15 (68%) and inflammation involving vessel walls in 14 (64%). The pathological findings were essentially the same as found in diabetic and non-diabetic LRPN. Given the clinicopathologic similarity to DLRPN these two disorders are categorized together in the spectrum of diabetic radiculoplexus neuropathy.

Painless Diabetic Motor Neuropathy

Garces-Sanchez and colleagues [96] described painless diabetic motor and lower limb-predominant neuropathy among 23 patients of mean age 62 years, 22 (96%) of whom had type 2 diabetes. Similar to those with DLRPN and LRPN, chronic diabetic complications were uncommon and weight loss was typical. Most patients had gradual onset of bilateral foot-drop that spread to the proximal legs and occasionally the arms. However, in comparison to DLRPN, the neurological deficits of those with PDMN were more severe with over one-half of patients confined to a wheelchair by the time of presentation. Despite the motor-predominant presentation, most had sensory symptoms, less than one-half of affected patients had ANS involvement, and significantly more patients had arm involvement compared to patients with DLRPN. Electrodiagnostic studies showed pan-modality sensory loss, ANS abnormalities, and axonal polyradiculopathy with lumbosacral paraspinal muscle denervation. Cutaneous nerve biopsy findings showed ischemic injury like other radiculoplexus neuropathies, with evidence of epineurial perivascular inflammation in all 23, with vessel wall invasion in 15 (65%) and microvasculitis in 4 (13%) of nerves. Given the absence of ischemic injury and microvasculitis in nerve biopsy specimens of analogous patients with diabetic chronic inflammatory demyelinating polyradiculopathy (CIDP), the authors [96] concluded that the patients with PDMN were best classified as a form of radiculoplexus neuropathy rather than a form of diabetic CIDP.

DIAGNOSIS

There is general agreement on four principles in the diagnosis of vasculitis which are applicable to peripheral nerve vasculitis [1]. First, vasculitis is a potentially serious disorder with a propensity for permanent disability owing to tissue ischemia and infarction. Therefore, prompt recognition of the typical neurologic manifestations of peripheral nerve vasculitis is key to placing it high up in the differential etiologic diagnosis of peripheral neuropathy. Second, undiagnosed and therefore untreated, there is a likelihood of excess morbidity. Third, a favorable response to an empiric course of immunosuppressive and immunomodulating therapy should never be considered a substitute for the absolute proof of the laboratory diagnosis of vasculitis. Fourth, histopathologic confirmation of vasculitis is essential for the accurate diagnosis of peripheral nerve vasculitis, such as by analysis of nerve and muscle biopsy tissue when PNS involvement is postulated.

All patients with peripheral neuropathy due to suspected primary or secondary peripheral nerve vasculitis should be thoroughly evaluated for systemic involvement including disease-specific serological studies guided by the clinical presentation and postulated etiologic diagnosis to avoid excessive cost and spurious results. ANCA serology is mandatory in the evaluation of suspected SVN. ANCA are a family of autoantibodies that react with proteins that are expressed in cytoplasmic granules of polymorphonuclear cells. The presumptive ANCA autoimmune response, which is regarded as a multifactorial process that includes genetic predisposition, environmental factors, an initiating antigen, and altered T-cell regulation, primes neutrophils by binding to certain antigens expressed on their surface, and ANCA-activated neutrophils contribute to an inflammatory amplification loop that recruits other effector cells leading to granuloma formation [97]. However, there are significant differences in sensitivity, specificity and predictive value among commercially-available ANCA enzyme-linked immunosorbent assay (ELISA) kits. An International Consensus Statement [98, 99] suggested guidelines for ANCA testing recommending screening by standard immunofluorescence tests (IFT) and mandatory antigen-specific ELISA for positive IFT tests. The three major IFT patterns [100] including, granular cytoplasmic neutrophil fluorescence with central interlobular accentuation, perinuclear neutrophil staining often with nuclear extension, and another comprising a mix of cytoplasmic and perinuclear fluorescence, correlate respectively with C-ANCA, P-ANCA, and atypical ANCA with multiple specificities. C-ANCA-seropositivity typically occurs in patients with active generalized GPA, whereas P-ANCA occurs in patients with MPA and EGPA; ANCA with multiple antigen specificities often occurs in the absence of vasculitis. Autoantibodies with specificity for myeloperoxidase are referred to as MPO-ANCA and those against proteinase-3 are PR3-ANCA. The c-ANCA pattern is in most cases caused by antibodies to PR3. P-ANCA pattern is less specific, but MPO is an antigen associated with this pattern [101].

Biomarkers are emerging as potentially useful predictors of disease activity including neurofilament light chain and VEGF [102, 103]. There are published consensus recommendations for the laboratory investigation of suspected vasculitic neuropathy (Table 2) [4].

Electrodiagnostic studies are useful in the initial investigation of vasculitis because they can identify areas of asymptomatic involvement, sites for muscle and nerve biopsy, and when combined with the clinical and laboratory evaluation, support the specific neuropathic syndrome with a high degree of certainty. A wide sampling of nerves and muscles should be examined, both distal and proximal, with side-to-side comparisons. Most patients with peripheral nerve vasculitis will have multiple, acute or subacute, axonal mononeuropathies. Over time, a distal symmetric or asymmetric pattern due to the confluent nature of additional superimposed vasculitic lesions may be appreciated.

Table 2. Recommended laboratory studies in suspected vasculitic neuropathy

<i>Initial studies:</i> Complete blood count with differential (for eosinophil count), comprehensive metabolic panel, urinalysis, erythrocyte sedimentation rate, C-reactive protein, anti-neutrophil cytoplasmic antibodies (autoantibodies to proteinase-3 and myeloperoxidase), serum protein electrophoresis, complement levels (including C3, C4, and total), glycosylated hemoglobin, or 2 hour glucose tolerance test, hepatitis B surface antigen, hepatitis C antibodies, cryoglobulins, chest x-ray, and urinalysis.
<i>Additional studies:</i> Extractable nuclear antigen profile (including SSA/SSB antibodies), double-stranded DNA antibodies, rheumatoid factor, cyclic citrullinated peptide antibodies, angiotensin converting enzyme, human immunodeficiency virus antibodies, paraneoplastic autoantibodies, salivary gland biopsy, and malignancy imaging.

In patients suspected to have a vasculitic neuropathy, open biopsy of a cutaneous sensory nerve and companion muscle tissue are indispensable in the evaluation of primary and secondary peripheral nerve vasculitis. However, they should only be performed at major neuromuscular centers to assure that all necessary specimens are obtained, and they are processed correctly for light microscopy of cryostat- and paraffin-stained hematoxylin and eosin (H&E) sections, supplemented by plastic embedded, 1-mm semithin sections, and teased nerve fiber analysis. Such studies generally show evidence of axonopathy with Wallerian degeneration due to nerve ischemia and vasculitis supported by the presence of myelin ovoids, myelin debris, macrophage recruitment along the course of degenerated fibers, marked fascicular depletion of myelinated and unmyelinated nerve fibers, and endoneurial fibrosis. Immunocytochemical studies including lymphocyte cell marker analysis and complement immunofluorescence can be performed to identify activated components of the cell-mediated and humoral immune system. Cutaneous nerve biopsy is generally unnecessary in those with obvious DLRPN, LRPN, DCRPN and new-onset of multifocal neuropathy and known systemic vasculitis. However, cutaneous nerve biopsy may be useful in cases of prolonged DLRPN, LRPN and DCRPN where the disease course is protracted a year or more, and the treating physician needs to know if there is active microvasculitis. It may also be beneficial in cases with atypical clinical, electrophysiological, and magnetic resonance imaging (MRI) features, to accurately confirm the diagnosis. The sural nerve and superficial fibular sensory nerves are the commonest nerves studied in the legs, likewise the superficial radial sensory nerve for the evaluation of vasculitis in the upper limbs [2]. The addition of soleus or peroneus brevis muscle from the same incision as the sural and superficial fibular sensory nerves increased the yield of vasculitis by 15 to 25%, to an estimated overall sensitivity of 50 to 60% in several series [2, 104, 105]. Deprez and coworkers [106] studied clinicopathologic correlations in 355 retrospective patients with peripheral neuropathies noting a greater yield of nerve biopsy in those with multifocal and asymmetrical patterns, and a clinical onset-to-biopsy interval of less than six months. Chalk and colleagues [107] studied the diagnostic usefulness of ANCA serology in 166 consecutive patients, noting ANCA-seropositivity in four of six patients with vasculitic neuropathy; however, false-positive results limits its diagnostic usefulness in peripheral neuropathy.

TREATMENT

Treatment of vasculitic neuropathy can be divided into 3 broad categories including treatment of non-infectious nerve large arteriole vasculitis (including primary SVN and secondary SVN); treatment of infectious nerve large arteriole vasculitis, and treatment of NSVN and other microvasculitides. Treatment of SVN should be initiated immediately as the one-year mortality rate approaches 90% in untreated patients with GPA and PAN compared to 12 to 20% among those promptly treated [4, 108]. The usual approach to treatment is induction of remission followed by long-term maintenance therapy which is continued for 18 to 24 months [109–113]. Corticosteroids are standard initial therapy for both SVN and NSVN. The addition of cyclophosphamide is usually necessary in those with MPA and GPA, and in others with NSVN who progress while on corticosteroids alone. A good tool for assessing response to treatment is the Neuropathy Impairment Score (NIS) because it

combines weakness, reflex changes and sensory loss, as well as a standard neurological examination and follow up electrodiagnostic studies. The 1996 and 2009 revised Five-Factor Score (FFS) can help prognosticate in patients with PAN, MPA, EGPA, and GPA [114, 115]. Four factors are each allocated one point: renal insufficiency, cardiomyopathy, severe gastrointestinal manifestations, and age >65. ENT involvement, the fifth factor, is considered protective, so if absent, is allocated one point. The fifth factor is only used for EGPA and GPA. Five-year mortality rates for scores of 0, 1, and >2 were 9%, 21%, and 40% respectively. Neuropathy itself does not affect survival. If new neurological deficits develop, treatment should be escalated [3, 4, 7, 27, 116–118]. The starting dose of prednisone is 1.0 mg/kg/day and in severe cases is administered intravenously as methylprednisolone at a dose of 1000 mg for 3 to 5 days, followed by oral prednisone [119]. Oral prednisone is slowly tapered by 5 to 10 mg every few weeks after one to two months depending on the patient's response and severity of the disease [7, 120]. The erythrocyte sedimentation rate (ESR) and other markers of acute inflammation [2], including ANCA levels in those with AAV [121], should be monitored at baseline and with treatment. Maximal improvement occurs in 6 to 24 months after initiation of corticosteroids due to the slow pace of axonal regeneration. When needed, cyclophosphamide can be administered as an intravenous pulsed dose or as daily oral therapy with anticipated equal efficacy, however oral cyclophosphamide is associated with a higher incidence of side effects [122–127]. Intravenous pulse therapy is associated with higher relapse rate upon follow up [127]. Once remission is achieved with cyclophosphamide and prednisone, methotrexate or azathioprine can be substituted for the cyclophosphamide [128–130]. Patients with refractory disease despite treatment with cyclophosphamide and corticosteroids can be treated effectively with rituximab [4, 131–133]. Newer treatment protocols that combine rituximab, intravenous cyclophosphamide and oral prednisone in AAV have recently been published [134]. There is continued research to determine the best regimen for AAV patients [135] with rituximab emerging as likely first line therapy [136]. Other options include intravenous immune globulin (IVIg), plasma exchange, and mycophenolate mofetil.

Azathioprine is used as alternative maintenance therapy to cyclophosphamide in those with SVN and NSVN especially those in whom remission has been induced with cyclophosphamide. The timing of discontinuation of azathioprine does not clearly influence the relapse rate in AAV [137]. Azathioprine should not be added to corticosteroids to induce remission in AAV as it does not improve remission rates, lower the risk of relapse, or spare steroids [138]. Methotrexate can be used with corticosteroids for induction of remission in mild, non-life-threatening AAV and in patients with SVN and typical NSVN in lieu of azathioprine for remission maintenance following cyclophosphamide induction [7]. Methotrexate should be continued for 18 to 24 months prior to attempted tapering. Methotrexate has been found to be non-inferior to cyclophosphamide in remission maintenance [139]. IVIG was found to be effective in patients with diverse forms of vasculitic neuropathy and in those with AAV refractory to standard therapy [140–143].

The chimeric anti-CD20 monoclonal immunoglobulin rituximab is first-line therapy for induction of remission in patients with GPA and MPA instead of cyclophosphamide [136]. It is also effective in patients with CV and RV [144–150]. Nearly 90% of patients with treatment-refractory AAV improved following rituximab treatment in uncontrolled series [72, 136]. Plasma exchange is an option in patients with fulminant vasculitis and significant organ

impairment, as well as, in HBV-associated PAN, HCV-associated CV, and HIV-associated systemic vasculitis [151–156].

For most HCV genotypes a combination of interferon-free antiviral drugs (sofosbuvir and ribavirin), immunosuppressive drugs, with or without plasmapheresis should be used [157, 158]. If the patient has HCV genotype 6, direct-acting antiviral drugs, such as pegylated interferon injections are used [158]. Rituximab may be more effective in patients with severe cryoglobulinemic vasculitis [71, 72, 146, 159]. For non-cytomegalovirus-related HIV vasculitis, treatment is similar to HBV-associated PAN using antiviral therapy and plasma exchange, although in clinical practice most use corticosteroids [28, 160]. The current recommendation is to treat HBV-associated PAN with lamivudine, corticosteroids and in severe cases, plasma exchange [161, 162]. Prolonged corticosteroid treatment should be avoided as it favors viral replication (163). The French Vasculitis Study Group [65, 155] treatment protocol for HBV-related PAN that included antiviral agents, therapeutic plasma exchange to remove circulating immune complexes followed by two weeks of corticosteroids to treat the severe symptoms, induced complete remission in 80 to 90% of patients.

The 2010 Peripheral Nerve Society published guidelines for the immunosuppressive therapy of classic NSVN [4] Since that time, most experts now recommend initiation of combination therapy (corticosteroids with cyclophosphamide, methotrexate, or rituximab) [9]. Azathioprine should not be used as induction therapy but can be used as maintenance therapy. Rituximab can be also be used as maintenance therapy [9].

Patients with progressive symptoms early in the course of DLRPN or LRPN are candidates for immunotherapy [166]. One prospective, randomized, double-blind, multicenter- controlled trial employing intravenous methylprednisolone in patients with DLRPN found improvements in indices of pain but not neurological function [167]. However, a concern is that patients may have been enrolled and treated too late in the disease course to affect impairment, and may not reflect a true degree of benefit of early treatment in a monophasic inflammatory disorder. One open uncontrolled study employing intravenous methylprednisolone in patients with clinically deteriorating LRPN, showed improvement in NIS commensurate with clinical improvement in all patients [168, 169]. While case series of patients [169–171] with radiculoplexus neuropathies suggest improvement in pain and strength with IVIg, there have been no randomized trials of plasma exchange in DLRPN or LRPN. One case series of five patients with DLRPN treated with plasma exchange demonstrated improvement [172]. Considering that DLRPN and LRPN are subtypes of NSVN, a similar treatment regimen for patients with LRPN should be undertaken.

Pain control is of utmost importance in vasculitic neuropathy and the usual medications employed include tricyclic antidepressants, pregabalin, gabapentin, serotonin-norepinephrine reuptake inhibitors, valproate, carbamazepine, tramadol, topical lidocaine, topical capsaicin, and narcotics [173]. Continued pain without progressive neurologic deficits is not an indication for high-dose corticosteroids.

CONCLUSION

Peripheral nerve vasculitis is commonly encountered in patients with primary systemic vasculitis, but may also be secondary to viral infections, malignancy, and concomitant

connective tissue disease. All peripheral nerve vasculitic neuropathies involve small blood vessels and classification is based upon separation into nerve large arteriole vasculitis (which typically has fibrinoid necrosis of the involved vessel) and nerve microvasculitis (which typically does not have fibrinoid necrosis). Primary and secondary systemic vasculitic neuropathies are forms of nerve large arteriole vasculitis. Non-systemic vasculitic neuropathy accounts for up to 30% of all vasculitic neuropathies. Altogether, NSVN, as well as some forms of secondary systemic vasculitic, and the radiculoplexus neuropathies including DLRPN, LRPN, DCRPN, and PDMN, the latter of which may be considered localized forms of vasculitic neuropathy, will likely be associated with peripheral nerve microvasculitis. Treatment employing corticosteroids, systemic immunosuppressive agents, and immune modulation with plasma exchange and intravenous immune globulin, all suitable options in patients with severe and progressive neurological deterioration, especially to reduce excess morbidity and mortality.

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Chapter 223

CENTRAL NERVOUS SYSTEM VASCULITIS DUE TO DRUG ABUSE

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ABSTRACT

Illicit drug abuse is a common differential diagnosis of acquired central nervous system vasculitis even though there are only a handful of histopathologically confirmed patients in the literature from among the many potential classes of abused drugs traditionally implicated in this disease. Since publication of the first edition of this chapter, there has been increasing interest in the acute neurotoxicity associated with adulterants. This chapter considers the major classes of illicit drugs in those with and without human immunodeficiency virus type 1 infection and acquired immune deficiency syndrome.

EPIDEMIOLOGY

Drug abuse is a significant public health burden [1]. Globally, it has been estimated that 3.5 to 5.7% of the population age 15 to 64 years, or approximately 250 million persons consumed an illicit drug once in the past year [2]. Taking into account the pattern of drug use, an estimated 16 to 38 million persons are considered regular or frequent users due to psychic and physical drug dependence or addiction, and an additional 11 to 21 million inject drugs [1]. This wide range of estimations are due to lack of reliable epidemiological data on specific

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drug abuse, all of which can be cause injury to the central nervous system (CNS) including opiates, heroin, cocaine, amphetamine, and methamphetamine.

The misuse and abuse of drugs in the United States (US) has reached epidemic proportion, and extends to both adolescents and adults. Although individuals with a drug addiction may favor one or another class of illicit drugs, most perform polysubstance abuse. Such a trend was discerned in an analysis of accidental overdose deaths in New York City between 1990 and 1998 due to heroin, cocaine and alcohol. That combination accounted for 97.6% of all deaths, 57% of which were attributed to two or more of these drugs in combination [3] among accidental drug overdose deaths attributed to one drug alone, those positive for cocaine only were the commonest representing 1.93 per 100,000 person-years. In developing countries, illicit use, non-pharmacy sales, counterfeit drugs, and self-treatment complicate the public health concern surrounding substance abuse.

CLASSIFICATION AND NOSOLOGY

The most widely used classification and nosology for the vasculitides is the 2012 Revised International Chapel Hill Consensus Conference [4] Nomenclature. There is a recent review of CNS vasculitis [5].

BLOOD BRAIN BARRIER

The past decade has witnessed extraordinary progress in our understanding of the blood brain barrier (BBB) [6], and progress in its understanding will likely afford new insights into our understanding of cerebral vasculitis. The neurovascular unit (NVU) of the BBB is comprised of capillary endothelial cells, pericytes, smooth muscle cells, astrocytes, and neuronal terminals, and white blood cells in the extended NVU.

Each of the components expresses a wide variety of receptors, ion channels, and transporters that reside in proximity to one another allowing for the dynamic modulation of blood flow, metabolism, and electrophysiologic regulation [7]. Many of the influx and efflux mechanisms of the BBB are present early in the developing brain, encoded by genes at much higher levels than in the adult [8]. The disruption of tight and adherens junctions, enzymatic degradation of the capillary basement membrane, or both, leads to disruption of tight junctions (TJ), altered expression and function of membrane transporters or enzymes, increased passage of inflammatory cells across the BBB from the blood to CNS, and dysfunction of astrocytes and other components [7]. This leads to aberrant angiogenesis and neuroinflammation with concomitant vasogenic edema, accumulation of toxic substances in the brain interstitial fluid, oxidative stress, and impaired ion and water homeostasis.

AMPHETAMINE AND RELATED AGENTS

Background

The earliest reports of misuse of amphetamine sulfate were in late 1930 when students to avoid sleep during examination periods [9] used it. This was followed by reports of death by those who ingested the drug repeatedly as a stimulant for the same purpose [10], in a suicide attempt that resulted in a fatal intracerebral hemorrhage [11], or accidentally, when dexamphetamine and phenelzine were fatally ingested together decades later [12].

During the Second World War, amphetamine and methamphetamine was used clinically and illicitly but its abuse soared in San Francisco after 1962 where it was illegally produced and distributed [13].

In 2009, the United Nations Office on Drugs and Crime (UNODC) estimated that 16 to 51 million persons between the age of 15 and 64 years consumed amphetamine drugs, with more than half using methamphetamine [14], exceeding the combined consumption of all other drugs of abuse except cannabis [15].

Neuropharmacology

The neuropharmacology of amphetamine, methamphetamine, and their derivatives has been recently reviewed [16, 17]. Such drugs agents comprise a large spectrum of agents [18] available in powder, capsule, tablet, and injectable fluid form that can be swallowed, snorted or taken intra-nasally, smoked or injected with highly variable purity and dosage equivalence. Their potent effects, which include elevation of blood pressure, pulse rate, and increased level of alertness, sometimes in association with insomnia, excitability, panic attacks, and aggressive behavior, can also be associated with seizure and stroke.

The effects of methamphetamine are distributed throughout the brain [19]. Ecstasy refers to the different hallucinogenic amphetamine derivatives that contain 3, 4-methylenedioxymethamphetamine (MDMA) and 3, 4-methylenedioxyethylamphetamine (MDE) as the main components [20]. Ecstasy alters brain serotonin concentrations, and postsynaptic 5-HT₂ receptors play a role in the regulation of brain microvessels.

The CNS toxic effects are mitigated through blocking of the reuptake of dopamine (DA) and stimulation of the release of DA and norepinephrine (NE), as well as, possible involvement upon serotonergic and endogenous opiate system. There can be DA receptor desensitization with marked reduction of DA transporters and drug levels, as well as other dopaminergic axonal markers. The neurotoxic effects of methamphetamine in particular, are believed to be mediated in addition by multiple additional mechanisms including generation of free radicals, nitric oxide, excitotoxicity, mitochondrial dysfunction, apoptosis, and the induction of immediate early inflammatory genes and transcription factors.

Methamphetamine is the most potent amphetamine and the most commonly abused. All forms of amphetamine administration increase the risk of stroke that may be ischemic, hemorrhagic and intraparenchymal [21], and which may be up to four-fold that of nonusers [22], surpassing the rate of hemorrhagic stroke caused by cocaine use with odds ratios respectively of 4.95 versus 2.33 [23]. Still, amphetamines and methamphetamine are the

second commonest cause of all strokes after cocaine, occurring largely in persons younger than 45 years.

Clinicopathological Spectrum of Amphetamine-Related Cerebral Vasculitis

Excluded Literature Patients

Amphetamine was not the definite causative agent of purported cerebral vasculitis in the patient described by Kessler and colleagues [24] with acute intracerebral hemorrhage, or in the patient reported by Bostwick [25] with ischemic stroke in two multi-drug abusers of heroin, cocaine, and amphetamine with beading of small tributaries of the middle cerebral artery (MCA) [24] or occlusion of the right internal carotid artery (ICA) [25]. Postmortem examination in the first patient [24] showed occasional intramural mononuclear and polymorphonuclear cellular infiltration of small leptomeningeal arteries, while histopathology of the second patient [25] was not provided.

Detailed histopathology was lacking in the patient described by Olsen [26] as “vasculitis and cerebritis” as the cause for subarachnoid hemorrhage in a drug abuser who injected Methedrine and soon afterward lapsed into a fatal coma. Cerebral angiography that demonstrated typical features of vasculitis in conjunction with a skin biopsy that revealed granular deposits of IgM and C3 component around the lumina of small vessels of the upper dermis consistent with immune complex disease were the supportive features of cerebral vasculitis in a patient who ingested methamphetamine and later developed headache, nausea and vomiting heralding subarachnoid, without other confirmatory histopathology [27].

Corroborative histopathology was not sought in 10 other often cited patients [28-30] including a young man with presumed cerebral vasculitis attributed to chronic exposure to methylphenidate for 7 years beginning at age 5 to treat hyperactivity and attention deficit disorder. At age 18 years, he was diagnosed with right hemidystonia, whereupon MRI of the brain disclosed chronic infarction in the head of the right caudate, putamen, pallidum, internal capsule and temporal lobe, with occlusion of the left anterior cerebral artery (ACA) and posterior branch of the left MCA on cerebral angiography [28].

Likewise corroborative histopathology was not sought in 8 patients described by Buxton and McConachie [29] who developed presumed intracranial vasculitis as cause for subsequent lobar (5 patients), subarachnoid (2 patients) or brainstem hemorrhage (1 patient) following oral or inhaled amphetamine in whom cerebral angiography showed beading in the one patient with subarachnoid hemorrhage, and normal in 6 others.

Moriya and Hashimoto [31], Shibata and coworkers [32], and Delaney and colleagues [33] each described a patient with fatal intracranial hemorrhages following intravenous injection of amphetamine (2 patients) alone [31, 32] or intranasal injection of methamphetamine (1 patient) [33]. Postmortem examination in one patient [31] did not reveal vascular lesions, while that of another patient [32], with evidence of necrosis of blood vessels walls along named cerebral arteries, failed to reveal cellular infiltration of vessels walls. Detailed gross and microscopic examination of the cerebral vessels in another patient [33] showed no evidence of cerebral vasculitis.

Moreover, there was no mention of vasculitic lesions at postmortem examination of the CNS among 13 patients with purported vasculitis following fatal intravenous injection (1 patient) [34] oral ingestion of methamphetamine (6 patients) [35] or amphetamine sulfate (1 patient) [11], oral ingestion of combination dexamphetamine and phenelzine (1 patient) [12]. There was no evidence of postmortem or brain biopsy studies to investigate the possibility of cerebral vasculitis among 4 other often cited patients [36], 1 of whom was fatally injected with intravenous methamphetamine leading to cerebellar and brainstem hemorrhage; or in 3 other patients who survived ischemic infarction (2 patients) or lobar hemorrhage (1 patient) associated with inhaled (1 patient) or an unknown mode of administered of methamphetamine ingestion.

Cerebral vasculitis was not mentioned in a recent series of 30 patients, one third each of whom carried the diagnosis of ischemic stroke, intracerebral hemorrhage, or subarachnoid hemorrhage [37]. Nor were the postmortem findings of multiple large intracerebral vessels occlusions attributed to cerebral vasculitis in a patient with a fatal stroke, and attributed instead to accelerated atherosclerosis. Histopathology was not sought in two other fatal strokes or a patient with fatal subarachnoid hemorrhage [37].

Pathologically-Verified Literature Patients

Cerebral vasculitis due to amphetamine, methamphetamine and related agents is exceedingly rare with only 3 histopathologically studied patients in the literature [38, 27]. This is surprising given the number of substances that could cause this disorder if there was a true association. Citron and colleagues [38] in a highly publicized report of 14 Los Angeles multidrug abusers demonstrated amphetamine-related multi-organ arteritis including the CNS. The drug closest to a common denominator was methamphetamine using intravenously by all but two patients and exclusively by one. Acute vessel lesions of fibrinoid necrosis of the media and intima with infiltration by polymorphonuclear cells, eosinophils, lymphocytes and histiocytes, was followed by vascular elastic and vascular smooth muscle destruction resulting in lesions considered typical for polyarteritis nodosa (PAN). Two patients one abbreviated D.G. and the other E.V., who injected methamphetamine via intravenous injection had arterial lesions in cerebral and cerebellar (D.G.) and brainstem pontine vessels (D.G. and E.V.), however detailed histopathologic descriptions were not provided. Their report was followed by correspondence by Gocke and Christian [39] who contended that exposure to the Australia antigen of hepatitis B antigen was likely in their cohort [38] conceivably associated with circulating immune complexes and complement activation as had recently been described [40, 41]. The authors [42] responded that no more than 30% of sera from drug abuse patients ultimately tested positive for the Australia antigen. Those with antigen-positive sera who had used drugs others than methamphetamine had no evidence of angiitis when studied angiographically.

Baden [43] wrote that he had not observed a causal relation between drug abuse and necrotizing arteritis at the Office of Chief Medical Examiner of New York City for the past one-half century among thousands of autopsied drug abusers. Further, 14 cases were claimed documentation for angiitis was presented in only 4 patients but no substantiation for the diagnosis was given in the remainder except that 5 were asymptomatic, and 5 had a variety of nonspecific systemic signs and symptoms. Citron and Peters [42] responded that evidence of aneurysms so noted in 13 patients, was in their opinion ample evidence of arteritis.

Almost two decades later, cerebral vasculitis was demonstrated in a dubious report [27] of a three-week postpartum woman who took her first over-the-counter Dexatrim diet pill in many months containing phenylpropanolamine, without a history of amphetamine abuse. This was followed 90 minutes later by sudden headache, nausea vomiting and detection of subarachnoid blood on CT neuroimaging and a frontal lobe hematoma. Bilateral carotid angiography demonstrated diffuse segmental narrowing and dilatation of small, medium and large vessels and branches of the anterior and posterior circulation. Evacuation and histopathologic analysis of the hematoma was performed showing necrotizing vasculitis of small arteries and veins with infiltration of polymorphonuclear leukocytes particularly prominent in the intima with fragmentation of the elastic lamina and areas of vessel occlusion. It was unclear whether the findings were related to primary or drug-related CNS vasculitis. However, treatment with cyclophosphamide for 6 months was associated with almost complete resolution of cerebral angiographic abnormalities.

Etiopathogenic Mechanisms

After the report of Citron and colleagues [38], Rumbaugh and colleagues [44] described the cerebral vascular changes due to methamphetamine abuse in five rhesus monkeys given amphetamine in dose ranges used by human addicts. Two of the five monkeys developed generalized arterial spasm during a two-week period following intravenous injection. Three of the five animals demonstrated decreased caliber of named cerebral artery branches and flow of the contrast agent with normalization one day later while two others showed marked general decrease in small branches and large named vessels that improved in one animal and progressed in another. Histopathologic changes at postmortem examination included microaneurysmal enlargement of arteriolar segments, mononuclear perivascular cuffing of small arterioles, parenchymal necrosis, petechial hemorrhages, and swelling of brain tissue, with most of the hemorrhagic lesions centered on small-size arteriolar and capillary vessels. Although reminiscent of the clinical and histopathologic findings of Citron and colleagues [38], necrotizing arteritis and transmural inflammation were lacking. Five years later, Rumbaugh and coworkers [45] subjected monkeys to short-duration (2 weeks) (5 animals), medium-duration (1 month) (3 monkeys), and long duration (one year) (3 monkeys) of thrice weekly (1.5 mg/kg body weight) intravenous amphetamine and related agents including methamphetamine, secobarbital, methylphenidate, and placebo, with performance of cerebral angiography and documentation of the resulting histopathology. Their studies showed relatively severe vascular injury and brain damage from intravenous methamphetamine that included occlusions and slow blood flow in small cerebral vessels respectively in two each of the five monkeys in the long-term administered drug, and in three each of those given drug for intermediate and short durations, with some animals and controls unaffected. There was less injury caused by secobarbital and methylphenidate. Further, the possibility of vascular spasm due to subarachnoid blood was excluded by lack of blood at postmortem examination in the subarachnoid space in any of the animals.

COCAINE

Background

A classic review of cocaine and stroke describes its abuse potential [46]. Cocaine, which is derived from the leaves of the *Erythroxylum coca* plant found primarily in the eastern mountains of Peru, Ecuador, and Bolivia, is available for abuse as cocaine hydrochloride, a water-soluble white salt in crystal, granular, and white powder that can be sniffed and “snorted” intranasal or injected parenterally [3]. The “free base” alkaloid form is known as “crack” [16] derives its name from the cracking sound that occurs after dissolution of the hydrochloride salt in water, heated, and mixed with ammonia without or without baking soda. This chemical reaction converts cocaine hydrochloride to a volatile form of the drug, almost pure cocaine. Street cocaine or the non-crack form is highly variable in purity, and often cut with various agents [47]. The alkaloid free-based form, which is inhaled or smoked, is accompanied by higher blood concentrations and more pronounced euphoria.

When smoked as free-base, it is absorbed into the pulmonary circulation and transmitted to the brain in <10 seconds. After appearance in the bloodstream, cocaine is rapidly hydrolyzed to benzoylecgonine [48], which can be accurately tested in the urine; however, levels may persist for up to 27 to 36 hours depending upon the route of administration and host cholinesterase activity [49-51]. In recent years, with increasing availability and purity, and a drop in the price of cocaine from the early 1970s, new cohorts from all socioeconomic backgrounds and age groups have been attracted to this highly addictive drug, and use has continued to expand on a year-by-year basis.

Neuropharmacology

Cocaine is a highly potent central nervous system (CNS) stimulant that rapidly crosses the BBB due to its highly lipophilic properties and is widely distributed through the brain with its major metabolites binding at receptors with varying affinities at presynaptic sites, stimulating the release of dopamine (DA) from synaptic vesicles and blocking DA reuptake resulting in enhanced dopaminergic neurotransmission, in addition to its local anesthetic properties [52-55]. The underlying molecular neurobiology and genetics of cocaine addiction and its treatment with an emphasis reviewed elsewhere [56]. The investigation of single nucleotide polymorphisms (SNP) that encode amino acid substitutions in opioid receptors and ligands implicated in drug addiction, particularly those of the mu opioid receptor (MOP-r) gene system (*OPRM1*) that releases DA from neural synapse when activated, and those of the kappa receptor (KOP-r) that instead lower extracellular dopamine levels, have contributed understanding to the variability in drug addiction among susceptible individuals [57].

Clinicopathological Spectrum of Cocaine-Related Cerebral Vasculitis

Excluded Literature Patients

Since the first reported patient with possible association of cocaine and ischemic stroke [58], both stroke and cerebral vasculitis have been described in the literature as features of cocaine drug abuse. One clinical series of 28 patients [59] and another of 15 patients [60] failed to identify vasculitis by cerebral angiographic data, and in a pathologically studied patient at postmortem examination [59]. Moreover, vasculitis was not suggested in a review of 13 patients from nine published reports by the same authors [61] of cocaine-associated cerebrovascular complications. Other cases of presumed vasculitis suggested by intracranial arterial narrowing [62] in the absence of confirmed histopathology were contested as probably representing vasospasm following subarachnoid hemorrhage [63].

Pathologically-Verified Literature Patients

Only ten histologically verified patients, including six men and 4 women, age 21 to 39 (mean age 28 years) occurred in the absence of other possible known causes including concomitant infection by human immunodeficiency virus type 1 (HIV-1 or HIV) infection and known causative coinfections [25, 64-70]. In all but 1 patient [68] who had a long-standing cocaine habit with abuse sometime in the 6 months before admission, onset of neurological symptoms immediately followed cocaine use that was intranasal cocaine in 6 patients [66-70], intravenous in 2 [64, 65], smoked in 1 [64], and acquired via unknown modality in 1 [64]. Cerebral vasculitis was associated with cerebral hemorrhage in 3 patients [67, 68] and ischemia in the 7 patients [25, 64-66, 69, 70] that typically presented with abrupt onset of headache and focal hemiparesis so noted in 6 patients [67, 68, 25, 64], confusion or agitation [65, 66, 68-70], and grand mal seizures [66] that progressed to stupor, coma and death in 3 patients [25, 64, 66]. Lumbar CSF analysis showed lymphocytic pleocytosis of 10 to 65 cells/ cm³ with elevation of the protein content from 185 to 630 mg/dL [65, 70], and was completely normal in 2 other patients [64, 68]. Cerebral angiography performed in 7 patients showed an avascular mass in the patient with a putaminal hemorrhage [67], abnormal large named vessel occlusions or segmental narrowing in 3 patients [64, 68, 25], poor filling and irregularities in vessel appearance in 2 [69, 70], and normal in one patient [65].

The pathology of cerebral vasculitis was established by brain and meningeal biopsy in seven patients [64, 65, 67-70], at postmortem examination in two patients [25, 66], and by both in one patient [64]. The underlying pathology of cerebral vasculitis was non-necrotizing with transmural mononuclear cell inflammation affecting small arteries and veins in three patients [64, 66, 67] or veins alone in three patients [68-70], and perivascular cuffing of small arteries and veins in another [65]. In two patients, there was necrosis of small cerebral vessels associated with polymorphonuclear cell inflammation of small arteries and veins [68] or large named vessels [25]. Among three patients so studied at postmortem examination, non-necrotizing small vessel vasculitis was noted in the brains of two patients without evidence of systemic involvement [64, 66], while necrotizing large vessel vasculitis was found in both the brain and systemic organs [25].

Treatment consisting of corticosteroid was administered to seven patients, five of whom improved [64, 65, 68, 70] and two who died with refractory seizures despite anticonvulsant medication [64] or because of infection, coma and decerebration [25]. There was no mention

of treatment or outcome in 3 patients, [66, 67, 69] including two patients who succumbed to coma, hypoxic ischemic decerebration, and death [66, 67].

Etiopathogenic Mechanisms

Although cocaine-associated cerebral vasculitis has not been rigorously studied, several independent lines of experimental evidence suggest possible etiopathogenic mechanisms in susceptible individuals.

The first was the observed effects of cocaine in the induction of adhesion molecules and endothelial leukocyte migration across cerebral blood vessel endothelia walls particularly under inflammatory conditions, which may disturb the function of the blood brain barrier.

Cocaine increased the expression of the endothelial adhesion molecules intercellular adhesion molecule (ICAM)-1, vascular cell adhesion molecule (VCAM)-1, and endothelial leukocyte adhesion molecule (ELAM)-1 on BMVEC with a peak effect on ICAM-1 expression between 6 and 18 hours after treatment in human brain microvascular endothelial cells (BMVEC) cultures and increased monocyte migration in an *in vitro* BBB model [71-74] constructed with BMVEC and astrocytes [75]. These effects of cocaine, exerted through a cascade of augmented expression of inflammatory cytokines and endothelia adhesion molecules, may contribute to the known cerebrovascular complications of cocaine abuse.

The second is the effect of cocaine on endothelial cell permeability and apoptosis as well as the induction of chemokines and cytokines. The immunomodulatory effects of cocaine on brain microvascular endothelial cells and its proinflammatory effects on induction of proinflammatory cytokines and chemokines was investigated using a human BBB model that included HIV neuroinvasion [76]. Cocaine increased the *in vitro* permeability of endothelial cells of the BBB model and induced apoptosis of mouse thymocytes in cultures of BMVEC and monocytes using an enzyme-linked immunosorbent assay (ELISA) of generated accompanied by up-regulation of macrophage inflammatory protein (MIP)-1, MIP-1 α , inducible protein (IP)-10, and interleukin (IL)-8 and TNF- α expression.

A third line of investigation has been the observed synergy of cocaine in facilitating pathogenic retroviral neuroinvasion, which may confer an independent risk factor for cerebral vasculitis. Both *in vitro* and *in vivo* studies have provided valuable tools in exploring the role of cocaine in mediating HIV-1-associated neuropathogenesis. The importance of drug abuse in conjunction with HIV-1 has been underscored by the ability of cocaine to induce retroviral replication in mononuclear cells [77] and enhance gp120-induced neurotoxicity [78].

OPIOIDS

Background

The opioid drugs comprise a large number of agonists, antagonists and mixed agonist-antagonists. Opioid overdose accounts for at least 16,000 deaths annually in the US [79] and occurs across sex, ethnic, age and geographic strata, and involves both medical and nonmedical opioid uses.

According to the Centers for Disease Control and Prevention (CDC), since 2003, opioid analgesic abuse [80] overdose deaths involving opioid analgesics exceeded those due to cocaine. For every unintentional overdose death related to an opioid analgesic, nine persons were admitted for substance abuse treatment, 161 reported drug abuse or dependency, and 461 reported nonmedical uses of opioid analgesic drugs [81].

Also known as diacetylmorphine, heroin was first synthesized by the Bayer Company in 1889 as a less addictive morphine sulfate substitute [82], however it has since become cheaper and more readily available.

There is extensive literature relating to the outcome of heroin abuse and overdose [83-87] with a reported the average mortality rate of 2% in regularly injecting persons, half of which is attributable to overdose and equal to 20 times the mortality rate expected in non-drug using peers.

Neuropharmacology

Opioids or narcotic drugs have pharmacologic properties similar to those of morphine that include the derivatives morphine, hydrocodone, oxycodone, hydromorphone, codeine, fentanyl, meperidine, methadone, and opium. Whereas the source of opioids is the exudate of seed from the poppy plant, heroin is derived from acetylation of morphine [21]. Heroin is administered intravenously, intranasal and subcutaneously.

A higher bioavailability of heroin is present after heating on foil for inhalation compared to smoking after heating. Intravenous injection leads to extreme euphoria that peaks at 10 minutes followed by profound sedation and analgesia that lasts for up to one hour. Opiate overdose produces the triad of coma, respiratory depression and meiosis. The medical complications of long-term heroin exposure includes endocarditis, pulmonary complications of embolism, pneumonia and granulomatosis or fibrosis, nephropathy, immunodepression, infection at the site of injection due to cellulitis, thrombophlebitis, and bacteremia, and hepatitis due to needle sharing [88].

It binds to endogenous opiate μ_1 receptors, which are responsible for most of the analgesic effects, and for the actions of the central nervous system and cardiovascular system leading to bradycardia, hypotension, and respiratory depression. Agonist actions at μ_2 receptors are responsible for respiratory depression, delayed gastrointestinal motility, meiosis, and physical dependence.

Agonist actions at kappa receptors lead to separate analgesia. Circulating serum morphine is transformed into morphine-3-glucuronide or morphine-6-glucuronide by the liver and the kidney. Most fatal and nonfatal overdoses occur when heroin is administered intravenously.

Clinicopathological Spectrum of Opioid-Related Cerebral Vasculitis

Excluded Literature Patients

Four often cited Brust, coworkers [58], Adle-Biasette, and colleagues [89] described patients with heroin abuse and cerebral vasculitis studied after death. In three patients [58] cerebral vasculitis was considered possible after exclusion of bacterial or fungal endocarditis,

focal ischemic during a period of shock after overdosage and hypoventilation, concomitant methamphetamine, drug allergy, and likely adulterants. One reported patient [58] died in methadone detoxification and postmortem revealed a massive hemorrhage of the right basal ganglia however, intracranial vessels were not examined. A second reported patient [58] developed unconscious followed by seizures, global aphasia and right hemiparesis in association with multiple occlusions on cerebral angiography before expiring, however neuropathological postmortem examination was not performed. A third reported heroin addict [58] who presented comatose with xanthochromic and bloody cerebrospinal fluid and died, was found to have a left intracerebral hemorrhage with normal large vessels on postmortem examination however, the smaller cerebral vessels were not commented upon.

Another often-cited pathological case [89] of possible cerebral infarction following inhalation of heroin in who was found dead one morning after the usual signs of recent heroin intake had ischemic cardiac lesions of varying ages and cortical watershed infarcts, reportedly had normal intracranial vessels at postmortem examination.

Confirmatory pathology was not sought among 5 often cited surviving heroin abusers [90-94] who presented with focal strokes on neuroimaging after inhalation [93, 94] or intravenous [90, 91] evidencing likely cerebral vasculitis on cerebral angiography; [90, 92], one of whom admitted to intermittent lysergic acid diethylamide (LSD) use [90]. All of the patients who had employed only heroin, cocaine or marihuana described by Halpern and Citron [38] in a report of necrotizing angiitis associated with drug abuse were included in the category of normal angiographic examinations, and their supporting pathology, even if available, was not described in the paper.

Pathologically-Verified Literature Patients

We could not identify any pathologically confirmed cases of heroin induced cerebral vasculitis reported in the literature, nor was cerebral vasculitis suggested as a likely occurrence in heroin abuse [95], heroin addiction [88, 96], or acute overdose [83]. Moreover, detailed neuropathological studies carried out on 134 victims of acute heroin intoxication including 18 who survived for periods of hours or days [97], who respectively demonstrated cerebral edema in conjunction with vascular congestion, capillary engorgement, and perivascular bleeding attributed to toxic primary respiratory failure; and ischemic nerve cell damage resembling systemic hypoxia, showed no evidence of cerebral vasculitis, and only one focus of lymphocytic perivascular inflammation. The brains of 10 intravenous drug abusers who died from heroin overdoses, including one due to gunshot injury [98] likewise showed no evidence of cerebral vasculitis at postmortem examination, manifesting only a few perivascular mononuclear cells associated with pigment deposition.

Etiopathogenic Mechanisms

The postulated mechanisms of opioid related neuronal and CNS vascular injury include increased oxidative stress, induction of inflammatory cytokines, and increased permeability of the BBB especially in intravenous drug abuse. Ramage and colleagues [99] described increased deposition of hyperphosphorylated tau in entorhinal cortex and subiculum of the hippocampus, AT8-positive neurofibrillary tangles in entorhinal cortex, and increase in β -

amyloid precursor protein (β APP) in both the hippocampus and brainstem of drug abusers compared to controls. Several postulated causative mechanisms included repeated head injury, hypoxic-ischemic injury associated with opioid induced respiratory depression, microglial associated cytokine release, and drug-associated neurotoxicity.

DRUG ABUSE AND HIV/AIDS

Background

Recognition of the propensity for cerebral vascular inflammation in association with HIV/acquired immune deficiency syndrome (AIDS) and drug abuse has provided new insights into the mechanisms of cerebral vasculitis.

Early in the HIV/AIDS epidemic, it was clear that a significant proportion of infected persons were intravenous drug users. Their associated risk behavior exposed them to infection through sharing of contaminated needles thereby increasing the risk of spread of HIV and other blood borne infections [100]. Among 50 patients with AIDS and neurological complication, six HIV-1 infected patients described by Snider and colleagues [101] were intravenous drug users (IVDU), the others being male homosexuals and recently arrived Haitian refugees. The two postulated periods in the neurobiology of HIV-1 when autoimmune disease manifestations can occur that appear to be significant for the development of cerebral vasculitis were shortly after seroconversion and before the spread of productive infection [98, 102]; and after initiation of highly active antiretroviral therapy (HAART) in association with the immune reconstitution syndrome (IRIS) [103]. The impact of IVDU in the development of cerebral vasculitis and other autoimmune sequel is not well understood. However there is an extensive literature suggesting an independent contribution of IVDU to immune suppression, breakdown of the BBB, microglial activation, and neuronal injury [104-110] and an additive or synergistic reinforcement of HIV-related brain damage by IVDU [111].

The timing of early HIV invasion has been difficult to ascertain based on the presence of one or more well-recognized clinicopathological HIV/AIDS syndromes including HIV encephalitis [112] HIV-associated dementia [113], and AIDS-dementia complex [114], all of which are indicative of symptomatic infection. HIV encephalitis is initially associated with myelin pallor and gliosis of the centrum semiovale found in more than 90% of brains from patients dying with AIDS [115]. With increasing severity of symptomatic disease, multiple glial nodules with the multinucleated cells characteristic of HIV encephalitis occur throughout the white matter, basal ganglia, cerebral and cerebellar cortex, brainstem and spinal cord. HIV has been demonstrated in monocytes and multinucleated giant cells by electron microscopy, immunocytochemical techniques and in situ hybridization. Guillemin [116] reviewed Vasculitides in the context of HIV infection.

Clinicopathological Spectrum of Drug Abuse and HIV/AIDS

HIV-Seropositive, Pre-AIDS Literature Patients

It has long been recognized that HIV antigens may be identified in CSF at, or shortly after seroconversion [117-119], and asymptomatic HIV-positive subjects [120] including seropositive men with normal CD4+ cell counts, neuropsychological, and neuroimaging, and normal neurophysiological investigations [121]. The examination of presymptomatic individuals has been virtually confined to intravenous drug abusers since other risk groups have a very low mortality before development of AIDS [106]. Gray and colleagues [122] described six patients with non-necrotizing cerebral vasculitis in a postmortem series of presymptomatic HIV-seropositive drug abusers, and Yankner and coworkers [123] with rapidly fatal necrotizing granulomatous angiitis of the brain without evidence of acquired immune deficiency, circulating HTLV-III or HIV-1 antibodies, described an analogous patient. Seven other patients were described by Bell and colleagues with lymphocytic infiltration of the walls of leptomeningeal and subarachnoid veins, without specific reference of cerebral vasculitis [102]. Gray and colleagues [122] studied two cohorts of 11 patients, one HIV-seropositive and non-AIDS, and the other HIV-seronegative heroin abusers, 10 patients of each died from heroin overdose and another of a fatal gunshot wound.

Neuropathological studies [122] showed varying degrees of vascular inflammation including "true vasculitis" exemplified by dense vascular inflammation extending through the vessel wall, associated with leptomeningitis in six of the 11 HIV-seropositive AIDS-negative patients. However, there was no mention as to whether inflammatory process involved arteries and vein or the vessel caliber. Vascular inflammation was comparatively mild or absent and restricted to a few perivascular mononucleated cells associated with pigment deposition, without transmural vascular inflammation or meningitis in the HIV-seronegative cohort. HIV immunocytochemistry was negative in both cohorts and multinucleated giant cells, considered the hallmark of productive HIV infection in the brain and an essential neuropathological feature of HIV encephalitis, were not seen. One year later, Bell and coworkers [102] described the neuropathological findings of 23 intravenous drug users from the Edinburgh HIV Autopsy Cohort who died suddenly after seroconversion but while still in the presymptomatic stage of HIV infection in comparison to 10 HIV-negative intravenous drug users, 12 non-intravenous drug user controls, and 9 patients with full-blown AIDS, who also died suddenly. Seven of the presymptomatic HIV-positive patients showed infiltration of T-cells in the walls of veins in association with low-grade lymphocytic meningitis; seven others demonstrated isolated lymphocytic meningitis, and one patient had focal perivascular lymphocytic cuffing and macrophage collections throughout the central white matter tissue of the brain and in basal ganglia. Neither conspicuous perivascular lymphocytic infiltration nor lymphocytic meningitis was noted in HIV-negative intravenous drug user controls or in those with no drug association, or others with full-blown AIDS.

Neuropathological examination in presymptomatic HIV-seropositive patients failed to reveal characteristic lesions of HIV encephalitis and none of the subjects showed immunocytochemical evidence of p24 antigen in brain tissue. Nearly a decade later, Bell and colleagues [105] reiterated that in more than 50% of pre-AIDS cases so studied, the brain was characterized by a low-grade lymphocytic meningoencephalitis in which T-cell infiltration was present in leptomeninges and the perivascular compartment, with an occasional HIV-p24

positive lymphocyte in the lymphocytic infiltrate, but not in brain parenchyma. According to the same authors [105] there was conversely no clear evidence of vasculitis among intravenous drug users with HIV encephalitis in the Edinburgh HIV autopsy cohort [124]. Yankner and colleagues [123] reported the clinicopathologic findings of a homosexual man with rapidly fatal cerebral granulomatous angiitis of the brain associated with isolation of human T-lymphotropic virus type III (HTLV-III) in CSF and brain tissue. Mononuclear cellular infiltrates were present at postmortem examination in the walls of affected large named arteries without involvement of small arteries and veins, and with rare microglial nodules and multinucleated giant cells.

The early CNS changes of HIV infection were investigated among hemophiliacs examined after sudden death from intracranial hemorrhage and liver cirrhosis [125] and in experimental animal models of simian immunodeficiency virus (SIV) syndrome [126] and feline immunodeficiency virus (FIV) infection [127]. They have comparable neuropathological changes of gliosis, occasional microglial nodules, perivascular mononuclear infiltrates, and occasional leptomeningeal meningitis in all three, characteristically without multinucleated giant cells or evidence of HIV in the brain [125-127]. HIV-infected cells were mainly perivascular and expressed macrophage markers in the SIV model [126] suggesting transit of virus across the BBB as the main source of entry into the CNS.

Moreover, the comparatively less pronounced vascular inflammation than that described in early HIV-infection associated with drug abuse, suggests that intravenous drug abuse contributes to vascular inflammation.

HIV/AIDS-Associated-IRIS Literature Patients

The introduction of HAART has changes the incidence, course and prognosis of the neurological complications of HIV infection concomitant with almost undetectable viral load in plasma and a rise in circulating T-lymphocytes [128]. One pathologically confirmed patient with cerebral vasculitis and van der Ven and colleagues [129] described IRIS. This HIV-seropositive homosexual man developed dysarthria and dysphagia after HAART with worsening and appearance of limb paresis after discontinuation of the medication. Treatment with corticosteroids preceded recommencement of HAART but there was worsening with discontinuation of corticosteroids. Biopsy of a hyperintense fronto-parietal lesion on T₂-weighted MRI showed small vessel lymphocytic vasculitis, with microglial activation in the surrounding parenchyma. A severe demyelinating leukoencephalopathy in association with intense perivascular infiltration by HIV-gp41 immunoreactive monocytes/macrophages and lymphocytes was described by Langford and colleagues [130] in seven postmortem patients. All were severely immunosuppressed and treated with HAART with presumed IRIS however, high not low levels of HIV replication were noted. However, there was no consideration of cerebral vasculitis. Confirmatory neuropathology was not sought however in a patient described by Patel and coworkers [131] with HIV-seropositive man who developed encephalitis 10 months after HAART in association with a lower thoracic dermatomal varicella zoster virus (VZV) rash.

Levamisole

Background

The anti-helminthic agent levamisole, first introduced for use in veterinary medicine was later discovered to have potent immunomodulation properties, prompting its application in inflammatory and oncologic conditions including rheumatoid arthritis, aphthous ulcers, and melanoma (132). The U.S. Food and Drug Administration as adjuvant therapy for the treatment of inflammatory conditions and cancer approved Levamisole. In Asia, it has been used as an anti-helminthic and pesticide agent.

Epidemiology

Levamisole was detected in cocaine bricks by the U.S. Drug Enforcement Agency in 2003 (133), noting an increase from 44.1% of specimens in 2008 to 73.2% in 2009 (134), signaling a rising public health problem. In 2011, Buchman and co-workers (135) reported a prevalence of 68% employing a combination of immunoassay and gas chromatography-mass spectroscopy detection methodologies. Other drugs noted in positive urine specimens included the opioid analgesics methadone (45%), codeine (16%), heroin/6-monoacetylmorphine (6%), and morphine or oxycodone (5%). The importance of detecting levamisole in urine concomitantly with cocaine in affected cases is in being able to ascertain its separate contribution to the observed neurotoxicity in suspected cases.

Neuropharmacology

Levamisole is 100- to 300-fold less potent than cocaine in blocking norepinephrine and dopamine uptake, and has a very low affinity for the serotonin transporter; and it does not trigger an appreciable substrate efflux. Nevertheless, the desired neuropharmacologic effects leads to its widespread contamination in cocaine production. It potentiates the euphoric effects of cocaine by inhibiting dopamine reuptake and forming amphetamine-like metabolites. Hofmaier and colleagues (136) studied the allosteric effects of levamisole and cocaine at 30 μ M, a concentration at which levamisole displayed already mild effects on norepinephrine transport but without an inhibitory action on cocaine. Levamisole metabolized to aminorex, an amphetamine-like substance that exerted strong effects on dopamine, serotonin and norepinephrine transporters in a manner that resembled amphetamine. They concluded that while the adulterant levamisole itself had only moderate effects on neurotransmission, its metabolite, aminorex, nonetheless exerted distinct psychostimulant effects and that after the cocaine effect “fades out,” the levamisole/aminorex effects “kicks in.”

Clinicopathologic Manifestations

Exposure to levamisole-adulterated cocaine is associated with a variety of well-described hematological, skin, renal and pulmonary pathologies (137) often in association with positive antineutrophil cytoplasmic antibody (ANCA) serology. Hematologic abnormalities include agranulocytosis and neutropenia, which occurs in a dose dependent fashion, which is not commonly associated with pure cocaine-linked side or a characteristic of drug-induced vasculitis. A distinguishing feature of levamisole-adulterated cocaine exposure is small vessel vasculitis (SVV) which involves the ear lobes and the skin overlying zygomatic arch or lower

extremities, often with purpuric plaques in a retiform pattern or central necrosis. Skin biopsy shows pathological involvement of superficial and deep dermal vessels associated with numerous neutrophils and eosinophils that surrounding and invade the walls of dermal vessels with extravasation of red blood cells, leukocytoclastic debris (nuclear dust), and fibrinoid necrosis on hematoxylin and eosin-stained tissue sections. Such findings are similar to children with chronic levamisole treated for nephrotic syndrome so noted in a minority of children who developed purpuric lesions of at least the ears and biopsies revealing cutaneous vasculitis (138). Although organ involvement has not been characteristic of levamisole-adulterated cocaine-induced autoimmune disease, there is an established association with proteinuria or hematuria, acute renal injury, focal necrotizing and crescentic pauciimmune glomerulonephritis in some cases, and increased titers to p-ANCA. As in other drug-induced vasculitides, pulmonary involvement can complete the triad of skin, kidney and lung pathology in the form of diffuse alveolar hemorrhages, idiopathic pulmonary hypertension, or other clinicopathologic presentations.

Multifocal Inflammatory Leukoencephalopathy

It has taken 25 years to recognize the causal association of levamisole-associated MIL in cocaine users. In 1992, Hook and colleagues (139) described three patients, ages 45 to 74 years, who developed a cerebral demyelinating disease within 3 to 5 months of beginning adjuvant therapy with 5-fluorouracil (5-FU) and levamisole. Two patients presented with progressive encephalopathy and ataxia, and a third had unexplained loss of consciousness. Brain MRI revealed multiple gadolinium-enhanced white matter lesions, predominantly in a periventricular distribution. Cerebrospinal fluid obtained in two patients showed oligoclonal bands (two patients) and pleocytosis (one patient). Pathological studies of brain biopsy specimens from two patients revealed cerebral demyelination and perivascular inflammation similar to multiple sclerosis (MS). There was clear improvement after discontinuation of chemotherapy and administration of corticosteroids. The pathogenesis was unclear, and the authors considered the etiological basis to be 5-FU toxicity although the role of levamisole was not excluded.

Three years later, Kimmel and colleagues (140) described a patient age 57 years, who developed progressive confusion and ataxia over a three-week period, five weeks after adjuvant therapy with levamisole for malignant melanoma. Brain MRI showed multifocal enhancing white matter lesions. Cerebrospinal fluid showed pleocytosis with an increased IgG index. The patient improved with a three-month tapering course of corticosteroids. The cause of the leukoencephalopathy in previously described cases (139) of 5-FU and levamisole was assigned at least in part, to levamisole.

One year later, Luppi and colleagues (141) described two patients, age 54 and 60 years, treated with adjuvant 5-FU and levamisole for colon cancer, who after 10 weeks and 6 weeks respectively from onset of treatment noted confusion, aphasia, ataxia, and progressive obtundation leading to decerebration (Case 1) and nasogastric feeding (Case 2). Brain MRI in both showed widespread bilaterally symmetric periventricular and hemispheric white matter hyperintensities compatible with MIL. Treatment with parenteral corticosteroids (Case 2) led to clinical improvement.

A decade later, Wu and coworkers (142) described a series of 31 patients with levamisole-induced MIL, including 7 from their institution and twenty-four from the medical

literature, treated with a combination of levamisole and 5-FU adjuvant therapy (21 patients) or levamisole alone (10 patients) for malignant cancer, most commonly colon cancer.

Onset of gait ataxia in two-thirds of cases, was delayed in those treated with combination 5-FU and levamisole compared with levamisole alone (11.7 weeks vs. 2.5 weeks). Brain MRI showed enhancing periventricular or supratentorial white matter lesions. Cerebrospinal fluid showed lymphocytic pleocytosis in 47% of cases. Treatment with corticosteroids and intravenous immunoglobulin (Ig) led to improved clinical status in 29 (94%) cases.

In 2009, Xu and coworkers (143) described the clinical and neuroradiological findings in 16 patients, age 8 to 52 years, treated with levamisole for recurrent aphthous ulcers or ascariasis infections noting weakness (75%), aphasia (50%), neurocognitive (50%), and facial palsy (44%) as the main presenting clinical features. Brain MRI showed typical plaque and round or oval demyelinating enhancing white matter lesions and hyperintense signal on T₂/FLAIR images. Brain biopsy in one case showed multifocal demyelinating lesions with lymphocytic perivascular cuffs. Treatment with corticosteroids and hyperbaric oxygen led was associated with full recovery.

In 2012, Blanc and colleagues (144) described a 29-year-old woman and active crack cocaine abuser with acquired immune deficiency syndrome (AIDS) presented with fever, malaise, and back pain and an unremarkable neurological examination. Cerebrospinal fluid showed acellular fluid with increased protein content and oligoclonal bands. A urine drug screen showed cocaine and opiates. Brain MRI showed lesions consistent with MIL. Sera later tested for both cocaine and levamisole by gas chromatography-mass spectroscopy were negative. The authors speculated that levamisole contamination was responsible for MIL citing that urine testing for levamisole would have been positive if performed at the time of cocaine detection.

In 2013, Yan and colleagues (145) described the clinical and neuroradiologic features of 15 patients, age 31 to 54 years, treated with levamisole for worm expulsion for two weeks to two months prior to onset of fever, headache, dizziness, neurocognitive disturbance, weakness, and visual impairment. Nine patients who underwent CSF examination showed only pleocytosis. Electroencephalography in all 15 showed high amplitude slow waves. Brain MRI showed multiple hyperintense T₂/FLAIR bilateral centrum semiovale and periventricular lesions (all patients), while two-thirds showed lesions in basal ganglia; with lesser frequency in the frontal (26%), occipital (6%), and temporal lobes (6%), brainstem or cerebellum (6%). Treatment with “hormone therapy” was effective in all patients.

In the same year, 2013, González-Duarte and Williams (146) described a 40-year-old woman with chronic daily use of cocaine admitted for acute confusion, aphasia, and fever. Cerebrospinal fluid showed neutrophilic pleocytosis. Brain MRI showed hyperintense signal in left parietal lobe white matter on T₂/FLAIR images. She developed sudden visual changes and hemiparesis 10 days later, and a week after, a new episode of expressive aphasia each associated with respective right and left frontal white matter lesions reminiscent of MIL. Complete recovery occurred in two weeks and she remained stable without further new episodes despite continued cocaine abuse. The authors speculated a relationship to levamisole adulteration.

In 2015, Vosoughi and Schmidt (147) described MIL in two cocaine abusers, age 25 and 41 years, who presented respectively with unilateral progressing to bilateral sensorimotor deficits; and confusion with impaired balance. Serial brain MRI in the first patient showed increasing bilateral T₂/FLAIR enhancing white matter hyperintensities in periventricular

white matter, pons and cerebellar peduncles, with similar presenting features in the second patients. Both patients improved with corticosteroids and plasma exchange. Urinary levamisole was not tested in either patient although the authors concluded that it was a likely cause of MIL in their cases.

Finally, Vitt and colleagues (148) described a case of MIL with positive urine testing for cocaine and levamisole in a cocaine abuser with a history of hepatitis C infection. This a 63-year-old woman presented with three days of progressive confusion, fever, and headache. Over two days she developed spastic quadriparesis and stupor. Cocaine tested positive in the urine. Brain MRI revealed T₂/FLAIR hyperintensities and incomplete ring-enhancement in periventricular subcortical white matter, many of which were ovoid shaped. Cerebrospinal fluid showed a lymphocytic pleocytosis and elevated protein content without oligoclonal bands. Gas chromatography-mass spectroscopy detected levamisole in the urine. High-dose intravenous methylprednisolone for five days followed by plasmapheresis was ineffective. The patient received intravenous cyclophosphamide with stabilization. Ten months later, the patient was minimally conscious with mutism and generalized spasticity.

Immunopathogenic Mechanism

The mechanisms underlying levamisole-adulterated cocaine-induced systemic pathology are not well understood but a causal relation to ANCA-associated disease is suggested by the correlation of disease pathology, clinical relapse with detectable autoantibodies, sensitivity to immune modulatory and immunosuppressive therapy, and predictable levamisole-induced histopathology. Levamisole potentiates the production of interferon- α and interleukin-2 as well as increases T-cell activation and proliferation, neutrophil mobility, adherence, and chemotaxis and increases the formation of antibodies to antigens (132). It acts as a hapten, triggering an immune response resulting in opsonization and leukocyte destruction. Levamisole may interact with neutrophil extracellular traps (NET) composed of a complex of deoxyribonucleic acid (DNA), histones, and neutrophil granules including myeloperoxidase (MPO), proteinase-3 (PR3), and human neutrophil elastase (HNE). Neutrophil extracellular traps release in response to stress and provide a source of antigen that can activate the immune system (137). Although there has not been a postmortem-studied case of MIL, for unclear reasons, such patients fail to demonstrate vasculitis in brain biopsy tissue or symptomatic vasculitic skin pathology, renal, hematologic, or pulmonary involvement in life

CONCLUSION

Drug abuse is a rare cause of histopathologically verified CNS vasculitis. Nonetheless, the complications of illicit substance use on the cerebral circulation can be highly lethal with secondary vasculopathy, hemorrhage and aneurysm formation especially when the illicit substances are delivered parenterally. With only a handful of confirmed patients in the literature, and rare association if ever, with progressive neurological deficits, there is generally little justification for invasive laboratory investigation, especially given the availability of highly accurate vascular neuroimaging techniques. Management rests upon avoidance of further exposure and minimizing the secondary neurotoxic effects of the abused substances and polypharmacy use.

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Chapter 224

AUTOIMMUNE ENCEPHALITIDES

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ABSTRACT

Autoimmune encephalitis is a severe inflammatory disorder of the brain with diverse causes and a complex differential diagnosis including central nervous system vasculitis. Recent advances in the past decade has led to the identification of new syndromes and biological markers of limbic encephalitis, the commonest presentation of autoimmune encephalitis. Autoimmune encephalitis is associated with serum and intrathecal antibodies to intracellular and surface neuronal antigens against constituents of the limbic system neuropil. This has led to a reconsideration of a number of neuropsychiatric and neurocognitive disorders as having shared mechanisms of origin. The successful use of serum and intrathecal antibodies to diagnose affected patients, and their subsequent improvement with effective treatment has resulted in relatively few biopsy and postmortem examinations. In those available, there can be variable infiltrating inflammatory T-cells with cytotoxic granules in close apposition to neurons, analogous to microscopic vasculitis.

Keywords: autoimmune, encephalitis, hashimoto, encephalopathy

INTRODUCTION

According to Dalmau [1], for many years, the only known disorders associated with autoantibodies were myasthenia gravis and Lambert-Eaton myasthenic syndrome (LEMS).

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These two predominantly B-cell peripheral nervous system (PNS) disorders targeted acetylcholine receptors or voltage-gated calcium channels resulting in reversible neuromuscular alterations that fully accounted for the observed symptoms and signs. In the central nervous system (CNS), paraneoplastic disorders associated with onconeural antibodies were cross-reactive with tumor nuclear and cytoplasmic neuronal antigens mediated by cytotoxic T-cells not B-cells. With the large group of undiagnosed encephalopathies, in particular syndromes characterized by limbic encephalitis, investigators returned to the laboratory to study the patterns of brain neuropil reactivity of newly recognized autoantibodies [2]. The result has been the recognition of newly characterized childhood and adult neurological and neuropsychiatric disorders termed autoimmune encephalitis or encephalopathy, mediated by antibodies against surface and intracellular antigens [3]. The successful use of serum and intrathecal antibodies to diagnose affected patients, and their subsequent improvement with effective treatment has resulted in relatively few biopsy and postmortem examinations. In those available however, the resulting neurodegeneration associated with autoantibodies appears to result from infiltrating inflammatory T-cells, especially those with cytotoxic granules in close apposition to neurons, analogous but distinct from microscopic vasculitis. With the ease of screening the serum and cerebrospinal fluid for a panel of pathogenic autoantibodies, and obtaining detailed morphologic and metabolic images of the brain specific for the disorders, autoimmune encephalitis is in the differential diagnosis of childhood and adult primary central nervous system angiitis [4, 5, 6], particularly before brain tissue biopsy is considered, or to avoid potentially harmful empiric immunosuppressant therapy [7]. This chapter reviews their historical background, epidemiology, clinical presentation, laboratory evaluation, histopathology, diagnosis and management of the autoimmune encephalitis

HISTORICAL PERSPECTIVE

In 1968, Corsellis and colleagues [8] coined the term limbic encephalitis (LE) noting a relation to bronchial cancer in three patients in the sixth to eighth decade of life. All three cases had subacute temporal lobe seizures, neuropsychiatric, and memory disturbances for two years before death. Postmortem examination revealed inflammatory lesions in limbic grey matter sections of the brain, notably in medial temporal lobe structures of the uncus and amygdala nuclei, and in the hippocampal, cingulum and dentate gyri. Case 2 had an undifferentiated non-metastatic lung carcinoma removed six months after onset of neurological symptoms, while two others had clinically unsuspected cancer at postmortem examination. Case 1 had a bronchial carcinoma restricted to a mediastinal lymph node without a primary lesion, while Case 3 had an unsuspected oat cell carcinoma infiltrating the main bronchi of both lungs and adjacent mediastinal nodes. Over the ensuing decades, attention turned away from limbic encephalitis and toward neurological autoimmune paraneoplastic syndromes with the discovery of several neuronal target antigens including Hu (ANNA-1) responsible for paraneoplastic encephalomyelitis (PEM) [9] in association with small cell lung cancer (SCLC); Ri (ANNA-2) responsible for paraneoplastic cerebellar degeneration [10] and motor neuronopathy [11] in association with breast cancer; and PCA-1 responsible for paraneoplastic cerebellar degeneration [12] in association with gynecologic

tumors. Other syndromes associated with paraneoplastic encephalitis were elucidated by Dalmau and colleagues [13, 14] in their descriptions of anti-MA1 and MA2 and testicular cancer; and the collapsin response mediator protein-5 (CRMP5/Cv2) in association with thymoma. Each with an intracellular target antigen, the resultant histopathology of these antibodies generally consisted of infiltrative cytotoxic (CD8+) T-cell destruction of neurons, with variable IgG and complement deposits in the CNS, with less helper (CD4+) T-cells, and generally absent B-cells. Bernal and colleagues [15] illustrated the role of infiltrating CD8+ T-cells in cell death by showing their close apposition to neurons.

In 2000, Bien and colleagues [16] revisited non-cancerous cases of LE in its relation to temporal lobe epilepsy. The interface of strictly paraneoplastic and autoimmune mechanisms was subsequently highlighted in the characterization of patients with stiff-person syndrome (SPS) associated with antibodies to glutamic acid decarboxylase (GAD); and the clinical neurological syndromes associated with voltage-gated potassium channel (VGKC)-complex antibodies. Solimena and colleagues [17] investigated the existence of non-paraneoplastic CNS autoimmunity in a patient with SPS, epilepsy and type-1 diabetes (T1D, and increased titers of oligoclonal CSF IgG. Both the serum and CSF produced identical intense staining of all gray-matter regions. GAD65 was thence an important autoantigen in T1D, being highly expressed in the cytoplasm of pancreatic β cells. GAD-derived peptides were presentable by main histocompatibility complex (MHC) class I molecules and recognized by CD8+ T-cells on the surface of β cells. Activation of CD8+ GAD-specific T-cells further differentiated into memory cells suggesting a pathogenic role in T1D. However, only patients with very high titers of GAD were associated with LE; and they typically presented with recent-onset temporal lobe epilepsy (TLE) and intrathecal secretion, defining a form of non-paraneoplastic LE. Other patients within the SPS spectrum harbored antibodies against other proteins of the GABAergic synapse, including amphiphysin and gephyrin, which were found to associate with lymphoma, and malignant tumors of the breast, colon, lung, and thymus [18].

Contemporaneously, the clinical phenotypes associated with autoantibodies to VGKC-complex ranged from peripheral nerve hyperexcitability (PNH), to Morvan's syndrome (MoS), and LE and autoimmune epilepsy [19, 20]. VGKC-complex antibodies were subsequently described in 2 patients with reversible LE [21]. Both patients were negative for typical paraneoplastic antibodies and with near-complete recovery, including one with recurrent thymoma after plasma exchange (PE), while the other patient recovered spontaneously without specific immunotherapy. The immunoprecipitation of VGKC-complexes linked a number of clinical syndromes that might otherwise have remained separate.

By 2010, Graus and colleagues [22] classified neuronal antibodies associated with syndromes resulting from CNS neuronal dysfunction into two groups according to the location of the target antigen. One group of well-characterized autoantibodies that recognized intracellular neuronal antigens included Ri, Yo, Hu, Ma2, CRMP5/Cv2 and GAD. These so called onconeural antibodies were useful in the designation of a specific paraneoplastic neurological disorder. Bien and colleagues [23] described qualitative and quantitative immunopathologic features of biopsy or postmortem brain tissue in 17 cases of autoimmune encephalitis (AE) associated with intracellular (IAg) (Hu, Ma2, GAD) or surface antigens (SAg) (VGKC-C and NMDA). Their studies noted higher CD8+/CD3+ ratio and more frequent appositions of granzyme-B (GrB)(+) cytotoxic T-cells to neurons, with associated

cell loss in the IAg-onconeural group compared to those in the SAg group. The exceptions were GAD cases that showed less intense inflammation and relatively low CD8/CD3 ratios compared to the IAg-onconeural cases. A role for T-cell-mediated neuronal cytotoxicity was found in encephalitides with antibodies against IAg, whereas a complement-mediated humoral immune mechanism was suggested in VDKC-complex encephalitis. There was apparent absence of both mechanisms in NMDA receptor encephalitis.

Bauer and Bien [24] suggested that neurodegeneration in brains of patients with antibodies against IAg was not simply induced by antibody reactivity with the target antigen, but rather by the inflammatory T-cells. To be pathogenic, they pointed out, the imputed antibody first had to transit the blood-brain barrier (BBB) and then the cell membrane of the target cell to a location where it could bind the pathogenic intracellular antigen. Depending upon protein conformation and folding, the antigenic site might be readily accessible before inactivation and ensuing irreparable cell damage. It is difficult to imagine that an intracellular antibody could easily overcome each of these obstacles. A major concern in managing these disorders has not only been prompt treatment of the tumor, but commencement of effective immunotherapy targeting mainly cytotoxic T-cells [25]. Vasculitis has not been a recognized mechanism of injury in intraneuronal antibodies, either in life or at postmortem examination [26].

The past decade witnessed the emergency of serum autoantibodies against SAg and synaptic-enriched regions leading to LE that spares the cytoplasm and nuclei of neurons such as those against GluN1 or GluN2/3 synaptic subunits of *N*-methyl-D-aspartate (NMDA) and glycine receptors; and to the amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl) propanoic acid (AMPA) receptor; and other novel neuropil antigens that localize to the cell surface of neurons and dendrites colocalized with synaptophysin and spinophilin [27, 28, 29, 30]. All supportive of LE or AE, these new antibodies share the property of strong immunolabeling of areas of dense dendritic network and synaptic-enriched regions in the neuropil of hippocampus. The clinical phenotype associated with the novel neuropil antibodies include dominant behavioral and psychiatric symptoms and seizures. With inconstant features of cognition and memory, brain-magnetic resonance imaging (MRI) and 2-deoxy-2-[fluorine-18] fluoro-D-glucose (^{18}F -FDG PET) abnormalities were less frequently restricted to the medial temporal lobe than in patients with classical paraneoplastic and VGKC-complex antibodies.

A role for the autoimmune dysfunction in neuropsychiatric illness has been sought since the 1930s when autoantibodies were first reported in a schizophrenia patient [31]. Since that time, there have been reports of specific autoimmune responses to self-antigens in psychosis, affective disorders, and other neurobehavioral abnormalities [32, 33]. Clinical neurologists, neuroscientists and psychiatrists, all have a stake in the emerging link between autoimmunity and resulting neurologic and psychiatric disorders in AE [34].

AUTOIMMUNE LIMBIC ENCEPHALITIDES

Three autoantibodies found in children and adults with LE target intracellular GAD65, and surface antigens of the NMDAR and VGKC-complex. Classically, the associated

symptoms, which evolve over days to weeks, include short-term memory loss, sleep disturbances, seizures, irritability, depression, hallucinations, and personality change.

Anti-GAD65 Encephalitis

Background

Autoimmunity targeting the 65 kilodalton (kDa) isoform of GAD65 encompass diverse autoimmune disorders such as T1D and rare neurologic disorders including LE, temporal lobe epilepsy (TLE), cerebellar ataxia, and large and small fiber peripheral and autonomic neuropathy [35].

Epidemiology

A review of adult-onset SPS showed a prevalence estimate of 1 in 1,250,000 [36] with a predominance of women, and average age of onset of 40 years. The frequency of high titers of anti-GAD antibodies defined an RIA value >1000 IU/ml in TLE of unknown origin is 21% [37] of cases, with the highest titers related to TLE. Affected patients are typically women with T1D, early-onset epilepsy, and concomitant hypothyroidism, psoriatic arthritis and Celiac disease, a third of whom reported onset of LE as the predominant feature, with supportive findings of amygdala and hippocampus signal intensities on brain MRI, and medial temporal hypometabolism on FDG brain PET. The levels of anti-GAD ranged from 1207 to 87 510 IU/ml, with absent OCB, and a ratio of serum/CSF GAD antibody levels >1 suggesting intrathecal synthesis. Malter [38] estimated the prevalence of GAD antibodies in LE to be 17%, noting a subgroup of patients with TLE who had very high titers equivalent to those with SPS, medial temporal inflammation on MRI, and concomitant LE. In the TLE cohort, GAD antibody encephalitis proved to be equally common to VGKC-complex antibodies but differed in younger age, female sex, and presentation of first seizure, CSF oligoclonal bands, and intrathecal autoantibody synthesis. Patients with high levels of GAD antibodies, and classic or other neurological syndromes not typically associated with GAD antibodies, were at higher risk for an underlying cancer.

Clinical Aspects

Gagnon and Savard [39] reviewed the clinical experience of 58 cases of GAD65-antibody LE beginning with the first reported case [40] inclusively through 2016, in 7 observational studies, 3 case series, and 21 published case reports providing a useful summary of the literature of anti-GAD65-associated LE. Among the 58 cases, there were 21 children and 37 adults, 59% of whom were female, with a median pediatric age of 10 years (range 1-17 years) and mean adult age of 39 years (range 19-70 years). Diabetes alone, generally T1D, was noted in 50% of cases, in association with thyroiditis, diabetes, Celiac disease, psoriasis, and common variable immune deficiency (CVID) respectively in 73%, 18%, 9%, and 9%. Cancer was noted in 6 (10%) cases, including 4 SCLC and 2 malignant thymomas, generally in men of mean age 61 years (range 38-70 years). The commonest presenting clinical features were seizures in 56 (97%) cases, most commonly refractory status epilepticus; cognitive impairment in 38 (59%) mainly affecting memory, language, executive function, and attention; psychiatric symptoms in 16 (28%) cases, most commonly depression, behavior,

perception, and anxiety. Less common clinical manifestations included fever, dysautonomia, cerebellar incoordination and headache respectively in 8 (12%), 7 (12%), 4 (7%), and 3 (5%) cases. The most common seizure presentation was refractory status epilepticus.

Cellular and Synaptic Antibody Effects

Low titers of anti-GAD65 antibodies, generally <20 nmol/L occur in T1D and in the general population, while cases of anti-GAD65-associated neurological disorders including LE are seen in the hundreds of nmol/L. Two GAD isoforms with distinct localizations and functions, GAD65 and GAD67, are expressed in presynaptic CNS GABAergic neurons, and in pancreatic β cells. Glutamic acid decarboxylase converts L-glutamate to GABA using pyridoxal-5'-phosphate (PLP) as a cofactor. GABA is the commonest inhibitory neurotransmitter in the CNS and the ligand for the inhibitory voltage-gated chloride channel GABA_A, and G-protein coupled GABA_B receptors. GAD67 commonly coexists with GAD65 antibodies in patients with neurologic autoimmunity. However GAD67 is rarely an autoantigen in isolation, found predominantly in the cytoplasm where it produces basal levels of GABA; whereas GAD65 is located predominantly in nerve terminals anchored to the cytoplasm-facing side of synaptic vesicles where it believed to synthesize GABA for neurotransmission supplementary to basal levels. The classification of high titers of anti-GAD65 autoantibodies has been problematic in being grouped with onconeural autoantibodies.

Laboratory Investigations

The dominant clinical phenotype of seizures, neurocognitive and neuropsychiatric disturbances in most patients with anti-GAD-autoantibody associated LE is explained by the frequent involvement of the medial temporal lobes; an inflammatory CSF with intrathecal secretion of the anti-GAD65 autoantibody, and oligoclonal bands. Bien and colleagues [41] described a 24-year-old woman with frequent temporal lobe seizures, non-paraneoplastic LE, and a serum anti-GAD65 antibody titer of 1:32,000, in whom T₂/FLAIR MRI evolved over a period of 8 months, demonstrating right hippocampal swelling and signal increase to sclerosis and atrophy on MRI commensurate with clinical progression. Among 58 literature patients [39], 45/58 (78%) patient MRIs were abnormal with specific involvement of the temporal lobes in 34 (59%), and multifocal abnormalities in 9 (16%); and 7 patient MRIs were normal. The results of electroencephalography (EEG) available in 35 cases, showed epileptiform discharges in 27 (77%), and focal temporal involvement in 19 (70%). Lumbar CSF so studied in 41 cases, showed pleocytosis in 11 (27%) with white blood cell (WBC) counts ranging from 7 to 114 cells/ul; and present oligoclonal bands (OCB) in one-half of cases. Hyponatremia was identified in 3 cases. There were significantly elevated titers of anti-GAD65 antibodies in both serum and CSF in 35 patients; and in either serum (in 18) or CSF alone in 3. Concurrent antibodies were reported in 11 cases, including those to GABA_A in 5 cases, and VGKC-complex or GABA_B in 3 cases. Antibodies to NMDAR, AMPAR, and onconeural antibodies were all absent. FDG brain PET imaging and MRI were complementary in 50% of cases [49]. Combining both MRI and PET, all patients had temporal lobe abnormalities. EEG may be useful in classifying the seizure type and directing the use of anticonvulsants especially when clinical seizures lack motor convulsions.

Histopathologic Correlation

The clinicopathologic features of anti-GAD antibody LE were described in a woman [41] who presented with frequent complex temporal lobe seizures at age 23. Over 8 months there was an evolution of right hippocampal swelling and signal increase on T₂/FLAIR MRI to sclerosis and atrophy. At the time of epilepsy brain surgery CSF showed 10 WBC and oligoclonal bands. Right-sided selective resection the sclerotic hippocampus showed strong encephalitic features. High-dose corticosteroid therapy administered over several months resulted in seizure-free status until weaning off 2.4 years later when she developed Cushing syndrome. She lapsed into a series of temporal lobe seizures and memory impairment accompanied by temporal left hippocampal swelling for which long-term corticosteroid and azathioprine therapy was started with slow clinical improvement. At follow-up 3.7 years later, she was still experiencing frequent partial temporal lobe seizures with memory deficits.

Bien and colleagues [23, 41] summarized the histopathologic features of selective resection of the sclerotic hippocampus in this patient that included neuronal loss and astrogliosis and a strong accumulation of inflammatory cells in the resected hippocampus. There was marked invasion of the hippocampus by lymphocytes that were mainly CD8+ T-cells with the cytotoxic effector molecule GrB, in addition to CD20+ B-cells and CD138+ plasma cells. The pattern of pyramidal cell loss was severe in sectors CA4 and CA3, with selective sparing of CA1 and 2. Surviving neurons were positive for MHC class I, fulfilling the prerequisite for attack by CD8+ T-cells. The authors [23] quantitated the number of parenchymal T-, B-, and plasma cells, macrophages and glial cells in 3 cases of anti-GAD65 autoantibody LE that included a previously reported case [41] differentiating them from the IAg-onconeural (Ma2 in 3 cases; Hu in 4 cases); SAg types in associated with VGKC-complex (4 cases) and NMDA receptor (3 cases); and Rasmussen encephalitis (22 cases) and neurodegeneration controls (25 cases). The percentage of CD8 T-cells in the IAg-GAD cases was intermediate (54%) between the IAg-onconeural and SAg cases. The CD8+/CD3+ ratio of the SAg cases was significantly different from the Rasmussen encephalitis controls. That ratio was lower than in the parenchyma confirming that CD8+ T-cells migrated into the parenchyma more readily than CD4+ T cells. Apposition of multiple GrB+ lymphocytes to single neurons, consistent with a specific cytotoxic T-cell attack in case GAD/3. Bien and colleagues [23] noted diffuse cytoplasmic IgG detected by anti-human IgG in both neurons and astrocytes in all cases similar to that of controls which they attributed to leakiness of damaged neuronal membranes. Staining of C9neo indicative of complement activation was negative in the IAg GAD cases. CD68+ cells comprised 0.2% in the IAg-GAD cases.

The finding of a reduced CD8+/CD3+ ratio of the IAg-GAD cases, all without concomitant tumor, was lower than the IAg-onconeural group. It was also within the highest ratios of the SAg group of NMDAR cases compatible with the hypothesis that T-cells were a necessary aspect for neuronal loss and hippocampal atrophy in the 2 GAD-associated LE (in GAD cases 2 and 3). Notwithstanding, the absence of an underlying malignancy could contribute to the long duration of disease and overall less intense inflammation. As noted by Bien and coworkers [23], the pathogenic role of GAD antibodies has not been certain because of the different associated clinical syndromes (SPS, cerebellar ataxia, TLE and LE). Multiple antibodies against IAg and SAg may explain the relatively low CD8+/CD3+ and GrB/CD3 ratios in the IAg-GAD cases.

Diagnosis and Treatment

The diagnosis of anti-GAD LE should be considered in patients with a clinical syndrome of temporal lobe seizures, and cognitive and psychiatric disturbances, brain MRI abnormalities on T₂FLAIR MRI implicating the medial temporal lobes; CSF pleocytosis and OCB; and EEG revealing temporal lobe epileptic or slow-wave activity, in association with high levels of anti-GAD65 autoantibodies on RIA. Most cases will fail to disclose an underlying malignancy. In the series of 58 literature case summarized by Gagnon and Savard [39] follow-up was available in 53 cases. Full recovery was noted in 4 (8%) cases, 3 of whom received corticosteroids alone, with intravenous immune globulin (IVIg), or in combination with PE; a fourth case received no immunosuppressant therapy and recovered. Death occurred in 4 (8%) cases, 3 of whom had an associated cancer. Sustained improvement was noted in 23 (43%) cases with followup of 96 months. A favorable outcome was noted in 45% of cases with positive CSF GAD65 antibodies compared to 56% of those with antibodies only in serum.

Anti-NMDA Receptor Encephalitis

Background

In 2007, Dalmau and colleagues [42] identified a new CNS antigen as NR1/NR2B12 heteromers of the NMDAR with predominantly neuropsychiatric symptoms from a cohort of 526 cases of noninfectious LE with antibodies against CNS proteins. The anti-NMDA receptor antibody appears to play a critical role in synaptic plasticity and memory. Although anti-NMDA receptor encephalitis is not by definition associated with cancer, 59% of patients had a tumor, most commonly benign-appearing cystic mature or immature teratomas tumors of the ovary. All showed serum or CSF antibodies to the NMDA receptor. A year later, the same investigators [27] described a case series of 100 patients with antibodies against NR1-NR2 heteromers of the NMDA receptor as measured by enzyme-linked immunosorbant assay (ELISA), 91 of whom were women, all with psychiatric symptoms or memory complaints. In addition, seizures were seen in 76 patients; 88 were unresponsive or had altered consciousness, 86 had dyskinesia, 69 had autonomic instability, and 66 showed hypoventilation. Three-quarters presented initially to a psychiatric service.

Epidemiology

Given its characteristic disease course, it is now assumed that a relevant proportion of patients previously diagnosed with encephalitis of unknown origin would have anti-NMDA receptor encephalitis [43] representing about 1% of all young patients' admissions to intensive care units (ICU). A French study [44] noted a frequency of anti-NMDA receptor encephalitis of 2% in febrile encephalitis that may be an underestimate because it excluded children. A multicenter, population-based, prospective study showed that anti-NMDA receptor encephalitis accounted for 4% of case of encephalitis in the United Kingdom (UK) making it the most common cause of AE after acute demyelinating encephalomyelitis (ADEM) in children [45].

Clinical Aspects

Clinically, anti-NMDA receptor encephalitis commences with nonspecific prodromal symptoms of headache, fever, nausea, or viral-infection like illness [46], but over days to weeks, seizures, neurocognitive and neurobehavioral complaints emerge including memory loss and frank neuropsychiatric manifestations of insomnia, mania, anxiety, depression, and paranoia [47, 48]. There can be movement disorders with oro-lingual-facial dyskinesia, autonomic manifestations, central hypoventilation, tachycardia and bradycardia. The eventual outcome of all patients was favorable in three-quarters who recovered or had mild deficits with immunotherapy, whereas one-quarter had severe persistent deficits or died. Relapses so noted in 25% to 30% of cases [49], were partly attributed to lack of treatment, while 12% of treated cases relapsed in the first two years in one long-term outcome cohort analysis [50].

Cellular and Synaptic Antibody Effects

Human embryonic kidney cells 293 (HEK293) ectopically expressing single or assembled NR1-NR2 subunits have been used to determine the epitope targeted by the anti-NMDA receptor, the extracellular N-terminal domain of the NR1 subunit. By quantitative analysis of the NMDA receptor in neuronal cell culture, there was a decrease in the numbers of cell-surface NMDA receptor, and NMDA receptor clusters in postsynaptic dendrites. Most patients with anti-NMDA receptor encephalitis have intrathecal synthesis of antibodies and numerous CD 138+ antibody-secreting plasma cells in perivascular, interstitial, and Virchow-Robin spaces with complement fixing IgG and IgG3 subtypes, as well as B- and T-cells in perivascular regions. Complement-mediated mechanisms in anti-NMDA receptor encephalitis studied in cultured rat hippocampal neurons tested for complement fixation [51] showed complement binding *in vitro* and in neural tissue of teratoma tumors, although not in the brains of affected patients.

Laboratory Investigations

Testing for NMDA receptor antibodies is recommended in patients who manifest encephalitic signs, psychiatric symptoms, seizures, and CSF inflammation, after exclusion of viral and bacterial causes of infection regardless of neuroradiologic investigation since the disorder may be associated with normal MRI findings in up to 50% of cases. The remaining one-half may include non-specific changes and abnormal T₂/FLAIR MRI hyperintensities in the mesial temporal lobe, cerebral or cerebellar cortex, basal ganglia or brainstem. There is typically no abnormal enhancement or hemorrhage. FDG brain PET may show hyper- or hypometabolism in the affected regions [52]. Up to 25% of patients have electrographic seizures. CSF analysis can show moderate lymphocytic pleocytosis, increased protein content, elevated IgG index, and CSF-specific oligoclonal bands which were typically negative at first testing, but can become positive later with disease progression in up to one-half of cases.

Histopathologic Correlation

The histopathologic aspects of NMDA receptor encephalitis have been studied in 14 cases, including 9 at postmortem examination, and 5 in brain biopsy tissue. Dalmau and colleagues [53] described 12 women with prominent psychiatric symptoms, amnesia, seizures, dyskinesia, autonomic dysfunction and altered consciousness. All had serum/CSF

antibodies that immunolabeled the neuropil of hippocampus/forebrain, in particular the cell surface of hippocampal neurons and reacted with NR2B, and to a lesser extent NR2A, subunits of the NMDA receptor. NR2B binds glutamate and forms heteromers (NR1/NR2B or NR1/NR2A/NR2B) that are preferentially expressed in the adult hippocampus/forebrain. Expression of functional heteromers, and not single subunits, was required for antibody binding. The CSF and serum of all 12 patients showed a distinctive pattern of reactivity with the neuropil of rat hippocampus, and the immunolabeling predominantly occurred with the cell membrane of neurons and was intense in the molecular layer of the hippocampus. Three patients age 14, 24 and 35 years of age (Cases 2, 6, 10) died, including one (Case 10) were previously reported [54], 3 to 6 months after symptom presentation. MRI showed T₂/FLAIR hyperintensities in the medial temporal lobes (Case 2); hyperintensity of the parietal sulci and enhancement of overlying meninges (Case 6); and a third (Case 10) showed normal findings. CSF in all three showed pleocytosis varying from 115 (Case 10) to 219 WBC (Case 6) with minimally increased or normal protein content, and positive oligoclonal bands. Immunofluorescence microscopy experiments demonstrated co-localization of antigens reacting with patient antisera and antibodies against NR2B, and co-localization of these antibodies in patients' tumor samples and in brain. Postmortem examination showed extensive gliosis, rare T-cell infiltrates, and neuronal degeneration predominantly involving, but not restricted to the hippocampus in all three. Microglial nodules and neuronophagia were rarely seen. In all cases, these findings predominated in the hippocampus but also affected other areas of the brain, brainstem, and spinal cord. There was intense IgG immunostaining of the hippocampi resembling rodent-staining of NMDA receptor in brain sections without complement immunostaining. The main epitope targeted by the antibodies is the extracellular N-terminal domain of the NR1 subunit. Patients' antibodies decreased the numbers of cell-surface NMDA receptor and clusters in postsynaptic dendrites, an effect that reversed by antibody removal. Tüzün and coworkers [55] extended the immunopathological analysis of Cases 6 and 10 reported previously by Dalmau and [53] noting that lymphocytic infiltrates were uncommon, and were rarely noted in the perivascular and leptomeningeal regions or scarcely distributed in the brain parenchyma. CD20+ B-cells and CD79a plasma cells were identified in the perivascular space including 1% cytotoxic T-cells and absence of GrB+, Fas and Fas ligand-positive cells. IgG, including deposits were noted in all areas of the CNS but most intense in the hippocampus, basal forebrain, and cervical spinal cord. Using HEK293 cells expressing NR1/NR2B, the NMDA receptor IgG were mainly IgG₁, but included IgG₂ and IgG₃ types. Tumor samples exhibited NR1/NR2-expressing tumor cells in varying amounts.

Camdessanché and coworkers [56] reported the postmortem findings of a brain biopsy specimen from an 18-year-old woman with NMDA receptor encephalitis who presented with subacute mood changes and facial jerks. Brain MRI showed foci of T₂ hyperintensities in the right frontal lobe, and CSF showed 21 WBC and oligoclonal bands. A frontal lobe showed that showed perivascular cuffing of CD20+ B-cells and a few CD138+ plasma cells, with few CD3+ T-cells or CD68+ macrophages scattered throughout grey and white matter and in perivascular spaces. Retrospective screening for anti-NMDA receptor antibodies was performed on a CSF sample that was positive at a dilution of 1:10, both in the neuropil of the rat hippocampus and in transfected HEK293 cells.

Martinez-Hernandez and coworkers [51] described 2 men, age 7 and 59 years, and three women age 5, 24 and 35 years, the latter two with ovarian teratomas, and anti-NMDA

receptor encephalitis who presented with subacute short-term memory deficits, psychiatric disturbances, seizures, movement disorders, and dysautonomia ranging from 22 days to 4 months. CSF showed protein elevation ranging from 94 to 219 mg/dL with oligoclonal bands; and brain MRI showed increased FLAIR signal in medial temporal lobes (Case 1), parietal cortex (Case 2), left temporal cortex (Case 3), and in the insula and anterior temporal lobes with atrophy in another (Case 5). Brain MRI was normal in Case 4. Treatment with combined immunotherapy in one patient who underwent a brain biopsy was effective, while the others died. One patient who died underwent earlier brain biopsy, and the remaining three patients were studied at postmortem examination. Patients' antibodies were able to fix complement on cultures of rat hippocampal neuron but were not detected in any of the brain regions of 3 patients, or in biopsies of 2 patients, all with anti-NMDAR encephalitis. The main histological findings were an abundance of infiltrating CD138+ plasma cells and plasmablasts in perivascular regions cuffing blood vessels, Virchow-Robin spaces, and lining the meningeal-brain surface in proximity to the CSF. Using cultures of rat hippocampal neurons, the patients' antibodies were able to fix complement but deposits of IgG were absent, nor was there complement immunostaining at postmortem examination or in brain tissue biopsies. In contrast to brain, tumor neural tissue showed complement immunoreactivity.

Bien and colleagues [23] examined brain biopsy tissue from 2 women and 1 man, age 17 to 22 years with NMDAR encephalitis, all three with encephalopathy lasting 2 months to 12 months, none with an associated tumor. Two were treated with immunotherapy before frontal (2 patients) or temporal lobe cortical biopsy. Serial MRI in one patient did not show hippocampal atrophy. Histopathology of the tissue specimens showed low density of T-cells, in the range of neurodegeneration controls. The ratio of perivascular CD8+/CD3+ was slightly elevated, and there were cytotoxic granules in some parenchymal T-cells, but no apposition of CD8++ T-cells to single neurons. Diffuse cytoplasmic IgG was evident in both neurons and astrocytes and C9neo deposition was present in the cytoplasm and on the surface of hippocampal CA4, dentate, and cortical neurons. The neocortex of NMDA receptor antibody-positive patients showed almost no inflammation, and no clear signs of neuronal loss. Even though NMDA receptor antibodies appeared to be involved in the clinical disease process, there was no evidence to suggest a classical mechanism of cytotoxic T-cell or humoral immune-mediated neuronal cell death. The possibility that a more active inflammatory infiltrate or antibody deposition could be found at an earlier disease stage in both the hippocampus and cortex, could not be excluded, although it was striking that MRI evidence of inflammation in the hippocampus was rare.

Collectively, the histopathologic findings were consistent with a selective and reversible decrease in NMDA receptor surface density and synaptic localization that correlated with patients' antibody titers. The mechanism of this decrease was selective antibody-mediated capping and internalization of surface NMDA receptors. This was supported by the experimental finding of Hughes and colleagues [57] who studied Fab fragments prepared from patients' antibodies that did not decrease surface receptor density. Subsequent cross-linking with anti-Fab antibodies recapitulated the decrease caused by intact patient NMDA receptor antibodies. These cellular mechanisms appear to be the cause of the specific titer-dependent and reversible loss of NMDA receptors. The loss of the subtype of glutamate receptors that eliminates NMDA receptor-mediated synaptic function may underlie the learning, memory and other behavioral deficits observed in affected patients.

Diagnosis and Treatment

Suggested criteria for the definite diagnosis of anti-NMDA receptor encephalitis [3] includes the presence of IgG anti-GluN1 antibodies in a suspected patient with subacute onset of psychiatric behavior or cognitive disturbances, seizures, movement disorder, and autonomic dysfunction; and abnormal EEG that shows focal or diffuse slowing or epileptic activity; and CSF pleocytosis or oligoclonal bands. Prompt diagnosis of anti-NMDA receptor encephalitis leads to improvement typically after removal and treatment of an offending cancer, or in the absence thereof. The demonstration of copious infiltrates of antibody-secreting cells in the CNS of affected patients provides an explanation for the intrathecal synthesis of antibodies, and implications for treatment used to arrest and reverse the disorder employing intravenous immunoglobulin (IVIg), corticosteroids, cyclophosphamide, or rituximab.

Given its characteristic disease course, it is now assumed that a relevant proportion of patients previously diagnosed with encephalitis of unknown origin would have anti-NMDA receptor encephalitis [43] representing about 1% of all young patients' admissions to ICU. A French study [44] noted a frequency of anti-NMDA receptor encephalitis in 2% in febrile encephalitis that could be an underestimate because of the exclusion of children. A multicenter population-based prospective study showed that anti-NMDA receptor encephalitis accounted for 4% of case of encephalitis in the UK, making it the most common cause of AE after ADEM in children [45].

Anti-VGKC-Complex Encephalitis

Background

About the same time that MoS was described, anti-VGKC-complex antibodies were determined using RIA in patients with noninfectious AE [19]. While the disorder was generally termed LE, the term limbic encephalopathy was also used as more patients were found to be seropositive without evidence of classical features of hyperintense signal intensities in the medial temporal lobes on brain MRI, and CSF inflammation [19].

Alteration of trans-synaptic scaffolding systems in AE that affects neuronal cell adhesion molecules are crucial for proper synapse formation and adhesion, plasticity, and function. In both developing and mature neurons, these molecules serve to recruit and anchor pre- and postsynaptic proteins to appropriate synaptic localizations, allowing for normal synaptic transmission. Autoantibodies against the VGKC-complex detected by RIA in the sera of patients with AE do not bind directly to VGKC-complex channel proteins proper, but instead to synaptic and axonal neuronal proteins that co-precipitate with detergent-solubilized VGKC [58, 59].

Attention has focused on identifying the principal autoantigens in the VGKC-complex and expanding the spectrum of corresponding phenotypes. Initial reports [60, 61] suggested that patients' antibodies were bound to the VGKCs Kv1.1 and Kv1.2. Subsequent studies showed that leucine-rich glioma-inactivated protein 1 (LGI1) LGI1, and contactin-associated protein-like2 (CASPR2) were the main autoantigens [58, 59] which associated with transiently expressed axonal glycoprotein (TAG1), post synaptic density protein-Drosophila disc large tumor suppressor-zonula occludens-1 protein (PDZ), and the ankyrin-spectrin

protein in both the peripheral and CNS. Antibodies against contactin-2 usually occur in association with those targeting LGI1 or Caspr2 were identified in other disorders, raising doubts about their importance. There is a diversity and overlap of neurological phenotypes associated with VGKC-complex-IgG in the serum and CSF, and distinct Ig-subtype specificity. The commonest presentation of VGKC-complex autoantibodies is LE in the CNS, and neuromyotonia or MoS in the periphery.

Epidemiology

In the UK, where the incidence of encephalitis is estimated at 5.23 cases/100,000/year based upon admissions to the National Health Service between 2005 and 2009, Granerod and colleagues [62] estimated the incidence of encephalitis as 4.32 cases/100,000 population/year. A capture–recapture model estimated the incidence of encephalitis to be 8.66 cases/100,000/year. Two percent of patients ($n = 216$) had >1 encephalitis admission during the study period; and the incidence did not change (4.20 cases/100,000/year) when subsequent admissions of these patients were excluded from the analysis. By using data restricted to the primary diagnostic field, the overall mean incidence was 2.75 cases/100,000/year (95% CI 2.39 cases–3.10/100,000/year). The results of multivariable analyses showed that compared with 2005–2006, incidence in all subsequent years was slightly higher but with little evidence of a trend ($p = 0.19$). The incidence rate was highest among patients <1 year of age, and in those >65 years of age. A retrospective study that reviewed antibodies to VGKC, LGI1 and CASPR2 in 46 children with severe acute encephalitis identified only one affected child (2.2%) among 46 children [63].

Clinical Aspects

Among 64 patients with VGKC-complex encephalitis [64] the clinical features overall included neuropsychiatric features, disorientation, confusion, or amnesia in 100% of patients; tonic-clonic seizures in 92%, delusions in 21%, hallucinations in 17%, agitation in 6%, pain in 4.7%, and peripheral neuropathy in 1.6% of cases. Neurocognitive complaints, psychiatric symptoms and seizures typical evolve over days to weeks, occasionally acutely, but more often insidiously over months before coming to medical attention. The finding of an apparent dementia in 72 affected patients was studied by Flanagan and colleagues [65]. Responsiveness to immunosuppressant and immunomodulatory therapy was predicted by seropositivity for neuronal VGKC-complex antibody more than calcium channel or neuronal acetylcholine receptor ($P = .01$). Up to 40% of patients may also manifest frontal lobe and frank psychiatric features. Parthasarathi and colleagues [66] described a 58-year-old man with panic attacks and psychogenic non-epileptic seizures who later developed delusions and hallucinations followed by confusion. He was found to have VGKC-complex antibodies and treated with immuno-modulatory therapy leading to near complete recovery. Bettcher and coworkers [67] delineated cognitive strengths and weaknesses among 12 subjects with VGKC-complex encephalitis noting mild to moderate impairment in memory and executive functions, with variable impairments in language and sparing of visuospatial skills that correlated with MRI findings of T_2 /FLAIR hyperintensities in medial temporal lobe (10/10) and basal ganglia (2/10). Serial cognitive examination revealed heterogeneity in cognitive function.

Seizures occur in up to 90% of cases and are most commonly focal in nature, with infrequent generalization, manifesting typical medial temporal lobe signature with hand and

orofacial automatisms. Three seizure semiologies, ictal bradycardia, piloerection, and fasciobrachial dystonic seizures (FBDS), show a strong associations to LE associated with LGI1 antibodies. FBDS consist of brief frequent episodes abnormal unilateral and bilateral movements of the arms, sometimes the ipsilateral muscles of the face, and more rarely the leg. Video electroencephalography shows an epileptic origin of these myoclonic-like movements however regular EEG with scalp electrodes often misses an interictal focus. If FBDS are recognized early, and serum LGI1 antibodies are detected, immunotherapy prevents progression to frank LE, which in one study arose after a median delay of 36 days. Kalachikov and colleagues [68] described autosomal dominant lateral temporal epilepsy (ADLTE) characterized by partial seizures and preceding auditory signs in the *LGI1/epitempin* gene expressed on chromosome 10q24. Mutations in this gene introduce premature stop codons and prevents production of full-length protein from the affected allele. Although LGI1 haploinsufficiency causes ADLT, the underlying molecular mechanism that results in abnormal brain excitability has instead been attributed to dysregulation of synaptic AMPA receptors in hippocampal neurons in the epileptic LGI1 knock-out mouse [69]. Fukata and colleagues [70] proposed that extracellularly secreted LGI1 linking two epilepsy-related brain receptors, a disintegrin and metalloproteinase domain 22 (ADAM22) and ADAM23, organize a transsynaptic protein complex that includes presynaptic potassium channels and postsynaptic AMPA receptor scaffolds. The lack of LGI1 disrupts this synaptic protein connection and selectively reduces AMPA receptor-mediated synaptic transmission in the hippocampus.

Younger [71] described new-onset FBDS and memory disturbances in association with distal large and painful small fiber peripheral neuropathy, dysautonomia without systemic malignancy in a patient with extrathecal VGKC-complex antibody production. Epidermal nerve fiber studies confirmed small fiber neuropathy in association with abnormal autonomic laboratory testing.

Neuropathic pain as a manifestation of VGKC-complex autoimmunity was noted in 316 (4%) of 1,992 patients evaluated neurologically at a tertiary referral center [72] that was typically subacute in onset, nociceptive, regional, or diffuse. In those suspected of peripheral neuropathy with mild subjective loss of temperature and pain attributed to small fiber dysfunction, electrodiagnostic studies show variable minor reduction of sural sensory nerve action potential amplitudes with motor hyperexcitability. The VGKC-complex antibody titers were often low (0.02-0.1 nM) and antibodies to GLI1 or CASPR2 were present in 28% overall, with the latter most common (7%).

Autonomic involvement was noted in 29% of the cohort studied by Klein and colleagues [72], and in 3 (60%) of the patients described by Lahoria and coworkers [73]. Hypothermia was described in association with VGKC-complex antibody-associated LE in 4 patients [22], Patient 1 of whom had concomitant neuropathic patient, and in the absence thereof in the others who were conjectured to have otherwise disturbed hypothalamic thermoregulatory mechanisms as the cause for dysautonomia.

Cellular and Synaptic Antibody Effects

LGI1 is a secreted synaptic protein that associates with, and regulates Kv1.1 and Kv1.2, as well as AMPA (128). Caspr2 is a transmembrane axonal protein of the neurexin IV superfamily that localizes to the juxtaparanode of myelinated axons, and its extracellular domain interacts with contactin-2, where it connects with the cytoskeleton via protein 4.1B.

Caspr2, contactin-2 and protein 4.1B, all of which are necessary to concentrate Kv1.1 and Kv1.2 channels in the juxtaparanode. Lai and colleagues [58] studied proteins associated with Kv1.1 and Kv1.2, noting that VGKCs themselves were the autoantibody targets, explaining the diversity of symptoms among patients with these antibodies. LGI1 is primarily a CNS protein, and LGI1 antibodies are associated with LE, seizures, and hyponatremia. LGI1 antibodies cause reversible CNS synaptic dysfunction by several mechanisms. The antibodies may prevent binding of LGI1 to the receptors that it regulates, or they might act on the LGI1–ADAM protein complex. Alternatively, LGI1 antibodies could disrupt currents mediated by Kv1.1 and Kv1.2, and/or impair AMPAR function, either indirectly by blocking LGI1-mediated regulation of these proteins or directly by disrupting the entire protein complex. The identification of LGI1 as a major target of so-called VGKC antibodies clarifies several aspects of the associated disorder.

Caspr2 antibodies are associated with autoimmune encephalitis, peripheral nerve hyperexcitability, and MoS. Peripheral nervous system manifestations may precede or follow those of the CNS by up to several years. Some affected patients may have an associated thymic tumor, but most do not. Mutations in the human gene encoding Caspr2 (*CNTNAP2*) are associated with autism, epilepsy, Tourette syndrome, cortical dysplasia, obsessive–compulsive disorder, Pitt–Hopkins syndrome, and other mental disabilities. Mice with a *caspr2* deletion show analogous behavioral defects and symptoms [74]. Interestingly, common variants of the *CNTNAP2* gene in healthy individuals are associated with abnormal language processing and are a risk factor for autism [75]. Caspr2 antibodies act by disrupting axonal potassium currents. Factors such as differences in time to establishment of intrathecal antibody synthesis, or in the structure of tight, septate-like junctions of myelinating cells around the axons may explain this variability. The VGKC–complex antibody levels also broadly differ between the different syndromes, with highest levels in LE and FBDS, moderate levels in MoS, and lowest levels (often <400 pM) in PNH.

Laboratory Investigation

The high proportion of VGKC-complex IgG-seropositive patients whose serum samples lack LGI1 IgG and CASPR2 IgG specificities, suggests that other VGKC-complex molecular targets remain to be discovered. Only about 4% to 5.5% of unselected cases were seropositive by RIA with confirmatory retesting using 125I- α -dendrotoxin alone (radioligand for Kv1.1, Kv1.2, and Kv1.6 channels) [76, 77], making the test unreliable as a screen for LE without further subtyping for LGI1 and CASPR2-IgG. So selected, 26% to 28% of seropositive VGKC sera revealed reactivity with LGI1 and/or CASPR2-IgG, with a significant association between LGI1-IgG-positivity and cognitive impairment and seizures ($P < .05$), and CASPR2-IgG-positivity and peripheral motor excitability ($P = .004$), however neither autoantibody was pathognomonic for a specific neurologic presentation. There has been concern for screening of unselected sera for VGKC-complex antibodies by RIA. It can be argued that VGKC-complex RIA antibody test should be used as initial screening to select positive samples that could then be confirmed by LGI1 or CASPR2-IgG antibody subtyping, however the latter may also be positive in selected VGKC-complex antibody-negative sera by RIA. Paterson and colleagues [78] noted positive VGKC-complex antibody values (>400 pm; >0.4 nM) that were likely to be relevant in LE and related syndromes, as well as low-positive values (<400 pm; 0.1–0.4 nM) in 32/44 cases considered to be non-autoimmune, 4 (13%) cases of which were found to have a definite or probable paraneoplastic neurologic disorder, neuromyotonia

or MoS. Ances and colleagues [30] noted that the RIA used in the clinical analysis of VGKC-complex antibodies identified a limited number of subunits (Kv1.1, Kv1.2 and Kv1.6) but that it was reasonable to speculate that antibodies to other subunits, K (+) channel families and VGKC ion channels might also associate with LE.

Cerebral imaging studies in VGKC-complex antibody associated LE show highly variable results. Both mesial temporal lobe hypometabolism on FDG brain PET, and hypermetabolism have been described [79, 80, 81]. In a patient with VGKC-complex LE [80] who did not definitively demonstrate structure abnormalities on serial brain MRI over time despite ongoing temporal lobe seizures captured on video-EEG, FDG brain PET fused with gadolinium-enhanced MRI later showed bitemporal hypometabolism. Baumgartner and colleagues [81] identified 9/18 (50%) patients positive for non-paraneoplastic antibodies against neuronal surface antigens (VGKC or NMDA-R), 2 of whom displayed mesiotemporal hypermetabolism on FDG brain PET, with 4 others were rated normal, and 3 displayed hypermetabolism outside the mesiotemporal region. The fraction of abnormal scans employing MRI was lower (10/16; 62.3%) than FDG brain PET (14/18; 77.7%).

CSF results were equally variable in VGKC-complex autoimmunity. Jarius and colleagues [82] performed 29 lumbar punctures in 17 patients with VGKC-complex LE noting normal findings in up to 53% of CSF specimens. There were no significant differences between the CSF findings and the titers of serum VGKC-complex autoantibodies. Slight pleocytosis, mainly consisting of lymphocytes and monocytes, and elevated total protein concentrations were present in 41% and 47%, respectively. A disturbance of the integrity of BBB was found in 6 (35%) patients based upon an abnormal CSF/serum humoral immune response. Absence of CSF-specific OCB, considered a marker of autochthonous antibody synthesis within the CNS in all patients [82] suggested an extrathecal origin of VGKC-complex autoantibodies. Vincent and colleagues [19] reported the CSF findings in 10 patients, all with VGKC-complex antibody-associated LE, noting mild lymphocytosis and mild or moderately raised protein content in one-half. OCB were noted in 1 patient, while 6 other OCB were identical to serum. VGKC-complex antibody assays on matched serum and CSF showed antibodies levels of the latter present in 4 patients that varied between <1 and 10% of the serum, and beneath 10% in one patient with the lowest serum value. These findings were consistent with extrathecal synthesis of VGKC-complex antibodies.

Irani and Vincent [64] estimated features of peripheral neuropathy in 1.6% of VGKC-complex antibody-positive LE cases. Lahoria and coworkers [73] described 5 patients with painful polyneuropathy, all positive for VGKC-complex autoantibodies (range 0.08 to 1.18 nM), two of whom had antigens positive for CASPR2 and LGI1-IgG, both at low VGKC-complex antibody titers (respectively 0.08 and 0.16 nM/L). Electrodiagnostic studies showed length-dependent sensorimotor polyneuropathy that was concordant with abnormal indices of axonal degeneration or demyelination in 4 nerves, and the latter with quantitative analysis of semithin sections in 2. All 5 showed absence of inflammatory cell infiltration. By comparison, the symptoms of small fiber neuropathy, which arise from dysfunction in nociception, temperature and autonomic modalities are most adequately assessed by epidermal nerve fiber density in a 3 mm punch biopsy of skin from the later calf and thigh, and a combination of cardiovascular, sudomotor and adrenergic functions tests with comparison to controls.

Histopathologic Correlation

Eight patients with VGKC-complex LE were studied histopathologically, including stereotactic brain biopsy in 3 [19, 23] at epilepsy surgery in 1 case [23], and at postmortem examination in 4 patients [23, 83, 84, 85]. Vincent and colleagues [19] described a 56-year-old man with 7 month history of confusion and memory impairment who developed partial focal seizures, anxiety and delusions. CSF showed mild pleocytosis and brain MRI showed unilateral left medial temporal lobe signal change with focal slow activity on EEG. The serum VGKC antibody titer was 2224 pM (normal 0-100pM; >400 pM highly elevated). Histopathology of a stereotactic biopsy of the left amygdala showed positive staining for perivascular and parenchymal CD45+ lymphocyte infiltrates, astrogliosis, and CD68+ microglial activation. He was received a course of intravenous dexamethasone with a slight beneficial response with persistent memory deficits. Follow-up brain MRI showed evolution of bilateral hippocampus atrophy and signal changes.

Dunstan and colleagues [83] reported a 78-year-old man with a 2 week history of confusion, cognitive impairment and hyponatremia. Brain MRI showed increased signal in the right medial temporal lobe with subcortical white matter changes. Cerebrospinal fluid was normal. Assay for VGKC antibodies were 1637 pM by RIA. He received anticonvulsants but deteriorated due to sepsis and died. Postmortem examination showed no evidence of a malignancy. The brain showed severe neuronal loss with multiple reactive astrocytes, macrophages, and scattered T-cells in the right amygdala nucleus and adjacent hippocampus.

Park and coworkers [84] described a 65-year-old woman with a 3 month history of amnesia, disorientation, memory loss, and partial complex seizures. Brain MRI was normal and CSF showed 17 WBC. EEG showed mild diffuse slowing. She later developed hyponatremia and serum VGKC-complex antibodies were 1.73 nmol/L (normal < 0.02 nmol/L) by RIA. Whole body FDG-PET showed mediastinal adenopathy. She was treated with intravenous corticosteroids for 5 weeks without improvement and later died. General autopsy limited to the chest showed no malignancy. Postmortem examination of the brain showed mild focal perivascular T-cell lymphocyte cuffing and infiltrates of overlying meninges and parenchyma of the cingulate gyrus, hippocampus, and amygdala and midbrain.

Khan and coworkers [85] reported a 56-year old man with a 4 month history of confusion, disorientation and seizures. A serum VGKC antibody titer was 3,327 pM by RIA and there was hyponatremia. Brain MRI showed left hippocampal atrophy on T₂/FLAIR images. General postmortem examination showed no malignancy. Examination of the brain showed pathological changes in both hippocampi and right amygdala regions comprised of pyramidal neuronal cell loss in the CA4 region, marked activation of CD68+ microglia and reactive GFAP+ astrocytosis extending to the subiculum, less so near the joining of the parahippocampus gyrus. There were perivascular infiltrates of CD20+ B-cells and a few CD4+ T-cells especially in the right hippocampus.

Bien and colleagues [23] summarized the histopathologic findings in the brain of 4 cases, 3 men and 1 woman, age 33 to 68 years, with LE (3 patients) and multifocal encephalitis in another, ranging from 5 to 9 months. Serum VGKC antibody titers were 167, 288, 958 and 2224 Pm respectively. Serial MRI showed an evolution from hippocampal swelling with T₂/FLAIR signal increase to frank hippocampal atrophy and increased signal intensities. Histopathologic examination including quantitative immunocytochemical studies showed variably intense inflammation and overall lower CD8/CD3 ratios, although there were GrB)+ T-cells present in the lesions without opposition to neurons or release of FrB, therefore T-cell

cytotoxicity was not a major contributor. Immunoglobulin and complement deposition on neurons was a prominent finding, and terminal deoxynucleotidyl transferase dUTP nick and labelling (TUNEL) reaction in the same area demonstrated acute neuron cell death suggesting antibody and complement mediated neuronal cell damage in these patients. The authors [23] noted that IgG4 rather than IgG1 antibodies dominated in the sera of those with VGKC-complex LE.

Diagnosis and Treatment

Suspected patients with new-onset and rapid progression of memory deficits, seizures, or psychiatric symptoms suggesting involvement of the limbic system; bilateral medial temporal lobe abnormalities on T2/FLAIR MRI, and CSF pleocytosis combined with TLE or slow-wave activity on EEG should be screened for VGKC-complex antibodies, with detection of LGI1 and CSFPR2 by RIA. The diagnosis of VGKC-complex LE can be established in suspected cases when serological studies are combined with clinical, neuroradiologic and CSF inflammatory parameters, and a reasonable exclusion of alternative diagnoses. If so, immunomodulatory and immunosuppressive therapy should begin. Less than one-half of affected patients fail to improve with first-line therapy employing IVIg, PE, or corticosteroids, needing to advance to second-line agents including cyclophosphamide and rituximab.

Bataller and colleagues [86] noted that treatment-responsiveness of LE was especially favorable among patients with antibodies to the VGKC-complex with overall improvement in two-thirds or more of patients. However, a favorable response to therapy was not limited to patients with VGKC-complex antibodies but extended to novel-cell-membrane antigens (nCMAg) expressed in the hippocampus. If the autoantigens were unknown but found to be highly enriched in neuronal cells membranes of the hippocampus, these antibodies were likewise associated with a favorable outcome emphasizing the usefulness of immunohistochemistry with PFA-fixed tissue and cultures of live hippocampus rat neurons in the analysis of highly-suspected patients with LE. The salutary effect of immunotherapy in the management of seizures in VGKC-complex antibody-associated LE is well supported by the autoimmune basis of FBDS [87].

HASHIMOTO ENCEPHALOPATHY

For nearly half a decade, investigators have been pursuing an associated rare encephalopathy associated with Hashimoto thyroiditis (HT). In 1966, the British neurologist, Lord Brain and colleagues [88] first described the entity of Hashimoto encephalopathy (HE) in a 40-year-old man with 12 ictal and stroke-like episodes of confusion and agitation one year after onset of treated hypothyroidism. The cerebral disorder remitted completely after 19 months commensurate with a decline in high serum thyroid- antibody levels. Treatment with prednisone and an anticoagulant for 3 months was ineffective. His neurologic symptoms remitted while he was taking only levothyroxine. The authors concluded that the likeliest explanation for this protracted and stuttering brain disorder was localized cerebral edema due to antibody-mediated autoimmunity, and that antibody studies in future cases of unexplained encephalopathy would show whether their findings constituted a syndrome or coincidence.

Jellinek and Ball [89] extended the results of Brain and colleagues [88], describing the original patient, who at age 62, later died 12 years later of an unrelated cause. Postmortem examination showed virtually no remaining thyroid tissue and atheromatous cerebrovascular changes with splenic atrophy. The authors postulated that underlying autoimmunity was the cause Hashimoto's thyroiditis and encephalopathy, and splenic atrophy. Almost one half decade later, Rowland and colleagues [90] characterized the clinicopathologic aspects of HE beginning with the patient described by Lord Brain and coworkers [88] and ending in 2002, adding a case of their own. The diagnosis of Hashimoto's encephalopathy, as described by Rowland and coworkers [90], which rests on the presence of HT with measurably high titers of TPO or Tg antibodies, clinical encephalopathy, and absence of cerebrospinal fluid evidence of bacterial or viral infection, serves as the standard for case selection. However then as now, it is unknown whether anti-thyroid antibodies and concomitant thyroid dysfunction contribute to the pathogenesis of HE.

Clinical Presentation

In the series of Rowland and coworkers [90] the mean age at onset of symptoms of Hashimoto's encephalopathy was 44 years (range, 9-78 years); 19 of whom were boys or girls, age 18 years or younger. Among the adults, there were 53 women and 13 men. In addition to encephalopathy as required, stroke-like signs presented in 23 (27%) case, seizure in 56 (66%), myoclonus in 32 (38%), and visual hallucination or paranoid delusion in 31 (36%). The course was relapsing and remitting in 51 (60%) of cases.

Laboratory Findings

Also in the series of Rowland and colleagues [90], both Tg and microsomal or TPO antibodies were found together in 60 (71%) cases with one antibody of the two normal in 20 (24%) cases. There was no relationship between the neurologic symptoms and signs and the type or serum concentration of anti-thyroid antibodies. Altogether, 30 (35%) cases were sub-clinically hypothyroid, 19 (22%) were euthyroid, and 17 (20%) were overtly hypothyroid. Fourteen (16%) cases had an elevated erythrocyte sedimentation rate or antinuclear antibody, and three had a concomitant connective tissue disease (psoriatic arthritis, Sjogren's syndrome, and sarcoidosis).

A 19 year-old male with HE and subacute neuropsychiatric complaints and HT recently seen at New York University Langone Health by this author, had HT demonstrated by ultrasound and fine needle aspiration (Figure 1). ¹⁸Fluorodeoxyglucose positron emission tomography (PET) of the brain fused with MRI demonstrated the typical features of autoimmune encephalitis. There was signal abnormality in the left hippocampal tail and hypometabolism in the (mesial) temporal and parietal lobes (Figure 2). Nuclear medicine cerebral perfusion (brain) single photon emission computed tomography (SPECT) showed bilateral temporal and right parietal lobe hypoperfusion.

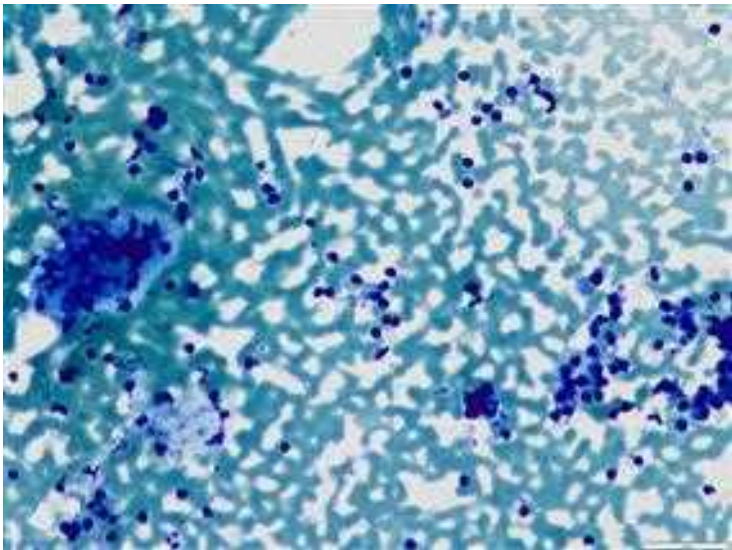


Figure 1. Hashimoto's thyroiditis. Fine needle aspiration in a Diff-Quik® staining of a goiter in a background of lymphocytic thyroiditis. There is a thin background of purple colloid in between grey staining red blood cells amid follicular cells and dark blue staining nucleated lymphocytes recognized by crush or stringing effects (Magnification 200X).

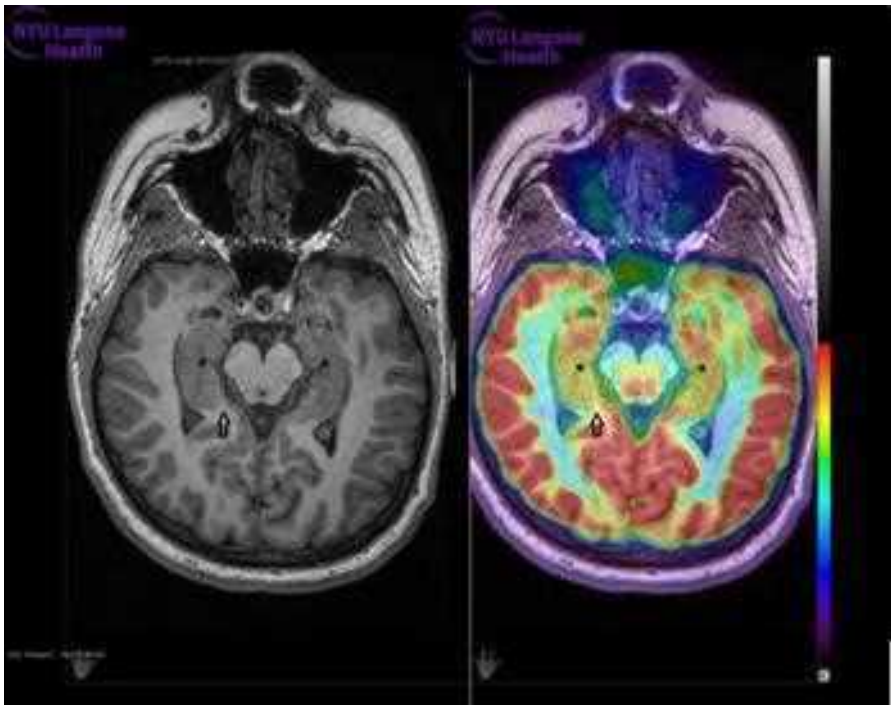


Figure 2. Hashimoto encephalopathy. Positron emission tomographic imaging (right panel) from the vertex to foramen magnum following injection of 10-mCi 18fluoro-D-glucose is fused with gadolinium-enhanced magnetic resonance imaging (left panel). There is hypometabolism of the medial temporal lobes (asterisks), and signal change in the tail of the hippocampus (arrows).

Cerebrospinal fluid was normal without evidence of infection or another pathogenic autoantibody, apart from TPO. An elevated CSF protein level was noted in 66 (78%) patients, with abnormal findings in neuroimaging in 40/82 (49%) or electroencephalography in 80/82 (98%) patients. A goiter was detected in 24/39 (62%) patients, with a serum microsomal antibodies in 55/58 (95%), TPO antibodies in 26/26 (100%), and Tg antibodies in 45/62 (73%) patients.

Immunopathogenic Mechanisms

Unlike the close relation between anti-thyroid antibodies and thyroiditis in HE, neither high titers of anti-thyroid antibodies nor the presence of subclinical or overt hypothyroidism accounted for the observed encephalopathy in the series of Rowland and coworkers [90]. The neurological findings in patients that were euthyroid were similar to those with subclinical or overt hypothyroidism. Given the lack of a well-defined pathophysiologic link between anti-thyroid antibodies or HT or HE, the term encephalopathy may be a misleading, as the disorder may be one of a larger group of autoimmune encephalopathies. Ochi and colleagues [91] provided a link between HT autoimmunity and the CNS. Using a human brain proteome map and two-dimensional electrophoresis to screen brain proteins reactive to serum antithyroid antibodies, the authors [91] identified α -enolase, a candidate marker for HE-related pathology, encoded on 1p36.23. Kishitani and coworkers [92] extended the findings of Ochi and colleagues [91] noting anti-NH₂-terminal of α -enolase antibodies in 24% of HE patient sera and limbic abnormalities on MRI demonstrating abnormal signal in unilateral or bilateral medial temporal lobes, and diffuse slow wave activity with epileptogenic discharges. These findings suggested that limbic encephalitis- associated with anti-NH₂-terminal of α -enolase antibodies could be a possible manifestation of HE in some cases. Graus and colleagues [3] proposed Hashimoto encephalopathy as an autoimmune encephalopathy or encephalitis after exclusion of other syndromes associated with well-defined autoantibodies. At present, it is unclear whether antithyroid antibodies represent an immune epiphenomenon in a subset of patients with encephalopathy or are truly associated with pathogenic mechanisms of the disorder.

According to Rowland and colleagues [90], one subgroup of patients with HE present with stroke-like episodes. Inoue and colleagues [93] described a patient with progressive Parkinsonism and normal cognitive and intellectual performance. Slow background activity on electroencephalography was the only sign of encephalopathy, which normalized after treatment with corticosteroids. Younger [94] described a patient with hemi-parkinsonism in a stroke-like onset. ¹⁸Fluoro-D-glucose- positron emission tomography metabolic imaging showed severe hypometabolism within the posterior aspect of the left putamen suggesting focal vascular injury, with superimposed left temporal and left parietal hypometabolism and mild volume loss relative to the rest of the brain (Figure 3).

A vasculitic pathogenesis appears to be equally likely in some cases of HE based upon the tendency for increased autoimmunity in HT. In addition, the available histopathology in HE also supports an inflammatory vasculopathy, so noted in one postmortem case that showed lymphocytic infiltration of brainstem veins [95], and in brain biopsy tissue from another case categorized as isolated angiitis due to lymphocytic infiltration of the walls of

arterioles and veins [96]. Brain biopsy tissue of second living patient showed perivascular cuffs of lymphocytic cells [90]. It is noteworthy that patients with HE and circulating α -enolase antibodies are at risk for heightened autoimmune activity, and a tendency for systemic and invasive autoimmune disorders including systemic vasculitis [97, 98].

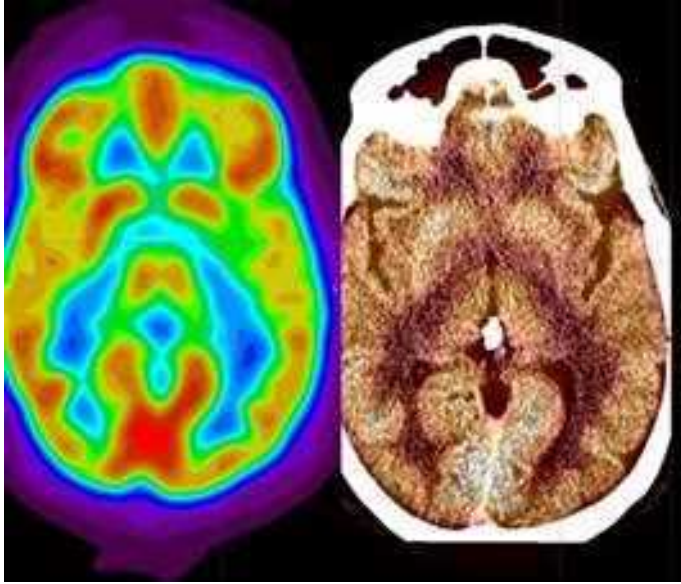


Figure 3. Hashimoto's encephalopathy. Positron emission tomographic (PET) imaging from the vertex to foramen magnum following injection of 10 mCi ^{18}F -fluoro-D-glucose (left image) shows severely reduced metabolic activity in the posterior half of the left putamen on standard PET imaging, and with fusion to gadolinium-enhanced magnetic resonance imaging (MRI) (right image).

Treatment

The significance of corticosteroid sensitivity in HE is widely accepted as a criterion for the diagnosis. However, as Rowland and colleagues suggested [90], it would be unwise to define any condition by response to any particular therapy especially if not replacing a specific deficit or directing it at a particular target. Patients with HE improve in association with, but not necessarily due to corticosteroid therapy. Moreover, those that respond to corticosteroids have no distinguishing clinical characteristics nor receive treatment in other fashions for a meaningful comparison.

CONCLUSION

There has been a rapid expansion in knowledge of autoimmune encephalitis neurological and neuropsychiatric disorders. Three well-describe disorders targeting antigens on the surface or in the cells of the temporal lobe neuropil manifest limbic and extra-limbic dysfunction. Patients with HT may develop a rare autoimmune encephalopathy. Recognition of these cases have shifted clinical paradigms and led to new insights into the mechanisms of

autoimmune encephalitis. Those with available histopathology show variable humoral and cell-mediated autoimmune, with cytotoxic T-cell inflammation targeting neuropil antigens, making them more similar than not, to primary CNS vasculitis. One important difference however is the more favorable outcome in autoimmune encephalopathy and HE compared to primary CNS vasculitis, making their recognition essential in choosing appropriate immunotherapy to achieve long-lasting remission.

CONFLICT OF INTEREST

None.

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Chapter 225

OVERVIEW OF THE TREATMENT OF PRIMARY SYSTEMIC VASCULITIS

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ABSTRACT

Vasculitis is a group of heterogeneous diseases that often involve organ- and life-threatening manifestations. Prior to effective therapy vasculitis had an extremely high mortality. However, the last 3 decades have seen continuous progress and substantial improvements in establishing early diagnosis and effective treatment for these diseases. These major advances are largely due to enhancement in the description and classification of vasculitis, the implementation of standardized outcomes, and the availability of large cohorts and randomized clinical trials due to ongoing collaborative efforts. This chapter will provide an overview of the general concepts of therapy for vasculitis, highlight the importance of randomized trials in establishing standard treatment algorithms for some forms of vasculitis, outline recent advances in the treatment of primary systemic vasculitis, and describe novel approaches being considered to treat the vasculitides.

Keywords: vasculitis, treatment, overview

INTRODUCTION

Primary systemic vasculitides are highly heterogeneous diseases in which inflammation of blood vessels, especially arteries, is the hallmark of the pathophysiology and usually the major source of morbidity for patients. The different forms of vasculitis affect different sized vessels and vary in the processes leading to inflammation, for example immune complex

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deposition or granulomatous pathology. These diseases can differ markedly in the predominant organ affected, the clinical manifestations, and the nature of the disease-related damage. Vasculitis ranges from a single-episode of mild annoyance to recurrent life- and organ-threatening disease. Approaches to the treatment of vasculitis can differ greatly and must take into account the great variation in disease type and extent.

Treatment of the primary systemic vasculitides has evolved over the past twenty years from a one-size-fits-all approach to more individualized therapy based on the type and severity of vasculitis. For some cases of vasculitis biomarkers or other prognostic factors affect treatment decisions. The great progress made in treatment of vasculitis is due to several advances that have occurred in parallel, including an increased understanding of disease pathogenesis, establishment of international clinical research networks, increased research funding, development of new drugs to treat autoimmune diseases, and conduct of high-quality, multinational randomized clinical trials (RCTs).

This chapter will describe the underlying concepts guiding treatment of vasculitis, clinical trial standards and individualization of therapy, and outline treatment of several types of vasculitis. Where possible the data presented will be based on clinical trials and other sources of good evidence. Details of treatment can be found in the chapters in this textbook dedicated to specific forms of vasculitis.

GENERAL APPROACH TO TREATMENT OF VASCULITIS

The treatment of primary systemic vasculitis largely depends on the specific type of vasculitis and the extent of organ involvement. Therefore, confirmation of the diagnosis and a comprehensive assessment of disease severity are necessary prior to initiating therapy. It is imperative to know the full extent of disease to both be sure that the level of treatment matches the most severe manifestations present, and to stage the extent of specific manifestations present at the start to therapy to allow for proper reassessment later in the treatment course.

Treatment of systemic vasculitis generally consists of a period of remission induction followed by remission maintenance, and long-term follow-up. The duration of therapy usually depends on the type and severity of vasculitis. Treatment also includes management of specific organ damage, prophylaxis against, and treatment of, medication-related toxicities.

Remission-Induction

Remission-induction is the period lasting from the initiation of treatment to the achievement of remission. The duration of this period is usually 3 to 6 months but may vary based on the severity and type of vasculitis. Some patients never achieve remission but most will achieve either remission or a state of low disease activity. Induction of remission almost always includes treatment with moderate-high doses of glucocorticoids alone or in conjunction with another form of immunosuppression. The most common immunosuppressive agents used for remission-induction of severe forms of vasculitis are cyclophosphamide and rituximab; however, several other agents are also used for induction.

Adjunctive therapies such as plasma exchange, renal replacement therapy, respiratory support, infection prophylaxis, and other interventions may be used during this period depending on the specific type of vasculitis and the presence of organ failure.

Remission-Maintenance

Remission-maintenance is the period that follows induction and is aimed at consolidating remission and preventing relapses. During this period glucocorticoids are tapered off or lowered to the minimum dose possible. If cyclophosphamide is used for remission-induction then during the maintenance phase, cyclophosphamide is replaced by a less toxic immunosuppressive agent. However, when rituximab is used for remission-induction then additional doses are often given for remission-maintenance. The concept of remission-maintenance was initially introduced and demonstrated to be effective in clinical trials of small-vessel vasculitides, notably anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). A similar approach is now frequently applied to medium-vessel vasculitis such as polyarteritis nodosa (PAN) and Kawasaki disease (KD), and the large-vessel vasculitides including giant cell arteritis (GCA) and Takayasu arteritis (TAK), and other types of vasculitis. The duration of the remission-induction period varies among the vasculitides. For some diseases with a lower probability of relapse, such as PAN, this period may be 12 months while for a disease with frequent relapses, such as granulomatosis with polyangiitis (GPA), remission-maintenance may be much longer. Cogan's syndrome and Behçet's disease are examples of variable-vessel vasculitides and are considered in greater depth elsewhere in this textbook.

Post-Treatment

Even after the remission-maintenance phase of treatment has ended and all immunosuppressive drugs are discontinued, it is imperative that patients are followed regularly for the possibility of disease relapse and to monitor for the occurrence of late-onset medication side effects and cardiovascular events.

RANDOMIZED CLINICAL TRIALS IN THE VASCULITIDES

Since the first curative randomized clinical trial in the history of medicine was conducted in 1946 to study the use of streptomycin in tuberculosis [1] the design and complexity of RCTs steadily evolved to include various study designs, often large number of study subjects, and an emphasis on multicenter studies. The regular conduct of clinical trials to study treatment of vasculitis is only a relatively recent development. The rarity of primary systemic vasculitis, the lack of adequate research funding, the challenges of studying complex heterogeneous disorders, and the small number of academic centers with expertise in these diseases meant clinical research in vasculitis initially consisted of single-center case series and cohort studies, small single-arm and open label trials in a small set of diseases.

The past twenty years has witnessed tremendous progress in the conduct of clinical trials in vasculitis. This progress has occurred due to several factors. First, the widespread adoption of standardized definitions [2, 3] and classification criteria [4, 5] for the vasculitides, leading to greater standardization of eligibility criteria.

Second, the use of validated outcome measures for vasculitis [6-8], although many forms of vasculitis still lack well-validated measures of disease activity or state for use in clinical trials. The Vasculitis Working Group of the Outcome Measures in Rheumatology (OMERACT) initiative is actively pursuing a variety of projects to advance development of valid measures in multiple forms of vasculitis [7, 9-11].

Third, the establishment of national and international research networks including the Vasculitis Clinical Research Consortium (VCRC) (www.RareDiseasesNetwork.org/vcrc), the European Vasculitis Society (EUVAS) (www.vasculitis.org), and the French Vasculitis Study Group (FVSG) (www.vascularites.org). These networks facilitate collaborations between academic institutions with expertise in clinical care and research in vasculitis. Many of the key multicenter trials in vasculitis have been conducted by these groups or the core personnel within the groups. The VCRC and the EUVAS are now conducting several large RCTs together, indicative of the growing international cooperative spirit within the vasculitis research community.

Fourth, the increased funding for clinical trials in vasculitis by governmental agencies, private foundations, and the biopharmaceutical industry, singly or in combination.

Fifth, the rapid growth of patient engagement and patients as research-partners, the close collaboration between various stakeholders, and the use of the Internet as a means of communication, recruitment, and dissemination have revolutionized the way some clinical research is done.

Advances in standardized approaches to conducting clinical trials was demonstrated by the publication in 2007 by a group that included leaders of these networks and other international experts in vasculitis of recommendations for conducting clinical trials in systemic vasculitis [12].

OVERVIEW OF THE TREATMENT OF VASCULITIDES

The treatment of primary systemic vasculitis substantially evolved over the years from extended courses of monotherapy with glucocorticoids to more complex, multi-stage regimens that combine glucocorticoids with additional immunosuppressive drugs. These progressions in therapeutic approach are due to several factors, including the implementation of successful larger randomized clinical trials as outlined above, the availability of targeted therapy with so-called “biologic” therapies, and incorporation of specific disease subtypes and prognostic factors that allow for greater individualization of treatment.

Prognostic Factors

A major advance in the field of vasculitis has been the recognition and data supporting the concept that certain clinical factors are associated with disease course in some forms of

vasculitis and can assist in the choice and duration of therapy. The clinical pattern, disease phenotype, and history of relapse in patients with GPA and microscopic polyangiitis (MPA) are each predictive of prognosis with treatment. Patients seropositive for anti-proteinase 3 ANCA are at substantially higher risk of relapse than patients with anti-myeloperoxidase ANCA [13, 14], while patients with GPA are more likely to relapse than patients with MPA, a finding not surprising given the much higher prevalence of anti-proteinase 3 ANCA among patients with GPA [14]. A history of relapse in AAV is highly predictive of future relapse. Thus, these prognostic factors are taken into consideration when developing a treatment regimen for patients with AAV, including duration of therapy.

The five factor score (FFS), a prognostic tool created by the FVSG [15-17], is another example of how severity and specific organ involvement may serve not only as a prognostic tool, but also help direct the therapeutic choice in systemic necrotizing vasculitis [18, 19]. The FFS is based on the presence of five clinical items: renal insufficiency, proteinuria, central nervous system involvement, cardiomyopathy, and gastrointestinal involvement. Each clinical item is assigned one point with a total maximum of five points. Patients with systemic vasculitis such as PAN, MPA, and eosinophilic granulomatosis with polyangiitis (EGPA) have a 5-year survival of 88% if FFS = 0, 74% if FFS = 1, and 54% if FFS $\geq$ 2 [15]. The FFS, which has only been substantively tested in PAN, MPA, and EGPA, is calculated at the initial presentation, and has been used to help decide among different treatment courses and whether to add another immunosuppressive agent to glucocorticoids for initial treatment of vasculitis [18, 20, 21]. The FFS was revised in 2011 to include GPA. The presence of ear, nose, and throat (ENT) involvement in GPA and EGPA was associated with a reduction in mortality. The revised FFS currently comprises: age $\geq$ 65 years, cardiac involvement, gastrointestinal involvement, renal insufficiency (stabilized peak creatinine $\geq$ 150 μ mol/L), and absence of ENT involvement [16].

The type of vasculitis can also dictate the treatment of primary systemic vasculitis. Some vasculitides, such as PAN and anti-glomerular basement membrane disease are more likely to have a single course of disease without relapse, while other diseases, such as GPA or GCA commonly relapse. Additionally, the severity or type of manifestations may change over time. All of these factors plus individual patient-specific variables are important when considering the treatment options for patients with vasculitis.

TREATMENT OF SPECIFIC VASCULITIDES

The following section will provide outlines on the treatment of specific forms of vasculitis with an emphasis on data derived from controlled clinical trials and will highlight some of the differences in the approach to treatment with the different forms of vasculitis. Many individual patient characteristics and disease variables will impact the decision to adopt and implement any of the treatment regimens described below. The treatment of affected patients with vasculitis should always be directed by physicians with experience in the treatment of vasculitides and the use of immunosuppressive medications. By far the most and highest quality data on treatment of vasculitis is available for GPA and MPA since AAV has been the focus of several large randomized controlled trials. The treatment recommendations

and drug dosages provided below pertain mainly to adults should be appropriately adjusted for use in children.

Glucocorticoids

The treatment of nearly all forms of vasculitis involves the use of glucocorticoids and these agents remain a mainstay of treatment, either as single therapy or as part of combination therapy. For severe disease intravenous pulses are usually given for 1 to 3 days followed by high-dose oral glucocorticoids, for example prednisone 1 mg/kg/day followed by a steadily tapering dose. Less severe disease may be treated initially with lower doses of glucocorticoids and mild flares may be treated with only a small increase in their dose. More recently, a large multinational clinical trial called “Plasma Exchange and Glucocorticoid Dosing in the Treatment of Anti-Neutrophil Cytoplasm Antibody Associated Vasculitis (PEXIVAS)” demonstrated that a reduced cumulative dose of glucocorticoids was as effective for induction of remission and long-term outcomes as the standard higher-dose regimen, with lower rates of infection seen in the lower-dose glucocorticoid arm. Glucocorticoids are usually given for at least 6 months or more after the initial presentation or after a moderate-severe flare. The total duration of therapy with glucocorticoids for vasculitis is controversial with some experts advocating for attempting to get patients fully off glucocorticoids in the first year of treatment and others promoting the extended use of low-dose glucocorticoids in the first 12 to 18 months of treatment [22, 23].

SMALL-VESSEL VASCULITIS

ANCA-Associated Vasculitis: Granulomatosis with Polyangiitis and Microscopic Polyangiitis

The treatment of GPA and MPA has evolved over the last four decades from glucocorticoids alone to extended use of cyclophosphamide [24] to several different treatment protocols based on disease severity, disease stage, and including substantially reduced cumulative doses of cyclophosphamide or the avoidance of this medication altogether [25]. For purposes of treatment, severe disease flare in AAV is generally defined as the presence of active disease manifestations that are organ- and/or life-threatening.

Remission-induction therapy for severe initial presentations or flares and relapses of disease in AAV currently involves the use of glucocorticoids in combination with a choice of cyclophosphamide or rituximab. Two clinical trials compared cyclophosphamide to rituximab for remission-induction and found these two treatments to have similar efficacy in inducing remission when used in combination with glucocorticoids [26, 27]. The standard dose of oral cyclophosphamide for remission-induction of AAV is 2 mg/kg/day for 3 to 6 months. Pulse intravenous cyclophosphamide therapy is a reasonable alternative to oral administration. A randomized trial (the “CYCLOPS” study) demonstrated equivalence of the two routes of administration of cyclophosphamide for remission-induction [28] and the use of intravenous cyclophosphamide is supported by other studies [29]. However, it is important to note that the

dosing of cyclophosphamide per the “CYCLOPS” regimen is 15 mg/kg every 2 weeks for 3 infusions then once every 3 weeks. The duration of cyclophosphamide use in the major trials was 4 to 6 months prior to transition to another agent. The dose of oral or intravenous cyclophosphamide should be adjusted down among patients with renal insufficiency, in response to leukopenia, and in older patients.

Remission-maintenance treatment in AAV following achievement of remission with cyclophosphamide involves the use of intravenous rituximab 500 mg every 6 months. Azathioprine at the dose of 2 mg/kg/day or methotrexate at doses of 20 to 25 mg/week can also be used for at least 1-2 years after cyclophosphamide and often much longer or indefinitely for patients at high risk of relapse [30-32]; one RCT found no difference in the efficacy of azathioprine and methotrexate for maintaining remission [33]. The choice between these two agents depends on individual patient factors and preferences; methotrexate should not be used by patients with renal insufficiency. The IMPROVE trial in AAV [34] showed that following induction of remission with cyclophosphamide, azathioprine was superior to mycophenolate mofetil for remission-maintenance making the latter a third choice for this indication, after azathioprine and methotrexate.

Rituximab was found to be as effective as cyclophosphamide at inducing remission in AAV [26, 27]. The induction regimen used in the trials was 375 mg/m² given intravenously weekly for 4 consecutive weeks. Rituximab is a reasonable alternative to cyclophosphamide for treatment of severe AAV. However, the high cost of this drug has resulted in wide variation internationally in the use of rituximab. In some countries it is a first-line treatment option, especially to treat younger patients seeking to preserve their fertility. In many countries use of rituximab is restricted to patients with relapsing disease, especially those who have had prior courses of cyclophosphamide who comprise a subset of patients for whom rituximab was found superior to cyclophosphamide in the RAVE trial [14]. In other countries rituximab is unavailable as a treatment option.

The appropriate choice of treatment for remission-maintenance following induction of remission with rituximab remains uncertain. In the RAVE trial [14] one course of rituximab was equally efficacious in maintaining remission as 18 months of cyclophosphamide and azathioprine. Single-center retrospective cohort studies provided evidence that repeated doses of rituximab helped maintain remission in many patients [35, 36]. However, due to the expense of rituximab and concerns about the impact of repeated dosing and hypogammaglobinemia, consideration has since been given to using more standard immunosuppressive agents such as azathioprine or methotrexate following rituximab. Different treatment strategies for maintenance of remission in AAV after induction with rituximab are currently being studied in a multinational clinical trial (RITAZAREM) (ClinicalTrials.gov Identifiers: NCT01697267)).

The role of plasma exchange in the treatment of AAV has been highly controversial. In one RCT of patients with AAV and severe rapidly-progressive renal impairment at diagnosis, the addition of plasma exchange reduced the frequency of progression to end-stage renal disease but not overall mortality [37]. Other studies did not clearly demonstrate the benefit of plasma exchange in AAV [38], including for the treatment of alveolar hemorrhage. A recent large multinational, randomized clinical trial involving 704 patients with GPA and MPA (the PEXIVAS trial), treatment of severe AAV in a large m [39] plasma exchange did not reduce the rate of end-stage renal disease or death.

Adjunctive therapy with high-dose intravenous immunoglobulin therapy has been used in patients who fail to achieve remission with standard approaches [40].

The data is mixed on the efficacy of trimethoprim-sulfamethoxazole as treatment for upper respiratory manifestations of AAV or in the maintenance phase of treatment [41-43]. This drug is routinely use for prophylaxis against *pneumocystis jirovecii* pneumonia for patients with AAV receiving immunosuppressive agents.

Two other immunomodulating drugs have shown promise in phase II clinical trials for the treatment of GPA and MPA including abatacept (CTLA4-Ig) for the treatment of non-severe relapsing GPA and an oral inhibitor of C5a (CCX168) for the treatment of GPA and MPA. The results of a phase III clinical trial are expected to provide more definitive data on the utility of the oral inhibitor of C5a (CCX168) for the remission and maintenance of GPA and MPA (ClinicalTrials.gov Identifier: NCT02994927).

The optimal duration of therapy for remission maintenance in GPA and MPA remains unknown. However, the trend has been towards longer courses of therapy with the remission-maintenance agent often continued for at least 12 to 18 months for treatment of new-onset disease and even longer or indefinitely for relapsing disease. Affected patients that demonstrate ANCA with specificity to proteinase 3 have substantially higher rates of relapse than those patients positive for antibodies to myeloperoxidase; relapse in AAV is itself predictive of future relapse [14].

Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss)

The approach to treatment of EGPA differs somewhat from the other AAV due to several factors including recognition that many patients may have a monocyclic course, identification of clinical prognostic factors influencing the choice of treatment, and the impact of recurrent asthma on clinical course.

A recent randomized trial demonstrated that blockade of IL-5 by a monoclonal antibody (mepolizumab) resulted in significantly more weeks in remission and a higher proportion of participants in remission than did placebo, thus allowing for reduced glucocorticoid use in patients with EGPA. This clinical trial led to the first FDA approval for a drug for the treatment of EGPA.

Several other clinical trials conducted in EGPA by the FVSG have provided guidance to treatment of this form of vasculitis; however, these studies have often included a mixture of patients with EGPA, MPA, and PAN making interpretation of results complicated. Glucocorticoids are the mainstay of therapy for EGPA and are included in all treatment regimens and are often the sole treatment for cases without poor-prognosis factors (FFS = 0) [18], or in combination with intravenous cyclophosphamide when the FFS ≥ 1 . In a trial of superiority of six versus twelve pulses of cyclophosphamide (600 mg/m² per pulse) in patients with a poor prognosis, defined as a FFS ≥ 1 , the longer duration of treatment was superior to shorter treatment for control of disease [19]. Patients treated with glucocorticoids alone had more frequent relapses suggesting the need for a revision in this treatment approach. A RCT of azathioprine and glucocorticoids as first-line treatment in EGPA without factors mitigating poor-prognosis demonstrated no additional benefits for remission rates, relapse risk, sparing of glucocorticoids, or diminishing the EGPA asthma/rhinosinusitis

exacerbation rate over glucocorticoids alone. Although the trials of EGPA mainly involve use of intravenous cyclophosphamide, many centers will apply the treatment regimens used for GPA and MPA for patients with severe EGPA and prescribe oral cyclophosphamide for several months, transitioning afterward to azathioprine or methotrexate for remission maintenance. Methotrexate combined with glucocorticoids is another regularly used remission-induction regimens to treat non-severe EGPA [44].

It remains intriguing yet controversial to consider the ANCA status when treating patients with EGPA, include for example, whether patients positive for ANCA should be treated according to strategies for GPA and MPA or whether patients negative for ANCA be treated in a different manner.

Newer agents such as other IL-5 inhibitors (reslizumab [ClinicalTrials.gov Identifier: NCT02947945] and benralizumab [ClinicalTrials.gov Identifier: NCT03010436]) are under investigation for the treatment of EGPA. While rituximab use has been limited to a few case series [45, 46], there is enthusiasm for using rituximab to treat EGPA based on experience with GPA and MPA, especially for patients who test positive for ANCA (ClinicalTrials.gov Identifier: NCT02947945).

The treatment of EGPA is complicated by the presence of asthma in the vast majority of patients. It is controversial whether to consider asthma as a manifestation of vasculitis or a separate aspect of the disease. Asthma is the most common disease manifestation of EGPA and may drive the clinical decision to treat with glucocorticoids, whether prescribed at chronic low maintenance doses or periodically at high-doses to control exacerbations of asthma.

IMMUNE COMPLEX-MEDIATED VASCULITIS

Cryoglobulinemic Vasculitis

The treatment of cryoglobulinemic vasculitis (CV) depends upon the etiology and the severity of associated organ involvement. While antiviral therapies remain the cornerstone of the treatment of hepatitis C virus (HCV)-related CV, glucocorticoids, immunosuppressive drugs, and plasma exchange can all be used for the acute treatment of HCV-associated CV. Two RCTs demonstrated the efficacy of rituximab to treat HCV-related CV with recurrent disease despite anti-viral therapy and standard immunosuppression [47-49]. Rituximab is prescribed in non-HCV-associated CV but data from clinical trials for this indication are lacking. Less severe cases of CV, such as mild skin disease and arthritis, can be treated with a short course of glucocorticoids. Persistent disease with idiopathic CV may necessitate treatment aimed at whatever is presumed to be the underlying plasma cell dyscrasia.

IgA-Vasculitis (Henoch-Schönlein)

IgA-vasculitis (IgAV) is a disease for which the course and treatment may be different between children and adults. The data for treatment of IgAV is derived from a few clinical trials in children and mostly case series for adults. There is neither consensus for the

treatment of IgAV, nor agreement as to whether available therapies change the course of the disease.

MEDIUM-VESSEL VASCULITIS

Polyarteritis Nodosa

In comparison to AAV, there are limited data from clinical trials to support the choice of treatment in PAN [50-52] and the often monocyclic nature of the disease may complicate the determination of risks and benefits any given immunosuppressant regimen. The practice of pooling patients with PAN, MPA, and EGPA within a single clinical trial can make study results difficult to interpret. The treatment of PAN generally follows a type- and severity-based strategy, including utilization of the FFS. Results from uncontrolled studies and expert opinion suggest that the primary treatment of hepatitis B virus (HBV)-associated PAN can be treated with antiviral therapies; however, a short course of glucocorticoids may be appropriate treatment of acute vasculitis-related complications. The role of plasma exchange in HBV-associated PAN remains controversial [53, 54].

The treatment of idiopathic PAN without HBV infection relies on immunosuppressive therapy. For limited cutaneous and mild systemic PAN (FFS = 0) prednisone in doses up to 1 mg/kg/day alone is often sufficient treatment; when the disease is controlled then the glucocorticoid dose is tapered slowly.

The treatment of patients with severe systemic PAN (FFS ≥ 1) associated with involvement of the kidney, heart, gastrointestinal tract, and the central nervous system (CNS) includes combination of high-dose glucocorticoids and another immunosuppressive agent. Pulse intravenous methylprednisolone at the dose of 1000 mg/day for 3 days followed by prednisone 1 mg/kg/day tapered over 6 months is the recommended glucocorticoid regimen. In addition, cyclophosphamide is given orally at a dose of 2 mg/kg/day or intravenously in doses of 600 to 750 mg/m² every 2 to 4 weeks for 6 months with subsequent transition to azathioprine at a dose of 2 mg/kg/day or methotrexate at doses of 20 to 25 mg weekly for remission maintenance [25]. Some centers treat systemic PAN by prescribing glucocorticoids at the outset in combination with azathioprine or methotrexate but without cyclophosphamide.

Kawasaki Disease

Kawasaki disease occurs almost exclusively in young children. Randomized trials have established the standard of treatment that includes aspirin, intravenous immune globulin, and comprehensive cardiac monitoring through centers experienced in the management of this disease [55-57].

LARGE-VESSEL VASCULITIS

There is ongoing controversy and interest in the question as to whether GCA and TAK constitute a single spectrum of large-vessel vasculitis and thus whether their respective treatments should be the same [58-60]. Glucocorticoids remain the mainstay of remission-induction and generally remission-maintenance therapy in both diseases. However, several recent clinical trials have provided evidence of the benefit of other immunosuppressive agents (anti-IL6R and anti-CTLA4) on disease remission and reducing glucocorticoids cumulative dose. Endovascular and surgical interventions may be required to manage the vascular damage leading to stenosis and aneurysm formation that may occur.

Giant Cell Arteritis

The usual starting dose of prednisone for the treatment of GCA ranges from 40 to 60 mg/day for four weeks with a subsequent gradual taper over many months [61]. The exact timing of glucocorticoid withdrawal is controversial with some centers seeking to attempt to withdraw them at six months and others advocating a longer course of low-dose daily prednisone for the first year of treatment. Intravenous pulse glucocorticoids for three consecutive days may be considered initially in cases of acute visual loss [62].

The benefit of tocilizumab, a monoclonal antibody directed against the IL-6 receptor, in combination with prednisone, was demonstrated in two randomized trials to effectively reduce the risk of relapse among patients with GCA compared to treatment with prednisone alone. Based on the results of these trials, tocilizumab was subsequently approved drug by the FDA and EMA for GCA. Abatacept, a CTLA4-IgG1 fusion protein that binds to the CD80/86 molecule and prevents the activation of T-cells, has also been shown in a double-blind RCT to reduce relapse rates in patients with GCA.

Weekly oral methotrexate can be used as a maintenance agent. The role of methotrexate as a glucocorticoid-sparing agent was studied in three RCTs [63-65] demonstrating conflicting results. However, an individual patient-level meta-analysis demonstrated that methotrexate was efficacious in preventing relapses and reducing total glucocorticoid usage [66]. While the overall efficacy of methotrexate in GCA appears to be modest, it is nonetheless frequently used to help avoid excess glucocorticoid use and to treat relapsing disease.

The use of anti-TNF alpha agents for treatment of GCA was studied in three RCTs, each of which failed to demonstrate efficacy for these agents [67-69]. A trial of infliximab also failed to demonstrate efficacy in polymyalgia rheumatic (PMR) [70].

Several other drugs have been proposed for use as glucocorticoid-sparing agents in GCA, including azathioprine, cyclophosphamide, cyclosporine, hydroxychloroquine, and leflunomide but there is no evidence large clinical studies or RCTs to support the use of these agents [71-74].

The results from an analysis of two large retrospective patient series supported the use of low-dose aspirin as adjunctive therapy in GCA to prevent ischemic complications [77, 78]; however, the routine use of aspirin in GCA remains an ongoing controversy.

Among the challenges of conducting RCTs in GCA are the lack of a clear definition of disease activity, the accepted efficacy and low cost of glucocorticoids, the acute nature of the clinical presentation necessitating immediate treatment, and the difficulty older individuals may have in participating in research studies. Nonetheless, there remains an unmet need to find alternative therapies to high-dose or recurrent courses of glucocorticoids in GCA.

Takayasu Arteritis

Only two RCTs have been conducted in TAK. The first was a trial of abatacept plus glucocorticoids vs. glucocorticoids alone for the treatment of TAK that did not demonstrate efficacy of this biologic agent. The second trial tested tocilizumab plus glucocorticoids vs. glucocorticoids alone and this trial had equivocal results but with some data that tocilizumab may help reduce the time to relapse. Treatment approaches for this rare disorder continue to be based instead on case series, expert opinion, and extrapolation from studies in GCA, which may not be an ideal approach. Glucocorticoids are the foundation of therapy for induction or remission in TAK and the dosing regimen is similar to GCA and other vasculitides with initial high-dose oral glucocorticoids followed by a slow taper over several months. Other immunosuppressive therapies, including azathioprine, cyclophosphamide, methotrexate, and mycophenolate mofetil are routinely prescribed in patients with severe disease or in those with recurrent or refractory disease [79]. Although initial case series reported high efficacy from use of anti-TNF-alpha agents, subsequent series demonstrated that these agents, while possibly helpful in some patients, were associated with substantial rates of disease relapse or incomplete remission-induction [80-83]. Initial patient reports of rituximab [84] to treat TAK have been promising, however, larger series with longer follow-up and RCTs are required to evaluate any agent in this chronic relapsing disease.

Surgical Intervention

Both GCA and TAK are associated with a variety of fixed vascular stenosis and aneurysm formation of the aorta and its main branches. Such lesions occur as a result of scarring after inflammation, even when the disease is seemingly well controlled. Aneurysms, once formed, tend to enlarge just as do aneurysms resulting from other etiologies such as hypertension. Patients with large-vessel vasculitis should be considered for surgical intervention to treat severe or functionally-limiting limb ischemia, cerebrovascular insufficiency, renal artery stenosis with associated severe hypertension, expanding aortic aneurysms, and severe cardiac valvular disease. There remains uncertainty regarding the relative efficacy and advisability of angioplasty, stents, and surgical repair for these vascular lesions. Regardless of which form of repair may be considered, the consensus is that particular attention should be given to controlling disease activity in the peri-procedure period [86-88]. Endovascular procedures in patients with vasculitis should be performed in specialized centers with experience with both the procedures and the management of vasculitis [25].

VARIABLE VESSEL VASCULITIS

Cogan's Syndrome

Most patients with Cogan's syndrome are treated with glucocorticoids with a favorable response for both vestibule-auditory and ophthalmologic manifestations. Other therapies, all based on small case series or expert opinion, included methotrexate, cyclophosphamide, azathioprine, anti-TNF alpha agents, hydroxychloroquine, and intravenous immunoglobulin. Surgical cochlear implantation can lead to objective and subjective benefits with improved hearing recognition in the majority of patients.

Behçet's Disease

Behçet's disease is a complex multisystem disorder in which several clinical trials have been conducted using a variety of different outcome measures. However, unlike most trials in other forms of vasculitis where overall disease activity is the outcome of interest, those in Behçet's disease have often focused on specific manifestation such as mucocutaneous lesions and uveitis. A RCT of apremilast for the treatment of oral ulcers in Behçet's disease showed promising results [11] and a larger Phase III has been completed (ClinicalTrials.gov Identifier: NCT02307513). Thus, treatment recommendations are complex and depend upon the stage of disease, sex of the patient, and disease manifestations of greatest concern.

PRIMARY CENTRAL NERVOUS SYSTEM VASCULITIS

There are no RCTs to guide treatment of primary central nervous system vasculitis (CNSV) also known as primary angiitis of the CNS. Treatment is based upon the clinical experience from case series, cohort studies, and expert opinion [89]. The initial treatment of CNSV includes prednisone 1 mg/kg/day often in combination with cyclophosphamide administered in monthly intravenous pulses with later transition to azathioprine, methotrexate, or mycophenolate mofetil for an additional period of 12 to 18 months as remission maintenance. TNF-alpha blocking drugs have been used to treat CNSV refractory to glucocorticoids and other immunosuppressive drugs [90, 91]. The treatment of childhood CNSV is reviewed elsewhere [92].

OTHER SYSTEMIC VASCULITIDES

There are several other types of vasculitis for which treatment is based on small case series and expert opinion when RCTs are unavailable. These vasculitides include anti-GBM disease, relapsing polychondritis, single-organ vasculitis (SOV), drug-induced vasculitis, and other unclassifiable vasculitides.

TREATMENT-RELATED TOXICITY

Much of the morbidity incurred by primary systemic vasculitis results from the treatment, rather than the disease itself. It is essential for physicians and patients to constantly monitor for side effects of drugs and use appropriate measures to minimize or prevent treatment-related complications. A detailed discussion of the proper use of immunosuppressive medications is beyond the scope of this chapter.

LONG-TERM COMPLICATIONS OF VASCULITIDES

Disease-related problems in vasculitis go beyond the acute organ damage that occurs due to active vasculitis. Long-term complications of both the underlying vasculitis and the treatments are increasingly recognized as contributing to the overall morbidity of patients with vasculitis. In addition to the direct damage caused by vasculitis such as renal failure, visual loss, aneurysm, lung impairment, and other problems, it is important to monitor and treat other long-term complications that may be more common with vasculitis but overlooked. These complications include, hypertension from renal insufficiency and renal artery stenosis, accelerated cardiovascular disease thought secondary to chronic inflammation, obesity from often repeated courses of glucocorticoids, malignancy associated with treatment and possible increased incidence of cancer associated with vasculitis, depression and other mood disorders common among patients with serious chronic illnesses, and physical disabilities that impair daily function and work productivity.

CONCLUSION

Despite the substantial progress made in the therapy of primary systemic vasculitis, the treatment of many vasculitides remains a challenge. Dividing therapy into an induction phase and maintenance phase to improve disease control and minimize side effects as well as individualizing medical management based on the severity, type, and prognostic factors have revolutionized the therapy of vasculitis. Multicenter RCTs have answered critical questions regarding the management of several primary systemic vasculitides but data from trials are still lacking for the majority of vasculitides and for treatment of children with vasculitis. The development of research networks including the VCRC, EUVAS, and FVSG, have all greatly facilitated RCTs in vasculitides and fostered collaboration among these networks to produce major new studies. Newer medications and novel approaches are constantly being tested to refine therapy and improve care in vasculitis. The rapid development of targeted immunomodulatory therapies will likely have a substantial positive impact on the treatment of vasculitis. Similarly, discovery and refinement of reliable biomarkers of disease activity, prognosis, and response to treatment, should usher in an era of individualized or personalized therapy for vasculitis.

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Chapter 226

HOW KNOWLEDGEABLE ARE YOUNG ADULTS ABOUT ALZHEIMER'S DISEASE?

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ABSTRACT

Alzheimer's disease is the most common subtype of dementia, with studies reporting that it makes up somewhere between 50-72% of dementia cases. Symptoms of Alzheimer's include significant episodic memory impairment, behavioural disturbances and psychopathological disturbances. At this moment there is no cure for Alzheimer's disease, so it is therefore important to promote increased awareness by family members, which could result in more conscientious caregivers and better quality of life. An international research group has conducted studies in the young adult population in various locations to estimate the knowledge about Alzheimer's disease. The results indicated that while only 48% of participants believed that they were knowledgeable about the disease, the assessment quiz indicated that 75% turned out to be very

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knowledgeable. This book will present the data from the studies around the different locations.

INTRODUCTION

Dementia is a broad term that includes a variety of disease subtypes, and is very common among those over the age of 65 years old. It can significantly alter the quality of life of affected patients, and when coupled with other medical conditions, can lead to suboptimal patient care as well [1, 2]. This under-management could snowball into a public health disaster with over 560,000 Canadians suffering from dementia, which accounts for \$10.4 billion in annual expenditure, and this statistic is expected to quadruple within the next 50 years [3, 4]. Tools have been developed by healthcare professionals to help improve the quality of care for these patients [5], but it is still far from a perfect solution.

Alzheimer's is the most common subtype of dementia, with studies reporting that it makes up somewhere between 50% to 72% of dementia cases [2, 6, 7]. Symptoms of Alzheimer's include significant episodic memory impairment, behavioural disturbances, and also psychopathological disturbances [6, 8]. With no cure to Alzheimer's on the horizon, increased awareness by family members could result in more conscientious caregivers and better quality of life.

With the frequency of dementia and its subtypes expected to increase in the future, coupled with the fact that there exists an aging population, it is important that young adults are aware of the disease as they will be responsible to care for the elderly population in the future. An original study was conducted among the young adult population in London, Canada [8]. The results indicated that while only 48% of participants believed that they were knowledgeable about the disease, the assessment quiz indicated that 75% turned out to be very knowledgeable. The authors also investigated into whether there were differences in scores between males and females, those under 20 years old and above 20 years old, and those who have a family member affected by the disease and not affected. There only existed differences in scores between males and females, with females proving to be more knowledgeable.

The trend revealed by the study [8] has important implications, in that it informs about the awareness level and even leads to inference about the prevalence of Alzheimer's among the family members of young adults. The studies contained herein looked to further examine the awareness level of young adults with respect to Alzheimer's disease at different geographical locations around the world.

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Chapter 227

AWARENESS OF ALZHEIMER'S DISEASE: ABOUT THE SURVEY AND SURVEY INSTRUMENT

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ABSTRACT

Infinitas Research Group, headquartered out of London, Canada, designed a survey with the aim to assess perceived awareness level and actual awareness level of young adults – the age cohort which will be most heavily relied on in the coming decade to care for patients with Alzheimer's disease. The primary objective of the survey was to determine the awareness of Alzheimer's disease, across all young adults (regardless of age, sex and other background). The secondary objectives were to determine whether there existed any difference in knowledge across different subgroups - between men and women, between younger and older young adults, and between those with and without family members with Alzheimer's disease.

INTRODUCTION

Dementia and its subtypes, such as Alzheimer's, is expected to increase over the next several decades. Given that there is no cure, the best means of management available today is to increase awareness of relatives and family members to hopefully have more conscientious caregivers (see Chapter 1).

Infinitas Research Group, headquartered out of London, Canada, designed a survey with the aim to assess perceived awareness level and actual awareness level of young adults – the age cohort which will be most heavily relied on in the coming decade to care for patients with

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Alzheimer's disease. The objective was to deploy the survey around the globe and assess awareness levels based on geography, age, sex, and familial ties to the disease.

SURVEY QUESTIONNAIRES

A survey was designed to evaluate the awareness of young adults (see Figures 1-4). The first page had a consent form for the study; participants had the option to enter their email and receive a copy of the consent form (see Figure 1). After consenting to the study, participants completed three questions to collect relevant demographics - primary place of residence, age and sex (see Figure 2). The third page had six questions, with the first being a reflection question and the next five being knowledge-based questions - a quiz about Alzheimer's disease (see Figure 3). The last page of the survey asked participants whether, to their knowledge, they have/had a family member affected by Alzheimer's; if they have/had, it also asked for how often they visit their relative (see Figure 4).

The primary objective of the survey was to determine the awareness of Alzheimer's disease, across all young adults (regardless of age, sex and other background). The secondary objectives were to determine whether there existed any difference in knowledge across different subgroups - between men and women, between younger and older young adults, and between those with and without family members with Alzheimer's disease.

STATISTICAL ANALYSIS

Descriptive statistics were used to report the six items - 1 reflection and 5 knowledge questions - on page 3. For each participant, an overall score out of 5 was generated for the number of questions they correctly answered, with the answer key being: Alzheimer's Disease is a form of dementia - True; Alzheimer's is part of the normal aging process - False; Alzheimer's worsens over time - True; There is no cure for Alzheimer's only treatments for symptoms - True; Alzheimer's is a leading cause of death - True. Participants with scores of 4 or 5 out of 5 were interpreted to be knowledgeable about Alzheimer's disease; those with 3 were marked as having satisfactory knowledge; those scoring 1 or 2 had poor awareness about the disease.

Subgroup analyses were conducted based on ages of participants (under 20 years old, and 20 years old and older), sex (male and female), and their family's history with Alzheimer's disease (affected and not affected). Fisher-exact tests were conducted to determine whether there was a difference in awareness between these groups. P-values less than 0.05 were deemed to be statistically significant. All analyses were conducted using the Statistical Analysis Software (SAS Version 9.4 for Windows).

Awareness of Alzheimer's Disease

INFORMED CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Principal Investigator: Ronald Chou

Infotrac Research Group

Lindor, ON, Canada

info@researchgroup.ca

<http://sites.google.com/view/info@researchgroup/about-us>

INFORMED CONSENT

You are being asked to consider participating in a research study. A research study is a way of gathering information on something that is not well understood.

Participating in this study is your choice (voluntary). You have the right to choose not to participate, or to stop participating in this study at any time.

INTRODUCTION

You are being asked to consider participating in this study because you are a young adult.

WHY IS THE STUDY BEING DONE?

Dementia and Alzheimer's is being ever more prevalent in the today's society, with the younger generation being relied on more to support those who suffer the debilitating illness. The purpose of this study is to investigate the current awareness and knowledge surrounding Alzheimer's disease among young adults.

BENEFITS AND COSTS

There are no direct benefits or costs to participating in the study. The results from this survey may be published in a manuscript, and benefit the scientific community.

HOW WILL MY INFORMATION BE SECURED?

The study is anonymous, and therefore no names or personal information will be involved in the process.

WHAT ARE THE RIGHTS OF PARTICIPANTS IN A RESEARCH STUDY?

You have the right to receive all information that could help you make a decision about participating in this study. You also have the right to ask questions about the study and your rights as a research participant, and to have them answered to your satisfaction, before you make any decision. You also have the right to ask questions and to receive answers throughout this study.

If you have any questions about this study you may contact the person in charge of this study, the Principal Investigator.

DOCUMENTATION OF INFORMED CONSENT

Participant:

By consenting to this form, I confirm that:

- ☐ I have been fully informed of the risks and benefits of participating in this research study.
- ☐ I have been informed of the rights of research participants.
- ☐ I have been informed of any alternatives to participating in this research study.
- ☐ I have been informed of the rights of research participants.
- ☐ I have this form in its entirety.
- ☐ I have agreed, or agree to allow the person I am responsible for, to participate in this research study.

A copy of your responses will be sent to your email address. The researchers will not be able to match your email address to your responses. If you would not like a copy of your responses sent to your email, feel free to fill in the "Email address" field with info@researchgroup.ca.

* Required

Email address *

Your email

Notice of Consent *

- ☐ 'Yes, I consent to this form'
- ☐ 'No, I do not consent to this form'

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Figure 1. Survey (page 1).

Awareness of Alzheimer's Disease

Demographics of Respondents

Which city do you live in for the majority of the year? *

If you are a post-secondary student, where is your institution located?

☐ Dublin, IRELAND

☐ Halifax, CANADA

☐ Hamilton, CANADA

☐ Ithaca, USA

☐ Kingston, CANADA

☐ London, CANADA

☐ Montreal, CANADA

☐ New York City, USA

☐ Rochester, USA

☐ Saskatoon, CANADA

☐ Singapore, SINGAPORE

☐ Toronto, CANADA

☐ Waterloo, CANADA

☐ Other: _____

What age group do you belong to? *

☐ Under 18 years old

☐ 18-19 years old

☐ 20-22 years old

☐ Older than 22 years old

What is your sex? *

☐ Male

☐ Female

☐ Prefer not to say

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Figure 2. Survey (page 2).

Awareness of Alzheimer's Disease

Assessment of Knowledge

Please answer as honestly as possible without aid of any kind.

I believe I am knowledgeable about Alzheimer's disease.

☐ Disagree

☐ Neutral

☐ Agree

Alzheimer's Disease is a form of dementia.

☐ True

☐ False

☐ I do not know

Alzheimer's is part of the normal aging process.

☐ True

☐ False

☐ I do not know

Alzheimer's worsens over time.

☐ True

☐ False

☐ I do not know

There is no cure for Alzheimer's, only treatments for symptoms.

☐ True

☐ False

☐ I do not know

Alzheimer's is a leading cause of death.

☐ True

☐ False

☐ I do not know

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Figure 3. Survey (page 3).

Awareness of Alzheimer's Disease

Personal Experience

To your knowledge, do you have a family member who has/is suffering from Alzheimer's Disease?

☐ Yes

☐ No

If "Yes" to the prior question, how often do/did you visit them?

☐ Weekly

☐ Monthly

☐ Every few months

☐ Few times a year

☐ Every few years

A copy of your responses will be emailed to the address you provided

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Figure 4. Survey (page 4).

Chapter 228

AWARENESS OF ALZHEIMER'S DISEASE AMONG YOUNG ADULTS IN LONDON, CANADA

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ABSTRACT

Alzheimer's disease is the most common subtype of dementia, with studies reporting that it makes up over 50% of dementia cases. Lack of awareness has often resulted in failing to diagnose dementia at its early-onset and perhaps failing to slow its deterioration. Better awareness could also be an asset for primary caregivers of individuals suffering from dementia - more knowledge and awareness could lead to better and more attentive quality of care delivered by caregivers. The aim of this study was to determine how knowledgeable young adults are about Alzheimer's disease in London, Canada. A survey was designed to evaluate the awareness of young adults in London, Ontario, Canada, with five quiz questions. Subgroup analyses were conducted to compare scores based on ages of participants (under 20 years old, and 20 years old and older), sex (male and female), and their family's history with Alzheimer's disease (affected and not affected). A total of 79 people completed the survey; 48% of them believed that they were knowledgeable about Alzheimer's disease, 35% reserved judgement, and 16% admitted that they did not know much about the disease. 31% of young adults have a family member affected by Alzheimer's disease. 75% of the young adult population are knowledgeable about the prevalent disease, and only 8% have extremely poor awareness. These findings indicate that young adults seem to be adequately aware of the disease and its implications. Future studies should look into verifying this study in other locations, and also look into whether young adults know how to care for these Alzheimer's patients.

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INTRODUCTION

Dementia is very common in those over 65 years of age and affects the quality of life of those afflicted; for long-term care (LTC) elderly residents, it substantially alters their quality of life (QoL) [1, 2]. For LTC residents, dementia coupled with other medical conditions leads to below-optimal QoL and suboptimal patient care [1]. For example, 80% of those residing in LTC suffer from pain but cannot properly verbalize their symptoms as a result of dementia - their pain is frequently underreported and undertreated, although many pain assessment tools have been constructed and validated [1, 3].

Alzheimer's disease is the most common subtype of dementia, with studies reporting that it makes up over 50% of dementia cases [2, 4]. It has been found however that the behavioural and psychopathological disturbances caused by dementia are universal across most subtypes [4]. Lack of awareness of these types of dementia, however, have often resulted in failing to diagnose dementia at its early-onset and perhaps failing to slow its deterioration [5]. Increasing awareness could also be an asset for primary caregivers of individuals suffering from dementia - more knowledge and awareness could lead to better and more attentive quality of care delivered by caregivers [3]. The aim of this study was to determine how knowledgeable young adults are about Alzheimer's disease in London, Canada.

OUR STUDY

A survey was designed to evaluate the awareness of young adults in London, Ontario, Canada, see chapter 2 [6]. The first page had a consent form for the study; participants had the option to enter their email and receive a copy of the consent form [6]. After consenting to the study, participants completed three questions to collect relevant demographics - primary place of residence, age and sex [6]; only those who recorded London, Canada, as their place of residence was included in this study. The third page had six questions, with the first being a reflection question and the next five being knowledge-based questions - a quiz about Alzheimer's disease [6]. The last page of the survey asked participants whether, to their knowledge, they have/had a family member affected by Alzheimer's; if they have/had, it also asked for how often they visit their relative [6].

The primary objective of the survey was to determine the awareness of Alzheimer's disease, across all young adults (regardless of age, sex and other background). The secondary objectives were to determine whether there existed any difference in knowledge across different subgroups - between men and women, between younger and older young adults, and between those with and without family members with Alzheimer's disease.

Statistical Analysis

Descriptive statistics were used to report the six items - 1 reflection and 5 knowledge questions - on page 3. For each participant, an overall score out of 5 was generated for the number of questions they correctly answered, with the answer key being: Alzheimer's Disease is a form of dementia - True; Alzheimer's is part of the normal aging process - False;

Alzheimer's worsens over time - True; There is no cure for Alzheimer's only treatments for symptoms - True; Alzheimer's is a leading cause of death - True. Participants with scores of 4 or 5 out of 5 were interpreted to be knowledgeable about Alzheimer's disease; those with 3 were marked as having satisfactory knowledge; those scoring 1 or 2 had poor awareness about the disease.

Subgroup analyses were conducted based on ages of participants (under 20 years old, and 20 years old and older), sex (male and female), and their family's history with Alzheimer's disease (affected and not affected). Fisher-exact tests were conducted to determine whether there was a difference in awareness between these groups. P-values less than 0.05 were deemed to be statistically significant. All analyses were conducted using the Statistical Analysis Software (SAS Version 9.4 for Windows).

FINDINGS

A total of 79 people completed the survey. 48% of them believed that they were knowledgeable about Alzheimer's disease, 35% reserved judgement, and 16% admitted that they did not know much about the disease. 80% correctly recognized that Alzheimer's disease is a form of dementia, with 9% answering incorrectly and 11% choosing not to use a binary response. Only 8% incorrectly believed that Alzheimer's is part of the normal aging process; 5% recognized they did not know the answer, while 87% correctly responded to the question.

Table 1. Awareness of all young adults

Evaluation Metric	All (n = 79)
Self-belief of being knowledgeable	
Yes	38 (48%)
Neutral	28 (35%)
No	13 (16%)
Alzheimer's is a subtype of dementia	
True	63 (80%)
False	7 (9%)
Not Sure	9 (11%)
Alzheimer's is normal with respect to aging	
True	6 (8%)
False	69 (87%)
Not Sure	4 (5%)
Alzheimer's worsens over time	
True	75 (95%)
False	0 (0%)
Not Sure	4 (5%)
No cure to Alzheimer's	
True	72 (91%)
False	0 (0%)
Not Sure	7 (9%)
Alzheimer's is leading cause of death	
True	30 (38%)
False	25 (32%)
Not Sure	24 (30%)
Overall Score	
Poor (1-2)	6 (8%)
Satisfactory (3)	14 (18%)
Knowledgeable (4-5)	59 (75%)

Almost all (95%) participants acknowledged that Alzheimer's worsens over time, with the other 5% acknowledging they were unsure. 91% correctly believed that there was no cure to Alzheimer's disease, with the remaining 9% not choosing a binary option.

There was no definitive majority answer in response to the statement "Alzheimer's is a leading cause of death" - while 38% correctly agreed with the statement, 32% incorrectly disagreed, and 30% admitted they were unsure. Overall, 75% of individuals were knowledgeable (had 4 or 5 correct questions), while 18% had satisfactory awareness and only 8% with poor understanding of the disease (see Table 1).

Table 2. Awareness of young adults by age

Evaluation Metric	Under 20 Years Old (n = 41)	20 Years Old and Older (n = 38)	p-value
Self-belief of being knowledgeable			0.9104
Yes	20 (49%)	18 (47%)	
Neutral	15 (37%)	13 (34%)	
No	6 (15%)	7 (18%)	
Alzheimer's is a subtype of dementia			0.9210
True	33 (80%)	30 (79%)	
False	4 (10%)	3 (8%)	
Not Sure	4 (10%)	5 (13%)	
Alzheimer's is normal with respect to aging			0.9999
True	3 (7%)	3 (8%)	
False	36 (88%)	33 (87%)	
Not Sure	2 (5%)	2 (5%)	
Alzheimer's worsens over time			0.9999
True	39 (95%)	36 (95%)	
False	0 (0%)	0 (0%)	
Not Sure	2 (5%)	2 (5%)	
No cure to Alzheimer's			0.7053
True	38 (93%)	34 (89%)	
False	0 (0%)	0 (0%)	
Not Sure	3 (7%)	4 (11%)	
Alzheimer's is leading cause of death			0.5597
True	18 (44%)	12 (32%)	
False	12 (29%)	13 (34%)	
Not Sure	11 (27%)	13 (34%)	
Overall Score			0.9999
Poor (1-2)	3 (7%)	3 (8%)	
Satisfactory (3)	7 (17%)	7 (18%)	
Knowledgeable (4-5)	31 (76%)	28 (74%)	

Under 20 Years Old vs 20 Years Old and above

There was no difference between the groups with respect to self-belief about awareness - 49% of those under 20 years old and 47% of those 20 years old and above believed they were well-aware ($p = 0.9104$). 80% and 79% of those under 20, and 20 and above, respectively, acknowledged that Alzheimer's is a subtype of dementia ($p = 0.9210$). The two age groups similarly believed that Alzheimer's is not part of the normal aging process ($p = 0.9999$), that

there is indeed no cure to Alzheimer's disease ($p = 0.7053$), and that it is a leading form of death ($p = 0.5597$). Those 20 years and above, and under 20 years old, had similar overall scores ($p = 0.9999$); 76% of the younger group and 74% of the older group were well-aware about the disease (see Table 2).

Males vs Females

Males and females had similar self-beliefs about their level of knowledge ($p = 0.9441$), with 48% of males and 49% of females stating that they are well-aware of the disease. 82% of females and 76% of males correctly recognized that Alzheimer's disease is indeed a subtype of dementia ($p = 0.7188$), while 81% of males and 89% of females agreed that Alzheimer's is not part of the normal aging process ($p = 0.3734$). The majority of both men (95%) and women (96%) recognized that Alzheimer's worsens over time ($p = 0.9999$). While only 81% of males recognized that there was no cure for Alzheimer's disease, a much higher proportion of females (96%) similarly recognized that ($p = 0.0419$). 24% and 44% of males and females, respectively, correctly answered that Alzheimer's is a leading cause of death ($p = 0.2500$). Overall, females were more knowledgeable than men ($p = 0.0408$) - 82% of females completed the quiz with a score of 4 or 5 out of 5, while only 57% of males received a similar score (see Table 3).

Table 3. Awareness of young adults by sex

Evaluation Metric	Male (n = 21)	Female (n = 57)	p-value
Self-belief of being knowledgeable			0.9441
Yes	10 (48%)	28 (49%)	
Neutral	7 (33%)	20 (35%)	
No	4 (19%)	9 (16%)	
Alzheimer's is a subtype of dementia			0.7188
True	16 (76%)	47 (82%)	
False	2 (10%)	5 (9%)	
Not Sure	3 (14%)	5 (9%)	
Alzheimer's is normal with respect to aging			0.3734
True			
False	3 (14%)	3 (5%)	
Not Sure	17 (81%)	51 (89%)	
	1 (5%)	3 (5%)	
Alzheimer's worsens over time			0.9999
True	20 (95%)	55 (96%)	
False	0 (0%)	0 (0%)	
Not Sure	1 (5%)	2 (4%)	
No cure to Alzheimer's			0.0419
True	17 (81%)	55 (96%)	
False	0 (0%)	0 (0%)	
Not Sure	4 (19%)	2 (4%)	
Alzheimer's is leading cause of death			0.2500
True	5 (24%)	25 (44%)	
False	9 (43%)	16 (28%)	
Not Sure	7 (33%)	16 (28%)	
Overall Score			0.0408
Poor (1-2)	3 (14%)	2 (4%)	
Satisfactory (3)	6 (29%)	8 (14%)	
Knowledgeable (4-5)	12 (57%)	47 (82%)	

Table 4. Awareness of young adults with family members affected/not affected

Evaluation Metric	Affected (n = 24)	Not Affected (n = 54)	p-value
Self-belief of being knowledgeable Yes Neutral No	16 (67%) 6 (25%) 2 (8%)	22 (41%) 21 (39%) 11 (20%)	0.1105
Alzheimer's is a subtype of dementia True False Not Sure	20 (83%) 2 (8%) 2 (8%)	43 (80%) 5 (9%) 6 (11%)	0.9999
Alzheimer's is normal with respect to aging True False Not Sure	2 (8%) 20 (83%) 2 (8%)	4 (7%) 48 (89%) 2 (4%)	0.7359
Alzheimer's worsens over time True False Not Sure	24 (100%) 0 (0%) 0 (0%)	51 (94%) 0 (0%) 3 (6%)	0.5486
No cure to Alzheimer's True False Not Sure	22 (92%) 0 (0%) 2 (8%)	50 (93%) 0 (0%) 4 (7%)	0.9999
Alzheimer's is leading cause of death True False Not Sure	13 (54%) 4 (17%) 7 (29%)	17 (31%) 21 (39%) 16 (30%)	0.0966
Overall Score Poor (1-2) Satisfactory (3) Knowledgeable (4-5)	2 (8%) 2 (8%) 20 (83%)	3 (6%) 12 (22%) 39 (72%)	0.3484

Affected vs Not Affected

There seems to be a trend that those who have a family member with Alzheimer's disease believe that they are more knowledgeable about the illness ($p = 0.1105$), with 67% compared to 44% claiming that they are more knowledgeable. There was no difference in knowledge about whether Alzheimer's is a subtype of dementia ($p = 0.9999$) - 83% and 80% of those affected and not affected, respectively, recognized Alzheimer's as a subtype. 89% of those without family members affected answered that Alzheimer's is not part of the normal aging process, compared to 83% for those affected by Alzheimer's disease ($p = 0.7359$). All (100%) and 94% of those affected and not affected correctly answered that the illness worsens over time ($p = 0.5486$). About 92-93%, in both groups, responded that there is no cure for Alzheimer's disease ($p = 0.9999$). There was a slight indication that those with family members affected by Alzheimer's more likely recognized it as a leading cause of death ($p = 0.0966$; 54% vs 31%). There was no difference in the overall score between the two groups ($p = 0.3484$), with 83% and 72% of those affected and not affected, respectively, correctly answering 4 or 5 questions (see Table 4).

DISCUSSION

This is the first study to our knowledge that looks to evaluate the awareness and knowledge of the general population with respect to Alzheimer's disease. Despite the fact that only 48% of young adults believe they are knowledgeable, it is reassuring to see that a vast majority, 75%, of young adults in London, Canada, are in fact well aware. Hopefully these high awareness levels will matriculate into better chances to diagnosing early-stage Alzheimer's when this cohort becomes of age, and brings the attention to their healthcare professionals at the first sign of symptoms.

Female young adults were more knowledgeable than male young adults about the disease, however. This may be a result of the culture/sex-role stereotypes developed in Canada, where daughters and granddaughters more frequently visit their relatives with Alzheimer's when compared to sons and grandsons, and hence would be more knowledgeable. However, when comparing the knowledge scores between those with family members affected by Alzheimer's disease and those not affected, it seems this may not be the case. Knowledge about the disease did not seem to be dependent on whether a family member has the disease. The difference in knowledge between the sexes may then simply be accounted for by this cohort of female's greater desire to educate themselves about this unfortunate disease.

The study also revealed the proportion of the general population who has a family member affected by Alzheimer's. According to this study, 31% of young adults know of a relative who is/has been affected by the disease. This proportion is fortunately lower than the awareness level; young adults hence seem to be adequately aware of the disease and some of its implications.

This study was not without limitations. The sample size of the study had good quality and quantity at times, but only lead to detection of trends rather than significant differences at other points - a large sample size would have mitigated this issue. A large sample size could perhaps been accrued should the study have been designed without the need to enter an email address, based on the researchers' personal interactions with the population and based on past experience [7-9]. Additionally, due to the nature of the quiz (online survey), there exists the possibility that participants could have employed reference resources to assist in their answers - this is unfortunately unavoidable due to the medium of the survey, but was hopefully minimized by assuring participants that the quiz is an assessment of knowledge and should be answered honestly without help.

In conclusion, this study revealed that 31% of young adults have a family member affected by Alzheimer's disease. 75% of the young adult population are knowledgeable about the prevalent disease, and only 8% have extremely poor awareness. These findings indicate that young adults seem to be adequately aware of the disease and its implications. Future studies should look into verifying this study in other locations, and also investigate whether young adults know how to care for these Alzheimer's patients.

ACKNOWLEDGMENT

We would like to thank all of those who participated in the questionnaire.

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Chapter 229

AWARENESS OF ALZHEIMER'S DISEASE AMONG YOUNG ADULTS IN KINGSTON, CANADA

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ABSTRACT

A study recently completed among young adults in London, Canada, surveyed 79 young adults about their awareness of Alzheimer's disease. While only 48% of participants believed that they were knowledgeable about the disease, the assessment quiz indicated that 75% turned out to be very knowledgeable. The aim of this survey is to evaluate whether there is a difference in awareness for those young adults in Kingston, Ontario, Canada. A survey was circulated to young adults in Kingston and completed by 45 individuals. 38% of participants had a family member affected by Alzheimer's disease, to their knowledge. While only 58% believed they were knowledgeable about the disease, it turns out that 80% were in fact knowledgeable. Young adults seem to be well-aware with respect to the disease, and this high level of awareness hopefully will matriculate into better caregivers as these young adults mature and play a greater role in caring for family members afflicted by the disease.

INTRODUCTION

Dementia can be debilitating to patients, and could lead to lower quality of life and less-than-ideal patient care [1]. This may be a result of their difficulty to verbalize their struggles

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[2]. One solution to improve patient care would be to increase the awareness and knowledge of caregivers, so that they can hopefully predict struggles and provide the best care possible.

Alzheimer's disease, which is the most common subtype, has been found to have behavioural and psychopathological disturbances [3]. A study recently completed by Chow et al. among young adults in London, Canada, surveyed 79 young adults about their awareness of Alzheimer's disease [4]. While only 48% of participants believed that they were knowledgeable about the disease, the assessment quiz indicated that 75% turned out to be very knowledgeable. The group also investigated into whether there were differences in scores between males and females, those under 20 years old and above 20 years old, and those who have a family member affected by the disease and not affected. There only existed differences in scores between males and females, with females proving to be more knowledgeable [4].

The aforementioned study surveyed a small cohort in a certain geographic area, but yielded very interesting results. The aim of this survey is to evaluate whether there is a difference in awareness for young adults in Kingston, Ontario, Canada.

OUR SURVEY

A survey was circulated to young adults in Kingston, Ontario, Canada, and was designed to evaluate the awareness of Alzheimer's disease, see chapter 2 [5]. A consent form was put on the first page - there was a field to enter an email for participants to receive a copy of the consent form, should they have desired [5]. Participants had to complete three demographic questions on the second page [5]; only those who resided in Hamilton, Canada, was included in this study. The third page had six questions, designed to evaluate the knowledge of participants with respect to Alzheimer's disease [5]. The final page of the survey asked participants whether, to their knowledge, they have/had a family member affected by Alzheimer's; if they have/had, it also asked for how often they visit their relative [5].

Similar to a prior study conducted [4], the primary objective was to determine the awareness of Alzheimer's disease of all young adults. The secondary objectives were to determine whether there existed any difference in knowledge between men and women, between younger and older young adults, and between those with and without family members with Alzheimer's disease.

Statistical Analysis

An overall score out of 5 was generated for each person for the number of questions they correctly answered, with the answer key being: Alzheimer's Disease is a form of dementia - True; Alzheimer's is part of the normal aging process - False; Alzheimer's worsens over time - True; There is no cure for Alzheimer's only treatments for symptoms - True; Alzheimer's is a leading cause of death - True. Those who scored 0, 1 or 2 had poor awareness, those with a score of 3 had satisfactory knowledge, and those with scores of 4 or 5 out of 5 were interpreted to be knowledgeable about Alzheimer's disease.

Descriptive statistics were used to report the six question items on page 3. Subgroup analyses were conducted based ages of participants (under 20 years old, and 20 years old and older), sex (male and female), and their family's history with Alzheimer's disease (affected and not affected). Fisher-exact tests were conducted as part of the subgroup analyses to evaluate whether there was a difference in awareness between these groups. P-values less than 0.05 were deemed to be statistically significant. All analyses were conducted using the Statistical Analysis Software (SAS Version 9.4 for Windows).

OUR FINDINGS

A total of 45 people consented and completed the study. Just over half (58%) believed that they were knowledgeable about Alzheimer's disease; 36% reserved judgement and 7% acknowledged that they were not knowledgeable about Alzheimer's disease. 84% of participants correctly answered that Alzheimer's is a subtype of dementia, with 9% incorrectly responding false and 7% acknowledging they are not sure. Only 3 people (6%) answered incorrectly or admitted a knowledge deficit with respect to Alzheimer's disease and the aging process. All 45 participants correctly answered that Alzheimer's worsens over time, while 96% correctly recognized that there is no cure to Alzheimer's disease. 42% incorrectly believed that Alzheimer's disease is not a leading cause of death, with only 27% of responders correctly answering the question. 80% of young adults scored 4 or 5 out of 5, while 18% scored 3 out of 5 and only 2% received a score between 0 and 2 out of 5 (see Table 1).

Under 20 Years Old vs 20 Years Old and above

Of the 45 participants, 22 were under the age of 20 years old and 23 were 20 years of age and older. 55% of those under 20 years old believed that they were knowledgeable, while 61% of those 20 years and older had a similar belief ($p = 0.9025$). 90% and 83% of the two groups, respectively, correctly believed that Alzheimer's is a subtype of dementia ($p = 0.7991$).

There was no difference between the two groups with respect to the question about Alzheimer's disease and normal aging ($p = 0.7385$); 90% of those under 20 years old and 96% of those 20 years and older correctly responded that Alzheimer's is not part of the normal aging process. All young adults, regardless of age, correctly believe that Alzheimer's worsens over time ($p = 0.9999$). While 90% of those under 20 years old correctly identified that there is no cure to Alzheimer's, all of those 20 years and older similarly responded ($p = 0.2333$). Both groups seemed to be equally-unsure about whether Alzheimer's is a leading cause of death ($p = 0.8666$), with only 45% and 39% of those under 20 and over 20, respectively, correctly answering the question. 14% and 13% of the two groups, respectively, had a satisfactory score, whereas 82% and 87% of the same two groups were knowledgeable according to the five-point score ($p = 0.8283$) (see Table 2).

Males vs Females

1 responder did not identify as male or female; 5 identified as male and 39 identified as female. There was no difference with respect to self-belief between the two genders ($p = 0.9999$), with 60% of males and 59% of females believing that they are knowledgeable. There seems to be a trend that females were more aware that Alzheimer's disease is a subtype of dementia ($p = 0.1300$), with 90% of females correctly answering the question compared to 60% of males. 80% of males correctly answered that Alzheimer's is not normal with respect to aging, while 95% of females similarly answered so ($p = 0.3100$).

Table 1. Awareness of all young adults

Evaluation Metric	All (n = 45)
Self-belief of being knowledgeable	
Yes	26 (58%)
Neutral	16 (36%)
No	3 (7%)
Alzheimer's is a subtype of dementia	
True	38 (84%)
False	4 (9%)
Not Sure	3 (7%)
Alzheimer's is normal with respect to aging	
True	1 (2%)
False	42 (93%)
Not Sure	2 (4%)
Alzheimer's worsens over time	
True	45 (100%)
False	0 (0%)
Not Sure	0 (0%)
No cure to Alzheimer's	
True	43 (96%)
False	0 (0%)
Not Sure	2 (4%)
Alzheimer's is leading cause of death	
True	12 (27%)
False	19 (42%)
Not Sure	14 (31%)
Overall Score	
Poor (0-2)	1 (2%)
Satisfactory (3)	8 (18%)
Knowledgeable (4-5)	36 (80%)

Table 2. Awareness of young adults by age

Evaluation Metric	Under 20 Years Old (n = 22)	20 Years Old and Older (n = 23)	p-value
Self-belief of being knowledgeable			0.9025
Yes			
Neutral	12 (55%)	14 (61%)	
No	8 (36%)	8 (35%)	
	2 (9%)	1 (4%)	
Alzheimer's is a subtype of dementia			0.7991
True	20 (90%)	19 (83%)	
False	1 (5%)	1 (4%)	
Not Sure	1 (5%)	3 (13%)	

Evaluation Metric	Under 20 Years Old (n = 22)	20 Years Old and Older (n = 23)	p-value
Alzheimer's is normal with respect to aging True False Not Sure	1 (5%) 20 (90%) 1 (5%)	0 (0%) 22 (96%) 1 (4%)	0.7385
Alzheimer's worsens over time True False Not Sure	22 (100%) 0 (0%) 0 (0%)	23 (100%) 0 (0%) 0 (0%)	0.9999
No cure to Alzheimer's True False Not Sure	20 (90%) 0 (0%) 2 (10%)	23 (100%) 0 (0%) 0 (0%)	0.2333
Alzheimer's is leading cause of death True False Not Sure	5 (23%) 10 (45%) 7 (32%)	7 (30%) 9 (39%) 7 (30%)	0.8666
Overall Score Poor (0-2) Satisfactory (3) Knowledgeable (4-5)	1 (5%) 3 (14%) 18 (82%)	0 (0%) 3 (13%) 20 (87%)	0.8283

Table 3. Awareness of young adults by sex

Evaluation Metric	Male (n = 5)	Female (n = 39)	p-value
Self-belief of being knowledgeable Yes Neutral No	3 (60%) 2 (40%) 0 (0%)	23 (59%) 13 (33%) 3 (8%)	0.9999
Alzheimer's is a subtype of dementia True False Not Sure	3 (60%) 1 (20%) 1 (20%)	35 (90%) 2 (5%) 2 (5%)	0.1300
Alzheimer's is normal with respect to aging True False Not Sure	0 (0%) 4 (80%) 1 (20%)	1 (3%) 37 (95%) 1 (3%)	0.3100
Alzheimer's worsens over time True False Not Sure	5 (100%) 0 (0%) 0 (0%)	39 (100%) 0 (0%) 0 (0%)	0.9999
No cure to Alzheimer's True False Not Sure	5 (100%) 0 (0%) 0 (0%)	37 (95%) 0 (0%) 2 (5%)	0.9999
Alzheimer's is leading cause of death True False Not Sure	3 (60%) 1 (20%) 1 (20%)	9 (23%) 17 (44%) 13 (33%)	0.2981
Overall Score Poor (0-2) Satisfactory (3) Knowledgeable (4-5)	1 (20%) 0 (0%) 4 (80%)	0 (0%) 7 (18%) 32 (82%)	0.1351

All responders of both groups responded that Alzheimer's does indeed worsen over time ($p = 0.9999$). There was no difference between males and females with respect to the answer about the cure for Alzheimer's ($p = 0.9999$) - 100% and 95%, respectively, answered that there is no cure for Alzheimer's disease. While 33% of females responded that they were unsure about whether Alzheimer's is a leading cause of death, only 20% of males similarly responded so ($p = 0.2981$). 80% of males and 82% of females received a score that led to an inference of them being knowledgeable about the disease ($p = 0.1351$) (see Table 3).

Table 4. Awareness of young adults with family members affected/not affected

Evaluation Metric	Affected (n = 17)	Not Affected (n = 28)	p-value
Self-belief of being knowledgeable			0.0186
Yes	10 (59%)	16 (57%)	
Neutral	2 (12%)	11 (39%)	
No	5 (29%)	1 (4%)	
Alzheimer's is a subtype of dementia			0.8317
True	14 (82%)	24 (86%)	
False	2 (12%)	2 (7%)	
Not Sure	1 (6%)	2 (7%)	
Alzheimer's is normal with respect to aging			0.2883
True			
False	1 (6%)	0 (0%)	
Not Sure	16 (94%)	26 (93%)	
	0 (0%)	2 (7%)	
Alzheimer's worsens over time			0.9999
True	17 (100%)	28 (100%)	
False	0 (0%)	0 (0%)	
Not Sure	0 (0%)	0 (0%)	
No cure to Alzheimer's			0.1373
True	0 (0%)	0 (0%)	
False	15 (88%)	28 (100%)	
Not Sure	2 (12%)	0 (0%)	
Alzheimer's is leading cause of death			0.1675
True	4 (24%)	8 (29%)	
False	10 (59%)	9 (32%)	
Not Sure	3 (18%)	11 (39%)	
Overall Score			0.2262
Poor (0-2)	0 (0%)	1 (4%)	
Satisfactory (3)	5 (29%)	3 (11%)	
Knowledgeable (4-5)	12 (71%)	24 (86%)	

Affected vs Not Affected

Of the 45 participants, 28 do not have a family member affected by Alzheimer's disease, to their knowledge. Those without familial ties to Alzheimer's are more likely to adopt a neutral stance on their belief about their knowledge - 39% compared to 12% reserved judgement ($p = 0.0186$). Of those affected and not affected by Alzheimer's disease, 82% and 86% respectively correctly acknowledged that Alzheimer's is a subtype of dementia ($p = 0.8317$). 94% and 93% respectively correctly responded that Alzheimer's is not normal with respect to aging ($p = 0.2883$). All participants answered that Alzheimer's worsens over time ($p = 0.9999$). Those not affected by Alzheimer's disease seemed to answer the question about cure to Alzheimer's disease better ($p = 0.1373$), with 100% of those not affected correctly

answering. Those affected by Alzheimer's disease more frequently responded that Alzheimer's is not a leading cause of death (59% vs 32%) as opposed to simply admitting they were unsure (18% vs 39%) ($p = 0.1675$). 29% and 11% of those affected and not affected, respectively, had a satisfactory score of 3 out of 5, while 71% and 86% respectively scored 4 or 5 out of 5 ($p = 0.2262$) (see Table 4).

DISCUSSION

This study validates a finding by Chow et al. conducted amongst young adults in London, Ontario, Canada [4]. The study in London showed that while only 48% of young adults believe they are knowledgeable, a surprisingly higher proportion (75%) turned out to be knowledgeable. This study reveals that young adults in London may be slightly more confident in their knowledge (58%), but that seems to be in line with a larger proportion being knowledgeable (80%). The high level of awareness would hopefully allow for better caregivers, as these young adults mature and have more family members afflicted by the disease.

The subgroup analyses of this study verified the original study [4] that there is no difference in knowledge between those under 20 years old and those 20 years old and older, as well as those with and without family ties to Alzheimer's disease. This study, however, did not find any differences in knowledge between the genders. It is important to note however that only 5 males answered the survey, hence making it difficult to find any noticeable difference in knowledge between the two groups.

The results also revealed that 17 of the 45 participants (38%) have a family member affected by Alzheimer's disease, to their knowledge. This has slightly higher than the 31% reported by Chow et al. among young adults in London, Canada [4].

This study was not without limitations. The sample size of the study had good quality and quantity at times, but only lead to detection of trends rather than significant differences at other points - a large sample size would have mitigated this issue. Additionally, a larger sample of males would have allowed for a better subgroup analyses between genders. Additionally,, there exists the chance that participants could have "cheated" and searched up the answers using reference material. This was hopefully minimized by requesting participants to answer the questionnaire honestly without any aid.

In conclusion, 38% of participants had a family member affected by Alzheimer's disease, to their knowledge. While only 58% believed they were knowledgeable about the disease, it turns out that 80% were in fact knowledgeable. Young adults seem to be well-aware with respect to the disease, and this high level of awareness hopefully will matriculate into better caregivers as these young adults mature and play a greater role in caring for family members afflicted by the disease.

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Chapter 230

AWARENESS OF ALZHEIMER'S DISEASE AMONG YOUNG ADULTS IN TORONTO, CANADA

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ABSTRACT

Alzheimer's disease accounts for the majority of dementia subdiagnoses. Increased awareness of the disease and its consequences may lead to early detection of Alzheimer's symptoms, resulting in earlier diagnosis and better patient outcomes. A recent study determined that the majority of young adults in London, Canada were knowledgeable about the disease. The aim of this study was to determine if these findings generalize to young adults in Toronto, Canada. A survey consisting of five quiz questions equivalent to that utilized in the London study was completed by young adults in Toronto to evaluate awareness levels. Subgroup analyses were conducted to compare scores based on participants' ages (under 20 years old, and 20 years old or older), sex, and family history with Alzheimer's (affected and not affected). 156 people completed the survey; 40% of them believed they were knowledgeable about the disease, and 39% of them had an affected family member. 60% of participants were knowledgeable about the disease, and only 10% were poorly informed. Sex differences in awareness levels exist; 65% of females were knowledgeable compared to 46% of males. Future research should aim to investigate the underlying reasons for these differences. Only 22% of all participants correctly identified that Alzheimer's disease is a leading cause of death; therefore future awareness campaigns should emphasize the high mortality rate associated with Alzheimer's. Overall, this study suggests that young adults in Toronto are generally knowledgeable about Alzheimer's disease.

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INTRODUCTION

There are currently over 560,000 Canadians living with dementia, amounting to Canadians spending over \$10.4 billion annually on dementia patient care [1]. Perhaps even more concerning is that there is a steady upward trend in dementia prevalence; studies indicate that prevalence rates could quadruple within the next 50 years [2]. Dementia is often coupled with other comorbidities and results in subpar quality of life and patient care [3]. While many pain assessment tools have been constructed and validated, pain associated with dementia is often under-reported and undertreated [3, 4].

Dementia is an umbrella term that describes a wide range of disease subtypes. The most common form of dementia is Alzheimer's disease. In a study of 474 patients presenting with dementia, an astounding 72% of patients received an Alzheimer's subdiagnosis [5]. Certain pre-clinical symptoms of Alzheimer's, including significant episodic memory impairment, are common in most manifestations of the disease [6]. Increased awareness of the disease and its consequences may lead to early detection of these symptoms, resulting in an earlier diagnosis and better patient outcomes [7]. While Alzheimer's has no cure, increased awareness could be a viable resource for caregivers of individuals with Alzheimer's, as more knowledge of the disease might translate to more conscientious care by caregivers [4].

A recent study by Chow et al. examined awareness of Alzheimer's disease among young adults in London, Canada. Its findings suggested that up to three-quarters of young adults were adequately aware of the disease and its implications, while less than 10% of young adults had extremely poor awareness [8]. The aim of this study was to determine if these findings generalize to young adults in Toronto, Canada.

OUR STUDY

A survey was designed to evaluate the awareness of Alzheimer's disease of young adults in Toronto, Ontario, Canada, see chapter 2 [9]. This survey was identical to the survey utilized by Chow et al. in London, Canada [8]. A consent form was included on the first page of the survey; participants had the option to have a copy of the consent form emailed to them [9]. After consenting to the study, participants completed three questions to collect relevant demographics - primary place of residence, age and sex [9]. Only those who recorded Toronto, Canada, or other locations in the Greater Toronto Area as their place of residence were included in this study. The third page had six questions, with the first being a reflection question regarding the participant's metacognition of Alzheimer's, and the next five comprising a knowledge-based quiz about Alzheimer's disease [9]. The final page of the survey asked participants if they have or had a family member who has been directly affected by Alzheimer's. For participants who have or had a family member affected by the disease, it also asked how often they visit or visited their relative.

The primary objective of the survey was to determine the awareness of Alzheimer's disease, across young adults in Toronto, regardless of other demographics. The secondary objectives were to determine whether there existed any difference in overall disease knowledge between different subgroups, including between males and females, between

younger and older young adults, and between those with and without family members affected by Alzheimer's disease.

Statistical Analysis

Descriptive statistics were used to report the six items (1 reflection question and 5 knowledge questions) on page 3. For each participant, an overall score out of 5 was generated for the number of knowledge-based questions they correctly answered. The answer key is as follows: Alzheimer's Disease is a form of dementia - True; Alzheimer's is part of the normal aging process - False; Alzheimer's worsens over time - True; There is no cure for Alzheimer's, only treatments for symptoms - True; Alzheimer's is a leading cause of death - True. Participants with scores of 4 or 5 out of 5 were interpreted to be generally knowledgeable about Alzheimer's disease; those with 3 were marked as having satisfactory knowledge; those scoring 1 or 2 had poor awareness about the disease.

Subgroup analyses were conducted based on ages of participants (under 20 years old, and 20 years old and older), sex (male and female), and their family's history with Alzheimer's disease (affected and not affected). Fisher-exact tests were conducted to determine whether there was a difference in awareness between these groups. P-values less than 0.05 were deemed to be statistically significant. All analyses were conducted using the Statistical Analysis Software (SAS Version 9.4 for Windows).

THE FINDINGS

A total of 156 individuals completed the survey. 40% of them believed they were knowledgeable about the disease, 46% reserved judgement, and 13% felt that they were ill-informed about Alzheimer's. 79% of individuals correctly identified that Alzheimer's disease is a subtype of dementia, with 8% answering incorrectly, and a further 13% admitting being unaware. Only 10% of participants incorrectly answered that Alzheimer's disease is a normal part of the aging process, while a promising 83% correctly identified that this is not true. A further 8% were not sure if Alzheimer's disease is normal with respect to aging. The vast majority (91%) of participants were aware that Alzheimer's disease worsens over time, with only 2% and 7% of individuals incorrectly identifying this as false or choosing not to select a binary response, respectively. 88% of participants correctly identified that Alzheimer's disease has no cure, while only 1% incorrectly answered this question, and 11% identified that they were unsure. Interestingly, 42% of participants were unsure if Alzheimer's is a leading cause of death; only 22% correctly identified that this statement is true, while 37% of individuals incorrectly answered that this statement is false. Overall, 60% of individuals were relatively knowledgeable about Alzheimer's disease (answered at least 4 of 5 questions correctly), 30% had satisfactory knowledge (answered 3 of 5 questions correctly), and 10% of participants have relatively poor awareness of Alzheimer's and its implications (10%) (see Table 1).

Table 1. Awareness of all young adults

Evaluation Metric	All (n = 156)
Self-belief of being knowledgeable	
Yes	63 (40%)
Neutral	72 (46%)
No	21 (13%)
Alzheimer's is a subtype of dementia	
True	123 (79%)
False	12 (8%)
Not Sure	21 (13%)
Alzheimer's is normal with respect to aging	
True	15 (10%)
False	129 (83%)
Not Sure	12 (8%)
Alzheimer's worsens over time	
True	142 (91%)
False	3 (2%)
Not Sure	11 (7%)
No cure to Alzheimer's	
True	138 (88%)
False	1 (1%)
Not Sure	17 (11%)
Alzheimer's is leading cause of death	
True	34 (22%)
False	57 (37%)
Not Sure	65 (42%)
Overall Score	
Poor (0-2)	16 (10%)
Satisfactory (3)	47 (30%)
Knowledgeable (4-5)	93 (60%)

Under 20 Years Old vs 20 Years Old and above

There was no statistically significant difference between age groups in terms of self-belief of knowledge of Alzheimer's disease; 37% and 48% of participants aged under 20 years old and aged 20 years old or older respectively indicated that they felt knowledgeable about the disease ($p = 0.3588$). Identical proportions (79%) of individuals in both age groups correctly recognized that Alzheimer's disease is a form of dementia ($p = 0.3025$). The two age groups also similarly acknowledged that Alzheimer's disease is not normal with respect to the aging process ($p = 0.5947$), that Alzheimer's worsens over time ($p = 0.6297$), and that there is no cure for Alzheimer's ($p = 0.6167$). Both groups were equally ill-informed that Alzheimer's is a leading cause of death; only slightly more than 20% of individuals in both age groups correctly identified the mortality associated with the disease ($p = 0.9054$). There was no difference between overall knowledge scores of the two groups ($p = 0.4654$) (see Table 2).

Table 2. Awareness of young adults by age

Evaluation Metric	Under '20 Years Old (n = 104)	20 Years Old and Older (n = 52)	p-value
Self-belief of being knowledgeable			0.3588
Yes	38 (37%)	25 (48%)	
Neutral	52 (50%)	20 (38%)	
No	14 (13%)	7 (13%)	

Evaluation Metric	Under '20 Years Old (n = 104)	20 Years Old and Older (n = 52)	p-value
Alzheimer's is a subtype of dementia			0.3025
True	82 (79%)	41 (79%)	
False	6 (6%)	6 (12%)	
Not Sure	16 (15%)	5 (10%)	
Alzheimer's is normal with respect to aging			0.5947
True	12 (12%)	3 (6%)	
False	84 (81%)	45 (87%)	
Not Sure	8 (8%)	4 (8%)	
Alzheimer's worsens over time			0.6297
True	93 (89%)	49 (94%)	
False	3 (3%)	0 (0%)	
Not Sure	8 (8%)	3 (6%)	
No cure to Alzheimer's			0.6167
True	90 (87%)	48 (92%)	
False	1 (1%)	0 (0%)	
Not Sure	13 (13%)	4 (8%)	
Alzheimer's is leading cause of death			0.9054
True	23 (22%)	11 (21%)	
False	39 (38%)	18 (35%)	
Not Sure	42 (40%)	23 (44%)	
Overall Score			0.4654
Poor (0-2)	13 (13%)	3 (6%)	
Satisfactory (3)	31 (30%)	16 (31%)	
Knowledgeable (4-5)	60 (58%)	33 (63%)	

Table 3. Awareness of young adults by sex

Evaluation Metric	Male (n = 41)	Female (n = 113)	p-value
Self-belief of being knowledgeable			0.9343
Yes	17 (41%)	46 (41%)	
Neutral	20 (49%)	51 (45%)	
No	4 (10%)	16 (14%)	
Alzheimer's is a subtype of dementia			0.0556
True	27 (66%)	94 (83%)	
False	6 (15%)	6 (5%)	
Not Sure	8 (20%)	13 (12%)	
Alzheimer's is normal with respect to aging			0.7699
True	4 (10%)	10 (9%)	
False	33 (80%)	95 (84%)	
Not Sure	4 (10%)	8 (7%)	
Alzheimer's worsens over time			0.6186
True	37 (90%)	104 (92%)	
False	1 (2%)	1 (1%)	
Not Sure	3 (7%)	8 (7%)	
No cure to Alzheimer's			0.0065
True	31 (76%)	105 (93%)	
False	1 (2%)	0 (0%)	
Not Sure	9 (22%)	8 (7%)	
Alzheimer's is leading cause of death			0.1058
True	9 (22%)	24 (21%)	
False	20 (49%)	36 (32%)	
Not Sure	12 (29%)	53 (47%)	
Overall Score			0.0308
Poor (0-2)	8 (20%)	7 (6%)	
Satisfactory (3)	14 (34%)	33 (29%)	
Knowledgeable (4-5)	19 (46%)	73 (65%)	

Males vs Females

Males and females reported self-knowledge in equivalent proportions; 41% of males and females alike felt that they were knowledgeable about the disease ($p = 0.9343$). 66% of males and 83% of females correctly identified that Alzheimer's disease is a subtype of dementia. While not statistically significant, there is a strong trend to suggest that females are more knowledgeable than their male counterparts for this evaluation metric ($p = 0.0556$). There does not appear to be any differences between the sexes for identifying if Alzheimer's disease is normal with respect to the aging process, with 80% of males and 84% of females correctly answering false ($p = 0.7699$). The vast majority of males (90%) and females (92%) were aware that Alzheimer's disease worsens over time ($p = 0.6186$). Females are more aware than males that Alzheimer's disease is not curable ($p = 0.0065$).

Table 4. Awareness of young adults with family members affected/not affected

Evaluation Metric	Affected (n = 61)	Not Affected (n = 95)	p-value
Self-belief of being knowledgeable			0.2163
Yes	30 (49%)	33 (35%)	
Neutral	24 (39%)	48 (51%)	
No	7 (11%)	14 (15%)	
Alzheimer's is a subtype of dementia			0.2483
True	48 (79%)	75 (79%)	
False	7 (11%)	5 (5%)	
Not Sure	6 (10%)	15 (16%)	
Alzheimer's is normal with respect to aging			0.7266
True	6 (10%)	9 (9%)	
False	49 (80%)	80 (84%)	
Not Sure	6 (10%)	6 (6%)	
Alzheimer's worsens over time			0.3591
True	58 (95%)	84 (88%)	
False	0 (0%)	3 (3%)	
Not Sure	3 (5%)	8 (8%)	
No cure to Alzheimer's			0.0473
True	57 (93%)	81 (85%)	
False	1 (2%)	0 (0%)	
Not Sure	3 (5%)	14 (16%)	
Alzheimer's is leading cause of death			0.0765
True	17 (28%)	17 (18%)	
False	16 (26%)	41 (43%)	
Not Sure	28 (46%)	37 (39%)	
Overall Score			0.4761
Poor (1-2)	4 (7%)	12 (13%)	
Satisfactory (3)	20 (33%)	27 (28%)	
Knowledgeable (4-5)	37 (61%)	56 (59%)	

While 93% of females correctly identified that there is no cure for Alzheimer's, only 76% of males answered similarly. There is also a trend to suggest differences exist between sexes in terms of identifying Alzheimer's as a leading cause of death ($p = 0.1058$). While males and females both correctly identified the high mortality associated with the disease only around 20% of the time, females (47%) were much more likely than males (29%) to admit that they were not sure about the answer to this evaluation metric. Overall, it appears that statistically significant sex differences in terms of Alzheimer's awareness do exist, with females generally

being more knowledgeable than males ($p = 0.0308$). While 65% of females were well-informed about Alzheimer's disease, only 46% of males were classified as being knowledgeable; 20% of males were fairly unaware of the disease and its implications, while only 7% of females had overall poor awareness.

Affected vs Not Affected

This study indicated that 39% of young adults in Toronto know at least one relative who has been affected directly by Alzheimer's disease (affected subgroup). It does not appear that individuals in this affected group believe that they are more knowledgeable about the disease than individuals who have not had a family member affected by the disease (unaffected/not affected subgroup); 49% of participants in the affected subgroup and 35% of participants in the not affected subgroup believe that they are well-informed about the disease ($p = 0.2163$). 79% of participants in both subgroups correctly identified that Alzheimer's is a subtype of dementia ($p = 0.2483$). Both subgroups are equally educated with respect to their awareness that Alzheimer's is not normal with respect to the aging process ($p = 0.7266$), and that Alzheimer's worsens over time ($p = 0.3591$). A difference was noted between the two groups with respect to their knowledge of whether Alzheimer's disease has a cure. It appears that participants who have an affected family member were more aware that Alzheimer's is incurable (93%) than the subgroup consisting of individuals who have not had an affected family member (85%) ($p = 0.0473$). While statistically insignificant, there is a strong trend to suggest that individuals in the affected subgroup are more aware than their not affected subgroup counterparts with regards to if Alzheimer's is a leading cause of death ($p = 0.0765$). 28% of individuals in the affected cohort correctly identified that Alzheimer's disease is a major cause of death, while only 18% of participants in the not affected subgroup correctly answered this question; however, relative awareness of the mortality of Alzheimer's disease is disturbingly low across both subgroups. There was no difference noted in terms of overall awareness scores ($p = 0.4761$); 61% and 59% of individuals in the affected and not affected cohorts, respectively, were generally well informed about Alzheimer's disease and its implications (see Table 4).

DISCUSSION

It is interesting that while only 40% of individuals believed they were well-informed about Alzheimer's, 60% of participants in this study were actually determined to be knowledgeable about the disease. However, overall awareness scores for individuals in Toronto, Canada appear to be significantly lower than those reported by Chow et al. where 75% to 80% of young adults were knowledgeable about the disease [8, 10]. This may be the result of the larger sample size of this study, but also slight sociocultural differences between the two populations may result in different levels of disease awareness in London, Kingston and Toronto. However, in both studies, overall Alzheimer's awareness is quite high. This high awareness among young adults might translate to earlier detection of the disease, and

ultimately earlier treatment and better prognosis, when this cohort approaches older ages at which Alzheimer's tends to develop.

It is interesting that no significant differences exist in terms of awareness levels between participants with a relative affected by Alzheimer's and those with unaffected relatives. However, it is encouraging that while approximately 39% of the young adult population knows of at least one family member who is or was affected by the disease, overall Alzheimer's awareness levels among young adults remain significantly higher than this proportion. This will hopefully translate to a continued high level of awareness of the disease and its implications in years to come.

This study validates the finding by Chow et al. [8] that young women are more knowledgeable than young men about Alzheimer's disease. This might be as a result of sex-role stereotypes in Canadian culture where young women are more likely to have an invested interest in their own well-being than that of young men. This may give rise to young women becoming more informed about prevalent diseases such as Alzheimer's disease. However, it is also quite possible that many of the young women in this particular cohort were particularly interested in educating themselves about Alzheimer's disease, or that the young men in this sample were generally uninterested in learning about the disease, or both. Further research should investigate if this pattern of better disease understanding by females is generalizable to other pathological conditions, and what the underlying reasons are for these differences.

Perhaps the most concerning finding of this study was the shockingly high proportion of young adults who were unaware of Alzheimer's lethal prognosis. Overall, only 22% of individuals were aware that Alzheimer's disease-related complications are a leading cause of death. This is alarming, especially considering that the Alzheimer's Association reports that Alzheimer's disease is the sixth leading cause of death in the United States, which means that it kills at a rate higher than breast cancer and prostate cancer combined [11]. It is possible that the unfortunate stigmatization of mental illnesses in contemporary society makes it difficult for individuals to draw a connection between a psychological disorder and negative physical outcomes. Programs centred around Alzheimer's disease awareness should consider placing greater emphasis on the high mortality rate associated with this psychopathological condition.

This study was not without limitations. The quiz consisted of an online survey, so there exists the possibility that participants could have employed reference resources to assist their answers. This is unavoidable due to the survey's medium, but was hopefully minimized by assuring participants that the quiz was merely an assessment of awareness and should be answered honestly and individually.

In conclusion, 60% of young adults in Toronto are generally well aware about Alzheimer's disease and its implications, while only 10% were poorly informed. No differences in awareness were noted between individuals aged under 20 years old or aged 20 years old or older. Up to 39% of participants knew at least one family member who has been affected directly by Alzheimer's disease, but no significant differences existed between their levels of awareness and awareness levels of individuals with no familial connections to the disease. It is interesting that females were significantly more aware than males regarding Alzheimer's disease; future research should aim to investigate the underlying reasons for these sex differences. It is concerning that only slightly more than 20% of young adults correctly identified that Alzheimer's is a leading cause of death; it may be worthwhile for future awareness campaigns to emphasize the high mortality rate associated with Alzheimer's

disease. Overall, much like the results reported by Chow et al. [8], this study is promising in that it suggests that young adults are relatively well-aware of Alzheimer's disease.

ACKNOWLEDGMENT

We would like to thank all of those who participated in the questionnaire.

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Chapter 231

AWARENESS OF ALZHEIMER'S DISEASE AMONG YOUNG ADULTS IN OTTAWA, CANADA

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ABSTRACT

Prior studies have been conducted to determine the awareness levels of young adults in London, Kingston and Toronto. While these studies have shown that young adults seem to be well-aware of the illness, there still exists variation between study locations in the proportion of individuals who have a family member affected, as well as the perceived and actual knowledge about the disease. The aim of this study was to investigate into the awareness of Alzheimer's disease among young adults in Ottawa, Canada. A survey, the same as those previously employed by other studies, was designed to evaluate the awareness of young adults in Ottawa, Ontario, Canada. Subgroup analyses were conducted based on ages of participants (under 20 years old, and 20 years old and older), sex (male and female), and their family's history with Alzheimer's disease (affected and not affected). A total of 13 people consented and completed the study. 85% of young adults in Ottawa, Canada are aware of Alzheimer's disease, although only 69% believed that they are knowledgeable. Given that 46% of young adults have a family member affected by the illness it seems that young adults are adequately aware such that they can understand the disease their family members are affected from. Future studies should look into repeating this study with a large sample size to determine if there is any difference in responses between subgroups.

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INTRODUCTION

Dementia is ever-present in our population [1], and coupled with comorbidities can often result in poor quality of life and quality of care [2]. Although tools have been developed for healthcare professionals to help care for these patients [3], there is additional onus on the family members to improve quality of care by educating themselves about the illness.

Prior studies have been conducted to determine the awareness levels of young adults in London [4], Kingston [5] and Toronto [6]. The original study conducted in London, Canada, determined that only 48% of the population believed that they were knowledgeable about the illness, but 75% were well-aware of the disease [4]. The survey determined that only 31% of young adults have a family member affected by Alzheimer's disease - a much larger proportion believed they were knowledgeable, and an even greater percentage were aware of the illness [4].

The studies by Chow et al. in Kingston [5] and Borean et al. in Toronto [6] confirmed these trends. 38% of individuals in Kingston have a family member affected by Alzheimer's disease, while 58% and 80%, respectively, believed they were knowledgeable and actually were knowledgeable [5]. In Toronto, 39% had familial ties to Alzheimer's disease, 40% believed that they were knowledgeable, and 60% completed the assessment such that they determined to be knowledgeable [6].

While these studies have shown that young adults seem to be well-aware of the illness, there still exists variation between study locations in the proportion of individuals who have a family member affected, and also the perceived and actual knowledge about the disease. The aim of this study was to investigate the awareness of Alzheimer's disease among young adults in Ottawa, Canada.

SURVEY METHOD

A survey, the same as that used by Chow et al. in London [4], was designed to evaluate the awareness of young adults in Ottawa, Ontario, Canada, see chapter 2 [7]. The first page had a consent form for the study; participants had the option to enter their email and receive a copy of the consent form [7]. After consenting to the study, participants completed three questions to collect relevant demographics - primary place of residence, age and sex [7]; only those who recorded Ottawa, Canada as their place of residence were included in this study. The third page had six questions, with the first being a reflection question and the next five being knowledge-based questions - a quiz about Alzheimer's disease [7]. The last page of the survey asked participants whether, to their knowledge, they have/had a family member affected by Alzheimer's; if they have/had, it also asked for how often they visit their relative [7].

The main objective of the survey was to determine the awareness of Alzheimer's disease, across all young adults (regardless of age, sex and other background). Other objectives were to determine whether there existed any difference in knowledge across different subgroups - between men and women, between younger and older young adults, and between those with and without family members with Alzheimer's disease.

Statistical Analysis

The six items - 1 reflection and 5 knowledge questions - on page 3 were presented using descriptive statistics. For each participant, an overall score out of 5 was generated for the number of questions they correctly answered, with the answer key being: Alzheimer's Disease is a form of dementia - True; Alzheimer's is part of the normal aging process - False; Alzheimer's worsens over time - True; There is no cure for Alzheimer's, only treatments for symptoms - True; Alzheimer's is a leading cause of death - True. Participants with scores of 4 or 5 out of 5 were interpreted to be knowledgeable about Alzheimer's disease; those with 3 were marked as having satisfactory knowledge; those scoring 1 or 2 had poor awareness about the disease.

Subgroup analyses were conducted based ages of participants (under 20 years old, and 20 years old and older), sex (male and female), and their family's history with Alzheimer's disease (affected and not affected). Fisher-exact tests were conducted to determine whether there was a difference in awareness between these groups. P-values less than 0.05 were deemed to be statistically significant. All analyses were conducted using the Statistical Analysis Software (SAS Version 9.4 for Windows).

WHAT WE FOUND

A total of 13 people consented and completed the study. Over half (69%) believed they were knowledgeable about Alzheimer's disease, 23% reserved judgement, 8% admitted that they were not knowledgeable about Alzheimer's disease. 77% of participants correctly answered that Alzheimer's is a subtype of dementia, with 23% incorrectly responding false. Only 2 people (15%) answered incorrectly or admitted a knowledge deficit with respect to Alzheimer's disease and the aging process. All 13 participants correctly answered that Alzheimer's worsens over time, and correctly recognized that there is no cure to Alzheimer's disease. 39% incorrectly believed that Alzheimer's disease is not a leading cause of death, with only 23% of responders correctly answering the question. 85% of young adults scored 4 or 5 out of 5, while 1% scored 3 out of 5 and 1% received a score between 0 and 2 out of 5 (see Table 1).

Under 20 Years Old vs 20 Years Old and above

Of the 13 participants, 7 were under the age of 20 years old and 6 were 20 years of age and older. 71% of those under 20 years old believed that they were knowledgeable, while 67% of those 20 years and older had a similar belief ($p = 0.9999$). 57% and 100% of the two groups, respectively, correctly believed that Alzheimer's is a subtype of dementia ($p = 0.3147$). There was no difference between the two groups with respect to the question about Alzheimer's disease and normal aging ($p = 0.9999$); 14% of those under 20 years old and 17% of those 20 years and older correctly responded that Alzheimer's is not part of the normal aging process. All young adults, regardless of age, correctly believe that Alzheimer's worsens over time as well as correctly identified that there is no cure for Alzheimer's ($p =$

0.9999). Both groups seemed to be equally-unsure about whether Alzheimer's is a leading cause of death ($p = 0.2424$), with only 57% and 17% of those under 20 and over 20, respectively, correctly answering the question. 14% of the individuals under 20, respectively, had a satisfactory score, whereas 71% and 100% of the same two groups were knowledgeable according to the five-point score ($p = 0.8283$) (see Table 2).

Table 1. Awareness of all young adults

Evaluation Metric	All (n = 13)
Self-belief of being knowledgeable	
Yes	9 (69%)
Neutral	3 (23%)
No	1 (8%)
Alzheimer's is a subtype of dementia	
True	10 (77%)
False	1 (23%)
Not Sure	2 (15%)
Alzheimer's is normal with respect to aging	
True	2 (15%)
False	11 (85%)
Not Sure	0 (0%)
Alzheimer's worsens over time	
True	13 (100%)
False	0 (0%)
Not Sure	0 (0%)
No cure to Alzheimer's	
True	13 (100%)
False	0 (0%)
Not Sure	0 (0%)
Alzheimer's is leading cause of death	
True	5 (39%)
False	5 (39%)
Not Sure	3 (23%)
Overall Score	
Poor (1-2)	1 (8%)
Satisfactory (3)	1 (8%)
Knowledgeable (4-5)	11 (85%)

Table 2. Awareness of young adults by age

Evaluation Metric	Under 20 Years Old (n = 7)	20 Years Old and Older (n = 6)	p-value
Self-belief of being knowledgeable			0.9999
Yes	5 (71%)	4 (67%)	
Neutral	1 (14%)	2 (33%)	
No	1 (14%)	0 (0%)	
Alzheimer's is a subtype of dementia			0.3147
True	4 (57%)	6 (100%)	
False	1 (14%)	0 (0%)	
Not Sure	2 (29%)	0 (0%)	
Alzheimer's is normal with respect to aging			0.9999
True	1 (14%)	1 (17%)	
False	6 (86%)	5 (83%)	
Not Sure	0 (0%)	0 (0%)	

Evaluation Metric	Under 20 Years Old (n = 7)	20 Years Old and Older (n = 6)	p-value
Alzheimer's worsens over time			0.9999
True			
False	7 (100%)	6 (100%)	
Not Sure	0 (0%)	0 (0%)	
	0 (0%)	0 (0%)	
No cure to Alzheimer's			0.9999
True	7 (100%)	6 (100%)	
False	0 (0%)	0 (0%)	
Not Sure	0 (0%)	0 (0%)	
Alzheimer's is leading cause of death			0.2424
True	4 (57%)	1 (17%)	
False	1 (14%)	4 (67%)	
Not Sure	2 (29%)	1 (17%)	
Overall Score			0.9999
Poor (1-2)	1 (14%)	0 (0%)	
Satisfactory (3)	1 (14%)	0 (0%)	
Knowledgeable (4-5)	5 (71%)	6 (100%)	

Males vs Females

1 responder did not identify as male or female; 4 identified as male and 8 identified as female. There was no difference with respect to self-belief between the two genders ($p = 0.4909$), with 50% of males and 75% of females believing that they are knowledgeable. Females and males were equally knowledgeable that Alzheimer's disease is a subtype of dementia, with 75% of each sex answering correctly ($p = 0.9999$). 50% of males and 100% of females correctly answered that Alzheimer's is not normal with respect to aging ($p = 0.0909$). All participants of both groups responded that Alzheimer's does indeed worsen over time and that there is indeed no cure to Alzheimer's ($p = 0.9999$). While 50% of females responded that they were unsure about whether Alzheimer's is a leading cause of death, only 25% of males similarly responded so ($p = 0.7576$). 75% of males and 88% of females received a score that led to an inference of them being knowledgeable about the disease ($p = 0.5758$) (see Table 3).

Affected vs Not Affected

Of the 13 participants, 7 do not have a family member affected by Alzheimer's disease, to their knowledge. Of those affected and not affected by Alzheimer's disease, 83% and 71% respectively correctly acknowledged that Alzheimer's is a subtype of dementia ($p = 0.9999$). 17% and 14% respectively correctly responded that Alzheimer's is not normal with respect to aging ($p = 0.9999$). All participants answered that Alzheimer's worsens over time and correctly identified that there is no cure to Alzheimer's disease ($p = 0.9999$). Those affected by Alzheimer's disease more frequently responded that Alzheimer's is not a leading cause of death (33% vs 43%) as opposed to simply admitting they were unsure (17% vs 29%) ($p = 0.9999$). 14% of those not affected had a satisfactory score of 3 out of 5, while 83% and 86% respectively scored 4 or 5 out of 5 ($p = 0.9999$) (see Table 4).

Table 3. Awareness of young adults by sex

Evaluation Metric	Male (n = 4)	Female (n = 8)	p-value
Self-belief of being knowledgeable			0.4909
Yes	2 (50%)	6 (75%)	
Neutral	1 (25%)	2 (25%)	
No	1 (25%)	0 (0%)	
Alzheimer's is a subtype of dementia			0.9999
True	3 (75%)	6 (75%)	
False	0 (0%)	1 (12%)	
Not Sure	1 (25%)	1 (12%)	
Alzheimer's is normal with respect to aging			0.0909
True	2 (50%)	8 (100%)	
False	2 (50%)	0 (0%)	
Not Sure	0 (0%)	0 (0%)	
Alzheimer's worsens over time			0.9999
True			
False	4 (100%)	8 (100%)	
Not Sure	0 (0%)	0 (0%)	
No cure to Alzheimer's			0.9999
True	4 (100%)	8 (100%)	
False	0 (0%)	0 (0%)	
Not Sure	0 (0%)	0 (0%)	
Alzheimer's is leading cause of death			0.7576
True	1 (25%)	4 (50%)	
False	2 (50%)	2 (25%)	
Not Sure	1 (25%)	2 (25%)	
Overall Score			0.5758
Poor (1-2)	1 (25%)	0 (0%)	
Satisfactory (3)	0 (0%)	1 (12%)	
Knowledgeable (4-5)	3 (75%)	7 (88%)	

Table 4. Awareness of young adults with family members affected/not affected

Evaluation Metric	Affected (n = 6)	Not Affected (n = 7)	p-value
Self-belief of being knowledgeable			0.3392
Yes	3 (50%)	6 (86%)	
Neutral	2 (33%)	1 (14%)	
No	1 (17%)	0 (0%)	
Alzheimer's is a subtype of dementia			0.9999
True	5 (83%)	5 (71%)	
False	0 (0%)	1 (14%)	
Not Sure	1 (17%)	1 (14%)	
Alzheimer's is normal with respect to aging			0.9999
True	1 (17%)	1 (14%)	
False	5 (83%)	6 (86%)	
Not Sure	0 (0%)	0 (0%)	
Alzheimer's worsens over time			0.9999
True			
False	6 (100%)	7 (100%)	
Not Sure	0 (0%)	0 (0%)	

Evaluation Metric	Affected (n = 6)	Not Affected (n = 7)	p-value
No cure to Alzheimer's			0.9999
True	6 (100%)	7 (100%)	
False	0 (0%)	0 (0%)	
Not Sure	0 (0%)	0 (0%)	
Alzheimer's is leading cause of death			0.9999
True	2 (33%)	3 (43%)	
False	3 (50%)	2 (29%)	
Not Sure	1 (17%)	2 (29%)	
Overall Score			0.9999
Poor (1-2)	1 (17%)	0 (0%)	
Satisfactory (3)	0 (0%)	1 (14%)	
Knowledgeable (4-5)	5 (83%)	6 (86%)	

DISCUSSION

This study validated those results revealed in prior studies [4-6]. In this population, 69% of respondents believed that they are well-aware of the illness, when it turned out that 85% were adequately aware. Both of these ratios are noticeably higher than the percentage of young adults who have a family member affected by Alzheimer's (46%). In line with other studies, the results suggest that young adults are more aware of the illness than they perceive themselves to be.

Between the three studies that previously looked into Alzheimer's awareness, two studies reported a statistically significant difference in awareness between sexes [4, 6], while one study found no difference [5]. The results of this study support the study by Chow et al. [5] conducted in Kingston, Canada, that there is no difference between males and females in terms of disease awareness. However, it is important to note that the sample size of this study and that by Chow et al. in Kingston [5] are substantially smaller than the other two studies [4, 6]; there is hence lower statistical power and it would be more difficult to detect a significant difference.

This study has its limitations. The sample size of this study was substantially smaller than prior studies and hence could have decreased statistical power when detecting for differences. A large sample size could have been accrued should the study have been designed without the need to enter an email address, based on the researchers' personal interactions with the population and based on past experience. Also, there exists the possibility of cheating when completing the quiz portion of the survey, which would lead to an artificially higher proportion of individuals who would be knowledgeable.

In conclusion, 85% of young adults in Ottawa, Canada, are aware of Alzheimer's disease, although only 69% believed that they are knowledgeable. Given that 46% of young adults have a family member affected by the illness, it seems that young adults are adequately aware of the disease that their family members are affected by. Future studies should look into repeating this study with a large sample size to determine if there is any difference in responses between subgroups.

ACKNOWLEDGMENT

We would like to thank all of those who participated in the questionnaire.

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Chapter 232

AWARENESS OF ALZHEIMER'S DISEASE AMONG YOUNG ADULTS IN HAMILTON, CANADA

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ABSTRACT

Alzheimer's disease is a subtype of dementia, which substantially impairs quality of life. A study conducted in the United States of America reports that 10.3% of those aged 65 and older were diagnosed with Alzheimer's disease. Many cases of Alzheimer's are not detected until the later stages, however this could be prevented by increasing the awareness of disease. The aim of this study was to investigate the awareness level of young adults in Hamilton, Canada. A survey was designed and circulated with the primary objective to identify how aware young adults were regarding Alzheimer's disease, regardless of age, sex and family history of the disease. The secondary objectives were to determine whether there existed any difference in knowledge across different subgroups - between men and women, between younger and older young adults, and between those with and without family members with Alzheimer's disease. This survey was completed by 67 participants, of which 34% believed they were knowledgeable about the disease while only 19% actually were; this study yielded the opposite trend from the previously conducted studies, which all supported a trend that more adolescents were knowledgeable about the disease than they believed. Steps should be taken to increase the awareness among young adults in this city.

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INTRODUCTION

Alzheimer's Disease is a very prevalent condition and a subtype of dementia that reduces the quality of life of many seniors [1]. According to a study conducted in the United States of America, an alarming 10.3% of those aged 65 and older were diagnosed with Alzheimer's disease [2]. This rate is especially concerning due to the multiple health conditions that have been proven follow the disease, including depression [3].

Many cases of Alzheimer's are not detected until the later stages of the condition. This could be prevented by increasing the awareness of the conditions in the general public. In order to assess the current knowledge level about Alzheimer's Disease, a study was conducted in several cities in Ontario, including London, Toronto, Kingston and Ottawa [4-7]. The original study conducted in London stated that 31% of respondents had a family member who was affected by Alzheimer's, yet 48% of those who answered believed they were knowledgeable about the disease [3]. Astonishingly, the results yielded 75% were actually quite knowledgeable about the condition, which suggests that having a family member affected by the condition does not correlated with the general knowledge in the population [3]. The subsequent studies conducted in Kingston, Toronto and Ottawa also support the trends that were unearthed in the London study [3-7]. In order to verify this trend and further assess the general knowledge regarding Alzheimer's disease, this study was conducted in Hamilton, Ontario, Canada.

OUR STUDY

A survey was created to evaluate how knowledgeable young adults in Hamilton, Ontario, Canada were about Alzheimer's disease, see chapter 2 [8]. On the first page, there was a consent form where participants could fill in their email and have a copy of the form sent to them [8]. Those who consented to the survey were redirectly to complete three demographics-related questions which inquired about the respondent's primary place of residence, age and sex [8]; only those who recorded Hamilton, Canada, as their place of residence were included in this study. The next page included a reflection question, followed by 5 knowledge-based questions regarding Alzheimer's disease [8]. Finally, the last page of the survey inquired about the participant's familial incidences of Alzheimer's disease and, if applicable, how often they visited an affected member [8].

This survey was designed to identify how aware young adults were regarding Alzheimer's disease, regardless of age, sex and family history of the disease. The secondary objectives were to determine whether there existed any difference in knowledge across different subgroups - between men and women, between younger and older young adults, and between those with and without family members with Alzheimer's disease.

Statistical Analysis

Descriptive statistics were used to report the six items - 1 reflection and 5 knowledge questions - on page 3. The correct answers for the knowledge based questions are as follows:

Alzheimer's Disease is a form of dementia - True; Alzheimer's is part of the normal aging process - False; Alzheimer's worsens over time - True; There is no cure for Alzheimer's only treatments for symptoms - True; Alzheimer's is a leading cause of death - True. Those with scores of 4 or 5 out of 5 were interpreted to be knowledgeable about Alzheimer's disease; participants with 3 were marked as having satisfactory knowledge; respondents scoring 1 or 2 had poor awareness about the disease.

Subgroup analyses were conducted based on the ages of participants (under 20 years old, and 20 years old and older), sex (male and female), and their family's history with Alzheimer's disease (affected and not affected). In order to determine whether there was a significant difference in the awareness among these groups, Fisher-exact tests were conducted. P-values less than 0.05 were deemed to be statistically significant. All analyses were conducted using the Statistical Analysis Software (SAS Version 9.4 for Windows).

FINDINGS

This survey was completed by 67 consenting participants. Of this population, 34% believed that they were knowledgeable about the condition, 13% said they had low knowledge of the subject and 52% were undecided. 73% of respondents correctly stated that Alzheimer's is a subtype of dementia, 12% reported it as false and 15% were unsure. The majority of respondents, 88%, correctly commented that Alzheimer's Disease is not normal with respect to aging, 4% said it was and 9% were unsure. 93% of the participants agreed that Alzheimer's worsens over time while 2% denied this and 6% were unsure. In terms of treating the disease, 96% correctly identified that there was no cure while 4% were unsure. 25% of respondents stated that Alzheimer's is a leading cause of death, 33% said it wasn't while 42% were unsure. Overall, 25% of participants lacked knowledge about the disease, 55% had a satisfactory level and 19% were very knowledgeable about the condition (see Table 1).

Under 20 Years Old vs 20 Years Old and above

There was statistically no difference between the two groups in terms of their self belief of the knowledge regarding the disease. 37% of those under 20 years old and 29% of those older than 20 years old ($p = 0.7765$) thought they were knowledgeable. Among those under age 20, 67% and 83% of those older than 20 believed that Alzheimer's is a subtype of dementia ($p = 0.3204$). 88% of both groups identified that Alzheimer's is normal with respect to aging ($p = 0.9999$). 93% of those under 20 years old and 92% of those older than 20 agreed that Alzheimer's worsens over time ($p = 0.7547$). Of those under 20, 98% and 92% of over 20 stated that there was no cure to cancer ($p = 0.2900$). 40% of those under age 20 and 21% of those older than 20 years old commented that Alzheimer's is not a leading cause of death ($p = 0.3363$). To sum, 58% and 50% of those 20 years old and younger and those older than 20 respectively had satisfactory knowledge about the disease ($p = 0.3303$) (see Table 2).

Table 1. Awareness of all young adults

Evaluation Metric	All (n = 67)
Self-belief of being knowledgeable	
Yes	23 (34%)
Neutral	35 (52%)
No	9 (13%)
Alzheimer's is a subtype of dementia	
True	49 (73%)
False	8 (12%)
Not Sure	10 (15%)
Alzheimer's is normal with respect to aging	
True	2 (4%)
False	59 (88%)
Not Sure	6 (9%)
Alzheimer's worsens over time	
True	62 (93%)
False	1 (2%)
Not Sure	4 (6%)
No cure to Alzheimer's	
True	64 (96%)
False	0 (0%)
Not Sure	3 (4%)
Alzheimer's is leading cause of death	
True	17 (25%)
False	22 (33%)
Not Sure	28 (42%)
Overall Score	
Poor (0-2)	17 (25%)
Satisfactory (3)	37 (55%)
Knowledgeable (4-5)	13 (19%)

Table 2. Awareness of young adults by age

Evaluation Metric	Under 20 Years Old (n = 43)	20 Years Old and Older (n = 24)	p-value
Self-belief of being knowledgeable			0.7765
Yes	16 (37%)	7 (29%)	
Neutral	22 (51%)	13 (54%)	
No	5 (12%)	4 (17%)	
Alzheimer's is a subtype of dementia			0.3204
True	29 (67%)	20 (83%)	
False	7 (16%)	1 (4%)	
Not Sure	7 (16%)	3 (13%)	
Alzheimer's is normal with respect to aging			0.9999
True	1 (2%)	1 (4%)	
False	38 (88%)	21 (88%)	
Not Sure	4 (9%)	2 (8%)	
Alzheimer's worsens over time			0.7547
True	40 (93%)	22 (92%)	
False	1 (2%)	0 (0%)	
Not Sure	2 (5%)	2 (8%)	
No cure to Alzheimer's			0.2900
True	42 (98%)	22 (92%)	
False	0 (0%)	0 (0%)	
Not Sure	1 (2%)	2 (8%)	

Evaluation Metric	Under 20 Years Old (n = 43)	20 Years Old and Older (n = 24)	p-value
Alzheimer's is leading cause of death			0.3363
True	10 (23%)	7 (29%)	
False	17 (40%)	5 (21%)	
Not Sure	16 (37%)	12 (50%)	
Overall Score			0.3303
Poor (0-2)	12 (28%)	5 (21%)	
Satisfactory (3)	25 (58%)	12 (50%)	
Knowledgeable (4-5)	6 (14%)	7 (29%)	

Males vs Females

36% and 34% of males and females respectively believed they were knowledgeable about Alzheimer's disease ($p = 0.9999$). 64% and 75% of males and females respectively stated that Alzheimer's is a subtype of dementia ($p = 0.6475$). 82% of males and 89% of females said that Alzheimer's was not a normal aging process ($p = 0.4889$). 91% of males and 93% of females identified that Alzheimer's worsens over time ($p = 0.6045$). All of the male respondents and 95% of the females correctly identified that there is no cure to the disease ($p = 0.9999$). 18% and 27% of males and females respectively said that Alzheimer's is the leading cause of disease ($p = 0.6448$). Overall, 55% of both cohorts had a satisfactory level of knowledge regarding the disease ($p = 0.5489$) (see Table 3).

Table 3. Awareness of young adults by sex

Evaluation Metric	Male (n = 11)	Female (n = 56)	p-value
Self-belief of being knowledgeable			0.9999
Yes	4 (36%)	19 (34%)	
Neutral	6 (55%)	29 (52%)	
No	1 (9%)	8 (14%)	
Alzheimer's is a subtype of dementia			0.6475
True	7 (64%)	42 (75%)	
False	2 (18%)	6 (11%)	
Not Sure	2 (18%)	8 (14%)	
Alzheimer's is normal with respect to aging			0.4889
True			
False	0 (0%)	2 (4%)	
Not Sure	9 (82%)	50 (89%)	
	2 (18%)	4 (7%)	
Alzheimer's worsens over time			0.6045
True			
False	10 (91%)	52 (93%)	
Not Sure	0 (0%)	1 (2%)	
	1 (9%)	3 (5%)	
No cure to Alzheimer's			0.9999
True	11 (100%)	53 (95%)	
False	0 (0%)	0 (0%)	
Not Sure	0 (0%)	3 (5%)	
Alzheimer's is leading cause of death			0.6448
True	2 (18%)	15 (27%)	
False	5 (45%)	17 (30%)	
Not Sure	4 (36%)	24 (43%)	
Overall Score			0.5489
Poor (0-2)	4 (36%)	13 (23%)	
Satisfactory (3)	6 (55%)	31 (55%)	
Knowledgeable (4-5)	1 (9%)	12 (21%)	

Affected vs Not Affected

50% of those with an affected family member and 29% of those who have never had an affected family member believed that they were knowledgeable about Alzheimer's ($p = 0.0694$). 72% of those affected and 73% of those who were not affected knew that Alzheimer's is a subtype of dementia ($p = 0.9999$). All of the participants who had a family member who was diagnosed with Alzheimer's identified that the disease was not normal with respect to aging, along with 84% of the other cohort ($p = 0.2929$). 100% of those affected and 90% of those who weren't were able to identify that Alzheimer's worsens over time ($p = 0.6841$). Of those affected and 94% of those who were not reported that there was no cure to Alzheimer's ($p = 0.5581$). 22% of those affected and 27% of those who weren't said that Alzheimer's was the leading cause of death ($p = 0.5010$). Overall, 61% of those affected and 53% of those who weren't answered 3 of the 5 questions correctly ($p = 0.8709$) (see table 4).

Table 4. Awareness of young adults with family members affected/not affected

Evaluation Metric	Affected (n = 18)	Not Affected (n = 49)	p-value
Self-belief of being knowledgeable			0.0694
Yes	9 (50%)	14(29%)	
Neutral	9 (50%)	26 (53%)	
No	0 (0%)	9 (18%)	
Alzheimer's is a subtype of dementia			0.9999
True	13 (72%)	36 (73%)	
False	2 (11%)	6 (12%)	
Not Sure	3 (17%)	7 (14%)	
Alzheimer's is normal with respect to aging			0.2929
True			
False	0 (0%)	2 (4%)	
Not Sure	18 (100%)	41 (84%)	
	0 (0%)	6 (12%)	
Alzheimer's worsens over time			0.6841
True	18 (100%)	44 (90%)	
False	0 (0%)	1 (2%)	
Not Sure	0 (0%)	4 (8%)	
No cure to Alzheimer's			0.5581
True	18 (100%)	46 (94%)	
False	0 (0%)	0 (0%)	
Not Sure	0 (0%)	3 (6%)	
Alzheimer's is leading cause of death			0.5010
True	4 (22%)	13 (27%)	
False	8 (44%)	14 (29%)	
Not Sure	6 (33%)	22 (45%)	
Overall Score			0.8709
Poor (0-2)	4 (22%)	13 (27%)	
Satisfactory (3)	11 (61%)	26 (53%)	
Knowledgeable (4-5)	3 (17%)	10 (20%)	

DISCUSSION

The results of this survey are different than the trend reported by the studies conducted in London, Toronto, Kingston and Ottawa [4-7]. 34% of respondents believed they were knowledgeable about Alzheimer's disease, however only 19% scored above a 4 on the

questionnaire. This result is disappointing, as participants are confident about their knowledge, however they are not very aware of the disease. A higher awareness would result in better future caregivers as these adolescents mature into adults, thus it is necessary to increase the awareness in this population.

The subgroup analyses further emphasizes this unique trend found in Hamilton, Canada. For those aged 20 and older, there were an equal number of participants who achieved a score of 4 or higher on the questionnaire as the number of individuals who believed they were knowledgeable. However, for the younger age cohort, there were less participants who were actually knowledgeable than those who believed they were. This trend continues when looking at the different sexes; both males and females thought they were more knowledgeable about the disease than they actually were. Those who had a family member affected by the disease were just as unaware about their metacomprehension as those who weren't as this categorization fell inline with the trend found in other subgroup analyses as well.

This survey also reports that 27% of participants had a family member who was affected by Alzheimer's disease, which is a lower rate stated by the studies conducted done in London (31%), Kingston (38%), Ottawa (46%) and Toronto (39%) [4-7].

There were a few limitations for this study. There was a small sample size, which led to a the detection of trends rather than significant differences, this issue could have been overcome with a larger sample size. A large sample size could perhaps been accrued should the study have been designed without the need to enter an email address, based on the researcher's personal interactions with the population and based on past experience [9-11]. Participants could have used external sources to help them with the answers; this limitation is hard to overcome as the survey was completed online. The respondents were informed that the survey was being done to assess their knowledge and thus should be answered honestly.

To conclude, 27% of respondents had a family member who was affected by Alzheimer's disease. While 34% of participants believed they were knowledgeable about the disease, this study shows that in reality only 19% were truly aware. This study yielded the opposite trend from the previously conducted studies, which all supported a trend that more adolescents were knowledgeable about the disease than they believed [4-7]. There should be some action taken to increase the awareness of this disease among the young adults in Hamilton, Canada. Increasing the knowledge of this population will have a plethora of benefits, as they will soon be the caregivers and health providers. In order to investigate whether the general awareness has gone up in the population, further studies should be conducted in Hamilton in the future.

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Chapter 233

AWARENESS OF ALZHEIMER'S DISEASE AMONG YOUNG ADULTS IN WATERLOO, CANADA

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ABSTRACT

Family members of patients suffering from Alzheimer's disease may help healthcare professionals improve standard of care and hence quality of life by being knowledgeable about the disease. The purpose of this investigation was to study the awareness level of young adults in Waterloo with respect to Alzheimer's disease. 100 young adults in Waterloo consented and completed a survey, and 41 of the 100 had a family member affected by Alzheimer's disease. Of the 100, 65% of the population were knowledgeable about the disease, although only 41% believed they were well-aware. This trend is very similar to those previously reported in Ontario.

INTRODUCTION

Family members of patients suffering from Alzheimer's disease may help healthcare professionals improve standard of care and hence quality of life by being knowledgeable about the disease [1].

A prior study [2] conducted in London, Canada examined the awareness of the young adults in that area. It discovered that 75% of the young adults were knowledgeable about the disease, but a much smaller number thought they were well informed (48%). 31% of the same

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group had a family member affected by Alzheimer's disease, and overall it appeared that young adults are generally quite knowledgeable in this area.

Several similar studies were conducted in order to confirm these conclusions in various areas [3-9]. In Ontario (the same province as Waterloo) three studies were conducted [3-5]. In Kingston, 60% of the population was knowledgeable, compared to the 58% that believed they were and the 38% who had a family member affected by the disease [3]. In Toronto, Borean et al. [4] also confirmed the trend, as 39% of the cohort had a family member with the disease, 40% believed they were knowledgeable and 60% actually were well-aware of the disease. In Ottawa, the same trend was found in young adult populations as 46% of the group had family members affected, 69% believed they were knowledgeable, and 85% were knowledgeable according to the assessment tool [5]. Finally, in Hamilton, the trend was contradicted as 34% of the cohort believed they were well-aware, yet only 19% were in reality. There was also a lower amount of people affected, as only 27% of participants were indirectly affected by the disease through family.

The aim of this study was to further pursue whether this trend holds true in another location in Ontario, Canada (Waterloo) using a more substantial sample size ($n = 100$).

OUR SURVEY

A questionnaire was made to evaluate the awareness of young adults in Waterloo, Canada, see chapter 2 [10]. The first page had a consent form for the study; participants had the option to enter their email and receive a copy of the consent form [10]. After consenting to the study, participants completed three questions to collect relevant demographics - primary place of residence, age and sex [10]; only those who recorded Waterloo as their place of residence were included in this study. The third page had six questions, with the first being a reflection question and the next five being knowledge-based questions - a quiz about Alzheimer's disease [10]. The last page of the survey asked participants whether, to their knowledge, they have/had a family member affected by Alzheimer's; if they have/had, it also asked for how often they visit their affected relative [10].

The main objective of the survey was to determine the awareness of Alzheimer's disease, across all young adults (regardless of age, sex and other background). Other objectives were to determine whether there existed any difference in knowledge across different subgroups - between men and women, between younger and older young adults, and between those with and without family members with Alzheimer's disease.

Statistical Analysis

The same statistical analysis was conducted by Chow et al. in the initial survey in London, Canada. Descriptive statistics were used to report the six items - 1 reflection and 5 knowledge questions - on page 3. For each participant, an overall score out of 5 was generated for the number of questions they correctly answered, with the answer key being: Alzheimer's disease is a form of dementia - True; Alzheimer's is part of the normal aging process - False; Alzheimer's worsens over time - True; There is no cure for Alzheimer's only

treatments for symptoms - True; Alzheimer's is a leading cause of death - True. Participants with scores of 4 or 5 out of 5 were interpreted to be knowledgeable about Alzheimer's disease; those with 3 were marked as having satisfactory knowledge; those scoring 1 or 2 had poor awareness about the disease.

Table 1. Awareness of all young adults

Evaluation Metric	All (n = 100)
Self-belief of being knowledgeable	
Yes	41 (41%)
Neutral	50 (50%)
No	9 (9%)
Alzheimer's is a subtype of dementia	
True	73 (73%)
False	8 (8%)
Not Sure	19 (19%)
Alzheimer's is normal with respect to aging	
True	11 (11%)
False	84 (84%)
Not Sure	5 (5%)
Alzheimer's worsens over time	
True	90 (90%)
False	5 (5%)
Not Sure	5 (5%)
No cure to Alzheimer's	
True	90 (90%)
False	3 (3%)
Not Sure	7 (7%)
Alzheimer's is leading cause of death	
True	16 (16%)
False	48 (48%)
Not Sure	36 (36%)
Overall Score	
Poor (0-2)	14 (14%)
Satisfactory (3)	21 (21%)
Knowledgeable (4-5)	65 (65%)

Subgroup analyses were conducted based on ages of participants (under 20 years old, and 20 years old and older), sex (male and female), and their family's history with Alzheimer's disease (affected and not affected). Fisher-exact tests were conducted to determine whether there was a difference in awareness between these groups. P-values less than 0.05 were deemed to be statistically significant. All analyses were conducted using the Statistical Analysis Software (SAS Version 9.4 for Windows).

OUR FINDINGS

In total, 100 young adults consented and completed the provided survey within the region of Waterloo. 50% of the group gave a neutral response pertaining to their believed awareness level of the disease. 41% of the cohort believed they had a high level while only 9% thought they had a low level of knowledge. Most of the participants (73%) correctly answered that

Alzheimer's is a subtype of dementia, 84% correctly responded that Alzheimer's is not normal with respect to the aging process, 90% said correctly that Alzheimer's worsens over time, and 90% detailed that there is no cure to Alzheimer's. On the contrary, only 16% of respondents correctly noted that Alzheimer's is a leading cause of death. Altogether 65% of participants were very knowledgeable, while 21% had satisfactory knowledge and 14% had little knowledge about the disease (see Table 1).

Under 20 Years Old vs 20 Years Old and above

39 of the 100 participants were under 20 years old, while 61 were 20 years old and older. There were no differences between the two age groups in any of the responses. 48% of those 20 years old and older refused to comment about their level of awareness, and similarly 54% of those under 20 years of age answered neutrally ($p = 0.5955$). Also, 77% and 70% of the younger and older group, respectively, recognized that Alzheimer's is a subtype of dementia ($p = 0.4465$). Thirdly, 85% and 84% of the two populations, respectively, chose that Alzheimer's is not part of the normal aging process ($p = 0.1064$). 95% of the younger group and 87% of the over 20 group correctly verified that Alzheimer's worsens over time ($p = 0.5254$). 95% of the younger cohort and 87% of the older cohort recognized that there is no cure for Alzheimer's ($p = 0.4359$). Unlike many of the other studies, most of the respondents recognized that Alzheimer's is a leading cause of death, with only 49% and 48% believing it is not ($p = 0.8553$). Altogether, 64% and 66% of the younger and older cohort, respectively, were deemed knowledgeable ($p = 0.1942$) (see Table 2).

Males vs Females

Of the 100, there were 30 male subjects and 69 female subjects, while one participant preferred not to answer. 53% of males and 48% of females remained neutral about they were knowledgeable about Alzheimer's disease ($p = 0.8056$). 78% of females and 63% of males, correctly stated that Alzheimer's is a subtype of dementia ($p = 0.0348$). Secondly, 90% of women responded that Alzheimer's is not part of the normal aging process while only 70% of males gave the correct response ($p = 0.0147$). Also, 94% of females correctly identified that Alzheimer's worsens over time, compared to only 80% for males ($p = 0.0359$). Fourthly, 93% of females chose that there is no cure to Alzheimer's compared to 83% of males ($p = 0.3561$). Finally, only 20% of women correctly recognized that Alzheimer's is a leading cause of death whereas only 7% for males made this correct selection ($p = 0.1734$). The data shows that females are clearly more knowledgeable than males about Alzheimer's disease, with 71% appearing to be well-aware, compared to only 53% of males ($p = 0.1439$) (see Table 3).

Affected vs Not Affected

41% of the 100 had family members who were affected by Alzheimer's disease, whereas 59% did not have a family member to their knowledge afflicted by the disease. Firstly, 27% of those not affected and 61% of those affected deemed themselves to be knowledgeable about the disease ($p = 0.0018$). Also, 76% and 71% of those affected and unaffected, respectively, correctly identified that it is a subtype of dementia ($p = 0.6207$). 89% and 81% of the same groups, noted that Alzheimer's is not normal with respect to aging ($p = 0.7076$). Meanwhile, 88% of those unaffected noted that Alzheimer's worsens over time and 93% for those affected gave the same answer ($p = 0.8745$). 92% of the unaffected correctly chose that there is no cure to Alzheimer's, compared to 88% of the affected ($p = 0.5791$). Finally, only 10% of those affected and an underwhelming 20% of those unaffected correctly thought that Alzheimer's is a leading cause of death ($p = 0.2760$), following the low percentage trend in this category. Overall, 68% of those affected and 62% of those unaffected had excellent knowledge about the disease ($p = 0.7255$) (see Table 4).

Table 2. Awareness of young adults by age

Evaluation Metric	Under 20 Years Old (n = 39)	20 Years Old and Older (n = 61)	p-value
Self-belief of being knowledgeable			0.5955
Yes			
Neutral	16 (41%)	25 (41%)	
No	21 (54%)	29 (48%)	
	2 (5%)	7 (11%)	
Alzheimer's is a subtype of dementia			0.4465
True			
False	30 (77%)	43 (70%)	
Not Sure	4 (10%)	4 (7%)	
	5 (13%)	14 (23%)	
Alzheimer's is normal with respect to aging			0.1064
True			
False	6 (15%)	5 (8%)	
Not Sure	33 (85%)	51 (84%)	
	0 (0%)	5 (8%)	
Alzheimer's worsens over time			0.5254
True	37 (95%)	53 (87%)	
False	1 (3%)	4 (7%)	
Not Sure	1 (3%)	4 (7%)	
No cure to Alzheimer's			0.4359
True	37 (95%)	53 (87%)	
False	1 (2.5%)	2 (3%)	
Not Sure	1 (2.5%)	6 (10%)	
Alzheimer's is leading cause of death			0.8553
True			
False	7 (18%)	9 (15%)	
Not Sure	19 (49%)	29 (48%)	
	13 (33%)	23 (38%)	
Overall Score			0.1942
Poor (0-2)	3 (8%)	11 (18%)	
Satisfactory (3)	11 (28%)	10 (16%)	
Knowledgeable (4-5)	25 (64%)	40 (66%)	

Table 3. Awareness of young adults by sex

Evaluation Metric	Male (n = 30)	Female (n = 69)	p-value
Self-belief of being knowledgeable			0.8056
Yes			
Neutral	11 (37%)	30 (43%)	
No	16 (53%)	33 (48%)	
	3 (10%)	6 (9%)	
Alzheimer's is a subtype of dementia			0.0348
True			
False	19 (63%)	54 (78%)	
Not Sure	1 (3%)	7 (10%)	
	10 (33%)	8 (12%)	
Alzheimer's is normal with respect to aging			0.0147
True			
False	5 (17%)	6 (9%)	
Not Sure	21 (70%)	62 (90%)	
	4 (13%)	1 (1%)	
Alzheimer's worsens over time			0.0359
True			
False	24 (80%)	65 (94%)	
Not Sure	4 (13%)	1 (1%)	
	2 (7%)	3 (4%)	
No cure to Alzheimer's			0.3561
True	26 (87%)	64 (93%)	
False	2 (7%)	1 (1%)	
Not Sure	2 (7%)	5 (7%)	
Alzheimer's is leading cause of death			0.1734
True			
False	2 (7%)	14 (20%)	
Not Sure	17 (57%)	29 (42%)	
	9 (30%)	26 (38%)	
Overall Score			0.1439
Poor (0-2)	7 (23%)	7 (10%)	
Satisfactory (3)	7 (23%)	13 (19%)	
Knowledgeable (4-5)	16 (53%)	49 (71%)	

Table 4. Awareness of young adults with family members affected/not affected

Evaluation Metric	Affected (n = 41)	Not Affected (n = 59)	p-value
Self-belief of being knowledgeable			0.0018
Yes	25 (61%)	16 (27%)	
Neutral	15 (37%)	35 (59%)	
No	1 (2%)	8 (14%)	
Alzheimer's is a subtype of dementia			0.6207
True	31 (76%)	42 (71%)	
False	4 (10%)	4 (7%)	
Not Sure	6 (14%)	13 (22%)	
Alzheimer's is normal with respect to aging			0.7076
True			
False	4 (10%)	7 (12%)	
Not Sure	36 (88%)	48 (81%)	
	1 (2%)	4 (7%)	
Alzheimer's worsens over time			0.8745
True			
False	38 (93%)	52 (88%)	
Not Sure	2 (5%)	3 (5%)	
	1 (2%)	4 (7%)	

Evaluation Metric	Affected (n = 41)	Not Affected (n = 59)	p-value
No cure to Alzheimer's			0.5791
True	36 (88%)	54 (92%)	
False	2 (5%)	1 (2%)	
Not Sure	3 (7%)	4 (7%)	
Alzheimer's is leading cause of death			0.2760
True	4 (10%)	12 (20%)	
False	23 (56%)	25 (42%)	
Not Sure	14 (34%)	22 (37%)	
Overall Score			0.7255
Poor (0-2)	6 (15%)	8 (14%)	
Satisfactory (3)	7 (17%)	14 (24%)	
Knowledgeable (4-5)	28 (68%)	37 (63%)	

DISCUSSION

This study followed the exact trend of the various other studies done in Ontario, as a large majority of the young adults were quite knowledgeable about the disease (65%), while many less had family affected by it (41%), and only 41% of participants initially believed that they would be knowledgeable. Interesting results are yielded from the gender-split results, as well as the results from the affected vs. non-affected portion. In the gender split, there was three instances of significant differences between male and female responses ($p\text{-value} < 0.05$) showing that for three of the quiz questions, females statistically gave the correct response much more than males, and overall were 18% more knowledgeable (71% vs 53%). This difference could be caused by more females conducting prior research about the disease, more females cheating during the quiz, or even more females taking the quiz more seriously. In the affected vs unaffected split, in all the questions, the affected are more knowledgeable (most likely resulting from additional research), except the last one, "Is Alzheimer's a leading cause of death?". This variation could possibly exist because although they might have a family member with the illness, the family member may not have passed away, causing them to believe it is not a big factor in death. Also, Alzheimer's does not directly cause the death of someone, so it is possible that in their research they discovered this and answered the question believing that because it is not a direct killer, it does not lead to death.

This study was not without limitations. Although this study did have a much larger sample size than the other studies in the series [3-9], 100 participants is still not as large as it could be. Also, while filling out the quiz portion of the survey, it is possible that participants could have used online resources or other assistance to cheat, thus skewing the amount of knowledgeable subjects.

In conclusion, the trend noted by other studies [3-9] was confirmed in Waterloo, Canada, as 65% of participants were knowledgeable whereas only 41% believed they were, while only 41% were affected by the disease. Further studies should attempt to identify the difference in male and female awareness level in the Waterloo area, investigate the reason of why the amount of correct responses to the last question were comparatively low, as well as try to identify if the same overall trend continues in more areas around the globe.

ACKNOWLEDGMENT

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Chapter 234

AWARENESS OF ALZHEIMER'S DISEASE AMONG YOUNG ADULTS IN SASKATOON, CANADA

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ABSTRACT

There have been studies that revealed a trend that young adults are adequately aware of the disease. However, there exists variation between the studies in the proportion of individuals who have a family member affected, who believed they are aware, and who are actually aware. Even among the four sample groups which are geographically close to each other, there is notable variation. It would be interesting to see the degree of variation between the studies in the Province of Ontario, Canada, and the Province of Saskatchewan, Canada. The aim of this study was to investigate the awareness of Alzheimer's disease among young adults in Saskatoon, Canada. A total of 37 individuals consented and completed a survey. While only 51% of participants believed that they were knowledgeable the disease, it turns out that 70% are well-aware of the disease. Coupled with the fact that only 19% of respondents had a family member affected by the disease, the young adult population seems to be adequately versed with the disease. It is important to note that, based on the sample size of this study, it seems that there is a lower occurrence of Alzheimer's disease in the Province of Saskatchewan compared to studies completed in the Province of Ontario. However, this should be interpreted with caution as this study only sampled a small cohort of young adults in Saskatoon and could hence easily be influenced by response bias. Future studies should look into repeating this study with a large sample size to determine if there is any difference in responses between subgroups, and verifying the results.

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INTRODUCTION

The increasingly-common disease of dementia, in conjunction with comorbidities, can yield inadequate care and poor quality of life for patients [1-2]. Literature has suggested that while healthcare professionals can improve standard of care through deploying new assessment tools, family members may be able to help to a greater extent to simply being educated about the illness and its implications [3].

Chow et al. [4] conducted a study among young adults in London, Canada, to assess how knowledgeable they were with respect to the Alzheimer's disease. The results showed that 75% of the cohort was well-aware of the disease, although only 48% of young adults believed that they were knowledgeable. Additionally, only 31% of the population had a family member, to their knowledge, with Alzheimer's disease. It hence seems that the sampled population was adequately aware of the disease, in order to care for their affected family members.

A validation study was conducted in Kingston, Canada [5], and noted similar trends. Chow et al. [4] reported that 60% of young adults were knowledgeable, while only 58% of them believed so. A lower 38% had a family member with Alzheimer's disease, again suggesting that the population was well-aware of the disease.

Studies were also conducted among young adults in Toronto, Canada [6], and Ottawa, Canada [7]. Borean et al. [6] reported that 39% of young adults in Toronto had familial ties to the disease, and 40% and 60% of the population believed they were aware and were actually aware respectively. Viehweger et al. [7] noted that 46% of family members were afflicted by Alzheimer's disease, and 69% and 85% believed they were knowledgeable and were actually knowledgeable, respectively in Ottawa.

These studies all revealed a similar trend that young adults are adequately aware of the disease. However, there still exists variation between the studies in the proportion of individuals who have a family member affected, who believed they are aware, and who are actually aware. Even among the four sample groups which are geographically close to each other, there is notable variation. It would be interesting to see the degree of variation between the studies in the Province of Ontario, Canada, and the Province of Saskatchewan, Canada. The aim of this study was to investigate the awareness of Alzheimer's disease among young adults in Saskatoon, Canada.

SURVEY METHOD

A survey, the same as that used by Chow et al. in London [4], was used to determine the awareness of young adults in Saskatchewan, Canada, see chapter 2 [8]. The first page had a consent form for the study; participants had the option to enter their email and receive a copy of the consent form [8]. After consenting to the study, participants completed three questions to collect relevant demographics - primary place of residence, age and sex [8]; only those who recorded Saskatoon, Canada as their place of residence were included in this study. The third page had six questions, with the first being a reflection question and the next five being knowledge-based questions - a quiz about Alzheimer's disease [8]. The last page of the survey asked participants whether, to their knowledge, they have/had a family member

affected by Alzheimer's; if they have/had, it also asked for how often they visit their relative [8].

The primary objective of the survey was to determine the awareness of Alzheimer's disease regardless of demographics (age, sex and other background). Secondary objectives were to determine whether there existed any difference in knowledge across different subgroups - between men and women, between younger and older young adults, and between those with and without family members with Alzheimer's disease.

Statistical Analysis

The six items - 1 reflection and 5 knowledge questions - on page 3 were presented using descriptive statistics. For each participant, an overall score out of 5 was generated for the number of questions they correctly answered, with the answer key being: Alzheimer's Disease is a form of dementia - True; Alzheimer's is part of the normal aging process - False; Alzheimer's worsens over time - True; There is no cure for Alzheimer's, only treatments for symptoms - True; Alzheimer's is a leading cause of death - True. Participants with scores of 4 or 5 out of 5 were interpreted to be knowledgeable about Alzheimer's disease; those with 3 were marked as having satisfactory knowledge; those scoring 1 or 2 had poor awareness about the disease.

Fisher-exact tests were conducted to determine whether there was a difference in awareness between these groups - ages of participants (under 20 years old, and 20 years old and older), sex (male and female), and their family's history with Alzheimer's disease (affected and not affected). P-values less than 0.05 were deemed to be statistically significant. All analyses were conducted using the Statistical Analysis Software (SAS Version 9.4 for Windows).

OUTCOMES

A total of 37 individuals consented and completed the survey. 51% remained neutral with respect to assessing themselves as knowledgeable about the disease, while 41% believed they were knowledgeable and 8% remarked they were not well-aware. The majority of participants (73%) correctly answered that Alzheimer's is a subtype of dementia, while 5% incorrectly answered the question and 22% admitted they were unsure. Only 5% of respondents incorrectly believed that Alzheimer's is part of the normal aging process, while 92% correctly identified it was not part of the process and 3% indicated they did not know. All of those (95%) who attempted to answer the question pertaining to progression over time correctly reasoned that Alzheimer's does worsen over time. An overwhelming majority (92%) responded that there was no cure for Alzheimer's, with 3% and 5% incorrectly remarking and withholding an answer, respectively. Only 24% of respondents correctly recognized that Alzheimer's is a leading cause of death, with 54% incorrectly identifying that it is not, and 22% deciding not to answer. Overall, 70% of respondents were knowledgeable with respect to Alzheimer's disease, with 22% having satisfactory knowledge and 8% having poor knowledge (see Table 1).

Table 1. Awareness of all young adults

Evaluation Metric	All (n = 37)
Self-belief of being knowledgeable	
Yes	15 (41%)
Neutral	19 (51%)
No	3 (8%)
Alzheimer's is a subtype of dementia	
True	27 (73%)
False	2 (5%)
Not Sure	8 (22%)
Alzheimer's is normal with respect to aging	
True	2 (5%)
False	34 (92%)
Not Sure	1 (3%)
Alzheimer's worsens over time	
True	35 (95%)
False	0 (0%)
Not Sure	2 (5%)
No cure to Alzheimer's	
True	34 (92%)
False	1 (3%)
Not Sure	2 (5%)
Alzheimer's is leading cause of death	
True	9 (24%)
False	20 (54%)
Not Sure	8 (22%)
Overall Score	
Poor (1-2)	3 (8%)
Satisfactory (3)	8 (22%)
Knowledgeable (4-5)	26 (70%)

Under 20 Years Old vs 20 Years Old and above

Of the 37 respondents, 18 were under the age of 20 years old and 19 were 20 years old or older. There seems to be a trend that the older cohort believed that they were indeed more knowledgeable than the younger group ($p = 0.1598$), with 53% and 28%, respectively, remarking that they believe they are knowledgeable. The younger and older cohort identified that Alzheimer's is a subtype of dementia at a 78% and 68% rate, respectively ($p = 0.8411$). 95% and 89% of the older and younger cohort, respectively, correctly remarked that Alzheimer's is not a normal process of aging ($p = 0.3544$). 100% of the younger and 90% of the older group answered that Alzheimer's does worsen over time ($p = 0.4865$), while 94% and 90% of the two cohorts respectively responded that there is no cure for Alzheimer's disease ($p = 0.4865$). The vast majority of both cohorts (56% of those below 20 years old, and 53% of those 20 years old and above) incorrectly responded that Alzheimer's is not a leading cause of death ($p = 0.8240$). There was no difference in level of awareness between the two age groups, with 72% of the younger group and 68% of the older group deemed as knowledgeable based on their responses to the questionnaire ($p = 0.9999$) (see Table 2).

Males vs Females

There were 16 males and 21 females that responded to the questionnaire. 50% and 33% of males and females, respectively, indicated that they believe they are knowledgeable about the disease. 69% and 76%, respectively, correctly remarked that Alzheimer's disease is a form of dementia ($p = 0.3647$), while 88% and 95%, for the same groups respectively, noted that Alzheimer's is not part of the normal aging process ($p = 0.1802$). Only 1 male (6%) and 1 female (5%) did not answer correctly that Alzheimer's worsens over time ($p = 0.9999$). 94% of males and 90% of females identified that there was no cure for Alzheimer's disease ($p = 0.9999$). There seems to be a trend that females are more aware that Alzheimer's is a leading cause of death as opposed to males (24% for females vs 19% for males; $p = 0.1318$). Males (75%) and females (67%), overall, were equally aware about Alzheimer's disease ($p = 0.4234$) (see Table 3).

Affected vs Not Affected

Only 7 of the 37 respondents had a family member with Alzheimer's disease, to the knowledge of the participants. There seems to be a trend that those with family members afflicted by the disease believe they are more knowledgeable (57% vs 37%) ($p = 0.3346$). 86% of those affected and 70% of those without a family member affected by Alzheimer's disease correctly acknowledged that Alzheimer's is a subtype of dementia ($p = 0.9999$). A higher proportion of those without a family member (97%) believed that Alzheimer's is not part of the normal process, while only 71% of those with family members afflicted by the disease had a similar response ($p = 0.0315$). 100% of those affected and 93% of those not affected correctly answered that Alzheimer's worsens over time ($p = 0.9999$), while 100% and 90% of the groups, respectively, correctly responded that there is no cure for Alzheimer's disease ($p = 0.9999$). There was a trend that those affected by Alzheimer's disease were more likely to acknowledge the Alzheimer's is a leading cause of death (57%) as opposed to those without family members affected by the disease (17%). Overall, there was no significant difference in awareness levels between the two groups ($p = 0.2856$) - 86% of those affected and 67% of those not affected were deemed knowledgeable based on how they answered the survey (see Table 4).

DISCUSSION

While only 51% of participants believed that they were knowledgeable the disease, it turns out that 70% are well-aware of the disease. Coupled with the fact that only 19% of respondents had a family member affected by the disease, the young adult population seems to be adequately versed with the disease. This trend is similar to previous studies [4-7], and shows that young adults in the Province of Saskatchewan are also very aware of Alzheimer's disease.

This study also validates the conclusions of two [5, 7] of four [4-7] past studies that there was no difference between males and females with respect to knowledgeability. This may be

due to low statistical power as a consequence of the sample size, as noted in the other two studies [5, 7].

Table 2. Awareness of young adults by age

Evaluation Metric	Under 20 Years Old (n = 18)	20 Years Old and Older (n = 19)	p-value
Self-belief of being knowledgeable			0.1598
Yes			
Neutral	5 (28%)	10 (53%)	
No	12 (67%)	7 (37%)	
	1 (6%)	2 (11%)	
Alzheimer's is a subtype of dementia			0.8411
True			
False	14 (78%)	13 (68%)	
Not Sure	1 (6%)	1 (5%)	
	3 (17%)	5 (26%)	
Alzheimer's is normal with respect to aging			0.3544
True			
False	2 (11%)	0 (0%)	
Not Sure	16 (89%)	18 (95%)	
	0 (0%)	1 (5%)	
Alzheimer's worsens over time			0.4865
True			
False	18 (100%)	17 (90%)	
Not Sure	0 (0%)	0 (0%)	
	0 (0%)	2 (10%)	
No cure to Alzheimer's			0.4865
True	17 (94%)	17 (90%)	
False	1 (6%)	0 (0%)	
Not Sure	0 (0%)	2 (10%)	
Alzheimer's is leading cause of death			0.8240
True			
False	5 (28%)	4 (21%)	
Not Sure	10 (56%)	10 (53%)	
	3 (17%)	5 (26%)	
Overall Score			0.9999
Poor (1-2)	1 (6%)	2 (10%)	
Satisfactory (3)	4 (22%)	4 (21%)	
Knowledgeable (4-5)	13 (72%)	13 (68%)	

Table 3. Awareness of young adults by sex

Evaluation Metric	Male (n = 16)	Female (n = 21)	p-value
Self-belief of being knowledgeable			0.3643
Yes			
Neutral	8 (50%)	7 (33%)	
No	6 (38%)	13 (62%)	
	2 (13%)	1 (5%)	
Alzheimer's is a subtype of dementia			0.3647
True			
False	11 (69%)	16 (76%)	
Not Sure	2 (13%)	0 (0%)	
	3 (19%)	5 (24%)	
Alzheimer's is normal with respect to aging			0.1802
True			
False	2 (13%)	0 (0%)	
Not Sure	14 (88%)	20 (95%)	
	0 (0%)	1 (5%)	

Evaluation Metric	Male (n = 16)	Female (n = 21)	p-value
Alzheimer's worsens over time True False Not Sure	 15 (94%) 0 (0%) 1 (6%)	 20 (95%) 0 (0%) 1 (5%)	0.9999
No cure to Alzheimer's True False Not Sure	 15 (94%) 0 (0%) 1 (6%)	 19 (90%) 1 (5%) 1 (5%)	0.9999
Alzheimer's is leading cause of death True False Not Sure	 4 (19%) 11 (69%) 1 (6%)	 5 (24%) 9 (43%) 7 (33%)	0.1318
Overall Score Poor (1-2) Satisfactory (3) Knowledgeable (4-5)	 2 (12%) 2 (12%) 12 (75%)	 1 (5%) 6 (29%) 14 (67%)	0.4234

Table 4. Awareness of young adults with family members affected/not affected

Evaluation Metric	Affected (n = 7)	Not Affected (n = 30)	p-value
Self-belief of being knowledgeable Yes Neutral No	 4 (57%) 2 (29%) 1 (14%)	 11 (37%) 17 (57%) 2 (7%)	0.3346
Alzheimer's is a subtype of dementia True False Not Sure	 6 (86%) 0 (0%) 1 (14%)	 21 (70%) 2 (7%) 7 (23%)	0.9999
Alzheimer's is normal with respect to aging True False Not Sure	 2 (29%) 5 (71%) 0 (0%)	 0 (0%) 29 (97%) 1 (3%)	0.0315
Alzheimer's worsens over time True False Not Sure	 7 (100%) 0 (0%) 0 (0%)	 28 (93%) 0 (0%) 2 (7%)	0.9999
No cure to Alzheimer's True False Not Sure	 7 (100%) 0 (0%) 0 (0%)	 27 (90%) 1 (3%) 2 (7%)	0.9999
Alzheimer's is leading cause of death True False Not Sure	 4 (57%) 3 (43%) 0 (0%)	 5 (17%) 17 (57%) 8 (27%)	0.0701
Overall Score Poor (1-2) Satisfactory (3) Knowledgeable (4-5)	 1 (14%) 0 (0%) 6 (86%)	 2 (7%) 8 (27%) 20 (67%)	0.2856

It is important to note that, based on the sample size of this study, it seems that there is a lower occurrence of Alzheimer's disease in the Province of Saskatchewan compared to studies completed in the Province of Ontario. However, this should be interpreted with caution as this study only sampled a small cohort of young adults in Saskatoon and could hence easily be influenced by response bias.

This study has its limitations. The sample size of this study could have decreased statistical power when detecting for differences. Also, there exists the possibility of cheating when completing the quiz portion of the survey, which would lead to an artificially higher proportion of individuals who would be knowledgeable.

In conclusion, 70% of young adults in Saskatchewan, Canada, are aware of Alzheimer's disease, although only 51% believed that they are knowledgeable. Given that 19% of young adults have a family member affected by the illness, it seems that young adults are adequately aware of the disease that their family members are affected by. Future studies should look into repeating this study with a large sample size to determine if there is any difference in responses between subgroups and verifying the results

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Chapter 235

AWARENESS OF ALZHEIMER'S DISEASE AMONG YOUNG ADULTS IN MONTREAL, CANADA

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ABSTRACT

Many symptoms of Alzheimer's are not recognized by the general population until later stages of the disease. One possible reason behind this may be that people are not aware enough about dementia and its consequences. In order to measure the level of awareness amongst people in several cities, numerous surveys were conducted on Alzheimer's awareness. A very similar study was conducted in Montreal, Canada, in order to further assess the general trends in Alzheimer awareness. 36 participants filled out the survey; 19 were under 20 years old and 17 were 20 years old and older; 7 males and 29 females responded to the survey; 14 had a family member affected by the disease while 22 did not. The young adults in Montreal were much more knowledgeable (78% scoring at four or above points) than they believed themselves to be (53% thought of themselves as knowledgeable). The results validate the general trend from prior studies that young adults are well-aware, given that 78% are knowledgeable compared to only 39% affected by the disease. The data herein validates prior general trends detailed in published literature. Although the population is well-aware, it is far from perfect; studies should look into how awareness can be increased further.

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INTRODUCTION

Alzheimer's is a subtype and common form of dementia that affects the quality of life of many seniors. In 2013, it was the cause of 84,767 deaths in the United States, making it the 6th highest cause of death in the country [1]. Although specific causes of the disease remain unclear, certain trends have been observed in the population. For example, it has been found that populations with lower levels or a lack of education are more likely to develop Alzheimers [2].

Many symptoms of Alzheimer's are not recognized by the general population until later stages of the disease. One possible reason behind this may be that people are not aware enough about dementia and its consequences. In order to measure the level of awareness amongst people in several cities, numerous surveys were conducted on Alzheimer's awareness [3-6]. A study conducted in London, Canada, showed that while only 48% of participants believed themselves to be knowledgeable about the disease, 75% proved to be so based on the evaluation system in the study [7]. A trend indicating that having a family member with Alzheimer's does not correlate with general knowledge about the disease was observed in prior studies [3-6]. A very similar study was conducted in Montreal, Canada, in order to further assess the general trends in Alzheimer awareness.

OUR STUDY

A survey was created to measure the awareness of young adults in Montreal, Canada, see chapter 2 [8]. The first page had a consent form for the study; participants could enter their email to receive a copy of the consent form [8]. Afterwards, the survey contained three questions regarding demographics, including the participant's primary place of residence, age and sex [8]; only those who recorded Montreal, Canada, as their place of residence were included in this study. The subsequent page had six questions; the first was a reflection question and the others were knowledge-based questions - a quiz about Alzheimer's disease [8]. The last page of the survey asked participants about their family history with Alzheimer's disease- whether, to their knowledge, they have/had a family member affected by Alzheimer's; and how often they visit their relative [8].

The main purpose of the survey was to determine the awareness of Alzheimer's disease, across all young adults (regardless of age, sex and other background). The secondary objectives were to determine whether there were any differences across different subgroups - between men and women, between younger and older young adults, and between those with and without family members with Alzheimer's disease.

Statistical Analysis

The analysis was similar to that conducted by Chow et al. [7]. Descriptive statistics were used to report the six items - 1 reflection and 5 knowledge questions - on page 3. For each participant, an overall score out of 5 was generated for the number of questions they answered correctly, with the right answers being: Alzheimer's disease is a form of dementia - True;

Alzheimer's is part of the normal aging process - False; Alzheimer's worsens over time - True; There is no cure for Alzheimer's only treatments for symptoms - True; Alzheimer's is a leading cause of death - True. Participants with scores of 4 or 5 out of 5 were interpreted to be knowledgeable about Alzheimer's disease; those with 3 were marked as having satisfactory knowledge; those scoring 1 or 2 had poor awareness about the disease.

Subgroup analyses were conducted based on ages of participants (under 20 years old, and 20 years old and older), sex (male and female), and their family's history with Alzheimer's disease (affected and not affected). Fisher-exact tests were conducted to determine whether there was a significant difference between these groups. P-values less than 0.05 were deemed to be statistically significant. All analyses were conducted using the Statistical Analysis Software (SAS Version 9.4 for Windows).

FINDINGS

36 participants filled out the survey. 53% of them believed they were knowledgeable about Alzheimer's disease, 42% were neutral and the remaining 6% were not confident about their knowledge. 81% of participants correctly chose that Alzheimer's is a subtype of dementia, 8% thought it was not and 11% were unsure. Most of the participants, 94%, believed that Alzheimer's is normal with respect to aging while 6% disagreed. 97% of participants stated that Alzheimer's worsens over time while 3% were unsure. Again, a majority of respondents (94%) chose that there was no cure to Alzheimer's, 3% disagreed and 3% were unsure. 22% of participants reported that Alzheimer's is a leading cause of death, 47% believed it was not and 31% were unsure. Overall, 78% of participants were knowledgeable about the disease, 14% had a satisfactory level of knowledge (answered 3 questions correctly) while 8% had relatively poor knowledge (only answered 1-2 questions correctly) about Alzheimer's (see Table 1).

Under 20 Years Old vs 20 Years Old and above

Of the 36 respondents, 19 were under 20 years old and 17 were 20 years old and older. 42% of the younger cohort believed they were knowledgeable about the disease while 65% of the older cohort did ($p = 0.3337$). 79% and 82% of the younger and older cohort respectively said that correctly identified that Alzheimer's is a subtype of dementia ($p = 0.9999$). 95% of the younger cohort and 94% of the older participants reported that Alzheimer's is not normal with respect to aging ($p = 0.9999$). 95% and 100% of the younger and older age cohort respectively believed that Alzheimer's worsens over time ($p = 0.9999$). 95% of those under 20 years old and 94% of those older than 20 years old and older stated that there is no cure to Alzheimer's ($p = 0.7286$). 21% of the younger cohort and 24% of the older cohort chose that Alzheimer's is the leading cause of death ($p = 0.2931$). In summary, 79% of the younger cohort and 76% of the older cohort were knowledgeable about the disease, meaning they answered 4-5 questions correctly ($p = 0.8600$) (see Table 2).

Table 1. Awareness of all young adults

Evaluation Metric	All (n = 36)
Self-belief of being knowledgeable	
Yes	19 (53%)
Neutral	15 (42%)
No	2 (6%)
Alzheimer's is a subtype of dementia	
True	29 (81%)
False	3 (8%)
Not Sure	4 (11%)
Alzheimer's is normal with respect to aging	
True	34 (94%)
False	2 (6%)
Not Sure	0 (0%)
Alzheimer's worsens over time	
True	35 (97%)
False	0 (0%)
Not Sure	1 (3%)
No cure to Alzheimer's	
True	34 (94%)
False	1 (3%)
Not Sure	1 (3%)
Alzheimer's is leading cause of death	
True	8 (22%)
False	17 (47%)
Not Sure	11 (31%)
Overall Score	
Poor (1-2)	3 (8%)
Satisfactory (3)	5 (14%)
Knowledgeable (4-5)	28 (78%)

Table 2. Awareness of young adults by age

Evaluation Metric	Under 20 Years Old (n = 19)	20 Years Old and Older (n = 17)	p-value
Self-belief of being knowledgeable			0.3337
Yes			
Neutral	8 (42%)	11 (65%)	
No	10 (53%)	5 (29%)	
	1 (5%)	1 (6%)	
Alzheimer's is a subtype of dementia			0.9999
True			
False	15 (79%)	14 (82%)	
Not Sure	2 (11%)	1 (6%)	
	2 (11%)	2 (12%)	
Alzheimer's is normal with respect to aging			0.9999
True			
False	1 (5%)	1 (6%)	
Not Sure	18 (95%)	16 (94%)	
	0 (0%)	0 (0%)	
Alzheimer's worsens over time			0.9999
True	18 (95%)	17 (100%)	
False	0 (0%)	0 (0%)	
Not Sure	1 (5%)	0 (0%)	
No cure to Alzheimer's			0.7286
True	18 (95%)	16 (94%)	
False	0 (0%)	1 (6%)	
Not Sure	1 (5%)	0 (0%)	
Alzheimer's is leading cause of death			0.2931
True			
False	4 (21%)	4 (24%)	
Not Sure	7 (37%)	10 (59%)	
	8 (42%)	3 (18%)	
Overall Score			0.8600
Poor (1-2)	2 (11%)	1 (6%)	
Satisfactory (3)	2 (11%)	3 (18%)	
Knowledgeable (4-5)	15 (79%)	13 (76%)	

Males vs Females

There were 7 males and 29 females who responded to the survey. 29% of males had self-belief of their knowledge regarding the disease, while 59% of the females were confident in their knowledge ($p = 0.2194$). 43% of males and 90% of females stated that Alzheimer's is a subtype of dementia ($p = 0.0192$), which is statistically significant. 86% of males and 97% of females stated that Alzheimer's is not normal with respect to aging ($p = 0.3556$). 86% of males and all of the female respondents commented that Alzheimer's worsens over time ($p = 0.1944$). 71% of males and 100% of the females said that there is no cure to Alzheimer's ($p = 0.0333$). 57% of males said that Alzheimer's is not a leading cause of death while 45% of females thought the same ($p = 0.9999$). Overall, only 29% of the male respondents answered 4-5 questions correctly while all of the female respondents had a high knowledge of Alzheimer's disease ($p < 0.0001$) (see Table 3).

Table 3. Awareness of young adults by sex

Evaluation Metric	Male (n = 7)	Female (n = 29)	p-value
Self-belief of being knowledgeable			0.2194
Yes			
Neutral	2 (29%)	17 (59%)	
No	4 (57%)	11 (38%)	
	1 (14%)	1 (3%)	
Alzheimer's is a subtype of dementia			0.0192
True			
False	3 (43%)	26 (90%)	
Not Sure	2 (29%)	1 (3%)	
	2 (29%)	2 (7%)	
Alzheimer's is normal with respect to aging			0.3556
True	1 (14%)	1 (3%)	
False	6 (86%)	28 (97%)	
Not Sure	0 (0%)	0 (0%)	
Alzheimer's worsens over time			0.1944
True			
False	6 (86%)	29 (100%)	
Not Sure	0 (0%)	0 (0%)	
	1 (14%)	0 (0%)	
No cure to Alzheimer's			0.0333
True	5 (71%)	29 (100%)	
False	1 (14%)	0 (0%)	
Not Sure	1 (14%)	0 (0%)	
Alzheimer's is leading cause of death			0.9999
True	1 (14%)	7 (24%)	
False	4 (57%)	13 (45%)	
Not Sure	2 (29%)	9 (31%)	
Overall Score			<0.0001
Poor (1-2)	3 (43%)	0 (0%)	
Satisfactory (3)	2 (29%)	0 (0%)	
Knowledgeable (4-5)	2 (29%)	29 (100%)	

Affected vs Not Affected

Of all the respondents, 14 had a family member affected by the disease while 22 did not. 71% of those affected and 41% of those who weren't believed that they were knowledgeable

about the disease ($p = 0.1700$). 86% and 77% of those affected and not affected respectively said that Alzheimer's is a subtype of dementia ($p = 0.4676$). All the participants who were affected and 91% of those who weren't affected said that Alzheimer's is not normal with respect to aging ($p = 0.5111$). All of the participants who were affected and 95% of those who weren't, commented that Alzheimer's worsens over time ($p = 0.9999$). 100% and 91% of those affected and not affected respectively said there was no cure to Alzheimer's ($p = 0.9999$). 43% of those affected said Alzheimer's is a leading cause of death while 9% of those who weren't affected said the same ($p = 0.0757$). 86% of those affected were quite knowledgeable and 73% of those who weren't affected were equally knowledgeable ($p = 0.4178$) (see Table 4).

Table 4. Awareness of young adults with family members affected/not affected

Evaluation Metric	Affected (n = 14)	Not Affected (n = 22)	p-value
Self-belief of being knowledgeable			0.1700
Yes			
Neutral	10 (71%)	9 (41%)	
No	4 (29%)	11 (50%)	
	0 (0%)	2 (9%)	
Alzheimer's is a subtype of dementia			0.4676
True			
False	12 (86%)	17 (77%)	
Not Sure	0 (0%)	3 (14%)	
	2 (14%)	2 (9%)	
Alzheimer's is normal with respect to aging			0.5111
True			
False	0 (0%)	2 (9%)	
Not Sure	14 (100%)	20 (91%)	
	0 (0%)	0 (0%)	
Alzheimer's worsens over time			0.9999
True	14 (100%)	21 (95%)	
False	0 (0%)	0 (0%)	
Not Sure	0 (0%)	1 (5%)	
No cure to Alzheimer's			0.9999
True	14 (100%)	20 (91%)	
False	0 (0%)	1 (5%)	
Not Sure	0 (0%)	1 (5%)	
Alzheimer's is leading cause of death			0.0757
True			
False	6 (43%)	2 (9%)	
Not Sure	5 (35%)	12 (55%)	
	3 (21%)	8 (36%)	
Overall Score			0.4178
Poor (1-2)	0 (0%)	3 (21%)	
Satisfactory (3)	2 (14%)	3 (21%)	
Knowledgeable (4-5)	12 (86%)	16 (73%)	

DISCUSSION

The young adults in Montreal were much more knowledgeable (78% scoring at four or above points) than they believed themselves to be (53% thought of themselves as knowledgeable). This difference is much greater than Chow et al. [9] presented on North Carolina, where 53% of participants believed themselves to be knowledgeable and 58%

actually were. The results validate the general trend young adults are well-aware [2-6, 9], given that 78% are knowledgeable compared to only 39% affected by the disease.

In general, it appears that females have a significantly higher awareness of the fact that Alzheimer's is a subtype of dementia (90% answered correctly), as only 43% of males gave the correct response. Males seem to be much more inclined to believe that a cure for Alzheimer exists or are not sure (29%), while females all agree that no such cure exists. Most significantly, 100% of females were deemed knowledgeable based on their answers, yet only 29% of males were similarly branded. This trend validates the observations by Chow et al. in London, Canada [7]. These disparities may stem from a varying levels of interest in personal and family health, as well as interests of these gender cohorts.

Furthermore, those individuals who have family members affected by the disease appear to be more knowledgeable about the fact that Alzheimer's is a leading cause of death, as opposed to those unaffected (43% vs. 9%). This statistic may be due to the fact that these people are much more exposed to information about the disease as a result of discussions regarding the family members' treatment.

This study was not without limitations. In order to be able to determine significant differences between groups as opposed to trends, a much larger sample size would have been ideal. Perhaps a larger sample size could have been acquired had an email address not been required in order to complete the survey. Additionally, due to the online nature of the survey, the participants may have resorted to using outside resources to answer certain questions. Though this is unavoidable with such a medium, the fact that participants were described the nature of the assessment and asked to answer honestly may have mitigated this issue.

In conclusion, the data collected shows that the young adults in Montreal are more knowledgeable about Alzheimer's than they believe themselves to be. Additionally, females seems to be better informed about the details of the disease than males, perhaps as a result of varying amounts of involvement in Alzheimer's education and involvement in family treatment. The data herein validates prior general trends detailed in published literature. Although the population is well-aware, it is far from perfect; studies should look into how awareness can be increased further.

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Chapter 236

AWARENESS OF ALZHEIMER'S DISEASE AMONG YOUNG ADULTS IN NORTH CAROLINA, UNITED STATES

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ABSTRACT

Family members can play a pivotal role in the care of Alzheimer's patients by increasing their knowledge and awareness of the disease. Studies have been conducted around the globe by a research group based out of London, Canada, to look into the awareness levels of young adults. Even though a similar trend was observed in all of the different geographical regions, there exists variation between distinct locations. The aim of this investigation was to study the awareness level of young adults in North Carolina, United States, with respect to Alzheimer's disease. A survey was designed to evaluate the awareness of young adults, and was completed by 38 respondents. 58% of the young adults in North Carolina were knowledgeable. This is a higher proportion than the self-perceived level and the percentage of the population that have a family member personally affected by the disease, both of which is 53%. This study did reveal that there seems to be a difference in awareness level between individuals with and without a family member suffering from Alzheimer's, which is a novel finding. Future studies should look into determining whether this was an anomaly, and perhaps explain why this finding may exist.

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INTRODUCTION

There have been many studies completed that look into tools to improve quality of life and standard of care for Alzheimer's and dementia patients. While healthcare professionals have gone to great extents to improve quality of care, family members can also play a great role by increasing their knowledge and awareness of the disease [1].

Studies have been conducted by a research group based out of London, Canada, to look into the awareness levels of young adults [2-10]. The first three studies looked to identify trends among the cohort in London, Kingston, and Toronto (all in Canada) [2-4]. In London [2], it was found that 75% of the population was well-aware of the disease, but only 48% and 31% believed they were knowledgeable and had a family member affected by the disease, respectively. The study carried out in Kingston noted a similar trend, with 60% knowledgeable, 58% believing they were knowledgeable, and only 38% of the group having a family member afflicted by the disease. Borean et al. noted that, among young adults of Toronto, 39% had familial ties and 40% acknowledged they were knowledgeable, which is lower than the 60% of those who actually are well-aware [4].

Follow-up studies were conducted in other cities in the Canadian Province of Ontario [5, 6, 10], Canadian Province of Saskatchewan [7], Dublin, Ireland [8], and Asia [9]. The trend was verified in all but one study [5] - in that study, there was not an observation that awareness level was higher than the proportion of those affected by the disease, but this may have been an anomaly due to the sample size.

Even though the trend was observed in all of the different geographical regions, there exists variation between distinct locations. In Asia, for example, the proportion of those who were well-aware and the proportion of those who were affected by the illness was equal; this finding contrasts with prior studies that indicated that a higher proportion were aware compared to the proportion who was affected by the disease [9]. The aim of this study was to discover the awareness level of young adults in North Carolina, USA, with respect to Alzheimer's disease.

OUR SURVEY

A survey was designed to evaluate the awareness of young adults in North Carolina, USA, among other places, see chapter 2 [2, 11]. The first page had a consent form for the study; participants had the option to enter their email and receive a copy of the consent form [11]. After consenting to the study, participants completed three questions to collect relevant demographics - primary place of residence, age and sex [11]; only those who recorded North Carolina as their place of residence was included in this study. The third page had six questions, with the first being a reflection question and the next five being knowledge-based questions - a quiz about Alzheimer's disease [11]. The last page of the survey asked participants whether, to their knowledge, they have/had a family member affected by Alzheimer's; if they have/had, it also asked for how often they visit their relative [11].

The primary objective of the survey was to determine the awareness of Alzheimer's disease, across all young adults (regardless of age, sex and other background). The secondary objectives were to determine whether there existed any difference in knowledge across

different subgroups - between men and women, between younger and older young adults, and between those with and without family members with Alzheimer's disease.

Statistical Analysis

The same statistical analysis that was conducted for the London study, and the other studies, [2-9] was carried out in this setting. Descriptive statistics were used to report the six items - 1 reflection and 5 knowledge questions - on page 3. For each participant, an overall score out of 5 was generated for the number of questions they correctly answered, with the answer key being: Alzheimer's Disease is a form of dementia - True; Alzheimer's is part of the normal aging process - False; Alzheimer's worsens over time - True; There is no cure for Alzheimer's only treatments for symptoms - True; Alzheimer's is a leading cause of death - True. Participants with scores of 4 or 5 out of 5 were interpreted to be knowledgeable about Alzheimer's disease; those with 3 were marked as having satisfactory knowledge; those scoring 1 or 2 had poor awareness about the disease.

Subgroup analyses were conducted based ages of participants (under 20 years old, and 20 years old and older), sex (male and female), and their family's history with Alzheimer's disease (affected and not affected). Fisher-exact tests were conducted to determine whether there was a difference in awareness between these groups. P-values less than 0.05 were deemed to be statistically significant. All analyses were conducted using the Statistical Analysis Software (SAS Version 9.4 for Windows).

OUR FINDINGS

38 individuals completed the survey, of which 53% believed that they were knowledgeable about Alzheimer's disease. 71% correctly responded that Alzheimer's is a subtype of dementia, 89% accurately noted that Alzheimer's is not normal with respect to aging, 89% remarked that Alzheimer's does worsen over time, 79% mentioned that there is no cure to Alzheimer's, and only 34% of the population correctly noted that Alzheimer's is a leading cause of death. Overall, 58% of the sample population were deemed knowledgeable, 32% had satisfactory knowledge, and 11% had poor knowledge (see Table 1).

Under 20 Years Old vs 20 Years Old and above

17 respondents were under the age of 20 years old, and the remaining 21 respondents identified themselves as 20 years old or older. 59% of the younger and 48% of the older group classified themselves as knowledgeable about the disease ($p = 0.5759$). While 65% of the younger cohort responded that Alzheimer's is a subtype of dementia, a higher 76% of the older cohort responded to the same answer ($p = 0.2306$). There was no difference in response between the groups with respect to whether Alzheimer's is a normal process of aging; 94% and 86% of the two groups, respectively, answered that it is not normal ($p = 0.9999$). All of those under 20 years old answered that Alzheimer's worsens over time, while 81% of older

adults similarly responded to the question ($p = 0.2383$). 88% and 47% of the younger group answered ‘True’ to the statements that there is no cure to Alzheimer’s and that Alzheimer’s is a leading cause of death, respectively. There were no difference between the overall knowledge scores of the younger and older cohort ($p = 0.7144$), with 65% and 52% of the groups, respectively, considered knowledgeable (see Table 2).

Table 1. Awareness of all young adults

Evaluation Metric	All (n = 38)
Self-belief of being knowledgeable Yes Neutral No	20 (53%) 16 (42%) 2 (5%)
Alzheimer’s is a subtype of dementia True False Not Sure	27 (71%) 6 (16%) 5 (13%)
Alzheimer’s is normal with respect to aging True False Not Sure	3 (8%) 34 (89%) 1 (3%)
Alzheimer’s worsens over time True False Not Sure	34 (89%) 3 (8%) 1 (3%)
No cure to Alzheimer’s True False Not Sure	30 (79%) 4 (11%) 4 (11%)
Alzheimer’s is leading cause of death True False Not Sure	13 (34%) 15 (40%) 10 (26%)
Overall Score Poor (1-2) Satisfactory (3) Knowledgeable (4-5)	4 (11%) 12 (32%) 22 (58%)

Table 2. Awareness of young adults by age

Evaluation Metric	Under 20 Years Old (n = 17)	20 Years Old and Older (n = 21)	p-value
Self-belief of being knowledgeable Yes Neutral No	10 (59%) 7 (41%) 0 (0%)	10 (48%) 9 (43%) 2 (10%)	0.5759
Alzheimer’s is a subtype of dementia True False Not Sure	11 (65%) 2 (12%) 4 (24%)	16 (76%) 4 (19%) 1 (5%)	0.2306
Alzheimer’s is normal with respect to aging True False Not Sure	1 (6%) 16 (94%) 0 (0%)	2 (10%) 18 (86%) 1 (5%)	0.9999

Evaluation Metric	Under 20 Years Old (n = 17)	20 Years Old and Older (n = 21)	p-value
Alzheimer's worsens over time True False Not Sure	17 (100%) 0 (0%) 0 (0%)	17 (81%) 3 (14%) 1 (5%)	0.2383
No cure to Alzheimer's True False Not Sure	15 (88%) 2 (12%) 0 (0%)	15 (71%) 4 (19%) 2 (10%)	0.4908
Alzheimer's is leading cause of death True False Not Sure	8 (47%) 4 (24%) 5 (29%)	5 (24%) 11 (52%) 5 (24%)	0.1945
Overall Score Poor (1-2) Satisfactory (3) Knowledgeable (4-5)	1 (6%) 5 (29%) 11 (65%)	3 (14%) 7 (33%) 11 (52%)	0.7144

Males vs Females

Of the 38 respondents, 11 identified as males and 26 recognized themselves as females. There seems to exist no difference in self-belief levels ($p = 0.4109$), with 9% of males and 4% of females remarking that they are not knowledgeable. There were no differences in responses between males and females with respect to questions probing about whether Alzheimer's is a subtype of dementia (64% for males vs 73% of females agreed; $p = 0.5283$), whether Alzheimer's worsens over time (82% vs 92% agree; $p = 0.4489$), and whether Alzheimer's is a leading cause of death (36% of males and 39% of females were unsure; $p = 0.7438$). Females were more aware that Alzheimer's is not part of the normal aging process, with 96% compared to 73% of males recognizing the fact ($p = 0.0212$). Females were also more aware that there was no cure for Alzheimer's (92% vs 46% for males; $p = 0.122$). Overall, females are more knowledgeable compared to males, with 65% (vs 36% for males) deemed knowledgeable ($p = 0.0084$) (see Table 3).

Affected vs Not Affected

20 of the 38 respondents had a family member affected by Alzheimer's disease, while 18 did not. Those with family members affected by Alzheimer's seem to be more confident in their awareness level, with 70% of affected compared to 33% of unaffected stating that they are knowledgeable ($p = 0.665$). There were no differences in any of the component questions between the two cohorts; those who had an affected member answered that Alzheimer's is a subtype of dementia 80% of the time (compared to 61%; $p = 0.4604$), Alzheimer's is not part of the normal aging process at 95% (vs 83%; $p = 0.0967$), Alzheimer's worsens over time at 90% (compared to 89%; $p = 0.7915$), Alzheimer's has no cure at 85% (compared to 72%; $p = 0.6223$), and that Alzheimer's is a leading cause of death at 27% (compared to 39%;

$p = 0.7439$). While 60% of those who had a family member affected by the disease were knowledgeable, 56% of those without an affected member were deemed knowledgeable ($p = 0.0872$) (see Table 4).

Table 3. Awareness of young adults by sex

Evaluation Metric	Male (n = 11)	Female (n = 26)	p-value
Self-belief of being knowledgeable			0.4109
Yes	4 (36%)	15 (58%)	
Neutral	6 (55%)	10 (38%)	
No	1 (9%)	1 (4%)	
Alzheimer's is a subtype of dementia			0.5283
True			
False	7 (64%)	19 (73%)	
Not Sure	3 (27%) 1 (9%)	3 (12%) 4 (15%)	
Alzheimer's is normal with respect to aging			0.0212
True	3 (27%)	0 (0%)	
False	8 (73%)	25 (96%)	
Not Sure	0 (0%)	1 (4%)	
Alzheimer's worsens over time			0.4489
True	9 (82%)	24 (92%)	
False	2 (18%)	1 (4%)	
Not Sure	0 (0%)	1 (4%)	
No cure to Alzheimer's			0.0122
True	5 (46%)	24 (92%)	
False	3 (27%)	1 (4%)	
Not Sure	3 (27%)	1 (4%)	
Alzheimer's is leading cause of death			0.7438
True			
False	3 (27%)	10 (39%)	
Not Sure	4 (36%) 4 (36%)	10 (39%) 6 (23%)	
Overall Score			0.0084
Poor (1-2)	4 (36%)	0 (0%)	
Satisfactory (3)	3 (27%)	9 (35%)	
Knowledgeable (4-5)	4 (36%)	17 (65%)	

Table 4. Awareness of young adults with family members affected/not affected

Evaluation Metric	Affected (n = 20)	Not Affected (n = 18)	p-value
Self-belief of being knowledgeable			0.0665
Yes			
Neutral	14 (70%)	6 (33%)	
No	5 (25%) 1 (5%)	11 (61%) 1 (6%)	
Alzheimer's is a subtype of dementia			0.4604
True			
False	16 (80%)	11 (61%)	
Not Sure	2 (10%) 2 (10%)	4 (22%) 3 (17%)	
Alzheimer's is normal with respect to aging			0.0967
True	0 (0%)	3 (17%)	
False	19 (95%)	15 (83%)	

Not Sure	1 (5%)	0 (0%)	
Evaluation Metric	Affected (n = 20)	Not Affected (n = 18)	p-value
Alzheimer's worsens over time			0.7915
True			
False	18 (90%)	16 (89%)	
Not Sure	1 (5%)	2 (11%)	
	1 (5%)	0 (0%)	
No cure to Alzheimer's			0.6223
True	17 (85%)	13 (72%)	
False	1 (5%)	3 (17%)	
Not Sure	2 (10%)	2 (11%)	
Alzheimer's is leading cause of death			0.5469
True			
False	8 (40%)	5 (28%)	
Not Sure	6 (30%)	9 (50%)	
	6 (30%)	4 (22%)	
Overall Score			0.0872
Poor (1-2)	0 (0%)	4 (22%)	
Satisfactory (3)	8 (40%)	4 (22%)	
Knowledgeable (4-5)	12 (60%)	10 (56%)	

DISCUSSION

The initial self-reported knowledge level of the young adults of North Carolina was noted to be 53%, which is slightly lower than the actual awareness level of 58%. The proportion of the population with a family member affected by the disease was also 53%, suggesting that the population is hence adequately about the disease such that it can care for their family members.

This study revealed that there seems to be a trend that females are more knowledgeable than males with respect to the disease, and also that those with a family member affected by the disease are more aware. The observed difference between sexes validates a previous finding by Borean et al. among young adults in Toronto [4]. However, the novel finding of a difference in awareness between cohorts with affected/unaffected family members has not been found in prior studies [2-9]. Future studies should look to see whether the finding in this study is an anomaly.

This study was not without limitations, as with the prior studies of this nature [2-9]. The sample size of the study had good quality and quantity at times, but only lead to detection of trends rather than significant differences at other points - a large sample size would have mitigated this issue. Additionally, due to the nature of the quiz (online survey), there exists the possibility that participants could have employed reference resources to assist in their answers - this is unfortunately avoidable due to the medium of the survey, but was hopefully minimized by assuring participants that the quiz is an assessment of knowledge and should be answered honestly without help.

In conclusion, 58% of the young adults in North Carolina were knowledgeable. This is a higher proportion than the initial self-reported level and the percentage of the population that have a family member personally affected by the disease, both of which is 53%. This study did reveal that there seems to be a difference in awareness level between individuals with and without a family member suffering from Alzheimer's, which is a novel finding. Future studies

should look into determining whether this was an anomaly, and perhaps explain why this finding may exist.

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Chapter 237

AWARENESS OF ALZHEIMER'S DISEASE AMONG YOUNG ADULTS IN NEW YORK STATE, UNITED STATES

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ABSTRACT

Alzheimer's has no cure, but increased knowledge of the disease among family members of patients suffering from the disease may lead to improved standard of care and quality of life. The aim of this study was to examine Alzheimer's disease awareness levels in young adults in New York State, USA. A survey was designed to evaluate the awareness of this age group. The main objective of the survey was to determine the awareness of Alzheimer's disease across all young adults (regardless of age, sex and other background). Other objectives were to determine whether there existed any difference in knowledge across different subgroups - between men and women, between younger and older individuals, and between those with and without family members with Alzheimer's disease. 51% of the population had a family member affected by Alzheimer's disease. While only 47% of individuals believed that they were knowledgeable about the disease, 60% of participants were deemed to be relatively well-aware. There is a trend to suggest that young females in New York State are more well-informed about the disease than young males. There were statistically significant differences in awareness levels between individuals who had family members affected by Alzheimer's and those who had no known affected family members.

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INTRODUCTION

Alzheimer's disease is neurodegenerative disease that is associated with comorbidities and results in a subpar quality of life [1]. Alzheimer's has no cure, but increased knowledge of the disease among family members of patients suffering from Alzheimer's may lead to improved standard of care and quality of life [2].

Chow et al. [3] examined disease awareness among young adults in London, Canada. Only 48% of the cohort believed that they were knowledgeable about the disease, but a full three-quarters of all participants were well-aware. Less than one-third of the sample population actually had a family member affected by the disease, which, when considering overall awareness levels, might indicate a trend that young adults are adequately aware of Alzheimer's disease.

Several follow-up studies [4-8] have been conducted to explore this trend in different geographic regions. 60% of participants in a study in Kingston were knowledgeable, despite only 38% of the cohort believing to have a family member affected by the disease [4]. In Toronto, Borean et al. [5] reported similar results; 60% of young adults were well-informed regarding the disease's implications, with only 39% reporting familial ties to the disorder and 40% believing that they were knowledgeable.

While similarities exist between different geographic regions, there are still variations between distinct demographics. The aim of this study was to examine Alzheimer's disease awareness levels in young adults in New York State, United States.

SURVEY

A survey was designed to evaluate the awareness of young adults in New York State [9]. The first page had a consent form for the study; participants had the option to enter their email and receive a copy of the consent form, see chapter 2 [9]. After consenting to the study, participants completed three questions to collect relevant demographics - primary place of residence, age, and sex [9]; only those who recorded New York State as their place of residence were included in this study. The third page had six questions - the first being a reflection question and the next five being knowledge-based questions - a quiz about Alzheimer's disease [9]. The last page of the survey asked participants whether, to their knowledge, they have/had a family member affected by Alzheimer's; if they have/had, it also asked for how often they visit their relative [9].

The main objective of the survey was to determine the awareness of Alzheimer's disease, across all young adults (regardless of age, sex and other background). Other objectives were to determine whether there existed any difference in knowledge across different subgroups - between men and women, between younger and older young adults, and between those with and without family members with Alzheimer's disease.

Statistical Analysis

The same statistical analysis conducted by Chow et al. [3] was executed. Descriptive statistics were used to report the six items - 1 reflection and 5 knowledge questions - on page 3. For each participant, an overall score out of 5 was generated for the number of questions they correctly answered, with the answer key being: Alzheimer's Disease is a form of dementia - True; Alzheimer's is part of the normal aging process - False; Alzheimer's worsens over time - True; There is no cure for Alzheimer's, only treatments for symptoms - True; Alzheimer's is a leading cause of death - True. Participants with scores of 4 or 5 out of 5 were interpreted to be knowledgeable about Alzheimer's disease; those with 3 were marked as having satisfactory knowledge; those scoring 1 or 2 had poor awareness about the disease.

Subgroup analyses were conducted based ages of participants (under 20 years old, and 20 years old and older), sex (male and female), and their family's history with Alzheimer's disease (affected and not affected). Fisher-exact tests were conducted to determine whether there was a difference in awareness between these groups. P-values less than 0.05 were deemed to be statistically significant. All analyses were conducted using the Statistical Analysis Software (SAS Version 9.4 for Windows).

SURVEY FINDINGS

47 individuals consented and completed the questionnaire. 47% reported self-belief of being knowledgeable about the disease, while 43% reserved judgment regarding their knowledge and only 11% believed that they were not knowledgeable. Most participants (64%) correctly identified that Alzheimer's is a subtype of dementia, 85% understood that Alzheimer's is not normal with respect to aging, 96% were aware that Alzheimer's worsens over time, and 87% acknowledged that there is no cure to the disease. Only 28% of participants correctly responded that Alzheimer's disease is a leading cause of death. Overall, 60% of participants were knowledgeable, while 26% and 15% had satisfactory and poor awareness, respectively (see Table 1).

Under 20 Years Old vs 20 Years Old and above

39 of the 47 participants were under 20 years old, and 8 were 20 years old and older. Both cohorts have similar self-beliefs regarding personal awareness levels; 44% of individuals under 20 years old believed that they were knowledgeable about Alzheimer's compared to 63% of participants over 20 years old ($p=0.5406$). While not statistically significant, there is a trend to suggest that individuals under 20 years old are more knowledgeable of the fact that Alzheimer's disease is a form of dementia – 69% of individuals under 20 years old correctly responded to this statement, compared to only 38% of participants older than 20 years old ($p=0.1297$). Both age cohorts were equally aware that Alzheimer's disease is not normal with respect to the aging process, with 82% and 100% of the individuals in the under 20 years old and over 20 years old age groups correctly answering this question ($p=0.9999$). Individuals under 20 years old are more well-informed that

Alzheimer's worsens over time, with all (100%) participants in this cohort correctly identifying this statement as true, compared to just 75% of individuals older than 25 years old ($p=0.0259$). With respect to the question regarding if there is a cure to Alzheimer's, younger individuals are more aware that there is no cure to the disease; 92% of individuals in the under 20 years old cohort correctly answered this question, compared to only 63% of participants in the older group ($p=0.0069$). Only 28% and 25% of individuals in the under 20 years old and 20 years old or older cohorts correctly identified that Alzheimer's is a leading cause of death; no difference was noted ($p=0.1634$). Overall, both age groups were equally knowledgeable regarding Alzheimer's disease and its implications, with 64% and 38% of individuals in the younger and older cohorts, respectively, being generally knowledgeable about the disease ($p=0.3379$) (see Table 2).

Table 1. Awareness of all young adults

Evaluation Metric	All (n = 47)
Self-belief of being knowledgeable	
Yes	22 (47%)
Neutral	20 (43%)
No	5 (11%)
Alzheimer's is a subtype of dementia	
True	30 (64%)
False	8 (17%)
Not Sure	9 (19%)
Alzheimer's is normal with respect to aging	
True	3 (6%)
False	40 (85%)
Not Sure	4 (9%)
Alzheimer's worsens over time	
True	45 (96%)
False	2 (4%)
Not Sure	0 (0%)
No cure to Alzheimer's	
True	41 (87%)
False	3 (6%)
Not Sure	3 (6%)
Alzheimer's is leading cause of death	
True	13 (28%)
False	22 (47%)
Not Sure	12 (26%)
Overall Score	
Poor (1-2)	7 (15%)
Satisfactory (3)	12 (26%)
Knowledgeable (4-5)	28 (60%)

Males vs Females

11 respondents were female, 35 were male, and 1 preferred not to select a binary option. 45% of males and 46% of females believed that they were knowledgeable about Alzheimer's; no difference was noted ($p=0.9999$). 55% of males and 66% of females correctly identified that Alzheimer's is a subtype of dementia ($p=0.7894$). There is a strong trend to suggest that females are more aware than males that Alzheimer's is not a normal part of the aging process; while 91% of females correctly identified that Alzheimer's is abnormal, only 64% of males

correctly identified that the disorder is not a normal part of aging ($p=0.0689$). Females may also be more well aware than their male counterparts that Alzheimer's worsens over time; 100% of females correctly identified this, compared to only 82% of males ($p=0.0531$). There is a statistically significant difference between the sexes in terms their awareness of the incurable nature of the disease, with females being more knowledgeable than males; 94% of females correctly identified that there is no cure to Alzheimer's, compared to just 64% of males ($p=0.0102$). Only 36% of males and 26% of females reported that Alzheimer's is a leading cause of death ($p=0.8272$). While not statistically significant, there is a strong trend to suggest that females are more knowledgeable than males in terms of overall levels of disease awareness; 66% of females were knowledgeable about Alzheimer's disease while only 36% of males were well-informed ($p=0.0863$) (see Table 3).

Table 2. Awareness of young adults by age

Evaluation Metric	Under 20 Years Old (n = 39)	20 Years Old and Older (n = 8)	p-value
Self-belief of being knowledgeable			0.5406
Yes			
Neutral	17 (44%)	5 (63%)	
No	18 (46%)	2 (25%)	
	4 (10%)	1 (13%)	
Alzheimer's is a subtype of dementia			0.1297
True			
False	27 (69%)	3 (38%)	
Not Sure	5 (13%)	3 (38%)	
	7 (18%)	2 (25%)	
Alzheimer's is normal with respect to aging			0.9999
True	3 (8%)	0 (0%)	
False	32 (82%)	8 (100%)	
Not Sure	4 (10%)	0 (0%)	
Alzheimer's worsens over time			0.0259
True	39 (100%)	6 (75%)	
False	0 (0%)	2 (25%)	
Not Sure	0 (0%)	0 (0%)	
No cure to Alzheimer's			0.0069
True	36 (92%)	5 (63%)	
False	0 (0%)	3 (38%)	
Not Sure	3 (8%)	0 (0%)	
Alzheimer's is leading cause of death			0.1634
True			
False	11 (28%)	2 (25%)	
Not Sure	16 (41%)	6 (75%)	
	12 (31%)	0 (0%)	
Overall Score			0.3379
Poor (1-2)	5 (13%)	2 (25%)	
Satisfactory (3)	9 (23%)	3 (38%)	
Knowledgeable (4-5)	25 (64%)	3 (38%)	

Affected vs Not Affected

24 individuals had family members who were affected by Alzheimer's, whereas 23 did not have a family member to their knowledge afflicted by this disease. There was a statistically significant difference in self-belief and actual knowledge. 71% of those with an

affected family member classified themselves as being knowledgeable, compared to just 22% of those without any familial ties ($p=0.0023$). While not statistically significant, there is a strong trend to suggest that people with affected family members are more well aware that Alzheimer's is a form of dementia than those without affected family members; 79% of participants in the affected cohort correctly identified this compared to 48% of those in the unaffected group ($p=0.0889$). Both groups are equally well-aware that Alzheimer's is not normal with respect to aging, with 92% and 78% of individuals in the affected and not affected cohort, respectively, correctly identifying the abnormality associated with the disorder ($p=0.4016$). 100% of participants in the affected cohort and 91% of those in the unaffected cohort correctly identified that the disease worsens over time; no difference was noted ($p=0.2340$). Both cohorts were equally well aware that there is no cure to Alzheimer's, with 96% of those in the affected group and 78% of those in the unaffected group responding correctly to this question ($p=0.1305$). With respect to the question that tests knowledge of the lethality of Alzheimer's, statistically significant differences exist between the two groups; 33% of those in the affected group were well aware that Alzheimer's is a leading cause of death, while only 22% of participants in the unaffected cohort were able to correctly identify this ($p=0.0021$). Overall, participants in the affected group are more knowledgeable than individuals who have not had family members affected by the disease; 75% of those in the affected cohort were deemed to be generally knowledgeable about the disease, compared to just 43% of those in the unaffected group ($p=0.0072$) (see Table 4).

Table 3. Awareness of young adults by sex

Evaluation Metric	Male (n = 11)	Female (n = 35)	p-value
Self-belief of being knowledgeable			0.9999
Yes	5 (45%)	16 (46%)	
Neutral	5 (45%)	15 (43%)	
No	1 (9%)	4 (11%)	
Alzheimer's is a subtype of dementia			0.7894
True	6 (55%)	23 (66%)	
False	2 (18%)	6 (17%)	
Not Sure	3 (27%)	6 (17%)	
Alzheimer's is normal with respect to aging			0.0689
True			
False	2 (18%)	1 (3%)	
Not Sure	7 (64%)	32 (91%)	
	2 (18%)	2 (6%)	
Alzheimer's worsens over time			0.0531
True	9 (82%)	35 (100%)	
False	2 (18%)	0 (0%)	
Not Sure	0 (0%)	0 (0%)	
No cure to Alzheimer's			0.0102
True	7 (64%)	33 (94%)	
False	3 (27%)	0 (0%)	
Not Sure	1 (9%)	2 (6%)	
Alzheimer's is leading cause of death			0.8272
True	4 (36%)	9 (26%)	
False	5 (45%)	16 (46%)	
Not Sure	2 (18%)	10 (29%)	
Overall Score			0.0863
Poor (1-2)	4 (36%)	3 (9%)	
Satisfactory (3)	3 (27%)	9 (26%)	
Knowledgeable (4-5)	4 (36%)	23 (66%)	

Table 4. Awareness of young adults with family members affected/not affected

Evaluation Metric	Affected (n = 24)	Not Affected (n = 23)	p-value
Self-belief of being knowledgeable			0.0023
Yes	17 (71%)	5 (22%)	
Neutral	6 (25%)	14 (61%)	
No	1 (4%)	4 (17%)	
Alzheimer's is a subtype of dementia			0.0889
True	19 (79%)	11 (48%)	
False	2 (8%)	6 (26%)	
Not Sure	3 (13%)	6 (26%)	
Alzheimer's is normal with respect to aging			0.4016
True			
False	1 (4%)	2 (9%)	
Not Sure	22 (92%)	18 (78%)	
	1 (4%)	3 (13%)	
Alzheimer's worsens over time			0.2340
True	24 (100%)	21(91%)	
False	0 (0%)	2 (9%)	
Not Sure	0 (0%)	0 (0%)	
No cure to Alzheimer's			0.1305
True	23 (96%)	18 (78%)	
False	0 (0%)	3 (13%)	
Not Sure	1 (4%)	2 (9%)	
Alzheimer's is leading cause of death			0.0021
True	8 (33%)	5 (22%)	
False	15 (63%)	7 (30%)	
Not Sure	1 (4%)	11 (48%)	
Overall Score			0.0072
Poor (1-2)	0 (0%)	7 (30%)	
Satisfactory (3)	6 (25%)	6 (26%)	
Knowledgeable (4-5)	18 (75%)	10 (43%)	

DISCUSSION

Only 47% of individuals believed that they were knowledgeable with respect to Alzheimer's disease, but the proportion of individuals who are actually knowledgeable is significantly higher (60%). Given that approximately half (51%) of respondents actually have had family members affected by the disease, it is likely that the young adult population in New York State is generally well-aware about Alzheimer's disease and its implications.

This study yielded results similar to prior studies at different geographic locations in that overall awareness levels were larger than the proportion of individuals with affected members [2-6]. This is reassuring in that it strongly suggests that the general young adult population possesses adequate awareness and knowledge about Alzheimer's disease. This study also appears to validate other previous findings regarding sex differences [3, 5]. While not statistically significant, there is a strong trend to suggest that young females in New York State are generally more well-informed about the implications of the disease than young males. Further research should investigate why these sex differences exist, and what can be done to increase overall male awareness levels.

This study provides evidence that young adults with affected family members are more knowledgeable about the disease than their unaffected counterparts. This trend is interesting, but perhaps understandable given that an individual is probably more likely to be willing to

learn about a health condition which he or she has been readily exposed to. Future studies should search for validation of this trend in other geographic locations, and programs should be devised to better inform young adults without familial ties to the disease about its nature and implications.

This study was not without limitations. The sample size of the study had good quality and quantity at times, but only lead to detection of trends rather than significant differences at other points - a large sample size would have mitigated this issue. Additionally, there exists the possibility that participants could have employed reference resources to assist in their answers - this is unfortunately avoidable due to the medium of the survey, but was hopefully minimized by assuring participants that the quiz is an assessment of knowledge and should be answered honestly without help.

In conclusion, 51% of the population had a family member affected by Alzheimer's disease. While only 47% of individuals believed that they were knowledgeable about the disease, 60% of participants were deemed to be relatively well-aware. There is a trend to suggest that young females in New York State are more well-informed about the disease than young males. There were statistically significant differences in awareness levels between individuals who had family members affected by Alzheimer's and those who had no known affected family members. Follow up studies should look to validate these trends in different regions across the globe.

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Chapter 238

AWARENESS OF ALZHEIMER'S DISEASE AMONG YOUNG ADULTS IN DUBLIN, IRELAND

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ABSTRACT

There have been numerous studies published that have looked into the awareness level of Alzheimer's disease amongst the young adult population. The trend seems to be similar in different geographic regions, but there does exist variation between data. It would be interesting to see how different regions vary, and perhaps advocate for positive change, if necessary. The aim of this study was to examine the awareness level of young adults in Dublin, Ireland, with respect to Alzheimer's disease. A survey was designed to evaluate the awareness of young adults. A total of 36 people consented and completed the questionnaire; 18 were under 20 years old and 18 were 20 years old or older, 10 were male and 26 were female, while 12 (29%) had family members affected by the disease and 24 (71%) did not. 77% of the participants were well-aware of the disease, although only 44% believed they were. It seems that the young adult population is adequately aware of the disease, and may be able to improve standard of care as a result of higher knowledgeability. Follow-up studies should look into whether this trend transcends into other regions of the globe, and to determine how the high level of awareness can be mobilized to improve patient care.

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INTRODUCTION

While healthcare professionals have developed many novel tools to improve the standard of care for Alzheimer's patients, awareness and knowledge about the disease by family members could further improve the quality of life of patients [1]. There have been numerous studies published that have looked into the awareness level of Alzheimer's disease amongst the young adult population.

The first study published looked into the awareness level of young adults in London, Canada [2]. The study concluded that a favourable 75% of the cohort was well-aware of the disease, while only 48% believed that they were knowledgeable. When these statistics are interpreted in lieu of the fact that 31% of the sample population had a family member affected by Alzheimer's disease, there seems to be a trend that young adults are adequately aware of the disease.

Four follow-up studies were conducted among young adults across the Canadian Province of Ontario [3-6]. In Kingston, 60% of the population was knowledgeable, compared to the 58% that believed they were, while 38% of the population had a family member affected by the disease [3]. Among young adults in Toronto, 39% had familial ties and 40% believed they were knowledgeable, yet it turned out that 60% were well-aware of the disease [4]. A similar trend was noted among the young adult populations in Ottawa (46% with family members affected, 69% believed they were knowledgeable, and 85% were knowledgeable according to the assessment tool) [5].

Viehweger et al. [7] studied the awareness level among young adults in the Canadian Province of Saskatchewan. While they reported a similar trend - higher awareness level (70%) than perceived awareness (51%) as well as the portion of individuals with affected family members (19%) [7] - they showed some variation in their results. Based on the sample size of the study, there is a lower proportion of individuals with family members affected by Alzheimer's disease.

The trend seems to be similar in different geographic regions, but there does exist variation between data. It would be interesting to see how different regions vary, and perhaps advocate for positive change, if necessary. The aim of this study was to study the awareness level of young adults in Dublin, Ireland, with respect to Alzheimer's disease.

OUR STUDY

A survey was designed to evaluate the awareness of young adults in Dublin, Ireland, see chapter 2 [2, 8]. The first page had a consent form for the study; participants had the option to enter their email and receive a copy of the consent form [8]. After consenting to the study, participants completed three questions to collect relevant demographics - primary place of residence, age and sex [8]; only those who recorded Dublin, Ireland, as their place of residence was included in this study. The third page had six questions, with the first being a reflection question and the next five being knowledge-based questions - a quiz about Alzheimer's disease [8]. The last page of the survey asked participants whether, to their knowledge, they have/had a family member affected by Alzheimer's; if they have/had, it also asked for how often they visit their relative [8].

The primary objective of the survey was to determine the awareness of Alzheimer's disease, across all young adults (regardless of age, sex and other background). The secondary objectives were to determine whether there existed any difference in knowledge across different subgroups - between men and women, between younger and older young adults, and between those with and without family members with Alzheimer's disease.

Statistical Analysis

The same statistical analysis conducted for the London study [2] was carried out in this setting. Descriptive statistics were used to report the six items - 1 reflection and 5 knowledge questions - on page 3. For each participant, an overall score out of 5 was generated for the number of questions they correctly answered, with the answer key being: Alzheimer's Disease is a form of dementia - True; Alzheimer's is part of the normal aging process - False; Alzheimer's worsens over time - True; There is no cure for Alzheimer's only treatments for symptoms - True; Alzheimer's is a leading cause of death - True. Participants with scores of 4 or 5 out of 5 were interpreted to be knowledgeable about Alzheimer's disease; those with 3 were marked as having satisfactory knowledge; those scoring 1 or 2 had poor awareness about the disease.

Subgroup analyses were conducted based ages of participants (under 20 years old, and 20 years old and older), sex (male and female), and their family's history with Alzheimer's disease (affected and not affected). Fisher-exact tests were conducted to determine whether there was a difference in awareness between these groups. P-values less than 0.05 were deemed to be statistically significant. All analyses were conducted using the Statistical Analysis Software (SAS Version 9.4 for Windows).

What Did We Find?

A total of 36 people consented and completed the questionnaire. Of these 36 participants, 47% reserved judgement about their belief of their knowledgeability, 44% believed that they are knowledgeable, and 8% acknowledged that they are not knowledgeable. 83% correctly identified that Alzheimer's disease is a subtype of dementia, while the remaining 17% of individuals, evenly-split, believed that Alzheimer's is not a subtype and reserved judgement. 3% were not sure whether Alzheimer's is a normal process with respect to aging, 16% incorrectly remarked that it was part of the normal aging process, and the remaining 81% accurately answered it was not normal. An overwhelming majority, 92%, recognized that Alzheimer's worsens over time, with 3% and 5% believing that it does not and are not sure, respectively. 88% of participants correctly answered that there is no cure to Alzheimer's, and 3% and 8% indicated there is a cure and that they were unsure. A majority of respondents noted that they are unsure whether Alzheimer's is a leading cause of death, while 25% and 22% incorrectly and correctly responded to the answer. Overall, 77% of participants were deemed knowledgeable, while 19% and 3% were noted as having satisfactory and poor knowledge, respectively (see Table 1).

Table 1. Awareness of all young adults

Evaluation Metric	All (n = 36)
Self-belief of being knowledgeable	
Yes	16 (44%)
Neutral	17 (47%)
No	3 (8%)
Alzheimer's is a subtype of dementia	
True	30 (83%)
False	3 (8%)
Not Sure	3 (8%)
Alzheimer's is normal with respect to aging	
True	6 (16%)
False	29 (81%)
Not Sure	1 (3%)
Alzheimer's worsens over time	
True	33 (92%)
False	1 (3%)
Not Sure	2 (5%)
No cure to Alzheimer's	
True	32 (88%)
False	1 (3%)
Not Sure	3 (8%)
Alzheimer's is leading cause of death	
True	8 (22%)
False	9 (25%)
Not Sure	19 (53%)
Overall Score	
Poor (1-2)	1 (3%)
Satisfactory (3)	7 (19%)
Knowledgeable (4-5)	28 (77%)

Table 2. Awareness of young adults by age

Evaluation Metric	Under 20 Years Old (n = 18)	20 Years Old and Older (n = 18)	p-value
Self-belief of being knowledgeable			0.9999
Yes	8 (44%)	8 (44%)	
Neutral	9 (50%)	8 (44%)	
No	1 (5%)	2 (11%)	
Alzheimer's is a subtype of dementia			0.9999
True			
False	15 (83%)	15 (83%)	
Not Sure	2 (11%)	1 (5%)	
	1 (5%)	2 (11%)	
Alzheimer's is normal with respect to aging			0.1774
True			
False	5 (27%)	1 (5%)	
Not Sure	13 (72%)	16 (88%)	
	0 (0%)	1 (5%)	
Alzheimer's worsens over time			0.9999
True	16 (88%)	17 (94%)	
False	1 (5%)	0 (0%)	
Not Sure	1 (5%)	1 (5%)	
No cure to Alzheimer's			0.2286
True	17 (94%)	15 (83%)	
False	1 (5%)	0 (0%)	
Not Sure	0 (0%)	3 (16%)	
Alzheimer's is leading cause of death			0.7486
True			
False	3 (16%)	5 (27%)	
Not Sure	5 (27%)	4 (22%)	
	10 (55%)	9 (50%)	
Overall Score			0.9999
Poor (1-2)	1 (5%)	0 (0%)	
Satisfactory (3)	3 (17%)	4 (22%)	
Knowledgeable (4-5)	14 (78%)	14 (78%)	

Under 20 Years Old vs 20 Years Old and above

Of the 36 participants, 18 people were under 20 years old and 18 individuals were 20 years old and older. There was no difference in self-belief level ($p=0.9999$), with 44% of both groups remarking that they are knowledgeable about Alzheimer's disease. There was also no difference in answers between the age groups with respect to whether Alzheimer's is a subtype of dementia ($p=0.9999$), with 83% of both groups correctly identifying that Alzheimer's disease is a subtype of dementia. It seems that the older cohort was more aware that Alzheimer's is not part of the normal aging process (88%, compared to 72%) ($p=0.1774$). There was also no difference in knowledge with respect to whether the disease worsens over time ($p=0.9999$); 5% of those under 20 years old and 5% of those 20 years and older are not too sure about the answer for the question. While 94% of those below 20 years old correctly recognized that there is no cure for Alzheimer's disease, only 83% of those 20 years and older similarly responded to the question ($p=0.2286$). For the question pertaining to whether Alzheimer's is a leading cause of death, 27% and 22% of those under and above 20 years old, respectively, incorrectly believed that it is not a leading cause of death ($p=0.7486$). Overall, there was no difference in knowledge level, with 78% of those under 20 years old and 78% of those 20 years old and above, being deemed knowledgeable ($p=0.9999$) (see Table 2).

Males vs Females

12 of the 36 respondents were male, with the other 24 identifying themselves as females. Males and females had similar self-belief levels ($p=0.5877$), with 42% of males and 46% of females proclaiming that they are knowledgeable. There was a trend that women are more aware that Alzheimer's is a subtype of dementia ($p=0.1032$), with 92% of females correctly remarking that it is a subtype of dementia as opposed to 66% of males. 83% and 79% of males and females, respectively, answered that Alzheimer's is not normal with respect to aging ($p=0.9999$). 83% of males and 96% of females answered that Alzheimer's worsens over time ($p=0.2527$). 92% of males and 88% of females recognized that there is no cure for Alzheimer's ($p=0.2011$). There was no difference in responses between males and females with respect to whether Alzheimer's is a leading cause of death ($p=0.3289$); 16% of males and 25% of females correctly remarked that Alzheimer's is a leading cause of death. Overall, 83% of males and 75% of females received a score of 4 or 5 out of 5, hence being classified as knowledgeable ($p=0.9999$) (see Table 3).

Affected vs Not Affected

Of the 36 participants, 10 have a family member affected by Alzheimer's disease to their knowledge. Those with family members affected Alzheimer's disease were more likely to rate themselves as knowledgeable (90% compared to 27%; $p=0.0024$). There was no difference in responses between the cohorts with respect to any of the five knowledge questions: Alzheimer's as a subtype of dementia (90% for affected vs 81% for those not affected correctly answered it is a subtype; $p=0.7928$); Alzheimer's as a normal process of

aging (70% vs 85%, respectively, properly answered it was not normal; $p=0.5103$); Alzheimer's worsens over time (90% and 92%, respectively, agreed with the statement; $p=0.3324$); cure for Alzheimer's (80% and 92%, respectively remarked that there is no cure; $p=0.4152$); Alzheimer's as a leading cause of death (30% and 19%, respectively, correctly identified it is a leading cause of death; $p=0.6926$). There was no difference in overall score between those with family members affected and not affected by the disease; 60% of those affected and 85% of those not affected by the disease received a score to be deemed as knowledgeable ($p=0.2066$) (see Table 4).

Table 3. Awareness of young adults by sex

Evaluation Metric	Male (n = 12)	Female (n = 24)	p-value
Self-belief of being knowledgeable			0.5877
Yes	5 (42%)	11 (46%)	
Neutral	7 (58%)	10 (42%)	
No	0 (0%)	3 (13%)	
Alzheimer's is a subtype of dementia			0.1032
True	8 (67%)	22 (92%)	
False	2 (17%)	1 (4%)	
Not Sure	2 (17%)	1 (4%)	
Alzheimer's is normal with respect to aging			0.9999
True			
False	2 (16%)	4 (16%)	
Not Sure	10 (83%)	19 (79%)	
	0 (0%)	1 (4%)	
Alzheimer's worsens over time			0.2527
True	10 (83%)	23 (96%)	
False	1 (8%)	0 (0%)	
Not Sure	1 (8%)	1 (4%)	
No cure to Alzheimer's			0.2011
True	11 (92%)	21 (88%)	
False	1 (8%)	0 (0%)	
Not Sure	0 (0%)	3 (12%)	
Alzheimer's is leading cause of death			0.3289
True	2 (16%)	6 (25%)	
False	5 (42%)	4 (16%)	
Not Sure	5 (42%)	14 (58%)	
Overall Score			0.9999
Poor (1-2)	0 (0%)	1 (4%)	
Satisfactory (3)	2 (17%)	5 (21%)	
Knowledgeable (4-5)	10 (83%)	18 (75%)	

DISCUSSION

While only 44% of participants believed that they were knowledgeable about Alzheimer's disease, their responses to the questionnaire showed that in fact 77% were well-aware of the disease. These results show that the trend reported by studies in Canada [2-7] are also observed among young adults in Dublin, Ireland.

The results revealed that only 29% of the population had a family member affected by Alzheimer's disease, which is lower than both the self-belief rate and the actual awareness rate. These results seem to indicate that the young adult population is adequately aware, as the

awareness level is higher than the incidence rate. The data validates the trend of all but one study [6], where the awareness level is higher than the incidence rate of Alzheimer's disease.

Table 4. Awareness of young adults with family members affected/not affected

Evaluation Metric	Affected (n = 10)	Not Affected (n = 26)	p-value
Self-belief of being knowledgeable			0.0024
Yes	9 (90%)	7 (27%)	
Neutral	1(10%)	16 (62%)	
No	0 (0%)	3 (12%)	
Alzheimer's is a subtype of dementia			0.7928
True	9 (90%)	21 (81%)	
False	0 (0%)	3 (12%)	
Not Sure	1(10%)	2 (8%)	
Alzheimer's is normal with respect to aging			0.5103
True			
False	3 (30%)	3 (12%)	
Not Sure	7 (70%)	22 (85%)	
	0 (0%)	1 (4%)	
Alzheimer's worsens over time			0.3324
True	9 (90%)	24 (92%)	
False	1 (10%)	0 (0%)	
Not Sure	0 (0%)	2 (8%)	
No cure to Alzheimer's			0.4152
True	8 (80%)	24 (92%)	
False	1 (10%)	0 (0%)	
Not Sure	1 (10%)	2 (8%)	
Alzheimer's is leading cause of death			0.6926
True	3 (30%)	5 (19%)	
False	3 (30%)	6 (23%)	
Not Sure	4 (40%)	15 (58%)	
Overall Score			0.2066
Poor (1-2)	1 (10%)	0 (0%)	
Satisfactory (3)	3 (30%)	4 (25%)	
Knowledgeable (4-5)	6 (60%)	22 (85%)	

This study was not without limitations. The sample size of the study had good quality and quantity at times, but only lead to detection of trends rather than significant differences at other points - a large sample size would have mitigated this issue. Additionally, there exists the possibility that participants could have employed reference resources to assist in their answers - this is unfortunately avoidable due to the medium of the survey, but was hopefully minimized by assuring participants that the quiz is an assessment of knowledge and should be answered honestly without help.

In conclusion, 29% of the population had a family member affected by Alzheimer's disease. 77% of the participants were well-aware of the disease, although only 44% of them believed so. It seems that the young adult population is adequately aware of the disease, and may be able to improve standard of care as a result of higher knowledgeability. Follow-up studies should look into whether this trend transcends into other regions of the globe, and to determine how the high level of awareness can be mobilized to improve patient care.

ACKNOWLEDGMENT

We would like to thank all of those who participated in the questionnaire.

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Chapter 239

AWARENESS OF ALZHEIMER'S DISEASE AMONG YOUNG ADULTS IN ASIA

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ABSTRACT

Family members of patients suffering from Alzheimer's disease may help healthcare professionals improve standard of care and hence quality of life by being knowledgeable about the disease. The aim of this study was to study the awareness level of young adults in Asia with respect to Alzheimer's disease. 14 individuals consented and completed a questionnaire, with their primary location of residence ranging from Taiwan to China to Dubai. 42% of the population had a family member affected by Alzheimer's disease. Exactly 42% of the participants were well-aware of the disease, although only 21% of them believed so. This trend is slightly different than those determined in previous studies, and this may be a result of the different geographical region and different education/awareness levels. Follow-up studies should look into whether this different trend transcends into other regions of the globe.

INTRODUCTION

Family members of patients suffering from Alzheimer's disease may help healthcare professionals improve standard of care and hence quality of life by being knowledgeable about the disease [1].

A study by Chow et al. [2] examined the awareness level of young adults in London, Canada. The study found that 75% of the cohort was well-aware of the disease, while only

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48% believed that they were knowledgeable. Given that 31% of the sample population had a family member affected by Alzheimer's disease, there seems to be a trend that young adults are adequately aware of the disease.

Multiple follow-up studies [3-8] have been conducted to validate the trend in different demographic regions. In Kingston, 60% of the population was knowledgeable, compared to the 58% that believed they were and the 38% who had a family member affected by the disease [3]. Borean et al. [4] also verified the trend, as while 39% had familial ties and 40% believed they were knowledgeable, it turned out that 60% were aware of the disease.

The trend seems to be similar in different geographic regions [8], but there exists variation between different regions. The aim of this study was to study the awareness level of young adults in Asia with respect to Alzheimer's disease.

OUR STUDY

A survey was designed to evaluate the awareness of young adults in Asia, see chapter 2 [2, 9]. The first page had a consent form for the study; participants had the option to enter their email and receive a copy of the consent form [9]. After consenting to the study, participants completed three questions to collect relevant demographics - primary place of residence, age and sex [9]; only those who recorded Asia as their place of residence were included in this study. The third page had six questions, with the first being a reflection question and the next five being knowledge-based questions - a quiz about Alzheimer's disease [9]. The last page of the survey asked participants whether, to their knowledge, they have/had a family member affected by Alzheimer's; if they have/had, it also asked for how often they visit their affected relative [9].

The main objective of the survey was to determine the awareness of Alzheimer's disease, across all young adults (regardless of age, sex and other background). Other objectives were to determine whether there existed any difference in knowledge across different subgroups - between men and women, between younger and older young adults, and between those with and without family members with Alzheimer's disease.

Statistical Analysis

The same statistical analysis conducted by Chow et al. [2] was executed. Descriptive statistics were used to report the six items - 1 reflection and 5 knowledge questions - on page 3. For each participant, an overall score out of 5 was generated for the number of questions they correctly answered, with the answer key being: Alzheimer's Disease is a form of dementia - True; Alzheimer's is part of the normal aging process - False; Alzheimer's worsens over time - True; There is no cure for Alzheimer's only treatments for symptoms - True; Alzheimer's is a leading cause of death - True. Participants with scores of 4 or 5 out of 5 were interpreted to be knowledgeable about Alzheimer's disease; those with 3 were marked as having satisfactory knowledge; those scoring 1 or 2 had poor awareness about the disease.

Subgroup analyses were conducted based on ages of participants (under 20 years old, and 20 years old and older), sex (male and female), and their family's history with Alzheimer's

disease (affected and not affected). Fisher-exact tests were conducted to determine whether there was a difference in awareness between these groups. P-values less than 0.05 were deemed to be statistically significant. All analyses were conducted using the Statistical Analysis Software (SAS Version 9.4 for Windows).

OUR FINDINGS

14 individuals consented and completed the questionnaire, with their primary location of residence ranging from Taiwan to China to Dubai. 71% reserved judgement about whether they were knowledgeable or not knowledgeable about the disease, with only 21% believing that they are indeed knowledgeable. A majority (57%) of participants correctly answered that Alzheimer's is a subtype of dementia, 79% responded that Alzheimer's is not normal with respect to the aging process, 93% acknowledged that Alzheimer's worsens over time, and 93% noted that there is no cure to Alzheimer's. Only 21% of respondents correctly noted that Alzheimer's is a leading cause of death. Overall, 42% of participants were knowledgeable, while 50% and 7% had satisfactory and poor awareness, respectively (see Table 1).

Under 20 Years Old vs 20 Years Old and above

4 of the 14 participants were under 20 years old, and 10 were 20 years old and older. There were no differences in responses between the two age groups. While 56% of those 20 years old and older refused to comment about their level of awareness, 100% of those under 20 years of age withdrew their judgement ($p=0.3257$). 60% and 56% of the younger and older cohort, respectively, recognized that Alzheimer's is a subtype of dementia ($p=0.2867$). 80% and 78% of the two groups, respectively, acknowledged that Alzheimer's is not part of the normal aging process ($p=0.9999$). With respect to the question of whether there is a cure for Alzheimer's, 80% of the younger cohort and 100% of the older cohort recognized that there is no cure ($p=0.3571$). The majority of the respondents failed to recognize that Alzheimer's is a leading cause of death, with 60% and 56% falsely believing it is not ($p=0.2867$). Overall, 60% and 33% of the younger and older cohort, respectively, were deemed knowledgeable ($p=0.1608$) (see Table 2).

Males vs Females

Of the 14 respondents, 7 were male and 7 were female. 71% of males and 71% of females remained neutral about they were knowledgeable about Alzheimer's disease ($p=0.9999$). 29% and 14% of males and females, respectively, answered that Alzheimer's is a subtype of dementia ($p=0.1434$). Among the females, 100% responded that Alzheimer's is not part of the normal aging process (vs 57% for males; $p=0.1932$), 86% answered that Alzheimer's worsens over time (compared to 100% for males; $p=0.9999$), 100% acknowledged that there is no cure to Alzheimer's (vs 86% for males; $p=0.9999$), and only 29% correctly recognized that Alzheimer's is a leading cause of death (compared to 14% for

males; $p=0.9999$). There was a trend that females are more knowledgeable than males about Alzheimer's disease, with 71% deemed as knowledgeable compared to 14% among males ($p=0.1026$) (see Table 3).

Table 1. Awareness of all young adults

Evaluation Metric	All (n = 14)
Self-belief of being knowledgeable	
Yes	3 (21%)
Neutral	10 (71%)
No	1 (7%)
Alzheimer's is a subtype of dementia	
True	8 (57%)
False	3 (21%)
Not Sure	3 (21%)
Alzheimer's is normal with respect to aging	
True	2 (14%)
False	11 (79%)
Not Sure	1 (7%)
Alzheimer's worsens over time	
True	13 (93%)
False	1 (7%)
Not Sure	0 (0%)
No cure to Alzheimer's	
True	13 (93%)
False	1 (7%)
Not Sure	0 (0%)
Alzheimer's is leading cause of death	
True	3 (21%)
False	8 (57%)
Not Sure	3 (21%)
Overall Score	
Poor (1-2)	1 (7%)
Satisfactory (3)	7 (50%)
Knowledgeable (4-5)	6 (42%)

Table 2. Awareness of young adults by age

Evaluation Metric	Under 20 Years Old (n = 5)	20 Years Old and Older (n = 9)	p-value
Self-belief of being knowledgeable			0.3257
Yes	0 (0%)	3 (33%)	
Neutral	5 (100%)	5 (56%)	
No	0 (0%)	1 (11%)	
Alzheimer's is a subtype of dementia			0.2867
True	3 (60%)	5 (56%)	
False	0 (0%)	3 (33%)	
Not Sure	2 (40%)	1 (11%)	
Alzheimer's is normal with respect to aging			0.9999
True			
False	1 (20%)	1 (11%)	
Not Sure	4 (80%)	7 (78%)	
	0 (0%)	1 (11%)	
Alzheimer's worsens over time			0.9999
True	5 (100%)	8 (89%)	
False	0 (0%)	1 (11%)	
Not Sure	0 (0%)	0 (0%)	
No cure to Alzheimer's			0.3571
True	4 (80%)	9 (100%)	
False	1 (20%)	0 (0%)	
Not Sure	0 (0%)	0 (0%)	

Evaluation Metric	Under 20 Years Old (n = 5)	20 Years Old and Older (n = 9)	p-value
Alzheimer's is leading cause of death			0.2867
True	0 (0%)	3 (33%)	
False	3 (60%)	5 (56%)	
Not Sure	2 (40%)	1 (11%)	
Overall Score			0.1608
Poor (1-2)	1 (20%)	0 (0%)	
Satisfactory (3)	1 (20%)	6 (67%)	
Knowledgeable (4-5)	3 (60%)	3 (33%)	

Table 3. Awareness of young adults by sex

Evaluation Metric	Male (n = 7)	Female (n = 7)	p-value
Self-belief of being knowledgeable			0.9999
Yes	2 (29%)	1 (14%)	
Neutral	5 (71%)	5 (71%)	
No	0 (0%)	1 (14%)	
Alzheimer's is a subtype of dementia			0.1434
True	2 (29%)	6 (86%)	
False	2 (29%)	1 (14%)	
Not Sure	3 (43%)	0 (0%)	
Alzheimer's is normal with respect to aging			0.1923
True	2 (29%)	0 (0%)	
False	4 (57%)	7 (100%)	
Not Sure	1 (14%)	0 (0%)	
Alzheimer's worsens over time			0.9999
True	7 (100%)	6 (86%)	
False	0 (0%)	1 (14%)	
Not Sure	0 (0%)	0 (0%)	
No cure to Alzheimer's			0.9999
True	6 (86%)	7 (100%)	
False	1 (14%)	0 (0%)	
Not Sure	0 (0%)	0 (0%)	
Alzheimer's is leading cause of death			0.9999
True	1 (14%)	2 (29%)	
False	4 (57%)	4 (57%)	
Not Sure	2 (29%)	1 (14%)	
Overall Score			0.1026
Poor (1-2)	1 (14%)	0 (0%)	
Satisfactory (3)	5 (71%)	2 (29%)	
Knowledgeable (4-5)	1 (14%)	5 (71%)	

Affected vs Not Affected

6 had family members who were affected by Alzheimer's disease, whereas 8 did not have a family member to their knowledge afflicted by the disease. There was no difference in self-belief and actual knowledge. 88% of those not affected and 50% of those affected did not classify themselves as knowledgeable or not unknowledgeable ($p=0.3287$). With respect to the question of whether Alzheimer's is a subtype of dementia, 50% and 63% of those affected and unaffected, respectively, acknowledged that it is a subtype ($p=0.7902$). 67% and 88% of the same cohorts, respectively, noted that Alzheimer's is not normal with respect to aging ($p=0.6923$). 100% of those unaffected noted that Alzheimer's worsens over time (compared to 83% for those affected; $p=0.4286$) and that there is no cure to Alzheimer's (compared to

83% for those affected; $p=0.4286$). 33% of those affected and 13% of those unaffected noted that Alzheimer's is a leading cause of death ($p=0.7902$). Overall, 50% of those affected and unaffected had satisfactory knowledge ($p=0.7669$) (see Table 4).

Table 4. Awareness of young adults with family members affected/not affected

Evaluation Metric	Affected (n = 6)	Not Affected (n = 8)	p-value
Self-belief of being knowledgeable			0.3287
Yes	2 (33%)	1 (13%)	
Neutral	3 (50%)	7 (88%)	
No	1 (17%)	0 (0%)	
Alzheimer's is a subtype of dementia			0.7902
True	3 (50%)	5 (63%)	
False	2 (33%)	1 (13%)	
Not Sure	1 (17%)	2 (25%)	
Alzheimer's is normal with respect to aging			0.6923
True	1 (17%)	1 (13%)	
False	4 (67%)	7 (88%)	
Not Sure	1 (17%)	0 (0%)	
Alzheimer's worsens over time			0.4286
True	5 (83%)	8 (100%)	
False	1 (17%)	0 (0%)	
Not Sure	0 (0%)	0 (0%)	
No cure to Alzheimer's			0.4286
True	5 (83%)	8 (100%)	
False	1 (17%)	0 (0%)	
Not Sure	0 (0%)	0 (0%)	
Alzheimer's is leading cause of death			0.7902
True	2 (33%)	1 (13%)	
False	3 (50%)	5 (63%)	
Not Sure	1 (17%)	2 (25%)	
Overall Score			0.7669
Poor (1-2)	1 (17%)	0 (0%)	
Satisfactory (3)	3 (50%)	4 (50%)	
Knowledgeable (4-5)	2 (33%)	4 (50%)	

DISCUSSION

21% of participants believed that they were knowledgeable with respect to Alzheimer's disease; according to the knowledge questions of the survey, 42% turned out to be aware of the disease. Given that 42% of respondents had family members affected by the disease, it seems that the young adult population of Asia is adequately aware.

The data reveals that there is not a surplus of individuals who are aware of the Alzheimer's disease. While prior studies [2-6] have yielded higher proportions of individuals with awareness as opposed to affected family members, this study shows that the proportions are just equal. This may be a result of different educational and medical systems, as well as different publicity levels of the disease, which may lead to different awareness levels.

This study was not without limitations. As with prior studies [6], the sample size of the study had good quality and quantity at times, but only lead to detection of trends rather than significant differences at other points - a large sample size would have mitigated this issue. Additionally, there exists the possibility that participants could have employed reference

resources to assist in their answers - this is unfortunately avoidable due to the medium of the survey, but was hopefully minimized by assuring participants that the quiz is an assessment of knowledge and should be answered honestly without help.

In conclusion, 42% of the population had a family member affected by Alzheimer's disease. Exactly 42% of the participants were well-aware of the disease, although only 21% of them believed so. This trend is slightly different than those determined in previous studies, and this may be a result of the different geographical region and different education/awareness levels. Follow-up studies should look into whether this different trend transcends into other regions of the globe.

ACKNOWLEDGMENT

We would like to thank all of those who participated in the questionnaire.

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Chapter 240

YOUNG ADULTS AND AWARENESS OF ALZHEIMER'S DISEASE: A META-ANALYSIS

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ABSTRACT

Studies have looked the awareness level of young adults across the globe. The aim of this review was to identify existing literature and synthesize the data to observe if there are any overarching trends between young adults in various locations. A literature search was conducted in many databases, such as Ovid MEDLINE and OLDMEDLINE, Embase Classic and Embase, PsycINFO. Relevant studies were screened to determine whether it reported about awareness level of young adults with respect to Alzheimer's disease. The extracted endpoints were: self-belief levels of awareness, and actual awareness levels based on scores of knowledge questions. A total of 12 studies were identified to be included in the meta-analysis. 44% of young adults perceived themselves as knowledgeable, which is lower than the actual rate of 62% unsheathed by the literature. There exist variations between geographic regions on awareness level: American young adults were the least knowledgeable, but were more knowledgeable about certain questions (i.e., recognizing that Alzheimer's is not normal with respect to aging). However, since the review did not employ any statistical analysis, it is difficult to interpret whether the variations are significant. What is known for sure is that it seems that young adults are much more aware and knowledgeable about Alzheimer's disease than they thought they were.

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INTRODUCTION

Tools have been developed for healthcare professionals to improve quality of care for dementia and Alzheimer's patients [1]. However, this is not a perfect solution. Since there is no cure for Alzheimer's disease on the horizon, another method to improve quality of life for patients would be to increase awareness of the disease amongst family members to have more conscientious caregivers [2].

Studies have looked the awareness level of young adults across the globe. For example, 75% of young adults in London, Canada, have been reported to be well-aware of the disease, but only 48% believed that they were knowledgeable [3]. The aim of this review was to identify existing literature and synthesize the data to observe if there are any overarching trends between young adults in various locations.

LITERATURE SEARCH

A literature search was conducted in databases, such as Ovid MEDLINE, OLDMEDLINE, Embase Classic, Embase and PsycINFO. Relevant studies were screened to determine whether it reported about awareness level of young adults with respect to Alzheimer's disease. The extracted endpoints were: self-belief levels of awareness, and actual awareness levels based on scores of knowledge questions. These endpoints were compiled into a table and summed to produce a weighted average for each endpoint.

SEARCH FINDINGS

A total of 12 studies [3-14] were identified to be included in the meta-analysis. Of the 12, six [3-8] were carried out in the Canadian Province of Ontario, and two more were carried out in the Provinces of Saskatchewan [9] and Quebec [10]. Another two studies [11, 12] were carried out in the States of New York and North Carolina, in the United States; two studies were conducted outside of North America, in Dublin, Ireland [13] and Asia [14].

43%, 31% and 53% of young adults in the Provinces of Ontario, Saskatchewan and Quebec, respectively, believed that they were knowledgeable about Alzheimer's disease. Across all Canadian studies, 44% acknowledged themselves as well-aware. 49% of young adults in the United States of America and 44% of those outside North America similarly recognized themselves as knowledgeable about the disease. Overall, 44% of young adults registered themselves as knowledgeable (see Table 1).

Table 1. I believe I am knowledgeable about Alzheimer's disease

Study	Response		
	True	Not Sure	False
Chow et al. [3]	38 (48%)	28 (35%)	13 (16%)
Chow et al. [4]	26 (58%)	16 (36%)	3 (7%)
Borean et al. [5]	63 (40%)	72 (46%)	21 (13%)
Viehweger et al. [6]	9 (69%)	3 (23%)	1 (8%)
Anpalagan et al. [7]	23 (34%)	35 (52%)	9 (13%)
Hollenberg et al. [8]	41 (41%)	50 (50%)	9 (9%)
<i>Province of Ontario</i>	200 (43%)	204 (44%)	56 (12%)
Viehweger et al. [9]	15 (41%)	19 (51%)	3 (8%)
<i>Province of Saskatchewan</i>	15 (41%)	19 (51%)	3 (8%)
Rzepka et al. [10]	19 (53%)	15 (42%)	2 (6%)
<i>Province of Quebec</i>	19 (53%)	15 (42%)	2 (6%)
Canada	234 (44%)	238 (45%)	61 (11%)
Chow et al. [11]	20 (53%)	16 (42%)	2 (5%)
Borean et al. [12]	22 (47%)	20 (43%)	5 (11%)
United States of America	42 (49%)	36 (42%)	7 (8%)
Chow et al. [13]	16 (44%)	17 (47%)	3 (8%)
Viehweger et al. [14]	3 (21%)	10 (71%)	1 (7%)
Outside North America	19 (38%)	27 (54%)	4 (8%)
TOTAL	295 (44%)	301 (45%)	72 (11%)

Young adults in the USA recognized that Alzheimer's is a subtype of dementia less frequently than those in Canada and Outside of North America (67%, vs 77% and 76%, respectively). Young adults in general, regardless of demographic region, correctly responded to the question at a rate of 76% (see Table 2).

Table 2. Alzheimer's is a subtype of dementia

Study	Response		
	True	Not Sure	False
Chow et al. [3]	63 (80%)	9 (11%)	7 (9%)
Chow et al. [4]	38 (84%)	3 (7%)	4 (9%)
Borean et al. [5]	123 (79%)	21 (13%)	12 (8%)
Viehweger et al. [6]	10 (77%)	2 (15%)	1 (8%)
Anpalagan et al. [7]	49 (73%)	10 (15%)	8 (12%)
Hollenberg et al. [8]	73 (73%)	19 (19%)	8 (8%)
<i>Province of Ontario</i>	356 (77%)	64 (14%)	40 (9%)
Viehweger et al. [9]	27 (73%)	8 (22%)	2 (5%)
<i>Province of Saskatchewan</i>	27 (73%)	8 (22%)	2 (5%)
Rzepka et al. [10]	29 (81%)	4 (11%)	3 (8%)
<i>Province of Quebec</i>	29 (81%)	4 (11%)	3 (8%)
Canada	412 (77%)	76 (14%)	45 (8%)
Chow et al. [11]	27 (71%)	5 (13%)	6 (16%)
Borean et al. [12]	30 (64%)	9 (19%)	8 (17%)
United States of America	57 (67%)	14 (16%)	14 (16%)
Chow et al. [13]	30 (83%)	3 (8%)	3 (8%)
Viehweger et al. [14]	8 (57%)	3 (21%)	3 (21%)
Outside North America	38 (76%)	6 (12%)	6 (12%)
TOTAL	507 (76%)	96 (14%)	65 (10%)

With respect to the question about whether Alzheimer's is a normal aspect of aging, young adults in USA responded at a higher frequency that it is not normal – 87%. Young adults in Canada made a similar remark at 81% frequency, followed by 80% for young adults outside of North America (see Table 3).

Table 3. Alzheimer's is normal with respect to aging

Study	Response		
	True	Not Sure	False
Chow et al. [3]	6 (8%)	4 (5%)	69 (87%)
Chow et al. [4]	1 (2%)	2 (4%)	42 (93%)
Borean et al. [5]	15 (10%)	12 (8%)	129 (83%)
Viehweger et al. [6]	2 (15%)	0 (0%)	11 (85%)
Anpalagan et al. [7]	2 (4%)	6 (9%)	59 (88%)
Hollenberg et al. [8]	11 (11%)	5 (5%)	84 (84%)
<i>Province of Ontario</i>	37 (8%)	29 (6%)	394 (86%)
Viehweger et al. [9]	2 (5%)	1 (3%)	34 (92%)
<i>Province of Saskatchewan</i>	2 (5%)	1 (3%)	34 (92%)
Rzepka et al. [10]	34 (94%)	0 (0%)	2 (6%)
<i>Province of Quebec</i>	34 (94%)	0 (0%)	2 (6%)
Canada	73 (14%)	30 (6%)	430 (81%)
Chow et al. [11]	3 (8%)	1 (3%)	34 (89%)
Borean et al. [12]	3 (6%)	4 (9%)	40 (85%)
United States of America	6 (7%)	5 (6%)	74 (87%)
Chow et al. [13]	6 (16%)	1 (3%)	29 (81%)
Viehweger et al. [14]	2 (14%)	1 (7%)	11 (79%)
Outside North America	8 (16%)	2 (4%)	40 (80%)
TOTAL	87 (13%)	37 (6%)	544 (81%)

Young adults answered that Alzheimer's worsens over time at a rate of 89% [11] to 100% [4, 6]. Young adults registered the correct answer at a 93% frequency, with Canadian and American young adults answering it correctly at a 93% frequency and those outside of North America registering the response 92% of the time (see Table 4).

Table 4. Alzheimer's worsens over time

Study	Response		
	True	Not Sure	False
Chow et al. [3]	75 (95%)	4 (5%)	0 (0%)
Chow et al. [4]	45 (100%)	0 (0%)	0 (0%)
Borean et al. [5]	142 (91%)	11 (7%)	3 (2%)
Viehweger et al. [6]	13 (100%)	0 (0%)	0 (0%)
Anpalagan et al. [7]	62 (93%)	4 (6%)	1 (2%)
Hollenberg et al. [8]	90 (90%)	5 (5%)	5 (5%)
<i>Province of Ontario</i>	427 (93%)	24 (5%)	9 (2%)
Viehweger et al. [9]	35 (95%)	2 (5%)	0 (0%)
<i>Province of Saskatchewan</i>	35 (95%)	2 (5%)	0 (0%)
Rzepka et al. [10]	35 (97%)	1 (3%)	0 (0%)
<i>Province of Quebec</i>	35 (97%)	1 (3%)	0 (0%)
Canada	497 (93%)	27 (5%)	9 (2%)
Chow et al. [11]	34 (89%)	1 (3%)	3 (8%)
Borean et al. [12]	45 (96%)	0 (0%)	2 (4%)
United States of America	79 (93%)	1 (1%)	5 (6%)
Chow et al. [13]	33 (92%)	2 (5%)	1 (3%)
Viehweger et al. [14]	13 (93%)	0 (0%)	1 (7%)
Outside North America	46 (92%)	2 (4%)	2 (4%)
TOTAL	622 (93%)	30 (5%)	16 (2%)

Canadian young adults were more likely to note that there is no cure to Alzheimer's, with a conglomerate frequency of 92%. Those outside of North America similarly answered at a rate of 90%, and those in the United States of America answered 84% of the time. The total rate was 90% (see Table 5).

Table 5. There is no cure to Alzheimer's disease

Study	Response		
	True	Not Sure	False
Chow et al. [3]	72 (91%)	7 (9%)	0 (0%)
Chow et al. [4]	43 (96%)	2 (4%)	0 (0%)
Borean et al. [5]	138 (88%)	17 (11%)	1 (1%)
Viehweger et al. [6]	13 (100%)	0 (0%)	0 (0%)
Anpalagan et al. [7]	64 (96%)	3 (4%)	0 (0%)
Hollenberg et al. [8]	90 (90%)	7 (7%)	3 (3%)
<i>Province of Ontario</i>	420 (91%)	36 (8%)	4 (1%)
Viehweger et al. [9]	34 (92%)	2 (5%)	1 (3%)
<i>Province of Saskatchewan</i>	34 (92%)	2 (5%)	1 (3%)
Rzepka et al. [10]	34 (94%)	1 (3%)	1 (3%)
<i>Province of Quebec</i>	34 (94%)	1 (3%)	1 (3%)
Canada	488 (92%)	39 (7%)	6 (1%)
Chow et al. [11]	30 (79%)	4 (11%)	4 (11%)
Borean et al. [12]	41 (87%)	3 (6%)	3 (6%)
United States of America	71 (84%)	7 (8%)	7 (8%)
Chow et al. [13]	32 (88%)	3 (8%)	1 (3%)
Viehweger et al. [14]	13 (93%)	0 (0%)	1 (7%)
Outside North America	45 (90%)	3 (6%)	2 (4%)
TOTAL	604 (90%)	49 (7%)	15 (2%)

Those outside of North America were least likely to accurately report that Alzheimer's is a leading cause of death, only at a frequency of 22%. Canadian young adults responded similarly at a rate of 25%, while American young adults noted it at 31%. Young adults, in general, responded to the question at 25% frequency (see Table 6).

Table 6. Alzheimer's is a leading cause of death

Study	Response		
	True	Not Sure	False
Chow et al. [3]	30 (38%)	24 (30%)	25 (32%)
Chow et al. [4]	12 (27%)	14 (31%)	19 (42%)
Borean et al. [5]	34 (22%)	65 (42%)	57 (37%)
Viehweger et al. [6]	5 (39%)	3 (23%)	5 (39%)
Anpalagan et al. [7]	17 (25%)	28 (42%)	22 (33%)
Hollenberg et al. [8]	16 (16%)	36 (36%)	48 (48%)
<i>Province of Ontario</i>	114 (25%)	170 (37%)	176 (38%)
Viehweger et al. [9]	9 (24%)	8 (22%)	20 (54%)
<i>Province of Saskatchewan</i>	9 (24%)	8 (22%)	20 (54%)
Rzepka et al. [10]	8 (22%)	11 (31%)	17 (47%)
<i>Province of Quebec</i>	8 (22%)	11 (31%)	17 (47%)
Canada	131 (25%)	189 (35%)	213 (40%)
Chow et al. [11]	13 (34%)	10 (26%)	15 (40%)
Borean et al. [12]	13 (28%)	12 (26%)	22 (47%)
United States of America	26 (31%)	22 (26%)	37 (44%)
Chow et al. [13]	8 (22%)	19 (53%)	9 (25%)
Viehweger et al. [14]	3 (21%)	3 (21%)	8 (57%)
Outside North America	11 (22%)	22 (44%)	17 (34%)
TOTAL	168 (25%)	233 (35%)	267 (40%)

American young adults seemed to have a lower percentage of young adults who were knowledgeable about the disease, with only 59% of young adults deemed as knowledgeable based on the study methods. Canadian young adults and those outside of North America had 62% and 68% of their populations, respectively, classified as knowledgeable. The consensus seems to be that 62% of the population is well-aware (see Table 7).

Table 7. Overall awareness of Alzheimer's disease

Study	Score		
	Poor (1-2)	Satisfactory (3)	Knowledgeable (4-5)
Chow et al. [3]	6 (8%)	14 (18%)	59 (75%)
Chow et al. [4]	1 (2%)	8 (18%)	36 (80%)
Borean et al. [5]	16 (10%)	47 (30%)	93 (60%)
Viehweger et al. [6]	1 (8%)	1 (8%)	11 (85%)
Anpalagan et al. [7]	17 (25%)	37 (55%)	13 (19%)
Hollenberg et al. [8]	14 (14%)	21 (21%)	65 (65%)
<i>Province of Ontario</i>	55 (12%)	128 (28%)	277 (60%)
Viehweger et al. [9]	3 (8%)	8 (22%)	26 (70%)
<i>Province of Saskatchewan</i>	3 (8%)	8 (22%)	26 (70%)
Rzepka et al. [10]	3 (8%)	5 (14%)	28 (78%)
<i>Province of Quebec</i>	3 (8%)	5 (14%)	28 (78%)
Canada	61 (11%)	141 (26%)	331 (62%)
Chow et al. [11]	4 (11%)	12 (32%)	22 (58%)
Borean et al. [12]	7 (15%)	12 (26%)	28 (60%)
United States of America	11 (13%)	24 (28%)	50 (59%)
Chow et al. [13]	1 (3%)	7 (19%)	28 (77%)
Viehweger et al. [14]	1 (7%)	7 (50%)	6 (42%)
Outside North America	2 (4%)	14 (28%)	34 (68%)
TOTAL	74 (11%)	179 (27%)	415 (62%)

DISCUSSION

This is the first meta-analysis to look into synthesizing the published data from literature that published about awareness levels at different geographic regions around the world. This review allows for those studies with small sample sizes, whose trends were previously overlooked due to low statistical power, to be conglomerated with other studies and examine for overarching trends.

Across all 12 studies, 44% of young adults perceived themselves as knowledgeable, which is lower than the actual rate of 62% unsheathed by the literature. There exists variations between geographic regions on awareness level: American young adults were the least knowledgeable, but were more knowledgeable about certain questions (i.e., recognizing that Alzheimer's is not normal with respect to aging).

This review was not without limitations. The review did not employ any statistical analysis, which did not allow for the detection of definitive differences between different regions with respect to knowledge, answer items, and awareness level.

In conclusion, this novel meta-analysis synthesized the published data to produce conglomerate rates. While 44% of young adults recognized themselves as knowledgeable about this disease, it turned out that 62% of young adults were actually knowledgeable. It seems that young adults are much more aware and knowledgeable about Alzheimer's disease than they thought they were.

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Chapter 241

YOUNG ADULTS AND AWARENESS OF ALZHEIMER'S DISEASE BY AGE, SEX AND FAMILIAL TIES: A META-ANALYSIS

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ABSTRACT

A prior meta-analysis documented the overall awareness level as detailed by the studies. However, the studies included within included subgroup data, allowing for re-analysis of the data. The aim of this review was to identify existing literature and synthesize the data to observe if there are any overarching trends between young adults in various locations between certain subgroups – age, sex, and relationship to disease. Similar to the prior review, the extracted endpoints were: self-belief levels of awareness, and actual awareness levels based on scores of knowledge questions. These endpoints were compiled into a table and summed to produce a weighted average for each endpoint. The endpoints were produced for multiple pairwise disjoint events – age cohorts (under 20 years old, and 20 years old and older), gender (male, and female), and familial ties to the disease (aware of a family member affected by Alzheimer's disease, and not aware of any family members affected by the illness). 37% of the population contained within the studies had a family member affected by Alzheimer's disease. Interpreted in lieu of the prior meta-analysis that suggested that 62% of the same population was knowledgeable about the disease, it seems that the young adult population is adequately aware of the disease. Additionally, this review suggests that there may exist differences in awareness between males and females, and between those with and without family members affected by Alzheimer's disease. However, given that this meta-analysis did not employ statistical analysis, it is difficult to definitively conclude that there exists a significant difference between the subgroups.

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INTRODUCTION

Past studies have revealed that healthcare professionals have developed standardized and validated tools to help improve quality of care for dementia and Alzheimer's patients, who frequently suffer undermanagement of their disease [1]. To improve quality of care even further, family members can educate themselves about the disease to be more diligent and conscientious caregivers [2].

A study conducted by Infinitas Research Group first examined into the awareness level of young adults in London, Canada, with respect to Alzheimer's disease [3]. The study determined that 75% of young adults reported to be well-aware of the disease, although only 48% of them were confident in themselves as being knowledgeable. Given that 31% of the sampled population has a family member affected by Alzheimer's disease, it seems that young adults are adequately aware.

Many similar studies were conducted [4-14], with the same aim. A prior review [15] documented the overall awareness level as detailed by the studies. However, the studies included within included subgroup data, allowing for re-analysis of the data. The aim of this review was to identify existing literature and synthesize the data to observe if there are any overarching trends between young adults in various locations between certain subgroups – age, sex, and relationship to disease.

OUR SEARCH

A literature search was conducted in many databases, such as Ovid MEDLINE and OLDMEDLINE, Embase Classic and Embase, PsycINFO. Relevant studies were screened to determine whether it reported about awareness level of young adults with respect to Alzheimer's disease.

Similar to the prior meta-analysis [15], the extracted endpoints were: self-belief levels of awareness, and actual awareness levels based on scores of knowledge questions. These endpoints were compiled into a table and summed to produce a weighted average for each endpoint. The endpoints were produced for multiple pairwise disjoint events – age cohorts (under 20 years old, and 20 years old and older), gender (male, and female), and familial ties to the disease (aware of a family member affected by Alzheimer's disease, and not aware of any family members affected by the illness).

OUTCOMES

Twelve studies were included in this meta-analysis. Eight looked into the awareness of Canadian young adults [3-10], two studied American young adults [11, 12], and another two documented the awareness level of young adults outside of North America [13, 14].

42% of under the age of 20 years old and 47% of those over the age of 20 regarded themselves as knowledgeable. Those under 20 years old and residing outside of North America had the lowest confidence level, at 35% (see Table 1). 76% of both groups recognized that Alzheimer's is a subtype of dementia (see Table 2); American young adults least commonly correctly answered the question – 68% for those under 20 years old and 66%

for those 20 years old and older. The older cohort was more likely to recognize that Alzheimer's is not normal with respect to aging, at a 88% rate compared to a 85% rate (see Table 3). The younger group more often correctly answered that Alzheimer's worsens over time (94% compared to 92%) (see Table 4), that Alzheimer's lacks a cure (92% compared to 89%) (see Table 5), and that Alzheimer's is a leading cause of death (26% compared to 24%) (see Table 6). In general, the young adults 20 years old and older seemed more knowledgeable, with 65% receiving a score of knowledgeable as opposed to 61% for the younger group (see Table 7).

Females were more likely to recognize themselves as well-aware of the disease (45% vs 41% for males) (see Table 8). Males, compared to females, failed to recognize that Alzheimer's is a subtype of disease, with a lackluster 64% rate compared to 81% rate of selecting the correct response (see Table 9). Males also were less likely to correctly note that Alzheimer's is not normal with respect to aging (77% compared to 88%) (see Table 10). Females reported that Alzheimer's worsens over time at 95%, and males similarly noted it at 89% (see Table 11). 81% of males and 94% of females acknowledged that there is no cure to Alzheimer's (see Table 12), and 21% and 26% of the same groups, respectively, answered that Alzheimer's is a leading cause of death (see Table 13). A larger proportion of females (67%) were considered knowledgeable when compared to males (50%) (see Table 14).

Young adults who have a family member afflicted by Alzheimer's disease were much more confident in their awareness of the disease, with 60% compared to 35% registering themselves as knowledgeable (see Table 15). There was a 5% difference in frequency of correctly answering that Alzheimer's is a subtype of dementia (79% for those affected, and 74% for those unaffected) (see Table 16). 87% and 86% of those affected and unaffected by the disease noted that Alzheimer's is not normal with respect to aging (see Table 17). Those with family members affected also noted that Alzheimer's worsens over time at a 96% frequency (compared to 92%) (see Table 18), that there is no cure to Alzheimer's at a 92% rate (compared to 90%) (see Table 19), and that Alzheimer's is a leading cause of death at 30% frequency (compared to 22%) (see Table 20). Overall, those with family members affected by the disease seem to be more knowledgeable, with 65% compared to 61% receiving a score deeming them knowledgeable (see Table 21).

Table 1. I believe I am knowledgeable about Alzheimer's disease – by age

Study	Response					
	True		Not Sure		False	
	Under 20	20 and Above	Under 20	20 and Above	Under 20	20 and Above
Chow et al. [3]	20 (49%)	18 (47%)	15 (37%)	13 (34%)	6 (15%)	7 (18%)
Chow et al. [4]	12 (55%)	14 (61%)	8 (36%)	8 (35%)	2 (9%)	1 (4%)
Borean et al. [5]	38 (37%)	25 (48%)	52 (50%)	20 (38%)	14 (13%)	7 (13%)
Viehweger et al. [6]	5 (71%)	4 (67%)	1 (14%)	2 (33%)	1 (14%)	0 (0%)
Anpalagan et al. [7]	16 (37%)	7 (29%)	22 (51%)	13 (54%)	5 (12%)	4 (17%)
Hollenberg et al. [8]	16 (41%)	25 (41%)	21 (54%)	29 (48%)	2 (5%)	7 (11%)

Table 1. (Continued)

Study	Response					
	True		Not Sure		False	
	Under 20	20 and Above	Under 20	20 and Above	Under 20	20 and Above
<i>Province of Ontario</i>	107 (42%)	93 (46%)	119 (46%)	85 (42%)	30 (12%)	26 (13%)
Viehweger et al. [9]	5 (28%)	10 (53%)	12 (67%)	7 (37%)	1 (6%)	2 (11%)
<i>Province of Saskatchewan</i>	5 (28%)	10 (53%)	12 (67%)	7 (37%)	1 (6%)	2 (11%)
Rzepka et al. [10]	8 (42%)	11 (65%)	10 (53%)	5 (29%)	1 (5%)	1 (6%)
<i>Province of Quebec</i>	8 (42%)	11 (65%)	10 (53%)	5 (29%)	1 (5%)	1 (6%)
Canada	120 (41%)	114 (48%)	141 (48%)	97 (41%)	32 (11%)	29 (12%)
Chow et al. [11]	10 (59%)	10 (48%)	7 (41%)	9 (43%)	0 (0%)	2 (10%)
Borean et al. [12]	17 (44%)	5 (63%)	18 (46%)	2 (25%)	4 (10%)	1 (13%)
United States of America	27 (48%)	15 (52%)	25 (45%)	11 (38%)	4 (7%)	3 (10%)
Chow et al. [13]	8 (44%)	8 (44%)	9 (50%)	8 (44%)	1 (5%)	2 (11%)
Viehweger et al. [14]	0 (0%)	3 (33%)	5 (100%)	5 (56%)	0 (0%)	1 (11%)
Outside North America	8 (35%)	11 (41%)	14 (61%)	13 (48%)	1 (4%)	3 (11%)
TOTAL	155 (42%)	140 (47%)	180 (48%)	121 (41%)	37 (10%)	35 (12%)

Table 2. Alzheimer's is a subtype of dementia – by age

Study	Response					
	True		Not Sure		False	
	Under 20	20 and Above	Under 20	20 and Above	Under 20	20 and Above
Chow et al. [3]	33 (80%)	30 (79%)	4 (10%)	3 (8%)	4 (10%)	5 (13%)
Chow et al. [4]	20 (90%)	19 (83%)	1 (5%)	1 (4%)	1 (5%)	3 (13%)
Borean et al. [5]	82 (79%)	41 (79%)	6 (6%)	6 (12%)	16 (15%)	5 (10%)
Viehweger et al. [6]	4 (57%)	6 (100%)	1 (14%)	0 (0%)	2 (29%)	0 (0%)
Anpalagan et al. [7]	29 (67%)	20 (83%)	7 (16%)	1 (4%)	7 (16%)	3 (13%)
Hollenberg et al. [8]	30 (77%)	43 (70%)	4 (10%)	4 (7%)	5 (13%)	14 (23%)
<i>Province of Ontario</i>	198 (77%)	159 (78%)	23 (9%)	15 (7%)	35 (14%)	30 (15%)
Viehweger et al. [9]	14 (78%)	13 (68%)	1 (6%)	1 (5%)	3 (17%)	5 (26%)

Study	Response					
	True		Not Sure		False	
	Under 20	20 and Above	Under 20	20 and Above	Under 20	20 and Above
<i>Province of Saskatchewan</i>	14 (78%)	13 (68%)	1 (6%)	1 (5%)	3 (17%)	5 (26%)
Rzepka et al. [10]	15 (79%)	14 (82%)	2 (11%)	1 (6%)	2 (11%)	2 (12%)
<i>Province of Quebec</i>	15 (79%)	14 (82%)	2 (11%)	1 (6%)	2 (11%)	2 (12%)
Canada	227 (77%)	186 (78%)	26 (9%)	17 (7%)	40 (14%)	37 (15%)
Chow et al. [11]	11 (65%)	16 (76%)	2 (12%)	4 (19%)	4 (24%)	1 (5%)
Borean et al. [12]	27 (69%)	3 (38%)	7 (18%)	2 (25%)	5 (13%)	3 (38%)
United States of America	38 (68%)	19 (66%)	9 (16%)	6 (21%)	9 (16%)	4 (14%)
Chow et al. [13]	15 (83%)	15 (83%)	2 (11%)	1 (5%)	1 (5%)	2 (11%)
Viehweger et al. [14]	3 (60%)	5 (56%)	0 (0%)	3 (33%)	2 (40%)	1 (11%)
Outside North America	18 (78%)	20 (74%)	2 (9%)	4 (15%)	3 (13%)	3 (11%)
TOTAL	283 (76%)	225 (76%)	37 (10%)	27 (9%)	52 (14%)	44 (15%)

Table 3. Alzheimer's is normal with respect to aging – by age

Study	Response					
	True		Not Sure		False	
	Under 20	20 and Above	Under 20	20 and Above	Under 20	20 and Above
Chow et al. [3]	3 (7%)	3 (8%)	2 (5%)	2 (5%)	36 (88%)	33 (87%)
Chow et al. [4]	1 (5%)	0 (0%)	1 (5%)	1 (4%)	20 (90%)	22 (96%)
Borean et al. [5]	12 (12%)	3 (6%)	8 (8%)	4 (8%)	84 (81%)	45 (87%)
Viehweger et al. [6]	1 (14%)	1 (17%)	0 (0%)	0 (0%)	6 (96%)	5 (83%)
Anpalagan et al. [7]	1 (2%)	1 (4%)	4 (9%)	2 (8%)	38 (88%)	21 (88%)
Hollenberg et al. [8]	6 (15%)	5 (8%)	0 (0%)	5 (8%)	33 (85%)	51 (84%)
<i>Province of Ontario</i>	24 (9%)	13 (6%)	15 (6%)	14 (7%)	217 (85%)	177 (87%)
Viehweger et al. [9]	2 (11%)	0 (0%)	0 (0%)	1 (5%)	16 (89%)	18 (95%)
<i>Province of Saskatchewan</i>	2 (11%)	0 (0%)	0 (0%)	1 (5%)	16 (89%)	18 (95%)
Rzepka et al. [10]	1 (5%)	1 (6%)	0 (0%)	0 (0%)	18 (95%)	16 (94%)
<i>Province of Quebec</i>	1 (5%)	1 (6%)	0 (0%)	0 (0%)	18 (95%)	16 (94%)

Table 3. (Continued)

Study	Response					
	True		Not Sure		False	
	Under 20	20 and Above	Under 20	20 and Above	Under 20	20 and Above
Canada	27 (9%)	14 (6%)	15 (5%)	15 (6%)	251 (86%)	211 (88%)
Chow et al. [11]	1 (6%)	2 (10%)	0 (0%)	1 (5%)	16 (94%)	18 (86%)
Borean et al. [12]	3 (8%)	0 (0%)	4 (10%)	0 (0%)	32 (82%)	8 (100%)
United States of America	4 (7%)	2 (7%)	4 (7%)	1 (3%)	48 (86%)	26 (90%)
Chow et al. [13]	5 (27%)	1 (5%)	0 (0%)	1 (5%)	13 (72%)	16 (88%)
Viehweger et al. [14]	1 (20%)	1 (11%)	0 (0%)	1 (11%)	4 (80%)	7 (78%)
Outside North America	6 (26%)	2 (7%)	0 (0%)	2 (7%)	17 (74%)	23 (85%)
TOTAL	37 (10%)	18 (6%)	19 (5%)	18 (6%)	316 (85%)	260 (88%)

Table 4. Alzheimer's worsens over time – by age

Study	Response					
	True		Not Sure		False	
	Under 20	20 and Above	Under 20	20 and Above	Under 20	20 and Above
Chow et al. [3]	39 (95%)	36 (95%)	2 (5%)	2 (5%)	0 (0%)	0 (0%)
Chow et al. [4]	22 (100%)	23 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Borean et al. [5]	93 (89%)	49 (94%)	8 (8%)	3 (6%)	3 (3%)	0 (0%)
Viehweger et al. [6]	7 (100%)	6 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Anpalagan et al. [7]	40 (93%)	22 (92%)	2 (5%)	2 (8%)	1 (2%)	0 (0%)
Hollenberg et al. [8]	37 (95%)	53 (87%)	1 (3%)	4 (7%)	1 (3%)	4 (7%)
<i>Province of Ontario</i>	238 (93%)	189 (93%)	13 (5%)	11 (5%)	5 (2%)	4 (2%)
Viehweger et al. [9]	18 (100%)	17 (90%)	0 (0%)	2 (10%)	0 (0%)	0 (0%)
<i>Province of Saskatchewan</i>	18 (100%)	17 (90%)	0 (0%)	2 (10%)	0 (0%)	0 (0%)
Rzepka et al. [10]	18 (95%)	17 (100%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)
<i>Province of Quebec</i>	18 (95%)	17 (100%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)
Canada	274 (94%)	223 (93%)	14 (5%)	13 (5%)	5 (2%)	4 (2%)

Study	Response					
	True		Not Sure		False	
	Under 20	20 and Above	Under 20	20 and Above	Under 20	20 and Above
Chow et al. [11]	17 (100%)	17 (81%)	0 (0%)	1 (5%)	0 (0%)	3 (14%)
Borean et al. [12]	39 (100%)	6 (75%)	0 (0%)	0 (0%)	0 (0%)	2 (25%)
United States of America	56 (100%)	23 (79%)	0 (0%)	1 (3%)	0 (0%)	5 (17%)
Chow et al. [13]	16 (88%)	17 (94%)	1 (5%)	1 (5%)	1 (5%)	0 (0%)
Viehweger et al. [14]	5 (100%)	8 (89%)	0 (0%)	0 (0%)	0 (0%)	1 (11%)
Outside North America	21 (91%)	25 (93%)	1 (4%)	1 (4%)	1 (4%)	1 (4%)
TOTAL	351 (94%)	271 (92%)	15 (4%)	15 (5%)	6 (2%)	10 (3%)

Table 5. There is no cure to Alzheimer's disease – by age

Study	Response					
	True		Not Sure		False	
	Under 20	20 and Above	Under 20	20 and Above	Under 20	20 and Above
Chow et al. [3]	38 (93%)	34 (89%)	3 (7%)	4 (11%)	0 (0%)	0 (0%)
Chow et al.[4]	20 (90%)	23 (100%)	2 (10%)	0 (0%)	0 (0%)	0 (0%)
Borean et al. [5]	90 (87%)	48 (92%)	13 (13%)	4 (8%)	1 (1%)	0 (0%)
Viehweger et al. [6]	7 (100%)	6 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Anpalagan et al. [7]	42 (98%)	22 (92%)	1 (2%)	2 (8%)	0 (0%)	0 (0%)
Hollenberg et al. [8]	37 (95%)	53 (87%)	1 (3%)	6 (10%)	1 (3%)	2 (3%)
<i>Province of Ontario</i>	234 (91%)	186 (91%)	20 (8%)	16 (8%)	2 (1%)	2 (1%)
Viehweger et al. [9]	17 (94%)	17 (90%)	0 (0%)	2 (10%)	1 (6%)	0 (0%)
<i>Province of Saskatchewan</i>	17 (94%)	17 (90%)	0 (0%)	2 (10%)	1 (6%)	0 (0%)
Rzepka et al. [10]	18 (95%)	16 (94%)	1 (5%)	0 (0%)	0 (0%)	1 (6%)
<i>Province of Quebec</i>	18 (95%)	16 (94%)	1 (5%)	0 (0%)	0 (0%)	1 (6%)
Canada	269 (92%)	219 (91%)	21 (7%)	18 (8%)	3 (1%)	3 (1%)
Chow et al. [11]	15 (88%)	15 (71%)	0 (0%)	2 (10%)	2 (12%)	4 (19%)
Borean et al. [12]	36 (92%)	5 (63%)	3 (8%)	0 (0%)	0 (0%)	3 (38%)

Table 5. (Continued)

Study	Response					
	True		Not Sure		False	
	Under 20	20 and Above	Under 20	20 and Above	Under 20	20 and Above
United States of America	51 (91%)	20 (69%)	3 (5%)	2 (7%)	2 (4%)	7 (24%)
Chow et al. [13]	17 (94%)	15 (83%)	0 (0%)	3 (16%)	1 (5%)	0 (0%)
Viehweger et al. [14]	4 (80%)	9 (100%)	0 (0%)	0 (0%)	1 (20%)	0 (0%)
Outside North America	21 (91%)	24 (89%)	0 (0%)	3 (11%)	2 (9%)	0 (0%)
TOTAL	341 (92%)	263 (89%)	24 (6%)	23 (8%)	7 (2%)	10 (3%)

Table 6. Alzheimer's is a leading cause of death – by age

Study	Response					
	True		Not Sure		False	
	Under 20	20 and Above	Under 20	20 and Above	Under 20	20 and Above
Chow et al. [3]	18 (44%)	12 (32%)	11 (27%)	13 (34%)	12 (29%)	13 (34%)
Chow et al. [4]	5 (23%)	7 (30%)	7 (32%)	7 (30%)	10 (45%)	9 (39%)
Borean et al. [5]	23 (22%)	11 (21%)	42 (40%)	23 (44%)	39 (38%)	18 (35%)
Viehweger et al. [6]	4 (57%)	1 (17%)	2 (29%)	1 (17%)	1 (14%)	4 (67%)
Anpalagan et al. [7]	10 (23%)	7 (29%)	16 (37%)	12 (50%)	17 (40%)	5 (21%)
Hollenberg et al. [8]	7 (18%)	9 (15%)	13 (33%)	23 (38%)	19 (49%)	29 (48%)
<i>Province of Ontario</i>	67 (26%)	47 (23%)	91 (36%)	79 (39%)	98 (38%)	78 (38%)
Viehweger et al. [9]	5 (28%)	4 (21%)	3 (17%)	5 (26%)	10 (56%)	10 (53%)
<i>Province of Saskatchewan</i>	5 (28%)	4 (21%)	3 (17%)	5 (26%)	10 (56%)	10 (53%)
Rzepka et al. [10]	4 (21%)	4 (24%)	8 (42%)	3 (18%)	7 (37%)	10 (59%)
<i>Province of Quebec</i>	4 (21%)	4 (24%)	8 (42%)	3 (18%)	7 (37%)	10 (59%)
Canada	76 (26%)	55 (23%)	102 (35%)	87 (36%)	115 (39%)	98 (41%)
Chow et al. [11]	8 (47%)	5 (24%)	5 (29%)	5 (24%)	4 (24%)	11 (52%)
Borean et al. [12]	11 (28%)	2 (25%)	12 (31%)	0 (0%)	16 (41%)	6 (75%)
United States of America	19 (34%)	7 (24%)	17 (30%)	5 (17%)	20 (36%)	17 (59%)
Chow et al. [13]	3 (16%)	5 (27%)	10 (55%)	9 (50%)	5 (27%)	4 (22%)

Study	Response					
	True		Not Sure		False	
	Under 20	20 and Above	Under 20	20 and Above	Under 20	20 and Above
Viehweger et al. [14]	0 (0%)	3 (33%)	2 (40%)	1 (11%)	3 (60%)	5 (56%)
Outside North America	3 (13%)	8 (30%)	12 (52%)	10 (37%)	8 (25%)	9 (33%)
TOTAL	98 (26%)	70 (24%)	131 (35%)	102 (34%)	143 (38%)	124 (42%)

Table 7. Overall awareness of Alzheimer's disease – by age

Study	Score					
	Poor (0-2)		Satisfactory (3)		Knowledgeable (4-5)	
	Under 20	20 and Above	Under 20	20 and Above	Under 20	20 and Above
Chow et al. [3]	3 (7%)	3 (8%)	7 (17%)	7 (18%)	31 (76%)	28 (74%)
Chow et al. [4]	1 (5%)	0 (0%)	3 (14%)	3 (13%)	18 (82%)	20 (87%)
Borean et al. [5]	13 (13%)	3 (6%)	31 (30%)	16 (31%)	60 (58%)	33 (63%)
Viehweger et al. [6]	1 (14%)	0 (0%)	1 (14%)	0 (0%)	5 (71%)	6 (100%)
Anpalagan et al. [7]	12 (28%)	5 (21%)	25 (58%)	12 (50%)	6 (14%)	7 (29%)
Hollenberg et al. [8]	3 (8%)	11 (18%)	11 (28%)	10 (16%)	25 (64%)	40 (66%)
<i>Province of Ontario</i>	33 (13%)	22 (11%)	78 (30%)	48 (24%)	145 (57%)	134 (66%)
Viehweger et al. [9]	1 (6%)	2 (10%)	4 (22%)	4 (21%)	13 (72%)	13 (68%)
<i>Province of Saskatchewan</i>	1 (6%)	2 (10%)	4 (22%)	4 (21%)	13 (72%)	13 (68%)
Rzepka et al. [10]	2 (11%)	1 (6%)	2 (11%)	3 (18%)	15 (79%)	13 (76%)
<i>Province of Quebec</i>	2 (11%)	1 (6%)	2 (11%)	3 (18%)	15 (79%)	13 (76%)
Canada	36 (12%)	25 (10%)	84 (29%)	55 (23%)	173 (59%)	160 (67%)
Chow et al. [11]	1 (6%)	3 (14%)	5 (29%)	7 (33%)	11 (65%)	11 (52%)
Borean et al. [12]	5 (13%)	2 (25%)	9 (23%)	3 (38%)	25 (64%)	3 (38%)
United States of America	6 (11%)	5 (17%)	14 (25%)	10 (34%)	36 (64%)	14 (48%)
Chow et al. [13]	1 (5%)	0 (0%)	3 (17%)	4 (22%)	14 (78%)	14 (78%)
Viehweger et al. [14]	1 (20%)	0 (0%)	1 (20%)	6 (67%)	3 (60%)	3 (33%)
Outside North America	2 (9%)	0 (0%)	4 (17%)	10 (37%)	17 (74%)	17 (63%)
TOTAL	44 (12%)	30 (10%)	102 (27%)	75 (25%)	226 (61%)	191 (65%)

Table 8. I believe I am knowledgeable about Alzheimer's disease – by sex

Study	Response					
	True		Not Sure		False	
	Males	Females	Males	Females	Males	Females
Chow et al. [3]	10 (48%)	28 (49%)	7 (33%)	20 (35%)	4 (19%)	9 (16%)
Chow et al. [4]	3 (60%)	23 (59%)	2 (40%)	13 (33%)	0 (0%)	3 (9%)
Borean et al. [5]	17 (41%)	46 (41%)	20 (49%)	51 (45%)	4 (10%)	16 (14%)
Viehweger et al. [6]	2 (50%)	6 (75%)	1 (25%)	2 (25%)	1 (25%)	0 (0%)
Anpalagan et al. [7]	4 (36%)	19 (34%)	6 (55%)	29 (52%)	1 (9%)	8 (14%)
Hollenberg et al. [8]	11 (37%)	30 (43%)	16 (53%)	33 (48%)	3 (10%)	6 (9%)
<i>Province of Ontario</i>	47 (42%)	152 (44%)	52 (46%)	148 (43%)	13 (12%)	42 (12%)
Viehweger et al. [9]	8 (50%)	7 (33%)	6 (38%)	13 (62%)	2 (13%)	1 (5%)
<i>Province of Saskatchewan</i>	8 (50%)	7 (33%)	6 (38%)	13 (62%)	2 (13%)	1 (5%)
Rzepka et al. [10]	2 (29%)	17 (59%)	4 (57%)	11 (38%)	1 (14%)	1 (3%)
<i>Province of Quebec</i>	2 (29%)	17 (59%)	4 (57%)	11 (38%)	1 (14%)	1 (3%)
Canada	57 (42%)	176 (45%)	62 (46%)	172 (44%)	16 (12%)	44 (11%)
Chow et al. [11]	4 (36%)	15 (58%)	6 (55%)	10 (38%)	1 (9%)	1 (4%)
Borean et al. [12]	5 (45%)	16 (46%)	5 (45%)	15 (43%)	1 (9%)	4 (11%)
United States of America	9 (41%)	31 (51%)	11 (50%)	25 (41%)	2 (9%)	5 (8%)
Chow et al. [13]	5 (42%)	11 (46%)	7 (58%)	10 (42%)	0 (0%)	3 (13%)
Viehweger et al. [14]	2 (29%)	1 (14%)	5 (71%)	5 (71%)	0 (0%)	1 (14%)
Outside North America	7 (37%)	12 (39%)	12 (63%)	15 (48%)	0 (0%)	4 (13%)
TOTAL	73 (41%)	219 (45%)	85 (48%)	212 (44%)	18 (10%)	53 (11%)

Table 9. Alzheimer's is a subtype of dementia – by sex

Study	Response					
	True		Not Sure		False	
	Males	Females	Males	Females	Males	Females
Chow et al. [3]	16 (76%)	47 (82%)	3 (14%)	5 (9%)	2 (10%)	5 (9%)
Chow et al. [4]	3 (60%)	35 (90%)	1 (20%)	2 (5%)	1 (20%)	2 (5%)
Borean et al. [5]	27 (66%)	94 (83%)	8 (20%)	13 (12%)	6 (15%)	6 (5%)
Viehweger et al. [6]	3 (75%)	6 (75%)	1 (25%)	1 (12%)	0 (0%)	1 (12%)
Anpalagan et al. [7]	7 (64%)	42 (75%)	2 (18%)	8 (14%)	2 (18%)	6 (11%)
Hollenberg et al. [8]	19 (63%)	54 (78%)	10 (33%)	8 (12%)	1 (3%)	7 (10%)
<i>Province of Ontario</i>	75 (67%)	278 (81%)	25 (22%)	37 (11%)	12 (11%)	27 (8%)
Viehweger et al. [9]	11 (69%)	16 (76%)	3 (19%)	5 (24%)	2 (13%)	0 (0%)
<i>Province of Saskatchewan</i>	11 (69%)	16 (76%)	3 (19%)	5 (24%)	2 (13%)	0 (0%)
Rzepka et al. [10]	3 (43%)	26 (90%)	2 (29%)	2 (7%)	2 (29%)	1 (3%)
<i>Province of Quebec</i>	3 (43%)	26 (90%)	2 (29%)	2 (7%)	2 (29%)	1 (3%)
Canada	89 (66%)	320 (82%)	30 (22%)	44 (11%)	16 (12%)	28 (7%)
Chow et al. [11]	7 (64%)	19 (73%)	1 (9%)	4 (15%)	3 (27%)	3 (12%)
Borean et al. [12]	6 (55%)	23 (66%)	3 (27%)	6 (17%)	2 (18%)	6 (17%)
United States of America	13 (59%)	42 (69%)	4 (18%)	10 (16%)	5 (23%)	9 (15%)
Chow et al. [13]	8 (67%)	22 (92%)	2 (17%)	1 (4%)	2 (17%)	1 (4%)
Viehweger et al. [14]	2 (29%)	6 (86%)	3 (43%)	0 (0%)	2 (29%)	1 (14%)
Outside North America	10 (53%)	28 (90%)	5 (26%)	1 (3%)	4 (21%)	2 (6%)
TOTAL	112 (64%)	390 (81%)	39 (22%)	55 (11%)	25 (14%)	39 (8%)

Table 10. Alzheimer's is normal with respect to aging – by sex

Study	Response					
	True		Not Sure		False	
	Males	Females	Males	Females	Males	Females
Chow et al. [3]	3 (14%)	3 (5%)	1 (5%)	3 (5%)	17 (81%)	51 (89%)
Chow et al. [4]	0 (0%)	1 (3%)	1 (20%)	1 (3%)	4 (80%)	37 (95%)
Borean et al. [5]	4 (10%)	10 (9%)	4 (10%)	8 (7%)	33 (80%)	95 (84%)
Viehweger et al. [6]	2 (50%)	8 (100%)	0 (0%)	0 (0%)	2 (50%)	0 (0%)
Anpalagan et al. [7]	0 (0%)	2 (4%)	2 (18%)	4 (7%)	9 (82%)	50 (89%)
Hollenberg et al. [8]	5 (17%)	6 (9%)	4 (13%)	1 (1%)	21 (70%)	62 (90%)
<i>Province of Ontario</i>	14 (13%)	30 (9%)	12 (11%)	17 (5%)	86 (77%)	295 (86%)
Viehweger et al. [9]	2 (13%)	0 (0%)	0 (0%)	1 (5%)	14 (88%)	20 (95%)
<i>Province of Saskatchewan</i>	2 (13%)	0 (0%)	0 (0%)	1 (5%)	14 (88%)	20 (95%)
Rzepka et al. [10]	1 (14%)	1 (3%)	0 (0%)	0 (0%)	6 (86%)	28 (97%)
<i>Province of Quebec</i>	1 (14%)	1 (3%)	0 (0%)	0 (0%)	6 (86%)	28 (97%)
Canada	17 (13%)	31 (8%)	12 (9%)	18 (5%)	106 (79%)	343 (88%)
Chow et al. [11]	3 (27%)	0 (0%)	0 (0%)	1 (4%)	8 (73%)	25 (96%)
Borean et al. [12]	2 (18%)	1 (3%)	2 (18%)	2 (6%)	7 (64%)	32 (91%)
United States of America	5 (23%)	1 (2%)	2 (9%)	3 (5%)	15 (68%)	57 (93%)
Chow et al. [13]	2 (16%)	4 (16%)	0 (0%)	1 (4%)	10 (83%)	19 (79%)
Viehweger et al. [14]	2 (29%)	0 (0%)	1 (14%)	0 (0%)	4 (57%)	7 (100%)
Outside North America	4 (21%)	4 (13%)	1 (5%)	1 (3%)	14 (74%)	26 (84%)
TOTAL	26 (15%)	36 (7%)	15 (9%)	22 (5%)	135 (77%)	426 (88%)

Table 11. Alzheimer's worsens over time – by sex

Study	Response					
	True		Not Sure		False	
	Males	Females	Males	Females	Males	Females
Chow et al. [3]	20 (95%)	55 (96%)	1 (5%)	2 (4%)	0 (0%)	0 (0%)
Chow et al. [4]	5 (100%)	39 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Borean et al. [5]	37 (90%)	104 (92%)	3 (7%)	8 (7%)	1 (2%)	1 (1%)
Viehweger et al. [6]	4 (100%)	8 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Anpalagan et al. [7]	10 (91%)	52 (93%)	1 (9%)	3 (5%)	0 (0%)	1 (2%)
Hollenberg et al. [8]	24 (80%)	65 (94%)	2 (7%)	3 (4%)	4 (13%)	1 (1%)
<i>Province of Ontario</i>	<i>100 (89%)</i>	<i>323 (94%)</i>	<i>7 (6%)</i>	<i>16 (5%)</i>	<i>5 (4%)</i>	<i>3 (1%)</i>
Viehweger et al. [9]	15 (94%)	20 (95%)	1 (6%)	1 (5%)	0 (0%)	0 (0%)
<i>Province of Saskatchewan</i>	<i>15 (94%)</i>	<i>20 (95%)</i>	<i>1 (6%)</i>	<i>1 (5%)</i>	<i>0 (0%)</i>	<i>0 (0%)</i>
Rzepka et al. [10]	6 (89%)	29 (100%)	1 (14%)	0 (0%)	0 (0%)	0 (0%)
<i>Province of Quebec</i>	<i>6 (89%)</i>	<i>29 (100%)</i>	<i>1 (14%)</i>	<i>0 (0%)</i>	<i>0 (0%)</i>	<i>0 (0%)</i>
Canada	121 (90%)	372 (95%)	9 (7%)	17 (4%)	5 (4%)	3 (1%)
Chow et al. [11]	9 (82%)	24 (92%)	0 (0%)	1 (4%)	2 (18%)	1 (4%)
Borean et al. [12]	9 (82%)	35 (100%)	0 (0%)	0 (0%)	2 (18%)	0 (0%)
United States of America	18 (82%)	59 (97%)	0 (0%)	1 (2%)	4 (18%)	1 (2%)
Chow et al. [13]	10 (83%)	23 (96%)	1 (8%)	1 (4%)	1 (8%)	0 (0%)
Viehweger et al. [14]	7 (100%)	6 (86%)	0 (0%)	0 (0%)	0 (0%)	1 (14%)
Outside North America	17 (89%)	29 (94%)	1 (5%)	1 (3%)	1 (5%)	1 (3%)
TOTAL	156 (89%)	460 (95%)	10 (6%)	19 (4%)	10 (6%)	5 (1%)

Table 12. There is no cure to Alzheimer's disease – by sex

Study	Response					
	True		Not Sure		False	
	Males	Females	Males	Females	Males	Females
Chow et al. [3]	17 (81%)	55 (96%)	4 (19%)	2 (4%)	0 (0%)	0 (0%)
Chow et al. [4]	5 (100%)	37 (95%)	0 (0%)	2 (5%)	0 (0%)	0 (0%)
Borean et al. [5]	31 (76%)	105 (93%)	9 (22%)	8 (7%)	1 (2%)	0 (0%)
Viehweger et al. [6]	4 (100%)	8 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Anpalagan et al. [7]	11 (100%)	53 (95%)	0 (0%)	3 (5%)	0 (0%)	0 (0%)
Hollenberg et al. [8]	26 (87%)	64 (93%)	2 (7%)	5 (7%)	2 (7%)	1 (1%)
<i>Province of Ontario</i>	94 (84%)	322 (94%)	15 (13%)	20 (6%)	3 (3%)	1 (1%)
Viehweger et al. [9]	15 (94%)	19 (90%)	1 (6%)	1 (5%)	0 (0%)	1 (5%)
<i>Province of Saskatchewan</i>	15 (94%)	19 (90%)	1 (6%)	1 (5%)	0 (0%)	1 (5%)
Rzepka et al. [10]	5 (71%)	29 (100%)	1 (14%)	0 (0%)	1 (14%)	0 (0%)
<i>Province of Quebec</i>	5 (71%)	29 (100%)	1 (14%)	0 (0%)	1 (14%)	0 (0%)
Canada	114 (84%)	370 (94%)	17 (13%)	21 (5%)	4 (3%)	2 (1%)
Chow et al. [11]	5 (46%)	24 (92%)	3 (27%)	1 (4%)	3 (27%)	1 (4%)
Borean et al. [12]	7 (64%)	33 (94%)	1 (9%)	2 (6%)	3 (27%)	0 (0%)
United States of America	12 (55%)	57 (93%)	4 (18%)	3 (5%)	6 (27%)	1 (2%)
Chow et al. [13]	11 (92%)	21 (88%)	0 (0%)	3 (12%)	1 (8%)	0 (0%)
Viehweger et al. [14]	6 (86%)	7 (100%)	0 (0%)	0 (0%)	1 (14%)	0 (0%)
Outside North America	17 (89%)	28 (90%)	0 (0%)	3 (10%)	2 (11%)	0 (0%)
TOTAL	143 (81%)	455 (94%)	21 (12%)	27 (6%)	12 (7%)	3 (1%)

Table 13. Alzheimer's is a leading cause of death – by sex

Study	Response					
	True		Not Sure		False	
	Males	Females	Males	Females	Males	Females
Chow et al. [3]	5 (24%)	25 (44%)	7 (33%)	16 (28%)	9 (43%)	16 (28%)
Chow et al. [4]	3 (60%)	9 (23%)	1 (20%)	13 (33%)	1 (20%)	17 (44%)
Borean et al. [5]	9 (22%)	24 (21%)	12 (29%)	53 (47%)	20 (49%)	36 (32%)
Viehweger et al. [6]	1 (25%)	2 (50%)	2 (25%)	2 (25%)	1 (25%)	4 (50%)
Anpalagan et al. [7]	2 (18%)	15 (27%)	4 (36%)	24 (43%)	5 (45%)	17 (30%)
Hollenberg et al. [8]	2 (7%)	14 (20%)	9 (30%)	26 (38%)	17 (57%)	29 (42%)
<i>Province of Ontario</i>	22 (20%)	89 (26%)	35 (30%)	134 (39%)	53 (48%)	119 (35%)
Viehweger et al. [9]	4 (19%)	5 (24%)	1 (6%)	7 (33%)	11 (69%)	9 (43%)
<i>Province of Saskatchewan</i>	4 (19%)	5 (24%)	1 (6%)	7 (33%)	11 (69%)	9 (43%)
Rzepka et al. [10]	1 (14%)	7 (24%)	2 (29%)	9 (31%)	4 (57%)	13 (45%)
<i>Province of Quebec</i>	1 (14%)	7 (24%)	2 (29%)	9 (31%)	4 (57%)	13 (45%)
Canada	27 (21%)	101 (26%)	38 (29%)	150 (38%)	68 (51%)	141 (36%)
Chow et al. [11]	3 (27%)	10 (39%)	4 (36%)	6 (23%)	4 (36%)	10 (39%)
Borean et al. [12]	4 (36%)	9 (26%)	2 (18%)	10 (29%)	5 (45%)	16 (46%)
United States of America	7 (32%)	19 (31%)	6 (27%)	16 (26%)	9 (41%)	26 (43%)
Chow et al. [13]	2 (16%)	6 (25%)	5 (42%)	14 (58%)	5 (42%)	4 (16%)
Viehweger et al. [14]	1 (14%)	2 (29%)	2 (29%)	1 (14%)	4 (57%)	4 (57%)
Outside North America	3 (16%)	8 (26%)	7 (37%)	15 (48%)	9 (47%)	8 (26%)
TOTAL	37 (21%)	128 (26%)	51 (29%)	181 (37%)	86 (49%)	175 (36%)

Table 14. Overall awareness of Alzheimer's disease – by sex

Study	Score					
	Poor (0-2)		Satisfactory (3)		Knowledgeable (4-5)	
	Males	Females	Males	Females	Males	Females
Chow et al. [3]	3 (14%)	2 (4%)	6 (29%)	8 (14%)	12 (57%)	47 (82%)
Chow et al. [4]	1 (20%)	0 (0%)	0 (0%)	7 (18%)	4 (80%)	32 (82%)
Borean et al. [5]	8 (20%)	7 (6%)	14 (34%)	33 (29%)	19 (46%)	73 (65%)
Viehweger et al. [6]	1 (25%)	0 (0%)	0 (0%)	1 (12%)	3 (75%)	7 (88%)
Anpalagan et al. [7]	4 (36%)	13 (23%)	6 (55%)	31 (55%)	1 (9%)	12 (21%)
Hollenberg et al. [8]	7 (23%)	7 (10%)	7 (23%)	13 (19%)	16 (53%)	49 (71%)
<i>Province of Ontario</i>	24 (21%)	29 (8%)	33 (29%)	93 (27%)	55 (49%)	220 (64%)
Viehweger et al. [9]	2 (12%)	1 (5%)	2 (12%)	6 (29%)	12 (75%)	14 (67%)
<i>Province of Saskatchewan</i>	2 (12%)	1 (5%)	2 (12%)	6 (29%)	12 (75%)	14 (67%)
Rzepka et al. [10]	3 (43%)	0 (0%)	2 (29%)	0 (0%)	2 (29%)	29 (100%)
<i>Province of Quebec</i>	3 (43%)	0 (0%)	2 (29%)	0 (0%)	2 (29%)	29 (100%)
Canada	29 (21%)	30 (8%)	37 (27%)	99 (25%)	69 (51%)	263 (67%)
Chow et al. [11]	4 (36%)	0 (0%)	3 (27%)	9 (35%)	4 (36%)	17 (65%)
Borean et al. [12]	4 (36%)	3 (9%)	3 (27%)	9 (26%)	4 (36%)	23 (66%)
United States of America	8 (36%)	3 (5%)	6 (27%)	18 (30%)	8 (36%)	40 (66%)
Chow et al. [13]	0 (0%)	1 (4%)	2 (17%)	5 (21%)	10 (83%)	18 (75%)
Viehweger et al. [14]	1 (14%)	0 (0%)	5 (71%)	2 (29%)	1 (14%)	5 (71%)
Outside North America	1 (5%)	1 (3%)	7 (37%)	7 (23%)	11 (58%)	23 (74%)
TOTAL	38 (22%)	34 (7%)	50 (28%)	124 (26%)	88 (50%)	326 (67%)

Table 15. I believe I am knowledgeable about Alzheimer's disease – by familial ties

Study	Response					
	True		Not Sure		False	
	Affected	Not Affected	Affected	Not Affected	Affected	Not Affected
Chow et al. [3]	16 (67%)	22 (41%)	6 (25%)	21 (39%)	2 (8%)	11 (20%)
Chow et al. [4]	10 (59%)	16 (57%)	2 (12%)	11 (39%)	5 (29%)	1 (4%)
Borean et al. [5]	30 (49%)	33 (35%)	24 (39%)	48 (51%)	7 (11%)	14 (15%)
Viehweger et al. [6]	3 (50%)	6 (86%)	2 (33%)	1 (14%)	1 (17%)	0 (0%)
Anpalagan et al. [7]	9 (50%)	14 (29%)	9 (50%)	26 (53%)	0 (0%)	9 (18%)
Hollenberg et al. [8]	25 (61%)	16 (27%)	15 (37%)	35 (59%)	1 (2%)	8 (14%)
<i>Province of Ontario</i>	93 (56%)	107 (37%)	58 (35%)	142 (49%)	16 (10%)	43 (15%)
Viehweger et al. [9]	4 (57%)	11 (37%)	2 (29%)	17 (57%)	1 (14%)	2 (7%)
<i>Province of Saskatchewan</i>	4 (57%)	11 (37%)	2 (29%)	17 (57%)	1 (14%)	2 (7%)
Rzepka et al. [10]	10 (71%)	9 (41%)	4 (29%)	11 (50%)	0 (0%)	2 (9%)
<i>Province of Quebec</i>	10 (71%)	9 (41%)	4 (29%)	11 (50%)	0 (0%)	2 (9%)
Canada	107 (57%)	127 (37%)	64 (34%)	170 (49%)	17 (9%)	47 (14%)
Chow et al. [11]	14 (70%)	6 (33%)	5 (25%)	11 (61%)	1 (5%)	1 (6%)
Borean et al. [12]	17 (71%)	5 (22%)	6 (25%)	14 (61%)	1 (4%)	4 (17%)
United States of America	31 (70%)	11 (27%)	11 (25%)	25 (61%)	2 (5%)	5 (12%)
Chow et al. [13]	9 (90%)	7 (27%)	1 (10%)	16 (62%)	0 (0%)	3 (12%)
Viehweger et al. [14]	2 (33%)	1 (13%)	3 (50%)	7 (88%)	1 (17%)	0 (0%)
Outside North America	11 (69%)	8 (24%)	4 (25%)	23 (68%)	1 (6%)	3 (9%)
TOTAL	149 (60%)	146 (35%)	79 (32%)	218 (52%)	20 (8%)	55 (13%)

Table 16. Alzheimer's is a subtype of dementia – by familial ties

Study	Response					
	True		Not Sure		False	
	Affected	Not Affected	Affected	Not Affected	Affected	Not Affected
Chow et al. [3]	20 (83%)	43 (80%)	2 (8%)	6 (11%)	2 (8%)	5 (9%)
Chow et al. [4]	14 (82%)	24 (86%)	1 (6%)	2 (7%)	2 (12%)	2 (7%)
Borean et al. [5]	48 (79%)	75 (79%)	6 (10%)	15 (16%)	7 (11%)	5 (5%)
Viehweger et al. [6]	5 (83%)	5 (71%)	1 (17%)	1 (14%)	0 (0%)	1 (14%)
Anpalagan et al. [7]	13 (72%)	36 (73%)	3 (17%)	7 (14%)	2 (11%)	6 (12%)
Hollenberg et al. [8]	31 (76%)	42 (71%)	6 (14%)	13 (22%)	5 (10%)	4 (7%)
<i>Province of Ontario</i>	131 (78%)	225 (77%)	19 (11%)	44 (15%)	18 (11%)	23 (8%)
Viehweger et al. [9]	6 (86%)	21 (70%)	1 (14%)	7 (23%)	0 (0%)	2 (7%)
<i>Province of Saskatchewan</i>	6 (86%)	21 (70%)	1 (14%)	7 (23%)	0 (0%)	2 (7%)
Rzepka et al. [10]	12 (86%)	17 (77%)	2 (14%)	2 (9%)	0 (0%)	3 (14%)
<i>Province of Quebec</i>	12 (86%)	17 (77%)	2 (14%)	2 (9%)	0 (0%)	3 (14%)
Canada	149 (79%)	263 (76%)	22 (12%)	53 (15%)	18 (10%)	28 (8%)
Chow et al. [11]	16 (80%)	11 (61%)	2 (10%)	3 (17%)	2 (10%)	4 (22%)
Borean et al. [12]	19 (79%)	11 (48%)	3 (13%)	6 (26%)	2 (8%)	6 (26%)
United States of America	35 (80%)	22 (54%)	5 (11%)	9 (22%)	4 (9%)	10 (24%)
Chow et al. [13]	9 (90%)	21 (81%)	1 (10%)	2 (8%)	0 (0%)	3 (12%)
Viehweger et al. [14]	3 (50%)	5 (63%)	1 (17%)	2 (25%)	2 (33%)	1 (13%)
Outside North America	12 (75%)	26 (76%)	2 (13%)	4 (12%)	2 (13%)	4 (12%)
TOTAL	196 (79%)	311 (74%)	29 (12%)	66 (16%)	24 (10%)	42 (10%)

Table 17. Alzheimer's is normal with respect to aging – by familial ties

Study	Response					
	True		Not Sure		False	
	Affected	Not Affected	Affected	Not Affected	Affected	Not Affected
Chow et al. [3]	2 (8%)	4 (7%)	2 (8%)	2 (4%)	20 (83%)	48 (89%)
Chow et al. [4]	1 (6%)	0 (0%)	0 (0%)	2 (7%)	16 (94%)	26 (93%)
Borean et al. [5]	6 (10%)	9 (9%)	6 (10%)	6 (6%)	49 (80%)	80 (84%)
Viehweger et al. [6]	1 (17%)	1 (14%)	0 (0%)	0 (0%)	5 (83%)	6 (86%)
Anpalagan et al. [7]	0 (0%)	2 (4%)	0 (0%)	6 (12%)	18 (100%)	41 (84%)
Hollenberg et al. [8]	4 (10%)	7 (12%)	1 (2%)	4 (7%)	36 (88%)	48 (81%)
<i>Province of Ontario</i>	14 (8%)	23 (8%)	9 (5%)	20 (7%)	144 (86%)	249 (85%)
Viehweger et al. [9]	2 (29%)	0 (0%)	0 (0%)	1 (3%)	5 (71%)	29 (97%)
<i>Province of Saskatchewan</i>	2 (29%)	0 (0%)	0 (0%)	1 (3%)	5 (71%)	29 (97%)
Rzepka et al. [10]	0 (0%)	2 (9%)	0 (0%)	0 (0%)	14 (100%)	20 (91%)
<i>Province of Quebec</i>	0 (0%)	2 (9%)	0 (0%)	0 (0%)	14 (100%)	20 (91%)
Canada	16 (9%)	25 (7%)	9 (5%)	21 (6%)	163 (87%)	298 (87%)
Chow et al. [11]	0 (0%)	3 (17%)	1 (5%)	0 (0%)	19 (95%)	15 (83%)
Borean et al. [12]	1 (4%)	2 (9%)	1 (4%)	3 (13%)	22 (92%)	18 (78%)
United States of America	1 (2%)	5 (12%)	2 (5%)	3 (7%)	41 (93%)	33 (80%)
Chow et al. [13]	3 (30%)	3 (12%)	0 (0%)	1 (4%)	7 (70%)	22 (85%)
Viehweger et al. [14]	1 (17%)	1 (13%)	1 (17%)	0 (0%)	4 (67%)	7 (88%)
Outside North America	4 (25%)	4 (12%)	1 (6%)	1 (3%)	11 (69%)	29 (85%)
TOTAL	21 (8%)	34 (8%)	12 (5%)	25 (6%)	215 (87%)	360 (86%)

Table 18. Alzheimer's worsens over time – by familial ties

Study	Response					
	True		Not Sure		False	
	Affected	Not Affected	Affected	Not Affected	Affected	Not Affected
Chow et al. [3]	24 (100%)	51 (94%)	0 (0%)	3 (6%)	0 (0%)	0 (0%)
Chow et al. [4]	17 (100%)	28 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Borean et al. [5]	58 (95%)	84 (88%)	3 (5%)	8 (8%)	0 (0%)	3 (3%)
Viehweger et al. [6]	6 (100%)	7 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Anpalagan et al. [7]	18 (100%)	44 (90%)	0 (0%)	4 (8%)	0 (0%)	1 (2%)
Hollenberg et al. [8]	38 (93%)	52 (88%)	1 (2%)	4 (7%)	2 (5%)	3 (5%)
<i>Province of Ontario</i>	161 (96%)	266 (91%)	4 (2%)	19 (7%)	2 (1%)	7 (3%)
Viehweger et al. [9]	7 (100%)	28 (93%)	0 (0%)	2 (7%)	0 (0%)	0 (0%)
<i>Province of Saskatchewan</i>	7 (100%)	28 (93%)	0 (0%)	2 (7%)	0 (0%)	0 (0%)
Rzepka et al. [10]	14 (100%)	21 (95%)	0 (0%)	1 (5%)	0 (0%)	0 (0%)
<i>Province of Quebec</i>	14 (100%)	21 (95%)	0 (0%)	1 (5%)	0 (0%)	0 (0%)
Canada	182 (97%)	315 (92%)	4 (2%)	22 (6%)	2 (1%)	7 (2%)
Chow et al. [11]	18 (90%)	16 (89%)	1 (5%)	0 (0%)	1 (5%)	2 (11%)
Borean et al. [12]	24 (100%)	21 (91%)	0 (0%)	0 (0%)	0 (0%)	2 (9%)
United States of America	42 (95%)	37 (90%)	1 (2%)	0 (0%)	1 (2%)	4 (10%)
Chow et al. [13]	9 (90%)	24 (92%)	0 (0%)	2 (8%)	1 (10%)	0 (0%)
Viehweger et al. [14]	5 (83%)	8 (100%)	0 (0%)	0 (0%)	1 (17%)	0 (0%)
Outside North America	14 (88%)	32 (94%)	0 (0%)	2 (6%)	2 (13%)	0 (0%)
TOTAL	238 (96%)	384 (92%)	5 (2%)	24 (6%)	5 (2%)	11 (3%)

Table 19. There is no cure to Alzheimer's disease – by familial ties

Study	Response					
	True		Not Sure		False	
	Affected	Not Affected	Affected	Not Affected	Affected	Not Affected
Chow et al. [3]	22 (92%)	50 (93%)	2 (8%)	4 (7%)	0 (0%)	0 (0%)
Chow et al. [4]	15 (88%)	28 (100%)	2 (12%)	0 (0%)	0 (0%)	0 (0%)
Borean et al. [5]	57 (93%)	81 (85%)	3 (5%)	14 (16%)	1 (2%)	0 (0%)
Viehweger et al. [6]	6 (100%)	7 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Anpalagan et al. [7]	18 (100%)	46 (94%)	0 (0%)	3 (6%)	0 (0%)	0 (0%)
Hollenberg et al. [8]	36 (88%)	54 (92%)	3 (7%)	4 (7%)	2 (5%)	1 (2%)
Province of Ontario	154 (92%)	266 (91%)	10 (6%)	25 (9%)	3 (2%)	1 (1%)
Viehweger et al. [9]	7 (100%)	27 (90%)	0 (0%)	2 (7%)	0 (0%)	1 (3%)
Province of Saskatchewan	7 (100%)	27 (90%)	0 (0%)	2 (7%)	0 (0%)	1 (3%)
Rzepka et al. [10]	14 (100%)	20 (91%)	0 (0%)	1 (5%)	0 (0%)	1 (5%)
Province of Quebec	14 (100%)	20 (91%)	0 (0%)	1 (5%)	0 (0%)	1 (5%)
Canada	175 (93%)	313 (91%)	10 (5%)	28 (8%)	3 (2%)	3 (1%)
Chow et al. [11]	17 (85%)	13 (72%)	2 (10%)	2 (11%)	1 (5%)	3 (17%)
Borean et al. [12]	23 (96%)	18 (78%)	1 (4%)	2 (9%)	0 (0%)	3 (13%)
United States of America	40 (91%)	31 (76%)	3 (7%)	4 (10%)	1 (3%)	6 (15%)
Chow et al. [13]	8 (80%)	24 (92%)	1 (10%)	2 (8%)	1 (10%)	0 (0%)
Viehweger et al. [14]	5 (83%)	8 (100%)	0 (0%)	0 (0%)	1 (17%)	0 (0%)
Outside North America	13 (81%)	32 (94%)	1 (6%)	2 (6%)	2 (13%)	0 (0%)
TOTAL	228 (92%)	376 (90%)	14 (6%)	34 (8%)	6 (2%)	9 (2%)

Table 20. Alzheimer's is a leading cause of death – by familial ties

Study	Response					
	True		Not Sure		False	
	Affected	Not Affected	Affected	Not Affected	Affected	Not Affected
Chow et al. [3]	13 (54%)	17 (31%)	7 (29%)	16 (30%)	4 (17%)	21 (39%)
Chow et al. [4]	4 (24%)	8 (29%)	3 (18%)	11 (39%)	10 (59%)	9 (32%)
Borean et al. [5]	17 (28%)	17 (18%)	28 (46%)	37 (39%)	16 (26%)	41 (43%)
Viehweger et al. [6]	2 (33%)	3 (43%)	1 (17%)	2 (29%)	3 (50%)	2 (29%)
Anpalagan et al. [7]	4 (22%)	13 (27%)	6 (33%)	22 (45%)	8 (44%)	14 (29%)
Hollenberg et al. [8]	4 (10%)	12 (20%)	14 (34%)	22 (37%)	23 (56%)	25 (42%)
<i>Province of Ontario</i>	44 (26%)	70 (24%)	59 (35%)	110 (38%)	64 (38%)	112 (38%)
Viehweger et al. [9]	4 (57%)	5 (17%)	0 (0%)	8 (27%)	3 (43%)	17 (57%)
<i>Province of Saskatchewan</i>	4 (57%)	5 (17%)	0 (0%)	8 (27%)	3 (43%)	17 (57%)
Rzepka et al. [10]	6 (43%)	2 (9%)	3 (21%)	8 (36%)	5 (35%)	12 (55%)
<i>Province of Quebec</i>	6 (43%)	2 (9%)	3 (21%)	8 (36%)	5 (35%)	12 (55%)
Canada	54 (29%)	77 (22%)	62 (33%)	126 (37%)	72 (38%)	141 (41%)
Chow et al. [11]	8 (40%)	5 (28%)	6 (30%)	4 (22%)	6 (30%)	9 (50%)
Borean et al. [12]	8 (33%)	5 (22%)	1 (4%)	11 (48%)	15 (63%)	7 (30%)
United States of America	16 (36%)	10 (24%)	7 (16%)	15 (37%)	21 (48%)	16 (39%)
Chow et al. [13]	3 (30%)	5 (19%)	4 (40%)	15 (58%)	3 (30%)	6 (23%)
Viehweger et al. [14]	2 (33%)	1 (13%)	1 (17%)	2 (25%)	3 (50%)	5 (63%)
Outside North America	5 (31%)	6 (18%)	5 (31%)	17 (50%)	6 (38%)	11 (32%)
TOTAL	75 (30%)	93 (22%)	74 (30%)	158 (38%)	99 (40%)	168 (41%)

Table 21. Overall awareness of Alzheimer's disease – by familial ties

Study	Score					
	Poor (0-2)		Satisfactory (3)		Knowledgeable (4-5)	
	Affected	Not Affected	Affected	Not Affected	Affected	Not Affected
Chow et al. [3]	2 (8%)	3 (6%)	2 (8%)	12 (22%)	20 (83%)	39 (72%)
Chow et al. [4]	0 (0%)	1 (4%)	5 (29%)	3 (11%)	12 (71%)	24 (86%)
Borean et al. [5]	4 (7%)	12 (13%)	20 (33%)	27 (28%)	37 (61%)	56 (59%)
Viehweger et al. [6]	1 (17%)	0 (0%)	0 (0%)	1 (14%)	5 (83%)	6 (86%)
Anpalagan et al. [7]	4 (22%)	13 (27%)	11 (61%)	26 (53%)	3 (17%)	10 (20%)
Hollenberg et al. [8]	6 (15%)	8 (14%)	7 (17%)	14 (24%)	28 (68%)	37 (63%)
<i>Province of Ontario</i>	17 (10%)	37 (13%)	45 (27%)	83 (28%)	105 (63%)	172 (90%)
Viehweger et al. [9]	1 (14%)	2 (7%)	0 (0%)	8 (27%)	6 (86%)	20 (67%)
<i>Province of Saskatchewan</i>	1 (14%)	2 (7%)	0 (0%)	8 (27%)	6 (86%)	20 (67%)
Rzepka et al. [10]	0 (0%)	3 (21%)	2 (14%)	3 (21%)	12 (86%)	16 (73%)
<i>Province of Quebec</i>	0 (0%)	3 (21%)	2 (14%)	3 (21%)	12 (86%)	16 (73%)
Canada	18 (10%)	42 (12%)	47 (25%)	94 (27%)	123 (65%)	208 (60%)
Chow et al. [11]	0 (0%)	4 (22%)	8 (40%)	4 (22%)	12 (60%)	10 (56%)
Borean et al. [12]	0 (0%)	7 (30%)	6 (25%)	6 (26%)	18 (75%)	10 (43%)
United States of America	0 (0%)	11 (27%)	14 (32%)	10 (24%)	30 (68%)	20 (49%)
Chow et al. [13]	1 (10%)	0 (0%)	3 (30%)	4 (25%)	6 (60%)	22 (85%)
Viehweger et al. [14]	1 (17%)	0 (0%)	3 (50%)	4 (50%)	2 (33%)	4 (50%)
Outside North America	2 (13%)	0 (0%)	6 (38%)	8 (24%)	8 (50%)	26 (76%)
TOTAL	20 (8%)	53 (13%)	67 (27%)	112 (47%)	161 (65%)	254 (61%)

DISCUSSION

This review is a follow-up meta-analysis one previously conducted [15]. 37% of the population contained within the studies had a family member affected by Alzheimer's disease. Interpreted in lieu of the prior meta-analysis that suggested that 62% of the same

population was knowledgeable about the disease, it seems that the young adult population is adequately aware of the disease.

According to subgroup analyses, it seems that females are more knowledgeable than males and those with family members affected compared to those without family members affected, were more well-aware of the disease. Both of these observations may be a result of more diligence and personal care about the disease. This review was not without limitations. The review did not employ statistical analyses, and hence the differences observed could not be determined to be statistical differences.

This secondary meta-analysis suggests that young adults are well-aware of Alzheimer's disease. Additionally, it suggests that there may exist differences in awareness between males and females, and between those with and without family members affected by Alzheimer's disease. However, given that this meta-analysis did not employ statistical analysis, it is difficult to definitively conclude that there exists a significant difference between the subgroups.

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Chapter 242

ASSOCIATIONS WITH OBESITY IN SUB-SAHARAN AFRICA

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HYPERTENSION

There is a strong association between obesity, hypertension, and obesity. About three-quarters of adult type II diabetics and some two-thirds of hypertensives are overweight (Modan et al., 1985). Obesity as defined as body weight 20% or more above average or standard weight appears to be the link between diabetes and essential hypertension in a large majority of cases. However about 15.0% of the study's hypertensive group were free of the other two conditions, and some 4.7% of the general population presented all three of them. Thus it can be estimated that nearly 1 out of 10 of those in middle age and having a Westernised lifestyle are heavier than normal weight, more or less glucose intolerant, and have systolic or diastolic hypertension (Ferranini & De Fronzo, 1989).

Hypertension is common in patients with diabetes. Studies within populations have shown that hypertension occurs more frequently in patients with diabetes than in nondiabetic individuals (Kannel & McGee, 1979). And it is more common for hypertensive patients to become diabetic than for diabetic patients to become hypertensive. Hypertension associated with diabetes may be of three types: a) systolic hypertension secondary to atherosclerosis, and about 2-5 times as prevalent in diabetes as in nonmatched nondiabetics; b) renal hypertension secondary to diabetic nephropathy; and c) essential hypertension.

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HYPERINSULINAEMIA

Plasma insulin levels are consistently increased in obese subjects (Salans, 1981). Likewise, patients with impaired glucose tolerance usually are hyperinsulinaemic even if their body weight is normal. Thus it is possible that patients with impaired glucose tolerance usually are hyperinsulinaemic even if their body weight is normal (De Fronzo & Ferranini, 1982). Thus it is possible that hyperinsulinaemia could be one link between diabetes, obesity, and hypertension. The association between hyperinsulinism and hypertension was noted in a large Israeli Jewish population characterised by a high prevalence of glucose intolerance and diabetes. The patients were stratified for age and body mass. It was found that the prevalence of hypertension as well as the actual BP rose from normal to overt diabetes. They concluded that hypertension per se is associated with hyperinsulinaemia, and there is common ground for the cluster of diabetes, obesity, and essential hypertension (Modan et al., 1985).

INSULIN RESISTANCE

Insulin resistance is reduced or impaired response of target tissues to insulin stimulation (Salans, 1981; Ferranini & De Fronzo, 1989). Insulin resistance occurs in 25% of normal people (De Fronzo & Ferranini, 1982). The impact of insulin on glucose may be unrelated to impacts of insulin on carbohydrate, fat, protein, or electrolyte metabolism. Insulin resistance occurs in obesity and in noninsulin-dependent diabetes. The actions of insulin can be studied with the insulin clamp technique.

AETIOLOGY OF THE INSULIN-RESISTANT STATE

Several causes may be associated with the aetiology of the insulin-resistant state, including genetics, hyperinsulinaemia, increased level of androgen with central obesity, elevated levels of free fatty acid, ageing, physical inactivity, diabetes and/or obesity, pregnancy, oral contraceptive pill, glucocorticoids, growth hormone, alcohol, and smoking (Lundgren et al., 1988; Pollare, 1989)..

ROLE OF INSULIN IN CAUSING HYPERTENSION

Insulin can raise BP by increased sodium retention (De Fronzo, 1981), or insulin can stimulate the activity of the sympathetic nervous system. An increased concentration of noradrenaline leads to increase in heart rate, vasoconstriction, sodium retention, and elevated BP (Rowe et al., 1981). Insulin also affects the transport of positive ions across the cell membrane. This affects sodium, potassium, calcium, and magnesium. An altered salt concentration in the endothelial cell can reduce the contractility of skeletal and heart muscle (James et al., 1985; Hilton, 1986). In theory, elevated insulin levels can increase the contraction of the vascular wall, resulting in an elevated BP.

OBESITY—THE HARMFUL MALE TYPE

Abdominal obesity, i.e., the male type of obesity, brings increased risk of cardiovascular disease, while female obesity of the hip and thigh is not associated with cardiovascular disease. Abdominal obesity is associated with the following features: a) higher fasting insulin levels, b) reduced glucose tolerance and an increased risk of hypertension and diabetes, c) reduced insulin sensitivity, d) blood lipid abnormalities, e) higher levels of free fatty acid, because adipose tissue is more sensitive to catecholamine lipolysis, and f) an increased number of fast-twitch, white muscle fibres in the thigh muscle. Abdominal obesity is associated with increased incidence of coronary heart disease (CHD) before ages 60-65 years.

TREATMENT

Treatment for obesity should be by weight reduction, a diet consisting of less fat and more fibre, and an increase in physical activity. Smokers should receive advice on how to stop. The entire cardiovascular profile can be improved with this regimen. Pharmacological agents that have no metabolic side effects should be considered. In the syndrome of hypertension, obesity, and diabetes, one should consider hypotensive agents that lower BP and enhance insulin sensitivity. In this setting, drugs should be considered that lower BP and improve insulin sensitivity, like angiotensin converting enzyme inhibitors. Of patients in one study who developed diabetes, 98% were treated with diuretics and/or beta blocking agents (Pollare et al., 1989).

LIFESTYLE

Two important low-cost measures are, first, a reduction of dietary salt and increased potassium intake, and second, a greater awareness of the serious implications of obesity. Increased exercise, decreased obesity, and cessation of smoking are all important in Blacks and whites in control of hypertension. Financial and cultural barriers constrain implementation of the DASH high-fruit, high-vegetable, low-salt diet which is very effective in U.S. Blacks. In Africa, one hypothesis is that the rural diet is relatively protective but is abandoned with urban exposure that entails less carbohydrate and higher fat intake. In West Africa, sodium restriction is feasible as a solitary measure, but to achieve general adoption, it requires persuasion at a governmental level and multiple messages from various sources, including rural clinics and television (Cappuccio et al., 2004). The major problem is how to get lifestyle messages across and how to implement them.

HYPERTENSION IN SUB-SAHARAN AFRICAN POPULATIONS

Hypertension in sub-Saharan African populations is a widespread problem of immense economic importance because of its high prevalence in urban areas, its frequent

underdiagnosis, and the severity of its complications. Mass migration from rural to periurban and urban areas probably accounts at least in part for the high incidence of hypertension in urban black Africans. In semirural areas, inroads in lifestyle changes associated with “civilisation” may explain the apparently rising prevalence of hypertension. Significant segments of the African populations are still afflicted by severe poverty, famine, and civil strife, making the prevalence of hypertension difficult to determine. Black South Africans have a stroke rate twice as high as that of whites. Two lifestyle changes that are feasible and can help stem the hypertension epidemic in Africa are a decrease salt intake and a decrease in obesity, especially in women (Opie & Seedat, 2005).

Exact data are difficult to obtain in South African surveys. In 1983 our age-adjusted prevalence study (Seedat, 1983) of the adult population of Durban (World Health Organisation criteria ≥ 160 mm Hg) showed that hypertension was highest in urban Blacks of the Zulu tribe (25%), followed by whites (17%), ethnic Indians (14%), and lowest in rural Blacks (9%). The first Demographic and Health Survey in South Africa was conducted in 1998 in a random sample of 13,802 subjects aged 15 years or older, of whom 76% were Black, 13% of mixed ancestry, 8% white, and 3% Indian/Asiatic. The age-adjusted incidence of hypertension, namely BP $\geq 140/90$ mm Hg on medication, measured automatically, for the predominantly Black South African population was 21% (equal rates among males and females). For those > 65 years of age, 50% to 60% were hypertensive (Steyn et al., 1998), a slightly higher rate than those of a similar age group in semi-urban West Africa (Cappuccio et al., 2004).

Increasing obesity has been associated with increasing BP levels in West African and U.S. Blacks. In the South African Demographic and Health Survey of 1998, the incidence of obesity (body mass index was about 30% in females and 8% in males) was as high as 40%-49% in females and 13% in men (Steyn et al., 1998). Abdominal obesity was particularly common in females. The more urbanised these communities were, the higher the rate of obesity and the less prudent their diets became. It is probable that the lower male prevalence relates in part to the higher rate of heavy manual labour.

DIABETES MELLITUS IN SOUTH AFRICAN INDIANS

A dramatic increase in the prevalence of type 2 diabetes is observed in many parts of the Indian diaspora, which includes the United Kingdom, Mauritius, and Fiji. Whilst there are marked cultural and social differences within the Indian racial group, Indians have the unenviable distinction of achieving a high death rate from CHD. Much of this additional high risk of type 2 diabetes may be due to the increased risk of type 2 diabetes (four times that of Europeans), which develops in Indians about 10 years earlier than in South African whites (Seedat, 1999; Seedat, 2005).

In a community study (World Health Organization, 1985) to determine the prevalence and known risk factors for CHD of 778 subjects in the metropolitan area of Durban, diabetes mellitus was present in 15.8% (age and sex adjusted for 12.4% of the total sample).

INCIDENCE OF INSULIN RESISTANCE

Insulin resistance consists of glucose intolerance, hyperinsulinaemia, hypertension, dyslipidaemia, low plasma HDL cholesterol, and high triglyceride (Reaven, 1988).²¹ We have found that important factors denoting insulin resistance were associated with hypertension; hypercholesterolaemia, low plasma HDL cholesterol, truncal obesity, diabetes, and hypertriglyceridaemia were clustered in Indians in Durban (Seedat et al., 1991).²² The Indian population has been shown to have high plasma insulin levels with insulin glucose tolerance. Young Indian medical students develop metabolic risk factors for CHD at an early age, compared with young Black medical students (Morar et al., 1998). It has been suggested that insulin resistance in the South Asians of London, U.K., leads to a high incidence of CHD (McKeigue et al., 1991). We consider that this interesting concept could explain the high incidence of CHD in migrant Indians throughout the world.

Our study shows that diabetes mellitus is common in the South African Indian population. The aetiology may consist of insulin resistance, abnormal dietary patterns consisting of low energy intake, high intake of polyunsaturated fatty acids, low fibre intake, and physical inactivity (Wolmarans et al., 1999). Because of the higher risk of cardiovascular disease with diabetes, Indian patients should be treated, with lower thresholds for intervention, for hypertension, dyslipidaemia, and hyperglycaemia compared to white patients.

CORONARY HEART DISEASE IN DURBAN BLACKS—LINKS IN URBAN RACIAL GROUPS

CHD is still relatively uncommon in the Black population of South Africa. We embarked on a study to determine the prevalence of risk factors leading to CHD in the Black population of Durban. A total of 458 patients attending a hospital dental clinic were studied. The prevalence of CHD was 2.4%. The prevalence of risk factors were as follows: hypertension (TSP $\geq$ 140 mm Hg systolic and/or $\geq$ 90 mm Hg diastolic), 28.0% (31.9% for males, 25.4% for females); protective levels of high-density lipoprotein / total cholesterol $\geq$ 20.0%, 81.3%; diabetes mellitus, 4.9% for males, 2.9% for females; smoking $\geq$ 10 cigarettes per day, 28.1% for males, 3.4% for females; obesity, 3.7% for males, 22.6% for females. We found the Minnesota Coding system for electrocardiographic changes and the Rose questionnaire to be unreliable for eliciting CHD in Blacks. Hypercholesterolaemia was found to be less common, and this may explain the low incidence of CHD in Blacks. Epidemics of CHD seen in Indian, Coloured, and white South Africans can still be prevented in the Black population, but preventive measures must be initiated rapidly (Seedat et al., 1992).

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Chapter 243

METABOLIC SYNDROME IN THE PHILIPPINES AND ASIA: CONCEPTS AND CONCERNS

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Metabolic syndrome is a clustering of interrelated risk factors namely, dysglycemia, increased blood pressure, elevated triglyceride levels, low high-density lipoprotein levels, and obesity, particularly central obesity. This syndrome has been known for decades now and has been observed with the rising prevalence of obesity and the modern-day sedentary lifestyle. Insulin resistance linked with central, essentially visceral, adiposity remains to be postulated as its underlying pathogenetic mechanism. It is significantly associated with increased risk for the development of cardiovascular disease, 2x and higher, and for type 2 diabetes mellitus, 5x and higher, in individuals fulfilling its diagnostic criteria (Alberti et al., 2009).

Defining the diagnostic criteria of the metabolic syndrome (MS) has been a major task of several health organizations representing major stakeholders in the fields of cardiovascular and metabolic diseases. Varying sets of diagnostic criteria have been recommended previously by different organizations such as the World Health Organization (WHO) in 1998, the European Group for the Study of Insulin Resistance (EGIR) in 1999, the National Cholesterol Education Program's Adult Treatment Panel III (ATP III) in 2001, the American

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Association of Clinical Endocrinologists (AACE) in 2003, the International Diabetes Federation (IDF) in 2005 and the American Heart Association (AHA) and National Heart, Lung and Blood Institute (NHLBI) also in 2005 (Sperling et al., 2015). The harmonized definition of the metabolic syndrome (summarized in Table 1) was issued in 2009 from the joint scientific statement of the International Diabetes Federation Task Force on Epidemiology and Prevention (IDF), National Heart, Lung and Blood Institute (NHLBI), American Heart Association (AHA), World Heart Federation (WHF), International Atherosclerosis Society (IAS) and the International Association for the Study of Obesity (IASO) (Alberti et al., 2009, Sperling et al., 2015).

Table 1. Criteria for the clinical diagnosis of metabolic syndrome (MS)

Measure	Categorical cut points
Elevated waist circumference	Population or country-specific definitions
Elevated triglycerides (drug treatment for increased triglycerides is an alternate indicator)	≥ 150 mg/dl
Reduced HDL-cholesterol (drug treatment for low HDL is an alternate indicator)	Males: < 40 mg/dl Females: < 50 mg/dl
Elevated blood pressure (antihypertensive drug treatment for elevated BP is an alternate indicator)	Systolic BP ≥ 130 mm Hg and/or Diastolic BP ≥ 85 mm Hg
Elevated fasting glucose (drug treatment for elevated blood sugar is an alternate indicator)	FPG ≥ 100 mg/dl

NOTE: The use of ethnic-specific cut-offs for waist circumference is recommended and thus applied. The Asian cut-offs, ≥ 90 cm for males and ≥ 80 cm for females are used for the Philippine data from 2008. The presence of 3 of 5 criteria in each individual fulfills the diagnosis of metabolic syndrome.

Metabolic syndrome evolved both as a public health and a clinical problem largely because obesity is at the core of this clustering that carries a very high cardiometabolic risk. The contribution of obesity is critical thus eliciting further examination of the nature of obesity, the phenotypic profile, including the age, gender, ethnicity of the individuals with this syndrome. It becomes evident that individual characteristics define the cardiometabolic profile of different populations that in turn define their cardiometabolic risk. Better measures of obesity, particularly central obesity, are necessary and hence, waist circumference as a simple and cost-effective measure of central obesity is a critical criterion in diagnosing metabolic syndrome. The important ethnic-specific and gender-specific cut-offs for waist circumference reflects the epidemiologic evidence of the differences in cardiometabolic risk between individuals and between populations (Blucher, 2014, Seo and Rhee, 2014).

Given this general background on metabolic syndrome, the current discussion will now focus on the epidemiology of this syndrome among Filipino adults, the similarities in the cardiometabolic profile of other Asian and Asia-Pacific populations vis-à-vis their Caucasian and non-Asian counterparts. The increasing prevalence of overweight and obesity is apparently driving the global diabetes epidemic and the consequent rise in cardiovascular and related diseases. This chain of events in the face of nutrition and lifestyle transition in amidst Westernization in developing countries is further magnified in the Asia-Pacific region where the majority of people with new-onset type 2 diabetes reside. Approximately half of the 422 million adults with diabetes in 2014 are from the Southeast Asia and Western Pacific regions

(WHO 2016). The magnitude of the obesity problem, while clearly on the rise as well in these regions, is not proportional to the staggering diabetes burden in these regions.

Table 2. Survey data used for Figure 1

	Survey year	Prevalence of overweight adults (%) ^a	Prevalence of obese adults (%) ^a	Prevalence of diabetes (%)
USA	1999-2000 ^a	34.0	10.0	
	1999-2000 ^a			8.2
India	1998-99 ^a	30.0	7.7	
	2000 ^a			13.1
Philippines	1998 ^a	16.9	3.3	
	1996 ^a			5.1
Taiwan	1993-96 ^a	21.1	4.0	
	1996 ^a			9.2
Hong Kong	1996-97 ^a	25.1	3.8	
	1995-96 ^a			9.8
China	1999-2000 ^a	25.0	4.0	
	2000-2001 ^a			5.5
Singapore	1998 ^a	24.4	6.0	
	1997 ^a			8.4
Korea	2001 ^a	27.4	3.2	
	2001 ^a			7.6
Thailand	1998 ^a	28.3	6.8	
	1995 ^a			11.9

^a25 kg/m²-BMI-30 kg/m²; 18BMI-30 kg/m².

Source: From Yoon, Lee, et al., Lancet 2006; 368: 1684.

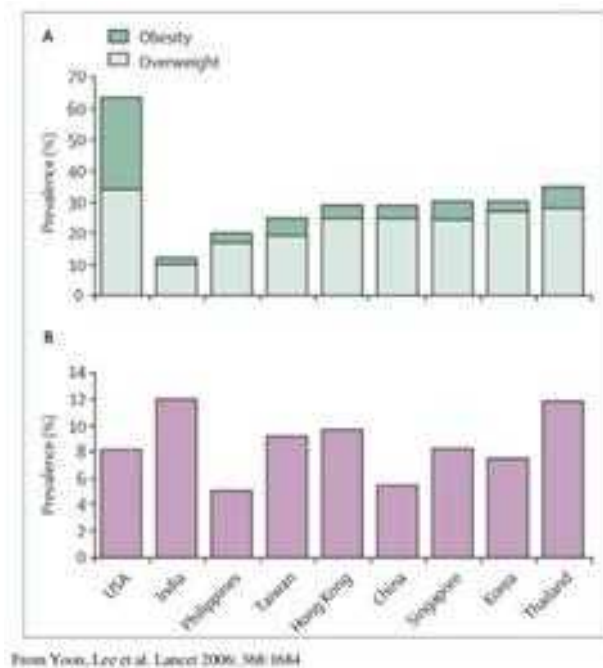


Figure 1. International comparison of prevalence of adult obesity and diabetes. (A) Proportion of overweight and obese adults, (B) Prevalence of diabetes.

In an international comparison in 2003, with 34% and 30% of Americans being overweight and obese, respectively, the US national prevalence of diabetes was 8.2%. The overweight and obese Asians, on the other hand, ranged then from 10 to 28% and 2 to 6.8%, respectively in 7 countries (India, Philippines, Taiwan, Hong Kong, China, Singapore, Korea, and Thailand) and yet the average diabetes prevalence in these countries already ranged from 5 to 12% (Figure 1 and Table 2) (Yoon, Lee, et al., 2006). Diabetes, an important component of the metabolic syndrome, appears to develop among Asians, including Filipinos, at lower levels of obesity. It thus becomes important to examine closely the distinguishing characteristics of Filipinos, and Asians for that matter, with metabolic syndrome.

THE PHILIPPINE DATA ON THE METABOLIC SYNDROME

In the Philippines, the national nutrition survey (NNS) provides critical data on food intake, nutrition and health status of Filipinos as mandated by Executive Order 352 guiding policy and decision-making in both the government and private sectors. Since the first survey in 1978, this statistical activity has been done regularly by the Food and Nutrition Research Institute (FNRI) of the Department of Science and Technology (DOST). The NNS has evolved in 1998 during the 5th NNS to include the clinical component in collaboration with the Department of Health and various health agencies and groups including medical specialty organizations. The NNS has been conducted every 5 years throughout the 17 regions of the Philippines covering the National Capital Region (NCR) and 80 provinces. In the 8th NNS in 2013, out of the 97.7 million Filipinos, 45,047 households with 172, 323 persons were used for the multi-staged stratified sampling design. The 9th NNS will be undertaken this year (2018). The NNS is clearly a veritable source of health information including prevalence and trends of leading health problems including non-communicable diseases in the country. The Philippine data on metabolic syndrome under discussion are derived from various reports, published papers and unpublished data from the NNS. (FNRI-DOST reports/pdf files, www.fnri.dost.gov.ph/nutrition-statistic). A few published articles outside the NNS have been included to elucidate the problem of metabolic syndrome in the Philippines.

From the 5th NNS (1998), analysis of data from 4541 Filipino adults aged 20 years and over showed the proportion of subjects with co-morbid factors increased with high fasting blood sugar (FBS), except for high cholesterol. Having high body mass index ($BMI \geq 25$), high waist-hip ratio ($WHR \geq 1.0$ in males, ≥ 0.85 in females) and high waist circumference ($WC \geq 102$ cm in males, ≥ 88 cm in females) in combination was associated with highest prevalence of high FBS in males (35.8%) and in females (14.5%) and with highest prevalence of hypertension in males (66.5%). Among females, the highest prevalence rate of hypertension (37.95) was seen among those with high FBS. This study indicated that waist circumference, with the higher cut-offs used, was the best predictor of metabolic risks, particularly of diabetes mellitus (Tanchoco et al., 2003).

Prevalence of metabolic syndrome among the same 4541 Filipino adults from the 5th NNS was determined using the NCEP and the IAS criteria in another study. For the IAS criteria, the Asian cut-offs for waist circumference, >90 cm in males and >80 cm in females, were used. Based on the NCEP criteria, the prevalence of metabolic syndrome was 14.2% and when stratified according to age, 6.6% (ages 20-39 years), 17.7% (ages 40-59 years), and

18.3% (ages 60 years and older). Using the IAS criteria, the prevalence of metabolic syndrome was 19.3% and with age stratification, 10.0%, 23.6%, and 24.1%, respectively. The study concluded that metabolic syndrome was common in this population and increased in prevalence with age. It was also noted that using NCEP criteria, instead of the IAS criteria, underestimated the prevalence of metabolic syndrome (Punzalan et al., 2004).

The 6th NNS, also called the National Nutrition and Health Survey (NNHeS) 2003-2004, also integrated the clinical component similar to the 5th NNS but also determined, for the first time, the national prevalence of 24 diseases and 11 risk factors. Using 3 sets of definitions/criteria of the metabolic syndrome, namely, NCEP/ATP III (2001), IDF (2005) and NCEP/ATP III-AHA/NHLBI (2005), the prevalence of metabolic syndrome in the adult Filipinos aged 20 years and older was found to be 11.9%, 14.5%, and 18.6%, respectively. Low levels of high-density lipoprotein cholesterol (HDL-C), mean level of 41.3 mg/dL, were seen in 60.2% of men and 80.9% of women, making it the most common component of the syndrome in the population (70.2%), similarly observed in the previous 5th NNS with prevalence of 84%. The prevalence rates of the other MS components were as follows: blood pressure $\geq 130/\geq 85$, 33.3%, abdominal obesity (WC ≥ 90 cm, male, ≥ 80 female), 26.1%, triglycerides ≥ 150 mg/dL, 20.6% and fasting blood sugar ≥ 100 mg/dL, 7.1%. Age-adjusted odds ratios showed that MS, by all 3 criteria, predisposed an individual to diabetes mellitus and stroke while MS using the IDF definition predisposed an individual to myocardial infarction (Morales et al., 2008).

In the analysis of data from the 7th NNS/ NNHeS 2008, the prevalence rate of MS utilizing the harmonized definition (Table 3) was 27.4%, significantly higher than the reported 18.6% in 2003. The prevalence rates of the individual components of MS similarly showed significant increases as follow: low HDL-C, 80.3%, abnormal BP, 39.3%, abdominal obesity, 29.8%, increased triglycerides, 30.1%, and elevated FBS, 12.2%. Both age and gender-related differences continued to be observed as in the previous NNS. Age-related increases in MS peaked in the age groups 50-59 years and 60-69 years, remaining high after age 70 years. Females had more abdominal obesity and lower HDL-C while men had higher BP and higher triglycerides (Table 4) (Jasul, unpublished data, 2008).

Table 3. Prevalence of metabolic syndrome among Filipino adults aged 20 years and above, based on the harmonized definition of the IDF, NHLBI, AHA, WHF, IAS and IASO 2009: NNHeS 2008

Age (years)	Males % (SE)	Females% (SE)	Both sexes % (SE)
20 - 29	12.3 (1.27)	8.4 (1.14)	10.4 (0.86)
30 - 39	26.7 (1.79)	20.1 (1.61)	23.3 (1.22)
40 - 49	31.7 (1.97)	31.5 (1.80)	31.6 (1.40)
50 - 59	38.9 (2.42)	45.6 (2.20)	42.7 (1.74)
60 - 69	28.3 (2.87)	46.8 (2.85)	38.7 (2.13)
≥ 70	15.8 (3.13)	38.3 (3.30)	29.3 (2.40)
All	25.8 (0.87)	28.9 (0.92)	27.4 (0.67)

More rigorous analysis of the data from the 7215 Filipino adults from the 7th NNS/NNHeS 2008 concluded that the prevalence rates of measured variables, particularly the components of MS and the risk factors for atherosclerosis, were higher compared with values obtained in 2003. Among adult Filipinos aged 20 years or older, the true prevalence of

hypertension was 20.6% and the prevalence of diabetes was 3.9% based on fasting blood glucose (FBG), 5.2% by FBG and history, and 6.2% with 2-hour post-load plasma glucose was determined. Obesity, defined as BMI ≥ 30 , was seen in 4.9% but obesity defined by abnormal waist-hip ratio (WHR) of 1.0 or higher in men and 0.85 in women, was seen in 10.2% and in 65.6%, respectively (Sy et al., 2012).

Table 4. Prevalence of the individual components of metabolic syndrome (MS) among Filipino adults aged 20 years and above, by sex

MS Component	Male % (SE)	Female % (SE)	Total % (SE)
Waist circumference Male ≥ 90 cm, Female ≥ 80 cm	17.8 (0.77)	41.0 (0.97)	29.8 (0.72)
Triglycerides ≥ 150 mg/dl	37.9 (0.95)	23.2 (0.80)	30.1 (0.67)
HDL, Males < 40 mg/dl, Females < 50 mg/dl	71.6 (0.90)	88.1 (0.71)	80.3 (0.62)
Blood Pressure, $\geq 130/\geq 85$ mm Hg	44.4 (0.98)	35.0 (0.88)	39.3 (0.70)
Fasting Blood Sugar, ≥ 100 mg/dl	11.9 (0.47)	11.6 (0.65)	12.2 (0.62)

Table 5. Prevalence of blood glucose abnormalities among Filipino adults aged 20 years and above: NNHeS 2008

Glucose abnormalities	Male	Female	Total
Impaired Fasting Glucose (IFG) (FBG >100 and <125 mg/dl) (%)	7.9	6.7	7.2
Impaired Glucose Tolerance (IGT) (2-hr PPBG >140 and <199 mg/dl) (%)	6.7	7.3	7.0
Combined IFG/IGT (%)	0.4	0.6	0.5
Diabetes Mellitus, DM (FPG ≥ 126 and 2-hr PPBG ≥ 200 mg/dl)(%)	7.0	7.4	7.2

Patterns of glucose abnormalities were analyzed in a sub-study of the 7th NNS/NNHeS 2008 to address the contrasting data on prevalence and incidence rates reported from studies outside the NNS. Using FBS, 2-hour post-load glucose and DM questionnaire, the true diabetes prevalence was 7.2% and the prevalence of pre-diabetes was summed at 10.2%, with impaired fasting glucose (IFG), 2.7%, impaired glucose tolerance (IGT), 7.0% and both IFG/IGT, 0.5% (Table 5). Differences in the prevalence rates of diabetes between urban and rural populations were significant at 8.3% versus 5.8%, respectively (Jimeno et al., 2015).

From the results of the 8th NNS/NNHeS 2013, the burden of non-communicable diseases (NCDs) was reported and summarized as prevalence rates of selected risk factors. NCDs accounted for two-thirds (67%) of total deaths in the country in 2012. Obesity (BMI ≥ 30) was seen in 6.8% (males, 5.2%, females, 8.3%), with higher rates in urban areas (10.1%, National Capital Region (NCR)) than rural areas (around 4% in Ilocos Region, Cagayan Valley, Western Visayas, Autonomous Region in Muslim Mindanao (ARMM)). Combining overweight and obesity (BMI ≥ 25) totaled 31.1% of adult population (males, 27.6%, females, 34.4%), simply put, three out of ten Filipinos were overweight or obese. Central or android obesity, based on high waist circumference (males, ≥ 102 cm, females, ≥ 88 cm), was seen in 3.8% of males and 23.1% of females and based on high waist-to-hip ratio (WHR) (males ≥ 1.0 , females ≥ 0.85), was seen in 8% of males and 63.2% of females. Hypertension (SBP ≥ 140 , DBP ≥ 90) was present in 22.3% of the adult population (males, 25.1%, females,

19.9%) while diabetes (fasting blood sugar (FBG) ≥ 126 mg/dl) was seen in 5.4% (males, 5.6%, females, 5.3%).

Abnormal cholesterol levels were reported as follows: total cholesterol (TC borderline 200-239 mg/dl to high ≥ 240 mg/dl), 46.9% (males, 41.5%, females, 51.4%), LDL cholesterol (LDL-C borderline 130-159 mg/dl to high ≥ 160 mg/dl), 47.2% (males, 40%, females, 53.6%) and triglycerides (TG borderline 150-199 mg/dl, high 200-399 mg/dl to very high ≥ 400 mg/dl), 38.6% (males, 46.4%, females, 31.8%). Low HDL cholesterol (HDL-C males, <40 mg/dl, females, <50 mg/dl) was seen in 71.3% (males, 63.2%, females, 78.2%). Insufficient physical activity (not meeting 3 or more days of vigorous-intensity activity of at least 20 minutes per day or 5 or more days of moderate-intensity activity or walking of at least 30 minutes per day) was seen in 45.2% (males, 36.7%, females, 52.7%) (FNRI DOST, 2013).

Prevalence of MS has not been reported from the 8th NNS/NNHeS 2013 data but clearly, the prevalence rates of the MS components remained significantly high. The trends in the prevalence rates of these important risk factors reflect continuing rise from 1993 (4th NNS) to 2013 (8th NNS). The accompanying figures (Figures 2-5) illustrate these alarming trends that point to unabated increasing cardiometabolic risk in the general adult Filipino population. While the prevalence of chronic energy deficiency has been slowly decreasing, the prevalence of overweight and obesity has almost doubled (Figure 2). The data on the pediatric age groups also show increasing trend but to a much lesser degree. Overweight in children below ten years of age was seen in around 2% and among adolescents, less than 5%. Central obesity has been similarly increasing and more markedly among females (Figure 3). Hypertension prevalence has been relatively steady in the 21-25% range (Figure 4) but the trends in high fasting glucose has been steadily increasing (Figure 5) (FNRI DOST 2013). The measures of glucose abnormality have varied in the different NNS and estimation of the true prevalence of diabetes mellitus may be limited by this variation, as addressed by Jimeno et al., (2015).

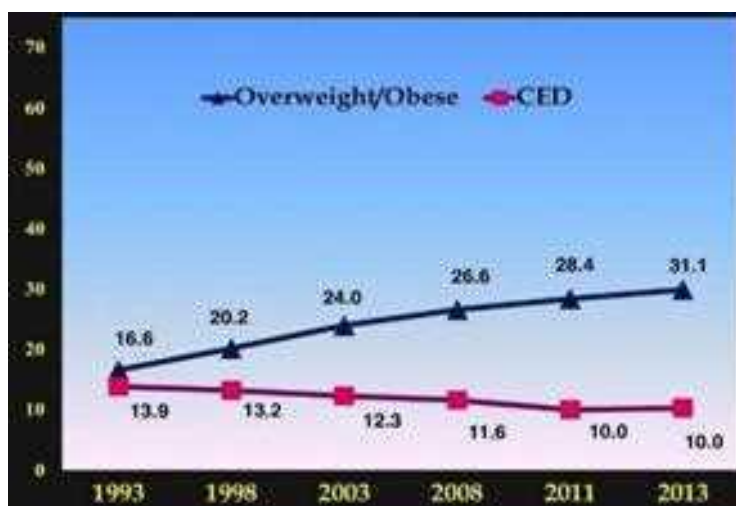


Figure 2. Prevalence of malnourished adults, ≥ 20 years old, Philippines, 1993-2013.

Differences in the cut-offs in the measured variables are common in published literature on obesity and metabolic syndrome. Determination of the cut-offs for BMI, WC and WHR that will help define levels of risk of co-morbidities was undertaken using data from the 6th

NNS/NNHeS 2003. This sub analysis from the 2003 results emphasized that with increasing body fatness, there is an increasing risk of related co-morbidities among adult Filipinos. The tentative cut-offs associated with risk of co-morbidities were BMI of 23 for overweight and 27 for obesity, WC of 90 cm for males and 85 cm for women and WHR of 1.0 for males and 0.95 for females. These tentative cut-offs were closer to the recommended cut-offs for Asia-Pacific islanders and Asians from the International Obesity Task Force (AP/IOTF) and were considerably lower than the WHO cut-offs (Florentino and Duante, unpublished data, 2004).

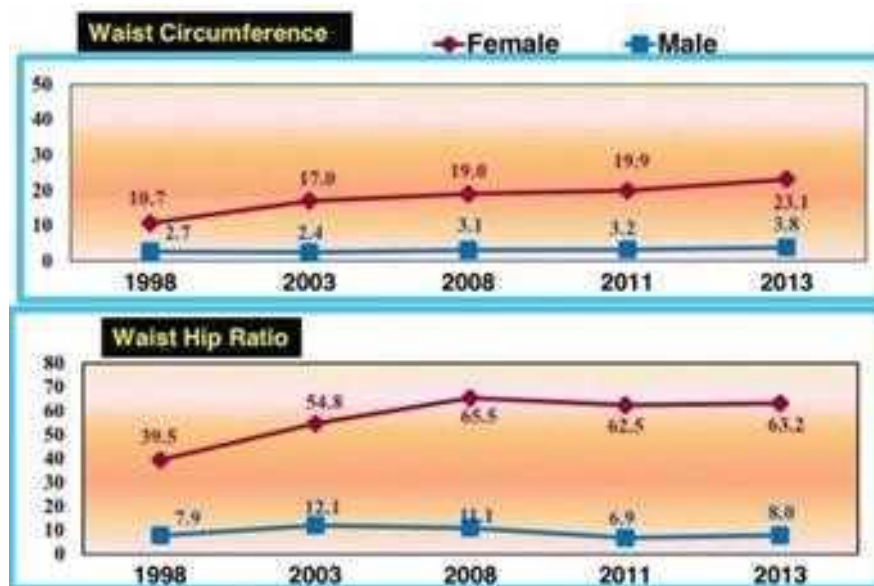


Figure 3. Trends in high waist circumference and high waist hip ratio prevalence among adults, 20 years old and over, Philippines, 1998-2013.

Similar analysis was done using the 7th NNS/NNHeS 2008 results and concluded that the odds of developing 2 or more risk factors among adult Filipinos were noted even at a much lower BMI (18 kg/m²) in both males and females. The tentative cut-offs from the 2008 data were BMI of 22.5 for overweight and 27 for obesity, WC of 78 cm for both males and females and WHR of ≥ 0.92 for males and ≥ 0.88 for females. These cut-offs were almost similar to the 2003 tentative cut-offs of the AP/IOTF (Duante, unpublished data, 2008).

Several studies independent of the NNS/NNHeS revealed similar findings of a very different profile of MS in Filipinos compared to Caucasians/non-Asians. In the Philippine cohort of the LIFECARE longitudinal study in Asia, 3,702 Filipinos aged 20 to 50 years old from Metro Manila and four nearby provinces were recruited. Prevalence of MS was 19.7%, based on the IDF criteria and 25.6%, based on the modified NCEP (mNCEP) or harmonized criteria (Table 1). The IDF criteria required the presence of abdominal obesity plus any 2 of the other risk factors while the mNCEP defined it as the presence of any 3 or more of the risk factors. This basic difference was reflected in higher MS prevalence in women by IDF, higher MS prevalence in men by mNCEP, with IDF missing 40% of men and 10% women identified as having MS by mNCEP. More males were categorized as having MS by mNCEP despite relatively normal waist circumference (mean WC 80.6 cm). MS was associated with increasing age, urban residence and employed status (Sy et al., 2014).

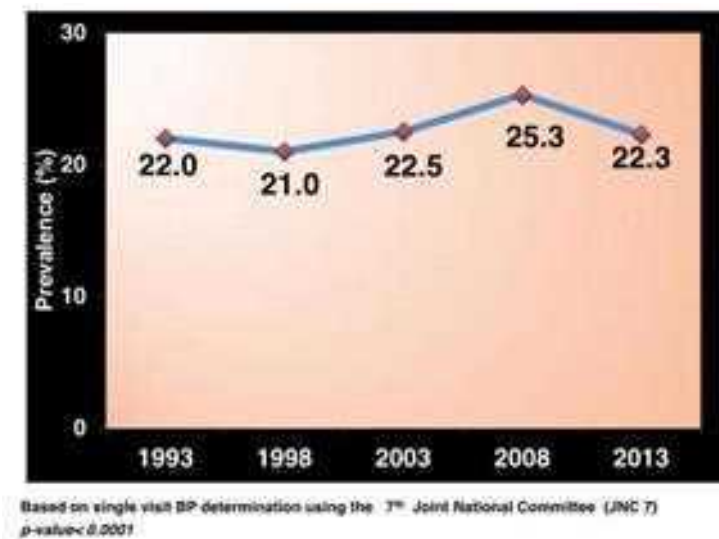


Figure 4. Trends in the prevalence of hypertension among adults ≥ 20 years old in the Philippines: 1993, 1998, 2003, 2008 and 2013.

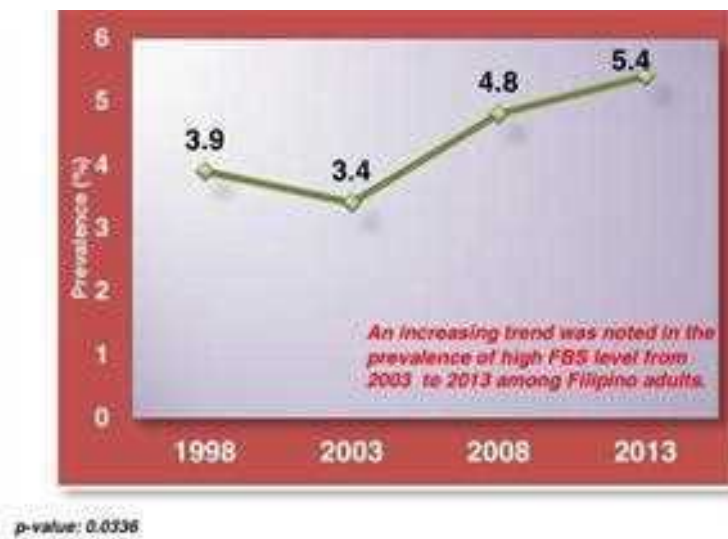


Figure 5. Trends in the prevalence of high fasting blood glucose among adults ≥ 20 years old, Philippines: 1998, 2003, 2008 and 2013.

In the Cebu Longitudinal Health and Nutrition Survey (CLHNS), the community-based survey followed a cohort of infants born in 1983 to 1984 with surveys immediately after birth, bimonthly for two years, in 1991, 1994-5, 1998-99, 2002, and 2005. In 2005, fasting blood were drawn for CVD biomarkers and genetics and 1,621 individuals aged 20-21 years (889 men and 732 women) were included in the cluster analysis using biomarkers. The study identified 5 distinct sex-specific clusters: 1) healthy/high HDL (with the addition of high LDL-C in women), 2) healthy/low blood pressure, 3) high blood pressure, 4) insulin resistant/high triglycerides, and 5) high C-reactive protein. Low HDL-C was the most prevalent risk factor at 65%. Men had higher prevalence of elevated triglycerides and

hypertension while women had higher prevalence of low HDL-C, elevated LDL-C and elevated HOMA-IR. Adiposity was most strongly associated with insulin-resistant/high triglyceride cluster. In this young (aged 20-21 years) and lean population (mean BMI 20-21, mean WC 72 cm (men), 68, (women), with 18% prevalence of overweight) with no significant clinical disease, cluster analysis identified patterns of cardiometabolic risk factors. Diet and environmental factors also influenced the predicted clustering of risk factors. The importance of screening both lean and overweight individuals for cardiometabolic risk was thus emphasized in such populations where the cardiometabolic risk is elevated even at lower BMI (Zubair et al., 2014).

In a rural community-based cross-sectional observational study in San Juan, Batangas, optimal cut-offs for BMI, WC and WHR for risk for cardiometabolic diseases were determined among 332 individuals, mean age of 48.4 years and 72% of whom were women. The optimal cut-offs for males and females were BMI of 24 and 23 kg/m², WC of 84 and 77 cm and WHR of 0.91 and 0.85, respectively. Similar to the analyses by Florentino and Duante and by Duante, lower indices of overweight and obesity, were associated with cardiometabolic diseases among Filipino adults in this rural community (Pagsisihan et al., 2016).

Table 6. Presence of metabolic syndrome in relation to different BMI categories and gender

BMI Category	Metabolic Syndrome		
	Male n (%)	Female n (%)	Total with Metabolic Syndrome n (%)
Normal (18.5-22.9 kg/m ²)	13 (21)	48 (33.3)	61 (29.6)
Overweight (23-24.9 kg/m ²)	41 (37.3)	59 (40.1)	100 (38.9)
Pre-obese (25-29.9 kg/m ²)	159 (63.5)	130 (53.1)	289 (58.9)
Obese (≥ 30 kg/m ²)	135 (64.6)	112 (69.9)	247 (62.4)
Overall			697 (51.0)

In a retrospective study of 1367 patient seen at the wellness center and the weight management center of a Philippine tertiary hospital, the prevalence of metabolic syndrome, defined by the mNCEP/harmonized criteria, and its individual components was determined across the different BMI categories. While the study population (mean age 53 years, mean BMI of 28 kg/m², and mean WC of 96.8 cm) did not reflect the general Filipino population, the finding of high prevalence of MS even in individuals with normal BMI (Table 6) suggests that cardiometabolic abnormalities are present even at lower and normal BMI levels (Mata and Jasul, 2017).

THE ASIAN DATA ON THE METABOLIC SYNDROME

In developing countries, the prevalence of obesity and metabolic syndrome is rapidly rising with the main causes all related to economic progress, namely, urbanization, nutrition transition and physical inactivity. This public health problem carries enormous burden of increased morbidity and mortality due to type 2 diabetes mellitus and cardiovascular disease and consequent effects on health expenditures and economic productivity. Nutrition transitioning led to a decrease in the undernourished population and an increase in the over

nourished population. This development is mirrored in the Philippines as described in the previous section of this discussion. Since the 1980s, obesity rates have increased three-fold or more in the Middle East, the Pacific Islands, Australasia, and China. Compiled data from developing countries on obesity, defined using varying BMI and WC cut-offs, showed rates as low as 2.9% to as high as 68%. Differences were evident based on gender, urban versus rural residence, educational attainment, and socioeconomic status, among others. Reported rates of metabolic syndrome using different definitions ranged from 6.5% to 46.5% in developing countries (Misra and Khurana, 2008).

Surveys from East Asian and Southeast Asian populations consistently showed increase in the prevalence of metabolic abnormalities associated with abdominal adiposity with cited MS prevalence of 10 to 30% using Asian-adapted definitions of obesity (BMI ≥ 25 kg/m²) and increased WC (males, ≥ 90 cm, females, >80 cm) (Nestel, et al., 2007). Defining obesity in the different Asian populations has become critical with the generally accepted observation that metabolic risks are greater in Asians than Caucasians at a given BMI. The inter-ethnic differences in percent body fat at a given BMI and in the metabolic responses to fatness have to be considered in setting which appropriate cut-offs to use for Asians in general and for individual ethnic groups (Pan and Yeh, 2008).

Considerations of the ethnic differences in abdominal and visceral fat distribution began early in the Asia-Pacific region. The influence of dietary patterns and physical activity on fat distribution and the development of MS even at lower or normal BMI supported the perspective that lower optimal cut-offs should be used not only for screening but also for strategies for intervention. Attention to lifestyle modification has been pushed early on in the Asia-Pacific region through public health initiatives to stem the tide of obesity and metabolic syndrome (Gill, 2001, Sullivan, 2001).

Recent systematic reviews however showed that the rising problem of MS in Asia remains staggering. Data from 15 Asia-Pacific countries showed the range of the prevalence rates of MS from a low of 11.9% in the Philippines to a high of 49% in urban Pakistan. Higher prevalence in women and in urban dwellers was consistent findings. Temporal trends were available for China, South Korea and Taiwan and all showed increasing prevalence for all three countries from 1993 to 2009. Despite differences in methodology, diagnostic criteria and age of subjects studied, MS is of epidemic proportion in the Asia-Pacific region, with nearly one-fifth of the adult population affected by MS in most countries (Ranasinghe et al., 2017).

Similar trends were reported in South Asia in a recent systematic review of 16 MS population-based prevalence studies from 5 countries. Four definitions of MS were used and the weighted mean prevalence rates of MS were 14.0% (WHO), 26.1% (ATPIII), 29.8% (IDF) and 32.5% (modified ATPIII). Half of the study population had low HDL-C levels and had hypertension. In general, females had a higher prevalence of MS and were more likely to have low HDL-C levels and central obesity. Males, on the other hand, were more hypertensive. These gender-based findings are consistent with the MS profile in Filipino and other Asian populations. Research remains limited despite the enormous burden of MS especially in Asian populations (Aryal and Wasti, 2006).

METABOLIC SYNDROME IN MIGRANT FILIPINOS AND MIGRANT ASIANS IN WESTERN COUNTRIES

Emerging data have shown that cardiometabolic diseases are common in Asian Americans despite mean lower BMI. Asian Americans are the fastest growing ethnic group in the US, numbering over 18 million in 2011. Filipino Americans (3.4 millions) are second only to the Chinese Americans (4.0 millions) and followed by Asian Indians (3.2 millions) and the rest of the migrant Asian population (Vietnamese, Korean and Japanese) (Hsu, et al., 2015). Striking differences in the risk of CVD, obesity, type 2 diabetes mellitus, hypertension, and other CVD risk factors are observed across the Asian-American population (Narayan et al., 2010). The large and the rising number of Asian Americans and their apparent high cardiometabolic risk present an important public health challenge needing better understanding and timely intervention (Palaniappan et al., 2011).

Seminal work by Araneta et al., showed that Filipina women aged 50 to 69 years, compared to Caucasian women, had larger WC and higher percentages of truncal fat, were less likely to be obese, less likely to smoke, consume alcohol, or take postmenopausal estrogen, and had lower HDL-C levels. Filipina women had higher prevalence of type 2 diabetes (36% vs 9%) and MS (34 vs. 13%). A total of 10% of Filipinas with diabetes were obese, compared with over 30% of Caucasians with diabetes. The high prevalence of diabetes in a non-obese ethnic group led to a realization that there is diversity in the development of diabetes across populations and that this high diabetes risk might be missed if Western standards of obesity were applied (Araneta et al., 2002).

Subsequent studies indicated that many Filipino Americans suffer from chronic illnesses, particularly type 2 diabetes, hypertension and dyslipidemia and central adiposity is a common. MS was seen in 18.3% of Filipino American men and women in Clark County, Nevada. Abdominal obesity was seen in 80.6%; hypertension in 47.7%; overweight in 36.7%; and type 2 diabetes in 11.7% (Dalusung-Angosta, 2013). Review of literature on the cardiovascular health of Filipinos in the US from 27 published studies concluded that Filipino Americans were at high risk for CVD, hypertension, type 2 diabetes and MS at lower BMI levels (Abesamis et al., 2015). A cross-sectional study of 335 Filipinos living in Rome, Italy similarly showed high prevalence of abdominal obesity (52.5%), BMI ≥ 25 kg/m² (44.5%), diabetes (6%), and hypertension (9%). Age and WC were associated with both diabetes and hypertension (Gentilucci et al., 2008).

Patterns seen in Filipino and Asian populations manifested as well in Asian Americans, similarly requiring the need to define obesity indices to better predict risk of developing diabetes and hypertension. In the Filipino American women cardiovascular study, using Asian-specific thresholds for BMI, WC and WHR increased the accuracy of prediction (Battie, et al., 2016). The high incidence of type 2 diabetes in non-obese Asian Americans, particularly Asian Indian and Filipinos, led to the recommendation that screening for type 2 diabetes in these populations should start at BMI of 23kg/m² (Wang et al., 2011, Hsu et al., 2015). Differences in the body fat percentages and body fat distribution are evident not only between Asian Americans and other ethnic groups but also between Asian Americans and Asian immigrants. These differences may largely affect susceptibility to developing cardiometabolic diseases (Alpert and Thomason, 2016, Unjali et al., 2017). Better measures of obesity, lower cut-offs for BMI, WC and WHR as indices of cardiometabolic risk, and

even newer indices such as triglyceride glucose (TyG), TyG waist circumference (TyG-WC), TyG-BMI and visceral adiposity index (VAI) may be helpful in predicting risk of developing cardiometabolic diseases, especially type 2 diabetes (Zheng, et al., 2016).

CONCLUSION AND RECOMMENDATIONS

Metabolic syndrome, as a public health and a clinical problem, develops along with increasing obesity. Distinct characteristics between individuals and between populations dictate the attendant cardiometabolic risk in metabolic syndrome. Filipinos, like other Asians, appear to develop metabolic syndrome at lower or even normal BMI levels and this observation maybe explained by higher visceral fat percentages. Gene-environment interaction evidently happened when westernization altered the lifestyle, dietary and physical activity patterns that led to obesity and metabolic syndrome. However, the similarities in cardiometabolic features in Philippine-based Filipinos and migrant Filipinos, as well as Asian residents and migrant Asians, are evidences of strong genetic influences in the disease causation. Characterization of the genetic factors underlying metabolic syndrome will help towards its better understanding, prevention and management. Definition of the syndrome with a universally accepted set of criteria with adjusted cut-offs for ethnic groups should be a goal so that future studies have standardized definitions, making comparisons meaningful. Population-based surveys on metabolic syndrome should be continued along with intervention studies to minimize, if not prevent, the attendant cardiometabolic risk.

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Chapter 244

BODY MASS INDEX, PERCENT BODY FAT AND FAT MASS INDEX AS SCREENING TOOLS FOR GENERAL OBESITY AMONG ADULT FEMALES OF AMRITSAR (PUNJAB)

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INTRODUCTION

Obesity has emerged as a chronic nutritional disorder almost three decades ago and still continues to escalate its dimensions as one of the most serious considerable non-communicable public health hazard (WHO, 2013). It is now so common that in many environments it is replacing more traditional public health concerns such as undernutrition, infectious diseases, communicable diseases and recognised as a major risk factor for developing hypertension (Warren et al., 2012), lipid disorders (Brown et al., 2000; Sherwood, 2010), glucose intolerance (Kannel, 1987), T2DM (Kahn et al., 2006), heart disease (Taylor et al., 2010), stroke (Oeschet al., 2017), osteoarthritis (King et al., 2013), CVDs (Vangaal et al., 2006), certain cancers (Singhal et al., 2013) and all-cause morbidity and mortality (WHO, 2000; Dalton et al., 2003; Kopelman et al., 2006; Whitlock et al., 2009; Shukla et al., 2014). It is estimated that 2.8 million people die each year and 35.8 million of global disability-adjusted life years (DALYs) across the globe are caused by overweight and obesity (WHO, 2016). The worldwide prevalence of obesity nearly tripled between 1975 and 2016. Very recent data shows that globally 650 billion adults (≥ 18 years) were observed to be obese. In other words, 13% of the world's adult population was diagnosed as obese, out of which 11% of males and 15% of females manifested obesity (WHO, 2016; Behl and Misra, 2017; Meharda et al., 2017). Obesity can be measured in two ways i.e., general obesity and central/abdominal obesity. The

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accumulation of fat to that extent that can impair health is known as general obesity. It is prime most important health concern especially among women (Amugsi et al., 2017). It is a critical force behind the progression of an asymptomatic cluster of non-communicable diseases called as metabolic syndrome (Grundy, 2004). However, obesity is not only pivotal cause for the occurrence of metabolic and cardiovascular diseases but also responsible for social stigmatization, psychosocial stress and psychological morbidity (Geiss et al., 2001; Kraig and Keel, 2001). Furthermore, the prevalence of obesity is more pronounced among those residing in the urban areas as compared to rural areas (Bhadra et al., 2005; Senet al., 2013; Kamboj et al., 2017). Currently, the obesity has attained an alarming figures in our nation with approximately 30-65% of adult urban Indians is either overweight, or obese (Mondal and Sen, 2014; Pradeepa et al., 2015). Importantly, this predominance is due to rapid demographic transitions, nutrition transitions and socioeconomic transitions. India, especially Punjab, is a unique example of such transitions, because it has undergone such transitions at a rate much faster than other states of India. However, to the best of my knowledge, there is no published data illustrating the comparative picture of general obesity among adult women using anthropometric and body composition variables from Amritsar. Therefore, in the present study, an attempt has been made to generate baseline data about the prevalence of general obesity among adult females of Amritsar on applying Body Mass Index (BMI), Percent Body Fat (PBF) and Fat Mass Index (FMI) criteria.

MATERIALS AND METHODS

The data for the present cross-sectional study was collected from adult females ranging in age 40-65 years and residing in various urban and rural areas of Amritsar district during the period from June 2013 to September 2016 by using a convenient sampling method. The participants were found in their homes and data was collected from door to door. At each urban and rural area, a uniform protocol of recruitment was followed. Ethical clearance from the Institutional Ethics Committee of Guru Nanak Dev University, Amritsar was obtained prior to carrying out the study.

The study group included 1520 females, out of which, 800 females were urban and 720 females were rural. First of all, women were taken into confidence and then contacted for the study according to their convenience and prior appointment. After fully explaining the nature, procedure, aims and objectives of the study to all the females in Punjabi language, verbal as well as written informed consent was obtained. In person interaction provides an opportunity to the investigator to extract maximum information from the participant about socio-demographic characteristics (name, caste, age and type of family), socioeconomic status (education, occupation and income), lifestyle habits (dietary pattern, physical activity pattern and sedentary behaviour) and menstrual status (regular/irregular/completely stopped) from each subject by investigator herself after ensuring confidentiality of the information. Anthropometric measurements (body weight, height) were taken on each subject using standard methodology given by Weiner and Lourie (1981) while subjects were lightly clothed and wore no shoes. Body weight was measured to the nearest 0.1 kg using automated calibrated electronic scale. Standing height was measured without shoes to the nearest 0.5centimetre using

anthropometric rod. From height and weight measurements, BMI was calculated by dividing weight in kilograms with height in metre squared as follows:

$$\text{BMI} = \text{Weight (kg)} / (\text{Height})^2 \text{ (m)}.$$

The suggested critical limits of BMI by WHO (2000) were used for the assessment of general obesity:

Category	WHO (2000) cut-offs
	BMI (kg/m ²)
Underweight	<18.5
Normal	18.5-22.9
Overweight	23.0-24.9
Obesity	≥25

Per cent Body Fat (PBF) is the percentage of total body weight that consists of fat only not fat-free mass (water, muscle, bone and vital organs). It is evident from the published literature that no criterion for the assessment of body composition has been recommended for South-Asians. Therefore, following criterion of PBF given by Gomez-Ambrosi et al. (2012) was used for the assessment of general obesity among adult females:

Category	PBF cut-offs
Normal	≤30
Overweight	30.1-34.9
Obese	≥35

Fat Mass Index (FMI) estimate or quantify fat stores accurately is the integral part of the prevention and treatment of obesity-related conditions. A potential, more simplified, accurate and highly useful indicator of body adiposity in field research is FMI. This index was first introduced in a study involving nutritional assessment (Van Itallie, 1990) and requires information on body height and fat mass content for calculations. It was calculated by dividing total body fat (kg) by square of height (m).

$$\text{FMI} = \text{Fat mass (kg)} / (\text{Height})^2 \text{ (m)}.$$

In the present study, the prevalence of general obesity was determined using FMI levels divided into separate quartiles for females. Following FMI quartiles recommended by Liu et al. (2013) were used for the assessment of general obesity:

Quartiles	FMI cut-offs (kg/m ²)	Category
Q1	<5.25	Underweight
Q2	5.25-6.32	Normal
Q3	6.33-7.93	Overweight
Q4	≥ 7.93	Obese

The data was analysed using the Statistical Package for Social Sciences (SPSS Inc, Chicago, IL, USA version 21). Mean and standard deviations were calculated for continuous variables and percentage for categorical variables. In order to test the level of significance of differences between the baseline characteristics of urban and rural women, Student's t-test was applied. The Chi-square test was applied to compare differences between the proportions.

RESULTS

The results of the present study have been arranged in tabular form as well as graphical form, wherever possible, along with the statistical interpretation.

Distribution of Participants According to Place of Residence

Out of 1520 subjects, 52.6% (800) females were urban and 47.4% (720) females were rural (Table 1, Figure 1).

Table 1. Distribution of participants according to place of residence

Category	Adult Females
Urban	52.6 (800)
Rural	47.4 (720)
Total	100.0 (1520)

Figures in parentheses indicate the number of subjects.

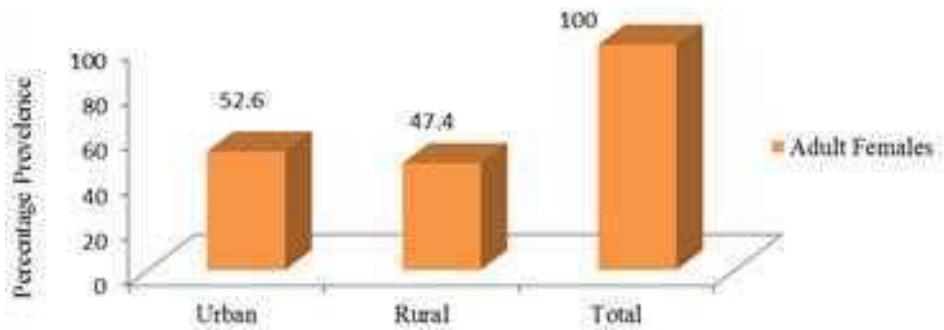


Figure 1. Histogram showing the distribution of adult females according to place of residence.

Anthropometric and Body Composition Variables Studied among Adult Females of Amritsar

Table 2 shows mean ($\pm$ SD) values of anthropometric and body composition variables studied among adult Amritsar females after stratification of females according to the region. Considering anthropometric variables, among urban and rural females, it was noticed that urban females were having more weight (65.90 ± 14.3 kg) than rural females (63.47 ± 14.0 kg) whereas rural females were taller (155.98 ± 6.0 cm) than urban females (154.91 ± 5.9 cm) and

the differences in weight ($p<0.01$) and height ($p<0.05$) were statistically significant between urban and rural females. Mean value of Body Mass Index (BMI) among urban and rural females was 27.45 ± 5.7 kg/m² and 26.09 ± 5.7 kg/m², respectively, and the difference in the mean values of BMI between the two groups was highly significant ($p<0.001$).

Table 2. Mean and standard deviation ($\pm$ SD) values of anthropometric and body composition variables of Amritsar adult females studied

Variable	Total (1520)				't'-value
	Urban (800)		Rural (720)		
	Mean	SD	Mean	SD	
Weight (kg)	65.90	14.3	63.47	14.0	3.345**
Height (cm)	154.91	5.9	155.98	6.0	3.456*
BMI	27.45	5.7	26.09	5.7	4.632***
TBF	33.16	8.0	28.93	9.3	6.019***
PBF	44.44	10.9	43.82	9.7	1.164***
FFM	37.32	7.4	38.23	9.8	2.019*
FMI	13.92	5.4	12.54	4.3	5.754***

*Significant at $p<0.05$, **Significant at $p<0.01$, ***Significant at $p<0.001$.

BMI: Body Mass Index (kg/m²), FFM: Fat-Free Mass (kg),

FMI: Fat Mass Index (kg/m²), PBF: Percent Body Fat,

TBF: Total Body Fat (kg).

In context to body composition variables, compared to rural counterparts, higher mean value of total body fat (urban 33.16 ± 8.0 kg vs. rural 28.93 ± 9.3 kg, $p<0.001$) was observed in urban females. In addition to this, the differences were found to be highly significant ($p<0.001$ for both variables) in the mean values of per cent body fat (urban: 44.44 ± 10.9 vs. rural: 43.82 ± 9.7) and fat mass index (urban 13.92 ± 5.4 kg/m² vs. rural 12.54 ± 4.3 kg/m²) between the two groups. In contrast to this, rural females were found to have significantly ($p<0.05$) elevated levels of fat-free mass (urban 37.32 ± 7.4 kg vs. rural 38.23 ± 9.8 kg) than urban females.

Assessment of General Obesity

BMI criterion of WHO (2000): Table 3 and Figure 2 shows the percentage prevalence of obesity in the study females using WHO (2000) criterion of BMI for Asian populations. According to this classification, the overall prevalence of obesity was 61.4% whereas 12.8% females were overweight, 19.6% females were normal and only 6.2% females were underweight. After stratification of females according to region, it was noticed that the prevalence of obesity was 68.7% and 53.3% among urban and rural females, respectively. The difference in the percentage prevalence of obesity between urban and rural females was found to be statistically significant ($\chi^2=37.37$, $df=1$; $p<0.001$). It is clear from the table that the prevalence of overweight, normal and underweight urban females was 10.6%, 15.4% and 5.3%, respectively, whereas the corresponding figures for rural females were 15.3%, 24.3% and 7.1%, respectively.

Table 3. Percentage prevalence of General Obesity according to Body Mass Index (WHO, 2000) criterion among adult females of Amritsar

CATEGORY	ADULT FEMALES			
	Urban (800)	Rural (720)	Total (1520)	χ^2 -value
Underweight	5.3 (42)	7.1 (51)	6.2 (93)	1.91
Normal	15.4 (123)	24.3 (175)	19.6 (298)	18.61***
Overweight	10.6 (85)	15.3 (110)	12.8 (195)	6.93**
Obese	68.7 (550)	53.3 (384)	61.4 (934)	37.37***

Figures in parentheses indicate the number of subjects.
*Significant at $p<0.05$, **Significant at $p<0.01$, ***Significant at $p<0.001$.

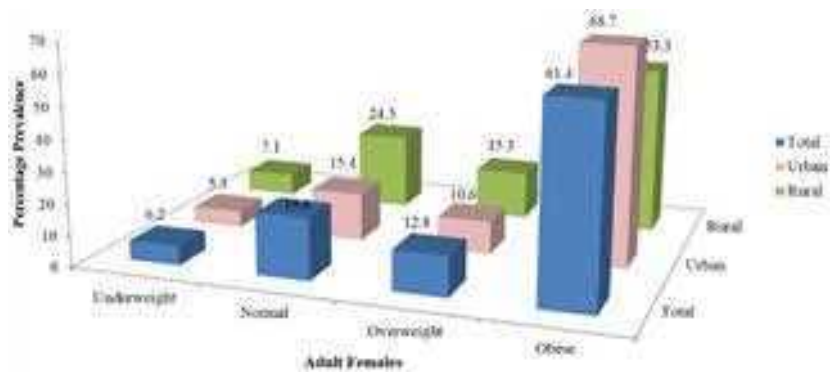


Figure 2. Histogram showing the percentage prevalence of underweight, normal, overweight and obese among adult females according to Body Mass Index (WHO, 2000) criterion.

Percent Body Fat (PBF)

It is defined as the proportion of total body fat mass of total body weight and it accurately predicts cardiovascular risks than BMI (Zenget al., 2012). Table 4 and Figure 3 depict the percentage prevalence of obesity assessed with the help of per cent body fat determined by Bioelectrical Impedance Analysis (BIA) among females according to per cent body fat criterion (Gomez-Ambrosiet al., 2012). The overall prevalence of obesity was 80.3% (urban 83.2% vs. rural 76.9%). On the other hand, 11.5% females were observed as overweight (urban 8.5% vs. rural 14.9%) and 8.2% as normal (urban 8.3% vs. rural 8.2%). The difference in the percentage prevalence of obesity between urban and rural females was statistically significant ($\chi^2=9.12$, $df=1$; $p<0.01$).

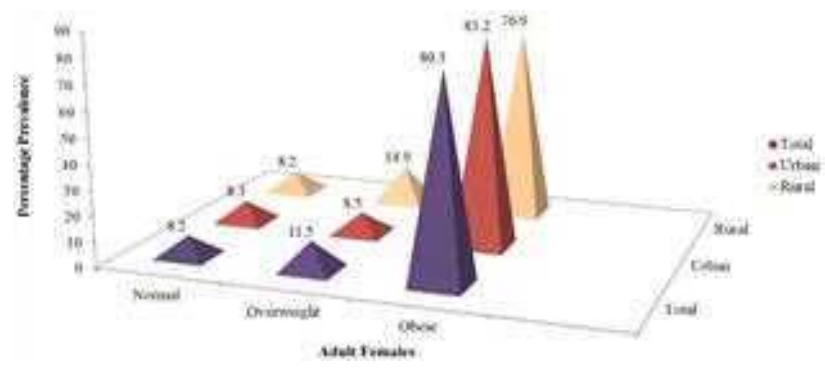


Figure 3. Histogram exhibiting the percentage prevalence of normal, overweight and obese among adult females using Percent Body Fat (PBF) criterion.

Table 4. Percentage prevalence of General Obesity using Percent Body Fat (PBF) criterion as given by Gomez-Ambrosi et al. (2012) among adult females of Amritsar

CATEGORY	ADULT FEMALES			
	Urban (800)	Rural (720)	Total (1520)	χ^2 -value
Normal	8.3 (66)	8.2 (59)	8.2 (125)	–
Overweight	8.5 (68)	14.9 (107)	11.5 (175)	14.43***
Obese	83.2 (666)	76.9 (554)	80.3 (1220)	9.12**

Figures in parentheses indicate the number of subjects.

*Significant at $p < 0.05$, **Significant at $p < 0.01$, ***Significant at $p < 0.001$.

Fat Mass Index (FMI)

Fat mass index was first introduced by Van Itallie et al., (1990) and is calculated by taking the total body fat mass component from bioelectrical impedance analysis and dividing it by height squared. Table 5 and Figure 4 demonstrate the percentage prevalence of obesity among participants using fat mass index criterion (Liu et al., 2013). In the present sample, the overall prevalence of obesity was 88.5%. In addition to this, 5.8%, 2.9% and 2.8% females were encountered as overweight, normal and underweight, respectively. Region-wise prevalence of obesity in the study participants was almost similar (urban 88.7% vs. rural 88.4%) and the difference between the two groups was statistically non-significant. Further, it was noticed that 4.6% (urban) and 7.1% (rural) females were overweight, 3.8% (urban) and 1.9% (rural) were normal, and 2.9% (urban) and 2.6% (rural) were underweight.

Table 5. Percentage prevalence of general obesity using Fat Mass Index (FMI) quartiles as given by Liu et al. (2013) among adult females of Amritsar

Category	Urban (800)	Rural (720)	Total (1520)	χ^2 -value
Underweight	2.9 (23)	2.6 (19)	2.8 (42)	0.02
Normal	3.8 (30)	1.9 (14)	2.9 (44)	3.79
Overweight	4.6 (37)	7.1 (51)	5.8 (88)	3.76
Obese	88.7 (710)	88.4 (636)	88.5 (1346)	0.03

Figures in parentheses indicate the number of subjects. *Significant at $p < 0.05$, **Significant at $p < 0.01$.

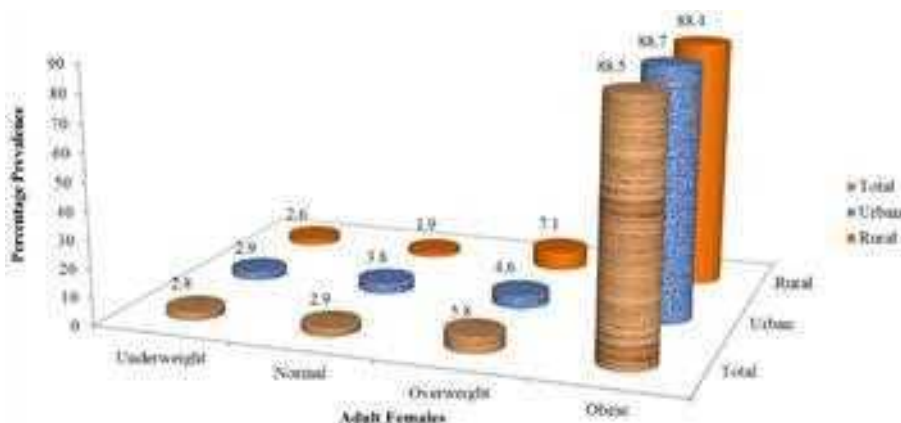


Figure 4. Histogram demonstrating the percentage prevalence of underweight, normal, overweight and obese among adult females using Fat Mass Index quartiles.

DISCUSSION

The anthropometry is pioneer in the series of obesity assessment methods in large field surveys and epidemiological studies. The measurement of anthropometric index known as Body Mass Index (BMI) is found as the simplest, easiest, non-invasive and cost-effective potential indicator of medical complications of obesity (Ouyang et al., 2015; Choi et al., 2017). In the nineteenth century, the mathematician and social statistician Adolphe Quetelet observed that the weight of the average person was proportional to the square of the height. The ratio of body weight measured in kilograms divided by the square of the height measured in metres was termed as quetelet's index and later renamed as body mass index (Keys et al., 1972). The simplicity and ease of measurement have entrenched the widespread use of BMI as a marker of adiposity not only for epidemiological purposes but also in clinical practice. In the present study, the mean values of BMI observed in urban and rural females were $27.45 \pm 5.7 \text{ kg/m}^2$ and $26.09 \pm 5.7 \text{ kg/m}^2$, respectively and the difference in the mean values of BMI between urban and rural females was statistically significant ($p < 0.001$).

WHO (2000) classification of BMI has been recommended for Asian population including lower cut-off of BMI for the assessment of obesity because Asian people depict substantial risk of T2DM and CVDs at lower weight or fat accumulation (WHO, 2004). The overall prevalence of obesity was found as 61.4% on applying BMI criterion of WHO (2000) in the females studied (Table 3). The difference in the prevalence of obesity between urban females (68.7%) and rural females (53.3%) was statistically significant ($\chi^2 = 37.37$, $df = 1$, $p < 0.001$). The results of the present study were compared with the general female populations of different parts of India to expedite a relative estimation of obesity prevalence. Table 6 presents the percentage prevalence of obesity according to BMI criteria of WHO (2000) among women residing in various urban regions of India. Nonetheless, the extent of obesity is not firmly comparable because of divergence in the methods of measurements, dissimilarity in sample size and study design, difference in age and socioeconomic status of subjects, ethnic variation, diverse food habits, their lifestyle and periodic dissimilarities in the studies. It is very clear from this table that the prevalence of obesity using BMI criterion of WHO (2000) among urban Indian females varies considerably from one region to another region with rates as high as 71.8% among females of West Bengal (Das and Bose, 2006) and as low as 15.6% among females of South Delhi (Misra et al., 2001). After three years in 2003, the prevalence of obesity was observed to be four times higher i.e., 66.7% in New Delhi females depicting a rising trend with the passage of time under similar geographical conditions (Misra et al., 2003). Apparently, the estimates of obesity in the present study were observed to be close to the females of New Delhi. In addition to this, Reddy et al. (2002) performed an epidemiological study among New Delhi females and examined 48.0% females as obese. In the western region, three cross-sectional studies were performed by Malshe and Udipi (2017), Rathi et al. (2014) and Senet et al. (2009), and reported 43.6%, 40.5% and 29.3% females as obese residing in Mumbai city and Pune city of Maharashtra and Jalpaiguri, West Bengal, respectively. Moreover, 30.2% prevalence of obesity was assessed among adult females of Rajasthan by Gupta et al. (2002). In the Southern region, the most latest study for the assessment of obesity among 1000 Karnataka females ranging in age 15-64 years was accomplished by Nagendra et al. (2017) and revealed 34.9% obesity. In an earlier study carried out in Dharwad, Dandeli and Belgaum districts of Karnataka, 63.3% females yielded

obesity (Goyal et al., 2012). Among Chennai females, Anuradha et al. (2011) observed the prevalence of obesity as 19.8% whereas 31.2% females were noticed as obese by Deepa et al. (2009). In the eastern region, a very recent cross-sectional study was executed by Senet al. (2017) and analysed 48.7% females falling in the category of obesity.

The prevalence of obesity among women of Punjab has also been studied by other investigators. Girdhar et al. (2016) and Singh et al. (2015) carried out two cross-sectional studies in Ludhiana on 324 females (20-60 years) and 618 females (25-64) of Ludhiana and diagnosed 29.6% and 28.8% females as obese according to BMI criterion of 2000 and 1998, respectively. On applying WHO (2000) criterion of BMI, the prevalence of obesity varied from 23.2 - 34.3% among 1088 females of Punjab ranging in age 45-69 years and 18-44 years, respectively (Tripathy et al., 2016). In Amritsar, the figures of obesity were found to be 56.4% on investigating 172 females by Randhawa and Sidhu (2014). One of the large sample size (N=3000) study conducted in Punjab by Sidhu and Randhawa (2014) reported 33.4% females as obese using Asian BMI cut-offs (≥ 25 kg/m²). In another study on Punjabi urban females, Sidhu et al. (2005) found 21.1% obese females as per BMI (WHO, 1998) criterion of obesity. Sidhu and Prabhjot (2004) performed a study on 500 Punjabi women and reported 15.0% prevalence of obesity. Sidhu and Tatla (2002) studied adult Punjabi females and reported 25.3% of them as obese (BMI ≥ 30.0 kg/m²). It can be deciphered from this table that Amritsar females were noticed to be more obese as compared to females residing in other districts of Punjab.

Table 7 presents a compilation of studies demonstrating the prevalence of obesity reported in rural females of India. A recent study performed by Bharali et al. (2017) involving adult Nyishi tribal females in Arunachal Pradesh found 9.5% prevalence of obesity according to WHO (2000) criterion of BMI. In addition to this, two cross-sectional studies were carried out among tribal females hailing from Assam (Mondal et al., 2016) and Manipur (Mungreiphy and Kapoor, 2008) and examined 15.2% and 27.1% females as obese (BMI ≥ 25 kg/m²). Furthermore, 36.9% females of Haryana aged ≥ 20 years were categorized as obese (BMI ≥ 25 kg/m²) during a population-based study attempted by Verma et al. (2016). Another study, among rural females of Tamil Nadu, the prevalence of obesity was found to be 21.2% by the WHO (2000) classification of BMI (Little et al., 2016). Assessment of obesity among females of union territory named as Puducherry was accomplished by Shrivastava et al. (2015) and findings of the study revealed that 27.3% females were obese as per BMI (2000) classification.

In the same year, a community-based study was conducted in Kerala by Bindhu et al. (2014) revealed 44.7% females as obese using BMI (≥ 25 kg/m²) cut-offs. The prevalence of obesity among Tamil Nadu females was studied by Chauhan et al. (2015) and found 23.8% females as obese (BMI ≥ 25 kg/m²). Almost similar prevalence of obesity was encountered among females of Uttar Pradesh (22.0%) and Maharashtra (22.7%) on employing WHO (2000) classification of BMI (Kumar et al., 2014; Rath et al., 2014). The higher rates of obesity (40.0%) were observed in Delhi females by Reddy et al. (2002) using BMI (≥ 25 kg/m²) cut-offs. Other than this, very few studies have been performed in rural areas of Punjab to assess obesity.

Comparison of three major studies conducted by National Family Health Survey (a multicentric study; NFHS-2 during the period from 1998-1999; conducted on 90,000 women in the age group of 15-49 years in 26 states), NFHS-3 (2005-2006, conducted on 1,24,385 women in the age group of 15-49 years in 29 states) and NFHS-4 (2015-2016, conducted on

6,99,686 women in 29 states and 7 union territories) was done. NFHS-2 and NFHS-3 used BMI ≥ 25 kg/m² criterion for the assessment of overweight and obese individuals while in NFHS-4, BMI ≥ 25 kg/m² criterion was applied for the assessment of obese individuals only.

Table 6. Percentage prevalence of general obesity among urban Indian females reported in various studies using BMI criteria of WHO (2000)

Place/Area/State	Age group (years)	No. of females	Percentage prevalence using BMI cut-offs	Investigator
			≥25 kg/m ²	
Other than Punjab				
Meerut	≥18	567	---	Kamboj et al. (2017)
Mumbai	21-45	1500	43.6	Malshe and Udipi (2017)
Agartala, Tripura	25-65	388	48.7	Senet al. (2017)
Karnataka	15-64	1000	34.9	Nagendra et al. (2017)
Udipi and Manipal areas of Karnataka	40-70	140	42.1	Ranasinghe et al. (2017)
Aligarh, Uttar Pradesh	15-65	2002	---	Khayyam et al. (2015)
Town in Central India	≥17	267	---	Jain et al. (2015)
Delhi	18-50	123	---	Dua et al. (2014)
Pune, Maharashtra	20-45	518	40.5	Rathi et al. (2014)
Ahmedabad, Gujarat	20-60	200	---	Saboo et al. (2014)
Pantnagar, Uttarakhand	18-28	629	---	Raguvanshi and Singhal (2013)
Jalpaiguri, West Bengal	20-60	300	29.3	Senet al. (2009)
Dharwad, Dandeli and Belgaum districts, Karnataka	41-50	30	63.3	Goyal et al. (2012)
Bhopal, Madhya Pradesh	>20	177	---	Nahar et al. (2012)
Tirupati, Andhra Pradesh	20-70	772	---	Reddy et al. (2012)
Salem, Tamil Nadu	20-59	262	---	Kanniyappan et al. (2011)
Urban slum Chennai	≥ 20	520	19.8	Anuradha et al. (2011)
Salem, Tamil Nadu	19-49	540	---	Aarthi et al. (2010)
Warangal, Andhra Pradesh	20-90	639	---	Eshtari et al. (2009)
Gwalior, Madhya Pradesh	≥30	755	---	Tiwari et al. (2009)
Chennai	≥ 20	2350	31.2	Deepa et al. (2009)
West Bengal	>20	110	71.8	Das and Bose (2006)
Hindu Bengali Females	20-50	854	---	Bhadra et al. (2005)
Punjabi Bhatia family, Jaipur	20-60	232	---	Gupta et al. (2004)
New Delhi	15-58	60	66.7	Misra et al. (2003)
Jaipur, Rajasthan	≥ 20	573	30.2	Gupta et al. (2002)
New Delhi	35-64	1456	48.0	Reddy et al. (2002)
South Delhi	>18	362	15.6	Misra et al. (2001)
Kashmir	≥ 40	2587	---	Zargar et al. (2000)
Punjab				
Ludhiana	20-60	324	29.6	Girdhar et al. (2016)
Punjab	18-44	1088	34.3	Tripathy et al. (2016)
	45-69		23.2	
Ludhiana	25-64	618	---	Singh et al. (2015)
Adult Amritsar females	30-50	172	56.4	Randhawa and Sidhu (2014)
Middle class females	20-50	3000	33.4	Sidhu and Randhawa (2014)
Punjabi females	20-45	900	---	Sidhu et al. (2005)
Punjab	≥ 18	500	---	Sidhu and Prabhjot (2004)
Adult Punjabi females	≥ 20	1000	---	Sidhu and Tatla (2002)
Urban areas of Amritsar district	40-65	800	68.7	Present study

According to these national reports, the prevalence of obesity has elevated among Indian women from 10.6% in NFHS-2 to 12.6% in NFHS-3 and to 20.7% in NFHS-4. This data shows that the prevalence of obesity has increased 10.1 percentage points higher during the period from 1998 to 2016. The prevalence of obesity is dramatically increasing among urban and rural females. It has been reported by NFHS-4 that 31.3% of urban women were obese as compared to 23.5% in NFHS-3 and 9.4% in NFHS-2.

In rural areas, the prevalence of obesity has also risen from 2.6% in NFHS-2 to 7.4% in NFHS-3 and to 15.0% in NFHS-4. These figures depict that the prevalence of obesity has increased 21.9 percentage points and 12.4 percentage points higher among urban and rural females, respectively from NFHS-2 to NFHS-4.

Table 7. Percentage prevalence of general obesity among rural Indian females using BMI criteria of WHO (2000)

Place/Area/State	Age group (years)	No. of females	Percentage prevalence using BMI cut-offs	Investigator
			≥25 kg/m ²	
Other than Punjab				
Tribal females, Arunachal Pradesh	15-44	543	9.5	Bharali et al. (2017)
Tribal females, Assam	20-49	544	15.2	Mondal et al. (2016)
Haryana	≥ 20	540	36.9	Verma et al. (2016)
Krishnagiri, Tamil Nadu	20-80	412	21.2	Little et al. (2016)
Hazratbal, Srinagar	≥ 18	2267	---	Nazki et al. (2015)
Rural Puducherry	>25	534	27.3	Shrivastava et al. (2015)
Tamil Nadu	≥ 15	143	23.8	Chauhan et al. (2015)
Meerut, Uttar Pradesh	≥ 18	656	22.0	Kumar et al. (2014)
Trivandrum, Kerala	≥ 18	---	44.7	Bindhu et al. (2014)
Pune, Maharashtra	20-45	545	22.7	Rathi et al. (2014)
Bhalwal, Jammu & Kashmir	≥ 30	1135	---	Raina and Jamwal (2009)
Tribal females, Manipur	20-70	346	27.1	Mungreiphy and Kapoor (2008)
Chittor, Andhra Pradesh Kammas Kailaka Malas	≥20	T= 394 146 101 147	---	Venkatrama et al. (2005)
New Delhi	35-64	1417	40.0	Reddy et al. (2002)
Punjab				
Punjabi females	≥ 20	800	10.2	Sidhu et al. (2005)
Rural areas of Amritsar district	40-65	720	53.3	Present study

Among Punjabi women, according to NFHS-2 report, the prevalence of obesity was 31.3%, it was 29.9% as per NFHS-3 report but in NFHS-4 report the estimates of obesity were noticed as 31.2%. This shows that there is decline in the prevalence of obesity among Punjabi females from NFHS-2 to NFHS-3 but in NFHS- 4 it was almost similar to the prevalence of obesity reported by NFHS-2. It is evident from these studies that the extent of obesity reported in these studies is not strictly comparable because of the variation in criteria of BMI used. Some of the states and union territories where the prevalence of obesity among women was found to be higher than national prevalence (20.7% in NFHS-4, Table 8) includes Puducherry (36.7%), Punjab (36.7%), Delhi (34.9%), Goa (33.5%), Andhra Pradesh (33.2%), Kerala (32.4%), Daman and Diu (31.6%), Odisha (31.3%), and Tamil Nadu (30.9%).

Table 8. Prevalence of obesity among Indian females according to National Family Health Survey (NFHS-4, 2015-2016) report

States	Obesity		
	Urban	Rural	Total
Andhra Pradesh	45.6	27.6	33.2
Arunachal Pradesh	25.7	16.3	18.8
Assam	26.1	10.9	13.2
Bihar	23.5	9.7	11.7
Chhattisgarh	24.4	7.8	11.9
Goa	36.3	28.5	33.5
Gujarat	34.5	15.4	23.7
Haryana	24.3	18.8	21.0
Himachal Pradesh	38.4	27.6	28.6
Jammu & Kashmir	40.6	24.1	29.1
Jharkhand	21.7	5.9	10.3
Karnataka	31.8	16.6	23.3
Kerala	33.5	31.5	32.4
Madhya Pradesh	23.8	9.1	13.6
Maharashtra	32.4	14.6	23.4
Manipur	31.2	22.4	26.0
Meghalaya	18.4	10.2	12.2
Mizoram	6.0	9.2	7.2
Nagaland	20.7	13.2	16.2
Odisha	32.0	30.6	31.3
Punjab	32.4	30.6	36.7
Rajasthan	23.7	10.7	14.1
Sikkim	34.1	23.1	26.7
Tamil Nadu	36.2	25.4	30.9
Telangana	39.5	18.5	28.1
Tripura	23.5	12.8	16.0
Uttar Pradesh	27.1	12.6	16.5
Uttarakhand	28.4	16.0	20.4
West Bengal	30.6	15.0	19.9
Andaman & Nicobar	38.3	26.6	31.8
Chandigarh	NA	NA	41.5
Delhi	34.9	29.2	34.9
Dadra and Nagar Haweli	34.2	6.9	19.2
Daman and Diu	32.7	29.0	31.6
Lakshadweep	42.4	28.2	41.4
Puducherry	38.1	33.6	36.7

Among urban and rural areas of Punjab, the epidemic of obesity has also increasing rapidly. NFHS-4 conducted field work on 19,484 urban and rural females during the period from 28 January, 2016 to 20 June, 2016 and observed that the prevalence of obesity was 32.4% in urban females and 30.6% in rural females. It is concluded from the present study that prevalence of obesity in Amritsar females is about 1.9 times and 2.9 times higher than the prevalence of obesity in Punjabi females and Indian females reported in NFHS-4, respectively.

Results from the 2011–2012 National Health and Nutrition Examination Survey (NHANES) among adults aged 20 and over, documented 35.1% prevalence of obesity (Fryar

et al., 2014) which is far less than reported in the present study of adult Jat-Sikh females of Amritsar. A total of 2,50,651 women (aged 15–49 years) from 32 Sub-Saharan countries were studied between January 2005 and December 2013 under Demographic and Health Survey (DHS), nationally representative cross-sectional study revealed 23.0% as the highest obesity estimates in Swaziland women (Neupane et al., 2016) which is no doubt less than assessed in the present study adult females. Ellulu et al. (2014) quoted that obesity is one of the most glaring body condition which increase the chances of a person to be the victim of various other non-communicable diseases and reported that in Europe, the figures of obesity among females were 22.0%, 17.0%, 16.0%, 7.0% and 6.0% residing in Germany, Latvia, Ireland, Sweden and Norway, respectively which are very less than present findings. Evidences of obesity from Pacific Islands put forward 79.0% obesity among females of Nauru which is higher than obesity found in Amritsar females. Moreover, 50.0% obesity was yielded by Cook Islands females which are in concordance with the current study estimates. Amugsi et al. (2017) elucidated increase in obesity among women hailing from urban settings of 24 African countries. The results documented that Egypt country, earlier ranked among the countries in the world with the most obese people reported 39% females as obese followed by Ghana (22%). The findings of the present study depicted that urban females had even higher prevalence of obesity than Egypt females residing in urban settings. It is absolutely marked from the comparative profile of Indian literature (Table 6) that obesity assessed in the adult urban Amritsar females in the present study is quite high as compared to most of the other national studies.

The present study investigated that obesity estimates were higher among urban dwellers than rural inhabitants. The overindulgence in high calorie diet and indoor sedentary leisure activities may contribute the higher risk of obesity among urban dwellers. The present findings are in agreement with urban-rural disparity study of Yangon region, Myanmar (Htet et al. 2016). They performed two cross-sectional studies in urban and rural regions of Yangon region including 379 (urban) and 362 (rural) females ranging in age 25 to 74 years between September and November of 2013 and 2014, respectively, and published results demonstrated that urban women had significantly higher prevalence of obesity (urban: 17.3% vs. rural: 11.5%) than rural women. In accordance with few other researchers (Sophal et al., 2010; Benjakul et al., 2013), the estimates of obesity are generally worse for urban populations than rural populations. Duda et al. (2007) also postulated that obesity was found to be more prevalent in the urban rather than rural areas. Data from the 2000–2001 Behavior Risk Factor Surveillance System (BRFSS) and the 1997–1998 National Health Interview Survey (NHIS) contradict present findings by revealing obesity prevalence higher in rural regions compared to urban counties (Patterson et al., 2004; Jackson et al., 2005). Similarly, National Center for Health Statistics (NHANES 2005–2008) included 7,325 urban and 1,490 rural adults ranging in age 20 to 75 years to assess the health and nutritional status of US population and demonstrated that rural regions significantly affected with higher rates of obesity than urban counterparts (Befortet al., 2012). It is striking to know that the prevalence of obesity among adult urban and rural females of Amritsar is tremendously higher than developed nation US, urban and rural populations (CDC, 2011; Hill et al., 2014). Disparity comes into existence from ethnic, nutritional, demographical and socioeconomic population dissimilarities.

With the advancement in technologies in digital age; more sophisticated measurement tools for the assessment of body composition rather than body mass is increasingly used to study obesity-associated health risks (Atanas and Georgi, 2011; Krachler et al., 2013). These

health conditions are attributed to distribution and pattern of fat in the body constituting total body weight. The true body fatness may be better evaluated by assessment of per cent body fat and fat-free mass (Thibault and Pichard, 2012). Therefore, obese individuals can be examined precisely by measuring body composition which has been considered as a better approach in the evaluation of nutritional and health status (Willet et al., 2006; Peppia et al., 2012; Zeng et al., 2012; Bintvibok et al., 2013). Body composition methods measure tissue conductivity of a body segment under stable conditions which is directly proportional to the amount of electrolyte-rich fluid present. Fat is anhydrous and their all body water and fluids are found in fat free mass body component (Heymsfield et al., 1996). Recent development in modern anthropology provided Computed Tomography (CT) scan, Dual-Energy X-ray Absorptiometry (DEXA) and Bioelectrical Impedance Analysis (BIA) devices for body fat measurement. CT scan and DEXA equipment estimates per cent fat mass with suitable accuracy and have emerged as the reference method for estimating body composition (Heymsfield et al., 1996). However, both these procedures drawbacks are radiation exposure, relatively high cost, non-portable and limited approachability for epidemiological studies. BIA depicted excellent correlation with CT scan and DEXA in assessing per cent body fat and is believed to be best replacement for these high-priced techniques to screen large group of individuals (Ryo et al., 2005; Jeong et al., 2006; Xu et al., 2011). Bioelectrical Impedance Analysis (BIA) has been extensively recognised as one of the simplest, safest, valid, portable and non-invasive procedure to determine the individual's body composition, particularly body fat (Houtkooper et al., 1996; Kyle et al., 2004; Rana and Sidhu, 2012; Rani and Gupta, 2014; Randhawa and Sidhu, 2014) and Percent Body Fat (PBF) is the percentage of total body weight that is only fat.

Table 9. Percentage prevalence of general obesity among females reported in various Indian studies using PBF cut-offs

Place/Area/State	Age group (years)	No. of females	PBF cut-offs used	Percentage prevalence	Investigator
Urban					
Mumbai	21-45	1500	>30	59.5	Malshe and Udipi (2017)
Raipur, Chhattisgarh	25-50	70	>30	70.0	Verma et al. (2015)
Amritsar	30-50	172	≥35	60.4	Randhawa and Sidhu (2014)
Amritsar	20-25	150		36.0	Rana and Sidhu (2012)
Hindu Bengali Females	20-50	854	≥30	36.5	Bhadra et al. (2005)
New Delhi	≥18	362		40.2	Misra et al. (2001)
Urban areas of Amritsar district	40-65	800	≥35	83.2	Present study
Rural					
Haryana	≥ 20	540	>30	43.1	Verma et al. (2016)
Rural areas of Amritsar district	40-65	720	≥35	76.9	Present study

In the present study, the mean values of percent body fat observed in urban and rural females were 44.44 ± 10.9 kg/m² and 43.82 ± 9.7 kg/m², respectively and the difference in the mean values of percent body fat between urban and rural females was statistically significant ($p < 0.001$). According to menstrual status, among urban and rural females, it was noticed that postmenopausal females had significantly ($p < 0.001$) higher mean value of percent body fat than premenopausal females (Table 2). The overall prevalence of obesity according to percent

body fat criterion was 80.3% (urban: 83.2% vs. rural: 76.9%) in the study population (Table 4). The difference in the prevalence of obesity between urban and rural females was statistically significant ($\chi^2=9.12$, $df=1$, $p<0.01$).

National studies for the assessment of obesity using PBF criterion was very scarce or may be unpublished in the literature. It is evident from Table 9 that adult Jat-Sikh urban females of Amritsar reported two times more PBF as compared to females of capital city of nation (Misra et al., 2001). It is worth mentioning that even rural counterparts of the present study reflected humongous accumulation of body fat than other female populations of country. This shows that Punjabi females have more propensity of amassing body fat due to their dietary habits and sedentary lifestyle pattern. Malshe and Udipi (2017) exhibited 59.5% females of Mumbai as obese (PBF >30). The females studied by Verma et al. (2015) yielded 70.0% obesity according to >30 criterion of PBF. In Amritsar, two studies were attempted within a gap of two years and to our surprise estimates of obesity regarding deposition of body fat in the concerned area females raised two fold from 36.0% (Rana and Sidhu, 2012) to 60.4% (Randhawa and Sidhu, 2014) with the passage of time. Among Hindu Bengali females, the figures of obesity were 36.5% on applying ≥ 30 cut-offs of PBF (Bhadra et al., 2005). With respect to rural dwellers, only one study was available which was performed by Verma et al. (2016) in Haryana and estimated that 43.1% females were inclined towards the excess building-up of body fat when >30 PBF criterion was incorporated. It is evident that both urban and rural females of Amritsar manifested quite high prevalence of general obesity using PBF cut-offs.

Furthermore, in the studied population, the difference was found to be highly significant ($p<0.001$) for fat mass index (urban 13.92 ± 5.4 kg/m² vs. rural 12.54 ± 4.3 kg/m²) between urban females and rural females (Table 2). In the present sample, the overall prevalence of obesity was 88.5% using FMI criterion (Table 5). Region-wise prevalence of obesity in the study participants was almost similar and the difference between the two groups was statistically non-significant. Unfortunately, there is no report in the current literature regarding the prevalence of obesity on the basis of FMI on Indian females. The outcome drawn by the results of the present study with respect to the assessment of general obesity confirms that adult Jat Sikh females of Amritsar were observed to be more obese using body composition method than the most frequently used diagnostic tool i.e., BMI. In other words, FMI assessed the highest prevalence of obesity followed by PBF and BMI. However, despite of the common usage of BMI among clinical settings and large scale field studies still its facing criticism in the terms of its diagnostic precision (Romero-Corral et al., 2008; Paniagua et al., 2013; Gurunathan and Myles, 2016).

BMI is not reliable to discriminate between total body fat and fat free mass. Even though BMI is the most commonly used index, it does not correspond to fatness uniformly in all populations, and inter-ethnic extrapolations are not possible (Deurenberg et al., 1998). The overestimation of adiposity in muscular body build and underestimation of obesity in the elderly is the evident shortcoming of using BMI (Kyle et al., 2004; Pasco et al., 2012; Liu et al., 2013). Therefore, it introduces misclassification problem by not providing information about fat free components (bone mass, muscle mass, mineral content and body fluids) for a given BMI across age, gender and ethnicity (Whitlock et al., 2009). Thus, resulting in variability in different individuals and populations (Gomez-Ambrosi et al., 2012). Various scientists (WHO, 1998; Raji et al., 2001; Deurenberg et al., 2002; Rush et al., 2004; Kagawa et al., 2006) reported that Asians like Indians have a smaller body frame and body mass index

classification of obesity based on large framed Euro pid populations may be inappropriate for them. In fact, BMI of 30 kg/m² among Europeans correlate with about 25% of percent body fat content in males and 30% of percent body fat in females, while for same age, gender and BMI; South Asians have an increased percent body fat and lesser fat free mass predicting higher risks for cardiovascular diseases (Bagry et al., 2008; Abdullah et al., 2010). Elucidating from the accumulating results set forth by influential researchers (Raji et al., 2001; Joshi, 2003; Lorenzo et al., 2003; Gupta et al., 2004) that for similar value of BMI, Asian Indians illustrate so called “Asian Indian Phenotype” characterized by less of general obesity as measured by BMI but have significantly large percentages of body fat and greater total abdominal and visceral fat area (McGee, 2005; Darokar et al., 2016) compared with white Caucasians resulting in metabolic disorders at much lower levels of BMI. Therefore, the BMI, usually used in population studies to diagnose obesity is unreliable and necessitate the screening of individuals for distribution of body fat rather than simply measuring the increase of body weight. Soni and Verma (2013) described BIA is the best option to measure body composition in field surveys.

Notably, BIA is dependent not only on body composition (fat mass and fat free mass components) but also on body size (cross-sectional areas in trunk and limbs). Since the proportions of body segments depend not only on weight, age and gender but also on race and ethnicity. Therefore, the estimation equations of percent body fat need to be population-specific and revalidated when applied in population that differs from the one in which original method was developed (Krachler et al., 2013). This seemingly obvious step is often overlooked by researchers (Heymsfield et al., 1996). Moreover, there is inadequacy of literature on population-specific studies to validate these equations. Further studies were warranted to generate consensus on the exact, usable and population-specific cut-offs for both PBF and FMI which can be used to counsel females of different races or ethnicity about their actual risk of morbidity based on their body fat distribution. For instance, to reduce the risk of obesity allied morbidity, White and Hispanic obese women could be advised to reduce their BMI levels 28-29 kg/m² as they have more deposition of body fat for a given BMI (≥ 30 kg/m²) than black women (Rahman et al., 2009). Similarly, ethnic-specific cut-offs of PBF and FMI are required to facilitate the assessment of obesity associated co-morbidities across the globe.

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Chapter 245

THE ASSOCIATION OF CENTRAL ADIPOSITY WITH METABOLIC SYNDROME AMONG THE BHUTIAS OF SIKKIM, INDIA

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ABSTRACT

Metabolic syndrome (MetS) or Syndrome – X is considered to be a major public health problem in the developed as well as developing countries. Present study has attempted to evaluate the plausible relationship between central adiposity and MetS, among the Bhutias of Sikkim, India. 428 adult Bhutias, an Indian tribe, were systematically chosen from urban and rural areas of the Himalayan State of Sikkim. Blood pressures and anthropometrics along with fasting glucose and lipid profile were recorded from all the participants (aged ≥ 20 years). Data on sociodemographic aspects and selected lifestyle related variables were collected by using pre-tested questionnaires. Prevalence of MetS was found to be significantly higher among the individuals with sedentary lifestyle, those who are engaged in less active job and those who regularly consume alcohol than their corresponding counterparts. After adjusting for significant lifestyle related predictors, abdomen circumference was found to predict MetS significantly. This small scale cross-sectional study evidently found the positive association of central adiposity related measures with MetS.

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INTRODUCTION

The World Health Organization (WHO) has considered the Metabolic Syndrome (MetS) as one of the most burning issues pertaining to health research in both developed and developing countries since decades (Alberti and Zimmet 1998). The MetS is a group of several risk factors such as excess body fat or obesity, higher lipid, blood pressure and glucose level, i.e, dyslipidaemia, hypertension and hyperglycaemia, respectively (Reaven 1988; Timer et al. 2000). Later, International Diabetes Federation (IDF) redefined MetS, where central obesity as measured by waist circumference (WC) is considered as the essential constituent (Alberti et al. 2005). Reaven (1988) coined the term ‘Syndrome X’, while for the first time he draw attention to this clustering of physiological abnormalities, mainly in overweight individuals.

The prevalence of MetS and cardiovascular disease (CVD) have radically risen in parallel with the global obesity epidemic (Zimmet et al. 2001; Ford et al. 2002). Study has shown that the development of MetS is based on certain complex interaction between genetics, lifestyles and other metabolic factors (Groop 2000). US population shows a prevalence of MetS of more than 20% (Park et al. 2003), while that of Australia is 35.8% (Vaughan et al. 2009) and of China is 21.3% (Xi et al. 2013). In addition to the developed countries, MetS becomes a burning issue in the health research of the developing countries. Transition from rural way of life to comparatively complex urban lifestyle was frequently reported to be a major causal factor pertaining to this abrupt increase in the prevalence of MetS in the developing nations. Since last two decades, many researchers of different countries have reported the prevalence of MetS. The prevalence of MetS is found to be 28.4% in Indonesia (Soweondo et al. 2010), 16.5% in Japan (Hao et al. 2007), 34.8% in Pakistan (Hydrie et al. 2009), 31.3% in South Korea (Park et al. 2015), 24.3% in Sri Lanka (Katulanda et al. 2012) and 24.6% in India (Ravikiran et al. 2010).

The association of dietary habits and physical activity pattern with MetS has been shown in developing countries (Solomons and Gross 1995). Study among urban population also shows sedentary lifestyle and physical inactivity as imperative factors in developing MetS (Torjensen et al. 1997). It is widely and universally accepted that central obesity in terms of waist circumference (WC) happens to be one of the most important and essential components in identifying MetS (NCEP and IDF). Many studies have reported the association between lifestyle related factors, including psychosocial factors and MetS, along with hypertension, obesity, hypertriglyceridaemia (Everson et al. 2002; Wardle et al. 2002; Brunner et al. 2002).

Among the north Indian population the prevalence of MetS was found to be 22.9% in males, 39.9% in females and 31.6% in total sample considering all ages (Gupta et al. 2004). Study pertaining to MetS among the Indian ethnic populations is almost lacking. However, comparison has been made between the Bhutias of Sikkim and Totos of West Bengal pertaining to MetS and its lifestyle related correlates (Sarkar et al. 2005). The aforementioned data prompted us to carry the present study on examining the association of central adiposity with MetS among the Bhutias, an ethnic group inhabiting the eastern Himalayan State of Sikkim. Specifically, attempt has been made to find out the set of adiposity related variables that are responsible for MetS in this population.

MATERIALS AND METHODS

The Bhutias, inhabiting the town of Gangtok, and also those residing in the rural villages under Ralong Revenue Block of South District were selected as study participants. The individuals of this ethnic group bear Mongoloid features. Agriculture, service in different Government and private sectors, business are their principal ways of earning. Other behavioural and population features can be found elsewhere (Sarkar and Mukhopadhyay 2008).

428 Bhutia individuals of both sexes aged 20 years and above were considered for the study. All the households were considered in case of Ralong Revenue Block and from Gangtok, 100 households were systematically selected. One male and one female, preferably the household head and his wife, were chosen to participate in the present study. Those who were under medication for any chronic disease(s), were excluded from the study. All the parameters pertaining to MetS, viz. blood pressures, lipid profiles, fasting blood glucose, skinfold thicknesses and circumferences were recorded from all the study participants following standard methods and techniques (Lohman et al. 1988). In addition, conicity index was deduced as per universally accepted formula. Summation of six skinfold thicknesses (biceps, triceps, sub-scapular, supra-iliac, abdominal and calf) was used as one of the overall adiposity measures. Bioelectrical impedance was used to know the percent body fat and fat mass of each study participant. Data on socioeconomic and lifestyle related variables (socioeconomic status, alcohol consumption, dietary practices, physical activity pattern) were collected from each study participant with the help of pre-tested questionnaires.

The categorization of the socioeconomic status variables were mentioned in an earlier study among the Bhutias of Sikkim (Mukhopadhyay and Sarkar 2018). Blood pressure (BP) measurements of each study participant were recorded following standard technique (Pickering et al. 2003). The average of two consecutive measurements was used in statistical analysis. Fasting blood glucose was examined by one drop of whole blood with the help of “Accutrend Alfa” glucometer. 2ml. blood sample was collected after 12 hours of fasting for estimating the lipid levels of the study participants. Present study follows the recommended criteria of the International Diabetes Federation (Alberti et al. 2005) for the diagnosis of the MetS (WC: > 94cm for males and > 80cm for females; TG: $\geq 150\text{mg/dL}$; HDL: < 40mg/dL for males and < 50mg/dL for females; SBP ≥ 130 mm Hg and/or DBP $\geq 85\text{mm Hg}$; Fasting blood glucose $\geq 100\text{mg/dL}$). Individuals, who satisfied WC cut-off and any two other conditions from the rest four criteria, were considered as having MetS. Informed consent was obtained from all the study participants before collecting any data.

Statistical Analyses

All statistical analyses have been done with the help of SPSS 16.0 for windows software. Test of equality of proportion and t-tests were performed to test the significance of difference between percentage and mean values of lifestyle related variables, respectively. Logistic regression analysis was used to evaluate the maximum odds ratios (ORs) of the prevalence of MetS. Multiple logistic regression analyses were performed to estimate the age adjusted ORs using lifestyle related variables as covariates. Further, multiple logistic regression analysis

was performed to find out the maximum odds of MetS after adjusting for significant lifestyle related variables. Level of significance was considered at $p < 0.05$.

RESULTS

Table 1 depicts the prevalence of MetS of the study participants. Irrespective of sex and total sample, significantly higher ($z = 3.79, 2.92$ and 4.76 respectively for males, females and total sample, $p < 0.05$) prevalence of metabolic syndrome has been noticed in case of urban study participants than that in case of rural participants. Considering urban habitat, markedly high prevalence of metabolic syndrome is found among males (43.75%), females (47.47%) and also in total sample (45.64%). Fact remains that the prevalence of metabolic syndrome is found to be alarmingly high among the rural females (27.27%), too.

Table 2 shows the mean and percentage values of different lifestyle related variables. Significant rural-urban differences are evident for almost all the quantitative and qualitative variables, irrespective of sex.

Table 3 shows the prevalence of MetS according to education, occupation and media exposure status by sex and total sample. It is evident that participants with lower level of education have lower prevalence of MetS. As expected, sedentary jobholders show significantly higher prevalence of MetS than those with non-sedentary jobs in males, females and in total sample ($z = 2.96, 10.47$ and 4.11 , respectively, $p < 0.01$). Considering both males and females, more than 30% of the sedentary jobholders are shown to have MetS. Irrespective of sex, participants exposed to mass media, show significantly higher prevalence of MetS compared to their media non-exposed counterparts. Media exposed females show a prevalence of 45.56% as against 34.62% for the male media exposed participants.

Table 4 depicts the prevalence of MetS according to activity level. As expected, irrespective of sex, less active participants show significantly higher prevalence (34.55% for males, 41.57% for females) of MetS compared to more active participants (16.35% for males, 28.00% for females) ($z = 3.13, p < 0.01$ for males; $z = 2.06, p < 0.05$ for females). Similar trend has also been noticed in case of total sample ($z = 3.40, p < 0.01$).

Table 5 shows the prevalence of MetS according to substance use. It is evident from the table, that irrespective of sex, smokers and smokeless tobacco users show lower prevalence of MetS, and the difference between these two groups in each sex is not statistically significant. On the other hand, prevalence of MetS is found to be significantly higher in the alcohol drinker group compared to non-drinker group for males, females and total sample, while the difference is significant in females ($z = 2.90, p < 0.01$) and in total sample ($z = 2.26, p < 0.05$). While drinker females have a prevalence of 46.08%, non-drinker females show a prevalence of 26.60%.

Table 6 depicts the result of multiple logistic regression analysis using lifestyle related variable adjusted MetS as dependent and adiposity related variables as independent variable. Only abdomen circumference was found to predict MetS significantly (Wald 4.737 with expB 0.951 95% CI = 0.908 – 0.995).

Table 1. Prevalence of MetS, by sex and habitat group

Trait	Male (%)		Female (%)		Total (%)	
	Urban (n = 96)	Rural (n = 94)	z (df = 1)	Urban (n = 99)	Rural (n = 88)	z (df = 1)
MetS	43.75	19.15	3.79*	47.47	27.27	2.92*
				45.64	23.08	4.76*

* Significant at < 0.01 level.

Table 2. Lifestyle related variables, by habitat and sex

Lifestyle related variable	Male		P	Female		P
	Urban (100)	Rural (114)		Urban (100)	Rural (114)	
Cereals	67.28 ± 13.65	66.26 ± 12.54	> 0.05	67.85 ± 13.73	68.19 ± 13.80	> 0.05
Pulses	28.42 ± 22.69	9.82 ± 10.77	< 0.0001	25.65 ± 23.40	9.58 ± 9.17	< 0.0001
Tubers	39.83 ± 24.36	13.19 ± 19.04	< 0.0001	45.75 ± 20.59	8.99 ± 14.33	< 0.0001
Vegetables	95.22 ± 32.38	60.49 ± 13.16	< 0.0001	92.35 ± 23.76	58.09 ± 14.46	< 0.0001
Red meats	37.95 ± 22.48	29.01 ± 20.58	< 0.01	34.26 ± 21.90	26.61 ± 21.62	< 0.05
Lean meat	3.46 ± 4.93	1.47 ± 2.01	< 0.001	3.37 ± 4.28	1.49 ± 3.51	< 0.0001
Eggs	10.23 ± 12.87	5.03 ± 6.07	< 0.001	10.53 ± 13.80	5.05 ± 6.65	< 0.001
Fish	2.59 ± 3.06	1.15 ± 1.96	< 0.001	2.42 ± 2.87	1.13 ± 2.16	< 0.001
Milk products	75.55 ± 30.32	24.03 ± 20.45	< 0.0001	80.05 ± 30.52	21.01 ± 16.97	< 0.0001
Fruits	16.80 ± 18.67	1.10 ± 6.44	< 0.0001	18.85 ± 22.22	1.02 ± 6.50	< 0.0001
PSSI	0.48 ± 0.06	0.22 ± 0.07	< 0.0001	0.48 ± 0.07	0.20 ± 0.05	< 0.0001
Energy Expenditure (Kcal)	2416.87± 554.25	3559.96± 1219.05	< 0.0001	2142.18± 419.69	23.6.64± 409.93	< 0.05
Activity level						
More active	20.00	73.68	< 0.0001	33.00	80.70	< 0.0001
Less active	80.00	26.32		67.00	19.30	

Table 2. (Continued)

Lifestyle related variable	Male			Female		
	Urban (100)	Rural (114)	P	Urban (100)	Rural (114)	P
Education level						
Upto primary	20.00	64.91	< 0.0001	45.00	79.82	< 0.0001
Above primary	80.00	35.09		55.00	21.18	
Occupation						
Non-sedentary	20.00	73.68	< 0.0001	12.00	19.30	> 0.05
Sedentary	80.00	26.32		88.00	80.70	
Household income						
< INR 10,000/m	28.00	82.45	< 0.0001	25.00	80.70	< 0.0001
≥ INR 10,000/m	72.00	17.55		75.00	19.30	
Media exposure						
Non-exposed	17.00	78.10	< 0.0001	18.00	91.60	< 0.0001
Exposed	83.00	21.90		82.00	8.40	
Alcohol intake						
Non-drinker	75.00	53.43	< 0.01	90.00	61.06	< 0.0001
Drinker	25.00	47.57		10.00	38.94	

Source: Mukhopadhyay and Sarkar 2018.

Table 3. Prevalence of MetS according to education, occupation and media, exposure status, by sex and total sample

Socioeconomic status variables including media exposure	Category	MetS (%)		
		Male	Female	Total
Education	Upto primary	20.43	33.58	28.26
	Above primary	29.75	33.77	31.31
	z	1.58	0.03	0.69
Occupation	Sedentary	32.31	34.29	33.53
	Non-sedentary	15.48	0.00	14.77
	z	2.96**	10.47**	4.11**
Media exposure	Exposed	34.62	45.56	39.69
	Non-exposed	18.48	23.81	21.32
	z	2.61**	3.25**	4.02**

* Significant at 0.05 level; ** Significant at < 0.01 level.

Table 4. Prevalence of MetS according to activity level, by sex and total sample

Activity level	MetS (%)		
	Male	Female	Total
More active	16.35	28.00	22.71
Less active	34.55	41.57	37.69
z	3.13**	2.06*	3.40**

* Significant at 0.05 level;

** Significant at < 0.01 level.

Table 5. Prevalence of MetS according to tobacco use and alcohol consumption, by sex and total sample

Substance use	Category	MetS (%)		
		Male	Female	Total
Smoking status	Smoker	20.83	33.33	23.33
	Non-smoker	29.03	36.76	33.24
	z	1.19	0.24	1.64
Smokeless tobacco use	User	25.00	30.43	26.26
	Non-user	28.35	37.36	33.55
	z	0.53	0.67	1.40
Alcohol consumption	Drinker	28.46	46.08	36.21
	Non-drinker	24.66	26.60	25.75
	z	0.59	2.90**	2.26*

* Significant at 0.05 level; ** Significant at 0.01 level.

Table 6. Multiple logistic regression analysis using significant lifestyle variables adjusted MetS as dependent and adiposity related measures as independent variables

Adiposity related variable	Wald	df	Sig.	Exp(B)	95.0% C.I.for EXP(B)	
					Lower	Upper
Abdomen circumference	4.737	1	.030	.951	.908	.995
Waist circumference	.613	1	.434	1.052	.926	1.195
Percent body fat	1.256	1	.262	.965	.906	1.027
BMI	1.639	1	.200	.848	.658	1.092
WHR	1.371	1	.242	24.347	.116	5.101E3
Conicity index	2.651	1	.104	.001	.000	4.002
Sum of skinfold	.127	1	.722	1.002	.991	1.014

DISCUSSION AND CONCLUSION

In the developing nations, including India, the forces of modernization play an important role in changing the lifestyle of the people. Availability of high fat rich food and accessibility to low cost vehicle are simultaneously affecting the health of the individuals in accumulating excess body fat, specifically at the central region of the body. This eventually increases the risk of certain CVD risk factors and MetS.

The present study portrayed a very high prevalence of MetS among the Bhutias, an ethnic group residing in the Himalayan State of Sikkim. Previously, in a different set of Bhutias, the present authors studied the MetS epidemiology (Mukhopadhyay and Sarkar 2018), where females showed a significantly higher prevalence of MetS which corroborates with the present study and the study among the US (Freiberg et al. 2004). On the other hand, higher prevalence of MetS among the males has been found elsewhere (Dallongeville et al. 2005).

It has been observed that the female study participants are mostly housewives and usually spend most of their times in doing household works. Bhutias were fond of fat and fiber rich food items like *chhurpi* (product made from buffalo milk), beef, pork and so on. Frequent consumption of fast food available in the market was also evident among them. Again, the energy expenditure was found to be very less due to availability of low cost transportation. This double effect of high fat rich food and less energy expenditure accumulates fat in their body and gradually harms their cardio-metabolic health. It can be intuitively stated that the transition from a rural traditional lifestyle to an urbanized modern lifestyle leads to a substantial change in socioeconomic and demographic changes. That in turn may change education level, occupational status and income level of the population. The changes in these attributes can have influence on dietary habits, behaviors and physical activity level that in turn affects the MetS.

Adjusted multiple logistic regression analysis showed the importance of central obesity in predicting MetS than overall obesity measured by BMI and bioelectrical impedance. Present study has uniquely found abdomen circumference as the most significant predictor of MetS,

even after adjustment for significant lifestyle related variables. Abdomen circumference as a significant predictor of different CVD risk factors was shown in a previous study among the Bhutias of Sikkim (Sarkar 2013). The central adiposity by means of abdomen circumference might be of interest in future in predicting chronic illnesses like CVD, MetS, diabetes, dyslipidaemia and so on.

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Chapter 246

BISEXUAL DIFFERENCES IN THE ASSOCIATION OF ADIPOSITY MEASURES WITH THE RISK OF HYPERTENSION AMONG THE TRIBES OF GUJARAT, INDIA

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INTRODUCTION

Obesity is a global epidemic health issue which is leading to several health problems like hypertension, diabetes, cardiovascular diseases (CVDs) and metabolic abnormalities (WHO, 2000; Amin, Fatima, Islam & Gilani, 2015). Increased urbanization and modernization has led to sedentary lifestyle belonging to all the age groups living in urban as well as rural parts of India (Yusuf, Reddy, Ôunpuu & Anand, 2001, WHO, 2008, Bansal et al., 2012, Kshatriya & Acharya, 2016). It has been reported that change in dietary and physical activity patterns are often the result of environmental and societal changes associated with development and lack of supportive policies in health, agriculture, transport, urban planning, food processing and education (WHO, 2016). According to ‘A Global Brief on Hypertension’ (WHO, 2013), about one million people around the world are affected by hypertension which causes strokes, heart attacks, kidney failure and other fatal conditions. Globally, complications out of increased blood pressure accounts for 9.4 million deaths every year (WHO, 2009; Lim et al., 2012). Furthermore, undetected high blood pressure has dangerous consequences which often lead to life-threatening complications (WHO, 2013).

It may be added here that hypertension is directly responsible for 57% of all stroke deaths and 24% of all coronary heart disease deaths in India (Anchala et al., 2014). Studies revealed that prevalence of hypertension in urban India is about 29-45% in males and 25-38% in females (Gupta et al., 2003; Gupta & Gupta, 2009). Obesity has long been established as an

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important and independent risk factor for the development and complication of hypertension (Misra, 2000; Hossain, Kavar & El Nahas, 2007; Redón et al., 2008; Park et al., 2013; WHO, 2013; 2016; Moraes, Lacerda, Moreno, Horta & Carvalho, 2014; Rizwan et al., 2014; Hall, Do Carmo, Da Silva, Wang & Hall, 2015; Jiang, Lu, Zong, Ruan & Lin, 2016; Kshatriya & Acharya, 2016). Body Mass Index (BMI), Waist Circumference (WC), Waist-to-height ratio (WHtR) and Waist-hip ratio (WHR) are simple and valid anthropometric measures for the assessment of obesity and risk of hypertension (Mello et al., 2011; Rodea- Montero, Evia-Viscarra & Apolinar-Jiménez, 2014; Zhang et al., 2017). WC has stronger positive association with elevated blood pressure (Yalcin, Sahin & Yalcin, 2005). Nyamdorj et al. (2008) found the association of the development of hypertension with BMI as strong as that with central obesity indicators in Mauritian Indian and Mauritian Creole. Body composition measures such as visceral fat (VF) and percent body fat (PBF) are also considered to be significant indicators of body fat distribution in association with hypertension risk found in populations with different ethnicities worldwide (Després et al., 2000; Gupta 2004; Lam, Koh, Chen, Wong & Fallows, 2015; Pereira et al., 2015). Asian Indians have higher abdominal body fat storage even at a lower BMI, and are susceptible to a higher risk of CVDs and metabolic syndrome (Chandalia, Abate, Garg, Stray-Gundersen & Grundy, 1999; Raji, Seely, Arky & Simonson, 2001; Raji et al., 2004; Forouhi, 2005; Bhat et al., 2005; Misra & Shrivastava 2013). Also, abdominal obesity leads to elevated blood pressure and insulin resistance (Poirier et al., 2005). Obese individuals with accumulated visceral fat have an increased risk for hypertension, type 2 diabetes mellitus and other cardiovascular events (Bidulescu et al., 2013) and variation in fat distribution mediates cardiometabolic risk factors (Neeland et al., 2012).

Several studies have reported the prevalence of hypertension in adults (Gupta & Mehrishi, 1997; Gupta, 2004; Thankappan et al., 2005; Kaur et al., 2007; Kaur et al., 2012; Rizwan et al., 2014; Panda et al., 2017) and children in urban areas of India (Mohan et al., 2003; Singh, 2007; Durrani & Fatima, 2011; Shetty, Shetty, Sasidharan & Shenoy, 2013; Singh et al., 2013; Kumar et al., 2017). Studies (Gerber, Schwartz, Schnall & Pickering, 1995; Dua & Kapoor, 2000) have shown sex differences in association of adiposity measures with blood pressure in urban populations. WHR, WHtR and conicity index (CI) are found to be higher in females due to the gynoid pattern of fat distribution (Mungreiphy et al., 2012). It has been found that males are more prone to abdominal fat deposition in comparison to females, which is responsible for higher central adiposity in them (Despres et al., 2000). Sex-wise studies on hypertension have highlighted that systolic blood pressure (SBP) levels increases with advancing age (Reddy, 1998; Raina, Chander, Prasher & Raina, 2016) and the increase has been reported to be more prominent in females than males (Dua, Bhuker, Sharma, Dhall & Kapoor, 2014; Raina et al., 2016).

Obesity and its association with elevated blood pressure has been reported among tribal populations of India (NNMB, 2009; Kapoor, Saluja, Verma & Kapoor, 2012; Kshatriya & Acharya, 2016). Meshram et al. (2012) found that the risk of hypertension was significantly higher among overweight/obese tribal men and women as compared to normal individuals. Similarly, Kapoor et al. (2012) reported a positive correlation of BMI and mid upper arm circumference (MUAC) and a negative correlation of PBF with risk of hypertension among tribal communities from different regions of India. Similar studies among tribes across varied ecological settings within India have observed association of hypertension with anthropometric indices (Babu, Kusuma & Naidu, 1996; Kusuma, Babu & Naidu, 2002;

Mukhopadhyay & Mukhopadhyay, 2001; Kerketta, Bulliyya, Babu, Mohapatra & Nayak, 2009; Maken & Verte, 2016). The nomadic tribal groups of Rajasthan have shown an increased hypertensive tendency at elevated abdominal and visceral fat adiposity as well (Sachdev, 2011). BMI and abdominal adiposity showed positive correlation with hypertension in tribal population of India (Kshatriya, 2014). However, to the best of our knowledge there is hardly any study on the association of adiposity measures with blood pressure among the tribal population groups of India. Therefore, the present study is an attempt to investigate the bisexual variations in the association of adiposity measures with the risk of hypertension among the three tribal populations namely Dhodia, Kukna and Choudhuri of Gujarat, India for a better understanding of correlates of hypertension among these socially and economically deprived populations.

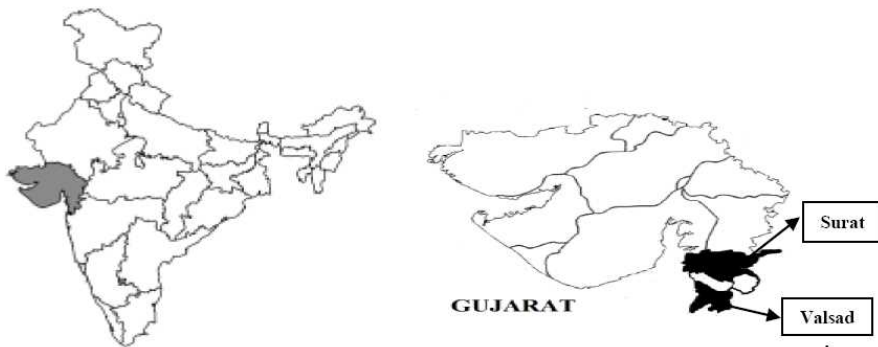
MATERIALS AND METHODS

Ethical Statement

Prior ethical clearance to conduct the research was obtained from the Institutional Review Committee, Department of Anthropology, University of Delhi. Informed written consent from each participant was obtained prior to the actual commencement of the study.

Area and People

The present study was conducted among three tribes namely Dhodia, Kukna and Choudhuri from Valsad and Surat districts of Gujarat, during August-September 2013 (Figure 1).



Source: <https://www.mapsofindia.com/maps/gujarat/>.

Figure 1. Geographical location of the selected districts in Gujarat.

The tribes of Gujarat are agriculturalists and have a sedentary life. They are also involved in other occupations such as government jobs, cattle rearing and manual labour. All the studied tribes have access to basic amenities such as water, electricity, education and healthcare. Ways of modern entertainments such as television, radio and music systems,

mobile phones are making their way into the life of these tribal communities replacing the traditional community activities such as folk singing, narrations and dancing. Prevalence of alcohol consumption was low in the tribes of Gujarat.

Sampling Method and Sample Size

A total of 30 villages from two districts namely Valsad and Surat of Gujarat were chosen on the basis of the residence in acculturated areas of development (areas where development activities have reached). These areas have comparatively closed access to “urban centers.” House listing was prepared for these selected villages. Subsequently, the age and sex composition of adult men and women was prepared for the studied three tribes from the house listing. A sample size of 120 adult men and 120 adult women from each of the three tribes was selected using simple random sampling. As a result, the study comprised of a total of 721 participants out of which 360 were men and 361 were women aged 20-60 years.

Exclusion criteria: People with any type of growth and developmental disorders, severe health issues in the past year, and the existence of any secondary cause of hypertension were not included in the current study. People who were hesitant about being part of the study were also excluded.

Data Collection and Measurements

Two trained anthropologists guided by the principal investigator constituted the field research team for data collection. To avoid any measurement of entry biases, one person was assigned the responsibility of taking all the measurements while the other used to enter data into the datasheet. Same set of instruments were used throughout for recording the measurements.

A structured format was used to collect demographic information such as name, age, sex, name of tribe from each of the participants.

Standard techniques were followed while taking all the anthropometric measurements (Lohman, Roche & Martorell, 1988). The standing height was measured to the nearest of 0.1 cm using a movable anthropometer. Skinfold thicknesses at four sites (biceps, triceps, sub-scapular and supra-iliac) were estimated using the Holtain’s skinfold thickness calliper and sum of four skinfolds (SF_4) was measured.

Percent body fat (PBF) and visceral fat (VF) were estimated by bioelectrical impedance analysis (BIA) using Omron Karada Scan Body Composition Monitor (Omron Health Care Co., Kyoto, Japan), which is a hand-held impedance analyser. Each participant’s particulars such as height, age and sex were recorded into the instrument after which the participant was instructed to stand on the platform with their feet placed on the scales present at the platform, the hand-held monitor was then held by them which scanned the body and gave recording of the impedance and body fat percentage calculation. The participants were encouraged to remove their shoes and heavy clothing before taking measurements. Weight was also recorded to the nearest 0.1kg with the help of this instrument.

Mid upper arm circumference (MUA), minimum waist circumference (MWC) and maximum hip circumference (MHC) were recorded using non-expandable measuring tape. Waist hip ratio (WHR) and waist height ratio (WHtR) were also estimated.

Blood pressure was measured following American Heart Association (AHA) guidelines (Liz, 2005). The systolic and diastolic blood pressure was measured using a standard mercury sphygmomanometer on the left upper arm of the participants in the sitting position. A minimum 15-minute rest before the measurement and a 5-minute interval between two consecutive measurements were ensured. The average of two readings was recorded.

Individual Classification

High body mass index (BMI) has been treated as a strong indicator of obesity and hypertension in various populations. Furthermore, the “obesity paradox” has been reported which indicated that low BMI was associated with hypertension (Hainer & Aldhoon-Hainerová, 2013). Therefore, we considered both low and high BMI statuses as predictors of hypertension risks. According to the World Health Organization (WHO) guidelines for Asian populations, individuals with BMI $<18.5 \text{ kg/m}^2$ were considered as underweight; $\geq 18.5 \text{ kg/m}^2$ but $<23 \text{ kg/m}^2$ as normal; $\geq 23 \text{ kg/m}^2$ but $<27.5 \text{ kg/m}^2$ as overweight and $\geq 27.5 \text{ kg/m}^2$ as obese (WHO, 1998; Kesavachandran, Bihari & Mathur, 2012). In the present study, we have combined the overweight and obese categories as the proportion for each of the two was found to be very low.

Several studies have demonstrated that WHtR is more closely associated with central obesity, encompassing the adjustment to various statures (Hsieh, Yoshinaga, Muto, Sakurai & Kosaka, 2000; Lin et al., 2002; Sayeed et al., 2003) and overcoming the negative correlation of height to metabolic syndromes (Henriksson, Kindblom, Agren, Nilsson-Ehle & Rastam, 2001). The mean height of Indian tribes is less than the mean height of the general Indian population (Gautam & Adak, 2006). Therefore, WHtR can be an ideal obesity measure and a strong indicator of health (Ashwell & Hsieh, 2005) in Indian tribal populations. In the present study, WHtR was classified into two categories: (1) <0.50 as normal (Peng et al., 2013); and (2) ≥ 0.50 as at risk for both males and females. MWC and WHR have also been associated with central obesity and cut-offs also vary sex-wise because of the differences in the deposition of fat in males and females. In case of minimum waist circumference (MWC), males with $<90 \text{ cm}$ and females with $<80 \text{ cm}$ were considered as normal, while males with $\geq 90 \text{ cm}$ and females with $\geq 80 \text{ cm}$ were considered as at-risk category (Alberti, Zimmet & Shaw, 2006; WHO, 2011). WHR was classified into two categories: 1) males with <0.90 and females with <0.85 as normal, and (2) males with ≥ 0.90 and females with ≥ 0.85 as at-risk category (WHO, 2011).

The 7th Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure cut off have been used for classifying the participants as normal, prehypertensive and hypertensive (Chobanian et al., 2003). Participants with SBP $<120 \text{ mm Hg}$ and DBP $<80 \text{ mm Hg}$ were recorded as normal, while those with SBP between 120 and 139 mm Hg or DBP between 80 and 89 mm Hg were classified as prehypertensive. Participants with blood pressure $\geq 140/90 \text{ mm Hg}$ were considered hypertensive (James, 2014).

Statistical Analysis

Data entry was done in Microsoft Excel 2007, and further analyses were carried out using SPSS version 16.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Descriptive statistics, such as mean and standard deviation (SD), were estimated for the selected anthropometric, body composition and physiometric variables. Student's t-test was performed to estimate the level of significance between the two sexes. Pearson's correlation coefficient was estimated for anthropometric, body composition measures and blood pressure. Furthermore, linear regression for total population as well as for males and females separately was used by taking SBP and DBP as dependent variables and MWC, MUAC, WHR, WHtR, BMI, SF₄, PBF and VF as independent variables. Data were cross tabulated by adiposity variables and sex, and analysed by using three-dimensional contingency chi-square test.

RESULTS

Table 1 describes the characteristics of the studied tribal populations of Gujarat. The mean values of height, weight, minimum waist circumference (MWC), mid upper arm circumference (MUAC), visceral fat (VF), waist hip ratio (WHR) and waist height ratio (WHtR) were observed to be higher in males as compared to females. The mean difference between males and females were found to be statistically significant.

Mean values of diastolic blood pressure (DBP), percent body fat (PBF) and sum of four skinfolds (SF₄) were found to be higher among females than males. Variables like PBF, DBP and SF₄ were found to be statistically significant between the two sexes.

Table 2 shows the partial correlation between adiposity variables (MWC, MUAC, BMI, WHR, WHtR, PBF, VF and SF₄) and physiometric variables (SBP and DBP) among the selected tribal groups of Gujarat. Findings indicate a significant positive correlation of all the adiposity measures with the physiometric variables.

Table 3 presents the linear regression analysis of physiometric measures with anthropometric and body composition measures as independent variables for the tribes of Gujarat. It can be seen that SBP and DBP have a significant positive impact on MWC (β -0.42, adj. R²-0.08; β -0.61; adj. R²-0.06) and PBF (β -0.14, adj. R²-0.04; β - 0.16; adj. R²-0.07) among the selected populations of Gujarat.

Table 4 shows sex-wise linear regression analysis for anthropometric and body composition measures with SBP and DBP as the dependent variables. It can be seen that among females, SBP has a significant positive impact on MWC (β -0.42; adj. R²-0.11) and PBF (β -0.21; adj. R²-0.09) while, DBP was found to have significant positive effect on MWC (β - 0.59; adj. R²-0.08), PBF (β -0.16; adj. R²-0.07) and VF (β - 0.38; adj. R²-0.09). However, in case of males, SBP and DBP had significant positive impact only on MWC (β -0.38; adj. R²-0.10; β - 0.68; adj. R²-0.18).

Further, a mutually independent hypothesis and a number of partially independent hypotheses were tested for various categories of blood pressure (normal, PHTN and HTN), normal and at risk anthropometric variables and sex using three-dimensional chi-square analysis. In partially independent hypothesis, we tested: (a) sex as independent of blood pressure and normal and at risk anthropometric variables, (b) blood pressure as independent

of sex, and normal and at risk anthropometric variables, and (c) normal and at risk anthropometric variables as independent of sex and blood pressure.

Tables 5, 6, 7 and 8 present the distribution of normal and at-risk categories of MWC, WHR, WHtR, BMI, and blood pressure by sex among the selected tribal groups of Gujarat. Our initial analysis showed that normal and at risk anthropometric variables, by sex and blood pressure were not mutually independent, which led us to test for partial independence. In partial independence, three of the one variable was tested as independent of the other two. It was found that except for BMI, all the chi-square tests for partial independence were statistically significant at $p < 0.05$. Thus, it can be inferred that adiposity measures and risk of hypertension by sex are strongly associated.

Table 1. Characteristics of the studied tribal populations of Gujarat (n= 721)

Variables	Male (n=360)	Female (n=361)	T
	Mean $\pm$ S.D.	Mean $\pm$ S.D.	
Age (year)	40.8 $\pm$ 12.39	40.3 $\pm$ 11.61	0.61
Height (cm)	162.3 $\pm$ 6.48	150.4 $\pm$ 5.02	27.60***
Weight (kg)	53.4 $\pm$ 9.54	44.9 $\pm$ 7.47	13.33***
MWC (cm)	78.9 $\pm$ 10.48	67.2 $\pm$ 8.15	16.67***
MUAC (cm)	25.9 $\pm$ 2.69	22.6 $\pm$ 2.42	17.16***
SBP (mm Hg)	127.7 $\pm$ 20.57	126.8 $\pm$ 19.80	0.59
DBP (mm Hg)	78.2 $\pm$ 11.57	80.8 $\pm$ 12.44	-2.92**
PBF	22.3 $\pm$ 6.08	29.9 $\pm$ 6.03	-16.70***
BMI (kg/m ²)	20.2 $\pm$ 3.16	19.8 $\pm$ 3.15	1.72
VF	5.3 $\pm$ 3.89	3.4 $\pm$ 2.39	8.23***
WHR	0.9 $\pm$.07	0.8 $\pm$.06	29.89***
WHtR	0.5 $\pm$.64	0.5 $\pm$.06	8.61***
SF ₄ (mm)	31.7 $\pm$ 14.45	45.6 $\pm$ 21.05	-10.33***

*** $p < 0.001$, ** $p < 0.01$.

Abbreviations: MWC- minimum waist circumference, MUAC- mid-upper arm circumference, SBP- systolic blood pressure, DBP- diastolic blood pressure, PBF- percent body fat, BMI- Body fat mass, VF- Visceral fat, WHR- waist hip ratio, WHtR- waist height ratio, SF₄- Sum of four skinfold thicknesses.

Table 2. Correlation of adiposity measures with physiometric variables (SBP and DBP) in the tribal populations of Gujarat (n= 721)

	MWC	MUAC	SBP	DBP	PBF	BMI	VF	WHR	WHtR	SF ₄
MWC		.802**	.288**	.246**	.101**	.669**	.733**	.837**	.935**	.277**
MUAC			.177**	.170**	-.059	.658**	.659**	.630**	.705**	.286**
SBP				.709**	.212**	.217**	.226**	.178**	.313**	.149**
DBP					.267**	.290**	.260**	.074*	.274**	.230**
PBF						.384**	.271**	-.164**	.309**	.476**
BMI							.866**	.348**	.721**	.548**
VF								.526**	.737**	.341**
WHR									.740**	-.066
WHtR										.407**
SF ₄										

** Correlation is significant at the 0.01 level (2-tailed).

* Correlation is significant at the 0.05 level (2-tailed).

Abbreviations: MWC- minimum waist circumference, MUAC- mid-upper arm circumference, SBP- systolic blood pressure, DBP- diastolic blood pressure, PBF- percent body fat, BMI- Body fat mass, VF- Visceral fat, WHR- waist hip ratio, WHtR- waist height ratio, SF₄- Sum of four skinfold thicknesses.

Table 3. Linear regression analysis of SBP and DBP with anthropometric and body composition measures among the tribes of Gujarat (n= 721)

Variables	SBP			DBP		
	β	T	Adj.R ²	β	T	Adj.R ²
MWC	0.421	2.737**	0.081	0.605	3.982***	0.059
MUAC	-0.046	-0.675	0.030	-0.076	-1.102	0.028
PBF	0.143	2.765**	0.044	0.163	3.177**	0.070
BMI	-0.182	-1.909	0.046	0.007	0.071	0.083
VF	0.066	0.806	0.050	0.054	0.666	0.066
WHR	-0.211	-2.369	0.030	-0.311	-3.535	0.004
WHtR	0.161	1.185	0.097	-0.105	-0.783	0.074
SF ₄	-0.020	-0.400	0.021	0.012	0.243	0.052

***p<0.001, **p<0.01.

Abbreviations: MWC- minimum waist circumference, MUAC- mid-upper arm circumference, SBP- systolic blood pressure, DBP- diastolic blood pressure, PBF- percent body fat, BMI- Body fat mass, VF- Visceral fat, WHR- waist hip ratio, WHtR- waist height ratio, SF₄- Sum of four skinfold thicknesses.

Table 4. Sex-wise linear regression analysis for anthropometric and body composition measures (n= 721)

Variables	Females (n= 361)						Males (n=360)					
	SBP			DBP			SBP			DBP		
	B	T	AdjR ²	β	T	adjR ²	β	T	adjR ²	β	T	adjR ²
MWC	0.418	1.973*	0.107	0.594	2.767**	0.083	0.375	2.015*	0.102	0.679	3.847***	0.179
MUAC	-0.059	-.548	0.029	-0.073	-.674	0.040	-0.027	-.333	0.043	0.043	.561	0.113
PBF	0.205	2.845**	0.090	0.145	1.984*	0.072	0.048	.784	0.033	0.071	1.209	0.047
BMI	-0.226	-1.295	0.047	-0.155	-.878	0.067	-0.207	-1.547	0.041	-0.014	-.112	0.112
VF	0.151	1.036	0.069	0.379	2.564**	0.094	0.102	.832	0.043	0.034	.292	0.102
WHR	-0.084	-.979	0.049	0.003	.038	0.028	-0.132	-1.185	0.062	-0.177	-1.671	0.080
WHtR	-0.029	-.134	0.109	-0.521	-2.384*	0.069	0.133	.652	0.095	-0.188	-.977	0.144
SF ₄	-0.053	-.752	0.015	-0.032	-.455	0.021	0.024	.337	0.049	0.006	.081	0.085

***p<0.001, **p<0.01, *p<0.05.

Abbreviations: MWC- minimum waist circumference, MUAC- mid-upper arm circumference, SBP- systolic blood pressure, DBP- diastolic blood pressure, PBF- percent body fat, BMI- Body fat mass, VF- Visceral fat, WHR- waist hip ratio, WHtR- waist height ratio, SF₄- Sum of four skinfold thicknesses.

Table 5. Distribution of normal and risk categories of MWC and blood pressure among the males and females of the selected tribal groups of Gujarat in three-dimensional contingency table and test for mutual independence (n=721)

	At risk (MWC)			Normal (MWC)			Total
	Normal	PHTN	HTN	Normal	PHTN	HTN	
Females (n=361)	2 (0.6%)	11 (3.0%)	15 (4.2%)	116 (32.1%)	142 (39.3%)	75 (20.8%)	361 (100%)
Males (n=360)	8 (2.2%)	18 (5.0%)	30 (8.3%)	124 (34.4%)	112 (31.1%)	68 (18.9%)	360 (100%)

Chi-square: 319.15; df: 7; p<0.05.

Table 6. Distribution of normal and risk categories of WHR and blood pressure among the males and females of the selected tribal groups of Gujarat in three-dimensional contingency table and test for mutual independence (n=721)

	At risk (WHR)			Normal (WHR)			Total
	Normal	PHTN	HTN	Normal	PHTN	HTN	
Females (n=361)	18 (5.0%)	31 (8.6%)	33 (9.1%)	100 (27.7%)	122 (33.8%)	57 (15.8%)	361 (100%)
Males (n=360)	110 (30.6%)	114 (31.7%)	90 (25.0%)	22 (6.1%)	16 (4.4%)	8 (2.2%)	360 (100%)

Chi-square: 319.15; df: 7; p<0.05.

Table 7. Distribution of normal and risk levels of WHtR and blood pressure among the males and females of the selected tribal groups of Gujarat in three-dimensional contingency table and test for mutual independence (n=721)

	At risk (WHtR)			Normal (WHtR)			Total
	Normal	PHTN	HTN	Normal	PHTN	HTN	
Females (n=361)	5 (1.4%)	25 (6.9%)	34 (9.4%)	113 (31.3%)	128 (35.5%)	56 (15.5%)	361 (100%)
Males (n=360)	29 (8.1%)	45 (12.5%)	61 (16.9%)	103 (28.6%)	85 (23.6%)	37 (10.3%)	360 (100%)

Chi-square: 114.94; df: 7; p<0.05.

Table 8. Distribution of BMI categories and blood pressure levels among the males and females of the selected tribal groups of Gujarat in three-dimensional contingency table and test for mutual independence (n=718)

	Underweight			Normal			Overweight			Total
	Normal	PHTN	HTN	Normal	PHTN	HTN	Normal	PHTN	HTN	
Females (n=361)	60 (16.6%)	60 (16.6%)	25 (6.9%)	49 (13.6%)	71 (19.7%)	41 (11.4%)	9 (2.5%)	22 (6.1%)	24 (6.6%)	361 (100%)
Males (n=357)	59 (16.5%)	35 (9.8%)	28 (7.8%)	59 (16.5%)	73 (20.4%)	37 (10.4%)	13 (3.6%)	20 (5.6%)	33 (9.2%)	357 (100%)

Chi-square: 52.16; df: 12; p<0.05.

DISCUSSION

The findings of the studied tribal communities of Gujarat showed that there are significant sex differences in several anthropometric measurements and blood pressure among the tribal populations. In addition, these groups also showed the risk of hypertension along with the burden of malnutrition (underweight and overweight). It may be noted here that obesity co-exists with underweight in India and hence, the country suffers from a double burden of malnutrition (Popkins, 2002; Kshatriya & Acharya, 2016). The development of obesity involves the amalgamation of numerous social, behavioural, cultural, physiological, metabolic and genetic factors (National Research Council [NRC], 1989; WHO, 2016). WHO (2011) reported the estimated prevalence for hypertension among the Indian National population as 32.5%, which was found to be higher than the estimated prevalence of 22.5%

among tribal populations. Increasing trend of hypertension among tribal populations was also observed in various studies (NNMB, 2009; Naidu, Nayak & Sadi, 2016; Rizwan et al., 2014; Kshatriya & Acharya, 2016). Kshatriya & Acharya (2016) reported that hypertension was observed to be higher among females as compared to males in tribal populations of India. Only few studies (Deshmukh, Gupta, Dongre & Bharambe, 2006; Chockalingam et al., 2005; Ghosh, 2007; Gupta et al., 2007; Kapoor et al., 2012; Singh et al., 2013) have been carried out on the factors determining hypertension risk among Indian people. However, to the best of our knowledge this is the first attempt to find out the bisexual differences in the association of adiposity variables with blood pressure among the tribal populations of Gujarat.

Men in the studied tribal groups had significantly higher mean height, weight, MWC, MUAC, VF, WHR and WHtR, while mean values of DBP, PBF and SF₄ were significantly higher among females, indicating sexual differences in adiposity measures. Various studies have shown that adiposity measures play a significant role in predicting hypertension risk among males and females (Yalcin, 2005; Ghosh, Mukhopadhyay & Barik, 2016; Kandpal, Sachdeva & Saraswathy, 2016; Kshatriya & Acharya, 2016). Pal et al. (2014) found that rural Bengalee females had significantly higher PBF and fat mass while males had central adiposity resulting in higher mean values of anthropometric measures such as MWC, WHR and WHtR. Significant sex differences were also observed in numerous studies conducted on urban population groups residing in India (Sanjeev, Indech, Jit & Johnston, 1991; Bhadra, Mukhopadhyay & Bose, 2002; Deshmukh et al., 2006). However, few studies (Kapoor, Kapoor & Durnin, 1999; Misra et al., 2001; Mungreiphy & Kapoor, 2010; Bansal et al., 2012) have reported higher percentage of females to be overweight than males and have higher mean for WHR, WHtR and BMI due to relatively more gynoidal pattern of fat distribution. Furthermore, significant positive correlations between adiposity measures (MWC, MUAC, PBF, BMI, VF, WHR, WHtR, SF₄) and physiometric variables (SBP and DBP) were also obtained. A strong positive correlation between BMI, WHR, MWC, WHtR and SBP and DBP was observed in many studies as well (Deshmukh et al., 2006; Gupta et al., 2007; Chakraborty, Bose & Bisai, 2009; Pal, De, Sengupta, Maity & Dhara, 2014).

The regression analysis indicates that SBP and DBP have a significant positive impact on MWC and PBF among the selected population groups. Sex-wise regression analysis indicated that among females SBP had a significant positive impact on MWC and PBF, while DBP had a significant impact on MWC, PBF and VF; while in case of males, SBP and DBP had significant positive impact only on MWC, which could be because men are prone to abdominal fat deposition in comparison to women (Deprés, 2000; Mungreiphy et al., 2012). Similar results have also been reported in a few studies earlier (Ghosh et al., 2016; Kandpal et al., 2016; Kshatriya & Acharya, 2016).

It was also attempted in the present study to find out the association of normal and risk categories of adiposity markers such as MWC, WHR, WHtR and BMI with blood pressure levels (normal, PHTN and HTN) among both the sexes of selected tribal groups using three-dimensional contingency chi-square analysis. A mutually independent hypothesis along with various partially independent hypotheses were tested to investigate the association of adiposity measures with risk of hypertension by sex. Bisexual differences were found to be statistically significant for MWC, WHR and WHtR and various categories of blood pressure. Mutual dependence was also reported between sex, anthropometric measures and blood pressure. Kshatriya & Acharya (2016) in their study reported that tribal women above 40 years of age are at a greater risk of suffering from undernutrition because of the social and

gender disparities faced by them leading to chronic health conditions. Low BMI and undernutrition was reported to be a risk factor for CVD (Pal et al., 2014; Kshatriya & Acharya, 2016). An increased visceral fat mass is responsible for greater blood pressure due to activation of several mechanisms such as leptin resistance, insulin resistance and inflammation (Sniderman, Bhopal, Prabhakaran, Sarrafzadegan & Tchernof, 2007). Tainget al. (2016) also found MWC and WHtR to be strongly associated with blood pressure than BMI. People belonging to Asian ethnicities have a high total body fat and a greater amount of abdominal and visceral fat at a given BMI in comparison to other ethnic groups (Lear et al., 2007; Misra & Shrivastava, 2013). Therefore, anthropometric measures (MWC, WHR and WHtR) which take into consideration central fat distribution may be more helpful in determining the adverse health conditions in various communities in India.

Differences in blood pressure between various ethnic groups have been observed in India and various studies suggest that numerous factors are associated with SBP and DBP in rural as well as urban population. Higher SBP and DBP are associated with malnutrition, inaccessible health services, alcohol consumptions and smoking in rural groups (Reddy, Rao & Reddy, 2002; Hazarika, Narain, Biswas, Kalita & Mahanta, 2004; Kusuma & Das, 2008; Kshatriya & Acharya, 2016), whereas sedentary lifestyle, unhealthy food habits, stress are being associated with high blood pressure levels in urban areas (Mungreiphy & Kapoor, 2010; Ibrahim & Damasceno, 2012; WHO, 2013). The tribal groups practicing farming have been reported for elevated risk of hypertension than those occupied in other occupations probably because of the unsatisfactory yield of crops leading to greater economic crisis and stress (Wasnik & Jawarkar, 2016).

Finally, the sex-wise differences and association of adiposity markers with hypertension observed in the current study will be helpful in extending these results to other tribal population groups for developing effective intervention strategies.

CONCLUSION

The findings of the present study show an increasing prevalence of prehypertension and hypertension among both the sexes in tribal areas at an alarming rate. The sex-wise differences and association of adiposity markers with hypertension in the current study would be helpful in designing better health care delivery systems in the areas of tribal concentration.

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CONFLICT OF INTEREST

The author reports no conflicts of interest.

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Chapter 247

**OBESITY AS AN IMPORTANT PREDICTOR OF
HYPERTENSION AMONG RAJSHAHI UNIVERSITY
STUDENTS IN BANGLADESH:
A CROSS-SECTIONAL STUDY**

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ABBREVIATIONS

AOR	Adjusted Odds Ratio
BMI	Body Mass Index
BP	Blood Pressure
BPC	Blood Pressure Category

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CI	Confidence Interval
DBP	Diastolic Blood Pressure
IBM	<i>International Business Machines</i>
mmHg	Millimeter of Mercury
R	Reference category
SBP	Systolic Blood Pressure
SE	Standard Error
SPSS	Statistical Package for Social Science
WHO	World Health Organization

INTRODUCTION

Hypertension or raised blood pressure is one of the important components of metabolic syndrome (Grundy et al., 2004). It is one of the major risk factors for cardiovascular diseases and affects one billion people in worldwide, leading to heart attacks and strokes (WHO, 2013). It is considered a major global public-health challenge because of its high frequency and has concomitant risks of cardiovascular and kidney diseases (Oyewole and Oritogun, 2012). The incidence and prevalence of hypertension continues to increase around the world (Chen and Lipscombe 2008; Karen et al., 2008). Globally, cardiovascular diseases account for approximately 17 million deaths a year, nearly one third of the reported total deaths (WHO, 2008). Of these, complications of hypertension account for 9.4 million deaths worldwide every year (Lim et al., 2012). Hypertension is one of the leading reported causes of death in Bangladesh and approximately 17,000 or 2.28% of total deaths is due to hypertensive problem as reported by World Health Organization (WHO) in 2014 (WHO, 2014).

The prevalence of pre-hypertension and hypertension in different countries, particularly among university students was reported for Saudi Arabian females at 13.5% (Koura et al., 2012), West Bank 27.1% (male 38% and female 11.2%) (Tayem et al., 2012), Malaysia 42.9% (Lee et al., 2010), and Kuwait 39.5% (Al-Majed and Sadek, 2012). Among medical students, 67% presented with pre-hypertension and hypertension (Kulkarni et al., 2011) in India, 12.8% in Chile (Palomo et al., 2006) and 6.9% to 24.9% in Portugal (Dores et al., 2010). Once hypertension is identified, the patients should be regularly checked for their blood pressure (BP), in order to monitor and maintain the blood pressure under control (Black and Hawks, 2005). Gender, age, parental history of hypertension, and behavioral factors, like body mass index(BMI), sleep duration, smoking status have all been identified as the risk factors in hypertension (Tadesse and Alemu, 2014).

Many studies have been carried out on hypertension among university students in Western countries (Tayem et al., 2012; Simão et al., 2008; Hujova 2013; Soliman et al., 2014). While in Bangladesh researchers have investigated the association between hypertension and socio-economic and demographic factors among patients and in the general population (Rahman et al., 2015; Yinon et al., 2013). University students need to be considered a valuable asset for any nation; thus, special attention should be paid to them because of their potential influence on their families and their contribution to the nation's workforce in the future. Thus, it is important to determine the prevalence of hypertension and pre-hypertension among university students and to investigate the relationship between high

blood pressure and socio demographic factors such as gender, residence, smoking, parents' history of hypertension, body mass index, religion, number of family members, parents' education, family income, sleeping duration and physical activities, in order to determine possible corrective measures.

Therefore, the aim of this study was to investigate the prevalence and associated factors of hypertension among university students in Bangladesh.

METHODS

Data

The cross-sectional study sample consisted of 911 (727 males and 184 females) university students. Data were collected from Rajshahi University, Bangladesh. Students were interviewed from January to June 2014. The age range of the subject's was 18-27 years old at the time of measurement. Rajshahi University was selected because it is the second largest university in Bangladesh, having a student population of nearly 25,000 students at any particular time. These students come from different parts of the country. Data were collected using a semi-structured pre- and post-tested questionnaire containing pre-coded and open-ended questions. Body height was measured as the distance from the top of the head in the midsagittal plane to the floor and body weight was taken while wearing thin clothing using an electronic weighing machine [Digital Display Height and Weight Tester (sgsport.en.alibaba.com)]. Body mass index was calculated as the ratio of weight in kilograms divided by the square of height in meters. i.e., $BMI = \text{weight (kg)} / (\text{height(m)})^2$. BMI was categorized into four groups as follows: underweight, $BMI \leq 18.5$; normal weight, $18.5 < BMI < 25$; overweight, $25 \leq BMI < 30$; and obese, $BMI \geq 30$ (Hossain et al., 2012).

Outcome Variable

Blood pressure (BP) was considered as an outcome variable. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were taken from each subject three times in the sitting position using mercury sphygmomanometers (Pickering et al., 2005), and the average value was taken for the analysis. Each subject was allowed to rest 5 minutes between measurements, and without having any drinks or smoking. The sample was classified into four classes according the range of blood pressure (BP); (i) Hypotension ($SBP < 90\text{mmHg}$ or $DBP < 60\text{mmHg}$), (ii) Normal ($90 \leq SBP < 120\text{mmHg}$ and $60 \leq DBP < 80\text{mmHg}$), (iii) Pre-hypertension ($120 \leq SBP < 140$ or $80 \leq DBP < 90\text{ mmHg}$), and (iv) Hypertension ($SBP \geq 140\text{ mmHg}$ or $DBP \geq 90\text{mmHg}$) (Tadesse and Alemu, 2014).

Independent Variables

In this study, we attempted to establish the relationship between hypertension and some of the selected risk factors. The possible predictors for hypertension of university students were selected based on the published studies of university students in other countries (Tayem et al., 2012; Simão et al., 2008; Hujova, 2013; Soliman et al., 2014). Gender was classified as male (code 1) and female (code 2), permanent residence, was classified into two groups; rural (code 1) and urban (code 2), cigarette smoking behavior was divided into two groups; non

smoker (no, code 0) and smoker (yes, code 1). Fathers' and mothers' education, were classified into four levels; uneducated (code 0), primary education (code 1), secondary education (code 2) and high education (code 3). Fathers' occupation was classified into three groups; agriculture (code 1), service (code 2) and business (code 3). Mothers' occupation was categorized into two groups; housewife (code 1) and non housewife (code 2). On the basis of the parents' history of hypertension the sample was categorized into two groups; parents' with hypertension, yes (code 1) and no (code 0). Body size was classified into three groups; underweight (code 1), normal (code 2) and overweight or obese (code 3), the subjects' religion was divided into two groups; Non-Muslim (code 0) and Muslim (code 1), family members were set up as ≤ 4 persons (code 1), 5-7 persons (code 2) and ≥ 8 persons (code 3). Parents' family income was divided into three groups; monthly income < Taka 10000 (code 1), 10000-20000 Taka (code 2) and $\geq$ Taka 20000 (code 3). Sleeping hours a night of the subjects was classified into two classes; <7 hours (code 1) and ≥ 7 hours (code 2), and finally, physical activity with 45 minutes a day on at least five days a week, was divided into two groups; no (code 0) and yes (code 1).

Sample Size Determination and Sampling

Since our target population is known (approximately 25000; male 20000 and female 5000), thus the significant sample size for this study would be calculated on the basis of population size, and the following formula was used for determining the sample size:

$$n = \frac{N}{1 + Nd^2}$$
 where, n = required sample size, N = population size (in here 25000), d = marginal error (we used, d = 0.032), lastly, a 95% confidence level was utilized (Rana et al., 2015). The formula provided the minimal sample size of 900 for this study. However, a total of 930 selected students were asked by one of our coauthors, using a standard questionnaire, to report their socio-demographic characteristics. Nineteen (female 12 and male 7) students who did not agree to provide their information were excluded from the current analysis. Consequently, 911 students were included in this study.

The population was considered heterogeneous, divided into two different groups (male and female). However, they were considered homogeneous within the groups. A two-stage stratified random sampling technique with a proportional allocation was used for selecting the samples from Rajshahi University. The proportional allocation technique indicated that 727 males and 184 female students would be needed for this study.

Statistical Analysis

The prevalence of each category of BP was determined using by frequency distributions. The Chi-square test was utilized to find the association between the categories of BP and some of the selected socio-economic, demographic, anthropometric and behavioral factors. Finally, multinomial logistic regression analysis was used to find the effect of socio-economic, demographic and behavioral factors on pre-hypertension and hypertension of university students. Data were analyzed using the Statistical Package for Social Sciences (SPSS, IBM version 20). A value of $p < 0.05$ was regarded as statistically significant in the analysis.

RESULTS

Background Information

A total of 911 university students were interviewed and examined. Among them 727 (79.8%) students were male and 184 (20.2%) were female. The age of the subjects varied from 18 to 27 years, with a mean age of 22.27 ± 1.86 years. The present study demonstrated that the prevalence of pre-hypertension and hypertension among university students were 42.50% and 25.60% respectively, while the prevalence of hypotension among university students was very low (1.50%) (Figure 1). Students with hypotension were excluded from further statistical analysis.

Three categories; normal, pre-hypertension and hypertension were considered in the further statistical analysis.

Association between Hypertension and Other Selected Variables

The Chi-square test (χ^2 -test) was used to find the association between the blood pressure categories (BPC) and various socio-economic, demographic, anthropometric and behavioral factors among the university students in Bangladesh. In this study, gender ($p < 0.001$), residence ($p < 0.05$), cigarette smoking behavior ($p < 0.05$), body mass index ($p < 0.001$), parents' education level ($p < 0.05$), fathers' occupation BPC ($p < 0.01$), family income ($p < 0.05$), sleeping duration a night ($p < 0.05$) and physical activity ($p < 0.01$) were significantly associated factors of university students' BPC.

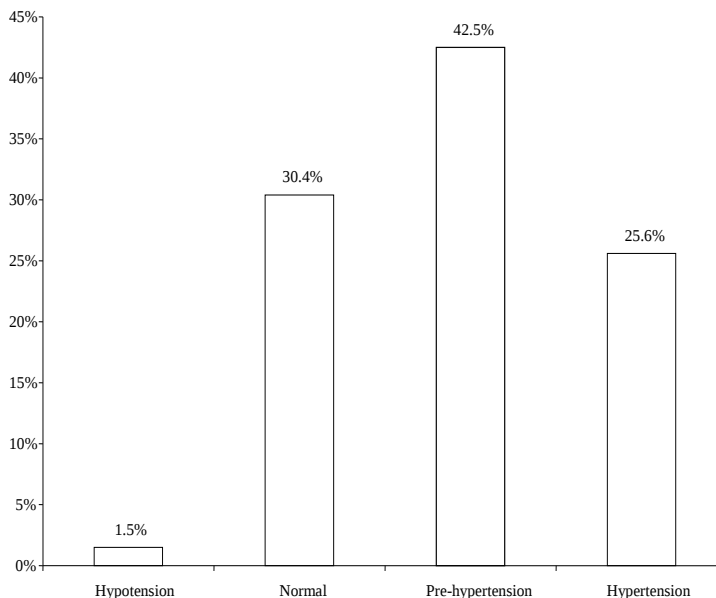


Figure 1. Prevalence of hypotension, normal, pre-hypertensive and hypertension of Rajshahi University students.

Table 1. Association of blood pressure and socio-economic, demographic and behavior factors of university students

Variables, N (%)	Normal, N (%)	Pre-hypertension, N (%)	Hypertension, N (%)	χ^2 -value	p-value
Gender					
Male, 717 (79.9)	152(21.2)	339(47.3)	226(31.5)	164.91	0.001
Female, 180 (20.1)	125(69.4)	48(26.7)	7(3.9)		
Residence					
Rural, 733(81.7)	211(28.8)	326(44.5)	196(26.7)	8.24	0.016
Urban, 164(18.3)	66(40.2)	61(37.2)	37(22.6)		
Cigarette Smoking behavior					
No, 761(84.8)	249(32.7)	324(42.6)	188(24.7)	8.99	0.011
Yes, 136(15.2)	28(20.6)	63(46.3)	45(33.1)		
Father hypertension					
No, 620(69.1)	191(30.8)	264 (42.6)	165(26.6)	0.47	0.715
Yes, 277(30.9)	86(31.0)	123(44.4)	68(24.5)		
Mother hypertension					
No, 619(69.0)	204(33.0)	262(42.3)	153(24.7)	4.31	0.116
Yes, 278(31.0)	73(26.3)	125(45.0)	80(28.8)		
Body mass index					
Under-weight, 120 (13.4)	73(60.8)	36(30.0)	11(9.2)	82.89	0.001
Normal, 709(79.0)	197(27.8)	325(45.8)	187(26.4)		
Over-weight or obese, 68(7.6)	7(10.3)	26(38.2)	35(51.5)		
Religion					
Non-Muslim, 79(8.8)	26(32.9)	32(40.5)	21(26.6)	0.27	0.875
Muslim, 818(91.2)	251(30.7)	355(43.4)	212(25.9)		
Household size					
≤4, 261(29.1)	82(31.4)	108(41.4)	71(27.2)	0.82	0.936
(5-7), 495(55.2)	150(30.3)	220(44.4)	125(25.3)		
≥8, 141(15.7)	45(31.9)	59(41.8)	37(26.2)		
Fathers' education					
No education, 282(31.4)	99(35.1)	112(39.1)	71(25.2)	16.25	0.012
Primary, 138(15.4)	27(19.6)	63(45.7)	48(34.8)		
Secondary, 209(23.3)	74(35.4)	90(43.1)	45(34.8)		
Higher, 268(29.9)	77(28.7)	122(45.5)	69(25.7)		
Mothers' education					
No education, 87(9.7)	38(43.7)	30(34.5)	19(21.8)	24.96	0.001
Primary, 178(19.8)	39(21.9)	73(41.0)	66(37.1)		
Secondary, 356(39.7)	121(34.0)	159(44.7)	76(21.3)		
Higher, 276(30.8)	79(28.6)	125(45.3)	72(26.1)		

Variables, N (%)	Normal, N (%)	Pre-hypertension, N (%)	Hypertension, N (%)	χ^2 -value	p-value
Fathers' occupation					
Farmer, 419(46.7)	108 (25.8)	198(47.3)	113(27.0)		
Service, 245(27.3)	79(32.2)	94(38.4)	72(29.4)	15.30	0.004
Business, 233(26.0)	90(38.6)	95(40.8)	48(20.6)		
Mothers' occupation					
Housewife, 835(93.1)	252(30.2)	367(44.0)	216(25.9)		
Others, 62(6.9)	25(40.3)	20(32.3)	17(27.4)	3.81	0.149
Family income					
≤Taka 10000, 447(49.8)	121(27.1)	200(44.7)	126(28.2)		
Taka 10001-20000 Taka, 160(17.8)	63(39.4)	63(39.4)	34(21.2)	9.07	0.049
≥20001 Taka, 290(32.4))	93(32.1)	124(42.8)	73(25.2)		
Sleeping hour					
≥7 Hours, 451(50.3)	155(34.4)	184(40.8)	112(24.8)		
<7 Hours, 446(49.7)	122(27.4)	203(45.5)	121(27.1)	5.18	0.045
Physical activity					
No, 798 (88.9)	233(29.2)	344(43.1)	221(27.7)		
Yes, 99(11.1)	44(44.4)	43(43.4)	12(12.1)	14.86	0.001
Extra salt intake					
No, 481(53.6)	136(28.3)	216(44.9)	129(26.8)		
Yes, 416(46.4)	141(33.9)	171(41.1)	104(25.0)	3.31	0.191

Table 2. Effect of socio-economic, demographic and behavior factors on university students' hypertension

Pre-hypertension	Variable	Category	AOR	95%CI for AOR		Variable	Category	AOR	95%CI for AOR	
				Lower	Upper				Lower	Upper
Pre-hypertension	Gender	Male	5.80**	3.67	9.16	Gender	Male	26.90**	11.41	63.45
		Female ^R	.	.	.		Female ^R	.	.	.
	Father's education	No education	0.92	0.53	1.61	Father's education	No education	0.89	0.45	1.74
		Primary	1.11	0.53	2.33		Primary	0.98	0.43	2.26
		Secondary	0.66	0.40	1.07		Secondary	0.63	0.34	1.15
Pre-hypertension	Mother's education	Higher ^R	.	.	.	Mother's education	Higher ^R	.	.	.
		No education	0.60	0.32	1.16		No education	0.79	0.36	1.76
		Primary	0.59	0.29	1.21		Primary	1.08	0.49	2.43
		Secondary	0.54	0.33	0.89		Secondary	0.46	0.25	0.83
		Higher ^R	.	.	.		Higher ^R	.	.	.

Table 2. (Continued)

Variable	Category	AOR	95%CI for AOR		Variable	Category	AOR	95%CI for AOR	
			Lower	Upper				Lower	Upper
Residence	Rural	1.05	0.64	1.73	Residence	Rural	1.02	0.56	1.89
	Urban ^R	.	.	.		Urban ^R	.	.	.
	Yes	1.12	0.66	1.89		Yes	1.18	0.67	2.13
	No ^R	.	.	.		No ^R	.	.	.
Cigarette smoking behavior	Farmer	1.35	0.83	2.09	Cigarette smoking behavior	Farmer	1.21	0.68	2.12
	Service	0.94	0.55	1.58		Service	1.43	0.76	2.70
	Business ^R	.	.	.		Business ^R	.	.	.
	≤10000	0.87	0.55	1.36		≤10000	1.02	0.59	1.75
Monthly family income (Taka)	10001-20000	0.72	0.43	1.20	Monthly family income (Taka)	10001-20000	0.70	0.37	1.30
	>20000 ^R	.	.	.		>20000 ^R	.	.	.
	≥7	0.65*	0.46	0.92		≥7	0.67*	0.45	0.95
	<7 ^R	.	.	.		<7 ^R	.	.	.
Sleeping time (hour)	Underweight	0.15**	0.06	0.41	Sleeping time (hour)	Underweight	0.03**	0.01	0.11
	Normal	0.45*	0.18	0.90		Normal	0.19**	0.07	0.47
	Overweight/obese ^R	.	.	.		Overweight/obese ^R	.	.	.
	No	1.14	0.68	1.91		No	2.38*	1.12	5.04
BMI category	Yes ^R	.	.	.	BMI category	Yes ^R	.	.	.
	Physical activities					Physical activities			

N.B.: AOR, Adjusted Odds Ratio; **, 1% level of significance; *, 5% level of significance; R, Reference case.

Factors Influencing Hypertension in University Students

Blood pressure (BP) category was our dependent variable, and it was three categories (i) normal (ii) hypertension and (iii) hypertension, the multinomial logistic regression model was selected to find the effect of socio-economic, demographic and behavior factors on pre-hypertension and hypertension, normal BP was considered as reference case. Only the significant associated factors got from the χ^2 -test were considered as independent variable of multinomial logistic model (Table 2). The coefficients and adjusted odds ratio (AOR) of multinomial logistic regression model demonstrated that male students were more likely to get pre-hypertension [AOR = 5.80, 95% CI, 3.67-9.16; $p < 0.01$] and hypertension [AOR = 26.90, 95% CI, 11.41-63.45; $p < 0.01$] than female students. Students slept less than 7 hours a night who was more prone to get pre-hypertension [AOR = 0.65, 95% CI, 0.46-0.92; $p < 0.05$] and hypertension [AOR = 0.67, 95% CI, 0.45-0.95; $p < 0.05$] compared with who slept ≥ 7 hours. Over-weight or obese students had higher chance in developing pre-hypertension and hypertension than those who were under-weight [AOR = 0.15, 95% CI, 0.06-0.41; $p < 0.01$] and [AOR = 0.03, 95% CI, 0.01-0.11; $p < 0.01$], and those of normal weight [AOR = 0.45, 95% CI, 0.18-0.90; $p < 0.05$] and [AOR = 0.19, 95% CI, 0.07-0.47; $p < 0.05$] students, respectively. Students performed a certain level of physical activity with 45 minutes a day on at least five days a week who was less likely to get hypertension [AOR = 2.38, 95% CI, 1.12-5.04; $p < 0.01$] than their counterparts (Table 2).

DISCUSSION

This study was aimed at assessing the prevalence and associated factors of pre-hypertension and hypertension among university students in Bangladesh. A total of 911 students from 7 residence halls at Rajshahi University were recruited using a simple random sampling strategy. The study duration was conducted from January to June, 2014. The cross-sectional study identified pre-hypertension and hypertension as a significant health problem among these university students aged 18-27 years. The present study demonstrated that more than one-third and near to one-fourth of the students were pre-hypertensive and hypertensive respectively of the students was pre-hypertensive. University students are young adults who are more likely to be in a pre-hypertension mode rather than displaying full hypertension. The category of pre-hypertension was created to alert people to their risk of developing high blood pressure (HBP) so they could make the necessary lifestyle changes that may avoid the development of hypertension. If the students could be induced to change to their lifestyle and food habits this may help in avoiding the development of high blood pressure and therefore avoiding hypertension in their life in the future.

Hypertension among university students in Bangladesh was identified as lower than in other developing countries such as the university students in Gambia (38.0%) (Van der Sande et al., 2000), Tunisia (35.1%) (Hajer et al., 2012) and Ethiopia (28.3%) (Awoke et al., 2012). However, the hypertension of Bangladeshi university students was higher than in some other countries such as in Nigeria (19.3%) (Isezuo et al., 2011), Kuwait (7%) (Al-Majed and Sadek, 2012) and Saudi Arabia (9.3%) (Ibrahim et al., 2014). The present study demonstrated that male students were more likely to get hypertension compared to female students, and our

results agree with the findings of studies in Kuwait (Al-Majed and Sadek, 2012), Tunisia (Awoke et al., 2012), Hungary (Katona et al., 2011), Qatar (Bener et al., 2004) and USA (Everett and Zajaacova, 2015). In this study, we observed that the prevalence of risk factors such as overweight or obese and cigarette smoking behavior among male students was higher than that of female students, while more number of female students (19.4%) performed physical activities than male (8.9%), these were the important reasons for gender differentiation in hypertension. Same causes were found in one of the USA studies, they also found young men were less likely to be aware of their hypertensive status compared to young women (Everett and Zajaacova, 2015).

It is also important to note that overweight or obese students were at higher risk of getting hypertension compared to underweight and normal weight students. This finding supports previous reports from Tunisia, Portugal, and sub-Saharan African countries (Tadesse and Alemu, 2014). A study conducted in sub-Saharan countries showed that blood pressure was associated with BMI (Tasfaye et al., 2007). A study in Tunisia also demonstrated this relationship between BMI and hypertension (Hajer et al., 2012). Physical activities can reduce body fat, and it is suggested as a significant lifestyle modification that may help in the prevention of hypertension. It was noted that only 11.1% Rajshahi university students performed physical activity with 45 minutes a day on at least five days a week, also observed that university students who performed physical activities was less likely to get hypertension. Same result had been found in other studies (Diaz and Shimbo, 2013; Kokkinos et al., 2009). It was found that habitual short sleep duration at night was an important risk cause for hypertension (Calhoun and Harding, 2010). This study also demonstrated that students who slept less than 7 hours at night had a higher probability of getting hypertension than their counterparts. It is thought that over time, a lack of sleep can damage human body's ability to regulate stress hormones, leading to hypertension, sleep can help to control human blood pressure and helps nervous system remain healthy. The duration of sleep at night seven to eight hours may play a role in the treatment and prevention of high blood pressure.

Limitation of the Study

Only students staying in the residence halls of Rajshahi University were involved in this study; therefore, the present data cannot reflect the prevalence of hypertension among university students in Bangladesh as a whole. This study should not be limited to only university students but must involve other young adults of the same age range, especially those who may have dropped out from school/college and are working. During the study, some students were not willing to freely give information about BP, while others agreed but gave incorrect information especially regarding their parents' income and social status, so these students had to be excluded. This study was conducted as preliminary work to investigate the prevalence of pre-hypertension and hypertension and its association with selected anthropometric measures, socio-demographic and behavior factors. However, it was not possible to look at other important factors that may also be directly related to hypertension, such as diabetes mellitus, alcohol consumption (Tadesse and Alemu, 2014), environmental factors (Simão et al., 2008), and sedentary lifestyle (Tayem et al., 2012). Clearly, more studies of this type are required.

CONCLUSION

The purpose of this study was to investigate the prevalence and associated factors of pre-hypertension and hypertension among Rajshahi University students in Bangladesh. The study showed that gender, residence, cigarette smoking behavior, BMI, parents' education, fathers' occupation, family income, duration of sleep a night and physical activities were significantly associated with categories of blood pressure among university students. Multinomial logistic regression exhibited that male students, less than 7 hours sleep in night and overweight or obese students were more likely to become pre-hypertensive and hypertension compared to their counterparts. It is also observed that a student did not perform a certain level of physical activity at least 45 minutes in a day (at least 5 days in a week) who was more likely to get hypertension than his/her counterpart.

The findings of this study have policy implications as well as leading to recommendations that would be helpful to health authorities and policy makers to lead to substantial improvements in the area of hypertension and public health. It would especially assist the government and other policy makers to take the proper initiatives to promote the awareness among young adults about the dangers of becoming hypertensive in Bangladesh and to begin to take steps to attempt to reduce the prevalence of hypertension. Government and non-government organization need to have awareness and provide the necessary counseling regarding the risks of overweight and obesity among university students. Physical activities is a most important predictors of hypertension, and it can help to reduce the body fat. The health authorities of Bangladesh government and university authorities should take initiative to ensure that all university students must perform exercise at least 45 minutes for at least 5 days in a week.

Additional Points

Availability of Data and Materials

Primary data was used in this study and data was collected from university students in Bangladesh. Many variables were collected from subjects. The dataset will be used for other propose, we do not wish to share our data.

Ethical Approval

This study obtained the permission from the authority of the University of Rajshahi, and the research has been approved by the ethical committee of the *institute of Biological Science (IBSC), Rajshahi University, Bangladesh*.

Consent

Written consent was taken from each participant after a detailed oral explanation about the study. We got consent from all subjects for publishing their data.

Disclosure

There was no grant, technical or corporate support for this research project.

Conflicts of Interest

All authors declared that there were no conflicts of interests in relation to this study.

Authors' Contributions

Golam Hossain and Sadekur Rahman designed the study, wrote the proposal, collected the data, analyzed the data and wrote the manuscript. Suhaili Mohd, Rashidul Alam Mahumud and Pete E. Lestrel approved the proposal and revised the manuscript.

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Chapter 248

INCREASING INCIDENCE OF MACROSOMIA: THE IMPACT OF MATERNAL SOMATIC AND BEHAVIORAL PARAMETERS ON NEWBORN WEIGHT STATUS

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INTRODUCTION

The prevalence of obesity and the so called “syndrome x” has increased drastically worldwide during the last 20 years. Consequently, many authors already warn of global epidemics (Ford & Mokard 2008, Rheeder 2006). 10 years ago, the number of obese people on earth exceeded the number of people suffering from starvation and malnutrition for the first time in the long history of *Homo sapiens* (FAO 2008). Currently more than 1.9 billion adults, 18 years and older, are overweight and more than 600 million are obese (WHO 2016). Obesity is commonly defined, as a level of adiposity that is sufficiently excessive to damage health, demonstrated by an increased risk of metabolic and cardiovascular diseases, such as diabetes, hypertension, stroke and some forms of cancer (Danaei et al. 2009). The clustering of metabolic symptoms, in particular insulin resistance, dyslipidemia (with hypertriglyceridaemia and low levels of high density lipoprotein cholesterol) and cardiovascular symptoms such as hypertension are called “syndrome x”, which is significantly related to obesity (Reaven 1988, Dwyer et al. 2002). The most severe expression of syndrome x is found in combination with central obesity and is often referred as the metabolic syndrome. To determine obesity commonly the body mass index (BMI) based on body weight and height (kilograms per square meter) is used. (WHO 1995). The World Health Organization (WHO) defines overweight as a BMI above 25.00kg/m², while a BMI above 30.00kg/m² is an indicator of obesity. A BMI above 40.00kg/m² is seen as morbidly

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obese (WHO 1995). These cut offs are defined for adults. Obesity however, is not only a problem of the adult population, currently overweight or obesity affects one in ten children or adolescents worldwide (WHO 2016). In Europe, one in five children can be classified as overweight or obese (WHO 2016). Since sub adult individuals are still growing, and the growth patterns differ according to sex, the use of BMI cutoffs for determining obesity is problematic among sub adults. Therefore, BMI percentiles for each separate sex and age class are widely used for the determination of overweight and obesity among children and adolescents (Wang & Wang 2000).

The strong association between obesity and the risk of several chronic diseases such as heart disease, stroke, hypertension, but also pancreatitis, osteoarthritis and cancer makes the high rates of obesity among children as well as adults to a major concern of public health (Kulie et al. 2011, WHO 2016). This is especially true of the association between obesity and insulin resistance. Insulin resistance or type II diabetes is one of the most serious metabolic diseases with disastrous long term consequences such as blindness, nephropathy or the amputation of the lower extremities. The past president of the American Diabetes association, Francine Kaufman pointed out exceptionally strong interaction between obesity and type II diabetes and introduced the term “diabesity” (Kaufmann 2005). There is no doubt that obesity and insulin resistance but also syndrome x represent a global health crisis that threatens the economies worldwide (Hu 2011). Consequently the prevention of obesity as well as syndrome x is the major goal of public health strategies. In order to develop strategies to reduce the risk of developing obesity and syndrome x, it is necessary to analyze the potential risk factors. During the last decade several potential risk factors of syndrome x have been identified. It is well documented, that beside genetic factors life style patterns such as hyper alimentation and physical inactivity have a significant impact on the development of obesity and syndrome x. The life style factors promoting syndrome x can be seen in a close context with westernized life style patterns and modernization (Fall 2001, Harell et al. 2015).

OBESITY, SYNDROME X AND NEWBORN SIZE

Recently there is growing interest in the association between newborn size and the risk of obesity, and syndrome x in later life (Ramadhani et al. 2006). Newborn size, mainly expressed by birth weight, reflects intrauterine growth patterns, which are determined by genetic factors but also intrauterine environment. Obesity and insulin resistance during later life are more common among small for gestational age newborns (SGA) but also among large for gestational age newborn (LGA) (Ramadhani et al. 2006, Hermann et al. 2010, Wang et al. 2009, Bamberg et al. 2013, Yu et al. 2015).

During the 1980s and the early 1990s the British epidemiologists Barker and Hales proposed the concept that environmental stress factors such as malnutrition in utero, might influence the development of obesity and syndrome x later on in life (Barker & Clark 1997; Barker 1999). According to Barkers so called thrifty phenotype hypothesis fetal undernutrition and therefore fetal programming are the causative factors a of later life metabolic diseases (Barker 1999, Robert & Woods 2014). In utero nutritional deficiencies lead to small for gestational age newborns who respond to their low level of nutritional intake in early life through alterations in growth and metabolism which increase the risk of obesity

and syndrome x in later life (Barker 1999). According to Barker and Hales hypothesis small for gestational age newborns have metabolically thrifty mechanisms for fat storage and glucose sparing with reduced rates of glucose oxidation in insulin-sensitive target tissues (Barker 1999). Consequently, low birth weight, which has been defined as a birth weight below 2500g regardless of gestational age, is on the one hand one of the strongest single risk factors for early neonatal mortality and morbidity (Mahumud et al. 2017). On the other hand low birth weight is also an important risk factor for developing obesity and syndrome x in later life. This association is of special concern because according to the World Health Organization (WHO) the prevalence of low birth weight is 15.5% globally and 96.5% of low birth weight infants are born in developing countries (Mahumud et al. 2017).

MACROSOMIA

As pointed out above birth weight as a predictor of health in later life showed a u-shaped curve with both low birth weight as well as high birth weight associated with increased risks. High birth weight or large for gestational age newborn is commonly called macrosomia, which defined a birth weight above 4000g or 4500g (Dennedy & Dunne 2013). The American College of Obstetricians and Gynecologists supports the use of a 4500g cutoff, irrespective of gestational age because a birth weight of more than 4500g increases the risk of adverse maternal and perinatal outcome (ACOG 2000). Unfortunately for the definition of macrosomia the cut offs of 4000g and 4500g are still used simultaneously. Another definition of macrosomia is a birth weight greater than 90% for gestational age after correcting for neonatal sex and ethnicity. Ye et al. (2015) plead for a population specific definition of macrosomia and suggested a cut-off of 4500g for African and Latin American newborn but a cut off of 4000g for Asian populations. Based on these, definitions macrosomia affects 1 to 10% of pregnancies worldwide. As to be expected the prevalence of macrosomia (birth weight above 4000g) widely from a low of 0.5% in India to a high of 14.9% in Algeria (Koyanagi et al., 2013). In Western countries macrosomia (> 4000g) is encountered in up to 10% of deliveries (Campbell 2014). In the United States approximately 7% of newborn had birth weight above 4000g, 1% had birth weight higher than 4,500g, and 0.1% had birth weight higher than 5000g (Dennedy & Dunne 2013).

Using the definition of fetal macrosomia as a neonate with a birth weight above 4.5 kg the prevalence of macrosomia ranges from 1.3 – 1.5% of all births in developed countries. Only few neonates are extremely large. According to the Guinness world record the heaviest infant born to a healthy mother, weighing 10.2kg was born in Italy in 1955. Few other infants weighing more than 6kg are recorded such as a newborn weighing 7kg from Cambria, UK in 1992, and an infant weighing 7.6kg in Bahia Brazil in 2005. In 2007, a newborn weighing 6.6kg was born in Cancun Mexico. In China, an infant weighing 6.2kg was born 2006 and in 2008, a Chinese baby weighing 5.5kg was delivered. The largest baby ever recorded in Bangladesh was born in 2008 weighing 6kg (Sultana et al. 2007). Without any doubt such extraordinary heavy newborn are extremely rare. What we can observe however are changes in mean birth weight. A secular trend in birth weight was observable in some countries from the mid to the late 20th century (Bralic et al. 2006; Oken 2013, Begic et al. 2016, Chegeni et al. 2016). In Moscow, Russia, for instance, the mean birth weight of boys increased from

3450g in 1987 to 3500g in 2002, among girl mean birth weight increased from 3360g to 3450g (Treyak et al. 2005). In Sweden, the mean weight at birth increased from 3596g to 3631g during the period 1992 and 2002 (Surkan et al. 2005). Furthermore, the prevalence of macrosome newborns ($> 4500\text{g}$) increased from 3.7% to 4.6% during this period (Surkan et al. 2005).

According to popular press and public perceptions birth weight seems to increase steadily during the last decades, but this is not true. Recent data indicate that in developed countries the mean birth weight has begun to decline. In the United States the incidence of low weight newborn ($< 2500\text{g}$) increased, while the prevalence of newborn weighing more than 5000g decreased. (Oken 2013). Similar trends are observed for France and Australia (Oken 2013). In Austria the prevalence of macrosome newborn ($> 4500\text{g}$) decreased from 7.1% in 2006 to 6.4% in 2016. (Statistik Austria 2017) These trends may be due to changes in population mixture but mainly due to changes in obstetric practice. Induction of labor, but also increased monitoring of diabetic and prediabetic women during pregnancy account for this decrease in macrosome newborn.

This reduction of macrosomia is of special importance because macrosomia increases maternal as well as newborn morbidity and mortality. Higher stillbirth rates but also higher fetal mortality rates are associated with a birth weight above 4250g in non-diabetic mothers and with a birth weight above 4000g among diabetic mothers (Mondestin et al. 2002, Najafian & Cheraghi 2012). Furthermore, macrosomia increases birth complication in particular the risk of shoulder dystocia and trauma to the birth canal, bladder, perineum and anal sphincter (Campbell 2014). This is especially true of birth weights higher than 4500 g and particularly among birth weight, which exceeds 5000 g. Consequently, fetal macrosomia is associated with increased risks for emergency Cesarean section (CS) and instrumental delivery (Campbell 2014). For the newborn macrosomia associated complications, include beside increased mortality, brachial plexus or facial nerve injuries, fractures of the humerus or clavicle and birth asphyxia (Campbell 2014)

Consequently, macrosomia is clearly associated with birth complications and maternal as well as newborn morbidity and mortality (Najafian & Cheraghi 2012, Campbell 2014). Additionally, many studies have shown that macrosomia is a risk factor for obesity and syndrome x in later life (Yu et al. 2008, Hermann et al. 2010). Therefore, the analysis of potential risk factors of macrosomia is essential.

Factors strongly associated with fetal macrosomia include genetics, ethnic factors, duration of gestation, presence of gestational diabetes, and maternal diabetes mellitus types I and II (Li et al. 2014, Kamana et al. 2015). It is well documented, that maternal diabetes-pregestational as well as gestational diabetes - is one of the strongest risk factors associated with macrosomia (Hammoud et al. 2013). Furthermore, maternal prepregnancy weight status affects birthweight (Pözlberger et al. 2017). Obese women but also women experiencing excessive gestational weight gain are more likely to give birth to larger infants (Kirchengast & Hartmann 2018). Additionally some studies plead for an association between macrosomia and multiparity as well as older maternal age (Li et al. 2015). An important fetal factor is sex. Male infants are heavier than female ones at any gestational age and the prevalence of macrosomia is higher among male newborns.

As mentioned above beside the perinatal complications, macrosomia represents an important risk factor of syndrome x and obesity in later life (Herrmann 2010). Therefore, the analysis of potential risk factor of macrosomia despite of maternal diabetes is of special

importance. In the present study, the impact of fetal sex but also maternal prepregnancy weight status and maternal behavior on newborn size was tested among more than 10 000 term births in Vienna, Austria.

MATERIAL AND METHODS

Data Set

This retrospective study is based on a data set of 10231 singleton births, which took place at the University Clinic of Gynecology and Obstetrics in Vienna, Austria between 1995 and 2000. Although, a total of 18425 births were collected, only 10231 met the strict inclusion and exclusion criteria. Following inclusion criterions have been defined:

1. Births between the 38th and 41th week of gestation, because only term births should be included in analyses to make maternal pregnancy weight gain and newborn anthropometric data more comparable.
2. Only pregnant women ageing between 18 and 45 years were enrolled in the present study whose first prenatal check took place during the eighth week of gestation.
3. All prenatal check-ups of the mother-child passport were completed.
4. Delivery of a single infant without congenital malformations
5. No registered maternal diseases before and during pregnancy i.e., no hypertension (BP < 150/90 mmHg), no preeclampsia, no protein or glucose in the urine, no pregnancy related immunization.

Additionally the following exclusion criteria have been defined:

1. Early Teenage pregnancy i.e., maternal age below sixteen years.
2. Coincident medical diseases such as diabetes mellitus or nephropathy.
3. Drug or alcohol abuse.
4. Twin birth or IVF.

Gestational age was calculated in terms of the number of weeks from the beginning of the last menstrual bleeding to the date of delivery (= duration of amenorrhoea). All subjects originated from Austrian or central Europe.

Maternal Parameters

All 10231 women enrolled in the present study aged between 17 and 49 years (mean = 25.3 yrs SD = 5.7). The following maternal somatometric parameters were determined at the first prenatal visit: Stature height was measured to the nearest 0.5cm and prepregnancy weight (PPW), was measured to the nearest 0.1kg on a balance beam scale. Additionally maternal weight at the end of pregnancy (EPW) was measured before birth. The weight gain during pregnancy (PWG) was calculated by subtraction of pre-pregnancy weight from body weight

at the end of pregnancy. Maternal weight status before pregnancy was described by means of the body mass index (BMI) (kg/m^2). Weight status was classified according to the recommendations of the WHO (1995).

- < 18.50 = underweight
- 18.50 - 24.99 = normal weight
- 25.00 - 29.99 = overweight
- 30.00 - 39.99 = obese
- > 40.00 = morbid obese

Newborn Parameters

Birth weight, birth length, head circumference, diameter fronto-occipitalis and acromial circumference were taken directly from newborn immediately after birth. Newborn weight status was defined as follows: low < 2500g, normal 2500 - 3999g, high 4000 - 4500g and macrosome > 4500g (Dennedy & Dunne 2013). Furthermore, the one- and the five minute APGAR scores (Casey et al. 2001) for the evaluation of the newborn were determined.

Mode of Delivery

Spontaneous vaginal birth and caesarean section were recorded. Caesarean sections requested by the mother without any medical indication were not carried out at this hospital.

Statistical Analyses

Statistical analyses were performed by means of SPSS for Windows program Version 22.0. After calculating descriptive statistics (means, SDs), group differences were tested regarding their statistical significance using Duncan analyses. Furthermore, χ^2 analyses and odds ratios were computed. Multiple regression analyses were performed to test the impact of maternal prepregnancy BMI, stature height, gestational weight gain on birth weight. Additionally binary logistic regressions were computed in order to test the association between maternal parameters and newborn weight status. Normal birthweight was coded as 1, high birth weight and macrosomia were coded as 2.

RESULTS

Sample Description

Altogether 10231 newborns have been enrolled in the present study. The number of male newborn ($n = 5249$; 51.3%) surpassed the number of female ones ($n = 4991$; 48.7%). The majority of mothers (73.3%) corresponded to the WHO definition of normalweight. 8.9 % of

the mothers were classified as underweight because their prepregnancy body mass index was below 18.50 kg/m². 14.2% of the mothers were classified as overweight (BMI 25.00 to 29.99kg/m²) and only 3.6% corresponded to the definition of obesity i.e., a prepregnancy BMI above 30.00 kg/m². Only 0.3% of the mothers were classified as morbidly obese (BMI > 40.00 kg/m²). The mean weight gestational gain was 12.9kg (SD = 5.5) ranging from 2 to 38 kg. The majority of mothers were nonsmokers before pregnancy (64.2%) and during pregnancy (72.0%). 22.8% of the mothers were classified as heavy smokers (> 10 cigarettes per day) before pregnancy and 7.6% of the mothers were still heavy smokers (>10 cigarettes per day) during pregnancy.

The Prevalence of High Birth Weight and Macrosomia

As to be expected the majority of newborn (90.3%) corresponded to the definition of normal weight (2500 - 3999g). 1.8% of the newborn were classified as low weight (< 2500g). 7.3% corresponded to the definition of high birthweight (4000 - 4499g) and only 0.8% corresponded to the definition of macrosomia (> 4500g). Male and female newborn differed significantly in weight status ($p < 0.0001$). The prevalence of high birthweight and macrosomia was significantly higher among male newborn. 9.5% of the male newborn showed a birth weight between 4000 and 4500g, 0.7% were heavier than 4500g. Among female newborn the prevalence of high birth weight was only 4.9% and only 0.2% of the female newborn were classified as macrosome.

As demonstrated in Table 1, high weight newborn and macrosome newborn were not only heavier than their normal weight and low weight counterparts, they were also significantly longer and exhibited significantly larger head dimensions and significantly higher acromial circumferences. Concerning vital parameters, however it turned out the one minute and five minute appear scores of high weight and macrosome newborn were only slightly decreased in comparison to their normal weight counterparts.

The Impact of Maternal Parameters on Newborn Weight Status

Newborn weight status was significantly associated with various somatic but also behavioral parameters of the mothers. As demonstrated in Table 1 the mothers of high weight or macrosome newborn were significantly older, taller and heavier than the mothers of normal weight or low weight newborns. Furthermore, they exhibited significantly larger pelvic dimensions and experienced a significantly higher gestational weight gain ($p < 0.0001$). Maternal prepregnancy overweight and obesity increased the risk of giving birth to high weight and macrosome newborn significantly. While the prevalence of high weight and macrosome newborn was below 5% among underweight mothers and 6.9% among normal weight mothers, 12.3% of overweight women, 13.9% of obese women and 33.4% of morbidly obese women gave birth to high weight or macrosome offspring. Smoking before and during pregnancy reduced the risk to give birth to a macrosome newborn.

Table 1. Maternal and newborn characteristics according to newborn weight status

n	Birth weight categories				
	< 2500g	2500 - 3999g	4000 - 4500g	> 4500g	.
	185	9241	746	59	Sig
	mean (Sd)	mean (Sd)	mean (Sd)	mean (Sd)	p-value
Maternal characteristics					
Maternal age (yrs)	25.4 (6.2)	25.2 (5.6)	26.3 (5.4)	28.0 (5.8)	< 0.0001
Stature height (cm)	161.1 (6.8)	163.0 (6.4)	165.6 (6.7)	166.7 (6.3)	< 0.0001
Prepregnancy weight (kg)	55.2 (9.5)	59.1 (9.9)	64.8 (11.8)	69.6 (11.9)	< 0.0001
End of pregnancy weight (kg)	65.0 (11.1)	72.4 (11.7)	81.3 (13.6)	95.9 (13.6)	< 0.0001
Prepregnancy BMI (kg/kh ²)	21.22 (3.15)	22.18 (3.47)	23.59 (4.21)	25.05 (4.61)	< 0.0001
Gestational weight gain (kg)	10.4 (5.3)	12.8 (5.4)	14.9 (5.6)	15.6 (5.2)	< 0.0001
Distantia spinarum (cm)	24.3 (2.0)	24.9 (2.0)	25.5 (2.1)	25.8 (1.6)	< 0.0001
Distantia cristarum (cm)	27.5 (2.0)	28.0 (2.1)	28.8 (2.0)	29.4 (1.7)	< 0.0001
Newborn characteristics					
Birth length (cm)	45.6 (1.9)	49.7 (1.7)	52.3 (1.5)	53.6 (1.6)	< 0.0001
acromial circumference (cm)	32.7 (1.4)	36.6 (2.1)	40.1 (1.9)	42.5 (2.2)	< 0.0001
Head circumference (cm)	32.0 (1.2)	34.3 (1.3)	35.9 (1.2)	36.8 (1.1)	< 0.0001
Diameter fronto-occipitalis	10.6 (0.7)	11.2 (0.7)	11.7 (0.7)	12.0 (0.7)	< 0.0001
Apgar 1 minute	8.0 (1.9)	8.6 (1.2)	8.4 (1.4)	8.2 (1.5)	< 0.0001
Apgar 5 minute	9.4 (1.4)	9.8 (0.7)	9.7 (0.8)	9.7 (0.6)	< 0.0001

**Table 2. Impact of maternal characteristics on newborn size.
Multiple regression analyses**

	R ²	B	Sig	95% CI
Dependent variable. Newborn weight				
Maternal age	0.28	4.59	< 0.001	2.42 – 6.77
Stature height		12.77	< 0.001	10.91 – 14.62
Prepregnancy BMI		25.37	< 0.001	22.19 – 28.54
Gestational weight gain		17.38	< 0.001	15.14 – 19.62
Newborn sex		- 126.4	< 0.001	-150.15 - -102.61
Prepregnancy nicotine consumption		- 2.96	< 0.001	- 4.57 - - 1.34
Nicotine consumption during pregnancy		- 8.53	< 0.001	- 11.07 - - 5.99

These findings were corroborated by the results of the multiple and the binary logistic regression analyses (see Tables 2 and 3). Maternal age, stature height, prepregnancy weight status and gestational weight gain were significantly positively associated with birth weight and macrosomia. Nicotine consumption before and during pregnancy were significantly

negatively associated with birth weight however only insignificantly negatively with macrosomia.

**Table 3. Impact of maternal characteristics on macrosomia.
Multiple regression analyses**

	Exp (B)	Sig	95% CI
Dependent variable: newborn weight status			
Maternal age	1.07	0.034	1.01 – 1.14
Stature height	1.09	0.003	1.03 – 1.16
Prepregnancy BMI	1.18	0.001	1.102 – 1.27
Gestational weight gain	1.11	0.001	1.04 – 1.18
Newborn sex	0.54	0.130	0.24 – 1.20
Prepregnancy nicotine consumption	0.99	0.646	0.94 – 1.04
Nicotine consumption during pregnancy	0.95	0.267	0.86 – 1.04

Newborn Weight Status and Delivery Mode

Delivery mode differed significantly according to newborn weight status (Chi-square = 24.8; $p < 0.0001$). Caesarean section rate of the whole sample was 21.5%. The lowest cesarean section rate was found among normal weight newborn (21.1%) the highest rate among low weight newborn (37.0%). High weight newborn (4000 - 4399g) and macrosome newborn (> 4500 g) showed a CS rate of 23.0% and 23.6% respectively. High birth weight (OR = 1.12 CI 0.93 - 1.32) and macrosomia (OR = 1.16, CI 0.62 - 2.15) increased slightly the risk to give birth via caesarean section in comparison to normal weight newborn.

DISCUSSION

Macrosomia is clearly an important risk factor of obesity and syndrome x during childhood and adult life (Yu et al. 2008, Wang et al. 2009, Hermann et al. 2010). Large for gestational age infants show distinctly different growth patterns from normal weight newborns during childhood. They experience higher weight gains and show significantly higher body mass indices than their normal weight counterparts (Yu et al. 2008, Bocca-Tjeertes et al. 2014). These high rates of obesity increase the risk of metabolic disorders from early childhood onwards (Bocca-Tjeertens et al. 2014). Therefore, the analysis of factors promoting macrosomia is of special importance. In the present study, the impact of fetal sex but also maternal somatometric factors as well as maternal behavioral factors on birth weight was analyzed. In detail a large sample of term births taking place in Vienna Austria were enrolled in the present analysis. Only 1.8% of the newborn were classified as low weight or small for gestational age (< 2500 g). This is much lower than the general prevalence of small for gestational age newborn in Austria (Statistik Austria 2016). Between 2007 and 2016 the rate of small for gestational age newborns ranges between 6.4 and 7.2%. This discrepancy is due to the fact, that exclusively term births have been included into the present study. The prevalence of high birth weight newborn (4000 - 4499g) was 7.3%. This rate is in accordance

with macrosomia rates ($> 4000\text{g}$) in other high-income countries (Campbell 2014). Only 0.8% of the newborn were heavier than 4500g. This low incidence of macrosomic newborn is comparable to that of the United States where about 1% of the newborn exhibit a birth weight above 4500g (Dennedy & Dunne 2013.) In the present study, fetal sex had a significant impact on macrosomia. The birth weight of 9.5% of the male newborn was between 4000 and 4500g, while only 4.9% of newborn girls were weighing between 4000 and 4500g and only 0.2% exhibited a birth weight above 4500g. These significant sex differences are in accordance with the results of several other studies. Male newborns typically weigh more than female newborns, in detail male newborns are generally approximately 150 - 200 g heavier than female newborn of the same gestational age near term (Kirchengast 2014). Furthermore, male newborn are more likely to be macrosomic than female ones (Di Renzo et al. 2007).

As to be expected, macrosome newborn were not only heavier they also were longer and had larger heads. This fact may be the main reason that caesarean section rates were significantly higher among mothers of macrosome newborns. In the present study, more than 23.0% of newborn weighing above 4500g were delivered via Caesarean section. This finding is in accordance with the results of numerous previous studies, which yielded significantly increased caesarean section rates among mothers of macrosome newborns (Barber et al. 2011, Kirchengast & Hartmann 2017)

Concerning maternal parameters, prepregnancy weight status was significantly associated with birth weight. While less than 7% of normal weight mothers gave birth to a newborn heavier than 4000g, this was true of more than 12% of overweight mothers, nearly 14% of obese mothers and more than 33% of morbidly obese mothers ($\text{BMI} > 40.00\text{kg/m}^2$). Maternal obesity is general seen as a main risk factor of newborn macrosomia (lit.). Additionally mothers of high birth weight (4000 - 4499g) and macrosome newborns ($> 4500\text{g}$) are taller and experienced a higher gestational weight gain than mothers of low weight and normal weight newborns. These findings corroborate the results of several previous study (Clausen et al. 2005, Pözlberger et al. 2017). Furthermore, the pelvic dimensions of mothers of high weight and macrosome newborns are larger than those of mothers of normal weight or low weight newborn. These increased pelvic dimensions may enable mothers of large fetuses to experience vaginal delivery despite of the large dimensions of the fetus.

Concerning maternal behavioral factors, the impact of nicotine consumption before and during pregnancy on newborn size was tested. Smoking before and during pregnancy increased the risk of giving birth to a small for gestational age newborn, but reduced the risk of giving birth to a macrosome one smoking however, should not be used to reduce the risk of macrosomia.

Macrosomia and associated obesity and syndrome x during later life are important issues of public health and obstetrics but these association patterns are also of interest from view point of evolutionary biology. Of course, it is not the task of evolutionary biology and/or evolutionary anthropology to develop new treatment strategies, but they may focus on the evolutionary basis of the prevalence of macrosomia on the one hand and the association between macrosomia and later life health issues on the hand. Evolution is the central paradigm in biological science and consequently Theodosius Dobzhansky stated “*Nothing in biology makes sense except in the light of evolution*” (Dobzhansky 1973). From this point of view, macrosomia and associated health risks in later life have to be considered, within the framework of human evolution.

The first hazard of an evolutionary analysis of macrosomia and associated health risks is that we have no information regarding newborn size and birth weight of our hominid ancestors. Only few fossil remains of hominid infants are known, for example the Neanderthal neonates from Mezmaiskaya 1 (Russia) and Le Moustier 2 (France) (Weaver et al. 2016). These rare skeletal remains allow us to reconstruct birth patterns among Neanderthals (Ponce de Leon et al. 2008), but we have no information regarding mean birth weights among different hominid species. The analysis of birth weight among our hominid ancestors is quite difficult. Wells (2009) used maternal height as predictor of birth weight and reconstructed birth weight trends from the Paleolithic onwards. According to Wells analyses birth weight declined from about 3500 to 3300 g during Paleolithic to about 2900 to 3000g during Neolithic times. Consequently, the transition from the Paleolithic hunter-gatherer subsistence to Neolithic agriculture was associated with a decrease of birth weight but also a deterioration of health. Nevertheless, we cannot assume that macrosomia was a common condition during Paleolithic times. The typical life style of our Paleolithic ancestors was characterized by a high level of physical activity because high levels in daily activity in search of food, water and sleeping sites were necessary. Diets consisted to a high degree of vegetable food, protein (50 to 80%) and a low fat content (Konner and Eaton 2010). It can be assumed, that typical non-communicable diseases such as hypertension, heart disease, cancer, diabetes or obesity have been rare or rather unknown during Paleolithic times (Lieberman 2003). The Neolithic transition changed the lifestyle of our ancestors drastically (Larsen 1995). The adoption of agriculture and animal husbandry allowed the production of a surplus of food and consequently population growth. Our ancestors developed semi-permanent settlements and gave up their mobile lifestyle. Dietary breadth declined dramatically and diet consisted of high carbohydrate crops such as rice, barley or wheat and tuber such as potatoes (Larsen 1995). Analyses of Neolithic skeletal remains indicate protein deficiencies and periodic food shortages. Furthermore, domestication of animals and plants changed the environments dramatically. The close proximity to domesticated animals exposed humans to a variety of new pathogens resulting in an increased frequency of infectious diseases (Armelagos et al. 1991). The use of feces as fertilizer and the construction of irrigation increased the contact with parasites. Many of these diseases had an important impact on early life. On the one hand, birth weight declined and this trend increased the risk of infectious diseases and increased infant mortality. On the other hand, maternal stature decreased during Neolithic transition and smaller birth size may be interpreted as an adaptation to this maternal somatic change (Wells 2009).

Birth weight increased again in recent times. The increase of macrosomia, which is evident for the last fifty years, can be interpreted as result of increasing affluence in developed but also developing countries. Rapid changes of our life style resulted in an obesogenic environment, which increased rates of obesity and type II diabetes but also gestational diabetes. Diabetes, first of all gestational diabetes are major risk factors for large for gestational age newborn (Kamana et al. 2015).

From an evolutionary viewpoint, increased rates of macrosomia in the second half of the 20th century may be an indicator of a mismatch between recent life circumstances and the environment in which our ancestors evolved. Modernization as well as urbanization took place, eating habits and physical workload changed dramatically. Especially a rapid transition in nutritional habits and general lifestyle increases the risk to be obese and to suffer from type II diabetes (Popkin 2003). This is especially true of rising economies in Asia. In 1980 less

than 1% of Chinese adults suffered from obesity and diabetes type II, in 2008 the prevalence had reached nearly 10% (WHO 2016). The prevalence of macrosomia (> 4000g) increased from 2.6% in the 1970s to 13.25 in the 1990s. Greatest increase occurred in urban areas. In Shanghai, the percentage of macrosomia increased by 50% from 1989 to 1999 (Yu et al. 2008).

Rapid modernization seems to enhance macrosomia rates. This is especially true of indigenous people experiencing rapid westernization. During the last 30 years, the incidence of macrosomia increased dramatically among indigenous populations in Canada. Among First Nations in Quebec and Ontario the a third of newborns is heavier than 4000g and a tenth is heavier than 4500g (Auger et al. 2013). Especially high rates of adult obesity and type II diabetes associated with westernization and modernization occur among Pacific Islanders (Jowitt 2014). The prevalence rates macrosomia (> 4500g) among Samoan mothers was 2.4%, while in developed countries less than 1% of the newborn are heavier than 4500g (Tsitas et al. 2015).

Macrosomia seems to be a problem of obesogenic environments, affluence and rapid modernization.

CONCLUSION

Macrosomia is strongly related to obesity and syndrome x in later life and have to be seen within the same context. Maternal obesity and high gestational weight gains enhance the risk of macrosomia independent of gestational diabetes. On the other hand macrosomia increases the risk of obesity and syndrome x.

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Chapter 249

METABOLIC DISORDER AND TYPE-2 DIABETES ASSOCIATIONS WITH ANTHROPOMETRIC MEASURES AMONG ADULT ASIAN INDIANS

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INTRODUCTION

The concept of the metabolic disorder (MetD) has now been in existence for several years. The MetD also known as syndrome-X was first described by Gerald Reaven in 1988. It is mainly characterized by insulin resistance, hyperinsulinemia, hyperglycemia, dyslipidemia and arterial hypertension. The MetD is defined as glucose intolerance, impaired glucose tolerance (IGT) or diabetes mellitus, or insulin resistance together with two or more other components {e.g., Raised arterial pressure, i.e., $\geq 140/90$ mmHg; raised plasma triglyceride (≥ 150 mg/dl) and/or low HDL-C (< 35 mg/dl in men and < 39 mg/dl in women); central obesity, i.e., waist/hip ratio (WHR) > 0.90 in men and > 0.85 in women and/or body mass index (BMI) > 30.00 kg/m², micro-albuminuria, i.e., urinary albumin excretion rate ≥ 20 μ gm/minute or albumin/creatinine ratio ≥ 30 μ gm/mg} (Parikh and Mohan 2012; Awasthi et al. 2017; Ricci et al. 2017). The MetD can also be defined in terms of the associations between obesity, insulin resistance (IR), hypertension and dyslipidemia (NCEP 2001; Grundy et al. 2004; Furukawa et al. 2017). Some other study groups have suggested several other definitions of MetD {For example, The European Group for Study of Insulin Resistance (EGIR); American Association of Clinical Endocrinologists (AACE) and International Diabetes Federation (IDF)} (Yankey et al. 2017) (Table 1). The main cause of increase in MetD is observed to be the increasing prevalence of obesity in populations worldwide (Grundy 2016; Saltiel and Olefsky 2017).

Table 1. Different criteria for type-2 diabetes mellitus proposed by different organizations

Reference	Criteria for Type-2 Diabetes Mellitus (T2DM) or Non-Insulin Dependent Diabetes Mellitus (NIDDM)
WHO (1999)	Insulin resistance (glucose uptake in the euglycemic clamp below the lowest quartile for the general population) or impaired glucose regulation (impaired fasting glycemia, impaired glucose tolerance, or type-2 diabetes), with 2 or more of the following: 1) BP of 140/90 mm Hg or higher, 2) Triglyceride levels of 150 mg/dL (1.7 mmol/L) or higher and/or HDL-C levels less than 35 mg/dL (0.9 mmol/L) in men and less than 39 mg/dL (1.0 mmol/L) in women, 3) Waist-hip ratio >0.90 in men and >0.85 in women and/or Body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters) greater ≥ 30.00 kg/m ²) and microalbuminuria.
NCEP (2001)	Insulin resistance and the presence of 3 or more of the following components: 1) Fasting plasma glucose concentration greater than 110 mg/dL (6.1 mmol/L), 2) Triglyceride concentration of 150 mg/dL (1.69 mmol/L) or greater, 3) HDL-C concentration less than 40 mg/dL (1.04 mmol/L) in men and less than 50 mg/dL (1.29 mmol/L) in women, 4) BP of 130/85 mm Hg or greater and 5), waist circumference (WC) greater than 102 cm in men and 88 cm in women.
NCEPATP3 (2005)	Presence of any three or more of the following: 1) Blood glucose greater than 5.6 mmol/L (100 mg/dl) or drug treatment for elevated blood glucose; 2) HDL cholesterol < 1.0 mmol/L (40 mg/dl) in men, < 1.3 mmol/L (50 mg/dl) in women or drug treatment for low HDL-C; 3) Blood triglycerides > 1.7 mmol/L (150 mg/dl) or drug treatment for elevated triglycerides; 4) Waist > 102 cm (men) or > 88 cm (women); 5) Blood pressure > 130/85 mmHg or drug treatment for hypertension.
International Diabetes Federation (IDF) (2006)	Presence of three or more of the five risk factors established by the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI): 1) Abdominal obesity (WC ≥ 90 cm in men and ≥ 80 cm in women), 2) Hypertriglyceridemia (triglycerides ≥ 150 mg/dL or use of medications to lower triglycerides), 3) Low HDL-C.

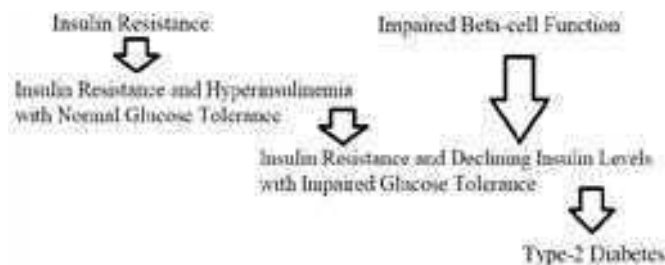


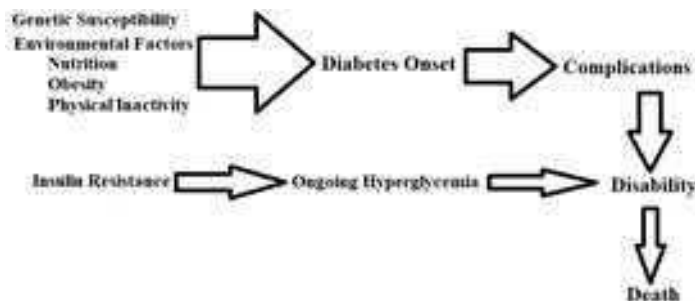
Figure 1. Development of type-2 diabetes mellitus.

Type-2 diabetes mellitus (T2DM) comprises of different degrees of β -cell failure relative to varying degrees of insulin resistance (Cnop et al. 2005; Tripathi and Srivastava 2006). The T2DM, also known as non-insulin-dependent diabetes mellitus (NIDDM) is a chronic condition that affects the way of metabolizing glucose. In this condition the body either resists the effect of insulin on glucose or does not produce enough insulin that can metabolize glucose (Tripathi and Srivastava 2006) (Figure 1). The T2DM is described as the MetD of multiple aetiology which can be characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from the defects in insulin secretion, insulin action or both (Kharroubi and Darwish 2015; Heindel et al. 2017). In this case hepatic insulin resistance is the leading cause of the inability to suppress hepatic glucose production and peripheral glucose uptake impaired by peripheral insulin resistance. This combination gives rise to fasting and postprandial hyper-glycemia (Tripathi and Srivastava 2006). It is a

long-term disorder that affects other health problems in individuals. The T2DM mainly occurs due to excess body adiposity or obesity but some studies also observed the effect of genetics and environment in it. Environmental factors also have significant effect on the predisposition of T2DM and excess adiposity. It also increases the risk of other major problems like Cardio-Vascular disease (CVD) and coronary heart disease (CHD) in population.

RELATIONSHIP BETWEEN TYPE-2 DIABETES MELLITUS AND METABOLIC DISORDER

According to, National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III), traits of the MetD include an increased waist circumference (WC), blood pressure elevation, low HDL cholesterol, high triglycerides and hyperglycemia (NCEP 2001; Grundy 2004; Nsiah et al. 2015) (Table 1). When at least 3 of the 5 traits are present and affected individuals are insulin resistant then the condition is considered as MetD. Several studies have reported that MetD is a common problem among the individuals with T2DM. The presence of T2DM increases the risk of MetD to a great extent (NCEP 2001; Wilson et al. 2005) (Table 1). Studies have reported that obese individuals with high BMI and MetDs were also predisposed with T2DM (Meigs et al. 2006; Kautzky-Willer et al. 2016). Obesity contributes to the premature mortality and morbidities associated with MetD (Furukawa et al. 2017; Saltiel and Olefsky 2017) including preventable non-communicable diseases in population (WHO 2000; WHO Expert Consultation 2004; Deaton 2017) (Figure 2). The prevalence of obesity has exploded during the past two decades so the occurrence of MetD. Among the several MetDs (e.g., T2DM, hypertension, dyslipidaemia and CHD) insulin resistance is one of the most prevalent problem occurring due to obesity in developing countries (Ruderman et al. 2013; Misra and Bhardwaj 2014; Pozza and Isidori 2018). According to IDF (2013) report, global prevalence of T2DM in adults (20-79 years) was 8.3% (382 million people; 198 million men and 184 million women). The number is expected to rise beyond 592 million by 2035 with the global prevalence of 10.1%. In India, over 62 million individuals are diagnosed with T2DM and topped by 31.7 million in 2000 in the world with the highest number of people with T2DM followed by China (20.8 million) and United States (17.7 million) in second and third place, respectively (Joshi and Parikh 2007; Kumar et al. 2013).



Source: American Diabetes Association (1998, 2003).

Figure 2. The continuum of type-2 diabetes mellitus.

In the developed countries obesity and MetD (e.g., insulin resistance and CVD) have reached epidemic proportions (Berghofer et al. 2008; van Vliet-Ostaptchouk et al. 2014). Among the United States adults, the prevalence of obesity ($\text{BMI} \geq 30.00 \text{ kg/m}^2$) has increased from 15% in the early 1970s to the most recent estimate of 34% in 2009 – 2010 (Freedman 2011; Ogden et al. 2012; van Vliet-Ostaptchouk et al. 2014). Developing countries like India are experiencing rapid demographic, epidemiological and economic transitions (Subramanian et al. 2007; Prasad et al. 2010; Kapil and Sachdev 2012; Popkin et al. 2012; Mondal et al. 2017; Phua et al. 2017). These transitions are the main contributing factors for rapid increase in sedentary lifestyles, less physical work outs leading to increased adiposity levels. According to the preliminary National Family Health Survey (NFHS)–4 data, obesity prevalence rates have rapidly increased across India in the past 10 years bringing the national average prevalence to 20% for both women (20.8%) and men (19.9%) (McMurry et al. 2017).

The NFHS-3 study in India reported that 13% of women and 9% of men are overweight or obese. The prevalence of obesity is more pronounced among those living in the urban areas as compared to the rural areas (Laxmaiah et al. 2007; Subramanian et al. 2007; Yang et al. 2009; Sen et al. 2013; Varadharajan et al. 2013; Mondal et al. 2015, 2017; Ajayi et al. 2016). The prevalence of insulin resistance or T2DM is a major global health problem based on the Diabetes atlas (International Diabetic Federation 2009). India having over 20 million diabetic patients have become diabetic capital of the world (Khandelwal et al. 2017). About 80% of T2DM is preventable by changing diet, increasing physical activity and improving the living environment. However, because of lack of effective prevention and control programs, the occurrence of diabetes is likely to continue rising worldwide (Chatterjee et al. 2017; Perreault 2018). Therefore, there is an urgent need to focus on the problem associated with T2DM to reduce the relative burden of morbidity and mortality in population.

ROLE OF ANTHROPOMETRY IN ADIPOSITY ASSESSMENT AND METABOLIC DISORDERS

Anthropometry is a widely used non-invasive, in-expensive and easy-to-use technique to assess nutritional status, adiposity and body composition in both epidemiological and clinical settings in populations. Anthropometric indicators have been widely used {e.g., BMI, WC and WHR} to assess the body composition, nutritional status and excess adiposity in both epidemiological and clinical investigations. It is evident that the Asian populations have shown the greater prevalence of morbidity and mortality at lower levels of body mass index ($\text{BMI} = \text{weight/height, kg/m}^2$) and smaller WC values in adults (WHO, 2000; WHO Expert Consultation, 2004). Moreover, this BMI classification measures relative weight gain that has been directly related to health risks and morbidity patterns in different populations. BMI has been used extensively in most of the studies for evaluating excess adiposity patterns and overweight-obesity (Snehalatha et al. 2003; Mohan and Deepa 2007; Prasad et al. 2010; Sen et al. 2013; Sengupta et al. 2014; Girdhar et al. 2016). BMI relates weight to height and is the most widely used measure of body size and to estimate the prevalence of obesity within a population (WHO 1999; Khullar et al. 2014). BMI has been extensively used to assess body size but it does not account for the variation in body adiposity distribution and abdominal fat mass (WHO 1999; Wells and Fewtrell 2006). Excess abdominal adiposity is associated with

greater risk of obesity and obesity-related morbidity (Visscher et al. 2002; Després 2017) (Figure 3). The associations of T2DM and standard epidemiological translations of BMI and WC have been observed in adults (Alberti et al. 2007; Hsu et al. 2015) (Table 2). In terms of clinical perspective, central obesity (approximated by WC or WHR) provides more information than general BMI (Vazquez et al. 2007). Thus, measurements of WC and WHR are viewed as alternatives to BMI, with both measures regularly used in the clinical and research settings. WC has been shown to be the best simple measure of both intra-abdominal fat-mass and total adiposity (Barreira et al. 2014; Ashwell and Gibson 2016). Several studies have observed that WC alone reflects abdominal adiposity (Mohan and Deepa 2007; Barreira et al. 2014; Ashwell and Gibson 2016).

Table 2. Co-morbidity risks associated with suggested BMI and WC in Asian adults (WHO 2000)

Classification	BMI (kg/m ²)	Risk of co-morbidity (WC)	
		<90 cm (in men) <80 cm (in women)	≥90 cm (in men) ≥80 cm (in women)
Underweight	<18.50	Low but increased risk of other clinical problems	Average
Normal range	18.50-22.99	Average	Increased
Overweight	≥23.00		
At Risk	23.00-24.99	Increased	Moderate
Obesity I	25.00-29.99	Moderate	Severe
Obesity II	30.00	Severe	Very Severe

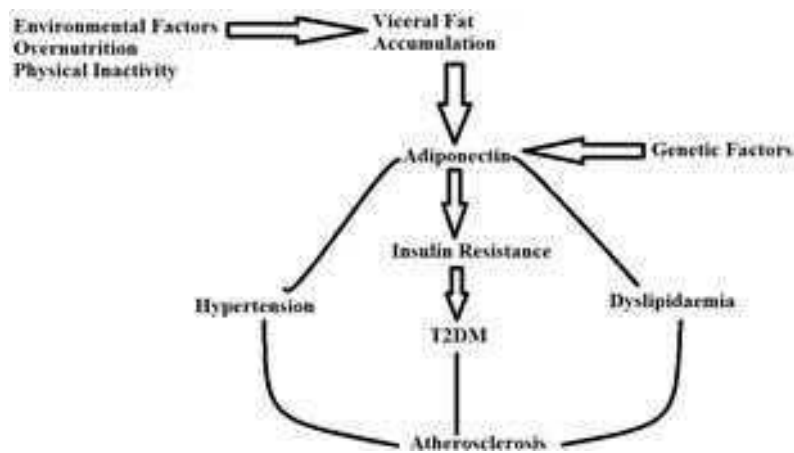


Figure 3. Factors affecting T2DM and Metabolic disorder.

In 1999, the WHO definition included a measure of obesity and defined obesity in terms of either BMI or WHR. WC in combination with BMI has been implemented in guidelines for the assessment and treatment of excess adiposity (obesity) related mortalities and morbidities (WHO 2000; Deurenberg-Yap et al. 2002; Mohan and Deepa 2007; Barreira et al. 2014; Ashwell and Gibson 2016). WHO (2000) has suggested co-morbidity risks associated with different levels of BMI with higher WC among Asian adults. Hence, WC has been advocated as a simple clinical alternative to BMI for detecting adults with possible health risks due to obesity (WHO 2000; WHO Expert Consultation 2004; Mohan and Deepa 2007;

Pratyush et al. 2012; Barreira et al. 2014; Ashwell and Gibson 2016). Abdominal obesity which is a condition due to increased amount of intra-abdominal fat including visceral adipose tissue (WHO 2000; Sullivan et al. 2015) is a major cause of T2DM. WC and WHR are useful indicators of abdominal obesity. Increased WC and WHR among the Asian populations reflect increased visceral adipose tissue and increased risks of MetDs (Deurenberg-Yap et al. 2002; Prasad et al. 2010; Soares and Müller 2017). Several studies have observed a higher percentage of body-fat, increased prevalence of metabolic risk factors at lower BMI levels among various Asian populations (Deurenberg-Yap et al. 2002; WHO 2004; Misra and Khurana 2011; Soares and Müller 2017). Increased prevalence of abdominal obesity in Asians as compared with those in Caucasians has also been reported (Deurenberg-Yap et al. 2002; Wang et al. 2005; Mohan and Deepa 2007; Misra and Khurana 2011). Hence, abdominal obesity assessed using WC is considered to be more appropriate to predict MetDs than generalized adiposity assessed using BMI. Several studies have suggested that Asian individuals tend to have increased level of WC (Prasad et al. 2010) with excess body-fat accumulation, abdominal and truncal/regional adiposity and insulin resistance (Hung et al. 2017). Several recent studies have observed strong relationship between waist to height ratio and T2DM (Liu et al. 2016; Hardy et al. 2017; Nagar and Jain 2017; Uday et al. 2017). The conicity index (CI) [$CI = WC(m) / 0.109 \times \sqrt{\{Weight(kg)/ Height(m)\}}$] which was developed as an indicator of obesity can also be used as an anthropometric indicator for T2DM. Body fat distribution and neck circumference (NC) have significant relationship with the occurrence of T2DM and obesity (Marques et al. 2015; Hingorjo et al. 2016; Papazafiropoulou et al. 2016; Wu et al. 2016; Marcadenti et al. 2017). Neck circumference (NC) was also observed to be associated with body adiposity and T2DM (Ghosh and Bandyopadhyay 2014; Marques et al. 2015; Papazafiropoulou et al. 2016; Wu et al. 2016; Marcadenti et al. 2017).

ASSOCIATION OF ADIPOSITY, TYPE-2 DIABETES MELLITUS AND ANTHROPOMETRIC MEASURES

According to WHO (1995, 2000), the health risks increase above the BMI cut-off ≥ 25.00 kg/m² that defined overweight in the current WHO classification (WHO 1995, 2000). According to WHO (2000), greater proportion of Asian people with lower BMI levels than the existing WHO cut-off (≥ 25.00 kg/m²) are at a high risk of T2DM. Due to this variation WHO (2000) has proposed a re-defined criteria of overweight (≥ 23.00 kg/m²) and obesity (≥ 25.00 kg/m²) among Asian populations as instances of co-morbidities and health risk factors occurred at the lower BMI (Table 2). It is evident that the age-sex specific body-adiposity distribution pattern and increase in excess adiposity ethnically vary among populations (WHO 2000; WHO Expert Consultation 2004; Subramanian et al. 2007; Sen et al. 2013). The proportion of Asian populations with a high risk of T2DM are substantial at BMIs lower than the existing WHO cut-off for overweight (BMI ≥ 25.00 kg/m²) and obesity (BMI ≥ 30.00 kg/m²). The cut-offs for observed risk varied from 22.00 kg/m² to 25.00 kg/m² in different Asian populations and the high risk group this cut-off varied from 26.00 kg/m² to 31.00 kg/m². Although, the WHO Expert Consultation (2004) reported that the current BMI cut-off should be retained as the international classification. It has been recommended for the

purpose of public health action. These cut-offs (23.00 kg/m^2 , 27.50 kg/m^2 , 32.50 kg/m^2 and 37.50 kg/m^2) and proposed methods could be considered and countries could make decisions for redefining obesity to take public health action (WHO Expert Consultation 2004). There are evidences of the association between high adiposity levels and the prevalence of T2DM in population (Yajnik 2004; Mohan and Deepa 2007; Mohan et al. 2007; Mondal and Sen 2014; Shrestha 2015; Jain et al. 2017)(Figure 3). The CI is another anthropometric index which is able to identify fat distribution and the risk of diseases therefore used as an indicator of obesity in populations (Roriz et al. 2016). The association between degree of excess adiposity, body-fat distribution and excess weight gain with subsequent incidence of T2DM, CHD and CVD has been examined in several prospective studies (Mohan et al. 2007; Mondal and Sen 2014; Shrestha 2015; Jain et al. 2017). The excess adiposity (e.g., BMI) is now a well-established independent risk factor for their development (Snehalatha et al. 2003; Yajnik 2004; Mohan and Deepa 2007; Mohan et al. 2007; Mondal and Sen 2014; Shrestha 2015; Jain et al. 2017).

ASSOCIATION OF ADIPOSITY, TYPE-II DIABETES MELLITUS AND ANTHROPOMETRY IN ASIAN INDIANS

The prevalence of obesity is considered to be the defined cluster of risk factors for non-communicable diseases (T2DM, CVD, dyslipidaemia and certain types of cancer). Most of the studies assessing the adiposity level have used BMI as an indicator. Several studies showed the need for a national level study based on obesity indices to determine the thresholds for obesity parameters for detecting high risk groups for metabolic abnormalities (Snehalatha et al. 2003; Nandimath et al. 2016). A study to identify obesity thresholds in rural Wardha, India (Deshmukh et al. 2006) showed the threshold for the obesity parameter (e.g., BMI) was same as compared to other studies in Asian Indians. Several recent studies have observed high prevalence of T2DM in Indian populations (Mahalakshmi et al. 2014; O'Keefe et al. 2016). There are geographical variations in obesity parameters and its associations with metabolic abnormalities (Ramachandran et al. 2001). Such regional variations have also been reported in the prevalence of T2DM with increasing BMI (Ramachandran et al. 2001; WHO Expert Consultation 2004). The risk of developing T2DM is high at relatively low BMI values in subjects originating from the South-east Asian populations when compared to the Caucasoids (Snehalatha et al. 2003; Yajnik 2004; Misra and Khurana 2011; Mondal and Sen 2014; Krugger et al. 2017). The BMI might not correspond to the same body-adiposity in different populations because of variations in body proportions, which can be the reason for lower BMI in Indians (WHO 2000; WHO Expert Consultation 2004). The relationship of T2DM and impaired glucose tolerance for BMI value of $>22.00 \text{ kg/m}^2$ had been established in Asian Indian populations (Ramachandran et al. 2001; Snehalatha et al. 2003; Yajnik 2004; Mondal and Sen 2014; Jayawardana et al. 2017). It has also been reported that the South Asian populations have BMI cut-off values lower than the Western populations due to greater level of mortality and morbidities in lower adiposity (WHO 2000; WHO Expert Consultation 2004; Hsu et al. 2015; Kruger et al. 2017). China being the largest developing country in the world is experiencing an epidemic of MetD (Lao et al. 2011; Li et al. 2016) and studies have observed high prevalence of MetD in both North and South China. This prevalence also

varies due to diverse populations of different regions, cultural behaviours, lifestyle habits and the use of different diagnosis criteria (Zhao et al. 2011; Lao et al. 2014; Xiao et al. 2015).

RECENT DEVELOPMENTS IN ANTHROPOMETRY, REGIONAL ADIPOSITY AND TYPE-2 DIABETES MELLITUS

Several recent studies showed that there are many medical conditions e.g., obesity, hypertension, elevated cholesterol levels (combined hyperlipidemia) and other MetDs which are also related to regional adiposity levels and can potentially give rise to T2DM (Alberti et al. 2005; Olokoba et al. 2012). A majority of individuals suffering from T2DM are obese, with central visceral adiposity. Therefore, the deposition of excess adipose tissue plays a crucial role in the pathogenesis of T2DM (Olokoba et al. 2012). Increasing trend of obesity, abdominal obesity and MetD is particularly worrisome since Asian Indians develop T2DM and atherogenic dyslipidemia at lower levels of BMI and WC (Gupta et al. 2012; Bodicoat et al. 2014). Onset of dyslipidemia and MetD are early contributing factors to the onset of T2DM (Gulati and Misra 2017). Several studies have used anthropometry as indicator of T2DM in Indian population using different cut-offs for adiposity levels (Table 3). Studies have shown that the proportion of intra-abdominal visceral adipose tissue specifically truncal/abdominal subcutaneous adiposity is higher in South Asians mainly in those with T2DM (Raji et al. 2001; Anoop et al. 2016; Gulati and Misra 2017). Moreover, a number of recent studies have reported in South Asians that there is excess of deep subcutaneous and abdominal adipose tissue which has high metabolic activity and may cause insulin resistance and CVD (Anand et al. 2011; Marinou et al. 2014). In a recent study by Anoop et al. (2016) it has been found out that increased adipose deposition in liver and pancreas in Asian Indians have potentials of predicting diabetes. Interestingly, the abdominal/regional subcutaneous adipocyte area is increased among South Asians (Anand et al. 2011). Further, Chandalia et al. (2007) observed that subcutaneous adipocyte size was inversely correlated to glucose disposal rate (the rate of glucose uptake from the blood by the peripheral tissues, such as skeletal muscle) in South Asians. This is also independent of intra-peritoneal body adiposity.

Several researchers have reported that heightened insulin resistance in South Asians was observed to be more related to increased truncal subcutaneous fat and adipose tissue dysfunction than to excess intra-abdominal visceral adipose deposition (Chandalia et al. 2007; Anand et al. 2011; Gulati and Misra 2017). Studies have observed low physical activity and low-protein diets among South Asians than among white Caucasians (Bhatt et al. 2012). Another study by Eastwood et al. (2014) observed there are relationships between T2DM, CHD and thigh muscle area which is lower in South Asians. Anbalagan et al. (2013) observed that in South Indian population 39.5% of the patients had pre-sarcopenia (characterized by low muscle mass, without any decrease in muscle strength or physical performance) which was independently associated with diabetes. These associations between adipose tissues/regional adiposity levels and diabetes observed by recent studies suggests that anthropometry by which adiposity levels can be measured almost accurately with high precession can be used as a very important tool in future for detection and screening of T2DM in populations.

Table 3. Indian studies done on type-2 diabetes mellitus (T2DM) or metabolic disorders (MetD) and anthropometry in adults

Population	Region/area	N	Measurements	Cut-off used for BMI or Type-2 Diabetes	Result	Cut-off proposed	Reference
Diabetic and non-diabetic individuals	Central India	100	BMI and Blood pressure	American Heart Association and US Center for Disease Control and Prevention	Anthropometric parameters were found to be high in diabetic subjects compared with non-diabetic subjects.	-	Meshram et al. 2013
Type-2 diabetics and non-diabetics of >30 years of age.	Karnataka, India	700	NC and BMI	WHO (1997) and Yang et al. (2010)	The NC in diabetics was significantly higher than in non-diabetics	-	Aswathappa et al. 2013
Asian Indian youth with type-2 diabetes mellitus and prediabetes	Chennai, India	114	BMI and WC	WHO Consultation group for Diabetes Mellitus (1999)	T2DM in Asian Indian youth and prediabetes subjects had higher BMI, WC and fasting insulin than NCT subjects	-	Mohan et al. 2013
Indian adults (aged: 20-90 years)	States and UT's of India	16,607	Weight, height, WC and BMI	WHO (2006)	29.5% had hypertriglyceridemia	-	Joshi et al. 2014
Overweight and obese people of semi-urban area of Assam	Assam, India	300	Weight, BMI and WC	WHO (2000, 2004)	Prevalence of T2DM and hypertension increases with increasing weight of the individuals	-	Mandal 2014
Healthy adults (20-30 years of age) of Amritsar	Punjab, India	200	BMI, WHR and WHR	WHO (1995, 2000)	All the derived anthropometric indices were significantly increased in young healthy adults (20-30yrs of age) having positive family history of T2DM.	-	Khanna and Sharma 2015
102 individuals	South India	102	BMI, WHR and WC	WHO (2004, 2008)	A strong association between obesity indices and diabetes was identified. BMI and WC could be used in clinical practice for suggesting life style modifications.	-	Awasthi et al. 2017
Indian population	India	875,711	BMI	-	7% adults with diabetes	-	Akhtar and Dhillon 2017
Urban slum	India		BMI, WC and WHR	-	Indian Diabetes Risk Score (IDRS) can be used as an effective tool for screening undiagnosed diabetes	-	Dudeja et al. 2017
Adult patients of type-2 diabetes	Surat, India	120	BMI, WC and WHR	WHO (1995), IDF (2006)	More than half (52.5%) of lean patients and 82.5% of IBW (Ideal Body Weight) patients had abnormal high WHR where as in obese group all patients (100%) were having abnormal WHR.	-	Ganit et al. 2017
Students aged 17-19 years	India	526	BMI	ADA (2005)	BMI and WC estimation can be done for early detection of pre-diabetes in adolescents	Cut-offs for WC for predicting pre-diabetes was found to be ≥ 82.5 cm for boys and ≥ 80.3 cm for girls.	Pandeya et al. 2017

GENETIC AND ENVIRONMENT FACTORS EFFECTING TYPE-2 DIABETES MELLITUS IN ASIAN INDIANS

T2DM being a complex disease involves a wide-range of genetic, lifestyle and environmental factors. Several studies have observed significant associations of T2DM, genetics and environment (Staiger et al. 2009; Banoo et al. 2015; Kharroubi and Darwish 2015) (Figure 3). It is typically a multi-factorial disease involving multiple genes and various environmental factors with different extents. Moreover, it is not an autoimmune disorder (Banoo et al. 2015). In most of the individual or populations there are susceptible genes predisposing to NIDDM which have not been identified till now (Banoo et al. 2015). Heterogeneity of the genes responsible for the susceptibility to T2DM may be one of the reasons for this problem of identification (Banoo et al. 2015). The variations in T2DM are directly or indirectly affected by overall genetic background of the individual, family or populations which are further more complicated by the interaction with variable environmental conditions/factors (Staiger et al. 2009; Kharroubi and Darwish 2015). Although, there are problems of identification of the genes but several research studies have observed genetic susceptibility of T2DM. Studies have also reported more than 200 T2DM susceptible genes such as Insulin receptor, GLUT, Glycogen Synthase (Mahajan et al. 2014; Zhao et al. 2017). Association between genetic polymorphisms and T2DM have also been observed in the genes encoding the peroxisome proliferators activated receptor, Insulin Receptor Substrate, inward rectifying potassium channel, zinc transporter and calpain-10 (Ali 2013; Banoo et al. 2015). The mechanisms increasing susceptibility of these genetic loci to T2DM are not clear, but most of them are predicted to be altering the function/ development/ insulin secretion (Banoo et al. 2015). Studies have observed Caucasians are affected by T2DM by 1 to 2% but it is much higher in some ethnic groups e.g., Pima- Indians and Arabs among South Indians it approaches 50% (Banoo et al. 2015). The risk of diabetes increases with age and in most of the cases it has been diagnosed at the age of 40 years and above. It is becoming an epidemic in some countries due to increase in aging population.

Genetic predisposition is a major reason among Asian Indians also called as “*Asian Indian phenotype*” which contributes to the increased predisposition of T2DM among Asian Indians (Mohan et al. 2007; Vimalaswaran et al. 2016; Soares and Müller 2017). Despite having lower prevalence of obesity as defined by BMI, Asian Indians tend to have greater WC and WHR thus having a greater degree of central obesity. Other reasons of T2DM are fast food culture and sedentary lifestyle in Indian population due to the major epidemiological changes going on in the country (Deepa et al. 2017; Mastorci et al. 2017). Genetic factors play an important role in the development of T2DM and mutations in a single gene or a multi-factorial origin can act as the genetic cause of T2DM (Horikawa et al. 2000; Kharroubi and Darwish 2015).

EFFECT OF MIGRATION AND TYPE-2 DIABETES MELLITUS IN ASIAN INDIANS

Several studies worldwide on migrant Indians have shown that Asian Indians have an increased risk of developing T2DM and related metabolic abnormalities (e.g., MetDs) compared to other ethnic groups (Mohan et al. 2007; Soares and Müller 2017). Genetic factors and environmental conditions are the main causes of these physiological conditions among Asian Indians. Migration is the movement of individual/population from one environment to another and it can bring several changes due to external or internal factors (e.g., social and cultural changes) among population. Studies have reported that migration from rural areas to urban slums in a metropolitan city in India have led to obesity, glucose intolerance and dyslipidaemia (Mohan et al. 2007). Several factors include genetic and pre-migration history (e.g., socioeconomic level, lifestyle habits, exposure to infections), as well as the quality of healthcare in the countries of destination controls the link between migration and prevalence of disease (Montesi et al. 2016; Girardi et al. 2017). Moreover, there are many factors (viz., urbanization, mechanization, changes in nutrition and lifestyle including physical inactivity, genetic environment/susceptibility interactions and stress) which expose the migrants to a higher risk of developing certain diseases after arrival in the host countries (Misra and Ganda 2007; Montesi et al. 2016; Girardi et al. 2017). Several conditions experienced by migrants moving from a poverty-ridden rural area in early life to an obesogenic urban environment in their later life increases the risk of obesity and T2DM among both inter- and intra-country migrants in developed and developing countries (Girardia et al. 2017). The adoption of sedentary lifestyles and availability and abundance of calorie-dense/low fibre foods is associated with increased risks of morbidity and mortality among the migrated populations. Several studies have investigated the link between migration and T2DM (Misra and Ganda 2007). Several studies have also reported that migration itself contribute to the increase in truncal/subcutaneous abdominal adiposity, which is also an observed phenomena in Asian Indians and South Asians (Raji et al. 2001; Girardiet al. 2017).

ASIAN ENIGMA IN REGIONAL ADIPOSITY, METABOLIC DISORDERS AND TYPE-2 DIABETES MELLITUS

Several studies have observed that South Asian populations have 3%-5% of greater body-adiposity than Caucasians at any given BMI with low adipokine production, lower lean body mass. Ethnic/genetic, environment, demographic, cultural, lifestyle and socioeconomic factors are being considered as potential contributors to an early age-onset of obesity-linked CVD risk and MetDs (WHO Expert Consultation 2004; Prasad et al. 2010; Misra and Khurana 2011; Hudda et al. 2017). The WHO has revised the BMI cut-off for Asian Indians and suggested a BMI ≥ 25.00 kg/m² to define obesity against the ≥ 30.00 kg/m² recommended for Europeans (WHO 2000) (Table 1). Asian Indians have the increased predispositions to T2DM (WHO 2000; WHO Expert Consultation 2004; Yajnik 2004; Ramachandran et al. 2014). This predisposition has been attributed to the Asian Indian Phenotype which is characterized by lesser than the generalized obesity as measured by BMI but greater than the

central obesity with respect to the WC and WHR (WHO 2000; Prasad et al. 2010; Vimalaswaran et al. 2016; Little 2017). This is the cause of biochemical and hormonal changes including higher plasma insulin levels, greater insulin resistance, lower HDL cholesterol, higher triglyceride levels, increased small dense LDL cholesterol as well as small dense HDL cholesterol and C-reactive protein and leptin levels but decreased adiponectin levels (Lele et al. 2006; Manoria et al. 2010). Asian Indians have higher total abdominal and visceral adiposity for any given BMI (WHO Expert Consultation 2004; Raji et al. 2001) and for any given body adiposity they have increased insulin resistance (Soares and Müller 2017). Other studies have shown that some genes seem to confer increased susceptibility to diabetes in Indians (Vimalaswaran et al. 2005). Europeans have some type of protective genes which do not appear to protect Indians (Radha et al. 2006; Radha and Mohan 2007). It is evident that the abdominal or central/regional obesity is closely linked with insulin resistance, enhanced lipolysis and release of free fatty acids which inhibits insulin stimulated peripheral glucose uptake in dose dependent manner while simultaneously inhibiting insulin secretion (Mohan and Rao 2007; Prasad et al. 2010). These features have been referred to as the Asian Indian Phenotype or Paradox (Vimalaswaran et al. 2016; Little 2017). Several studies on neonates have suggested that Indian babies are smaller born but relatively fatter compared to Caucasian babies and are referred to as “the thin fat Indian baby” (Yajnik et al. 2003; Krishnaveni et al. 2005). Neck circumference (NC) is also observed to be associated with the occurrence of MetDs (Hingorjo et al. 2016). Anthropometric measures which have strong association with the occurrence of T2DM can contribute highly in risk detection of T2DM in populations worldwide. Anthropometric measures (e.g., BMI, WHR, WC, NC and CI) can also be used very accurately to control and/or monitor the increasing trend of T2DM/MetDs in population.

LIMITATION OF ANTHROPOMETRIC MEASURES

Several research studies have reported the associations between anthropometry and MetD, but several questions critical to the use of anthropometry as a direct indicator of MetD or T2DM remain in doubt. It is important to test whether standard metrics of adiposity used in clinical settings (e.g., BMI, WC, WHR and CI) adequately reflect the accurate level of visceral (or subcutaneous) adiposity and the subsequent risks of MetD as well as T2DM. Whether only the high adiposity levels alone explains the cause of MetD or T2DM remains unanswered due to the effect of environmental factors, genetic predisposition to the disease as well as other external factors (viz., socioeconomic, occupation, migration, lifestyle effect, predisposition to other diseases and early life experiences). In this context anthropometry has its limitation because biochemical and genetic methods can give much greater accurate measure of MetD as well as T2DM.

CONCLUSION

The prevalence of T2DM is reaching potentially epidemic proportions in India. The mortality and morbidity associated with T2DM and the potential complications associated with T2DM are enormous, and pose significant burdens of healthcare on both families and

society. Therefore, it is very necessary to detect and control the risks of T2DM by using improved intervention techniques and policies. There are evidences from recent studies that strong associations between anthropometric, genetic and biochemical risk for T2DM as a non-communicable disease and MetD are present in populations. Due to the wide population diversity of India based on ethnicity, culture, socioeconomic conditions, resource distribution and nutritional conditions the need for establishing ethnic-specific anthropometric (e.g., BMI, WC and WHR) cut-offs are becoming very much necessary for the proper identification of the relative risks of MetDs and T2DM. Moreover, practical implementations of those cut-off values of anthropometric measures are very necessary. It is possible to minimise the relative risks by only controlling the lifestyles of the individuals and therefore it is very necessary to introduce region/ethnic specific policies to control T2DM and MetDs. Prevention of T2DM and its micro- and macro-vascular complications should be an essential component for future public health strategies for the countries. Collection and reporting of obesity data should be systematically included in all nutrition surveys which are very necessary in prevention of T2DM and MetDs. Extensive studies by researchers are necessary for establishing proper measure for assessing the risk of T2DM in terms of adiposity levels/regional body adiposity as several recent studies have observed significant association between regional adiposity and T2DM and/or MetDs in populations. Moreover, epidemiological and operational information on obesity and T2DM should be integrated into existing international nutrition forums. Proper lifestyle modifications should be induced in populations to minimise the prevalence of T2DM. Also, public/private partnerships are necessary to properly implement the public healthcare policies for controlling the epidemic of T2DM/MetDs. A large proportion of cases of T2DM are preventable therefore initiatives for consumer education to promote a healthy diet could be reinforced by government's involvement towards the problem.

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Chapter 250

C-REACTIVE PROTEIN AND FAMILY HISTORY: A FUTURE THREAT TOWARDS DIABETES AND SYNDROME X

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INTRODUCTION

Type II Diabetes: A Global Menace

Type II diabetes mellitus is a long term metabolic disorder that consists of an array of dysfunctions characterized by hyperglycemia and resulting from the combination of resistance to insulin action, inadequate insulin secretion, and excessive or inappropriate glucagon secretion. Common symptoms include increased thirst, frequent urination, and unexplained weight loss. Symptoms may also include increased hunger, feeling tired, and sores that do not heal (NIDDKD, 2014). Long-term complications from high blood sugar include heart disease, strokes, diabetic retinopathy which can result in blindness, kidney failure, and poor blood flow in the limbs which may lead to amputations (WHO 2011).

Globally, an estimated 422 million adults are living with diabetes mellitus, according to the latest 2016 data from the World Health Organization (WHO 2016). Diabetes prevalence is increasing rapidly; previous 2013 estimates from the International Diabetes Federation put the number at 381 million people having diabetes. The number is projected to almost double by 2030. Type II diabetes makes up about 85-90% of all cases (New York Times 2006). Increases in the overall diabetes prevalence rates largely reflect an increase in risk factors for Type II, notably greater longevity and being overweight or obese (Melmed et al., 2011).

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Indian Scenario

Until recently, India had more diabetics than any other country in the world, according to the International Diabetes Foundation, although the country has now been surpassed in the top spot by China, Diabetes currently affects more than 62 million Indians, which is more than 7.1% of the adult population. The average age on onset is 42.5 years. Nearly 1 million Indians die due to diabetes every year (Gale 2010).

According to the Indian Heart Association, India is projected to be home to 109 million individuals with diabetes by 2035 (IHA 2016). A study by the American Diabetes Association reports that India will see the greatest increase in people diagnosed with diabetes by 2030. The high incidence is attributed to a combination of genetic susceptibility plus adoption of a high-calorie, low-activity lifestyle by India's growing middle class (New York Times 2006).

A considerable variability in the incidence and prevalence of Type II diabetes (T2D) coheres with an important contribution of multigenetic predisposition in the development of T2D. Some genes, which probably participate in the pathogenesis of Type II diabetes, also play a role in the regulation of blood pressure, familial hyperlipidemia, familial hypertension and other diseases of the cardiovascular system Demova et al., 2012.

Human C-reactive protein (CRP) is an acute phase reactant involved in chronic and acute inflammation. CRP production is rapidly stimulated in response to infection, tissue injury or inflammation. In a recent study, increased levels of CRP are reported to be associated with metabolic syndrome, obesity, atherosclerosis, unstable angina, insulin resistance and diabetes. Family and twin studies suggest that genetic factors account for 40% of the variance in plasma CRP levels + 1059 G > C (rs1800947) is a single nucleotide polymorphism (SNP) in exon 2 of the *CRP* gene. + 1059 G > C is a silent or synonymous polymorphism at the amino acid level (CTG → CTC, Leu → Leu at codon 184) which has been reported to affect the protein levels of CRP and contribute towards the progression of CAD (coronary artery disease) and T2D Kaur et al., 2013.

METHODS

Study Population

This is a longitudinal follow-up study and present study was being done in continuation with the earlier work. The medical history of the patient's family was recorded. Determination of presence or absence of other risk factors – high cholesterol levels, cigarette smoking, hypertension, and diabetes in first-degree relatives (biological parents, siblings, and offspring) – was recorded. The present study was conducted on 160 healthy (non-diabetic, normotensive) adult Asian Indian women [including 90 with and 70 without family history of diabetes (FHD)] living in and around Kolkata, India. This sample size was sufficient to test all the research hypotheses at the 5% level of significance. During the gestation period they were studied twice, first within 12 weeks and second by 30 weeks. They were then followed up till delivery. During delivery both mothers' venous blood and cord blood were collected to estimate the metabolic variables and genetic polymorphisms of the respective mothers and

their new born babies. All the experiments were done according to the “Ethical guidelines for Biomedical Research on Human Participants” published by Indian Council of Medical Research (2006). The Institutional Ethics Committee (IEC) of Heritage Institute of Technology, Kolkata, approved the study. Written consent was obtained from the subjects prior to actual commencement of the study.

Anthropometric Measurements

Demographic profiles including name and age were obtained from participants. Informed consent was obtained from participants prior to the actual commencement of the study. Height was measured to nearest 0.1 cm with a Martin’s Anthropometer and weight to the nearest 0.5 kg with a portable weighing machine in light clothing and bare feet.

Blood Pressure Measurements

Left arm systolic (SBP) and diastolic (DBP) blood pressure was taken from each participant with the help of an Omron M1 digital electronic blood pressure/pulse monitor (Omron Corporation, Tokyo, Japan). Two blood pressure measurements were taken and averaged for analysis. A third measurement was taken when the difference between the two measurements was ≥ 5 mmHg, and a subsequent mean was calculated. A five minute relaxation period between measurements was maintained for all participants. The working condition of the instrument was checked periodically using a mercury sphygmomanometer and stethoscope (auscultator procedure). Subjects with SBP/DBP values $> 130/85$ mm Hg were considered as Hypertensive, according to NCEP and ATPIII guidelines, 2005 (NCEP 2005).

Estimation of Metabolic Profiles

A fasting blood sample (7 ml) was collected from each subject for the determination of fasting blood glucose (FBG), Total cholesterol (TC), Triglycerides (TG), and High density lipoproteins (HDL). All subjects maintained an overnight fast of ≥ 12 h prior to blood collection. The plasma was separated within 2 h of blood collection using a microcentrifuge at 1000 rpm for about 20 min at room temperature. Estimation of FBG, TC, TG, CRP and HDL were carried out using a Robonik Biochemistry Analyzer (Robonik India, Mumbai, India). Low-density lipoprotein (LDL) and very low density lipoprotein (VLDL) were then calculated by using the standard formula: $LDL = TC - (HDL + TG/5)$ and $VLDL = TG/5$. All the metabolic profiles were estimated according to NCEP and ATPIII guidelines 2005 (NCEP 2005).

Genotyping of CRP

- The DNA was isolated from whole blood by HiPurA™ Blood Genomic DNA Miniprep Purification Spin Kit. The DNA was amplified by PCR (ABI Biosystems, USA).
- Amplification refractory mutation system-polymerase chain reaction (ARMS-PCR) which is based on allele specific amplification of desired fragment using primers corresponding to the alleles has been used for genotyping of +1059 G > C SNP in the CRP gene.
- The sequences of specific primers used are:
 1. Constant forward:
5'-CATTGTACAAGCTGGGAGT-3',
 2. Allele C-specific reverse:
5'-ATGGTGTTAATCTCATCTGGTGGG-3',
 3. Allele G-specific reverse:
5'-ATGGTGTTAATCTCATCTGGTGGC-3'.
- The conditions included initial denaturation (95°C for 5 min) following a touchdown PCR with denaturation at 94°C for 45 secs, annealing at 66°C to 62°C with 1°C decrease in temperature for the first 4 cycles followed by 29 cycles at 61°C for 45 secs, extension at 72°C for 45 secs each cycle and final extension at 72°C for 10 min (Cao & Hegele 2000).
- CRP+1059 G > C genotypes were assessed from the presence/absence of PCR amplicon (237 bp), corresponding to the specific allele (C/G) on 1.5% agarose gel stained with Ethidium bromide.
- The genotyping of CRP genes yielded PCR products of size 744 bp. Digestion of the less common 1059C allele produced two smaller fragments, with sizes of 434 and 310 bp. Digestion of the more common 1059G allele produced three fragments, with sizes of 310, 233, and 201 bp.

Statistical Analyses

Mean and SD for all the metabolic variables, hormones and blood pressure measurements were calculated by conventional statistical methods. Group differences (with and without FHD) for all the variables (18 and 30 months) were tested by One-way ANOVA ($p \pm 0.05$). Differences in CRP values by FHD were estimated by 2X2 Contingency Chi-square analysis ($p \pm 0.05$). Differences in birth outcomes by FHD and CRP values of mothers was estimated by Chi-square analysis ($p \pm 0.05$). All statistical tests were performed on Statistical Package for Social Sciences (IBM-SPSS version 16) and significance was set at $p < 0.05$ two tailed.

RESULTS

Biochemical Analyses of Metabolic Risk Factors

Statistical Analyses of the comparison of the Group differences (with and without FHD) for all the variables (12 and 30 weeks) were tested by One-way ANOVA ($p < 0.05$). Table 1 shows the anthropometric measurements and biochemical parameters which were considered during the study.

A comparison of the metabolic variables among the subjects with and without FHD revealed that there were significant differences among them with respect to Waist circumference, Triglycerides, HDL-Cholesterol, VLDL-Cholesterol, Fasting Blood Glucose and Blood pressure, both at the gestational period of 12 weeks and 30 weeks. It indicates that family history plays an influencing metabolic factors and triggering the risk factors early in the gestational phase leading to complications in adult life.

Table 1. Baseline characteristics of the study population by family history (n = 160)

VARIABLES	BY 12 WEEKS			BY 30 WEEKS		
	Both/Either*	None**	ANOVA	Both/Either	None	ANOVA
	(n = 90)	(n = 70)	P	(n = 90)	(n = 70)	P
AGE (yrs)	31 (6.3)	27 (3.2)	0.258	32 (6)	30 (6)	0.323
WEIGHT (kg)	68 (13)	63 (8)	0.240	74 (10)	72 (10)	0.061
BMI (kg/m ²)	25.4 (3.8)	27.3 (3.7)	0.415	36.5 (4.1)	32.5 (3.9)	0.416
WC (cm)	91 (13)	79 (9)	<0.001	132 (14)	110 (12)	<0.001
TC (mg/dl)	211 (16)	155 (14)	0.122	217 (21)	210 (20)	0.069
TG (mg/dl)	159 (27)	124 (21)	<0.001	243 (32)	176 (29)	<0.001
HDLc (mg/dl)	54 (9)	44 (10)	<0.001	53 (8)	42 (9)	<0.001
LDLc (mg/dl)	115 (11)	100 (12)	0.001	117 (13)	108 (10)	0.009
VLDLc (mg/dl)	35 (5)	28 (4)	<0.001	55 (10)	34(7)	<0.001
FBG (mg/dl)	117 (10)	98 (12)	<0.001	110 (12)	94 (11)	<0.001
SBP (mmHg)	122 (11)	108 (12)	<0.001	138 (14)	118(16)	<0.001
DBP (mmHg)	83 (10)	77 (9)	<0.001	95 (8)	88 (6)	<0.001

Read as Mean and $\pm$ SD within parentheses; *Both/Either - Participants having positive FHD present in both or either parents; **None - No FHD.

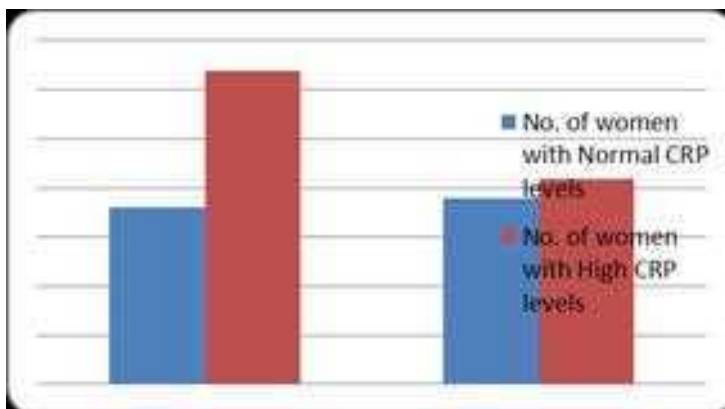


Figure 1. Showing statistically significant difference in C-reactive protein (CRP) levels by FHD ($p = 0.0109$).

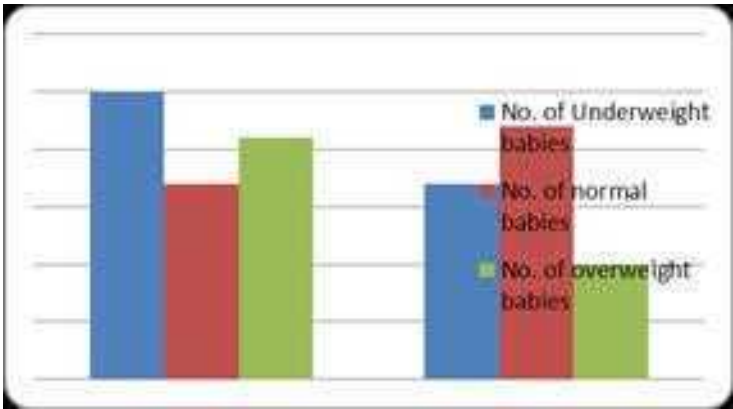


Figure 2. Showing statistically significant differences in birth outcomes (birth weight in kg) by FHD and CRP of the mothers ($p = 0.0252$).

Table 2. Differences in C-reactive protein (CRP) of the babies by mothers' CRP and FHD

CRP of the Babies	Mothers with +FHD and high CRP (n = 66)	Mothers with -FHD and normal CRP (n = 45)	ANOVA
Mean	0.45	0.25	P < 0.001
SD	± 0.087	± 0.025	

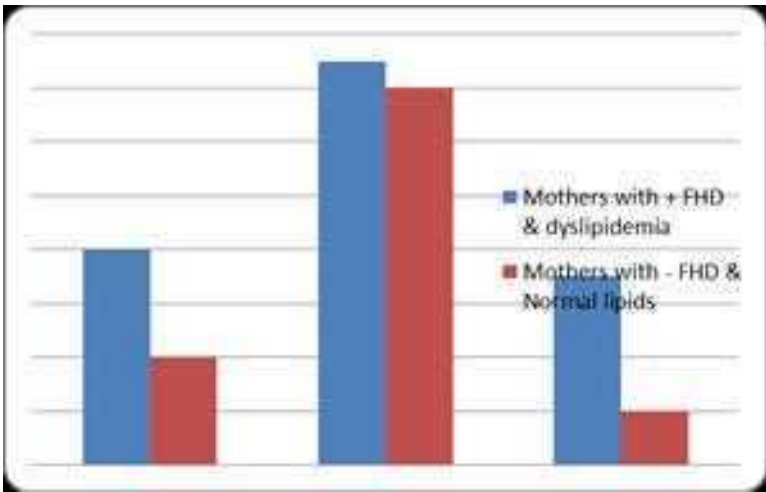


Figure 3. Showing genotyping results of CRP genes of newborn babies, w.r.t their mother's health status.

Comparison of subjects in the CRP levels between the same groups also revealed a statistically significant difference in subjects with a positive FHD and high CRP levels in comparison to normal cases (Figure 1 & 2).

Comparison of birth outcomes in terms of birth weights was done between subjects with and without a positive family history of T2DM and high CRP levels (Figure 1), which revealed a significant difference between the two groups. This shows that family history and perturbations in the gestational period are reflected in the birth outcomes, affecting the next

generation (Table 2). It is evident from the results that there is a significant difference in inflammatory status in those newborns whose mothers have a positive FHD compared to their normal counterparts.

DISCUSSION

The Family History of Diabetes (FHD), evidently, has been found to be most useful for predicting T2DM when the disease is premature, that is, it occurs at younger ages than would be expected. This FHD information in combination with other known risk factors could be used to provide more personalized information about our risk for such diseases. Yang et al., (2010) further suggested that adding FHD could provide significant improvements in detecting undiagnosed diabetes; however, it needs further validation with larger cross-sections of population. In another study, it was found that not only the adults but even the young population with a positive FHD showed signs of increased risk for these conditions which indicates the importance of family history approach to screening for children at risk of T2DM and CVD (Valdez et al., 2007).

In our present study, we noticed a population trend where individuals with positive family history of diabetes had significantly higher prevalence of metabolic risk factors and its confounding factors as compared to their counterparts during pregnancy, which is also affecting their next generation leading to childhood obesity. Therefore, based on this observation, it can be stated that positive FHD and CRP status plays an important role in triggering the activation of metabolic risk factors during the pregnancy period, and this could be one of the major factors for development of T2DM and metabolic syndrome in the next generations. These findings suggest that family history could be used as a tool for genomic studies among the Asian Indians.

CRP is a potential biomarker for prediction of future risk of cardiovascular disease (CVD) both in diabetic and non-diabetic individuals, because even a small rise in plasma CRP levels leads to cardiovascular events. In the present investigation of the association of CRP+1059 G>C polymorphism with the progression to T2D, we have observed that the frequency of G-allele is high in the Asian Indian population (70%). Similarly high frequency for the G-allele (~90.0%–96.3%) has been reported in studies conducted on other world populations (Pasalic et al., 2009; Tanja et al., 2008).

Heterozygous carriers of C allele (GC) in the present studied population have shown protection towards the disease manifestation. The GC genotype is highest in controls (9.8%) as compared to cases (2.3%–3.4%) suggesting that some kind of selection pressure is operating on the GC genotype. Considering the thrifty genotype hypothesis, the ancestral version of the alleles proves to be deleterious in the present day environment while the rarer alleles which may have protective effects against the disease have evolved lately (Sharma 1998). Fernandez-Real and Ricart have implicated the role of genes encoding for cytokine synthesis as thrifty genes (Fernandez-Real & Ricart, 1999). The hypothesis suggested that higher secretion of cytokines and increased acute phase response were an evolutionary adaptation to phases of acute infections and trauma. In the ancestral period, outbreaks due to infections were higher. Simultaneously due to exposure to famines, metabolic pathways favored insulin resistance to survive in low food situations. It has been proposed that insulin

resistance and cytokine responder genotypes were favorable adaptations to low fat, high fiber and high physical activity environment. The genomes of the present day human are still genetically adapted to ancestral conditions which are designed to fight against infection with minimal food intakes and high physical activity. However, environmental transition is more rapid, and evolution being a slow process, our genotypes have not modified according to the present day environments of lower infections, availability of surplus food and low physical activity. In the absence of the favorable conditions and with advancement of age, insulin resistance ensues which further activates inflammatory cascade that eventually results in atherosclerosis. Thus, in the presence of insulin resistance genotypes and western lifestyle, a high cytokine responder genotype would be more prone to develop T2D and atherosclerosis. Although +1059 G > C polymorphism is a silent polymorphism, yet the ancestral allele of the polymorphism (G-allele) has been associated with higher CRP levels in various studies as discussed above. Higher CRP levels are suggestive of inflammatory response which may get accentuated in the background of obesity and insulin resistance condition in T2D. The higher frequency of the G-allele in most of the populations and the protective effect of GC genotype in the present study could be viewed in the background of its role as a thrifty genotype.

CONCLUSION

From our study, we therefore can conclude that the CRP +1059 G > C polymorphism seem to have functional effects on protein production (Eklund et al., 2005). It has also been proposed that silent SNPs can lead to protein product with the same amino acid sequence, but with different structural and functional properties which might play an important role in defining the protein levels (Radha & Mohan 2007). The reason for discrepancies in association studies across populations may be explained by diverse ethnic background of different populations as different ethnic groups have different susceptibility towards the disease (Komar 2007).

Taken together, these observations raise the possibility that these polymorphisms in combination with both family history and environmental factors may account for the phenotype of peripheral insulin resistance and impaired insulin secretion, the two typical features of Type II diabetes.

Also, having observed that family history of diabetes (FHD) is indeed an important and independent risk factor for genomic studies of complex diseases like T2DM, efforts should be made toward translating this knowledge for use in public health programmes designed to detect and prevent diabetes. Once this is achieved, FHD should be incorporated into the screening and prevention programmes for T2DM as rigorously as possible to make these programmes significant and cost-effective.

However, the present study has several limitations. In the limitations of the present study, firstly, the association of polymorphism with the protein levels needs to be established. Secondly further studies relating the protein levels with studied polymorphism and other functionally relevant polymorphisms which may be in LD with the studied SNP are required on larger sample size to validate the findings of the present study with more statistical power.

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Chapter 251

SENSITIVITY AND SPECIFICITY OF BODY MASS INDEX TO ASSESS EXCESS ADIPOSITY

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INTRODUCTION

Since the introduction of the Quetelet index (QI) {body mass index (BMI)} in 1832 (Eknoyan, 2008), it was widely used as a measure of excess adiposity or obesity (Price et al., 2018; Volkovicher et al., 2018). Not only that, BMI was also found to be associated with different metabolic and physiological abnormalities (Ghosh and Bandyopadhyay, 2007; Xu et al., 2008; Kaplan et al., 2014; Leonska-Duniec et al., 2018). However, epidemiological studies in Asian populations, especially in Indians revealed higher prevalence of cardiovascular disease and type 2 diabetes with a lower mean BMI, but interestingly had higher percent body fat (PBF) at a corresponding BMI value than Europeans (Razak et al., 2007; Xu et al., 2008). Therefore, using a BMI cut-off value based on adult Europeans may not truly identify Asian Indians with excess adiposity, as the relationship between BMI and PBF varied among different ethnic groups (Gurrici et al., 1998; Deurenberg et al., 2000).

As a consequence, in 2000 a WHO expert consultation on the obesity issues in Asia–Pacific region suggested redefining the criteria for obesity, recognizing the necessity for ethnic specific cut-off points. However, they recommended that the conventional (WHO, 1995) BMI cut-off point of ≥ 30 kg/m² should be retained as an international classification for obesity. In a publication of this WHO consultation, the proposed BMI cut-off point for overweight was 23–24.9 kg/m², and that for obesity was ≥ 25 kg/m² (WHO, 2000).

In a succeeding publication in 2004, another WHO consultation resolved that the available data do not necessarily indicate one clear BMI cut-off for all Asian Indians for overweight and obesity. No attempt was made therefore to redefine cutoff points for each population separately (WHO, 2004).

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In the present study, an attempt has been made to test the ability of different BMI cut-off points to predict high percent body fat by sensitivity/ specificity analysis. This would help to develop population specific BMI cut-off value for identifying individuals with truly excess adiposity. This was more important for Asian populations, because for every level of BMI the predicted fat mass was higher in Asian populations (Dudeja et al., 2001; Deurenberg et al., 2002). Thus, the purpose of this study was to examine the sensitivity and specificity of BMI in adult Asian Indian women to detect excess adiposity.

MATERIALS AND METHODS

The present community-based cross-sectional study comprised adult Asian Indian women living in and around Kolkata, India. A total of 364 participants aged 18–70 years took part in the study. Pregnant and lactating women, women undergoing hormone therapy as well as under medication or with chronic disease were not included in the study. Prior to participation, individuals were informed by public advertisement and oral communication about the study with the help of the local officials. Individuals who responded to the advertisement were selected randomly. Informed verbal consent was obtained from each participant before commencement of the study. Age was obtained by interview and verified with horoscope or birth certificate whenever possible.

Anthropometric measurements namely height (HT) and weight (WT) were measured using standard procedures (Lohman et al., 1988). HT was measured to the nearest 0.1 cm using moveable anthropometer. WT was measured to the nearest 0.5 kg using weighing machine. BMI (kg/m^2) was derived subsequently. Percent body fat (PBF) was measured using bioelectrical impedance analysis (BIA) (OMRON HBF-302). Several studies have shown a strong correlation between PBF, FM, and FFM as measured by BIA and dual-energy-X-ray-absorptiometry (DEXA) (Goldfield et al., 2006; Boneva-Asiova and Boyanov, 2008). The BIA has also been validated for Asian Indians (Vasudev et al., 2004).

Descriptive statistics for anthropometric variables were computed by mean and standard deviation (SD). Pearson correlation coefficient was used to quantify the relation between BMI and PBF. The receiver operating characteristic (ROC) curve analysis was used to evaluate the ability of BMI for assessing excess adiposity and the accuracy was determined by examining the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), Youden's index and overall misclassification. Excess adiposity was defined as total body fat greater than thirty percent (Hortobagyi et al., 1994; Dudeja et al., 2001). Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS). A p value of <0.05 was considered as significant.

RESULTS

Characteristics of the studied population are shown in Table 1. The mean age was 31.88 years (SD 14.26 years), with a range of 18 to 70 years. The mean BMI and PBF was 23.61 kg/m^2 (SD 4.43) and 28.47 (SD 6.45), respectively. When conventional BMI cut-off value of $\geq 30 \text{ kg/m}^2$ was applied, 30 (8.2%) women were obese or have excess adiposity. However, the

result varied considerably when PBF was used as the measurement of excess adiposity. Based on PBF, 132 (36.3%) women had excess adiposity. Result of the Pearson correlation analysis revealed significant positive correlation between BMI and PBF ($r = 0.561$) and BMI explained 31.4% of variance of PBF ($p < 0.01$). Table 2 shows the results of the ROC curve analysis for the BMI cut-off values in relation to excess adiposity by PBF. The results revealed that the sensitivity and specificity as well as the PPV and NPV of the conventional BMI cut-off value for excess adiposity were 18.93%, 97.84%, 83.32% and 67.93%, respectively. However, based on the ROC curve (Figure 1) and the trade-offs between improving BMI's sensitivity and specificity, the optimal cut-off value was BMI ≥ 23.4 kg/m² with a sensitivity and specificity 77.27% and 72.84%, respectively in assessing excess adiposity. With this cut-off value, the sensitivity of BMI in relation to PBF increased but the PPV was low. Moreover, lowering the BMI cut-off value from ≥ 30 kg/m² to ≥ 23.4 kg/m² increased Youden's index from 0.17 to 0.50 and decreased overall misclassification 5.22%.

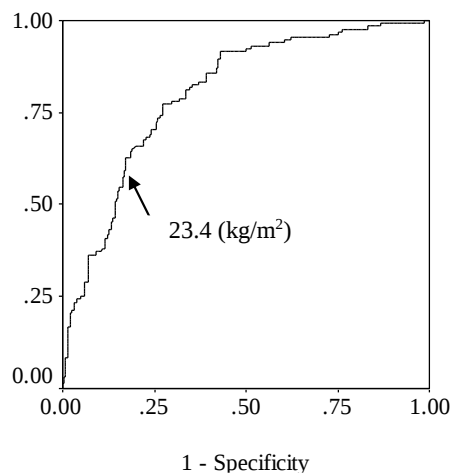


Figure 1. Receiver operating characteristic curve of BMI (kg/m²) in assessing obesity.

Table 1. Characteristics of the study population

Variables	Mean	SD
Age (year)	31.88	14.26
Height (cm)	152.81	6.14
Weight (kg)	55.19	11.13
Percent body fat	28.47	6.45
Body mass index (kg/m ²)	23.61	4.43

SD, standard deviation.

DISCUSSION

The present study examined the sensitivity and specificity of BMI to detect excess adiposity in adult Asian Indian women. In epidemiological studies and in clinical practice BMI was widely used as a proxy measure of excess adiposity. However, the efficiency of BMI is depends on its sensitivity and specificity to detect excess adiposity. This varied with

ethnicity, due to the biological variation in body shape and composition. However, the ROC curve analysis in the present study demonstrated low sensitivity (18.93%) and high specificity (97.84%) of the conventional BMI cut-off value to detect excess adiposity. Such a low value of sensitivity and high specificity suggested that this BMI cut-off value failed to detect excess adiposity in ~ 80% of subjects who had truly excess adiposity. In other words, conventional BMI cut-off value was not useful to detect individuals with excess adiposity. A recent study in Saudi adults also revealed low sensitivity and high specificity of BMI in assessing excess adiposity (Habib, 2013). Study in Asian-American women also revealed poor sensitivity of BMI to detect PBF (Carpenter et al., 2013). Dudeja et al. (2001) and Hortobagyi et al. (1994) also observed similar results.

The ROC analysis revealed that the best compromise between sensitivity and specificity for optimal BMI cut-off value to detect excess adiposity was 23.4 kg/m², and the corresponding sensitivity and specificity was 77.27% and 72.84%, respectively. However, this cut-off value was lower than the conventional cut-off value to detect excess adiposity and thus, could identify individuals who would otherwise be considered as normal by the conventional cut-off value. In relation to the conventional cut-off value for excess adiposity, a lower BMI cut-off of 23.4 kg/m² produced increased sensitivity (18.93% vs. 77.27%) and moderately decreased specificity (97.84% vs. 72.84%). In reality, it was difficult to achieve high sensitivity and specificity simultaneously, thus relative importance of sensitivity vs. specificity was taken into consideration. However, the BMI cut-off value of 23.4 kg/m² instead of 30 kg/m² increased the likelihood (Youden's index 0.50 vs. 0.17) ~ three times for detecting individuals with excess adiposity, who had truly excess adiposity. Additionally, this lower BMI cut-off value decreased 5.22% overall misclassification. However, it is noteworthy to mention that for women in our sample, the proposed BMI cut-off value (≥ 25 kg/m²) of WHO (2000) revealed only 44.7% sensitivity and 83.6% specificity. In a study, Bozkirli et al. (2007) also observed that the conventional BMI cut-off value underestimated the prevalence of excess adiposity in Turkish population. Moreover, several other studies also revealed that lowering the BMI cut-off value improved its ability to assess excess adiposity (Dudeja et al., 2001; Ko et al., 2001; Ghosh and Bandyopadhyay, 2007).

Table 2. Sensitivity and specificity of BMI (kg/m²) as a measure of obesity

Cut-off points	Sensitivity (95%CI)	Specificity (95%CI)	PPV	NPV	Youden's index	Overall misclassification
BMI ≥ 30 kg/m ²	18.93% (14.9-22.9)	97.84% (96.4-99.3)	83.32%	67.93%	0.17	30.78%
BMI ≥ 25 kg/m ²	44.7% (39.6-49.8)	83.6% (79.8-87.4)	60.83%	72.62%	0.28	26.64%
BMI ≥ 23.4 kg/m ²	77.27% (73.8-80.8)	72.84% (68.3-77.4)	61.81%	84.91%	0.50	25.56%

PPP, positive predictive value; NPV, negative predictive value; BMI, body mass index

The cardinal feature of the present study was the predictive values (i.e., PPV and NPV) of BMI in relation to the PBF. As shown by the PPV of the conventional BMI cut-off value, almost 17% of women with high PBF (PBF >30%) had BMI < 30 kg/m². On the other hand, high NPV indicates that almost one out of three (~32%) women with normal PBF (<30%) had

high BMI (≥ 30) kg/m². However, the PPV of the optimal BMI cut-off value in our sample was 61.81%. Indicated that approximately 38% of women who had a BMI ≥ 23.4 kg/m² did not have high PBF ($< 30\%$). Thus, the results indicated that BMI was a relatively poor predictor of excess adiposity in the studied population. One possible reason might be the weaker association between BMI and PBF in the studied population. Because, BMI as a proxy measure of adiposity explained only 31.4% of variance of PBF. A recent study by Carpenter et al. (2013) also observed weak association between BMI and PBF among Asian-American women.

Moreover, the weak association between BMI and PBF might be due to the fact that BMI does not measure fat mass or percentage fat only, but measures both fat mass and fat free mass without distinguish between them (Garn et al., 1986; Hortobagyi et al., 1994; Charbonneau-Roberts et al., 2005; Rona et al., 2011). Therefore, individuals with the same BMI may have different proportions of fat mass. Furthermore, it has been observed that BMI underestimate excess adiposity among those with long legs and overestimate excess adiposity among those with short legs relative to torso length (Garn et al., 1986; Charbonneau-Roberts et al., 2005).

CONCLUSION

Therefore, measuring body fat instead of BMI could be an appropriate way to categorize individuals with excess adiposity. Although BIA is a validated measure of body composition, acknowledging that the use of more accurate measures like DEXA would have improved our analysis. However, this preliminary finding warranted further studies in other Asian ethnic groups to understand whether the same relationships exist. Since, it is the amount of excess body fat, rather than the amount of excess weight that determines the health risks of obesity (Deurenberg et al., 1998; Deurenberg et al., 2001).

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Chapter 252

FRAMING OBESITY AND UNDERNUTRITION AS PROBLEMS FOR GOVERNMENTS

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INTRODUCTION

The epidemiologies of obesity and undernutrition are conducted using standardized metrics in very regulated ways. From the 1950s, anthropometric measures have been used overwhelmingly as measures of social welfare in public health, economics and national statistics (Uljaszek and Komlos 2010). Their predominant use in most recent decades has been as proxies of human nutritional health (both under- and over-nutrition) and well-being (or lack thereof), as well as of physical productivity and health, in relation to measures of economic productivity, morbidity and mortality risk, where non-normative values of body size, usually height and weight, are interpreted as carrying risk. The procedures and protocols involved in these specific usages have been critiqued in various ways. For example, measurement in public health practice has been criticized as universalizing the human body when relating individuals to norms (Mol 2009) and of health to measurement (Yates-Duerr 2013). Issue has also been taken with the stigma that accompanies the measurement and medicalization of bodies (Rubin and Joseph 2013). Bodies are physical entities with economic, social and medical correlates, and the standardization of bodily measures of obesity and undernutrition have political and economic implications. This paper describes the now-historical process of nutritional assessment in public health anthropometry, and examines how public health reporting of obesity and undernutrition informs the discourse about nutritional health at governmental level. Examples are predominantly taken from India and the United Kingdom (UK).

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NUTRITIONAL CLASSIFICATION USING ANTHROPOMETRY

In nutritional epidemiology, anthropometry can be used as a proxy for nutritional status, or as a measure of exposure to nutritional stress. Anthropometry became a proxy for nutritional status with the World Health Organization Technical Report 'Assessment of the Nutritional Status of the Community' (Jelliffe 1966). This became the standard text for relating anthropometry to nutrition and to social welfare in the subsequent two decades. The use of anthropometry in health and nutritional assessment has a formal scientific basis which stems from life insurance estimation of mortality prediction from the early twentieth century. The publication of 'standard height-weight' tables by the life insurance industry began with the *Medico-Actuarial Mortality Investigations of 1912* (Keys et al., 1972). These tables provided 'ideal' weight for ranges of height for use among insured adults in the United States (US) and Canada, according to sex and three categories of body frame. The first version of these standard tables, based on actuarial data relating to blood pressure (as a proxy for chronic disease risk), was brought into general use for assessing ideal body weight in the US in 1942/43 by the Metropolitan Life Insurance Company (Weigly 1984). Stature and weight continue to be the most widely used measures of nutritional status and disease risk at both extremes of body size. They give the simplest measure of attained frame, or skeletal size, and of soft tissue mass (Uljaszek 1997).

Obesity came to be measured with the body mass index (BMI), subsequent to its being described as the least-worst anthropometric measure of this phenomenon. The BMI had its origins in the Metropolitan Life Insurance Company tables. While body weight is always related to stature, the relationship is non-linear, and even direct correction for height does not remove this relationality completely. The height dependency of weight and stature-based measures of nutritional status was of concern for early epidemiological investigation of the health impacts of excess body fatness (Boe et al., 1957), because it made nutritional assessment difficult. After examining the height dependency of a number of weight-height indices and ratios, Boe et al., (1957) concluded that weight over height squared (W/H^2) gave the best height independent measure of relative weight. Subsequent studies in British, Cook Islander and US populations confirmed this view (Uljaszek 2017). In an analysis of the relative height independence of body fat prediction using different weight to height ratios, Keys et al., (1972) found generally much lower correlations of height with W/H^2 than with either weight over height (W/H) or weight over height cubed (W/H^3). These authors concluded that the ratio W/H^2 was clearly better than other measures of relative weight, and declared that this ratio be named the body mass index.

The cut-offs for ideal weight used in the Metropolitan Life Insurance Company tables are similar to those that were subsequently recommended for nutritional assessment using BMI by the Royal College of Physicians (1983) in the UK. The adoption of the closest whole-number BMI equivalent value to the very lowest and very highest boundaries for healthy weight in the Metropolitan Life Insurance Company tables by the Royal College of Physicians (1983) permitted ideal healthy weight to be determined without having to consider or measure frame-size (an undefined construct within these tables), simplifying anthropometric obesity assessment (James 2004). The BMI cut-offs of 18.5, 17.0 and 16.0 kg/m^2 were accepted for the assessment of different grades of adult undernutrition, or chronic energy deficiency, in 1992 (Shetty and James 1994), while BMI cut-offs of 25 and 30 kg/m^2

were accepted for classifying overweight and obesity by the World Health Organization (WHO) in 1997 (World Health Organization 2000). Alongside the acceptance of BMI as the measure of nutritional status of adults came the standardization of risk of mortality (Flegal et al., 2007) and morbidity (Campbell and Ulijaszek 1994; Canoy et al., 2007) at both lower and higher extremes of BMI.

At the upper end of population distribution, BMI shows strong associations with morbidity and mortality from number of chronic diseases and disorders for adults (World Health Organization 2000), and among a limited number of risk markers for chronic disease among adolescents (Bhargava et al., 2004). Figure 1 shows all-cause mortality according to BMI from the largest meta-analysis of BMI against mortality to date, the Prospective Studies Collaboration (2009), which includes nearly a million adults from 57 prospective studies.

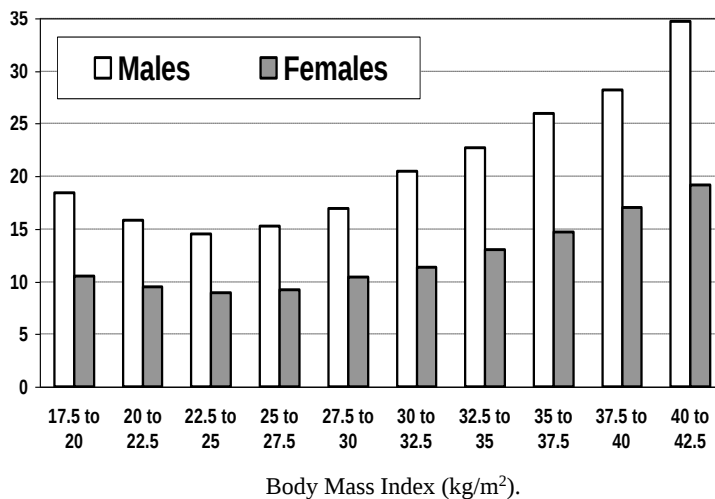


Figure 1. All-cause mortality relative to body mass index, for 894,576 adults in 57 prospective mortality studies in industrialized countries (data from Prospective Studies Collaboration 2009).

Epidemiological studies relating BMI to mortality have methodological biases, however, including reverse causation and confounding by related factors such as smoking (Hu 2008). Epidemiological critiques of BMI include its inconsistent relationship with body fatness (Gallagher et al., 1996; Freedman and Sherry 2009), that it does not distinguish between potentially harmful fat in the liver and viscera (Carroll et al., 2008), and that it does not reflect health risk very well, except at the extremes (Lee et al., 2008).

BMI persists as a standard anthropometric measure of adult obesity, however, for both pragmatic and historical reasons. The BMI has been used for far longer than any other anthropometric measure, and was the first to be appropriated for the assessment of obesity rates in populations, after measures of stature and weight had been formalized for predicting mortality. Furthermore, there is no alternative measure of obesity that is collected nearly as systematically as the BMI. While waist circumference and waist hip ratio show as good, if not better, associations with mortality and morbidity risk (World Health Organization 2011), their possible adoption for international comparison would risk delegitimising programs and policies for obesity control that have used population monitoring of BMI as the measure of success or failure, at a time when adult obesity rates continue to rise (Stevens et al., 2012).

While the BMI has been universally adopted for obesity assessment, it does not have the best fit for all the purposes to which it has been assigned: individual classification; screening and monitoring for medical purposes; population monitoring for public health purposes; and econometric modelling. As the relationships between BMI, fatness and morbidity vary across populations (World Health Organization Expert Consultation 2004), there remain problems of how best to classify obesity using BMI. Relationships with morbidity and mortality vary according to the measure of obesity used, the population under investigation (be it of European, Asian, or African ancestry, whether it is young or old, male or female), and among the various classificatory boundaries that are used in obesity research and practice (World Health Organization 2000). In some Chinese (Li et al., 2002) and Asian (World Health Organization Expert Consultation 2004) populations, there is increased chronic disease risk at lower levels of BMI than among European populations (Li et al., 2002), and this has prompted recommendations for lower cut-offs for overweight and obesity for people of Asian origin (World Health Organization Expert Consultation 2004). At the other extreme, Pacific Islander populations generally have lower body fatness relative to lean body mass at any level of BMI, prompting the suggestion that higher BMI cut-offs should be used to assess overweight and obesity in these populations (Swinburn et al., 1999).

The BMI is also used to classify childhood obesity. This is more problematic than among adults, because of the variability in the growth rates of children both within- and between-populations which alters the normative range of BMI according to different normative bodily proportions at different ages, making fixed obesity cut-offs inappropriate. Age-specific cut-offs for childhood overweight and obesity that pass through adult classification cut-offs for overweight and obesity have been accepted for international use, however, using normative distributions that vary by age and sex (Cole et al., 2000). Evidence from systematic reviews of adult chronic disease subsequent to childhood obesity shows there to be significantly increased risk of premature mortality with child and adolescent overweight or obesity, as well as significantly increased risk of cardiometabolic morbidity (diabetes, hypertension, ischaemic heart disease, and stroke) in adult life (Reilly and Kelly 2011). Cardiovascular disease risk is, however, dependent on the tracking of BMI from childhood to adulthood, with the risk of raised blood pressure in adult life being highest among those at the lower end of the BMI scale in childhood, but overweight in adulthood (Lloyd et al., 2010).

In the formalization of BMI for international use for the measurement of obesity (World Health Organization 2000), the overarching aim was to provide simplicity for assessment and monitoring of obesity world-wide. Standardized classification of obesity was accepted by the World Health Organization (2000) because it claimed that it allowed meaningful comparisons within and between populations, the identification of individuals and groups at increased risk of morbidity and mortality, the identification of priorities for intervention at individual and community levels, and a firm basis for evaluating interventions.

Reporting Obesity

Both height and BMI are positively associated with socioeconomic status (SES) in India (Som et al., 2014), and a positive secular trend in increased body size has been observed in some populations there (Khanna and Kapoor 2004). There has also been an increase in

obesity rates among children and adolescents (Mistry and Puthussery 2015) and among adults in most Indian States (Bharati et al., 2007). While there has been an emergence of the dual burden of undernutrition and obesity across much of India (Bharati et al., 2007) (Table 1), such dual burden does not exist yet among those of low SES, suggesting that transition towards energy-dense, nutrient-poor diets and low physical activity (Popkin 2002) in India is at an early stage (Subramanian et al., 2009).

Table 1. Percent obesity, overweight and undernutrition, India, adult women
(data from Bharati et al., 2007)

State	Obesity (BMI>30)	Overweight (BMI 25-30)	Undernourished (BMI<18.5)	Combined burden
Punjab	9.0	21.1	16.4	46.5
New Delhi	8.9	24.1	12.2	45.2
Goa	4.4	16.7	26.8	47.9
Gujarat	4.3	11.3	36.3	51.9
Maharashtra	4.1	12.6	33.2	49.9
Kerala	3.8	17.0	18.0	38.8
Haryana	3.7	12.3	25.6	41.6
Himachal Pradesh	3.3	13.2	26.5	43.0
Jammu	3.3	11.7	24.7	36.4
Tamil Nadu	3.1	13.4	26.1	42.6
Karnataka	2.8	10.3	38.2	51.3
All India	2.6	9.4	31.2	43.2
Sikkim	2.3	12.1	10.9	25.3
West Bengal	2.3	10.3	37.9	50.5
Andhra Pradesh	2.2	9.9	36.5	48.6
Tripura	1.8	6.5	34.5	42.8
Uttar Pradesh	1.5	5.8	34.7	42.0
Rajasthan	1.4	5.0	35.2	41.6

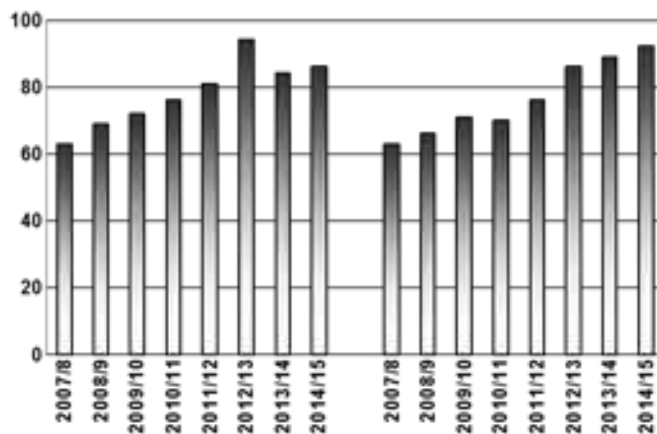


Figure 2. Percentage difference in obesity rates between the least (1st decile) and most (10th decile) deprived Index of Multiple Deprivation Local Authority Districts based on school postcode, England, between 2007/8 and 2013/14, children aged between four and five years, and between ten and eleven years (data from Public Health England 2016).

In the UK, various surveys from the start of the nineteen hundreds onwards show there to have been a secular trend towards increased height and weight until the 1970s (Floud et al., 1990), followed by emergent overweight and obesity among children (Chinn and Rona 2001) and adults (Garrow 1978) especially among those of lower SES (Ulijaszek 2014). In the UK and other high income countries (HICs), rates of childhood overweight and obesity appear to have plateaued (Wabitsch et al., 2014), although this effect has been shown mostly in studies of short duration (Visscher et al., 2015). Where rates of childhood and adolescent obesity have been shown to plateau, socioeconomic inequalities in obesity rates have persisted or increased (Ulijaszek et al., 2016), as in the US (Frederick et al., 2013) and the UK (Stamatakis et al., 2010). Data that is taken to be nationally-representative in England show this effect between 2007 and 2015 (Figure 2) (Public Health England 2016), expressed as percentage differences in obesity rates between the least and most deprived Local Authority Districts.

Anthropometry as Evidence in Policy Making

The most basic form of evidence for policy on nutritional status is nationally-representative data across administrative units and across time. The use of the concept of human capital, which includes adult height, educational achievement, income and birth weight, expresses the economic logics that underpin the intervention, that good nutrition is a prerequisite for economic development (Bryce et al., 2008). Nutrition came to the policy forefront in India in the 1990s, with the National Nutrition Policy (1993) and the 1995 National Plan of Action on Nutrition (Mohmand 2012). With respect to undernutrition in India, two data sources for nationally-assessed nutritional status for policy purposes have predominated. The first of these, the National Family Health Survey (NFHS) is collected periodically by the International Institute for Population Sciences, and is a large-scale, household level sample survey conducted across India that provides information on the main outcome indicators of malnutrition - underweight, stunting and wasting, along with a host of other health indicators. This survey has been repeated periodically, with NFHS-1 having been conducted in 1992-93, NFHS-2 in 1998-99 and NFHS-3 in 2005-06. The second of these, the Integrated Child Development Services (ICDS) scheme of the Ministry of Women and Child Development carries out regular monitoring of the weight of children under the age of 6 years, among its many functions. Anthropometric nutritional assessment has been used in both NFHS and ICDS surveys to identify the regions of India with highest burdens of undernutrition. Obesity has never been measured or reported systematically using the NFHS or ICDS surveys. However, at the national level, obesity policy in India is observed in the reporting of data to the WHO and some compliance to WHO obesity policy (World Health Organization 2000; 2016).

As with measures of anthropometric undernutrition, the measurement of obesity rates and its reporting provides evidence for the existence of population obesity and its changing patterns across time, and for identifying possible governmental interventions against it. Speaking to the importance of data collection for childhood obesity policy, Nathan et al., (2005) assert that policy can be made in the absence of strong research evidence, but where powerful and competing groups contest possible policy options, the evidence required needs

to be substantial. Nationally-representative data on obesity rates are often illustrated using obesity prevalence maps, where obesity rates are shown according to administrative units within-nation. Figure 3 shows such a map for England, according to Local Authority. Such maps have been used to illustrate inequalities in rates of obesity according to social class, gender, ethnicity and geography across the country and within cities. By combining categories, such mapping has also been used to demonstrate regional differences due to variations in proportions of the population of low SES across the country and according to levels of deprivation (Moon et al., 2007).

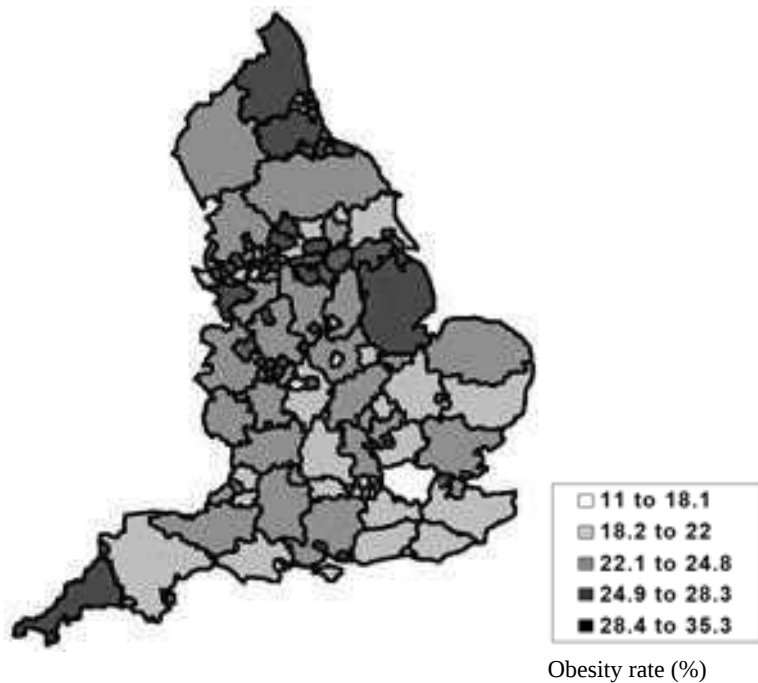


Figure 3. Obesity rates in adults, England 2012.

Epidemiological data collection and reporting, and the use of obesity epidemiology in econometric modelling of the impacts of obesity, are usually starting points for state-led obesity interventions (Malik et al., 2013). The spur to policy action by most nation-states is overwhelmingly economic (Ulijaszek 2017). The most persuasive political arguments usually involve framing obesity as a significant burden to the economy and health service, usually through costs to employers, its medical management, and of the chronic diseases associated with it (Wang et al., 2011). In the UK, obesity has also been compellingly depicted as a drag on the economy, both in terms of lost productivity and in terms of costs to state-provided health care provision (House of Commons Health Committee 2004). Obesity assessment from annual data collection of adult heights and weights by Health Survey for England (HSE) was initiated in 1993, while the National Child Measurement Programme (NCMP) was set up to monitor childhood obesity in 2007 by the National Obesity Observatory (NOO). The NCMP continues as an annual programme of measurement of heights and weights of the vast majority of children in the first and final years of State-funded primary schools in England.

Both HSE and NCMP obesity monitoring hold UK National Statistics status in the same way that the reporting of births, deaths and marriages does.

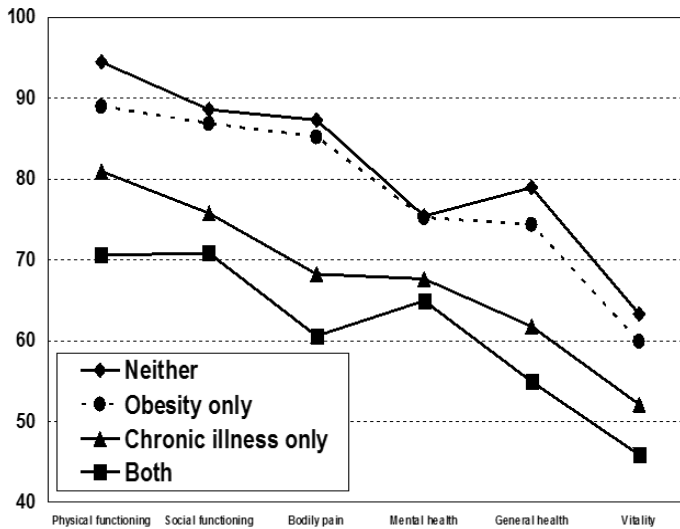


Figure 4. Distribution of self-reported health scores (the higher the healthier) according to obesity (according to body mass index) and chronic illness, after adjusting for age, gender, and frequency of health service utilization, United Kingdom (data from Doll et al., 2000).

The categorization of obesity as a disease in the US and by the WHO has aimed to raise the profile of obesity for medical intervention, but this categorization continues to be contested (Rich et al., 2011). Obesity as risk factor also has a place in the framing of health policy, because it sits among other risk categories such as smoking, unhealthy diet, and physical inactivity for chronic disease onset and progression (Erlichman et al., 2002). Categories of risk have ambivalent status in policy-making, however. For example, smoking damages health and human productivity, but its taxation gives a steady stream of reliable income to governments (Chaloupka and Warner 2000). Similarly, unhealthy diet is damaging, but the food industry, which supplies uncontaminated and affordable food to large populations, primarily seeks to continue its operations without undue regulation (Uljaszek and McLennan 2016).

DISCUSSION

Undernutrition reduces work capacity and productivity among adults, reducing earning capacity and aggravating poverty, as well as enhancing mortality and morbidity among children (Anish et al., 2013). Furthermore, poverty in childhood increases risk of non-communicable diseases in adult life (Conroy et al., 2010). While nutrition policy in India remains focused on undernutrition, the collection of nationally-representative data on anthropometric nutritional status has highlighted the decline in nutritional stunting, if not of wasting (Mohmand 2012), and the rise in obesity in more recent years (Bharati et al., 2007). The emergence of the dual burden of both undernutrition and obesity across the nation, even

if not yet located among those of low SES (Subramanian et al., 2009), has led to calls for national nutrition policy that can address this new problem (Mohmand 2012). The economic costs of obesity to India include those of lost productivity, but increasingly the costs of treating the rapidly rising rates of type two diabetes (Mohan et al., 2007).

While BMI cut-offs for obesity classification are viewed as being meaningful according to epidemiological analyses (World Health Organization Expert Consultation 2004), they can differ from individual health perceptions of health and well-being. For example, self-reported health status of adults in the UK among obese people who have not experienced chronic disease is similar to that of people categorized as being of normal weight (Figure 4), with respect to physical function, bodily pain, general health and vitality, social functioning and mental health (Doll et al., 2000).

Obesity may not be perceived as a problem among those carrying excess body fatness prior to experiencing any of the chronic diseases associated with it. Anthropometric measurement of obesity has been critiqued by social scientists for its medical distancing of the individual experience of living with a fat body (Yates-Doerr 2013), whether or not such experience has been linked to chronic disease experience. It has also been viewed by social scientists as a way of universalizing the human body by governmental institutions through epidemiological reporting, by relating individuals to norms and health to measurement (McCullough and Hardin 2013). Brewis et al., (2011) note the stigma that accompanies the measurement and medicalization of fat bodies, while Puhl and Brownell (2001) have reported the widespread stigma attached to obesity. The stigma attached to undernutrition has also been reported to be a barrier to the uptake of medical treatment and nutritional rehabilitation by mothers and young children in Pakistan (Mull 1991), Tanzania (Howard and Millard 1997) and Kenya (Bliss et al., 2016).

The policy uses of anthropometric nutritional status combine it with other nationally-oriented data such as birth, death, disease and economics. The reported numbers and their use in policy are a long way from the individuals that data collection is designed to serve. Undernutrition in India persists, and is framed as an object for policy intervention, as good nutrition is seen as a prerequisite of economic development in low income countries. In HICs, obese people are shamed and obesity is viewed as a drag on the economy. Through reporting nutritional status, ideal citizen-bodies are constructed through growth and body size references, not in relation to individual well-being, but in relation to the best economic functioning of the State. Neoliberal politics forces ideal body citizenship on the individual, however, despite individuals and populations being urged, in the case of India, to develop (Berg 1973), and in the case of the UK, to consume (Ulijaszek and McLennan 2016). Thus measuring and reporting nutritional status and obesity raises questions about differing forms of biological citizenship.

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Chapter 253

MODERNIZATION AND OBESITY: A PANDEMIC ISSUE

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OBESITY

Concept and Epidemiology

Overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health. Body Mass Index (BMI) is a simple index of weight-for-height that is commonly used to classify overweight and obesity in adults. It is defined as a person's weight in kilograms divided by the square of his height in meters (kg/m²) i.e., $BMI = Wt \text{ in Kg} / Ht \text{ in m}^2$. The WHO defines overweight as BMI greater than or equal to 25kg/m² but less than 29.9kg/m²; and obesity as BMI greater than or equal to 30 kg/m²(WHO, 2017a). Though for the Asian population a BMI of 27kg/m² is equivalent to a value of 30 kg/m² in other groups (WHO, 1998). Overweight means excess in body weight and may be the resultant of higher lean body mass (muscle, bone, or body water content) but not only because of the weight of the total body fat. Obesity, on the other hand, denotes the presence of excess body fat. All obese persons are overweight, but all overweight persons are not necessarily obese as the excess body weight may arise from the lean body mass as well (Mandal, 2010). The adverse health outcomes associated with overweight and obesity range from an increase risk of mortality to a non-fatal debilitating disease (WHO, 1998). Obesity therefore is a medical

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condition of excess of body weight due to the accumulation of fat leading to an adverse effect on health, reduced life expectancy and/or increased health problems.

Genetics, environmental, metabolic, behavioral, and socio-cultural factors play major roles in pre disposing a person to obesity. Genetics plays an important role in shaping the BMI status of an individual. How much variation in weight gain among individuals can be accounted for by genetic factors? Obesity frequently begins in childhood and generally the obese parents may likely have overweight children. Familial association is not a proof of genetic inheritance for families having shared eating and exercise habits. However, familial association cannot be considered as a proof of genetic inheritance-as families share common lifestyle pattern such as dietary pattern and exercise habit. It is claimed that about 200 different genes or loci have been linked with controlling obesity in humans (Lau, 1999). However, the pattern of inheritance of obesity suggests that the effect is polygenic, with each variant of many different genes making a small difference in effect (Sorensen and Soren, 2001). Apart from this, both age and sex have role to play in causing obesity. Many studies have shown that excessive weight gain leading to overweight and obese condition usually develops slowly through adulthood and most weight gain occurs between the age of 25 to 44 years. Again females are more prone to obesity as compared to males because of their anatomical structure and physiological features such as not losing the weight they have gained during pregnancy and gaining body weight by about 12-15 pounds with the attainment of menopause.

When we talk of the environmental factors, it encompasses the totality of the surrounding in which we find ourselves. Gaining excessive body weight leading to overweight and obese condition is a long term process brought about by a number of socio-cultural practices and habits. The way of eating during childhood can affect the way one eats as adults. The way of eating over many years becomes a habit. What we eat, when we eat, and how much we eat is certainly a determinant of weight gain and obesity. Certain habits such as eating more food than our body can use, drinking too much alcohol, not getting enough exercise, quit smoking, stress, anxiety, feeling sad, or not sleeping well are said to be important contributory factors for gaining excessive weight and obesity. At the same time certain medical problems or treatments cause weight gain including underactive thyroid gland (hypothyroidism), medicines such as birth control pills, antidepressants, and antipsychotics.

On the whole, the potential contributory factors culminating to global increase in overweight and obesity in the past three decades are changing lifestyle patterns such as increase in calorie intake, changes in the composition of diet, decreasing levels of physical activity, and changes in the gut microbiome as well (Bleich et al., 2008, Astrup and Brand-Miller J, 2012, Drewnowski and Popkin, 1997, Popkin, 2001, Blair, 2013). Though there are multiple causal factors associated with the rise in obesity in developing countries, the two most important factors are urbanization and globalization (Benjamin Caballero, 2007, Nanan, 2002). In short, urbanization and globalization have resulted in modernization which is the key causal factor for overweight and obesity. The urban lifestyle as compared to the rural setting has difference in energy balance as a result of difference in energy intake and energy expenditure. The energy consuming manual labor, long walks to work places for earning their livelihood and also procuring their subsistence typical of rural areas are replaced by sedentary lifestyle characterized by mechanized system of transportation, machineries and desk or sidewalk job. In short the urban lifestyle demands much lower energy expenditure as compared to the rural way of living in rural settings. On the other hand, the urban dwellers

consume more energy dense food readily available in the urban market in contrast with low energy expenditure thus culminating to gradual weight gain. Whereas the reverse is the condition of the rural dwellers as they expend more energy and consume low nutrient and less energy content food conditioned by low economy on one hand, and unavailability of energy dense food on the other. As such the children in rural areas cannot achieve normal growth thus resulting into underweight adults. As economic development bring some characteristics of urban lifestyle to rural communities, these populations also begin to show increasing rates of obesity, particularly among women these days (Mendez, 2005). Unhealthy dietary habits and less physical activity are likely to endure thereby increasing the risk among today's youth for obesity and chronic diseases in future unless the public health initiatives are designed to be multilevel and take into consideration the multiple correlations that influence behaviour surrounding dietary intake and physical activity (Sandra et al., 2012).

Obesity is a major risk factor for cardiovascular disease (CVD) and Type 2 diabetes mellitus (DM) and in the presence of other risk factors for non-communicable diseases (NCDs) such as smoking, hypertension, elevated blood cholesterol and it has a multiplicative effect (Thorkhild et al., 2000, Blackburn and Luepker, 1986). A number of literatures reveals that the consequences of obesity include various diseases and morbid conditions which increase the chances of mortality such as Diabetes, Coronary Heart Disease, Peripheral Artery Disease, Stroke, Hypertension, Hyperlipidemia, Arthritis, Obstructive sleep apnea, Pulmonary disease, PCOS/infertility, Dysmenorrhea, Pregnancy complications, Gallbladder disease, Skin infections, Urinary incontinence, Depression, Eating disorders, social stigma, Cancers: breast, endometrial, colon, prostate, gallbladder, kidney, esophagus, etc.

Global Scenario

The worldwide prevalence obesity has nearly tripled since 1975. In 2016, more than 1.9 billion adults, 18 years and older, were overweight. Of these over 650 million were obese. As many as 39% of adults aged 18 years and above were overweight in 2016, and 13% were obese. Most of the world's population live in countries where overweight and obesity kill more people than underweight. As many as 41 million children under the age of 5 were overweight or obese in 2016. Over 340 million children and adolescents aged 5-19 were overweight or obese in 2016 (WHO, 2017a). Obesity has reached pandemic proportions globally with at least 2.8 million people dying each year as a result of being overweight or obese. Once associated with high-income countries, obesity is now also prevalent in low- and middle-income countries (WHO, 2017b). It has been reported that number of overweight and obese individuals increased from 857 million in 1980, to 2.1 billion in 2013. The worldwide prevalence of overweight and obesity combined rose by 27.5% for adults and 47.1% for children between 1980 and 2013 (Emmanuela et al., 2014).

It is a well-established and known fact that the prevalence of overweight and obesity is overwhelmingly increasing globally during the last few decades. Several studies have revealed that it has become a global pandemic issue (Roth et al., 2004, Swinburn et al., 2011, Popkin and Adair, 2012). In 2010, a worldwide estimate reveals that overweight and obesity resulted in 3.4 million deaths, 4% of years of life lost, and 4% of disability-adjusted life-years (Lim SS, 2010), thus resulting in future fall of life expectancy.

**Top 10 Countries with most obese population size in order of ranking
as on July 1st, 2017**

1.	US	–	109,342,839
2.	China	–	97,256,700
3.	India	–	65,619,826
4.	Brazil	–	41,857,656
5.	Mexico	–	36,294,881
6.	Russia	–	34,701,531
7.	Egypt	–	28,192,861
8.	Turkey	–	23,819,781
9.	Iran	–	21,183,488
10.	Nigeria	–	20,997,494

Source of Data; Renew Bariatrics, 2017.

Getting little bit acquaintance with the numerical figure, the total population of the world is 7,505,257,673 while 774,000,000 of them are obese thus constituting almost 10.5%. New research suggests that, there are about 775 million obese people in the world including adults, children, and adolescents. Our research suggests that, there are nearly 650 million obese adults on the planet, as defined as a body mass index (BMI) over 30. There are also about 125 million obese children and adolescents in the entire world according to a BMI over 30 kg/m². The majority of the obesity on the planet resides in a few countries. The following data will reveal top ranking status in relation to obesity parameter.

**Top 10 Countries with most obese population percentage in order
of ranking as on July 1st, 2017**

1.	Cook Islands	–	50.80%
2.	Palau	–	47.60%
3.	Nauru	–	45.60%
4.	Samoa	–	43.40%
5.	Tonga	–	43.30%
6.	Niue	–	43.20%
7.	Marshal Islands	–	42.80%
8.	Qatar	–	42.30%
9.	Kiribati	–	40.60%
10.	Tuvalu	–	40.30%

Source of Data; Renew Bariatrics, 2017.

**Top 10 Countries with least obese population percentage in order
of ranking as on July 1st, 2017**

1.	Central African Republic	–	5.10%
2.	India	–	4.90%
3.	Uganda	–	4.90%
4.	Somalia	–	4.60%
5.	Democratic Republic of the Congo	–	4.40%
6.	Niger	–	4.30%
7.	Eritrea	–	4.10%
8.	Ethiopia	–	4.00%
9.	Rwanda	–	4.00%
10.	Bangladesh	–	3.60%

Source of Data; Renew Bariatrics, 2017.

The health risks associated with rising obesity being well aware universally; member states of WHO have introduced a voluntary target to stop the rise in obesity by 2025, (WHO 66.10, 2013) and also to address the issue by regular monitoring and assessing the trend in the prevalence of overweight and obesity in all populations (Swinburn BA, 2008, Cole TJ et al., 2000, Gortmaker SL et al., 2011).

Substantial rise in the prevalence of overweight and obesity with marked variations and distinct regional patterns across countries has been observed in the past three decades. Though the trend of increasing overweight and obesity is expected to continue in developing countries, as suggested by the fact that two in three of the world's obese people live in such countries, it has started gradually attenuating in the past 8 years in developed countries where increase in obesity that began in the 1980s (Emmanuela et al., 2014).

Excess adiposity/body weight is now widely recognized as one of today's leading health threats in most countries around the world and as a major risk factor for type 2 diabetes, cardiovascular disease, and hypertension (Fogel, 1986). Until the last decades of the 19th century, developed countries were still struggling with poverty, malnutrition, and communicable diseases. These health problems were considered a major cause of low industrial productivity (Fogel, 1997).

Until relatively recently, obesity was considered a condition associated with high socio-economic status. Indeed, early in the 20th century, most populations in which obesity became a public health problem were in the developed world primarily the United States and Europe. In more recent decades, available data shows that the most dramatic increases in obesity are in developing countries such as Mexico, China, and Thailand (Popkin and Gordon, 2004). The global nature of the obesity epidemic was formally recognized by a World Health Organization consultation in 1997 (WHO, 2004).

Indian Scenario

According to a study published in the noted journal *Lancet*, India is just behind the US and China in this global hazard list of top 10 countries with highest number of obese people (Emmanuela, 2014, Sharma, 2014)). Report of the first phase of the National Family Health Survey (NFHS-4) 2015-16 shows that among the males the highest obesity is observed in the population of Andaman and Nicobar Union territory, followed by Goa, Andhra Pradesh, Sikkim, Punjab, Dadra & Nagar Haveli, Daman and Diu, Puducherry, Mizoram and Telangana in order of ranking. As for female population is concerned, the top 10 ranking States and Union territories are Chandigarh, Lakshadweep, Andhra Pradesh, Puducherry, Delhi, Goa, Punjab, Telangana, Tamil Nadu and Daman and Diu. The report also clearly reveals that in all the states and Union Territories, the number of obese women almost doubled that of males. On comparing the report of NHFS 4 with that of NFHS 3 and NFHS 2, the percentage of overweight and obese population has risen substantially in India during the last one and a half decade among the female population. The overweight and obese population increased by almost 60% and 80% respectively among the females during the said period. As for male population is concerned, a marked increase of almost 90% for overweight population and 400% for obese population is seen during the last decade.

**Top 10 States/Union Territory of India with most obese population
percent in order of ranking as for 2015-2016**

Ranking	Most obese male population		Most obese female population	
	State/ Union Territory	Percentage	State/ Union Territory	Percentage
1	Andaman & Nicobar	8.1	Chandigarh	14.9
2	Goa	7.7	Lakshadweep	14.6
3	Andhra Pradesh	7.7	Andhra Pradesh	10.3
4	Sikkim	5.9	Puducherry	10.2
5	Punjab	5.1	Delhi	10.1
6	Dadra & Nagar Haveli	4.8	Goa	9.9
7	Daman & Diu	4.8	Punjab	9.2
8	Puducherry	4.8	Telangana	8.6
9	Mizoram	4.8	Tamil Nadu	8.3
10	Telangana	4.8	Daman & Diu	8.1

Source: NFHS data.

**Top 10 States/Union Territory of India with least obese population
percent in order of ranking as for 2015-2016**

Ranking	Least obese male population		Least obese female population	
	State/ Union Territory	Percentage	State/ Union Territory	Percentage
1	Jharkhand	1.2	Meghalaya	1.7
2	Nagaland	1.3	Jharkhand	2.1
3	Bihar	1.3	Assam	2.1
4	Meghalaya	1.4	Bihar	2.2
5	Chhattisgarh	1.4	Tripura	2.4
6	Uttar Pradesh	1.6	Chhattisgarh	2.4
7	Madhya Pradesh	1.6	Nagaland	2.7
8	Tripura	1.7	Arunachal Pradesh	2.9
9	Assam	1.7	Madhya Pradesh	3.1
10	West Bengal	1.8	Rajasthan	3.3

Source: NFHS data.

While considering the Union territory and State-wise distribution of least obese population among the males, it is observed that Jharkhand has the least obese population followed by Nagaland, Bihar and Meghalaya. As for female population, the least is observed in Meghalaya followed by Jharkhand, Assam and Bihar. Interestingly almost all the States of North East India has a very high percentage of normal BMI ranging from 66.4% to 78.4% among the males and 65% to 75.8% among the females.

According to World Health Organization (WHO), many low-and middle-income countries are now facing a double burden of disease which means that while they continue to struggle with infectious disease and under-nutrition, they are also experiencing a sharp rise in non-communicable disease risk factors such as obesity and overweight. Several research findings reveals that obesity is rising during the last few decades and NFHS, 1998-199, 2005-2006 and 2015-2016 data confirms the trend. This could be a result of lifestyles changing over the years and is a confounder of a large number of non-communicable diseases,” said Sutapa Agrawal, an epidemiologist with Public Health Foundation of India, a public-private initiative involving Indian and international academics, and state and central governments (Live Mint, 2016).

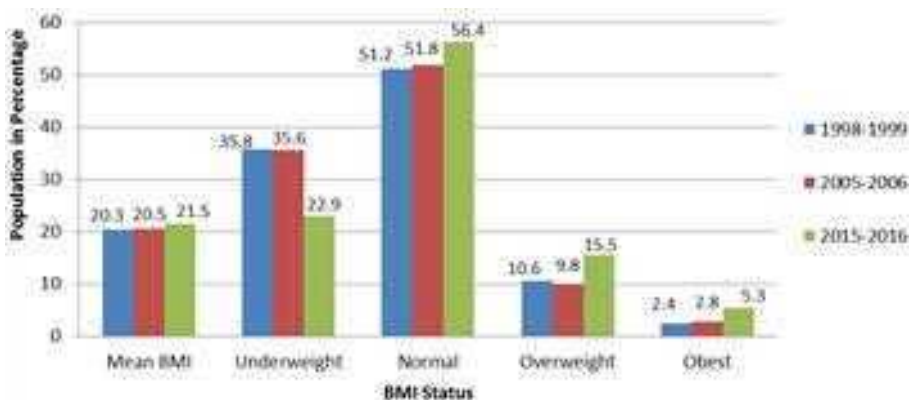
**Top 10 States/Union Territory of India with Normal BMI population
percent in order of ranking as for 2015-2016**

Ranking	Normal BMI male population		Normal BMI female population	
	State/ Union Territory	Percentage	State/ Union Territory	Percentage
1	Meghalaya	78.4	Meghalaya	75.7
2	Nagaland	74.7	Arunachal Pradesh	72.7
3	Mizoram	71.9	Nagaland	71.6
4	Arunachal Pradesh	71.1	Mizoram	70.6
5	Manipur	69.1	Sikkim	66.9
6	Haryana	68.7	Manipur	65.2
7	Tripura	68.4	Tripura	65.0
8	Jammu and Kashmir	68.0	Haryana	63.2
9	Lakshadweep	67.7	Chhattisgarh	61.4
10	Assam	66.4	Uttarakhand	61.1

Source: NFHS data.

Strategy for Management and Prevention

It is globally known fact that, excessive weight gain carries significant high mortality health risks diseases - cancers, diabetes, heart diseases and strokes. And it is not a time to keep watching the menace, allowing ourselves to be controlled by a “pandemic” but to address it through timely intervention. Swinging back the pendulum for achieving a healthier bodyweight and desirable BMI level is the need of the hour so as to prevent from undesirable morbid condition. For the last few decades, numerous scientists and organizations around the world have worked tirelessly to address the issue of obesity though with only modest success. Continuous efforts are needed for improving and standardizing strategic planning for fighting this pandemic issue.

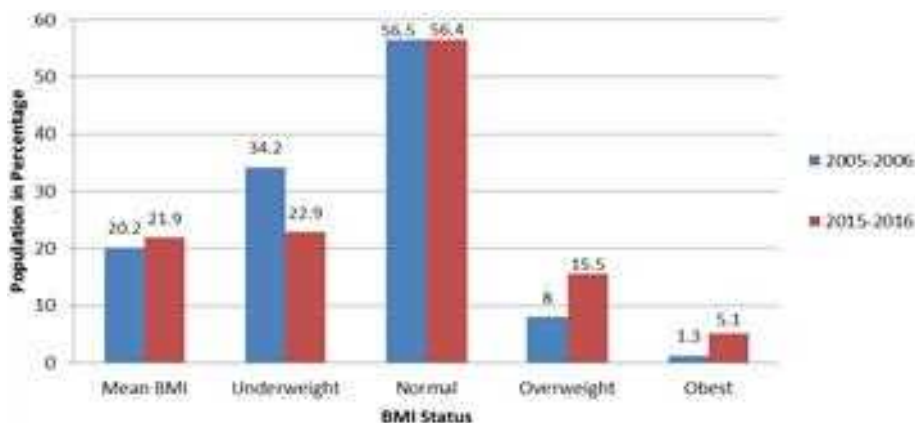


Source of Data: NFHS.

Figure 1. BMI trend of Indian women population observed from 1998 to 2016.

One of the most effective steps is changing the “obesogenic” environment toward reducing obesity. Reducing the excess caloric intake and equalizing it with energy expenditure by way of increasing physical activities is one of the best ways to fight obesity. There is no single or simple solution to the obesity epidemic. So this complex problem can be

addressed by a multifaceted approach. Policy makers, state and local organizations, business and community leaders, civil society organizations, educational institutions, childcare and healthcare professionals, and individuals must put their heads together and work together to create an environment that supports a healthy lifestyle. To reverse the obesity epidemic, community efforts should focus on supporting healthy eating and active living in a variety of settings. Learn about different efforts that can be used in early childhood care, hospitals, schools, and food service venues (CDC, 2015).



Source of Data: NFHS.

Figure 2. BMI trend of Indian male population observed from 2005 to 2016.

There are several ways by which state and local organizations and NGOs and Government allied system can create a supportive environment and awareness to the general public to promote healthy living behaviours that prevent obesity. The etiology of obesity is multifaceted; there are factors from multiple contexts, and interactions between factors that led to obesity are not yet well understood (Jhan et al., 2010). Indeed, a comprehensive approach is needed to potentially reverse the global pandemic of obesity (Jhan et al., 2010, Reed, 2011). Globally, there is also solid consensus on the steps taken up to stop the obesity epidemic which were outlined in the Food and Agriculture Organization/World Health Organization global strategy for the prevention of diet-related chronic diseases (WHO, 2003). Researchers and medical scientists can also play major roles by researching the epidemiology and etiology of obesity in order to fight this pandemic issue.

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Chapter 254

OBESITY AND SYNDROME X

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Metabolic Syndrome is a group of health conditions like obesity, high blood pressure, high blood sugar, high serum triglycerides and low high density lipoprotein (HDL) level. This combination is also known as Syndrome X. Hence, metabolic syndrome is a group of risk factors but not a disease. The main sign of metabolic syndrome is obesity. Obesity goes together with unhealthy level of cholesterol, high blood pressure and excess blood sugar (Ganong 2008).

Obesity turned into epidemic and became a public health challenge throughout the world. In past few years, the prevalence of obesity has been increased significantly across the world no matter whether it is a developed or developing or underdeveloped country. According to World health Organization, more than 1.9 billion adults aged 18 or older were reported overweight. Of these, over 650 million were obese. 39% of adults aged 18 year and over were overweight and 13% were obese in 2016 according to WHO report. 41 million children under the age of 5 were overweight or obese, whereas 340 million children and adolescent aged 5-19 were overweight or obese in 2016. Once considered to be a high-income country problem, overweight and obesity are now on the rise in low, and middle income countries also, particularly in urban settings (WHO 2012; Adhikari 2014; WHO 2018).

Obesity is a health problem associated with accelerated atherosclerosis and increased incidence of gall bladder and other diseases like type two diabetes. Not only that, recent studies reported death from many kinds of cancer in obese people. The causes for obesity in general population are due to multiple reasons. The primary cause of obesity is excess intake of energy over energy expenditure. The other causes are genetic and decrease sensitivity to leptin. Genetic factors are also responsible for obesity in some cases and causes excessive accumulation of body fat. Though, genetic tendency does not necessarily cause obesity, but it helps to accumulate more fat in right environment for the genetically susceptible individuals. A faulty gene or obese gene inside the fat cell produce Leptin, which after entering into blood, stimulates the hypothalamic area which controls the appetite and metabolism, causing

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fat accumulation. But genetic factors are not the reason for worldwide obesity epidemic. Instead, misbalance between energy intake and energy expenditure is the main reason for obesity (Frisch et al. 1987; Frisch et al. 1989; Bouchard et al. 1990; Stager & Halter 1995; Bouchard 1997; Fogelholm et al. 1998; Elchebly 1999).

While expressing body composition and related health risks of excessive body fat, three terms are used -over weight, overfat and obese. There is a confusion over the meaning of precise terms for overweight, overfat, and obese. Each term has a different meaning when using in different circumstances. Still there is a need to make a distinction between overweight, overfat and obese during interpretation. In most cases the term overweight is meant for an overfat condition even in the absence of accompanying body fat. Within this context, obesity then refers at the extreme of overweight continuum. This is precisely the frame of reference which is used to define the body fat range by means of BMI. Thus, weight-for-height at a given age has provided the most suitable index to express body fat and accompanying health risks. However, the overweight refers to a body weight greater than the average for stature. Overweight is not always due to presence of fat, it may be due to presence of muscle mass. For example, man with more muscle mass will be overweight (male power athletes). The overweight condition may or may not go with glucose intolerance, insulin resistance, dyslipidemia, and hypertension (e.g., physically fit overfat men and women). But obesity or overfat condition will go with one or all of the following components of the syndrome X like insulin resistance, glucose intolerance, dyslipidemia, type 2 diabetes, hypertension, high serum triglycerides, elevated plasma leptin concentrations, increased visceral adipose tissue, and increased risk of coronary heart disease and cancer etc. Syndrome X is related with excess body fat not with excess body weight which is due to more muscle mass or having more mesomorphic component which was revealed by different studies. Person may be overweight or overfat but does not have the syndrome X sign and symptoms. Men above 20% and women above 30% may be considered as overfat but it may vary population to population.

There are two types of regional fat distribution. When fat deposits more in abdominal area causing obesity, is called Android type obesity. This is particularly internal visceral deposition which is due to catecholamine secretion resulting lively lipolysis of tissues. The other type of deposition where fat deposit more in gluteal and femoral region, is called as Gynoid type obesity. The Android type obesity which causes deposition of more fat in central region causes heart disease. For men, percentage of visceral fat increases gradually with age, whereas in women, it starts at the onset of menopause. In Android-type obesity where fat deposits centrally, results risk of hyperinsulinemia, glucose intolerance, type 2 diabetes, hypertriglyceridemia, endometrial cancer, hypercholesterolemia and negative altered lipoprotein profile, hypertension, and atherosclerosis. The waist to hip ratio can be considered as an indicator of health risk when the ratio exceeds 0.80 for women and 0.95 for men. Excess fat distribution in abdomen area also increases the risk for colorectal cancer. Thus Android -type obesity has a greater risk than gynoid-type obesity where fat deposit at thighs and buttocks instead of central region of the body.

Less energy expenditure than energy intake causes fat accumulation which results body weight gain. Similarly when energy expenditure is more than energy intake causes weight loss. Thus three ways can reduce body weight. If calorie intake goes down below the daily energy requirement by dieting, it causes weight loss. Similarly, when energy expenditure exceed than normal calorie intake by means of physical activities causes weight loss. One

more method, when reducing the daily calorie intake by dieting but increasing the daily energy expenditure by means of physical activities, causes weight loss.

Weight loss through dietary restriction for short period results more water and carbohydrate loss per unit weight loss than the loss of fat. But dieting by low carbohydrate for long period may have some adverse effects which are dehydration, frequent urination, muscle cramp, constipation, irregular menstruation etc. Studies reveal that long term maintenance of weight loss through dietary restriction could be followed by return of lost weight within few years once restriction is stopped. Though careful dieting results weight loss but it may cause loss of Fat Free Mass (FFM), lethargy, possible malnutrition, and depressed resting metabolism (Miller 1999; Jeffrey et al. 2000; National Task Force 2000).

The best way to reduce body weight or excess body fat is regular physical exercise. Increased physical activity with dietary restriction causes weight loss more effectively than long term caloric restriction alone. Aerobic exercise and resistance training are more effective for weight loss for obese population. Aerobic exercise reduces the amount of fat and resistance training increase muscle strength and muscle mass which ultimately increase Fat Free Mass (FFM). Studies revealed that 40 -50 min aerobic exercise comprises of running and jogging for five days a week for 3-4 months significantly reduces excess body fat for obese population (vanEtten et al. 1994; Kraemer et al. 1995; Owens et al. 1999). Active children gain more Fat Free Mass (FFM) and loss total fat compare to their inactive children. Similarly, adolescent males who do regular aerobic exercise, reduce total body fat significantly faster than their sedentary counterparts.

Aerobic exercise or endurance run very effective for the obese population to reduce excess body weight by burning excess body fat. Endurance run or aerobic exercises increase the aerobic metabolism where energy releases from the breakdown of carbohydrate and fat in the presence of oxygen.. Walking, jogging, running, biking, aerobic dances are the best examples of aerobic exercises which help the obese people to reduce fat as well improve cardiovascular fitness, reduce syndrome X risk factors. While walking, it is recommended for more than one hours walking with fast pace for 3-4 days in a week. If someone wants jogging, it is recommended to walk first, then after few weeks start jogging and then running gradually. Biking is also very good aerobic exercise. Obese people also can join with aerobic dance program in a gymnasium which is also an effective aerobic exercise for reducing excess body fat. Dancing is also an effective aerobic exercise. But before starting any exercise program, one must see the family physician if they already have syndrome X rich factors and should take the physicians advice before any aerobic exercise program.

To fight against the obesity epidemic, promotion of aerobic exercise is needed which will increase the total energy expenditure significantly and regularly rather than increase exercise intensity. An obese person can expend more calories if he or she starts with slow walking or jogging with simply extending for long duration as duration of exercise significantly affects fat loss. It is important to note that recommended aerobic exercise should be minimum 3 days in week to have a good impact on fat loss. Regular aerobic exercise delay lean tissue loss, while resistance training increases Fat Free Mass. To combat against obesity and syndrome X, aerobic exercise should be popularized more and more across the world.

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Chapter 255

SYNDROME X: SOME COMMON DETERMINANTS WORLDWIDE

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Syndrome X or Metabolic Syndrome (MetS) is defined as a constellation of several cardiovascular disease (CVD) risk factors including genetic and environmental factors that is responsible for ultimate predisposition of the disease (Grundy 2005). The constellation of centrally distributed obesity; decreased high density lipoprotein cholesterol (HDLc); elevated triglycerides; elevated blood pressure and hyperglycemia is known as the MetS. Persons with MetS are at twice the risk for CVD compared with those without the syndrome. It further raises the risk for type 2 diabetes mellitus (T2DM) by about five-fold (Zimmet et al., 2005; Grundy et al., 2008). This chapter will highlight the common determinants/factors associated with Syndrome X worldwide, which include: Family history of chronic diseases, Physical Inactivity, Dietary Intake of Fatty Acids, and Epigenetic Modifications.

FAMILY HISTORY OF CHRONIC DISEASES

Most of the common chronic diseases are the result of interactions between multiple genetic variants and environmental vis-à-vis lifestyle factors. Although there have been significant advances in the last decade in the understanding of our genome, there are certain limitations in epidemiological and analytic approaches to studying the effects of chronic diseases. Family history has been shown to be a risk factor for a majority of chronic diseases of public health significance, including Syndrome X, CVD, diabetes etc. Family history of specific diseases reflects the consequences of genetic susceptibility, shared environment and common behaviors (Yoon et al., 2002). Family history has been recognized in clinical medicine as an important, yet non-modifiable, disease risk factor that when present could

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influence the probability of a suspected diagnosis. However, collection and interpretation of family history has rarely been applied in the practice of preventive medicine to assess disease risk and influence early detection and prevention strategies (Scheuner et al., 1997; Williams et al., 2001). The advantages of family history over other genomic tools include a lower cost, greater acceptability, and a reflection of shared genetic and environmental factors. However, the utility of family history in public health has been poorly explored (Valdez et al., 2010). Professional guidelines usually include family history to assess health risk, initiate interventions, and motivate behavioral changes.

Family history of diabetes is not only a risk factor for the disease but is also positively associated with risk awareness and risk-reducing behaviors. It may provide a useful screening tool for detection and prevention of diabetes (Hariri et al., 2006). In a study among the adult Chinese, it was found that sufficient physical activity and negative family history of diabetes might jointly reduce the risk of developing hyperglycemia and T2DM (Xu et al., 2011). In the US population, family history of diabetes showed significant, independent, and graded association with the prevalence of diabetes. This association not only highlights the importance of shared genes and environment in diabetes but also opens the possibility of formally adding family history to public health strategies aimed at detecting and preventing the disease (Valdez et al., 2007). In another study on a nationally representative sample of US adults without diabetes, family history of diabetes showed a significant, independent association with syndrome X and its traits. This association supports the idea that shared genes and environment contribute to the expression of complex traits such as diabetes and syndrome X (Ghosh et al., 2010). Evidence suggests that family history by itself is most useful for predicting disease when there are multiple family members affected, the relationship among relatives is close, and disease is premature, that is, it occurs at younger ages than would be expected. It has been mentioned that family history information in combination with other known risk factors could be used to provide more personalized information about our risk for common diseases (Yoon et al., 2002). Moreover, it has been suggested that adding family history of diabetes could provide significant improvements in detecting undiagnosed diabetes (Yang et al., 2010). In another study, it was found that not only the adults, even the youths with a positive family history showed signs of increased risk for these conditions which indicates the importance of family history approach to screening for children at risk of diabetes and CVD (Valdez et al., 2007). In a study from India, it was found that individuals with positive family history of diabetes had significantly higher prevalence of syndrome X and its confounding factors as compared to their counterparts (Das et al., 2012).

It suggests that family history could be used as a tool for genomic studies among the Asian Indians as well as in other world populations. It is however reasonable to argue that in developing countries including India, a large section of the community remains undiagnosed and therefore accuracy of self-reported family history could be challenging. In addition to risk assessment, family history information can be used to personalize health messages, which are potentially more effective in promoting healthy lifestyles than standardized health messages (Janssens et al., 2012). Having a family history of a disease increases its salience and does not change one's perceived ability to prevent the disease (Acheson et al., 2010). To establish family history as a public health tool, it needs to be evaluated within the ACCE (analytical validity; clinical validity; clinical utility; and ethical, legal, and social issues) framework. These advances will help realize the potential of family history as a public health tool (Valdez

et al., 2010). It seems that population screening would be of substantial importance for further research as family history of chronic diseases plays a vital role in better understanding of the etiological factors related to such complex traits, and hence could be used as a tool for preventive strategies.

PHYSICAL INACTIVITY

The identification and modification of the root cause, overweight/obesity, physical inactivity, and the closely associated condition - syndrome X, needs to be one of the initial strategies that are addressed by the clinician (Borgman et al., 2006). Each component of syndrome X predisposes people to atherosclerosis, and when clustered together, these components promote atherosclerosis even more prominently. It has been found that lifestyle modification, such as physical activity level (PAL) and dietary habits reduces the risk of syndrome X (Yao et al., 2003; Katzmarzyk et al., Panagiotakos et al., 2004).

Studies have shown that sedentary lifestyle could predict the development of syndrome X. Both vigorous and moderate leisure-time activities were found to be beneficial to the metabolic syndrome cluster of cardiovascular risk factors among the adult men and women of U.K It was suggested that even modest increases in physical activity was worthwhile in public health targets (Rennie et al., 2003). In a study from India, it was found that individuals with low physical activity level (PAL) had much higher prevalence of MetS than individuals with moderate PAL. The lowest prevalence was observed among the individuals with high PAL (Das et al., 2012). It has been evidenced that Asian Indians who are physically active have a favorable metabolic profile which highlights the need to encourage physical activity in Asian Indian immigrants, particularly women, to reduce prevalence of MetS (Misra et al., 2005). Physical inactivity has also been found to be associated with the components of MetS and coronary artery disease (CAD) among the urban south Indian population. Lifestyle changes focusing on increasing physical activity supposed to prevent the exploding epidemic of MetS and CAD in India (Mohan et al., 2005).

The China National Nutrition and Health Survey (2002) reported that individuals who were active or very active were 40% less likely to have MetS compared with those who were leading sedentary life (Ma et al., 2008). Among the middle-aged and old Chinese adults, physically active individuals were found to have been associated with a better profile of inflammatory factors and adipocytokines and a reduced risk of having MetS (Zhijie et al., 2009). In a Finnish cohort study, baseline total leisure-time physical activity was found to be inversely associated with the risk of developing MetS during a 4-year follow-up (Laaksonen et al., 2002). In an another study among the adult men and women of Chinese Taipei, it was also found high amount of physical activity was inversely correlated with the left ventricular hypertrophy (LVH) and prevalence of MetS (Dao et al., 2009). Moderate and vigorous physical leisure-time activities were each associated with reduced risk of being classified with MetS independently of age, smoking, and high alcohol intake both among the U.S. men and women (Rennie et al., 2003). Total physical activity (measured as habitual energy expenditure) and fitness (measured as maximal oxygen consumption per kilogram) shown to have independent effects on the components of MetS (Wareham et al., 1998). It has been found that insulin action could be modulated by body weight and physical fitness which is a

core feature of MetS (Reaven 2001). It therefore seems that modulation of MetS is a plausible biological pathway through which physical inactivity may affect cardiovascular health.

To prevent increasing morbidity and mortality due to obesity-related diabetes and CVD in developing countries, there seems to be an urgent need to initiate large-scale community intervention programs focusing on increased physical activity and healthier food options (Misra & Khurana 2008). In the World Health Survey (2002–2003), data of 212,021 adults from 51 countries, most of which were from developing countries showed that about 15% of men and 20% of women were at risk for chronic diseases due to physical inactivity (Guthold et al., 2008). Among the Asian Indian immigrants living in U.S (Misra et al., 2005) as well as those living in Indian (Mohan et al., 2005) it was found that physical inactivity was highly associated with MetS phenotypes. Although at what intensity activity may be of benefit in reducing the risk of MetS is not yet clearly understood, but one thing is clear that active lifestyle could curb this epidemic of obesity related metabolic disorders.

DIETARY INTAKE OF FATTY ACIDS

Lack of habitual physical activity and certain dietary patterns, including high saturated fatty acids (SFA) and low vegetable intakes, contribute to weight gain and increase the risk of metabolic disturbances (Feskens et al., 1995). Saturated fat intake is associated with increased risk of coronary heart disease (CHD); the greatest risk reduction is associated with poly unsaturated fatty acids (PUFA) followed by mono unsaturated fatty acids (MUFA) (Kris-Etherton et al., 2001). In Asian Indians, there existed significant inverse association between central obesity measures and intake of unsaturated fatty acids due to recent shift in dietary habits causing an increase in the prevalence of obesity and dyslipidemia in this region. It was that intake of saturated fat may be a major risk factor for the onset of MetS in adult Asian Indians. Moreover, it appears that it is not the total fat but the amount of saturated fat consumed in association with TFA:SFA, SFA:MUFA, and SFA:PUFA was adversely affecting the adiposity level, lipids, blood pressures, and blood glucose levels in this population and in turn cumulatively enhancing the possibility to predispose to MetS phenotypes ((Ghosh 2006; Ghosh 2007; Das et al., 2010). The findings of an adverse impact of TFA:SFA intake and inverse relation of adiposity with PUFA, i.e., protection of polyunsaturated fat concerning the association with MetS is in accordance with the finding of several other investigations (Das et al., 2010).

Certain dietary patterns, including high SFA and low vegetable intake, contribute to weight gain and increase the risk of metabolic disturbances, whereas such potentially modifiable lifestyle factors may reduce cardiovascular risk (Feskens et al., 1995; van Dam et al., 2002). In a study from India revealed that increased dietary ω -6 PUFA and saturated fat intake are significantly associated with fasting hyperinsulinemia and subclinical inflammation, respectively, and found to be responsible for the increasing prevalence of insulin resistance, the MetS and diabetes (Feskens et al., 1995; Misra & Misra 2003; Misra & Khurana 2009; Ghosh 2009). In another study, it was found that the dietary total fat may increase whereas linoleic acid intake may reduce the risk of MetS in Japanese descendants living in Brazil (Cardoso et al., 2005). Study from the United Arab Emirates (UAE) pointed out that poor dietary habits including consumption of high-energy foodstuffs, diets high in total carbohydrates, fat, and

simple sugars were associated with MetS (Al-Sarraj et al., 2010). In a multiethnic study (comprising of African-Americans, Whites and Hispanics) on healthy children aged 7–12 years revealed that diet composition was more closely related to the components of the MetS than was physical activity, with carbohydrate intake being adversely related to WC, TG levels, and glucose levels. Moreover, relationships among diet and MetS outcomes were stronger among African-American children (Casazza et al., 2009) reflecting ethnic variation. It seems that while dealing with MetS in Asian Indians, or any world populations, researchers and clinicians should consider obesity measures, metabolic profiles and dietary fatty acids simultaneously. Since it is not the amount of calorie intake but the amount of fatty acids which seems to be associated with obesity related metabolic disorders.

EPIGENETIC MODIFICATIONS

The term epigenetics itself describes the concept as ‘epi’ means above and it was Conrad Waddington who, in 1940, provided the first broad and operational definition of epigenetics as “the causal interactions between genes and their products, which bring the phenotype into being” (Waddington 1940). Epigenetics has been defined as the study of heritable changes in gene expression that occur in the absence of a change in the DNA sequence itself. In mammals, these changes are mediated through DNA methylation, covalent histone modifications, microRNA, and poly-comb group complex recruitment (Dolinoy 2008; Schwartz & Pirrotta., 2008). The epigenetic marks either alone or in combination alter the chromatin structure and function, and thereby promote or inhibit gene transcription. Therefore, chromatin is the ideal substrate for nutrient-sensitive transcriptional instructions, existing in multiple permutations leading to multiple phenotypes. In addition, the epigenetic state of chromatin can undergo transgenerational epigenetic inheritance, a process facilitated by the incomplete erasure of epigenetic modifications during gametogenesis and embryogenesis, resulting in a maintained epigenetic state in future generations (Bruce & Hanson 2010).

Susceptibility to Syndrome X has an inherited or familial component. Although some fixed genomic variations have been associated with high risk but such single nucleotide polymorphisms attribute very little to the overall risk in the population (Gluckman et al., 2007). Whereas, subtle alterations in gene expression are responsible for an increased risk of disease outcome in many members of the population to a variable extent, rather than genomic alterations, such as those involved in placental nutrient transport. In recent years, epigenetic regulation leading to such subtle modulations in gene expression (without a change in DNA sequence) of key metabolic genes has emerged as a contributing factor to increased susceptibility to Syndrome X (Bruce & Hanson 2010).

Positive natural selection describes the increase in the prevalence of beneficial traits in a population, and is one of the factors driving evolution. A trait under positive selection must be beneficial, thus increasing survival and reproduction, and the trait must also be heritable. This positive selection has been attributed to particular DNA variants that become more common since of the beneficial effects on those who carry them (Kelley & Swanson 2008). However, a trait that may be advantageous at one point in human history may be detrimental under different environmental conditions. Here comes the classic example of *‘thrifty*

genotype,' a concept coined by the geneticist James Neel to explain the prevalence of obesity and diabetes (Neel 1962). Neel hypothesized that people with diabetes often have allelic variations in certain genes that enable them to efficiently collect and utilize food. The human variations which were favorable in populations facing challenges of episodic undernutrition might be disadvantageous when food supplies became abundant. It provides a possible explanation for why the propensity to diabetes varies greatly among populations. Carriers of these variations are, therefore, at a high risk of developing obesity and diabetes when exposed to abundant and cheap supply of energy, and a dramatic reduction in energy expenditure. This thrifty genotype would have been beneficial during periods of history characterized by food instability (Stoger 2008). In contrast to the long-term nature of the selective forces that are hypothesized to have positively selected the thrifty genotype, epigenetic changes occur rapidly to alter metabolism. There are ways in which epigenetic changes increase disease risk, perhaps in combination with evolutionarily mediated phenotypes.

Throughout history, humans have had to cope with adverse environmental changes such as periods of plague or famine. Famines provide an ideal setting to examine the biological adaptation and long-term consequences of unfavorable conditions, especially during human development. One of the most well documented events is the Dutch Hunger during the winter of 1944–1945. It was suggested that epigenetic mechanisms underlie the increased incidence of Syndrome X in adults prenatally exposed to the Dutch famine and the transgenerational effects of prenatal exposure to the Dutch famine in the grandchildren of women exposed (Painter et al., 2008). A sex-specific increased risk of obesity, dyslipidemia, and cerebrocardiovascular-related deaths has been observed six decades later among those whose mothers were exposed to famine early in gestation (Kyle & Pichard 2006). The outcomes of these studies strongly support that *in utero* exposure to famine may result in adverse metabolic phenotypes, which depend on the sex of the exposed individual, and the timing of exposure during gestation as the embryo is more vulnerable around the time of conception. Similar observations inspired the Barker's hypothesis almost three decades ago, also known as the '*thrifty phenotype*' that malnutrition acts not as a selection acting over many generations to alter the genetic make-up of the population, rather the early environmental (including prenatal environment) influence acting in an individual to increase the susceptibility of the disease (Hales & Barker 2003) .

In Neel's hypothesis, entire populations have an increased predisposition to diabetes due to genetic selection. They are better adapted to different nutritional circumstances than those they experience today. In Baker's hypothesis, maladaptive responses occur as a result of environmentally induced alteration of physiology in the early life of the individual. Both hypotheses offer explanations of why the frequency of diabetes and obesity differ in different populations. People in the Indian subcontinent, for example, have faced undernutrition for many generations, and Indian babies (new born) are among the smallest in the world (Yajnik 2003). However, diabetes epidemic is of recent origin, and it is more common among urban than rural Indians despite the higher birth weight of urban babies. The two explanations (hypotheses) are therefore not necessarily exclusive and may complement each other. Then there is a third hypothesis called the '*common soil*' hypothesis as proposed by Lebovitz (2006) that diabetes and CVD might share underlying cause(s) – hence termed common soil. It was mentioned that insulin resistance is central to the progression from normal glucose tolerance to diabetes and to a constellation of CVD risk factors known as Syndrome X.

Changes in adipose tissue and metabolism (perhaps mediated through epigenetic changes) might link insulin resistance and visceral obesity – a condition that is common in diabetes.

Epigenetics may provide a mechanism by which developmental plasticity mediates developmental priming. Therefore, epigenetics may be the interface between nutritional stimuli during development and resulting phenotype, thus being central to the developmental origins of the Syndrome X (Bruce & Hanson 2010). The genomic information is the same in all our cells and during our entire lifespan, whereas, the epigenomic information varies from cell to cell and during the lifetime of the individual. An increased understanding of epigenetic mechanisms may lead to the development of novel and targeted therapies that will act not only at the risk-factor level, but also directly on the vascular system (Ordovas & Smith 2010). This makes epigenomic information more important for pharmacological interventions. In a recent epigenome wide association study (EWAS) it was found that methylation in *CPT1A* was significantly associated with syndrome X and it's confounding factors in both European and African ancestry participants. It indicated a promising epigenetic marker for metabolic disorder which could become useful for treatment target (Das et al., 2016).

Several compounds have been identified that are able to regulate DNA methyl transferase or histone deacetylase activity. DNA methylation is not just the driving force behind the developmental priming of disease but also a channel that transfers information of the transcriptional patterns required in a particular environment. Epigenetic modifications facilitate a transcriptional state, which may be inherited and may impart an increased risk of Syndrome X development in the context of unfavourable environmental conditions. Therefore, it is not the epigenetic landscape that is ultimately causal to the phenotype but the stimulus that it receives at the cellular level. This in part explains tissue-specific epigenetic modulations, because each particular tissue will receive specific stimuli and resides within a unique milieu (Bruce & Hanson 2010). Epigenetic control of key genes is central to the developmental priming of the metabolic syndrome (Syndrome X) phenotype, and provides a likely target for pharmacological therapies in near future.

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Chapter 256

BREAK THE CYCLE OF CHILDREN'S ENVIRONMENTAL HEALTH DISPARITIES

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ABSTRACT

Break the Cycle of Children's Environmental Health Disparities (*Break the cycle*) is an annual collaborative interdisciplinary research and training program involving university students in academic tracks that focus on the impact of adverse social, economic and environmental factors on children's health, development, and education. The target populations are communities where environmental hazards are related to circumstances of social and economic disadvantage. Each student develops a project that focuses on preventing or reducing adverse environmental factors to benefit the children who live in these communities. At the end of the project, the students present their studies and findings at a national conference, and write papers which are then published in a journal issue. The projects cover a range of factors that operate over the lifespan, and have an influence on individual, community, and social perspectives. Most importantly, they inform us about children's environmental health disparities, and propose solutions to reduce and eliminate health disparities and promote health equity for all children.

INTRODUCTION

The papers in this book represent the work of students who participated in the 12th Annual *Break the Cycle* program. The phrase *Break the Cycle* in this context uses the ecological construct of a cycle of environmental health disparities (Figure 1) and represents a strategy for reducing health disparities and promoting health equity among children who are vulnerable as a consequence of adverse social, economic environmental factors, thereby 'breaking the cycle'.

Children who grow up in poverty are often exposed to poor indoor air quality, which increases the risk for asthma and respiratory disorders, and to high lead levels from old paint which can result in brain damage. In addition, they are at risk for a variety of other environmental exposures, stresses, and abuses including food insecurity, housing insecurity, and fear of physical injury, with real experiences of neglect and abuse which, cumulatively, can result in the physiological phenomenon of chronically elevated cortisol levels and "toxic stress" which is associated with adverse structural and functional changes in the brain with life-long implications that can result in reduction in brain volume in white matter, in grey

matter, and specifically in the hippocampus and amygdala [1]. As they reach adolescence, these children are more likely to engage in risky behaviors, including unprotected sexual activity that can result in teenage pregnancies or sexually transmitted diseases, substance abuse, school failure, gang membership, and crimes which can result in incarceration or death from drugs or gun violence. The elevated cortisol levels associated with toxic stress also affect the cardiovascular, immune and hormonal systems, and, as adults, they are more likely to have adverse health outcomes such as obesity, diabetes, and hypertension, with associated morbidity and mortality [2].

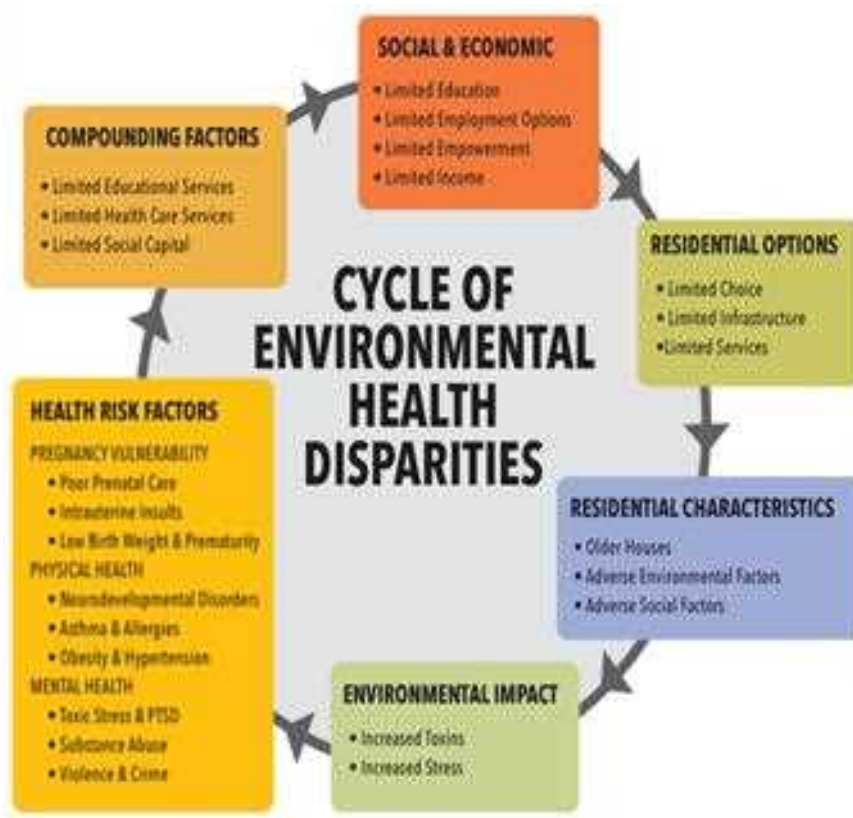


Figure 1. Cycle of environmental health disparities [3].

The physical, chemical, biological, and social environments that children experience before birth, early in life and through adolescence may have life-long consequences that also affect subsequent generations. There is ample evidence that children who grow up in poverty and experience adverse social and environmental factors will have more health problems, neurodevelopmental disorders, learning disabilities, attention difficulties, and school failure. These children have relatively poor educational opportunities and limited access to quality healthcare services, which contribute to the social determinants of adverse health and developmental outcomes [3]. The unfavorable health, developmental, and educational outcomes compromise the child's opportunity for economic and social success and often result in an intergenerational cycle. It is the codification of this construct that embodies the concept of the cycle of children's environmental health disparities. Figure 1 captures the

interrelationship between economic, social and environmental factors, and the health outcomes of children, as well as the intergenerational trajectory that serves to perpetuate the cycle.

BREAK THE CYCLE PROGRAM

“Break the Cycle of Children’s Environmental Health Disparities” (*Break the cycle*) is an annual collaborative interdisciplinary research and training program involving university students in academic tracks that focus on the impact of adverse social, economic, and environmental factors that affect children’s health, development, and education. The target populations are communities where environmental hazards are related to circumstances of social and economic disadvantage. Each student develops a project that focuses on preventing or reducing environment related disorders for children who live in these communities. At the conclusion of the project, the students present their studies and their findings at a national conference and write papers which are then published in a journal supplement devoted to the collection of projects from each given year [3].

Proposals are submitted by students to a competitive review process that evaluates the quality of the proposal, relevance to children’s environmental health disparities, creativity, and feasibility. The selected students will work with their academic mentors and with the *Break the cycle* faculty. The students and their mentors participate in monthly conference calls, during which the progress of each project is reviewed, additional perspectives are explored, and constructive guidance is provided. During these conference calls, the students and their mentors have an opportunity to communicate and collaborate with their counterparts at other universities.

Since the inception of the Break the cycle program in 2004-2005, we have had 11 annual programs and worked with over 100 students representing 30 different university departments in 10 states in the United States (US), as well as students from countries in Latin America, Europe, and Africa. To date, we have had nine monographs published in international journals and nine books in a public health series. In 2012, we completed a survey of past students who rated their experience with *Break the cycle* valuable, and many reported that they pursued careers relating to their *Break the cycle* projects [4].

We started the program with the expectation was that the projects would make a difference in improving the health and well-being of the children, their families, and their communities. We also envisioned that the students would be inspired to pursue careers that focused on reducing health disparities and in becoming our future leaders. Furthermore, because each student has a mentor at their home university, we were hopeful that the faculty mentors would add elements of the concept and literature on the subject into their curricula, and thereby promote further research and academic interest in this field (see Table 1).

We also expected that the participating students would inspire others in their academic, social and professional circles, and that the interdisciplinary nature of the program with participation of students at other universities around the world would be stimulating and inspiring (see Table 2). The 2012 survey also showed that the students derived significant benefit from all aspects of their participation in the process, which included the practical aspects of conducting a research project, experience in preparing and delivering a

presentation and writing a manuscript. Each student gained knowledge about children's environmental health and environmental health disparities, and was exposed to different perspectives from the other student projects. Many participants reported that their participation in the program influenced their career choice [4].

Table 1. Project guidelines

- University faculty identify students who have an interest in this topic area, and encourage and support the student in the selection of an idea for research, specifically looking at projects that address environmental factors that adversely affect the health of children living in circumstances of social and economic disadvantage. Alternatively, students interested in a specific project can identify mentors to work with them.
- The students submit a proposal which is subject to review by the *Break the cycle* faculty. The process is competitive with approximately 10 projects being selected each year.
- During the project period, there are monthly conference calls with all students and mentors to monitor the progress of the research projects, share ideas, and assure that the project is consistent with the spirit of the *Break the cycle* concept.
- At the end of the project period, the students present their projects at a conference with a keynote speaker of national stature.
- The students write papers on their projects, which are submitted for publication in an international journal as a monograph of the *Break the cycle* projects. The papers are also published as chapters in a book.
- Funding of travel expenses within the United States and accommodation for the conference are provided for the student and faculty mentor. A modest stipend is provided to the students once they have completed the project and submitted their paper.
- The progress and careers of the participating students are tracked to evaluate the impact of their participation in the *Break the cycle* program.

Table 2. Desired outcome

- To inspire students from a variety of academic disciplines to explore the relationship between adverse social, economic and environmental factors and the health, development and education of children and to creatively generate strategies to address the challenges
- To collaborate with an interdisciplinary team of academic leaders from different universities and colleges to creatively examine the broader issues of this topic area
- To encourage faculty at universities who participate in this program to promote academic interest and social awareness in children's environmental health particularly in children's environmental health disparities
- To cultivate future leaders

BREAK THE CYCLE 12 PROJECTS

We are pleased again to have a wonderful interdisciplinary array of creative projects developed by students in six states in the US and one from Zambia. The papers in this volume cover the lifespan from consideration of prenatal vulnerabilities of the fetus, to the outcomes

of premature newborn infants through personal, family, community and social perspectives. They look at health, nutrition, education, environmental exposures, legal aid, incarceration, education of children and community engagement. Of note is that they cover the full cycle of children's environmental health disparities and provide solutions to reduce and eliminate these disparities. The following are brief reviews of the *Break the cycle* 12 student projects:

Prenatal Exposures and Their Consequences

We have been aware of concerns around the adverse effects of prenatal exposures on the developing fetus for decades. Our first shocked realization came in the late 1950s, when we recognized that infants born to mothers who had taken the drug thalidomide had limb reduction anomalies directly attributable to the drug [5]. The drug was immediately withdrawn from the market, the field of teratology gained credence and, since then, we have become aware of the risks to the developing fetus of maternal ingestion of medications. In the 1960's, we recognized that infections during pregnancy such as rubella could result in significant harm to the developing fetus [6]. We now recognize that vaccines administered prior to and during pregnancy prevent intrauterine infections and result in improved outcomes for mothers and babies [7]. In the 1970s, we learned that alcohol consumption during pregnancy can result in serious physical and neurological effects and abnormal fetal development and infant behavior [8]. We have become increasingly aware that infectious agents, chemicals, and maternal behaviors such as smoking and taking drugs can adversely affect the fetus [9].

In the paper by Pratibha Agarwal, MD, a pediatric resident at the East Tennessee State University in Johnson City, Tennessee, we get a glimpse into the current national epidemic of opioid abuse. Opioid addiction has led to a startling increase in drug related deaths in the USA. When pregnant women abuse opioids, it leads to the clinical phenomenon of Neonatal Abstinence Syndrome (NAS) [10]. Tennessee and Kentucky have higher death rates from overdose of opioid painkillers, combined with other drugs such as heroin, than other states and both have seen an increase in the death rate from 2014-2015 [11]. The involved population tends to be Caucasian rather than African-American. This phenomenon is related to education, employment, changing socioeconomic status, and disparities in access to health care. In this study, the babies with neonatal abstinence syndrome were predominantly children of mothers who were poor, had limited education, had unstable family relationships, and had used multiple substances.

As of this writing, steps have been taken to reduce the risk of addiction by raising awareness nationally particularly among prescribing physicians, limiting the number of tablets that can be prescribed, and developing rehabilitation programs based on the Alcoholics Anonymous (AA) model. It is also interesting to note that many individuals who are addicted to opioids end up incarcerated and become the mothers who are described in the paper by Tatenda Mangurenje in this volume. It is also of note that the US has the highest rate of incarceration in the world and some of the reason (as stated in the referenced paper) relates to its policy on drugs. In contrast to the US, other countries view substance abuse as an illness that requires treatment, and have a lower rate of substance abuse, lower rates of mortality from drugs, and much lower incarceration rates.

Promoting Breastfeeding among Adolescent Mothers

For educated mothers, the benefits of breastfeeding may appear obvious. Breast milk is readily available, provides incalculable nutrients with immune properties, and has been the sole sources of nutrition for infants since the dawn of mammalian evolution. Breastfeeding is convenient, inexpensive, and it promotes mother infant bonding. What happened to change breastfeeding practices? Historically [12], high maternal mortality rates threatened the survival of the infant as there would be no source of nutrition, and, unless a substitute 'wet nurse' could be found, the infant would be at risk for dying of malnutrition. The use of milk from domestic animals provided that life-saving intervention. Initially, improvised modes of dispensing the milk were used, but as technology advanced, glass bottles with modified 'nipples' were developed. As our technology advanced, a milk substitute was developed, and bottles and artificial nipples were produced. The marketing of this form of infant feeding resulted in a dramatic drop in breast feeding and almost total reliance on artificial formula feeds. While this was a regrettable trend among high resource locales, it was devastating in low resource areas as it significantly contributed to illness and high infant mortality from malnutrition and diarrheal diseases.

In low resource areas of the world, water is added to a milk powder to provide liquid formula. Poor sanitation and the use of contaminated water for the formula is likely to result in diarrheal disease. Low income mothers tend to use more water than recommended to stretch their supply of milk powder, which results in malnutrition and susceptibility to infections such as pneumonia, tuberculosis and diarrheal illnesses; all of which can be fatal in malnourished infants. The United Nations Children's Fund (UNICEF) reports that breastfed children have at least six times greater chance of survival in the early months than non-breastfed children, and that an exclusively breastfed child is 14 times less likely to die in the first six months than a non-breastfed child. Despite this, it is estimated that only 39 percent of children less than six months of age in the developing world are exclusively breastfed [13]. There is still much work to do to promote breastfeeding, and thereby reduce infant mortality in low resource countries, as well as in countries where there is high income disparity and consequently high disparities in children's health. The paper by Colleen Clark, a student, in the Public Health Program, Center for Graduate Studies at Lenoir-Rhyne University, in Asheville, North Carolina, looks at helping to promote breast feeding among low income adolescent mothers and thereby break the cycle for their children and future generations – a worthy project with substantial benefits and need for expansion and replication.

Coordination of Care for Premature Infants and Their Families

Since the 1970s, when technology was harnessed to improve the survival of premature infants, we have witnessed a dramatic increase in the survival rate of extremely premature infants. We now see survival of infants born at 23-24 weeks gestation weighing a little over 500 grams or 1 pound. Premature infants may spend 3-5 months in the neonatal intensive care unit (NICU), where the costs in the US now average \$3,000 a day; the average cost of NICU care of a premature infant is \$40,000. With increasing prematurity, there is an increasing likelihood of long term neurological and medical complications, which come with their own

long-term costs. But costs in dollars are only part of the picture; the emotional, psychological, social and economic burdens that families of premature infants face are complex and daunting.

Although the over-all rate of prematurity is 1 in 10 pregnancies, poor African American women have a much higher rate than Caucasian women – 13% vs 9% [14]. Many of these premature infants are born into poorer African American families, with limited access to quality healthcare, early intervention services, good education, or legal assistance. These factors make the long-term outcome for the children much less promising, perpetuating the cycle of health disparities.

In the paper by Lea Redd, a student in the Department of Pediatrics and Neonatology, at the University of Chicago Medical Center, in Chicago, Illinois, the mobilization and utilization of the Health Law Partnerships to assist low income-low resource families in their practical struggles was demonstrated to be of significant benefit in breaking that cycle. This increased access led to improved developmental outcomes for the infants and less stress for the mothers. There are many Medical Legal Partnerships across the country, and the recommendation is that every NICU should have such a program in place to enhance services for the vulnerable infants and their families [15].

Impact of Early Life Housing on Child Behavior at Age Seven

Children who are born into circumstances of social and economic disadvantage tend to suffer additional adverse life experiences that can affect their physical and mental health and well-being during childhood, adolescence and adult life. Adverse childhood experiences [16], such as death of a family member, a move, and illness or natural disaster, do not necessarily result in long term adverse consequences if there is a supportive and nurturing family member to help with the reestablishment of a regular life routine, indeed, the children recover and may even be strengthened by their experiences. However, repeated and relentless emotional and physical assaults without the buffer of a supportive and nurturing family member can have serious lifelong negative impacts on the child's health. These adverse experiences may come in the form of neglect, with emotional, physical, or sexual abuse, with fear of abuse, and with insecurity of different types including food insecurity, financial insecurity, and/or living/housing insecurity. These children suffer from chronically elevated stress hormones in the form of cortisol which, in the long term, has a damaging effect on the hormone system, the immune system, and brain metabolism and brain architecture. This state has been termed 'toxic stress', and is associated with physical and mental disorders in childhood, adolescence and adulthood, with a reduced life expectancy from drugs and gun violence in young adulthood, to chronic cardiovascular, pulmonary, metabolic and immune disorders in older adults [17].

In her project on housing and child behavior, Abby Gaylord, from the Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York City, explores the impact of housing insecurity on the development and behavior of children at age seven years. She notes that there is a serious pattern among low income families who cannot afford stable housing and must settle for less than optimal rental homes. These homes are likely to be old, with poor heating and ventilation systems and increased risk

of lead exposure due to deteriorated old paint. These homes are often situated in older decaying neighborhoods, with air, water and soil pollution, increased exposure to a drug culture, and crime and poor quality schools. Families face the monthly struggle of paying rent to avoid eviction and the inconvenience and expense of moving to a home of comparable quality. In his book entitled "Eviction," Matthew Desmond paints the picture of poor families in Milwaukee who struggle to find and stay in safe and secure homes. Unreliable employment and unforeseen expenses lead to frequent difficulties in paying rent, which leads to evictions by landlords trying to maintain properties and make a profit [18].

In her study, Abby Gaylord found that children who experienced multiple moves were more likely to have adverse developmental and behavioral consequences. She also found that material hardships were strongly associated with an increased likelihood of moves, and explored strategies to reduce socioeconomic strain, which, she postulates, will have the greatest impact on breaking the cycle in reducing children's health disparities related to housing instability.

Home, Belonging and the Incarcerated Mother: A Study on the Effects of Mass Incarceration on Children's Behavioral Health Outcomes

The original conceptualization of the "Cycle of environmental health disparities" was focused more on the social and economic elements with poverty at its core and hence poor education and poor health care services (see Figure 2) [19]. At the time, we characterized the cycle as involving children growing up in poverty with limited education and employment opportunities, and a dim view of the future which lead to disillusionment and despair. As a consequence of limited mental health care services, the adolescents would turn to tobacco, alcohol and other drugs to self-medicate. Young women with no access to contraception would get pregnant, receive little prenatal care, abuse illicit drugs, and often deliver premature infants. These children would grow up at a neurological disadvantage from birth and then enter into unstable homes with the possibilities of neglect and abuse. Thus the cycle would be repeated. What we had not written into our narrative at the time were the results of substance abuse and its behavioral consequences, and the lack of employment and income, leading to the need for getting money by less than socially acceptable means such as stealing or prostitution. The next step in this process is not difficult to see – arrest and incarceration. Although this is the likely mechanism for incarceration for many, the harsh laws that were enacted in the 1990's have resulted in an explosion in the prison population that puts the US at the top of the list of countries in the world, with a per capita incarceration rate of greater than 700 per 100,000 of the population! In Russia the rate is 581 and at 145 in Britain which is at about the midpoint worldwide [20].

This prison population not only costs the US taxpayer approximately \$50,000 per year per person in prison, but the real cost to families and society is far greater because it perpetuates the dissolution of the family as well as the community and society, robbing children of opportunities to have parents in their lives and of society to have active participating and contributing members of society to build and stabilize society.

Tatenda Mangunje, a student in the Department of Anthropology and Global Health at Emory University in Atlanta, Georgia, studied a population of women in prison and looked at

the impact on the children's development and behavior. Needless to say, she found that the children whose mothers were in prison suffered significantly, not only in the present, but for their futures. She challenges us to look at ways of protecting the children, whose mothers are incarcerated, to help them to survive the difficult times and thereby have more chance of success in life. The greater challenge is to our society, to change the harsh and unfair practices and help to assure that future generations of adolescents and parents-to-be have opportunities to have a good education and the hope of gainful and meaningful employment. That would be a good outcome.



Figure 2. The original conceptualization of the “Cycle of environmental health disparities.”

Neurodevelopmental Outcomes of Recent Exposure to DDT in Children of Selected Communities of Zambia

DDT (dichloro-diphenyl-trichloroethane) was developed as the first of the modern synthetic insecticides in the 1940s [21]. It was initially used with great effect to combat malaria, typhus, and the other insect-borne human diseases among both military and civilian populations. It also was effective for insect control in crop and livestock production, institutions, homes, and gardens. The problem, however, arose with its widespread and indiscriminate use being sprayed from trucks and from airplanes over vast areas, resulting in extensive exposures and bioaccumulation with a set of unanticipated consequences. Because it is one of the fat soluble persistent organic compounds, it bio-accumulates in fatty tissues, particularly the brain, and can result in a variety of neurological effects in humans as well as in animals. It can also affect the liver, kidneys, and immune system. Because DDT enters the

bodies of the insects, and birds eat the dying insects, the toxin bioaccumulates in the birds and can cause brain damage. In addition, it interferes with calcium metabolism, resulting in weak egg shells which then results in the breaking of the shells when the birds sit on the eggs to incubate them. This phenomenon, along with the acute brain and liver toxicity associated with high doses of the DDT, resulted in a dramatic drop in certain bird species, with local extinctions in some areas. This threat to birds was the centerpiece of the 1962 book “Silent Spring” by Rachel Carson [22] that resulted in sufficient scrutiny on DDT to lead to the banning of DDT in the USA and then subsequently in other parts of the world. It was also a factor in the formation of the US Environmental Protection Agency (EPA).

In reality, Carson did not advocate that DDT should be totally banned; she recommended measured and judicious use, citing concerns around toxicity to humans and animals, concern around upsetting the ecosystem and possibly resulting in the proliferation of other pests, and the concern around the development of resistance among the insects, particularly the mosquito. The use of DDT had effectively eradicated malaria from some parts of the world, which remains a scourge and cause of death for much of the developing world. In Africa, malaria is the fourth leading cause of death after HIV/AIDS, respiratory infections, and diarrhea. It therefore is critically important to reduce or eliminate the malaria mosquito; it is in this context that careful and judicious use of DDT could be warranted. In her paper, Nosiku Munyinda, from the Department of Public Health at the University of Zambia in Lusaka, Zambia, examined the possible adverse neurodevelopmental consequences on children of the use of DDT in preventing malaria in a poor area of Lusaka. Interestingly, she did not find a correlation with DDT levels and neurodevelopmental problems. On the contrary, she found that psychological, social, and economic factors played a larger role in adverse developmental outcomes. It may be that the DDT levels were not sufficient to affect the central nervous system (CNS) or that positive psychological and social factors could mitigate the adverse effects of the DDT. As always in medical management, the risks and benefits need to be thoughtfully weighed to determine the best possible approach to management. But ultimately, wherever there is poverty, there is more likely to be an adverse effect on a child's development. We know that early intervention can make a difference even for the poorest and most involved infants and children in the poorest countries [23], so early intervention should be provided for all infants in low resource communities.

Racial Disparities in Access to Municipal Water Supplies in the American South: Impacts on Children's Health

In high resource countries, we take clean water for granted; we turn on our taps and there is clean water that we can drink – we assume safety. But this is not the case for many parts of the world with limited resources. The World Health Organization (WHO) reports that 884 million people lack even a basic drinking-water service; including 159 million people who are dependent on surface water, and more than double that number use water that is potentially contaminated, resulting in an estimated 500,000 deaths from diarrheal illnesses a year – most of those are children [24]. The Sustainable Development Goal #6 is to *ensure availability and sustainable management of water and sanitation for all* so there is a significant challenge ahead [25]. In our 10th Annual Break the Cycle program, Chalwe Chanda, a student at the

University of Zambia, looked at environmental risk factors in children living in a poor area on Lusaka, Zambia and found a significant association between the combined factors of water supply and sanitation with malnutrition in the children [26]. We do know that diarrheal illness in a malnourished child is associated with a high mortality.

This year, Frank Stillo, a student in the Gillings School of Global Public Health, at the University of North Carolina in Chapel Hill, looked at an African American community in North Carolina, where the water source was from unregulated private wells rather than from municipal sources, and reflects health disparities attributed to social and economic factors. Frank and his mentor, Jackie McDonald Gibson had already reported on the presence of microbial contaminants in this water source [27], and, in this study, they looked at the presence of lead contamination. The presence of lead in drinking water is of serious concern for children whose developing brains are acutely sensitive to lead, which can result in significant functional impairment. This reality was highlighted in the recent finding of contamination in the Flint, Michigan water supply [28].

The lesson from these studies is that we need to be constantly vigilant about our water supply, whether it is the water supply for low resource regions of the world or for low income minority or marginalized populations in high resource counties.

Interactive Educational Lead Hazards Class to Children at the Boys and Girls Club in Metro Atlanta

Lead is the most common heavy metal neurotoxin in our environment. Human history has a trail of lead and lead toxicity for thousands of years. In the mid-20th century, lead was present in significant quantities in gasoline and paint, and was the primary source of lead poisoning for children sometimes resulting in severe and permanent brain damage. During that time, clinicians were concerned with lead levels higher than 60 micrograms per deciliter ($\mu\text{g}/\text{dL}$). These levels resulted in severe encephalopathy and were an indication for chelation. Thanks to the indefatigable advocacy of Dr Herbert Needleman (1927-2017) for prevention of lead poisoning in children by removing lead from gasoline and paints [29], we have seen a substantial decline in the blood lead levels of children, and the recognition of developmental and behavioral consequences of lead levels below 5 $\mu\text{g}/\text{dL}$ [30]. The problem is that lead persists in our environment, mainly in older houses that still contain lead paint. It also persists in soil and in water, such as in the water supply in Flint, Michigan [28] and, as noted in the paper by Stillo in this volume, in other unexpected sources of water. There is also lead in some pottery, glassware, toys and folk remedies from other countries. In fact, internationally there have been major epidemics of lead poisoning, as an example from illegal mining in Nigeria using children for labor. That particular epidemic resulted in substantial long term neuroglial consequences for the children as well as a significant number of deaths [31].

The good news is that today we are aware of the harm to children's brains from even low levels of lead. As a result of legislation banning lead from paint and gasoline and actions taken by local, state and federal agencies, blood lead levels in children have fallen dramatically. We screen for blood lead levels above 5 $\mu\text{g}/\text{dL}$, because we know it can have a significant adverse effect on brain function. This is why we need to continue to be so vigilant. In their project on educating children about the risks and prevention of lead poisoning,

Catherine Evans, Amrita Mahtani, Sam Peters, and Patrick Fueta, students in the Department of Environmental Health, Rollins School of Public Health, at Emory University, in Atlanta, Georgia, developed a lead education program that they piloted at the Samuel L Jones Boys and Girls Club in Decatur, Georgia. This program “works to save and change the lives of children and teens, especially those who need us most, by providing a safe, positive, and engaging environment and programs that prepare and inspire them for healthy living and academic success to achieve ‘great futures’.” The Emory team found the children in the program to be very receptive, and their project was such a success that the US EPA plans to use their curriculum.

Educating children about toxins in their environment, as well as how to recognize it and what to do about it, is an invaluable way to promote children's environmental health and prevent exposure to lead and its serious consequences. This type of education will help provide children with the knowledge to influence their peers, their parents and the next generation.

The Effectiveness of a Community-Based Program of Nutrition Education and Physical Activity to Decrease Health Disparities of Childhood Obesity

Childhood obesity is a major challenge for families, their communities, and our society. Not only are children at risk for social, emotional and educational difficulties, but also for health complications with diabetes and hypertension that persist into adulthood and worsen physical and mental health, employment opportunities, and longevity. This presents a major cost, not only to the individual and his or her family, but also to society in terms of health care costs and productivity. This is particularly a challenge among low income African American children who suffer from food insecurity and tend to consume high calorie, high salt, and processed foods. They often live in so-called “food deserts,” with limited access to healthy fresh fruits and vegetables. These neighborhoods often lack green space for outdoor activities and exercise; consequently, the children are more likely to stay indoors and engage in sedentary activities, such as watching television (TV) or playing videogames. The combination of high calorie foods, low physical activity level, and stress is a toxic combination for the genesis of obesity.

To address this challenge, Hope Bentley, a student in the Department of Nursing and Allied Health, in the College of Veterinary Medicine, at Tuskegee University, in Tuskegee, Alabama, developed a program to address those very issues. She recruited economically disadvantaged youth from the Tuskegee Youth Safe Haven, which is an after-school program for youth 6-18 years old. She provided them with education in healthy eating and with an organized physical activity program. The good news is that, even for the relatively small size of her project and small number of children involved, she saw a significant benefit. This project, like so many others in the *Break the cycle* program, is small in scale but large in impact.

CONCLUSION

This publication of our 12th Annual *Break the Cycle* program reflects a diversity of projects and perspectives on the expressions of environmental health disparities in our societies and provides strategies that break the cycle. It is gratifying to see that the efforts of each student make a positive difference in our understanding of the health and wellbeing of children most impacted by adverse social, economic, and environmental factors.

We feel humbled by the magnitude of the challenges presented in the WHO Sustainable Development Goals (SDG) 2030 [25], particularly as our global community is dealing with causes and consequences of war, famine and disease, as well as the unpredictable hardships resulting from the impacts of climate change. The frequency of weather related disasters is increasingly considered to be responsible for the displacement of people from drought and famine in parts of Africa, and may have played a role in starting the war in Syria [32] with its devastating destruction of property, disruption of society and displacement of people. Such events result in political destabilization in the region, the loss of lives and livelihood, and a global refugee crisis. The planet is one global village, and environmental and political changes that take place at any particular place tend to affect everyone. However, just as we are affected by the negative events, we are heartened by the efforts that have been made around the world by large and small organizations, including the United Nations, the Bill and Melinda Gates Foundation [33], and not insignificantly, the students from the “Break the cycle” program. As long as the positive efforts continue, we have a good chance of achieving the Goals of SDG 2030, and having a future of health and wellbeing for all life on the planet.

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Chapter 257

RESILIENCE: A COMMENTARY ON BREAKING THE CYCLE

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ABSTRACT

Resilience can be defined as achieving a positive outcome in the face of adversity. Resilience relies on the protective response of an organism from threats to survival. Human physiology has built-in mechanisms for dealing with all manner of threats with an immediate ‘fight, fright or flight’ response, followed by a more complex set of physiological, psychological and behavioral responses for sustained threats. This commentary offers an exploration of the phenomenon of resilience and will examine the physiological, psychological and social mechanisms that assure not only survival, but success as well. Perspectives on the anthropology, genetics, physiology, neurology, psychology and sociology of adverse childhood experiences will be explored, and strategies for enhancing the ability of children and adults to overcome the threats of negative psychological, social, economic and environmental factors will be offered. Personal narratives of individuals who had adverse childhood experiences and were able to rise above them and become successful are presented as examples of resilience.

INTRODUCTION

This commentary is the product of a symposium held during the “12th Annual Break the Cycle of Environmental Health Disparities Conference” in Atlanta, Georgia, in April 2017. In it, the author attempts to capture some of the current concepts of resilience as they may apply

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to vulnerable children born into poverty and adverse experiences. It also offers insights on how to apply our understanding of resilience to provide enhanced support for these vulnerable children and promote their resilience to help them break free of the cycle to become self-respecting, respectable, and contributing members of society.

It is not the strongest of the species that survives, nor the most intelligent that survives. It is the one that is the most adaptable to change. Charles Darwin (1809-1882)



Figure 1. Cycle of environmental health disparities [1].

The conceptualization of the impact of adverse social, economic, and environmental factors on the health, growth and development of children offered here is based on the ecological framework of the “Cycle of Environmental Health Disparities” (see Figure 1) [1]. The cycle presupposes an intergenerational legacy of adverse experiences associated with poverty, in the context of cultural and political factors. For children who are born and grow up in this ecosystem, there are substantial risks for repeating the pattern [2]. For an individual to break out of this cycle, the challenge is to become aware of and examine the predicament, conjure up a vision of the future, generate and fire up the determination to make the necessary changes, and amass necessary internal resources to not only break out of the cycle and gain measures of self-respect, but also to take advantage of available opportunities to attain personal and social success. This process can be viewed as resilience. Resilience is defined as achieving a positive outcome in the face of adversity. However, it is more than overcoming adverse factors, it includes the quintessentially human phenomenon of rising above the experiences, adapting to a new set of circumstances, and of achieving success with a positive impact on the society at large.

BIOLOGY AND ANTHROPOLOGY OF ADAPTATION AND RESILIENCE

All life forms have mechanisms and systems of adaptation to adverse environmental factors that threaten their survival. Simple bacteria have survived almost since the origin of life on this planet because of their ability to adapt to environmental changes and threats to their survival. Some pathologic bacteria have developed resistance to many antibiotics, even some of the more potent ones.

More complex animals and plants each have their unique ecological niches that require a finite range of environmental elements to be compatible with life. These elements include ambient temperature, weather patterns, availability of water and nourishment, with effective strategies to deal with predators or competition, and some measure of climate change, that enable them to survive. When animals and plants experience threats to their existence, their genetically determined processes of adaptation are critical to resilience in overcoming the threat and continuing to survive.

For humans, interestingly, the ability to adapt to different and changing environments is so great that the species is able to live in the most varied and often inhospitable environments. Humans can live in and adapt to extreme temperatures, some live in hot dry deserts, while some live in frozen and icy environs, such as the Arctic Circle; some live in large crowded cities and some live in rural areas or on small islands in small communities.

In trying to explore and understand the realities and challenges of how humans survive in our modern communities, it is helpful to reflect on how our remote primal ancestors lived and survived in their environments when faced with the threats of harsh climates, predatory animals and real competition for food with minimal resources but their creative intellect. In his research on the hunter-gatherers of Southern Africa, primarily the !Kung San from Northwest Botswana, the anthropologist, Melvin Konner described the challenges to individual, family and community life [3]. These groups of people, who live in a harsh and arid climate, have survived for millennia, having adapted to their environment and circumstances. Day to day struggles and stresses of finding food and water in harsh surroundings challenge the physiological and psychological resources and resilience of this nomadic population. The necessity to find water, hunt for food, and deal with the real threats posed by predators, activates the physiological mechanisms of adaptation and resilience, which translates into psychological awareness, with corresponding physical and social action. There are also internal threats within the community to family and clan cohesion, such as conflicts between individual families, for example around food distribution or territory, or challenges to leadership, that require social constructs and narratives to provide the framework for resolution. The social and cultural infrastructure developed by these hunter-gatherers serves an essential guide in determining how individuals are expected to act, and what mechanisms are in place to ensure not only peace and harmony, but of survival of the individuals and the social group. Naturally, as environmental circumstances change, so do adaptations to the new set of realities evolve and engender resilience [3]. This exploration of resilience in a contemporary community of people who live as our ancestors did, is instructive as we look at the patterns of coping and resilience in our modern, highly industrialized societies.

PHYSIOLOGY OF THREATS TO SURVIVAL AND RESILIENCE

Dealing with threats to survival requires biological systems to identify and characterize the threats and then generate a corresponding response that will assure either removal of the threat or escape from the threat. The neurological infrastructure of this response resides in the hypothalamic-pituitary-adrenal axis which generates the hormonal releases that act on the physiological processes of various organ systems, such as the cardiovascular system, respiratory system, musculoskeletal system, endocrine system, immune system, and on the brain to execute the necessary responses for resilience, adaptation and survival [4]. In acute threats, the adrenergic reaction is activated which causes the heart to beat faster, blood pressure to rise, the blood flow to be diverted to the muscles where it is needed, and emotions to engage in an appropriate action that is characterized as the fright, fight, flight response [5].

Additionally, the corticosteroid system is activated to increase and maintain blood glucose levels because of the critical need for a source of energy, as well as activation of inflammatory and immune responses. Corticosteroids also act directly on the central nervous system (CNS), specifically the hippocampus, amygdala and frontal lobes stimulating arousal and memory, which are critical in determining action in times of stress. At a neurochemical level, serotonin levels are increased and play an active role in enhancing mood and positive behavior, which play a significant role in developing attitudes to overcoming threats.

The release of oxytocin in response to stress plays a key role in the activation of social considerations. Oxytocin release in childbirth and breast feeding promotes mother-infant bonding [6]. Oxytocin is also active in promoting positive social interaction and relationships and, during stress, is found to raise awareness about caring for others [7]. The ‘women and children first’ response in threats to group survival, is one such example of a biological imperative, because, teleologically, the survival of women and children assures the perpetuation of the species better than if men alone survive. Oxytocin may also play a role in the notion of self-sacrifice for the greater good of the family, clan or social group, as is required during grave threats to communal survival as often occurs during war.

It is important to note that psychological stresses evoke the same physiological reactions as actual physical threats to survival, with the corresponding adrenergic, corticosteroid, serotonin and oxytocin responses [8, 9]. The interplay between emotional stress, neurochemical and physiological responses, and the corresponding emotional reactions, represents a complex dynamic. Emotional reactions to dramatic and immediate threats or stresses, manifest as psychological states of anxiety, depression, obsessiveness, fear, anger, aggression, or even the paralyzing outcome of panic. The effect on the individual of these stresses and corresponding responses are influenced by many factors that play a part in resilience, including genetic, epigenetic, and environmental factors as well as the concept of ‘personality’ [10]. This dynamic not only plays out in determining responses to stresses, but also in modifying patterns of adaptation and resilience once the stressors have been removed and environmental factors become more favorable [4, 10]. It is this complex interaction that will be explored in this commentary.

GENETICS OF RESILIENCE

To understand the physiology and psychology of stress and resilience, it is helpful to consider genetic and epigenetic factors. Seminal work on patterns of maternal behavior in two groups of mother rats with their newborn pups illustrates the phenomenon of epigenetics [11, 12] (see Figure 2). One group of mother rats were nurturing, frequently engaged in the process of licking and grooming their offspring. Their offspring, in turn, grew up healthy and resilient and had offspring of their own, whom they licked and groomed, as they had been. A contrast group of mother rats were not nurturing at all, they neglected their offspring and did not lick and groom them much. Their offspring grew up to be malnourished, had high anxiety and were maladaptive in their behavior; when they, in turn, had their offspring, they likewise did not lick and groom their pups. This might lead the observer to presuppose that this phenomenon is genetic, that the pups are destined to carry on the intergenerational ‘gene’ for a pattern of maternal behavior. However, when the rat pups from the neglectful mothers were placed with the nurturing mothers and were licked and groomed during their newborn period, they grew up to be healthy; and, when they had pups of their own, they also licked and groomed them. The phenomenology of this finding was based on the epigenetic mechanism of switching genes on or off, triggered by external or environmental factors. In this case, the physical experience of the pups during the licking process initiated a cascade of biochemical events that resulted in the switching on of the gene for glucocorticoid receptor expression. The consequent physiological processes resulted in a profile of low glucocorticoid levels and low anxiety in the pups who were licked and groomed; in contrast to the increased glucocorticoid levels with a high anxiety level in the pups who had been neglected [12]. Thus, the physiological, psychological and behavioral characteristics of the mother instinct in the rat pups, once established, became the inherent set of genetic determinants of the future behavior in the pups. Although this is a rather simplistic rendition of the phenomenology of epigenetics, it nonetheless serves to illustrate how a physical experience in early life can have long term consequences even into the future generations.

Multiple genetic and epigenetic mechanisms relating to stress and resilience are expressed through the hippocampus and amygdala, which play out in the hypothalamic-pituitary-adrenal axis and noradrenergic, serotonergic and other neurochemical and neurohumoral pathways to affect response to acute and chronic stress [4]. The nature of epigenetics is a dynamic interaction between environmental stimuli and gene expression. The interaction between genetics, epigenetics and the environment not only plays a role in determining whether an individual may become resilient or not, but also in what symptoms and individual may develop, such as anxiety, depression, post-traumatic stress disorder (PTSD), or any other set of emotional and behavioral outcomes. Some of the biochemical factors under epigenetic influence involved in resilience include neuropeptide Y, which plays a role in regulating stress and anxiety, and brain derived neurotrophic factor (BDNF), which supports neuronal proliferation, differentiation and growth during development, and plays a major role in resilient adaptations to chronic stress. Furthermore, chronic stress may also result in shortened telomeres on the genes, which are also associated with reduced life expectancy [13].

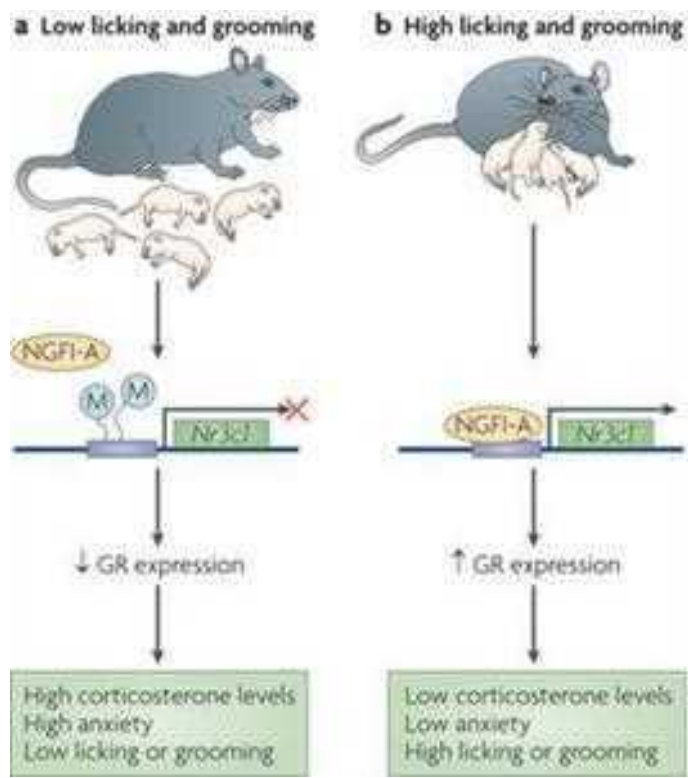


Figure 2. Epigenetic mechanism phenomenology [12].

A review of other epigenetic and biochemical processes that have been identified can help to understand the variability within individuals or groups of individuals, but more importantly can assist in developing strategies to enhance resilience in children and hold the promise of developing preventive strategies and of reversing some of the long-term consequences of adverse childhood experiences [4].

REACTIONS TO STRESS IN CHILDREN

In children, physiological responses to physical, psychological and emotional stress result in the release of the same set of hormones as in adults, with the corresponding physical and physiological reactions in the brain, cardiovascular, hormonal, and immune systems. The singular and critical difference is that children are more vulnerable because their organ systems, physiological mechanisms, and brains are in the active process of growth and maturation. Therefore, the possibility of epigenetic modification of physiological response mechanisms, especially neurophysiological pathways, may be significantly altered with serious long-term consequences [14].

Not all stress that children experience is the same. Much depends on the timing, nature, severity, and duration of the adverse experience, as well as associated factors. Categorizing degrees of stress and their responses in children by levels is helpful in this context [14]. These degrees can be stratified into the mild, moderate and severe.

Mild, or mundane, levels of stress accompany inevitable events that may occur in an otherwise secure, everyday life and do not necessarily require major modification to life's journey. Examples include minor injuries or illnesses, or emotional reactions of separation or disappointment that occur in day to day life. The relatively low level of stresses in these examples results in low levels of physiological reactions with minimal permanent changes and merely the fine tuning of natural maturation.

Moderate levels of stress involve more dramatic events in life, such as a major injury or illness, a move from a familiar home, a family divorce, death of a familiar person, or a natural disaster. Physiological and psychological reactions and responses are correspondingly more dramatic and are more likely to become a significant and permanent part of the narrative of life for the child. However, with the support and nurturing of a concerned and involved parent figure, not only is the child expected to survive the ordeal, but to adapt in a positive way and gain from it, to be strengthened by it, even prepared with a greater likelihood of success in life.

Severe levels of stress, recognized, codified and studied as adverse childhood experiences (ACEs) [15], often referred to as toxic stress [14], are considered to involve psychological stresses related to more serious life episodes and experiences of chronic neglect, or elements of physical, emotional, verbal or sexual abuse of the child that is unrelenting and cumulative, in the absence of a consoling adult. These levels of stress inevitably result in the persistent and chronic release and circulation of neuroendocrine and corticosteroid hormones, which, while having a positive effect in the short term, have a potentially destructive effect in the long term. Persistent changes are found in the brain where the neural circuitry of the reward feedback is overwhelmed by the circuitry of fear, and the hippocampus and amygdala are reduced in size and functionally compromised [14, 16]. CNS disturbances may result in an increased risk of learning disabilities, ADHD, behavioral disturbances, PTSD, anxiety, depression, OCD and other mental health problems. Children who experience these negative effects to their CNS structure and function, are more likely to become pregnant as teenagers, have high risk pregnancies with an increased risk of premature births, engage in substance abuse and, if pregnant have infants with intrauterine exposure to the drugs (such as fetal alcohol syndrome), commit crimes, be incarcerated, and die young, often related to drugs or violence [17]. In the longer term, the neuroendocrine and immune systems are also compromised which can result in an increased likelihood of metabolic disturbances such as obesity and diabetes, as well as respiratory disturbances with an increased likelihood of asthma, and cardiovascular disturbances with an increased likelihood of hypertension and stroke, and autoimmune disorders. Consequently, there is an increased likelihood of intergenerational perpetuation of the cycle of health disparities [1, 2, 15, 17]. In addition, these organ system disorders can significantly reduce life expectancy [13, 14, 15].

It is therefore imperative that stress on children is minimized and resilience is promoted so that children live healthier lives with the promise of success in their future and for their offspring. Improving outcomes for children increases the likelihood that they will become active, participating members of society, and will make positive contributions to society when they grow up healthy in body and mind [1, 17]. James Heckman, Nobel Laureate in Economics, has demonstrated that investing in the promotion of child education and nurturing, especially among low resource families, translates into a real return on financial and social investment. These financial and social rewards come not only from the contributions that are made to society in practical and financial terms, but also the reduced

costs related to being less dependent on public welfare funds and to reduced likelihood incarceration. Using data from the Perry Preschool Program, Heckman and his colleagues estimate a total benefit of 7 percent per annum from all sources for each dollar spent on the preschool program, even counting the social costs of taxation [18].

RESILIENCE OF CHILDREN

Factors that predict positive outcomes for children who experience stress are 3-fold: the individual child's physiological and psychological genetic endowment and 'personality' [4, 10]; the nature and duration of the adverse experience; and, the availability support and encouragement of a concerned adult, who may be a parent or other parent figure [14]. The type and nature of support and encouragement that a child receives and the factors that mitigate the effects of the adverse experiences are critical in enabling the child to overcome the potential negative consequences of adverse experiences and go on to a promising future.

A loving, caring and nurturing parent is a primal need for a child. The early effects of this bonding relationship form the epigenetic underpinnings of a resilient child. The early work on human and primate maternal-infant bonding [19], and seminal work on the nurturing behavior of mother rats to their offspring [11, 12], has demonstrated that the impact of the intimate physical contact between a mother and her offspring has a lasting effect, protecting the child from the potential negative consequences of adverse experiences by stimulating the physiological and psychological processes that enhance resilience, in addition to being epigenetically transmitted to the next generation. Furthermore, ongoing supportive relationships that children have with their parents, or other significant adults in their lives, continue to promote resilience in the teaching of skills and strategies to overcome inevitable adverse challenges in life. Lessons about interpersonal relationships from parents, teachers, or with siblings and peers, nurture an ability to relate to other individuals and have lasting meaningful relationships as friendships and in marriage.

The teaching of moral and prosocial behaviors is also critical to the development of children, not only for them to become competent individuals but also to participate as contributing members of society. Participation in peer social groups at all ages provides the framework for teamwork and collaboration with others to accomplish a common goal. For example, participation in team sports and recreational activities has been shown to teach the importance of physical health and fitness, of working with others to achieve a common goal, and of the determination to win, and the ability to lose with grace [20].

The resilience of these children to adverse life experiences translates into their adult lives, not only by ensuring health and success, but also the ability to overcome adversities that inevitably arise through the lifespan. Adverse experiences and the stresses that accompany them are critical elements in the process of growth and development toward building strength and essential physical, emotional and social strategies to overcome adversity in the future. In turn, when these children become parents themselves, they are equipped to provide the same benefit to their offspring.

Questions arise as to what factors predict whether an individual child will succumb to adverse experiences, or if he or she will be resilient and adapt to the situation and work with it to overcome the challenge. There are a host of genetic, epigenetic and physiological factors

involved that not only help to explain the general reactions and responses that are associated with resilience, but also explain the high variability of individuals' responses and outcomes [4]. As an example, although the presence of a nurturing adult is critical in the process of adaptation, in overcoming adversity and being strengthened from the experience, there are children who have not had the benefit of a nurturing adult, but who have nonetheless have been able to grow beyond the adverse experiences and become functional and successful adults. While these successful adults are not necessarily without scars from their experiences, which inevitably shape their personalities, choices in life, nature of their lifestyles, and even how they handle their successes, less than 10% of children who experience ACEs will develop PTSD [21]. Furthermore, there is an ongoing dynamic interaction between the individual, other people and environmental factors that influence physiological operations that hold the promise of positively influencing neurochemistry and brain function towards greater degrees of survival, resilience, and functional success [4]. This is precisely where the promise for a positive outcome for a child who has experienced adverse experiences can be shaped by timely and appropriate interventions [18].

RESILIENCE OF ADULTS

The study of resilience in adults may be viewed from two different sets of circumstances. There are those individuals who had adverse experiences during childhood with the associated physiological and psychological consequences; and, there are others who have experienced adversity during adulthood such as, for example, adversity that commonly accompanies a traumatic personal experience, exposure to military conflict, or experiencing a natural disaster [22]. Rather than review the extensive literature on the subject of adults who struggled with adversity in their childhood and have had to live with the psychological and physiological consequences, we have chosen to offer personal narratives from three individuals who participated in the "12th Annual Break the Cycle Symposium on Resilience", as well as one narrative drawn from a published interview [23].

Natalie D Hernandez, PhD, MPH, is Assistant Professor, Prevention Research Center, Post-Doctoral Fellow, in the Center of Excellence on Health Disparities, Department of Community Health and Preventive Medicine, Morehouse School of Medicine, in Atlanta, Georgia. Hernandez describes her childhood in a poor and dangerous neighborhood, with a family who worked hard to support their children and thereby provided support, guidance and role models for their children. The lessons are that parental care and instilling values in their children by love and by the example of their actions, resulted in the determination and ultimate success of their child [24].

Started from the Bottom Now I'm Here: My Resilience Story

Growing up in the South Bronx, you are presented with many barriers and challenges. If you can make it there you can make it anywhere. I was in the cycle of environmental health disparities. You see, where I came from you have no choice but to be resilient. Here is some context because context matters. I grew up in one of the poorest districts in the nation. For a while we lived in a housing project known to locals as "Vietnam", due to the frequent violence that resembled a war zone. This caused a lot of stress among my family due to its

inadequate structure, exposures to drugs and violence. I was never allowed to go out and play because of these concerns. My parents were among the 60% of Bronx residents that had a high school diploma.

Growing up I saw my parents struggle to provide for me and my siblings. My dad worked two jobs and went to vocational school, while my mom stayed home to take care of us. They did their best to shelter us from our surroundings, by instilling the values of education and hard work. I escaped my environment by reading and excelling in school. I knew if I wanted out I needed the best education. I was constantly teased and ridiculed for being “a nerd”, but that only pushed me further. My first big opportunity came in my last year of junior high school. Due to my academic achievements I was asked to apply to a program that assisted academically-talented, underserved minorities gain access to some of the nation’s top independent schools in the country. I was accepted into the program, and that is where my story began to change. Although I was no-longer considered at-risk, I was now an outsider at the school and in my community. I was constantly having to hop-scotch between different cultural and linguistic spaces and different parts of my own identity—sometimes within a single interaction. It was a bittersweet time because I was attaining the best education but feeling more isolated and alone than ever. These feelings of isolation became worse as I applied to college and when I was enrolled. Although I had what every college would want in a prospective student I did not get into many colleges; additionally, when I did get in, my parents could not afford to pay for it. I had to manage five-plus classes, a job, extracurricular activities, events and workshops, studying, relaxing and other commitments. There was no wiggle room for messing up because as a low-income, minority, first-generation student. I was already identified as someone who will likely not graduate. It was a terrifying time because half the time, I didn’t even know what I was doing, or what I needed to do. These expectations and not knowing what to do followed me through my Master’s and PhD programs. Through these times I faced a host of behavioral and mental health issues. What got me through most of these challenges were my family and my passion for underserved communities. I now know that I had to experience these personal public health challenges to motivate me and make me good at what I do now. This is why my research is focused on low-income, underserved ethno-racial minority populations. This is why I now make it a priority to mentor students and be an educator at a Historically Black College and University.

I still face many challenges and struggle as a Latina researcher. I struggle with my identity, where I came from and the perceptions others have on me, especially in academia. But then I think back to that little girl who grew up in the South Bronx and had big dreams of helping others to have the opportunities she had. When the odds were against her, when people told her and still tell her she may not make it, she did. The opportunities I gained helped build me with skills and knowledge, but I also remember and remind myself of the strengths and talents I bring. Through my work I am contributing and dedicated to breaking the cycle that contributes to health inequities. My future career plans and goals with respect to health inequity are tied directly to my role as a researcher and a woman of color from the South Bronx. They are to strengthen health programs and policies, to reduce ethno-racial disparities, and to ensure that all people receive comprehensive, culturally appropriate, healthcare. The future health of America will be increasingly influenced by the success or failure of improving the health of ethno-racial minorities and I hope to be a part of the solution. This is what motivates me, and this is why I tell my story.

Lucy Hall, Founder and CEO of Mary Hall Freedom House in Atlanta, Georgia, describes her experience of being trapped in an intergenerational cycle of substance abuse, and only when she was to become a mother herself and faced the perpetuation of the cycle, did she find her faith and determine to change her lifestyle to care for and change the lives of her daughter and others for the better [25].

Transformation from Poverty and Substance Abuse to a Powerhouse of Support

I grew up surrounded by poverty and addiction, not knowing there was another way of life. At age 6 years, I lost her mother to alcoholism, and later lost two brothers to substance abuse. I was struggling with her own addictions when, at the age of 27 years, I gave birth to a daughter. Fearing that my daughter was destined to repeat the cycle of generational addiction that had plagued my childhood, I decided to get help and entered a treatment program for substance abuse.

Once I completed the recovery program, I was ready to start life afresh. The impression my mother left in my life inspired me to reach out to women who suffer from addiction and women with children. I decided that I wanted to help bridge the gap from troubled lives and help women become independent and self-sufficient. In

1996, I founded Mary Hall Freedom House (MHFH) in honor of my mother, Mary Hall. The mission of MHFH is to empower women to break the cycle of homelessness, poverty and addiction for themselves and for their children. The organization began in one apartment housing with two women. Today, MHFH is a leader in gender-specific behavioral healthcare, housing, and support services. Over the past 21 years, MHFH has blossomed into a vital community asset, with a dedicated staff of 65 who serve nearly 600 women and children annually. Eight of MHFH's staff are former graduates of the program—living proof of the power of the organization's programs and services.

Today, my dream has become a reality with MHFH. Through a community of sisterhood, I coach women to free themselves from the past and live every day for the future. Over 10,000 women and children have achieved recovery through MHFH since its founding in 1996. Everyone here knows that G-d is really the head of this agency. He has made it possible for us to minister to the women, children, and families sent through our doors.

Jessica Spraggins MPH, CCHP, is a health communications specialist in the Division for Heart Disease and Stroke Prevention at the Centers for Disease Control and Prevention (CDC). Ms. Spraggins relates how she grew up with almost every stressful experience possible and suffered for much of her life from the effects of the Adverse Childhood Experiences. Because of her spirit of determination, she became socially successful, but remained psychologically imprisoned by her past. Then one day she had an epiphany and resolved to change her personal life and has now become a successful advocate for children who are suffering as she did [26].

Jessica Spraggins – from ‘Welfare Brat’ to Advocate

My name is Jessica Spraggins and I am a Health Communications Specialist with the Centers for Disease Control (CDC). I have a BA from The George Washington University and MPH from Yale. I came from a dysfunctional, abusive home. I am also a survivor of childhood rape. I am one of nine kids. My parents had five children and adopted four more children out of the foster care system. We switched schools and emergency rooms often, usually when the staff at either facility ‘had the nerve’ to question how much and what type of attention we were getting from our mom. We were welfare brats.

As a welfare brat you move to the places that have available section 8 housing or that would accept vouchers. This includes drug houses. You’d learn to pick the needles up off of the playground before letting the younger kids come out to play. The best places were the ones out in the country, because even if they were full of rats and roaches and the well water stunk of sulfur and was barely drinkable, we could escape outside where our imaginative play was a hundred times better than the hitting, yelling, or ignoring that we would experience inside.

The movie “Mommy dearest” came out when I was a little kid. My best friend had watched it and was telling me how the mom in this movie was so scary and mean and awful, she even hit her daughter with a wire hanger! So, I had to watch this movie and see this awful, horrible, terrible mom. Except when I watched this movie Joan Crawford didn’t seem that awful to me, she seemed like my mom, only with more money, a cleaner house, and fewer cigarettes. So, in my little 1st grade mind I was really puzzled as to why my best friend thought this movie mom was so terrible.

I first read “I know why the caged bird sings” by Maya Angelou when I was about 9 years old and I had heard some 8th grade girls on the school bus talking about the scandal in the book. Within these pages Maya Angelou describes her rape as an 8-year-old girl. She plainly talks about the man who assaulted her, the justice system that failed her, the family that surrounded her, and her escape into books. I thought: how can THAT be the drama? It happens all the time. That same thing happened to me when I was even younger than Maya and nobody made a big deal about it.

Abuse and poverty can shape you in ways that you don’t even realize as a child. For me it pushed me to work harder, to want more, and to be the exact opposite of the little girl I was growing up. So, I worked hard, I got an education, became a professional, became a mother and a wife and told the right stories and did the right things and gave of myself, while smiling and carrying my babies in their ergonomically correct Maya wraps.

But then I hit a point in my life where it got hard to keep smiling and to get out of bed every day to keep doing the “right” thing. In November 2012, I called the police for the first time in our marriage on my then-husband after he threatened me *again*, broke down our back door *again*, and shoved me around *again* all while

in a drunken rage *again*. That was the day that I had had minor surgery to get my tubes tied and our youngest son was eight weeks old. The police officer that showed up that night was kind, but he asked me the most brutal questions. Has he done this before? Yes. Was it reported? No. Has he broken anything else in the house? Yes. Was it reported? No. Has he physically or sexually assaulted you before? Yes. Was it reported? No. Has he been arrested before? Yes. Was it from something you reported? No.

As hard as I worked to be better than the life I grew up in, I had spent eight years in an abusive marriage with an alcoholic drug user. I had no self-esteem and felt no self-worth, and I was more than 100 pounds overweight. I was miserable and wanted to run away from my own life, so I knew that for my sake and the sake of my children I had to figure this out.

I read about the work that CDC was doing on the adverse childhood experiences (ACE) study. The ACE Study findings suggest that certain childhood experiences are major risk factors for the leading causes of illness and death as well as poor quality of life. There is even a questionnaire that grades you 0-10 on how messed up your childhood was. I took it and I got a 9, which included a statistically greater risk for heart disease, stroke, and a host of other chronic diseases. What I realized, there and then, was that I had to find a way to take control of my life.

I have found with kids that grew up with little to nothing they seem to sway one of two ways. Either growing up with a sense of entitlement, as in “I had nothing, so the world owes me everything”, or growing with a sense of gratitude, as in “I had nothing, so I am thankful for what I do have”.

Most of the kids that I grew up with, including some of my siblings, chose the path of entitlement. They had it hard, so they wait, and they expect, and they resent and, while they do that, they miss the opportunities that pass them by, thus perpetuating the cycle that defined their life of poverty and abuse.

The other path of gratitude seems to be less popular, mostly I think because it requires action and initiative. I have to say, when I look at how I ended up here instead of there, I think it comes down to some very conventional, not at all exciting ways of pulling through. I have also had some amazing people support me during this process and they have asked me how I seem so normal. Though I certainly don’t feel normal I know what they mean.

This has been a personal journey for me. But it is also a story showcasing a greater public health issue. D. Robert Block, former president of the American Academy of Pediatrics said that: “Children’s exposure to adverse childhood experiences are the greatest unaddressed public health threat facing our nation today.” My story of resilience doesn’t have to be the exception. With the science that we have on ACEs and the information that we are learning on resilience every day, positive outcome from childhood trauma can and should be the norm.

Nate Awan is an African-American man who grew up in poverty in a rough neighborhood and became rough himself, then found himself in prison. When he realized the path he was on, he was determined to make a better life for himself. He took advantage of the opportunity to enroll in a rehabilitation program, studied and on release from prison, became a pipefitter. He is now gainfully employed in a job he likes, supports a family and is a steady citizen contributing to society.

Nate Awan: The Pipe Fitter [23]

From the job site in Roxbury where he works as a union pipe fitter, Nate Awan can see the building that once housed the Phillis Wheatley Middle School, from which he was expelled for fighting and other misbehavior. “That was back in my knucklehead time,” he said.

The fifth child of an overwhelmed single mother, Awan was kicked out of four schools and took a bullet in the shoulder before going to prison at 18 years for trying to shoot a rival gang member. While serving a three-year sentence, he resolved that he would change his fate.

With the help of a former prosecutor who took an interest in his rehabilitation, Awan found his way into Operation Exit, a program founded in 2014 in which the city of Boston partners with unions to channel residents with criminal backgrounds into the trades. Having sampled carpentry, sheet-metal work and other options, Awan, who had always been fascinated by welding but doesn’t like heights, chose pipe fitting over iron work.

There’s plenty of politics in the building trades, but there’s also an ethos of craft meritocracy. “It’s not what you look like, it’s what your clevis hangers look like,” Awan said, referring to the brackets used to support

pipes. “All at the same level, nothing crooked. It’s about your work ethic.” He’s already planning to get his 5-year-old son into the local when he’s old enough.

Awan, who is 28 years and currently a second-year apprentice making \$30 an hour plus benefits, can become a journeyman in three years, and he looks forward to continuing up the scale of seniority and pay toward the top rate of \$50 or so an hour. He still lives near the Four Corners section of Dorchester where he grew up, but he’s shopping for a house outside the city. “You come from no money for food, nothing, to where you’re buying a house, buying a car,” he said. “Your son needs a school uniform, you can get him one.”

Boston’s mayor, Martin Walsh, intends Operation Exit to enable this kind of transformation of prospects and consciousness. Walsh, who also grew up in Dorchester and had his own troubles (a bullet grazed his leg) before putting his life on course in the building trades, says, “We’ve had 80 graduates come through this program, and we’re expanding from the building trades into coding and culinary arts. Some of these guys were impact players on the street. It has an effect.”

Programs that reduce crime by connecting offenders and potential offenders to meaningful work are getting more attention across the country. Some, like Operation Exit, focus on re-entry after prison; others, like the Chicago CRED initiative recently started by the Emerson Collective and Arne Duncan, the former US secretary of education, try to reduce gun violence by teaching job and life skills to young men adrift from both school and the labor market. It takes a significant investment of time and resources to shift a life from a dead-end trajectory to a viable future in this way, but Awan testifies to the approach’s effectiveness. “I’m no surgeon or big-time prosecutor,” he said, “but for me — a product of his environment, taken from my mother at 9 years, incarcerated at 18 years, sweeping and mopping in the hole in prison for 19 cents an hour, living like a peasant — this here is a lottery ticket.”

RESILIENCE IN A GLOBAL CONTEXT

History is replete with examples of personal and collective adverse experiences and tragedies that shaped humans’ personal and collective understanding of adaptation and resilience. An example of an individual in a global community who embodies the spirit of adaptation, resilience and ultimate success is Nelson Mandela (1918-2013). Mandela grew up in rural South Africa in a tribal culture. He went to school and became a lawyer. His sense of justice focused on the inequity and injustice of Apartheid South Africa, so he became an activist and eventually, out of frustration, became involved in the armed resistance movement. He and his co-conspirators were caught, arrested, tried, convicted and imprisoned on Robben Island, far away from civilization. His intellect, his pride and his sense of justice did not fail him. After 27 years on this prison island he was released and went on to become the first President of the new multiracial South Africa. His spirit of courage, steadfastness and magnanimity resulted in a relatively peaceful political transition process while many other countries in Africa shed their colonial pasts with bloody struggles. His resilience and his achievements justifiably earned him the Nobel Peace Prize.

Other examples of resilience can be found in one of the defining global events of the 20th Century in the World War of 1939-1945 and the Holocaust [27]. Survivors of these horrors embody the spirit of resilience and have made contributions to society in significant ways. Elie Wiesel (1928-2016), whose detailed descriptions of his experiences and observations during the Holocaust, most notably, his first book “Night” [28], as well as novels, essays and speeches depicting the suffering endured by so many of his fellow Jews and other persecuted people, helped shape the post-war moral thinking in terms of understanding, compassion and justice. This earned him a well-deserved Nobel Peace Prize. Another survivor who described his experience in similar circumstances was Viktor Frankl (1905-1997), who captured the elemental spirit of survival in the title of his book “Man’s search for meaning” (the original title was “From death camp to existentialism”) [29], enriching the field of psychology and providing us with a deeper understanding of resilience. While in the concentration camps,

Frankl noted that there were people who were determined to go on living regardless of the circumstances and those who had ‘given up’. Based on his observations and his own personal experiences, he developed the psychiatric approach of Logotherapy, which embodies the notion that finding meaning and purpose in one’s life is the most important and powerful motivating force to continue to go on living [30].

In the aftermath of the suffering and horrors of World War II, the world body came together to establish the United Nations and craft a Charter of the United Nations and Statute of the International Court of Justice to promote human rights, freedom, equality and justice and a check on preventing such atrocities from ever happening again [31]. These noble thoughts, statements and actions have served to improve the health and stability of an ever-changing, fractious and, at times, volatile world. The Millennium Development Goals 2015 [32] and the Sustainable Development Goals 2030 [33] are testaments and guidelines to demonstrate how the world body strives to continue to reduce health disparities by promoting health equity and striving to improve the health of all the people in our global village.

MAKING A POSITIVE DIFFERENCE

In order to make the world a better place, we need to make sure that all children who grow up in it are equipped to deal with the challenges that come their way, at a personal level, at an interpersonal level, at a community level and at a global level. Obviously, children need adequate nourishment and protection to survive, but we must also provide children with the necessary emotional support and guidance that will enable them to survive and adapt to challenges that they may encounter.

The following are some distillations of strategies to promote resilience:

- Assure that every child is loved and protected from physical and emotional harm
- Provide support for parents, particularly those who are stressed [34]
- Provide a good education for children about life and the necessities for survival and success [18]
- Promote good eating habits and exercise to maintain good health
- Encourage children to engage in team sports and activities to help learn how to work together whether you win or lose [20]
- Provide for a sense of community in developing personal relationships with individuals and with groups of individuals
- Offer a moral compass as a vital necessity for a shared communal life
- Offer a role model on how to help others in distress
- Promote an understanding of the larger world stage will help us learn to live together with people of other cultures and instill a sense of responsibility in environmental stewardship
- Provide guidance and strategies on how to deal with hardships in a constructive manner [35]
- Cultivate a spirit of optimism which will lead to constructive approaches to life’s challenges
- Demonstrate humility and encourage a sense of humor

For those children who have experienced adverse childhood events, there is an additional set of recommendations to improve resilience and reduce the likelihood of negative long-term consequences [36]:

- Treat maternal mental health problems
- Promote self-care skills and routines
- Assure a positive and secure home environment which may involve foster care
- Provide early intervention for children
- Enhance trauma understanding
- Offer counseling or peer-based support groups to the children and their families
- Provide a Pediatric Medical Home for the children and their families [37, 38]
- Promote strategies and programs to Break the Cycle of Health Disparities [1, 17]

CONCLUSION

Up to almost 50% of children will experience an adverse life event. Most, however, are resilient and adapt to the experience, and may even be strengthened by the experience. There are many, however, who are likely to experience serious long-term consequences that manifest in the emotional and mental health concerns such as anxiety, depression, OCD, and PTSD among others. These conditions seriously affect the child's ability to function, and may persist into adult life with adverse experiences for them and their offspring and thus perpetuate a cycle of health disparities. Children who experience ACEs may also develop physiological and immunological disturbances that may manifest as adverse health effects which affect quality of life, productivity and happiness, and shorten their lifespan.

Our responsibility is to improve our understanding and awareness of the impact of adverse physical, emotional, social, economic and environmental factors have on children, especially if they are cumulative and have a basis in poverty. With increased awareness, our role is to implement strategies to prevent these adverse events, promote resilience in children and their families, and support and assist children and their families who are struggling with the outcomes of ACEs. With help in mitigating the effects of these adverse events and guidance on overcoming them, children can gain the necessary self-confidence, self-respect, self-esteem and skills to go on to become successful and contributing members of society.

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Chapter 258

MATERNAL DRUG USE AND THE SEVERITY OF NEONATAL ABSTINENCE SYNDROME

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ABSTRACT

East Tennessee and Middle Appalachia is the epicenter of the prescription drug epidemic, with approximately 15% of women giving birth at our institution documented as suffering from drug addiction. Objective: In this chapter we describe our sample of women giving birth to infants who were drug exposed and experienced Neonatal Abstinence Syndrome (NAS) and to determine the maternal and neonatal factors associated with the severity of NAS as measured by the length of stay (LOS) in the Neonatal Intensive Care Unit (NICU). Methodology: This was a retrospective chart review of 73 infants diagnosed with NAS and treated in the NICU. We conducted bivariate analyses and multivariate modeling (least squares regression with backward elimination) of the significant variables ($p < .10$) against the infant's LOS. Results: The mean LOS for infants with NAS was 17.7 days ($sd = 11.6$); 75.3% received nonpharmacological and 86.3% received pharmacologic (morphine) treatment. Of 73 women, 53.4% had a history of mental illness; 53.4% smoked >5 cigarettes per day in last trimester; 89% were taking buprenorphine, 9.6% had cord tissue positive for benzodiazepine. Term infants had 2.3 day longer LOS on average ($p = 0.027$) compared to preterm infants; infants exposed to benzodiazepines had 12.7 day longer LOS on average ($p = 0.07$) and prenatal exposure to >5 cigarettes per day in last trimester increased the hospital stay by 6.4 days ($p = 0.022$). Conclusion: We found that exposure to benzodiazepines and cigarette smoking were associated with an increased LOS.

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INTRODUCTION

Over the last decade, use of prescription opioids such as morphine, hydrocodone, and oxycodone for pain during pregnancy has increased substantially [1]. Tennessee has the second highest rate of opioid use in the country [2] with use concentrated in the Appalachian regions of the state and neighboring states [3]. Use of these substances often continues into pregnancy [4], potentially impacting the exposed fetus. Misuse of prescription opioids contributes to a substantial portion of the growing burden, with nonmedical use of prescription opioids increasing 162% over the last decade and surpassing all drugs other than marijuana [5]. Among rural pregnant women, prescription opioids are the most frequent drugs of abuse [6]. In addition, for those who enter pregnancy using high levels of prescription opioids or illicit opioids, medically assisted treatment (MAT) approaches involving prescribed opioid medications, methadone or buprenorphine which block opiate withdrawal symptoms, have the potential to affect the fetus negatively [7].

Neonatal abstinence syndrome (NAS) is a drug withdrawal syndrome that can occur in newborns after exposure to a variety of drugs, prescribed or illicit. The signs and symptoms of NAS are both broad and multi-system, with the more common symptoms affecting the central nervous and gastrointestinal system. NAS is diagnosed by following exposed infants for 4-5 days and monitoring for withdrawal symptoms. About one third of exposed infants develop symptoms severe enough, as rated by the Finnegan Scoring Scale, to warrant the diagnosis of NAS [8]. Based on the severity of the clinical signs, infants may need non-pharmacologic (swaddling, breastfeeding, quiet environment, etc.) and/or pharmacologic treatment (primarily morphine or methadone but other medications are also used). The management of drug withdrawal in neonates can necessitate prolonged stays in the Neonatal Intensive Care Unit (NICU) that can lead to a huge financial burden on the health care system, primarily borne by state Medicaid programs. A study done by Patrick, et al. showed the mean cost of a hospitalization for NAS was \$53 000 per newborn [9]. Over a period of four years, from 2009 to 2012, the hospital charges for NAS have increased from \$732M to \$1.5B ($p < 0.001$) [10]. Also of importance, long NICU stays impose a heavy emotional burden on the family.

Using Tennessee Medicaid claims data, Patrick et al. [11] demonstrated that the likelihood an infant exposed to opioids in utero would be diagnosed with NAS increased with exposure to a higher cumulative opioid exposure of short-acting vs. long-acting opioid preparations, number of daily cigarettes smoked, and exposure to selective serotonin reuptake inhibitors (SSRIs) [11]. However, while some factors have been identified that predict the severity of withdrawal symptom and resulting length of stay for the neonate, a comprehensive profile of demographic and clinical factors have yet to be described. The objective of our study was to describe a sample of women from Central and Southern Appalachia giving birth to infants who were drug exposed and experienced Neonatal Abstinence Syndrome, and to determine the maternal and neonatal factors associated with the severity of Neonatal Abstinence Syndrome (NAS), as measured by the length of stay in the Neonatal Intensive Care Unit (NICU). Knowledge of these factors will help us identify the high-risk population and tailor the interventions accordingly early in the pregnancy to reduce the incidence and severity of neonatal abstinence syndrome.

OUR STUDY

This study was conducted within a regional health system with six delivery hospitals in Central and Southern Appalachia. All newborns admitted to a Neonatal Intensive Care Unit (NICU) with a diagnosis of NAS between the years 2011 and 2016 were eligible for study inclusion. There were approximately 500 infants in this period that were exposed to opioids. This study reports on the first 73 eligible infants selected and abstracted across the five year sample. A retrospective chart review was conducted, and relevant information was manually extracted from the electronic health record from the delivery and newborn hospital stay.

VARIABLES

The specific variables were abstracted from the electronic health record that included multiple sources including prenatal records, information reported by the patient during the intake nursing assessment, prenatal care physician documentation, and delivery record and hospital stay summaries. Variables constructed from multiple sources within the medical record are explained below. Results of maternal and infant urine drug testing, and cord tissue analysis, were also collected. The primary outcome of interest was infant length of hospital stay, utilized as a proxy for NAS severity. Recorded in days, this variable represented the length of time between admission to NICU and hospital discharge.

Primary predictors of length of stay were classified as variables representing demographic and medical characteristics of mother and newborn, and variables related to prenatal substance exposure. For newborns, we collected gestational age in weeks based on estimated due date from ultrasound, and weight at birth in grams. Additional infant variables collected included whether the infant received breastmilk (yes or no) and types of treatment for NAS (pharmacologic and non-pharmacologic). For mothers, we collected basic demographics including age in years, marital status (married or non-married), highest education level (less than a high school diploma, high school diploma only, and more than a high school education). Whether the mother received income-based government medical insurance (i.e., some type of Medicaid) was indicated and the final dichotomous variable (government or no medical insurance vs private insurance) was used as a proxy for income. Number of previous births (grouped as any vs none) and delivery type for this birth (vaginal vs cesarean) were also recorded. We also abstracted the following maternal variables as potential predictors: Maternal mental health problems (yes/no, yes if the mother reported being diagnosed with or reported receiving a medication for a mental health condition), hepatitis C diagnosis (yes vs no), and use of buprenorphine as medication assisted treatment during pregnancy (yes vs no).

Substantial information about maternal substance use during pregnancy was extracted and multiple measures were created. Tobacco use was coded as any versus none (yes/no). The degree of smoking was assessed as comparing those who smoked at least five cigarettes per day in the final month of pregnancy versus those who did not. For use of buprenorphine, other opiates (prescription or illicit), and benzodiazepines, two variables were constructed for each. The first was an “any evidence” variable that was positive if any source of information indicated use of that drug during pregnancy. Sources of information included documented

prescription for that type of drug, self-report during prenatal care or at delivery, positive maternal urine drug screen during pregnancy or at delivery, positive newborn urine drug screen, or positive cord tissue test. A second variable for each drug type was also constructed and was positive only if the cord tissue was positive for the drug, possibly indicating a higher and later level of exposure. Finally, for buprenorphine use, a third variable was constructed representing amount of use (<10mg/day vs 10+ mg/day). Reliable data was not consistently available to construct amount of use variables for benzodiazepine or other opiate use.

STATISTICAL ANALYSIS

Descriptive statistics were used to detail sample characteristics. Independent groups t-test were used to examine bivariate relationships between each individual potential predictor and newborn length of hospital stay. Finally, least squares multiple regression analysis was used to develop the best prediction model for infant length of stay. Backward entry of potential confounders included maternal age, maternal marital status, maternal education, maternal insurance status, parity, infant gender, delivery type, gestational age at birth, infant birth weight, and maternal mental health status. Substance exposure variables significant ($p < .10$) at the bivariate level were forced entered in the final step (buprenorphine exposure not included due to high rate use/lack of variance in this mostly MAT sample).

OUR FINDINGS

The infants in the study sample, all of whom had prenatal drug exposure and were diagnosed with NAS, averaged 17.7 days (sd = 11.6). for their newborn hospital stay. Additional sample characteristics are presented in Table 1. Overall, rates of low birth weight and preterm birth were low for our NAS sample. Most of the infants received both pharmacologic and non-pharmacologic treatment for NAS. Data available on the mothers revealed that the vast majority were unmarried and relied on government health insurance and 34% had not graduated from high school. Nearly four in five mothers had given birth previously. More than half experiencing a mental health condition, and more than one third had been diagnosed with hepatitis C. Nearly all had received buprenorphine as part of treatment for opioid addiction during pregnancy.

The associations between infant length of stay and newborn and maternal characteristics are presented in Table 2. Higher levels of buprenorphine exposure (as indicated by a positive cord tissue) increased length of stay by nearly five days, while higher levels of tobacco exposure (as indicated by 5 + cigarettes per day in the final month of gestation) increased length of stay by over four days. The strongest predictor was higher levels of benzodiazepine use (as indicated by positive cord tissue), which increased length of stay by nearly 10 days. Finally, length of stay was increased almost four and a half days for newborns whose mothers had a mental health condition.

Table 1. Demographic characteristics of sample

	Percentage
Newborn characteristics	
Gender (male)	60.3%
Gestational age (preterm < 37 weeks)	13.7%
Birth weight (low birth weight < 2500g)	15.1%
Delivery type (vaginal)	65.8%
Breastfeeding status (being breast fed)	41.1%
Received pharmacologic treatment for NAS	86.3%
Received non-pharmacologic treatment for NAS	75.3%
Maternal characteristics	
Background	
Age (< 25 years)	26.0%
Unmarried	72.6%
Highest education level	
<High school graduate	34.2%
High school graduate only	38.4%
Beyond high school	27.7%
Medical insurance (government, income based)	87.7%
Parity (1+ previous births)	79.5%
Medical	
Mental health diagnosis	53.4%
Hepatitis C	37.0%
Received medication assisted treatment	97.3%
Substance Use	
Any tobacco use during pregnancy	90.4%
Tobacco use 5+ cig/day final month of pregnancy	53.4%
Any buprenorphine use during pregnancy	89.0%
Cord tissue positive for buprenorphine	61.6%
Buprenorphine amount (of those receiving it)	
<10 mg/day	53.1%
10 + mg/day	46.9%
Any benzodiazepine use during pregnancy	34.2%
Cord tissue positive for benzodiazepine	9.6%
Any opioid (non-MAT) use during pregnancy	97.3%
Cord tissue positive for opioid (non-MAT)	5.5%

N = 73

Table 2. Bivariate relationships between newborn and maternal characteristics and newborn length of hospital stay

	Mean length of stay (days)	Standard Deviation	p*
Newborn characteristics			
Gender (male)			.267
No	17.0	9.8	
Yes	18.8	14.2	
Gestational age (preterm < 37 weeks)			.382
No	18.6	7.3	
Yes	15.2	12.6	
Birth weight (low birth weight < 2500g)			.225
No	18.2	12.5	
Yes	15.3	3.9	
Delivery type (vaginal)			.334
No	18.6	13.3	
Yes	17.3	10.8	
Breastfeeding status (receiving breast milk)			.450
No	17.9	12.5	
Yes	17.5	10.5	
Received pharmacologic treatment for NAS			.002
No	7.8	4.5	
Yes	19.3	11.7	

Table 2. (Continued)

	Mean length of stay (days)	Standard Deviation	p*
Received non-pharmacologic treatment for NAS			.046
No	13.7	12.1	
Yes	19.1	11.3	
Maternal background characteristics			
Age (<25 years)			.209
No	17.8	5.1	
Yes	15.4	6.2	
Married			.183
No	18.8	12.2	
Yes	16.0	10.3	
Highest education level			.334
<High school graduate	18.4	7.6	
High school graduate only	18.9	8.1	
Beyond high school	15.8	6.4	
Medical insurance (government, income based)			.193
No	14.6	7.8	
Yes	18.2	12.1	
Parity (1+ previous birth)			.460
No	17.5	8.3	
Yes	17.8	12.4	
Maternal medical characteristics			
Mental health diagnosis			.050
No	15.4	7.7	
Yes	19.8	14.0	
Hepatitis C			.217
Negative	18.6	12.0	
Positive	16.3	11.1	
Received medical assisted treatment			.476
No	17.3	1.5	
Yes	7.8	11.9	
Maternal substance use			.138
Any tobacco use			
No	13.1	6.9	
Yes	18.2	12.0	
Tobacco use 5+ cig/day last 30 days			.066
No	15.5	8.5	
Yes	19.7	13.7	
Any buprenorphine use during pregnancy			.119
No	13.1	4.1	
Yes	18.3	12.2	
Cord test positive for buprenorphine			.038
No	14.7	8.2	
Yes	19.6	13.1	
Buprenorphine amount			.154
<10 mg/day	16.9	9.8	
10+ mg/day	20.0	14.5	
Any benzodiazepine use during pregnancy			.200
No	16.8	8.9	
Yes	19.6	15.7	
Cord tissue positive for benzodiazepine			.019
No	16.8	9.8	
Yes	26.4	22.4	
Any opioid use (non-MAT) during pregnancy			.324
No	14.0	11.3	
Yes	17.8	11.7	
Cord tissue positive for opioid (non-MAT)			.137
No	18.1	11.9	
Yes	11.8	3.6	

* Probability associated with 1-tailed t-test for the mean difference between groups.

Table 3. Regression results predicting newborn length of stay**

Predictor	Unstandardized coefficient	Standardized coefficient	p
Gestational age at delivery (weeks)	2.33	.353	.027
Infant birth weight (100g)	-.50	-.223	.149
Prenatal benzodiazepine exposure + cord tissue	12.69	.325	.007
Prenatal exposure to 5+ cig/day final gestational month	6.40	.274	.022

**Results are from backward entry of potential confounders: maternal age, maternal marital status, maternal education, maternal insurance status, parity, infant gender, delivery type, gestational age at birth, infant birth weight, and maternal mental health status. Substance exposure variables significant ($p < .10$) at the bivariate level were forced entered in the final step (buprenorphine exposure not included due to high rate use/lack of variance in this mostly MAT sample).

Overall results of the regression model predicting newborn length of stay are presented in Table 3. Of the background and medical factors, only gestational age at delivery remained a significant predictor after inclusion of other significant predictors. In this case, greater gestational age at delivery predicted longer hospital stay, with each additional gestational week increasing length of stay by 2.3 days. Both having a positive cord tissue for benzodiazepines and prenatal exposure to five or more cigarettes per day in the final month of gestation also significantly predicted newborn length of stay after control for all other significant predictors. Specifically, exposure to this level of tobacco in the final weeks of gestation increased length of stay by over six days, while having a cord tissue sample positive for benzodiazepines increased newborn hospital stay by an average of twelve to 13 days.

DISCUSSION

In our study of 73 women in Central and Southern Appalachia, we found that women were not young nor first time mothers which is consistent with the findings from other studies [12]. The average age of women was 28.3 years with a mean parity of almost two (indicating most of them had been pregnant at least twice). Their lives were characterized by disadvantage and/or abuse, as exemplified by the high rate of relationship instability (less than a third were married), low educational levels (only a quarter of the women were educated beyond high school) and high rates of poverty (the vast majority of women had government health insurance compared to 50% of births nationally). Almost all of the women reported some smoking and about half reported smoking over five cigarettes per day in their last month of gestation. Many women had a history of poly drug use in addition to medically assisted therapy for opioid abuse. This was evidenced by the fact that all infants in our sample were exposed to both opioids and other drugs.

We found that exposure to smoking in the last trimester can prolong the length of hospitalization in neonates with NAS. Similar findings were obtained in a study done by Jones et al. [13]. They demonstrated that there is a positive association between the average number of cigarettes smoked and several poor neonatal outcomes; for each additional cigarette smoked there was an increase of about 6% in the total amount of morphine needed to treat the withdrawal symptoms, 4% increase in the number of days of being on medication and 3% increase in the length of hospitalization [13]. Another important predictor of total length of hospital stay is the use of benzodiazepine along with opioids. Two other studies

have established this association but unlike our study, the infants in these studies were exposed to methadone and not buprenorphine [14, 15]. The finding of longer length of stay in infants with greater gestational age is also in line with the existing literature. Gibson et al proved that among infants who required pharmacologic treatment for NAS, term infants were treated longer than preterm infants [16].



Figure 1. Cycle of environmental health disparities.

NAS can be prevented or its severity reduced through primary and secondary prevention strategies. A primary prevention strategy to prevent pregnancy in women who are opioid dependent or in Medically Assisted Therapy. Studies have shown that in opioid users, more than 85% pregnancies are unintended (as compared to approximately 50% in the general population) [17]. An effective strategy is to reach out to women in MAT and improve access to long-acting reversible contraception (LARC) methods to decrease the rate of unplanned pregnancies [18]. We found that heavier cigarette smoking (>5 cigarettes per day in the last trimester) were associated with an increased LOS, our proxy for the severity of the NAS episode. Secondary prevention strategies to reduce the severity of NAS should be targeted at reducing smoking and poly drug use during pregnancy. Studies have shown that the use of an escalating voucher programs for smoking cessation in pregnant women with concurrent opioid abuse helped the women reduce their smoking and improve birth outcomes [19]. Health care providers in our area should identify women with smoking and substance abuse early in pregnancy and provide individually tailored programs aimed at reducing the smoking rates during pregnancy. Lastly, we found that the use of benzodiazepines with opioids greatly increased the severity of NAS. Pregnant women on MAT should be counseled to avoid benzodiazepines and clinicians caring for these women should consider using alternatives to benzodiazepines while treating mental health disorders in pregnant women with opioid addiction.

Using “Break the cycle” framework (see figure 1) help us identify and tie together the factors that contribute to the poor outcomes we document in our study. The women in our sample experienced multiple social and emotional disadvantages as evidenced by their poverty, low educational achievement and relationship instability. Life course theory posits that cumulative experiences can determine an individual’s future health and development [20]. Cumulative disadvantages and stress increase the risk of poor life outcomes, mental health problems and addictions, which we saw in our sample. Therefore, primary prevention measures to prevent NAS should target the root causes of maternal drug use such poverty, inadequate education, relationship stability and mental illness. The women in this group generally face social exclusion and economic and environmental inequalities which eventually lead to unhealthy behaviors such as substance abuse and cigarette smoking. Their children are raised in the same adverse social conditions leading to similar outcomes and thus the vicious cycle of disadvantage perpetuates. To break this cycle, we need address the larger social and structural issues leading to economic disadvantage and isolation in Appalachia. Substantial research exists to show that evidence based interventions early in life to support the social, emotional and cognitive development of the child and support the mother pay significant dividends in adult life that includes higher education levels, and lower rates of unhealthy behaviors such as smoking and drug use [21, 22]. Programs such as high quality preschool and family home visiting and support services such as the Nurse Family Partnership should be funded to help prevent the Cycle of Disadvantage that result in maternal drug abuse and neonatal abstinence syndrome.

The current study is not without limitations. First, it was retrospective, and thus was limited by the availability of data abstracted from electronic health record. However, use of electronic health record data did provide for a rich data set by allowing the construction of variables from multiple data sources. Another study limitation was that the sample size was small and represented only our initial chart reviews. However, the study did benefit from a sample that was representative of a wide geographic area. Lastly, a further limitation of our study is that we lack information on alcohol ingestion by the women in our study. However, alcohol ingestion, while very important for long-term child outcomes, may not have a major impact on our major outcome of NICU length-of-stay.

CONCLUSION

Maternal use of prescription or illicit opioids is rooted in women’s life histories characterized by material disadvantage and multiple vulnerabilities such as mental illness and relationship instability, smoking and poly drug abuse. Primary prevention efforts should target the root causes of maternal drug use including poverty, inadequate education and mental illness as well as helping women dependent on opioids prevent pregnancy. Secondary prevention interventions to reduce the severity of NAS should be targeted at reducing smoking, opioid addiction and poly drug use prior to and during pregnancy.

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Chapter 259

MOTHERS IN PRISON

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ABSTRACT

The aim of this chapter is to investigate how the socio-environmental conditions that lead to poverty are associated. The objectives: 1) to draw attention to the incarceration experience of, women and children; and 2) to examine whether incarceration among Georgia women is associated with child behavioral health outcomes. Data was drawn from secondary analysis of a clinical sample of 40 children receiving services from the Emory Neurodevelopmental and Exposure Clinic (ENEC) in Atlanta, Georgia in 2017. Results showed increased levels of internalizing and externalizing behavior problems amongst children of incarcerated mothers compared to population norms. However, we also showed high rates of internalizing and externalizing behavior problems in a contrast group, which was comprised of children who were separated from their mothers at birth due to maternal drug use. Qualitative results suggest that incarcerated women and women whose children were removed from their custody at birth had similar life history trajectories leading to similar outcomes. Qualitative results also revealed that children in both case and contrast groups were exposed to stressful environments either in utero and/or while in their mother's care. Collectively, these results suggest that although maternal incarceration is a stressor, the adverse early social environments have an equally negative effect on internalizing and externalizing behavior problems in children. In order to break the cycle of social-environmental health disparities, future research and interventions should focus on how to protect these vulnerable children from the factors that lead to maternal incarceration and its consequences.

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INTRODUCTION

The last three decades of the United States' (US) war on drugs have seen an increase in incarceration and concern about its effects. Much of the focus has centered on the vulnerability of men, particularly young men of color, with little attention paid to the possible impacts of this war on women and children [1, 2]. Although males constitute most of the US prison population, there are an increasing number of female prisoners [3]. According to the American Civil Liberties Union (ACLU), women constitute the fastest growing segment of the American prison system [3]. Beginning in 1985, female incarceration rates have increased twice as much as those of their male counterparts [3]. As such, women constitute a growing but hidden segment of the American criminal justice system.

This gender bias underscores the need to study further the effects of incarceration on female inmates. The limited body of existing research on female inmates demonstrates that, similar to their male counterparts, women also are likely to experience the poor physical and mental health outcomes and worse self-reported health, which has been associated with incarceration [4-8]. Additionally, children might be at risk because approximately 70% of women in prison have children under the age of 18 and roughly 62% of these women were their children's primary caregivers and financial providers at the time of their incarceration [9-11]. Parental incarceration can negatively impact outcomes such as housing and schooling; indeed, evidence is emerging that children with incarcerated mothers are more likely to live in poverty, report poor academic performance, abuse drugs and develop mental health problems such as depression and anti-social behavior [12-14]. These children are also more likely to be incarcerated themselves later in life [12, 15]. The adverse effects of incarceration are suggested to be greater when mothers instead of fathers are incarcerated, since mothers are usually the primary caregivers [9, 10, 16].

Incarceration is a critical issue in understanding the impact of these children's separation from their mothers. Typically, incarceration is measured at the individual level rather than at the family level. Such measurements often obscure how mass incarceration affects children. From an anthropological perspective, examining incarceration's impact on children is important, as other adverse early life experiences as it not only affects individual's life histories but also those of their surrounding social networks [17, 18]. Understanding the impact of early life experiences on human development demands fundamental anthropological inquiry, for example into how both society and culture construct individuals over time. Understanding the impact of mass incarceration on women and children also is increasingly important from a drug use and addiction perspective [19-22]. Over the past few years there has been a growing recognition of the opioid epidemic in the US [23, 24]. Focus on drug use and addiction as a public health problem, instead of a deviant behavior should elucidate root causes which could ultimately lead to a decrease in the number of incarcerated individuals in the criminal justice system. Furthermore, a health focused approach, in which offending women receive treatment and probation instead of prison sentences, can potentially mitigate the negative effects of maternal incarceration. The aim of this paper is to examine how children are affected by maternal incarceration, and what factors protect or increase their risk for the negative effects of incarceration.

Georgia provides a valuable case study for female incarceration and its impacts on child development. According to the Georgia Department of Public Health, deaths related to drug overdose are now almost equivalent to those reported for motor vehicle accidents [25]. This increase in drug overdose deaths has left Georgia among the top 11 states in prescription drug overdose deaths [25]. Additionally, statistics on the prescription drug overdose upsurge across the state also illustrates that overdose deaths are rising among women [23]. Moreover, state-wide data on opioid addiction and overdoses have shown that the individuals at elevated risk are those that subsist among low-income populations, who reside in rural or urban areas. In addition, this population includes those who may have a record of mental illness and addiction to alcohol and/or drugs like cocaine or prescription pain medications [23]. The economic and health services resource divide between rural and urban populations leaves the majority of people living in rural communities with fewer employment opportunities and less access to adequate health care, particularly, drug treatment programs [25]. Therefore, many rural poor migrate to urban areas such as Atlanta with the hopes of improving their economic and health outcomes. Recent figures by the Brookings Institute have shown that Atlanta has consecutively held the top rank for the highest rate of income inequality in the US in recent years [26, 27] with increasing concentrations of people falling below the poverty line [28]. In such contexts, local prisons become safety nets for communities as they aim to separate themselves from the city's most vulnerable [19, 29].

A growing body of literature has demonstrated the extent to which drug addiction co-occurs with female incarceration [15, 30]; however, few studies have investigated the combined impact on child development [31-33]. This study examines effects of maternal incarceration on child development, among children of female inmates in the US criminal justice system. The intersection between incarceration and child behavioral health outcomes is particularly concerning as the US female prison population continues to increase [10]. Negative child behavioral health outcomes may be higher in this population as suggested by the substantial body of literature on maternal and child separation [34-39]. A large contributing factor to this lack of information may be the difficulty in conducting research within the prison system. As such, the effects of female incarceration on child development has been difficult to assess in part because few large-scale studies on the topic [40]. The current study uses data from a cross-sectional clinical sample of children from all over the State of Georgia who visit a clinic in Atlanta that provides care to children exposed to alcohol and drugs. These data were used to address the following hypotheses:

- Maternal incarceration leads to increases in internalizing and externalizing behavior problems in children.
- Among children of drug/alcohol using women, those who spend longer periods of consecutive time in their birth mother's custody report higher rates of internalizing and externalizing behavior problems
- Among children of drug/alcohol using women, those who spend longer periods of consecutive time in the custody of a non-maternal caregiver report lower rates internalizing and externalizing behavior problems.

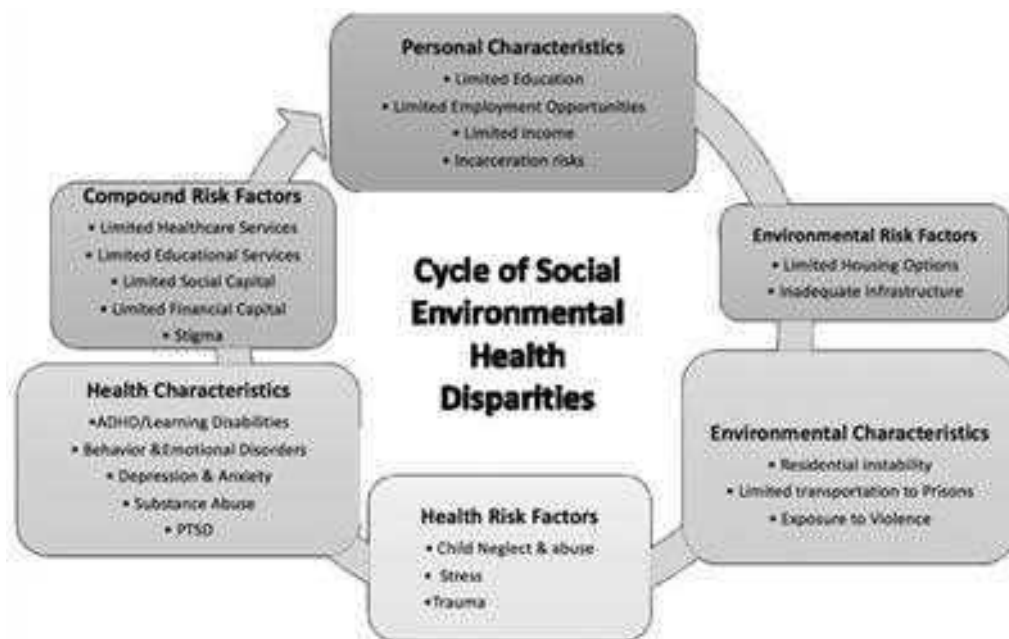


Figure 1. Cycle of social environmental health disparities.

By examining the effects of maternal incarceration on child development, this paper intends to shed light on the causes of environmental health disparities amongst this population. Existing literature has demonstrated that children can be negatively impacted by their parent's incarceration in areas such as housing and schooling, all of which can lead to poverty and mental health problems [12-14]. Therefore, by examining the hypotheses, this paper aims to provide ideas of interventions that can be useful to researchers and policy-makers alike, as they attempt to decrease social-environmental health disparities in our communities.

OUR STUDY

Secondary data were collected for this study from a database maintained by the Emory Neurodevelopmental and Exposure Clinic (ENEC) in the Department of Psychiatry and Behavioral Science, Emory University School of Medicine. ENEC serves children with behavioral and developmental problems with known or suspected prenatal exposure to alcohol and drugs. All patients applying for diagnostic services at ENEC may agree to participate in this database for the purpose of research by signing an informed consent document. Data are abstracted from questionnaires and medical records. The clinic serves a diverse population from the State of Georgia and the Atlanta metropolitan area ranging in age from birth through adolescence. For the current pilot study, records of 40 preschool and school aged children were selected. Data collection took place between February and April 2017. Only children who had data on all the variables of interest were included.

Convenience sampling was used to select children whose mothers were incarcerated at the time of the clinic visit. Of the participants (20 case and 20 contrast), the case group

consisted of children who were separated from their mothers because of maternal incarceration. The contrast group consisted of children who were separated from their mothers at birth due to maternal drug use but not incarceration. The contrast group was chosen because it was demographically similar to the case group apart from incarceration (see Table 1). Individuals in both groups were selected because they were similar ages, shared similar prenatal exposures to drug and alcohol and were not in their birth mother's custody at the time of data collection. All data were first entered into a RedCap database and then transferred to Microsoft Excel for analysis. All participants provided consent as noted above and prior approval for the study was obtained from the Emory Institutional Review Board.

The variables of interest were defined and searches for children with relevant data were initiated with the key search terms including: jail, probation, arrest, prison, incarceration as well as foster care, birth mother, protective custody, after birth and Georgia Division of Family and Children Services (GDFCS) (a sub-division of the Health and Human services department that assists children in cases of child abuse or neglect) [41]. In addition to placing children in safe care, ideally with extended family members but predominately in foster or adoptive homes, GDFCS also provides financial assistance and psychological services to families in hopes of keeping children with their parents [41]. These search variables allowed us to find children that fit our study criteria.

Children in these searches who met both age and custody criteria were included in the final sample. For those children who did not qualify, the primary reasons for exclusion were age, paternal, not-maternal incarceration, lack of clarity on whether the children were in their birth mother's custody or in another form of placement. This initial search produced 100% of the contrast participants. However, it produced 75% of the case participants; thus, to collect the remaining 25% of the case participants, manual searches of children's records were conducted from the entire ENEC database which is comprised of approximately 600 children. Manual searches were conducted from the ENEC database because not all records were digitized into RedCap at the time of data collection. Data collection was completed following manual searches. Additionally, children whose caregivers had no knowledge of their background and biological family history were excluded from the study.

Quantitative Data Collection

Demographics: Basic demographic information (see Table 1) included age, race and sex. Age was determined through the question, "How old is the child?" Race was ascertained via the question, "What racial group does the child identify with?" Response options included "African American/black," "Asian/Asian American," "Caucasian/White," "Mixed Race/Other". Child sex was established via the question, "Is the child male or female?"

Child Behavior Checklist (CBCL): Internalizing and externalizing behaviors were examined by reference to the results of the Child Behavior Checklist (CBCL) that had been administered to all children receiving clinical services at ENEC. This widely used 113-item questionnaire assesses behavioral problems in children [42]. A reliable and well-validated instrument, the CBCL's targeted symptoms include aggression behavior, anxious/depressed, attention problems, rule-breaking behavior, somatic complaints, thought problems, withdrawal/depressed and social problems [42]. Child behaviors were classified as either internalizing or externalizing to be consistent with the study hypothesis. Internalizing

behaviors are seen as behaviors through which children may focus their thoughts, feelings and emotions inwardly [43]. These include “fear of trying new things, avoiding looking at others in the eye, and a lack of concentration” [42]. On the other hand, children who exhibit externalizing behaviors, are those who focus their thoughts, feelings and emotions in an outward way [44]. These include being “cruel to animals, defiant, and oppositional behavior, and demands that their needs be met immediately” [42]. Respondents were asked to consider the presence of each item/symptom over the child’s life and to rate each item along a Likert scale from 0 (never true) to 2 (very true or often true). Possible CBCL scores range from 50 to 100. CBCL scores are T-Scores meaning the mean of 50 for the population and a standard deviation of 10. Scores greater than 70 are considered clinically significant, however, scores 60 to 69 are possibly ‘borderline’ [45]. As such, the CBCL does not report scores less than 50 as these are not considered to be meaningful in terms of identifying behavior problems. This article therefore presents CBCL scores of ≥ 60 as these scores are indicative of internalizing/externalizing problems [45].

Quantitative Variables

In addition to maternal incarceration, this study also investigated the effects of time in current caregiver’s care and time in birth mother’s care. These two variables were chosen in an effort to understand whether stable caregiving following separation from the birth mother had the potential to decrease negative child behavioral health outcomes. Additionally, time in birth mother’s care was selected as a variable of interest in order to understand whether separation from birth mother after living in her custody for longer periods increased negative behavior health outcomes. These two variables were also chosen because the case group had spent time in their birth mother’s custody, while the contrast group had not. This was done in order to understand whether the case group would exhibit negative behavioral health outcomes due to this separation. Additionally, this variable was selected because living with a drug using mother can also be a stressor for children. Thus, separation due to incarceration could potentially yield positive results.

Table 1. Participant demographics: Case and contrast

Characteristic	Case				Contrast	
Sex	Male (n = 12)	Female (n = 8)	Total (n = 20)	Male (n = 13)	Female (n = 7)	Total (n = 20)
Age	Mean = 5 years, 6 months	Mean = 5 years, 1 month	Mean = 5 years, 3 months	Mean = 5 years, 5 months	Mean = 6 years, 4 months	Mean = 5 years, 9 months
Race						
Black	3	5	8	2	4	6
White	6	3	9	8	1	9
Mixed Race	3	0	3	2	2	4
Asian	0	0	0	1	0	1

Qualitative Data Collection

The qualitative data presented in this article come from clinical records of children's biological family histories. These records were collected from children's caregivers at the time of the child's clinic visit. Major themes in these interviews revolved around child's relationship with birth parents, reasons for separation from birth parents, and birth parent's childhood, educational history, and birth parent's criminal records. These reports served as semi-structured interviews because they were nested within children's clinical evaluations in which caregivers were given prompts and in return they gave detailed open-ended responses. Family and social histories not only provided information not only on the child's background but also provided information on the birth mother's background as birth mother's life histories were included in these documents. The depth and breadth of these histories differed due to a caregiver's knowledge of a child's background. Some caregivers were relatives or had been given detailed case histories by children's case managers. As a result, they were able to provide detailed information on the child's background.

Data Analysis

The analytic approach undertaken aimed to determine whether maternal incarceration influences CBCL scores; that is, whether the case group reported higher CBCL scores than the contrast group. Univariate tests (t-tests) were used to statistically assess whether differences would be observed between the two groups. A multivariate logistic regression was used to estimate the effects of maternal incarceration and the other covariates on internalizing and externalizing CBCL scores. Statistical analyses were performed using the software program, Microsoft Excel.

Qualitative interviews were de-identified and exported into MAXQDA (a qualitative data analysis software program). In MAXQDA, content analysis was used to identify discussions around separation from birth mother, incarceration, and child behavior. Initially, five cases and five contrast participants were coded. This was done in order to create a codebook. The codebooks were comprised of recurrent codes that were appearing in the respective interviews. Following the creation of the codebook, the remaining documents were coded, only rarely adding new codes. Examples of these key codes included mentions of maternal incarceration, reasons for incarceration, mentions of child abuse, maternal background, and descriptions of the child's behavior. These codes led to three thematic sections. The first theme emerged around maternal incarceration and reasons for maternal incarceration. The second theme consisted of topics discussing maternal childhood and personal history. The final theme was comprised of topics related to descriptions of the child's behavior.

RESULTS

There were no significant differences in demographics. Case and contrast groups were evenly matched as children were comprised of similar age, sex and race categories.

T-Tests

Both case and contrast groups had similar CBCL scores. The mean CBCL score for internalizing behavior for case participants was 59.0 and the mean CBCL score for internalizing behavior for contrast participants was 58.95. Both case and contrast groups were therefore higher than the normative mean CBCL score which is 50. However, these scores were both less than 60, meaning they are not indicative of a clinical level of internalizing behavior problems. Alternatively, the mean CBCL score for externalizing behavior for case participants was 63.47 and the mean CBCL score for externalizing behavior for contrast participants was 63.35. Both case and contrast scores were significantly higher than the normative mean CBCL score of 50. They were also above 60 meaning the total externalizing scores of case and contrast participants were indicative of externalizing behavior problems.

Table 2. Case and contrast internalizing and externalizing CBCL scores

	Case Mean	Contrast Mean	Mean diff	5%	95%	t	df	p
Internalizing Scores	59.00	58.95	0.050	-8.296	8.396	0.01201	36.01	0.9904
Externalizing Scores	63.47	63.35	0.124	-8.984	9.232	0.028	35.74	0.9782

Multivariate Regression Analysis

Multivariate regressions were used to examine other factors that might be affecting the CBCL scores.

In addition to maternal incarceration, the other variables considered for this model were: time spent with birth mother and time spent with current caregiver. In this analysis neither of these variables influenced internalizing behavior significantly. The p-value for time spent with current caregiver was 0.247; for time spent with birth mother was 0.181 and for maternal incarceration was 0.327. None of these p-values are statistically significant, therefore the proposed hypotheses were not supported. The R-squared statistic demonstrated that the model only explained 5% of the variance in internalizing behavior scores. Thus, other etiological variables are influencing internalizing behavior; however, these were not accounted for in this model.

Table 3. Internalizing behavior multivariate scores

Variable	Coefficient	p-value
Time with current Caregiver (months)	-0.074	0.247
Time with Birth Mother (months)	-2.229	0.181
Maternal Incarceration	3.298	0.327
Intercept	63.53	3.55e-12
R-squared	0.05	

In this analysis as well, none of the independent variables had a statistically significant influence on externalizing behavior. The p-value for time spent with current caregiver was 0.396; for time spent with birth mother was 0.113; for maternal incarceration was 0.141. None of these p-values are statistically significant, therefore my model did not support the proposed hypotheses. R-squared demonstrated that the model only explained 8% of the variance in externalizing behavior scores. Therefore, as with internalizing behavior, other unknown factors not accounted for in this model are influencing externalizing behavior.

Table 4. Externalizing behavior multivariate scores

Variable	Coefficient	p-value
Time with current Caregiver (months)	0.002	0.396
Time with Birth Mother (months)	-3.131	0.113
Maternal Incarceration	8.473	0.141
Intercept	62.99	5.35e-11
R-squared	0.08	

Qualitative Results

Although the T-test results illustrated that both case and contrast participants report higher than normal internalizing and externalizing CBCL scores, the regression model suggested that factors other than those in the model affected CBCL scores. A subsequent examination of children's family and social histories was attempted to better understand the factors that could be affecting these results. The family and social histories of these children revealed some of the other factors that might be influencing these high CBCL scores.

These family and social histories illustrated that there is more to these women than incarceration. The biological mother's life histories revealed childhood trauma, sexual and physical abuse, poverty, and limited education. Mothers reported 8th or 9th grade education and most significantly, adolescent alcohol and drug use, which continued throughout their lives and pregnancies. Two excerpts from birth mothers' life histories reflect these points:

Her biological mother initiated substance use as young as 11 years of age when she began smoking. Her mother reportedly had her first child at 14 and was forcibly raped before she was 16 years of age. She reportedly quit school during the 9th grade as a result of her 1st pregnancy. She also had a long history of stays with the juvenile justice program in her youth. (Case, B32: Names are changed to preserve anonymity)

Ben was born to Quinn McBerry, who was 20 years old at the time of Ben's birth. Ms. McBerry completed the 8th grade. Per reports, Ms. McBerry drank alcohol while pregnant, with a pattern of binge-drinking on weekends, and was also using marijuana, methamphetamine, and tobacco during the pregnancy. (Contrast, F15: Names are changed to preserve anonymity)

These family histories are illustrative of both case and contrast maternal life histories. They demonstrate that both groups of mothers experienced early life trauma and have been abusing substances since they were younger. Additionally, both mothers in these groups have limited education as their highest level of education is 9th and 8th grade, respectively. These two examples serve to suggest that these two groups have similar life histories, which could be a contributing factor as to the lack of differences between case and contrast groups.

These family and social histories also revealed that the lives of these children prior to maternal incarceration contained information pertaining to drug and alcohol abuse, neglect, housing instability and poverty.

Excerpts from children's lives with their birth mothers also reveal similarities:

The Department of Children and Family Services removed her from her biological mother as a result of neglect, substance abuse, unstable housing and unemployment, a previous removal of her other two children, and incarceration related to a probation violation for a shop-lifting conviction." (Case, B32: Names are changed to preserve anonymity)

Jeremy was taken into the Brown home immediately from the neonatal nursery and has never lived elsewhere. His biological mother had a history of substance abuse and social and legal problems." (Contrast, F15. Names are changed to preserve anonymity)

These family histories illustrate that although the contrast participant was adopted at birth, he was pre-exposed to his mother's negative environment in utero. Additionally, the case participant's life history also suggests exposure to negative early life events as his mother's incarceration for shoplifting coincided with other charges such as child neglect, unstable housing and substance abuse, all of which are detrimental to child development. These accounts suggest that maternal incarceration is an additive not definitive factor in the children's behavioral health outcomes.

DISCUSSION

Anthropologists have long focused on child development, maternal and child relationships and psychosocial stress in efforts to understand the biological and sociocultural underpinnings of development [46-50]. As such, anthropological research has provided evidence for the ways through which biological and psychosocial early-life stress can influence adult health and disease outcomes [17, 48, 51].

As prior research has suggested, maternal incarceration as an early-life stressor can have long-term consequences that affect children well into adulthood [16, 40]. Evidence has demonstrated that children of incarcerated women are themselves likely to abuse drugs, develop mental health problems and be incarcerated later in life [16, 40]. These effects illustrate that maternal incarceration may have influences that extend beyond the individual child, but can potentially influence subsequent generations, thereby reproducing the cycle of incarceration. Furthermore, the transgenerational effects of maternal incarceration could lead to similar health and social effects as those experienced by individuals living in poverty [17]. In continuation of this investigative tradition, this study aimed to examine the impact of maternal incarceration as a psychosocial stressor on child development. However, this study did not demonstrate statistically significant results regarding the effects of maternal incarceration on children's behavioral health outcomes when a contrast group with similar demographic characteristics was used. However, the t-tests illustrated that both case and contrast participants report higher than normal -'borderline' clinical internalizing and externalizing CBCL scores. Although the internalizing score for either group were not indicative of problems, the externalizing scores for both groups were elevated. Therefore,

although these groups exhibit results that suggest clinical problems, we cannot conclude that maternal incarceration itself had any additional effects.

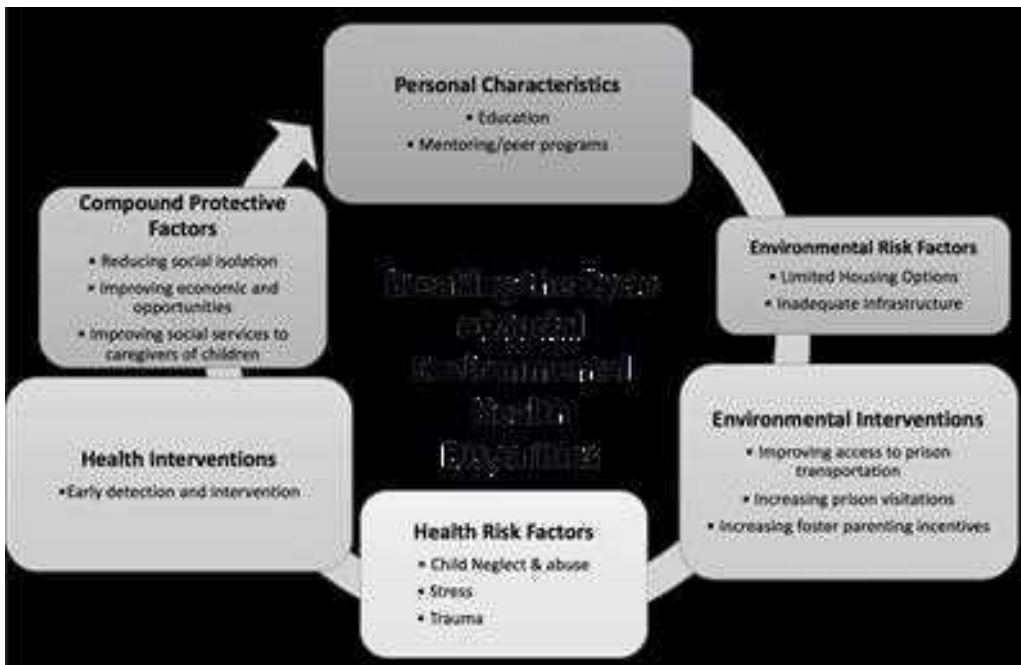


Figure 2. Breaking the cycle of social environmental health disparities.

A large contributing factor to the similarities in these results is that both groups of children have experienced stressful conditions. Both groups have experienced disruptive childhoods as they have been separated from their biological mothers and have also been prenatally exposed to drugs and/or alcohol. Most significantly, the mothers of these children also experienced traumatic childhoods and subsequently continued these patterns of abuse and neglect with their own children.

The qualitative results suggest that psychosocial stressors such as child neglect, drug addiction, poor education and poverty contribute to negative CBCL scores for children. Additionally, these qualitative results illustrate that it can be difficult to isolate a single psychosocial stressor as the independent cause of negative child behavioral outcomes as they overlap and co-occur [18]. Maternal incarceration in this case occurred in the presence of child neglect, poverty, limited education and substance use. The qualitative results therefore suggest that in living with mothers and/or simply being prenatally exposed to their birth mother's negative environments such as maternal drug use, these children were already at risk of negative child behavior outcomes regardless of maternal incarceration. Therefore, to better understand the causes of negative CBCL scores, it is important to not only examine maternal incarceration or the variables included in the regression, but to also examine the social environments that these children were exposed to while in their birth mother's custody.

Study Limitations

The biggest limitation of the study was the sample size. This total sample of 40 participants may have been underpowered and therefore too small to yield any statistically significant results. Thus, the small sample size may erroneously suggest that incarceration is not a factor in child behavior (as suggested by the observed trends). Follow up studies with larger sample sizes are needed to determine the effects of maternal incarceration on child behavioral health outcomes. Another limitation of this study is that the sample is a self-selected clinical sample, meaning that the children in this sample were individuals whose caregivers knew about their possible prenatal exposure to alcohol and/or drugs and chose to bring them in for an evaluation at ENEC. These children are therefore not representative of the general population and may have been more likely to have behavior problems.

CONCLUSION

Despite these limitations, this study provides a starting point for efforts to understand the effects of maternal incarceration on children's behavioral health outcomes. The qualitative data were able to elucidate some of the challenges in studying this population. The qualitative data demonstrated that the point of examination or intervention for negative child behavioral health outcomes is not when mothers are incarcerated but before, as the factors that lead to both maternal incarceration and unfavorable CBCL scores occur when children are in their mother's custody. Because the contrast participants were comprised of children who also experienced disruptive childhoods, they served as an important comparison as they showed similar CBCL scores. The contrast group therefore suggested that the behavioral problems experienced by this clinical population may occur before incarceration.

This study was also able to produce valuable information on breaking the cycle of poverty. It demonstrated that although maternal incarceration is a stressor in children's lives, the points of intervention are before mothers are incarcerated. The qualitative data revealed how these women's lives developed from their limited education to their adolescent and early adult drug use and their subsequent incarceration and loss of child custody are emblematic of their social environments. The two main points of intervention when attempting to break the cycle of poverty are early education and drug treatment. Early education will break the cycle as by keeping children in school they are more likely to be exposed to positive influences, not engage in drug use, and instead of being on a path to incarceration, they can find employment and be productive members of society. Drug treatment can help mitigate some of the negative effects of drug use on child development as the qualitative data illustrated that maternal substance abuse was one of the main reasons as to why children were removed from their birth mother's custodies. Additionally, providing women with drug treatment can decrease the number of those incarcerated as health focused approaches attempt to keep families together. As US maternal incarceration rates continue to rise, the question of what leads to maternal incarceration will remain salient, as will that of its impact on children. It is therefore crucial for researchers and policy-makers alike to implement supportive interventions that are aimed at breaking the cycles of poverty and incarceration before more women are incarcerated.

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Chapter 260

HOUSING INSTABILITY AND CHILD GROWTH AND DEVELOPMENT

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ABSTRACT

Housing instability is thought to be a major influence on children's healthy growth and development. However, little is known about the factors that influence housing instability, limiting the identification of effective interventions. The goals of this chapter were to 1) explore factors, including material hardship, satisfaction with living conditions and housing disrepair, that predict housing instability (total number of moves that a child experienced in the first seven years of life); and 2) examine the relationship between housing instability and child behavior at age 7 years, measured by the Child Behavior Checklist. We analyzed these associations among children enrolled in the Columbia Center for Children's Environmental Health (CCCEH) Mothers and Newborns study. In our analysis, we found that housing disrepair predicted residential change after three

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years of age, but not before. Persistent material hardship over the seven-year time period from pregnancy through age 7 years was associated with increased number of moves. Children who experienced more than three moves had significantly more thought- and attention-related problems compared to children who experienced fewer than three moves over the same time period. Children who experienced more than three moves also had higher total and internalizing problem behavior scores, although these differences were not statistically significant. We conclude that housing instability is associated with problem behavior related to thought and attention in early childhood and that interventions to reduce socioeconomic strain may have the greatest impact in breaking the cycle of children's environmental health disparities related to housing instability.

INTRODUCTION

Housing instability is a growing problem in the United States, particularly for those living in urban, low-income neighborhoods [1, 2]. Despite the importance of stable housing, current research has struggled to define and identify housing instability and its effects on children's health. Previous studies have used different parameters to measure housing instability, including frequent moves and living with relatives and friends [4-6] and the US Department of Health and Human Services has defined housing instability using housing cost, housing quality, neighborhood stability, crowding, and homelessness [3].

Recent research has begun to focus on the impact of housing instability, in its many forms, on child health and development [1]. It is hypothesized that young children are at greater risk of adverse effects of living environments, as this time period serves as a critical window for establishing socialization and learning habits [7, 8]. Additionally, the effects of housing instability may be compounded when combined with other challenges faced by low-income families, such as lack of resources [1]. Previous studies have found that housing instability is associated with deficits in overall academic achievement [9], emotional regulation [7, 8], and verbal abilities [10]. These health outcomes can have serious long-term effects as children progress through adolescence and adulthood, including decreased educational attainment [11], increased participation in risky behaviors [12, 13], and a greater risk of adult-onset chronic diseases [14].

In the present paper, we explore the predictors of housing instability, including physical characteristics of housing and measures of socioeconomic strain in a low-income urban population of minority mothers and children. We also evaluate how housing instability, characterized by frequency of residential moves, affects child behavior assessed at age 7 years. We expect these results will inform future public health programs focused on identifying appropriate intervention points at which to break the cycle between unstable housing and child health outcomes.

OUR STUDY

The Mothers and Newborns Study is a longitudinal birth cohort maintained by the Columbia Center for Children's Environmental Health (CCCEH). The study enrolled 727 pregnant women living in Northern Manhattan and the South Bronx between 1998 and 2006.

Study participants were African American or Dominican and were between the ages of 18 and 35 years at the time of recruitment. Subjects were excluded from the cohort if they reported smoking cigarettes or using other tobacco products during pregnancy, used illicit drugs, had their first prenatal visit after the 20th week of pregnancy, or had one of the following pre-existing conditions: diabetes, hypertension, or known HIV infection. Cohort participants were excluded from the current analysis if they did not have complete information on residential history at the prenatal and ages 1, 2, 3, 5 and 7-year follow up visits or if the mother was not administered the Child Behavior Checklist (CBCL) at the 7-year visit (see Figure 1). All study protocols were approved by the Institutional Review Board of Columbia University. Before each visit, mothers were informed about all study procedures and provided written informed consent to participate.

Mothers and their children were followed up at approximately 1, 2, 3, 5 and 7 years after birth. Research workers conducted a structured interview to ascertain demographic characteristics of the mother (i.e., age at delivery, ethnicity, education, relationship status) and child (i.e., gender). Maternal demoralization, defined as the extent to which a mother experiences nonspecific psychological distress, was additionally assessed at each study visit using the Psychiatric Epidemiology Research Instrument- Demoralization (PERI-D) scale [15].

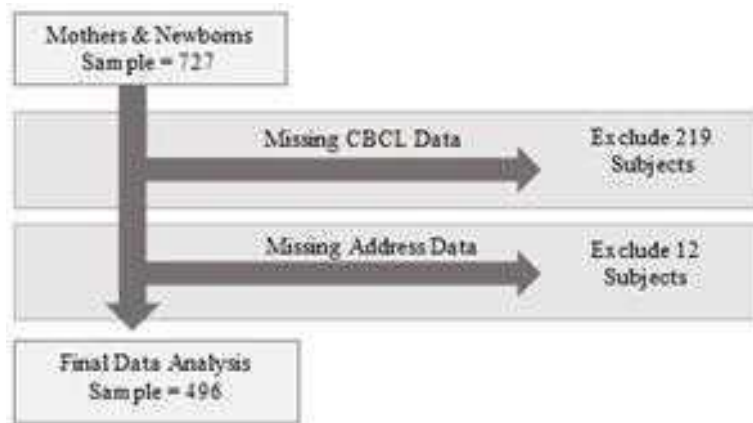


Figure 1. Final data analysis sample.

Residential History, Building Disrepair and Housing Satisfaction

At each study visit research assistants recorded all addresses at which the mother-child pair resided since the previous study visit. We summed the number of study visits for which an address change occurred since previous study visit to create an index of instability experienced by each child. We defined unstable housing as a greater than 3 moves from the prenatal period to age 7 years. Research workers also collected information on maternal-report of paint chips or dust, holes in the ceiling or walls, mold, and leaky pipes in their current residence. We coded these building disrepair variables as 1 or 0 based on whether they were present or not. Similarly, pest variables, including maternal report of roaches, rodents, and other insects were also recorded and coded as 1 or 0 based on their presence. At

each time point, we summed the number of building disrepair and pest items to create a visit-specific measure of housing disrepair (range: 0 to 7), which we subsequently categorized into three levels: no housing disrepair, one housing disrepair item, or two or more housing disrepair items. Finally, mothers rated their level of satisfaction with their current living conditions on a scale of one to five (one indicating “very satisfied” and five indicating “very dissatisfied”) at each interview. We created a dichotomous variable by collapsing “very satisfied,” “somewhat satisfied,” or “neither satisfied nor dissatisfied” into one level and “very dissatisfied” or “somewhat dissatisfied” responses into a second level.

Material Hardship

At each study visit mothers were asked a series of questions adapted from a survey designed to measure material hardship among urban populations [16] to determine the level of economic strain that they were experiencing. This included questions about the mother’s self-reported ability to afford housing/rent, gas and/or electricity, food, and clothing. We summed the number of ‘hardships’ at each time point to create a material hardship scale ranging from 0 to 4. As previously described [17], we used Latent Class Growth Analysis to empirically estimate trajectories of material hardship from pregnancy through age 7 years. We found that mothers belonged to one of four hardship trajectories: increasing over time, decreasing over time, persistent low, and persistent high. Given our interest in socioeconomic strain, in all analyses we compared the persistent high hardship trajectory to the other three trajectories (low or fluctuating hardship) collapsed into a single group.

Child Behavior

At the seven-year follow-up visit, mothers were administered the Child Behavior Checklist (CBCL), which is a validated tool for assessing behavior problems in children [18]. Mothers rated their children’s behavior on 113 items as never present, sometimes present, or often present. Scores on these items are summed and grouped into syndrome scales, which provide information across several behavioral domains. We analyzed the scores from several scales, including: attention and rule breaking (collectively: externalizing behaviors), anxiety/depression, withdrawn, and somatic complaint (collectively: internalizing behaviors), and attention, thought, and social problems. A total behavioral problem score is obtained from the sum of all eight syndrome scores.

Data Analysis

To better understand the predictors of housing instability, we examined the relationship between housing disrepair, maternal satisfaction with housing, and housing instability (see Figure 2). We analyzed the relationship between housing disrepair and maternal satisfaction with living conditions at each time point using a logistic regression. Satisfaction with living

conditions and housing disrepair at each time point was analyzed as a predictor of having moved by the time of the next interview.

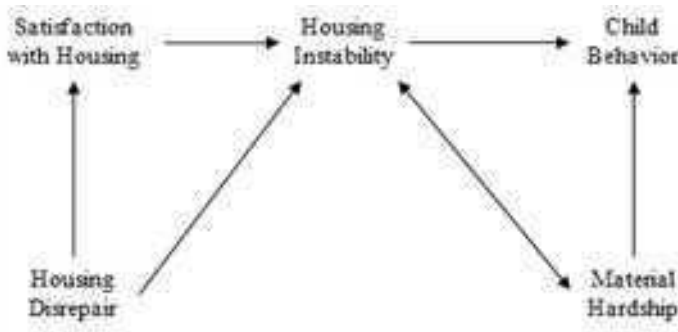


Figure 2. Conceptual diagram of predictors and outcomes of housing instability.

We assessed CBCL outcomes using the raw scores from the checklist in a negative binomial regression model, which is better suited for this type of count data and has been used in previous studies with the CBCL [19]. The number of moves over 7 years was treated as a categorical predictor of CBCL scores using the following groups: 0-1 moves, 2-3 moves, and more than 3 moves. Since the CBCL is a maternally-reported questionnaire, and responses may be affected by the mother's psychosocial well-being, we included maternal demoralization score, or the extent to which a mother experiences nonspecific psychological distress, in our final model [15]. Additional covariates included in the model were maternal education, child age, child gender, and child ethnicity, based on their prior association with child behavior [19].

We also examined the role of material hardship in the main analysis, since material hardship has previously been shown to predict behavior problems in childhood (see Figure 2) [11]. In order to understand how long-term hardship was related to housing instability, total material hardship over the seven years was analyzed using a latent variable model, which categorized each participant into one of four categories: increasing hardship over time, decreasing hardship over time, consistently low hardship, and consistently high hardship [17]. In our final model for this analysis, we analyzed the total number of moves over the seven-year time period as a mediator in the relationship between material hardship and housing instability.

OUR RESULTS

The final sample for this analysis included 496 subjects of the original 727 subject cohort. As illustrated by Table 1, the study population was completely of Dominican or African American ethnicity. These demographic characteristics were not significantly different between the participants included ($N=496$) and those excluded ($N=231$) due to missing residential history or CBCL scores. The average age of the mother at the prenatal visit was approximately 25 (25.2 ± 4.96) years old and approximately three-quarters (74.2%) of the mothers were single. Almost one quarter (21.4%) of the study population experienced persistent high material hardship throughout the study period.

Housing Disrepair, Satisfaction with Living Conditions and Housing Instability

We assessed the relationships between housing disrepair, satisfaction with living conditions, and housing instability using Pearson's chi-squared tests. Higher housing disrepair scores at each time point after birth were associated with lower maternal report of satisfaction with living conditions at the same time point (see Table 2). However, dissatisfaction with living conditions did not always predict movement at the following interview. We did observe a difference in the probability of a change in housing in families with older versus younger children. Although this was not the case for children under three years, there was a statistically significant positive association between at least one address change and housing disrepair at the 3-year visit (OR=1.81, $p<0.05$) and 5-year visit (OR=1.67, $p<0.05$) (see Table 2).

Table 1. Characteristics of maternal-child pairs included in the analysis (N=496)

	N (%) or Mean±SD
Maternal age at prenatal visit	25.2 ± 4.96
African American	188 (38.0)
Dominican	307 (62.0)
<HS education at prenatal visit	178 (32.2)
Married or stable relationship at prenatal visit	128 (25.8)
Maternal demoralization at 7 year visit	0.97 ± 0.68
Male	229 (46.2)
Child age at Child Behavior Checklist	7.06 ± 0.20
Persistent high material hardship	106 (21.4)
Maternal dissatisfaction with living conditions:	
Prenatal visit	49 (9.88)
1 year visit	57 (11.5)
2 year visit	70 (14.1)
3 year visit	62 (12.5)
5 year visit	62 (12.5)
7 year visit	64 (12.9)
Ever move since previous study visit:	
1 year visit	80 (16.1)
2 year visit	84 (16.9)
3 year visit	104 (20.9)
5 year visit	146 (29.4)
7 year visit	145 (29.2)
Total number of study visits between which a residential move occurred:	
0-1	301 (60.6)
2-3	173 (34.8)
>3	22 (4.44)
≥2 building disrepair items	
Prenatal visit	379 (76.4)
1 year visit	324 (65.3)
2 year visit	320 (64.5)
3 year visit	302 (60.8)
5 year visit	285 (57.4)
7 year visit	272 (54.8)

Housing Instability and Child Behavior

The relationship between housing instability and child behavior was examined using a negative binomial regression model that controlled for material hardship, maternal demoralization, maternal education, child age, child gender, and child ethnicity. In the adjusted model, we found that children who experienced housing instability, defined as a residential move at more than three study visits (N=22, 4.44%), had 1.95 ($p<0.05$) and 1.56 ($p<0.05$) times the odds of thought-related and attention-related problems compared to children with stable housing (defined as a residential move between 1 or fewer study visits), respectively. The total number of behavior problems and overall internalizing problems were also higher in children who experienced more than three moves over seven years, but these associations were not statistically significant after adjusting for confounders (see Table 3).

Table 2. Association between housing disrepair, satisfaction with living conditions, and residential moves

	Dissatisfied vs. satisfied with living conditions OR (p-value)	Ever vs. never move since previous study visit OR (p-value)
Housing disrepair: ≥ 2 items vs. 0 items		
Prenatal	0.812 (0.544)	N/A
1 year	2.12 (0.023)	0.842 (0.541)
2 year	2.16 (0.009)	1.40 (0.198)
3 year	2.42 (0.005)	0.895 (0.629)
5 year	2.21 (0.008)	1.81 (0.005)
7 year	3.07 (0.000)	1.67 (0.012)
Dissatisfied vs. satisfied with living conditions		
Prenatal	N/A	N/A
1 year	N/A	0.687 (0.416)
2 year	N/A	1.07 (0.856)
3 year	N/A	1.32 (0.372)
5 year	N/A	3.26 (0.000)
7 year	N/A	0.913 (0.767)

Table 3. Summary of CBCL results in relation to housing instability and persistent material hardship included in the same model^a

CBCL Syndrome	Housing instability ^{b, c} IRR (p-value)	Persistent hardship ^d IRR (p-value)
Anxiety/Depression	1.24 (0.32)	1.27 (0.04)
Withdrawn	1.46 (0.20)	1.34 (0.05)
Somatic complaints	1.10 (0.72)	1.40 (0.01)
Social problems	1.37 (0.13)	1.13 (0.26)
Thought problems	1.95 (0.02)	1.56 (0.01)
Attention problems	1.58 (0.04)	1.27 (0.05)
Rule breaking behavior	1.27 (0.29)	1.15 (0.24)
Aggressive behavior	0.00 (0.99)	1.19 (0.14)
Internalizing behavior problems	1.25 (0.25)	1.33 (0.01)
Externalizing behavior problems	1.08 (0.71)	1.18 (0.13)
Total behavior problems	1.29 (0.15)	1.23 (0.03)

Abbreviations: CBCL- Child Behavior Checklist

^a Models also adjusted for maternal demoralization, maternal education, child gender, child ethnicity, and child age at time of CBCL.

^b Defined as more than 3 residential moves from the prenatal period to age 7 years.

^c Reference group defined as 0-1 moves over the first 7 years.

^d Reference group defined as to low or fluctuating hardship.

The Role of Material Hardship

Compared to families with low or fluctuating material hardship, we found that families experiencing persistent high material hardship were significantly more likely to experience housing instability (Incidence Rate Ratio (IRR)=1.36, $p<0.05$). Additionally, children in families who experienced persistent material hardship had significantly higher internalizing (IRR=1.32, $p<0.05$) and total (IRR=1.22, $p<0.05$) problem scores as well as significantly higher anxiety/depression (IRR=1.25, $p<0.05$), somatic complaint (IRR=1.41, $p<0.05$) and thought-related (IRR=1.53, $p<0.05$) problem scores. When we adjusted for the number of moves a child experienced, the effect of persistent material hardship on anxiety/depression, somatic complaint, thought-related, internalizing, and total problems was virtually unchanged. The results for all syndrome scores from the adjusted model are presented in Table 3.

DISCUSSION

We examined the predictors of housing instability, as well as behavioral outcomes of housing instability among a subset of participants enrolled in the CCCEH Mothers and Newborns birth cohort. We observed significant inverse associations between housing instability and child behavior at age 7 years. Material hardship over time was a significant predictor of poor behavior outcomes, and was also associated with housing instability. Housing disrepair was associated with an address change at 3 and 5 years of age, indicating that housing disrepair may predict housing instability as children grow older.

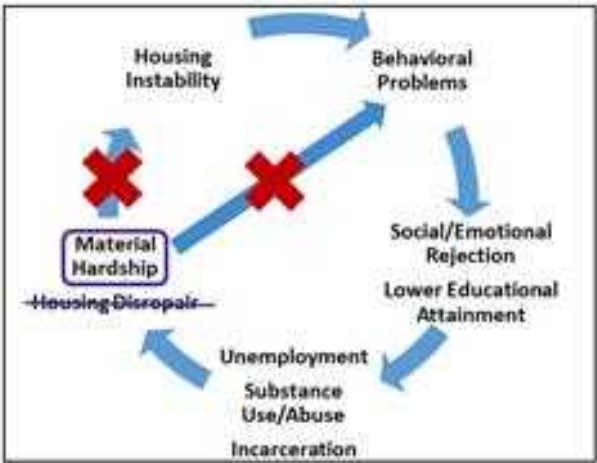


Figure 3. Breaking the cycle of environmental health disparities related to housing instability and child behavior.

These findings demonstrate the importance of material hardship as a predictor of housing instability as well as an independent predictor of child behavior outcomes. While building disrepair had some effect on movement, it was only a significant predictor in the later years of early childhood. We found that both attention- and thought-related behavior problems were

associated with housing instability, even when controlling for material hardship. Problems with attention may include concentration difficulties, impulsivity, day dreaming, difficulty sitting still, nervousness, and poor performance in school [18]. Thought-related problems may include seeing or hearing things, repeating acts, and having strange ideas and behaviors [18]. These are issues that can have serious consequences for children, especially in terms of their academic performance and social and emotional well-being [7, 8, 11]. These results are consistent with those from the Fragile Families and Child Wellbeing Study, which saw increased attention problems in children who experienced both housing instability and poverty [11].

The results from this analysis indicate that economic strain may be an optimal point of intervention in order to both reduce frequent moves and decrease the effects of housing instability on child neurobehavioral development (see Figure 3). Previous research shows that families who receive subsidies or energy assistance are less likely to experience frequent moves [20]. However, families eligible for housing subsidies rarely receive them due to the high demand and low availability, especially in large urban areas [21]. There is a clear need for greater financial support for low-income families experiencing material hardship, but recent investment has instead addressed the issue with new structural development and improvement. These efforts to improve neighborhoods and living conditions often backfire on the immediate community, leading to increased cost of living, higher property taxes, and eventual gentrification [22]. Other housing programs, such as the Moving to Opportunity for Fair Housing initiative (MTO), focus on increasing a family's upward mobility rather than stability [23]. This analysis suggests that financial capital may be better spent on programs that increase a family's ability to remain in a long-term home, particularly for those living in urban neighborhoods.

Study Limitations

There are several limitations to our analysis. We did not have information on why the mothers in the study cohort moved, so we cannot determine if the move was forced or a choice. Additionally, it was not feasible to determine whether a move was lateral, downwards, or upwards in terms of living conditions or neighborhood indicators of poverty, based on the available measures. Our exclusion parameters prevented subjects with incomplete address data, likely due to loss to follow up or inability to locate, from being included in the analysis. These mothers may have experienced high levels of housing instability, introduced selection bias and prevented us from evaluating the full impact of housing instability in this cohort. The CBCL, which was used to measure child behavior, was completed by the mother rather than direct observation of the child, which introduces reporting bias. However, we included maternal demoralization to lessen this bias. This analysis was done in a cohort of low-income, urban, minority mothers, and the results may not be reproducible in other highly mobile families, such as migrant workers or military families. Despite these limitations, our analysis included detailed and thorough information on housing characteristics and material hardship. These parameters were collected at several time points throughout the study period, allowing us to understand the longitudinal effects of possible predictors of housing instability.

CONCLUSION

Material hardship is a predictor of behavior problems in childhood and is also significantly associated with housing instability. Housing instability is associated with increased behavior problems in childhood, particularly in relation to thought- and attention-related processes. These results support the idea that housing assistance in the form of subsidies may be the most effective use of spending to combat the issue of housing instability for families living in low-income neighborhoods.

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Chapter 261

DDT EXPOSURE, SOCIO-ECONOMIC STATUS AND NEURODEVELOPMENTAL OUTCOMES IN CHILDREN

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ABSTRACT

Owing to high malaria burden, the Government of the Republic of Zambia is implementing an Integrated Vector Control Program. This encompasses Indoor Residual Spraying using Dichlorodiphenyltrichloroethane (DDT), and other chemicals. DDT, a persistent organic pollutant, is banned in the developed world, due to its toxic effects on the environmental and human health. Despite the country using DDT in the last 15 years, there have been no corresponding studies to establish whether it has any effects on human health. This study focused on studying the association of recent exposures on the neurodevelopmental outcomes of children in selected locations. Further, we evaluated the role other factors contributed to the outcomes. We conducted a survey targeting mother and child pairs in the Chawama and Mongu townships of Zambia. Utilizing the Ages and Stages Questionnaire (ASQ), we assessed children's abilities in communication, gross motor, fine motor, problem solving, and personal social interaction domains. We also collected information about maternal characteristics. Our results revealed median neurodevelopmental scores within the range that warranted further attention. Age seemed to modify the effect of chemical exposure on fine motor and personal social domains. Generalized linear models showed the strongest predictors of the children's neurodevelopment were mother's marital status, role in the family, income levels, and type of house. The area of chemical application was a significant factor. These results call for increased investment in improving the socio-economic status of communities and women in particular. This will enable them provide a more nurturing and stimulating environment for their children.

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INTRODUCTION

A child's physical and social environment plays a key role in their development and health. Because of poverty and other limiting socio-economic factors that remain a challenge in many countries, an infant's neurodevelopment may be compromised by a host of influences ranging from genetics to socio-cultural factors [1]. Environmental factors, including chemicals such as lead, mercury and persistent organic pollutants (POPs), are principally detrimental during prenatal and early child development of the brain. These are largely dose and time dependent, and can affect the same developmental process differently depending on its particular vulnerability at that point in time [2]. Dichlorodiphenyl-trichloroethane (DDT) is one of the chemicals in the class of POPs that are still present in Zambia, despite its being banned in the developed world. It has, in the last 15 years, been used for malaria control as an indoor residual spraying (IRS) insecticide, owing to its long lasting effect and relatively cheaper cost when compared to other chemical alternatives [3].



Figure 1. Cycle of environmental health disparities.

There are other factors that determine human infant development, which when combined with exposure to chemicals such as DDT, may predispose a child to adverse health risk factors and neurodevelopmental outcomes. These are grouped into four main categories: socio-economic, residential options and characteristics, environmental impacts, and other compounding factors as presented in Figure 1 [4]. All these factors have to be considered together when studying infant neurodevelopment, as they may lead to effects which are more pronounced when combined in a single individual [5-9]. These disturbances to the brain during prenatal development have been shown to cause a wide range of outcomes in later years ranging from clinical ones such as dyslexia, epilepsy and schizophrenia to antisocial behaviors such as substance abuse and criminality [2].

Worldwide, several epidemiological studies have been conducted on effects of DDT on health outcomes, such as reproductive indicators, neurological symptoms and other associated impacts [10-27]. However, these have been on previously exposed communities or occupationally exposed individuals.

In Africa, some countries are still using DDT for malaria control. Studies have been carried out in South Africa, Botswana, and Mozambique to map DDT exposure in various environmental media such as soil, water and fish [28-30]. In terms of human matrices, studies have been conducted in South Africa on concentrations in breast milk and blood serum [29]. Important to note is that the only studies that have been undertaken looking at an association between exposure and a health outcome have been in South Africa, with the study population drawn from former male spray operators and residentially exposed males with specific focus on male reproductive health [31, 32].

Children in already marginalized populations are more likely to be impacted by DDT as this pesticide is applied only to rough, un-plastered surfaces often housing economically disadvantaged people. Children are highly vulnerable to chemicals, due to their unique characteristics. They play on polluted grounds and surfaces, have hand-to-mouth behavior, and usually follow a specific set-out diet. The persistence of IRS chemicals on environmental media, such as soil and water in addition to household items like furniture, beddings and other absorbent surfaces, places children at the highest risk of exposure. Additionally, children have decreased abilities to detoxify and excrete some chemicals, potentially impairing their rapid growth and development of their vital organ systems [33].

Given the HIV pandemic and the incidence of poverty in Zambia, it is highly likely that these effects will be more pronounced in the Zambian population. Cumulatively, a massive 246,000 kg of DDT have been brought into the country since 2000 and applied in people's homes. However, no studies have been carried out in Zambia to ascertain the fate of these chemicals in the environment and the impact on human health, despite the emphasis placed by the Stockholm Convention on the need to monitor the use and the impact on human health arising out of the use of DDT. This study therefore aimed to establish the prevalence of DDT in selected communities of Zambia and assess the neurodevelopment outcomes in children within these communities. It further evaluated the influence of socio-economic and environmental factors on the observed outcomes. This paper presents results from the neurodevelopment assessment and evaluation of factors influencing the outcome.

OUR STUDY

This was a mixed methods study, due to the paucity of local studies on DDT. There was a vital need to establish the prevalence of DDT in the environment of the selected communities. This Environmental exposure assessment was undertaken prior to the determination of the possible effects this could have on the infant neurodevelopmental processes. The methods and results of the initial survey have been published elsewhere [34]. The second phase was a study looking at neurodevelopmental aspects, as well as collecting of primary data to gather other supplementary information on socio-economic, residential and environmental factors that might contribute to the neurodevelopment of the infant.

The study was conducted in the Chawama and Mongu areas of Zambia, a peri-urban area in Lusaka and a mixed urban and rural area, respectively. Chawama was randomly chosen from among four other peri-urban areas, including George, Kanyama, and Garden compounds of Lusaka. Among the selection criteria considered were that they are typical townships with a high population density and a long history of IRS application and high malaria burden, and are accessible logistically.

The study could not have a non-exposed control group, since DDT may be present in the study areas due to historical exposure and its ubiquitous presence in the environment. Consequently, it is not possible to have zero exposure, as background levels may already exist in the environment and everyone's body, even without direct exposure through IRS application. In this context, Mongu was chosen as the reference area, as there had not been any recent exposure to DDT there through IRS.

The mother and child pairs were recruited from families attending antenatal clinics in the selected areas by health personnel who were incorporated into the study team. The inclusion criteria were as follows: Gave consent to participate in the study, 18 years of age and generally healthy. The only exclusion criterion was that the infant should have been a singleton birth.

The Ages and Stages Questionnaire (ASQ), which is used extensively to assess the development of children, was used for the Neurodevelopmental Assessment. Typically, this is a parent-completed, child monitoring system screening tool that uses parent/outsider observation to assess child development and behavior. Age specific questionnaires from 2-43 months are available for the assessment. Questions are written in very simple English, so that most people can complete the tool independently. The test has been validated to measure each of the five developmental domains, namely Communication, Fine Motor, Gross Motor, Problem-Solving, and Personal Social behavior of children, from one to 60 months of age. The questionnaire contains six questions in each of the five domains. Answers of "yes," "sometimes" or "not yet" are given 10, 5 and 0 marks respectively. A cut of value has been set for each domain at each age stage at 2 SD below the mean, using reference norms derived from a sample of US children. The ASQ has been validated for use in Zambia as well [35]. Clearly indicated thresholds have been set for children "below," "in need of attention" and "above" the cut off value for each domain. The test is given on an individual basis and takes about 15-20 minutes to complete.

For our study, an interview format was used, as most mothers could not read the language in the ASQ very well and, in some cases, both interpretation and translation were required. A practicing child psychologist was incorporated into the study for this assessment. The psychologist was blinded to the possible exposure status of the children to avoid bias. She presented a series of test materials to the child and observed the child's responses and behaviors while doing the scoring [36].

Information on the medical, socio-cultural and environmental factors that could modify or confound the possible neurodevelopmental effect on the children was gathered by use of an interviewer administered questionnaire. Other covariates measured for the mothers were: medical history, concomitant medicines, smoking status, level of education, employment status and level of income. For the children, a physical examination and where possible, hearing and visual screening was done given that these could affect the neurodevelopmental assessment scores.

We analyzed the data using STATA version 13. Assessment of normality for continuous variables was done using histograms. We considered the median and interquartile ranges and numbers of participants, frequencies and percentages for continuous and categorical variables, respectively. Both parametric and non-parametric analyses were employed in the study. We used the Wilcoxon Rank Sum test to explore the differences between variables of the two areas. For investigations of associations, the Chi-square test or Fishers exact test were used between categorical variables such as gender, presence of medical problems and behavior concerns. Owing to the non-normal distribution of our dataset, Spearman's Rho Correlation was used to evaluate associations between continuous variables, including all the neurodevelopment domains and maternal characteristics. Generalized linear models were used to generate a final model that would best explain the associations. We reported significant associations at 0.05 level of significance and their corresponding 95% confidence intervals.

Ethical approval was granted by the University of Zambia Biomedical Research Ethics Committee under IRB No. 0000131. Further, parents were approached in their homes by the health personnel, and the study explained to them in their local language. A copy of the Study Information Sheet was left at the home for further reference. Thereafter, if they were willing to participate in the study, they signed the IRB approved consent prior to the assessments being done. A nominal transport refund was paid to the parents to cover their cost of travel and a protein milk drink was given to the children if they had been waiting for more than an hour.

OUR FINDINGS

Out of a final sample of 104 children, the median age was 17.92 months with the youngest being two months and the oldest 42 months. The age was significantly different between sites, with Mongu having a higher median age of 21 months ($p = 0.00$). The children were evenly distributed by sex, with each area having 50% of each sex represented. More than 45% of the children were born first in their families and only 3% were born last.

Socioeconomic Status

The mothers in the study were found to have a median age of 24 [16, 53] with the Mongu mothers being slightly older, but not significantly so; 53% were married, 40% single and the rest either widowed or divorced. When it came to role in the family, more than a third of the mothers were bread winners, with 49% in informal income generating activities and 35% with some kind of family support. Only a small fraction of the women was in formal employment. It is noteworthy that there was a significant difference (<0.01) between the two areas, with more women from Mongu being bread winners and engaged in informal employment. More than half of the mother population had secondary education, and 35% had primary education, with less than 1% having no education. None of the mothers studied had any tertiary education. Table 1 summarizes the results obtained for the mothers of Chawama and Mongu.

Residential Characteristics

Almost 85% of the families lived in low cost housing, with 60% reporting that their walls were un-plastered. The difference between the areas was significant, with Mongu recording more houses with un-plastered walls. More than 67% of the mothers had lived in the area for more than four years prior to the study being undertaken. More than half of the women confirmed having used chemicals in their homes, most for pest control activities. There was a significant difference ($p = <0.01$) between the areas, with Chawama reporting a higher rate of using chemicals. This application of chemicals is in addition to the spraying conducted by the Ministry of Health annually for malaria control, of which 63% of the women affirmed having their houses sprayed in the previous ten years. The respondents in Mongu reported having a higher incidence of side effects ($p = < 0.01$), despite reporting a higher compliance rate to environmental safeguards given by the MoH prior to conducting spraying.

Table 1. Socio-demographic characteristics of mothers in Chawama and Mongu

Variable	Chawama n = 47	Mongu n = 36	Combined n = 83	p value*
Maternal age (Yrs) (Median and IQR)	24 (19-46)	25 (16-53)	25 (16-53)	0.63
Marital Status				
Married	30	14	44	0.06
Single	13	21	34	
Others	4	1	5	
Educational Level				
None	3	3	6	0.52
Primary	16	14	30	
Secondary	28	19	47	
Role in family				
Breadwinner				<0.01
Dependent	11	21	32	
Both	35	15	50	
	1	0	1	
Source of Income				
Formal	13	0	13	0.78
Informal	14	27	41	
Family Support	20	9	29	
Average monthly Income range				
<20\$				<0.01
20-30\$	12	21	33	
30- 50\$	5	5	10	
50\$	9	5	14	
	21	5	26	

* Wilcoxon Rank Sum test was used in all data analysis in this table.

With regards to access to drinking water, 74% of the mothers stated that they had a water source within the proximity of their homes. About 41% of the respondents affirmed the presence of a variety of vegetables (26%) and tubers, such as cassava and sweet potatoes (11%), with the rest being maize, as growing within the vicinity of their houses. Only 23% of the mothers reported the presence of any livestock around the houses, most of which were chickens and pigs.

Maternal Characteristics

Almost all (99%) of the mothers had had access to antenatal care at the health facility during their pregnancies. However, close to half of the mothers (39%) confirmed having suffered from some type of complication during pregnancy, which ranged from malaria, high blood pressure, and taking some kind of medication during the pregnancy, ranging from anti-malarial drugs, antibiotics, nutritional supplements, and anti-retroviral drugs.

None of the mothers reported smoking during the pregnancy, although 11% acknowledged consuming alcohol during the pregnancy. There were 23% of homes where another member of the family smoked, thereby potentially exposing the unborn baby to passive cigarette smoke.

Infant Neurodevelopmental Scores

The children's neurodevelopment scores were categorized into the 18 age groups provided in the ASQ. While 22% of the scores were above the cut off points for those specific ages, more than 50% of the children's scores lay in the gray area which stipulates that the children required further assessment and attention. The last 22% were the children below the cut off scores for those age groups. At six months of age, median scores for fine motor and personal social were below the cutoff points as were those for gross motor at 22 months. The children from Chawama were found to score higher in all the neurodevelopmental domains compared to those of Mongu. These differences are statistically significant for all domains except for fine motor domain. Table 2 provides the summary scores and Figures 2 and 3 show medians and IQR for each age group.

Table 2. Neurodevelopment assessment scores for selected children in Chawama and Mongu: Scores are summarized across ages

ND Scores*/**	Chawama	Mongu	Combined	p value***
Communication	55 (5, 50)	45 (10, 60)	50 (5, 60)	<0.01
Gross Motor	55(0,60)	45 (10, 60)	52.5 (5,60)	<0.01
Fine Motor	50 (0,60)	45 (10, 60)	45 (0,60)	0.09
Problem Solving	50 (0, 60)	35 (0, 60)	40 (0, 60)	<0.01
Personal Social	50 (0, 60)	40 (5, 60)	45 (0,60)	< 0.01

* A cut of value set for each domain at 2 SD below the mean, using reference norms from a sample of US children. The scores are given to a maximum of 60.

**Scores are reported as medians and IQRs.

***Wilcoxon Rank Sum test.

Usage of Chemicals

Multiple weak non-statistically significant negative correlations were found between use of chemicals and all domains of neurodevelopment. Upon stratifying by sex, the results showed more negative associations with males in all domains with personal social being significant ($\rho = -0.34$, $p = 0.02$). After categorizing the neurodevelopment scores by age, at

27 months, use of chemicals was significantly negatively correlated with all domains; these were significant for communication and personal social ($\rho = -0.85$, $p = 0.03$ and $\rho = -0.84$, $p = 0.03$) respectively. When categorized according to the area, the children from Chawama had more negative associations in all domains when compared to those of Mongu, who only showed weaker negative correlations in gross motor and personal social behavior.

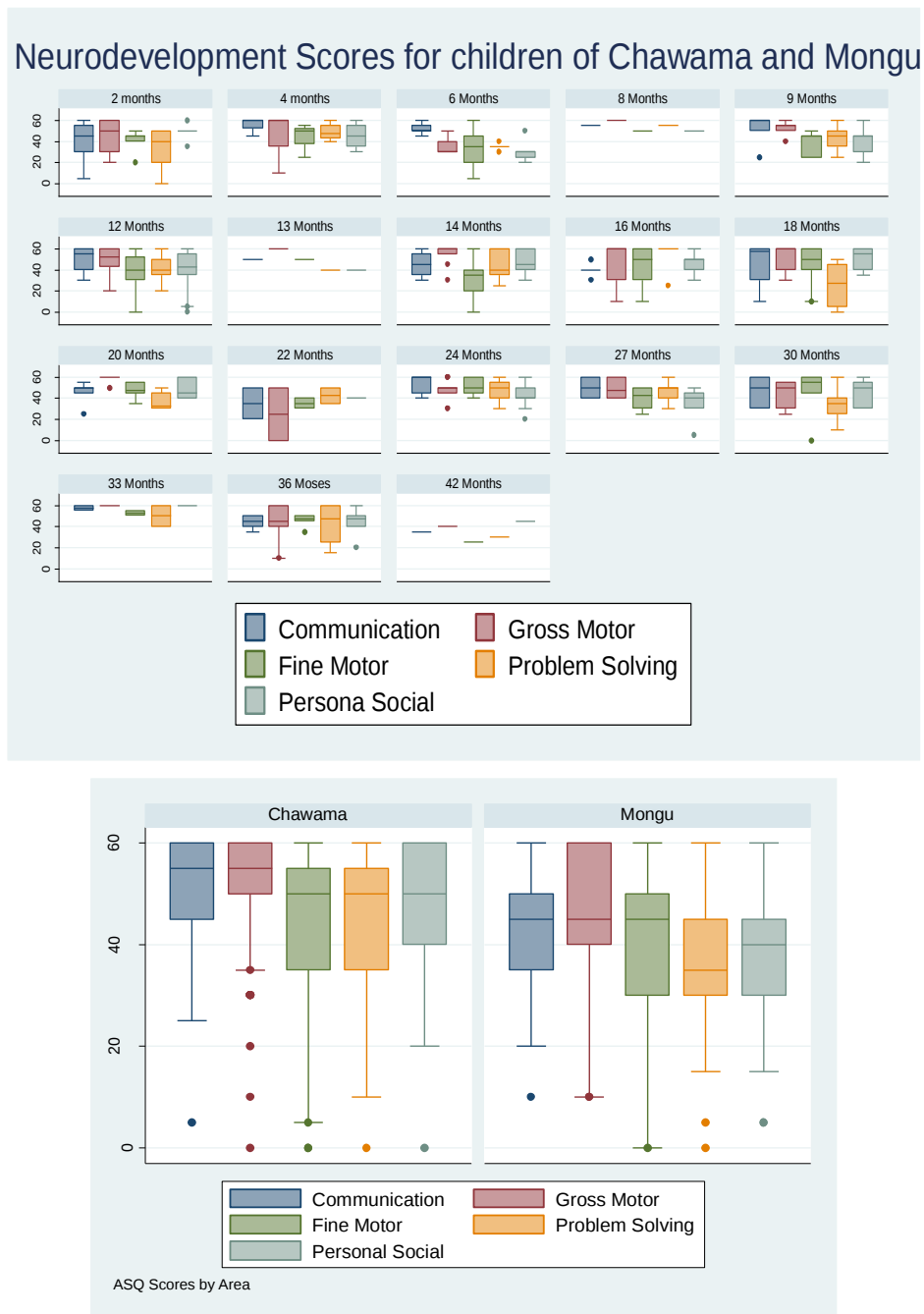


Figure 2. Children’s neurodevelopment scores at each age group (Figure 2a) and summarized (Figure 2b).

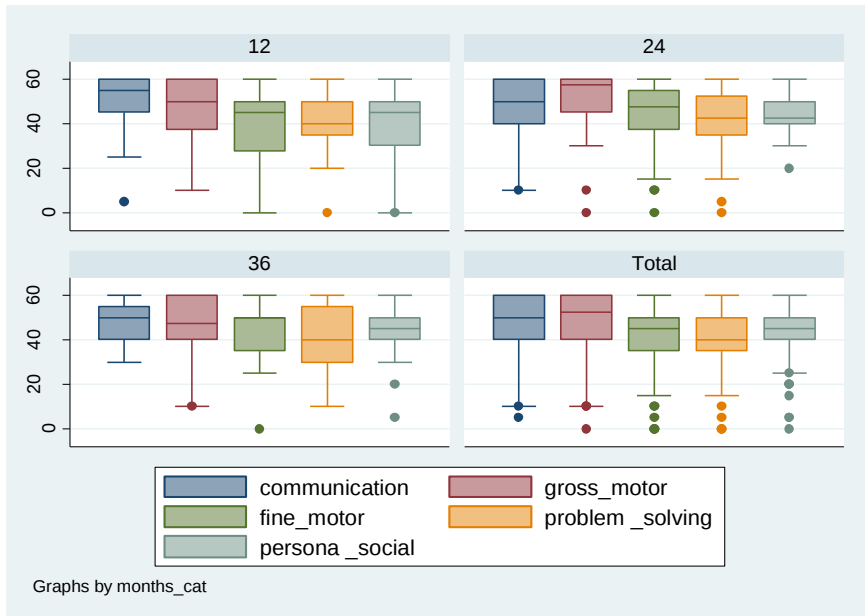


Figure 3. Associations of maternal characteristics with child neurodevelopment scores.

Socio-Economic Status

Maternal age was negatively associated with problem solving and none of the other functions. Marital status was found to influence all domains negatively with higher scores being found among children born of married mothers. The role the mother plays in the family was found to be ($p = 0.06$) associated with problem solving skills in the children, with the higher scores found in children whose mothers were dependents. Positive associations were found between educational level of the mother and problem solving ($p = 0.07$) and personal social behavior ($p = 0.08$), with children of mothers who had secondary education scoring higher points in these domains. Source of income, level of income, and type of house did not seem to influence any of the domains significantly.

Medical Factors

No significant associations were found between complications during pregnancy and any of the neurodevelopmental domains. Mode of delivery seemed to have a weak association with personal social behavior, as could be seen with children born of vaginal delivery doing better than those born of Caesarian section. The taking of vitamin supplements and anti-malarial drugs seemed to have a positive significant influence on gross motor, fine motor and problem solving scores. None of the other medical factors had any significant influence on the children's ASQ scores in all the domains.

Housing and Environmental Factors

None of the variables showed any significant influence on the neurodevelopmental scores. However, it is worth noting that there was more chemical usage in the low cost homes with unplastered walls.

Generalized linear models showed that the strongest predictors of the children's neurodevelopment were mother's marital status, role in the family, income levels and type of house. The area of chemical application was also found to be a significant factor.

DISCUSSION

The neurodevelopmental scores for the two areas show significant differences, with the Chawama children obtaining higher scores than their Mongu counterparts. This is despite the fact that Chawama children had recent exposure to DDT and its metabolites, and the presence on previous environmental exposure assessments of much higher DDT levels in the soils and water samples from Chawama when compared to Mongu [34]. It gives credence to the arguments advanced by other scholars that SES is an important determinant of an infant's neurodevelopment. SES in addition to being a confounder may also be an effect modifier to the health effects of chemicals [37, 38].

That notwithstanding, the correlations found in this study, albeit not statistically significant, point to the plausibility of a negative association between use of chemicals and child neurodevelopment. Given a larger sample size of participants, these correlations might rise to the level of statistical significance. These seem in addition to maternal and housing factors to be influenced area and age differences. This trend has been observed in previous studies which show significant negative associations between DDT/DDE levels in biological matrices and infant neurodevelopmental outcomes. A few of these have adjusted for socio-economic factors, such as maternal age and IQ. However, all these studies were carried out in the Western world where Socioeconomic Status are vastly different from those found in Zambia, a typical developing country. Our study has also revealed that, despite being better off socio-economically, compared to the Western world, the children in Chawama had lower minimum scores in almost all the domains.

The Mongu mothers from our study, were mostly single mothers who were also the bread winners of their families and subsequently engaged in informal income generating activities. This might explain the negative significant association found with the problem solving and personal social functions of their children. Black et al. [39] in discussing their 2000 study conducted on 87 children and toddlers from low income families, state, "Children who are raised in poverty may be particularly vulnerable if their caregivers are unable to provide the enriching environment that toddlers need to develop the language and problem-solving skills that emerge in the second year of life" [39]. The other reason put forward is that children growing up in resource-constrained settings are usually left in the care of older siblings or domestic helpers. These caregivers may not have the requisite characteristics or time to provide enough stimulation to the child and engage them in activities that will offer them opportunities for learning and refining of problem solving and personal social skills. [39].

Koutra et al. [1] show that, in a Greek cohort of 605 mother and child pairs, maternal characteristics played a big role in infant neurodevelopment. Using the Bayley Scales of Infant Development (BSID), they found that higher maternal education level is positively correlated with almost all the neurodevelopmental domains assessed. In contrast to our study, they found that a mother's employment status seemed to also have a positive effect on the children's performance. This finding is explained in part by Van Heerden et al. [35], who postulate that children raised by stay-at-home mothers spend a lot of time with their mothers, and this close proximity helps the babies feel secure. This, according to them, may be responsible for the early advances seen in most domains by the children from Chawama, whose mothers were mostly dependents.

The cultural and social differences between Chawama and Mongu may also partially explain the results that were obtained. The ASQ questionnaire is in English, and therefore requires translation in the local language. Chawama mothers being in the capital city, Lusaka, could understand some English and most of them spoke the language familiar to the child psychologist. In contrast, the Mongu mothers did not speak much English and the local language was not very familiar to the administrator; thus, a member of staff at the health center was co-opted to translate the questions. In addition, some of the test items such as the "piggy bank" and games like "peekaboo" are not widely used in rural Zambia. This could have also hindered the understanding of the children, thereby lowering their overall performance. Some of the test items, particularly as they relate to color identification, ordering building blocks, and others, could have also been unfamiliar to the children, thereby affecting their performance in the problem solving domain [35].

Other potential effect modifiers including childhood illnesses, nutrition and HIV status were not measured in this study. These have been shown elsewhere to affect infant neurodevelopment.

CONCLUSION

Taken in totality, 55% of the scores of all the children are in the range that requires attention and further assessment. We believe that this demonstrates that many children of Zambia are still at risk, despite lack of evidence that recent exposure to DDT is significantly influencing their developmental growth.

There is an urgent need to take a wider view in solving the malaria problem in Zambia, starting with investments which will improve the lives of women. Improving their housing and improving their educational status would help to provide a secure and nourishing environment necessary for a child's development. Our study suggests that, as demonstrated in studies in other cultures as well, there is a much stronger influence from maternal characteristics on their children's development. Improving socio-economic factors, including better education, employment options and marital status, will afford mothers more contact time with children. The increased income could break the cycle of the disparities related to housing and environmental factors. The health risks to the mothers and children may be significantly reduced by addressing these very fundamental needs.

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Chapter 262

RACIAL DISPARITIES IN ACCESS TO MUNICIPAL WATER SUPPLIES IN THE AMERICAN SOUTH

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ABSTRACT

More than five decades after the Civil Rights Act, systematic exclusion of African-American neighborhoods on the fringes of cities and towns from municipal services, including water service, continues. Throughout the American South, many such neighborhoods still rely on unregulated private wells for their drinking water despite their close proximity to municipal water lines. Little is known about water quality, including lead contamination, in these communities. In this chapter kitchen tap water samples were collected and tested for lead in 29 households recruited from peri-urban African-American communities in Wake County, North Carolina, relying on private wells. The Integrated Exposure Uptake Biokinetic (IEUBK) Model for Lead in Children was used to estimate blood lead levels in children resulting from lead in water. Results: In eight (28%) of the 29 households, tap water lead exceeded the 15-ppb health-based action level in at least one of two samples. In seven homes, the average lead in two samples exceeded 15 ppb. The IEUBK model predicts that in 3 (10%) of the households, water lead could elevate children's blood lead above the current 5 µg/dL reference level. Discussion: The lead prevalence in households in this study was comparable to that in the most-exposed neighborhoods of Flint, Michigan, during the recent lead-in-water crisis. These results indicate the need for interventions to decrease lead exposure in peri-urban African American communities excluded from nearby municipal water service.

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INTRODUCTION

Several studies in the last 30 years have documented the systematic exclusion of African-American neighborhoods on the fringes of cities and towns from access to municipal services, including water and sewer service, trash collection, paved roads, and police and fire protection [1–6]. Demographer Charles Aiken termed this exclusionary zoning practice “municipal underbounding” [1]. Aiken and others have documented instances in which cities and towns gerrymandered their boundaries to leave out African-American neighborhoods, even when those neighborhoods were fully enclosed by town boundaries [1–3, 5–8]. Because they lack access to municipal water and sewer service, underbounded neighborhoods rely on private wells for their potable water and on septic systems for their sewage disposal—even though their neighborhoods may be encircled by water and sewer pipes. Unlike in adjacent neighborhoods included within municipal boundaries, each underbounded household must operate and maintain its own private well and septic system, without financial or technical assistance.



Figure 1. Cycle of environmental and health disparities experienced by communities that remain excluded from municipal services on the basis of race. Educating the communities and public health officials on well water quality and subsequent health effects can help to break this cycle of disparity.

Little is known about drinking water quality in underbounded neighborhoods, in part due to lack of private well monitoring [9]. To our knowledge, only three previous research studies have tested water quality in such neighborhoods [4, 10, 11]. The most recent study (by our team) tested 57 wells in underbounded communities in Wake County, NC, for microbial contaminants; we found contaminants in tap water in 37 (65%) of the households [10]. A 2011 study of an underbounded community in Alamance County, NC, found that 6 (13%) of private well samples tested positive for both fecal coliform and *E coli* bacteria. [11] A 2013 study of the underbounded Rogers-Eubanks community in Orange County, NC, tested for

microbial and selected chemical contaminants in 12 wells [12]. This study found fecal coliforms in 5 (42%) of the wells. In addition, in several wells, concentrations of selected metals exceeded federal recommended drinking water limits: five for iron and manganese and one for lead. The nearly uniformly low pH of water from these wells—11 of 12 were below the federally recommended lower limit of 6.5 pH units—suggested high potential for plumbing corrosion to serve as a continuing source of metals.

In the current study, we examine lead contamination in private wells and the contribution of water lead exposure to health in children 6-84 months old in underbounded neighborhoods of Wake County, NC, excluded from municipal water service. Recent events in Flint, MI, have renewed attention to water as a potentially important source of exposure to lead, a long-established neurotoxin even at low levels [13, 14]. On average, lead levels in African-American children are higher than in white or Hispanic children [15]. It is possible that disparities in lead exposure via drinking water could in some cases contribute to this racial disparity in children's blood lead. The aforementioned study in the Rogers-Eubanks community suggests the potential for increased lead exposure in water in underbounded communities, but apart from that study, no research on lead exposure in water in such communities has occurred. The Rogers-Eubanks study may have underestimated lead exposure risks because some samples were collected at the well head or from an outdoor spigot, rather than from an indoor tap, and in all cases the water was run for three minutes prior to sample collection. Flushing of samples and collection from the wellhead rather than the household tap can mask the presence of lead and other metals introduced through corrosion of household plumbing [16]. In this study, we evaluate the concentration of lead in unflushed, indoor tap water samples in 29 underbounded households. We then estimate how lead exposure via drinking water in these households could affect blood lead levels and IQ in children aged 6-84 months.

CYCLE OF CHILD ENVIRONMENTAL HEALTH DISPARITIES

Currently, residents in racially underbounded communities face a cycle of environmental disparities, in comparison to neighboring communities that are included within municipal boundaries. One disparity (shown in Figure 1) with potentially important impacts on children's health is the lack of protections afforded to municipal water system customers under the EPA Lead and Copper Rule [17], established in 1991 to prevent lead exposure in drinking water. Under the Lead and Copper Rule, all large community water systems (those serving more than 50,000 people) must treat their water with corrosion inhibitors to prevent lead release from water distribution pipes and household plumbing. In addition, all community systems, regardless of size, must monitor tap water for lead every six months in multiple households throughout their distribution networks, focusing on houses that, due to their age, are most likely to have leaded plumbing or solder. If lead concentrations exceed 15 ppb (the EPA action level) in 10% or more of the samples, then the water utility must implement corrosion control (if it has not done so already), optimize its existing corrosion control, and/or replace lead service lines.

Data from selected municipal water utilities suggest that the preventive measures established under the Lead and Copper Rule have substantially decreased lead exposure in

drinking water in households with access to municipal water infrastructure. For example, in New York City, average tap water lead concentrations decreased by 62% (from 4.0 to 1.5 ppb) between 1992 and 2003 due to the addition of orthophosphate corrosion inhibitors to the treated drinking water [18]. The recent lead-in-water crisis in Flint illustrates that lead exposure concerns may remain in some municipal water systems. Nonetheless, the Flint crisis represented an extraordinary occurrence, in which the city failed to implement adequate corrosion control as part of a cost-saving measure initiated by financial managers who took over the city during bankruptcy and in which subsequent data that would have alerted officials to the lead problem were concealed [19, 20]. In general, compared to households relying on private wells, those with municipal water service have the benefit of regular water quality monitoring and centrally managed corrosion control to prevent lead exposure in drinking water.

As shown in Figure 1, lack of municipal water system access could lead to an increased risk of exposure to lead in drinking water, due to the leaching of lead from well components or household plumbing in the absence of adequate corrosion control. Private well households typically lack the knowledge and/or the means to adequately monitor their water quality and to install and maintain appropriate treatment when water quality problems are discovered [21–23]. Many private wells deliver water with low pH, increasing the risk of lead corrosion, compared to higher pH waters or waters to which corrosion inhibitors have been added [24]. In turn, an increased risk of exposure to lead—even at low levels—increases the risk of permanent loss of intellectual function and behavioral disturbances among children [14, 25, 26]. The identification of lead exposure in drinking water has already helped other communities, like Flint, appreciate and begin to act in an attempt to provide safe drinking water to the community. Educating private well owners and public health officials of lead exposure risks and health effects in underbounded communities can help break the cycle of children’s environmental health disparities in these marginalized communities.

OUR STUDY

To characterize lead exposure risks in drinking water in underbounded African-American communities, we conducted a pilot study involving 29 households recruited from majority African-American census blocks within the municipal extraterritorial jurisdictions of Wake County. In North Carolina, municipalities can control zoning and land use decisions in extraterritorial jurisdictions at a distance of up to 3 miles from city boundaries, depending on population size, without providing municipal services (including public water supply) or voting rights in municipal elections [27]. The 57 participants from our previous study of microbiological water quality in underbounded communities [10] were each contacted by telephone to inquire about their interest in the present study. The first 29 to respond and agree to participate were enrolled (available resources could support sampling only in 29 households). Participants received a \$25 gift card as compensation after completing a survey following water sample collection. This study was approved by the University of North Carolina, Chapel Hill, Institutional Review Board.

Water Sample Collection

All household water samples were collected during August 2016. One day before sample collection, sample kits were delivered to each household. The kits included detailed instructions for collecting first-draw morning samples from the kitchen tap after an overnight stagnation period and two 10-mL metal-free sampling vials (VWR, Radnor, PA). Instructions for sample collection followed the Environmental Protection Agency's (EPA) Lead and Copper Rule Sample Collection Form [28], with the exception of the size of the sample collection bottles (smaller than 1 liter). Consistent with EPA-recommended procedures, instructions directed homeowners to collect samples from the kitchen tap using cold water after a minimum 6-hour stagnation period. Participants were instructed to fill both vials without flushing and to label each vial with the date and time. The filled vials were then collected by research staff on the same day. After collected vials were transported to the lab, each 10-mL vial was digested in 70% concentrated nitric acid to a 2% by volume solution for a minimum of 24 hours.

Quantification of Lead

Metals (lead along with aluminum, cadmium, copper, nickel, and zinc) were analyzed using standard methods [29] using an inductively coupled plasma mass spectrometer (Agilent Technologies 7500cx, Santa Clara, Calif.). Validity of the data was assessed through analysis of replicate samples (10.3% of total samples), quality control standards spanning concentration ranges of analytes, and blanks. Quality control standards were prepared from National Institutes of Standards and Technology traceable solutions (High Purity Standards, Charleston, SC, USA). The statistical package *R* was used to calculate summary statistics for lead and other metals.

Comparison to Lead in Municipal Water and in Wells Outside Study Communities

To compare water lead in the study communities to that in nearby homes served by the Raleigh municipal water supply, we extracted data on lead concentrations in Raleigh municipal water from the Safe Drinking Water Information System (<https://www.pwss.enr.state.nc.us/NCDWW2/>). We obtained all lead measurements collected during 2016 in single-family households throughout the Raleigh water distribution system (65 samples in total). All sampling locations were labelled as Tier 1, meaning the Raleigh Public Utilities Department has identified them as at highest potential risk of lead exposure in water due to the age and type of the household plumbing and/or service lines delivering water to the homes. All reported samples were first-flush samples collected from the kitchen tap.

We obtained summary statistics on lead concentrations in private wells throughout Wake County from the NC Division of Public Health (NCDPH). The NCDPH maintains a web site (http://epi.publichealth.nc.gov/oe/wellwater/by_county.html) with summary statistics for private well water samples tested by the State Laboratory for Public Health during 1998-2010. In total, the state lab tested 3,188 well water samples for lead during this time period.

Health Impact Assessment

To estimate potential impacts of lead in drinking water on children's blood lead levels, measured water lead concentrations for each household were input into the Integrated Exposure Uptake Biokinetic Model for Lead in Children (IEUBK; U.S. EPA 2010, *IEUBKwin32* Lead Model Version 1.1 Build 11) [30]. This physiologically based pharmacokinetic model compartmentalizes the human body and predicts the absorption, distribution, metabolism and excretion of lead. The IEUBK model estimates the predicted geometric mean blood lead level for children aged 6-84 mo., in one-month age groups, for a given level of exposure to lead from drinking water and other sources (soil, dust, and air) that the user can specify. The model also estimates the probability of a child in each one-month age group having a blood lead level greater than 5 µg/dL, the current reference level recommended by the Centers for Disease Control and Prevention (CDC) for identifying elevated lead exposure risks. For each household, we ran the IEUBK model twice for each of the two water samples: once using the average water lead level measured in the two samples while assuming no lead exposure from other sources and a second time including the model's default assumptions for lead exposure from soil, dust, and air (200 µg/g, 150 µg/g and 0.1 µg/m³, respectively). These results were used to estimate the expected excess blood lead attributable to water alone and the chance that water lead exposure could cause a child's blood lead to exceed 5 µg/dL, when considering water exposure and exposure from other sources.

To estimate the potential effects of the estimated blood lead levels on children's IQ, we used the multiple regression model from Lanphear et al. [25]. The model was run for each household and each one-month age group. The model form is:

$$\text{IQ Loss} = \beta * \text{Ln}(BLL_{ij}) \quad (\text{Equation 1})$$

where $\beta = -2.70$ (95% CI = -3.74 to -1.66) is the coefficient from Lanphear et al. for mean adjusted changes in full-scale IQ score associated with an increase in blood lead concentration [25] and BLL_{ij} is the blood lead concentration estimated by the IEUBK model at household i for age j (in months). Uncertainty in the estimated IQ loss was estimated via Monte Carlo simulation using *Analytica* (Lumina Decision Systems, Los Gatos, CA) (10,000 iterations per household). In the Monte Carlo simulation, β was represented as normally distributed (mean = -2.70, standard deviation = 0.531). Blood lead levels were estimated as lognormally distributed using the geometric mean estimates from the IEUBK model output and a geometric standard deviation of 1.6 µg/dL (as specified in the IEUBK model user manual) [30].

OUR FINDINGS

Enrolled participants were located throughout underserved areas of Wake County. As Figure 2 illustrates, participating households were in neighborhoods that are surrounded by areas with community water supplies, as indicated with blue shading. However, these households lack access to the nearby community water supplies.

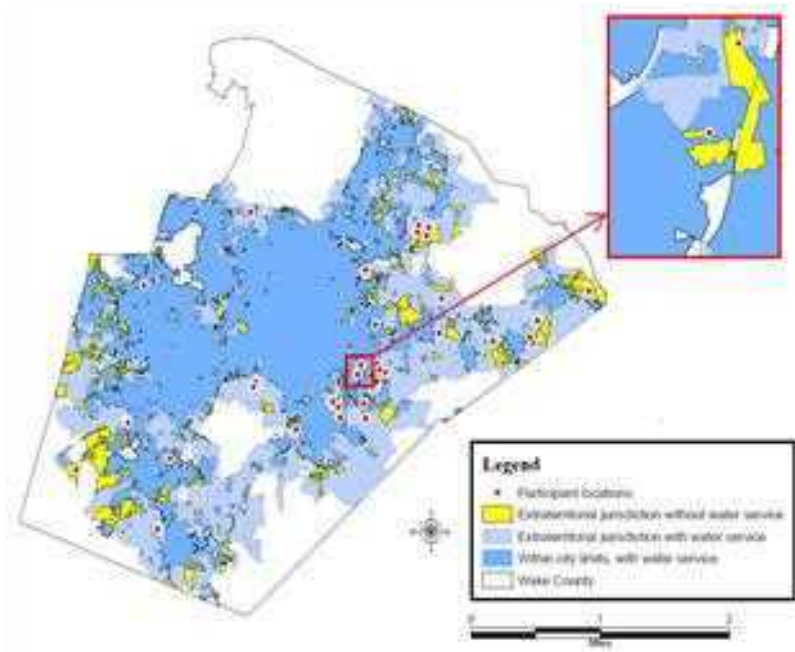


Figure 2. Locations of the 29 households participating in this study. Dark blue shading indicates areas that are within municipal boundaries. Participating households were not located within municipal boundaries, even if very close to those boundaries, as shown in the insets. Light blue shading indicates areas that are within extraterritorial jurisdictions of municipalities (meaning the municipalities control land use decisions in those areas) but have community water service, even though they are outside of town boundaries. Yellow areas and all participating households are in extraterritorial jurisdictions but lack community water service.

Table 1. Characteristics of study participants and their wells

	Study Participants	Wake County	<i>p</i> Value for Difference
Race (n = 21)			
Black/African-American	62%	21%	<0.001
White	33%	69%	<0.01
Asian/Asian American	5%	7%	NS
Other	0%	3%	NS
Education (n = 20)			
High school or higher	95%	92%	NS
Bachelor's degree or higher	60%	49%	NS
Home ownership (n = 20)	100%	64%	<0.01
Median household income (n = 20)	\$62,500	\$67,309	NS
Median age of well (n = 19)	30 years	NA	NA

Note: Some participants did not respond to the demographic questions on our survey. Numbers responding to each question are indicated in parentheses. NS = not significant; NA = information not available.

Among participating households, a significantly ($p < 0.001$) higher percentage (62%) identified as African American than in Wake County (21%) (see Table 1). The median household income among participants (\$62,500) was slightly lower than that in Wake County (\$67,309), although this difference was not statistically significant. The study population had a larger proportion with bachelor's degrees or higher (60%) than Wake County as a whole (49%), but this difference was not statistically significant. The study population had a much

higher rate of home ownership than Wake County (100% as compared to 64%, $p < 0.01$). This latter finding is consistent with previous studies of racially underbounded communities in North Carolina [3, 31], which have documented generations of land ownership within the same family, in some cases dating back to land granted to freed slaves after the Civil War. Current patterns of racial underbouding thus have longstanding historical roots.

Lead Prevalence

To evaluate exposure to lead in drinking water in the participating households, two first-flush water samples were collected from the kitchen faucet and analyzed for lead. In eight (28%) of the households, the tap water lead concentration exceeded the 15-ppb health-based action level in at least one of the two samples. In seven (24%) of the homes, the average of the two samples exceeded 15 ppb (see Figure 3). Across all 58 samples, the average concentration was 8.19 ppb, and the maximum was 79.4 ppb (see Table 2).

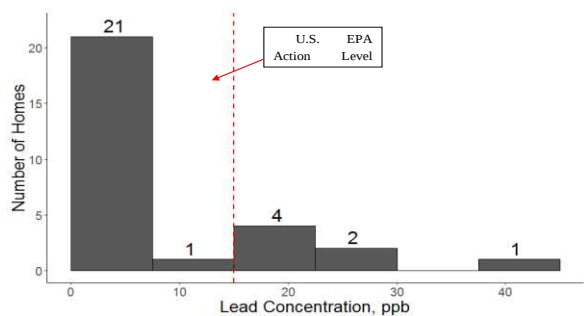


Figure 3. Average concentration of lead in tap water from 29 households, each sampled twice, in African American peri-urban communities excluded from the public drinking water system in Wake County, NC, USA. U.S. Environmental Protection Agency (EPA) action level is health based standard for drinking water.

Table 2. Metals (µg/L) in drinking water in private wells in peri-urban areas of Wake County, NC (n = 29)

Constituent	Mean	Median	Max	Standard ^a	Samples Exceeding Standard
Aluminum	36.3	6.50	436	50-200 (NSDWR)	3.45%
Cadmium	0.591	0.0355	19.7	5 (MCL)	1.72%
Nickel	8.57	1.17	129.1	NA	NA
Zinc	1,562	388	9,346	5,000 (NSDWR)	12.1%
Copper	629.5	135.4	5,645	1,300 (action level)	10.3%
Lead	8.19	3.00	79.4	15 (action level)	15.5%

^a MCL: Maximum Contaminant Level, established for contaminants associated with risk to human health. National SMCL: Secondary Drinking Water Standard, established for contaminants that may cause aesthetic problems. Action level, established for contaminants regulated on the basis of treatment technologies; if exceeded in more than 10% of homes, the system must undertake additional action to control corrosion and inform the public.

Lead Sources

To evaluate potential lead sources, we also tested concentrations of other metals known to be associated with plumbing corrosion (see Table 2). We found strong and statistically

significant ($p < 0.01$) correlations between lead and zinc ($\rho = 0.51$), nickel ($\rho = 0.49$), and aluminum ($\rho = 0.34$) (see Figure 4).

The high correlation with zinc suggests that corrosion of galvanized pipes may be a lead source. Galvanized pipes are lined with a zinc coating also containing up to about 2% lead. Recent research has concluded that these pipes can be a major source of lead in drinking water [32].

To further explore the hypothesis that galvanized steel is a lead source, we compared the lead concentrations in samples without and with detectable cadmium, which can serve as another marker of galvanized steel corrosion [32]. The mean lead concentration in the 11 samples without detectable cadmium was 0.607 ppb. By comparison the mean lead concentration in the 47 water samples also containing cadmium was 9.96 ppb—16 times higher than in the samples without cadmium. This difference was highly statistically significant (one-tailed t -test $p < 0.0001$), even though the concentrations of lead and cadmium were not significantly correlated ($\rho = 0.075$, $p = 0.57$). The finding of much higher lead concentrations in samples with cadmium than in those without supports the hypothesis that galvanized steel corrosion may be introducing lead into the water.

Corrosion of brass fittings, which contain 60-80% copper along with zinc (4-32%) and lead (2-8%), could be another lead source [24]. The presence of high copper concentrations in some of the samples (with 10% exceeding the federally recommended action level of 1300 μL , as shown in Table 2) indicates potential brass corrosion. However, the correlation between lead and copper ($\rho = 0.21$) did not reach statistical significance.

Other potential sources include lead solder and nickel-plated brass, the latter suggested by the significant correlation ($\rho = 0.49$) between lead and nickel.

Comparison to Lead in Municipal Water and in Other Wake County Private Wells

To compare lead concentrations in the study households to concentrations in households served by municipal water supplies and in other Wake County households with private wells, we extracted water sample test results from relevant NC databases. The average lead concentrations in the study households is nearly three times as high as in households served by the City of Raleigh municipal water supply (8.19 vs. 2.83 ppb, $t = 2.38$, $df = 46$, $p = 0.01$). In addition, the proportion of households testing above the 15-ppb action level is significantly higher in the study sample than in community samples (24% versus 1.5%, chi-square = 13.2, $df = 1$, $p = 0.00014$). The average concentration in the study households is greater than that in the 3,188 Wake County wells tested between 1998 and 2010 (8.19 vs. 7.8 ppb), but this difference is not significantly different. However, the proportion of wells exceeding 15-ppb in the study samples is nearly five times higher than in the other Wake County wells (24% versus 5.4%, chi-square = 19.2, $df = 1$, $p = 5.8 \times 10^{-6}$). These results indicate that lead exposure risks in drinking water are higher in the underbounded neighborhoods of this study than in neighborhoods served by the Raleigh municipal water supply and also are higher than in other areas of Wake County served by private wells (for example, rural areas outside of municipal extraterritorial jurisdictions).

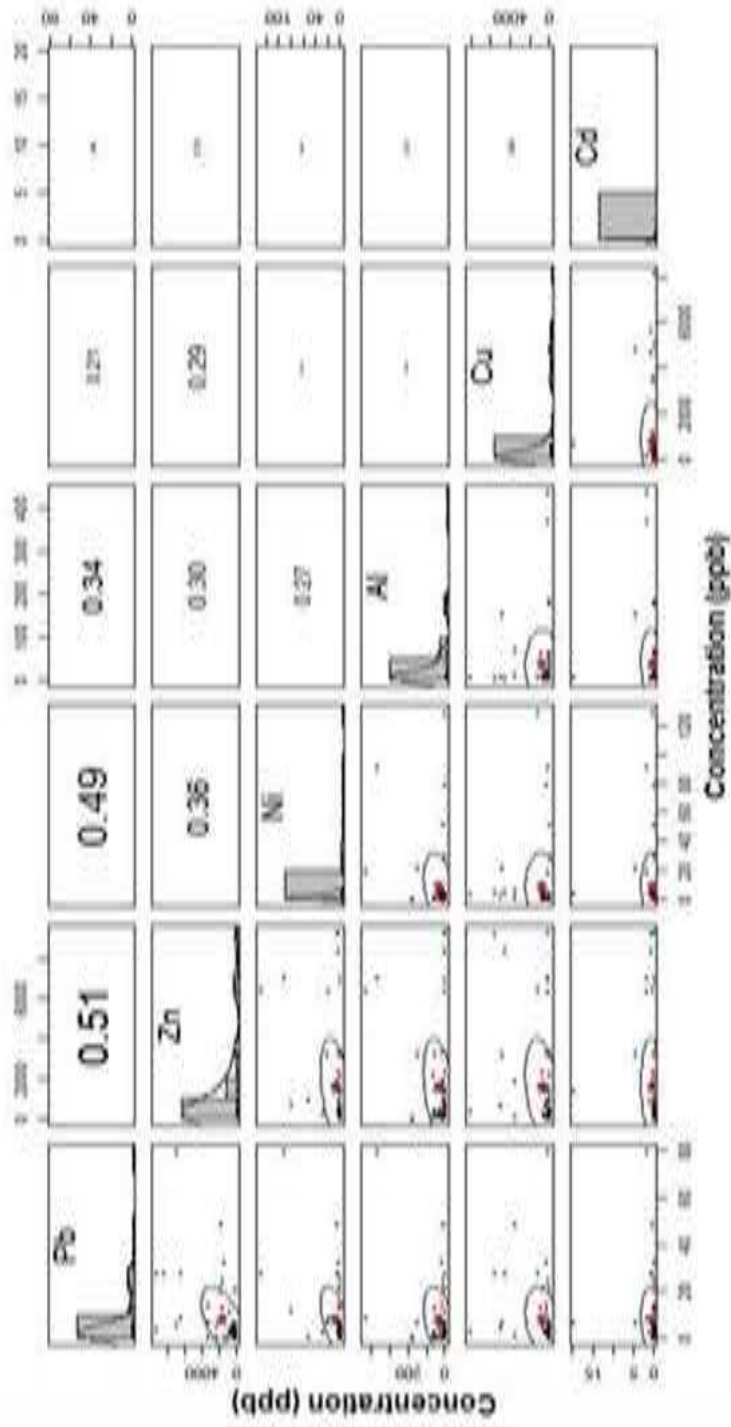


Figure 4. Bivariate correlation plots of metals in tap water from 29 households, each sampled twice, in African American peri-urban communities in Wake County, NC, relying on private wells. Ellipses show 95% confidence regions; red dots are confidence region centroids.

Health Impacts of Lead Contamination

To estimate the potential impact of lead contamination on children's health in the participating households, we applied the IEUBK model to predict the how the observed water lead levels could affect the concentration of lead in children's blood. Among the 29 households, considering children aged 6 months to 7 years, the average predicted blood lead level arising from water lead alone was 1.06 $\mu\text{g}/\text{dL}$, and the maximum was 4.55 $\mu\text{g}/\text{dL}$.

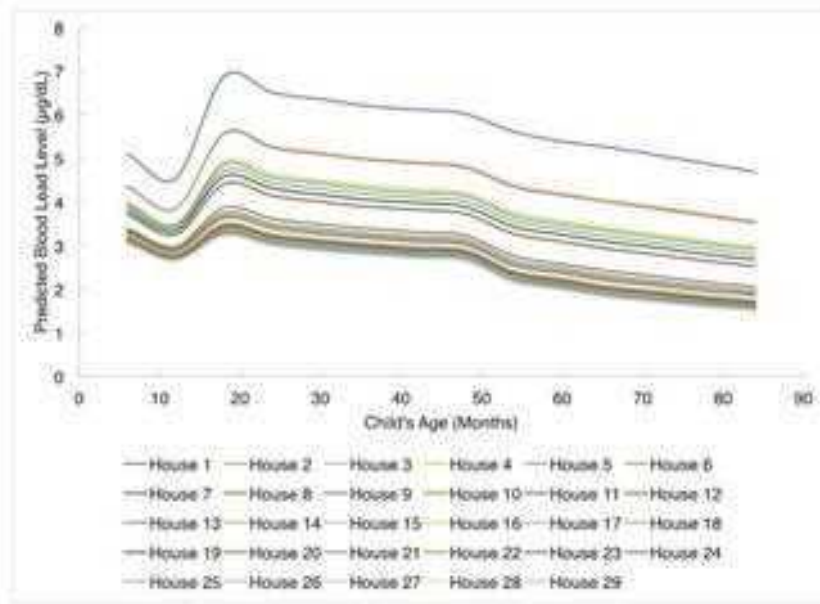


Figure 5. Predicted blood lead levels in children consuming water with lead levels as measured in the study households.

Because exposure to lead in water must be considered in the context of other lead sources, we also evaluated whether exposure to lead in water could elevate a child's blood lead above the CDC high-blood-lead threshold of 5 $\mu\text{g}/\text{dL}$, when added to lead exposure from other sources. On average across households and ages, the IEUBK model predicted that blood lead levels would be 3.03 $\mu\text{g}/\text{dL}$, when considering combined lead exposure from water, soil, dust, and air, with a maximum of 6.88 $\mu\text{g}/\text{dL}$. Figure 5 shows that predicted blood-lead levels are highest for children aged 18 months. For this age group, the contribution of lead from water results in a total blood lead level of greater than 5 $\mu\text{g}/\text{dL}$ in three households (see Figure 6). In another five houses, water lead in combination with lead from other sources results in a predicted blood lead level within 1 $\mu\text{g}/\text{dL}$ of the 5 $\mu\text{g}/\text{dL}$ threshold among 18-month-old children.

For each household, we also used the uncertainty features in the IEUBK model to estimate the probability that the child's blood lead level could exceed 5 $\mu\text{g}/\text{dL}$. On average across all households and age groups, the risk that water lead alone will result in a blood lead levels above 5 $\mu\text{g}/\text{dL}$ is 1.9%. Across households and among 18-month-old children, the IEUBK model predicts a 3.1% risk of having an elevated blood lead level from water lead alone, on average, and a 42% risk of exceeding this threshold in the highest-risk household

(see Figure 7). When considering water in addition to other lead sources among 18-month-olds, the average probability that blood lead levels will exceed 5 $\mu\text{g}/\text{DL}$ is 30% across the 29 houses, with a probability greater than 50% in three homes and a maximum of 75%.

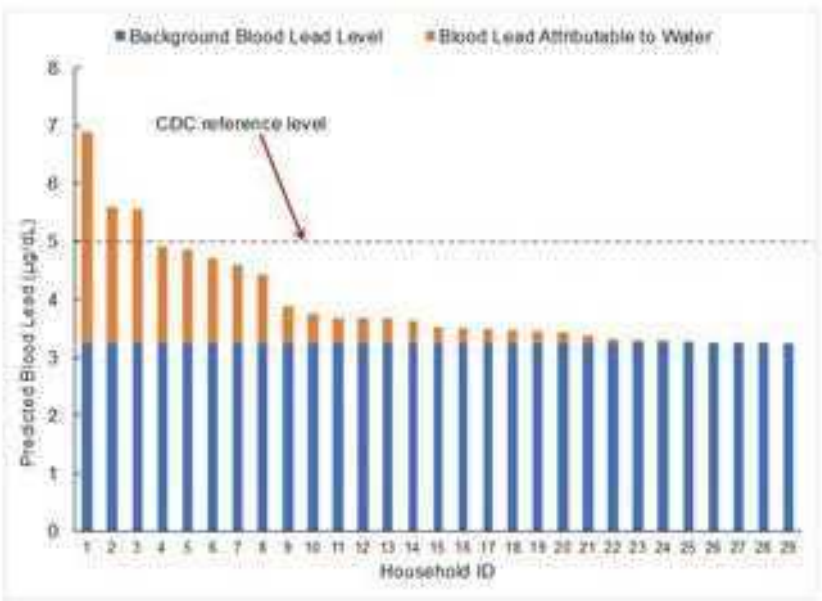


Figure 6. Predicted median blood lead levels in 18-month-old children consuming water with lead levels as measured in the study households.

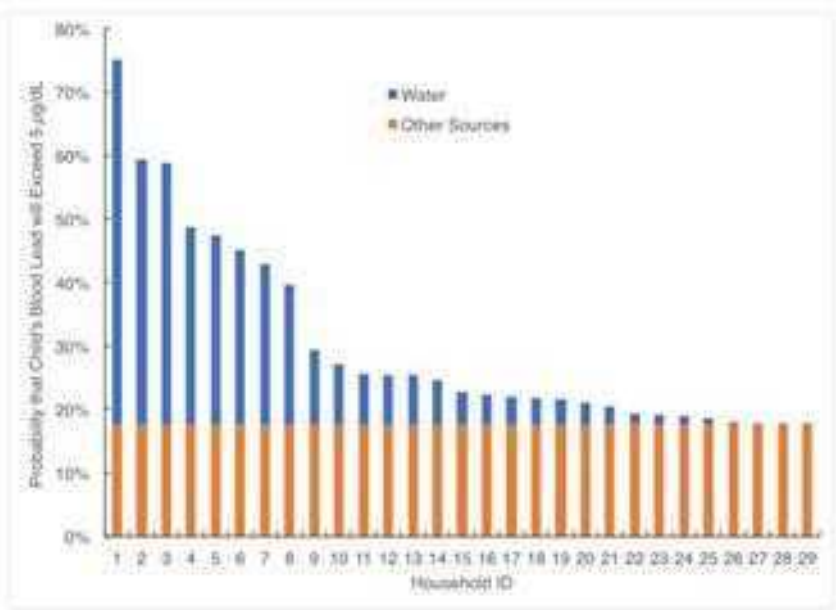


Figure 7. Predicted probability that blood lead in an 18-month-old child in the stuy households will exceed the 5 $\mu\text{g}/\text{dL}$ reference level established by the Centers for Disease Control and Prevention.

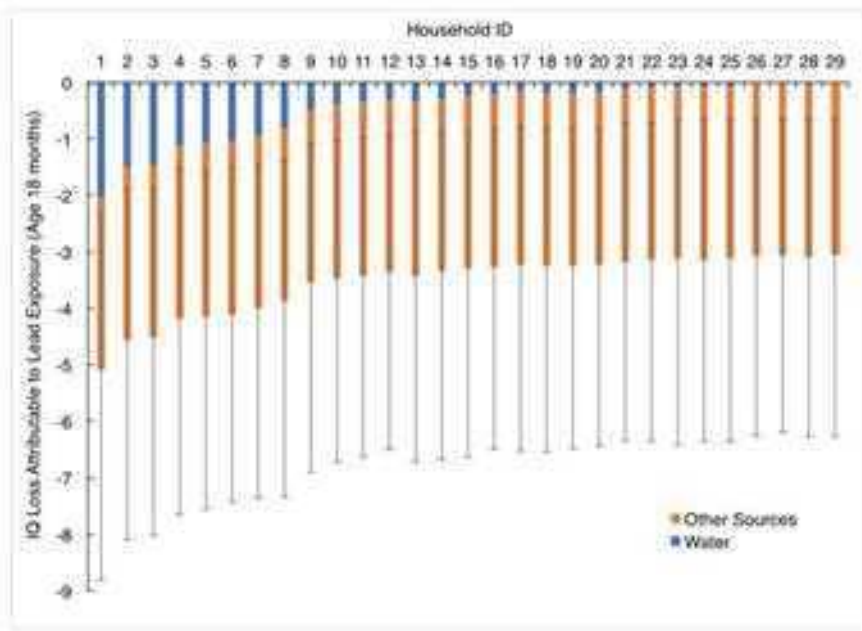


Figure 8. Predicted median IQ loss associated with exposure of an 18-month-old child to environmental lead in the study households. NOTE: Error bars represent 95% confidence intervals on total IQ loss.

To estimate the potential effects of lead on childhood IQ, we combined the IEUBK model output with statistical estimates of the relationship between blood lead and IQ developed by Lanphear et al. [25] Across households and among 18-month-olds, the mean predicted IQ loss attributable to water alone was estimated to be -0.86 IQ points (median = -0.24), with the highest household exposures resulting in an estimated mean -4.1 IQ points (median = -4.0) lost attributable to water alone (Figure 8). When considering total exposure to lead (water in addition to the default assumed background exposure from other sources), the mean IQ loss across all 29 households was -3.6 points (median = -3.4). The mean value in the highest-risk household was -5.2 points (median = -5.1) (see Figure 8). Previous studies have indicated a decrease of about 2% in lifetime earnings with each one-point decrease in IQ. [33] As a result, a child relying on water from this highest-risk household could experience a decrease of more than 10% in lifetime earnings.

DISCUSSION

Our results suggest that lead contamination is prevalent at concentrations that exceed the EPA 15-ppb action level in racially underbounded Wake County, NC, neighborhoods excluded from municipal water service. Lead exposure in these communities may increase the risk of elevated blood lead levels in young children, potentially causing permanent neurological damage. Exposure to lead in water is just one of the environmental disparities these communities may face. Our previous research, for example, documents a much higher risk of exposure to bacterial contaminants in drinking water in underbounded communities of Wake County than in areas served by municipal water supplies [10]. It is possible that

exposures to other drinking water contaminants may be higher, as well, but these exposures have yet to be assessed. The potential for synergistic effects resulting from these exposures is unknown.

Notably, the prevalence of elevated waterborne lead in the samples we collected is similar to that observed in Flint during the recent water crisis. At least one of the two samples we collected exceeded the 15-ppb action level in 8 (28%) of the 29 houses we sampled. By comparison, Hanna-Attisha et al. [34] reported that during the Flint water crisis, the percentage of samples with lead above 15 ppb ranged from 10–32% across Flint's nine wards; they defined wards with more than 25% of samples having elevated lead as “high water lead-level (WLL)” areas. By this definition, the underbounded communities we sampled would qualify as having high WLL.

Our water quality results show a somewhat higher lead prevalence than observed in previous studies of rural private wells. A study of private water systems (private wells, springs, and cisterns) in the rural Blue Ridge-Piedmont region of Virginia found that 19% of 2,144 households tested had lead levels above 15 ppb [24]. A study of 251 Pennsylvania private wells reported 12% of households had elevated water lead levels [35]. Variation in lead prevalence, as suggested in both studies, could be the result of private water system characteristics (e.g., well type, plumbing components, use of household filters) [24, 35] and geologic characteristics (e.g., pH, alkalinity) of the aquifer from which the wells draw their water [36]. Both studies found that household age was highly correlated with lead concentration: the Virginia study found that lead concentrations were significantly higher in homes built before 1988 than in those constructed after 1988, and the Pennsylvania study reached a similar conclusion for houses constructed before 1991 as compared to after 1991. The authors of the Virginia study suggested that these differences could “reflect the 1986 Lead Ban, which required the use of ‘lead-free’ plumbing components in the installation or repair of any . . . residential building . . . connected to a municipal system after June 1988.” The authors suggest that although the lead ban did not apply to private wells, the increased demand for lead-free components could have influenced the availability of such components for newer private well households. Half of the wells included in our study were constructed before the lead ban.

Like the Virginia study, our results also suggest corrosion of plumbing components as a likely lead source. The Virginia study found strong ($\rho > 0.50$) and statistically significant correlations between lead and zinc, copper, and nickel (in order of decreasing correlation) and a weak but significant correlation between lead and aluminum ($\rho = 0.27$). Similarly, our study found a strong ($\rho = 0.51$) correlation between lead and zinc and significant but weaker correlations between lead and aluminum and nickel. The Virginia study authors noted that brass is composed largely (60–80%) of copper and also includes a large proportion of zinc (4–32%), along with lead (2–8%); on this basis, they hypothesized that brass plumbing is a major lead source. The relatively low and statistically insignificant correlation between lead and copper in our study ($\rho = 0.21$) could suggest that components other than brass are a more important source of lead in these households, compared to in the Virginia households.

To our knowledge, only one previous study has analyzed water samples for lead in underbounded African-American neighborhoods excluded from community water service [4]. The previous study found that 1 of 12 private wells in the Rogers–Eubanks community in Orange County, NC, exceeded the 15 ppb action level [4]. However, some of the samples

were collected from the wellhead or outdoor spigot, rather from an indoor tap, therefore overlooking household plumbing as a lead source. In addition, water taps were flushed for three minutes prior to sample collection, also potentially masking key lead sources and underestimating the prevalence of lead [37].

The IEUBK model prediction that water lead in the underbounded households in this study would increase the risk of elevated BLL by 1.9%, on average, in children ages 6-84 is similar to the 2.5% observed increase in the prevalence of elevated blood lead levels in Flint during the water crisis [34]. The model prediction that children in this community would, on average, have blood lead levels of 3.03 $\mu\text{g}/\text{dL}$ is similar to the concentration of 2.4-3.4 $\mu\text{g}/\text{dL}$ predicted by the IEUBK model for a sample of children in Montreal households, the majority of which had lead service lines [38].

Limitations

There are a number of limitations of our study. The samples were collected in August, when temperatures in NC peak and lead releases are expected to be highest. As a result, exposures during other months could be lower. On the other hand, samples were collected at low flow rates due to the small mouths of the sample collection bottles, which could have underestimated exposures due to lower release of lead particles than occurs under standard water flow rates. Similarly, the sample collection bottles we used were smaller than the 1L wide-mouth containers the EPA recommends (although there are no standardized sampling protocols for private wells). Lack of temporal sampling may have resulted in an underestimate of particulate lead due to the failure to capture episodic releases of lead particles.

Our estimates of blood lead levels and associated IQ impacts are based on models rather than measurements. The background exposure to soil and dust lead assumed in the IEUBK model, and used in our analysis, could be too low, especially given the older age of some of the households in our study. For example, Lanphear et al. [26] reported that measured soil lead concentrations were more than 12 times as high as default assumptions in the IEUBK model. In addition, a previous systematic review of racial and ethnic differences in childhood blood lead levels found that African-American children have the highest mean blood lead levels [39], but the IEUBK model does not account for the effects of race. At the same time, the IEUBK estimates of the probability of having lead above the CDC reference level (5 $\mu\text{g}/\text{dL}$) do not agree with observed data from blood lead monitoring in Wake County. From 2011-2015, 96 out of 10,294 children (0.933%) tested in Wake County had blood lead levels above 5 $\mu\text{g}/\text{dL}$ [40]. On the other hand, this sample of children may not be representative of the underserved communities in this research.

CONCLUSION

Our results suggest that many homeowners in underbounded communities of Wake County, NC, are not adequately managing lead corrosion within their private well water system. Children in these communities potentially face increased risk of exposure to lead

compared to neighboring children consuming municipal water, with 24% of the study households exceeding the 15-ppb action level for lead in water, in comparison to 1.5% of households served by the nearby Raleigh municipal water supply. In addition, these children may be at increased risk of exposure to lead from sources other than water due to the older housing in their neighborhoods. The lead exposure risks may be a legacy of a practice of municipal underbounding, contributing to a continuing cycle of increased exposure to environmental lead. To break the cycle of increased risks in these communities, financial and technical support may be needed to enable communities to either advocate for connections to the municipal water supply or to follow recommended well water testing, treatment, and maintenance procedures.

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Chapter 263

A SILVER LINING FOR NEONATAL INTENSIVE CARE (NICU) GRADUATES: COORDINATED SERVICES FROM 0-6 YEARS

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ABSTRACT

The objective of this chapter is to describe the implementation of preventative medical-legal consultations in a NICU follow-up clinic. Preventative medical-legal consultations involve an enhanced neonatal team consisting of a pediatrician, social worker and lawyer working together to assist families of medically complex children access public benefits. We evaluate the success of this program using metrics of parent and child functioning over time. Methods: NICU graduates, as patients at the Center for Healthy Families at the University of Chicago (CHF), were enrolled in the Silver Linings Project after screening when a disconnect between public benefits and developmental and financial needs was identified. At their regularly scheduled pediatrician visits, a legal advocate from the Chicago Medical-Legal Partnership for Children (CMLPC) worked with the medical team during consultation to build an action plan to improve access and utilization of public benefits. Within a year of enrollment, action plans were reviewed, measuring progress on action items in three domains: family items, medical items, and legal items. Results: Twenty-five families participated in this program over 18 months. The physicians, lawyers, and parents completed 80% of total action items across the

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sample. Completion of these action items resulted in improved access compared to the time of enrollment in Early Intervention (EI), food benefits (SNAP and WIC) and Individualized Educational Plans (IEP) for children involved. Conclusions: A preventative strategy to reduce social barriers for NICU graduates using a medical-legal consultation and action plan is feasible and effective at improving access to public benefits and decreasing reported parental stress.

INTRODUCTION

Over the last three decades, considerable progress has been made in understanding the harmful effects of poverty and its correlates on family functioning and early childhood development [1–8]. Research also indicates that risk is cumulative: children who experience multiple risk factors (e.g., abuse or trauma), in addition to poverty, are at increased risk for poor outcomes [9, 10]. Significant progress has been made in developing interventions to ameliorate the effects of poverty and other risk factors. Notably, comprehensive and integrated systems of health, educational and social services are viewed as promising strategies to support healthy family functioning, child health and development, and, in turn, adult health and well-being [1, 2, 7, 8, 11–13].

Among the most vulnerable are graduates of the neonatal intensive care unit (NICU), many of whom have complex medical and developmental needs that continue long after they are discharged home. NICU graduates are either premature, very low birth weight (VLBW) infants weighing less than 1,500 grams (3 pounds 5 ounces) at birth, or those born with congenital anomalies (e.g., cardiac) or severe illness (e.g., infectious, hematologic, respiratory) requiring protracted NICU care. Given the significant brain growth during the third trimester of pregnancy, premature birth can have lifelong effects on cognitive, emotional, social and physical functioning [14]. Supported by technology and clinical expertise in the NICU, these tiny infants stabilize and survive at ever-increasing rates, and the birth age at which most infants are viable continues to decline. Because of this medical success, most NICU graduates survive, but they face extensive neuro-developmental and psychosocial needs and are more likely to require specialized health, education, and social services. Indeed, the rate of childhood disability in the United States has been increasing steadily over the past twenty years, due in part to increases in the numbers of low-birth-weight babies and in the survival rate of babies born prematurely [15–17].

Families of NICU graduates must work with multiple entities which have complicated guidelines, restrictive qualifications, and insurmountable bureaucracies to secure much needed services and supports. As a result, many children with complex developmental needs do not receive the therapies, equipment, monetary supports and services that are needed and medically indicated to protect and nurture their health, growth and development. Thus, many NICU graduates from the inner city face social inequities that can demand legal advocacy and action.

Medical Legal Partnerships (MLPs) were created in the last twenty years out of the recognition that there are health inequities and injustices that can be addressed with legal assistance specifically oriented to social determinants of health, and that addressing barriers to social services can have major impacts on outcomes in both medical and social domains. Currently there are 294 MLPs in 41 states. The Chicago Medical Legal Partnership for

Children (CMLPC) was created in 2006 after a research study showed that inner city NICU graduates faced 3-6 unmet legal needs [1, 18, 19]. In particular, the CMLPC facilitates legal care when patients and families are referred from the Center for Healthy Families (CHF), the University of Chicago NICU follow up clinic. The CHF serves 500 children annually, providing primary and developmental care throughout early childhood from 0-6 years of age. Most families who visit the CHF are at or below 200% of the federal poverty level and qualify for income support programs such as Women, Infants and Children Nutrition Program (WIC), social security, Temporary Assistance for Needy Families (TANF), and Supplemental Nutrition Assistance Program (SNAP). The majority (80%) of families are black; about 10% are Hispanic; and about 10% are white.

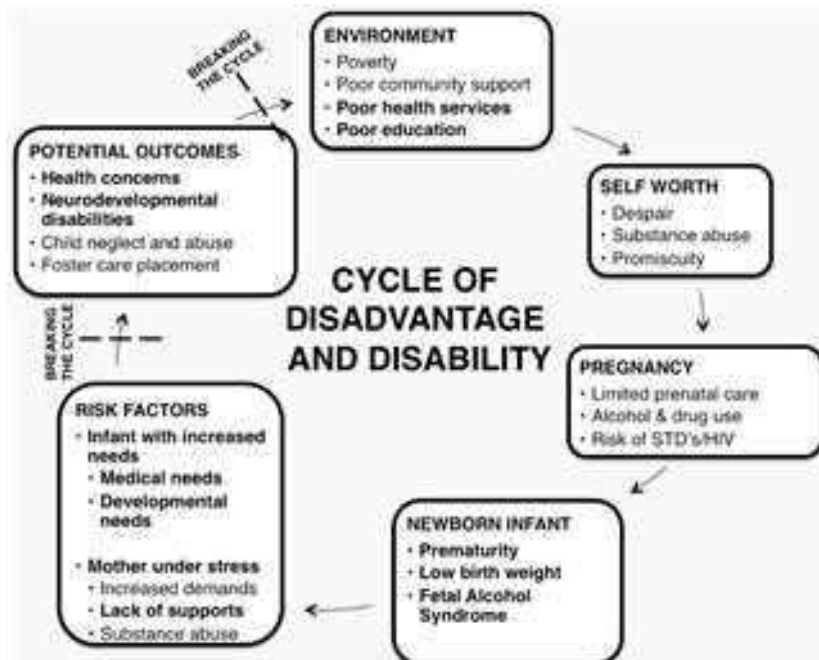


Figure 1. The cycle of disadvantage and disability as it pertains to VLBW newborns. Dashed lines indicate the processes intercepted by our medical-legal intervention.

At present, medical teams help families identify the factors in their lives (e.g., inadequate developmental and educational resources) that can impact child health, and coordinate a legal referral to CMLPC. In the typical legal referral model, about 5-10 families per year are referred to the CMLPC for legal care, however, these referrals are at critical junctures, when a child is facing a dire health consequence due to inequity in services. A more progressive and effective approach is to identify families early, before crisis occurs to anticipate and prevent adverse outcomes; CHF embarked on this approach the details of which, are presented in this chapter [20].

Recognizing that social and economic factors have a profound effect on the medical care of high risk infants, our objective was to determine when and how to best connect families to legal care in order to maximize access to necessary services and supports, and minimize parental stress. We also aimed to optimize this proactive model for medical-legal intervention, with opportunities for replication in MLPs across the country.

This intervention has implications for demonstrating the value of a more holistic and integrated system of services for VLBW and other NICU graduates to break the cycle of disparities that exist for families living in poverty and facing the medical challenges of fragile children. Figure 1 demonstrates how our intervention attempts to ‘Break the Cycle.’

OUR STUDY

Between January 2016 and June 2017, candidate families were identified from the population of NICU graduates served by the CHF following a review of their clinical records. When there was a seeming gap between the need for public benefits and access to benefits, the family was considered appropriate for the project. Parents were approached to enroll for enhanced legal services within multidisciplinary meetings to build action plans at two key times after NICU discharge:

- Between 4-24 months, children with developmental delays should receive federally mandated, state-provided services such as Early Intervention (EI) and Supplemental Security Income (SSI) benefits. They may also be eligible for ongoing family benefits such as TANF, SNAP and WIC.
- At 36 months, when children should qualify for and receive special education services in public schools based on developmental and educational needs.

Enrollment: Parental consent was obtained at enrollment for the project which included consent for multi-disciplinary meetings in person and by phone, legal care by the CMLPC, assessment of patient data such as medical complexity, evaluation using Warner Initial Developmental Evaluation of Adaptive and Functional Skills [WIDEA-FS] and the Parenting Hassles Index [PHI]), and evaluation of public benefit data including documents from schools and developmental programs.

At the time of enrollment to this project, a medical, family, and legal action plan was created for each family. In the first meeting, legal advocates evaluated eligibility criteria for public benefits and suggested concrete action items for the pediatrician, attorney, and family to complete, with the goal of enrollment in all indicated and eligible social services. For each indicated benefit where gaps in coverage were identified, additional action items were defined for parents, the medical team and the legal team. A document was produced that included contact information for relevant organizations and personnel. Action items for families were written in simple English. Figure 2 outlines enrollment and study flow for the project. Figure 3 is an example of a de-identified action plan from the study.

In addition, follow-up phone discussions and clinic visits were conducted after the initial consultation meetings to 1) assess how families are progressing using the action plan and whether there was any additional need for legal intervention or representation through the medical-legal system; 2) identify perceived and actual bureaucratic “hot spots” that may hinder a family’s ability to continue receiving a particular social or medical support, and 3) to assess and capture the impact of the intervention on parent and child functioning.

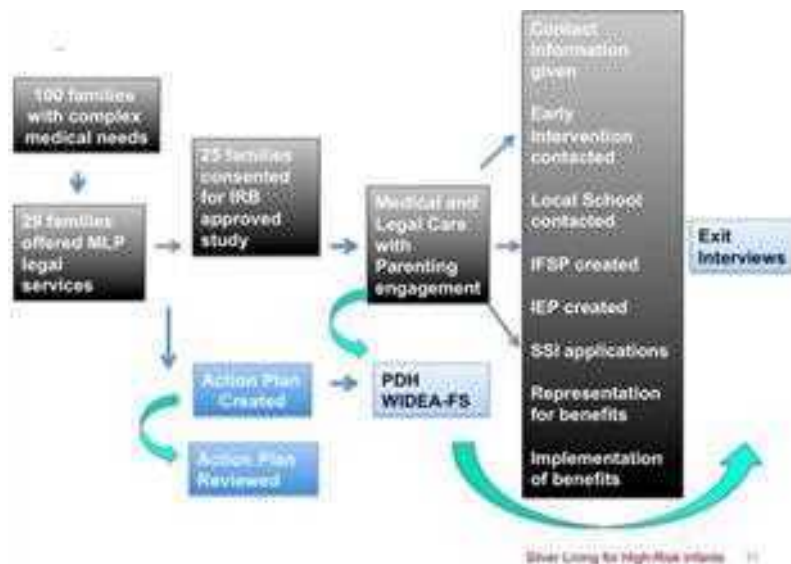


Figure 2. Enrollment and study flow among participants.

Measurement Instruments. The Bayley Scales of Infant and Toddler Development, 3rd Edition (“Bayley III”) was used as a baseline measure of development at the time of enrollment. This is a standardized measure of infant development allowing the measurement of infant cognition, language and motor development. Standard Scores have a mean of 100 and a standard deviation of 15. Scores less than 85 are generally considered to be of clinical concern.

Both the WIDEA-FS and the PHI were performed pre- and post-intervention to objectively evaluate the impact of this study on the day-to-day functioning of the participants. The WIDEA-FS is a functional scale evaluating the domains of self-care, mobility, communication and social cognition [21]. It consists of 50 questions and has a maximum score of 200. Higher scores are assigned to children with higher levels of functioning. The scores are scaled for age. Parents respond to statements such as ‘my child holds up [his] arms so I can put a shirt on [him]’ using the schema 1 = Never to 4 = All of the time. The PDH has 20 questions that asks a parent to assess the frequency of a behavior such as ‘my child is a picky eater’ (rarely—constantly) as well as the intensity of that behavior (low---high) [22]. Higher scores indicate a higher likelihood of disruption in parent functioning due to day-to-day hassles.

Every 3-6 months, the action plan was revisited with the family (either by telephone or in person) to assess completion of action items.

This project was approved by the IRB of the University of Chicago Biological Sciences Division. Its assigned IRB number was 15-1262.

FINDINGS

The PI, clinical social worker, and nurse audited 100 patient charts to evaluate gaps in service and legal needs that might be best addressed with legal advocacy and services. 29

families were identified and approached for participation; 25 consented to enrollment in the project.

80% of infants enrolled were born extremely low birth weight (ELBW = less than 1,000 grams) or very low birth weight (VLBW = less than 1,500 grams), and had early developmental or school needs evaluated by the CMLPC. 20% had delays associated with other NICU morbidities (two children with neural tube defects, one who had required extracorporeal membranous oxygenation, and one diagnosed with a primary genetic condition) and were also referred. Table 1 outlines basic demographics of the study participants.

At the start of the project, the Bayley III Scores and WIDEA-FS scores were at least one standard deviation below average for age equivalency, demonstrating marked developmental and functional needs across our sample. The PDH scores were higher than normal for all enrollees for both the frequency and intensity of child behaviors, indicating the chronic difficulty parents had in caring for their children with impairments. The average number of action items identified by the action plan was 6 per family.

At completion of the project, the WIDEA-FS scores were on average 15 points higher and parenting hassles scores were slightly improved on average by five points, for participating families. Most importantly, 80% of action items had resolution upon follow up with families at the end of the study. Table 2 shows the enrollment and post-intervention results.

Table 1. Patient demographics

Patient Population:	Pre-Term Infants (n = 21)	Term Infants (n = 4)
Mean NICU Length of Stay:	100 days	60 days
Mean Birth Weight:	820 grams	2650 grams
Mean GA (weeks):	26 wks ± 1.7 wks	36 wks ± 2.5 wks
Male: Female	13:8	3:1
Mean age at enrollment:	3.3 yrs/39 months	2.4 yrs/29 months

Table 2. Developmental and parenting stress metrics at enrollment and follow-up

Evaluation (mean +/- 1SD)	Enrollment (n = 25)	6-12 months after enrollment
Bayley III		
Cognitive	70 +/- 12	n/a
Motor	76 +/- 14	
Language	84 +/- 13	
WIDEA-FS score	125+/-11	140+/- 15
PDH Scores		
Frequency	50+/-10	45 +/-8
Intensity	70+/-15	65 +/-10
Action Items (identified/remain)	6+/- 2	2+/-1

In the qualitative interviews with parents, the overarching themes that parents voiced were enthusiasm for having ‘doctors and lawyers located in the same office’ and ‘working together’ to help obtain the best services for their children. Of the eight families interviewed,

all stated that having more ‘written’ and ‘correct’ information about their services on the action plan was helpful. A family who had a lawyer attend an IEP meeting stated, “the school behaved differently when I had a lawyer with me, the IEP was enhanced, and I felt better knowing I had done everything right to help him in school.”

Of note, six families required direct representation by a legal advocate regarding a conflict with the public school system. In these six cases, a lawyer provided representation to assist in appropriately revising the student Individualized Educational Plans. Legal advocacy with use of preventative legal advocacy and service per family ameliorated the need for direct representation in the remaining 19 families.

DISCUSSION

Although graduation from the NICU represents a major medical and emotional accomplishment, NICU graduates face early childhood challenges, especially in terms of access to developmental and social services. Although comprehensive medical care with a medical home is essential, additional social, therapeutic and educational services do have a positive impact on the graduates. Although the CMLPC has provided consultation and legal services to the patients at the University of Chicago for 10 years, in this project, we implemented a broader proactive framework, by using an action plan to better describe and delineate the medical, legal and family action items that would enhance services for the child and family.

Implementation of the medico-legal intervention before discharge and the organization and codification of the action plan resolved 80% of action items, far surpassing initial expectations of this project. Although many of the action items defined were simple, such as making a phone call to a service agency or obtaining a document, others were more complex and required intervention by the pediatrician, attorney or another professional such as a social worker, nurse, or paralegal.

Parents reported slightly better functioning of their children over time and experienced fewer parenting ‘hassles,’ as compared to the time of enrollment, although a control group was not measured for comparison over time. Qualitative feedback from parents indicated that the coordinated nature of this project with a defined action plan was a welcome and valuable intervention.

When we designed the intervention, we anticipated that families would need preventative legal care at two time-points corresponding to the enrollment windows for social and educational resources (4-24 months and 36 months, respectively). We found that most families facing barriers to public benefits identified their needs at later stages than anticipated. The four families approached who did not consent to our study all had infants who were 24 months or younger. It appears that families may be able to navigate public benefits adequately when they are in the immediate wake of NICU discharge but that this process becomes more challenging with time.

There are some limitations in the current study. As mentioned above, a control group was not measured for comparison and some changes from baseline may be related to the natural course of the child’s development. Because of the short time frame, we do not have ongoing information about Early Intervention or school attendance with appropriate IEP services or

about the maintenance of public benefits after the study. In addition, we were not able to obtain Bayley III scores within 6-12 months after enrollment, making it difficult to follow developmental progress over time. However, these children will be followed with appropriate developmental testing in the next 6 months to further document the impact of this study.

Silver Linings Action Plan

Date: 2/2/2016

Name: _____

Parent Name/Phone/Email: _____

Issue Identified	Pathways for Success	Completed	Outcomes
No school enrollment because no IEP and no assurance of 1:1 nursing at school for child in wheelchair with tracheostomy	Parent action item(s): Call or visit local school and request enrollment Medical action item(s): Complete all school forms with requests for specialized services Legal action item(s): Explore whether home nursing or a school nurse is appropriate and viable	Yes Yes Yes	Local school could not accommodate pt but gave testing date/visit date at another school Forms were not enough, discussion of 504, home nursing and IEP with school admin complete The new school permits home nurses to travel with patient, but home nursing hours had be filled
SNAP benefits appear to be lower than per guidelines for a family of 4—perhaps due to WIC+ stamps but also new household member	Parent action item(s): Find out when/how determination was made—call DHS. Medical action item(s): Continue to fulfill WIC guidelines Legal action item(s): Assist with reapplication/renewal of SNAP	Yes Yes Ongoing	Outcomes Difference in benefits received/deserved is \$40. Renewal requested.

Local school: Address: Phone: Nurse fax: Names of possible other schools that can service children with wheelchairs/nursing: Names of nursing agencies used by CPS:	DHS hotline: SNAP benefit grid available: CMLPC Lawyer: Phone: Fax:	Physician: Email: Phone:
<i>Together we can make a difference!</i>		

Figure 3. Sample medical-legal action plan.

CONCLUSION

Families of NICU graduates face complex medical and social needs often requiring interaction with many government agencies. Although formal legal representation may not always be necessary or practical, the medical and legal action plan we developed can be viewed as being similar to the Asthma Action Plan that is widely used and considered a marker of quality and adherence in pediatric practice [23]. Having a physical document articulating the action plan that can be referenced by families, with key phone numbers and collective goals, can be helpful in improving interdisciplinary connectedness and the receipt of public benefits indicated for infants and children with complex needs and their families. The implementation of medical-legal action plans was feasible and efficacious in terms of improving parent and child functioning and parent satisfaction for low income families in an inner city NICU follow-up clinic.

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Chapter 264

EXPLORING THE ROLE OF SOCIAL SUPPORT IN UNDERSTANDING BARRIERS TO BREASTFEEDING PRACTICES FOR ADOLESCENT MOTHERS

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ABSTRACT

Although breastfeeding has many nutritional, immunological, and positive health outcomes for both mother and infant, the prevalence of breastfeeding among adolescent mothers is low. Understanding the needs of this vulnerable population and the obstacles they face could assist in the development of health promotion strategies and lead to greater participation in breastfeeding practices. The purpose of this chapter was to understand the role of social support in adolescent mother's breastfeeding practices. Adolescent mothers were recruited at community agencies that implement a North Carolina Health and Human Services funded Adolescent Parenting Program (APP). The project focuses on breastfeeding experiences of APP participants in Western North Carolina, part of the Southern Appalachian region. Participants completed a self-report survey regarding their breastfeeding experiences. Of the 16 participants, most (87.5%) attended a prenatal class where breastfeeding was discussed and most (75%) initiated breastfeeding their infants, while only 12.5% sustained a breastfeeding practice past 4 months. Few felt comfortable breastfeeding at work (31%) or at school (43.8%). All mothers had a healthcare provider or someone at the hospital speak to them about breastfeeding. Perceptions of social support were gathered using the ESSI instrument, validated in cardiac patients. Mothers reported that they had "someone available" to them who showed them "love and affection" ($M = 4.625$ on 5 point scale). A mother's

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interpersonal relationship with her healthcare provider, family, and peers can help cultivate empowerment in order for her to navigate the challenges of breastfeeding and directly improve the long-term health outcomes for both the mother and child.

INTRODUCTION

Despite the nutritional, immunological, and positive health outcomes breast milk offers for mother and infant, the prevalence of breastfeeding among adolescent mothers is low. Understanding the specific needs of this vulnerable population and the obstacles they face could help develop effective health promotion strategies and lead to greater participation in breastfeeding practices. Compared to mothers twenty years or older, rates of adolescent breastfeeding for eight weeks or longer is 40% lower [1]. While breastfeeding initiation practices have been increasing about 2% per year since the new millennium, adolescent mothers' practices remain low or underreported [1]. Lack of breastfeeding can be a major public health concern as benefits for both mother and baby are striking.

Benefits of Breastfeeding

There are many benefits of breastfeeding for both mother and infant [2, 3]. Breast milk contains essential nutrients needed for an infant's growth. Colostrum, a thick yellow substance secreted at the beginning of lactation, is high in carbohydrates, proteins, and antibodies [4]. The nutrients in human milk are specific to the needs of the human infant. Human milk is easy for the infant to digest, more bioavailable, and provides immunological benefits that an infant can only obtain by receiving human specific milk [5].

Breastmilk has been shown to reduce the risk of gastrointestinal infections, respiratory infections, otitis media, serious cold and throat infections, and sudden infant death syndrome (SIDS) [2]. The protective nature of breastmilk against SIDS has incited recommendations to include breastfeeding in risk reduction messages [6]. In cases of extreme prematurity, an exclusive breastmilk diet can significantly reduce the risk and subsequent complications of necrotizing enterocolitis, which can be life-threatening [7, 8]. Physical health benefits of breastfeeding continue through a child's life. Breastfed babies have lower rates of celiac disease, inflammatory bowel disease, adult obesity, type 1 diabetes, type 2 diabetes and childhood leukemia [2]. A 2017 study by Ahmadizar et al [9] found that within a pediatric population with asthma, increased duration of breastfeeding decreases the number of asthma exacerbations.

Mothers also experience physical benefits of breastfeeding. Godfrey and Lawrence [10] found mothers who breastfeed two years or more have a decreased risk of heart disease and type 2 diabetes. Breastfeeding mothers have a decreased incidence of postpartum depression [10, 11]. Enhanced infant bonding through skin to skin contact between mother and infant during breastfeeding increases endogenous oxytocin, a neurohormone that induces milk release. Oxytocin levels have been shown to positively affect maternal attachment behaviors [12]. A mother's touch, gaze, vocal, and facial expressions that occur during breastfeeding are important physiological processes of attachment [13]. Breastfeeding can be seen as essential

in creating healthy life outcomes for both mother and baby physically, socially and emotionally.

In 2012, the American Academy of Pediatrics (AAP) stated that maximal benefits of breastmilk are reached when mothers follow the recommended six month sustained breastfeeding practice that is followed by a year of continued breastfeeding [2]. Healthy People 2020 highlights the importance of breastfeeding by setting six-month breastfeeding goals to 60.6 percent from 43.5 percent and to increase the proportion of breastfeeding at one year to 34.1 percent from 22.7 percent [3]. Understanding adolescent mothers' barriers while examining possible ways to increase social support can help this population reach the recommended breastfeeding duration and full benefits of breastmilk.

Adolescent Mothers' Breastfeeding Barriers

Multiple individual, practical, cultural, social and economic factors may keep adolescent mothers from breastfeeding. Though some obstacles such as physical barriers or general breastfeeding stigmas may be of concern to all mothers, adolescent mothers face unique roles and challenges that may disrupt their success. Social support systems play an essential role to an adolescent mother's empowerment and breastfeeding practice [14, 15]. Levels of social support from co-workers (or fellow students), family members, significant others, peers, and healthcare professionals can serve as a barrier, if low, or an advantage if high [14].

Adolescent mothers, like their adult counterparts, often are juggling multiple roles as a new mother. However, compared to their older counterparts, adolescent mothers are more likely to be lower income and lack access to educational opportunities [14, 15]. Tucker et al. [14] found that almost half of new adolescent mothers identified returning to school as one of the reasons for not initiating breastfeeding and more than a third included this as one of the reasons they stopped breastfeeding. Support from schools and workplaces that have resources, such as nursing rooms, can create a positive breastfeeding culture for new mothers [16]. In the state of Illinois, new legislation was passed in August 2017 requiring all public and charter schools to provide students with a place to lactate and store pumped milk. In addition, the law states adolescent mothers cannot be subject to academic penalty for using the nursing room and that they must receive academic accommodations. Policies for adolescent mothers within a school setting send a message of support that has the potential to decrease stigma among peers.

Peer acceptance and support significantly influences breastfeeding practices. Adolescent mothers cite that some peers offer more negative outlooks on breastfeeding through little understanding of breastfeeding or their own personal difficulty with breastfeeding [14, 15]. Conversely, when teens encounter positive peer or family modeling they are often motivated to continue breastfeeding [15]. Support from family during school hours can be essential. Family members who are willing to bring the infant to the mother is a practical necessity while also demonstrating support for importance of the breastfeeding practice [15]. Tucker et al. [14] found that when participants had female family members who were encouraging, adolescent mothers consistently breastfed two months or longer.

Some of the practical barriers that inhibit adolescent mothers from continuing breastfeeding are similar to older mothers. These physical obstacles include difficulty with correct attachment to the breast, concerns about the infant getting enough milk, and feelings

of pain and discomfort [14, 15]. Prompt management of these common concerns in the early post-partum period is associated with increased duration of breastfeeding. Like all mothers, adolescent mothers need proper technical guidance when latching the baby to the breast, education regarding feeding cues, proper voids and stools and prevention and management of sore nipples.

Healthcare workers play an essential role in helping adolescent mothers cultivate empowerment through better understanding of breastmilk's benefits [14]. Lower breastfeeding rates were found to be significant in adolescents who had no prenatal healthcare provider, or who were absent from prenatal classes [17]. Gaining breastfeeding knowledge and setting intention are crucial and an estimated 60% of mothers who intended to breastfeed sustained a longer practice [17]. Cultivating empowerment through word choice can improve outcomes. Statements that focus on the mother and what she can personally do for her baby are more effective. One breastfeeding teen stated that breastfeeding: "Was very important because the first milk is something that can help jumpstart your baby's brain" [14]. It is important for healthcare workers to provide consistent information when advocating and supporting breastfeeding. Additionally, many mothers find it hard to access outpatient professional assistance when needed [14]. Lack of technical guidance from their providers or access to lactation specialists can discourage mothers from continuing breastfeeding.

Different sociological factors can also determine a mother's ability to sustain a breastfeeding practice. Lack of social support, the demands of work/school, and access to breastfeeding knowledge are some of the many obstacles that have been found to make breastfeeding difficult for adolescent mothers.

In North Carolina obstacles to adolescent mothers' breastfeeding practices have been recognized by the North Carolina Department of Health and Human Services. This department funds selected local health departments, organizations, and public schools that wish to implement an Adolescent Parenting Program (APP) in their community. The goal of these programs is to provide support while creating a positive peer community amongst adolescent mothers. Aims for the program include increasing maternal self-sufficiency, decreasing second pregnancies, and increasing high school graduation rates. The aims for the children of APP participants include increasing cognitive development, establishment of a medical home, and the creation of a safe home environment. Breastfeeding can be an essential way for the program to help meet their goals. The purpose of this study was to gauge current breastfeeding practices among this population and identify the influences social supports have on the breastfeeding practices.

In reviewing the literature, no published studies examining cumulative adolescent mothers' attitudes, practices, and social support in rural Western North Carolina (WNC) were found. Smith et al. [15] used qualitative methods to look at the role of social support of adolescent mothers in urban, Greensboro, NC while Tucker et al. [14] used PRAMS to look at adolescent mother's feeding practices in North Carolina. No research to date has looked at breastfeeding practices among APP participants.

OUR STUDY

Participants of four Western North Carolina APP agencies were contacted for recruitment. The agencies are located in four different Western NC counties (Buncombe, Catawba, Henderson, and Caldwell). A survey was developed to gain insight into breastfeeding behaviors in our study location. A non-experimental cross-sectional study design was used to assess the knowledge, attitude, current practice of breastfeeding, and perceptions of social support. Adolescent mothers who participated in programs held within community organizations in Western NC were recruited to participate in this anonymous, confidential survey. The target population was adolescent mothers, ages 16-21 years old. This study was approved by the Institutional Review Board of Lenoir-Rhyne University.

The survey collected self-reported data, to be completed in a single 15-minute time period (Appendix A). Most questions regarding mothers' experiences (with prenatal classes, feeding practices, potential obstacles, healthcare services, and social support) required a yes/no response. The social support survey items were adapted from the ENRICH Social Support Instrument (ESSI) which was validated in cardiac patients [18]. The ESSI gauges social support through open ended or Likert scale questions. Social media questions were included to gauge interest in using this platform for connecting with other mothers and educational purposes.

Table 1. Adolescent mothers in Western North Carolina Adult Parenting Programs: Demographics

Demographics	<i>n</i>	%
Age		
16	1	6.3
17	8	50.0
18	2	12.5
19	5	31.3
Education		
10 th grade	29	27.9
11 th grade	32	30.8
12 th grade	43	41.4
Race		
African-American	2	12.5
Caucasian	9	56.3
Hispanic	4	25.0
Other	1	6.3
Child's Age in months		
0 to 6	6	37.5
7-12	1	6.3
13-18	3	18.8
19-24	4	25.0
>24	2	12.6

The adolescents were recruited through local agencies and distributing surveys at organizational events. The survey was distributed by the principal investigator or the director of the program on dates that were convenient for the agencies due to planned organizational events. At the beginning of each event, mothers were informed of the study, educated about potential risks and benefits to participation and then invited to participate. Although this

research included minors, it was verified by the IRB that an informed consent from the adolescent mothers' parents was not needed. After informed consent was obtained, selection criteria were verified, and the surveys were distributed. In order to maintain anonymity, the signed informed consent form was collected and saved in a letter envelope separately from the anonymous survey. SPSS was used to analyze the results.

FINDINGS

Participation rates for completing the survey was 100% among the 16 mothers who met selection criteria and consented to participate. This study was self-selecting. The participants ranged in age from 16 to 19 years old. The participants identified as White (56.3%), Black (12.5%) or Hispanic (25%). A majority had children aged two years or younger (87.4%) (see Table 1).

Most mothers (87.5%) attended a prenatal class with breastfeeding instruction. The majority (81.3%) reported an intention to breastfeed, with more than 40% indicating breastfeeding was "very important." A common theme stated by the participants about breastfeeding was that it is "healthier", gives "nutrition [nutrients, nutritious]," and "breast is best." The majority of the mothers initiated breastfeeding (60%) but only 12.5% sustained the practice past four months. Many participants reported using formula (87.5%) for an average of 8.3 months and 56.3% of mothers attempted combined formula/breastfeeding. Many (62.5%) reported experiencing pain and 43.8% reported the pain affected their decision to breastfeed. When the participants were asked specifically why they chose either breastmilk or formula, they cited not producing enough milk (43.8%), nipple pain (12.5%), and difficulty latching (6.25%) as the reasons they chose formula. Mothers often described their feeding decision by first stating, "I tried" or "I really wanted to" breastfeed, but started to use formula because of a physical barrier. One of the adolescent mothers who sustained an 18-month practice reported, "I thought that breastfeeding was a better choice for both my son and I."

Out of the 81.8% that answered work related questions, only 25% reported having a place to pump their breastmilk at work. Only 31% reported that they would feel comfortable pumping at work. In the same vein, 62.5% reported having a place to pump at their high school but only 43.8% admitted to being comfortable doing so. 56.3% of the respondents reported being breastfed as a child and 37.5% knew that their mothers were breastfed when they were infants (see Table 2).

All mothers had a healthcare provider or someone at the hospital speak to them about breastfeeding, and most (81.3%) received outpatient services regarding breastfeeding feeding concerns. Few mothers (31.3%) reported receiving encouragement to breastfeed from the father of the child, but many received encouragement from family (75%) or friends (68.8%). In all, most (87.5%) felt supported in their feeding choices (see Table 3a).

Using the ESSi five-point Likert scale, mothers reported how often they felt supported (higher scores indicating greater support). Of the six items rated, mothers most frequently reported that they had "someone available" to them who showed them "love and affection" ($M = 4.625$). Social support scores are described in Table 3b.

Adolescent mothers reported using social media such as Instagram, Facebook, Snapchat, and Youtube for educational purposes (87.5%) and as a way to connect with other mothers

(100%). Many (62.5%) were interested in creating a breastfeeding website for young mothers as displayed in Table 4.

Table 2. Adolescent mothers' experiences of breastfeeding

Adolescent mothers' experiences		<i>n</i>	%
Attended a prenatal class with breastfeeding education		14	87.5
Planned to breastfeed		13	81.3
Importance of breastfeeding			
Not important		0	00.0
Somewhat important		4	25.1
Important		5	31.3
Very important		7	43.8
Breastfed or breastfeeding their child		12	75.0
# months of breastfeeding	<i>Mean (range) =</i>	4.81	1-24
Use of formula		14	87.5
# months of formula feeding	<i>Mean (range) =</i>	8.29	1-18
Combined breastfeeding with formula feeding		9	56.3
Currently employed		10	62.5
Place to pump at work		4	25.0
Likely to pump at work if place was provided		7	43.8
Comfort level of pumping at work (5 pt Likert scale)	<i>Mean (range) =</i>	2.85	1-5
Very uncomfortable		3	18.8
Somewhat uncomfortable		4	25
Neither comfortable or uncomfortable		1	6.3
Somewhat comfortable		2	12.5
Very comfortable		3	18.8
Place to pump at school		10	62.5
Pumps available at school		3	18.8
Comfort level of pumping at school (5 pt Likert scale)	<i>Mean (range) =</i>	3.29	1-5
Very uncomfortable		3	18.8
Somewhat uncomfortable		1	6.3
Neither comfortable or uncomfortable		3	18.8
Somewhat comfortable		3	18.8
Very comfortable		4	25
Pain while breastfeeding		10	62.5
Pain affected decision to breastfeed		7	43.8
Health complications affected decision to breastfeed		5	31.3
Mother/respondent was breastfed as a child		9	56.3

Table 3a. Mothers' support for breastfeeding

Mothers' support for breastfeeding	<i>n</i>	%
Healthcare provider discussion of breastfeeding	16	100.0
Lactation outpatient services	13	81.3
Family Encouragement	12	75.0
Father of Child Encouragement	5	31.3
Colleague Encouragement	11	68.8
Felt supported	14	87.5
Felt in control	13	81.3

Table 3b. Mothers’ perceptions of social support

Mothers’ perceptions of a person available for social support	Mean	SD
Whom you can count on to listen	4.125	.72
Gives good advice about a problem	4.188	.66
Shows love and affection	4.625	.72
Helps with daily chores	3.563	1.36
Provides emotional support	4.188	.98
You can trust and confide in	4.125	1.26

Table 4. Mothers’ social media use

Mothers’ social media use	n	%
Use of social media for educational purposes	14	87.5
Use of social media to connect with other mothers	16	100
Interested in creating a breastfeeding website	10	62.5

DISCUSSION

This preliminary study surveyed 16 adolescent mothers to better understand their beliefs, behaviors, and barriers that may either encourage or hinder them from breastfeeding practices. Although a majority of the mothers (81.3%) intended on breastfeeding and all (100%) deemed breastfeeding “somewhat” to “very” important, only 75% initiated breastfeeding their babies and only two mothers (12.5%) surpassed the 6-month goal set by Healthy People 2020 [2]. Though initiation rates were higher in this population (75%) than the national average of a little over 50%, the rate of breastfeeding past 6 months was lower than the national average of 19% [1, 14]. It is encouraging that adolescent mothers in this population initiated breastfeeding, which may, in part, be due to the participation in an Adolescent Parenting Program. Nevertheless, greater support, specifically technical breastfeeding support, can help adolescent mothers in this population achieve their intention and the optimal 6-month goal.

Best practices for adolescent mothers to sustain breastfeeding can be ascertained through the use of the socioecological model. This behavioral model describes effective health promotion as a synergistic effort between five different levels: the individual, interpersonal relationships, organizations, communities, and society. Much like the ecology of the natural world, each level depends on each other for change. For example, Illinois’ state breastfeeding legislation supports an adolescent mother’s breastfeeding practice in school and this influences adolescents in a positive, supportive manner. An adolescent mother’s immediate environment is influenced by the many interpersonal conversations she encounters as she connects with and learns through her inner trusted circle. For example, the possibility of pumping during the day in a safe environment may not only support and teach the mother during lactation, but also influences peers, family members, and healthcare providers who interact with others experiencing similar issues.

Results from this study indicate that some women are uncomfortable pumping/expressing their milk at work or at school. Assessing the availability of time for a mother to pump without penalty at work or school may be a better indicator for breastfeeding success

than access to a breast pump. To help overcome this barrier, schools and worksites should be required to offer an on-site nursing room to ensure privacy and cultivate peer support.

The mothers in this study were specific to the Adolescent Parenting Program. At the core, programs like the APP help adolescent mothers navigate and utilize resources to optimize health and personal growth for mother and baby. Organizational support and interpersonal connections with other adolescent mothers is an important service the program provides. This may explain the high, positive report of social support from these mothers. Although only a third of these mothers received encouragement to breastfeed from the father of the child, the rate of encouragement from family and friends was high. High rates of initiation and perceived importance of breastfeeding among this population may be due to participation and peer support from the APP. Nevertheless, consistent with previous literature, technical breastfeeding support is deeply important and not always included in programs where social support is given [14].

According to Tucker, Wilson and Samandari [14], adolescent mothers can be inhibited from continuing to breastfeed due to practical difficulties, e.g., from improper infant latch, concerns about the infant getting enough milk, or pain and discomfort. At least one of these reasons was echoed by 62.5% of the participating mothers of this study as the main reasons for choosing formula. Healthcare providers and lactation outpatient services are an important source of technical information to overcome some of the initial hurdles of breastfeeding. Interestingly, 81.3 % of the participating mothers received outpatient education but only 43.8% were offered a breast pump. There seem to be gaps in outpatient education that may result in breastfeeding discontinuation. Research focusing on the adolescent mothers' technical conversations with healthcare providers may provide insight to this finding. In addition, eliciting the technical breastfeeding knowledge of peers and family members may help adolescent mothers anticipate potential complications and empower mothers to better utilize their healthcare providers. The APP may be able to increase their participant's breastfeeding rates by opening discussion on common pitfalls as well as to the benefits of breastmilk.

In addition to feeling supported in their breastfeeding decisions, it is important that adolescent mothers receive ongoing social support for breastfeeding practices [19, 20]. Health outcomes and healthy behaviors are improved when people perceive they are supported in their lives, at home, online, at work, or at school [18].

Smartphones play an important role in adolescent communication. Health initiatives such as the adolescent suicide prevention hotline Crisis Text Line and the adolescent smoking cessation program SmokeFreeTeen recognize this importance and utilize smartphones to reach the adolescent population. Questions on this survey regarding social media use and participant interest in an adolescent mother group were designed with quick access to social support and education in mind. The perception of social support through the use of social media may be influential since most adolescents use popular sites as ways to connect with one another and obtain information.

While many North Carolina initiatives focus on reducing teen pregnancy and teen birth rates [21], adolescent parenting programs can have an impact on the quality of mothering practices by providing social support and addressing barriers that impede new mothers in breastfeeding initiation. Since breastmilk has numerous benefits over formula feeding [2, 4, 5, 22], the emphasis can shift toward supporting and educating adolescent mothers in order to "break the cycle" of health disparities (see Figure 1). Breastfeeding is an affordable and

sustainable quality source of nutrition for the baby that improves long term health outcomes and decreases unwanted health risks. The process of breastfeeding improves maternal and infant health and naturally increases maternal child bonding. By focusing on social support and breastfeeding education together, adolescent mothers will be equipped for breastfeeding success which directly improve the long-term health outcomes for both the mother and child.

CONCLUSION

There were many limitations of this study which can provide insight on future opportunities for research within this population. This population was self-selecting which may affect the outcome of this data. The participating adolescent mothers may have been more willing to communicate their experiences which may present bias to the results. Though the APP is required to have thirty participants at each event, the actual attendance was low at the time of enrollment. Many of the adolescents work and depend on unreliable transportation which may limit attendance. Perhaps in the future, an online survey may reach participants and yield a better sample.

Detailed examination of agency and institutional breastfeeding programs may better inform future directions for this research. A broader qualitative study design may help explain the high initiation rates followed by low continuation rates among adolescent mothers. Demographic information such as income, access to transportation, parity, and marriage information may have also been fruitful.

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Chapter 265

A COMMUNITY-BASED PROGRAM TO DECREASE THE RISK OF CHILDHOOD OBESITY

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ABSTRACT

In the United States 80% of obese adolescents, 50% of obese preschool-aged children, and 50% of school-aged children are prone to develop adult obesity. Health education and physical activity for children at risk for obesity are key to mitigating the risk of developing obesity as an adult. Health education and physical activity complement each other, improving children's behaviors and attitudes towards health. This study builds upon an existing body of knowledge about the prevention of obesity and long-term morbidity among rural youth from disadvantage backgrounds. The purpose of this study was to improve the attitudes and behaviors towards healthy eating through combining health education and physical activity among children of Macon County, Alabama. We conducted a mixed method design with a cluster sample of 11 participants. We used a pre/posttest lifestyle student created questionnaire guided by the Institut de Recherches Cliniques de Montréal (IRCM) lifestyle questionnaire and the Simple Lifestyle Indicator Questionnaire to characterize health behaviors (i.e., consumed vegetables, fruits, sweet drinks and water) and attitudes (i.e., enjoyment of exercise, emotional eating, ways of staying active when the weather is bad). Our study concluded that an interactive health education and physical activity interventions positively influenced healthy eating behaviors and attitudes in nine out of eleven participants for attitudes and six out of eleven participants for behaviors on healthy eating.

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INTRODUCTION

The prevalence of childhood obesity in the United States (US) tripled in the 1980s and 1990s, earning the recognition of being the most common chronic childhood disorder [1]. The prevalence of obesity among US children and adolescent's ages 2-19 year is approximately 17% [2], but obesity prevalence varies across different ethnicities. According to the National Health and Nutrition Examination Survey (2015-2016) there is an 8.9% difference between obesity in African Americans compared to non-Hispanic white youth [3]. There are several diseases and disorders that obese children can develop. These include high blood pressure, dyslipidemia, metabolic syndrome, obstructive sleep apnea and other breathing problems, osteoarthritis, anxiety, depression, and low self-esteem [1].

A child's diet plays a major role in obesity. Children ages 6-18 years are more likely to consume foods from fast food restaurants which is one of the causes of overweight and obesity [4]. A study conducted by Choi et al [5] investigating the attitude and behaviors towards nutrition and diet of elementary school children concluded that, for the improvement of nutrition knowledge, education about nutrition attitudes and dietary behaviors is required [5]. Roe et al., [6] investigated health promotion interventions (health education, nutrition, and dietary change strategies) in community settings, and concluded that the greatest changes in dietary behaviors were seen in studies with highly motivated volunteers in intensive health education programs [6]. A study by Shariff et al., [7] showed that a nutrition education program compared to a health and physical education curriculum has a greater impact on changing the knowledge, attitudes, and practices of primary school children towards healthy nutrition; the study used the "fun while learning" concept engaging with the participants through group discussions on nutrition topics, demonstrations, nutrition contests, workbook assignments, and singing sessions to keep their attention as opposed to using the traditional classroom style teaching method [7]. Mealtime has been demonstrated to be a time for adults to promote healthy eating habits with children [8]. Children who eat at least three meals per week with family are more likely to eat breakfast regularly and have increased intake of fruits and vegetables which is beneficial for health and nutrition [1].

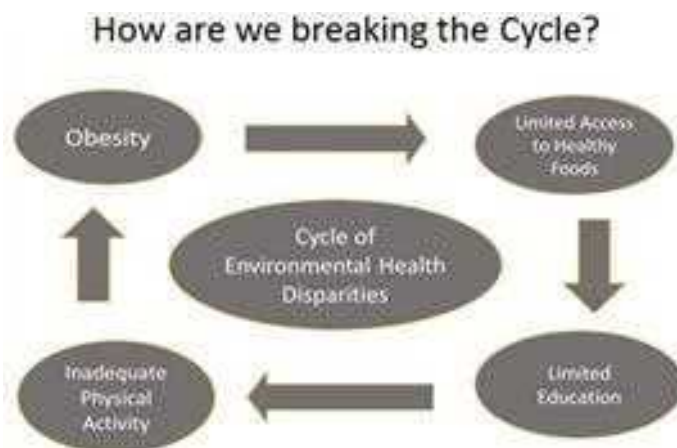


Figure 1. Break the cycle diagram.

Sedentary lifestyles and poor dietary habits increase prevalence of obesity-related comorbidities [9]. Physical activity has an important role in the treatment of obese and overweight children [10]. According to Lazaar [11], increasing physical activity or exercise is one of the cornerstones in treating pediatric obesity. A meta-analysis addressing the effects of physical activity (strength training and aerobic) for seven weeks, 2-5 times per week, 10-60 minutes in treatment of obese and overweight children, concluded that physical activity reduces body fat in obese and overweight children and adolescents [10]. A moderate amount of physical activity for at risk children can provide substantial health benefits. According to the Centers for Disease Control and Prevention (CDC), children and adolescents should engage in 60 minutes a day of moderate- (3.0 to 6.0 METs; 3.5 to 7 kcal/min) or vigorous- (> 6.0 METs; more than 7 kcal/min) aerobic physical activity [12].

This study implements a combined physical activity and health education intervention to increase healthy eating behaviors and attitudes in African American children residing in Macon County, Alabama. Our study was informed by the cycle of environmental health disparities ecological framework created by the Southeast Pediatric Environmental Health Specialty Unit (PESHU) in Atlanta, Georgia (see figure 1). This model includes compound risk factors (i.e., limited educational services), personal characteristics (i.e., limited education), environmental characteristic (limited access to healthy food), and health characteristics (obesity) that can lead to serious adverse health effects when children transition into adulthood if they remain obese [13].

OUR STUDY

To better understand the potential effects of physical activity and nutrition education on behaviors of children in Tuskegee, Alabama, we used both quantitative and qualitative designs. The study was approved by the Institutional Review Board at Tuskegee University. The City of Tuskegee is located in Macon County (rural Alabama). According to the Data USA 2015, the population of Tuskegee is 9,218 and 20,018 for Macon County [14, 15]. Macon County is among the 18 Black Belt counties of Alabama.

Our study focused on three components that contribute to obesity: limited access to healthy foods, limited health education, and limited community physical activity accessibility. The 2014 preschool obesity rates in Macon County and Tuskegee, are 17.3% and 31.7% respectively [16]. Macon County is a food desert which is defined as an “area in which it is difficult to gain access to or buy affordable, good quality food” [17]. Some residents in Macon County reside approximately 20-25 miles away from grocery store where there is affordable, good quality food. As of 2014 the percentage of individuals consuming a healthy diet in Macon County and Tuskegee, Alabama is 50.2% and 48.2% respectively [16]. We have no formal information on programs that target health education and physical activity combined in Tuskegee, Alabama.

PARTICIPANTS AND MEASUREMENT

The study used cluster sampling to recruit children between the ages of 6-14 years with six girls and five boys. We recruited 11 African American children from disadvantaged backgrounds, living in Tuskegee, Alabama. All were participants in the Tuskegee Youth Safe Haven Program, which is an afterschool program for youth 6-18 years old located in Macon County, serving economically disadvantaged neighborhoods [18]. The program provides services to improve living conditions of its participants and provide pre-professional youth development resources for youth in Macon County. Informed consent (voluntary agreement of the guardians for the participants to participate in research) was obtained from parents. Informed assent (willingness to participate in the research from youth under 18 years) was obtained from the children.

Table 1. Student Created Lifestyle Questionnaire guided by the IRCM healthy lifestyle and the Simple Lifestyle Indicator Questionnaire (19, 20)

Questionnaire	A	B	C
How many meals do you eat a day?	1-2 meals a day	3 meals a day	4 or meals a day
How many veggies do you eat?	Less than 1 a day	2-3 a day	More than 4 a day
How many fruits do you eat?	Less than 1 a day	2-3 a day	More than 4 a day
How often do you eat sweet foods? (candies, chocolate, table sugar, honey, jam)	3 times a week or less	4-5 times a week	Every day
Do you drink sweet drinks? (Fruit juice or fruit drinks, soft drinks or energizing drinks, iced tea, lemonade)	1 cup a day	1-2 cups a day	2 or more cups a day
How many cups of water do you drink a day?	1 cup a day	1-2 cups a day	2 or more cups a day
How often do you walk or ride a bike?	1-2 times a week	More than 3 times a week	Most of the time
How many times a week do you move around for at least 30 minutes?	Never	2-3 times a week	4-6 times a week
Do you like working out?	A lot	A little	Not at all
Do you find different ways to exercise when it's raining and you don't want to go outside to exercise?	Never	Sometimes	Always
Do you drink enough during and/or after a training session?	Never	Sometimes	Always
I am in school for long hours and when I get the chance to relax, I just want to sit in front of the TV.	Never	Sometimes	Always
What I eat now is not going to make a difference for my health.	Never	Sometimes	Always
When I eat chips or cookies, I have to eat the whole bag.	Never	Sometimes	Always
I eat a lot when I am happy, sad, angry.	Never	Sometimes	Always
I easily feel upset.	Never	Sometimes	Always

The 11 participants were administered a modified questionnaire guided by the Institut de Recherches Cliniques de Montréal (IRCM) lifestyle questionnaire and the Simple Lifestyle Indicator Questionnaire [19, 20] consisting of two sections; behaviors and attitudes of healthy eating (see table 1). Participants engaged in one hour of health education and one hour of

physical activity once a week over 18 weeks from September 2016 to February 2017 for a total of 18 sessions. The modified lifestyle questionnaire was used as a pre/post-test method with details pertaining to behaviors and attitudes towards health (i.e., meals consumed a day, intake of water, engagement in exercise, and enjoyment of exercises) [19, 20]. Participants wore pedometers during the physical activity intervention to provide information on the number of steps taken. During the health education intervention, the study children met in classroom settings, used visual aids, used worksheets on balanced meals, gardening using fruits and vegetables, and prepared and consumed vegetables, and fruit ‘smoothies’ provided by the local food bank. Educational sessions were interactive; the children worked in groups and presented to each other their worksheets or posters at the end of the health education intervention. During physical education, the children engaged in kickball, relay racing, sack racing, bean bag toss, football, basketball, and a simulated jeopardy game. All activities physical activities were outdoor and limited to three games a session.

FINDINGS

Figures 2 and 3 present the results of the differences in average scores from the pretest and posttest for the student created lifestyle questionnaire guided by the IRCM lifestyle questionnaire and the Simple Lifestyle Indicator Questionnaire.

Overall the results from pretest to posttest were as follows: 45% of the participant’s behaviors towards healthy eating increased, 65% of the participant’s attitudes towards healthy eating increased, 27% of the participants had no change in behaviors towards healthy eating and 0.09% of the participants had no change in attitudes towards healthy eating. 28% of the participants had a decrease in behaviors towards healthy eating and 34.9% of the participants had a decrease in attitudes towards healthy eating.

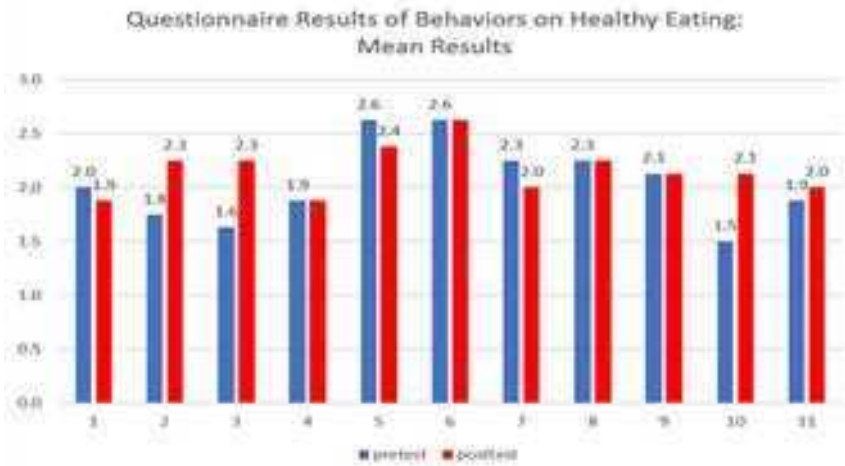


Figure 2. Average scores of the Lifestyle Questionnaire Pretest and Posttest of Behaviors on Healthy Eating.

After 18 sessions of intervention, results from the posttest on behaviors of healthy eating revealed that 82% of the children eat three meals a day (18% increase from pretest score

64%), 55% of the children consumed two-three vegetables a day (19% increase from pretest score 36%), 45% eat sweets every day (19% decrease from pretest score of 64%), 73% of the children drink one-two cups of sweet drinks a day (18% increase from the pretest score 55%), 64% drink one-two cups of water a day (28% from pretest score 36%), 55% of children walk or bicycle most of the time (9% decrease from the pretest score of 64%) and 91% engage in exercise for at least 30 minutes for four-six times a week (18% increase from the pretest score 73%) (see table 2.)

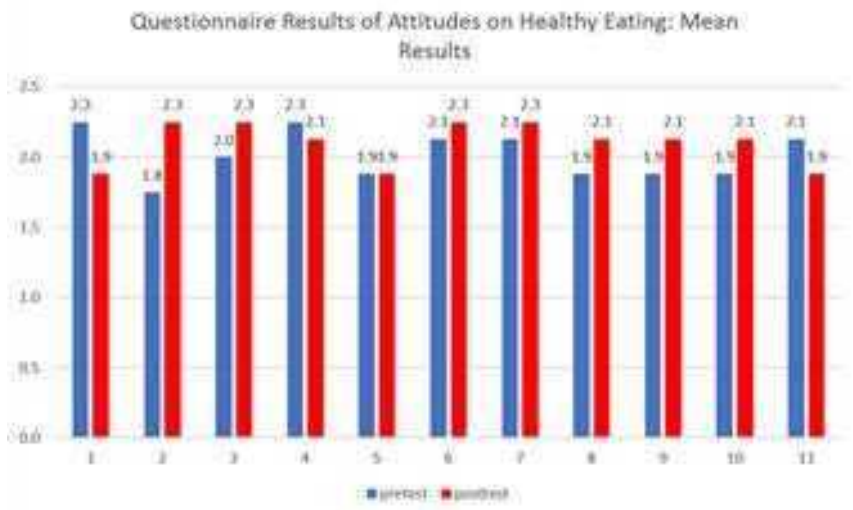


Figure 3. Average scores of Lifestyle Questionnaire Pretest and Posttest of Attitudes on Healthy Eating.

Table 2. Behaviors of healthy eating

	Pretest	Posttest	Pretest	Posttest	Pretest	Posttest
	1-2 meals a day (A)		3 meals a day (B)		4 or meals a day(C)	
1. How many meals do you eat a day?	36%	18%	64%	82%	0%	0%
	Less than 1 a day		2-3 a day		More than 4 a day	
2. How many veggies do you eat?	55%	27%	36%	55%	9%	18%
3. How many fruits do you eat?	45%	36%	36%	45%	18%	18%
	3 times a week or less		4-5 times a week		Every day	
4. How often do you eat sweet foods? (candies, chocolate, table sugar, honey, jam)	27%	18%	9%	36%	64%	45%
	1 cup a day		1-2 cups a day		2 or more cups a day	
5. Do you drink sweet drinks? (Fruit juice or fruit drinks, soft drinks or energizing drinks, iced tea, lemonade)	18%	0%	55%	73%	27%	27%
	1 cup a day		1-2 cups a day		2 or more cups a day	
6. How many cups of water do you drink a day?	36%	18%	36%	64%	27%	18%
	1-2 times a week		More than 3 times a week		Most of the time	
7. How often do you walk or ride a bike?	27%	18%	9%	27%	64%	55%
	Never		2-3 times a week		4-6 times a week	
8. How many times a week do you move around for at least 30 minutes?	0%	0%	27%	9%	73%	91%

At the completion of 18 sessions of intervention, the significant results from the posttest on attitudes of healthy eating concluded that 82% of the children do not like working out (18% increase from the pretest score 64%), 82% of the children always find different ways of staying active when the weather is bad (73% increase from pretest score of 9%), 55% of the children always drink water after exercising (28% increase from pretest score 27%), 64% of the children sometimes watch TV after long hours at school (9% increase from pretest score 55%), 73% of children believe being careful now will not make a difference with their health (37% increase from pretest score 36%), 45% of the children eat chips and cookies (9% increase from pretest score 36%), 82% of the children never eat due to emotional upset (no change from pre-posttest score) and 73% of the children sometimes feel easily upset (9% increase from pretest score 64%) (see table 3).

Table 3. Attitudes of healthy eating

	Pretest	Posttest	Pretest	Posttest	Pretest	Posttest
	A lot(A)		A little (B)		Not at all (C)	
1. Do you like working out?	0%	9%	36%	9%	64%	82%
	Never		Sometimes		Always	
2. Do you find different ways to exercise when it's raining and you don't want to go outside?	64%	9%	27%	9%	9%	82%
3. Do you drink enough water after exercising?	27%	9%	45%	36%	27%	55%
4. I am in school for long hours and when I get the chance to chill, I just want to sit in front of the TV.	0%	18%	55%	64%	45%	18%
5. What I eat now is not going to make a difference for my health.	18%	9%	45%	18%	36%	73%
6. When I eat chips or cookies, I have to eat the whole bag.	18%	27%	36%	45%	45%	27%
7. I eat a lot when I am happy, sad, angry.	82%	82%	9%	9%	9%	9%
8. I easily feel upset.	27%	9%	64%	73%	9%	18%

DISCUSSION

The study targeted economically disadvantaged youth 6-18 years old located in Macon County, Alabama, a food desert with limited access to healthy foods, limited health education, and limited access to community physical activity. The 2014 preschool obesity rates in Macon County and Tuskegee, are 17.3% and 31.7% respectively. This study was designed to begin the discussion and introduce an alternative way to “break the cycle” of obesity in Macon County.

The study implemented interactive health education and physical activities with expectation of changing behaviors and attitudes towards healthy eating. Our measurements revealed that there was a positive increase in the attitudes of participants to recognizing that they can make choices, in that, unhealthy patterns of behavior, such as eating an entire bag of chips or watching television for a prolonged period of time, can be substituted by healthy behaviors such as riding a bicycle or walking more and eating more fruits and vegetables.

There were several limitations in our study. This study was limited by the fact that the study period was brief. In addition, at times, the answers provided by the children on the questionnaire were limited by their ability to fully comprehend the questions and also to carry over learned behaviors from the intervention sessions to make daily healthy food choices independently. There was also no easy way to measure other physical activities that they engaged in outside of the intervention sessions. Also, we could not use our results from the pedometers due to frequent malfunctions.

Table 4. Average scores Lifestyle Questionnaire Pretest and Posttest of Behaviors and Attitudes on Healthy Eating

Behaviors				Attitudes			
Participants	Pretest average scores	Posttest average scores	Score difference between pre/posttest	Participants	Pretest average scores	Posttest average score	Score difference between pre/posttest
1	2.00	1.88	0.12	1	2.25	1.88	0.37
2	1.75	2.25	0.50	2	1.75	2.25	0.50
3	1.63	2.25	0.62	3	2	2.25	0.25
4	1.88	1.88	0.00	4	2.25	2.13	0.12
5	2.63	2.38	0.25	5	1.88	1.88	0.00
6	2.63	2.63	0.00	6	2.13	2.25	0.12
7	2.25	2.00	0.25	7	2.13	2.25	0.12
8	2.25	2.25	0.00	8	1.88	2.13	0.25
9	2.13	2.13	0.00	9	1.88	2.13	0.25
10	1.50	2.13	0.63	10	1.88	2.13	0.25
11	1.88	2.00	0.12	11	2.13	1.88	0.25
Aggregate participants scores	2.05	2.16	0.23		2.01	2.11	0.23

Despite these limitations, our study provided a glimpse into the impact of our interventions on the behavior and attitudes of the children towards choices of foods, as well as, desire to participate in some physical activities. Although the results were not strong, we believe that health education and physical activity interventions positively influenced healthy eating attitudes through the several weeks of interactive interventions, that included visual aids, worksheets on balanced meals, gardening using fruits and vegetables, prepared and consumed vegetables, and fruit ‘smoothies,’ with kickball, relay racing, sack racing, bean bag toss, football, basketball, and a simulated jeopardy games. Some students demonstrated the ability to broaden their scope of exposure and understanding of healthy behaviors and attitudes (see table 4). We would like to see the results of a long term lifestyle program, at

least 2-3 times a week, combining health education and physical activity interactive interventions with continued research on behaviors and attitudes of healthy eating in children.

ACKNOWLEDGMENT

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Chapter 266

A LEAD EDUCATION PROGRAM WITH THE BOYS AND GIRLS CLUB OF METRO ATLANTA

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ABSTRACT

Approximately 3% of children in the United States have levels of lead in their blood above our currently established level of concern. Exposure to lead is a significant environmental health concern for children living in older housing, especially for low income and minority groups. Education and outreach programs can improve environmental health literacy regarding lead exposure and mitigation. Methods: We designed a curriculum to educate and change behaviors related to sources of lead and mitigation. The curriculum drew upon expert and community partner input. We carried out a one-time class pilot for 3rd, 4th, and 5th grade children at a metro Atlanta Boys and Girls Club. The class contained an interactive game, visual aids, and an outreach component through a parents' night. Curriculum performance was evaluated using student knowledge pre, mid-point, and post course surveys. Results: We observed increases following the program for five knowledge categories; Hazard identification, routes of exposure, characteristics of lead, exposure sources and mitigation. Mean scores in all categories were higher than 50% in a post-course evaluation. Discussion with parents following the program indicated a need and appreciation for information regarding lead exposures and health effects. Conclusions: This curriculum demonstrated evidence for an increase in environmental health literacy regarding lead exposure and mitigation. Students were able to identify sources of lead and understand best behaviors for reducing exposures after participating in the interactive program. Stakeholder and community engagement were beneficial in creating this curriculum. Large scale implementation and continued curriculum refinement is recommended.

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INTRODUCTION

Lead is a metal that is colorless and odorless when dissolved in water, and is toxic. Children are at the greatest risk for both ingestion of lead contaminated materials and its corresponding long lasting adverse effects on cognitive function, cardiovascular and immune systems [1]. Children can be exposed in their homes from products coated or contaminated with lead such as paint, pottery, medicines, soil, dust, and water. Older homes pose a higher risk for lead exposure, as lead was only banned in paint in 1978 in the United States [1]. While elevated levels of lead in blood have been reduced significantly after the removal of lead from gasoline and paint, the Centers for Disease Control and Prevention (CDC) estimates that nationwide there are 500,000 children that have blood lead levels (BLLs) greater than or equal to 5 micrograms per deciliter ($\mu\text{g/dL}$). The BLL of $5\mu\text{g/dL}$ has been deemed the level at which children require case management to reduce exposure and mitigate effects [2]. In 2015, the CDC's National Surveillance Data program found 0.5% of children tested in the US had levels that are greater than or equal to $10\mu\text{g/dL}$ and approximately 3% of children were reported to have levels between $5\mu\text{g/dL}$ and $9\mu\text{g/dL}$ [2]. Since 2012, the CDC Advisory Committee on Childhood Lead Poisoning Prevention (ACCLPP) has stated that there is no safe BLL [1].

Race, socioeconomic status, and housing conditions are risk factors for elevated BLL's. The National Health and Nutrition Examination Surveys (NHANES) data and other studies have found that lead levels are higher among children who are non-Hispanic black, enrolled in Medicaid, have families with below median or income less than or equal to \$30,000, and/or live in homes built before 1946 [3-6]. Childhood exposure to a harmful built environment, specifically overcrowded housing, has been shown to perpetuate the cycle of social inequality later on in life [7]. Low income and minority communities are at the highest risk for such hazardous living conditions, creating a cycle where these groups who are at risk for a number of health and economic issues are exposed to potentially high levels of lead in older homes early on in life [8].

On a state level, the lead surveillance program by the Georgia Department of Public Health (GA DPH) reported that of the 120,369 children screened in 2016, 0.04% had levels greater than or equal to $10\mu\text{g/dL}$, and 2.02% had levels between $5\mu\text{g/dL}$ and $9\mu\text{g/dL}$ [9]. Children in Georgia are being exposed to lead in both their homes and schools. The 2000 Georgia state census reported that 23.6% of children under the age of six years live in homes that are below the poverty level, and 12.7% live in housing units built before 1950 [10].

Lead can also be found in drinking water often as a result of older service lines, pumping equipment, or fixtures. All buildings in the Atlanta public school district were tested for lead from water fountains and kitchen taps in 2016. Over 40% of the schools tested found levels of lead greater than 15 parts per billion (ppb) in at least one source. 3% of all sources tested had elevated lead concentrations [11]. 15 ppb is the level at which the Environmental Protection Agency (EPA) recommends actions be taken to reduce lead exposure [12]. Two neighboring school districts to Atlanta, Dekalb and Fulton, also tested their school systems in 2016/2017 and found that 3.7% and less than 3% of sources tested, respectively, had lead above 15 ppb [13, 14]. The effect of poverty on drinking water lead was observed during the Flint water crisis. From April 2014 to October 2015, approximately 99,000 residents of Flint, Michigan were exposed to drinking water with high levels of lead after switching from the Detroit

Water Authority to the Flint Water System. The Flint Water System did not properly control for corrosion, and lead reached the water system through pipe corrosion. A significantly higher percentage of children had BLL's greater than 5 µg/dL after switching water systems [15]. The largest increases in lead concentration were seen in socioeconomically disadvantaged neighborhoods [16].



Figure 1. Depiction of where our program intends to break the cycle of environmental health disparities. Overall, education to increase environmental health literacy and awareness will reduce exposure to lead in the home environment.

Due to the prevalence of lead poisoning nationwide and in Georgia, we aimed to reduce lead exposure and disrupt the cycle of environmental health disparities among children. Environmental health disparities arise from a complex sequence of factors relating to compound risk personal characteristics, environmental risk, environmental characteristics, health risk, and health characteristics. Figure 1 is a modified environmental health disparities cycle from a previously developed general model [17] with our project's aims to alleviate environmental characteristics and health risks relating to lead exposure. We intended to disrupt the cycle by increasing environmental health literacy among children and their families.

Health literacy is defined as “the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions” [18]. Environmental health literacy is then the “understanding of the connection between environmental exposures and human health” [19]. Because household lead exposure is preventable, the intent of our program was not only to increase environmental health literacy in children and families about household lead hazards, but also to provide them with accessible tools to screen their homes and connect them with local professionals. We intended for our project to raise awareness about household lead mitigation factors to help reduce toxicant exposure which has the potential to reduce cases of neurotoxicity, learning disabilities and behavioral disorders attributed to lead poisoning.

While the EPA, CDC, and other agencies and organizations have developed educational materials online and in-print for children and adults, they have not monitored and evaluated the success of their programs. To address this gap, our program included outreach to parents, as well as monitoring and evaluation components. We used the EPA's Recipes for Healthy Kids and a Healthy Environment as a template for our curriculum to "excite kids about environmental health and empower them to take steps in their everyday lives" relating to household lead hazards [20].

OUR STUDY

To develop our pilot curriculum, we collaborated with local partners and stakeholders, as community-academic partnerships and broad expertise are beneficial to environmental health literacy research [19]. Our initial and primary curriculum development stakeholder was the EPA Region 4's Children's Health and Lead Programs. The EPA provided educational materials from their previous programs and mentorship regarding curriculum development. We also researched other publically available materials on lead education to inform our program development. We included experts from the Georgia Department of Public Health and the CDC to assess the accuracy of the information in our program. Because the Recipes for Healthy Kids and a Healthy Environment was originally designed through a partnership with the EPA and Boys and Girls Clubs (BGC), we sought out a local BGC. We contacted several local BGC's that were located in areas where older housing and lead exposure could be a potential issue. We partnered with the Samuel L. Jones BGC in Decatur, GA due to its close proximity to the research team. We wanted to create a project that could be helpful within our own community and build a close partnership between the research team and the BGC. In addition, we believe that this project could be the impetus for more collaborations between Emory University Students and the local community. The 2010-2014 census reported the median household income of Decatur as \$73,679. By race, Decatur is 69.8% white, 22.2% black, 4.4% Asian and 3.6% other [21]. In the Oakhurst neighborhood directly surrounding the Samuel L. Jones BGC, over half of the homes were constructed before 1950, creating an area at high risk for exposure from lead paint [22].

Curriculum Design

We designed our class to improve behaviors related to lead exposures (see Figure 2) for the students in the class. In addition, we intended to engage not only the individual students but their families and peers. We aimed to do this by advocating for students to teach their younger siblings, friends, and parents about the hazards of lead to increase household environmental literacy.



Figure 2. The five core behaviors we intended to change with our curriculum based on our Theory of Change. Each behavior is paired with a vignette photo used in the course itself.

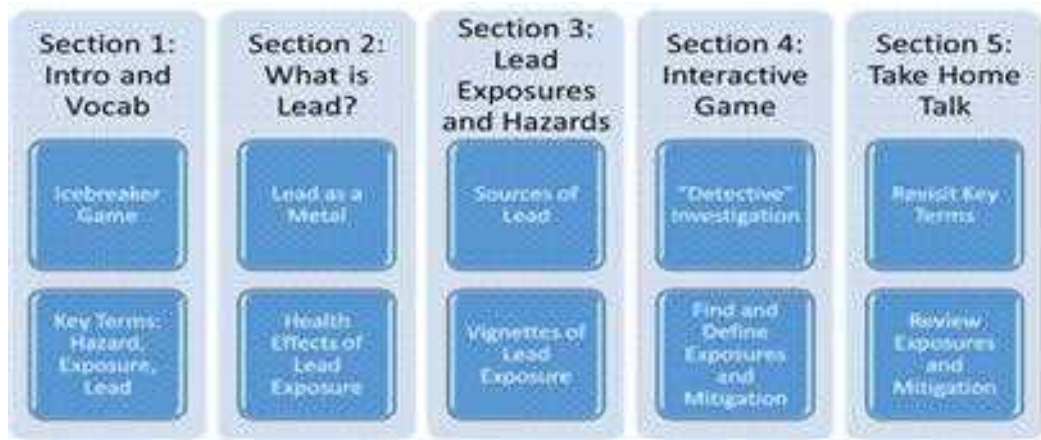


Figure 3. The curriculum was divided into the above five sections. All sections were designed to increase the environmental health literacy of the students regarding lead exposure.

We designed the curriculum using chapters from *Recipes for Healthy Kids* and a *Healthy Environment* as a framework which was developed for children aged 9–13 years [20]. Project stakeholders suggested tailoring our program to this age group, as they would be able to grasp the concepts and likely have siblings under the age of 6 who are at the highest risk for adverse effects resulting from lead poisoning. The introduction of our curriculum contains the course objectives and key vocabulary terms (see Figure 3). We then created a five-part lesson plan based on these key learning elements. To supplement the verbal information of our class, we generated a variety of course materials including visual aids (Appendix A), an interactive game (Appendix B), and take home pamphlets for parents (Appendix C). The take home pamphlet was designed to be a stand-alone item, able to inform adults who were not present for the program, and a visually appealing reference and contact guide. We wrote a script for the entire lesson to create a structure that can be followed by others who want to implement the program (Appendix A). We pre-tested the program with children of the target age group and surveyed them on what parts were engaging and what information they retained. We also included additional resources as take home exercises to supplement the content delivered in the class (Appendix A). These additional resources were not piloted in this study.

Curriculum Outline

The curriculum was divided into five sections as shown in Figure 3. All sections were designed to increase the environmental health literacy of the students regarding lead exposure:

- Section One: We opened the program with an icebreaker game designed to have the students interacting verbally and moving around the room. The icebreaker game consisted of “get to know you” questions and some questions pertaining to lead sources and exposures.
- Section Two: After the icebreaker game, we defined our three key terms; Hazard, Exposure, and Lead. In Section Two, we focused on describing lead as a metal and why it was dangerous.
- Section Three: We synthesized the first two sections as we presented lead exposures and hazards. The verbal descriptions were coupled with staged pictures of exposures that the students were asked to interact with and explain. This dual medium provided the opportunity to engage multiple learning styles.
- Section Four: We asked children to participate in an interactive “detective game”, where the students were asked to explore the room and identify pictures of lead sources and mitigating behaviors. The game was designed to stimulate critical thinking through physical activity.
- Section Five: Everyone was brought back to a classroom configuration for Section Five. Here we reiterated the key terms and concepts from the program. This reinforced the main verbal descriptions from the curriculum.

Lead Screening

We had an additional research goal of promoting screening for lead in the homes of the children who participated in the pilot program. We distributed 3MTM LeadCheck™ swabs, which are a safe and reliable first assessment of lead levels on home surfaces to parents [23]. We designed a text-based survey using Telerivet [24] for parents to relay the results of their test to the research team. The text application also provided parents with information on professional resources if the lead screening swab indicated a positive result. To assist parents in performing the tests, we also created step-by-step instructions in color with visual aids (Appendix D).

Pilot Study Design

We carried out the pilot program in March of 2017 at the Samuel L Jones BGC in Decatur, Georgia. The students who attended the class were a convenience sample but represented the target age range that was available at the club that day. Forty-one children in 3rd, 4th, and 5th grades attended the program. Four instructors and two BGC employees were present for the class. Each developer taught part of the curriculum. Two identical visual aid

stations were set up on either side of the room due to the large class size. Two instructors simultaneously taught the lesson at each station to reduce the overall class size. The lesson was divided into five sections (see Figure 3) and took place over 1 hour and 15 minutes.

After the program, we gave parents/guardians a packet that included an informational pamphlet, a lead screening test and instructions, and contact information for expert local resources related to residential lead exposure. Also included in the packet was a flyer advertising the curriculum's parents' night. One week following the lesson, we hosted parents' night at the BGC to reinforce the behavior change outputs, such as recognizing potential sources of lead in the home. The event intended to bring together experts from the EPA, CDC, and GA DPH to discuss exposure sources, mitigation strategies, and publically available resources with parents. On the day of parents' night, we had a small group of parents, the developers of the program, and a representative from the CDC to answer questions by parents. After the parents' night, we proactively met parents picking up their children from the BGC, introduced ourselves and our project, and answered their questions. We also distributed program materials to all club parents as they picked up their children, in order to expand the impacted audience.

Data Collection and Analysis for Program Evaluation

Student knowledge comprehension was tested at three time-points throughout the program: before the class, in-class during the interactive detective game, and one week following the class (Appendix E). Before the presentation of our curriculum, we distributed a paper survey on understanding of hazards, exposures, and lead. The detective game sheet assessed knowledge directly following the presentation of all information contained in the curriculum. The children's answer sheets for the detective game served as a midpoint evaluation assessing knowledge retained immediately following the lessons. While each student completed their own answer sheet, they worked in small groups to find the pictures throughout the room. This is different from the pre-class survey which was done individually. For the post-intervention evaluation, we revised the pre-class survey for clarity and formatting. We administered it using an online Google survey to determine knowledge retention one week after the program. The selection of post-course survey participants was random and uninfluenced by any factors known to the research team.

The pre-course survey was the counterfactual in this program evaluation. Student answers from all time points were analyzed for differences in mean class knowledge using pre, midpoint, and post scores.

Program Ethics

No identifying personal information was asked for in the surveys used for course evaluation or the home screening kits, ensuring confidentiality. Verbal proxy consent was given by the BGC for all children who participated in the class with the stipulation that no identifiable photos would be taken and distributed of the children.

FINDINGS

We divided the pre, in-class, and post knowledge surveys into five assessment categories: Hazard Identification, Routes of Exposure, Characteristics of Lead, Exposure Sources, and Mitigation (see Table 1). We calculated the mean score of each category at each time point to determine change in knowledge. Figure 4 shows the change in category understanding before the program began, during the detective game previously discussed, and one week after the curriculum was implemented. The pre-course survey was administered on paper to 41 children that were present on the day of the class while the post-course survey was administered digitally one week later to a convenience sample of 16 children that participated in our class.

Table 1. Five main curriculum concepts

Assessment Category	Learning Goals	Example Question
Hazard Identification	-Define “hazard” -Identify typical household hazards	“Name a dangerous thing from the picture above (Appendix B) and explain why this is dangerous.”
Routes of Exposure	-Define “exposure” -Explain major routes of exposure	“How can you get exposed (or come into contact) with harmful products or chemicals?”
Characteristics of Lead	-Describe lead as a harmful metal -Outline the potential negative health impacts of lead	“Why is lead harmful to you, younger siblings, or your friends?”
Exposure Sources	-Understand potential sources of lead in the home -Be able to explain these to younger siblings or friends	“Name five hazards related to lead in the room.”
Mitigation	-Practice behaviors that reduce lead exposure in the home	“Draw and label three foods that reduce the bad effects of lead.”

Note: The five main concepts of the curriculum including goals and example questions that were used in the actual curriculum.

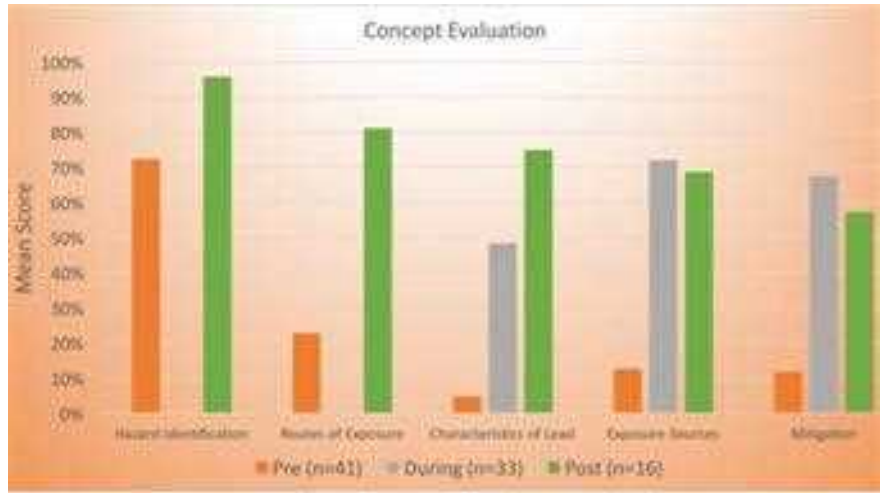


Figure 4. Change in category understanding before the program began, in-class through the detective game, and one week after the curriculum was implemented.

Questions relating to Hazard Identification assessed the children's ability to identify exposures that could harm their health in the household scene poster (Appendix B) (pre: 72.3%; post: 95.8%). Common answers were: the snake in the garden, the hot grill, and the power tools. The other concepts tested were: identification of Routes of Exposure (ingestion, inhalation, dermal contact) in which a hazard can affect the body (pre: 22.7%; post: 81.2%), Characteristics of Lead (pre: 4.8%; mid: 48.4%; post: 75.0%), Exposure Sources where people could encounter lead (pre: 12.7%; mid: 72.%; post: 68.7%), and healthy behaviors to Mitigate the effect of lead on the body or reduce lead exposure (pre: 11.8%; mid: 67.5%; post: 57.3%). Scores that do not have a midpoint monitoring score were not evaluated during the interactive detective game. Mean scores increased after the class. There is attrition between in-class class monitoring and the assessment one week later for the Exposure Sources and Mitigation categories. We did not receive results from the voluntary take home screening tests and text message surveys.

DISCUSSION

The baseline (pre-class survey) and follow-up (post-class survey) knowledge assessments were critical components of our project evaluation as it provided a tool to measure the effectiveness of our materials and methods. We expected Hazard Identification scores to be the highest pre-class score because it asked the children to identify common household and environmental items in the visual (Appendix A), that could be harmful to their health. We attribute the increase in score after the class to many students not answering the question in the pre-course survey because of distractions in the room and confusion about instructions.

Scores for routes of exposure, characteristics of lead, exposure sources, and mitigation all increased from the pre to the post class evaluation. This increase is a possible indication of the effectiveness of our curriculum across all four areas. The detective game worksheet was a useful midpoint monitoring point for the program across three areas: characteristics of lead, exposure sciences, and mitigation. The Characteristics of Lead category scores increased at the midpoint, and from the midpoint to the final evaluation. We hypothesize this increase is due to a second iteration of the concept during the wrap-up after the detective game monitoring point that added clarity. The Exposure Sources and Mitigation category scores were higher during the midpoint monitoring than the final monitoring, but this drop after a one-week interim is expected. We surmise that attrition in knowledge over time is expected across all the categories. There was a reduction in sample size between children who submitted a pre-class survey and a post-class survey which was primarily due to logistical issues at the BGC

Class Logistics

Due to limited availability of space, the pre-planned room set up was not implemented on the day of the class. The initial plan was to have a total of four rooms with 10-15 children in each, with the class administered by one of the four developers of the project. A staff member of the Boys and Girls Club also planned to be part of the class to assist with logistics while

the class was in session. The actual class was conducted in one large room that housed all 41 students, four instructors, and two BGC staff members. Despite the large class, the children remained engaged in the class, answered questions posed to them, and asked questions on the content of the class. Transition times of the different sections were not seamless due to the class size, and this contributed to the class exceeding the originally allotted time of one hour. The pre-course survey also took more than the allotted time due to some difficulty in understanding some of the instructions.

Parental Engagement

Parental engagement was used to inform legal guardians of all children at the BGC. Despite the low small group attendance, the parents' night was engaging with important questions raised and addressed. Parents asked questions that were focused on lead contamination in the water system in Flint, Michigan and how lessons learned can be adopted to prevent recurrences in other locations across the country [16, 17]. They also raised questions on the recent issue of lead detection in school water sources, and what danger that poses to their children.

Recommendations

As this was a pilot exercise, we believe there to be three primary recommendations to improve large-scale implementation – smaller class sizes, reinforcement of materials, and incentivizing parent's night.

Due to timing and logistical issues, we recommend small class sizes of 10-15 children to enable smooth transitions between sections of the curriculum. In addition, smaller class sizes would allow the team to adapt the lesson plan to specific needs, provide more individualized attention, allow for children to ask more questions during the lesson, and minimize distractions.

Additionally, we suggest reinforcing the curriculum at later time points and keeping the classroom posters accessible after each implementation as a reminder of the course content.

The parents' night was an important component of our program because it enabled us to inform adults on the hazards of household lead exposure. However, parent participation rate for our program was low. Feedback from the BGC highlighted that lack of incentivizing parents night was a contributing factor. We also received feedback suggesting that children should have been reminded about parents' night at the end of the class. We hypothesized that parents may have been oversaturated with information contained in the packages we put together. This large amount of information may have led to low participation at the parents' night because they may have not seen the flyer advertising the event. It is important to emphasize that the incentive adopted by future users of this curriculum should be tailored to the setting where it is implemented to ensure effectiveness.

CONCLUSION

Lead exposure is deleterious to health, and children age five and under are more susceptible to adverse health outcomes from exposure [1]. For this reason, we chose to design and implement a pilot educational program for children centering on lead exposure and mitigation at a local Boys and Girls club. We focused our intervention on increasing environmental health literacy regarding the issues of lead exposure and mitigation. Developing the curriculum required collaborating with a multi-disciplinary team that contributed their respective expertise to its success. We found significant improvements among the class participants in five knowledge categories: hazard identification, routes of exposure, characteristics of lead, exposure sources and mitigation. These results demonstrate increased environmental health literacy on the subject of lead exposure among children who participated in the class. Environmental health literacy research and education such as this curriculum should be replicated and brought to individuals and communities at risk for environmental exposures to create a large impact [20]. The curriculum was presented to EPA's Office of Children's Health Protection at the invitation of their Director for their feedback and comments. Currently, EPA intends to incorporate this curriculum in its Recipes for Healthy Children and a Healthy Environment Curriculum which is implemented nationally and especially targeted for low income communities and families.

Unfortunately health disparities exist and perpetuate the cycle of toxic environmental exposure to low income families. By incorporating a low-cost interactive educational curriculum, we intended to disrupt the cycle of lead exposure and its effects by informing children and families of the hazards of lead toxicity, preventative measures and tools and resources to screen and remove lead in their homes. We have made our curriculum available to the EPA, other governmental institutions and private organizations who can use our curriculum as a template and tailor it to their specific audiences with respect to demographics, culture, and language.

ACKNOWLEDGMENT

We thank the Break the Cycle Program for financial support. We also thank the EPA and CDC for helping with curriculum development. Finally, we would like to thank the Boys and Girls Club for generously partnering on the pilot program and the children who participated.

APPENDICES

Appendix A: Curriculum Outline and Script (Includes Visual Aids and Additional Materials)

Break the Cycle Year 12
Lead Education for Elementary Age Children
Curriculum Outline

Snapshot

Preparation and Materials:

- Nametags
- Visual Aids
- Worksheet for interactive game
- Pencils
- Red and Green Post its or sticky notes
- Posters used in Part 2
- Detective worksheets
- Colored photos of additional hazards/mitigation factors not in the room
- Props of hazards/mitigation factors (fruits, brooms etc.)
 - Hide some of these props in areas that are not obvious to find
 - Include props that are not part of a lead mitigation plan but may be found in homes

Objectives: Students will be able to

- Define hazard and exposure
- List potential sources of lead in their environment
- Understand how lead exposure can impact their health
- Understand how their actions can help reduce their lead exposure

Vocabulary

Lead, Exposure, Hazard

Procedure

1. Introduction and Vocabulary (10 minutes)
2. Where does lead come from (10 minutes)
3. Lead Exposure and Hazards (5 minutes)
4. How to limit lead exposure (15 minutes) - This lesson aims at educating students on identifying and practicing steps geared at reducing their exposure to lead in their environment, as well as identify foods that reduce the absorption of lead from diet and reduce storage in the body. This will be done with an interactive game whereby children will play the part of a detective and explore a room to determine hazards and mitigating factors.
5. Take-Home Talk (5 minutes)

Lesson: Lead in the environment

1. Introduction and Vocabulary (10 Minutes):

EXPLAIN: We are students and scientists from Emory University. We study how the world around us can affect our health in good and bad ways.

ASK: We are going to play a quick game to get to know each other. Everyone get up and stand in a circle. We are going to ask a few fun questions. If your answer is yes, run to the other side of the circle. If your answer is no, stay on the edge of the circle.

- Who has a birthday in the summer?
- Who has a birthday in the winter?
- Who has a name that has a “C” in it?
- Who likes to eat macaroni and cheese?
- Who has younger siblings?
- Who has ever played in the dirt or a garden?
 - Who has brought the dirt inside?
- How many of you have helped your parents paint?
 - Did you ever notice paint peeling or chipping?
- Who has helped their parents cook in the kitchen?
 - Who has been warned about touching a hot stove?

EXPLAIN: The hot stove was dangerous for me to touch. Another word for something dangerous is hazard.

Everyone come back and sit down around the poster so we can talk more about some other hazards.

A hazard is something you can come in contact with that could be dangerous. Hazards can be found in many different places, but can usually be avoided if you are careful.

ASK: Can you name other hazards around your home or school?

EXPLAIN: You can be exposed to things when you come into contact with something in your environment. This can be by breathing, smelling, touching, eating, or drinking something.

ASK: For example, how can you be exposed to a hot stove?

EXPLAIN: You can be exposed to a hot stove if you touch it.

ASK: Now, if a stove is turned off and cold, is it dangerous and a hazard when you touch it?

EXPLAIN: It’s only dangerous when it’s turned on and hot and you touch it.

There are two parts to a hazardous exposure, they have to be a hazard (like a stove being hot) AND you have to be exposed to them (like touching the stove).

ASK: Can you tell me again how you can be exposed?

Answer: touch, eat or drink, breathe in, hear, smell



DO: Show Poster #1

EXPLAIN: Here is a picture that might have some different hazards you have seen before. Like the sun. The sun on its own is not a hazard but if you get too much exposure like by staring right at it or laying out all day then it is not good for you.

On a sunny day, you should wear sunglasses to protect your eyes and sunscreen to protect your skin.

ASK: Can anyone see other hazards on this picture? Grab a red sticky note and come up to mark it on the poster. Can you tell everyone in the room why you think this is a hazard? How can you become exposed to that hazard? *(Let/help kids identify 5 hazards)*

Example Hazards [Exposures]: Traffic (speeding cars, air pollution), Grill (touching hot grill, starting a fire), Pool (drowning), Sun (sun burn, in your eyes), Ladder (falling off ladder), Paint (getting it on your skin), Power Tools (touching the sharp parts of them), Soccer Ball (mom can trip on it), Dirt (Baby playing in the dirt and eating it),

2. Where does lead come from? (5 minutes)

ASK: Can anyone name a type of metal? **Have Vignettes up and behind the speaker.**

EXPLAIN: Some types of metals are silver, gold, and iron that are safe for us to wear or use in buildings. Lead is another metal. Lead is a poisonous metal that harms our bodies if we are exposed to it.

ASK: Who has heard of lead?

EXPLAIN: Lead has been in the news recently because there are some cities in the US that have lead in their drinking water. Old pipes that carry water to your sink can have lead in them. Sometimes that lead can leave the old pipes and get into the water you drink.

People used to put lead in paint and even gas for cars. Then scientists found that lead was dangerous to people's health and so they stopped using it in paint and gas. But because lead used to be in paint, some older homes and apartments may still have that lead paint on the walls. Or if it's not on the walls, there can be little pieces of the paint that chip and peel off which can fall on the ground.

Lead is also sometimes found in some toys or jewelry that some people play with or in the soil and dust.

EXPLAIN: If you are exposed to lead, then you could get lead poisoning. Even if you only come into contact with a small amount of lead it can be harmful to your health partially because our bodies don't get rid of lead well, it stays in our bodies for a long time. Lead poisoning can make it harder to pay attention in school, or remember what you learned in class the day before. It is especially not good for babies and young kids. This means that pregnant mothers also have to be careful about lead exposure to protect the baby growing inside of them.

ASK: How tall were you guys when you were 2? And see much you've grown since then! Now, why do you think lead is not good for babies like 6 month olds and young kids like toddlers?

EXPLAIN: Babies and young kids are still growing. As they get bigger and taller, their insides like their brains and immune system, which helps them fight off disease, grow and become stronger. If the babies or young kids have lead poisoning, it can hurt the way that their insides grow and can make it harder to learn or hear or speak and sometimes can change how they behave. Lead is also harmful to adults because their bodies don't need it but it is especially a problem for children.

ASK: How many of you sucked your thumb when you were little? Why might this be bad for babies?

EXPLAIN: Because they may have touched something with lead on it, like paint or certain toys, and then when they put their thumb in their mouth they are exposing themselves to lead.

Since lead is hazardous, scientists have ways to find lead in our environment. Now we're going to talk about where lead can be in our environment and ways to stay safe from becoming exposed to lead.

3. Lead Exposure and Hazards (10 Minutes)

DO: Poster #2 (Specific lead hazards and exposures - **Vignette Images**). Let's take a look at these pictures. Just like before, there are some pictures of hazards in the top 4 pictures, but this time each image has a lead hazard in it.



Come up, grab a red sticky note, and put it on the hazard. How do you think you could be exposed to that hazard?

(Refer to boy in dirt) What is the child in this photo doing? That's right, she's playing in the dirt. How could she be exposed to the dirt while she is playing? On her hands. What do little kids sometimes do with their hands while they are playing? Right, they sometimes put their hands in their mouths even if they are dirty.

(Refer to the boy drinking water) What is the boy in this picture doing? Right, he's getting water from the faucet and then drinking water. And what could be in his water if he lives in an old house? Yes, there could be lead in the old pipes in houses.

(Refer to the baby with toys) What is the baby in this picture playing with? Toys or jewelry could have lead in them or get dust on them. And how could the baby be exposed to the lead in the toy? If they put the toy or their hands in their mouths, they can expose themselves to the hazard.

(Refer to girl near window) What is the child doing in this photo? Great! She is touching the window. How can she be exposed to lead? She is very close to the window sill and dust can gather here, it may have lead in it and it can get on her hands. Again, where do children put their hands? Sometimes in their mouths.

ASK: Now that we've seen some hazards that have lead in them, can anyone think of some ways to stay safe from getting exposed to them?

EXPLAIN/DO: Let's look at the pictures of hazards from before and figure out some ways to stay safe from lead. When you think of a way to stay safe from lead, come up and put a big green sticky note over the red one and tell us why.

(Refer to boy in dirt) Remember we talked about how playing in the dirt can expose you and little kids to lead. How could you protect yourself and others from the lead if you get dirt on your hands or clothes? Right, you can wash your hands and clothes. And remember to watch any younger siblings or friends so they don't put their hands in their mouths.

(Refer to the boy drinking water) How can you stay safe if there is lead in the drinking water? There are filters your family can buy to remove lead from the drinking water or you can use bottled water.

(Refer to the baby with toys) How can you stop babies or little kids from getting exposed to lead in toys? Be sure to always be on the lookout for people younger than you when they are playing with toys. You can then tell them not to chew or lick the toys and to always wash their hands after they play.

(Refer to girl near window) What could you do to clean the windowsill and keep the lead away from this girl? You can use a wet rag or mop with a cleaning solution to clean lead and dust from surfaces around a room. It's also important to keep younger kids from eating the paint or dust on the windowsill. Sometimes it can taste sweet, but it's very dangerous.



(Man mopping in the kitchen) What is the man doing in the picture? Why is he mopping the floor? Great! He is trying to get the dust off the floor. Who remembers what can be in dust? The dust on the floor may contain chipped paint from the walls, and can cause exposure to lead.

(Woman on the phone with the hotline) What is the woman in this picture doing? She's on the phone. Who is she calling? The lead hotline. Why would she be calling the lead hotline? The lead hotline can help you and your family if there is lead in your house. Does the paint behind her look old and chipped? Could be a hazard if she is exposed. Who can help

you when you call the hotline? Lots of people like doctors and people who can clean up dangerous paint from your home.

There are some lead screening kits that your parents can use to see if there is lead in your home. These kits can be used on metal surfaces, paint, dust, your computer, couches, fabric, clothing, or rugs, really anywhere you think might have lead. We'll be giving your parents a lead screening kit when they pick you up today so remember to tell them to test your home. After they use the kit in your home, you can help your parents text us to let us know if you found lead in your house or not.

EXPLAIN: We've learned a bunch of ways to stay safe from lead in the environment. Now, let's talk about one really good way to prevent health problems if you are exposed to lead. Eating certain foods that have iron like fish and chicken, or foods high in calcium like milk and cheese foods with a lot of Vitamin C like fresh fruits and vegetables, can stop lead from getting into your body and piling up. This keeps you healthy and safe from lead poisoning.

ASK: What are some healthy foods that you guys like to eat?

4. How to limit lead exposure? (15 minutes)

Introduction of game

EXPLAIN: Remember, a hazard is something you can come in contact with that could be dangerous. Hazards can be found in many different places, but can usually be avoided if you are careful. An exposure is when you come into contact with a hazard. All on its own, a hazard can't hurt you, but when you are exposed, that's when it can be dangerous.

ASK: Today you are all lead detectives. I would like you to get up and search the room for clues and signs for possible lead hazards and exposures in this room. There's a prize for every detective! *Give each child a detective sheet.*

Visuals:

Necklace, apple, chicken, yogurt, cake, faucet, hand washing, orange, dirt, pear, candy, cheese, lead hotline, dusty chair, paintbrush, potato chips, mop, milk, french fries, gloves, banana, fish, duster, dusty desk

EXPLAIN: I would like you to go around this room and find 5 hazards in this room. Then, find 4 ways to clean up this room to reduce being exposed or coming into contact with lead. Next, find 3 foods that will help reduce the bad effects of lead. Last, find 1 place to do a lead screening test. Use your worksheet to write down what you find. **There will be some pictures in the room that do not belong on the detective sheet.**

DO: Allow kids to walk around the room to identify hazards in the room and ways that they can prevent or reduce the hazards. The instructors will walk around the room to help and ask critical thinking questions to the students.

ASK: *When the kids come back together after 15 minutes.* What did you all learn from being lead detective? What sorts of things did you find around the room?

DO: Go over the correct possible answers for each section of the detective sheet and let the kids correct their sheets if they have incorrect answers. Tell them to look out for the incorrect answers.

Answer Key for Detective Sheet

Lead Hazards: Dirt, dusty chair, paint brush, faucet

Protective: mop, gloves, lead hotline, hand washing

Good foods: apple, chicken, yogurt, orange, pear, cheese, milk, banana, fish

Where to do a test: metal surfaces, paint, dust, computer, couches, fabric, clothing, rugs

Bad foods: cake, french fries, potato chips, candy

5. Take Home Message

- What was the coolest thing you learned from talking about this topic with family and friends?
- Lead is a metal that is harmful to your health. It can hurt your brain and immune system.
- Places where you can find lead include paint from buildings, contaminated soil and dust. Other sources may include pipes with lead and toys painted with lead
- Washing your hands, washing fruits and vegetables that you eat, and eating certain foods can reduce chances of being exposed to lead or prevent lead from staying in your body
- I also want you to talk to your parents and other adults about what you learned today.
- I have some activities for you to take home and show your parents. I will be at Parent's Night next Friday so tell your parents to come and learn more about lead from us.
- Thanks!

Take-Home Talk with Parents:

- Lead is colorless, odorless and tasteless, so we may be exposed to it without even knowing it
- In Flint, MI the water source was changed to a polluted river that was very acidic. Because the water treatment plant did not treat the water properly, this acidic water went through the pipes into people's homes. This acidic water damaged the lining of the water pipes. The water pipes were very old and therefore had lead in them. Since the lining has been damaged, the lead was still able to contaminate the water supply even though the source has been changed. The lead contamination will not stop until all the damaged pipes are replaced. People can drink and use the local water if they

have a special filter that removes the lead (this is not the same as the water filters we regularly find at the store, they must be specially designed to remove lead).

- Atlanta Metro Schools recently tested the drinking water fountains in their schools for lead. They found lead in several of the fountains and closed those fountains. If your child attends a school that tested and found lead you should have received information from the school about it. You can contact your child's school office if you are unsure if they tested for lead or found lead.
- 4 million households in the US have children living in them that are exposed to high levels of lead.
- Lead exposure can be prevented by washing hands whenever they get in contact with dirt from working in the garden or playing, cleaning dusty surfaces with a mop, or sponge and general all-purpose cleaners, avoid playing in rooms that are dusty, avoid eating chipped paint, and using special, lead specific, filters on water that may be contaminated with lead, or using bottled water.

Additional Resources: Lead Awareness Resources for Teachers (Grades 3-5) - Lesson plans, posters, and online activities for students

Class Activity:

- EPA: Get the Lead Out Relay - A class activity to emphasize that certain foods can block the absorption of spread of lead in the body. This class may be for younger children below grade 2.
 - Instructions - construct a tri-fold poster of photos and labels of food by their content (use chart below)
 - Place the photos and labels of food randomly on the tri-folder poster and include foods not listed such as seafood, nuts and grains
 - Divide the class into groups and ask the students to run up and identify lead blocking foods on the poster

Iron	Calcium	Vitamin C	Fat Foods
Lean Meat (turkey, chicken)	Milk	Oranges	Bacon
Liver	Cheese	Grapefruits	Cakes
Steak	Yogurt	Potatoes	French Fried
Dried Peas	Greens	Bell pepper	Cookies
Beans	Cottage cheese	Watermelon	Sausage
Dark Greens		Tomato	Ice Cream
			Chips

Educational Videos:

- “Lead Away” - Video developed by the Southwest Pediatric Environmental Health Specialty Center with Sesame Street.
English version: <https://www.youtube.com/watch?v=7FHdoz MqFCQ>
- “Mysterious Case of Lead” - Video developed by the Southwest Pediatric Environmental Health Specialty
English versions:
https://www.youtube.com/watch?v=RtmKnrvQ7uI&list=PL1Ts7ShDxOJILmC4Ce-o3H9Orv_5OcH5O&index=1

https://www.youtube.com/watch?v=uadC9qWcaCU&index=2&list=PL1Ts7ShDxOJILmC4Ce-o3H9Orv_5OcH5O

Spanish versions:

<https://www.youtube.com/watch?v=xGZTSRKZq2U>

<https://www.youtube.com/watch?v=Bgf3mG5lB84>

Games & Activities:

- Word Search Game - A fun game to print and complete where you have to find the words hidden in the puzzle.



- Coloring Activity 1 - Coloring book with a story for children to follow to understand exposures and hazards to lead (Charlie Goes to Town)
- Coloring Activity 2 - Placemat for children to color and use at home to remind parents about behaviors to do to reduce lead contamination in the home



Appendix B: Detective Game

Name: _____			
Grade: _____			
Instructions: You are on a mission to keep your family safe! To complete this mission, you must: - Find 5 hazards related to lead in this room. - Find 4 ways to clean up this room to reduce coming into contact with lead. - Find 3 foods that will help reduce the bad effects of lead. - Find 1 place to do a lead screening test. - Answer why is lead bad for you in one sentence? You may also draw your answers on the back of this sheet.			
Hazards Related to Lead in the Room: 1. _____ 2. _____ 3. _____ 4. _____ 5. _____		Ways to Reduce Contact with Lead: 1. _____ 2. _____ 3. _____ 4. _____	
Draw and Label Foods to Reduce Bad Effects of Lead:			Where to do a Lead Screening Test:
Food 1	Food 2	Food 3	1. _____
Why is lead bad for you? _____			

Appendix C: Take Home Pamphlet

Hazard: Why is Lead Harmful? Lead is a poisonous metal that is bad for our bodies. It is colorless, odorless, and tasteless. Lead poisoning can cause learning, hearing, and behavioral problems. • Pregnant women who are exposed to lead are at risk for miscarriages or low birth weight. • Young children are at higher risk because their brains and immune systems are developing. • Lead can harm a child's brain, kidneys, and other organs. • In 2014, more than 2,500 children in Georgia had elevated blood lead levels, according to the Georgia Department of Public Health.  Exposure: Where is the Lead? Paint • Homes built before 1978 are more likely to contain lead-based paint. • Lead-based paint is a hazard if it is peeling, flaking, chipping, rubbing off, or cracking. • The break-down of paint can make lead dust in the home or mix lead into the soil if the paint is on the outside of the building.	Other Sources of Lead • Include drinking water from lead pipes, lead-based paints, toys, dusty household furniture, artificial turf, and pottery.  • Gardens around buildings that have lead-based paint can be contaminated.  Children can become exposed when they— • Eat paint chips or soil that contains lead or put their hands in their mouths after touching these objects. • Eat food from gardens that are polluted with lead. • Breathe in lead dust, especially during home repairs that break down painted surfaces.	Foods that Protect Children from Lead Iron-Rich Foods • Lean red meats, fish, chicken, and iron-fortified cereals.  Calcium-Rich Foods • Milk, yogurt, cheese, and green leafy vegetables (spinach, kale, collard greens).  Vitamin C-Rich Foods • Fresh fruits and juice from oranges, grapefruits, and tomatoes. 
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If you Think your Home has High Levels of Lead:

- **Don't try to remove any paint yourself!**
- Get your home tested for lead if it was built before 1978.
- Get your kids tested for lead by their doctor, even if they seem healthy.
- Do not use imported pottery to store or serve food or water.
- Always wash your hands with soap before eating.
- Get your tap water tested for lead.
- Wash children's hands, bottles, pacifiers, and toys with soap and water.
- Regularly clean floors, window sills, and other surfaces using wet cloths or wipes to remove dust.



- Wipe shoes before entering the house.
- Use a certified contractor for any home repair.

If you rent...

It is your landlord's responsibility to keep paint in good condition. Report peeling or chipping paint to your landlord, and call your health department if the problem continues.



Contact Information

Below is a list of contacts that may be useful if you find lead, or if you think there is lead in your home, water or environment:

- **Family Pediatrician**
Call and schedule an appointment with your child's pediatrician as soon as possible.
- **GA Department of Public Health**
Phone number: 1-800-438-7442
Direct number to Lead Poisoning Prevention Program: (404) 657-6534
Hours: M-F: 8:00am - 5:00pm EST
- **Environmental Protection Agency (EPA) Lead Hotline:**
Phone Number: 1-800-424-LEAD [5323]
Hours: M-F: 8:00am - 6:00 pm EST
- **EPA Safe Drinking Water Hotline**
Phone number: 1-800-426-4791
Hours: M-F: 8:00am - 6:00 pm EST

Clean and Safe Homes

Keeping Kids Safe from Lead



Appendix D: Lead Screening Test Instructions

TAKE HOME LEAD TEST INSTRUCTIONS

How to use the DTMTM LeadCheckTM Swabs

Keep away from children. Contact medical professional. Swabs are intended to use only in contact with you. These Swabs and Confirmation CardTM into the package after use.

STEP 1: Squeeze and crush the point, marked A on the tube. Keep the glass tube inside the cardboard tube.

STEP 2: Squeeze and crush the point marked B on the tube.

STEP 3: With the white swab tip facing down, shake vigorously to mix.

STEP 4: Gently squeeze the tube, at joint A and B until yellow liquid comes to the tip of the swab. The lead is now ready for testing.

STEP 5: Squeeze the tube gently while rubbing the swab tip on the surface you are testing for 30 seconds. If the tip turns red, refer to the lead awareness pamphlet for contacts.

STEP 6: To make sure your result is working correctly, use the Confirmation Card. Rub the activated swab tip on one dot of the card. If the dot does not turn red, that swab is defective. Use a new swab.

Refer to package directions for confirmation and details on specific surfaces.
Text "LEAD" is 218-363-5886 after you finish the first step to send in your results and get more information about lead.



Appendix E: Monitoring Items (Pre/Post Knowledge Surveys)

Facts about Covid - Knowledge Survey

Circle _____

Here are five questions about the environment and health. Answer as many as you can. It is okay if you skip some the answer.



- A. Which door is the most dangerous thing burning picture above _____
- B. Why is this item dangerous? _____
- C. Which door is the most dangerous thing burning picture above _____
- D. Why is this item dangerous? _____

- E. Which door is the most dangerous thing burning picture above _____
- F. Why is this item dangerous? _____
- Questions 1:
- How can you get rid of or remove the most dangerous thing burning picture above? Choose all answers that are correct.
- 1. Using a vacuum cleaner
 - 2. Using a fire extinguisher, something like that
 - 3. Putting something
- Questions 2:
- What is a reason that can be found in your neighborhood. Why is each harmful to you, younger siblings or friends?
- _____
- _____
- _____
- Questions 3:
- Which can you find in your neighborhood? Choose all answers that are correct.
- 1. Vacuum cleaner
 - 2. Fire alarm
 - 3. Fire extinguisher
 - 4. Fire alarm
 - 5. Fire alarm
 - 6. Fire alarm
 - 7. Fire alarm
 - 8. Fire alarm
- Questions 4:
- Which can you find in your neighborhood? Choose all the answers that you think are right.
- 1. Fire alarm
 - 2. Fire alarm
 - 3. Fire alarm
 - 4. Fire alarm
 - 5. Fire alarm
 - 6. Fire alarm
 - 7. Fire alarm
 - 8. Fire alarm
- Questions 5:
- Which can you find in your neighborhood? Choose all the answers that you think are right.
- 1. Fire alarm
 - 2. Fire alarm
 - 3. Fire alarm
 - 4. Fire alarm
 - 5. Fire alarm
 - 6. Fire alarm
 - 7. Fire alarm
 - 8. Fire alarm
- Thank you for answering the questions!

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Chapter 267

**REPORT TO CONGRESS ON TRAUMATIC BRAIN
INJURY IN THE UNITED STATES: UNDERSTANDING
THE PUBLIC HEALTH PROBLEM AMONG CURRENT
AND FORMER MILITARY PERSONNEL^{*}**

CDC, NIH, DOD, and VA Leadership Panel

PREFACE

Since the beginning of Operation Enduring Freedom (OEF) (Afghanistan) and Operation Iraqi Freedom (OIF), public health and health care-communities have become aware of the increased rates of traumatic brain injury (TBI) among active duty U.S. military personnel. Epidemiologic and clinical studies suggest that many of these military service-related injuries have serious long-term health and socioeconomic consequences.

In response to these public health and medical concerns, Congress passed the Traumatic Brain Injury Act of 2008 (*TBI Act of 2008*), which requires the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH), in consultation with the Department of Defense (DoD) and Department of Veterans Affairs (VA), to determine how best to improve the collection and dissemination of information on the incidence and prevalence of TBI among persons who were formerly in the military; and to make recommendations on the manner in which CDC, NIH, DoD, and VA can collaborate further on the development and improvement of TBI diagnostic tools and treatments. To that end, the CDC, NIH, DoD, and VA formed a Leadership Panel of experts with extensive experience in epidemiologic and clinical research, and in treating and managing TBI and its consequences.

This report presents the major findings and recommendations of the Leadership Panel and a review of relevant scientific literature and a thorough examination of current TBI-related activities and programs conducted by the four agencies/departments. It describes the public

^{*} This is an edited, reformatted and augmented version of a publication from the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH) in collaboration with the Department of Defense (DOD) and the Department of Veterans Affairs (VA), June 2013.

health importance of military service- related TBI, recommends how to measure the magnitude of the health and socioeconomic impact of TBI and suggests ways in which the four agencies/departments can collaborate further on the development and improvement of TBI diagnostic tools and treatments.

LIST OF ACRONYMS

AFIP:	Armed Forces Institute of Pathology
AMS:	Army Medical Surveillance Activity
BRFSS:	Behavioral Risk Factor Surveillance System
BROS:	Blind Rehabilitation Outpatient Specialists
BTBIS:	Brief TBI Survey
BTF:	Brain Trauma Foundation
BTP:	Blast Tracker Program
CDC:	Centers for Disease Control and Prevention
CDMRP:	Congressionally Directed Medical Research Program
CIDNE:	Combined Information Data Network Exchange
CNRM:	Center for Neuroscience and Regenerative Medicine
DHHS:	Department of Health and Human Services
DHMIS:	Defense Health Information Management System
DMDC:	Defense Manpower Data Center
DoD:	Department of Defense
DVBIC:	Defense and Veterans Brain Injury Center
FIRP:	Federal Individual Recovery Plan
FRC:	Federal Recovery Coordinator
FRCP:	Federal Recovery Coordination Center
GCS:	Glasgow Coma Scale
HRSA:	Health Resources and Services Administration
IOM:	Institute of Medicine
JIEDDO:	Joint Improvised Explosive Device Defeat Organization
LOC:	Loss of consciousness
LRMC:	Landstuhl Regional Medical Center
MACE:	Military Acute Concussion Evaluation
MCS:	Millennium Cohort Study
MHS:	Military Health System
NCAT:	Neurocognitive Assessment Tool
NCHS:	National Center for Health Statistics
NCIPC:	National Center for Injury Prevention and Control
NCMRR:	National Center on Medical Rehabilitation Research
NDAA:	National Defense Authorization Act
NDSC:	National Data and Statistical Center
NHANES:	National Health and Nutrition Examination Survey
NHIS:	National Health Interview Survey
NHLBI:	National Heart, Lung, and Blood Institute

NIA:	National Institute of Aging
NIAAA:	National Institute on Alcohol Abuse and Alcoholism
NICHD:	Eunice Kennedy Shriver National Institute of Child Health and Human Development
NIDA:	National Institute on Drug Abuse
NIDRR:	National Institute on Disability and Rehabilitation Research
NIH:	National Institutes of Health
NIMH:	National Institute of Mental Health
NINDS:	National Institute of Neurological Disorders and Stroke
NINR:	National Institute on Nursing Research
OAFME:	Office of The Armed Forces Medical Examiner
OEF:	Operation Enduring Freedom
OIF:	Operation Iraq Freedom
OPD:	Outpatient department
PCS:	Post-concussive syndrome
PDHA:	Post-deployment health assessments
PH:	Psychological health
PHI:	Protected health information
PRC:	Polytrauma Rehabilitation Center
PTSD:	Posttraumatic stress disorder
QUERI:	Quality Enhancement Research Initiative
SLAITS:	State and Local Area Integrated Telephone Survey
SM:	Service member
SME:	Subject matter expert
SMs:	Service members
TBI:	Traumatic brain injury
TBIMS:	TBI Model Systems
TMDS:	Theater Medical Data Store
TSWG:	Technical Support Working Group
USAMRMC:	U.S. Army Medical Research and Materiel Command
USUHS:	Uniformed Services University of the Health Sciences
VA:	Department of Veterans Affairs
VCSA:	Vice Chief of Staff of the Army
VHA:	Veterans Health Administration
VHR:	Veterans Health Registry
VIST:	Visual Impairment Service Team
WARCAT:	Warrior Administered Retrospective Casualty Assessment Tool

GOALS OF THE REPORT

To respond to the mandate of the *TBI Act of 2008* and to accomplish the goals of this report, CDC, NIH, DoD, and VA formed a Leadership Panel comprising representatives from each of these four agencies/departments. These persons were researchers and investigators with extensive experience in TBI-related epidemiologic and clinical research and in treating

and providing rehabilitation for TBI survivors. To prepare their respective contributions to the report, members of the panel reviewed all current TBI-related activities and programs conducted by the four agencies/departments and relevant scientific literature.

This report represents the culmination of the Leadership Panel's deliberations and summarizes findings and recommendations. By sharing the results of this effort, CDC, NIH, DoD and VA aim to:

- **Raise Awareness:** Describe the public health importance of TBI among people currently or formerly in the military;
- **Improve Surveillance:** Recommend how to better measure the magnitude and impact of this condition in this population and the country; and
- **Strengthen Collaboration:** Suggest how the four agencies/departments can collaborate further on the development and improvement of TBI-related diagnostic and prognostic tools, treatment, management, and rehabilitation.

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EXECUTIVE SUMMARY

Background and Key Findings

Traumatic brain injury (TBI) is one of the highest priorities in public health and medicine because of its magnitude, cost, and consequences (e.g., death and disability), and because it is often preventable. The Centers for Disease Control and Prevention's (CDC) National Center for Injury Prevention and Control (NCIPC) estimates that each year approximately 1.7 million civilians in the United States sustain a TBI. Of these TBI injuries, which can occur alone or in combination with other injuries, about 1.36 million are treated and released from emergency departments (EDs), 275,000 are hospitalized, and 52,000 die. However, not all of these ED visits, hospitalizations and deaths are attributable to TBI, but might be due to other co-occurring injuries. These data suggest that the majority of TBIs (approximately 80%; *Coronado, Thurman, Greenspan, and Weissman, 2009*) are mild. These figures might not reflect the true incidence of TBI because they do not include people who are treated in physicians' offices or outpatient facilities or those seeking medical care in non-civilian facilities (*Faul, Xu, Wald, and Coronado, 2010*).

TBI among U.S. military personnel is a critically important health concern for veterans of the current Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF); these operations comprise several subordinate operations in Afghanistan, Horn of Africa, Trans Sahara, Philippines, Kyrgyzstan, as well as earlier theaters of military operations. According

to a Defense and Veterans Brain Injury Center (DVBIC) analysis of surveillance data released by the Department of Defense (DoD), 33,149 U.S. military personnel were diagnosed with a TBI in 2011 alone. This number includes service members (SMs) from the Army, Navy, Marine Corps, Air Force, and from the active duty and reserve components of the National Guard. (*U.S. Dept. of Defense*: http://www.health.mil/Research/TBI_Numbers.aspx). The U.S. Department of Veterans Affairs (VA) estimates that of the 771,874 veterans who sought care from a VA Medical Center from the start of OEF in October 1, 2001 to December 31, 2011, a total of 59,218 unique OEF and OIF veterans were evaluated or treated for a condition possibly related to a TBI (*U.S. Dept. of Veterans Affairs, 2012*: <http://www.publichealth.va.gov/docs/epidemiology/healthcare-utilization-report-fy2012-qtr1.pdf>).

In response to these public health and medical concerns, Congress reauthorized the Traumatic Brain Injury (TBI) Act of 1996 with the passage of the Traumatic Brain Injury (TBI) Act of 2008 (P.L. 110-206; U.S. GPO 2008), which requires CDC and the National Institutes of Health (NIH), in consultation with the Department of Defense and the Veteran's Administration, to

- Determine how best to improve the collection and dissemination of information on the incidence (rate at which new cases of a condition occur in the population) and the prevalence (proportion of a population at any given time that is experiencing the effects of a condition) of TBI among persons who were formerly in the military; and
- Make recommendations on the manner in which CDC, NIH, DoD, and VA can collaborate further on the development and improvement of TBI diagnostic tools and treatments.

This report responds to these mandates. It was developed through a collaborative effort of a Leadership Panel made up of representatives from the four participating agencies/departments and was reviewed, cleared, and approved by the participating agencies/departments. Members of this Leadership Panel were clinicians, researchers, investigators, and science administrators with extensive experience in epidemiologic and clinical research and in treating and managing persons with TBI.

Advances in TBI research in the past 30 years have created new opportunities for improved surveillance and for effective, acute and long-term medical care and rehabilitation; however, as detailed in this report, many important data and knowledge gaps persist. Several critical concerns and challenges related to the population of U.S. SMs who have sustained a TBI while in military service drive the recommendations included in this report. Although DoD and VA have made substantial progress in helping military personnel who have sustained a TBI, critical gaps remain in surveillance, epidemiology, clinical diagnosis, management, and rehabilitation, including a need to continue developing standard surveillance definitions, clinical definitions, and data collection methods as new knowledge and technology emerge. Some recent and current challenges include the following:

- The annual rate of TBI among active duty personnel increased substantially from 2000 to 2011. A majority of the increases occurred from 2006 through 2008 (*U.S. Department of Defense, unpublished data*).

- As is experienced in the general population, the actual rate of TBI among military personnel is potentially underestimated by existing TBI surveillance efforts. This is especially true for identification of personnel who have sustained a mild TBI.
- The total burden of TBI among current and former military personnel, including medical costs, rehabilitation costs and lost productivity/income, is difficult to determine from existing data sources.
- Evidence on the effectiveness of acute and post-acute treatment is limited. Although some guidelines and recommendations exist for the acute and post-acute treatment and rehabilitation of persons sustaining a TBI, they are generally derived from expert consensus or case series studies, as evidence-based scientific knowledge is sparse or is less than optimal to justify the strongest clinical recommendations.
- The influence of blast exposure on the risk for later developing neurodegenerative disorders is unknown.

Recommendations

The following general recommendations were developed in response to these concerns and to the questions posed in the *TBI Act of 2008*:

- **IMPROVE IDENTIFICATION:** Strengthen the identification of military service-related TBI among current military SMs and veterans, including those who do not seek care from the military or VA health-care systems. Emphasis will be given to improving data-collection initiatives and data sources to obtain a more comprehensive picture of the problem and impacts of TBI in this population. All four participating agencies should continue to foster and strengthen collaboration to this aim.
- **STANDARDIZE DEFINITIONS:** Use standard clinical and surveillance definitions and severity classification of TBI among U.S. military and civilian health-care providers and researchers to improve reporting. Update these definitions periodically as more precise, sensitive, and valid terms and definitions are available.
- **STANDARDIZE CLASSIFICATION:** Improve the coding and classification of TBI by working across agencies. All four participating agencies should continue to meet with professional, academic, health care, and coding organizations to discuss improvements in ICD-10-CM and TBI severity measures that can allow comparison of cases and outcomes.
- **ENHANCE DISSEMINATION:** Promote dissemination of information to non-VA facilities regarding TBI services available through the VA health-care system since 2007 including baseline screening and follow-up assessment and evaluation.
- **STRENGTHEN RESEARCH:** Continue research into the consequences of deployment-related TBI, including prospective investigation of the impact of single or multiple insults to the brain and risk for cognitive decline or other health conditions later in life, which might occur among SMs and veterans. Share findings with civilian health-care providers.

- **FOLLOW EVIDENCE-BASED PREVENTION STRATEGIES:** Continue reducing risk factors, improving quality of protective equipment, and ensuring adherence to evidence-based strategies and guidelines.

Evidence indicates that TBI in the U.S. population, including among those who served in the military, is a public health problem, the magnitude and impact of which are underestimated by current civilian and military surveillance systems. Much research is needed to determine the full magnitude of TBI, identify preventable and modifiable risk factors, develop and test strategies to reduce TBIs in civilian and military life, and improve health and social outcomes and quality of life for those who sustain these injuries. Such research will inform the development of more effective primary prevention strategies and policies, diagnostic tools, and therapeutic interventions and will allow for improved rehabilitation and recovery of TBI survivors.

More details on each of the recommendations, including the rationale and potential benefits, can be found in this document. Imperative in planning for the future is recognizing that the public health and medical communities' understanding of TBI is evolving, with many gaps in knowledge for both military and civilian populations. This report offers recommendations for future TBI-related epidemiologic and clinical research; however, refinement and periodic review of the recommendations and their impact will be necessary.

INTRODUCTION

In response to public health concerns, Congress passed the *TBI Act of 2008 (P.L. 110-206; U.S. Government Printing Office 2008)*, requiring the Secretary of the U.S. Department of Health and Human Services (DHHS), acting through the Directors of CDC and NIH, in consultation with the Secretary of Defense and the Secretary of Veterans Affairs, to submit a report on TBI to the relevant committees of Congress. It will contain the findings derived from an evaluation of activities and procedures that can be implemented by CDC to improve the collection and dissemination of compatible epidemiologic studies on the incidence and prevalence of TBI in persons who were formerly in the military. This report addresses that mandate and, as requested by Congress, also includes recommendations on the manner in which CDC, NIH, DoD, and the VA can collaborate further on the development and improvement of TBI diagnostic tools and treatments.

Definition of TBI

TBI was recently defined by a consensus panel of experts “as an alteration in brain function, or other evidence of brain pathology, caused by an external force” (*Menon, Schwab, Wright, and Maas, 2010*).

TBI results from blunt or penetrating trauma to the head, or indirect acceleration and deceleration forces or blasts. These forces might temporarily or permanently disrupt the functioning of the brain. The extent and severity of a TBI after an initial mechanical event depends on many factors, including 1) the magnitude of direct or indirect forces applied to the

head; 2) the direction of the force; and 3) the subsequent direction, duration and amplitude of angular accelerations to which the brain is subjected (Gaetz M. 2004). Other factors influencing the nature and severity of a TBI might include age, sex, body size and weight, comorbidities, alcohol use, genetics, and previous brain injuries, although the evidence on the specific positive or negative effects of each of these is limited. (Förstl, Haass, Hemmer, Meyer, and Halle., 2010; Coronado et al., 2009; Moppett, 2007; León-Carrión, Dominguez-Morales, Barroso y Martin, and Murillo-Cabezas, 2005; D'Ambrosio and Perucca, 2004; Roof, Duvdevani, and Stein, 1993; Pelligrino, Santizo, Baughman, and Wang, 1998). The use of protective gear can reduce the occurrence and severity of brain injuries.

The functional consequences of TBI range from transient, reversible alterations in brain function to profound disability or death. Recovery of neurologic functioning after TBI might or might not occur and varies in its time course from a few minutes to many years. More severe injuries require longer recovery periods. However, even in the case of mild TBI, a subset of persons develop post-concussion syndrome, a syndrome characterized by headaches, depression, irritability, sleep disorder, poor concentration, and fatigue; various studies indicate that 38-80% of those with mild TBI may develop post-concussion syndrome (Hall, Hall, and Chapman, 2005). The effects of a prior TBI on the aging brain are not clear. Multiple severe concussive and sub-concussive injuries, like those reported in boxers who engaged in the sport for several years, are known to cause a delayed dementia syndrome (*dementia pugilistica* or chronic traumatic encephalopathy) (Zetterberg et al., 2006; Zetterberg et al., 2009; McKee et al., 2009; Gavett et al., 2011) that also might be evidenced by a Parkinson-like movement disorder. As described later in this report, case-controlled and cohort studies provide conflicting reports on whether a prior TBI is a risk factor for Alzheimer's disease (Van Den Heuvel C, Thornton, and Vink, 2007; Fleminger S, Oliver, Lovestone, Rabe-Hesketh, and Giora, 2003). Overall, the scope, complexity, and heterogeneity of TBI present challenges for developing precise, sensitive, and accurate diagnostic and prognostic tools and effective medical and other health-related (e.g., rehabilitation) interventions.

PATHOPHYSIOLOGY AND MECHANISMS

TBIs can be classified in many ways (Saatman et al., 2008). For the purposes of this report, TBI is classified as follows: by physical cause, by functional severity, or by the physical changes associated with TBI. The initial impact to the brain in TBI might result in one or more direct effects. For example, a blow to the head from a fall can cause bleeding and bruising of the brain. The result of the initial impact often gives rise to a number of secondary effects that further worsen the severity of the injury.

Brain injuries also can be characterized as focal (localized) or diffuse (widespread); the localization of injury depends primarily on the initial mechanical trauma. The features of TBI include bleeding around the brain or between the brain and the skull, bruising to the brain that is either localized or diffuse. Other features include decreased blood flow to the brain or swelling of brain tissue, which can contribute to complex secondary outcomes. TBI is sometimes also discussed in the context of primary or immediate injury versus secondary or delayed injury. The physical cause of primary injury can be classified as closed, penetrating,

or blast. Classification based on patterns and types of injury is essential for therapy development but is also challenging (*Marshall et al., 1992*).

Primary Injury

Primary injury occurs immediately and as direct result of mechanical trauma. Depending on the injury mechanism and severity, the initial event might cause direct or primary mechanical alterations of the brain tissue (e.g., widespread damage to the axons that provide support and structure to the brain, laceration of the brain, bleeding around the brain or between the brain and the skull, and bruising to the brain). Autopsy studies following fatal TBI have reported large variability in primary and secondary injuries (*Adams, Mitchell, Graham, and Doyle, 1977; Bigler and Maxwell, 2011*). These types of injuries can occur alone or in combination and are often accompanied by other traumatic injuries to multiple organs or body parts.

Secondary Injury

Secondary brain injuries arise from complications initiated by the primary injury itself and via other mechanisms, including inflammation, cell receptor mediated dysfunction, free radical and oxidative damage, and calcium or other ion-mediated cell damage (*Graham, Gennarelli, and McIntosh, 2002*). Primary mechanical changes are generally followed by several biologic processes that occur in the minutes to days following TBI (*Scalea, 2005; Gennarelli and Graham, 2005; Granacher RP, 2007*), resulting in secondary brain injuries that can include the build-up of excess fluid in the brain that gives rise to elevated intracranial pressure (*Granacher, 2007; Porth, 2007; Sullivan et al, 2000; Sauaia et al., 1995*). In turn, these secondary processes modulate gene expression and/or protein regulation that lead either to cell death or repair (*Graham et al., 2002; Luukinen et al, 2005*). Researchers have pursued many of these processes as potential targets for therapies that might limit the extent and severity of injury after TBI.

As in other tissue injuries, an inflammatory reaction to TBI also can occur. Inflammation is involved in the repair of brain tissue after injury, but it can also contribute to secondary brain damage. Secondary injury also might result from other systemic events related to multiple injuries in other organs or body parts; for example, an overall drop in blood pressure might reduce the blood flow to the brain, which contributes to the severity and extent of the initial injury (*Scalea 2005*). Alterations in the regulation of brain blood flow also occur after TBI. Focal constriction of major brain arteries has recently been described after blast TBI (*Bell et al., 2009*). Such large artery vasospasm confined to a small area is considered unusual after non-blast TBI, although it also might be an underappreciated problem (*Shahlaie, Boggan, Latchaw, Ji, and Muizelaar, 2009*). Because the brain is enclosed in the non-expandable skull, brain swelling and hemorrhage added to the intracranial compartment can lead to distortion and compression of brain structures and to raised intracranial pressure (ICP). Elevated ICP after TBI can impede blood flow and thereby cause widespread lack of oxygen to the brain that can result in brain death (*Wijdicks, 1995*).

Focal and Diffuse Injury

TBI can present as a focal (localized) or diffuse (widespread) injury. Some patients may exhibit both focal and diffuse injuries. A focal injury results when bleeding, bruising or a penetrating injury is isolated to a portion of the brain. Focal injury causes neurologic deficits that are related to the functions that take place in the damaged region of the brain. Diffuse brain injury to the axons that connect brain structures is also common, as these “brain wires” provide the major mechanical support to brain tissue and are subject to damaging strain forces upon impact or rapid acceleration/deceleration. Though the neuropathology of blast injury in service members has not been studied systematically, animal studies demonstrate diffuse brain injury after blast trauma (Cernak, 2005). Diffuse brain injury also might occur from rapid acceleration and deceleration forces to the head, a common factor in motor vehicle crashes. The neurologic deficits caused by diffuse brain injury also can affect overall brain function.

Closed: Impact and Acceleration/Deceleration

Impact of the head against another object (Adams, Victor, and Ropper, 1997) can cause focal brain injury under the skull at the site of impact and sometimes at a site on the opposite side of the head, called contrecoup. These focal impact injuries, termed contusions, are prone to bleeding. Bleeding also can occur into other intracranial spaces, including the space that contains the cerebrospinal fluid that surrounds the brain (known as traumatic subarachnoid hemorrhage) and the space underneath the thick leathery dura that is attached to the undersurface of the skull (known as traumatic subdural hematoma). When a skull fracture disrupts arteries that lie over the dura, bleeding might occur between the dura and the skull (epidural hematomas). Intracranial bleeding can lead to death or permanent disability and might worsen over variable periods (minutes to days) post-TBI. Because the skull is a rigid structure and not expandable, the volume of blood that can be accommodated is limited before pressure inside the skull begins to rise and distortion of brain structures occurs. Evacuation of posttraumatic intracranial blood is one of the most common neurosurgical interventions after TBI (Bullock et al 2006).

The most common form of TBI is caused by a combination of impact and acceleration/deceleration forces, such as what occurs in high-speed motor vehicle crashes (Kotapka et al., 1991; Adams, Graham, Murray, and Scott, 1982). Acceleration/deceleration creates forces that can damage the brain even if no actual impact of the head against another object occurs, (although the latter is unusual and requires much higher forces; (Duhaime, 2006]). Impact combined with acceleration/deceleration injury causes shearing of the connecting fibers in the brain. After death, in brains viewed under a microscope, shearing is visible as disruption and focal swelling of the nerve axons. Visualizing shear injury on standard neuroimaging is difficult (Hammond and Wasserman, 2002; Gold and Lipton, 2008). New advanced magnetic resonance imaging (MRI) techniques, might improve imaging of brain lesions, especially those in the mild spectrum and help in the diagnosis of brain injuries. Because these technologies are continuously evolving, they must be refined and validated. (Kirov et al., 2013)

Penetrating Injury

Penetrating TBI occurs when an object enters the brain, whether a bullet, shrapnel, knife, bone fragment, or other material. Penetrating injury is focal because of the mechanical disruption of specific brain regions along the track of the object. However, injury also can occur further away from the object's track because of the transmission of kinetic energy from a high-speed projectile to the brain. Penetrating head injury causes a greater risk of posttraumatic seizures and epilepsy than closed head injury (*Temkin, 2009*).

Blast Injury

Blast injury is the result of pressure waves interacting with the body following exposure to a high-order explosion, that is, an explosive event where the blast pressure front moves rapidly, shattering objects in its path. Though studied in the past, blast injury is subject to more intensive scrutiny since the onset of Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF). The blast environment presents a high risk for penetrating TBI related to shrapnel and forces that cause rapid head movement or impact against other objects, resulting in shear injury or contusion, respectively. Current evidence from animal studies suggests that brain injury can occur as a result of blast pressure waves—even if the wave is directed at the chest (*Courtney and Courtney, 2009*). Whether lung injury itself contributes to brain injury, or whether the structures of the chest participate in transmitting the blast forces to the brain, is not definitively known. For this reason, body armor might offer some brain protection. Although helmets protect the brain from penetrating injury, skull fracture, and contusion, they might not dampen a blast wave and injury may still occur.

The details of how a blast wave causes brain damage are still poorly defined; standard neuroimaging is generally unrevealing. Major questions remain, including the following: What levels of a single blast intensity or distance from the blast are tolerated without permanent injury? Do repeated prior exposures to blast increase vulnerability? Are any longer term-consequences to blast exposure evident? A major gap in understanding is caused by the lack of information about the pathology of blast injury in humans, which is related to limited research on post-mortem brains. In addition, because of the combination of different mechanisms of TBI in the blast area, differentiating the primary blast pathology from those caused by blunt injury, penetrating objects, or shear injury is difficult. Moreover, biological processes that occur as a result of primary and secondary injuries of any external cause, including blast-related TBIs, are not well understood.

Preliminary data suggest that major differences in symptom etiology and pathophysiology are evident between SMs with blast-related closed TBI and non-blast closed TBI (*Moore et al., 2009; Hoffer, Donaldson, Gottshall, Balaban, and Balough, 2009; Hoffer et al 2010*). Scientists have used a brain- imaging technique called diffuse tensor imaging (DTI) to identify the effects of different injury mechanisms. A DTI study comparing blast and non-blast injury determined that blast injuries resulted in more diffuse damage than non-blast injuries. Blast injuries, but not non-blast injuries, were associated with changes in blood flow or structural brain abnormalities (*Moore, 2009; Huang et al., 2009*). In Landstuhl Regional Medical Center, an MRI study of military personnel with a mild TBI diagnosis after exposure to blast demonstrated subtle abnormalities on diffusion imaging in a subset of patients (18/63) (*MacDonald et al., 2011*). Single photon emission CT (SPECT) and positron emission tomography (PET) both demonstrate hypoperfusion (decreased blood flow through an organ) of the frontal lobes, possibly explaining many of the cognitive and behavioral symptoms

associated with mild TBI (Nakayama, Okumura, Shinoda, Nakashima, and Iwama, 2006; Gowda et al., 2006).

Research Relevant to Active Duty Personnel and Veterans

Research collaborations among the four participating agencies (CDC, NIH, DoD, VA) is a fundamental starting point to solving the various problems associated with TBI. Current research is the foundation on which further endeavors can build consensus and effort.

Several clinical trials have attempted to slow secondary processes that contribute to additional damage following TBI. Despite potent neuroprotection of certain chemical compounds in rodent models of head injury, no strategy has so far succeeded in humans. Scientists continue to attempt developing an effective neuroprotective treatment to be administered within hours of the initial trauma to improve patient outcome, including a recently launched multi-center study of progesterone, a treatment modality that demonstrated promise in animal models (*U.S. National Institutes of Health, 2012*). NIH also funds research examining brain recovery after injury. In a collaborative effort, NIH and DoD have established the Federal Interagency TBI Research (FITBIR) Informatics database to facilitate comparison among studies and enhance comparative effectiveness research in TBI.

Studies have found that approximately one-third of SMs with mild TBI also have PTSD (Hoge et al, 2008; Brenner et al, 2009). Because of the overlap in symptoms and this common co-occurrence of PTSD and TBI in SMs, studies related to hormonal differences and imaging findings between PTSD and TBI are ongoing. In the interim, several programs, including those at Fort Campbell, Landstuhl Regional Medical Center, Waco Veterans Affairs Medical Center (VAMC), National Intrepid Center of Excellence in Bethesda, and Cincinnati VAMC have developed programs to treat both mild TBI and PTSD simultaneously.

Without published reports of blast neuropathology in soldiers, scientists are unable to compare what they find in animal models to what is actually happening in persons who have suffered from TBI. To help build pathology data, DoD and others have begun postmortem tissue banks. DoD has developed the TBI Brain Bank through the Armed Forces Institute of Pathology (AFIP), with support from DVBIC, where appropriate patient data and brain specimens of deceased SMs can be archived for further clinical and pathological studies. Officially begun in 2009, this DoD program has the potential to be used for the congressionally mandated 15-year longitudinal study of returnees and veterans of OIF and OEF. Study participants will be invited to consider post-mortem donation of their brains to the DoD TBI Brain Bank as a secondary study arm. In comparison with severe TBI, much less is known about the pathoanatomical or pathophysiological alterations that are produced by mild or concussive injuries, because only in rare cases are these injuries fatal and standard neuroimaging is unrevealing. There may be other opportunities for sharing brain bank resources across agencies to further advance the state of the science.

Research Programs Related to Active Duty Personnel

In the last decade, much work was done to elucidate problems associated with military service-related TBI. A primary focus has been on understanding blast injury (*Lee et al., 2011; MacDonald et al., 2011*) primarily because of the high rate of TBI and blast-related

concussion events resulting from combat operations and the limited knowledge about the blast effects on the central nervous system. These blast-related injuries directly affect the health and safety of individual SMs and thereby also affect the level of unit readiness and troop retention (*Defense and Veterans Brain Injury Center [DVBIC], 2012: <http://www.dvbic.org/about/tbi-military>*). In response, on July 5, 2006, DoD issued DoD Directive 6025.21E “Medical Research for Prevention, Mitigation, and Treatment of Blast Injuries” in compliance with Section 256 of Public Law 109–163 (*U.S. Dept. of Defense, 2006*).

This DoD Directive formally established the DoD Blast Injury Research Program that coordinates and manages the medical-research activities and programs of DoD relating to the prevention, mitigation, and treatment of blast injuries. Through this program, increased funding has been made available for projects that will help identify effects of blast on the brain, mitigate risks, and develop diagnostics and interventions to mitigate brain damage and promote recovery. Through a series of delegations of authority, the United States Army Medical Research and Materiel Command (USAMRMC), a subordinate command of the U.S. Army Medical Command (USAMEDCOM), was selected to carry out the Program's day-to-day coordination and management activities because of its unique position and expertise as the Army's total life cycle medical research, development, acquisition, procurement, and logistical support command (*U.S. Dept. of Defense, 2011: <https://blastinjuryresearch.amedd.army.mil/index.cfm?f=application.introduction>*). Under this research program, studies using advanced imaging techniques have demonstrated that structural pathology associated with persistent symptoms in those with blast-related TBI might be evident (*Peskind et al., 2011; Matthews et al., 2011*). The Blast Injury Research Program is focused on filling gaps in the blast-injury knowledge base. Key research topics by program area, for example, include the following:

- **Acute Treatment:** In this area, DoD is working to
 - Develop diagnostics and neuroprotective drugs for TBI.
 - Develop hemorrhage control and blood products.
 - Develop treatments for psychological trauma.
- **Reset** (a term used in the military to describe a concept that extends beyond rehabilitation to include all activities necessary to return injured SMs to duty or to productive civilian life). In this area, DoD is working to
 - Advance tissue engineering and prosthetics.
 - Improve recovery of physical and mental functioning.
 - Develop return-to-duty standards.

Studies examining the effects of blast injuries are ongoing. Preliminary data suggest that major differences exist in pathophysiology between service members with blast-related TBI and blunt TBI (*Moore et al., 2009*). In a DTI study comparing blast and blunt injury, blast injuries revealed a more diffuse pattern than blunt injuries (*Moore, 2009; Huang et al., 2009*). Blast injuries were associated with abnormalities in the apparent diffusion coefficient, a measure of the movement of water through cell membranes and other parts of the brain, not seen in blunt injuries.

The Breacher Injury Study, conducted by the Defense Advanced Research Projects Agency and the Office of Naval Research (*Applied Research Associates, 2009; Combating*

Terrorism Technical Support Office, 2008) examines the physiological effects or the risks of cognitive impairment as a result of repeated, low-level blast exposures. This is the first prospective study with humans to quantify blast-related TBIs. Aspects of this study were conducted in Breacher trainees (personnel trained to use explosives to gain rapid entry into a facility) from the U.S. Marine Corps' Weapons Training Battalion Dynamic Entry School. The study determined that the trainees did not demonstrate any negative effects due to the exposure. However, the trainers who had greater accumulated exposure over time experienced subtle, reversible cognitive changes after training practices. As a result, the Technical Support Working Group (TSWG) recommended various mitigation measures. The personnel-borne data-acquisition systems used in this study were miniaturized, enabling instrumentation of each Breacher during breaching events. Results of this study are being used to direct future research into protective gear for Breachers (*Applied Research Associates, 2009; Combating Terrorism Technical Support Office, 2008*), and findings can be extrapolated to other branches of the U.S. military to prevent injuries. Understanding the effects of the levels of exposure to blasts on the brain might help to improve surveillance by allowing a better diagnosis and case ascertainment, especially in patients with mild TBIs. Findings from efforts like the Breacher Injury Study might result in better follow up, rehabilitation, and provision of services.

Research Programs Related to Veterans

VA has undertaken various activities to understand better the impact of TBI among veterans. Some of the most persistent and disabling consequences include the ability to select and retain goal-relevant information and to use it for decision-making and goal management in daily life (Ry, Cullen, and Bayley, 2010)—skills that persons without TBI take for granted. Common symptoms of these deficits are being easily distracted, and difficulty with concentration, organization, prioritization, and planning. The VA sponsored two special issues of the *Journal of Rehabilitation Research and Development* that focused on TBI and polytrauma in the veteran population (Department of Veterans Affairs [VA], 2007 & 2009). PTSD, auditory, visual, motor impairment, balance, and other clinical concerns were featured, along with polytrauma, rehabilitation, telemedicine for TBI, and research opportunities. More recently, investigators identified a strong relationship between PTSD and post-concussive syndrome (PCS) and determined that evaluation of both factors is important in clinical management (Benge, Pastorek, and Thornton, 2009). VA researchers are focused on a number of veteran-centric TBI research projects that can be searched through the NIH RePORTER system at <http://projectreporter.nih.gov/> (enter "TBI" in the *Text Search* field and select VA in the *Agency/Institute/Center* field and submit query). Selected relevant publications include the following:

- Evaluation of DTI, Magneto Encephalography (MEG), and Computed Tomography (CT) scans to detect mild TBI indicated that MEG might be more sensitive than DTI and CT scans (Huang *et al.*, 2009).
- A study on visual impairment and dysfunction in SM TBI cases suggests that combat troops exposed to a blast with a mild TBI are at increased risk for visual dysfunction such as blurred vision, difficulty reading or squinting (Brahm *et al.*, 2009).

- A randomized trial comparing cognitive and functional rehabilitation approaches documented better short-term cognitive performance among participants receiving cognitive treatment (Vanderploeg et al., 2008).

DIAGNOSIS

Screening for symptoms possibly associated with TBI involves a quick evaluation of possible exposure to an injury event to determine if an alteration of consciousness (AOC) was evident, if it was associated with the event, or if the event resulted in any neurologic changes or symptoms (*Department of Defense, 2007*). The majority of cases of TBI in the U.S. military are mild TBI and although mild TBIs are often difficult to detect, TBI in persons with multiple trauma—major injuries to the chest, abdomen, pelvis, or extremities—also might be overlooked as other more life-threatening injuries are addressed. Positive TBI screening results should be followed up with a comprehensive evaluation from which a diagnosis is made. This comprehensive TBI evaluation should include identifying the external cause of the patient's injury, assessment for neurobehavioral symptoms, a targeted physical examination, and a follow-up treatment plan.

Pre-Deployment Neurocognitive Baseline Testing

On May 28, 2008, the Assistant Secretary of Defense for Health Affairs (ASD/HA) issued an interim policy letter calling for the Services to “begin implementing baseline pre-deployment neurocognitive assessments for deploying SMs.” The DVBIC was designated the Office of Responsibility for this DoD program known as the Neurocognitive Assessment Tool (NCAT) Program. ASD/HA selected the Automated Neuro-psychological Assessment Metric (ANAM) as the neurocognitive assessment tool; this instrument allows acquiring a baseline assessment of cognitive performance areas most likely affected by mild TBI, including attention, judgment, and memory.

Baseline pre-deployment neurocognitive assessments are administered to all SMs 4–6 months before deployment and sequenced with the pre-deployment training plan (PTP). This sequencing allows the respective commander and command surgeon the timely opportunity to evaluate SMs who might screen positive. This window also provides the greatest opportunity for the unit's medical assets to evaluate, re-evaluate, refer, and begin a medical regimen based upon local treatment protocols. This timeliness allows commanders and medical treatment facilities the opportunity to better manage manpower resources to meet mission requirements.

The goal of this pre-deployment testing is to have the capability to compare assessment results before and after an SM is exposed to a blast event, to improve the detection and treatment of mild TBI. This practice will ultimately affect return-to-duty decisions. From June 2007 through March 2012, 743,309 SMs (35.3% of all who deployed during that period) had completed pre-deployment baseline cognitive testing. The NCAT is used in conjunction with clinical practice guidelines for managing concussion in deployed and non-deployed settings.

The pre-deployment testing program also includes a self-report historical questionnaire screen to determine if TBI or concussion occurred in the past. If an affirmative answer is given in the initial question, additional information is sought regarding loss of consciousness or alteration in consciousness and post-concussive symptoms immediately following the injury and experienced in the 2-year period before testing. The presence of this self-report historical screen and modules other than cognitive evaluation on pre-deployment testing are under review by the Defense Health Board.

In-Theater Screening

In-theater screening occurs immediately following an injury event or as soon as operationally feasible, using the Military Acute Concussion Evaluation (MACE) developed by DVBIC in 2006 (*McCrea, Jaffee, Guskiewicz, and Doncevic, 2009*). MACE allows medics, corpsmen and frontline providers to assess quickly the history of what happened during the event, current symptoms that the SM might experience, a focused neurological exam, and measurement of four cognitive domains: orientation, immediate memory, concentration, and memory recall. The cognitive exam is the Standardized Assessment of Concussion (*McCrea, Kelly, and Randolph, 2000*), which is commonly used as a sideline assessment of sports-related TBI. When combined with other clinical information, this tool helps reveal the presence of any red flags that should prompt an immediate referral because of concerns of a more severe brain injury or to further evaluation and treatment. The currently deployed MACE has been revised substantially (May 2012) and has been validated in combat environments.

In terms of clinical care, before 2010, screening was customarily self-initiated by SMs with potential injury. As a result of an evaluation of in-theater TBI care by both medical and line leadership, concerns were addressed regarding whether this process likely under-evaluated many of those at risk. Subsequently, policy changes now require that every deployed SM involved in a traumatic event, such as motor vehicle collision, and/or within 50 meters of a blast, undergo mandatory medical screening and a 24-hour period of rest (*Department of Defense Instruction 6490.11, 2012*). This practice ensures that all SMs who are involved in a potentially concussive event are screened in a timely fashion to promote early detection of concussion, which will lead to prompt treatment.

SMs with injuries or medical conditions that require evacuation from theater to Landstuhl Regional Medical Center (LRMC) in Germany undergo further evaluation, including screening for concussion or mild TBI using MACE. This process also identifies any history of prior combat or non-combat TBI and assesses for the presence of concussion or mild TBI-related signs and symptoms. Patients with ongoing symptoms are triaged to a stateside medical facility for further evaluation and, if necessary, treatment.

Post-Deployment

Because concussion or mild TBI is not always recognized in theater, screening also occurs through post-deployment health assessments (PDHA). Four questions, adapted from

the Brief TBI Survey (BTBIS) (Schwab *et al.*, 2007), currently appear on the PDHA; positive responses to all four questions prompt a clinical interview to evaluate fully for mild TBI. Although this criterion is more specific than the DoD definition (positive response to questions 1 and 2 only), it allows identification of those with ongoing symptoms who are likely in need of medical services. The Institute of Medicine (IOM) recommended continued use of MACE and BTBIS for screening of combat-related TBI (Institute of Medicine, 2008). Some military treatment facilities perform additional screening. For example, Ft. Carson uses the Warrior Administered Retrospective Casualty Assessment Tool (WARCAT) to fully assess possible injuries (Terrio *et al.*, 2009).

VA Clinical Screening and Diagnosis Tools

Since April 14, 2007, all VA health-care facilities screen all veterans from OEF/OIF for possible TBI upon initial contact with the VA health system (England and Mansfield, 2008; U.S. Dept. of Veterans Affairs VHA Directive 2007-013). Those who screen positive are referred for follow-up evaluations that include a history of the veteran's injury, a physical examination targeted to the veteran's symptoms, and administration of the 22-item Neurobehavioral Symptom Inventory, an inventory that has been adapted by the VA for use in their Comprehensive TBI Evaluation. Veterans Health Administration (VHA) staff received training in administering the screening tool and follow-up evaluation, and the computerized medical record system was modified to include a TBI screening clinical reminder that 1) identifies who needs screening, 2) presents the screening tool to the provider, and 3) enters results into progress notes and into the electronic health record. VA policy requires that a veteran who screens positive be offered a follow-up evaluation with a specialty provider who can determine whether the patient has a TBI and then develop a treatment plan. The evaluation process includes a standardized evaluation template of common problems following brain injury, including a complete TBI-specific eye examination (Schwab *et al.*, 2007).

Civilian Clinical Screening and Diagnosis Tools

The clinical diagnosis of acute TBI in the civilian population is usually based on a history of multiple signs and symptoms, including acute alterations in alertness or consciousness or memory problems that occur immediately after the event. If the traumatic event is witnessed, confirmation of a change in consciousness by an observer (in the context of the mechanical injury) makes the diagnosis. Unconsciousness is usually easy to identify, except if brief, whereas alterations in consciousness might require confirmation through an interview conducted by a medical expert. Most often the witnesses note abnormal behavior, such as disorientation for place or time, poor ability to attend or make new memories, or impaired balance and gait. Sports coaches use standardized tests applied shortly after the injury to diagnose less marked alteration in consciousness in athletes (Lovell, 2009).

In moderate and severe TBI, memory impairment during the period of depressed consciousness results in retrograde amnesia, lack of memory extending back in time, and

impaired memory for details of the injury itself and extending for some time after the injury or anterograde amnesia (*Sigurdardottir Sigurdardottir, Andelic, Roe, and Schanke, 2009*). If unwitnessed, the clinical diagnosis of TBI can be made in the context of a mechanical event involving the head (scalp wound, hematoma, skull fracture, blood behind the tympanic membrane of the ear, or other evidence of a head injury) in someone who has amnesia for the time around the event. Persons with isolated head trauma with minimal alteration in consciousness might not seek medical attention, making unbiased ascertainment of these cases of mild TBI challenging.

Diagnosis is further complicated by other conditions that might cause alteration or loss in consciousness. Alcohol or drug intoxication, hypoglycemia, cardiac arrhythmia, stroke, and seizures can cause rapid change in consciousness and might contribute to falls and other mechanisms of injury that can result in TBI. Although alcohol can contribute to these injuries, including TBIs, the effect of its role after a TBI has occurred is unclear. A study of 38,019 patients with moderate to severe head injuries documented that patients who tested positive for alcohol were less likely to die than patients who had no alcohol in their bloodstream. These patients had more medical complications during their hospital stay and were younger and had less severe injuries (*Salim et al., 2009*). Additional research indicated that high admission blood- alcohol level in patients with isolated moderate to severe TBI was independently associated with improved survival (*Berry et al. 2010; Berry et al., 2011*). These findings suggest that additional research is needed to investigate the potential therapeutic use of alcohol in the management of TBI (*Salim et al., 2009; Berry et al. 2010; Berry et al., 2011*).

The diagnosis of TBI is usually made clinically, and no well-accepted diagnostic tests (e.g., biomarkers or imaging) are available for use in standard medical practice to diagnose mild and even some moderate TBI. However, neuroimaging is commonly used to detect bleeding inside the skull in persons with TBI because posttraumatic bleeding is associated with worse prognosis and can be life threatening. On occasion, such evidence of TBI is discovered on neuroimaging in persons in which the clinical suspicion of TBI was low. Although not all neuroimaging modalities are able to identify all TBIs, some techniques, for example MRI, are better able to identify patients with some potentially critical injuries such as diffuse axonal injury (DAI) (*Belanger, Vanderploeg, Curtiss, and Warden, 2007; Levine et al., 2006*).

Clinical Presentation/Symptoms

Diagnosis of acute TBI is based on several criteria, including history of the event, clinical and functional assessment, and CT scanning and other neuroimaging. Some of the pathoanatomical features of TBI can be diagnosed with neuroimaging. However, standard neuroimaging does not enable comprehensive quantitative assessment of the brain injury, so a substantial discrepancy between the degree of clinical impairment and the degree of injury is often seen on neuroimaging. This is a major clinical concern, especially when trying to understand the neurological mechanisms associated with PCS. Major research advances in neurotraumaproteomics (a study of protein complexes that make up the nervous system) have identified several candidate markers that are under evaluation as TBI biomarkers. Early

research has uncovered several candidates that have shown some preclinical potential; these include lactate dehydrogenase (LDH), glial fibrillary acid protein (GFAP), neuron specific enolase (NSE), and S-100 β . Unfortunately these proteins lack either the necessary sensitivity or brain specificity or both to be used effectively alone (Pineda, Wang, and Hayes. 2004; Pelsers, Hermens, and Glatz, 2005; Ingebrigtsen and Romner, 2003; Bandyopadhyay, Hennes, Gorelick, Wells, and Walsh-Kelly, 2005; Siman et al., 2004). More recently, new candidate biomarkers have been discovered; these include: UCH-L1, MAP-2, and TAU proteins (Kobeissy et al., 2006; Zemlan et al., 1999; Folkerts, Berman, Muizelaar, and Rafols, 1998), and the II-spectrin protein breakdown products (SBDPs) (Pike et al., 2004; Pike et al., 2001; Pike et al., 2000; Ringger et al., 2004; Pineda et al., 2007). These findings highlight the need for biomarker development and validation.

Table 1. Glasgow coma scale

Ability	Score
Eye Opening (E)	
Spontaneous	4
To voice	3
To pain	2
None	1
Motor Response (M)	
Normal	6
Localized to pain	5
Withdraws to pain	4
Flexion-abnormal (<i>an abnormal posture that can include rigidity, clenched fists, legs held straight out, and arms bent inward toward the body with the wrists and fingers bent and held on the chest</i>)	3
Extension (<i>an abnormal posture that can include rigidity, arms and legs held straight out, toes pointed downward, head and neck arched backwards</i>)	2
None	1
Verbal Response (V)	
Normal conversation	5
Disoriented conversation	4
Words, but not coherent	3
No words, only sounds	2
None	1
Score: Eye Score (E) + Motor Score (M) + Verbal Score (V) = 3 to 15	
Teasdale & Jennett, 1974	

Clinical signs and symptoms can occur alone or in combinations and might result in functional impairment. These signs and symptoms appear to be independent of pre-existing conditions except in cases of exacerbation of pre-existing conditions. They usually can be defined by one or more of the three following categories:

Physical: headache, nausea, vomiting, dizziness, blurred vision, sleep disturbance, weakness, paralysis, sensory loss, spasticity, disorders of speech or language, swallowing disorders, balance disorders, disorders of coordination, seizure disorder;

Cognitive: attention, concentration, memory, speed of processing, new learning, planning, reasoning, judgment, executive control, self-awareness, language, abstract thinking;

Behavioral/emotional: depression, anxiety, agitation, irritability, impulsivity, aggression and violence, acting out, noncompliance, social inappropriateness, emotional outbursts,

childish behavior, impaired self-control, impaired self-awareness, inability to take responsibility or accept criticism, or alcohol or drug abuse/addiction. Additional neuropsychiatric problems associated with TBI include apathy, paranoia, confusion, frustration, agitation, sleep problems, or mood swings (*American Psychiatric Association 2000*).

The signs and symptoms listed above are typical of each category but are not an exhaustive list of all possible signs and symptoms.

Severity

TBI is often characterized by severity that is usually based on various clinical factors, including duration or length of LOC, coma scaling, or imaging. Clinicians and investigators have classified TBI as mild, moderate, or severe by scores on the Glasgow Coma Scale (GCS), a widely used scoring system to assess coma and impaired consciousness (*Teasdale and Jennett, 1974; Rimel, Giordani, Barth, Boll, and Jane, 1981; Rimel, Giordani, Barth, and Jane, 1982*). The GCS is an algebraic scale consisting of three components: eye opening, verbal response, and motor response (Table 1). Patients with scores of 8 or less are classified as “severe”; scores of 9 to 12 are “moderate”; and scores of 13 to 15 are “mild” (*National Center for Injury Prevention and Control 2003*).

Although not intended or designed as a severity classification, the LOC duration is often used as an approximation of TBI severity by certain users, including CDC. In addition to brief LOC, mild TBI also might be characterized by confusion or disorientation or loss of memory for events immediately before or after the injury. In contrast, more severe TBI is associated with extended periods of unconsciousness of more than 30 minutes, or prolonged post-traumatic amnesia of more than 24 hours. Although the distinction between mild TBI and more severe TBI seems straightforward, establishing definitive, measurable criteria to identify and quantify the occurrence of mild TBI is challenging because clinicians and investigators have been using different diagnostic criteria and methodologies to study this condition (*Ruff and Jurica, 1999; American Congress of Rehabilitation Medicine, 1993; National Center for Injury Prevention and Control, 2003*).

The DoD and VA classify severity for non-penetrating TBI (Table 2) as mild TBI if the length of time of LOC was 0 to 30 minutes, provided that the patient does not have a clinical or imaging diagnosis indicative of more severe TBI (e.g., a patient with an abnormal imaging who had a LOC of 5 seconds). This LOC-related criterion for mild TBI is consistent with the corresponding CDC criterion and ICD-9- CM classification for concussion (850 series) (*National Center for Injury Prevention and Control, 2003*). DoD and VA also classify TBI as a moderate TBI if the patient has a LOC greater than 30 minutes and less than 24 hours; and severe TBI if the patient has a LOC greater than 24 hours. If a patient meets criteria in more than one severity category, the higher severity level of severity is assigned. CDC concurs with DoD and VA criteria.

Current DoD surveillance methods capture penetrating injury as a separate category, regardless of injury severity because this injury pattern might have more substantial long-term consequences than non- penetrating injury. TBI severity for non-penetrating injuries was determined using standard DoD/VA severity algorithms.

Table 2. DoD/VA severity stratification for non-penetrating TBI

	Mild	Moderate	Severe
Structure Imaging	Normal	Normal or abnormal	Normal or abnormal
Length of Time of Loss of Consciousness	0-30 mins	>30 mins and < 24 hours	> 24 hrs
Alternation of Consciousness/Mental State	A moment up to 24 hrs	>24 hrs Severity based on other criteria	
Post-Traumatic Amnesia	0-1 day	>1 and <7 days	> 7 days
Glasgow Coma Scale*	13-15	9-12	3-8

*For purposes of injury stratification, the Glasgow Coma Scale (GCS) is measured at or after 24 hours (*Malec et al. 2007; Esselman and Uomoto 1995; American Congress of Rehabilitation Medicine, 1993; Saatman et al. 2008; Model System*).

Source: Department of Defense and Department of Veterans Affairs.

Note: Although the initial severity level might have some prognostic value, it does not necessarily reflect the patient's ultimate level of functioning. This requires serial assessments of the patient's cognitive, emotional, behavioral, and social functioning.

If not clinically possible to determine the brain injury level of severity because of medical complications (e.g., medically induced coma), other severity markers are required to determine the severity of the brain injury. For example, one or more of the following may be useful: imaging studies; monitoring intracranial pressure; electroencephalography that may demonstrate absence of electrical brain activity; and, transcranial doppler that may detect the absence of blood flow in the brain.

TREATMENT

Various TBI-related activities are being pursued in the areas of medical care, research, and interagency collaboration.

Persons with isolated mild TBI are usually treated and released from emergency departments. These patients might receive guidance upon discharge regarding when to seek medical care if symptoms persist or worsen and when to return to work, school or sports play (*CDC Heads Up to Clinicians* available at <http://www.cdc.gov/concussion/clinician.html>). In contrast, TBI survivors with moderate to severe injuries are likely to receive treatment in intensive care units and neurosurgical units (*U.S. National Institutes of Health, February 2002*). Treatment depends on the recovery stage of the patient and other factors (e.g., concurrent injuries, comorbid conditions). In the acute stage, the primary aim is to stabilize the patient and to prevent secondary injuries (*U.S. National Institutes of Health February, 2002*). Rehabilitation is the primary treatment for the sub-acute and chronic stages of recovery (*U.S. National Institutes of Health, February 2002*).

Acute Care

TBI care in the Military Health Service (MHS) varies by TBI severity, interval from injury to presentation, and physical location where the injury occurs. In 2005, the Brain Trauma Foundation (BTF), in collaboration with DVBIC and the Uniformed Services

University of the Health Sciences (USUHS), published the *Guidelines for the Field Management of Combat-related Head Trauma* (Knuth et al., 2005). These guidelines relied on extrapolated data from civilian trauma settings and recognized that tactical operations might alter the care that is provided in the combat setting. A decision-tree included in the document gives frontline providers triage decision-making assistance.

Severe and penetrating TBIs are recognized and triaged at the time of injury. Acute care for conditions such as intracranial pressure management, nutrition, and general critical care are consistent with civilian best practices (Bullock and Povlishock, 2007). DVBIC, in conjunction with the American Association of Neuroscience Nurses, supported recommendations for the Nursing Care of Patients with Severe TBI (McIlvoy and Meyer 2008). Military data suggest that patients with combat-related severe and penetrating TBI are at higher risk than patients with less severe or non-penetrating injuries for the development of cerebral vasospasm and vascular injury (Armonda et al., 2006).

To assist with management of acute injury in theater, civilian and military experts developed clinical practice guidelines, Evaluation and Management of Mild TBI/Concussion in the Deployed Setting (Defense and Veterans Brain Injury Center, 2008). These guidelines incorporate consideration of the limited resources available in an austere environment, and the co-morbid psychological health (PH) conditions that might be present. The Guidelines provide indications for urgent CT scanning, strategies for symptom management, and instructions for return to duty evaluations. In most cases, patients with mild TBI can be evaluated and treated at the Forward Operating Base for up to 7 days, or up to 30 days at more sophisticated recovery centers.

In late 2009, Concussion Care Centers were established in Afghanistan to provide supervised rest, education, treatment, and recovery for SMs with concussion. Using this model of primary care decreases the stigma of TBI care, any association with PH, and the development of perceptions of chronic illness. For patients not improving in primary care, specialty referrals and management in a dedicated TBI clinic are indicated. Neurocognitive testing done in theater can be compared with the patient's baseline, thereby better informing return to duty decisions. Since 2010, current DoD guidelines have mandated that deployed service members who are in specific, potentially concussive events will undergo standardized evaluation with MACE, which avoids reliance on self-reporting and broadens in-theater screening from symptom-based to incident-based and includes recommendations for a more detailed evaluation of those sustaining recurrent concussions.

To advance care with best practices, a VA/DoD evidence-based workgroup performed a rigorous literature review and developed a Clinical Practice Guideline for the Management of Concussion/Mild TBI (Defense and Veterans Brain Injury Center & Defense Centers of Excellence, 2008). These guidelines focus on the management of those with sub-acute to chronic injury and include an educational component regarding the natural history of concussion and the expectation of recovery.

Clinical and surgical guidelines have been proposed to guide decisions in TBI treatment, as defined by an authoritative examination of current evidence (Maas, Stocchetti, and Bullock, 2008; Brain Trauma Foundation, 2011). Surgical interventions, such as those for subdural and epidural hematomas, are effective (Bullock et al., 2006). Although some consistency is evident in the clinical management of patients with moderate or severe TBI, which is based upon the best available evidence, few of these management guidelines are based on large, well-controlled clinical trials (Maas et al., 2012). Difficulty in conducting

rigorous studies arises because the pathophysiology of TBI is complex and the disruption in brain function rarely occurs in isolation. Additionally, heterogeneity in neuropathology occurs from person to person (*Jennett, Adams, Murray, and Graham, 2001; Adams, Graham, and Jennett, 2001; Maxwell et al., 2004*). For example, despite success in preclinical or smaller clinical studies, more than 20 drugs or other therapies for moderate or severe TBI have not demonstrated a positive effect on outcome in large, multi-center phase III clinical trials. Numerous explanations for explaining this discordance exist, but the heterogeneity of the patient population is one of the most noteworthy contributing factors (*Narayan et al., 2002; Saatman et al., 2008*). Therefore, nearly all of the treatment guidelines are based on smaller studies and case reports, including medical and surgical interventions to attenuate some types of acute neurotraumatic injuries. A neurosurgical intervention to reduce intracranial pressure, decompressive craniectomy, is one example, although this procedure also remains controversial (*Bullock et al., 2006*). The Brain Trauma Foundation (BTF) has developed guidelines for the management of severe TBI based on the best available evidence (Brain Trauma Foundation, 2007); improvements in outcomes have been reported in an international study when these guidelines were followed (*Arabi et al., 2010*). Similarly, definitive studies to demonstrate the effectiveness of cognitive therapy and other types of rehabilitation are lacking, but numerous smaller studies have provided a basis for rehabilitation guidelines for TBI (*Fadyl and McPherson, 2009; Lane-Brown and Tate, 2009; Cicerone et al., 2008; Borg et al., 2004*). Large-scale comparative effectiveness research that leverages the variability in practice patterns also has been proposed as a means of identifying those treatments associated with better outcome (*Maas et al., 2011*). Despite the lack of class I clinical trials, implementation of guidelines (e.g., the BTF's guidelines) has resulted in improved TBI outcomes (*Bulger et al., 2002; Clayton, Nelson, and Manara, 2004; Elf, Nilsson, and Enblad, 2002; Fakhry, Trask, Waller, and Watts, 2004; Patel et al., 2002; Stein Georgoff, Meghan, Mirza, and El Falaky, 2010; Suarez et al., 2004; Varelas et al., 2006*).

Long-Term Care

Improving continuity of quality care and service delivery along with inter-service, interagency, intergovernmental, and public and private collaboration for care are all critical to the success of long-term care. In addition, management, transition, and associated training, tracking, and accountability for this care are essential for administering such programs. Work in this area includes establishing multiple reforms (e.g., implementing uniform training for recovery coordinators and medical and non-medical care/case managers, establishing a single tracking system, and providing a comprehensive recovery plan for the seriously injured).

The joint Federal Recovery Coordination Program (FRCP) trains and deploys Federal Recovery Coordinators (FRCs) to support medical and non-medical care/case managers in the care, management, and transition of seriously wounded and ill SMs, veterans, and their families.

For veterans and active duty personnel with any loss of vision, blurred vision, or difficulty reading or squinting, VA provides comprehensive vision rehabilitation services—often while the injured SM is still a patient at a military treatment facility. One hundred and sixty four Visual Impairment Service Team (VIST) Coordinators provide lifetime case

management for all legally blind veterans and all OEF/OIF patients with visual impairments. Additionally, 75 Blind Rehabilitation Outpatient Specialists (BROS) with the VA provide blind rehabilitation training to patients who are unable to travel to a center for the blind. These BROS are certified in low-vision rehabilitation and orientation and mobility training and work closely with neuro-ophthalmologists and optometrists who specialize in low vision problems.

VA's Vet Centers

VA's Vet Centers, operated by the Readjustment Counseling Service in the VHA, provide community outreach and professional readjustment counseling services for war-related psychological readjustment problems (*England and Mansfield, 2008*). Vet Centers treat and address PTSD, family relationship problems, lack of adequate employment, lack of educational achievement, social alienation and lack of career goals, homelessness and lack of adequate resources, and other psychological problems such as depression or substance use disorder. They are community-based facilities, located outside of the larger VA medical centers in convenient easy-to-access settings; they embrace a mission that goes beyond medical care in providing a holistic mix of services. Vet Centers offer an alternative to traditional mental health care that helps many combat veterans overcome the stigma and fear related to accessing professional assistance for military-related problems. Eligibility for Vet Center services is based on military service in a combat theater and does not require a veteran to complete the enrollment process.

VA expanded the number of its Vet Centers nationally from 209 in 2007 to 300 facilities and 70 mobile units in 2012.

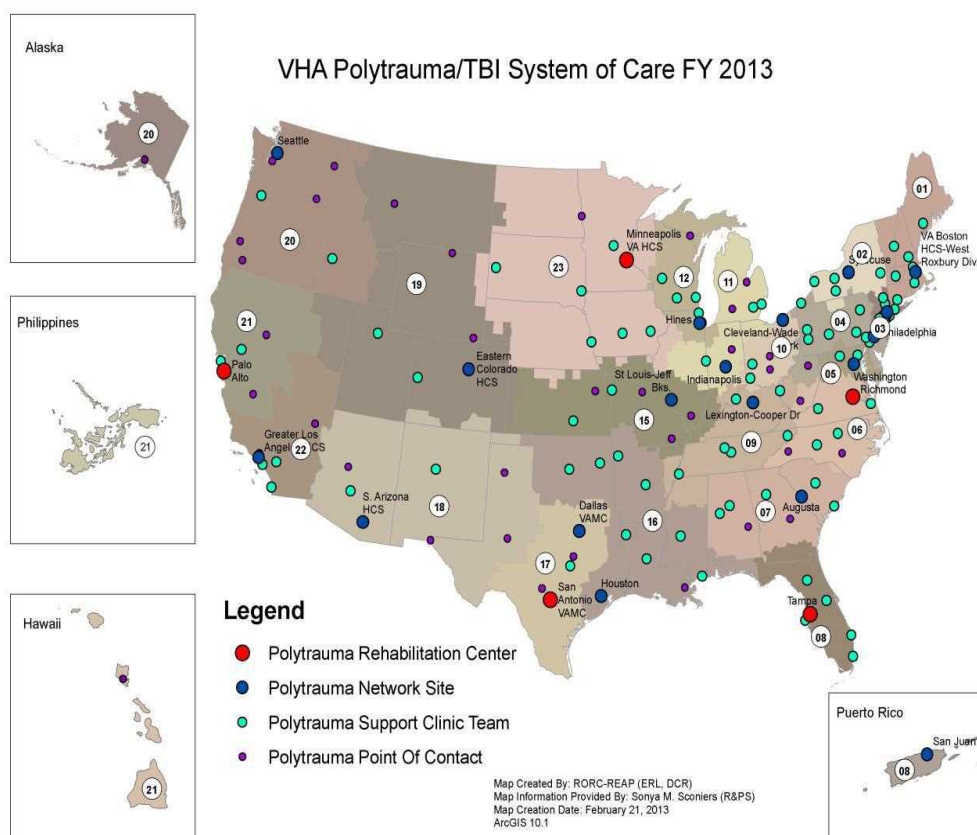
Since the beginning of OEF/OIF, the focus of the Vet Center program has been on outreach at military demobilization, at National Guard and Reserve sites, and at community locations that feature high concentrations of veterans and family members. To promote early intervention, the Vet Center program hired 100 OEF and OIF veteran returnees to provide outreach services to their fellow combatants. These fellow veteran outreach specialists are effective in mitigating veterans' stigma and establishing immediate rapport. For example, from early in FY 2003 through the end of FY 2007, Vet Centers have provided readjustment services to approximately 268,987 veteran returnees from OEF and OIF. Of this total, more than 205,481 veterans were provided outreach services, and 63,506 were provided clinical readjustment services by mental health providers in Vet Centers such as individual and group counseling for veterans and their families, substance abuse assessment and referral, and screening and referral for medical issues.

VA's Polytrauma System of Care

In its polytrauma system of care (that is, treatment for multiple complex injuries from the same event— for example, amputations, burns, hearing loss, and PTSD), the VA offers comprehensive primary and specialty health care to veterans and seriously injured active-duty service members and is an acknowledged national leader in providing specialty care in the

treatment and rehabilitation of TBI and polytrauma (Feeley 2007). Since 1992, the VA has maintained four specialized TBI Centers that have served as the primary VHA receiving facilities for military treatment facilities seeking specialized care for brain injuries and complex polytrauma. In 2005, the VA established its Polytrauma System of Care, leveraging and enhancing the existing expertise at these TBI centers to meet the needs of seriously injured veterans and active duty service members from operations in Iraq, Afghanistan, and elsewhere.

The mission of the Polytrauma System of Care is to provide the highest quality of medical, rehabilitation, and support services for veterans and active duty service members injured in the service. This integrated nationwide system of care has been designed to provide access to life-long rehabilitation care for veterans and active duty service members recovering from polytrauma and TBI. The polytrauma system of care is composed of four component layers as described below and shown on this map.



Component 1: Regional. The five flagship facilities of the Polytrauma System of Care are Polytrauma/ TBI Rehabilitation Centers (PRC) in Minneapolis, MN; Palo Alto, CA; Richmond, VA; Tampa, FL, and San Antonio, TX. These centers serve as hubs for acute medical and rehabilitation care, research, and education related to polytrauma and TBI. The specialized services provided at each PRC include comprehensive acute rehabilitation care for complex and severe polytraumatic injuries, emerging consciousness programs, outpatient programs, and residential transitional rehabilitation programs. Clinical care specific to TBI is

provided by a staff of rehabilitation specialists and medical consultants in such fields as physiatry (doctors who specialize in physical medicine and rehabilitation), rehabilitation nursing, neuropsychology, psychology, speech-language pathology, occupational therapy, physical therapy, social work, therapeutic recreation, prosthetics, and rehabilitation for blind SMs.

One of the newest programs within the PRCs is the treatment program for patients with severe disorders of consciousness. Provision of rehabilitation services for patients who are minimally conscious or minimally responsive is based on expert opinion rather than scientific evidence. Cornerstones of treatment for patients with severe disorders of consciousness include aggressive medical care to treat potential reversible causes of impaired consciousness (infection, sedation, hormone imbalance); prevention of complications (contracture, pressure sores, malnutrition); family support and education. Additional interventions often include structured sensory stimulation and trials with medications to increase responsiveness. The Disorders of Consciousness Scale is used to monitor response to treatment.

In 2007, staffing for the PRC teams was increased at each center in response to increased demands of patient workload, coordination of care, and support for family caregivers. The PRCs have affiliations and collaborative relationships with academic medical centers, enabling a substantial number of PRC's clinical providers to share VA and affiliated positions in training and medical rehabilitation. The inpatient rehabilitation programs at the PRCs maintain accreditation by the Commission on Accreditation of Rehabilitation Facilities (CARF) for both Traumatic Brain Injury and Comprehensive Rehabilitation.

Component 2: Network. The Polytrauma/TBI Network Sites (PNS), designated in December 2005, represent the second echelon within the Polytrauma System of Care, with one PNS located within each of VA's 21 Veterans Integrated Service Networks (VISN). The PNS provides key components of post-acute rehabilitation care for persons with polytrauma/TBI, including, but not limited to inpatient and outpatient rehabilitation and day treatment programs. The PNS is responsible for coordinating access to VA and non-VA services across the VISN to meet the needs of patients recovering from polytrauma and TBI and their families. The PNS consults, whenever necessary, with the PRC.

Components 3 and 4: Facility. In March 2007, the Polytrauma System of Care network was expanded to include two new components of care: Polytrauma Support Clinic Teams (PSCT) and Polytrauma Points of Contact. With their geographical distribution across the VA, 85 PSCTs facilitate access to specialized rehabilitation services for veterans and active duty SMs at locations closer to their home communities. These interdisciplinary teams manage the care of patients with stable treatment plans, provide regular follow-up visits, respond to new medical and psychosocial problems as they emerge, and consult with their affiliated PNS or PRC when more specialized services are required.

The remaining 40 VA medical centers have an identified Polytrauma Point of Contact who manages consultations for patients with polytrauma and TBI and assists with referrals. The Polytrauma Telehealth Network links the PRC and PNS through state-of-the-art multipoint videoconferencing capabilities. This Network also ensures that polytrauma and TBI expertise are available throughout the system, that care is provided at locations and times most accessible to patients, and that clinical activities include remote consultations and evaluations of patients and education for providers and families.

Another model for using telehealth technology and the sharing of electronic health information along the continuum of care is the rural networks of non-VA health facilities

currently funded by the Health Resources and Services Administration's (HRSA's) Rural Veteran's Health Access Program (RVHAP). A key feature of these networks is collaboration between rural healthcare providers and the Department of Veteran's Affairs. These networks are intended to help eligible entities coordinate innovative approaches, collaborative networks, and virtual linkages to increase the delivery of mental health and other healthcare services to meet the needs of veterans of Operation Iraqi Freedom and Operation Enduring Freedom that reside in remote rural areas.

Coordination and Transition of Care. Care management across the entire continuum is a critical function in the Polytrauma System of Care to ensure lifelong coordination of services for patients recovering from polytrauma and TBI. Consistent, comprehensive procedures and processes have been put in place to ensure transition of patients from military treatment facilities to VA care at the appropriate time, under optimal conditions of safety and convenience for patients and their families. At the direction of the VA's Secretary, 100 Transition Patient Advocates have been recruited nationwide. In addition, the VA assigns a care manager to every admitted patient to coordinate services, address emerging medical, psychosocial, or rehabilitation needs, and provide patient and family advocacy.

To facilitate the continuity of medical care, the PRC receives advanced notice of potential admissions, initiates a pre-transfer review, and follows the clinical progress until the patient is ready for transfer. In addition to record review, clinician-to-clinician communication occurs to allow additional transfer of information and resolution of any outstanding questions.

The DoD and VA also have made substantial progress sharing available electronic health information to further coordinate care. DoD is currently transferring DoD medical digital images and electronically scanned inpatient health records to the VA polytrauma centers from Walter Reed National Military Medical Center, and Brooke Army Medical Center. VA hopes to add the capability to provide this data bi-directionally to support any patients returning to DoD for further care. Additionally, VA and DoD are supporting the secure direct connection of authorized providers at VA polytrauma centers into the health-information systems at Walter Reed National Military Medical Center.

In addition, the Department of Health and Human Services Office of the National Coordinator and the Under Secretary for Health of the Veteran's Health Administration (VHA) have established a Memorandum of Understanding to examine ways to leverage existing resources to develop potential pilot sites for Health Information Exchange between rural providers and the VHA. The VHA Office of Rural Health continues to partner with stakeholders to identify and improve technology adoption in order to expand services to the 3.4 million Veterans that live in highly rural areas.

Psychosocial support for families of injured service members is paramount as decisions are made to transition from the acute care setting of a military treatment facility to a rehabilitation setting. This encompasses psychological support, education about rehabilitation, the next setting of care, and information about benefits and military processes and procedures. VA social worker or nurse liaisons are located at 10 military treatment facilities, including Walter Reed National Military Medical Center. In addition, a Certified Rehabilitation Registered Nurse is available to provide education to the family on TBI, the rehabilitation process, and the PRCs. The Admission Case Manager from the PRC maintains personal contact with the family before transfer to provide additional support and further information about the expected care plan. VA also has benefit liaisons located at military

treatment facilities that refer large numbers of patients to the VA to provide an early briefing on the VA services and benefits available to patients and families.

Lastly, the transition from the PRC to the VA Medical Center in or near the home community must ensure that the treatment plan is maintained. Records for VA medical care are readily available through remote access across the VA system. Follow-up appointments are made before discharge, and the transferring practitioners are readily available for personal contact with the receiving provider to ensure full communication. Care managers at the PNS and the home VA medical center provide ongoing support and problem resolution in the home community, while continually assessing for new and emerging concerns. Finally, each PRC team assesses the expected needs at discharge for transportation, equipment, home modifications, other such needs, and makes arrangements for assessed needs.

Recent studies indicate that the number of medical, physical and psychological injuries that are occurring as a result of combat injury are resulting in a greater functional burden on SM's with the need for integrated, interdisciplinary care, longer acute and inpatient rehabilitation stays and greater health care costs (*Sayer et al., 2008; Schneiderman, Braver, and Kang, 2008*). One of these studies examined long-term treatment in four VA acute PRCs for polytrauma and other combat injuries acquired during the first 4 years of the Global War on Terror (i.e., between October 2001 and January 2006) (*Sayer et al., 2008*). In this study of 188 persons, 56% had blast-related combat injuries; 53% had closed head injuries and 44% had penetrating head injuries; and 56% had craniectomy or craniotomy before PRC admission. Additionally, those with TBI-related blast injury had a significantly greater number of multiple injuries. After rehabilitation, 64% were discharged to home or military bases, 27% to other inpatient service or military treatment facilities, 6% to residential day programs, and 3% to nursing homes. The other was a recent cross-sectional study of veterans following deployment to OEF/OIF examined prevalence of mild TBI and PTSD. In the population surveyed, approximately 12% of 2,235 respondents reported history consistent with mild TBI, and 11% for PTSD (*Schneiderman et al., 2008*).

Care in the Civilian Health System

Transporting severely injured patients directly to the highest level of trauma care (Level I or II trauma centers) has been shown to lower mortality (*Sampalis et al, 1997; Nirula, Maier, Moore, Sperry, and Gentilello, 2010*). Trauma centers demonstrate better adherence to the American Association of Neurologic Surgeons Guidelines for the Management of Severe Traumatic Brain Injury, including immediately available CT scanning, prompt neurosurgical care, and the ability to monitor intracranial pressure (ICP), and treatment of intracranial hypertension (*Hesdorffer and Ghajar, 2007; Fakhry et al, 2004*).

CT scanning is used emergently to identify intracranial bleeding, contusion, or consequences of penetrating injury. These patients might be unconscious on arrival and require stabilization, mechanical ventilation, and intensive care services. In addition, management of co-occurring injuries and meticulous medical care is required to prevent deterioration and the many potential complications, such as infections, acute respiratory distress syndrome, disseminated intravascular coagulation, brain swelling, and multi-organ failure. Monitoring of intracranial pressure is common, and algorithms are in use for lowering

raised intracranial pressure to preserve cerebral blood flow and prevent pressure-related distortion of the brain (herniation syndromes). Intracranial bleeding or hematoma might also require neurosurgical intervention.

Guidelines and Best Practices in Civilian Healthcare Systems

Professional medical societies developed detailed best practice guidelines for the management of severe TBI as shown in Table 3.

Table 3. Guidelines for the management of TBI

Guideline	Source
Guidelines for prehospital management of severe TBI second edition	Badjatia et al., 2006
Guidelines for the management of severe TBI third edition	Brain Trauma Foundation., 2007
Guidelines for the surgical management of severe TBI	Bullock et al., 2006
Guidelines for the acute medical management of severe TBI in infants, children and adolescents second edition	Kochanek et al., 2012
Guidelines for field management of combat-related head trauma 2005	Knuth et al., 2005
The Clinical Policy on Neuroimaging and Decision making in Adult Mild Traumatic Brain Injury in the Acute Setting	American College of Emergency Physicians and CDC (Jagoda et al., 2008)

Although guidelines for neuroimaging and decision making in adult mild TBI exist (Jagoda et al., 2008), there is variability in the use of neuroimaging, decision to admit to hospital or discharge to home, and any follow-up planning (*Miele and Bailes, 2009; Timmons and Winestone, 2009; Heller and Mass, 2009*). Focus is usually on identifying those who are at risk for deterioration, usually caused by post-traumatic intracranial hemorrhage. Many patients with mild TBI are discharged from emergency departments to their home with instructions to return should symptoms worsen. If all goes well, follow-up is usually first suggested with the patient's primary physician but often this follow-up does not occur (*Sosin et al., 1996*). U.S federal agencies, international agencies, and professional organizations have developed best practice guidelines for the management of TBI. For example, the VA and DoD have developed joint clinical practice guidelines for the management of concussion/mild TBI (*U.S. Dept. of Veterans Affairs & U.S. Dept. of Defense, 2009*); the American Academy of Neurology has developed guidelines for neurologists regarding the management of concussion in sports (*American Academy of Neurology, 1997*); the CDC, convening an expert panel, developed guidelines for coaches on how reduce the numbers of mild TBI and how to recognize cases of mild TBI (http://www.cdc.gov/concussion/HeadsUp/online_training.htm); and an expert consensus group from Canada has developed clinical guidelines for mild TBI and persistent symptoms (*Marshall, Bayley, McCullagh, Velikonja, and Berrigan, 2012*). Certain states also have enacted legislation requiring student athletes who sustain a concussion to be seen by a medical expert before they can return to play (*National Conference of State Legislatures, 2013*).

Rehabilitation

A 1998 NIH Consensus Conference on TBI concluded that some evidence supported the use of rehabilitation strategies for TBI, but definitive evidence from large well-controlled clinical trials was lacking. Despite more than 10 years of effort, clinical practice for the rehabilitation of patients with TBI has not advanced substantially. Only limited interventions have demonstrated effectiveness in improving outcomes for patients in rigorous controlled studies (*Vanderploeg et al., 2008; Cicerone et al., 2005; Levine et al., 2000*). One study actually reported that the overall benefit of inpatient cognitive rehabilitation for patients with moderate to severe TBI was similar to that of in-home rehabilitation (*Salazar et al., 2000*). Thus, the translation to wide-scale clinical adoption is still premature. In the absence of strong evidence, and faced with pressing clinical needs, providers have adopted practices based upon consensus and clinical experience (*Fadyl and McPherson, 2009; Lane-Brown and Tate, 2009; Cicerone et al., 2008*). The challenge to develop effective rehabilitation strategies for TBI patients overlaps with those described earlier in this report regarding acute treatment. At the same time, the progress in contemporary neuroscience, imaging, and cell biology is noteworthy—it will ultimately provide the foundation for effective remediation of TBI.

PROGNOSIS AND RECOVERY

Proper identification of the long-term and lifelong medical signs and symptoms of TBI are critical to the study of the epidemiology of TBI-related disability, including the identification of cases of TBI; this however, poses some challenges. Recovery after severe TBI can be protracted. Patients might partially or completely improve after spending weeks, months, or years in states devoid of purposeful behavior; patients might recover their ability to speak, walk, and make new memories. The ability to predict which TBI survivors will recover functional independence in society is poor (*Mushkudiani et al., 2007*).

Moreover, what prompts recovery and the speed, duration, and extent of recovery is not well understood. Predicting the future ability of the severe TBI survivor to return to the workforce is even more difficult. Meticulous medical care in the rehabilitation setting enables recovery, but the role of specific rehabilitation strategies in accelerating recovery after the various forms of TBI is unknown. The majority of scientific investigations of recovery after brain injury focus on focal brain injury, especially stroke. Whether or not the lessons learned from these studies can be extrapolated to TBI is not clear. Intense study of the biology that underlies the recovery processes associated with functional recovery after TBI is warranted.

Gaps in knowledge severely complicate surveillance methodologies and processes to define the burden of illness related to previous TBI. Most difficult is identifying those persons who develop a post-concussive syndrome after a mild TBI. This is further complicated in persons with comorbidities, such as depression, personality disorder, or substance abuse, which can cause some of the symptoms seen in post-concussive syndrome. Another challenge for surveillance of TBI is the lack of a working definition of “full recovery” vs. “persistent disability,” which can occur in persons following TBI.

Recovery from TBI

Recovery after TBI is highly variable (Moppett, 2007) and depends on many factors. Outcomes and recovery can be measured in several forms and aspects. The 25 most common measures used in the field of brain-injury rehabilitation and assessment have been compiled by the Center for Outcome Measurement in Brain Injury (COMBI). COMBI is a collaborative project of 16 brain-injury facilities or centers, most of them Traumatic Brain Injury Model Systems (TBIMS) through grants funded by the Department of Education's National Institute on Disability and Rehabilitation Research (U.S. Dept. of Education, 2012). The most important factor appears to be the severity of the injury (Schretlen and Shapiro, 2003). Milder injuries, which are present in 80% – 90% of TBI survivors, are associated with better outcomes than those with more severe injuries. Many people classified as having a mild TBI might experience complete resolution of symptoms and return to work and other pre-injury activities. Return to work is considered an important metric of recovery, although it is inadequate for children and retired adults and it is important to recognize that many adults with disabilities successfully participate in the workplace. Estimates indicate that 10% – 50% of persons with a mild TBI experience long-term health issues such as persistent headache, difficulty with memory or concentration, or mood changes (Moppett, 2007; Thornhill et al., 2000). Persons who sustain more severe injuries have worse outcomes, with only 20% making a good recovery, as assessed by the Glasgow Outcome Scale (Thornhill et al., 2000). The course of recovery is also faster following mild TBI, occurring largely within 1 – 3 months, compared with 2 or more years in more severely injured groups. In rare cases, and for unknown physiological reasons, recovery from a persistent vegetative state or minimally conscious state can occur years after the TBI (Schiff et al., 2007; Berube et al., 2006). The ability to predict which severe TBI survivors will recover functional independence is poor (Mushkudiani et al., 2007).

A retrospective analysis of data from clinical trials that tested treatments in adults with severe TBI revealed that increasing age was strongly predictive of worse outcomes (Mushkudiani et al., 2007). Race and education also might affect outcomes. Studies have determined that African Americans and Asians with a history of TBI have lower odds of being employed up to 5 years post injury compared with whites who have a history of TBI. (Gary et al., 2009; Berry, Ley, Mirocha, and Salim, 2010). In 1998, another report indicated that persons who were employed at the time of injury, had higher educational levels, and less disability from their injuries were most likely to be employed at 1–3 years after their injury (Gollaher 1998). The reasons for these findings need to be explored further. Some studies suggest that women have worse outcomes following TBI (Slewa-Younan van den Berg, Baguley, Nott, and Cameron, 2009), whereas others report no gender difference (Mushkudiani et al., 2007). Further complicating this picture are animal studies that have demonstrated better recovery in females (Stein, 2004).

Research has demonstrated that the type of injury and certain complications might influence the acute and long-term consequences of TBI. Penetrating injuries have worse outcomes than closed injuries (Wertheimer, Hanks, and Hasenau, 2008). Comorbidities and secondary injuries, such as low blood pressure that might result from severe blood and fluid loss from other injuries, negatively affect outcomes after TBI (Butcher et al., 2007). Genetic factors also might play a role. Certain reports indicate that those persons who have a gene

variant associated with Alzheimer's disease, apolipoprotein E4, also are more likely to have poorer outcomes following TBI (*Nathoo Chetty, van Dellen, and Barnett, 2003; Wilson and Montgomery, 2007*). The majority of experimental preclinical investigations of recovery after brain injury use models of focal brain injury. Clarifying whether this information can be extrapolated to diffuse forms of TBI such as diffuse axonal injury and edema is critical. Intense study of the biology that underlies the recovery processes associated with functional recovery after TBI is warranted.

Post-Concussive Syndrome (PCS)

PCS is a term used to describe disabling symptoms following a neurotraumatic event even when no intracranial pathology is detected with imaging (*Bigler, 2008*). At least two major hypotheses exist regarding the neural substrate for PCS. One is that PCS is caused by diffuse axonal injury, which results in a loss of connectivity between regions of the brain and subsequent behavioral alterations (*Smith, Meaney, and Shull, 2003; Bazarian et al., 2007; Gold and Lipton, 2008*). Diffuse axonal injury is not yet reliably detected with CT scans or other neuroimaging tools, but rapid progress is being made in this area. DTI appears to be a promising diagnostic tool for diffuse axonal injury (*Inglese et al., 2005; Sharp and Ham, 2011*).

A second hypothesis is that persistent metabolic alterations in injured, but not lethally injured, brain cells result in neuronal dysfunction and subsequent behavioral impairments (*Marcoux et al., 2008*). Metabolic alterations following TBI have been reported using sophisticated imaging tools, such as SPECT, PET, and functional MRI, but these methods lack accepted validation for routine clinical use. These hypotheses might both be correct, occurring in separate subsets of persons with TBI. These processes also might both be linked to one underlying mechanism of injury. For example, that metabolic alterations in grey matter are caused by reduced neuronal activity secondary to a loss of connectivity from diffuse axonal injury might be possible.

A better understanding of the pathophysiology of PCS and mild TBI and the development and validation of more sensitive imaging tools is a priority for TBI research. Although many persons seek medical attention immediately or shortly after a TBI, diagnosis can occur at later points in time. Other potential (not yet validated) diagnostic tools for TBI include electroencephalography (EEG); near infrared spectroscopy (NIRS); sensory tests for vision, hearing, and balance, and cognitive and motor assessments (*Suchoff et al., 2008; Arenth, Ricker, and Schultheis, 2007; Pickett, Radfar-Baublitz, McDonald, Walker, and Cifu, 2007*).

Posttraumatic Stress Disorder (PTSD)

PTSD is defined by the DSM-IV criteria as a syndrome occurring in response to a stressor that was a serious threat and the person's response to that threat includes intense fear, helplessness, or horror (*American Psychiatric Association, 2000*). Although PTSD symptoms have been reported in patients with moderate and severe TBI, preliminary data from DoD suggests that TBI patients who have lost consciousness tend not to acquire this condition.

Persons with LOC resulting from TBI and no memory for the traumatic event might not experience the PTSD-like response to the trauma. Similarly, persons with PCS infrequently recall the event or have persistent avoidance of stimuli associated with the trauma. The symptoms of PCS and the PTSD symptom cluster, called hyper-arousal symptoms, tend to overlap. Symptoms such as irritability or outbursts of anger, concentration difficulties, and sleep disturbances occur in both PCS and PTSD and are included in the DSM-IV criteria for PTSD (*American Psychiatric Association, 2000*). They also occur in various physical and psychological disorders. Hypervigilance and excessive startle response are included in the hyper-arousal symptom cluster for PTSD but are not common in PCS. Symptoms common to PTSD appear to occur in greater proportions in those with mild TBI compared with other injuries (*Hoge et al., 2008*). In a study of 2,525 soldiers returning from OEF/OIF, headache was found to be the only symptom with strong association to mild TBI alone (*Hoge et al., 2008*). The approximately one-third of SMs with mild TBI who are also diagnosed with PTSD fare worse on neurocognitive tests of executive functioning and processing speeds than those diagnosed only with mild TBI (*Nelson, Yoash-Gantz, Pickett, and Campbell, 2009; Hoge et al., 2008; Brenner et al., 2009*).

Long-Term Health Outcomes or Disability

The list of neurologic and other problems associated with TBI is long. Cognitive deficits, such as memory impairments, are hallmarks of TBI. Tasks involving complex cognition, including executive function requiring attention, judgment and insight, are particularly problematic for people with TBI, whereas simpler cognitive tasks such as keeping track of daily responsibilities or appointments might not reveal deficits (*Silver, McAllister, and Arciniegas, 2009*).

Neuropsychiatric disorders, including depression, anxiety, PTSD, suicidal tendencies, disinhibition, and substance abuse, have been reported following TBI (*Silver et al., 2009; Belanger et al., 2011*). These neuropsychiatric and emotional disorders might create the most serious challenges to returning to work or other pre-injury activities and to community reintegration. Posttraumatic seizures are common after penetrating head injury or traumatic intracranial hemorrhage; TBI is the largest known risk factor for epilepsy (*Temkin, 2009*).

TBI also can produce movement and sensory disorders that disturb balance, vision, perception, and hearing (*Katz, Zasler, and Zafonte, 2007*). Headaches, pain, sleep disturbances, and fatigue are other frequent symptoms following TBI (*Formisano, Bivona, Catani, D'Ippolito, and Buzzi, 2009; Nampiaparampil, 2008; Rao et al., 2008*). The association of TBI with later development of Alzheimer's disease or chronic traumatic encephalopathy is the subject of continued study.

On December 10, 2012, VA published a proposed rule to amend its adjudication regulations concerning service connection for secondary illnesses associated with TBI. The proposed amendment is in response to a report of the National Academy of Sciences, Institute of Medicine (IOM), *Gulf War and Health, Volume 7: Long-Term Consequences of Traumatic Brain Injury*. The effect of this proposal would be to establish that if a veteran who has a service-connected TBI also has one of five diagnosable illnesses, then that illness will be

considered service connected as secondary to the TBI, which may provide additional benefits to the veteran.

Specifically, VA's proposed regulation states:

- (d) Traumatic brain injury. (1) In a veteran who has a service-connected traumatic brain injury, the following shall be held to be the proximate result of the service-connected traumatic brain injury (TBI), in the absence of clear evidence to the contrary:
 - (i) Parkinsonism following moderate or severe TBI;
 - (ii) Unprovoked seizures following moderate or severe TBI;
 - (iii) Dementias (presenile dementia of the Alzheimer type and post-traumatic dementia) if manifest within 15 years following moderate or severe TBI;
 - (iv) Depression, if manifest within 3 years of moderate or severe TBI, or within 12 months of mild TBI; or
 - (v) Diseases of hormone deficiency that result from hypothalamo-pituitary changes if manifest within 12 months of moderate or severe TBI.

VA received over 200 public comments on the proposed rule and is now preparing the final rule for publication.

Risk of Neurodegenerative Disease Following TBI

Epidemiologic evidence indicates that synergy exists between TBI and permanent neurodegeneration. Longitudinal MRI-based studies have demonstrated brain atrophy occurring in the months to years after TBI (*Ross, 2011*). Contradictory findings regarding the relationship between TBI and Alzheimer's disease exist (*Van Den Heuvel et al. 2007*). Evidence suggests that risk for dementia is increased two to four fold after moderate or severe TBI, but risk following mild TBI is unclear (*Shively, Scher, Perl, and Diaz-Arrastia, 2012*).

Additionally, evidence indicates that repetitive TBI can cause a unique neurodegenerative disorder first reported in boxers and called *dementia pugilistica* (*Martland, 1928*). Now termed chronic traumatic encephalopathy (CTE), this disorder is characterized by the aggregation of the microtubule-associated protein called tau in nerve cells. This is the same protein that aggregates inside dying neurons in Alzheimer's disease and in the brains of persons with a tau gene variant that causes fronto-temporal dementia. Some studies demonstrate that tau aggregation, once started, has the ability to spread from one nerve cell to another; this could explain how an initial focal injury could lead to widespread damage over time (*de Calignon et al. 2012*). The genetic variant apolipoprotein E4, a known risk factor for Alzheimer's disease, has been associated with poorer outcomes after head injury (*Nathoo et al., 2003*) and in some studies with increased risk for the later development of Alzheimer's disease (*Graham et al., 2002; Luukinen et al., 2005; Rabadi and Jordan, 2001; Jordan et al., 1997*). However, this association has not been found in all studies (*Jellinger, 2004*). More recently, CTE has been described in athletes who participated in contact sports and in 21 veterans (86% of whom were also athletes) (*Goldstein et al. 2012; McKee et al., 2009*). Sharing symptoms with PTSD, patients who died with CTE have been described to present

with poor concentration and memory, irritability, depression, and suicidality. The extent of the burden of CTE in service members exposed to TBI is unknown.

SURVEILLANCE

Case Definition Background

Public health surveillance is the ongoing, systematic collection, analysis, interpretation, and dissemination of data on a health-related event, such as TBI, for use in reducing morbidity and mortality and to improve health (CDC, 2001). Surveillance is a labor-intensive process and requires adequate funding, manpower, and, very frequently, a solid public health infrastructure to be successful and sustainable (CDC, 2001). For the purposes of this report and based on accepted requirements for identifying cases for surveillance purposes, CDC and NIH, in consultation with the Secretary of Defense and the Secretary of Veterans Affairs, have defined a case of “traumatic brain injury (TBI) in people formerly in the military” as any combat or non-combat TBI that occurred in a person while serving in the U.S. military (from now on termed *military service-related TBI*) since the beginning of military operations in the first Gulf war on January 17, 1990 (Atkinson, 1993). This time-linked case inclusion criterion can be modified if additional resources become available (i.e., supplementing or changing existing systems).

Surveillance data can be used to estimate the magnitude of a public health problem, understand the natural history of a condition, detect epidemics, document the distribution and spread of a health event, test hypotheses about etiologies, evaluate control measures and develop and implement prevention interventions (Teutsch, 2000).

Standard clinical and surveillance case definitions assist in identifying new cases of TBI and cases with persistent symptoms, impairments, functional limitations, or disabilities resulting from this condition. Historically, each of the departments and agencies involved in this report has used agency/department- specific standard TBI definitions to meet their mandates and needs, but for public health surveillance, the definition described above is used. TBI definitions used by clinicians and investigators may vary, especially for cases of mild TBI (National Center for Injury Prevention and Control, 2003; Culotta, Sementilli, Gerold, and Watts, 1996). The WHO Collaborative Center Task Force on mild TBI published a comprehensive review of definitions. They found that 62% of the definitions reviewed incorporated GCS scores, but differing ranges of scores (13–15, 14–15, or only 15) was evident. LOC or amnesia was required in some definitions, but the duration of LOC varied. The WHO task force concluded that surveillance would benefit from a common definition and collaborated with CDC and other agencies and groups to develop one (Carroll, Cassidy, Holm, Kraus, and Coronado, 2004).

In 2009, TBI researchers from CDC/NCIPC, NIH, DoD, VA, and other federal and nonfederal partners recommended standardized clinical and surveillance case definitions and data elements for TBI research (National Institute for Neurological Disorders and Stroke, 2013). Although certain evidence-based definitions are still under revision due to the paucity of research, their use by all federal agencies and partners might allow better TBI-related research and comparability of data collected in the United States.

Although CDC, NIH, DoD, and VA agree on a common clinical definition for TBI, different perspectives are evident among CDC, Centers for Medicare and Medicaid Services (CMS), NIH, VA, and DoD, and other stakeholder groups, on how to code multiple clinical manifestations of this condition with codes of the International Classification of Diseases (ICD). CDC, NIH, DoD, and VA believe that ongoing interaction and discussion is foundational to advancing TBI-related epidemiologic and clinical research. As more is learned about the natural course of TBI, CDC, NIH, DoD, and VA have committed to continue their collaborations and to extend that to other public and private sector stakeholders and partners to improve and standardize TBI-related definitions (for clinical and epidemiologic purposes), which will be used in all federally funded TBI research. As such, codes of the ICD-9-CM (to identify TBI survivors), ICD-10 (to identify TBI deaths) and the future ICD-10-CM (to identify TBI survivors) classifications will be evaluated continuously. This evaluation process will improve identification of cases of TBI when analyzing ICD-coded administrative or vital statistics databases in the United States. The agencies and partners are committed to this collaborative work that will improve TBI coding and classification, while adhering to structure and conventions of the ICD.

Conceptual and Operational Definitions

To properly and accurately identify patients with TBI, clinicians, researchers, and investigators use conceptual and operational definitions.

A **conceptual case definition** provides criteria to identify a case of TBI for surveillance purposes based on selected clinical signs, symptoms, and neuroimaging. This definition is necessary as a reference standard for the evaluation of operational or working definitions of mild TBI used by surveillance systems.

An **operational case definition** provides quantifiable criteria to consistently identify cases of TBI for surveillance purposes when reviewing ICD-coded health-care administrative or vital statistics databases, when abstracting information from medical records, or when analyzing data from surveys and personal interviews. Operational definitions should be designed to approximate the conceptual definition as closely as possible. Operational definitions might be based on clinical symptoms, clinical records (clinical definition) or based on existing diagnostic coding (e.g., those found in death certificates or administrative hospital data bases).

Clinical Case Definition

CDC issued the following clinical case definition for TBI regardless of injury severity in its 1995 publication, *Guidelines for Surveillance of Central Nervous System Injury* (Thurman *et al.*, 1995).

Clinical Case Definition

For surveillance systems using data from clinical records, a case of TBI (craniocerebral trauma) is defined as an occurrence of injury to the head that is documented in a medical record, with one or more of the following conditions attributed to head injury:*

- observed or self-reported decreased level of consciousness,[†]
- amnesia,[‡]

- skull fracture,
- objective neurological or neuropsychological abnormality,§ or
- diagnosed intracranial lesion**

* Injuries to the head might arise from blunt or penetrating trauma or from acceleration-deceleration forces.

† Decreased level of consciousness refers to partial or complete loss of consciousness. This includes states described as less than full mental capacity, stupor, or coma.

‡ Amnesia might include loss of memory for events immediately preceding the injury (retrograde amnesia), for the injury event itself, and for events subsequent to the injury (posttraumatic amnesia).

§ Neurological abnormalities are determined from neurological examination. Examples include abnormalities of motor function, sensory function, or reflexes; abnormalities of speech (aphasia or dysphasia); or seizures acutely following head trauma. Neuropsychological abnormalities are determined from mental status and neuropsychological examinations. Examples include disorders of mental status (such as disorientation, agitation, or confusion) and other changes in cognition, behavior, or personality.

**Examples of diagnosed intracranial lesions include traumatic intracranial hematomas or hemorrhage (epidural, subdural, subarachnoid, or intracerebral), cerebral contusions or lacerations, or penetrating cerebral injuries (e.g., gunshot wounds). The diagnosis of such intracranial lesions is usually confirmed with a CT or MRI brain scan or by other neurodiagnostic procedures.

The clinical definition of TBI excludes the following:

- lacerations or contusions of the face, eye, ear, or scalp, without other criteria listed above
- fractures of facial bones, without other criteria listed above
- birth trauma
- primary anoxic, inflammatory, infectious, toxic, or metabolic encephalopathies that are not complications of head trauma
- neoplasms
- brain infarction (ischemic stroke) and intracranial hemorrhage (hemorrhagic stroke) without associated trauma

Definition of TBI Based on ICD Diagnostic Coding

The ICD has been used worldwide to code and classify morbidity and mortality data enabling health-care providers to code specific diagnoses. In the United States, some versions of the ICD are used to code and classify mortality data only; since 1999, the tenth version of WHO's ICD-10 (*World Health Organization 1992*) is used to code and classify such data from death certificates.

Clinical modifications (CM) of the ICD have been produced with authorization from WHO to classify morbidity (as opposed to classify mortality). A clinical modification of the

WHO ninth revision of ICD (ICD-9-CM; *Centers for Disease Control and Prevention, 2009*) is being used in the United States to code diagnoses, including those of TBI. To replace ICD-9-CM, a clinical modification of the ICD-10, known as ICD-10-CM, has been developed by CDC/National Center for Health Statistics (NCHS) with input from health-care industry stakeholders; this version will be implemented on October 1, 2014.

TBI Morbidity

Morbidity codes currently in use were last updated in 2001. The ICD-9-CM codes recommended for inclusion in the definition of TBI at this time include the following:

800.0 – 801.9	Fracture of the vault or base of the skull
803.0 – 804.9	Other and unqualified and multiple fractures of the skull
850.0 – 854.1	Intracranial injury, including concussion, contusion, laceration, and hemorrhage
950.1 – 950.3	Injury to the optic chiasm, optic pathways; and visual cortex
959.01	Head injury, unspecified (beginning 10/1/97)
995.55	Shaken Infant Syndrome

Since 2001, additions have been made to ICD-9-CM codes to address emotional and behavioral symptoms of TBI. VA and DoD proposed these additions in response to a request from Congress to address concerns by SMs and veterans who are receiving mental health diagnoses for symptoms of TBI. This is particularly important due to the stigma related to mental health issues as compared to physical injuries. Some of these changes were consistent with ICD and accepted by NCHS. These changes resulted in the inclusion of TBI as a clinical term in ICD-9-CM. VA and DoD also proposed a new code for history of traumatic brain injury (V15.52) and a new code section for signs and symptoms involving emotional state. These new codes allow emotional and behavioral symptoms of TBI and other conditions to be coded without assigning a mental health diagnosis. In addition, VA and DoD have proposed including these codes for several TBI-associated cognitive symptoms.

As the United States starts to replace the current ICD-9-CM coding system with ICD-10-CM, an opportunity exists to improve TBI classification. Federal stakeholders have been concerned regarding the need for a better classification for TBI symptoms using ICD codes as acute or persistent (or chronic) for both epidemiologic and clinical uses. CDC, NIH, DoD, VA, and other federal agencies are reviewing proposed codes of ICD-10-CM classification and making suggestions for changes that would improve TBI reporting in the United States.

Although different perspectives exist among CDC, NIH, DoD, VA and other stakeholders, and because knowledge gaps are apparent regarding the natural course of TBI, these agencies support ongoing interaction and discussion, which is foundational to advancing TBI-related epidemiologic and clinical research. For example, little is known about the pathophysiology and the long-term effects of blast-related TBI. CDC, NIH, DoD, and VA will continue to work together and with other public and private sector stakeholders to 1) standardize all TBI-related definitions to be used in all federally funded TBI research in the United States (*Thurmond et al., 2010; National Institute for Neurological Disorders and Stroke, 2013*) and 2) propose modifications to the ICD-CM that are consistent with the structure and conventions of the classification that will improve identification of cases of TBI in the United States.

TBI Mortality

For TBI Mortality (based on ICD-10 codes). The ICD-10 codes recommended for inclusion in the definition of TBI at this time include the following:

S01.0 – S01.9	Open wound of the head
S02.0, S02.1, S02.3, S02.7 – S02.9	Fracture of skull and facial bones
S04.0	Injury to optic nerve and pathways
S06.0 – S06.9	Intracranial injury
S07.0, S07.1, S07.8, S07.9	Crushing injury of head
S09.7 – S09.9	Other and unspecified injuries of head
T01.0	Open wounds involving head with neck
T02.0	Fractures involving head with neck
T04.0	Crushing injuries involving head with neck
T06.0	Injuries of brain and cranial nerve with injuries of nerves and spinal cord at neck level
T90.1, T90.2, T90.4, T90.5, T90.8, T90.9	Sequelae of injuries of head.

Case Ascertainment by Severity

The use of ICD-9-CM to classify TBI severity is problematic since coding is not consistent with conceptual and clinical definitions for mild, moderate, and severe TBI. This is especially problematic for differentiating mild from moderate TBI. As illustrated by Table 4, persons with LOC 30 minutes to 1 hour would be categorized as mild, rather than moderate since ICD 9-CM, does not differentiate persons with LOC of less than 30 minutes from those with LOC of 30 minutes to 1 hour. Injuries that include brain contusion, hemorrhage, or laceration will be categorized as moderate or severe, depending on LOC and the severity of the focal injury. However, it may not always be possible from ICD-9-CM codes to distinguish between moderate and severe TBI, especially if LOC is not stated. For persons with more than one TBI diagnosis, severity should be consistent with the most severe diagnosis.

Table 4. Stratification of severity by length of time of loss of consciousness

Classification	Mild	Moderate	Severe
DoD/VA Common Definition	0-30 mins	>30 mins and < 24 hrs	>24 hrs
Classification	Brief LOC	Moderate LOC	Prolonged LOC
ICD-9-CM	No LOC; brief <1 hr (30 mins or less, 31 mins to 59 mins)	1 to 24 hrs	>24 hrs
V15.5 DoD/VA Extenders	< 1 hr	1 to 24 hrs	>24 hrs

Source: Department of Veterans Affairs (VA) and Department of Defense (DoD).

Because of these inconsistencies, VA and DoD previously proposed adding synonyms in ICD-9-CM as follows: “mild TBI” for LOC <30 minutes, “moderate TBI” for LOC >30 minutes to <24 hours, and “severe TBI” for LOC > 24 hours. This proposal was intended to

aid clinicians and coders in selecting the correct acute injury code. In the ICD-9-CM review process, the proposals, however, were not supported by stakeholders. VA continues to advocate for a simple revision to ICD-10-CM before the activation in 2014. This revision would eliminate possible coding errors with “concussion” by limiting that section to true concussion (mild TBI, LOC < 30 minutes), and move the remainder of codes in that section to “other intracranial injuries” (S06.89).

DoD V15.5 Code-Related Extenders to Stratify TBI Severity

DoD uses an additional set of internal codes to stratify injury. A series of extenders appended to ICD-9-CM code V15.5 (i.e., personal history of injury) indicate severity based on LOC and to indicate SM's deployment. These extenders are not valid ICD-9-CM codes and are not recognized by other users of the ICD-9-CM classification in the United States. Therefore, any data collected using these codes will be applicable to military settings only. In addition, new V15.5 codes were proposed and implemented (e.g., code V15.52 - History of TBI, was implemented on October 1, 2009).

Mild TBI

In 2003, a CDC Definitions Subgroup of the CDC Workgroup on mild TBI produced and recommended a definition for mild TBI (CDC, 2003). This definition for mild TBI, however, does not categorize other levels of TBI severity (i.e., moderate or severe) and might not be well suited for surveillance of mild TBI not treated in hospital or Emergency Department (ED) settings. Based on this definition (CDC, 2003), the CDC mild TBI Working Group recommended the following three operational or working definitions for case ascertainment based on 1) interviews and surveys; 2) health-care administrative data sets; and 3) clinical records.

Interview/Survey

Mild TBI is recognized when a person or proxy surveyed or interviewed affirms the occurrence, in the period under surveillance, of a nonfatal injury to the head that is accompanied by the following conditions:

- Criteria consistent with the recommended conceptual case definition (occurrence of injury to the head resulting from blunt trauma or acceleration or deceleration forces that result in any period of observed or self-reported transient confusion, disorientation, impaired consciousness, and amnesia around time of injury; or observed signs of other neurological or neuropsychological dysfunction, such as seizures, headache, irritability, fatigue and poor concentration);
- Loss of consciousness or altered consciousness;
- Loss of memory for events immediately before, during, or after the injury.

Surveys and interviews should ask whether health-care professionals evaluated such injuries and, if so, what level of care was provided. Where possible, analyses of data should distinguish among persons who received no medical care, non-hospital-based care which includes physician office visits, hospital emergency department care, inpatient hospital care up to 24 hours, and inpatient hospital care of greater than 24 hours. Unfortunately, these data

have not typically specified whether the TBI or some other injury was the reason for the length of stay, but occurrences of brain injury with inpatient hospital care of greater than 24 hours may be classified as more severe because they do not meet the criteria for mild TBI.

ICD-9-CM Based Definition

Mild TBI is recognized among persons treated in health-care facilities and who are assigned the following ICD-9-CM (International Classification of Diseases, Ninth Revision, Clinical Modification) diagnostic codes:

ICD-9-CM First Four Digits = 800.0, 800.5, 801.0, 801.5, 803.0, 803.5, 804.0, 804.5, 850.0, 850.1, 850.5 or 850.9: 800-804- Skull Fracture; 850-854 Intracranial Injury, excluding those with skull fracture

ICD-9-CM Fifth Digit subclassification is required for categories 851 to 854 to identify loss of consciousness, if any, and the length of time as follows:

- 0, unspecified state of consciousness;
- 1, with no loss of consciousness;
- 2, with brief (less than one hour) loss of consciousness;
- 6, with loss of consciousness of unspecified duration; and
- 9, with concussion, unspecified.

ICD-9-CM First Four Digits = 959.0: Injury, Other and Unspecified

ICD-9-CM Fifth Digit = 1, with no loss of consciousness.

These codes indicate either skull fracture or concussion without evidence of underlying brain hemorrhage or contusion, and no more than brief LOC. It is important to note that although the fifth digit 2 is being used to indicate mild TBI, this ICD-9-CM code is problematic for indicating severity. A fifth digit of 2 indicates loss of consciousness less than 1 hour. As mentioned above (Table 4), the clinical definition used by DoD/VA of mild TBI includes only those patients with loss of consciousness of less than 30 minutes. However, the ICD-9-CM does not differentiate between LOC of less than 30 minutes and 30 minutes to 1 hour. The latter would actually indicate moderate TBI. Thus, use of the fifth digit “2” as mild overestimates the number of persons with mild TBI and underestimates the number of persons with moderate TBI.

Clinical Records Definition. Mild TBI is recognized when the medical records document any one of the following conditions:

- Criteria consistent with the recommended conceptual case definition;
- GCS score between 13 and 15 assigned at the time of first medical evaluation at a health-care facility;
- Abbreviated Injury Severity Scale score of 2 for the head region (*Gennarelli and Wodzin, 2008*).

Exclusions: Injuries accompanied by indicators of neurological deterioration during the course of acute care, such as cases in which subsequent GCS scores fall below 13 are excluded (*NCIPC, 2003*).

TBI-Related Disability

Ascertaining the prevalence of disability attributable to severe TBI relies on medical records, access to supportive services, and school or work status. Persons with severe TBI frequently have residual cognitive or other neurological disability (e.g., weakness, stiffness, slurred speech, incoordination, posttraumatic epilepsy) and commonly require long-term assistance. Patients with severe TBI who survive their injuries frequently require extensive rehabilitation, first as an inpatient and later as an outpatient. Neurological recovery might take place over months or even years; however, many do not recover to independent functioning or enter/re-enter the work place, and carry a diagnosis of chronic brain injury caused by trauma (*Riggio, 2011*).

TBI-related disability is identified over time during the continuum of assessment and management of TBI. Ascertaining the prevalence of disability because of TBI is difficult for mild and moderate TBI. Patients with mild TBI can acquire conditions such as disordered sleep, fatigue, headache, dizziness, poor concentration, anxiety disorder, memory, and depressed mood. While recovery usually occurs during the first few months following injury, 10% – 50% might have symptoms that last more than a year (*Riggio, 2011*). In addition, evidence suggests that persons with repeated events of TBI tend to recover more slowly after each ensuing event and in extreme cases might develop chronic neurodegenerative changes—first seen as *dementia pugilistica* in boxers but now termed chronic traumatic encephalopathy (CTE) (*McKee et al., 2010*).

Specialized survey techniques are necessary to quantify the incidence and duration of post-concussive syndrome. Batteries of standardized neuropsychological testing can determine the level of cognitive function in specific domains: attention, memory, executive function, processing speed, verbal ability, spatial ability, depressed mood, and symptom validity. However, pre-testing is not routinely done for most persons, making these comparisons challenging. Determining pre-injury levels of function is more difficult, but can be estimated based upon previous level of achievement in education or employment. Comparison of scores on pre-injury and post-injury tests of cognitive abilities might be the most reliable means to determine if the effects of TBI are persistent.

Data Sources

Civilian

The primary responsibility for public health surveillance in the civilian system resides at the state level (*Jacobson, Hoffman, and Lopez., 2007; Horan and Mallonee, 2003*). Since the mid-1990s, CDC and at least 30 states have developed injury surveillance systems, including TBI (*CDC State Programs, 2009*); the capacity of these state systems is variable (*CDC unpublished data*). States must improve their capacity to identify all injuries and yet have the specificity to identify TBI events and use linkages between data systems or other indicators to identify veterans with military service-related TBI in all 50 states and territories. A number of civilian health and injury surveillance systems already exist and could incorporate additional measures to capture or validate information specific to TBI and/or military service (Table 5).

Department of Defense

Armed Forces Health Surveillance Center (AFHSC)

The Armed Forces Health Surveillance Center (AFHSC) was established in February 2008 by the DoD to be the central epidemiology health resource for the U. S. military. It merges the capabilities and resources of the Army Medical Surveillance Activity (AMSA), the DoD Global Emerging Infections Surveillance and Response System (DoD-GEIS), and the Global Health Surveillance Activity of the Force Health Protection Directorate of the Office of the Assistant Secretary of Defense for Health Affairs. Also, AFHSC assumed responsibility for AMSA's Defense Medical Surveillance System (DMSS) and the DoD Serum Repository (DoDSR). DMSS contains up-to-date and historical data on diseases and medical events (e.g., hospitalizations, laboratory tests, immunizations) affecting SMs throughout their military careers. DMSS contains over two billion records on nine million service members and other beneficiaries of the MHS.

Table 5. Civilian public health surveillance systems

Name of Surveillance System (in alphabetical order)	Agency	Design and Use
Behavioral Risk Factor Surveillance System (BRFSS)	CDC and health departments in 50 states, District of Columbia, Puerto Rico, Guam, and Virgin Islands	Population based, random-digit dialed telephone survey of adults (aged ≥ 18 years) in the United States; three components: core, optional, state-specific. Used to track health conditions, disability, and risk behaviors and to collect state/territory data on preventive health practices linked to chronic diseases, injuries, and preventable infectious diseases.
CDC Traumatic Brain Injury Surveillance System (CDC TBI SS)	CDC/National Center for Injury Prevention and Control: Core Violence and Injury Prevention Program (VIPP)	Statewide representative ongoing population-based surveillance system. Used to identify, track, and analyze statewide trends in TBI. Information used to inform primary and secondary prevention strategies.
National Ambulatory Medical Care Survey (NAMCS)	CDC/National Center for Health Statistics	Nationally representative multistage probability survey based on a sample of visits to non-federal office-based physicians engaged primarily in direct patient care. Excludes those in anesthesiology, radiology, and pathology. Representative sample used to identify and track ED and outpatient department visits.
National Electronic Injury Surveillance System – All Injury Program (NEISS-AIP)	Consumer Product Safety Commission (CPSC) and CDC/National Center for Injury Prevention and Control	Nationally representative, stratified probability sample of all U.S. hospitals that have at least 6 beds and provide 24 hour ED services. Used to identify, track, and analyze national trends in injury-related ED visits.
National Health Interview Survey (NHIS)	CDC/National Center for Health Statistics	Population-based, nationally representative, face-to-face probability sample survey among civilian, non- institutionalized U.S. population. Used to monitor trends in illness and disability, track progress toward achieving national health objectives, characterize various health problems, determine barriers to access and use of health care, and evaluate federal health programs.
National Hospital Ambulatory Medical Care Survey– Emergency Department and Outpatient Department Modules (NHAMCS)	CDC/National Center for Health Statistics	Nationally representative multistage probability sample of visits to emergency and outpatient departments and to ambulatory surgery facilities in noninstitutional general and short-stay hospitals, excluding Federal, military, and Veterans Administration hospitals, located in the 50 States and the District of Columbia. Used to identify and track ED and outpatient department visits.

Table 5. (Continued)

Name of Surveillance System (in alphabetical order)	Agency	Design and Use
National Hospital Discharge Survey (NHDS)	CDC/National Center for Health Statistics	Nationally representative three-stage stratified sample survey of inpatient hospital records acquired from probability sample of ~500 non-federal short-stay hospitals. Provides information on characteristics of patients of all ages that were hospitalized and discharged from hospitals in sample.
Nationwide Inpatient Sample (NIS)	Agency for Healthcare Research and Quality (AHRQ)	Nationally representative multi-state health data system of all hospital discharges from a stratified probability sample of non-federal short-stay hospitals (40 states; 1,044 hospitals in 2007). Used to identify, track, and analyze national trends in health-care utilization access, charges, quality, and outcomes by diagnoses.
State and Local Area Integrated Telephone Survey (SLAITS)	CDC/National Center for Health Statistics	Collection of broad-based ongoing surveillance systems; uses sampling frame of CDC's National Immunization Survey (NIS), following NIS random-digit dialed telephone survey; surveys vary, based on need of sponsors. Tracks and monitors health and well-being of children and adults in 50 states, District of Columbia, and 27 urban areas. Contacts more than 1 million households annually.
The National Health and Nutrition Examination Survey (NHANES)	CDC/National Center for Health Statistics	Nationally representative survey of 5,000 persons annually, combining interviews and physical exams; focus on different population groups or health topics. Used to determine prevalence of chronic conditions, risk factors for disease, nutritional status; helps to develop public health policy, direct and design health programs and services, and expand health knowledge.

The AFHSC maintains, promotes, and enhances the health of military and military-associated populations through development, refinement, and improvement of surveillance methods; coordinates a global program of militarily relevant infectious disease surveillance.

Defense Medical Surveillance System (DMSS)

In 1997, The Army Medical Surveillance System transitioned to the Defense Medical Surveillance System (DMSS). This is the primary tool used by AFHSC for all its public health surveillance. It combines data from inpatient, outpatient, and purchase care databases maintained by TRICARE Management Activity and contains personnel data from Defense Manpower Data Center and health assessments completed by SMs. The DMSS contains data from three main sources: Standard Ambulatory Record Data (SADR) and Comprehensive Ambulatory Professional Encounter Record (CAPER); Standard Inpatient Data Records (SIDR); and TRICARE Encounter Data (TED)/Health Care Service Record (HCSR). DMSS data are integrated in a continuously expanding longitudinal surveillance data base for all persons who have served since 1990 and facilitate the efficient analyses of morbidity among SMs.

Theater Medical Data Store (TMDS)

The TMDS receives data from various military and civilian systems, which allows the following: view clinical information; view, track, and manage ill or injured patients through

continuum of care; access data on critically injured patients before they arrive a next point of care; access to deployment-specific medical data; access to blood inventory management activity; and, view pre-deployment health information.

Blast Tracker Program (BTP)

The Army National Guard designed the Blast Tracker Program (BTP) as a secure data base accessible to all service branches via defense link website. It will be incorporated into the Combined Information Data Network Exchange of U.S. Central Command data system. The goal is to capture blast and related events and identifies persons in proximity to blasts. Units and individual persons can receive reports and previously deployed units can add past exposure information.

VA

The following systems are implemented by the Veterans Health Administration (VHA) to identify veterans receiving health care within VA who have a possible TBI.

VA TBI Screening and Evaluation Program

The TBI Screening and Evaluation Program is a web-based tracking application that began in 2007 to capture information on veterans who screen positive for mild TBI using a TBI Clinical Reminder tracking system. The system was designed to improve screening for veterans of Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) for mild TBI. The program provides information to confirm diagnosis and provide treatment.

VA TBI Health Registry

The TBI Health Registry is a secure web-based portal for VA users to evaluate data, develop policies, assess resource demands, determine incidence/prevalence of TBI and evaluate treatment and outcomes. The system provides prospective longitudinal health surveillance, epidemiologic, and health-care quality analysis for OEF/OIF veterans.

Challenges/Limitations

The identification of veterans who had a military service-related TBI in the immediate or remote past in the civilian systems poses many medical, epidemiologic, methodologic, and administrative challenges. Collecting data, standardizing collection methods, and sharing data among partner agencies is a critical component of an overall plan to improve the outcome of TBI injuries. Furthermore, these data will support future efforts related to the implementation of prevention measures.

Veterans with moderate or severe military service-related TBIs have the potential to be counted easily because their injuries are often self-evident. They frequently have clear clinical signs of brain injury or with imaging results (CT and/or MRI) that are abnormal. Similar to civilians, veterans with less severe TBIs might be more difficult to identify if their signs and symptoms were not evaluated immediately after the injury, not recorded (*National Center for*

Injury Prevention and Control [NCIPC], 2003), or not diagnosed (Andary et al., 1997; Chambers, Cohen, Hemminger, Prall, and Nichols, 1996). Long-term dysfunction might be related to multiple events of mild TBI, making the number of exposures as important as the severity of any single exposure. Accurate measures of the accumulated number of blast exposures add further complexity to accurate data gathering. Moreover, diagnosing TBIs that occurred years previously, such as during the First Gulf War, might be difficult because of substantial memory loss and inability to recall the initial diagnosis, external causes, or risk factors (Jekel, Katz and Elmore, 2001; Paterson and Scott-Findlay, 2002). Survivors also might have comorbidities, such as PTSD, that might mimic or overlap with the signs and symptoms of TBI (Glaesser, Neuner, Lutgehetmann, Schmidt, and Elbert, 2004; McMillan et al., 2001; Schneiderman, Braver, and Kang, 2008). In other instances, health-care providers might not be able to detect or diagnose (Jekel, 2001) TBIs and/or determine causative factors, especially if they are mild (Andary et al., 1997; Chambers et al., 1996). Other medical concerns include malingering (Halligan, Bass, and Oakley, 2003; Sweet et al., 2000; Bianchini Curtis, and Greve, 2006) or the inability of the civilian provider to access military medical records documenting the injury event, diagnosis and risk factors.

Identifying veterans who had a military service-related TBI since the beginning of the First Gulf War in the civilian system requires data sharing among interested parties. Such sharing of data might be particularly useful for identifying those veterans who are subsequently receiving care in the civilian health-care system. However, this poses administrative challenges, including the Health Insurance Portability and Accountability Act of 1995 (HIPAA) Privacy Rule (United States Department of Health and Human Services, 2009) that regulates uses and disclosures of “protected health information” (PHI) by covered entities (45 CFR 164). The HIPAA Privacy Rule defines covered entities as health-care providers, health plans, and health-care clearinghouses (45 CFR 160.103 (B)(3)). Examples of PHI include information that identifies or can be used to identify a person who is related to any physical or mental health condition, or treatment, or payment for treatment of a person by covered entities.

The HIPAA Privacy Rule permits the disclosure of PHI without the authorization of the individual for specified purposes including disclosures required by law and disclosures to public health authorities who are authorized to collect it. HIPAA generally requires the disclosure of the minimum amount of information necessary to achieve the intended purpose (45 CFR 162.502 (b)). CDC and state health departments, as public health agencies with public health authority, may obtain protected TBI-related health information for public health purposes (under 45 CFR 164.512(b)(2)) from VA and DoD to identify the target population of this report in the civilian system. Various applicable laws regulate the disclosure of identifiable information from CDC and state health departments (e.g., the Privacy Act, HIPAA Privacy Rule, state laws). Development and dissemination of veterans’ TBI-related information in the civilian health-care and public health systems will require high levels of cooperation and collaboration among various federal (CDC, NIH, DoD, and VA), state, local entities, and other stakeholders. Despite these hurdles, the Federal TBI Common Data Elements project is developing standards so that TBI in persons formerly in the military is effectively measured and data shared among interested parties while maintaining appropriate privacy protections. The ongoing activities of this interagency group can go a long way towards further strengthening collaboration and data sharing among organizations responsible

for conducting, monitoring, and evaluating current civilian and military TBI- related surveillance systems.

EPIDEMIOLOGY

Epidemiology is the study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to the control of health problems (*Last, 1988*).

The epidemiology of a condition, like TBI, can be characterized using data collected via surveillance systems as described in the surveillance section above. Injury surveillance data are useful for several reasons. Even the simplest surveillance programs are designed to identify as many persons as possible who have a particular injury or disease. Other programs, like the CDC Core Violence and Injury Prevention Program surveillance system (*Marr and Coronado, 2004*), might collect additional data about selected demographic and clinical characteristics of the injured population, cause of injury, alcohol use, and use of protective devices, such as seat belts or motorcycle helmets.

Although surveillance systems typically do not collect data at the same level of detail as research studies, they provide more current data than research data. Furthermore, they can generate data on an ongoing basis, which is useful for studying, for example, trends or the efficacy of preventive interventions (*Coronado et al., 2009*). Obtaining more detailed epidemiologic data requires in-depth and time- consuming studies of specifically defined populations (*Coronado et al., 2009*). In most cases, researchers find it feasible to collect the necessary amount of details from samples of persons drawn from a population of interest rather than study the entire population (*Coronado et al., 2009*). These limitations contribute to the difficulty of extrapolating results from detailed studies to surveillance data. However, data from both approaches are necessary to understand the magnitude and effects of injuries and diseases.

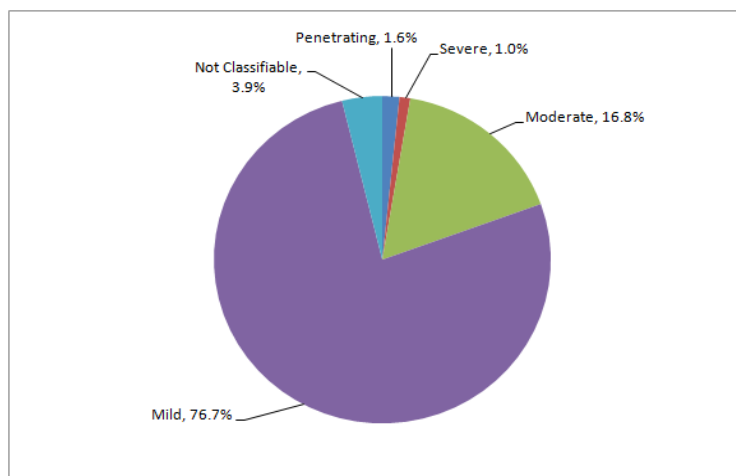
Incidence: Traumatic Brain Injury

Incidence indicates the number of new cases that occur over time. It is usually expressed as a percentage of persons who will be affected during a year, or as a rate calculated as the number of persons who develop the condition during a period divided by the number of person-years at risk.

From 2000 through 2011, a total of 235,046 service members (SMs) (4.2%) of the total 5,603,720 who served in all components of the Army, Air Force, Navy, and Marine Corps were diagnosed with a TBI. Most of these SMs with a TBI (76.7%) had a mild TBI (Figure 1). Less than 3% of SMs with a TBI had severe and penetrating TBIs (Figure 1).

The overall rate of TBI among active duty service members more than doubled from 720.3 per 100,000 SMs to 1,811.4 per 100,000 SMs from 2000 to 2011 (Table 6 and Figure 2). The TBI rate increased dramatically from 2006 to 2008 followed by slight increases in 2010 and 2011. This may reflect an actual increase in TBI, but may also reflect an increased number of SMs deployed along with increased awareness of the need to seek care and

improved recognition and diagnosis. Overall TBI rates increased in every active-duty service branch from 2000 through 2011 (Figure 3). The largest increases were among active-duty Army and Marine Corps members. The rate of TBI in the active-duty Army was 3.3 times higher in 2011 than in 2000 (2,717.9 versus 815.6 per 100,000 service members). The TBI rate among active-duty Marine Corps personnel in 2011 was 2.4 times higher than in 2000 (2,286.3 versus 959.8 per 100,000 SMs).



Source: Defense and Veterans Brain Injury Center.

Figure 1. Percentage of U.S. military service members diagnosed with a TBI, by TBI severity, 2000-2011 (N = 235,046).

The mild TBI rate among active-duty service members increased from 2000 through 2011 (Table 6 and Figure 4). The increase in the rate of mild TBIs accounted for most of the increase in the overall TBI rate in the active-duty military population. The rate of moderate TBIs in this population decreased from 2000 through 2005 and then increased in 2006 and 2007, followed by a decrease in 2008 and then increased each year through 2011 (Table 6 and Figure 4). The rates of penetrating and severe TBIs among active-duty service members increased dramatically from 2006 through 2009 (Table 6 and Figure 5). However, these rates decreased substantially after 2009 (Table 6 and Figure 5). In 2010 and 2011, the rate of penetrating TBIs among active-duty service members decreased 43.9%. During those 2 years, the rate of severe TBIs decreased 33.4%; this decrease is likely a function of multiple factors including fewer people deployed and improvements to both vehicles and personal protective equipment.

The incidence of blast-induced TBI in U.S. civilian populations is low, with a report of 0.2% of TBI cases in a major urban trauma center (Bochicchio *et al.*, 2008); however, civilian blast injuries are becoming an increasing problem worldwide (Summers *et al.*, 2009). Data for TBI in the civilian population from 1995 to 2009 show that the rate for emergency department visits increased significantly from 434.1 per 100,000 population in 1995 to 686.0 per 100,000 in 2009. During the late 1990s, the rate of TBI hospitalizations decreased significantly from 95.5 per 100,000 population in 1995 to 77.9 per 100,000 in 2000 but then the rate increased over subsequent years and the rate for 2009 was similar to that reported in 1995. Deaths in which a TBI was listed either as an isolated injury or in conjunction with

other injuries decreased significantly from 19.9 per 100,000 in 1995 to 16.6 per 100,000 in 2009 (Coronado et al., 2012).

Table 6. Estimated annual rates* of TBI among active-duty U.S. military service members by TBI severity, 2000-2011

Year	Penetrating	Severe	Moderate	Mild	Not Classifiable†	Overall
2000	17.9	11.6	274.8	413.7	2.3	720.3
2001	19.4	12.6	234.4	506.0	2.3	774.7
2002	13.9	9.2	192.3	553.7	2.4	771.5
2003	16.0	10.4	150.1	563.5	1.8	741.8
2004	17.1	9.0	128.5	614.7	2.1	771.4
2005	13.9	9.8	108.3	581.5	2.3	715.9
2006	19.7	11.1	145.3	835.7	3.4	1015.1
2007	23.9	13.3	216.9	1087.5	13.8	1355.3
2008	27.7	15.1	193.6	1289.5	169.7	1695.6
2009	28.2	18.5	205.0	1279.8	126.6	1658.1
2010	17.1	13.3	236.8	1405.6	90.7	1763.6
2011	15.8	12.3	239.4	1429.1	114.8	1811.4

* Incidence Rates per 100,000 service members.

† Changes were made to the DoD TBI case definition in 2008 to include codes that do not provide information about the severity of the TBI.

Source: Defense and Veterans Brain Injury Center.

Although additional research is required to understand the specific causes, a number of factors may have contributed to the significant increase in the rate of TBI-related emergency department visits including the increased awareness of head injury through education campaigns (for example, CDC's *Heads Up: Concussion* campaign), the efforts of various sports organizations to reduce TBI among athletes, and the media attention given to TBI among military service members fighting in Iraq and Afghanistan. In addition, a number of states have passed legislation to reduce TBI in youth sports, further raising awareness of the importance of addressing these kinds of injuries among coaches, athletic trainers, parents, and youth. While a number of factors likely contributed to the decline in TBI-related deaths, the largest single contributor is the reduction in the number of transportation related deaths (Coronado et al, 2012).

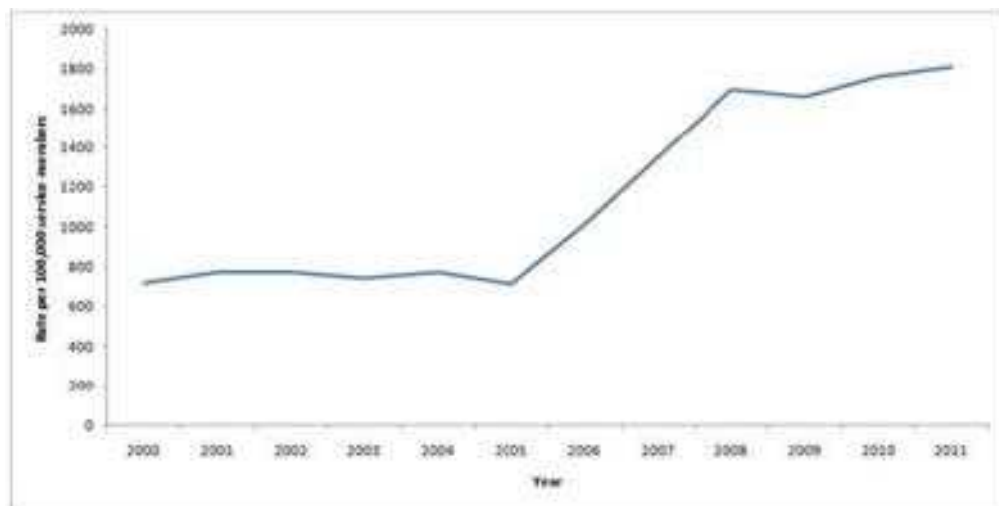
Prevalence: Traumatic Brain Injury

Prevalence is the number of all new and old cases of a disease or occurrences of an event (in this case TBI) during a particular period (*Mosby 2009*).

Active Duty Military Personnel

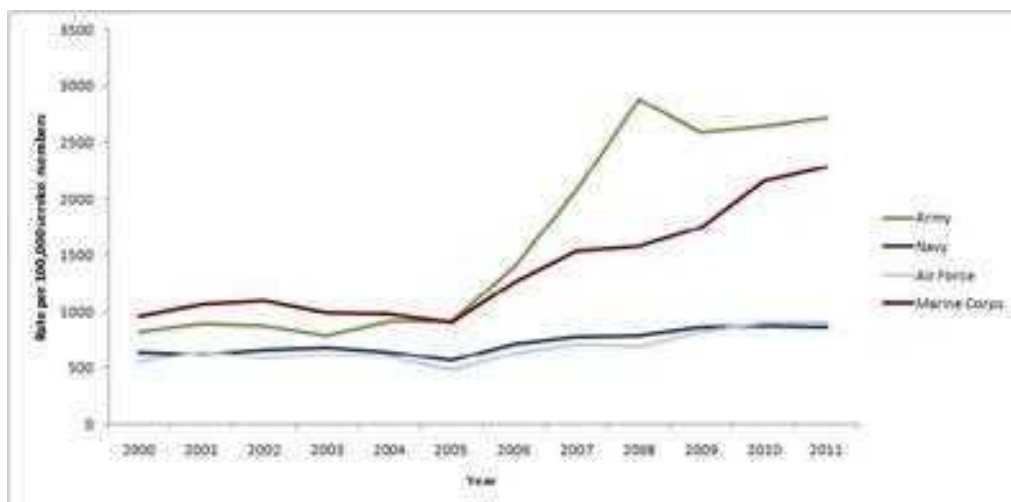
Determining the prevalence of TBI in the transient military population remains challenging as it might not allow accounting for all those who are living with the consequences of this condition. Other challenges stem from the use of multiple databases and electronic medical records that lead to duplication of cases or inability to locate records and inconsistencies in coding that might contribute to inappropriate symptom attribution.

Another concern that can affect reporting prevalent cases is the lack of chronic TBI codes. Commonly, SMs might be seen and treated for persistent headaches following TBI. The primary diagnostic code is captured as headache. Unless a history of TBI code is also used, this person might not be captured in reporting. The DoD, CDC, VA, and other federal agencies collaborated to revise the ICD-9 codes that most accurately reflect TBI. These revisions that are already in use incorporated consideration of co-morbid conditions and were publicly reviewed, discussed, and adapted by all partners. The addition of cognitive-behavior codes is important because many of the symptoms of mild TBI overlap with psychological comorbidities, in particular PTSD.



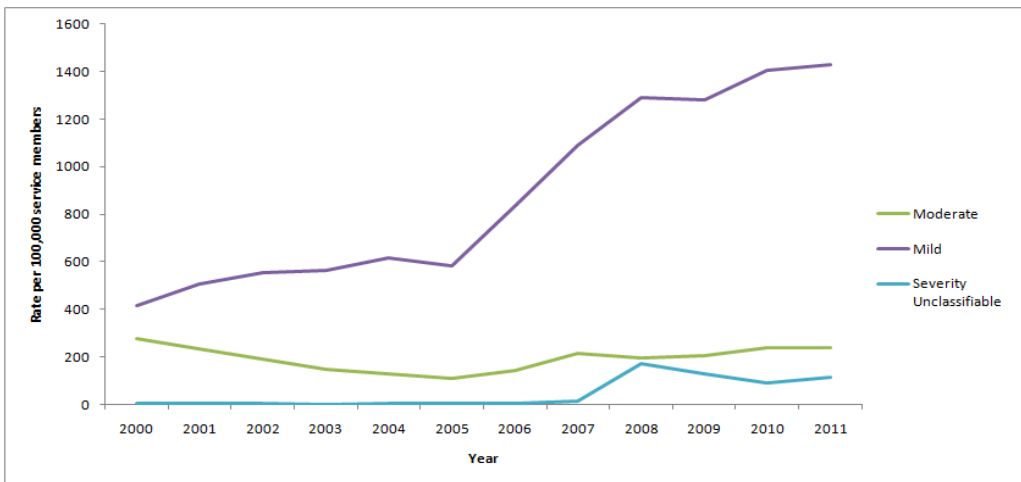
Source: Defense and Veterans Brain Injury Center.

Figure 2. Estimated overall annual incidence rates of TBI among active-duty U.S. military service members, 2000–2011 surveillance systems.



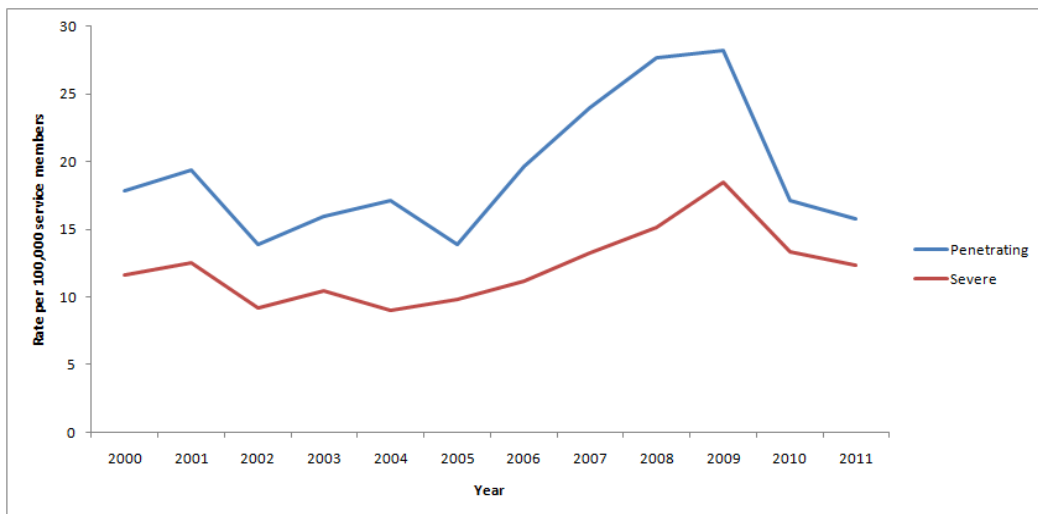
Source: Defense and Veterans Brain Injury Center.

Figure 3. Estimated overall annual incidence rates of TBI among active-duty U.S. military service members by service branch, 2000–2011.



Source: Defense and Veterans Brain Injury Center.

Figure 4. Estimated annual incidence rates of mild and moderate TBIs and TBIs with unclassifiable severity among active-duty U.S. military service members, 2000–2011.



Source: Defense and Veterans Brain Injury Center.

Figure 5. Estimated annual incidence rates of penetrating and severe TBIs among active-duty U.S. military service members, 2000–2011.

Inconsistencies in coding also might affect reporting. To overcome these problems, educational activities are underway to ensure that providers and medical coders consistently use recommended codes that will enhance incidence and prevalence detection. Guidance documents have been developed to assist in improving documentation (*TRICARE 2010*; *Defense Centers of Excellence, 2010*).

To better estimate the prevalence of TBI in the military, MHS requires continuing the practice of conducting pre-deployment screening to have baseline measures; after a possible TBI, screening all SMs as soon as possible; training all medical personnel in the detection of TBI and coding methods for TBIs; improving and maintaining better medical record keeping

and reporting; and expediting the standardization of the multiple and disparate databases in the military. Efforts have been initiated to coordinate databases within the DoD and other federal agencies as mandated by the National Defense Authorization Act (NDAA).

Table 7. Numbers of OEF/OIF Veterans reported with ICD-9-CM codes indicative of TBI diagnosis or a selected TBI outcome or other type of head injury commonly associated with TBI who were evaluated or treated in the VA health-care system from October 2001 through December 2011

Diagnosis/Health Outcomes	Number ¹ of Veterans (N = 59,218)
Postconcussion syndrome	12,367
Fracture of skull ²	113
Fracture of base of skull ²	113
Fracture of face bones ²	3,237
Other and unqualified skull fracture ²	90
Multiple fractures involving skull or face with other bones ²	209
Concussion ³	36,412
Cerebral laceration and contusion ³	392
Subarachnoid, subdural, and extradural hemorrhage following injury ³	243
Other and unspecified intracranial hemorrhage following injury ³	62
Intracranial injury of other and unspecified nature ³	18,509
Injury to optic nerve and pathways ²	257

Source: Epidemiology Program, Post Deployment Health Group, Office of Public Health, Veterans Health Administration, Department of Veterans Affairs, March 2012.

¹The sum of the number of veterans corresponding to each ICD-9-CM code is more than 59,218 because a patient might have more than one ICD-9-CM code.

²ICD-9-CM codes that are commonly associated with TBI.

³ICD-9-CM codes with specific TBI diagnoses.

The majority of TBIs are mild (approximately 80%; *Thurman, Alverson, Dunn, Guerrero, Sniezek, 1999; Defense and Veterans Brain Injury Center, unpublished data*) and less likely to yield chronic symptoms. If mild TBI-related symptoms are present, they are often non-specific headaches, dizziness, or cognitive or neuropsychiatric difficulties. According to current coding guidelines, chronic symptoms, such as headache, are recorded but often without information necessary to determine whether and how they may be attributed to a prior TBI. Therefore, the prevalence of mild TBI is difficult to ascertain. SMs who have sustained a moderate, severe, or penetrating TBI and who are represented in the TBI database are more likely to have disability linked to their TBI. However, with the exception of post-traumatic epilepsy, no process is in place for determining and recording long-term consequences.

Veteran Population

The overall U.S. veteran population is diverse and includes those who served during various eras, including WWII, the Korean conflict, the Vietnam War, the First Gulf War, OEF/OIF, and other conflicts and operations. The number of women veterans has steadily increased; beginning in the First Gulf War, women have played an increasingly important role in the U.S. military. Estimating the TBI prevalence in veteran population should optimally consider services provided by both the VA health-care system and civilian medical facilities

outside of that system. Prevalence among OEF/OIF veterans seen by VA is defined by data from VA's Inpatient (PTF) and Outpatient (OPC) treatment records data and is presented in Table 7.

Epidemiologic studies of the long-term consequences of TBI, including those that focused on veterans who served during WWII, the Korean conflict, and the Vietnam War have been reviewed by the Institute of Medicine (IOM 2009). Many of the early studies of TBI reviewed by IOM focused on moderate or severe TBI or pre-date contemporary improvements in assessment, treatment, and rehabilitation, highlighting the ongoing need for additional research.

Several factors have contributed to current interest in understanding the epidemiology, early detection, treatment, and rehabilitation of not only moderate and severe TBI but also mild TBI. This includes increased use by enemy forces of improvised explosive devices (IEDs) and rocket propelled grenades (RPGs); increased survival of military service men and women who are critically injured on the battlefield; and recognition of the potential for overlap between mild TBI and PTSD. In the last decade studies within the U.S. military and VA systems have addressed the long-term consequences of military service-related TBI. Of these studies, most address the consequences of military service-related mild TBI (*Hoge et al., 2008; Schneiderman et al., 2008; Taber and Hurley 2009; Rona et al., 2012*).

The National Defense Authorization Act of Fiscal Year 2008 (Public Law 110-181, Section 1704 (d) requires the VA Secretary to establish and maintain a TBI Veterans Health Registry (VHR). The registry must include information about each person who served as a member of the Armed Forces in OEF/OIF who exhibits symptoms associated with TBI and who applies for services or files a disability claim. Section 1704 also stipulates that the VA shall collaborate with facilities that conduct research on rehabilitation for persons with TBI, facilities that receive grants for such research from the National Institute on Disability and Rehabilitation Research (NIDRR), DVBIC, and other relevant programs of the Federal government, including the Defense Centers of Excellence.

Pursuant to this statutory requirement, VA sought an interagency agreement with NIDRR through which VA can draw upon the expertise of NIDRR's TBI Model Systems (TBIMS) program—the largest longitudinal database for TBI in the country. With NIDRR's assistance, VA is working to develop a TBI VHR housed on secure web-based portal at the TBIMS National Data and Statistical Center in Denver, Colorado. The portal will be accessible to authorized VA users and developed in compliance with VA data security regulations, HIPAA, and Privacy Act considerations. A custom-built web portal will enable authorized VA users to access data to support policy development and evaluation; assess resource usage and health-care needs; determine incidence and prevalence of TBI among OEF/OIF veterans; and evaluate course of treatment and outcomes.

Characterizing the prevalence and long-term consequences of military service-related TBI in the civilian system will require even greater manpower and economic resources to ensure that appropriate linkages are made between the military, VA, and civilian health care systems. There is also an absence of fully valid and reliable screening instruments to diagnose TBI, especially cases of mild TBI, and the co- occurrence of cases of PTSD and TBI that are not correctly classified. Moreover, the natural history of combat-related TBI, especially its long-term consequences, has not yet been fully explained (*Ramchand et al., 2008*).

Because the VA system provides medical care to a subset of all eligible veterans, conducting studies of the prevalence of military service-related TBI will likely require the use

of civilian databases, for example, the TBIMS or the Framingham Study. The Framingham Study has been conducting research on neurological disorders for decades. In 1997, for example, it began a post-mortem Brain Tissue Donation Program that has enrolled more than 600 participants and analyzed approximately 100 brains—yielding substantial information on genetics, the environment, the aging process, stroke, Alzheimer's disease, Parkinson's disease, or other neurological illness. Because the program can also document the extent of a disease, military service-related TBI and civilian TBI could also be studied.

Civilian Population

Certain challenges related to TBI prevalence in military-associated cases also affect civilian populations. An estimated 3.2 million Americans are living with long-term consequences from TBI (Zaloshnja, Miller, Langlois, and Selassie, 2008). This estimate reflects the use of updated methodology and is based on the results of statistical modeling and analysis of 2005 TBI hospitalization incidence data from Maryland, Vermont, and New Jersey. A previous CDC estimate indicated that approximately 2% (approximately 5 million) of the U.S. population live with the long-term consequences of TBI (CDC, 1999). These estimates, likely underestimate the prevalence of TBI-related disability as they do not include persons with TBI who were treated and released from emergency departments or other health-care settings, those who were treated in a DoD or VA facility, or who did not seek treatment. With current resources and limitations in surveillance methodology, the prevalence of TBI-related impairment and disability in the United States cannot be measured with confidence (Coronado et al., 2009).

Interview surveys that attempt to link history of TBI to a disability are prone to underreporting, mainly because of poor or no recall of past injuries (Walker, Logan, Leukefeld, and Stevenson, 2004). Population-based prospective cohort studies of persons recently diagnosed with an acute TBI might be more promising. Using this method, two studies examined the occurrence of TBI-related disability in representative samples of persons followed 1 or more years after hospitalization for TBI (Whiteneck et al., 2004; Pickelsimer et al., 2007). Since information on annual disability (Selassie et al., 2008) does not account for the cumulative prevalence of TBI, statistical methods must be applied to estimate such figures (Zaloshnja et al., 2008). The true prevalence of military and civilian TBI and TBI-related disability in the general U.S. population will remain elusive without continued investment in sound, long-term, representative follow-up studies or adding questions into existing national surveys, such as, NHIS, NHANES, and SLAITS.

The Economic Costs of TBI

The economic costs of TBI are difficult to estimate in both the military and civilian populations. Some of the reasons include 1) uncertainty about which outcomes can be attributed specifically to TBI, 2) variability in the types of TBI-related outcomes, 3) inability to measure the precision of cost estimates, and 4) limited resources (including data available for research) to conduct more complex and long-term economic studies. Some estimates are more straightforward whereas others can only be derived using a large number of

assumptions and complicated econometric and statistical methods that distance the estimates from actual cost data (*Coronado et al., 2009*).

Because of these difficulties, few attempts to estimate the costs of TBI have been undertaken, especially those costs faced by society as a whole. One recent study estimated the annual economic burden of TBI in the United States in year 2000, including direct medical and rehabilitation costs and societal costs, to be \$60 billion (*Finkelstein, Corso, and Miller, 2006*). The few studies that have attempted to estimate the cost of TBI injury among military SMs have had major limitations such as including only hospitalized cases of TBI and studies with small sample sizes. Despite these limitations, available data suggest that the total costs might be substantial (*Ommaya, Ommaya, Dannenberg, and Salazar, 1996; Wallsten and Kosec, 2005; Eibner, Ringel, Kilmer, Pacula, and Diaz, 2008*).

Certain studies have attempted to estimate the costs of TBIs that have resulted from OEF/OIF. One study estimated that the total lifetime cost of severe TBIs sustained in OIF through August 2005 to be \$16 billion (*Wallsten and Kosec, 2005*), but it has two limitations that must be considered. First, the authors estimated that 20% of all SMs wounded in OIF had a severe TBI, which is high when compared with DoD data. DoD TBI surveillance data indicate that only 1% of all SMs with a TBI during that time sustained a severe TBI (*Defense and Veterans Brain Injury Center, unpublished data*). Furthermore, the estimated proportion was obtained from a newspaper article rather than actual surveillance data. The second limitation was that the lifetime cost of severe TBI was based on numerous assumptions and estimated costs that might not be applicable to SMs with TBI. For example, the data used to estimate lifetime-treatment costs was derived from civilian sources and might not be applicable to the DoD and VA health systems. A 1996 study of costs for acute treatment of TBI among SMs and their beneficiaries suggests that costs in military hospitals might be lower than costs in private hospitals (*Ommaya, 1996*). Furthermore, a highly variable and controversial cost, known as the value of a statistical life (VSL), was used to estimate other aspects of the lifetime cost of severe TBI, such as lost wages. The VSL is the value that a person places on a marginal change in their likelihood of death; it is estimated by looking at the risks that people are voluntarily willing to take and how much they must be paid for taking them (*Viscusi and Aldy, 2003*). A review of literature about VSL indicated that it can vary from \$4 million to \$9 million per life, depending on the assumptions made and methodology used to estimate it (*Viscusi and Aldy, 2003*).

In 2008 the RAND Corporation released a report estimating TBI costs resulting from OEF/OIF (*Eibner et al., 2008*). The report provided cost estimates for acute treatment and rehabilitation, mortality and suicide, and lost income. In the first year following injury, costs were estimated to be \$27,260 to \$32,760 per case for mild TBI and up to \$408,520 for those with moderate to severe injury. The estimated overall cost for acute treatment of deployment-related TBIs in the hospital in 2005 ranged from \$6.9 million to \$14.3 million. The estimated cost of inpatient rehabilitation was \$1.9 million and the estimated cost of outpatient rehabilitation ranged from \$377,000 to \$907,000. The estimated costs associated with mortality from deployment-related TBIs in 2005 ranged from \$67 million to \$89 million, unemployment associated with deployment-related TBI was \$13 million, and reduced wages associated with deployment-related TBI was \$1.2 million.

These estimates have the same serious limitations as those calculated by Wallsten and Kosec in 2005. Treatment cost estimates are derived from civilian cost data that might be different from costs incurred by military hospitals. In addition, estimated costs resulting from

the death of a SM are based on the VSL, which can vary substantially. Another serious limitation is that the estimated treatment cost per case of mild TBI in the RAND report is for SMs who required hospitalization. This estimate is likely too high for most SMs with a TBI because most persons with mild TBI only are not hospitalized. More problematic is the lack of evidence regarding the extent of long-term disability resulting from blast exposure and whether other major health effects such as neurodegenerative disorders might arise years later.

Table 8. Estimated median acute hospitalization cost per patient for military personnel hospitalized with TBI (in 2011 Dollars)

TBI Characteristics	Cost/Patient†	
	Military Hospital	Private Hospital
TBI with no LOC*	\$1,773	\$5,308
TBI with any LOC*	\$2,299	\$8,216
TBI with LOC of unknown duration	\$2,901	\$6,051
TBI with LOC >1 hour	\$8,237	\$22,744
TBI with other type of injury	\$10,245	\$10,991
TBI with other health condition	\$3,967	\$7,835

Source: Defense and Veterans Brain Injury Center.

† Costs presented in this table are medians of actual costs incurred by military hospitals and allowable expenses paid by the MHS to private hospitals in fiscal year 1992 (*Ommaya et al.1996*). These costs have been adjusted to 2011 dollars using the U.S. city average CPI for medical care (*US Bureau of Labor Statistics*). Military and private hospital cost estimates might not be directly comparable because of the different methods used to compute them. However, the military hospital costs include the clinic proportion of total facility expenses including construction, maintenance, staff wages, equipment, and supplies.

Using 1992 data, the Defense and Veterans Head Injury Program, now DVBIC, published estimates of TBI-related costs in the military (*Ommaya et al., 1996*). These costs were estimated from a study of 5,568 SMs and other beneficiaries of the MHS who were hospitalized for TBI in both military and private hospitals in FY 1992. The authors attempted to compare costs from both types of hospitals. Although outdated, these estimates are the only ones known to be published that were derived from actual costs incurred by the MHS. The overall estimated cost of TBI-related hospitalizations in the U.S. military medical system in 1992 was approximately \$42 million (*Ommaya, 1996*).

Current military per-patient hospitalization costs associated with TBI in the military can be estimated by adjusting Ommaya et al.'s estimates for inflation. This method has been used by others to update older cost estimates (*Thurman, 2001*). Table 8 presents Ommaya et al.'s per patient cost estimates adjusted to 2011 dollars. However, these estimates have limited reliability because the inflation factor used for adjustment was not just for hospitalizations, and included all types of health care. Furthermore, the inflation rate for TBI treatment costs might be different from treatment cost inflation for other conditions.

Estimating the Cost of TBI

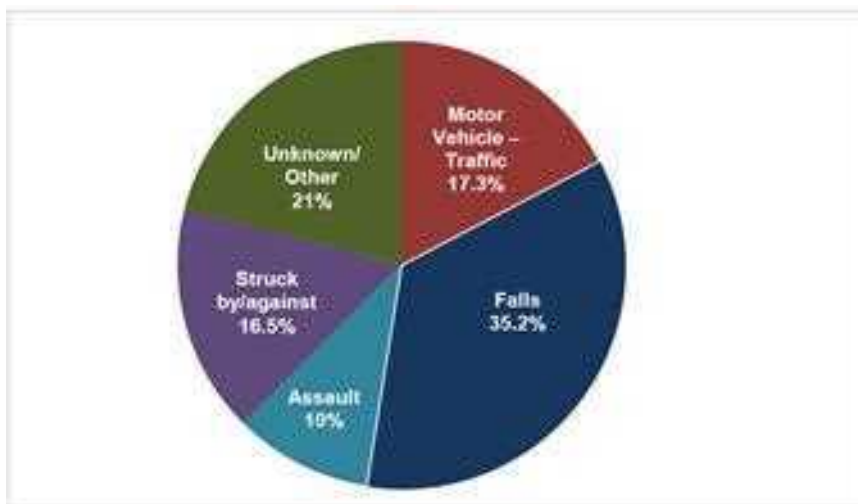
The only way to obtain realistic estimates of TBI-related costs in the military is to perform a comprehensive long-term study that obtains actual cost data at the level of individual patients, based on specific TBI characteristics, treatments, comorbidities, health

consequences, rehabilitation needs and long-term disability. Such a study must follow injured SMs and veterans over a long period to collect accurate cost data for services they receive. It must also account for the effects of improvements in technology and treatment on costs to ensure compatibility of cost estimates from different periods. To obtain information about the economic consequences of TBI-related mortality, families of those SMs who died from TBIs also can provide insight. Without continued study of the outcomes of military service-related TBI, estimates of the total costs of TBI to society will continue to rely mostly on assumptions and complex economic modeling techniques that might result in estimates that are imprecise or unreliable.

PREVENTION

Preventing TBI

Many potential ways exist to prevent TBI and the poor outcomes that can result when TBIs are sustained. Improving outcomes from TBI includes pre-hospital care and faster transport to medical centers. Early detection with better diagnostic tools also can lead to better outcomes when paired with timely interventions. Reducing risk of injury and preventing further damage after initial injury are essential to ensuring improved outcomes. Protective gear, including helmets, can prevent or reduce the severity of TBI. Helmet use is recommended in many sports and combat situations, and improved helmets with stronger and lighter weight ballistic materials for the helmet's outer shell as well as new helmet pads to provide greater blunt impact protection are under development as part of a developmental program known as the Soldier Protection System (SPS).



Source: Faul M, Xu L, Wald MM, Coronado VG, 2010.

Figure 6. Fatal and nonfatal traumatic brain injuries either occurring alone or in conjunction with other injuries by mechanism - US, 2002-2006.

The goal of SPS is to do development and testing during FY13 and FY14 with the intention of beginning production in FY15. The use of seatbelts in motor vehicles is required, as are motorcycle helmets for SMs in the non-deployed setting. Although not yet well understood, chest protection also seems to reduce blast TBI severity in rats, possibly by preventing systemic changes in blood pressure (*Long et al., 2009*). Enhanced forms of hard armor ballistic plates, improved outer tactical vests, pelvic protection systems, ballistic eyewear, and limited numbers of face shields and lower mandible protectors have already been fielded and will be further enhanced through the SPS. All of these improvements to personal protective gear are crucial advances for SMs moving outside of the forward operating bases and especially when dismounted from a vehicle. In addition, improved vehicle armor has also been instituted over the last several years to mitigate blast effects on vehicle occupants. Improvements in protective eyewear not only minimize fragment penetration to the eyes but also penetration to the brain.

Among veterans and SMs returning to the United States who are no longer at risk for deployment-related injuries, the prevention of TBI is similar to the civilian population (Figure 6). The majority of TBIs, either occurring alone or in conjunction to other injuries, are caused by several factors (e.g., falls, motor vehicle traffic crashes, and striking or being struck by an object or person, or acts of violence against oneself and others) (*Faul et al., 2010*).

Preventing TBI Associated with Motor Vehicle Traffic Crashes

Motor vehicle crashes and resulting injuries are a serious public health problem among civilian and military populations. Implementing prevention strategies to decrease the occurrence of these incidents is a public health priority.

Mortality rates from severe TBI in motor vehicle crashes (a leading cause of severe TBI in civilians and SMs) have declined since the 1970's, but remain unacceptably high. Programs and policies that encourage improvements in vehicle design, the road environment, and reductions in risky behaviors such as speeding, alcohol-impaired and distracted driving can reduce the risk of crashes. Activities that encourage improvements in occupant protection such as appropriate seat belt use and air bags can reduce the risk of injury in the event of a crash. Programs and policies to protect motorcyclists from injury include those that promote the use of helmets. Risks to pedestrians can be reduced through various measures that include vehicle, environmental and behavioral factors. (*NHTSA, 2011; Elvik, Høy, Vaa, and Sørensen, 2009*)

Preventing TBI Associated with Falls

Causes of falls vary, whether they occur as a result of falls among adults who might slip in their homes or teenagers who fall while engaging in athletic activities. Among older adults, fall-related injuries can be reduced by programs supporting regular weight-bearing and balance exercises; over the counter and prescription medication review to reduce use of those causing dizziness or drowsiness; annual eye exams to optimize vision; and home modifications when prescribed by an occupational therapist (e.g., reducing tripping hazards,

adding grab bars inside and outside the tub or shower and next to the toilet, adding stair railings and improving lighting) (Stevens, 2010; Gillespie *et.al.*, 2009). Injuries from falls among working-aged adults are most commonly experienced on the same level, on/from stairs or steps, or from a height such as on ladders or scaffolds; fall injuries during work are similar to those that are non-work related, suggesting that programs and policies successful in one arena might be applicable to others (Smith, Sorock, Wellman, Courtney, and Pransky, 2006).

Preventing TBI Caused by Striking or Being Struck

Struck by/against events are those in which a person was struck and unintentionally injured by another person or object (e.g., falling debris, a ball in sports) or a person struck against an object, such as a person struck against a wall or a collision between two or more people (Rutland-Brown *et. al.*, 2006). Many sports-related TBIs are included in this category. Sports and recreation-related TBIs can be prevented by programs and policies encouraging appropriate use of safety gear (such as helmets), environmental changes (such as padding goal posts and padding or removing other obstacles), strict officiating and enforcement of rules and sportsmanship, and examination of effects of select rule changes (Gilchrist, Saluja, and Marshall, 2007).

Rest before returning to play or work after even mild TBI is equally important. Re-injury leading to sudden death (second-impact syndrome) has been reported in some athletes who returned to sports after symptomatic concussions (Franklin, 2012). As described in the In-theater Screening section under Diagnosis, the military has implemented required rest periods following TBI.

Preventing TBI Associated with Intentional Injury

In addition to assaults, TBIs can result from self-directed violence, which is included as “other/unknown” in Figure 6. Interpersonal conflicts, relationship problems, and alcohol/drug use are common circumstances preceding homicides and suicides (Karch, Logan, and Patel, 2011). Suicide and violence- prevention strategies can reduce the risk of TBI by enhancing social problem solving and coping skills, improving access and reducing barriers to appropriate mental health care, and providing support and services to those struggling with multiple life stresses, including financial, substance abuse, and family violence-related challenges (Lubell and Vetter, 2006; Goldsmith, Pellmar, Kleinman, and Bunney, 2002; CSPV, 2012). In addition to individual and family-level factors, suicide and violence prevention strategies also need to address community-level factors such as norms about violence and help-seeking, access to education and employment opportunities, and the level of connectedness or social bonds among people (CDC, 2010).

Prevention of Secondary Brain Injury

Improved Emergency Medical Services (EMS) or pre-hospital care has substantially improved outcomes from TBI. In the prevention of secondary brain injury, pre-hospital care focuses on keeping airways open, maintaining blood and oxygen flow to the brain, and controlling blood pressure and hemorrhage, which can all improve survival and reduce long-term damage. Implementation of other types of early interventions to prevent secondary damage (e.g., hypothermia and administering osmotic agents) might depend on the situation, nearby infrastructure, and availability of experienced emergency teams (*Boer et al, 2012*).

Biomarkers for diagnosis also have the potential to improve early intervention and prevention of secondary injury. Research to identify TBI biomarkers is ongoing (*Schiff, 2012; Papa, 2012*). Some gene variants might have positive or negative effects on TBI outcomes (*Dardiotis et al., 2010; Miller et al., 2010; Al Nimer et al., 2012; Darrah et al., 2012*).

RECOMMENDATIONS

CDC, NIH, DoD and VA acknowledge that the military service-related TBI cases will be difficult to identify in civilian systems because several of these cases occurred in the past (e.g., during the early years of OIF). However, the majority of the incident and prevalent cases of military service-related TBI can be identified through TBI screening and reporting conducted by DoD and VA. Identifying cases of TBI not diagnosed while in service or by the VA system, although more difficult, might be possible by conducting surveys on veteran status; by educating health-care providers to ask their patients with TBI-related signs and symptoms about previous military service and risk factors, and to use, when appropriate, the terrorism and war-related ICD-9-CM external cause of injury (E) codes.

To accomplish the mandates of the *TBI Act of 2008* and to address identified public health concerns, CDC, NIH, DoD, and VA produced general recommendations applicable to all federal agencies and departments. In addition, recommendations specific to each agency and department might be useful for guiding their interactions with stakeholders. Underlying these recommendations is a commitment to using data sources that are accessible, valid, and reliable.

General Recommendations

CDC, NIH, DoD, and VA concur on the following key recommendations:

- **STRENGTHEN COLLABORATION:** Continue to foster and strengthen collaboration related to identifying military service-related TBI among current military SMs and veterans, including those who do not seek care from the military or VA health-care systems. Improving data collection and sources will be emphasized.
- **UTILIZE STANDARD DEFINITIONS:** Improve reporting through federal agencies that use and promote standard clinical and surveillance definitions and

severity classification of TBI among U.S. military and civilian health-care providers and researchers.

- **ENHANCE CODING AND CLASSIFICATION:** Continue to foster and strengthen collaboration with each other and other relevant organizations on coding and classification of TBI. All four participating agencies should continue to meet with professional, academic, health care, and coding organizations to discuss improvements in ICD-10-CM, including the classification of TBI and concussion and differentiation of self-limited and persistent symptoms. Revise the intracranial injury code set in ICD-10-CM to improve the accuracy of disease coding consistent with accepted case definitions before ICD-10-CM implementation on October 1, 2014.
- **IMPROVE DISSEMINATION:** Promote dissemination of information by federal agencies to non-VA facilities regarding TBI services available through the VA health-care system since 2007, including baseline screening and follow-up assessment and evaluation.
- **BUILD EVIDENCE BASE:** Continue research on the neurological consequences of blast events and TBI among SMs and veterans; the research should include 1) systematic neuropathological study in blast-exposed SM's and veterans who have died; 2) correlation of neuropathological and brain imaging findings; 3) prospective investigation of whether blast exposure increases risk for subsequent cognitive decline and neurodegenerative diseases such as chronic traumatic encephalopathy, Alzheimer's, Parkinson's and amyotrophic lateral sclerosis.

Recommendations to Improve TBI Diagnosis and Treatment

Military Health System

Development and validation of helmet-mounted sensor systems (HMSS). The Vice Chief of Staff of the Army (VCSA) directed that soldier combat helmets be fitted with electronic sensors that can record helmet response to dynamic events (blunt impacts, ballistic impacts, and/or exposure to blast events). Sensors that could be able to predict when someone has reached a threshold for exposures are under development (*McAllister et al., 2012; Broglio, Surma, and Ashton-Miller, 2012*). Development of a signal library of carefully controlled blunt, ballistic, and blast signatures will allow indirect identification of mechanical insults (exposure) of HMSS signals from the field. This will allow the development of an injury assessment tool, as the first approximation of a dose-response curve. Expanding the use of these sensors to the USMC and others with these types of exposures will be based on the efficacy of the Army's initial use of them.

Development of therapeutics to improve the outcome of mild, moderate, and severe TBI. Despite advances in basic and clinical research and neurological intensive care in recent years, and despite promising pre-clinical data, most of the clinical trials have failed to yield any significant improvement in TBI outcome. Nevertheless, DoD is currently exploring combination drug therapies, novel drugs, and small-volume resuscitation liquids (i.e., fluids administered to patients in relatively small amounts to restore and maintain adequate blood circulation following severe blood loss) for their ability to improve functional recovery from TBI.

Development of animal/computer model for TBI, most importantly for blast TBI.

No validated animal model exists for blast TBI. Development of a clinically and physiologically relevant model is critical for the successful validation of helmet-mounted sensors, SMS' protective armor, and for the evaluation of therapeutic interventions. Through a collaboration among Joint Improvised Explosive Device Defeat Organization (JIEDDO), DVBIC, and the Institute of Soldier Nanotechnology at MIT, the most advanced computer model of the brain and blast effects on the brain has been developed (*Moore et al., 2009*). Work to determine characteristic pathology of human blast injury is underway.

Identification of biomarker(s) to identify mild TBI/assay to discriminate between mild TBI and PTSD. Distinguishing between mild TBI and PTSD is complicated because of partial overlap in symptoms, including irritability, memory and concentration difficulties. The development of rapid, non-invasive, reliable testing is needed to discriminate between the subtle cognitive deficits of mild TBI and PTSD. Serum biomarkers such as S-100 protein show promise, although utility has been limited by its short half-life. Other biomarkers, including lactate dehydrogenase, neuron specific enolase, also might be useful but lack sensitivity and specificity (*Ingebrigtsen and Romner, 2002; Pike et al., 2004; Ringger et al., 2004; Pineda et al., 2007; Papa et al., 2010*). Preliminary results from ongoing serum biomarker studies are more promising. If these injuries could be detected objectively, quickly, and non-invasively, medical personnel would be able to begin early interventions.

VA Health System

The VA Office of Research and Development sponsored a State of the Art Conference in 2009 to identify research priorities for TBI. Representatives from DoD, NIH, DVBIC, and VA attended. A planning committee commissioned background papers for workgroup discussions. The papers examined topics such as the pathology of blast-related brain injury; diagnosis; comorbidities, including mental health issues and sensory deficits; brain imaging; care management; community reintegration; and, the role of veterans' families in TBI care. Six work groups focused on different aspects of TBI (i.e., basic science, neuroimaging, sensory deficits, comorbidities, rehabilitation and community reintegration, and care management) and then presented summaries of their findings and research recommendations for discussion with the entire group. An issue of the *Journal of Rehabilitation and Development* was dedicated to this meeting (Volume 46, Issue 6) and the research recommendations of the work groups were grouped into three main categories: (1) Diagnosing TBI (e.g., screening and imaging), (2) understanding short- and long-term effects of TBI (e.g., co-occurring conditions, severity, neurodegenerative disease), (3) understanding existing treatment approaches and developing new treatments (e.g., neurotrophins, neuroplasticity, case-management, community re-integration).

Civilian Health System

Although many opportunities exist to advance opportunities for TBI research and improve diagnosis and treatment in the civilian health system—that is, the organization of people, institutions, and resources to deliver health care services for the general population, a few strategic future directions for the field, with leadership from CDC, NIH, DoD, and the VA, include the following:

Developing a pathoanatomical classification system for TBI. During the past two decades much has been learned about TBI at a cellular and molecular level. Applying this knowledge to develop effective therapies for specific subtypes of injury, rather than for the entire constellation of injuries, is likely the key to developing successful interventions. Characterizing the pathophysiology and temporal evolution of these subtypes of injury would provide a foundation for identifying therapeutic targets and the window of opportunity for using them. It would provide the necessary scientific rationale for testing single and combined agents to hit these targets to attenuate injury or promote repair processes. A new classification system based on the pathoanatomy, rather than on the Glasgow Coma Scale also would inform chemical biomarker development and correlation of pathology with neuroimaging for these subtypes of injury. Surrogate markers would make it possible to identify people who have these subtypes of injury and also to monitor the biological effects of experimental interventions during clinical trials. Overall, breaking down the complex problem that TBI presents into smaller, more manageable parts should make it a more tractable problem.

Discovering the biological basis of mild TBI. This builds upon the previous recommendation because the milder injuries are often less complex than more severe injuries. Current research should be further enhanced to identify the biological mechanisms responsible for persistent deficits such as PCS and concurrent conditions including PTSD and to develop diagnostic tools for persons currently classified as having a mild TBI. Because a subset of persons described as having a mild TBI experience persistent disabilities, the term “mild” is often misleading.

Developing more effective and efficient approaches for preclinical drug development. Approximately 130 agents with proven preclinical efficacy for TBI are available, and more are under development and testing (*Marklund, Bakshi, Castelbuono, Conte, and McIntosh, 2006*). An efficient testing system for optimizing the dose and timing and for comparing effectiveness of interventions, alone and in combination, is needed to accelerate therapy development.

Facilitating data sharing. To date, much of the research on TBI has been small studies across agencies and centers, without definitively answering important research questions. A federal interagency project developed standardized terminology and a data dictionary for TBI to enable data sharing and secondary analysis and meta-analysis. In addition, the Federal Interagency TBI Research Informatics, a DoD and NIH collaboration, is available for aggregating and sharing data. Use across federal agencies is encouraged. Ongoing and new research on biomarkers would be accelerated by sharing data and supporting larger, multicenter projects to rapidly obtain greater numbers of samples and subjects. This is also true for advancing the development of neuroimaging and other diagnostic tools and biomarkers and for the validation of outcome measurement tools for clinical trials.

Coordinating and collaborating on clinical studies for TBI. A large, prospective observational comparative effectiveness research study is an efficient way to address some of the major gaps in knowledge regarding the validity of diagnostic tools and biomarkers and the effectiveness of various medical and surgical interventions for TBI. A coordinated and collaborative effort would enhance trial designs, increase the rate of subject enrollment and data collection, and optimize statistical analysis and data interpretation. Studies would be completed more quickly, and if successful, this collaborative approach would also facilitate implementation of these valid diagnostic tools, biomarkers, and proven interventions into clinical practice. TBI clinical studies should include subjects across the spectrum of injury

severity, across the lifespan, during acute and chronic stages of injury, and should evaluate pharmacologic and non-pharmacologic interventions.

Methodological Concerns and Research Priorities

Evidence indicates that continued research is needed to 1) determine the magnitude and socioeconomic and medical impact of military service-related TBI; 2) identify preventable and modifiable risk factors to reduce injury; 3) reduce impairment and disability; and 4) develop and evaluate evidence-based interventions.

CDC, NIH, DoD, and VA recommend that studies of the incidence and prevalence of military service-related TBI must include the following:

- Designed with clear and relevant research questions and methodology;
- Involve statistically representative populations;
- Allow determination of risk factors and the socioeconomic and demographic characteristics of these populations; and
- Allow characterization of the acute and long-term outcomes for TBI.

Such studies could assist in developing primary, secondary, or tertiary prevention programs, especially if modifiable risk factors are identified. Moreover, prevalence studies have the potential to identify gaps and guide resource allocation.

CDC, NIH, DoD, and VA also recommend continued evaluation and improvement of screening tools for TBI, especially tools used to identify milder forms of TBI. These studies are important to assess the incidence, prevalence, and long-term consequences of TBI, and the availability of and access to TBI-related support and rehabilitation services.

Finally, the four agencies also recognize that the recommendations in this report and all TBI-related management and treatment guidelines used by CDC, NIH, DoD, and VA need to be updated every 3 to 5 years to incorporate findings of epidemiologic, clinical, social, and behavioral research. The agencies are already working together through the Common Data Elements project and this provides one useful forum for regular reviews of important issues.

Morbidity and mortality associated with TBI affect civilian, military, and veteran populations. The leading causes of these injuries vary according to age and sex of injured persons. Therefore, these recommendations, prepared by the four participating agencies, will ensure that present practices in diagnosis of TBI and treatment for those persons affected by it will be sustained and improved. Additional progress to improve structural changes in defining TBI, improving surveillance systems, and recording epidemiologic data will assist in forming an achievable plan for the future.

Recommendations to Improve TBI Surveillance

Military Health System

To better estimate the incidence and prevalence of TBI in the MHS, DoD recommends:

- Screening all SMs as soon as possible following a possible TBI-causing event,
- Using the MACE or other appropriate screening tools; and
- Training all medical personnel (from theater through the VA system) in the detection and correct coding of TBI.
- Improving record keeping and standardizing multiple and disparate databases in the U.S. military using standardized common, streamlined questionnaires with variable complexity, depending on the level of care provided by the reporting medical facility (e.g., uncomplicated questionnaires for medics in theater to complex questionnaires for tertiary care facilities.) Coordination of databases has been initiated among DoD, VA, and NIDRR model systems.

Veterans Health System

Recommendations to better estimate the incidence and prevalence of TBI in the VA include:

- Continue screening all OEF/ OIF veterans upon contact with the VA health system;
- Training of all medical personnel in the detection of TBI and in the methods to correctly code for TBI; and,
- Timely and comprehensive follow-up evaluation of all veterans who screen positive for possible TBI.

Civilian Health System

Recommendations to improve surveillance of TBI in the civilian health system include:

- Expand surveillance activities by ensuring that TBI surveillance is part of comprehensive state injury surveillance systems,
- Continue to collaborate with DoD and VA to identify strategies for improving surveillance of TBI among veterans.

Methods for Detecting TBI Incidence and Prevalence

Military Health System

Key areas have been identified to improve measuring the incidence and prevalence of TBI in the military system, including case ascertainment; case documentation and reporting; follow-up; and, data dissemination. Specifically:

- Continue to use the established guidelines and strategies for identifying and treating TBI as described in this report; evaluate and update such guidelines every 3 years to reflect the advances in methods and technology.
- Produce portable data collection instruments to capture TBI data in the military, the VA, and civilian systems. These instruments should be specific to the level of care (e.g., a standard instrument to be used in theater only).

- Use TBI-specific diagnostic and external cause ICD-10 and ICD-9-CM codes to identify new cases (incidence) and history codes to ensure capturing prevalence data, recognizing the challenges of current coding and classification of TBI.
- Expand current care coordination and case management programs within DoD and VA to facilitate follow-up care and to document patients with persistent symptoms.
- Coordinate and exchange aggregated-level data (excluding personal identifiers) with CDC/NCIPC to produce a yearly report on TBI in the military by race/ethnicity, sex, age group, and risk factors. This report also should include information on the clinical characteristics, comorbidities, and concurrent injuries in persons with acute and chronic TBI.

VA Health System

Key areas have been identified to improve measuring the incidence and prevalence of TBI in the VA including:

- VA health-care system facilities should screen for TBI among eligible OEF/OIF veterans upon contact with the VA health system and further evaluate those who screen positive.
- Timely and comprehensive follow-up evaluation should be offered to veterans who screen positive for possible TBI.
- Medical personnel should be trained in TBI and in the methods to correctly code for TBI, recognizing the challenges with regard to current coding and classification of TBI.

Civilian Health System

Key areas have been identified to improve measuring the incidence and prevalence of TBI in the civilian health system including:

- Enhance capabilities to conduct surveillance at the state level; using national surveys, including public and private telephone and internet-based systems; and encouraging civilian and military health-care providers to document and report war and terrorism-related external cause-of-injury codes (E-codes).
- For all federally funded TBI research, use the newly recommended common operational clinical and surveillance definitions described earlier in this report, including all TBI-related ICD-10 and ICD-9-CM diagnostic, external cause of injury, terrorism, and war-related codes.
- Reporting incident cases of military service-related TBI while SMs are in the military. Collaborate with DoD, VA, and Defense Medical Surveillance System to share aggregated level data via CDC, and through peer and non-peer reviewed publications, periodicals, mass media, and books. Aggregate DoD TBI surveillance data is currently available at <http://www.dvbic.org/dod-worldwide-numbers-tbi>.
- Identification, surveillance, and burden of cases of military service-related TBI in veterans seeking care outside the VA system, which might include those who have not sought medical care or were not diagnosed while SMs in the military or VA health-care systems.

- Initiate research that examines disability, quality of life, and long-term outcomes associated with all severity levels of TBI.
- Add questions to federal or state sponsored population-based follow-up studies to determine the occurrence and the epidemiologic and clinical characteristics of the long-term consequences of TBI among eligible persons.
- Use existing civilian and military-related TBI surveillance systems and registries to develop prospective follow-up studies to determine the long-term epidemiologic, clinical, cognitive, and socioeconomic characteristics among eligible persons; and to determine if these persons have access to and receive appropriate social and rehabilitation services.
- Share TBI systems and registries available in the civilian, DoD, and VA Health Systems to determine the occurrence and the long-term medical and socioeconomic characteristics of TBI among eligible persons.
- Assess the burden of military service-related TBI in veterans receiving care outside the VA system. Routinely use the recommended federal TBI definitions when analyzing data from large national surveys and surveillance systems conducted by CDC/NCHS and other federal agencies (see Data Sources in Chapter VI).

Recommendations to Improve TBI Prevention

Ultimately the goal is to prevent the occurrence of TBI for SMs on- and off-duty. During off-duty hours and those retired from active duty, the risks are similar to the civilian population, with falls and motor- vehicle crashes among the major causes. Active-duty SMs face additional risk from blast and penetrating injuries. Further research is needed to ensure these risks are reduced. Where evidence-based strategies exist, it is imperative that there is strict adherence to those practices. The recommendations below focus on continued research to reduce risk factors, improve the quality of protective equipment, and ensure that current guidelines and evidence-based strategies are adhered.

- Enhance research to reduce the risk of TBI from blast injury.
- Research to promote adherence to current guidelines on returning to active-duty following TBI.
- Conduct more research to improve the quality of protective equipment such as helmets.
- Strengthen evidence on the risk and protective factors associated with a TBI or the prevention of a TBI. Research may include but is not limited to reducing use of alcohol, ensuring adherence to use of seatbelts, motorcycle helmets and other protective equipment.
- Provide meaningful education to veterans who have sustained a TBI, their families and their clinicians about the elevated risk for subsequent TBI and actions that can be undertaken to mitigate this risk.

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Chapter 268

THE SPATIAL ANALYSIS OF AIR POLLUTION PARAMETERS (PM₁₀, SO₂ AND NO₂): A CASE STUDY OF THE MARMARA REGION (2014-2017)

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ABSTRACT

Air pollution is the increase of foreign matters in the air above normal number and density. This affects the health living creatures in a negative way or may cause physical injuries, while air pollution-related effects and health problems can be also observed in healthy people, in especially elderly people and children, air pollution creates serious health problems on human health and causes more than 3 million people's death every year. This necessitates the examining and monitoring processes of air pollution and taking precautions against it, whenever needed. In this study, spatial pollution distribution maps of the Marmara Region that receives migration in high amount because of the intensive industrial activity in Turkey, are created by the identification of air pollutant parameters' (PM₁₀, SO₂ and NO₂) patterns which are obtained by air quality monitoring stations of Marmara Clean Air Central and Ministry of Environment and Urbanization between the years of 2014-17.

Keywords: air pollution, geostatistical analysis, spatial analysis, GIS

INTRODUCTION

Urbanization is defined as the increase in the urban population by the breakdown of the population between the cities and rural areas, and by the migration of people from rural areas

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to the cities. It is argued that within the period between the 1800s to these days, world population approximately doubled and this increase brought significant problems. While the living rate was 2,4% in the locations that have 20.000 and more population in the 1800s, this rate increased to 4,3% in the 1850s and to 9,2% in the first years of the 1990s. The highest increase took place in the 1950s as 20,9%. Along with the rapidly increasing population in a very short time period, pollution in cities showed a rapid increase (Demirarslan and Akıncı, 2018; Partigöç and Cubukcu, 2017).

Air pollution is the increase of foreign matters in the air above normal number and density. This pollution that affects the health of living creatures' in a negative way or cause physical injuries. . Air layer, by getting polluted with the waste that emerges as a result of human beings' various activities and shows up during production and consumption activities, affects the life of human beings on earth in a negative way (Akyurek et al., 2013). Global warming, industrial activities, consumption of fossil fuel that are used in motor vehicles, uncontrolled population growth and unplanned urbanization are listed as the primary factors that cause increase in pollution (Partigöç and Cubukcu, 2017).

Particulate matters (PMs) are the tiny granular solid or liquid particles that are spreading in the atmosphere and stay suspended in air. PMs may consist of several natural and artificial sources like burning of fuels, diesel engines, construction and industrial activities, secondary aerosols (reactions of ammoniac, Sulphur and nitrogen oxides in the air), herbal pollens and dusts that are raised from the ground. PMs cause serious health problems according to their sizes. As the sizes of PMs become smaller, they enter into the deepest points of lungs and destroy the structure and chemistry of lungs.

Sulphur dioxide (SO₂) is a colorless, suffocating and acidic gas released by the burning of the Sulphur compounds that are found in its structure. Main existing Sulphur dioxide producing activities are industrial applications, domestic fuels that are used for heating purposes, steam power plants and the use of diesel vehicles (Akyurek et al., 2013; Demirarslan and Akıncı, 2018).

Nitrogen dioxide (NO₂) is a reddish-brown, pungent gas. Primary sources of NO₂ are the fuels that are used in vehicles, industrial plants and domestic heating. Its stay in the atmosphere changes according to the height. It can stay several months at the sublayers of the atmosphere, at the upper layers, on the other hand, it can stay only a few days. It causes serious problems in respiratory tracts and it may be fatal if it is inhaled in high doses (Cetin, 2006).

It is stated in the previous studies that long exposure to the air pollution has detrimental effects on human health. Diseases like cough, bronchitis, heart disease and lung cancer show an increase depending on the air pollution. While air pollution-related effects and health problems are also seen in healthy people, especially elders and children, it creates serious health problems on human health. Therefore, examining, monitoring and taking precautions for air pollution is a significant issue. This problem causes more than 3 million people's death every year.

Geostatistics is an applied branch of statistics and it is a set of statistical methods which are evaluated with spatial data in earth sciences. Apart from the classical statistical methods, population parameters can be estimated related to the examples that are depended on one another instead of the examples that are independent of each other rule. Geostatistical analyses are used for predicting the value of the locations, in which observation is not carried out. In this sense, continuous surface format maps of data are obtained by making

interpolation at the points that are not measured in the land (Akyurek et al., 2013). In literature, there are many studies that have investigated and analyzed air pollution via geostatistical methods (Elbir, 2004; Fedra and Haurie, 1999; Lin and Lin, 2002; David et al., 1997; Briggs et al., 2003; Chen et al., 2015; Hee-Jae and Myung-Jin, 2014; Xiao et al., 2014; Rohde and Muller, 2015; Matejicek, 2005; Song, 2008, Demirarslan and Akıncı, 2018; Kim et al., 2018, Moral et al., 2010, Esperanza et al., 2004, among others).

This study aims to create spatial pollution distribution maps of the Marmara Region, which receives migration in high amounts because of the intensive industrial activity in Turkey, by the identification of air pollutant parameters' (PM₁₀, SO₂ and NO₂) patterns which are obtained by air quality monitoring stations of Marmara Clean Air Central and Ministry of Environment and Urbanization between the years of 2014-17.

MATERIALS AND METHODS

Study area, the Marmara Region, is a region that is located between the 26° and 31° east longitudes, 38° and 42° north, hosts Turkey's cities which are developed industrially, and has 24,816,023 population according to the Turkish Statistical Institute's data and address-based population information. Increasing population and rapid industrialization bring along rural-urban migration movement. The Marmara Region, which is one of the important industrial zones of Turkey, and has been exposed to continuous movement of migration. It received 3,240,686 immigrants from the other cities between the years of 2014 and 2017, which is the period of study, according to the Turkish Statistical Institute's data. When the highest migration receiving cities are examined, cities like Istanbul, Bursa, Kocaeli and Tekirdag that have developed industrial activities, come to the forefront (Figure 1).

The increase in the urban population brings along various environmental pollution issues. One of the most important pollutions is the air pollution. Air quality monitoring stations have been established throughout the country since 2005 in order to detect, analyze and take necessary precautions, in a timely fashion, for air pollution. Air quality is monitored with hourly measurements by 125 stations that are established by the Ministry of Environment and Urbanization in 81 provinces and 39 stations that are established by the Marmara Clean Air Center. In many countries, limit values, which are determined by the European Union and World Health Organization, are used as the local limit values in order to keep air pollution under control. Limit values for air pollutants in long term, short term and winter periods are determined in the regulations of Air Quality Evaluation and Management that was published in 2008 in Turkey. PM₁₀ and SO₂ pollutants' limit values that belong to Turkish Limit Values, European Union and World Health Organization are shown in Table 1.

Table 1. PM₁₀ and SO₂ pollutants with the national and international annual limits

Pollutant	Turkish Limit Values (AQEMR) (µg/m ³)	EU Regulations (µg/m ³)	WHO Guidelines (µg/m ³)
PM ₁₀	44	40	20
SO ₂	20	20	-
NO ₂	44	40	40

Data used in this study is obtained by the 45 Air Quality Monitoring Stations that are located in the Marmara Region between the years of 2014 and 2017. Air Quality Monitoring Stations' locations are shown in Figure 2. Hourly recorded PM₁₀, SO₂ and NO₂ pollutant parameters are used in the analyses conducted by the transformation of daily values first, and then monthly and yearly values.

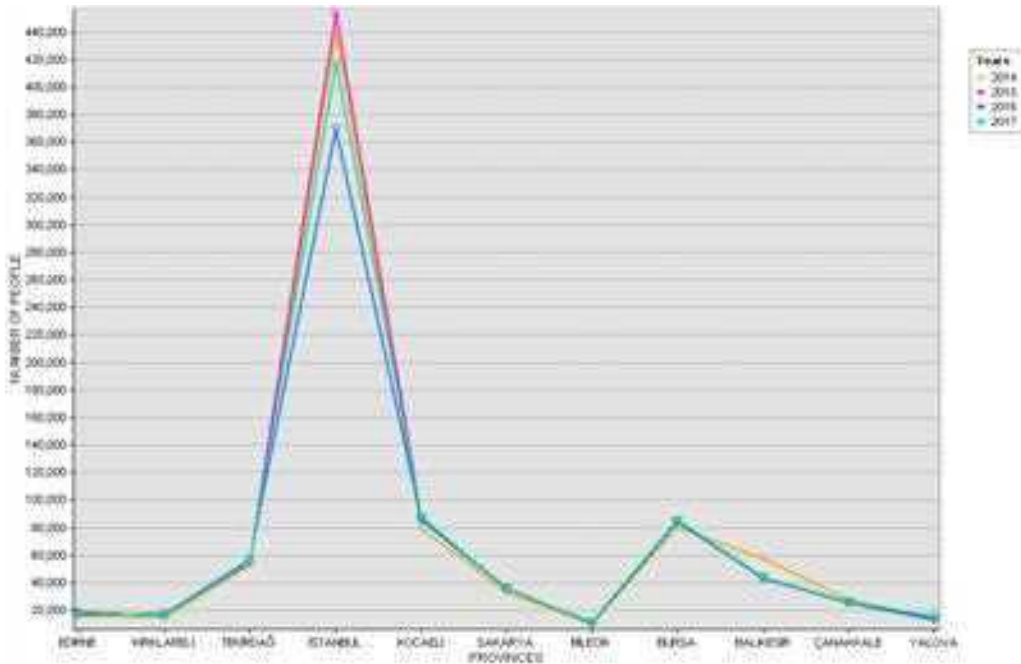


Figure 1. Migration distribution diagram according to the provinces.

The problem of classical statistical methods is the assumption that data variables are independent of each other. It is not possible to obtain exact statistical independence for the values that are distributed in a specific structure. According to Tobler (1970), closer things are more related to each other than the further ones. The spatial dependence, which is defined as the observations that are close to each other are more similar than the observations that are remote to each other, invalidates classical statistics' independence assumption (Atkinson, 2002). Geostatistics is a statistical calculation method that approaches the relationship among the data by also taking account of their locations. The method has significant advantages like the detection of the error quantity at particular confidence levels. Geostatistical analyses are used for predicting the values of the locations, in which observation is not carried out. In this sense, continuous surface format maps of data are obtained by making interpolation at the points that are not measured in the land. These operations consist of two parts: modelling (semivariogram calculations) and spatial interpolation (Kriging method). The semivariogram is the calculation of the sample variance's change with the distance. Closer samples show similar variance value and generally show an increase with the distance between variance samples compared to the distant ones. The Kriging method, on the other hand, is used to predict features of spatial structure between the samples that are obtained by the semivariogram calculations, at the points that sampling is not done (Akyurek et al., 2013; Yesilkanat et al., 2014).

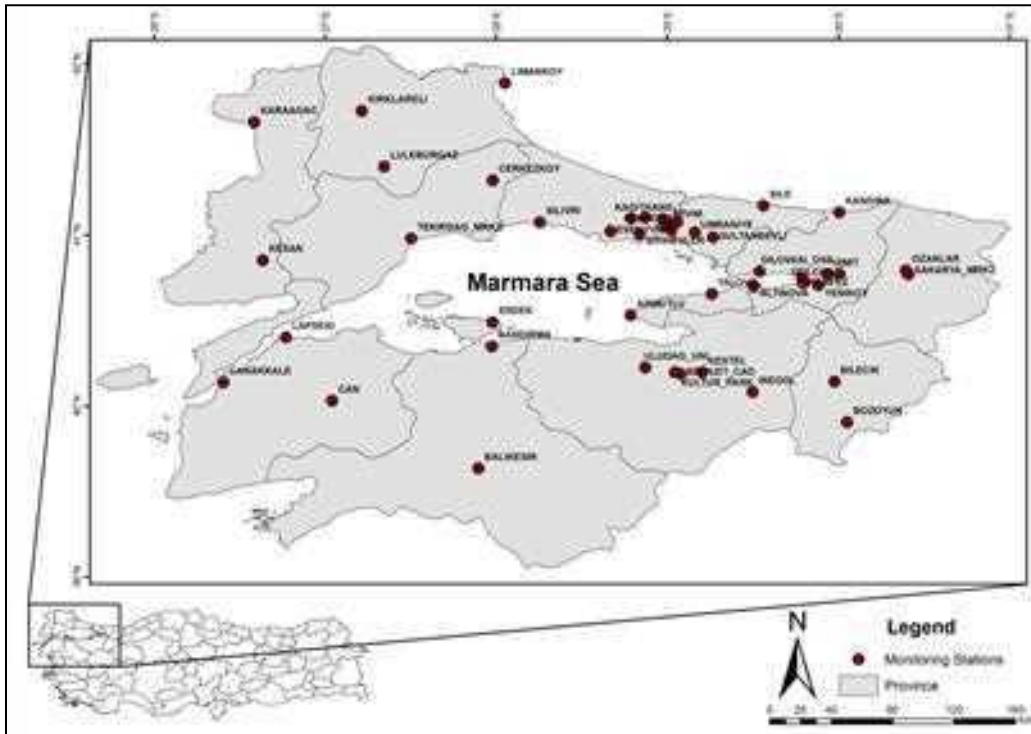


Figure 2. 45 Air quality monitoring stations available in the Marmara Region.

The semivariograms are specified for the study area, in which the measurement is made, as in the equation below;

$$\gamma(h) = \frac{1}{2N(h)} \sum_{i=1}^{N(h)} \left(Z(x_i) - Z(x_j + h) \right)^2 \quad (1)$$

Here, $\gamma(h)$ demonstrates the semivariance value, the distance between h , i and j points, $N(h)$ demonstrates the number of dot pairs at h distance, $Z(x_i)$ demonstrates the measurement value of data in the data set at the i point and $Z(x_j+h)$ demonstrates the measured value of the data in h distance.

One of the semivariogram parameters as seen in Figure 3, nugget, is the point where the theoretical curve intercepts vertical axis at $h=0$ point. It does not affect the prediction value, it only causes change in the Kriging variance. Partial Sill is the vertical scale value for the structural components of the variogram. Range is the horizontal distance of the variogram. After this length, the data are uncorrelated with each other. The variogram or covariance values remain stable after this length. The change in the range causes also the change of interpolation value. The Llag distance is the horizontal distance between the sampling points and inter sampling points or interpolation points. The sill is the total vertical scale value of the variogram function. It does not affect the prediction value, it only causes change in the Kriging variance (Akyurek et al., 2013).

The Kriging, which is the geostatistical analysis method at Geostatistics, is used to determine the quadrennial air quality in the area examined, and it is carried out by aiming to map spatial distribution of the pollutant parameters by the geostatistical analysis.

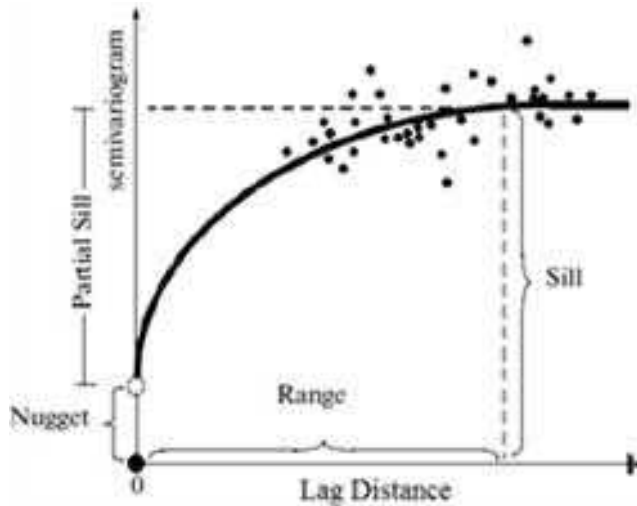


Figure 3. The semivariogram model and its parameters.

RESULTS AND DISCUSSION

The annual mean values that are calculated from the pollutant parameters (PM_{10} , SO_2 and NO_2) and obtained as hourly average from the 45 Air Quality Monitoring Centers in the Marmara Region between the years of 2014 and 2017, are used in the study. Firstly, the comparison of the limit values is carried out with the calculated annual means. Accordingly, the number of the stations that exceed the limit values according to the Turkish Limit Values are detected and shown in the Table 2.

When the number of the stations, which exceed the limit values are examined, for the particular matters and SO_2 , it is found that they are the air quality stations in which industrial plants are located generally. It is observed that the limit values exceeded especially in the stations that were in Istanbul, Bursa, Tekirdag and Kocaeli. Also, the PM_{10} and SO_2 values were calculated far above the limit values in Kesan province that used solid fuel for domestic heating and the Can province that had thermal power plant within its borders, during the time period when the data were collected. It is observed that the SO_2 values that were calculated in Kesan and Can were ten times higher than the limit values. When the stations that exceeded the NO_2 limit value were examined, it was evident that these stations were the stations in the provinces that generally had high values in terms of population. The main sources of the NO_2 were the fuels that were used by the vehicles which re used for transportation and industrial plants. When the quadrennial period was examined, the NO_2 value was calculated above the limit values especially in the stations in the provinces that weres crowded both in terms of population and industrial plants such as Istanbul and Bursa.

In the creation of the spatial distribution maps, the weights and possibilities that were determined by the semivariograms by the help of ordinary Kriging method, were used. With the help of this method, the pollution distribution maps of three pollutant parameters were created belonging to four different years (from 2014 to 2017).

Table 2. The number of stations that exceed the Turkish Limit Values by years

	PM ₁₀	SO ₂	NO ₂
2014	18	6	8
2015	20	8	7
2016	18	13	8
2017	21	10	8

The distribution maps that belonged to the PM₁₀ pollutant parameter are shown in Figure 4. In Figure 4-a, in the distribution map that belonged to 2014, it is seen that Bursa province, which is one of the industrial cities of the Marmara Region, and Istanbul Esenyurt district were high in terms of the PMs . Also, it was observed that PM densities in the air were above the limit values in Kesan, Can and Bozuyuk districts and also in Tekirdag city center. In Figure 4-b, it the distribution map that belonged to 2015, it is seen that PM density in Esenyurt and Tekirdag city center was higher than the previous year. In other centers, on the other hand, it is observed that it remained at similar levels. In Figure 4-c, in the distribution map belonging to 2016, it is seen that pollution level went down the limit level and below in the other stations except in Tekirdag city center and the Bursa province. In Figure 4-d, in the distribution map that belonged to 2017, it is seen that pollution level maintained the tendency of the previous year.

The biggest source of the SO₂ pollutant is the solid fuels that are used for domestic heating. Because of the fuels that have high Sulphur rate are not burned properly, the Sulphur amount extracted to the atmosphere is measured very high in the locations that use solid fuels for domestic heating. The SO₂ pollutant parameter's distribution maps are shown in Figure 5. In Figure 5-a, the distribution map that belonged to 2014 is shown. It is seen that the values were exceedingly above the limit value in Edirne's Kesan district that used stove and its derivatives for domestic heating during the time of data collection and Canakkale's Can district that had coal-fired thermal power plant, which was used for power generation within its borders. Also, it is found out that calculated values were above the limit values again in the Bursa province and Kocaeli's Kandira district. The distribution maps that belonged to 2015 and 2016 are shown in Figure 5-b and c. It is seen that the values in Kesan and Can districts were still far above the limit values although the other stations went down the limit value level. In Figure 5-d, it is observed that the SO₂ level measured in the stations, fell down thanks to the precautions taken. It is seen that while the measured pollutant values reached the limit values in Can, they were at lower levels compared to the previous years in Kesan.

The biggest sources of the NO₂ pollutant are the fuels that are used at the transportation vehicles, industrial plants and fluid fuels that are used for the domestic heating. The distribution maps that belong to the NO₂ pollutant parameter are shown in Figure 6. In Figure 6-a, in the distribution map that belonged to 2014, it is seen that the NO₂ pollutant parameter was close to the limit value and above in Istanbul, Bursa, Kocaeli and Tekirdag provinces that had industrial plants intensively, were the highly populated provinces and had the highest migration rates every year. In Figure 6-b and c, a similar situation is seen in the distribution maps that belonged to 2015 and 2016. But in Figure 6-d, in the distribution map that belonged to 2017, it is seen that the measured values distributed to the entire provincial border with a rapid increase especially for Istanbul and Bursa.

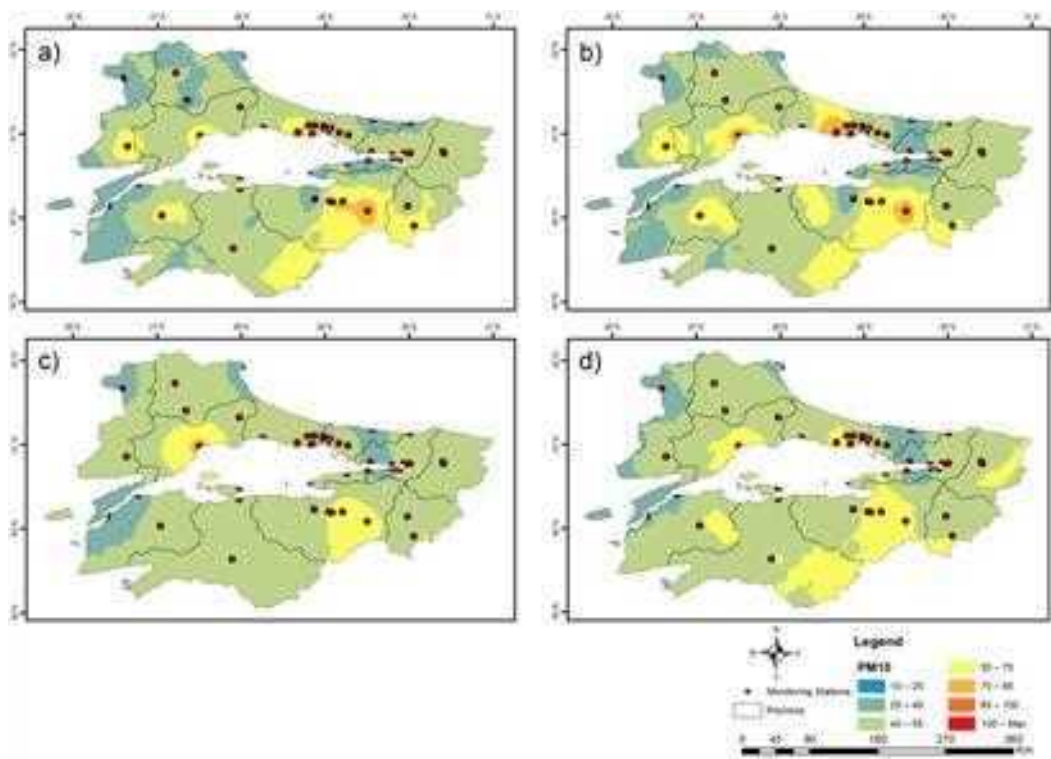


Figure 4. The PM₁₀ Pollutant's Distribution Maps; a) 2014, b) 2015, c) 2016 and d) 2017.

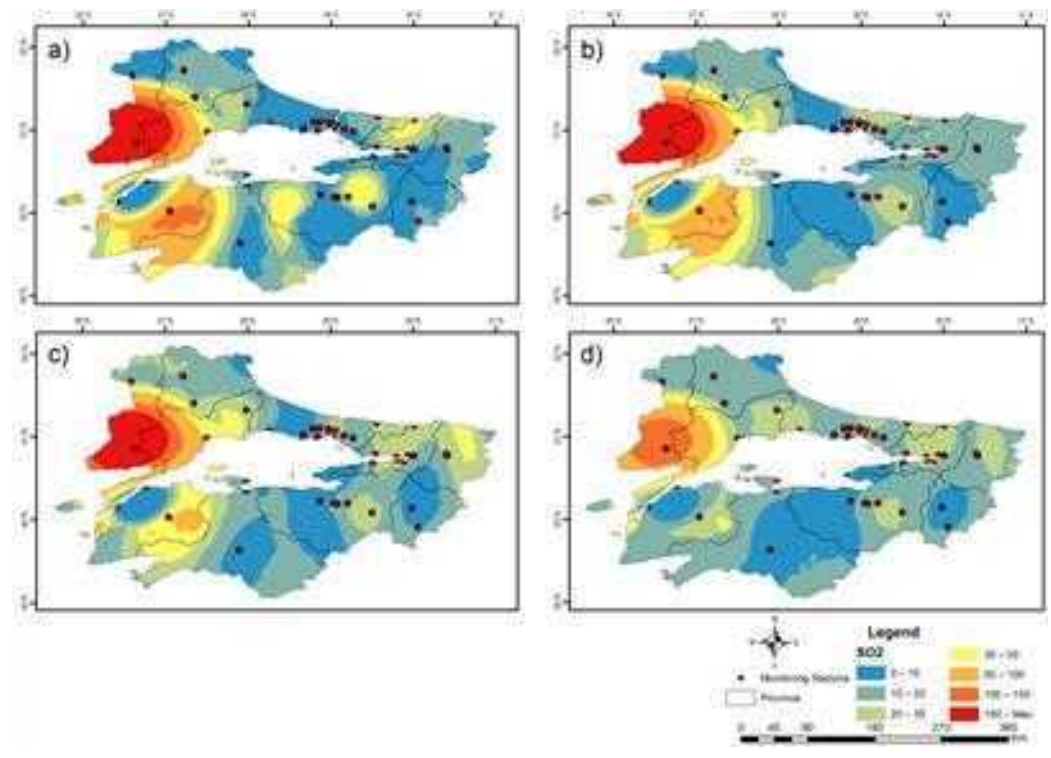


Figure 5. The SO₂ Pollutant's Distribution Maps; a) 2014, b) 2015, c) 2016 and d) 2017.

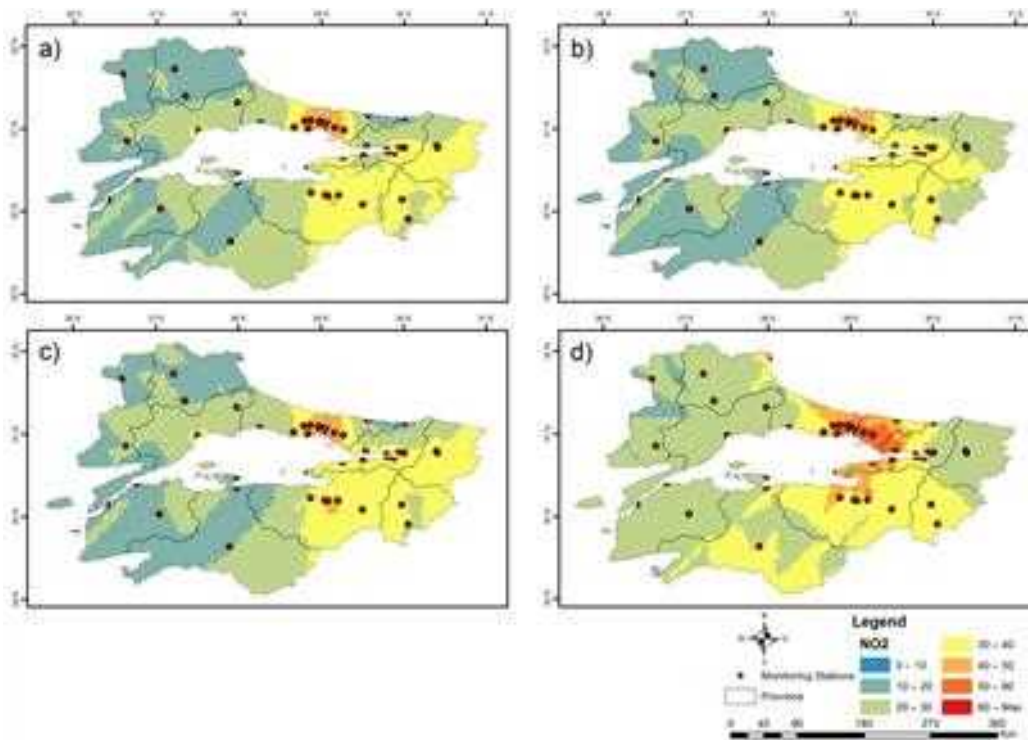


Figure 6. The NO_2 Pollutant's Distribution Maps; a) 2014, b) 2015, c) 2016 and d) 2017.

CONCLUSION

In this study, the pollutant parameters' distribution maps by years were created by using spatial analysis of the air pollutant parameters that were measured by 45 Air Quality Monitoring Stations in the Marmara Region between the years of 2014 and 2017. With Geostatistics technique, the spatial pollution distribution maps were created by the identification of spatial patterns regarding to the air quality parameters and the station-based statistics were evaluated with the dynamic mapping. The findings of this study revealed that the Geostatistics-based spatial statistical applications are an effective tool for the air quality management.

It was observed in the maps, which were used in this study that PMs showed higher distributions in the locations that had more amount of industrial plants and they reached to high values also in the locations that used solid fuels for domestic heating. When the SO_2 's distribution maps were examined, the Kesan and Can districts reached to excessive values in terms of this pollutant but it was observed in the distribution maps that precautions taken were effective. When the NO_2 's distribution maps were examined, it was observed that the cities that had higher population density, had higher values in terms of this pollutant. The effect of population on this parameter might be clarified with intensive vehicle traffic, fluid fuels that were used for heating and intensive industrial plants.

Air is a vital environmental element. This environmental element, which is vital to maintain life, is essential for human life as a physical factor. The air is breathed between ten

thousand and twenty thousand liters per person in a day. The air that is used in such a high rate must have high quality. Low air quality causes fatal effects. Air quality needs to be examined regularly and kept under control. Geostatistics is an effective tool for monitoring and examining air quality. The pollution distribution maps that are created with the help of Geostatistics, turns into a source of information that provides prominent information for air quality determination and enhancement. It provides useful information to the decision-makers for the precautions that will be taken in the future. With the help of spatial mapping that can be updated instantly, people will be provided with information about the quality of the air they breathe and decision makers can provide a healthier environment and clean air for the people who live in these places.

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Chapter 269

OBESITY, OBESITY SURGERY AND NURSING CARE

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ABSTRACT

Obesity is not just an emerging health problem, it also leads to other public health problems, including: diabetes, hypertension, cardiovascular diseases, cancer, depression, infertility, and it negatively affects social life as well. In the simplest terms, obesity is an energy irregularity characterized by abnormal or excessive fat accumulation.

The increase in obesity incidence is a common situation for all countries that is parallel with their development level and increased consumption of ready-to-eat foods. According to the World Health Organization (WHO), obesity has increased nearly threefold worldwide since 1975. In 2016, more than 1.9 billion adults over 18 years of age were overweight, and over 650 million of them were obese. The obesity rate in Turkey was 15.2% in 2008, and it increased by 31.1% and reached 19.9% in 2014. Globally, many factors contribute to increasing in obesity rates due to reduced physical activity as a result of jobs that require minimal physical activity become more common, less mobility, changing modes of transport, the consumption of fatty and high calorie foods and increased urbanization.

Obesity is an important public health problem in our country and worldwide, and it causes a variety of physiological, psychological and social complications by negatively affecting obese people's quality of life and many organ systems in their bodies. Although diet, physical activity, psychological support and pharmacotherapy are commonly used treatments for obesity, obesity surgery (bariatric surgery) has recently emerged as a contemporary treatment modality.

The success of obesity surgery requires a multidisciplinary team approach including surgeons, psychiatrists, nutritionists, nurses, physiotherapists and other health professionals from the moment patients apply to hospital until being discharged. It is also very important to meet special needs due to the accompanying diseases of obesity surgery patients.

Providing personalized, individualized and holistic nursing care and counseling services to the patients who will undergo obesity surgery patients to reduce possible risks in their care, and preventing complications and difficulties before, during and after

surgery are very crucial. These services are also important to increase patients' quality of life.

Keywords: obesity, obesity surgery, bariatric surgery, nursing care

INTRODUCTION

Nowadays, obesity is considered as a chronic, progressive and life threatening disease because of the comorbidities and obesity-related psychological problems. Obesity which is defined as “excessive fat accumulation in the body to the extent that derange health” by the World Health Organization (WHO), is a disorder that needs to be treated endocrinally, metabolically, and psychologically. Normally, fat tissue constitutes 15-20% of body weight on average in adult males while it constitutes 25-30% of body weight on average in adult females. When the ratio of fat tissue exceed 25% of body weight in males and 30% of body weight in females, this condition is called as obesity (Bozbora, 2002; Turkish Public Health Institution, 2013).

The prevalence of obesity which has become an increasingly important health problem, increases in all ages and socio-economic groups in all developed and developing countries. According to the obesity rates in the Organisation for Economic Cooperation and Development (OECD) countries, the ratio of obese persons in the adult population is 19.5%. This rate varies according to countries, it is lower than 6% in Korea and Japan and higher than 30% in Hungary, United States of America, New Zealand and Mexico. More than a quarter of adult population is affected by obesity in the United Kingdom, Chile, Australia, Canada and South Africa. The ratio of overweight and obese individuals has increased in the United States, France, Mexico, Canada and Switzerland while it has not changed in Korea, Spain, England and Italy within last decade (OECD, 2017). In Turkey, the obesity rate was 15.2% in 2008, increased by 31.1% and reached to 19.9% in 2014 (TUIK, 2015). According to the OECD 2017 data, the prevalence of obesity in Turkey (22.3%) is higher compared the average obesity prevalence in the OECD countries. Obesity rates are expected to be high especially in the United States (47%), Mexico (39%) and England (35%) in the year of 2030 (OECD, 2017).

Obesity is accepted as a natural consequence of modern life by many individuals while it is usually related with diseases such as cardiovascular diseases, metabolic syndrome, type 2 diabetes mellitus (DM), a decrease in physical activity due to lifestyle especially in transportation, production and agriculture along with advancing technology, the changing eating habits in modern life play roles in the increasing prevalence of obesity. Fast-food is a diet being rich in terms of fast-eating unhealthy foods, carbohydrates and refined sugar and which is poor in terms of vegetable fiber, leads to obesity. In addition, the widespread use of high-tech devices (mobile phones, televisions, computers, home cinema systems, etc.) that easily fill our leisure time, has an important contribution to the increase of obesity. In addition, endocrine disorders such as diabetes mellitus, hypothyroidism, growth hormone deficiency and drugs that disrupt metabolic control such as antipsychotics, glucocorticoids, anabolic steroids also play an important role in increasing prevalence of obesity (Turkey Endocrinology and Metabolism Society, 2017; Turkish Public Health Institution, 2013).

Nowadays, there are three methods to determine obesity. These three methods are ideal weight, body mass index (BMI or Quetelet index) and the measurement of subcutaneous fat. Individuals having a body weight which is 10% higher than ideal weight, are defined as overweight while individuals having a body weight which is 20% higher than ideal weight, are defined as obese. BMI is a practical method used to classify obese people and to plan treatment methods (Asoglu, 2008; Bozbora, 2002). The World Health Organization (WHO) defines overweight and obesity based on body mass index ($\text{BMI} = \text{Weight [kg]} / \text{Height [m}^2\text{]}$). According to this definition, individuals having a BMI between 18.5-24.99 kg/m^2 are classified as normal weight; individuals having a BMI between 25.0-29.9 kg/m^2 are classified as overweight; individuals having $\text{BMI} \geq 30 \text{ kg/m}^2$ are classified as obese; individuals having a BMI between 30-34.9 kg/m^2 are classified as class 1 obese; individuals having a BMI between 35-39.9 kg/m^2 are classified as class 2 obese; individuals having a $\text{BMI} \geq 40 \text{ kg/m}^2$ are classified as class 3 obese (Turkey Endocrinology and Metabolism Society, 2017; WHO 2018). In the measurement of subcutaneous fat tissue, which is another method for the diagnosis of obesity, the sum of the thickness of skin across scapula and triceps which is $>55 \text{ mm}$ in females and $>32 \text{ mm}$ in males is defined as obesity (Bozbora, 2002).

Obesity creates a fertile environment for the development of many health problems such as cardiovascular diseases, hypertension, diabetes, certain types of cancer, respiratory system diseases, musculoskeletal system diseases. It also increases health care expenditures and negatively affects the quality and duration of life (Turkey Endocrinology and Metabolism Society, 2017). Advanced obesity is often called as morbid obesity because of the diseases associated with obesity. Morbid obesity is a metabolic disease and is associated with numerous medical problems. In fact, most of these problems are not observed in the absence of obesity while many health problems arise with weight gain. The most common problems are arthritis and degenerative joint diseases; at least 50% of the patients who undergo surgery due to morbid obesity have these accompanying diseases. Premature deaths are more frequent in children of obese individuals; the death rate of morbid obese individuals is 12 times higher compared to normal-weight individuals in 25-35 years old male individuals. Obesity is observed in 25% of asthmatic patients, 30% of hypertensive patients, 20% of diabetic patients and 20-30% of the patients with gastroesophageal reflux. The incidence of these comorbid diseases increases according to the duration of obesity and age. The number of comorbidities (Bozbora, 2002; Sakrak and Dikmen, 2010), socioeconomic problems, psychological disorders and premature death risk increase in patients over 50 years of age (Asoglu, 2008).

TREATMENT OF OBESITY

The goal of obesity treatment is to alleviate obesity-related morbidity and mortality risks, to bring individuals adequate and balanced nutrition habits and to improve the quality of life (Turkey Endocrinology and Metabolism Society, 2017). Obesity is a global pandemic and is also considered as a treatable and preventable health problem. It can be treated by medical nutrition (diet), physical exercise, behavioral change, pharmacological and surgical methods (Alican, 2007). The diet succeeds only in a small part of the patients and does not take a long time for the patients to regain their lost weight. An effective and safe pharmacological agent has not been developed in the treatment of obesity. Pharmacological preparations in use are

not effective or not preferred due to their adverse effects. In this context, it has been stated that diet, physical exercise and behavioral change are indispensable in obese patients while pharmacological and surgical treatment can be applied if required. Surgical treatment may be effective for the treatment of morbid obese patients (Asoglu, 2008; Yuksel, 2016).

Medical Treatment

Obesity treatment is a combination therapy that includes lifelong adequate and balanced nutrition, increased physical activity and behavioral therapies. Essentially, medication is not recommended for the treatment of obesity at the beginning. However, drug treatment may be applied temporarily for selected patients (patients in the high-risk group ($BMI \geq 30 \text{ kg/m}^2$)) by an endocrinologist (Turkish Public Health Institution, 2013).

In obesity treatment, behavioral change therapy is absolutely necessary along with nutritional therapy and increased physical activity. In combined treatment, nutritional therapy, exercise and behavioral change therapy are used in combination and provide great success in both weight loss and maintenance of weight loss. The goals of medical nutrition therapy in obesity are:

1. To provide adequate and balanced nutrition which is appropriate for the individual's age, gender, physical activity status, life style and physiological condition.
2. To provide proper and lasting nutrition habits instead of wrong nutrition habits.
3. To decrease the body weight to the desired level (this level may be an ideal weight or a weight over ideal weight).
4. To stop regaining weight, thus individuals lost body weight and to keep it at the desired level lastingly.
5. To maintain normal growth and development in children (Turkey Endocrinology and Metabolism Society, 2017).

Surgical Treatment

The surgical treatment of obesity is the only proven method for achieving long-lasting weight loss by controlling and potentially resolving life-threatening comorbidities and improving the quality of life of morbid obese patients at the same time. It was showed that the expected length of life increased by 12 years after the surgical treatment of obesity (Frantzides et al., 2013). Obesity surgery (bariatric surgery) is one of the increasingly popular obesity treatment methods in the world in the last decade. The number of patients undergoing bariatric surgery increase day by day because obese patients lose weight rapidly in addition to a decrease in comorbid diseases after bariatric surgery (Yuksel, 2016).

The aim of surgical treatment is to reduce morbidity and mortality due to obesity and to improve metabolism and organ functions. Thus, obesity-related comorbidity, drug expenditure and time lost due to being ill decrease while the quality of life improves (Turkey Endocrinology and Metabolism Society, 2017).

Despite the significant developments in technique, care and follow-up in bariatric surgery, the risk and perioperative complications have not been alleviated. Therefore the selection of appropriate patient and appropriate technique is very important (Turkey Endocrinology and Metabolism Society, 2017). A bariatric surgical team consists of an endocrinologist, nutritionist, anesthetist, operating room nurse, operating room technician, nurse care coordinator (advanced nurse or a well-educated nurse), a psychiatrist, a psychologist, cardiac, pulmonary, gastrointestinal, endocrine, musculoskeletal and neurological specialists (Frantzides et al., 2013; Sakrak and Dikmen, 2010; Turkish Public Health Institution, 2013; Yurdakul, 2015).

The selection of an appropriate patient should be meticulously performed according to the recently adopted criteria of the National Health Institution (NIH) independently of the type of surgery, to be able to perform bariatric surgery. For performing bariatric surgery, a patient must have a Body Mass Index (BMI) ≥ 40 kg/m²; if a patient's BMI is >35 kg/m², he/she must have obesity-related comorbidities (Type 2 diabetes, severe HT, arthritis, sleep apnea syndrome, etc.), inability to control it with medical treatment and lifestyle changes, previous unsuccessful attempts with non-surgical methods (diet, medicine, etc.), an age between 18 and 60 years and the duration of obesity >5 years (Bozbora, 2002; Frantzides et al., 2013; Sakrak and Dikmen, 2010; Turkey Endocrinology and Metabolism Society, 2017). The inability to adapt daily life conditions because of obesity and having some psychological problems due to obesity are relative indications for surgical intervention. Inability to follow the postoperative follow-up protocol, excessive amounts of medication, alcohol or drug use, mental retardation, the presence of brain tumors affecting the satiety center and severe psychiatric disease (major depression and psychosis) or advanced cardiac disease are among the contraindications for surgical intervention (Bozbora, 2002; Turkey Endocrinology and Metabolism Society, 2017).

The surgical treatment of obesity (bariatric surgery) is preferred more compared to the past in which applied surgical procedures lead to weight loss by causing malabsorption or restricting food intake. There are also combined surgical procedures that use both methods together (Turkey Endocrinology and Metabolism Society, 2017).

- a) Restriction of Food Intake: The food storage capacity of the stomach is reduced by resection, bypass or narrowing the upper part of the stomach of the patient, thus the patient consumes less food. Vertical band gastroplasty (VBG), sleeve gastrectomy (SG) and laparoscopic adjustable gastric band (LAGB) are restrictive surgical procedures. There is no change in the absorption function of small intestine after these procedures (Turkey Endocrinology and Metabolism Society, 2017).
- b) Surgery for malabsorption: Nutrient absorption is reduced by shortening the length of the small intestine by bypassing the absorbing area or by distracting the bileopancreatic secretions facilitating absorption. Jejunoileal bypass (JIB) and duodenal switch (DS) are these type operations. However, protein-calorie malnutrition and the deficiency of some micronutrients develop when the malabsorption is too high (Turkey Endocrinology and Metabolism Society, 2017).
- c) Restrictive and malabsorptive, combined effective procedures: Roux-en-Y gastric bypass (RYGB), biliopancreatic diversion (BPD) and biliopancreatic diversion / duodenal switch (BPD / DS) are these type operations. In RYGB, malabsorption is

provided with small intestine reconstruction while restriction is provided with small stomach pouch (Turkey Endocrinology and Metabolism Society, 2017).

Totally, 468,609 bariatric procedures was performed in 2013 while 95.7% of the procedures were carried out laparoscopically according to the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) consisting of 50 nations or national groups. The highest number (n = 154, 276) of procedures was performed in the USA/Canada region. Roux-en-Y gastric bypass (RYGB) was the most common procedure in the world with the ratio of 45%; sleeve gastrectomy (SG) was the second most common procedure with the ratio of 37%; adjustable gastric banding (AGB) was the third one with the ratio of 10%. The prevalence of SG increased from 0% to 37% worldwide from 2003 to 2013 while the prevalence of AGB decreased from its' peak to 68% from 2008 to 2013. SG is currently the most frequently performed procedure in the USA/Canada and in Asia/Pacific regions and second most frequently performed procedure after RYGB in the Europe and Latin America/South America regions (Angrisani et al., 2015).

NURSING CARE IN OBESITY SURGERY

The presence of comorbidities such as diabetes, hypertension and respiratory problems caused by obesity requires that the care of the patients undergoing obesity surgery before, during and after the surgery should differ from the care of other patient groups.

Preoperative Nursing Care

- It is very important that the patient is prepared well before the surgery for success in the obesity surgery. The patient's anxiety must be reduced by giving information about the needs of the patient before, during and after the surgery (Bozbora, 2002).
- Other risk factors leading to obesity such as gender, age, educational level, occupation, marital status, monthly income level, number of pregnancies and deliveries, smoking, alcohol use, psychosocial factors and chronic stress, drugs (antidepressants, antiepileptics, corticosteroids, progestational steroids, hormonal contraceptives, etc.) and the symptoms of the diseases leading to secondary obesity, obesity complications, the symptoms of the comorbidities (type 2 diabetes, HT, dyslipidemia, cardiovascular and respiratory diseases, joint diseases, non-alcoholic fatty liver disease (NAFLD) and sleep disorders) must be examined (Turkey Endocrinology and Metabolism Society, 2017).
- During the preparation period, blood tests (hemoglobin, hematocrit and whole blood count, prothrombin (PT) and partial thromboplastin time (PTT), cholesterol, triglyceride, urea, creatinine, electrolyte levels), urinalysis, radiological examinations (chest X-ray, gallbladder and liver ultrasonography), cardiogram and echography and tests for special conditions due to obesity must be performed (Bozbora, 2002; Garza, 2003; Sakrak and Dikmen, 2010).

- Determining the level of nutrition during the routine examination of the patient is very important in terms of the effectiveness of the treatment methods to be performed. This assessment includes the size and weight of the patient, nutritional anamnesis, anthropometric measurements and physical examination (Bozbora, 2002; Neil, 2013; TUIK, 2015). The food preferences of the patient, the amount and time of eating must be found out. The status of having a chronic, systemic disease is important in evaluating the nutritional status of the patient (Bozbora, 2002).
- In morbid obese, important physiopathologic changes are observed in the gastrointestinal cardiovascular and respiratory systems. In obese patients, oxygen consumption and carbon dioxide production increase in the respiratory system because of the high energy consumption and metabolic demand (Tanaka and Peniche 2009). When sleep apnea is diagnosed, a treatment such as continuous positive airway pressure (CPAP) can be started before surgery and some arrangements are made to monitor O₂ saturation of patients via pulse oximetry; CPAP can be continued after surgery (Garza, 2003).
- In the preparation of the patient for laparoscopic bariatric surgery, mechanical bowel cleaning is performed for 2 days. Patients are free to drink water until one day before surgery therefore they are protected from dehydration (Sakrak and Dikmen, 2010).
- The patient must take a shower to clean the skin before the obesity surgery. Skin hairs must also be removed with epilators or hair removal creams if necessary.
- Skin risk assessment (e.g., Braden Score) must be performed at hospital admission, with continuous monitoring during hospitalization and follow-up care of infection, ulceration of skin folds, irritation, atypical and pressure ulcers (Mulligan et al., 2009).
- Chairs, operating room tables, stretchers, wheelchairs, commodes, patient scrubs and sphygmomanometer cuffs must be prepared in sizes which are suitable for the patient before surgery. In order to ensure the confidentiality of the patient, the patient must be allowed to live alone in a private room (Asoglu, 2008).
- Before the surgery, wide vein path are opened with a foley catheter for each patient. In super obese patients, foley catheter placement maybe difficult due to covering of the perineum by the belly. In obese patients with increased subcutaneous fat tissue, central venous catheterization should be preferred because of the difficulty of finding a peripheral vascular access and the difficulty of maintaining continuity in the postoperative period. Arterial catheterization for invasive blood pressure monitoring facilitates blood pressure monitoring in the early postoperative period in intensive care (Asoglu, 2008; Otmalaz and Ece, 2016).
- The importance of early post-operative ambulence, deep breathing and coughing exercises and the use of spirometers must be emphasized and taught to the patient (Garza, 2003).
- Prophylaxis is provided against deep vein thrombosis (DVT) and pulmonary embolism. For this purpose, important measures are taken such as early mobilization within 4-6 hours after surgery, the use of pressure socks and shoes to pressure lower extremities and subcutaneous administration of low molecular weight heparin. High-risk patients need to administer heparin for 2 weeks after discharge therefore

subcutaneous administration must be taught to high risk patients before discharge (Sakrak and Dikmen, 2010).

- Patients' post-operative anticipations must be discussed with them, to ensure that their goals are realistic. They must be informed about all possible complications in detail and their written consents should be obtained (Turkey Endocrinology and Metabolism Society, 2017).
- The preoperative nurse needs to note abnormalities about the patient, adds them in the care plan and shares their concerns with the surgeons and anaesthesiologists.

Intraoperative Nursing Care

- While the standard operating tables have a weight limit of 200 kilograms, the weight limit of the tables designed for bariatric surgery is 450 kilograms. Since most of the bariatric interventions may be required to position the patient, it must be ensured that the patient does not fall from the table and is safe (Asoglu, 2008). The nurse must ensure that adequate number of personnel are in the operating room to safely move and position the patient (Neil, 2013).
- The healthcare staff must be attentive to protect the patient from pressure ulcers and nerve damages by supporting pressure points with pads. This is especially important for advanced obese and diabetic patients (Asoglu, 2008). In the intraoperative period, the nurse, who is primarily responsible for the safety and care of the patient, should take necessary precautions and applied interventions to prevent pressure sores during the operation.
- The perianesthesia nurse needs to be prepared to help the positioning of the patient for ideal tracheal intubation (Mulligan et al., 2009).

Postoperative Nursing Care

- Vital findings that provide a potential sign to important problems should be evaluated carefully. Patients should be monitored for the first 24 hours after surgery for the complications such as hypoxia, hypercapnia and sleep apnea (Turkey Endocrinology and Metabolism Society, 2017).
- Oxygen saturation should be monitored by pulse oximeter for the first 24-48 h after surgery. So emergency tracheostomy may be required, the necessary equipment have to be available at the bedside.
- The pain management is very important for the patients' early ambulation, spirometer use and participation to deep breathing and coughing exercises. A PCA (patient controlled analgesia) device must be provided to the patient, thus the patient keep his/her pain under control. Pain control is important for ambulation and breathing exercises, both of them are important to protect the patient from respiratory problems such as atelectasis or infection and thrombosis (Mulligan et al., 2009; Owers et al., 2012; Sakrak and Dikmen, 2010).

- Morbid obese patients have decreased blood supply due to excessive fat tissue while wound healing is also delayed in these patients. Therefore nurses must perform daily wound care and dressing to prevent delay in wound healing due to infection, and observe wounds in terms of color and drainage (Barth and Jenson, 2006).
- The prevalence of venous thromboembolism is higher in obese patients, because of that ambulation and physical activity are important. Nurses must observe the patient for venous thromboembolism symptoms (e.g., swelling, pain or tenderness, warmth, or redness in legs or one leg) and note information about their observations in the postoperative teaching materials. Compression socks, early and frequent ambulation, leg exercises in the bed once in two hours, anticoagulant or low-molecular-weight heparin must be applied as a common prophylactic intervention to prevent DVT (Barth and Jenson, 2006; Mulligan et al., 2009; Neil, 2013; Sakrak and Dikmen, 2010; Tanaka and Peniche 2009).).
- It is very important to monitor fluid intake and fluid loss of the patient and proper liquid replacement system functions (Barth and Jenson, 2006; Mulligan et al., 2009). Fluid electrolyte imbalances due to overfeeding and heavy diets should not be overlooked.
- In the postoperative period, cardiac rhythm and blood pressure must be monitored at regular intervals to be aware of the increase in heart rhythm, one of the symptoms of complications such as hemorrhage and anastomosis (Barth and Jenson, 2006; Neil, 2013).
- Diabetic subjects must be monitored in terms of blood glucose level and hypoglycemia (Turkey Endocrinology and Metabolism Society, 2017).
- It is important to position the patient. The weight of the abdominal contents compress the diaphragm and makes breathing more difficult, therefore the standard supine and Trendelenburg positions must be avoided. For preventing respiratory distress, the patient's head and neck must be raised 30°-45° to be flat, and the improvement of tidal volume should be allowed (Barth and Jenson, 2006; Mulligan et al., 2009; Neil, 2013).
- In patients undergoing obesity surgery, sleep apnea incidence is high. Nurses must be aware of potential undiagnosed sleep apnea in patients undergoing obesity surgery (Neil, 2013).
- The most lethal complication of bariatric surgery is leakage from the gastrointestinal system. Tachycardia, occasional tachypnea and agitation can be the only signs of a serious intraabdominal problem (Sakrak and Dikmen, 2010).
- The ambulation of the patient must be started as early as possible, the nurse must ensure that required equipments are available to help the patient for upstanding and position changing. Use of special bariatric beds, air-assisted transfer devices, mechanical patient lifts, bed trapezes and other equipment helps ensuring the safety of nurses and patients in the mobilisation and positioning of patients (Barth and Jenson, 2006; Mulligan et al., 2009; Neil, 2013).
- In restrictive and disruptive surgery or combined techniques, oral feeding is not started at early period due to impaired gastrosintestinal integrity and the adaptation of patients to the newly created gastrointestinal system anatomy takes time. Nurses'

support for nutrition during the hospitalisation period reduces patients' anxiety (Otmalaz and Ece, 2016).

- The written materials which contains information about the progression of the diet, appropriate food choices, bowel habits changes, drugs, physical activity, wound care, signs and symptoms to report to the physician, follow-up visits, vitamin and protein supplements, and the importance of drinking required amount of liquid (hydration) after discharge, should be provided to patients (Garza, 2003).
- Long term psychological support should be provided to the patients from the preoperative period to postoperative period, so the problems such as low self esteem, decreased socialization, intensive shame and fear can be alleviated (Barth and Jenson, 2006).
- Nurses need to know probable difficult parts of the care of obese patients. For instance, they have higher difficulty in urinary catheter and intravenous access placement, have changed social, emotional or psychological necessities, need higher amount of time for dependent-care requisites. It is very important to perform nursing care and to determine nursing diagnoses and plan nursing care.

CONCLUSION

Obesity is a chronic and relapsing disease due to it's complications and comorbidities. It is a complex disease and a result of genetic, environmental, biological, sociocultural and behavioral factors. Obesity has an increasing prevalence in the world and decrease the quality of life. It is an important health problem in terms of community health due to the related cardiovascular, pulmonary, endocrine, metabolic, psychological and other diseases. Obesity can be treated with surgical intervention and a multidisciplinary team approach. It is very crucial to provide personalized, individualized and holistic nursing care and counseling services to patients who undergo obesity surgery for reducing possible risks in their care and preventing complications and difficulties before, during and after surgery. These services are also important to increase patients' quality of life.

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Chapter 270

EFFECT OF GLOBAL CLIMATE CHANGE ON OCCUPATIONAL HEALTH: HEAT STRESS

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ABSTRACT

The potential consequences of global climate change have been investigated over the past 20 years, and researchers believed the elderly, newborn, or pregnant people, especially those in the equatorial countries and small islanders are at risk. In addition to these risk groups, another risk group is the workers working outside with brute strength.

The American National Institute for Occupational Safety and Health (NIOSH) reported 423 deaths between 1992 and 2006, mainly due to the rise in temperature and heat waves. Causes of these deaths are often identified as “heatstroke” and other heat-related diseases. It has been determined that 24% of these people were working in forestry, agriculture, fishing, and hunting fields.

The publications between June-July 2018 were scanned through the “PubMed,” “CDC” and “WHO” official websites, and the literature on heat stress was examined related the effects of global climate change on occupational health.

This study emphasizes the effect of greenhouse gases emitted uncontrollably and intensely to the atmosphere with the Industrial Revolution on working health as a cause of global climate change.

Keywords: global climate change, occupational health, heat stress

INTRODUCTION

Without greenhouse gases such as carbon dioxide, the earth’s temperature would be around -18°C, and it probably wouldn’t be possible to talk about life as it is today. With

technological improvements, the release of greenhouse gases has also increased, and it has brought a new predicament over the years, global climate change.

Global climate change is making radical changes that cause degradation of ecological balance such as temperature increase, extreme weather phenomena, natural disasters, deterioration of water cycle, change in air quality, increase in sea level, and in human life such as ecological migration, new diseases.

Between the years of 1860-2000, it is recorded that the temperature increased in the world is between 0,5-0,7°C (Brass, 2002). Depending on the climate change caused by human or natural factors, a temperature increase of only 2-4°C is expected in this century alone (Brass, 2002; Alley et al., 2007; Kjellestrom et al., 2011).

Global climate change has direct effects such as an increase in temperature, changes in ozone activity, increase in solar radiation due to the variety of air pollutants, and rise in air moisture content are among the predictions (Grandi et al., 2016). These changes are accompanied by indirect effects such as deterioration of human health. In a report published by the International Panel on Climate Change (IPCC) (2014), among the health problems to be encountered in the future due to the consequences of global climate change, lethal hot strokes, heart attack, drought-related nutritional disorders and infectious diseases, injuries due to extreme air temperatures were found to be equally possible (Smith et al., 2014).

Considering about 1/3 of human life is spent on working, it is one of the expected results that climate change affects work life along with occupational health.

Increased exposure to solar radiation, increase in toxic effects of certain chemical substances due to temperature increase, increase in the number of vectors and pathogens, loss of former value due to the migration of workforce due to migrations, workplace violence or precarious work, work accidents due to extreme temperatures are among the future risks threatening the occupational health and safety. Particularly, the sectors most affected by climate change are the ones that complete the majority or most of their shifts in the outdoor environment or in isolation exposed to extreme temperatures, radiation and high humidity such as agricultural workers, road and construction workers, archaeologists, fishermen, firefighters, disaster emergency workers in fire brigade and ambulance.

METHODS

In this study, the literature review of heat stress related to the effects of global climate change on occupational health was conducted from June to July 2018 using the official publications “PubMed,” “CDC,” and “WHO” and the written sources in this issue.

Temperature and Physiological Effect

Deaths due to high temperatures in the United States cause almost the same amount of deaths as natural disasters such as earthquakes, lightning strikes, and storms. For this reason, high-temperature fluctuations due to global climate change are considered “silent killers” (Jacklitsch et al., 2016), as they do not leave devastating traces behind like any other natural disasters. While even people in resting circumstances are losing their lives due to high

temperatures, it would not be wrong to say that workers who are working with physical strength in unsupervised conditions and not provided with adequate measures are seriously endangered by extreme temperatures.

For the human body to function properly, it is necessary to keep the body temperature constant. The temperature of the brain, the thorax, the abdomen, which is called the core temperature, is not the same thing as the surface temperature. Core temperature is $37 \pm 1^{\circ}\text{C}$, whereas the surface temperature is $2\text{--}4^{\circ}\text{C}$ lower (Marchetti et al., 2016). The body uses a thermoregulation mechanism to keep its temperature persistent. In this mechanism, the hypothalamus works as a thermoregulation center, while the frontal lobe reduces the body temperature, and the posterior lobe works to raise the body temperature together with peripheral vessels, striated muscles, and thermoreceptors. The human body can survive in environments at a temperature of 10°C below the core temperature but cannot survive in environments at the temperature of 5°C above the core temperature (Marchetti et al., 2016). For this reason, convection, conduction, radiation, and evaporation develops in the body to stabilize the rising body temperature.

Convection: It is defined as the temperature change between the skin and the ambient air surrounding the skin. If the ambient temperature is larger than 35°C , body temperature increases. If the ambient air temperature is below 35°C , body temperature decreases.

Conductivity: The temperature difference between the skin and the surface directly contacting it. In some special CBRN (Chemical, Biological, Radiological and Nuclear Threats) uniforms, furnace work uniforms, liquid circulation special work uniforms, cooling is done with this logic.

Radiation: Heat is displaced by radiation. The body's thermal radiation is usually persistent.

Evaporation: It is defined as heat loss caused by sweat evaporation from the body. The amount of relative humidity in the environment affects the amount of maximum perspiration (Jacklitsch et al., 2016).

Severe physiological changes transpire when the ambient temperature reaches or exceeds the core temperature (Kjellstro et al., 2009; Parsons, 2003). When the body temperature exceeds 38°C , a decrease in physical and mental abilities is observed, a heat stroke when the temperature exceeds 39°C , damage in large organs, loss of consciousness and death when it exceeds $40,6^{\circ}\text{C}$ (Marchetti et al., 2016).

The sun exposure in the working environment, the humidity and the temperature of the environment, the worker's uniform, the body surface area, and the worker's job are directly influential in the degree of influence from temperature.

Thermal Comfort

The heat, humidity, airflow conditions are called thermal comfort which is substantial for the most of the workers' relaxation in the working environment. The temperature range of the working environment isn't the only criteria that determines thermal comfort (CDC, 2017), although the temperature range that most people feel comfortable is between $20\text{--}26^{\circ}\text{C}$. In addition to temperature, humidity is another important criterion. While the very low humidity in the environment can dehydrate the body surface, evaporation does not occur sufficiently

under very high humidity conditions. Therefore, the body cannot sweat, and the body temperature cannot be adjusted, it can cause “heat stress” and “hot impact.” Ideally, the relative humidity in the working environment should be between 30-80% accordingly the weight of the work done, the season characteristics, the temperature of the environment. The airflow rate is an important factor that causes the exchange of the temperature between the environment and the workers, and the removal of pollutants such as odors and dust in the environment. NIOSH recommends a working airflow rate of 20-150 mm/sec (CDC, 2017; Jacklitsch et al., 2016).

Radiant heat is one of the most important factors that affect working ambient temperature. Radiant heat is electromagnetic waves emitted by radiation from heat and light sources and their heat effect. The solar rays also affect the thermal comfort as solar radiation as well as artificial materials like raw materials produced in the working environment such as glass, molten metal.

Wet Bulb Globe Temperature (WBGT) value is used to determine thermal comfort (Jacklitsch et al., 2016). The WBGT value is the heat load the worker is exposed to in the working environment. In other words, it is the effective temperature that is felt. In other words, it is the effective temperature that is felt. This value is the result of measuring the dry bulb temperature, radiant temperature, and wet bulb temperature in the environment using a formula.

A 1% increase in body temperature leads to a 10% increase in metabolism rate, an increase in the number of pulses, a very slight decrease in systemic blood pressure, and an increase in fluid loss (Yenen, 2017). In addition to these physiological changes, there are risky situations that threaten job security such as careful reduction, fatigue, exhaustion, a decrease in mental functions. Many studies indicate that temperature increase affects the emotional state, prolongs the duration of the reaction, and reduces mental activity in a variety of complex tasks (Lenzuni et al., 2014; Fisk, 2000). While the effective temperature of 29°C leads to a 5% decrease in the work efficiency of the worker, the decrease reaches 30% at 32°C effective temperature.

Heat Stress

The net heat load resulting from the combined contribution of the worker’s metabolism, environmental factors, and the working clothing is defined as heat stress (Jacklitsch et al., 2016). This load causes an increase in body temperature by heat storage in the body, which triggers physiological changes. Due to this situation, the respiratory and cardiovascular system may be affected, resulting in acute or chronic insufficiency due to muscle destruction and dehydration (Hansen et al., 2008; Kjellstrom et al., 2010; Blois et al., 2015).

If the heat stress is not prevented, meaning the worker is not taken to rest, if the liquid intake is not provided, and if the person is not cooled, hot cramps, hot syncope and finally heat strokes can be expected. In heat stress, the main factor that determines the answer of the person is the acclimatization, meaning adaptation to work. If the worker is not in acclimatization, he is more affected by the temperature change. If the worker is in acclimatization, the temperature he can tolerate is higher, the duration of endurance is longer without strain. For workers to get the least damage from the heat, NIOSH and ACGIH

(Association Advancing Occupational and Environmental Health) regulated workers' working and rest periods according to ambient temperatures (Table 1).

Heat cramps: Basic skeletal muscle cramps is seen because of lack of water and salt replacement lost during perspiration.

Heat syncope: There is an enlargement to cool the body in the peripheral superficial veins, where the water and the salt lost by sweating are not replaced, and the heat exposure continues. This vasodilatation causes blood pressure in the brain to drop and temporary loss of consciousness.

Heat stroke: Working in a hot environment with physical power can increase body heat production from 1 kcal/min to 20 kcal/min. This means that the core temperature increases by 1°C every 5 to 7 minutes (Marchetti, 2016). When exposed to high temperature and moisture for long periods of time, the body uses all means to lost heat. The method of losing most heat is the perspiration. Despite the rising body temperature, sweating on the body may not be enough due to intense moisture in the environment, or perspiration stops because sweat is not replaced. In this case, while the body temperature is above 40°C/104°F the activity of the nervous system over the thermoregulation ceases to exist, and uncontrolled temperature increase and significant tissue damage and death due to this increase can be seen (rhabdomyolysis, thrombocytopenia, coagulopathy and multi-organ failure) (Nag et al., 2009; Parsons 2014). A form of hyperthermia associated with a systemic inflammatory response leading to a syndrome of multi-organ dysfunction in which encephalopathy predominates (Bouchama and Knochel, 2002).

With the global climate change, especially for the workers working in daylight, the risk of heat stress and other heat cramps, syncope and heat stroke risks are increasing, and it is expected that this risk will be higher if the precautions aren't taken (Kjellstrom et al., 2016).

Table 1. NIOSH and ACGIH recommended working/rest periods in hot environment

Recommended work/rest periods	Work load weight*		
	Heavy	Medium	Light
	Environment Temperature (°C)		
Continuous working	25	26.7	30
75% working 25% rest (for every hour)	25.9	28	30.6
50% work 50% rest (for every hour)	27.9	29.4	31.4
25% working 75% rest (for every hour)	30	31.1	32.2

*: Work Load Weight Assessment: Light jobs: 200 kcal/hour (Example: Writing-like office work), medium jobs: 200-350 kcal /heavy work :> 350 kcal/h (Example: digging works).

Studies in various countries in the world (Table 2) show that extreme heat at work can cause deaths, heat exhaustion, major organ damage, job accidents, and changes the emotional state and attention resulting in a decrease in performance and economic loss.

In a study conducted in Puerto Rico between 2012 and 2013, it is discovered that the highest death rate was recorded between May and October when the death rates within 2 years were compared. The risk of life loss because of illnesses like stroke (brain hemorrhages, clots, paralysis), hypertension has increased between 2 and 3 times in the 2012-2013 Fall in comparison to the 2009-2010 Fall (Mendez Lazaro et al., 2016). In a study conducted by OSHA between 2012 and 2013, 20 workers who had died or suffered from overheating were

examined and one of them had died and the others had been exposed to high temperature related illnesses.

More than half of the working hours of workers besides home workers, especially farmers and construction workers, are spent outside. Naturally, the changes in climate characteristics are affecting/will affect the health of this working group, as well as occupational health and safety.

In Paris in 2003, it was seen that most of the women lost their lives because of extreme temperature fluctuations were in high age group, and the males were included in the working group between the ages of 25-64 (Pachauri et al., 2014; Robine et al., 2008). Outside workers will be exposed to high temperatures, radiation, chemical substances and it will threaten the occupational health, mainly because of climate change. In a study conducted by NIOSH, 423 workers lost their lives due to high temperatures between 1992 and 2006, and 102 (24%) of them have been working in forestry, agriculture, fishing, hunting fields (CDC, 2008).

Table 2. Situations that develop because of exposure to high heats in workplaces

Effect	Research Area	Researchers
Heat Stroke	South African Mine Workers, US Agricultural workers, China, India, Qatar and other countries	Tustin et al., 2018; Gibson and Pattison 2014; Nag and Nag, 2009; Grandjean and Grandjean 2007;
Unusual severe heat stroke, heat exhaustion	Some hot workplaces in China, India, England, runners in US and Brasil, footballers in US	Nag and Nag, 2009; Parsons 2014; Zhao et al., 2009; WHO, 2014; Pachauri et al., 2014; Watkins et al., 2018; De Martini et al., 2014; Castro et al., 2018; Kerr et al., 2014.
Kidney damage, Major organ damage	US sugar workers, migrant construction workers in Qatar, agricultural workers in Cameroon,	Garcia Trabanino et al., 2005; Kjellstrom et al., 2010; Tawatsupa et al., 2012; Wesselling et al., 2013, Ekiti et al., 2018
Heat-related accidents	Europe, Thailand	Ramsey et al., 1983; Tawatsupa et al., 2013
Behavioral and psychological changes decrease in mental functions	South African miners, Australian farmers, student children in Thailand, Cameroon	Tawatsupa et al., 2010; Berry et al., 2010; Dapi et al., 2010
Decrease in working capacity, economic loss, migration	India, USA, South Africa	Dell et al., 2009; Burke et al., 2015; Kjellstrom, 2016; Kjellstrom, 2011; Kjellstrom, 2009

(Kjellstrom T., Briggs D., Freyberg C., Lemke B., Otto M., Hyatt O. Heat, Human Performance, and Occupational Health: A Key Issue for the Assessment of Global Climate Change Annu. Rev. Public Health 2016. 37:97-112).

In a study conducted by Eisenberg and Methner (2018), which examined the heat stress conditions of the park workers, didn't detect dehydration and muscle destruction while the decrease in the working efficiency of the people, the increase in the pulse was recorded. Nag and Nag (2009) recorded the most intense heat stress findings (e.g., headache, palpitations, systolic pressure, apathy etc.) in the rock crushing workers working outside among workers working in ceramic, mine (iron), and rock breaking. Tawatsupa et al., (2012) found that, in Thailand, labor-intensive workers were significantly more likely to experience heat stress than workers in the office and that they were experiencing kidney dysfunction due to heat stress, even more in 2009 than in 2005. Gracia Trabanino et al., (2005) emphasized that chronic renal failure and proteinuria in agricultural workers in El Salvador may be due to heat stress. Ekiti et al., (2018) found parallel results in a study conducted by agricultural workers in Cameroon. In a study conducted by Tustin et al., (2018), 78.6% of 25 outside workers in the United States between 2011 and 2016 were exposed to fatal heat stress in acclimatization.

Beck et al., (2018) found that WBGT and UV exposures of workers engaged in gardening work were above the legal limits.

It is estimated that in addition to direct health problems of global climate change such as the heat stress, in 2030-2050, particularly in South East Asia and the Ecuadorian belt countries, a decrease in working capacity and a 50% loss in production due to a temperature increase of 2°C is reported (Kjellstrom et al., 2013). In another study, a modeling study in Southeast Asia has shown that in 2050 more than half of the working hours in the afternoon will be lost due to the greater need for rest breaks. It is estimated that global gross national income will decrease by 23% in the 2100s due to shortening of working hours, reduced work efficiency and other climate-related problems (Kjellstrom et al., 2016).

It is claimed that labor productivity losses will occur in the whole Aegean and Mediterranean coasts in the south of İzmir, and 1% of the losses in the Central Anatolian Region can reach to 7-8% (Altinsoy and Yıldırım, 2013). In a study conducted in our country, a 2001-2050 projection connected to global warming has been made with the labor productivity loss between 1970-2000, and while there is a loss of productivity in the range of 3-18% in İzmir, Aydın, Mersin, and Adana in the past, losses are predicted to rise to 25% in the future.

CONCLUSION

Global climate change is a threat to occupational health due to temperature rise, humidity and extreme warming. In terms of occupational health and safety, the following measures will help to reduce the risk of heat stress and reduce the threat of occupational health and safety; adapting to the NIOSH recommended study/rest periods, taking a 250cc (at a temperature below 15°C) fluid every 20 minutes, supporting workers with athletic liquids in case of extreme perspiration, no alcohol in hot weather, wearing air-permeable thin clothes, the presence of a radio on their side, carrying out an air conditioning which can provide thermal comfort in indoor environments, determining working hours not only by the effect of sunlight but also by the temperature of the air for those who work outside for the following years, and frequent control of WBGT values.

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Chapter 271

PHYSICAL ACTIVITY IN WOMEN

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ABSTRACT

Intentional physical activity has become necessary with today's evolving technology. However, individuals need a routine in their lives. Individuals are able to complete a lot of work in their daily lives using technology, but this increases their sitting time. This situation emerges into a sedentary lifestyle. There is a negative relationship between sedentary lifestyle and physical activity. As sitting time increases, physical activity decreases. This situation differs between the genders. One reason for this is that women are still an influential value to society, culture, and the economy. Therefore, women and physical activity need to be examined even in today's conditions.

When women perform physical activity, due to physiological structure, menstruation, pregnancy, hormones, emotional state changes, elastic structures, daily life activities, etc. many factors are involved. For this reason, physical activity in women can have different results at different times. In studies, the tendency toward sedentary behaviors of women are higher than that of men. This section includes evidence-based information on the implementation and effects of physical activity in women.

Keywords: exercise, physical, women, sedentary lifestyle

INTRODUCTION

Human survival depended on being physically active and talented in ancient times. People had to live a nomadic lifestyle to meet basic needs such as food and shelter. Thus, they frequently ran, jumped, fought, and walked long distances, thereby performing excessive physical activities. After many centuries, a decrease in physical activity rates occurred. Although the number of cultural and social classes has decreased compared to the past,

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individuals have begun to be inactive after the developments in technology and industry (Brown, 2016).

Today, the definition of physical activity has changed. Physical activity is now defined as entire body movements during which muscles work with a level of energy that is higher than the metabolism relaxation level. This definition includes four headings: 1. Physical activities during leisure time, 2. Physical activities in the workplace, 3. Physical activities during housework, and 4. Physical activities in society (Brown, 2016; Timperio, 2015).

This classification may vary by country. For example, Brazilian public health studies report that physical activities at home or in the workplace should not be calculated. In Latin America, upper limits are exceeded when physical activities at home and in the workplace are calculated. Therefore, physical activities are categorized into two groups: leisure time activities and social physical activities. These differences between countries are important and should be taken into consideration during academic studies. In particular, information should be obtained from the relevant public health departments regarding the definitions of physical activity (Brown, 2016; Timperio, 2015).

Physical inactivity is a life-threatening factor around the world according to the World Health Organization (WHO) that particularly affects women. Approximately 3.2 million people die because of physical inactivity every year. Regular physical activity and exercise protects health and physical fitness and prevents many health problems. Previous studies report strong effects of regular and evidence-based physical activities and exercises on health (Arslan, 2016; Brown, 2016; Timperio, 2015).

Women's health state is dynamic because their hormonal levels are dynamic. Changes in the osseous-muscular organs in non-disease periods such as menstruation, pregnancy, or menopause affect women's health state and quality of life. Thus, the target level of physical activity varies by the phase of the woman's life. In addition, the effect of sociocultural and environmental factors makes women's daily lives complicated (Arslan, 2016; Brown, 2016; Timperio, 2015; Cooke, 2017). This paper aims to reveal the details on the relationship between physical activity and women's health.

EXERCISE AND BONE HEALTH IN WOMEN

Bone health plays an important role in health and the quality of life. Bone tissue is home to minerals in addition to its functions including preventing injuries, protecting bodies, and moving. Thus, it contributes to the normal functions of other organs (from regulating the functionality of endocrine organs to hematopoiesis). An unhealthy bone may lead to breaks and functional losses, which result in disability. This may lead to undesired results including functional dependency and premature death. Osteoporosis is a bone health issue widely observed in women. Many factors affecting bone strength such as changes in bone tissue, decreases in bone density, and changes in bone architecture emerge during osteoporosis. As a result, bones can break easily. For example, one in every two Caucasian women is diagnosed with osteoporosis and osteoporotic fractures are widely observed (Xu, 2016; Zhou, 2014). Although one in every five men also experience osteoporotic fractures, women are at greater risk during their lifetime. Postmenopausal women have increased expenses for synthetic drugs used in the treatment of their higher osteoporosis prevalence. Expenses for elderly

women in England are expected to reach 25.3 million dollars by the year 2025 (Herrmann, 2012; Xu, 2016). Thus, an increase in non-pharmacological interventions is desirable. Exercise prevents breaks and falls in postmenopausal and elderly women, reduces or stabilizes bone loss in middle-aged women, and increases bone density in girls. The WHO, American Collage of Sport Medicine (ACSM), National Institutes of Health (NIH), and National Osteoporosis Foundation (NOF) provide suggestions for the treatment and prevention of osteoporosis. However, these are general suggestions that are not valid for specific age groups. High quality systematic reviews and meta-analyses suggest that exercises done for bone health of women from diverse age groups have positive effects (Xu, 2016).

EFFECT OF EXERCISE ON GIRLS

School practices consisting of short-term plyometric exercises are adequate for the bone health of girls. Exercise programs for 60 minutes or more three days a week or 10- to 20-minute programs performed daily for 12 months or longer are effective for bone development. These programs will be particularly useful for girls with precocious puberty. Awareness should be raised in schools to enable young girls to have healthy bone development, and emphasis should be placed on the effect of school-based exercise programs on bones (Ubago-Guisado, 2015; Xu, 2016).

EFFECT OF EXERCISE ON PREMENOPAUSAL WOMEN

Studies show that regular physical activities have a limited effect on the bones of premenopausal women. However, regular exercises have an effect on the femur neck, lumbar vertebra, and trochanter. In this period, the aim is not to increase bone strength as in girls, but to protect strength and prevent it from decreasing. Resistance exercises tolerated or performed by individuals with moderate to high effects are preferred for bone health during this period. Exercises performed 30- to 60-minutes at least three days a week for 10 months or longer are effective for maintaining bone health in premenopausal women (Xu, 2016).

Home or office exercises are sought for women who do not have enough time for traditional exercises due to familial matters or workload (Xu, 2016). Short-term, high-volume vertical jumping or hopping performed in 1 to 5 sets of 10 to 20 repetitions at 8- to 15-second intervals at least three times a week for six months are recommended (Xu, 2016; Farr, 2013).

EFFECT OF EXERCISE ON ELDERLY POSTMENOPAUSAL WOMEN

Because the prevalence of osteoporosis is higher in the postmenopausal period, the importance of exercises for bone health remains throughout aging. Combined exercise methods are frequently recommended in this period. Exercises lasting for 30- to 60-minutes for a minimum of three days a week for more than 10 months are recommended. Recommended exercises include running, steps, plyometric exercises, jogging forward or

backward, etc. Performing these exercises together protects the structure of bone tissue (Xu, 2016; Chastin, 2014).

EXERCISE IN THE PREGNANCY PERIOD

Many women hesitate to perform exercises during the pregnancy period. Physiotherapists recommend women who were physically active before pregnancy reduce their activity levels. However, exercises have been optimized for pregnant women, as resources from the last 30 years show. Today, physically active pregnant women perform their activities in the same way as they did before pregnancy. Even those who were not active before pregnancy tend to increase their physical activities during pregnancy (Bredin, 2013).

In the past, the primary goal was to protect the fetus and the mother. At that time, people thought that the fetus could be harmed by several factors such as energy substrates or increased body temperatures in addition to the increased oxygen required by the working muscles of the mother. Furthermore, performing too much exercise during the pregnancy period was considered risky because it may increase the likelihood of injuring the lower back or the musculoskeletal system, such as chronic fatigue or hypoglycemia. Therefore, many physicians suggested reducing physical activities during pregnancy (Bredin, 2013).

Systematic reviews between 1982 and 2009 show that exercises performed by pregnant women with no contraindications are only slightly risky (Bredin, 2013). Uterine contractions that can last for 72 hours are the leading side effect. However, previous studies show that fetal bradycardia is the most severe side effect. On the other hand, leg cramps, fatigue, and weakness are defined as temporary problems rather than side effects (Bredin, 2013).

If women want to exercise during pregnancy, a health care professional should accompany them. Health care professionals should examine the general health of the mother before preparing the exercise program. They should first eliminate the risks that have side effects. Then, they should prepare a program that will last at least 30 minutes in a day, three days a week during the second trimester with a level that is 50-70% of the maximum heart rate. Water activities such as steady cycling, walking, and swimming are among recommended exercises (Bredin, 2013; PAR-Q+ Collaboration (PAR-Q+), 2011; PAR-Q+ Collaboration (ePARmed-X+), 2011). Bredin et al. (2013) suggested professionals design a flow chart similar to Figure 1.

Medium-level exercises have no side effects or they have only slight side effects for healthy mothers or their children if this is the mothers' first pregnancy and there are no complications. Being inactive before pregnancy is not a reason for not doing exercise during pregnancy. If the examination conducted by a health care professional shows a pregnant woman is at low risk, there is also a low likelihood for the emergence of side effects from the exercises. A screening process should certainly be conducted before calculating the rate of physical activity or starting any activity program (Bredin, 2013; PAR-Q+ Collaboration (PAR-Q+), 2011; PAR-Q+ Collaboration (ePARmed-X+), 2011).

Although regular physical activity is recommended during pregnancy, pregnant women consider that loss of balance and joint or connective tissue traumas may occur. They sometimes avoid performing an activity for fear of causing trauma to the fetus. The most

significant point here is that pregnant women should exercise with a health care professional (such as a physiotherapist) (Bredin, 2013).

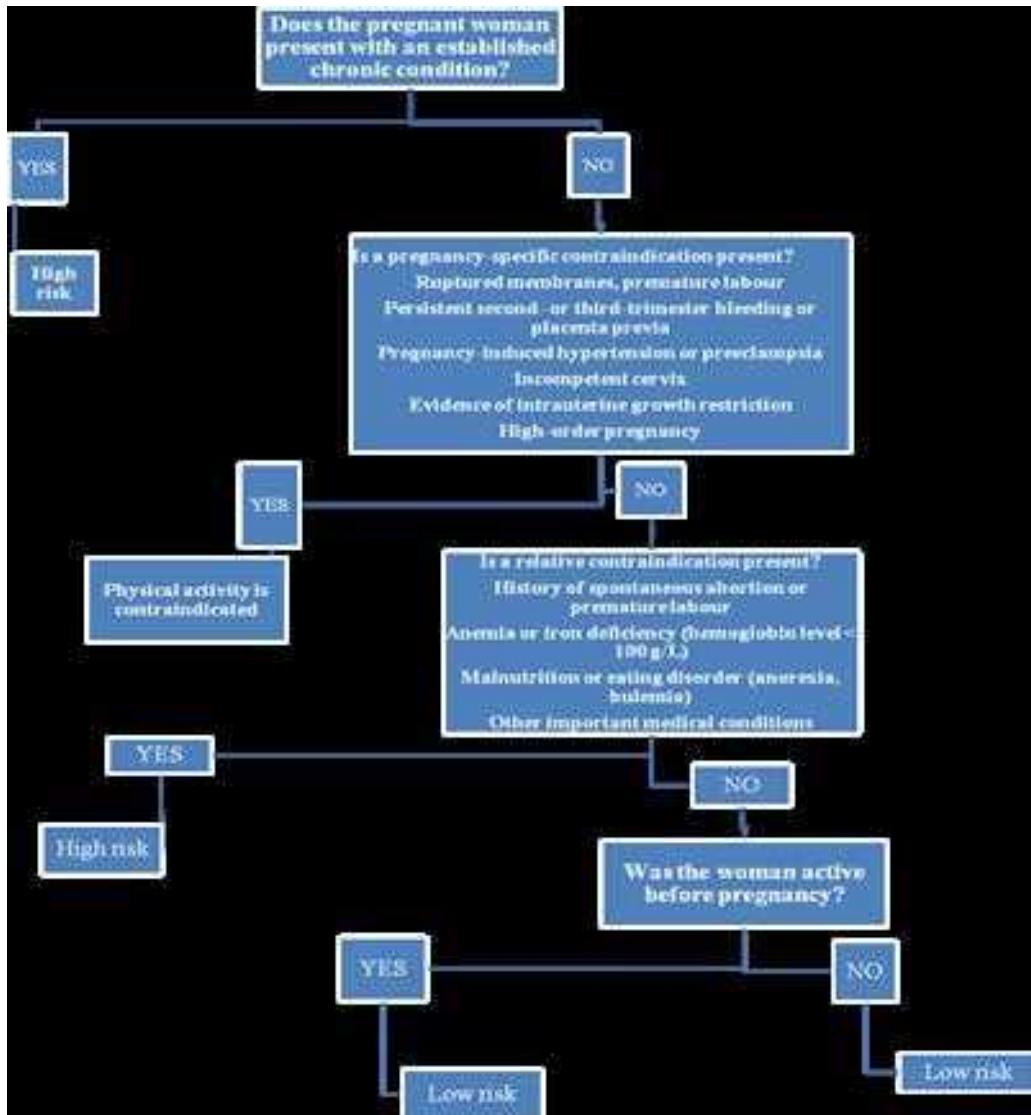


Figure 1. Professionals design for assessing the risk of adverse events during physical activity in pregnant women at clinic (Bredin, 2013).

Thus, the question “Does the emergence of side effects from regular physical activity among inactive or active women during pregnancy differ by fetus or mothers’ themselves?” which was specified in the previous literature is still valid, and there is a need for further research. This study implies that pregnant women with no contraindications should be directed to medium-level activities. The relevant literature does not provide precise information about the level of physical activity acceptable during the pregnancy period. For example, whether sportswomen can continue performing their activities at the same intensity level during pregnancy is still unknown (Bredin, 2013; Cooke, 2017).

Studies conducted between 1950 and 2015 indicate that exercise has no side effects. A study conducted in the 1960s reported that being inactive during the pregnancy might lead to negative outcomes such as premature labor, miscarriage, or placental abruption (Bredin, 2013). The application method of exercises is not clear during the pregnancy of sportswomen with high levels of physical activity (Bredin, 2013; Cooke, 2017). Future studies on exercise during pregnancy should question if women's exercise level depends on factors such as education and socioeconomic levels. However, exercise during pregnancy has positive physical and psychological effects. Women's physical activity level before the pregnancy and the sports played before pregnancy should be questioned. The upper limit of the exercise level during pregnancy is still unknown for women who play sports or have high levels of physical activity.

WOMEN AND SPORTS

Previous studies report an increase in the rate of women who play sports. The Lancet Series published in 2016 found a relationship between public health and physical activity starting from the 2012 London Olympics to the 2016 Rio Olympics. In the 2020 agenda of the International Olympic Committee, a participation rate of 50% for women and girls in sports activities is targeted (Cooke, 2017). Participation of women in the Olympics should be encouraged because men fill the open positions because they participate in more sports than women do (Sallis, 2016). Interestingly, the universal estimations of the WHO report the rate of physical activity except sports among women is 35% higher than among men (WHO Global Health Observatory, 2018). Here, the definition and types of physical activity should be closely examined. In addition to leisure time activities, workplace activities or physical activities performed during travel should be considered while preparing the reports. Thus, women may be considered more physically active than men, particularly in countries with low-income levels because women have higher workloads than men do. However, the mean score for women's leisure time activity was 13.7 minutes/day whereas this rate was 25.3 minutes/day among men in low- or middle-income countries (Cooke, 2017).

Participation in sports increases leisure time activities among women. It not only improves physical health, but also mental health and social participation. The UN Inter-Agency Task Force on Sport for Development and Peace reported that as the number of people participating in sports activities increases, the number of physically active individuals also increases. Additionally, the rates of education, maintenance of peace, reduction of trauma, and economic development also increase (Brown, 2016; Cooke, 2017).

The rate of participating in physical activities among different countries varies by gender, age, disability, education level, and socioeconomic status. However, while sports are the fastest way to enable individuals to lead an active life, there is no specific method to increase participation in sports activities. This is apparently due to the presence of different methods performed during the activities (Cooke, 2017). Gender differences in sports participation occur in low- or middle-income countries due to several factors such as cultural/religious values and the role of women in the society. For example, countries such as Qatar, Saudi Arabia, and Brunei had teams of women who participated in the 2012 Summer Olympics for the first time dressing in accordance with their beliefs (Brown, 2016; Cooke, 2017).

WOMEN AND E-HEALTH

Previous studies show physical activity is a highly modifiable health behavior. The WHO suggests 150-minutes of medium-level aerobic activities per week. Although regular physical activity is useful for many conditions from hypertension to depression, the rate of physical activity among women ranges from 3% to 14% (Reed, 2015).

Modern life has placed many additional burdens on women who work outside the home. Women try to exist in every facet of life including the workplace, home, and social areas. High levels of physical activity do not occur during childcare, cooking, gardening, and house cleaning. Thus, women's participation rate in physical activities is 22 to 33% lower than men's is. In low-income families, women even tend to find a second job. Many women report that they too busy to spare time for sports. In this case, e-health services promote physical activities and facilitate their follow-up (Qualcomm Wireless Reach, 2014; Reed, 2015; World Health Organization, 2014).

In a general sense, e-health service is the use of emergency information and communication technology. Previous studies found that e-health services are effective for fitness, nutritional practices, weight loss and conservation, management of chronic diseases and medications, psychological factors, health risks, and health care expenses. E-health services have allowed an increase in the rate of physical activities among women and raised awareness of health interventions such as quality of life, blood pressure, and glucose levels. E-health allows individuals to see their electronic health records when required (Qualcomm Wireless Reach, 2014; Reed, 2015; World Health Organization, 2014).

E-health services in developing countries include age, education level, number of children, work status (part time, full time, or casual work), country, income level, physical activity level, type of e-health service (short message or online web form, virtual care programs, phone or smart phone applications, or gathering data from wearable physical activity measurement instruments), and intervention mode (wearable, telemedicine, mobile devices, health informatics, or multi-single component). However, further studies are required to determine which e-health service is most effective and how it increases physical activities because e-health services have not been included in the relevant literature, yet.

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Chapter 272

THE ENHANCED RECOVERY AFTER SURGERY PROTOCOL AND THE ROLE OF SURGICAL NURSES

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ABSTRACT

The protocols were established to reduce the length of hospital stay of patients because the healing of patients is negatively affected due to long hospitalization as a result of traditional practices. Enhanced Recovery After Surgery Protocol (ERAS) is a evidence-based care model which was designed to accelerate post-operative healing and provide recommendations for patient care applications to be performed before, during and after the surgery. In the protocol that requires a multidisciplinary approach, surgical nurses play an active role at each stage of the process. Therefore, surgical nurses should be aware of their dependent and independent roles in the ERAS protocol, reflect them in the care of the patient, follow the current publications about the protocol and be open to develop. In this chapter, the ERAS protocol components, recommendations and the role of the nurses in the surgical process are emphasized.

Keywords: enhanced recovery after surgery protocol, fast track surgery, surgical nurse

INTRODUCTION

It is known that healing after surgery can be accelerated and surgery-related deaths can be reduced by the current approach for treatment and care and evidence-based applications in surgery. One of the evidence-based applications in this direction is the Enhanced Recovery After Surgery (ERAS) or Fast Track Surgery (FTS) protocol developed by the ERAS Society (Abdikarim et al. 2015). The ERAS program is evidenced-based protocols which were designed to standardize and optimize perioperative medical care in order to reduce surgical trauma, perioperative physiological stress and organ dysfunction related to elective

procedures. In addition, improved outcomes, decreased hospital length of stay and faster patient recovery to normal life are expected to be obtained. Other advantages of this philosophy are the reduction of clinical complications and the health costs together with and increase of patient satisfaction (Jimenez et al. 2014, p.487).

The ERAS protocol is a combination of evidence based findings which works synergistically to accelerate the post-surgical recovery period, contains recommendations for patient care at different stages of the operation and requires multidisciplinary (surgeons, anesthetists, nurses, physiotherapists and dietitians) approaches (Kehlet and Wilmore 2005, Varadhan et al. 2010, Demirhan and Pınar 2014, Neville et al. 2014, Karen et al. 2015, Çilingir and Candaş 2017, Watson 2017).

The main goals of the protocol is to reduce postoperative morbidity and mortality, to reduce the duration and cost of hospital stay and to affect patients' perceptions about surgery positively by reducing the reaction of the body to surgical stress via optimizing perioperative nutritional status and promoting analgesia without opioids and postoperative early nutrition (Ljungqvist et al. 2017, Karen et al. 2015, Thorell et al. 2016, Çilingir and Candaş 2017, Yang et al. 2017, Aksoy et al. 2018, Li et al. 2018, Persico et al. 2018). In addition, it is aimed to minimize the pain, complications and functional disorders that may occur after discharging, with the ERAS protocol (Jimenez et al. 2014, Hübner et al. 2015, Çilingir and Candaş 2017). The success of the ERAS protocol depends on the preferably complete fulfillment of the protocol; nurses are an important part of this program. The components and recommendations of the ERAS protocol and the role of surgical nurses before, during and after the surgery are described below.

PREOPERATIVE PERIOD

Preadmission Information, Education and Counselling

Perioperative education for patients and their family members is essential for successful navigation through the surgical experience. There are limited studies that address the benefits of education before surgery; however, evidences show that preoperative teaching conducted before hospital admission is mostly successful. Ronco et al. (2012) found that patient information provided before surgery and reviewed after admission is more effective than information solely received before surgery. After the plan for surgery is confirmed, the patient should begin to receive information from the medical team. The education that the patient receives in the office will set the tone for the surgical experience. The goal of an effective patient education plan is to inform the patient and his or her family members about what to expect during each phase of the experience. Patients often worry about how long they will be hospitalized, types of dressings, driving restrictions, and when they can return to work and household activities, among other things. The goal of the education is to address these stresses and to help patients adequately prepare for and anticipate needs during recovery. A comprehensive education plan helps patients and caregivers engage in the process to prepare for the surgical experience. Including caregivers in the education process helps minimize stress and provides patients and their family members with more realistic expectations to better prepare for returning to home (Karen et al. 2015).

Optimisation of the Patient's Health before Surgery

It is emphasized that smoking and alcohol use should be quit four weeks before surgery. Alcohol users are at high risk for wound healing, cardiopulmonary function and bleeding; mortality rates are 2-3 times higher in alcohol users (Gustafsson et al. 2013). Pulmonary function and wound site complications are more frequent in smokers (Tunç Tuna and Kurşun 2018).

Preoperative Colon Cleansing

Mechanical colon cleansing is traditionally thought to alleviate the severity of sepsis in the event of anastomotic leakage. However, recent studies have shown that mechanical intestinal cleansing which was started to be applied in 1887, caused stress, dehydration, electrolyte imbalance, long-lasting hunger and delayed normalization of bowel functions; new methods are used instead of this application (Aksoy et al. 2018).

Preoperative Fasting and Carbohydrate Therapy

Stopping oral solid and liquid food intake as from the midnight before elective surgery applications, has been started to apply to reduce the possibility of pulmonary aspiration; it is applied daily as a routine today. However, it has been reported that there is a decrease in the well-being of the patient and some metabolic adversities, especially post-operative insulin resistance after this application (Ersoy and Gündoğdu 2007; Demirhan and Pınar 2014). Today, the accepted fasting protocol is to consume clear liquid food for up to two hours before surgery and to consume solid foods for up to six hours before surgery (Ersoy and Gündoğdu 2007; Yang et al. 2017). In addition, it has been stated that giving 800 ml of carbohydrate fluid until midnight before surgery and giving 400 ml of carbohydrate fluid until 2-3 hours before surgery, accelerate healing after surgery, reduces insulin resistance and significantly shortens the length of hospital stay (Ersoy and Gündoğdu 2007, Demirhan and Gündoğdu 2007, Demirhan and Pınar 2014, Aksoy et al. 2018). It has been suggested that diabetic drugs can be given in combination with carbohydrate therapy in diabetic patients (Gustafsson et al. 2013). In this period, nurses should ensure fasting of patients in the pre-operative period and apply medications.

Tromboembolism Prophylaxis

In patients having symptoms, it has been foreseen to use it in appropriate doses (Ersoy and Gündoğdu 2007). In addition, thromboembolism preventive compression socks have been recommended (Demirhan and Pınar 2014).

Antimicrobial Prophylaxis

Antibiotic prophylaxis is used to reduce wound infections after surgery. The antibiotics affecting both aerobic and anaerobic organisms should be administered only once (30 min) before the surgical incision (Demirhan and Pınar 2014, Yang et al. 2017). It has been recommended to repeat a second dose in prolonged surgery (longer than 3 hours) (Ersoy and Gündoğdu 2007, Demirhan and Pınar 2014).

Premedication

The use of antiarrhythmic drugs, beta blockers and statins is also appropriate if there is an indication for premedication (Aksoy et al. 2018). It has been not recommended to administer long or short-acting sedative drugs before surgery because it will delay the healing after surgery (Gustafsson et al. 2013, Solak-Kabataş and Özbayır, 2016).

INTRAOPERATIVE PERIOD

Anesthesia Protocol

In the ERAS, it is aimed to reduce the surgical stress response. The anesthetic technique should be applied in a way to allow the patient to recover quickly and minimize the opioid effect during the recovery period (Demirhan and Pınar 2014, Solak-Kabataş and Özbayır 2016). The application of the rapid onset and short-acting hypnotic anesthetics, opiates and muscle relaxants shortens the healing period in the postoperative period (Ersoy and Gündoğdu 2007, Demirhan and Pınar 2014). If possible, thoracic epidural analgesia should be used in laparoscopic colon surgery. The application of anesthesia and analgesia via epidural catheters in colorectal surgery reduces insulin resistance, increases motility via preventing sympathetic inhibition of the gastrointestinal tract and makes the use of narcotic analgesics unnecessary (Ersoy and Gündoğdu 2007, Solak-Kabataş and Özbayır 2016).

Selection of Surgical Incisions

The use of transverse or oblique incisions in abdominal surgery can reduce pain and pulmonary risks. A vertical incision can be preferred if adequate vision is achieved. According to the ERAS protocol, it is not a definite binding rule but it is necessary to use the shortest possible time (Demirhan and Pınar 2014).

Nasogastric Intubation

The ERAS protocol has argued the idea that drains, tubes and catheters should be used limitedly and removed immediately after surgery even if they were placed during the

operation (Ersoy and Gündoğdu 2007, Demirhan and Pınar 2014, Aksoy et al. 2018). It has been stated that the use of nasogastric intubation does not alter the rate of bowel function recovery, reduce pulmonary complications and hospital stay or other postoperative complications but it delays oral feeding and increases the incidence of pneumonia, atelectasis and fever (Aksoy et al. 2018).

Use of Drains

Postoperative draining has not been recommended because it may prevent the mobility of the patient (Demirhan and Pınar 2014, Solak-Kabataş and Özbayır 2016). It has also been stated that the use of drains has no effect on anastomotic leaks (Ersoy and Gündoğdu 2007).

Urine Catheter

Bladder catheter should be taken early because of disadvantages such as urinary infection and mobility restriction. However, the probability of urinary retention increases as a result of epidural blockage, it is necessary to keep the catheter as long as the blockage continues (Ersoy and Gündoğdu 2007, Demirhan and Pınar 2014).

Perioperative Fluid Management

In modern fluid therapy, fluid infusion which is enough to keep the patient as hydrated, is accepted as adequate. The hyperhydration in intraoperative and early postoperative periods (especially NaCl containing fluids) has been reported to increase the complication rate and the length of stay in the hospital (Ersoy and Gündoğdu 2007). The fluids (colloids and crystalloids) should be administered at the optimal level thereby monitor the cardiac function of the patients during the operation. It is aimed to decrease the length of hospital stay of patients and to improve gastrointestinal function of patients in a short time (Solak-Kabataş and Özbayır 2016).

Prevention of Intraoperative Hypothermia

Hypothermia that occurs during surgery stimulates sympathetic discharge and metabolic endocrine response, increases bleeding via disrupting clotting balance, causes postoperative dizziness and also increases pain at the incisional site via increasing oxygen consumption. Nowadays, it is recommended to start to warm up before the surgery to reduce the central and peripheral temperature differences of the patients and to ensure normothermia (Aksoy et al. 2018). In the literature, it has been reported that this practice reduces blood loss, wound infection, unwanted cardiac events, patient discomfort, the starting time of intestinal motility and the duration of hospitalization (Alfonsi et al. 2014, Aksoy et al. 2018).

It has been recommended that heaters should be used to prevent hypothermia during surgery; the IV fluids should be above 36°C to maintain the body temperature (Gustafsson et al. 2013, Solak-Kabataş and Özbayır 2016). The heating should be continued until the patient's body temperature increases up to 37°C. Active heating should be stopped when body temperature is above 37°C (TARS 2013). It has also been shown that a 1,90°C decrease in body temperature increases the risk of wound infection and the duration of hospitalization by 20% (Mehta and Barclay 2014). Maintaining body temperature at normal levels is one of the critical components of the care before, during and after surgery. Nurses should prevent the frequency of complications in patients by accurate follow-up of patients' body temperature (Oshvandi et al. 2014).

POSTOPERATIVE PERIOD

Elimination of Nausea and Vomiting after Surgery

Postoperative nausea and vomiting are important determinants of well-being and should be prevented because they limit oral feeding of patients in early period (Ersoy and Gündoğdu 2007). The prevention or reduction of nausea and vomiting can reduce fluid electrolyte imbalance, wound dehiscence, haemorrhage, the risk of aspiration pneumonia, the duration of hospitalization and re-hospitalization rates (Miles et al. 2015). The first strategy to reduce nausea and vomiting after surgery is antiemetic prophylaxis. The second strategy is to avoid the use of general anesthesia, propofol and nitric oxide and to reduce opioid use for reducing nausea and vomiting after surgery (Aksoy et al. 2018).

Stimulation of Gastrointestinal Motility

Stimulating gastrointestinal motility and more importantly, avoiding from the use of agents that adversely affect motility is essential for the maintenance of early enteral feeding (Yang et al. 2017). For this purpose, it has been recommended to use epidural analgesia, to avoid the use of opioids, excessive hydration and to use oral magnesium oxide 2x1 gr/day (Ersoy and Gündoğdu 2007, Demirhan and Pınar 2014).

Postoperative Fluid Intake

Oral fluid intake should be started as early as possible after surgery and patients should be encouraged to consume fluids (Yang et al. 2017). High-energy fluids contribute to the normal healing process because of the protein/carbohydrate in their contents. In addition to vitamins, minerals and trace elements, it is recommended that carbohydrates be prescribed as 150 kJ/100 ml and proteins as 3-6 g/100 ml. Balanced crystalloid solutions such as 0.9% sodium chloride to prevent hyperchloremic acidosis. The dose and application duration of starch solutions should be limited due to side effects such as renal dysfunction and bleeding. The urine output is the first symptom of hemorrhoids after surgery and therefore oliguria

should be evaluated well by nurses. The medical examination of the lungs, neck and veins, heart, abdomen, and extremities provides information about the volume (Aksoy et al. 2018).

Postoperative Analgesia

Optimal control of the pain along with reducing opioid use in surgery as much as possible, is one of the most important components of the ERAS protocol (Aksoy et al. It has been recommended that the postoperative pain control should be performed without the use of opioid analgesics as much as possible because they negatively affect gastrointestinal system, respiratory functions and central nervous system (Solak-Kabataş and Özbayır 2016, Yang et al. 2017).

The long-continued studies on the multimodal analgesic approach proposed by the ERAS protocol have shown that the use of non-steroidal anti-inflammatory (NSAID) drugs (acetaminophen, gabapentin and dexamethasone) reduces pain and minimizes opioid use (Khan et al. 2009, Thorell et al. al. 2017, Aksoy et al. 2018).

Early Removal of Nasogastric Tube, Foley Catheter, and Drainage Tube(s)

All indwelling catheters and tubes will potentially increase the incidence of infection and sepsis, although most ERAS protocols and expert consensus recommend minimizing the use of indwelling catheters and tubes. If medically needed, those inserted catheters and tubes should be removed as soon as medical conditions allow. For patients needing indwelling centralvenous catheterization, the catheter should be removed and replaced in no >1 week or whenever the patient's body temperature escalates (Yang et al. 2017).

Postoperative Nutrition

One of the most important criteria for postoperative well-being and early discharge is early oral feeding (Ersoy and Gündoğdu 2007). Postoperative intravenous fluids should be prematurely cut; oral feeding should be started as soon as possible. Early postoperative oral feeding has been shown to reduce postoperative complications, mortality and the length of hospital stay (Solak-Kabataş and Özbayır 2016). Patients should be encouraged to drink liquid at 2nd hour after surgery and to eat solid food at 4th hour after surgery. Oral nutrition solutions should be provided as a supplement until the maintenance of adequate oral nutrition. Postoperative nutritional support should be continued for at least 8 weeks in patients taking preoperative nutritional support due to their impaired nutritional status (Ersoy and Gündoğdu 2007, Demirhan and Pınar 2014).

Early Mobilisation

Post-operative bed rest is not desirable because it causes to lose muscles, to decrease muscle strength, respiratory function and tissue oxygenation, venous stasis and thromboembolism (Demirhan and Pınar 2014, Yang et al. 2017, Aksoy et al. 2018). According to the ERAS protocol, patients should be kept out of bed for 2 hours on the operation day and for 6 hours a day until the discharge on the following days (Ersoy and Gündoğdu 2007, Khan et al. 2009, Tunç-Tuna and Kurşun 2018). One of the responsibilities of nurses is to help early ambulation (Çam 2015, Tunç-Tuna and Kurşun 2018).

Duration of Hospital Stay and Discharging Criteria

Since the duration of hospital stay is shortened as the primary outcome of the ERAS, planning of discharge should be emphasized both during preoperative patient informing program and hospitalization. A careful and detailed discharge planning should be done to reduce the number of re-applications to the hospital, to improve patient safety and satisfaction (Demirhan and Pınar 2014). Tolerating normal diet well and becoming mobilized adequately by the patient, maintaining sufficient pain control and eliminating intravenous fluid dependency have been stated as discharge criteria (Ersoy and Gündoğdu 2007, Solak-Kabataş and Özbayır 2016).

In the literature, randomized controlled clinical and meta-analysis studies have reported that patients followed-up with the ERAS protocols have shortened total duration of hospital stay and fallen half complications (Adamina et al. 2011, Thorell et al. 2016, Yang et al. 2017, Li et al. 2018, Persico et al. 2018).

Follow-up

Discharged patients should be called by phone 24-48 hours apart; their situation should be got to know. If there is no problem, the patient should be invited on the seventh to tenth days postoperatively to control the wound and remove the sutures (Demirhan and Pınar 2014). The ERAS protocol will come to the fruition via sharing and discussing the data. Thus the protocol will be developed and, if necessary, halting points will be changed (Ersoy and Gündoğdu 2007, Demirhan and Pınar 2014).

The Role of Nurses in Implementation of the Accelerated Healing Protocol after Surgery

Not only surgeons but also anesthesiologists, nurses, and physiotherapists actively participate in the protocol, which is different from traditional approaches, and even patients are included (Karen et al. 2015, Ljungqvist et al. 2017, Aksoy et al. 2018).

Since surgical nursing covers nursing care before, during and after the surgery, it continues from the admission of the patient to the discharge of the patient; nurses play active

roles in every step of the surgical procedure (Demirhan and Pınar 2014, Hübner et al. 2015). The ERAS protocol is one of the current evidence-based approaches to which surgical nurses should adapt (Mitchell 2011, Karen et al. 2015, Çilingir and Candaş 2017). For this reason, surgical nurses should know their dependent and independent roles in the ERAS protocol, use these information in patient care, follow the current publications about the ERAS protocol and be open to develop. Evidence based nursing practices provide quality care in terms of bio-psychosocial health, improve the quality of care and its outcomes, create a difference in clinical practice and patient care outcomes, standardize care, minimize administration errors and increase nurse satisfaction (Karen et al. 2015, Aksoy et al. 2018).

Surgical nurses should continue patient education during the surgical procedure by especially identifying the problems that individuals may experience after discharge with good planning in the preoperative period. The fact that the ERAS is a multidisciplinary approach; the presence of surgical nurses at every step supports this consideration (Karen et al. 2015, Çilingir and Candaş 2017). In this approach, nurses have a key role in fulfilling the somatic and physiological needs of patients. The ERAS protocol is a model which consists of the applications involving nurses' dependent and independent roles. In the ERAS protocol, nurses have a role in psychological support especially for decreasing the stress of patients, restarting normal diet by patients, early mobilization and early rehabilitation of patients as soon as possible (Solak-Kabataş and Özbayır 2016). Nurses are also primarily responsible for the monitoring of the surgical procedure because nurses are health professionals in contact with patients for 24 hours therefore they also primarily responsible for the application and maintenance of the ERAS program (Hübner et al. 2015, Ljungqvist et al. 2017, Watson 2017). According to the literature, it has shown that the surgical nurses use their time more effectively and have lower workload as a result of the application of the ERAS protocol (Bianchini et al. 2014, Hübner et al. 2015, Pędziwiatr et al. 2015, Persico et al. 2018).

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Chapter 273

CURRENT APPROACHES TO PREVENT DIABETIC FOOT ULCERS

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ABSTRACT

Diabetes mellitus (DM) is a common metabolic disorder that can cause various complications. According to the literature, the prevalence of diabetes is rapidly increasing both in Turkey and worldwide. DM is an important health issue due to the high costs of healthcare and serious complications that may affect patients in different ways. Diabetic foot ulcer is a major complication of DM. Although highly preventable, diabetic foot ulcer places a mental, physical, social, and economic burden on patients, and it significantly affects their quality of life. Besides longer bed occupancy and higher healthcare costs, diabetic foot ulcer also increases the risk of lower limb amputation and mortality. Almost 12-25% of diabetic patients will suffer from diabetic foot ulcer during their lifetime, and 10-15% of patients admitted with diabetic foot require surgical intervention. The amputation rate in diabetic foot disease throughout Europe was reported as 0.5-0.8%. In the United States, 85% of lower-extremity amputations are preceded by foot ulcers in patients with DM. Evidence-based guidelines for the management of diabetic foot problems have noted that diabetic foot ulcers can be prevented to a great extent through regular foot examinations and proper therapeutic measures. The treatment and care of diabetics require a multidisciplinary approach because of the extensive nature of the problem. Regular diabetic neuropathy assessment, vascular assessment, joint and muscle examination, and walking analysis are thus recommended. Care of the pressure points on the plantar aspect of the foot is also essential to prevent diabetic foot ulcers. The main objective of a healthcare team in the management of a diabetic patient is to achieve metabolic control with an emphasis on health education, and to improve survival and quality of life.

Keywords: diabetic foot ulcers, prevention, podology, podiatry, walking analysis, personal shoes and insoles

INTRODUCTION

Diabetes mellitus (DM) is one of the most common chronic diseases. It is expensive to treat and its complications have a major impact on health expenses. DM was predicted to affect about 171 million people worldwide in 2000; this was predicted to rise to more than 340 million in 2030 (Wild et al., 2004). DM leads to multi faceted complications. Diabetic foot ulceration is one of the common complications related to the disease, and it can result in lower limb amputations (Boulton and Vileikyte, 2000; Reiber, 2001; Dang and Boulton, 2003; Pinzur et al., 2005).

Foot and lower extremity complications have become an increasingly significant public health concern in people with diabetes in both developed and developing countries. Foot problems are the most important and expensive complications of DM. These complications, such as neuropathy, ischemia and diabetic foot ulcers, typically lead to infection and lower extremity amputation. However, it is possible to prevent amputation in diabetic patients. An approach that involves prevention, patient education, staff education, a multidisciplinary diabetic foot team, and foot screening can reduce amputation rates by 49–85% (Stephanie et al., 2007).

The etiological factors for the development of diabetic foot ulcers can be determined in a clinical environment using inexpensive, everyday equipment designed for foot examination. Preventing diabetic foot ulceration is possible through foot screenings which analyze the protective sensation via the Semmes-Weinstein monofilament, as well as vascular (Doppler ultrasound and ankle-brachial blood pressure), orthopedic, dermatological, biomechanical (plantar foot pressure) issues and include a physical examination with a brief history. These measurements, and the findings of the physical examinations, help health providers to categorize patients based on risk and to decide what approach to use. Regular foot care, patient education, glycemic control and quitting smoking are other effective clinical interventions (Stephanie et al., 2007).

ETIOLOGY AND PATHOPHYSIOLOGY OF DIABETIC FOOT ULCERS

The etiology of diabetic foot ulcers usually has many constituents. The most frequent underlying etiologic factors of diabetic foot ulcers are peripheral neuropathy, trauma, foot deformity and high plantar pressures. Peripheral neuropathy plays a central role in most patients: up to 50% of diabetic patients have diabetic peripheral neuropathy and are at risk of developing diabetic foot ulcers. Neuropathy causes an insensitive and deformed foot, often with problems in walking. Walking barefoot and/or in ill-fitting shoes can induce a chronic ulcer in neuropathic people, as can acute trauma. Thickened skin (callus) grows as a result of the abnormal biomechanical loading of foot due to a foot deformity, limited joint mobility, poor-fitting shoes or a loss of sensation. A subcutaneous hemorrhage forms after this abnormal biomechanical loading of the foot. Peripheral vascular problems may result in an ischemic foot ulcer caused by a minor trauma. Symptoms may be absent in patients with neuropathy, ischemia or neuroischemic foot (Frykberg et al., 2000; Boyko et al., 1999, Pecoraro et al., 1990; Armstrong and Lavery 1998; IWGDF Guidelines, 2011).

Most of the risk factors for foot ulceration are also predisposing risk factors for amputation, because foot ulcers are the prime reason for amputation (Pecoraro et al., 1990; Armstrong and Lavery, 1998). Ulcerations can result in limb loss for two reasons. They can lead poor wound healing and to progressive tissue necrosis in the presence of critical ischemia (Armstrong and Lipsky, 2004).

PREVENTION

The prevention of diabetic foot ulcers in diabetic patients is a major clinical goal of healthcare professionals, as foot problems can result in lower extremity amputations. Studies of the causes of amputation show that ulcers lead to 84% of diabetes-related amputations. (Pecoraro et al., 1990). Prophylactic foot care has been shown to be connected with decreased morbidity, lower health costs and a reduced risk of amputation (Pinzur et al., 2005). Approaches that involve the classification of risk factors, as well as patient and family education and podiatric care, have been proven to be cost-effective and to reduce costs (Moreland et al., 2004; Singh et al., 2005; Ragnarson et al., 2004). Proven strategies for prevention of ulceration involve having a *multidisciplinary team approach to foot care, patient screening and follow-up, professional foot care for pre-ulcerative signs (debridement of hyperkeratosis, callus, corn and nails), patient education and therapeutic shoes* (Pecoraro et al., 1990; Dargis et. al., 1999; Apelqvist and Agardh, 1992).

Multidisciplinary Foot Care

Diabetic foot is a frequent problem and leads to high costs. A multidisciplinary foot approach to diabetic foot ulcerations has been shown to reduce the cost of diabetic foot treatment. Studies from around the world show a larger per capita expense for diabetics in general compared to other patients. This high cost is more evident when associated with diabetic foot problems, and is correlated to the length of hospitalization. Multidisciplinary team work with diabetic foot problems has been shown to decrease ulcer and amputation rates, and reduce the costs of the treatment itself (Matricali et al., 2007).

A team of dedicated health care professionals is essential for preventing lower limb amputation. Those responsible for foot care may include a diabetologist, vascular surgeon, podiatrist, orthopedic surgeon, pedorthist, general surgeon, and plastic surgeon. New studies have shown that podiatrists and vascular surgeons are the primary members of the diabetic foot care team. A podiatrist conducts regular screening and offers professional foot care; when a vascular problem appears a vascular surgeon carries out revascularization and after the operation the podiatrist continues to provide foot care (Lee et al., 2010). An ostomy nurse, specialist diabetes nurse, dietician and physical therapist can also participate in the team if required (Lee et al., 2010).

A prospective study noted fewer recurring ulcerations in diabetic foot ulcer patients after the formation of multidisciplinary diabetic foot care teams (Oyibo et al., 2001). Studies from Asia have shown that teamwork and the frequent implementation of preventive diabetic foot protocols strongly decreased the incidence of amputation (Burns et al., 2003). It has also been

proven that the use of multidisciplinary diabetic foot teams including podiatrists reduced amputations by 34% (Connor and Oz, 2004).

Patient Screening and Follow-Up

Patient screening and follow-up means to evaluate the patient's actual risk of developing a diabetic foot ulcer or undergoing amputation using the risk classification system and to carry out reassessments at regular intervals. If there is no peripheral neuropathy, the patient should have a foot examination once a year; if the patient has peripheral neuropathy, they should have a foot examination once every 6 months; if the patient has peripheral neuropathy with peripheral artery disease and/or a foot deformity, they should have a foot examination once every 3-6 months; if the patient has peripheral neuropathy and a history of foot ulcer or a lower-extremity amputation, they should have foot examination once every 1-3 months.(NICE, 2015). A foot examination can be repeated very often (every 1–2 weeks etc.) for high risk patients if there is urgent concern.

Professional Foot Care for Pre-Ulcerative Signs (Debridement of Callus and Nails)

Professional foot care for pre-ulcerative signs means the treatment of any pre-ulcerative sign on the foot. This includes:

- Treatment of calluses;
- Treating blisters and making them safe;
- Treatment of ingrowing or hypertrophic/thick nails;
- Treatment of hemorrhages;
- Treatment protocols for fungal infections.

The usefulness of the treatment of pre-ulcerative signs for preventing foot ulcers has not yet been clearly studied. However, removing calluses has been shown to be beneficial as it decreases plantar pressure which is a significant risk factor for ulcer formation (NICE, 2014; IWGDF, 2015).

Some images of our patients receiving foot care treatment are provided in Figures 1-7.

One randomized controlled study (RCT), one non-RCT and three non-controlled studies showed a dramatically lower rate of recurring foot ulceration in patients who received holistic foot examinations and care compared with those who did not (Dargis et al., 1999; Plank et al., 2003; Hamonet et al., 2010; Marcinia and Chantelau, 1998).



Figure 1. Removing calluses.



Figure 2. Callus before and after treatment and at 18 months' follow-up.



Figure 3. Treatment of pre-ulcerative lesion.



Figure 4. Treatment of a neuropathic ulcer.



Figure 5. Treatment of an ingrown nail with nail brace.



Figure 6. Treatment of an ingrown nail with nail brace.



Figure 7. Treatment of hypertrophic nail

Patient Self-Management Education

Education of the patient and their family should aim to provide the correct information about foot care and how to practice it. It is very important to support the patient in following the advice given. The education should involve how to self-manage their condition, what to do in foot care emergencies, recommendations about shoes, the patient's risk of developing a foot ulcer, and information about DM and blood glucose control. Patient education should be repeated regularly (NICE, 2015).

A diabetic person should practice the following self-management activities in an organized manner:

- Inspection of the feet and the inside of shoes every day;
- Washing the feet every day (drying them carefully especially between the toes);
- Refraining from using chemicals and plasters to treat callus and corns;
- Using balsam oil on the skin;
- Cutting nails straight;
- Monitoring the temperature of the skin on the feet to avoid the recurrence of plantar foot ulcerations (NICE, 2015; IWGDF, 2015).

Therapeutic Footwear

Foot ulcerations/amputations are connected to poorly fitting shoes in diabetic patients so off-loading techniques and different shoes are commonly using for the prevention and treatment of foot problems. Wearing incorrect shoes both indoors and outdoors is a major cause of foot ulcers. Shoes should be adapted to changing biomechanics and to foot deformities. Diabetic people with normal protective sensation can choose their shoes themselves. In people with peripheral neuropathy/ischemia and foot deformities extra attention must be paid when fitting footwear (Pecoraro et al., 1990; Dargis et al., 1999; Apelqvist and Agardh, 1992; Armstrong and Lipsky, 2004).

The patient should be directed to use special diabetic shoes, slippers, socks and insoles at home and when outside. To prevent a recurrent non-plantar ulcer, patients need to use therapeutic shoes, custom-made insoles or a toe orthosis (Chantelau, 1993; IWGDF, 2015).

Patients should use custom-made shoes and insoles to treat a plantar foot ulcer as standard or conventional therapeutic shoes are inadequate for treatment. Traditional half shoes which are designed for off-loading of the forefoot and which only support the heel and midfoot, are unsuitable because of the risk of a midfoot fracture (IWGDF, 2015).

Casual footwear, shoe modifications and toe orthoses can be used to treat and produce off-loading for non-ischemic, non-plantar or under control infection ulcers. Patients should wear well-fitting footwear for a recurrent non-plantar ulcer. Custom-made insoles and shoes, therapeutic shoes and a toe orthosis are required if a foot deformity or a pre-ulcerative sign is present (IWGDF, 2015).

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Chapter 274

A REVIEW OF STUDIES ON THE APPLICATION OF COUMARIN AND ITS DERIVATIVES IN PLANTS

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ABSTRACT

This chapter summarizes the use of coumarin, a secondary metabolite, and its derivatives in different aspects of plant growth and formation. Coumarin and its derivatives have broad biochemical and pharmacological activities. They also have allelopathic effects on plants. In this chapter, summaries and review of previous research are presented by pointing out significant contributions and effects of coumarin and its derivatives in plant growth and inhibition. Nowadays, the active use of coumarin and its derivatives, which are used as defense elements in several areas such as agriculture, food, cosmetics and medicine, necessitates the clarification of action mechanisms of coumarin. In order to understand these compound's allelopathic and toxic effects completely, it is essential to carry out cytological, genetic, biochemical and physiological tests altogether. In the studies on plants, it is very important to understand the defense mechanisms in plant species that make them resistant to stress conditions in order to minimize yield loss in terms of nutrition and agricultural economics.

Keywords: allelochemical, coumarin, cytotoxicity, genotoxicity, plants

INTRODUCTION

With their broad range and biomass, distribution of plants that constitute the first step of food chain is determined by the biotic (plants that belong to the same species, plants that belong to the different species, animals, bacteria and fungi) and abiotic (temperature, geographical formations, soil composition, water and solar rays) factors. One of these factors,

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secondary metabolites, are the components that are excreted by the plants. These components affect the choice of the plants' habitats to a large extent. These components' mechanism of action can produce inhibitor effects to a certain extent and may generate physiological, cytotoxic or genetic changes in the organism. Hereditary variations that emerge when these components compete with the organisms' DNA may, in turn, cause decrease in their population or extinction. Also, these components may affect product quantity and quality in a negative way by generating physiological and biochemical damage. The plants appeal to their molecular defense mechanisms in order to minimize or prevent negative effects completely. These components may generate adverse outcomes in the organisms when they are consumed. Coumarin is one of the highly studied secondary metabolites.

Coumarin was purified in its free form for the first time in 1820 by Vogel from the dried sweet-smelling seeds of *Dipteryx odorata* (*Coumarouna odorata*) tree called 'tonka bean,' which grows in South America from the Fabaceae family. In plants, coumarin and coumarin derivatives are commonly found on their own or compositely. Because of their various biological activities, these kinds of compounds are natural compounds that have gained significance in recent years. Coumarin's chemical structure is first explained by Strecker (1867) and Fitting (1870) according to Coffey (1977). Today, apart from the tonka bean, coumarin derivatives are isolated from 600 kinds of plants. Coumarin is found, especially, in Orchidaceae, Leguminosae, Rutaceae, Apiaceae and Lamiaceae families' plants' fruits, leaves, roots, stems and shell sections at a certain rate (Boga, 2005).

Crystal-like, white and solid coumarins are composed of aromatic rings that are fused with condense lactone ring. 1,2-benzopiran, 2H-1-benzopyran-2-one, *cis*-o-coumaric acid lactone and coumarinic anhydride are the other names that are used commonly. Its molecular formula is C₉H₆O₂ and its molecular weight is 146,14 g/mol. While coumarin's melting point is 68-70°C, its boiling point is 297-299°C. Coumarins can be soluble in ethanol, chloroform, diethyl ether and oil, but it is slightly soluble in water. While first class coumarins are isolated from Indian beans, coumarins, which are used for commercially, are synthesized by salicylaldehyde (Yuce, 2006).

Herbal coumarin derivatives have broad biochemical and pharmacological activities. Cinnamic acid and its derivatives, which are the pioneers of coumarin and its derivatives, are the substantial compounds of sweeteners, perfumes, synthetic dye and pharmaceuticals (Bickers et al. 2005). Because of their significant bioactivity power, new types of coumarin derivatives, which have efficient pharmacological value, have been synthesized in recent years. Antibiotic, anti-coagulant, anti-cancer, anti-inflammatory and bacteriostatic effects that are found in coumarin and its derivatives, make them a significant matter in biology and medicine (El-Khatib et al. 2007). They also have antioxidant, vasodilator, anti-inflammatory, immune stimulant, antiallergic and antiviral effects. At the same time, the studies conducted on humans and animals have indicated that coumarins decrease the risk of catching cardiovascular and cancer diseases (Cirico et al. 2006). Although it was used in food industry because of its redolence for a period of time, the studies that were conducted on animals revealed its toxicity and its use was abandoned in this field (Guenther, 1975). These phenolic compounds' toxic aspects are revealed by different researchers. According to the previous research, phenolic compounds like tannic acid, coumarin, vanillin, caffeine and cinnamic aldehyde had mutagenic effects on mammalian cells (Sanyal et al. 1997). High doses of phenolic compounds' genotoxic effects occurred by the mechanisms like DNA intercalation,

DNA topoisomerase II damage, free radical production and key enzyme inhibition (Stopper et al. 2005).

When the topic is approached from plant stress physiology perspective, the agents that are applied on plants generate various changes on plant metabolism. In order to determine physiological and biochemical changes, one has to have knowledge about the transmitter and the target plant. At the same time, knowing these agents' structure and mechanism of action eases the description of morphological, cytological and genetic changes that they cause. For instance, abnormal rhizogenesis indicates that inhibitor material prevents the microtubule formation. Lateral rhizogenesis or damage of primary root indicates that hormonal balance is destroyed. The difference between the length of the root and stem indicates that plant growing is affected at the primary level. These effects depend on the impact of the compound's mechanism of action and biologic effect, which have extracted an allelochemical effect, as well as the target plant's physical and biochemical tolerance status (Erez, 2009). As a result of the secondary metabolites' or allelopathic compounds' interaction with the target plant, temporary pores may open on the cell membrane or they may cause membrane disintegration. Thus, by increasing cell membrane permeability, they may make them open to exogenic materials (Wink, 2010). Also, these compounds can easily react with proteins and toxic materials, which have a significant role in metabolic and structural events, gene regulation and interaction. As a result of this interaction, protein conformation may easily become active or inactive. Secondary metabolites perform this effect by connecting proteins covalently, especially with their own reactive functional groups (Wink & Latzbruning, 1995). Moreover, allelopathic agents, which contain phenol, may decrease, increase or cap off the plant hormones' physiological activities. This situation inhibits plants' normal physiological development process. In general, phenolic compounds' effect on germination and early seedling development may be activating or inhibiting depending on the compound that is used, concentration and target plant (Reigosa et al. 1999).

PREVIOUS STUDIES ON THE EFFECTS OF COUMARIN ON PLANTS

Coumarin's significant effects such as acting like an antioxidant, an enzyme inhibitor and in repressing toxicants are examined in plant biochemistry and physiology (Yuksel, 2017; Abenavoli et al. 2003; Saleh et al. 2015). Coumarins in plants facilitate or inhibit plant development depending on their types and concentrations. A plant affects call differentiation and auxin metabolism by acting like development promoter (Abenavoli et al. 2003; Demiralay, 2005; Yuce, 2006).

Coumarin's influence on *Vicia faba* L was examined by considering some parameters like germination and growth in the study of Saleh et al. in 2015. To determine coumarin's influence on germination, the *Vicia faba* L seeds were treated with coumarin in different concentrations. It is stated that coumarin influenced the plant more in growth phase, significantly enhanced phytohormone rates as well as primary and secondary metabolites. Results of Saleh et al.'s study indicated that coumarin might influence plant's growth and physiology as an active growth substance and it might have an interaction with phytohormone metabolism.

In Razavi's (2011) study, it is stated that some coumarin derivatives like imperatorin and psoralen may be used for producing eco-friendly pesticide chemicals. Mata et al. (1998) used *Amaranthus hypochondriacus*, which is an imperatorin of a natural coumarin derivative on *Echinochloa crusgalli*, *Lactuca sativa* and *Lycopersicum esculentum*. They examined the effects of coumarin on radicle growth and germination. Based on their findings, they reported that, imperatorin inhibited ATP synthesis and phosphorylation mechanisms, and acted like an allelopathic agent on these plants.

Wu et al. (2016) applied 40 $\mu\text{g mL}^{-1}$ coumarin on Italian rye flower (*Lolium multiflorum* Lam.), common knotgrass (*Polygonum aviculare*), red clover (*Trifolium pratense*), veronica (*Veronica persica*), *Poa pratensis* L., *Chenopodium album* and *Plantago asiatica* plants and found out that coumarin, in these plants, significantly inhibited the seed germination and seedling growth. It is stated that important inhibition effects denoted both seed germination and seedling growth on all coumarin applied test plants in 80 $\mu\text{g mL}^{-1}$. They also stated that coumarin completely hindered Italian rye flower's and red clover plant's seed germination and seedling growth. Results of their study revealed that coumarin was the dominant allelochemical substance of yellow sweet oat and this substance had a powerful inhibition effect on seed germination and seedling growth on many weeds. According to the results of this study, coumarin may be used as a natural herbicide.

Razavi et al. (2010) conducted a study on *Zosima absinthifolia* plant which belongs to the Apiaceae family. This plant is used as food aroma and food product in Iran. In this study, imperatorin, which is one of the plant seeds known as furanocoumarin, 7-preniloksi coumarin, and auraptene were purified. Results of their study revealed that imperatorin displayed a fungi toxic effect against *Sclerotinia sclerotiorum*, which is a common plant pathogen. It is stated that compounds also had phytotoxic effects and they played an allelochemical role.

Findings of Shettel and Balke's (1983) study revealed that coumarin derivative umbelliferon inhibited the growth of *Zea mays* L., *Glycine max* L., *Abutilon theophrasti* Medic., *Amaranthus retroflexus* L., and *Panicum miliaceum* L. plants. In the study of Kupidowska et al. (1994), the effects of coumarin and xanthotoxin substances on *Allium cepa* plant were examined. It is reported that these substances retarded mitosis in *Allium cepa* root tips meristematic cells, decreased oxygen uptake by its meristematic cells, created structural changes in mitochondrial matrix and caused changes in organelles' formation and physiology. The results of third study revealed that coumarin increased succinate dehydrogenase enzyme production more than xanthotoxin, and energy metabolism was affected as a result of the subsequent changes. Similar to the findings of Razavi et al. (2010), they found that coumarin acted like allelochemicals.

In another study, Brooker et al. (2007) examined coumarin's six different derivatives in terms of their antifungal activity against pathogen fungi on various soil plants. They were specifically interested in *Macrophomina phaseolina* and *Pythium* spp., pathogens amongst these fungi. Their results supported previous studies about natural insecticide development with the help of coumarin and its derivatives.

Al-Barwani et al.'s (2004) study found that coumarin derivative furanocoumarins were dominant antifungal compound on *Conium maculatum* plant. Along with these compounds' absence in healthy plant structurally, they increased 103 times more in plants that got stressed compared to the control group. The findings of their study suggested that these compounds

might be considered as stress compounds because they increased as a result of chemical stress.

There were some other studies on coumarin, which examined its insecticidal effects. For example, Olson and Roseland (1991) and Stevewnson et al. (2003) found that coumarin and its derivatives had insecticidal effects. In the light of the findings of these studies, it is stated that working on coumarin may bring a new approach to the development of genetic plants that produce coumarin by using genetical engineering and to the control of insect herbivores.

In another study Ahrabi et al. (2011) investigated the biochemical and physiologic reactions of para-hydroxybenzoic acid and coumarin, which are the secondary metabolites from phenolic compounds that affect plant growth and development on canola. Chlorophyll, carotenoid and anthocyanin ingredients were identified and catalase activities were measured. Moreover, lipid peroxidation was measured with thiobarbituric acid. The results of the study revealed that seedling growth decreased significantly. It is stated that chlorophyll ingredient decreased with the increase in phenolic compounds' concentrations however carotenoids and antioxidants like anthocyanin that had low molecular weight decreased significantly. It is reported that antioxidant enzyme guaiacol peroxidase activity increased along with the increase in phenolic compound concentration but catalase activity did not change significantly. In spite of the increase in the antioxidant capacity of canola seedlings, it is explained that lipid peroxidation increased in the presence of these phenolic compounds. The results revealed that some plants' allelopathic potential was related with its phenolic compounds and allelochemical research may cause development of herbicides that had less negative effect on environment and ecosystem. It is reported that these phenolic acids' presence may decrease canola yield and it is prominent to destroy these weeds for the production of canola in terms of an allelopathic angle.

In their study, Abenavoli et al. (2006) investigated allelochemical coumarin on *Triticum turgidum sperması durum* Desf. plant. Findings of their study revealed that coumarin inhibited the seed germination in high concentrations. More specifically, coumarin blocked the water intake, lessened the electrolyte storage capacity and O₂ consumption during early germination stage and delayed the activation of peroxidases. It also increased superoxide dismutase activity, decreased some enzymes' (APX, CAT) activities and suppressed some molecular chaperons' transcriptions. In another study, Aliotta et al. (1992) investigated coumarin's effects on radish. The results of the study revealed that coumarin was an effective inhibitor and it inhibited the root growth of carboxylic group in the side chain.

Zhou et al. (2013) investigated the effects of coumarin application on the growth of *Medicago Sativa*, net nitrate intake, nitrate (NO₃⁻) and ammonium (NH₄⁺) concentration, the amount of soluble protein and the effects on nitrate reductase, glutamine synthase and glutamate dehydrogenase activities. They found out that coumarin decreased the fresh weight production and root/body development rate at shoots and roots in high concentrations. Net nitrate intake was stimulated significantly at the seedlings that were exposed to coumarin in low concentrations but it diminished with the increase in coumarin amount. Their results also revealed that while low coumarin application increased NO₃⁻ ingredient prominently, it decreased in high coumarin application. NH₄⁺ rate, on the other hand, decreased in low coumarin concentration, but increased in high concentration. It is reported that nitrate reductase activities were suppressed in high coumarin concentrations and glutamine synthase rates decreased at first but then increased. It is also stated that glutamate dehydrogenase activities were precluded at roots in the highest coumarin concentrations. According to these

results, it is stated that coumarin in low concentrations stimulated net nitrate intake and N metabolism at roots but in high concentrations it affected the basic enzymes of nitrogen metabolism in clover.

Based on the results of their study, Li and Gao (2011) stated that a coumarin derivative 4-metilumbelliferon (4-MU) inhibited seed germination by decreasing primary root growth in *Arabidopsis thaliana*. It is also found that 4-MU contributed to the hypocotyl formation and auxin distribution. In another study, Abenavoli et al. (2003) applied coumarin (1,2 benzopyrone) on *Daucus carota* L. Cv. Saint Valery. As a part of their study, they generated plant culture in order to investigate the effects on cell growth and nitrate intake and the use of ammonium and carbohydrates on this plant. While coumarin application caused cell growth inhibition, free amino acids, ammonium rates and glutamine synthetase; glutamate dehydrogenase, glukoz-6-fosfat dehydrogenase and phosphoenolpyruvate carboxylase enzyme activities increased in cells. It is stated that malate dehydrogenase, on the other hand, was inhibited. These effects were interpreted from the point of protein catabolism's stimulation and/or intervention with the protein biosynthesis which was induced by coumarin. Similar to other studies discussed in this review, in this study, it is stated that allelochemical compound coumarin might act as an inhibitor of cell cycle and/or as a senescence-promoting substance.

In another study, Abenavoli et al. (2004) investigated the effects of coumarin on corn seedlings (*Zea mays* L. cv. Cecilia) when the parameters like the length, diameter of different root types and branching density were taken into consideration. The amount of applied coumarin inhibited the root length. It is also found that especially 1 and 0.25 mM coumarin concentration decreased radical, seminal and nodal root lengths, respectively. In the light of the results that they found, it is stated that nodal > seminal > radical plant roots were more sensitive to coumarin.

Another study that investigated the allelochemical effects of coumarin was Lupini et al. (2010). It focused on the effects of coumarin on root elongation speed at three different maize primer root zones, transition zone and two non-growing zones. ATPase activity, pH changes and cell membrane potentials at root zones were evaluated. According to the results of the study, it is stated that coumarin increased root elongation speed at root transition zone thus, it caused an increase in ATPase activity. It is reported that cell membrane permeability changed by causing proton amount change.

In a different study, Al-Wakeel et al. (2013) applied three different concentrations of coumarin and salicylic acid against charcoal rot disease caused by *Macrophomina phaseolina* (Tassi) Goidanich on sunflower (*Helianthus annuus* L.). It is stated that the preparation of sunflower seed with 0.3 mM coumarin or 1.0 mM salicylic acid reduced the degree of disease and provided approximately 50% protection on the length of root lesions at greenhouse conditions and more than 80% decrease. It is reported that both coumarin and salicylic acid applications caused accumulation of soluble sugars and phytoalexins, at the same time they also stimulated β -1,3-glucanase and chitinase activities.

Pergo et al.'s (2008) study focused on nine different plants against *Bidens pilosa* L in terms of phytotoxicity. *Bidens pilosa* L grows in Brazil and it is responsible for yield loss at some products. In their study, while coumarin treatment inhibited *Bidens pilosa* L development, it did not affect the development of surrounding useful plants (*Senna obtusifolia* L., *Euphorbia heterophylla* L. ve *Ipomoea grandifolia* L.). Among the results of the study, it is stated that coumarin acted like a cytostatic agent which retarded germination.

Saleh and Madany's (2015) study investigated the effects of coumarin in increasing endurance against salinity stress of the plant. They covered wheat germs with coumarin (50ppm) and then grew them under different NaCl levels (50, 100, 150 mM) during two weeks. Because of the accumulation of osmolytes like soluble sugars and proline with coumarin pretreatment, it enhanced the growth of wheat germs under salinity compared to the seedlings that coumarin was not applied. Also, coumarin treatment significantly increased K^+/Na^+ rates at plants' seedlings' shoots that were under salinity stress. In addition to this, it is stated that at roots, this rate increased in the plans that have no salinity stress. It is found that phenolic materials and flavonoids accumulated with coumarin treated Phenylalanine ammoniac lyase (PAL). Salt stress significantly stimulated peroxidase (POD) activity at the seedlings that were pretreated with coumarin. Additionally, the effects of coumarin on total antioxidant capacity was obtained only with the highest NaCl doze (150 mM).

Saleh and Kebeish (2017) demonstrated that coumarin and its derivatives had different physiologic effects on tissue and organ levels. In their study, coumarin's effect on redox homeostasis of wheat germs at aleurone layers was investigated. The results revealed that both coumarin and GA3 implementations induced α -amylase production but inhibited superoxide dismutase, catalase and ascorbate peroxidase activities. Antioxidant enzymes' downregulation by coumarin and GA3 caused both H_2O_2 and significant accumulation of malondialdehyde. The results showed that coumarin might ruin redox balance at aleurone layers by inactivating enzymatic antioxidant system. It is stated that, coumarin may show gibberellin-like activity. In another study, Saleh and Abu El-Soud (2015) also found that coumarin had a gibberellin-like effect and it was effective in germination and sapling formation.

In the investigation of new plant killer compounds that cover weeds, Araniti et al. (2015) examined the effects of three synthetic coumarin derivatives on two harmful weeds, *Amaranthus retroflexus* and *Echinochloa crus*' germination and rhizogenesis. All of the coumarin derivatives that they synthesized affected both weed germination and rhizogenesis. Findings of their study revealed that coumarin and its derivatives might have promising herbicide activity potential.

Niro et al. (2016) define coumarins as having allelopathic characteristics. In their study, researchers investigated the effects of different doses of coumarin on a weed (wild oat), crop (wheat) and microbial community in natural soil conditions. Findings of their study reaffirmed that coumarin was a natural herbicide that had a prominent potential in sustainable agriculture. In another study, Grana et al. (2017) evaluated the mechanism of action and phytotoxic potential of scopoletin, which is a natural compound that belongs to the coumarin group. Results of their study demonstrated that scopoletin caused mitochondrial membrane depolarization and rhizogenesis that stimulated cell death. With the analysis conducted, they observed cell and tissue anomalies at roots, such as cell wall deformations, multinucleate cells, abnormal nuclei and tissue disorder.

Lupini et al. (2014) also defined coumarin as an active allelopathic compound that played a key role in plant-plant interaction and communication. The interaction between coumarin and auxin was examined at *Arabidopsis thaliana* (Col-0) on root system's development. It is stated that coumarin strongly affected *Arabidopsis* seedling's primary root extension and root development. It is also found that especially 10^{-4} M coumarin significantly inhibited main root extension by increasing lateral root numbers and root bristle length. Also, coumarin addition increased the negative effects of TIBA and NPA which were the two auxin transport

inhibitors that caused lateral root formation's inhibition. These results revealed that there was a functional interaction between coumarin and auxin in the root development of *A. thaliana*.

Yuksel and Aksoy (2017) examined the cytological effects of Coumarin (2H-1-benzopyran-2-one) on *Lens Culinaris Medic* in terms of cell response, mitotic index, mitotic abnormalities and chromosome aberrations. Germination percentages of *L. culinaris* roots decreased with increasing coumarin concentrations. Cytological observations demonstrated that the mitotic frequency in root meristematic cells decreased and that abnormality frequency also decreased in parallel to the increase in concentrations of coumarin. The results indicated that this active ingredient had the ability to cause a reduction in the seed germination percentage in the number of different phases of mitosis and increased chromosomal aberration of *L. culinaris*.

CONCLUSION

As I have tried to present in this chapter, coumarin and its derivatives have a wide range of applications in different plants for different purposes. Nowadays, the active use of coumarin and its derivatives, which are used as defense elements, in several areas such as agriculture, food, cosmetics and medicine, necessitates the clarification of action mechanisms of coumarin. In order to understand these compound's allelopathic and toxic effects completely, it is essential to carry out cytological, genetic, biochemical and physiological tests together. With the studies that are conducted on plants, it is highly important to understand the defense mechanisms in plant species that are resistant to stress conditions in order to minimize yield loss in terms of nutrition and agricultural economics. For this purpose, most of the studies have focused on the production of plant species that are resistant to stress conditions in recent years. These studies are also offering solutions to prevent nutrition problems that are likely to emerge in the near future.

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Chapter 275

AWARENESS OF BRUCELLOSIS: A WORLDWIDE ZONOSIS

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ABSTRACT

Brucellosis, which is one of the most common zoonotic diseases, causes abortion, infertility and reduced milk production in animals. Brucellosis in humans, on the other hand, is defined as an acute or sub-acute febrile illness including an intermittent or remittent fever. Because of brucellosis, many countries run the risk of suffering from economic and health problems like losing husbandry and infection risks. *Brucella*, which dates back to the 5th plague of Egypt around 1600 BC in history and which was named after the research of Sir David Bruce, is an important disease and *brucella* genus has 11 species. The aim of this chapter is to define this disease and its species and biovars, to explain its historical background, and to reveal the ways it affects animals and humans.

Keywords: biovar, *Brucella melitensis*, brucellosis, Malta fever, zoonosis

INTRODUCTION

Brucellosis is one of the most common zoonotic diseases caused by *Brucella (B.)* spp., which causes important health and economic problems (Godfroid et al., 2005; Songer & Post, 2012; Yumuk & O'Callaghan 2012). This disease, which has subacute or chronic forms, affects many different animal species (Corbel, 2006). It causes both economic and health problems through the loss of husbandry and it brings about risks due to the infections appearing via dairy products (Pappas et al., 2006a; Seleem et al., 2010). The distribution of host includes humans, wild and domestic animals such as sheep, goat, cattle, camel, pig, boar,

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rabbit, dog, marine mammals, fox, and baboon (Corbel, 2006; Godfroid et al., 2005; OIE, 2016; Songer & Post, 2012). It is defined as a chronic contagious disease causing necrotic inflammatory infections and complications such as abortion, infertility, arthritis, orchitis and mastitis in susceptible hosts (Alton et al., 1988; Aydin, 1997). Moreover, World Health Organization (WHO) laboratory biosecurity manual describes *Brucella* organisms as belonging to risk group 3 microorganisms (OIE, 2009a; OIE, 2012; WHO, 2004).

As *Brucella* species can be transmitted via aerosol way, it is classified as a potential bioterror agent as well. It is also stated that there are no vaccines for human beings (Godfroid et al., 2005; Songer & Post, 2012). Because of its significance as a potential agent of bioterrorism, the pathogen is on the category B biodefense research list of the Centers for Disease Control and Prevention (CDC) and the National Institute of Allergy and Infectious Diseases (NIAID). The non-stratified lists of potential biological weapons of other organizations, such as the WHO, the North Atlantic Treaty Organization (NATO), and the Biological and Toxin Weapons Convention (BTWC) also include brucellosis (Pappas et al., 2006a). When it is used as a weapon for agroterrorism, it might ruin the economy (DelVecchio & Mujer, 2013).

Brucellosis is known as ‘undulant fever’, “Mediterranean fever” or “Malta fever” (Corbel, 2006; Godfroid et al., 2011; Matthew & Leland, 2004) and it is transmitted through infected animals or their products (Corbel, 2006). However, Mediterranean fever, which is synonymous with brucellosis, should not be confused with familial Mediterranean fever. (Matthew & Leland, 2004). Brucellosis, especially caused by *Brucella melitensis*, remains one of the most common zoonotic diseases worldwide with more than 500,000 human cases reported annually (Bosilkovski et al., 2009; Pappas et al., 2006b; Seleem et al., 2010).

Brucellosis in cattle is usually caused by biovars of *Brucella abortus*. In some countries, especially in southern Europe and western Asia, where cattle are kept together with sheep or goats, *B. melitensis* might cause this infection (OIE, 2012). Brucellosis in cattle is known as Bang’s disease and epizootic abortion and contagious abortion are the terms that also used in veterinary medicine. (Matthew & Leland, 2004). Brucellosis in sheep and goats (excluding *Brucella ovis* infection) is primarily caused by one of the three biovars of *B. melitensis*. (OIE, 2009a). *Brucella ovis* causes a disease unique to sheep and it is one of the most common causes of epididymitis in rams and a rare cause of infertility and abortion in ewes and neonatal mortality in lambs (OIE, 2015a). Sporadic infections caused by *B. abortus* or *B. suis*, which are rare cases, have been observed in sheep and goats. On the other hand, it is possible to observe *Brucella melitensis* infection in domestic and wild susceptible species when these species are kept together with sheep and goats in enzootic areas (OIE, 2009a). Out of 5 biovars of *B. suis*, biovars 1, 2 and 3 are responsible for the infection in pigs (OIE, 2009b). Canine brucellosis, which is a zoonotic disease and caused by *Brucella canis*, is an important cause of reproductive failure, particularly in kennels (CFSPH, 2012).

THE HISTORY OF THE DISEASE

It is possible to trace the roots of this disease in the 5th plague of Egypt around 1600 BC. When ancient Egyptian bones dating to around 750 BC were examined, some evidence of sacroiliitis and other osteoarticular lesions, common complications of brucellosis was found

out (Pappas, 2006a; Seleem et al., 2010). In addition, a researcher named L. Capasso found the bone lesions which were typical of brucellosis in the skeletal remains of people who died during the first volcanic eruption of Mount Vesuvius. He also analyzed a buried carbonized cheese through electron microscopy and his analysis revealed that there were coco-like forms which were morphologically consistent with *Brucella* spp. (D'anastasio et al., 2011; Godfroid et al., 2005; Seleem et al., 2008). Since people domesticated animals, brucellosis has affected human populations. There is evidence that Hippocrates might have mentioned it in his book titled 'On Epidemics' and it was a common disease in the ancient world (Matthew & Leland, 2004).

The disease, which is known as brucellosis, was first found out in Malta in 1850s. It was the British medical officers serving on the island who spotted the disease after the Crimean War (Wyatt, 2013). In 1859, Marston made one of the earliest descriptions of the disease in 1859 except for the biblical references (Nicoletti, 2002). He also described typhoid fever and differentiated it from 'Undulant fever', what is known as brucellosis (Nicoletti, 2002; Wyatt, 2013). The research of Sir David Bruce with the military and civilian population in Malta started the modern understanding with the help of the identification of a micrococcus from a patient who died of undulant fever in 1887 and it was named '*Micrococcus melitensis*' (Godfroid et al., 2005; Matthew & Leland, 2004; Poester et al. 2013; Wyatt, 2013). In 1905, again in Malta, Themistocles Zammit isolated it from goat's milk accidentally and thanks to this, he was able to illustrate the zoonotic nature of the disease. Before that, it was considered to be a vector-borne disease (Nicoletti, 2002; Seleem et al., 2010). This bacterium was renamed '*Brucella melitensis*' in Sir David Bruce's honor by Meyer and Shaw in 1920 (Poester et al., 2013).

Afterwards, L.F. Bernhard Bang, who was a Danish vet, mentioned an organism that he named *Bacillus abortus* which caused contagious abort cases in cattle, which was later found to be associated with Bruce's organism (Matthew & Leland, 2004; Nicoletti, 2002; Seleem et al., 2010). The name of the disease was changed from 'Bovine infectious abortion to Bang's disease in 1930 (Nicoletti, 2002). An American scientist, Alice Evans, who carried out important work on pathogenic bacteria in dairy products identified once again the relationship between Bang's disease and Malta Fever and she renamed the genus *Brucella* to honour David Bruce (Parascandola, 1998; Seleem et al., 2010).

Brucellosis in pigs caused by *Brucella suis* was first reported in 1909 by Huntyra in Hungary (Ozcanarlan, 2011). Soon after that, in 1914, Jacob Traum isolated it from aborted swine fetuses in Indiana, USA. (Nicoletti, 2002; Ozcanarlan, 2011; Poester et al., 2013). *B. ovis*, which causes epididymitis in rams, was first isolated in New Zealand by McFarland and his colleagues. In 1953, Buddle ve Boyes stated that this agent was a variant of *B. melitensis*. This agent was named as *B. ovis* in 1956. (Nicoletti, 2002; Ozcanarlan, 2011; Poester et al., 2013). *B. neotomae* was first isolated in Utah, USA in 1957 from the wood rat *Neotoma lepida* by Stoenner ve Lackman. This organism was defined as a new *Brucella* species on the basis of its behavior on differential dye media, CO₂ requirements, and H₂S production (Cameron & Meyer, 1958). *B. canis* was discovered in beagle dogs in the USA in 1966 and named as a distinct species by Carmichael in 1968 (Thimm, 1982). It is the germ of contagious abortion of kennel dogs and stray dogs as well. In 1994, British researchers isolated an unknown *Brucella* organism from stranded harbor seals (*Phoca vitulina*), harbor porpoises (*Phocoena phocoena*) and common dolphins (*Delphinus delphis*) on the coast of Scotland, and American researchers isolated it from an aborted foetus of a captive bottlenose

dolphin (*Tursiops truncatus*) in California (Godfroid et al., 2005). The distinguishing metabolic profiles, dye and phage sensitivities of these isolates were found to be the same and then, they were labelled as *B. maris*. (Ozcanarslan, 2011). Later on, *B. maris* was categorized as *B. ceti*, which affects porpoises and dolphins, and *B. pinnipedialis*, which affects mainly seals. (Pappas, 2010). Previously, brucellosis was not recognized, not even suspected in marine mammals; however, as marine mammal *brucella* strains have been isolated, the ecologic range of the genus and its scope as a zoonosis have been extended. (Godfroid et al., 2005).

In Turkey, the first brucellosis case was identified by Husamettin Kural and Mahmut Sabit Akalin in 1915 in a soldier who was being treated in Istanbul Kuleli Military Hospital. The first isolation in cattle was made in 1931 by Berke and in sheep by Koylubag and Aktan in 1944 in Bandirma Merinos Farm (Aydin, 1997; Celebi, 2003; Cevik, 2001; Golem, 1949; Iyisan et al., 2000). Golem revealed the existence of brucellosis in humans and animals through serological methods (Aydin, 1997; Iyisan et al., 2000). In Turkey, the first documented case of brucellosis, which was confirmed by a laboratory, was in 1915 despite the fact that it is believed that Florence Nightingale got this disease during the Crimean War in Turkey (Young, 1995; Yumuk & O'Callaghan, 2012).

BRUCELLA SPECIES AND BIOVARS

The microorganisms belonging to *Brucella* genus are not mobile; they are sporeless and gram-negative and in the form of small coccobacilli (Aydin, 1997; OIE, 2012; Thimm, 1982). They are bacteria-like rods and they are 0.5 - 1.5µ in length and 0.5 - 0.7 µ in breadth (Alton et al., 1988; Corbel & Banai, 2005; OIE, 2012; Thimm, 1982). They grow in the presence of oxygen at an optimal temperature of 37°C (within the range of 20 - 40°C) and an optimal pH of 6.6-7.4.(Corbel & Brinley Morgan, 1982; Thimm, 1982; WHO, 1986). Another characteristic of *Brucella* spp. is that even though they are defined as immobile, they possess all the genes required to form a functional flagellum except the chemotactic system (Seleem et al., 2008; 2010).

In general, the morphology of *Brucella* strains is constant and pleomorphic forms are rare, except in old cultures growing under adverse conditions. Just because they are small and coccoid, they can be confused with cocci (Alton et al., 1988; Corbel & Banai, 2005). When serum or blood is added to the media, they foster the growth of *Brucella* spp. and a 5-10% CO₂ atmosphere is a necessity for some strains of *B. abortus* (biovars 1 - 4 and 9) (Aydin, 1997; Perez-Sancho et al., 2015). They produce oxidase, catalase, nitrate reductase, urease; they do not produce indole; they are not hemolytic, do not melt gelatine, and also Methyl Red (MR) and Voges-Proskauer (VP) test results are negative. Most of them, except for *B. ovis*, use glucose as the source of energy (Songer & Post, 2012). When *Brucella* microorganisms are listed as taxonomies, the *Brucella* genus is defined as belonging to the family *Brucellaceae* within the order Rhizobiales of the class *Alphaproteobacteria* (Godfroid et al., 2011; Songer & Post, 2012). They belong to the alpha-2 subcategory of the *Proteobacteria*, together with *Ochrobactrum*, *Rhizobium*, *Rhodobacter*, *Agrobacterium*, *Bartonella*, and *Rickettsia* (Seleem et al., 2010). Molecular studies have shown that a non-pathogenic soil organism was possibly the predecessor of *Brucella* as true pathogens (Bardenstein et al.,

2010). *Brucella* bacteria are genetically related to some plant pathogens and symbionts of the genera *Agrobacterium* and *Rhizobium*, in addition to animal pathogens (*Bartonella*) and opportunistic or soil bacteria (*Ochrobactrum*) (OIE, 2012). The closest phylogenetic neighbor of the genus *Brucella* is the genus *Ochrobactrum anthropic* as a saprophyte, which rarely infects animals (Godfroid et al., 2011). It is also claimed that *Brucella* organism is a species of *Ochrobactrum* (Pappas, 2010).

After *Brucella* bacteria have been observed in different animal species and different environments, *Brucella* genus is claimed to include 11 *Brucella* species (OIE, 2016). *B. abortus*, *B. melitensis*, *B. suis*, *B. ovis*, *B. neotomae* ve *B. canis* are considered to be classical species. This classification is based on pathogenic differences and host preferences (Altöparlak, 2003; ICSP, 2014; Vicente et al., 2014), specific phages and lysis sensitivity, their oxidation ways in various carbohydrate and amino acid substrates (Gorvela & Moreno, 2002; Yumuk & O'Callaghan, 2012) and their other phenotypic characters. Out of 6 classical species, 5 of them lead to infection on one or more animal hosts and cause clinical symptoms. 4 of them; namely, *B. melitensis*, *B. suis*, *B. abortus* and *B. canis* (listed according to their pathogenicity) cause infection on humans (Corbel, 2006; Matthew & Leland, 2004; Seleem et al., 2010).

Biotyping is considered as a perfect way of finding and clarifying epidemiological data (Thimm, 1982). It is possible to divide *B. melitensis*, *B. abortus* ve *B. suis* into different biotypes based on the analysis of their requirements of CO₂, their production of H₂S, their growth on cultural media which contain dyestuffs, and their reaction to monospecific antisera (Cloeckaert et al., 2002; OIE, 2012; Thimm, 1982). *B. pinipedialis* and *B. ceti*, which are hosted by marine mammals, are different from other *Brucella* species phenotypically with regards to their metabolic activity (Jahans et al., 1997; Seleem et al., 2010). The types which have recently been recognized as related to marine animals can also cause human disease (Corbel, 2006; Seleem et al., 2010). Another new species that has been recognized in central Europe in common voles and red foxes is *B. microti*. It is also considered to be a persistent soil contaminant. The agent has not been linked with human disease but if it has an anthroponozoonotic risk, a particular target group would be hunters (Pappas, 2010). Hosts preferred mainly by *Brucella* species and their pathogenicity levels are shown in Table 1 (Godfroid et al., 2011; OIE, 2016).

Two new strains, in addition to the already recognized *Brucella* strains, have each been isolated from a single human case (Pappas, 2010). The first one (BO1T) has been labelled as *Brucella inopinata*. The name '*inopinata*' comes from Latin, which means '*unexpected*'. It was isolated from the breast implant wound fluid and blood of a female patient, who was 71 years old and who had the clinical symptoms of brucellosis. (Scholz et al., 2010). The second strain (BO2 strain) was isolated from the lung biopsy of a 52-year-old patient in Australia, who had a history of chronic destructive pneumonia. The analysis of the isolate has shown similar characteristics with *B. inopinata* (Tiller et al., 2010).

Strains are either smooth or rough, which express smooth lipopolysaccharide (S-LPS) and contain O-chain, or rough lipopolysaccharide (R-LPS), and which lack O-chain, as major surface antigen, respectively (Cloeckaert et al., 2002). S-LPS is the most significant antigenic form in the infections caused by smooth *Brucella* organisms and it serologically belongs to immunodominant epitopes, O-polysaccharide (O-PS) section. LPS layer of rough mutant *Brucella* bacteria lacks O-PS and they just carry coreolysaccharide-Lipid A part (Cloeckaert et al., 2002; Godfroid et al., 2011). LPS is a very important form for the structural and

functional integrity of the outer membrane of the gram-negative bacteria. When compared to the classical enterobacterial LPS, the ones belonging to *Brucella* are a lot less active and less toxic than *Escherichia coli* (Seleem et al., 2008).

Table 1. *Brucella* species, preferred hosts and pathogenicity for humans

Species	Biotype	Preferred hosts	Pathogenicity for humans
<i>B. melitensis</i>	1 - 3	Goat, sheep	High
<i>B. abortus</i>	1 - 6,9	cattle	High
<i>B. suis</i>	1 - 3	pig	High
	2	wild boar, hare	None ^a
	4	Reindeer, caribou	High
	5	Rodents	High
<i>B. neotomae</i>	-	Desert wood rat (<i>Neotomalepida</i> Thomas)	High
<i>B. ovis</i>	-	Ram	None
<i>B. canis</i>	-	Dog	Moderate
<i>B. ceti</i>	-	Ceteceans	Unknown ^b
<i>B. pinnipedialis</i>	-	Pinnipeds	Unknown ^b
<i>B. microti</i>	-	Soil, vole, fox	Unknown
<i>B. inopinata</i>	-	Unknown	High
<i>B. papionis</i>	-	Unknown	Unknown

a. One case of *B. suis* biovar 2 infection in an immuno-compromised hunter has been described in France.

b. One human laboratory contamination has been described in the UK. Two naturally acquired cases have been described, although the source of infection could not be traced back to marine mammals.

B. ovis ve *B. canis* are two *Brucella* species which are currently known as being naturally in the rough phase. *B. ovis* has similarities with other *Brucella* species in that they are alike in terms of their morphology, their staining properties and their cultural characteristics; however, the reactions of *B. ovis* to the oxidase and urease tests are negative. *B. ovis* colonies are not haemolytic. They are circular and convex and they have edges, which are unbroken. Moreover, they are always rough when they are examined by oblique illumination and test positive in the acriflavine test (Alton et al., 1988; OIE, 2015a). *B. ovis* requires an incubating atmosphere which has 5 - 10% CO₂ for growth. In addition, it is lysed by Rough/Canis phage (Alton et al., 1988; OIE, 2015a).

Finally, a new species, *B. papionis*, has been added to the *Brucella* genus (OIE, 2016). The phenotypic and genotypic analysis of 2 isolates obtained from stillborn baboon offsprings has shown that these isolates belong to *Brucella* genus. Detailed analysis of the strains has illustrated that these two strains have a new lineage within the genus *Brucella* (Whatmore et al., 2014). All these developments have brought to mind the question whether *Brucella* agents started to appear in the woods as well as the oceans (Pappas, 2010).

The studies of DNA-DNA hybridization have illustrated that there is more than 90% homology between recognized *Brucella* species (Cloeckaert et al., 2002). For this reason, in 1985, combining the 6 species into one single species, which is *B. melitensis*, and recognizing the other species as biovars, was suggested (for example, *B. melitensis* biovar abortus 1) (Cloeckaert et al., 2002; Godfroid et al., 2011; Pappas, 2010; Verger et al., 1985). However, in 2003, the subcommittee on *Brucella* taxonomy decided to go back to the previous version of the taxonomic treatment of *Brucella* genus and approved once again the six classical *Brucella* nomenspecies with their corresponding biovars (Pappas, 2010).

It is known that *Brucella* spp. can persist in milk for a period of time (even when the milk turns sour) and they continue growing in soft fresh cheese. They may also persist in ice-cream for weeks and in butter for months. Thus, it is suggested that these products should be made from pasteurized milk. What is more, *Brucella* spp. can also persist in soil and tap water (Godfroid et al., 2005). In moist soil and in dung, *Brucella* spp. can persist for 70 - 80 days. It is also stated that *B. melitensis* can persist for 15 - 40 days in dust but it depends on the humidity (Doganay & Aygen, 2003). Another point is that hard cheese made through lactic and propionic fermentation is less risky because *Brucella* agents die fast when acidity decreases below pH 4, and they die very fast when it drops below pH 3.5. It has also been pointed out that yoghurt and sour milk are less dangerous. For this reason, soft cheese made from fresh milk can include a lot of *Brucella* organisms and that is why, the products prepared from untreated milk should be avoided (Corbel, 2006). The increase of sodium chloride (NaCl) in dairy products can inhibit *Brucella* spp. (Rowe, 2014).

BRUCELLOSIS IN ANIMALS

It is stated that ingestion of bacteria coming from diseased animals or contaminated feedstuffs lead to most infections. Respiratory exposure and contamination of abraded skin and mucosal surfaces are also the other sources of the infection (Corbel, 2006). On the other hand, *Brucella melitensis*, *B. abortus* and *B. suis* might also be transmitted between animals vertically (Aparicio, 2013). The nasal and oral mucosae, where the organisms are flown into the regional lymph nodes from are the most important points of entry for bacteria. A bacteraemia might be formed from these focal points and the organisms might be situated in other lymphoid tissues such as the spleen and the iliac, mesenteric and supramammary lymph nodes, in which they may bring about a granulomatous reaction. Another bacteraemia leads to a general infection which influences some other organs such as the pregnant uterus, the udder, and their lymph nodes. Uterine lesions are mainly situated in the placentomes. Aborted fetuses and fetal membranes include a high amount of bacteria; thus, they lead to the contamination of the environment, which creates a high risk of infection of sensitive hosts (Poester et al., 2013).

Many factors such as vaccination, age, sex and herd size and density determine whether the disease is severe or not. Abortions stemming from brucellosis are more common in animals which are not vaccinated and there are more organisms shed (Corbel, 2006). More than 85% of *Brucella* might be found in the cotyledons, placental membranes, and amniotic liquid, which might reach up to 1×10^{10} colony-forming units (CFU)/ml in allantoic fluid and 1×10^{13} CFU/g of tissue in the cotyledons in ruminants, which are pregnant (Poester et al., 2013; Yumuk & O'Callaghan, 2012)

The excretion of the organisms in uterine discharges and in milk are considered as the main characteristics of the disease (OIE 2009a; OIE, 2012). Despite the fact that infected animals may abort only once, they remain carriers till the end of their lives. In the mean time, they expel many organisms in their milk and in the following parturitions, which are apparently normal (Yumuk & O'Callaghan, 2012). All infected goats do not abort; however, they can all shed *Brucella* into the environment. Under normal conditions, the main way of infection is not venereal transmission but artificial insemination with contaminated semen

might lead to infection (Poester et al., 2013). When it was found out that healthy goat can carry the disease, it was considered to be one of the most important discoveries carried out in the field of epidemiology (Seleem et al., 2010).

It was pointed out that consumption of feed which was contaminated by birth and/or abortion products and uterine discharges are the main ways of the transmission of the disease in pigs. Pigs can eat fetuses which are aborted and also placental membranes. Transmission of brucellosis during copulation is very common and this process is influential on artificial insemination. *Brucellae* may be excreted in the semen by the boar even though there is nothing abnormal in their sexual organs and it does not interfere with their sexual activity (OIE 2009b; Poester et al., 2013). Infected boar can shed 10^4 - 10^5 CFU/ml of semen, which makes venereal transmission an important way of infection (Perez-Sancho et al., 2015).

All the information regarding animal brucellosis is present on the website of the Office International des Epizooties (OIE) (<http://www.oie.int>) and it can be accessed via the HandiStatus tool (i.e., Help with World Animal Disease Status, version 2). The information of this website is updated regularly depending upon emergency and based on the monthly and annual reports which are sent to OIE by the veterinary administrations of the countries and other official sources (Godfroid et al., 2005). Production systems, agro-ecological zones, husbandry practices, contact with wildlife, and management factors are the main factors, which affect the prevalence of Brucellosis (Godfroid et al., 2011).

Among the pre-defined 6 classical *Brucella* species, except for *B. canis*, *B. ovis* and *B. neotomae*, all these species of *Brucella* form polycyclic chain of infection and they might be transmitted to other animal species and to man when the necessary ecological-epizootic conditions are suitable (Thimm, 1982). In spite of the successful results obtained in most of the industrialized countries, in which bovine brucellosis is no longer a big problem, small ruminant brucellosis is still an important issue (Godfroid et al., 2005). It is widely known that in the Mediterranean region, *B. melitensis* is endemic but it is a widespread worldwide disease. North America including Australia, New Zealand, South-East Asia, Northern and Central Europe (except for Mexico) are thought to be free from the agent (OIE, 2009a). In some Mediterranean countries such as Israel, Kuwait, Saudi Arabia, and Egypt, *B. melitensis* infection in cattle is particularly important and they exemplify *Brucella* agents' potential of causing infection in other hosts as well as its main hosts (Corbel, 1997; Perez-Sancho et al., 2015).

In addition to cattle and small ruminants, it was also reported that brucellosis was identified in both one-humped (*Camelus dromedarius*) and two-humped (*C. bactrianus*) camels as well as South American camelids, llama (*Lama glama*), alpaca (*L. pacos*), guanaco (*L. guinicoe*), and vicuna (*Vicugna vicugna*) (OIE, 2012; WHO, 1986). According to Saleem et al. (2010), when camels are pastured together with infected sheep and goats, they can be infected by *B. abortus* and *B. melitensis*. Although it has been belittled in the Middle East, milk coming from infected camels is one of the most important sources of infection. In some countries, camel brucellosis stemming from *B. melitensis* and *B. abortus* infections is a major source of human infections (Godfroid et al., 2005).

Infected ewes might shed *B. ovis* through their vaginal discharges and their milk. In accordance with this, the transmission from ewe to lamb and the transmission from ewe to ram might be considered as the main source of infection. For this reason, it is important for researchers to consider ewes in accordance with the infection's epidemiology, which is necessary for the effective eradication of *B. ovis* infection. It has also been reported that

infected rams might shed *B. ovis* in their semen for years (OIE, 2015a). The domestic goat, mouflon (*Ovis musimon*), white-tailed deer (*Odocoileus virginianus*) and red deer (*Cervus elaphus*) are also open to infection despite the fact that the most important host species for *B. ovis* is sheep. As stated by (Poester et al., 2013), *B. ovis* is very frequently observed in countries in which sheep raising is common, and which have flock prevalence ranging from 9.1% to 46.7%. *B. ovis* has been observed in the countries of America and Europe and also, in New Zealand and South Africa and it is probable that this disease also occurs in other countries where sheep-raising is common (OIE, 2015a). The prevalence of Brucellosis in pigs is generally low except for such countries as South America and South-East Asia (OIE, 2009b).

B. melitensis bv-2 has recently been reported in catfish in Egypt, which revealed that fish might also be a new source of infection (Yumuk & O'Callaghan, 2012). This fish, namely, *Clarias gariepinus*, is found in the freshwater of the Nile. It has been predicted that this fish has been infected through the meat waste of infected animals which was illegally thrown into the water. Since this fish is edible by humans, it might be a new source of entry of the pathogen to the human food chain. It has been stated that *Brucella* has started to appear in rivers after its existence in oceans and the jungle (Pappas, 2010).

Each *Brucella* type has its peculiar epidemiologic features and as new types appear, the interaction between *Brucella* genus with animals and humans has become complicated. As stated by Corbel (1997) and Godfroid et al., (2005), new *Brucella* strains and types adapt to the social and agricultural practices which are continuously changing. In order to improve the quality of studies, it is necessary to train researchers in terms of formal epidemiology and statistics. If a more integrated approach to disease surveillance, which includes human health and veterinary services is used, it could be easier to understand the dynamics of the disease within the scope of animal-human relationship and resources could be used more cost-effectively (Dean et al., 2012).

HUMAN BRUCELLOSIS

Major risks of brucellosis include contaminated food and the contact with the disease due to people's occupations. In addition, consumption of unpasteurized milk coming from cows, small ruminants or camels and also some other milk products such as cheese, sour milk are the main ways of infection. Similarly, if the meat of animals infected with brucellosis is consumed without being sufficiently cooked, it might be another source of infection (Godfroid et al., 2005; Godfroid et al., 2013; Yumuk & O'Callaghan, 2012). However, meat products are rarely the major sources of infection as they are generally cooked and in muscle tissue, the amount of bacteria is low (Doganay & Aygen, 2003; Matthew & Leland 2004). Infection may be due to the bacteria from infected animals that enter into the body via skin lesions or mucous membranes or when contaminated dust or aerosols are inhaled (Doganay & Aygen, 2003; Godfroid et al., 2005).

Even though *Brucella* is thought to be very infectious when it causes infection through the respiratory route, inhalation is not one of the primary means of infection. However, some occupations such as vets, people working in laboratories or abattoirs are the main risk groups. *Brucella* spp. are believed to be the most common pathogens acquired in laboratories and

they are responsible for up to 2% of all infections coming from laboratories (Seleem et al., 2010). It is stated that infection might occur during the handling of animals, which are infected particularly when these animals are around the time of parturition (Yumuk & O'Callaghan, 2012). The occupation of vets is risky both through the infected animals and their products and through the needlestick injuries when they are inoculating animals with live *Brucella* vaccines (Madkour, 2001; Matthew & Leland, 2004).

It is important to consider evaluating the fever in travelers coming from abroad, particularly the ones who are coming from endemic areas and the ones that report that they were exposed to unpasteurized milk products due to their occupation or diets (Matthew & Leland, 2004; Ragan, 2002). In some countries, the prevalence of human brucellosis coming from dairy products is seasonal and it reaches the highest numbers usually after kidding and lambing (Seleem et al., 2010). *Brucella* in humans is related to many different factors such as geographical factors, husbandary practices, techniques of food preparation, etc. It is also stated that infection can affect all human beings regardless of their age and sex (Bosilkovski, 2015).

When the epidemiology of the disease is considered, humans are believed to be an 'epidemiological cul de sac' of the infection (Thimm, 1982). The transmission of the disease from human to human is rare; therefore, it is not significant in the epidemiology of the disease (Perez-Sancho et al., 2015). Brucellosis in human is not regarded as a contagious one (Godfroid et al., 2005). It is stated that there are very few reported cases occurring through blood transfusion, bone marrow transplant, transplacental way, breastfeeding, sexual intercourse, congenital way and laboratory infection (Godfroid et al., 2005; Godfroid et al., 2013; Poulou et al., 2006; Wang et al., 2015).

In many different geographical regions, which are traditionally regarded as endemic such as France, Israel, and Latin America, the disease is under control. However, human brucellosis now has new foci, especially in central Asia and in certain countries of the near east such as Syria, it is getting worse (Pappas et al., 2006b). In a study published in the year 2006, which outlined the global epidemiology of the disease, it is seen that Central Asia and the Middle East are the main regions of the disease. For this reason, the global map of the disease is the same in 2010 despite the new hot spots added, it even exists in regions in which the infection is least expected (Pappas, 2010). It has been pointed out that in western Europe, where the existing surveillance systems are sufficient, it is not possible for human brucellosis to re-emerge. There are also some eradication campaigns in southern European member countries which will make the spread of the disease inside the EU impossible. (Pappas et al., 2006b). Brucellosis, which is especially caused by *B. melitensis*, is still the most common zoonotic disease worldwide (Pappas et al., 2006a). In addition, when 76 diseases and syndromes observed in animals are reviewed, brucellosis is among the top 10 of the list, which affect poor people (Dean et al., 2012).

The real incidence of human brucellosis worldwide is not known (Corbel, 1997; Doganay & Aygen, 2003). According to the numbers provided by World Health Organization (WHO), there are 500,000 reported Brucellosis cases annually worldwide (Doganay & Aygen, 2003; Perez-Sancho et al., 2015). However, it is estimated that unreported cases, which are happening because of unspecific clinical symptoms, are thought to be ten times higher (Godfroid et al., 2013) or 26 times higher (Bosilkovski et al., 2009). The incidence of the disease, which is reported in endemic areas changes from < 0.01 to > 200 per 100,000 population. The reported low value of incidence in brucellosis-endemic areas which are

known might be because of the lack of surveillance and reporting (Corbel, 1997). Geographic areas, which are regarded as having high level of the prevalence of brucellosis include the Middle East, the Mediterranean Basin (Portugal, Spain, Italy, Greece, Turkey, Near East, North Africa), South and Central America, South-Eastern Europe, Asia, Africa, and the Caribbean (Godfroid et al., 2005; Pappas et al., 2006b; Perez-Sancho et al., 2015).

Despite the fact that there are few reported cases of human-to-human brucellosis cases, human infection mainly stems from domestic and wild animal reservoirs (Godfroid et al., 2011; Godfroid et al., 2013; Thimm, 1982). As human-to-human transmission is rare, infected people do not constitute a threat to the ones around them. Thus, if the disease is eradicated from the animal reservoirs, it will also lower the incidence of human brucellosis (Perez-Sancho et al., 2015; Seleem et al., 2010). In order to overcome the problem of human brucellosis, it is necessary to control and eradicate animal brucellosis (Perez-Sancho et al., 2015).

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Chapter 276

MUTAGENIC POTENTIAL OF THE INSECTICIDE ARRIVO 25 EC ON MITOSIS AND MEIOSIS OF *HYACINTHUS ORIENTALIS*

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ABSTRACT

The effects of Arrivo 25 EC (250g/l, Cypermethrin), a pyrethroid insecticide, were investigated on *Hyacinthus orientalis* grown in greenhouse. The insecticide was applied to *H. orientalis* at recommended dosage and double the recommended dosage by manufacturing company. Mitosis was examined in root tip cells and meiosis was examined in anthers. It was observed that the insecticide used in trial applications caused abnormalities in mitosis and pollen meiosis in parallel with the increase in dosage. It is obvious that this condition will have a negative effect on pollen fertility.

Keywords: cypermethrin, *Hyacinthus orientalis*, meiosis, mitosis, mutagenic

INTRODUCTION

Pesticide applications in agricultural and ornamental plants have harmful effects on their cytological mechanisms. Cypermethrin is a synthetic pyrethroid insecticide used to control many pests, including moth pests of cotton, fruit and vegetable crops (Meister, 1992). It is also used for crack, crevice and spot treatment for control of insect pests in stores,

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warehouses, industrial buildings, houses, apartment buildings, greenhouses, laboratories and on ships, railcars, buses, trucks and aircraft. It may also be used in non-food areas in schools, nursing homes, hospitals, restaurants, hotels, and in food processing plants and as a barrier treatment insect repellent for horses (USEPA, 1989). Cypermethrin is a moderately toxic material by dermal absorption or ingestion (Meister, 1992; OHS, 1993). It may cause irritation to skin and eyes. Symptoms of dermal exposure include numbness, tingling, itching, burning sensation, loss of bladder control, incoordination, seizures and possible death. Pyrethroids may adversely affect the central nervous system (OHS, 1993). Cypermethrin is extremely toxic to fish and aquatic invertebrates. The 96-hour LC₅₀ for cypermethrin in rainbow trout is 0.82 ppb, and in bluegill sunfish is 1.78 ppb. Its acute LC₅₀ for *Daphnia magna*, a small freshwater crustacean, is 0.2 ppb. The bioconcentration factor for cypermethrin in rainbow trout was 1200 times in a flow through study (USEPA, 1989). If exposed to cypermethrin during pregnancy, rats give birth to offspring with developmental delays. In male rats exposed to cypermethrin, the proportion of abnormal sperm increases. It also causes genetic damage: chromosomal abnormalities increased in bone marrow and spleen cells when mice were exposed to cypermethrin (Amer et al., 1993). One study showed that cypermethrin inhibited gap junctional intercellular communication, which plays an important role in cell growth and is inhibited by carcinogenic agents (Tateno et al., 1993). Studies have shown that residue from cypermethrin can last for 84 days in the air, on walls, floor and furniture (Wright et al., 1993). Cypermethrin is an environment pollutant and, due to its use, toxicity and persistence, it may cause significant damage to non-target organisms and various ecosystems. This necessitates the development of an effective tool to eliminate or obstruct the concentration of this pesticide (Gangola et al., 2018). Insecticides affect the plants by causing harm to their metabolism, photosynthesis, development and yield. To give an example, malathion formation and carbaryl formulations obstruct the photosynthesis of field grown soybean or the four formulation insecticides, namely flucythrinate, chlordimeform, carbaryl and malathion, lessen the stomatal conductance and lint yield.

The effects of insecticides on growth, fruiting patterns, and yield of Acala-SJ-2 cotton were observed in Wen, et al. (2017). In another study, Sheo Mohan Prasad et al. (2015) found that the decrease in photosynthetic rate caused decreased growth of *A. pinnata* at higher concentrations of both chlorpyrifos and cypermethrin.

Pollen germination was reduced by *in vitro* fungicide applications and degeneration in pollen tubes occurred (Pavlik & Jandurova 2000). Tort et al. (2005) observed that pyrimethanil fungicide caused changes in the structure of tomato pollens. Moreover, it was reported that fungicides resulted various chromosomal abnormalities, such as Deltan applications (0.3%) gave rise to chromatid and subchromatid breaking in red pepper (Prakash & Prathapasanen, 1988). Thiodan, Folithion, Lebaycid and Kitazin caused fragmentation, lagging chromosomes, bridges, tripolar and tetrapolar spindle in barley (Grover & Tyagi, 1980). Therefore, it is necessary to study the effect of overdose application of common pesticides on plants. In this study, the effects of different concentrations recommended and double of the recommend dosages of Arrivo 25 EC on mitosis and meiosis of *H. orientalis* were investigated.

MATERIALS AND METHODS

Plant Material and Arrivo 25 EC

The selected plant material healthy *H. orientalis* bulbs were obtained from the market. The insecticide used in the study was Arrivo 25 EC (250g/l Cypermethrin, $C_{22}H_{19}Cl_2NO_3$), which was produced and distributed by the company Hektaş.

Application of Arrivo 25 EC

The commercially maintained and selected *H. orientalis* bulbs were germinated for primary roots of 1–2 cm long in erlenmeyer flasks containing distilled water. The germinated primary roots were treated with three different concentrations of (%0.5, %1, %2.5 ml) Arrivo 25 EC. All experiments were carried out in three repetitions.

Mitotic Analysis

The flower buds were fixed first in Carnoy solution (3:1 alcohol-acetic acid) and hydrolyzed in 1 N HCl at 60°C for 5–10 minutes. They were, then, crushed in a 2% orcein stain in 45% acetic acid and the slides were examined immediately. The mitotic frequency was determined by examination of 1000 cells per slide.

Detection of Chromosomal Abnormalities

To investigate the abnormality percentages (chromosomal bridges, lagging chromosomes, chromosomal fragments, etc.) in different stages of mitosis and meiosis I, II, abnormal cells were counted and the percentage of abnormal cells was determined in each phase. Chromosomal abnormalities were evaluated separately in all phases of mitosis and photographic data was obtained using an Olympus BX51 photomicroscope.

Statistical Analysis

The statistical analyses of data were carried out using SPSS for Windows version 11.0 statistical software (SPSS Inc., Chicago, USA). Statistically significant differences between the groups were compared using both one-way analysis of variance (ANOVA) and Chi-Square Test. The data were displayed by mean $\pm$ standard deviation (SD). P-values less than 0.05 were considered statistically significant.

RESULTS AND DISCUSSION

Mitotic index (MI), which reflects the frequency of cell division, is an acceptable measure of cytotoxicity for all living organisms. If the mitotic index decreases below 22% of the control, it can cause lethal effects on the test organism (Cavusoglu et al., 2011). This study demonstrated the use of higher concentrations of each different Arrivo 25 EC concentration in the various phases of mitosis. Cytotoxicity was defined as decrease in mitotic index revealed the mitodepressive effect of Arrivo on mitotic index (MI) of *H. orientalis*. While treating seeds with different concentrations of Arrivo 25 EC, we observed that Mitotic Frequency Percentage decreased while the concentrations increased for each concentration of Arrivo 25 EC. The mitotic index of 0.5 ml and 2.5 ml % concentrations was slightly higher compared to control. The Arrivo 25 EC concentrations used had a negative effect on mitotic division. The mitotic frequency was 15.3% in the control group and decreased to 12.9% at 0.1ml concentration, 10.8% 0.5 ml concentration and 8.0% at 2.5 ml concentration Arrivo 25 EC (Table 1). The Arrivo 25 EC concentrations used had a negative effect on mitotic division. In high Arrivo 25 EC concentration, mitotic frequency reduced to almost half of that of the control (Figure 1), which affirmed the relationship between this parameter and morphological characters as previously reported by Abderrhman (1998), Abou Elkheir (1992) and Alam et al. (1987). This increase may due to shortening the duration of mitotic cycle and enhancing the interphase cells that entered the subsequent division stages (Haroun & Al shehri 2001) or because of the prompting of the synthesis of DNA in dividing cells (Badr et al., 1985; Chand & Roy 1981). Inhibition of mitotic activities was often used for tracing cytotoxic substances.

Table 1. The effect of Arrivo 25 EC concentrations on mitotic frequency percentage

Concentration (ml)	Cell numbers	Prophase	Metaphase	Anaphase	Telophase	Divided Number of Cells	Mitotic Frequency Percentage (%)
Control	1000	79	16	21	37	153	15.3
0.1	1000	58	21	13	37	129	12.9
0.5	1000	53	15	13	27	108	10.8
2.5	1000	45	11	11	13	80	8.0

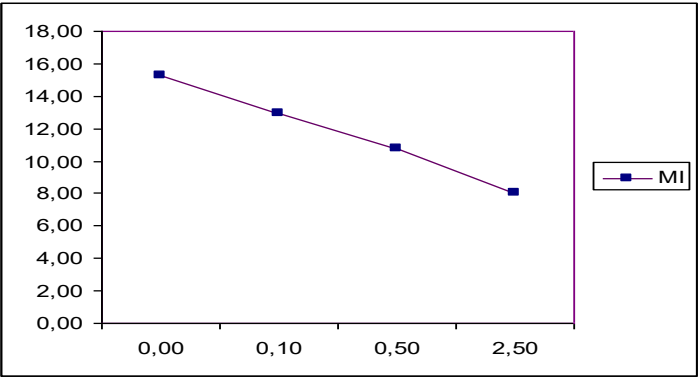


Figure 1. Mitotic frequency percentage in *H. orientalis* treated and control groups in root meristematic cells.

We also examined the mitotic abnormality percentages and frequencies for prophase, metaphase, anaphase and telophase for different concentrations at different hours (Table 2). We observed that mitotic abnormality increased for all measurements as the concentration amount increased. For example, for prophase, the abnormality percentage was 0% in the control but increased to 66.6% at 0.1 ml, 66.6% at 0.5 ml and 2.5 and 100% at 2.5 ml concentration Arrivo 25 EC.

Table 2. The effect of Arrivo 25 EC concentrations on the mitotic abnormality percentage and frequencies

Concentration %ml	Prophase I			Metaphase I			Anaphase I			Telophase I		
	N	A	%A	N	A	%A	N	A	%A	N	A	%A
Control	2	-	-	3	79	96.3	-	4	100	2	-	-
0.1	1	2	66.6	3	33	91.6	-	3	100	2	3	60
0.5	2	4	66.6	3	4	57.1	1	8	88.8	2	-	-
2.5	-	2	100	-	8	100	-	4	100	-	1	100

N; Normal cell, A; Abnormal cell.

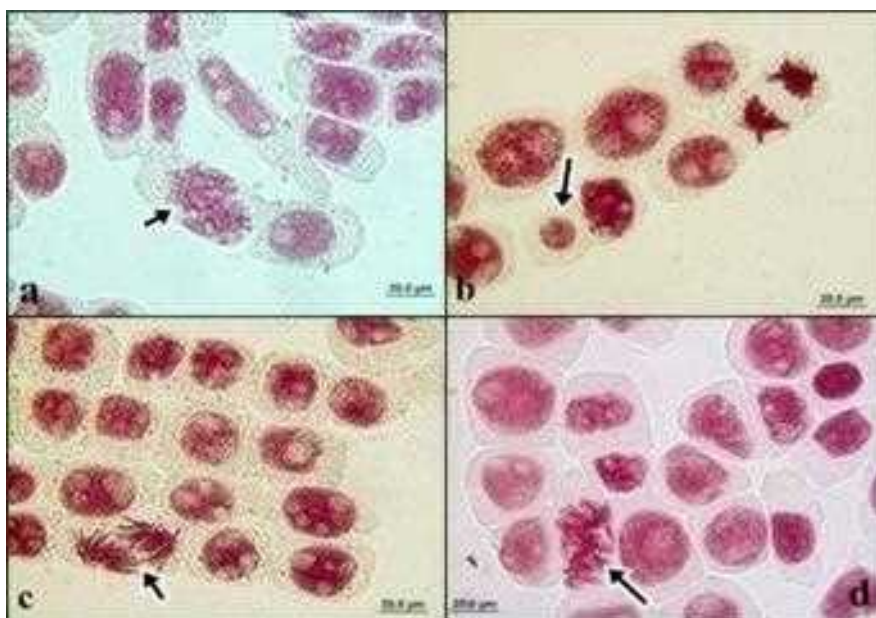


Figure 2. The following common abnormalities were observed at 0.5 ml Arrivo 25 EC;

a) Chromosomal bridge in telophase, b) Picnotic nucleus, c) Multipolar anaphase
d) Multipolar metaphase. The abnormalities present are indicated by arrows.

It was determined that the chemical treatment (including Arrivo) had drastic impact on non-target insect species (Lovei & Sunderland, 1996). Detrimental effects of insecticides, acaricides or other chemical compounds on pollen germination, fruit set and/or yield were reported on apple (Mayer & Lunden, 1986; Bound & Jones, 2004; Nichols et al., 2004). Mayer and Lunden (1986) noted that acaricides used during bloom influenced pollen viability of apple and pear.

The 0.5 ml Arrivo 25 EC concentration were found in *H. orientalis* Chromosomal bridge in telophase, Picnotic nucleus, Multipolar anaphase, Multipolar metaphase (Figure 2).

The 2.5 ml Arrivo 25 EC concentration were found in *H. orientalis* Chromosomal bridge in telophase, Laggard chromosome in anaphase, Normal mitosis, Multipolar anaphase (Figure 3).

The 2.5 ml Arrivo 25 EC concentration were found in *H. orientalis* at meiosis I Laggard chromosomes in interphase, abnormal prophase, chromosomal bridge in anaphase, chromosomal bridge and micronucleus formation in telophase (Figure 4).

The 2.5 ml Arrivo 25 EC concentration were found in *H. orientalis* at meiosis II Picnotic nucleus, deformations in nuclei, chromosomal bridge in anaphase, micronucleus, Laggard chromosome, chromosome decondensation and micronuclei formation (Figure 5).

To investigate the effects of toxic substances applied to plant organisms, it is important to investigate the chromosome anomalies and mitotic index in the root meristematic cells. The mitotic index reflects the frequency of cell division and is used as an important parameter in determining the rate of root development (Jiang et al., 2000). The mitotic index decrease is defined as the lethal effect (Antonsie-wiez, 1990), which falls below 22% when compared with control groups, and the sublethal effect, which falls below 50% (Panda & Sahu, 1985). These values were defined by the researchers as cytotoxic limit values (Sharma, 1983). Schulze and Kirscher (1996) have claimed that the mitotic index depression is due to the fact that genotoxins with mitochondrial deprivation have the power to block DNA and nucleoprotein synthesis. El-Ghamery et al. (2000) demonstrated that mitochondrial inhibition is caused by blockage of G1 phase and suppression of DNA synthesis in S phase. Based on the results of their study, Bal (1995) suggested that mitotic index depression may be due to mitotic cycling, as a physiological response to unprotected cells against toxic chemical agents such as energy pathway, inhibition of protein, RNA and DNA synthesis. Kaymak (2005) suggested that various chemicals might be the result of the influence of microtubules on the chromosomes, which are essential proteins that provide the formation of spindle fibers necessary for mitosis. Eun et al. (2000) noted that chemical agents altered microtubule organization and indirectly inhibited mitotic activity.

Changes in the number and structure of chromosomes occur as a result of abnormal placement of chromosomes by the effect of toxic chemical agents. Examples of loss of chromosome include backward chromosome, adhesiveness, multipolarity and c-mitosis. Materials that cause fractures in chromosomes can cause changes in chromosome bridge formation or chromosome structure (Leme & Marin-Morales, 2009; Radic et al., 2010).

Backward chromosomes might form as a result of the disorders which occur in the organization or functions of the spindle threads (Yıldız et al., 2009; Fındıklı & Türkoğlu, 2010; Türkoğlu, 2012); anaphase bridge might form as a result of the translocation with unequal chromatin changes and presence of chromatin breakage (Liman, 2013); c-mitosis formation is seen as a result of degradation of spindle yarns (Yoshida et al., 1983); hyperhomologous chromosomes arise as a result of backwardness in chromosomes, inadequacy of chromosomal motions or irregularities in the signaling process, depending on the state of the spindle fibers being affected; multipolarity emerges as a result of partial influences of spindle fibers (Ahmad 1992); whereas adhesion in chromosomes occurs as a result of physical adhesion of chromatin proteins. Moreover, it has been reported that bridge formation may occur during chromosomal adhesions, disentric chromosome formation, merger in sister chromatids and chromosomes moving towards the poles. In addition, fragments of broken chromosomes can cause micronucleus formation and loss of genetic material (Topaktas & Rencuzogullari, 1995).

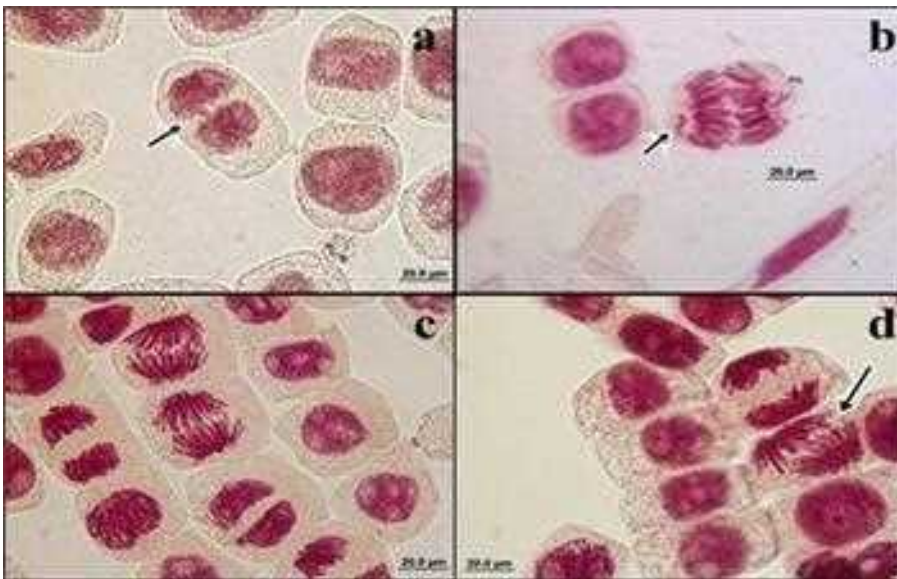


Figure 3. The following common abnormalities were observed at 2.5 ml Arrivo 25 EC; a) Chromosomal bridge in telophase, b) Laggard chromosome in anaphase, c) Normal mitosis, d) Multipolar anaphase. The abnormalities present are indicated by arrows.

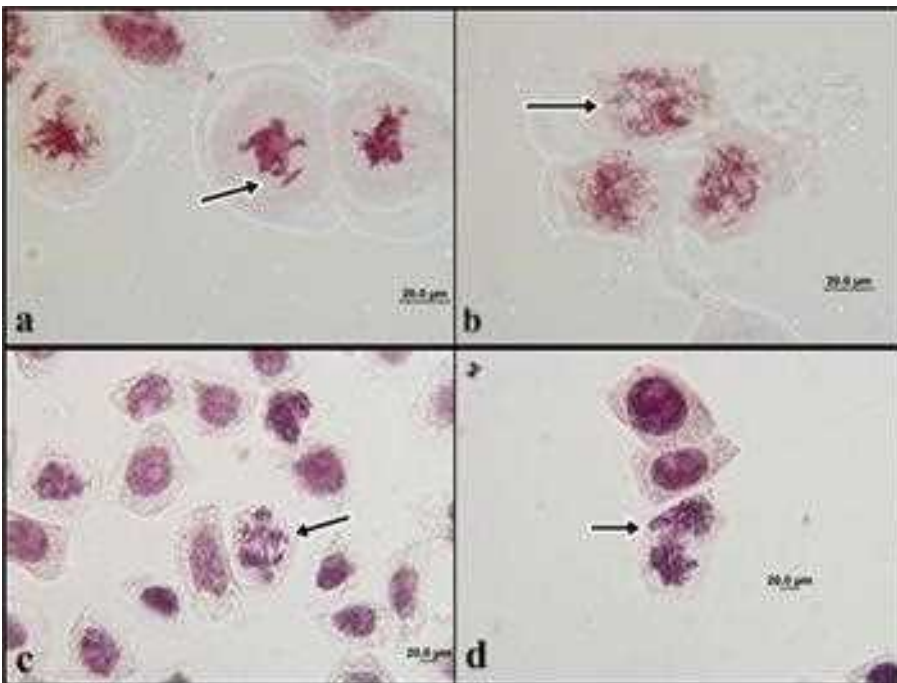


Figure 4. The following common abnormalities were observed at 2.5 ml Arrivo 25 EC at meiosis I. a) Laggard chromosomes in interphase, b) Abnormal prophase, c) Chromosomal bridge in anaphase, d) Chromosomal bridge and micronucleus formation in telophase. The abnormalities present are indicated by arrows.

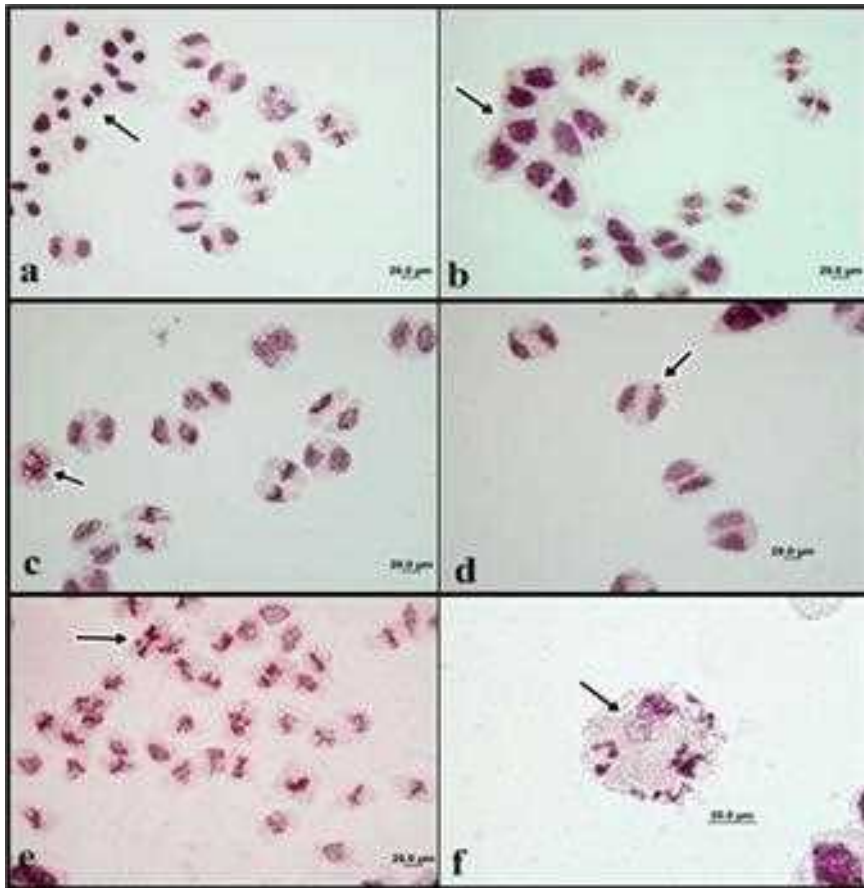


Figure 5. The following common abnormalities were observed at 2.5 ml Arrivo 25 EC at meiosis II. a) Picnotic nucleus, b) Deformations in nuclei, c) Chromosomal bridge in anaphase, d) Micronucleus, e) Laggard chromosome, f) Chromosome decondensation and micronuclei formation. The abnormalities present are indicated by arrows.

As stated before, decreases in the mitotic index, increases in the numbers of abnormally dividing cells and increases in chromosomal abnormalities are caused by the inhibition of energy pathway, protein, RNA and DNA synthesis, the alteration of the microtubule organization and the synthesis mechanism of the main proteins that provide the formation of spindle spinning, affecting genes or gene products that regulate cell division control points (Yuksel & Aksoy 2017; Aksoy et al., 2012). Based on these results, we can infer that Cypermethrin acts like a cytotoxic agent.

Occurrence of chromosomal bridges, laggard chromosomes and multipolar anaphases clearly shows the accumulated effects of Arrivo on the spindle formation. The phenomenon of chromosome stickiness indicates the toxicity of Arrivo and occurrence of breaks and bridges show that it is a potent clastogen. In sum, the present study shows that Arrivo, commercial formula of Cypermethrin, is genotoxic because this pesticide induced chromosome abnormalities in *H. orientalis*. Since, mitotic index is decreased, Arrivo has high cytotoxic effects. As a result of cytological studies, it can be said that Cypermethrin is effective both in chromosome organization and DNA level. Hence, more care should be given to the application of Arrivo in agriculture, in countries where it is widely used.

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Chapter 277

ALUMINUM-INDUCED TOXICITY AND PROGRAMMED CELL DEATH IN PLANTS

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ABSTRACT

Wild flora and agricultural crops are faced with a variety of environmental stress factors culminating in considerable economic losses worldwide. Aluminum toxicity is one of the important abiotic stresses limiting plant growth. Aluminum (Al) is the third most abundant element in the soil, after oxygen and silicone; comprising approximately 7%. Whereas it exists primarily in the form of insoluble aluminosilicates or oxides, the complex Al becomes solubilized in acidic soils (< pH 5.0). After Al absorption, the toxicity effects root growth adversely resulting in poor uptake of water and nutrients. The root apex consisting root cap, meristem and elongation zone has a major role in Al-penetration mechanism and accumulates more Al. The common effects of Al are thick, cracked and stubby roots, inhibited cell and root elongation, increment in cell wall rigidity, callose formation, alteration of plasma membrane and cytoskeleton, production of oxygen-free radicals, and interaction with DNA. These cellular alterations lead to oxidative stress and programmed cell death. Programmed cell death (PCD) is genetically controlled and highly regulated cell disassembly, which appears during development or under stressful conditions. During PCD, some common cellular characteristics such as cell shrinkage, vacuolization, cytochrome c release from mitochondria, specific protease activation, chromatin condensation and DNA fragmentation become apparent both in plants and animals. A few researchers indicate that Al toxicity also causes PCD. It has been known that some of the plant species have self-tolerance metabolism against Al toxicity. However, Al toxicity may be alleviated by exogenous application of organic and inorganic compounds. Even if many researchers have performed to understand the mechanism of Al toxicity and tolerance, it has not yet been fully characterized because of the complicated chemical nature of Al. Moreover, the underlying molecular, genetic and

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physiological features are still not clear. Although this review will describe Al toxicity and PCD principles generally, our aim is to focus especially on the mechanisms of Al-induced PCD which have been largely ignored with the goal in mind for environmental monitoring.

Keywords: acid soil, aluminum toxicity, aluminum tolerance, plant, programmed cell death, root

INTRODUCTION

Although aluminum (Al) is one of the most abundant and prevalent mineral in the earth's crust (7%), it is not assumed as an essential element for living organisms (Matsumoto, 2000; Abate et al., 2013). Al, as an abiotic stress factor, is one of the major plant growth-limiting factors at low pH (acid) soils. It has been thought that 67% of the world's potential farmable lands have acid soil below pH 5.0 and face to Al toxicity (Kochian et al. 2004; Abate et al. 2013; Ma et al. 2014). Al is a non-toxic constituent in the neutral or weakly acidic soils as insoluble aluminosilicates or oxides, but when the soil turns out to be more acid, complex Al is solubilized into phytotoxic forms. $\text{Al}(\text{H}_2\text{O})_6^{3+}$ dissolve to Al^{3+} ion and it is the most toxic and dominant form in low pH soils (Matsumoto, 2000; Vardar and Ünal, 2007). Whereas occurrence of acidic soil is a natural occurrence in tropical and subtropical zones such as South America, Central Africa and Southeast Asia, it is also a critical environmental problem in temperate zones. In industrial regions such as USA, Canada and Europe countries environmental pollution and acid rains raise the solubilized Al^{3+} ions in the soil (Vitorello et al., 2005). Soil acidity is also attributed to exhaustive agriculture, inappropriate farming and over leaching with basic actions. As a broad notion, acid soil fertility is regressed by the reason of toxic (Al, Cd and Mn) and deficient minerals (P, Ca, Mg and Mo). It has been stated that solubilized Al presents at the range of 10–100 μM in acid soils, and regarded as a primary constraint for crop production. Researchers also evidenced that Al adversely affect plant growth and development within a few minutes even at low micro-molar doses in acid soils (Eswaran et al., 1997; Ciamporova, 2002; Vitorello et al., 2005; Vardar and Ünal, 2007; Abate et al., 2013).

Considering the whole plant, toxic Al ions have adverse effects such as structural and anatomical deformation, chlorosis and necrosis. Besides, reduction in total leaf number, decreased photosynthetic activity due to chlorosis, reduction of stomatal aperture, regression in shoot biomass, inhibition of root growth also occur under Al stress. Although Al toxicity symptoms are also apparent in the shoots, the roots are the first affected organ. Several researchers indicated that Al-induced root growth inhibition causes poor uptake of soil water and mineral elements such as Ca, Mg, K, Fe and P resulting in decreased yield and crop quality (Jones and Kochian, 1995; Miyasaka et al., 2001; Delhaize et al., 2004).

Several studies prove that root apex (consisted of root cap, meristem and elongation zone) as a first target plays a critical role in Al penetration. This root region also absorbs more Al (Matsumoto, 2000). As a result of Al uptake morphology of root apices change to swollen, cracked, stubby and stiff appearance (Vardar et al., 2006). Reduction in fine branching and root hairs are also evident (Ciamporova, 2002). Root growth inhibition is the most noticeable and evident characteristics of Al toxicity (Singh et al., 2017). It has been considered that

reduction of root growth is the consequence of interfered cell elongation and expansion, prior to arrested cell division (Frantzios et al., 2001; Ciamporova, 2002; Vardar et al., 2007). Several researches revealed that plant genotype, cell/tissue type, pH and content of external solution (types of chelators, concentrations of Ca^{2+} and other cations) are decisive on the severity of Al toxicity (Kinraide and Parker, 1987). Table 1 presents some sample of Al toxicity researches performed in different plant species and cell types with different concentration and exposure time.

Al ions interact with cell wall (apoplastic target), plasma membrane and cytosol (symplastic target) within seconds to minutes resulting toxic symptoms (Kochian et al., 2005). It has been identified that Al binds and accumulates in root apoplasm predominantly. Positive charged Al has the ability of binding negatively charged carboxyl groups of pectin building cross-links in cell wall (Blamey et al., 1993; Singh et al., 2017). Al also binds to apoplasmic side of plasma membrane. These reactions cause to the displacement of other positively charged ions such as Ca^{2+} responsible for strength of cell-wall. Al toxicity also induces rapid callose (β -1,3-glucane) synthesis and accumulation on plasma membrane integrating into apoplasm (Tabuchi and Matsumoto, 2001). Callose synthesis which is one of the important markers of Al toxicity may assists plant to manage with Al toxicity by blocking the plasmodesmata. Thus, callose plugs block movement of water and solutes through cell to the apoplasm causing reduction of nutrient supply (Blamey, 2001). Alterations of structural and mechanical functions of cell wall, as a result of strong and rapid binding of Al, cause more rigid and reduced mechanical extensibility. Eventually, disrupted growth orientation together with unusual periclinal divisions occurs (Kochian et al., 2005).

Because of its negatively charged surface, plasma-membrane is one of the important targets for Al^{3+} (Kinraide et al., 1998). It has been reported that Al^{3+} binds to both phospholipids and proteins of the membrane altering the structure by inducing lipid peroxidation (Panda et al., 2009). Al has approximately 560-fold more affinity than other positively charged ions (e.g., Ca^{2+}) for the choline head of phosphatidylcholine. Al forms positively charged bridges between head groups of the phospholipid in the plasma membrane resulting in displacement of other cations (Akeson and Munns, 1990; Singh et al., 2017). The positively charged layer changes the movement of ions through the plasma membrane. This situation commonly results in inhibited cation movement and increment in anion movement (Nichol et al., 1993). Consequently, the structure and charge of plasma membrane, phospholipid fluidity altered leading to perturbation of cellular homeostasis (Kochian et al., 2005). It has been also suggested that Al-induced cation displacement triggers callose synthesis (Gupta et al., 2013). Although the Al-specific carrier protein has to be discovered yet, it can interact with different channel proteins inhibiting the uptake of essential ions such as Ca^{2+} , K^{+} , Mg^{2+} and NH_4^{+} . Moreover, Al significantly disrupts H^{+} gradient altering the ionic condition and balance of root cells (Piñeros and Tester, 1997; Kochian et al., 2005; Singh et al., 2017).

The cytoskeleton (microtubules, actin filaments and intermediated filaments) is one of the potential targets for Al in the cell causing damage in cytoskeletal dynamics. Cytoskeletal stabilization is important during cell-wall biosynthesis and cell division, principally. Al disrupts cytoskeletal dynamics and stabilization via directly interacting cytoskeletal elements/subunits or altering their signaling cascades (Sivaguru et al., 1999). Researches also revealed that lateral cell swelling is the result of microtubule and actin filament disruption in their organization after Al exposure (Frantzios et al., 2001; Sivaguru et al., 2003). Moreover,

Al changes the signal transduction pathways affecting the whole plant. Protein phosphorylation and dephosphorylation are also regulated by Al induction (Matsumoto, 2000; Singh et al., 2017).

Table 1. Some sample researches concerning Al toxicity conditions

Plant material	Cell-organ	Growth solution	pH	Al concentration	Exposure time	Reference
<i>Chamelaucium uncinatum</i>	Pollen	Germination medium with boric acid	4.5-6.0	10, 20 μM AlCl_3	2 h	Zhang et al., 1999
<i>Hordeum vulgare</i> cv CK218	Root	Nutrient solution	3.5	0.1, 1.0, 10, 30, 50 mM AlCl_3	8 h	Pan et al., 2001
<i>Nicotiana tabacum</i> cv Karabağlar	Pollen	Germination medium with boric acid	Unspecified	50, 100, 150, 200 μM AlCl_3	24 h	Tuna et al., 2002
<i>N. tabacum</i> cv Samsun	Root	MS medium	4.5	50, 100, 150, 200 μM AlCl_3	16 days	Vardar et al., 2006
<i>Zea mays</i> cv Karadeniz Yıldızı	Root	Pretreatment with CaCl_2	4.5	150, 300, 450 μM AlCl_3	24-48-72-96 h	Vardar et al., 2011
<i>Gossypium hirsutum</i> cv Nazilli 84S	Leaves	Soil	4.5	100, 150, 200 μM AlCl_3	3 months	Ozyigit et al., 2013
<i>Triticum aestivum</i> , <i>Triticale wittmack</i> , <i>Secale cereale</i>	Root	Direct exposure with Al	4.5	100 μM AlCl_3	15-30-60-120 min	Vardar et al., 2015
<i>Solanum lycopersicum</i> cv esculentum and cv cerasiforme	Root and shoot	Clay and sandy soil	Unspecified	280, 560, 1120, 2240 mg/kg Al	18 days	Nogueirol et al., 2015
<i>Arachis hypogaea</i> cv Zhonghua 2' and cv. '99-1507'	Root	Direct exposure with Al	4.2-4.5	100 μM AlCl_3	4-8-12 h	Yao et al., 2016
<i>Citrus sinensis</i> cv Xuegan' and <i>C. grandis</i> cv sour pummelo	Leaves	Nutrient solution	4.1-4.2	1.2 mM AlCl_3	18 weeks	Li et al., 2016
<i>T. aestivum</i> , <i>H. vulgare</i> , <i>T. wittmack</i> , <i>S. cereale</i> , <i>Avena sativa</i> , <i>Z. mays</i>	Root	Direct exposure with Al	4.5	100 μM AlCl_3	0-1/2-1-2-3-4-5-6-7-8 h	Vardar et al., 2016
<i>H. vulgare</i> cv Sebastian	Root	In Hoagland's nutrient solution	4.0	20, 30, 40 μM AlCl_3	48-96-144 h	Jaskowiak et al., 2018
<i>N. tabacum</i> cv BY-2	Root and cell culture	Hydroponic culture and MS medium	4.5	50-100 μM AlCl_3	3 days	Kariya et al. 2018

Al has a genotoxic profile and long term Al exposure can lead detrimental effects on DNA composition and DNA replication by constructing more rigid double helix and chromatin structure. Many researchers observed that Al toxicity reduces mitotic index and increases abnormal chromosome movements which are related to Al-induced alterations in tubulin polymerization and depolymerization. Besides, chromosome laggards, bridges,

micronuclei and c-mitosis are revealed during Al stress (Silva et al., 2000; Frantzios et al., 2000; Vardar et al., 2011).

Al toxicity increases the production and accumulation of reactive oxygen species (ROS) in mitochondria, chloroplast and peroxisome (Kochian et al., 2004) which trigger oxidative damage in cell (Darko et al., 2004; Sharma and Dubey, 2007; Gupta et al., 2013). Under stress conditions various forms of ROS species ($O_2^{\cdot-}$, $\cdot OH$, $HO_2^{\cdot}$, H_2O_2 and 1O_2) are generated in plant cell inducing lipid peroxidation, DNA damage, protein denaturation, distribution of antioxidant enzyme balance, carbohydrate oxidation, pigment breakdown leading to programmed cell death.

ALUMINUM INDUCED PROGRAMMED CELL DEATH

In natural habitats, environmental stresses affect plants frequently because of being sessile organism. Excessive stress conditions, can damage wild flora and agricultural crops with regard to environmental and economic losses worldwide (Tuzhikov et al., 2011). Otherwise, plants have evolved alternative adaptive mechanisms to enable the survival of whole organism. Programmed cell death (PCD) is one of the adaptive mechanisms under extreme environmental stresses (Jackson and Armstrong, 1999; Drew et al., 2000). PCD can be described simply as a genetically regulated and coordinated cell elimination process in certain cells by specific proteases and nucleases during development and biotic–abiotic stresses (Wang et al., 2011; Vardar and Ünal, 2012; Wituszynska and Karpinski, 2013; Petrov et al., 2015).

PCD as a well-organized cell suicide process has common characteristics in eukaryotic cells such as shrinkage of cell, vacuolization, cytochrome c release from mitochondria to cytoplasm, specific protease activation, chromatin condensation, DNA fragmentation and finally breakdown of cellular contents (Qiao et al., 2003; Brighigna et al., 2006; Vardar and Ünal, 2008; Papini et al., 2011; Wang et al., 2012; Poor et al., 2013). Comparing plants and animals, plants have evolved their own pathways due to the existence of cell walls as a barrier. In dying plant cells, the cell wall prevents them from being phagocytosed by neighboring cells as it is in animals. Furthermore, among eukaryotic PCD forms rare conserved regulatory proteins or protein domains have been identified at the molecular level (Danon et al., 2004).

Plant growth and development are mediated and regulated by endogenous factors under environmental stress. One of these endogenous factors is ROS acting as signaling molecules (Nath and Lu, 2015). The ROS are generated as byproducts of respiration and photosynthesis in cellular organelles such as chloroplasts, mitochondria and peroxisomes. Superoxide anion ($O_2^{\cdot-}$), hydroxyl radical ($\cdot OH$), hydrogen peroxide (H_2O_2) and singlet oxygen (1O_2) are the most common produced free and non-radicals (Sharma et al., 2012). Lower doses of ROS act as a secondary signaling molecule that mediates the responses toward stress. But higher concentrations of ROS induce oxidative stress which damage macromolecules such as DNA, RNA, protein and lipid leading to PCD (Woo et al., 2013; Coll et al., 2014; Petrov et al., 2015). Even if there are a lot of researches on PCD, the relation between abiotic stress-induced as well as Al stress-induced PCD is still unclear and need to be investigated in molecular aspects.

There are several studies concerning increase of Al-induced ROS and antioxidant enzyme activities which are their scavengers in different plant species. In general, lipid peroxidation, superoxide dismutase, catalase, glutathione and guaiacol peroxidase activities increase in dose and/or time dependent manner (Boscolo et al., 2003; Vardar et al., 2011; Malekzadeh et al., 2015; Nogueirol et al., 2015). Lately, antioxidant enzyme activities and related defense gene expression in two passion fruit cultivars were also evaluated by Pretti et al. (2018). According to their results Al induced oxidative stress and increased both activity and gene expression of catalase and superoxide dismutase characterized by RT-PCR (semi-quantitative reverse transcription-polymerase chain reaction).

It has been revealed that under stress conditions ROS weaken binding of the cytochrome c (cyt c) to the inner mitochondrial membrane and cause its diffusion to the intermembrane space. At the same time, ROS also provoke the mobilization of Ca^{2+} ions from the endoplasmic reticulum to mitochondria. Ca^{2+} ions act as secondary signaling molecules and induce to reduce the mitochondrial membrane potential ($\Delta\Psi_m$). Subsequently the mitochondrial permeability transition pores (MPTP) are opened in the outer mitochondrial membrane permitting cyt c pass into the cytosol (Ott et al., 2007; Williams et al., 2014). The cyt c extrusion triggers more ROS generation in the mitochondria amplifying the signal. According to the researches, enhanced ROS generation and cyt c release trigger caspase-like activities in plants (Gunawardena and McCabe, 2015).

Li and Xing (2011) investigated possible mechanisms of PCD induced by Al. The researchers used to monitor the behavior of mitochondria and increase of caspase-3-like activity. They detected a quick burst of mitochondrial ROS, swelling of mitochondria, loss of MTP (mitochondrial transmembrane potential) and caspase-3-like activation prior to PCD in Arabidopsis. The researchers concluded that mitochondrial events such as swelling, generation of ROS and loss of MTP have critical roles triggering caspase-3-like activity and PCD providing a new perspective about Al-induced PCD mechanism.

Huang et al. (2014) reported that Al-induced ROS accumulation and PCD are closely related. According to their results 100 μM AlCl_3 caused ROS burst and up-regulation of *Rboh* and *COX* expression related to ROS mediation in peanut roots. Besides, the researchers also revealed increased MPTP opening, decreased $\Delta\Psi_m$, cyt c release from mitochondria to cytoplasm and caspase 3-like protease activity. The researchers concluded that Al induced PCD is regulated via a cascade of cellular events depending on mitochondrial pathway and ROS mechanism. Zhan et al. (2014) undertook a research to establish the role of mitochondria in Al-induced PCD in both Al-tolerant and sensitive peanuts. It has been reported that increase in mitochondrial ROS production and MDA were enhanced in two peanut cultivars. Besides, reduction of mitochondrial Ca concentration, opening of MPTP, collapse of $\Delta\Psi_m$ and cyt c release were more extensively in Al sensitive cultivar depending on Al concentration.

In animals, caspases regulate the PCD. Caspases are cysteine-dependent proteases and cleave their substrates after an Asp (aspartic acid) residue (Cai et al., 2014). It has been indicated that there are no caspase homologs in plant genomes, but caspase-like proteases and caspase-like activities were also identified in plants recently (Rocha et al., 2017). Synthetic animal caspase substrates were also used to determine caspase-like activities in plant PCD types (McStay et al., 2007; Ayturk and Vardar, 2015). In last decades, plant metacaspases are accepted as distant relatives of animal caspases (Uren et al., 2000). Metacaspases prefer to cleave their substrates after arginine (Arg) or lysine (Lys) as distinct from animal caspases

(Watanabe and Lam, 2005; He et al., 2008; Salvesen et al., 2016). Similar to caspases and metacaspases, vacuolar processing enzymes (VPEs) are also cysteine proteases (Hatsugai et al., 2004; Cai et al., 2014). VPEs cleave their substrates after an asparagine (Asn) residue distinct from caspases and metacaspases, but interestingly they also interact and cleave caspase-1 substrate (YVAD). Moreover, VPE activation repressed by inhibitor of synthetic caspase-1(ac-YVAD-CHO) (Sexton et al., 2007; Misas-Villamil et al., 2013). It has been reported that both metacaspases and VPEs have a regulatory role during environmental stress-induced PCD.

Kariya et al. (2013) investigated the role of vacuole in Al-induced PCD mechanism in *Nicotiana tabacum* L. cv BY-2 cell line. After 18 h Al treatment (0-150 μ M), cell growth and the integrity of plasma membrane were reduced, whereas VPE activity was increased dose dependently. Besides, morphological alterations of vacuole were also evident. They also observed that the presence of inhibitor of VPE (Ac-YVAD-CHO) suppressed the loss of plasma membrane integrity. The researchers evidenced that Al-induced VPE activity is controlled at transcriptional level, and loss of integrity of the plasma membrane and a loss of growth capacity are regulated by VPE activity. Lately Kariya et al. (2018) reported an increase in gene expression of *VPE1a* and *VPE1b*, but there were no change in *VPE2* and *VPE3* gene expression at tobacco roots after Al exposure.

Several studies using synthetic caspase substrates revealed caspase-like activities under Al stress conditions. Aytürk and Vardar (2015) indicated caspase-3, -8 and -9 like activities in triticale, barley, rye and oat roots after 100 μ M Al exposure. Similarly, Yao et al. (2016) used synthetic caspase-1, -2, -3, -4, -5, -6, -8 and -9 substrates in Al tolerant and Al sensitive peanut roots after 100 μ M Al. The results demonstrated that especially caspase-1 and -3 activities showed the highest activity in both cultivars. Besides, Al toxicity caused nuclear degeneration and DNA fragmentation.

DNA fragmentation originates from internucleosomal DNA cleavage by specific proteases and nucleases. Whereas ultrastructural features such as cell shrinkage and vacuolization points PCD (Liu et al., 2018), DNA fragmentation analysis is the most sensitive parameter of PCD. DNA fragmentation can be monitored by using TUNEL (Terminal deoxynucleotidyl transferase dUTP nick end labeling) reaction histochemically, comet assay, flow cytometry and laddering on the agarose gel.

In one of the early studies assessing Al-induced DNA fragmentation, barley roots were exposed to Al within a range of 0.1–50 mM (Pan et al., 2001). It has been revealed that Al concentrations between 0.1–1 mM induced clear DNA fragmentation, but the higher concentrations (10–50 mM) caused necrotic DNA smear. Comet assay can be also used to indicate DNA damage by measuring the DNA tail. Achary et al. (2008) demonstrated Al-induced breaks in double stranded DNA in *Allium cepa* roots by comet assay. Subsequently, Achary and Panda (2009) also evaluated Al-induced DNA damage in a range of 200-800 μ M Al in *A. cepa*. Achary et al. (2012) revealed a dose-dependent DNA damage in *H. vulgare* roots with different concentrations of Al (2.5, 5 and 10 mM). Furthermore, in peanut (*Arachis hypogaea*) roots 100 μ M AlCl_3 induced DNA fragmentation (Huang et al., 2014) revealed time dependent DNA damage by comet assay in wheat, rye and triticale roots after 100 μ M AlCl_3 exposure. Similarly, Vardar et al. (2016) demonstrated DNA fragmentation by agarose gel electrophoresis in wheat, oat, rye and triticale. Otherwise, Jaskowiak et al. (2018) reported Al-induced DNA fragmentation by TUNEL reaction in barley roots. The researchers also tested cell cycle profile and DNA integrity after Al exposure by flow cytometry. According to

the results, Al reduced the frequency of S phase cells and altered the cell cycle profile significantly. The delay of mitotic divisions caused increased cells frequency in G2/M phase.

Although there are several researches on Al-induced DNA damage, Al induced DNA methylation and polymorphism on LTR retrotransposons were also reported recently (Guo et al., 2018; Taşpınar et al., 2018). The researchers suggested that transposon polymorphism and methylation may be a part of the defense mechanism under Al stress.

ALUMINUM TOLERANCE AND ALLEVIATION

It has been known that some plant genotypes are Al tolerant. Because of the agronomic importance of Al resistance, the underlying molecular and physiological principles have become an important research area. The mechanisms of Al tolerance can be regulated both exclusion of Al from the root apex or intracellular tolerance of Al being transported into the symplast (Kochian et al., 2005).

It has been known that Al as a very reactive cation tends to form strong complexes with oxygen donor ligands. Several researches revealed that root exudates or mucilage (glucose, galactose, arabinose and uronic acids) make complexation with Al via chelation or direct binding preventing the accumulation of Al in apoplast or symplast (Barceló and Poschenrieder, 2002). Root apex secretes phosphate, carboxylate, phenolic substances, pectates, mucopolysaccharides and/or siderophores which can make complexes with Al ions (Winkler et al., 1986). Chelation of Al blocks the activity of Al ions preventing their binding to Al targets such as cell wall and plasma membrane. Although roots secrete different variety of exudates, carboxylates such as malate and citrate are most commonly detected (Barceló and Poschenrieder, 2002).

Whereas root exudates seem to be the most important Al tolerance mechanism restricting Al transport to the upper organs, several plant genotypes may tolerate high Al levels in their cell vacuoles or apoplast with ligands in an innocuous form by complexation and detoxification of Al. For example, *Hydrangea macrophylla* leaves accumulate Al making complex with citric acid and their sepals turn red to blue due to accumulated Al concentration. This situation also related to soil acidification resulting in Al dissolution (Takeda et al., 1985). The stated internal detoxification mechanism occurs with Al chelation in the cytosol and storage in the vacuole as Al-carboxylate complex.

Recently several types of ameliorating chemicals against Al toxicity have attracted attention in breeding crops because of their agronomic importance. Based on this, many researchers experienced some chemicals exogenously which are tend to make strong complexes with Al (Table 2). The most prominent chemicals are citric, oxalic, malic, oxalic and tartaric acids which are oxygen donor ligands (Hue et al. 1986; An et al., 2014). Yalçın and Vardar (2016) reported that both pre-treatment and co-treatment of salicylic acid alleviated Al toxicity, possibly stimulating the roots to secrete organic molecules such as citrate which are able to make chelation with Al. Pandey et al. (2013) alleviated Al toxicity applying Ca, Mg and salicylic acid. According to their results, the exogenously supplied chemicals suppressed ROS mediated oxidative stress, but salicylic acid was more effective in alleviation than Ca and Mg. Besides Chen et al. (2013) investigated the possible role of H₂S against Al toxicity. The researchers revealed that H₂S reduced Al accumulation and ROS

generation by increased antioxidant enzyme activities. They also indicated that H₂S increased both citrate secretion and citrate transporter gene expression. Wang et al. (2013) determined the alleviation effect of indol-3-acetic acid through reducing Al uptake and stimulating malic acid secretion in wheat roots. Moreover, it has been reported that silicone reduces Al uptake and ameliorates Al toxicity by making complexes with Al ions (Kopittke et al., 2017).

Table 2. Some ameliorating chemicals against to Al toxicity

Plant material	Plant organ	Growth solution	Al conc.	Alleviation agent	Reference
<i>Oryza sativa</i>	Root, shoot	Direct exposure	0.5 mM AlCl ₃	1 mM CaCl ₂ 0.25 mM MgSO ₄ 60 µM Salicylic acid	Pandey et al., 2013
<i>Triticum aestivum</i>	Root	CaCl ₂	50 AlCl ₃	25 µM Indol acetic acid 5 µM Niflumic acid 5 µM 2,3,5-triiodobenzoic acid	Wang et al., 2013
<i>Medicago sativa</i>	Leaves	Hoagland solution (spray)	100 µM AlCl ₃	100 µM Succinic acid 100 µM Citric acid 100 µM Malic acid 100 µM Oxalic acid	An et al., 2014
<i>T. aestivum</i>	Root	Nutrient solution	100 µM AlCl ₃	125- 625-2500 µM CaCl ₂	Hossain et al., 2014
<i>Brassica napus</i>	Shoot, root, leaves	Hoagland solution	0.1-0.2-0.3-0.6-1 mM AlCl ₃	0.3 mM NaHS	Ali et al., 2014
<i>Citrus grandis</i>	Shoot, root	Nutrient solution	1.2 mM AlCl ₃	2,5-20 µM H ₃ BO ₃	Zhou et al., 2015
<i>T. aestivum</i>	Shoot, root	Oxisol slury	-	Silicon (Si) rich biochar	Qian et al., 2016
<i>Hordeum vulgare</i>	Root	Direct exposure	20 µM AlCl ₃	5 -10 µM Salicylic acid	Yalcin and Vardar, 2016
<i>Borago officinalis</i>	Root, shoot	Hydroponic solution	20-60 mM AlCl ₃	0.2-1-2 mM Si	Delavar et al., 2016
<i>Glycine max, Sorghum bicolor</i>	Root	Direct exposure	5-10-25-30 µM AlCl ₃	2 mM Si	Kopittke et al., 2017
<i>O. sativa</i>	Root, shoot	Nutrient solution	0.19 mM Al	0.11 mM Si	Freitas et al., 2017
<i>O. sativa</i>	Root	CaCl ₂ solution	50 µM Al	10 µM La 400-600 µL/L CO ₂	Zhu et al., 2017
<i>Vigna radiata</i>	Leaves	Direct exposure	0.5 mM AlCl ₃	0.3 mM spermidine	Nahar et al., 2017
<i>H. vulgare</i>	Root, shoot	Hoagland solution	2-4-6 mM	2 mM Ascorbic acid 250 µM Salicylic acid	Shahnawaz et al., 2017
<i>Trifoliate orange</i>	Root	Direct exposure	400 µM AlCl ₃	10 µM H ₃ BO ₃	Riaz et al., 2018
<i>O. sativa</i>	Root	CaCl ₂ solution	30-50-100 µM AlCl ₃	1-2-5-10 µM NaHS	Zhu et al., 2018
<i>T. aestivum</i>	Root	CaCl ₂ solution	30 µM AlCl ₃	0.1-0.3-0.5 mM glucose oxidase 100 µM NO scavenger 100 µM diphenylene iodonium 5 mM dimethylthiourea 100 µM nitrate reductase 100 µM nitric oxide synthase	Sun et al., 2018

It has been known that polyamine (putrescine, spermidine, spermine) accumulation has a correlation with stress tolerance and adaptation (Nahar et al., 2017). Based on this, Yu et al. (2016) indicated a different mechanism on the alleviation of Al toxicity by using putrescine. The researchers revealed that putrescine induced on ethylene synthesis mechanism and decreased ethylene production alleviating root growth inhibition under Al stress conditions. Similarly, Nahar et al. (2017) reported alleviating effects of spermidine in mung bean seedlings under Al stress. The researchers also suggested that polyamines might have roles in regulating the antioxidant enzyme activities to decrease oxidative stress during Al stress.

In conclusion; Al toxicity especially in acidic soils has adverse effects on plant growth and development, as a result of this the productivity of crop reduces. Although the toxic effects of Al are well documented, the molecular signaling mechanism of Al toxicity is not clear. Besides, there is limited studies on Al-induced PCD and needs more detailed and sensitive research. To identify the Al toxicity and tolerance mechanism may help to improve Al tolerant varieties. Although several researches performed to mitigate Al toxicity using several types of chemicals, their alleviation mechanisms are still need to be clarified. Beside the Al tolerant varieties, proven chemicals might be used to ameliorate the adverse effects of Al to enhance the crop quality.

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Chapter 278

COMPARATIVE ANALYSIS OF DIFFERENT REGIONS OF RAT BRAIN TISSUE BY FT-IR SPECTROSCOPY

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ABSTRACT

The brain is a very complex system of millions of nerve cells and consists of anatomically and functionally independent structures, all of which having many functions to control living organisms. The complexity of the brain tissue arises from its heterogeneity, distinct structural ordering, chemical composition and functional activity. Due to such complexity, region specific investigations of brain tissue may have prominent importance for identification of pathological conditions. In the present study, whole brains of Wistar rats and different brain regions such as right-left hemisphere, hippocampus and cerebellum were comparatively analyzed by Fourier transform infrared (FT-IR) spectroscopy. Within the scope of detailed spectral analysis, the frequency and areas of some specific modes such as olefinic, CH₂ asymmetric and symmetric, amide I, C=O and PO₂⁻ asymmetric stretchings were evaluated. In addition, the bandwidths of CH₂ asymmetric and symmetric bands were analyzed. Also, olefinic = CH/lipid, CH₂/lipid, lipid/protein ratios were calculated. Thus, differences in parameters such as protein and lipid amounts, lipid packing and lipid fluidity were observed. As a result, corresponding findings support that FT-IR spectroscopy can be successfully applied for comparative analysis of distinct parts of the same tissue.

Keywords: brain, hemisphere, cerebellum, hippocampus, FT-IR

INTRODUCTION

The brain serves as the central organ of the nervous system; and together with the spinal cord, it constitutes the central nervous system in all vertebrates and most invertebrates. The brain controls most of the activities of the body such as processing, integration, and coordinating the information as well as receiving data from sensory organs and making decisions as to the instructions sent to the rest of the body (Krafft et al., 2006; Hackett et al., 2011). As having a very important role for most of the animals including humans, the brain tissue represents very complex structure with varied anatomic areas.

In general, the brain consists of right and left hemispheres, which results in hemispheric asymmetry defined as the presence of functional, anatomic or neurochemical differences between distinct hemispheres in a variety of species including rodents and humans (Reddon et al., 2009). (Hering-Hanit et al., 2001; Avci et al., 2008; Gökçer et al., 2012). Although two hemispheres are specialized in different functions, they are not isolated from each other, and research has focused on how they cooperate. Molecular and functional imaging techniques have revealed evidence of neurochemical asymmetries in brain and provided information about the relationship between brain lateralization and animal behavior and function (Sang et al., 2015).

A major component of the brains of humans and other vertebrates is the hippocampus located in the medial part of the temporal lobe extending along the temporal horn of the lateral ventricle (Songur et al., 2001; Spring et al., 2009; Spasojevic et al., 2013; İzci et al., 2015). The hippocampus belongs to the limbic system. Despite its close relationship with many other regions of brain makes hippocampal function difficult to define, it plays important roles in the consolidation of information from short-term memory to long-term memory, and in spatial memory that enables navigation (Yassa et al., 2011). Since different neuronal cell types are organized into layers in the hippocampus, it has frequently been used as a model system for studying neurophysiology, therefore; this region is the most studied one on compared to other brain regions.

The second major part of the brain is the cerebellum, which consists of two small half-cylinders attached to the back of the brain and at the front of the spinal cord. It is located in the posterior fossa and occupies 10% of the brain's volume (Derman et al., 1986). This specialized part is well-known for its role in coordinating motor output and adapting involuntary repetitions to support sensory pre-defined hat-based learning (Parmar et al., 2018) and in motor, cognitive and behavioral development as obtained from the evidence from the fetal, neonatal and pediatric populations (Andreottia et al., 2018).

Regional differentiation of brain tissue results from region specific structural and functional variations of biomolecules being major building blocks of brain (Krafft et al., 2006; Hackett et al., 2011). Thus, the investigation of such alterations depending on distinct parts of the brain can be pivotal for understanding of the mechanisms of different diseases and disorders. (Samuel et al., 2008; Engel et al., 2013; Dixit et al., 2016). For this purpose, infrared (IR) spectroscopy is very suitable for analysis of brain tissue due to its ability in detection of the changes on content, structure and dynamics of biomolecules in cells and tissues (Cakmak et al., 2012; Derenne et al., 2012; Nallala et al., 2013; Ozek et al., 2014; Turker-Kaya et al., 2016). IR spectroscopy does not require any staining or complicated sample preparation (Derenne et al., 2012; Turker et al., 2014a). An IR spectrum of a

biological sample is the sum of various contributions from lipids, proteins, carbohydrates, nucleic acids and all other chemical species (Carmona et al., 2008; Miller et al., 2013; Ozek et al., 2014; Turker et al., 2014a,b). The intensities and/or areas provide quantitative information, peak positions relate to physical states of molecules, and bandwidth gives dynamic information (Severcan et al., 2005; Carmona et al., 2008; Miller et al., 2013; Ozek et al., 2014; Kumar et al., 2014; Turker et al., 2014a,b; Turker-Kaya et al., 2016). Due to such advantages, FT-IR spectroscopy has been increasingly employed to investigate molecular variations between different tissues and alterations induced by drugs, and even disease states which are not easily detectable by morphological methods in cells and tissues (Berger et al., 2010; Leskovjan et al., 2010; Cakmak et al., 2011; Bozkurt et al., 2012; Travo et al., 2012; Bellisola et al., 2012; Turker et al., 2014a,b; Turker-Kaya et al., 2016).

In the present study, we aimed to analyze left and right hemisphere, hippocampus and cerebellum regions of rat brain tissue in comparison to whole brain by FT-IR spectroscopy as similarly performed in our previous studies (Turker et al., 2014a,b; Turker-Kaya et al., 2016; Turker-Kaya et al., 2017). We monitored the relative changes in lipid and proteins content, membrane lipid packing, membrane fluidity, and lipid peroxidation products (LPPs), all of which are very important parameters for proper functioning of brain.

MATERIAL AND METHODS

A. Animal Experiments

Adult Wistar rats were used for animal experiments carried out at Kocaeli University/Turkey. The animals were kept in a constantly warm room for 12 hours in the light-12 hour dark cycle with 60% relative humidity. The rats were decapitated and their brains removed out under deep ether anesthesia. The dissected brains were separated into 4 groups as whole brain (WB, $n = 7$), left hemisphere (LH, $n = 6$), right hemisphere (RH, $n = 6$), hippocampus (HP, $n = 6$) and cerebellum (CR, $n = 6$). The removed brain tissues were stored at -80°C deep freeze till spectroscopic analysis. All procedures involving animals were in compliance with the European Community Council Directive of 24 November 1986, and ethical approval was granted by the Kocaeli University Ethics Committee (Number: 2017/091 and 2018/040HD, Kocaeli, Turkey).

B. FT-IR Spectroscopy Studies

For sample preparation, earlier studies were followed (Elilbol-Can et al., 2011; Turker-Kaya et al., 2016). Briefly, freeze-drying was performed using a (Labconco FreeZone®, Benchtop Freeze Dry System Model 77520) for 24 hours to remove excess water from brain tissues. Fully dried tissues were ground and each tissue powder (2 mg) was mixed with 100 mg of pre-dried Potassium Bromide (KBr). Later, the mixture was dried again in the freeze drier for 18 hours to remove all traces of remaining water. The prepared mixture was applied placed a pressure of 100 kg/cm^2 for 5 minutes to obtain a solid KBr pellet.

A Perkin-Elmer Spectrum One FT-IR spectrometer (Perkin-Elmer Inc., Norwalk, CT, USA) equipped with a MIR TGS detector was utilized for spectral acquisition. All spectra were recorded in the 4000–450 cm^{-1} region at room temperature. Each interferogram was collected with 100 scans at 4 cm^{-1} resolution.

Although special effort was given to produce same thickness of each KBr pellet, to minimize intra-sample variability which may be due to variations in experimental conditions, two independent pellets prepared by taking separate portions randomly from the same sample were scanned. The average spectrum of these two replicates giving identical spectra representing one animal was used in detailed data analysis.

C. Data Analysis

Each spectrum was analyzed by the Perkin Elmer Spectrum One program to reveal the spectral differences between the groups in terms of band area, band position and band width. The band positions (wavenumber) values were calculated by taking 70% of the peak height by evaluating the center of gravity of the bands. The bandwidth was calculated by converting peak height at 70% to cm^{-1} . The peak area was calculated as related to a linear baseline between two baseline points which involve the maximum peak height. The baseline point was identified according to start and end points of the peak. Later, the corrected area which is the area between the spectrum and the marked baseline within the marker bar limits was found the peak area value of the peak of interest.

Taking possible interference due to detectable variability of sample thickness into consideration, area ratios of some specific IR modes were also evaluated to approximate content changes in biomolecules. The lipid/ protein ratio was obtained by proportioning the total area under the CH_2 asymmetric and the CH_2 symmetric stretching (2925 cm^{-1} and 2852 cm^{-1}) bands to the total area under the bands amide I and amide II (1645 cm^{-1} and 1547 cm^{-1}). For olefinic = CH/lipid and CH_2 /lipid ratios, the areas under the olefinic = CH (3012 cm^{-1}) and the CH_2 asymmetric stretching (2925 cm^{-1}) modes were divided to the total saturated lipid (the sum of the area under the CH_2 asymmetric and symmetric stretching bands).

RESULT AND DISCUSSION

As being major components of brain tissue, any change in the structure and function of biomolecules such as lipids and proteins directly affects the proper functioning of the neural network.

In the current study, we analyzed distinct regions of brain, each of which contains various cellular and molecular components. In this complexity FT-IR spectroscopy is insufficient to provide information about specific components. However, as a result of the Conne advantage, the vibrations of functional groups in different biomolecules appear at distinct wavenumber values in an FT-IR spectrum. This enables separation of the peaks from different biomolecules to be analyzed even in weak absorption modes (Gasper et al. 2009; Leskovjan et al. 2010; Elibol-Can et al. 2011; Turker et al. 2014b). Therefore, it is possible to monitor saturated lipids, unsaturated lipids, cholesterol ester, triglycerides, proteins, nucleic acids and

carbohydrates. The present study was conducted to comparatively analyze whole brain, right and left hemispheres, hippocampus and cerebellum sections of Wistar rats. To achieve this, we monitored the variations in the frequencies, bandwidths and peak areas of some vibrational modes of biomolecules as previously performed in other reports (Cakmak et al. 2011; Ozek et al. 2014; Turker-Kaya et al. 2016).

According to Beer–Lambert law, the intensity and area of an absorption band in an FT-IR spectrum offers relative information on the content of corresponding functional groups within complex tissue systems (Berger et al. 2010; Leskovjan et al. 2010). This has been previously confirmed by biochemical assays for LPPs (Severcan et al. 2005; Leskovjan et al. 2012; Turker et al. 2014a), proteins (Bozkurt et al. 2012) and lipids (Derenne et al. 2012). By utilizing this, in the current study, we evaluated area ratios of some modes to predict the changes in the content of these molecules without need of biochemical assays.

An FT-IR spectrum obtained from rat brain tissue sample is shown in Figure 1. As demonstrated in the figure, there are many bands of at different wavenumbers in the spectrum of the brain tissue, so the spectrum is quite complex. Table 1 illustrates assignment of each infrared band based on the literature (Wetzel et al., 1999; Toyran et al., 2004; Demir et al., 2015).

In order to show the spectral differences among the groups in more detail, spectra were divided into two separate regions, 3050-2800 cm^{-1} and 1800-900 cm^{-1} . Figure 2 and 3 illustrate average spectra of WB, LB, RB, CR, and HP groups in 3050-2800 cm^{-1} and 1800-900 cm^{-1} region, respectively. Table 2 represents numerical results of spectral analysis of each group.

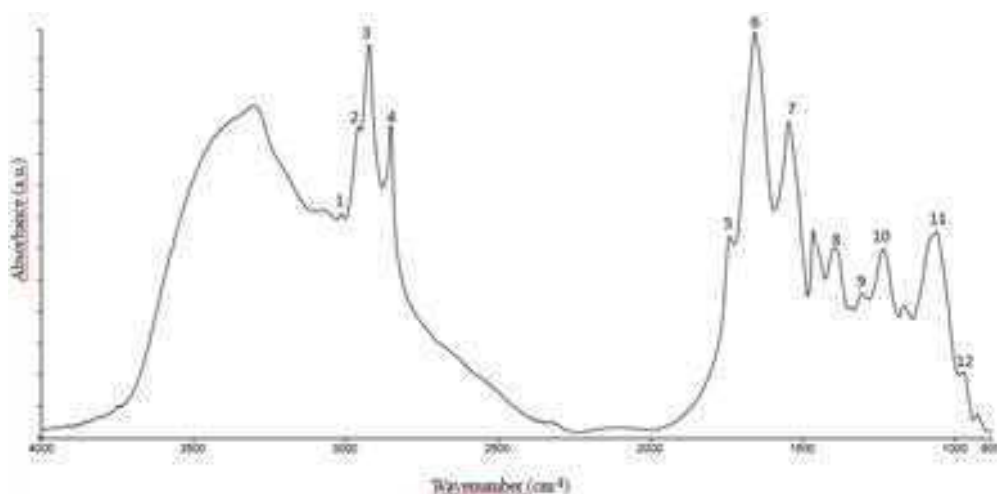


Figure 1. An average FT-IR spectrum obtained from rat brain tissue sample in 4000-900 cm^{-1} wavenumber range.

The myelin sheath, a phospholipid layer surrounding the axons of neurons, has a very high lipid content due to its multilayer structure and a greater lipid-protein ratio than most cellular compartments. Thus, the lipid bands observed in the brain tissue may originate from the myelin sheaths. For this reason, it is important to define such differences in lipid molecules that may cause deterioration in signal transmission in the brain (Palus et al., 2017).

Table 1. General band assignments of average FT-IR spectrum of rat brain based on the literature

No	Frequency (cm ⁻¹)	Definition of the spectral assignments
1	3012	Olefinic = CH stretching: unsaturated lipid
2	2956	CH ₃ asymmetric stretching: mainly lipid with little contribution from protein, carbohydrate and nucleic acid
3	2925	CH ₂ asymmetric stretching: mainly lipids with little contribution from protein, carbohydrate and nucleic acid
4	2852	CH ₂ symmetric stretching: mainly lipid with the little contribution from protein, carbohydrate and nucleic acid
5	1740	Saturated ester C=O stretch: phospholipid, cholesterol esters triglyceride
6	1645	Amide I (protein C=O stretch): protein
7	1547	Amide II (C=N and N-H stretching): protein
8	1400	COO ⁻ symmetric stretching: fatty acid
9	1306	Amide III: protein
10	1236	PO ₂ ⁻ asymmetric stretching: phospholipid and nucleic acid
11	1080	PO ₂ ⁻ symmetric stretching: phospholipid and nucleic acid
12	970	C ⁺ -N-C stretching: nucleic acid, ribose phosphate main chain vibrations of RNA

Similarly, brain tissue depends on oxidative pathway to utilize fuels, and has high content of unsaturated lipids when compared with other organs. This also brings about high level of mitochondria where reactive oxygen species are produced (Adam-Vizi et al., 2005). These molecules readily attack lipids and lipid peroxidation occurs, and LPPs are released into extra and intracellular site of cell (Cakmak et al. 2011; Turker et al. 2014a). Therefore, the detection of LPPs may provide information about not only possible pathogenesis of any condition but also antioxidant capacity of an agent in tissues, also shown by earlier studies (Battisti et al. 2008; Ramana et al. 2014). For this reason, in the current study, we specifically compared brain regions in terms of content of unsaturated lipids and presence of LPPs. In Figure 1, the olefinic band at 3012 cm⁻¹ originates from the C-H stretching mode of the HC = CH groups. It gives information about the degree of unsaturation of the acyl chains, particularly in the membrane lipids and lipid peroxidation (Turker-Kaya et al., 2016). Normally, when a decrease in unsaturated lipids occurs, a lower value in both olefinic mode area and olefinic/lipid ratio is expected. However, when reduced amount of unsaturated lipids is caused by lipid peroxidation, presence of LPPs results in an increase in olefinic mode area and olefinic/lipid ratio is observed as reported earlier (Turker et al. 2014a). This may be due to the loss of unsaturation being compensated by the presence of = CH groups in LPPs such as lipid aldehydes and alkyl radicals (Liu et al., 2002; Turker-Kaya et al., 2016). The ratio values of olefinic/lipid for all groups are given in Table 2. As seen from the table, when compared to the others, the lowest value was obtained in CR. The obtained finding may be resulted from low level of unsaturated and LPPs and high content of saturated lipids and/or both. On the other hand, while HP was same with WB, there was no difference between RH and LH. This shows that the unsaturated lipids and LPPs are accumulated least in CR in contrast to other regions of brain.

Membrane proteins such as membrane-bound enzymes, ion channels and receptors are dominantly present and function in nerve cell activity (Turker et al., 2014a). These types of proteins are classified as integral membrane proteins and peripheral membrane proteins.

Integral membrane proteins are in contact with with fatty acyl chains of membrane lipids whereas peripheral membrane proteins are predominantly bound to lipid head groups (Boggs et al., 1987; Brasseur et al., 1997; Turker et al., 2014b). Due to these bilateral interactions between membrane lipids and proteins, physical properties of lipids and proteins mutually affect their activity (Sandermann et al., 1978; McElhaney et al., 1982; Yeagle et al., 1992). To evaluate distinct brain regions in terms of physical state of membrane lipids, which determine their packing within bilayer, we monitored the frequency changes of the CH₂ asymmetric (2925 cm⁻¹), the CH₂ symmetric (2852 cm⁻¹), the C=O (1740 cm⁻¹), the PO₂⁻ asymmetric (1236 cm⁻¹) stretching bands. The CH₂ asymmetric and CH₂ symmetric stretching bands are mainly due to acyl chains of membrane lipids (saturated lipids) (Turker et al., 2014a; Turker et al., 2014b).

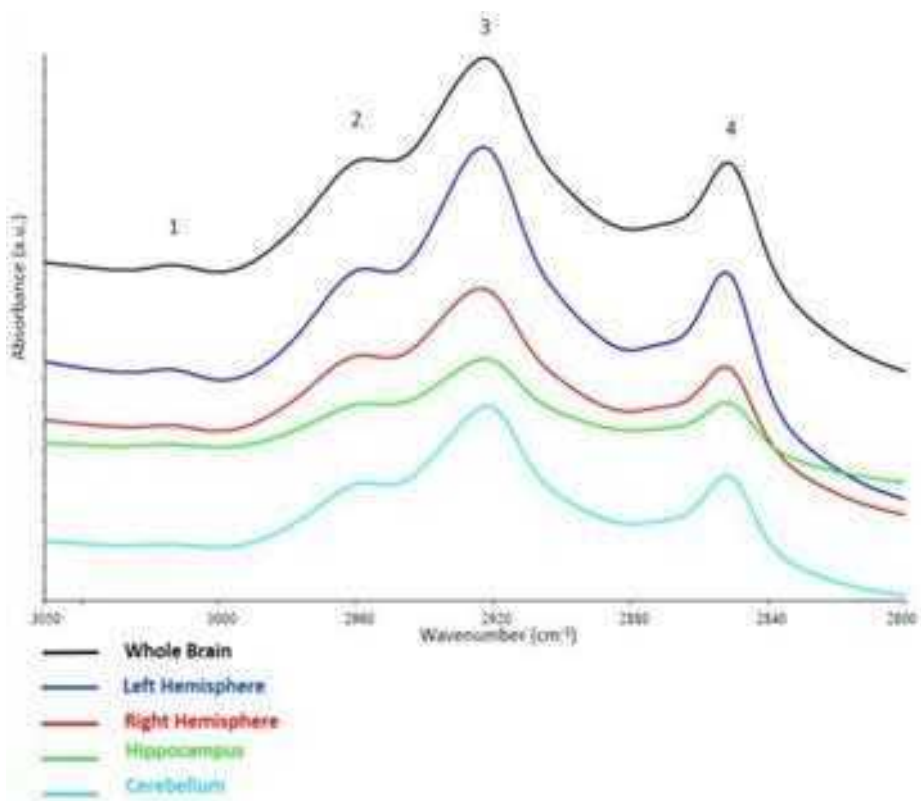


Figure 2. Representative FT-IR spectra of WB, RH, LF, CR, HP groups in the region between 3050–2800 cm⁻¹.

And, the monitoring of frequency shifting of these bands give information about order and disorder state of membrane (Turker et al., 2014b). Changes in the frequency values of such modes is related with the alterations in amount of gauche or trans conformers in the acyl chains. This may further cause the membrane to be loose or tightly packed (Senak et al., 1993, Akkas et al., 2007; Turker et al., 2014a). Evaluation of the frequency values of the CH₂ asymmetric and CH₂ symmetric band revealed no significant differences among all groups (Table 2). This may mean that there is no prominent variation in membrane order and acyl chain packing parameters of the regions in compared to WB. On the other hand, in Figure 3,

the C=O stretching band at 1739 cm^{-1} is a band that attributes to triglycerides, cholesterol, and carbonyl groups of phospholipids (Severcan et al., 2005; Turker et al., 2014a). The PO_2^- asymmetric stretching band at 1229 cm^{-1} is bound to the phosphodiester backbone of phospholipids and cellular nucleic acids (Cakmak et al., 2006). The shifts in the C=O and the PO_2^- asymmetric modes to lower wavenumbers suggest an increase in the hydration state of the glycerol backbone near the hydrophilic part and polar head group of the membrane lipids. The hydrogen bonding might be between water molecules and the oxygen molecules of both carbonyl and phosphate groups of phospholipids or hydrophilic protein residues (Akkas et al., 2007). As seen in Table 2, the C=O frequency value shifted to higher values in both RH and LH but lower values HP and CR when compared to WB. On the other hand, any significant shifting in PO_2^- asymmetric frequency value was not observed among the groups. These corresponding findings may mean that physical state of glycerol backbone near the hydrophilic part of membrane lipids show variations depending on specific brain regions. Nevertheless, state of acyl chain and phosphate groups of membrane lipids do not differ in distinct part of investigated regions of brain. Such parameter also reflects packing parameter of acyl chains of membranes.

Table 2. The values are the mean $\pm$ standard deviation for each sample

	WB (n = 7)	RH (n = 6)	LH (n = 6)	HP (n = 6)	CR (n = 6)
Frequency					
CH ₂ asymmetric	2924.42 $\pm$	2923.88 $\pm$	2924.49 $\pm$	2923.32 $\pm$	2923.22 $\pm$
CH ₂ symmetric	0.05	0.07	0.08	0.07	0.13
Amide I	2852.48 $\pm$	2852.17 $\pm$	2852.06 $\pm$	2852.27 $\pm$	2852.45 $\pm$
C=O	0.05	0.02	0.03	0.05	0.03
PO_2^-	1655.29 $\pm$	1652.71 $\pm$	1652.53 $\pm$	1653.04 $\pm$	1652.71 $\pm$ 0.3
Band area ratio	0.09	0.22	0.14	0.12	1736.58 $\pm$
Olefinic/lipid	1739.59 $\pm$	1745.65 $\pm$	1745.8 $\pm$ 0.07	1737.52 $\pm$	0.07
CH ₂ asym/lipid	0.02	0.09	1234.7 $\pm$ 0.12	0.05	1234.28 $\pm$
Lipid/protein	1235.33 $\pm$	1233.74 $\pm$		1235.32 $\pm$	0.17
Bandwidth	0.19	0.12	0.10 $\pm$ 0.003	0.17	
CH ₂ asymmetric			0.38 $\pm$ 0.020		0.07 $\pm$ 0.012
CH ₂ symmetric	0.08 $\pm$ 0.004	0.10 $\pm$ 0.02	1.26 $\pm$ 0.07	0.08 $\pm$ 0.004	0.39 $\pm$ 0.05
	0.33 $\pm$ 0.012	0.36 $\pm$ 0.019		0.36 $\pm$ 0.04	0.73 $\pm$ 0.09
	0.99 $\pm$ 0.07	0.85 $\pm$ 0.014	21.47 $\pm$ 0.11	1.01 $\pm$ 0.09	
			8.14 $\pm$ 0.04		20.52 $\pm$ 0.04
	22.85 $\pm$ 0.16	20.67 $\pm$ 0.14		21.41 $\pm$ 0.14	9.71 $\pm$ 0.008
	9.82 $\pm$ 0.06	8.14 $\pm$ 0.03		9.71 $\pm$ 0.005	

Changes in the fluidity of the cell membrane can be determined by investigating the bandwidth values of the CH₂ asymmetric stretching mode (Severcan et al., 2010, Turker-Kaya et al., 2016). The bandwidth value of this band gives information about the dynamics of the system (Turker et al., 2014b). As illustrated in Table 2, the highest value of CH₂ asymmetric bandwidth values is observed in WB. The obtained lower values in other regions may imply reduced lipid fluidity (Turker-Kaya et al., 2016). Here, it should be emphasized that this result related with fluidity is about all membraneous structures in brain rather than specific subcellular membranes of organelles. In other words, our samples contain all membrane compartments in addition to cell membrane. For that reason, the obtained outcome reflects cumulative fluidity parameter. Decrease in fluidity might have resulted from

variations in unsaturated lipids, which in turn causing the formation of kinks and force the molecules further apart and allow for more movement. Thus, a lowered membrane fluidity found in the current study can be another indication of functional changes of membrane proteins.

CH₂/lipid ratio was calculated to determine the alterations in the membrane phospholipids chain length (Cakmak et al., 2016). When the ratio of CH₂/lipid is examined in Table 2, it is seen that this value is similar in the HP and RH, while the highest value is in the CR and the lowest value is in the WB.

The bands at 1645 cm⁻¹ and 1540 cm⁻¹ in Figure 3 correspond to amide I and amide II bands of proteins, respectively. Amide I is mainly caused by C=O stretching of proteins while amide II is reassigned to N-H and C-N stretching (Cakmak et al., 2006; Turker et al., 2014a). They are used to determine protein structure or conformation and functional differences (Yan et al., 2014). When the 1650 cm⁻¹ amide I band frequency values are examined in Table 2, the highest value was observed in WB, then the HP value came. The RH and CR tissues were similar. The lowest frequency value was observed in the LH. This means that there are structural variations in protein among brain regions.

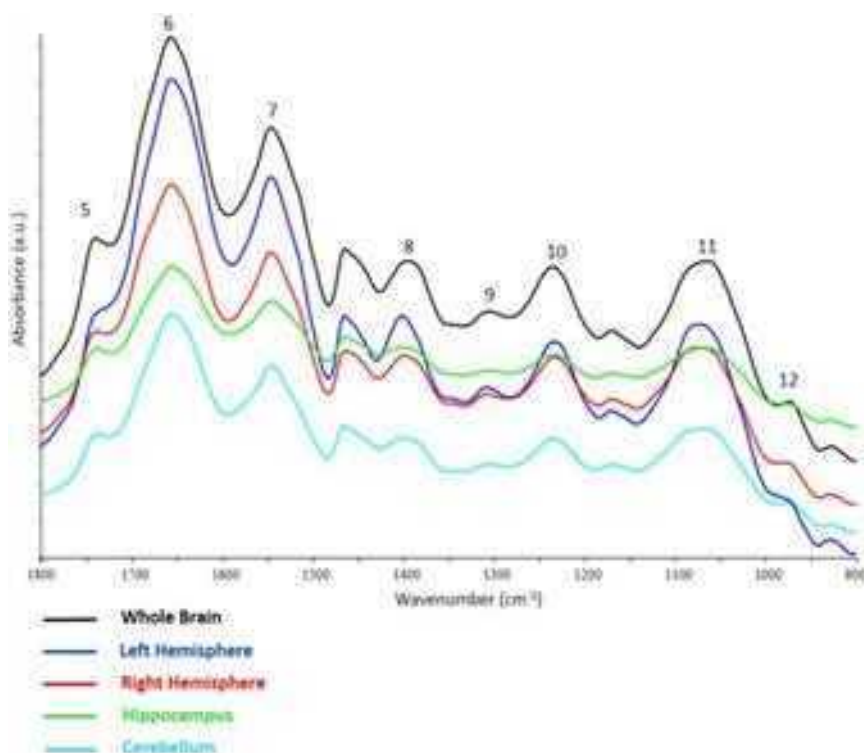


Figure 3. Representative FT-IR spectra of WB, RH, LF, C, H groups in the region between 1800–900 cm⁻¹.

When membrane lipids and proteins are thought to be in contact with each other, any change in the ratio of these molecules can alter membrane thickness and affect lipid regulation and fluidity (Awayda et al., 2004; Cakmak et al., 2011; Turker et al., 2014a). In this context, we calculated the lipid/protein ratio. As shown in Table 2, this ratio is similar in

WB and HP tissues and the highest value is in the LH tissue. The lowest values belong to the right RH and CR tissues.

As a result, when all these differences are taken into account, changes in fatty acids, protein conformation, and ratios in different brain tissues support neurochemical asymmetry studies between brain regions. At the same time, the parameters of the right-left hemisphere, cerebellum, and hippocampus tissues may be related to the functions of the brain parts, which are different from whole brain tissue parameters. However, the relationship between neurochemical changes and functions is not yet known.

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Chapter 279

SINGLE CELL GEL ELECTROPHORESIS FOR DETERMINATION OF PLANT RESPONSES TO GENOTOXIC STRESS

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ABSTRACT

The transmission of the energy to the higher levels is through the food chains, starting from the main source plants. There is a balance between all the livings in the ecosystem in which the plants are the first ring of this chain. Environmental mutagens and other related substances threaten humans and all other living organisms in an ecosystem. Plants are exposed to various types of environmental agents such as agricultural pesticides and plant growth regulators, or accidentally present in polluted air, soil or water. While pesticides used against harmful effects of agricultural production affect the target organisms, they can affect the non-target organisms through wrong and especially excessive applications. The adverse effects of toxic agents that accumulate in aquatic and terrestrial crops in an ecosystem and accumulate there as a bioindicator in plants should be identified?. Plant biotests are very important methods for evaluating the genotoxic contamination in the environment. For quick determination and measurement of the genotoxicity for these stress factors various molecular and biochemical tests are required. Single cell gel electrophoresis is also known as Comet assay that is used to investigate the cell response to several biotic and abiotic genotoxic agents leading to oxidative DNA damage. The Comet assay is used as a useful tool in assessing the potential of plants as source of information on the genotoxic impact of dangerous pollutants and sensitive sensors in ecosystems. This technique is based on the quantification of denatured DNA fragments migrating out of the cell nucleus during

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electrophoresis. Current review aims to give information about Comet assay and its applications as a valuable tool for monitoring DNA damage in different plant systems. The single cell gel electrophoresis studies were performed by our group to determine the genotoxic effects of different concentrations of pesticides, heavy metals and different plant growth regulators used in tissue culture applications in tobacco as model organisms, cereals (barley and wheat) and sunflower.

Keywords: COMET, biomonitoring, genotoxic effect, plant

INTRODUCTION

As it is known, plants are the main source in energy transmitting to higher levels in the food chain. The first ring of this chain are plants, the next rings are herbivores and carnivorous containing animals and humans. There is a balance between all living things in an ecosystem. The change that occurs at any level causes fluctuations in the different stages, causing the distortion of the existing balance. Today, the balance in different ecosystems is affected negatively by genotoxic agents in particular. Environmental mutagens and other related substances threaten humans and all other living things in an ecosystem. For example, pesticides are one of the chemicals that all living beings in the nature are exposed to. Pesticides are harmful to other living organisms as well as the target they are applied to, but they are the most effective fighting methods used to prevent the waste of agricultural products. Therefore, with proper use, the effects on other living things outside the target organisms should be tried to be minimized.

The adverse effects of toxic agents that accumulate in end-of-year aquatic and terrestrial ecosystems and accumulate in fisheries and plants that are studied as bioindicators should be identified. It is also a necessity for human health and well-being.

Genotoxic damage has negative effects on the important physiological conditions required for healthy life such as rejuvenation of living things, genetic characteristics and population dynamics. Various methods are currently being used to determine whether the DNA molecule is at risk for mutagenic effects and genotoxicity. One of the methods used to examine the genotoxic risk ratios is the Comet test, where direct DNA damage is measured. Single cell gel electrophoresis (SCGE) or so-called "Comet assay"; is a more sensitive and reliable method that results in shorter time than conventional cytogenetic methods used in measuring genotoxic risk ratios (Gichner et al., 2003; Lin et al., 2007). The Comet method has also the advantages such as allowing direct measurement at the DNA level and detecting genetic damage in a short time and directly. Use of this technique also extends the utility of plants in basic and applied studies in environmental mutagenesis.

The DNA breaks which migrate out of the nuclei embedded in a thin agarose layer can be measured by comet assay (Menke et al., 2001). The preparation of uniform and stationary gels in the slides is crucial to ensure that the cells embedded in the gel can be retained intact until the end of the experiment phase and to remove the factors that could affect the background appearance of the samples and in order to increase the gel fixation, roped lamellae are used (Tatli et al., 2008). The slides are placed in the electrophoresis tank containing the buffer solution and allowed to stand for a while in order to unwinding the DNA. If the unwinding and electrophoresis steps are carried out in an alkaline pH

environment, the breaks of the double and single strand in the DNA can be determined. If both the unwinding and the electrophoresis are more than carried out in pH 13, the base damage in the crosslinks as well as the breaks in the double and single strand can be determined. It is very important to keep the temperature constant during electrophoresis in order to avoid the differences that may occur between samples. The slides are washed at room temperature with 0,4 M Tris-HCl (pH 7,5) to neutralize the resulting alkali medium following electrophoresis and to provide a clear image under the microscope (Gichner et al., 2008b; Rank et al., 2009).

Detection of DNA single strand breaks in cells was first described by Rydberg and Johanson (1978). Cells were embedded with agarose on a microscope slide and cell lysed under lightly alkaline conditions to allow partial dissolution of DNA. The cells were stained with acridine orange after neutralization and photometrically analyzed. The proportion of double-stranded DNA to single-stranded DNA, the proportion of green fluorescence to red fluorescence, and the extent of DNA damage were determined. Ostling and Johanson (1984), have increased the sensitivity in the detection of DNA damage in cells by improving the Microgel Electrophoresis techniques. The technique proposed by Ostling and Johanson is based on spiral breaks in DNA and the mechanism by which this structure can be pulled out and attenuated by electrophoresis. Singh et al. (1988) have developed a method that allows detection of DNA damage under alkaline conditions by modifying the microgel electrophoresis technique. In this technique, electrophoresis is carried out at high pH.

Table 1. Types of DNA damage that can be detected by Comet assay at different pH

N/N (pH: 7-8)	A/N pH: 10-12	A/A pH > 13
Double strand breaks	Double strand breaks	Double strand breaks
Cross links	Single strand breaks	Single strand breaks
	Excision repair sites	Excision repair sites
	Cross links	Cross links
		Alkali injuries

Versions such as N/N (Neutral Dissolution/Neutral Electrophoresis), A/N (Alkaline Dissolution/Neutral Electrophoresis) and A/A (Alkaline Dissolution/Alkaline Electrophoresis, pH 13) developed for different pHs (Table 1) are also used in the Comet assays (Gichner and Plewa, 1998; Lin et al., 2007).

After the neutralization step, the slides are stained and analyzed within a maximum of 6 hours. If analysis can not be done immediately, the preparations are kept in cold water for 10-15 minutes, then dehydrated in 100% ethanol and left to dry. The slides can be stored for a few months under appropriate conditions (Kocyigit et al., 2005, Gichner et al., 2008 a, b).

The comet formation of nuclei followed by electrophoresis enables quantification of DNA in comet tails after staining with an appropriate fluorochrome such as propidium iodide or ethidium bromide (Olive and Banath, 2006). Despite the use of sensitive but quite expensive dyes such as YOYO-1 (benzoxazolium-4-quinolinone oxazole yellow homodimer), DAPI (4,6-diamidino-2-phenylindole) in the detection of lower levels of DNA damage, it is reported that the efficiency of the cheaper etidium bromide was not different from other dyes mentioned (Gichner et al. 2006).

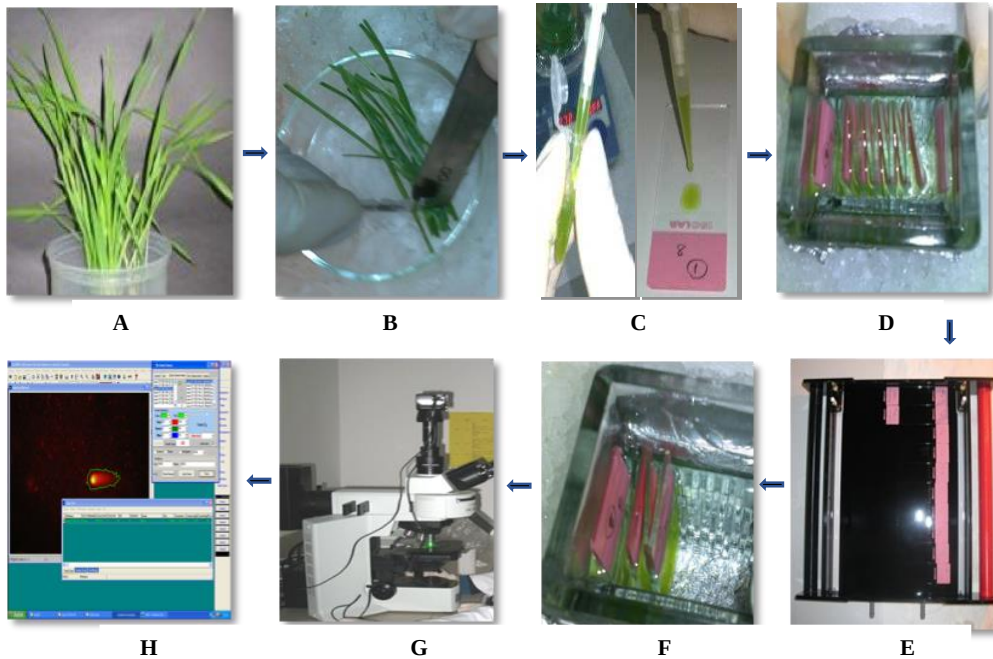


Figure 1. General illustration of the Comet assay. (A, B) Isolation of nuclei from plant leaf tissue, (C) The mix of isolated nuclei and LMP agarose transfer onto the slides, (D) Unwinding of the slides in fresh alkaline or neutral electrophoresis buffer, (E) Electrophoresis of the slides in the alkaline or neutral buffer, (F) Neutralize the slides, (G) Stain the slides with a DNA binding dye and view under fluorescence microscope, (H) Analyse the results (Akan, 2012).

Following staining, migration of DNA from the nucleus is observed in damaged cells. Each damaged cell; a brilliant fluorescence head and length and fluorescence intensity has a comet image consisting of a tail connected to the number of DNA strand breaks in the cell. Undamaged cells appear as untailed, undisturbed nuclei. DNA images emerging at varying degrees of damage from circular to comet-like form are examined under a fluorescent microscope.

Utilizing the feature that the amount of DNA in a particular region is directly proportional to the fluorescence intensity in that region, and in parallel with the progress in digital imaging systems and analysis software programs, more accurate quantification methods have been developed. Image analysis systems can measure various comet parameters such as head length of damaged cells, percentage of DNA in head and tail, tail length and tail moment (Tice ve ark., 2000; Hartmann ve ark., 2003).

According to its head and tail shape of comet, the migration of DNA could be classified from 0 (no tail) to 4 (almost all DNA in tail) by visually (Kobayashi et al., 1995; Gichner et al., 2003; Kocyigit et al., 2005).

The use of Comet test with different methods affects the results. For instance, electrophoresis conditions (duration, applied voltage), lysis solution content (salt concentration and pH) and duration of application affect the sensitivity of the method. For this reason, optimizing the technique in comet labs is an important step (Hartmann et al., 2003).

COMET ASSAY IN PLANTS

Comet is an effective tool that can be applied easily to fungi, algae, plants, sea creatures, insects, vertebrate animals and humans, and to give information on environmental health (Gichner and Plewa 1998, Angelis et al., 2000; Menke et al., 2001; Dhawan et al., 2009). Although almost all plants are available for the Comet test, they are potatoes (*Solanum tuberosum*), tobacco (*Nicotiana tabacum*), soya bean (*Vicia faba*), onion (*Allium cepa*) and *Arabidopsis thaliana* in terms of ease of cultivation and cell isolation (Gichner et al., 2006; Mancini et al., 2006; Lin et al., 2008). Gichner and Plewa (1998) found that after exposure to *N. tabacum* plants with 1-8 mM Ethyl Methane Sulphonate (EMS), the highest amount of DNA damage was found in the plants exposed to the highest EMS concentration. Menke et al. (2000) investigated that the N-methyl-N-nitroso Urea (MNU) was genotoxic effective agent in *V. faba* plants in comparison with three different comet technique protocols (neutral/neutral, alkaline/neutral, alkali/alkaline). Gichner et al. (2008) conducted that comet analysis under alkaline conditions to determine the increase in induced DNA damage in *S. tuberosum* L. plant treated with EMS, Cd²⁺ and γ -rays, showed that the best dose-response curve was detected with the alkaline Comet technique.

SCGE, in combination with detection of Reactive Oxygen Species (ROS) and expression analysis of both DNA repair and antioxidant genes, can be used for the plant genotypes (Ventura et al., 2013). The accumulation of reactive oxygen species (ROS) are damage the cellular components such as DNA, proteins and lipids (Lopez et al., 2006).

The overproduction of ROS induced by some heavy metals can lead to the DNA damage in plants, animals and microorganisms living in aerobic conditions (Gichner, 2003; Mittler, 2002; Mancini et al., 2005), are the early responses of plant to heavy metals (Mittler, 2002; Hartley-Whitaker et al., 2001). Lin et al. (2007) reported that the enhancement in DNA damages was correlated to oxidative stress induced by Cd in leaves of *Vicia faba*, indicating that ROS accumulation in tissues caused subsequently DNA damage.

Comet assay has been used in different studies by use of plants particularly in environmental risk assessment (Table 2). Despite the fact that almost all plants are available for comet analysis, studies on *S. tuberosum*, *N. tabacum*, *V. faba*, *A. cepa* and *A. thaliana* have been found more widely in the literature (Gichner et al. 2006; Mancini et al., 2006; Lin et al., 2008).

Programmed Cell Death (PCD) is genetically controlled death and mediated by specific proteases and nucleases. During PCD cells are executed in a biological process and characterized by cell shrinkage, vacuolization, nucleus deformation and DNA fragmentation. In detailed studies of PCD DNA fragmentation is accepted as the most apparent indicator of PCD. DNA fragmentation in dying cells is visualized/measured by several analyses such as DAPI staining, TUNEL reaction, flow cytometry, gel electrophoresis and Comet assay (Vardar et al., 2011; 2012; 2015; 2016). Although the DNA damage can be visualized and measured by Comet assay, the whole of comets may not be considered as PCD. It is the fact that the damaged cells will subsequently be undergone irreversible PCD. Considering the fact that DNA damage might be repairable, the Comet tail can be no longer seen under proper conditions. Besides damaged cells die and disappear, but in comet assay the damaged cells are still present and detectable. Moreover, DNA fragmentation during PCD is characterized by DNA cleavage into 180-200 bp length oligonucleosomal fragments. During

electrophoresis in Comet assay such small parts of DNA will probably disappear (Collins et al., 1995; Collins, 2004). To overcome these difficulties Singh (2000) described a visualization method of dying cells. In this technique cells are embedded in the agarose and lysed. But the researcher precipitated the DNA, instead of electrophoresis. The dying cells distinguished by halo of granular DNA and a hazy outer boundary (Singh, 2000). The inverse relationship between the application time and the DNA damage can be explained by the partition of the enzymatic processes in the formation of DNA damage of pollutants causing toxicity (Ali and Kumar, 2008). Akan (2012) reported that CPF application in barley plant demonstrated that there was an inverse relationship between DNA damage and application time. Long-term studies are required to examine the repair of DNA damage, protective mechanisms and enzymatic processes is suggested in this study.

Table 2. Selected Comet assay studies in plant toxicology (Santos et al., 2015)

Stress	Species	Tissue	Comet type
Radiation			
Light	<i>A. thaliana</i>	Leaves	A/ApH > 13
UV	<i>A. thaliana</i>	Leaves	A/ApH > 13
X-ray	<i>A. thaliana</i>	Leaves	A/ApH > 13
Metals			
Monovalent	<i>V. faba</i>	Roots, leaves	A/ApH > 13
Divalent	<i>A. cepa</i>	Roots	A/ApH > 13
Trivalent	<i>A. thaliana</i>	Roots	N/N pH 8.4
Oxoanions	<i>A. cepa</i>	Roots	A/ApH > 13
Nanocompounds			
MWCNT	<i>A. cepa</i>	Roots	A/ApH > 13
Metal NPs	<i>A. cepa</i>	Roots, leaves	A/ApH > 13
Metal oxideNPs	<i>A. cepa</i>	Roots	A/A pH > 12.3
Quantum dots	<i>M. sativa</i>	Cell suspension	A/ApH > 13
Organic pollutants			
Dyes	<i>A. cepa</i>	Roots	A/ApH > 13
Pesticides	<i>A. cepa</i>	Roots	A/ApH > 13
Polyhalogenated	<i>A. cepa</i>	Roots	A/ApH > 13
Phytocompounds			
	<i>A. cepa</i>	Roots	A/ApH > 13
Others			
Osmostressors	<i>A. thaliana</i>	Seedlings	N/N pH 8
Control mutagens			
	<i>A. cepa</i>	Roots, leaves	A/ApH > 13

Agronomic crops as well as other plants are deliberately exposed to pesticides and other chemicals applied in modern agriculture. These pollutants are hazardous for the plants. Basudine and antracol pesticides, destroys crop and livestock. In our study, genotoxic potential of Basudine and Antracol were determined using Single Cell Gel Electrophoresis (SCGE) in tobacco (*Nicotiana tabacum* L.) which is model plant and it is suitable for genetic and physiological studies. The Comet assay has been widely used in the fields of genetic toxicology and environmental biomonitoring by evaluating DNA strand breaks.

Pesticide applications can cause damage due to many factors. These factors include the form of dose (how much is applied), duration (how long it is applied), and how contact occurs. In addition, the presence of any other chemicals exposed, the age and other characteristics of the organism must be taken into consideration.

In the study conducted by Aydın et al. (unpublished data), possible genotoxic effects of Basudin (fungicide - active ingredient: Diazinon) and Antrakol (insecticide - active ingredient: Probinex) pesticides on model organism tobacco plant (*Nicotiana tabacum* L.) were evaluated by single cell gel electrophoresis. Diazinon can reduce its fixation ability by nitrogenous soil organisms, an important plant nutrient and nitrogen fixation is a process that transforms atmospheric nitrogen into a form that can be used by plants. Diazinon applied to the soil is absorbed by plant roots and can be translocated in plants (Kamrin, M. A., 1997). Their half-life ranges from 2 to 14 days. Low temperature and high fat content increase the durability of diazinon in plants (Kamrin, M. A., 1997). Diazinon also causes genetic damage in plants. Diazinon application with onion (Grover et al., 1987) and barley (Kour and Grover, 1985a, Grover et al., 1987) resulted in abnormal chromosomal occurrences. In addition, seeds obtained from diazinon-treated plants contain mutations that reduce the proportion of chlorophyll in cells following germination (Grover et al., 1987). Diazinon applications to barley seeds or seedlings cause abnormal chromosomes to form in pollen cells (Kour and Grover, 1985b). Antrakol is used to destroy fungi causing damage to various vegetables and fruits (tomatoes, potatoes, onions, grapes, melons, etc.).

In this study, Basudin and Antrakol pesticides are used extensively controlling of pests on park and garden especially in İstanbul, Turkey. The genotoxic effects of these pesticides are not completely understood and the Comet assay was used for detecting DNA damage by these pesticides exposed to the model organisms, tobacco (*N. tabacum*).

Thus, the aim of this study was to evaluate the genotoxic effects of acute exposures (24, 48, 72 and 96h) to 0.925, 1.85, 2.775 mg/ml of Basudin and 0.5, 1, 1.5 mg/ml of Antrakol on two-week-old tobacco seedling. Tobacco plants germinated in MS (Murashige and Skoog, 1962) medium and nucleus isolated from their leaves. Leaf samples from non pesticide treated tobacco seedlings grown on MS medium were used as negative controls, and leaf samples from seedlings treated with distilled water containing 0.1% H₂O₂ (during 24 hours) were used as positive controls. Leaf tissues were disrupted with sharp razors adding cold 0.4 M Tris-HCl buffer (pH7.5). The tissues were gently sliced and isolated for collection of nuclei in the buffer. The mixture was centrifuged to remove the debris. All steps were performed in dim light and ice to prevent induction of DNA damage. Nuclei suspension was mixed with the liquid Low Melting Agarose (LMA) (1:1) by gently pipetting and as soon as agarose/nuclei mixture were spread on the slide that previously coated with High Melting Agarose (HMA). The slides were incubated in electrophoresis buffer to facilitate DNA unwinding. Thereafter, the slides were placed on horizontal electrophoresis tank filled with fresh, cold electrophoresis buffer kept cold using ice followed by performing electrophoresis. After neutralization each slide was stained with ethidium bromide and kept at 4°C until analysis. These slides observed under an epifluorescence microscope (BX51TF, Olympus) equipped with a CCD camera (Canon A640) and fifty cells per slide were analyzed with the Comet image analysis system (BAB BS200ProP). For each sample, 50 random cells were scored. The % tail DNA and olive tail momentum parameters were calculated as a measure of DNA damage. % Tail DNA values were shown as the percentage of DNA in comet tail. Olive tail moment values were shown as multiplication of % tail DNA and difference between center of

gravity of DNA in the tail and center of gravity of the head DNA. The results showed that Basudin and Antrocol produce genotoxic damage in leaf nucleus of *N. tabacum*. The comet scores obtained for tobacco after all time points of exposure to Basudin and Antrocol were significantly higher than the respective negative control ($P < 0.001$). In conclusion the result of this work showed that Basudin and Antrocol induced genotoxic effects on the plant species *N. tabacum*. The genotoxic effects were observed in all Basudine and Antracol concentrations and exposure times in tobacco (Table 3, Figure 2 and Figure 3).

It has been determined that diazinon inhibits the activity of an enzyme in soil microorganisms that “plays an important role” in the nitrogen cycle (Frankenberger and Tabatabai, 1991). Diazinon also reduces the amount of nitrogen compounds in the soil (Ingham and Coleman, 1984).

Comet analysis of the findings, as well as the determination of pesticide spraying and harvesting time of use to determine appropriate doses contributed to the work.

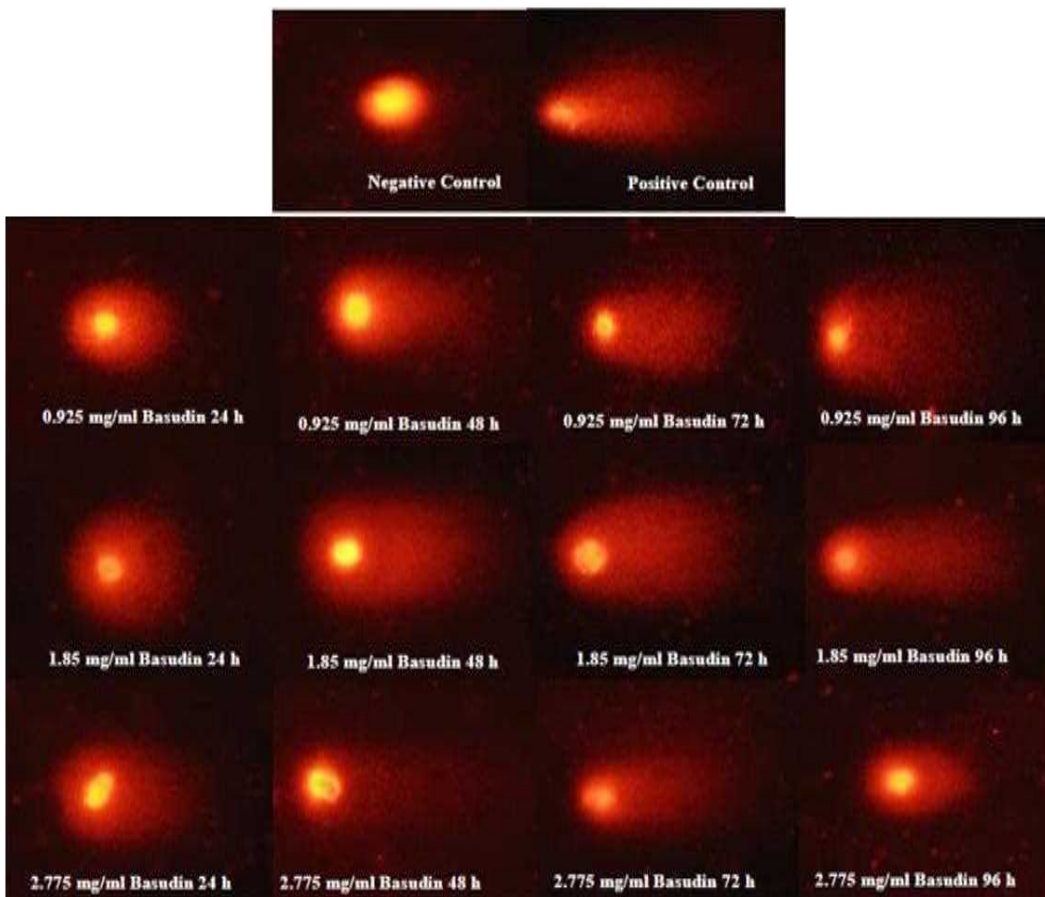


Figure 2. DNA migration pattern from *Nicotiana tabacum* L., exposed to different concentrations of Basudin with different exposure times. Objective: 20X. Dye: EtBr (Unpublished data).

In vitro culture factors could apparently lead to oxidative stress and genotoxicity. The plants produce oxine and cytokine in their own tissues. These hormones can reach high doses in plants by supplementing these plant growth regulators from outside in plant tissue culture

studies. The production of auxin and cytokine may be distinct in plants for different gene sources. In recent years, in vitro techniques have been extensively used for abiotic stress (Şen, 2012) and genotoxic effects.

Table 3. DNA damage at different concentrations and exposure times of Basudin and Antracol (%DNA tail and Olive tail moment)

Pesticide	Dose	Time (hour)	%DNA tail	Olive tail moment
Basudin	(-) control		26	0.26
	(+) control	18	36	0.26
	0.925 mg/ml	24	29	0.20
		48	28	0.21
		72	38	0.29
		96	36	0.34
	1.85 mg/ml	24	33	0.20
		48	27	0.12
		72	29	0.16
		96	23	0.17
	2.775 mg/ml	24	18	0.17
		48	30	0.18
		72	23	0.21
		96	31	0.15
Antracol	(-) control		26	0.26
	(+) control	18	36	0.26
	0.5 mg/ml	24	26	0.15
		48	28	0.17
		72	27	0.15
		96	23	0.13
	1 mg/ml	24	20	0.12
		48	17	0.14
		72	32	0.16
		96	20	0.16
	1.5 mg/ml	24	26	0.15
		48	33	0.22
		72	28	0.12
		96	25	0.11

In another study conducted by our group, it was evaluated the changes on genotoxicity derived from androgenic callus tissues with the effect of plant growth regulators, genotypes and pretreatments in sunflower by Comet assay. The method of Çavaş and Könen (2007) was used by some modifications in this study. Obtaining callus tissues were used as material to detect the DNA damage levels by Comet assay. Leaf of sunflower grown in MS medium for two weeks was used as a negative control and leaf of sunflower that grown in MS medium supplemented with 150 μM AlCl_3 for two weeks was used as positive control. Callus and leaf tissues were disrupted with sharp razors adding cold 0.4 M Tris- HCl buffer (pH=7.5). The slides were analyzed under a fluorescent microscope at 20X magnification. For each sample, 50 random cells were scored. Comet parameters were measured and analyzed using KAMERAM software. The % tail DNA and olive tail momentum parameters were calculated as a measure of DNA damage. % Tail DNA values were shown as the percentage of DNA in comet tail. Olive tail moment values were shown as multiplication of % tail DNA and difference between center of gravity of DNA in the tail and center of gravity of the head

DNA. Overall results we obtained indicated that genotype, medium type and pretreatment factors especially plant growth regulators could apparently lead to genotoxicity and medium type is the most effective parameter for genotoxic effect on sunflower (unpublished data).

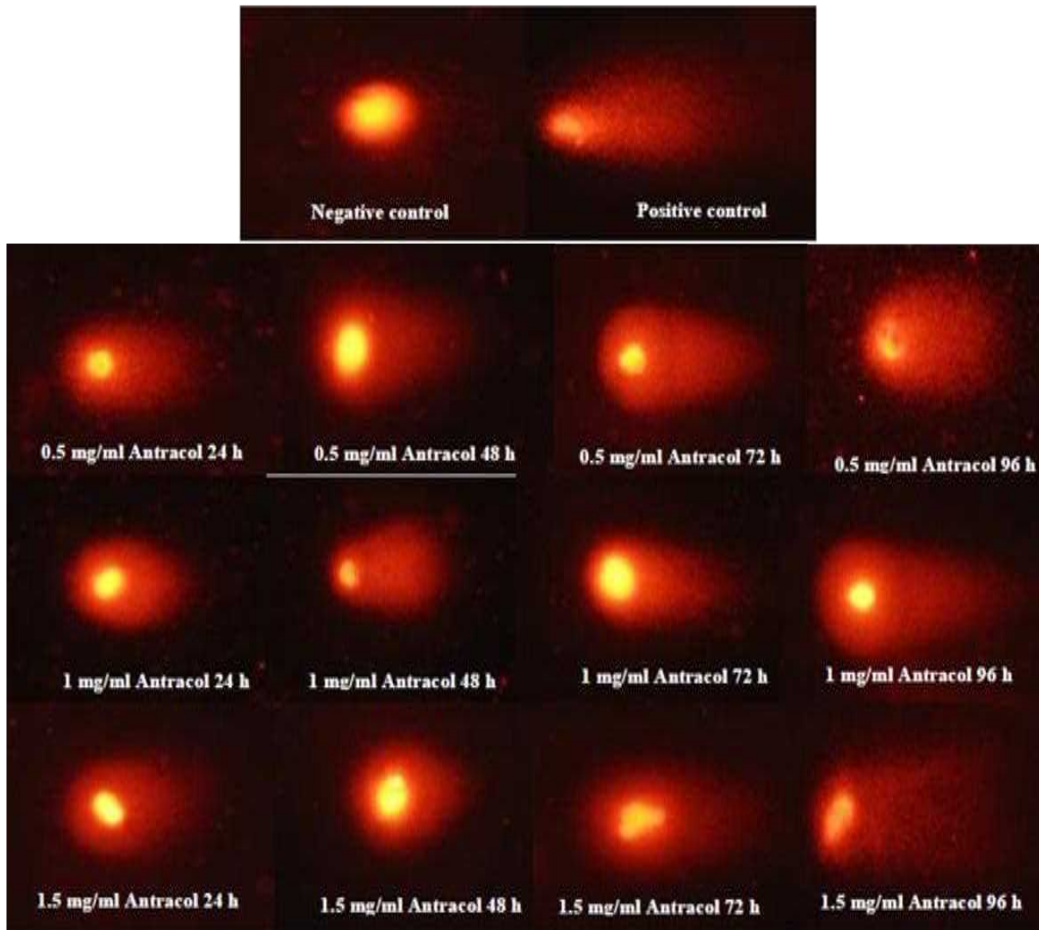


Figure 3. DNA migration pattern from *Nicotiana tabacum* L., exposed to different concentrations of Antracol with different exposure times. Objective: 20X. Dye: EtBr (Unpublished data).

In conclusion; Comet assay is a fast, easy and reliable method to evaluate DNA damage on living organisms and in vitro and in vivo studies with different concentration and exposure periods induced by various types of genotoxic agents. Comet assay also can be employed in specific tissues or cells such as roots and leaves. These characteristics of the assay make it to be used in evaluating various types of environmental toxic conditions. Although Comet assay is most used the evaluating the acute effects of genotoxic agents, it can be also used to reveal DNA repair in plant physiology, as this technique may help elucidating pathways involved in plant development, cell cycle/programmed cell death, or even plant disease resistance. Long-term genotoxicity studies can be an important approach to gaining insight into the ability of organisms to repair DNA and other protective mechanisms.

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Chapter 280

EVALUATION OF THE SENSITIVITY OF THE NURSES WORKING IN SURGICAL SERVICES OF A PUBLIC HOSPITAL TO PATIENT RIGHTS

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ABSTRACT

This study was designed as a descriptive study, to analyze the sensitivities of the nurses working in the surgical services of a state hospital on patient rights. The universe of the study consisted of 61 nurses working in the surgical services of a state hospital while the sample of the study consisted of 54 nurses volunteered to participate in the study between July 26 and October 1, 2010. The data of the study were collected with the personal information form and the Belief of Patient Rights Form (BPRF). In the statistical analysis of the results, frequency, percentage, mean, standard deviation, Mann Whitney U and Kruskal Wallis-H tests were used. The mean total score of BFRF of the nurses was 32.85 ± 6.66 ; the differences between the nurses' scores on the BFRF and the subscales of privacy and private life and application were significant according to their ages ($p < 0.05$); the difference between the nurses' scores on the consent subscale was significant according to their education levels ($p < 0.05$). It was determined that the surgical nurses who were 29 years old or younger, university graduates, had less than 5 years' study period and took courses on patient rights, had high sensitivity to patients' rights. It can be recommended to add related courses in the curriculum during the education and to plan training programs by considering age group, the level of education, working time and the status of taking related courses, for improving nurses' sensitivity to patient rights.

Keywords: surgical nursing, surgical service, hospital, awareness, patients' rights

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INTRODUCTION

Patient rights are defined as the rules of conduct between people who benefit from health services and the health institutions and personnel who provide them (Teke et al., 2007; Ozakar Akca et al., 2015). As these rights relate to particular circumstances in human life, it is also defined as third generation human rights and covers the application of human rights and values in health services. Top priorities of patient rights include: to be respected as a human being, receive health service in a high level, get information, get confirmation for medical processes, privacy, and respect for private life, while receiving care and treatment continuity (Erbil, 2009; Ozakar Akca et al., 2015).

In recent years, advances in science and technology have made being informed about treatment and care initiatives necessary for patients (Savaskan, 2006). This change and development has led the nurse's care function to mainly focus on new roles. One of the contemporary roles of the nurse is to stand up for patient rights (Ardahan, 2003). In this context, nursing is aimed to be a discipline protecting patient rights, implementing care and treatment, ensuring the safety of the patient, advocating and implementing the right thing for the patient (Ardahan, 2003; Ozer et al., 2009; Erzincanli & Zaybak, 2015). Therefore, nurses have obtained the identity of being a health professional being a guide of the patients to know and acquire their rights. Patients who can not choose the best for themselves, often do not have knowledge of their rights therefore they need the help of a nurse who can guide them on how to obtain these rights. Nurses have more interactions with patients than other health care team members. For this reason, it is very important that nurses have enough information about the subject and can apply this knowledge in practice (Teke et al., 2007, Zaybak et al., 2012, Ozakar-Akca et al., 2015, Oztas & İyigun, 2016). The sensitivity of nurses to patient rights also positively affects the satisfaction levels of patients in the institution (Tanriverdi & Ozmen 2011; Erzincanli & Zaybak, 2015).

It is the ethical responsibility of nurses to undertake the role of patient advocacy in this period because the individuals/patients undergoing surgical intervention experience anesthesia and sedation. In surgical departments in which invasive procedures are mostly performed, it is also important to obtain the patient's informed consent, the nurse has the ethical responsibility to obtain the informed consent after understanding of the operation by the patient (Karaoz, 2000; Temiz et al., 2017). In the study of Ozer et al., (2009) which investigated the knowledge levels of patients treated in surgical clinics, it was reported that the mean knowledge scores of the patients was 11.67 ± 3.32 on a 17 point scale, 86.1% of the patients did not receive information about patient rights during hospitalization, the patients stated that the highest importance was given to the right of having a hospital attendant and while the lowest importance was given to the right of requesting information about their health status verbally and by writing in the services in which they stayed.

Within the scope of ethical principles, securing confidentiality of patients is also among the responsibilities of nurses when patients are not able to protect their own privacy due to their state of consciousness during the surgical preparation period, during the procedure, and in the postanesthesia care unit (Karaoz, 2000; Tumer et al., 2011; 2017). It was determined that most of the studies related to the subject analyzed the level of knowledge of the medical staff (Teke et al., 2007; Zincir & Kaya 2009; Kavak et al., 2014; Khalaf et al., 2014; Ozakar-Akca et al., 2015) and the patients (Ozer et al., 2012; Erzincanli & Zaybak 2015; Oztas &

İyigun 2016) about patient rights. Therefore, this study was designed and carried out in order to determine the sensitivity of the nurses working in surgical units to patient rights because of lack of the studies on the sensitivity of nurses working in surgical units about patient rights. For this purpose, three questions below were asked

- What are the knowledge levels of the surgical nurses about patient rights?
- How is the surgical nurses' sensitivity to patient rights?
- Is there any difference between personal and occupational characteristics of surgical nurses and sensitivity to patient rights?

MATERIALS AND METHODS

Universe and Sample of the Study

The study was planned as a descriptive and cross-sectional study and was carried out between July-October 2010. The universe of the study consisted of 61 nurses working in the surgical clinics of a state university. No sample selection criteria were used, 54 nurses who agreed to participate in the study were included in the study.

Data Collection

The research data were collected with the personal information form and the Belief of Patient Rights Form (BPRF). In the personal information form, the information such as age, gender, marital status, education status, duration of study, education about patient rights, meeting with the patient rights concept, having a problem related with patient rights and the presence of a unit related to patient rights in the institution where the nurse works are included.

The BPRF is a 5-point liker-type scale that consists of 6 sub-dimensions (human rights and values in health care services, informing, approval, privacy and private life and application) and 18 questions determining the views of nurses on their beliefs about patient rights. The participants in the study were asked to mark one of the following expressions: "absolutely agree", "I agree", "I slightly agree", "I disagree", "I absolutely disagree". In the evaluation of the form, 1 point was given for the answer "Absolutely Agree", 2 points was given for the answer "Agree", 3 points was given for the answer "Slightly Agree", 4 points was given for the answer "Disagree" and 5 points was given for the answer "Absolutely disagree". The lowest possible score is 18 while the highest possible score is 90. Low scores indicate high agreement on patient rights (high sensitivity), and high scores indicate low agreement on patient rights (low sensitivity).

Statistical Analysis

The data were analyzed by SPSS 20 package program. Mann Whitney U and Kruskal Wallis-H tests were used because the data did not fit normal distribution. $p < 0.05$ was considered as statistically significant.

Ethical Statement

The written permission was obtained from the Hospital Directorate. Participants were informed about the aim of the study; A verbal permission was obtained from each participant who voluntarily participated in the study. Participants were reassured about the confidentiality of their information; they were informed about the aim and scope of the study.

Limits of the Study

The study was conducted with the surgical nurses in a state hospital, this may be accepted as a limitedness of the study in terms of generalizability.

RESULTS AND DISCUSSION

The study was conducted to determine the sensitivity of surgical nurses to patient rights; the results were interpreted and discussed below. No study was found to analyze the sensitivity of surgical nurses to patient rights as a result of that some difficulties were experienced in the discussion of our findings.

It was found that 40.7% of the nurses were between the ages of 30-34, 94.4% of them were female; 72.2% of them were married; 51.9% of them had an associate's degree; 31.5% of them started to work 11-15 years before. The findings on the personal and professional characteristics of the nurses were similar to the findings of Zincir & Kaya (2009), Kavak et al., (2014).

Table 2 shows where the nurses first met with the concept of patient rights, the status for taking a training about patient rights and having a problem about patient rights and the presence of the patient rights unit at the hospital. Accordingly, it was determined that 55.6% of the participant nurses met the concept of patient rights for the first time in the hospital. The patient rights need to be known and implemented by every health care staff in order to increase the quality of the service provided in the field of health, to prevent patient rights violations both morally and legally and to increase the satisfaction level of the patients by meeting their expectations (Tanrıverdi &, Özmen 2011; Öztas &, İyigün 2016). Similarly, Ozakar-Akca et al., (2015) also found that 75.9% of nurses heard the concept of patient rights in the hospital for the first time; Teke et al., (2007) found that 64.2% of nurses met patient rights by using out of school sources. This condition suggests that nurses who are very close to the patients and who spend most of their daily working time with the patients do not learn enough information about patient rights in school education and practices.

Table 1. The frequency distribution related with the personal and professional characteristics of the nurses (n = 54)

Characteristics		n	%
Age	≤29	17	31,5
	30-34	22	40,7
	≥35	15	27,8
Gender	Female	51	94,4
	Male	3	5,6
Marital status	Married	39	72,2
	Single	15	27,8
Educational status	HS/VHS	16	29,6
	Associate Degree	28	51,9
	Bachelor	10	18,5
Working time	0-5 years	15	27,8
	6-10 years	13	24,1
	11-15 years	17	31,5
	≥16 years	9	16,6
Total		54	100,0

HS: High School; VHS: Vocational High School.

Table 2. Distribution of the nurses' knowledge on patient rights (n = 54)

Knowledge about patient rights		n	%
The place for meeting the concept of patient rights for the first time	Not meet	1	1,9
	Book, brochure	2	3,6
	TV	3	5,6
	Symposium, conference	6	11,1
	School	12	22,2
	Hospital	30	55,6
The status for getting training on patient rights	Yes	42	77,8
	No	12	22,2
The status for experiencing a problem related with patient rights	Yes	17	31,5
	No	37	68,5
The presence of the patient rights unit in the hospital	Yes	50	92,6
	No	4	7,4
Total		54	100,0

It was determined that 77.8% of the participant nurses received education on patient rights. There is a close relationship between the essential values that constitute the nursing profession (Karaoz, 2000; Acaroglu, 2014) and the values that constitute patient rights (Patient Rights Regulation 1998). For providing ethical based care, the required importance should be given to teach care philosophy and care behaviors to them during their education period. According to Karaoz (2000), Kurtz & Wang (1991), educators, researchers and managers should collaborate in order to achieve this goal. 48.7% of the nurses got education on patient rights in the study of Savaskan (2006); 55% of the nurses got education on patient rights in the study of Teke et al., (2007); 47.2% of the nurses got education on patient rights in the study of Kavak et al., (2014); 92.3% of the nurses got education on patient rights in the study of Ozakar Akca et al., (2015). The studies have shown that health staff generally have information about the application of patient rights. According to the findings of our study and other studies (Teke et al., 2007; Kavak et al., 2014), it can be stated that the majority of nurses who got education on patient rights did not constitute the majority of educated nurses;

more importance should be given to the education about patient rights before and after the education.

In the study, it was determined that 68.5% of the nurses did not encounter a problem about patient rights while 31.5% of them encountered a problem. It is known that patients undergo extreme stress and need help from someone else to cope with this stress, from hospital application to discharge. Nurses are the most important health staff that can help patients by giving explanatory information about what to do in the treatment process. In this context, the nurses fulfill their own responsibilities by protecting the rights of the patient or by helping the protection of patient rights (Teke et al., 2007, Ozakar-Akca et al., Similarly, Ozakar-Akca et al., (2015) found that 43.8% of the nurses encountered a problem about patient rights while Teke et al., (2007) found that 18.3% of them encountered a problem about patient rights. It is remarkable that nurses who have the most interaction with patients in healthcare and who have an important role in advocating patient rights, encounter problems with patient rights at the rate of 18% to 44%. Patient rights are the rights that hospital management, patients and health professionals should protect together for a healthier care environment (Karaoz, 2000; Ozer et al., 2009; Erzincanlı & Zaybak 2015). We suggest that the intensification of educational programs, including patients-patient relatives and healthcare staff, will result in a positive change in behavior for resolving the problems related to patient rights and ensuring a healthier, more satisfying care environment. The patient rights related problems being encountered by nurses in practice is a different research subject.

In this study, it was determined that 92.6% of the nurses stated that there was a patient rights unit in the hospital. The Patient Rights Unit is a unit that is responsible for the training of health staff and patients about patients 'rights (Patients' Rights Regulation 1998), which accepts applications to prevent violations related with patient rights, provides solutions to urgent problems and informs a higher unit. Contrarily, 65.2% of the nurses stated that they did not have a board protecting the patient rights in the institution while 26.6% of the nurses stated that there was no information about the presence of the institution according to the findings of Savaşkan (2007). High awareness of the nurses about the presence of the patient rights unit in the hospital is a positive result for us.

Table 3. Distribution of the scores of the nurses on the overall BRPF scale and its subscales

Subscales	n	Mean	SD	Med	Min - Max
Human rights and values in health services	54	4,33	1,39	4	3 - 7
Informing	54	4,94	1,47	5	3 - 8
Consent	54	5,89	1,7	6	3 - 9
Privacy and private life	54	4,41	1,22	4	3 - 6
Care and treatment	54	6,13	1,52	6	3 - 11
Application	54	7,15	1,95	7	3 - 12
Total	54	32,85	6,66	34	19 - 47

Med.: Median; Min.: Minimum; Max.: Maximum; SD: Standard Deviation.

When the mean scores of the nurses on the overall BRPF and all subscales of it were analyzed (Table 3), the mean score of the nurses on the subscale of human rights and values in health services was 4.33 ± 1.39 ; the mean score of the nurses on the subscale of informing was 4.94 ± 1.47 ; the mean score of the nurses on the subscale of consent was 5.89 ± 1.7 ; the

mean score of the nurses on the subscale of care and treatment was 6.13 ± 1.52 ; the mean score of the nurses on the subscale of application was 15 ± 1.95 ; the mean total score of the nurses on the BRPF scale was 32.85 ± 6.66 . The scores can be obtained from the BRPF Scale varies between 18 and 90, therefore it can be said that the mean score of the nurses on the BRPF Scale was low. This result indicates that the sensitivity of the nurses to patient rights was high and the result was at the desired level.

Table 4. Distribution of the scores of the nurses on the overall BRPF scale and its subscales according to their ages

Subscales		Age					KW H Test	
		n	Mean	SD	Med	Min - Max	H	p
Human rights and values in health services	≤29 years	17	4,06	1,39	3	3 - 6	1,22	0,542
	30-34 years	22	4,36	1,33	4	3 - 6		
	≥35 years	15	4,6	1,5	5	3 - 7		
Informing	≤29 years	17	4,47	1,46	5	3 - 8	4,28	0,117
	30-34 years	22	5,0	1,6	6	3 - 8		
	≥35 years	15	5,4	1,18	6	3 - 8		
Consent	≤29 years	17	5,29	1,72	5	3 - 9	3,52	0,172
	30-34 years	22	6,14	1,78	6	3 - 9		
	≥35 years	15	6,2	1,47	6	3 - 8		
Privacy and private life	≤29 years	17	3,76	1,15	3	3 - 6	7,89	0,019*
	30-34 years	22	4,59	1,22	4	3 - 6		
	≥35 years	15	4,87	1,06	5	3 - 6		
Care and treatment	≤29 years	17	5,71	2,11	6	3 - 11	2,33	0,312
	30-34 years	22	6,27	1,28	6	4 - 9		
	≥35 years	15	6,4	0,91	6	5 - 8		
Application	≤29 years	17	6,12	2,18	5	3 - 10	6,84	0,033*
	30-34 years	22	7,55	1,41	8	5 - 10		
	≥35 years	15	7,73	2,02	8	5 - 12		
Total	≤29 years	17	29,41	7,44	26	19 - 47	7,18	0,028*
	30-34 years	22	33,91	6,18	34	24 - 44		
	≥35 years	15	35,2	5,05	36	22 - 42		

*p < 0,05; Med.: Median; Min.: Minimum; Max.: Maximum; SD: Standard Deviation; KW: Kruskal Wallis.

In Turkey, the most important regulation on patient rights is the Patient Right Regulation, it was published in the Turkish Official Gazette (No. 23420) at 1 August 1998. This ordinance is an important document that directly and perceptibly regulates patient rights in Turkey. In the Patient Rights Regulation, the rights such as “benefiting from health services, asking for information, choosing and changing the health institution, appropriate diagnosis in compliance with medical requirements, treatment, requesting respect for privacy, not being subjected to medical applications without consent, requesting confidentiality of information, refusing the treatment” (Patient Rights Regulation 1998: 23420). The result of this study related with the mean total score of the nurses on the BRPF Scale was similar to the results of Savaskan (2006); this result suggested that the nurses provided care for the essential principles that constitute patient rights.

In Table 4, there was not a statistically significant difference between the scores of the nurses on the ‘human rights and values in health services’, ‘informing’, ‘consent’, ‘care and treatment’ subscales according age groups ($p > 0.05$). There were statistically significant differences between the scores of the nurses on the ‘privacy’ and ‘private life’, application

subscales and overall scale ($p < 0.05$). In general, the nurses with the ages of 29 years or younger had lower scores on the overall BRPF and all subscales; they had higher sensitivity to patient rights. The studies comparing the sensitivity of the nurses to patient rights according to age groups, have found different results. There was no statistically significant difference between the nurses' sensitivity to patient rights according to age groups ($p > 0.05$) in the study of Savaskan (2006) and Kavak et al., (2014). In the study of Zincir & Kaya (2009), it was reported some similar which are similar to our results, the mean knowledge level of the health workers with the ages of 29 or younger was significantly higher than the others in the older age group ($p < 0.05$). In addition, Khalaf et al., (2014) analyzed the knowledge and attitudes of health care staff about patient rights. It was found that slightly more than one third of the participants (36%) knew patient rights (40.4% of the doctors, 34.2% of the nurses); it was reported that the rights of having 'a good care and management' and 'privacy and confidentiality' were the best known rights. In this study, the nurses aged 29 years or younger had higher mean scores compared to older age group. The reason is thought to be the fact that the patient rights regulation that went in effect in 1998 and after that year this regulation started to be taught as a course in pre-graduation education. Moreover, it can be suggested that the nurses in the young age group are more likely to adopt these rights by considering the fact that the significant differences were found for the subscales of 'privacy and private life' and application'.

There was no statistically significantly difference but the scores of the nurses that with a bachelor's degree were lower on the overall BRPF and it's subscales as 'human rights and values in health services', 'informing', 'privacy and private life', 'care and treatment', 'application' subscales compared to the nurses with an associate's degree ($p > 0.05$). A statistically significant difference was found between the scores of the nurses on the consent subscale according to their educational status ($p < 0.05$, Table 5). It was observed that the mean score of the nurses having a bachelor degree on the 'consent' subscale was significantly lower compared to the nurses having an associate's degree. The nurses with a bachelor degree were generally more sensitive to patient rights. It is a legal and ethical obligation to obtain verbal and written consent from the patient or his/her relatives prior to the initiation of any surgical procedure to be applied to the patient (the Patient Rights Regulation 1998). In the study of Kavak et al., (2014), there was a statistically significant difference between the scores of the nurses on the consent subscale according to their education status ($p < 0.05$); it was found that the nurses who graduated from a health vocational high school had significantly higher knowledge level on patient consent. In the study of Zincir & Kaya (2009), there was a significant correlation between the nurses' educational status and their knowledge scores ($p < 0.05$); it was stated that the nurses having a bachelor or postgraduate degree known patient rights better than the nurses having a high school diploma and an associate's degree. Although it was determined that there were a study (Zincir & Kaya, 2009) having similar results and a study having different results (Kavak et al., 2014), the results showed that the nurses with a bachelor's degree had higher sensitivity to patient rights. In addition, the sensitivity of the nurses having a bachelor degree to patients' right of 'approval' was higher so we suggest that the nurses having a bachelor degree adopt and take care this right more.

There was no statistically significant difference between the mean scores of the nurses on the overall BRPF Scale and its all subscales according to their working time, the nurses having < 5 working years had a lower mean overall BRPF score; their sensitivity to patient rights was higher. Our results are similar to the results of the study of Savaskan (2006) in which there was no significant difference between the nurses' beliefs about patient rights according to their working years. Savaskan, (2006) stated that the nurses having < 5 working years had a lower mean overall BRPF score. In conclusion, it can be suggested that more place has been given to patient right in the curricula in the recent time because patient rights has been a topical issue, this condition may increase nurses' sensitivity to patient rights; increasing working years cause a decrease in the willingness of nurses to follow innovations.

There was no statistically significant difference between the mean scores of the nurses on the overall BRPF scale and its subscales according to their status for patient rights education ($p > 0.05$, Table 7). The nurses who got education about patient rights, had lower scores on the subscales of 'human rights and values in health services', 'informing', 'consent', 'care and treatment' and 'application', the nurses who got education were generally more sensitive to patient rights. Teke et al., (2007) showed that there was no statistically significant correlation between the nurses' education status about patient rights and their mean knowledge and attitude scores related to patient rights ($p > 0.05$). It can be suggested that nurses who are educated about patient rights are more sensitive.

Table 5. Distribution of the scores of the nurses on the overall BRPF scale and its subscales according to their education status

BRPF Subscales		Education Status					KW H Test	
		n	Mean	SD	Med	Min - Max	H	p
Human Rights and Values in Health Services	HS/VHS graduate	16	4,69	1,4	5	3 - 6	3,73	0,155
	Associate's Degree	28	4,39	1,42	4	3 - 7		
	Bachelor Degree	10	3,6	1,07	3	3 - 6		
Informing	HS/VHS graduate	16	5,06	1,61	5,5	3 - 8	0,57	0,753
	Associate's Degree	28	5,0	1,44	5	3 - 8		
	Bachelor Degree	10	4,6	1,43	5	3 - 6		
Consent	HS/VHS graduate	16	5,56	1,59	6	3 - 8	8,99	0,011*
	Associate's Degree	28	6,5	1,4	6	3 - 9		
	Bachelor Degree	10	4,7	2	4	3 - 9		
Privacy and Private Life	HS/VHS graduate	16	4,5	1,26	4,5	3 - 6	2,31	0,315
	Associate's Degree	28	4,54	1,17	4,5	3 - 6		
	Bachelor Degree	10	3,9	1,29	3	3 - 6		
Care and Treatment	HS/VHS graduate	16	6,63	1,59	6	4 - 11	3,84	0,146
	Associate's Degree	28	6,14	1,38	6	3 - 9		
	Bachelor Degree	10	5,3	1,57	5,5	3 - 8		
Consent	HS/VHS graduate	16	7,13	2,55	6,5	3 - 12	0,51	0,775
	HS/VHS graduate	28	7,25	1,67	7,5	3 - 11		
	Associate's Degree	10	6,9	1,73	7	5 - 10		
Total	Bachelor Degree	16	33,56	8,09	33,5	19 - 47	4,12	0,127
	HS/VHS graduate	28	33,82	5,21	34	24 - 42		
	Associate's Degree	10	29,0	7,12	25	22 - 40		

* $p < 0,05$; HS: High School; VHS: Vocational High School; Med.: Median; Min.: Minimum; Max.: Maximum; SD: Standard Deviation; KW: Kruskal Wallis.

Table 6. Distribution of the scores of the nurses on the overall BRPF scale and its subscales according to their working years

BRPF Subscales		n	Working Years				KW H Test	
			Mean	SD	Med	Min - Max	H	p
Human rights and values in health services	0-5 years	16	4,0	1,32	3	3 - 6	3,985	0,263
	6-10 years	13	4,38	1,33	4	3 - 6		
	11-15 years	16	4,19	1,42	3	3 - 6		
	≥16 years	9	5,11	1,45	6	3 - 7		
Informing	0-5 years	16	4,63	1,5	5	3 - 8	4,152	0,245
	6-10 years	13	4,54	1,51	4	3 - 7		
	11-15 years	16	5,38	1,54	6	3 - 8		
	≥16 years	9	5,33	1,12	6	3 - 6		
Consent	0-5 years	16	5,06	1,61	5	3 - 8	5,736	0,125
	6-10 years	13	6,54	1,85	6	3 - 9		
	11-15 years	16	6,06	1,61	6	3 - 9		
	≥16 years	9	6,11	1,45	6	3 - 8		
Privacy and private life	0-5 years	16	3,88	1,15	3	3 - 6	7,6	0,055
	6-10 years	13	4,15	1,21	4	3 - 6		
	11-15 years	16	4,81	1,11	5	3 - 6		
	≥16 years	9	5,0	1,22	5	3 - 6		
Care and treatment	0-5 years	16	6,19	1,87	6	3 - 11	1,733	0,63
	6-10 years	13	5,69	1,89	6	3 - 9		
	11-15 years	16	6,44	1,15	6	5 - 8		
	≥16 years	9	6,11	0,6	6	5 - 7		
Application	0-5 years	16	6,69	1,89	6,5	4 - 10	4,78	0,189
	6-10 years	13	6,69	2,32	7	3 - 10		
	11-15 years	16	8,06	1,81	8	6 - 12		
	≥16 years	9	7,0	1,32	7	5 - 9		
Total	0-5 years	16	30,44	6,97	28	23 - 47	4,981	0,173
	6-10 years	13	32,0	7,98	32	19 - 44		
	11-15 years	16	34,94	5,26	36	25 - 42		
	≥16 years	9	34,67	5,52	37	22 - 40		

*p < 0,05; Med.: Median; Min.: Minimum; Max.: Maximum; SD: Standard Deviation; KW: Kruskal Wallis.

Table 7. Distribution of the scores of the nurses on the overall BRPF scale and its subscales according to their education status about patient rights

BRPF Subscales		n	Education Status about Patient Rights				MW U Test	
			Mean	SD	Med	Min - Max	z	p
Human rights and values in health services	Yes	42	4,31	1,37	4	3 - 7	-0,14	0,885
	No	12	4,42	1,51	4	3 - 6		
Informing	Yes	42	4,76	1,38	5	3 - 8	-1,57	0,116
	No	12	5,58	1,68	6	3 - 8		
Consent	Yes	42	5,67	1,73	6	3 - 9	-1,79	0,073
	No	12	6,67	1,37	6	4 - 9		
Privacy and private life	Yes	42	4,48	1,23	5	3 - 6	-0,67	0,503
	No	12	4,17	1,19	4	3 - 6		
Care and treatment	Yes	42	6,02	1,39	6	3 - 9	-0,78	0,438
	No	12	6,5	1,93	7	4 - 11		
Application	Yes	42	6,88	1,93	7	3 - 12	-1,82	0,068
	No	12	8,08	1,78	8	6 - 11		
Total	Yes	42	32,12	6,71	33	19 - 44	-1,23	0,219
	No	12	35,42	6,08	35,5	24 - 47		

*p < 0,05; Med.: Median; Min.: Minimum; Max.: Maximum; SD: Standard Deviation; MW: Mann Whitney.

CONCLUSION

The sensitivity of the nurses in surgical services to patient rights was high; it was determined that the nurses who were at the ages of 29 or younger, undergraduates, worked 1-5 years and got educated about patient rights, had higher levels of patient rights sensitivity. According to these results, more time should be allocated for this subject in the curricula before the graduation and training programs should be planned for nurses after graduation according to their age groups, working years, their status for getting the education on patient rights, for raising the awareness of nurses about the sensitivity to patient rights, for knowing the problems related with patient rights, for providing solution. The effect of provided education on the knowledge, attitudes and behaviors of nurses should be monitored. It may also be beneficial to conduct further studies in larger groups, including other members of the healthcare team, for determining the different factors that can affect the sensitivities of surgical nurses to patient rights.

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Chapter 281

CONTROL AND ERADICATION OF ANIMAL BRUCELLOSIS

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ABSTRACT

Brucella spp. causes brucellosis, which is one of the most common zoonotic diseases and which brings about important problems related to health and economy. Direct or indirect contact with infected animals or their products is the main way of transmission of the infection. If brucellosis in animal reservoirs can be controlled, it will be easier to see a decline in the incidence of human brucellosis as well. The primary means of fight against animal brucellosis includes test-and-slaughter programs, routine screening, and control of animal movement, hygiene, herd management, and vaccination. In many countries, achieved success in control and eradication of brucellosis has a governmental regulation/legislation background. Control and eradication require effective collaboration between veterinarians and all the sectors of public health. The aim of this chapter is to reveal general aspects of control and eradication of this disease and it specifically gives information about the case in Turkey.

Keywords: brucellosis, control, eradication, vaccine, vaccination

INTRODUCTION

Almost 2/3 of human pathogens are zoonotic and more strikingly, ¾ of emerging and re-emerging diseases in humans are also zoonoses (Godfroid et al., 2013). Some precautions against specific zoonoses and zoonotic agents in animals and animal products used to prevent outbreaks of food-borne infections and intoxications have been revealed by the European

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Union (EU) through some specific regulations (Council Directive 92/117/EEC). Problems related to brucellosis clearly illustrate the need for a ‘One World, One Health’ strategy because if the public and animal health authorities work together, control and subsequent eradication of the disease could be achieved (Perez-Sancho et al., 2015). The term ‘eradication,’ in veterinary medicine, means eliminating an infectious agent and up to now very few diseases have been eradicated. On the other hand, ‘control of a zoonotic disease,’ refers to all the measures taken in order to decrease the incidence and prevalence of the disease in an animal population (Minas, 2006).

The control of animal brucellosis has been successfully implemented with the help of the combination of vaccination and test-and-slaughter programs in the developed countries. They also succeeded in controlling human brucellosis via milk pasteurization in combination with effective surveillance of the disease and the control of animal movement. (McDermott & Arimi, 2002; Pappas et al., 2006). For this reason, it has been recommended that communities’ needs and perceptions should be included in any disease control strategies (Marcotty et al., 2009). For any strategy used for controlling and eradicating brucellosis to be effective, it is necessary for farmers to support the process and collaborate with other stakeholders (Ragan, 2002). It is also necessary for the sectors of public health and veterinarians to collaborate (Yumuk & O’Callaghan 2012).

CONTROL AND ERADICATION

Decreasing the prevalence and incidence will lead to minimal effects on human health and regional economy. For brucellosis, the control measures taken should include monitoring brucellosis-free flocks and preventing the spread of the infection, reducing the rate of infection, and making animals more resistant (Minas, 2006). According to OIE, there are some specific requirements for a country/zone to be considered as free from brucellosis (Resmi Gazete, 2009; Perez-Sancho et al., 2015):

- Bovine brucellosis should be declared as notifiable
- An official veterinary control system including the whole bovine population should be established
- The flock prevalence of the disease should be lower than 0.2%
- There should not be any vaccination that has been conducted in the last three years
- All flocks should be subject to periodical serological testing
- All reactors should be culled
- New animals should be introduced to the regions which are parts of officially brucellosis-free herds

In order for an eradication program of brucellosis to be implemented, flocks should be under strict surveillance and movement control, individual identification of animals should be supplied and veterinary service, which is effective and well organized, should be adopted for surveillance and laboratory testing in place (Minas, 2006). When choosing the best approach to deal with the disease, the prevalence of animal brucellosis should not be considered as the only parameter by the decision makers because in order to use the most sufficient control

strategy in each region, other epidemiological and economic aspects should also be taken into consideration (Perez-Sancho et al., 2015).

Even if all the tools to be used to eradicate the disease are existent in eradication and control program, adequate surveillance is a critical first step (Ragan, 2002; Yumuk & O'Callaghan, 2012). Permanent identification of animals is a fundamental element in a successful surveillance program (Ragan, 2002). After the initial phase, where the infection is controlled through obligatory vaccination, vaccination is restrained step by step and it is eventually banned; however, in order to eradicate the infection, a 'test-and-slaughter' policy is carried out (Godfroid et al., 2013).

The most influential strategies used to control this pathology in livestock include strict biosafety, management precautions and test-and-slaughter strategy. There are 3 main strategies which are used in brucellosis control of domestic animals: hygienic measures, test-and-slaughter programs, immunization. As optimal results are gathered through using at least two of them together, the use of only one of these measures is not effective enough (Nicoletti, 2010). To be able to be successful in the program, which includes animal identification, animal movement control, economic compensations, and other complimentary tools should also be added to these already-known strategies (Crespo et al., 2012).

In terms of biosafety and management, what is necessary includes both finding the disease and eliminating it and also doing it before it reaches susceptible herds. If there is success in identification, control and eradication of the disease before it spreads, then it is possible for eradication to be achieved. Understanding of the epidemiology and pathogenesis of brucellosis in eradication is a very important step (Ragan, 2002). Precautions of hygiene and management against brucellosis must emphasize decreasing the possibility of contact with viable *brucella* which includes animals that are infected and contaminated environments. For this reason, in order to prevent the disease from entering in an epidemiological unit, suitable biosecurity precautions should be taken. Hygiene precautions are used to decrease the possibility of contact with viable bacteria and they are also used to control and constrain the bacterial load in the environment. (Perez-Sancho et al., 2015).

It is believed that the existence of the disease in wild animals depends on its existence in domestic animals. The point of connection is that fact that aborted foetuses and foetal membranes are carried by carnivores and it also causes the disease to spread to domestic herds and pastures which are free from brucellosis (Thimm, 1982). Only if infected animals' prevalence is 2% or less, the flocks are kept in a strictly controlled environment and they are protected from the re-entry of infection is it possible for an eradication program including a test-and-slaughter policy to be implemented on the related economic grounds (Minas 2006, Yumuk & O'Callaghan, 2012).

The main objective of the test-and-slaughter approach is detecting and removing possible sources of infection, which will automatically prevent the circulation of *brucella* strains. Because of the silent carriers that are keeping the pathogen in the flock, there might be abortion storms if the immunity of the herd decreases. This strategy seems most useful when there are necessary economic resources and veterinary expertise in places where the prevalence of the disease is low (Perez-Sancho et al., 2015).

Despite the fact that the counter actions against brucellosis in small ruminants have been characterized well, socio-economic factors affect the selection of the most appropriate control measures in most endemic areas. For instance, because pastoral ecosystems, which are traditional ways of management used in low-income areas in which *B. melitensis* is endemic,

have led to the continuation of the disease as it is difficult to detect the disease in the early stages and to take necessary control precautions (Perez-Sancho et al., 2015). It was stated that it is possible to implement eradication through a test-and-slaughter policy if sheep and goats are controlled strictly and the type of husbandry is not extensive and grazing of herds is not common (Minas, 2006).

It must also be taken into consideration that the tests used in diagnosis cannot detect all infected animals and they might give false negative results because of the period of incubation, latency or the criteria that are considered for the interpretation of the results (Minas, 2006). For this reason, for the success of the test-control strategies used in the eradication programs, the certainty of the approval of laboratories and diagnostic tests are mentioned as the important factors (Perez-Sancho et al., 2015; Ragan, 2002). For instance, it is stated that the silent carriers of the disease, which are the infants infected congenitally in utero or through the ingestion of contaminated milk or colostrum, may still be seronegative by the time a problem in their reproductivity appears (Perez-Sancho et al., 2015). Therefore, it is necessary to integrate laboratory testing with epidemiological investigation in order to overcome false-positive findings of laboratories as *Brucella* bacteria might be used as potential bioterror agents (Godfroid et al., 2005).

In the case of bioterrorism, it is very important to differentiate between true brucellosis and other diseases which appear in the differential diagnosis of brucellosis. Among these are infections which appear because of cross-reactive bacteria in the serology of brucellosis, such as YO9 (Gourdon et al., 1999). It was stated that there might be the possibility of having laboratory-acquired infections due to the inhalation of infective aerosols which are produced accidentally by microbiological techniques. Thus, it is necessary to utilize biosafety level 3 cabinets in the laboratories which include work related to *Brucella* spp. (Godfroid et al., 2005).

At present, trading takes place between countries which are 'officially free from brucellosis'. Alternatively, the herds/flocks, which are brucellosis-free, might also be preferred for trading. But, there are also some other possibilities; namely, traded animals might be recently infected but the infection might not have been detected yet, they might be infected during transportation or when they are together with other animals at market places. It shows that tests which are recommended for trading can detect acute infections in animals. It must also be taken into account that the only diagnosis of certainty is bacteriology (Godfroid et al., 2013).

Generally, endemic regions are defined as the ones that are structurally weak and the ones which might become worse as proficient veterinary service requires the use of current vaccines effectively. This requirement relates in part to some of the limitations of currently available brucellosis vaccines, and it seems likely that a perfect vaccine could greatly facilitate control and eradication (Godfroid et al., 2011). It was stated that if the population's resistance to disease could be increased with the help of vaccination, it could be possible to control brucellosis. For this reason, vaccination is regarded as more acceptable and efficient when compared to other methods used for this purpose. Moreover, depending upon the vaccines' practical use to eliminate the clinical signs of brucellosis, the environment would be less contaminated and the population's risk to the infection's agent would decrease (Minas, 2006).

TREATMENT

Winning the fight against human brucellosis depends upon the control and eradication of animal brucellosis (Boschioli et al., 2001; Corbel, 1997; Godfroid et al., 2005). Control and prevention are significant for animals; when it comes to humans, treatment gains more importance. Brucellosis is mentioned as ‘cattle brucellosis’ and ‘sheep-goat brucellosis’ in notifiable animal diseases list of ‘the Regulation of Reporting of Notifiable Animal Diseases’ (Resmi Gazete, 2011). As stated in the *Regulation of Fighting Brucellosis*, it is obligatory to notify the authorities in the case of the existence or the suspicion of brucellosis in cattle, sheep and goats. In the same regulation, it is also pointed out that it is prohibited to take action to treat brucellosis in cattle, sheep and goats (Resmi Gazete, 2009).

Antibiotics have been utilized with success in the treatment of some dogs affected by *B. canis*. Even though it is required to use two different antibiotics simultaneously, the use of only enrofloxacin seemed to be successful in one case. It has also been stated that no treatment has proved to be successful to eliminate *B. canis*. The organism of the disease might appear to have disappeared but it is possible for it to reappear in tissues such as lymph nodes, spleen, uterus and prostate (CFSPH, 2012). In a study by Wanke et al. (2006), enrofloxacin could not effectively treat canine brucellosis but it could help them remain fertile and it also prevented them from aborting and infecting the puppies and spreading the microorganisms during parturition.

When it comes to humans, as *Brucella* bacteria can adapt to the environmental conditions that are met during their replicative niche (Seleem et al., 2008) and their intracellular localization, the rates of treatment failure and relapse are high and they are changeable depending on the combination of drugs and the compliance of patients (Seleem et al., 2010). Because it is highly probable for monotherapies with single antibiotics to relapse, the best treatment for brucellosis is using a combination of two antibiotics. The best option, especially for the acute brucellosis cases, seems to be utilizing doxycycline in combination with streptomycin (DS) as it leads to fewer side effects and relapses (Matthew & Leland, 2004; Seleem et al., 2010). World Health Organization (WHO) has regarded DS combination as the standard treatment against brucellosis for years. In 1986, joint FAO/WHO committee suggested using doxycycline and rifampin (DR) together for 6 weeks for the treatment of adult acute brucellosis (WHO, 1986). However, the studies comparing and contrasting the effects of DR with traditional DS found out that DR, particularly in patients suffering from acute brucellosis, is not as effective as DS (Solera et al., 1997).

If the treatment is inadequate, severe and debilitating chronic courses and long-term sequelae may appear. For this reason, the most important aim is two-folded: controlling acute illness and preventing some possible complications and relapses. In the treatment, utilizing at least two synergistic antibiotics, including doxycycline, rifampin, streptomycin (or other aminoglycosides) or trimethoprim-sulfamethoxazol is a necessity for prolonged chemotherapeutic regimens (Godfroid et al., 2011). After the treatment is over, titers will decrease step by step but IgG antibodies decrease faster than IgM antibodies. Even though there is no active infection, in some cases, low tiers of IgM antibodies might persist for months or years (Doganay & Aygen, 2003; Matthew & Leland, 2004). For this reason, measuring IgG is traditionally used to see whether the therapy is effective or not (Matthew & Leland, 2004).

VACCINATION

Immunization against agents of infection has become a key element in the process of controlling the most significant infectious diseases since Eduard Jenner's description of first vaccine against smallpox in 1796 (Perez-Sancho et al., 2015). The only way to control and eradicate brucellosis is believed to be vaccinating all the hosts which are susceptible and eliminating all of the infected animals in the regions in which the prevalence of the disease is high (Briones et al., 2001).

The most common vaccines which are used against bovine brucellosis are *B. abortus* strain 19 and RB51, which were recently approved by USDA and which do not interfere with serological diagnoses (Moriyon et al., 2004). As can be seen in all highly contagious diseases, the effect of vaccination augments as the coverage of vaccination increases. Only if the vaccine is a high quality one and if it can be administered to at least 80% of the risk-group animals, sufficient protection can be possible (Minas, 2006).

B. abortus S19 and *B. melitensis* Rev1, which are considered to be the best two attenuated vaccines developed in the past century, have both a good degree of residual virulence. Rev1 vaccine is not only used against *B. melitensis* in sheep and goats but also against *B. ovis*. S19 strain has appeared as a result of accidental attenuation, which was due to the long laboratory storage under insufficient conditions and Rev1 strain is a revertant of a streptomycin-dependent mutant with a known ribosomal mutation and possibly other genetic defects (Godfroid et al., 2011). The first step for the eradication of *B. melitensis* infection in the areas, where it is endemic or where the prevalence of the disease is high, is controlling the disease through the vaccination of animals. For small ruminants, the vaccine used is Rev-1 vaccine. An alternative method for brucellosis control, particularly in the endemic areas where the prevalence of the disease is more than 5%, is vaccination of all animals in the flock/herd regardless of their age. There are good results in different areas with sufficient financial resources (Minas, 2006).

There is evidence that Rev1 vaccine is resistant to streptomycin, which is used in the treatment of human brucellosis and S19 vaccine is resistant to penicillin G. In addition, it is stated that RB-51, which was prepared for cattle, has resistance to rifampicin, which is again used against human brucellosis (Grillo et al., 2000). S19 and Rev1 vaccines carry a smooth (S) lipopolysaccharide (S-LPS) and an O-polysaccharide (PS), which is similar to brucellae that are of wild type. In the controlled experiments, only one dose of Rev1 provides 80-100% protection against challenge strains (Barrio et al., 2009).

Rev1 strain is regarded as the reference vaccine to immunize the sheep and goats which are at risk for infection and it needs to be compared and contrasted with other vaccines (OIE, 2009a). The disadvantages of this vaccine include its causing abortion during pregnancy, its interference in serological diagnosis, its virulence for human beings, its resistance to streptomycin and its tendency to dissociate into rough mutants which are ineffective (Godfroid et al., 2011; Seleem et al., 2010). Moreover, because it might be difficult to discriminate the antibody response to vaccination from the ones seen after field infection, they might interfere with control programs. There are still attempts to develop new live attenuated rough vaccines for *B. melitensis*, which are deprived of O-side chain. These vaccines need further evaluation in field experiments (Adone et al., 2008; Blasco, 1997; Garin-Bastuji et al., 1998).

It is possible to partially go beyond these limitations through vaccinating animals conjunctivally when they are younger than 4 months old. It will decrease the amount of interference in serological diagnosis and abortions caused by vaccines. Thanks to a minimal amount of personal protection, Rev1 vaccine becomes safe and there are well-established protocols of quality control (Godfroid et al., 2011). Despite the insufficiency of related studies, it is pointed out that *B. melitensis* in cattle might be controlled with the help of S19 vaccine. All the successful programs in cattle have utilized S19 except for a number of countries with good conditions of geography and management (Godfroid et al., 2011). Thanks to adult vaccination with S19, it is possible to increase herd resistance and to decrease shedding of *B. abortus* at calving or abortion (Ragan, 2002). When animals are younger than 4 months old, conjunctival vaccination including smaller doses will reduce serological interference and udder infections. S19 vaccine used in cattle is both economical and it is not resistant to antibiotics. Even though it is not as virulent as Rev1 for humans, it needs minimum level of individual protection (Godfroid et al., 2011).

Vaccination of both rams and ewes is the most feasible way of providing the control of *B. ovis* in places having a high prevalence of infection because both of them play an important role in the transmission of infection. There is not a certain vaccine against *B. ovis* but live *B. melitensis* strain Rev1 vaccine is appropriate for stimulating immunity against *B. ovis*. It is also possible to use a single dose of Rev1 (10^9 cfu) given subcutaneously or conjunctivally to overcome *B. melitensis* infection (OIE 2015). There is not an existing vaccine for pigs (Godfroid et al., 2011). In China, *B. suis* biovar-2 vaccine is used to immunize pigs but in order to recommend strain 2 vaccine for general use, the results obtained in China should be confirmed (OIE, 2009b).

It is stated that RB51 vaccine might lead to abortions and shedding. Its use should be limited with animals which are not pregnant. RB51 can induce abortions and can be excreted (Moriyon et al., 2004). It is also claimed that RB51 vaccine is more attenuated and as a result, it is considered to be less dangerous than S19 and there are only a few human cases mentioned (Ashford et al., 2004; Godfroid et al., 2011). But for human brucellosis, the number of unreported human cases might be more as the lack of anti-O-PS antibodies makes RB51 difficult to detect in standard laboratory tests. For this reason, it is necessary to keep biosafety practices while utilizing RB51. A further disadvantage of RB51 is the resistance to rifampin since this antibiotic is more preferable than streptomycin or gentamicin for treatment (Godfroid et al., 2011).

There have been several attempts to develop a killed *Brucella* vaccine for human use but so far, they have not been utilized extensively because there is no long-lasting immunity (Matthew & Leland, 2004). There is not an existing vaccine for human brucellosis (Godfroid et al., 2005; Godfroid et al., 2011; Yumuk & O'Callaghan, 2012). Under the WHO global program on vaccination and immunization, priority should be given to the development of such a vaccine (Godfroid et al., 2005).

THE FIGHT AGAINST BRUCELLOSIS IN TURKEY

In Turkey, the first brucellosis case was identified by Husamettin Kural and Mahmut Sabit Akalin in 1915 in a soldier, who was being treated in Istanbul Kuleli Military Hospital

(Celebi, 2003; Cevik, 2001; Golem, 1949; Iyisan et al., 2000). In the Turkish context, the first documented case of brucellosis, which was confirmed by a laboratory was in 1915 despite the fact that it is believed that Florence Nightingale got this disease during the Crimean War in Turkey (Young, 1995; Yumuk & O'Callaghan, 2012). In many regions, pasteurizing fresh milk protects the city population from this disease; however, there is still some risk for people who are in direct contact with infected animals and who consume fresh milk (Kuplulu & Sarimehmetoglu, 2004; Yumuk & O'Callaghan, 2012).

It is stated that the control of the disease is the responsibility of veterinarians as almost all cases of human brucellosis are originated from animals (Nicoletti, 2002; Yumuk & O'Callaghan, 2012). In this context, the precautions against this anthroponozoonosis should include the control and eradication of the disease in the animal reservoir (Thimm, 1982). The initial work on the control and eradication of brucellosis started in 1930 for *Brucella abortus* in cattle. In this sense, the Brucella Laboratory established within Ankara Etlik Institute of Veterinary Bacteriology and Serology moved to the Institute of İstanbul Pendik Veterinary Bacteriology and Serology in 1951. *Brucella melitensis* laboratory was founded in 1965 and later on, the production of *B. melitensis* Rev-1 started in 1969 (GTHB, 2012).

In Turkey, 'National Brucella Control and Eradication Project' was implemented in 1984 by the Ministry of Agriculture and Forestry. For this project, a 26-year-period (1984-2010) was determined and vaccination of calves, labs and ewes was the main aim. (GTHB, 2012; Iyisan 2006). After this project, the authorities tried to find out about the prevalence of the disease in cattle and sheep in 2011 and it was revealed that herd prevalence of brucella in cattle is 7.8% and in sheep it is 22.5% (GTHB, 2012).

Experts in the Ministry evaluated the results of the work carried out in 2011 on the prevalence of Brucellosis and focused on the strategies adopted by the countries to eradicate this disease. They decided that mass vaccination is the most feasible method and they also decided that mass vaccination should be through conjunctival vaccination of animals of all ages. In this context, 'The Project of the Control and Eradication of Brucella through Conjunctival Vaccines' started in 2012 and it is planned to continue for 10 years in cattle, for 6 years in sheep and goats (GTHB, 2012). After this mass vaccination which started in 2012, Brucellosis outbreaks and human cases were evaluated. Except for the vaccine-related abort cases in 2013, there are dramatic decreases in outbreaks and very significant declines in human cases. It is possible to state that the continuation of mass vaccination as well as other control and sanitary measures should be the main approach (Saytekin et al., 2015).

If brucellosis incidence in animal reservoirs is controlled, there can be a related decrease in the incidence of human brucellosis as well. After the long and successful efforts of developed countries which were able to control bovine brucellosis, there was also a visible decrease in the incidence of human infection. Therefore, the eradication of brucellosis can be achieved only if all the parties are involved in the process of finding a solution (Seleem et al., 2010).

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Chapter 282

SMALL RUMINANT MORBILLIVIRUS

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ABSTRACT

Small ruminant morbillivirus (SRM), also known as ‘goat plague’, ‘Kata’, ‘syndrome of stomatitis-pneumoenteritis’ or ‘ovine rinderpest’, is a viral disease of sheep, goats and small wildlife ruminants characterized by fever, sores in the mouth, diarrhea, pneumonia, and sometimes death. The disease is considered to be a major barrier to the development of sustainable agriculture across the developing countries in the world. The global eradication of the disease has been targeted by the World Organisation for Animal Health (OIE) and the Food and Agriculture Organisation (FAO) by 2030. This chapter aims to share current information about the disease.

Keywords: goat, Kata, morbillivirus, peste des petits ruminants virus, sheep

INTRODUCTION

The genus *Morbillivirus* belongs to the virus family *Paramyxoviridae*, contains highly infectious viruses that spread via the respiratory route and causes immune suppression. Because of these features, they have a potential causing large outbreaks associated with high morbidity and mortality in previously unexposed humans and animals. *Small ruminant morbillivirus*, *Rinderpest morbillivirus*, *Canine morbillivirus*, *Newcastle Disease Virus* and *Measles morbillivirus* are some of these viruses. Recently, new morbilliviruses, *Phocine morbillivirus* and *Cetacean morbillivirus*, have been detected in marine mammals (Chauhan et al., 2009).

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Small ruminant morbillivirus (SRM), also named as Peste des Petits Ruminants Virus (PPRV), causes a severe disease, Peste des petits ruminants (PPR), in sheep, goats and small wildlife ruminants. PPR was first described in the Ivory Coast in West Africa (Gargadennec & Lalanne, 1942). The disease has since been recognized as endemic in West and Central Africa (Scott, 1981) and in the north-east of the continent, Kenya and Uganda (Wamwayi et al., 1995), Sudan (Haroun et al., 2002) and Ethiopia (Reoder et al., 1994; Abraham et al., 2005). In 1987, it appeared in the Middle East and has since then been confirmed in Jordan (Lefevre et al., 1991), Pakistan (Amjad et al., 1996), southern India (Nanda et al., 1996), Turkey (Ozkul et al., 2002; Dagalp et al., 2015; Sevik & Sait, 2015). The detection of the disease in Tunisia (Ayari-Fakhfakh et al., 2010), Morocco (FAO, 2009) and Algeria indicates that the infection has reached the border of the European Union (Banyard et al., 2010). Moreover, the detection of the disease in the Thrace region of Turkey in 1996 has led to questioning the potential spread of the disease to other parts of Europe (Ozkul et al., 2002; Banyard et al., 2010). While this article was being prepared, the *World Organisation for Animal Health* (OIE) informed that the disease was detected in Bulgaria for the first time (OIE, 2018).

Etiology

The causal agent, *Small ruminant morbillivirus* (SRM), belongs to the genus *Morbillivirus* in the family *Paramyxoviridae* (Gibbs et al., 1979; Bailey et al., 2005). SRM has single stranded nonsegmented negative sense RNA genome, which encodes six structural proteins: nucleocapsid protein (N), phosphoprotein (P), matrix protein (M), fusion (F) protein, hemagglutinin (H), and polymerase (L) protein. The P gene also encodes two non-structural proteins, C and V, which are thought to function in viral evasion of the host immune responses (Nanda & Baron, 2006). Due to its biological and antigenic properties, it has been closely related to *Rinderpest morbillivirus* and other morbilliviruses (*Canine morbillivirus*, *Measles morbillivirus*, *Phocine morbillivirus* and *Cetacean morbillivirus*) (Gibbs et al., 1979; Baron et al., 2011). Molecular techniques and nucleic acid sequence analysis studies have proven that the SRM is completely separate from the *Rinderpest morbillivirus* (Gopilo, 2005). As a result of molecular epidemiological studies, the SRM has been divided into 4 different genetic lineages according to the F and N gene partial sequence analysis. It has been observed that there are nucleotide changes between SRM isolates in these 4 different genetic lineages that are compatible with the geographical distribution but do not express a separate serotype or strain (Chard, 2008). According to geographical distribution, lineages I and II have been found in West Africa, whereas lineage III has been found in eastern Africa, Arabian Peninsula and southern India. Lineage IV is found in the Middle East, south Asia and China (Dhar et al., 2002; Banyard et al., 2010; Kwiatek et al., 2011). Used as vaccine strains, Nigeria75/1 strain was located in lineage I, and Sungri96 strain was located in lineage IV (Shaila ve ark., 1996; Dhar ve ark., 2002; Muthuchelvan, 2006).

Hosts

SRM is an important pathogen of small ruminants and clinical disease is seen in sheep and goats and has been described in wild small ruminants (Hamdy et al. 1976; Reoder and Obi 1999). However, subclinical infections have been reported in cattle, which formed cross protection against virus (Diop et al. 2005). Buffaloes, camels and pigs may be infected with the virus, but show little or no clinical symptoms (Chauhan et al., 2009). Antibody production against virus was also detected in camels (Roger et al., 2001). SRM could infect wild animals both naturally and experimentally. Antelope and other small wild ruminants including Laristan sheep (*Ovis gmelini laristanica*), Dorcas-type gazelles (*Gazella granti*), gemsbok (*Oryx gazelle*), and the Nubian ibex (*Capra ibex nubiana*) are severely affected by the disease (Hamdy & Dardiri, 1976; Abu Elzein et. al. 2004; Gur & Albayrak, 2010). Balamurugan et al. (2012) reported that the virus obtained from frozen tissue taken from Asian lion (*Panthera leo persica*) belongs to lineage IV according to the partial sequence of N, F and M genes. At the same time, this report was the first report on SRM isolation in Asian lions. The disease does not pose any risk to humans (OIE, 2013).

Transmission

Contagion of SRM from infected to susceptible animals is via by direct contact, close contact and oral routes (Chauhan et al. 2009). Since the virus has lost its viability in the outdoors in a short time, the most important way of transmission is the close contact of the patients in the acute febrile period with the susceptible animals. The aerosol droplets and stools of the infected animals contain high amounts of virus. Small infective droplets spreading to the area, especially by sneezing and coughing, transmit the disease to the susceptible animals through respiration. Besides the close contact, the contaminated bed, feed and water also form an additional source of contamination (Gopilo, 2005). It has been found that viral antigens are scattered in stools until the 11th week after SRM infection (Ezeibe et al., 2008). This suggests that naturally infected animals may pose a significant risk for susceptible populations.

As a current issue, the role of wildlife in the transmission of SRM attracts attention. However, since there is not enough epidemiological data yet, more detailed investigations are needed (Baron et al., 2011).

Clinical Signs

SRM infection is characterized by different clinical patterns ranging from perakut, acute and subacute depending on the various factors such as species and age of the animal, virulence and amount of the virus, secondary infections, etc. (Diallo, 1988; Lefevre ve Diallo, 1990). The mortality rate in the infected herd may vary between 10-90%, and especially in naive population it can be up to 90%. These rates are usually lower in endemic areas, where mortality may be 20% or less, and serosurveillance is sometimes the only indicator of infection. The incubation period varies between 3-9 days depending on the amount of

virus and the route of infection (Baron et al., 2011). During the incubation period, the virus replicates in oropharyngeal lymph nodes and then spreads to other tissues and organs. After the incubation period, body temperature increases by 40-41,5°C. A peracute form that results in death a few days after the onset of fever is rare (Gibbs et al., 1979).

In acute form, which is common, the fever lasts for up to a week and the symptoms of the disease are seen in this form. In this period, leucopenia, hyperemia in the mouth mucosa, congestion in the nose and eye mucosa and oculonasal discharge are remarkable. After the fever begins to rise, scales (accumulations of surface skin cells, such as seen in *dandruff*) and erosive lesions begin to appear in the mouth and vulva. Initially, the foci of necrosis in small gray-white color and dot shape grow and spread over time. Then, necrotic areas start to appear on the gums, dental pad, palate, lips, inner aspects of the cheeks and upper surface of the tongue. These areas increase in number and size and join together. The necrotic foci in the mouth and on the cheek rapidly become eroded and covered with yellow-matte white cell destruction. The erosions can spread to the lower face of the tongue and the pharynx. Then, the necrotic areas are covered with exudate released from the inflamed tissue. Excessive salivation and water consumption are seen in sick animals; moreover, these are restless, depressive and anorexic. They have superficial respiration and their breath has a bad smell (Baron et al., 2011). The serous nature of the mouth, nose and eye fluids at the beginning is intense and yellow due to secondary bacterial infections. Diarrhea occurs 1-3 days after the onset of the infection and death generally occurs 5-12 days later. Abortions may occur during infection (FAO, 1999).

The subacute form of the disease is characterized by mucosal discharge that lasts for 2-3 days and does not attract much attention, with a moderate increase in body temperature for 1-2 days. There is no death in this form of the disease (Diallo, 2006).

Diagnosis

The use of rapid, specific, sensitive laboratory methods in the diagnosis of SRM is crucial for the effective implementation of control programs (Diallo et al., 1995). The disease can be confused with cattle plague, foot and mouth disease, pasteurellosis, ectima, sheep and goat pox, pneumoniae, bluetongue, coccidiosis, colibacillosis, poisoning, cryptosporidiosis and pestivirus infections. Although infection is suspected in the light of clinical findings, laboratory tests are essential for differential diagnosis (Diallo, 1988; Scott, 1990). Laboratory tests include viral antigen detection, virus isolation, nucleic acid detection and detection of specific antibodies in serum samples taken at 14 days intervals (Gopilo, 2005). The collection of samples at the correct time is important to achieve diagnosis by virus isolation. Anticoagulant-treated blood and swab samples (conjunctival discharges, nasal secretions, buccal and rectal mucosae) should be taken from live animals in the acute phase of the disease when clinical signs are apparent (OIE, 2013). Tissue samples (pulmonary, spleen, lymph nodes) should be obtained from dead animals for virological diagnosis within the 2 hours after the death. The samples should be delivered to the laboratory in the cold chain as soon as possible.

There are several methods available for the diagnosis of SRM. Some of them are virus isolation, reverse transcription polymerase chain reaction (RT-PCR) and enzyme-

linked immunosorbent assay (ELISA). Because it's a cheap method that allows to work with many samples, ELISA is now widely used in the labs (Libeau et al., 1995). Virus isolation in cell culture is a specific technique that needs experience and time, but it has low efficiency. For this reason, it is not widely used in routine diagnosis. RT-PCR allowing to nucleotide sequencing and subsequent phylogenetic analysis and the real time RT-PCR (rRT-PCR) performing quantification of viral loads are the current diagnostic methods for all morbillivirus infections (Forsyth & Barrett, 1995; Shaila *et al.*, 1996; Couacy-Hymann *et al.*, 2002).

Protection and Control

SRM control measures mainly involve disease surveillance, vaccination, stamping out and to strict control of illegal or uncontrolled animal movements (Abubakar et al., 2011).

Surveillance should aim identification of the prevalence of the disease, new outbreaks and disease free areas, monitoring of the disease trends, and informing what should be made at critical control points. Risk-based surveillance is the most cost-effective way to identify and monitor the disease. While high-risk based surveillance focuses on the detection of incursions at critical points, low risk based surveillance focuses on early detection and the response of disease in areas free from disease (SADC 2012).

Since the prevention of illegal animal movements is difficult to implement successfully in the Middle East, Africa and Asia, where the disease is endemic, vaccination is regarded as the most basic way of controlling PPR (Diallo, 2003). Sheep and goats probably do not have multiple infections with SRM throughout their economic lives. Those animals vaccinated with Nigeria75/1 vaccine strain have up to 100% immunity and 12 months of protection against the disease (Awa et al., 2002). Neutralizing antibodies are responsible for immunity. SRM specific neutralizing antibodies were detected on the 16th day of vaccination (Gulyaz et al., 2005). It has been reported that vaccination is safe in field trials and can be used easily even in pregnant animals (Diallo et al., 1995). Maternal antibodies can be detected up to 6 months in lambs and kids born from vaccinated mothers; but it can provide protection for 3.5 months in the lambs and 4.5 months in the kids. For this reason, lambs should be immunized in the 4th month and the kids in the 5th month (Awa et al., 2002). It is considered that the immunity is lifelong in animals recovering from the disease (OIE, 2013).

Treatment

There is no specific treatment for PPR but antibiotics and other supportive treatment may prevent secondary infections and decrease mortality (OIE 2013).

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Chapter 283

ULTRA-HIGH MOLECULAR WEIGHT POLYETHYLENE FOR MEDICAL APPLICATIONS

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ABSTRACT

Ultra-high molecular weight polyethylene (UHMWPE) is a subset of the engineering thermoplastic polymers with extraordinary mechanical and physical properties with a molecular weight of $2\text{--}6 \times 10^6 \text{ g mol}^{-1}$. It is well known that UHMWPE has a great complex of convenient properties including thermal stability, wear resistance, and high impact strength, compared to customary polyethylene attained at low pressure. Additionally, UHMWPE has exceptional sound dampening characteristics, excellent electrical insulating properties, superior dielectric, chemical resistance, and low moisture permeability. All these inherent properties have enabled it to find widespread usage in various applications. This polymer has been extensively utilized in implants and orthopaedics as a biomaterial for total joint replacement applications since the 1960s. It enables effective transfer load due to having extremely long chains. It is so flexible and light, has less weight, good impact strength when compared to metals. Recently, all these outstanding properties have enhanced the demand for this polymer for biomedical applications, including artificial hips, knees, elbows, as well as in shoulders, spinal disks, and wrists. The morphological structure and properties of UHMWPE and its applications for the manufacturing of medical devices were discussed in this chapter.

Keywords: implants, medical applications, total joint replacements, UHMWPE

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INTRODUCTION

UHMWPE is a linear, low-pressure polyethylene homopolymer with a very long chain. It is one of the most important high performance polymers owing to extraordinary physical and mechanical properties: excellent impact and wear resistance, very low coefficient of friction, ease of manufacture, high impact toughness, outstanding dielectric properties, excellent aesthetics, noise and energy attenuation, good abrasion resistance, high resistance to cyclic fatigue, high fiber modulus and toughness, very low service temperature, resistance to radiation, and more (Hambir, 2000; Keller et al., 1994; Rein et al., 2007; Yilmaz et al., 2017; Živić et al., 2014).

Due to high impact strength and abrasion resistance properties of UHMWPE, it has the low friction coefficient which yields a self-lubricating nonstick surface. Besides, UHMWPE has a very low water absorption, high chemical and corrosion resistance, stability and biocompatibility in the body and it is one of the most available and cheap polymeric materials (Gabriel et al., 2010; Selyutin et al., 2010).

As the chemical structure and molecular architecture, UHMWPE is rather similar to high-density polyethylene (HDPE) differing in the average molecular chains lengths and molecular weights. Because it is produced by a process in suspension with Ziegler-Natta catalysts, which assigns the getting of plastics with molecular weight in the range of two and six million g/mol is 10–100 times higher than that of HDPE, it's called as "ultra-high" in linear polyethylene class (Haas et al., 2013; Kelly, 2002; Morais et al., 2017; Rein et al., 2007; Salles & Goncalves, 2003). The physical properties of UHMWPE in comparison to HDPE were summarized in Table 1.

Table 1. Typical physical properties of UHMWPE and HDPE
(Fang et al., 2003; Kurtz, 2004)

Property	HDPE	UHMWPE
Molecular Weight (10^4 g/mol)	0.05-0.25	2-6
Melting Temperature (°C)	130-137	125-138
Poisson's Ratio	0.40	0.46
Specific Gravity	0.952-0.965	0.932-0.945
Tensile Modulus of Elasticity (GPa)	0.4-4.0	0.8-1.6
Tensile Yield Strength (MPa)	26-33	21-28
Tensile Ultimate Strength (MPa)	22-31	39-48
Tensile Ultimate Elongation (%)	10-1200	350-525
Degree of Crystallinity (%)	60-80	39-75

Owing to outstanding physical, chemical, and mechanical properties, it has been employed in many successful applications in different areas such as pulleys, textile, paper, the sliding parts of production lines, machinery, bumpers, mining, naval ropes, bearings, high-performance fiber products, artificial joints replacement in the human body (Forte & Ronca, 2017; Shafiee et al., 2014; Yilmaz et al., 2017).

UHMWPE FOR MEDICAL APPLICATIONS

UHMWPE is an ideal material for total joints with extremely large molecular chains which allow it to be used as a bearing surface and highly entangled chains make it resistant to wear. In 1962, Sir John Charnley used UHMWPE for joint articulation for the first time instead of polytetrafluoroethylene (PTFE) component because of its extensive wear resistance, lower friction and biocompatibility and it has been the crucial standard to produce one of the articulating surfaces of total knee, shoulder, and hip prostheses as well as elbow, ankle, total disc replacements (Musib, 2011). The main demands for a medical implant device in total joint replacements are low wear and friction, biological stability, biocompatibility, high toughness and creep resistance (Barbour et al., 1999).

To be used for biomedical applications, the resin powder must meet the essential properties as given in ISO 5834-1 and ASTM F648 standards (Kurtz, 2004). UHMWPE is initially fabricated as a micron sized resin powder (Fang et al., 2003; Musib, 2011). Later it is converted into consolidated form as a sheet, rod, or near shaped implant under high pressure and temperature by different thermoplastic-processing methods, including hot pressing, ram extrusion, sintering, compression moulding, spraying (hot flame, electrostatic) and gel formation for getting fibre (Figure 1). Because of the long polymer chain lengths, it has an enormously low melt flow index (MFI) or high melt viscosity of flow, 0.06 g/10 min, which restricts the processing of UHMWPE powder by conventional processing techniques, including screw extrusion, injection moulding, etc. (Gabriel et al., 2010). In the last step, it is machined from consolidated form into its final shape (Chilukoti & Periyasam, 2012; Kurtz, 2009).

The material must be sterilized before it's implanted into the human body. UHMWPE is generally sterilized with gamma irradiation in air or in a controlled environment with a sterilization dose of 25 and 40 kGy. The conventional sterilization techniques like autoclaving by steam cannot be used because the polymer begins to deform under high temperature conditions (Fang et al., 2003; Jones & Lauer, 1979). However, gamma sterilization can cause crosslinking, chain scission, and oxidation (Kurtz, 2004). The other methods for sterilization are ethylene oxide gas sterilization, low-temperature gas plasma sterilization, etc.



Figure 1. UHMWPE as a) resin powder form, b) sheet form, c) shaped form as a tablet.

The mechanical properties, oxidative degradation, and especially wear of UHMWPE are major problems for the longevity and performance of implants utilized in total joint replacements (Bracco et al., 2017; Fu et al., 2013; Fung et al., 2018; Jones & Lauer, 1979; Kurtz, 2004; Suñer et al., 2014; Wang et al., 1995; Wang et al., 1998). The bulk of the material is biocompatible, but particle debris due to wear are not biocompatible with the human body. It has been determined that millions of particles are taken apart from the surface of a total hip replacement (Kurtz et al., 1999). These wear debris can react with the tissue surrounding the bone, results in many problems for the patient such as cytotoxic reactions, inflammatory, and osteolysis (bone resorption). These reactions can cause loosening of the prosthesis. The improvement of the wear resistance could extend the clinical life span of total joint replacement and there has been ongoing research to solve the wear problem of UHMWPE (Affatoto et al., 2018; Baena et al., 2015; Holland et al., 2018). Oxidation is straightly correlated with the sterilization process of UHMWPE components. Sterilization with high-energy radiation causes high levels of oxidizing. Basically, high energy radiation creates free radicals which are highly reactive, and they easily react with oxygen causing oxidation on the backbone of the UHMWPE (Berry et al., 2012; Bracco et al., 2017). Besides, sterilization with gas or ethylene oxide (EtO) is the only method that effectively removes the oxidation (Affatoto et al., 2018; Del Prever et al., 2009; Mckellop et al., 2000). Oxidation causes to the formation of wear debris and makes changes in the mechanical properties of UHMWPE. Toughness of the UHMWPE composites is another important property for successful implementation of total joint replacements (Macuvele et al., 2017). High toughness restrains fracture and the creep resistance decreases the cold flow of the acetabular cup around the femoral head or into metal backings (Barbour et al., 1999).

CROSSLINKING OF UHMWPE

For nearly sixty years, UHMWPE has been commonly utilized as a bearing surface material in artificial bones and total joint replacements (Kurtz, 2009; Xiong et al., 2009). This semicrystalline polymer was selected for medical applications since it offers exclusive comprehensive properties like dynamic toughness, biocompatibility, high melt viscosity, high levels of strength, a low friction coefficient, creep resistance, and good wear resistance (Ansari et al., 2016; Macuvele et al., 2017; Pruitt, 2005). Owing to excessive adhesive/abrasive wear and resulted clinical complications like peri-prosthetic osteolysis are a major problem limiting the life span of implanted UHMWPE parts (Macuvele et al., 2017; Oral et al., 2009). Filling modifications for UHMWPE, like whisker, fiber, and particle reinforced UHMWPE composites have been researched to enhance its wear resistance rate (Xiong et al., 2009). Crosslinking of UHMWPE is an effective method to improve the wear resistance of polymer, to make it more durable and stable both in vitro and in vivo. First clinical research for crosslinked UHMWPEs demonstrated importantly a decrease in osteolysis and the wear rates, compared to original UHMWPE (Oral et al., 2008; Oral & Muratoglu, 2011). There are three classes of sterilization processes that have been utilized in crosslinking polymers such as chemical crosslinking using organic peroxides (chemical-induced crosslinking), ionizing radiation (radiation-induced crosslinking e.g., electron beam or γ -rays), and using silanes (silane compound-induced crosslinking) (Lewis, 2001;

Muratoglu et al., 2001). Crosslinking is generated interchain covalent bonding of the long chains of the polymer by the reaction of the free radicals by these ways (Ansari et al., 2016). Despite crosslinking enhances the wear resistance, it can also lead to a decrease in the hardness, toughness, elongation at break, ultimate tensile strength, resistance to fatigue crack propagation, elastic modulus, and yield strength of the UHMWPE (Muratoglu et al., 2001). In 2000s, ionizing radiation crosslinked UHMWPE materials were introduced to clinical practice. This method forms free radicals and generates crosslinking mostly in the amorphous phase of the polyethylene while these free radicals formed throughout ionizing irradiation in the crystalline phase remained active for a long time (Oral et al., 2010). Residual free radicals are trapped into the amorphous phase which caused decomposition of mechanical properties and reduced the molecular weight of the UHMWPE in the long-term oxidative degradation with diffused oxygen (Fu et al., 2013; Oral et al., 2008; Oral et al., 2009).

Therefore, to mitigate the crucial problem, the crosslinked UHMWPE polymers were thermally treated (melted or annealed) after irradiation. Post-irradiation re-melting or annealing is used to enhance oxidation resistance in the first generation crosslinked UHMWPEs (Figure 2). Annealing method does not eliminate free radicals in long-term oxidation, but it stabilizes the mechanical and crystallinity properties of crosslinked UHMWPE. Post-irradiation re-melting as another approach decreases the free radicals, it also reduces fatigue strength of the radiation crosslinked UHMWPE owing to crystallinity loss during melting. The first generation of crosslinked materials was utilized to quench the free radicals which resulted in successful reducing wear, but reduced the crystal size, crystallinity, and the mechanical properties of these polymers like ductility, strength, and fracture toughness (Fu et al., 2013; Sobieraj & Rimnac, 2009). Accordingly, a second generation of crosslinked UHMWPEs enhances mechanical properties and oxidative stability, besides preserving the wear resistance of the first generation. Recently, different processing approaches including mechanical deformation, high pressure crystallization after melting highly crosslinked UHMWPE, solid-state deformation, 3-step annealing post-irradiation, and incorporation of vitamin-E have been proposed for the second generation (Puppulin et al., 2016; Sobieraj & Rimnac, 2009).

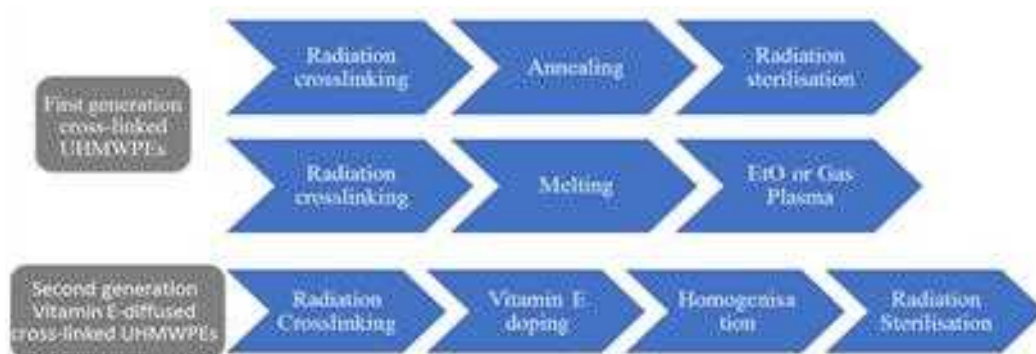


Figure 2. Schematic representation of processing of crosslinked UHMWPE (Oral & Muratoglu, 2011).

As an important alternative approach, free radical scavengers and/or antioxidants have been successfully utilized to promote the radiation crosslinked UHMWPE instead of post-irradiation melting (Oral & Muratoglu, 2011). Vitamin E (α -tocopherol) is widely used as a

biocompatible, natural antioxidant agent in the medical fields and has been designed to enhance fatigue strength and mechanical properties of crosslinked UHMWPE compared to thermal treatments without sacrificing wear and oxidative stability (Oral et al., 2008). Because it can also act as an antioxidant during irradiation, it has successfully provided termination of free radicals to preserve long-term oxidative stability of UHMWPE. Conventional first and second generation crosslinking processes of UHMWPE are schematically depicted in Figure 2 (Oral & Muratoglu, 2011). Two methods of incorporate vitamin E in UHMWPE can be utilized to improve its wear resistance and mechanical properties; the first is to blend UHMWPE powders with vitamin E prior to irradiation and consolidation, and the second is to provide diffusion of vitamin E into molded and irradiated bulk UHMWPE blocks (Baena et al., 2015; Oral & Muratoglu, 2007; Oral & Muratoglu, 2011; Sobieraj & Rimnac, 2009).

TOTAL JOINT REPLACEMENTS

Joint replacement surgery takes out disturbed or diseased parts of a joint and repairs them partially or completely with new, synthetic parts called prosthesis. UHMWPE is the best material ever for most common artificial joints like hip and knee as well as shoulder, spinal, ankle or elbow prosthesis. UHMWPE parts of the joints are main load bearing surfaces that articulate against metal counterfaces like acetabular cup of the hip implants and tibial plateau of the knee implants. Each year, nearly 1.4 million or more joint replacement procedures are applied around the world. The hip and knee replacements are the most common joint replacements types.

Although ceramic-on-ceramic or metal-on-metal total joint replacements are experienced during the past decades, metal-on-UHMWPE is an international gold standard for damaged or diseased joints. UHMWPE coats the metallic surface of the joint to give a smooth surface and if the joints are not coated, friction can occur which is painful for the patients. Despite the enormous success and worldwide acceptance of this medical usage of UHMWPE, wear and resulting loosening problems limit the average life-span of the implants from 10-20 years as well as the specific conditions of each patient. There have been many efforts to solve this problem in UHMWPE at every stage of its productions from original to implanted forms (Baena et al., 2015; Kurtz et al., 1999; Li & Burstein, 1994). Especially, Kurtz and co-workers conducted numerous studies for the enhancement of UHMWPE and to improve its usage in total joint implants (Kurtz et al., 1999; Kurtz, 2004; Kurtz, 2009; MacDonald et al., 2018). Hydroxyapatite (HA), which is the major component of the mineral part of the human bone as reinforcement agent, was also used to improve the UHMWPE properties for biomedical applications (Macuvele et al., 2017).

Total Hip Replacements

The hip is the largest weight-bearing joint which consists of a ball and socket where thighbone joins with the pelvis and it is also enclosed by ligaments, muscles and cartilage inside the body. When some parts of the hip are destroyed, the joint movement becomes rigid

and here occur fractures in the cartilage. The cartilage cannot repair or replace itself like other tissues in the body. Therefore, once cartilage is damaged, it is gone forever, and replacement is needed. In total hip replacement, which is also called total hip arthroplasty, the disturbed cartilage and bone are removed and replaced with orthopedic implants. The general concept of an implant is a combined system consisting of an acetabular component, a femoral stem with a femoral head and a plastic liner which is made from UHMWPE fixed between the femoral stem and acetabular component (Burger et al., 2007).

Various materials are used in total hip replacement such as metals, ceramics and polymeric materials. As mentioned before, UHMWPE was first used in total hip replacements in 1962 as an alternative material to PTFE and later gamma irradiated UHMWPE was introduced in 1968 by Sir John Charnley. Initially, PTFE was used as an acetabular cup, but UHMWPE has been widely used for its low friction and high wear-resistance. At high temperatures or under high stress, UHMWPE is easily deformed, and the resulting wear problem limits the long-term performance of joint prosthesis. In late 1990s, highly crosslinked and thermally treated polyethylenes (HXLPEs) were clinically introduced for total hip replacements to enhance wear resistance of the UHMWPE liners (Kurtz et al., 2011; Kurtz et al., 2015; McKellop et al., 1999; Muratoglu et al., 1999). These UHMWPEs became the alternative bearing material and showed an extreme wear resistance on hip simulators compared with conventional UHMWPE. It offers design flexibility, including smaller sizes. However, its usage is new, its long-term performance is still being closely studied (Ghalme et al., 2016; Teeter et al., 2017; Yamamoto et al., 2017).

Knee Replacements

Total knee replacements (total knee arthroplasty) are the other most successful joint procedures. UHMWPE was first used in the 1960's in knee replacement surgery. It is reported by the Agency for Healthcare Research and Quality that 600,000 or more knee replacements are applied in the United States every year. UHMWPE is a crucial material for total knee replacements and there is no other bearing material instead of it in the knee (Kurtz, 2004).

Implant design and geometry also play significant role in preventing wear in knee arthroplasty. The design of knee implants is more complicated than hip implants. There are two basic total knee implants: The most common one is fixed-bearing knees where UHMWPE of the tibial component is fixed tightly to the metal component and the second one is mobile-bearing or rotating platform implants which UHMWPE insert can rotate short distance inside the metal tibial tray and facilitates movement of the insert relative to the tray. The mobile-bearing knee implant was designed to reduce contact stress on the bearing UHMWPE surface and resulting wear. Even though this design has advantages due to the potential for reduced polyethylene wear and component loosening compared to fixed-bearing knee, this has not been exactly proven by clinical studies yet (Aglietti et al., 2005; Bartel et al., 1986; Hernigou et al., 2018; Huang et al., 2007; Kim et al., 2018; McEwen et al., 2005; Utzschneider et al., 2009). In addition, the thickness of UHMWPE insert for tibial components is a major factor that effects the contact stress and it was reported that the thickness of UHMWPE layer in tibial components for knee replacement should be at least eight to ten millimeters (Bartel et al., 1986; Chakravarty et al., 2015).

Shoulder Replacement

Shoulder replacement (total shoulder arthroplasty) is less common than knee or hip replacements. The first shoulder replacement was performed in the 1950s to treat shoulder fractures and UHMWPE has been used in shoulder replacements since 1970s (Barret et al., 1987; Neer et al., 1982). Total shoulder arthroplasty consists of a humeral stem which is generally made of a metal and a glenoid component which is a concave shaped UHMWPE socket. UHMWPE is responsible for motion and load bearing. The glenoid part is generally fixed by bone cement (polymethyl methacrylate, PMMA) or uncemented press-fit fixation can be used, too (Van Vrekhem et al., 2018).

Several types of implant design and fixation of the glenoid component have been described. The round-backed, all UHMWPE components with peg fixation have been reported as clinically performing better than flat-backed, metal-backed, or keeled components (De Wilde et al., 2013). The thickness of UHMWPE of glenoid components varies from 3 to 15mm. It is reported that thicker components are subjected to reduce polyethylene wear and stress. The size of the glenoid part below 4mm is not suitable while the thickness of 6mm seems the optimal size for reducing wear whenever the soft tissue tension allows it (Harryman et al., 1995; Terrier et al., 2012).

Ankle Replacement

Total ankle replacement (total ankle arthroplasty) is a surgical procedure for the treatment of end-stage ankle osteoarthritis. Initial total ankle replacement with a ball and socket type implant on the basis of total hip replacement was designed by Lord and Marotte in 1970 (Kurtz, 2009; Jamal et al., 2014). The first generation of total ankle replacements consisted of two components, a concave UHMWPE articular surface on the tibia and a metal (usually cobalt-chrome alloy) convex surface on the taller component. In some of the designs, the tibial and taller components were reversed (Bonasia et al., 2010).

Second generation implants are consisting of a UHMWPE bearing surface combined with the talar component or tibial plate. In this type implants cement is not used. The third-generation implants composed of three parts with a third UHMWPE component as the mobile bearing meniscus which is constrained to a minimum (Kim et al., 2016). There have been many commercially available ankle implant types, such as cemented, uncemented types, and implant designs could be classified by implant properties and surgical technique (Jamal et al., 2014; Yu & Sheskier, 2014; Barg et al., 2015; Sopher et al., 2017). There is no obvious information about the thickness of UHMWPE that should be used in total ankle replacement. The optimal UHMWPE component should be strong and thin, without the risk of impairing bony strength at the bone–implant–interface (Espinosa & Klammer, 2010).

Elbow Replacement

The elbow is a complex joint consisting of three bones: Humerus is the upper part, ulna and radius are the lower parts of the hinge joint. In total elbow replacement (total elbow

arthroplasty), an artificial hinge, which is made of UHMWPE and special metal alloys, is located into the joint so all the bones can move smoothly on each other. Metal and UHMWPE hinge joints the stems together and allows the artificial joint to bend (Prkić et al., 2016). UHMWPE also minimizes the wear at the contact between the implant parts. Artificial joints come in different sizes to fit patients of different sizes.

There are mainly two types of implants: Linked types which have a mechanism linking the humeral and ulnar components and unlinked types (Sanchez-Sotelo, 2011). Both types of design rely on a metal on UHMWPE bearing couple for function (Kurtz, 2004). The unlinked elbow implants consist of two metal stems which are not mechanically jointed. The stems slide smoothly on each other and UHMWPE is used for minimizing the wear at the contact between the implant parts. Linked implants are also comprised of two metal stems which are connected with a metal locking pin. The locking pin attaches the ends of stems that are covered with UHMWPE (Bachman & Cil, 2017).

Total Disc Replacement

Total disc replacement (total artificial disc) is a surgical method in which degenerated intervertebral discs in the spinal column are replaced with artificial discs, a mobile bearing prosthesis made of metal and plastic, in the cervical (upper) or lumbar (lower) spine. Disc replacement surgery is a newer procedure that aims to preserve the intervertebral disc height of the spinal column, enhances disc flexibility, eliminates or reduces pain from motion, improves the quality of life of the patient. Total disc replacements are performed to relieve chronic low back pain caused by compressed nerves, weakness, and other symptoms due to damaged or diseased discs. They have been utilized in the lumbar spine since the late 1980s and recently in the cervical spine (Kurtz et al., 2005; Vital & Boissière, 2014). Total disc replacement devices typically include a CoCrMo alloy (Cobalt Chrome Molybdenum) socket articulating against an UHMWPE ball. Owing to its tribological properties and high chemical reaction resistance in part, UHMWPE has been commonly used as a core between the metal plates in joint disc arthroplasty as a bearing surface. There are two designs such as the Prodisc-L (Spinal Solutions) and SB Charité III (Link Spine Group) that include these components for their implant (Eckold et al., 2015). These modern devices are produced with a γ -inert-sterilized UHMWPE polymer to enhance wear performance and oxidation resistance of the cores. Wear debris is a major problem due to its effect on both implant longevity and the biological reactions that can occur in vivo as with all artificial joints (Eckold et al., 2015, Veruva et al., 2014).

SURGICAL SUTURE (NON ABSORBABLE)

UHMWPE fibers have been used in the fields of medical applications, including ligament repair, surgery and trauma of the spine, high-strength sutures, arthroscopic procedures, motion-preserving spinal applications etc. For these fibers, suture technology was one of the first applications, with the trade name of Dyneema Purity, in 2004 (Kurtz, 2009). Sutures made with UHMWPE fiber are non-absorbable which present an exciting medical bio-

engineering challenge. In the other words, it is displayed for use in ligation and/or approximation of tissue like cardiovascular surgeries and allograft tissue for orthopedic surgical procedures (Hapa et al., 2012; Kurtz, 2009).

Newer high-strength sutures comprised either partially or totally of UHMWPE demonstrate increased biomechanical properties over those of absorbable monofilament polydioxanone or nonabsorbable braided polyester suture utilized conventionally in arthroscopic repairs (Hapa et al., 2012). Sutures comprised of UHMWPE fiber were advanced to enhanced handling properties, tensile strength, limit gap formation, and decrease suture breaking. These UHMWPE sutures have submaximal resistance to slippage but certainly higher load to failure strengths than traditional braided polyester sutures (Barber et al., 2006; Barber et al., 2009). The strength of UHMWPE sutures was investigated in a porcine cadaveric model and determined that self-adjusting, UHMWPE suture-comprising meniscal repair instruments were comparable to isolated UHMWPE-containing suture repairs on load testing (Barber et al., 2006). Especially, UHMWPE sutures in equipment have further enhanced the mechanical fixation properties of meniscus repair devices. In another study, it was reported that inside meniscus repair by using UHMWPE sutures supplied greater load to failure strength than other repair techniques that utilize traditional sutures (Barber et al., 2009).

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Chapter 284

NURSING CARE FOR THE SYMPTOMS OF CANCER TREATMENT

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ABSTRACT

Cancer is the most common disease nowadays and it has lots of side effects for patients. Nursing care for symptoms of the cancer is very important for patients. This chapter reviews the symptoms of cancer treatment and nursing care.

Symptoms of cancer include skin-related side effects, hematologic side effects, side effects related to the nervous system, respiratory system, cardiovascular system, gastrointestinal system and genitourinary system and psychoemic side effects.

Keywords: cancer, nursing care, physiological systems, symptoms

INTRODUCTION

Cancer is a complex disease caused by uncontrolled division and proliferation of cells under the influence of genetic and environmental conditions. Serious systemic side-effects are observed both in the disease period and in the treatment period; nursing care for the symptoms comes into prominence.

This article, first, discusses the side effects of the cancer and then lists what the nurses should do for the care for symptoms during the treatment period.

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SKIN RELATED SIDE EFFECTS

Alopecia

Hair loss begins 2-3 weeks after the use of the medications, the hair grows again 4-6 weeks after the end of the treatment.

Nursing Care:

- Hair loss and hair regrowth after the end of treatment should be explained to patients.
- Patients should be informed about various materials such as hats, caps, wigs, etc., which can be used to hide temporary hair loss.
- Paying attention to ensure that the material to be applied to the head should be non-irritating for the head skin.
- Short-cut hair can be suggested before chemotherapy, eye pencil, eyebrow pencil, fake eyelashes can be suggested; use of a soft brush, hair drying without using hair dryer can be suggested for the remaining hair.
- Wearing a cold weather headgear for 30 days before and after the treatment can be suggested (Kanan, 1993; Ozbas, 2003; Akdemir & Birol, 2004).

Redness of the Skin

Nursing Care:

- The patient should be informed about the possibility of skin redness, pruritus, skin drying, dermatitis and the risk of staying too long under the sun.
- The possibility of discoloration of skin and nail, the use of different colored nail polishes to hide this condition and the impermanence of this condition.
- The nails should be cut short; cotton clothes should be preferred.
- The importance of both the maintaining of hepatic enzyme control for hepatitis and daily control of the skin and sclera should be explained to the patient (Ertem et. al., 2009; Walter et. al., 2015).

Pruritus

Nursing Care:

- The skin should be dry and clean.
- Cold compresses, antihistamines and corticosteroids may be used.
- It should be explained to the patient that the skin should not be scratched to not exacerbate itching and to protect the integrity of the skin (Wu & Lacouture, 2018).

Hypersensitivity

Nursing Care:

- Urticaria, erythema, hyperpigmentation and acne-like reaction are observed within 1-3 days following the drug administration. It most commonly develops due to methotrexate, fluorouracil and doxorubicin.
- The patient avoids direct sun exposure during chemotherapy application.
- Cortisone is given as a premedication according to the request of the doctor.
- The patient is supplemented in terms of liquid.
- The patient is monitored for 2 hours after the end of chemotherapy. The patient's blood pressure is measured; adrenaline is available to be administered (Aydemir & Birol, 2004).

Extravasation

Extravasation is the penetration of vesicant chemotherapeutic agents into the subcutaneous tissues via veins.

Nursing Care:

- The procedure which is administered is explained to the patient in detail; the patient is informed that there is no pain while the medication is giving.
- The anatomic region of injection or catheterization is monitored for an abnormal symptom such as swelling, redness.
- The physiological saline solution is given into the vein rapidly. Meantime the patient is asked to say when there is any discomfort.
- Chemotherapeutic drugs, primarily vesicants are administered in accordance with the standards established by the institution.
- Medications which are suitable for the diameter of the vein are given at the recommended dose.
- The needle/catheter is frequently checked to see if it is in place.
- The pressure is monitored when drug injection is required, the operation is stopped if there is a resistance.
- The anatomic region of injection or catheterization is carefully monitored.
- The information about the drugs that cause local reactions such as erythema and urticaria was known.
- The anatomic site of injection or catheterization is constantly checked by taking into account the sensitivities which are observed at the entry site or along the vein.
- After drug infusion, 10-20 ml of physiological saline solution is given rapidly.
- If there is any doubt about the vessel patency, the infusion is stopped immediately.
- The administration of the medication is stopped, the infiltrated amount is determined, the remaining amount in the injection syringe is determined.
- The chemotherapy injector is replaced with a new injector (20 ml).

- The drug or blood remaining up to 20 mL in the IV set was attempted to aspirate.
- If the indication is known, the antidote is slowly administered through the needle or catheter (IV).
- If it is not possible to aspirate the vesicant drug from the set, the needle is removed. Local ethyl chloride is applied to this numb region; the antidote is injected subcutaneously with a 25-gauge syringe.
- Bandages are applied without pressing on the affected area. The extravasation site is immobilized and the arm is held high for three days. It is regularly monitored in terms of pain, erythema and stiffness.
- If the pain still persists after 72 hours, a plastic surgery consultation may be needed (Chanes et al., 2012).

Skin Irritation

The aim of care in skin irritation is to minimize the skin reactions by assessing the site of the treatment and to maintain the integrity of the skin to prevent the development of infection.

Nursing Care:

- Keeping the area clean and dry.
- Not rubbing and scratching the treatment region.
- Lightly washing the area with warm water and non-perfumed soft soap, drying with a soft towel.
- Not using talc powder, lotion or deodorant because they increase irritation.
- Wearing sweat absorbing, soft and abundant clothes, wearing long sleeved dress to protect the region from extreme heat and cold, direct sunlight, wearing wide-edge hats and using sun screen creams are important (Tuna 2014).

HEMATOLOGICAL SIDE AFFECTS

Anemia

The aim is to monitor signs of anemia, to detect them early and to take necessary precautions.

Nursing Interventions:

- Anemia signs such as fatigue, dizziness, trembling or tachypnea should be monitored.
- If orthostatic hypotension dizziness is observed, the patient should be informed to move slowly, especially when lying down and getting up.
- Hemoglobin and hematocrit should be monitored at regular intervals.
- The patient may need blood transfusion and erythropoietin according to the request of the doctor (Sabol et. al., 2010).

Neutropenia

- The signs of infection (fever, redness, temperature, edema, pain, inflammation, etc.) should be monitored.
- The sites where infection is mostly observed such as skin and mucous membranes, oral cavity, respiratory system and urinary system should be monitored; patient's oral and body hygiene should be attached importance and be performed daily, the skin should be protected from trauma.
- Perianal region should be cleaned with warm water and soft soap.
- Nails are cut short and straight.
- Skin integrity should be protected; skin should be cleaned Daily.
- The patient, his/her family and health personnel should take care to wash hands.
- The rest and nutrition of the patients should be cared (Vioral & Wentley, 2015).

Thrombocytopenia

The aim is to observe and to detect bleeding signs early, to prevent trauma related bleeding, to assess bleeding and to control bleeding.

- The blood count of the patient, especially the platelet level should be monitored.
- The platelet count should be kept above 20000.
- Patients should be protected from trauma.
- Soft materials should be used for oral care.
- Aspirin and non-steroid anti-inflammatory drugs should not be used.
- IM injections should be avoided; if necessary, pressure should be applied for 3-5 minutes after the procedure.
- Skin should be evaluated for petechial-ecchymosis.
- Unusual bleedings should be reported.
- If necessary, blood or platelet transfusion should be performed according to the physician's request (Esencan & Merih, 2010).

NERVOUS SYSTEM RELATED SIDE EFFECTS

Cerebral Edema

It is important to diagnose the symptoms of cerebral edema in the treatment of primary brain tumors or brain metastases by radiotherapy. These symptoms are considered as headache, nausea, vomiting, visual disturbances, inadequacy in motor function, and changes in mental status. It is stated that regular monitoring of the life signs of the patient with cerebral edema, the application of the planned treatment in the direction of the physician's request, frequent controls of the patient's level of consciousness are important (Jha, 2003).

RESPIRATORY SYSTEM RELATED SIDE EFFECTS

Radiation Pneumonia

It is known that the possibility of the development of radiation pneumonia is high 1-3 weeks after the radiotherapy administered to lungs. It is emphasized that the presence of signs of fever and dyspnea indicates pneumonia in patients. Nursing interventions applied in patient care include administering steroids and antibiotics according to the physician's request and ensuring bed rest of the patient in addition to the interventions applied the patient with a coughing problem (Yılmaz et. al., 2014).

Radiation Fibrosis

It is stated that treatment related radiation fibrosis 6-12 weeks after the completion of radiotherapy is a restrictive pulmonary disease. The determination of dyspnea as the first symptom and the application of nursing interventions related to it have been addressed (Giridhar et. al., 2015).

Coughing

It is important to define the frequency, severity and characteristics of coughing that develops as a side effect of radiotherapy. The aim of care is to provide an effective open airway and to prevent both the deterioration of airway functions and the development of infection.

Nursing Interventions:

- Positioning the patient with the purpose of ensuring and maintaining airway patency.
- The application of respiratory exercises.
- Providing oral care frequently.
- Frequent ventilation of the room.
- Giving training to patients to prevent the use of irritant substances such as cigarettes that exacerbate coughing (Harle et. al., 2012; Molassiotis et. al., 2017).

CARDIOVASCULAR SYSTEM RELATED SIDE EFFECTS

Cardiotoxicity

- It may develop in the patient depending on the use of doxorubicin. If the patient takes the medication with a total dose of $<550 \text{ mg/m}^2$, the incidence of cardiomyopathy is 0.5%. But, if the patient takes the medication with a total dose of $>600 \text{ mg/m}^2$, the incidence of cardiomyopathy increases up to 30%.

- Changes in ECG such as tachycardia, extrasystoles, changes in ST-T waves were observed within the first week of drug administration. Rhythm changes are reversible. Congestive heart failure becomes chronic if it results in chronic cardiomyopathy.
- Doxorubicin should be limited to the dose of 450 mg/m².
- Congestive heart failure should be treated by using diuretics, digoxin and other cardiotonic drugs (Vasiliadis et. al., 2014).

GASTROINTESTINAL SYSTEM RELATED SIDE EFFECTS

Stomatitis

It usually develops 7-14 days after the administration of the chemotherapeutic agent. Doxorubicin causes reduction in saliva production. Oral epithelial exfoliation occurs. Oral cavity erythema edema, mouth dryness, lips irritation, tongue edema or infection, superficial inflammation that may cause white irregular spots, fever blister like lesions are observed.

Nursing Care:

- Good oral hygiene is provided before and during chemotherapy.
- Oral cavity is checked and evaluated every day.
- Appropriate oral care is taught to the patient.
- If there is no lesion, the teeth are brushed with a soft toothbrush in 4 hours, mucostatin and betadine are used to gargle.
- If there is a lesion, oral care is carried out with hydrogen peroxide solution every two hours, it is followed by oral care with physiological saline solution, after that Vaseline is applied on the lips.
- Fluid balance is maintained.
- It is recommended to avoid from acidic, spicy, minty, salty and savory foods.
- If the lips are dry, they are softened with Vaseline or vitamin E preparations (Farrington et. al., 2013; Araújo et. al., 2015).

Diarrhea

The aim is to prevent diarrhea, to meet the needs of the body with an adequate and balanced diet and to maintain normal weight.

Nursing Care:

- The daily number of defecations and the characteristics of defecations are identified and recorded.
- Intestinal habits are defined.
- The fluid intake of the patient is monitored, lost fluid is replaced.
- The number of feces is recorded and each feces is assessed in terms of bleeding.

- Low fibrous foods, cooked foods are included in the menu.
- Milk products are avoided; if there is no objection, banana, orange, potatoes are given to compensate loss of potassium.
- The amount of fat in the diet is reduced.
- Patients should sparingly and frequently eat foods having low sugar content which are not too hot or not too cold (Shaw & Taylor, 2012).

Constipation

It is quite common because of the opioids used for the control of pain. 50% of cancer patients experience constipation, 78% of these patients are terminal-stage cancer patients.

Nursing Care:

- Fibrous foods are recommended (vegetables, fruits, oats, etc.).
- Fluid intake increase (at least 2lt per day).
- Physical activity is recommended.
- When non-pharmacological practices are not beneficial, laxatives may be given to the patient according to the physician's request, but enema application may be objectionable in these patients (Yu & Ko, 2010).

Nausea-Vomiting

Nausea and vomiting usually occur within the first 6 hours after the treatment. The aim of the care is to maintain fluid and electrolyte balance, to provide adequate nutrition and to protect the oral mucosa.

Nursing Interventions:

- It is important to evaluate and record vomited material in terms of quantity, content and color.
- It is important to administer antiemetic drugs at least half an hour before meals and the administration of chemotherapeutic drugs.
- It is important to provide oral care frequently.
- It is important to monitor body weight, fluid intake and fluid output and electrolyte values.
- The patient's methods to cope with nausea-vomiting are found out.
- The physical environment is kept clean and odorless; the clothes of the patient are ensured to be comfortable.
- Before and during the treatment, a cold pad is placed on the eyes of the patient; liquid and food restriction is done 4-6 hours before the treatment.
- It is suggested that the patient eat gradually and frequently, chew well, and avoid taking liquid at meals (Haugland & DeVon, 2018).

Anorexia

There is an unwillingness to eat and as a result of that the body weight decreases in time.

Nursing Interventions:

- Nurses should plan the nutrition program of the patient in cooperation with a dietitian.
- Nurses should encourage the patient to eat high calorie and protein foods.
- Nurses should recommend to eat gradually and frequently.
- Nurses should recommend to perform oral care after each meal.
- Nurses should eliminate unpleasant odors or odors that the patient does not like.
- Nurses should maintain feeding via enteral nutrition or intravenous nutrition when the patient cannot feed orally (Berry et. al., 2018).

Hepatotoxicity

Prolonged use of methotrexate causes damage to the liver. Preexisting liver disease increases the risk. Hepatic fibrosis, hepatitis and an increase in liver enzymes are observed in the patient. The patient's liver function tests should be checked before chemotherapy begins (Cai et al., 2014).

Dryness of the Mouth

Saliva production decreases as a result of the effect of radiotherapy on salivary gland and therefore dryness of the mouth may occur.

Nursing Interventions:

- Informing the patients and their families.
- Emphasizing the importance of oral care.
- Encouraging the patient to eat juicy foods with meals.
- Giving advice to the patient to avoid from the foods containing lemon, glycerin and alcohol.
- Using commercial solutions to eliminate dryness of the mouth.
- Humidifying the patient's room.
- Encouraging the patient to intake plenty of fluid (Riley et. al., 2017).

Orthodontic Problems and Tooth Decay

It is stated that orthodontic problems and tooth decay are widespread as a result of dryness of the mouth in the patients who are treated with radiotherapy.

Nursing Interventions:

- Nurses should emphasize the importance of dental examination of the patient by a dentist before the treatment.
- Nurses should give a training on daily fluoride applications on teeth.
- Nurses should restrict the fluid intake for at least 30 minutes after fluoride applications (Gallarreta et al., 2013).

Osteoradionecrosis

Osteoradionecrosis is considered as a late and chronic side effect of radiotherapy, is known to be a side effect that can occur in situations in which jaw bone structure is affected as a result of both tooth decay and infection. In the literature, it is stated that hyperbaric oxygen therapy may play a role in the healing of the bone as well as antibiotic applications in the treatment of osteoradionecrosis.

Nursing Interventions:

- Maintenance and support of oral care.
- Guidance for regular dental examinations.
- Monitoring of the suitability and comfort of dental prostheses.
- Informing the patient to decrease oral irritations caused by the use of substances such as cigarettes/alcohol comprise the goals of the nursing care (Firdoose & Hasoon, 2018).

Esophagitis

Esophagitis is seen during radiotherapy applications involving the esophagus region. The patient may report a pain/difficulty during swallowing and swelling in the throat. It is emphasized that it may be serious enough to prevent the practice of radiotherapy.

The intake of sweet, soft and liquid nutrients containing high amount of calorie and protein should be controlled in the diet of the patient. It should also be kept in mind that analgesics given 1-2 hours before meals may be effective in relieving pain and in maintaining nutrition of the patient (Etiz et al., 2013).

GENITOURINARY SYSTEM RELATED SIDE EFFECTS**Renal Toxicity**

It occurs secondarily due to the collapse of the renal tubules. It most commonly occurs due to methotrexate.

Nursing Interventions:

- Fluid balance is maintained.
- Blood urea nitrogen (BUN), serum creatinine levels are checked.
- Creatinine clearance is measured.
- Uric acid and electrolytes in blood serum are analyzed and evaluated (Lydon, 1989; Mallick et. al., 2015).

Cystitis

It is reported that cystitis seen as a result of bladder radiotherapy, appears with thrombocytopenia, a decrease in bladder capacity and nocturia. In the literature, it has been stated that hyperbaric oxygen therapy improves the oxygenation of the tissues by providing granulation tissue formation and vascular growth; it is useful in the treatment of cystitis depending on radiotherapy.

Nursing Interventions:

- Fluid balance is maintained.
- BUN, serum creatinine levels are checked.
- The creatinine clearance is measured.
- Uric acid and electrolytes in blood serum are analyzed and evaluated (Lydon, 1989; Mallick et. al., 2015).

PSYCHOEMOTIONAL SIDE EFFECTS**Fatigue**

Fatigue is one of the most common problems in cancer patients and is related with the factors such as nausea, vomiting, diarrhea, pain, immobility, anemia and malnutrition.

Nursing Care:

- The care needs of the patient should be fulfilled in a short time.
- Selecting light exercises according to the type of the treatment may help increase the energy level of the patient.
- It is ensured that patients do important activities when they have a high energy level, but they do not do these activities in a way that cause them to feel more fatigued afterwards; patients are ensured to get adequate amount of nutrition according to the Daily Living Activities Scale (DLA).
- It is recommended to drink at least 8-10 glasses of water per day in order to be able to remove collapsed cells and residual products (Mitchell et. al., 2014).

Pain

According to the suggestion of the WHO

- Non-narcotic analgesics + adjuvant therapy (aspirin, paracetamol) for mild pain.
- Poor narcotics + nonopioid-adjuvant therapy (tolvin, dihydrocodeine, demoral) for moderate pain.
- Strong narcotics + nonopioid drugs + adjuvant therapy (morphine) for severe pain.

Nonpharmacological applications recommended for pain control include position change, massage, warm or cold application, warm baths, providing a quiet and calm environment, teaching relaxation techniques, radio, television, reading, listening to music and dreaming (Yamanaka, 2018).

Anxiety and Depression

The symptoms such as stress, restlessness, headache and anorexia can be seen in the patient due to the remission (relief of symptoms of the disease), relapse (recurrence) and exacerbation (exacerbation) periods in chemotherapy.

Nursing Care:

- Positive communication and cooperation with the patient and his/her family should be maintained.
- If the patient feels a loss of control, his/her control should be restored or the patient should be ensured to feel that he/she controls his/her environment; this situation encourages the patient to struggle against difficulties.
- Sufficient psychosocial support should be provided to the patient and his/her family.
- For this reason, social counselors should be in the oncology centers.
- Physicians, nurses and other health professionals who are interested in oncology should be raised awareness on psychosocial oncology.
- The social services needed by the patient and his/her family should be determined.
- When giving information about the diagnosis and treatment, the patient should be informed with clear and understandable information (Yoo et. al., 2009; Tsaras et. al., 2018).

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Chapter 285

MORTALITY AND LIFE EXPECTANCY IN POST-COMMUNIST COUNTRIES: WHAT ARE THE LESSONS FOR OTHER COUNTRIES?

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INTRODUCTION

The transition to the market economy and democracy in Eastern Europe and former Soviet Union countries in the 1990s caused a dramatic increase in mortality, shortened life expectancy, and led to depopulation. In Eastern European countries (including East Germany), in most cases life expectancy fell by 2-3 years at the beginning of the 1990s; the most pronounced decline was observed for men in their 40s and 50s. In Russia, the steep upsurge in mortality and the decline in life expectancy were the biggest ever recorded anywhere in peacetime and in the absence of physical catastrophes, such as wars, plague, or famine. This type of natural experiment provides rich material for understanding the impact that different types of social upheavals and stresses have on mortality and life expectancy.

There have been numerous studies and explanations of the increase in mortality (e.g., stress associated with the transition to the market economy and privatisation; alcoholism, economic hardship, and the ‘demographic echo’), but there is still no agreement among scholars as to the most important drivers of the mortality crisis in post-communist countries during transition.

This book compares different explanations and to summarises ‘state of the art’ research on the mortality crisis in post-communist countries. This crisis is also compared with other major cases of known decline in life expectancy due to social, ‘non-material’ reasons (e.g., the transition from the Palaeolithic to the Neolithic age; the enclosure movement and the industrial revolution in Britain over the course of the 16th and 18th Centuries; the aftermath

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of the abolition of slavery and the civil war in the US; and the recent rise in mortality among the non-Hispanic white population in the US since 1999, to name but a few) in order to draw out lessons about the type of stress shocks that can lead to an increase in mortality.

STYLISTED FACTS

Dramatic increases in mortality rates and a shortening of life expectancy were a truly unprecedented, unexpected, and still little-discussed phenomenon, leading to depopulation throughout the entire region of Eastern Europe (EE) and the former Soviet Union (FSU) during the transition to the market economy and democracy in the 1990s. In fact, the steep upsurge in mortality and decline in life expectancy in the FSU and EE states were the greatest ever recorded anywhere in peacetime and in the absence of catastrophes like wars, epidemics, natural disasters, or famine.

This unique part of the transition story, which does not have analogues in other countries, was associated with comprehensive market-type reforms which added an additional shock to the shock of democratisation. Deregulation of prices and ensuing changes in relative prices led to mass reallocation of capital and labour, and hence greatly contributed to stress factors like increased unemployment, migration, labour turnover, divorce, and income inequalities. However, generally, countries with stronger institutions, either democratic (like EE), or authoritarian (like China and Vietnam), managed to cope with stress factors better than others. Furthermore, only authoritarian regimes (China is the primary example) were able to choose and implement a strategy of gradual transition which allowed a stretching out of the required restructuring – the reallocation of capital and labour – over a considerable period of time and thus mitigated the stress associated with unemployment, migration, and labour turnover (Popov, 2007).

Generally, countries which proceeded with more gradual reforms (e.g., China, Uzbekistan, and Belarus) also managed to preserve institutional capacity and either to avoid completely, or at least to mitigate, a collapse of output and the increase in mortality (Popov, 2000; Popov, 2007). The decline in life expectancy in Belarus, for example, from 72 years to 68 compared favourably against a decline from nearly 70 years to 64 in Russia (Figure 1).

China and Vietnam did not experience a transformational recession during transition and life expectancy in these countries grew steadily – although in China this occurred very slowly in comparison with the rise in life expectancy during Mao's rule (life expectancy increased from 35 to 65 years between 1949 and 1976) and in comparison with other countries with similar levels of GDP per capita and similar expectations for life expectancy. Besides, in countries with strong institutions, there was at least one case (Cuba), where the reduction of output (about 40% across the 1989-94 period) did not translate into a mortality crisis. Life expectancy in Cuba increased from 75 years in the late 1980s to 78 years in 2007.

In Russia, the increase in mortality was especially pronounced. The mortality rate increased by 60%, from 1.0% to 1.6%, whereas life expectancy fell from 70 in 1987 to 64 in 1994 (Figure 1). In fact, mortality increased to levels never observed from the 1950s to the 1980s, i.e., for a period of at least 40 years. One has to go as far back as 1940 to find mortality rates higher than in the 1995-2005 period (data for the 1941-49 period – representing World War Two and post-war reconstruction – are missing).



Source: Goskomstat.

Figure 1. Mortality rate (per 1000, left scale) and average life expectancy (years, right scale).

The increase in mortality in Russia occurred across two periods: an initial mortality hike with a peak in 1994, with a subsequent decline, and a later increase in mortality after the 1998 financial crisis up until 2003 (see Figure 1). The rise in mortality after the August 1998 crisis (1998-2003) went hand in hand with growing output, but with fluctuating (i.e., growing and declining) unemployment rates, so at least one of the stress factors was not contributing to the new upsurge in mortality. However, the sharp decline in real incomes that occurred after the August 1998 crisis could have become a major stress factor in itself, even though its direct impact (via a deterioration of nutrition) on mortality could have been limited. Besides, income inequalities, labour turnover, migration indicators, and the divorce rate did not show any signs of decline after the 1998 crisis and before 2002-03. After 2002-03, unemployment continued to decline and the divorce rate also began to fall.

It is also noteworthy that there was no decline in life expectancy during the 2008-09 recession in Russia (Belarus and Poland were the only two European economies which avoided the 'great recession'), although the reduction of output and real incomes was significant – over 10% from a peak to a trough, from the highest month to the lowest month, and the unemployment rate increased from 5.4% in May 2008 to 9.4% in February 2009. Perhaps, over the last two decades of transition, people have already adjusted to stress (and those who have failed to adjust have died out), such that economic downturns are no longer associated with an increase in mortality.

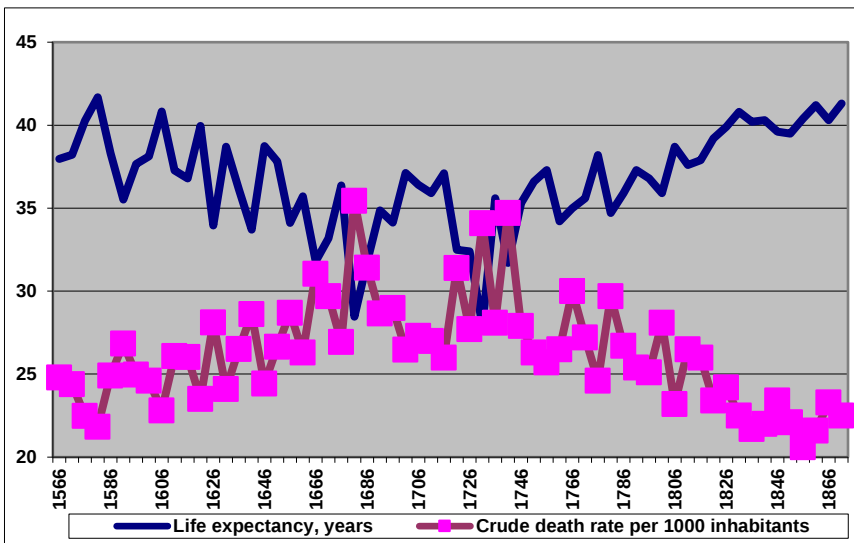
There is, therefore, an even more compelling reason to consider the 1990-2003 fall in life expectancy as an exceptional development.

The increase in mortality rates in post-communist states has a few parallels in history. One is the transition from the Palaeolithic to the Neolithic age from about 7,000 to 3,000 BC, when life expectancy fell by several years – possibly due to changes in diet and lifestyle (i.e., the transition from hunting and gathering to horticulture and husbandry). Another comparable case is the increase in mortality during the time of Britain's Enclosure Acts and Industrial Revolution from the 16th to the 18th Century, when life expectancy fell by approximately 10 years (from about 40 years to slightly over 30 years) because of changes in lifestyle, increases

in income inequalities, and the impoverishment of the masses (Figure 2). Cases of reduced life expectancy due to social changes are rare and do not involve a fall in life expectancy by six years for the entire population of a large state (Cornia, 2004).

A recent stagnation (and even decline in 2015-16) in life expectancy has occurred in the US: a fall of 0.1 years from 2014 to 2015, and then of another 0.1 years from 2015 to 2016. Among OECD countries, the US experienced the second smallest overall increase in Health-Adjusted Life Expectancy (HALE) between 2000 and 2015, just 1.9 years, whereas more than half of the other OECD countries enjoyed an increase of more than 3 years (Sachs, 2018).

Moreover, there has been a rise in age-adjusted mortality for the white non-Hispanic working age population – a very rare phenomenon in a high-income country (Squires and Blumenthal, 2017). Case and Deaton (2015) document a marked increase in the mortality of middle-aged white non-Hispanics in the US after 1998 in all 5-year age groups from 30 to 55. The leading immediate causes for increased mortality were poisoning, suicide, chronic liver disease, and cirrhosis. Increasing mortality for the middle-aged white population was matched by increasing morbidity. When seen side by side with the mortality increase, declines in self-reported health and mental health, increased reports of pain, and greater difficulties with daily living show increasing distress among the white midlife population after the late 1990s.



Source: Data from Wringley and Schofield (1981); figure by the present author.

Figure 2. Mortality rates and life expectancy (at birth) in the course of early urbanisation in England, 1540-1870.

Sachs (2018) points out three major reasons: obesity, drug use, and depression. The latter can be caused by stress due to a loss of social status, social dynamism, and life perspective. The relative position of the non-Hispanic white population in recent decades declined more than any other segment of the population.

“Although the epidemic of pain, suicide, and drug overdoses preceded the financial crisis, ties to economic insecurity are possible. After the productivity slowdown in the early 1970s, and with widening income inequality, many of the baby-boom generation are the first to find, in midlife, that they will not be better off than were their parents. Growth in real median

earnings has been slow for this group, especially those with only a high school education. However, the productivity slowdown is common to many rich countries, some of which have seen even slower growth in median earnings than the United States, yet none have had the same mortality experience.... The United States has moved primarily to defined-contribution pension plans with associated stock market risk, whereas, in Europe, defined-benefit pensions are still the norm. Future financial insecurity may weigh more heavily on US workers, if they perceive stock market risk harder to manage than earnings risk, or if they have contributed inadequately to defined-contribution plans” (Case and Deaton, 2015).

LITERATURE REVIEW

What caused an increase in mortality during transition? Of course, there was a transformational recession in the 1990s; crime, murder, and suicide rates sharply increased as well. However, the staggering increase in mortality that occurred during transition (most pronounced for middle-aged men and mostly caused by cardiovascular diseases) cannot be fully explained by ‘material’ factors like falls in real incomes leading to poor nutrition, deterioration in the quality of the environment and health care system, alcoholism, and smoking (Shapiro, 1995; Leon, Chenet, Shkolnikov, Zakharov, Shapiro, Rakhmanova, Vassin, and McKee, 1997). It has been pointed out that a change in diet (from meat and milk products to bread and potatoes) would not have been able to cause an increase in cardiovascular diseases. Furthermore, emissions of pollutants actually decreased with the collapse of industrial output, and a major impact in terms of deteriorating health care, smoking, and alcoholism (as well as changes in diet) should only result in increased mortality with a lag of several years, but this was evidently not the case (Cornia, 1997; Cornia and Panizza, 2000).

The upsurge in mortality also cannot be explained by the ‘demographic echo’ theory – that the increase in mortality in 1989-94 was merely an echo of the decrease that occurred during Gorbachev’s anti-alcohol campaign in 1985-87 (Avdeev, Blum, Zakharov, and Andreev, 1998). The echo, in this case, seems to be several times larger than the initial shock.

Whereas most experts would agree that the deterioration of the diet and the deterioration of the health care system, as well as increases in deaths from external causes (accidents, murders, suicides), contributed to the general increase in mortality in Russia and many other post-communist countries, they would not, for the most part, regard them as primary factors. Today, there seem to be two major competing theories: One states that the transition mortality crisis is generated by stress factors; another attributes the rise in mortality to alcohol consumption.

Stress factors are associated with the transition to the market economy, driven by rises in unemployment, labour mobility, migration, divorce, and income inequalities (Cornia, 1997; Cornia and Panizza, 2000). It has been found that a stress index constructed out of the aforementioned variables serves as a good predictor of changes in life expectancy in post-communist economies. Men in their 40s and 50s who either lost their jobs (or had to move to another job or another region); or whose country or region encountered increased inequality; or who divorced their wives, were the first candidates to die prematurely in the 1990s (Cornia and Panizza, 2000). The mortality crisis has revealed, like nothing before, the role of social stress on life expectancy. In a sense, this was a natural experiment of a kind that happens only

once every thousand years, and it has shown how much stress a society can take without dying out. Accordingly, King, Stuckler, and Hamm (2006) argued that mass privatisation programmes created psychological stress which directly resulted in higher mortality.

The major theory that competes today with the stress-related explanation of the upsurge in mortality is the increase in alcoholism (Leon, Chenet, Shkolnikov, Zakharov, Shapiro, Rakhmanova, Vassin, and McKee, 1997; Vishnevsky and Shkol'nykov, 1999; Pridemore, 2008). An increase in alcohol consumption only occurred in the early 1990s (see Figure 3). At first glance, it does appear that alcohol consumption is closely related to deaths from external causes (murders, suicides, and accidents) as well as to the general mortality rate (Squires and Blumenthal, 2017). Death rates per 100,000 inhabitants due to alcohol poisoning increased from 10 in 1990-91 to nearly 40 in 1994, exceeding the number of deaths due to suicide and murder (Figure 3).

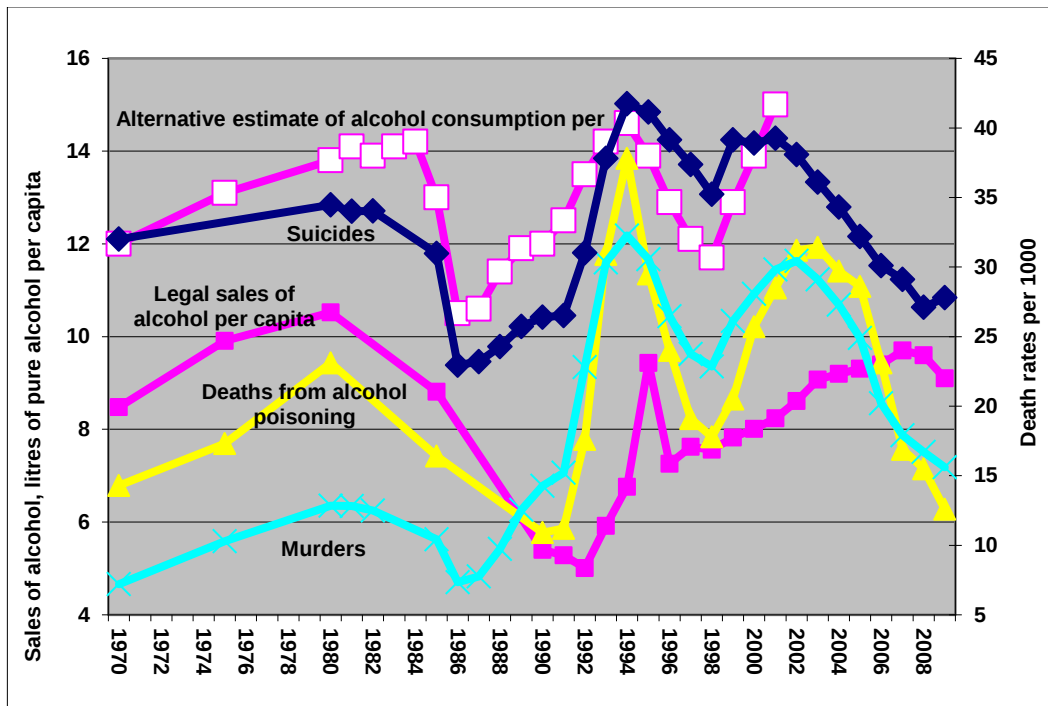
Stress, of course, is related to alcoholism and may, in fact, be the major cause of it (see, for example, Dawson, Grant, and Ruan, 2005; Childs, O'Connor, and de Wit 2011), so it is difficult to separate these two hypotheses. But stress can cause increased mortality even without an increase in alcoholism, whereas an increase in the consumption of alcoholic beverages can occur without stress. In the Russian case, an increased intake of alcohol can be attributed to a decline in the relative prices of spirits in the early 1990s.

Treisman (2010) argues that the surge in alcohol-related deaths – and premature deaths in general – was fuelled by a dramatic fall in the real price of vodka, which dropped 77% between December 1990 and December 1994. Variation in vodka prices – both over time and across Russia's regions – closely matches variation in mortality. Although market competition and weak excise collection help explain the fall in prices, the main reason appears to be populist price regulation during inflationary periods. Bhattacharya, Gathmann and Miller (2013) use an oblast-year [1] dataset spanning 1978–2000 and find a variety of evidence suggesting that the end of Gorbachev's anti-alcohol campaign explains the mortality crisis to a significant extent, whereas Russia's transition to capitalism and democracy was not as lethal as sometimes suggested.

The increase in consumption of alcohol really occurred in the early 1990s, according to official data, and even in the late 1980s – during the anti-alcohol campaign – according to unofficial estimates (Figure 4). Deaths from alcohol poisoning are often regarded as better indicators of alcohol consumption (because some alcohol is produced illegally and smuggled). Deaths per 100,000 inhabitants increased from 10 in 1990-91 to nearly 40 in 1994 and exceeded the number of deaths due to suicide and murders (Figure 3). Later, however, by 2007, the rate of these alcohol-related deaths fell to late Soviet levels, even though total mortality rate remained considerably above late/Soviet levels (Figures 1, 4). The increase in the intake of alcohol, in turn, is attributed to the decline in relative prices of spirits in the early 1990s. It has been shown that the demand for alcohol, like the demand for other goods, is negatively affected by price and positively affected by personal income (Andrienko and Nemtsov, 2006).

Nemtsov (2002) attributes as much as one-third of total deaths in Russia to alcohol-related causes (including indirect causes), which is much higher than official estimates (less than 4% deaths from causes directly related to alcohol consumption), a view widely held by Western experts: "Despite the improving situation, one-third of all deaths in Russia are directly or indirectly related to alcohol, requiring intervention at a variety of levels" (Pridemore, 2008). Many experts consider these estimates exaggerated. Official statistics

report that only 3% of all deaths are caused by alcohol (alcohol poisoning, liver cirrhosis, alcoholism, and alcoholic psychosis). Anatoly Vishnevsky (in personal communications) attributes about 12% of all deaths to alcohol-related causes [2].



Source: For death rates, WHO database and Goskomstat; for legal sales of alcohol, Goskomstat; for alternative estimates of alcohol consumption, Demoscope, No. 263-264, Oct. 30–Nov. 12, 2006.

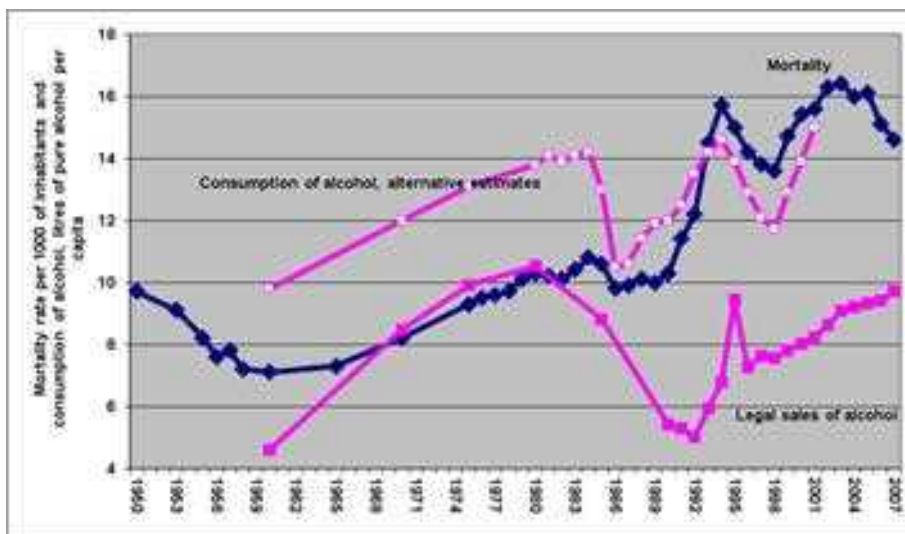
Figure 3. Sales of alcohol, litres of pure alcohol per capita (left scale); death rates per 100,000 from alcohol poisoning, murders, and suicides (right scale).

It seems obvious that increased alcohol consumption contributed to the rise of deaths due to external causes – accidents, murders, suicides (Figure 4). In 2002, the death rates from external causes in Russia was not among the highest, but were the highest in the world. There is also an apparent correlation between alcohol consumption and deaths from all causes, but this does not necessarily imply causation.

Firstly, there is controversy over the impact of increases in the intake of alcohol on cardio-vascular diseases. A recent (Arriola et al., 2009) 10-year survey of 41,000 people aged 29-69 found that, compared with male non-drinkers, those that drank before but later quit drinking have a 10%-lower chance of heart problems; those that drink small amounts (less than 0.5 grams per day) have a 35%-lower chance; those that drink moderately (5-30 grams per day) have a 54%-lower chance; and big drinkers (30-90 grams per day) and alcoholics (more than 90 grams per day) have a 50%-lower chance of heart problems.

Secondly, there are some periods when per capita alcohol consumption and death rates moved in opposite directions – in 2002-07, deaths from external causes, including murders, suicides, and poisoning, fell alongside rising alcohol consumption (Figure 5). Similar inconsistencies exist for the 1960s: From 1960 to 1970, alcohol consumption increased from 4.6 to 8.5 litres per capita, according to official statistics, (and from 9.8 to 12 litres according

to alternative estimates), whereas life expectancy did not change much: 69 years in 1960; 70 in 1965; 69 in 1970.



Source: Goskomstat.

Figure 4. Mortality and alcohol consumption.

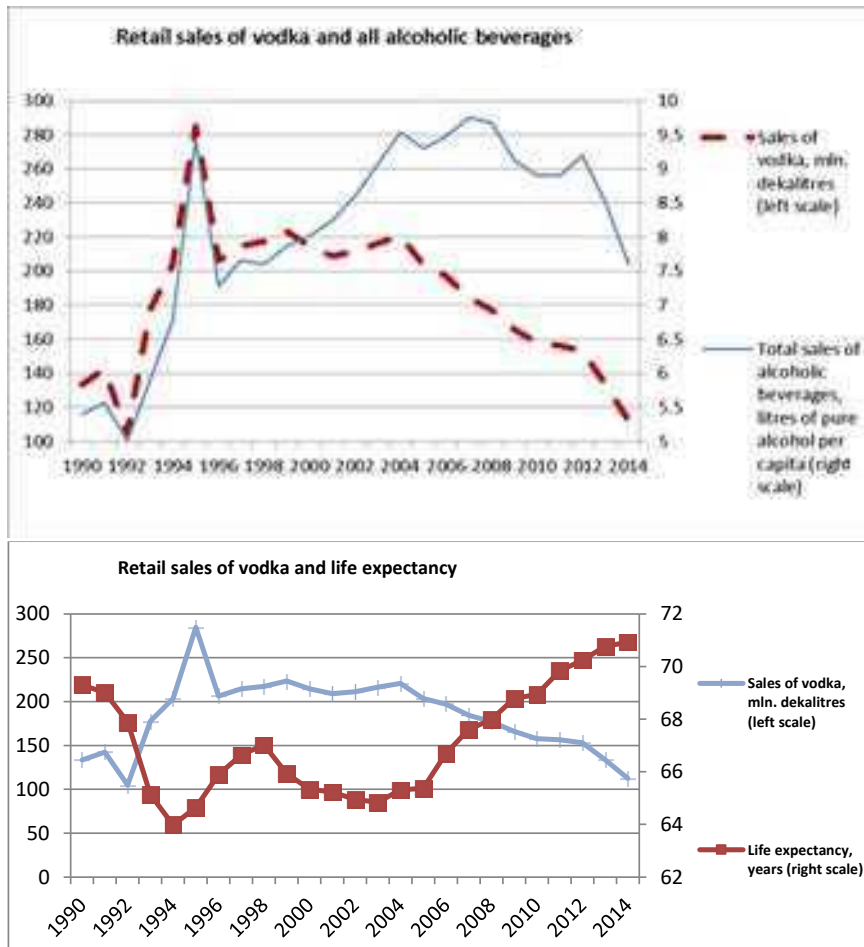
And thirdly, levels of per capita alcohol consumption in the 1990s, according to both official statistics and alternative estimates, were equal to or lower than in the early 1980s, whereas deaths from external causes doubled and the total death rate increased by 50% (compare Figures 1 and 3). It appears, therefore, that we can observe a simultaneous increase in variables (total death rate and deaths from external causes, as well as alcohol consumption) that are all driven by another factor, which is very likely stress.

Grigoriev and Andreev (2015) show that in the 1980–2013 period only a limited number of causes of death for the male population can be attributed to alcohol-related reasons: accidental poisoning by alcohol; liver cirrhosis; ischemic heart diseases; stroke; transportation accidents; and other external causes. They argue that a continuous reduction in adult male mortality seen in Belarus and Russia cannot be fully explained by the anti-alcohol policies implemented in these countries, although these policies likely contributed to the large mortality reductions observed in Russia in 2005–2006 and in Belarus in 2012. Anti-alcohol measures implemented in Belarus and Russia simply coincided with fluctuations in alcohol-related mortality, which had their origins in the past. If these trends had not been underway already, these huge mortality effects would not have occurred.

The counterargument is that it is not the consumption of all alcohol, but of hard spirits, vodka, in particular, that should be blamed for the increase in mortality. It is noteworthy that the consumption of vodka in Russia has fallen sharply in recent years (from over 200 million dekalitres in the early 1980s and in the 1990s to about 100 million in 2015), whereas the share of wine and beer in total alcohol consumption increased markedly (Figure 5).

Finally, there is a view that the stress of the transition to the market economy causes both a rise in mortality and an increase in alcohol consumption, such that both phenomena go hand in hand, but do not necessarily cause one another. Popov (2010) shows that vodka

consumption itself was strongly correlated with stress factors in Russian regions. The most successfully performing regions, such as resource-rich regions, were relatively worse off in terms of stress factors, leading to greater increases in mortality, greater increases in vodka consumption, and greater reductions in life expectancy (Popov, 2010; Walberg, 1998).



Source: Goskomstat.

Figure 5. Retail sales of vodka and all alcohol alongside life expectancy.

Cross-country and cross-regional regressions of changes in life expectancy and mortality in relation to stress factors and alcoholism do not shed light on the true impact of these variables, due to the high level of multicollinearity between them; so it is necessary to examine individual life histories in order to understand what the contribution of various factors is. One such study, by Denisova (2010), is based on twelve rounds of the Russian Longitudinal Monitoring Survey of households spanning the 14-year period from 1994 to 2007. 1,245 adults (5% of the adults in the sample) died, with 546 deaths in the 18-65 age group (3% of the adults of the age group). It was found that relative status measured in non-income terms, labour market behaviour, sectoral and occupational mobility, and smoking and alcohol consumption have a strong effect on longevity, but there is no evidence that the low relative price of vodka led to greater alcohol consumption.

A recent project on the impact of privatisation on mortality and life expectancy (Irdam, 2016; Azarova, 2017; PRIVMORT, 2017) used micro-level data with enterprise and settlement-level data to enable a comprehensive analysis of both distal and proximal causes of mortality. It was based on an extensive survey of households in Belarus, Hungary, and Russia[3] and found that privatisation, and especially fast privatisation, even after controlling for alcoholism, smoking, age, marital status, and financial deprivation, increase mortality significantly (Irdam et al., 2016; Azarova et al., 2017).

PUZZLES AND HYPOTHESES

How do changes in living standards affect life expectancy? The impact is often counterintuitive – that is, the fall in material wellbeing leads to a rise in life expectancy. It is well known, for example, that during the Great Depression in the US life expectancy rose considerably (faster than the previous trend suggested) – from 57.1 years in 1929 to 63.3 years in 1932; the increase occurred for both men and women, and for both the white and non-white populations; mortality rates from all causes of death, except for suicides, fell (Granados, Roux, 2009).

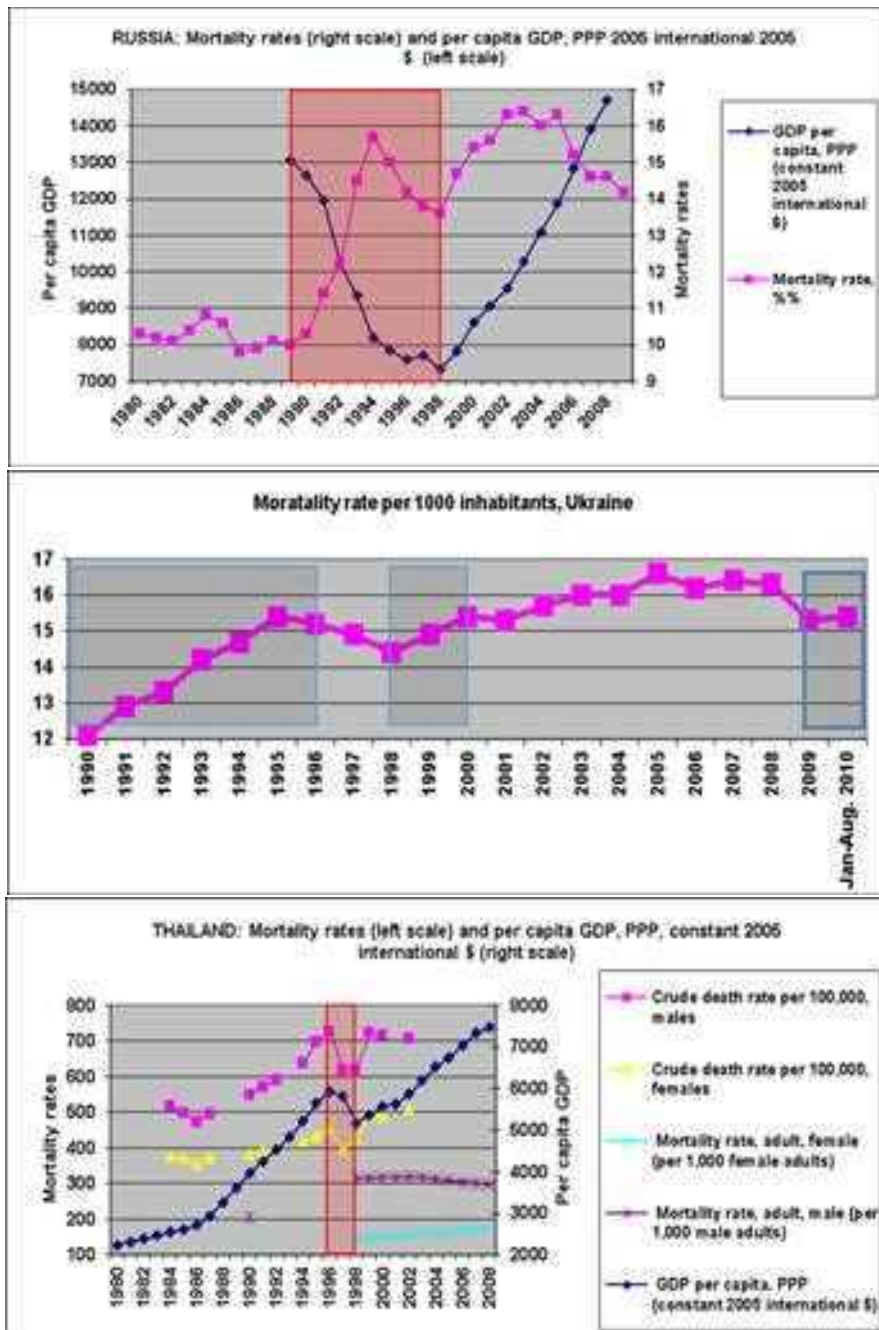
During the 1998 Asian currency crisis, the fall in GDP in many countries was accompanied by a fall in mortality (Figure 6); but in Russia, Belarus, Ukraine, and other economies in transition, transformational recession has resulted in an increase in mortality rates.

Recent research on the link between mortality rates and economic conditions has identified a pro-cyclical relationship. Ruhm (2000), who uses state-level data for the US and a fixed-effect model, shows that a fall in the unemployment rate leads to a sustained rise in the mortality rate. Except for suicides and deaths from cancer, this pro-cyclicality between unemployment and the mortality rate is robust for ten other causes of mortality, especially for motor-vehicle accidents and heart diseases. Gerdtham and Ruhm, (2006) find similar evidence for OECD countries.

Other researchers, however, have found a negative impact of recessions on mortality in developing countries and even in developed countries too, for particular groups. For example, Reichmuth and Sarferaz (2008) show that young adults in France, Japan, and the US exhibit increased mortality in a recession, whereas most of the other age cohorts between childhood and old age react to increased unemployment or decreased GDP growth with lower mortality rates. Using individual data records from Dutch registers for birth, marriage, and death certificates, covering the period 1815-2000, Van den Berg, Lindeboom and López (2006) demonstrate that recessions have an adverse impact on mortality, although not immediately, but rather later in life, due to lower levels of nutrition in early life. Being born in a recession increases mortality rates later in life for most of the population and especially for poorer social classes. Based on social security data for the US, Sullivan and von Wachter (2009) estimate that a higher mortality rate due to unemployment persists up to 20 years after the job loss and leads to an average loss of life expectancy of 1-1.5 years.

There is also evidence that in developing countries, unlike developed countries, recessions have a strong adverse effect on social indicators, including life expectancy and infant mortality. Conceição and Kim (2009) find that life expectancy for a sample of over 200

countries falls by an average of over four years during episodes of growth deceleration (defined roughly as three or more years of falling output) as compared to periods of rapid growth, whereas infant mortality and mortality for the under-5 age group nearly doubles.



Source: WDI database.

Figure 6. Mortality rates in Thailand, Russia, and Ukraine.

Among all causes of death, only one – suicide – always seems to be correlated with economic conditions (unemployment). During the Great Depression, for example, the suicide rate in the US increased by about 20% from 14 to 17 suicides per 100,000 people. The Asian economic crisis in 1997 led to an estimated 10,400 additional suicides in Japan, Hong Kong, and South Korea, with suicides spiking more than 40% among some demographic groups. The unemployed commit suicide at a rate two or three times the national average, researchers estimate. And in many cases, the longer the spell of unemployment, the higher the likelihood of suicide. Suicide prevention hotlines also showed signs of stress in the recent ‘great recession’. In January 2007, as the recession began, there were 13,423 calls to the National Suicide Prevention Lifeline, a toll-free nationwide hotline. A year later, there were 39,467. In August 2009, the call volume peaked at 57,625 (Huffington Post, 2017).

What remains to be figured out is why recessions in some instances (when output falls and unemployment rises) do not lead to a general increase in mortality, whereas in other cases recessions cause a marked increase in mortality.

Another puzzle is the stagnation of life expectancy in Russia for the 20 years between 1965 and 1985 and the rapid recovery of life expectancy after the transition’s mortality crisis. In Russia, after diverging with developed countries in the period of social stagnation (1970-80s) and decline (1990s), life expectancy is rapidly rising again (Figure 7). In 2016, it reached 72 years – the highest level ever.



Source: WDI database.

Figure 7. Life expectancy at birth in Russia and the US, 1966-2013, total (years).

It remains to be seen whether this growth of life expectancy will continue. Former communist countries with free healthcare, good levels of social protection, and even income distribution always had higher life expectancy compared with non-communist countries at the same level of development. Even in 2000, after the decline of the early 1990s, life expectancy in transition economies was five years higher than per capita GDP would suggest.[4] And the scores of communist and former communist countries in the Human Development Index (which includes life expectancy and the level of education in addition to per capita income) were always higher than GDP per capita scores. Will former communist countries be able to retain this advantage in the future?

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Chapter 286

A THEORY OF WHY POTENTIALLY FAVOURABLE POLITICAL AND ECONOMIC CHANGES MAY LEAD TO MORTALITY CRISES

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INTRODUCTION

Potentially positive systemic economic and political changes have in the past at times entailed large transitional health costs. These have often been underestimated ex-ante and are often neglected ex-post by incumbent governments. With the aim of drawing lessons for future transformations and the actions of policymakers, this chapter reviews five past episodes of political, economic, and social transformation that were expected to improve political freedom, economic prosperity, and individual wellbeing, but that instead generated substantial increases in death rates, particularly among low-income groups. This chapter suggests that the frequency of such type of unexpected crises might increase in the future owing to the current acceleration of economic, social, demographic, and technological change.

The chapter presents a taxonomy of causal factors behind the mortality crises that followed the introduction of what were considered ex-ante positive political and economic reforms that were expected to move a country from a low a high social equilibrium. The taxonomy of factors responsible for the discrepancy between ex-ante expectations and ex-post outcomes includes: (i) the unexpected effects of rural-urban migration combined with an inelastic supply of public infrastructure; (ii) political reforms carried out in the absence of adequate administrative, legal, and redistributive institutions; (iii) the introduction of economic reforms under conditions of incomplete or distorted markets and institutions; and (iv) the unchecked contact between socio-economic groups characterised by different disease profiles.

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SOURCES OF FUTURE FAVOURABLE CHANGES

The last three decades have been characterised by rapid changes in the political, demographic, technological, and economic areas. Such changes are bound to continue in the decades ahead. Far from witnessing ‘the end of history’ predicted by Frances Fukuyama, the last thirty years have seen an acceleration of change in many areas, and – as argued below – this trend is poised to continue in the years ahead. Some of the changes discussed below may be a source of gains but also of potential problems. As such, they are briefly discussed below.

To start with, since the early 1980s there has been a major paradigmatic shift towards the liberalisation of domestic and international markets and the globalisation of the world economy. This shift has taken place through a near universal application of structural adjustment programmes that limited the role of the state in the economy, privatised state assets, and liberalised labour, financial, and product markets in most developed and developing countries, and, since 1989, in the former socialist economies (Table 1). While in China and Vietnam, transition reforms were implemented in a gradualist fashion, in the former Soviet bloc they were carried out in an accelerated fashion that simultaneously entailed a swift redefinition of national borders, the introduction of new political institutions, a radical reorientation of the economy, and the adaptation of a disoriented population to a previously unknown way of life (see chapter 3). Considerable, if less dramatic, liberalisation was introduced also in the labour markets of advanced economies such as Japan, South Korea, and Italy, which as a result of these policies, experienced greater employment informalisation and instability, faster job turnover, longer search times, and a shorter duration of each employment spell. Second, the last decade also witnessed a rapid globalisation of the world economy and, in particular, an explosion of cross-border financial transactions (Table 1).

Overall, these changes seem to have generated not only some efficiency gains but also growing instability, as shown by the rise in the number of currency, stock market, and banking crises that have had devastating effects on the countries concerned and on the world economy. After the 2007-08 Lehman Brothers crisis and the 2011 European Sovereign Debt crisis, the drive towards capital account liberalisation has slowed down (Table 1, bottom panel).

Furthermore, the last three decades recorded fast progress and extensive investments in the fields of information and communication technology (ICT), biotechnology, and pharmacology. In 1990, the price of a memory chip was 1200 times lower than it was in 1975 (Pohjola, 2001) and it is continuing to fall. Meanwhile (even leaving aside the controversial GMOs), progress in biotechnology raised farm yields in several developed and developing countries. At the same time, since about 2005, productivity growth has declined in all OECD countries. This is a bit of a mystery in view of the large investments in ICT mentioned above. This might have been because R&D has diminishing returns or that it just takes time for productivity growth to pick up again as it did after the ICT revolution of the 1990s. Meanwhile, the deciphering of DNA enabled the development of a new range of ‘target drugs’ that enhance perceptibly the treatment of previously incurable diseases. Finally, the introduction of digitalisation generated productivity gains but also generated, in many countries and sectors (such as banking, insurance, and general administration), a huge substitution of labour with capital.

Table 1. Trends in domestic financial liberalisation and capital account openness, 1982–2010

Region	1982–90	1991–7	1998–2002	2002–10
<i>Index of domestic financial liberalisation</i>				
South America	5.1	6.8	6.9	7.7
Central America and Mexico	6.7	7.3	7.5	8.4
Sub-Saharan Africa	4.5	5.1	6.6	7.4
Middle East and North Africa	3.6	4.6	5.8	6.5
South Asia	4.7	5.6	6.4	7.4
East and South East Asia	5.9	6.9	6.6	8.2
China and Vietnam	0.0	2.9	4.6	8.0
Eastern Europe and Central Asia	0.5	3.2	7.4	8.7
Advanced economies	7.6	8.2	8.6	8.8
<i>Kaopen index of capital account openness</i>				
South America	−0.78	−0.17	0.76	1.00
Central America and Mexico	−0.84	0.29	1.18	1.67
Sub-Saharan Africa	−0.91	−0.82	−0.59	−0.56
Middle East and North Africa	−0.64	−0.35	0.02	0.36
South Asia	−1.29	−0.74	−0.93	−0.90
East and South East Asia	0.85	0.96	0.50	0.57
China and Vietnam	−1.73	−1.31	−1.07	−1.00
Eastern Europe and Central Asia	−1.84	−0.53	0.01	0.65
Advanced economies	0.83	1.89	2.28	2.32

Source: own compilation on the basis of the 2011 version of the Economic Freedom Dataset of the Fraser Institute and of The Chinn and Ito Index, which is a *de jure* measure of financial liberalisation⁷ (2011 version). Note: The index of domestic financial liberalisation ranges between 0 and 10 (complete liberalisation). The Kaopen index ranges between −2.5 (closed capital account) and 2.5 (completely open capital account).

Similar or more marked effects may be generated in the years ahead by robotisation and Artificial Intelligence (AI). Robots have not yet had a big impact but the channels through which they will enhance productivity are well known (Aghion, Jones, and Jones, 2017). Nanotechnology and robotisation could one-day lead to the complete automation of manufacturing, while AI may do the same for many services. Indeed, AI seems to be poised to automate many tasks once thought to be out of its reach. It is not clear how this will affect growth, employment, the distribution of income, and wellbeing, as many tasks will succumb to automation. Only non-routine tasks requiring high levels of skill and lab-based research performed by highly skilled workers may survive. In the extreme case, AI will generate innovations itself without even the help of skilled workers. While most of these changes have had, and may have in the future, favourable long-term effects on growth, the duration of work, wellbeing, and longevity, their short-term effects are far from clear and require at least the setting up of offsetting measures in the field of employment, income distribution, leisure, and stress management. For instance, progress in the field of information and telecommunications eliminated millions of jobs and exported many more from developed to developing countries. It is likely that future changes in these areas will entail a large inter-country and intersectoral reallocation of labour that – if not properly managed – may raise personal stress and political turmoil.

Third, political systems have witnessed rapid change too. Following the downfall of Soviet-type communism in Europe and Asia, the number of countries embracing different types of political democracy literally skyrocketed. Gone, therefore, in many cases are systems

based on authoritarian regimes, military dictatorships, and neo-colonial institutions. These favourable political transitions were at times, however, accompanied by a surge in other forms of social instability, as vividly illustrated by a rise in crime rates in Russia and South Africa and – more worryingly – in the number of local conflicts and humanitarian crises.

Finally, demography has also been and will be a source of important change. While population growth declined in Europe, much of Latin America, and China, it continued increasing at a rapid rate or did not decline in Africa, the Middle East, and parts of South Asia (Table 2).

Such demographic imbalances, the persistence of intrastate conflicts often linked to ‘democratic revolutions,’ as well as the reduced cost of information about migration options, have fuelled sustained South-North and South-South legal migration, as well as a surge in the number of asylum seekers and irregular migrants. This has generated important political changes in the countries of destination. As noted by a study by UN-DESA (2017), the number of international migrants worldwide has continued increasing since 2000, reaching 258 million in 2017, up from 220 million in 2010, and 173 million in 2000.

This implies that while between 2000 and 2005, the international migrant stock grew by an average of 2% per year, the rate rose to 2.9% over 2005-2010 and it is likely it will continue growing in the decades ahead. In view of the high population growth projected for future decades in the low income South Asian, Central American, and, especially, Sub-Saharan African countries (Table 2), and of the limited job creation prospects in several source countries, it is likely that the pressure to emigrate to high-income countries will increase. In 2017, for instance, high-income countries hosted 64% of all international migrants worldwide – equal to 165 million international migrants – while 92 million migrants lived in middle-income or low-income countries. In comparison to 2000, the share of international migrants living in high-income countries increased slightly.

**Table 2. Annual percentage rate of natural population growth
by main region and countries**

	1950-5	1960-5	1970-5	1980-5	1990-5	2000-05	2010-15	2015-20
World	1.77	1.92	1.96	1.78	1.54	1.24	1.18	1.09
Developed	1.18	1.03	0.65	0.47	0.23	0.07	0.10	0.26
Developing	2.04	2.29	2.43	2.18	1.89	1.52	1.40	1.26
S.S. Africa	2.19	2.51	2.72	2.89	2.62	2.49	2.60	2.65
Asia, of which	1.91	2.11	2.30	1.97	1.68	1.24	1.04	0.92
- China	1.91	1.87	2.29	1.48	1.24	0.59	0.54	0.46
- India	1.71	2.05	2.31	2.31	1.98	1.65	1.19	1.04
L. America	2.71	2.87	2.58	2.30	1.87	1.56	1.19	0.94
- Central Am.	2.88	3.08	2.88	2.32	1.88	1.51	1.39	1.23
Europe	1.03	0.94	0.54	0.40	0.17	0.10	0.18	0.12
N. America	1.65	1.40	0.95	0.95	1.02	0.93	0.79	0.65
Oceania	1.51	1.56	1.47	1.24	1.20	1.07	1.04	1.37

Source: Own compilation based on United Nations Population Division (2015 and 2017).

Indeed, high-income countries have absorbed most of the recent growth in the global population of international migrants, absorbing 64 of the 85 million migrants added worldwide between 2000 and 2017. As a result, in high-income countries the rate of growth of the migrant population rose during 2000-2017 to the 2.9% a year mentioned above, while it

fell to 1.4% in middle-income countries. Because of rapid domestic population growth, despite this continued outflow, international migrants accounted for two% or less of the total population of Africa, Asia, Latin America, and the Caribbean. By contrast, in Europe, Northern America, and Oceania, international migrants accounted for at least 10% of the total population. The number of international migrants worldwide has grown faster than the world's population. Thus, the share of migrants in the total population increased from 2.8 in 2000 to 3.4% in 2017.

Meanwhile, because of unabated internal conflicts, the global level of forced displacement across international borders continues to rise. By the end of 2016, the total number of refugees and asylum seekers in the world was estimated at 25.9 million representing 10.1% of all international migrants. The developing regions (starting with Turkey, Palestine, and Lebanon) hosted over 80% of refugees and asylum seekers in 2016. Given that a large majority of refugees are hosted by developing countries, and that many refugees reside in countries of first asylum for over a decade, there is an urgent need for the sharing of burdens and responsibility for hosting and caring for refugees more equitably.

Growing international migration has been accompanied by massive regional and rural-urban migration in developing and transitional countries, as symbolised by the acceleration in the rate of growth of cities in most of the developing world, or by the emergence of a tolerated 'urban floating population' of 120 million informal workers providing cheap labour to the construction and service sector of urban China. In both populous South Asia and Sub-Saharan Africa, the present low level of urbanisation (less than 30%) is likely to increase in the years ahead – possibly facing some of the problems encountered in the past in now developed countries. Growing rural-urban migration is often associated with a growth acceleration induced by economies of scale and agglomeration that accompany the industrialisation and overall modernisation of a country. But it is necessary to also consider carefully the problems brought about by such rapid transfers of population from the countryside, as discussed in this chapter's case studies.

On current trends, rapid change in all the variables discussed above is likely to intensify in the future. Global financial markets seem poised to continue expanding despite their high volatility and recurrent crises. And the ageing and demographic decline in the Old Continent and rapid population growth in Sub-Saharan Africa and parts of South Asia (combined with the persistence of huge differentials in living standards and human freedom between these regions) may lead to an intensification of global legal and irregular migration, regardless of the migration policies that will be adopted in countries of origin and destination. In turn, rural-urban migration will increase in both Asia and Sub-Saharan Africa. Rapid economic, social, and institutional change – in other words – is not over and, indeed, it may intensify in the years ahead.

In principle, most of the prospective changes alluded to above were supposed to have – and should have in the future – the potential to improve political freedom, living standards, and health conditions. Yet, as discussed in the case studies presented in this chapter, these potentially positive changes may take place in an abrupt, unexpected, and uncontrolled way, and in the absence of policies to improve their success and control their negative side effects. For these reasons, they may weaken collective and individual abilities to adjust harmoniously to new situations and enjoy the benefits of the changes underway. As has already happened in the past, the difficulties in foreseeing, understanding, and harnessing 'unexpected change in situations of institutional weakness' may thus entail considerable health costs, including in

terms of higher mortality. In addition, even when the aggregate health impact of rapid change may turn out to be favourable, a rise in social stratification may reduce the relative health gains of marginal groups with low levels of education, a limited capacity to participate in new economic and political institutions, or those living in remote areas. The combination of rapid change and social segmentation may thus led to a highly skewed distribution of the health gains generated by the new changes. In fact, in the past, the transition from a low social equilibrium to an ex-ante higher equilibrium seldom occurred in a linear way. In many cases, it generated large ‘transformational costs.’

Hereafter I illustrate five episodes of past and recent political and economic reforms that – despite expectations of improvements in living conditions and life expectancy – led to a surge in mortality. The chapter deliberately ignores the negative impact of recessions, contractionary adjustment policies, wars, sanctions, and environmental disasters that were indeed expected ex-ante to negatively affect the health status of the population involved. The main aim of this review is to understand the pathways that caused a health deterioration in spite of the favourable impact expected ex-ante. Tentatively, one can identify four types of situations.

PROGRESSIVE POLITICAL REFORMS AND RISING MORTALITY

The Abolition of Slavery in the US, 1850-1880

A classic example of the negative impact of a positive political change is offered by the abolition of slavery by means of the Emancipation Proclamation of Abraham Lincoln on 1 January 1863, right in the midst of the 1861-65 Civil War (Meeker, 1976). Life expectancy at birth for the black population declined sharply between the last decade of slavery (1850-60) and 1880, due to rising incidence of nutritional and infectious diseases such as smallpox and cholera. Downs (2012) estimates that about a quarter of the 3.1–4 million liberated Southern slaves either died or suffered from serious illness between 1862 and 1870. The primary reason for the rise in death rates was not so much a change in disease patterns and medical practices, but the disruptions in social organisation and living conditions associated with the abolition of slavery. During the era of slavery, the health and nutrition of slaves depended on their owners, who had an economic incentive to keep them in good health. The health and nutrition of the freed black population, in contrast, were influenced by their inability to obtain medical care from a non-existent public health system and costly private providers while the Northern political authorities did not introduce any basic health schemes for them. Declines in health status were also due to negative changes in housing conditions and income-earning opportunities. Many freed slaves were placed in unhealthy ‘contraband encampments’ near union army barracks, and were unable to obtain compensation for their enslavement or land to grow food, a fact that reduced their agricultural output and food intake. Most of them had in fact to survive by selling their labour as casual workers during a period of extreme turmoil.

Thus, while the abolition of slavery was a noble and idealistic decision, as well as a shrewd political manoeuvre by Abraham Lincoln who, in this way, increased the number of soldiers fighting for the North by 200,000 units, the freeing of the 3.1-to-4 million slaves in

the South without simultaneously ensuring them minimum income-earning opportunities and access to basic housing and health turned out to be the cause of sharp health deteriorations.

The South African Transition to Democracy, 1989-2004

South Africa's transition from a supremacist regime to a multiparty 'rainbow' democracy was not an easy one (Desmond and Boyce, 2003). The country experienced two different, if interconnected, transitions. The first was from Apartheid to democracy, the second from an inward-looking to a neoliberal market economy.

The political transition had began in the late 1970s and early 1980s with the introduction of a few adjustments motivated by the poor economic performance of the country and the desire to raise an abysmally low supply of skilled African workers, whose shortage was a key factor in limiting growth potential and domestic demand. The years between 1982 and 1987 saw the creation of the first political organisations, the dismantling of petty Apartheid, and the creation of the Tricameral Parliament. Despite these concessions, political violence intensified. The state responded in 1986 by declaring a state of emergency, handing over power to the security establishment, and launching urban renewal programmes in townships characterised by political tensions. This response raised death rates among the black population and, to a lesser extent, among the white population. By the early 1990s, political compromise began to prevail, leading to the end of Apartheid in 1994.

The newly acquired political freedom was accompanied by considerable debate about the choice of policies in the field of nationalisation, land reform, fiscal policy, taxation, and FDI. In the end, the ANC government gave priority to growth driven by the 'trickle down approach' and the provision of urban basic services to reduce poverty and tensions. The neoliberal nature of these reforms became clearer with the adoption in 1996 of the Growth Employment and Redistribution (GEAR) programme that focused on private investment-led growth, with no explicit targets for the reduction of poverty and inequality.

The restoration of democracy, end of sanctions, and election of a government committed to social change were expected ex-ante to positively affect growth, poverty reduction, and health status. However, existing data do not enable the tracing of the health impact of the transition due to long-standing registration problems and the blurring effect of HIV-AIDS. Nevertheless, the available evidence suggests that – on balance – the positive political reforms introduced since 1994 did not improve health status. Three factors explain this unexpected outcome.

Table 3. Income distribution changes in South Africa, 1991-2001

Households	Share of total income			Changes	
	1991	1996	2001	1991-1996	1996-2001
Bottom two quintiles	3.8	3.4	3.3	-11.0	-3.0
Third quintile	7.6	7.4	7.3	-0.3	-0.1
Fourth quintile	17.6	17.4	17.2	-0.1	-0.2
Top quintile	71.0	71.8	72.2	1.1	0.6

Source: Adapted from Terreblanche (2002), p33, cited in Desmond and Boyce (2003).

Economic performance improved only modestly in relation to the Apartheid years. Per capita income growth was negative over 1990-5 and barely turned positive after 1996. Meanwhile, income inequality worsened (Table 3). As a result, poverty increased, with likely negative effects on health. This disappointing performance can, at least in part, be attributed to the legacy of Apartheid. Yet, the key issue was that while GEAR improved the macro fundamentals, it failed to create jobs (Streak, 2004; and Terreblanche, 2002; cited in Desmond and Boyce, 2003). As a result, poverty and inequality continued to increase in the second part of the 1990s.

Public policy deliberately aimed to improve social conditions. Government spending on health, welfare, education, and housing rose from around 50% of non-interest expenditure in 1990-91 to an average of 60% between 1995 and 2002. Free healthcare was made available to pregnant women and small children, a school-feeding scheme was started, healthcare was decentralised and a programme of clinic building and renovation was initiated. Though hampered by limited capacity and expenditure constraints, these programmes were expected to favourably affect health and start reversing long-standing health inequities. Nevertheless, in the end, only 20% of the poor received a grant, owing to limited fiscal capacity (Streak, 2004). Another priority of the new government was to increase access to water, sanitation, and electricity, and as a result, the availability of piped water rose from 78 to 83% between 1995 and 1999 (Desmond and Boyce, 2003). Despite these improvements, the country experienced two cholera epidemics after 1994, because the programme did not reach the ultra-poor and due consumption remaining low because of high costs and distance.

With the removal of influx control, rural-to-urban migration to already overcrowded townships rose sharply due to lack of employment opportunities in rural areas. The new government embarked on a massive low-cost housing programme that produced over a million new homes after 1994, with the result of raising the share of families living in formal housing. Yet, for a variety of reasons, including an acceleration of rural-urban migration, the share of households living in informal housing rose from seven to 12% during the same period, thus offsetting the impact of the programme in reducing the spread of TB, pneumonia, and HIV.

A second unexpected pathway through which the political transition affected health status was via a surge in violent deaths and political assassinations that increased sharply over the 1987-1990 period, then to subside from the early 1990s. As a result, cases of political violence in urban areas fell from 2,500 in 1990 to less than 500 in 1994 (Barbarin et al., 1999). Yet such a fall appears to have been accompanied by a rise in criminal violence (*ibid*). Indeed, the political transition occurred in an environment of widespread violence, easy access to weapons, little confidence in an ill-equipped police force and weak capacity of the criminal justice system. During the Apartheid years, civil disobedience, boycotts, and even political violence were widely considered legitimate tools of political struggle. In turn, the state responded to these acts in an even more brutal way. All this contributed to the creation of a culture in which violence was the main tool for resolving all political and personal disputes.

The longer-term impact of all this was a sharp rise in criminal activity and violent deaths between 1987 and 1990 and after 1990. Between 1980 and 1990, the murder rate rose by 32%, rape by 24%, and burglary by 31% (Shaw, 1996). In turn, over 1990-94, the number of murders fell only marginally, from 16,000 cases in 1990 to close to 15,000 in 1994, as the fall in political assassinations was almost completely offset by a rise in criminal ones. In addition,

other crimes continued to increase, with assaults climbing by 18%, rape by 42%, robbery by 40%, and burglary by 20% (ibid). By 1996, hospital records showed a daily average of 2,500 South Africans received treatment for stabbings, assaults, and shootings. Data for 1994–1997 from the key districts of Soweto and Gauteng confirm the trend towards falling political brutality but rising criminal violence (Barbarin et al., 1998). The sense of insecurity and fear of being attacked while at home or in the street rose for all ethnic groups. Such fear and stress-related mortality may be another channel through which the transition affected health status.

Finally, over the 1980–2005 period, South Africa experienced an HIV-AIDS epidemic, the incidence of which started declining slowly only from around 2005. No doubt, the epidemic would have occurred regardless of the political transition, but the latter may have accelerated its diffusion. The removal of control on internal migration, political violence, and reforms-induced urbanisation increased mobility within the country, thus facilitating the spread of the epidemic. The increase in rape associated with political violence was another means of infections. The inefficient management of the healthcare system during the reform process reduced the quality of medical assistance (Desmond and Boyce, 2003). Finally, by attracting most of the public attention, the political transition inadvertently contributed to a neglect of the disease and of the initial signs of its diffusion.

While the overall effect of the transition was certainly positive, path dependence and the adoption of neoliberal policies did not enable achievement of better health outcomes. In turn, fiscal restraint prevented benefits from new expenditure priorities being realised. Therefore, while if compared to no action, health outcomes have most likely been better because of the transition, they are possibly not what they could have been if some of the problems discussed above had been anticipated.

RURAL-URBAN MIGRATION, INADEQUATE PUBLIC URBAN INFRASTRUCTURE, AND RISING MORTALITY

A third case in which potentially positive long-term changes can lead to a worsening of health conditions concerns the unplanned acceleration of migration to urban areas. Over the short-to-medium term, uncontrolled migration has been shown to reduce life expectancy in several cases. Indeed, while higher incomes per capita, improved access to public services, and enhanced collective hygiene generally lessens mortality over the long term, the short-term effects can be quite negative. A first cause of this problem is the rigid supply of social infrastructure. While city-based industrialisation offers more jobs and higher wages than in the countryside, the inability to rapidly expand water, sewerage, and transport services can raise the incidence of airborne, waterborne, and infectious diseases in peripheries that have become reservoirs of various kinds of epidemic. A second cause concerns the equally rigid supply of housing. The result is overcrowding in low-standard barracks where bad hygienic conditions create an inviting milieu for tuberculosis and other infectious diseases. A third factor relates to human behaviour. Immigrants mostly come from rural societies where strong social control prevails and opportunities for deviant behaviour are few. Once in the cities, the new immigrants can easily be lured into deviant activities or the consumption of alcohol, drugs, or other substances that increase the risk of violent death.

Rapid Urbanisation and Mortality Increases in 19th-Century Britain

An example of deterioration in mortality during a period of growth and overall improvement in living standards is that observed during the rapid industrial growth of the second and third quarter of the 19th century in Britain (Szreter, 1997). During this period, mortality deteriorated because of the disruptions caused by rapid urbanisation, the inadequate development of water and sanitation systems, residential segregation, and rising income and wealth inequality. While during the period of moderate growth of 1730-1820, nationwide life expectancy at birth rose from 32 to 40 years, between the 1820s and 1870s large industrial cities such as Manchester and Liverpool and small but fast-growing towns experienced an upsurge in mortality. The rise in mortality was mainly due to the spread of infectious and waterborne diseases, particularly among the infants of new migrants who lived in quarters without safe water supply and adequate sanitation. As a result, life expectancy in these cities did not rise, and fell by about one year in some of them, despite a steady increase in urban wealth.

More generally, distress migrants – and especially their children – face greater mortality risks than people who remain in their community. Poor migrants often do not have the resources to access the rental market and – in the absence of public interventions in the housing sector – end up living in slums characterised by the lack of basic water, sanitation, and power supplies. Indeed, because of the considerable costs and time required to develop basic urban infrastructure, a rapid surge in migration tends to be accompanied by overcrowding and poor sanitation and reduced access to potable water. In addition, distress migration entails considerable material hardship, disorientation, the inability to operate easily in new environments, the breakdown of social relationships, redefinition of survival strategies, and greater stress. Unsurprisingly, in very many developing countries, while the Infant Mortality Rate (IMR) of urban areas is consistently lower than that of rural areas, IMRs in slums – especially slums hosting new migrants – are higher than the average for rural areas.

The policy message of the Szreter study is clear. While ‘governed migration’ has been shown to generate considerable productivity and welfare gains in both places of origin and destination (Williamson, 1996), sudden and uncontrolled surges in migration tend to generate pressure on urban infrastructure and rental prices, overcrowding, and the risk of spreading infectious, waterborne, and other ailments among both the migrant and local populations.

Rising Male Mortality during the Urbanisation of Sweden, 1810-50

Until the early 19th century, Sweden was an agrarian society dominated by Lutheran values where the church exerted strong social control on the rural population (Sundin and Willer, 2002). The transition from this pre-industrial society began with the slow urbanisation of the early 1800s, though significant industrialisation took off only after 1849 and peaked around 1870. Indeed, new farming techniques increased productivity in agriculture and so released part of the rural workforce that migrated to the cities to find jobs as servants or unskilled labourers in small foundries and sawmills.

This migration was accompanied by perceptible demographic and social changes. To start with, the difficulties encountered in finding steady jobs in the cities raised the average age of marriage among the lower classes as well as the illegitimacy rate, a trend made possible by the loosening up of social control. The crime rate rose too, in parallel with growing social polarisation and alcohol consumption. Violations ranged from minor episodes, to aggression against members of the upper class, to theft and homicide. Health status showed important changes during this period. While mortality among children and women declined, that among adult males rose or stagnated at high levels. IMR declined steadily from 190 per thousand in 1810 to 120 per thousand in 1860 (ibid), thanks to the growth in food production, spread of health infrastructure, and improved urban sanitation (Edvinsson and Nielsson, n.d.). For instance, a growing number of district physicians and trained midwives offered greater curative care and actively promoted breast-feeding, modern childcare practices, and child immunisation. In the cities, the decline in infant mortality was also driven by improvements in sewerage, garbage collection, and protection of water sources (this point is however questioned by Edvinsson and Nilsson, n.d.). Mortality among young and middle-aged women followed a pattern similar to that of children, likely because of the general improvement of nutrition and sanitary conditions and the rise in the proportion of births assisted by trained midwives. Yet, for older women, mortality did not decline at the same pace, because of the material deprivation in which poor spinsters and widows had to live.

In contrast, mortality among men rose and remained at levels higher than that of 1800 until around 1840–50. This meant that the male-to-female mortality differential – already high prior to 1810 – rose further during the first half of the 19th century. The biggest male-female differentials were recorded for deaths due to alcohol intoxication, accidents, violence, suicides, and tuberculosis. This rise in the mortality gap was not so much due to differences in income, as men's salaries were generally higher than those of women, but rather to differences in lifestyle. Unmarried men were more likely to adopt unhealthy behaviour, while unmarried women internalised gender roles emphasising quieter conduct and participation in supportive social networks. For men, secularisation, greater anomia, and the decline of social control that accompanied migration to the cities led to the adoption of more violent and risky lifestyles. In addition, the old norms of reciprocity and survival strategies of the agrarian society no longer worked in the cities. Finding oneself in a new milieu often generated a sense of being uprooted, especially for those lacking kinship networks on which to rely in case of need. Under these new circumstances, alcohol emerged as an important stress reliever.

Although there are no reliable data for the first half of the 19th century, several factors suggest there was a substantial increase in alcohol consumption during this period. For instance, registered deaths due to alcohol intoxication peaked in the 1840s (Sundin and Willer, 2002). In towns, alcohol could be bought everywhere at a low price and restrictions on production and sales were minimal. Certainly, the mortality impact of alcohol consumption was greater than that indicated by the registered cases of acute intoxication. Heavy drinking affected also nutritional status, housing conditions, and hygiene. Even lung diseases, strokes, accidents, and suicides occurred in part due to excessive drinking. Another factor that contributed to the adverse mortality trend among adult males was the slow improvement of public sanitation. As in the United Kingdom, the development of public water and sewerage systems in the new settlements inhabited by migrants in fact lagged behind the growth of cities and so contributed to a rise in deaths due to waterborne and airborne diseases.

CONTACT AND CONTAGION BETWEEN HETEROGENEOUS POPULATIONS

The demographic crisis that hit Panama City and Colon on occasion of the construction of the Panama Canal is a good example of the economic, social, and environmental imbalance in various parts of Panama, including in its rainforest, generated by the massive influx of workers. The arrival of the French Canal Company was expected to generate a favourable impact on employment, growth, and health. However, it instead led to speculative increases in rents and food prices that made the life of poor Panamanians more difficult (Jackson et al., n.d.). In addition, the intrusion into Panama's rainforest upset the delicate balance between urban and forest disease pools.

An analysis of the death registers of two parishes shows a marked if diversified increase in mortality over 1884–89, which is the period of the first attempt to build the canal by the French Canal Company. During this period, diseases such as malaria and yellow fever – the etiologies of which were not fully grasped at that time – decimated the workers of the French Canal Company and took the lives of approximately 20,000 able-bodied workers (Mina Stern, 2005). The analysis of death registers also shows a major mortality decline between the period 1884–89 and the 1890s, which are the years in which the project was abandoned and mortality returned to its normal level. Finally, it also shows a sharp mortality differential between the poor parish of Santa Ana and the better off La Merced. Indeed, between 1884–89 and 1889–93, death rates dropped from 38 to 13 per thousand in La Merced and from 66 to 28 in the poor neighbourhood of Santa Ana.

How did the construction of the Canal cause such a health crisis? The influx of thousands of West Indian workers caused overcrowding and severe sanitation problems in the urban areas of the city. Overcrowding facilitated the spread of contagious diseases, while the deterioration of drainage and garbage collection created numerous locations for mosquitoes to breed. Since these were the main vector for malaria and yellow fever, the incidence of both maladies rose sharply in urban areas. However, mortality rose as sharply in the work camps along the Canal route, if for a different reason. Indeed, thousands of workers came into contact with a mosquito unique to the Panama rainforest and endemic in wild primates living in it. This mosquito acted as the main vector of yellow fever, thus sharply increasing the contagion in the work camps.

With the suspension of the construction of the Canal and the exodus of the workers, the mortality crisis abated. The construction of the Canal was resumed by the US government, which took possession of the Isthmus of Panama in 1903. The large-scale effort was not followed by a mortality crisis like that of the 1880s. The US government had learned the public health lesson of the first attempt and instituted large-scale public health measures to eliminate the threat of yellow fever, malaria, and other tropical diseases before continuing the construction of the Canal to its completion. President Roosevelt dispatched a public health team to Panama with the brief of eliminating the mosquitoes carrying yellow fever and malaria. This was achieved through the systematic destruction of the mosquito larvae, eliminating any body of standing water (such as water tanks and cisterns), by introducing quarantine stations, increasing the supply of running water, and introducing other public health measures such as fumigation and garbage collection, which led, among other things, to the eradication of yellow fever from the area.

LIBERAL MARKET REFORMS AND HEALTH CRISES

In some cases, the introduction of potentially beneficial economic reforms generated negative health outcomes (see also chapter 3 of this volume). A first explanation of this unexpected outcome is that reforms were applied under conditions of incomplete markets and institutions. Another explanation focuses instead on the problems caused by incomplete reforms, as the changes introduced were only a subset of those that needed to be introduced. This means that each reform taken alone may not generate improvements that depend on simultaneous changes in many areas. A third explanation concentrates on the ‘sequencing problem’ that arises when reforms are introduced in the wrong order. This problem is well known in macroeconomics (when, for instance, the liberalisation of capital movements takes place before macroeconomic stabilisation is achieved) or in transition economics (when price liberalisation and privatisation were introduced before competition reforms were introduced). A final explanation focuses on workers and entrepreneurs and their ‘inability to adjust’ to sudden and unanticipated changes in economic circumstances.

Hereafter we discuss the case of market liberalisation and the rising suicide rate among cotton farmers in Andhra Pradesh over 1997-06. In spite of its recent success in diversifying its economy, in the late 1990s and early-mid 2000s, India still depended on agriculture as the main source of livelihood for 70% of its population. It is no surprise, therefore, that in the 1970s and 1980s, the years of the Green Revolution, policymaking focused strongly on this sector. Indeed, success in raising agricultural output and reducing rural poverty during the 1980s depended to a considerable extent on policies that increased public support in the field of rural credit, input subsidies, and stable input and output prices.

However, following a severe macroeconomic crisis, in July 1991 the government introduced a new policy approach emphasising the reduction of state controls, subsidies and investment in agriculture, the enlargement of the role of the market, and greater integration with the global economy. Within this approach, the agricultural reforms emphasised a reduction in price support and input subsidies, the encouragement of subsistence farmers to enter input-intensive productions for the domestic and international markets, and the liberalisation of the imports and exports of agricultural commodities. In particular, subsidies on fertilisers, electricity, irrigation, and credit were reduced, interest rates on farm loans liberalised, and rural banking privatised. In political-economy terms, such changes signalled the marginalisation of the farming community in the policymaking process.

When markets are complete and function well, the kind of reforms introduced in India in 1991 may lead to a more profitable allocation of resources among crops, continuous adjustments to changing market opportunities, faster growth of agricultural incomes, and better health for rural dwellers. Such a policy approach was, however, far less favourable in many areas of India during the 1990s and 2000s, in part because of the weakness of the safety nets established to deal with the transitory costs associated with the liberalisation of agriculture, but mainly because of the inherent weaknesses of credit, insurance, input and output markets, and a surge in uninsured price volatility following the globalisation of Indian agriculture. Lack of statewide regulation also led to a ‘fallacy of composition’ as many farmers experienced increased dependence on groundwater and credit to finance a growing number of bore-wells. This led to a rapid depletion of the water table, followed by repeated attempts to deepen the wells. Galab, Prevathi, and Reddy (2012) report the case of a village,

where 35 years ago, there were only six tube-wells and the water table was at six feet from the surface. Yet, by 1998, there were 1,800 bore wells, half of which were dry, and the water table had fallen to 240 feet.

The first spurt in farmers' suicides occurred in 1986-87, i.e., before the introduction of the neoliberal reforms of 1991 mentioned above. There were also a few cases of suicide in later years, but these early warnings of rural stress were ignored as aberrations. It is with the second spurt that began in 1997 that the farmer suicide problem intensified and became a structural phenomenon.

One of the districts where the impact was most visible is the semi-arid and so-called 'backward' Warangal district of Telangana state in Andhra Pradesh, which experienced a surge in suicides among small cotton farmers over 1998-2006 and beyond (Table 4, left panel). A study by Sudhakumari (2002) covering the years 1997-2002 analysed the economic circumstances of the households of 50 randomly selected suicide victims who lived in 5 Mandals of Warangal, the district that recorded the highest number of suicides in Andhra Pradesh. The study shows that 66% of the farmers who committed suicide were less than 40 years old, an age group usually characterised by a low suicide rate, while 48 of them were male, and all were married and belonged to low-income families with limited resources and education. Indeed, 31 out of 50 were illiterate, 44 belonged to 'backward' communities or scheduled castes, 18 were landless leaseholders, and 22 had less than 2 acres of land.

Galab, Revhati, and Reddy (2012) extend analysis to 2006 using a broader information basis (including the systematic compilation of suicide reports mentioned in the local Telugu press) and focussed on four districts, one of which was Warangal. Except for the latter, agriculture was the main source of income in each district. Their study confirmed the findings of Sudhakumari (2002) about the socio-economic characteristics of the farmers that committed suicide. In particular, they found that 86 to 97% of the deceased were men in the 30-50 age group. 46-63% were illiterate and belonged to 'Backward' Castes and Scheduled Castes and Tribes. The majority were marginal and small farmers (who experienced higher suicide rates than farmers with a few hectares of land) while some 10-15% were tenants or tenants cum-owner and upwardly mobile middle level farmers.

The study by Galab, Revhati and Reddy (2012) and the studies cited therein identified the main correlates of the increase in suicides. These included dependence on ground water (i.e., dug wells and bore wells) as a source of irrigation; a high share of non-food commercial crops in total output; dependence on expensive informal credit for working and fixed capital (89% among micro farmers versus 50% for farmers with more than 10 hectares); high dependence on market inputs; the volatility of output prices, and the proportion of income that farmers were forced to spend on education, health, and social events. In contrast, the risk of suicide fell when the sources of household income were more diversified.

These personal correlates point to a class of ill-trained and ill-financed small farmers who entered commercial production without the technical support needed to deal with the complexity of the new productions, or adequate arrangements to withstand the problems caused by incomplete credit and insurance markets and volatile world commodity prices.

What led to the increase in suicides? During the period under examination, Andhra Pradesh was affected by adverse weather and pest conditions that caused severe crop losses and could have – in principle – contributed to a surge in suicides. However, such problems were not new in the region and had not caused any perceptible rise in suicides in the past. The cause of the crisis therefore lay elsewhere.

Table 4. Suicides among cotton farmers in Warangal district and Andhra Pradesh, 1997-2006

Year	Number of suicides in Warangal		Number of suicides in Andhra Pradesh	
	Sudhakumari (2002)	Galab, Revathi and Reddy (2012)	Sudhakumari (2002)	Galab, Revathi and Reddy (2012)
1997	16	52	28	108
1998	109	69	307	190
1999	71	100	211	180
2000	50	98	147	220
2001	31	119	89	357
2002	39	123	120	328
2003	---	92	---	342
2004	---	88	---	1795
2005	---	51	---	617
2006	---	26	---	369
Total	316	819	902	4403

Source: based on State Crime Records Bureau cited in Sudhakumari (2002) and on Galab, Revathi and Reddy (2012).

In Warangal and the other three villages analysed, the drive to integrate subsistence farmers into the market economy also entailed a considerable increase in the input-intensity of production, particularly in the case of cotton, a crop that requires improved seeds, electricity, water, fuel, fertilizers, and pesticides. Expectations of high world prices, encouragement to enter commercial farming by the local government and private distributors of seeds produced by multinationals convinced many small farmers to shift from low-risk/low-input subsistence crops to high-risk/high-cost export crops with potentially high-returns. As a result, the area under pulses fell, that under wheat and rice stagnated, and that under commercial crops rose. For instance, in Warangal, 89% of the families of the farmers who killed themselves grew only cotton.

Second, the change in the crop mix and the subsidy cuts mentioned above caused considerable shifts in the economic circumstances of small farmers. To start with, the input intensity of production rose in line with the shift to export crops that required much larger input costs per acre. For instance, in the late 1990s, land cultivated with cotton entailed an expenditure of 18,250 rupees per hectare, against one of 4,700 rupees for maize. As four-fifths of the cultivable land in the region needed irrigation, the shift to cotton induced a sharp increase in capital and recurrent costs for well irrigation. Dependence on purchased seeds increased as well, right after seed subsidies were withdrawn, a fact that caused a large rise in seed costs for farmers.

Table 5. Structure of the indebtedness of the farmers (Rupees)

Sources	Total amount borrowed	% of total borrowing
Commercial Bank	343,012	8
Co-operative Bank	214,382	5
Money Lender	1586,430	37
Pesticide Shop Owner	728,900	17
Middle Man	1200,342	28
Private Financial	85,753	2
Institutes/Friends/Relatives	128,629	3

Source: Sudhakumari (2000).

Third, the purchase of growing amounts of inputs entailed a rise in the borrowing requirements of small farmers. While under normal market conditions, the latter would have counted on a capillary banking system providing credit at competitive rates, the weakness of the local financial sector, the exclusion of a third of the deceased farmers from credit because they did not own the land they cultivated, the retrenchment of institutional credit, and the crisis of cooperative credit pushed the small farmers into the arms of moneylenders and pesticide dealers (Table 5) who charged interest rates ranging between 36 and 60%.

A fourth factor was the volatility of cotton prices. Trade liberalisation exposed the Indian farmers to the vagaries of global commodity markets, without providing them with any mechanism (such as crop insurance or a price stabilisation fund) to compensate them for swings in world prices and international competitiveness. While in 1994–95, the domestic price of cotton rose steeply, it then began to fall, against all expectations, from 1997, in line with the decline of world prices and the rise of cheap imports. In addition, credit dependence on moneylenders and middlemen forced the indebted farmers to sell them most of their output at prices below those prevailing on the local market. Government policies did not help either as they allowed the textile mills to import cheap cotton lint despite the existence of a growing domestic cotton surplus. Thus, from the perspective of becoming an exporter, the country became an importer of cotton produced in countries that subsidised its production and sale.

The withdrawal of input subsidies was a fifth source of economic stress. As noted, after the introduction of structural adjustment policies in 1991, the price of fertilizers doubled while subsidies to canal irrigation and electricity were cut. Public investment in irrigation fell to a minimum, thus unloading the cost of irrigation onto the farmer. A final factor was the failure of public extension services that, during liberalisation, suffered a major reduction in the number of agricultural officers. Even though the agriculture department was well aware that the red soils of Warangal were not suitable for cotton cultivation, they never advised the farmers to stop growing cotton or bothered to advise them about the proper amount and type of pesticides required per acre. As a result, 83% of the households interviewed in Warangal cultivated cotton based on limited knowledge or depended for new information on unscrupulous private dealers of pesticides and seeds who often provided interested and inaccurate advice and sold low quality seeds and inputs.

The rise in the suicide rate in Andhra Pradesh shows that three interlinked factors – the instability of globalised agriculture lacking any insurance or price stabilisation mechanism; the decline in state support to public investment, rural credit, and agricultural extension; and the absence, inefficiency, and interlocked-ness of liberalised output and inputs markets – played a key role in raising indebtedness and economic desperation among cotton farmers. Some cotton farmers – facing a major dislocation of their livelihoods – experienced despair, loss of self-respect, and the inability to cope with such cataclysmic changes so that, in the end, they took their lives. Galab, Revathi, and Reddy (2012) place the Andhra Pradesh suicide crisis in the context of the agrarian crisis that affected the state and argued that the suicide increase was only a symptom of a broader crisis that emanated from population pressure and falling farm sizes; the introduction in the early 1990s of rural reforms that were insensitive to the regional specificity of agriculture; the erosion of public institutions for agricultural extension, credit, coordination, and public investment; the adoption of yield-increasing technologies without the prior introduction of adequate infrastructure and state coordination and without resolving the problems caused by an irrational distribution of land prior to the introduction of the reforms.

CONCLUSION

This chapter has argued that profound social changes such as those observed on occasion of important political or economic reforms may have unexpected and long-lasting negative effects on the health conditions of large sections of the population. The analysis of past and current cases of social change confirms that the search for political and economic improvements may lead to considerable social dislocations and severe mortality crises over the short and medium term.

The chapter (as well as chapter 4) has also argues that the mortality crises that have followed episodes of rapid social change or epochal transitions have affected different social classes, although in the majority of cases low-income groups were most affected. Among the latter, one can include immigrants to cities (as in the case of urbanising Britain and Sweden), workers in cities exposed to problems of overcrowding, inadequate housing, and sanitation, workers exposed to an untouched pool of diseases (as on the occasion of the construction of the Panama Canal), illiterate, low-caste cotton farmers (as in Andhra Pradesh), freed slaves (as in the US), and an underclass of newly unemployed workers with low education, living in incomplete families, and from a minority background (as in several Eastern European economies in transition; see chapter 3). In some cases (as in Panama and South Africa), the crisis also affected part of the middle and upper class, indicating that while these crises may hit the lower strata of society particularly hard, better-off groups cannot consider themselves immune from problems. Evidence also suggests that the stronger the initial stratification, the higher the likelihood that low-income groups will be disproportionately affected, leading in this way to a widening of health inequality and possible political turmoil.

The chapter has also suggested that these mortality crises have generally affected two well-defined age-gender groups, i.e., adult males and children. The analyses of Andhra Pradesh, Sweden, South Africa, and the European economies in transition (see chapter 4) show that adult males are especially vulnerable to stress-related mortality, their greater vulnerability being due to differences in behaviours and gender roles rather than biology. Mortality crises have also hit some biologically vulnerable groups, such as infants and children, especially when the main causes of death were infectious, nutritionally related, respiratory, and waterborne diseases.

There appears to be four broad pathways through which potentially positive social change may adversely affect health status: (a) due to the unexpected effects of political transitions carried out in the absence of adequate administrative, legal, and redistributive institutions and a modicum of economic democracy; (b) through increased geographical mobility combined with the inelastic supply of health infrastructure and housing leading to overcrowding, deteriorations in environmental conditions, and the rise of infectious and social diseases; (c) via the introduction of economic reforms under conditions of incomplete markets and missing institutions; and (d) due to contact between different pools of disease.

While the pathways through which rapid change impact mortality for infectious and poverty-related diseases are well known, less is known about the economic and social factors that may raise stress levels among populations affected by rapid change. Such factors (such as rising unemployment, the inability to honour economic commitments, and the fear of violence) are generally unexpected due to never having been experienced before, or because people only have generic expectations about the probability of their occurrence. Unexpected

events cannot be insured against or prevented through structural interventions. At the time, social change is also sudden, a fact that compresses the response time available to society and communities to introduce counter-measures to offset its impact.

Because of people's inability to prepare for and deal with rapid change (even if potentially favourable), it can increase the sense of uncertainty about the future, the fear about one's own security, the perceived risk associated with human activities, the sense of loss of control and self-confidence, and psycho-social stress. The breakdown in social networks and the lack of institutional responses and practicable coping strategies tend to aggravate the situation. In addition, growing uncertainty has well-known economic effects including an increase in the riskiness of investment, a rise in interest rates, and higher savings propensities and risk aversion, i.e., changes that depress the current levels of investment and production. Rapid and unexpected change may also increase sectoral and spatial mobility and organisational change, in this way increasing anomy and eroding social capital, the sense of community participation, and the ability to undertake collective action. In times of rapid change, old rules, norms, and institutions no longer function as efficiently as they did in the past. If pre-existing informal institutions – such as voluntary associations, social networks, religious institutions, the family, and other primary support groups – are weakened, it is likely there will be nefarious effects for social stability and security.

The nature and breadth of public response to crises induced by rapid change have varied sharply. Yet less is known about why some societies respond in a collective fashion to the dislocations caused by social change while others do not (Eyer and Sterling, 1977). Initial social stratification, as well as political ideology, have affected the willingness and ability of governments to respond to health crises once these have exploded. In egalitarian societies, public policy deliberately aimed at containing the health impact of transformational recessions. In turn, in the highly polarised Southern States of the US, the health and nutrition problems faced by the disenfranchised slaves took a very long time to be addressed. Likewise, in the highly unequal economies in transition of the Russian Federation and South Africa, the crises were dealt with only in part by national authorities. One of the possible explanations of this kind of policy stance is that the new elites of an increasingly unequal society were not concerned by a crisis that mostly hit an economically and politically disorganised group of marginal people with low levels of education and skills, poorer jobs, and lower incomes, and poorer political representation. Truly democratic and participatory societies appear better able to respond to the social and health challenges posed by rapid economic and social transformations. The same can be argued for societies benefitting from a wide range of genuine 'intermediate institutions' that help to channel political consensus, keep up the pressure on incumbent governments, undertake collective action, and defend the interests of the most vulnerable sections of society.

The acceleration of technological, institutional, policy and demographic changes observed over the last two decades is likely to continue in the years ahead. In view of this, the lessons of recent or past cases of political, economic, and social upheaval constitute a valuable lesson for understanding the potential health impact of expected future changes that are already on the horizon or are likely to emerge soon, such as Africa's accelerating mass migration towards Western Europe or the employment impact of robotisation. It is therefore essential that policymakers systematically analyse the evidence on the health impact of past systemic changes before new changes occur. Only this can constitute an efficient guide to policymaking that aims to prevent important dislocations during an era of rapid change.

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Chapter 287

MORTALITY CRISES IN HIGH-INCOME COUNTRIES: EVIDENCE FROM THE UNITED STATES, THE UNITED KINGDOM, ITALY, AND GREECE

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INTRODUCTION

Over the last decades, life expectancy at birth (the average number of years a newborn would be expected to live if a set of age-specific death rates in a given year continues to apply) has increased steadily all over the world (World Health Organization [WHO], 2006). Although quality of life may be even more important than the quantity of years a person is expected to live, life expectancy at birth is generally regarded as the most important measure of the overall health status of a population. This indicator is widely used by policymakers, the public, media, and other key societal stakeholders to compare and measure progress in the health of people and assess the quality of a health system in delivering optimal health outcomes.

Thus, if we assess the world's health by using life expectancy at birth, one can easily infer that people all over the world have never been healthier than today. In the last centuries and especially in the last decades, both adult and infant mortality rates have steadily decreased in all regions of the world. Yet, in spite of such improvements, the world is still facing numerous health challenges, including the high inequalities in longevity between socioeconomic groups as well as numerous cases of sudden "health reversals" or unexpected increases of cause-specific death rates and even all-cause mortality rates. Are these mortality crises happening by chance? Or are they by-products of some key determinants of health? Are there country-specific mechanisms behind such mortality crises or are there general patterns of explanations? Are these crises avoidable and what policy changes can prevent them in the future?

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Although there is no exact definition of health crisis, it is simply referring to a sudden increase in the level of mortality due to a wide variety of determinants of health (Bacci, 2000). Throughout human history the most important determinants of mortality crises included material conditions such as the plague or epidemics of infectious diseases, absolute poverty, famines, wars, and other natural occurrences. Material deprivation is still responsible for a high proportion of deaths today, especially in the developing world. Yet, as socioeconomic conditions have been improving over the centuries and especially in the last decades, material determinants of health such as epidemics, famines, and absolute poverty have played an increasingly relatively less important role in explaining modern mortality crises. Instead, psychosocial determinants such as mental health problems, social isolation, hopelessness, stress, and meaninglessness have become more and more relevant in understanding trends in population health in high-income countries. As often noted by epidemiologists, quoting a very popular definition of the WHO, health is far more than the absence of disease (an outcome of material circumstances), but should be viewed as “a state of complete physical, psychological and social wellbeing.”

Rather than providing a comprehensive picture of recent mortality crises, this chapter addresses a few examples and case studies from high-income countries. The chapter focuses particular attention to four countries for analytical comparison: the United States, the United Kingdom, Italy, and Greece. First, it examines potential explanations for the recent unexpected reductions in life expectancy in high-income nations including these four countries. Then, it investigates the multiple determinants of the sharp and surprising rise of mortality due to suicides, alcohol abuse, and drug overdoses among middle-aged White Americans since the early 1990s, a time of steady health improvements for all other ethnic and age categories. The rise of these so-called deaths of despair followed the adoption of a trade liberalisation treaty with China that cost about 6 million job losses in the manufacturing sector in the United States. Finally, the chapter will focus on the mental health crisis (the rise of suicides and mental health illnesses) in the United States and Europe after the outbreak of the 2008 global financial crisis that heavily affected the United States, the United Kingdom, Italy, and Greece. It will also analyse the health effects of austerity measures that were adopted by all four countries (though in different degrees) to reduce mountain budget deficits.

A key objective of the chapter is to assess common determinants and shared patterns of explanations for these mortality crises and identifying different possible mechanisms connecting political and economic changes, psychosocial factors, and unexpected increases in mortality. The final part of the chapter will include a discussion of future research and implications for policy and health promotion as well as an analysis of policy responses by different countries affected by economic crises and social instability.

‘HEALTH REVERSALS’: THE UNEXPECTED DECLINE OF LIFE EXPECTANCY AT BIRTH IN HIGH-INCOME NATIONS IN 2015

People in developed nations are living in the healthiest of all times. The advances in life expectancy in the 20th century and the beginning of the 21st century are remarkable by any standard. In spite of the paucity and unreliability of historical mortality data, experts agree that human life expectancy during the time of and before the Roman Empire did not

overcome the threshold of 30 years. The Industrial Revolution, however, changed radically the conditions of living and consequently generated a critical increase of longevity in industrial societies. Yet, by the beginning of the last century, life expectancy had been extended only 9 years, to an average of 37 years throughout the globe (Evans, 2001). The fastest and most unprecedented improvements in population health worldwide occurred in recent decades. Both adult and infant mortality decreased in every region of the world, and by the year 2015, global life expectancy had increased to over 72 years. It was just over 52 in 1960 (World Development Report database). To put this increase in context, it is sufficient to state that global life expectancy increased faster in the last 50 years than it did in the preceding 5,000 years.

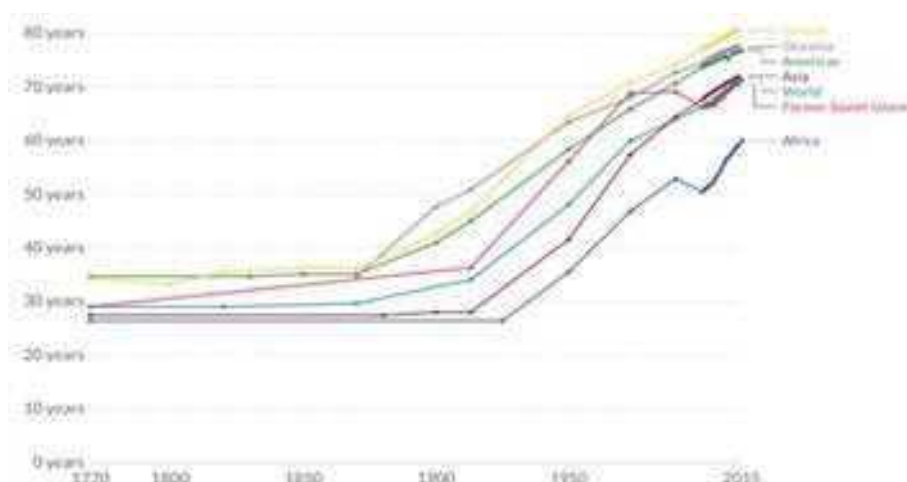
Although many multiple factors contributed to this rapid and unprecedented rapid rise of life expectancy, by far the most important are the socioeconomic changes triggered by the Industrial Revolution. As clearly argued by McKeown, in a very famous project in the field of historical epidemiological in England and Wales, the largest proportion of the increased life expectancy did not occur because of healthcare improvements, but as a consequence of socioeconomic conditions (McKeown & Record, 1962) and related changes in nutrition, hygiene, and sanitation.

When considering the gross domestic product (GDP) per capita of the four case studies of this chapter, it is possible to see how in all countries rapid increases in GDP per capita occurred after the year 1800. As the Industrial Revolution originated in the United Kingdom, it provided a comparative advantage in terms of GDP per capita: In 1835, GDP per capita in the United Kingdom, Italy, United States, and Greece was \$3,786, \$3,338, \$2,660, and \$2,579, respectively. By the end of World War II, GDP per capita reflected a new distribution of power and wealth in the world, and it was affected by the destructive effect of the conflict especially in Europe. The GDP per capita in the United States reached \$16,401, in the United Kingdom it was \$11,574, while in Italy it was half that of 1939 at \$3,663 and \$2,147, respectively. Steady and rapid increases of GDP per capita occurred in all these nations after the war, although there was an abrupt end of this positive trend by the year 2008 at the outburst of the global financial crisis. In 2014, GDP per capita was \$51,664 in the United States, \$36,436 in the United Kingdom, \$32,829 in Italy, and \$22,344 in Greece.

The increase of GDP per capita since the Industrial Revolution, first experienced in the United Kingdom and then in the rest of the world, has generally been associated with improvements in health. In spite of numerous episodes of economic stagnation and recessions, world's life expectancy has increased steadily. The only two departures from secular trends towards better health in the last 50 years were experienced in the former Soviet Union and in sub-Saharan Africa in the 1980s. In more recent decades (the 1990s and after the year 2000), however, even these two regions restarted a pattern of health improvements enjoyed by the rest of the world.

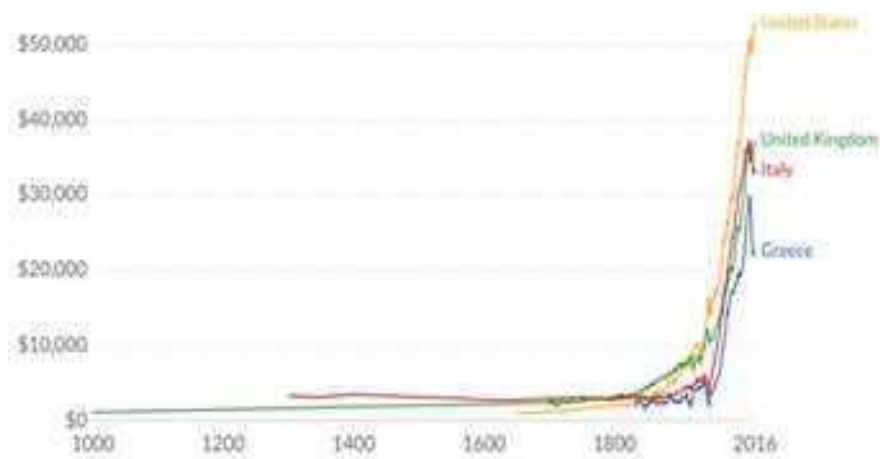
In 2015, however, steady progress towards better health has surprisingly halted, and life expectancy started to fall in several high-income countries. A recent article analysing declines in life expectancy in 2014 by Ho and Hendi (2018) showed that declines occurred in 12 out of 18 high-income countries investigated. When examining updated information from the World Development Indicators database (accessed on July 8, 2019), it is possible to observe that 19 out of the 30 top economies in the world experienced declines in life expectancy at birth between 2014 and 2015. Such health reversals cannot be attributed to wars or new pandemics, though it is possible that socioeconomic changes such as the global financial crisis that began

in 2008 and austerity policies including budget cuts in healthcare and social welfare that were first introduced in 2010 may have exerted lagged effects on health and played a role in driving these declines.



Sources: Our World in Data (2018) based on Riley for data from 1770 to 1990 and WHO and World Bank for data points from 1990 to 2015.

Figure 1. Life expectancy at birth in Europe, Oceania, Americas, Asia, Former Soviet Union, and Africa (1770–2015).



Source: Our World in Data based from Maddison Project database (2018).

Figure 2. GDP per capita (adjusted for inflation and price differences between countries and measured in international dollars in 2011 prices) in the United States, United Kingdom, Italy, and Greece.

When considering the four countries considered in this chapter, it is first interesting to note how their position changed substantially in the last half century. In 1960 life expectancy at birth was 71.12 in the United Kingdom, 69.77 in the United States, 69.12 in Italy, and 68.16 in Greece. By 2015, however, although there had been a reduction of longevity in all of these four countries, in the United Kingdom life expectancy in 2014 was 81.30 and went down to 80.95 in 2015, in the United States it moved from 78.84 in 2014 to 78.53 in 2015, in

Italy from 83.09 in 2014 to 82.54 in 2015, and in Greece from 81.38 in 2014 to 81.03 in 2015. In 2016, life expectancy stagnated in Italy and Greece and increased in most high-income nations (Ho & Hendi, 2018), but in the United States and United Kingdom it continued to decline.

Table 1. Differences in life expectancy at birth in 30 high-income countries between 2015 and 2014

Country Name	2014	2015	2016	2017	Diff. 2015-2014
Australia	82,3	82,4	82,4	82,4	0.1
Austria	81,4	81,1	81,6	81,6	-0.3
Belgium	81,2	80,9	81,4	81,4	-0.3
Canada	81,8	81,9	82,3	82,4	0.3
Switzerland	83,1	82,8	83,6	83,6	-0.3
Czech Republic	78,8	78,5	79,0	79,4	-0.3
Germany	81,0	80,6	80,9	80,9	-0.4
Denmark	80,7	80,7	80,8	81,0	0.0
Spain	83,2	82,8	83,3	83,3	-0.4
Finland	81,1	81,4	81,4	81,4	0.3
France	82,6	82,3	82,5	82,5	-0.3
United Kingdom	81,3	80,9	81,1	81,1	-0.4
Greece	81,3	81,0	81,3	81,3	-0.3
Croatia	77,4	77,2	78,0	77,8	-0.2
Hungary	75,7	75,5	76,06	76,0	-0.2
Ireland	81,3	81,4	81,7	81,9	0.1
Iceland	82,8	82,4	82,2	82,2	-0.4
Israel	82,1	82,0	82,4	82,6	-0.1
Italy	83,0	82,5	83,2	83,2	-0.5
Japan	83,5	83,7	83,9	84,0	0.2
Korea, Rep.	81,7	82,0	82,2	82,6	0.3
Netherlands	81,7	81,5	81,5	81,5	-0.2
Norway	82,1	82,3	82,4	82,5	0.2
New Zealand	81,4	81,4	81,6	81,6	0.0
Poland	77,6	77,4	77,8	77,8	-0.2
Portugal	81,1	81,1	81,1	81,1	0.0
Slovak Republic	76,8	76,5	77,1	77,1	-0.3
Slovenia	81,0	80,7	81,1	81,1	-0.3
Sweden	82,2	82,2	82,3	82,3	0.0
United States	78,8	78,6	78,5	78,5	-0.2

Source: World Development Indicators (2018).

The simultaneous reversal of life expectancy in high-income countries around the year 2015, after more than a century of steady increases, caught many epidemiologists by surprise. What can explain such a sudden change of direction in so many diverse, though economically developed, countries? In spite of the obvious national and cultural heterogeneity, are there common patterns of explanations that can help to understand mortality crises across high-income countries?



Source: World Development Indicators database (2018).

Figure 3. Life expectancy at birth in Italy, Greece, United Kingdom, and United States (1960–2017).

A variety of authors have provided different explanations for the health reversals in high-income nations that include the following:

1. Peak longevity
2. Rise of infant mortality
3. Deaths in old ages
4. Suicides and drug overdose in working-age men

Potential Explanations for the Decline

Peak Longevity

The search for the main determinants of the decline in life expectancy around 2015 in high-income countries should start from a simple question: Is it possible that “the human race has finally reached its biological limits of longevity?” Indeed, life expectancy cannot be expected to increase forever. The peak longevity hypothesis is worth further investigation; however, it is challenged by evidence of the relentless improvements of population health at the country and subpopulation level. First, longevity has increased beyond the average of most high-income nations and well beyond the longevity of the United States (79 years) and the United Kingdom (81 years) in many countries. It is sufficient to state that in 2017 life expectancy at birth reached 85, 84, and 84 years in Hong Kong, Japan, and Switzerland, respectively. Second, in the best performing countries and population groups that achieved exceptional levels of longevity, life expectancy continues to improve, and there is no indication of slowing down (Christensen, Doblhammer, Rau, & Vaupel 2009; Jasilionis & Shkolnikov, 2016; Oeppen & Vaupel, 2002). The most important causes of death, heart diseases and malignant neoplasm, are still in steady decline in most high-income nations.

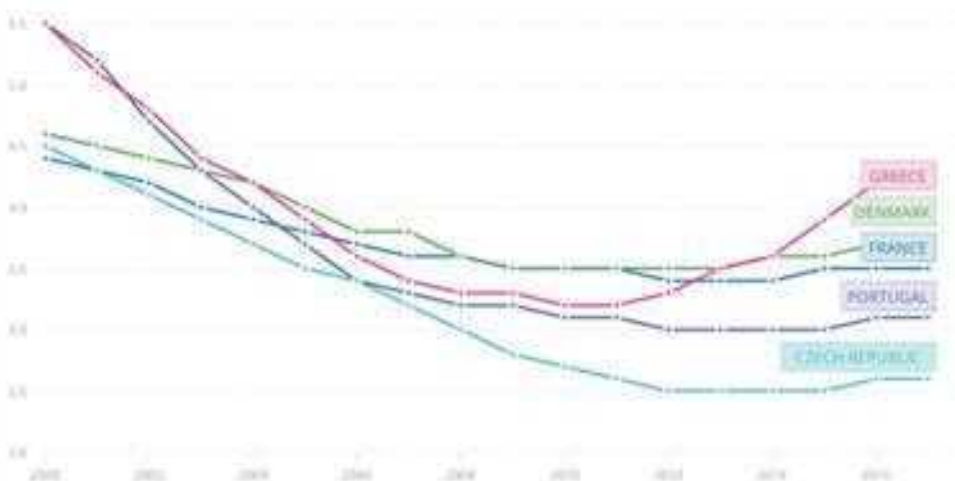
Data from the WHO Mortality database clearly show that standardised mortality for all cancers have been reducing in United States, United Kingdom, and Italy, and only in Greece it has started to rise since 2011. More importantly, recent advances in longevity and reductions in mortality occurred in most age groups, including the elderly and those aged more than 80 years (Christensen et al., 2009).

In spite of the impressive improvements in health achieved in the last decades, evidence seems to indicate that there is still some room for improvement in health in the healthiest and most advanced economies.

Rise of Infant Mortality

Some authors indicate that infant mortality may be a possible culprit for the reduction in life expectancy in high-income nations around 2015. Recently, the Office for National Statistics (2018) warned against the worrisome rise of infant mortality rate in England and Wales since 2014 and highlighted that it especially affected the poorest and underserved communities. Indeed, after a steady decline since the 1980s, infant mortality increased from 3.6 deaths per 1,000 live births in 2014 to 3.8 deaths per 1,000 live births in 2016.

Recent deteriorations in child health have not only been experienced in the United Kingdom, but even more worrisome trends occurred in Greece where infant mortality rate sharply increased from 3.2 per 1,000 live births in 2011 to 4.3 per 1,000 live births in 2017. According to a study based on the Global Burden of Disease (GBD), the under-5 mortality rate in Greece has increased especially in connection with deaths due to neonatal hemolytic disease and neonatal sepsis in children younger than 5 years (GBD Study Collaborators, 2018). Numerous authors have attributed such trends not only to the effects of the global financial crisis, but also to the application of austerity policies that have generated important changes in the quality and accessibility of healthcare services for maternal and child health.



Source: World Development Indicators (2018) based on estimates from the UN inter-agency Group for Child Mortality Estimation (UNICEF, World Bank, WHO, UN DESA, Population Division).

Figure 4. Infant mortality rates (per 1,000 live births) in Greece, Denmark, France, Portugal, and Czech Republic (2000–2017).

When considering other high-income nations, however, apart from the discrepancy between data in infant mortality between ONS and the World Development Indicator (WDI) in the United Kingdom (the former indicates an increase of infant mortality while the latter a decrease from 3.8 to 3.7 per 1,000 live births), the case of Greece is really exceptional. In most high-income nations, between 2014 and 2017, infant mortality continued to decrease, and it increased slightly (0.1 per 1,000 live births) only in four additional advanced economies: from 3.6 to 3.7 per 1,000 live births in Denmark, from 3.4 to 3.5 per 1,000 live births in France, from 3.0 to 3.1 in Portugal, and from 2.5 to 2.6 per 1,000 live births in the Czech Republic. In the United States and Italy, infant mortality reached a plateau at 5.7 deaths per 1,000 live births and 2.9 deaths per 1,000 live births in 2016, respectively.

Worsening Elderly Health

Another hypothesis for the decline of life expectancy in 2014 regards the worsening health status of the elderly population. Evidence from the United Kingdom has shown that the population over 65 years old have borne the brunt of deceleration in life expectancy gains and may be the key reason for the decline after 2015 (Hiam, 2018). Indeed, research shows that an increase of premature deaths in the population over 65 years in 2014–15 has been experienced in several European countries (European Monitoring of Excess Mortality for Public Health Action, 2016).

A recent article by Ho and Hendi (2018) indicated that the increasing mortality in older ages was associated with deaths due to respiratory diseases in the same year. In 2014–2015 there was a particularly severe influenza season that may have put old people at higher risk of mortality, especially those affected by Alzheimer's disease and other nervous system disorders and cardiovascular diseases. Cold weather has also been cited as one of the potential causes for the increase of mortality in England in 2015 by another study (Newton et al., 2016). As noted by Hiam, Dorling, Harrison, & McKee (2017), however, winters in most high-income countries have become progressively milder in the last few years due to climate change, and in the same years there has also been a decrease in funding to healthcare and social welfare programmes (Green, Dorling, Minton, & Pickett, 2017).

Other drivers of the increase in old-age mortality include circulatory diseases, Alzheimer's disease, mental disorders, and other problems of the nervous system. Yet, research seems inconclusive in establishing whether the generalised decline in 2015 was driven by any particular cause-specific mortality increase among the elderly. Moreover, according to Ho and Hendi, 2018, the declines in life expectancy across selected high-income nations were gender-specific and some countries did not experience them at all: Finland, Japan, Australia, Norway, Canada, and Denmark. The only two countries that experienced declines in life expectancy for two consecutive years, both in 2015 and 2016, were the United States and the United Kingdom. It is possible, as admitted by the authors of the analysis, that contributing factors for the decline of life expectancy in 2015 may include socioeconomic inequality, and erosion of social protection may have played a role in elderly health and these mortality crises.

Drug Overdose in Working-Age Men

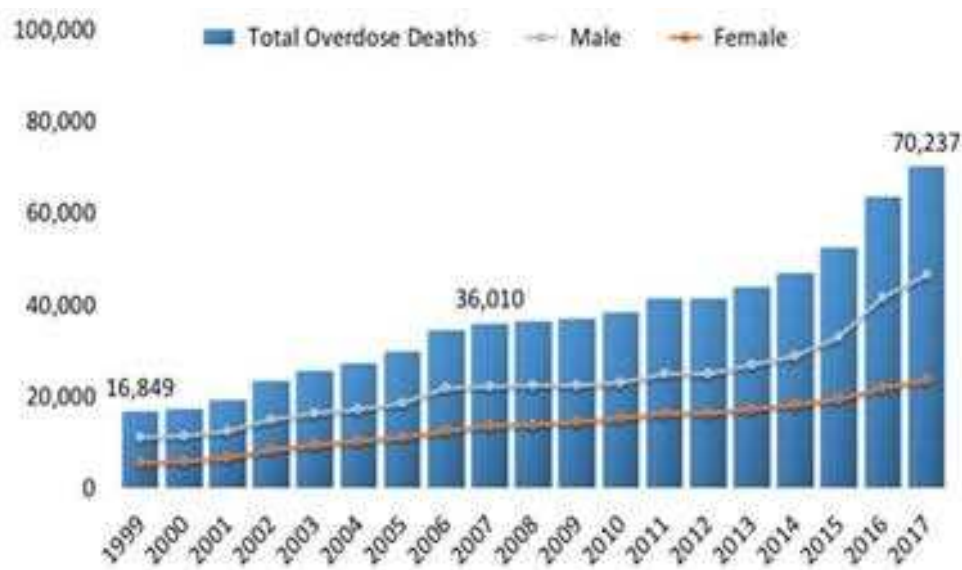
Some authors have highlighted the importance of declining health status in working-age men as the key explanatory factor for the rise of mortality in 2015. Numerous reports indicate that the decline of life expectancy in the United States and a major reason for its poor health

performance in the last decades include a sharp rise of drug overdose (Barbieri, 2018; Ho & Hendi, 2018). Indeed, the number of deaths due to drug overdose in the United States rose from 16,849 in 2000 to 70,237 in 2017 (Centers for Disease Control and Prevention [CDC] Wonder Online database, 2019). This rapid increase is exceptional by any standard, and the United States, with about 4% of the world's population, has now approximately 33% of the world's drug overdose deaths.

Table 2. Infant mortality rates (per 1,000 live births) in 20 high-income countries (2014–2017)

Country Name	2014	2015	2016	2017	Diff. 2017 - 2014
Australia	3,3	3,2	3,1	3	-0,3
Austria	3,1	3	3	2,9	-0,1
Belgium	3,3	3,2	3,1	3,1	-0,2
Bulgaria	7,4	7	6,7	6,3	-1,1
Canada	4,7	4,7	4,6	4,5	-0,2
Switzerland	3,8	3,8	3,8	3,7	-0,1
Czech Republic	2,5	2,5	2,6	2,6	0,1
Germany	3,3	3,3	3,2	3,1	-0,2
Denmark	3,6	3,6	3,7	3,7	0,1
Spain	2,8	2,7	2,6	2,6	-0,2
Estonia	2,6	2,5	2,3	2,1	-0,5
Finland	2,1	2	1,9	1,9	-0,2
France	3,4	3,5	3,5	3,5	0,1
United Kingdom	3,8	3,8	3,7	3,7	-0,1
Greece	3,6	3,9	4,2	4,3	0,7
Croatia	4,2	4,1	4	3,9	-0,3
Hungary	4,5	4,3	4,1	3,8	-0,7
Ireland	3,2	3,1	3	3	-0,2
Iceland	1,8	1,7	1,7	1,6	-0,2
Israel	3,2	3	2,9	2,9	-0,3
Italy	3	3	2,9	2,9	-0,1
Japan	2,1	2,1	1,9	1,9	-0,2
Lithuania	4	4	3,8	3,4	-0,6
Luxembourg	2,2	2,2	2,1	2,1	-0,1
Latvia	4,7	4,3	3,9	3,6	-1,1
Monaco	2,9	2,8	2,8	2,7	-0,2
Netherlands	3,5	3,4	3,4	3,3	-0,2
Norway	2,3	2,2	2,1	2,1	-0,2
New Zealand	4,7	4,6	4,5	4,4	-0,3
Poland	4,3	4,2	4,1	4	-0,3
Portugal	3	3	3,1	3,1	0,1
Romania	8,4	7,8	7,2	6,6	-1,8
Slovenia	2	1,9	1,8	1,7	-0,3
Sweden	2,4	2,4	2,4	2,3	-0,1
United States	5,9	5,8	5,7	5,7	-0,2

Source: World Development Indicators (2018) based on estimates from the UN inter-agency Group for Child Mortality Estimation (UNICEF, World Bank, WHO, UN DESA, Population Division).



Source: Centers for Disease Control and Prevention (CDC), National Center for Health Statistics, Multiple Causes of Death (1999–2017) on CDC Wonder online database.

Figure 5. Total number of deaths due to drug overdose among all ages, by gender in the United States (1999–2017).

Although deaths due to drug overdose can be a key contributor for the decline of longevity in the United States, it does not seem to be as important in other high-income nations. According to a report by Public Health England, drug misuse among younger people has been mentioned as one of the causes for the decline in life expectancy in the United Kingdom in 2014 (Hawkes, 2018), and indications of recent increases of drug overdose have also been recorded in Australia and Canada. Yet, these figures remain far below and not comparable to that experienced in the United States (Ho & Hendi, 2018). Using the Human Mortality Database of the World Health Organization (WHO), Barbieri (2018) conducted a cross-national analysis of twelve high-income countries to estimate the contribution of drug-related deaths to explain the US disadvantage in mortality. Results showed that drug-related deaths contributed to about 40% of the US disadvantage in mortality among working-age men. However, they also showed that the exceptional increase in drug-related deaths was specific to the United States only and not very relevant to explain the mortality crisis of 2014 other high-income nations.

The Need for a Comprehensive Approach in the Study of Mortality Crises

There is a substantial degree of heterogeneity in the identification of plausible factors behind the 2015 mortality crisis in high-income countries: In Greece, there has been a significant rise of infant mortality rate, in England and other European nations the decline in life expectancy seems attributable to a worsening of health conditions among the elderly, while in the United States the role of drug overdose seems having played an important role

compared to other countries. Further research is needed to investigate the factors that led to a concomitant mortality crisis in 2015. On the one hand, it is necessary to investigate the causes of the causes of such mortality crises including socioeconomic changes and policies. In the United States, several authors have studied the decline in life expectancy in the context of the so-called deaths of despair, which, in turn, have been associated with policies of de-industrialisation, the rise of income inequality, and the socioeconomic decline affecting middle-aged White Americans. In Greece and the United Kingdom, researchers have contextualised the rise of infant mortality and old-age mortality, respectively, to austerity policies and budget cuts that have undermined important social and health services, disproportionately affecting the most underserved populations in both countries.

While investigating the political and contextual determinants of recent mortality crises, it is equally important to investigate the protective effects of reforms and to understand why some countries have not experienced mortality crises in 2015. Possible reasons may include stronger social protections, higher levels of social cohesion and social support, and lower levels of economic inequality.

**‘THE LIBERALISATION OF DESPERATION’:
THE RISE OF SUICIDES, ALCOHOL DEATHS, AND DRUG
OVERDOSES AMONG MIDDLE-AGED WHITE AMERICANS
AFTER TRADE LIBERALISATION POLICIES IN 2000**

The decline in life expectancy among so many high-income nations in 2015 raised several questions for researchers, along with hypotheses on mechanisms explaining why the United States lags behind other advanced economies in terms of longevity. Since the mid-1980s, the United States experienced a slow increase in life expectancy at birth compared to other high-income nations and now ranks below nations with much lower GDP per capita such as Portugal (81.12 years), Cuba (79.92 years), and the Czech Republic (79.47 years). What can explain the poor health record of the United States and such progressive deterioration of the US position in terms of health since the mid-1980s?

There are several explanations in the literature for the slower declines in mortality of major causes of death in the United States compared to other nations. Except for cancer mortality, which is lower in the United States than in other high-income nations, all causes of death seem to contribute to this health gap. As shown by Wilkinson and Pickett (2009), when compared to other rich nations, the United States performs quite poorly in a long list of health and social indicators including obesity and diabetes, infant mortality, mental health disorders, homicide, and economic and political determinants of health such as inequality, social distrust, access to healthcare, and access to education and social safety nets (Wilkinson & Pickett, 2009). However, a key health indicator that distinguishes the United States from other advanced economies is the sharp rise of mortality rates among White men aged 35–64 years around the early 2000s (Barbieri, 2018). In a widely publicised paper, Case and Deaton surprised the world of epidemiology by highlighting the fall of life expectancy among middle-aged White men as the only demographic group experiencing a mortality crisis in the United States and other high-income nations (Case & Deaton, 2017). This trend is exceptional

not only because it did not affect other nations and other underserved ethnic groups such as African American and Latinx populations, but also because the causes of deaths leading to the mortality crisis in the United States clustered around the determinants of psychosocial stress and mental health outcomes: suicides, alcohol-related deaths, and drug overdoses (Garcia, 2017). Some authors have called these cases “deaths of despair.”

What is behind the rise of suicides, alcoholism and chronic liver diseases, and drug abuse (or poisoning) among middle-aged White men since the early 2000s? Why are these mortality trends different among other ethnic groups such as African American and Latinx? In order to address these questions, it would be useful to first examine the different determinants of the deaths of despair in a coherent sequence of distal economic and political factors (e.g., globalisation, trade liberalisation, delocalisation, and decline of manufacturing industry, unemployment, and increasing income inequality) and proximal determinants (e.g., psychosocial stress, meaninglessness, sense of unfairness, and psychological resilience).

Distal (Economic and Political) Determinants

A rapid rise of deaths due to alcohol, suicides, and drug overdose does not occur in a vacuum, but it is often the result of upstream changes or societal level variations that may often involve other psychosocial mediators such as stress, depression, hopelessness, and meaninglessness. However, these variations are often connected to trends or policy changes that profoundly affected society, social relations, and individuals. Several authors have suggested that the rising rates of suicides and overdose among middle-aged White Americans may be attributable to the declining socioeconomic conditions of the working class due to an epidemic of job losses caused by labour market changes deriving from globalisation and trade liberalisation policies in the early 2000s.

Globalisation and Trade Liberalisation Policies

During the last four decades, there has been an acceleration of social, economic, and political change worldwide. Globalisation was supposed to bring about positive changes including higher living standards, higher access to goods and services, wider freedom of choice, and even better health conditions. However, some of these changes have also caused adverse consequences, especially in populations whose ability to adjust to the new circumstances was limited. Policies of globalisation and market deregulation, defined as the “degree to which market forces are allowed to operate without interference from outside intervention, especially in the form of government ownership, regulations and taxes” (De Vogli, 2013) have produced not only sharp increases of income inequality, but also changes in the labour market affecting the employment and job security of millions of families and workers.

Particular importance for the rise of mortality due to suicides, alcohol and drug-related deaths in the United States must be given to a specific type of globalisation and market deregulation policy: trade policies. Since the creation of the General Agreement on Tariffs and Trade (GATT) in 1947, economic growth has historically been the rationale and the justification behind trade liberalisation—the reduction of trade barriers such as tariffs, quotas, and import taxes—and the development of new free trade agreements (FTAs) (Khan, Pallot,

Taylor, & Kanavos, 2015). Trade liberalisation policies that increase export opportunities to foreign markets, lower the cost of imported goods, and attract foreign investment can, in theory, promote economic growth (Chang, 2002). Income generated from trade policies may, in turn, lead to better health given the historical link between GDP per capita and life expectancy across nations.

However, the impact of trade policies on population health largely depends on their distributional effects: Income-generating reforms can lead to better health to the extent that such income “trickles down” to the lowest socioeconomic strata of the population and reduce economic inequality. Trade liberalisation policies have been found to create a few “winners,” such as large transnational corporations (TNCs) that exploit lower tariffs abroad and delocalise production in countries where labour is cheaper, and far too many “losers,” such as low-skilled workers (EPHA, 2015; McNamara, 2015; Ottersen, 2014). Evidence from the North American Free Trade Agreement (NAFTA), for example, showed that it facilitated the penetration of TNCs into foreign markets, but reduced employment and wage levels in the United States especially in the manufacturing sector (Scott, 2003). Some authors, however, downplay the role of trade policies in the increase of inequality. Helpman and Limao (2016), for example, conducted a recent literature review and concluded that globalisation and trade policies explain only a fraction of increased inequality, which is largely due to an increase in the wages of low-skilled workers (which is expected to produce positive health effects on such populations). Pavcnick (2017) focused on low- and middle-income countries and reached similar conclusions, emphasising that, although the association between trade policy and inequality is real, it depends on contextual factors such as the mobility of workers and capital across firms, industries, and geographic locations.

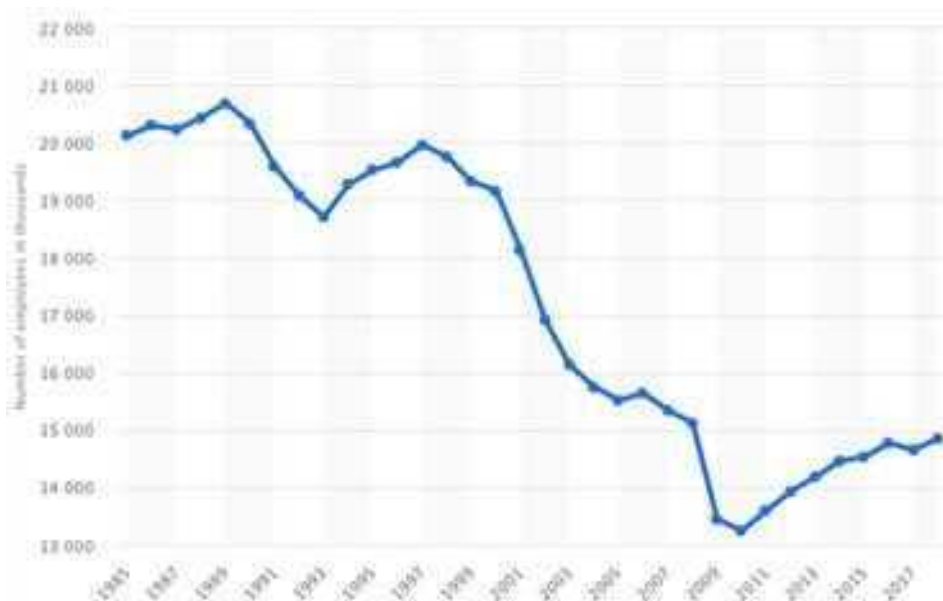
The proposed connection between trade policies and the rise of deaths due to suicides, alcohol use, and drug overdose since the year 2000 sounds like mere academic speculation. Yet, a few studies have already found empirical support for the hypothesis and identified a plausible relationship between macro-level economic and political factors and the deaths of despair in the United States. Pierce and Schott (2018) showed that US counties exposed to exogenous changes in international trade policy have experienced sharper increases in fatal drug overdoses, especially among Whites. According to these authors, the starting point of this epidemic of deaths of despair was October 2000, when the United States passed a bill granting permanent normal trade relations (PNTR) with China, eliminating the need for annual renewals of a policy of low tariffs between the United States and China and rendering production in China for export to the United States easier and more attractive than ever before. Although employment opportunities for low-wage workers have been declining before this trade policy, PNTR seems to have played a key role in the rise of the deaths of despair because its effects were abrupt, creating reallocation of large number of workers in a short period of time, and long-lasting at the same time. Hollingsworth (2017) found that macroeconomic changes at the county and state level were associated with increases in deaths and emergency room visits due to opioid overdoses. Another study by Adda and Fawaz (2016) showed that in areas with larger increases in import competition there were increased mortality and worsening of health indicators. Clearly, it is possible that the job losses experienced in the United States that led to the epidemic of deaths of despair can be attributable to other factors, not only to the passage of the PNTR. A recent paper by Handley and Limao (2017) emphasised the importance of China’s accession to the World Trade Organization (WTO) in 2001 which (together with other factors such as the particularly

favourable low exchange rate of the Chinese Yuan) may have improved competitiveness of Chinese goods and their successful export growth to the US market.

Labour Market Changes, Job Losses, and Job Insecurity

The first mechanism by which globalisation and trade liberalisation policies increased the deaths of despair is through changes in the labour market such as an increase of short-term employment, changes of labour types, reallocation of workers or career changes, and changes of regulations regarding workers' security and right. A study by Sullivan and Wachter (2009) found that mass layoff experiences were associated with a sharp increase in the probability of death among high-tenure workers. Browning and Heinsen (2012) and Classen and Dunn (2012) showed that employment duration mediated the association between job loss and deaths of despair.

Research showed that changes in labour force participation, especially in the manufacturing industry, have been pivotal in mediating the relationship between trade liberalisation policies and the rise of deaths of despair (Pierce & Schott, 2018). Autor (2014) found that workers with greater exposure to imports from China exhibited a stark decline in relative earnings. Of course, the reduction of employment in the manufacturing industry (Krueger, 2017) after trade liberalisation policies has been exacerbated by the outbreak of the 2008 global financial crisis. Such changes have disproportionately affected less educated Whites living in suburban areas, smaller cities, and rural areas in the heartland of the United States. There was a dramatic reduction of the number of private-sector manufacturing employees, from 19,167 million in 2000 to 13,251 million in 2010, for a total of almost 6 million jobs lost, mostly to China.



Source: Bureau of Labour Statistics.

Figure 6. Number of private-sector manufacturing employees in the United States from 1985 to 2018 (in thousands) after the US-China free trade agreement in 2000.

All these economic stressors took a heavy toll on White Americans. Unemployment is a serious risk factor for poor health not only because it is associated with decreased access to basic material items, housing, healthcare, and education, but also for its psychosocial effects. According to Amartya Sen (1997), who was awarded a Nobel Prize in economics, unemployment generates psychological harm because of loss of self-confidence, disruption of social role, anxiety about the future, sense of exclusion, and disruption of family and social relations. Unemployment can also be associated with social isolation and social exclusion. Researchers have found that unemployment correlates with a long list of adverse health effects including suicide, psychiatric morbidities (Ferrie, 2001), high blood pressure, and the onset of an array of different diseases (Catalano, Rook, & Dooley, 1986). The loss of emotional balance caused by unemployment seems also to be a major risk factor in the adoption of health-damaging behaviours such as alcohol consumption (Catalano, Dooley, & Wilson, 1993).

Another possible effect of globalisation and trade liberalisation is job insecurity. Job insecurity is a powerful chronic stressor because it increases life and economic uncertainty especially among low-skilled workers. For young people, it is a major obstacle for having a stable life, a marriage, vacations, and choices. Job insecurity makes also people more likely to change residence and disrupt family life and the pattern of social relationships that buffer them against stressful life situations. A group of social scientists investigated the health effects of job loss and insecure reemployment among white-collar civil servants after the privatisation of public services in England. According to their findings, insecure reemployment was associated with increases in minor psychiatric morbidities and with having four or more consultations with a general health practitioner in the last year, independent of financial strains and health behaviours (Ferrie et al., 1998). A recent study examined changes in the health status of civil servants whose employment security was threatened. A study of the effect of job losses resulting from a factory closure found that health began to deteriorate when redundancies were first announced, before people became actually unemployed (Beale, 1998). Job uncertainty has also been associated with a variety of adverse mental and physical health outcomes. Ferrie and colleagues (2002) found that loss of job security has adverse effects on self-reported health and minor psychiatric morbidity, which are not completely reversed by removal of the threat and which tend to increase with chronic exposure to the stressor. With regard to health behaviours, some studies reported higher unhealthy behaviours among people employed in insecure jobs (Domenighetti, D'Avanzo, & Bisig, 2000).

Increasing Income Inequality and Downward Social Mobility

Some authors have maintained that the epidemic of deaths of despair is associated with growing social deprivation for the most disadvantaged groups and growing economic inequalities. A number of studies have tried to explain the surprising trend of increasing mortality among Whites in the United States by focusing on “fear of downward social mobility” (Cherlin, 2016) and “inequality of opportunity” (Chetty, 2014). A corollary of this conceptual framework is the hypothesis of cumulative disadvantage for less educated workers, that is, the decline of their wages, social status, and purchasing power and a parallel increase in economic power in the top income brackets at the same time.

Since the early 1980, with the advent of neoliberalism, there have been increasing economic inequality in the United States and most high-income countries and a progressive

erosion of the purchasing power of the middle classes. These trends may have created a set of frustrating and stressful patterns, especially among low-educated Whites, as widening economic disparities distanced them from the most fortunate White reference points in higher social classes. According to Richard Frank, as inequalities widen, and the top earners set new standards in the pattern of material well-being and conspicuous consumption (e.g., bigger houses, bigger cars), the rest of society is forced, especially those who view them as “reference points,” to engage in “defensive spending” to maintain relative status (Frank, 1999). Earning enough extra income to keep up with the rising levels of conspicuous consumption becomes more and more important as standards of living rise and social comparison may create status anxiety. It is possible that White Americans have been disproportionately affected by status anxiety for the sense of entitlements given by their ethnicity and therefore have been hit most severely by the erosion of their socioeconomic conditions.

In an editorial published in the *New York Times*, Cherlin (2016) asked the question, “Why are White deaths rising?” Reference group theory may help. White Americans may be comparing their conditions against prior generations of working-class Whites, who fared better in terms of employment opportunity and wages. This comparison may make them feel worse off. Conversely, minorities may compare themselves against prior generations who had fewer opportunities, and this may make them feel better off (Monnat, 2017). African Americans and Latinx may feel a sense of progress that resonates with the natural inclinations of people to improve their own status. Whites may, on the other hand, feel that their status is getting worse.

Note that during the years of increasing inequality in the United States, while gaps in educational achievement and proficiency have widened across income groups, they have narrowed between minorities (Blacks and Latinx) and Whites (Porter, 2015; Reardon & Portilla, 2015). Inequality in life expectancy between Blacks and Whites have moved from 7 years in 1990 to 3.4 years in 2014 (Case & Deaton, 2017; Tavernise, 2016). These figures indicate a special, unique type of effect of policies on White Americans. The relationship between inequality and frustration, unhappiness, and anger of White Americans was highlighted after the 2016 US election of Donald Trump. A study found that in those US counties where a higher percentage of deaths of despair have occurred, there has also been a higher proportion of votes for Trump (Monnat, 2016). Another study showed that these areas are also disproportionately affected by high levels of inequality and unemployment, especially jobs lost in the manufacturing industry.

Proximal (Psychosocial) Determinants

Chronic Stress, Status Anxiety, Social Exclusion, and Powerlessness

A key mediator between trade liberalisation, job loss, and deaths of despair is stress. Although stress is largely related to objective stressors in the environment, perceived stress is mediated by people’s appraisal of the external situations. When confronting socioeconomic stressors, people evaluate whether these demands pose a potential threat (primary appraisal) and whether sufficient adaptive capacities are available to cope with them (secondary appraisal). If they find the socioeconomic demands taxing or threatening, and at the same

time view their coping resources as inadequate, they perceive themselves as under stress. The negative appraisal of stress may result in negative emotional states such as anxiety, loss of self-esteem, and powerlessness. It may also affect the deeper feelings of individuals including life purpose (Cohen, 1997).

Researchers have identified marked differences in terms of stress, worrying, and anger between Whites and minorities (Graham, 2017). White Americans, in spite of their higher life expectancy and better material conditions, are in general worse off in terms of mental health indicators such as depression, anxiety, and suicides than African Americans (Assari & Lankarani, 2016). The former group performs poorly across most psychosocial factors, indicating a high level of distress and hopelessness at all income levels. Reasons explaining why Whites have higher level of stress than minority counterparts include lower levels of resilience and poorer coping strategies.

When confronting stress such as being fired, individuals evaluate their resources to determine whether they can cope with the situation. Coping strategies refer to the specific efforts, both behavioural and psychological, that people employ to master, tolerate, reduce, or minimise stressful events. Two general coping strategies have been distinguished: actions designed to directly alter the threatening conditions (e.g., flight or fight) or thoughts or actions whose goals are to relieve the emotional stress response such as cognitive restructuring and denial of danger (Cohen, Underwood, & Gottlieb, 2000). When stressors exceed the adapting capacity of an individual to deal with it and coping strategies are unsuccessful, the results are psychological states associated with poor health and unhealthy behaviours such as hopelessness, learned helplessness, and powerlessness (Syme, 1991), or the belief that an individual cannot determine the occurrence of outcomes (Seeman, 1959).

Stress-Relieving, Self-Destructive Behaviours

When people are affected by chronic stress and status anxiety, certain behavioural responses such as alcohol consumption and drug use may be viewed as having perceived adaptive benefits in the short run as stress relievers, although in the long run they will produce damaging effects (McEwen & Seeman, 2000). In a sense, they are acts of self-medication. Under the influence of economic problems, stressful social and physical environments, low job satisfaction, unemployment or the threat of unemployment, and lack of influence and control over one's life, the individual is more likely to adopt poor health behaviours. These behaviours are functional because they may give short-term relief in a stressful situation. In constrained economic circumstances, alcohol and drug use can be one of the few activities undertaken for personal pleasure and one that provides some respite from the strain of coping with the consequences of material deprivation and status inferiority (Davey-Smith, 1996).

Lack of Sense of Purpose/Meaninglessness

Researchers have found that an important determinant of health is meaning in life and an overall sense of coherence that life makes sense. People are more likely to cope and succeed in dealing with stressors if they possess a positive motivational state, a determination to meet personal goals and a will to survive under adverse social, economic, and political conditions. Exposure to adverse circumstances of life, together with unsuccessful coping strategies and learned powerlessness, however, can lead to depression and a sense of meaninglessness. Lack of purpose in life, or the lack of belief that life provides suitable challenges and rewards, such

that life continues to be worth living, has been associated with poorer health outcomes and self-destructive behaviours (Antonovsky, 1979; Burton, 1988).

Socioeconomic stressors can make people question the meaning of their life through uncertainty and loss of control. Sense of purpose can also be lost when people lose their social roles (social integration) and lose social bonds (social control). Stressors—whether social, economic, or political—make it more difficult to predict the future. This uncertainty means that it is difficult for anyone to set out where they expect to be in 5 or 10 years' time. This raises particular difficulties for individuals and families. This affects people's ability to plan their life and their vision of the future. Loss of purpose in life can even increase the risk of suicide or affect a person's motivation to adopt healthy behaviours (Cohen et al., 2000).

Social Exclusion and Social Support

A possible mediator between changes in labour market, declining social status, and the rise of deaths of despair is social exclusion. Social integration is the extent to which an individual participates in a broad range of relationships. Those who participate in a social network are subject to social controls and peer pressures that influence normative health behaviours. Integration in a social network is also presumed to provide a source of positive effects such as self-worth because of demonstrated ability to meet normative role expectations. These positive psychological states are presumed to be beneficial because they reduce psychological despair, result in greater motivation to care for oneself, or result in suppressed neuro-endocrine response and enhanced immune function. Having a wide range of network ties also provides multiple sources of information and thereby increases the probability of having access to an appropriate information source. Information could influence health-relevant behaviours or help one to avoid or minimise stressful or other high-risk situations. Being part of a large social network may also operate to prevent disease by providing tangible and economic services that result in better health and better healthcare for network members (Cohen et al., 2000).

The feeling of being ostracised by the rest of society because of declining social status and loss of employment produces shame, depression, anxiety, anger, and a sense of alienation, and it decreases feelings of control and self-esteem. Social exclusion, or inadequate participation in a society's structure of opportunities, can interact with other socioeconomic stressors in determining self-damaging behaviours. Acquisition of core social roles, such as the work role, the family and marital role, and civic roles, contribute to self-regulation in adult life, strengthening a sense of self-esteem, self-efficacy, and belonging (self-integration). It is argued that exclusion from or loss of core social roles impairs personal self-regulation and triggers a state of "social reward deficiency." This state, in turn, elicits prolonged stressful experience, and it may reinforce a person's craving for stress-relieving, potentially addictive health-damaging behaviour. In extreme cases, it may lead to suicide (Siegrist, 2000).

Social support can also protect individuals against stressful events by preventing a particular situation from being appraised as highly stressful. The belief that others will provide necessary resources may redefine the potential for harm posed by a stressful situation. Support beliefs may reduce or eliminate the affective reaction to a stressful event, calm the neuroendocrine system, dampen physiological responses to the event, or prevent maladaptive behavioural responses (Cohen, 1989).

Psychological Resilience

Resilience refers to an individual's ability to adapt to stressful circumstances and remain healthy in spite of adversity. The increase of mortality due to suicides, alcohol use, and drug overdose among only White Americans raises several questions on the characteristics that make them less resilient than minorities when facing adverse circumstances. Researchers found that Whites not only have a higher proportion of mental health disorders and higher level of unhappiness, but also are less optimistic and more hopeless compared to African Americans and Latinx (Graham, 2017).

There may be several reasons why African Americans and Latinx are more resilient than Whites. First, minorities that used to be disproportionately exposed to history of deprivation and structural injustices may be better equipped in coping with adversity because they have more experience of it (Assari & Lankarani, 2016). In this regard, the role of expectations seems particularly important: White Americans expecting a higher status and better treatment in society may make them disproportionately at risk of stress and frustration. This explanation relies on what has been called "happy peasant, frustrated achiever" effect. As Paul Krugman, who was awarded a Nobel Prize in economics, once noticed, "we are probably referring to individuals who were raised to believe in the American Dream and are coping badly with its failure to come true" (Krugman, 2015).

A second potential reason may be the differential impact of labour market disruption and stronger competition for fewer jobs intensified by trade liberalisation policies and the global financial crisis. Such changes have made less educated Whites worse off, relatively speaking, compared to their minority counterparts. Paradoxically, the disappearing manufacturing jobs that contributed to the decline of social status among Whites may have resulted in minorities gaining ground and reduced the social gap between them and Whites. Researchers have found that both absolute income and relative social status relate to health.

A third possible explanation is that minorities may have access to stronger social support and social cohesion. Social cohesion refers to those features of social organisations such as networks of associations, high levels of interpersonal trust, and norms of mutual aid and reciprocity that act as resources for individuals and facilitate collective action (Coleman, 1990; Putnam, 1993). A large body of evidence shows that social cohesion is strongly related to mortality and other health indicators (Kawachi & Berkman, 2004). A county-level study showed that areas with higher levels of social cohesion experienced lower mortality rates for suicides, alcohol use, and drug use (Monnat, 2017) than areas characterised by low social connectedness or what some sociologists called "civic deserts." Latinx communities have been singled out in epidemiology for their high level of cohesion and strong social relations in what some have defined as the "Health Latino paradox" (Franzini, Ribble, & Keddie 2001). The role of community may also be a protective factor in African American lives, too.

Finally, minorities have been reported to be more religious than their White counterparts. Spirituality has been identified as an important factor in reducing the impact of stressors on health status. Religion and spirituality are possible stress-buffering mechanisms that reduce self-destructive behaviours (e.g., suicide, alcohol abuse) because they fulfil the functions of finding a meaning and purpose to life, and bind people together. Protective factors such as participation in community activities and religious attendance therefore play key roles in modifying the negative relationships between exposure to stressors such as unemployment and financial strain (Chatters, 2000) due to trade liberalisation policies and de-industrialisation.

‘ECONOMICALLY SUICID(ED)’: THE MENTAL HEALTH MORTALITY CRISIS IN THE UNITED STATES AND EUROPE AFTER THE 2008 GLOBAL FINANCIAL DOWNTURN AND AUSTERITY POLICIES

In the search of the putative causes of the decline in life expectancy among high-income countries, including the United States, United Kingdom, Italy, and Greece, some authors have highlighted the role of austerity policies and budget cuts in healthcare and social protection following the 2008 global financial crisis. Before examining the health effects of austerity and the economic crisis, it is necessary to analyse why austerity policies have been the implemented and the underlying causes of the global financial downturn.

The Causes of the 2008 Global Financial Crisis

In 2008, the world was hit by one of the worst economic recessions since the 1929 Great Depression. The outbreak of the financial downturn originated in the United States with the crisis of subprime mortgages, including infamous NINJA (no income, no job, no assets) loans or high-interest loans given to otherwise unqualified individuals. These loans, that often included low interest rates that increased sharply after an initial period of time, were sold to Wall Street investment banks that pooled them and repackaged them into “mortgage-backed securities” (securitisation). The proliferation of these securities tied to subprime mortgages created a “housing bubble” that eventually burst after many of those who had taken risky loans were unable to meet the loan repayments, creating panic in the global market and the bankruptcy of big banks like Lehman Brothers.

According to the Financial Crisis Inquiry Report of the Financial Crisis Inquiry Commission (2011), the “crisis was avoidable” and its major causes included:

1. Collapsing mortgage-lending standards and the mortgage securitisation pipeline
2. Over-the-counter derivatives
3. Excessive borrowing, risky investments, and lack of transparency
4. Dramatic failures of corporate governance and risk management at many systemically important financial institutions
5. Government that was ill-prepared for the crisis and delivered an inconsistent response
6. Failures of credit rating agencies
7. Widespread failures in financial regulation and supervision
8. Systemic breakdown in accountability and ethics

Although all these factors have importantly contributed to the Great Recession, it is also important to highlight the root causes of the downturn, including the policies and ideology that promoted financial deregulation and indiscriminate capital mobility in the last four decades. Using data on temporal trends in the frequency of banking crises over the last century in connection with an index of international capital mobility in the same period from Kaminsky and Reinhart (2008), it is possible to observe that both the 1929 Great Depression

and the 2008 Great Recession were anticipated by years of speculation, indiscriminate capital flow (Kaminsky & Reinhart, 2008), and excessive deregulation of financial markets. Just to put things into perspective, in 2007 mortgage-backed securities had risen to \$3 trillion (Johnson & Kwak, 2010), while credit-default swaps reached over \$50 trillion (Tett, 2009). In 2010, the total volume of off-exchange trading of financial derivatives, which Warren Buffet once called “financial weapons of mass destruction,” was estimated at \$601 trillion (Central Intelligence Agency, 2013). The world GDP in the same year was about 70 trillion.

Evidence shows that the frequency of banking crises was very low during the postwar period (1945–1971), a time characterised by low levels of capital mobility worldwide due to effective capital controls and regulations of the Bretton Woods System. The dismantling of this global system of regulations under the influence of the neoliberal ideology and the myth of the “self-correcting market” that guided national and global policies since the late 1970s, however, made the world at higher risk of financial instability and vulnerability to crises.

Global and national deregulation policies have also increased inequality both nationally and internationally. Historical trends from 1910 to 2010 show that peaks of excessive deregulation of financial markets and indiscriminate capital mobility coincided with the times when the highest percentage of total income went to the top 1% of the population in the United States (De Vogli, 2013b). The two most notable peaks are the Great Depression in 1929 and the Great Recession in 2008.

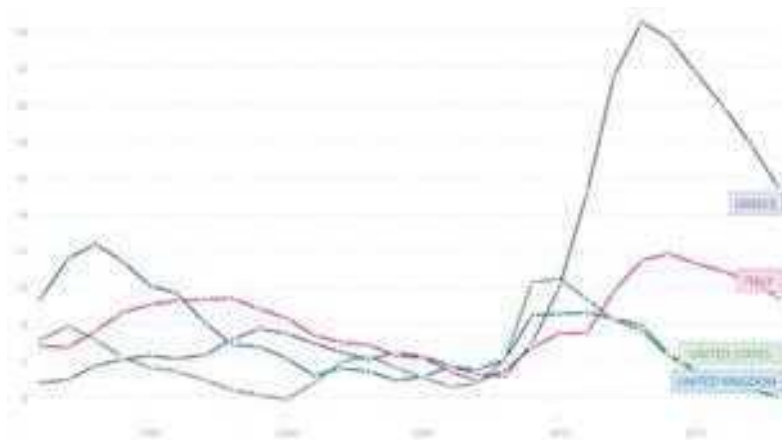
This may be no more than mere coincidence; however, there are plausible explanations to regard inequality as a determinant of financial instability. On the one hand, inequality may be a precondition of overspending and consumer indebtedness in low- and middle-income populations. On the other hand, high inequality may be associated with over-investment in short-term financial profiteering among the very wealthy, a precondition of price distortions and asset bubbles. Even economists associated with the International Monetary Fund (IMF) argued that there is a connection between inequality and financial instability and highlighted the importance of “restoring the bargaining power of low income groups as the most effective strategy to prevent future economic meltdowns” (Kumhof & Ranciere, 2011).

The Socioeconomic Effects of the Crisis: Unemployment, Poverty and Inequality

The crisis spread from the United States to the rest of the world and from the financial sector to the “real economy.” Europe was hard hit in 2010 by the so-called sovereign debt crisis that began in Greece when the new government revealed that previous administrations (helped by investment bank Goldman Sachs) had been misreporting budget data. From Greece the crisis spread to other European economies, especially those with a high debt over GDP ratio, or what The Economist magazine called the PIIGS: Portugal, Ireland, Italy, Greece, and Spain.

The effects of the crisis included millions of jobs lost, countless foreclosures, increased poverty, reduced spending and consumption, and the bankruptcy of innumerable banks and companies. According to the International Labour Organization (ILO), since 2007, worldwide unemployment has increased by more than 67 million people due to the crisis (ILO, 2013). At the same time, about 60 to 100 million people have been pushed into severe poverty (ILO, 2010). Male workers were particularly affected by the crisis and job losses. Greece was the hardest hit: The Greek male unemployment went from 5.14% in 2008 to 24.51% in 2013! Italy, too, experienced a severe male unemployment crisis that increased from 5.5% in 2008

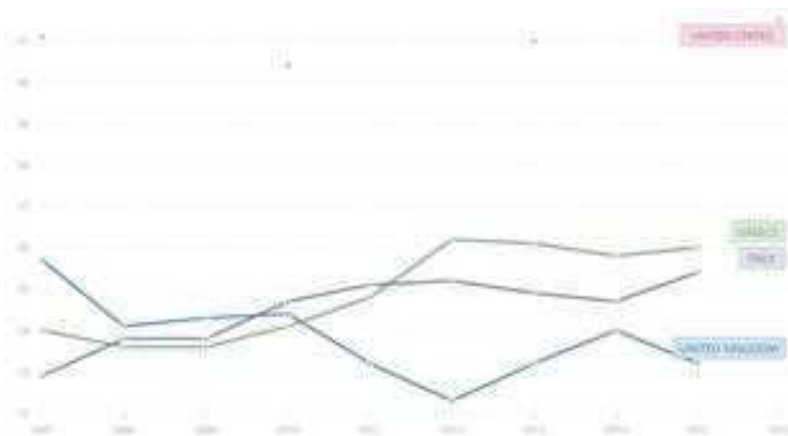
to 11.86%. In the United States, male unemployment changed from 6.09% in 2008 to 10.55% in 2010. In the United Kingdom, it grew from 6.06% in 2008 to 8.56% in 2010.



Source: World Development Indicators database (2018).

Figure 7. Male unemployment rate in Italy, Greece, United Kingdom, and United States (1991–2018).

Some authors have claimed that crisis and austerity produce regressive effects and have widened economic gaps both in Europe and in the United States (De Vogli, Kouvonen, & Gimeno, 2014; Piketty & Saez, 2014). When looking at the World Development Indicators (WDI) database, it is possible to notice that the Gini coefficient has increased in all four countries, but with some important differences. In Italy and Greece, it increased sharply. In Italy, the Gini index rose from 33.0 in 2007 to 35.5 in 2015, while in Greece it increased from 34.0 in 2007 to 36.0 in 2015. In the United States and the United Kingdom, the Gini index increased only slightly, from 41.0 in 2007 to 41.1 in 2016 in the United States and 33.0 in 2007 to 33.1 in 2015 in the United Kingdom.



Source: World Development Indicators database (2018).

Figure 8. Gini coefficient in Italy, Greece, United Kingdom, and United States (2007–2016).

The Mental Health Crisis: The Rise of Suicides and Mental Illnesses

After producing important economic and social consequences, the crisis resulted in changes in the health status of entire populations worldwide. Since 2008, suicides have increased in the United States and the Eurozone. A study conducted by Reeves and colleagues (2012) estimated that during the recessionary period after 2007, there were an estimated 4,750 excess suicide deaths in the United States alone. In Europe, as already pointed out by previous authors (Stuckler, Basu, Suhrcke, Coutts, & McKee, 2009a), standardised death rates for self-inflicted injuries increased in the years of the crisis reversing a decade of steady decline before 2007.

In the UK, between 2008 and 2010, there were an estimated 846 more suicides among men and 155 more among women than expected based on historical trends (Barr, Taylor-Robinson, Scott-Samuel, McKee, & Stuckler, 2012). In Greece, a country hard hit by the crisis, suicides have increased by 17% from 2007 to 2010 (Kentikelenis et al., 2011). Moreover, there was a 40% rise in the first half of 2011 compared with the similar period in 2010, with suicide attempts significantly elevated among persons with high scores of economic distress (Economou, 2011). In Italy, another country heavily affected by the Great Recession, a new study updating previous analysis on excess deaths due to suicides attributable to the crisis (De Vogli, Marmot, & Stuckler, 2012) showed that there were 1,251 and 123 excess suicides due to the economic crisis in men and women, respectively (De Vogli et al., 2019). Most of these excess suicides due to the crisis were attributable to a single age group: men from 45 to 64 years of age.

The crisis increased not only suicides but also mental health outcomes. A cross-national study in the United States and 13 European countries found that job losses among 50- to 64-years-olds were associated with a 28% and 8% increase in depressive symptoms in the United States and Europe, respectively (Riumallo-Herl, 2014). A study from Italy showed that the fall of GDP per capita and the rise of unemployment following the 2008 financial crisis resulted in a sharp increase of deaths due to mental and behavioural disorders across Italian regions, though many of these deaths were due to dementia and diseases of the nervous systems that are especially high among old ages (De Vogli, 2013a). In Greece, the prevalence of major depression increased from 3.3% in 2008 to 12.3% in 2013 (Economou, 2016).

A few years after the outbreak of the Great Recession, some commentators talked about “the hoax of suicides due to crisis” and belittled the effects of the economic slump describing temporal trends on suicides as “normal fluctuations” over time. The evidence, however, has now unequivocally shown that there have been indeed additional suicides due to economic problems created by the crisis that cannot be ascribed to normal secular trends. This is now supported three systematic reviews that robustly established that the Great Recession has increased suicides (Oyesanya et al., 2015), mental health problems (Frasquilho et al., 2016), and stress (Mucci, 2016) in Europe and the United States.

Austerity Policies and Health

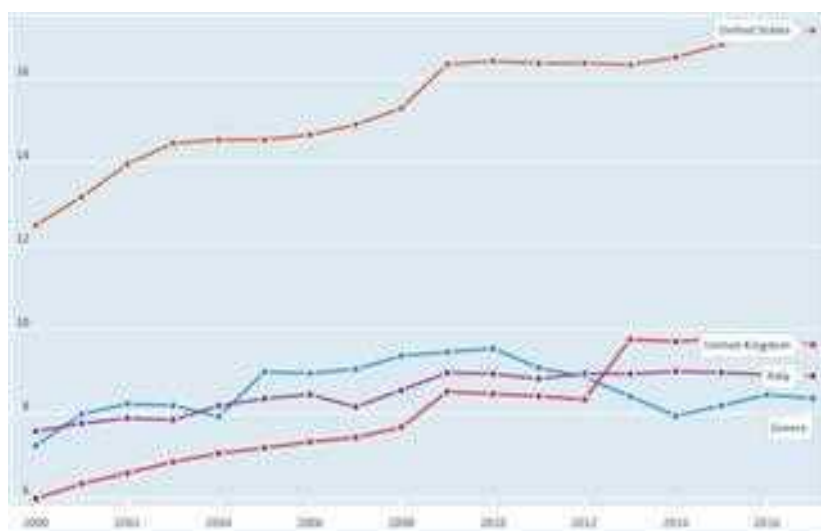
The decline of GDP per capita in the aftermath of the global financial crisis caused numerous governments to impose austerity policies to reduce budget deficits. While some countries decided to implement stimulus packages, others, especially in the Eurozone, implemented policies of fiscal consolidation imposed by the so-called troika formed by the European Commission, European Central Bank, and International Monetary Fund. In theory, austerity policies of deficit reduction do not need to be regressive and can be achieved by

increasing taxation for the top incomes; in practice, however, they place a disproportionate burden on the lowest incomes as they largely consist of reducing government expenditures by cutting social protection programmes and introducing user fees in healthcare. In Europe, about 80% of fiscal consolidation policies consisted in budget cuts instead of tax increases (Reeves et al., 2013).

When considering the impact of austerity policies on health expenditures from 2010 onwards, notice that indeed there was a relevant budget cut in healthcare in Greece, whose health expenditure (as percentage of GDP) moved from 9.5% in 2010 to 8.5% in 2017. Yet, it remained about at 9% in Italy, and even increased from 16.5% in 2010 to 17.5% in 2017 in the United States and from 8.5% in 2010 to 9.5% in 2017 in the United Kingdom.

Austerity measures produce several direct and indirect effects of physical and mental health (Stuckler et al., 2017). Directly, they can affect access to healthcare services that can result in increased risk for death and diseases. Indirectly, austerity policies may increase unemployment and poverty through the weakening of social protections that buffer health risks especially among low-income populations.

When considering direct effects, some authors have speculated that austerity measures have contributed to the rise in old-age mortality observed in 2014 in high-income countries (Dorling & Stuckler, 2017). A recent study in the United Kingdom found that cuts to social care and financial support for elderly pensioners were related to a rise of mortality among people aged 85 years and over (Loopstra, 2016). The introduction of user fees and cost shifting measures after the crisis increased out-of-pocket expenditures and catastrophic health expenditures among people aged 50 years old and over, according to the Survey of Health, Ageing and Retirement in Europe (SHARE). In Europe, the crisis consisted in an increase of “self-reported unmet medical need” that rose from 0.4% in 2010 to 3.4% in 2012, corresponding to an extra 1.5 million people, especially those affected by chronic diseases and low-income status.



Source: OECD Database (2019). Suicide rates (indicator).

Figure 9. Health spending (total of % of GDP) in United States, United Kingdom, Italy, and Greece, 2000–2017.

In terms of indirect effects, austerity measures may result in reducing public-sector employment causing job losses that can lead to suicides and mental health problems and reducing expenditures or eligibility for unemployment insurance. In the United Kingdom, for example, the Office of National Statistics indicated that there have been 500,000 public-sector job losses between June 2010 and September 2012 (Reeves et al., 2013). Moreover, austerity policies have been found to depress economic growth and prolong recessions. This may, in turn, promote a longer and deeper exposure to joblessness and poverty, especially among socioeconomically vulnerable people and communities.

Life Expectancy Improvements in Times of Recession

While financial crises are associated with rising unemployment, social instability, the rise of suicides and mental health disorders, unmet medical needs, and catastrophic health expenditures, evidence also shows that in the aftermath of the crisis, life expectancy at birth continued to rise in all high-income nations. With the exception of suicide rates, several studies have reported an overall reduction in mortality during times of economic recession (Gerdtham, 2006; Ruhm, 2008a, 2008b; Tapia-Granados, 2005a, 2005b, 2008). A review of economic recessions in Europe between 1970 and 2008 found that, although suicides tended to rise, road traffic fatalities were reduced, producing a slightly favourable net effect on overall mortality (Stuckler, Basu, Suhrcke, Coutts, & McKee, 2009b). Evidence on the improvements of longevity during crises is quite robust, and even in the years following the outbreak of the Great Recession (from 2008 to 2014), longevity showed a continuous upward trend halted by the generalised health reversal in high-income nations in 2015.

While searching for the causes of the decline in longevity around 2015, some authors have wondered whether such mortality crisis can be just a lagged effect of the global financial crisis in 2008. This is uncertain. What seems clearer is that economic crises produce differential impacts on different populations. Although recessions are likely to be detrimental for individuals who lose their jobs, houses, and businesses, and for poor households that experience severe reductions in savings, they may not necessarily cause unhealthy effects in the general population. Little research has analysed the mechanisms by which economic slumps lead to favourable health outcomes, but it seems that crises decrease exposure to dangerous working conditions, overwork, work-related stress, and environmental pollution. Recessions may also increase leisure time and physical activity that, in turn, can lead to activities that enhance health and well-being. Recessions may also have positive effects on social support, a key determinant of health and stress-buffering mechanism, because during recession there is more free time to engage with families and friends and to participate in community and civic activities in society.

Such favourable health outcomes in times of crises are more likely to occur in nations that have strong social protections. Economic buffering mechanisms, such as income subsidies and programmes, reduce stress and can allow people to reintegrate into the workforce after job loss. Targeted government support can also decrease the risk of depression and suicidal ideation (Jääntti, 2000; Vuori, 2002). A cross-national analysis showed that the historical association between unemployment and suicides in Europe varies with the level of investment in unemployment and family support programmes. In countries with low social investment, such as Spain, there was a positive correlation between unemployment and suicide; in countries with high social investments, such as Sweden, however, a rapid increase of unemployment was associated with in suicide reductions over time (Stuckler et al., 2009b).

A similar pattern was observed in Italy, where a study showed that the temporal correlation between unemployment and suicide rates from 2000 to 2010 was negatively associated with per capita expenditure on social services (De Vogli, 2013).

The role of social protection in buffering vulnerable populations from the negative effect of the crisis was highlighted by studies prior to the outbreak of the Great Recession. A study comparing the effects of the 1997 financial crisis in three emerging Asian economies found that, although the crisis increased mortality rates in Thailand and Indonesia, Malaysia—which rejected the IMF and World Bank structural adjustment programmes that required cuts of government spending and austerity—did not experience similar adverse health effects (Hopkins, 2006). An analysis of Eastern European countries showed that those nations that adopted harsher budget cuts after the collapse of the former Soviet Union in 1989 experienced higher tuberculosis incidence rates than countries that did not implement the same policies (Stuckler, King, & Basu, 2008). A study on the 1929 Great Depression in the United States found that American states that introduced greater social welfare spending as a result of the New Deal experienced faster reductions in infant mortality, respiratory diseases, and all-cause mortality (Fishback, 2007).

It may also be plausible to expect that recessions do not necessarily lead to worsening health outcomes in countries committed to progressive taxation or a relatively egalitarian distribution of resources. Notable examples of rising life expectancy in times of economic recession include those experienced by Japan and Finland, for example. In the 1990s, Japan suffered an economic recession that lasted for more than a decade, but experienced faster reduction in chronic diseases mortality than in preceding years of economic growth (Kondo, Subramanian, Kawachi, Takeda, & Yamagata, 2008). In Finland, the collapse of the Soviet Union in 1989 caused the Finnish GDP to drop by a third. Surprisingly, the Finnish all-cause mortality rate also dropped—more sharply during this recession than in the subsequent economic boom. As incomes fell, alcohol consumption declined by more than 10%, and road traffic injuries dropped by one-half (Valkonen et al., 2000). Another case is Cuba, which plunged into its worst economic crisis in history after the collapse of the former Soviet Union; in spite of the sudden deterioration of its economy, the health of the Cuban population actually improved (Franco et al., 2007).

POLICY RECOMMENDATIONS FOR HEALTH PROTECTION IN TIMES OF SOCIOECONOMIC AND POLITICAL CHANGE

This chapter was designed to provide technical assistance for the analysis of population-level mortality crises in times of socioeconomic and political change. It also aimed at discussing future research directions and implications for policy and health promotion in countries affected by economic crises and social instability. The chapter also focused on a few case studies of unexpected mortality crises such as the reductions in life expectancy in advanced economies in 2015, the surprising rise of mortality due to suicides, alcohol abuse, and poisoning among middle-aged White Americans since the early 2000s and the mental health crisis in the United States and Europe in the aftermath of the 2008 global financial crisis. Particular attention has been paid to four countries—the United States, the United

Kingdom, Italy, and Greece—as they represent important case studies for analytical comparison. What have we learned from these case studies?

(1) The analysis of the potential causes of the surprising decline in life expectancy in 2015 among high-income nations raised more questions than answers, for it is still unclear what really caused this unexpected mortality crisis. Hypotheses include the increased mortality in old-age groups in several European countries, including the United Kingdom and Italy, the rise of infant mortality that particularly affected Greece, and the rise of overdose deaths in working-age men that disproportionately influenced the health status of the United States. Paradoxically, it seems almost as if the two countries with the strongest economies and less rapid and lower increase of unemployment, such as the United States and UK, have seen their longevity more affected by the crisis than two countries, such as Italy and Greece, hit hard both by the drastic reduction of GDP per capita and the harsh austerity measures implemented by governments under the pressure of troika. In line with the sharp increase of suicides and mental health problems due to the crisis, Italy and Greece are the two high-income nations that experienced the most rapid decreases of happiness indexes from 2008–2010 to 2015–2017 according to the World Happiness Report, 2018 (Helliwell, Layard, & Sachs, 2018). Italy and Greece also have a quite low happiness index overall, as they occupy the 47th and 79th positions in the ranking, while the United States and United Kingdom occupy the 18th and 19th positions in the Happiness Index. It is still unclear what buffered Greece's and Italy's physical health and why the United States and the UK, which had experienced a small reduction of GDP and applied less harsh austerity measures, are the only two countries that experienced two consecutive years of longevity reduction in 2015 and 2016. Putative mechanisms may include not only stronger welfare policies, but also psychosocial factors such as social cohesion and social relations. Yet, more research is needed to verify such hypotheses.

(2) In spite of differences in terms of possible factors explaining the mortality crisis in different countries, general patterns seem to indicate a need to use a holistic perspective and pay attention to the multiple implications of socioeconomic and political changes that can produce a cascade of effects on health at the individual level. This view is corroborated by considering the crisis of deaths of despair since the adoption of trade liberalisation policies in the United States and the analysis of the health effects of the global financial crisis and austerity policies that have placed a heavy burden on vulnerable populations exposed to job losses, foreclosures, cuts of social protection, increased out-of-pocket health expenditures, and reduced access to healthcare services in both the United States and Europe. There is a need to do more research on the “political economy of health” to assess not only proximal determinants of mortality at the individual level, but also “the causes of the causes” of health by integrating different levels, pathways, and mechanisms of influence between policy change and health outcomes.

(3) The mortality crises that followed policy and socioeconomic change affected different social classes differently. Affected populations include those who lost their job after trade liberalisation policies in the manufacturing sector, or those who lost their businesses after the recessions of the global financial downturn, or those who could no longer afford to pay for healthcare services after the adoption of austerity policies to reduce budget deficits caused by the crisis. Evidence shows that unless governments intervene boldly to protect the most vulnerable populations from its effects, financial crises can have detrimental effects of health. Yet, not all people have been hurt by the crisis. Counterintuitively, however, life

expectancy continued to rise in the aftermath of the global financial downturn, corroborating previous evidence showing that recessions, especially for countries that have stronger welfare services and lower inequality, can even result in a “healthy degrowth.” Although recessions can kill some of the populations affected by its economic changes, they may not necessarily cause unhealthy effects for the general population. Economic slumps may lead to favourable health outcomes such as decreased exposure to dangerous working conditions, overwork, work-related stress, and environmental pollution. Recessions may also increase leisure time and physical activity, and free time for social relations and social engagement that, in turn, can lead to activities that enhance health and well-being.

(4) In spite of country-specificity and contextual factors, there may be a few lessons to be learned about common determinants and shared patterns of explanations for these mortality crises. On the basis of existing scientific literature and ad hoc descriptive data analyses, it would be useful to develop coherent conceptual frameworks that focus on a variety of possible mechanisms connecting political and economic changes and unexpected increases in mortality. Psychosocial factors must be given particular attention for modern mortality crises are increasingly affected by mental health problems and psychological and social issues. In times of crises, it is essential to develop interventions that promote psychological resilience and restore hope and sense of purpose in a population affected by the loss of identity and meaninglessness of adverse socioeconomic and political change. Individual-level and structural-level programmes can complement one another and work effectively in saving lives and promote health in times of crisis.

(5) Large and sudden socioeconomic changes following policies such as a trade liberalisation and austerity, even when they are truly necessary and important for economic benefits, can entail not only enormous social and health problems but also political turmoil. Social costs of underserved communities on the receiving end of trade liberalisation and deregulation policies are generally underestimated or neglected by governments, mainly driven by the need to promote GDP growth and meet the interests of the most influential sectors of society including banks and large corporations. Yet, profound social changes, such as those observed on occasion of recent political or economic reforms, may have unexpected long-standing effects on society and exacerbate social conflicts, anger, government distrust, and the rise of populist and extreme right-wing parties such as those who have gained support in the United States and Europe since 2008. Evidence on the association between the area-level prevalence of deaths of despair and support for Trump in 2016 US election is revealing (Monnat, 2016). The analysis of past and current cases of social examples of political change following socioeconomic crises and austerity programmes, such as the rising support to the Nazi party after the introduction of fiscal consolidation measures in Germany between 1929 and 1933 (Galofre-Vila et al., 2017), may be crucial in informing policy leaders how to prevent future political crises.

(6) The rise of overdose deaths after the implementation of trade liberalisation policies in the United States in the early 2000s caught most epidemiologists by surprise. Usually, addictions are conceptualised and treated as psychological problems, and interventions are performed at the individual level. Some authors have reduced the case of the so-called deaths of despair to a mere increased availability of drugs and have thus called for interventions to reduce the supply side of opiates. Of course, clinical interventions and policies to restrict availability of drugs are important. Yet, the root causes of the rise of mortality due to drug overdose deaths need to be found in the social, economic, and political factors that caused

massive job losses in the manufacturing sector. Individual-level interventions to deal with mental health disorders caused by an economic problem are not very effective, because they do not tackle the upstream factors influencing mental health in the first place. Reducing availability of drugs may be useful. However, if people take drugs out of despair or sense of meaninglessness and powerlessness, even if you remove all drugs from the market, the desperation remains. Mentally affected people will find other way to express their psychological suffering. Economists and politicians designing policy changes such as trade liberalisation measures should be expected to deliver a health and mental health impact assessment to make sure that the economic benefits of a free trade agreement do not come at high social and psychological costs.

(7) Austerity policies are a failed, unhealthy experiment on countries and populations. They have not only harmed the most vulnerable sectors of society, but also failed to restore economic growth, especially in the Eurozone. Austerity policies have been revealed to be self-defeating not only because they further increased inequities in wealth and health, but also because they exacerbated the debt crisis they were supposed to overcome. Countries that have applied harsher budget cuts experienced sharper declines of GDP per capita and rises of unemployment rates. In a recent empirical analysis, even the IMF, which championed austerity and structural adjustment programmes in the developing world for over three decades, admitted that “fiscal consolidation has contractionary effects on private domestic demand and GDP” (Guajardo, Leigh, & Pescatori, 2011). Clearly, countries with a high debt-over-GDP ratio, such as Portugal, Ireland, Italy, Greece, and Spain, must find revenues to contain the deficit. Yet, rather than operating regressive cuts on social welfare and healthcare, they can resort to progressive taxation and targeted social benefits. It is time to make the rich and multinational corporations pay their fair share of taxation. Top marginal tax rates are at the lowest level since the end of World War II in most high-income nations, and a large proportion of world’s wealth is hidden in tax havens. This, for example, allowed about 60 multinational corporations, including Amazon, Netflix, IBM, and General Motors, to pay 0% in taxes in 2018!

(8) Action to reduce inequality and limit or abolish tax havens is urgent. The lost tax revenue from money transferred offshore is partly responsible for the high levels of debts, and it is forcing governments to resort to austerity and budget cuts on healthcare, social services, and education. A report entitled *The Price of Offshore Revisited* from the Tax Justice Network (2012) estimated that the global super-rich have between \$21 and \$32 trillion hidden in tax havens. The report estimated that this amount of unreported wealth would have generated income tax revenues of between \$190 and \$280 billion a year. Recently, a group of progressive Europeans led by the economist and author Thomas Piketty has drawn up a bold new blueprint for a fairer Europe, in response to the increasing inequality in high-income nations. The plan, crafted by more than 50 economists, historians, and former politicians from half a dozen countries, includes huge levies on multinationals, millionaires, and carbon emissions to generate funds to tackle the most urgent issues of the day, including poverty, migration, climate change, and the EU’s so-called democratic deficit. There is strong evidence that a more equitable society is a happier, healthier, and more economically successful society. The IMF indicates that an optimal level Gini coefficient to perform well in terms of poverty reduction and economic growth is about 27, or the level of inequality of Northern European countries (Grigoli & Robles, 2017). IMF economists have also recognised that more equity can be a protective factor against future financial crises. As they wrote,

“redistribution policies that prevent excessive household indebtedness and reduce crisis-risk ex-ante can be more desirable from a macroeconomic stabilisation point of view than ex-post policies such as bailouts or debt restructurings” (Kumhof, 2011).

(9) The crisis represented a unique opportunity to tackle the root causes of the global financial crisis such as financialisation, deregulation, and indiscriminate capital mobility and reevaluate some of the policies and principles that increased inequality and guided economic development since the late 1970s. As the IMF admits in a surprising report entitled “Neoliberalism: Oversold?” (Ostri, Loungani, & Furceri, 2016), the current model of economic development is increasing inequality, which in turn generates social, economic, and environmental crises. It is time to evaluate the feasibility of a new system that promotes equity, well-being, and sustainable development. However, policy responses following the beginning of the Great Recession were regressive and inadequate. They consisted in expensive bailouts for the “too-big-to-fail banks” exposed to toxic mortgage debts that had accumulated from reckless investments during the years of financial speculation and large operations of quantitative easing. IMF economists estimated that, worldwide, the bailouts cost taxpayers a staggering \$11.9 trillion, about a fifth of the entire globe’s annual economic output. This made the banks that caused the 2008 financial collapse even more powerful. They are now larger, still unregulated, full of toxic assets, and capable of neutralising governments’ attempts to introduce more stringent financial regulations. A second major policy response after the crisis was a massive operation of quantitative easing that consisted in an impressive 21 trillion dollars globally (Global Central Bank Balance Sheet Assets, 2018). This vast amount of financial resources, however, hardly trickled down to the real (nonfinancial) economy, small businesses, households, and people affected by the crisis. In the United Kingdom, the Bank of England created a quantitative easing (QE) programme of £375 billion, corresponding to about £6,000 for every person. However, it has been estimated that for every £1 created under QE only 8p trickled down to the real economy (Al-Daini, 2015), with the rest getting trapped in financial markets, boosting the value of bonds and stock markets that are disproportionately owned by the top socioeconomic classes in society. Ironically, both John Maynard Keynes and Milton Friedman were in favour of quantitative easing aimed at the real economy. Some alternative ways to stimulate the economy are needed. Some have proposed that a most effective way to boost the economy would be for central banks to create money and grant it directly to governments or public institutions and allow governments to spend it directly into the real economy (New Economics Foundation, 2013). These types of proposals include “People’s Quantitative Easing,” “Sovereign Money Creation,” and “The Helicopter Money.”

(10) National and international institutions have missed not only the opportunity to move away from the neoliberal economic paradigm that led to the 2008 global financial downturn, but they have also failed to legislate new reforms necessary to prevent another financial downturn from occurring in the future and avoid the side effects of trade liberalisation policies. John Maynard Keynes showed lucidly that although unfettered free markets have a built-in predisposition to crash at intervals, it is possible to reduce the risk of financial instability through government interventions, as demonstrated by the very low number of banking crises during the postwar era of New Deal-style policies and the Bretton Woods System. Yet, in spite of some financial reforms such as the Dodd-Frank Act in the United States, little action has been taken to reduce systemic risk internationally. A new system of financial regulation at the global level is necessary. Some have proposed a new Bretton Wood

System of capital controls, bank regulations, and containment of financial speculation. A set of comprehensive and stringent regulations of global finance and taxes on international financial transactions has been advanced by numerous writers including John Eatwell and Lance Taylor, authors of *Global Finance at Risk: The Case for International Regulation*. They proposed a new economic architecture regulated by a new “World Financial Authority,” specifically designed to manage the threat of systemic risk and financial contagion. In the same vein, a 2009 report from the United Nations Conference on Trade and Development (UNCTAD), entitled “The Global Economic Crisis: Systemic Failures and Multilateral Remedies,” called for a new system of global financial regulations to curb the indiscriminate speculation and financial risk taking that caused the 2008 Great Recession.

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Chapter 288

THE MORTALITY CRISIS OF THE FORMER SOVIET BLOC COUNTRIES, 1989-2014

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INTRODUCTION

The transition to the market economy and liberal democracy of the former communist countries of Europe represents the most vivid example of how potentially favourable economic and political reforms may lead to massive mortality crises. The transition of these countries was universally greeted as a key step towards world peace and economic progress. The months preceding the beginning of this historic watershed were characterised by widespread hopes for improvements in political freedoms, economic growth, living standards, and life expectancy which, during the prior 20 years had improved more slowly than in capitalist OECD countries, or had deteriorated. Despite these hopes, the years after 1989 were characterised by a severe transformational recession, a fall in output and incomes, the rapid impoverishment of large sections of the population, rising income and assets concentration, widespread social dislocations and an acute mortality crisis.¹

Despite its magnitude and a growing number of studies, the transition mortality crisis has attracted limited political attention by national authorities and international agencies. When it was acknowledged, it was attributed to past shocks or irrelevant factors, retarding in this way the introduction of appropriate policy responses. In a way, the recent European mortality crisis is a telling example of how potentially favourable reforms may lead to large health and social costs.

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¹ Over 1989 and 1996 alone, the number of poor and unemployed in the region rose respectively by 100 million and 10 million while the crime rate tripled (UNICEF, 2000).

MORTALITY AND LIFE EXPECTANCY TRENDS

With the exception of Slovenia, during the first reform years, male life expectancy at birth fell and the Crude Death Rate rose in all European economies in transition. For instance, over 1990–91, Poland recorded about 30,000 excess deaths in relation to 1989, while Hungary registered about 7,000 excess deaths over 1992–93 (Table 1 and Annex Table 1). Thus, in Central Europe too, the loss of human life was sizeable from a welfare perspective, though not in terms of demographic trends. In this sub-region, the economy, living standards, and life expectancy at birth (LEB) already started to recover in 1992–94 while mortality rates and the number of deaths declined. As a result, over 1989–2014, the five Central European countries taken together recorded about 730,000 fewer deaths than would have been the case had the 1989 number of yearly deaths remained constant throughout this period (Table 1 and Annex Table 1). While country-specific factors played a role, the steady fall in death rates in these countries after 1991–92 appears to have also been due to some common factors. All of them began the transition with much smaller economic and social distortions than the CIS countries, they all experienced less acute and short-lived recessions and inflationary spikes, and only moderate surges in income and asset inequality.² All of them introduced extensive labour market programmes to soak up transitional unemployment, while public expenditure on health increased, and alcohol consumption either stagnated or increased modestly. Family instability and distress migration during this period were also modest. Moreover, none of these countries experienced the massive weakening of state institutions in the area of law-and-order and personal security that was observed in several CIS countries. Finally, their faster political democratisation and the active role played by intermediate social bodies (such as cooperatives, churches, trade unions, cultural and sports associations, and so on) contributed to keeping up the pressure on incumbent governments to tackle the social dislocations inevitably entailed by the transition.

The mortality crisis was much sharper in South Eastern Europe, the Baltic States, and especially the members of the former Soviet Union mainly inhabited by Slavic populations, that is Belarus, Kazakhstan, Moldova, the Russian Federation (henceforth Russia), Ukraine, and Lithuania. In these countries, the initial recovery in economic activity and male LEB recorded over 1995–98 was interrupted in 1998–2003 by the 1998 Rouble crisis and subsequent devaluation, default on the public debt, and capital flight, and a sluggish economic performance over 2000–2002 that were quickly transmitted to neighbouring countries. LEB started recovering steadily in 2003 in Russia and in 2005 in Belarus and Ukraine. In Russia, male LEB rose by 6.7 years between 2003 and 2014, suggesting that the country had exited

² Popov (2000) and Cornia and Popov (2001) developed a cumulative measure of ‘initial distortions’ as a percentage of GDP for all economies in transition. This measure is the sum of defence spending exceeding 3% of GDP (a level regarded as normal), deviations from a normal level of the industrial structure (particularly the over-representation of the inefficient heavy industry) and heavily distorted trade among the former Soviet republics and lightly distorted trade within the other socialist countries. While Hungary and Slovenia had an index of initial distortions equal to around 4% of GDP, in the Baltics the index ranged between 67 and 71 and in Russia it reached 41. Regression analysis showed that this measure of initial distortions retarded growth in a statistically significant way. Other initial distortions included very different degrees of money overhang, i.e., the excess amount of cash in circulation as a share of GDP that, with a rapid price liberalisation, caused very different rises in the rate of inflation and macro instability, from moderate in the Czech Republic to hyperinflation in Russia. This problem, and the inability to develop rapidly a new tax system contributed to the Ruble crisis, and to the default on the public debt of 1998–99, which were years when LEB fell again.

the mortality crisis of the prior 15 years. Yet the 1989 level of male LEB was only reached again in 2012. In Belarus and Ukraine, the 1989 level of male LEB was reached again in 2013 (Table 1).

What were the factors behind this rebound? Grigoriev et al. (2014) show that the main causes of death that triggered the increase in mortality over 1989–94 (that is, cardiovascular and external causes) were the same that explained its decline over 2004–10 and beyond (see later). The possible explanations put forward to explain such an important rebound in Russia include a declining consumption per capita of spirits, accompanied by an increase in wine and beer drinking. It also includes a decline in alcohol poisoning; diet improvement (but no changes in smoking); a rise in health expenditure per capita from \$PPP 300 in 1995 to \$PPP 998 in 2010; an increase in cardiac surgeries per 100,000 people of over 35 years of age from 21.7 in 1995 to 97.5 in 2010. The sources of social stress also became less threatening, with a return to a more stable life. With the recovery of the Russian economy over 2003–10, there was a fall in the unemployment rate from 9.8% to 7.5%, a drop in the poverty rate from 29% to 12.6% and a modest fall in the crime rate. Similar gains were recorded in Belarus and the Baltic countries, while in Poland, Czech Republic, and other Central European countries these kind of improvements had occurred just after the initial crisis of 1989–1992. In turn, the marriage rate recovered after the 1999–2005 while the total divorce rate declined, starting in 1993 in Ukraine, in 2000 in Estonia, and in 2002 in Belarus and other countries (Transmonee, 2017). Income inequality seems also to have stabilised since the early 2000s, although in the CIS countries the available data are not very reliable because of the under-reporting of top incomes.

While these trends are a source of hope, it is equally true that except for the Central European countries besides Hungary, male LEB in the region only returned to its 1989 level in the early 2000s or over 2011–2013 (Table 2). This has entailed a large loss of male life expectancy that continued in some cases until 2011–2013. The trend in female LEB is similar if more attenuated (Table 3).

How large was the human cost of the transition? Calculating the number of ‘excess deaths’ during the transition requires the availability of the Standardised Death Rate (SDR) for each of the 21 countries in Table 1 and the years 1989 to 2014 – using 1989 as the base year for which the age structure of the population is assumed to remain constant over 1989–2014. This would enable a separation of the increase in the number of deaths due to higher age-specific mortality rates from those due to population ageing. However, at the moment, the SDR for all these countries and years is not available to this author. To give the reader an idea of the impact of ageing on the total number of deaths, the last four columns of Table 1 list the changes over 1989–2014 in the age dependency ratio (65+/15-24). These data indicate that with the exception of Slovenia, the Baltics, Romania, and Bulgaria, population ageing seem to have been a moderate entity in most regions, especially in the Slavic and Central Asian countries. This seems to suggest that, at least in these countries, a good part of the ‘transition mortality crisis’ was due to an increase in age-specific death rates, rather than to population ageing. In any case, the last four columns of Table 1 give an initial idea of the bias introduced by the use of the CDR instead of the SDR. Except for the countries marked in yellow, this bias seems limited.

Table 1. Number of excess deaths, over 1990-2014 in relation to 1989, country groups*

	Number of deaths (1989)	Excess deaths over 1989 in worst year	Cumulated change in number of excess deaths 1989-2000	Cumulated change in the number of excess deaths 1989-2014	Age dependency ratio 65+ / 15-64			
					1989	2000	2014	Δ 2014-1989
Czech Rep.	127.734	1.791 (1990)	-123.253	-412.535	18.9	19.8	25.7	+6
Hungary	146.171	4.182 (1993)	-22.603	-230.920	19.9	22.0	25.8	+5
Poland	382.298	22.749 (1991)	37.632	-79.779	15.1	17.8	21.2	+6
Slovakia	53.782	919 (1990)	-11.089	-28.607	15.8	16.6	19.0	+3
Slovenia*	18.669	1.367 (1993)	4.287	5.204	15.9	19.8	25.7	+10
Total	728.654	19.267 (1991)	-115.025	-746.637				
Estonia	18.507	3.924 (1994)	15.247	-8.628	17.2	22.1	27.9	+10
Latvia	32.570	9.521 (1994)	35.980	17.156	17.6	22.1	28.8	+11
Lithuania	38.052	8.614 (1994)	46.504	107.279	15.9	20.8	27.5	+11
Total	89.129	22.060 (1994)	97.730	115.807				
Albania	17.876	2.791 (2014)	-711	-626	8.6	9.0	17.5	+8
Bulgaria	108.223	14.062 (1997)	60.675	98.833	18.7	23.8	29.3	+10
Romania	246.773	39.855 (1996)	209.425	365.668	15.2	19.3	24.3	+9
Total	372.872	48.566 (1996)	269.389	463.876				
Belarus	103.290	43.883 (2002)	282.915	738.392	16.6	19.7	19.8	+3
Moldova	40.002	13.051 (1995)	62.985	85.054	12.7	14.0	13.6	+0
Russian Federat.	1.380.286	792.049 (2003)	4.873.075	12.284.636	14.3	17.8	18.6	+4
Ukraine	599.822	195.812 (1995)	1.465.142	3.221.594	17.5	20.2	21.9	+4
Total	2.323.400	1.003.957 (2003)	6.634.116	16.329.676				
Armenia	20.635	8.401 (2011)	40.459	127.531	8.8	13.9	15.1	+6
Azerbaijan	43.630	11.660 (2014)	48.512	158.904	7.6	8.3	8.1	+0
Georgia	49.574	10.294 (1993)	12.134	-31.824	13.3	18.7	20.3	+7
Total	113.839	25.763 (1993)	101.106	254.612				
Kazakhstan	125.947	44.437 (1995)	289.467	589.105	8.7	10.3	9.9	+1
Kyrgyzstan	30.781	7.570 (2006)	32.167	102.998	8.7	9.1	6.6	-2
Uzbekistan	125.788	22.684 (2014)	12.5071	297.454	7.4	7.3	5.9	-1
Total	282.516	68.510 (1995)	446.706	989.558				

Source: own compilation based on Transmonex (2017).

Overall, the European transition crisis caused some 18 million cumulative excess deaths over 1989–2014, of which a rough estimate (taking into account the 1989–2014 changes in the age dependency ratio 65+/15-64) suggests that at least 80% were due to a rise in age-specific death rates. The most shocking increase in excess mortality was observed in the Slavic countries of Russia, Ukraine, and Belarus (Table 1). At the same time, the Central European countries recorded 746,000 fewer deaths due a steady decline in the number of yearly deaths. Analysis of the mortality dynamics over 1989–2014 shows that because of the sharp fall of LEB over 1993–94 and again over 1999–2005, the number of yearly excess deaths in relation to 1989 in Russia exceeded 700,000 units (Table 1 and Annex Table 1). While over 2002–05, part of this excess mortality was due to population ageing (ibid), the second dip in health conditions of 1999–2005 generated 3.2 million excess deaths, as opposed to roughly 1.6 million over 1989–1994. Overall, over 1989–2014 in Russia, the sum of yearly excess deaths in relation to the 1989 level reached a staggering level of 12.2 million (Table

1). Also in this case, a modest part of this figure is explained by a (limited) ageing of the population, especially over 1989–2000 (last three columns of Table 1). Indeed, much of the excess mortality in these countries was due to a rapid rise in death rates for the male 15-59 age group, which peaked in the mid-to-late 1990s and again over 1998–2003/04 (TransMonEE, 2017).

Large increases in the number of deaths relative to 1989 and the population of that year were also observed in Ukraine and Belarus. In the latter country, male LEB fell for 11 years in a row from 1989, stagnated for another five years, then only returned to its 1989 level in 2012–13. In Estonia and Latvia, male LEB returned to its 1989 level in 2002 and in Lithuania in 2009 (Table 2). The crisis was also acute and long lasting in the countries of Southeast Europe.

Table 2. Changes in male LEB in 21 European transitional economies, 1989-2014

	Male life expectancy at birth					
	1989	1989-1991	Maximum LEB loss since 1989 and year	Year in which the 1989 LEB level was reached again	Change over 1989-1999	Change over 1999-2014
Czech Rep	68.1	- 0.5*	-0.5 (1990)	1991	3.3	4.4
Hungary	65.4	- 0.4	-0.9 (1993)	1996	0.9	5.8
Poland	66.7	- 0.6	-0.6 (1991)	1992	2.1	5.0
Slovakia	66.8	- 0.2*	-0.2 (1990)	1991	2.2	4.2
Slovenia	68.8	0.7	n.a.	1989	2.6	6.6
Albania	69.6	-0.3	-1.1 (1996)	1999	2.1	4.7
Bulgaria	68.6	-0.6	-1.5 (1996)	2004	-0.7	3.3
Romania	66.5	0.1	-1.3 (1997)	2000	-0.4	5.1
Estonia	66.7	-1.3	-4.6 (1994)	2003	-0.3	6.9
Latvia	65.3	-1.4	-4.6 (1994)	2002	-0.4	4.4
Lithuania	66.9	-1.7	-4.3 (1994)	2009	-0.5	2.7
Belarus	66.8	-1.3	-4.6 (1999)	2013	-4.6	5.6
Moldova	65.5	-1.2	-3.7 (1994)	2008	-1.8	3.8
Russian Fed.	64.2	-0.7	-6.6 (1994)	2012	-4.2	5.3
Ukraine	66.0	0.0	-5.0 (1996)	2011-13	-3.0	3.3
Armenia	66.0	-0.1	-1.1 (1994)	1996	1.7	1.1
Azerbaijan	66.6	-0.3	-1.4 (1995)	1997	1.5	3.0
Georgia	67.3	-0.2	-2.9 (1993)	1994	0.2	1.1
Kazakhstan	63.9	-1.3	-5.9 (1994)	2011	-3.3	6.5
Kyrgyzstan	64.3	0.3	-2.9 (1995)	1999	0.6	1.6
Uzbekistan	67.3***	n.a.	-1.2 (1995)	1997	1.3**	2.4

Source: Author's elaboration on TransMonEE Database 2017 <http://www.transmonee.org>.

Notes: *1989-90; **1991-1999; *** refers to 1991. n.a. means 'not applicable' as the country recorded improvements throughout the transition; n.d. means not available. Two central Asian countries and all countries of the former Yugoslavia except Slovenia were dropped because of missing data, lack of comparability, border changes and war.

Table 3. Changes in female LEB in 21 European transitional economies, 1989-2014

	Changes in female LEB					
	1989	1989-1991	Maximum LEB loss since 1989	Year in which the 1989 LEB level was reached again	1989-1999	1999-2014
Czech Rep	75.4	0.3	n.a.	n.a.	2.7	3.6
Hungary	73.8	-0.1*	-0.1 (1990)	1991	1.3	3.8
Poland	75.5	-0.2	-0.2 (1991)	1992	2.0	4.1
Slovakia	75.2	0.0	n.a.	n.a.	1.8	3.0
Slovenia	76.7	0.7	n.a.	n.a.	2.1	4.7
Albania	75.5	-0.1	-1.2 (1993)	1999	0.9	3.9
Bulgaria	75.1	-0.4	-0.7 (1997)	2000	-0.3	3.5
Romania	72.4	0.7	n.a.	n.a.	1.3	5.2
Estonia	74.7	0.1	-1.6 (1994)	1996	1.4	5.4
Latvia	75.6	-0.4	-2.3 (1994)	1996	1.0	3.3
Lithuania	76.2	-0.4	-1.4 (1994)	1997	0.7	2.9
Belarus	76.4	-0.9	-2.5 (1999)	2008/9	-2.5	4.5
Moldova	72.3	-1.3	-2.6 (1995)	2007	-1.3	4.6
Russian Fed.	74.5	-0.2	-3.3 (1995)	2009	-2.0	4.0
Ukraine	75.1	0.0	-2.3 (1995)	2010	-1.3	2.7
Armenia	74.7	0.9	-0.3 (1993)	1994	0.8	2.6
Azerbaijan	74.2	0.3	-1.3 (1995)	1997	0.9	1.7
Georgia	75.0	0.0	-1.8 (1993)	2003	0.1	2.1
Kazakhstan	73.1	-0.7	-3.7 (1995)	2009	-2.2	5.0
Kyrgyzstan	72.4	0.3	-2.0 (1995)	2008	0.2	1.9
Uzbekistan	75.3*	n.d.	-2.1 (1994)	2001	0.2**	2.3

Notes: * 1989-95. ** 1991-92. indicates that the maximum loss was realised over the first two reform years.

n.a. means that the country recorded steady improvements throughout the transition.

To put things into perspective, it must be noted that by 1994, the LEB of Russian males had already fallen to 57.6 years, that is, 6.6 years less than in 1989 and three years less than that of India, which was then a poor agrarian economy. Likewise, over 1998–2003, male LEB fell by 2.7 years. This crisis was unprecedented in the 20th century for countries at peace and unaffected by famines or major epidemics. To underscore the dramatic nature of these figures, it suffices to mention that World War Two caused 3.3–4.6 million civilian casualties in Poland and 7 million in the USSR (Alderson, 1981). Likewise, the 1929–33 famine caused by the collectivisation of the Kulaks' land in Russia, Ukraine, and Belarus caused an estimated additional 9 million deaths.

The transition mortality crisis resulted from the overlay of a long-term pre-1989 stagnation in health conditions (not the focus of this chapter) and of an acute adjustment crisis. As a result, the mortality gap with the Western European countries and between Russia and its former satellites rose sharply. For instance, the male LEB gap between Poland and

Russia rose from 4.5 to 8.5 years over 1989–2014 and that for female LEB from 1.0 to 5.1 years (Tables 2 and 3). In turn, the male and female LEB gap in relation to Italy respectively rose from 6.9 to 14.7 years and from 5.1 to 8.2 years. It is thus important to understand why in an era of growing opportunities associated with the market economy, the health status of many CIS countries fell further behind those of their former satellites of Central Europe and of Western Europe. The rapid reduction in cardiovascular mortality that began in Russia during the last decade, however, has started closing this health gap.

IMMEDIATE CAUSES OF DEATH

What were the disease-specific causes of the fall of LEB during the transition? Overall, the surge in death rates resulted from diverging trends for different groups of diseases.

Diseases Exhibiting a Stable or Declining Trend in Death Rates

Mortality due to respiratory ailments mainly followed a declining trend, possibly because of the fall in the emission of pollutants into the atmosphere due to the sharp industrial recession experienced during the initial years. From the mid-1990s, the trend became less stable, but in no country did it lead to a sizeable rise in deaths. Also of limited importance were the increases in cancer mortality, which showed a stable, slow, upward trend that played a greater role in countries with smaller shifts in overall mortality.

Diseases Showing a Fast Increase in Death Rates

Close to 40% of the increase in standardised male mortality and a smaller but non-negligible share of female mortality was caused by an epidemic of heart diseases, such as ischaemic heart diseases, sudden deaths due to circulatory problems, and strokes. Interestingly, the fall in deaths due to these diseases and to external causes accounted for most of the decline in mortality recorded in the Central European countries after 1991, and in the Baltic States after 1995–96. In Russia, mortality due to these causes started dropping from the mid-2000s due to the ‘preventative cardiovascular revolution’ that took place following a rise in the implantation of stents and bypasses (Grigoriev et al., 2014). Indeed, the number of cardiac interventions per 100,000 people of over 35 years of age quadrupled between 2000 and 2010 (ibid). In the countries of the former Soviet Union, the external causes of death (poisoning, suicide, homicide, and all sorts of accidents) also explain an important share of the overall increase in mortality among young people, especially men. For instance, in the Russian Federation the murder rate among 35–39 year-old males increased by 223% between 1989 and 1993 alone (UNICEF, 1994). The transition was also characterised by an increase in deaths due to motor, train, and plane accidents, alcohol and other types of poisoning, accidental drowning, fires, and work accidents, that is, deaths related to the weakening of the state’s regulatory capacity and the erosion of safety at work.

The escalation in mortality was also in part explained by an upswing in deaths due to cerebrovascular and digestive diseases, including stress-related diseases such as ulcers and cirrhosis of the liver. Finally, there was also a sharp percentage increase from very low levels in mortality due to diseases of poverty (that is, infectious, nutritionally-related, parasitic, and sexually transmitted diseases) such as diphtheria, tuberculosis, and – later on – HIV-AIDS. While very pronounced in relative terms, this rise was almost negligible in absolute terms and was possibly related to the emergence of an underclass of ‘marginal’ people (vagrants, intravenous drug users, and commercial sex workers) unreached by the public health system. Yet because this rise took place from a very low level, it explains little of the aggregate mortality rise.

POPULATION GROUPS AFFECTED

A priori, one might have plausibly surmised that the health dislocations caused by the transition would have most affected the biologically more vulnerable groups: children, pregnant women, the elderly, and the disabled. In reality, the mortality crisis affected other social groups.

Gender

In most countries and for all age groups, men were far more affected than women. Indeed, where death rates soared, the transition exacerbated an already high gender gap. In Russia, for instance, the female-male LEB gap rose between 1989 and 2014 from 10.3 to 11.2 years (Transmonee, 2017). In contrast, in countries where death rates fell, the gender mortality gap narrowed: in the Czech Republic, the female-male LEB gap dropped over 1989–2014 from 7.3 to 5.9 years (*ibid*). The production of specific hormones, testosterone in particular, seems to provide women with greater protection against stress-related mortality. In addition, women generally depend on a more diversified portfolio of activities and social relations. Such diversification shelters them from the anxiety and dejection experienced by men during periods of rising unemployment, loss of social status, inability to provide for one’s own dependents, and deteriorating family life.

Age Groups

The fastest relative upswing in mortality rates over 1989–1994 and 1998–2005, and its drop since 2005, was recorded for 20-39 year-olds (who were affected mostly by a sharp rise in external causes of death), while the most rapid absolute increase was observed for 40-59 year olds (who were mainly hit by a rise in cardiovascular deaths). For people above 60 years of age, and even more so for those above 70, there was only a small increase or even a decline in mortality (Cornia and Panicià, 2000). Likewise, infant and child mortality rates declined everywhere (Transmonee, 2017).

Level of Education

Previous studies have documented the steep mortality gap existing among people with different levels of education. Higher education allows individuals to acquire and process new types of information more easily than people with 'low' education, an essential advantage during periods of rapid transformation. Higher education also favours greater employment mobility, better management of limited financial resources, and a prudent screening of the risks connected with smoking, taking drugs, and excessive drinking. *Ceteris paribus*, a rise in overall mortality was therefore expected to disproportionately affect people with low education. But the reality has been grimmer than such predictions. Indeed, mortality differentials by level of education widened during the transition. Shkolnikov et al. (1998), for instance, showed that in Russia, the temporary life expectancy gap between the best and least educated men and women in the 20-69 age group rose from 1.63 and 1.44 in 1988-89 to 1.89 and 1.75 in 1993-94. And Shkolnikov et al. (2006) show that the life expectancy differentials at age 40 between people with high and low education hardly changed over 1988 and 1998 in the Czech Republic, while rising in Russia and Estonia from 5.14 to 10.21 years and from 3.30 to 8.97 years.

Marital Status

The rise in death rates disproportionately hit a growing number of people living alone. A drop in the marriage rate and – in the Slavic countries of the former Soviet Union – a rise in the divorce rate, raised the number of adults living alone. This phenomenon was exacerbated by the surge in the number of widows and widowers due to the initial (1989-95) and subsequent (1998-2003) surge in adult male mortality, and to a lesser extent female mortality, that raised the number of widows and widowers.

Migrant Populations and Place of Residence

Migrants, especially distress migrants, normally face a higher risk of mortality than people who remain in their communities. The impact on aggregate mortality of this phenomenon rose in intensity, as domestic and international migration skyrocketed in the region following the breakdown of states, the return of troops posted abroad, the inflow of refugees fleeing ethnic strife, industrial restructuring, and unemployment.

In most of the region, mortality rates have historically been higher in rural than urban areas. Since 1990-92, however, this tendency started to be reversed, because of the greater unemployment, stress, and crime levels of cities, particularly in mono-industrial cities affected by the collapse of dominant state factories (Milanovic, 1996). Urban mortality also increased because of a surge in the number of deaths among vagrant rural residents who moved to towns after the abolition of residence permits and the liberalisation of internal migration. In Russia, for instance, the rural-urban LEB difference decreased from 2.4 to 0.8 years between 1992 and 1994 due to a faster rise in urban mortality rates linked to violent causes and cardiovascular problems (Shkolnikov and Cornia, 2000).

Ethnic Origin and Employment Status

Mortality appears to have risen more rapidly among certain ethnic groups. For instance, Krumins and Usackis (2000) showed that before the transition, the standardised death rate in Latvia was 10% higher among ethnic Russian males than among ethnic Latvians. This differential rose to 17% by the mid-1990s. Similarly, in the Czech Republic, Dzúrová (1996) found a high correlation among cross-district mortality, ethnic heterogeneity, and the proportion of the population of Romany origin. Jozan (1997) reported similar results for Romania and Hungary. It is unclear, however, whether these differentials would still be valid after controlling for levels of education and skills, unemployment, and so on. Finally, Shkolnikov and Cerviakov (2000) found that in Udmurtia (Russia), the mortality among 20-59 year-old males was higher among the Udmurt population than among people of Slavic and Tatar origins, but were unable to conclude whether this depended on genetic or socio-economic factors. Finally, mortality grew faster among the unemployed, people with part-time jobs, handicapped pensioners, and people affected by fast labour turnover. This point is discussed further in the next section.

In conclusion, the evidence suggests that the transitional mortality crisis mainly affected an underclass of young and middle-aged men and – to a lesser degree – women with low-level education and skills and unfavourable labour market conditions. These people often lived in poverty (which affected their psychological status and alcohol consumption), inhabited in or migrated to urban areas, lived alone, had been detained in the past by the police for more than three days, and were of migrant or ethnic-minority backgrounds. The retrospective case-control study conducted in 1999 on 500 men of 20-55 years of age in the Udmurt republic of Russia confirms that the victims of the transition had this kind of social profile (Shkolnikov and Chervyakov, 2000; Shkolnikov et al., 2004).

UNDERLYING CAUSES OF THE MORTALITY INCREASE³

Several hypotheses have been put forward to explain the increase in transitional mortality. Some have shown their limited relevance and are no longer the object of discussion. They are briefly mentioned hereafter for completeness. Others emphasised factors that do not require a policy response, either because the problem does not exist anymore, or because it stems from past problems, the influence of which can no longer be offset.

Explanations of No or Limited Relevance

Glasnost in Statistics

According to this explanation, a large part of the mortality rise was due to changes in statistical conventions and greater transparency. It is well known that the former communist

³ Schiering et al. (2018) reviewed 39 cross-national, multi-variable, peer-reviewed studies on the causes of the transition mortality crisis in Eastern Europe and the former Soviet Union. They found that inequality, unemployment, social subsidies, a lack of democracy, poor economic performance, and religious composition were the leading factors explaining the observed mortality outcomes. At the same time, the reviewed studies failed to establish a connection between mortality and diet, drinking patterns, liberalisation, trust, health expenditure, and war. Such results coincide to a great extent with those reported below.

authorities deliberately misclassified the number of deaths due to alcoholism and violent causes. Yet the removal of this distortion barely affected the global mortality picture. Second, the pattern of mortality changes observed in the 1990s throughout the region was uniform, a fact it is hard to attribute to coordinated data falsification by many independent statistical agencies. Third, detailed investigations of death statistics indicate that for several decades, their quality and coverage were – with few exceptions – of standards similar to those of Western countries (Anderson and Silver, 1990). The new mortality data could also have been affected by changes in statistical conventions, disease classifications, and geographical boundaries. However, an examination of the data showed that these changes explained only small variations in mortality for narrow subpopulations.

Ecocide

According to this argument, the mortality crisis was largely due to the current and lagged impact of past environmental neglect. During the socialist era, acute environmental problems led to a high incidence of deaths due to bronchitis, pneumonia, influenza, neoplasms, and genetic disorders. Yet ecocide cannot explain the transitional mortality crisis because during the initial phase of the reforms, emissions of harmful substances declined sharply in line with a contraction of industrial production and the adoption of more efficient and less polluting technologies. In Russia, for instance, the emission of harmful substances into the air dropped from 34 million tons in 1990 to 21 million tons in 1995–96 (Goskomstat, various years). The irrelevance of this explanation is confirmed by the steady decline of mortality due to respiratory diseases.

Cohort Effects

The mortality crisis in Russia and Ukraine also cannot be explained by the delayed consequences of the debilitation experienced by people born during the 1929–34 famine and World War Two. Indeed, an analysis of cohort mortality in Ukraine over 1965–94 concluded that the male war birth cohort experienced higher mortality in the 1990s than the adjacent cohorts, but also that this was not enough to explain the overall increase in mortality after 1989 (Godek, 1997). A similar analysis for Russia (Blum, Avdeev, and Zakharov, 1997) shows that in the 1990s, the three-year cohort born during the difficult years of 1942–44 experienced an increase of 16% in the risk of dying in relation to the adjacent cohorts. Similarly, the cohorts born between 1933 and 1934 experienced a 9% higher risk of dying in relation to the cohorts born in 1931–32. However, the share of deaths explained by this ‘debilitation hypothesis’ is not too important, as the overall increase in death rates over 1991–94 among males aged 40–50 and 50–60 years exceeded 75%. Second, the percentage increase in death rates during the transition was much higher among 20–40 year-olds, that is, cohorts born during a period of relative prosperity. Also, women born during World War Two and 1929–33 should have also suffered higher risks of death later in life, a fact only partially borne out by the data for the 1990s. Fourth, during the transition, the rise in mortality also affected areas of the former Soviet Union that had not been hit by the demographic catastrophes of the 20th century. Likewise, in Poland the mortality rates of cohorts born during World War Two fell more quickly than those of the preceding cohorts. Finally, the ‘postponed death hypothesis’ (which suggests that the liberalisation of alcohol sales of 1989 led to an increase in consumption that proved lethal for socially weak groups whose life was saved by Gorbachev’s anti-alcohol campaign) does not stand up to scrutiny. A comparison of

LEB gains during the anti-alcohol campaign, with its rises over 1989–1994 suggests that this hypothesis may explain only a modest part of the surge in deaths over 1989–94 and none of the 2.6-year decline in male LEB that took place over 1998–2003 in the aftermath of the Ruble crisis and devaluation.

Recession, Impoverishment, and Malnutrition

To be sure, the belt-tightening imposed by the transitional recession entailed a sizeable drop in food expenditure. Yet in view of the high food intake prevailing in the region before the transition and of the considerable scope for substituting cheap sources of nutrients for expensive ones, even large drops in consumption expenditures did not seriously exacerbate the risk of death due to undernutrition (Cornia, 1994). The increase in deaths due to infectious and nutrition-related diseases among male adults was caused by reduced access to shelter, poor hygiene, and inadequate healthcare among a class of ‘marginals,’ vagrants, and homeless people. Thus, impoverishment and malnutrition may have been relevant only in very few poor and isolated parts of Romania, Russia, and Ukraine. Adamets (1997) reports that in Ukraine, only 25 deaths due to starvation were recorded in 1995 out of a total of almost 800,000 deaths that year.

Unhealthy Lifestyles (Poor Diet, Smoking, and Drinking)

This explanation focuses on causes of death and population groups similar to those observed during the transitional crisis. However, accepting this explanation entails that mortality should have risen slowly and should have done so after an extended exposure to risky behaviours. In addition, the risk factors mentioned above should have worsened, a fact not always borne out by the evidence. Furthermore, changes in relative prices and improvements in trading raised the consumption of vitamins and minerals from fruits and vegetables. Similarly, a rise in the relative prices of meat, milk, and dairy products reduced the intake of saturated fats, thus lowering the risk of cholesterol-induced mortality. Mielecka-Kubien and Zatonski (1997) claim that the drop in cardiovascular mortality among Polish men after 1992 was largely driven by respective falls of 25% and 60% in the consumption of animal fat and butter. Likewise, over 1989–95, tobacco consumption appears to have slightly declined or stabilised at a high level throughout the region, as incomes dropped, the prices of imported cigarettes soared, and educational efforts started producing an effect. In any case, as noted, death rates due to lung and other types of cancer rose along a slow stable trend and seem to be little related to recent changes in smoking prevalence. They cannot explain the rapid surge in circulatory and violent deaths.

Relevant but Incomplete Explanations

Weakening Healthcare Systems

Since the onset of the transition, most Central European countries increased public health expenditure per capita and made greater use of modern drugs such as beta-blockers, which reduced the incidence of cardiovascular deaths. For instance, in the Czech Republic, the decline in cardiovascular mortality among middle-aged and old-aged people coincided with a surge in public health expenditure from 5% to 7.4% of GDP between 1990 and 2004

(Rychtarikova, 2004). These higher allocations fostered an increase in the number of heart interventions and improved the overall quality of public health. In contrast, countries such as Russia, Ukraine, Latvia, and Lithuania experienced a fall in health expenditures per capita of between 15 and 30% during the initial phase of the transition and stagnation since then. This gap has partly been reduced over time, and World Bank-WDI data for 2015 show that the Public Health Expenditure/GDP ratio ranged between 4.5% and 6% in Central Europe versus 2.9% in Ukraine and 3.4% in Russia.

In Russia and other CIS countries, the rise in the number of deaths for curable diseases among hospitalised patients and the temporary breakdown of vaccination systems in the early 1990s (Shkolnikov and Cornia, 2000) suggests that cuts in public expenditure played a role in the early years of the crisis. According to some estimates, one-fifth to one-quarter of the LEB gap between Russia and Western Europe could be attributed to deaths from amenable diseases.

Yet the reduced access to and declining quality of health services and their subsequent slower increase in quality cannot explain why mortality rose faster among men than women and why it surged only for a few diseases but not for others such as cancer, respiratory diseases, and neonatal and perinatal problems. Finally, it cannot explain the jump in the number of non-amenable causes of death such as strokes and violent deaths, that is, deaths that accounted for an important share of the total increase in mortality. Indeed, the relation between health spending per capita (and indirectly health spending/GDP) and LEB is concave.

While an initial growth in health spending per capita generates a rapid increase in LEB, beyond a threshold of around 2,000 international 2010 dollars, the gains in LEB are modest and likely to depend mainly on other factors discussed later on such as unemployment, the distribution of income, family arrangements, social cohesion, and so on.

Relevant Explanations

Mounting Alcohol Consumption

Official past data suggested that national sales statistics covered less than 50% of real consumption (Tremblay, 1997). Alcohol intake during the transition was thus estimated indirectly based on increases in alcohol-related deaths. This and other indirect methods suggest that alcohol consumption rose perceptibly in several economies in transition (see Shkolnikov and Nemtsov, 1997). In Russia, indirect estimates by Shkolnikov and Nemtsov (1997) showed that average alcohol intake jumped from 11.8 litres per capita in 1989 to 14.5 litres in 1993 and that this increase contributed to a rise in accidental deaths. Likewise, in Poland, per capita consumption rose from 8 to 11 litres between 1988 and 1991, and fluctuated around that level over the subsequent five years. These estimates allowed Moskalewicz et al. (2000) to conclude that 32% of the overall surge in male mortality in Russia over 1990–94 can be tentatively attributed to greater alcohol consumption and that the equivalent figures for Lithuania (1990–94) and Poland (1989–91) were 40% and 27%. Given the fragility of the alcohol consumption estimate, these conclusions have to be taken with a pinch of salt. Indeed, a key issue in this debate concerns the causes of the increase in alcohol consumption (Paniccià, 1997). Possible explanations include: trend inertia reflecting deeply rooted

consumption habits; changes in incomes and the relative prices of alcohol;⁴ a relaxation of the anti-alcohol policy during the transition; and psychosocial stress.

However, the ‘alcohol hypothesis’ does not explain why alcohol related-mortality fell during the successful transition of the Czech Republic and why alcohol consumption remained constant in Poland after 1992. Similarly, in the 2000s, the number of alcohol-related deaths fell in Russia and the Baltics, where there is no evidence of a drop in total alcohol intake, though this was accompanied by a drop in the consumption of hard liquors and a rise in that of beer and wine. Moreover, it cannot explain the huge rise – and subsequent fall – in cardiovascular and other deaths that, while related to stress, are not mediated by alcohol intake. Moreover, in Russia, per capita alcohol consumption and alcohol-related deaths (from external causes, including murders, suicides, and poisoning) moved in opposite directions over 2002–07.

Subsequent analyses have focused on the way alcohol is consumed. While in Mediterranean countries, important amounts of alcohol are consumed every day, mainly with meals, in Russia, Belarus, Ukraine, and the Baltics, the same weekly amount is likely to be consumed on a single occasion, a drinking pattern termed binge drinking. Research suggests that the latter is causally associated with cardiovascular death. However, a study of 25,000 autopsies carried out in Barnaul (Siberia) over 1990–2004 suggests that 21% of adult male deaths attributed to circulatory diseases induced by alcohol consumption were caused by alcohol poisoning, i.e., lethal or near-lethal levels of ethanol concentration in the blood (Brainheard and Cutler, 2005).

Overall, alcohol has likely been an associated factor in 27–40% of the rise in male mortality and in a smaller proportion of female mortality, but fails to explain two-thirds of the rise in male mortality and over nine-tenths of that in female mortality. The main cause of this epochal disaster must therefore still be sought elsewhere.

Acute Psychosocial Stress

Acute psychosocial stress has been increasingly recognised as a key factor in sudden deaths, that is, deaths due to heart problems and hypertension, alcohol psychosis, neurosis, homicide, suicide, accidental deaths, ulcers, and cirrhosis of the liver, that is, the very causes of death that rose in importance during the transition. According to Serafino (1994, cited in Shapiro, 1994),

⁴ In Russia, for instance, the alcohol purchasing power of wages rose by 48% between 1989 and 1993 because of a drop in the price of alcohol greater than that in the average wage. However, a study by Denisova (2010), based on twelve rounds of the Russian Longitudinal Monitoring Survey covering the years 1994–2007 found that while social status, labour market behaviour, sectoral and occupational mobility, and smoking and alcohol consumption had a strong effect on longevity, there was no evidence that the low relative price of vodka led to greater alcohol consumption. Likewise, the meta-analysis of 39 studies on the determinants of the transition mortality crisis Schiering et al., (2018) found no evidence that alcohol consumption and drinking patterns were consistently associated with higher death rates, while Popov (2018) presents several other reasons why an increase in alcohol intake fails to provide a consistent explanation of the surge in transition mortality. Finally, Razvodovsky (2016) analyzed trends in sex-specific suicide rates and alcohol sales per capita from 1980 to 2010 in Russia, Belarus and Ukraine by means of a Spearman’s rank-order correlation analysis. The estimates based on the Soviet period suggest a strong association between alcohol sales and suicide rates in Russia, Belarus, and Ukraine. At the same time, the relationship between alcohol sales and suicide rates was negative in the post-Soviet period. The author concludes also that alcohol cannot fully explain the fluctuations in the suicide mortality observed in these countries during the Soviet period. The similar regional pattern of suicide trends does not support the hypothesis that alcohol policy was responsible for the decline in Russian suicide mortality during the recent decade.

“Stress is the condition that results when person/environment transactions lead the individual to perceive a discrepancy – whether real or not – between the demands of the situation and resources of the person’s biological, psychological or social systems.”

Deaths due to acute psychosocial stress thus entail growing strain and pressures to adapt to unexpected situations for which established individual responses are no longer effective, appropriate coping behaviours are unknown, and the public policy response is inadequate.

Epidemiological research has shown that, in the absence of mitigating factors, acute stress leads to physiological and psychological arousal that affects health status via direct and indirect pathways. Marmot and Bobak (2000) have reviewed the direct effects of stress. They found that stressful situations cause a higher secretion of cortisol, endorphins, platelets, fibrinogens, and fibrinolysis, that is, substances that affect the level of plasma lipids, blood coagulability, blood pressure, cardiovascular reactivity, the development of central obesity, responses to inflammation or infection, and the risk of depression. Chronic exposure to stress has also been found to cause coronary artery atherogenesis and to affect the immune system through a significant suppression of T-cell immune response. Finally, psychosocial stress has been shown to provoke an indirect effect on health via the increased use of stress-relievers such as alcohol, tobacco, and drugs, which influence health and social behaviours, as well as the ability to maintain emotional balance and coherent comportment.⁵

What were the main socio-economic sources of stress during the transition? The first was an unexpected rise in unemployment, employment instability, and rapid labour turnover. Mortality rose most in countries, districts, and years that recorded adverse labour market changes starting with a rise in ‘unexpected unattended unemployment’ and in other adverse labour market changes (Cornia and Panicià, 2000). This confirms the results of controlled studies carried out in Western countries on factory closures and significant lay-offs and follow-up studies on unemployment; that is, studies that replicate quasi-experimental conditions. These have shown that the sudden loss of employment and similar events are a major cause of stress, cardiovascular and mental problems, and death (Beale and Nethercott, 1985; Warr, 1987; Martikainen and Valkonen, 1996). These studies have provided evidence of higher mortality for accidents and violence, alcohol-related diseases, traffic accidents, and circulatory diseases among the unemployed (Smith, 1992). Grouped data for the economies in transition (Cornia and Panicià, 2000) confirm the existence of a strong correlation between the rise in unemployment and other adverse labour market changes and mortality changes in Czech Republic, Russia, Latvia, the former GDR, and Poland.

A specific pathway through which adverse labour market changes emerged in the transition economies concerns the approach followed to the privatisation of state-owned enterprises. A study based on Russian micro-level data by Azarova et al. (2017) uses enterprise and settlement-level data to enable a comprehensive analysis of both underlying and proximate causes of mortality in mono-industrial towns. This retrospective cohort study compares mortality in 10 fast-privatised factories with that in 10 slow-privatised ones. It found that fast privatisation – which is often associated with factory closures and asset stripping – raised workers’ mortality by between 13% and 21% (depending on the model specification used) in relation to slow-privatisation, after controlling for alcoholism, smoking, age, marital status, and financial deprivation. While in Soviet times, SOEs hoarded labour,

⁵ The health impact of stress varies considerably, however, from one person to another due to genetic differences and differences in individual abilities to adjust to new situations.

resisting massive layoffs in slow-privatising SOEs possibly reduced the stress related to sudden unemployment. Being employed, even nominally, provided people with minimal security and gave them the feeling of being in control of their lives. Likewise, before being privatised, SOEs offered a wide range of social benefits to employees and their families in the form of housing, healthcare, day care, and holiday recreation. When these enterprises were privatised, such benefits ended abruptly in the case of fast privatisation, but more gradually in the case of slow privatisation, giving workers the time to adjust to the new circumstances. Municipal authorities were often charged with taking responsibilities for these services but, due to serious financing problems, were unable to adequately fulfil such new obligations.

Through what pathways does unemployment affect health? The most obvious effect is that mediated by the loss of income. Unemployment, however, also affects people in other ways. Indeed, unemployment generates a loss of skills, cognitive abilities, motivation, and the sense of confidence and control (Sen, 1997). Unemployment can also be a source of psychological harm because of the loss of self-respect, feelings of being unwanted, unproductive, dependent, and without a social role, and due to rising anxiety about the future. Unemployment may also erode social norms and cause an increase in crime rates among the jobless. While material deprivation plays a role in the increase in crime, so does the greater sense of exclusion felt by the jobless. Finally, the loss of employment disrupts family and social relations and is associated with mounting alcohol consumption and family violence (ibid). There is also evidence that the impact of joblessness is related to the lack of expectations of becoming unemployed. Indeed, the impact seems to be greater among workers who were permanently employed and had no expectation of being laid off, as happened in many transition countries. It is moderate among workers whose fixed-term contracts are expiring and minimal among those who had never been employed and continue to be unemployed (Björklund and Eriksson, 1995).

Growing Undeserved Income and Asset Inequality

Growing undeserved income and asset inequality, i.e., inequality unrelated to differences in talent, effort, and human capital. Previous analyses of market economies have emphasised the negative correlation between income concentration and health outcomes (Wilkinson, 1996; Kawachi et al., 1999; Pickett and Wilkinson, 2010). Unequal societies are also afflicted by a high incidence of cardiovascular problems caused by low involvement in community life. Rising income and asset inequality may erode social cohesion, that is, the relations of interpersonal trust, mutual insurance, collective action, and redistribution at the local level. Social cohesion enhances health status by promoting the diffusion of health information, exerting control over deviant health behaviour and criminal activity and providing interpersonal help among community members. Finally, health status in an unequal society is also influenced through psychosocial pathways. Strongly hierarchical societies appear to be subject to a high incidence of cardiovascular problems, less social integration, less involvement in community life, and greater personal isolation, which is an important cause of morbidity and mortality.

Several of these effects have occurred in the countries in transition exhibiting rapid rises in social stratification. On one hand, the economies of Central Europe experienced moderate initial increases (4-6 Gini points) in income inequality (Cornia, 2004). These countries contained the fall in the tax/GDP ratio and were thus able to continue financing the social services and benefits inherited from the socialist era and to introduce new provisions (for

unemployment compensation and social assistance) that are needed in a market economy. On the other hand, in the former Soviet Union and South-eastern Europe, the Gini coefficients rose by an astounding 10-20 points, that of the asset distribution by even more, social transfers collapsed, and the targeting of transfers deteriorated (Cornia, 2001). As a result, in 2014, the Gini coefficient of the distribution of gross income was 25-27 in Central Europe – apart from Poland – and 35-41.6 in South-eastern Europe, the Baltics, and Russia (WIDER, 2018).

Third, these distributive changes placed a heavy psychological burden on the losers, namely, middle-aged, unemployed, semi-skilled industrial workers, collective farmers, and party cadres. As the new elites often reached their positions through ascription, capture of state assets, and corruption, the losers experienced rage, hostility, humiliation, lack of recognition, and unwontedness. Disorientation was also acute among the elderly and middle-aged adults who saw the values, norms, and savings of their lifetimes vanish.

Growing Numbers of People Living Alone

At all ages, stress-related mortality is higher among people (men in particular) who are widowed, divorced, separated, or who never married than among those who live in a stable partnership (Martikainen, 1995). The latter presumably lead healthier lifestyles, are less exposed to stress, and have greater access to support networks than people living alone. This regularity was confirmed during the transition, as the percentage of widows and widowers in the adult population rose, the crude marriage rate fell by between 16 and 54%, and the divorce rate edged up until the early 2000s by 10-15% in Russia, Ukraine, Belarus, and Moldova. These are the countries which experienced the most pronounced mortality rises. While even large annual shifts in these rates modestly affect the percentage of people living alone in the total, a continuation of this trend for a decade perceptibly raised the number of single adults who faced higher health risks. In addition, the unmarried-married mortality differential widened further during the transition, contributing in this way to a rise in aggregate mortality. For instance, even in the Czech Republic – which experienced a fall in death rates after 1991 – the risk of death of divorced men relative to married men rose from 2.03 in 1990–91 to 2.27 in 1995 (Dzurova, 2001).

The number of people living alone also rose because the number of divorces rose over 1989–96 and 2000–2003 (Transmonee, 2017). In Russia, the general divorce rate rose from 42.1 to 73.2 per 100 marriages in 2003, the year that recorded the highest number of excess deaths (Annex Table 1). Moreover, Pridemore and Shkolnikov (2004) found that in Russia, homicide mortality was 2.86 times higher among divorced people than among married people, and 9.3 times higher among divorced people with low education versus married people with high education.

Distress Migration

Previous analyses have shown that migrants face greater mortality risks than people who remain in their communities (Eyer and Sterling, 1977). This finding was confirmed during the transition as, after 1989, at least nine million people moved within or between the countries of the CIS alone, seeking work, fleeing conflicts, as political refugees, or returning from abroad. For many of them, migration entailed considerable material hardship, disorientation, and a loss of control due to the difficulties encountered in new environments, the breakdown in

social relationships, the redefinition of survival strategies, housing problems and, as a result of all this, greater stress and, at times, homelessness.

THE IMPACT OF POLITICAL DEMOCRATISATION

A limitation of the above analysis concerns the puzzling differences in national policy responses to the mortality crisis. There is a need therefore to develop an accepted theory of why such responses differed so much among countries. For instance, despite its magnitude, the mortality crisis of CIS countries during the early years of the transition generated a limited response by several incumbent governments, a fact that may raise questions about the degree of democratisation and social concern that prevailed therein. The fact that the crisis hit most marginal groups with no ‘political voice’ may explain why this response was so limited. But other hypotheses may also be explored. Thus, the 16 million excess deaths recorded in Russia, Ukraine, Moldova, and Belarus between 1990 and 2014 still lack a comprehensive political theorisation.

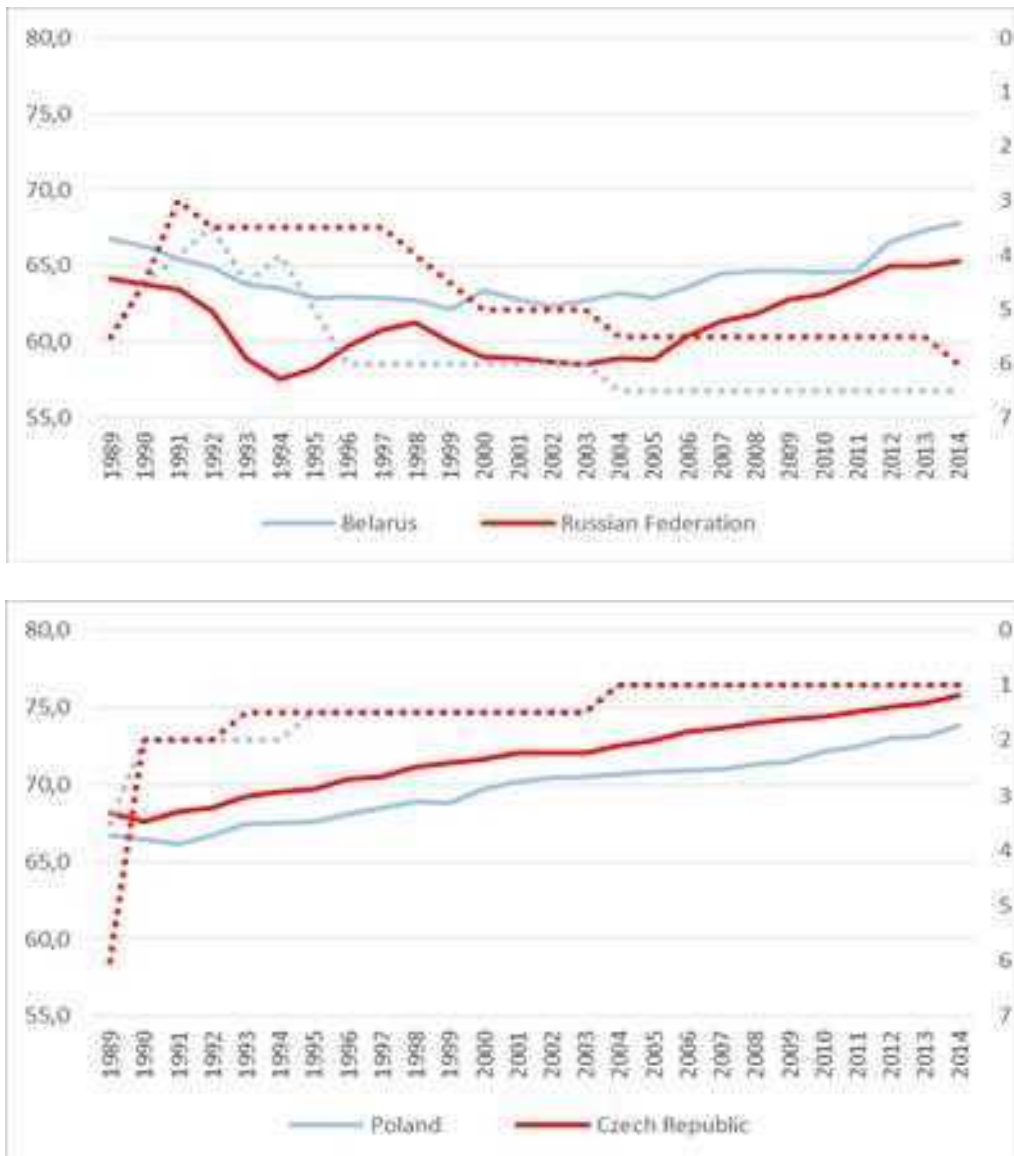
Plotting the trends of LEB and the Freedom House Index of democracy for Russia and Belarus shows that there is a fairly close correlation (at least between 1992 and 2005) between the worsening of the Freedom House Index (FHI) and male LEB.⁶ These two countries experienced a fall in LEB until 2005 in parallel with a worsening in the FHI. In contrast, a similar scatterplot for Poland and the Czech Republic (Figure 1, bottom panel) confirms the close statistical association between the trend in LEB and the FHI. Indeed, in both these countries, these two variables improved, hand in hand, throughout the period analysed.

The same relation was also plotted for all European economies in transition over 1989 and 2014 (Figure 2). Also in this case, it appears that the two variables correlate closely. On the basis of Figure 2 – and pending a more detailed investigation taking care of the problems of endogeneity and variable specification – it appears that countries that introduced truly democratic institutions (scores 1 and 2) enjoy a male LEB of 7-8 years higher than those with a low score.

Public choice theory suggests that when income inequality is high, governments (as well as a self-interested bureaucracies) are likely to implement suboptimal policies that retard the provision of essential pro-growth public services. Rising divergence of interests and types of public services demanded by the rich and the poor leads to an overall drop in the supply of basic public services essential for growth, such as personal security, contracts enforcement, security of property rights, and human capital formation. Indeed, the rich resist taxation as they perceive that the supply of public services funded by an increase in revenue will bring little benefit to them. In extreme cases, the high income groups support policies that preserve their privileges even at the cost of slow or stagnant aggregate growth. The problem is particularly severe when the concentration of income in the upper deciles is accompanied by

⁶ The yearly scores of the Freedom House Index of democracy summarize the subjective values assigned by experts to 10 political rights areas grouped into three subgroups. These cover the electoral process, political participation and pluralism, and the functioning of the government) and 15 civil liberties covering the freedom of expression and belief; associational rights, rule of law, and personal autonomy and individual rights. Such different aspects of democracy are then summarized by means of the arithmetic mean, that ranges between 0 (perfect overall democracy) and 7 (total absence of it).

widespread poverty at the bottom of the distribution, without a middle class capable of challenging politically inefficient government decisions. The Guatemala of the early 2000s, where the tax/GDP ratio was 8% and the coverage of public services minimal, is a good example of this state of affairs (since 2003 taxation has risen and inequality declined, if modestly).



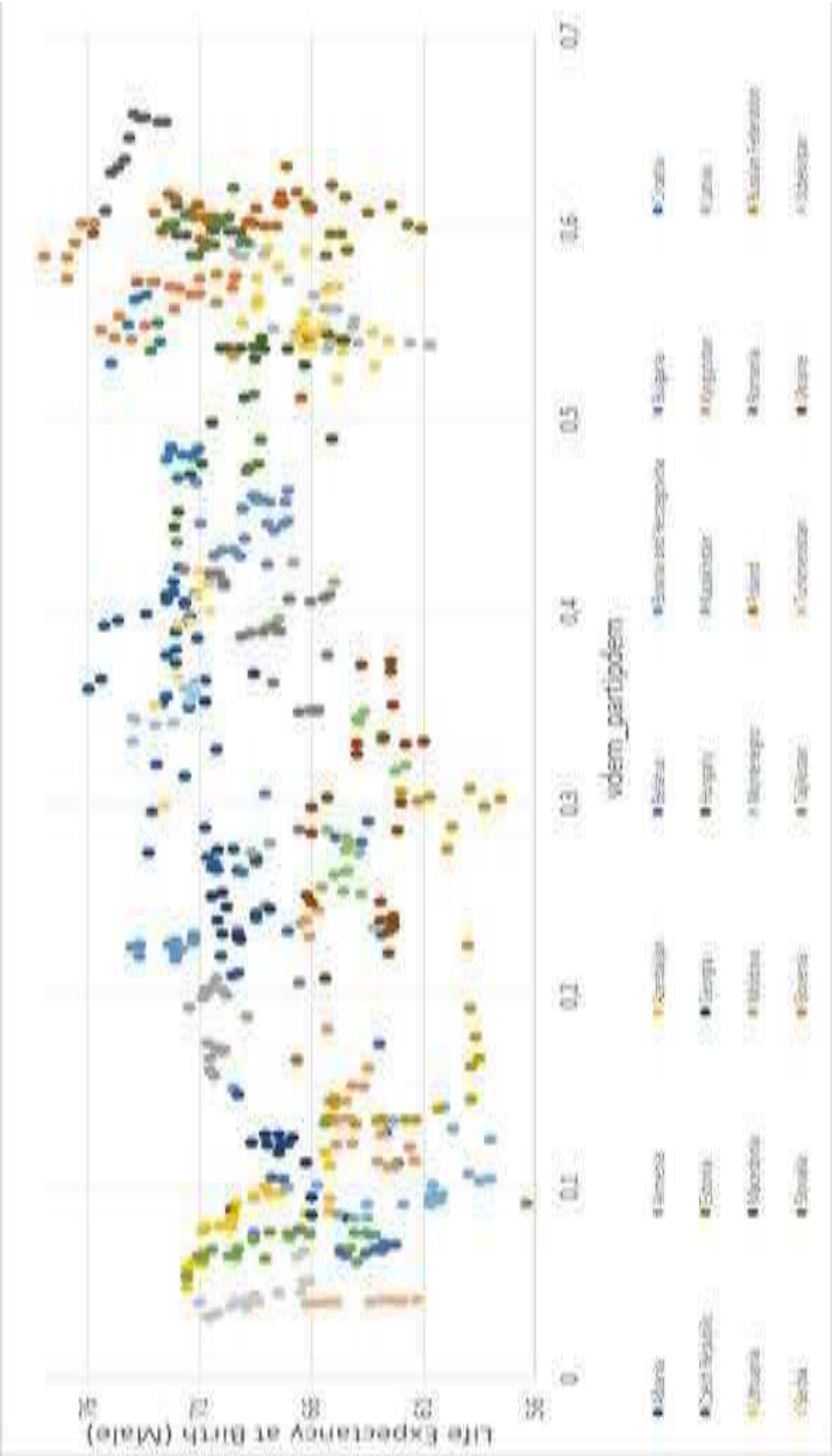
Source: own elaboration on Transmonee 2017 and the Freedom House Index database.

Figure 1. Evolution of male LEB (left scale, solid line) and the Freedom House democracy index (right scale, dotted line) in Belarus and Russia (top figure) and Poland and the Czech Republic (bottom figure).



Source: own elaboration on data from Freedom House (2018) and Transmonee (2017).

Figure 2. Scatterplot of the relation between the Freedom House Index (x axis) and male life expectancy at birth for all transition countries with data, years 1989–2014.



Source: Own elaboration using the index of participatory democracy 'partidem' and Transmones (2017).

Figure 3. Relation between the Participatory Democracy Index (horizontal axis) and male life expectancy at birth (vertical axis) for all transition countries and years with data, 1989-2014.

Because of the criticism that is often addressed to the FHI, and of the problems posed by equating democracy with ‘electoral democracy,’ the relation between ‘political democratisation’ and male LEB was also tested using an alternative indicator that emphasises ‘participatory democracy,’ such as the ‘vdem partidem’ indicator. This index is extracted from the ‘Varieties of democracy V-Dem’ website and is the average of three components: the first is a ‘participatory component index’ that emphasises the active participation by citizens in all political processes, electoral and non-electoral. This index takes suffrage for granted, but emphasises also the engagement in civil society organisations, direct democracy, and the election of subnational bodies. ‘vdem partidem’ includes also a (fairly similar) ‘Participatory democracy components’ indicator that emphasises active participation by citizens in all political processes. The index also includes the level of electoral democracy. And, third, the index includes a ‘Political Participation Rights’ component that measures the extent a country enacts political participation rights by law and respects them in practice. The overall index varies between 0 (no participatory democracy) and 1 (when participatory democracy and participatory rights are fully realised).

As shown in Figure 3, this index identifies very different situations of ‘participatory democracy.’ Some countries (such as Uzbekistan, Turkmenistan, and Belarus) have very low scores of 0.1–0.2; others (especially in Central Europe) have scores of up to 0.65. Russia’s score ranges between 0.27 and 0.32, Ukraine’s between 0.48 and 0.52, and the Baltics between 0.55 and 0.59. Also, in this case, the male LEB difference between the best and worst performers is about 6–7 years, while a considerable amount of variance remains – as expected – unexplained.

There seems, therefore, to be a fairly solid empirical association between electoral democracy, participatory democracy, and civil rights on one side, and male LEB on the other. Beyond differences in the ‘initial distortions’ mentioned in the first part of the chapter, the depth and nature of democracy thus helps explain the different national policy responses to the transitional mortality crisis and – in the end – the losses/gains in male LEB.

The relation between participatory democracy and male LEB is also tested econometrically hereafter over the years 1990–2014 and for the 21 countries included in Table 1 after introducing the yearly GDP/capita in a quadratic form as a control. Indeed, the impact of GDP per capita on male LEB is highly concave, as its effect is strong at the beginning, to decline after about 6,400 1990 international dollars. This relation – known as ‘the Preston Curve’ from the name of the demographer Samuel Preston who first described it in 1975 – suggests that GDP/capita should be introduced in a nonlinear form among the determinants of LEB. Furthermore, an analysis of the scatterplot suggests that the impact of GDP/capita on male LEB was particularly pronounced over the years 1989–2002, and for this reason we introduced a 1990–2002 ‘dislocation dummy’ that turns out to be highly significant in regression.

The results of this econometric test are reported in Table 4. They show that, after introducing as controls the GDP/capita (that has the right sign and is statistically significant at the 1% level) and the ‘dislocation dummy’ 1990–2002 (that is equally statistically significant and with the expected sign), the variable v-partidem is statistically significant at the 5% probability level, while the overall R² is high (0.9). An increase of v-partidem by 0.1 points would raise – *ceteris paribus* – life expectancy by about 0.2 years. For instance, if Russia’s current v-partidem score (about 0.3) rose to that of the Czech Republic (0.65), its male LEB would improve by about 0.7 years. If the analysis were conducted for years prior to 2002, the

favourable effect on male LEB would have exceeded 2 years. The level of participatory democracy therefore influenced the level and trend of male LEB in a non-negligible way, especially for the initial transition years. Of course, the other variables discussed above concur in explaining the large cross-country male LEB gap observed among the European transition economies.

Table 4. Regression results: OLS with country dummies., 1989-2014

	Male LEB
Partipdem	2.097** [1.035]
Gdp/c	0.038*** [0.005]
Gdp/c ²	-0.000*** [0.000]
Period dummy 1990-2002	-1.340*** [0.192]
Constant	71.146*** [0.491]
Country dummies	Yes
Observations	584
R-squared	0.90

Robust standard errorism in brackets. *** p < 0.01, **p < 0.05, *p < 0.1.

How can one support this conclusion theoretically? An initial argument has to do with asset and income inequality. To start with, in the 1990s, all European countries in transition (apart from the Central Asian countries and Belarus) shifted from a uniform model of authoritarian centralism to different shades of ‘Western-type democracy.’ Yet, in itself, greater ‘electoral democracy’ did not help to improve human wellbeing and health status, unless ‘participatory democracy’ and ‘economic democracy’ improved in parallel and unless the economic base of the disenfranchised populations did not deteriorate.

‘Economic democracy,’ in turn, depends on historical path-dependent factors affecting the current asset and income distribution. In this regard, the very different models of privatisation of state assets followed in the region after the collapse of communism influenced to a large extent the degree of asset concentration in the region, the distribution of political power, and the current level of income inequality. As noted earlier, the current Gini coefficient of income inequality in Central Europe is 40% lower than in Russia.

In this regard, public choice theory suggests that the high-income polarisation observed in the several CIS countries led to a divergence in the types of public expenditure demanded by different income groups. In countries with rising asset concentration, the new elites increased their political ability to resist taxation and influence the allocation of public expenditure towards activities (including prestige items and national defence) that were perceived to benefit them the most, while neglecting public expenditure on health, education, housing, and income support. Greater public expenditure on these items would have substantially benefited the marginal groups hit by the mortality crisis. Yet, the elites perceived such expenditures would have brought little gains to them. Indeed, where asset and

income polarisation rose, the state provision of educational and health services declined, or was privatised, while residential segregation increased. Elite-friendly governments neglected the health needs of the masses when deciding resource allocation, reducing in this way the prospects of the poor and of the middle-class for achieving adequate income levels and effective access to public healthcare. What is observed in the region may therefore confirm the conclusions of the literature that suggests that when asset and income inequality are high, governments and self-interested bureaucracies are likely to implement suboptimal policies that retard or reduce the provision of essential pro-poor and pro-growth public services. Rising divergence about the types of public services demanded by the rich and the poor often lead to an overall drop in the supply of basic public services that are essential for growth, such as personal security, contracts enforcement, and human capital formation.

A second way through which high inequality may affect health status is that the 'procedural democracy' and formal political freedom typical of polarised societies may not guarantee 'political stability' and health-enhancing social cohesion. During the communist period in much of the former Soviet Union, official organisations affiliated to the Communist Party, such as the Pioneers and sport and leisure associations, took the place of civil society organisations that had developed spontaneously in the West, or that had not disappeared during the communist era. This is the case of trade unions and church organisations in Poland, cooperatives in Hungary, or pre-communist institutions (such as neighbourhood associations like the Mahallas in Uzbekistan and similar groups in Armenia).

The preponderant role of the Communist Party and the limited scope for independent self-organisation generated a deep-rooted apathy among individuals and led, after the political liberalisation and subsequent collapse of the Communist Party, to the creation of a 'shallow democracy.' This lacked a well-developed network of civil society organisations (associations, NGOs, and churches working in the social sphere, trade unions, producers' associations, and self-governing bodies). These organisations help the formation and channelling of political consensus, democracy at the local level, defence of the interest of marginalised populations, and active political participation, i.e., all institutions and organisations that would have likely helped to contain the increase in mortality. For instance, a study on Russia (Stuckler et al., 2009) found that every one percent increase in the share of the population who were members of at least one social organisation decreased the associated risk of mortality by 0.27%. When more than 45% of the population surveyed was socially organised, the mortality differential with privatisation was no longer there.

CONCLUSION

The eruption of a massive transformational mortality crisis following the introduction of market reforms that were expected ex-ante to generate positive economic, social, and health effects confirms that poorly managed societal transformations may generate acute deteriorations in the economic and health spheres. The 35% increase in male suicides over 2007–2011 recorded in Greece during the recent years of austerity (that in the view of the EU and IMF was to lead to a rapid economic turnaround) provides another example of the need to adopt measures to control the rise of instability, unexpected job losses, inequality, and personal insecurity. Swift policy responses in these areas are needed both for the specific

benefits they produce (e.g., better labour market outcomes) as well as because of their positive health impact.

Acceptance of the psychosocial stress explanation has important policy implications. Supporters of 'big bang policy reforms' tend to ignore the social and health impact of such reforms, to ascribe them to problems inherited from the past or to the unavoidable chaos brought about by profound political transformations, and to suggest that there are no quick fixes for such problems. Meanwhile, conservative forces (like the unreformed neo-Soviet parties) argue that the mortality crisis has been caused by the sheer impoverishment brought about by the introduction of capitalist institutions, and that most liberal reforms (including privatisation) should thus be reversed or drastically amended.

The implications of the analyses presented in this chapter are substantially different from either of these two views. Vigorous market reforms are necessary. But – as shown by the case of the Czech Republic and Poland or by the gradual two-track price liberalisation followed in China over 1978–84 – they need to be characterised by a realistic pace of restructuring and privatisation, strong labour market and social sector policies, maintenance of law and order, and the strengthening of healthcare. To finance all this in a non-inflationary manner it is necessary to generate adequate revenue.

A solution to the mortality crisis that has affected the countries of the former Soviet bloc will require vigorous measures to prevent or control transition-related psychosocial stress. Measures needed under such circumstances include properly paced macroeconomic adjustment and industrial restructuring, adequate credit and technical assistance policies for small firms, job re-training, public works, unemployment compensation, wage subsidies, and measures to contain surges in inequality, social exclusion, family breakdowns, and distress migration. Deaths due to violent causes and infectious diseases can also be avoided by strengthening the police and social assistance services dealing with people marginalised by the crisis. A stricter regulation of alcohol consumption and other stress relievers is also needed to reduce violent and cardiovascular deaths. Reversing the negative long-term trend in health status will also require efforts at improving lifestyles, educating people about the risk of smoking, poor diets, and excessive drinking, and a strengthening of preventative and curative healthcare, especially in the case of heart problems. Initiatives in this area would have the double advantage of reducing the rise in violent deaths (thanks to better policing, efficient deterrence by the courts, and active assistance for and control of marginalised groups) and of containing overall stress by improving security. Greater regulation of alcohol consumption will also be needed to reduce violent deaths, cirrhosis, and throat cancer. This can be accomplished through higher alcohol prices, a reduction in the number of outlets, reduced opening hours and reduced sales to minors (key measures which require strong government commitment), and educational campaigns aiming at modifying drinking behaviour.

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ANNEX

Table 1. Number of excess deaths in relation to the 1989 level

一	二	三	四	五	六	七	八	九	十
十一	十二	十三	十四	十五	十六	十七	十八	十九	二十
二十一	二十二	二十三	二十四	二十五	二十六	二十七	二十八	二十九	三十
三十一	三十二	三十三	三十四	三十五	三十六	三十七	三十八	三十九	四十
四十一	四十二	四十三	四十四	四十五	四十六	四十七	四十八	四十九	五十
五十一	五十二	五十三	五十四	五十五	五十六	五十七	五十八	五十九	六十
六十一	六十二	六十三	六十四	六十五	六十六	六十七	六十八	六十九	七十
七十一	七十二	七十三	七十四	七十五	七十六	七十七	七十八	七十九	八十
八十一	八十二	八十三	八十四	八十五	八十六	八十七	八十八	八十九	九十
九十一	九十二	九十三	九十四	九十五	九十六	九十七	九十八	九十九	一百

Chapter 289

MORTALITY CRISIS IN RUSSIA REVISITED: EVIDENCE FROM A CROSS-REGIONAL COMPARISON

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INTRODUCTION

This chapter attempts to present a cross-regional comparison to analyse the Russian mortality crisis of the 1990s; the mortality rate increased from 1.0% to 1.6% in 1989-1994 and remained at a level of 1.4-1.6% thereafter. Mortality peaked in 2003-05 before beginning to subside (Figure 1), and we now have a full dataset with which to examine the dramatic upsurge in mortality from the beginning to end. I argue that the drastic increase in mortality during the first half of the 1990s was only weakly associated with deterioration of the healthcare system. The jump was instead largely due to stress-related factors (e.g., increased labour turnover, migration, divorce, and income inequality) along with an increase in unnatural deaths (e.g., murders, suicides, and accidents) and somewhat less attributable to alcohol consumption during the transition. Cross-regional differences in healthcare facilities (e.g., the number of doctors, nurses, and hospital beds) did not exert much influence on life expectancy. After the collapse of the free healthcare system in the Soviet Union, legal and illegal user fees became common in the 1990s and beyond. The poor segment of the population could thus not take advantage of healthcare facilities regardless; essentially, health infrastructure only positively affected life expectancy in regions with marked income inequality (i.e., regions with a large share of the highest-income group).

STYLISTED FACTS AND THEORIES

The transition to a market economy and democracy in the 1990s in Eastern Europe and former Soviet Union countries led to a dramatic increase in mortality and shorter life expectancies, resulting in depopulation. Notably, output fell by 45% in 1989-1998, and social

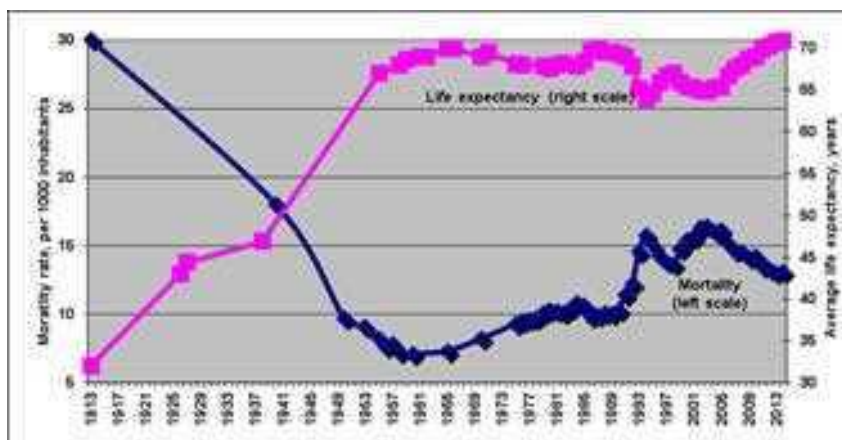
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indicators (e.g., rates of crime, murder, suicide, and income inequality) declined sharply as well. Mortality in Russia increased to levels unlike those of the 1950s-1980s; that is, such rates had been unprecedented for at least 40 years (Figure 1). One must go as far back as 1940 to find mortality rates higher than those in 1995-2005; data for the 1941-49 period (the Second World War and post-war reconstruction) are unavailable.

The 1990-2003 fall in life expectancy was truly exceptional. Russia's transition story was associated with comprehensive market-type reforms, which added another shock to the shock of democratisation. Price deregulation and ensuing changes in relative prices led to a mass reallocation of capital and labour that contributed greatly to stress-related factors: increased rates of unemployment, migration, labour turnover, divorce, and income inequality. However, the general rule was that countries with stronger institutions, whether democratic (e.g., Eastern Europe) or authoritarian (e.g., China and Vietnam), managed to cope with stress-inducing factors better than others. Moreover, only authoritarian regimes (China is the top example) managed to choose and implement a gradual transition strategy wherein the necessary restructuring - reallocation of capital and labour - could be stretched over a considerable period and thus alleviate the stress associated with unemployment, migration, and labour turnover (Popov, 2006, 2007).

As a rule, countries that proceeded with more gradual reforms (from China to Uzbekistan and Belarus) also managed to preserve their institutional capacity and completely avoid, or at least mitigate, a collapse in output and increase in mortality (Popov, 2000, 2007).

Several theories in the literature have delineated reasons behind the mortality crisis in Eastern European countries and former Soviet republics (see Chapter 1). Relevant factors include a decline in food consumption due to economic hardship, deterioration of the healthcare system, the stress associated with transitioning to a market economy and democracy, increased crime and accidents, pollution, increased alcohol and tobacco consumption, the 'demographic echo' (see survey in Chapter 2; Cornia, 1997, 2004; Cornia & Panicià, 2000). More recently, these theories were reduced to two: stress and alcohol. Numerous other explanations, such as accidents, crime, nutrition, a deteriorating healthcare system, and smoking, definitely played distinct roles; for instance, per-capita sales of cigarettes in Russia in 1996-2006 doubled due to free advertising.



Source: Goskomstat.

Figure 1. Mortality and life expectancy in Russia (1922-1991 [USSR]), 1913-2014.

Yet these factors cannot explain several trends: the rapid and steep rise in mortality (there should be a lag with regard to increased smoking, poorer nutrition, and declining healthcare services); the magnitude of the crisis (additional annual deaths due to increased mortality in the 1990s totalled about 1 million per year in Russia alone, whereas total additional deaths due to murders, suicides, and accidents were lower by an order of magnitude - about 100,000); and the predominantly cardiovascular causes behind the increased death rate (i.e., a dramatic increase in mortality from such diseases among 40-to-50-year-old men).

Cross-regional comparisons for the Russian Federation, drawing from data on about 80 regions, can shed light on major drivers of the mortality crisis. The most successfully performing regions, such as resource regions, demonstrated high employment elasticity in terms of output along with relatively (as measured against the magnitude of reduced output) high unemployment rates (Popov, 2001a). Such a pattern suggests a likely trade-off between performance and employment downsizing, with a price to pay for better performance in the form of a higher relative increase in unemployment (per unit change in output) due to restructuring (Gaddy & Hill, 2003; Korel & Korel, 1999). In absolute terms, unemployment levels in better-performing regions were quite close to the national average despite more favourable output dynamics. Another 'cost of success' came in the form of higher labour mobility and growing income inequality. The Gini coefficient of income distribution did not seem to depend on performance: regions with smaller declines in industrial output in the 1990s did not exhibit lower income inequality. As a result, regions that were relatively better off in terms of output change were relatively worse off in terms of stress-related factors, leading to higher increases in mortality and greater reductions in life expectancy (Walberg et al., 1998).

DATA AND METHODS

The dependent variable is the change in life expectancy in 1990-2003¹. Unlike the mortality rate, life expectancy does not depend on the age structure of a population, leading to one less factor to control for when seeking explanations. Relevant explanatory variables can be divided into three groups:

1. Objective conditions (climate, proxied by average January temperature; degree of urbanisation; population density; and Far East and Moscow dummy variables).
2. Economic variables (investment and income) and indicators of regional governments' institutional capacity (increase in murder rates; share of small

¹ Russia's mortality crisis primarily consisted of increasing mortality among working-age individuals. Mortality in individuals younger than age 15 and older than age 70 (women) declined after 1991. Life expectancy at birth is affected by mortality during working age, by infant and child mortality, and by old-age mortality. As a result, changes in life expectancy at birth are confounded by changes in child mortality having the opposite direction than during adult ages. Hence, age-adjusted mortality during working age (15-60 or 20-60 years old) or life expectancy during working age may be a better mortality indicator when studying the Russian mortality crisis. However, data on age-adjusted mortality during working age (15-60 or 20-60 years) or life expectancy during working age were unavailable in the regional breakdown. Instead, I introduced another independent variable: the share of population at working age in 1998 (the middle of the study period). This variable was insignificant in all specifications. One could also argue that stress and alcoholism affect the elderly and children as well - the elderly for obvious reasons, and because children in stressed families with high alcohol consumption are exposed to greater health risks.

enterprises in regional employment, adjusted for degree of urbanisation). Murders clearly affect mortality directly, but they are also good indicators of the state's institutional capacity (monopoly on violence - see Popov, 2001a, 2001b, 2007). The share of small enterprises in total employment characterises the regional government's ability to create a business environment rooted in law and order (Popov, 2001a, 2001b). This institutional capacity is necessary to manage restructuring and associated stress.

3. Stress-related indicators (increases in labour mobility and unemployment, migration, divorce, income inequality, and poverty).
4. Level of alcohol consumption and associated increase.
5. Healthcare system deterioration, proxied by the change in the number of doctors per capita.
6. Political orientation of regional governments, proxied by the percentage of votes received by communists during elections in the 1990s.

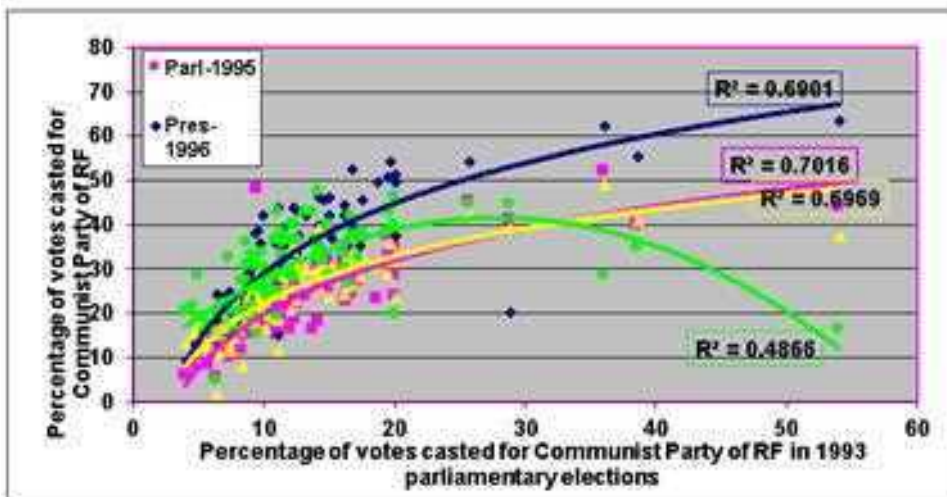
All indicators were taken from Goskomstat (Regiony Rossii) unless otherwise specified. The Goskomstat database contains data on 89 regions, but not all data were available for each region. Increment indicators capture the period under investigation (1990-2003) except for the following. The increase in per-capita vodka sales was measured from 1997 to 2003 because there were no data; the same applies to the increase in poverty level (1994-2003), increase in inequality (the ratio of the share of 20% of the wealthiest population to the share of 20% of the poorest population in total income; 1995-2003). The change in regional investment (compared to the Russian average) was measured from 1990 to 1998, as 1998 was the lowest point of investment decline in most regions. The change in real income was measured from 1990 to 1999 because the trough in real incomes occurred in 1999, the year following the currency crisis of August 1998 that led to dramatic devaluation of the Soviet ruble and a reduction in real income. Investment and real income each recovered after 1998-99, but this gradual (and incomplete, in the case of investment) recovery was allegedly less important to the change in life expectancy than the sharp reduction during the first half of the 1990s².

Level indicators refer to the middle of the period in question (i.e., 1997). An exception is the labour turnover variable, which was only available for 1995. The unemployment level variable for 2003 was used in the regression to explain the increase in alcohol sales in 1997-2003. The share of votes cast for communists was measured based on the results of the 1996 presidential election, but other elections in the 1990s were not drastically different in this respect (Figure 2).

AVTEMP, the average temperature in January 1997, had a predictable negative effect on life expectancy change, suggesting that it was more difficult to contain the rise in mortality in cold regions due to collapsing infrastructure during the transition. URB, the share of the urban population on January 1, 1997, had a negative impact on life expectancy because economic restructuring was occurring mostly in urban areas. FAREAST, a dummy variable for Far East regions, perhaps surprisingly influenced life expectancy positively - presumably because the largely migrant population in this region (virtually everyone was a migrant in the second and third ancestor generations) retained a greater capacity to cope with stress-related factors. MOSCOW, the Moscow dummy variable, had a negative impact on the change in life

² This assumption was tested and confirmed.

expectancy; the magnitude of restructuring in this city was the highest in the country, and stressors were numerous.



Source: Central Electoral Commission, Russian Federation. The list of variables can be found in the Appendix.

Figure 2. Percentage of votes cast for the Russian Federation Communist Party in various elections in the 1990s.

INVincr, investment in 1998 as a % of 1990, had a predictable positive impact due to better infrastructure and job prospects. Yincr, representing personal real income in 1999 as a % of 1990, had a negative impact on life expectancy, suggesting that stress played a prominent role in influencing changes in mortality, such that regions with higher growth in real income (i.e., more rapid restructuring) paid a high price in the form of greater increases in mortality.

Institutional capacity indicators had predictable (positive and negative, respectively) effects on life expectancy. SMent, the share of small enterprises in total employment in 1997 adjusted for the degree of urbanisation (the higher the share, the better the regional business climate), affected life expectancy positively. CRIMEincr, the increase in the crime rate in 2003 compared to 1990, and HOMIClevelINCR, the increase in the number of murders per 1,000 inhabitants in 2003 compared to 1990, affected life expectancy negatively - both directly (through greater mortality from crimes and murders) and indirectly (as shown by proxies for regional governments' deteriorating capacity to cope with stress-related factors) - and served as proxies for stress factors (i.e., insecurity) in and of themselves.

Stress-related factors had the greatest effects on changes in life expectancy. Specifically, the following factors negatively and significantly influenced changes in life expectancy: labour turnover (i.e., hiring and layoffs) as a % of employment (LABmob); the Gini coefficient of income inequality in 1997 (GINI97); the share of the richest 20% of the population in total income in 2003 (SHrich03); the share of the poorest 20% of the population in total income in 2003 (SHpoor03); the ratio of the share of the richest 20% to the share of the poorest 20% of the population in 2003 (INEQ03); the increase in the number of immigrants arriving in the region per 10,000 inhabitants in 2003 compared to 1990

(MIGRgrINCR); and the increase in the number of divorces per 1,000 inhabitants in 2003 compared to 1990 (DIVrateINCR).

The Gini coefficient considers the deviation in income shares across all income groups from the absolutely even income distribution line and therefore provides a more accurate assessment of inequality compared to the share of the 20% richest and 20% poorest population in total income. However, Gini coefficients for regions of interest were only available for 1997; they were not taken from Goskomstat, which does not report regional Gini coefficients, but from Shevyakov and Kyruta (1998). So as not to waste this information, I considered it alongside other indicators of income inequality.

To potentially shed light on major causes of the increase in mortality, I ran cross-regional regressions. I first regressed changes in life expectancy on all available explanatory variables: objective conditions, economic restructuring and institutional degradation, stress-related indicators, vodka sales, healthcare system deterioration, and regional governments' political orientation. All variables were significant when added separately, although some were correlated. An increase in vodka sales was strongly associated with labour mobility and other stress-related factors. If an increase in alcohol consumption was also driven by stress factors, such as the growth of unemployment, labour mobility, migration, and inequalities, then it would be reasonable to consider residuals from the equation explaining alcohol consumption and then use these residuals as an explanatory variable in the equation for life expectancy change. Doing so would help test whether the exogenous (i.e., not stress-driven) increase in alcohol consumption affected life expectancy.

RESULTS: INITIAL CONDITIONS, ECONOMIC RESTRUCTURING, STRESS, AND ALCOHOL CONSUMPTION

Overall, initial and objective conditions (i.e., climate, urbanisation, and regional dummies for the Far East and Moscow), regional governments' institutional capacity (i.e., share of employment at small enterprises, crime rate, and murder rate), economic indices (investment and income), stress-related factors (labour turnover, migration, divorce, income inequality, and crime), and healthcare system developments (even without alcohol consumption indicators) explained more than 80% of regional variations in changes in life expectancy in 1990-2003 (Table 1).

Alcohol Consumption

Increased alcohol consumption evidently contributed to the rise in deaths due to external causes (i.e., accidents, murders, and suicides). In 2002, death rates from external causes in Russia were the highest in the world (Table 2). Alcohol consumption was also correlated with death rates from all causes, but this relationship does not necessarily imply causation. As was pointed out in Chapter 1, there are some important inconsistencies in the dynamics of alcohol consumption and mortality.

Table 1. Cross-region regressions: Factors affecting changes in life expectancy in Russian regions in 1990-2003 (robust estimates, t-statistics in parentheses; constant not shown) dependent variable - change in life expectancy in 1990-2003, years

Equations, # of variables/variable	1, N=64	2, N=62	3, N=62	4, N=62	5, N=62	6, N=63	7, N=63
Average temperature in January 1997, degrees	-0.99*** (-2.99)	-0.37** (-2.06)	-0.30 (-1.62)	-0.28 (-1.53)	-0.39** (-2.29)	-0.43*** (-2.75)	-0.52*** (-3.39)
Share of urban population, 1997, %		-0.62*** (-3.19)	-0.56*** (-3.55)	-0.56*** (-3.35)	-0.62*** (-4.58)	-0.66*** (-3.80)	-0.66*** (-4.02)
Dummy variable for Far East regions		1.07** (2.90)	0.83* (1.90)	0.90** (2.02)	1.01** (2.40)	1.42*** (3.26)	1.38*** (3.40)
Moscow dummy			-7.37*** (-4.66)	-8.35*** (-3.29)	-7.63*** (-5.05)	-4.91** (-2.47)	-5.78*** (-2.87)
Investment in 1998 as a % of investment in 1990	0.14*** (4.22)	0.08** (2.52)	0.09** (2.11)	0.08** (2.30)	0.08** (2.43)	0.08*** (3.32)	0.08*** (3.72)
Real personal income in 1999 as a % of 1990			-0.24* (-1.71)	-0.2 (-1.33)	-0.25** (-2.19)		
Share of employment at small enterprises (adjusted for share of urban population in the region), 1997, %		0.64* (1.68)	0.10** (2.50)	0.77* (1.76)	0.88** (2.39)		
Crime rate in 2003 as a % of 1990		-0.01 (-1.48)				-0.04* (-1.68)	-0.04* (-1.82)
Increase in number of murders per 1,000 inhabitants in 2003 compared to 1990	-10.4*** (-2.99)	-11.1*** (-4.41)	-12.0*** (-4.98)	-12.4*** (-5.01)	-13.5*** (-5.42)	-13.4*** (-6.15)	-13.7*** (-6.17)
Labour turnover as a % of employment in 1995	-0.71*** (-3.90)	-0.57** (-3.13)	-0.54*** (-2.92)	-0.33* (-1.78)	-0.66*** (-3.20)	-0.35* (-1.66)	-0.28 (-1.28)
Gini coefficient of income inequality in 1997		-0.084*** (-3.21)	-0.092*** (-3.81)	-0.093*** (-3.74)	-0.101*** (-3.99)	-0.099*** (-3.35)	-0.090*** (-3.17)
Ratio of share of richest 20% to share of poorest 20% of population in 2003, squared		-0.16*** (-3.94)					
Increase in number of immigrants to region per 10,000 inhabitants in 2003 compared to 1990, %	-0.06** (-2.33)	-0.04** (-2.26)	-0.03* (-1.72)	-0.03 (-1.39)	-0.04*** (-2.24)	-0.05** (-2.37)	-0.05** (-2.32)
Number of divorces per 1,000 inhabitants in 2003 as a % of 1990	-4.7*** (-3.87)	-3.7*** (-3.65)	-4.2*** (-3.94)	-4.2*** (-3.85)	-4.0*** (-4.30)	-3.5*** (-4.36)	-3.4*** (-4.23)
Sales of vodka per capita in 2003, litres				-0.51** (-2.06)		-0.69*** (-3.22)	-0.74*** (-3.60)
Number of doctors per 10,000 inhabitants in 2003		-39*** (-5.39)	-31*** (-6.22)	-30*** (-5.44)	-31*** (-6.88)	-0.28*** (-5.18)	-30* (-4.98)
Interaction term = Number of doctors * Share of richest 20% in income		0.09*** (5.62)	0.08*** (6.36)	0.07*** (5.49)	0.07*** (7.03)	0.06*** (5.27)	0.06*** (5.05)
Interaction term = Number of doctors * Communist vote					0.007* (1.89)	0.007** (2.09)	0.007** (2.16)
Adjusted R ²	60	80	81	83	83	84	85

*, **, *** Significant at the 10%, 5%, and 1% level, respectively.

Cross-regional comparisons present an additional argument. There is a negative relationship (Figure 3) between the levels of vodka consumption and the level of life expectancy by region: high vodka consumption and low life expectancies in Northern and Eastern resource regions (with extensive restructuring and great stress) compared to low vodka consumption and high life expectancies in southern regions, especially in the North Caucasus (with low levels of restructuring and less stress). Again, one possible explanation would be that higher alcohol consumption leads to higher mortality (lower life expectancy), but the other explanation is that higher stress has two effects - it reduces life expectancy and drives up alcohol consumption, which by itself does not contribute to higher mortality.

A closer look reveals that VODKAincr, which indicates the increase in vodka sales per capita in 1997-2003, was not significant when added into the right-hand side (RHS) of the equation. The level of vodka consumption - VODKA03, per-capita vodka sales in dekalitres in 2003 - affected changes in life expectancy negatively. This pattern was likely due to the variable's correlation with stress-related indicators, particularly with labour mobility (Figure 4); thus, including both variables on the RHS of the same regression could make LABmob insignificant (see the last equation in Table 1). When vodka consumption was included separately, without other control variables (labour mobility, crime rate increase, real income change, and share of employment in small enterprises), it was significant (see Table 1).

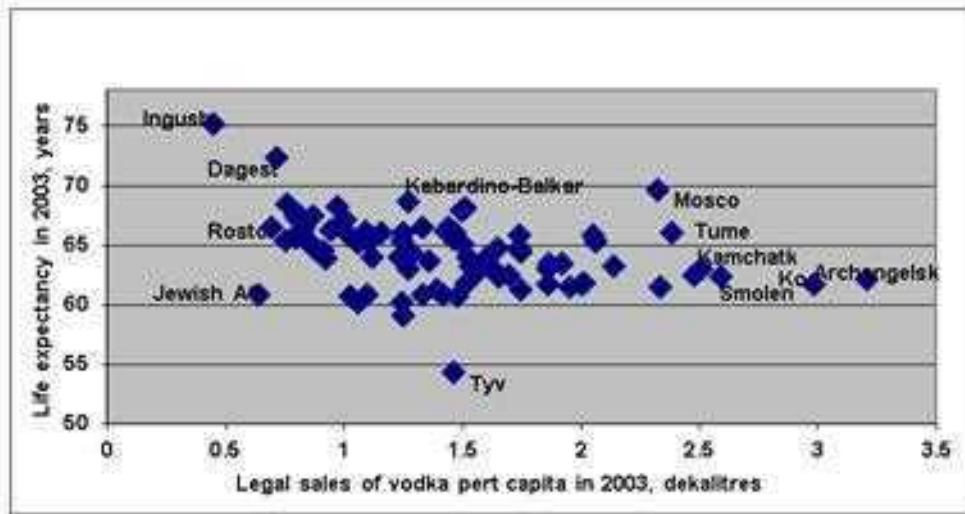
The high correlation between labour mobility in 1995 and vodka consumption per capita in 2003 ($R = 0.58$) may have simply been spurious, as the association with vodka consumption in 1997 was only 0.26 and 0.38 with the increase in vodka consumption in 1997-2003. However, the increase in vodka consumption may have also been driven by the same stress factors that contributed to higher mortality. After controlling for population density (POPdens) and the level of vodka sales in the beginning of the 1997-2003 period (VODKA97), 50% of the cross-regional variation in VODKAincr (i.e., the increase in per-capita vodka sales in 1997-2003) could be explained by exactly the same stress indicators discussed previously: the unemployment level in 2003 (UNEMPL03); labour turnover in 1995 (LABmob; no data for later years); increase in migration inflows to the region in 2003 compared to 1990 (MIGRgrINCR); increase in inequality, namely the ratio of the richest group to the poorest in 2003 compared to 1995 (INEQincr); and increase in the share of the population living below the poverty line in 2003 compared to 1994 (POVERTYincr).

Table 2. Number of deaths from external causes per 100,000 inhabitants in 2002 - Countries with highest rates

Country/Indicator	Deaths from external causes, total	Including deaths from			
		Accidents	Suicides	Murders	Other*
Russia	245	158	41	33	11
Sierra-Leone	215	148	10	50	7
Burundi	213	64	7	18	124
Angola	191	131	8	40	11
Belarus	172	120	38	13	0
Estonia	168	124	28	15	0
Kazakhstan	157	100	37	20	0
Ukraine	151	100	36	15	0
Cote d'Ivoire	148	86	31	27	24
Colombia	134	36	6	72	19
Niger	133	113	6	14	0

Source: WHO.

* Deaths due to unidentified external causes, wars, police operations, and executions. Totals may differ slightly from the sum of components due to rounding.



Source: Goskomstat.

Figure 3. Life expectancy and sales of vodka per capita in Russian regions.

The following equation best explains changes in vodka sales in 1997-2003:

$$\begin{aligned}
 VODKAincr = & -1.2 - 0.65VODKA97 + 0.002POPdens + 0.03UNEMPL03 + \\
 & +0.001MIGRgrINCR + 0.01INEQincr + 0.04LAEmob + 0.002POVERTYincr \\
 & (3.88) \quad (-3.74) \quad (2.90) \quad (1.97) \\
 & (2.49) \quad (1.66) \quad (6.40) \quad (1.69)
 \end{aligned}
 \tag{1}$$

(N = 75, R² = 0.49; robust standard errors, t-statistics in parentheses; all coefficients significant at the 10% level or better)

A similar equation can explain the level of vodka consumption in 2003:

$$\begin{aligned}
 VODKA03 = & -0.6 + 0.001MIGRgrINCR + 0.03INEQ03 + 0.043LAEmob + 0.01URB \\
 & (2.58) \quad (1.76) \quad (1.76) \quad (4.49) \quad (2.43)
 \end{aligned}
 \tag{2}$$

(N = 79, R² = 0.41; robust standard errors, t-statistics in parentheses; all coefficients significant at the 10% level or better).

When the residuals from the above two equations (explaining changes in vodka sales and level of consumption, respectively) were introduced into the RHS of the best equation to explain changes in life expectancy, these residuals had predicted (negative) sign and were statistically significant. In other words, regional variations in alcohol consumption, even when not determined by stress-related factors, adversely affect life expectancy. However, this impact appeared rather modest: the coefficient linking life expectancy change in years and vodka sales per capita in dekalitres was about 0.5; that is, for life expectancy to fall by 1 year, vodka sales per capita must increase by roughly 20 litres per year. Clearly, the size of the effect was too small to explain the decline in life expectancy by 5 years on average with average vodka sales of 14-15 litres.

Deterioration of the Healthcare System

The impacts of healthcare system developments on life expectancy were rather weak and could not be traced when including indicators of healthcare system capacity (i.e., number of doctors, mid-level medical personnel, hospital beds, and polyclinics' patient capacity) as linear variables on the RHS. This pattern echoes that noted by King, Stuckler, and Hamm (2006). However, when the number of doctors per capita was interacted with the inequality variables and communist vote variable, the coefficients became significant. Equation #6 in Table 1 is best in this case and is presented below to render the impact of the number of doctors explicit:

$$\Delta LE = CONST + CONTR + DOCT03(.0007 COMMvote + .006 SHrich03 - .28)$$

(all coefficients, including control variables, are significant at 10% or less, $R^2=0.84$, $N=63$),

Where

DOCT03 – number of doctors per 10,000 inhabitants in 2003,

SHrich03 – share of richest 20% of the population in total income in 2003,

COMMvote – share of votes cast for the communist candidate at 1996 presidential elections, % (strongly correlated with the share of votes cast for communists at other presidential and parliamentary elections – see “data and methods” section).

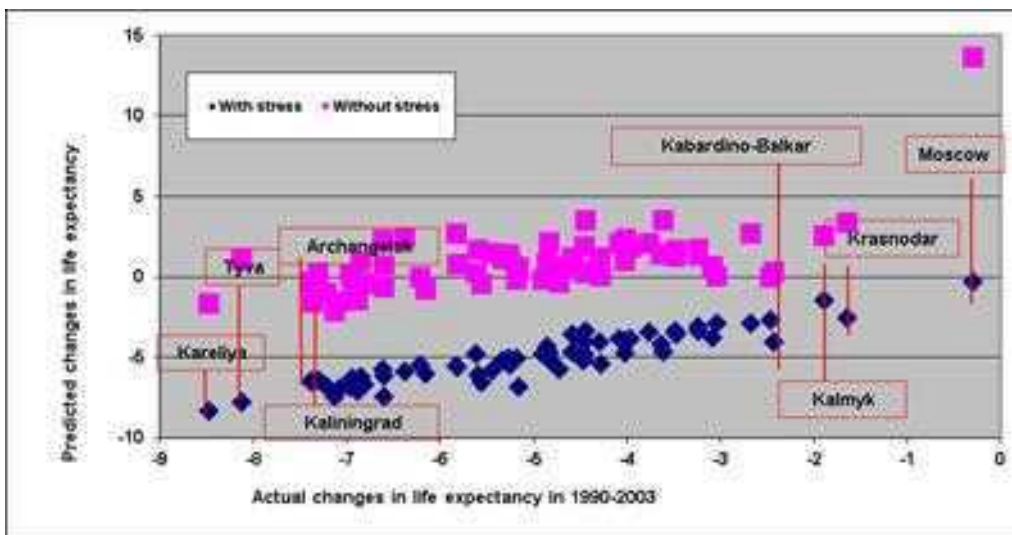
(3)

This regression has a threshold, as the equation implies that the number of doctors per capita positively influenced changes in life expectancy only under certain conditions: (1) when the share of the highest income group was sufficiently high (i.e., nearly 40% or over); and (2) when the share of votes cast for communists was sufficiently high. The interpretation of this threshold is rather straightforward: a high healthcare facility capacity exerted a favourable impact on life expectancy only if there were enough rich people in the region who could afford to pay for such healthcare and/or if the regional government was distributing healthcare services in an egalitarian manner (proxied by the communist vote variable). In fact, the coefficient of the COMMvote variable was so small that it could not counteract the inequality effect when the share of the richest 20% in total income was lower than 35%; in this case, the impact of the greater number of doctors on life expectancy was consistently negative, even if 100% of voters voted for communists.

Overall, in 1990-2003, healthcare facilities in Russia contributed to the increase in life expectancy only in regions with very high income inequality (i.e., high shares of the richest income group in total income); in other regions, the impact of a greater number of doctors per capita on life expectancy was negative if this variable had any effect at all. One should note that there were only 10 regions in 2003 where the share of the top 20% of the population in total income exceeded 45% - a necessary condition to enjoy the positive impact of a higher number of doctors on life expectancy (given the actual percentages of votes cast for communists). Furthermore, the impact of healthcare system capacity on life expectancy change was extremely modest compared to the effects of stress-related factors, which clearly dominated.

CONCLUSION

To reiterate, the Russian mortality crisis of the 1990s was caused by a shock-therapy-type marketisation of the economy that led to mass reallocation of labour over the course of industrial restructuring and to a dramatic rise in various stress-related factors - income inequality, unemployment, labour turnover, migration, crime, and divorce - that were largely responsible for an unprecedented 60% increase in mortality. Alcohol consumption, although strongly correlated with a rise in mortality, was likely not an important driver behind this increase but was instead determined by the same stress factors as the rise in mortality rate itself. Deterioration of healthcare facilities only had a modest impact on life expectancy, and solely in regions with a small rich population and non-equitable political orientation (i.e., a low share of votes cast for communists).



Source: Goskomstat (Regiony Rossii) and author's calculations.

Figure 4. Predicted (with and without stress) and actual changes in life expectancy in Russian regions in 1990-2003 (years).

Therefore, the roles of stress factors in this sharp rise in mortality is predominant. Consider predicted changes in life expectancy (according to the regression equation in the second-to-last column in Table 1) and hypothetical changes that would have occurred if stress-related factors were absent (i.e., no increases in crime and homicide rates or in migration, labour turnover, divorce, and income inequality). These two indicators (i.e., predicted changes in life expectancy with and without stress-related factors) are plotted in Figure 4 against actual changes in life expectancy shown on the horizontal axis. Excluding stress-related factors, life expectancy would have been higher by 2003 in every region by roughly 5 years on average. In fact, without these factors, life expectancy figures that had fallen by anywhere from 9 to 0.1 years (5 years on average) in 1990-2003 would have increased in all regions except for 15; thus, on average, life expectancy would have been 1 to 2 years longer in 2003 than in 1990. To be sure, this would not be a great record for 13 years, but at least no reduction in life expectancy would have actually occurred.

APPENDIX

List of Variables

AVTEMP	-	average temperature in January 1997
COMMvote	-	share of votes cast for communist candidate in 1996 presidential election, % (strongly correlated with share of votes cast for communists in other presidential and parliamentary elections)
CRIMEincr	-	crime rate in 2003 as a % of 1990
deltaLE	-	increase in life expectancy in 1990-2003, years
DIVrateINCR	-	increase in number of divorces per 1,000 inhabitants in 2003 compared to 1990
DOCT03	-	number of doctors per 10,000 inhabitants in 2003
FAREAST	-	dummy variable for regions of the Far East
GINI97	-	Gini coefficient of income inequality in 1997 (unofficial estimate; Shevyakov & Kyruta, 1998)
HOMIClevelINCR-		increase in number of murders per 1,000 inhabitants in 2003 compared to 1990
INEQ03	-	ratio of share of richest 20% to share of poorest 20% of population in 2003
INEQincr	-	ratio of richest 20% to share of poorest 20% of population in 2003 minus the same ratio in 1995
INVincr	-	investment in 1998 as a % of 1990
LABmob	-	labour turnover (hiring and layoffs) as a % of employment in 1995
MIGRgrINCR	-	increase in number of immigrants to the region per 10,000 inhabitants in 2003 compared to 1990
MOSCOW	-	dummy variable for Moscow
POPdens	-	population density in 1997, persons per 1 sq. km.
POVERTYincr	-	percent of people below the poverty line in 2003 minus the same percent in 1994, per person
SHpoor03	-	share of poorest 20% of population in total income in 2003, %
SHrich03	-	share of richest 20% of population in total income in 2003, %
SMent	-	share of employment at small enterprises (adjusted for share of urban population in the region) in 1997
UNEMPL03	-	level of unemployment in 2003, %
URB	-	share of urban population on Jan. 1, 1997
VODKA03	-	sales of vodka in dekalitres per capita in 2003
VODKA97	-	sales of vodka in dekalitres per capita in 1997
VODKAincr	-	increase in sales of vodka in dekalitres per capita in 1997-2003
Yincr	-	personal real income in 1999 as a % of 1990

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Chapter 290

THE PATH OF ECONOMIC DEVELOPMENT AND HEALTH STATUS: EVIDENCE FROM CHINA

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INTRODUCTION

The last two decades of the 20th century witnessed a wave of deep, radical socioeconomic restructuring in (former) socialist countries (or communist countries in more Western terminology) in Central and Eastern Europe and East and Southeast Asia. The transition from a centrally planned political-economic system to a market economy and, at least, a de jure democracy fundamentally changed not only the political and economic profiles of countries in question but also the welfare of individuals living in those countries. Such a transition was presented by the supporters of the Washington Consensus as a rapid shift from low to high socioeconomic equilibrium. However, without appropriate governance and management, abrupt and uncontrolled transition can lead to huge socioeconomic costs, especially through unattended unemployment, loss of social status, and social stress (Cornia, 2004; Chapter 2). Indeed, the transition led to severe economic recession and social chaos in countries such as the former Soviet Republics, which followed so-called ‘shock therapy.’ Consequently, the biological and psychological welfare of the population (e.g., living standards and health status) experienced a substantial regression and failed to revive even one decade after the collapse of the socialist regime. Russia’s gloomy record of rising mortality, declining life expectancy, and deteriorating lifestyle is the most typical example of such effects in the literature. Apart from problematic economic reform, the absence of strong political institutions, due to the lack of either Central Europe-type effective democracy or China-type effective authoritarian control, serves as another contributor to health recession and stress during the transition (see Chapter 1).

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On the contrary, (former) Asian socialist countries, except for Mongolia (which is similar to the Central and Eastern Europe case) and North Korea, have followed a gradualist approach towards political-economic reform. In 1978, China initiated its ‘Reform and Openness’ effort, and the Vietnamese and Lao counterpart (‘Renovation and Openness’) started in 1986. Under the gradualist approach, East Asian socialist countries have avoided the socioeconomic recession that occurred in former Soviet Republics and have instead experienced rapid economic growth since the 1980s (the 1990s for Vietnam and Laos). In particular, the case of China has been widely perceived as an economic miracle with the most rapid and vast poverty reduction in human history. Since 1978, China’s GDP per capita has grown by 8.4% annually on average. In 1978, China’s GDP per capita (2010 constant International Dollar) ranked fourth from the bottom, only marginally higher than Myanmar, Burundi, and Nepal;¹ by contrast, China’s GDP per capita ranked between 70th and 80th globally in 2018.²

Given the substantial success of economic growth and liberalisation, the extent to which the transition has influenced individual welfare in China is of great interest. Indeed, the peculiar institutional framework and political orientation of this country represent a radically different approach to the ‘shock therapy’ transition of the former Soviet Union. Despite China’s unprecedented economic growth, the extent to which the benefits of such growth have translated into better human welfare remains controversial. Whilst Chinese life expectancy today is approaching the (stagnating) level of the United States (see Chapter 3), initial stages of the reform indicate much poorer outcomes that vary widely across social groups. Lu (2006) concluded that the health status of the Chinese population during the reform years was at best mixed at least until the early 2000s, and the state’s withdrawal from healthcare and the consequential marketisation of healthcare have led to this mixed outcome.

This chapter aims to trace the evolution of health status in China during the reform period, namely from 1978 until the present, placing China’s case in a global comparison with other world regions and examining the situation across regions within China. In particular, we follow Wang (2008) and Lo (2016a) in dividing China’s economic reform in the past 40 years into three *de facto* distinct phases based on the policy orientation towards the role of the state in the economy and the progressivity of the policy regime. We then explore the evolution of health status and healthcare in China within these three periods. From the beginning of the reform in 1978 until 1992, the state maintained a dominant role in not only the economy but also broader socio-political spheres. Despite increasing marketisation in many areas of the economy (e.g., the product market, labour market, and capital market), market forces have not completely ‘invaded’ non-economic spheres (Wang, 2008). The continuation of the strong presence of the state and the egalitarian institutional arrangement allowed, to a certain extent, some improvements in the welfare of most of the population during this period. Then, from 1993 to 1999, China adopted a neoliberal reform and followed a market-friendly (but labour-unfriendly) pattern via privatisation of state-owned enterprises (SOEs) and by laying off SOE employees for efficiency (减员增效, *jian yuan zeng xiao*). The state substantially withdrew from most socioeconomic spheres, and market force eventually ‘invaded’ most social spheres. The state largely discarded the egalitarian ideology and passed a substantial part of the

¹ However, it should be noted that GDP per capita did not fully reflect the real level of welfare and economic development for China’s centrally planned economy in 1978.

² The actual rank depends on which country list is used.

provision of public service, especially education and healthcare, onto the market. The burden of education and healthcare was therefore shouldered by individuals, resulting in rampant social inequality (Duckett, 2007; Wang, 2008). Market fetishism led both the state and society to prioritise economic growth over welfare. As a result, by the end of the 1990s, China had transitioned from a high-welfare country to a low-welfare country. Since the early 2000s, China has shifted to a state-led development path and has been approaching the so-called ‘Golden Age’ model, similar to what took place in developed countries between the 1950s and early 1970s (Lo, 2016a). This model features significant state involvement in public service and strong economic performance driven by capital-deepening industrialisation and technological and skill upgrading, leading to the growing provision of public service and improved labour welfare and rights. The institutional arrangement of this model can be summarised as ‘Big Business, Big Labour, and Big Government’ (Lo, 2016a). Underlying this model is China’s ongoing economic rebalancing away from a labour-intensive growth pattern. In contrast to the 1990s, China’s growth path since the 2000s has reconciled economic growth and social development (Lo, 2016a).

The three growth models represent *de facto* orientations towards the role of the state in public service and welfare. The progressivity of the policy regime is higher in the third phase than the first two phases. The three models/phases are also associated with different state capacities to provide public services. Therefore, the three model/phases can be conceptualised as ‘a proactive state with limited resources available for public service’ (1978–1992), ‘a passive state with limited resources available for public service’ (1993–1999), and ‘a proactive state with sufficient resources available for public service’ (2000–now). Having identified the three models/phases, we can next examine how the role of the state in healthcare has evolved under these models/phases and consider how health status has consequentially evolved.

This chapter is organised as follows. Section 2 briefly reviews China’s economic reform and health policy during the three models/phases since 1978. Section 3 presents the evolution of health status as measured by various indicators of healthcare, mortality, and life expectancy at macro and micro levels; the section also includes various econometric estimates to individuate socioeconomic determinants of health status and its trends across Chinese provinces and individuals during transition. Section 4 introduces the concept of comparative political economy to discuss the impact of China’s peculiar transition strategy on the country’s health status, characterised by a competition-driven local developmental state and the consequential low-wage and labour-repressed regime. Section 5 concludes this chapter.

REFORM AND HEALTH POLICY IN CHINA

Beginning in 1978, Beijing started to reform its economic guidelines, gradually and pragmatically, and transformed from a centrally planned economy into a ‘socialist market economy.’ The literature on China’s development suggests various alternative schematisations of the reform period since 1978, depending on whether the focus is on economic targets, domestic events, or international relations (Biggeri & Gambelli, 2008; Wang, 2008; Zhu, 2012). For simplicity, this chapter divides China’s reform into three periods as discussed above.

The reform began in 1978 when Deng Xiaoping emerged in the internal fight for the succession to Mao Zedong.³ The reform started allowing market incentives in rural areas through the Household Responsibility System. Gradually, this led to a reduction in state intervention, liberalisation of prices, opening up of Special Economic Zones, and dismantling of the commune system. However, a new institution, Township and Village Enterprises, emerged in this period, combining the local government's (top-down) and peasants' (bottom-up) initiatives. Indeed, the role of the state was reallocated from central to local governments, rather than tout-court opposed (Lu, 2000). This phase was also labelled 'reform without losers,' characterised by "the central government strategy of letting the nonstate sector grow without downsizing the state sector" (Zhu, 2012, p. 116), so that the resistance against the reform was minimal. This phase, especially between 1978 and 1984, was characterised by an increase in employees' income share (Molero-Simarro, 2015).

To accelerate reform, Deng carried out a tour in South China in 1992, investigating and promoting the experience of some areas that benefitted most from previous liberalisation (i.e., those benefitting from favourable natural advantages, as shown in Goodman and Segal, 2002). This travel is also recalled for Deng's famous slogan "Let some people get rich first" and for revealing the acceptability of an unbalanced trajectory across provinces as well as a conception of development in which income growth is paramount. In 1993, the 14th National Congress of the Communist Party of China endorsed the creation of a modern enterprise system. This implied restructuring and privatising SOEs under the guiding principle of 'retain the large, release the small': small firms were sold and leased, while the government maintained control over larger, more strategic ones. After Deng's death (1997), Jiang Zemin implemented similar policies, favouring the inflow of foreign direct investment, reforming the banking system, and adopting other policies in favour of privately owned and foreign-invested manufacturing enterprises for the purpose of admitting China to the World Trade Organization.

The neoliberal approach that typified the 1990s was abandoned in the new millennium, leaving room for what Lo (2016a) called the 'Golden Age' model, featuring rapid growth in wages (higher than GDP growth) and in labour productivity (driven by productive investments). This phase is also characterised by new relations with the rest of the world. The 1997–1998 Asian crisis called into question the effectiveness of neoliberal receipts (based on the assumption of capital flows towards poorer countries) and taught China not to implement uncritically the Washington Consensus receipts (Lo, 2016b). The new millennium has also been characterised by a stronger focus on redistribution: in 1999, China launched its 'Western Development' campaign to promote growth in inner backward areas; and in 2005, the new leadership adopted the goal of making China a 'harmonious society' (和谐社会), prioritising issues such as rural development, employment, healthcare and education, environmental protection, the legal system, and social security. The current president Xi Jinping has maintained coherent policies, targeting poverty eradication and the achievement of a 'moderately prosperous' society within his 'Chinese Dream' discourse.

The aforementioned reform approaches involve several aspects of economic activity, living conditions, and beliefs. The healthcare sector is no exception. Before 1978, under the

³ We cannot neglect the importance, for better or worse, of previous policies by Mao Zedong. Deng's reform did not occur in a vacuum; results achieved since 1978 are related to previously implemented infrastructure and human capital investments (Arrighi, 2007; Lu, 2000).

centrally planned system, communes and brigades were the core institutions responsible for the production and distribution of goods and services. Amongst the welfare services provided, theoretically with full population coverage, there was the healthcare sector, efficiently managed thanks to mass mobilisation (in health education and public hygiene) and the guidance of a 'prevention first' principle. These factors, and the work of a system of barefoot doctors, enabled China to achieve remarkable results despite its low level of income (Lu, 2006).

Subsequent reform, especially during the 1993–1999 phase, reversed this condition, shifting attention almost entirely towards economic growth. This strategy did not favour the translation of GDP growth into health conditions (and, more generally, welfare), with lower-than-expected health outcomes, breaking the virtuous circle between economic and human development and eventually leading to unsustainability and population risks (Biggeri, 2007; Duckett, 2007).

Some features of the transition had severe impacts on healthcare. For example, the dismantling of the commune system implied the collapse of public institutions in charge of health services provisions;⁴ the end of the full employment policy (the 'iron-rice bowl') endangered not only jobs but also all workers' social security schemes; the regional imbalance between growth rates implied inequality in the state's capacity to provide healthcare and welfare (Lu, 2006). Duckett (2007) identified 'overlapping patterns of inequality' in access to healthcare services, resulting in discrimination against women, middle-aged men, peasants, and inhabitants of inner provinces. The outcomes of health policies during the first two phases of reform (between 1978 and 1999) appeared in a World Health Organization report (2000), which ranked China 188th in the 'fairness of financial distribution' in its health system.

Another variable that is a testament to the negative influences of reform on China's health sector is life expectancy at birth. Cornia, Rosignoli, and Tiberti (2009) compared the trend of life expectancy before and after 1980, finding that between 1980 and 2000, Chinese people lost 3.6 years on average against a counterfactual scenario based on the continuation of pre-reform policies (despite the positive effect of improved income per capita).⁵ Analogously, Lu (2006) investigated the causes of poor life expectancy improvements and the reappearance of infectious diseases between 1978 and 2002, identifying three main elements: marketisation, privatisation, and adoption of the 'treatment first' approach. The official data on health expenditure shown in Figure 1 support the conclusion about the first two points.⁶

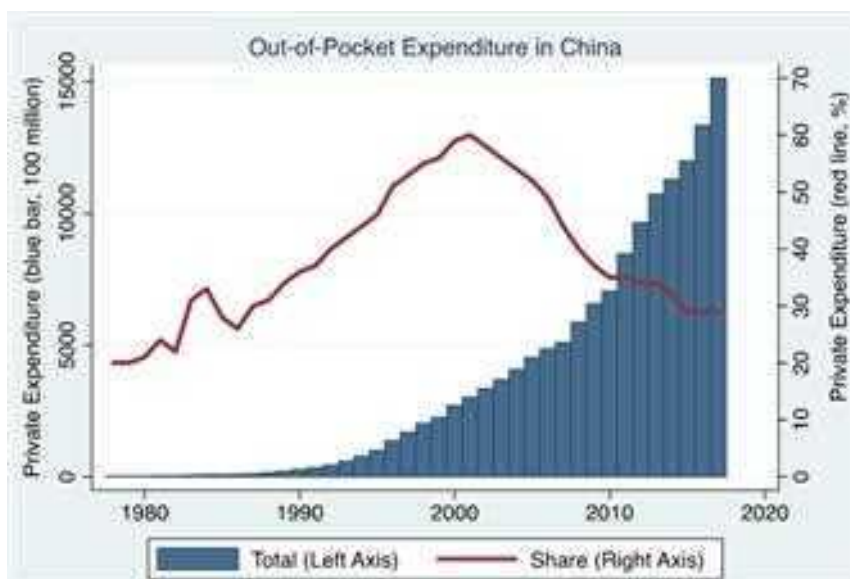
Figure 1 also indicates how, during the latest phase of reform, the state has (re)gained increasing importance consistent with the 'Golden Age' model. In dealing with channels through which the government re-launched its presence, an important aspect has been the reconstruction of insurance schemes to address the deleterious health consequences of dismantling the commune system. In 1998, Urban Employee Basic Medical Insurance (UEBMI) was launched in an attempt to expand the number of beneficiaries of health insurance services within the formally employed urban population. The rural population, excluded from UEBMI, was reached by the New Cooperative Medical Scheme; this

⁴ This choice resulted in an urgent but long-unaddressed problem of a lack of public support in the healthcare sector.

⁵ Among the possible causes of such an impressive reduction, the authors listed income inequality and volatility, psychosocial stress, gender discrimination in education, and declining access to healthcare services.

⁶ The burden of paying for market and private health services led health, along with education and housing, to be one of the 'three big mountains' faced by Chinese people.

programme was introduced in 2003 to cover the rural population on a voluntary basis and constituted a major turning point in Chinese health policies. Finally, Urban Resident Basic Medical Insurance, which was launched in 2007, has further enlarged the number of beneficiaries, including the entire urban population based on residence status. The literature has been quite cautious in describing the positive impacts of such programmes, pointing out their high costs (Yang & Wu, 2014), geographic inequality (Huang, 2015), and limited efficiency (Huang & Gan, 2017). The government, however, is strengthening relevant efforts with the aim of achieving universal health coverage by 2020, which could result in further improvements, especially if the current fragmentation in health institutions and policies is addressed properly (Meng, Fang, Liu, Yuan, & Xu, 2015).



Source: 2016 China Statistical Yearbook.

Figure 1. Private health expenditure in China, 1978–2015.

Finally, it is important to realise that the effects of transition and modernisation throughout the health sector are not limited to the direct effects of health reforms and facilities (Cao, Hansstein, & Liu, 2014) but rather involve various elements related, for better or worse, to Chinese residents' new lifestyles, consumption behaviours (Li, Miao, & Chen, 2015), and productive structure (e.g., industrial pollution and artificial intelligence that can perform medical activities).

HEALTH STATUS OUTCOMES

China has achieved tremendous improvements in population health status throughout past decades, such as increasing life expectancy and reduced mortality. However, these improvements were realised largely during the pre-reform period, with a substantial slowdown in growth since the 1970s. In this section, we aim to contribute to the debate about

China's health status and life expectancy during the reform period by providing a systematic historical and global comparison of China's health status since the 1960s (data prior to 1960 are scarcely available).

Life Expectancy

China's life expectancy increased from 35 years of age in 1949 to 77 years of age in 2018. However, as pointed out in Lu (2006), such success was mostly achieved before the reform; strong growth in life expectancy was lost after the reform began. Dividing China's post-1949 history into two periods, namely pre-1979 (pre-reform) and post-1979, the improvement in life expectancy was much greater before 1979 than afterwards. The first row in Table 1 shows the annual growth in life expectancy between 1960 and 1978 as 1.38%. Annual data on life expectancy between 1949 and 1960 are unavailable. The life expectancy was 35 years in 1949 and 44 in 1960, indicating that a nine-year increase was realised in 11 years. Then, it took only seven years for life expectancy to increase by another nine years. Thus, if the period of 1949–1959 is included, then the pre-1979 growth rate will be marginally lower than 1.38% but still quite high, especially compared with post-1979 growth. This evidence substantiates the argument that China's improvement in life expectancy has substantially underperformed during the reform period.

Although the weak improvement in life expectancy during the reform period is apparent, the aforementioned statement may not hold water. Figure 2 presents the life expectancy of twelve world regions, including China, since 1960. China's growth in life expectancy was rapid during the 1960s but decelerated throughout the 1970s. This visual illustration is supported by time series analyses on the growth rates of China's life expectancy during various periods since 1960. The fifth row of Table 1 shows that, between 1979 and 2017 – namely the entire reform period until the present – life expectancy grew by 0.27% per annum, much lower than the 1.38% during the pre-reform period. However, the decline in growth had already started in the beginning of the 1970s (i.e., before 1979). Therefore, it is safe to say that the substantial pre-reform growth in life expectancy was largely due to the great jump in the 1950s and the 1960s and would never be reached again thereafter (see Table 1 and Figure 2). The year 1970 represents a watershed in life expectancy growth, despite the economic situation during the 1970s being better than that during the 1960s; only 1976 showed negative GDP per capita growth, -3.08%. Another hypothesis about the driver of the decline in life expectancy in the 1970s is the Cultural Revolution, during which China suffered from severe socioeconomic turbulence.

How did life expectancy evolve during different phases of the reform? The last three rows of Table 1 reveal no qualitative differences in growth of life expectancy throughout the reform; growth rates for the initial phase, neoliberal phase, and 'Golden Age' phase are 0.26, 0.28, and 0.24. The neoliberal period demonstrated even higher growth, despite such a marginally higher rate potentially not having economic significance (we will return to this point in our econometric analysis of mortality).

Has China's performance during the reform fallen behind that of other world regions? As Figure 2 shows, the jump in the 1950s and 1960s led China's life expectancy to exceed other developing regions since the 1970s, second to only traditional developed countries and

transition countries (until the early 1990s). Since the 1980s, China’s life expectancy has even surpassed that of Russia and less advanced transition countries. Since the 2000s, China’s life expectancy has remained nearly the same as that of advanced transition countries, only second to traditional developed countries. Therefore, despite the slowdown in life expectancy improvements during transition, China has continuously moved upward in the global hierarchy of life expectancy.

Table 1. Growth rate of life expectancy in China since 1960

Period	Growth Rate	Adj. R ²	Life Expectancy Range
1960–1979 (pre-reform)	1.38***	0.97	43.7–65.9 (1.23 per annum)
1970–1990 (post-1960s–Reform 1)	0.48***	0.91	59–62.3 (0.52 per annum)
1970–2000 (post-1960s–Reforms 1 & 2)	0.35***	0.9	59–72 (0.43 per annum)
1970–2017 (post-1960s)	0.32***	0.98	59–76.4 (0.47 per annum)
1979–2017 (Reforms 1, 2, & 3)	0.27***	0.99	66.4–76.4 (0.26 per annum)
1979–1990 (Reform 1)	0.26***	0.96	66.4–69.3 (0.26 per annum)
1991–2000 (Reform 2)	0.29***	0.66	69.4–72 (0.29 per annum)
2001–2017 (Reform 3)	0.24***	0.96	72.4–76.4 (0.25 per annum)

Note: Growth rate (r) is estimated by the following trend equation: $\ln(\text{Life Expectancy}) = a + rt + u$. *** $p < 0.01$, ** $p < 0.05$, * $p < 0.1$. Reforms 1, 2, & 3 refer to the three distinct phases of China’s reform (exploratory phase, neoliberal phase, and ‘Golden Age’ model, respectively).



Source: World Development Indicators.

Figure 2. Life expectancy: A global comparison.

Visual inspection does not indicate that China's life expectancy growth has significantly lagged behind other developing regions since 1979. The time series analysis in Table 2 shows that the annual growth rate of life expectancy in China since 1979 is comparable to middle-income countries (0.28%), Latin America and the Caribbean (LAC), and Sub-Saharan Africa (SSA) but lower than low-income countries, those in the Middle East and North Africa (MENA), and South Asia. Traditional developed countries and transition countries exhibit the lowest growth. Except for Sub-Saharan Africa, growth in life expectancy appears to decline with income; China's performance is consistent with this trend. Moreover, China's absolute level of life expectancy is higher than the average level of countries with a similar income level. Given that the growth in life expectancy has a decreasing margin, China's growth performance may be better than the average performance of countries with a similar income level. Between 1979 and 2000, Russia experienced declining life expectancy, and Central Europe and the Baltics had much lower growth rates, whereas MENA and LAC countries showed more rapid growth in this period (which has slowed since 1990 and since 2000). Considering the decreasing margin of life expectancy of MENA and LAC, China has not underperformed with respect to other developing countries; rather, the difference compared with other transition economies favours China and is remarkable.

Table 2. Life expectancy growth since 1978: A global comparison

World Region	1979–2017	1979–2000	1990–2017	2000–2017
China	0.27*** (66.4)	0.23***	0.3*** (69.0)	0.25*** (72)
Russia	0.07** (67.1)	-0.11**	0.2*** (68.9)	0.46*** (65.5)
Central Europe & the Baltics	0.20*** (70.2)	0.09***	0.27*** (70.7)	0.27*** (72.7)
Europe & Central Asia (excl. high-income)	0.15*** (66.2)	0.02	0.24*** (68.2)	0.38*** (67.6)
High-income Countries	0.21*** (73.2)	0.21***	0.21*** (75.4)	0.19*** (73.6)
Middle-income Countries	0.28*** (60.7)	0.27***	0.29*** (64.1)	0.29*** (66.7)
Low-income Countries	0.42*** (47.6)	0.26***	0.52*** (50.7)	0.58*** (53.7)
OECD Countries	0.23*** (72.2)	0.23***	0.22*** (74.7)	0.2*** (77.1)
Latin America & the Caribbean	0.32*** (63.6)	0.37***	0.3*** (67.5)	0.25*** (71.3)
Middle East & North Africa	0.41*** (57.5)	0.62***	0.26*** (66.1)	0.23*** (69.3)
South Asia	0.42*** (53.5)	0.45***	0.4*** (58.2)	0.37*** (62.9)
Sub-Saharan Africa	0.32*** (47.9)	0.09***	0.48*** (49.9)	0.65*** (50.5)

Note: Growth rate (r) is estimated by the following trend equation: $\ln(\text{Life Expectancy}) = a + rt + u$.

*** $p < 0.01$, ** $p < 0.05$, * $p < 0.1$. Life expectancy at birth in the starting year is given in brackets.

Mortality

Mortality in China since the 1960s shows a pattern consistent with life expectancy; although China witnessed a great improvement in the 1960s, the improvement has been quite modest (if any) since the late 1970s. As Figure 3 shows, in the first two years of the 1960s, the death rate per 1,000 people declined suddenly from almost 26 to only 10. Then, except for 1964, the death rate fell continuously until the late 1970s. On the contrary, the early years of

the reform showed a slight increase in mortality that remained thereafter at around 6.5–7 until another increase in the late 2000s. The slight increase in most recent years is likely due to aging. To account for this effect, as well as the role of other covariates, we have run a panel regression (see *infra*).

China's reduction in mortality before reforms has stood out in a global comparison. Between the late 1960s and early 1990s, China's mortality was lower than all other world regions (excluding developing countries in East and Southeast Asia). Since the early 1990s, LAC and MENA countries have had lower mortality than China; however, this may be due to the younger age structure in these countries (since the early 1970s, the LAC's and, especially, MENA's population share aged 65 and above has been significantly lower than that of China). Similarly, China's high proportion of a young population in the 1960s and 1970s may elucidate its low mortality during those decades. Therefore, the already lowest mortality in the world and increasing aging can both explain stable mortality during the reform period. By contrast, Russia and less advanced transition countries (former Soviet Republics and Albania) showed a modest increase in mortality between the early 1960s and early 1990s and a sudden, huge increase since then, consistent with the hypothesis of the detrimental effect of transition on health.

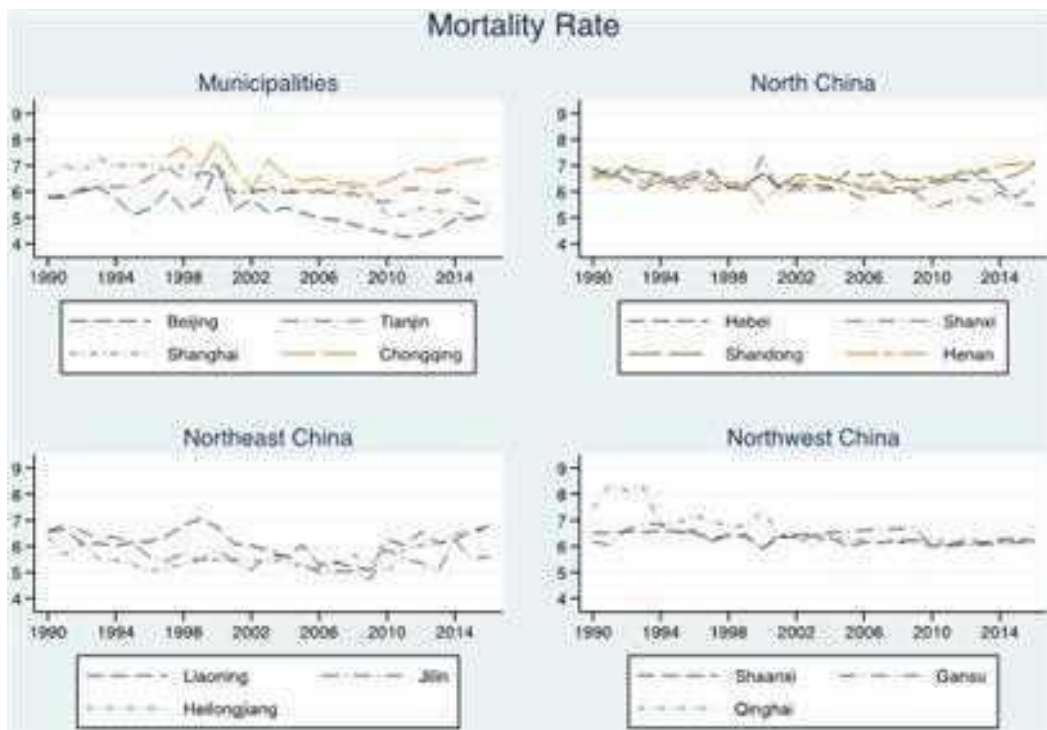


Source: Authors' own calculation based on WDI data.

Figure 3. Mortality: A global comparison

Figures 4 and 5 display the evolution of mortality in 31 provinces from 1990 to 2016, indicating strong cross-provincial variance in the results. The three provinces in Southwest China (Sichuan, Guizhou, and Yunnan), three provinces in Central China (Jiangxi, Hubei, and Hunan), and four autonomous regions (Inner Mongolia, Guangxi, Tibet, and Xinjiang) had the highest mortality in the 1990s. All autonomous regions have demonstrated significantly reduced mortality and the lowest mortality since the 2000s, whereas Southwest China, despite a reduction, still exhibits higher mortality than other regions. North China, Northwest China,

and Central China have each had less change in mortality than other regions. Surprisingly, Northeast China had very low mortality between the mid-1990s and late 2000s (except Liaoning in the late 1990s). This region is notorious for restructuring, inefficient SOEs, and great waves of layoffs, all of which are associated with high levels of stress. Guangdong, another province with one of the greatest degrees of restructuring, has also had lower mortality than most other provinces; indeed, it has had one of the lowest mortality rates amongst all provinces since the 2010s. Guangdong and Northeast China represent two polar examples of restructuring: in the former, restructuring has been associated with emerging opportunities and higher labour intensity (even sweatshops); in the latter, restructuring has been tied to decreasing opportunities and shrinking employment. According to Biggeri (2003), North China, Central China, Northwest China, and Southwest China appear less dynamic, with a lower degree of restructuring and marketisation; their mortality trends are heterogeneous (stagnant in North China, slight declines in Northwest and Central China, and a substantial decline in Southwest China).⁷ At any rate, the geographical pattern of mortality across provinces does not show a clear relationship between restructuring (and thus stress) and mortality.

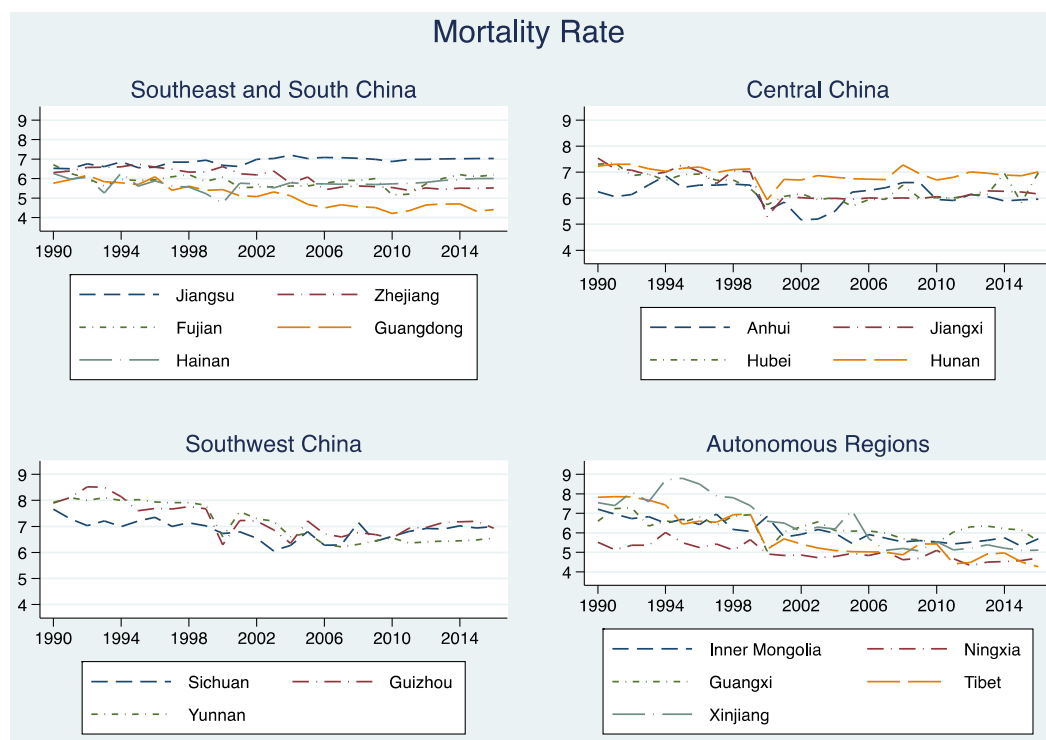


Source: China Health Statistical Yearbook (various years).

Figure 4. Mortality at the regional level.

⁷ Jiangsu and Zhejiang also had very little change, but these provinces already had a much lower share of state-owned enterprises in terms of total industrial output compared with other provinces in 1986. Mortality in autonomous regions may be unique, as these regions tend to have a severe natural environment (e.g., Tibet and part of Inner Mongolia and Xinjiang) and receive special policy.

Mortality may be attributable to various factors, amongst which stress due to socioeconomic restructuring can emerge as a critical phenomenon during transition phases (Cornia, 2016). For large transition countries (e.g., Russia and China), different regions may experience distinct levels of socioeconomic restructuring. Popov (2011) found that, in Russia, regions with higher real income growth and higher labour turnover, which indicate faster restructuring, have higher mortality. Moreover, regions with more economic opportunities (e.g., resources) and thus greater economic restructuring and stress, such as the North (Arkhangelsk and Komi), Siberia and Far East (Tyumen and Kamchatka), and Moscow, tend to have lower life expectancy than regions with fewer economic opportunities and thus less restructuring and (at least economically related) stress, such as North Caucasus (Ingush, Dagestan, and Kabardino-Balkar).⁸



Source: China Health Statistics Yearbook (various years).

Figure 5. Mortality at the regional level (Cont'd).

How can cross-regional variation in mortality in China be explained? Did the neoliberal 1990s negatively influence mortality? We have implemented a fixed-effects panel regression on province-level mortality with respect to socioeconomic factors for 31 provinces in the Chinese mainland from 1990 to 2016. Variables of interest include age structure (the share of population aged 65 and above), development level (GDP per capita; beds and doctors per 10,000 people), growth (GDP per capita growth rate), economic restructuring (unemployment; the ratio of employees in the urban public sector and formal private business

⁸ It should be noted that North Caucasus has a unique culture and lifestyle (e.g., stronger family ties) that may influence the local population's response to restructuring and change.

to total urban employment), neoliberal reform (time dummy for the 1990s), divorce rate (available from 1999), urban–rural disparity (the ratio of urban income to rural income), and year trend. In China, public-sector employees, including some (i.e., those with permanent employment) in state-owned and collective enterprises, receive exclusive state-provided welfare and security, especially healthcare. Those working for large private companies and multinational enterprises have higher and more stable salaries and are more likely to have better access to public services. Conversely, employees working in small private enterprises and those who are self-employed tend not to be covered by formal welfare and security and must cope with problems, risks, and uncertainties using their own (typically limited) resources. This population group is more likely to suffer from stress. The ratio of those who are ‘institutionally protected’ by the state or by ‘money’ to those who are ‘unprotected’ measures the share of people without (much) stress and with security. As pointed out by Graham, Zhou, and Zhang (2017), the lack of security during China’s reform has been a major source of life dissatisfaction. A reduction in this ratio may be driven by two factors: a reduction in the numerator and an increase in the denominator. The first case indicates the laying off of employees from the ‘protected’ sector, resulting in higher levels of stress. The second case may indicate the growth of the urban labour force in the private sector due to peasant immigration from rural areas or shrinking inactive and unemployed population segments. The second case therefore has a more ambiguous association with stress.

Table 3 presents the results of panel regressions. Because GDP per capita, doctors per 10,000 people, and beds per 10,000 people are highly correlated (i.e., correlation coefficients greater than 0.6), they are used separately in different specifications to control for the effect of development level. Urbanisation is often used as a control variable in the mortality literature, but it could not be controlled over our sample because its measurement is subject to inconsistency before and after 1998.⁹ The exclusion of urbanisation should not be a problem, as it is closely correlated with GDP per capita and beds and doctors per 10,000 people.

Aging significantly increases mortality. A one-standard-deviation increase in aging increases mortality by around 0.44‰ across the four specifications. GDP per capita is not statistically significant, while a one-standard-deviation increase in doctors and beds per 10,000 people increases mortality by 0.26‰ and 0.22‰. The finding that more sufficient healthcare facilities increase mortality seems counterintuitive, despite the actual effect being relatively small. However, Popov (2011) similarly found a slightly negative impact of beds per capita on life expectancy in Russia. He suggested that the collapse of the free healthcare system in the post-Soviet period caused the poor to be unable to afford health facilities and that only relatively rich people could take advantage of improved health facilities. Lu (2006) argued that the retreat of the state from healthcare, the shift from prevention to treatment, and the overall marketisation of healthcare have shifted healthcare services to a profit-making orientation and, in many cases, improvements in health facilities have exceeded the affordability of ordinary people. In this sense, our finding lends support to the argument that healthcare marketisation during the transition period is not friendly to the poorer population in China, as with the case of Russia.

⁹ Data on province-level urbanisation from 1990 to 2008 are from the China Compendium of Statistics 1949–2008; data for the period of 1998 to 2018 are from the China Statistical Yearbook (the pre-1999 Yearbook was not available to us). The two datasets have significant discrepancies.

GDP percapita growth slightly reduces mortality in the first two specifications (a one-standard-deviation increase reduces mortality by 0.038). Unemployment is not statistically significant. Notably, our data on unemployment are from the China Statistical Yearbook, and the reliability of China's official unemployment data has often been doubted.¹⁰ The public ratio significantly increases mortality in two out of three specifications. The impact of a one-standard-deviation increase is 0.3. This result seems to counter the hypothesis that higher shares of employees in 'institutionally protected' sectors lead to better overall health status. Time series analysis reveals that the public ratio exhibits significant downward trends for all 31 provinces, and mortality shows decreasing trends in all but three provinces since 1990 (results are available upon request). A declining public ratio implies growth in the urban private sector and transformation of the rural labour force into an urban labour force. This process is driven by economic growth and stimulates further economic growth, which leads to higher living standards and more resources and capacities related to healthcare (that was no longer freely available from pre-reform public institutions). Moreover, peasants' immigration from the countryside to urban areas, namely the transformation from peasants to (peasant) workers, has increased the material living standards of this population segment (through higher wages and a better living environment). Since the early 2000s, the state has played an increasing role in public healthcare, and social security and health insurance have been established and strengthened. These factors are expected to reduce the healthcare differential between the 'institutionally protected' sector and 'unprotected' sector. In this sense, economic development and positive institutional change (e.g., the proactive establishment and expansion of social security) may have compensated for or even reversed the otherwise 'painful' transition from 'institutionally protected' to 'unprotected' firms. Provinces with a more dynamic private sector generally succeed in collecting more resources to enforce inclusive social services, given the highly decentralised financial regime established by Beijing (Shue & Wong, 2007). These empirical findings suggest that such provinces tend to have lower mortality, thereby compensating for the adverse effects of privatisation.

Table 4 presents the results after including divorce rate, another indicator used in the transition literature to proxy the extent of social and individual stress. Divorce data were only available from 1999, reducing our sample size. Consistent with findings from other transition countries, divorce significantly increases mortality in all specifications, suggesting stress as an important contributor to mortality in China. Moreover, in this context (a country with Confucian traditions and strict control over citizens' personal lives during Mao's era), divorces can be a proxy for shifting social norms around relationships and marriage.

Overall population mortality may be ascribed to many factors, some of which are not directly related to health facilities or healthcare input; rather, maternal and early-childhood mortality directly reflects the sufficiency and quality of health facilities and personnel. Similar to life expectancy and overall mortality, China has tended to outperform other developing regions in maternal and early-childhood mortality. Figure 6 shows that, in the early 1990s, China's maternal mortality was already lower than in other developing regions – particularly compared to that of middle-income countries – and was close to the level of Russia and less advanced transition countries. Over the past three decades, maternal mortality in less advanced transition countries, including China, has continued to approach that of

¹⁰ See, for example, Athukorala et al. (2009). The highest unemployment rate in our database is only 7.4%; a clearer picture of unemployment can be provided by micro-level analysis (see *infra*).

traditional developed countries and advanced transition countries. No significant difference has emerged between the two groups since the early 2010s. China's reduction in maternal mortality is highly linear without significant differences across the three phases of reform.

Table 3. Panel regression for mortality across 31 provinces between 1990 and 2016

DepVar	(1)	(2)	(3)	(4)
Mortality	1990-2016	1990-2016	1990-2016	1990-2016
Ageing	0.138*** (0.0278)	0.172*** (0.0306)	0.166*** (0.0271)	0.147*** (0.0266)
GDP p.c.	0.0747 (0.242)	0.00858 (0.229)		
GDP p.c. Growth	-0.00263 (0.00211)	-0.00348* (0.00185)	-0.00193 (0.00152)	-0.00295* (0.00159)
Unemployment	-0.0269 (0.0373)		-0.0383 (0.0377)	-0.0129 (0.0445)
Time Trend	-0.0488 (0.0356)	-0.0158 (0.0375)	-0.0003*** (0.0107)	-0.0417*** (0.0136)
Neoliberal Period	0.352*** (0.0976)	0.370*** (0.106)	0.245** (0.109)	0.237** (0.109)
Urban-Rural Income	-0.128 (0.0823)	-0.0284 (0.112)	-0.0764 (0.0794)	0.00639 (0.100)
Public Ratio		0.0555** (0.00711)	0.00939* (0.00506)	0.00795 (0.00515)
Doctors per 10,000			0.0260*** (0.00785)	
Beds per 10,000				0.0140** (0.00577)
Constant	102.6 (69.05)	35.37 (73.49)	64.73*** (21.37)	87.42*** (27.05)
Observations	307	804	773	773
Adjusted R-squared	0.383	0.432	0.409	0.410
Number of Provinces	31	31	31	31

Robust standard errors in parentheses; *** $p < 0.01$, ** $p < 0.05$, * $p < 0.1$.



Source: Authors' own calculation based on WDI data.

Figure 6. Maternal mortality: A global comparison.

Other indicators that offer insight into the association between transition and health status are the top causes of death. What are the major causes of mortality in China? How have they changed over the past decades? Tables 5 and 6 list the top five reasons for death in China's urban and rural areas, which exhibit different rankings. Death by cause has remained highly stable in urban areas, but some significant changes have occurred in rural areas. Respiratory diseases ranked first on the list of death by cause until 2005 but fell to 4th place in 2010 and 2015. Malignant neoplasms, cerebrovascular diseases, and heart disease have emerged as the top three causes of death. Because the morbidity of respiratory diseases is closely related to healthcare and health facilities, its declining rank may indicate improving health conditions across China's rural areas. Conversely, the rise in malignant neoplasms, cerebrovascular diseases, and heart disease may imply that, like their urban counterparts, the rural population has increasingly suffered from stress and an unhealthy lifestyle, presumably as a socioeconomic effect of transition.

Table 4. Panel regression for mortality across 31 provinces between 1999 and 2016

DepVar	(1)	(2)	(3)	(4)
Mortality	1999–2016	1999–2016	1999–2016	1999–2016
Aging	0.0979*** (0.0240)	0.0877*** (0.0238)	0.121*** (0.0229)	0.117*** (0.0239)
GDP p.c.	0.257 (0.228)	0.375* (0.216)		
GDP p.c. Growth	-0.00522* (0.00274)	-0.00612** (0.00266)	-0.00193 (0.00158)	-0.00200 (0.00153)
Unemployment	-0.114* (0.0585)		-0.127** (0.0551)	-0.122** (0.0582)
Time Trend	-0.0921** (0.0344)	-0.0871*** (0.0301)	-0.0465*** (0.00875)	-0.0520*** (0.00899)
Divorce	0.0441*** (0.0139)	0.0458*** (0.0136)	0.0359** (0.0238)	0.0341** (0.0134)
Urban-Rural Income	-0.0161 (0.0968)	-0.0289 (0.0896)	-0.0101 (0.0931)	-0.0771 (0.0930)
Public Ratio		0.0110** (0.00526)	0.00710* (0.00379)	0.00748** (0.00364)
Doctors per 10,000			0.0121* (0.00603)	
Beds per 10,000				0.00907** (0.00442)
Constant	187.6*** (66.81)	175.6*** (58.31)	97.87*** (17.54)	108.7*** (17.90)
Observations	549	558	549	549
Adjusted R-squared	0.206	0.224	0.211	0.222
Number of Provinces	31	31	31	31

Robust standard errors in parentheses; *** $p < 0.01$, ** $p < 0.05$, * $p < 0.1$.

Table 5. Top 5 causes of death in urban areas

Disease	1990	1995	2000	2005	2010	2015
Malignant neoplasm	1	2	1	1	1	1
Cerebrovascular diseases	2	1	2	2	3	3
Heart disease	3	4	3	3	2	2
Respiratory disease	4	3	4	4	4	4
Injury and poisoning	5	5	5	5	5	5

Source: Authors' own calculation based on China Health Statistical Yearbook.

Table 6. Top 5 causes of death in rural areas

Disease	1990	1995	2000	2005	2010	2015
Respiratory disease	1	1	1	1	4	4
Malignant neoplasm	2	2	3	3	2	1
Cerebrovascular diseases	3	3	2	2	1	2
Heart disease	4	5	4	4	3	3
Injury and poisoning	5	4	5	5	5	5

Source: Authors' own calculation based on China Health Statistical Yearbook.

Mortality and Health Status amongst Chinese Individuals

Micro-level data provide another perspective on the evolution of mortality and health status in China. This type of analysis is less suited to delineating the structural transformation of society as a whole, but it can reveal how different individuals react to such changes over time. Several datasets are available to analyse the socioeconomic characteristics of Chinese households. Amongst these, we refer to data from the China Health and Nutrition Survey (CHNS); this dataset is provided by the Carolina Population Center at the University of North Carolina at Chapel Hill and the National Institute for Nutrition and Health at the Chinese Center for Disease Control and Prevention. The CHNS is widely appreciated in the literature owing to its focus on health, having collected panel data over a relatively long time: the first wave of information dates back to 1989 (before the neoliberal phase); the latest wave, the tenth, occurred in 2015. The CHNS sample is selected through a multistage random cluster process, resulting in a sample of about 30,000 individuals in twelve (out of 31) Chinese provinces in the eastern, central, and western regions of the country.

Besides data regarding objective and self-reported health status, CHNS questionnaires collect information about each sample's socioeconomic characteristics. Our analysis considers variables such as educational attainment, employment, and income to observe how the health status of different social groups has been affected by the Chinese transition. Whilst life expectancy can only be computed over an aggregated sample, we can focus at the individual level on age at death (see also Chapter 5). This variable can be computed only amongst the subsample of individuals who were alive during the initial waves of CHNS and died before 2015 (the year for which data are most recently available). This subsample includes 2,302 observations and shrinks to 2,255 when only adults are considered.¹¹ We computed pairwise correlations to investigate which socioeconomic characteristics contribute to higher (or lower) ages at death; see Table 7. Positive correlations indicate longer lifetimes and are therefore considered positive factors. Our regression analysis was less informative, as the sample size (already reduced due to excluding surviving individuals) was further reduced by sensitive questions that were not asked in every wave or for which missing values were

¹¹ The exclusion of non-adult individuals from the sample is necessary to allow for comparability across observations (variables such as smoking habits or employment conditions are distributed differently amongst non-adults) and to discard cases of infant mortality related to causes that were not massively affected by transition (Chapter 4).

frequently reported. However, the significance level of most correlations indicates that the results are robust, and their interpretations appear consistent with our expectations.

The variable showing a stronger negative correlation with age at death (i.e., the variable that reduces longevity most) is unemployment. Smoking and alcohol behaviours and belonging to an ethnic minority also significantly reduce the age at death.¹² Women have died later on average. Household income per capita and geographical residence also seem to affect longevity. Other significant positive correlations include belonging to coastal provinces (i.e., the area that has benefitted most from reforms as evidenced by higher economic growth and modernisation) or to urban areas and having an urban hukou.

Table 7. Correlation between individual characteristics and age at death

Negative Correlation		Positive Correlation	
Unemployed	-0.17***	Female	0.15***
Ever Smoked	-0.09***	Lives in Coast Area	0.11***
Ethnic Minority	-0.09***	Urban hukou	0.10***
Alcohol consumption	-0.04*	Lives in Urban Area	0.09***
		Income per capita	0.05**

Source: Authors' own calculation based on CHNS.

The hukou, or household registration, is a system of domestic passport introduced in China in the Maoist period. The hukou identifies each citizen's official residence area; more importantly, given the close association between official residence and the welfare system, the hukou identifies the administration responsible for providing healthcare, education, and other social security services. This institution gained relevance with market reform beginning in 1978 because the dismantling of the commune system and the growing importance of market mechanisms in the labour market compelled many people – especially rural peasants – to move from their hometowns to areas with more or better-paying jobs. Domestic migration driven by reform thus implied a separation between the official hukou and the actual places where individuals live and work. The government partially relaxed the hukou system thereafter, of which the 2014 reform is arguably the most notable example. However, domestic migrants' and locally born workers' access to welfare services still constitutes a major form of discrimination (Pi & Zhang, 2016; Zhang, Wang, & Lu, 2019).

Returning to the longevity analysis, the hukou system remains a crucial element, as the advantages bestowed upon individuals with an urban hukou even exceed those granted to individuals effectively residing in urban areas. Therefore, rural people's migration to urban areas appears insufficient in closing the gap between urban and rural life expectancy without the government further addressing the complete integration of domestic migrants into recipient areas.

The aforementioned factors are also intercorrelated. For example, drinking and smoking are strongly related and are each significantly correlated with unemployment status. Even so, smoking and drinking do not overlap geographically: smoking is more widespread in poorer regions (rural and inner areas), whereas alcohol consumption demonstrates the opposite pattern.

¹² These are binary variables, referring respectively to reporting a frequency of alcohol consumption equal to or greater than three times per week and to ever smoking a cigarette or pipe.

Another way to explore health status through micro-level data is by investigating the determinants of health problems and unhealthy behaviours (e.g., smoking and drinking, whose longevity-related effects were just discussed). To perform such an analysis, we can broaden the sample to all surveyed individuals, obtaining a sample of 99,106 adults (the final sample was slightly smaller due to missing information). We consider the following five indicators of health problems, including objective and subjective measures: undernutrition, obesity, high blood pressure (HBP), dissatisfaction, and sickness. These indicators are all binary variables, where 1 corresponds to the presence of a given health problem and 0 otherwise; this similarity favours the comparability of regression analysis across different specifications of health problems and unhealthy behaviours. Undernutrition, obesity, and HBP are identified by the standard thresholds (respectively a body mass index below 18.5; body mass index above 30; and systolic pressure above 140 and diastolic pressure above 90). Dissatisfaction corresponds to individuals who answered ‘poor’ in response to the question “Right now, how would you describe your health compared to that of other people your age?”; this variable was recorded in only three survey waves (1991, 1993, and 1997), leading to a much smaller sample size for this analysis. Sickness corresponds to individuals who reported having been sick or injured within four weeks before the interview.

Table 8 reports the coefficients of probit regressions that explain these eight binary variables for health status with socioeconomic characteristics: age; the number of years under study; belonging to an ethnic minority (0 = Han majority, 1 = any other ethnic group); gender; living in an urban area and possessing an urban hukou (the interaction between living in an urban area and having a rural hukou is named ‘irregular’ and captures the effect of domestic migrants living in an urban area without being able to fully enjoy the rights of urban-born citizens); employment status; household income per capita; and living in a coastal province. Finally, trend coefficients are computed based on the observation year.

These regressions provide new insight into the channels through which Chinese individuals’ health conditions are (unequally) affected. It is important to note that all variables of interest, whether self-reported or based on objective indicators, are positively correlated with health problems: negative coefficients indicate a healthy status and vice versa.

As expected, age represents one factor exerting the most significant negative impact on health. Further analyses, which are not reported due to space limitations, reveal age to exhibit a non-linear inverted U-shaped trend. Another element correlated with general worsening of health status is unemployment. The negative effect of unemployment, which was not fully captured with macro-level data, emerges clearly at the micro level, affecting self-reported and objective indicators.

Another factor whose coefficient maintains its sign irrespective of the health specification is education, which remains positive for all health conditions. Similarly, income is generally positive, the most notable exception being a higher risk of becoming obese. Ethnicity, gender, and geographical residence (effective and official) have contrasting effects; for example, more advanced areas (i.e., coastal and urban) report lower cases of undernutrition, but obesity is more common, and people report more frequent sickness (this pattern may also be attributable to greater awareness of such problems).

The exogenous trend characterising these indicators is also mixed. While negative behaviours generally decline, the number of individuals experiencing HBP or reporting cases of sickness increases; the shrinking of undernutrition cases is counterbalanced by the emergence of an obesity problem.

Table 8. Health-related probit regression

	(1)	(2)	(3)	(4)	(5)	(6)	(7)
	under nutrition	obesity	HBP	unattended	sick	alcohol	smoke
alcohol	-0.132*** [-6.16]	0.0506 [1.07]	0.149*** [8.11]	-0.211*** [-4.42]			
smoke	0.0551** [3.2]	-0.117*** [-4.89]	-0.0104 [-1.07]	-0.129** [-3.21]	0.0302* [1.99]		
age	0.000386 -0.79	0.00337*** [-5.29]	0.0258*** [-50.32]	0.0211*** [-10.91]	0.0179*** [-42.5]	0.0112*** [-25.59]	0.00464*** [-11.77]
education	-0.0114*** [-5.47]	-0.00467 [-1.79]	-0.00614** [-3.16]	-0.0164*** [-3.58]	-0.00980*** [-5.20]	-0.00459* [-2.45]	-0.0256*** [-14.77]
minority	0.185*** [9.83]	-0.0977*** [-3.45]	-0.111*** [-5.32]	-0.0587 [-1.77]	-0.137*** [-7.45]	0.0681*** [4.93]	0.103*** [5.42]
female	0.0233 -1.31	0.0713** [3.25]	-0.125*** [-7.77]	-0.145*** [-3.62]	0.0968*** [6.59]	-1.445*** [-93.06]	-2.155*** [-159.57]
urban	-0.0293 [-1.02]	0.104*** [5.14]	-0.0345* [-2.22]	0.0434 [1.09]	0.310*** [15.76]	0.037 [1.92]	-0.0295 [-1.01]
irregular	0.0728*** [4.04]	-0.217*** [-9.58]	-0.0916** [-2.97]	0.0213 [0.52]	-0.0724*** [-4.65]	0.0924*** [5.74]	0.0510*** [3.51]
unemployed	0.103*** [5.52]	0.0748*** [3.56]	0.0742*** [4.2]	0.143** [2.99]	-0.0153 [-0.98]	-0.0921*** [-4.39]	0.0914*** [5.2]
income	-3.13E-06*** [-5.18]	7.71E-07* [2.1]	-2.83E-07 [-0.67]	-0.0000296*** [-4.94]	-1.88E-06*** [-4.99]	7.55E-07* [2.25]	-4.8E-07 [-1.46]
coast	0.0276* [2.07]	0.0814*** [4.88]	0.00962 [0.74]	-0.0739* [-2.41]	0.0057*** [7.42]	0.00054 [0.72]	-0.0801*** [-7.38]
trend	-0.0135*** [-12.30]	0.0300*** [22.21]	0.0108*** [10.81]	-0.00497 [-0.74]	0.0119*** [13.68]	-0.0149*** [-16.46]	-0.0102*** [-12.32]
_cons	25.49*** [12.78]	-82.10*** [-29.07]	-24.25*** [-12.16]	7.52 [0.56]	-25.81*** [-14.92]	-28.64*** [-15.94]	20.73*** [12.6]
Observations	88521	88531	88242	26043	30017	09907	90490

Source: Authors' own calculation based on CHNS.

Another variable in the CHNS is ownership of medical insurance. Although this information reflects the healthcare system rather than health outcomes, it is interesting to consider how the variable correlates with socioeconomic characteristics. An econometric regression (results available upon request) shows that, *ceteris paribus*, people with insurance are significantly richer, more educated, older, and live in urban and coastal areas. By contrast, migrants without the urban hukou and ethnic minorities possess significantly less insurance coverage. The trend in this healthcare variable is, as expected, significantly positive; the greatest improvements in health insurance diffusion occurred in the new millennium, consistent with the 'Golden Age' model. In other words, analysis of health insurance indicates that the most vulnerable social groups are also those who generally encounter discrimination in health insurance access, underscoring the importance of the inequality issue from a healthcare perspective (even though the government's recent efforts to rebalance the transition have proven effective).

WHAT MAKES CHINA UNIQUE?

Although China's health performance during the transition (especially in the neoliberal phase) has been weaker than before, a comparison with other transition economies reveals clear differences. In contrast to countries that followed the Washington Consensus, Chinese life expectancy has grown during the transition period, and economic restructuring has contributed to lower mortality. This anomalous case of transition presents interesting questions. Domestically, how could China maintain such stable growth in life expectancy – even in the neoliberal period – despite a rather regressive healthcare policy regime? Globally, why has China maintained stable improvements in life expectancy in the absence of a downturn or stagnation (despite slower growth than in the 1960s) compared with other transition countries, especially the former Soviet Republics?

China's stronger performance in life expectancy can likely be ascribed to a gradualist reform strategy (in contrast to 'shock therapy') and strong institutions (i.e., the state's strong control over its economy and society under the Communist Party regime, despite marketisation). A gradualist approach towards marketisation, to some extent, saves the economy from great unemployment, bankruptcy, and loss of labour rights after privatisation. Moreover, when these detrimental phenomena occur, they are arguably less unexpected and unattended, limiting their effects in terms of stress-related mortality. Strong institutions control a range of social problems related to socioeconomic liberalisation from the previous highly planned and regulated regime, particularly violent crime. Moreover, these institutions can be (perceived as) elements that prevent further deterioration of quality of life (further analysis on the roles of institutions in addressing stress-related mortality are provided in Chapter 2). As a result, under a relatively stable, less uncertain, and less volatile transition, China has managed to maintain an improvement in life expectancy.

China's transition, attacked by supporters of the Washington Consensus for being too smooth and incomplete, appears to be a rather effective strategy for preventing individual and social stress. By contrast, shock therapy and a sudden transition to (de jure) democracy led to uncertainty and volatility in other transition countries that lack a strong democratic tradition and good institutions, especially the former Soviet Republics. A direct consequence is strong stress amongst the population, especially fragile segments, and an accompanying deterioration in life expectancy.

Moreover, China's case may not be explained by the gradualist approach and strong institutions alone; the unique nature of Chinese capitalism underlying the nation's strong economic growth is another possible contributor to its better health performance. A major difference between China and other transition countries is that, as a late industrialiser, China's priority during the economic reform is to develop its economy through industrialisation. Conversely, other transition countries in Central and Eastern Europe had already achieved industrialisation by the 1940s, meaning that they were already developed countries in absolute terms. For these countries, transition is more driven by the goal of transforming a centrally planned political and economic system into liberal capitalism, whereas China's transition has a clear dual goal of not only reforming the political and economic system but also achieving economic growth. This latter aspect has led the Chinese state to become a developmental state, which corresponds to the cases of South Korea and Taiwan during their

economic catch-up.¹³ The Chinese state as a developmental state has been a core driver of strong growth since 1979, which thus enhanced, along with strong institutions, the stable improvement in life expectancy and mortality reduction.

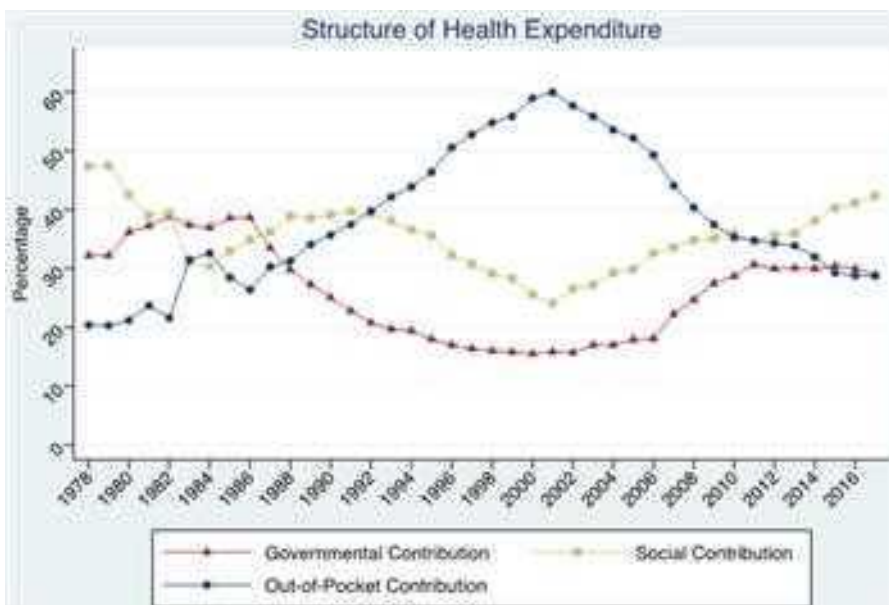
China's Competition-Driven Local Developmental State

In this section, we introduce the 'Varieties of Capitalism' (VoC)/'Comparative Capitalism' approach from comparative political economy to provide new insight into the influence of China's political economy on health status in addition to its gradualist strategy and strong institutions. China's reform since 1978 represents an inherent transition from a typical centrally planned economy to a unique type of capitalism. The three distinct phases of reform reflect a process of exploration and adjustment. In the 1980s, the state cautiously launched marketisation, and economic growth emerged as the top goal. The 1990s witnessed radical marketisation in the spirit of neoliberal economic ideology and the permeation of market principles into most socioeconomic spheres. Economic growth then became the government's top priority to the neglect of social development and the environment. Since the 2000s, although economic growth has remained a priority amongst the central and local governments, distribution, welfare, and sustainability have been explicitly placed on the policy and development agenda, especially at the central level. The China-specific competition-driven local developmental state is a variant of both state-permeated capitalism and the developmental state formed during these three phases of reform. China's structure of multilevel governance and the relatively great autonomy of the local government are also crucial to understanding the impact of political economy on healthcare from a local perspective.

The VoC approach is dominant in research on the institutional arrangement of contemporary capitalism and China's capitalism (Ahrens & Jünemann, 2010; Andreosso-O'Callaghan & Gottwald, 2014; Witt, 2010). In their landmark book *Varieties of Capitalism: The Institutional Foundations of Comparative Advantage*, Hall and Soskice (2001) conceptualised the institutional arrangement of the capitalist system in developed countries and identified two distinct types of market economies, namely liberal market economies, represented by the United States and the United Kingdom, and coordinated market economies, such as Germany and Japan. These models are distinct in their firm coordination, corporate governance, labour relations, role of the financial sector, and vocational training. In recent years, as a result of the development of the market economy outside traditional core countries (e.g., Western Europe, North America, Oceania, and East Asia apart from China), the original VoC classification has been extended to accommodate new types of capitalist systems: dependent market economies in Central and Eastern Europe (Nölke & Vliegenthart, 2009); and state-led/influenced market economies/SMEs in emerging countries (Schmidt, 2009).

¹³ We must point out that a gradualist strategy and developmental state are non-overlapping elements. China's developmental state originates from the experience of Asian Tigers' state-led capitalism, industrial strategy, and industrialisation; this is unrelated to a gradualist transition. However, both share a strong role of the state in the economy, which counters neoliberal ideology. The developmental state opposes 'shock therapy' in terms of the role of the state but not directly in terms of the pace of reform.

The ‘influencing’ state is the feature that distinguishes SMEs from other regimes (Hall & Soskice, 2001; Schmidt, 2007, 2009; Streeck, 1997). China is undoubtedly classified as an SME. Based on the observation that the state always assumes a pro-business and pro-development role in the national economy in large emerging countries, ten Brink (2013) dubbed the capitalist system in large emerging countries ‘state-permeated market economies.’ The replacement of ‘state-led/influenced’ with ‘state-permeated’ has occurred because, in large emerging countries, the state does not have an ‘all-powerful, centralised, steering’ role or status as conceptualised in the classical developmental state theory inspired by South Korea’s experience (Nölke, ten Brink, Claar, & May, 2015). Instead, the role of the state is realised through state-business coalitions at the central and local levels, which form a fragmented but permeating state presence; that is, the government at each administrative level serves as a local developmental state responsible for local development. Fragmentation and permeation lead to a model of a competition-driven local developmental state. Insiders in state-business coalitions (e.g., a coalition between the provincial government and local businesses) share common interests and goals. Typically, a developmentally oriented government needs to stimulate local economic growth and businesses need to increase profits, meaning that their interests overlap and their coalition is based on reciprocal loyalty and trust (Nölke et al., 2015). Coalitions compete with each other (e.g., between provinces or prefectures) for economic opportunities such as investments. Such coalitions started to develop under rapid marketisation in the 1990s, during which the previous strategy of ‘wearing a red hat’ (de jure state-owned but de facto private enterprises) shifted to formal privatisation, but the state-business coalition was strengthened (ten Brink, 2011).



Source: China Health Statistical yearbook (various years).

Figure 7. Structure of health expenditure.

In many cases, local state-business coalitions compete for economic opportunities at the expense of labour welfare and sustainability. This was particularly the case in the 1990s,

which witnessed a kind of ‘growth fetishism.’ In conjunction with a reserve of cheap labour, this competition has preserved China’s low-wage regime through the intentional absence of intervention in business misconduct, selective implementation of labour laws, decentralisation of regulation of employment at the firm level, and a lack of collective bargaining (ten Brink, 2016). In addition to relatively high labour skills and productivity, the combination of ‘liberal’ industrial relations and low labour costs has served to attract multinational enterprises. The central government’s political approach and competition between local state-business coalitions has placed further downward pressure on labour welfare.

Since the 2000s, China has gradually diverged from the neoliberal doctrine, approaching the ‘Golden Age’ model. The central government has proposed an economic rebalancing, with a shift from investment- and export-led growth to consumption- and service-led growth. This rebalancing implies increasing demand and income, especially amongst poorer segments of the population. Figure 7 displays the three pillars of China’s total health expenditure since 1978. Since the early 1990s, social and governmental health expenditure has followed similar trends, reaching a low point around 2000 and then rebounding during the ‘Golden Age’ period.

Despite its positive role in stimulating economic growth and capital accumulation in the 1990s and 2000s, China’s competition-driven local developmental state, which is embedded in a multilevel governance structure, has weakened the superior government’s control over the inferior government and hindered the central government’s policy and strategy implementation. Beijing’s relatively weak influence has thus hampered the promotion of rebalancing. In this sense, as pointed out by ten Brink (2013), China has produced its own structural and institutional obstacles to economic rebalancing and social upgrading.

Competition-Driven Local Developmental State and Health Status

The implications of China’s competition-driven local developmental state for health status may be complex. Competition between local state-business coalitions suppresses a return to and welfare of labour and increases labour intensity, leading to relatively unfavourable working and living conditions and greater stress. Meanwhile, growth fetishism, embedded in the ‘mindset’ of governments, squeezes healthcare’s position in the policy agenda, reflected in declining governmental contributions to health expenditure. The relatively loose central–local relation also tempers the promotion of rebalancing towards a more pro-poor/labour growth pattern, weakening the positive effect of the transition from neoliberal reform to the ‘Golden Age’ model.

The competition-driven local developmental state may provide additional insight into the retreat of the state, at the central and local levels, from healthcare. As shown in Section 3, in all provinces, governmental contributions to healthcare bottomed out in the late 1990s and early 2000s. The root of this retreat lies in marketisation reform and the state’s shifting role in the economy and politics. If the transition leads to a healthcare recession, which is an unavoidable outcome of marketisation, then competition for economic opportunities, a China-specific factor, may strengthen the negative outcome of the retreat.

At least until the recent decade, the central and local governments had each stimulated economic growth and industrialisation at the expense of population welfare. At the

international level, China preserved its low-wage regime to compete with other low-cost countries for investment. Domestically, as suggested above, local state-business coalitions compete with each other to attract investments in their own territories. The state benefits from such a labour regime through economic growth and industrial development, and businesses benefit from this regime through profit generation. In theory, the state's retreat from healthcare must be compensated by the development of a high-welfare labour regime as an institutional complementarity; however, the competition-led low-wage regime also leads to a vicious complementarity.

Has the central government's relatively loose control over local government dampened the shift in the growth model from neoliberal reform to a 'Golden Age' model or impeded socioeconomic rebalancing? This supposition may not be directly verifiable, but the increasing share of health expenditure to total governmental expenditure in all provinces since the mid-2000s suggests that the local state has positively altered its role in healthcare. This change is consistent with the strategy of socioeconomic rebalancing set by the central government. However, another possibility is that reversal of the previous growth model is a natural reaction to economic growth and capital accumulation. The space and need for further growth and accumulation are likely to follow a declining margin or an inverse U-shaped pattern. After a certain point, a growth model based on low-wage regime will inhibit further growth. When growth and accumulation have reached a certain level, the government will naturally move to a more pro-poor and high-welfare policy regime, either due to the need to shift its growth pattern or in response to public pressure. As suggested in our discussion of health status outcomes, substantial expansion of the resources and technology available for healthcare may compensate for the side effect of the transition and a competition-driven local developmental state. If this pattern holds, then the competition-driven local developmental state has produced its own stimulator of change through its growth-enhancing effect. In this sense, China is a special case compared with other transition countries, at least Russia and those less advanced nations that experience socioeconomic turbulence. Essentially, the key to compensating for the dark side of transition is robust economic growth backed by strong institutions and a developmental state.

CONCLUSION

The transition from a centrally planned economy to a market economy that took place in the 1980s and 1990s across the land between the Oder and the Bering Strait fundamentally changed the politics, economy, and society of those (former) socialist countries.¹⁴ This transition led to severe socioeconomic turbulence and psychological stress in Russia and other former Soviet Republics. The population's health status experienced a great recession in the 1990s and did not return to its pre-transition level until the early 2000s. On the contrary, China has followed a gradualist approach, driven by strong institutions that refused ideological implementation of the Washington Consensus agenda. China has effectively avoided major socioeconomic turbulence and experienced robust and rapid economic growth over the past four decades of reforms.

¹⁴ The transition of the former German Democratic Republic is unique; thus, we use the Oder (the German–Polish border) as the west boundary of the transition.

In this chapter, we have considered China's health achievements during three distinct phases of reform, namely the exploratory transition to a market economy (the 1980s), neoliberal reform (the 1990s), and the adoption of a 'Golden Age' model (since the 2000s), to compare health outcomes amongst provinces, households, and other countries. The growth rate in life expectancy has declined with respect to pre-reform achievements realised in the 1960s. Moreover, health outcomes have been affected by unemployment, inequalities in the distribution of income and education, unhealthy behaviours, and a growing divorce rate. Amongst the major causes of death, the relative importance of stress-related diseases has increased as well. All these factors are consistent with the literature regarding stress and mortality in transition economies. Yet China's achievements in life expectancy have not underperformed in comparison with most other countries, especially transition economies who experienced a 'shock therapy' transition. Indeed, China's improvement in health status has remained quite stable since 1979 despite a regressive healthcare regime and economic restructuring between the late 1980s and early 2000s (i.e., the neoliberal phase, characterised by a higher mortality rate): China did not experience any major downturns even in this phase.

Different from other cases of transition, Chinese provinces with a more active private sector recorded better health outcomes. This pattern may be due to the growth-enhancing effect of China's model of a developmental state. Similarly, inequality between rural and urban areas characterises health outcomes under the hukou system (i.e., China's internal passport) that discriminates against domestic migrants in access to healthcare and in some – but not all – health-related indicators.

In other words, China's transition has led to heterogeneous outcomes, but the country is not underperforming and appears healthier than other transition economies on average. The latest phase of the reform, since the turn of the century, has featured more resources and a greater willingness to invest in the welfare sector, thereby rebalancing economic development towards consumption-led growth. The 2003 health reform was a major policy in this direction.

To conclude, we suggest that robust economic growth and the underlying developmental state, along with gradualist reform and strong institutions, have been key in avoiding a health status recession during the reform: a pragmatic approach to transition can thus elicit more favourable outcomes in terms of human lives with respect to the uncritical adoption of 'shock therapy.'

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Chapter 291

POLICY REFORM FROM THE EARLY 1990S AND CHANGES IN HEALTH STATUS IN INDIA: 1991–2016

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INTRODUCTION

This chapter is concerned with examining the changes in health status that occurred during the years following major economic reforms in India and exploring to what extent and how they were related to the policy changes instituted under the new regime.

In an important paper, Cornia (2018, p.1), argued that there have been “episodes of political, economic and social transformation that were expected to generate greater political freedom, economic prosperity and individual wellbeing, but that instead generated substantial increases in death rates, particularly among low income groups.” Cornia identified various mechanisms for such outcomes, including “the unexpected effects of rural-urban migration combined with an inelastic supply of public infrastructure; political reforms carried out in the absence of adequate administrative, legal and redistributive institutions; the introduction of economic reforms under conditions of incomplete or distorted markets and institutions; and the unchecked contact between socio-economic groups characterized by different disease profiles.” In this chapter, we focus specifically on one of these mechanisms, the introduction of economic reforms, to consider the impact on changing health status in India over the past three decades. We ask whether the various reforms introduced in India since the early 1990s had any impact on changing the environment for achieving better health outcomes and explore the extent to which they can be linked to the relatively poor progress in the health status of the bulk of the population.

We begin with a brief description of the main economic reforms in India since 1991, followed in the next section by an examination of the trends in the important indicators of health since 1991. The fourth section considers the differential behaviour of health indicators

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in some Indian states, given that there is wide interstate disparity in both levels and trends of health indicators, and a significant part of both health policy and public health expenditure is the responsibility of state governments within India's federal system. The fifth section takes up one particular issue in which public policy appears to be directly related to mortality: agrarian distress and farmers' suicides.

ECONOMIC REFORMS IN INDIA FROM THE EARLY 1990S

While the neoliberal economic reforms in India were accelerated by the balance-of-payment crisis that erupted in mid-1991, the basic thrust of the policy reforms was broadly in alignment with the Washington Consensus. The underlying premise was that the state's economic presence should be substantially reduced, not only with the aim of curbing excessive fiscal deficits, but also to open up new fields to the private sector and do away with the bureaucratisation, overstaffing, and soft budget constraints typical of state enterprise. Imports were to be liberalised, not only to provide the domestic private sector with access to the capital goods, intermediates, and raw materials needed to restructure and become internationally competitive, but also to expose it to the cutting edge of international competition. Domestic deregulation was seen as providing the flexibility required for restructuring and allowing market forces to play their role in disciplining economic activity. Greater freedom was to be provided to international capital, both productive and financial, so as to increase access to foreign finance as well as to exploit the benefits of the improved technology, modern management practices, and the links to international markets that transnational firms offer. To ensure that private initiatives would more than adequately replace the state as the locomotive of growth, tax policies were sought to be rationalised and the tax regime rendered less "burdensome," so that the taxation regime would not act as a disincentive to saving and investing. These parameters determined the large number of policy shifts that, during the 1990s, helped put in place a qualitatively new policy regime in India and gave the liberalisation of that decade its distinctive character.

Reduction of the fiscal deficit was central to both the stabilisation and structural adjustment components of the neoliberal reform package. From the argument that the fiscal deficit of the government should be reduced from the rather high levels in 1991, this led to the enactment of the Fiscal Responsibility and Budget Management Act, 2003 (FRBMA), which sought to bring down the public deficit down to 3% of gross domestic product (GDP) over a specified period. In fact, the goals set by that act have never been achieved. Even the excess deficits reflect various forms of creative accounting, such as not including items that were declared "extra-budgetary," forcing public-sector enterprises to take on debts because of non-payment of dues by the government and forcing them to buy each other's shares to declare greater revenues from "privatisation." These dubious accounting practices have been carried out simply to disguise the actual fiscal deficit, to appear to at least attempt to comply with the act. Nevertheless, despite these sleights-of-hand, the FRBMA has led to certain self-imposed constraints on state fiscal policy. The first is the pressure to reduce expenditures other than those on interest payments, especially the expenditures of the government on subsidies and administration, both of which are considered excessive and reflective of inefficiency. The major item of expenditure that has been targeted to be pruned is the outlay on subsidies, but

success of that endeavour has been mixed. In fact, other expenditures, such as capital expenditure, were cut back even more drastically.

The principal aims of the structural adjustment policies adopted as a part of the reform process were (a) to do away with or substantially reduce controls on capacity creation, production, and prices, and to let market forces influence the investment and operational decisions of domestic and foreign economic agents within the domestic tariff area; (b) to allow international competition and therefore international relative prices to influence the decisions of these agents; (c) to reduce the presence of state agencies in production and trade, except in areas where market failure necessitates state entry; and (d) to liberalise the financial sector by reducing controls on the banking system, allowing for the proliferation of new financial institutions and instruments and permitting foreign entry into the financial sector. As noted earlier, these were all based on the notion that greater freedom given to private agents and market functioning would ensure more efficient and more dynamic outcomes.

For industry, this meant that interventionist barriers to entry of domestic and foreign investors into a number of industries were substantially diluted or eliminated, resulting in what has been proclaimed as a much more competitive environment in the industrial sector. It was hoped that this more competitive environment would in itself induce higher rates and greater efficiency of investment and thereby lead to accelerated industrial growth in both output and employment. An implicit assumption was that the beneficial effects of this would far outweigh any negative impetus of reduced public investment. However, after an initial spurt led by an import-based consumer goods boom, growth rates in the industrial sector slumped once again, and the manufacturing industry did not grow in shares of national income or employment. Liberalisation per se was not enough to ensure high rates of growth of investment and productive activity. Since the middle of the current decade, investment in manufacturing stalled and then declined, reflecting inadequate demand within the domestic economy and declining export demand.

The major policy shift contributing to heightened competition in the domestic market was the liberalisation of the import trade. A distinguishing feature of the economic reforms of the 1990s was the effort to dilute import controls by rapidly reducing the number of tariff items subject to quantitative restrictions, licensing, and other forms of discretionary controls on imports. By now, most of these have since been abolished except in a very few industries. In addition, there were continuous cuts in the tariff rates on a wide range of commodities. By 2001, apart from a very few items, the only form of protection provided to the domestic productive sectors was that offered by tariffs, which were also simultaneously being reduced. The peak tariff rate fell from more than 300% at the start of the 1990s to less than 40% by 2001 and then to around 20% by 2010. By 2017, average applied tariffs were only around 7% (WTO, 2018).

Obviously, given the largely “closed” structure of the Indian economy over much of the post-Independence period, this had very significant effects on patterns of production and viability of different types of economic enterprise. The government’s aim was to restructure production towards areas of international “comparative advantage” (defined in static rather than dynamic terms). These areas were also seen as inherently more labour-intensive, which led to the further prediction that, after an initial brief period of net job loss, such a strategy of trade liberalisation would actually create more employment over time and in more sustainable ways. There are, of course, problems with such an argument. The first is the implicit assumption that international markets in most traded goods are actually free and competitive

and do not reflect the very extensive implicit and explicit subsidies provided by states across the world on various forms of production or the market imperfections created by concentration and centralisation. This is obviously not the case, and therefore the resulting patterns of trade were quite different from those anticipated based on such an assumption. The second false premise is that capital and labour can move (with relatively little cost) from one activity to another and enable structural transformation through trade. But the most significant assumption of all is the implicit assumption of full employment, which has obviously not been met, as well as other crucial assumptions relating to the nature of technology and economic organisation. Recognising the existence of economies of scale and learning effects allows for the possibility of dynamic comparative advantage that require quite different policy responses. Since the basic assumptions underlying trade reform were not valid in the Indian context during this period, it is not surprising that the actual effects of such liberalisation were quite different from those anticipated. The trade strategy has not entailed a major positive shift in the structure and growth of production or exports. Instead, most Indian producers have experienced an erosion of competitive position (in both export and import markets), even as their costs have continued to rise in important areas such as infrastructure and finance.

This trade strategy had a direct impact on agriculture, which grew even more intense over the decades. While the economic reforms did not include any specific package specifically designed for agriculture, the presumption was that freeing agricultural markets and liberalising external trade in agricultural commodities would provide price incentives leading to enhanced investment and output in that sector, while broader trade liberalisation would shift inter-sectoral terms of trade in favour of agriculture. However, there were other changes in patterns of government spending and financial measures that also necessarily affected the conditions of cultivation, often in ways very different from those that were anticipated by the architects of the reform process.

Thus, the post-reform strategy involved the following measures that specifically affected the rural areas: declines in central government revenue expenditure on rural development, cuts in particular subsidies such as on fertiliser in real terms, and an overall decline in per capita government expenditure on rural areas. There were also very substantial declines in public infrastructure and energy investments in rural areas. These were especially marked in irrigation and transport, both of which matter directly and indirectly for agricultural growth and productivity through their linkage effects. The public distribution system for food experienced reduced spread and rising prices, which had a significant effect on household food consumption in some areas of the country and was sought to be reversed through the National Food Security Act 2014. Financial liberalisation measures, including reducing priority-sector lending by banks, effectively reduced the availability of rural credit and thus made farm investment more expensive and more difficult, especially for smaller farmers. And there was significant liberalisation of external trade, first through lifting restrictions on exports of agricultural goods, and then by shifting from quantitative restrictions to tariffs on imports of agricultural commodities. A range of primary imports were removed from state control and thrown open to private agents. Import tariffs were substantially lowered over the decade. Exports of important cultivated items, including wheat and rice, were freed from controls, and subsequent measures were directed towards promoting the exports of raw and processed agricultural goods. Although the proponents of such policies argued that they would lead to an acceleration of output growth in agriculture by increasing market-based

incentives for agricultural investment and output, such an acceleration did not occur. In fact, agricultural growth decelerated compared to the previous decade, and there have been declines in per capita food-grain output and reduced (and more recently negative) rates of agricultural employment generation, in a context of inadequate expansion of non-agricultural income opportunities. The implications of this, specifically related to the agrarian crisis and farmers' suicides, are considered in the fourth section.

Many would argue that financial-sector reform and the associated dependence upon internationally mobile finance capital has been qualitatively the most significant aspect of the reforms. This is because such moves then make the other features of reform inevitable, in that no other measures would be seen as viable since they would be presumed to fail to retain investor confidence. In India such liberalisation touched on diverse aspects of the financial sector's functioning. In the banking sector, which dominates India's financial system, the reform involved measures aimed at increasing the credit-creating capacity of banks through reductions in the statutory liquidity and cash reserve ratio, while offering them greater leeway in using the resulting liquidity by drastically pruning priority sector lending targets. This was combined with greater flexibility in determining the structure of interest rates on both deposits and loans.

In addition, there were structural changes in the banking sector. While the existing public sector banks were permitted to sell equity to the private sector, private investors were allowed to enter the banking area. Foreign banks were given greater access to the domestic market, both as subsidiaries and branches, subject to the maintenance of a minimum assigned capital and being subject to the same rule as domestic banks. Finally, a degree of 'broad-banding' of financial services was permitted, with development finance institutions being allowed to set up mutual funds and commercial banks, and banks themselves permitted to diversify their activity into a host of related areas. The public-development banks were turned into commercial banks, thereby depriving industry of a critical source of patient finance that is willing to invest for the long term (Mazzucato and Penna, 2016). Banks were also given greater freedom in determining their asset portfolios. They were permitted to cross the firewall that separated the banking sector from the stock market and invest in equities, make advances against equity provided as collateral, and offer guarantees to the broker community.

The reforms in the banking sector were accompanied by measures aimed at liberalising financial markets. Companies could freely seek finance through the capital market, subject to the guidelines and regulations specified by the newly created Securities and Exchange Board of India (SEBI). Selected Indian companies were allowed to access international capital markets through Euro-equity shares. A range of nonbank financial companies, including private mutual funds, were allowed to operate. Investment norms for non-resident Indians (NRIs) were liberalised, and portfolio finance companies in the form of foreign institutional investors (FIIs) were allowed to register and invest in India's stock markets, subject to some ceilings that were then continuously relaxed. In addition, the government did away with the higher rate of capital gains taxation that applied to foreign and non-resident India investment in the stock market that departed in a short period of time.

In terms of GDP growth, this strategy was clearly associated with more rapid expansion, as is evident from Table 1. This indicates that the acceleration of the rate of growth was not too significant during the initial years of reform. It was during the period since 2004–05 that India moved on to a substantially higher rate of GDP growth, though the figure for growth after 2011–12, computed using a new series of GDP estimates with 2011–12 as base, has

been the subject of controversy. An important feature of the growth process under reform, and especially during the high-growth years, has been the sectoral distribution of growth, with evidence of deceleration of growth in the commodity-producing sectors. The growth of gross value added (GVA), at constant prices, in agriculture and allied activities has fallen from 6.3% in 2016–17 to 3.4% in 2017–18, that in mining and quarrying from 13% to 2.9%, and that in industry from 7.9% to 5.8%. The growth rates in 2017–18 have risen only in construction (13% to 5.7%); trade, hotels, transport, and communication (7.2% to 8.0%); and financial, real estate, and professional services (6.0% to 6.6%). Meanwhile, conservatism in public spending has meant that GVA growth in public administration and defence has fallen from 10.7% to 10%. And without support from the commodity-producing sectors, GVA growth in electricity, gas, water supply, and other utility services has decelerated from 9.2% to 7.2%.

Table 1. GDP growth rates

1951–52 to 1964–65	4.0
1964–65 to 1974–75	3.2
1974–75 to 1984–85	4.1
1984–85 to 1994–95	5.3
1994–95 to 2004–05	6.0
2004–05 to 2012–13	8.1
2011–12 to 2017–18	7.0

Source: Central Statistical Organisation National Income Accounts, various issues.

This focus of growth on a few service sectors and absence of dynamism in the commodity-producing sectors has meant that services account for a significant part of the increment in GVA in recent years. Considering the period since 2011–12, when the current national accounts series became available, we find that while agriculture and allied sectors accounted for just 7.4% of the increase in aggregate GVA over 2011–12 to 2017–18 and industry for 28.5%, services contributed 64.4% (Figure 1).

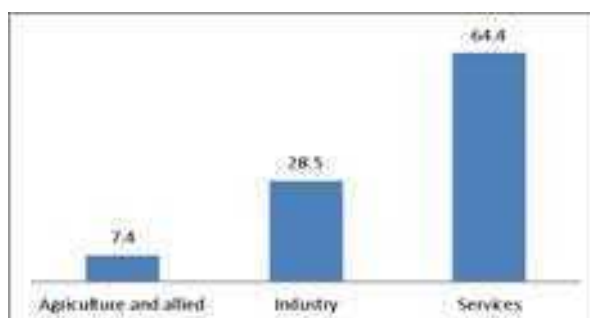


Figure 1. Sectoral shares in growth of value added at constant prices Between 2011-12 and 2017-18.

Services are of two kinds. Those characterised by high value added per worker (because of high per-worker revenues, such as in IT services, or per-worker state expenditures, such as in some social services) and relatively low absolute employment measures and those with

extremely low valued added per worker, but high absolute employment numbers. The latter kinds of services are the sink for the large workforce unable to find employment in the poorly performing commodity-producing sectors. The high share of services in the increment in GVA points to partly self-fuelling growth of the “new services” and their reliance on low-cost, outsourced domestic services of various kinds, such as logistics, catering, and security. The so-called high productivity services derive their high value added by contracting those operating with low-cost workers in precarious employment.

A significant failure of the reform process was that it did not generate a pattern of growth associated with rapid productive employment generation. Instead, both aggregate employment creation and structural transformation remained sluggish – and in recent years have even backtracked, despite apparently rapid rates of aggregate income expansion. While employment growth did not keep pace with population growth throughout the post-reform years, and the proportion of workers in informal activities without formal employment contracts remained stubbornly high at more than 90%, employment trends appear to have deteriorated further in the past decade. Data from the latest Survey on Employment and Unemployment of the National Statistical Organisation of India suggest that, almost unbelievably, aggregate employment shrank by about 7 million in the period 2011–12 to 2017–18, while the open unemployment rate was at a 45-year high of 6.1%. These extremely weak labour market conditions obviously create adverse conditions for health. And this was associated with substantial increase in inequality over this period, such that a recent study (Chancel & Piketty, 2017) found that income inequality in India is at its highest level since 1922. This had also led to bad health outcomes, because low and unequally distributed incomes tend to be linked with poor nutrition and prevent poor people from being able to access appropriate health services. Fiscal constraints (and the lack of political will) prevented the required expansion of public expenditures in the physical and social infrastructure and amenities that could have led to improving health conditions, thereby accentuating the problem.

HEALTH OUTCOMES IN INDIA SINCE 1991

As India nears the completion (in 2021) of 30 years of the “economic reform” process that dismantled the post-Independence policy structure of state intervention (involving widespread regulation and expanding state presence), health outcomes do not seem to have met even official expectations. The structure of reform was one where growth (reflected in an obsession with GDP) was left to private initiatives “disciplined” by the operations of a liberalised market, whereas advance on the human development front was to be realised through public action. Two factors limited the gains made on the human development front through the pursuit of this strategy. The first was the fact that the trajectory of growth was deeply inequalising, reducing the capacity of a majority to access the services (now increasingly provided at a cost) needed to improve their status in areas like education and health. The second was that the promised “public action” that was supposed to accompany the growth process was not realised, because financial allocations fell far short of requirements as a result of the combination of a lenient tax regime aimed at incentivising private investment

and an emphasis on fiscal conservatism and austerity that was an essential component of neoliberalism.

Table 2. Life expectancy at birth in 1991 (years)

Mexico	71.2
Malaysia	71.0
Vietnam	70.8
Thailand	70.3
Sri Lanka	69.6
China	69.4
Brazil	65.7
Philippines	65.5
Indonesia	63.6
Namibia	61.6
Pakistan	60.3
Bangladesh	59.0
India	58.4
Ghana	57.2
Kenya	56.9
Sudan	55.7

Source: World Bank WDI Database.

In 1991, India was far short of providing to its citizens what could be considered a healthy life based on a comparison of health status indicators in similarly placed poor countries. Taking the most summary measure, in the form of life expectancy at birth, India, with a national Figure of 58.4 years, was not performing as well as its South Asian neighbours, especially Sri Lanka (69.6 years), and was way short of many other emerging markets, albeit ones with a relatively higher per-capita income (Table 2).

If we examine more specific data reflective of the success of health interventions and market-mediated availability, such as the infant and maternal mortality rates, the picture is even more dismal. India's infant mortality rate in 1991 of 86.3 per 1,000 live births was better than only that of Nepal, Bangladesh, and Pakistan in the sample of developing countries chosen for comparison and was much cause for concern when compared with neighbouring Sri Lanka, which recorded a creditable Figure of 18.1 per 1,000 live births (Table 3). The situation was similar to the World Bank's modelled estimates of the maternal mortality ratios provided in Table 4.

The problem, however, is not just concerning the initial conditions but also the pace of improvement – in which India fares worse than many poorer countries. In the case of the under-5 mortality rate, for example, Bangladesh and Nepal were worse off than India in 1990, with figures of 143.6 and 141.9, respectively, per 1,000 live births. India recorded a figure of 125.6 that year. But in the 22 years between 1990 and 2012, while Bangladesh registered an annual average rate of reduction of 4.7 units a year and Nepal of 4.6 units a year, India's average rate of decline was 3.2 units. As a result, the former two countries recorded better

under-5 mortality rates than India in 2012, pointing to poor progress in the Indian case despite the other structural and growth potential benefits India possessed (Table 5). As expected, the annual average rate of reduction tends to be low in countries where initial conditions reflect low under-5 mortality rates, such as Sri Lanka, for example. But what is noteworthy is that when India is compared with countries that started at similar or even higher levels of under-5 mortality, the average rate of decline in the mortality figure was lower, resulting in India falling behind those countries in mortality reduction. The experience has been similar with respect to infant mortality as well (Table 6).

Table 3. Infant mortality rate, 1991 (per 1,000 live births)

Malaysia	13.8
Chile	15.1
Sri Lanka	18.1
Thailand	29.7
Mexico	34.8
Vietnam	35.6
Philippines	38.6
China	41.7
Namibia	48
Brazil	50.4
Kenya	67.3
Ghana	76.9
Sudan	80.9
India	85.3
Nepal	93.1
Bangladesh	95.9
Pakistan	104.6

Source: World Bank WDI Database.

Table 4. Maternal mortality ratio, 1991 (modelled estimate, per 100,000 live births)

Thailand	38
Chile	42
Sri Lanka	73
Malaysia	79
Mexico	87
China	92
Brazil	109
Vietnam	133
Philippines	134
Namibia	305
Pakistan	418
India	538
Bangladesh	550
Ghana	600
Kenya	678
Sudan	728
Nepal	951

Source: World Bank WDI Database.

Table 5. Under-5 mortality rate (per 1,000 live births)

	Earliest (1990)	Latest (2012)	Average Annual Rate of Decline
China	54.0	14.0	1.4
Indonesia	83.8	31.0	1.6
Malaysia	18.6	8.5	0.3
Myanmar	106.4	62.3	1.8
Philippines	58.5	29.8	1.3
Thailand	38.2	13.2	0.9
Viet Nam	50.5	23	1.3
Bangladesh	143.8	40.9	3.0
India	125.8	58.3	2.0
Nepal	141.9	41.6	3.0
Pakistan	136.4	85.9	1.7
Sri Lanka	21.4	8.6	0.5

Source: ESCAP, ADB, & UNDP (2016). Making It Happen: Technology, Finance and Statistics for Sustainable Development in Asia and the Pacific. Asia-Pacific UN SDG Report 2014-15, Bangkok: UN-ESCAP.

In the case of maternal mortality, India's intertemporal record was comparable to that of Bangladesh and Myanmar, but fell short of that of Nepal, while being better than that of Pakistan and Indonesia, which had started with significantly lower levels of mortality (Table 7).

Table 6. Infant mortality rate (per 1,000 live births)

	Earliest (1990)	Latest (2012)	AARD
China	42.2	12.1	1.4
Indonesia	61.7	25.8	1.6
Malaysia	14.3	7.3	0.3
Myanmar	76.1	41.1	1.6
Philippines	41.0	23.5	1.3
Thailand	31.1	11.4	0.9
Viet Nam	36.4	18.4	1.3
Bangladesh	99.5	33.1	3.0
India	88.2	43.8	2.0
Nepal	98.5	33.6	3.0
Pakistan	105.9	69.3	1.7
Sri Lanka	18.2	8.3	0.5

Source: ESCAP, ADB, & UNDP (2016). Making It Happen: Technology, Finance and Statistics for Sustainable Development in Asia and the Pacific.

Table 7. Maternal mortality ratio (per 10,000 live births)

	Earliest (1990)	Latest (2013)	AARD
China	97	32	2.8
Indonesia	430	190	10.4
Malaysia	56	29	1.2
Myanmar	580	290	16.5
Philippines	110	120	-0.4
Thailand	42	26	0.7
Viet Nam	140	49	4.0
Bangladesh	550	170	16.5
India	560	190	16.1
Nepal	790	190	26.1
Pakistan	400	170	10.0
Sri Lanka	49	29	0.9

Source: ESCAP, ADB, & UNDP (2016). Making It Happen: Technology, Finance and Statistics for Sustainable Development in Asia and the Pacific.

An examination of changes in age-specific mortality rates at the all-India level since 1990–91 reveals a few significant trends. First, two indicators point to shortfalls or inadequacies in health services provision during the years of reform. One is that while under-5 mortality rates have registered declines, starting from 26.5 in 1991, they still remain high, at 9.4 per 1,000 in 2016. The other is that when compared across age groups, mortality rates show a significant rise at a relatively early age, starting at the 45–49 age group and going on to 70-plus. Third, there are significant differences in mortality rates in different age groups between rural and urban areas, with rural areas that are likely to have limited access to quality health resources recording much higher rates. And finally, in both urban and rural areas, gender differentials in mortality rates in almost all age groups are not too significant.

There have been some changes in the causes of death over the first decade of this century. During 2001–03 non-communicable diseases, which were the leading causes of death, accounted for 42% of all deaths. That figure had risen to 49% by 2010–13. Communicable, maternal, perinatal, and nutritional conditions accounted for another 38% of deaths in 2001–03, with that figure falling to 28% during 2010–13. Injuries and ill-defined causes account for 10% each in 2001–03 and 11% and 12%, respectively, in 2010–13. So a shift from communicable to non-communicable disease in terms of proportionate contributions to mortality is visible during those years of high growth.

It is noteworthy that in rural areas the decline in deaths due to communicable maternal, perinatal, and nutritional conditions fell quite sharply from 41% of all deaths in 2001–03 to 29% during 2010–13. In urban areas, however, the decline was smaller in magnitude, starting from a significantly lower figure – from 25% to 22% between these two periods. However, it needs to be said that with more than a quarter of all deaths still due communicable diseases, the problem is still woefully inadequate public health interventions (Motkuri and Khan, 2018). Even in 2010–13, tuberculosis, respiratory diseases, and respiratory infections still accounted for 3.7%, 3.9%, and 7.6% of deaths, respectively; diarrhoeal and digestive diseases for as much as 10%; and perinatal conditions for 5.6%. Meanwhile, cardiovascular diseases rose from 18% of deaths in 2001–03 to 23% of deaths in 2010–13.

The areas in which India's record during the reform years leave much to be desired are maternal and child mortality. Though estimates point to a reduction in the rate of maternal mortality from 556 per 100,000 live births in 1990 to 174 in 2015, the annual rate of reduction, despite fluctuations, has not changed very much over the reform years (Tables 8 and 9). The outcomes on child mortality are more disconcerting. As noted in *The Lancet* (Liu et al., 2019), "An estimated 1.201 million deaths occurred in children younger than 5 years in India in 2015 – the largest number of such deaths among all countries. The number reduced from 2.516 million in 2000, yet despite this progress, India did not meet target 4 of the Millennium Development Goals (MDG 4) of a two-thirds reduction in under-5 mortality rate between 1990 and 2015." The data show that "the leading causes of death were preterm birth complications, pneumonia, and intrapartum-related events. Neonatal sepsis or meningitis, diarrhoea, and injuries were also important causes."

Table 8. Maternal mortality in 1990–2015

Year	Maternal mortality ratio* per 100,000 live births	Maternal deaths	AIDS-related indirect maternal deaths	Live births, 1,000s	Proportion of maternal deaths among deaths of female reproductive age (%)
1990	556 [445–685]	152,000	5	27,430	19.7
1995	471 [396–560]	130,000	53	27,671	16.4
2000	374 [324–437]	104,000	280	27,884	13
2005	280 [240–324]	77,000	520	27,634	9.8
2010	215 [183–255]	57,000	400	26,566	7.6
2015	174 [139–217]	45,000	280	25,794	6.2

Note: MMR and PM are calculated for women aged 15–49 years.

Sources: WHO, UNICEF, UNFPA, World Bank Group, and United Nations Population Division Maternal Mortality Estimation Inter-Agency Group; Live birth data are from World Population Prospects: the 2015 Revision. New York, Population Division, Department of Economic and Social Affairs, United Nations Secretariat; 2015.

Table 9. Maternal mortality ratio annual rate of reduction (%)

1990–2015	4.6	[3.5–5.7]
1990–2000	4	[1.8–5.6]
2000–2015	5.1	[3.7–6.7]
2005–2015	4.7	[2.9–6.7]

The disparities in the rate of improvement of outcomes point to provision of and access to different kinds of facilities. The fact that deaths due to preterm complications (annual rate of reduction 1.1%) did not change much, even as intrapartum deaths fell substantially over the 15 years ending 2015, show that while measures adopted during delivery had improved, investments and other measures to increase access to and use of institutional facilities for

births and caesarean sections, ambulance support, and so forth, were inadequate. But even access to institutional facilities does not guarantee success, as “the establishment of several hundred district neonatal intensive care units does not appear to have had a noticeable effect on mortality due to preterm birth complications.” (Li Liu et al., 2019, p. e731) On the other hand, the near-halving of under-5 mortality rate (annual rate of reduction of 5.2%) was due to the rapid decline of causes that were addressed with better provision and use of vaccines.

It is worth noting in this context that even official sources now recognise that India is facing a “triple burden of diseases”: inadequate control of communicable diseases, emerging non-communicable diseases (some of which result from changing diet and lifestyles), and new infectious diseases (Government of India, 2015). A significant proportion of these are preventable, which puts the responsibility on public health measures for prevention. However, inadequate public expenditures as well as insufficient intervention for control have meant that India’s aggregate performance with regard to such diseases has been poor.

This intertemporal performance suggests that while initial conditions with respect to health status in India were already relatively poor, India’s record over the reform years fell short of expectations and was also worse than similarly placed countries within the region. Clearly, levels of and changes in per-capita incomes are not the principal determinants of health status outcomes, which can and have been modified significantly by patterns of development and public action. This is remarkable because, as noted earlier, the period under consideration was one in which India recorded reasonable and even high rates of growth and with growth accelerating after 2003. This suggests that the pattern of growth during the reform era and the nature of state intervention were not the most conducive for improving the health status of the population. The adverse effects that state policies have had on the relationship of growth and employment, on the one hand, and on welfare measures and public provision of social services, on the other, were bound to affect livelihoods and the quality of life.

INTERSTATE VARIATIONS IN HEALTH OUTCOMES

India contains such vast regional diversity that it is often very misleading to treat it as one unit. Health indicators in Kerala, for example, have long been substantially better than those in other states, despite Kerala being only a middle-income state within the country. As Table 10 indicates, Tamil Nadu ranks second best in terms of both infant mortality rate (IMR) and maternal mortality ratio (MMR), but that gap with Kerala is large. However, Tamil Nadu achieved this rank through much faster improvement than most other states over the previous two decades. The other states among the top five are Maharashtra, West Bengal, and Punjab, but then the differences with other states become much less. The states with the highest IMR and MMR are Uttar Pradesh, Rajasthan, Assam, Madhya Pradesh, and Orissa. Bihar, Jharkhand, and Chhattisgarh have slightly better IMRs but poor MMRs. Further, the gap between states like Tamil Nadu and Maharashtra, which are on the top, and states like Uttar Pradesh and Madhya Pradesh, which are at the lower end, is significantly large. For instance, the IMR in Uttar Pradesh is more than twice that in Tamil Nadu and the MMR in Uttar Pradesh is almost four times that in Tamil Nadu.

Table 10. Education and health indicators across Indian states

State	Literacy rate (2011)	Expected years of schooling (2011)	Infant mortality rate (2010)	Maternal mortality ratio (2007-09)	Life expectancy (2002-06)
Andhra Pradesh	67.7	9.86	46	134	64.4
Assam	73.2	9.54	58	390	58.9
Bihar	63.8	9.58	48	261	61.6
Chhattisgarh	71.0	9.31	51	269	58.0
Gujarat	79.3	9.79	44	148	64.1
Haryana	76.6	9.68	48	153	66.2
Himachal Pradesh	83.8	11.05	40	NA	67.0
Jammu and Kashmir	68.7	NA	43	NA	NA
Jharkhand	67.6	9.68	42	261	58.0
Karnataka	75.6	9.75	38	178	65.3
Kerala	93.9	11.33	13	61	74.0
Madhya Pradesh	70.6	8.95	62	269	58.0
Maharashtra	82.9	9.86	28	104	67.2
Orissa	73.5	8.74	61	258	59.8
Punjab	76.7	9.80	34	172	69.4
Rajasthan	67.1	9.19	55	318	62.0
Tamil Nadu	80.3	10.57	24	97	66.2
Uttar Pradesh	69.7	9.19	61	359	60.0
West Bengal	77.1	8.97	31	145	64.9
India	74.0	9.62	47	212	63.5

Source: Sinha (2016).

Disparities in the annual rates of reduction during 2000–15 were significant across states as well. One major and persistent disparity is that between the eight socioeconomically backward states of Bihar, Chhattisgarh, Jharkhand, Madhya Pradesh, Orissa, Rajasthan, Uttaranchal, and Uttar Pradesh, referred to as the Empowered Action Group (EAG) states, and the other states of the nation. As Table 11 shows, life expectancy in the EAG states and Assam was reduced because of much higher mortality in the 0–4 age group and noticeably higher mortality in the 5–29 age groups. As expected, non-communicable diseases such as cardiovascular diseases are less important as causes of death in the backward states as compared with the other states, whereas perinatal conditions, respiratory diseases, diarrhoeal and digestive diseases, and respiratory infections are relatively more important as causes of death in the former. That is, conditions that are addressed more easily with medical health interventions still remain the most important causes of death in backward states (Table 11).

An analysis based on National Sample Survey 71st round data (Kumar & Singh, 2016, p. 269) found that a leading reason for the persisting lag in these states was the inadequate availability and access to public sources of healthcare. According to that study, “the EAG states could ensure access to public sources of healthcare to a limited population (30% rural and 22% urban). Among the EAG states, Odisha performed the best in securing access to public health services to a large proportion of inpatients in both rural (71%) and urban areas (47%), followed by Uttarakhand (61% rural and 31% urban) and Rajasthan (44% rural and 39% urban). The inpatients of Chhattisgarh also reported better accessibility (42% rural and 26% urban) to public sector facilities in comparison to Uttar Pradesh (16% rural and 14%

urban) and Bihar (16% rural and 18% urban). Similarly, the results reveal that accessibility to public sources of healthcare is better in Madhya Pradesh (27% rural and 29% urban) and Jharkhand (25% rural and 20% urban) in comparison to Uttar Pradesh and Bihar.” In addition: “Long waiting time in seeking healthcare from public health facilities is a major public health challenge in the EAG states. A large proportion of inpatients (14% rural and 24% urban) of the EAG states do not access public sources of healthcare as they have to wait for a long time in a queue while seeking these facilities. Surprisingly, due to long waiting in public health facilities 74% of inpatients of rural areas of Uttarakhand do not access these facilities. Similarly, longer waiting time dissuades a large proportion of inpatients of urban areas of Uttar Pradesh (30%) and Bihar (30%) from accessing public health facilities.”

Table 11. Distribution of deaths by age in EAG states and Assam and other states, 2010–2013

Age group years	Empowered Action Group states & Assam		Other states	
	Person	Percent	Person	Percent
0–1	10,257	15.7	8,528	7.3
1–4	2,314	3.5	1,567	1.3
0–4	12,571	19.3	10,185	8.7
5–14	1,870	2.9	1,512	1.3
15–29	4,815	7.4	7,186	6.1
30–34	1,663	2.5	3,020	2.6
35–44	4,008	6.1	7,950	6.8
45–54	5,446	8.3	11,948	10.2
55–69	14,657	22.4	30,698	26.1
70+	20,262	31.0	45,026	38.3
Total	65,292	100.0	117,535	100.0

Table 12a. Top ten causes of death in EAG states (all ages), 2010–2013

Rank	Causes of death	Deaths (%)		
		Male	Female	Person
EAG states and Assam				
1	Cardiovascular diseases	17.2	13.6	15.6
2	Un-defined: All other symptoms, signs, and abnormal clinical and laboratory findings	10.9	14.4	12.4
3	Prenatal conditions	8.4	6.7	8.5
4	Respiratory diseases	8.8	7.7	9.2
5	Diarrhoeal diseases	6.0	9.0	7.6
6	Respiratory infections	5.2	5.8	5.4
7	Digestive disorders	5.7	4.8	5.3
8	Unintentional injuries other than motor vehicle accidents	5.4	6.3	5.9
9	Malignant and other neoplasms	4.3	4.7	4.5
10	Tuberculosis	5.4	3.2	4.4
	All other remaining causes	22.2	22.9	22.5
	Total	100.0	100.0	100.0

Table 12b. Top ten causes of death in other states (all ages), 2010–2013

Rank	Causes of death	Deaths (%)		
		Male	Female	Person
Other states				
1	Cardiovascular diseases	19.4	24.9	21.5
2	Is-defined all other symptoms, signs, and abnormal clinical and laboratory findings	9.0	18.0	12.3
3	Respiratory diseases	7.2	7.4	7.3
4	Malignant and other neoplasms	6.0	7.7	6.0
5	Digestive diseases	5.1	2.8	4.7
6	Unintentional injuries, other than motor vehicle accidents	4.5	4.3	4.4
7	Perinatal conditions	3.9	4.2	4.0
8	Diarrhoeal diseases	2.8	4.7	3.6
9	Tuberculosis	4.0	2.6	3.4
10	Intentional injuries, suicide	3.4	3.1	3.2
	All other remaining causes	22.5	22.5	22.5
	Total	100.0	100.0	100.0

It is evident that public interventions play a major role in determining these varying health outcomes. Basic infrastructure and amenities that are driven by public spending play a huge role in ensuring better health outcomes. For example, Sinha (2016) pointed out that Tamil Nadu is the state with highest immunisation coverage, while the percentage of deliveries assisted by health personnel is highest in Kerala, followed by Tamil Nadu, with other states substantially lower. While the percentage of deliveries assisted by health personnel is about 91% in Tamil Nadu, it is only about 75% in the next state, Andhra Pradesh. The gap with lower-ranking states is much wider: The percentage of births delivered with skilled attendance is less than 30% in Bihar, Jharkhand, and Uttar Pradesh. It is obvious why skilled attendance during delivery is seen as a proxy of maternal health, since immunisation and safe deliveries contribute in major ways to decreasing neonatal and infant mortality, as well as maternal mortality.

AGRARIAN CRISIS AND FARMERS' SUICIDES

The neoliberal reforms from 1991 onward did not really focus on agriculture – instead, the emphasis was put on non-agricultural sectors as the means to both faster economic growth and development in terms of structural transformation. The basic economic strategy pinned its faith on large investments by private corporate capital, and so various controls on such capital, in the form of internal and external regulation, were sought to be removed, and in

addition, over time various incentives were provided to encourage more rapid rates of private investment.

This strategy had very little for small producers, whether in agriculture or other activities. In the early 1990s, it was felt that the devaluation of the rupee already provided sufficient incentive to agriculture, because the expectation was that this would make it more attractive to export crops, which would thereby improve farm incomes. Subsequently, the presumption was that freeing agricultural markets and liberalising external trade in agricultural commodities would provide price incentives leading to enhanced investment and output in that sector, while broader trade liberalisation would shift inter-sectoral terms of trade in favour of agriculture.

But other economic policies and changes in government spending and financial measures had significant implications for cultivation. Four important policy areas that had effects on agriculture related to public expenditure, food management, access to institutional finance, and trade liberalisation. Initially, there were absolute actual declines in central government revenue expenditure on agriculture and rural development. Thereafter, there were cuts in particular subsidies in real terms, such as on fertiliser, and the 1990s experienced an overall decline in per-capita government expenditure on rural areas. There were also very substantial declines in public infrastructure and energy investments that affect rural areas, especially in irrigation and transport. In addition, financial liberalisation measures, including the emerging scope of what was designated as priority-sector lending by banks, effectively reduced the availability of institutional credit for farmers. Bank branches, accounts, and lending to agriculture all decelerated, and in some states they showed declines. This forced many cultivators, particularly smaller farmers, tenant farmers, and those without clear titles to land, to seek recourse from informal channels of credit like input dealers and traditional moneylenders. All this made farm investment and working capital for cultivation more expensive and more difficult, especially for smaller farmers.

Inputs for cultivation became a particular concern, as public extension services no longer provided adequate information, access to subsidised quality inputs was reduced, and various subsidies were sought to be lifted. Spurious seeds, greater reliance on expensive seeds provided by large domestic and multinational companies that involved “terminator genes” that did not allow subsequent local reproduction, problems with price and quality of fertiliser and pesticides and excessive use of both, often in wrong proportions – all of these became frequent problems that affected the quantity and quality of output as well as the margins available to farmers.

All these forces led to a slowdown in agricultural growth and, by the late 1990s, widespread distress in the countryside. The most extreme form of expression of such distress was in the spate of farmers’ suicides, which occurred typically when heavily indebted farmers whose farms had lost viability could find no other recourse. By the mid-2000s, it was evident that the problems facing agriculture were severe and would require prompt policy attention. The Congress-led United Progressive Alliance (UPA) government that came to power in 2004 had in fact made the problems facing cultivation and rural distress generally a major plank of their electoral campaign. They sought for some years to reverse the pattern of declining public spending, with increased public investment on irrigation and rural infrastructure, and more central government spending on agricultural research and extension, as well as increased credit to rural areas. These positives were very limited in extent, but they did

partially reverse the trend of rural decline, aided by high and rising prices of agricultural goods in global trade.

Liberalisation of external trade became an important element of the reform process, first through lifting restrictions on exports of agricultural goods, and then by shifting from quantitative restrictions to tariffs on imports of agricultural commodities. A range of primary imports was liberalised and thrown open to private agents. Import tariffs were very substantially lowered over the decade. Exports of important cultivated items, including wheat and rice, were freed from controls, and subsequent measures were directed towards promoting the exports of raw and processed agricultural goods. Indian agriculturalists were increasingly exposed to global competition even as the protections they had in terms of support prices, input assistance, and public extension services were gradually being reduced or even withdrawn.

For Indian agriculture, this led to a peculiar combination of low prices and output volatility for cash crops. While output volatility increased especially with new seeds and other inputs, the prices of most non-food-grain crops weakened, and some cases plummeted. Further, farmers were squeezed as input costs kept rising, either because reduced subsidies and rising input prices, or because of the need to use more and more inputs (such as seeds, fertiliser, and pesticides) to achieve the same levels of output. This reflected not only domestic demand conditions but also the growing role played by international prices as a consequence of greater integration with world markets in this sector. Indian farmers had to operate in a highly uncertain and volatile international environment, effectively competing against highly subsidised large agribusinesses in the developed countries.

In recent years, farmers' movements and farm loan waivers in different states across India have driven home the fact that the viability of agriculture is under challenge. This is surprising, since the comprehensive framework for reviving agricultural production, introduced in response to the agricultural crisis in the mid-1960s, is in principle still in place. There were many components to that framework besides the adoption of green revolution technology. The most relevant aspects of this discussion are the measures that were aimed to ensure the viability of agriculture.

The measure directly relevant to the purpose was the promise to procure, at a pre-specified, cost-plus remunerative price, any supplies of identified crops that farmers chose to sell to the government. With these minimum support prices (MSPs) revised each year, this measure was aimed at ensuring that there was a rising floor to agricultural prices, which would stabilise income increases and guarantee farmers a return on investments that would help raise productivity. There were two problems deriving from this measure that needed to be addressed: managing the supplies procured by the government and insulating the consumer from increases in market prices at rates much higher than the procurement price. With respect to the first, the government decided to dispose of the stocks it procured and accumulated through the public distribution system, which was already in place to manage regional differences in food grain availability. This was to be done at affordable prices, which given the procurement, storage, and transportation costs incurred by the government, had to include a subsidy that moderated prices paid by the consumer. Thus, it was hoped that agricultural production would be incentivised, farmer incomes would be stabilised, and consumers would be protected against agricultural price inflation.

Many years have passed since this system was first put in place, so countrywide coverage should have been ensured and the government should have accumulated enough experience to

implement it without difficulty. The result should have been a viable agriculture and satisfied consumers. But instead, there is clear evidence that crop production is increasingly unviable. There are two reasons for this: the fact that procurement prices have not kept pace with actual costs of cultivation, rather than the notional national averages computed for the purpose, and the fact that procurement operations are so limited (covering only an estimated 6% of farmers) and, in any case, do not really work other than for the major food grains, so that they do not provide the expected floor prices for markets.

In recent years, annual increases in the MSP have been smaller than earlier with farmers complaining that support prices have not kept pace with costs. A research report from the rating agency CRISIL found that the average annual growth of the MSP fell from 19.3% in the period 2008-09 to 2012-13, to only 3.6% in the period 2013-14 to 2016-17 (Chandrasekhar and Ghosh, 2017). This deceleration added significantly to farmers' distress.

In addition, the gradual liberalisation of trade in agricultural commodities has increasingly linked domestic to international prices. Overall, policies deregulating input prices, curtailing subsidies, freeing imports, and lowering import tariffs have subjected agriculturists to rising costs and competition from low-cost imports. This is true across crops, including those crops supposedly under the MSP. This has also meant that in poor harvest years, farmers are not necessarily compensated by an increase in crop prices, while in bumper years, low prices would hit their net incomes, depending on how global prices move. Farmers can lose out as a result of falling market (as opposed to procurement) prices in good harvest years, but not gain in terms of higher prices (even if affected by lower output and revenues) in bad or indifferent monsoon years.

As a result of all of these factors, the viability of crop production has been eroded and farmers hit by slowly rising or falling market prices and/or rising costs find their net returns and income squeezed. An estimate, based on the official National Accounts Statistics, indicates that over the 3-year period 2014-15 to 2016-17, the income per head of the agriculture-dependent population increased by 16% in nominal terms. Over the same period inflation based on the Consumer Price Index for rural India rose by 16.3%. This implies that the real, inflation-adjusted incomes of the agriculture-dependent population have stagnated. A further consequence is that farmers taking working capital and/or consumption loans, as well as loans for investment, are unable to pay off their debts.

There is a further problem that public procurement operations do not reach all farmers and all crops, even for commodities with officially declared MSPs. There are regions of the country where the procurement programme is weak and not accessible to many farmers; there are constant complaints that procurement operations are too tardy, brief, and inadequate to be of real benefit in ensuring a minimum price for farmers. An official assessment conducted in 2010-11 found that, while there were significant regional variations, on average the awareness and use of the MSP programme was high. Yet, sales can occur at prices below MSP partly because of tardy procurement and partly because trade and other policies can depress market prices in good harvest years. The latter transpires, for example, because the government, which fears inflation that may hurt corporates and vocal urban consumers, often chooses to address production shortfalls and actual or potential price increases by releasing accumulated stocks and augmenting domestic supplies with imports from abroad. This dampens price inflation. On the other hand, in good harvest years, neither are minimum support prices increased adequately to ensure a floor price that covers costs and offers a remunerative return, nor is enough procured to ensure that even the MSP offered serves as a

floor for market prices. Thus, market prices have typically been below the MSP for many commodities in many markets.

There were other sins of commission, as demonetisation destroyed rural markets and demand for farmers for a prolonged period, and the imposition of the Goods and Services Tax (GST) added to their cultivation costs. Demonetisation was a severe blow to farmers, as they found it very difficult to sell their crops or access the required inputs. It led to a prolonged collapse in rural livelihoods and demand. This has persisted to the point where even when there is high output because of a good monsoon, farm incomes do not rise because of low prices. The poor implementation of the GST has added to the travails of small and medium enterprises and further affected demand for agricultural produce, leading to persistently low crop prices.

In this bleak context, the expected improvements in crop insurance have also not materialised. Instead, the revised crop insurance scheme has essentially profited private insurance companies. Farmers and state and central governments have paid out increasing amounts as premiums for insurance but have not received the expected compensation when required because of rigid rules about claim settlement. Farmers reeling under dry spells or sudden hailstorms that destroy standing crops are provided no compensation for their losses. A further blow has come to on-farm non-cultivation activities like livestock rearing, which has saved farmers from penury and now accounts for nearly one-third of agricultural value added. This has come under threat from cow vigilantes, who are allowed and even encouraged to run riot and lynch innocent people, and this has generally damaged the livestock trade. As a result, older cattle are simply released by farmers who cannot bear the cost of their upkeep, and the menace of stray cattle roaming the fields has become another factor contributing to the increased costs borne by farmers.

This massive agrarian distress has found some outlet in large protests by farmers across the country, but is more worryingly reflected in a spate of farmers' suicides across the country, especially in the dryland regions that are the worst affected by climate change and rising costs. While recent data on farmers' suicides have not been released, evidence from the Crime Record Bureau suggests that between 1995 and 2012, close to 300,000 farmers committed suicide in the country (Nagaraj, Sainath, Rukmani, and Gopinath, 2016). Even that number is likely to be a significant underestimate, because the major states of Tamil Nadu and Rajasthan, as well as some smaller states, did not report any suicides at all in some years. Further, the stringent definition of farmer based only on land titles meant that many suicides were not recorded as farmers' suicides. As Nagaraj et al. (2016, p. 57) noted, "this often left out a genuine farmer from the count. For example, a tenant farmer who leased in land and hence did not have a title to the land, or a farmer whose land title was in his father's name, or a woman farmer whose land title was in her husband's or father-in-law's name, all could be denied the status of a farmer."

The data suggest that an overwhelming proportion — nearly 85% — of farm suicides are by male farmers, and young farmers account for nearly 30% of the total. The problem of farm suicides has been especially intense in some pockets of certain states: The Vidarbha region in Maharashtra, the Deccan and Hyderabad-Karnataka regions in Karnataka, and the Telangana and Rayalaseema regions in Andhra Pradesh and Chhattisgarh, as well as Wayanad in Kerala (Nagaraj et al., 2016). Most of these sub-regions constitute a contiguous region in the heartland of India. This is a relatively backward region, with poor infrastructure, and very water-stressed with low levels of surface irrigation and scanty, uncertain rainfall. Crop

diversification has added to instability and vulnerability because many of the cash crops that farmers have turned to require groundwater, which is increasingly scarce. This, combined with worsening soil quality because of the increased use of chemical inputs over time, has become associated with falling yields, even as output prices have become more volatile and have not kept pace with rising input costs. This leads to a scissors crisis in the countryside, when initial accumulation of debt for cultivation becomes impossible to repay, and the burden of mounting debt – and finally, the inability to access fresh credit – become the proximate causes of the desperation that leads farmers to take their own lives.

This in turn suggests that the problem of farm suicides is particularly acute when there are pre-existing conditions of very high vulnerability in the region and an absence of alternative livelihood opportunities. Combined with the severe agrarian crisis (largely policy-driven as we have noted above), a toxic mix results that leads to higher mortality among those who find that they simply cannot cope with the material pressure brought about by the collapse in the viability of cultivation.

APPENDIX

Table A1a. Age-specific mortality rate by sex and residence from 1991 to 2016 at interval of 5 years – total

Age group	Total								Rural								Urban							
	1991	1996	2001	2006	2011	2013	2016		1991	1996	2001	2006	2011	2013	2016		1991	1996	2001	2006	2011	2013	2016	
1	2	3	4	5	6	7	8		9	10	11	12	13	14	15		16	17	18	19	20	21	22	23
Total																								
0-4	26.9	23.8	19.8	17.1	12.1	11.1	9.4		29.1	26.1	21.1	18.1	13.1	12.1	10.1		16.1	14.1	11.1	10.1	7.4	6.4	6.1	5.1
5-9	27.9	23.8	19.8	14.1	10.1	9.8	9.7		30.1	28.1	23.1	18.1	13.1	12.1	9.9	9.8		15.1	13.1	11.1	9.7	8.3	8.4	8.4
10-14	13.1	13.1	13.1	13.1	9.7	9.6	9.5		14.1	14.1	14.1	13.1	9.8	9.6	9.6		10.1	9.9	9.9	9.8	9.4	9.4	9.4	9.3
15-19	21.1	16.1	17.1	14.1	13.1	10.1	9.9		23.1	18.1	19.1	18.1	14.1	11.1	9.8		14.1	12.1	10.1	10.1	12.1	9.9	9.8	9.6
20-24	20.1	23.1	23.1	20.1	14.1	15.1	12.1		30.1	23.1	26.1	23.1	18.1	17.1	13.1		19.1	18.1	18.1	14.1	12.1	12.1	12.1	1.1
25-29	33.1	25.1	27.1	23.1	18.1	18.1	13.1		33.1	28.1	29.1	28.1	19.1	20.1	16.1		24.1	23.1	23.1	17.1	15.1	14.1	14.1	1.1
30-34	33.1	29.1	29.1	27.1	23.1	22.1	19.1		33.1	31.1	32.1	29.1	25.1	24.1	21.1		23.1	22.1	22.1	20.1	17.1	14.1	14.1	15.1
35-39	39.1	34.1	36.1	34.1	27.1	30.1	25.1		41.1	37.1	38.1	38.1	30.1	31.1	28.1		33.1	32.1	30.1	29.1	20.1	24.1	24.1	19.1
40-44	48.1	45.1	44.1	42.1	40.1	39.1	37.1		51.1	52.1	47.1	44.1	42.1	42.1	41.1		43.1	37.1	36.1	33.1	33.1	33.1	33.1	29.1
45-49	74.1	67.1	62.1	60.1	53.1	57.1	52.1		78.1	70.1	64.1	63.1	57.1	64.1	56.1		63.1	57.1	56.1	50.1	49.1	45.1	45.1	45.1
50-54	11.1	10.1	9.1	7.7	6.1	6.5	6.6		11.1	11.1	9.9	7.8	6.6	9.3	9.7		10.1	9.9	9.7	7.3	7.3	6.7	6.9	6.9
55-59	17.1	15.1	15.1	13.1	12.1	12.1	12.1		17.1	16.1	16.1	13.1	12.1	12.1	14.1		17.1	14.1	14.1	12.1	10.1	10.1	11.1	11.1
60-64	4.1	7.1	8.1	8.1	7.1	7.1	7.1		4.1	7.1	8.1	8.1	7.1	9.1	8.1		7.1	4.1	6.1	7.1	6.1	6.1	6.1	6.1
65-69	26.1	26.1	22.1	21.1	20.1	18.1	18.1		29.1	26.1	22.1	21.1	21.1	19.1	20.1		26.1	26.1	21.1	19.1	16.1	15.1	15.1	15.1
70-74	41.1	36.1	38.1	33.1	33.1	29.1	28.1		42.1	38.1	39.1	36.1	36.1	31.1	29.1		38.1	32.1	35.1	30.1	24.1	25.1	25.1	25.1
75-79	91.1	88.1	76.1	77.1	76.1	78.1	45.1		83.1	83.1	77.1	78.1	72.1	62.1	47.1		84.1	61.1	72.1	76.1	68.1	67.1	68.1	68.1
80-84	4.1	4.1	6.1	5.1	5.1	7.1	4.1		3.1	6.1	5.1	5.1	6.1	6.1	9.1		3.1	4.1	9.1	2.1	2.1	6.1	6.1	6.1
85+							64.1																	65.1
85+							11.1																	97.1
85+							19.1																	1.1
85+							39.1																	18.1
85+							8.1																	6.1
85+	9.8	9.0	8.4	7.3	7.1	7.0	6.4		10.1	9.7	9.1	8.1	7.6	7.5	6.9		7.1	6.2	6.3	6.0	5.7	5.6	5.6	5.4

**Table A1b. Age-specific mortality rate by sex and residence from 1991 to 2016
at interval of 5 years – male**

[illegible]

**Table A1c. Age-specific mortality rate by sex and residence from 1991 to 2016
at interval of 5 years – female**

[illegible]

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Chapter 292

LACTIC ACID BACTERIA AGAINST SPOILAGE AND PATHOGENIC MICROORGANISMS IN FOOD

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ABSTRACT

Advances in the microbiological safety of foods have been largely driven by public demand in response to disease outbreaks. A vast array of possibilities has emerged straightforward, being biopreservation the most suitable alternative to please consumers claims for healthier and “greener” foods. Biopreservation uses microorganisms, generally lactic acid bacteria (LAB) as protective cultures (PC). LAB can be added not only to prolong the shelf-life but also to preserve the microbial and/or sensorial quality of food products. The microbial antagonism of LAB against undesirable microorganisms has been attributed in many cases to the effect of one or synergism between several mechanisms, such as competition for nutrients, and production of different metabolites, including bacteriocins. Having GRAS status, LAB-PC can be safely added to foods. Advantages of PC include additive-free preservation, natural image, and food safety improvements. Hundreds of strains from many LAB species have been extensively studied for the preservation of foods showing promising results. The objective of this chapter is to describe current methods and developing technologies for the application of LAB-PC in food products throughout the world. The benefits of new technologies and

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their industrial limitations are also presented and discussed. Information given will provide an integrated approach on this topic.

INTRODUCTION

Food matrices are prone to microbial colonization due to their nutritional compounds. Some of these microbes are responsible for food spoilage, and some others are food-borne pathogens which can cause serious health problems once consumed (Varsha & Nampoothiri, 2016). Hence, it is necessary the implementation of adequate technologies to preserve and prolong the shelf-life of food products as well as the health of consumers. Moreover, there is a rising consumer demand for chemical preservative-free products, which results in a perfect opportunity for the implementation of natural additives with antibacterial and antifungal properties.

Among the new approaches, the so-called biopreservation stands out as a promising alternative, specifically the protective cultures (PC) incorporation into food matrices. Microorganisms that produce inhibitory substances, are able to compete against spoilage bacteria and fungi, and extend food shelf life, are consider as PC (Alexandraki et al., 2013; Fernández et al., 2017). The practice of PC inoculation into food matrices is the conception of the biopreservation approach.

Lactic acid bacteria (LAB) have been used traditionally as starter cultures in fermentation processes, being natural inhabitants of fermented food products. Besides, their implementation provides several technological advantages (Bourdichon et al., 2012). LAB incorporation also results in properties changes of the matrix that are non-beneficial for pathogenic and spoilage microorganisms. Furthermore, considering their GRAS (Generally Regarded as Safe) status (EFSA, 2011), LAB become a potential perfect group to be regarded as PC contributing to biopreservation (Divya et al., 2012 a,b).

Lactic acid is the main metabolic end-product from LAB, as a result of carbohydrates degradation. Its production causes a pH decrease, preventing undesirable microorganism proliferation. Lactic acid together with carbon dioxide, hydrogen peroxide, acetoin and other organic acids, all products from LAB metabolism, induce physicochemical changes on food matrices which create a disadvantageous environment for the development of spoilage and pathogenic fungi and bacteria (Deegan et al., 2006). Despite LAB metabolism products have been studied throughout, being their beneficial effects widely known, other LAB molecules have gained newly interest. Among them, bacteriocins are bioactive peptides ribosomally synthesized that have antimicrobial activity against other bacteria (Field, Ross & Hill, 2018). Bacteriocins are produced by many Gram-positive and Gram-negative species (Riley & Wertz, 2002). In spite of this, the ones produced by LAB are of particular interest to the food industry. LAB bacteriocins demonstrated antagonistic action against many food spoilage and pathogenic microbes, in consequence they are an important alternative to chemical additives, prolonging food shelf life, improving safety and preserving quality of food products (Gálvez et al., 2007; Field, Ross & Hill, 2018). Likewise, as mentioned before, many bacteriocinogenic LAB have GRAS status, which make them potentially applicable to food products being non-toxic to consumers and even enhancing health effects. Beside small metabolites, also peptides with antifungal activity have been reported as resulting from LAB

bioactivity. These antifungal peptides are not produced *de novo* by LAB; however, they are produced during proteolysis of proteins present in their surroundings (Siedler et al., 2019).

Table 1. Brief compilation of several LAB PC species, target microorganisms and food matrices comprised within the scope of bioprotective cultures.

LAB strain	Food product	Target microorganism	Reference
<i>Lb. curvatus</i> 54M16	Italian Fermented sausage	<i>L. monocytogenes</i> Spoilage microorganisms	Gilleo et al., 2018
<i>Lb. curvatus</i> <i>Lb. sakei</i>	Vacuum-packaged sliced raw beef	Spoilage microorganisms	Zhang et al., 2018b
<i>Lb. plantarum</i> subsp. <i>plantarum</i> CICC 6257	CO ₂ -MAP Ground Pork	<i>L. monocytogenes</i>	Zhang et al., 2018a
<i>Lb. plantarum</i> PSC20	Chorizo sausage	<i>L. monocytogenes</i>	Nikodinoska et al., 2019
<i>Lb. plantarum</i> EC52	Meat sausage	<i>L. monocytogenes</i> – <i>E. coli</i> O157: H7	Díaz –Ruiz et al., 2012
<i>Lb. plantarum</i> LMG P-26358 <i>Lc. lactis</i> CSK2775	Cheese	<i>L. innocua</i>	Mills et al., 2017
<i>Lb. plantarum</i> B2	Melon	<i>L. monocytogenes</i>	Russso et al., 2015
<i>Lb. plantarum</i> CUK-501	Cucumber	<i>Aspergillus flavus</i> , <i>Fusarium graminearum</i> , <i>Rhizopus stolonifer</i> and <i>Botrytis cinerea</i>	Sathe et al., 2007
<i>Lb. Plantarum</i> <i>Lc. lactis</i>	Sea bass	<i>Listeria</i> spp.	Boulares et al., 2016
<i>Lb. rhamnosus</i> GG	Fresh-cut pear	<i>Salmonella</i> and <i>L. monocytogenes</i>	Iglesias et al., 2018
<i>Lb. rhamnosus</i> 131RZFAUU	Domiat soft cheese	<i>St. aureus</i>	Ibrahim et al., 2017
<i>Lb. harbinensis</i> K.V9.3.1Np	Yogurt Fermented milk	<i>Yarrowia lipolytica</i> <i>Penicillium expansum</i> Spoilage fungi	Mieszin et al., 2017 Mosbah et al., 2018 Delavenne et al., 2013, 2015
<i>Lb. fermentum</i> R6	Chicken breast meat	<i>C. perfringens</i>	Li et al., 2017
<i>Lc. lactis</i> CBM21	Apple Lamb's lettuce	<i>L. monocytogenes</i> Yeasts Native microflora	Siroli et al., 2016 Siroli et al., 2017
<i>Lc. lactis</i> PSY 2	Reef cod	Total mesophilic, psychrophilic LAB, <i>Staphylococcus</i> sp., Enterobacteriaceae and <i>Pseudomonas</i> spp.	Sarika et al., 2012
<i>Lc. lactis</i> CH-HP15	Model ham liquid medium	Pathogenic or spoilage spore-forming species	Ramaroson et al., 2018
<i>Lc. piscium</i>	Shrimps	<i>Br. thermosphacta</i>	Fall et al., 2007
<i>Ec. lactis</i> 4CP3	Chicken breast	<i>L. monocytogenes</i>	Ben Braïek et al., 2019
<i>Ec. mundtii</i> CRL 35	Beaker sausage	<i>L. monocytogenes</i>	Orihuel et al., 2018
<i>Ec. faecium</i> DM224 and DM270	Whey cheese	<i>L. monocytogenes</i>	Aspri et al., 2016 (a, b), 2017
<i>Leuc. mesenteroides</i> CM135, CM160 and PM249	Golden Delicious apples and Iceberg lettuce	<i>L. monocytogenes</i>	Trias et al., 2008
<i>Carnobacterium</i> spp.	Ricotta	<i>Pseudomonas</i> spp.	Spanu et al., 2017, 2018
<i>Cb. maltaromaticum</i>	Filletts of surubim	<i>L. monocytogenes</i>	dos Reis et al., 2011
<i>Cb. maltaromaticum</i>	Lean beef	<i>Salmonella</i> spp.	Hu et al., 2019
<i>Ped. acidilactici</i> CRL 1753	Bread	Spoilage fungi	Bustos et al., 2018

The objective of this chapter is to describe current methods and developing technologies for the application of LAB-PC in food products throughout the world. The benefits of new technologies and their industrial limitations are also presented and discussed. Information given will provide an integrated approach on this topic. Table 1 is presented herein as a brief sample of the magnitude of the diversity of LAB species, target microorganisms and food matrices comprised within this biopreservation approach.

SCREENING METHODOLOGIES AND STRAIN SELECTION FOR FOOD BIOPRESERVATION

LAB bacteriocins play an important role in the future of food biopreservation. Their narrow killing spectrums and their antimicrobial mechanisms distinguish them from traditional antibiotics. These particular characteristics infer an alternative to fight against drug-resistant bacteria, preserving and prolonging food shelf-life and also decreasing antibiotics ingestion by the consumers, fulfilling consumer demands for more natural and chemical preservative-free products (Cavera et al., 2015; Kaskoniene et al., 2017; Zou et al., 2018).

Bacteriocin-producing LAB strains are isolated from diverse sources, but it is considered that those isolated from a certain matrix constitute the best candidates for biopreservation in that particular matrix, since they have better adaptability to the source environment than LAB isolated from other sources (Castro et al., 2011). In recent years bacteriocins have been discovered from various sources, particularly fermented food products (Castro et al., 2011; Abdel-Halim et al., 2013; Gao et al., 2015; Gautam & Sharma, 2015) but also fish (An et al., 2015), chicken intestines (Rani et al., 2016), soil (Smitha & Bhat, 2013; Lim and Balolong, 2016), human body and its excrement (Lakshminarayanan et al., 2013; Wannun et al., 2014; Maldonado-Barragán et al., 2016) and citrus (Noda et al., 2015), among others. However, in the USA and Canada, the only bacteriocins commercially available are pediocin, produced by *Pedococcus* (*Ped.*) *acidilactici*, Micocin®, a blend of three bacteriocins (carnocyclin A, carnobacteriocin BM1, and piscicolin 126) produced by *Carnobacterium* (*Cb.*) *maltaromaticum* UAL307, and nisin, produced by *Lactococcus* (*Lc.*) *lactis*. Considering these commercial bacteriocins, nisin is the only one approved by the FDA as a food preservative (Martin-Visscher et al., 2011; Huang et al., 2016; Zou et al., 2018).

Hence, as a result of the multiples sources in which bacteriocins can be found, the processes implied in their discovery are very complex and significant resources and time must be invested in the screening, identification, purification, and characterization stages (Kaskoniene et al., 2017). Then, it has become a necessity the development of novel and faster methods to search new bacteriocins as an alternative to the traditional slower and laborious ones.

Traditional screening methodologies for antagonistic activity of bacteriocins, like disc-diffusion, agar well diffusion and spot-on-lawn assays, uses strains in the exponential phase of *Escherichia* (*E.*) *coli*, *Staphylococcus* (*S.*) *aureus* or *Listeria* (*L.*) *monocytogenes* as indicators to inoculate a soft agar culture media (Pingitore et al., 2007; Song et al., 2014a; Pasteris et al., 2014; Gao et al., 2015; An et al., 2015; Maldonado-Barragán et al., 2016). Samples are centrifuged to obtain free-cells supernatant possibly containing the bacteriocin if

the evaluated bacteria are bacteriocinogenic. With a plastic straw, wells are created on the inoculated soft agar media and they are filled with the supernatant or with a purified extract for the spot-on-the-lawn assay (Zou et al., 2018). After incubation, the presence of a clear zone around the wells is considered as a positive inhibitory effect, and its activity is related to the measure of the area of these inhibitory zones. Even though the positive results are easy to identify and discriminate from negative ones, these colonies based assays turn out to be time-consuming since the samples screened are often quite numerous.

One of the novel methods is the PCR array assay developed to identify the presence of genes that codify for bacteriocin production on LAB isolated from food samples. This screening methodology is based on the comparison with known bacteriocin-related genes from the NCBI GenBank database (Macwana & Muriana, 2012; Juturu & Wu, 2108). However, PCR-based methods require the design of primers for each bacteriocin-producing strain since different strains contain different gene sequences that codify for bacteriocin production (Zou et al., 2018). Therefore, PCR-based methods are user-friendlier but also time-consuming. Another new screening methodology is the multi-well plate protocol for bacteriocin detection and it is based on an *in vivo* screening platform that uses 96-well plates and fluorescence imaging analysis to identify bacteriocins from natural sources (Son et al., 2016). The simplicity, fastness, reliability and the high cost-effective ratio of this method are the main advantages against traditional ones.

Once the screening process is complete, the identification of bacteriocin-producing strains is the next step. Normally, the identification of bacteriocin-producing species and strains is based on physiological and biochemical features and 16S rDNA gene sequences (Barbosa et al., 2014; Zhu et al., 2014; Gao et al., 2015). Subsequently after the identification comes the most critical and complex step, purification. This process implies an intensive labor and it is also quite time wasting. Purification of bacteriocins is directly related with applications, purity and price of the end product. The methodology applied to purify bacteriocins depends on the features of each particular bacteriocin, so there is not a single method suitable for all of them and each applied technique has its advantages and disadvantages (Sabo et al., 2018; Zou et al., 2018; Juturu & Wu, 2108). Afterward the screening, identification and purification phases, the characterization of bacteriocins is the last step. There are novel methods, capillary electrophoresis-mass spectrometry designed by Catala-Clariana et al., (2010) for the identification of bioactive peptides in hypoallergenic infant milk formula and, the micellar electrokinetic chromatography, developed by Soliman & Donkor (2010) to quantify nisin on food products. These methods possess the advantage of being faster, more sensitive and efficient than traditional ones.

As mentioned before, the best candidates as biopreservatives on a given matrix are the strains isolated specifically from that matrix, although not always the bacteriocin-producing LAB discovered from a given source is applied on the same source. Hence, an additional and necessary step is to prove the strains on different model mediums, changing certain conditions to determinate the adaptability of the strains to the new environment and confirm the production of the bacteriocin on those conditions, the so-called selection phase.

Selection consists on examination of the strains that exhibited inhibitory activity on the screening stage, and determinate their survival in simulated conditions, such as starvation, presence of NaCl and bile salts, low pH and high temperatures (Matamoros et al., 2009). Another important aspect is to confirm the maintenance or improvement of the sensory, chemical and physical properties of the target matrix since LAB may have negative effects in

different types of food and contribute to food spoilage (Gram et al., 2002; Maragkoudakis et al., 2009). Then, innocuousness is also a factor to take into account, specifically no biogenic amine production and antibiotics resistance. As an example, in Wessels & Huss (1996) research work, some selected strains presented good efficiency in model medium but cannot be applied in seafood because their growth was inhibited by this low-sugar and low-temperature environment, and even could spoil the product.

Summarizing, there are many methods to select, identify, purify and characterize bacteriocin-producing LAB strains in search for the best candidates as biopreservatives. Even though there are no severe rules on the order of the steps to follow or the methodologies to implement, the chosen method must be in accordance to the future application together with the enhancement of food safety and quality.

LIMITATIONS AND FURTHER CONSIDERATIONS

Despite the fact that LAB can produce a variety of compounds with antimicrobial activity, the amounts of individual compounds produced by LAB are often insufficient to sustain the inhibitory phenotype, which is most likely to arise from synergistic or additive bioactivity of the blend of compounds. Thus, identification of new antimicrobial compounds is hampered by their occurrence in low amounts in complex matrices. Moreover, they may not exert inhibition *per se*, which hinders the identification by fractionation techniques. According to Siedler et al., (2019), new approaches are needed to identify and study these complex relationships. Furthermore, knowledge on the physiology of the spoilage organisms is required to understand the mechanisms behind the bioactive compounds.

The main drawback in LAB-PC application into food is the inherent antimicrobial activity loss due to interactions with ingredients and/or processing driven physicochemical instability. Peptide function can be affected by several factors, such as fat content, proteolytic degradation, polar or non-polar food components, pH (which influences the solubility of the bacteriocin) and sodium chloride concentrations, among others. To overcome these obstacles, many bacteriocins have undergone several bioengineering strategies to improve bacteriocin efficacy in the food environment. These strategies comprised a wide array of alternatives, from solubility enhancement (Rouse et al., 2012) to new bacteriocin biosynthetic gene clusters which could be used to guide the bioengineering of new and existing peptide structures (Song et al., 2014b; Sun et al., 2015). The driving force behind these scientific facts is that bioengineered strains which have been tailored through food-grade approaches are not considered genetically modified microorganisms (GMMs) and can be directly added to food (Field et al., 2018). To expand these concepts, the reader would find interesting the reviews from Field et al. (2015), and Ramu et al., (2015).

Among the emerging potential roles for bacteriocin-producing LAB, one of the most outstanding is in functional foods where they will be playing a health-promoting task beyond the biopreservative one. The use of multipurpose bacteria will enable to market food products with an over-the-counter formula that could provide, for instance, a positive modulation of the gastrointestinal (GI) microbiome. As an illustration, a study showed that the strain *Lactobacillus (Lb.) salivarius* UCC118 was able to modify the GI microbiota in diet-induced obese mice whereas its bacteriocin-free derivative did not exert this effect (Murphy et al.,

2013). Conversely, many LAB strains with proved probiotic activity, intended at a beginning to be used as health enhancers, are being under study in order to expand their utility to PC. *Lb. sakei* CRL 1862 comprises a good example of this fact, being a well-known antihypertensive biopeptide producer, it had been proved to control food pathogens (*L. monocytogenes*) colonization on food-industry surfaces (Pérez Ibarreche et al., 2014, 2016).

APPLICATIONS OF PROTECTIVE CULTURES IN MILK AND DAIRY PRODUCTS

Milk and dairy products owe their excellent growth medium conditions to their highly nutritious nature. As a matter of fact, microbial contamination of milk and dairy products is a worldwide problem. Currently, foodborne illnesses from consumption of dairy products have been mainly related to *Campylobacter* (C.) *jejuni*, *E. coli* 0157:H7, *L. monocytogenes*, *Salmonella* spp., *Yersinia* (Ye.) *enterocolitica*, and *Bacillus* (B.) *cereus*. Moulds, mainly species of *Aspergillus*, *Fusarium*, and *Penicillium*, can grow in milk and dairy products. Under the appropriate conditions, these moulds may produce mycotoxins which can be a health hazard. Contamination of raw milk comprises the main microbiological hazard associated with dairy products; pathogens like *S. aureus* may be part of the resident microflora of the living animal, whereas other pathogens such as *E. coli* 0157:H7 or *Salmonella* spp. may originate from faecal contamination during initial milk collection. Despite the many methods applied to control it, contamination post processing can also happen in every stage of the product shelf-life, such as transport, storage and handling. LAB occur naturally in foods and have a long history of safe use in dairy industry. Lack of health risk concerns make them the best candidates for biopreservation and a great alternative to the use of chemical preservatives in dairy products, where they can be introduced as part of the fermentation process or as adjuvant cultures. A number of applications of bacteriocin-producing LAB have been reported to successful control pathogens in milk, yogurt, and cheeses (Silva et al., 2018). Applying bacteriocin-producing LAB strains as antibacterial starter cultures and PC may confer an advantage over the use of semi-purified/purified bacteriocins as much as they are adsorbed into food matrices and are easily degraded, which results in a loss of antibacterial activity.

Anti-listerial activity of many LAB strains has been exploited to control *Listeria* growth in different ripened and fresh cheeses (Coelho et al., 2014; Ibrahim et al., 2017; Silva et al., 2018), while their ability to exert antifungal activity has been optimally used to preserve fermented milk, cheeses and yogurt (Mieszkina et al., 2017; Mosbah et al., 2018; Leyva Salas et al., 2018). Studies described herein have been selected from a vast amount of scientific reports taking into consideration their relatively novelty and groundbreaking practices.

Milk and dairy products are recognized as a good source for the isolation of bacteriocin-producing LAB. Accordingly, donkeys' milk has been a subject of research in recent years, even though its nutritional and therapeutic properties have been recognized since ancient times. Resembling human milk in many ways, donkey milk is recommended as a substitute for individuals presenting cows' milk protein allergy. Aspri et al., (2016 a, b; 2017) had isolated LAB from raw donkey milk and characterized the strains by phenotypical and molecular methods. Besides, they evaluated their technological properties and safety

characteristics as potential starter or adjunct cultures in the production of fermented dairy products. Based on these features, 79 strains were selected and analysed for inhibitory activity against spoilage bacteria and foodborne pathogens. Amongst them, 3 strains belonging to *Enterococcus* (*Ec.*) *faecium* displayed antimicrobial activity against *L. monocytogenes*, *S. aureus* and *B. cereus*. Bacteriocins produced by these strains were tested for their capability to control post-processing contamination and growth of *L. monocytogenes* during refrigerated storage of artificially contaminated fresh whey cheese; two of them (*Ec. faecium* DM 224 and 270) were bactericidal while one was bacteriostatic (*Ec. faecium* DM 33). These strains were tested in a food model and showed a good performance within the cheese matrix, thus they have a promising perspective for biopreservation.

Cheese is considered to be one of the foods most frequently contaminated with *L. monocytogenes* (Aspri et al., 2017). In particular, blue-veined and mould cheeses such as Brie, Camembert, Danish Blue, Stilton and Gorgonzola represent a suitable substrate for the growth of this pathogen (Ramaswamy et al., 2007). The famous Italian PDO Gorgonzola cheese is made using pasteurized cow's milk inoculated with thermophilic cultures (*Streptococcus thermophilus* and *Lb. delbrueckii*), yeasts and, finally, *Penicillium* spp. which confers the typical blue-green veined. Albeit different physical treatments had been studied to control *Listeria* in Gorgonzola rinds, irregular and rough surfaces hampered treatment efficacy and imparted visible changes in the aspect of the rinds. As a consequence, the use of LAB-PC resulted in a promising alternative to limit the growth of *L. monocytogenes* and *L. innocua* on Gorgonzola surface during ripening process (Morandi et al., 2019). The anti-*Listeria* activity differed among the LAB strains and it was *Listeria* biotype-dependent. Amongst 27 strains, *Carnobacterium* SCA, SCB, *Lb. plantarum* NA18, *Lb. sakei* SCC, *Lc. lactis* FT27, N16 and SV77 were selected for their marked anti-*Listeria* activity. When *Listeria* was inoculated on the cheese surface at the end of ripening process (after 50 days; pH: 6.7), only *Lc. lactis* FT27 exerted a significant inhibition on the growth of the two *Listeria* species if the cheese was strictly maintained at 4°C. Hence, this research highlighted that the susceptibility of *Listeria* biotypes to LAB antimicrobial activity is strain-dependent, thus a blend of different LAB strains could represent an effective tool to develop PC for blue-veined cheeses. Seemingly, Mills et al., (2017) proposed a multi-strain approach to tackle this problem. They generated single- and double-bacteriocin-producing cultures of *Lc. lactis* CSK2775 with the capacity to produce the class I bacteriocins lacticin 3147 (lacticin), nisin A (nisin), or lacticin and nisin. This multi-bacteriocin producer was used in combination with plantaricin from *Lb. plantarum* LMG P-26358 to create a cheese starter system.

When PC are meant to be incorporated into a cheese making process, one of the main aspects to be aware of is their contribution to the sensory profile of the final product. The application of new strains to the cheese making process requires a positive sensory acceptance by the consumers. Consequently, regardless of the antimicrobial efficiency of the culture, the generation of volatile compounds (possibly off-odors), and/or high acidification (potential off-flavors) have to be checked and control throughout the cheese manufacture and ripening. In a study by Coelho et al., (2014), 8 bacteriocin producer strains identified as *Lc. lactis* (1) and *Ec. faecalis* (7) were assessed in order to identify those with the greatest potential in reducing *L. monocytogenes* in fresh cheese. A non-trained panel evaluated the attributes acidity, salty taste, firmness, flavor and general acceptability of cheeses made with the bacteriocin-producer strains. All cheeses made with LAB cultures were found to have flavor, salty taste and general acceptability comparable to the control cheese made without

any PC, i.e., no significant differences from control cheeses were found among the sensory attributes tested. According to Pereira et al., (2011), microorganisms inoculated in cheeses made with cows' milk do not exert any influence on the flavor of the cheese in the early days of ripening, which confirms the results obtained in the aforementioned study since LAB-PC were intended to be applied to fresh cheeses with short ripening periods. Regarding bacteriocin activity, its availability comprised the determining factor for an *in situ* antibacterial action. Hence, bacteriocin-like activity should be produced at sufficient levels and be active enough during cheese manufacture and storage. Results derived from this study showed that *in situ* bacteriocin producers clearly showed a high antilisterial activity in fresh cheese made with the *Enterococcus* strains. The *Lc. lactis* strain tested produced lacticin 481, which proved to be less effective in reducing *L. monocytogenes* (Coelho et al., 2014). In accordance to the latter study aims, *Lb. rhamnosus* 131RZFAUU was tested in Domiati soft cheese as a PC against *S. aureus* without affecting flavor acceptability of final product. This LAB-PC was selected among three potential candidates which were analyzed separately and all together. Interestingly, no negative sensory properties were observed by the panelists in fresh cheeses made with LAB strains as a single culture. Conversely, unacceptable flavor was observed in Domiati cheese made with a combination of three strains (Ibrahim et al., 2017).

Ricotta fresca is a whey cheese susceptible of secondary contamination mainly due to its naturally poor competitive microflora and composition, inherent physical and chemical properties and the absence of preservatives. *Pseudomonas* spp, yeasts, molds and *Enterobacteriaceae* comprise the main psychotropic microorganisms usually found in refrigerated whey cheeses (Pala et al., 2016). The use of biopreservatives against these psychotropic spoilage microorganisms was preliminary assessed by Spanu et al., (2017, 2018) on the surface of MAP *ricotta fresca* during refrigerated storage. A commercial biopreservative, Lyofast CNBAL, comprising *Carnobacterium* spp. was tested against *Pseudomonas* spp. This was the first successful attempt to use biopreservatives against psychotropic spoilage microorganism in sheep ricotta cheese.

Selected LAB strains (as in fermentation) or the bioactive compounds purified from the culture medium can be exploited as efficient alternatives for food preservation. Eleven antifungal *Lactobacillus* strains, isolated from cow and goat milk, were fully characterized by Delavenne et al., (2013) using molecular and phenotypic methods. Their antifungal activities were tested in milk and yogurt, against fungal species (*Debaryomyces hansenii*, *Kluyveromyces lactis*, *K. marxianus*, *Penicillium brevicompactum*, *Rhodotorula mucilaginosa* and *Yarrowia* (Y.) *lipolytica*) commonly involved in the spoilage of dairy products. The antifungal strains belonged to *Lb. paracasei*, *Lb. rhamnosus*, *Lb. zeae* and *Lb. harbinensis* species and showed different acidifying and growth capacities in milk. The antifungal activity in milk developed by lactobacilli had a strain-dependent activity spectrum. A very strong antifungal effect in yogurt was displayed by *Lb. harbinensis* against all tested fungi as compared to control. Accordingly, the strain *Lb. harbinensis* K.V9.3.1Np showed a remarkable antifungal activity for the bioprotection of fermented milk without modifying their organoleptic properties (Delavenne et al., 2015). In keeping with these findings, Mieszin et al., (2017) studied the action mechanism of this bioprotective strain against the spoilage yeast *Y. lipolytica*. The tested supernatants were obtained after milk fermentation with yogurt starter cultures either in co-culture with *L. harbinensis* K.V9.3.1Np (active supernatant) or not (control supernatant). Morphological changes (membrane collapsing and cell lysis) were observed in the target yeast. The authors attributed these effects to the synergistic action of

organic acids since 5 of the 8 organic acids quantified in the active supernatant (acetic, lactic, 2-pyrrolidone-5-carboxylic, hexanoic and 2-hydroxybenzoic acids) were at significantly higher concentrations than in the control one. These physiological mechanisms induced by an antifungal LAB could be used as part of the hurdle technology to prevent fungal spoilage in dairy products. On the other hand, Mosbah et al., (2018) studied the antifungal molecules produced by *Lb. harbinensis* K.V9.3.1Np when used in yogurt fermentation. Activity tests against *Penicillium* (*Pe.*) *expansum* and *Y. lipolytica* showed that the active compounds from this LAB-PC were benzoic acid and a polyamine identified as a spermine analog, which had not been reported earlier. Nevertheless, the highest activity was shown by a mixture of short polycyclic lactates.

Leyva Salas et al., (2017) found that, for a same antifungal LAB culture, a variable antifungal activity occurred between different semi-hard cheeses, suggesting a role of biotic and abiotic factors resulting from interactions between the food, the antifungal cultures and the fungal contaminants. The potential influencing factors could be the dry matter content in cheeses, ripening chamber humidity, interactions between the smear and the fungi, and non-sterility of the ripening chambers.

APPLICATIONS OF PROTECTIVE CULTURES IN MEAT PRODUCTS

Meat and meat products are perishable foods and they should be properly handled along the productive chain in order to prevent microbial growth. If spoilage microorganisms such as *Pseudomonas*, *Acinetobacter*, *Brochothrix thermosphacta*, *Moraxella*, *Enterobacter*, *Lactobacillus*, *Leuconostoc*, and *Proteus* are present and highly proliferated, the meat will spoil and will be unfit for human consumption (Jayasena & Jo, 2013). Additionally, pathogenic bacteria such as *Salmonella* spp., thermophilic *C. jejuni*, enterohemorrhagic *E. coli* O157:H7, *Clostridium* (*Cl.*) *perfringens*, anaerobic *Cl. botulinum*, *L. monocytogenes*, *S. aureus*, *B. cereus*, and *Ye. enterocolitica*, can be present in meat and meat products turning them hazardous for consumers (Hui, 2012). Therefore, assurance of meat safety and quality is of utmost importance. In this sense, LAB have been used as PC alone or in combination with several physicochemical treatments, modified atmosphere packaging (MAP), high hydrostatic pressure (HHP), and chemical preservatives, as an additional hurdle to control the proliferation of spoilage and pathogens microorganisms in meat and meat products. An endless variety of studies regarding LAB-PC application against target microorganisms on several meat products can be profoundly found in the literature (Castro et al., 2016, Castellano et al., 2017, Oliveira et al., 2018). Nevertheless, in this section the studies have been compiled with the selection criteria of up-to-date alternatives for meat biopreservation.

Several LAB species, including *Lactobacillus*, *Lactococcus*, *Pediococcus* and *Enterococcus* spp., have been evaluated to enhance microbial safety of meat and meat products due to their ability to produce bacteriocins active against *L. monocytogenes* (Oliveira et al., 2018, Woraprayote et al., 2016). As demonstrated by Giello et al., (2018), the use of the bacteriocin-producing *Lb. curvatus* 54M16 in fermented sausages could be an important contribution to improve the quality of final product. This strain produced several bacteriocins: sak X, sak T α , sak T β and sak P which are active against *L. monocytogenes*. The anti-listerial effect during the manufacture of fermented sausages naturally contaminated and co-

inoculated with a mixture of *L. monocytogenes* OH and Scott A (10^4 CFU/g) was investigated. Although this LAB-PC was partially effective in the control system against *L. monocytogenes* OH and Scott A, it was able to inhibit native *L. monocytogenes* over the course of the fermentation. Besides, *Lb. curvatus* 54M16 dominated and affected the bacterial ecosystem as it was determined by 16S rRNA-based analysis. It could be assumed that inoculated samples with PC helped on the dominance of *Lactobacillus* since un-inoculated sausages showed more diverse microbiota in which spoilage-associated bacteria, such as *Brochothrix*, *Psychrobacter*, *Pseudomonas* and some *Enterobacteriaceae*, were metabolically active until the end of the ripening.

Application of CO₂ modified atmosphere packaging in combination with antagonistic strain *Lb. plantarum* subsp. *plantarum* CICC 6257 as PC resulted in an effective strategy for enhancing microbiological safety of ground pork (Zhang et al., 2018a). The solely use of *Lb. plantarum* CICC 6257 had no significant effect on the lag-phase (λ) of *L. monocytogenes*, whereas its combination with CO₂ – MAP prolonged the λ and reduced the maximum specific growth rate ($\mu_{\max}$) and $N_{\max}$ of the pathogen in meat. The selected optimal treatment was the combined effect between *Lb. plantarum* CICC 6257 and 60% CO₂, by means of which the λ of *L. monocytogenes* increased from 3.43h to 8.33h, and the $N_{\max}$ and $\mu_{\max}$ were decreased by 46% and 66%, respectively.

Even though *Enterococcus* spp. are able to produce bacteriocins with strong anti-listerial activity (Khan et al., 2010; Gaaloul et al., 2015), safety aspects should be carefully assessed before their use as PC in meat and meat products since enterococci are known to be opportunistic pathogens causing several nosocomial infections (Rehaïem et al., 2014). In this sense, Ben Braïek et al., (2017, 2018) confirmed the innocuity of two *Ec. lactis* strains named Q1 (producer of enterocin P) and 4CP3 (producer of the enterocins A, B and P) to determine the effect of separate addition of these two strains in the control of *L. monocytogenes* in refrigerated chicken breast meat. These meat models were artificially contaminated with 10^5 CFU/g of *L. monocytogenes* and inoculated with each of the enterocin-producing *Ec. lactis* strains at a concentration of 10^7 CFU/g. In the presence of *Ec. lactis* Q1, viable populations of *L. monocytogenes* were reduced to 1.90 log CFU/g after 14 days, and then remained constant up to the end of the challenge experiment. While the addition of *Ec. lactis* 4CP3 caused a significant decrease of *Listeria* counts below the detection limit after 7 days and totally inhibited pathogen growth after 14 days of refrigerated storage (Ben Braïek et al., 2019). On the other hand, *Ec. mundtii* CRL 35 was found a promising strain to be used as a safe adjunct culture in sausage fermentation (Orihuel et al., 2018). This strain produces Enterocin CRL35, a pediocin like bacteriocin with anti-listerial and anti-viral activity (Salvucci et al., 2010; Wachsman et al., 2003). The effect of this PC on *L. monocytogenes* growth was evaluated in a meat model (beaker sausage) in the presence or absence of curing additives (NaCl, NaNO₂ and ascorbic acid). *L. monocytogenes* inhibition was enhanced when beaker sausage was supplemented with the curing mixture reaching a decrease greater than 2 log CFU/g. These results demonstrate that *Ec. mundtii* CRL 35 could be an efficient PC able to enhance hygienic quality of fermented sausages.

The effect of PC on other pathogenic microorganisms associated to meat and meat products has been also informed. *Cl. perfringens* strains have been implicated in outbreaks of food poisoning, particularly of meat and meat products (Grass et al., 2013). *Cl. perfringens* and its spores are supposed to grow or germinate under temperature abuse conditions, which commonly occur during the transportation, storage, or retail display of the meat chill chain. In

order to present a viable alternative for the control of *Cl. perfringens* on chicken breast meat, Li et al., (2017) investigated the effects of five LAB strains on *Cl. perfringens* growth, germination, and outgrowth of its spores under temperature abuse conditions. Among strain tested, *Lb. fermentum* R6 and *P. pentosaceus* P1, effectively inhibited the growth of vegetative cells and repressed germination and outgrowth of *Cl. perfringens* spores. However, the growth of *P. pentosaceus* P1 caused a deep decrease in pH values to 5.3 which made it not suitable as PC for this food matrix.

Ramaroson et al., (2018) selected LAB strains to be used as PC in cooked ham based on their antagonistic activity against pathogenic or spoilage spore-forming species as *B. cereus*, *Clostridium* sp. like *botulinum*, *Cl. frigidicarnis*, and *Cl. algidicarnis* and. Besides, the authors tested LAB-PC ability to resist High Pressure Processing (HPP). According to the results in model ham liquid medium, one *Lc. lactis* strain was selected because of its widest inhibitory spectrum, potential production of bacteriocin and ability to regrow following HPP. This PC could bring the opportunity of combining biopreservation and HPP to control spore-forming pathogens in cooked ham.

On the other hand, the combination of PC and chemical additives represents an alternative for the control of contaminants in meat environments, mainly enteric pathogens. Regarding this, Casquete et al., (2016) reported the efficacy of chitosan in combination with *P. acidilactici* bacteriocinogenic and non-bacteriocinogenic strains, in the control of *L. innocua*, *S. aureus*, *E. coli* and *Salmonella* Typhimurium in the fermented paste meat product Alheira (Portugal). Similarly, Hu et al., (2019) demonstrated that the combined use of chitosan and a bacteriocin-producing *Cb. maltaromaticum* strain reduced cell counts of *Salmonella* in lean beef.

The use of LAB as PC to inhibit growth of spoilage bacteria has been suggested by many authors (Hu et al., 2008; Jones et al., 2009; Biscola et al., 2014), and it is being considered as a strategy to improve the shelf life of meat and meat products. For instance, Zhang et al., (2018b) studied the bacterial diversity of vacuum-packaged sliced raw beef inoculated with the commercial cultures Bactoform B-2 (*Lb. sakei*) and SafePro B-LC-48 (*Lb. curvatus*) as PC by means of polymerase chain reaction-denaturing gradient gel electrophoresis (PCR-DGGE). The DGGE profiles of DNA extracted from non-inoculated samples showed that *Enterobacteriaceae* and *Pseudomonas fragi* emerged early, then *Brochothrix thermosphacta* shared the dominant position, and finally, *Ps. putida* showed up to become predominant. The addition of either *Lb. sakei* or *Lb. curvatus* reduced the complexity of microbial diversity and inhibited the growth of spoilage bacteria with *Lb. sakei* exerting greater inhibitory effect. In other study, Comi et al., (2016) examined the use of the strains *Lb. sakei* (B-2 Safe Pro® e CHR HANSEN) and *Lc. lactis* subsp. *lactis* (Rubis e CHR HANSEN) as PC to reduce the risk of *Leuconostoc* (*Leuc*) *mesenteroides* spoilage in artisanal cooked bacon. LAB strains were inoculated on pieces of bacon together with a mix of three different *Leuc. mesenteroides* strains isolated from spoiled cooked bacon and responsible for the greening color and spoilage. After 90 days of storage, sticky-white slime and a greening color were observed in the cooked bacon inoculated only with *Leuc. mesenteroides*. While cooked bacon with PC did not present greening, slime or inflated packaging. At this stage of the storage, the ratios *Leuc. mesenteroides*/*Lc. lactis* subsp. *lactis* and *Leuc. mesenteroides*/*Lb. sakei* were about 1/100 and 1/1000, respectively. Based on these results, the authors assumed that substrate competition by PC was responsible for *Leuc. mesenteroides* growth inhibition, thus suppressing its spoilage effects. Moreover, the acceptability of the bacon added with PC was

confirmed with sensorial analysis. These results illustrate the benefits of inoculation with LAB, especially *Lb. sakei* as a potential way to inhibit growth of spoilage microorganisms and to prolong the shelf life of meat and meat products.

APPLICATIONS OF PROTECTIVE CULTURES IN FRESH SEAFOOD AND SEAFOOD PRODUCTS

Fish is a very delicate product since its shelf life is remarkably short due to autolytic reactions and microbial proliferation. Autolytic reactions involve the action of proteases that generate an increase of free amino acids and free volatile bases (Huss, 1995), which allow microbial growth to be faster than in other types of meat. Main deteriorative strains present in fish include Gram negative microorganisms such as *Shewanella* sp., *Aeromonas* sp., *Pseudomonas* sp., *Photobacterium* sp., Enterobacteriaceae and some Gram positive bacteria such as LAB, including *Carnobacterium* sp., and *Lactobacillus* sp. (Cifuentes Bachmann & Leroy, 2015). Main pathogenic bacteria responsible for fish poisoning are *Aeromonas hydrophila*, *Cl. botulinum*, pathogenic *Vibrio* spp. and *L. monocytogenes* (Løvda, 2015). Additionally, fatty fish lipid composition is characterized for a high proportion of polyunsaturated fatty acids, which are highly oxidable, and thus, nutritional value is lost at very fast rates. Furthermore, after fish is captured in coastal areas, it is firstly stored at fishing boats, and then distributed to non-coastal areas, so a long period of time passes before fish products reach consumers (Wiernasz et al., 2017). All these characteristics make fish an important vector for food-borne diseases, yielding between a 10% and a 20% of total food borne diseases worldly (Pilet & Leloir, 2011).

In the last years LAB have been widely studied to be used on fish preservation. Even though their main action is usually against Gram positive microorganisms, -as an extra hurdle, they contributed to control native fish flora and specifically to control *L. monocytogenes* growth. Additional hurdles in fish preservation include modified atmosphere package, vacuum package, addition of essential oils, plant extracts, refrigeration, addition of active films, marinade and diminishment of water activity (Boulares et al., 2016; Concha-Meyer et al., , 2010; López de Lacey, López-Caballero, & Montero, 2013; Sarika et al., 2012).

LAB have been added to fish products in different manners: as PC, as bacteriocins purified or semi purified, and either LAB or bacteriocins immobilized in different films or coatings. Regarding the application as protective culture, LAB may produce bacteriocins *in situ* and compete with native fish bacteria, generating a bacteriostatic effect as well as a bactericidal one. Limitations to these applications may include the generation of off flavors (Saraoui et al., 2017) and the difficulty of LAB to grow and produce bacteriocins *in situ*. To partially overcome LAB *in situ* lack of activity, antagonist activity may be tested in fish juice (Wiernasz et al., 2017), to get a more accurate prediction of LAB activity when applied to fish products. When purified or semi-purified bacteriocins are applied directly to fish, issues related to cell viability are bypassed, but it is necessary to foresee a bacteriocin concentration capable to maintain a threshold concentration at which native flora would stay inhibited, since bacteriocin concentration may be affected by lytic action of proteolytic bacteria (Giribaldi et al., 2018). Finally, when immobilizing bacteriocins, their structure may be protected, and

their release modulated (Settier-Ramírez et al., 2018). When LAB are immobilized, they may be released in a controlled manner to food, thus preventing them from overgrowing and acidifying. Anyhow, immobilization must ensure cell viability and bacteriocin bonding in a manner that would not affect their antagonist action.

Comparing some of the aforementioned preservation techniques, Gómez-Sala et al., (2016) evaluated the use of *Lb. curvatus* BCS35 and *Ec. faecium* BNM58 on young hake and megrim, both applied as PC, liquid food ingredient or lyophilized food ingredient. In this case, when strains were used as PC the best results were achieved: coliform population was diminished throughout 14 days of storage, as well as the total mesophilic count, and fish appearance was improved, compared to control system. Boulares et al., (2016), added *Lb. plantarum* and *Cb. piscicola* and *Lc. lactis* as PC to sea bass, and found an improvement on fatty acid composition, and protein profile, indicating that the use of both LAB could control both proteolytic and lipolytic activities of deteriorative native bacteria. Their study also showed that the best combinations to control the growth of *Listeria* spp. population were mixtures of *Lc. lactis*-*Lb. plantarum* and *Lc. lactis*-*Cb. piscicola*, and a mixture of *Lb. plantarum*-*Cb. piscicola*, which was the best to control total basic volatile nitrogen and trimethylamine. Co-cultures had also been capable of diminishing undesired off-flavors generated by very active bacteriocinogenic strains, which by itself could not be applied to fish products. Such is the example of a co-culture of *Lc. piscium* and *Cb. divergens* since the addition of *Lc. piscium* inhibited the production of off flavors produced by *Cb. divergens* in shrimp preservation, extending their shelf life for 10 extra days in comparison to shrimps only inoculated with *Cb. divergens* (Saraoui et al., 2016). From these studies it may be concluded that the use of LAB strains may control different aspects of fish deterioration, and that there is a strong dependence on strain mixture.

The application of LAB cell free supernatant (CFS), purified or semi purified bacteriocins has also been assessed on fish preservation. The most used purified bacteriocin has been nisin in combination with extra hurdles. Novel applications of nisin include the addition of the bacteriocin in alginate films. Concha-Meyer et al., (2010), applied nisin together with two different LAB strains of *Cb. maltaromaticum*, to prolong shelf life of smoked salmon, and analyzed the anti-*Listeria* effect on samples. Systems containing nisin alone, or together with both LAB strains, showed a bacteriostatic effect on *L. monocytogenes*; in addition, in systems inoculated with both LAB, there was a decrease of the pathogens on day 28, due to the release of the bacteriocinogenic strains into the salmon filets. Lu et al., (2009), managed to increase the shelf life of northern sea snake filets by adding nisin together with EDTA, mixed or not on a calcium alginate film. Their results showed that the coating did not improve overall quality indicators (total mesophilic and psychrophilic bacterial counts, TBV-N, TMA-N, pH, or TBA) compared to samples only sprayed with the antimicrobials. Still, all treated samples showed values below maximum allowed for fish products throughout the storage, indicating that the mixture of nisin and EDTA had a positive effect on fish shelf-life. Nevertheless, sensory characteristics were improved by the application of the preservatives together with the alginate coating. These results showed that coatings are a promising technique to use on fish preservation, but factors such as release speed of antimicrobials (related to calcium-alginate concentration) should be further studied (Fang & Tsai, 2003).

Biopreservation of fish, has also been used together with other naturally occurring additives such as plant extracts, since they have been informed to have antagonist activity

against Gram negative microorganisms (Djeussi et al., 2013), and their richness in polyphenols and components with antioxidant activity may favor fish preservation. López de Lacey, López-Caballero, & Montero (2013) used a bioactive film prepared with agar in addition with green tea and *Lb. paracasei* L26 and *Bifidobacterium lactis* B94, obtaining a shelf life extension of hake fillets for 7 extra days (14 days in total). This study also showed that the probiotic strains could migrate from the film to the fillets increasing their population. It is important to highlight that the green tea extract did not affect the viability of inoculated bacteria, but diminished the presence of native LAB on samples. Dos Reis et al., (2011) investigated the synergic action of two different strains of *Cb. maltaromaticum* cultures and hydroalcoholic extract of *Lippia sidoides* (LSE) on fish food models: surubim fish peptone broth and surubim homogenate. In this case, *Cb. maltaromaticum* by itself did not control the growth of *L. monocytogenes*, neither did the LSE, but a synergic activity of both antimicrobial factors was found, and the pathogen population was controlled for 28 days on fish homogenate.

LAB can be used as an extra hurdle together with other preservation techniques which require LAB to grow under refrigeration, without the presence of oxygen as well as under low water activity conditions. Giribaldi et al., (2018) obtained an improvement on swordfish fillets fatty acid profile, for 60 days, on ready to eat fillets treated with marinade water solution containing 3% NaCl for 2 days together with an immersion on a probiotic culture of *Lb. paracasei* IMPC 2.1. Tomé, Gibbs, & Teixeira (2007) used another preservation technique (dry salted for 6 hours; drying for 6 hours; smoking for 2 hours), and compared the biopreservation capacity of 5 LAB (*Enterococcus faecium* ET05, *Lb. curvatus* ET06, *Lb. curvatus* ET30, *Lb. delbrueckii* ET32 and *Ped. acidilactici* ET34) on salmon. After 21 days of storage at 5°C, the growth of *L. innocua* 2030c was best controlled by the strain *E. faecium* ET05, achieving a reduction of 5 log UFC at the end of storage in comparison to control samples.

PROTECTIVE CULTURES IN THE BIOPRESERVATION OF FRUITS, VEGETABLES AND MISCELLANEOUS FOOD PRODUCTS

Fruits and Vegetables

Fruits and vegetables are highly perishable foods. Their deterioration is the result of biochemical changes, physiological ageing and microbial spoilage. Most of the bacteria causing the spoilage of fruits and vegetables are Gram-negative and belong to the genera *Pseudomonas* and *Enterobacteriaceae*. Within the present Gram-positive bacteria, it is usual to detect LAB. Regarding pathogenic microorganisms, fruits and vegetables may harbor *L. monocytogenes*, *Salmonella* spp. and *Escherichia coli* O157:H7. Finally, fungi and yeasts could also be found, which cause the deterioration of these foods although to a minor proportion than bacteria (Rico et al., 2007; Oliveira et al., 2015).

Taking into account the risks to consumer health and the economic losses that microorganisms' proliferation in fruits and vegetables may cause, the application of some preserving methods is necessary. However, in this type of food it is extremely important to maintain its condition of "fresh" or "minimally processed," being inconvenient to use severe

methodologies. In this context, the combination of various emerging preservation technologies is presented as a possible solution. Among them, the use of PC or the bacteriocins produced by them is outstanding. While the biopreservation of fruits and vegetables has not been studied as well as the biopreservation of other types of foods, there are numerous reports regarding its effect on these matrices and some of them are summarized in Table 1.

Regarding minimally processed fruits, a large amount of investigations has focused on isolating native LAB showing inhibitory activity against the deteriorative or pathogenic microorganisms usually found in these products. For example, Siroli et al., (2015) isolated native LAB from sliced apples and reported that, among the isolates with inhibitory activity against *L. monocytogenes*, *Salmonella enteritidis* E5 and *E. coli* 555, the strains identified as *Lb. plantarum* CIT3 and *Lb. paracasei* M3B6 were the most notable. The latter significantly decreased the population of *L. monocytogenes* and *E. coli* in minimally processed apples. In addition, when *Lb. plantarum* CIT3 was combined with natural antimicrobials the observed effect was greater. In a similarly targeted study, Siroli et al., (2016) evaluated the application of *Lc. lactis* CBM21, alone or in combination with natural antimicrobials, as PC in sliced apples. The authors reported that the use of *Lc. lactis* limited the growth of yeast and inhibited the development of *L. monocytogenes*. The effectiveness of the PC in controlling the growth of *L. monocytogenes* was attributed to the ability of the former to produce nisin. It should be noted that the inhibitory effect was greater when the PC was combined with natural antimicrobials.

Probiotic fortification has been extensively studied to produce foods with functional properties. Regularly, dairy products are more prone to be labelled as functional foods; however, probiotic fruits and vegetables could provide a good alternative for vegetarian or vegan consumers. In addition to beneficial effects on the health of consumers, some probiotic microorganisms can act as PC. Russo et al., (2015) studied the capability of *Lb. plantarum* B2 and *Lb. fermentum* PBCC11.5 to control the growth of *L. monocytogenes* in refrigerated melon and found that the 2 PC showed antagonistic activity against the pathogen. Furthermore, Iglesias et al., (2018) reported that the probiotic *Lb. rhamnosus* GG inhibited the growth of *L. monocytogenes* on fresh-cut pear but did not show antagonistic action against *Salmonella*.

In products derived from fruits, such as juices, the application of PC has not been widely studied. However, the application of bacteriocins has proved to be very effective. *Alicyclobacillus acidoterrestris* is a spoilage-causing bacterium in fruit juices. The addition of different bacteriocins, for example enterocin AS-48, nisin or bificin C6165, produced the inhibition of this microorganism and in some cases inactivated its endospores (Grande et al., 2005; Walker & Phillips, 2008; Pei et al., 2014).

The use of native flora to control microbial growth was also studied in vegetables. Siroli et al., (2015) isolated LAB from lamb lettuce and selected *Lb. plantarum* V7B3 and *Lb. casei* V4B4 as potential biocontrol agents for minimal processed lamb lettuce. Both PC were able to inhibit the growth of *L. monocytogenes* and *E. coli*, and also reduced the population of aerobic mesophilic microorganisms. Seemingly to the aforementioned application on apples, the combination of the PC with natural antimicrobials improved the biopreservation results. In another study using the same raw matrix, Siroli et al., (2017) compared the effectiveness of different washing solutions for lettuce. For this purpose, the samples were washed with: i) chlorine 120 mg/L, ii) thyme essential oil 250 mg/L, iii) *Lc. lactis* CBM21 10^6 CFU/ml, iv)

thyme essential oil and *Lc. lactis* CBM21. The results showed no differences between the populations of microorganisms in the different systems. In addition, the sensory characteristics of the samples washed with thyme essential oil and *Lc. lactis* CBM21 were superior.

Moreover, Trias et al., (2008) studied the effect of 3 strains of *Leuc. mesenteriodes* (CM135, CM160 and PM249), previously isolated from fresh fruits and vegetables, on the development of *L. monocytogenes* in Iceberg lettuce. Before being applied to vegetables, the 3 strains were characterized and it was found that 2 of them (CM135 and CM160) produced bacteriocins with antagonistic activity against *L. monocytogenes* and against other LAB. When inoculating the lettuce with 10^9 CFU/g of *Leuc. mesenteriodes*, no development of *L. monocytogenes* was detected. However, as the concentration of PC decreased, the inhibitory effect also declined. The application of these 3 strains to fresh fruits and vegetables did not cause sensory changes.

As mentioned above, the deterioration of vegetables may be a consequence of the development of fungi and yeasts. In this context, Sathe et al., (2007) isolated LAB from different vegetables and studied their antifungal activity. Among the isolated strains, *Lb. plantarum* CUK-501 showed antifungal activity against all the indicators studied *in vitro*. For *in vivo* studies, *Lb. plantarum* was inoculated into cucumber. Results showed that *Aspergillus flavus*, *Fusarium graminearum*, *Rhizopus stolonifer* and *Botrytis cinerea* growths were delayed. Similar results were found when the PC was replaced by the CFS.

As well as fruit juices, the use of PC has not been studied in canned vegetables. However, studies were carried out applying bacteriocins. Lucas et al., (2006) studied the antimicrobial activity of the enterocin AS-48 against *B. coagulans* in canned vegetables. After 24 hours of storage at different temperatures, the enterocin AS-48 reduced *B. coagulans* population, and after 15 days of storage, no viable cells were detected. In addition, the enterocin AS-48 increased the thermal sensitivity of *B. coagulans* spores.

Finally, lactic acid fermentation of vegetables should not be omitted. This technology has historically been used in many cultures as an effective method of food preparation and preservation. Lactic acid fermentation is a simple and valuable biotechnological tool to maintain and/or improve the safety, nutritional, sensory and preservation properties of fruits and vegetables (Di Cagno et al., 2013). In general, the starters cultures are selected because of their technological potential, such as the production of acid or exopolysaccharides. However, their antimicrobial activity should not be ignored (Settanni & Corsetti, 2008). For example, Di Cagno (2008) isolated autochthonous microorganisms (*Ln. mesenteroides* C1, *Lb. plantarum* M1 and *Ped. pentosaceus* C4) from carrots, French beans and marrows, and applied them as fermentation starters for the same vegetables. In addition to the good sensory characteristics, the authors found that the starters were able to inhibit the growth of *Enterobacteriaceae* and yeasts.

Considering the topics discussed, it can be concluded that the use of PC and bacteriocins plays a determining role in the control of deteriorative and pathogenic flora of fruits and vegetables. However, in both cases, they should always be applied within the context of hurdle technology, since their spectrum of action is reduced. In addition, it is important to note that each strain used as PC must be tested on the food to be applied and against a broad spectrum of indicator microorganisms.

Miscellaneous Food Products

Bioprotective cultures are also used to preserve a diverse kind of food products such as different beverages and bakery products. Bakery products are prone to post-treatment contamination by mold spores. Fungal development conducts to mycotoxin production and sensory spoilage which limit shelf life and causes significant health and economic losses. To overcome this issue, the search for bioprotective cultures exhibiting antifungal activity has gained interest in the last years as an alternative to chemical preservatives. Furthermore, some LAB also exhibited antimycotoxin properties (Guimarães et al., 2018; Juodeikiene et al., 2018). Le Lay et al., (2016) isolated several strains for the species *Leuc. citreum*, *Lb. sakei*, *Lb. plantarum*, *Lb. spicheri*, *Lb. reuteri* and *Lb. brevis* which were able to delay fungal growth by surface spraying to bakery products. Furthermore, some of these protective cultures led to delay fungal growths after incorporation in milk bread rolls preparation. Cizeikiene et al., (2013) used a spray containing a mixture of *Ped. acidilactici* KTU05-7, *Ped. pentosaceus* KTU05-8 and KTU05-10 strains that produce organic acid and bacteriocin like inhibitory substances to suppress superficial mold development on bread for 8 days of storage at 15°C in polyethylene bags. Trends commented suggest that bioprotective cultures can be used for controlling molds in bakery products.

Guimarães et al., (2018) selected the strain *Lb. plantarum* UM55 among different LAB due to its ability for inhibiting the growth of *Aspergillus (A.) flavus*. Furthermore, the cell-free supernatant (CFS) of this strain was able to inhibit by 91 % the production of aflatoxins (AFLs). It had also inhibited the growth and AFLs production of *A. parasiticus*, *A. arachidicola*, *A. nomius* and *A. minisclerotigenes*. This antimycotoxyn activity was due to the presence of phenyllactic acid, hydroxyphenyllactic acid, and indole lactic acid, being phenyllactic acid the one that exerted the stronger effect. Similar results were found by Schmidt et al., (2018) who reported that *Lb. reuteri* R29 exhibited a broad spectrum of antifungal activity due to the presence of phenyllactic acid. Based on mentioned trends, Bustos et al., (2018) using a factorial design optimized a low-cost medium to obtain biomass and phenyllactic acid production by *Ped. acidilactici* CRL 1753 strain. Furthermore, this strain was proposed to be used as a biopreservative in bread making to increase the shelf life of wheat bread.

Although is it known that nisin producer strains could prevent malolactic fermentation in wines and also they may serve to reduce the amount of sulfur dioxide, their use in winemaking to control bacterial spoilage (Daeschel et al., 1991) was evaluated only recently. Fernández-Perez et al., (2018) assessed the use of *Lc. lactis* LM29 under enological conditions to decrease sulfur dioxide addition. Results showed that this lactococci strain was able to produce nisin in the presence of 2 and 4% ethanol (v/v), while higher concentrations of ethanol fully inhibited bacteriocin production. Furthermore, the use of 50 mg/L nisin as additive decreased fourfold the concentration of sulfur dioxide required to prevent LAB growth during wine ageing.

CONCLUSION

Taking into consideration the abundant advantages of LAB strains, their potentiality as PC or biopreservatives is undeniably, providing therapeutic value to fermented food products, contributing to public health and reducing economic losses related to spoilage. Since fermented foods are consumed daily by people, the proper selection of protective cultures with different beneficial properties to enhance safety and promote health is a need within novel and reliable methods for food preservation.

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Chapter 293

THERMOTOLERANT PROBIOTIC LACTIC ACID BACTERIA IN COOKED MEAT PRODUCTS

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ABSTRACT

Lactic acid bacteria are part of the native flora in fresh meat, but certain strains have been employed as starter cultures in fermented meat products, becoming dominant flora due to lactic acid production, and a natural preservative. Nonetheless, although lactic acid bacteria are mesophilic, they cannot be employed as starter cultures in cooked meat products due to their limited survival to thermal processes. However, certain lactic acid bacteria isolated from cooked meats present the characteristics of thermotolerance, i.e., they survive thermal processes above 70°C for at least 30 min. These bacteria can overexpress heat shock proteins that are produced in response to exposure to a stressful environment, such as temperature or pH. These thermotolerant lactic acid bacteria present probiotic characteristics: being able to survive gastric tract conditions to colonize the small intestine and cell adhesion capacity. In addition, inoculation of these lactic acid bacteria in on cooked meat batters has no detrimental effect on texture, yield, color and sensory acceptance. The probiotication of cooked and emulsified meat products can be achieved with thermotolerant probiotic lactic acid bacteria.

INTRODUCTION

Lactic acid bacteria (LAB) are a group of Gram-positive bacteria, nonsporing cocci or rods, which produce lactic acid as the major end product of the fermentation of carbohydrates (Axelsson, 2004). They have a low content of GC, tolerate acidic conditions, are immobile, nutritionally demanding and must be administered vitamins, amino acids, purines and

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pyrimidines, lack catalase and facultative anaerobes, but are sometimes classified as aerotolerant anaerobes (Willey et al., 2008). They are found in dairy products, meat products and the human body, and are classified as GRAS (generally recognized as safe).

Lactic acid bacteria are divided into homolactic and heterolactic fermentative. Homolactic fermentation (Glycolysis Embden-Meyerhof-Parnas pathways) results almost exclusively in lactic acid as the end product, and heterolactic fermentation (the 6-phosphogluconate/phosphoketolase pathways) results in significant amounts of other end products, such as acetate, ethanol, CO₂ and lactic acid (Axelsson, 2004).

The LAB considered natural strains in meat and meat products are *Carnobacterium piscicola*, *Carnobacterium divergens*, *Lactobacillus sakei*, *Lactobacillus curvatus*, *Lactobacillus plantarum*, *Leuconostoc mesenteroides*, *Leuconostoc gelidum* and *Leuconostoc carnosum* (Hugas, 1998). LAB are employed as starter cultures in non-thermal processed fermented meat products, such as salami, but can easily grow at refrigeration temperatures, although they are considered mesophilic.

In this chapter, probiotic characteristics of thermotolerant LAB such as the survival in the gastrointestinal tract, the colonization of the intestine and cell adhesion capacity of thermotolerant lactic acid bacteria will be presented. In addition the inoculation of these LAB on cooked meat batters will be discussed.

THERMOTOLERANCE

Thermal tolerance or thermotolerance has been defined as the ability of an organism and of its cell structures to withstand (survive) destructive heat stress exceeding the range of optimal temperature for its development (Parsell and Lindquist, 1993). Mammalian cells can dramatically increase their tolerance to thermal damage after prior heat conditioning. The evidence suggested that heat shock proteins (HSP) provide the protective mechanism (Burdon, 1987).

Heat Shock Proteins. Classification

The first to publish the observation that cells could mount very strong transcriptional activity when exposed to elevated temperatures was Ritossa (1962), being coined the heat shock response. This discovery led to the identification of heat shock proteins.

Heat shock proteins (HSPs), or stress proteins, are present in all organisms and in all of their cells. Selected HSPs, also known as chaperones, play crucial roles in folding/unfolding of proteins, assembly of multiprotein complexes, transport/sorting of proteins into correct subcellular compartments, cell-cycle control and signaling, and protection of cells against stress/apoptosis (Li & Srivastava, 2003).

HSPs are broadly classified by molecular weight into distinct families: Hsp100, Hsp90, Hsp70, Hsp60, Hsp40, small Hsp and Hsp10 (Richa et al., 2007). The functions of the Hsp are acting like chaperones to maintain and control protein and proteases native structure. All HSP families possess chaperone activity (Sikora & Grzesiuk, 2007). Many members are

present constitutively in cells while some are only expressed after stress. Table 1 shows the HSP Family, localization and functions.

Table 1. HSP Family, localization and function in the tissue

Family	Localization	Function	Reference
Hsp100	Cytosol	Chaperones	Mogk et al., 2015
Hsp90	Cytosol	Chaperones	Pearl & Prodromou, 2006
Hsp70	Cytosol	Chaperones	Schuermann et al., 2008
Hsp60	Mitochondria, cytosol and nucleus	ATP-dependent chaperone	Okamoto et al., 2017.
Hsp40	Nervous system	Co-chaperones	Gorenberg & Chandra, 2017
sHsp	Ubiquitous, heart, muscle, placenta, cytoplasm.	Chaperones	Bakthisaran et al., 2015; Garrido et al., 2012.
Hsp10	Mitochondria, cytosol	Co-chaperones	Fan et al., 2017; Jia et al., 2011.

Hsp100

The Hsp100 family of molecular chaperones shows a unique capability to resolubilize and reactivate aggregated proteins. The Hsp100-mediated protein disaggregation is linked to the activity of other chaperones from the Hsp70 and Hsp40 families. The best studied members of the Hsp100 family are the bacterial ClpB and Hsp104 from yeast. Hsp100 chaperones are members of a large super-family known as AAA+ ATPases (Zolkiewski et al., 2012). The AAA (ATPases associated with various cellular activities) family is a large group of ATPases found in all biological kingdoms and characterized by the presence of one or two conserved ATP-binding domains of a type called the AAA motif. This 200–250 amino-acid domain is defined by sequence and structural properties (Bar-Nun & Glickman, 2012).

The Hsp100 forms a bi-chaperone system composed of ATP-dependent Hsp70 and hexameric Hsp100 (ClpB/Hsp104) chaperones, which rescues aggregated proteins and provides thermotolerance to cells (Mogk et al., 2015).

Hsp90

The 90 kDa heat shock proteins are a family of molecular chaperones found in bacteria and all eukaryotes, but are absent in archaea. Many eukaryotes possess multiple Hsp90 homologues, including endoplasmic reticulum and mitochondrial isoforms (Pearl & Prodromou, 2006). The Hsp90 chaperone family includes the eponymous Hsp90 (90 kDa heat shock protein) of the eukaryotic cytosol, termed variously Hsp90 α and β in humans (corresponding to a major and minor isoform), Hsp86 and Hsp84 in mice, Hsp83 in *Drosophila*, and Hsc82 and Hsp82 in yeasts. Other family members are HtpG in the bacterial cytosol, Grp94/gp96 in the endoplasmic reticulum of eukaryotes, and the Hsp75/TRAP1 in the mitochondrial matrix (Young et al., 2001).

The Hsp90 is a key regulator of proteostasis under both physiological and stress conditions in eukaryotic cells. As Hsp90 has several hundred protein substrates (or “clients”), it is involved in many cellular processes beyond protein folding, which include DNA repair, development of the immune response and neurodegenerative disease. Owing to the importance of Hsp90 in the regulation of many cellular proteins, it has become a promising drug target for the treatment of several diseases, which include cancer and diseases associated with protein misfolding (Schopf et al., 2017).

Hsp70

Hsp70s are a diverse family of chaperones involved in a variety of protein processing reactions, including import into the endoplasmic reticulum and mitochondrion, protein folding, and the remodeling of protein complexes (Schuermann et al., 2008). Hsp70 has two isoforms of 66 and 76 kDa, both called Hsp70, which is derived from a gene with the same name (Evans et al., 2010). HSPs prevent incorrect folding. Hsp70 plays a role in folding of proteins that have been destroyed and damaged by stress. The most important roles of Hsp70 are the management of folding of damaged and abnormal proteins (Valizadeh et al., 2017).

Hsp60

The eukaryotic heat shock protein Hsp60 (GroEL) belongs to the group I of chaperonins and is classically defined as an intramitochondrial protein that assists with the correct folding of other mitochondrial proteins, together with its co-chaperonin Hsp10 (GroES) (Bukau & Horwich, 1998).

Hsp60 plays an essential role in protein homeostasis through mediating protein folding and assembly. It was found that Hsp60 has different properties with respect to allostery, complex formation and protein folding activity, depending on the nucleoside triphosphate present (Okamoto *et al.*, 2017). Since the initial discovery of Hsp60 as the mitochondrial molecular chaperone many studies have shown that it is also localized outside mitochondria with perhaps both chaperoning and non-chaperoning activities. Therefore, it is not surprising that many different disease states, especially autoimmune diseases and cancers, have presented altered expression levels of Hsp60 (Meng et al., 2018). Recent investigations have suggested that Hsp60 functions and interactors may vary, depending on its cell and tissue localization, giving this protein the capacity to be a multifaceted molecule in the middle of the delicate balance between health and disease (Marino et al., 2018).

Hsp40

Ohtsuka et al., (1990) discovered a novel 40-kDa protein in addition to the classical heat shock proteins with molecular sizes of 110-, 90-, 70-, and 47-kDa. The p40 was induced not only by heat shock but also by arsenite and 2-azetidine carboxylic acid. It was induced in rat, mouse and chicken cells by these stresses. The p40 is a novel heat shock protein in mammalian and avian cells.

Heat shock proteins also called DnaJ/Hsp40 proteins have been preserved throughout evolution and are important for protein translation, folding, unfolding, translocation, and degradation, primarily by stimulating the ATPase activity of chaperone proteins, Hsp70s. DnaJ/Hsp40 proteins actually determine the activity of Hsp70s by stabilizing their interaction with substrate proteins (Qiu et al., 2006). Hsp40s are defined by their conserved J domain and typically have large variation in the rest of the protein. Classical Hsp40s have both a J domain as well as a zinc finger domain that regulates client protein binding. The J domain of Hsp40 proteins consists of a 70-amino acid sequence with four alpha helices (Gorenberg & Chandra, 2017).

sHsp

Small heat shock proteins (sHsp) were discovered in *Drosophila melanogaster* salivary glands as a set of sHsp, with small molecular weight (15–30 kDa) induced after a heat shock and accumulating in the cells after many different environmental, physiological or pathological stresses (Tissieres et al., 1974). The human sHsp family contains ten members and one related protein (HSP16.2/HSPB11) is ubiquitously expressed while others are only expressed in specific tissues (Garrido et al., 2012).

Small heat shock proteins (sHsps) are conserved across species and are important in stress tolerance. Many sHsps exhibit chaperone-like activity in preventing aggregation of target proteins (Bakthisaran et al., 2015). The sHsp participate in a large number of fundamental cellular processes such as controlling protein folding, F-actin-dependent processes, cytoprotection/anti-apoptosis, differentiation, cell proliferation, and gene expression, and therefore are involved in many pathologies, such as neurodegenerative diseases, cancer, and cardiovascular diseases (Guo & Wu, 2015).

Hsp10

Protein folding in mitochondria is mediated by the chaperonin Hsp60, the homologue of *E. coli* GroEL. Mitochondria also contain a homologue of the cochaperonin GroES, called Hsp10. Hsp10 is required for the folding and assembly of proteins imported into the matrix compartment, and is involved in the sorting of certain proteins, such as the Rieske Fe/S protein, passing through the matrix en route to the intermembrane space (Hohfeld & Ulrich, 1994).

Hsp10, an important member of Hsps family, classically works as a molecular chaperone folding or degradating of target proteins. Evolutionarily, Hsp10 is also reported to be involved in immunomodulation and tumor progression (Fan et al., 2017). Hsp10 appears to be related to pregnancy, cancer and autoimmune inhibition. It can be released to peripheral blood at a very early time point of pregnancy and received another name, early pregnancy factor (EPF), which seems to play a critical role in developing a pregnant niche (Jia et al., 2011).

HSP IN LACTIC ACID BACTERIA

LAB are important starter, commensal, or pathogenic microorganisms. The stress physiology of LAB has been studied in depth for over 2 decades, fueled mostly by the technological implications of LAB in the food industry (Papadimitriou et al., 2016).

Hartke et al., (1996) studied the lactic acid tolerance of *Lactococcus lactis* subsp. *lactis*. The results showed a dramatic increase in survival to severe acid stress during 30 min at pH 3.9. One protein extract analysis revealed that the major heat shock proteins DnaK and GroEL are produced during acid tolerance. Highly conserved chaperones, DnaK, DnaJ, GrpE, GroES, GroEL, and proteases Clp, HtrA, and FtsH, have been detected in LAB (Guchte et al., 2002). Lactobacilli respond to stress in specific ways dependent on the strain, species, and the type of stress.

Coucheney et al., (2005) studied the *Oenococcus (O.) oeni*, a lactic acid bacterium mostly responsible for malolactic fermentation in wine. This bacterium produces an 18 kDa sHSP, called Lo18 that is induced by multiple stresses, such as heat, ethanol, sulphites, and low pH,

among others. *O. oeni* cells showed that purified Lo18 interacts with the liposomes and increases the molecular order of the lipid bilayer in these membranes when the temperature reaches 33.8°C. These data suggest that Lo18 could be involved in an adaptive response allowing the maintenance of membrane integrity during stress conditions in *O. oeni* cells.

Spano et al., (2005) using a molecular approach based on PCR, RT-PCR and Northern blot analysis, described a new member of the small heat shock family of wine, *Lactobacillus (Lb.) plantarum*. The protein had a calculated molecular of mass of 18.548 kDa and was named Hsp18.55. Expression of the newly identified small heat shock gene was induced by a wide range of abiotic stresses including heat, cold and ethanol, suggesting that the small family of heat shock genes is probably involved in the general stress response in *Lb. plantarum* from wine.

Capozzi et al., (2011) studied the *Lb. acidophilus* hps16 gene structure, genomic organization, and deduced amino acid sequence. The results indicated a strong evolutionary relationship within members of the *Lb. acidophilus* group. This species is used to drive dairy fermentations and in functional probiotic foods and is therefore commonly exposed to multiple physiological stresses. Wu et al., (2014) reported that a small heat shock protein (18 kDa) probably indicated the link between the osmotic tolerance of *Lb. paracasei* during fermentation due to salt stress response.

Pandi and Basher (2016) studied the stress resistance of *Lactobacillus* strains and concluded that the genus *Lactobacillus* contains many stress resistant organisms. They can produce stress resistant metabolites like trehalose and heat shock proteins during growth at high temperatures, which helps the growth of microorganisms at high temperatures. Serata et al., (2016) reported Hsp18 and GroEL as one gene involved in oxidative stress resistance in *Lb. casei* strain Shirota.

Wang et al., (2017) studied the characteristics of four isolated LAB and their effects on fermentation quality of Italian ryegrass (*Lolium multiflorum* Lam.), which is difficult to silage on the Tibetan Plateau due to the low temperature. The results showed that *Lb. plantarum* strains overproducing Hsp 18.5, Hsp 18.55, and Hsp 19.3 can grow better at low temperatures.

THERMOTOLERANT LACTIC ACID BACTERIA IN MEAT PRODUCTS

The three-dimensional structure of cellular proteins is sensitive to small increases when they are exposed to high temperature, and the misfolding and aggregation of unfolded proteins are the primary problems for cells subjected to heat stress (Varmanen and Savijoki, 2011).

LAB are employed as starter cultures for the fermentation of meat products. In some countries, cooked meat products undergo a heat treatment of 70°C (pasteurization temperature) in their processing; some LAB can survive this treatment due to the production of Hsp.

The role of LAB in both cooked and fresh meat products is controversial due to the spoilage characteristic of LAB. On one hand, several species are able to dominate the meat system in VP and MAP storage conditions and can release odor-impact molecules, which may alter the sensory profile of raw or cooked meat. On the other hand, LAB have a bioprotective

function since they can provide favorable antagonistic activity against other undesired microorganisms (Pothakos et al., 2015).

Chenoll et al., (2006) analysed the presence of LAB associated with a variety of vacuum-packed fresh and spoiled meat products. From a total of 18 samples, *Lactobacillus Leuconostoc*, *Carnobacterium*, and *Enterococcus* were the predominant species. Victoria-Leon et al., (2008) isolated eight strains of LAB from commercial sausages. The strains were heated in water baths to 50, 60 and 70°C, during 30-60 min. Four strains survived the treatments and were identified as *Lb. alimentarius*, *Lactococcus (L.) lactis*, *Lb. piscicola* and *Enterococcus sp.* These strains were considered thermotolerant. Ramírez-Chavarrín et al., (2010) isolated a total of 68 presumptive LAB from commercial cooked sausages collected in Mexico City supermarkets. Based on biochemical tests, 22 strains were selected and their thermotolerant capacity determined. Only 10 strains were considered thermotolerant after surviving thermal treatments at 70°C during 30 min. The genera identified by phenotypic and genotyping analyses were *Pediococcus*, *Lactobacillus*, *Aerococcus* and *Enterococcus*.

Chávez-Martínez et al., (2016) quantified and identified LAB in thirty samples of sliced cooked ham, reporting that enterococci showed the lowest count and lactobacilli the highest counts; 23.8% of the strains were identified as thermophilic *Lactobacillus*. Saucedo-Briviesca et al., (2017) studied the effect of probiotic thermotolerant LAB on the physicochemical, microbiological and sensorial characteristics in a meat batter. Two thermotolerant probiotic LAB were used: *Pediococcus pentosaceus (Ped.)* and *Enterococcus (Ec.) faecium*, which were inoculated to 5% in a meat batter. The results showed that the stability to cooking, expressible moisture, hardness and cohesion increased during storage in the batters inoculated with the 2 strains of LAB. The count of LAB increased in the inoculated meat batters and the coliforms decreased overall. When the strain mixture was used, inhibition of coliforms was total at day 6. Sensory analysis showed that judges detected when *Ec. faecium* was inoculated. Thermotolerant LAB can be used as functional ingredients in meat batters.

When a LAB demonstrates its resistance to thermal stress it is very possible that this bacterium can resist another type of stress. Fragoso et al., (2016) studied this and demonstrated that the use of thermotolerant probiotic LAB in fat reduced ice cream with inulin as fat replacer could be a good alternative to formulate symbiotic foods.

PROBIOTICS: DEFINITION AND CHARACTERISTICS

Several specific LAB strains are marketed on the basis of their beneficial effects on the consumer's health, representing an explosively growing market for the products containing these so-called probiotics (Bron & Kleerebezem, 2011).

Etymologically, the term probiotic is derived from the Greek language meaning "for life." The first definition of probiotics was coined by Lilly and Stillwell (1965) to describe substances produced by one microorganism that stimulate the growth of another, thus meaning the opposite of antibiotics. Later, Fuller (1989) redefined the term probiotics:

"Probiotics are live microbial feed supplements which beneficially affect the host animal by improving its intestinal microbial balance."

The FAO/WHO (2002) describes them as:

“Live microorganisms which when administered in adequate amounts confer a health benefit on the host.”

This is the more widely accepted definition.

The principal characteristics of probiotics include: tolerance to human gastric juice and bile, adherence to epithelial surfaces, persistence in the human gut, immune stimulation, antagonistic activity toward intestinal pathogens, production of antimicrobial substances, safety in food and clinical use, susceptibility to antibiotics and bile salt hydrolase activity (Parvez et al., 2006). Among the benefits of probiotics are improvements of intestinal health, enhancement of the immune response, reduction of serum cholesterol and cancer prevention (Kechagia et al., 2013).

The most common microorganisms used as probiotics are from the *Lactobacillus* and *Bifidobacterium* genera; other bacterial genera, including *Enterococcus*, *Streptococcus*, and *Escherichia*, are also used. Some strains of the fungus *Saccharomyces boulardii* are also considered probiotics (Mack, 2005).

THERMOTOLERANT LACTIC ACID BACTERIA AS PROBIOTICS

Ramírez-Chavarrín et al., (2013) evaluated 10 thermotolerant LAB (*Ped. pentosaceus* (4 strains), *Lb. plantarum* (3 strains), *Ec. faecium* (2 strains) and *Aerococcus viridans* (1 strain) to identify their probiotic properties. The results showed that 50% of the strains were intolerant to low pH and simulated gastric juice. All strains grew in taurocholic acid and bile concentrations greater than 0.3%, indicating they are good probiotic candidates. Less than 20% of the strains coaggregated with an *E. coli* indicator while 30% coaggregated with a *Salmonella* ssp. Eight of the strains exhibited good autoaggregation capacity at 24 h and all ten had a high adherence capacity for HEp-2 cells. The studied thermotolerant LAB are promising ingredients in the production of cooked meat products with probiotic potential. Alginate and other gelling hydrocolloids encapsulation of thermotolerant and probiotic LAB is a good alternative to protect them in their passage through the pH of the stomach (Totosaus et al., 2013).

Tatsinkou et al., (2017) studied the protective effect of minerals such as calcium and magnesium on probiotic strains. This protective effect is due to the fact that calcium and magnesium ions have the property of stabilizing certain structural proteins and even enzymatic ones. Their presence may prevent the rapid denaturation of membrane proteins. These results showed that mineral salts increase the thermotolerance and resistance to bile salts of probiotic strains. They concluded that calcium and magnesium could be used to monitor the viability of probiotic strains in probiotic products.

Hernández-Alcántara et al., (2018) isolated and evaluated the probiotic properties of six thermotolerant LAB. The bacteria were typed by determination of the DNA sequence of their 16S rRNA coding genes, as one *Ec. faecium* (UAM1 strain) and five *Ped. pentosaceus* (UAM2-UAM6 strains). *In vitro*, these strains showed desirable probiotic properties. These trials are promising for the application of *Ec. faecium* UAM1 as a novel probiotic strain in the food industry, since it can be employed as bioprotective culture due to its thermotolerant capacity in functional foods.

SYNBIOTICS

Synbiotics are used for the improved survival of beneficial microorganisms added to food or feed, and to stimulate the proliferation of specific native bacterial strains present in the gastrointestinal tract (Markowiak & Slizewska, 2017). Gómez-Chávez et al., (2011) studied the prebiotic effect of cacao flour on the growth of probiotic thermotolerant lactic acid bacteria in a meat batter. The *in vitro* growth of lactic acid bacteria using cacao flour as carbon source was acceptable compared with the growth obtained using glucose. No differences in physicochemical analysis were shown. Those authors concluded that the use of this kind of bacteria in cooked meat products leads to a foodstuff with high nutritional and symbiotic value that enhances microbial intestinal flora as a result of its intake.

Díaz-Vela et al., (2015) studied the effect of fruit peels as prebiotic and probiotic thermotolerant lactic acid bacteria in the structural characteristics of cooked meat products. Scanning electron microscopy showed the development of LAB in the sausages. In the control treatment (not inoculated with bacteria, no fruit peel flour added), some LAB colonies were visible between the components of the meat batter, above all after 20 days of storage. Analysis showed the production of exopolysaccharides by thermotolerant LAB. The incorporation of fruit peel flour into the formulation increased the number of bacteria in cooked meat emulsions.

Lactic acid bacteria viability was improved by the incorporation of different compounds during alginate ionotropic gel matrix coencapsulation, enhancing the resistance to acidic conditions as well. The strong prebiotic effect of inulin and apple marc flour was to enhance bacterial viability due to insoluble carbohydrate content, resulting in higher particle size with a higher number of viable bacteria. Symbiotic co-gelification of alginate gel matrix with prebiotic compounds to protect probiotics can be employed in order to ensure the delivery of probiotic strains in the colon throughout the gastrointestinal tract (Serrano-Casas et al., 2017).

CONCLUSION

Lactic acid bacteria have been used for many years in fermented meat products. It has been shown that LAB can produce heat shock proteins (Hsp) that make them capable of resisting the heat treatments suffered by meat products in their preparation. Additionally, these bacteria may have probiotic characteristics. The use of probiotic thermotolerant lactic acid bacteria in cooked meat products is a good alternative in the manufacture of functional meat foods.

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Chapter 294

MICROENCAPSULATED LACTIC ACID BACTERIA IN MEAT PRODUCTS

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ABSTRACT

The lactic acid bacteria (LAB) that belongs to the *Lactobacillaceae* family is classified into fifteen different genera. Some LAB, including the *Lactobacillus casei*, *Lb. delbrueckii*, *Lb. acidophilus*, *Lb. fermentum*, *Lb. reuteri*, *Lb. sakei*, and *Lb. plantarum*, are recognized worldwide as probiotics. International agencies such as the United Nations' Food and Agricultural Organization and the World Health Organization have defined probiotics as "living microorganisms of which when administered in adequate amounts confer a health benefit on the host." LAB selection as probiotics must include criteria such as safety for human consumption, stability against acid and bile conditions, and the capacity to colonize the human gastrointestinal tract. Probiotic microorganisms have been associated with improvements in the host's health, which has stimulated the consumption of LAB-added functional foods. There are some concerns associated with probiotics survival during manufacturing, storage, and specific preparation processes for the final product. Different approaches have been studied in order to increase LAB feasibility in meat products. Microencapsulation could be employed as an alternative since it is a LAB protective method consisting of isolating the microorganism to obtain spherical-shaped and micrometer-sized products, in which a membrane shields the LAB. The probiotics ought to survive and dominate other microorganisms present in the food product, evidencing the use of microencapsulation for cellular viability increase. The probiotics used in fermented meat products are primarily associated with salami, which differs in terms of raw material composition, ripening time, appearance, and flavor. Fermented meat products encounter some barriers such as pH, water activity, lower sugars content, temperature, and preparation form limitations. On the other hand, the

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instinctive search for better a quality of life demands practical and functional foods and the added value is imperative to make a difference in the meat food industry. In this context, microorganisms are added to food aiming at increasing its properties, creating new functional foods capable to promote healthy benefits to the host. This chapter focused on the microencapsulated probiotic LAB potentials and their application in fermented meat products.

INTRODUCTION

The concern about food and health is reflected in the lifestyle of the population. Food habits change according to what is offered and made available in the market, favoring and encouraging the consumption of foods with functional properties. Consumers' acceptance of functional foods is complex and influenced by product-related factors such as sensorial characteristics, price, healthy ingredients, related claims, and also by consumer-related factors (Shan et al., 2017).

Functional foods potentially promote health benefits, they can provide nutrients associated with probiotics that may contribute diminishing intestinal disorders (Kapasob, Kerdchoechuen & Laohakunjit, 2018). Probiotics are defined as microorganisms that, under certain conditions, confer the host some health benefits. Many LAB are probiotic microorganisms and they are especially associated with milk-based products. The most important LAB probiotic genera are *Lactobacillus* and *Bifidobacterium* (Ferreira & Silva, 2016).

Probiotics are associated with intestinal microbiota control, pathogens population decrease, intestinal microbiota stabilization after the use of antibiotics, lactose digestion, constipation relief, host immune system stimulation, short chain fatty acids production (acetate and butyrate), inhibitory effects on mutagenicity, and colon cancer risk reduction (Ferreira & Silva, 2016).

Probiotics offer some limitations for their application in foods. There are some concerns associated with probiotics survival during manufacturing, storage, and specific preparation processes to obtain the final product. In this respect, microencapsulation ought to improve the probiotic stability, proving to be an interesting alternative for adverse conditions. Different microencapsulation methods and wall materials have been tested in order to ensure high stability.

Pork consumption has been on the rise and is expected to reach 43,619 tons worldwide by 2026 (Oecd/Fao, 2017). A great part of its consumption is related to industrialized products, and it should be diversified to achieve consumer's preference. Probiotic meat products are mainly associated with fermented meat products. Salami is an excellent alternative for probiotic addition because it could be consumed without preheating.

In this way, LAB microencapsulation appears as an alternative to producing probiotic meat products, by breaking technological barriers. Additionally, probiotics could improve food safety and preservation, sensory characteristics development, acceptability, nutritional value, and health benefits.

LACTIC ACID BACTERIA

LAB are Gram-positive ubiquitous microorganisms, which are found in plants, mammals' intestinal mucosa, as well as in fermented foods (Teneva-Angelova et al., 2018). LABs have a long history of use for food production and conservation, as they are comprised of a wide group of microorganisms. Originally, LAB group included four kinds of great importance genera for food industry, including *Lactobacillus*, *Leuconostoc*, *Pediococcus*, and *Streptococcus*. Currently, it consists of fifteen classified genera based on morphology, glucose fermentation mode, the configuration of lactic acid produced, growth at certain temperatures, high NaCl concentration and pH, and catalase activity (Table 1) (Kalschne et al., 2015).

LAB are mesophilic, non-sporogenic, devoid of cytochromes, facultative anaerobes, fastidious, acid tolerant, catalase, and oxidase negative (Khalid, 2011). However, their main characteristic is carbohydrates fermentation with lactic acid production. The differences between homofermentative and heterofermentative carbohydrate metabolism involves LAB genetics and their physiological basis. Homofermentative carbohydrate metabolism use aldolase and hexose isomerase enzymes by the Embden-Meyerhof-Parnas pathway to produce two lactic acid molecules from a one glucose one. In contrast, the heterofermentative metabolism uses phosphoketolase enzyme by hexose monophosphate pathway or pentose degradation of glucose to produce lactic acid, ethanol, and carbon dioxide from glucose (Kalschne et al., 2015).

The *Bifidobacterium* genus is classified as a LAB since it shares a few characteristics, despite being phylogenetically unrelated. *Bifidobacterium* differs from other LAB genera on glucose fermentation mode, which occurs via fructose-6-phosphate due to the presence of fructose-6-phosphate phosphoketolase enzyme (Mazo et al., 2009).

Table 1. LAB key phenotypic characteristics

Genera	Morphology	CO ₂ from glucose	Lactic acid isomer	Growth at 10°C	Growth at 45°C	Growth in 18% NaCl	Growth at pH 4.4	Growth at pH 4.5	Catalase activity
<i>Aerococcus</i>	C ^a	-	L	+	-	-	-	-	-
<i>Atopobium</i>	C/R	-	-	-	-	-	-	-	-
<i>Bifidobacterium</i>	R	+ ^b	L	-	+	-	-	-	-
<i>Brochothrix</i>	C/R ^d	-	L	-	- ^f	-	-	-	+
<i>Carnobacterium</i>	R	- ^e	L	+	-	-	-	-	-
<i>Enterococcus</i>	C	-	L	+	+	-	+	-	-
<i>Lactobacillus</i>	R	±	D, L, DL	±	±	-	±	+	- ^f
<i>Lactococcus</i>	C	-	L	+	-	-	±	-	-
<i>Leuconostoc</i>	C	+	D	+	±	-	±	-	-
<i>Oenococcus</i>	C	+	D	+	±	-	±	-	-
<i>Pediococcus</i>	C ^a	-	L, DL	±	±	-	+	-	-
<i>Streptococcus</i>	C	-	L	-	±	-	-	-	-
<i>Tetragenococcus</i>	C ^a	-	L	+	-	+	- ^c	- ^c	-
<i>Vagococcus</i>	C	-	L	+	-	-	±	-	-
<i>Weissella</i>	C/R	+	D, DL	+	-	-	±	-	-

Source: Adapted from Kalschne et al., (2015).

C: cocci; R: rod-shape; L, D and LD: optical isomers; +: positive; -: negative; a: cocci may also be tetrad formation; b: differ from bacterial homo and heterofermentative on fermentation of glucose, which occurred via fructose-6-phosphate; c: grow did not occur at pH 5.0 or lower; d: in older cultures the rod may give rise to coccoid forms, which will develop into rod forms when subcultured onto a suitable medium; e: small amounts of CO₂ from glucose might be produced; f: growth did not occur at 37 °C; f: can be present pseudocatalase activity.

LAB are usually of great biotechnological interest due to their morphological, metabolic, and physiological characteristics. The addition of LAB to foods have some positive characteristics such as a probiotic appeal, desired sensory characteristics development in fermented meat products, and food safety due to bacteriocin production and/or also due to competition with the microbiota present in food (Domínguez, Agregán & Lorenzo, 2016; Juturu & Wu, 2018; Ahn, Kim & Kim, 2017; Ruggirello et al., 2018).

Probiotics

Probiotics have been getting various definitions since their discovery. According to Fuller (1989) probiotics are living microbial food supplements that beneficially affect the host by improving their intestinal microbiota balance. International agencies such as the United Nations' Food and Agricultural Organization and the World Health Organization defined probiotics as "living microorganisms that when administered in adequate amounts confer a health benefit on the host" (Hill et al., 2014; FAO/WHO, 2001). In this way, a food is considered functional in terms of probiotic activity when it generates a beneficial effect to the host that receives it, besides its nourishing ability.

Probiotics are microorganisms present in the intestine on a constant survival contest and they are associated with many beneficial effects at this level, as was explained above (Ferreira & Silva 2016). Additionally, a recent study about *Lactobacillus plantarum* KX881772, a new probiotic from camel milk, observed potential anti-diabetic activities in camel fermented sausages and beef by α -amylase (A) and α -glucosidase (B) inhibitions, and they also showed anti-hypertensive and cytotoxicity activities (Ayyash et al., 2019).

LAB selection as probiotics includes anti-pathogenic activity and other criteria for safety assessment such as taxonomy identification, virulence absence, enterotoxins production, hemolytic activity, and transferable antibiotic resistance genes. Additionally, probiotics must exhibit stress tolerance to salivary and gastric enzymes, body temperature, low pH, gastric juice and bile salts, and adhesion ability to colonize the human gastrointestinal tract demonstrating functional efficacy (Distrutti et al., 2016; Pereira et al., 2018).

Strains of probiotics for use in humans have been selected mainly among the genera *Lactobacillus* and *Bifidobacterium*. They are commonly found in the intestines and mucosal surfaces of healthy humans or in spontaneously fermented foods (Balakrishnan & Floch, 2012; Vinderola et al., 2017). However, Pereira et al., (2018) also emphasized that *Lactococcus*, *Streptococcus*, and *Enterococcus* have a long history of safe use as probiotics.

Lactobacillus is the main LAB genus present in the small intestine, and it is susceptible to changes due to the entry of exogenous bacteria; thus *Lactobacillus* consumption during several days might be necessary to achieve the probiotic effect. In contrast, *Bifidobacterium* is mainly present in the large intestine and it does not offer a practical use as probiotics due to difficulties of its isolating and manipulating (anaerobiosis) and also, it does not tolerate acidic environments, hampering its use when fermented products are used as carriers. The microbiota in the large intestine is more stable and suffers less influence from exogenous bacteria due to the effect of consumed prebiotics. However, the large intestine is the first one to be attacked by antibiotics (Ferreira & Silva, 2016).

In this sense, there are some concerns associated with probiotics survival during manufacturing, storage, and specific preparation processes for the final product. In general, the use of LAB in food products depends on the lactic acid amount reduced, the type of glucose fermentation (homo or heterofermentatives), growth at different temperatures, and the tolerability to acidic and alkaline substances.

The standard for health-claiming-probiotics-added foods follows FAO/WHO recommendations per plate count with a minimum 10^6 to 10^7 UFC/g (FAO/WHO, 2001). Similarly, Minelli et al., (2008) recommended 10^6 CFU/mL and 10^8 CFU/mL as minimum probiotic concentrations in the small intestine and in the colon, respectively.

There are some concerns associated with the survival of probiotic strains during the manufacturing, storage, and high quantification number in the final product (Leroy, Verluuyten & De Vuyst, 2006). Different approaches have been studied in order to increase the resistance of these sensitive microorganisms to adverse conditions, being probiotics microencapsulation one of them. Many authors have reported the advantages of this method in prolonged preservation and controlled release of probiotics (Etchepare et al., 2015; Shori, 2017; Huq et al., 2017; Prisco & Mauriello, 2016; Arepally & Goswami, 2019; Mao et al., 2018).

MICROENCAPSULATION

Different approaches have been studied in order to increase LAB feasibility in meat products. Microencapsulation is a promising alternative that could be employed as a LAB protective method, consisting of the coating of microorganisms to obtain spherical-shaped and micrometer-sized products, in which a membrane shields the LAB (Arepally & Goswami, 2019). The probiotics can survive and dominate over other microorganisms present in the food product, emphasizing the use of microencapsulation to increase cellular viability.

Microencapsulation is a coating process of small particles or droplets; or the compounds incorporation in a homogeneous or heterogeneous matrix, obtaining small capsules. Microencapsulation promotes a physical barrier between the core and wall materials, enabling a controlled release (Prisco & Mauriello, 2016).

Probiotics can be kept viable by microencapsulation, depending on processing conditions both during food manufacturing process and in the final product. Microencapsulation allows the coating material, capable of withstanding extrinsic conditions adverse to microorganisms, to protect the culture. On the other hand, coating should be released upon reaching the intestines so that probiotics can be able to perform their functions there (Arslan et al., 2015; Martín et al., 2015).

Several factors affect the protection and survival of encapsulated probiotics during gastric transit. The most important factors are probiotic strains' acid resistance properties, wall materials and their concentrations, encapsulation methods, and polymers incorporation in the matrix (Shori, 2017).

Microencapsulation has different uses, namely the food industry has reported the implementation of increasingly complex formulations with microorganisms encapsulated in fermented meat; the addition of polyunsaturated fatty acids susceptible to auto-oxidation in milk, yogurts or ice creams; and the use of highly volatile flavor compounds in instant foods,

which oftentimes can only be achieved by microencapsulation (Khan et al., 2011; Gharsallaoui et al., 2012).

Microencapsulation Techniques

The most common methods used for probiotic microencapsulation are emulsion, spray drying, and extrusion, due mainly to their efficiency and low costs (Santos et al., 2019; Holkem et al., 2017; Ramos et al., 2018; Shori, 2017; Prisco & Mauriello, 2016). Furthermore, complex coacervation is an emerging method also used for probiotic encapsulation that results in an increase of probiotics feasibility and great encapsulation efficiency (Bosnea, Moschakis & Biliaderis, 2014; Bosnea, Moschakis & Biliaderis, 2017). Gelation, including the alginate-based, has been investigated (Kia, Alizadeh & Esmaili, 2018; Huq et al., 2017). Often, probiotic microcapsules obtained by coacervation, emulsion or gelation methods are posteriorly freeze-dried to ensure preservation and microorganisms' viability (Silva et al., 2018; Halim et al., 2017; Huq et al., 2017).

Choosing microencapsulation for a specific process will depend on factors such as particle size, the microcapsules biocompatibility and biodegradability, core and coating physical and chemical properties, microcapsules application, proposed active core release mechanism, and process costs (Dubey, Shami & Bhasker Rao, 2009). For probiotic applications, it is important that microcapsules be water-insoluble so the structure could be maintained during food and beverages processing, and through the digestive system (Ramos et al., 2018).

The spray drying technique is viable and effectively applicable for microorganism's encapsulation. This microencapsulation technique has been largely used for microorganisms' preservation (Arslan-Tontul & Erbas, 2017; Arepally & Goswami, 2019; Santos et al., 2019; Loyeau et al., 2018; Mao et al., 2018; Prisco & Mauriello, 2016). It may offer advantages such as ease of operation and cost-effectiveness, and that it is already available for industrial use. The atomization process consists in numerous droplets formation by solution, emulsion or suspension spraying into the drying chamber where they make contact with the hot gas (air or nitrogen) for subsequent dehydration, transforming the liquid component in a powdered solid one, later recovered in the cyclone (Burgain et al., 2011).

The risk of cell death associated with high temperatures is one of the disadvantages of spray drying. However, some authors mention temperatures ranging from 70 to 130 °C in the drying chamber to promote microorganisms' microencapsulation (Anekella & Orsat, 2013), considering that the contact time between microorganisms and the heat source is quite short, and the chamber outlet temperature is around 30-40 °C lower than the inlet temperature (Mao et al., 2018).

Wall Materials

The correct selection of wall material is associated with microcapsules' stability, process efficiency, and active core protection level. The ideal wall material should be non-reactive with the core, capable to seal and keep it within the capsule, provide core maximum

protection against adverse conditions, no unpleasant taste, and be economically feasible (Nazzaro et al., 2012).

For food applicable microencapsulation, the wall materials normally include proteins (whey protein, soy protein, caseinate, and gelatin), carbohydrates (starch, alginate, maltodextrin, pectin, inulin, gum arabic, chitosan, carrageenan, cellulose nanocrystal, β -cyclodextrin, dextrans, and fructo-oligosaccharides) or their mixtures (Etchepare et al., 2015; Shori, 2017; Huq et al., 2017; Prisco & Mauriello, 2016; Arepally & Goswami, 2019; Mao et al., 2018; Loyeau et al., 2018; Arslan-Tontul & Erbas, 2017). Most wall materials do not have all the desired properties, thus the mixture of two or more is a common practice.

The release of microcapsules content at controlled rates could be triggered by shearing, heating, pH, and enzymatic action (Lam & Gambari, 2014) and are mainly related to the wall material employed. Carbohydrates are often mixed with proteins in order to improve emulsifying and film-forming properties during their encapsulation (Mao et al., 2018; Loyeau et al., 2018).

In addition to being biodegradable and biocompatible materials, the wall materials should release the microencapsulated probiotics in the intestines without earlier release due to the wall materials solubility in water. Thus, probiotic microcapsules pH dependence is an interesting alternative to release the microorganisms at the correct time in the small intestine. Most foods have acidic pH, and the conditions for probiotics in the digestive tract before reaching the small intestine are acidic; however, pH increases when the probiotics enter in the intestine, surpassing neutrality and reaching alkaline levels. In this way, pH-dependent wall materials, especially with probiotic release at alkaline pH are the most favorable ones.

PROBIOTIC LAB ADDED IN FERMENTED MEAT PRODUCTS

Several foods of various products categories have been added with probiotics such as bakery products (bread, biscuits, chocolate soufflé, and stuffed cakes), fruit and vegetable juices (acerola nectar, longan, cranberry, pomegranate, berries, carrot, orange, peach, and apple), dairy products (yoghurt, ice cream, and fermented soured milk beverage), cheese (feta, cheddar, white Iranian brined cheese, white brined cheese, kasar, mozzarella, fiordilatte, pecorino, and oxaca) and others (i.e., mayonnaise). For meat products, only fermented ones have been associated with probiotics (Prisco & Mauriello, 2016).

Fermented meat products such as salami have some technical limitations regarding probiotics addition. Barriers such as pH, water activity, lower sugars content, and preparation form limitations, mainly associated with high cooking, baking, and frying temperatures need to be surpassed. In order to overcome this problem, the addition of microencapsulated probiotics in fermented meat products has been discussed (Barbosa et al., 2015; Muthukumarasamy & Holley, 2006; Macedo et al., 2008). However, these food products added with microencapsulated probiotics should be consumed without pre heating at preparation in order to preserve the microorganisms.

Salami is prepared by mixing all of its ingredients (pork shoulders, pork fat, salt, curing salts, sugars, spices, antioxidant, and starter culture), stuffing in artificial casings, fermentation/drying for a few days, and ripening for some days up to reaching the desired water activity in the final product (Alamprese, Fongaro & Casiraghi, 2016).

The fermentation process is defined as the anaerobic metabolism of carbohydrates by microorganisms. It has been used to extend foods expiration date, with an important role in diets worldwide offering a variety of benefits. Starter cultures were initially used for food preservation, including sensory characteristics, acceptability, nutritional value, and food safety improvements while also providing diet diversification (Malo & Urquhart, 2016).

Salami starter cultures generally combine the *Micrococcaceae* family represented by *Staphylococcus* (S.) *xylosus* and *S. carnosus* species, and LAB *Pediococcus* (Ped.) *pentosaceus*, *Ped. acidilactici*, and *Lactobacillus* (Lb.) *sakei*. The *Debaryomyces hansenii* yeast and *Penicillium nalgiovense* mold were also included in some commercial starter cultures (Alves et al., 2018).

The cited *Staphylococcus* species are associated with bacteriocins production and lipolytic and proteolytic activities, while the LAB are associated with the lactic acid production. *Debaromyces hasenni* and *Penicillium nalgiovense* also have lipolytic and proteolytic activities. *Penicillium nalgiovense* provide a fungal mycelium on salami's external surface, offering a protective effect against some undesirable microorganisms during the ripening process, and it is a good quality indicator by manufacturers (Galvalisi et al., 2012; Mattei, 2012).

In terms of starter cultures and probiotics, two important issues need to be mentioned. First, not all LAB used in food products fermentation are considered probiotic, since the probiotic is related to the colonization of the intestines benefiting its host. Second, the fermentative LAB microorganisms are not always present in amounts required to obtain the beneficial properties of a functional food. Therefore, there is a close link between the possibilities that a fermenter LAB be a microorganism with probiotic characteristics.

Overall, during the fermentation and ripening processes, the sugar present in the salami is fermented by homofermentative *Lactobacillus* and converted to organic acids, mainly lactic acid by Embden-Meyerhof-Parnas, resulting in pH reduction (Krummenauer et al., 2015). The pH decreases and reaches the isoelectric point of proteins (neutral charge) promoting myofibrillar proteins insolubilization and the consequent water loss by dehydration.

Therefore, acid pH is one of the main physicochemical and sensorial characteristics of salami, which usually reach values around 5.0 and, increasing to 5.3 after proteolysis (Massaguer, 2006). Acid pH also works as a barrier to the development of undesirable microorganisms in the product, especially when associated with low water activity.

Probiotic microorganisms in salami must withstand the product's (pH from 4.5 to 6.0) and the human stomach's (pH from 1.0 to 3.5) acidic conditions. Microencapsulation allows greater probiotic stability against adverse pH conditions. Alternatively, the wall material could be pH dependent as it remains intact at acidic pHs but is disrupted by releasing the probiotics at the small intestine alkaline pH (pH around 7.4 in the jejunum and up to 7.7 in the ileum) (Ekmekcioglu, 2002). In this sense, more studies should be conducted to evaluate the probiotic effect of microencapsulated LAB applied in a fermented meat product.

CONCLUSION

The consumers' search for better quality of life and the increase in quality of life demand practical and functional foods and the added value is imperative to make a difference in the

meat industry. Functional foods are an option in order to add value and make a difference in the meat industry for the consumers that search for better quality of life. Probiotic LAB are recognized to offer different possibilities in physicochemical and sensory innovations and microbiological safety. In this context, alternatives such as probiotic microencapsulation help to protect the microorganisms and promote a wide range of options to enrich complex food matrices with probiotics. Among the different microencapsulation techniques, spray drying is characterized as ease of operation and cost-effective for microorganism's microencapsulation. Different wall materials are available, and the combination of carbohydrates and proteins normally promote greater functional properties. Considering that the meat products industry has been growing year by year in line with an increasing demand for functional foods, efforts have been made to produce functional meat products. Fermented products such as salami are an excellent alternative for probiotics addition, as they are consumed without any preheating, a thermal process that could kill microorganisms.

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Chapter 295

LACTIC ACID BACTERIA RESPONSES TO OSMOTIC CHALLENGES

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ABSTRACT

Lactic acid bacteria (LAB) stress responses and adaptation mechanisms have been the epicenter of intensive study over the last decades due to their importance for food industry. Among the stresses encountered, cells are subjected to osmotic pressure during production of starter cultures as well as during food fermentations. Cells react to fluctuations in external osmotic pressure by accumulating or releasing compatible solutes, which aid the microorganism to support a constant positive turgor, by balancing the osmotic difference between cell surroundings and cytosol. The function of cells is determined by the semipermeable attributes of cell membrane, functioning as a barrier for most solutes. The use of specific osmoprotectants is facilitated by certain transporters, whose intercommunication with membrane lipids defines their response to osmotic up- and down- shifts. Glycine betaine (GB) is considered the most efficient osmoprotectant in restricting the repressive effects of NaCl, while carnitine (CA) offers protective action to LAB in a more moderate way. In case the osmotic pressure drops, compatible solutes are released via mechanosensitive channels (MSC), acting as emergency release valves. In the present chapter current knowledge on the LAB osmoprotection mechanisms along with aspects of their genomic and transcriptomic organization is assembled and critically reviewed.

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INTRODUCTION

Lactic acid fermentation has been used for centuries as a method to preserve foodstuff. It has been exercised on practically any type of substrate, either of plant or animal origin. Through this biotransformation, the final product gains enhanced shelf-life, sensorial properties and nutritional value. Lactic acid bacteria that drive this process have been in the epicenter of intensive study over the last decades. Their responses to environmental stimuli as well as their metabolic properties are constantly assessed and our understanding of their physiology accordingly improved.

During fermentation, lactic acid bacteria have to address a series of stresses, such as the osmotic stress due to NaCl that is used as a selective agent, acidic stress due to the acidity that develops as a consequence of their metabolic activity, oxidative stress due to the production of reactive oxygen species (ROS), starvation stress due to the depletion of the available nutrients, etc. It can be claimed that growing in stressful environments is the routine for LAB. In order to address effectively these challenges, a series of tuning activities, collectively referred to as stress response, is required.

Osmotic stress is among the most important ones from a technological perspective. It is the result of dissolved solute abundance and quite different from the desiccation stress, which is the result of lack of water. It may be encountered during production of starter cultures; their preservation may include dehydration and/or freezing. In addition, as already mentioned, the presence of NaCl creates an osmotic pressure to the cells. Finally, the increased osmolarity that characterizes the upper small intestine needs to be effectively addressed in order to exert all the health benefits through the probiotic action.

The aim of the present chapter is to collect all available information regarding the osmoprotection mechanisms of LAB as well as aspects of their genomic and transcriptomic organization and present them in a comprehensive way.

BACTERIAL RESPONSES TO OSMOTIC STRESS

Bacteria protect themselves against detrimental fluctuations of external osmotic pressure by accumulating compatible solutes, i.e., water soluble compounds that may accumulate intracellularly without affecting negatively any cellular functions. In that way the osmotic difference between the environment and cytosol is counter-balanced, and water loss and plasmolysis are prevented. These osmolytes may be either *de novo* synthesized or transported from the environment through specific permeases; depending on the biosynthetic capacity of the bacterium and the growth medium. The latter constitutes the most rapid and effective response, since the former may require additional time and is therefore slower, especially if protein synthesis is involved. Compatible solutes can be classified into three categories: a) sugars and polyols, such as trehalose and glycerol; b) amino acids, such as glutamate and proline; c) amino acid derivatives, such as betaines, ectoines and N- acetylated amino acids. Adjustment of their intracellular concentration is achieved through the coordinated action of specific transporters and mechanosensitive channels (Figure 1). Apart from their osmoprotective action, additional roles have been claimed for glycine betaine, ectoine and proline. The first has been reported to assist *in vivo* protein folding (Bourot et al., 2000) as

well as protection against cold and heat stress (Holtmann & Bremer, 2004; Hoffman & Bremer, 2011); ectoine against cold and heat stress (Bursy et al., 2008; Kuhlmann et al., 2011) and proline is involved in protein stability, ROS scavenging, redox homeostasis and signaling (Liang et al., 2013).

Cell wall of Gram positive bacteria is comprised of a peptidoglycan layer (PG), also known as murein, enclosing the cytoplasmic membrane. This polymer consists of N-acetylglucosamine (GlcNAc) and N-acetylmuramic acid (MurNAc), cross linked by peptide side chains (Chapot-Chartier & Kulakauskas, 2014). The penicillin binding proteins (PBPs) play a crucial role in PG synthesis, which are involved in glycosyltransferase and transpeptidase reactions. Except for the presence of PG sacculus, cell wall of Gram positive bacteria includes teichoic acid polymers as well, being separated into wall teichoic acid (WTA) and lipoteichoic acid (LTA). The former is covalently linked to the PG molecule, while the latter is attached to the membrane by a lipid ligand. The backbone chains of both WTA and LTA can be replaced by D- alanine residues, which reduce the negatively charged phosphate groups of TAs by offering protonated amino groups, thus regulating ionic attributes of TAs. Finally, the existence of O- acetyl groups in PG molecule is highly related to resistance to lysis by hydrolases. LAB lysis/autolysis is a defining parameter for controlling and accelerating ripening events and contributes to the sensory profile of the end product.

In hypertonic conditions, where the concentration of solutes in the environment is higher than that of the cytosol, osmotic pressure stimulates water efflux, resulting in loss of turgor or plasmolysis. Conversely, in hypotonic circumstances, where the culture media is characterized by lower concentration of solutes, compared to cytosol, water diffuses into the cell, increasing its volume, thus leading to cell lysis. The cell membrane plays a crucial role in osmotic regulation; it acts as selective barrier, hindering the passage of solutes, while allowing water permeation in both directions. An alternative response to osmotic gradient includes water transportation through channel like structures, called aquaporins of the MIP (major intrinsic protein) family. A subset of aquaporins, aquaglyceroporins are responsible for glycerol transit. There is evidence that except for water and glycerol, some aquaporins transport CO₂, NH₃, NO, NO₂, H₂O₂ and even ions, K⁺, Cl⁻ (Verkman, 2014).

COMPATIBLE SOLUTES ACCUMULATION IN LAB

The main response of LAB to osmotic challenges, involves the transport of compatible solutes from the surrounding media, since they are characterized by rather narrow biosynthetic potentials. The selection of specific osmoprotectants is facilitated by certain transporters, whose intercommunication with membrane lipids defines their response to osmotic up- and down- shocks.

The beneficial effect of a number of potential osmoprotectant solutes has been experimentally evaluated for a rather restricted number of LAB species, namely *Enterococcus* (*Ec*). *faecalis*, *Lactobacillus* (*Lb*). *plantarum*, *Lactococcus* (*Lc*). *lactis*, *Oenococcus* (*O*). *oeni*, *Pediococcus* (*Ped*). *pentosaceus* and *Tetragenococcus* (*T*). *halophila*, and the results are summarized in Table 1. In all cases, except for *O. oeni*, glycine betaine and carnitine have been reported to effectively restore growth under osmotic pressure. Further examination revealed that the *O. oeni* genome lacked genes homologous to the ones encoding the

transporters of glycine betaine and proline that have been reported for *Lb. plantarum* and *Lc. lactis* (Le Marrec et al., 2007). Except from the accumulation of quaternary ammonium compounds, adjustment of specific amino acids concentration inside the cytosol represents a different strategy to alleviate the adverse effects of osmotic challenges. Robert et al. (2000) reported the accumulation of glutamate, proline and aspartate in *T. halophila* under osmotic constraint. However, uptake of the specific amino acids was restricted in the presence of glycine betaine in a high- osmolarity medium. Similar effect, where concentrations of alanine, glutamate and proline increased in the absence of glycine betaine, was also observed in *Lb. plantarum* (Glaasker et al., 1998). In contrast to the previously mentioned studies, glycine betaine had no protective effects on *O. oeni*, while exogenously supplemented aspartate was able to alleviate the restrictive action of osmotic up- shifts on the cell turgor (Le Marrec et al., 2007). Finally, ectoine, a compatible solute found in halophilic microorganisms, exerted protective effects on *T. halophila* stressed cells (Baliarda et al., 2003b). One last approach reported, includes exogenously supplied osmolytes, such as proline and glutamate-containing peptides conferring protective effects on *O. oeni* sugar induced stressed cells (Le Marrec et al., 2007). Its role as osmoprotectant has been also reported for protease, PrtP, being activated during growth of *Lb. casei* in hyperosmotic conditions (Piuri et al., 2005).

Table 1. Compatible solutes assessed for their osmoprotective effect on LAB

	<i>Lb. plantarum</i> ^{a, d, e, f}	<i>Lc. lactis</i> ^g	<i>Ped. pentosaceus</i> ^a	<i>Ec. faecalis</i> ^c	<i>T. halophila</i> ^{a, b}	<i>O. oeni</i> ^h
carnitine	+	+	+	+	+	-
choline	+	-	+	nd	+	-
DMSA	nd	+	+	+	+	-
DMSP	nd	+	-	+	+	nd
ectoine	-	nd	-	-	+	-
glycine betaine	+	+	+	+	+	-
pipecolate	nd	-	-	-	-	nd
proline	+	-	+	-	-	-
sarcosine	-	nd	-	nd	-	nd
taurine	nd	nd	-	nd	-	nd
arsenobetaine	nd	+	nd	+	nd	nd
γ-butyrobetaine	nd	nd	nd	+	nd	nd
DMG	nd	nd	nd	+	nd	nd
glutamate	+	nd	nd	nd	nd	-
alanine	+	nd	nd	nd	nd	-
glycine	+	nd	nd	nd	nd	nd
betaine	+	nd	nd	nd	nd	nd
acetylcholine	+	nd	nd	nd	nd	nd
aspartate	nd	nd	nd	nd	nd	+

Lb.: *Lactobacillus*; *Lc.*: *Lactococcus*; *Ped.*: *Pediococcus*; *Ec.*: *Enterococcus*; *T.*: *Tetragenococcus*; *O.*: *Oenococcus*
DMSA, dimethylsulfonioacetate; DMSP, dimethylsulfoniopropionate; nd: not determined, DMG: dimethyl glycine.

+: compound exerted osmoprotective action; -: compound did not exert osmoprotective action; nd: not determined

^aBaliarda et al. (2003); ^bRobert et al. (2000); ^cPichereau et al. (1999); ^dGlaasker et al. (1996b); ^eKets et al. (1997); ^fKets et al. (1997); ^gUguen et al. (1999); ^hLe Marrec et al. (2007).

LAB CYTOPLASMIC MEMBRANE AND OSMOTIC STRESS

As previously mentioned the cell cytoplasmic membrane functions as a barrier for most solutes, while is highly permeable to water molecules, thus its coordinated response to osmotic challenges regulates growth restoration. Degree of saturation, fatty acid (FA) composition and size of cells are attributes directly connected to membrane stability, and their behavior in hypertonic media determines the osmotic adaptation of cytoplasmic membrane. It has been shown that proline transport on the hyperosmotic medium of *T. halophila* led to an increase in the amounts of unsaturated FA, as well as the levels of cyclopropanoic FA (He et al., 2017), determining its crucial part in the regulation of fatty acid composition. However, it has also been reported that salt stress conditions favor the saturation degree of FA, often accompanied by FA cyclization, with the latter one being perceived as a process of controlling membrane fluidity (Machado et al., 2004). The presence of saturated FA was also validated by Tymoczyszyn et al. (2005), as a basic component of membrane rigid structure of *Lb. bulgaricus* grown in MRS, supplemented with polyethylene glycol (PEG). In addition a smaller shrinkage of cells, grown in MRS-PEG, was observed due to a higher anisotropy rate (a capability to exhibit variations in physical properties along different molecular axes). Similarly the existence of larger cells of *Lb. casei* in osmotically stressed conditions compared to those under unstressed, was also documented by Piuri et al. (2005).

Growth under high salt circumstances has been shown to facilitate the access of antibiotics to their target, validated by the increased sensitivity of cells to nisin (Piuri et al., 2005; Palomino et al., 2013). This observation was attributed to a decrease in peptidoglycan (PEPG) cross- linkage, caused either by a lower expression of PBP genes or by discrepancies in their appropriate folding in the cell envelope. Another alteration during growth of *Lb. casei* under hypertonic media was the decreased production of a cell wall component, namely lipoteichoic acid (LTA). The specific change was followed by a decline in LTA D-alanylation, generating a negatively charged cell wall, thus hindering the passage of Na⁺ to the cytoplasm. Decreased LTA substitution by D-alanine residues in combination with the participation of LTA in attachment of autolysins develops a PEPG more vulnerable to lysis. Lysis of LAB is crucial for the development of texture and flavor in food products and the harmony between autolysed and intact cells determines the fate of various ripening events.

Osmoprotectants are accumulated in the cytosol via active transport (Figure 1), upon osmotic up- shifts; however, upon decrease of the osmotic pressure, they are released from the cell via mechanosensitive channels (MSC). In fact, MSC function as biological emergency release valves, by facilitating a compatible solute efflux, having been accumulated in the cytosol, upon osmotic stimulation of the OpuA transport system (Booth & Blount, 2012). As the OpuA uptake system is activated by sensing the interactions between protein module and lipid membrane, so do MSC, which sense possible distortion of the lipid bilayer. The osmoprotectant role of MSC was determined with the presence of two MSC in *E. coli*, namely MscS (mechanosensitive channel small conductance) and MscL (mechanosensitive channel large conductance) (Levina et al., 1999). The MSC study has been restricted in LAB, from which only the *Lc. lactis* mechanosensitive solute transfer system has been reported (Folgering et al., 2005). Their results revealed the presence of two different genes, *yncB* and *mscL*, regulating MscS and MscL, respectively, with MscL being preferentially activated by *Lc. lactis* under osmotic down- shock. Despite the fact that *yncB* gene was transcribed, MscS

stimulation was not confirmed. MscS and MscL detected in *Lc. lactis* shared many similarities with those identified in *E. coli*; nevertheless the medium ionic strength had no effect on the transcription process of the corresponding genes in the case of *Lc. lactis*, but was determinant for the gene expression in *E. coli*.

Mechanosensitive ion channels play a crucial role in sensing membrane tension within a cell's surroundings and transducing mechanical constrain into an electrochemical response. The *E. coli* MscS homoheptameric structure (MscS-Ec) is strongly dependent on the TM1-TM2 region, which senses membrane distortions and its interaction with TM3 helix, forms specific channels, comprised of Gly and Ala residues (Booth & Blount, 2012). The block complex, identified in the open structure of A106V mutant of the MscS-Ec channel, is based on the presence of 2 rings of Leu residues and is highly hydrophobic, hindering the passage to ions and water. The transition of close to open state of MscS starts with the TM1-TM2 helix being triggered by ionic changes in lipid membrane. Then, a further stimulation of the TM3 domain follows, which is accompanied by a slight rotation, resulting in the discharge of Leu residues and generating the open configuration. As for MscL, they respond to osmotic challenges, sensed by alterations in membrane tension, by opening a large water- filled pore, thus aiding as osmoprotective emergency valves. MscL was first identified in *E. coli* constituting a non- selective ion pathway, but a three dimensional (3D) conformation of MscL from *Mycobacterium tuberculosis* (MtMscL) revealed the basic elements defining its structure. In brief, crystal structure of MtMscL indicates a highly α - helical homopentamer, with N- and C- terminal regions facing the cytoplasm, TM1, TM2 transmembrane helices and a periplasmic loop connecting them (Chang et al., 1998; Pivetti et al., 2003; Bavi et al., 2017).

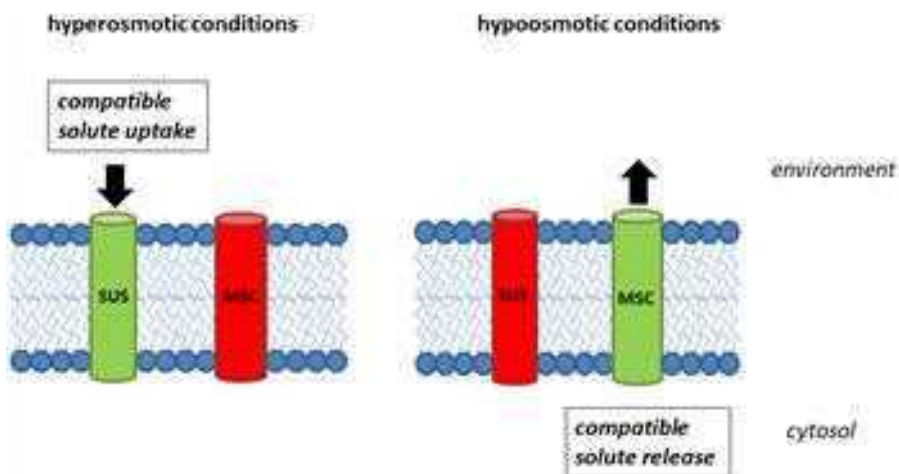


Figure 1. Schematic representation of a generic LAB osmotic adaptation mechanism.

Upon hyperosmotic stress, osmolytes are accumulated in the cytoplasm, via a compatible solute uptake system (SUS), while they are released to the culture media via mechanosensitive channels (MSC), upon osmotic downshifts. Green color designates open configuration to the respective system; red color designates close configuration.

Questionable was the role of C- terminal domain in the regulation of the MscL opening, with many studies supporting its complete dissociation, and others arguing that the helical bundle remained intact, all along its transition pathway from close to open state. Bavi et al. (2017)

reported the partial dissociation of the MscL-Ec channel under different conditions, favoring the open channel conformation. More analytically, the results showed that the gating of the MscL channel was accompanied by a restricted dissociation of the top part of the C- terminal region, due to weak hydrogen bonds between subunits, while the residual domain of the central and the end bundle remained associated. A study employing various experimental circumstances for studying 3 different states of MscL, close, intermediate and open was performed by Perozo et al. (2002). The conversion pathway of close- intermediate conformation initiates imperceptible shifts in the transmembrane helix, TM1; while TM2 does not rotate about its central axis. Further transition to the open state, is followed by crucial structural changes, with TM1 actively participating in the channel gating. The transition to the open MscL conformation, escorted by the presence of an open pore, 30- 40 Å° in diameter, was triggered by adding lysophosphatidylcholine (LPC) into phosphatidylcholine (PC) vesicles.

Lactococcus lactis

Lc. lactis possesses an uptake system for the osmoprotectant GB, known as BusA/OpuA, linked with the ATP- binding cassette (ABC) superfamily of transporters. The system has high compatibility with GB and a lower one with proline. It is comprised of 2 nucleotide-binding domains (NBD) integrated into cystathionine-β-synthase (CBS) domains, forming the OpuAA subunit and 2 substrate binding domains embedded in transmembrane domains, constituting the OpuABC subunit (Mahmood et al., 2009). The osmotic stimulation of OpuA is based on regulating the on/off mode of the transporter, through (inter) mediate action of a protein module (CBS domains) with charged membrane surface. Its activation involves intensity levels of ionic strength, sensed by tandem CBS domains, found at the C- terminal end of OpuAA complex (Biemans-Oldehinkel et al., 2006). The negatively charged C-terminal tail coordinates the sensing of internal ionic strength. Briefly, below the intensity levels of ionic strength, the transporter is kept in an inactivate mode, while at higher medium osmolality, the osmosensing mechanism shifts the “electrostatically sealed mode” of the transporter to an “active” one.

BusR protein has been in the epicenter of intensive study due to its repressor character on the osmotically activated system, BusA, of *Lc. lactis*. Upon osmotic down-shock, BusR attaches the BusA promoter (BusAp) in a manner determined by the ionic concentration. In more detail, BusR reacts to hypoosmotic conditions, by forming a ternary structure with RNA polymerase, found at the promoter site. When cytoplasmic ionic strength increases, BusR detaches from BusAp, facilitating the initiation of busA operon transcription.

An osmosensitive phenotype in *Lc. lactis* subsp. *cremoris* has been described by Obis et al. (2001), having been associated with a limited capability of betaine uptake. This contrasting behavior with the rest *Lc. lactis* strains could be attributed to a deficiency of the busA operon or moderate expression or even restricted/poor activity of the BusA transporter.

Lactobacillus plantarum

As previously mentioned, LAB are characterized by restricted biosynthetic capabilities, making the transport of osmoprotectants from the surrounding media, critical for their survival under osmotic constraints. *Lb. plantarum* possesses a transport system, termed QacT (quaternary ammonium compound transporter), driven by ATP, with high affinity for GB and CA and a lower one for proline (Glaasker et al., 1998). As the GB uptake system is stimulated at elevated osmolality conditions until osmotic balance is achieved, so does the GB efflux from the cytosol, upon hypoosmotic circumstances. GB release from the cells include an accelerated initial phase, facilitated by a stress regulated mechanosensitive channel and a second slower one, enhanced by a carrier- like protein (Glaasker et al., 1996a; b). Therefore the up and down- regulation of GB transport system in *Lb. plantarum* is crucial for osmostasis control.

The addition of chlorpromazine, a cationic amphipath, reinforces the open state of MSCs and imitates osmotic down- shifts, by facilitating GB efflux from the cytosol (Glaasker et al., 1998). The release of osmoprotectants is accompanied with a lag time of 15 sec, when chlorpromazine is added, whereas it is extremely rapid upon osmotic down- shifts, highlighting the characteristics differentiating the QacT system from the common transport mechanisms.

Tetragenococcus halophila

T. halophila (formerly *Pediococcus halophilus*) is a moderately halophilic bacterium, characterized by the capacity to tolerate high salt concentrations. Sharing analogous biosynthetic attributes with other LAB, *T. halophila* cannot synthesize *de novo* effective compatible solutes, therefore it is strongly dependent on their presence in the defined media. Except from the compatible solute uptake system, activated under hyperosmotic conditions, *T. halophila* is the first lactic acid bacterium, in which the existence of a choline- GB pathway, under aerobic conditions, has been reported (Robert et al., 2000). Baliarda et al. (2003a) documented the presence of two GB accumulation systems, the former carrying GB only and the latter facilitating the transport of betaines, choline and carnitine. The identification of ButA protein from the osmotolerant *T. halophila* has been linked with the betaine choline carnitine transporter (BCCT) family, involving divergent osmoprotectant uptake systems, for instance BetL from *Listeria (L.) monocytogenes* and OpuD from *Bacillus (B.) subtilis*. Except from the osmoprotective role of GB on *T. halophila*, the exogenously supplied DMSA and DMSP (GB structural analogues) also relieve inhibitory effects of NaCl stress. In addition, presence of tetrahydropyrimidine ectoine in the surrounding media of the halophilic bacterium has been found to enhance its osmoprotection (Baliarda et al., 2003b).

Additional Lactic Acid Bacteria

Although the aid of compatible solutes like GB, CA and choline was previously described and highlighted for a variety of LAB, *Lb. bulgaricus* was not able to accumulate

those osmolytes under stressed conditions (Chun et al., 2012). In other words, GB and proline uptake system was not activated, which was associated with a lack of genes regulating the transport mechanism in the genome of *Lb. bulgaricus*. More analytically, *B. subtilis* uptake system, also known as OpuA, preferentially accumulates GB; however, the genes encoding the specific transport system were not identified in *Lb. bulgaricus*. The amino acids aspartate and alanine could counterbalance the osmotic suppression caused under NaCl stress.

Similar osmotic response was observed in *O. oeni*, the predominant bacterium of malolactic fermentation (MLF). GB accumulation system was not up-regulated, probably due to a lack of uptake mechanisms related to the BusA/OpuA- BusA/OpuC GB transporters (Le Marrec et al., 2007). Inability to concentrate choline was also reported, validating the absence of choline- GB pathway in *O. oeni*. Nevertheless, the exogenously added aspartate exhibited its osmoprotective role, restoring the ionic imbalance between cell's surroundings and cytosol.

As for *Streptococcus (Str.) mutans* UA159, resided in oral cavity, an *opc/opu* gene array was identified (Abranches et al., 2006). The specific gene complex, belonging to the Opu family of ABC transport systems, seems homologous with corresponding genes in *Str. agalactiae* as well as the OpuC transport mechanism of *L. monocytogenes*.

CONCLUSION

The response of some LAB with technological significance to osmotic changes has been studied to some extent. Current available data, although revealing, are based on a rather limited number of strains. Therefore it is practically impossible to assess strain diversity and include it to the already discovered differences between species. In addition, identification of the transcription factors that are activated by this environmental stimulus as well as their regulons is still to be explored. Taking into consideration the importance of an effective osmotic stress response, it is reasonable to expect our knowledge to expand within the next few years.

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Chapter 296

LACTIC ACID BACTERIA AS SOURCE OF BIOSURFACTANTS

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ABSTRACT

Nowadays consumers demand for healthier foods and for chemical free additives products. Lactic acid bacteria (LAB) have a generally recognized as safe (GRAS) status according to Food and Drug Administration Agency. Furthermore, they are an important source of bioactive compounds with wide applications in the food industry. Some of these compounds are *in situ* produced while others are *ex situ*. LAB have been used to produce fermented products since ancient times and the safety and sensory characteristics of these products rely on a diversity of metabolites produced *in situ* by LAB. In the last decades, the possible application of LAB metabolites as preservatives has increased; mainly bacteriocins, which were even approved worldwide. However, the use of LAB metabolites as additives is still emerging, particularly in the case of biosurfactants. These can exhibit emulsifying, antiadhesive and antimicrobial activity. The main objective of this chapter is to review the current status of the knowledge and possible applications of biosurfactants as additives for the formulation of foods.

INTRODUCTION

Biosurfactants are amphiphilic compounds produced by microorganisms, mainly bacteria and yeasts. They are multipurpose additives since they can reduce surface and interfacial

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tension, act as emulsifying, antiadhesive and antimicrobial agents. Furthermore, they are environmental friendly, biodegradable, and show low toxicity. Consequently, their search has attracted the attention in the last decades. Most studies were focused on bioremediation and few were done about the food industry, although the increasing demands for replacing synthetic additives by naturals (Nitschke & Costa, 2007).

Biosurfactants can be classified according to their chemical composition and microbial source. Regarding their chemical composition, some of them are low-molecular mass compounds while others are high molecular mass ones. The first group includes glycolipids, lipopeptides and phospholipids that are efficient for lowering surface and interfacial tension, the second ones are of polymeric nature and act as emulsions stabilizers (Nitschke & Costa, 2007).

Most biosurfactants are produced by bacteria belonging to *Pseudomonas*, *Bacillus*, *Acinetobacter* and by lactic acid bacteria (LAB). The latter, include different genera, particularly, *Lactobacillus*, which constitutes part of the indigenous flora of the gastrointestinal track of humans, and is generally recognized as safe. For this reason, its application is considered safe.

The main drawbacks from LAB biosurfactants are that they are less effective to reduce the surface tension, they have higher critical micelle concentrations (CMC), they are produced in lower amounts and finally, they are cell-bound being necessary an extraction process for their recovery (Nitschke & Sousa e Silva, 2018).

Regarding the chemical composition of biosurfactants produced by lactobacilli, they are glycolipids, glycoproteins, lipopeptides, glycopeptides or phosphoglycoproteins, independently of the strain and culture conditions used (Hajfarajollah et al., 2018).

The role of biosurfactants *in vivo* is still a matter of debate. One proposal is that they are implicated in the emulsification of water-insoluble substrates improving their absorption. Also, they are considered as components of cellular metabolism, motion and defense since they take part in cell adhesion to interfaces (Sharma et al., 2016).

Food products have pH values within the range of 3.0 to 7.0, they content salts that modify ionic strength and during processing and storage they are exposed to different temperatures. Therefore, the biosurfactant must be selected taking into account that it will have to be stable in the conditions of use. For example, Rodrigues et al., (2006 a) evaluated surface tension within the range of pH 4 to 10 for the crude and purified biosurfactant produced by *Streptococcus (Strep.) thermophilus* A. They found that the ability to reduce surface tension remained stable in the range studied but a purified fraction precipitated at pH 4, limiting its use in this condition.

Optimal conditions for production depend on the producing microorganism and also on the nature of biosurfactant. In most cases, the amount of biosurfactant released by *Lactobacilli* is maximum during the stationary growth phase (Velraeds et al., 1996; Golek et al., 2009). In the case of *Acinetobacter (Ac.) calcoaceticus*, biosurfactant production was directly associated with the growth of the microorganism (Desai & Desai, 1993). Furthermore, the C:N ratio seems to be a critical factor in the production of biosurfactants and a 1:1 ratio would be optimal (Bakhshi et al., 2018).

It is well known that one of the drawbacks for biosurfactant uses is the high cost of production and particularly, for LAB biosurfactants, their low productivity. For this reason, many investigations have been done looking for the conditions to optimize production. Moreover, alternatives culture media using renewable and low-cost raw materials such as

agricultural wastes were evaluated. For example, hemicellulosic sugars from vineyard pruning waste were successfully applied to obtain a glycolipopeptide with promissory emulsifying capacity from *Lactobacillus (Lb.) pentosus* fermentation (Vecino et al., 2015). Moreover, rice, wheat bran and straw were evaluated for biosurfactant production by *Lb. plantarum* subsp. *plantarum* PTCC 1896 and it was reported that only the rice bran hydrolysate was adequate as substrate for biosurfactant production (Bakhshi et al., 2018). Finally, biosurfactant production by *Lb. pentosus* using whey as culture media was assayed and compared to production using MRS and it was found that biosurfactant production was similar in both media. However, the strain did not growth well in the whey media, probably due to the lack of nutrients (Rodrigues et al., 2006 b). The satisfactory results of the use of wastes for biosurfactant production encourage the continuous search for the optimal conditions of production and the study of the structure–function relationship in food systems. According to Mouafo et al., (2018) a reduction of 30-50 % of production cost can be obtained by using alternative substrates.

Regarding the use of different culture media, it must be stressed that most of the biosurfactants are cell bound; consequently, their extraction from culture medium is necessary. After the incubation of LAB at selected conditions for production and centrifuging to remove the supernatant, bound to cells biosurfactant can be extracted by re-suspension in PBS and gentle stirring or by re-suspension in distilled water and extraction using an ultrasonic cell disintegrator. Use of phosphate buffer saline (PBS) together with gentle stirring is the most common procedure (Hajfarajollah et al., 2018).

Main biosurfactants can be applied as emulsifying, antiadhesive and antimicrobial agents as it will be discussed in the next sections. In addition to this, they can be used to control flat globules agglomeration, stabilize foams and improve bakery products texture (Nitschke & Costa, 2007). Finally, some recent studies proposed their use as antioxidant agents, for example, a lipopeptide from *Bacillus subtilis* exhibited good activity to scavenge free radicals (Nitschke & Sousa e Silva, 2018).

APPLICATIONS OF BIOSURFACTANTS AS EMULSIFIER AGENTS

Emulsions are colloidal dispersions of lipids and water that need the addition of a surfactant to lower the interfacial tension in order to decrease the superficial energy between the two phases. Different types of surfactants are used in the food industry, some of them are synthetic compounds and, as previously mentioned, there is a trend to replace them by natural products. There are a large number of excreted biosurfactants derived from *Pseudomonas* and *Bacillus* strains that have potential capacities to be used as emulsifiers, such as rhamnolipids, emulsan and liposan. However, their origin limits their use in the food industry. Therefore, the biosurfactants derived from LAB are an alternative option, although they are less effective in reducing surface tension of water than the former (Mouafo et al., 2018).

The potential application of biosurfactants as emulsifying agents is measured by their effectiveness in reducing superficial tension, in having low CMC and high emulsification capacity. Table 1 shows parameters of several biosurfactants obtained from LAB. Reductions of surface tension of water higher than 8 mN/m are considered as the minimum for a biosurfactant to be effective. Furthermore, CMC expresses the concentration which

corresponds to the minimum value of the surface tension that can be obtained with each compound. Important surface tension reductions (41.90 and 46.20 mN/m), low CMC (8 and 15 mg/mL) and high emulsification indexes (77.25 and 89.00% after 24 h) were observed with *Lb. delbrueckii* N2 using molasses or glycerol as substrates (Mouafo et al., 2018). Morais et al., (2017) extracted surface active compounds from *Lb. jensenii* P6A and *Lb. gasserii* P65 with potential application as bioemulsifiers in food (Table 1).

Biosurfactant production is not a simple matter. The extraction yields and structures are dependent on the right balance of culture media nutrients, microbial growth phase, and conditions of growth such as fermentation time, pH and temperature. These factors should be controlled to assure biosurfactant production with well-defined and consistent functionality and quality. Sugar cane molasses or glycerol were evaluated for biosurfactants production by *Lb. cellobiosus* TM1, *Lb. delbrueckii* N2, and *Lb. plantarum* G88. Mainly glycoproteins were obtained with molasses and glycolipids with glycerol indicating that biosurfactant composition is also substrate dependent. Yields obtained with both substrates were higher than those obtained with MRS broth whereas high surface tension reductions and emulsification indexes were observed with molasses as substrate (Mouafo et al., 2018).

In relation to microbial growth phase and growth conditions, Madhu and Prapulla (2013) observed that biosurfactant released by *Lb. plantarum* CFR 2194 was higher under stationary than shaking conditions and it was maximum after 72 h of fermentation showing a decrease of surface tension of 44.3 mN/m, a CMC of 6 g/L and high emulsification indexes against coconut and sunflower oils (Table 1). These emulsions were more stable than emulsions formed with hydrocarbons and they could be of interest for application in food formulations.

Regarding the effects of other additives and conditions used for biosurfactant production, Vecino et al., (2015) studied the effect of NaCl concentrations, time and temperature of extraction on emulsifying ability of the biosurfactant produced by *Lb. pentosus* through a Box-Behnken response surface methodology. The extraction was carried out at the beginning of the stationary phase, after 24 h of fermentation, when biomass concentration was at its maximum. All variables affected the ability of the biosurfactant to act as emulsifier being the most influential variables the time of extraction, followed by temperature, and salt concentration. The optimal conditions were 9 g/kg salt, 45°C and 120 min. From the chemical point of view, the biosurfactant extracted was a mixture of carbohydrate, protein and lipid in a combination of 1:3:6, respectively. Then, this biosurfactant was successfully used to stabilize a rosemary oil/water emulsion with most droplets diameter < 100 µm and which exhibited a creamy consistency. On the contrary, the same emulsion stabilized with polysorbate 20 was less consistent and more unstable.

Sharma et al., (2014) studied the effect of pH (4, 6, 7, 8 y 10), temperature (4, 22 y 37°C), NaCl concentration (4, 6, 8 y 10%), carbon and nitrogen sources on emulsification index of different biosurfactants produced by *Lactobacillus* strains isolated from milk samples. The decrease in salt level and temperature promoted an increase in emulsification index. Strains preferred yeast extract as nitrogen source instead of urea, and there was no marked preference between glucose and sucrose as a carbon source.

Table 1. Compilation of some uses of biosurfactants as emulsifier agents

LAB Strain	Substrate used for production	Emulsion formation	Assay performed and trends observed	Reference
<i>Lb. pentosus</i>	Hemicellulosic sugars from vineyard pruning waste	Rosemary oil/water emulsions	- CMC*: 2 mg/L (measured as surfactin equivalents, 25°C) - Relative emulsion volume of 55.5% after 24 h of emulsion formation Emulsions of water and rosemary oil stabilized with the biosurfactant were more stable than those stabilized with polysorbate 20.	Vecino et al., (2015)
<i>Lb. plantarum</i> subsp. <i>plantarum</i> PTCC 1896	Rice and wheat bran and straw	Canola oil emulsion	- Maximum emulsification index was 64.70% - Maximum emulsion stability was 97.73%	Bakhshi et al., (2018)
<i>Lb. delbrueckii</i> N2, <i>Lb. cellobiosus</i> TM1, <i>Lb. plantarum</i> G88	Sugar cane molasses or glycerol	Refined palm oil emulsion	- STR* ranged from 49.00 to 41.90 mN/m; - Emulsification index ranging from 41.81 to 81.00%. - CMC: 8 to 20 mg/mL	Mouafo et al., (2018)
<i>Lb. jensenii</i> P6A <i>Lb. gasserii</i> P65	MRS broth	Emulsification of several hydrocarbons and cotton, olive and sunflower oils.	For <i>Lb. jensenii</i> P6A: - STR to 42.5 mN/m - CMC: 8.58 mg/mL - Maximum emulsifying activity: at 5 mg/mL - Emulsification activity values ranged from 71 to 75% for cotton, olive, and sunflower oils For <i>Lb. gasserii</i> P65: - STR to 42.5 mN/m - CMC: 8.58 mg/mL - Maximum emulsifying activity: at 5 mg/mL - Emulsification activity values ranged from 71 to 75% for cotton, olive, and sunflower oils.	Morais et al., (2017)
<i>Lb. Plantarum</i> CFR 2194	MRS broth	Coconut and sunflower oils emulsions	- STR to 44.3 mN/m - CMC: 6 g/L - Emulsification index: 37.9% for coconut oil and 19.43% for sunflower oil. Coconut and sunflower oils emulsions were more stable than emulsions formed with hydrocarbons.	Madhu and Prapulla (2013)

Table 1. (Continued)

LAB Strain	Substrate used for production	Emulsion formation	Assay performed and trends observed	Reference
<i>Lb. helveticus</i> MRTL	MRS-Lac (glucose replaced by lactose)	Emulsification with kerosene	- STR to 39.5 mN/m - CMC: 2.5 mg/mL - Emulsification index of 65% Biosurfactant was stable at pH range (4.0-12.0), it was more effective at pH 7 and surface properties were kept after heat treatment at 125°C for 15 min. -Emulsion stability from 70.4 to 93.3% depending on growth media	Sharma and Saharan (2016)
<i>Lb. pentosus</i>	Residual stream after tartaric acid extraction from vinasses	Emulsification with kerosene		Salgado et al., (2013)
<i>Lb. coryniformis</i> ssp. <i>torquens</i> CECT 25600 <i>Lb. plantarum</i> A14 <i>Leuconostoc mesenteroides</i> <i>Lb. paracasei</i> ssp. <i>paracasei</i> A20	MRS-Lac Different nitrogen sources in MRSLac broth (peptone, meat extract, and yeast extract) on <i>L. paracasei</i> ssp. <i>paracasei</i> A20	_____	- STR from 69.6 to 50.0 mM/m after 8 h of fermentation for all strains. <i>Lb. paracasei</i> ssp. <i>paracasei</i> A20 showed the higher reduction. Higher biosurfactant production in presence of peptone and meat extract for <i>Lb. paracasei</i> ssp. <i>paracasei</i> A20, with a STR of 24.5 mN/m.	Gudiña et al., (2011)
Eight strains of <i>Lactobacillus</i> spp.	<i>Pendidam</i> (fermentative acid milk)	Emulsification with refined palm oil	- STR from 45.09 to 53.68 mM/m - Emulsification index from 10 to 56.80%	Mbawala and Mouafo (2012)
<i>Lactobacillus acidophilus</i> CECT-4179 (ATCC 832) <i>Debaryomyceshanseni</i> NRRL Y-7426	Synthetic hemicellulosic sugars Hemicellulosic vine-shoot trimming hydrolysates	_____	- STR of 24.5 mN/m <i>Lb. acidophilus</i> STR in synthetic sugars and 18 mM/m in trimming vine shoots. - Dilutions (biosurfactant extract volume/total volume) to achieve CMC were 0.138 for synthetic sugars and 0.152 for trimming vine shoots.	Portilla et al., (2008)
<i>Lactobacillus pentosus</i>	Hydrolysates of vine pruning waste	gasoline/water emulsions	Studied the effect of pH, temperature and salinity on surface-active properties. - STR from 53.8 to 69.3 mM/m - Emulsion volume up to 47.48% - Emulsion stability up to 100% Maximum emulsifying capacity and emulsions stability were achieved at temperatures below 30°C, salinity below 3%, and pH higher than 5.	Vecino et al., (2012)

*STR: Surface tension reduction, CMC: Critical Micellar Concentration.

Since most of chemical structure of biosurfactants contains proteins, the thermal stability is an important property to be studied. Producing a biosurfactant with high thermostability extends its range of application. Vecino et al., (2015) observed that as the production temperature increases, the emulsifying capacity of the biosurfactant obtained from *Lb. pentosus* increases, therefore, being thermostable makes it have better functionality. Bakhshi et al., (2018) extracted a water soluble extracellular high molecular weight α -glucan bound with protein, with high melting point (182.0°C) and high degradation temperature (211.74°C). Morais et al., (2017) evaluated the effect of pH, temperature (100°C) and salt concentrations (NaCl, KCl and NaHCO₃) on the activity of biosurfactants extracted from *Lb. jensenii* P6A and *Lb. gasseri* P65. They obtained stable emulsions after 60-min of incubation at 100°C, at pH 2–10, and after the addition of KCl and NaHCO₃.

APPLICATIONS OF BIOSURFACTANTS AS ANTIADHESIVE AGENTS

A large number of foodborne bacteria are capable of adhering to and forming biofilm on different surfaces, such as stainless steel, plastic, glass (Wang et al., 2014) and even food surfaces, like fruits and vegetables (Bilek et al., 2013). The adhesion of bacteria on surfaces compromises food safety, and produces food spoilage, generating huge economic losses (Van Houd & Michiels, 2010). Consequently, there is a focus of interest around the development of innovative techniques to overcome this issue.

One possible application of biosurfactants produced by LAB is as an antiadhesive agent (Table 2). It could be used as a surface conditioner, preventing the adhesion of microorganisms and the subsequent formation of biofilm, avoiding the use of synthetic disinfectants with considerable toxicity levels. For this reason, LAB surfactants present a great potential in food industry. Nevertheless, it is notorious that in most cases the applications studied are closely related with the biomedical area and used as conditioners of silicone rubber normally used in catheters and prosthesis (Rodrigues et al., 2004; Ceresa et al., 2015; Sharma et al., 2016). Furthermore, it was proved the anti-adhesion effect against strains isolated from voice prosthesis (Rodrigues et al., 2006, a), from the mouth and blood (Fracchia et al., 2010), uropathogenic bacteria (Velraedes et al., 1998) and skin pathogens (Vecino et al., 2018). To our knowledge only one study has reported the use of LAB biosurfactant as stainless steel conditioner, material commonly used in food industry (Meylheuc et. al, 2006), and none on the effects against film forming microorganisms isolated from food environments, nevertheless there is an expansion in the knowledge in these promising fields.

The genres of LAB biosurfactant producers showing antiadherent capability are *Lactobacillus*, *Lactococcus*, and *Streptococcus*. Many researchers have shown that biosurfactants produced by *Lactobacillus* strains are capable to reduce the adherence of bacteria to different surfaces. An early investigation on this subject has reported the ability for biosurfactant production of fifteen *Lactobacillus* strains and investigated further to determine their capacity to inhibit the initial adhesion of *Enterococcus* (*Ec.*) *faecalis* 1131 to glass.

Table 2. Compilation of some uses of biosurfactants as antiadhesive agents

LAB strain/source	Target m.o. for antiadhesive activity	Assay performed	Effect	Reference
<i>Lc. lactis</i> 53 / Nutricia (The Netherlands)	<i>S. epidermidis</i> GB 9/6, <i>Strep. salivarius</i> GB 24/9, <i>S. aureus</i> GB 2/1, <i>Rothia</i> (R.) <i>dentocariosa</i> GBJ 52/2B, <i>Candida</i> (C.) <i>albicans</i> GBJ 13/4A, <i>C. tropicalis</i> GB 9/9	Anti-adhesion assay in polystyrene 96 wells plate	Adhesion reduction of 70% for <i>S. aureus</i> GB 2/1 and <i>S. epidermidis</i> GB 9/6 at concentration 25g/L	Rodrigues et al., (2006 a)
<i>Strep. thermophilus</i> A / NIZO	<i>S. epidermidis</i> GB 9/6, <i>Strep. salivarius</i> GB 24/9, <i>S. aureus</i> GB 2/1, <i>R. dentocariosa</i> GBJ 52/2B, <i>C. albicans</i> GBJ 13/4A, <i>C. tropicalis</i> GB 9/9	Parallel-plate flow chamber on silicone rubber and image analysis	Adhesion reduction of 89-97% for bacteria and 67-70% for yeasts at concentration 3g/L	Rodrigues et al., (2006 b)
<i>Lb. helveticus</i> 1181 /Cheese industry	<i>L. monocytogenes</i> CIP103574, <i>L. monocytogenes</i> CIP104794, <i>L. monocytogenes</i> CIP103573 <i>L. monocytogenes</i> CIP78.39	Co-incubation assays on metallic supports	Adhesion reduction of 93.62–99.77% at concentration 5g/L.	Meylheuc, et al., (2006)
<i>Strep. mitis</i> / Human oral cavity	<i>Strep. sobrinus</i> HG1025 <i>Strep. mutans</i> ATCC 25175 <i>Strep. mitis</i> BMS	Co-incubation of enamel particle and atomic force microscopy	The biosurfactant generate an increase in the repulsive forces between the surface and the microorganism.	Van Hoogmoed, et al., (2006)
<i>Lb. acidophilus</i> - H-1, <i>Lb. acidophilus</i> -336, <i>Lb. acidophilus</i> -Ch-2 / Rhodia Food Biolacta Company, Olsztyn, Poland	<i>S. aureus</i> - ATCC 29213, <i>S. aureus</i> -1474/01, <i>S. aureus</i> -A3, <i>S. epidermidis</i> -6756/99, <i>S. epidermidis</i> -A4c, <i>S. epidermidis</i> -RP12	Initial adherence evaluation by MTT*-reduction assay/ Confocal microscopy	Biofilm covered less surface area, decrease in their total biovolume and have a lower mean biofilm thickness. LAA strain H-1 produced the best anti-adhesion active agent.	Walencka et al., (2008)
<i>Lb. paracasei</i> / Portuguese dairy industry	<i>E. coli</i> , <i>P. aeruginosa</i> , <i>S. aureus</i> <i>S. epidermidis</i> , <i>Strep. agalactiae</i> <i>Strep. pyogenes</i>	Anti-adhesion assay in polystyrene 96 wells plate	Adhesion reduction of 72.0% for <i>S. aureus</i> at a concentration 25 g/l.	Gudiña et al., (2010, a)
<i>Lb. paracasei</i> ssp. <i>paracasei</i> A20	<i>Lb. casei</i> 36, <i>Lb. Casei</i> 72, <i>Lb. reuteri</i> 104R, <i>Lb. reuteri</i> ML1.1, <i>S. mutans</i> NS, <i>Strep. mutans</i> HG985, <i>Strep. oralis</i> J22, <i>Strep. sanguis</i> 12, <i>E. coli</i> , <i>P. aeruginosa</i> , <i>S. aureus</i> , <i>S. epidermidis</i> , <i>Strep. agalactiae</i> , <i>Strep. pyogenes</i> , <i>C. albicans</i> , <i>Malassezia</i> sp., <i>Trichophyton</i> (T.) <i>mentagrophytes</i> , <i>T. rubrum</i>	Anti-adhesion assay in polystyrene 96 wells plate	Adhesion reduction of 87,7% for <i>L. reuteri</i> ML1.1 at a concentration 50 g/L	Gudiña et al., (2010, b)
<i>Lactobacillus</i> sp. CV8/LAC / Fresh Cabbage	<i>C. albicans</i> DSMZ, <i>C. albicans</i> CA-2894	Pre-coating and co-incubation assay in polystyrene 96 wells plate	Adhesion reduction of 86% for <i>C. albicans</i> CA-2894 at a concentration 25g/L in the pre-coated surface and 86% for <i>C. albicans</i> DSMZ 1122 in the co-incubate plate at concentration 160.5 µg/well.	Fracchia et al., (2010)

LAB strain/source	Target m.o. for antiadhesive activity	Assay performed	Effect	Reference
<i>Lb. plantarum</i> CFR 2194 Arenahalli / kanjika	<i>E. coli</i> ATCC 31075, <i>E. coli</i> MTCC 108, <i>Salmonella typhi</i> , <i>Yersinia</i> (Y.) <i>enterocolitica</i> MTCC 859, <i>S. aureus</i> F 722	Anti-adhesion assay in polystyrene 96 wells plates.	Adhesion reduction of 67.18% for <i>S. aureus</i> at concentration 25 g/L	Madhu and Prapulla (2013)
<i>Lb. brevis</i> CV8LAC /Fresh cabbage	<i>C. albicans</i>	Co-incubation assays on silicone surface and precoating assays in silicone surface SEM analysis	Adhesion reduction of 90% at the concentration 4g/L, using co-incubation assay Adhesion reduction of 50% at the concentration 3g/L, using precoating assay	Ceresaet al., (2015)
<i>Lb. helveticus</i> / Yak milk cheese	<i>E. coli</i> ATCC 25922, <i>P. aeruginosa</i> ATCC 15442, <i>S. typhi</i> MTCC 733, <i>Shigella flexneri</i> ATCC9199, <i>S. aureus</i> ATCC 6538P, <i>S. epidermidis</i> ATCC12228, <i>L. monocytogenes</i> MTCC 657, <i>L.</i> <i>innocua</i> ATCC 33090, <i>Bacillus</i> (B.). <i>cereus</i> ATCC 11770	Anti-adhesion assay in polystyrene 96 wells plate and co- incubation assays on silicon tubes.	Adhesion reduction of 87% <i>B. cereus</i> at concentration 25 g/L. Decrease of adhesion on silicone tube at concentration 25 mg/mL for all strains	Sharma & Saharan (2016)
<i>Lb. pentosus</i> CECT-4023T (ATCC-8041) / Spanish Type Culture Collection (Valencia, Spain) <i>Lb. paracasei</i> / Portuguese dairy industry	<i>E. coli</i> , <i>P. aeruginosa</i> , <i>S. aureus</i> , <i>S. epidermidis</i> , <i>Strep. agalactiae</i> , <i>Strep. pyogenes</i> , <i>C. albicans</i>	Anti-adhesion assay in polystyrene 96 wells plate	Adhesion reduction of 77% for using biosurfactant produced by <i>L. pentosus</i> and extracted with PB, at concentration 25g/L Adhesion reduction of 81% for <i>S.</i> <i>agalactiae</i> using biosurfactant produced by <i>L. paracasei</i> extracted with PBS, at concentration 25g/L	Vecino et al., (2018)

*MTT: 4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide.

This research showed that *Lb. acidophilus* RC14 and *Lb. fermentum* B54 were able to produce a biosurfactant, which reduced the deposition of *Ec. faecalis* by an average of 70% and the adhesion by an average of 77% (Velraeds et al., 1998). Those strains of *Lactobacillus* biosurfactant producers were two of many others found in the last decades capable to produce biosurfactants which reduced the adhesion of bacteria to surfaces. *Lb. paracasei* isolated in a Portuguese dairy industry produced a biosurfactant capable to reduce the adhesion of *Staphylococcus* (*S.*) *aureus* to polystyrene by a percentage of 72.0%, 62.1%, for *S. epidermidis* and *Strep. agalactiae*, respectively in a biosurfactant concentration of 25 mg/mL. However, a lower activity was observed for decreasing the adhesion of *Pseudomonas* and *Escherichia* strains, at the same biosurfactant concentration (Gudiña et al., 2010 a). On the other hand, biosurfactants produced by *Lb. helveticus* inhibit the adhesion of *Escherichia* (*E.*) *coli* ATCC 25922 in a 50.1% at a concentration of 25 mg/mL (Sharma & Saharan, 2016). Hence, the antiadhesive capability of a biosurfactant against a pathogenic strain is different according to the bacterium that is producing the biosurfactant and also the target of the bacterium which is desirable to control.

As previously commented, there are several studies reporting *Lactobacillus* strains as producers of biosurfactants, but there are few studies about the ability to produce biosurfactants by strains of *Lactococcus*. Three *Lactococcus* strains were reported as biosurfactant producers, *Lc. lactis* 53 (Rodrigues et al., 2004; Rodrigues et al., 2006 b), *Lc. lactis* CECT-4434 (Rodriguez et al., 2010; Souza et al., 2017), *Lc. lactis* (Saravanakumari & Mani, 2010), but only for *Lc. Lactis* 53 the anti-adhesive potential had been studied. According to Rodrigues et al., (2006 b), the biosurfactant produced by *Lc. lactis* 53 shown three fractions, isolated by hydrophobic interaction chromatography. All fractions shown antiadherent activity, but the best result was provided by the fraction A, inhibiting the adhesion to polystyrene of all microorganisms target even in a concentration of 5 mg/mL. The crude biosurfactant produced by *Lc. lactis* 53 has been also proved as conditioner of silicone rubber (Rodrigues et al., 2004). This study has been performed in a parallel-plate flow chamber equipped with a microscope allowing *in situ* observation and images analysis. In these experimental conditions, the surfactant adsorbed on the silicone rubber reduced the deposition rate above 90% for *S. epidermidis* GB 9/6, *Strep. Salivarius* GB 24/9, and *S. aureus* GB 2/1, the same percentage of reduction was reached for the cells adhering after 4h.

Some *Streptococcus* strains have been identified as producer of biosurfactants exhibiting anti-adherent activity. Rodrigues et al., (2006 a) studied the biosurfactant produced by *Strep. thermophilus* A, reporting a reduction of adhesion after 4 hours of 89-97% for bacteria and 67-70% for yeasts on silicon rubber, using the biosurfactant at a concentration on 3 mg/mL. Moreover, Van Hoogmoed et al., (2006), Busscher and Van der Mei (1997) have reported two strains of *Streptococcus* biosurfactant producers with antiadhesive activity. But all these studies were focused on biomedical applications.

It was demonstrated that not only the strain of the bacterium is responsible for the biosurfactant characteristics; also the method of extraction can change the anti-adherent properties of a biosurfactant. For example, when extraction of biosurfactants produced by *Lb. pentosus* and *Lb. paracasei* were done using phosphate buffer (PB), the adherence of *S. epidermis* and *Strep. pyogenes* were decreased in 57 and 69 % respectively. But, when extraction was done using PBS, the decrease in adherence was 38% and 52%, respectively (Vecino et al., 2018).

One emerging trend is the incorporation of anti-adhesive agents into the packaging material. According to Abdul et al., (2014), the addition of a biosurfactant produced by *Lb. rhamnosus* to a polyvinyl alcohol film prevented the biofilm formation of *S. aureus* and *Pseudomona (P.) aeruginosa*.

The main pathogenic bacteria related to the food industry that is of interest to prevent biofilm formation are *Listeria (L.) monocytogenes*, *E. coli (enteropathogenic strains)* and *S. aureus*.

Listeria monocytogenes is linked with many outbreaks and cause a food illness that presents a mortality rate of 25% worldwide (de Noordhout et al., 2014). It can be found in a high concentration in foods, especially ready-to-eat foods (Buchanan et al., 2017). It is capable to form biofilm even at refrigeration temperatures (Moltz & Martin, 2005) and can persist in food process environments for years (Hoelzer et al., 2015). For these reasons it is necessary to develop strategies to combat the adhesion of cells to surfaces and the subsequent formation of biofilm. So far, the effect of two biosurfactants produced each one by a *Lb. helveticus* strains were reported showing very promising results (Meylheuc et al., 2006; Sharma & Saharan, 2016). The biosurfactant produced by *Lb. helveticus* (Sharma & Saharan, 2016) at a concentration of 25 mg/mL, inhibited the adhesion of *L. monocytogenes* MTCC 657 and *L. innocua* ATCC 33090 to polystyrene in a percentage of 84% and 82%, respectively.

Escherichia coli is identified as responsible for outbreaks of foodborne illness (Greig & Ravel, 2009; Bélanger et al., 2015). It is a strong biofilm former that persists in the equipment of food industries (Yang et al., 2018), produced in presence of food residues (Dutra et al., 2018). Therefore, it is of interest to find approaches that prevent *E. coli* biofilm formation. Some researchers studied the use of LAB as inhibitors of adherence to surfaces for different *E. coli* strains (Gudiña et al., 2010 a, b; Madhu & Prapulla, 2013; Sharma et al., 2016; Vecino et al., 2018). The results by the time, present LAB as substances capable to produce a low degree in the adhesion of *E. coli* to polystyrene, been the highest reduction percentage scored of 56.78% using the biosurfactant produced by *Lb. plantarum* CFR 2194 in a concentration of 25 mg/mL, against the strain *E. coli* MTCC 108 (Madhu & Prapulla, 2013).

Staphylococcus aureus is well known as a foodborne pathogen, which produces enterotoxins that can poison food (Le Loir et al., 2003), form biofilm on surfaces used in food industries (Dutra et al., 2018) and under food-related stress conditions (Rode et al., 2007). Many researchers reported positive results for the anti-adhesive LAB properties against different *S. aureus* strains in two type of surfaces, polystyrene (Rodrigues et al., 2006 a, b; Madhu & Prapulla, 2013; Gudiña et al., 2010 a, b; Sharma et al., 2016; Vecino et al., 2018) and silicone rubber (Rodrigues et al., 2004; Sharma et al., 2016). In polystyrene, the highest inhibition of adhesion reported was 83%, conditioning the surface with a biosurfactant produced by *Lb. helveticus* in a concentration of 25 mg/mL, against the strain *S. aureus* ATCC 6538P (Sharma and Saharan, 2016). In silicone rubber, the initial deposition of *S. aureus* GB 2/1 was reduced in 90%, conditioning the surface with the biosurfactant produced by *Lc. lactis* 53 (Rodrigues et al., 2004). Even though LAB look to be great surface conditioners in polystyrene and silicon rubber, no results are reported for the effect of the adherence of *S. aureus* in common surfaces used in food industry such as stainless steel.

Regarding the spoilage bacteria, *P. aeruginosa* has the ability to form biofilm and exhibits several virulence factors coordinately by quorum sensing when it is contaminating foods (Viola et al., 2018). It is closely related with waterborne diseases, wet environments are

ideal for the formation and proliferation of biofilm, as different components of water systems (Walker & Moore, 2015). Some researchers studied the anti-adherence capability of LAB against the adhesion of *P. aeruginosa* to polystyrene surfaces, and all of them obtained positives results but with different degrees of inhibition (Gudiña et al., 2010 a; Sharma et al., 2016; Vecino et al., 2018). The best result was obtained using the biosurfactant produced by *Lb. paracasei* and extracted with phosphate buffer saline in a concentration of 25 mg/mL, obtaining an inhibition of 72% (Vecino et al., 2018). This degree of inhibition was higher than the previously reported values of 49% (Sharma et al., 2016) and 16.5% (Gudiña et al., 2010 a) for the same biosurfactant concentration.

According to results previously commented, there is a huge potential in the use of biosurfactants produced by LAB as anti-adherence agents. However, there are not many studies about the effective reduction of adhesion of many foodborne bacteria. The lack of these studies opens a door for novel investigations in the field of food microbiology.

APPLICATIONS OF BIOSURFACTANTS AS ANTIMICROBIAL AGENTS

The search for natural antimicrobials is of increasing concern to mitigate the development of antibiotics resistance against clinical pathogens and also to satisfy consumer demands for chemical additives free and healthier foods. Antimicrobials obtained from microbial sources present a huge potential due to their high biological activity and the possibility of production at low cost in an industrial scale.

The main advances in the knowledge of antimicrobial action of biosurfactantes were done in the field of biomedical sciences (Nitschke & Costa, 2007; Sharma et al., 2016). Conversely, they are very few research focused on the food industry.

Biosurfactants present antimicrobial activity; they exhibit action against virus, algae, bacteria, yeast and molds. Furthermore, several hypotheses are proposed to explain the mechanism of action: i) adhesion to cell surfaces damaging cell membrane integrity; ii) insertion of fatty acids from biosurfactant into cell membrane promoting changes in its composition and functionally; iii) ability to form pores in the membrane altering its functions (Sharma et al., 2016).

The main genera within LAB producing biosurfactants with antimicrobial activity was *Lactobacilli*. Different studies reported that they were able to inhibit the growth of bacteria and yeasts. Gram positive bacteria were more sensitive than Gram negative and yeasts were the more resistant. These trends were related to the fact that Gram negative present a polysaccharide layer in the external membrane which acts as a barrier to biosurfactant. In addition, yeasts present higher phospholipid content into the membrane which facilitates the interaction with biosurfactant (Mouafo et al., 2018).

Table 3 shows a compilation of biosurfactant producing LAB exhibiting antimicrobial activity. It can be observed that most of the strains were isolated from food. In addition, the target microorganisms evaluated were pathogens, in some cases isolated from medical uses. Finally, in all cases the activity was only tested *in vitro*.

Table 3. Compilation of some uses of biosurfactants as antimicrobial agents

LAB strain/source	Target m.o. for antimicrobial activity	Assay performed	Effect	Reference
<i>Strep. thermophilus</i> A/ Nizo (The Netherlands)	<i>S. epidermidis</i> GB 9/6, <i>Strep. salivarius</i> GB 24/9, <i>S. aureus</i> GB 2/1, <i>R. dentocariosa</i> GBJ 52/2B, <i>C. albicans</i> GBJ 13/4A, <i>C. tropicalis</i> GB 9/9 Isolated from explanted voice prostheses	Agar diffusion assay	Antimicrobial action depended on concentration. At 40 g/L all microorganisms were inhibited. Most sensitive was <i>C. tropicalis</i>	Rodrigues et al., (2006 a)
<i>Lc. lactis</i> 53 / Nutricia (The Netherlands)	<i>S. epidermidis</i> GB 9/6, <i>Strep. salivarius</i> GB 24/9, <i>S. aureus</i> GB 2/1, <i>R. dentocariosa</i> GBJ 52/2B, <i>C. albicans</i> GBJ 13/4A, <i>C. tropicalis</i> GB 9/9 Isolated from explanted voice prostheses	Agar diffusion assay	Antimicrobial action depended on biosurfactant fraction concentration.	Rodrigues et al., (2006 b)
<i>Lb. casei</i> 8/4/ Culture collection University of Warmia, Poland	<i>S. aureus</i> 11, <i>B. subtilis</i> , <i>Micrococcus (M.) roseus</i>	Agar diffusion assay	Antimicrobial action depended on incubation time.. Maximum activity was found after 18 h where all bacteria growth was inhibited	Golek et al., (2009)
<i>Lb. paracasei</i> / Portuguese dairy industry	<i>E. coli</i> , <i>P. aeruginosa</i> , <i>S. aureus</i> , <i>S. epidermidis</i> , <i>Strep. agalactiae</i> , <i>Strep. pyogenes</i>	Broth microdilution method and absorbance reading at 600nm	Crude biosurfactant showed antimicrobial activity against all tested bacteria	Gudiña et al., (2010 a)
<i>Lb. plantarum</i> CFR 2194 / kanjika	<i>E. coli</i> ATCC 31075, <i>E. coli</i> MTCC 108, <i>Salmonella typhi</i> , <i>Y. enterocolitica</i> MTCC 859, <i>S. aureus</i> F 722	Agar diffusion assay	Antimicrobial action depended on concentration. All bacteria assayed were inhibited except <i>S. typhi</i>	Madhu & Prapulla (2013)
<i>Lb. casei</i> MRTL3/ Raw milk	<i>S. aureus</i> ATCC 6538P, <i>S. epidermidis</i> ATCC 12228, <i>Shigella flexneri</i> ATCC 9199, <i>Salmonella typhi</i> MTCC 733, <i>P. aeruginosa</i> ATCC 15442, <i>B. cereus</i> ATCC 11770, <i>L. monocytogenes</i> MTCC 657, and <i>L. innocua</i> ATCC 33090	Agar diffusion assay	Crude biosurfactant inhibited all pathogens assayed	Sharma & Saharan (2014)
<i>Lb. agilis</i> CCUG31450/ Culture Collection of University of Gothenburg (Sweden)	<i>E. coli</i> , <i>P. aeruginosa</i> , <i>S. aureus</i> , <i>Strep. agalactiae</i> and <i>C. albicans</i>	Broth microdilution method and absorbance reading at 600nm	No antimicrobial activity was observed against <i>E. coli</i> and <i>C. albicans</i>	Gudiña et al., (2015)
<i>Lb. helveticus</i> / Yak milk cheese	<i>E. coli</i> ATCC 25922, <i>P. aeruginosa</i> ATCC 15442, <i>Salmonella typhi</i> MTCC 733 <i>Shigella flexneri</i> ATCC9199, <i>S. aureus</i> ATCC 6538P, <i>S. epidermidis</i> ATCC12228, <i>L. monocytogenes</i> MTCC 657, <i>L. innocua</i> ATCC 33090, <i>B. cereus</i> ATCC 11770	Broth microdilution method and absorbance reading at 600nm	Biosurfactant concentrations between 1.56 and 25 mg/mL promoted different degree of inhibition of all bacteria evaluated	Sharma & Saharan (2016)

Table 3. (Continued)

LAB strain/source	Target m.o. for antimicrobial activity	Assay performed	Effect	Reference
<i>Pediococcus acidilactici</i> / Artisanal milk cheese	<i>S. aureus</i> CMCC 26003	Broth microdilution method and visual evaluation of turbidity and time–kill assay	MIC was higher than 100 mg/mL and a 50 mg/mL affected the growth.	Yan et al., (2019)
<i>Lactobacillus acidophilus</i> , <i>L. pentosus</i> , <i>L. fermentum</i> , <i>L. plantarum</i> , <i>L. lactis</i> , <i>L. casei</i> / Fermented foods	<i>P. fluorescens</i> , <i>P. aeruginosa</i> , <i>E. coli</i> , <i>Salmonella typhimurium</i>	Agar diffusion assay	Biosurfactants obtained from <i>L. plantarum</i> inhibited all bacteria tested	Abdalsadiq Nagea & Zaiton (2018)
<i>Lactobacillus jensenii</i> P6A and <i>Lactobacillus gasseri</i> P65/ Women vaginal fluids	<i>E. coli</i> , <i>Klebsiella pneumoniae</i> , <i>Enterobacter aerogenes</i> , <i>S. saprophyticus</i> , <i>C. albicans</i> ATCC 18804, <i>C. krusei</i> ATCC 20298, and <i>C. tropicalis</i> ATCC 750	Broth microdilution method and visual evaluation of turbidity	No antimicrobial activity was observed against <i>C. krusei</i> and <i>C. tropicalis</i> . The rest of microorganisms tested were inhibited.	Morais et al., (2017)

Very few studies were done proposing the use of biosurfactants as antimicrobials compounds *in vivo*. For example, Abruzzo et al., (2018) evaluated successfully phosphatidylcholine based vesicles containing a biosurfactant produced by *Lb. gasseri* and econazole for the treatment of vaginal *Candida* infections. Mbawala et al., (2017) applied a crude surfactant extracted from a fermented milk to improve the microbial quality of yellow achu soap, a typical African meal. They used the crude surfactant as a dual agent, emulsifier and antimicrobial and they could decrease total aerobic and coliform populations. Also, a complete inhibition of *Salmonella* spp. and faecal streptococci was reached.

CONCLUSION

Regarding the attempts made to apply biosurfactants produced by LAB, the following facts can be remarked:

- The number of studies on this field has increased in the last years, especially in relation to medical uses. However, the cost is still a problem to solve since chemical surfactants are cheaper, even using agricultural wastes as substrates.
- In the food applications, up to now only one product, named Pre-liminate® is produced at an industrial scale, this formulation can be applied to surfaces in contact with food and it is designed to prevent biofilm formation.
- To increase food uses, *in vivo* studies must be performed in order to understand how the biosurfactants interact with other additives and/or food components. Also it is essential to know the sensorial impact of the biosurfactant and its stability during the food shelf life.
- In relation to the antimicrobial activity of biosurfactants, no information is available about their action on food spoilage microorganisms. It can be stressed that growth of spoilage microorganisms is responsible for high economic losses in the food industry.
- Studies about the interaction with other biosurfactants or with other additives in order to find synergic combinations are useful approaches to facilitate biosurfactant uses.

Outcomes shown herein highlight that biosurfactants from LAB present a huge potential and there are many unexplored areas that need to be studied in order to develop novel applications for the food industry.

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Chapter 297

**ANTIMICROBIAL BACTERIOCINS AND
PEPTIDOGLYCAN HYDROLASES:
BENEFICIAL METABOLITES PRODUCED
BY LACTIC ACID BACTERIA**

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ABSTRACT

Lactic acid bacteria (LAB) involve a diverse group of gram-positive bacteria that primarily produce lactic acid. For centuries LAB have been recognized as safe and employed for food processing due to their ability to control the adventurous microbiota in the elaboration of dairy products, vegetables, meats, coffee, cocoa, silages and fermented beverages; but also because of their contribution to the taste, flavor and texture. Moreover, probiotic LAB may offer health benefits by acting in the modulation of the immune system, helping to manage allergies and lactose intolerance; in addition to the prevention of gastrointestinal and urinary infections by reduction of pathogens. The ability of LAB to inhibit spoilage and pathogenic microorganisms is based on several mechanisms that include acidification, production of antimicrobials and competition for nutrients and adhesion niches. Antimicrobials include the lactic and acetic acids, but also a complex range of metabolites like hydrogen peroxide, diacetyl, antifungal short-chain fatty acids, pyroglutamic acid, as well as, antimicrobial peptides known as bacteriocins and antibacterial peptidoglycan hydrolases (PGHs). Bacteriocins refer to a diverse group of ribosomal antimicrobial peptides mainly active against closely-related and sensitive bacterial strains by formation of pores in the cytoplasmic membrane causing reduction of

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microbial competitors. Among them, nisin and other bacteriocins have been applied in the food and pharmaceutical industry to control *Listeria monocytogenes* and *Staphylococcus aureus*. On the other hand, PGH are proteins capable to cleave the peptidoglycan cell wall of gram-positive and gram-negative bacteria, examples include lysostaphin and lysozyme, which are highly active against *Staphylococcus aureus*. The objective of this chapter is to offer an overview of the characteristics and applications of bacteriocins and peptidoglycan hydrolases as part of the beneficial metabolites produced by LAB.

INTRODUCTION

Lactic acid bacteria can be found in several habitats such as the gastrointestinal tract of animals and humans, as well as in the microbiota in several foods. This microbial group comprises gram-positive, facultative anaerobic, non-spore forming, non-motile and acid tolerant bacteria from the genus *Aerococcus*, *Alloiococcus*, *Carnobacterium*, *Enterococcus*, *Lactobacillus*, *Leuconostoc*, *Oenococcus*, *Pediococcus*, *Streptococcus*, *Tetragenococcus*, *Vagococcus* and *Weissella*. Those are low G+C (31 - 49%) and belong to the *Lactobacillales* order within the *Firmicutes* phyla. Besides, the *Bifidobacterium* genus with a high G+C content (58 - 61%) belongs to the *Actinobacteria* phylum (Khalid 2011; Giraffa, 2014; Fraqueza, 2015). LAB are also classified into homofermentative and heterofermentative according to the end products derived from the glucose metabolism into lactic acid, carbon dioxide, ethanol or acetic acid.

LAB have been safely used for centuries and therefore recognized as safe (GRAS and QPS qualified presumption of safety) by the FDA and EFSA authorities. They are widely employed as starter cultures in the food industry to accelerate ripening or to control de adventitious microbiota for elaboration and preservation of several fermented foods. Applications include the processing of fermented milks, chesses, vegetables, meats, coffee, cocoa, silages, sourdough bread and wine, among others. But, LAB also contribute to the taste, flavor and texture as a result of several reactions, including lipolysis, proteolysis, conversion of lactose in citrate and various aromatic compounds, such as diacetyl, acetoin, acetaldehyde and acetic acid. In addition, their proteolytic activity induces the accumulation of small peptides and free amino acids that are further transformed into alcohols, aldehydes, acids, and esters responsible for the flavor profile and organoleptic characteristics of fermented foods. Some LAB can produce a range from 10 to > 2,000 kDa exopolysaccharides that not only confer protection to the cell producer, but may improve texture and mouthfeel of yogurt and other low-fat milk products. Moreover, LAB are industrially involved in the production of some macromolecules and enzymes (Gad, Abdel-Hamid & Farag, 2014; Özogul & Hamed, 2016).

A number of LAB strains have been used as probiotics and considered desirable members of the intestinal microbiota, including *Lactobacillus*, *Bifidobacterium*, *Propionibacterium* and *Enterococcus* strains present in foods and in dietary supplements. Other reported health benefits associated to LAB probiotics include an antihypertensive effect, reduction in the cholesterol level, antioxidant effect, relief of the allergy symptoms, decrease in dental caries and protection against colon cancer. Such, as the production of the antihypertensive angiotensin-converting enzyme produced through the proteolytic system of *Lb. helveticus*, *Lb.*

acidophilus and *Lb. delbrueckii* (Giraffa, 2014; Sharma et al., 2014). Therefore, LAB are also recognized to improve healthiness due to their influence on the immune system and reduction of pathogens, in addition to their positive role in the control of some infections during pregnancy, antibiotic-derived diarrheas and intestinal inflammation, or to alleviate some allergies, as well as, to deliver vaccines and other metabolites directly in the gastrointestinal tract (Sharma et al., 2014).

Among all these beneficial metabolites produced by LAB, a major attribute is their ability to inhibit spoilage and pathogenic microorganisms based on the competition, their great acid tolerance and production of several antimicrobials (Khalid, 2011; Giraffa, 2014). These antimicrobial metabolites include lactic and acetic acids, ethanol, hydrogen peroxide, diacetyl, antifungals (short chain fatty acids derived from lipolysis reactions), and antimicrobial peptides known as bacteriocins and other antibacterial proteins like peptidoglycan hydrolases (PGHs) (Khalid, 2011; Giraffa, 2014; Sharma et al., 2014). The last two metabolites, bacteriocins and PGHs constitute an important and viable alternative to antibiotics and food grade preservatives due to their antimicrobial action against several pathogens including multi-antibiotic-resistant strains (Álvarez-Cisneros & Ponce-Alquicira 2018).

BACTERIOCINS

Most bacteria may produce antimicrobial proteins, which can be ribosomally synthesized or non-ribosomally synthesized (Chikindas et al., 2018). Bacteriocins produced by LAB constitute a heterogeneous group of ribosomal antimicrobial peptides, varying in size, structure and specificity. They are active against closely related species found in the same environmental niche where the producer strain is protected by the presence of specific immune proteins (O'Connor et al., 2015). Genes responsible for their production and immunity are usually grouped in the same cluster (Perez, Zendo and Sonomoto 2014; O'Connor et al., 2015; Chikindas et al., 2018; Field, Ross & Hill, 2018). Several studies have demonstrated the potential of LAB bacteriocins to be applied for food preservation, or an alternative antibiotics in the clinical area, mainly due to their tolerance to high temperatures and their activity over a wide pH range against spoilage microorganisms and pathogens such *Bacillus*, *Clostridia*, *Listeria (L.) monocytogenes* and methicillin-resistant *Staphylococcus (S.) aureus* and vancomycin-resistant *Enterococci* at concentrations lower than that for conventional antibiotics (Schneider et al., 2006; Alvarez-Cisneros et al., 2010; Martin-Visscher et al., 2011; Perez, Zendo & Sonomoto, 2014). Generally, LAB bacteriocins are considered food-grade because the GRAS or QPS status of most bacteriocinogenic strains (Perez, Zendo & Sonomoto, 2014). Bacteriocins do not impart color or flavor and are easily degraded by the proteolytic enzymes, especially those formed in the pancreas (trypsin and chymotrypsin) and gastric tract (pepsin) that makes them safe for human consumption, thus minimizing the opportunity of target strains to interact and develop resistance (Zacharof & Lovitt, 2012). However, bacteriocins may have some limiting factors such as a restricted inhibitory spectrum, lack of purification protocols and/or acceptable recovery yields, a producer strain classified with non GRAS recognition, and/or the development of bacteriocin-resistant bacteria. Nonetheless, the ribosomal origins of bacteriocins enable their

bioengineering either to modulate their physicochemical properties and improve their stability in food systems, or to enhance the inhibiting activity and spectra; in addition, their heterologous expression in other hosts could be a valid alternative to increase yield or induce multiple bacteriocin production (Alvarez-Cisneros et al., 2011; Field, Ross & Hill, 2018).

Bacteriocins are diverse, some authors such as Chikindas et al., (2018) point that the primary action of bacteriocins are for signaling and repelling at their low concentration that occurs in natural environments; for instance, nisin (produced by *Lactococcus lactis*) and subtilin (from *Bacillus subtilis*) participate as modulators for their own production and transport (Balciunas et al., 2013). But, mutacin V produced by *Streptococcus* (*Strep.*) *mutants* can act as lytic agent against the producer cell to facilitate the exchange of genetic material with non-lysed competent cells. While, other bacteriocins can inhibit the quorum sensing at sub-MBC (minimal bactericidal concentration) to prevent the settle down and biofilm formation of competitors. In contrast, when bacteriocins are employed at MBC or at higher levels they can induce permeation and formation of pores in the cytoplasmic membrane and/or interfere with the cell division process and with other biological functions thus inactivating sensitive cells (Chikindas et al., (2018).

A restriction in the use of bacteriocins may be the presence of innate or acquired resistance observed in some susceptible strains. In particular, *L. monocytogenes* has shown resistance when exposed to high levels of nisin (> 10 fold MBC), as well as resistance to class IIa bacteriocins due to changes in the cell membrane properties. Also, *Bacillus* (*B.*) *cereus* can produce the enzyme nisinase capable to degrade the bacteriocins nisin and subtilin. However, no significant data is available for the resistance mechanism and the resistance can be solved by changing the pH, the type of carbohydrates or the salt concentration of the environmental growth (Ahmad et al., 2017; Balay, Gänzle & McMullen, 2018).

The number of reported bacteriocins is continuously growing, but to date the BACTIBASE, an open-access database (<http://bactibase.pfba-lab-tun.org>), contains calculated or predicted physicochemical and structural properties of 230 bacteriocins produced by 206 gram-positive bacteria and 19 gram-negative, being LAB the predominant bacteriocin producers. The database allows a better comprehension of the bacteriocins functionality towards the development of applications and classification by the use of tools such as similarity, sequence alignment, physicochemical profile, hidden Markov Models and structure prediction. In addition, the BAGEL4 webserver (<http://bagel4.molgenrug.nl/>) allows the meta-genomic DNA search for bacteriocins and post-translationally modified peptides (RIPPs) providing databases and BLAST (basic local alignment search tool) for the core peptide databases.

Bacteriocin Classification

There are several classifications of bacteriocins, mainly based in their post-translationally modification through biosynthesis and transport to the extracellular media, as well as, on their mode of action and structure. Most bacteriocins are synthesized as an inactive precursor peptide precursor having an N-terminal leader peptide, attached to the C-terminal core peptide that is removed by proteases to yield the mature bacteriocin. The leader peptide usually serves as a recognition sequence for biosynthetic enzymes; also serves to modulate

the enzyme–substrate interaction for the post-translational modification (PTM) of the inactive pre-peptide that is later transported to the cell surface and transformed into the active peptide. The genetic determinants for bacteriocins production consist of less than 21 genes and their biosynthesis greatly differs, as some bacterial strains may produce more than one bacteriocin in addition to the production of PGH's (Acedo, et al., 2018).

The regulation system for the bacteriocin production is composed of an inducing peptide or pheromone–activating factor, the transmembrane histidine kinase and a response regulator. The inducer peptide is synthesized in the ribosome at low levels as a pre-peptide, which is then cleaved and secreted extracellularly by a carrier. At certain threshold concentrations the response phosphorylation receptor further activates the bacteriocin transcription. Lantibiotics (Class I) bacteriocins such as nisin act as pheromones or signal-involved membrane proteins that regulate their own production and transport; while accessory proteins induce the translocation for Class II bacteriocins (Balciunas et al., 2013).

The first bacteriocin classification scheme was proposed by Klaenhammer (1993) who defined four classes:

- Class I Lantibiotics (< 5kDa membrane-active peptides containing unusual amino acids as lanthionine, β -methyl-lanthionine and dehydrated residues);
- Class II [< 10 kDa heat-stable non-lanthionine containing membrane-active peptides with three sub-groups: IIa *Listeria* active peptides (with a consensus sequence in the N-terminal of Tyr-Gly-Asn-Gly-Val-Xaa-Cys- and a leader peptide GG), IIb complexes consisting of two leader GG peptides and IIc thiol-activated peptides];
- Class III for large heat-labile proteins and,
- Class IV for complex bacteriocins with a lipid or carbohydrate moiety.

Later, Cotter, Ross and Hill (2005) proposed the elimination of larger proteins from the bacteriocin classification arguing that bacteriocins should be referred as antimicrobial peptides, proposing the following classification:

- Class I for those bacteriocins subjected to an enzymatic PTM that was sub grouped according to their structure into twelve groups (MccC7-C57, lasso peptides, linear-azole, lantibiotics, linaridins, proteusins, sactibiotics, patellamide-like cyanobactins, anacyclamide-like cyanobactins, thiopeptides, bottromycins and glycocins).
- Class II included the unmodified or cyclic bacteriocins with five subgroups (IIa pediocin PA-1-like, IIb, IIc, IId and IIE peptides).
- Class III or “bacteriolysins” for thermo-labile high molecular weight peptides.

Recently, novel bacteriocins have been reported with the emerging of genome tools applied for the screening of published LAB genomes, resulting in 785 putative bacteriocin gene clusters, which also contain new RPPs different from the previously known bacteriocins. Therefore, a modification in the classification for most LAB bacteriocins was proposed by Alvarez-Sieiro et al., (2016). Class I resulted more diverse with six RPP subclasses, Class II comprises four subclasses and Class III for unmodified bacteriocins > 10 kDa with bacteriolytic and non-bacteriolytic activity (Table 1). Furthermore, Acedo et al.,

(2018) presented an overview of the structural variety of bacteriocins and their interactions with receptors and possible modes of action.

**Table 1. Classification for bacteriocins from LAB
(modified from Alvarez-Sieiro et al., 2016; Acedo et al., 2018)**

Class	Subclasses
Class I Heat stable < 10 kDa Posttranscriptional modified peptides (RIPPs)	Class Ia. Lanthipeptides (types I, II, III ¹ , IV ¹)
	Class Ib. Head-to-tail cyclized or circular peptides
	Class Ic. Sactibiotics ²
	Class Id. Linear azo(in)e-containing peptides (LAPs)
	Class Ie. Glycocins
	Class If. Lasso peptides ²
Class II Heat stable < 10 kDa Unmodified peptides Leader peptide GG	Class IIa. Pediocin-like linear (YGNGVXCXXXXCXV conserved at N-terminus)
	Class IIb. Two peptides
	Class IIc. Leaderless
	Class IId. Non pediocin-like, single-peptide
Class III Thermo-labile >10kDa	Bacteriolysins
	Non-lytic
	Tailocins (phage tail-like) ²

¹Types III and IV do not have known antimicrobial activity.

²None reported LAB bacteriocins, but putative clusters have been identified *in silico*.

However, many other bacteriocins are under study and some of the criteria used to classify bacteriocins are not fully applicable, such as the enterocins because they have common characteristics to more than one of the currently described bacteriocins classes or subclasses (Alvarez-Cisneros et al., 2011). For example, hemolysin from *E. faecalis* belongs to the lanthibiotic group (Class I), but its activity depends on the joint action of two peptides (Class IIb). Also enterocin P could be included in Class IIc because it is secreted by a pre-peptide translocase, but it has the YGNGV consensus sequence typical of Class IIa. Therefore, Franz et al., (2007) proposed a specific classification for enterocins that includes four main classes: lanthibiotic enterocins (Cass I), non-lanthibiotic enterocins (Class II), cyclic enterocins (Class III) and large proteins (Class IV). Class II was subdivided into three subclasses: the pediocin family of enterocins (IIa), enterocins synthesized without a leader peptide (IIb) and linear enterocins that do not belong to the pediocin family (IIc). Likewise, Ahmad et al. (2017) presented two schemes of classification, one based on the bacteriocin physicochemical properties, and other based on the presence of consensus sequence motifs claiming to include > 70% of the known bacteriocins.

Class I Bacteriocins

Class Ia of lanthipeptides or lantibiotics are small heat stable peptides that undergoes PTMs resulting in the formation of lanthionine (Lan), β -methyl-lanthionine (MeLan) and other unusual dehydrated amino residues. Serine and threonine residues go a two-step process that involve an enzymatic dehydration forming dehydroalanine (Dha) and dehydrobutyrine (Dhb), followed by a Michael-type condensation with the thiol-group of a neighboring cysteine residue to the β -carbon of Dha or Dhb forming a Lan or MeLan internal rings, that impart resistance to proteases (Acedo et al., 2018). Then the modified pre-peptide is transported and activated to the extracellular environment. The leader peptide for lantibiotics

have a conserved FNLD box with helical structure essential for the ring formation through the action of a cyclase enzyme, such as the NisC cyclase for nisin (Abts et al., 2013). Nisin A produced by *Lactococcus (Lc.) lactis* ssp *lactis*, lacticin 3147-A1 and lacticin 3147-A2 from *Lc. lactis* are the best studied subtype I and II from the Class Ia. The mechanism of action for most lantibiotics relies on the binding to the lipid II, a universal receptor and the main subunit transporter of peptidoglycan from the cytoplasm to the cell wall. Thereby, bacteriocins Ia block the proper cell wall synthesis that leads to the cell death. In particular, nisin A binds to Lipid II by its N-terminal rings forming a complex of eight lantibiotic bacteriocins molecules with four lipid II molecules with two dependent-concentration modes of action. At high levels, nisin A triggers the process of membrane insertion and pore formation, which leads to rapid cell death; but at low concentration, cell wall synthesis is repressed (Cotter, Hill & Ross, 2005.; Breukink & De Kruijff, 2006; Alvarez-Cisneros et al., 2011).

The head-to-tail circular, Class Ib bacteriocins, includes a group of RiPPs whose N- and C-termini are linked by a peptide bond. This group has recently attracted the attention because of their wide inhibitory action and their remarkable stability to proteases and heat treatments (Borrero et al., 2011; Grande-Burgos et al., 2014; O'Connor et al., 2015; Perez, Zendo & Sonomoto, 2018). Up to date, fourteen circular bacteriocins have been described and sub-divided in two groups according to their biochemical characteristics (Table 2).

Table 2. Classification and examples of circular bacteriocins (modified from Grande-Burgos et al., 2014; Perez, Zendo and Sonomoto 2018)

Group	Name	Producer strain
Group i (Highly cationic peptides with predicted pI > 9)	Carnocyclin A	<i>Carnobacterium maltaromaticum</i> UAL307
	Garvicin ML	<i>Lc. garvieae</i> DCC43
	Leucocyclin Q	<i>Leuconostoc (Leuc.) mesenteroides</i> TK41401
	Lactocyclin Q	<i>Lc.sp</i> QU12
	Enterocin AS-48	<i>Ec. faecalis</i> UGRA10
	Uberolysin	<i>Strep. uberis</i> 42
	Amylocyclin	<i>B. amyloliquefaciens</i>
	Circularin A	<i>Cl. beijerinckii</i> ATCC 25752
	Enterocin NKR-5-3B	<i>Ec. faecium</i> NKR-5-3
	Pumilarin	<i>B. pumilus</i> B4107
Group ii (Hydrophobic cationic peptides with predicted pI < 7)	Gassericin A	<i>Lbgaseeri</i>
	Butyrvibriocin AR10*	<i>Butyrvibrio fibrisolvens</i>
	Acidocin B	<i>Lb. acidophilus</i> M46
	Plantaricyclin A	<i>Lb. plantarum</i> N326

*negatively charged, predicted pI 3.88.

The biosynthesis of circular bacteriocins involves three stages: the cleavage of the leader peptide, circularization and extra-cellular secretion. The biosynthetic gene cluster includes a series of five to seven genes encoding for the precursor peptide, a cationic and hydrophobic immunity protein, an ABC transporter (composed by an ATPase and a membrane protein involved in the protein secretion that also confers partial immunity), and a membrane protein that participates in the circularization. The leader peptides for these bacteriocins are heterogeneous in size and sequence (ranging from 2-48 residues) with a non-clear role in the biosynthesis process but essential for the precursor peptide folding and interaction with processing enzymes. The dehydration and cyclization are catalyzed by the bifunctional

enzyme LanM, which has an N-terminal dehydratase domain and a C-terminal cyclase domain. LanM phosphorylates Ser/Thr, the resulting phosphate ester is eliminated to form Dha/Dhb (Acedo et al., 2018). Although the mode of action of most circular bacteriocins has not yet been elucidated, their antimicrobial action relies on their high net charge that facilitates their interaction with the negatively charged bacterial cell membrane causing non-selective ion channels, leaking of ions, dissipation of the membrane potential and eventually the cell death (Cebrián et al., 2012; Perez, Zendo & Sonomoto, 2018). Recent reports for the Enterocin AS-48 suggest a two stage mode of action, based on an electrostatically approach of the inactive water-soluble dimer towards the cell membrane followed by dissociation and insertion into the lipid bilayer and establishment of electrostatic and hydrophobic interactions with the monomeric bacteriocin (Cebrián et al., 2015; Perez, Zendo & Sonomoto, 2018).

Other Class I are the sactipeptides (Class Ic) that are described as sulfur-to- α -carbon-containing peptides. Examples include the subtilisin A produced by *B. subtilis* with high activity against *Clostridium (Cl.) difficile* and thurincin CD produced by *B. thuringiensis*, but only putative clusters have been identified in silico for LAB. Besides, the linear azol(in)e-containing peptides (Class Id) are composed by various heterocyclic rings of thiazole and methyl-oxazole derived from cysteine, serine and threonine residues. Being the streptolysin S produced by *Strep. pyogenes* the most representative, but also described as to potent cytolytic toxin and virulence factor (Wessel, 2005). Moreover, the Glycocins (Class Ie) are bacteriocins that contain glycosylated residues such as Glycicin F produced by *Lb. plantarum*, or the enterocin F4-9 from *Enterococcus (Ec.) faecium*. Finally, the lasso peptides (Class If) are RiPPs with an amide bond between the first residue in the core peptide chain and a negative charged residue in positions 7 to 9 generating a ring that includes de C-terminal. These bacteriocins display antimicrobial, antiviral and anti-carcinogenic activities as the Microcin J25 produced by *Eacherichia (E.) coli*, but non-reported bacteriocins from this type are produced by LAB (Alvarez-Sieiro et al., 2016).

Class II Bacteriocins

Class IIa pediocin-like bacteriocins are heat stable (< 10 kDa) and particularly active against *Listeria*. Their structure is characterized by a cationic and heat stable peptides lengthen from 37 to 48 amino acid residues, with isoelectric points (pI) varying from 8.3-10. The N-terminal contains two cysteine residues joined by disulfide bridges and a conserved YGNGVXCXXXXCXV motif. The C-terminus is less conserved and participates in the target cell specificity. The gen cluster is plasmid encoded and contains four genes such as the structural *pedA*, the immunity *pedB*, the *pedC* and *pedD*, which encode an ABC transporter and accessory proteins for pediocin PA-1. Other IIa bacteriocins include the enterocins such as the *Ec. faecium* MXVK29 that shows accessory genes (*entK*, *entR* and *entT*) adjacent to the structural and immunity and inducer genes. The leader peptide from most Class II bacteriocins poses a highly conserved double glycine motif that serves as recognition signal for the bacteriocin production and secretion; it can also be constitutively produced or regulated by a quorum sensing system. The mode of action comprises three steps: (1) link with the mannose phosphotransferase system (Man-PTS) receptors, (2) insertion into the cytoplasmic membrane and (3) hydrophilic pore formation that induces dissipation of proton motive force, the subsequent acceleration of ATP consumption to restore the proton motive force that leads to the cell death. However, the target membrane composition plays a role for the proper bacteriocin insertion and the final pore formation and allows the exit of ions,

amino acids and other essential molecules. Pediocin PA-1 (pediocin AcH) is the most studied IIa bacteriocins produced by *Pedococcus (Ped.) acidilatici* and *Lb. plantarum*, respectively; other examples include leucocin A, acidocin A, mesenterin and sakacin P. Those bacteriocins show antagonistic activity against several spoilage and pathogen microorganisms, including *L. monocytogenes*, *S. aureus* and *Cl. perfringens* (Alvarez-Cisneros et al., 2011; Balciunas et al., 2013; Alvarez-Sieiro et al., 2016; Escamilla-Martínez et al., 2017; Ríos-Colombo, Chalón & Navarro, 2018).

Class IIb bacteriocins require the presence of two complementary peptides, at about equal quantities, that work together for their antimicrobial action forming a membrane-penetrating helix-helix structure causing membrane leakage in sensitive bacteria, such as the lactococcin G produced by *L. lactis*, the lactacin F produced by *Lb. johnsonni* and plantaricins S and T produced by *Lb. plantarum*. Although, some individual peptides can present antimicrobial activity with synergistic action like for thermophilin 13 produced by *Strep. thermophilus*, as well as, plantaricins A, E/F, J/K and W produced by *Lb. plantarum* strains. Their synthesis is regulated by at least five genes, organized in one or two operons, containing two structural genes codifying for the pre-bacteriocins, in addition to immunity, ABC transporter and accessory proteins. Their synthesis is regulated by a quorum sensing system that involves an induction factor, a membrane protein histidine kinase and response regulators. However, both two-peptide-lantibiotic and non-lantibiotic have been reported, such as the enterocin W a two-peptide-lantibiotic produced by *Ec. faecalis* NKR4-1 (Barbosa et al., 2016; O'Connor et al., 2015).

There are several reports for leaderless IIC bacteriocins conformed by one, two or more peptides, in general they are cationic with high pI values. Examples include the single peptide LsbB from *Lc. lactis* BGMN1, enterocin Q from *Ec. faecium* L50, Enterocin K1 from *E. faecium* EnGen0026, Aureocin A53 from *S. aureus* A53, Lactacin Q from *Lc. lactis* QU5, weissellicin Y and M both from *Weissella hellenica* QU13, among others. In addition to the two-peptide enterocin L50 produced by *Ec. faecium* L50 and the multi-peptide garvicin KS from *S. aureus* A70. The IIC leaderless bacteriocins are synthesized without an N-terminal leader peptide; they do not undergo any PTMs and become active after translation, but self-immunity and the secretion mechanisms remain unclear for these bacteriocins. However, Miljkovic et al., (2016) revealed that expression of LsbB requires the presence of a complete transcription terminator located downstream of the *lsbB* gene. On the other hand, the production of weissellicin Y and M has a nutrition adapted control; while the production of enterocin L50 seems to be regulated by temperature within the range of 16 - 32°C. In relation to their mode of action, they do not require receptor molecules to form huge-pore-like structures (HTP) that cause leakage of large intracellular components lately inducing cell death (Alvarez-Sieiro et al., 2016; Perez, Zendo & Sonomoto, 2018).

Class IID or non-pediocin-like bacteriocins refer to unrelated single linear bacteriocins with different structures and mechanisms of action. Examples include lactococcin 972, lactococcin A and enterocin B, among others (Alvarez-Sieiro et al., 2016).

Class III Bacteriocins

Class III includes heat labile antimicrobial proteins with high molecular weight (> 10 kDa) with bacteriolytic and non-bacteriolytic activity. Most LAB bacteriolysins manifest their antimicrobial activity by cleaving the peptidoglycan cross-links of the target cell wall and fall into the peptidoglycan hydrolases (PGHs) group described in another section of this chapter.

On the other hand, the non-lytic bacteriocins execute their antimicrobial action interfering with some biological functions that finally leads to the inactivation of sensitive cells. Examples include the dysgalactin produced by *S. pyogenes* that inhibits the sugar uptake by interfering with the phosphotransferase systems (PTS) glucose and mannose causing membrane leakage of small molecules. As well as, caseicin from *Lb. casei* that inhibits the biosynthesis of DNA and proteins (Alvarez-Sieiro et al., 2016). Tailocins comprise large multiprotein complexes that take the shape of nanotubes larger than one million Da, resembling the tail structure of bacteriophages and causes cell death by inserting themselves into target membranes; examples include the pyocin produced by *Pseudomonads aeuroginosa* and diffocin from *C. difficile*, but no tailocins produced by LAB have been reported (Acedo et al., 2018).

Bacteriocin Applications as LAB Beneficial Metabolites

There is a worldwide demand for natural and safe products, with use of natural preservatives in combination of clean and environmentally-friendly processing technologies. From this point of view, LAB bacteriocins offer an important area of interest as they are recognized as natural and safe antimicrobials, especially those capable of inhibiting the growth of spoilage and foodborne pathogens, as well as methicillin-resistant *S. aureus* and vancomycin-resistant *Enterococci* at concentrations lower than that for conventional antibiotics. Bacteriocins differ from antibiotics in several aspects, first they are primary metabolites with a less complex biosynthetic mechanisms in comparison to the secondary metabolites antibiotics; most bacteriocins possess a narrow inhibitory activity by the action at the membrane and/or cell wall, they are active at nano- or micro-molar range, are sensible to proteases and temperature, do not alter color, taste or odor and present relatively low toxicity for eukaryotic cells, therefore they can be used for food preservation and therapeutics. In contrast, antibiotics are only approved for therapeutically use, have a broad spectrum, with activity at micro- to milli-molar range either inhibiting the synthesis of the cell wall or the cytoplasmic membrane, blocking the protein synthesis or the DNA copying processes or altering the metabolism that also may affect eukaryotic cells (Perez, Zendo & Sonomoto, 2014; Alvarez-Cisneros & Ponce-Alquira, 2018).

López-Cuellar, Rodríguez-Hernández & Chavarría-Hernandez (2016) published a ten years review of the LAB bacteriocin application, reporting a database of 429 papers and 245 patents between years 2004 to 2015 around the world. Articles were further classified by application topics, 29% were related to food preservation; 37% focused on biomedical applications for alternative treatment of systemic, oral, stomach, vaginal and respiratory infections, contraception, cancer, skin and personal care; 25% for bio-nanomaterials and packaging materials and 9% for their veterinary use. While patents were classified by the same application topics including also their production, purification and molecular modifications; 31% patents focused on biomedical uses, 29% on food preservation, 5% on veterinary applications, and 29% for production-purification processes and recombinant molecules. The application of bacteriocins include several strategies, such *in situ* by the direct inoculation of a LAB bacteriocinogenic strains as starters in fermented products, or *ex situ* by the addition of a purified or semi-purified bacteriocin as an additive, as well as, the

incorporation of a previously fermented product that contain bacteriocin-producer strain as an ingredient and immobilized bacteriocins into packaging film surfaces. But most industrially produced and commercially available purified or semi-purified bacteriocin preparations include nisin, pediocins, and carnocyclin A (Silva, Silva & Ribeiro, 2018).

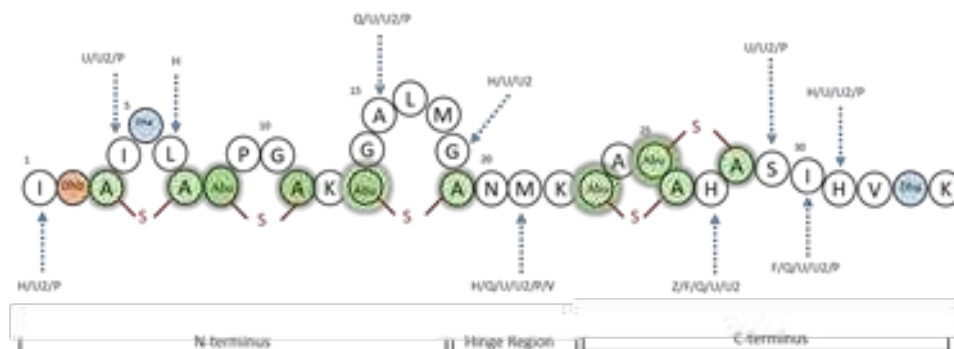


Figure 1. Representation of the nisin A structure with the Lan (A-S-A) and MeLan rings (Abu-S-A), dehydroalanine (Dha) and dehydrobutyryne (Dhb). Arrows indicate the amino acid substitution sites for natural variants (F, Q, Z, U, U2, P and H) and the semi-synthetic nisin V (Modified from Shin et al., 2016 and Campion et al., 2013).

Nisin

The Class Ia bacteriocin nisin is the most studied bacteriocin; it has been recognized as safe and approved as natural food preservative by the Joint Food and Agricultural Organization/World Health Organization (FAO/WHO) since 1969. The United States Food and Drug Administration (FDA) also approved nisin in 1988 as well as the European Food Safety Authority (EFSA) with the number E234. It has been commercially used in several countries with differences in their level and application to inhibit the growth spoilage gram-positive bacteria, especially *Bacillus*, *Clostridium* and *Listeria* on meat, dairy and vegetables. The most known brand is Nisaplin™ (2.5% Nisin A), but some other commercial presentations, include nisin alone or in combination with other bacteriocins and/or other natural antimicrobials that can be found from Danisco and Chr Hansen, among other companies. There are eight natural nisin variants (A, F, Q and Z produced by *Lactococcus lactis* strains, as well as the U, U2, P and H variants produced by *Streptococcus* strains) along with several semi-synthetic nisin variants (Shin et al., 2016). Nisin A contains 34 amino acid residues with five internal ring structures generated by PTMs. The N-terminal domain contains one Lan and two MeLan rings linked through an intermediate flexible hinge region to the C-terminal containing two intertwined rings (Figure 1). The N-terminal domain binds to the pyrophosphate moiety of lipid II and facilitates the pore formation by the C-terminal domain, thus interfering with the cell wall biosynthesis and the cell membrane permeation (Campion et al., 2013). Nisin Z differs from nisin A in one amino acid residue at position 27 with an asparagine instead a histidine and possess higher solubility. Nisin F has two amino acid substitutions at positions 27 and 30; while nisin Q has four substitutions at positions 15, 21, 27 and 30. All of them are highly active against *S. aureus* and *L. monocytogenes* and other gram positive foodborne bacteria. Variants U and U2 are produced by *Strep. uberis*, in their structure contain nine and ten amino acid substitutions in comparison to nisin A. Nisins H and

P were detected from *Strep. hyointestinalis* and *Strep. gallolyticus* subsp *pasteurianus*, respectively.

The combination of nisin with other antimicrobials and the semi-synthetic variants have demonstrated an increased inhibitory activity against other non-food bacteria such as multidrug resistant pathogens such methicillin-resistant *S. aureus* (MRSA), vancomycin intermediate and heterogeneous *S. aureus*. However, semi-synthetic o bioengineered variants such as nisin V have shown an enhanced activity with therapeutic potential and great thermal stability and solubility, active against *Shigella*, *Pseudomonas* and *Salmonella* species (Campion et al., 2013; Shin et al., 2016).

Pediocin PA-1

Among the Ila bacteriocins, pediocin PA-A is the most studied due to its great ability to permeabilize the membrane of *L. monocytogens*, *S. aureus*, as well as, *Pseudomonas* and *E. coli*. It is thermally stable in a wide pH range, produced by *Pedococcus* spp and resistant to heating and freezing (Schneider et al., 2006; Silva, Silva & Ribeiro, 2018). Commercial pediocin presentations include ALTA® (Kerry Bioscience), MicroGard™, Fargo 23® (Quest International) and Bactoferm F-LC® (combination of pediocin and sakacin by Chr. Hansen) mostly recommended for preservation of dairy and meat products (López-Cuellar, Rodríguez-Hernández & Chavarría-Hernandez, 2016).

Carnocyclin A

Carnobacterium maltaromaticum UAL307 that was isolated from fresh pork, produces the class Ib bacteriocin Carnocyclin A, a circular 60 residues peptide that forms anion selective channels in the lipid membrane. This bacteriocin with the commercial brand Micocin® (Griffith Laboratories) has been approved for vacuum packaged meat products in United States, Canada Costa Rica, Colombia and Mexico against *Listeria monocytogenes*; but carnocyclin can also inhibit *E. coli*, *Pseudomona aeruginosa* and *Samonella* Typhinurium (Martin-Visscher et al., 2008; 2011; Marketwire, 2011; Koné et al., 2018).

Application of Bacteriocins to Improve Food Preservation

There are several reports in relation to the use of bacteriocins for food preservation as these antimicrobial peptides can prevent the growth and transmission of spoilage and food borne pathogens by preventing the biofilm (surface-associated microbial communities) formation on surfaces, retarding the microbial growth and the biogenic amines formation during refrigeration, thus increasing the shelf life of foods while maintaining their nutritional and sensory qualities (Galié et al., 2018; Özogul & Hamed, 2018). Bacteriocins can be used in several forms, either produced *in situ* by the incorporation of LAB bacteriocinogenic strains in fermented and non-fermented foods, or produced *ex situ* by addition of a previously purified or concentrated bacteriocin in a food grade substrate. The use of bacteriocinogenic LAB for food preservation is attractive due to their GRAS status that fulfill the consumer's demands for minimally processed foods and ready-to-eat (RTE) products free from artificial additives. The producer strain can serve as a starter or be added as an additional protective culture. Protective bacteriocinogenic strains may grow and produce bacteriocins during

refrigeration storage in which may be part of the predominant microbiota, thus inhibiting the proliferation of pathogenic bacteria especially during temperature abuse conditions in meat and dairy products. The use of multiple bacteriocins or multibacteriocinogenic strains seems to be more effective for food preservation; as reported by Mills et al. (2017) that generated a double bacteriocin producer (*Lc lactis* CKS2775) via conjugation capable to produce nisin and lacticin providing a multihurdle approach to control pathogens in cheese.

Other food applications include immobilized preparations applied on the surface of the food product or included in antimicrobial active packaging, coatings and nanocomposite films. For instance, Martinez-Murillo et al., (2013) incorporate nisin into whey protein isolate film with antibacterial activity against *Listeria innocua* (ATCC 33090) and *Brochothrix thermosphacta* (NCIB10018) (Khaneghah et al., 2018).

Immobilized bacteriocins are more stable as the carrier protects them from inactivation due to variations in the pH, prevention of their interaction with enzymes and other food components (including lipids and other proteins). Furthermore, immobilization can regulate the bacteriocin release into the food system (Balcinas et al., 2013). Bacteriocins have been encapsulated using several methodologies including liposome formation, coextrusion, spray coating, fluid-bed coating, complex coacervation and formation of silver nanoparticles, alone or in combination with other antimicrobials, preserving their antimicrobial action (Calderón-Oliver, et al., 2017).

The thermal stability of bacterial spores is a major problem in the food industry; LAB bacteriocins may be involved as part of a hurdle processing due to their anti-spore activity against dormant spores and/or germinated spores. The bacteriocins nisin, enterocin-AS48 (produced by *Ec. faecalis* A-48-32), lacticin 3147 (produced by *L. lactis* subsp. *lactis* DPC3147), plantaricin TF711 (produced by *Lb. plantarum* TF711), as well as, the bacteriolysins pentocin L and pentocin S (produced by *Ped. pentosus* L and S) have shown inhibitory action against spores of *Cl. perfringens*, *Cl. sporogenes*, *Cl. botulinum*, *Cl. difficile* and *B. cereus* with differences in their mode of action. In particular nisin reduces the thermal stability of bacterial spores and prevents the outgrowth of survival spores in heat threatened milk and apple juice. Similar data was observed in food models subjected to non-thermal food preservation processes such as high-pressure processing and pulsed electric field, or in systems of bacteriocins combined with plant extracts, sucrose fatty esters and potassium sorbate (Egan et al., 2016).

Bacteriocins in Human Health and Skin Care

Penicillin resistant *S. pneumonia*, vancomycin resistant enterococci (VRE), MRSA, intermediate and heterogeneous *S. aureus*, *Strep. pneumoniae* and *Cl. difficile*, among other bacteria represent a major medical risk all around the world, for their incidence in bacteremias, pneumonia and postsurgical infections, especially for immunocompromised patients. Those bacteria can be adhered or implanted on the surface of medical devices or damaged tissues in the form of a biofilms, thus causing chronical infections. Bacteriocins show a promising alternative to traditional antibiotics, their primary difference is their activity against closely related bacteria. In particular, Nisin A in combination with conventional antibiotics, lysozyme and lactoferrin can promote a synergistic effect against MRSA and

reduce the biofilm formation. Therefore, this bacteriocin and other natural and bioengineered lantibiotics such as NVB302 (semi-synthetic derivate from actagardine), microbisporicin, mutacin 1140 (produced by *Strep. mutants*) and the lantibiotic lactacin are examples of bacteriocins under clinical trial to treat hospital related infections, including drug-resistant infections, as an option to substitute or decrease the use of antibiotics.

Shin et al., (2016) present a review of the biomedical applications of nisin as a promising tool to improve human health, including the treatment of oral infections and cancer. For instance, the development of an antimicrobial nanofiber wound dressing containing nisin was used to reduce the colonization of MRSA and accelerate healing with non-adverse histological effects (Heunis, Smith & Dicks, 2013). Other applications include the topical nisin application to treat mastitis and reduce the staphylococcal count in the breast milk of nisin treated woman. Moreover, this bacteriocin has a synergistic action with poly-lysine and sodium fluoride for the prevention of planktonic and biofilm forms of the cariogenic bacteria *Strep. mutants*, and other gram-positive and gram-negative oral colonizing bacteria, as well as, an anti-biofilm effect on saliva without causing cytotoxicity to human oral cells. In addition, nisin has a potential to reduce periodontal disease by inhibiting *Ec. faecalis* (frequently present in infected teeth root canals) and for the prevention of oral candidiasis caused by *Candida albicans*, a prevalent pathogen that cause mucosal fungal infections.

Cancer is characterized by the dysregulated growth of abnormal cells, usually threatened by chemo- or radiotherapy and surgery with the concomitant detrimental of normal cells and severe affectation to the patients. Nisin and other bacteriocins such pyocin, colicin S4, defensin, pediocin, microcin may play a role for the treatment of cancer because of their activity against various types of cancer (Shin et al., 2016; Baidara, Korpole & Grover, 2018). In particular the use of nisin A in low concentrations (2.5%) showed an antitumor potential in head and neck squamous cell carcinoma (HNSCC) *in vitro* and *in vivo*, but higher concentrations of a combination of nisin Z and P (95%) had greatest level of apoptosis in HNSCC cells and decreased their proliferation demonstrating the potential of nisin as an anticancer agent (Kamarajan et al., 2015). Also the combination of nisin with conventional cancer drugs such doxorubicin potentiated the effectiveness against skin carcinogenesis (Preet et al., 2015). Recent data demonstrates the anti-carcinogenic effect of nisin due to the selective toxicity on melanoma cells, as well as, on gastrointestinal, hepatic and blood cancer cell lines (Lewies et al., 2018; Goudarzi et al., 2018).

Bacteriocins such as lactacin and fermenticin HV6b are potential spermicidal agents that induce reduction in the motility of human spermatozoa or sperm tail damage when used at high levels. In addition, other bacteriocins produced by *Ped. pentosaseus* SB83, *Ec. faecium* and *Lb. rhamnosus* can inhibit pathogenic vaginal bacteria such *Gardnerella vaginalis*, *Prevotella bivia*, *Bacteroides*, *Peptostreptococcus* and *Mobiluncus* spp (López-Cuellar, Rodríguez-Hernández & Chavarría-Hernandez, 2016).

There are several products containing bacteriocins from probiotic LAB bacteria to prevent and treat skin diseases, including external signs of aging, acne, rosacea, bacterial and yeast infections, psoriasis and dermatitis. All these applications derive from the bacteriocin contribution to the modulation of the skin microflora, and their action in the immune system and reduction of inflammatory processes. Examples include saivaricin, nisin, mersacidin, lactacin and leucocin A (López-Cuellar, Rodríguez-Hernández & Chavarría-Hernandez, 2016).

Bacteriocins in Veterinary and Agriculture

Antibiotics are commonly used in livestock and aquaculture for the treatment of bacterial infections as a prophylactic method to prevent bacterial diseases in healthy animals; they are also used as growth promoters to improve feed conversion and body-weight gain. This issue has become one of the main safety problems worldwide and several organizations such as the WHO, the FDA and EFSA, have raised awareness to stop using antibiotics in healthy animals, in order to reduce the emergence of antibiotic-resistance bacteria strains that could be potentially transmittable to humans and to preserve the effectiveness of antibiotics. The antibiotic-resistance can take place when microorganisms are continuously exposed to sublethal doses of antibiotics as a result of an adaptation process (Álvarez-Cisneros & Ponce-Alquicira, 2018). Therefore, there is an urgent need for novel antimicrobials that can be used for animal production with low development of resistance, where bacteriocins are of great interest mainly because of their antagonism against *Cl. perfringens*, enterotoxigenic *E. coli*, *Campylobacter jejuni* and *Salmonella enterica* that can affect both animal and human health, as well as, against *Streptococcus suis* a zoonotic agent that causes economic losses for swine production. In addition the administration of bacteriocinogenic strains, such as *Lb. salivarius* can help to modulate the gastrointestinal microbiota of healthy pigs reducing the levels of gram-negatives and the presence of opportunistic pathogens thus improving the meat microbial quality (Lagha, Hass, Gottschalk & Greiner, 2017).

PEPTIDOGLYCAN HYDROLASES (PGHS)

Peptidoglycan Structure

The peptidoglycan (PG) is a hetero-polymer of glycan backbones crosslinked by peptides forming a mesh-like layer in the bacterial cell wall. It is responsible for the rigidity and shape of bacterial cells; it is also involved in the bacterial resistance mechanisms to antibiotics, immune responses, phage susceptibility, serological behavior and protects against osmotic lysis, among others. The cell wall of gram-negative bacteria contains less than 10% PG. But for gram positive the PG content varies from 30-70% showing structural variations that may be considered a criterion for bacteria differentiation. In addition, the PG layer is highly dynamic showing structural changes during the cell growth and cell division processes (Meroueh et al., 2006; Bourhis & Werts, 2007; Wang & Shaevitz, 2013; Sharma et al., 2016).

The glycan backbone is made of alternating units of *N*-acetylglucosamine (NAG) and *N*-acetylmuramic acid (NAM) linked by β -1,4 glycosidic bonds. The peptide subunits contain four and occasionally five alternating L- and D- amino acids residues joined to the lactyl group of the NAM units. In general, L-alanine is directly bound to the NAM, followed by two amino acid residues with three functional groups (D-glutamic acid or threo-3-hydroxyglutamic [Hyg] at position 2) attached to an L-diamino acid at position 3, and a final D-alanine residue at position 4. But in some cases an additional L-alanine is also present at the C-terminus forming a penta-peptide subunit. The peptide subunit for most Gram-positive bacteria presents a L-Lysine residue at position 3, while a meso-diaminopimelate (mDAP) occurs for gram-negative and some gram-positive such as *Listeria*. Structural modifications give

rise to more than 100 different PG variants arranged into types A and B according on their peptide cross-linkage. The free amino group of the L-diamino acid residue (at position 3) directly participates in the cross-linkage to the D-alanine carboxyl group at (position 4) of an adjacent peptide subunit for the PG type A. In the case of PG type B the cross-linkage involves an inter-peptide bridge consisting of 1-7 glycine residues (Schumann, 2011).

Characteristics of Peptidoglycan Hydrolases

The enzymes capable of hydrolyze the PG cell wall promoting cell lysis, are known as peptidoglycan hydrolases (PGHs) and found in several organisms, including animals, plants, bacteria and viruses. Their synthesis is highly regulated, from their transcription to the posttranslational level in order to prevent the cell lysis (Kelly & Bayles 2003; Vollmer et al., 2008). PGHs have an important role as they participate in different phenomena of lysis, either to lyse host cells or to re-model the cell wall during growth and division (Bustamente, et al., 2012). Bacterial division results from the combination of membrane constriction with expansion and remodeling of the cell wall. For many bacteria, the cell lysis is a natural part of the life cycle and, in some cases, is useful to eliminate damaged cells within the population (Regulski et al., 2012; Høltje & Tuomanen, 1991; Smith, Blackman & Foster, 2000). PGHs represent a novel class of antimicrobials, as they can act selectively in the rapid killing of pathogenic bacteria without affecting the normal microbiota; also present low toxicity, moderate inhibition by the host immune response and low probability of developing resistance. All these features result of great interest for their biotechnological and pharmacological exploitation for food preservation and for the treatment of drug resistant infections (Bustamente, et al., 2012).

The activity of the PGHs also generates rotational products that serve as signaling molecules for the recognition of bacteria by other organisms and, in some bacteria, for the induction of β -lactamase that may provide resistance to β -lactam antibiotics. In addition, these hydrolases are also responsible for the autolysis under certain conditions. Most PGHs present a specific activity for each glycoside and amide bridges in the peptidoglycan (Vollmer et al., 2008). Although the PGHs physiological functions include the regulation of cell wall growth, the replacement of peptidoglycan during growth, the separation of daughter cells during cell division, it is difficult to assign a function other than a PGHs, because many bacteria have a high number of hydrolases with redundant roles, as they are able to break covalent bonds in sacs of peptidoglycan or their fragments (Høltje & Tuomanen, 1991; Smith, Blackman & Foster, 2000; Heidrich et al., 2001). Some specialized hydrolases enlarge the pores in the peptidoglycan in a temporal and controlled way, allowing the insertion of multiprotein complexes in the cellular sheath (pili, flagella, secretion systems), or split the PG during sporulation or germination of spores (Vollmer et al., 2008; van Heijenoort 2011; Høltje 2013; Maxime et al., 2018).

It has been proposed that some PGHs cooperate with other enzymes splitting the existing PG polymer allowing the insertion of new material, but the direct evidence for such a mechanism has not yet been proven. The role of PGHs involved in the cell separation and autolysis has been reported. Little is known about the cellular function of those PGHs involved in the maturation of PG, which includes the regulation of the length of the chains of

glycans and peptides, as well as the degree of cross-linking. In a very general way, PGHs functions include regulating the availability of PG precursors, PG maturation, septum splitting, cell separation and autolysis (Höltje & Tuomanen, 1991; Höltje, 1998; Smith, Blackman & Foster, 2000; Vollmer et al., 2008; van Heijenoort, 2011; Maxime et al., 2018).

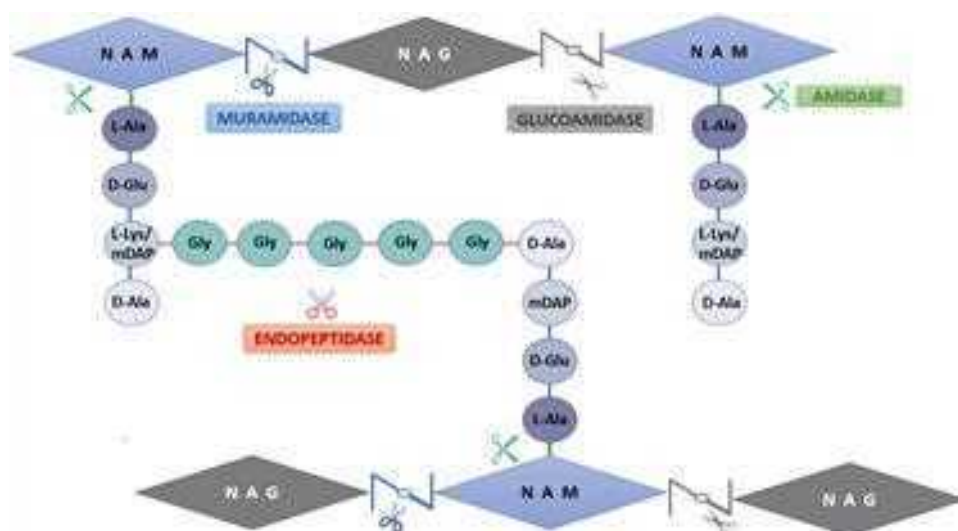


Figure 2. Representation of the of peptidoglycan (PG) structure showing the N-acetylglucosamine (NAG) and N-acetylmuramic acid (NAM) subunits linked by β -1,4 glycosidic bonds and the glycine inter-peptide bridge for PG type B. Also the sites of peptidoglycan hydrolases (PGHs) action are presented for muramidases, glucoamidases, amidases and endopeptidases (Modified from Sharma et al., 2016,; García-Cano, 2013).

Classification of Peptidoglycan Hydrolases

The PGHs are widespread in bacteria and also known as autolysins classified according to the cleavage site. The three main classes include: (1) the glucosidases that fragment the glycan backbones; (2) the amidases or peptidoglycan amidases (*N*-acetylmuramyl-*L*-alanine amidases) that hydrolyze the amide bond between NAM and the N-terminal *L*-Alanine residue, thus separating the peptide subunits from the glycan backbone; and (3) the peptidases (endopeptidases and carboxypeptidases) that act within the PG peptide side chains (Figure 2).

Specifically, the glucosidases consist of *N*-acetyl- β -D-glucosaminidases, lysozymes and lytic transglycosylases. The first is an endo-glucoamidase that catalyzes the hydrolysis of the glycosidic bond between NAG and adjacent monosaccharides in different oligosaccharides such as PG, chitin and other N-glycans. These enzymes have a catalytic domain and one or more associated substrate-binding domains (CBDs), such as one to six LysM motifs generally located at one end of the protein, that bind directly to the PG thus affecting the substrate binding and the hydrolysis efficiency. The latter two glucosidases are known as *N*-acetyl- β -D-muramidases or muramidases that hydrolyze the β -1,4-glycosidic bonds between the NAM and NAG residues of PG. The resulting product from the lysozyme action is a terminal reducing NAM residue; while the lytic action of transglycosylases induces a

transglycosylation reaction resulting in the formation of 1,6-anhydro ring in the NAM residue.

The PG amidases or *N*-acetylmuramyl-*L*-alanine amidases hydrolyze the amide bond separating the peptide subunits from the glycan backbone. They are members of the bacterial autolytic systems and carry a signal peptide in their N-terminal site that allows their transport across the cytoplasmic membrane; while bacteriophage PG amidases are endolysins with no signal peptides (Vollmer et al., 2008). On the other hand, the peptidases that hydrolyze the amide bonds between amino acids in the PG, according to their specificity are endopeptidases (cleaving bonds within the peptide chain) or carboxypeptidases (removing the C-terminal amino acid). These PGHs are also named DD-peptidases, when cleaving between two D-amino acid residues, and LD- or DL- peptidases if the hydrolysis takes place between an L- and D- amino acid residues (Ghuysen, Tipper & Strominger, 1966; Layec, Decaris & Leblond-Bourget, 2008; Vollmer et al., 2008; Reith & Mayer, 2011; Johnson, Fisher & Mobashery, 2013; Johnson & Klaenhammer, 2016; Sharma et al., 2016).

Applications of Peptidoglycan Hydrolases as LAB Beneficial Metabolites

There is an increased interest in the study of natural antimicrobials that help to fight bacterial infections and the presence of opportunistic fungi. As they are associated with high mortality rates due to the emergence of antibiotic resistance. In this sense, PGHs are considered valuable alternatives or complements of the classic antifungal agents to fight infection by fungi (Delattin et al., 2017; Owen et al., 2018). On the other hand, multidrug-resistant strains are becoming more frequent and represent one of the main causes of morbidity and mortality. For this reason, new strategies are urgently needed to combat multi-drug-resistant pathogens. In this scenario, PGHs represent a valuable alternative as antibacterial agents due to its unique property of breaking the cell wall peptidoglycan of fungi, as well as, gram-positive and gram-negative bacteria with a low incidence to induce resistance; therefore they may replace or be used in combination with antibiotics (Sharma et al., 2016; Kashani et al., 2017).

PGHs may inhibit spoilage bacteria and food pathogens. In recent years lysozyme has been used as a natural antimicrobial, approved as a preservative in foods in USA and other countries. Its main applications have been in the prevention of gram-positive contamination in cheese and control of bacterial activity in wine. Another example is the lysostaphin active against *Staphylococcus aureus*, important pathogens in the food industry. But there is a wide range of PGHs which are being studied and that arise as an important alternative to combat a broad spectrum of bacteria, both gram-positive and gram-negative bacteria, which could be used as natural agents to fight against food-borne diseases (Callewaert et al., 2011; Carrillo et al., 2014).

Food Applications of Peptidoglycan Hydrolases

The two most studied PGHs in the food industry are lysozyme and lysostaphin. Lysozyme is a naturally occurring N-acetylmuramidase in both the animal and plant kingdoms that plays an important role in the natural defense mechanism and discovered by Alexander Fleming in 1922. Many researchers have described various biological activities of this

protein, including its antibacterial activity against gram-positive bacteria and harmless to human cells. However, their antibacterial spectrum has reached some gram-negative bacteria if their outer membrane is disrupted prior to exposure through thermal, chemical or enzymatic modifications, genetic mutations and synergistic effects with other compounds. It has been used by plants and animals as a natural defense mechanism against pathogenic bacteria and it is allowed as a food additive. For instance lysozyme is used in casings and cooked RTE meat and poultry products with the GRAS Notice No. 000064 given by the USDA.

Lysostaphin (also classified as a Class III bacteriocin) has been highlighted as a next-generation agent for the treatment against *S. aureus*, one of the main pathogens transmitted by food and nosocomial infections around the world, that causes diseases such as endocarditis, pneumonia and toxic-shock syndrome, among others (Kadariya, Smith & Thapaliya, 2014). Lysostaphin is a Zn^{2+} dependent endopeptidase with a molecular mass of ~ 27 kDa, a PI of 9.5 and a pH optimum of 7.5, also classified as bacteriocin. It consists of two domains (Figure 3), the N-terminal responsible for the catalytic activity of Gly-Gly bonds, and a C-targeting domain (CWT) that specifically binds to the pentaglycine bridge of the PG cell wall of *S. aureus* and *S. epidermidis* (Ojha et al., 2018; Tossavainen et al., 2018).

This PGH is produced by *S. simulans*, which represents a main concern for their use in the food industry. Therefore, lysostaphin has been cloned and expressed in various heterologous systems including BAL. For instance, food-grade lysostaphin has been produced in *Lc. lactis* and *Ped. acidilatici* using the NICE (Nisin-controlled gene Expression) system at industrial scale (Mierau et al., 2005; García-Cano et al., 2015).

PGHs have been proposed as a tool to prevent bacterial diseases transmitted by foods, which are associated with high morbidity, death and economic losses (Fischetti 2010). These hydrolytic enzymes could inhibit the growth of *E. coli* (including the pathogenic serotypes), *L. monocytogenes* (a ubiquitous bacteria that can cause abortion in pregnant women and other serious complications in children and elderly), *Salmonella enterica* serovar Typhimurium (which can cause massive outbreaks and even death in children and elderly), and *S. aureus* (Galié et al., 2018). Recently, several PGHs have been evaluated during the cheese manufacture, where the presence of non-starter BAL contribute to the development of desirable flavor characteristics and to the quality and safety of the final product due to the production of autolysins (Cibik & Chapot-Chartier, 2004; Aldrete-Tapia et al., 2018). Although few autolysins produced by the *Lactobacillus* genus have been characterized; the autolysin AclB produced by *Lb. casei* was purified and fully characterized. AclB was recognized as a species-specific cell separating enzyme responsible for the cell separation of *Lb. casei* after cell division, which helps to accelerate cheese ripening (Xu et al., 2015), in advantage with other autolysins such as the LytF produced *B. subtilis* as that only contributes synergistically to the cell separation (Margot, Pagni & Karamata, 1999; Xu et al., 2015). Some other autolysins could be applied in a similar way to improve food fermentations, such as the autolysin Acm2, required for cell separation in *Lb. plantarum* and *Lc. lactis* (Palumbo et al., 2006). There are also reports on the PGH endopeptidase activity for the surface layer (S-layer) of *Lb. acidophilus* against the cell wall of some bacteria. The S-layer is a bifunctional array of proteins or glycoproteins that overlay the cell surface of several *Eubacteria* and *Archaea*. The S-layer proteins are directly in contact with the bacterial environment and involved in surface phenomena such as bacterial co-aggregation, adhesion, protection and recognition or as carriers of virulence factors (Gerbino et al., 2015). The S-layer reported for *Lb. acidophilus* ATCC 4356 is composed of a single protein (protein S_A) of

~ 45 kDa, with endopeptidase activity against the cell wall of *Salmonella enterica*, *E. coli* and *Micrococcus luteus*. Therefore this S-layer proteins may in theory be use to prevent the growth of food spoilage microorganisms (Prado-Acosta et al., 2008; Hynönen & Palva 2013; Meng et al., 2015). Other similar PGHs like the Msp1/p75 produced by the probiotic *Lb. rhamnosus* GG that was initially reported as an anti-apoptotic and growth-promoting of intestinal cells, also shows PGH activity with D-glutamul-L-lysyl endopeptidase specificity for daughter cell separation of *Lb. rhamnosus*. In addition thirteen PGHs were detected in *Lb. casei* BL23 where the Lc-p75 was identified; this protein is the homolog of the previously mentioned Msp1/p75. Both PGHs are attached to the cell wall and secreted in the culture supernatant, which also have been confirmed being responsible for the cell wall lysis of different food deteriorating microorganisms (Claes et al., 2012; Regulski et al., 2012).

Another interesting example is the first bifunctional PGH reported, produced by *Ped. acidilactici* ATCC 8042 that possess two identified lytic sites: N-acetylglucosaminidase and N-acetilmuramoyl-L-alanine amidase activities (Figure 3). These results could help in the design of new antibacterial agents of natural origin that can combat food-borne diseases and improve hygienic practices in the industrial sector (Carrillo et al., 2014; Serrano-Maldonado et al., 2018). Moreover, the search for new and natural antimicrobials includes the PGH produced by *Lb. sakei* active against various food-spoilage microorganisms. As shown in Figure 3, this PGH possess a lytic domain with N-acetyl-muramoyl-L-alanine amidase activity joined to a LysM region (small globular domains ranging in length from 44 to 65 amino acids that bind to various PG types) (Mesnage et al., 2014; López-Arvizu, García-Cano & Ponce-Alquicira, 2017). In similar studies from the twelve predicted PGH-encoding genes in the genome of *Lb. plantarum*, two PGHs were identified, the N-acetylglucosaminidase Acm2 and NpIC/P60 D,L- endopeptidase LytA. Both enzymes revealed a potential hydrolytic activities being the Acm2 the mayor autolysin produced by *Lb. plantarum* (Rolain et al., 2012). *Lb. plantarum* extracts with N-acetylglucosaminidase activity were capable to inhibit several microorganisms such as *Listeria innocua*, *Staphylococcus aureus*, *Weissella viridescens* and *Leuconostoc (Leuc.) mesenteroides* and where been applied to increase the shelf life of type Vienna sausage (García-Cano, 2013; Roa, 2017).

Clinical Applications of Peptidoglycan Hydrolases

It has been claimed that PGHs can help modulate the bacterial colonization of the gastrointestinal mucosa and the control of pathogenic bacteria that would be beneficial for human and animal health. The effectiveness of antibiotics against bacterial infections is decreasing due to the development of resistance in bacteria. Therefore, there is an increasing need for potential alternatives to the use of antibiotics. PGHs can be used as alternative antibacterial agents by its ability to hydrolyze the bacterial and fungi cell wall (Sharma et al., 2016). The medical applications of the recombinant lysostaphin are moving and some have entered into clinical trials (Nelson et al., 2012). The CWT domain of lysostaphin has also been considered as a promising source for alternative chemotherapy (Schmelcher et al., 2012; Osipovitch and Griswold 2014; Jagielska, Chojnacka, & Sabała, 2016) and has been redesigned to suppress its immunogenic potential (Blazanovic et al., 2015; Tossavainen et al., 2018).

As previously mentioned, lysostaphin is active against the cell wall of *S. aureus*, this microorganism has an annual incidence rate of infections from 20 to 50 cases/100,000 habitants, with 10 to 30% mortality especially for the presence of resistant strains in elderly

patients (van Hal et al., 2012). In addition to the health problem, productivity losses and the economic impact involved for the control of *S. aureus* represents a burden to society (van Hal et al., 2012; Lee et al., 2012; Kashani et al., 2017). Studies of peptidoglycan hydrolase like lysozyme and lysostaphin have been used successfully to control pathogenic bacteria resistant to antibiotics in animal models (Nakimbugwe et al., 2006; García-Cano et al., 2011).

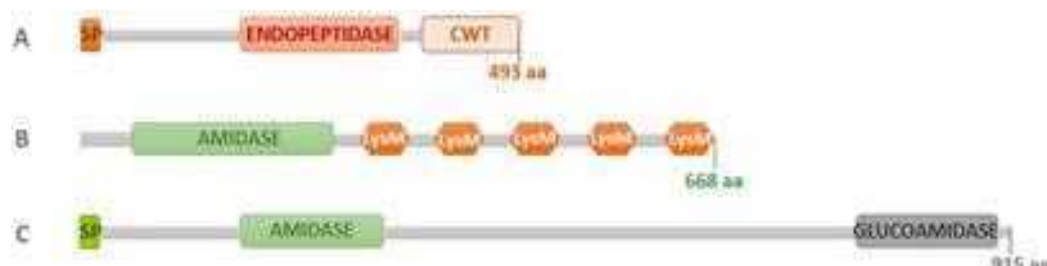


Figure 3. Domain organization of (A) lysostaphin, B) N-acetylmuramoyl-L-alanine amidase produced by *Lb. sakei* and C) Bifunctional PGH produced by *Ped. acidilactici* ATCC 8042 (Modified from Sabala et al., 2014; García-Cano et al., 2015; López-Arvizu, García-Cano & Ponce-Alquicira, 2017).

The N-acetylmuramidases Lb GH25B and Lb GH25N produced by *Lb. buchneri* CD034 and NRRL B-30929 were identified as cell wall associated proteins with hydrolyzing activity. The stability of these proteins was determined through studies of thermal denaturation getting an assessment of the conditions that maintain biological activity with values of T_m around 49°C, reflecting the thermal stability of enzymes as needed for biotechnology and drug exploitation (Anzengruber et al., 2014). These values are consistent with those obtained for the glycanhydrolase Cpl-7 of *Strep. pneumoniae* bacteriophage Cpl17 recently studied as an antibacterial agent (Bustamante et al., 2012). N-acetylmuramidases from the *Lb.* genus contribute to the of cell wall hydrolases (CWHs), whose development as novel therapeutic proteins represent some advantages over conventional antibiotics, mainly due to their low probability for developing resistance (Parisien et al., 2008; Anzengruber et al., 2014). Surprisingly, LbGH25B and Lb GH25N do not contain any of the typical domains that generally exhibit the PGH; a multi-domain structure that includes a catalytic domain and multiple copies of a cell wall binding domain. The binding domains that are often found in this type of proteins are LysM, SH3, PG-binding, CW-binding, or Cpl-7 known to be present in the cell wall-associated proteins (Layec, Decaris and Leblond-Bourget 2008; Anzengruber et al., 2014).

It is interesting to mention that these domains give better anchoring properties to the cell wall of sensitive microorganisms and are also present in many PGHs; Alternatively, these structural domains, can be used for the identification of foreign peptides in the cell surface or for improvement of adhesion of host bacteria; as it has been used in the administration therapeutic proteins and vaccines to the mucosa (Berlec, Ravnikar & Strukelj, 2012). The oral administration of the traditional intravenous or intramuscular vaccine minimizes possible side effects while increasing the specificity of the mucosa chronic diseases and infections (Bermudez-Humarán et al., 2011; Wyszynska et al., 2015; Hynönen & Palva, 2013).

As already mentioned, activities of endopeptidases present in the S-layer of *Lactobacillus* also show potential for use as carriers of antigens in the design of live oral vaccines because of its adhesive and immunomodulatory properties, that can also be used in the mediation of

bacterial attachment to host cells (Prado-Acosta et al., 2008; Hynönen & Palva, 2013). Bacteria treated with this type of proteins, examined by electron microscopy reveal that they exert their lethal effects forming holes in the cell wall through the digestion of PG. The high internal pressure of bacterial cells (approximately 3 to 5 atmospheres) is controlled by the highly cross-linked cell wall. Any deterioration in the integrity of the wall will result in the extrusion of the cytoplasmic membrane and the final hypotonic lysis (Loessner et al., 2002).

Currently, with the exception of the polysporin and mupirocin, which are commonly used topically, no other antimicrobials may control pathogenic bacteria colonizing the mucous membranes. The selectivity for their inhibitory action against pathogenic bacteria without affecting the normal mucosa microbiota and the low likelihood of bacterial resistance, improves the potential of PGHs as a novel antimicrobials (34). Another example already mentioned is the application of the Lc-p75 (γ -D-glutamyl-L-lisil-endorpeptidase) produced by the probiotic *Lactobacillus casei* BL23, which presents an anti-inflammatory activity (Regulski et al., 2012).

CONCLUSION

Bacteriocins and peptidoglycan hydrolases are beneficial metabolites produced by lactic acid bacteria. LAB bacteriocins constitute a diverse and heterogeneous group of ribosomal antimicrobial peptides, varying in size, structure and specificity, active against closely related species. These peptides are considered food-grade because the GRAS or QPS status of most bacteriocinogenic strains, do not impart color or flavor and are easily degraded by the proteolytic enzymes, that makes them safe for human consumption, minimizing the opportunity of target strains to interact and develop resistance. Therefore, bacteriocins can be applied for food preservation, as well as, an alternative antibiotics in the clinical area, mainly due to their tolerance to high temperatures and their activity over a wide pH range against spoilage microorganisms and pathogens such *Bacillus*, *Clostridia*, *L. monocytogenes* and methicillin-resistant *S. aureus* and vancomycin-resistant *Enterococci* at concentrations lower than that for conventional antibiotics. Nevertheless, more research is needed in order to expand their inhibitory spectrum, stability and increase the recovery yields; where the bioengineering offers a possibility to enhance the inhibiting activity and spectra, as well as their heterologous expression in other hosts.

There is still few data in relation to PGHs produced by lactic acid bacteria in relation to their function and characterization. But PGHs offer a wide opportunity as alternative antimicrobials from GRAS microbial sources, with great prospects for new food applications as natural antimicrobial agents.

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Chapter 298

BIOACTIVE PEPTIDES GENERATED BY LACTIC ACID BACTERIA

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ABSTRACT

Numerous chronic diseases, including heart disease, stroke, cancer, and diabetes, have a significant influence on the health of people worldwide. Along with numerous preventive and therapeutic drug treatments, important advances have been achieved in the identification of bioactive peptides (BP) that may contribute to long-term health. Biopeptides with various biological activities have been found in several food matrices and by-products. Since microbial fermentation is one of the mechanisms for BP generation, lactic acid bacteria (LAB) arise as an ideal cell factory for their production. This chapter reviews the generation and biofunctional properties of various BP derived from meat and meat products, milk and dairy products, together with some other food substrates as beans and pseudo-cereals, which had been generated by several strains of LAB. Many apprehensions regarding their functionality and health-claims have been also considered.

INTRODUCTION

Bioactive peptides (BP) have been defined as specific protein fragments that have a positive impact on body functions and may influence health. They are encrypted within the sequence of the parent protein and can be released through hydrolysis by proteolytic enzymes.

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Hydrolysis can be performed either by endogenous enzymes in ripened foods, or by the combined action of endogenous and microbial enzymes when fermented, and/or by exogenous proteolytic enzymes (e.g., enzymes derived from microorganisms and plants) on isolated food proteins (Toldrá et al., 2016; Brown et al., 2017). Health benefits of BP are continuously being explored and discovered, hence, there are still controversies regarding their magnitude and significance. Lafarga & Hayes (2014) indicated that BP have antimicrobial, antioxidative, antithrombotic, antihypertensive, anticarcinogenic, satiety regulating and immunomodulatory activities and may affect the cardiovascular, immune, nervous and digestive systems. Peptides may also be effective in the treatment of mental health diseases, cancer, diabetes and obesity. Furthermore, many known BP are multifunctional and can present two or more health promoting activities which may or may not be related (Di Bernardini et al., 2011).

Among hydrolysis processes used to generate BP, microbial fermentation is the one addressed herein by lactic acid bacteria (LAB). The proteolytic system of LAB consists of a three steps breakdown process which comprises: I) a cell envelope-associated proteinase (CEP) - a key factor since it is responsible for the first breakdown of high molecular weight proteins, such as casein in milk-, II) specialized transport systems enabling the uptake of the resulting peptides, and III) numerous intracellular peptidases, which degrade peptides to amino acids. The activity of these biofunctional peptides relies on their inherent amino acid composition and sequence. The size of active sequences may vary from 2 to 30 amino acid residues, which can have one function or multifunctional health-beneficial properties. Once released, the BP may provide different functions that can be reproduced *in vitro* with biochemical assays or *in vivo* in cell or animal models and humans. Bioactive peptides that are being discovered are reported in several databases (BIOPEP, PEPBANK, ERP-Moscow and Brainpeps, among others), together with data about their chemical and structural characteristics, IC₅₀ (concentration necessary to inhibit 50% of enzymatic activity), protein of origin, etc. (Van Dorpe et al., 2012; Toldrá et al., 2018). The degree of proteolysis and the amount of generated BP depends on numerous variables including raw materials, type of enzyme activity, microbial population, and processing conditions. Up to the present time, the most studied biological functions have been antioxidant activity, and ACE-inhibitory activity, while antimicrobial activity, opioid activity, immunomodulation and antithrombotic activities have been lightly examined.

The production and commercialization of hydrolysates containing one or more BP have proved to be successful; however, many industrial obstacles limit the sales of nutraceutical or functional products. One of the main drawbacks is the regulation aspect and the application for a health claim authorization (Arroume et al., 2016). In this sense, foods fermented by LAB are of special interest to food manufacturers and consumers because of their additional probiotic health-promoting and therapeutic benefits.

Along with the advent of increasing analytical technology comes the discovery of 'functional foods' which -unsurprisingly- have been nurturing human beings since ancient times. Such is the case of a broad spectrum of food sources, i.e. animal, plant, microalgae and fungi, which have been delivering BP through microbial fermentation. Lactic acid bacteria comprise a widespread microbiota responsible for many of these fermentations. In the following sections, an overview of this topic is presented focusing primarily on the bioactivity displayed by the BP generated in each food substrate.

ANTIOXIDANT ACTIVITY

The mechanism of antioxidant activity of peptides is yet not sufficiently elucidated in the literature. Based on current knowledge, it is supposed that they may exert their antioxidant effect through the scavenging of free radicals and reactive oxygen species (ROS), inhibiting lipid peroxidation and chelating transition metal ions. Their action may be determined by factors such as position of the peptide in the protein structure, hydrophobicity, protein isolation method, degree of hydrolysis, type of enzymes used, concentration of peptide and amino acid configuration (Standik & Keska, 2015). The antioxidant activity of the peptides depends on the type of their component amino acids (Toldrá et al., 2018). As regards to amino acid types, aromatic amino acids such as *Tyr*, *His*, *Trp*, and *Phe* are prone to donate protons contributing to the radical-scavenging properties (Rajapakse et al., 2005). Besides, the hydrophobic amino acids have been described to be able to increase the presence of peptides at the water-lipid interface and then access to scavenge free radicals from the lipid phase (Ranathunga et al., 2006). Lastly, acidic amino acids utilize carbonyl and amino groups in the side chain which function as chelators of metal ions (Suetsuna et al., 2000).

In the last decade, several studies have evaluated the potential effect of LAB strains in the production of antioxidant peptides in different food matrices aiming at endorsing the health benefits associated with functional foods. Keska & Standik (2018) evaluated the stability of antiradical activity of protein extracts from LAB-inoculated dry-cured pork loins during long-term aging before and after simulated gastrointestinal digestion with pepsin and pancreatin. The microorganisms tested were *Lactobacillus* (*Lb.*) *rhamnosus* LOCK900, *Lb. acidophilus* BAUER L0938, and *Bifidobacterium* (*B.*) *animalis* ssp. *lactis* BB12. The highest antiradical effects were achieved for loins with *Lb. acidophilus* BAUER L0938 after 90 and 180 days of aging and *B. animalis* ssp. *lactis* BB12 in 270 days in the water soluble protein fraction. The highest biological activity was reached after 90 days of aging due to the hydrolytic degradation of proteins under the action of pepsin. During this period, *B. animalis* ssp. *lactis* BB12 showed higher values of biological activity. Mejri et al., (2017) evaluated the generation of antioxidant peptides in dry fermented camel sausages inoculated with different starters cultures: *Staphylococcus* (*S.*) *xylosus* and *Lb. plantarum*; *S. xylosus* and *Lb. pentosus*; *S. carnosus* and *Lb. sakei*. They observed a significant increase in the production of antioxidant peptides during camel sausage ripening for 28 days, particularly in the release of peptides of molecular weight above 3 kDa. The accumulation of antioxidant peptides achieved the highest antioxidant values at the end of ripening, measured by ABTS, DPPH, inhibition of hydroxyl radicals, and FRAP assays. This bacterial growth resulted in an increasing amount of peptides with molecular weights below 3 kDa. In general, antioxidant capacities in non-inoculated sausages were lower than the observed for inoculated sausages, especially for the sausage inoculated with *S. xylosus* and *Lb. plantarum*. In keeping with these results, Ayyash et al., (2019a) found that the smallest peptides (<3kDa) were the ones linked with the most potent antiradical activity; being these peptides mostly generated by *Lb. plantarum* KX881772 in camel meat dry sausages.

Regarding milk as a substrate, several authors reported antioxidant activity peptides generated by LAB. Aguilar-Toalá et al., (2017) described that the growth of *Lb. plantarum* strains in whole bovine milk led to the production of crude extracts rich in antioxidants. After the isolation of two fractions (<3 kDa and 3-10 kDa), these authors observed a strong

relationship among small peptides (<3 kDa) with antioxidant activity measured by DPPH and ABTS assays. Nevertheless, they found that peptides of molecular weight in the range 3-10 kDa also contributed to antioxidant potential of fermented whole bovine milk. Moreover, other studies support the use of different LAB, such as *Lb. helveticus* (Elfahri et al., 2016); *Lb. rhamnosus*, *Lb. paracasei*, and *Lb. casei* (Solieri et al., 2015), to induce the release of antioxidant peptides in milk. Mohanty et al., (2016) reported *Lb. delbrueckii* subsp. *bulgaricus* IFO13953 as a producer of an antioxidant peptide whose amino acid sequence was identified. Besides, antioxidant activities were reported from cow and camel milks fermented by specific strains of *Lb. plantarum*, *Lb. paraplantarum*, *Lb. kefir*, *Lb. gasseri*, and *Lb. paracasei* (Soleymanzadeh et al., 2016). Ayyash et al., (2017) also reported antioxidant activity in camel and cow milks fermented with *Lb. plantarum* and *Lb. reuteri*. El-Fattah et al., (2016) reported ACE inhibition and antioxidant activities after milk fermentation in 14 commercial dairy starters, which exhibited different degrees of proteolysis.

On wheat and other cereals, antioxidant peptides were described as the result of LAB activity (Coda et al., 2012). Generally, the high proline content of gluten alpha gliadins prevents hydrolysis by enzymes of the gastrointestinal tract, whereas LAB possess proline-specific peptidase systems. Alternatively, peptide degradation was achieved by the combined action of peptidase from different LAB strains simultaneously present in fermented food (Gerez et al., 2008). Ayyash et al., (2019b) investigated antioxidant activities on solid-state fermented (SSF) whole grain lupin, quinoa and wheat using *Lb. reuteri* KX881777 and *Lb. plantarum* KX881779. All quinoa fractions had an increase in DPPH after 24 h of fermentation. *Lb. reuteri* had the highest DPPH % in quinoa fraction compared with lupin and wheat fraction. Likewise, quinoa fermented by *Lb. reuteri* and *Lb. plantarum* had the greatest ABTS % compared with lupin and wheat fraction. The higher antioxidant activities in fermented quinoa fraction may be attributed to the nature of proteolytic products released and to other non-phenolic compounds with antioxidant activities. The antioxidant results in lupin fraction were in agreement with those reported by Fernández-Orozco et al., (2008) who run a similar fermentation with a strain of *Lb. sakei*. Besides, the fermentation of quinoa flour by *Lb. plantarum* (22 strains), *Lb. rossiae* (1 strain) and *Pediococcus* (*Ped.*) *pentosaceus* (3 strains) produced fermented quinoa flour extracts of high antioxidant activity (Rizzello et al., 2017). The authors observed that antioxidant activity was strain-dependent wherein *Lb. plantarum* strains displayed the highest capacity to breakdown quinoa proteins to antioxidant. The antioxidant activities in quinoa fermented for 24 h by *Lb. plantarum* was attributed to short chain peptides (<9.0 kDa).

ANTIHYPERTENSIVE ACTIVITY

The BP with antihypertensive activity - which mainly takes place through inhibition of the angiotensin I-converting enzyme (ACE) - has become of particular interest to the scientific community over the last few years. Within the regulation of blood pressure, ACE is a key enzyme that catalyzes the conversion of angiotensin I into angiotensin II, a potent vasoconstrictor, and inactivates bradykinin, a vasodilator (Ondetti & Cushman 1977). The higher the ACE activity, the higher the angiotensin II level, and the more likely that malignant hypertension (high blood pressure) develops. Hypertension is one of the risk

factors for coronary heart disease and stroke, being closely linked to the eating habits of industrialized countries (Lin et al., 2012).

Despite the fact that herein BP antioxidant and ACE inhibitory activities are presented separately, they usually appear together in the literature since the same sample fraction is implicated in both determinations. Hence, many of the studies aforementioned will sound familiar for the reader who had read the previous section.

The study of biopeptides generated in meat and meat products implies the acceptance of the presence of existent BP in the matrix before fermentation, hampering the determination of those BP generated exclusively by inoculated LAB. As an illustration, the increased ACE inhibition observed in fermented camel sausages suggested that the strain *Lb. plantarum* KX881772 improved the bioactivity of this meat product (Ayyash et al., 2019). The higher ACE inhibition in fermented camel sausages, compared with beef sausages, was attributed by the authors to a high degree of hydrolysis and/or the nature of camel meat peptides released during fermentation and storage. Mejri et al., (2017) also studied camel meat sausages whereas inoculated with different starter bacteria. They reported that the percentage of ACE inhibition was increased significantly in the whole extract and in all fractions during the 28 days of ripening. It could be noted that the highest ACE inhibition capacity was always observed for the fraction with peptides below 3 kDa. This assumption was in keeping with Escudero et al., (2013) and Mora et al., (2015) results, which stated that low molecular weight peptides (<3 kDa), contributing to the development of flavor in dry fermented meat products, could also exert antihypertensive activity. Moreover, ACE inhibition through ripening was significantly affected by the addition of a starter (*S. xylosus* and *Lb. plantarum*). These results were in accordance with those of Flores & Toldrá (2011) and Mora et al., (2015) who found that the action of microorganisms such as LAB could influence the last period of fermentation, contributing to the generation of small peptides and free amino acids.

Considering milk, the number of BP increases during the production of fermented milk products compared to raw milk and the composition of the peptide fraction changes due to the proteolytic action of the employed microorganisms (Hayes et al., 2007). Some studies investigated BP in traditional fermented milk products and identified, for instance, that the major ACE inhibitory peptide of Manchego cheese was attributed to the di-peptide FP, originated from hydrolysis of various casein fractions. A single peptide was responsible for the ACE inhibitory activity, which had an IC₅₀ value of 592 μ m (Gómez-Ruiz et al., 2002). Casein, as well as whey milk proteins, in particular α -lactalbumin and β -lactoglobulin, are a rich source of ACE-inhibitory peptides. These BP are naturally present in dairy products, generated during processing and ripening due to endogenous enzymes and microbial fermentation; besides, they are also released from milk protein sequences during gastrointestinal digestion by gastric and pancreatic enzymes (Seppo et al., 2003). The most significant examples of BP produced by *Lactobacillus* species in cheese are the antihypertensive tripeptides, Ile-Pro-Pro (IPP) and Val-Pro-Pro (VPP) -also called lactotripeptides-, generated from casein hydrolysis by different *Lb. helveticus* strains (Pihlanto, 2013). Moreover, sour milk fermented by *Lb. helveticus* contained ACE inhibitory tri-peptides (IPP and VPP) that lowered blood pressure in mild hypertensive subjects (Fekete et al., 2015). Jin et al., (2016) and Rutella et al., (2016) reported the presence of antihypertensive BP in yogurts and fermented milk products which are already being marketed (Hafeez et al., 2014; Raveschot et al., 2018). The magnitude of proteolysis would depend on the strain used. A good example of this situation is the work reported by Ahn et al.,

(2009) where whey fermented by *Lb. brevis* had a stronger ACE inhibitory ability than those fermented with *Lb. acidophilus*, *Lb. bifementans*, *Lb. casei*, *Lb. helveticus*, *Lb. paracasei*, *Lb. plantarum* and *Lb. reuteri*. Consequently, the functionality of protein hydrolysates may differ between cultures since microorganisms have different proteolytic systems. Even within the same species, different extent of hydrolysis, titratable acidity, free amino nitrogen and ACE inhibitory activities can be expected, as reported in skim milk fermented with 37 different *Lb. helveticus* strains (Chen et al., 2014).

In addition to the milk products already mentioned, kefir comprises another source of BP. Quirós et al., (2005) revealed two ACE inhibitory peptides in caprine kefir. Compared to some other fermented dairy products, kefir showed a higher rate of proteolysis and could, therefore, be a good source of physiologically active peptides (Ebner et al., 2015). Results from the latter study demonstrated that fermentation caused the additional release of peptides compared to unfermented milk. It could be concluded that the fermentation process improved the health promoting effects of milk that arose from the presence of bioactive peptides, namely 236 of the identified peptides were unique for kefir. Consequently, not only the concentration of bioactive peptides may increase during the fermentation process, but the bioactivity profile may also be completely different in kefir compared to milk. While the milk peptides are generated mainly by the action of endogenous proteinases like plasmin, cathepsins B, D and G, microbiological degradation plays a key role in fermented products. Two general specificity classes of proteinases are reported for lactococci, which are merely one part of the complex kefir microflora. As reported by Ebner et al., (2015), two of the identified bioactive peptides were of particular importance, i.e., casecidin 17 -a multifunctional peptide exerting antimicrobial, ACE-inhibitory, immunomodulating, antioxidant, and antithrombotic activities (Birkemo et al., 2009; Rojas-Ronquillo et al., 2012), and the peptide V- β -casomorphin-9 another multifunctional peptide showing ACE-inhibitory, antioxidant, and opioid activity (Eisele et al., 2013).

Soybean proteins have also been used as a source of ACE inhibitory proteins. According to Daliri et al., (2018) soy protein isolates consists of 90% protein; their components being 34% glycininand and 27% β -conglycinin. The many benefits of soybean proteins to reduce cholesterol levels (Hoie et al., 2007), reduce the risk of cardiovascular disease (Xiao, 2008), reduce the risk of breast cancer (Nagata et al., 2007), and lower blood pressure (Aluko, 2015) are well established and correlated with intensive studies. Vallabha & Tikku (2014) used a *Lb. casei* spp. *pseudopplantarum* strain to produce fermented soy protein concentrates. Their results showed a strong ACE inhibitory potency ($IC_{50} = 3.7$ mg/mL) of the fermented concentrate, while its isolated ACE inhibitory peptide LIVTQ displayed a higher potency ($IC_{50} = 0.087$ μ M). ACE inhibitory peptides (IFL and WL) isolated from tofu also displayed strong ACE inhibitory abilities (IC_{50} values of 44.8 and 29.9 μ M, respectively) indicating their potential to reduce high blood pressure (Kuba et al., 2003). Moreover, fermentation *Ped. pentosaceus* SDL1409 on soybean protein isolates for 48 h at 37°C generated a strong angiotensin I-converting enzyme inhibitory ability of $65.1 \pm 0.78\%$ ($IC_{50} = 0.123 \pm 0.02$ mg protein/mL). In this sense, Daliri et al., (2018) demonstrated that *Ped. pentosaceus* SDL 1409 could be useful for developing antihypertensive functional foods from soybean proteins.

EMERGING BIOACTIVITIES

In addition to both main health-promoting activities previously mentioned, several other bioactivities have been related to peptides generated by LAB fermentation. Hypocholesterolemic and antithrombotic peptides have been described to modulate the cardiovascular system whereas mineral binding and immunomodulatory peptides act in gastrointestinal and immune systems, respectively. Some groups of peptides are able to participate in multiple system reactions. Thus, opioid agonist and antagonists can act on nervous, gastrointestinal, and immune systems, whereas antimicrobial peptides can modulate gastrointestinal and immune systems (Lafarga & Hayes, 2014). The main problem of naturally generated peptides is the difficulty in controlling the hydrolysis conditions because many endogenous enzymes are acting at the same time and a wide profile of peptides showing different sizes and characteristics is generated (Mora et al., 2015). Despite the well documented evidence supporting these peptides bioactivities, trials were mainly conducted *in vitro*, giving scarce information about the availability and functionality of BP *in vivo*. For this reason, only few studies herein have been selected to illustrate the emerging bioactivities that had been investigated until the present time, taking into consideration that this scenario will evolve quickly, and that deeper comprehensive investigations would have to enrich this description in the near future.

The antithrombotic peptide YQEPVLGPVRGPFPIIV was generated by *Lb. casei* from bovine casein. This peptide not only presented antithrombotic activity but also inhibited ACE when tested *in vitro*. Besides, the peptide was able to maintain its bioactivity after enzymatic treatment with pepsin and trypsin (Rojas-Ronquillo et al., 2012). Very few meat-derived antithrombotic peptides have been described in the literature, being the few ones derived from the hydrolysis of papain, namely not from bacterial activity (Morimatsu et al., 1996; Shimizu et al., 2009).

Beta-caseins (β -CNs) harbor β -casomorphins (β -CMs) which are opioid peptides encrypted in an inactive form and can be released by enzymatic hydrolysis during fermentation and *in vivo* or *in vitro* gastrointestinal digestion (Asledottir et al., 2017; De Noni et al., 2015). Beta-CN fragments, β -CM5 (Tyr-Pro-Phe-Pro-Gly) and β -CM7 (Tyr-Pro-Phe-Pro-Gly-Pro-Ile) have strong opioid activity and are currently being extensively studied for their biological activity and their occurrence in a wide range of dairy products (Boutrou et al., 2013; De Noni et al., 2015; Nguyen et al., 2015). Nguyen et al., (2018) found that there were significant differences between the peptides generated by either *Streptococcus (Strep.) thermophilus* or *Lb. delbrueckii* ssp. *bulgaricus* fermenting UHT milk alone. They also determined that even the peptide profile generated by both strains as a mixed culture had a different peptide composition. These findings suggested that a new peptide was released by *Lb. delbrueckii* ssp. *bulgaricus* at the expense of an unknown enzyme derived from *Strep. thermophilus*.

Immunomodulating activity has been especially detected in peptides derived from milk and dairy products. These studies show that their length can be very different comprising from 2 to 64 amino acids, although those smaller than 3 KDa are the most abundant (Reyes-Díaz et al., 2016). Milk fermented by *Lb. helveticus* showed immunomodulating effect after administration to mice, whereas this bioactivity was not observed when mice were treated with milk fermented by a non-proteolytic variant of the same *Lb. helveticus* strain (Matar et

al., 2001). Additionally, the possible impact of milk fermented by *Lb. helveticus* on sleep efficiency in elderly subjects was demonstrated in a clinical study (Yamamura et al., 2009). A beneficial effect of fermented milk on bone metabolism was observed in animal or human clinical studies, probably because of the high calcium concentration and bioavailability in these products (Rizzoli & Biver, 2017). A previous work by Kim and coworkers (2009) showed a positive influence on bone metabolism in ovariectomized rats exerted by milk fermented with *Lb. casei* 393. Seemingly, Narva et al., (2004 a,b) observed improvements in bone metabolism of rats fed with milk fermented by *Lb. helveticus* strains, and even on calcium metabolism in postmenopausal women.

CONCLUSION

Despite the relatively inexpensive production cost of BP by LAB species compared to the use of purified enzymes, there are still some challenges for further industrial exploitation of these bacteria; mainly the poor characterization of CEPs from different species and the low yields of peptide production by fermentation. Future and deeper studies employing LAB as BP factories have the potential to generate new peptide sequences and, therefore, new biopeptides with specific biological properties. According to Raveschot et al., (2018), metabolic engineering of the proteolytic system of LAB could overcome these challenges.

A few functional, peptide-based, products have already been launched on the market. Most of these were derived from milk, plant and marine sources. This trend is likely to continue as knowledge about the bioactivities and properties of peptides increases (Lafarga & Hayes, 2014). However, a word of caution is to be addressed on BP as a whole, since there are yet no general rules for determining the best hydrolysate with the most important activity. Each raw material, each enzyme and each hydrolysis conditions will give different final peptides. Hence, health claims and beneficial effects for the general population must be considered as ‘potential advantages’ more than ‘effective health promoters.’

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Chapter 299

ANTIMICROBIAL PRODUCTS: AN IMPORTANT FEATURE OF LAB AND THEIR APPLICATIONS

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ABSTRACT

Lactic acid bacteria (LAB) are known to be present in diverse origins which are rich in nutrients and energy sources, for instance, milk, meat, plants and gastrointestinal tract of humans and animals. LAB that have extensively been found to belong to the genera *Lactobacillus* (Lb), *Streptococcus* (Strep), *Enterococcus* (Ec), *Pediococcus* (Ped), *Lactococcus* (Lc), *Leuconostoc* (Leuc), *Aerococcus* (A), *Oenococcus* (O), *Carnobacterium* (Cb), *Vagococcus* (V), *Tetragenococcus* (T), *Weissella* (W) and *Fructobacillus* (F) (a genus of fructophilic lactic acid bacteria). They can produce lactic acid as the primary metabolic end product via carbohydrate metabolisms. Therefore, various fermented foods are developed by the action of these bacteria. Antimicrobial compounds secreted by LAB have long been recognized to prolong the shelf-life and improve the safety of foods. LAB produce a variety of compounds, including lactic acid, acetic acid, hydrogen peroxide (H₂O₂), ethanol, formic acid, fatty acids, diacetyl, acetaldehyde, acetoin, reuterin, reutericyclin, bacteriocins, bacteriocin-like compounds and other low molecular mass compounds which exhibit the antimicrobial activity against spoilage and pathogenic microorganisms and germination of spore as well. LAB cultures are marketed today as protective cultures against common food spoilage bacteria and pathogens. Consequently, the application of such cultures may lead to improvements in food quality and sensory attributes by controlling spoilage microbiota. The use of antimicrobials from LAB as food preservatives has become a popular practice. Moreover, the addition of LAB as probiotics into food and medical products has also been reported.

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INTRODUCTION

The interest in naturally- or bio-preservation has been increasing during recent years. For this reason, many researchers have been paying attention on antagonistic microorganisms and their antimicrobial metabolites for application in the food industry (Reis et al., 2012). Among the microorganisms, lactic acid bacteria (LAB) are fascinating since ancient time; many kinds of food are fermented naturally by autochthonous LAB, which form the desirable characteristics of the products. The action of these bacteria can improve texture, flavor, odor and taste of foods. These phenomena are responsible from the generation of numerous metabolites such as lactic acid, acetic acid, ethanol, diacetyl, acetone, exopolysaccharide, specific proteases and bacteriocin by fermentation (Porto et al., 2017). The reduction of pH and conversion of sugars to organic acids are the primary preserving actions that these bacteria provide to fermented food. Therefore, shelf-life of foods is extended and the safety for consumption is ensured. In addition to organic acids, other antimicrobials produced by LAB; H₂O₂, ethanol, formic acid, fatty acids, diacetyl, acetaldehyde, acetoin, reuterin, reutericyclin, bacteriocins, bacteriocin-like substances (BLIS) also exhibit antagonistic activity against undesirable microorganisms (Šušković et al., 2010).

In regard to antagonistic property, LAB are used as protective cultures and preservatives in food-based products because of their bioactive compound production. Furthermore, they are also developed as the pure and mixed culture for the alleviation of human suffering from the pathogenic infection. In this chapter, we focus on the diversity of LAB distributed in natural materials, their antimicrobials, antimicrobial spectrum and application of LAB in food products and clinical alleviation.

LAB AND HABITATS

LAB comprise a clade of Gram-positive bacteria integrated by a cluster of morphological, metabolic, and physiological characteristics (Axelsson, 2004). They are catalase-negative, acid tolerant, non-sporulating, non-respiring rods or cocci that produce lactic acid as the major metabolic end-product of carbohydrates fermentation (Salminen et al., 1996; Klaenhammer & de Vos, 2011). They have less than 55% mol G+C content in their DNA (Stiles & Holzapfel, 1997). LAB consisted of several genera including *Lactobacillus* (Lb), *Streptococcus* (Strep), *Enterococcus* (Ec), *Pediococcus* (Ped), *Lactococcus* (Lc), *Leuconostoc* (Leuc), *Aerococcus* (A), *Oenococcus* (O), *Carnobacterium* (Cb), *Vagococcus* (V), *Tetragenococcus* (T), *Weissella* (W) and *Fructobacillus* (F) (Axelsson, 2004). Among these genera, *Lactobacillus* is the largest genus (Parte, 2018). LAB can be divided into two groups based on their glucose metabolisms including homofermentative LAB which converted glucose almost quantitatively to lactic acid (more than 85%) through Embden-Meyerhof-Parnas or glycolysis pathway and heterofermentative LAB which fermented glucose to lactic acid (50%), ethanol/acetic acid, and CO₂ through the phosphoketolase pathway (Reddy et al., 2008).

LAB require numerous essential nutrition for their growth; hence, distribution of LAB is associated with the sources containing the high concentration of carbohydrates, amino acid, vitamins, purines and pyrimidines (Saguir et al., 2007). Consequently, LAB are typically

detected in a large number of natural sources that are rich-nutrients such as dairy, meat, cereal, plants, and their fermentative products, and functioned as natural inhabitants gastro-intestinal (GI) tract of human and animals. These bacteria produce many metabolic products especially, lactic acid that provide a unique characteristic of each fermented product. *Lactobacillus* seems to be the most widespread LAB which distributed in these environments. *Lb. plantarum*, *Lb. reuteri*, *Lb. delbrueckii* subsp. *lactis*, *Lb. delbrueckii* subsp. *bulgaricus*, *Lb. paracasei*, *Lb. curvatus*, *Lb. rhamnosus*, *Lb. fructivorans*, *Lb. parabuchneri*, *Lb. brevis*, *Lb. animalis*, *Lb. curvatus*, *Lb. fermentum*, *Lb. helveticus*, *Lb. kefir*, *Ec. faecium*, *Ec. faecalis*, *Ec. devriesei*, *Ec. durans*, *Ec. saccharominimus*, *Lc. lactis*, *Lc. garvieae*, *Leuc. pseudomesenteroides*, *Leuc. mesenteroides*, *Leuc. lactis*, *Leuc. citreum*, *W. viridescens*, *Strep. thermophilus* and *Strep. bovis* are isolated from dairy-based products including camel milk, goat milk, cow milk, Greek traditional yoghurt, fermented milk, Maroilles (French cheese) and Romanian dairy products (Zamfir et al., 2006; Tormo et al., 2015; Abushelaibi et al., 2017; Georgalaki et al., 2017; Nacef et al., 2017). Various species of LAB including *Lb. sakei*, *Lb. casei*, *Lb. plantarum*, *Lb. paraplantarum*, *Lb. paracasei*, *Lb. johnsonii*, *Lb. brevis*, *Lb. curvatus*, *Lb. fermentum*, *Lb. graminis*, *Lb. carnosus*, *Ped. pentosaceus*, *Ped. acidilactici*, *Ec. faecalis*, *Ec. faecium*, *W. cibaria*, *W. confusa*, *W. halotolerans*, *Leuc. inhae*, *Leuc. mesenteroides*, *Leuc. carnosum*, *Leuc. citreum*, *Lc. lactis* and *Carnobacterium* spp. are existed in meat-originated products such as Ciauscolo salami, dry-salted cod and albacore muscle, Harbin dry sausages, Uzicka sausages, Pastırma (traditional meat product in Turkey) and Lukanka (traditional Bulgarian fermented meat product) (Federici et al., 2014; Gómez-Sala et al., 2015; Moracanin et al., 2015; Han et al., 2017; Öz et al., 2017; Todorov et al., 2017). *Lb. plantarum*, *Ped. pentosaceus*, *Ped. acidilactici*, *Lb. brevis*, *Lb. coryniformis*, *Lb. paracasei*, *Lb. fermentum*, *Lb. rhamnosus*, *Lb. sakei*, *Lb. sanfranciscensis*, *Lb. crustorum*, *Lb. paralimentarius*, *Lb. rossiae*, *Lb. mindensis*, *Lb. helveticus*, *Lc. lactis*, *Lc. garvieae*, *Ec. casseliflavus*, *Ec. faecium*, *Ec. faecalis*, *Ec. mundtii*, *Ec. hirae*, *Ec. gallinarum*, *Ec. hermanni*, *Leuc. citreum*, *Leuc. mesenteroides* and *W. confusa* are involved in cereal-based products i.e., wheat, brewer's grains, quinoa grains and sourdough, Nigerian fermented cereal-based foods and Chinese traditional sourdough (Asurmendi et al., 2015; Carrizo et al., 2016; Liu et al., 2016; Alfonzo et al., 2017; Adesulu-Dahunsi et al., 2018). *Lb. plantarum*, *Lb. brevis*, *Lb. paracasei*, *Lb. fermentum*, *Lb. casei*, *Lc. lactis*, *Lc. mesenteroides*, *Ped. pentosaceus*, *Lb. kunkeei*, *Lb. florum*, *F. pseudoficulneus*, *F. fructosus*, *Ec. durans*, are found in plant-derived product for instance; fruit (pulp and byproduct of *Malphigia glabra* L. and *Mangifera indica* L., and *Annona muricata* L.), fresh flowers and fruit peels, Kahudi (traditional rapeseed fermented food) (Endo et al., 2009; Endo et al. 2010; Goswami et al., 2017; Da Costa et al., 2018). Noteworthy, the species belonged to genus *Fructobacillus* are found only in fructose-rich origins such as flower and fruit. The indigenous species to human, *Lb. paracasei*, *Lb. casei*, *Lb. gasseri*, *Lb. fermentum*, *Lb. rhamnosus*, *Lb. oris*, *Lb. vaginalis*, *Lb. ruminis*, *Lb. plantarum*, *Lb. pentosus*, *Lb. salivarius*, *Lb. saerimneri*, *Lb. johnsonii*, *Lb. reuteri* and *W. confusa* are presented in GI tract of human (Ladda et al., 2015; Noguchi et al., 2012; Rubio et al., 2014; Taweechotipatr et al., 2009; Spinler et al., 2008). Intestine samples of summer adult worker bees (*Apis mellifera* L.) from different hives are used for LAB isolation. *Lb. acidophilus*, *Lb. crispatus*, *Lb. johnsonii*, *Ec. faecium*, *Lactobacillus* spp. and *Enterococcus* spp. are found in the samples (Audisio et al., 2011). In marine animals, *Leuc. mesenteroides*, *Leuc. lactis*, *Lb. pentosus*, *W. cibaria*, *W. confusa*, *Lb. plantarum*, *Ped. pentosaceus* are isolated from fish gut, marine fish, shellfish and shrimp (Hongpattarakere et

al., 2012; Gurovic et al. 2014). *Lb. johnsonii*, *Lb. mucosae*, *Lb. murinus*, *Lb. salivarius*, *Lb. amylovorus*, *Lb. fermentum*, *Lb. perolens*, *Lb. reuteri*, *Lb. johnsonii*, *Lb. acidophilus*, *Lb. animalis*, *Lb. casei*, *Lb. farciminis*, *W. paramesenteroides*, *W. cibaria*, *W. hellenica* and *Ec. faecium* are existed in GI tract of calves (Maldonado et al., 2012; Sandes et al., 2017). *Ec. durans*, *Ec. faecium*, *Ec. hirae*, *Ped. acidilactici*, *Ped. pentosus*, *W. paramesenteroides*, *Lb. acidophilus*, *Lb. amylovorus*, *Lb. buchneri*, *Lb. mucosae* and *Lb. plantarum* are isolated from cattle faeces (Maldonado et al., 2018).

ANTIMICROBIAL PRODUCTS

LAB can produce several active metabolites against other microorganisms such as organic acids (lactic, acetic, formic, propionic and butyric acids), that intensify their action by reducing the pH of the media, and other substances, such as ethanol, fatty acids, acetoin, hydrogen peroxide, diacetyl, antifungal compounds (propionate, phenyl-lactate, hydroxyphenyl-lactate, cyclic dipeptides and 3-hydroxy fatty acids), bacteriocins (nisin, pediocin, lacticin, enterocin and others) and bacteriocin-like inhibitory substances (BLIS), reuterin and reutericyclin (Reis et al., 2012). These LAB metabolic products have a positive effect on food taste, smell, color, and texture, but they may also have the beneficial side effects of extending shelf-life and inhibiting the growth of pathogenic organisms (O'Bryan et al., 2015). Antimicrobial substances produced by LAB can be divided into two groups (Šušković et al., 2010) including:

Table 1. Low molecular mass antimicrobial metabolites of lactic acid bacteria (modified from Šušković et al., 2010)

Compound	Producers	Indicator strains
Lactic acid	All LAB	Yeasts, Gram-positive bacteria, Gram-negative bacteria
Acetic acid	Heterofermentative LAB	Yeasts, Gram-positive bacteria, Gram-negative bacteria
Diacetyl, acetaldehyde, acetoin	Variety of genera of LAB including: <i>Lactococcus</i> , <i>Leuconostoc</i> , <i>Lactobacillus</i> and <i>Pediococcus</i>	Yeasts, Gram-positive bacteria, Gram-negative bacteria
Hydrogen peroxide	All LAB	Yeasts, Gram-positive bacteria, Gram-negative bacteria
Carbon dioxide	Heterofermentative LAB	Most of microorganisms
Reuterin	<i>Lb. reuteri</i>	Fungi, protozoa, Gram-positive and Gram-negative bacteria
Reutericyclin	<i>Lb. reuteri</i>	Gram-positive bacteria
Cyclic dipeptides	<i>Lb. plantarum</i> , <i>Lb. pentosus</i>	Fungi
3-Phenyllactic acid, 4-hydroxyphenyllactic acid	<i>Lb. plantarum</i> , <i>Lb. alimentarius</i> , <i>Lb. rhamnosus</i> , <i>Lb. sanfranciscensis</i> , <i>Lb. hilgardii</i> , <i>Leuc. citreum</i> , <i>Lb. brevis</i> , <i>Lb. acidophilus</i> , <i>Leuc. mesenteroides</i>	Fungi
3-Hydroxy fatty acids	<i>Lb. plantarum</i>	Fungi
Benzoic acid, methylhydantoin, mevalonolactone	<i>Lb. plantarum</i>	Fungi, Gram-negative bacteria

1) Low molecular mass substances (< 1,000 Da): Organic acids, hydrogen peroxide, diacetyl, acetaldehyde and acetoin, carbon dioxide, reuterin, reutericyclin, cyclic dipeptides, phenyllactic acid, 4-hydroxyphenyllactic acid and 3-hydroxy fatty acids (Table 1)

2) High molecular mass substances (> 1,000 Da): Bacteriocins are ribosomally-synthesized peptides or proteins with the anti-microbial activity that are produced by different groups of bacteria including many members of LAB (Gálvez et al., 2007.) Bacteriocins released from LAB are generally recognized as safe substances (GRAS); they have attracted interest to use extensively as food preservatives. Since nisin A was recognized in 1928, diverse bacteriocins have been identified from LAB (Zendo and Sonomoto, 2011). Interfering of the cell wall and or the membrane of target organisms, either by inhibiting cell wall biosynthesis or causing pore formation, consequently resulting in death, are the proposed anti-microbial mechanism of bacteriocins (O'Sullivan et al., 2002). Bacteriocins are classified into 4 groups based on their structures and characteristics (Table 2.).

Table 2. Suggested classification of bacteriocins from LAB (modified from Cotter et al., 2005; Šušković et al., 2010)

Classification	Major characteristics	Examples
Class I lantibiotics/lanthionine-containing bacteriocins subdivided into: Type A lantibiotics Type B lantibiotics	Small (< 5 kDa) membrane-active peptides containing unusual amino acids; – elongated peptides with a net positive charge – smaller globular peptide with negative or no net charge	Type A: Nisin, lactacin 481, lactacin S Type B: Mersacidin
Class II non-lanthionine-containing bacteriocins Subdivided into: Subclass IIa Subclass IIb Subclass IIc	Heterogeneous class of small (< 10 kDa) heat-stable post-translation unmodified non-lantibiotics IIa: pediocin-like IIb: two-peptide IIc: with wide range of effects on membrane permeability and cell wall formation	IIa: Pediocin PA1, sakacin A, sakacin P, leucocin A, curvacin A IIb: Lactococcin G, lactococcin M, lactacin F, plantaricin A IIc: Acidocin B, enterocin P, enterocin B, reuterin 6
Class III Bacteriolysins	Large (> 30 kDa) heat-labile antimicrobial proteins, complex proteins with domain-type structure that function through the lyses of sensitive cell by catalyzing cell wall hydrolysis	Lysostaphin, enterolysin A, helveticin J, helveticin V-1829
Class IV	Complex bacteriocins carrying lipid or carbohydrate moieties	Plantaricin S, leuconocin S, lactacin 27, pediocin SJ1

ANTIMICROBIAL SPECTRUM OF ANTIMICROBIALS AGAINST SPOILAGE AND PATHOGENIC MICROORGANISMS

Bactericidal Activity

Gram-Negative Bacteria

Helicobacter pylori

Helicobacter (H) pylori was successfully cultivated by Warren and Marshall in 1983 who first described that this bacterium is associated with chronic gastritis and peptic ulcer (Warren

& Marshall, 1983). *H. pylori* commonly colonized on the mucous layer of the gastric epithelium of the human stomach. Hence, it has been isolated from materials of gastric sites of diverse populations throughout the world (Owen, 1995). Over the past two decades, increased attention had been paid on *H. pylori* since it plays an important role in the pathogenesis of chronic gastritis and peptic ulcer diseases. Both epidemiological and clinical evidence has indicated that *H. pylori* is associated with an increased risk of gastric carcinoma (Heavey & Rowland, 2004). The International Agency for Research into Cancer (IARC) and the World Health Organization (WHO) have classified this bacterium into Class I (definite) biological carcinogen in humans (Park et al., 2004). Nowadays, *H. pylori* infection remains a commonly spread disease with definite morbidity and mortality (Zullo et al., 2012). Moreover, the prevalence of infection in the developing countries was higher (greater than 80%) than the developed ones (less than 40%) (Vale & Vitor, 2010).

European guidelines suggested the standard triple therapies including a proton pump inhibitor (PPI), clarithromycin (500 mg) plus amoxicillin (1 g) or metronidazole/tinidazole (500 mg), all given twice daily for 7–14 days for *H. pylori* eradication (Zullo et al., 2012). Unfortunately, the decrease in the efficacy of this regimen occurred throughout the world during the last decade. Consequently, the sequential therapy 10-days therapy (was proposed to get better results than triple therapies. This novel regimen consisted of a PPI plus amoxicillin 1 g (both twice daily) given for the first five days followed by a triple therapy including a PPI, clarithromycin 500 mg, and tinidazole (all drugs were given twice daily) for the remaining five days. However, antibiotic-based treatment for *H. pylori* infection had a higher effect on the composition of intestinal microbiota (Myllyluoma et al., 2007). Besides, antibiotic-based therapy would not be cost-effective, causes side effects and in particular, encourages the spread antibiotic resistance (Michetti, 2001). Therefore, an increased interest of many researchers had been paid on LAB since some strains of these bacteria had exhibited antagonistic activity against *H. pylori*. Organic acids especially, lactic acid produced by LAB has well known to exhibit antibacterial activity against *H. pylori* which are related to pH value in the medium. Lactic acid produced by *Lb. acidophilus* suppresses the growth of all seven strains of *H. pylori* *in vitro* (Bhatia et al., 1989). Extracellular lactic acid secreted by *Lb. acidophilus* and *Lb. rhamnosus* inhibited the growth of *H. pylori* (Midolo et al., 1995). The spent culture supernatant (SCS) of the *Lb. acidophilus* strain LB (LB-SCS) dramatically decreased the viability of *H. pylori* *in vitro* independent of pH and lactic acid levels (Coconnier et al., 1998). LB activity was strain-dependent and better at low pH. *Lb. paraplantarum* KNUC25 isolated from over-fermented kimchi, is effective in inhibiting the growth of *H. pylori*, which is related to pH and the adherence of *cagA*-positive *H. pylori* to gastric cells (Ki et al., 2010). *Lb. acidophilus* LY5 produced lactic and acetic acid that reduced urease activity and the viability of both *H. pylori* BCRC 17021 and CMU83 (Lin et al., 2011). The investigation of Zheng et al. (2016) reported that *Lb. pentosus* strain LPS16 had the broad-spectrum antibacterial activity against multidrug-resistant *H. pylori* strains, suggesting that it can be used to prevent *H. pylori* infection. *Lb. fermentum* UCO-979C significantly inhibited *H. pylori*-induced IL-8 production in AGS cells and reduced the viability of *H. pylori* (García et al., 2017). The strains of *Lb. delbrueckii* subsp. *bulgaricus* inhibited many *H. pylori* strains, including antibiotic resistant strains by secreting lactic acid, bacteriocins-like substances or other bioactive substances (Boyanova et al., 2009). In addition to lactic acid and low pH, viable and nonviable *W. confusa* strain PL9001 inhibited the binding of *H. pylori* ATCC 43504 to human gastric-cell line MKN-45 cells by more than

90%. The spent culture supernatant of PL9001 rapidly decreased the viability of *H. pylori* and ruptured the cell walls by the action of bacteriocins (Nam et al., 2002). Kim et al. (2003) reported that the bacteriocins; nisin A, lacticin A164, lacticin BH5, lacticin JW3 lacticin NK24, pediocin PO2, and leucocin K produced from *Lc. lactis* subsp. *lactis* ATCC 11454, *Lc. lactis* subsp. *lactis* A164, *Lc. lactis* BH5, *Lc. lactis* JW3, *Lc. lactis* NK24, *Ped. acidilactici* PO2, and *Leuconostoc* sp. LAB145-3A, respectively, showed the anti-*H. pylori* activity. MICs of these bacteriocins were ranged from 0.39–25, 0.097–12.5, 0.097–12.5, 0.195–25, 0.097–25, 6.25–50 and 25 mg/L, respectively, that varied among the *H. pylori* strains tested, of which strain ATCC 43504 was the most tolerant. The inhibitory activity of *Ec. faecium* TM39 against *H. pylori* could result from the inhibition on *H. pylori* urease activity and the secreted bacteriocin-like substances (Tsai et al., 2004). *Lb. delbrueckii* subsp. *bulgaricus* BB18 isolated from authentic Bulgarian dairy products produced a novel bacteriocin (bulgaricin BB18) which contained the antagonistic activity against four tested strains of *H. pylori* (Simova et al., 2009). The cell-free culture supernatants obtained from *Lb. brevis* BK11, *Lb. acidophilus* BK13, *Ped. pentosaceus* BK34, *Lb. paracasei* BK57, and *Lc. lactis* BK65 strains producing very high levels of lactic acid dramatically decreased the viability of *H. pylori*. In addition, the bactericidal activity of *Lb. plantarum* BK10, *Lb. brevis* BK11, *Lb. acidophilus* BK13, *Lb. paracasei* BK57, and *Ec. faecalis* BK61 strains was significantly correlated with their bacteriocin production (Lim, 2014). Purified bacteriocin BK11 and BK61 (MW 6.5 and 4.5 kDa) produced from *Lb. brevis* BK11 and *Ec. faecalis* BK61, exhibited anti-*H. pylori* activity and lowered the urease activity of *H. pylori* (Lim, 2015).

Other Gram-Negative Bacteria

Bacteriocins produced by LAB generally possess antibacterial activity against Gram-positive foodborne pathogens (Zendo & Sonomoto, 2011). In recent years, many bacteriocins active against Gram-negative bacteria have been identified proving their efficacy in foods and treating infections (Ghodhbane et al., 2015). Therefore, the limitation of bacteriocins has been improved. There are some reports that demonstrated that bacteriocins have the ability to inhibit Gram-negative bacteria. In addition to anti-*H. pylori* activity, bulgaricin BB18 has an effect on the growth of other Gram-negative pathogens such as *Escherichia* (*E*) *coli* WF and *Salmonella* (*S*) *Typhimurium* FVK781 as well (Simova et al., 2009). Bacteriocin 7293A and B from *W. hellenica* BCC 7293 have broad antimicrobial spectra against many strains of tested Gram-positive bacteria and exceptionally inhibited several important Gram-negative food-borne pathogens such as *Pseudomonas aeruginosa*, *Aeromonas hydrophila*, *S. Typhimurium* and *E. coli* (Woraprayote et al., 2015). Strains of *Lc. lactis* isolated from tropical rainforest wild-type fruits produce antimicrobial substances which suppress the growth of 3 strains of *E. coli*, *S. enterica* subsp. *enterica*, *S. enterica* subsp. *Abaetetuba*, *Salmonella* sp., *Enterobacter* sp. and *Shigella sonnei* and *Shigella* sp. (Tenea et al., 2018). Active compounds in CFS from *Ec. faecalis* KT11 show antimicrobial activity against significant Gram-negative bacteria including *Klebsiella pneumoniae*, *Serratia marcescens*, *Enterobacter aerogenes*, *Pseudomonas aeruginosa* and *Kocuria rhizophila* (reclassified name of *Micrococcus luteus*) (Abanoz & Kunduhoglu, 2018).

Gram-Positive Bacteria

Listeria monocytogenes

Listeria (L) monocytogenes causes listeriosis, a rare foodborne disease with a mortality rate of 20%–30%. The elderly and immunocompromised hosts are particularly susceptible to listeriosis. *L. monocytogenes* is ubiquitous and can contaminate food-processing environments, posing a threat to the food chain. This is particularly important for ready-to-eat foods as there is no heat treatment or other antimicrobial steps between production and consumption. Thus, occurrence and control of *L. monocytogenes* are essential for industry and public health. Advances in whole-genome sequence technology are facilitating the investigation of disease outbreaks, linking sporadic cases to outbreaks, and linking outbreaks internationally. Novel control methods, such as bacteriophage and bacteriocins, can contribute to a reduction in the occurrence of *L. monocytogenes* in the food-processing environment, thereby reducing the risk of food contamination and contributing to a reduction of this public health issues (Jordan & McAuliffe, 2018).

Tomé et al. (2006) reported that lactic acid, hydrogen peroxides (H_2O_2) and bacteriocin produced by strains of *Lb. plantarum*, *Lb. brevis* and *Lc. lactis* showed inhibitory activity against *L. monocytogenes* isolated from cold smoked salmon. Two strains of *Ped. pentosaceus* isolated from Alheira, a traditional Portuguese fermented sausage demonstrated anti-*Listeria* activity of a proteinaceous nature (Albano et al., 2007). *Ec. faecium* MMZ17 isolated from Gueddid, a traditionally Tunisian fermented meat, produced enterocin MMZ17 which exhibited anti-*Listeria* activity. Enterocin MMZ17 can be classified as a small, heat-stable anti-*Listeria*-active peptide, presumably belonging to class IIa bacteriocins (Belgacem et al., 2008). Two bacteriocins similar to pediocin PA-1 and enterocin B secreted by *Ec. faecium* ALP7 and *Ped. pentosaceus* ALP57 (isolated from non-fermented seafood), reduced the growth of *L. monocytogenes* (Pinto et al., 2009). *Ped. pentosaceus* BCC 3772 isolated from Nham (a Thai fermented pork sausage), produced anti-*Listeria* activity during the early logarithmic growth phase with the maximum production of 520,000 AU/mL detected at 12 h of growth. The anti-*Listeria* substance was found to be a class IIa bacteriocin, subsequently identified as pediocin PA-1/AcH (Kingcha et al., 2012). Kimchi-derived *Ped. pentosaceus* showed an anti-*L. monocytogenes* activity. The active compound was identified the active moiety as a LysM domain in a 23-kDa protein that could potentially be a peptidoglycan hydrolase enzyme. This protein was stable over a wide pH range (pH 4–8) and heat treatment (80–100°C for 20 min) (Jang et al., 2014). *W. hellenica* BCC 7239, isolated from Thai fermented pork sausage called Nham, produced two putatively novel bacteriocins, 7293A and 7293B with the molecular mass 6249.302 and 6489.716 Da, respectively. Antimicrobial activity of both peptides was not inactivated by organic solvents (ethanol, isopropanol, acetone, acetonitrile) and surfactants (Tween 20, Tween 80 and Triton X-100). Both novel bacteriocins hold promise for applications in the prevention or treatment of pathogenic infections as food and feed additives to replace antibiotics for enhancing the productivity and sustainability of food production (Woraprayote et al., 2015). A bacteriocin with antagonistic activity against *L. monocytogenes* was produced by a strain of *Lc. lactis* (L3A21M1) which isolated from an Azorean cheese. This bacteriocin with a molecular mass of 2900.23 Da, similar to that of lacticin 481, was heat stable (100°C for 30 and 60 min), active across a wide pH range (2.0–12.0) that is useful for application in the fermentation process (Ribeiro et al.

2016). The two bacteriocins produced by *Ec. durans* 152 were characterized and identified as Dur 152A (an enterocin L50A derivative with two amino acid substitutions of I/M) and enterocin L50B. At 400 AU/mL, the bacteriocins prevented growth of *Listeria* in deli ham for at least 10 weeks at 8°C and at least 30 days at 15°C. For comparison, 500 ppm Nisin controlled *Listeria* growth for up to 6 weeks at 8°C and up to 18 days at 15°C (Du et al., 2017). Plantaricin LPL-1, produced by *Lb. plantarum* LPL-1, was a novel class IIa bacteriocin with bactericidal activity against *L. monocytogenes* 54002. The minimal inhibitory concentration (MIC) was confirmed as 16 µg/mL, and the time-kill kinetics showed that plantaricin LPL-1 significantly decrease the viable cell numbers of *L. monocytogenes* 54002 in a time-dependent and dose-dependent manner (Wang et al., 2019).

Other Gram-Positive Bacteria

Various organic acids, including acetic acid, lactic acid, citric acid, and malic acid have been shown to possess antibacterial effects and therefore are used as antibacterial additives. Organic acids released by *Ped. pentosaceus* strain T1 exert inhibiting effects against the significant pathogenic bacteria; *L. grayi*, *L. ivanovii* subsp. *ivanovii*, *L. innocua*, *L. seeligeri*, *Staphylococcus* (*St*) *aureus* subsp. *aureus*, *St. epidermidis*, *St. saprophyticus* subsp. *saprophyticus* and *Bacillus* (*B*) *cereus* (Jang et al., 2014). Bacteriocins produced by LAB have been widely known to inhibit their related species especially to Gram-positive bacteria (Zendo & Sonomoto, 2011). Several studies have reported that bacteriocins released by LAB had an interesting feature to decrease the number of Gram-positive pathogenic bacteria in many foods and clinical trials. Bacteriocin-containing CFS collected from *Ec. faecium* strains exhibited the suppression against *L. innocua*, *L. ivanovii* and strains of LAB such as *Lc. lactis* subsp. *cremoris*, *Lb. casei*, *Lb. curvatus*, *Lb. delbrueckii*, *Ec. faecalis*, *Ec. faecium* and *Ped. acidilactici* (Belgacem et al., 2008). The study of Woraprayote et al. (2015) indicated that many strains of Gram-positive bacteria (*B. circulans*, *B. coagulans*, *B. subtilis*, *Ec. faecalis*, *Ec. faecium*, *Lb. sakei* subsp. *sakei*, *Lc. lactis* subsp. *lactis*, *Leuc. mesenteroides* subsp. *mesenteroides*, *L. innocua*, *Ped. pentosaceus*, *St. aureus*, *St. xylosus*, *W. confusa*, *W. cibaria*, *W. paramesenteroides*, *W. hellenica*) are inhibited by the action of bacteriocin 7293A and 7293B secreted by *W. hellenica* BCC 7923. Methicillin-resistant *St. aureus* (MRSA) is a multidrug-resistant micro-organism and the important nosocomial pathogen worldwide. Antibacterial compounds produced by *Lb. acidophilus* LC1285 and *Lb. casei* LBC80R strains were active against clinical isolates of MRSA strains 43, 64, 75, 27, 61, 22, 18, 69, 80, 36 and ATCC 43300 (Karska-Wysocki et al., 2010).

Fungicidal Activity

Fresh fruits, vegetables, and also grains and nuts are rich sources of nutrition which is important for fungal growth (Bueno et al., 2004). Food spoilage by mold and the occurrence of their mycotoxins constitute a potential health hazard. Development of biological control should help improve the safety of products by controlling mycotoxin contamination (Dalié et al., 2010). LAB have a GRAS status. They have been used to ferment foods for many years, which suggest the nontoxic nature of metabolites produced by these organisms. Moreover, it is believed that the metabolic activity of LAB that may contribute in many ways to the control

of bacterial pathogens, and improvement of shelf life and sensory qualities, might also have applications for preventing mold growth (Bianchini, 2015). To date, the use of LAB and their antifungal compound for controlling growth of fungi have received much attention by researchers. The growth of *Aspergillus (A) nidulans* was inhibited during co-cultivation with *Lb. plantarum* MiLAB 393 and the expression of fungal proteins was altered. Cyclo (L-Phe–L-Pro), lactic acid and 3-phenyllactic acid were the active compounds produced by this LAB strain which affected on the growth of *A. nidulans* (Ström et al. 2005). *Lb. acidophilus* LMG 9433 suppressed the growth of *Penicillium (Pe)* spp. The supernatant of *Lb. amylovorus* DSM 20532 was fairly inhibiting for *Cerinosterus* sp., *Cladosporium* sp., *Endomyces (Ed) fibuliger* MUCL 11443, *Penicillium* spp. A, F and G and *Rhizopus (R) oryzae* MUCL 20145. With *Lb. coryniformis* subsp. *coryniformis* LMG 9196, clear inhibition zones were detected against *Cerinosterus* sp., *Cladosporium* sp., *Penicillium* spp. F and G and *R. oryzae* MUCL 20145. The antifungal properties of supernatants collected from these LAB were due to organic acids and other pH-dependent antifungal substance (De Muynck et al., 2004). Bacteriocin-synthesizing *Lc. lactis* strains 194 and K-205 were isolated from raw cow milk. These strains had high antibiotic activity against *Eurotium (Er) repens* up to 3600 and 2700 IU/mL as compared to nisin and up to 2500-1700 IU/mL as compared to fungicidal antibiotic nystatin (Stoyanova et al., 2010). *Ec. durans* A5-11 was isolated from traditional Mongolian airag cheese. This strain inhibited the growth of several fungi including *Fusarium (F) culmorum*, *Pe. roqueforti*, *Pe. expansum*, *Debaryomyces (D) hansenii*, *Candida krusei* and *Mucor plumbeus*. It produced two bacteriocins: durancin A5-11a and durancin A5-11b which contained antagonistic activity against tested *D. hansenii* strain LMSA2.11.003 (Belguesmia et al., 2012). The antifungal properties of cell-free culture filtrate (CCF) from *Lb. casei* AST18 were detected, and the antifungal compounds of CCF were found to be lactic acid, cyclo-(Leu-Pro), 2,6-diphenyl-piperidine, and 5,10-diethoxy-2,3,7,8-tetrahydro-1H,6H-dipyrrrolo[1,2-a;1',2'-d]pyrazine. The antifungal activity against *Penicillium* sp. of *Lb. casei* AST18 was a synergistic effect of lactic acid and cyclopeptides (Li et al., 2012). An anti-*Candida* protein (ACP) produced by *Ec. faecalis* showed a broad-spectrum activity against multidrug-resistant *Candida albicans* strain MTCC 183, MTCC 7315, MTCC 3958, NCIM 3557, NCIM 3471 and DI. A molecular weight of ACP was approximately 43 kDa, stable after heat-treatment at 90°C for 20 min, maintained activity over a pH range 6–10 and remained active after treatment with α -amylase, lipase, organic solvents, and detergents (Shekh & Roy 2012). Lactic, acetic and phenyllactic acids (PLA) were responsible for antifungal activity produced by *Lb. casei* CRL 239, *Lb. plantarum* CRL 681, 788, 759, 142, *Lb. fermentum* CRL 220, 236, 251, *Lb. reuteri* CRL 1098 and *Lb. acidophilus* CRL 1070. Among these strains, *Lb. fermentum* CRL 251 produced fungus inhibitory peptide/s, smaller than 10 kDa, thermostable, active in the pH range of 4-7 and sensitive to trypsin (Gerez et al., 2013). *Lb. casei*, *Lb. rhamnosus*, *Lb. fermentum*, *Lb. acidophilus*, *Lb. plantarum*, *Lb. sakei* and *Lb. reuteri* had the capabilities to produce 3-phenyllactic acid which exhibited the inhibition of *Colletotrichum gloeosporioides*, *Botrytis cinerea*, *Pe. expansum* and *A. flavus* (Cortés-Zavaleta et al., 2014). Phenyllactic, OH-phenyllactic and benzoic acids were the active compounds produced by *Lb. amylovorus* DSM 19280 and *Lb. reuteri* R29 which were active against *F. culmorum*. *Lb. amylovorus* DSM 19280 cell-free-supernatant (CFS) inhibited *F. culmorum* spores at levels of 10^4 spores/mL, for seven days, whereas *Lb. reuteri* R29 CFS inhibited up to 10^5 spores/mL for the same time (Oliveira et al., 2015). The organic acid content of crude antifungal substances produced by *Lb. sakei* ALI033 showed high

concentrations of lactic acid (502.47 mg/100 g). Antifungal substance against *Pe. brevicompactum* FI02 produced by *Lb. sakei* ALI033 is most likely due to its ability in producing organic acid (Huh & Hwang, 2016). Reuterin produced by *Lb. reuteri* ATCC 53608 showed a fungicidal activity (killed 99.9% of all tested microorganisms) against *Aspergillus* spp., *Paecilomyces* spp., *Penicillium* spp., *Candida* spp., *Aureobasidium pullulans*, *Er. rubrum/amstelodami*, *Kluyveromyces* spp., *Saccharomyces* spp., *Lachancea thermotolerance*, *Rhodotorula mucilaginosa*, *Torulospira delbrueckii*, *Wickerhamomyces anomalus*, *Zygosaccharomyces rouxii*. MICs of reuterin ranged from 1.0 to 4.8 mM (Vimont et al. 2019).

Sporicidal Activity

Control and eradication of *Bacillus* and *Clostridium* spores are one of the most challenging aspects of microbial control faced by the modern food industry. Traditionally, spores have been controlled using extreme treatments such as high heat alone or in combination with chemical additives. However, modern consumers are more conscious than previous generations of the adverse health effects associated with the consumption of certain chemical preservatives and the significant effects of heat on the nutritional value and flavor of many foods (Egan et al., 2016). Therefore, application of LAB containing sporicidal activity in medium and food model has been widely investigated. *B. cereus* cultures were inoculated into the nonfat milk medium at 0, 24, and 48 h after the growth of LAB (*Strep. lactis*, *Strep. thermophilus*, *Lb. acidophilus*, and *Lb. bulgaricus*). After 72 h of fermentation of all the tested LAB, *B. cereus* declined to less than 10 CFU/mL within 40 min. Spore germination of *B. cereus* was not affected in media that were fermented for 24 h. Germination frequencies were lowered to 33 to 43% and 23 to 27% in media fermented for 48 and 72 h, respectively (Wong et al., 1988). The bacteriocinogenic *Lb. plantarum* BN, *Lc. lactis* ATCC 11454 and *Ped. pentosaceus* ATCC 43200 and 43201 inhibited the germination of *Clostridium* (*Cl*) *botulinum* spores (10^4 spores/mL) at the incubation temperature of 4, 10, 15 and 30°C. *Lc. lactis* 11454 was the most active and was followed by *Ped. pentosaceus* 43200 and 43201 and *Lb. plantarum* BN. Increasing the bacteriocinogenic cell inoculum levels from 10^2 through 10^4 to 10^6 CFU/mL increased the radio of inhibition zones (Okereke et al., 1991). In the present work, bacteriocins produced by *Lc. lactis* subsp. *lactis* INIA 415 apparently inhibited outgrowth of *Cl. beijerinckii* spores, since spore counts remained fairly constant in cheese made from milk inoculated with this culture and clostridial spores throughout the ripening period (Garde et al., 2011). Ávila et al. (2014) reported that *Lb. reuteri* INIA P572 was used as reuterin-producing strain. Reuterin were able to inhibit the growth of vegetative cells and spores of all assayed *Clostridium* strains (*Cl. tyrobutyricum*, *Cl. butyricum*, *Cl. beijerinckii* and *Cl. sporogenes*) in milk and modified RCM broth. In milk, the MICs of reuterin suppressed the vegetative cells and spores of *Clostridium* ranged from 1.02–16.25 mM and 4.06–32.50 mM, respectively. In mRCM, the concentration of reuterin required to inhibit the growth of vegetative cells (0.51–8.13 mM) of the four tested species of *Clostridium* was lower than that required to inhibit the spores (2.03–16.25 mM). Reuterin, with a broad inhibitory activity spectrum against *Clostridium* spp. spores and vegetative cells, may be the best option to control *Clostridium* growth in dairy products and to prevent associated

spoilage, such as late blowing defect of cheese. The sensitivity of *Cl. perfringens* to reuterin which is produced by *Lb. reuteri* INIA P572, was depended on strain and culture medium. In general, vegetative cells exhibited higher sensitivity than spores. Reuterin (MIC values 2.03–16.25 mM) inhibited the growth of vegetative cells and the outgrowth of spores of all tested *Cl. perfringens*, both in mRCM and milk, with higher resistance in milk (Garde et al., 2014).

USE OF LAB WITH ANTIMICROBIAL ACTIVITY AND THEIR ANTIMICROBIALS IN FOOD AND CLINICAL APPLICATIONS

In the past, fermentation was the process used to improve the quality and shelf life of food products and the secret of their extended shelf life is the presence of antimicrobial LAB, which are natural inhabitants of fermented foods (Varsha & Nampoothiri, 2016). Then, application of pure or mixed culture of LAB as starter culture has become widespread in the industrial production of fermented food products (Brashears et al., 2005). Nowadays, the employment of LAB containing antagonism effect has extended not only in fermented foods but also in fresh and minimally processed foods. Numerous studies have shown the potential use of either LAB cells or antimicrobial compounds from them as protective cultures or biopreservatives in food products for many years. Moreover, LAB have shown to be probiotic cultures based on their GRAS status and probiotic features including antagonistic activity against pathogens, acid and bile resistance, ability to colonization on the digestive tract, immunomodulatory modulation, antimutagenic and anticarcinogenic properties (Saarela et al., 2000; Saad et al., 2013).

In the past years, there has been a particular focus on the application of bacteriocins produced by LAB in controlling the growth of pathogenic bacteria in foods. In six of the CFSs, different class IIa bacteriocins, namely leucocin A and B, mundticin L, pediocin PA-1, sakacin A, and sakacin X produced by *Leuc. carnosum* IDE1105, *Enterococcus* sp. IDE0886, *Ped. acidilactici*, *Lb. plantarum* IDE0105, *Lb. sakei* IDE0216 and *Lb. curvatus* IDE0444, respectively, were identified as the major anti-*Listeria* compounds. The minimal effective concentration (MEC) of the individual CFSs to achieve a 2.3 log₁₀ reduction of *L. monocytogenes* was determined in culture broth, whole milk, and ground beef at 4°C. Best results were obtained using CFSs containing pediocin PA-1, that displayed only three- and ten-times higher MECs in milk (307 AU/mL) and ground meat (1024 AU/g) compared to the broth, respectively. A twenty-fold increase in the MEC (2048 AU/mL) was observed for a mundticin L-containing fermentate, and a CFS containing leucocin A and B was inactivated more than fifty-fold (> 1280 AU/mL) in both food matrices. Remarkably, the sakacin A and sakacin X containing CFSs displayed very selective inactivation rates, in which sakacin A was only effective in meat (512 AU/g), while sakacin X was only effective in milk (2048 AU/mL) (Hartmann et al., 2011). Moreover, the effect of poly (lactic acid) (PLA)/sawdust particle (SP) biocomposite film incorporated with pediocin PA-1/AcH (Ped) on the reduction of *L. monocytogenes* in raw sliced pork was investigated. A model study of PLA/SP + Ped as a food-contact antimicrobial packaging on raw sliced pork suggests a potential inhibition of *L. monocytogenes* (99% of the total listerial population) on raw sliced pork during the chilled storage (Woraprayote et al., 2013). Pathogens were inoculated on freshly harvested spinach, followed by application of the LAB antimicrobial (LactiGuard™, commercial LAB product).

Treated spinach was aerobically incubated up to 12 days at 7°C and surviving pathogens enumerated via selective/differential plating. L-lactic acid and a bacteriocin-like inhibitory substance (BLIS) were detected and quantified from cell-free fermentates obtained from LAB-inoculated liquid microbiological medium. Application of 8.0 log₁₀ CFU/g LAB produced significant reductions in *E. coli* O157:H7 and *Salmonella* populations on spinach of 1.6 and 1.9 log₁₀ CFU/g, respectively (Cálix-Lara et al. 2014). Using bacteriocin-producing strains in the manufacture of fresh cheese might contribute to preventing the growth of undesirable pathogenic bacteria such as *L. monocytogenes*. Fresh cheese was made from pasteurized cows' milk inoculated with bacteriocin-producing LAB and artificially contaminated with approximately 10⁶ CFU/mL of *L. monocytogenes*. In comparison, an increase of 4 log CFU/mL in pathogen numbers in cheese was detected over the same period, in the absence of bacteriocin-producing LAB. The combination of two bacteriocin producing *Enterococcus* sp. optimized the reduction of *L. monocytogenes* counts in fresh cheese, reducing by approximately 5 log units after seven days (Coelho et al., 2014). The biopreservative effect of the cell-free supernatant containing bacteriocin on quality and shelf life of fresh pork stored for 16 days at 4°C were investigated. The antimicrobial substance could retain the good quality and extend the shelf life pork during storage and 1.2% antimicrobial substance could extend the shelf life to 12 days and the meat showed good characteristics (Miao et al., 2015). Outbreaks of food-borne disease associated with the consumption of fresh and minimally processed fruits and vegetables have increased dramatically over the last few years. Traditional chemical sanitizers are unable to completely eradicate or kill the microorganisms on fresh produce. These conditions have stimulated the search for alternative methods for increasing food safety. The use of protective cultures, particularly LAB, has been proposed for minimally processed products (Siroli et al., 2015). Applying the *Lb. plantarum* strains CIT3 and V7B3 to apples and lettuce, respectively, increased both the safety and shelf-life. The *Lb. plantarum* CIT3 strain achieved a significant inhibition of *E. coli* and *L. monocytogenes* in sliced apples. In fact, in the products inoculated with *Lb. plantarum* CIT3, the kinetics of *E. coli* death accelerated significantly and was below the limit of detection after seven days (Siroli et al., 2015). In fermented meat, *Clostridium* spp. growth is kept under control by the addition of nitrite. The growing request of consumers for safer products has led to consider alternative bio-based approaches, the use of protective cultures being one of them. When *Lb. plantarum* PCS20 (initial concentration 9 log CFU/ g) was added to the batter without nitrite treatment, a significant reduction of *Cl. perfringens* was observed between day 2 and 5 in comparison with the batch containing only the pathogen. The results from the last sampling day showed that, after nine days of the fermentation process, *Cl. perfringens* growth was inhibited to 1.5 log CFU/g in the batches inoculated with the protective culture (Di Gioia et al., 2016). *Vibrio* (*V*) *parahaemolyticus* is recognized as the main cause of gastroenteritis associated with the consumption of seafood. Bacteriocin-producing *Lb. plantarum* FGC-12 isolated from golden carp intestine had strong antibacterial activity toward *V. parahaemolyticus*. This bacteriocin showed MIC for *V. parahaemolyticus* at 6.0 mg/mL. The addition of the fish-borne bacteriocin to shrimps leaded *V. parahaemolyticus* to reduce 1.3 log units at 4 °C storage for six day (Lv et al., 2017). *Lb. curvatus* 54M16 produced bacteriocins *sak* X, *sak* T_α, *sak* T_β and *sak* P containing antibacterial activity against *L. monocytogenes*. In MRS broth, *Lb. curvatus* 54M16 was able to inhibit *L. monocytogenes* to undetectable levels after 48 h at 20°C or 5 days at 15°C. Anti-

Listeria activity was lower during the production of fermented sausages with pathogen inoculation at levels of approximately 4 log CFU/g. However, total inhibition of *L. monocytogenes* native to the raw ingredients was achieved after the fermentation period (Giello et al., 2018). *Ped. acidilactici* CRL 1753 produced phenyl-lactic acid was used as a liquid bio-preserver in bread making to increase the shelf life of wheat bread. A significant increase in shelf life was observed when CRL 1753 culture (incubated for 48 h) and calcium propionate (CP) were combined into the bread formulation; at 18 days of storage no molds were observed when the lactic strain was added while 70% of bread was spoilage in the bread made with CP alone (Bustos et al., 2018).

Dietary components such as vegetable or probiotic microorganisms have been proposed as an alternative solution to decrease *H. pylori* colonization in at-risk populations. Some strains of LAB have been shown to exert bacteriostatic or bactericidal effects against *H. pylori* in *in vitro* and *in vivo* models. The study of Cruchet et al. (2003) suggested that regular ingestion of a probiotic strain, *Lb. johnsonii* La1, may interfere with *H. pylori* colonization in asymptomatic children and may be an effective alternative to modulate *H. pylori* infection and its associated gastritis in pediatric populations with high prevalences of infection by this pathogen. The patients received the probiotic therapy (*Lb. rhamnosus* GG, *Lb. rhamnosus* LC705, *Bifidobacterium* (*B*) *breve* Bb99 and *Propionibacterium* (*P*) *freudenreichii* subsp. *shermanii* JS) or a placebo during *H. pylori* eradication and for three weeks following the treatment and their daily symptoms were recorded in a standardized diary. No significant differences were found between the two groups for individual symptoms. However, the probiotic group showed less treatment-related symptoms throughout the *H. pylori* eradication therapy in contrast to the placebo group (Myllyluoma et al., 2005). In 40 *H. pylori*-positive subjects receiving *Lb. reuteri* once a day for four weeks or placebo, *Lb. reuteri* ATCC 55730 reduces *H. pylori* load as semi-quantitatively, assessed by both ¹³C-urea breath test δ -value and *H. pylori* stool antigen quantification after four weeks of treatment ($p < 0.05$). No changes were observed in patients receiving placebo. *Lb. reuteri* administration was followed by a significant decrease in the gastrointestinal symptom as compared to pretreatment value that was not present in those receiving placebo. No difference in eradication rates was observed (Francavilla et al., 2008). In another study, people infected with *H. pylori* ingested probiotic apple snack containing 10⁸ CFU of *Lb. salivarius* subsp. *salivarius* for four weeks. A decrease in the values of ¹³C in the expired breath of subjected was observed. This probiotic strain showed the beneficial effects against *H. pylori* infection (Betoret et al., 2012). A total of 229 patients were randomly assigned to either a 1-week triple therapy of rabeprazole (10 mg bid), amoxicillin (750 mg bid), and clarithromycin (200 mg bid) or triple therapy plus *Lb. gasseri*-containing yogurt. In the yogurt-plus-triple therapy groups, yogurt containing *Lb. gasseri* OLL2716 (112 g) was given twice daily for four weeks (3 weeks pretreatment and also one week during eradication therapy). Overall eradication (intention to treat/per protocol) was 74.5% for the triple-only group, and 85.6% for the yogurt-plus-triple group. Eradication of primary clarithromycin-resistant strains tended to be higher for yogurt-plus-triple therapy than triple-only therapy (38.5 vs 28.0%, respectively) (Deguchi et al., 2012). A meta-analysis study of Fang et al. (2018) concluded that *Lactobacillus*, as an adjunct to triple therapy, can increase *H. pylori* eradication rates as well as reduce the incidence of therapy-related diarrhea in children. Moreover, a higher dose and a longer duration of supplementation may conduce to the positive impact of *Lactobacillus* on *H. pylori* eradication.

A total of 64 children with acute watery diarrhea were studied. The probiotic group received 10^8 CFU *Lb. reuteri* DSM 17938 for five days in addition to oral rehydration solution (ORS) and the second group was treated with ORS only. The mean duration of diarrhea was significantly reduced in the *Lb. reuteri* group compared to the control group (approximately 15 h, 60.4 ± 24.5 h vs. 74.3 ± 15.3 h). The percentage of children with diarrhea was lower in the *Lb. reuteri* group (13/29; 44.8%) after 48 h than the control group (27/31; 87%) (Dinleyici et al., 2015). The intervention was a 28 day, the once-daily course of a four-strain oral probiotic capsule containing *Lb. acidophilus* NCFM, *Lb. paracasei* Lpc-37, *B. lactis* Bi-07 and *B. lactis* Bl-04. Probiotic adjunct therapy was associated with a significant improvement in diarrhoea outcomes. The primary duration of diarrhoea outcome (0.0 versus 1.0 days) and two exploratory outcomes, total diarrhoea days (3.5 versus 12.0 days) and rate of diarrhoea (0.1 versus 0.3 days of diarrhoea/stool diary days submitted), all decreased in participants with probiotic use compared with placebo. There was no significant difference in the rate of *Clostridium difficile* infection (CDI) recurrence or functional improvement over time between treatment groups (Barker et al., 2017). The oral administration of *Ped. pentosaceus* LI05 improved the survival rate and alleviated the histopathological impact of *Cl. difficile* in mice. Compared to the CDI group, the levels of inflammatory mediators in the colon, as well as inflammatory cytokines and chemokines in serum, were substantially attenuated in the LI05 group (Xu et al., 2018). Over 70% of patients are prescribed antibiotics during their intensive care unit (ICU) admission. The gut microbiome is dramatically altered early in an ICU stay, increasing the risk of antibiotic-associated diarrhea (AAD) and *Cl. difficile* infections (CDI). Evidence suggests that some probiotics are effective in the primary prevention of AAD and CDI. In a recent study, where thirty-two patients participated, there were no serious adverse events in the probiotic group, compared to three in the control group. AAD was documented in 12.5% of the probiotic group and 31.3% in the control group. One patient in the probiotic group developed CDI compared to three in the control group (Alberda et al., 2018).

CONCLUSION

LAB are found in a variety of natural habitats, not only in dairy, meat, cereal, plants and their fermentative products but also in GI tract of human and animals. These niches are suitable sources for the isolation of LAB. *Lactobacillus* seems to be frequently detected in these origins. Antimicrobials such as organic acids, ethanol, fatty acids, acetoin, hydrogen peroxide, diacetyl, antifungal compounds, reuterin, reutericyclin and bacteriocins released by LAB, have significant effects against spoilage and pathogenic microorganisms which are fascinating for food and clinical applications. In consequence, LAB have extensively served as protective cultures or biopreservative agents in various food products instead of the use of chemical a method named “bio-control approach.” Based on GRAS status, LAB have also been used as probiotics which are combined with antibiotic-based therapy for treating patients suffering from some bacterial infections.

Table 3. Use of LAB and their antimicrobials in food products

Food model	Producer	Antagonistic substance	Tested bacteria	Reduction in pathogenic population	Reference
Whole milk and Ground beef	<i>Enterococcus</i> sp. IDE 0886, <i>Lb. curvatus</i> IDE 0444, <i>Lb. plantarum</i> IDE 0105, <i>Lb. sakei</i> IDE0216, <i>Leuc. carnosum</i> IDE1105, <i>Ped. acidilactici</i>	Mundticin L, sakacin X , pediocin PA-1, sakacin A, leucocin A and B pediocin PA-1	<i>L. monocytogenes</i>	2.3 log ₁₀ reduction (MEC: 2048, 2048, 307, >1280, >1280 and 307 AU/mL in whole milk MEC: 2048, >10,240, 1024, 512, >1280 and 1024 AU/mL in ground beef)	Hartmann et al. (2011)
Raw slice pork	<i>Ped. pentosaceus</i> BCC 3772	Pediocin PA-1/AcH in poly (lactic acid)/sawdust particle biocomposite film	<i>L. monocytogenes</i>	2 log cycles or 99% of total listerial population	Woraprayote et al. (2013)
Fresh spinach	LactiGuard™ (commercial LAB product)	L-Lactic acid and a bacteriocin-like substance	<i>E. coli</i> O157:H7 and <i>S. enterica</i>	1.6 and 1.9 log ₁₀ CFU/g	Cáliz-Lara et al. (2014)
Azorean artisanal cheese (Pico cheese)	<i>Lc. lactis</i> and <i>Ec. faecalis</i>	bacteriocin	<i>L. monocytogenes</i>	~ 5 log ₁₀ CFU/g	Coelho et al. (2014)
Fresh pork	<i>Lb. paracasei</i> subsp. <i>tolerans</i> FX-6	Bacteriocin with broad- spectrum	Spoilage bacteria (Total viable bacteria)	Maintain total viable count at 4 log ₁₀ CFU/g	Miao et al. (2015)
Minimally processed apples and lamb's lettuce	<i>Lb. plantarum</i> CIT3 and V7B3	-	<i>E. coli</i> and <i>L. monocytogenes</i>	below the limit of detection	Siroli et al. (2015)
Pork ground meat	<i>Lb. plantarum</i> PCS20	-	<i>Clostridium</i> spp.	1 to 1.5 log ₁₀ CFU/g	Di Gioia et al. (2016)
Shrimp (<i>Penaeus vannamei</i>)	<i>Lb. plantarum</i> FGC-12	Bacteriocin	<i>V. parahaemolyticus</i>	1.3 log ₁₀ CFU/g	Lv et al. (2017)
Fermented sausages	<i>Lb. curvatus</i> 54M16	bacteriocin	<i>L. monocytogenes</i>	<1 log ₁₀ CFU/g	Giello et al. (2018)
Wheat bread.	<i>Ped. acidilactici</i> CRL 1753	Phenyllactic acid + calcium propionate	<i>A. niger</i> CH2, <i>A. japonicus</i> CH5, <i>Pe. roqueforti</i> CH4, <i>Pe. digitatum</i> CH10 and <i>Metschnikowia pulcherrima</i> CH7	None mould observed	Bustos et al. (2018)

-; not determined. MEC, Minimal effective concentrations.

Table 4. Use of LAB containing antibacterial activity as probiotics in clinical application

Infectious disease	Products	LAB strain	Dose and duration time	Results	Reference
<i>H. pylori</i> infection	Probiotics	<i>Lb. johnsonii</i> La1	>10 ⁷ CFU/mL for 4 weeks	Regular ingestion of a product containing <i>Lactobacillus</i> La1 represent an interesting alternative to modulate <i>H. pylori</i> colonization in children	Cruchet et al. (2003)
	Probiotics	<i>Lb. rhamnosus</i> GG, <i>Lb. rhamnosus</i> LC705, <i>B. breve</i> Bb99 and <i>Propionibacterium freudenreichii</i> subsp. <i>shermanii</i> JS	10 ⁹ CFU twice a day for 13 weeks	The <i>H. pylori</i> eradication rate was non-significantly higher in the group receiving probiotic therapy compared with control group	Myllyluoma et al. (2005)
	Probiotic tablets	<i>Lb. reuteri</i> ATCC 55730	10 ⁸ CFU for 4 weeks	<i>Lb. reuteri</i> effectively suppresses <i>H. pylori</i> infection in humans and decreases the occurrence of dyspeptic symptoms.	Francavilla et al. (2008)
	Probiotic apple snack	<i>Lb. salivarius</i> subsp. <i>salivarius</i>	10 ⁸ CFU/d for 4 weeks	Decrease in the values of ¹³ C in the expired breath	Betoret et al. (2012)
	Probiotic yoghurt	<i>Lb. gasseri</i> OLL2716	≥10 ⁹ CFU twice daily for 4 weeks	Improves the efficacy of triple therapy in patients with <i>H. pylori</i> infection	Deguchi et al. (2012)
	Probiotics or yoghurt supplemented with probiotics	<i>Lactobacillus</i> spp.	-	Increase <i>H. pylori</i> eradication rates as well as reduce the incidence of therapy-related diarrhea in children	Fang et al. (2018)
<i>Clostridium difficile</i> associated diarrhea	Probiotics	<i>Lb. reuteri</i> DSM 17938	10 ⁸ CFU/d for 5 days	Significantly reduces the mean duration of diarrhea in children.	Dinleyici et al. (2015)
	Probiotics	<i>Lb. acidophilus</i> NCFM, <i>Lb. paracasei</i> Lpc-37, <i>B. lactis</i> Bi-07 and <i>B. lactis</i> Bi-04	1.7 × 10 ¹⁰ CFU/d for 4 weeks	Decrease significantly the duration of CDI diarrhea.	Barker et al. (2017)
	Probiotics	<i>Ped. pentosaceus</i> LI05	3 × 10 ⁹ CFU/d for 14 days	Reduce the risk of CDI by down-regulating the degree of intestinal inflammatory response and the production of serum inflammatory mediators, protecting the intestinal barrier function.	Xu et al. (2018)
	Probiotic yoghurt drink	<i>Lb. casei</i>	10 ⁹ CFU twice a day for 30 days	A probiotic containing drink can safely be delivered via feeding tube and should be considered as a preventative measure for AAD and CDI in ICU.	Alberda et al. (2018)

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Chapter 300

DIVERSITY AND PRODUCTION OF γ -AMINOBUTYRIC ACID BY LACTIC ACID BACTERIA

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ABSTRACT

Gamma-aminobutyric acid (GABA) is a non-protein amino acid, which is produced from the decarboxylation of L-glutamic acid by glutamate decarboxylase. GABA provides beneficial effects for human health, inhibiting cancer cell proliferation, helping the recovery from alcohol-related symptoms, controlling stress, improves memory and learning abilities. Therefore, it has been classified as a bioactive compound in foods and medicine. GABA was produced by various micro-organisms including fungi, yeasts and lactic acid bacteria (LAB). Currently, LAB strains are accepted for high-performance GABA production including *Lactobacillus* (*Lb*) and *Pediococcus* (*Ped*) from Nham (Thai fermented pork sausage), *Lb. senmaizukei* from traditional pickles and *Lactococcus* (*Lc*) from cheese in Japan, *Lb. paracasei* from cheese in Italy and Japanese traditional fermented fish, *Lb. brevis* from many fermented foods (Korean fermented vegetable kimchi, Chinese traditional paocai, fresh milk, alcohol distillery lees, and black raspberry juice); and *Lb. plantarum*, *Leuconostoc* (*Leuc*) and *Weissella* (*W*) from kimchi in Japan and Korea. The production of GABA by microorganisms is dependent on several factors, including pH, temperature, glutamate concentration, medium component, and cultivation time. These factors have been optimized by the one-factor-at-a-time method. The limitation of this method varies only one independent factor at a time while fixing all others, and the interactions between each factor are neglected. Eventually, response surface methodology (RSM), as a statistical method, is more rapid, reduces the number of experiments and studies interactions several factors, which saves the cost of experiment and time. The statistical RSM method will be applied.

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INTRODUCTION

Gamma-aminobutyric acid (GABA) is an amino acid that consists of four carbons, nine hydrogens, two oxygens, and one molecule of nitrogen. The chemical formula is $C_4H_9NO_2$ and molecular weight of 103.12 g/mole. GABA is widely distributed in nature including microorganisms, plants and animals (Ueno, 2000). Many microorganisms such as fungi, *Monascus purpureus* (Su et al., 2003) and *Rhizopus microsporus* (Aoki et al., 2003); and LAB strains of the genera *Lactobacillus*, *Pediococcus*, *Lactococcus*, *Leuconostoc* and *Weissella* are reported to produce GABA (Dhakal, BajpaiBaek, 2012). GABA has shown several important functions in humans and animals (Foster & Kemp, 2006), therefore some high GABA-producing LAB have been emphasized for GABA production and GABA-enriched in fermented food. Furthermore, GABA or GABA-enriched in fermented food has been entering the commercial process as food additives and functional food supplements. In this chapter, GABA structure and function, diversity of GABA producing LAB, the method for the determination, improvement and development process for high yield of GABA, application, and benefits of GABA have been described.

γ -AMINOBUTYRIC ACID (GABA): STRUCTURE AND FUNCTION

GABA was first synthesized in 1883 and was known only as a plant and microbial metabolic product; however, it was found to be an integral part of the mammalian central nervous system in 1950. Until 1959, it was shown to be an inhibitory synapse on crayfish muscle fibers and GABA acted to stimulate the inhibitory nerve. Both inhibitions by nerve stimulation and the application of GABA were blocked by picrotoxin (Roth, Cooper & Bloom, 2003). GABA was decarboxylated from L-glutamic acid, catalyzed by α -glutamate decarboxylase (GAD) with pyridoxal 5' phosphate (PLP: the active form of vitamin B6) as a cofactor. This process converts irreversible alpha-decarboxylation of L-glutamate (the principal excitatory neurotransmitter) into GABA (the principal inhibitory neurotransmitter) (Figure 1).

GAD, a catalyzed enzyme for GABA, is generally discovered in eukaryotes and prokaryotes such as in microorganisms, plants, and animals. Although some GABA can be found in pancreatic cells and kidney, there is no significant amount of GABA in mammalian tissues other than in the nervous system. In addition, GABA in many foods such as tea, benikoji, and germinated brown rice also have been found (Thwe et al., 2011).

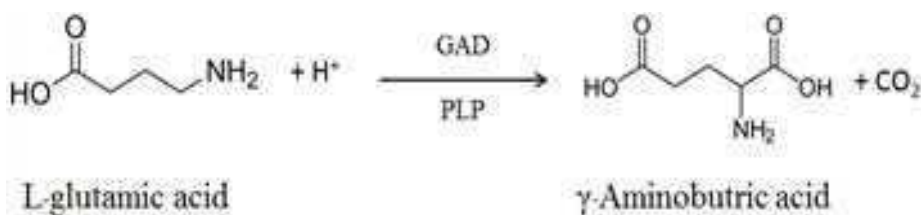


Figure 1. The decarboxylation of L-glutamic acid to GABA GAD, Glutamate decarboxylase; PLP, Pyridoxal-5'-phosphate.

GABA is an inhibitory neurotransmitter in the central nervous system of mammals by binding to specific transmembrane receptors in the plasma membrane of both presynaptic and postsynaptic neurons (Kinnersley & Turano, 2000). GABA plays a role in regulating neuronal activation in the nervous system. This binding causes the opening of ion channels to allow the flow of either negatively-charged chloride ions into the cell or positively-charged potassium ions out of the cell. This action results in a negative change in the transmembrane potential, usually causing hyperpolarization. Three typical classes of GABA receptor are known: GABA_A and GABA_C ionotropic receptors, which are ion channels themselves, and GABA_B metabotropic receptors, which are G protein-coupled receptors that open ion channels via intermediaries (G proteins) (Olsen & DeLorey, 1999).

GABA is found mostly as a zwitterion, which is when the carboxyl group deprotonated and the amino group protonated. Its conformation depended on the environments. In the gas form, a highly folded conformation is strongly favored due to the electrostatic attraction between the two functional groups. The stability is 50 kcal per mole according to quantum chemistry calculations. In the solid form, more extensively modeled variants are found at the end of the amino end and the concave form at the end of the carboxylate. This is due to the packing interactions with the neighboring molecules. In solution form, five different conformations, some folded and some extended are found as a result of solvation effects. The conformational flexibility of GABA is important for its biological function, it has been found to bind to different receptors with different conformations. Many GABA analogues with pharmaceutical applications have more rigid structures in order to control the binding better (Majumdar & Guha, 1988; Sapse, 2000).

DIVERSITY OF γ -AMINOBTYRIC ACID PRODUCING LACTIC ACID BACTERIA

GABA was produced by various microorganisms based on glutamate decarboxylase (GAD). Furthermore, LAB used for the production of GABA-enriched in fermented foods has increasingly attracted great attention due to they are safe and several health-promoting properties associated with LAB themselves (Nejati et al., 2013).

Currently, GABA production using LAB has been the focus of research (Li & Cao, 2010). LAB are getting a lot of attention because they could produce bioactive peptides, amino acids, volatile fatty acids, and lactic acid throughout the fermentation process (Lahtinen, Tuomivan & Dijken, 2011). Nonetheless, to produce functional foods with the potential of modulating the blood pressure, production of GABA and L-glutamic acid in a sustained fashion is of primary importance (Li & Cao, 2010). L-Glutamic acid serves as a precursor for the formation of GABA. Addition of glutamate to the fermentation process could have an adverse effect on the accumulation of GABA (Li & Cao, 2010). Furthermore, the addition of GABA to a food matrix is recognized to be illegal (Kim et al., 2009). With such drawbacks for the development of GABA-containing foods, incorporation of L-glutamic acid-producing LAB into the fermentation process is a great advantage.

The GABA-producing ability varies widely among the strains and some GABA-producing LAB strains have shown a great promise potential in large-scale fermentation for the production of GABA (Li et al., 2010). Some fermented products enriched in GABA using

LAB as starters such as in dairy products (Hayakawa et al., 2004), black raspberry juice (Kim et al., 2009), soy milk (Tsai et al., 2006), kimchi (Seok et al., 2008), and cheese (Nomura et al., 1998) have been developed.

Currently, *Lactobacillus* (*Lb*), *Pediococcus* (*Ped*), *Lactococcus* (*Lc*), *Leuconostoc* (*Leuc*), *Streptococcus* (*Strep*), and *Weissella* (*W*) strains including *Lb. plantarum*, *Leuc. mesenteroides*, *W. cibaria*, *Lb. paracasei*, *Lb. brevis*, *Lb. casei*, *Lb. pseudomesenteroides*, *Lc. lactis*, *Lb. delbrueckii* sub sp. *bulgaricus*, *Lb. rhamnosus*, *Strep. thermophilus* and *Enterococcus* (*Ec*) *durans* has been accepted for high performance GABA production (Dhakal, BajpaiBaek, 2012). They were isolated and screened from traditional fermented food. *Lb. namurensis* NH2 and *Ped. pentosaceus* HN8 were isolated from Nham (Thai fermented pork sausage) (Ratanaburee et al., 2013). *Lb. senmaizukei* was isolated from traditional pickles kimchi (Hiraga et al., 2008). *Lb. rhamnosus* YS9 was isolated from Chinese traditional food (Lin, 2013). *Lb. paracasei* was isolated from cheese in Italy and Japanese traditional fermented fish (Komatsuzaki et al., 2005). *Lb. buchneri* and *Lb. brevis* were isolated from many fermented foods including Korean fermented vegetable kimchi, Chinese traditional paocai, fresh milk, alcohol distillery lees and black raspberry juice (Kim et al., 2009; Park & Oh 2006). The strains of *Lb. senmaizukei* from pickles (Park & Oh, 2006). *Lb. plantarum*, *Leuc. mesenteroides*, *Leuc. lactis* and *W. viridescens* were isolated from kimchi in Japan and Korea (Kim & Kim, 2012). *Lc. lactis* strains were isolated from cheese starters and cheese in Japan (Lu et al., 2008; Nomura et al., 1998). Moreover, LAB were isolated from black raspberry juice and soymilk (Tsai et al., 2006). The high GABA producing strains, *Lb. paracasei* PF6, *Lb. delbrueckii* sub sp. *bulgaricus* PR1, *Lc. lactis* PU1 and *Lb. brevis* PM17 have been isolated from Pecorino di Filiano, Pecorino del Reatino, Pecorino Umbro, and Pecorino Marchigiano cheeses in Italy, respectively (Siragusa et al., 2007).

Multitudinous of GABA-producing LAB are important for the food industry (Komatsuzaki et al., 2005). Because of the potential for producing GABA-enriched foods, LAB are received a lot of attention. The ability of LAB to produce GABA is varied among species and the strains as shown in Table 1.

Table 1. GABA produced by lactic acid bacteria

Strain	Source	Medium	GABA Yield	Time (h)	Reference
<i>Bifidobacterium dentium</i> NFBC2243, DPC6333 and UCC35624	Dental carries, Infant feces and ileal-caecal region	MRS with 5% (w/v) MSG	8.63, 6.16 and 2.04 g/L	48	Barrett, 2014
Co-fermented with <i>Leuc. mesenteroides</i> SM and <i>Lb. plantarum</i> K154	Carrot juice and kimchi	MRS with 3% (w/v) MSG	10 mg/ml	30	Kwon et al., 2016
<i>Ec. faecium</i> NCIM 5593	Takarishita	Rice flour medium (3% w/v) with 1% (w/v) glutamate	750.55 mg/100g DM	48	Divyashri & Prapulla, 2016
<i>Lb. brevis</i> CECT 8183	Goat cheese	Sourdough medium	0.96 mM	24	Diana et al., 2014
<i>Lb. brevis</i> CRL 1942	Quinoa sourdough	MRS with 270 mM MSG	255 mM	48	Villegas et al., 2016
<i>Lb. brevis</i> GABA100	-	Black raspberry juice with 2% (w/v) MSG	26.5 mg/ml	12 day	Kim et al., 2009
<i>Lb. brevis</i> HYE1	Kimchi	MRS with 1% (w/v) MSG	18.76 mM	48	Lim et al., 2017
<i>Lb. brevis</i> NCL912	Paocai (Chinese fermented vegetable)	MRS with 134.45 mM glutamate	1005.81 mM	48	Li et al., 2010

Strain	Source	Medium	GABA Yield	Time (h)	Reference
<i>Lb. brevis</i> NPS-QW-145, NPS-QW-171, NPS-QW-177, NPS-QW-193, NPS-QW-216, NPS-QW-242, NPS-QW-255 and NPS-QW-267	Korean kimchi	MRS with 7% (w/v) MSG	25.831, 19.631, 24.098, 23.33, 21.694, 22.986, 19.072, and 24.992 g/L, respectively	72	Wu & Shah, 2015
<i>Lb. brevis</i> TCCC 13007	Pickled Chinese vegetables	3.6 g corn steep liquor, 22 g glucose, 15 g yeast extract, 2 g sodium acetate, 0.2 g MgSO ₄ , 0.2 g (NH ₄) ₂ SO ₄ with 7% (w/v) MSG	61 g/L	66	Zhang et al., 2012
<i>Lb. buchneri</i> WPZ001	Fermented sausages	MRS, Corncob hydrolysate with 0.1% MSG	129 g/L, 117 g/L	48	Zhao et al., 2015
<i>Lb. bulgaricus</i> CFR 2028	CFTRI culture collection centre	MRS with 1 % (w/v) MSG	22.7 mM	48	Gangaraju, Murty & Prapulla, 2014
<i>Lb. paracasei</i> 15C	Nostrano-cheeses	MRS	14.8 mg/kg	24	Franciosi et al., 2015
<i>Lb. paracasei</i> NFRI 7415	Fermented fish (funa-sushi)	MRS with 500 mM glutamate	302 mM	144	Komatsuzaki et al., 2005
<i>Lb. plantarum</i> MNZ	Malaysian fermented foods	MRS with 5% (w/v) MSG	115.2 mg/kg dosa	120	Zareian et al., 2015
<i>Lb. plantarum</i> NDC75017	Fermented dairy products in China	MRS with 80 mM MSG	314.56 mg/100 g substrate	-	Shan et al., 2015
<i>Lb. plantarum</i> Taj-Apis362	Honeybees	MRS with 497.97 mM of glutamate	7.15 mM	60	Tajabadi et al., 2015
<i>Lb. rhamnosus</i> 21D-B	Nostrano-cheeses	MRS with vancomycin 8 μ g/mL	11.3 mg/kg	24	Franciosi et al., 2015
<i>Lb. rhamnosus</i> GG	Bioresource and Collection Center	MRS with 2.27% (w/v) MSG	1.13 mg/mL	36	Song & Yu, 2018
<i>Lb. rhamnosus</i> YS9	Chinese pickles	MRS with 200 mM glutamate	187 mM	84	Lin, 2013
<i>Lb. senmaizukei</i> L13	Japanese pickles	GYP with 5%MSG	Not report	48	Hiraga et al., 2008
<i>Lc. lactis</i> subsp. <i>lactis</i>	Kimchi	MRS with 1% MSG	3.68 g/L	48	Lu et al., 2008
<i>Lc. lactis</i> subsp. <i>lactis</i> B	Kimchi and yoghurt	MRS with 1% (w/v) MSG, brown rice juice, germinated soybean juice and skim milk (33:58:9, v/v/v)	3.68 g/L, 6410 mg/l	48	Lu et al., 2008
<i>Lc. lactis</i> subsp. <i>lactis</i> PU1	Cheese	Wheat flour sourdough	258.71 mg/kg	48	Rizzello et al., 2008
<i>Monascus purpureus</i> CMU001	-	Rice	28370 mg/kg	7 days	Jannoey et al., 2010
<i>Ped. pentosaceus</i> NH102	Fermented pork	MRS with 0.5% (w/v) MSG	8.386 g/L	24	Ratanaburee et al., 2013)
<i>Ped. pentosaceus</i> HN8	Fermented beef	MRS with 0.5% (w/v) MSG	9.06 g/L	24	Ratanaburee et al., 2013
<i>Ped. pentosaceus</i> HN8 and <i>Lb. namurensis</i> NH2	Fermented meat (Nham)	MRS with 0.5% (w/v) MSG	4051 mg/kg	48	Ratanaburee et al., 2013
<i>Strep. thermophilus</i> 84C	Nostrano-cheeses	M17	80.0 mg/kg	24	Franciosi et al., 2015
<i>Strep. thermophilus</i> ST110	Yogurt starter	Tryptone, yeast extract-lactose (TYL) with 100 mM MSG	655 mg/L	16	Somkuri et al., 2012

MSG, Monosodium glutamate; MRS, de Man, Rogosa and Sharpe.

Although there have been many studies on GABA production by LAB, the isolation of GABA-producing LAB and the development of their GABA production need to be further explored since fermented foods as the isolation sources for GABA producers have various kinds and diverse LAB (Lim et al., 2017).

METHODS FOR THE DETERMINATION OF γ -AMINOBUTYRIC ACID

The monitoring of GABA production can be determined using several techniques, including qualitative and quantitative analysis. Thin layer chromatography (TLC) is the most primary screening method for GABA qualitative analysis. This method is simple, rapid and does not require the derivatization process for GABA, but TLC method does not provide enough accuracy for quantifying GABA. Therefore, it is only an initial analysis and requires other techniques to confirm the results. Following derivatization, GABA is measured using High-performance liquid chromatography (HPLC). This technique is extremely rapid, efficient and can be analyzed both qualitatively and quantitatively. However, it was necessary to derivative the sample before being analyzed using HPLC. Many studies usually combine TLC and HPLC methods together to evaluate and quantify GABA. The detailed analysis is summarized in Table 2.

Table 2. Determination of GABA using TLC and HPLC

TLC technique	HPLC technique		Reference
	Derivative	Condition	
-	Phenylisothiocyanate (PITC)	MP , 60% solution A (10.2 g sodium acetate, 0.5 ml triethylamine and 0.7 mL acetic acid in 1 L), 12% solution B (acetonitrile) and 28% solution C (water); Column , C18; Flow rate , 0.6 ml/min; Temp , 27°C; Detector , UV at 254 nm	Zareian et al., 2015
SP , silica gel plate; MP , n-butyl alcohol: glacial acetic acid: DW(distilled water) (3:1:1 v/v/v); Visualization , 0.2% ninhydrin in acetone, heat at 105°C	Phenylisothiocyanate (PITC)	MP , 100% Solvent A (140 mM sodium acetate, 0.15% triethylamine, 0.03% EDTA, 6% acetonitrile) and ending at 100%; Solvent B (60% acetonitrile, 0.015% EDTA), during 30 min; Column , C18; Flow rate , 1.0 ml/min; Detector , UV at 254 nm	Kwon et al., 2016
SP , silica gel plate; MP , 1-butanol: acetic acid: distilled water (3:2:1 v/v/v); Visualization , 0.5% (w/v) ninhydrin and exposing the plates to a heat source	Phenylisothiocyanate (PITC)	MP , 80% solution A (1.4 mM sodium acetate, 0.1% triethylamine, and 6% acetonitrile) and 20% solution B (60% acetonitrile); Column , Cosmosil 5C18-AR-II; Flow rate , 1.0 ml/min; Temp , 27°C; Detector , UV at 254 nm	Kim & Kim, 2012
SP , silica gel plate; MP , acetic acid:1-butanol:distilled water (1:4:5 v/v/v); Visualization , 0.2% (w/v) ninhydrin	Ortho-phthalaldehyde-mercaptoethanol	MP , sodium acetate (1.64 g) and triethylamine (200 μ l) in 1 L (20%, v/v acetonitrile); Column , Hypersil ODS; Flow rate , 0.8 ml/min; Temp , 30°C; Detector , UV at 338 nm	Kangaraju, Murty & Prapulla, 2014
SP , silica gel plate; MP , n-butanol:acetic acid:distilled water (5:3:2); Visualization , 0.4% (w/v) ninhydrin then heated to visualize the spots	O-phthalaldehyde 3-mercaptopropionic acid (OPA-3MPA)	MP , solution A (40 mM monosodium phosphate) and solution B (acetonitrile: methanol:H ₂ O; 45:45:10 (v/v/v)); Column , Hypersil ODS C18 reverse phase; Flow rate ; 1.0 ml/min; Temp , 40°C; Detector , Fluorescence detector with excitation at 340 nm, emission at 450 nm	Villegas et al., 2016

TLC technique	HPLC technique		Reference
	Derivative	Condition	
-	Phenylisothiocyanate (PITC)	MP , solution A (0-100% after 50 min) and solution B (0.1M ammonium acetate: acetonitrile: methanol (44:46:10 v/v/v)) (0-100% after 50 min); Column , C18 reversed-phase; Flow rate , 1.0 ml/min; Detector , UV at 254 nm	Song & Yu, 2018
-	2,4-Dinitrofluorodinitrobenzene (FDNB)	MP , solution A (acetonitrile: H ₂ O (1:1) and solution B (0.02 M phosphate buffer); Column , C18 reversed-phase; Flow rate , 1.0 ml/min; Temp , 35°C; Detector , UV at 360 nm	Yingguo Lü et al., 2010
SP , silica gel plate; MP , n-butanol: acetic acid: water (5:3:2, v/v/v); Visualization , 0.2% (w/v) ninhydrin then develop at 60°C	O-phthaldialdehyde (OPA)	MP , solution A (0.05 M sodium acetate) solution B (the mixture of 0.1 M sodium acetate, acetonitrile and methanol (46:44:10 v/v/v); Column , XTerra column reversed-phase; Flow rate , 1.0 ml/min; Temp , 35°C; Detector , UV at 358 nm	Kook & Cho, 2013

SP, Stationary phase; MP, Mobile phase; Temp, Temperature.

Table 3. The advantage and disadvantage of GABA determination methods

Determination Methods	Advantage	Disadvantage	Reference
Thin layer chromatography	Expedient, rapid and accurate, not require the derivatization process	Not quantitative analysis, requires a number of plates and a large volume of solvents	Kim & Kim, 2012; Kwon et al., 2016
Gas chromatography	Rapid and accurate quantitative and qualitative measurements	High cost of machine, non-volatile matrices, requires additional derivatives, an experienced technician, and be careful in using gas	Kagan et al., 2008
Gas chromatography-Mass spectrometry	Rapid and accurate, strong analytical tool, good technique for simple mixtures, accurate quantitative and qualitative	High cost of machine and requires an experienced technician	Lim et al., 2017
HPLC	Rapid and accurate, accurate quantitative and qualitative	High cost of machine and derivatives method, time consuming for sample derivatives	Zareian et al., 201; Kwon et al., 2016; Kim & Kim, 2012
Gas release-based assays	Rapid, not require the derivatization process	Expensive, not a completely accurate method to identify high GABA	Wu & Shah, 2015
pH indicator method	Expedient and rapid, not require the derivatization process	Using mechanism only, not detect the quantitative analysis	Yang et al., 2006
Enzyme assay	Specific technique, easily measurable reaction	Complicate and expensive reaction	Barla et al., 2016
Amino acid analyzer (AAA)	Expedient and rapid	Using mechanism only, high cost of machine	Lu et al., 2008; Barla et al., 2016; Chung et al., 2009
Liquid chromatography (LC)	Accurate and detect in qualitative and quantitative technic	Expensive, not portable, requires an experienced technician, and only moderate throughput	Wu & Shah, 2017; Dhakal, Bajpai & Baek, 2012
Electrospray tandem mass spectroscopy (ESI-MS)	For biological samples analysis, high amount of accuracy, accurate quantitative and qualitative measurements	Cannot analyze mixtures very well, difficult to clean and the multiple charges attached to the molecular ions will make confusing for spectral data	Gangaraju, Murty & Prapulla, 2014

Although TLC is the first choice for screening of GABA producers, it also has some limitations such as requirement of many plates and a large volume of solvents (Li et al., 2010). In addition, pre-screening methods are normally developed based on the decarboxylation of glutamate into GABA by glutamate decarboxylase; this reaction eliminates a proton and also produces carbon dioxide. Spectrophotometry assay involves using GABase enzyme. Thus, glutamate decarboxylase-based microtiter plate assay (Tsukatani, Higuchi & Matsumoto, 2005), pH indicator method (Yang et al., 2006) and gas release-based assays are suitable for high-throughput pre-screening of GABA producers with remarkable improvements in testing time and economic practice (Wu & Shah, 2015). Moreover, chromatography-based techniques such as amino acid analyzer (AAA), liquid chromatography (LC), gas chromatography (GC), are also an alternative for determining GABA amounts in many kinds of food samples (Li et al., 2010). The distinctive of AAA is does not require the derivatization process prior to analysis. LC method normally requires pre-column derivatization with dansyl chloride by an addition of chromophore to GABA that could be detected by fluorescence spectroscopy (Wu & Shah, 2015). For GC method, pre-column derivatization of GABA is usually achieved with norvaline to form a volatile compound, which could be separated and detected by GC equipped with a flame ionization detector (FID) or mass spectrometry (MS) (Kagan et al., 2008) and Gas chromatography-mass spectrometry (GC-MS) (Lim et al., 2017). The above methods are time-consuming due to tedious sample preparation processes according to analytical protocols; this requires high work-load for screening GABA-producing microorganisms and is neither economical nor rapid. Hence, a pre-screening method is necessary for identifying GABA producers prior to determining their capability to produce GABA by chromatography-based methods (Kim & Kim, 2012). The advantages and disadvantages of each technique mentioned above are summarized in Table 3.

IMPROVEMENT OF γ -AMINO BUTYRIC ACID PRODUCTION

The optimum conditions vary among the fermenting microorganisms due to the different properties of the GAD, characterization of the biochemical properties of the GAD will be required in the interested microorganisms to achieve the highest GABA production. Several fermentation factors affect the rate of GABA production by microorganisms are summarized below, especially on the effects of pH, temperature, cultivation time, glutamate concentration, and media additives of culture.

Effect of pH on GABA Production

LAB produce lactic acid as the end product through a variety of carbohydrate catabolism including Embden-Meyerhof-Parnas (EMP), Leloir pathways and pentose phosphate pathways (Kandler, 1983). This acidic environment causing LAB to be acid resistant and also GABA is an amino acid as the end product of the decarboxylation of glutamic acid, therefore this acid-resistant property has benefit for their high GABA production.

The important role of bacterial amino acids decarboxylase occurred in LAB resulted in the stoichiometric including considered regulate of acidic pH by utilization of proton ions and produced GABA as the end product, also the net effect of this reaction increases the alkalinity of the cytosol and environment (De Biase et al., 1999).

GABA production was depended on GAD and the highest yield of GABA might be obtained when the cultivation conditions were the same as that of enzyme catalysis. However, decarboxylase reaction was not enhanced under lower pH 4 (Komatsuzaki et al., 2005). In another report, the optimum of pH 5.0 which showed the highest GABA production of 1005.81 mM was obtained from *Lb. brevis* NCL912, while the cell growth was inhibited at pH 3.0 and the cell mass was decreased at pH 6.0, resulting in no GABA production. The higher or lower pH may lead to the partial loss of the GAD activity therefore, pH affected significantly on the production of biomass and GABA of *Lb. brevis* NCL912 (Li et al., 2010). Similarly, the optimum pH for GAD activity on extracellular GABA production from *Lb. paracasei* NFRI 7415 was 5.0. The glutamate content 500 mM with the addition of PLP in the culture medium was converted to 302 mM (Komatsuzaki et al., 2005). The GABA production by *Strep. salivarius* subsp. *thermophilus* Y2 was also enhanced by optimizing fermentation at pH 4.5 and by the addition of PLP (Yang et al., 2008). For the GAD of *Lb. rhamnosus* YS9, the optimal pH was determined by the measurement of enzyme activity in cells under various pH conditions. GAD activity dramatically decreased at pH 4.0 than pH more than 4.8. *Lb. rhamnosus* YS9 did not show high GAD activity at low pH, although it was believed that bacterial GAD plays a key role in the acid-resistance mechanism. The optimum pH for GAD activity was 4.4. Accordingly, GABA production was measured by *Lb. rhamnosus* YS9 under pH-regulated conditions at 43°C, 200 μ M PLP, and 200 mM MSG), *Lb. rhamnosus* YS9 produced the maximum to 187 mM of GABA by *Lb. rhamnosus* YS9 at pH 4.4, which might be due to the pH condition consistent with the optimal pH for GAD activity (Lin, 2013).

Also, there are many studies that support the effect of pH values for maintaining the activity of LAB. GAD exhibited activity ranged from 4.0 to 5.0 (Komatsuzaki et al., 2008; Huang et al., 2007; Ueno et al., 1997). It was reported that pH affected on the GABA production in LAB (Yang et al., 2008; Komatsuzaki et al., 2005; Li et al., 2010).

Effect of Temperature on GABA Production

The cell growth of *Lb. brevis* NCL912 increased when temperature was increased and the maximum was at 35°C (Li et al., 2010). Likewise, production of GABA was a similar profile to cell growth. This phenomenon could be explained that high cell density was required for effective production of GABA. Nevertheless, GABA concentration at 30°C was almost the same to that at 35°C, but biomass at 30°C was less than that at 35°C. In addition, *Lb. brevis* NCL912 could not produce GABA at 45°C while the strain could grow at this temperature. Accordingly, the production of GABA by *Lb. paracasei* NFRI 7415 was increased rapidly at 37°C but GABA production and growth rate were drastically inhibited at 43°C. These results suggested that 37°C was optimum condition for GABA production by *Lb. paracasei* NFRI 7415 (Komatsuzaki et al., 2005). On the other hand, the optimal cultivation temperature of *Lb. rhamnosus* YS9 for GABA production was 43°C (Lin, 2013), which would dramatically

inhibit other LAB's growth rate, such as *Lb. paracasei* NFRI 7415 (Komatsuzaki et al., 2005) and *Lb. brevis* NCL912 (Li et al., 2010). This might be due to the different physiological and enzymatic character (Lin, 2013). The results from the above reports indicated that appropriate temperature is beneficial to produce GABA, and excessively high temperature is unfavorable to the GABA production; and high efficient conversion glutamate to GABA required not only high growth rate but also appropriate temperature.

Effect of Glutamate Concentration on GABA Production

LAB fermented monosaccharide to produce a low molecular organic acid, resulting in acidic conditions to inhibit the growing bacteria. However, some LAB employed glutamic acid decarboxylase (GAD) system for maintaining neutral cytoplasmic pH when the external pH decreased because the decarboxylation of glutamate within the LAB cell exterminates an intracellular proton. Comparison of the adding and not adding glutamic acid appeared that the pH value of the culture without glutamate decreased to 3.4 after 24 h of fermentation by *Lb. brevis* NCL912 while pH values of the cultures supplemented with glutamate were maintained at 5.0. This indicated that GAD system of *Lb. brevis* NCL912 acted under low pH and resulted in an increase of pH in the medium by glutamate, and protected cell survival from the acidic condition. However, the extra high concentration of glutamate was harmful to the cell growth (over 0.5 M). Therefore the concentration of glutamate was optimum in the range of 0.25-0.50 M for the cell growth and GABA production by *Lb. brevis* NCL912 (Li et al., 2010). The optimum of MSG for extracellular and intracellular GABA content produced by *Lb. rhamnosus* YS9 was 100 mM at 37°C (Lin, 2013).

Effect of PLP Addition on Extracellular GABA Production

PLP, a GAD coenzyme is necessary in decarboxylation reaction. Therefore, an addition of PLP to the medium could be increased GAD activity to enhance the GABA production (Tong et al., 2002). The appropriate concentration of PLP added to the culture medium was 200 µM gave the maximum of GABA to 187 mM ((Lin, 2013). The higher concentration of PLP, resulted in higher extracellular released of GABA by *Lb. rhamnosus* YS9. The result according to the previous research of Komatsuzaki et al. (2005), when 10 µM PLP was added at initial cultivation, the GABA production was enhanced by *Lb. paracasei* NFRI 7415 and even though 100 µM PLP was added in the medium, it did not strongly inhibit the cell growth. However, this was different from that observed with *Strep. thermophilus* Y2 (Yang et al., 2008) and *Lb. brevis* NCL912 (Li et al., 2010). Consequently, it could not be concluded that the PLP will always promote GABA accumulation by LAB because some researchers reported that the addition of PLP did not affected on cell growth and not increased GABA production by *Lb. brevis* NCL912 (Li et al., 2010). They explained that the strain *Lb. brevis* NCL912 could synthesize sufficient PLP for themselves.

Effect of Cultivation Time

GABA is a growth associate product, therefore, the cultivation time has an effect on the production. LAB strains have different growth profiles depending on their biochemical properties. The main isolates from cheese produced GABA under fermentation conditions at 30°C and pH 4.7 for 24 h (Seok et al., 2008). Among the strains, GABA was produced within 24-60 h as described in Table 1.

The production of GABA by the microorganism is depended on several factors, including pH, temperature, glutamate concentration, medium component, and cultivation time. The primary objective of LAB fermentation is the highest yielding of the target product. The factors of the physical and medium component have been optimized by conventional or statistical methods, providing basic information to develop the bioprocess for commercial GABA production (Kumar & Satyanarayana, 2007). The most significant stages in the biological process are modeling and optimization to improve a system and increase the efficiency of the process. The biochemical differences of the species used for the optimal condition for GABA production are different as discussed above. Therefore, the optimum conditions vary among the fermenting microorganisms due to the different properties of the GAD. Currently, a single variable optimization design used as the first step was efficient for identifying which the ranges of fermentation factors, had a significant effect on the GABA production. The response surface methodology was used to optimize the fermentative parameter for the high production of GABA (Tajabadi et al., 2015).

The conventional method is the one-factor-at-a-time (OFAT) method. The limitation of OFAT method varies only one independent factor at a time while fixing all the other interactions between each factor are neglected resulting in just local optimum points being obtained. Eventually, response surface methodology (RSM), as a statistical method, uses an experimental design to obtain the optimum point of response, and experiments can be easily organized and translated using efficient design. In addition, RSM is more rapid, reduces the number of experiments and considering interactions between each factor, which saves the cost of experiment and time (Lim et al., 2017).

The optimizations of GABA production by LAB have focused on the conventional determination of optimal pH, temperature, PLP and glutamate concentration (Komatsuzaki et al., 2005; Li et al., 2010; Lin, 2013). Although the statistical RSM method is more efficient compared with the conventional OFAT method, there have been a few studies on the optimization for GABA production via the RSM method.

The optimum condition for GABA production by *Ped. pentosaceus* HN8 and *Lb. namurensis* NH2 using the Central Composite Design (CCD) has been reported (Ratanaburee et al., 2013) using 0.5% (w/v) MSG, inoculum size of roughly 6 log CFU/g of each two strains. The GABA production gave the maximum of 4051 mg/kg in the 'GABA Nham' product. Using the same experimental design, CCD of RSM was used to define conditions for maximum GABA production by *Lb. plantarum* Taj-Apis362. The maximum GABA of 7.15 mM was obtained under 497.97 mM of MSG, 36°C, at pH 5.31, and 60 h for cultivation time (Tajabadi et al., 2015).

In addition, the Box-Behnken Design (BBD) of RSM was used to optimize GABA production by *Lb. brevis* HYE1. The optimum conditions for maximum GABA production of 18.76 mM were obtained using 2.14% (w/v) maltose, 4.01% (w/v) tryptone, 2.38% (w/v)

MSG, and pH 4.74 (Lim et al., 2017). This was similar to the results using BBD of RSM to optimize 3 variables such as level of MSG, PLP, and culture temperature for GABA production by *Lb. plantarum* NDC75017 (Shan et al., 2015). The optimal conditions were 80 mM of MSG, 18 μ M of PLP, and temperature of 36°C, gave the maximum GABA to 314.56 mg/100 g. *Lb. plantarum* NDC75017 was a commercial starter culture that produced high GABA production in fermented yogurt. Recently, the adzuki bean milk inoculated with *Lb. rhamnosus* GG increased GABA from 0.05 mg/mL to 1.13 mg/mL after 36 h optimized by RSM, using 1.44% galactose, 2.27% MSG, and 0.20% PLP. The GABA production was increased higher than 22.4 times compared to unfermented adzuki bean milk (Song & Yu, 2018).

The secondary objective is improvement and development of the GABA production process concerning the cost-effectiveness and simple production of bio-products. It is important to select a proper process that allows of the highest yielding of the target product. For batch fermentation systems, the substrate should be put in the tank once only from the start fermentation. The limitation is that the higher initial concentration of fermentation substrate which inhibit the cell growth or residual material resources and the higher yield of product resulted in the product inhibition effect. Consequently, fed-batch fermentation system, one or more components are supplied to the fermenter while cells and products remain in the tank until the end of the operation. The optimum starting substrate concentrations, which solves the problem of substrate inhibition, and limiting fermentation can be added by feeding in the fermentation course. It may be an improvement to obtain a high yield and productivity (Krause et al., 2010). Fed-batch fermentations was used for GABA production by *Lb. brevis* NCL912 at pH, temperature, and initial glutamate concentration was fixed at 32°C, pH 5.0 and 400 mM, respectively and after 280.70 g (1.5 mol) and 224.56 g (1.2 mol) glutamate were supplemented into the bioreactor at 12 h and 24 h, respectively. Under the selected fermentation conditions, GABA was rapidly produced at 36 h other than in stationary phase. The GABA concentration was improved to 1005.81 mM, and the residual glucose and glutamate were 15.28 g/L and 134.45 mM at 48 h (Li et al., 2010). Furthermore, GABA concentration in fed-batch fermentation was improved from 660 mM to 1000 mM by *Lb. brevis* B3-18 in the batch fermentation (Kook & Cho, 2013). These experiments showed that a simple and effective fed-batch fermentation method was developed for GABA production by LAB.

APPLICATION AND BENEFITS OF GABA

The available amount of GABA normally has major inhibitory neurotransmitters in the sympathetic nervous system (Mody et al., 1994) and plays an important role in cardiovascular function (DeFeudis, 1983). Moreover, physiological action of GABA includes induction of hypotensive, diuretic effects, tranquilizer effects, prevention of diabetic conditions in humans, anterograde amnesia and retrograde amnesia and anti-convulsive effects (Wong, Bottiglieri & Snead, 2003). GABA provides beneficial effects for human health, treatments for sleeplessness, depression, autonomic disorders (Okada et al., 2000), inhibits development of cancer cells, helping the recovery from chronic alcohol-related symptoms, controlling stress and lipid levels in serum because it promotes fat loss by the stimulation of human growth

hormone production, treatment of anxiety disorders, lowers blood pressure, boosts immune system (Oh & Oh, 2003), antihypertension, anticancer, anti-inflammatory and anti-hepatitis agents (Kang et al., 2011; Ali et al., 2013). In addition, GABA increases a strong secret of insulin from the pancreas and may prevent diabetic conditions (Adeghate & Ponery, 2002) and has preventive effects on Alzheimer's disease such as amnesia and dementia; also it improves memory and the learning abilities (Nakashima et al., 2009).

These multiple benefits of GABA on human health have led to the development of GABA-enriched fermented foods, a bioactive component, a primary element of food ingredients, and application in pharmaceuticals (Kim & Kim, 2012). For GABA in food enrichment, there is an idea of producing GABA-rich wheat germ food in normal daily consumption in a relatively large population that can be beneficial to those suffering pain from chronic hypertension. Several GABA-enriched functional foods are currently manufactured such as tea leaves treated anaerobically, rice germ soaked in water, red mold rice, tempeh-like fermented soybeans, and dairy products such as yogurt, fermented milk products and cheese (Thwe et al., 2011). Therefore, great efforts are focused on mass production of GABA and its utilization as a bioactive food ingredient in the modern food industry (Kim & Kim, 2012). GABA-enriched fermented food can reduce blood pressure after consuming such products (Inoue et al., 2003). It is worth noting that the human body can generally produce its own supply of GABA; however, GABA production is inhibited by an extra amount of salicylic acid or food additives or by the lack of vitamins, zinc or estrogen (Tenpaku, 1997). Therefore, GABA enriched food is required because the GABA content in typical human diets is relatively low.

GABA-enriched fermented foods with LAB included yogurt and cheese (Park & Oh, 2006; Nomura et al., 1998), sourdough (Diana et al., 2014) and kimchi (Seok et al., 2008). The highest content of GABA was found in Pecorino di Filiano (391 mg/kg) among 22 different varieties of Italian cheeses, in which the responsible microorganisms for the GABA production were *Lb. paracasei* PF6, PF8, and PF13, *Lb. plantarum* PF14, *Lactobacillus* sp. PF7 (Siragusa et al., 2007). In shochu distillery-lees, a Japanese distilled alcoholic beverage, most of the free glutamic acid (10.50 mM) was converted to GABA (10.18 mM) by *Lb. brevis* IFO-12005 (Yokoyama, Hiramatsu & Hayakawa, 2002). GABA-enriched grape-free grape preparation must beverage, which has a potential anti-hypertensive effect and dermatological protection was manufactured by fermentation using *Lb. plantarum* DSM19463 (Di Cagno et al., 2010). In addition, (Zareian et al., 2015) reported that biosynthesis activities for the production of glutamic acid and GABA in the fermentation of dosa (contains wheat and flour, a carbohydrate-rich food) by *Lb. plantarum* MNZ provided a GABA-enhanced functional food such as antihypertensive effects on spontaneously hypertensive.

However, the direct addition of chemical GABA to food is considered unnatural and unsafe. So it is necessary to find a natural method to produce an increase GABA in food with safely and effectively. Therefore, great efforts are focused on mass production of GABA and its utilization as a bioactive food ingredient in the modern food industry (Kim & Kim, 2012).

CONCLUSION

Numerous functions of GABA are summarized to develop foods enrichment, pharmaceutical and to provide the natural products. Therefore, the production of GABA by LAB is interesting; however, many factors have been shown to affect microbial GABA production that is dependent on their biochemical properties and GAD. Also, the optimization of many factors including pH, temperature, medium component, medium concentration and cultivation time is required; thus the first step is to define the appropriate conditions to improve a high yield of GABA by microorganisms. Currently, the conventional method and statistical method are used for optimization condition. Furthermore, the second is the improvement and development of the GABA production process taking into account the cost-effective and simple production of bio-products. This type of fermentation including batch and fed-batch are compared. All these processes will lead to the higher expedient of microbial fermentation for universal applications of GABA.

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Chapter 301

LACTOCOCCUS LACTIS AS A DNA VACCINE DELIVERY SYSTEM*

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ABSTRACT

DNA vaccines, which consist of plasmids encoding antigens of interest, emerge as novel options to protect hosts against new emerging infectious diseases. As most pathogens affect or initiate their infection at mucosal surfaces, this is a strategic route to induce specific immune responses. However, to make it possible, many environmental barriers must be surpassed. In this context, the use of bacteria, like *Lactococcus lactis*, as vehicles to deliver vaccine plasmids by the mucosal route is a promising strategy. Native *Lc. lactis* was used for this purpose and, aiming to make the plasmid delivery more efficient, invasive recombinant *Lc. lactis* strains were constructed and tested, thus showing to be able to deliver DNA vaccines more efficiently than the wild type strain. Therefore, in summary, this chapter presents a general view of DNA vaccines and the use of bacteria, especially *Lc. lactis*, to deliver them to intestinal eukaryotic cells, representing a new strategy for the tuberculosis control.

INTRODUCTION

Vaccination stimulates the development of immune responses to avoid infection and protect the individual from establishing a disease. Many diseases like tetanus, diphtheria,

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polio and hepatitis A and B have decreased significantly with the advent of vaccines (Roush et al., 2007). However, emerging infectious diseases have become challenges to be faced by the vaccinology field and new strategies must be developed to produce more efficient vaccines to protect the population worldwide. Within this scenario, DNA vaccines emerge as good alternatives to invest time and efforts, as they may be a way to overcome these new obstacles. DNA vaccines consist of eukaryotic expression plasmids that have the coding sequence of an antigen of interest inserted into their multiple cloning sites. Although different administration routes exist, the goal of these vaccines is that the plasmid DNA reaches the host cell nucleus so that it can be transcribed, translated and expressed by the eukaryotic cell and, in this way, elicit the expected immune responses (Pereira et al., 2014).

The first findings that reported about the potential of vaccines occurred in 1990, when Wolf and colleagues injected a DNA plasmid containing the coding sequence of β -galactosidase and verified the expression of this protein in quadriceps muscle sections of mice (Wolf et al., 1990). In 1992, after injecting a plasmid encoding the human growth hormone (hGH) into mice's skin, Tang and colleagues observed the production of specific antibodies against the protein, indicating that the injected DNA was expressed and elicited a specific humoral immune response (Tang et al., 1992). Subsequently, in 1993, two independent research groups vaccinated mice with DNA plasmids encoding different viral proteins and showed success when challenging against lethal influenza (Fynan et al., 1993; Ulmer et al., 1993). These studies were fundamental to understand how DNA could be used for vaccination and thus, protect against a pathogen or an antigen. To date, the scientific community has been striving for the use of DNA vaccines to become a reality around the world.

Since the discovery that DNA vaccines could be valuable tools to generate immune responses, four DNA vaccines have been approved for veterinarian use (Kutzler & Weiner, 2008). In 2005, two prophylactic vaccines against infection with the West Nile Virus in horses and the Hematopoietic Necrosis Virus in salmon were licensed in The United States and Canada, respectively. Following, in 2008, a therapeutic vaccine against fetal loss, which expressed the growth hormone releasing hormone (GHRH), was licensed for use in swine in Australia and in 2010 a therapeutic vaccine to treat oral melanoma in dogs was licensed in the United States. The success of these approved DNA vaccines showed perspectives of an innovative platform to prevent and treat emerging diseases.

STRUCTURE OF DNA VACCINES

DNA vaccines are bacterial-derived plasmids essentially composed of two distinguishable backbones: one for prokaryotic propagation and the other for eukaryotic expression (Liu, 2003). The prokaryotic propagation backbone consists of an origin of replication, which allows the plasmid to multiply during cell division and thus, to be passed on to daughter cells. Additionally, to ensure that all bacterial cells are carrying the plasmid of interest, DNA vaccines have a prokaryotic selectable marker generally consisting of a resistance gene to a specific antibiotic. The eukaryotic expression backbone comprises a transcriptional unit that allows for antigen expression in eukaryotic cells. A constitutive or inducible promoter has to be carefully chosen according to the desired expression, as, for

example, to enhance protein expression and immunogenicity, strong viral promoters, such as the cytomegalovirus (CMV) and Simian Virus 40 (SV40) promoters, are good options. For correct recognition of messenger RNA (mRNA) and initiation of the translation process by the eukaryotic machinery, a consensus sequence, called Kozak sequence, is present after the promoter and includes the start codon (ACCATGG). Following is the coding sequence of the antigen of interest, which is transcribed, translated and, if necessary, post-translationally modified by the eukaryotic host cell. At the end of the gene sequence, there is the stop codon, which follows the correct reading frame to accurately end translation. Finally, the backbone presents the polyadenylation sequence (poly A), which stabilizes the mRNA and ensures that it is exported from the nucleus to the cytoplasm of eukaryotic cells without degradation.

Over the years, strategies aiming at increasing the effectiveness of DNA vaccines have been developed. Because prokaryotes prefer codons that differ from those more frequently used in mammalian cells, in order to achieve optimal expression by the host cells, the coding sequence of the antigen of interest can be adapted for codons with more available corresponding transfer RNA (tRNA) (Wang et al., 2006). Strategies to enhance non-specific and antigen-specific responses and stimulatory cytokines are also encouraged, and include the use of immunostimulatory sequences, co-injection of immunomodulatory plasmids or use of adjuvants (Bode et al., 2011; Marc et al., 2015). Moreover, to increase the number of plasmids that reach the host cell nucleus and, consequently, are expressed, DNA nuclear targeting sequences (DTS) can be added to the eukaryotic backbone of DNA vaccines (Miller & Dean, 2009).

CHARACTERISTICS OF DNA VACCINES

DNA vaccination is a strategy designed to comply with efficient and effective immunization. Clinical trials have shown bottlenecks that need to be improved as well as the advantages of DNA vaccines, highlighting the potential of this innovative vaccination platform (Marc et al., 2015). At first, a recurrent concern was whether plasmids could integrate into the mammalian genome and its consequent unknown implications. However, the probability of plasmid integration into the host genome could be considered negligible, making vaccination with DNA safe (Glenting & Wessels 2005). The time spent to develop and produce DNA vaccines is short, compared to other platforms such as egg-based protein vaccines, and can rapidly be manufactured in large-scale to meet global demands (Moss 2009). In addition, the production of DNA vaccines is inexpensive compared to conventional vaccines, making this vaccination strategy even more attractive. Due to their composition, DNA vaccines are thermally stable, allowing for easy storage and shipping, making it possible to reach locations that do not have the appropriate refrigerated structure storage that some vaccines require (Ghanem et al., 2013).

The ability to elicit humoral and cell-mediated immune responses is one of the main advantages of DNA vaccines. While conventional protein-based vaccines commonly only induce antibody production, this new vaccination strategy can stimulate B and T cells, inducing antibody production and cellular responses, supporting their potential to confer protection against different pathogens (Li et al., 2012). The use of genetic material avoids manipulation of deadly infectious microorganisms and results in more safety during the

production of DNA vaccines. Additionally, the formulation of DNA vaccines allows for the insertion of distinct antigen-coding sequences into the same plasmid, resulting in a broader immune response. Finally, DNA vaccines can be administered through different routes, increasing the range of strategies to reach the desired immunization process (Reyes-Sandoval & Ertl, 2001; Laddy & Weiner, 2006).

MUCOSAL DNA VACCINES

The respiratory, gastrointestinal and urogenital tracts are covered by mucosal surfaces, which are large tissues protected by a highly specialized innate and adaptive immune system. As the majority of infections affect or start at mucosal surfaces, the mucosal immune system can prevent infectious agents from attaching, colonizing, penetrating and replicating, blocking microbial toxins in the mucosal epithelium (Holmgren & Czerkinsky, 2005).

The preferred mucosal routes for vaccination are the vaginal (Kanazawa et al., 2008), intranasal (Brave et al., 2008) and oral mucosae (Chatel et al., 2008). However, the oral route is the most commonly used because the gastrointestinal tract has the largest surface area in the body, with more than 200m² of mucous membrane (Andrew et al., 2011). Thus, the gut-associated lymphoid tissue (GALT) is the largest immune compartment in the body, containing the highest number of immune cells (Schroeter & Klaenhammer, 2009; Mowat & Agace, 2014).

The GALT has two prominent non-encapsulated structures, which are the induction sites of immune responses, known as Peyer's patches (PPs), and isolated lymphoid follicles. Additionally, the effector sites include lymphocytes, dendritic cells (DCs) and macrophages that are also dispersed throughout the epithelial layer and lamina propria (Brandtzaeg et al., 2008; Wells, 2011; Mowat & Agace, 2014).

The GALT is characterized by an overlying follicle-associated epithelium (FAE), with low levels of digestive enzymes and less pronounced villi, and is infiltrated by a large number of immune cells. The most notable feature of the FAE is the presence of Microfold cells (M cells), which are specialized for the uptake and transport of particulate antigens from the lumen into an underlying DC-rich subepithelial dome (SED) region, where they can be presented to the adaptive immune cells. PPs, on the other hand, are macroscopic lymphoid follicles located on the antimesenteric side of the small intestine. They are composed of numerous B cell lymphoid follicles, which are flanked by smaller T cell areas. The mesenteric lymph nodes (LM) drain all these sites and connect the mucosal and the systemic immune systems (Mowat, 2003; Wells, 2011; Mowat & Agace, 2014).

The efficacy of oral DNA vaccines depends therefore on whether the administered agents can survive the gastric and intestinal environments, which include pH-induced degradation, enzymes and diffusion across the mucus layers, and whether their residence time in the intestine is sufficient for interaction with and endocytosis by target cells. Therefore, oral administration of vaccines often requires delivery systems that protect against enzymatic degradation and elimination in the gastrointestinal tract, maintaining their high bioavailability (Chadwick et al., 2009). However, results of experimental approaches have proven difficulty to induce strong intestinal immune responses with a single oral administration

of naked DNA vaccines and development of effective mucosal delivery systems remains therefore an active area of research.

BACTERIA AS A VEHICLE FOR MUCOSAL DELIVERY OF DNA VACCINES

Initially, DNA vaccines consisted in direct immunization with naked plasmid in tissues, which internalized and expressed the immunogenic antigen (Liu et al., 2011). However, to reach significant levels of cellular transfection, very high doses of plasmids and multiple boosts were required (Van Drunen Littel-van den Hurk et al., 2000; Le et al., 2000; Babiuk et al., 2003), mainly due to high DNA degradation and low efficacy to overcome membrane permeability and cellular uptake, resulting in poor gene expression and low immunity (Miller & Dean, 2009). This showed that potent transfection methods had to be developed for the success of DNA vaccines.

In this context, the use of bacteria to transfer vaccine plasmids to mammalian host cells showed to be a promising strategy. In 1980, Schaffner was the first to observe the transfer of DNA from bacterial to mammalian cells, when tandem copies of the SV40 genome, carried by *Escherichia (E.) coli* strains, were transferred to co-cultured mammalian cells (Schaffner, 1980). Since then, many bacterial transfer systems have been developed and improved to transfer plasmid DNA to eukaryotic host cells.

This approach has several advantages, such as (i) protection of the DNA vaccine from physical elimination and enzymatic digestion, (ii) targeting of the inductive sites of the body, allowing stimulation of the immune system and (iii) appropriate stimulation of the innate immune system to generate effective adaptive immunity (Holmgren & Czerkinsky, 2005).

Moreover, bacterial carriers are easy to manufacture and able to maintain the plasmids with high copy numbers. Circumventing the need to co-administrate plasmid selection markers, required for vaccination with naked DNA, stable replication of plasmids can be further improved by the introduction of bacterial genes essential for survival within their host (Pilgrim et al., 2003). Additionally, in contrast to immunization with naked plasmid DNA, no further plasmid purification steps are needed, reducing costs and labor (Schoen et al., 2004; Becker et al., 2008). Furthermore, the World Health Organization (WHO) recommends the use of mucosal vaccines because of economic, logistic and security reasons (Holmgren & Czerkinsky, 2005; Wells, 2011).

IMMUNOLOGICAL ASPECTS OF BACTERIAL DNA DELIVERY TO THE ORAL MUCOSA

After oral administration, bacteria carrying plasmids are recognized by immune cells and intestinal epithelial cells (IECs) coating mucosal surfaces. Some attenuated pathogenic bacteria can invade IECs by the expression of virulence factors (invasins) to deliver DNA vaccines while other bacteria can be sampled by intestinal lamina propria DCs or by specialized epithelial M cells overlying PPs (Weiss & Chakraborty, 2001).

After bacterial delivery, innate immune receptors expressed by IECs and DCs, such as pattern recognition receptors like Toll-like and Nod-like receptors, can respond to some bacterial components, which serve as natural antigens after host cell invasion (Barbosa & Rescigno, 2010). Bacterial recognition by the immune system modulates the innate immune response thus, promoting a robust and lasting adaptive response (Hoebe et al., 2004).

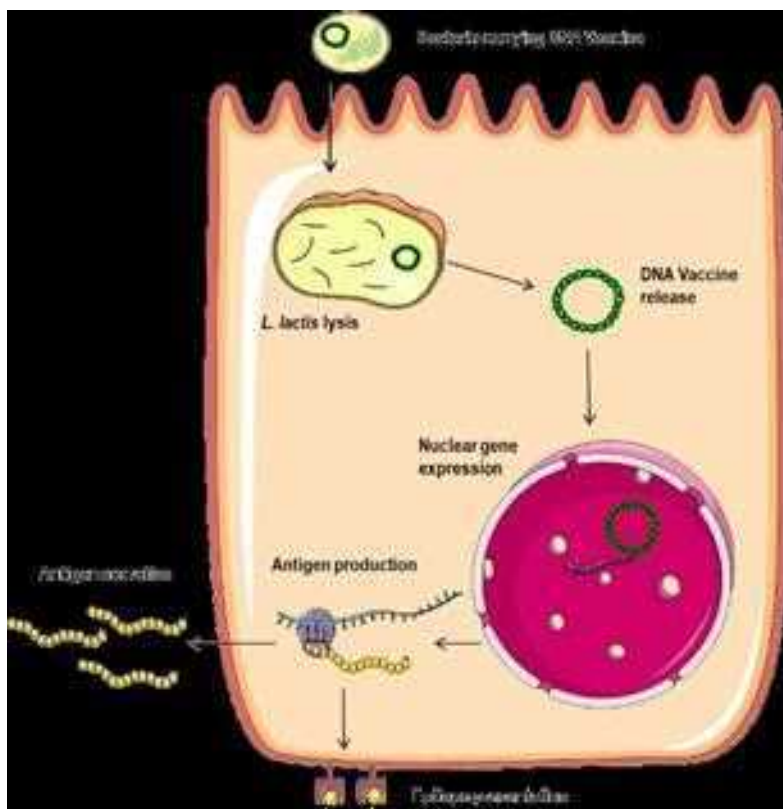


Figure 1. Representation of bacteria-mediated DNA vaccine delivery into intestinal cells. Bacteria enter the host cells and are lysed. The DNA plasmids are released in the cytoplasm and transferred into the nucleus, where expression of the open reading frame (ORF) of interest occurs. After protein synthesis by the host cell machinery, the antigen is processed for immune presentation or for secretion to the extracellular medium, eliciting specific prophylactic immune responses.

Once inside mammalian cells a primary vesicle, the phagosome, involves the bacteria. This vesicle fuses to a lysosomal compartment where bacterial lysis occurs releasing the DNA plasmids that then reach the host cytosol. The DNA vaccines then migrate to the cell nucleus, where the gene of interest is transcribed for subsequent cytoplasmic protein synthesis by the host cellular machinery (Grillot-Courvalin et al., 1999; Schoen et al., 2004). Exogenous antigens are presented on the surface of epithelial cells or secreted to the extracellular medium, where they can be transported by antigen presenting cells (APCs), especially DCs present in lymphoid follicles, to the nearest mesenteric lymph nodes and be presented to naïve T cells, resulting in the induction of specific cellular and humoral immune responses (Figure 1).

The induction of mucosal immunity, in which antigen-stimulated T cells migrate to the systemic blood and then head to other mucosal surfaces, occurs thus, demonstrating the importance of mucosal immunization to protect against pathogens that infect through this route (Brandtzaeg et al., 2008; Mowat & Agace, 2014). Furthermore, plasma cells primed in the mucosa are also attracted to these sites resulting in secretory IgA (sIgA) in the mucosal tissues around the body (Barbosa & Rescigno, 2010). Consequently, effector T lymphocytes and sIgA-producing plasma cells are able to protect the mucosal surfaces. In addition, effector memory cells are also induced, accumulating preferentially in non-lymphoid tissues, especially in the intestinal mucosa (Sallusto et al., 1999).

LACTOCOCCUS LACTIS AS DNA DELIVERY SYSTEM

The non-pathogenic and food-grade bacteria *Lactococcus (Lc.) lactis* is an attractive alternative for mucosal delivery of DNA vaccines. *Lc. lactis* is the lactic acid bacteria (LAB) model, is very easy to manipulate and has a large number of genetic tools developed (De Vos & Simons, 1994; Bolotin et al., 2001). Additionally, as these bacteria have been used for food fermentation and preservation for centuries, the Food and Drug Administration (FDA) considers *Lc. lactis* a generally regarded as safe (GRAS) microorganism for human consumption (Van de Guchte et al., 2001).

Therefore, the use of *Lc. lactis* for mucosal delivery of DNA vaccines can be justified by the fact that this bacteria (i) does not contain endotoxins, such as lipopolysaccharides (LPS), on their cell wall, eliminating the risk of anaphylaxis and can be therefore delivered safely at high doses in immunization programs, (ii) can be easily engineered for DNA delivery (Mercenier et al., 2000; Miyoshi et al., 2004; Wells & Mercenier, 2008; Brondyk, 2009), and (iii) its administration induces high production of antigen-specific sIgA (Neutra & Kozlowski, 2006).

USE OF WILD TYPE LACTOCOCCUS LACTIS AS A VEHICLE FOR DNA DELIVERY

The use of *Lc. lactis* as a potential DNA vaccine delivery system has been successfully shown (Pontes et al., 2011; Chatel et al., 2008). Firstly, in 2006, Guimarães and colleagues used a wild type (wt) *Lc. lactis* strain harboring a DNA plasmid coding for bovine β -lactoglobulin (BLG) to deliver DNA into mammalian cells. Production and secretion of BLG were observed in the intestinal epithelial cell line Caco-2 after its co-culture with the recombinant *Lc. lactis* strain, demonstrating that this bacterium could efficiently deliver a fully functional plasmid into epithelial cells *in vitro* (Guimarães et al., 2006). Then, Chatel and colleagues (2008) confirmed the ability of wt *Lc. lactis* to transfer DNA to mice IECs *in vivo*. This strain demonstrated its ability to translocate the intestinal membrane, as BLG cDNA was detected in the enterocytes of mice immunized with *Lc. lactis* carrying the same eukaryotic expression plasmid (Chatel et al., 2008).

Although these studies successfully demonstrated that *Lc. lactis* can be used as a DNA delivery system, different strategies have been developed to increase the ratio of gene transfer and therefore boost the immune response. One of these strategies includes chemical treatments to weaken bacterial cell walls: glycine-treated *Lc. lactis* NZ3900 showed a higher transfer frequency of a eukaryotic expression plasmid encoding for the red fluorescent protein (RFP) to Caco-2 cells (Tao et al., 2011).

Another approach was a new plasmid (pExu) constructed for DNA delivery using *Lc. lactis*, with a theta origin of replication and the pCMV expression cassette. An *in vitro* assay showed that 15.8% of CHO cells were able to express the *enhanced green fluorescent protein* (eGFP) protein after pExu:egfp transfection. Additionally, *Lc. lactis* MG1363 (pExu:egfp) were administered by gavage to Balb/C mice and the eGFP protein was detected in mice enterocytes (Mancha-Agresti et al., 2016). Also using wt *Lc. lactis* for DNA delivery, a different research group showed that this strain efficiently delivered the pPERDBY reporter plasmid encoding the eGFP to Caco-2 cells *in vitro* (Yagnik et al., 2016).

Furthermore, as described in the following section, a very interesting approach based on the use of recombinant invasive *Lc. lactis* strains have already been successfully demonstrated both *in vitro* and *in vivo*.

RECOMBINANT INVASIVE *LACTOCOCCUS LACTIS* AS DNA DELIVERY VEHICLES

Pathogenic bacteria have refined strategies to overcome host defenses and to interact with the host's immune system. To explore this concept and to increase the ability of lactococci to deliver DNA vaccines, some *Lc. lactis* strains expressing invasins have been constructed and shown to improve DNA delivery (Guimarães et al., 2005; Sleator & Hill, 2006). One such strategy engineered *Lc. lactis* to express InlA from *Listeria monocytogenes*. InlA is a cell wall-anchored protein that binds to the extracellular receptor E-cadherin (Gaillard et al., 1991; Mengaud et al., 1996). The recombinant lactococci (*Lc. lactis* InlA⁺), efficiently displaying the cell wall-anchored form of InlA, showed invasion rates in Caco-2 cells that were approximately 100-fold higher than those of wt lactococci. *In vivo* the invasive InlA⁺ strain also proved its capacity to enter epithelial Caco-2 cells with subsequent GFP expression after oral administration to guinea pigs and delivery of a functional eukaryotic plasmid (Guimarães et al., 2005).

To optimize the use of *Lc. lactis* as a DNA delivery system, a new plasmid (pValac - Vaccination using lactic acid bacteria) of 3,742 bp was constructed. The pValac plasmid consists of the cytomegalovirus promoter (pCMV) and polyadenylation sequences from the bovine Growth Hormone (BGH), which allows for the transcription of the ORF of interest with a PolyA tail that is essential to stabilize the mRNA transcript in eukaryotic cells. The pValac also contains origins of replication for its propagation in both *E. coli* (OriC) and *Lc. lactis* (OriA), and a chloramphenicol resistance gene for selection of strains harboring the specific plasmid. To evaluate its functionality, the gfp ORF was cloned into the pValac (pValac:gfp) and fluorescence was observed after PK15 cells transfection. Moreover, the *Lc. lactis* InlA⁺ strain invaded and delivered the pValac:gfp to Caco-2 cells (Guimarães et al., 2009).

However, the use of the *Lc. lactis* InlA⁺ strain presented a major bottleneck: InlA cannot bind to murine E-cadherin receptors, preventing *in vivo* experiments in these animals and limiting its study only in guinea pigs, which may be difficult to handle and/or expensive (Wollert et al., 2007). In this context and in order to increase the delivery of DNA to mammalian cells (Innocentin et al., 2009), a new recombinant *Lc. lactis* strain, expressing Fibronectin Binding Protein A (FnBPA) of *Staphylococcus aureus*, and that could be used in mice was constructed (Que et al., 2001). FnBPA is a virulence factor, which mediates bacterial adhesion to the host tissue and its entry into host cells (Sinha et al., 1999). FnBPA showed increased interaction and entrance of *L. lactis* in IECs and thus levels of DNA vaccine delivery. *Lc. lactis* FnBPA⁺ and *Lc. lactis* InlA⁺ presented comparable *in vitro* internalization rates by Caco-2 cells. After co-incubated of *Lc. lactis* FnBPA⁺ with Caco-2 cells, the pValac:gfp plasmid was more efficiently delivered than by non-invasive strains (Innocentin et al., 2009). Additionally, this strain was successfully used to deliver DNA vaccines encoding the BLG allergen and GFP *in vivo*, showing to be more effective than the wt strain (Pontes et al., 2012).

Another interesting work was performed using the mutated form of Internalin A (mInlA), which can bind to murine E-cadherin. mInlA was successfully expressed at the surface of *Lc. lactis* and showed higher invasion rates into Caco-2 cells and consequently higher delivery levels of BLG-coding plasmid when compared with the wt strain. Furthermore, *in vivo* studies demonstrated that *Lc. lactis* mInlA⁺ tended to increase the number of mice producing BLG (De Azevedo et al., 2012).

All these engineered strains to be used as DNA vaccine delivery systems represent promising tools for mucosal immunization and the strategy to use *Lc. lactis* to deliver prophylactics plasmids has proved to be relevant and possible. Our research group is currently working on the validation of this strategy in the development of DNA vaccines against tuberculosis, a re-emerging infectious disease that deserves great attention in current researches. This approach could therefore allow the use of *Lc. lactis* as efficient DNA vaccine delivery vehicles in a near future.

LACTOCOCCUS LACTIS AS A DNA VACCINE DELIVERY SYSTEM AGAINST TUBERCULOSIS DISEASE

Tuberculosis (TB), which is caused by *Mycobacterium tuberculosis*, is an infectious disease that affects one third of the global population in its latent form. This, in turn, makes TB one of the main social, economic and public health problems worldwide (Lugo & Bewley, 2008). The only available vaccine for clinical use, the BCG (Bacillus Calmette-Guérin), has a variable efficacy in adolescents and adults, requiring the development of more effective and economically viable vaccines.

In this context, *Lc. lactis* appears as an attractive alternative for a TB DNA vaccine delivery system, because it elicits an immune response as efficient as the other mucosal bacterial DNA delivery systems (Table 1). Moreover, *Lc. lactis* does not present risk in future clinical use when compared to attenuated pathogenic bacteria.

Thus, our research group developed new strategies for DNA vaccination against TB using the invasive *Lc. lactis* FnBPA⁺ strain (Innocentin et al., 2009) and the pValac vaccinal

Finally in 2016, Prósperi developed a *Lc. lactis* strain carrying a multigenic DNA vaccine in which the coding sequences of ESAT-6 and Ag85A were fused [*Lc. lactis* FnBPA⁺ (pValac::e6ag85a)]. After oral administration of this strain to mice, INF- γ , TNF- α and IL-17 levels increased significantly and it was also observed activation of specific cytotoxic T lymphocytes. Additionally, this strategy elicited an antigen-specific mucosal immune response shown by a significant increase in sIgA production in the colons of mice (Prósperi, 2016).

[illegible]

CONCLUSION

The applicability and efficacy of DNA vaccines carried by *L. lactis* strains, administered by mucosal routes, have been successfully established, generating a specific and broad immune response. Therefore, this immunization strategy can be used in research and development of DNA vaccines against other pathogens, with applications in the fields of immunization and immunomodulation.

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Chapter 302

BILE SALT HYDROLASE ACTIVITY OF LACTIC ACID BACTERIA: A POTENTIAL FOR HEALTH

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ABSTRACT

Many species of lactic acid bacteria (LAB) were usually found and isolated from various sources such as fermented foods (fermented meats, fermented dairy products, fermented fish, fermented vegetables, fermented fruits, fermented cereals and fermented legumes), dairy products, gastrointestinal tract of humans and animals, plant materials, feces, and sewage. LAB are a major group of probiotics, live bacteria that are good for host health. Several LAB express bile salt hydrolase (BSH) activity. Frequently, the bile salt hydrolase (BSH) activity of LAB have been involved with cholesterol-lowering effects and are exhibited by numerous genera, especially *Enterococcus* (*Ec*), *Bifidobacterium* (*Bf*), *Lactobacillus* (*Lb*), *Lactococcus* (*Lc*), *Leuconostoc* (*Leuc*), *Pediococcus* (*Ped*), *Clostridium* (*Cl*), and *Bacteroides* (*B*). They have shown the ability to lower serum cholesterol. Cholesterol is an essential building block for biological synthesis in the human body (hormone, vitamin D and bile acid) and is the important hypocholesterolemic role of bile salt hydrolase (BSH). One of the reasons that LAB have a hypocholesterolemic effect is bile salt hydrolase production or deconjugation of bile acid. Bile acids are made from cholesterol and amino acids (Taurine or Glycine) and metabolized *de novo* in the human liver via conjugation. Conjugated bile acid then flows into the intestine, where the amide bond of conjugated bile acid react with the bile salt hydrolase (BSH) that is produced by LAB. The amino acids were disintegrated from steroid core, and then transformed into a final form of bile acid is called deconjugated or unconjugated bile acid, which is less effectively reabsorbed than its conjugated form. Deconjugated bile salt results in the excretion of greater amount of free bile acids in feces, that is less solubility and absorption in intestine; therefore, enterohepatic recirculation, the homeostasis of bile acid, and could be consequently dragged into a

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reduction in serum cholesterol by augmentation the demand of cholesterol for *de novo* synthesis of bile acid to substitute those are eliminated in feces or by decreasing cholesterol solubility and thereby absorption of cholesterol through the intestinal lumen.

INTRODUCTION

Cholesterol is an essential building block for maintaining good health; however, hypercholesterolemia has been recognized as a major risk factor in atherosclerosis and coronary heart diseases (Brown & Goldstein, 1984; Khedkar, 1993; Smet et al., 1994). Bile salt hydrolase (BSH) activity of LAB may reduce the serum cholesterol level as suggested by (De Smet et al., 1995; Ahn et al., 2003). BSH enzyme is synthesized by several LAB and hydrolyzes either glycine- or taurine-link bile acids deconjugation reaction. The deconjugated bile acids are less soluble and less reabsorbed than conjugated bile acids, which results in excretion of larger amounts of free bile acids in feces; consequently, the cholesterol is taken up for *de novo* bile acid synthesis to maintain bile acid levels. Therefore, the deconjugation of bile acids by LAB bacteria could lead to a reduction in serum cholesterol (Pereira, McCartney & Gibson, 2003). Bile salt hydrolase (BSH) activity has been detected in many LAB living in the various sources (Jarocki et al., 2014; Ding et al., 2017; Xu et al., 2016; Saravanan & Shetty, 2016; Hou et al., 2015; Du Toit et al., 1998; Tanaka et al., 2000; Grill, Manginot-Durr et al., 1995; Öner, Aslim & Aydaş, 2014; Shekh, Dave & Vyas, 2016; Abushelaibi et al., 2017; Sirilun et al., 2010; Liu et al., 2017; Argyri et al., 2013; Franz et al., 2001; da Silva Ferrari et al., 2016; Elkins, Moser & Savage, 2001; Shehata et al., 2016; Corzo & Gilliland, 1999; Pato et al., 2004; Patel et al., 2010). Additionally, other researchers suggested the importance roles of BSH enzyme so that the bacterial cells can be detoxified of conjugated bile acids for microbial bile tolerance and survival in the intestine, liberating of amino acids from bile acids for bacterial growth, and alteration of bacterial membrane (Tanaka et al., 2000; Tannock, Dashkevich & Feighner, 1989; De Smet et al., 1995; Dambekodi & Gilliland, 1998; Taranto et al., 1998; Taranto et al., 2003).

Furthermore, some studies suggested undesirable effects of bacterial BSH activity on human health. It is possible that the deconjugated bile acids may impair digestive system and colonic mucosal function, play a role in gallstone formation and also cause DNA damage that promotes colon cancer (Jarocki et al., 2014). Thus, the bacterial BSH activity has been included among the criteria for the selection of probiotic strains. However, the bacterial BSH activity has been argued to be potentially harmful to human, and therefore it is as yet not clear whether BSH activity is, in fact, a desirable trait in a probiotic bacterium. This chapter gathered, described and summarized the available literature in the characteristic of bile, bile salt hydrolase (BSH) enzyme, mechanisms of cholesterol-lowering by LAB, bile salt hydrolase producing LAB, the effects of bacterial bile salt hydrolase on hosts and the beneficial effects of BSH activity to bacteria.

CHARACTERISTIC OF BILE AND FUNCTION

Bile is a dark green to a yellowish brown aqueous solution whose major constituents include cholesterol, bile acids, phospholipid, and the pigment biliverdin (Begley, Hill & Gahan, 2006). Bile is produced in the pericentral hepatocytes of the liver, stored and concentrated in the gallbladder interdigestively, and secreted into the first part of the small intestine which is named duodenum. Bile plays an essential role in fat digestion, which acts as a biological detergent, helping to emulsify and solubilize fats in food. Because of its biological detergent and membranolytic activity, bile is also an antimicrobial agent, a feature considered important for inhibiting the bacterial colonization in the proximal small intestine (Tremblay et al., 2017).

Bile acids are hydroxylated steroids. The two primary bile acids are cholic acid and chenodeoxycholic acid that are synthesized *de novo* from cholesterol in the liver. After that, the primary bile acid is also metabolized via conjugation (N-acyl amidation) to taurine (tauroconjugated) or glycine (glycoconjugate). The conjugation in the liver increases the solubility of the hydrophobic steroid nucleus; consequently, these molecules are amphipathic and can solubilize lipid to form mix micelles. Bile acids are conserved by a process named enterohepatic recirculation. Both conjugated and deconjugated bile acids are absorbed via active transport in the distal part of ileum and via passive transport (Kumar et al., 2012). Reabsorbed bile acids flow into the portal bloodstream and are taken up by hepatocytes. Later, reabsorbed bile acids are reconstituted and resecreted into bile. Secondary bile acids are produced by intestinal bacteria. According to Bortolini, Medici & Poli (1997), “approximately 5% of the total bile acid pool (0.3 g to 0.6 g) per day eludes epithelial absorption and may be extensively modified by the indigenous intestinal bacteria.” One of the main bile acids conversions is deconjugation (Batta et al., 1990). Deconjugation is the reaction that hydrolyzes the amide bond and liberates the glycine or taurine moiety from the steroid core. Finally, the bile acids are termed deconjugated or unconjugated.

BILE SALT HYDROLASE ENZYME

Bile salt hydrolase enzyme (BSH) (Cholylglycine hydrolase, E.C.3.5.1.24) has been found and characterized from many bacteria such as LAB, and mammalian gut microbiota. BSH enzyme is responsible for bile acid metabolism and plays a vital role in their colonization and survival in the mammalian intestine or harsh environments. BSHs are characterized as intracellular enzymes which belong to cholylglycine hydrolase family (Patel et al., 2010; Bi et al., 2013). The characteristics of BSHs are oxygen insensitivity, and the optimal pH normally between pH 5 and 6. In addition, one of the important factors is biomass production, since BSHs activity depends on biomass production (Begley, Gahan & Hill, 2005). Furthermore, bile deconjugation also leads to decreasing of serum cholesterol and alterations in energy homeostasis. The presence of an active BSH enzyme has long been considered as a criterion for the selection of potential probiotics (Food & Group, 2002).

MECHANISMS OF CHOLESTEROL-LOWERING BY BILE SALT HYDROLASE OF LAB

Numerous mechanisms to lower cholesterol have been proposed in previous researches, such as enzymatic deconjugation of bile salt by LAB. LAB reducing cholesterol activities are described here. The mechanism of cholesterol-lowering by LAB is to deconjugated bile acids by bile salt hydrolase enzyme. Bile acids are hydroxylated steroids, synthesized in the pericentral hepatocytes of the liver from cholesterol. The primary bile acids, such as cholic and chenodeoxycholic acids, are *de novo* synthesized in the liver and conjugated to either glycine (glycoconjugated) or taurine (tauroconjugated) via an amide linkage at the C24 carboxyl. They are excreted across the canaliculi to the biliary system. Over than 95% of bile acids secreted in bile are reabsorbed in the distal part of ileum and return to the liver because bile acids are conserved under normal condition by a process which is called enterohepatic circulation. In addition, bile acids play an important role in lipid-soluble nutrient and dietary lipid absorption (Korpela, Adlercreutz & Turunen, 1988; Kurdi et al., 2003). Unabsorbed bile acids flow into the colon and then they are catalyzed by bacterial metabolism such as deconjugation with bile salt hydrolase enzyme (BSH) which is generated by LAB. The conjugated bile acids are transformed to the deconjugated form. Most deconjugated bile acids are excreted and found in human feces because of their lower solubility and absorption. Consequently, it causes a reduction in serum cholesterol by increasing cholesterol demand for *de novo* bile acid synthesis to compensate the eliminated part. In a homeostatic response, new bile acids are synthesized from cholesterol for maintaining bile acid level, resulting in decreasing of serum cholesterol (Moser & Savage, 2001; Ahn et al., 2003; Ooi & Liong, 2010; Kumar, Ghosh & Ganguli, 2012; Bi et al., 2013). In conclusion, the BSH enzyme performance has a cholesterol-lowering effect.

BILE SALT HYDROLASE PRODUCING LAB

Bile salt hydrolase activity has been detected in LAB such as *Lactobacillus* (Tannock, Dashkevich & Feighner, 1989; Lundeen & Savage, 1990; Christiaens et al., 1992; Lundeen & Savage, 1992; Bateup et al., 1995; De Smet et al., 1995; Taranto et al., 1996; Du Toit et al., 1998; Elkins & Savage, 1998; Corzo & Gilliland, 1999; De Boever & Verstraete, 1999; Tanaka et al., 1999; Grill et al., 2000; Elkins, Moser & Savage, 2001; Pereira, McCartney & Gibson, 2003; McAuliffe, Cano & Klaenhammer, 2005; Argyri et al., 2013; Hou et al., 2015; da Silva Ferrari et al., 2016; Shehata et al., 2016; Shekh, Dave & Vyas, 2016; Abushelaibi et al., 2017), *Lactococcus* (Pato et al., 2004; Shehata et al., 2016; Abushelaibi et al., 2017), *Bifidobacterium* (Grill, Manginot-Durr et al., 1995; Grill et al., 1995; Grill et al., 2000; Tanaka et al., 2000; Kim et al., 2004; Kim, Yi & Lee, 2004; Kim, BrochetLee, 2005; Jarocki et al., 2014; Öner, Aslim & Aydaş, 2014), *Enterococcus* (Franz et al., 2001; Knarreborg et al., 2002; Veysey et al., 2001; Xu et al., 2016), *Pediococcus* (Xu et al., 2016), *Leuconostoc* (Saravanan & Shetty, 2016; Xu et al., 2016), and also in *Clostridium* (Coleman & Hudson, 1995; Pereira, McCartney & Gibson, 2003), and *Bacteroides* strains (Kawamoto, Horibe & Uchida, 1989; Stellwag & Hylemon, 1976) which have been isolated from traditional fermented foods, dairy, plant, sewage, feces, animal, and the human gastrointestinal tract. The

presence of BSH producing LAB is mostly found in the bile acid-rich environment (Tanaka et al., 1999). Generally, bifidobacteria and lactobacilli are used as probiotic, whereas *Enterococcus*, *Clostridium*, and *Bacteroides* strains are mostly found in the gastrointestinal tract. Numerous studies have reported BSH-positive strains as shown in Table 1.

Table 1. Bile salt hydrolase positive strains of LAB isolated from various sources

Species	Strain	Source	Reference
<i>Lb. acidophilus</i>	ATCC 4356	Human	Elkins, Moser & Savage, 2001
	ATCC 53544	Human infant, rectal swab	
	JCM 1034	Human intestine	
	O16	Human intestine	Corzo & Gilliland, 1999
	BFE 1059	Pig faeces	Du Toit et al., 1998
<i>Lb. brevis</i>	BCCM 7944	Human feces	Elkins, Moser & Savage, 2001
	BCCM 11998	Starter from dairy	
	BCCM 18022	Zabady (yogurt)	
	UNIVASF CAP 16, UNIVASF CAP 279	Goat milk	da Silva Ferrari et al., 2016
<i>Lb. rhamnosus</i>	BO3	Boza	Shehata et al., 2016
<i>Lb. reuter</i>	Iso66	Camel milk	Abushelaibi et al., 2017
<i>Lc. lactis</i> subsp. <i>lactis</i>	BO37	Boza	Shehata et al., 2016
	RM39	Rayeb milk	
	IS-10285	Dadih	Pato et al., 2004
<i>Lc. lactis</i>	Iso15, Iso76	Camel milk	Abushelaibi et al., 2017
<i>Lc. garvieae</i>	Iso47	Camel milk	Abushelaibi et al., 2017
<i>Lb. paracasei</i>	BO51, BO52	Boza	Shehata et al., 2016
	UNIVASF CAP 45, UNIVASF CAP 84	Goat milk	da Silva Ferrari et al., 2016
<i>Lb. delbrueckii</i> subsp. <i>bulgaricus</i>	BO34	Boza	Shehata et al., 2016)
	D11, D14	Dongbei kimchi	Xu et al., 2016
<i>Lb. fermentum</i>	ATCC 11976	Infant intestine	Elkins, Moser & Savage, 2001
<i>Lb. gasseri</i>	BCCM 9203	Human	Elkins, Moser & Savage, 2001
	JCM 1025	Human intestine	Elkins, Moser & Savage, 2001
	RM28	Rayeb milk	Shehata et al., 2016
<i>Lb. johnsonii</i>	JCM 1022	Human intestine	Elkins, Moser & Savage, 2001
	JCM 8791	Human feces	Elkins, Moser & Savage, 2001
	BFE 1061	Pig feces	Du Toit et al., 1998
<i>Lb. plantarum</i>	BCCM 18021	Milk	Elkins, Moser & Savage, 2001
	BCCM 18027	Laban rayeb	Elkins, Moser & Savage, 2001
	D24, D25	Dongbei kimchi	Xu et al., 2016
	B282, E45, E10, E73	Naturally fermented olives	Argyri et al., 2013
	RC	Raw cheese	Shekh, Dave & Vyas, 2016
	GV	Guava	
	SG	Sugarcane	
	GP	Grapes	

Table 1. (Continued)

Species	Strain	Source	Reference
<i>Lb. plantarum</i>	OP	Prickly pear	Shekh, Dave & Vyas, 2016
	Iso34, Iso70	Camel milk	Abushelaibi et al., 2017
	TGCM 15, TGCM 33	Thai fermented food	Sirilun et al., 2010
	LA3, GD2	Breast-fed infants' feces	Öner, Aslim & Aydaş, 2014
	Lp3	Fermented yak milk	Ding et al., 2017
	LP96	Fermented food	Liu et al., 2017
<i>Lb. pentosus</i>	B279, B283, E43, E100, E128	Naturally fermented olives	Argyri et al., 2013
<i>Ec. faecium</i>	B20, B21	Stinky soybean	Xu et al., 2016
	C10	Rubing	
	P1, P7, P8	Guizhou kimchi	
	V24	Sichuan kimchi	
	FAIR-E 154	Food	Franz et al., 2001
<i>Ec. durans</i>	C12, C5, C3	Rubing	Xu et al., 2016
	V18	Sichuan kimchi	
	FAIR-E 231	Food	Franz et al., 2001
<i>Ped. ethanolidurans</i>	D13	Dongbei kimchi	Xu et al., 2016
	K2	Kimchi	
<i>Leuc. mesenteroides</i>	V12, V21	Sichuan kimchi	Xu et al., 2016
	D10	Dongbei kimchi	
<i>Leuc. lactis</i>	KC117496	Idli batter	Saravanan & Shetty, 2016
<i>Lb. reuteri</i>	NCIMB 30242	Pig	Hou et al., 2015
	BFE 1058	Pig feces	Du Toit et al., 1998
<i>Bf. longum</i>	SBT2928	Human feces	Tanaka et al., 2000
	BB536	Human	Grill et al., 1995
	BASO9, BASO15	Breast-fed infants' feces	Öner, Aslim & Aydaş, 2014
<i>Bf. longum</i> subsp. <i>longum</i>	NRRL B-41409	Adult intestine	Jarocki et al., 2014
<i>Bf. adolescentis</i>	DSM 20087	Bovine serum	Jarocki et al., 2014
<i>Bf. animalis</i> subsp. <i>animalis</i>	NRRL B-41406	Rat feces	Jarocki et al., 2014
<i>Bf. animalis</i> subsp. <i>lactis</i>	NRRL B-41405	Yoghurt	Jarocki et al., 2014
<i>Bf. longum</i> subsp. <i>infantis</i>	ATCC 15697	Infant intestine	Jarocki et al., 2014
<i>Bf. longum</i> subsp. <i>suis</i>	NRRL B-41407	Pig feces	Jarocki et al., 2014
<i>Bf. bifidum</i>	DSM 20456	Breast-fed infant stool	Jarocki et al., 2014
<i>Bf. breve</i>	DSM 20091, NRRL B-41408	Infant intestine	Jarocki et al., 2014
	A19, A26	Breast-fed infants' feces	Öner, Aslim & Aydaş, 2014
<i>Bf. catenulatum</i>	DSM 20224	Sewage	Jarocki et al., 2014
<i>Bf. pseudocatenulatum</i>	DSM 20439	Infant intestine	Jarocki et al., 2014
<i>Bf. longum</i> subsp. <i>suis</i>	NRRL B-41407	Pig feces	Jarocki et al., 2014
<i>Bf. pseudolongum</i> subsp. <i>pseudolongum</i>	DSM 20095	Chicken feces	Jarocki et al., 2014

Bf, Bifidobacterium; *Ec*, Enterococcus; *Lb*, Lactobacillus; *Lc*, Lactococcus; *Leuc*, Leuconostoc.

EFFECTS OF BACTERIAL BILE SALT HYDROLASE ON HOSTS

Cholesterol-lowering Effect of LAB: Hypcholesterolemic Benefits

Hypercholesterolemia is the major risk factors of cardiovascular disease (CVDs) that is the main cause of the mortality (Labarthe & Dunbar, 2012; Roth et al., 2011). The coronary

arteries are affected by high serum cholesterol. Atherosclerosis, the hardening of the arteries, is a condition where the arteries become narrowed and hardened due to a buildup of plaque around the artery wall. Atherosclerosis begins when the endothelium becomes damaged, allowing the harmful type of cholesterol to make up part of the artery wall. Thus, dietary modification and functional foods are becoming an interesting issue to reduce the risk of heart diseases (Aronow, 2013; Lichtenstein & Goldin, 1993; St-Onge, Farnworth & Jones, 2000). Functional food is an interesting alternative choice to manage serum cholesterol due to the effect of LAB or other probiotics. LAB consist as a major group of probiotic bacteria: live bacteria that are good for host health. Several LAB express cholesterol-lowering effects (Jones, 2002).

Even though there have been several medicines for the treatment of hypercholesterolemia, these medicines are expensive and have negative side effects. In these senses, it is possible that the using of BSH enzyme to reduce serum cholesterol levels in the patient with hypercholesterolemia and also prevent hypercholesterolemia in normal people has arisen as an interesting alternative to drugs available today (Chae et al., 2013).

Impaired Digestive Functions

In lipid digestion and absorption, the BSH activity may compromise the mechanisms of lipid emulsification and micelle formation due to lack of conjugated bile acids which are more efficient than deconjugated bile acids (Nagpal et al., 2012). The growth defects in chicken have been found with microbial BSH activity correlation (Walker & Gilliland, 1993; Du Toit et al., 1998). However, there is no association between the growth defects and the BSH activity in mice (Kumar et al., 2012).

Disruption of Intestinal Conditions and/or Gallstones

Several studies have reported that the deconjugated bile acids may disturb colonic mucosal function which would be the causes of diarrhea or inflammation. In addition, it is assumed that colon cancer as a result of DNA damage can be caused by deconjugated bile acids. (Kandell & Bernstein, 1991; Bernstein et al., 2005; Marteau et al., 1995; Nagengast, Grubbenvan & Munster, 1995; Pazzi et al., 1997).

Additionally, the alterations of the bile acids concentration may lead to bile being supersaturated with cholesterol. This cholesterol may precipitate together with calcium salts and bile pigments to form solid build-ups of crystallized bile termed gallstones, which may build up and impede the biliary ducts (Low-Beer & Nutter, 1978; Marcus & Heaton, 1986; Veysey et al., 1999). Interestingly, the increasing deconjugated bile acid formation has been observed in gallstone sufferers (Berr et al., 1996; Mamianetti et al., 1999).

BENEFICIAL EFFECTS OF BSH ACTIVITY TO BACTERIA

Firstly, studies strongly support the hypothesis that bacterial BSH depress the antimicrobial properties of bile acid; consequently, the bacterial BSH producing strains can better survive and persist in the human gastrointestinal tract. Since the deconjugated bile acids have decreased solubility and diminished detergent activity, these can be less toxic to bacteria in the intestine. Secondly, other studies suggested that some bacterial species may be given carbon, nitrogen and sulfur sources by deconjugation with BSH enzyme (Tanaka et al., 2000; Van Eldere et al., 1996; Jarocki et al., 2014). Finally, there is a possibility that the BSH facilitates incorporation of cholesterol moiety or bile into bacterial membranes. This incorporation may probably modify and improve fluidity, permeability and the net charge of the bacterial membranes; consequently, this alteration improves the colonization ability and survival of these microbes in the gut. Because the bacterial cell modification, which is the result from BSH activity, could protect the bacteria from the immune system (Dambekodi & Gilliland, 1998; Taranto et al., 1997; Taranto et al., 2003). However, this incorporation may be the important resistance mechanisms that are the cause of persistent pathogen infection (Begley, Hill 6 Gahan, 2006).

In conclusion, BSH activity is desirable for enhancing the overall probiotic beneficial effects correlated with each strain. For the human supplementation, the safety of administering BSH producing bacteria as probiotic must be considered in order to prevent undesirable side effects (Ahn et al., 2003; Gilliland & Speck, 1977; Takahashi & Morotomi, 1994).

CONCLUSION

Increasingly, it is becoming apparent that microbial BSH activity may confer a selective benefit on probiotic strains in the highly competitive environment of the human intestinal tract. Moreover, the manipulation of BSH activity may ultimately lead to the development of more robust probiotics with improved competitiveness and performance. Finally, targeting the bacterial BSH to modify cholesterol and bile acid metabolisms might be interestingly alternative choices to prevent or treat various diseases such as hypercholesterolemia and cardiovascular diseases.

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Chapter 303

EXOPOLYSACCHARIDES FROM *LACTOBACILLUS*: BIOSYNTHESIS, CHARACTERIZATION, FUNCTIONAL ASPECTS AND APPLICATIONS IN FOOD INDUSTRY

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ABSTRACT

Exopolysaccharides (EPS) are high molecular weight biopolymers produced by a wide range of microorganisms, including lactic acid bacteria (LAB). These polymers can be secreted to the external environment (slime EPS) or adhered to the cell bacterial surface (CPS). Once they are released to the medium, they are able to change its rheology, property that was frequently used by the food industry. Likewise, EPS have been associated with beneficial health effects, making them attractive molecules to be applied as food ingredients.

Lactobacillus is a wide genus of LAB including more than 200 species which has been of great interest because strains with technological, as well as functional (probiotic) properties were described. The present chapter reviews the current knowledge about the role of EPS production in lactobacilli strains, as well the aspects regarding biosynthesis, chemical structure, screening and quantification methods, focusing on the impact of their chemical structure and composition on the possible health benefits and their technological application in novel food products.

INTRODUCTION

Some lactic acid bacteria (LAB) are able to produce exocellular polymers or exopolysaccharides (EPS) which can be secreted to the medium (slime EPS) or remained attached to the cell wall (capsular polysaccharides or CPS). These molecules are frequently

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used by the food industry, for example by the application of EPS-producing strains in the manufacture of fermented milk and different types of cheese, improving their textural and organoleptic properties. Furthermore, some EPS are able to reduce syneresis in yogurts due to their water-retention properties and, besides, they can be used as fat replacers in low-fat dairy products, allowing the design of healthy products with acceptable sensory characteristics. Furthermore, EPS were associated with positive health effects, among these are their bifidogenic/prebiotic role, stomach ulcer protection, cholesterol-lowering and immunomodulatory properties. It has also been described that EPS provide protection against different pathogens (virus and bacteria) and present antioxidant and antitumor effects.

Particularly for LAB, the ecological or physiological role of EPS for the producing bacterium remains unclear, and has been associated with a protective role in various niches (biofilm formation) and with carbon catabolism (Schwab et al., 2007; Zannini et al., 2016). In general, it is believed that EPS are not used as an energy source by the producer strain, but there might be some exceptions (Baruah et al., 2018). In some cases, the presence of CPS may protect the producing cell by preventing phagocytosis (Tahoun et al., 2017; Meijerink et al., 2012). A possible hypothesis indicates that some protective roles of these molecules can be associated to the adaptation of the producing bacteria to the stressful conditions of their natural ecosystems such as the gastrointestinal tract and fermented foods (Ruas-Madiedo et al., 2008). EPS have been associated with both rheological and functional effects on the matrix where they are added or synthesized, but the final response strongly depends on their chemical structure and the way of interaction with the medium components. Among LAB, *Lactobacillus* is a wide genus including more than 200 species (Salveti et al., 2018) which has been of great interest because strains with technological, as well as functional (probiotic) properties were described, frequently associated to the synthesis of EPS.

The aim of this chapter is to review the current state of the art about the chemical structure and genetic organization of EPS in the *Lactobacillus* genus, the methods for EPS isolation and optimization, the potential benefits on human health and the technological applications for the design of novel techno-functional foods, focusing on the structure-function correlation.

CLASSIFICATION, BIOSYNTHESIS AND GENETIC ORGANIZATION

Bacterial EPS are carbohydrate polymers which generally present glucose, fructose, galactose, rhamnose and fucose in their structure (Ruas-Madiedo et al., 2002). In some cases, the presence of different isomers, linkage types and organic and inorganic monosaccharide substituents could be found as well. The oligosaccharide repeating units can present different degrees of polymerisation and branching patterns and are responsible for the great diversity among lactobacilli EPS.

These relatively long-chain and high-molecular-mass polymers can be classified into two main groups: they can be composed of only one type of monosaccharide (homopolysaccharides, HoPS), or can present more than one type of monosaccharide in their structure (heteropolysaccharides, HePS); the mechanisms of biosynthesis are different between them (Cerning, 1990; 1995). HoPS are formed by the action of enzymes called glucansucrases (or glucosyltransferases, GTF) and fructansucrases (or fructosyltransferases,

FTF), depending on the composition of the polysaccharide in formation (glucans and fructans, composed exclusively by glucose or fructose, respectively). Both enzymes are glucoside hydrolases that catalyze transglycosylation reactions in the extracellular environment, using sucrose as substrate and obtaining the necessary energy from the molecule breakdown (Figure 1A). The structures of these enzymes are very different, glucansucrases have numerous domains that belong exclusively to LAB, and synthesize α -glucans that differ in their type of glycosidic bounds, degree and type of branches, molecular mass and solubility. On the other hand, fructansucrases are present in Gram positive and Gram negative bacteria, and synthesize β -fructans with $\beta(2,6)$ (inulin) or $\beta(2,1)$ linkages (levan) (Hijum et al., 2006). HoPS can be classified in four subgroups according to the monomers and linkages involved: α -D-glucans (dextrans), β -D-glucans, β -fructans (such as levan and inulin), and others like polygalactans. They are produced by several LAB genera, including *Lactobacillus*, *Streptococcus*, *Leuconostoc*, *Oenococcus*, and *Weissella* (Dimopoulou et al., 2017; Hijum et al., 2006). Thus, due to the great diversity of species that form part of the *Lactobacillus* genus, the EPS synthesized by them seem to be very attractive molecules for numerous novel applications. In the case of β -glucans, only one gene is required for their biosynthesis, which encodes a β -glycosyltransferase, a membrane protein whose topological prediction indicates that β -glucan, or at least its repeating unit precursors, are synthesized in the cytosol (Werning et al., 2006; Werning et al., 2012). Besides, *in vitro* recent experiments indicate that the β -glucan is synthesized directly from activated UDP-glucose (Fraunhofer et al., 2018; Werning et al., 2008), similarly to HePS. This could explain the production of a β -glucan with only glucose as the C source for *Lactobacillus (Lb.) fermentum* Lf2 (a widely studied strain from our group), and not sucrose, as it would be expected for HoPS (Ale 2018; Vitlic et al., 2018). Werning et al., (2012) suggested that the association of several GTF monomers could form a pore for extrusion of the EPS. However, other alternative mechanisms might allow the translocation or secretion of β -glucans across LAB membranes, such as those mediated by ABC-like transporters, related to the export of various bacterial polysaccharides (Silver et al., 2001). In the presence of certain sugar acceptors (like maltose), glycansucrases can form low-molecular-mass oligosaccharides from sucrose (Korakli & Vogel, 2006). Their synthesis occurs via successive transfer of glucosyl or fructosyl units to the acceptor rather than the glucan or fructan polymer, with the consequent formation of glucooligosaccharides (GOS) or fructooligosaccharides (FOS), respectively (Lynch et al., 2018).

On the other hand, HePS are molecules composed by repetitive units which present mainly D-glucose, D-galactose and L-rhamnose, and are formed by 2 to 8 monomers. Other monosaccharides, such as fructose, fucose, mannose, N-acetylglucosides, and glucuronic acid, as well as noncarbohydrate moieties (phosphate or acetyl groups) can be present as well (De Vuyst & Degeest, 1999a; Werning et al., 2012), conferring them particular characteristics. HePS are produced by the polymerization of sugar-nucleotide precursors (e.g., UDP-glucose and UDP-galactose) provided by the cell, and the biosynthesis is controlled by several glycosyltransferase genes that are involved in the regulation, chain-length determination, polymerization and export of the repeating units. These genes are generally located together in an operon and constitute an EPS biosynthesis cluster (Werning et al., 2012). All the details of the mechanism are not yet fully understood, but a flippase enzyme may be involved in the transfer of the lipid-bound polymer to the external side of the membrane, where the polymerization of the repeating units takes place (Lebeer et al., 2009). Figure 1B shows the main steps for the synthesis of HePS in LAB. Briefly, activated sugar

nucleotides bind to a phosphorylated lipid carrier (such as C55- polyprenyl phosphate) located on the cytoplasmic side of the cell wall by the enzymatic activity of a priming glycosyltransferase associated to the membrane. After this, a series of additional glycosyltransferases catalyze the synthesis of the repetitive unit of the EPS, which is then transported to the outer surface of the bacterial membrane by a flippase (Flippase-like Transmembrane Lipid Transporter, FTLT, also identified as Wzx/Wzy-dependent pathway, according to the nomenclature described for *Escherichi (E.). coli*; Schmid 2018). Once it is outside, the repetitive units are polymerized and the chain length seems to be regulated by a phosphatase that hydrolyzes the lipid diphosphate anchor of the membrane. These genetic clusters are located mainly in the bacterial chromosome, as it was described for *Streptococcus (Strep.) thermophilus*, *Lb. plantarum* or *Lb. fermentum* (De Vuyst & Degeest, 1999b; Siezen et al., 2010; Stingelet al., 1996; Dan et al., 2009). As it was mentioned above, the genes involved in the HePS synthesis are usually located in operons, with all of them oriented in the same direction, allowing the transcription of a single mRNA molecule (Jolly & Stingelet, 2001; Lebeer, Vanderleyden & Keersmaecker, 2008) and are highly conserved among lactobacilli (Lebeer, Vanderleyden & Keersmaecker, 2008). Until now, the genes involved in the regulation of HePS synthesis were detected in lactobacilli but not in bifidobacterial *eps* clusters (Jiang and Yang 2018). A conserved “consensus” *eps* cluster structure for *Lactobacillus* (among other LAB) was proposed starting (from 5’ to 3’) with genes responsible for the transcriptional regulation and chain-length determination, followed by a core of GTF and ending with genes for polymerisation/export, all flanked by transposases (and derivatives) or insertion sequences (Figure 2) (Castro Bravo et al., 2018).

A typical characteristic found in *eps* clusters is the presence of mobile genetic elements in the DNA region involved in HePS or HoPS synthesis (Péant et al., 2005; Tiekings et al., 2005; Hijum 2004). These elements allow horizontal transfer between different genera and their presence could justify the instability of the HePS- producer phenotype of some strains (Ruas-Madiedo et al., 2009). The *gtf* genes (coding for β -glycosyltransferases) of LAB are usually flanked by genes which could be involved in functions of conjugation and recombination. Thus, horizontal transfer mediated by plasmids, or transposition events, might explain the wide distribution and high degree of *gtf* gene preservation in β - glucan-producing strains along different genera (Werning et al., 2006).

METHODS FOR ISOLATION AND PURIFICATION OF EPS AND CPS

The total yield of EPS produced by the LAB strongly depends on the composition of the medium (C and N sources) and the conditions in which the strains develop, such as temperature, pH, oxygen tension, and incubation time (Degeest, Vaningelgem & De Vuyst; 2001). It has been described that the adjustment of the fermentation conditions can lead to higher EPS levels (Ale et al., 2016b; Zisu & Shah, 2003; Petry et al., 2000). For example, temperature modifications presented varying effects on EPS production (De Vuyst & Degeest, 1999b). It has been shown that lower temperatures are better for HoPS synthesis, as glycanucrases have a lower optimum temperature range (Kang, Oh & Kim, 2009). In a recent study by our group, the statistical optimization of the EPS production by *Lb. fermentum* Lf2 was achieved, doubling the yield obtained under non-optimized conditions

(1 to 2 g/L, approximately). In this case, sucrose was more effective than glucose as the C source, and the proportions of the three nitrogen sources of the semidefined medium applied were critical (SDM, Kimmel & Roberts, 1998), as well as the pH and time of fermentation (Ale, 2018).

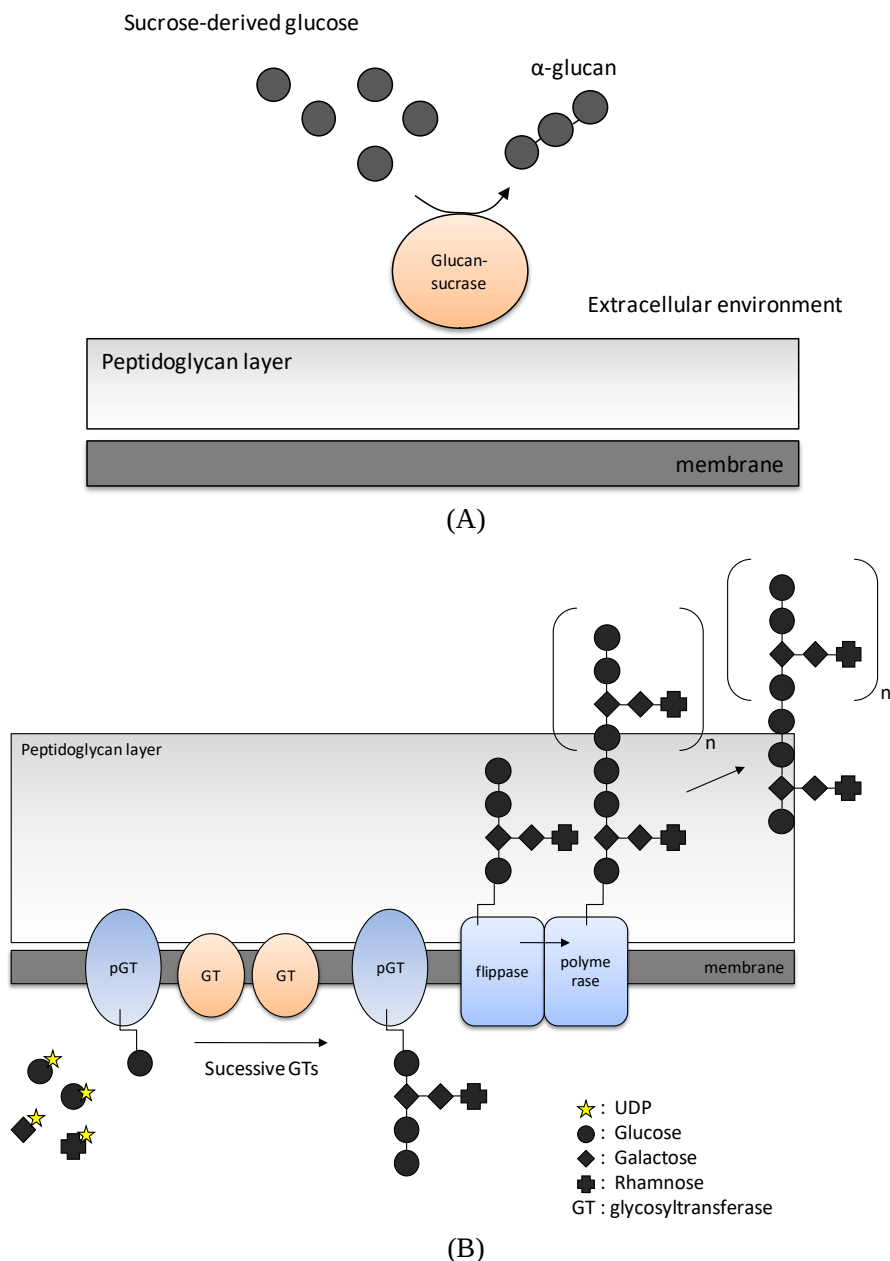


Figure 1. EPS-biosynthesis pathways proposed for homopolysaccharides (HoPS, A) and heteropolysaccharides (HePS, B).

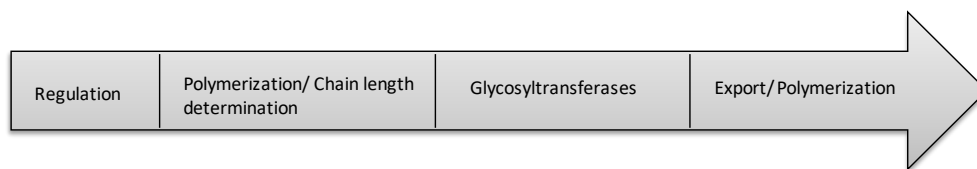


Figure 2. Organization described for the HePS gene clusters.

When quantification of the EPS yield is approached, it is important to highlight that the presence of glucomannans (originating from yeast extract and peptone, both included in general media for lactobacilli, like MRS) can co-precipitate with EPS. For this reason, the use of semi-defined media for EPS quantification and purification is recommended (Ruas-Madiedo & de los Reyes-Gavilán, 2005).

In general, the molecular mass of HoPS is greater than 10^3 kDa (Ruas-Madiedo et al., 2009) and are produced in amounts higher than HePS, in the range of g/L, reaching values of up to 10 g/L (Lynch et al., 2018). HePS are synthesized in low amounts, in the range of mg/L, and their molecular mass ranges from 40 to 9×10^3 kDa (Ruas-Madiedo et al., 2009).

Several screening strategies have been applied to detect EPS-producing bacteria. For example, Vedomuthu & Neville (1986) used 1.0 mL pipettes to test the ropiness of acidified reconstituted skimmed milk, assessing mucoidness by the stringiness of the free flowing gel. This method was also described by Mozzi, Torino & de Valdez (2004), defining ropy as strings longer than 6 mm. A variant to the ropy-screen method employs an inoculation wire loop to assess string formation upon touching a colony. In this case, when the string was longer than 5 mm, the strain was considered ropy (Dierksen, Sandine & Trempey, 1997). Although these techniques are easy to perform, they are difficult to standardize since the results obtained are qualitative rather than quantitative. A screening approach using microhaematocrit capillaries to measure efflux, a parameter that correlates with viscosity measurements was also described (Ricciardi, Parente & Clementi, 1997). In general, visualization of slimy or mucoid colonies on solidified media is probably the most frequently used screening method for EPS production, with the disadvantage of only detecting strains with an evident ropy phenotype.

Staining methods are also used for detecting EPS-producing cells, for example by the use of ruthenium red, neutral red, calcofluor white, congo red or Indian ink. Ruthenium red was used to detect *Strep. thermophilus* mutants with loss of ropy phenotype, which appeared as red colonies on milk agar media, while ropy wild-type strains appeared white (Stingele et al., 1996). Although staining assays are relatively easy to perform, the visual interpretation can be difficult when small differences between positive and negative signals occur (Zeidan et al., 2017).

All the screening approaches mentioned above rely on the presence of a physical change in the environment that can be observed by visual inspection. A more direct approach involves gravimetric quantification of the EPS produced. Depending on the medium, certain pre-treatment steps are required in order to obtain the EPS extract with the minor interferences as possible. For example, heating steps are used to inactivate endogenous enzymes that could degrade the polysaccharides (Shao et al., 2014). In general, for broths like MRS, centrifugation is typically carried out to separate the cells, and then the EPS are precipitated from the supernatant with chilled absolute ethanol (Juvonen et al., 2015; Dilna et

al., 2015; Hermann, Petermeier & Vogel, 2015; Zarour et al., 2017). Briefly, the protocol applied could be summarized as follows: (i) cell removal by centrifugation or filtration; (ii) EPS precipitation from the supernatant by the addition of chilled absolute ethanol or acetone (2-3 volumes); (iii) dialysis to remove low molecular mass contaminants (12-14 kDa cut off); and (iv) freeze-drying of the precipitated polysaccharide. In some cases, a second precipitation and dialysis step is carried out (Torino, de Valdez & Mozzi, 2015; Ruas-Madiedo & de los Reyes-Gavilán, 2005). Polak-Berecka et al., (2013) found that a heat treatment at first step is critical to inactivate EPS or CPS-degrading enzymes. Besides, they do not recommend too high centrifugal rates ($> 10,000$ g) to discard the cell pellet, since part of the EPS could be eliminated as well.

Further purification could include more sophisticated steps such as membrane-filtration, anion-exchange and/or gel permeation chromatography (Leivers et al., 2011; Sanz & Martínez-Castro, 2007; Shao et al., 2015).

The quantification of EPS yield may be gravimetric (expressing the yield as mg/L) or colorimetric, by the phenol-sulphuric acid method (Dubois et al., 1956). In this last case, simple sugars, oligosaccharides, polysaccharides and their derivatives (including the methyl ethers) give an orange-yellow colour when they are treated with phenol and sulphuric acid.

When the EPS is isolated from high protein content media, such as dairy products, proteins are usually precipitated with trichloroacetic (TCA) acid, or removed by hydrolysis with proteases or by a combination of both (Torino, de Valdez & Mozzi, 2015), followed by the alcohol precipitation, dialysis and freeze-drying steps.

Regarding CPS, they can be visualized by microscopy after negative staining with Indian ink (Mozzi et al., 1995), a technique that evidences a bright white layer surrounding the cells when CPS are present. For the same purpose, Malang et al., (2015) used crystal violet to stain the cells blue to facilitate the differentiation of CPS in the dark background. To isolate the CPS, the cell pellet can be washed with PBS buffer and, after resuspending the cells in NaCl (1 M), a sonication step is applied to detach the CPS from the cells. Then samples are centrifuged to eliminate insoluble material and the supernatant is precipitated with chilled ethanol as described previously for EPS (Fraunhofer et al., 2018; Tallon, Bressollier & Urdaci, 2003; Toba, Kotani & Adachi, 1991). An alternative method with ethylenediamine tetraacetic acid (EDTA) has also been described (Tallon, Bressollier & Urdaci, 2003); in this case, the cell pellets are resuspended in 0.05 M EDTA. Then, the mixture is incubated under gentle agitation for 4 h at 4 °C and centrifuged and a precipitation step with ethanol is done as described above. The efficiency of this last technique will depend on the nature of the bonds between CPS and the cell wall. In another work (Mende et al., 2013), CPS were detached from the harvested cells suspended in water by applying a heating step (90 °C, 15 min), cells were then removed by centrifugation and the detached CPS was isolated from the supernatant.

CHEMICAL AND STRUCTURAL CHARACTERIZATION OF EPS

In relation to the chemical characterization of EPS, the polymer molecular weight (MW) can be measured by HPSEC-RI (High Performance Size Exclusion Chromatography-Refractive Index) and an increased use of SEC-MALLS (Size Exclusion Chromatography - Multi-Angle Laser Light Scattering) was observed lately (Picton, Bataille & Muller, 2000;

Leivers et al., 2011; Patten et al., 2014). There are other complex techniques that can also be used to determine the average MW, such as Field Flow Fractionation (FFF) and Hydrodynamic Chromatography (HDC) (Isenberg et al., 2010; Galle et al., 2011).

Table 1. Lactobacilli EPS-producing strains, chemical characteristics and potential applications

Strain	EPS	Application	Reference
<i>Lb. sanfranciscensis</i> LTH2590 (= TMW 1.392)	β (2,6) levan	Improvement of bread texture and dough rheology	Brandt et al., 2003
<i>Lb. buchneri</i> FUA3154	Galactose, glucose, one unidentified; MW $10\text{-}10^2$ kDa	Wheat and sorghum sourdough rheology	Galle et al., 2011
<i>Lb. plantarum</i> BR2	Glucomannan; MW 2.38×10^3 kDa	Antioxidant and lowering cholesterol activities, antidiabetic potential	Sasikumar et al., 2017
<i>Lb. kefiranofaciens</i> 1P3 <i>Lb. satsumensis</i> 10P and 10P2	Glucans, most of the residues linked by α -(1,6) glycosidic bonds (~90%); estimated MW 8×10^2 kDa	Increase in IgA ⁺ B cells, suitable for food ingredient	Paiva et al., 2016
<i>Lb. paracasei</i> CIDCA 83123 <i>Lb. paracasei</i> CIDCA 8339 <i>Lb. paracasei</i> CIDCA 83120 <i>Lb. paracasei</i> CIDCA 83121 <i>Lb. paracasei</i> CIDCA 83124	Main component: a fraction of MW $10\text{-}10^2$ kDa, but a high MW fraction was also observed: EPS produced by <i>Lb. paracasei</i> CIDCA 8339 and <i>Lb. paracasei</i> CIDCA 83124 had a MW fraction of 10^2 Da– 10^3 kDa. EPS produced by <i>Lb. paracasei</i> CIDCA 83120, <i>Lb. paracasei</i> CIDCA 83121 and <i>Lb. paracasei</i> CIDCA 83123 had a fraction with MW $> 10^3$ kDa	Interesting rheological properties in fermented milk, which would be useful for food application	Hamet, Piermaria & Abraham, 2015
<i>Lb. mucosae</i> DPC 6426	Mannosyl residues, with mannose, glucose and galactose found to be the major sugar residues present in an approximate ratio of 3:2:2	Decrease in syneresis in low-fat yogurt and viscosity increased for the EPS-rich yogurts; improved sensory properties of Swiss-type cheese	London et al., 2014 ; 2015; Ryan et al., 2015
<i>Lb. fermentum</i> Lf2	Glucose and galactose 2:1, composed of a high MW fraction ($> 1 \times 10^3$ kDa) and a low MW fraction (90 kDa)	Increase of the hardness and consistency index of low-fat yogurts, with no sensory defects	Ale et al., 2016b; Vitlic et al., 2018
<i>Lb. suebicus</i> CUPV225 <i>Lb. suebicus</i> CUPV226	Glucose, galactose, N-acetylglucosamine and phosphate (in different ratios), mixture of polysaccharides; two fractions: 2×10^4 and $1.5\text{-}7.8 \times 10^6$ g/mol, depending on the C source	Potential immunological and technological properties	Ibarburu et al., 2015
<i>Lb. paracasei</i> 20408	EPS with unknown structure	EPS ⁺ mutant showed a positive impact on the textural, melt, proteolysis, and sensory characteristics of half-fat Cheddar cheese, useful as fat replacer	Zhang et al., 2015

The EPS monomer composition can be determined by total acid hydrolysis (sulphuric or trifluoroacetic acid at 120 °C) followed by detection using high performance anion exchange chromatography (Ale et al., 2016b; Fraunhofer et al., 2018). Additional information about the

structural characteristics can be studied by ^1H and ^{13}C NMR spectroscopy (Leivers et al., 2011; Balzaretti et al., 2017). This method provides information of the type of monosaccharides, ring size, anomeric configuration and positions of the glycosidic linkages (Torino, de Valdez and Mozzi 2015). In fact, more than fifty different NMR-EPS repeating unit structures have been described for lactobacilli and bifidobacteria (Castro-Bravo et al., 2018), representing in some cases unique structures (Ruas-Madiedo, 2005). In Table 1, some characteristics of EPS from lactobacilli were summarized, together with their potential food applications. For example, in a recent study of our group (Ale, 2018; Vitlic et al., 2018), the structure of two EPS produced by *L. fermentum* Lf2 was elucidated by NMR. The two EPS were separated by preparative size exclusion chromatography to give a high molecular mass β -glucan (1.23×10^3 kDa) and a medium molecular mass heteroglycan (88 kDa), the last composed of glucose and galactose. Their structures were determined using a combination of NMR spectroscopy, monomer and linkage analysis.

Recently, a high-throughput screening method was described for the determination of EPS concentration and monosaccharide composition (Rühmann, Schmid, and Sieber 2016). The method consists of the following steps: cultivation, cell removal by centrifugation and filtration, sugar monomer removal by gel filtration, EPS hydrolysis with trifluoroacetic acid and derivatization with 1-phenyl-3-methyl-5-pyrazolone (PMP) and monomer detection by UHPLC-UV-ESI-MS (Ultra High Performance Liquid Chromatography with Ultra Violet and Electrospray Ionization Ion Trap Mass Spectrometer).

Molecular screening approaches have also been applied to the search for new EPS-producing isolates. The strategy comprises the design of degenerate primers based on LAB gene sequences followed by PCR reaction and sequencing of PCR products. This approach has been mainly applied to identify glucan and fructan-producing strains (Krajl et al., 2003; Malik et al., 2009). With genome sequencing, it is currently easier to study EPS-related gene sequences and the structure of the clusters involved in EPS synthesis. However, this technique is not suitable for arising to conclusions regarding yield and type of polysaccharides, or even rheological properties when applied in different food matrices.

POTENTIAL APPLICATIONS OF EPS FROM THE GENUS *LACTOBACILLUS* IN THE FOOD INDUSTRY

EPS are attractive molecules with great potential to be used as ingredients in food matrices since they are natural and safe components when they are produced by GRAS (General Recognized as Safe) microorganisms, such as lactobacilli. Although they have low yields, their production *in situ* is suggested as an option for the food industry, for example by the application of EPS producing adjunct or starter cultures (Hassan, Awad & Muthukumarappan, 2005; Ryan et al., 2015; Han et al., 2016; Amatayakul, Sherkat & Shah, 2006b; Hassan et al., 2003; Yilmaz et al., 2015). EPS, mainly HePS, have been widely used in the dairy industry, since they are able to improve certain attributes due to their thickening properties. Besides, they have been related to syneresis reduction and firmness increase (Ale, et al., 2016b; Dabour et al., 2006; Zisu & Shah, 2005).

For the design of novel foods with improved technological and functional characteristics, it is crucial to find new EPS-producing strains able to impart the expected characteristics to a

specific food matrix. In this sense, an important number of EPS-producing *Lactobacillus* was isolated from diverse food matrices, mainly those in which a spontaneous fermentation was implicated as part of processes (Table 1). For example, it was described that certain polymers produced by lactobacilli could beneficially affect the water absorption of dough, dough rheology and machinability, its stability during frozen storage, loaf volume and bread staling (Tieking & Gänzle, 2005). Besides, the EPS produced from sucrose by *Lb. sanfranciscensis* LTH2590 presented the potential to affect the rheological properties of the dough, as well as the texture, volume, and keepability of bread (Korakli et al., 2001). In general, EPS isolated from sourdough include mainly HoPS; however, Meulen et al., (2007) described the production of HePS from a sourdough isolate, a strain of *Lb. curvatus*, whose EPS is composed of galactosamine, galactose, and glucose (in relation 2:3:1, respectively). Galle et al., (2011) studied the HePS-producing strains *Lb. casei* FUA3185, *Lb. casei* FUA3186, and *Lb. buchneri* FUA3154, the last was a ropy strain isolated from bread drink (a German fermented grain beverage), regarding their impact on wheat and sorghum sourdough rheology. *Lb. buchneri* FUA3154 showed the highest viscosity at low shear rate when it was grown in MRS. Despite the fact that glycosyltransferase genes responsible for HePS synthesis from the three strains were expressed in sorghum and wheat sourdough, only HePS from *Lb. buchneri* impacted on the rheological properties of sorghum sourdoughs, decreasing resistance to deformation and elasticity.

Regarding the culture conditions that favor the application of EPS-producing strains, Bengoa et al., (2018) analyzed the effect of growth temperature on EPS production of different *L. paracasei* strains isolated from kefir grains and showed that suboptimal temperatures enhanced the EPS yield and polymerization, but their probiotic properties (adhesion to Caco-2 cells and modulation of the epithelial innate immune response) were not affected by this parameter.

Paiva et al., (2016) characterized the EPS produced by novel *Lactobacillus* strains from Brazilian milk or sugar water kefir when they are grown with sucrose as C source. *Lb. kefiranofaciens* 1P3 and *Lb. satsumensis* 10P and 10P2 synthesized EPS composed of glucose, and most of the glucose residues were linked by α -(1,6) glycosidic bonds (~90%) and the estimated molecular weight was 800 kDa. Since the intestinal IgA⁺ B cells were significantly higher in mice that received the EPS, the authors suggested that these EPS might be useful as food additives.

In this direction, Hamet, Piermaria & Abraham (2015) studied the effect of 28 lactobacilli on the texture of acid milk gels and observed that those gels obtained from the fermentation with all the *Lb. paracasei* strains (5 in total) were the ones that presented the highest viscosities, probably due to the presence of a high MW fraction. Nevertheless, the viscoelastic characteristics of the resulting acid gels were different; one of the strains produced a viscous behavior whereas the others presented gel structures.

Another species studied regarding its EPS production was *Lb. fermentum* (Zhang et al., 2011; Leo et al., 2007; Shi et al., 2014). In a recent study of our group (Ale et al., 2016b), the EPS extract from *Lb. fermentum* Lf2 (a strain isolated from an Argentinian cheese with blowing defects) and its impact on the technological properties when applied to yogurts as a natural ingredient, were analyzed. Yogurts with EPS showed higher hardness values than the controls and this difference remained stable during time. The consistency index was also higher for the treated samples at both times evaluated (3 and 25 days), being significantly different for samples with 300 mg/L of EPS extract, while the flow behavior index was lower

for EPS-added yogurts. The thixotropic index was lower for samples with the highest EPS extract concentration at the end of the storage time. Regarding the sensory analysis, no defects were detectable, making it suitable for food applications. Syneresis was also decreased for samples with 600 mg/L of EPS extract at 25 days of storage. These results showed the potential of this extract to be used as a technofunctional natural ingredient, also considering its positive impact on health according to previous studies (Ale et al., 2016a). From another report, sixteen EPS-producing *Lb. fermentum* strains isolated from West African fermented millet dough presented desirable technological and probiotic characteristics *in vitro* (Owusu-Kwarteng et al., 2015). The authors suggested that these strains could function as potential probiotic cultures.

London et al., (2015) applied an EPS-producing strain of *bL. mucosae* as adjunct culture in low-fat yoghurt manufacture. The treated yogurts presented a significant decrease in syneresis and increased viscosity as a consequence of the EPS produced *in situ* during fermentation.

Diverse works described the specific interactions among these polymers and the food matrix in which they are employed. In yogurts, it has been shown by confocal scanning laser microscopy that caseins form a gel and polysaccharides are located in pores containing whey. It is probable that the chemical nature of this EPS was responsible for its incompatibility with proteins aggregates (Hassan et al., 2003). In another study, Folkenberg et al., (2005) described two different sensory profiles which depended on the protein-EPS interactions. They observed two types of microstructures: in one of them EPS were associated with the proteins surrounding the pores, while in the other, incompatibility between the EPS and the protein network existed, causing EPS depletion. In this case, the polymers were found inside the pores. Yogurts with the first type of microstructure presented high ropiness, low serum separation and were more resistant to stirring, and yogurts with the second type of microstructure were less ropy, had high serum separation and showed increased mouth thickness as a result of stirring.

In cheeses, HePS produced by lactobacilli strains such as *Lb. delbrueckii* subsp. *bulgaricus*, *L. helveticus* and *L. casei* promoted water retention and positively modified the texture, avoiding alteration of the structure (Zisu & Shah, 2007). This modification of the textural characteristics often permits the reduction of calories in the final product, for example in low-fat cheeses (Oberg et al., 2015; Zisu & Shah, 2005; Zhang et al., 2016). Accordingly, EPS-producing lactobacilli or EPS (as ingredients) were described as interesting fat replacers to improve the rheological parameters of the final product (Broadbent et al., 2001; Perry, McMahon & Oberg, 1998; Ryan et al., 2015). In this direction, Zhang et al., (2015) studied the yield, textural, proteolysis, melting, and sensory properties of half-fat Cheddar cheese including an EPS-producing *Lb. paracasei* strain. The results revealed that cheeses made with the high yield EPS-producing strain, in combination with the commercial Cheddar culture, presented increased moisture content and yield compared with the half-fat controls. The melting properties were significantly improved as well, and the sensory characteristics were similar to the full-fat controls.

From non-dairy industries, the EPS production by two *bL. suebicus* strains (isolated as responsible of an alteration from ropy ciders) was examined in a semidefined medium (Ibarburu et al., 2015). Both strains were able to use glucose, ribose and xylose as C sources, and synthesize a mixture of complex HePS.

In the light of this information, it is important to remark the relevance of the isolation and characterization of new EPS- producing strains, mainly from artisanal or spontaneously fermented products (even when they were present in a food matrix as non-desirable organisms), representing the principal source of new cultures and ingredients (such as EPS), which are essential to diversify the market of techno-functional food.

FUNCTIONAL ASPECTS OF EPS FROM THE GENUS *LACTOBACILLUS*

The presence of *Lactobacillus* within the intestinal microbiota has been linked to a healthy status of the host and, in general, low levels have been associated with specific health problems as IBS (Irritable Bowel Syndrome; Liu et al., 2017). Although lactobacilli represent just 0.01 % of total faecal bacteria (Walter 2008), it seems that this genus plays an important role in maintaining the normal intestinal homeostasis, knowing that its addition as a probiotic supplement could help balance an aberrant intestinal microbiota (Staudacher et al., 2017). Probiotics are “live microorganisms which, when administered in adequate amounts, confer a health benefit on the host” (Hill et al., 2014). Some strains with scientifically demonstrated probiotic properties were included in diverse functional foods and, although the mechanisms by which they exert their action are uncertain, it has been suggested that the health-promoting effects of EPS-producing strains are related to the biological activities of these biopolymers (Figure 3). In fact, diverse scientific reports indicate that EPS from diverse *Lactobacillus* species can contribute to human health by means of numerous demonstrated effects: prebiotic role, modulation of the immune system, antioxidant, antitumor, antiulcer or cholesterol-lowering activities, etc. (Ruas-Madiedo, Hugenholtz & Zoon, 2002). However, since not all EPS can improve the technological properties of fermented foods (Hassan, 2008), not all are able to promote health benefits (Amrouche et al., 2006), being their chemical structure and MW relevant characters to define their health-promoting function (Hidalgo Cantabrana et al., 2012). The topics mostly supported by an adequate amount of scientific evidence refer to the ability of EPS to act as immunomodulators and prebiotic compounds and will be discussed in independent sections of this chapter.

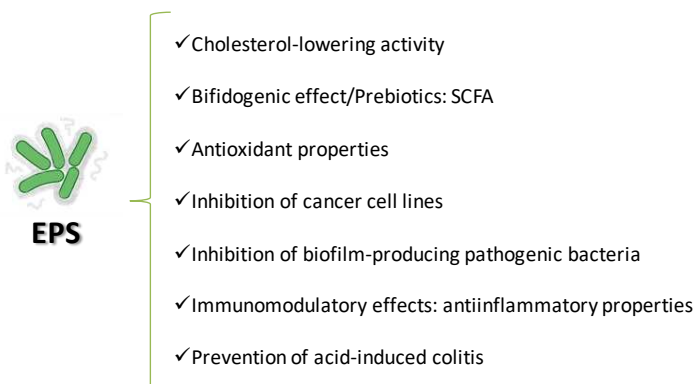


Figure 3. Health-promoting effects related to EPS produced by lactobacilli. Immunomodulatory properties of EPS.

Besides the physiological role of EPS for the producing bacteria and their relevance for industrial applications, in the last decade there has been increasing evidence about the impact on the human health bias the interaction of the EPS-producing lactobacilli and the host by modulating the immune response.

Notably, carbohydrates were considered as traditional T-cell-independent antigens that do not elicit cell-mediated responses and fail to induce immunologic memory and immunoglobulin class-switching. However, in the last decades, certain microbial polysaccharides have been described as potent immunomodulators with specific activity against both T-cells and antigen-presenting cells such as monocytes and macrophages (Cobb & Kasper, 2005).

Several works in the literature reported the ability of EPS from lactobacilli to elicit immune responses and some authors linked the intrinsic physicochemical characteristics of these molecules with their functional properties (López, 2012), indicating two different types of behaviors or patterns. The first pattern associates functional properties with the presence of acidic substituents as phosphate groups (conferring negative charges) in the molecule, which seem to induce the immune response compared with neutral polymers. For example, the EPS from *bL. delbrueckii* subsp. *bulgaricus* OLL-1073-R1 is composed of two fractions of glucose and galactose: the acidic one (containing phosphate) showed a strong immune profile, inducing the proliferation and activity of macrophages; while the neutral fraction evidenced the opposite behavior, being unable to elicit stimulation (Kitazawa et al., 1998; Nishimura-Uemura et al., 2003; Uemura et al., 1998). The second proposed pattern links the immune response with the MW of the polymer. It has been postulated that EPS having high MW (HMW, $> 10^3$ kDa) could act as strong suppressors of the immune response (Hidalgo Cantabrana et al., 2012), as occurred with the EPS from *Lb. casei* Shirota, a HMW polysaccharide able to induce (by cell culture) the production of diverse cytokines (TNF- α , IL-12, IL-10 and IL-6) in lower extent than EPS⁻ knockout-mutants (Yasuda, Serata & Tomoyuki, 2008). Bleau et al., (2010) showed that murine peritoneal macrophages stimulated with the HMW-EPS-producing *Lb. rhamnosus* RW-9595M, an isogenic mucous variant of the strain ATCC9595, induced lower levels of TNF α and IL-6 than the parental strain, which also evidenced a decrease in IL-10 production. Similarly, Nicolik et al., (2012) reported a suppressive immune response when the HMW-EPS-producing *Lb. paraplantarum* BGCG11 was used for inducing human peripheral blood mononuclear cells (PBMC), in comparison with its novobiocin EPS⁻ mutants. In a study from our group, the EPS from *Lb. fermentum* Lf2 showed a mild suppressive profile when administered to mice, increasing s-IgA levels and reducing the proinflammatory cytokine IL-6 in the small intestine when added in a dairy matrix (Ale et al., 2016a). In this case, based on preliminary evidence indicating a relatively low MW (< 100 kDa in average) and the absence of charged substituents, the observed mild stimulation of immune cells when administered to mice could obey the patterns previously proposed by Bleau et al., (2010) and López et al., (2012). In these cases, a HMW-EPS could be purified from the crude extract, consisting of a β -glucan (1.23×10^3 kDa) which was able to inhibit the rises of TNF- α levels in peripheral blood mononuclear cells pre-treated with lipopolysaccharide (LPS) or phytohemagglutinin (PHA). The results indicate a role of this polysaccharide in modulating the immune response after exposure to agonists such as bacterial LPS.

The cytokine profiles produced by EPS are not always clear. For example, EPS from *Lb. rhamnosus* KL37 and *Lb. reuteri* 115 were able to stimulate the simultaneous secretion of

both anti-inflammatory (IL-10) and proinflammatory (TNF- α and IL-6) cytokines from peritoneal mouse macrophages (Ciszek-Lenda et al., 2011). Vinderola et al., (2006) demonstrated that the oral administration of a high dose of kefiran, an EPS produced by *Lb. kefiranofasciens*, showed an immunomodulation (mediated by IgA, IL-2, IL-6, IL-10, TNF- α) at the level of large intestine and blood, suggesting a potential role in intestinal homeostasis. Additionally, another study showed that the systemic administration of *Lb. rhamnosus* KL37C EPS stimulated a significant decrease in the serum concentration of type II collagen-specific IgG antibodies in a murine model of mild rheumatoid arthritis, consequently improved the condition (Nowak et al., 2012).

The role of polysaccharides in the balance of the immune status associated with inflammatory disorders caused by infections has been also reported. One of the traditional phenotypic features tested during *in vitro* probiotic characterization is the ability to coaggregate with pathogens, since it is believed that co-aggregation decreases the accessibility of the harmful microorganisms to the intestinal epithelium (Castro-Bravo et al., 2018). In this sense, the activities against *Candida* of *Lb. rhamnosus* GG, its EPS deficient mutant, and the purified EPS were analyzed, showing that the EPS layer might be involved in the reduction of hyphal formation and in the competition with *Candida* during adhesion to vaginal epithelial cells (Allonsius et al., 2017). Another study with a *Lb. paracasei* subsp. *paracasei* BGSJ2-8 EPS-deficient mutant, producing an EPS with a different composition, indicated that the wild-type EPS is essential to reduce *Escherichia* (*E.*) *coli* association with Caco-2 cells, while the mutant strain was not able to counteract this interaction (Živković et al., 2016). This highlights the importance of EPS composition and not only EPS production in the potential interaction with pathogens. Also, EPS isolated from *Lb. delbrueckii* subsp. *delbrueckii* were able to significantly down-regulate the expression of enterotoxigenic *E. coli*-induced proinflammatory cytokines (IL-6, IL-8 and MCP-1) in porcine intestinal epithelial cells (Wachi et al., 2014). Regarding *in vivo* experiments, different animal models have been used to study how EPS-producing strains interfere with pathogen activity. For instance, *Lb. johnsonii* FI9785, a poultry derived isolate producing two different EPS, was effective to suppress the colonization and persistence of *Clostridium* (*Cl.*) *perfringens* in poultry and to reduce colonization by *E. coli* in the small intestine (Dertli et al., 2013). In case of the crude EPS from *Lb. fermentum* Lf2, it showed a mild protection against *Salmonella* infection in a survival murine model when suspended in milk, in a dose feasible to be used as a food ingredient. In this same study, the survival proportion for the treated group (31%) resulted significantly higher than that of the control group (9%), thus representing another mode of action of this EPS to elicit positive health benefits (Ale et al., 2016a). This property could be related with the increased s-IgA levels in the intestinal fluid of mice also observed for this extract when used as an ingredient in yogurts. Similar survival rates were observed by Nagai et al., (2011) when evaluating the effect of an EPS from a strain of *Lb. delbrueckii* subsp. *bulgaricus* on the influenza virus infection after 21 days of administration of yogurts. Although they evaluated the capacity of EPS against a virus, the survival of mice ranged from 0% for the control groups to 38.9% for diverse EPS-fractions.

The molecular mechanisms by which lactobacilli interact with immune cells have not been entirely elucidated. The highly multifunctional Toll-like receptor (TLR) family, which are able to recognize a vast range of extracellular bacterial products (Patten & Collett, 2013; Patten et al., 2014), could mediate these interactions. Particularly, TLR-2 is known to interact with a diverse range of microbial components (Akira, Uematsu & Takeuchi, 2006; Takeda,

Kiasho & Akira, 2003). The LPS receptor, TLR-4 (Hoshino et al., 1999), is also a promising candidate, and a response in which a combination of TLR-2 and TLR-4 takes place was also suggested (Wachi et al., 2014).

It has been previously proposed that bacterial EPS could exert their immunomodulatory action via the mannose receptor (Chabot et al., 2001). However, the feasibility of this hypothesis is questionable due to the structural heterogeneity of microbial EPS. Taking into account the immune parameters and the diverse responses according to their physicochemical characteristics (high or low MW, presence or absence of charged substituents and even, ramifications), EPS from lactobacilli with an evident positive health effect could be included in the diet of patients suffering diseases associated with an increased inflammatory status, such as allergy and inflammatory bowel disease, or other auto-immune disorders, as well as in functional foods formulated for the elder population.

EPS as Prebiotics

Prebiotics are non-viable substrates that function as nutrients for beneficial microorganisms harbored by the host (probiotic strains and indigenous microorganisms). Thus, a prebiotic should favor a metabolism biased towards health-promoting microorganisms within the indigenous ecosystem. According to the consensus statement by ISSAP (International Scientific Association for Probiotics and Prebiotics), the definition of a prebiotic has been recently modified to “a substrate that is selectively utilized by host microorganisms providing a health benefit” (Gibson et al., 2017). Health effects of these substances include benefits not only to the gastrointestinal tract (inhibition of pathogens and immune stimulation), but also to the cardiometabolism (reduction in blood lipid levels and effects upon insulin resistance), mental health (metabolites that influence brain function, energy and cognition) and bone (mineral bioavailability), among others (Gibson et al., 2017; Collins & Reid, 2016). In addition, the term synbiotics refers to a combination of both, probiotics and prebiotics, and a synergic interaction among them (Cencic & Chingwaru, 2010).

The catabolism of prebiotic carbohydrates by the metabolic activity of intestinal bacteria produces mainly three SCFA (Short Chain Fatty Acids): acetate, propionate and butyrate. Thus, the prebiotic substrates can induce increased values of the levels of these acids in healthy individuals as end products of human colonic bacteria metabolism (Lecerf et al., 2012). SCFA contribute to the normal large bowel function and prevent pathology through their actions in the lumen and on the colonic musculature and vasculature, and through their metabolism by colonocytes. The most abundant SCFA in the colon is acetate and represents, in general, more than half of SCFA detected in faeces (Louis et al., 2007). It has been shown that bifidobacteria can protect the host against enteropathogenic infections through the production of this acid (Fukuda et al., 2011). In addition, this acid and propionate are produced mainly by species belonging to the *Bacteroidetes* phylum, while butyrate is produced predominantly by the metabolism of some species of the *Firmicutes* phylum (Walker et al., 2005). Acetate has also been related to appetite reduction through its interaction with the central nervous system (Frost et al., 2014) and the three SCFA have been associated with intestinal anti-inflammatory properties (Tedelind et al., 2007). Particularly,

butyrate is thought to play a role in maintaining a normal colonocyte population and participates in the motility of the colon, reducing inflammation, increasing visceral irrigation, inducing apoptosis and inhibiting the progression of tumor cells, properties that contribute with the prevention of colorectal cancer (Canani, 2011; Zhang et al., 2010). It was also described that, as a result of a lower luminal pH, all SCFA can inhibit pathogens (Gibson & Roberfroid, 1995).

The most studied prebiotic compounds include inulin (composed by fructose), fructooligosaccharides (FOS), galactooligosaccharides (GOS) and glucooligosaccharides such as β -glucans. In this scenario and taking into account their analogous chemical composition, EPS from lactobacilli can be considered *per se* as prebiotic substances. In some cases, and depending on their chemical nature, they can be fermented by the gut microbiota and, in consequence, associated with a SCFA increase. For example, Zhang et al., (2017) found that the EPS produced by a strain of *Lb. plantarum* was able to improve the oxidative and health conditions of the host intestinal tract in an aging mice model induced with D-galactose. They reported high contents of nitrogen oxides together with gut microbiota regulating activities, evidenced by increased levels of SCFA and higher counts of some members considered beneficial (*Blautia* and *Butyricoccus*), together with a simultaneous reduction of microbial groups recurrent in humans with inflammatory diseases. Bello et al., (2001) and Korakli, Gänzle & Vogel (2002) revealed that EPS from strains of *Lb. sanfranciscensis* have bifidogenic effects on cultures of fecal bacteria and monocultures of *Bifidobacterium* (*Bf.*) *breve*, *Bf. bifidum*, *Bf. infantis* and *Bf. adolescentis*. More recent studies also demonstrated the bifidogenic properties of EPS isolated from strains of *Lb. rhamnosus* and *Lb. plantarum* (Das, Baruah & Goyal, 2014; Polak-Berecka et al., 2013). Hamet et al., (2016) evaluated the activity of kefir on intestinal bacterial populations in BALB/c mice and confirmed by DGGE its bifidogenic effect. Furthermore, a study by Tsuda and Miyamoto (2010), for which an EPS isolated from an EPS-overproducing mutant strain of *L. plantarum* was used, described an increase in the proliferation of a number of other known beneficial bacteria, including *Pediococcus* (*Ped.*) *acidilactici* ID-7 and 5885, *bL. casei* L-49, *Lb. plantarum* IFO 3070 and *Lb. delbrueckii* subsp. *lactis* 306701. Besides, the EPS from *Lb. plantarum* mutant can be used by the probiotic parental strain *Lb. plantarum* 301102.

In a recent study (Ale 2018), we demonstrated using a mice model that when added as a food ingredient in yogurts, the EPS from *Lb. fermentum* Lf2 exerted a possible prebiotic role reflected in an increase of SCFA levels (mainly acetate and butyrate) in faeces, accompanied by an increase in the levels (determined by qPCR) of the bacterial cluster XIVa of *Clostridium* (also known as *Cl. coccoides* group) that are known to produce these beneficial acids for health. When this EPS was combined with the probiotic strain *B. animalis* subsp. *lactis* INL1, a bifidogenic effect throughout the treatment was observed, improving the effect conferred by both individual ingredients, a fact that could be associated with a possible synergism between them suggesting a possible symbiotic role.

In all the cases described, it would be necessary to demonstrate the effective health benefit associated with the recent definition of prebiotic by means of human clinical trials or, at least, animal *in vivo* assays. Taking into account the current difficulty of some countries in carrying out clinical studies, as well as their high costs, it would seem reasonable that these results will be provided by research groups from highly developed countries.

Other Health Effects Associated with EPS

A recent perspective for EPS is related to their antitumor and antioxidant (property related to the anticancer activity) bioactivities, and their ability to inhibit the biofilm formation in pathogenic bacteria as well, as revised by Jiang and Yang (2018). In this review, it has been summarized that eight strains of *Lb. plantarum* had antitumor and antioxidant activities, being effective (at least *in vitro*) on colonic, liver, gastric, colon and pancreatic cancer, as well as on breast adenocarcinoma and oxidative stress. The authors suggested the use of these EPS as antitumor adjuvants. However, this claim is too hasty considering that anti-cancer properties are attributed to these molecules based exclusively on *in vitro* tests and, *in vivo* or human clinical studies result mandatory to effectively demonstrate these results, as mentioned above. In another recent work, Riaz et al., (2018) described the functional properties of the EPS from strains of *Lb. rhamnosus* isolated from breast milk. They found the EPS exhibited potent antioxidant activity, antitumor activity against Caco-2 cells and strong antibacterial activities against *E. coli* and *Salmonella* Typhimurium, corresponding to an excellent biofilm inhibition activity against *S. Typhimurium* *in vitro*. Furthermore, cell bound polysaccharides (CPS) were studied regarding their functional properties. Li et al., (2015) studied the CPS of a strain of *Lb. helveticus*, a HePS with an average MW of 1.83×10^2 kDa composed of glucose, mannose, galactose, rhamnose and arabinose. Preliminary *in vitro* tests revealed that this polymer significantly inhibited the proliferation of cancer cell lines. In another previous work, Li et al., (2014) showed that the same EPS presented potent antioxidant effects, chelating ability on ferrous ion and antibiofilm activities by inhibition of three biofilm forming foodborne pathogenic bacteria.

Antimutagenic activity (binding ability to different mutagens such as heterocyclic amines, 4-Nitroquinoline-N-oxide and 2-Nitrofluorine) from EPS-producing lactobacilli (*Lb. plantarum* and *Lb. rhamnosus*) was also reported (Tsuda, Hara & Miyamoto, 2008; Thapa & Zhang, 2009). In one of these works, the authors proposed a binding mechanism of ion-exchange and hydrophobic bonds by which the EPS would bind mutagens in the intestine (Tsuda et al., 2008).

In addition, there is some evidence that certain EPS have a protective role against microbial toxins, as reported for the EPS of *Lb. rhamnosus* ATCC9595, with demonstrated cholera toxin-binding activity (Kim et al., 2006). Similarly, kefiran counteracted the cytotoxic effect of extracellular toxins produced by *Bacillus cereus* in cell cultures (Ruas-Madiedo et al., 2010).

EPS have also been related to alleviate acetic acid-induced experimental colitis model in rats (Şengül et al., 2006). In this work, the effect of the EPS-producing *Lb. delbrueckii* subsp. *bulgaricus* B3 strain was compared with another one with low ability to synthesize EPS (*Lb. delbrueckii* subsp. *bulgaricus* A13), analyzing the role of the EPS dose on colitis. Authors observed that those rats treated with both EPS-producing strains presented lower histologic scores of colonic damage than the control group, demonstrating an improvement by *Lb. bulgaricus* B3. Consequently, a probiotic role associated with the high production of EPS was suggested for this particular strain, showing its therapeutic potential.

An important aspect of the EPS functionality obeys to their general resistance to gastrointestinal conditions (Khalil et al., 2018) resulting from the action of the gastrointestinal tract of the host. Sönmez, Önal Darılmaz, and Beyatli (2018) evaluated the protective effects

of EPS production on resistance to gastrointestinal digestive conditions and to oxalate by probiotic strains of the species *Lb. rhamnosus*, *Lb. fermentum* and *Lb. brevis*. The high-EPS-producing *Lb. fermentum* IP5 and *Lb. brevis* YG7 strains showed high oxalate-degrading activity, whereas the low-EPS-producing strain *Lb. fermentum* BP5 demonstrated low ability to degrade oxalate. These results suggest that dietary supplementation with *Lb. fermentum* IP5 could prevent oxalate stone disease, assuming that the EPS produced by this strain is the responsible of this beneficial response.

EPS from lactobacilli have also been related to the adsorption of heavy metals. For example, Feng et al., (2012) demonstrated the biosorption of Pb(II) ions by an EPS isolated from *Lb. plantarum* 70810. EPS also demonstrated antioxidant and metal ion chelating activities (Li et al., 2014; Kodali & Sen, 2008). EPS from *Lb. rhamnosus* E/N (Polak-Berecka et al., 2013), *Lb. plantarum* C88 (Zhang et al., 2013), *Lb. plantarum* LP6 (Li et al., 2013) and *Lb. helveticus* MB2-1 (Li et al., 2014) have all exhibited moderate free radical scavenging and metal ion chelating activities in *in vitro* systems.

Some other studies associate the administration of EPS with modifications on the cardiometabolism. For example, spontaneously hypertensive stroke-prone rats fed with kefir exhibited significantly lower blood pressure and lower levels of cholesterol and triglycerides in serum and liver, when compared to untreated rats (Maeda et al., 2004). Additionally, EPS fractions from *Lb. casei* LC2W exhibited a moderate reduction in blood pressure (Ai et al., 2008), without significantly affecting the heart rate. In this direction, Tok and Aslim (2010) suggested that an EPS isolated from *Lb. delbrueckii* subsp. *bulgaricus* was able to sequester cholesterol from conditioned media *in vitro*. Sasikumar et al., (2017), who characterized the EPS extract produced by the strain *Lb. plantarum* BR2, described that this polymer consisted of a HMW glucomannan with antioxidant and lowering cholesterol activities, together with antidiabetic potential.

CHEMICAL STRUCTURE AND FUNCTIONAL/ TECHNOLOGICAL PROPERTIES RELATIONSHIP

Many structural factors were reported to affect EPS properties, such as monosaccharide composition, molecular size, glucosidic bond, charge, presence of side chains and rigidity of the molecules (Salazar et al., 2014). From their functional aspects, EPS having negative charges (phosphate or sulfate), glucose and/or galactose in their composition, and/or low molecular weights were shown to act as mild stimulators of immune cells, whereas neutral polymers with higher molecular weights exhibited a suppressive profile (Caggianiello, Kleerebezem & Spano, 2016; Yasuda, Serata & Sako, 2008). In general, small negative EPS are thought to be able to stimulate professional immune cells and larger neutral EPS believed to possess more immune-suppressive qualities (López et al., 2012; Hidalgo-Cantabrana et al., 2012). Besides, an interrelation between the types of bonds of the HePS and their rigidity has also been found: $\beta(1,4)$ bonds result in more rigid chains than $\alpha(1,4)$ or $\beta(1,3)$ bonds. In consequence, β bonds are able to give more chain stiffness compared to α bonds (Jolly et al., 2002). Side chains can also affect stiffness and, therefore, increase their efficiency as thickeners.

It was also described that EPS surrounding the bacterial surface, mainly those having a high MW, might reduce adherence to intestinal cells, and even to abiotic surfaces, due to shielding of surface macromolecules acting as adhesins. For example, deletion of the *cps2*-like gene cluster on *Lb. plantarum* Lp90 improved its adhesion to Caco2 cells in comparison with its parental strain (Lee et al., 2016). In accordance to this result, Dertli, Mayer, and Narbad (2015) suggested that EPS may hinder molecular interactions with host epithelial membranes. HMW-EPS reduce the adhesion capacity of the EPS-producing strain *in vitro*, which may also have a negative impact on intestinal colonization, as demonstrated for some *Bifidobacterium* strains (Castro-Bravo et al., 2017). In fact, the same conclusion was previously reported for *Lb. rhamnosus* GG through deletion of the priming-GTF, which abolished the synthesis of a long, galactose-rich EPS (Lebeer et al., 2009). However, while the non EPS-producing mutant presented good adhesion *in vitro*, an *in vivo* study showed that it was more sensitive toward host innate defenses; thus the EPS would favor its persistence in the murine gut (Lebeer et al., 2011). Branches may also be related to EPS functionality, Huazano-García and López (2013) suggested that there is a relationship between the structure of fructans (chain length and branches) with the production of SCFA. They observed that branched fructans induced higher levels of SCFA than linear polysaccharide.

Apart from the influence of the chemical characteristics of these molecules on their functionality, their impact on the technological properties was studied as well. Some structure/function relationships have been proposed, for example, polysaccharides that present $\beta(1,4)$ linkages were associated with stiffer chains able to provide high consistency to the food matrices. Those containing $\alpha(1,6)$ linkages in the main chain, such as dextran, presented both good thickening and stabilizing effects (Zannini et al., 2016). Furthermore, polysaccharides with high molecular masses and a stiff conformations are important in order to obtain an increase in viscosity (De Vuyst & De Vin, 2007).

Other important physicochemical characteristic is the degree of branching, which may contribute to the stiffness of the polymer, while their primary structure (MW, monomer composition, type of linkages, presence of side-groups) also affect the rheology of EPS solutions (Tuinier et al., 2001).

Regarding the influence of the charge on the technological properties, it has been described that neutral EPS contributed to viscosity but not to elasticity. The contrary behavior was observed for negatively charged EPS which were able to interact with positive charges of caseins (Duboc & Mollet, 2001). The amount of EPS is not always the most important parameter for viscosity, in contrary to its structure which is the determinant for the interactions with casein. For this reason, although LAB synthesize EPS in small quantities, these could be enough to deliver rheological changes on the texture of dairy products.

When neutral or positively low charged EPS interact with caseins, a depletion effect can occur, leading to the formation of protein and EPS aggregates in the serum phase (Buldo et al., 2016; Costa et al., 2012). This phenomenon has been related to decreasing viscoelastic properties due to the interference of the EPS with the protein network formation, or increasing viscoelastic properties, as a consequence from the formation of a dense casein network (Amatayakul et al., 2006a; Hassan et al., 2003; Buldo et al., 2016). The presence of EPS in the serum phase also leads to higher water-binding capacity, resulting in lower syneresis and high viscosity (Gentès, St-Gelais & Turgeon, 2013). Future studies are required to establish clearer structure-functional/technological properties relationship.

CONCLUSION

An increasing number of EPS produced by *Lactobacillus* strains have been isolated and characterized in the last few years, evidencing a high diversity among them. Despite the unknown physiological role of EPS in the producing bacteria, it seems to be related to the recognition of the external environment, thus exerting a protective effect.

The integral characterization (structure, MW, presence of charged residues, type of branches, etc.) of these macromolecules is essential when EPS (as an ingredient) or the EPS-producing strain is included in a food matrix, since recent studies strongly associated these characteristics with their rheological and health-promoting properties. In this way, the characterization of the EPS molecule to be added in a food matrix would allow to infer the techno-functional properties of the final product.

Although their low production compared with EPS produced by non-LAB bacteria, EPS from lactobacilli are, from their technological point of view, able to improve the rheological properties of dairy products. According to their structural and chemical properties, in some cases, even present in low concentrations in the final product, they are adequate to positively change the rheology, as occurs in some low-fat cheeses. Furthermore, some EPS produced by lactobacilli have the ability to exert a wide range of beneficial effects on human health: immunomodulation, prebiotic role, antioxidant, anticarcinogenic, among others. As these properties were extensively demonstrated *in vitro* and at high EPS concentrations, an interesting challenge for the future will be the elucidation of the physiological mechanisms of actions and the demonstration, by *in vivo* studies, of the real effect on the intestinal environment when the EPS are included in applicable concentrations in a real food matrix.

The use of HoPS or HePS from *Lactobacillus* or the EPS-producing bacteria could have a promising future for their application as potential techno-functional ingredients for the design of novel foods. An interesting alternative is the optimization of the environment conditions to increase the yield of EPS when they are to be used as food ingredients. A further possibility is to use engineered food-grade lactobacilli strains with the aim of specifically modifying certain genes associated with the polymer synthesis, for the design of new fermented foods.

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Chapter 304

SPORE-FORMING LACTIC ACID BACTERIA AND THEIR ABILITIES FOR UTILIZATION

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ABSTRACT

Nowadays, many studies have reported the potential spore-forming lactic acid bacteria (SFLAB) with the high performance of lactic acid production and high specificity of lactic acid isomers. This group of bacteria belongs to the genera *Bacillus* and *Sporolactobacillus*. Most of the SFLAB are homofermentative bacteria which can only produce lactic acid from sugar. Additionally, these SFLAB strains are dominant to produce an optically pure D(-)- or L(+)-lactic acid which is preferred to the specific application, especially in the manufacturing of biodegradable and biocompatible polylactic acid (PLA) which can be a replacement of synthetic plastics derived from petroleum resources. Considering the general characteristics of SFLAB, both genera are endospore-forming, rod-shaped, and gram-positive bacteria. The members of the genus *Bacillus* include *B. coagulans*, *B. stearothermophilus*, *B. licheniformis*, *B. subtilis*, and *Bacillus* sp. All of these *Bacillus* species could grow and form endospore under aerobic condition. On the other hand, the genus *Sporolactobacillus* differs from strains of *Bacillus* species in its response to oxygen, because the optimal growth has been found in microaerophilic or anaerobic condition. At the present, increasing the *Sporolactobacillus* species has been reported, including *S. inulinus*, *S. laevolacticus*, *S. nakayamae*, *S. racemicus*, *S. terrae*, *S. kufoensis*, *S. lactosus*, *S. putidus*, *S. vineae*, *S. pectinovorans*, *S. shoreicoticis*, *S. shoreae* and *S. spathodeae*. A few years ago, the novel genus

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Terrilactibacillus was discovered and reported as a potential spore-forming lactic acid bacterium. The type species is *Terrilactibacillus laevilacticus* which has individual characteristics compared to the others. Currently, SFLAB have been applied in the wide range of applications, including biochemical compounds, probiotics, and commercial enzymes. This chapter describes the recent status of SFLAB strains and their advantages which could be found from the studies and their applications.

INTRODUCTION

Generally, lactic acid production has been well recognized from the biological conversion of carbohydrate by lactic acid bacteria (LAB). Plenty information of this bacteria group can be easily found. The phenotypic characterization of this group is Gram-positive, fastidious, non-spore forming rods or cocci which mainly produce lactic acid from carbohydrates under anaerobic environment. The group members of LAB comprise of genera *Lactobacillus*, *Leuconostoc*, *Pediococcus*, and *Streptococcus* (Lui et al., 2014). At the present, spore-forming lactic acid bacteria (SFLAB) are one of the potential lactic acid producers, including the genera *Bacillus* and *Sporolactobacillus*. Historically, the definition of a spore-forming organism was originally referred to the genus *Bacillus* that are able to form endospores which are heat-resistant bodies that were not easily killed by mere boiling (Cohn, 1876; Koch, 1876). The ability to form endospores of the bacteria results in resistance to unfavorable growth conditions. Later, the first classification of endospore-forming bacteria was proposed by de Bary (1884) and by Hüppe (1886) but the generic name *Bacillus* was more used for various rod-shaped bacteria (Fritze & Clausen, 1995). However, to define as SFLAB, the genus *Bacillus* was respected as comprising spore-bearing rod producing lactic acid, which is facultative anaerobic or aerobic catalase positive, following the 8th edition of Bergey's Manual Determinative Bacteriology (Abriouel et al., 2011). Another SFLAB member is defined to the genus *Sporolactobacillus*. These bacteria strains were classified using the phylogenetic data between *Lactobacillaceae* and *Bacillaceae* (Nakayama & Sakaguchi, 1950). The phenotypic characterization was described as Gram-positive, microaerophilic, mesophilic rods, and catalase negative. Comparing to LAB, the group members of SFLAB were smaller discovered. Nowadays, some *Bacillus* and *Sporolactobacillus* species have been reported as lactic acid producer, including *B. coagulans*, *B. stearothermophilus*, *B. licheniformis*, *B. subtilis*, *Bacillus* sp., *S. inulinus*, *S. laevolacticus*, *S. nakayamae*, *S. terrae*, *S. kofuensis*, *S. lactosus*, *S. putidus*, and *Sporolactobacillus* sp. (Abdel-Rahman et al., 2013; Doores, 2014). Besides, most of SFLAB strains produced an optically pure lactic acid isomer (D(-) or L(+)-lactic acid) with a high lactic acid titer, depending on their cultivation conditions. Additionally, the recent novel genus *Terrilactibacillus* has been found as a promising D-lactic acid producer. This finding indicates that the novel strains could be a candidate for D-lactic acid production (Prasirtsak et al., 2016; 2017). Besides, the several performances of SFLAB to produce a wide range of products using the alternative substrates are now being developed.

Recently, the spore-forming lactic acid bacteria are being explored for the variety of applications. Besides their ability to produce lactic acid, the probiotics aspect is being widely studied. Additionally, another feature of this SFLAB group is the source of enzymes which can be applied in food and non-food industries. This information indicates that SFLAB could

be a candidate for a variety of industry. This chapter updates the research regarding the spore-forming lactic acid strains and highlights the utilization of SFLAB strains in various applications.

SPORE-FORMING LACTIC ACID BACTERIA

SFLAB are microorganisms which mainly produce lactic acid and relates to lactic acid bacteria (LAB) strains. In particular, due to the remarkable and resistant dormancy of their spores and response to oxygen these characteristics are used to differentiate between SFLAB and LAB. In order to obtain interesting strains, several environment resources, including soil, foods, and feed were used for screening and isolation (Doores, 2014; Chang & Stackebrandt, 2014; Abriouel et al., 2011). Previously, the genus *Bacillus* and *Sporolactobacillus* were classified as a member of SFLAB. Besides, some basic characterizations of these 2 genera were different. The genus *Bacillus* is facultatively anaerobic or aerobic and catalase positive. Most of the *Bacillus* strains are able to grow and ferment the hexoses and pentoses to L(+)- or DL(-)-lactic acid. Moreover, they can produce lactic acid in the thermal fermentation (Abdel-Rahman et al., 2013). On contrary, *Sporolactobacillus* strains were described as the mesophilic, catalase negative, microaerophilic, and produce D(-)-lactic acid by a homofermentative pathway (Doores, 2014; Chang & Stackebrandt, 2014). Recently, the novel genus *Terrilactibacillus* has been discovered and published as a Gram-positive, catalase-positive, facultatively anaerobic, spore-forming, rod-shaped bacterium. It was found as the homofermentative D(-)-lactic acid producer (Prasirtsak et al., 2016). Additionally, their differentiating characteristics were also clarified (Table 1).

The Genus *Bacillus*

The genus *Bacillus* has long been known to be spore-forming bacteria due to its endospore formation in adverse environments. The generic name *Bacillus* was established by a German Botanist, Ferdinand Cohn, who has discovered rod-shaped bacteria which grow in filaments (Cohn, 1872). Later, in this genus the resting stages resistant to various adverse environments were detected; it was not killed by heat (Cohn, 1876; Koch, 1876). According to its heat-resistant behavior, it was found that the genus *Bacillus* was able to form endospores that are more resistant than vegetative cells to heat, drying, and other destructive agents (Gordon et al., 1973). The classification of *Bacillus* species was originally proposed by de Bary (1884) and Hüppe (1886). However, the *Bacillus* lactic acid producing strains were officially published in the Bergey's Manual of Determinative Bacteriology. According to the publication, the genus *Bacillus* was defined as the spore-forming rods capable of lactic acid production. Additionally, the general characterizations of the strains are Gram-positive, facultatively anaerobic or aerobic, and catalase positive (Abriouel et al., 2011; Zeigler and Perkins, 2008).

Bacillus strains have been utilized in a wide range of the applications, including enzyme technology, probiotics, food industry, medicine, cosmetics, agriculture, and chemistry (Poudel et al., 2016). In order to obtain the new functions and improve existing applications,

the novel *Bacillus* strains have been continuously screened. Recently, the *Bacillus* strains have been recognized as a potential L(+)-lactic acid producing strain. The list of *Bacillus* lactic acid producing strains includes *B. coagulans*, *B. stearothermophilus*, *B. licheniformis*, *B. subtilis*, and new isolated *Bacillus* species. All these *Bacillus* strains produced an optically pure L(+)-lactic acid (97 - 100%) (Poudel et al., 2016). Interestingly, *Bacillus* species are able to grow and produce L(+)-lactic acid by using a simple mineral salts medium with a small amount of yeast extract (Poudel et al., 2015; Wang et al., 2011; Heriban, 1993). Furthermore, this species can tolerate high temperatures (45 - 60°C) and pH (5.0 - 9.0) (Thitiprasert et al., 2017; Poudel et al., 2015; Ma et al., 2014; Ye et al., 2013; Ou et al., 2009; Ramos et al., 2000). These characteristics indicate the several advantages can be gained in the L(+)-lactic acid fermentation by these *Bacillus* species. First, to operate the fermentation at high temperature could reduce the cooling cost, comparing to mesophiles which require the temperature control during fermentation (Abdel-Rahman et al., 2013). Second, to control the high-temperature fermentation would prevent contamination problems (Ye et al., 2013). Third, there are some researches that have claimed that the rate of L(+)-lactic acid production could be improved by operating the fermentation at high temperature (Heriban et al., 1993). Fourth, to use the thermophilic *Bacillus* species could provide the benefit on the simultaneous saccharification and fermentation (SSF) of lignocellulosic biomass with hydrolytic enzymes (cellulase, amylase) at an optimum temperature (Budhavaram & Fan, 2009; Maas et al., 2008a; Ou et al., 2011; Patel et al., 2006). In addition, the thermotolerant *Bacillus* species, including *B. coagulans* and *B. licheniformis* have been used for open fermentation using nonsterile media at high temperature (Wang et al., 2011; Wang et al., 2019).

Table 1. Characteristics of *Bacillus*, *Sporolactobacillus* and *Terrilactibacillus*

Characteristic	<i>Bacillus</i>	<i>Sporolactobacillus</i>	<i>Terrilactibacillus</i>
Cell form	Rods	Rods	Rods
Endospore position	Terminal	Terminal/subterminal	Terminal
Oxygen requirement	Aerobe or facultative anaerobe	Facultative anaerobe	Aerobe or facultative anaerobe
Growth temperature (°C)	Wide range (psychrophilic to thermophilic species)	15-45	20-45
pH range	Wide range (acidophilic to alkaliphilic species)	5-8	5-8.5
Maximum NaCl (%) for growth	Some are halophilic, some are salt tolerant	10	3
Catalase production	+	-	+
Oxidase	+/- depended on species	-	-
Nitrate reduction	+/- depended on species	-	+
Homolactic acid fermentation	Depended on species and cultivation conditions	+	+
Isomer of lactic acid	Most optically pure L(+)-lactic acid	D(-)-lactic acid	D(-)-lactic acid
G+C mol %	32-69	43-50	42.6

In sugar metabolism, the *Bacillus* species are able to metabolite hexose and pentose sugars via the Embden-Meyerhof-Parnas and the pentose-phosphate pathway, respectively. The maximum lactic acid yield that could be achieved was up to 1 g/g-consumed sugar (Patel et al., 2006; Ye et al., 2013, 2014). Currently, the alternative carbohydrate resources have been extensively determined for lactic acid production using the *Bacillus* strains. A variety of crops have been being investigated for lactic acid production, including lignocellulosic

biomass (e.g., crop residues), sucrose (e.g., sugar cane and beet molasses), starchy materials (e.g., cassava, potato, cereal-based products), and food-wastes (Abdel-Rahman et al., 2013; Poudel et al., 2016). However, the use of these alternative carbohydrates is still limited; in particular these materials require pretreatments that form the inhibitor compounds (e.g., furfural, 5-hydroxymethylfurfural, and some organic acids) resulting in decreasing the performance of microbial lactic acid production (Jönsson and Martín, 2016). On the other hand, there are some reports that have investigated the fermentation of lactic acid in lignocelluloses containing inhibitors medium. It was found that the *Bacillus* strains could tolerate to the pretreatment inhibitors and convert them to less-toxic substance. Especially, *B. coagulans* has been reported the resistant performance of the inhibitors at certain levels (Peng et al., 2013; Ye et al., 2013; Bischoff et al., 2010; Zhang et al., 2014).

Commonly, lactic acid bacteria producing strains employ a facultative anaerobic environment to produce lactic acid because of their lack of an oxygen electron acceptor, leading to a small amount of lactic acid production although they are able to grow in an environment presenting oxygen (Hofvendahl & Hahn-Hägerdal, 2000; Bobillo et al., 1991). Considering to the *Bacillus* strains, they can produce lactic acid as a main metabolite either under strict anaerobic or aerobic condition (Thongpim et al., 2014; Thitiprasert et al., 2017).

In view of the aforementioned studies, it should be noted that the *Bacillus* lactic acid producing strains have been gained popularity as an interesting lactic acid producer. Particularly, *B. coagulans*, *B. subtilis*, *B. licheniformis*, and *B. thermoamylovorans* have been recognized as the promising L(+)-lactic acid strain (Poudel et al., 2016). Furthermore, the *Bacillus* species are recently determined for other applications, including probiotics, thermostable enzymes, and antimicrobial activity (Konuray & Erginkaya, 2018; Elshaghabee et al., 2017; Pandey 2017; Tolieng et al., 2018).

The Genus *Sporolactobacillus*

A spore-forming and homofermentative lactic acid bacteria in the genus *Sporolactobacillus* was originally isolated from chicken feed by Kitahara and Suzuki (1963). *Sporolactobacillus inulinus*, the type species was a Gram-positive, catalase negative, microaerophilic, mesophilic rods, producing exclusively D(-)-lactic acid, motile by a small number of peritrichous flagella and formed oval endospores in the terminal position (Kitahara and Suzuki, 1963; Suzuki & Kitahara 1964). Later, another species of spore forming lactic acid bacteria were isolated from the soil of the plant rhizospheres (Nakayama & Yanoshi, 1967a, 1967b). The species showed different catalase activity and an enantiomeric form of lactic acid production. In the group of catalase-positive which consisted of *B. laevolacticus* and *B. racemilacticus*, optically pure D(-)-lactic acid and DL-lactic acid were produced, respectively. For the catalase negative strains which related to *S. inulinus* the production of DL-lactic acid were found. However, the bacterial names proposed by Nakayama & Yanoshi (1967a) were not included in the Approved Lists of Bacterial names (Skerman et al., 1980). According to the proposal of Andersch et al. (1994), they determined the strains of *B. laevolacticus* genetically and phenotypically distinct from other lactic acid-producing, aerobic, spore-forming bacteria. Then the name *B. laevolacticus* was revived and assigned to the same taxon as it was originally located, following the International Code of Nomenclature of Bacteria. Based on the properties of the single strain resulted in the name *B. racemilacticus*

could not be validated (Andersch et al., 1994). In the year 2006, from the results of phylogenetic analyses, as well as chemotaxonomic and phenotypic characterization revealed that *B. laevolacticus* was not included in the cluster of the genus *Bacillus* but should be reclassified into the genus *Sporolactobacillus*. Therefore, *B. laevolacticus* was reclassified as *S. laevolacticus* comb. Nov. (Hatayama et al., 2006). Initially, the species were considered to be similar to *Bacillus* and *Lactobacillus* (Kitahara & Lai, 1967). Furthermore, there are more studies on the phenotypic and genotypic characterizations of the strains. Studies have indicated that the *Sporolactobacillus* species show a separate phylogenetic position and differ in phenotypic properties from the genera *Bacillus* and *Lactobacillus* (Fox et al., 1980; Ash et al., 1991; Farrow et al., 1994; Suzuki & Yamasato, 1994; Yanagida et al., 1997). According to the previous findings, the members of the genus *Sporolactobacillus* could be divided into 2 major clusters, including catalase positive and catalase negative cluster. *S. laevolacticus* is a member in the catalase positive cluster which referred to mesophilic, gram-positive, an optically pure D(-)-lactic acid-producing, motile, and spore-forming organism (Andesch et al., 1994; Chang & Stackebrandt, 2014). In the cluster of catalase-negative bacteria, the *Sporolactobacillus* species are included *S. inulinus*, *S. nakayamae* subsp. *nakayamae*, *S. nakayamae* subsp. *racemicus*, *S. terrae*, *S. kufoensis*, and *S. lactosus* (Yanagida et al., 1997). Recently, more novel *Sporolactobacillus* species have been discovered, that include *S. putidus* (Fujita et al., 2010), *S. vineae* (Chang et al., 2008), *S. pectinovorans* (Lan et al., 2016), *S. shoreicoticis* (Toleing et al., 2017), *S. shoreae*, and *S. spathodeae* (Thamacharoensuk et al., 2015).

Since these studies, the screening and isolation of the new *Sporolactobacillus* species have been successfully done. It was found that simple techniques can be applied. From various environmental resources, e.g., natural samples (soil and tree barks), spoiled foods, and feed can be heated at high temperature (~ 80°C) to eliminate the asporogeneous cells (Yanagida & Suzuki, 2009). In the enrichment step, the GYP medium containing glucose, yeast extract, peptone, and other minerals have been used for the cultivation of the isolates. For the selection, both MRS and GYP medium have been used. However, the previous study reported that the *Sporolactobacillus* species require a non-complex medium in particular GYP containing CaCO₃ medium (Chang & Stackebrandt, 2014). Until now, the phenotypic and molecular analysis of all *Sporolactobacillus* species have been clarified (Table 2). All of them are homofermentative D(-) or DL-lactic acid producer with using a variety of carbohydrates, e.g., glucose, fructose, and sucrose. Additionally, other medium components are required for growth and product formation. Most of the essential nitrogen sources, e.g., yeast extract, peptone, and inorganic nitrogen sources (NH₄Cl, NaH₂PO₄), play an important role on the concentration and productivity of lactic acid. While the free amino acids and peptides also influence in the fermentation of *Sporolactobacillus* strains, the lactic acid production might be limited by the concentration of free amino acid in the medium. The trace elements could affect lactic acid production in particular phosphate is necessary for the phosphorylation in a biological reaction which causes a significant product formation. Additionally, lactate dehydrogenase activity is induced by Mn (Klotz et al., 2017). At present, many studies have investigated using the alternative nutrition resources, e.g., protein hydrolysate from agricultural wastes for replacing the complex nutritional resources; especially yeast extract. However, lower product yield and productivity were found, compared with using yeast extract supplemented medium (Lu et al., 2009; Altaf et al., 2005).

Table 2. Differential characteristics of the *Sporolactobacillus* species*

Characteristic	1	2	3	4	5	6	7	8	9	10	11	12
Optimum temp. (°C) for growth	30	30	37	37	30	30	30	30	30	30	37	30
Optimum pH for growth	6.0	6.0 - 7.0	5.0	5.0	6.0 - 7.0	6.0 - 7.0	6.0 - 7.0	6.0 - 7.0	6.0 - 7.0	6.0 - 7.0	6.0	ND
Growth in 2% NaCl	w	-	-	+	+	+	+	+	+	w	w	+
Growth in 3% NaCl	-	-	-	+	+	+	+	+	+	-	-	+
Acid production from:												
D-Cellobiose	+	-	-	-	-	-	-	-	+	w	-	ND
D-Galactose	+	+	+	-	-	-	-	-	+	-	-	+
D-Lactose	-	-	-	-	-	-	-	-	-	w	ND	-
D-Maltose	-	-	w	+	-	-	+	-	+	+	-	w
D-Sorbitol	-	-	-	w	+	-	+	-	-	+	-	-
Starch	-	-	-	-	-	-	-	-	-	w	-	-
Sucrose	+	-	+	+	+	+	+	+	+	+	+	+
D-Trehalose	-	-	+	w	+	+	+	+	+	+	-	+
Enzyme activity												
Acid phosphatase	w	w	+	w	w	w	-	-	w	-	ND	+
Cystine arylamidase	w	-	-	-	+	-	-	-	w	-	ND	-
Esterase (C4)	-	-	-	-	-	-	-	-	w	-	ND	w
α -Galactosidase	-	-	-	-	-	-	-	-	+	-	ND	+
β -Galactosidase	-	-	-	-	-	-	-	-	+	w	ND	+
α -Glucosidase	-	-	+	w	-	-	-	-	w	-	ND	ND
Leucine arylamidase	+	+	w	+	+	+	+	-	+	+	ND	w
Naphthol-AS-BI-phosphohydrolase	-	-	-	-	+	-	+	-	w	-	ND	w
Valine arylamidase	+	+	-	+	+	+	+	-	+	-	ND	w

Strains: 1, *S. shoreae* BK92^T; 2, *S. spathodeae* BK117-1^T; 3, *S. putidus* JCM 15325^T; 4, *S. vineae* JCM 14637^T; 5, *S. inulinus* JCM 6014^T; 6, *S. terrae* JCM 3516^T; 7, *S. nakayamae* subsp. *nakayamae* JCM 3514^T; 8, *S. kofuensis* JCM 3419^T; 9, *S. nakayamae* subsp. *racemicus* JCM 3417^T; 10, *S. laevolacticus* JCM 2513^T; 11, *S. pectinivorans* GD201205^T; 12, *S. shoreicorticis* MK21-7^T. +, Positive; w, weakly positive; -, negative reaction;

ND, no data.

*Data from Thamacharoensuk et al. (2015), Lan et al. (2016), and Tolieng et al. (2017).

Recently, the members of genus *Sporolactobacillus* have been extensively studied their performance on another application, including probiotics. Furthermore, the high efficient D(-)-lactic acid-producing *Sporolactobacillus* strains are still being explored in order to obtain the strains are able to produce high lactic acid concentration and optically pure D(-)-lactic acid for supporting the synthesis of polylactic acid (PLA) application.

The Novel Genus *Terrilactibacillus*

The novel genus *Terrilactibacillus* was firstly reported by Prasirtsak et al. (2016) in their screening and isolation of lactic acid-producing bacteria from soil samples in Thailand. The strain NK26-11^T was isolated and defined as a Gram-positive, catalase-positive, facultatively anaerobic, endospore-forming, rod-shaped, and motile by means of peritrichous flagella. The isolate showed the performance of homofermentative D(-)-lactic acid production from glucose medium. Based on its 16S rRNA gene sequence analysis, it was found that strain NK26-11^T was located between the genera *Bacillus* and *Sporolactobacillus*. *Terrilactibacillus laevilacticus* is a type species for the genus *Terrilactibacillus*. Later, during more screening and isolation on D(-)-lactic acid-producing bacteria conducted by Prasirtsak et al. (2017), *T. laevilacticus* SK5-6 as a potential D(-)-lactic acid producer was also isolated. The strain was studied the fermentation optimization in 5 L stirred fermenter using glucose medium. The results indicated that this strain could be used in industrial fermentation. Furthermore, the 2-phase fermentation approach revealed that the use of catalase-positive bacteria provides the advantage of homofermentative lactic acid production (Prasirtsak et al., 2017).

PERFORMANCE OF SPORE-FORMING LACTIC ACID BACTERIA IN VARIOUS APPLICATIONS

Lactic Acid Production

Lactic acid has long been known as a utility organic acid which can be applied in a variety of applications such as in food and non-food industries. In the field of food industry, lactic acid is well known to be used as food acidulant, preservative, flavoring, pH regulation, and mineral fortification. Lactic acid can be used as active ingredients in cosmetics industry which has the functionality as moisturizers, skin-lightening agents, humectants, anti-acne agents, and skin-rejuvenating agents (Wee et al., 2006). Considering its chemical functional groups containing a carboxylic and a hydroxy group; lactic acid can be utilized as precursors in the formulation of cleaning reagents, green solvents, and descaling agents. Moreover, lactic acid is able to be raw materials for synthesizing the useful chemicals such as propionic acid, acetic acid, acrylic acid, etc. (Dimerci et al., 1993; John et al., 2007). Currently, lactic acid is an important chemical which used as a monomer for the production of biodegradable and biocompatible polylactic acid (PLA). From the distinctive feature of PLA, it has received wide attention for utilizing in several applications, including pharmaceutical (prosthetic devices, sutures), textile (protective clothing), packaging and labeling (Wee et al., 2006; Martinez et al., 2013). Naturally, lactic acid has a chiral carbon atom which exists in two

enantiomeric forms, including L(+)-lactic acid and D(-)-lactic acid. Because its optically pure isomer affects a polymer grade of PLA; therefore, the use of optically pure isomer is more preferred than a racemic mixture of lactic acid. The recent lactic acid production is manufactured from the biotechnological process. Lactic acid bacteria (LAB) are a mandatory group as the lactic acid producer in particularly the genus *Lactobacillus*. Several advantages could be obtained from the microbial lactic acid fermentation such as high yield and productivity of lactic acid production. Moreover, the biotechnological lactic acid production provides high specificity to produce an optically pure L(+)- or D(-)-lactic acid (Pandey et al., 2001). However, the limitations and challenges of lactic acid fermentation are being continuously discussed. This includes the use of renewable resources (cellulosic sugar, food carbohydrates) as substrates, low pH inhibition, contamination due to the mesophilic characteristic of LAB strains, and decrease optical purity (Abdel-Rahman et al., 2016). Therefore, numerous researchers have studied the isolation of new microbes from natural resources and also the improvement of existing microbes by molecular technology.

Table 3. Lactic acid production by the recent strains of spore-forming bacteria

Strain	Substrate	Fermentation mode	Lactic acid				Reference
			Titler (g/L)	Yield (g/g)	Productivity (g/L·h)	%ee (Isomer)	
<i>B. coagulans</i> IPE22	Non-sterile soluble starch	SLSF ^a Batch	68.72	0.99	1.72	N/D ^b	Wang et al., 2019
<i>B. coagulans</i> arr4	Granulated sugar and yeast extract	Exponential fed-batch	206.81	0.97	5.30	99.11(L)	Coelho et al., 2018
<i>B. coagulans</i> NRBC 12714	Glucose	Open batch	99.84	0.99	3.99	99.9 (L)	Ma et al., 2016
<i>B. coagulans</i> NRBC 12714	Xylose	Open batch	92.82	0.93	2.90	99.8 (L)	Ma et al., 2016
<i>B. coagulans</i> NRBC 12714	Corn stover hydrolysate	Open batch with	98.25	0.93	2.90	> 99.5 (L)	Ma et al., 2016
<i>B. coagulans</i> NRBC 12714	Corn stover hydrolysate	Open cell-recycle and repeated batch	93.76	0.93	3.80	> 99.5 (L)	Ma et al., 2016
<i>B. coagulans</i> NRBC 12714	Corn stover hydrolysate	Open cell-recycle and continuous	92	0.92	13.80	> 99.5 (L)	Ma et al., 2016
<i>Bacillus</i> sp. BC-001	Glucose	3000 L Batch	104.11	0.87	6.31	100 (L)	Thitiprasert et al., 2017
<i>B. licheniformis</i> BL1	Glucose	2 L Batch	Up to 130	0.86	Up to 7.80	> 99 (L)	Wang et al. 2011
<i>S. nakayamae</i>	sugar, yeast extract, mineral salts	Multipulse fed-batch	122.41	N/D	3.65	N/D ^b (D)	Beitel et al., 2017
<i>S. nakayamae</i>	Sucrose and peanut flour	Batch	112.93	0.98	1.57	98.75 (D)	Beitel et al., 2016
<i>Sporolactobacillus</i> sp. CASD	Glucose and peanut meal	30-L Pulse fed-batch	207	0.93	3.80	99.3 (D)	Wang et al., 2011
<i>S. laevolacticus</i> JCM 2513	Raw cane sugar	Continuous	67.3	0.98	11.20	N/D ^b (D)	Mimitsuka et al., 2012
<i>T. laevilacticus</i> SK5-6	Glucose	5-L Batch	92.60	0.84	1.93	99.56 (D)	Prasirtsak et al., 2017

Note: ^aOne-step simultaneous liquefaction, saccharification and fermentation.

^bThere is no report for the quantity of isomeric lactic acid purity.

Currently, SFLAB are gained attractive attention for high performance of lactic acid production with optically pure lactic acid isomer (Table 3). The genus *Bacillus* is the most used as a L(+)-lactic acid producer due to its special features compared to other genera. There are several L(+)-lactic acid fermentations using *Bacillus* strains that have been developed. Strains of *Bacillus coagulans* are reported for their remarkable L(+)-lactic acid production features, including low nutrient requirements, tolerance to high temperature and pH, strong ability to ferment both hexose and pentose sugars to high optically pure L(+)-lactic acid via pentose phosphate pathway (PPP) with 98 - 100% theoretical yield (Wang et al., 2013, 2015; Patel et al., 2006; Ye et al., 2013, 2014). The novel homofermentative *Bacillus* sp. BC-001 was firstly reported as the potent industrial L-lactate-producing strain with a high lactic acid yield (0.96 and 0.87 g/g) and productivity (2.8 and 2.6 g/L·h) using glucose and sucrose as substrates. Interestingly, the pH during L-lactic acid fermentation by the novel BC-001 could be simply controlled using monovalent bases (NH₄OH, NaOH, and KOH) (Thitiprasert et al., 2017).

According to D-lactic acid production, the wild-type *Sporolactobacillus* strains have recent been described as potential D-lactic acid producer which could produce D-lactic acid from a simple medium composition and provide a high optically pure D-lactate isomer. Additionally, the *Sporolactobacillus* species is being explored for their ability to utilize the alternative resources as substrate for D-lactic acid production. The efficient D- lactic acid production by *S. nakayamae* utilizing cheap peanut flour as a nitrogen source and commercial sucrose as a carbon source was determined. The results indicated that *S.*

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pure lactic acid isomer and high efficiency of lactic acid production could lead SFLAB to be the lactic acid-producing candidate in future approaches.

Probiotics

The recent trend of probiotics has been extensively increasing. Probiotics are live microorganisms which identified as the beneficial microbes providing the several applications in health and clinical scenarios (Elshaghabee et al., 2017). The spore-forming lactic acid bacteria have long been explored and commercially produced as probiotics for human and animal health, in particular, *Bacillus* species (Table 4) (Khatri et al., 2016; Elshaghabee et al., 2017; Cutting, 2011; Hong et al., 2005), although a number of SFLAB information is not compared to LAB species. The findings have presented that the strains of *Bacillus* are remarked as probiotics due to their inherent ability of secretory proteins, enzymes, antimicrobial compounds, and vitamins. Various *Bacillus* lactic acid-producing species have been studied to examine their probiotic attributes. Among the *Bacillus* species, the candidate probiotic of *Bacillus* lactic acid-producing strains includes *B. subtilis*, *B. coagulans*, and *B. licheniformis*. Furthermore, the genus *Bacillus*, spore-forming lactic acid strains, is mostly recognized as the Generally Regarded As Safe (GRAS) microorganisms (Khatri et al., 2016). The distinctive endospores characteristic of the *Bacillus* species is able to resist in extreme conditions, including nutrient deprivation and environment stress (low pH, high temperatures, UV irradiation, and solvents). By their spore-forming character, the strains of *Bacillus* play a crucial role as the potential probiotic functionalities by mean of bile and acid tolerance, mucin binding, immune stimulation ability, and clinical efficacy (Khatri et al., 2016; Elshaghabee et al., 2017). Recently, several studies have reported the beneficial effect of *Bacillus* strains on the gut metabolism and physiology. Different *Bacillus* strains have shown their ability as antimicrobial, anti-oxidative and immune-modulatory in the host (Elshaghabee et al., 2017). Additionally, the *Bacillus* strains exhibit the antagonist activity which suppresses the pathogenic activities. *B. subtilis* strains were reported their antagonist activity by exhibiting aninocoumarin A activity which could attribute to the anti *H. pylori* activity (Pinchuk et al., 2001). In 2016, Gobi et al. reported the impact of *B. licheniformis* Dahb1 on reducing the formation of biofilm in the virulent *V. parahaemolyticus* Dahv2, an Asian catfish. Bacteriocin-producing strains of probiotic *B. coagulans* have been also identified. The bacteriocins of *B. subtilis* strains have a great antimicrobial activity against food-born and related clinically relevant pathogens, besides having lower cytotoxicity (Abdhul et al., 2015). Also, *B. coagulans* has been evaluated because of beneficial effect on the gut metabolism. It was indicated that feeding of *B. coagulans* to cholic acid fed rat, improved intestinal permeability and reduced the bactericidal effect of bile acid (Lee et al., 2016). Furthermore, the positive effect of *Bacillus* strains to distant cells, beyond GIT has also been established by numerous studies (Foligné et al., 2012; Abhari et al., 2016). At present, the potential probiotic *Bacillus* species are being explored for more applications. Lee et al. (2012) studied the effect of *B. subtilis* CSY191 that secretes a surfactin like compound which could inhibit the growth of anti-human breast cancer cells. Additionally, the direct effect of active compounds, which are produced by the *Bacillus* species have been determined as the alternative and effective therapy for metabolic syndromes (Choi et al., 2016; Yang et al., 2014; Ghoneim et al., 2016;

Zouari et al., 2015). Commercially, the probiotic products are under regulated, depending on the regulatory system of the country. In terms of the *Bacillus* lactic acid-producing strains, these are one of the mostly commonly used as probiotic based products in the range of human health supplements, animal feed, and aquaculture (Elshaghabee et al., 2017).

Table 4. Probiotics of spore-forming LAB in the worldwide market

Strain and description	Probiotics	Target
<i>B. licheniformis</i> (NCTC 13123) at 10^9 - 10^{10} spores/kg, non-bacteriocin strain and not licensed in the EU.	AlCare™	Swine
<i>B. licheniformis</i> (1.6×10^9 CFU/g) and <i>B. subtilis</i> (1.6×10^9 CFU/g).	BioGrow®	Poultry, calves and swine
Mixture (1/1) of <i>B. licheniformis</i> (DSM 5749) and <i>B. subtilis</i> (DSM 5750) at (1.6×10^9 CFU/g) of each bacterium. EU approved.	BioPlus 2B®	Piglets, chickens, turkeys for fattening
Carries 4 strains of <i>B. subtilis</i>	Promarine®	Aquaculture shrimps
<i>B. coagulans</i> (1.0×10^9 spores/dose)	Lactopure	Poultry, swine, calves
<i>B. coagulans</i> and <i>B. subtilis</i>	NutriCommit	Human
<i>B. coagulans</i> (1.0×10^9 spores/dose)	Lactospore	Human
<i>B. coagulans</i> GBI-30	Sustenex	Human
<i>B. coagulans</i>	Neolactoflorene	Human
<i>B. coagulans</i> 15B and fructooligosaccharide	Nutrition essentials Probiotic	Human
Labelled as dietary supplement contained a stable <i>B. coagulans</i> that survives in stomach acid and retains its potency in the intestines.	THORNE®	Human
<i>B. coagulans</i> (<i>B. coagulans</i> GBI-30, 6086)	GanedenBC ³⁰	Human and animal

*Information was modified from Cutting (2011), Elshaghabee et al. (2017), Konuray and Erginkaya (2018), and Hong et al. (2005).

The spore former *Sporolactobacillus* species have been also studied as probiotics. However, only a few studies have worked on the function of probiotic *Sporolactobacillus* species. Hyrominus et al. (2000) studied the performance of various *Sporolactobacillus* strains for being as probiotics by testing their acid and bile tolerance in different cultivations. The study reported that the examined *Sporolactobacillus* strains could survive in acidic conditions (pH 2.5 - 3) and some are weakly tolerant to 0.3% bile. Moreover, the study suggested that other parameters such as the spore-forming behavior in the gastrointestinal tract should be considered. The basic characteristics of *S. inulinus* BCRC 14647 were determined for its potential probiotic properties. Several factors, including acid and bile tolerance, adhesiveness, and antagonistic effects on pathogenic *Salmonella enteritidis* BCRC 10744 were tested. The results revealed that the vegetative cell form of *S. inulinus* exhibits probiotic features (Huang et al., 2007). The draft genome sequence of *S. vineae* SL153^T was analyzed to determine its probiotic characteristics. The study found that *S. vineae* SL153^T presents a high level of cell adhesion activity and growth inhibitory effect on pathogenic bacteria, including *Vibrio cholerae*, *Vibrio alginolyticus*, *Vibrio fluvialis*, *Vibrio parahaemolyticus*, *Aeromonas bivalvium*, *Listonella anguillarum* which improves the effectiveness of the prevention and treatment of disease infected by these pathogenic microorganisms (Kim et al., 2012).

Several numbers of researches have been developing in both phenotypic and genotypic probiotics in order to achieve the greatly beneficial human and animal health. Thereby, in

order to promote health benefits, suitable probiotic formulations should be considered. Furthermore, a little information on probiotics spore-forming bacteria for clinical trial testing has been revealed. It is noted that further studies on the functionality and safety of probiotic spore-forming bacteria are required.

Other Applications and Future Perspectives

SFLAB, especially the *Bacillus* strains, have long been considered as the cell factories for the production of significant substances. Enzyme technology is one of the most important application that could be obtained from SFLAB. Various extracellular enzymes are commercially produced by *B. subtilis*, *B. licheniformis*, and *B. coagulans*. Moreover, most of enzymes produced by *Bacillus* strains have been used as thermostable enzymes (Friszte & Claus, 1995). Bacterial enzymes including amylase, pullulanase, xylanase, lipase, proteinase, α -glucosidase, cyclodextrin glycosyltransferase, glucose isomerase, 1,4- β -galactosidase, protease, DNA polymerase and restrict endonucleases have been used by food, pharmaceutical, textile, cosmetic, and household detergents industry (Meima et al., 2004; Kumar et al., 2005; Kanwar et al., 2006).

As previously mentioned for probiotics, SFLAB strains have the ability to produce antimicrobial substances against different food-borne pathogens, such as *Salmonella typhimurium*, *Clostridium perfringens*, and *Escherichia coli* (Shivaramaiah et al., 2011; Tactacan et al., 2013; La et al., 2001). Additionally, *Bacillus* strains are also the commercial product in the field of agriculture. *Bacillus subtilis* has been found as a promotor of plant growth by improving the survival and robustness of the seedlings (Cavaglieri et al., 2005; Ugoji et al., 2005).

Nowadays, the trend of healthy and functional food is widely interesting. Probiotic SFLAB have been extensively explored. However, compared with LAB, the lactic acid spore formers have not gained high popularity yet. Thereby, there is a need to elucidate and evaluate the features of spore former probiotic strain. Moreover, the association of safety and licensing issues that influence the use of bacteria spore former should be clarified. In addition to improve the polymer grade, SFLAB is presented as a good lactic acid producer which provide a high product yield and the desired stereoisomer, optically pure L(+)- or D(-)-lactic acid. So far, a stable and highly productive lactic acid fermentation is required. Therefore, the potential of SFLAB should be further explored. Furthermore, the cost reduction of biotechnological lactic acid production is now being developed.

CONCLUSION

SFLAB have been gaining attractiveness as microorganisms because of their many efficacies utilized in many applications. The endospore-forming characteristic provides an excellent ability of SFLAB to tolerate extreme conditions (like high temperature, pH, salts, and reagents). Interestingly, SFLAB has resilient features, for instance, the SFLAB strains could grow and produce product either under aerobic or facultative anaerobic condition, including the use of alternative resources as a substrate. Thereby, SFLAB have become an

attractive outcome for being lactic acid-producing candidate and probiotics. Additionally, SFLAB are able to be the enzymes factory which produce variety of enzymes. Furthermore, most of these SFLAB enzymes are now applied in various industries. Nonetheless, there is a little information regarding SFLAB; therefore, it is necessary to develop more studies for understanding SFLAB features.

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Chapter 305

PUBLIC HEALTH SIGNIFICANCE OF FRINGILLIDAE: VIRAL, BACTERIAL, MYCOTIC, PARASITIC AND ALLERGENIC APPROACHES

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ABSTRACT

Finches are the most popularly kept passerine species within aviculture. The zoonotic diseases of Fringillidae have always been a major concern for owners. Various *viral, bacterial, fungal, parasitic and* allergenic agents of Aves are able to transmit to humans. In the present chapter, emphasis will be placed on the significance of each of the mentioned agents for public health. The subheading will exist on specific subjects such as the etiology of the disease; epidemiology, economic significance, public health significance, transmission, clinical signs, diagnostic procedures and principle of disease prevention thus making the owners aware of the serious threat of finches.

INTRODUCTION

Zoonoses refer to infectious animal diseases that are communicable to humans. Avian and humans have different physiologies, and consequently, most avian diseases do not pose a serious threat, but owners should be aware that some avian diseases transmit to humans. Many zoonotic diseases can be prevented by understanding basic disease transmission principles and the criteria of preventive practices.

Infectious organisms are transmitted by five categories including zoonoses: the pathogen is transmitted via direct or indirect contact, and does not pass through the life cycle; saprozoonosis: spread by the alimentary tract; metazoonosis: by biological and mechanical vectors; cyclozoonosis: vertebrates are intermediate hosts and xenozoonosis: by transplantation of organs from infected animals. Individual susceptibility and the seriousness of zoonotic disease varies with age, health status, immune status (immunodeficient or immunosuppressed), virulence of the organism, the dose to which the person is exposed, the duration of exposure as well as route of infection.

The order Passeriformes contains over 5700 species. The most common representatives of the passerines in captivity are finches. This chapter primarily covers zoonotic diseases that occur in passerine birds. It should be expected that the zoonotic disease in finches is similar to other passerines and the disease characteristics, transmission, and diagnosis are essentially the same. If evidence of variations is mentioned in literatures, it will be described.

Infections of passerines with zoonotic pathogens can be grouped into 5 categories, each of which is the subject of a separate section of this chapter. The first section discusses infections with the viral pathogens such as arboviral infections, orthomyxovirus type A and avian paramyxovirus type 1, which generally have a worldwide distribution. Arbovirus is referred to viruses that transmit to vertebrates by the bite of arthropod vectors such as mosquitoes, flies, and ticks. Various arboviruses are able to cause disease in humans. However, the discussion here will be limited to 2 that are reported in both humans and finches: Eastern equine encephalitis virus and West Nile virus. The second section of this chapter discusses infections with the numerous bacteria. These bacterial diseases, include, arizonosis, campylobacteriosis, chlamydiosis, colibacillosis, erysipelas, listeriosis, tuberculosis, salmonellosis, staphylococcosis and yersiniosis. The third section discusses infections with fungi pathogens. Fungal infections are a significant problem in Fringillidae. The first focus is cryptococcosis, followed by other infections. Cryptococcosis is one of the most prevalent mycosis of birds. Dermatophytosis is the principal fungal infection of the keratinized areas of the body, including the hair, nails, and skin. Dermatophytosis was reported in passerines and is notable as a public health hazard. Histoplasmosis and microsporidiosis are associated with a wide spectrum of clinical illness, especially in human. Avian mite dermatitis and toxoplasmosis have been detected in passerines and these are described in the fourth section of this chapter. These zoonoses are caused by parasitic organisms. The final section of this chapter discusses zoonoses due to allergenic agents. Allergic alveolitis, which is connected with the allergens in bird feathers, droppings, epithelium or fecal dust, also merits mention.

Diseases are presented alphabetically within categories defined by the type of infectious agent (i.e., viral, bacterial, fungal, parasitic and allergenic). For each disease, there is a subheading on specific subjects such as the etiology of the disease, epidemiology, economic significance, public health significance, transmission, clinical signs, diagnostic procedures and principle of disease prevention.

SECTION 1: VIRAL DISEASES

Eastern Equine Encephalitis

Etiology and Organism Biology

Eastern equine encephalitis virus causes eastern equine encephalitis. The disease is an arbovirus infection. Arbovirus is a generic term referring to viruses transmitted to vertebrates by the bite of arthropod vectors.

Epidemiology

Many outbreaks of eastern equine encephalitis were reported in pheasants and chukar partridges flocks, but it usually occurs sporadically in other birds. The disease is found in some areas such as North and South America. Eastern equine encephalitis outbreak often occurs in late summer and fall following increasing numbers of mosquito vectors. Outbreak of eastern equine encephalitis has been reported in finches [1, 2].

Economic Significance

Treatment, prevention or control measures requires the aid of a formal economic appraisal.

Public Health Significance

Clinical manifestations of human infection with eastern equine encephalitis virus are flu-like disease with fever, headache, and fatigue. Some patients exhibit neurological signs, including meningitis or encephalitis. Recovery can take several weeks to a few months. The major mode of transmission to human is from the bite of an infected arthropod vector. The primary enzootic transmission cycle occurs between birds and mosquitoes.

Hosts

Outbreaks of eastern equine encephalitis have been reported in various avian species, including pheasants [3], pigeons [4], chukar partridges [5, 6], turkeys [7, 8], ducks [9] and finches [1, 2, 10].

Transmission, Carriers, Vectors, Spread

- 1) Vectors of eastern equine encephalitis virus are ornithophilic mosquito (*Culiseta melanura*), *Culicoides*, *Aedes sollicitans*, *Coquilletia perturbans*, *Culex melanura*, *Culex pancossa*, *Culex dunni*, *Culex sacchettae*, simuliid flies, mites and lice [11, 12]. Transmission to mammalian species can occur by mosquitoes such as *Aedes* spp. and *Coquilletia* spp.
- 2) In some birds, transmission occurs following feather picking, cannibalism, and oral inoculation [13]. Transmission of virus by semen also has been reported [14].
- 3) Passeriformes are the principal vertebrate hosts of eastern equine encephalitis virus [15, 16]. These birds rarely become ill but serve as maintenance and amplifying hosts for the virus.

Incubation Period

In experimental studies, many wild birds were found to have viremia lasting up to 4 days [16].

Clinical Signs

Clinical disease produced by eastern equine encephalitis virus in finch is usually attributed to central nervous system infection (paresis) with or without involvement of viscera. Death is also demonstrated to occur [1, 2].

Diagnostic Procedures

The diagnosis of eastern equine encephalitis disease is based on clinical symptoms, histopathological examination, virus isolation and laboratory diagnostics.

Laboratory Diagnostics

- 1) Detection of viral RNA by molecular techniques such as RT-PCR [17].
- 2) Detection of viral antigens by antigen-capture ELISAs [18, 19], or immunohistochemistry [20].
- 3) Serologic testing [21].
- 4) Isolation requires inoculation of blood or tissue (brain, spleen, liver, heart) into cell cultures, embryonated chicken eggs or mice.

Prevention

The following criteria should be considered to prevent and control the eastern equine encephalitis.

1) Biosecurity

Biosecurity keeps the disease from entering into the finch facility. Prevention of eastern equine encephalitis is associated with measures aimed at reducing vector populations. If practicable, aviaries should be located away from wetlands and other areas that are habitats for vectors.

2) Vaccination

No commercial vaccine is licensed for prevention of eastern equine encephalitis in finches.

West Nile Viral Encephalitis

Etiology and Organism Biology

West Nile virus is an arthropod-borne virus (arbovirus) in the family Flaviviridae, genus *Flavivirus*. Flaviviruses are single-stranded, positive-sense, enveloped RNA viruses with icosahedral nucleocapsid symmetry.

Epidemiology

West Nile virus has been described in Africa, Europe, the Middle East, West and Central Asia, Oceania and in the Western Hemisphere.

Economic Significance

Treatment, prevention or control measures requires the aid of a formal economic appraisal.

Public Health Significance

Infection usually occurs as a result of a mosquito bite while taking blood. Non-arthropod-borne routes of transmission have been reported. These transmission routes in humans include infection through contaminated organ transplantation, blood transfusion, vertical transmission by breast milk and intrauterine transmission and occupational exposure through laboratory [22, 23].

Hosts

West Nile virus has also been reported in Passeriformes and finches [24-27].

Transmission, Carriers, Vectors, Spread

- 1) Transmission occurs between susceptible vertebrate hosts by blood-feeding arthropod mosquitoes, sand flies, ceratopogonids, and ticks [27-31].
- 2) Experimentally, infection has been reported following oral exposure in cats fed infected birds [32, 33].
- 3) Fecal shedding was identified as a potential route of transmission between bird aviaries [24, 34].
- 4) Birds are the natural reservoir species, they may act as dead-end hosts or viral amplifiers [23].
- 5) Human and domestic animals may show clinical signs, but often are incidental or “dead-end” hosts because they do not exhibit significant viremia and do not contribute to the transmission cycle.

Clinical Signs

Infected birds in North America have a spectrum of clinical outcomes ranging from no disease to death [23]. In most species of birds, common clinical signs include depression, recumbency, anorexia, weight loss and death, with no previous clinical signs of illness. Neurologic signs (disorientation, ataxia, circling, abnormal head posture, tremors, impaired vision,) have also been reported [26, 35-40].

Diagnostic Procedures

The diagnosis of disease is based on clinical symptoms, histopathological examination, virus isolation and laboratory diagnostics.

Laboratory Diagnostics

- 1) Detection of viral genome by molecular technique such as PCR.
- 2) Detection of viral antigens by antigen-capture ELISAs or immunohistochemistry in tissue, blood, CSF, or other body fluid [23].
- 3) Hematologic abnormalities such as leukocytosis and heterophilia, infrequent monocytosis and reactive lymphocytes were reported in some species [35, 38, 41].

Prevention

The following criteria should be considered to prevent and control the infection.

1) Biosecurity

Biosecurity keeps the disease from entering into the finch facility. Prevention of disease is associated with measures aimed at reducing vectors such as mosquitoes, sand flies, ceratopogonids, and ticks.

The virus may also be transmitted through contact with infected animals, birds, their blood, or other tissues. Thus, laboratory and clinical workers as well as owners who handle infected birds, tissues or fluids are at risk of virus exposure. To minimize risk, persons should have appropriate personal protective equipment such as gloves, gowns and masks. Owners must wash hands and other skin surfaces with soap and water immediately after contact with infected birds and contaminated materials.

2) Vaccination

No commercial vaccine is licensed for prevention of eastern equine encephalitis in finches.

Influenza

Etiology and Organism Biology

Influenza is described as an infection of avian caused by Type A influenza. The influenza viruses are classified in family *Orthomyxoviridae* genus *Influenzavirus* A. The severe and lethal disease caused by influenza viruses is referred to as “highly pathogenic avian influenza” or HPAI. Milder forms of influenza have been named “low pathogenic” or “non-highly pathogenic” avian influenza (LPAI). The World Organization for Animal Health (OIE) suggests the terms “highly pathogenic notifiable avian influenza (HPNAI) and “low pathogenic notifiable avian influenza (LPNAI)” for influenza viruses[42].

Virions lengths are about 120 nm with spherical, pleomorphic or filamentous shape. Two types of glycoprotein projections are located on the viral surface: (1) hemagglutinin (HA) which are rod-shaped trimers and (2) neuraminidase (NA) which are mushroom-shaped tetramers. The viral genome includes eight segments of single-stranded, negative-sense RNA and codes 10 or 11 proteins as follows: (1) Eight structural protein (HA, NA, NP, M1, M2, PB1, PB2, and HA), and (2) nonstructural protein (NS1 and NS2) (NS1). Type A influenza viruses are subtyped based on sequence analysis of HA and NA genes or serologic reactions of the HA and NA surface glycoproteins. Eighteen subtypes of HA (H1-18) and eleven subtypes of NA (N1-11) are recognized for avian influenza viruses.

Epidemiology

Avian influenza viruses have a worldwide distribution and infections with influenza virus have been reported in many avian species [43-50]. Unfortunately, in most areas of the world, the type of influenza virus subtypes currently circulating among finches is not clearly defined.

Economic Significance

Passerines diseases have a significant impact on human welfare, especially in areas where finches rearing is a source of income. Owners also expend large amounts of money to prevent influenza, to maintain an influenza-free aviary, or control disease after an outbreak.

Public Health Significance

Influenza viruses possess host species adaptation, but interspecies transmission of avian influenza to humans has been reported. Interspecies transmission may occur via (1) transmission of complete virions and (2) transmission of viral gene segments. The H5 or H7 HPAI viruses are important among avian influenza viruses and have more public health significance than all the other influenza viruses.

Clinical manifestations of human infections with AI viruses vary from mild to severe and depend on the subtype. The H7 subtype has mainly been associated with conjunctivitis and mild influenza-like illness, whereas H5N1 viruses have been associated with more severe respiratory disease. Clinical manifestations of human infections with avian influenza include fever, dyspnea, pneumonia, cough, myalgia and gastrointestinal signs [51, 52].

Hosts

Avian influenza viruses have been demonstrated to infect a wide variety of wild and domestic birds [50, 53-59]. Therefore, it is concluded that almost all finches are susceptible to infection, at least until further data are provided on resistance for specific species.

Transmission, Carriers, Vectors, Spread

- 1) In various species of birds, avian influenza viruses replicate in the respiratory, intestinal, renal, reproductive and epidermis (including feather follicles for HPAI viruses) and are shed from the nares, mouth, conjunctiva, and cloaca of infected birds into the environment. In this regard, Tavakkoli et al. [60] assessed the excretion time of H9N2 avian influenza subtype in zebra finch. H9N2 avian influenza subtype was shed in tracheal and cloacal swabs of the infected finches, three and five days post inoculation, respectively. The maximum virus titer in tracheal and cloacal swabs was detected on days 2 and 3 post inoculation. In comparison to the trachea, the virus was recovered in cloaca for a longer time.
- 2) The virus is transmitted by direct contact between infected and susceptible birds or indirect contact through aerosol droplets or exposure to contaminated fomites.
- 3) Avian influenza viruses are readily transported to aviaries by human (contaminated shoes and clothing), wild bird, imported birds and contaminated equipment.

Incubation Period

The incubation period for the avian influenza viruses is various and ranges from as little as a few hours for HPAI subtype to several days in birds. The incubation period depends on the various factors such as the dose of the virus, the age of exposure, etc.

Clinical Signs

The virulence of avian influenza virus (LPAI or HPAI) has a critical impact on the clinical outcome of the disease. However, clinical signs of influenza are variable and depend

on many factors, including host immunity, age, sex, environmental factors and concurrent infections.

In companion birds, it is reported that the influenza causes non-specific signs. The disease can cause mortality in birds within several days of infection. Depression and neurologic signs may present. These signs include attenuated motor functions, such as paresis to paralysis, vestibular dysfunction as indicated by torticollis and nystagmus, and general behavior aberrations such as loss of balance. Following intranasal inoculation of H9N2 virus, the zebra showed clinical signs including decreased activity, lethargy, ruffled feathers and decreased feed consumption. The course of the disease was three to five days [60]. Damage of Zebrafish skeletal muscle was also reported following influenza A Virus Infection [50].

Diagnostic Procedures

It can be especially difficult to recognize the disease due to variable and non-specific clinical signs. The diagnosis of influenza disease is based on clinical symptoms, histopathological examination, virus isolation and laboratory diagnostics.

Laboratory Diagnostics

- 1) Molecular techniques such as RT-PCR and RRT-PCR. These assays detect viral RNA in swab samples or tissues.
- 2) Immunohistochemistry, immunocytochemistry, and immuno-fluorescent techniques. These assays detect the specific locations of the viral antigens in tissues or cells.
- 3) Serologic techniques such as agar gel immunodiffusion (AGID), ELISA and HI. These assays detect and quantify antibodies to influenza virus. AGID detects anti-NP antibody to all influenza A viruses.

ELISA assay detects antibodies to AI viruses. If the ELISA kit were available for finches, it would be useful for testing the finch's sera, but that specific kit is not always available. HI assay detects antibodies to the HA antigene of the influenza virus. The HI test cannot differentiate antibodies induced from an infection with influenza virus or those induced by vaccination with commercial vaccines. The sera of many passerines may contain nonspecific inhibitors and cause problems in HI assay. Therefore, sera should be treated to decrease or destroy such inhibitors. The two techniques used for these inhibitors are receptor destroying enzyme (RDE) and potassium-periodate. In addition, chicken red blood cells are usually used in HI tests. Caution should be taken when using sera from species other than chickens (such as finches) in the HI test because they may cause false positives due to nonspecific agglutination. So, the pre-treatment procedure is needed prior to HI test. This problem may also be avoided by using erythrocytes in the HI test of the same species. Attention should be paid to the OIE approved protocol to avoid variations in results from different laboratories [61, 62].

Prevention

The following criteria should be considered to prevent and control the influenza disease.

1) Biosecurity

Biosecurity keeps the disease from entering into the finch facility and prevents susceptible finches from infection. So each method of disease transmission and spread must be noticed in this policy.

2) Disinfection

It is critical that organic matter be removed before the disinfection protocol. Physical conditions such as dryness, heat and extremes of pH can inactivate avian influenza viruses. Avian influenza viruses have lipid envelopes and they are destroyed by detergents. Commercial disinfectants such as phenol, quaternary ammonium and sodium hypochlorite will inactivate influenza viruses.

3) Vaccination

Vaccination reduces the number of susceptible birds, decreases morbidity, mortality and viral shedding into the environment [63-66]. The most frequently licensed influenza vaccine in most countries is inactivated vaccine for LPAI. However, protection is virus subtype specific. Birds are susceptible to all of the HA subtypes, and there is no way to predict their infection to any particular subtype. Therefore, it is not practical to use preventive vaccination against all influenza subtypes. However, if a particular HA subtype is at risk in a certain area, vaccination can be a useful tool in a control program. Unfortunately, at this time there are no substantive data about certain HA subtypes, which are circulating in finches in most parts of the world.

Inactivated vaccines are given intramuscularly or subcutaneously. They are often mixed with other vaccines as a multivalent product to decrease the cost of administration. Vaccination programs may be arranged by veterinarian policies in each area and depend on the status of the disease in the region, maternal immunity, the quality of biosecurity, available vaccines, use of other vaccines and cost. Some owners have a regulated program for vaccination. Based on the author's experience, it is useful for finches to receive at least 2 inactivated LPAI influenza vaccines over the year in the areas where the LPAI influenza is endemic. Additional considerations that influence the decision on vaccination for HPAI are based on the government program. Because differentiating vaccinated from infected (DIVA) strategies does not exist for influenza in many finch aviaries, it is difficult to discern infected from vaccinated birds.

Newcastle Disease

Etiology and Organism Biology

The virus family Paramyxoviridae is classified in order Mononegavirales that is a single-stranded, nonsegmented, negative-sense, enveloped RNA virus with helical capsid symmetry. Eleven serotypes of avian paramyxoviruses (APMV) have been recognized: APMV-1 to APMV-11. Of these, APMV-1 remains the most important pathogen for passerines. APMV-2 and APMV-3 are also isolated from passerines with no public health significance.

Newcastle disease is described as an infection of avian caused by avian APMV-1. The disease is caused by infections with virulent isolates of APMV-1 that meet one of the following aspects for virulence:

- 1) By an intracerebral pathogenicity index (ICPI) in day-old chickens (*Gallus gallus*) of 0.7 or greater.
- 2) Demonstration of multiple basic amino acids in the virus genome at the C-terminus of the F2 protein and a phenylalanine at residue 117, which is the N-terminus of the F1 protein.

Epidemiology

There are few regions in the globe, which have not been affected by Newcastle disease viruses. Newcastle disease is particularly problematic for finches reared in close proximity to other avian species. The spread of Newcastle disease virus between various countries including Asia, the Middle East, Europe, and Africa has also been documented [67]. Unfortunately, in most areas of the world, the type of Newcastle disease virus strain or genotypes that are currently circulating among finches is not clearly defined.

Economic Significance

Finch diseases have a significant impact on human welfare, especially in areas where finches rearing is a source of income. Owners also expend large amounts of money to prevent Newcastle disease, to maintain a Newcastle disease-free aviary, or eradicate disease after an outbreak.

Public Health Significance

The isolation of Newcastle disease virus from humans is rare; however, when it does arise it is often isolated from those who have close contact with passerines, or have an infection from live vaccines during vaccination, or acquired from laboratory infections. The recovery will happen in 7–20 days. Following direct contact of the eye with infective fluids or aerosols, a self-limiting conjunctivitis without involvement of the cornea was reported. Furthermore, after ocular contamination, in humans flu-like symptoms may occur. Intravenous inoculation of the Newcastle disease virus in humans led to general malaise, neutropenia, leucopenia, thrombocytopenia and flu-like symptoms. However, risk factors such as immunosuppression in human may increase the possibility of Newcastle infection and severe pneumonia. There are no reports of human-to-human transmission [68, 69].

Hosts

Newcastle disease has been documented in at least 241 species [70-74] (150). Therefore, it is concluded that almost all finches are susceptible to infection at least until further data are provided on resistance for specific species.

Transmission, Carriers, Vectors, Spread

- 1) The principal mode of viral transmission is horizontal through respiratory, fecal and oral secretions. Infected birds shed Newcastle disease virus in oropharyngeal and

fecal secretions. Finches may also become infected by inhaling contaminated dust or aerosolized virus or by ingesting such material.

- 2) It is difficult to prove vertical transmission of Newcastle disease virus from parent to offspring, but it is reported in some references [75]. Hatchling birds may be infected by contact with contaminated feces through eggshell cracks or by exposure to a contaminated environment.
- 3) Vaccinated birds can shed the Newcastle disease virus for several days and are the sources of viruses to other susceptible birds. For example, immunized chickens shed Newcastle disease virus for 6–9 days after challenge [76]. Parrots, cormorants, and pigeons have longer time of Newcastle disease virus shedding, usually in feces, without clinical signs [77-79]. Based on these results it is concluded that the vaccinated finches can shed and spread the virus in the environment/or to healthy finches; but the time of shedding is not clearly defined and needs further study.
- 4) The infected birds can be carriers for months before the clinical symptoms become manifest.
- 5) The virus can be spread by humans through transport of contaminated fomites.
- 6) Mechanical vectors (equipment, clothing, shoes, feed, water, infected avian products) may spread the virus.
- 7) Wild or domestic infected birds that are moved or placed into contact with susceptible finches may lead to the spread of Newcastle disease virus through inhalation or ingestion.
- 8) Migratory birds have been suggested in the introduction of the disease in certain areas.
- 9) Two different fly species can carry Newcastle disease virus. Flies can be considered competent vectors [80].

Incubation Period

The incubation period may be between 3 and 28 days depending on the age of the bird, immune status of the bird, the virulence of the virus and the dosage of the virus.

Clinical Signs

Clinical signs of infected birds vary depending on the virulence and the dosage of the infecting virus, the immune status and age of the finches as well as environmental conditions. In passerines, APMV-1 may result in sudden death. Clinical signs can involve the CNS (head shaking, head tremors, head tilt, circling, paralysis, ataxia, twisted neck, opisthotonos, torticollis), respiratory (conjunctivitis, nasal discharge), gastrointestinal (diarrhea, melena, intestinal hemorrhage) and urogenital (polyuria, drop in egg production) systems. General signs such as depression and varying degrees of weight loss were also noted. Some infected birds may survive for up to several months after developing CNS signs.

Diagnostic Procedures

It can be especially difficult to recognize the disease due to various clinical signs of infected birds. The diagnosis of Newcastle disease is based on clinical symptoms, histopathological examination, virus isolation and laboratory diagnostics.

Laboratory Diagnostics

- 1) Molecular techniques such as RT-PCR and RRT-PCR. These assays detect viral RNA in swab samples or tissues.
- 2) Immunohistochemistry, immunocytochemistry, and immuno-fluorescent techniques. These assays detect the specific locations of the viral antigens in tissues or cells.
- 3) Serologic techniques such as ELISA and HI. These assays detect and quantify antibodies to Newcastle disease virus. ELISA is usually specific for the host species. If the ELISA kit were available for finches, it would be useful for testing the finch's sera, but that specific kit is not always available. HI assay detects antibodies to only the HN gene of the Newcastle disease virus. The HI test cannot differentiate antibodies induced from an infection with Newcastle disease virus or those induced by vaccination with commercial vaccines. Chicken red blood cells usually are used in HI tests. Caution should be taken when using sera from species other than chickens (such as finches) in the HI test because they may cause false positives due to nonspecific agglutination [81]. So, the pre-treatment procedure is needed prior to HI test. Attention should be paid to the OIE approved protocol to avoid variations in results from different laboratories[82]. When applying 4 HA or 8 HA units of antigen, titers greater than 1:16 or 1:8 are considered positive, respectively.

Prevention

The following criteria should be considered to prevent and control the Newcastle disease.

- 1) **Biosecurity**

Biosecurity keeps the disease from entering into the finch facility and prevents susceptible finches from infection. So each method of disease transmission and spread must be noticed in this policy.

- 2) **Disinfection**

It is critical that organic matter be removed before the disinfection protocol. Commercial disinfectant such as phenol and quaternary ammonium will inactivate Newcastle disease viruses.

- 3) **Vaccination**

Vaccination reduces the number of susceptible birds, decreases morbidity, mortality and viral shedding into the environment. Two types of commercial vaccines are available in most countries: inactivated and live vaccines. Strains of low virulence, such as B1 and LaSota, are the most common vaccine strain. Other strains such as Ulster, QV4, I-2 and VG/GA are also commercially used especially in chicken farms. Live vaccines can be administered by various methods, but ocular delivery provides the best response compared to drinking water or spray. Inactivated vaccines are given intramuscularly or subcutaneously. Inactivated vaccines produce high neutralizing antibody levels and they are less affected by maternal antibodies. They are often mixed with other vaccines as a multivalent product to decrease the cost of administration.

Vaccination programs may be arranged by veterinarian policies in each area and depend on the status of the disease in the region, maternal immunity, the quality of biosecurity, available vaccines, use of other vaccines and cost. Some owners have a

regulated program for vaccination. Based on the author's experience, it is useful for finches to receive at least 3 live vaccines with 2 inactivated over the year in the areas where the Newcastle disease is endemic. Because differentiating vaccinated from infected (DIVA) strategies does not exist for Newcastle disease in many finch aviaries, it is difficult to discern infected from vaccinated birds.

SECTION 2: BACTERIAL DISEASES

Arizonosis

Etiology and Organism Biology

Arizonosis is a septicemic disease of birds caused by the bacterium *Salmonella enterica* subsp. *Arizonae*. The organism is Gram-negative nonsporogenic bacilli that are motile by flagella.

Epidemiology

Avian arizonosis occurs worldwide.

Economic Significance

Avian arizonosis has considerable economic significance for the pet bird owners through increased mortality in birds and affected egg production in breeders and decreased hatchability. Cost is incurred in testing carrier birds, cleaning and disinfection, treatment of affected birds and preventing the disease.

Public Health Significance

In humans, diarrhea is the most common symptom. Many infections are subclinical. Septicemia can occur in immunocompromised individuals.

Hosts

Many species of avian, mammalian, and reptilian are susceptible.

Transmission, Carriers, Vectors, Spread

- 1) Infected birds are intestinal carriers and spreaders of *Salmonella entericaarizonae* for long periods.
- 2) Wild birds, rats, mice, and reptiles are common sources of the organisms for aviaries.
- 3) Transmission is by the fecal-oral route.
- 4) Transmission of the organism through eggs has been reported in some birds.
- 5) *Salmonella entericaarizonae* is transmitted in the incubator by direct contact. The organism can also transmit through contaminated feed and water.

Incubation Period

In general, the incubation period of the disease in birds is 6-72 hours, although 12-36 hours is most common, but it is not clearly defined in finches.

Clinical Signs

In most birds, infection results in weakness, anorexia, mortality, reduced egg production and hatchability.

Diagnostic Procedures

The diagnosis of arizonosis is based on clinical symptoms, histopathological examination, bacterial isolation and laboratory diagnostics.

Laboratory Diagnostics

The organisms may be recovered from affected tissues, including liver, spleen, heart, blood, intestine, lung, kidney and brain.

Prevention

The following criteria should be considered to prevent and control the arizonosis.

1) **Biosecurity**

Finch aviary can be contaminated with *Salmonella* in many different ways. So each method of disease transmission and spread must be noticed in this policy.

2) **Disinfection**

Salmonella entericaarizonae are readily destroyed by heat and common disinfectants.

Campylobacteriosis

Etiology and Organism Biology

The genus campylobacter contains 18 species, with *Campylobacter fetus* being the type species. They are thermophilic and Gram-negative bacteria. The most frequent and apathogenic *Campylobacter* spp. in passerines is *Campylobacter fetus* subsp. *jejuni*. There are at least 50 serovars of *Campylobacter jejuni*. *Campylobacter Coli* is also isolated from birds, but is considered to be apathogenic. *Campylobacter jejuni* and *Campylobacter Coli* reside in the intestinal tract of birds.

Epidemiology

Campylobacter jejuni has a worldwide distribution [83-85]. Outbreaks of campylobacteriosis have been reported in finches [86, 87].

Economic Significance

Treatment, prevention or control measures requires the aid of a formal economic appraisal.

Public Health Significance

Most human infections are caused by the *Campylobacter jejuni* and *Campylobacter Coli*. Clinical manifestations of human infection, include fever, abdominal pain and profuse or bloody diarrhea. Transmission occurs by ingestion of the organisms.

Hosts

The host spectrum is large and includes chickens, pheasants, turkeys, gulls, ducks, geese, crows, pigeons, Pekin nightingale, shorebirds, nandu, Great bustard, Psittaciformes and canaries. *Campylobacter jejuni* is often found in tropical finches, especially in Estrildidae.

Transmission, Carriers, Vectors, Spread

- 1) Horizontal transmission from the environment to finch's aviaries is an important mode of transmission.
- 2) Potential sources of infection for birds include feces, contaminated or unchlorinated water and equipment, farm animals (pigs, cattle, and sheep), domestic pets, wildlife birds and maybe owners.
- 3) In some species, vertical transmission of campylobacter was suggested but few documented cases have been reported in passerines [88].
- 4) Society or Bengalese Finches (*Lonchura domestica*) can be carriers without conspicuous clinical symptoms [83]. But, when they are used as foster parents for finch chicks, the chicks suffer.
Insects (houseflies, cockroaches, mealworms, etc.) can act as mechanical vectors.
- 5) Rodents and raccoons harbor campylobacter in their intestines, and thus animals can potentially introduce campylobacter to aviaries.
- 6) Dogs can be a reservoir for human infections, but it is not clear if they can transmit the organisms to birds. Therefore, dogs should not be allowed direct access to finch's house.
- 7) *Campylobacter jejuni* can be shed from the intestinal tract of clinically affected and asymptomatic birds.

Incubation Period

The incubation period of campylobacter is not clearly defined in finches. But, in other avian species *campylobacter* colonization could occur as early as one day after inoculation [89-91].

Clinical Signs

Clinical signs include apathy, emaciation, yellow droppings, retarded moulting and high mortality, especially among fledglings. The yellow droppings contain large amounts of amylum (undigested suspension). Sometimes parts of or whole seeds are seen in the droppings. The disease has been associated with the production of pale voluminous droppings and nestling mortality [86]. The pale fecal color is due to the presence of undigested starch. Sudden death due to liver rupture is possible. Finches can also be carriers without conspicuous clinical symptoms [83]. The disease frequently occurs in birds with parasitic infections (coccidia and nematodes), and these agents have been suggested as predisposing factors.

Diagnostic Procedures

The diagnosis of *campylobacteriosis* is based on clinical symptoms, histopathological examination, bacterial isolation and laboratory diagnostics.

Laboratory Diagnostics

- 1) The diagnosis is confirmed by demonstrating the bacteria in smears from the droppings, affected tissues or gut contents. *Campylobacter jejuni* may appear in different forms, including a short comma, s-shaped, long spiral or coccoid form. The diagnosis is also confirmed by cultivating the bacteria on special microaerophilic media.
- 2) Phase-contrast microscopy of bile to demonstrate organisms may provide a tentative diagnosis.
- 3) Heterophilia and thrombocytophilia are the most consistent changes in the hematology examination.
- 4) Various commercial ELISA kits have been developed for direct detection of *Campylobacter*. Most of these assays have been evaluated with human stool samples or animal feces, but their utility for detection of *campylobacter* in finch feces remains to be determined.
- 5) PCR method has been widely used for detection and identification of *Campylobacter* spp.

Prevention

The following criteria should be considered to prevent and control the *campylobacteriosis*.

- 1) **Biosecurity**

Finch aviary can be contaminated by *Campylobacter* in many different ways. Biosecurity keeps the disease from entering into the finch's facility and reduces the colonization level of *campylobacter* insusceptible finches. So each method of disease transmission and spread must be noticed in this policy. Because *Campylobacter* spp. are commonly present in the environment, it is rather difficult to eliminate *campylobacter* from finch aviaries by biosecurity practices alone. Some studies investigated competitive exclusion as a means of preventing *campylobacter* colonization of *Campylobacter* spp. in birds [92-94]. Several feed additives (fatty acids, plant derived additives, etc.) were also evaluated for their effects on *campylobacter* colonization in broiler chickens [95, 96]. These phenomena require further researches in finch rearing.

- 2) **Disinfection**

Chlamydiosis (Psittacosis)

Etiology and Organism Biology

Avian chlamydiosis is caused by the *Chlamydophila psittaci* which belong to the family Chlamydiaceae, order Chlamydiales. The organism is an obligate intracellular and Gram-negative bacterium. The disease in birds and humans is called chlamydiosis and psittacosis, respectively.

Epidemiology

Avian chlamydiosis has a worldwide distribution. Based on literatures, geographical areas and different test assays which give large differences.

Economic Significance

Treatment, prevention or control measures requires the aid of a formal economic appraisal.

Public Health Significance

Psittacosis is a respiratory disease in humans. The clinical signs vary, ranging from a mild flu-like to severe pneumonia with respiratory distress and death. Common signs include fever, headache, chills, myalgia and nonproductive cough. Other signs and complications include, rash, enlarged spleen, myocarditis, endocarditis, hepatitis, arthritis, keratoconjunctivitis, and encephalitis.

Chlamydophila psittaci can be transmitted to humans and care should be taken when handling infected birds or contaminated materials. *Chlamydophila psittaci* shed in the feces or respiratory secretions of infected birds. Humans become infected by direct contact with infected birds and tissues or by inhalation of the organism.

Hosts

Chlamydophila psittaci or chlamydial antibodies have been demonstrated in about 465 bird species including 30 bird orders [97, 98].

Transmission, Carriers, Vectors, Spread

- 1) Horizontal transmission from one infected bird to another susceptible bird is an important mode of transmission. Transmission of *Chlamydophila psittaci* occurs through inhalation or ingestion of contaminated material.
- 2) Vertical transmission has been demonstrated in some species including turkeys, chickens, ducks, parakeets, seagulls, and snow geese [99, 100].
- 3) The organism is excreted in feces and nasal discharges.
- 4) Intermittent fecal shedding by subclinically infected birds may occur. *Chlamydophilas* pp. has also been isolated from the droppings of clinically normal finches [101].
- 5) In poultry, shedding may occur for several months but it is not well demonstrated in finches [102].
- 6) Common reservoirs of chlamydiae include wild and feral birds. *Chlamydophila psittaci* can be carried by and shed without any apparent effect on those hosts.

Incubation Period

The incubation period for chlamydiosis in finch is not known.

Clinical Signs

The clinical signs are non-specific, and may include apathy, debilitation, diarrhea, nasal exudates and conjunctivitis. Mortality may occur. In passerines, the disease should be expected with recurrent respiratory disease, especially if birds are exposed to psittacines.

Diagnostic Procedures

The diagnosis of avian chlamydiosis is based on clinical symptoms, histopathological examination, bacterial isolation and laboratory diagnostics.

Laboratory Diagnostics

- 1) Isolation requires inoculation of the living *Chlamydophila psittaci* into cell cultures, embryonating SPF chicken eggs or mice. Samples should be preferably collected from pharyngeal or choanal slit swabs in live birds. Feces or cloacal swabs are less proper because pathogen shedding is intermittent.
- 2) The diagnosis is also made at necropsy by the presence of the chlamydial organism in impression smears from the affected organs and using special staining techniques. In birds, lungs, spleen, liver, free exudates and exudate-coated air sacs can be sampled.
- 3) A number of manufacturers produce ELISA kits for detection of *Chlamydophila* spp. in humans, but none of the kits is licensed for *Chlamydophila psittaci* in finches.
- 4) The tissues can be collected for antigen detection by PCR.

Prevention

The following criteria should be considered to prevent and control the chlamydiosis.

- 1) **Biosecurity**

Finches should be kept in aviaries without contact with contaminated equipment or premises. Contact with reservoirs or vectors such as wild and feral birds should also be prevented.

- 2) **Disinfection**

Chlamydophila is highly susceptible to chemicals that affect their lipid content or their cell walls. Commercial disinfectant such as quaternary ammonium, benzalkonium chloride, silver nitrate, alcoholic iodine solution, 70% ethanol, 3% hydrogen peroxide, and lipid solvents will inactivate the bacterium.

Colibacillosis

Etiology and Organism Biology

The etiology of colibacillosis is avian pathogenic *Escherichia coli* (APEC). A particularly virulent O86 APEC, recently reclassified as *Escherichia albertii*, caused significant mortality in free-living finches in Britain [103, 104]. *Escherichia coli* is categorized in the family Enterobacteriaceae and is a gram-negative, nonspore-forming bacillus. The organism is often considered as secondary pathogen and should be considered as a sign of poor hygiene or management conditions. Infection with *Escherichia coli* is also the result of fecal contamination of water, food, perches, and environment.

Epidemiology

Escherichia coli has a worldwide distribution. Outbreaks of colibacillosis have been reported in finches [105-107].

Economic Significance

Treatment, prevention or control measures requires the aid of a formal economic appraisal.

Public Health Significance

The enterohemorrhagic strains of *Escherichia coli* (EHEC) (e.g., O157:H7) and some strains of extra-intestinal pathogenic *Escherichia coli* (ExPEC) are considered to be zoonotic pathogens. The EHEC cause intestinal injuries while ExPEC cause disease outside the intestinal tract. Infection with EHEC causes abdominal cramps, watery or bloody diarrhea, hemolytic uremic syndrome (HUS), thrombocytopenia, microangiopathic hemolytic anemia and renal failure. Infection with ExPEC causes various illnesses, including septicemia, urinary infection and newborn meningitis [108].

Hosts

Most avian species are susceptible to colibacillosis.

Transmission, Carriers, Vectors, Spread

- 1) In diseased passerine birds, *Escherichia coli* are often shed from the feces, but in healthy passerines, the bacterium is absent in the intestines.
- 2) Direct or indirect contact with infected bird or feces can introduce *Escherichia coli* into the finch's aviary. Free-living birds such as waterfowl [109-111] and passerine birds [112, 113] are an important source of infection because they are colonized with strains that are already adapted to avian species.
- 3) In nesting birds, infection can occur at any time from egg formation, incubation period or hatching time following fecal contamination.
- 4) Houseflies (*Muscadomestica*) serve as mechanical vectors of *Escherichia coli*.

Incubation Period

The time between infection and onset of clinical signs varies with the type of disease produced by *Escherichia coli*. The incubation period depends on the factors such as dosage of bacterium, the age of exposure, etc.

Clinical Signs

Clinical signs depend on the specific type of disease produced by *Escherichia coli*. Localized infections result in milder clinical signs than systemic infection. The clinical signs are not pathognomonic. In general, clinical signs include chronic weight loss, diarrhea or severe septicemia (lethargy, anorexia, weakness, fluffed appearance, and death). *Escherichia coli* can also cause polyuria, infertility, egg-related peritonitis, conjunctivitis, rhinitis, respiratory infections, ingluvitis, arthritis and death. Infection during the first few days of life can cause enteritis from enterotoxin production. The chicks can quickly dehydrate and become cachexic. The nests become dirty, wet and yellowish. The brooding female also appears wet. Young birds may die within a few days. In one case of enteric colibacillosis, the passage of whole seeds in the droppings was noted before death [105]. Localized infections in various tissues may also occur. Clinical signs of co-infections or predisposing factors are often seen concurrently with signs of *Escherichia coli* infections.

Escherichia coli is also cultured from passerine nestlings with diarrhea ('sweating disease'). Septicemic form of colibacillosis is a major cause of mortality in newly arrived shipments of finches.

Diagnostic Procedures

The diagnosis of colibacillosis is based on clinical symptoms, histopathological examination, bacterial isolation and laboratory diagnostics.

Laboratory Diagnostics

- 1) Diagnosis is confirmed by demonstrating the *Escherichia coli* from lesions typical of colibacillosis.
- 2) Detection of acute phase proteins or calculating the heterophil/lymphocyte ratio can serve as nonspecific markers of the inflammatory condition such as colibacillosis.

Prevention

The following criteria should be considered to prevent and control the colibacillosis.

1) **Biosecurity**

Prevention of colibacillosis is associated with the identification and elimination of sources of infection such as avoiding contaminated feed, water, dust, animal feces, rodent droppings and wild birds. Protecting the finches from viral infections increases host resistance. Pelleted feed has fewer *Escherichia coli* than mash and reduces the colibacillosis. Proper ventilation reduces the levels of bacteria in enclosed aviaries. Wet perch provides a proper environment for *Escherichia coli* to persist and reach high numbers.

2) **Disinfection**

Physical conditions such as dryness and heat are detrimental to the organism. Inactivation of most strains occurs at temperatures ranging from 60 °C for 30 minutes to 70 °C for 2 minutes. *Escherichia coli* is destroyed by disinfectants such as chlorine dioxide.

Erysipelas

Etiology and Organism Biology

The etiologic agent of erysipelas is *Erysipelothrix rhusiopathiae*. The organism belongs to the family Lactobacillaceae and is a small Gram-positive bacterium.

Epidemiology

Erysipelothrix rhusiopathiae is occasionally isolated from passerine [114].

Economic Significance

Erysipelas can cause death in avian and is considered to be a zoonotic pathogen. Treatment, prevention or control measures requires the aid of a formal economic appraisal.

Public Health Significance

Infection with *Erysipelothrix rhusiopathiae* in humans is called erysipeloid that may be a local or systemic, and occasionally fatal infection. The clinical manifestations of infection with *Erysipelothrix rhusiopathiae* in humans are localized cutaneous lesion, pain, swelling, arthritis and peritonitis. Diffuse cutaneous and systemic forms of the infection are much less common. Transmission occurs by the bacterium entering into a cut or abrasion wound when working with infected birds or contaminated environments. Person-to-person transmission of *Erysipelothrix rhusiopathiae* has not been improved.

Hosts

Erysipelas affects a wide variety of avian, mammalian reptiles and amphibians.

Transmission, Carriers, Vectors, Spread

- 1) Contaminated material is an important source of infection.
- 2) Entry through breaks in the mucous membranes or skin is the most frequent portal of entry.
- 3) Fishmeal and fish are probable sources of infection for avian species.
- 4) Soil serves as a temporary reservoir for the organism.
- 5) Mosquito and fly are considerable in mechanical transmission of *Erysipelothrix rhusiopathiae*.
- 6) Rodents, pigs and red mite have all been implicated as reservoirs for the bacterium.

Incubation Period

The incubation period of erysipelasis not defined in finch.

Clinical Signs

Erysipelas is a septicemic disease, which generally occurs sporadically in various avians. Clinical signs of the disease are suggestive of acute to subacute septicemia [115, 116].

Diagnostic Procedures

The diagnosis of erysipelas is based on clinical symptoms, histopathological examination, bacterial isolation and laboratory diagnostics.

Laboratory Diagnostics

- 1) *Erysipelothrix rhusiopathiae* can be isolated by microbiological culture from infected organs. Rapid presumptive diagnosis is provided by demonstrating the bacteria in smears from the liver, spleen, heart blood, or bone marrow. The bacterial morphology is clumps and segregated Gram-positive, beaded, slender, and pleomorphic rods.
- 2) Immunoperoxidase staining can be used to detect *Erysipelothrix rhusiopathiae* from the affected tissues [117].
- 3) PCR method has been used for detection and identification of *Erysipelothrix rhusiopathiae* [118-120].

Prevention

The following criteria should be considered to prevent and control the erysipelas.

1) Biosecurity

Finch aviary can be contaminated by *Erysipelothrix rhusiopathiae* in many different ways. Biosecurity keeps the disease from entering into the finch facility and reduces the bacterial load in aviaries. So each method of disease transmission and spread must be noticed in this policy. It has been suggested that various environmental factors (e.g., rainy and cold weather, sexual maturity) make avian species more susceptible to *Erysipelothrix rhusiopathiae* infection. This may apply to aviary of finches [121].

2) Disinfection

Disinfectants such as phenol, quaternary ammonium, chlorine and sodium hydroxide are effective against *Erysipelothrix rhusiopathiae*. These disinfectants are only effective when surfaces are clean and devoid of any material.

Listeriosis

Etiology and Organism Biology

Listeriosis is caused by *Listeria monocytogenes*. Thirteen serotypes of pathogen have been recognized.

Epidemiology

Listeria monocytogenes has a worldwide distribution. The organism is commonly found in feces and soil. Wet conditions are risk factors for disease.

Economic Significance

Treatment, prevention or control measures requires the aid of a formal economic appraisal.

Public Health Significance

The *Listeria monocytogenes* is important because of its ability to cause human disease following contact with infected birds. Serotypes 1/2a, 1/2b, and 4b are often associated with human disease. Clinical manifestations of human infections with *Listeria monocytogenes* vary, including gastroenteritis, septicemia, focal infections such as brain and hepatic abscesses, conjunctivitis, endocarditis, cholecystitis, joint abscesses, osteomyelitis and skin infections. Infection of pregnant women may cause meningoencephalitis in neonates and fetal death. In immunocompromised adults, septicemia and meningoencephalitis may also occur [122-124].

Hosts

Outbreaks of listeriosis caused by *Listeria monocytogenes* occur in chickens, turkeys, waterfowl, pigeons, passerines and other avian species [125].

Transmission, Carriers, Vectors, Spread

Infection can occur following inhalation, ingestion, or wound contamination.

Incubation period

It is not defined in finches.

Clinical Signs

Young birds are most susceptible. Septicemic and encephalitic forms of listeriosis are noticed in birds [126]. Birds may exhibit emaciation, diarrhea, depression and neurological signs (incoordination, ataxia, torticollis, and opisthotonos).

Diagnostic Procedures

The diagnosis of listeriosis is based on clinical symptoms, histopathological examination, bacterial isolation and laboratory diagnostics.

Laboratory Diagnostics

Listeria can be isolated by microbiological culture from infected organs. For identification of species, *Listeria* isolates should be evaluated in haemolysis, D-mannitol, D-xylose and L-rhamnose.

Prevention

The following criteria should be considered to prevent and control the listeriosis.

1) **Biosecurity**

Prevention of listeriosis is associated with identification and elimination sources of infection such as avoiding wet conditions, contaminated water and soil, and animal feces.

2) **Disinfection**

Tuberculosis

Etiology and Organism Biology

Mycobacterium avium complex and *Mycobacterium genavense* are the most common mycobacterial species, which are associated with passerines disease.

Epidemiology

Avian tuberculosis is worldwide in distribution. Tuberculosis with *Mycobacterium avium* complex is most commonly found in finches [127-129]. Avian mycobacteriosis appears to be overrepresented in Gouldian Finches compared with other passerines [129]. *Mycobacterium genavense* is also involved in avian tuberculosis, and is isolated from human patients with AIDS.

Economic Significance

Treatment, prevention or control measures requires the aid of a formal economic appraisal.

Public Health Significance

The *Mycobacterium avium* complex and *Mycobacterium genavense* are responsible for most cases of human tuberculosis [130]. The common clinical signs associated with human infection are weight loss, fever, night sweats, chills, pulmonary disorder (chronic cough, dyspnea), lymphadenitis (swelling of the submandibular, submaxillary, cervical, or preauricular lymph nodes), and disseminated infection. Human may be infected by ingestion or inhalation of organisms from the environment.

Hosts

All species of passerines can be infected with *Mycobacterium avium* complex and *Mycobacterium genavense*.

Transmission, Carriers, Vectors, Spread

- 1) Mycobacteria are ubiquitous in the environment and are commonly isolated from soil, litter and water. Therefore, the contaminated environment is the most important source for the transmission of the organism to passerines.
- 2) Infection can occur by ingestion (via infected feces, contaminated food and water) or inhalation of organisms.
- 3) Birds may serve as a reservoir of some *Mycobacterium avium* strains.
- 4) Insects may act as mechanical vectors.
- 5) Infected birds shed mycobacteria in their feces and fecal material is important for the dissemination of avian tuberculosis.
- 6) The respiratory tract is a potential source of organism, especially if lesions occur in tracheal and lung.
- 7) Mycobacteria can be disseminated by the carcasses of the infected birds.
- 8) The spread of mycobacteria by contaminated shoes, equipment, and materials (crates and feed sacks) can occur from diseased to healthy aviaries.
- 9) Wild and imported birds may be infected with mycobacteria and spread the organism to finch's aviaries.

Incubation Period

The incubation period following infection can be months or years.

Clinical Signs

Tuberculosis is commonly an enteric infection, respiratory or disseminated. Tuberculosis in passerines usually produces diffuse granulomatous, noncaseous lesions rather than discrete tubercles as found in galliforms [87, 129]. Clinical signs are not pathognomonic. In advanced infections, the most consistent clinical signs of avian tuberculosis are weight loss and severe muscle atrophy. Feathers may have a dull and ruffled appearance. Gross abnormality such as abdominal distension, fluid-filled, hepatomegaly and thickened intestines may be palpable. Lameness may be present in patients with arthritis or osteomyelitis. Sudden death may be the

only presenting sign, although affected birds are usually thin [127-129, 131]. The CNS alteration has been reported in finches [132]. Affected birds may die within a few months or live, depending on severity of the disease. A bird may die suddenly due to hemorrhage from the rupture of the internal organs such as liver or spleen.

Diagnostic Procedures

The diagnosis of tuberculosis is based on clinical symptoms, histopathological examination, bacterial isolation and laboratory diagnostics.

Laboratory Diagnostics

- 1) Diagnosis is confirmed by demonstrating the acid-fast bacteria in tissue smears, especially in the intestinal wall, liver, spleen and bone. Fecal acid-fast stains may reveal the organism antemortem, but the organism usually sheds intermittently.
- 2) Diagnosis is possible using PCR techniques on cloacal swabs or infected tissues.
- 3) Diagnosis can be based on marked leukocytosis with monocytosis and elevations in AST and bile acids.
- 4) Radiographs may show tissue enlargement (enlarged liver, kidney and spleen), as well as bone abnormality (focal, cloudy densities in the medullary cavities of long bones with osteolysis).
- 5) Endoscopy and biopsy can confirm the diagnosis. Endoscopy reveals granulomas in the internal organs such as liver, spleen and intestinal tract. There may be hepatomegaly, splenomegaly and thickened intestines.

Prevention

The following criteria should be considered to prevent and control the tuberculosis.

1) **Biosecurity**

Prevention of tuberculosis is associated with the identification and elimination of sources of infection such as avoiding contaminated water and soil, and animal feces. Providing proper fencing can prevent exposure from wild birds and prevent housing previously used by infected birds. Removal of birds from soil-floored aviaries is an important way of minimizing the impact of this disease within a collection. Collecting the eggs from the affected flock and fostering them under less susceptible finches has also been suggested. Carcasses of infected birds that show lesions of tuberculosis must be burned. In some instances, the infected birds may be culled due to the possible zoonotic implications. When morbidity is high in an aviary, it is practical to eliminate the infected birds and establish a new flock in the new environment.

2) **Disinfection**

Mycobacteria may resistant to typical chemical disinfection. They can survive for several months to a few years in the environment. Ordinarily, it is impractical to keep the environment satisfactorily safe by disinfection.

Salmonellosis

Etiology and Organism Biology

Paratyphoid salmonellae are members of the family Enterobacteriaceae, which are (usually) motile, gram-negative, nonspore-forming rods and often nonhost-adapted bacteria. They affect birds, animals and humans.

Epidemiology

Paratyphoid salmonellae found nearly ubiquitously in wild and domestic birds. Outbreaks of the disease have been reported in finches [133-135].

Economic Significance

Salmonellosis causes economically significant losses for owners in many regions, especially in areas where finch rearing is a source of income. The disease also absorbs large investments of public resources in testing, prevention and control efforts.

Public Health Significance

Salmonella Typhimurium and *Salmonella Enteritidis* are the 2 most common paratyphoid salmonellae isolated from humans. Infection with paratyphoid salmonella may cause fever, gastroenteritis, acute enterocolitis, headache, abdominal pain, diarrhea, nausea and vomiting. Often the disease is self-limiting after 3-7 days. Adverse consequences of bacteremia may occur and include disseminated focal infections and arthritis. Transmission can be made by direct contact with infected feces or indirectly by the consumption of contaminated food products. Infection occurs by the fecal-oral route.

Hosts

Paratyphoid salmonellae infect a wide variety of hosts, including invertebrate and vertebrate (wildlife, domestic animals, birds and humans) [136-139].

Transmission, Carriers, Vectors, Spread

- 1) Paratyphoid salmonellae can be introduced into finch's aviary from various sources. For example, contaminated feeds, vegetable, cereals, vermin or wildlife are potential sources of salmonella. Feeds containing contaminated animal proteins may also contain salmonella.
- 2) Paratyphoid salmonellae are able to colonize into the gastrointestinal tracts of a wide range of hosts including animal and birds. Feces of infected birds are one of the most common sources of infection.
- 3) Ingestion of contaminated food or water is the most common mode of transmission.
- 4) In poultry, vertical transmission of salmonellae to the progeny of infected breeding flocks can result in internal or external contamination of eggs. Transovarian transmission of infection to progeny was also reported [140]. These forms of transmission need future evaluation in finches.
- 5) Chronically and asymptomatic infected birds may present.
- 6) Insects and other invertebrates, including flies [141], ground beetles [142], cockroaches [143], red mites [144], and centipedes [142] can carry salmonella

organisms externally or internally. Mice [145] and roof rats [146] are important vectors for salmonella.

- 7) Contaminated dust from feces and feathers may aid aerosol spread [101].
- 8) Improper handling and sanitation can spread the organism through the contaminated seed, fruits, vegetables, drinking water and food.

Incubation Period

In general, the incubation period of the disease in birds can be as short as 3-5 days in acute cases.

Clinical Signs

Salmonellosis can be peracute, acute, chronic or subclinical depending on the number of organisms, the age and condition of the host. In passerines, the disease more often has a chronic course.

The clinical signs are often non-specific and include depression, lethargy, anorexia, weight loss ruffling of the feathers, diarrhea, soiled vent and dehydration. High mortality, neurological signs (convulsions), crop stasis lameness and wing droop may also present. Lameness and wing droop are associated with septic arthritis. In breeding birds, there is often poor hatching or excessive fledgling mortality.

Diagnostic Procedures

The diagnosis of salmonellosis is based on clinical symptoms, histopathological examination, bacterial isolation and laboratory diagnostics.

Laboratory Diagnostics

- 1) The diagnosis is confirmed by isolation and identification of causative organisms.
- 2) Various commercial ELISA kits have been developed for direct detection of salmonella. Agglutination tests have also been used to detect infections with paratyphoid salmonellae. However, their utility for detection of salmonella in finches remains to be determined.
- 3) PCR method has been widely used for detection and identification of *Salmonella* spp.

Prevention

The following criteria should be considered to prevent and control the salmonellosis.

1) **Biosecurity**

Finch's aviary can be contaminated by salmonella in many different ways. So each method of disease transmission and spread must be noticed in this policy. Control of vectors and prevention of contamination of food and water are required. Furthermore, good hygiene practices must be implemented. Some studies investigated competitive exclusion as a means of preventing salmonella colonization [147, 148]. This phenomenon requires further researches in finch rearing.

2) **Disinfection**

Salmonellae can survive for long periods in organic matter, feces and dirt (up to two years). Salmonellae are generally susceptible to destruction by heat and irradiation

(gamma and ultraviolet radiation) [149-151]. Steam pelleting treatment of feed under standard conditions inactivates salmonellae.

Chemical disinfectants such as phenolic and quaternary ammonium compounds, formalin and formaldehyde fumigation can be used in finch's house and facilities. Organic acids such as zinc acetate and zinc propionate can be applied in feed. Disinfectants such as formaldehyde [152], hydrogen peroxide [153], ozone [149], lactic acid [154] and peroxidase catalyzed compounds [153] were applied to hatching eggs.

Staphylococcosis

Etiology and Organism Biology

The etiologic agent of staphylococcosis is *Staphylococcus aureus*. The organism belongs to the family Staphylococcaceae and genus *Staphylococcus*. Staphylococci are Gram-positive and coccoid. They appear in clusters when grown on solid media and in liquid media, they may be found in short chains. *Staphylococcus aureus* frequently colonizes on the skin and mucous membranes of birds, humans and animals. It is a commensal bacterium and frequently causes clinical diseases.

Epidemiology

Staphylococcus aureus has a worldwide distribution. Outbreaks of staphylococcosis have been reported in finches [19].

Economic Significance

Staphylococcal infections cause economic losses due to bird losses from septicemia. It is also a significant zoonotic disease and treatment, prevention or control measures requires the aid of formal economic appraisal [155, 156].

Public Health Significance

Staphylococcus aureus causes various clinical manifestations ranging from cutaneous infections (cellulitis, impetigo, abscesses, folliculitis, carbuncles and furuncles) to septicemia and death. Bloodstream spread of localized infections may result in adverse consequences including endocarditis, osteomyelitis, arthritis, meningitis, pneumonia, and sepsis. Infants and the chronically ill patients are at increased risk of exhibiting severe skin alterations. In recent years, antibiotic-resistant strains, especially methicillin-resistant *Staphylococcus aureus* (MRSA), have become increasingly common [157]. In human, the anterior nares are the important site for bacterium colonization. Transmission is due to direct or indirect contact. Hands are the most important vehicle for transmission. Airborne transmission may also occur.

Hosts

All avian species are susceptible to staphylococcal infections.

Transmission, Carriers, Vectors, Spread

In general, infection can occur following a breakdown in the natural defense mechanisms of the host. In most cases, this would be due to a skin wound or inflamed mucous membrane. Furthermore, hematogenous spread of pathogen is a locus of infection.

Incubation Period

The incubation period is short in poultry, but is not defined in finch.

Clinical Signs

The clinical signs include dermatitis, folliculitis, abscesses, conjunctivitis, sinusitis, bumble foot, arthritis, pneumonia and death. In generalized skin infection, the skin is usually very pruritic, and often erythematous. *Staphylococcus aureus* has been associated with pododermatitis, respiratory disease, gastrointestinal alterations and septicemia in finches [105].

Diagnostic Procedures

The diagnosis of staphylococcosis is based on clinical symptoms, histopathological examination, bacterial isolation and laboratory diagnostics.

Laboratory Diagnostics

- 1) Staphylococcosis is diagnosed by microbiological culture from suspected exudates or swabs of infected organs.
- 2) Cocci will be seen in the impression smears.
- 3) In skin infection, diagnosis requires a skin biopsy (including follicles) and culture.

Prevention

The following criteria should be considered to prevent and control the staphylococcosis.

- 1) **Biosecurity**
- 2) **Disinfection**

Staphylococci are usually hardy and remain viable for long periods in exudates.

Yersiniosis

Etiology and Organism Biology

Yersiniosis is an infectious disease caused by *Yersinia pseudotuberculosis*. The organism is one member of a generic triad of pathogenic bacteria within the family Enterobacteriaceae. *Yersinia* spp. are Gram-negative ovoid to coccoid rods that are able to replicate in the environment at low temperatures (+4°C) if provided the proper sources of organic nitrogen.

Epidemiology

The geographical distribution of the organism includes many parts of the globe. Infection with *Yersinia pseudotuberculosis* is regularly seen in wild finches [114, 158-160].

Economic Significance

Treatment, prevention or control measures requires the aid of a formal economic appraisal.

Public Health Significance

Human infection is 1) related to consumption of food contaminated from avian or rodent sources and 2) person-to-person spread. *Yersinia pseudotuberculosis* causes abdominal disease, which includes enteritis, typhlitis, mesenteric lymphadenitis, and abscessation of liver and spleen. The disease also results in septicemia, abdominal pain, fever, simulating acute appenditis and arthritis.

Hosts

Infection has been described in various species of birds, mammals and rodents [161].

Transmission, Carriers, Vectors, Spread

- 1) Infection is probably spread by contamination of food by an infected host. The organism may enter through the intestinal mucosa or through breaks in the skin.
- 2) *Yersinia pseudotuberculosis* can be a normal gut inhabitant of a variety of migratory avian species and this may be relevant to the introduction of bacterium into an area.
- 3) Natural reservoirs include birds and rodents.
- 4) Birds, rats, mice, and other small rodents may become infected and not develop the disease. They are considered as chronic carriers of *Yersinia pseudotuberculosis* with fecal shedding of the organism. These animals are believed to serve as the primary reservoir of infection.
- 5) Free-range birds are considered asymptomatic carriers.

Incubation Period

The incubation period of yersiniosis is not defined in finch.

Clinical Signs

The clinical signs are non-specific and may be associated with peracute, acute or chronic clinical signs. Peracute death without clinical signs may occur. Clinical signs following acute disease include lethargy, ruffling of the feathers, debilitation, dehydration, diarrhea and dyspnea. Emaciation, wasting and flaccid paresis or paralysis are described with subacute or chronic cases [159, 160].

Diagnostic Procedures

The diagnosis of yersiniosis is based on clinical symptoms, histopathological examination, bacterial isolation and laboratory diagnostics.

Laboratory Diagnostics

Laboratory confirmation requires isolation of *Yersinia pseudotuberculosis*. Rod-shaped bacteria are seen in impression smears from affected organs, and diagnosis is confirmed by culturing the bacterium.

Prevention

The following criteria should be considered to prevent and control the yersiniosis.

- 1) **Biosecurity**
- 2) **Disinfection**

SECTION 3: FUNGAL DISEASES

Cryptococcosis

Etiology and Organism Biology

Cryptococcosis is a fungal infection caused by *Cryptococcus neoformans*, a member of the genus *Cryptococcus*. The fungus reproduces by budding and cells are spherical and surrounded by a thick capsule.

Epidemiology

Cryptococcus neoformans has a worldwide distribution. The disease is reported in passerines as well as finches, but it is very rarely seen as a serious problem in these birds [162, 163].

Economic Significance

Cryptococcosis is a significant zoonotic disease. Treatment, prevention or control measures requires the aid of a formal economic appraisal.

Public Health Significance

Human infection with *Cryptococcus neoformans* occurs most frequently in immunocompromised persons. The central nervous system alteration (meningitis) and pulmonary diseases are the most frequent clinical diseases. Humans, birds and animals acquire infection from environmental sources. Humans are infected with *Cryptococcus neoformans* by inhalation of yeast cells or basidiospores from the environment. Owners must use extreme care when handling contaminated materials that may contain yeast cells or basidiospores. Most human infections occur through contact with contaminated exudates, fecal material and non-clinical infected or diseased birds. Person-to-person transmission has been reported [164].

Hosts

Birds, humans and animals are infected with *Cryptococcus neoformans*[165, 166].

Transmission, Carriers, Vectors, Spread

- 1) Birds usually acquire infection from environmental sources.
- 2) *Cryptococcus neoformans* may be carried asymptotically in the upper respiratory tract.

Incubation Period

The incubation period following natural infection is not defined in finches.

Clinical Signs

In birds, the central nervous system, respiratory tract and digestive tract may be involved. Infections may produce necrotic granulomatous lesions and characteristically thick, pale, gelatinous exudates. *Cryptococcus neoformans* has been reported to cause subcutaneous nodules on the head and body skin, nodular lesions on the face and beak, beak necrosis, nasal and sinus infections, pulmonary diseases and air sac diseases [75, 105, 167, 168].

Diagnostic Procedures

The diagnosis of cryptococcosis is based on clinical symptoms, histopathological examination, fungal isolation and laboratory diagnostics.

Laboratory Diagnostics

- 1) Infections can be diagnosed by culturing the organism.
- 2) Histopathology is a useful method of diagnosis.
- 3) Mucicarmine stain is used to demonstrate the thick capsule and budding spores.
- 4) Gram's stain, India ink, and Wright's stain have also been used to diagnose this infection. Wright's-stained smears of exudates often reveal encapsulated yeast organisms measuring 6 to 10 μm within 8 to 12 μm non-staining capsules.

Prevention

The following criteria should be considered to prevent and control the cryptococcosis.

- 1) **Biosecurity**
- 2) **Hygiene**

Dermatophytosis

Etiology and Organism Biology

Dermatomycosis are occasionally reported in passerines. *Microsporium* spp. and *Trichophyton* spp. are the most common etiological agents. The infection is contagious and transmissible to humans.

Epidemiology

Dermatomycosis has a worldwide distribution, but its occurrence is usually sporadic.

Economic Significance

Treatment, prevention or control measures requires the aid of a formal economic appraisal.

Public Health Significance

Dermatophytes affect keratinized areas of the body, including the skin, hair and nails. Alterations begin as small areas of erythema and scaling, and subsequently spread peripherally. Transmission occurs by direct contact with infected birds or humans, or indirect contact via contaminated fomites. Dermatophyte infections can transmit from person-to-person while lesions are present.

Hosts

Dermatomycosis occurs in birds, humans and animals.

Transmission, Carriers, Vectors, Spread

- 1) The infection is contagious. Therefore, transmission may occur by direct contact with infected birds or indirect contact via contaminated fomites.
- 2) The organism may remain viable on contaminated objects for a long period.
- 3) Contaminated soil maybe considered as a reservoir.

Incubation Period

The incubation period following natural infection is not defined in finches.

Clinical Signs

In passerines, dermatomycosis generally causes alopecia of the head and neck, or hyperkeratosis.

Diagnostic Procedures

The diagnosis of dermatomycosis is based on clinical symptoms, histopathological examination, fungal isolation and laboratory diagnostics.

Laboratory Diagnostics

- 1) Infected tissues should be stained with periodic acid-Schiff or Gomori's methenamine silver stains to evaluate the fungal morphology.
- 2) For visualizing the hyphae, skin scrapings can be treated with 10% KOH on a glass slide, which is then gently heated over a flame. Scrapings can also be cultured on sabro dextrose agar for microbiological examination.

Prevention

The following criteria should be considered to prevent and control the dermatomycosis.

- 1) **Biosecurity**

Prevention of dermatomycosis requires management protocols that remove the source of infection by preventing contact with infected birds and animals as well as contaminated fomites.

- 2) **Hygiene**

Use of examination gloves is encouraged to prevent transmission to owners.

Histoplasmosis

Etiology and Organism Biology

Histoplasmosis is caused by the fungus *Histoplasma capsulatum*, which is a mycotic infectious, but not a contagious disease, which has been reported in human and zoo birds. The soil-borne organism has the potential to grow within dirt substrates of enclosed aviaries and is commonly associated with fecal material from birds. The *Histoplasma capsulatum* is a dimorphic fungus that appears as an environmental mold and as yeast in its warm-blooded hosts.

Epidemiology

Histoplasma capsulatum has worldwide distribution and is endemic in some areas including eastern and central USA. The disease is reported in passerines, but it is very rarely seen as a serious problem in these birds [169].

Economic Significance

Treatment, prevention or control measures requires the aid of a formal economic appraisal.

Public Health Significance

In human, histoplasmosis produces various diseases, including sporadic infections or acute pulmonary histoplasmosis that is characterized by fever, dyspnea, nonproductive cough, myalgia and chest pain. Most human infections are usually self-limiting, but immunocompromised cases or those exposed to a large volume of organisms, may exhibit severe respiratory distress. *Histoplasma* grows in the soil, particularly in areas contaminated with bird droppings such as aviaries and wild bird roosts [55]. Humans become infected by inhalation of airborne microconidia. Vertical transmission has occurred, but contact transmission from animal-to-person or from person-to-person is not reported [170, 171].

Hosts

Histoplasmosis occurs in birds, humans and animals.

Transmission, Carriers, Vectors, Spread

- 1) Infection is acquired by inhalation of conidia produced by the mold form.
- 2) *Histoplasma capsulatum* grows in soil and material contaminated with bird droppings.
- 3) *Histoplasma capsulatum* is found in the bird house, litter, and bird roosts.
- 4) Bird droppings are a nutrient source for the growth of the organism in the soil.
- 5) The organism can be carried on the wings, feet, and beaks of birds and contaminate soil under roosting sites or manure accumulations inside or outside buildings.

Incubation Period

The incubation period is not defined in finches.

Clinical Signs

In birds, the most common histoplasma infection is considered as respiratory disease. An initial pneumonia can progress to disseminated disease with the formation of necrotic granulomas.

Diagnostic Procedures

The diagnosis of histoplasmosis is based on clinical symptoms, histopathological examination, fungal isolation and laboratory diagnostics.

Laboratory Diagnostics

- 1) In histopathological examination, the characteristic of the disease is histiocytic to granulomatous inflammation with intra-cytoplasmic budding yeasts measuring 2-4 μm in diameter.
- 2) Histoplasmin sensitivity test has also been used to diagnose this infection

Prevention

The following criteria should be considered to prevent and control the histoplasmosis.

- 1) **Biosecurity**
- 2) **Disinfection**

Equipment can be disinfected with phenol-based disinfectants.

Microsporidiosis

Etiology and Organism Biology

Microsporidia are intracellular obligate eukaryotic parasites related to fungi. More than 1200 species of microsporidia in approximately 150 genera have been described [172]. Among these species, *Encephalitozoon hellem* was reported in finches [173]. *Encephalitozoon hellem* is a single-celled, intracellular parasite of the phylum Microspora.

Epidemiology

Disease associated with microsporidial parasites has been described in birds since the 1980s [174]. Infection appears to be able to occur in a wide range of species of birds. Outbreak of *Encephalitozoon hellem* has been reported in finches [173].

Economic Significance

Microsporidiosis is a significant zoonotic disease. Treatment, prevention or control measures requires the aid of a formal economic appraisal.

Public Health Significance

In 1991, *Encephalitozoon hellem* was first recognized in patients with HIV-AIDS [175, 176]. These patients exhibited keratoconjunctivitis and sinusitis [177, 178]. Some cases of systemic *Encephalitozoon hellem* have also been reported. These patients presented with ocular disease, bronchi, severe infection of the trachea, lungs, kidneys, and the bladder [179-

181]. Recently, microsporidiosis is usually recognized as an opportunistic disease in immunodeficient patients (e.g., acquired immunodeficiency syndrome (AIDS) patients), children, elderly, transplant recipients, travelers and contact lens wearers. The four most common human microsporidian species, *Enterocytozoon bieneusi*, *Encephalitozoon intestinalis*, *Encephalitozoon hellem* and *Encephalitozoon cuniculi* have also been reported in various species of birds [182-185].

Hosts

Microsporidia infect a wide range of vertebrate and invertebrate hosts [186]. Increasing evidence strongly suggests that birds are the definitive host for *Encephalitozoon hellem* [187]. The disease is reported in various species of birds including lovebirds [188, 189], ostrich [190, 191], hummingbirds [192], cockatoo [185], parrot [193], budgerigars [194], pigeons [195, 196] and finches [173].

Transmission, Carriers, Vectors, Spread

- 1) Microsporidian spores shed in the droppings of birds.
- 2) Infected birds are major sources of infection for other birds.
- 3) Companion birds without obvious clinical illness shed microsporidian spores. These birds may be a source of spore contamination for infections in humans and birds [188].
- 4) Improper husbandry, malnutrition, and concurrent infections with other pathogens may predispose to the development of disease.

Incubation Period

The incubation period is not clearly defined in finches. Nevertheless, following natural infection in nestling Gouldian finches, mortality occurred at approximately 12 days of age [173].

Clinical Signs

Signs of *Encephalitozoon hellem* infection in birds are typically vague and nonspecific. Some infections are self limiting and do not result in disease and some present as an unexpected death [197]. The duration of antemortem signs is reported to be a few hours to several days. Depression, decreased appetite, and weight loss are the most commonly reported clinical signs. The majorities of birds that develop disease are either juveniles or are immunosuppressed or both.

Encephalitozoon hellem infection has been reported in nestling Gouldian finches (*Erythrura gouldiae*) that were being fostered by Bengalese finches (*Lonchura domestica*) [173]. The infection resulted in death in 95% of the nestlings. Clinical signs were revealed as cessation of begging for food and retarded growth. Birds died within 2 days of the onset of signs. Gouldian finches raised by their parents did not show disease and it was therefore suggested that the Bengalese finches might have been the source of the infections.

Diagnostic Procedures

The diagnosis of microsporidiosis is based on clinical symptoms, histopathological examination, fungus isolation and laboratory diagnostics.

Laboratory Diagnostics

- 1) Detection of organism RNA by molecular technique such as PCR [181, 186].
- 2) Detection of organism antigens by immunohistochemical method [198].

Prevention

- 1) **Biosecurity**

Because shedding is so common in some birds such as lovebirds, practitioners should advise owners not to keep infected or suspected lovebirds in aviaries.

- 2) **Hygiene**

SECTION 4: PARASITIC DISEASES

Avian Mite Dermatitis

Etiology and Organism Biology

Avian mite dermatitis is most frequently caused by *Dermanyssus gallinae* or *Ornithonyssus sylviarum*. They are classified as blood-sucking mites.

Epidemiology

Avian mites have a worldwide distribution.

Economic Significance

In severe infestations, mite can produce anemia and result in increased mortality, especially in fledglings.

Public Health Significance

Mites are not typically observed on human skin. They can bite people when they are cleaning cages. Furthermore, when no birds are available, the mites will seek out other food sources, including humans. Therefore, humans are an accidental host of avian mites. Common clinical signs in humans include dermatitis, pruritic erythematous papules and vesicles on the skin. Signs are often alleviated when the mites are removed.

Hosts

Broad varieties of avian species serve as the natural hosts for *Dermanyssus* and *Ornithonyssus*.

Transmission

Dermanyssus gallinae spends the day in the cracks and bird-room crevices, moving onto birds at night to feed, but *Ornithonyssus sylviarum* spends its entire life on the host. *Dermanyssus* and *Ornithonyssus* can survive at least 5 months and 3 weeks, respectively without a host [199].

Clinical Signs

Common clinical signs in affected birds are depression and anemia. In heavy infestations, respiratory symptoms and a PCV of less than 30 per cent should be suspected. Blood-sucking mite can cause serious mortality among fledglings as well as adult birds.

Diagnostic Procedures

The diagnosis of avian mites is based on clinical symptoms, gross examination, isolation of mite and laboratory diagnostics. The *Dermanyssus gallinae* may not be detected on the birds because it spends the day in the nest or bird-room, and ventures out at night to suck the bird's blood.

Intervention Strategies

Intervention strategies consists of dusting or spraying the affected birds with a safe insecticide and vacating the cage or nest during the day and thoroughly cleaning it.

Toxoplasmosis

Etiology and Organism Biology

Toxoplasmosis is caused by infection with the obligate intracellular protozoan *Toxoplasma gondii*.

Epidemiology

Toxoplasmosis is worldwide in distribution.

Economic Significance

Toxoplasmosis is a significant zoonotic disease. Treatment, prevention or control measures requires the aid of a formal economic appraisal.

Public Health Significance

Congenital infections with *Toxoplasma gondii* can result in neural disorder (hydrocephalus, intracranial calcifications, and mental retardation) and chorioretinitis. Infection of pregnant women may lead to infection of the fetus or abortion, but it is often asymptomatic. Postnatal infection is usually asymptomatic in immunocompetent children and adults, but the clinical signs, including transient cervical or occipital lymphadenopathy may also present. Immunocompromised persons exhibit severe signs including pneumonia, encephalitis, and chorioretinitis[200, 201].

Humans become infected by ingesting oocysts that are shed by cats or by consuming infected intermediate hosts. *Toxoplasma* can be transmitted from mother to fetus. Person-to-person transmission does not occur by direct contact, but transmission by blood transfusion or organ transplantation has been reported.

Hosts

Toxoplasmosis is a parasitic disease of mammals, birds, and reptiles. More than 63 species of birds and 27 species of other animals become infected from ingestion of oocysts

and develop cysts in tissues without passing oocysts in the feces [202]. Cats are the definitive host for *Toxoplasma gondii*. Mammals and birds are considered as intermediate hosts. *Toxoplasma gondii* infection is noted primarily in Galliformes and passerines [203], but has been diagnosed in other avian species such as parrots, raptors and owls [75].

Transmission, Carriers, Vectors, Spread

- 1) Cats become infected following ingesting an infected intermediate host, and will shed oocysts in their feces for 1-3 weeks following infection. Oocysts become infective at 1-5 days after excretion. Oocysts can remain viable in the environment for several months.
- 2) Cats shed the infective oocysts, which are then consumed by an intermediate host such as a bird.
- 3) The route of infection is not known, but it is suggested that oocysts excreted in cat feces get into the aviary.
- 4) Flies and cockroaches can serve as transport hosts for the toxoplasma.
- 5) Earthworms ingest *Toxoplasma oocysts* and are a source of infection.

Incubation Period

The incubation period following natural infection is not defined in finches.

Clinical Signs

In general, toxoplasmosis affects mainly the central nervous system, but the reproductive system, skeletal muscles, and visceral organs may also be affected. Sometimes, the disease is inapparent or latent, with overt symptoms resulting at times of stress or immunosuppression. In birds, clinical signs include anorexia, diarrhea, blindness, conjunctivitis, head tilt, circling and ataxia. In the acute phase of toxoplasmosis, the birds may show severe respiratory signs. Birds may become blind several weeks after infection.

Diagnostic Procedures

The diagnosis of toxoplasmosis is based on clinical symptoms, histopathological examination, organism isolation and laboratory diagnostics.

Laboratory Diagnostics

- 1) The trophozoites are identified in impression smears of infected tissues.
- 2) Diagnosis is confirmed by injecting suspensions of infected tissues into mice, chicken embryos, or cell cultures.
- 3) PCR assay has been used for detection and identification of toxoplasmosis [204].
- 4) Serological tests for avian toxoplasmosis were considered impractical because most avian species do not seroconvert using the human dye test. A number of manufacturers produce ELISA kits for detection of toxoplasmosis in humans, but none of the kits is licensed for toxoplasmosis in finches.

Intervention Strategies

The following criteria should be considered to prevent and control the toxoplasmosis.

- 1) **Biosecurity**

Prevention of toxoplasmosis requires management protocols that remove the source of infective tachyzoites and oocysts by preventing contact with cats, rodents and arthropods.

- 2) **Disinfection**

Oocysts are destroyed by ammonia, drying, and a temperature of 55°C [205].

SECTION 5: ALLERGIC DISEASES

Allergic Alveolitis

Etiology

The allergens contained in feathers, epithelium, dander or fecal dusts are associated with allergic alveolitis. It is believed that there are about 300 factors which cause this disease, and it can occur at any age [206]. Various mechanisms are involved in the pathogenesis of the disease. The major mechanism of the disease is a type III allergic reaction. The antigens enter into the bronchioles and alveoli. After the release of vasoactive amines, there is a hypersensitivity reaction and increase in vascular permeability. Another suggested mechanism in the pathogenesis of this disease is type IV (cellular) reaction. Such reaction is due to the activation of T lymphocytes and macrophages, which are involved in development of alveolitis and subsequently lung lesions.

Public Health Significance

The duration of symptoms can vary from several months to several years following antigen exposure. Three forms of the disease are recognized: acute, subacute, and chronic. In the acute form, signs appear within a short time after exposure to an allergen and include cough, difficult respiration, fever, and chills. If exposure ceases at this point, the symptoms disappear and no treatment is necessary. In the subacute form, symptoms may not be found or are difficult to see, but in the chronic form, the disease may not be visible for several months. Affected humans have a chronic nonproductive cough, exercise intolerance, and weight loss. Chronic allergic alveolitis can develop in as little as 2 years, but usually takes at 10-20 years. The consequences of the disease are impaired ventilation, a reduction in total lung capacity (TLC) and permanent lung lesions such as pulmonary fibrosis [206, 207].

Prevention

The severity of the disease can be reduced by installing air purification systems as well as wearing facemasks while cleaning cages and bathing birds. Patients diagnosed with the chronic form of the disease may have no choice except to eliminate all exposure to birds.

CONCLUSION

This chapter provides an overview of public health issues of diseases that are communicable from Fringillidae to humans. All owners that work around finches should be

made aware and educated on zoonoses. Individuals with immune dysfunction, young children, pregnant women and the elderly are at increased risk for contracting various zoonotic diseases. Common biosecurity practices, including the use of masks, gloves, boots and coveralls are all important elements for prevention of zoonotic diseases. Routine injury prevention and appropriate hand hygiene are also essential. Eating and drinking should also be done away from the finch aviary.

APPENDIX 1. ZONOTIC DISEASES POTENTIALLY PRESENT IN PASSERINES AND/OR FRINGILLIDAE

Pathogen	Diseases/Etiology
Viruses	
	Arboviral Encephalitis (Eastern equine encephalitis, West Nile viral encephalitis)
	Influenza (Orthomyxovirus type A)
	Newcastle disease (Avian Paramyxovirus type 1)
Bacteria	
	Arizonosis (<i>Salmonella arizona</i>)
	Campylobacteriosis (<i>Campylobacter jejuni</i>)
	Chlamydiosis/Psittacosis (<i>Chlamydophila psittaci</i>)
	Colibacillosis (<i>Escherichia coli</i>)
	Erysipelas (<i>Erysipelothrix rhusiopathiae</i>)
	Listeriosis (<i>Listeria monocytogenes</i>)
	Tuberculosis (<i>Mycobacterium avium</i> , <i>Mycobacterium genavense</i>)
	Salmonellosis (<i>Salmonella typhimurium</i> , <i>Salmonella enteritidis</i>)
	Staphylococcosis (<i>Staphylococcus aureus</i>)
	Yersiniosis (<i>Yersinia pseudotuberculosis</i>)
Fungi	
	Cryptococcosis (<i>Cryptococcus neoformans</i>)
	Dermatophytosis (<i>Trichophyton</i> spp., <i>Microsporum</i> spp.)
	Histoplasmosis (<i>Histoplasma capsulatum</i>)
	Microsporidiosis (<i>Encephalitozoon hellem</i>)
Parasites	
	Avian Mite Dermatitis (<i>Dermanyssus gallinae</i> , <i>Ornithonyssus sylviarum</i>)
	Toxoplasmosis (<i>Toxoplasma gondii</i>)
Allergens	
	Allergic alveolitis

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Chapter 306

**THE ROLE OF *SPHINGOMONAS PAUCIMOBILIS* IN
INTERGENERIC CO-AGGREGATION AND MIXED
BIOFILM FORMATION WITH WATER BORNE
PATHOGENIC BACTERIA IN THE DISTRIBUTED
DRINKING WATER SYSTEM:
IMPLICATIONS OF PUBLIC HEALTH RISK**

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ABSTRACT

Sphingomonas a resident microorganism, is often encountered in the drinking water systems (DWDS). Its capability of growth over a range of temperatures, tolerance to chlorination and antimicrobial resistance patterns have recently raised health concerns. Several physiological aspects, for instance role of co-aggregation and biofilm formation especially with water borne pathogens by *Sphingomonas* remains largely unknown and deserve attention. In this study, a *Sphingomonas paucimobilis* strain isolated from Indian drinking water system was evaluated for its ability to co-aggregate and form mixed biofilms with *Salmonella typhimurium*, *Shigella flexneri*, *Escherichia coli* O157:H7. Strong co-aggregation of *Sphingomonas* with the waterborne pathogens *Escherichia coli* O157:H7 ATCC 32150, *Shigella flexneri* 2a and *Salmonella typhimurium* ATCC 25315 was observed by qualitative and quantitative methods with individual pathogens as well with a cocktail of the above three water borne pathogens. Highest aggregation index was observed with *Shigella flexneri* 2a followed by *Salmonella typhimurium* and *Escherichia coli* O157:H7. The aggregation with *Escherichia coli* O157:H7 could not be reversed by heat, protease and sugars (lactose and galactose). The results of this study have a strong implication on risk of mixed biofilms of these water borne pathogens in DWDS which

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may have re-grown or introduced (either through leakage or faulty treatment processes) and eventually develop into biofilms with pre existing *Sphingomonas*. An effective, non invasive treatment strategy preferably aimed in disrupting signalling molecules of *Sphingomonas* may be of value, for assuring safety of drinking water.

Keywords: co-aggregation, adhesin, biofilms, *sphingomonas*, protease

INTRODUCTION

The microbial ecology of water distribution systems has been an area of continued research, driven by the necessity to design innovative and effective control strategies for ensuring safe and high-quality drinking water. Existing results of microbial ecology of drinking water distribution systems indicate that pathogen resistance is greatly affected by the biodiversity of community and interspecies relationships. Biofilms have assumed considerable significance in this regard and biofilm formation and adhesion of bacteria on different surfaces and the EPS production by biofilm forming microbes have been well studied in general (Flemming et al., 2007; Furuhashi et al., 2008; Simoes et al., 2007a; Skillman et al., 1998; Tsuneda et al., 2003). *Sphingomonas* has been a recent focus for study on account of its ubiquitous presence in water, persistence under low nutrient conditions and potentially pathogenic features highlighting the concern in the presence of these bacteria in drinking water distribution system. The biological safety issues which are caused by *Sphingomonas* in the distribution systems stem from their persistence and ability to secrete exopolysaccharides as major components of biofilm (Johnsen et al., 2000). Bereschenko et al. (2010) demonstrated that Sphingomonads were responsible for initial biofilm formation. Aggregation has been established as one of the essential steps towards biofilm formation and it depends on a range of interactions such as synergistic, antagonistic, mutualistic, competitive, and commensalism interactions (Simoes et al., 2007b). Bacterial co-aggregation is essential for the development of multispecies biofilm communities' i.e., the adherence of different bacterial species to each other. Furthermore, co-aggregation is a significant phenomenon that facilitates interaction among different bacterial species in the biofilm (Foster et al., 2004; Rickard et al., 2003a). The interactions may occur between protein adhesins and polysaccharide receptors (Kline et al. 2009; Kolenbrander et al., 2006) or between proteinaceous adhesin-receptors (Daep et al., 2008). Therefore co-aggregation of *Sphingomonas* with waterborne pathogens may assume significance in view of development of multispecies biofilms of potential concern. Few studies, however have systematically analyzed aggregation, co-aggregation and biofilm formation by *Sphingomonas* sp. isolated from drinking water (Buswell et al., 1997; Simoes et al., 2007a,b; Simoes et al., 2008; Yu et al., 2010) In an earlier study, we isolated a *Sphingomonas* sp. from public drinking water system and characterized its biofilm formation (Gulati and Ghosh, 2017); simulation studies indicated that this strain was able to form biofilms on various plumbing materials used in drinking water systems. The objective of the present study was to further characterize the aggregation and co-aggregation behavior with water borne pathogens of this *Sphingomonas* strain. We envisaged that investigations of these interactions will help shed light on the role of *Sphingomonas* in formation of mixed species biofilms and enable designing of effective treatment strategies for safe drinking water.

MATERIAL AND METHODS

Bacterial Strains and Culture Conditions

Drinking water samples were collected from twenty different municipal sites and one hundred and forty isolates were screened by growing on *Sphingomonas*- specific growth medium (Yim et al., 2010) at 30°C and 120 rpm for 24 hours. One isolate with demonstrable biofilm forming ability was selected for further studies. 16S sequence of the isolate was submitted in genbank database as *Sphingomonas paucimobilis* strain MG6. The standard strain of *Sphingomonas terrae* MTCC 7766 was used in parallel for the sake of comparison. The following water borne pathogens were used in coaggregation studies: *Escherichia coli* O157:H7 ATCC 32150, *Shigella flexneri* 2a and *Salmonella typhimurium* ATCC 25315. Prior to experiments, cultures were revived, grown on BHI agar thrice, individual colonies were inoculated in BHI (Brain Heart Infusion Broth, Himedia, India) broth and processed as described above.

Mixed Biofilm Profile by *S. paucimobilis* MG6

The mixed biofilm of *S. paucimobilis* MG6 and *S. terrae* 7766 with water borne pathogens was formed by Crystal violet assay with modifications of Merritt et al. (2005). Standardized suspension of mid-log phase bacterial cultures were dispensed in each well of the polystyrene plates and incubated at 30°C. The unbound cells were removed by inverting the micro titer plate and vigorous tapping followed by rinsing the wells with phosphate buffer (pH 7.2). The adherent cells were stained with 200µl of 1% (w/v) crystal violet solution for 5 minutes. The wells were washed with deionized water extensively and the plates were allowed to dry. Following washing, 200µl of 30% (v/v) acetic acid was added to each well for 15 minutes; 100µl aliquots were then transferred to fresh micro titer plate and the absorbance measured at 585 nm. The variation from control *S. paucimobilis* MG6 was further confirmed by SEM.

Aggregation Assay

Both *S. terrae* MTCC 7766 and *S. paucimobilis* MG6 were further explored for their aggregation property. Fifty ml of the strains were harvested in their growth phases at 7000 *g for 5 minutes at 4°C. After washing it twice in Phosphate Buffered Saline (PBS), the cells were resuspended in PBS and OD₆₀₀ was adjusted to 1.0. The adjusted stock was used for aggregation analysis.

Visual Aggregation Assay

The degree of auto- and co-aggregation was determined qualitatively by the scoring method of Cisar et al. (1979). To determine auto aggregation, both the strains were

transferred to different test tubes, while in the case of co-aggregation, the cultures were mixed in pairs with each of the three pathogen, i.e., *Escherichia coli* O157:H7 ATCC 32150, *Salmonella typhimurium* ATCC 25315 and *Shigella flexneri* 2a. The pure and mixed cultures in pairs were vortexed for 30 sec and incubated at room temperature for 72 hours. The scoring range used is as follows: 0 represents no aggregation and turbid suspension; 1 represents small uniform aggregates in a turbid suspension; 2- easily visible aggregates in a turbid suspension; 3 -clearly visible aggregates which settles leaving a clear supernatant; 4 - large flocs of aggregates that settle instantaneously (Cisar et al. 1979; Simoes et al. 2008).

Spectrophotometric Assay

In order to quantitatively determine aggregation, test cultures in triplicates were prepared as described above for auto- and co-aggregation and incubated at room temperature. One hundred microlitre of the aqueous phase was transferred to microtitre plate and absorbance was recorded at 0, 2, 4, 24, 48 and 72 hours. Percentage of aggregation was measured using the following formula:

$$\text{Percentage of Aggregation} = [(A_{600} \text{ initial} - A_{600} \text{ after incubation}) / A_{600} \text{ initial}] * 100$$

Aggregation Studies by Fluorescence Microscopy

Cell aggregates were fixed in 10 ml of a 1% paraformaldehyde solution in 1X PBS for 2 hours at room temperature. The aggregates were mounted on a sterile glass slide and allowed to dry. Stained the slides with DAPI (4',6'-Diamidino-2-phenylindole) and observed under epifluorescence microscope (Zeiss Axio Scope A1 Microscope, USA).

Coaggregation Reversal: Effect of Heat, Protease and Sugars

To study the effect of heat treatment on the aggregation ability of *Sphingomonas* and the waterborne pathogens, both treated and untreated auto- and co-aggregating bacterial pairs were used for visual and spectrophotometric analysis. The bacterial cultures were incubated at 85°C for 30 minutes for describing co-aggregation reversal by heat treatment (Kolenbrander et al., 1985). The method described by Rickard et al. (2003b) and Simoes et al. (2008) was used to understand the protease sensitivity of the aggregation. The protease type XVI from *Streptomyces griseus* (Himedia, India) was added at the final concentration of 2mg ml⁻¹ and incubated at 30°C for 2 hours. After incubation, cells were harvested, washed twice and O.D. was adjusted to 1.0 at 600 nm. The untreated and treated strains were mixed in equal ratios. The experiment was carried out in triplicates (Ramalinganam et al. 2013). To study the effect of sugars on aggregation, filter-sterilized solutions of lactose and galactose were added to coaggregating partners to final concentrations of 50 mM to study the effect of sugars.

Mixtures were vortexed and tested for coaggregation using the method of Rickard et al. (2003a).

RESULTS

Mixed Biofilm Profile by *Sphingomonas*

The sequence of the isolate has been deposited in GenBank database (Accession No KX594380). Both biomass quantity and microbial activity are the parameters mostly used to estimate the amount of biofilm (Characklis et al., 1990). The Crystal violet assay has been described as a rapid method for calculating cell biomass; maximum biofilm production occurred between 24 to 48 hours as the cells are in the late stationary phase before senescence phase starts. Cells in the stationary phase start synthesizing the EPS which facilitates the attachment of cells to the surface (Dunne 2002). Mixed biofilms (*S. paucimobilis* MG6/*S. terrae* 7766 + *E. coli*, *S. flexneri* 2a and *S. typhimurium*) exhibited variation than that observed in the controls and reached maturation with 65-70 hours by the kinetics (Figure 1). Scanning electron microscopy (SEM) was used to visualize the cell-surface of biofilm forming *Sphingomonas* with adhered pathogens on PVC coupons. Tight adherence of the biofilm cells with PVC was observed for *S. paucimobilis* with the cells being enmeshed in exopolysaccharides (Figure 2). Though *S. terrae* produced less exopolysaccharides, adherence was observed on PVC. The results suggested stable attachment of pathogen-*S. paucimobilis* biofilm on PVC matrix.

Visual Aggregation Assay

Based on the scoring method, results of auto- and co-aggregation were analyzed. No aggregation of pure cultures as well as combinations after zero hour of incubation was observed. Hence the cultures were further incubated at room temperature. Aggregation was visible as turbid suspension after 24 hours and clear supernatant with clear aggregates after 72 hours (Figure 3). Based on the visual observation, scores were provided following the scoring range used in literature (Cisar et al., 1979; Simoes et al., 2008).

Spectrophotometric Analysis

The incubation time is an important requisite for determining the aggregation index of auto-aggregating bacteria as well as co-aggregating bacterial pairs as reported by Saravan et al. (2014). Therefore the aggregation index was determined for all the cases at 0, 2, 4, 24, 48 and 72 hours. Aggregation indices of *S. terrae* MTCC 7766 and *S. paucimobilis* MG6 were calculated to be 74.5% and 82.75% respectively after 72 hours of incubation (Figure 4). Aggregation index of *Sphingomonas* with *Shigella flexneri* 2a was found to be approx. 84.8% -highest when compared to other pathogens.

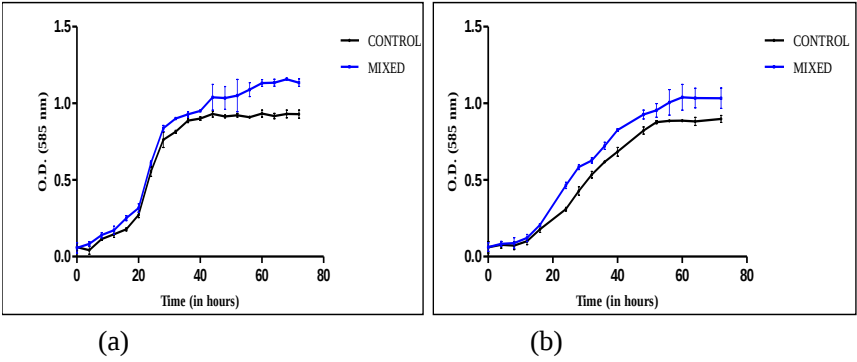


Figure 1. Kinetics of mixed biofilm formation of (a) *S. paucimobilis* MG6 (b) *S. terrae* 7766 with water borne pathogens (*E. coli*, *S. flexneri* 2a and *S. typhimurium*).

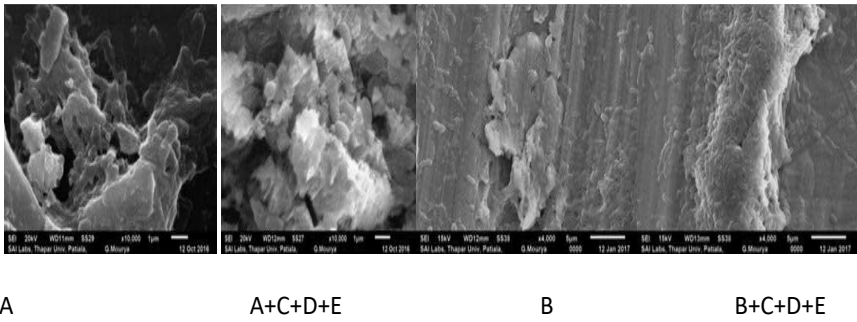


Figure 2. Scanning electron Micrographs of mixed biofilms of (a) *S. paucimobilis* MG6 (b) *S. terrae* 7766, where, A=*Sphingomonas* isolate; B=*Sphingomonas terrae* MTCC 7766; C= *Salmonella typhimurium* ATCC 25315; D= *Escherichia coli* O157:H7 ATCC 32150; E= *Shigella flexneri* 2a. Mixed biofilms were developed on PVC coupons.

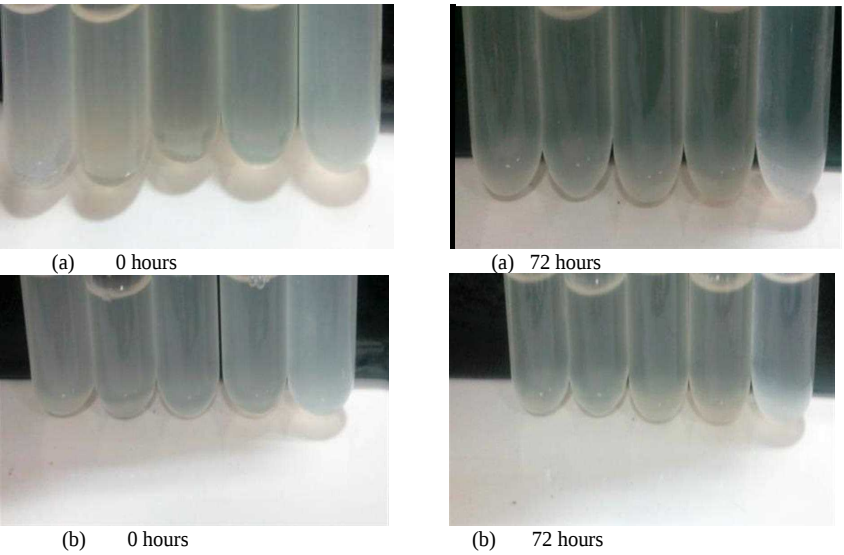


Figure 3. Visual aggregation assay of (a) *Sphingomonas paucimobilis* strain MG6 (b) *Sphingomonas terrae* MTCC 7766.

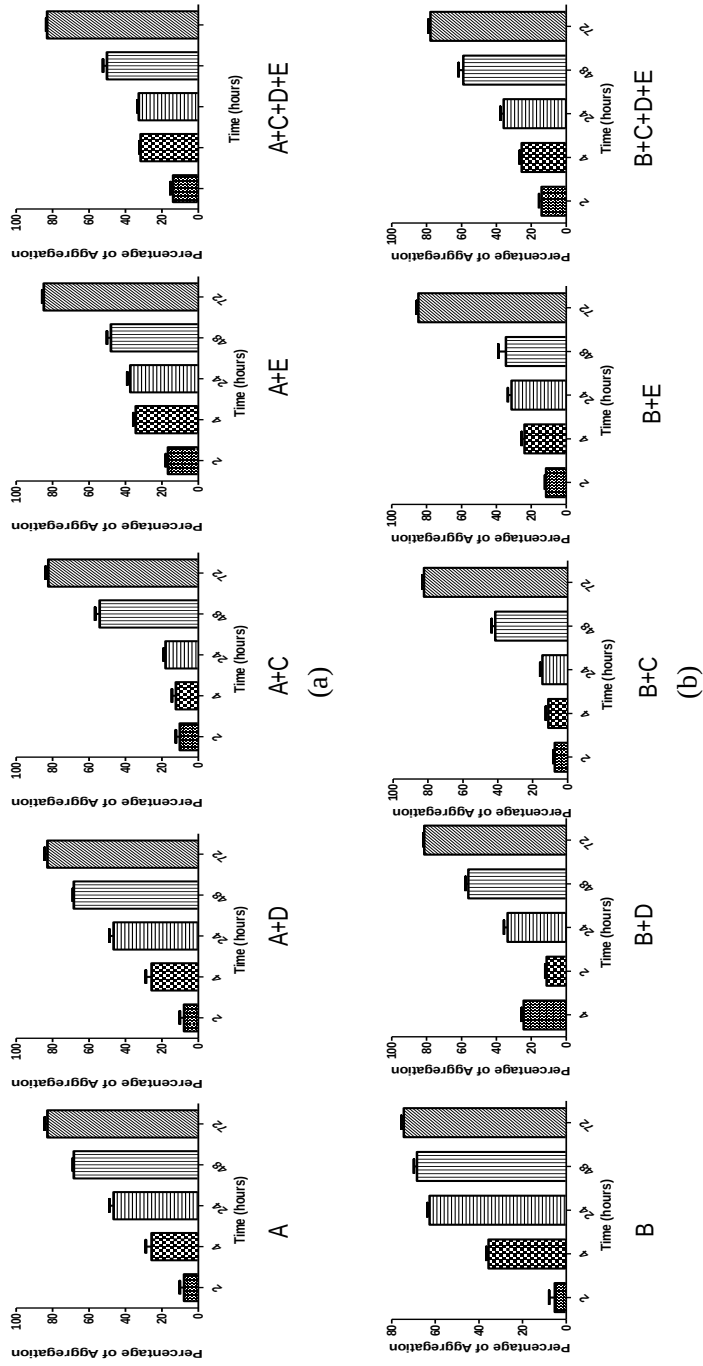


Figure 4. Aggregation Index at different interval of time (a) *Sphingomonas paucimobilis* MG6 and its various combinations (b) *Sphingomonas terrae* MTCC 7766 and its combinations; where, A = *Sphingomonas paucimobilis* MG6; B = *Sphingomonas terrae* MTCC 7766; C = *Salmonella typhimurium* ATCC 25315; D = *Escherichia coli* O157:H7 ATCC 32150; E = *Shigella flexneri* 2a.

Visualization of Aggregates by DAPI

Direct staining by DAPI (4',6-diamidino-2-phenylindole) is a method of choice, the DAPI molecules bind to DNA and fluoresce intensely. The enhancement in aggregation ability of *S. paucimobilis* MG6 in the presence of three pathogens could be clearly depicted by DAPI staining. Furthermore, a cocktail of all three pathogens used to co-aggregate with *Sphingomonas* indicated a similar result. In fact the aggregating pairs showed a higher level of interactions as compared to the visual aggregation test for these strains when observed by microscopy (Figure 5 and 6).

Nature of Interactions between Bacterial Strains

The heat treated and untreated pure cultures did not aggregate either after zero hour of incubation or following 2 hours of incubation. Co-aggregation between different combinations was significantly affected ($p < 0.05$) upon heat treatment with the exception of *E.coli* O157:H7, since aggregation index remained at 80% in both treated and untreated samples (Figure 7). Several *E. coli* O157:H7 surface proteins are thought to be important for adhesion and/or biofilm formation, therefore it is possible that the treatment processes failed to exert a substantial effect on binding. Co-aggregation reversal by Lactose and galactose was not observed, suggesting possibilities with other sugars.

The inhibition of aggregation of *Sphingomonas* with its aggregating partners might be due to surface protein like attachment (Figure 8s). *Sphingomonas* with its aggregating partner, *E.coli* O157:H7 showed no decrease in aggregation index. Treatment with sugars-lactose and galactose failed to revert co-aggregation (Figure 9 & 10)–. The differential behavior observed may be attributed to the enzyme type and concentration (Goldhar, 1995) important for affecting lectins during the treatment process, in addition to the nutritive media which modulates lectin production (Gilboa-Garber, 1988; Goldhar, 1995). However, further possibility of co-aggregation reversal need also be examined with other sugars.

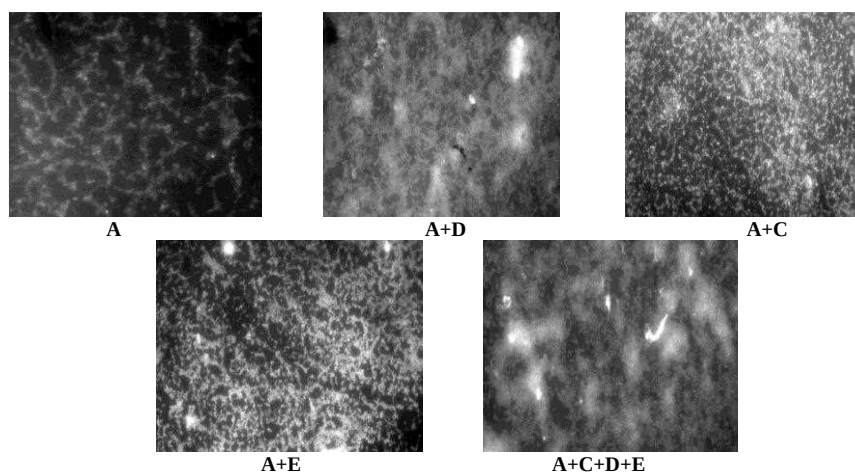


Figure 5. Photomicrograph of DAPI stained cells of auto- and co aggregating *S. paucimobilis* MG6 and its various combinations with pathogens.

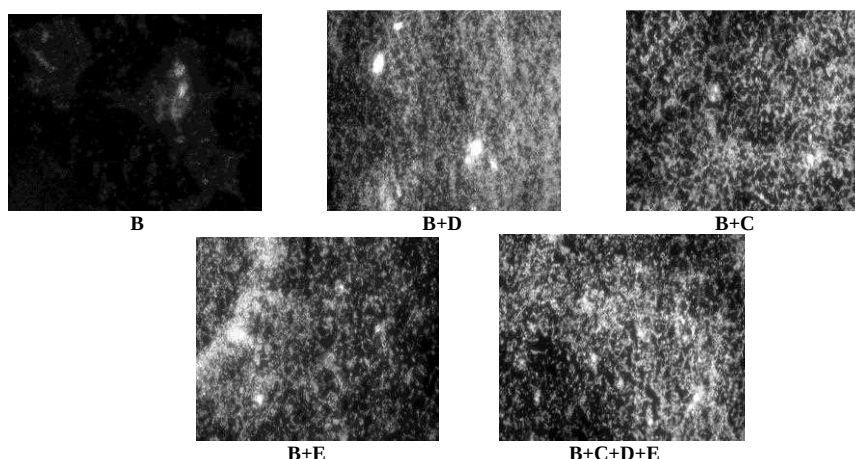


Figure 6. Photomicrograph of DAPI stained cells of auto- and co aggregating *Sphingomonas terrae* MTCC 7766 and its various combinations.

DISCUSSION

Previous studies have demonstrated that pathogens can be incorporated into heterotrophic drinking water biofilms enhancing their persistence (Gião *et al.*, 2008, 2009). It has also been suggested that for multi-species biofilms, it is very difficult to determine the positive or negative impact of different sessile microorganisms on pathogens, particularly the associations that occur within biofilms. Bacterial cells can interact within their own type or with other bacterial cells and facilitate the formation of biofilm. Aggregation has been well described for dental plaque isolates in complex media and aquatic species in potable water (Buswell *et al.*, 1997; Kolenbrander and London, 1993; Rickard *et al.*, 2003a). Cell to cell communication is requisite for initial colonization and therefore, biofilm formation. Both, autoaggregation and co-aggregation are significant in the process of communication. Autoaggregation in the biofilm boosts the adherence of genetically identical strains; these interactions are enhanced by increased hydrophobicity (Basson *et al.*, 2008). Whereas, in co-aggregation genetically different bacteria adhere to each other via specific molecules (Rickard *et al.*, 2003b). In the present study, we isolated and identified the *Sphingomonas* strain from municipal sites. This strain was chlorine resistant and could form biofilm in several plumbing materials commonly used in water distribution pipelines (unpublished observations). Detection of *Shigella*, *Salmonella* and *E. coli* O157:H7 from water samples of the *Sphingomonas* isolate prompted further exploration of the physiology of interactions of this isolate with water borne pathogenic bacteria. The aggregation, co-aggregation and biofilm formation by both the *Sphingomonas* sp. were evaluated. To the best of our knowledge, coaggregation of *Sphingomonas* with *E.coli* O157:H7, *Shigella* and *Salmonella* have not been reported. Our preliminary studies with the *Sphingomonas* have demonstrated the capability of this strain to produce EPS in line with earlier observations (Ashtaputre and Shah, 1995) and it also determines the immediate conditions of the life of biofilm cell (Flemming *et al.*, 2007) by providing a variable gel matrix.

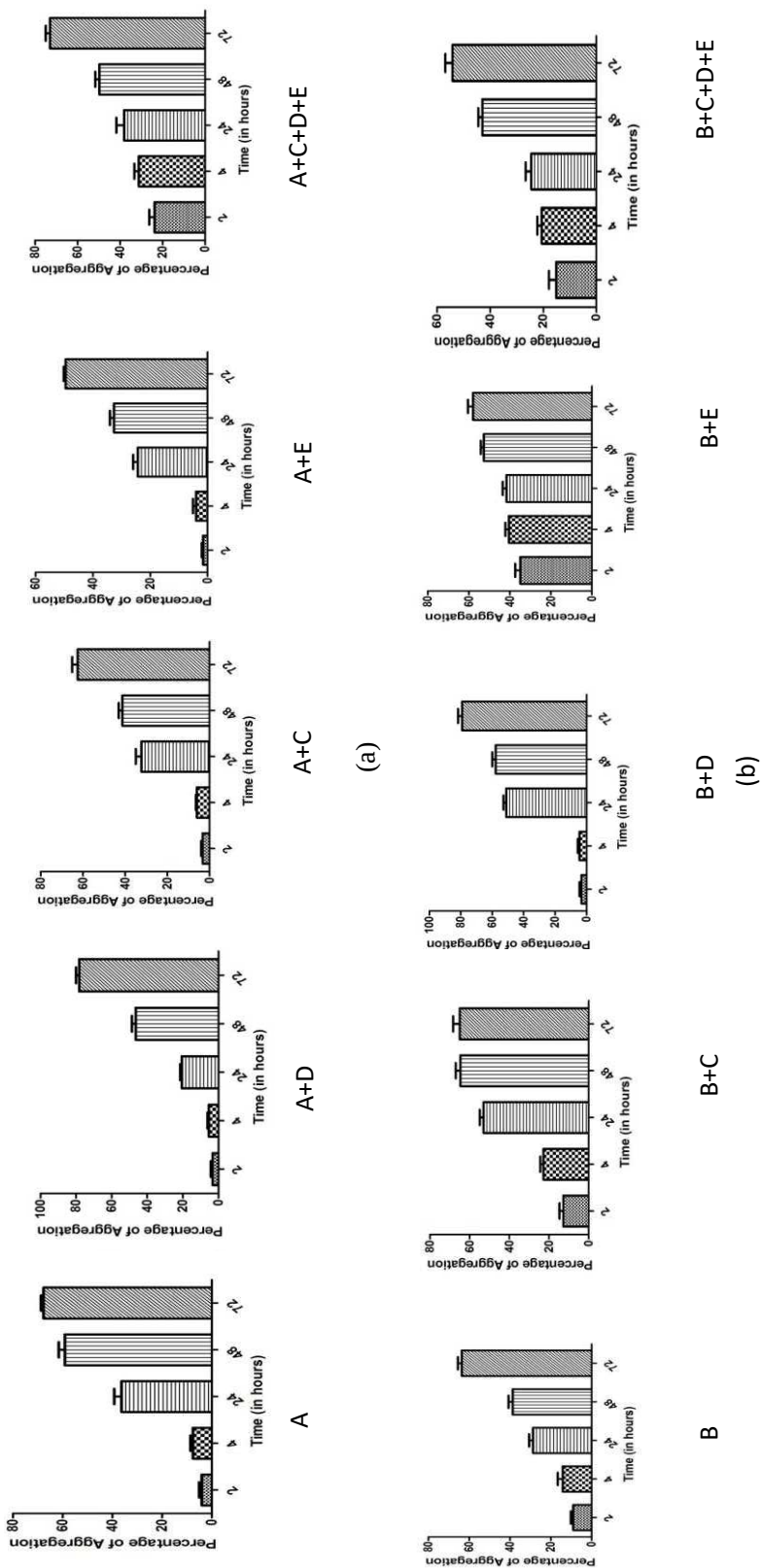


Figure 7. Aggregation Index observed at different time intervals after heat treatment (a) *S. paucimobilis* MG6 and various combinations (b) *Sphingomonas terrae* MTCC 7766 and various combinations.

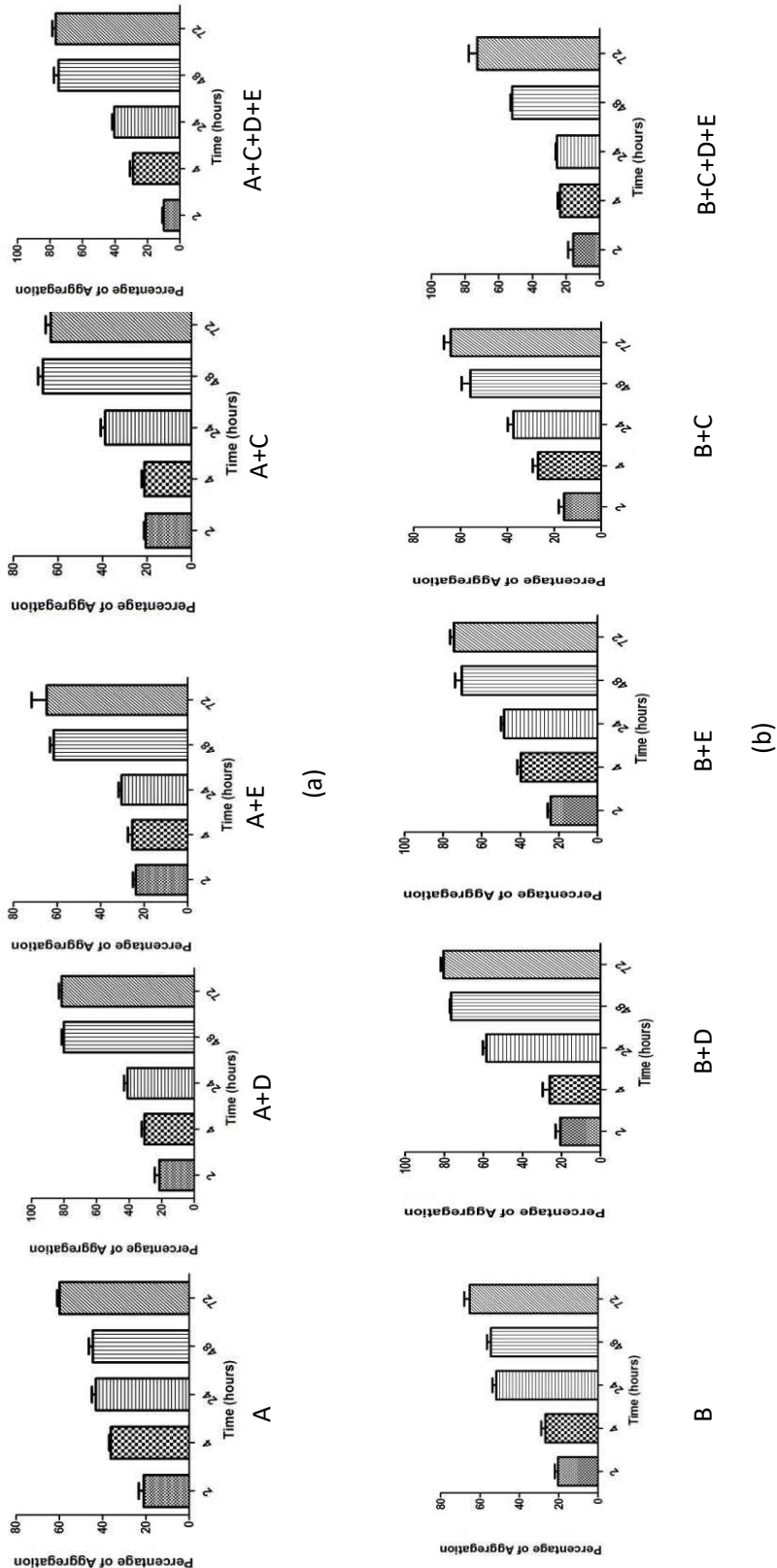


Figure 8. Aggregation Index observed at different time intervals after protease treatment (a) *S. paucimobilis* MG6 and its various combinations (b) *S. terrae* 7766 and its various combinations.

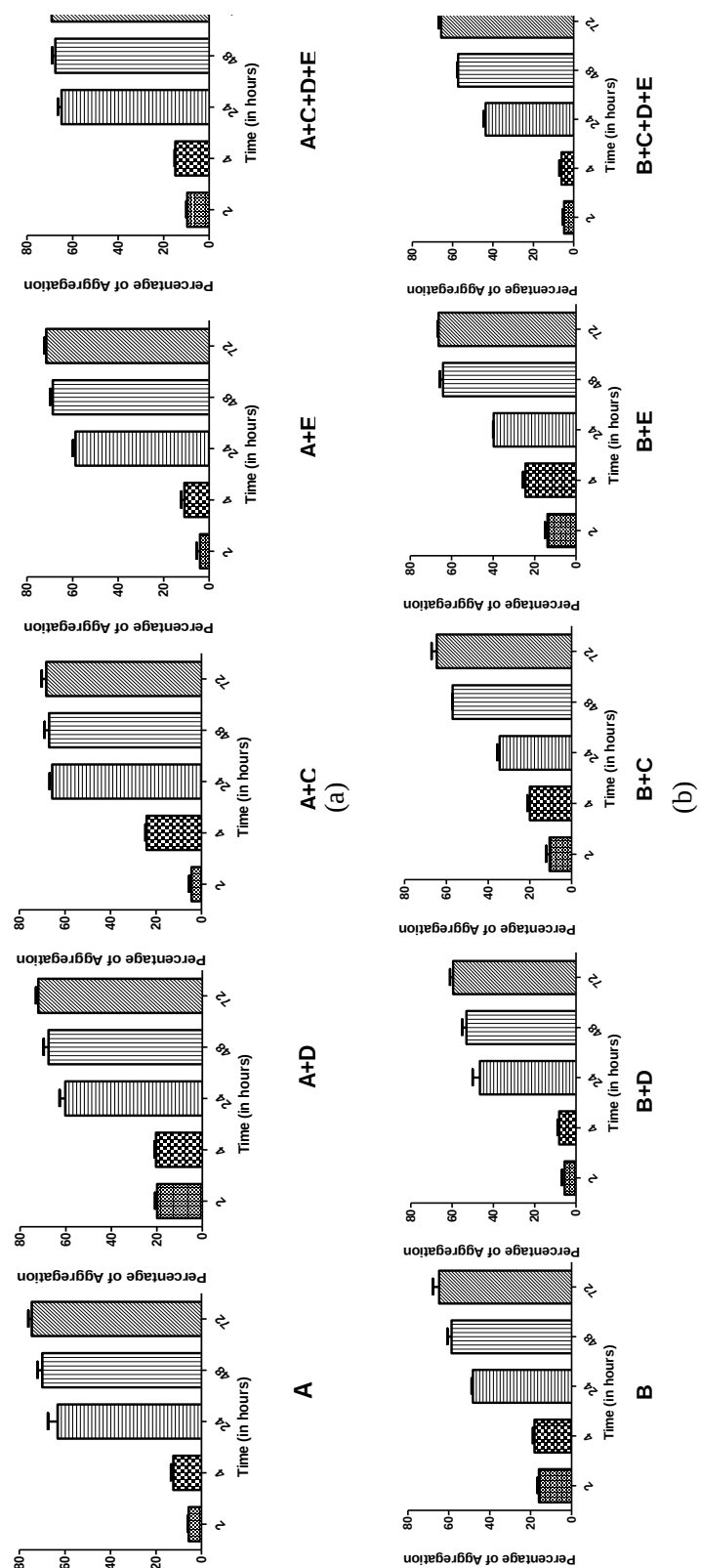


Figure 9. Aggregation Index observed at different time intervals after treatment with lactose (a) *Sphingomonas paucimobilis* MG6 and various combinations (b) *Sphingomonas terrae* MTCC 7766 and various combinations.

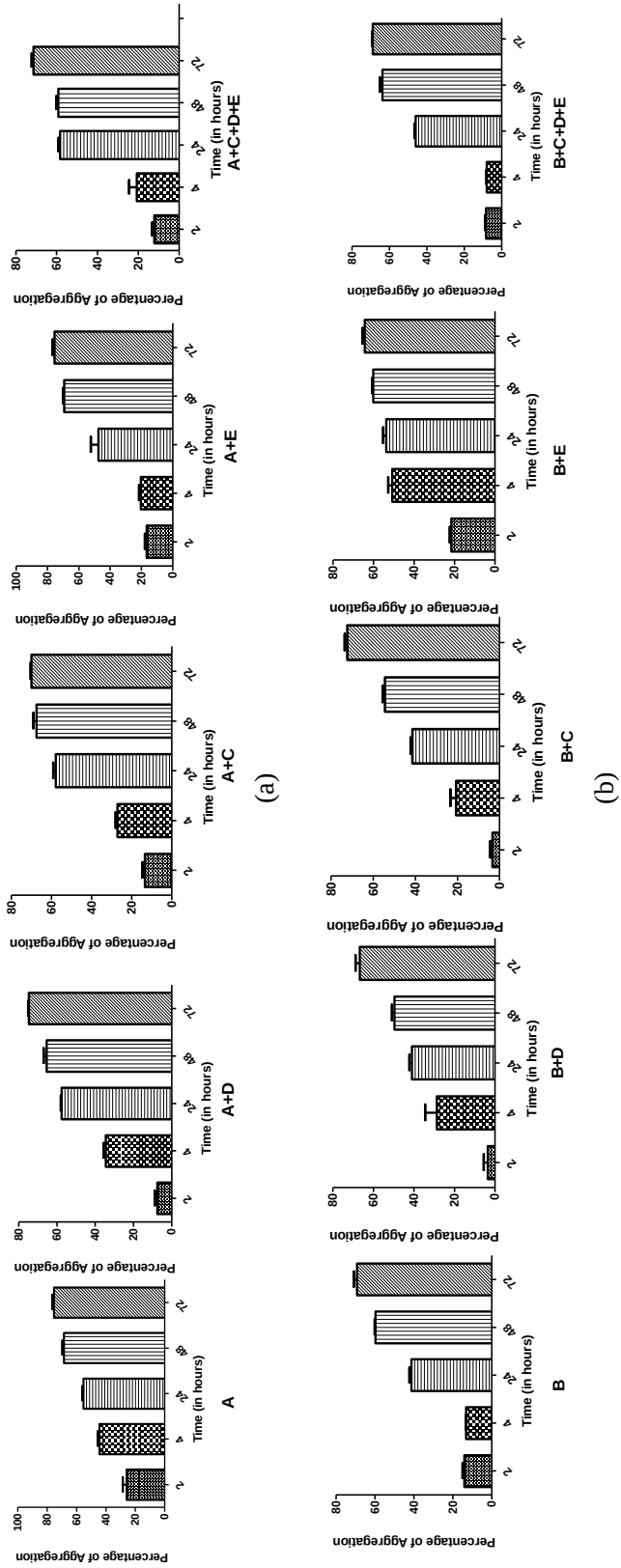


Figure 10. Aggregation Index observed at different time intervals after galactose treatment (a) *Sphingomonas paucimobilis* MG6 and various combinations (b) *Sphingomonas terrae* MTCC 7766 and various combinations.

Spectrophotometric analysis of aggregates indicated that with the increase in incubation time, percentage of aggregation increased. Also, co-aggregation of *Sphingomonas* with different pathogens was higher as compared to autoaggregation of *Sphingomonas*. It was observed that co-aggregation by bacteria promotes biofilm development by facilitating the attachment to the partner species, indicating the possibility of *Sphingomonas* to form biofilms with *Shigella flexneri* (Min and Rickard, 2009). This observation may be explained by the fact that aggregation depend on morphological features of bacteria such as size and density (Cisar et al., 1979) and require adequate incubation time prior to visualization. The results indicated both *S. terrae* and *S. paucimobilis* MG6 as floc formers. It was reported that visual aggregation testing is not an authentic method of measuring interactions between aggregating pairs (Buswell et al., 1997). Therefore, use of microscopic methods to investigate the potential aggregation between co-aggregating partners becomes inevitable beyond the screening test of the visual aggregation. DAPI staining was further used to investigate the role played by this bacterium in the co-aggregate formation.

Autoaggregation has been proposed to be an important mechanism whereby a bacterial strain within a biofilm expressed polymers to enhance the integration of genetically identical strains. Autoaggregating strains of freshwater bacteria were found to be numerically dominant in freshwater biofilm communities; moreover, autoaggregation together with co-aggregation has been shown to enhance the development of freshwater biofilms (Rickard et al., 2003a). Therefore, it was important to further investigate the co-aggregative abilities of *Sphingomonas* with waterborne pathogens.

Previous studies reported that the formation of co-aggregates by bacteria is the result of specific lectin-carbohydrate interactions between aggregating partners (Cisar et al., 1979; Simoes et al., 2008). Protein molecules present on cell surface of one partner behaves like adhesin and the saccharide molecule present on other one behave like receptor (Rickard et al., 2000; Rickard et al., 2003a). The sensitivity of adhesin molecules to heat and protease has been suggested as evidence for presence of lectin-carbohydrate interactions occurring between aquatic bacteria as well as pathogens (Rickard et al., 2000; Rickard et al., 2003a).

Co-aggregation by *Sphingomonas natatoria* have been shown to be important in promoting dual species biofilms (Rickard et al., 2000) and the importance of surface proteins in mediating co-aggregation and biofilm development has been emphasized. The results of our study suggest the ability of *Sphingomonas terrae* and *Sphingomonas paucimobilis* MG6 to show aggregation and co-aggregate three water borne pathogens (albeit with variation) and role of surface proteins/lectins in according the interactions; both strains could form biofilms. The ability to co-aggregate supposedly confers protection of the *Sphingomonas* cells from directed shear forces and enables them to proceed to a multigeneric biofilm. Overall our results imply that mixed biofilms involving either or more of the pathogens with *Sphingomonas* could be of public health concern in drinking water distribution system and more effective treatment systems need to be developed in light of these observations.

CONCLUSION

The present study demonstrated that *Sphingomonas terrae* MTCC 7766 and *Sphingomonas paucimobilis* MG6 isolated from Indian drinking water distribution system

possessed abilities to form biofilm, aggregation. Co-aggregation was observed with the water borne pathogens: *Shigella flelneri*, *Salmonella typhimurium* and *E. Coli* O157:H7; coaggregation reversal studies involving heat, protease treatment and sugars (lactose and galactose) indicated possibility of surface proteins or lectin to be in mediating the interaction; however conclusive evidence of interaction in case of *E. coli* O157:H7 could not be obtained. The results of this study provide valuable insights in the physiological behavior of *Sphingomonas* specifically towards waterborne pathogens which could be important when designing interventions for water safety.

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Chapter 307

PARENTING AND FAMILY LIFE IN HONG KONG: TRADITIONAL PERSPECTIVE, CONTEMPORARY RESEARCH AND INTERVENTION

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ABSTRACT

In the traditional Chinese culture, families showed several characteristics. First, male members generally held a superior position whereas females typically occupied a submissive role. Second, under the strong influence of Confucianism, filial piety was strongly upheld with a central focus on the father-son relationship. Third, because of the importance of maintaining harmony in the family, the collective interest (i.e., family interest) was placed above individual interest. In this book we try to convey the traditional and contemporary influences of parenting and family life in Hong Kong. We

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also attempt to conduct more theoretical integration and consider ways that can help to promote the family life of adolescents in the Chinese setting.

INTRODUCTION

Family is the cornerstone of the society. With specific reference to Hong Kong, there are several sources of the influence which affect family development. Primarily, as a Chinese society, Hong Kong families are under the influence of traditional Chinese cultural beliefs, although the related impact has gradually weakened. In the traditional Chinese culture, families showed several characteristics. First, male members generally held a superior position whereas females typically occupied a submissive role. Second, under the strong influence of Confucianism, filial piety was strongly upheld with a central focus on the father-son relationship. Third, because of the importance of maintaining harmony in the family, the collective interest (i.e., family interest) was placed above individual interest.

Because of the above attributes of traditional families, there are several characteristics of traditional Chinese parenting. First, gender-specific parenting was strongly upheld in traditional Chinese societies. For example, girls were socialized to be submissive to boys as reflected in the cultural belief of “*san cong si de*” (obeying the father before marriage, obeying the husband after marriage, and obeying the son when getting old). Second, fathers were expected to teach their children because of their superior role in the family. This is reflected in the traditional Chinese saying of “*yang bu jiao, fu zhi guo*” (it is the father’s fault to only feed his son, but not teach him). Finally, children were taught to regard family interests over their own interests, such as bringing honor to the family name. These expectations can be clearly reflected in the traditional writings guiding the behaviors of children, such as “*San Zi Jing*” (*Three character classic*) and “*Di Zi Gui*” (*Standards for being a good student and child*). In short, parenting in traditional Chinese culture can be regarded as “parent-centered” [1, 2].

As Hong Kong has been under the British rule for almost 150 years, families in Hong Kong have also been influenced by the Western cultural influences which are characterized by gender equality, respecting the interests of children, and emphasis of children rights. In terms of socialization, there are several characteristics of the related parenting characteristics. Fundamentally, children are not regarded as “property” of parents. Hence, their characteristics and interests are respected. Second, as the rights of children are emphasized, boys and girls are treated equally, such as having the equal right for getting formal education. Third, instead of focusing on suppressing one’s needs (because of the need to maintain harmony), children are encouraged to express themselves and demonstrate their talents and competence. In short, parenting under the Western influence can be regarded as “child-centered” [1, 2].

With reference to contemporary Hong Kong, families are under the influence of traditional Chinese cultural beliefs and Western ideologies. Besides, there are several social factors which also shape parenting in Hong Kong. First, with the highest housing price and cost of living in the world, both parents usually have to work to provide a sound financial foundation for the family. In fact, some parents take up more than one job in order to meet the expenses of the family. Obviously, this would adversely affect parenting quality because the related stress would have negative impact on individual and marital well-being of the couple. Second, several studies show that Hong Kong people had the longest working hours. Again,

this would adversely affect parenting quality as the availability of “quality time” of the parents may be limited. Third, poverty is a growing problem in Hong Kong. Roughly speaking, one out of four children experience economic disadvantages. Existing research findings show that poverty would adversely affect parenting quality in families experiencing economic disadvantages [3, 4]. Finally, divorce and re-marriage have grown in the past two decades. As there would be adjustment in divorced and re-married families, parenting would also be affected.

In view of the above-mentioned influences, it would be both theoretically and practically important to understand parenting phenomena in Hong Kong. Unfortunately, compared to research in the Western context, parenting research in Hong Kong are comparatively fewer. Hence, we have put together several papers on Chinese parenting and parent-child relationship in this special issue. The first four chapters are based on a large-scale study supported by the Research Grants Council of the University Grants Committee in Hong Kong. In the first paper, we examined the profiles of parental expectations in a sample of Chinese parents in Hong Kong. While Chinese parents showed conventional and high expectations on most aspects of their children’s future, they showed diverse attitudes in some areas, such as involvement in politics. In the second paper, we examined Chinese parents’ expectations towards sons and daughters where we found that there were different expectations about sons and daughters in contemporary Hong Kong. In the third paper, division of labor in parenting was examined in the same sample where parental differences in division of labour were shown. In the final paper, findings revealing profiles of Chinese parents’ beliefs about parental roles and responsibilities in Chinese parents were reported. In these four papers, besides normative profiles of responses, we also found that there were demographic correlates of parental beliefs and parenting practice amongst Chinese parents in contemporary Hong Kong.

As traditional Chinese cultural beliefs are influential for parental behaviors, we attempted to analyze a classic document on how children should be taught. In the fifth paper, we analyzed “Di Zi Gui” (Standards for Being a Good Student and Child). From the analyses, we found that some of the principles of “modern” parenting based on scientific studies are in fact reflected in Di Zi Gui, although some of the values and emphases on parenting are different in traditional Chinese and contemporary parenting. In the next paper, we attempted to review parenting in Hong Kong which provide interesting leads for theory development and future research. For example, it would be helpful to understand differences in parental influences (i.e., fathers versus mothers) on adolescent development. In the final paper, we examined how family life could be promoted via structured adolescent development programs. We argued that through positive youth development programs as exemplified by the Project P.A.T.H.S. in Hong Kong [5-8], adolescents could be helped to develop competence which would eventually promote the quality of family life.

It is our sincere hope that through this book, we can appreciate more the traditional and contemporary influences of parenting and family life in Hong Kong. With these papers, we attempt to conduct more theoretical integration and consider ways that can help to promote the family life of adolescents.

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Chapter 308

PARENTAL EXPECTATIONS AMONGST CHINESE PARENTS IN HONG KONG: PROFILES AND DEMOGRAPHIC CORRELATES

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ABSTRACT

Parental expectations and aspirations for their children's future is an important domain that exerts profound impacts on children's development. However, research on parental expectations in Hong Kong is grossly inadequate. Using a culturally-sensitive measure of parental expectations, the present study investigated the profiles of Hong Kong Chinese parents' expectations on their children's future and the related demographic correlates. Based on the responses of 5,707 parents recruited through a non-probabilistic quota sampling involving five generational cohorts of Chinese parents in Hong Kong, the present study showed that Hong Kong Chinese parents generally possessed conventional and high expectations on most aspects of their children's future. However, the parents possessed diverse attitudes toward children's involvement in politics, being exceptional, having a good social status, and pursuit of equality. Regarding demographic correlates, it was found that parental expectations were significantly associated with parents' age, parental role, education level, employment status, and family income. Specifically, mothers or parents who were older, receiving a lower level of education, retired or living on social security assistance or earning lower family income had more conventional and higher expectations on children's future. The present pioneer findings portray a holistic picture showing both commonality and variance of Hong Kong Chinese parents' expectations.

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INTRODUCTION

According to the ecological perspective, family as the primary ecosystem where children grow up plays an important role in shaping child developmental outcomes. Parents' expectations, which represent parents' values and aspirations for their children's future achievements in education, social and economic domains, are considered one of the most influential family factors [1]. For example, parental expectations on their children's academic success were positively associated with children's learning motivation and academic performance [2-4]. There is also a wealth of empirical evidence showing that parental expectations on children's future significantly predicted children's psychosocial competence and behavior, including self-efficacy, cognitive competence, depressive symptoms, prosocial behaviors, aggression, and so forth [4-8]. To some extent, parents' actions in socialization practices stem from their parental goals and expectations about what qualities a child should have and what a child should do [6, 9].

Based on the existing literature on parental expectations on children's future, three observations could be highlighted. First of all, parents generally have a high expectation on children's academic performance and educational achievement, which is closely associated with children's developmental outcomes in academic domain [4, 10]. In fact, the majority of studies in this area emphasized only on the educational dimension where researchers operationalized parental expectations by asking parents their expectations on children's course grades or future academic achievement indicated by the highest level of education [4, 11]. In contrast, parental expectations on their children's non-academic attributes, such as independence or autonomy, self-confidence and "family-related" qualities have only been considered in relatively fewer studies. For example, it was mentioned that parents adopting progressive child-rearing beliefs often emphasize children's independence or autonomy [6]. Few recent studies stressed on the importance of "fulfilling family obligations" such as "obedience" or "respect for parents" in parental expectations [12, 13]. To conclude, in addition to the dimension of education, it is necessary to investigate parental expectations from other aspects such as career development, economic status, family obligations, positive qualities, and so forth.

The second observation is that parental expectations on children's future vary from culture to culture. According to ecocultural theory, parenting practices and behavior are guided by parental expectations and parenting goals, which are deeply rooted in cultural beliefs such as ideological values, social norms and institutional patterns [9]. While Western parents' expectations are built on individualistic values, Chinese parents are influenced by collectivistic Confucian thoughts. For example, while American mothers placed more emphases on children's independence and anticipated self-confidence and assertiveness in their children, Chinese mothers highly valued interdependence and they stressed on the importance of children's good relationships with others [14]. A recent study also suggested that Chinese parents tended to rate children's family obligations as more important than European American parents [12]. Therefore, investigation of parental expectations on children's future should be done with reference to social values and beliefs embedded in a specific culture.

A related issue is that there is a severe lack of research on parental expectations in the Chinese context. As pointed out by McCoy, Maître, Watson and Banks [15], "much of the

research around parental educational expectations has come from the United States” (p. 537). Computer searches in Feb 2019 based on Scopus for the period of 1990-2019 using the term of “parent* expectation” as the search term yielded 1,291 publications, among which 42 results are related to “child’s future”. The number dropped to 11 when using the search terms “parent* expectation”, “child* future,” and “Chinese.” One possible reason is that cultural-specific measurement tools for Chinese parents’ expectations on children’s future are basically non-existent [16]. Against this background, it is necessary to investigate Chinese parents’ expectations of their children’s future by operationally defining the concept with culture sensitivity. It is especially critical when studying the relevant topic among Hong Kong Chinese parents given Hong Kong’s unique history.

On the one hand, Hong Kong is predominantly a Chinese community where parental belief systems are profoundly shaped by Confucian philosophy. Specifically, cultivation of virtues such as “*li*” (“propriety”), “*yi*” (“righteousness”), “*ren*” (“benevolences”), “*zhi*” (“wisdom”) and “*xin*” (“trustworthiness”) is of principal importance in Confucianism. Besides, Confucian thoughts consider education the primary means of achieving personal success and highlight related attributes that lead to educational achievement, such as diligence and effort. These ideas are clearly reflected in traditional Chinese sayings like “*wan ban jie xia pin, wei you du shu gao*” (“all jobs are low in status, except study which is the highest”) and “*qin neng bu zhuo*” (“diligence is a means by which one makes up for one’s dullness”). Fulfilling family obligation constitutes another important element of traditional Chinese culture. Children are socialized to prioritize familial and societal needs rather than individual needs. For instance, “*xiao*” (“filial piety”), “*chuan zong jie dai*” (“pass the line”) and “*guang zong yao zu*” (“bring honor to one’s families”) are traditionally emphasized as children’s obligations and responsibilities. Influenced by these ideas, Chinese parents would expect their children to have high educational achievement, fulfill family obligations and develop traditional virtues such as politeness, morality, and righteousness [16].

On the other hand, after being a British colony for nearly 150 years, Hong Kong becomes a melting point for Chinese and Western cultural values. It is argued that subculture in Hong Kong is more modernized and Westernized than that of Mainland China, which may result in less collectivism and more individualism in Hong Kong than in Mainland China. Thus, although traditional Chinese values have significant influence in Hong Kong, Hong Kong Chinese parents may differ from their Mainland Chinese counterparts regarding parenting practices and socialization goals. This argument has been supported by several pieces of empirical evidence [17, 18]. However, most studies on parenting in Hong Kong were guided only by Confucian values but failed to acknowledge the different historical and cultural contexts of Hong Kong from the generalized Chinese culture [19]. This is the case in the research field of parental expectations. For example, several recent studies have investigated Hong Kong Chinese parents’ expectations on their children’s future by taking into account only traditional Confucian values [13, 20]. Therefore, to fully address the related research gaps, the investigation of Hong Kong Chinese parents’ expectations should consider both traditional Chinese values and Western values, such as democracy, independence and justice.

The third observation is that there may be linkages between parental expectations of children’s future and demographic factors, such as parental roles (i.e., fathers versus mothers), parents’ education level and economic status. This is because parents’ own knowledge, learning experiences and living conditions may exert influence on their understanding and interpretation of parenting and socialization goals. For example, Tocu’s

[21] study showed that parents with a higher level of education had stronger progressive childrearing beliefs and considered children's autonomy more important. This study also found that fathers had stronger traditional attitudes toward childrearing and valued children's conformity more than mothers. Additionally, middle-class fathers and mothers were more likely to value autonomy in their children than their working-class counterparts [22]. Apart from these indirect supportive findings, direct evidence comes from research on parental educational expectation for their children. For example, parental expectations on children's academic achievement were positively predicted by parents' own education level and family income [23-25]. However, none of these studies were carried out in the Chinese context. Furthermore, to expand the scope of research, not only the educational dimension, but also economic, familial and social dimensions of parental expectations should be covered.

To sum up, there are mainly two research gaps. First, compared with ample research on parents' educational expectation for children, there is a dearth of research considering other dimensions of parental expectations on their children's future. Second, given the unique history of Hong Kong, it is important to investigate Chinese parents' expectations in Hong Kong as a special Chinese community that is different from Mainland China. However, limited evidence is available for understanding the profiles and demographic correlates of Hong Kong Chinese parents' expectations on children's future. To address these two research gaps, the present study attempted to investigate Hong Kong Chinese parents' expectations on children's future using a culturally-sensitive measurement tool. Profile of responses and demographic correlates of parental expectations were the foci of the present study.

OUR STUDY

The present study was approved by the Survey and Behavioural Ethics Committee of The Chinese University of Hong Kong. A non-probabilistic quota sampling method was used to recruit Chinese parents from five generational cohorts between the 1970s and the 2010s in Hong Kong. With the aim of achieving a sample of 0.1% of each cohort based on the most updated census data [26], parents were recruited through multiple sources including elderly centers, NGOs, parent education association, universities, secondary and primary schools, kindergartens, and the Internet.

The final sample consisted of 5,707 participants, among whom 1,770 (31.0%) were fathers and 3,710 (61.5%) were mothers. The participants aged between 21 to 97, and the mean age of fathers and mothers was 54.11 ($SD = 12.20$) and 51.00 ($SD = 13.94$), respectively. Regarding the participants' educational achievement, around 14.2%, 17.1%, 31.1%, 6.7%, 24.2%, and 4.7% participants had an education level at primary school or below, junior secondary school, senior secondary school, matriculation, college or university, and postgraduate or above, respectively. Besides, 45.7% and 10.6% of participants had full-time or part-time jobs, respectively. Among the remaining, 17.7% were homemakers, 1.3% were unemployed or between jobs, 20.9% were retired, and 1.8% were living on social security schema. With regard to monthly family income, 21% had HK\$14,999 or below, 46% were between HK\$15,000 and HK\$49,999, and around 27% had HK\$50,000 or above. More details about the demographic profile of the respondents are reported elsewhere [27].

Measures

Multiple measures were used in the survey. The parental expectation of Hong Kong Chinese parents was the focus of the present study. The participants were asked to rate the importance of 24 parental expectations for their children's attributes on a 5-point scale (1 = "not at all important," 5 = "very important"). Sample items included "I expect my children to be able to distinguish between right and wrong," "I expect my children to respect the elders," "I expect my children to respect human rights" and "I expect my children to have a successful career". A higher score indicates that a more conventional parental expectation which represents a higher expectation as well.

The Hong Kong Chinese Parental Expectation Scale (HKCPE) used in the present study was developed by the research team using a three-step process. First, in-depth individual interviews with 60 parents (two 1.5-hour interviews for each parent) on their offspring rearing experiences were conducted. Based on the interviewees' responses, a culturally adapted scale on parents' expectations on their children's future was created. Second, four professors in the research team conducted expert rating to examine the face validity of the original items. After dropping redundant or ambiguous items and items which were difficult to categorize, 34 items were retained to form a preliminary quantitative measure. Third, the 34-item scale was subject to preliminary reliability analyses in a pilot validation trial involving 805 Hong Kong Chinese parents. After deleting 10 items with low reliability, a 24-item HKCPE was obtained and further tested in the present study. The 24 items represented parental goals reflecting both traditional Chinese cultural (e.g., respect for the elders, honesty, and establishment of a normal family) and Western cultural (e.g., independence, respect for human rights, and pursuit of equality) values.

Apart from the above measure, we also included measures of gender expectation differences, division of labour in parenting tasks, beliefs in parental roles and responsibilities [27]. Finally, we also collected information on the socio-demographic characteristics of the respondents, including age, parental role (i.e., fathers or mothers), educational achievement, employment status, and family income.

Data Analyses

All data analyses were performed by the statistical package of SPSS 25 (IBM Corp., Armonk, NY, USA). First, reliability analyses were performed to investigate the psychometric properties of the HKCPE. Second, profile of participants' responses on each item was examined. Third, a correlational analysis was conducted to examine the correlation coefficient between parental expectation and age. Finally, several one-way between-subjects analyses of variance (ANOVAs) were conducted to examine the differences in parents' expectation on children's future in relation to different conditions of socio-demographic variables including parental role, educational achievement, employment status, and family income.

FINDINGS

Reliability analyses showed that the Cronbach's alpha of the HKCPE was .92, suggesting good internal consistency among the items. In addition, item-total correlation coefficients ranged between .31 and .66 and the mean inter-item correlation was .35. These findings suggest good reliability of the 24-item HKCPE used in the present study.

Profile of Responses

As shown in Table 1, except for three items (item 12, 13, and 15), other 21 items had a mean score over 4 on a 5-point rating scale, suggesting that Hong Kong Chinese parents considered most of the listed qualities important in children, reflecting a relatively conventional expectation on offspring's future. Over 70% of the participants considered the respective expectations important on 20 items. For example, over 95% of the respondents rated "be able to distinguish between right and wrong," "respect the elders," and "have a sense of responsibility" as important. For the four exceptions (i.e., item 12, 13, 17, and 24), 34.27%, 56.14%, 50.64%, and 66.80% of the participants considered "not involve in politics," "be an ordinary person," "have a good social status," and "pursue equality" important, respectively. These findings indicate that while Chinese parents in Hong Kong generally hold a conventional expectation on most aspects, they had diverse views on children's involvement in politics, being exceptional, having a good social status and equality.

Socio-Demographic Correlates

First, Person correlational analysis showed that parents' expectation was significantly correlated with age ($r = 0.08$, $p < .001$, $r^2 = 0.006$), suggesting that parental expectation was more conventional and higher if the parent was older.

Second, results of several one-way ANOVAs indicated the significant effects of the demographic variables on parents' expectation (F ranged between 6.47 and 29.42, $ps < 0.001$, see Table 2). Post-hoc comparisons using the Least Significant Difference (LSD) test were further performed to investigate how parents differed from each other in their expectation with regard to different demographic conditions.

For parental role, mothers ($M = 4.30$, $SD = 0.45$) held a more conventional and higher expectation on children's future than did fathers ($M = 4.23$, $SD = 0.47$, $F = 29.42$, $p < 0.001$, see Figure 1).

Table 1. Profile of responses (N = 4,989-5,692)

	SD	1		2		3		4		5		Positive response (options 4-5)	
		Not important at all		Slightly unimportant		Neutral		Slightly important		Very important			
		N	%	N	%	N	%	N	%	N	%	N	%
I expect my children to													
能夠分辨是非 be able to distinguish between right and wrong	4.73	0.58											
是有家教的人 is a well-bred person	4.67	0.60											
懂得待人接物 have interpersonal skills	4.59	0.64	19	0.33	21	0.37	285	4.99	1618	28.35	3739	65.52	93.87
尊敬長輩 respect the elders	4.67	0.59	14	0.25	23	0.40	205	3.59	1329	23.29	4117	72.14	95.43
包容及接納別人 be inclusive and accept others	4.52	0.66	13	0.23	31	0.54	369	6.47	1829	32.05	3434	60.17	92.22
不貪便宜, 能吃虧 will not go after petty advantages and can bear losses	4.39	0.74	28	0.49	46	0.81	569	9.97	2105	36.88	2936	51.45	88.33
做正直的人 be an honest person	4.65	0.61	14	0.25	26	0.46	238	4.17	1375	24.09	4030	70.62	94.71
可以建立正常家庭 be able to establish a normal family	4.52	0.71	18	0.32	42	0.74	491	8.60	1543	27.04	3580	62.73	89.77
追求公義 pursue justice	4.20	0.82	33	0.58	93	1.63	963	16.87	2180	38.20	2408	42.19	80.39
尊重人權 respect human rights	4.25	0.81	31	0.54	69	1.21	929	16.28	2092	36.66	2556	44.79	81.44
有責任心 have a sense of responsibility	4.71	0.56	13	0.23	20	0.35	157	2.75	1200	21.03	4286	75.10	96.13
不碰政治 not involve in politics	3.26	1.07	404	7.08	573	10.04	2705	47.40	1066	18.68	890	15.59	34.27
做個普通人 be an ordinary person	3.70	0.96	159	2.79	246	4.31	2039	35.73	1917	33.59	1287	22.55	3204
人生能有自主 have independent life	4.39	0.71	18	0.32	38	0.67	530	9.29	2183	38.25	2889	50.62	88.87
事業有成 have a successful career	4.03	0.86	45	0.79	146	2.56	1322	23.16	2222	38.93	1934	33.89	72.82
能自力更生 be independent	4.61	0.63	15	0.26	29	0.51	268	4.70	1525	26.72	3828	67.08	93.80
有好的社會地位 have a good social status	3.57	0.97	173	3.03	375	6.57	2223	38.95	1820	31.89	1070	18.75	50.64
能有競爭力 be competitive	4.11	0.82	40	0.70	118	2.07	1019	17.86	2498	43.77	1984	34.76	78.54
會結婚, 有同伴 will get married and have a partner	4.07	0.97	109	1.91	198	3.47	1202	21.06	1811	31.73	2347	41.12	72.86
至少大學畢業 graduate from university	4.01	1.00	151	2.65	227	3.98	1234	21.62	1877	32.89	2175	38.11	71.00
是異性戀 are homosexual	4.01	1.19	380	6.66	226	3.96	1009	17.68	1321	23.15	2681	46.98	70.12
有解難的能力 have the ability of problem solving	4.50	0.67	16	0.28	31	0.54	372	6.52	1944	34.06	3306	57.93	91.99
尊重法治 respect the rule of law	4.39	0.77	23	0.40	64	1.12	544	9.53	1620	28.39	2639	46.24	74.63
追求平等 pursue equality	4.12	0.84	40	0.70	99	1.73	938	16.44	1980	34.69	1832	32.10	66.80

Table 2. One-way ANOVAs

Variables	N	M	SD	F
Parental role				29.42***
Father	1769	4.23	0.47	
Mother	3709	4.30	0.45	
Education level				6.47***
Primary school or below	812	4.35	0.56	
Junior secondary school	976	4.28	0.48	
Senior secondary school	1773	4.27	0.47	
Matriculate	380	4.30	0.41	
University/Higher Education	1380	4.26	0.39	
Graduate school or above	268	4.19	0.45	
Employment status				14.80***
Work full-time	2608	4.23	0.44	
Work part-time	606	4.27	0.44	
Full-time homemaker	969	4.31	0.43	
Unemployed or between jobs	75	4.25	0.49	
Retired	1191	4.36	0.53	
Social security recipient	101	4.36	0.52	
Family monthly income (HK\$)				14.19***
< 4,000	397	4.46	0.46	
4,000 – 9,999	284	4.22	0.57	
10,000 – 14,999	494	4.31	0.53	
15,000 – 19,999	569	4.30	0.45	
20,000 – 29,999	869	4.23	0.47	
30,000 – 49,999	1167	4.23	0.43	
50,000 – 79,999	864	4.25	0.41	
≥80,000	690	4.27	0.41	

*** $p < 0.001$.

For educational achievement, parents with the lowest level (i.e., primary school or below) had a highest score ($M = 4.35$, $SD = 0.56$), suggesting a most conventional parental expectation among them. In contrast, parents with the highest educational achievement (i.e., graduate school or above) scored lowest ($M = 4.19$, $SD = 0.45$), suggesting that these parents held a least conventional expectation. Parents who completed junior ($M = 4.28$, $SD = 0.48$) or senior secondary ($M = 4.27$, $SD = 0.47$) school, matriculated ($M = 4.30$, $SD = 0.41$), or completed university education ($M = 4.26$, $SD = 0.39$) did not significantly differ from each other in their expectations on children's future (see Figure 2).

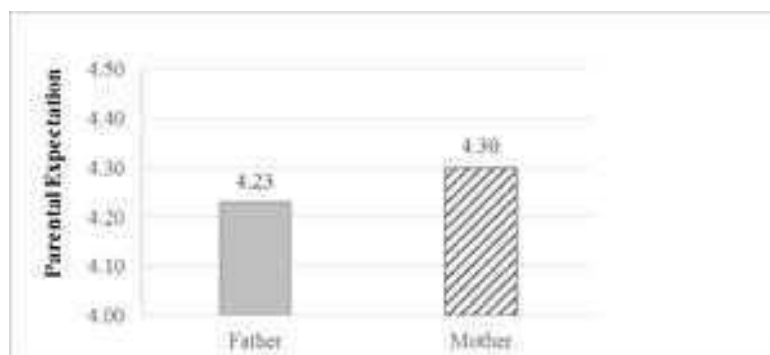


Figure 1. Parental expectation as a function of parental role.

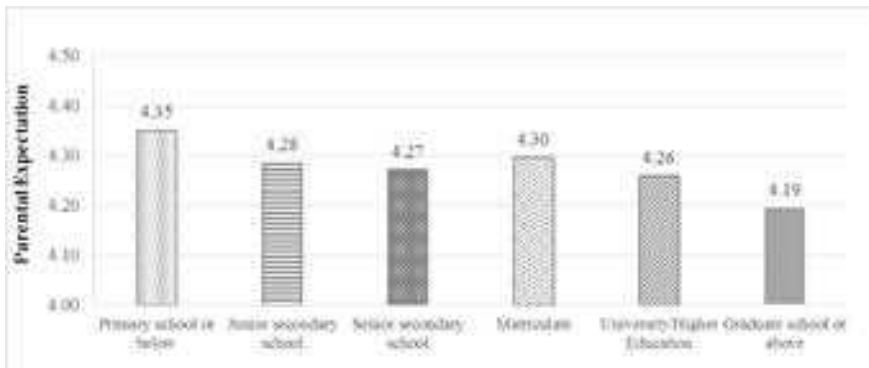


Figure 2. Parental expectation as a function of parents' education level.

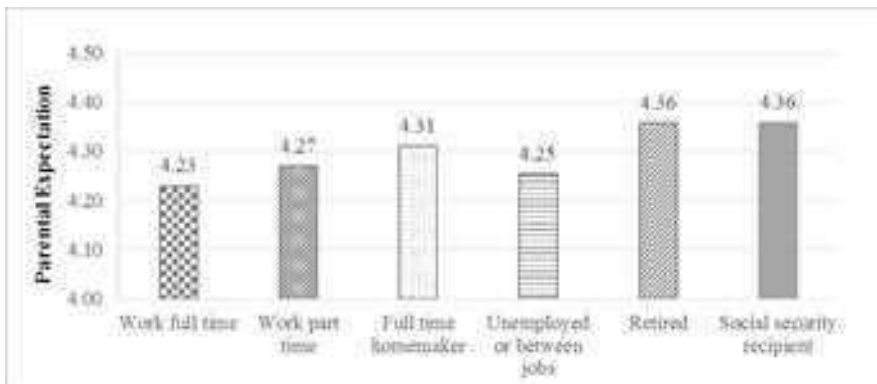


Figure 3. Parental expectation as a function of parents' employment status.

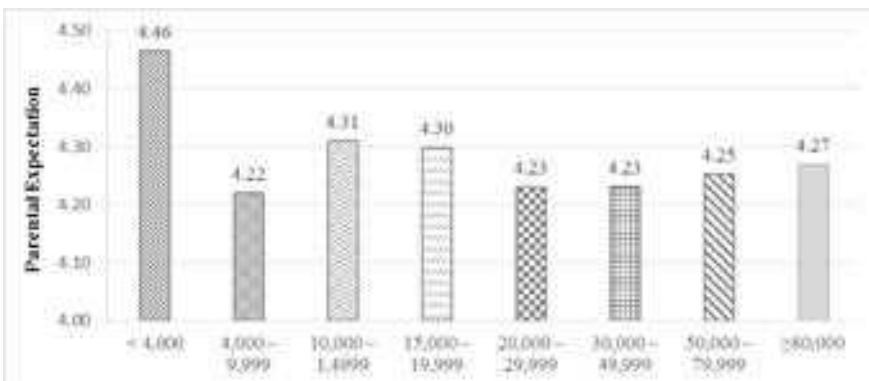


Figure 4. Parental expectation as a function of family monthly income (\$HK).

With regard to employment status, participants working full-time had the least conventional expectation, with their mean score ($M = 4.23$, $SD = 0.44$) significantly lower than that of participants working as full-time homemaker ($M = 4.31$, $SD = 0.43$), being retired ($M = 4.36$, $SD = 0.53$), or receiving social security allowance ($M = 4.36$, $SD = 0.53$). In contrast, participants who were retired or social security recipients had the most conventional expectation as they scored significantly higher than parents with other types of employment status (see Figure 3).

For family income, parents with lowest family monthly income (i.e., less than HK\$4,000) scored highest ($M = 4.46$, $SD = 0.46$), indicating that they had the most conventional parental expectation. For parents having other levels of family monthly income (all above HK\$4,000), there were only minor or insignificant differences in their expectations on children's future (see Figure 4).

DISCUSSION

The present study represents a pioneer attempt to examine the profile of responses and demographic correlates of Hong Kong Chinese parents' expectations on children's future. There are several strengths of the present study. First, this study investigated parental expectations in a sample of Chinese population, who constitute one-fifth of the world's population but have been under-researched in related fields [15]. Second, the culturally-sensitive measurement tool on parental expectations used in the present study took into account values and beliefs embedded in both Chinese and Western cultures. This ecological approach adds great value to the existing literature on parenting in Hong Kong which commonly ignored the influence of Western values [19]. Third, instead of focusing merely on parents' educational expectation for children, the present study looked at parental expectations from multiple aspects including economic, familial and social dimensions. Such a comprehensive investigation helps delineate a holistic profile of Chinese parents' expectations on children's future in Hong Kong.

Generally speaking, Hong Kong Chinese parents perceived that most of the expected achievements and qualities (e.g., establishing family, successful career, and virtues) were important, reflecting a conventional and relatively high expectation regarding children's future. For instance, over 70% of the parents treated "successful career", "competitiveness" and "completion of university study" as important for their children, echoing the general consensus that Chinese parents place great importance on children's academic achievement [28, 29]. Furthermore, over 90% of the parents highly expected morality, politeness, honesty, responsibility, and social skills in their children. Noteworthy, these qualities can be regarded as features of a "virtuous person" stressed by Confucianism, suggesting that parents' socialization goals are consistent with core Confucian values. Basically, our observation is consistent with a recent finding that poor Chinese parents in Hong Kong had high expectation toward children's education, fulfillment of family obligation and behavior [20]. These findings together echo the famous Chinese saying about parental expectation: "*wang zi cheng long*" ("hope that children will become outstanding and successful persons").

However, parents' diverse views toward some aspects of children's future should also be noted. First, although most parents expected their children to become good, well-educated and successful persons, nearly half of the parents did not consider "a good social status" as important for children. This appears inconsistent with a finding in another Confucian Heritage Culture society, South Korea, where parents had high expectations as well and strongly emphasized on their children's academic achievement as a means to gain wealth and higher social status [30, 31]. One possible reason of the present finding is that Hong Kong Chinese parents see that attainment of wealth and high social status are very stressful for their children. As a result, they tend to place less emphasis on the importance of high social status.

Second, over 65% of the parents did not mind children's involvement in politics and agreed that "pursuit of equality" was important. At the same time, "pursuit of justice", "respect for human rights" and "respect for the rule of law" in children were endorsed by the majority of the parents. These findings imply that a considerable proportion of Chinese parents in Hong Kong are open to Western liberal thoughts that value equality, democratic and young people's voice in social issues including political issues. Recently, other scholars also noticed that Hong Kong Chinese parents may adhere to both Chinese and Western values in childrearing and parenting actions [7, 27]. However, nearly 35% of the parents thought that not engaging in politics is important. This may be due to the fact that involvement in politics might be harmful to young people when we look at Chinese history in the past century.

Regarding demographic correlates, several observations could be highlighted. First, parental expectation was positively correlated with parents' age, indicating that younger parents imposed more unconventional expectations on their children. Besides, parents who were retired reported most conventional and highest expectations, which is related to the age effect as the retired parents should be older. Similar to our findings, a recent study reported that younger generations of parents in Hong Kong adopted love and nurturing parenting beliefs more than the older generations, suggesting a changing conception of childrearing and parental goals [27]. As the present study is the first one that directly relates parental expectations to their age, the finding should be tested in more studies in future.

Second, mothers' expectation was higher than that of fathers. This appears to be inconsistent with Tocu's finding that fathers had stronger traditional attitudes toward childrearing in Romania [21]. However, the present finding is in line with the result of one previous study in Hong Kong which found that Chinese mothers scored higher than did fathers on parental expectations of children's future [20]. Mothers' higher expectations echo the shift of a traditional thesis from "strict fathers and kind mothers" to "kind fathers and strict mothers" [32]. One possible explanation is that Chinese mothers have been playing a more and more salient role in taking care of and educating children in family [20], which shapes the mothers to have higher expectations on children.

Third, parents with lower educational achievement or lower family income had more conventional parental expectations such as higher expectation on children's educational, career, and familial achievement. A related finding is that social security recipients, who are supposed to have low family income, reported higher expectations on children's future. Our finding seems to be in line with Tocu's observation that parents with a lower education level had stronger traditional childrearing beliefs [21]. However, these findings are inconsistent with a recent study conducted in mainland China reported that parents with lower social economic status had lower expectations for their children [29]. Previous research in other cultures ALSO showed that parental educational expectation for children was positively associated with parents' own education level and family income [23-25]. Given the equivocal findings, future research needs to directly compare the associations between parental expectation and parents' education level and income in different cultures.

While the present study is pioneer in nature, it has several limitations. First, a quantitative research design was used. As the quantitative findings obtained in the present study are not able to reveal in-depth subjective feelings behind the numbers, such as why some parents did not value social status in children, future research should apply mix-methods design consisting of both quantitative and qualitative methodologies. Second, although Hong Kong represents a unique Chinese community and it is of great importance to examine parental

expectations in Hong Kong, it is necessary to conduct related research in other Chinese communities to enhance the universality of the present findings. Besides, it will be illuminating to compare findings obtained in different Chinese communities and reveal potential differences. Third, the present study only considered parents' gender but not children's gender. Although it is traditionally believed that Chinese parents put higher expectations on sons, there is empirical research failed to identify such a gender effect in Macao [33]. Another study even identified unexpected higher parental expectation on daughters in Mainland China [29]. Concerning the inconclusive findings, it will be interesting to directly compare parental expectations on boys and girls in Hong Kong and other Chinese societies. Nevertheless, together with other papers generated from this project [34, 35], this research project promotes our understanding of parenting expectations in Hong Kong.

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Chapter 309

GENDERED EXPECTATION TOWARDS SONS AND DAUGHTERS IN CHINESE PARENTS IN HONG KONG

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ABSTRACT

Based on the responses of 5,707 parents, this pioneer study examined Chinese parents' expectations about sons and daughters using the 12-item Chinese Parental Gendered Expectations for Sons and Daughters Scale (PGE). Results showed that the PGE was internally consistent. An examination of the profiles of responses to the items of the scale showed several observations: a) a significant proportion of parents held traditional expectations about sons and daughters; b) differentiation of expected parental roles in taking care of sons and daughters still persisted; c) traditional gendered expectations about sons and daughters were gradually changing. Results also showed that fathers and mothers did not significantly differ from each other regarding their gendered expectations about sons and daughters. However, lower educational level, occupational status in terms of engagement in non-full-time work, and low family income were associated with parents' higher endorsement of traditional gendered expectations about sons and daughters.

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INTRODUCTION

Parental expectation reflects the objective and requirement parents set for rearing children [1]. It entails significant implications for children's development. Studies showed that parents' expectation influences parenting attitudes, mediates parenting style, and shapes children's academic performance, psychosocial competence and developmental trajectories [1-4]. In Chinese culture, parental expectation has often been discussed with gender, i.e., sons versus daughters, the reason of which may be ascribed to the deeply ingrained gender ideology that women are inferior to men. According to Shek and Sun [5], this gender inequity has its social and cultural roots. In agricultural society, men naturally occupied the dominant position as they had more physical strengths and advantages in social production. As a result, men within the family usually had greater say and more authority in handling family matters, including child-rearing matters. Women, on contrary, became dependent on men to gain status, power and wealth [5]. From a cultural perspective, the ethics of Confucianism, which have prevailed China for more than two thousand years, advocate a submissive role of women to men and code of conduct women should obey [5-7]. The inferiority of women is well reflected in traditional Chinese sayings such as, "*nan zhu wai nü zhu nei*" ("men are breadwinners and women are homemakers") and "*nü zi wu cai bian shi de*" ("innocence is a virtue for women").

Against this social and cultural background, Chinese societies have been well documented with the gender ideology of son preference, together with social phenomena such as sex-selected abortion and sex-ratio imbalance [8-11]. An extensive review of literature reveals three observations. First of all, gender-stereotypic expectations are intrinsic to the socialization from parents which are often defined by traditional gender traits and identities [10, 12, 13]. For example, Liu's [13] study indicated that parents considered it critical to cultivate masculine characteristics for sons (e.g., strong, manly and ambitious) and feminine characteristics for daughters (e.g., gentle, considerate and sentimental). Higher socio-economic families seemed to adopt a more gender-neutral approach but did not go too far. Her findings were somewhat echoed by Ge's [12] study, which also suggested that Chinese parents largely expect the masculine characteristics (e.g., humorous, athletic, independent and creative) for sons, but both masculine and feminine characteristics (e.g., kind, independent, neat and creative) for their daughters. However, as Ge [12] argued, there were still noticeable features of gender stereotype, suggesting a relative stability of gender ideology. According to Sadker [14], these gender stereotypes can underestimate daughters' potentials and restrict their career choice.

Second, research shows a contradictory picture of parents' educational expectation for sons and daughters. Some researchers claimed that sons received higher educational aspirations from parents and bore more pressure, especially in rural areas of China [9, 10, 15]. In a study carried out in rural region of Gansu, one of the most impoverished regions in China, findings suggested higher maternal aspirations for boys (although the aspirations for girls were also high) and that girls were more likely to be called on for household chores [10]. The higher expectation was well reflected in practice that more domestic resources were invested in sons' schooling, which resulted in lower educational attainment of rural girls [11, 16].

Nevertheless, different voices also emerged where researchers argued no son preference in terms of parents' educational expectation [17-20]. For example, two recent studies [18-19] suggested that parents in fact held higher expectations for daughters for their secondary education, indicating a major improvement of gender ideology. This improvement for girls, asserted by many scholars, was an unintended consequence of Chinese one-child policy [18, 20] and the upheaval of society in the past few decades where younger generations of women had played a more active social role than ever before [7, 12]. It is also noted that most of these studies were conducted in more developed regions in Greater China. As Wang [11] argued, "children who live in urban areas with educated parents received better educational opportunities and experience less gender bias" (p. 3). Obviously, there are urban-rural differences in gendered expectations for sons and daughters in China.

Third, the favor of sons is highly associated with family responsibility. Research provides empirical evidence that in many regions, especially rural China, parents still expected their sons to provide support to them in their old age [6, 10]. This perspective gave rise to parents' beliefs that educating girls was a waste [10]. This pragmatic attitude was prevalent in families with limited resources who hoped to seek the maximum return of educational profits [21]. In addition, parents might feel obliged to shoulder the financial responsibility of their sons' marriage, making investment within a family even more tilted towards sons [22]. This expectation stems from the traditional agricultural society where daughters would leave the family after marriage, which means a loss in manpower. As a result, investment in daughters is comparatively less because they will become "outsiders" after marriage.

To sum up, the aforementioned literature indicates a general perpetuated gender differentiation in the light of parental expectation. Interaction effects were also found between geography, SES, generation, education and gender. Therefore, parents' expectations towards sons and daughters should be understood in specific sociocultural contexts. The focused context of our study, Hong Kong, is a unique place in terms of culture and society. On one hand, Hong Kong is a Chinese society with Confucian ethics and patriarchal norms permeating every aspect of society, including unequal gender role positioning [23]. Furthermore, Buddhist and Taoist thoughts also highlight the importance of men to women. On the other hand, it embraces Western cultural values to a larger extent than other communities in Mainland China, as it had been a British colony for over a century. The rapid social and economic development has led to a more favorable status of women. Recent statistics [24] show that female students have outnumbered male students in UGC-funded undergraduate (54.6%) and taught postgraduate programmes (62.5%), and reached 41.9% in research postgraduate programmes. In career field, women professionals such as Certified Public Accountant and lawyers have witnessed a continuous increase in the past decade [24], which all suggests a more equal gender status in Hong Kong.

Despite such a unique blend of Eastern and Western cultures in Hong Kong society, there is a scarcity of research that has attempted to explore parents' gender perspectives towards child rearing. As a response, we fill a gap in the literature by systematically examining Hong Kong Chinese parents' expectations towards sons and daughters. The present study draws on a culturally-sensitive measurement tool and includes various demographic correlates in the analysis. There are several objectives of this study. First, we attempted to examine the reliability of an indigenous developed measure of parental expectations about sons and daughters in a large sample of Chinese parents in Hong Kong. Second, we investigated the profile of responses to the items in the indigenous scale. Finally, socio-demographic

correlates of parental expectations about sons and daughters, including parental gender, education level, occupation status and family income were examined.

For the socio-demographic correlates, several hypotheses were proposed. For age, before of cohort effect (i.e., older people are more susceptible to traditional influences), it was predicted that age would be negatively related to gendered expectations about sons and daughters. On the other hand, because the Western influence and Hong Kong is quite a gender-equal society, it was expected that there would not be difference between fathers and mothers on the gendered expectations about sons and daughters. Regarding the educational and income correlates, it was expected that higher education background (hence higher family income) would be associated with a weaker endorsement of traditional gender stereotype expectations.

OUR STUDY

Ethical approval for this study was obtained from the “Survey and Behavioural Ethics Committee” at The Chinese University of Hong Kong. The participants in this study were 5,707 Chinese parents recruited from 5 out of 13 geographical districts in Hong Kong, including “Sham Shui Po”, “Wan Chai”, “Yau Tsim Mong”, “Northern”, and “Eastern Hong Kong Island”. The participants were recruited through the method of quota sampling to comprise five generational groups who had child/children born from 1970s to 2010s. The different generational and geographical groups collectively provided a mixed socioeconomic background of the participants who were from households with high, middle, or low income. These participants were recruited through multiple methods and sources. Specifically, for the participants coming from the oldest generational group, we recruited them through NGO service centers for elders, research institutes for aging, and associations on parental education. For the participants whose children were born in 1980s and 1990s, we recruited them through secondary schools, higher education institutions, NGOs and the Internet. For the participants who had children born in 2000s and 2010s, we recruited them through kindergartens and primary schools.

Among the final sample, around one third of the participants were men (31.7%) and two thirds were women (67.5%). The age scope of the participants was wide, ranging from 20s to 90s. Around half of the participants had two children and one third of them had one child. Less than one third of the participants had completed college or university education (24.2%) whereas a much smaller proportion of them completed postgraduate education (4.7%). Participants’ detailed demographic profile can be found elsewhere [25].

Instruments

The participants completed a questionnaire including demographic information and four scales measuring “Parental Expectations for Children”, “Parental Gendered Expectations for Sons and Daughters”, “Parental Roles”, and “Parental Beliefs”, respectively. In the present study, we focused on profiles of the “Parental Gendered Expectations for Sons and Daughters” (PGE here after) and related demographic correlates. The PGE scale contained 12

items outlining traditional parental expectations for sons and daughters, such as “sons are more responsible than daughters”, “sons are in greater need of ability to bring home bacon than daughters”, and “marriage is more important than a career to daughters”. A five-point rating scale (1 = “strongly disagree” and 5 = “strongly agree”) was applied with a higher score representing a more traditional gendered expectation for sons and daughters. The scale showed good internal reliability in this study with the Cronbach’s alpha of 0.90 and the mean inter-item correlation of 0.43.

The demographic information measured the socio-demographic characteristics of the participants, including gender, parental role (i.e., father or mother), age, educational level, occupational status, and total family income.

Data Analyses

We conducted the following analyses. First, we examined the reliability of the scale in terms of internal consistency. Second, we computed the percentage of positive or negative responses for each item to form the response profiles. Third, we conducted correlation analysis to examine the linkage between participants’ age and their gendered expectation for sons and daughters. Finally, several one-way ANOVAs were performed to see whether parents’ gendered expectations for sons and daughters could be related to different demographic factors including parenting role, educational level, working condition, and family income.

FINDINGS

Reliability analyses showed that the scale was internally consistent (Cronbach’s alpha = 0.90), with acceptable mean inter-item correlation (0.43) and mean item-total correlation (0.62).

Table 1 shows participants’ responses on each item. For 10 out of 12 items, a significant proportion of the participants (between 27.8% and 49.5%) gave positive responses which represent their endorsement of the traditional parental expectations for sons and daughters. For the two exceptional items (Item 6 and Item 12), over half of the participants (between 55.0% and 57.3%) endorsed the respective traditional gender beliefs about sons and daughters.

More specifically, for parents’ differentiated expectations towards sons and daughters (Items 1-3), over one third of the parents expected that “sons are more responsible than daughters” (34.9%), “sons are more capable of supporting the family” (48.7%), and “sons have stronger leadership than daughters” (34.6%). Regarding parental responsibilities and practices towards sons and daughters (Items 4, 9, 10, and 12), parental belief appeared to shift from “parents should always take care of children” as less than 30% of the parents thought that “parents must help sons to get married and establish family” (Item 4). However, 46.5% and 57.3% of the parents had an expectation that “father takes a more important role in educating sons” (Item 9) while “mother take a more important role in educating daughters”

Table 1. Profile of responses (N = 5,490-5,635)

I expect my children to	Mean	SD	1		2		3		4		5		Positive response (options 4-5)	
			Strongly disagree		Slightly disagree		Neutral		Slightly agree		Strongly Agree		N	
			N	%	N	%	N	%	N	%	N	%	N	%
兒子比女兒更有承擔 Sons are more responsible than daughters	2.91	1.36	1,284	22.79	778	13.81	1,609	28.55	1,091	19.36	873	15.49	1,964	34.85
兒子比女兒更需要有能力養家活兒 Sons are more capable of supporting the family than daughters	3.29	1.34	873	15.53	566	10.07	1,447	25.75	1,493	26.57	1,241	22.08	2,734	48.65
兒子比女兒更有領導能力 Sons have stronger leadership than daughters	2.96	1.30	1,119	20.0	714	12.7	1,835	32.7	1,162	20.7	775	13.8	1,937	34.56
父母有責任協助兒子成家立室 Parents must help their sons to get married and establish family	2.85	1.24	1,047	18.6	985	17.5	2,028	36.1	897	16.0	662	11.8	1,559	27.75
女兒會嫁得出 Daughters are able to get married	3.49	1.18	450	8.0	498	8.9	1,878	33.6	1,401	25.0	1,368	24.5	2,769	49.49
女兒斯文，賢淑 Daughters are decent and virtuous	3.63	1.08	262	4.7	423	7.6	1,826	32.7	1,707	30.6	1,367	24.5	3,074	55.04
如果女兒太能幹，會難找伴侶 If daughters are too capable, it will be difficulty for them to find a partner.	2.91	1.24	1,014	18.1	916	16.4	1,862	33.3	1,181	21.1	618	11.1	1,799	32.18
對女兒來說，婚姻比事業成功更重要 A marriage is more important than a successful career to daughters.	3.08	1.20	753	13.5	811	14.5	2,024	36.2	1,233	22.1	766	13.7	1,999	35.78
父親在教養兒子方面的角色比較重要 Father takes a more important role in educating sons.	3.35	1.19	530	9.4	670	11.9	1,799	32.1	1,514	27.0	1,096	19.5	2,610	46.53
我對兒子管教比對女兒嚴厲 Compared to daughter, I discipline my son much more rigorously.	2.88	1.25	1,089	19.5	811	14.5	2,004	35.9	1,045	18.7	634	11.4	1,679	30.07
可以的話希望能有個兒子 if possible, I wish to have a son.	2.93	1.32	1,160	21.1	638	11.6	1,972	35.9	875	15.9	845	15.4	1,720	31.33
母親在教養女兒方面的角色比較重要 Mother takes a more important role in educating daughters.	3.61	1.17	427	7.6	430	7.7	1,535	27.4	1,748	31.2	1,466	26.2	3,214	57.33

(Item 12), respectively. Besides, some parents (30%) reported that they disciplined sons much more rigorously. With reference to gender beliefs for daughters (Items 5-8), nearly half of the parents expected their daughters to get married (Item 5) and 55% of them expected their daughters to be decent and virtuous (Item 6). Besides, 32.2% of the participants held a view that “it will be difficulty for daughters to find a partner if they are too capable” (Item 7). Likewise, 36.8% of them regarded a marriage as more important than a successful career to their daughters (Item 8). Finally, 31.3% of the participants reported that they “wish to have a son if possible” (Item 11), indicating that nearly one third of the parents held traditional son preferences.

Based on the response profiles outlined above, it appeared that while most Chinese parents in Hong Kong generally did not show extreme gendered expectations towards their children, some parents still held gender stereotypical attitudes towards sons and daughters.

Regarding socio-demographic correlates of gendered expectations towards their children, the correlational analysis showed that parents' expectation for sons and daughters was significantly and positively associated with their age ($r = 0.24$, $p < .001$, $r^2 = 0.06$), meaning that the older the parents are, the more likely they hold a traditional gendered view towards sons and daughters.

Table 2. One-way ANOVAs

Variables	N	Mean	SD	F	η_p^2
Parental role				0.15	0.00002
Father	1762	3.16	0.83		
Mother	3677	3.15	0.86		
Educational level				94.42***	0.08
Primary school or below	795	3.61	0.89		
Junior secondary school	970	3.31	0.83		
Senior secondary school	1764	3.10	0.81		
Matriculate	379	3.12	0.85		
University/Higher Education	1372	2.94	0.78		
Graduate school or above	267	2.69	0.79		
Employment status				54.13***	0.05
Work full time	2596	3.01	0.79		
Work part time	601	3.13	0.84		
Full time homemaker	967	3.14	0.82		
Unemployed or between jobs	75	3.12	0.96		
Retired	1173	3.46	0.91		
Social security recipient	100	3.56	0.79		
Family monthly income				44.60***	0.06
< 4,000	383	3.65	0.97		
4,000 – 9,999	283	3.32	0.82		
10,000 – 14,999	490	3.29	0.89		
15,000 – 19,999	567	3.19	0.85		
20,000 – 29,999	864	3.20	0.80		
30,000 – 49,999	1165	3.05	0.78		
50,000 – 79,999	862	2.97	0.78		
≥80,000	682	2.87	0.79		

*** $p < 0.001$.

Second, as shown in table 2, parental role did not show a significant effect on parents' different expectations for sons and daughters ($F = 0.15$, $p = 0.70$), suggesting that fathers and mothers did not differ significantly in their gendered expectations for sons and daughters

(also see Figure 1). Different from parental role, educational achievement ($F = 94.42, p < 0.001, \eta^2_p = 0.08$), occupational status ($F = 54.13, p < 0.001, \eta^2_p = 0.05$) and family income ($F = 44.60, p < 0.001, \eta^2_p = 0.06$) served as significant predictors.

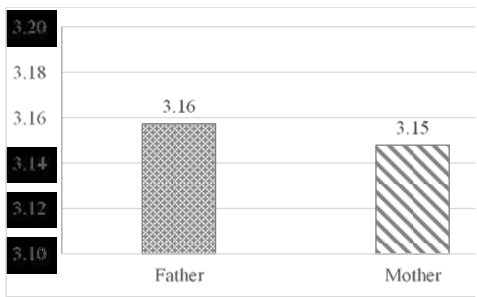


Figure 1. Parental gendered expectation towards sons and daughters as a function of parental role.

Further comparisons employing the LSD (“Least Significant Difference”) test indicated that parents’ score on gendered expectations for children decreased as their educational achievement increased (see Figure 2). Specifically, parents with primary school or below levels of education (i.e., the lowest education achievement) had a highest score of gendered expectations for children ($M = 3.61, SD = 0.89$), indicating a most traditional and gender stereotypical view towards sons and daughters among these parents. Parents who completed education at junior secondary school level showed the second highest mean score ($M = 3.31, SD = 0.83$), followed by the scores among parents having education at senior secondary ($M = 3.10, SD = 0.81$) or matriculated levels ($M = 3.12, SD = 0.85$), which were significantly higher than the score of parents who completed university/higher education ($M = 2.94, SD = 0.78$). Finally, parents had the highest level of education (i.e., graduate school or above) showed the least gender stereotypical expectations for sons and daughters as reflected by their lowest mean score ($M = 2.94, SD = 0.78$).

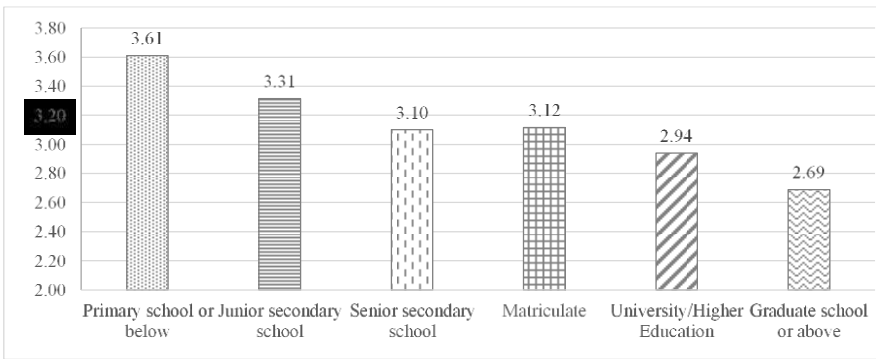


Figure 2. Parental gendered expectation towards sons and daughters as a function of parents’ education level.

Referring to parents’ occupational status, respondents who had full-time jobs showed the lowest mean score ($M = 4.23, SD = 0.44$), indicating their least traditional expectations for sons and daughters. Compared with these respondents, parents who had part-time jobs, or worked as full-time homemakers, or did not find a job had significant higher mean scores (M

ranged between 3.12 and 3.14). As depicted in Figure 3, parents who had been retired or living on social assistance scored the highest (M ranged between 3.46 and 3.56) and held the most traditional different expectations for sons and daughters.

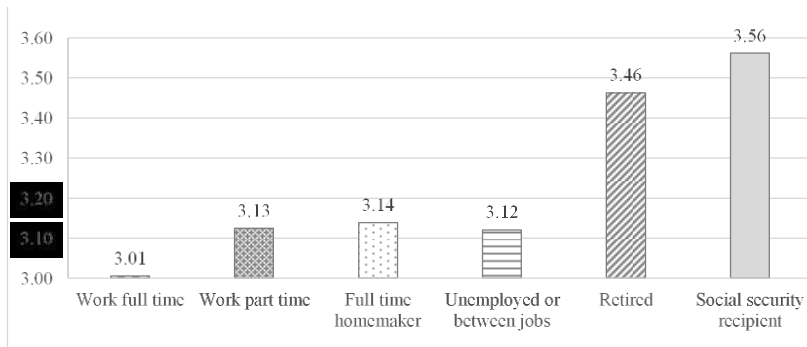


Figure 3. Parental gendered expectation towards sons and daughters as a function of parents' employment status.

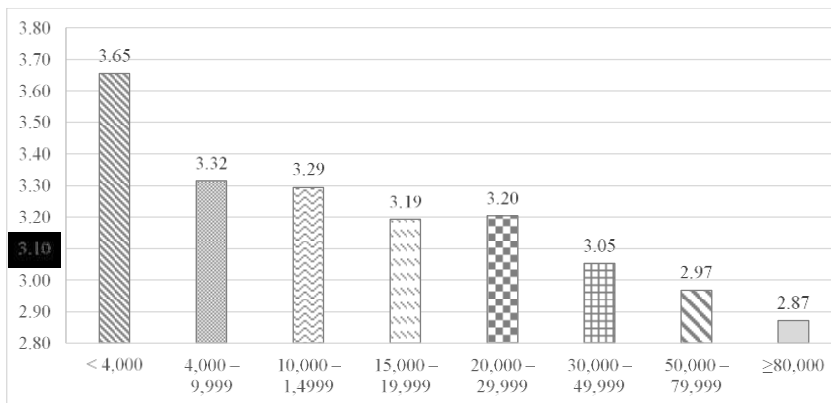


Figure 4. Parental gendered expectation towards sons and daughters as a function of family monthly income (\$HK).

Based on Figure 4, there is an obvious trend that parents' mean scores on gendered expectations for sons and daughters decreased as their family income increased. For example, parents who earned the highest monthly income (i.e., more than HK\$80,000) showed the lowest mean score ($M = 2.87$, $SD = 0.79$), suggesting that these parents upheld the least traditional and gender stereotypical expectations for their children. In contrast, parents who had lowest level of monthly income (i.e., below HK\$4,000) demonstrated the most traditional gendered expectations for sons and daughters indicated by the highest mean score ($M = 3.65$, $SD = 0.97$) (see Figure 4).

DISCUSSION

This pioneer study attempted to investigate the profiles of responses of Chinese parents' gendered expectations for their sons and daughters in Hong Kong as well as how their

traditional beliefs for sons and daughters were associated with demographic variables such as parental role, educational achievement, and family income. Generally speaking, the majority of Chinese parents in Hong Kong have changed their traditional gender stereotype towards sons and daughters in terms of differential expectations and parenting practice for sons and daughters. Yet, there are still some parents who held traditional gender views in some aspects such as son preference and importance placed on daughters' characteristics related to female gender role of home maker. In conjunction with other empirical findings [7, 22], our observations in this study suggest that while some traditional family and gender values have been changing gradually in Chinese communities with the influence of rapid social transitions and economic development, some traditional Chinese beliefs about sons and daughters still have place in the contemporary society [26].

Several observations could be highlighted from the present findings. First, traditional gendered expectations about sons and daughters were gradually changing. For instance, only around one third of parents expected sons to be more responsible and to have stronger leadership than daughters. As these qualities can be regarded as gender traits associated with men's traditional social role of resource providers as well as their superiority to women, this observation suggest that Chinese parents' socialization goals may have shifted away from the traditional Chinese gender ideology that "*nan zhu wai nü zhu nei*" ("Men are breadwinners and women are homemakers"). This speculation is consistent with the fact that in the past several decades, women have substantially participated in the labor market and provided financial support for the family through having full-time jobs [26]. Echoing this finding, shifts in parents' traditional gender beliefs for daughters were also observed. Specifically, around two thirds of parents did not agree that daughters' capability would hinder their intimate relationship, which appeared to be inconsistent with Chinese traditional belief that "*nü zi wu cai bian shi de*" ("innocence is a virtue for women"). Likewise, more than 60% of the parents tended not to regard daughters' marriage as more important than career, suggesting that parents placed more importance on daughter's career success than before. These findings are in line with previous conclusion that Chinese women have been encouraged to pursue educational and career opportunities and take other responsibilities than merely being housewives [7, 24].

Second, it is notable that a considerable proportion of parents still held traditional expectations for sons and daughters. For example, nearly half of parents still expected their sons to be more capable of supporting family and their daughters to get married. Besides, over half of parents expected their daughters to have feminine characteristics such as decent and virtuous that are considered important for women to fulfill their responsibilities in looking after family and attending to children. Besides, nearly one third of parents indicated their willingness to have a son, which reflected their traditional son preference. These findings indicate that traditional Chinese beliefs and gender ideology still affect parental expectations for sons and daughters in some aspects to a certain extent despite the increasing gender equality. This is consistent with Ge's [12] suggestion that gender ideology is relatively stable and noticeable gender stereotypical features still exist in Chinese society. The finding is also in accordance with the picture that parents imposed higher educational aspirations for sons than for daughters and devoted more resources to sons' schooling while required daughters to assist more with household chores [10-11].

The third observation is that differential parental roles in taking care of sons and daughters still persisted. Particularly, more than 46% of parents assumed fathers' greater

responsibilities in educating sons whereas over 57% of participants advocated the more important role of mothers in educating daughters. Noteworthy, different parental roles of fathers and mothers are largely attributable to their culturally prescribed gender roles in family. Traditionally, men bear obligations to secure family income and maintain family honor whereas women are responsible for “interior chores” (i.e., “*nan zhu wai nü zhu nei*” mentioned before). This gender expectation makes a Chinese father the more appropriate educator and role model in family to discipline sons who are expected to be a qualified father one day and further expand the reputation of the family lineage [27]. Likewise, a mother in family is more likely to be a role model for daughters in everyday parenting practice. Such differentiated parental roles of fathers and mothers in educating sons and daughters can be reflected in well-known idiomatic Chinese expressions such as “*yang bu jiao, fu zhi guo*” (to feed but not teach the child, the father’s fault indeed”) and “*fu zi zhi yan, bu ke yi xia*” (“the father should be strict with the son and not improperly close”).

Apart from the above mentioned findings, this study also delineated associations between demographic variables and Chinese parents’ expectations for sons and daughters. First, fathers and mothers did not significantly differ from each other in their expectations. This finding is consistent with previous evidence that differences between paternal and maternal perceptions of the ideal child in Hong Kong were minimal [28]. A more recent study also reported that women in general were as traditional as men regarding their attitudes towards gender roles [7]. This finding shows that paternal and maternal expectations about sons and daughters are not much differentiated in contemporary Hong Kong. Third, older parents showed greater adherence to traditional expectations for sons and daughters. Echoing this age effect, retired parents who were older reported a higher level of traditional gender stereotypical attitudes towards sons and daughters. Again, this finding is in line with Hu and Scott’s [7] observation that younger women were less traditional than their senior counterparts towards gender values. The significant effect of age is probably a reflection of cohort effect.

Third, consistent with previous studies on demographic correlates of parental beliefs and practice [7, 29], we found that higher educational level, employment with full-time work, and higher family income were linked with less traditional expectations and attitudes towards sons and daughters. The findings are consistent with a general expectation that social and economic development enables endorsement of less traditional attitudes towards gender values and gender equality [26].

Despite the above important findings revealed by the present study, several limitations are noted. First, this study is quantitative in nature which is unable to inform subjective perceptions underlying the quantitative results. For example, we do not know what factors and possible mechanisms make some parents not see daughters’ marriage as more important than career. Thus, to portray a holistic picture about parental expectations for sons and daughters, both quantitative and qualitative research methods should be applied in future research. Second, geographic influence on traditional beliefs has been identified [7]. As Hong Kong is a very urbanized city, it will be insightful to compare parental expectations for sons and daughters in different regions in Greater China. Finally, the present study investigated the demographic correlates to parental expectations towards sons and daughters while not taking into account the influence of other psychosocial factors, such as beliefs of collectivism or individualism and self-identity. Future research should include rich influential variables.

Nevertheless, the present study adds value to the existing literature and advances our knowledge of Chinese parents' expectations for sons and daughter in Hong Kong.

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Chapter 310

DIVISION OF LABOR IN PARENTING AMONGST CHINESE PARENTS IN HONG KONG

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ABSTRACT

In this chapter we report on an investigation into the family division of labor among Chinese parents in Hong Kong and its association with gender, educational level, occupational status and family income. It drew on a culturally sensitive scale developed for the people under studied. A total of 5,707 questionnaires were included in the analysis, and respondents showed a diversity of demographic characteristics. Analyses of the profiles of responses showed a persistence in gendered share of childcare responsibilities with mothers playing the main role in childcare and fathers playing an assisting role, although a more equalitarian gender attitude was noticed. Regarding other socio-demographic correlates, it was found that parents' educational level, intensity of market work, and family income in general were negatively correlated to the participation in childcare duties, a possible explanation of which was time availability. Endorsement of traditional gender stereotype was also related to the background socio-demographic factors.

INTRODUCTION

Gendered division of labor has been widely studied in Western societies. The higher level of women employment has been witnessed with a slow course towards an equal share of

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housework [1]. Women still tend to undertake the majority of housework and parenting routines [2]. On the other hand, a more equal share of child rearing duties has many benefits. Positive father's involvement is associated with children's wellbeing, as it decreases children's problem behaviors and facilitates their cognitive and linguistic development [3-6]. It is also highly related with marital satisfaction, although a complex picture has been presented across cultures [7, 8]. However, gendered division of labor has been an understudied field in Hong Kong. Against this background, the present study adds to the scientific literature in the field in two notable ways. First, it draws on a culturally sensitive scale to study division of labor in the local context. Second, as few researchers have specifically examined how division of labor interacts with socio-demographic factors as standalone factors besides gender, this study includes educational level, occupational status and family income in the analysis.

There has been a considerable body of literature focusing on gender inequality in sharing childcare duties with reference to factors such as policy, socioeconomic status and gender perception in Western societies. In general, the extant literature suggests a persistence in gendered division of labor in parenting, with mothers undertaking more intensive parenting while fathers taking a back seat, despite the fact that fathers are seen with increased participation in childrearing and other household responsibilities [9-14].

From a macro level, researches have specifically looked into social policy and gender norms and perspectives [14-17]. Most studies have found positive effect of family-friendly social policies such as supportive leave policy and flexible work arrangements on promoting gender equality in childcare and supporting work-family reconciliation [16, 18-20]. However, some studies have raised doubts about the extent to which the policy can be translated into practice. For example, Windebank [14] argued that in French society, the social policy aiming at promoting gender equality in domestic matters had limited effect in that it helped women reconcile work-family conflicts but failed to encourage or coerce men, or take care of the social feedback for them to engage more in childcare. Indeed, supportive non-parental childcare, as argued by Craig and Powell [15], did relieve mothers of childcare responsibilities to some extent. However, it was accompanied by the additional time devoted to paid work and higher subjective time pressure, while "fathers' time is more constant" (p.100). Therefore, they argued for a more father-friendly policy instead.

The gender perspective has been perceived as an important underlying reason to explain gendered division of labor at home [14, 21]. An egalitarian gender attitude very often predicts a more equal share of responsibilities [16, 22], but it presents a complex picture as it interplays with many other factors. Highly educated parents are often more receptive to progressive gender norms and have better understanding of proper childcare [9]. In a quantitative study of highly educated, dual-earner household in Spain, Martínez and his colleagues [23] found these parents tended to agree more with egalitarian gender roles in parenting. The factors of country and culture are also at play. For example, in a study of gender attitudes conducted by Buber-Ennsner and Panova [24], substantial variation was found among 14 European countries, Australia and Japan in terms of level of traditionalism. To be specific, Norway and Estonia held the most egalitarian view towards mother's role in childcare, while Hungary, Georgia and Russia held the most conservative view, for which the researchers postulated that the diversity could be ascribed to influences such as provision of public childcare, maternal leave, religion and culture.

From a micro level perspective, parent's educational level, income or work status have been a focus of concern [9, 12, 25, 26], although researchers did not always distinguish housework from childcare duties. Käsäälä and Oinas [26] carried out a study on dual-career couples ("career" was defined as performing professional or managerial work) in Finland who had higher educational level, work status and earning capacity. They found that dual-career couples assumed more equal responsibility in domestic division of labor than no-career parents, male-career couples and female-career couples did, which might be attributed to the limited time availability of dual-career women, or their likelihood to outsource or bargain their way out of unpaid domestic housework. Heisig's [12] quantitative study involving 33 countries echoes Käsäälä and Oinas' [26] findings to some extent, as it also revealed that household income found its expression in housework time. High-income couples devoted less time in housework than their low-income counterparts, and the contrast was even starker for women. Differed from these arguments based on the economic perspective, Craig [9] argued for a contradictory effect amongst educational level, earning capacity and time spent with children. In fact, her research provided empirical evidence that university-educated parents had higher receptivity to attentive child rearing and allocated more time to care of children, the effect of which outweighed the effect of a pull to the market. Her findings are consistent with a prior study conducted by Sundström and Duvander [27] in Sweden. Drawing on parental leave as a proxy for time for childcare, they found that both fathers' and mothers' income and educational level were positively associated with paternal leave use.

As can be seen from the above review of literature, the division of labor in childcare presents a complicated picture with sometimes contradictory results [28, 29]. Admittedly, participation in childcare is often conditioned by many different forms of social influences, and therefore cannot be easily generalized across countries and cultures. As argued by many researchers [30-32], cultural sensitivity should constitute a pivotal part in the study of parenting and always reflect culturally-appropriate values and beliefs.

Most of the related studies in the field have been carried out in Western contexts. Only a few studies have been conducted to examine how participation of housework duties interplays with social variables in mainland China [33, 34]. Overall, a gendered division of labor was found in these studies, with a conformity to traditional gender norms that women undertook the major housework and childcare. After all, "work-family balance is considered a woman's problem" [33]. Little research has been conducted in the context of Hong Kong.

In the traditional Chinese culture, men and women were seen to be very different. For men, as they have more strength, they are primarily responsible for farming activities. Therefore, men have more authority in agricultural society and they are leaders of the society. In contrast, women are basically responsible for domestic chores in the family and they serve as subordinate role to men. With reference to the role of men and women in the family, the husband has authority over his wife and he can divorce his wife if she does not perform well. These differences are further translated into the differential roles of fathers and mothers, where fathers are typically regarded as the leader of the family whereas mothers take up the caregiving tasks. These differences are existing in contemporary Hong Kong society [32].

Against this background, this article attempts to look at the profiles of responses of Hong Kong parents' division of labor and examine the socio-demographic correlates including gender, educational level, occupational status and family income. It draws on the Parental Division of Labor Scale which assesses three constructs: participation in childcare as the main

caregiver; participation in childcare as the assisting caregiver; attitude towards traditional gender stereotype. The research questions and hypotheses are as follows:

- 1) What are the response profiles of Chinese parents to the items in the scale?
- 2) Is there any gender difference in parental division of labor and gender belief?
 - Hypothesis 1a: Compared with fathers, mothers would be more involved as main caregivers.
 - Hypothesis 1b: Compared with mothers, fathers would be more involved as assisting caregivers.
 - Hypothesis 1c: Compared with mothers, fathers would have a stronger endorsement of traditional gender stereotypes.
- 3) Are parental division of labor and gender belief related to the educational level of the parents?
 - Hypothesis 2a: Because of work constraint, parents with higher education attainment would be less involved as main caregivers.
 - Hypothesis 2b: Because of work constraint, parents with higher education attainment would be less involved as assisting caregivers.
 - Hypothesis 2c: Parents with higher education attainment would have lower endorsement of the traditional gender stereotype.
 - Hypotheses 2d, 2e and 2f: similar expectations were proposed for spouse.
- 4) Are parental division of labor and gender stereotypes related to the occupational status of parents?
 - Hypothesis 3a: Compared with parents who committed more time to market work, parents who committed less time to market work would involve more as main caregivers.
 - Hypothesis 3b: Compared with parents who committed more time to market work, parents who committed less time to market work would involve more as assisting caregivers.
 - Hypothesis 3c: Compared with parents who committed more time to market work, parents who committed less time to market work would have stronger endorsement of the traditional gender stereotype.
 - Hypotheses 3d: Parents with spouse who committed less time to market work would involve less as main caregivers.
 - Hypotheses 3e: Parents with spouse who committed less time to market work would involve less as assisting caregivers.
 - Hypotheses 3f: Parents with spouse who committed more time to market work would have lower endorsement of the traditional gender stereotype.
- 5) Are parental division of labor and gender belief related to family income?
 - Hypothesis 4a: Family income would be negatively related to endorsement of main caregiving role.
 - Hypothesis 4b: Family income would be negatively related to endorsement of assisting caregiving role.
 - Hypothesis 4c: Family income would be negatively related to endorsement of the traditional gender stereotype.

OUR STUDY

This study is a part of the project entitled “Raising children in Hong Kong” which adopts a cultural-intergenerational perspective into Hong Kong parents’ beliefs in parental roles and responsibilities [31]. Researchers developed several scales in this project. In the present paper, we focus on division of labor in child rearing (“gendered parental roles”) assessed by the Parental Division of Labor Scale. There are five items in this scale, i.e., Item 1: In the domestic division of labor, I take charge of childcare. Item 2: In the domestic division of labor, I assist in childcare. Item 3: I am an implementer in childcare. Item 4: I am a decision-maker in childcare. Item 5: I agree with the perspective “men are breadwinners and women are homemakers”. Respondents were asked to score on a 5-point Likert scale with 1 indicating “disagree very much” and 5 indicating “agree very much”. These items assess three aspects of division of labor in the family, including whether one plays the role of main caregiver (items 1, 3 and 4), whether one plays an assisting role in childcare (item 2) and attitude towards the traditional view on family division of labor (item 5).

Table 1. Demographic characteristics of the participants (n = 5707) [31]

Variable	Percentage
Gender	
Male	31.7
Female	67.5
Missing	0.8
Age	
21–30	2.0
31–40	20.4
41–50	28.9
51–60	22.8
61–70	15.7
71–80	6.2
81–90	3.7
91 or above	0.3
Missing	0
Number of children	
1	30.9
2	48.5
3	14.4
4 or more	6.2
Cohort of first child born	
1970s or before	17.6
1980s	17.4
1990s	17.2
2000s	31.0
2010s	12.5
Missing	4.3
Educational level	
Primary or below	14.2
Junior secondary	17.1
Senior secondary	31.1
Matriculation	6.7
College / University	24.2

Table 1. (Continued)

Variable	Percentage
Postgraduate	4.7
Missing	2.1
Employment status	
Full-time employee	45.7
Part-time employee	10.6
Homemaker	17.0
Unemployed	1.3
Retired	20.9
On social assistance	1.8
Missing	2.7
Monthly family income in HK\$	
\$4000 or below	7.0
\$4000 - \$9000	5.0
\$10,000 - \$14,999	8.7
\$15,000 - \$19,999	10.0
\$20,000 - \$29,999	15.2
\$30,000 - \$49,999	20.4
\$50,000 - \$79,999	15.1
\$80,000 or above	12.1
Missing	6.5

In total, 5,707 valid questionnaires were collected and included in the analysis. The sample included five generational cohorts of Hong Kong parents with different demographic characteristics in terms of gender, age, number of children, educational level and employment status. The profiles of respondents are shown in Table 1. Cronbach's α reaches .765 for the five items, suggesting a moderate to high reliability. In the analysis, hypotheses were tested using one-way ANOVA. For each of these three categories, this study aims to investigate the association of the scale scores with gender, educational level (of both the respondent and his/her spouse), occupational status (of both the respondent and his/her spouse), and family income.

Table 2. Division of labor by gender

	Father Mean (SD)	Mother Mean (SD)	<i>F</i>
Main role	3.18 (.92)	3.60 (.98)	224.49**
Assisting role	3.30 (1.07)	3.03 (1.24)	62.13**
Traditional belief about gender role	3.04 (1.23)	2.93 (1.28)	9.76**

** $p < .005$.

FINDINGS

Table 2 presents the descriptive statistics for the domestic division of labor in childcare by gender. Fathers reported lower scores in assuming the main role of child rearing ($M = 3.18$) than mothers did ($M = 3.60$), but higher scores in taking the assisting role (father: $M = 3.30$; mother: $M = 3.03$). Significant difference was observed for both roles (main role, $F = 224.49$, $p < .005$, $\eta^2 = .04$; assisting role, $F = 62.13$, $p < .005$, $\eta^2 = .011$). Significant

difference was also found between men and women in their degree of approval of the traditional belief that men as breadwinners and women as homemakers ($F = 9.76, p = .002, \eta^2 = .002$). In short, Hypotheses 1a, 1b and 1c were supported.

Table 3. Division of labor by educational level

	Main role Mean (SD)	Assisting role Mean (SD)	Traditional belief about gender role Mean (SD)
Primary or below	3.61 (1.06)	3.56 (1.26)	3.40 (1.40)
Lower secondary school	3.47 (1.00)	3.26 (1.23)	3.14 (1.34)
Completed secondary school	3.45 (.97)	3.10 (1.19)	2.92 (1.23)
College	3.53 (.98)	3.05 (1.14)	2.96 (1.22)
University/ Higher education	3.44 (.92)	2.90 (1.09)	2.78 (1.15)
Graduate School	3.24 (1.00)	2.69 (1.05)	2.46 (1.09)
<i>F</i>	6.39***	42.07***	37.36***

*** $p < .001$.

Table 3 indicates that participants' educational level had a negative association with involvement as main caregivers ($F = 6.39, p < .001, \eta^2 = .005$). A general decrease of mean for the "main role" was observed with the increase of educational level. Post-hoc comparisons using the Least Significance Difference (LSD) Test were conducted to identify pairs of means that differ. The result showed that the mean difference did not generate a statistical difference at .05 significant level between the groups of "lower secondary school", "completed secondary school", "college" and "university/higher education". However, the group of "primary or below" stood out with significant mean higher score in performing the main role than the rest of the groups (except for the group of "college"), while parents with postgraduate degree were the least likely to engage as the one in charge of childcare. The findings supported Hypothesis 2a. The participant's educational level was also negatively related to performing assisting role ($F = 42.07, p < .001, \eta^2 = .036$). The LSD post hoc tests revealed that the variance of mean between the groups all reached .05 significant level (except for between "completed secondary school" and "college", $p = .52$). The findings supported Hypothesis 2b. With regard to the gender belief, parents received more education scored significantly lower score on approving the gender stereotype ($F = 37.36, p < .001, \eta^2 = .032$). It is noted that the groups of "primary or below" and "lower secondary school" differed significantly from the rest four groups. The findings supported Hypothesis 2c.

Similar to the result shown in Table 3, there was significant difference between the educational level of the spouse and the respondents involving as the main caregivers (see Table 4) ($F = 4.28, p = .001, \eta^2 = .004$), as the assisting role ($F = 16.90, p = .000, \eta^2 = .019$), and the degree of agreeing with the gender stereotype ($F = 17.29, p = .000, \eta^2 = .019$). The general decreasing mean for both the "main role" and "assisting role" suggested that highly educated spouse was accompanied by less participation in childcare for the respondent. Similar association was found for the gender stereotype. The findings supported Hypotheses 2d, 2e and 2f.

Table 4. Division of labor by educational level (spouse)

	Main role Mean (SD)	Assisting role Mean (SD)	Traditional belief about gender role Mean (SD)
Primary or below	3.56 (.99)	3.39 (1.24)	3.34 (1.33)
Lower secondary school	3.44 (.99)	3.20 (1.19)	2.99 (1.27)
Completed secondary school	3.43 (.94)	3.10 (1.15)	2.93 (1.21)
College	3.38 (.97)	2.97 (1.11)	2.98 (1.17)
University/ Higher education	3.32 (.93)	2.88 (1.07)	2.75 (1.16)
Graduate School	3.35 (.93)	2.79 (1.08)	2.59 (1.11)
<i>F</i>	4.28**	16.90**	17.29**

** $p < .005$.

Table 5. Division of labor by occupational status

	Main role Mean (SD)	Assisting role Mean (SD)	Traditional belief about gender role Mean (SD)
Work full time	3.35 (.93)	2.99 (1.11)	2.75 (1.18)
Work part time	3.49 (.99)	3.02 (1.22)	2.87 (1.25)
Full time home-maker	3.63 (.97)	3.02 (1.23)	3.13 (1.23)
Unemployed or between jobs	3.56 (.96)	3.15 (1.22)	2.95 (1.37)
Retired	3.54 (1.06)	3.52 (1.24)	3.32 (1.38)
Social security recipient	3.71 (.97)	3.22 (1.29)	3.53 (1.28)
<i>F</i>	15.56***	35.10***	42.45***

*** $p < .001$.

As shown in Table 5, there were significant differences amongst the occupational groups in terms of undertaking the main role ($F = 15.56$, $p = .000$, $\eta^2 = .013$). Parents working full time scored the lowest, and post hoc LSD tests showed that it differed significantly with the other four groups (except for “unemployed or between jobs”, $p = .06$). According to the results, the four groups who committed less time to market work (i.e., “full time home-maker”, “unemployment or between jobs”, “retired” and “social security recipient”) reached higher mean scores in taking the main role in childcare than the rest two groups who devoted more time to market job (i.e., “work full time” and “work part time”). As to the assisting role, although a significant difference was found between groups ($F = 35.10$, $p = .000$, $\eta^2 = .03$), post-hoc comparisons indicated that only the group “retired” which was found with the highest score were different from the other five groups. The rest of the pairs did not generate significant difference at .05 level. Groups also varied with regard to the gender belief ($F = 42.45$, $p = .000$, $\eta^2 = .036$). The incremental mean scores suggested that more intensive workforce participation (i.e., “work full time” and “work part time”) was accompanied by higher tendency to reject this gender stereotype. Generally speaking, the findings provided support for Hypotheses 3a, 3b and 3c.

Table 6. Division of labor by occupational status (spouse)

	Main role Mean (SD)	Assisting role Mean (SD)	Traditional belief about gender role Mean (SD)
Work full time	3.46 (.94)	2.92 (1.11)	2.80 (1.16)
Work part time	3.32 (.90)	3.19 (1.10)	2.99 (1.21)
Full time home-maker	3.08 (.90)	3.32 (1.09)	3.25 (1.24)
Unemployed or between jobs	3.34 (.94)	3.07 (1.21)	2.91 (1.25)
Retired	3.41 (1.03)	3.34 (1.24)	3.09 (1.37)
Social security recipient	3.67 (.88)	3.35 (1.11)	3.56 (1.28)
<i>F</i>	12.28***	21.63***	16.56***

*** $p < .001$.

As presented in Table 6, groups differed for the three measures according to spouse's occupational status. For the main role ($F = 12.28$, $p = .000$, $\eta^2 = .013$), the status with the spouse performing as a full-time home-maker was found with the respondent scoring the lowest in assuming the main role. Post hoc tests showed the mean was significantly lower than the rest groups. However, respondents with spouse as social security recipient were very likely to take the main role ($M = 3.67$). Table 5 also shows that respondents with spouse's occupational status as "social security recipient" ($M = 3.35$), "retired" ($M = 3.34$) and "full time home-maker" ($M = 3.32$) were more likely to perform the assisting role ($F = 21.63$, $p = .000$, $\eta^2 = .024$). As to the gender perception ($F = 16.55$, $p = .000$, $\eta^2 = .018$), it saw the least acceptability among respondents with spouses working full time ($M = 2.80$), and the most ($M = 3.56$) among those with spouses as social security recipient. In general, the findings did not give strong support to Hypotheses 3d and 3e, but confirmed Hypothesis 3f.

Table 7. Division of labor by monthly family income (HKD)

	Main role Mean (SD)	Assisting role Mean (SD)	Traditional belief about gender role Mean (SD)
<4,000	3.69 (1.15)	3.61 (1.32)	3.45 (1.45)
4,000 – 9,999	3.53 (.97)	3.17 (1.18)	3.05 (1.32)
10,000 – 14,999	3.56 (1.01)	3.22 (1.26)	3.05 (1.33)
15,000 – 19,999	3.42 (1.02)	3.16 (1.22)	3.01 (1.25)
20,000 – 29,999	3.42 (.95)	3.18 (1.17)	2.97 (1.24)
30,000 – 49,999	3.46 (.93)	3.04 (1.12)	2.88 (1.22)
50,000 – 79,999	3.39 (.95)	2.92 (1.12)	2.74 (1.16)
>80,000	3.38 (.97)	2.84 (1.10)	2.79 (1.18)
<i>F</i>	5.48***	20.18***	16.56***

*** $p < .001$.

Table 7 presents the mean scores for the three measures in different family income groups. For the main role in parenting, there was an overall reduced mean along with greater earning capacity of a family. The mean difference between groups is statistically significant ($F = 5.48$, $p = .000$, $\eta^2 = .006$). Post hoc tests indicated that the five higher-income groups (i.e., 15,000 – 19,999 and above) did not differ in terms of taking the major responsibility of child rearing, but they reported significant lower scores than the rest three groups did (10,000 – 14,999 and below). For performing assisting role, diminishing mean score was also found between groups with the household monthly income increased ($F = 20.18$, $p = .000$, $\eta^2 =$

.025). Post hoc comparison tests showed that parents from the highest income groups, i.e., groups 7 (50,000 – 79,999) and 8 (>80,000), reported significant lower scores in performing assisting role while the lowest income group, group 1 (<4,000), reported the highest. Similarly, as to the traditional belief ($F = 15.42$, $p = .000$, $\eta^2 = .019$), parents from group 1 were more likely to hold the traditional gender ideology, whereas parents from group 7 and 8 were less conservative on this matter. These findings basically supported Hypotheses 4a to 4c.

DISCUSSION

The purpose of the present study was to explore whether background socio-demographic factors are related to domestic division of labor in childcare in the context of Hong Kong. The first set of hypothesis (1a, 1b and 1c) were confirmed by the results shown in Table 2 that there was a gendered, unequal share of childcare among Hong Kong parents. Consistent with the majority of existing studies conducted elsewhere [10-12, 14, 33], Hong Kong mothers still assumed the main responsibility of childcare while fathers assumed the assisting role. We should also emphasize that the effect size for involving as main caregivers was medium ($\eta^2 = .04$), indicating a modest effect of gender on how childcare was divided between parents in practice. Meanwhile, results also showed that men were more likely to persist in believing the traditional gender concept “men are breadwinners and women are homemakers”, although the effect size was very small. The present findings are generally consistent with previous studies [35] that a more egalitarian gender attitude could not always be fully translated into a reshuffle of family roles in practice. This gendered phenomenon may have its root in Chinese cultural values. Chinese society has long held a cultural belief of gender differentiation in parenting, in which paternal role is to engage with market work while maternal role is to meet basic needs of children [32].

It is demonstrated by our findings that, in general, parents’ educational levels, family income and intensity of market work all negatively correlated to undertaking the main role in child rearing labor (although in some cases the effect size is very small), which supported hypotheses 2a, 2d, 3a and 4a. Results also suggested a negative association between these variables and taking an assisting role in parenting, which in general supported hypotheses 2b, 2e, 3b and 4b. The two results combined imply that higher educational and income level, and intensifier market work may suggest less engagement in parenting. It contradicts the findings in several existing literature [9, 27] in which they argued the opposite was true.

One possible explanation for this can be drawn from a rational economic perspective – time availability [36, 37]. Researchers argued that allocation of domestic tasks depended on the time availability of partners. This theorization, among others such as “doing gender” perspective [38] and relative resource perspective [39], may entail stronger explanatory power to the society of Hong Kong, due to the stressful living in the metropolis of Hong Kong with a high cost of living. Reports and studies [40, 41] have confirmed the situation of long working hours in Hong Kong. For example, The Swiss Investment Bank (UBS): Price and earning report (2015) [41] shows that Hong Kong people work for an average of more than 50 weekly working hours and 2,606 working hours per year, ranking the highest out of 71 cities across the world. It is likely that parents with higher educational level, greater earning

capacity and higher intensity of workforce participation may all inform more amount of time devoted to market work and therefore less free time available for performing childcare duties. In contrast, parents with less breadwinning stress or capability are more able to transfer their time into childcare.

This study also provides some empirical evidence that overall parents with better education, greater earning capacity and/or more commitment to market work tended to be more open-minded and hold a progressive gender attitude. In contrast, less education, less earning power and more free time lead to a more conservative attitude and conformity to the traditional gender norms. Therefore, hypotheses 2c, 2f, 3c, 3f, 4c were confirmed. The results are largely in tune with the positive association found between an equal gender attitude and multiple social variables such as education and income in other cultures [42, 43]. Given the observed positive association, our findings demonstrate that education and work can function as a vehicle to change one's gender attitudes and encourage gender equality in childcare participation.

While the findings are interesting and pioneer in nature, there are several limitations of the study. First, only five items were used to assess three aspects of family division of labor. Obviously, it would be helpful to use more items to assess these dimensions to make the measures more reliable. Second, the findings are based on self-report measures. It would be helpful to understand the actual behavior of oneself and one's spouse. Finally, as the data collected are cross-sectional in nature, it would be theoretically interesting to look at the impact of these socio-demographic factors over time. Despite these limitations, the present findings shed light on family division of labor in a Chinese context and the related socio-demographic correlates.

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Chapter 311

PARENTAL BELIEFS ABOUT PARENTAL ROLES AND RESPONSIBILITIES IN CHINESE PARENTS: PIONEER FINDINGS

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ABSTRACT

In this chapter we examine parental beliefs of 5,749 Chinese parents based on an indigenous scale developed in the Chinese context. Results showed that the scale and the subscales were internally consistent. Findings based on frequency analyses revealed that Chinese parents generally held positive beliefs about their roles and responsibilities in parenting. However, Chinese parents showed more conservative attitudes in educating children on sexuality issues. Some parents also did not realize the necessity of learning about parenting, implying that they may be ill-prepared for parenting. Further analyses revealed that mothers possessed stronger parental beliefs than fathers did. Parents with lower educational levels tended to be more conservative in parental beliefs. Family income and employment status were also identified to be predictors of parental beliefs. In general, parents with lower family income or being unemployed tended to hold stronger traditional beliefs about roles and responsibilities in parenting than did high-income or employed parents. The research findings underscore the importance of understanding parental beliefs in Chinese societies.

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INTRODUCTION

Parental beliefs refer to parents' knowledge, attitudes, ideas, and concepts in parenting that are accepted to be correct which guide their parenting behavior [1, 2]. Parental beliefs provide parents with cognitive frameworks which they can follow to set parenting goals, identify children's demands, use parenting strategies, and lay the base of parenting practices [1, 3]. Previous research has demonstrated the positive effect of parental beliefs on child development, especially on children's academic performance and persistence [4].

Most research on parenting was conducted in the West or relied on frameworks developed in Western contexts. For example, parenting styles identified by Baumrind, including authoritarian, authoritative, permissive, traditional and rejecting-neglecting parenting [5], have been widely adopted as the theoretical framework of research on parenting. However, researchers trying to relate these styles in non-Western cultures often encounter difficulties when using this framework to interpret indigenous phenomena [6]. Wang and Chang [7] suggested that Western concepts and frameworks can hardly capture the essence of parenting in non-Western cultures. The reasons are twofold. Primarily, some concepts developed in Western cultures could be unidentified, vague or even misleading in other cultures [8]. Secondly, some indigenous phenomena in parenting practices, such as "training" (Jiao Xun) and "to love and to govern" (Guan) in Chinese culture, can be largely overlooked [8, 9]. This echoes LeVine's model of parenting, which identifies universal as well as cultural aspects of socialization goals of families [10]. As the majority of the existing scales measuring parenting were developed in Western cultures and in English, researchers have been calling for the development of indigenous scales that fit specific cultural contexts [11, 12].

Different from parenting in Western cultures, parenting in Chinese societies is strongly guided by Chinese philosophies such as Confucianism, Taoism, and Buddhism. Shek and Sun [12] identified some characteristics of Chinese parenting, including strict parental control, little personal space for children, different gender role expectation, and strong emphases on harmony, obligations, filial piety, and continuity of the family name. As for parenting in contemporary Chinese societies, Shek and Sun [12] also noted the changing nature of parenting in the Chinese contexts over time. For example, changes in the gender parental role expectation have been observed. Traditionally, Chinese fathers were considered "the masters of the family" who set strict regulations on children's behavior, while mothers were normally regarded as the "obedient one" taking care of the family and maintaining the harmony. However, mothers in contemporary China seem to be more involved in the socialization process and stricter than fathers do. Although researchers have been gradually aware of the importance of developing culturally sensitive instruments, many of them still rely on concepts and measures derived from the Western contexts [13]. Hence, there is a need to further examine parental beliefs in the Chinese context using indigenous scales.

Previous research has also highlighted the role of parental background socio-demographic characteristics in shaping parental beliefs. For example, as discussed earlier, gender differences between fathers and mothers have been observed. The role expectation of "strict father and kind mother" rooted in traditional Chinese culture may modify fathers' and mothers' parental beliefs [12]. Educational level has been considered another influential factor affecting parental beliefs. It is suggested that well-educated parents may be more

equipped with knowledge and skills in parenting, have a strong level of efficacy, and be less conservative in parenting. They may also hold more liberal attitudes toward human behavior, such as emphasizing gender equality and fair share in family responsibilities. Besides, family economic status is also believed to influence parental beliefs. Leung and Shek [14] pointed out that the primary mission of economically disadvantaged families is to get their children out of the poverty trajectory and to step into a more economically successful future. On the other hand, families with a higher economic status possess more educational resources, which may exert an impact on their parental beliefs. In the present study, gender, educational level, employment status, and family income were included as important parental socio-demographic characteristics. As few studies have examined beliefs about parental responsibilities in Chinese parents and the related correlates, this study attempted to examine the related normative profiles and the demographic correlates.

OUR STUDY

A total of 5,749 questionnaires were collected. After removing 42 invalid cases, 5,707 valid responses were used for analyses. Among them, 31% were fathers ($N = 1,770$) and 65% were mothers ($N = 3,710$). The age of the respondents ranged from 21 to 97 years old (mean = 52.3 years, $SD = 13.67$). Nearly half of the respondents (48.5%) reported having two children, 30.6% had one child, and 14.3% had three children. As to the educational level, 14.2% of the respondents attained primary school education or below, 17.1% completed lower secondary education, 31.1% finished secondary school, 6.7% attained matriculation education, 24.2% completed university or higher education, and 4.7% finished graduate school or above. Regarding employment status, 45.7% of the respondents were full-time employees, 10.6% worked part-time, 17% were homemaker, 20.9% were retired, and 1.3% were unemployed. As to the monthly family income, 21% of the participants reported a family income lower than HK\$14,999, 46% were between HK\$15,000 and HK\$49,999, 27% of the respondents had a family income higher than HK\$50,000.

Instruments

The Parental Roles and Responsibilities – Chinese Parental Beliefs Scale was administered in the present study. The initial scale contained 42 items. Participants were asked to indicate the degree of agreement with statements on parents' beliefs about their parental roles and responsibility on a five-point Likert scale (1 = strongly disagree; 5 = strongly agree). In the study of Lam, To and Kwong [13], the factorial validity of the questionnaire was examined by exploratory factor analysis (EFA) and confirmatory factor analysis (CFA). The working sample was randomly split into two subsets. EFA was performed on one subset ($N = 2,925$), which resulted in a five-factor solution. Next, CFA was conducted on the second subset ($N = 2,596$). The results showed an acceptable goodness-of-fit indices of the tested model. Details of the development of the instrument, and the findings of EFA and CFA were reported in Lam, To and Kwong's work [13]. The final solution constituted of 23 items, which were categorized under five factors (i.e., subscales): parental

love and nurturing (7 items), parenthood as a normative life stage (4 items), readiness to relax and restrict parental control (4 items), parental guidance of the young (4 items), and fulfillment of children's needs (4 items).

Data Analyses

Descriptive statistics were used to generate percentage findings. A one-way analysis of variance (ANOVA) was used to investigate the relationships between parental beliefs (and the five factors) and the background socio-demographic characteristics, including gender, educational level, employment status, and family income. All analyses were performed using SPSS (Version 25.0).

FINDINGS

The scale showed good reliability ($\alpha = .80$). As shown in Table 1, the five subscales also demonstrated acceptable reliability ($\alpha s > .60$). The average inter-item correlation of the entire sample yielded a value of 0.23. The inter-item correlations among the five factors showed a relatively high inter-item correlation of each factor, ranging from .30 to .48 (see Table 1). Ferketich [15] suggested that for scales containing 10 or more items and with an alpha of .71, an average inter-item correlation of 0.2 is acceptable. These findings support the internal consistency of the scale. Cronbach's alpha, mean inter-item correlations, mean, standard deviation and correlation coefficients amongst the five subscales and the whole scale are shown in Table 1.

Table 1. Cronbach's alpha, mean inter-item correlations, mean, standard deviation and correlation coefficients amongst the five subscales and the whole scale

Subscales	Cronbach's alpha	Mean inter-item correlations	Mean (SD)	Subscales				
				1	2	3	4	5
Parental love and nurturing (7 items)	0.866	0.489	4.28 (0.59)	—	—	—	—	—
Parenthood as a normative life stage (4 items)	0.599	0.375	3.02 (0.87)	.039	—	—	—	—
Readiness to relax and restrict parental control (4 items)	0.709	0.304	3.87 (0.68)	.392	.227	—	—	—
Parental guidance of the young (4 items)	0.739	0.437	4.40 (0.58)	.544	.138	.222	—	—
Fulfillment of children's needs (4 items)	0.749	0.427	3.62 (0.78)	.417	.394	.160	.453	—
38-item whole scale	0.847	0.223	3.90 (0.46)	.755	.556	.585	.674	.736

Note. N = 5,707. All correlation coefficients are statistically significant at $p < .01$ (two-tailed).

Findings Based On Frequency Data

The details of the descriptive statistics and frequency data are illustrated in Table 2.

Parental Love and Nurturing

Most respondents showed a positive attitude in this domain ($M = 4.28$, $SD = .59$). For example, 87.98% agreed that parents should always pay close attention to their children's emotions. Similarly, almost 90% of the respondents agreed that parents should spare time to accompany their children as far as possible. However, around 6% of the respondents disagreed with the statement "parents have to teach their children knowledge about sex" ($M = 4.03$).

Parenthood as a Normative Life Stage

Respondents presented a neutral attitude of their perception of parenthood as a normative life stage ($M = 3.02$, $SD = .87$). The ratings ranged between 2.56 and 3.65. For example, 25.65% agreed that parenthood is developed naturally that there is no need to learn. If the number of neutral responses was taken into account, roughly half of the respondents did not feel the necessity to learn how to parent. Only 20.68% agreed that fostering children can allow the parents to be looked after when getting old.

Readiness to Relax and Restrict Parental Control

Participants showed a moderately positive attitude towards the four statements in this domain ($M = 3.87$, $SD = .68$). The ratings ranged between 3.21 and 4.27. The majority of respondents agreed that parents should respect the wishes of their children (87.10%) and not to impose their wishes on their children (72.48%). However, the statement "parents have to accept their children's sexual orientation, no matter it is homosexual or heterosexual" yielded a relatively low rating ($M = 3.21$). Almost one-third of the respondents disagreed with this statement.

Parental Guidance of the Young

Most respondents presented a clear and positive perception of their roles and responsibilities in providing guidance of the youth ($M = 4.40$, $SD = .58$). Among the four items, the lowest mean score was 4.21 and the highest was 4.57. For example, 91.44% of respondents agreed that when children do not meet the requirements, parents ought to provide appropriate guidance. In particular, around 93% of the respondents agreed that parents are responsible for preventing their children from getting into bad company.

Fulfillment of Children's Needs

The respondents reported a moderately positive attitude in this domain ($M = 3.62$, $SD = .78$, range from 3.06 to 3.87). The majority of respondents would try to meet their children's needs but in a reasonable manner. For example, 65% agreed that parents are responsible to provide financial support for their children to complete university education. Besides, although 65.6% agreed that if financially possible, parents should provide the best resources for their children, only 31.4% agreed that parents should meet the needs of their children as far as possible.

	Mean (SD)	1	2	3	4	5	Negative responses options (1-2)	Positive responses options (4-5)
		Strongly disagree	Disagree	Neutral	Agree	Strongly agree		
11 Parents have to keep the values of their own	3.65 (0.99)	188 (3.34%)	365 (6.49%)	1855 (33%)	2019 (35.92%)	1194 (21.24%)	553 (9.84%)	3213 (57.16%)
Subscale 3 Readiness to relax and restrict parental control								
12 Children's future development cannot be controlled by their parents	4.01 (1.01)	145 (2.58%)	262 (4.65%)	1168 (20.75%)	1872 (33.26%)	2182 (38.76%)	407 (7.23%)	4054 (72.02%)
13 Parents should respect the wishes of their children	4.27 (0.72)	17 (0.3%)	50 (0.89%)	660 (11.71%)	2551 (45.26%)	2358 (41.84%)	67 (1.19%)	4909 (87.1%)
14 Parents have to accept their children's sexual orientation, no matter it is homosexual or heterosexual	3.21 (1.31)	828 (14.74%)	753 (13.4%)	1578 (28.09%)	1329 (23.66%)	1130 (20.11%)	1581 (28.14%)	2459 (43.77%)
15 Parents should not impose their wishes on their children	4 (0.92)	89 (1.58%)	191 (3.4%)	1267 (22.54%)	2186 (38.89%)	1888 (33.59%)	280 (4.98%)	4074 (72.48%)
Subscale 4 Parental guidance of the young								
16 Parents' responsibility is to educate (to teach and to nurture) their children; to teach is to discipline, to nurture is to provide them needs such as food and clothing	4.21 (0.95)	122 (2.17%)	195 (3.46%)	768 (13.63%)	1865 (33.11%)	2683 (47.63%)	317 (5.63%)	4548 (80.74%)
17 Parents are responsible for preventing their children from getting into bad company	4.57 (0.67)	13 (0.23%)	49 (0.87%)	335 (5.94%)	1565 (27.74%)	3680 (65.23%)	62 (1.1%)	5245 (92.96%)
18 When children do not meet the requirements, parents ought to provide appropriate guidance	4.48 (0.68)	11 (0.2%)	29 (0.52%)	442 (7.85%)	1940 (34.46%)	3207 (56.97%)	40 (0.71%)	5147 (91.44%)
19 If circumstances allow, parents have to provide resources and opportunities so as to lay a good foundation for their children	4.35 (0.76)	30 (0.53%)	73 (1.29%)	609 (10.8%)	2114 (37.48%)	2815 (49.9%)	103 (1.83%)	4929 (87.38%)

Table 2. (Continued)

	Mean (SD)	1	2	3	4	5	Negative responses options (1-2)	Positive responses options (4-5)
		Strongly disagree	Disagree	Neutral	Agree	Strongly agree		
Subscale 5 Fulfillment of children's needs								
20 Parents should assist their children in preventing them from running into obstacles on important matters	3.68 (1.03)	161 (2.86%)	496 (8.81%)	1681 (29.85%)	1924 (34.16%)	1370 (24.33%)	657(11.67%)	3294(58.49%)
21 Parents are responsible to provide financial support for their children to complete university education	3.86 (1.03)	163 (2.89%)	319 (5.66%)	1485 (26.34%)	1861 (33.01%)	1810 (32.1%)	482(8.55%)	3671 (65.11%)
22 If financially possible, parents should provide the best resources to their children	3.87 (0.99)	127 (2.26%)	303 (5.39%)	1508 (26.81%)	1939 (34.47%)	1748 (31.08%)	430(7.64%)	3687(65.55%)
23 Parents should meet the needs of their children as far as possible	3.06 (1.11)	536 (9.52%)	1050 (18.65%)	2278 (40.46%)	1095 (19.45%)	671 (11.92%)	1586(28.17%)	1766(31.37%)

Relations between Parental Beliefs and Background Socio-Demographic Characteristics

The relationships between omnibus parental beliefs scale (including the five subscales) and parent's gender, educational level, employment status, and family income were examined.

Parental Gender

In general, mothers' scores on parental beliefs about parental roles and responsibilities ($M = 3.91$) were significantly higher than fathers' scores ($M = 3.86$, $F(1,5450) = 9.62$, $p < .01$). Compared to fathers, mothers tended to hold a stronger belief about loving and nurturing children, parenthood as a normative life stage and readiness to relax and restrict parental control. As to parental guidance of the young, no significant difference between fathers and mothers was observed. Different from other domains, fathers presented a stronger belief in responsibility in fulfilling children's needs than mothers did. Details of the means and the ANOVA results are shown in Table 3.

Table 3. Mean and ANOVA results: Parental beliefs and gender

Scale	ANOVA	Mean	
		Father	Mother
Whole scale	$F(1,5450) = 9.62$, $p = .002$	3.86	3.91
Factor 1	$F(1,5345) = 35.85$, $p < .001$	4.21	4.32
Factor 2	$F(1,5353) = 4.92$, $p = .027$	2.97	3.02
Factor 3	$F(1,5358) = 24.31$, $p < .001$	3.81	3.90
Factor 4	$F(1,5376) = 1.2$, ns	4.41	4.39
Factor 5	$F(1,5367) = 7.26$, $p = .007$	3.65	3.59

Note. Factor 1: Parental love and nurturing; Factor 2: Parenthood as a normative life stage; Factor 3: Readiness to relax and restrict parental control; Factor 4: Parental guidance of the young; Factor 5: Fulfillment of children's needs.

Educational Levels

Parents with higher educational level tended to report a lower level of parental belief about their parental roles and responsibilities than parents with a lower educational level ($F(5,5556) = 17.05$, $p < .001$). The results of post-hoc analyses indicated that parents with primary education or less held significantly stronger parental beliefs of their responsibilities than did parents with other educational levels. As to the subscales, similar patterns were found in loving and nurturing children, parenthood as a normative life stage and fulfillment of children's needs. No significant difference was found amongst parents with different educational levels regarding their beliefs in guidance of the young. Interestingly, parents with a higher educational level tended to possess a stronger belief in the readiness to relax and restrict parental control more than parents with lower educational levels (see Table 4).

Employment Status

The results of ANOVA revealed that parental beliefs differed among parents with different employment status ($F(5,5520) = 28.08$, $p < .001$). Generally speaking, parents who were employed, including full-time and part-time workers, tended to hold a weaker traditional parental belief than parents who were retired or social security recipients. Employment status was also significantly linked to parental beliefs in all of the five subscales (see Table 5).

Table 4. ANOVA results: Parental beliefs and respondent's educational levels

Scale	ANOVA	Mean					
		Primary or below	Lower secondary(a)	Completed secondary school(b)	Matriculate(c)	University/ Higher Education(d)	Graduate school or above(e)
Whole scale	$F(5,5556) = 17.05, p < .001$	4.02abcde	3.91	3.88	3.90	3.86	3.81
Factor 1	$F(5,5448) = 12.9, p < .001$	4.16abcde	4.25	4.28	4.30	4.36	4.33
Factor 2	$F(5,5457) = 151.77, p < .001$	3.69abcde	3.13	2.94	2.92	2.76	2.67
Factor 3	$F(5,5464) = 2.29, p = .043$	3.86c	3.83	3.86	3.94	3.89	3.94
Factor 4	$F(5,5480) = 1.88, ns$	4.46bde	4.40	4.38	4.39	4.40	4.37
Factor 5	$F(5,5473) = 27.5, p < .001$	0.88abcde	0.83	0.76	0.78	0.69	0.68

Note. Factor 1: Parental love and nurturing; Factor 2: Parenthood as a normative life stage; Factor 3: Readiness to relax and restrict parental control; Factor 4: Parental guidance of the young;

Factor 5: Fulfillment of children's needs. ns: not significant. abcde: Significant results of post-hoc comparison, $p < .05$.

Table 5. ANOVA results: Parental beliefs and respondent's employment status

Scale	ANOVA	Mean					
		Work full time	Work part time(a)	Full time homemaker(b)	Unemployed or between jobs(c)	Retired(d)	Social security recipient(e)
Whole scale	F(5,5520) = 28.08, p < .001	3.84bde	3.84	3.90	3.92	4.02	4.02
Factor 1	F(5,5415) = 11.78, p < .001	4.28bd	4.27	4.39	4.32	4.19	4.27
Factor 2	F(5,5426) = 95.56, p < .001	2.87cde	2.92	2.88	3.08	3.45	3.55
Factor 3	F(5,5433) = 5.98, p < .001	3.85d	3.80	3.88	3.97	3.95	3.74
Factor 4	F(5,5449) = 12.5, p < .001	4.36bd	4.33	4.42	4.38	4.51	4.44
Factor 5	F(5,5439) = 37.08, p < .001	3.53de	3.55	3.54	3.59	3.87	3.92

Note. Factor 1: Parental love and nurturing; Factor 2: Parenthood as a normative life stage; Factor 3: Readiness to relax and restrict parental control; Factor 4: Parental guidance of the young;

Factor 5: Fulfillment of children's needs. abcde: Significant results of post-hoc comparison, $p < .05$.

The results and patterns found in parenthood as a normative life stage and fulfillment of children’s needs were similar to the findings derived from the analysis based on the whole scale. As to the domain on parental love and nurturing, full-time homemakers displayed the highest level of parental belief. Regarding the readiness to relax and restrict parental control, parents who were unemployed and retired showed a stronger belief than did parents with other types of employment status. As to parental guidance of the young, the biggest difference was found between parents who were full time employed ($M_s < 4.36$) and retired ($M = 4.51$). Details of the means and the ANOVA results are shown in Table 5.

Family Income

Generally speaking, parents with a relatively lower family income (i.e., lower than HK\$14,999) tended to present a stronger parental belief about their roles and responsibilities than did parents with relatively higher family income (i.e. between HK\$15,000 and HK\$49,999, and above HK\$50,000), $F(2,5304) = 24.36, p < .001$. Post-hoc analyses revealed a significant difference between parents having a family income below HK\$14,999 and parents in the other two groups. As to parental guidance of the young, no significant difference was observed. However, high-income parents reported stronger beliefs about their responsibilities in love and nurturing. Details of the means and the ANOVA results are shown in Table 6.

Table 6. ANOVA results: Parental beliefs and respondent’s family income

		Mean		
		Below HK\$ 14,999	HK\$15,000 – HK\$49,999(a)	Above HK\$50,000(b)
Whole scale	$F(2,5304) = 24.36, p < .001$	3.96ab	3.86	3.86
Factor 1	$F(2,5206) = 10.85, p < .001$	4.23b	4.26	4.33
Factor 2	$F(2,5220) = 142.61, p < .001$	3.32ab	2.97	2.78
Factor 3	$F(2,5228) = 5.88, p = .003$	3.87	3.84	3.91
Factor 4	$F(2,5236) = 2.25, ns$	4.41	4.37	4.40
Factor 5	$F(2,5227) = 42.31, p < .001$	3.77ab	3.58	3.50

Note. Factor 1: Parental love and nurturing; Factor 2: Parenthood as a normative life stage; Factor 3: Readiness to relax and restrict parental control; Factor 4: Parental guidance of the young; Factor 5: Fulfillment of children’s needs. ns: not significant. ab: Significant results of post-hoc comparison, $p < .05$.

DISCUSSION

Based on the data collected from 5,707 parents in Hong Kong, the present study provides pioneer findings of Chinese parental beliefs about roles and responsibilities. Some unique features of the present study should be highlighted. First, this indigenous scale used in the present study is the first known scale developed using a “bottom-up” approach to explore parental beliefs in Hong Kong. As studies on parenting have recognized the tremendous influence of cultural context in shaping parents’ beliefs and behaviors [16], this culture sensitive measure of parental beliefs can help researchers pursue in-depth understanding of parental beliefs in Hong Kong, where the local culture is a mix of traditional Chinese and contemporary Western influence [13]. Second, the large sample used in the present study contributed to the robust findings. In particular, the sample presented a good mix of different

levels of socioeconomic status. Third, this study collected survey data from both fathers and mothers. This fills the research gap that studies on parenting in Chinese societies primarily focus on maternal parenting [17, 18]. Finally, the findings have theoretical and practical implications for parenting in the Chinese context.

The study examined the reliability and frequency percentage of Chinese Parental Beliefs Scale, and explored the relation between parental beliefs and their background socio-demographic characteristics. The findings showed that the scale and subscales possessed good internal consistency. Given that related psychosocial measures in different Chinese societies are rare, this measurement is shown to be a valid and useful tool measuring parental beliefs in the Chinese context.

The percentage findings showed that Hong Kong parents in general held positive beliefs about their roles and responsibilities in parenting. This is in line with Chinese culture which emphasizes parental responsibilities in raising, educating and guiding children to become respectable and functioning members of the family and the society. For example, in the family instruction of Master Yan (*The Yan Shi Jia Xun*), one of the most influential Family Instruction books, parental strictness, dignity, and parental love are emphasized, as these factors will lead the children to the feelings of respect, politeness, and filial piety [19]. This can be further explained by a Chinese saying, “It is the fault of the father if he only raises the child without teaching him” (*yang bu jiao, fu zhi guo*), which indicates strong parental responsibilities perceived by Chinese parents.

Although parents can be aware of their responsibilities in preparing their children to lead a worthy life and to become a good person [16], they seemed to be less affirmative about their role in providing knowledge and guidance of sex-related issues. For example, the results indicated that almost a quarter of respondents did not regard teaching children knowledge about sex as parents’ responsibilities. Similarly, more than half of the respondents did not agree that parents should accept children’s sexual orientation no matter homosexual or heterosexual. Previous studies on sex education in Chinese societies revealed that Chinese parents tend to be conservative about direct discussion of sex-related issues with their children or provide direct guidance to them [20, 21]. Leung and colleagues [22] reviewed sexuality education programs in both Western and non-Western contexts, noted that the perception of sex as a “taboo” is still deeply rooted in Chinese cultures, and even school sexuality programs were covered by conservative materials in mainland China. Besides, roughly half of the respondents did not realize the necessity of learning about parenting. This may imply a lack of awareness of the importance of parenting skills and strategies on child development among some parents in Hong Kong. This finding suggests that some parents are not well-prepared for parenting, which would lead to parenting and parent-child relationship problems. In traditional Chinese culture, people held the belief that “God will help feed all the children that one has faith to bear” (*tian sheng tian yang*). Hence, Chinese people do not hold a strong belief that parenting education is needed for being a parent.

The results also revealed how parental beliefs vary among parents with different background socio-demographic characteristics. First, gender difference was observed, showing that mothers held stronger parental beliefs than fathers did. The result is consistent with the gender expectations of Chinese society where men are often seen as breadwinner and women as housemakers. This finding also echoes some related empirical studies. For example, some cross-sectional and longitudinal studies have suggested that mothers scored higher on positive parenting qualities than fathers in Chinese societies [23, 24]. Shek and Sun

[12] pointed out that mothers were seen as more positive in parental control and parent-child relational measures, and are also more involved and stricter than fathers did in contemporary China.

Regarding the educational level, parents who had completed a relatively lower education level showed more conservative or collectivistic attitudes of parenting. The results also indicated that the retired or social security recipients tended to possess stronger parental beliefs than parents with other working status. Similarly, low-income parents seemed to hold stronger beliefs about parental responsibilities and roles than high-income parents. A possible explanation for these findings is that parents of low socioeconomic status may feel unable to fully meet their children's needs. Therefore, they may set a higher standard for themselves for being responsible parents. However, those with higher educational level tended to show a higher acceptance level for their children. They may also hold more liberal parenting beliefs.

Although the present findings are pioneer in nature, some limitations of the present study should be addressed. First, this culture sensitive scale was developed via a "bottom-up" approach based on interview data collected from 120 Hong Kong parents. Therefore, it is necessary to include other samples such as Chinese parents in Mainland and Macau. Second, existing scales can be used as validated external criterion measures to consolidate the validity of the scale. Third, as the sample was not randomly selected, obtaining a random sample of parents would be helpful to give a more representative picture of parental behavior in Hong Kong. Finally, besides sexuality, it would be illuminating to understand parental expectations of roles and responsibilities in different domains of child development, such as intellectual and interpersonal competence development.

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Chapter 312

PARENTING IN CONTEMPORARY HONG KONG: OBSERVATIONS AND REFLECTIONS

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ABSTRACT

Parenting in Hong Kong is shaped by traditional Chinese collectivistic values and contemporary Western individualistic influences. In this chapter, we focus on parenting phenomena in Hong Kong. While traditional Chinese parenting goals are still dominant, there are gradual changes in parenting in Hong Kong. The traditional pattern of “strict fathers, kind mothers” has changed to “kind fathers, strict mothers” and “detached fathers, involved mothers”. Consistent with the Western literature, parenting is related to different child developmental outcomes, although the influences of paternal and maternal parenting lead to different outcomes. Relative to families without risk, financially poor and non-intact families show poorer parenting quality. Parenting is also related to other family processes, including family functioning and dyadic family processes such as parent-child relational qualities. The unanswered questions and future research directions are also highlighted.

INTRODUCTION

Parenting research is dominated by Western studies. As such, whether Western findings are generalizable to non-Western societies and whether unique parenting phenomena exists in non-Western contexts are questions to be addressed. Against this background, there are two

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reasons why researchers should understand parenting in Chinese societies. First, as roughly one-fifth of the world's population are Chinese, generalizability of Western parenting theories and research should be examined in Chinese people [1]. Second, parenting is strongly emphasized in traditional Chinese culture, as reflected by the existence of many Chinese family instruction books. Hence, it is theoretically and practically interesting to understand Chinese parenting [2]. For example, as shown in Table 1, traditional Chinese parenting literature emphasizes the importance of self-cultivation, particularly the development of virtues and character of children. Besides, parents should nurture frugality, simple life, as well as gratefulness to nature and other people in their children.

Furthermore, traditional Chinese parenting also emphasizes the role modeling of filial piety. Adults exercise a high level of filial piety to their parents; at the same time, they are the role models of their children. Moreover, one of the major goals of parenting is to maintain family harmony. These emphases are in sharp contrast to the focus of Western parenting literature which highlights the importance of well-being (such as happiness and life satisfaction), holistic development, individual rights, and personal autonomy in children.

Parenting research in Hong Kong is reviewed in current paper. Hong Kong can be regarded as a paradise for parenting research because roughly 92% of the population in Hong Kong are Chinese, where Chinese cultural values, such as filial piety and academic excellence, shape people's parenting practice. Besides, Hong Kong is a melting pot of Chinese and Western parenting beliefs and practice. This review focuses on the following issues: a) parenting phenomena in Hong Kong; b) parenting differences between fathers and mothers; c) parental influences on adolescent development; d) paternal versus maternal influence on adolescent development; e) parenting in high-risk families; f) parenting and other family processes; and g) limitations of the existing scientific literature and future research directions.

Table 1. Examples of traditional Chinese parenting instructions

《誠子書》——諸葛亮（三國時期） 『夫君子之行，靜以修身，儉以養德。非淡泊無以明志，非寧靜無以致遠。』 Jie Zi Shu (Admonition to My Son) -- Zhuge Liang (Three Kingdoms Period) “The practice of a cultivated man is to refine himself by quietude and develop virtue by frugality. Without detachment, there is no way to clarify the will; without serenity, there is no way to get far.” Xie, B.K. & Chen, Q.D. (2013). English Bus. Retrieved from: http://www.en84.com/dianji/wenji/201301/00011820.html 《朱子家訓》——朱柏廬（明末清初） 『黎明即起，灑掃庭除，要內外整潔；既昏便息，關鎖門戶，必親自檢點。一粥一飯，當思來處不易；半絲半縷，恒念物力維艱。宜未雨而綢繆，毋臨渴而掘井。自奉必須儉約，宴客切勿留連。器具質而潔，瓦缶勝金玉；飲食約而精，園蔬愈珍饈。勿營華屋，勿謀良田。三姑六婆，實淫盜之媒；婢美妾嬌，非閨房之福。童僕勿用俊美，妻妾切忌豔妝。祖宗雖遠，祭祀不可不誠；子孫雖愚，經書不可不讀。居身務期儉約；教子要有義方。莫貪意外之財，莫飲過量之酒。與肩挑貿易，毋佔便宜；見窮苦親鄰，須加溫恤。刻薄成家，理無久享；倫常乖舛，立見消亡。兄弟叔姪，須分多潤寡；長幼內外，宜法肅辭嚴。聽婦言，乖骨肉，豈是丈夫？重賞財，薄父母，不成人子。嫁女擇佳婿，毋索重聘；娶媳求淑女，勿計厚奩。見富貴而生諂容者，最可恥；遇貧窮而作驕態者，賤莫甚。居家戒爭訟，訟則終凶；處世戒多言，言多必失。勿恃勢力而凌逼孤寡；毋貪口腹而恣殺牲畜。乖僻自是，悔誤必多，類情自甘，家道難成。狎昵惡少，久必受其累；屈志老成，急則可相依。輕聽發言，安知非人之謬想？當忍耐三思；因事相爭，焉知非我之不是？須平心再想。施惠無念，受恩莫忘。凡事當留餘地，得意不宜再往。人有喜慶，不可生妒忌心；人有禍患，不可生喜幸心。善欲人見，不是真善；惡恐人知，便是大惡。見色而起淫心，報在妻女；匿怨而用暗箭，禍延子孫。家門和順，雖饗饕不繼，亦有餘歡；國課早完，即囊橐無餘，自得至樂，讀書志在聖賢，非徒科第；為官心存君國，豈計身家？守分安命，順時聽天。為人若此，庶乎近焉。』

Master Chu's Homilies for Families – Zhu Bolu (End of Ming Dynasty and Beginning of Qing Dynasty)

“Rise up by dawn's early light; clean up, put everything right; keep the home tidy and clean. Go to bed early at night; check that the doors are locked tight; sleep now secure and serene. The growing of rice and of grain Think on whenever you dine; remember how silk is obtained which keeps you warm and looks fine. In periods of drought wise birds mend their nest so when the clouds burst they snugly may rest; never be the fool who starts to dig a well in the ground when he wants a drink of water and water can't be found. Restrained and frugal be in all your private life; that party quickly flee with drinking and flirting rife. Oh better earthen mugs and plates in household neat and clean than vessels made of gold and jade and suited for the queen; eat good food from garden fresh downed with a cup of tea Shun exotic, unknown foods from far across the sea. Build not a house too pretentious and grand; never, no never take anyone's land. Matchmaker ladies who wander out and in don't mediate matches, they mediate sin; a beautiful and lusty young wife may complicate a family's life. A page-boy clever, quick and sharp you should never, never hire; of over made-up, dressed-up wife you certainly will tire. Memorial service for forebears you now and then should hold; to learn from them and show you care, their story should be told. Confucius' classic sayings all children should retain, specially when it's evident They do not have much brain. Honest and righteous be and committed to good deed; your children then will see example they should heed. You can only make a fortune by Striving, working hard; no money falls from out the sky on your own backyard. Only drink a small amount of good wine never let yourself across the sober line. Bargain you not with the traveller who vends; share of your wealth with your neighbors and friends. The man who gets rich through his lying and cheating, will find that his joy -- if any -- is fleeting. A person who commits incest Is foul knave whom all detest. When splitting the family fortune be fair so siblings and cousins will each get their share; domestic law rates everyone par no matter how haughty or humble you are. No worthy son his honor stains by giving any credence when wife, in pillow talk, complains about his antecedents. When selfish son for riches seeks neglecting aging parents then all should treat him as a freak, his actions an aberrance. A costly betrothal cannot ensure, that daughter's marriage will always endure. A nice woman with no dowry makes a good wife; a woman with large dowry may bring stress and strife. To fawn on the rich detracts from your fame and despising the poor redounds to your shame. Don't take into court your family disputes, unpleasant endings emerge from lawsuits; to comport yourself well in society restrain loose tongue's impropriety. Use not your bow and arrow to bully orphan and widow. Do not dumb animals slaughter at will your appetite greedy to over fulfil. Egocentric people grow, much regret and sorrow; lazy, slothful people sow, poverty tomorrow. He who with crooks his way does wend, into crime will surely drift; rely on honest upright friend, when from plight you need a lift. A remark that's made with seeming candor, could really be malicious slander; so carefully now think it through. And when with friend you've had a fight, consider this: perhaps he's right; it may be that fault is with you. In proclaiming your virtue go slow; and be mindful of mercy you owe. Leave room for retreat when trying new feat. You will try, try in vain to repeat windfall gain. Don't envy other's success; don't gloat o'er other's distress. To brag of the good you have done will never impress anyone. Personal scandals you try hard to hide, will soon be known far and wide. The husband who yields to his lustful desire. By letting his lewd fancies roam, thus forfeits his privilege to hope or aspire, to having a warm, happy home. A stab in the back of a man that you hate, will subject your sons to an even worse fate. The family that lives in love and peace, is garnering joys that never will cease even though your food may decrease. Paying tax early to the state, makes you feel contented and great even though your purse will deflate. Sages and men of good virtue inspire, true scholar's heart with a studious fire. If to high office you truly aspire, you must be loyal to king and empire. You are not far from being a good person, if you abide by the law, believe in destiny, following the trend of the time sand adapt to the changes of nature.”

Chang, H.T. (1993). Chinese Encyclopedia Internet Institute. Retrieved from:
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《孝經》—— 儒家經典 (秦、漢時期)

『孝子之事親也，居則致其敬，養則致其樂，病則致其憂，喪則致其哀，祭則致其嚴。五者備矣，然後能事親。』

The Classic of Filial Piety – Confucianism classic (Qin Dynasty and Han Dynasty)

“The service which a filial son does to his parents is as follows: In his general conduct to them, he manifests the utmost reverence. In his nourishing of them, his endeavor is to give them the utmost pleasure. When they are ill, he feels the greatest anxiety. In mourning for them (dead), he exhibits every demonstration of grief. In sacrificing to them, he displays the utmost solemnity. When a son is complete in these five things, (he may be pronounced) able to serve his parents.” (p. 480)

Legge, J. (1879). *The Sacred Books Of China*. Oxford: The Clarendon Press.

《孟子》——孟子（戰國時期）

『公孫醜曰：「君子之不教子，何也？」』

孟子曰：「勢不行也。教者必以正；以正不行，繼之以怒；繼之以怒，則反夷矣。『夫子教我以正，夫子未出於正也。』則是父子相夷也。父子相夷，則惡矣。古者易子而教之。父子之間不責善。責善則離，離則不祥莫大焉。」

The Works of Mencius – Mencius (Warring States Period)

“Gong Sun Chou said, ‘Why is it that the superior man does not himself teach his son?’

Mencius replied, ‘The circumstances of the case forbid its being done. The teacher must inculcate what is correct. When he inculcates what is correct, and his lessons are not practised, he follows them up with being angry. When he follows them up with being angry, then, contrary to what should be, he is offended with his son. At the same time, the pupil says, ‘My master inculcates on me what is correct, and he himself does not proceed in a correct path.’ The result of this is, that father and son are offended with each other. When father and son come to be offended with each other, the case is evil. The ancients exchanged sons, and one taught the son of another. Between father and son, there should be no reproving admonitions to what is good. Such reproofs lead to alienation, and than alienation there is nothing more inauspicious.” (p. 308)

Legge, J. (1895). *The Works of Mencius*. Canada and the United Kingdom: General Publishing Company and Constable and Company.

PARENTING PHENOMENA IN HONG KONG

Table 2. Frequency of responses to the items of the Chinese Paternal Control Scale (CPCS) and Chinese Maternal Control Scale (CMCS)

Item	Responses to the Chinese Paternal Control Scale (Grade 7 to Grade 9)	Responses to the Chinese Maternal Control Scale (Grade 7 to Grade 9)
1. My father/mother expects me to be mature (sheng xing).	Ranged from 86.4% to 91.0%	Ranged from 91.9% to 95.3%
2. My father/mother expects me to be obedient (“guai” and “ting hua”).	Ranged from 90.0 to 91.9%	Ranged from 94.1% to 96.0%
3. My father/mother expects me to have good virtues and behavior.	Ranged from 93.4 to 94.5%	Ranged from 94.9% to 96.9%
4. My father/mother expects me to have good behavior so that I will not bring dishonor to the family (“you ru jia sheng”).	Ranged from 51.1% to 52.0%	Ranged from 53.5% to 54.8%
5. My father/mother expects me to have good behavior so that he/she will not be criticized by others as having no family teaching (“wu jia jiao”).	Ranged from 47.6% to 58.6%	Ranged from 41.2% to 62.5%
6. My father/mother expects me to respect him/her.	Ranged from 73.0% to 75.5%	Ranged from 78.6% to 80.0%
7. My father/mother is very harsh in his/her discipline.	Ranged from 34.3% to 59.7%	Ranged from 40.6% to 47.1%
8. My father/mother always teaches me about the ways of dealing with one self and others.	Ranged from 72.8% to 74.4%	Ranged from 73.0% to 75.6%
9. When I do something wrong, my father/mother requires me to have self-reflection.	Ranged from 67.0% to 69.3%	Ranged from 74.7% to 75.3%
10. When I do something wrong, my father/mother teaches me (“jiao xun”).	Ranged from 58.5% to 59.8%	Ranged from 68.8% to 70.0%
11. When I don’t meet my father’s/mother’s expectation, he/she urges me (“du cu”) to work hard.	Ranged from 72.6% to 75.5%	Ranged from 83.0% to 85.3%
12. My father/mother expects me to interact with older people (“zhang bei”) with respect and courtesy.	Ranged from 92.1% to 94.2%	Ranged from 95.1% to 96.9%

Note: Cumulative percentage figure for each grade = sum of the percentage of responses to the “Agree” and “Strongly Agree” response options. Re-constructed from Shek (2008).

There are several unique parenting features in contemporary Hong Kong. First, Shek [3] found that traditional Chinese socialization goals, such as expectations about maturity, having good virtues and respecting old people, still occupied a strong role in Hong Kong (see Table 2). Second, contemporary Chinese parents emphasized on three socialization goals, which were academic excellence, “obeying” parental instructions and non-engagement of problem behavior [4]. Third, Hong Kong parents still strongly emphasized their children’s academic excellence and they tended to sacrifice their own interests to facilitate their children’s education [5]. Fourth, Chinese parents exercised high behavioral control in academic domain but not in peer domain [6]. Fifth, some of the traditional features of Chinese parenting have been weakened, such as decline in parental harshness, parental teaching (“jiao xun”), and avoidance of bringing dishonor to the family (Table 2). Sixth, Chinese parents typically exhibited high psychological control, although they also showed concerns about their children [7]. In Chan, Leung, Tsang, Lu, and Fok’s [8] study on parenting practice in Hong Kong, it was found that parental warmth has increased in the past 15 years.

Finally, Shek and Sun [2] pointed out that there were several worrying parenting phenomena in contemporary Hong Kong, including the lack of time to spend with children, drop in family solidarity, over-reliance on imported domestic helpers, and comparatively poorer parenting attributes as compared to those in other places. In addition, Shek [9] pointed out that the pragmatic emphases, such as the parenting beliefs of “not to lose at the starting line” and “academic excellence is the most important attribute of a good child”, are shaping parenting practice in contemporary Hong Kong.

PATERNAL PARENTING VERSUS MATERNAL PARENTING

Differences between fathers and mothers on different parenting measures have been reported. For example, Shek [10] found that fathers were seen as higher in restrictiveness but lower in concern as compared to mothers among high school students. Utilizing longitudinal data collected from adolescents, Shek [11] found that while fathers were seen as less responsive, demanding, concerning, communicative, and being liked by their children as compared to mothers, adolescents perceived paternal harshness to be higher than maternal harshness. In another three-year longitudinal study, Shek [12] found that paternal knowledge, expectation, monitoring, discipline, responsiveness, demandingness, parental control defined by indigenous Chinese concepts and dyadic relational qualities (mutual trust and communication) were poorer than those of mothers. However, maternal psychological control was higher than paternal psychological control [12]. In a recent 6-year longitudinal study [13], perceived maternal behavioral control, knowledge, expectations and monitoring were found to be more positive as compared to perceived paternal behavioral control, knowledge, expectation and monitoring. The study further showed that differential parenting persisted in the senior high school years. Such observation is important because “differences between maternal and paternal parenting styles have received less attention, particularly in the case of late adolescents” [14].

In another study conducted by Chan et al. [8], maternal warmth was higher than paternal warmth amongst children aged 9-14 years. However, compared with mothers, fathers showed lower dysfunctional parenting practice, behavioral control, psychological control and Chinese

parental control. Similar findings were reported in secondary school students [15]. Based on the responses of adolescent children, Leung and Shek [16] reported that fathers were less responsive, demanding, controlling and sacrificial for children's education than did the mothers, and the differences were triangulated by the findings based on the responses of both parents.

Interestingly, the available research showed that there was a shift in parenting attributes in contemporary fathers and mothers in Hong Kong. Traditional Chinese parenting was commonly conceived in terms of "strict fathers, kind mothers", where fathers were harsh while mothers were lenient. However, parenting research in Hong Kong suggested that Chinese parenting has been changed to "kind fathers, strict mothers" and "detached fathers, involved mothers", where mothers are relatively more demanding, controlling and have more monitoring about their children than fathers [12]. Besides, as compared to fathers, mothers are also more involved and show more affection in children's socialization process.

PARENTING INFLUENCES ON ADOLESCENT DEVELOPMENT

Consistent with the Western literature, cross-sectional studies suggested that parenting influences the development of children and adolescent in Hong Kong. Shek [17] found that the parental treatment styles were negatively related to high school students' psychological symptoms (anxiety, depression, somatic symptoms and general psychological symptoms) and positively related to their positive mental health (purpose in life and ego strength). Based on Chinese high school students, Shek [18] found that while global parenting style and specific parenting behavior were negatively related to general psychological symptoms and hopelessness, these parenting attributes were positively related to purpose in life, life satisfaction, self-esteem, academic achievement and school conduct. Parenting characteristics were also positively related to adolescent developmental outcomes in the general adolescent population [8] and high-risk families [19]. McBride and Chang [20] pointed out that while authoritative parenting style was related to autonomy, parenting style was not related to school achievement. Parenting emphasizing autonomy in children also facilitated prosocial behavior [21].

There are not many longitudinal studies examining the impact of parenting on child developmental outcomes in Hong Kong. Shek [22] showed that adolescents who perceived their parents as concerning, restrictive, responsive or demanding had better positive mental health, including purpose in life and life satisfaction. Similarly, those who had a more positive perception of parenting attributes displayed fewer psychological symptoms. In a 6-year longitudinal study in the Project P.A.T.H.S. [13], it was found that higher parental control and better parent-child relationship were related to higher life satisfaction, purpose in life and psychosocial competence (such as emotional competence and resilience), and lower adolescent risk behavior, including hopelessness, Internet addiction, delinquency, consumption of pornography, self-harm and suicidal behavior. On the other hand, psychological control was negatively related to psychological well-being but positively related to risk behavior [13]. Similar findings were observed in high-risk families. Based on two waves of data collected from poor families, Shek [23] showed that more positive

parenting attributes were related to better subjective well-being and lower psychological morbidity and hopelessness.

PATERNAL INFLUENCE VERSUS MATERNAL INFLUENCE ON CHILD DEVELOPMENT

Although there are studies examining the influence of parenting on child development, only few studies have examined the relative contribution of fathers and mothers to different aspects of adolescent development. Primarily, there are studies showing the relatively stronger influence of paternal parenting relative to maternal parenting. Based on the responses of high school students to questionnaire measures over two years, Shek [22] showed that parenting styles and parenting behavior were related to psychological symptoms and positive mental health concurrently and over time, and the relationships were reciprocal in nature. Besides, paternal parenting showed stronger influence on adolescent development. Based on the same study, Shek [24] integrated questionnaire (global and specific parenting) and interview measures (feelings about parenting, parent-adolescent communication) to form new measures of “paternal parenting qualities” and “maternal parenting qualities”. While maternal parenting qualities did not predict changes in the adolescent developmental outcomes, paternal parenting qualities predicted changes in psychological morbidity indexed by hopelessness, general psychological symptoms, and eudaimonic mental health indexed by life meaning, life satisfaction, and self-esteem.

There are also studies showing that paternal parenting and maternal parenting are both related to different child outcomes, but their effects may differ across genders of adolescents. Shek [23] examined the influence of paternal and maternal parenthood qualities on development of adolescents from poor families. At a particular time, different parenting factors were correlated with adolescent developmental outcome measured using cross-sectional data. However, there was no strong support for the hypothesis that adolescent developmental outcomes were influenced by parenting over time. Nevertheless, while paternal parenting influenced mental health and problem behavior in adolescent boys, but not in adolescent girls, maternal parenting influenced mental health and problem behavior in adolescent girls, but not in adolescent boys [23]. Based on poor Chinese families, Leung and Shek [25] found that while the expectation of fathers on the future of their children predicted perceived maternal control and adolescent development, maternal control mediated the influence of parental beliefs on adolescent psychosocial competences. Ren, Zhang, Yang, and Song [26] also found that supportive parenting and the role of fathers were important in shaping mathematics competence and behavioral problem in young children.

PARENTING QUALITIES IN HIGH-RISK FAMILIES

Compared with non-vulnerable families, parenting in vulnerable families are relatively poorer. In several cross-sectional studies, compared to intact families (i.e., parents were in their first marriage), parents in non-intact families (i.e., divorced, separated, remarried and other forms of marriages of the parents) showed less concern, responsiveness, knowledge and

monitoring to their children, but more and harsher punishment [27]. Similar results were reported in the Chan et al. [8] study on parenting in Hong Kong, which indicated that parenting attributes were more positive in intact families than in non-intact families.

The relative poorer parenting attributes in non-intact families were also reported in longitudinal studies. In a 3-year longitudinal study, we found that perceived parental behavioral control, responsiveness, demandingness, and perceived parenting based on indigenous Chinese concepts were comparatively poorer in adolescents from families experiencing parental marital disruption as compared to those from families with no parental marital disruption [28]. In another longitudinal study utilizing six waves of data, adolescents in non-intact families had a less favorable perception of paternal behavior control, including parental knowledge, expectation and monitoring. Similar findings were obtained for maternal behavioral control, maternal knowledge, maternal expectations and monitoring and maternal psychological control in each wave of data [13].

Economic disadvantage is also a risk factor in parenting. In several cross-sectional studies, adolescents from poor families perceived parenting to be less favorable as compared to adolescents from non-poor families [29]. Similar findings were revealed in a three-year longitudinal study, which showed that adolescents from poor families perceived parental behavioral control (indexed by Western measures of parental knowledge, expectation, monitoring, discipline, demandingness and indigenous Chinese measure of parental control) to be less favorable than did adolescents from non-poor families. In contrast, adolescents with family economic disadvantage perceived psychological control to be stronger than did adolescents without family economic disadvantage [30]. In the 6-wave longitudinal study in the Project P.A.T.H.S., adolescents from poor families perceived parental behavioral control and parent-child relational quality to be lower as compared to adolescents from non-poor families at different time points [13]. In addition, relative to adolescents from non-poor families, adolescents from poor families perceived parental psychological control to be higher.

PARENTING AND OTHER FAMILY PROCESSES

Research showed that different types and dimensions of parenting were inter-related. With reference to the different components of behavioral control (expectations, discipline, monitoring and knowledge), cross-sectional and longitudinal findings suggested that they were generally related in a positive manner [12]. For example, parents who have higher monitoring of their children would have more knowledge about their children. Besides, parental behavioral control (such as monitoring the whereabouts of children) was negatively associated with psychological control (such as withdrawal of love and inducing guilt in children). Furthermore, Shek [31] showed that different dimensions of global parental treatment styles (concern and harshness) and specific parenting behavior (responsiveness and demandingness) were inter-related. In addition, global parenting was associated with specific parenting. While parental responsiveness was positively related to different measures of parental behavioral control, it was negatively related to parental psychological control [12].

Furthermore, parenting quality is related to other dyadic family processes. Shek [32] showed that higher parental behavioral control and lower parental psychological control were

related to higher perceived parental trust of children and children's trust of their parents. Based on two waves of longitudinal data, Shek [33] showed that parenting attributes were related to parent-adolescent conflict at the same time and over time. Besides, findings showed that while parenting influenced parent-adolescent conflict, parent-adolescent conflict also influenced parenting.

Finally, parenting as a dyadic family process is related to systemic family functioning. Shek [34] examined the relationships between dyadic family relationships, which included measures based on parents and adolescent children reports of parenting style and parent-adolescent conflict and systemic family functioning measures. He found that family functioning based on the perspectives of parents and children was related to dyadic family processes, including parenting. Relative to perceived mother-child relationship and marital quality reported by mothers, perceived father-child relationship and marital quality showed stronger influence on systemic family functioning over time. In the six-wave longitudinal study in the Project P.A.T.H.S., while parental behavioral control and parent-child relationship were positively related to family functioning, parental psychological control was negatively related to systemic family functioning [13].

There are also findings showing that parenting mediates the impacts of parental behavior on child developmental outcomes. Based on the data collected from single-parent families, Leung and Shek [35] found that responsiveness and demandingness of mothers influenced filial piety which in turn affected positive development in adolescents. Filial piety was also identified as a moderator of the influence of maternal control on mother-adolescent relationship [36].

UNANSWERED QUESTIONS AND FUTURE RESEARCH DIRECTIONS

Based on 90 studies captured by PsycINFO, Fok and Shek [37] highlighted three conceptual limitations of parenting research in Hong Kong. These included paucity of parenting research utilizing indigenous Chinese parenting concepts, inadequate conceptual models examining causes, correlates and consequences of parenting, and failures to consider alternative explanations for the findings for those studies examining relationship between parenting and other constructs. In another paper [38], they further argued that there were eight methodological limitations of parenting research in Hong Kong, including predominant use of translated and non-validated Western measures, lack of longitudinal research studies, infrequent employment of multiple indicators to assess different parenting constructs, over-reliance on convenience sampling, insufficient use of hierarchical linear modeling looking at individual and cluster effects, paucity of qualitative studies of parenting.

With reference to the conceptual and methodological limitations of the field, there are several future research directions. First, with five thousand years' history, research on traditional Chinese parenting is grossly inadequate. It would be helpful to understand indigenous forms of parenting [38]. Besides, it would be helpful to understand more on how traditional parenting is related to modern parenting science. In a recent study of *Di Zi Gui* [39], the author argued that many ideas in traditional parenting are in fact similar to the propositions in modern parenting science. For example, trustworthiness is strongly emphasized in *Di Zi Gui*, which is consistent with the emphasis on the importance of gaining

trust from others in the literature of positive youth development. Integrating the ideas in traditional Chinese family instruction books with modern parenting science is undoubtedly interesting yet challenging task to be done. Second, there is a need to develop more assessment tools on Chinese parenting based on imported and indigenous Chinese concepts, such as honoring parents and parental sacrifice.

Third, in view of the unique Chinese cultural emphases (such as emphasis on obedience of children) and Hong Kong ideologies (such as emphasis on academic excellence), there is a need to build up Chinese models of parenting, including its antecedents, concomitants and consequences. For example, it would be important to understand how traditional Chinese parenting beliefs (e.g., emphasis on academic excellence) and contemporary Hong Kong parenting beliefs (e.g., striving for achievement) shape the parenting practices in Hong Kong. Fourth, with time and place as the varying dimensions, it would be exciting to examine how parenting across time (e.g., inter-generational differences in parenting beliefs and practices) and places (e.g., Hong Kong, mainland China, Taiwan and ethnic minority group in China). Comparative studies in different Chinese communities would be important.

Fifth, with long working hours, super-high property price and obsessive emphasis on achievement, there is a great need to understand how parents cope with parental stress in the unique socio-cultural contexts of Hong Kong. In fact, many studies suggest that excessive parenting stress is an emerging family problem in Hong Kong. Sixth, with growing children mental health issues, there is a need to understand the stress and coping of families with children with special needs. Finally, there is a need to step up research to develop parenting education programs in Hong Kong. Although parenting programs flourish in Hong Kong, most of them are not based on well-articulated theoretical models and evaluation is conducted in some isolated programs only [40]. Obviously, there is a need to promote evidence-based parenting policies and programs in Hong Kong.

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Chapter 313

“DI ZI GUI” (STANDARDS FOR BEING A GOOD STUDENT AND CHILD): IMPLICATIONS FOR CHILDREN AND YOUTH DEVELOPMENT AND PARENTING

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ABSTRACT

“*Di Zi Gui*” (*Standards for being a good student and child*) is a classic Chinese text outlining the proper behavior of a good student and child. It covers the “desired” behavior of children at home and away from home, things that one should pay attention to in daily life, trustworthiness, love of humanity, learning from people with virtue and compassion, and further study after accomplishing the basic tasks. In this chapter, the basic assertions in different chapters of *Di Zi Gui* were examined with reference to contemporary scientific literature on youth development and parenting. Several observations can be highlighted from the review. First, some assertions in *Di Zi Gui* (such as the emphases on bonding and character) are similar to the emphases in the contemporary youth development literature. Second, some assertions (such as the thought of undermining the rights of children) are not consistent with the contemporary views. Third, *Di Zi Gui* offers novel insights (such as emphasis on the importance of self-cultivation) into the youth development and parenting theories. Finally, there are practical implications of *Di Zi Gui* for youth development and parenting. It is concluded that although *Di Zi Gui* is a classic Chinese text written several centuries ago, some assertions

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show striking resemblance to the contemporary scientific findings and it has tremendous implications for contemporary youth development and parenting science and practice.

INTRODUCTION

In many cultures, there are two questions confronting young people, parents, youth workers, allied professionals and policy makers. The first question is what should the developmental “ideals” for children and adolescents should be. In the cultures emphasizing hunting, good physical strengths and independent living skills in children are usually emphasized. On the other hand, as order and social harmony are indispensable to crop growing in the agricultural societies, children are taught to be patient and respect the social norms. The second question is how parents should nurture their children to attain such developmental ideals. Again, different cultural characteristics with reference to the children’s rights or parental power would suggest different strategies in the socialization process.

Regarding the developmental ideals for youth development, different attributes such as positive self-concept, high self-esteem, meaningful engagement and good interpersonal relationship have been proposed by Western theorists. With particular reference to the positive youth development perspective [1-4], the developmental ideals of young people focus on their talents and potentials. According to Catalano, Berglund [5], a thriving young person has the attributes of bonding, resilience, psychosocial competence, self-determination, self-efficacy, positive identity, meaningful life, identification with prosocial norms and meaningful community engagement [6]. According to Lerner, Brentano [7], the developmental ideals for young people include competence, character, connection, confidence, caring and compassion. According to Park and Peterson [8], there are 24 character strengths which can be regarded as the developmental ideals for young people.

Concerning how parents nurture the developmental ideals in young people, it is a question of parenting. In the Western literature, there are two commonly used frameworks of parenting. The first one is based on the work of Baumrind [9] which suggests that there are three types of parenting – authoritarian parenting (absolute control of the child with little freedom), permissive parenting (absolute freedom for the child with little control) and authoritative parenting (appropriate control and freedom for the child). In the second framework proposed by Maccoby and Martin [10], it is proposed that parenting is defined in terms of two dimensions (responsiveness and demandingness). As a result, four types of parenting emerge, including authoritarian parenting (low responsiveness but high demandingness), authoritative parenting (high responsiveness and high demandingness), permissive parenting (high responsiveness but low demandingness) and neglectful parenting (low responsiveness and low demandingness). There are also studies proposing that dyadic and systemic family processes influence adolescent development [11, 12].

In the past few decades, researchers have commonly used the Western models of youth development and parenting to understand Chinese children and parents. In the process, the question of whether the Western notions of youth development and parenting frameworks are applicable to our understanding of Chinese behavior has been raised [13]. One response is that the Western concepts may not be totally applicable and we need to use indigenous Chinese concepts to understand youth development and parenting. In addition, it can be

argued that Chinese writings such as the classics can contribute to our understanding of the developmental ideals for youth development and parenting.

In the traditional Chinese culture, there are writings on the developmental ideals of children and adolescents [14-16]. For example, filial piety was described in the examples in the classic 24 stories of filial piety. The key messages are that the children should obey and serve their parents because their parents gave birth to and take care of them; filial children are blessed by Heaven. Besides, there are many parenting books (“*jia xun*”) which emphasize the developmental ideals of the children and family practice (“*jia gui*”) governing the “proper” behavior of the children [12, 15].

In this paper, we reviewed the Chinese Classic entitled *Di Zi Gui* to understand how the child developmental ideals and parenting were conceived under the traditional Chinese culture. *Di Zi Gui* was written by Li Yu-xiu in the Qing dynasty when Kangxi was the emperor of China. Same as *San Zi Jing* (Three character classic), it takes the form of a three-character verse. The main ideas of *Di Zi Gui* are based on the Confucian thoughts, including the emphases on filial piety, family harmony, self-cultivation of virtues and morality, and maintenance of good interpersonal harmony. In this paper, we will analyze this problem with reference to four topics: a) areas of similarity between the propositions and modern parenting science; b) areas of dissimilarity between the propositions and modern parenting science; c) novel or non-conventional views offered; and d) implications of the propositions about nurturance of the child developmental ideals and parenting. It is noteworthy that there are different versions of *Di Zi Gui*. In this paper, the English version of *Di Zi Gui* is based on the English translation of Pure Land Learning College Association [17]. In this paper, the children refer to the human beings below the age of 18.

REVIEW OF THE OUTLINE

總敘：弟子規 聖人訓；首孝弟 次謹信；汎愛眾 而親仁；有餘力，則學文。

“Outline: *Di Zi Gui* or *Standards for Being a Good Student and Child* is a book that was taught by Chinese saints and sages of the ancient past. The book first teaches us how to be dutiful to our parents, and how to be respectful and loving to our siblings. It then teaches us how to be cautious with all people, matters, and objects in our daily lives; how to be a trustworthy person; and to believe in the teachings of the ancient saints and sages.”

Several observations can be highlighted from the Outline of *Di Zi Gui*. First, the assertions are the teachings of saints and sages of the past. While great men in the past should be respected, it is “authority-based” knowledge rather than “evidence-based” knowledge [18]. Hence, it is questionable whether the related assertions are effective in reality. On the other hand, if the “authority-based” knowledge is consistent with the knowledge derived from contemporary youth development and parenting science, it can be argued that traditional wisdom has contemporary relevance.

Second, family, particularly the father-child relationship and the sibling relationship, is regarded as the central developmental context of the children and adolescents, with filial piety as the cornerstone of child development. A review of the child and adolescent developmental theories shows that many theories are individualistic in nature. For example, Freudian

theories focus on the inner dynamics of human development and cognitive theories focus on the schematic changes throughout the development. While the micro psychological theories have generated much research about the child and adolescent development, they have been criticized for ignoring the environmental influences. Hence, there are theories that focus on how different social systems influence child development. Amongst them, the family-based developmental perspectives focus on the development of children within the family context and how family processes shape the developmental trajectories of adolescent development [19]. *Di Zi Gui* clearly highlights the importance of the family to child development.

Third, the Outline describes the things that one must pay careful attention to. With reference to the expectations about hygiene and daily living, the related measures can be regarded as self-management issues. This feature is quite unique because self-management is an emergent field in the child and youth development in the past few decades. Besides, the focus on “cautions” also hinges on prevention which is an important focus in child and adolescent psychology and prevention science.

Fourth, *Di Zi Gui* emphasizes the importance of trustworthiness of oneself as a cornerstone of selfhood and interpersonal relationship. This point is interesting because trustworthiness (i.e., trust from others) is not a major focus in the contemporary theories of youth development, although self-confidence (i.e., trusting oneself) is commonly emphasized in the positive youth development theories. Obviously, gaining trust from others is much more difficult than gaining trust from oneself.

Fifth, *Di Zi Gui* does not focus on self-cultivation alone. It also emphasizes the importance of loving other human beings. This focus has three unique features. Primarily, it is collectivistic rather than individualistic (i.e., focusing on others is more important than focusing on oneself). Besides, it focuses on the possible contribution of young people to the society. Furthermore, the focus of youth development is on a higher ideal when we cover mankind.

Sixth, it is emphasized that learning from those with virtue and compassion is important. This addresses an important issue about identity formation when the adolescents may model themselves on the significant-others. This point is also related to the adolescent development literature that modeling on positive adults and peers (i.e., bonding) is important for positive youth development [6].

Seventh, one interesting observation from *Di Zi Gui* is that learning from the literature is the last emphasis for youth development. In fact, learning is the last thing when a child has “spare effort”. This is in sharp contrast to the Eriksonian view that children and adolescents should learn the “technological ethos” of the culture. This is also not consistent with the emphasis of the modern societies that formal education is an important developmental task for children and adolescents. Most important of all, this is inconsistent with the contemporary Chinese parenting value, “do not lose at the starting line”.

Finally, the general outline is consistent with the ecological model that different systems should be considered in child and adolescent development. In *Di Zi Gui*, children are taught about the importance of family duties within and outside the family (family system), things that should be cautious (individual system), doing good for other people and loving others (interpersonal system), learning from people with virtue and good reputation (interpersonal system) and learning from literature (historical system).

REVIEW OF CHAPTER 307

入則孝

父母呼，應勿緩。父母命，行勿懶。父母教，須敬聽。父母責，須順承。
冬則溫，夏則清；晨則省，昏則定。出必告，反必面；居有常，業無變。
事雖小，勿擅為；苟擅為，子道虧。物雖小，勿私藏；苟私藏，親心傷。
親所好，力為具，親所惡，謹為去；身有傷，貽親憂，德有傷，貽親羞。
親愛我，孝何難；親憎我，孝方賢。親有過，諫使更；怡吾色，柔吾聲。
諫不入，悅復諫；號泣隨，撻無怨。
親有疾，藥先嘗；晝夜侍，不離床。喪三年，常悲咽；居處變，酒肉絕。
喪盡禮，祭盡誠；事死者，如事生。

“At Home, Be Dutiful to My Parents

When my parents call me, I will answer them right away. When they ask me to do something, I will do it quickly. When my parents instruct me, I will listen respectfully. When my parents reproach me, I will obey and accept their scolding. I will try hard to change and improve myself, to start anew.

In the winter, I will keep my parents warm; in the summer, I will keep my parents cool. I will always greet my parents in the morning to show them that I care. At night I will always make sure my parents rest well. Before going out, I must tell my parents where I am going, for parents are always concerned about their children. After returning home, I must go and see my parents to let them know I am back, so they do not worry about me. I will maintain a permanent place to stay and lead a routine life. I will persist in whatever I do and will not change my aspirations at will.

A matter might be trivial, but if it is wrong to do it or unfair to another person, I must not do it thinking it will bear little or no consequence. If I do, I am not being a dutiful child because my parents would not want to see me doing things that are irrational or illegal. Even though an object might be small, I will not keep it a secret from my parents. If I do, I will hurt my parents' feelings.

If whatever pleases my parents is fair and reasonable, I will try my best to attain it for them. If something displeases my parents, if within reason I will cautiously keep it away from them. When my body is hurt, my parents will be worried. If my virtues are compromised, my parents will feel ashamed.

When my parents do wrong, I will urge them to change. I will do it with a kind facial expression and a warm gentle voice. If they do not accept my advice, I will wait until they are in a happier mood before I attempt to dissuade them again, followed by crying, if necessary, to make them understand. If they end up whipping me, I will not hold a grudge against them.

When my parents are ill, I will taste the medicine first before giving it to them. I will take care of them night and day and stay by their bedside. During the first three years of mourning after my parents have passed away, I will remember them with gratitude and feel sad often for not being able to repay them for their kindness in raising me. During this period, I will arrange my home to reflect my grief and sorrow. I will also avoid festivities and indulgence in food and alcoholic drinks. I will observe proper etiquette in arranging my parents' funerals. I will hold the memorial ceremony and commemorate my parents' anniversaries with utmost sincerity. I will serve my departed parents as if they were still alive.”

Two observations can be highlighted in Chapter 1 of *Di Zi Gui*. First, parents play a superior and dominant role in the family (i.e., parent-centered family). Second, children are expected to fulfil many family duties, particularly for their parents. As far as the child development is concerned, an “ideal” development would be to learn the duties and execute them well. As far as parenting is concerned, children should be taught or socialized to be filial

at home. These observations are consistent with the analyses of Shek and Chan [20] on the attributes of an ideal child.

An examination of the assertions in chapter 1 shows that some of them are consistent with the propositions of the contemporary scientific literature on children and youth development and parenting. First, the focus on respect for parents and duties of children is consistent with the notion of “demandingness” of the notion of authoritative parenting [10]. Instead of providing everything for children as denoted in permissive or indulgent parenting, children are expected to learn and perform their filial piety duties.

Second, the assertions about self-improvement, striving for excellence and perseverance are consistent with the expectations of positive youth development. Primarily, it is conjectured that the duties to be accomplished by the children and adolescents are “doable,” which can be improved through perseverance and a strong motivation to excel. This view is consistent with the positive youth development approach that young people have potential to excel and striving for excellence is possible through perseverance and effort. This view is obviously positive, which sees the children and adolescents as an active agent learning the good things of life and developing virtues [21].

Third, concern for parents is a strong emphasis in this chapter. In terms of family functioning, concerning for one’s parents is a sign of “mutuality” which is basic to the well-functioning families. In the previous studies, it was found that “mutuality” is an important dimension of Chinese family functioning and it has positive relationships to the well-being of Chinese adolescents [22]. Psychologically speaking, showing love to one’s parents will elicit love from the parents. The loving behavior of the children will also foster a warm and reciprocal loving environment within the family.

Fourth, besides taking care of the daily living and physical well-being of their parents, the children are also expected to take care of the “feelings” of the parents (i.e., children should not do things that hurt their parents). This point underscores the importance of cultivation of “empathy” in children and adolescents and the starting point is to practice it within the family. In contemporary adolescent psychology, empathy has been identified as an important factor governing adolescent development [23, 24].

Fifth, the children are expected to follow their family rules, such as telling their parents where they go. In some contemporary family models of family functioning, having family rules is an important sign of family functioning. For example, in McMaster Model of family functioning, it is proposed that “family rules” is an important dimension of effective family functioning. In the parenting literature, following the family rules is an important component of parental behavioral control such as whether the parents know the whereabouts of their children [25, 26]. In fact, parenting workers usually suggest that the families should have clear and reasonable family rules to regulate the behaviors of their children.

Sixth, *Di Zi Gui* asserts that children should love their parents even if their parents hate them. By doing this, the children are learning resilience and forgiveness. Regarding resilience, the children have to learn how to interact with their parents in adversity. Regarding forgiveness, the children have to learn how to accept the wrongdoings of their parents and help them to change. Furthermore, the role of children to dissuade their parents is consistent with some of the family theorists’ propositions that the children can also assume an “adult” role in pointing out the wrongdoings of their parents and inviting them to reflect.

Finally, the assertion on mourning is consistent with the contemporary literature that bereavement takes time [27]. The suggestion of mourning for three years is in fact very

psychological and consistent with the literature that premature termination of mourning is detrimental to one's well-being. The practice of remembering the ancestors also provides psychological support and cultural resources to those family members who are still living (e.g., to complete the good work of the ancestors).

On the other hand, some of the assertions in this chapter are not consistent with the contemporary literature on child development and parenting. Fundamentally, the parent-child relationship is a hierarchical one, with the parents higher than their children. According to Maccoby and Martin [10], this is a form of authoritarian parenting where the children should strictly follow the parental expectations and prescriptions.

The expectation of absolute obedience of children may also be against the United Nations Convention on the Rights of the Child. Besides, contemporary literature highlights the duties of parents instead of children in the socialization process. Some examples are illustrated below:

- **Article 12:** States Parties shall assure to the child who is capable of forming his or her own views the right to express those views freely in all matters affecting the child, the views of the child being given due weight in accordance with the age and maturity of the child.
- **Article 13:** The child shall have the right to freedom of expression; this right shall include freedom to seek, receive and impart information and ideas of all kinds, regardless of frontiers, either orally, in writing or in print, in the form of art, or through any other media of the child's choice.
- **Article 18:** States Parties shall use their best efforts to ensure recognition of the principle that both parents have common responsibilities for the upbringing and development of the child. Parents or, as the case may be, legal guardians, have the primary responsibility for the upbringing and development of the child. The best interests of the child will be their basic concern.

There are two novel points regarding youth development in this chapter. First, one should remember that one's body is inherited from their parents and one should take care of their own body. This view is novel because the emphasis on one's responsibility of taking care of their body is intrinsic to the Western scientific literature. By focusing on the view that one's body is from their parents, one would take into account of the effort that their parents pay in the socialization process. This would reinforce the value of his/her body that the child should take great care of. Besides, this view will also provide an additional perspective for the child to consider when he/she attempts to harm or kill oneself.

Another novel point covered in this Chapter is the notion of having awareness of the feelings of the parents. With growing egocentrism in young people, there is a need to promote empathy in the adolescents. By focusing on the feelings of their parents, it is easier for the children and adolescents to learn empathy. Also, family is a good venue for them to practice empathy. Unfortunately, as Chinese people are quite reserved to express their emotions [28, 29], whether the children can really learn to understand the feelings of their parents is an important question to be considered.

There are four implications of this chapter for child development and parenting. First, young people and parents should develop the belief that young people can excel themselves

and do well with perseverance and motivation as the key processes are involved. Second, promotion of empathy in children can start with helping them to understand the feelings and experiences of their parents. Third, we should reinforce the notion that one's body comes from their parents and one should take care of their own body. This strategy would have important implications for health promotion and prevention of self-harm and suicide. Finally, the notion of the children "advising" their parents is opening up the possibility of more active involvement of children and communication between parents and children.

REVIEW OF CHAPTER 308

出則弟

兄道友，弟道恭，兄弟睦，孝在中。財物輕，怨何生；言語忍，忿自泯。或飲食，或坐走，長者先，幼者後。長呼人，即代叫；人不在，己即到。稱尊長，勿呼名；對尊長，勿見能。路遇長，疾趨揖，長無言，退恭立。騎下馬，乘下車，過猶待，百步餘。長者立，幼勿坐；長者坐，命乃坐。尊長前，聲要低；低不聞，卻非宜。進必趨，退必遲；問起對，視勿移。事諸父，如事父；事諸兄，如事兄。

“Standards for a Younger Brother When Away from Home

If I am the older sibling, I will befriend the younger ones. If I am the younger sibling, I will respect and love the older ones. Only when I can maintain harmonious relationships with my siblings, am I being dutiful to my parents. When I value my familial ties more than property and belongings, no resentment will come between me and my siblings. When I am careful with words and hold back hurtful comments, my feelings of anger naturally die out.

Whether I am drinking, eating, walking, or sitting, I will let the elders go first; the younger ones should follow. When an elder is asking for someone, I will get that person for him right away. If I cannot find that person, I will immediately report back, and put myself at the elder's service instead.

When I address an elder, I should not call him by his given name. This is in accord with ancient Chinese etiquette. In front of an elder, I will never show off. If I meet an elder I know on the street, I will promptly clasp my hands and greet him with a bow. If he does not speak to me, I will step back and respectfully stand aside.

Should I be riding a horse and spot an elder I know walking, I will dismount and pay respect to the elder. If I am riding in a carriage, I will stop, get out of the carriage, and ask if I can give the elder a ride. If I meet an elder passing by, I will stand aside and wait respectfully. I will not leave until the elder disappears from my sight. When an elder is standing, I will not sit. After an elder sits down, I sit only when I am told to do so.

Before an elder, I will speak softly. But if my voice is too low and hard to hear, it is not appropriate. When meeting an elder, I will walk briskly towards him; when leaving, I will not exit in haste. When answering a question, I will look at the person who is asking me the question. I will serve my uncles as if I am serving my parents. I will treat my cousins as if they are my own siblings.”

In chapter 2 of *Di Zi Gui*, some assertions are consistent with the contemporary scientific literature. First, the duties of the elder siblings (to befriend the younger ones) and younger brothers (respect and love the older ones) are clearly defined, which surround the notion of filial piety. If the elder siblings are friendly to the younger ones and the younger ones respect

and concern about the elder ones, it would result in a harmonious family. In fact, in some of the contemporary family therapy models, there is an emphasis on playing the appropriate roles by different family members [25]. In fact, if the members do not play their appropriate roles, the family will become chaotic and cannot function properly. This chapter also focuses on the importance of taking up appropriate roles by the family members.

Second, consistent with the contemporary theories and research on youth development, some important elements of social competence are emphasized in the assertions. Primarily, it is emphasized that one should be careful about words. From an interpersonal communication perspective, appropriate verbal responses such as appreciating or praising others would enrich the relationship. On the other hand, hasty or impulsive words would definitely hurt the interpersonal relationship. Hence, the expectation to “hold back hurtful comments” is in fact positive and even therapeutic in interpersonal relationships.

Third, consistent with the clinical literature, it is asserted that it is important to reduce bitterness and anger [30]. From an intervention point of view, many unsolved human problems stem from bitterness, such as regarding one as unfairly treated or other people being better than us. Similarly, anger also makes interpersonal relationships complicated. In *Di Zi Gui*, it is asserted that through careful verbal communication, anger would subside. Fourth, both assertions and the contemporary scientific literature mentioned controlling one’s bitterness and anger. Fifth, with reference to the propositions of the positive youth development approach, the notion of not to show off in front of elder people is to practice humility, which is regarded as a character strength.

On the other hand, two areas of inconsistency with the contemporary literature can be identified. First, while respect for old people is part of the Chinese culture, it is not consistent with the United Nations Universal Declaration of Human Rights that “everyone is entitled to all the rights and freedoms set forth in this Declaration, without distinction of any kind, such as race, colour, sex, language, religion, political or other opinion, national or social origin, property, birth or other status”. Obviously, the phrase “or other status” clearly suggests that old and young people should be treated equally in terms of their rights.

The second inconsistency is about “showing off” in front of an elder. It is noteworthy that under the influence of the “self-esteem” movement, children are usually taught to show what they can do and they should appreciate their own talents. Having “shows” in front of other people is commonly encouraged in the contemporary parenting writings because such a behavior can promote self-confidence and self-efficacy in young people, hence contributing to the positive identity in young people.

As far as the novel messages noted in this chapter, there are two distinct observations. First, it is asserted that the family ties should be considered as more important than property and belongings. In other words, a good family is priceless and beyond material calculation (i.e., spiritual emphasis). This point immediately brings the importance to a spiritual level. While many people regard families as important, few theorists have an attempt to assert that the families are more important than material possession.

Second, the saying of “serving your uncles as if they are your fathers and treating your cousins as if they are your brothers” is a good gesture embracing humanity. There are two elements intrinsic to this saying. In the first place, one loves all people instead of categorizing them into “intra-familial” or “extra-familial” people. Besides, one attends to the needs of any people who come into contact with the young person. In terms of Kohlberg’s theory of moral

development, it would be the highest level of moral development involving the universal ethical principle – having universal love for all [31].

There are two implications for child development in this chapter. First, parents should teach their children to say words carefully. With an advance on the Internet, the kids usually give “likes” or leave impulsive comments in the virtual world. Hence, it would be important to promote “careful words” among children while balancing it with encouraging them to express their views. Second, parents can use the family-versus-material possession dilemma to encourage their children to make their choices and understand the reasoning behind [32].

REVIEW OF CHAPTER 309

謹

朝起早，夜眠遲，老易至，惜此時。晨必盥，兼漱口，便溺回，輒淨手。冠必正，紐必結，襪與履，俱緊切。置冠服，有定位，勿亂頓，致污穢。衣貴潔，不貴華，上循分，下稱家。對飲食，勿揀擇，食適可，勿過則。年方少，勿飲酒，飲酒醉，最為醜。步從容，立端正，揖深圓，拜恭敬。勿踐闕，勿跛倚，勿箕踞，勿搖髀。緩揭簾，勿有聲；寬轉彎，勿觸棱。執虛器，如執盈；入虛室，如有人。事勿忙，忙多錯；勿畏難，勿輕略。鬥鬧場，絕勿近；邪僻事，絕勿問。將入門，問孰存，將上堂，聲必揚。人問誰，對以名，吾與我，不分明。用人物，須明求，倘不問，即為偷。借人物，及時還，後有急，借不難。

“Be Cautious in My Daily Life

I will get up each morning before my parents; at night, I will go to bed only after my parents have gone to sleep. When I realize that time is passing me by and cannot be turned back, and that I am getting older year by year, I will especially treasure the present moment. When I get up in the morning, I will wash my face and brush my teeth. After using the toilet, I will always wash my hands.

I must wear my hat straight, and make sure the hooks of my clothes are tied. My socks and shoes should also be worn neatly and correctly. I will always place my hat and clothes away in their proper places. I will not carelessly throw my clothes around, for that will get them dirty.

It is more important that my clothes are clean, rather than how extravagant they are. I will wear only what is suitable for my station. At home, I will wear clothes according to my family traditions and customs. When it comes to eating and drinking, I will not pick and choose my food. I will only eat the right amount; I will not over-eat.

While I am still young, I must not drink alcohol. When I am drunk, my behavior will turn ugly. I will always walk composed, with light and even steps. I will always stand up straight and tall. My bows will always be deep, with hands held in front and arms rounded. I will always pay my respect with reverence.

I will not step on doorsills or stand leaning on one leg. I will not sit with my legs apart or sprawled out. I will not rock the lower part of my body while standing or sitting down. I will always lift the curtain slowly, and quietly. I must leave myself ample space when I turn so I will not bump into a corner.

I will hold empty containers carefully as if they were full. I will enter empty rooms as if they were occupied. I will avoid doing things in a hurry, as doing things in haste will lead to many mistakes. I should not be afraid of difficult tasks, and I will not become careless when a job is too easy.

I will keep away from rowdy places. I will not ask about things that are abnormal or unusual. When I am

about to enter a main entrance, I must first ask if someone is inside. Before entering a room, I must first make myself heard, so that those inside know someone is approaching.

If someone asks who I am, I must give my name. To answer ‘It is me’ or ‘Me’ is not sufficient. Before borrowing things from others, I must ask for permission. If I do not ask, it is stealing. When borrowing things from others, I will return them promptly. Later, if I have an urgent need, I will not have a problem borrowing from them again.”

Regarding chapter 3, there are several areas of consistency that can be highlighted from the assertions. First, the emphasis on personal hygiene (e.g., washing one’s face and brushing one’s teeth after waking up, washing hands after going to the toilet) and posture (i.e., standing and sitting properly) is consistent with the modern guidelines on parenting and the expectation that young people should stay healthy [33]. As promotion of physical health of children is emphasized in modern medicine and parenting, it is interesting to note that this was highlighted in *Di Zi Gui* roughly three centuries ago. Second, the focus on tidiness in the dress code is also emphasized in modern parenting and professions (such as occupational therapy) because tidiness in clothing is a social skill. Dressing in a tidy and decent manner can create a sense of “positive social identity” for the child, which would eventually create self-confidence in young persons.

Third, appropriate eating and drinking are also highlighted in modern child care and developmental psychology. Having good eating habits does not only ensure nutritional needs of the child; it also promotes a “non-choosy” habit in children. Fourth, there are also some assertions related to “accident prevention” (to lift the curtain slowly and quietly and not to bump into corners). This is in line with the literature on accident prevention [34].

Fifth, regarding risk behavior, it is asserted that young children should not drink alcohol and the negative consequence of drinking too much alcohol is emphasized. This point closely echoes to the proposition of prevention science that children should stay away from alcohol. Sixth, regarding the expectation that the children should keep away from the rowdy places, this view is consistent with prevention science that children stay away from the rowdy places, which are commonly regarded as risk factors precipitating risk behavior in the adolescents [35].

The assertion that is not consistent with the contemporary knowledge is on the expectation that the children should dress in a tidy manner. Besides the argument that the children have the right to dress in the way they want, there are also views suggesting that the non-conventional ways of dress are signs of creativity and innovation. Besides, the assertion that one should avoid doing things in a hurry manner is somehow not consistent with the contemporary view that one should learn multi-tasking (i.e., doing many things at one time is actually a merit).

There are several unique features of the assertions in this chapter. First, the focus on child development is quite holistic in nature, ranging from physical health to social health. Second, the focus on cleanliness rather than extravagance underscores the importance of the non-materialistic values. Third, setting rules on borrowing can promote social competence of young people. Fourth, it is asserted that children should treasure time which is not commonly described in the literature on child development.

The implications of this chapter on child development are multiple. First, the parents should nurture the self-management skills in children in different domains. Second, the children should develop a sense of treasuring time [36].

REVIEW OF CHAPTER 310

信

凡出言，信為先，詐與妄，奚可焉。話說多，不如少，惟其是，勿佞巧。奸巧語，穢污詞，市井氣，切戒之。見未真，勿輕言，知未的，勿輕傳。事非宜，勿輕諾，苟輕諾，進退錯。凡道字，重且舒，勿急疾，勿模糊。彼說長，此說短，不關己，莫閒管。見人善，即思齊，縱去遠，以漸躋。見人惡，即內省，有則改，無加警。唯德學，唯才藝，不如人，當自礪。若衣服，若飲食，不如人，勿生感。聞過怒，聞譽樂，損友來，益友卻。聞譽恐，聞過欣，直諒士，漸相親。無心非，名為錯，有心非，名為惡。過能改，歸於無，倘揜飾，增一辜。

“Be Trustworthy

When I speak, honesty is important. Deceitful words and lies must not be tolerated.

Rather than talking too much, it is better to speak less. I will speak only the truth, and I will not twist the facts.

Cunning words, foul language, and philistine habits must be avoided at all costs. What I have not seen with my own eyes, I will not readily tell to others. What I do not know for sure, I will not easily pass on to others.

If I am asked to do something that is inappropriate or bad, I must not agree to it. If I do, I will be doubly wrong. I must speak clearly and to the point. I must not talk too fast or mumble.

Some like to talk about the good points of others, while some like to talk about the faults of others. If it is none of my business, I will not get involved. When I see others do good deeds, I must think about following their example. Even though my own achievements are still far behind those of others, I am getting closer.

When I see others do wrong, I must immediately reflect upon myself. If I have made the same mistake, I will correct it. If not, I will take extra care to not make the same mistake. When my morals, conduct, knowledge, and skills seem not as good as those of others, I will encourage myself to be better.

If the clothes I wear, and the food I eat and drink are not as good as that of others, I should not be concerned. If criticism makes me angry and compliments make me happy, bad company will come my way and good friends will shy away.

If I am uneasy about compliments and appreciative of criticism, then sincere, understanding, and virtuous people will gradually come close to me. If any mistake I make is inadvertent, it is merely a mistake. If it is done on purpose, however, it is an evil act. If I correct my mistake and do not repeat it, I no longer own the mistake. If I try to cover it up, I will be doubly wrong.”

Consistent with the positive youth development perspective, honesty, non-tolerance of deceitful words and lies, speaking the truth and keeping one's promise is emphasized in the assertions in this chapter [37]. Second, the assertions that speaking should be clear and messages should be succinct are consistent with the principles underlying social competence. Finally, the assertion that one should not be concerned about one's food and clothes not as good as others' is consistent with the view of the cognitive-social perspective that one should not have unnecessary competition.

There is one area that is inconsistent with the contemporary literature – one should not be angry about criticisms and happy about compliments while one should appreciate criticisms

and be uneasy about compliments. This assertion is not consistent with the psychological principle that one should be true to one’s feelings and one should feel good if they receive compliments from others.

There are several unique points covered in this chapter. First, one should not use cunning words and foul language. Second, it is emphasized that one should be careful about witnessing and should not gossip about others. Third, the assertions emphasize self-reflection. Fourth, while one should not compare with others in terms of clothes and food, we should compare with others in terms of morals, conduct, knowledge and skills.

The present chapter has several implications for youth development and parenting. First, young people should learn to use their words in a careful and decent manner. Unfortunately, the general public tend to endorse the use of foul language and regard it as “entertaining.” Second, no gossip is good for child development because it creates hatred, misunderstanding and even bullying. Third, children should be encouraged to reflect, including both the good things and bad things about themselves. Finally, learning not to compare with others on material possession is needed because the contemporary societies are very materialistic in nature. On the other hand, sensitivity about one’s virtues relative to others for improvement is helpful to child development.

REVIEW OF CHAPTER 311

汎愛眾

凡是人，皆須愛；天同覆，地同載。行高者，名自高；人所重，非貌高。才大者，望自大；人所服，非言大。己有能，勿自私；人有能，勿輕訾。勿諂富，勿驕貧；勿厭故，勿喜新。人不閒，勿事攪；人不安，勿話擾。人有短，切莫揭；人有私，切莫說。道人善，即是善，人知之，愈思勉。揚人惡，即是惡，疾之甚，禍且作。善相勸，德皆建；過不規，道兩虧。凡取與，貴分曉；與宜多，取宜少。將加人，先問己；己不欲，即速已。恩欲報，怨欲忘；報怨短，報恩長。待婢僕，身貴端，雖貴端，慈而寬。勢服人，心不然，理服人，方無言。

“Love All Equally

Human beings, regardless of nationality, race, or religion – everyone – should be loved equally. We are all sheltered by the same sky and we all live on the same planet Earth. A person of high ideals and morals is highly respected. What people value is not based on outside appearance.

A person’s outstanding abilities will naturally endow him with a good reputation. Admiration from others does not come from boasting or praising oneself. If I am a very capable person, I should use my capabilities for the benefit of others. Other people’s competence should never be slandered.

I will not flatter the rich, or despise the poor. I will not ignore old friends, only taking delight in new ones. When a person is busy, I will not bother him with matters. When a person’s mind is not at ease, I will not bother him with words.

If a person has a shortcoming, I will not expose it. If a person has a secret, I will not tell others. Praising the goodness of others is a good deed in itself. When people are being praised and approved of, they will be encouraged to try even harder.

Spreading rumors about the wrongdoings of others is a wrongdoing in itself. When the harm done has reached the extreme, misfortunes will surely follow. When I encourage another to do good, both of our virtues are built up. If I do not tell another of his faults, we are both wrong.

Whether I take or give, I need to know the difference between the two. It is better to give more and take less. What I ask others to do, I must first ask myself if I would be willing to do. If it is not something I would be willing to do, I will not ask others to do it.

I must repay the kindness of others and let go of my resentments. I will spend less time holding grudges and more time paying back the kindness of others. When I am directing maids and servants, I will act honorably and properly. I will also treat them kindly and generously. If I use my influence to make them submissive, their hearts will not be with me. If I can convince them with sound reasoning, they will have nothing to object to.”

The present assertions on loving each other and contribution to society are consistent with the emphases on “compassion” and “contribution” under the positive youth development approach. Besides, the expectation of not slandering the ability of other people is in line with the principle of respecting others in the positive youth development literature. Furthermore, the notions of kindness to others and forgiveness are also in line with the spirit behind spirituality. Finally, using reasoning instead of authority to make people submissive is consistent with the principles of modern psychology.

There are several unique emphases in this chapter. First, outer appearance is not as important as ideals and morals (i.e., non-material attributes are more important than material attributes). Second, young people should not discriminate against others based on their material possession and social status. Third, children should learn to praise the goodness of others but should not gossip about the rumors of others.

The assertions in this chapter have several implications for youth development and parenting. First, cultivation of a sense of love for others is important. Second, it is helpful to teach the children about the importance of inner virtues instead of outer appearance. Third, using one’s ability to serve the society is a good developmental goal. Fourth, accepting people with different backgrounds and treating them equally. Fifth, praising others and do not gossip about others’ faults [5].

REVIEW OF CHAPTER 312

親仁

同是人，類不齊；流俗眾，仁者希。果仁者，人多畏；言不諱，色不媚。能親仁，無限好；德日進，過日少。不親仁，無限害；小人進，百事壞。

“Be Close to and Learn from People of Virtue and Compassion

We are all human, but we are not the same. Most of us are ordinary; only a very few have great virtues and high moral principles. A truly virtuous person is greatly respected by others. He will not be afraid to speak the truth and he will not fawn on others.

If I can be close to and learn from people of great virtue and compassion, I will benefit immensely. My virtues will grow daily and my wrongdoings will lessen day by day. If I choose not to be close to and learn from people of great virtue, I will suffer a great loss. People without virtue will get close to me and nothing I attempt will succeed.”

Three interesting observations can be highlighted in this chapter. First, the assertion that few of us have great virtues and high moral principles is consistent with the view that few of us can proceed to the post-conventional level [31]. Second, it underscores the importance of moral courage of speaking the truth and not fawning on others [8]. Finally, the teaching of being close to people with great virtue and compassion but staying away from people without virtue is consistent with the principle of “bonding” that healthy adults and peers are important to the healthy development of children.

REVIEW OF CHAPTER 313

餘力學文

不力行，但學文，長浮華，成何人。但力行，不學文，任己見，昧理真。
讀書法，有三到，心眼口，信皆要。方讀此，勿慕彼，此未終，彼勿起。
寬為限，緊用功，工夫到，滯塞通。心有疑，隨札記，就人問，求確義。
房室清，牆壁淨，几案潔，筆硯正。墨磨偏，心不端；字不敬，心先病。
列典籍，有定處；讀看畢，還原處。雖有急，卷束齊，有缺壞，就補之。
非聖書，屏勿視，蔽聰明，壞心志。勿自暴，勿自棄，聖與賢，可馴致。

“Be Close to and Learn from People of Virtue and Compassion

If I do not actively practice what I have learned, but continue to study on the surface, even though my knowledge is increasing, it is only superficial. What kind of person will I be? If I do apply my knowledge diligently, but stop studying, I will only do things based on my own opinion, thinking it is correct. In fact, what I know is not the truth.

There are methods to study correctly. They involve concentration in three areas: my mind, my eyes, and my mouth. To believe in what I read is equally important. When I begin to read a book, I will not think about another. If I have not completed the book, I will not start another.

I will give myself lots of time to study, and I will study hard. If I devote enough time and effort, I will thoroughly understand. If I have a question, I will make a note of it. I will ask the person who has the knowledge for the right answer.

I will keep my room neat, my walls uncluttered and clean, my desk tidy and my brush and ink stone properly placed. If my ink block is ground unevenly, it shows I have a poor state of mind. When words are written carelessly, showing no respect, this shows my state of mind has not been well.

My books should be classified, placed on the bookshelves, and in their proper places. After I finish reading a book, I will put it back where it belongs. Even if I am in a hurry, I still must neatly roll up and bind the open bamboo scroll I have been reading. All missing or damaged pages ought to be immediately repaired.

If it is not a book on the teachings of the saints and sages, it should be discarded and not even looked at. Such books can block my intelligence and wisdom, and will undermine my aspirations and sense of direction. Neither be harsh on myself, nor give up on myself. To be a person of high ideals, moral standards and virtue is something we can all attain in time.”

Several observations in this chapter are consistent with the scientific literature. First, the urge to continue studying is in line with the principle of life-long learning. Second, the propositions on the methods of learning (involvement of mind, eyes, mouth and

concentration) and devotion of time and effort are consistent with the work of educational psychology. Third, asking people when one has questions is also consistent with the social support literature.

Regarding the key to studying, the assertions can be regarded as not comprehensive enough because besides effort, concentration and involvement, there are many other factors. For example, those with learning difficulties may exert effort without academic success. Besides, the suggestion that one should not read the books not written by saints and sages is not consistent with the contemporary view that one should read any books widely with different viewpoints.

There are four unique messages in this chapter. First, it focuses on the importance of practice and learning. Second, the emphasis on the tidiness in studying is quite novel. Third, the last assertion that one should not be harsh or give up on oneself is very humanistic. Furthermore, the promise that one can be a person with high moral standards is also empowering in nature.

The assertions have several implications for youth development and parenting: First, do not simply focus on the superficial study; practice is important. However, practice without studying is also no good. Second, never be harsh on oneself or give up. Third, have a belief that if one tries hard, high ideals and virtue can be attained.

DISCUSSION

The pioneer review attempts to examine *Di Zi Gui* with reference to four issues: a) the consistency between the related assertions and the views of the contemporary youth development literature; b) the inconsistency between the related assertions and the contemporary views; c) the novel or alternative views on youth development and parenting; and d) the implications of *Di Zi Gui* for youth development and parenting.

Although *Di Zi Gui* was written several centuries ago, some of its assertions have striking consistency with the contemporary models of youth development and parenting. For example, the focus on physical health and character development is in line with the contemporary models on youth development and parenting (e.g., Australia National Health and Medical Research Council [38]). Hence, it can be concluded that traditional wisdom does have contemporary scientific support. Nevertheless, some of the assertions, such as following traditions without doubt, one should only read sacred books and the de-emphasis of the rights of children are not consistent with the contemporary views of youth development and parenting. Furthermore, *Di Zi Gui* offers some novel ideas, such as the emphasis on the inner qualities rather than the external attributes of a person and the importance of social competence, such as not to gossip about others and accept the wrongdoings of others. Finally, *Di Zi Gui* has useful implications of the assertions for youth development and parenting.

Three observations can be further highlighted in the present review. First, *Di Zi Gui* shows the fundamental attributes of the youth developmental ideals and parenting of the traditional Chinese culture. According to Shek and Lai [39], traditional Chinese families had a strong emphasis on family harmony, as exemplified in the popular sayings of “*yi he wei gui*” (harmony is golden) and “*jia he wan shi xing, jia shuai kou bu ting*” (if a family lives in harmony, everything will prosper; a family will wither if there are a lot of quarrels). To

achieve family harmony, every family member had the obligations and duties defined by the five cardinal relationships [14]. With a specific focus on children, the children were taught about the importance of “*bai shan xiao wei xian*” (filial piety ranks the top in all behaviors). An ideal family in the traditional Chinese culture was characterized by “*fu ci zi xiao, xiong you di gong*” (kind father and filial son, affectionate brothers).

The assertions in *Di Zi Gui* are also consistent with the attributes of the traditional Chinese socialization practice summarized by Yang [16]. These attributes included dependence training (children should obey their parents and depend on them), conformity training (interpersonal harmony should be valued but interpersonal conflicts should be avoided), self-suppression training (training of self-inhibition and self-sacrifice), humility training (one should learn to be humble), contending mentality (one should accept one’s situation), punishment orientation (harsh punishment for non-conforming behavior), and parent-centeredness (parents determine the socialization goals).

Second, the present review highlights a question that should be further examined – is the teaching of the traditional Chinese classics useful? With the advance of Western technology and industrial might, many people have held the belief that the traditional Chinese teaching is not useful. Some may even outright reject the traditional Chinese views and uncritically accept the usefulness of the Western ideas. However, there are two problems of a total abandonment of the traditional Chinese ideas. First, there is teaching in the Chinese classics which has been practiced for a very long time. As shown by the present review, such cultural wisdom is in fact consistent with the contemporary scientific literature. Second, when one views the Western theories and findings, it is important to ask how such ideas fit into the cultural context of China. For example, while the Western emphasis on the children’s rights is important, the duties and obligations of children are relatively neglected. At the same time, one should ask whether the traditional Chinese teaching can effectively be used in the contemporary world.

Third, to answer the question of whether the traditional Chinese teaching is useful or not, we have conducted research on two levels. For example, Shek and Sun [15] pointed out that Chinese parental control is a mixture of behavioral control (e.g., high parental expectation and monitoring) and psychological control (e.g., guilt induction). How this strange mixture might be translated to motivation to excel in academic excellence is an important issue to be addressed. Therefore, future research should focus on how the traditional Chinese teaching on youth development and parenting is aligned with the contemporary scientific theories and findings at the conceptual level.

Finally, it is interesting and important to ask how the elements of *Di Zi Gui* can possibly be utilized in the youth development and parenting programs. In particular, with reference to the growing emphasis on character education for young people, the teaching of *Di Zi Gui*, such as striving for excellence in morality and focus on the inner quality instead of the outer appearance of a person, has obvious practical implications. Most important of all, it is interesting to ask whether the children under the influence of *Di Zi Gui* thrive better than the children without the influence of *Di Zi Gui*.

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Chapter 314

**PROMOTION OF FAMILY LIFE QUALITY
AMONGST ADOLESCENTS:
THE PROJECT P.A.T.H.S. IN HONG KONG**

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ABSTRACT

Adolescence is a period during which adolescents and their parents have to re-define the ways of interaction and resolution of parent-adolescent conflicts. As such, how to help adolescents learn the ways to interact with their parents in a healthy manner is an important question to be considered. Adopting a positive youth development perspective, it is argued that promotion of psychosocial competencies of adolescents can help adolescents to develop better emotional and social competencies, which would eventually promote family cohesion and harmony. In this paper, several units in the Project P.A.T.H.S. with reference to bonding and resilience are outlined to illustrate how positive youth development programs may help to promote family quality of life amongst families with adolescent children.

INTRODUCTION

Adolescence is a transitional stage full of challenges. During this critical period, different risk factors, such as undesirable peer influences and low self-efficacy, lead to poor adolescent

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development. At the same time, different protective factors, such as support from family as well as significant carers, school, and peers, can help adolescents to build up their competences and character strengths. Among these protective factors, family serves as one vital factor for adolescent development, especially a family with good family relationship and a high level of functioning [1].

Family functioning refers to “the quality of family life at systemic and dyadic levels and concerns wellness, competence, strengths, and weaknesses of a family” [2]. A high level of mutuality of the family, good conflict management within the family, and good communication are three main dimensions of family functioning [3]. A well-functioned family can always promote the well-being for family members. For example, high quality of parent-child communication can prevent children from engaging in different risk behaviors, and it also benefits their psychological health [4, 5]. In fact, a positive parent-child relationship does not only promote adolescent development [6], but also benefits the functioning of the whole family. If both parents and the child are satisfied with their relationship, this would help to promote mutuality of the family as well as to minimize the negative consequences generated from parent-adolescent conflicts.

Theoretically, bonding and mutual trust between parents and children are generated from a good parent-child relationship [7, 8]. Bonding is the “attachment behavior held to characterize human beings from the cradle to the grave” [9]. It refers to the emotional attachment between an individual and others, such as parents, siblings, schoolmates, peers, and teachers. There is a large body of literature supporting the notion that family bonding can benefit self-esteem, problem solving skills and other competencies in children and adolescents [7, 10]. Family bonding can also nurture children and adolescent resilience and help seeking practice. Resilience is an important character for individuals to adapt to challenging events in a healthy way and bounce back from difficulties [11]. Nurturing resilience is one of the major tasks during adolescence [12]. Research showed that bonding contributes to the enhancement of resilience among the youths [13-15]. Moreover, building up a healthy help-seeking style can prevent adolescents from using inappropriate ways to tackle their problems. Different researchers argued that family bonding can facilitate adolescents to have appropriate help-seeking practice [16, 17].

However, as the society changes and evolves, there are more and more obstacles to the development of family bonding and parent-child relationships. For example, parents’ long working hours and stressful work life are some factors which impede the parent-child relationship, especially in Hong Kong [18-20]. Most Hong Kong parents are burdened by unreasonable long working-hours, and it is not easy for them to spend time to communicate with their children or provide advice. Therefore, misunderstandings within the family and parent-adolescent conflicts are likely to occur. Furthermore, it may also affect the help-seeking practice of adolescents as they are not able to or willing to seek help from their parents or other family members.

To solve the above problems, family education is one effective way. However, it is not easy to implement family education for parents due to their limited time and resources [21]. As such, another possible way is to start the prevention work in the school context, such as enhancing students’ understandings of their parents, equipping positive communication skills, and nurturing their healthy help-seeking style.

In this chapter, a positive youth development program entitled the Project P.A.T.H.S. is used to demonstrate how school programs can be implemented in the school context to promote family life for secondary school students.

PROJECT P.A.T.H.S.

Project P.A.T.H.S. is the first and only systematic youth development program in Asia with positive evaluation findings based on multiple evaluation strategies [22, 23]. This project was launched in 2005 with four main components, including (i) curriculum development; (ii) interactive training for frontline teachers and social workers; (iii) implementation of the program in secondary schools; and (iv) systematic evaluation.

For curriculum development, 271 teaching units were developed for Secondary 1 to Secondary 3 students, which included 120 original teaching units, 60 special units (focus on 5 special themes on adolescent developmental issues), 61 updated teaching units, and 30 revamped teaching units. The design of the teaching units included different interactive learning activities and multi-media activities. The package for each teaching unit contains a detailed lesson plan together with all teaching materials, such as worksheets, PPT slides, guidelines for students' discussion or sharing, and different multi-media activities (e.g., video clips, mobile app, and computer games). An interactive learning platform has been established to facilitate students' learning through online interactive activities, such as online polling, drawing activities. To facilitate teacher's teaching and preparation for the class, procedures of each activity are clearly listed in the lesson plan, together with teaching tips for the teacher's reference. Also, a video clip for each original unit has been recorded by real frontline teachers for sharing with teachers and social workers. In addition, to share practical ideas amongst teachers, ten video clips have been developed which are based on different themes of teaching skills and classroom management skills. Since 2005, more than 357,839 students (with 674,637 man-times) participated in this project from more than 360 schools and agency units.

As training is the backbone for successful program implementation, the P.A.T.H.S. Project emphasizes the importance of providing quality training for teachers before they start teaching the teaching units. In the past 15 years, around 300 interactive training workshops have been conducted for 9,400 teachers, social workers, or other related professionals. Also, a well-designed e-learning program has been developed by the research team. Participants can join a 20-hour e-learning program (for each grade) to become qualified teachers.

Finally, a systematic evaluation design was conducted to generate useful information for researchers and frontline teachers on the effectiveness of the program as well as areas to be improved. In the Project P.A.T.H.S., a comprehensive evaluation design using multiple methods which included both qualitative and quantitative research elements. All results were well documented and published [22-27]. In this paper, three units are used as examples to demonstrate how the P.A.T.H.S. Project helps to promote family life of adolescents through classroom learning activities.

RESILIENCE

To build up good resilience, family belongingness is one important external protective factor for optimal adolescent development. To help secondary students promote this PYD quality, the Research Team developed a teaching unit named “Those were the days” (RE1.1) for Secondary One students [28; Appendix 1). The objectives of this unit are helping students:

- To learn to seek help from different people under different circumstances.
- To understand parents’ communication style and thus promote trust toward parents and a sense of belonging within the family.

In this teaching unit, through group and classroom discussion, students can learn to reduce their hesitation and uneasiness when they seek help from parents. It is expected that students can recognize the potentially positive messages behind parents’ words and actions. The lesson plan and teaching materials are presented to Appendix 1.

BONDING

As discussed in the previous section, family bonding is one source of emotional attachment and support for adolescents in facing challenges and difficulties. In this paper, two units are presented to demonstrate how to help secondary students to build up a stronger bonding with their parents through classroom learning activities.

The first unit is entitled “What can I do for my family?” (BO2.1) which is a unit developed for Secondary 2 students (29; Appendix 2). The objectives of this unit are helping students:

- To recall the occasions on which students received care from their parents.
- To explore their roles playing at home and to enhance motivations to contribute to families.

In this teaching unit, teaching activities have been developed to promote student reflection. At the beginning of this unit, students are asked to describe their meanings of “family” and share their ideas of an ideal family. After this, two activities are developed for students to reflect and explore how they can contribute to their own families. The lesson plan and teaching materials are outlined in Appendix 2.

Another teaching unit is entitled “Parents’ message” (BO2.2) which was developed to equip students’ communication skills with their parents, and to strengthen parent-child relationships (30; see Appendix 3). The objectives of this unit are helping students:

- To analyze parents’ messages from people-oriented and task-oriented points of view.
- To demonstrate proper response to parents’ messages and establish a good relationship with the parents.

In this unit, students are divided into different groups for discussion. A video clip is included to help students to reflect parents' underlying messages from different scenarios, and learn to use appropriate responses towards parents in order to avoid miscommunication with their parents.

DISCUSSION

In this chapter, we present three units of the Project P.A.T.H.S. to illustrate how positive youth development programs can help to promote family life quality in adolescents. As family life education has been commonly conducted within the framework of parent education, it is important to consider family life education from another side of the coin – promoting family life quality in adolescents.

There are several observations deserving our attention. First, it is important to promote the psychosocial competence of adolescents as a strategy to promote the quality of their family life. The basic reasoning is that by promoting the psychosocial competence of young people, their relationships with the parents would improve, hence promoting the family quality of life. Second, the units illustrate the feasibility of developing curricular-based training programs to promote family quality of life of adolescents. As there are few validated PYD programs in different Chinese contexts, the units developed can help professionals who would like to promote family quality of life in adolescents. Third, as there is a general drop in PYD attributes in early adolescence [1, 31], there is a need to devise ways to promote the PYD development of early adolescents. The Project P.A.T.H.S. units provide a way to nurture the PYD attributes in adolescents. Finally, although there is support that the P.A.T.H.S. programs can help to promote holistic youth development [27, 32], there is a need to further explore how improvement in PYD might contribute to improvement in family quality of life.

APPENDIX 1: UNIT RE1.1 “THOSE WERE THE DAYS”

Construct

- Resilience

Target Participants

- Secondary One students

Unit Aims

- 1) To learn to seek help from different people under different circumstances
- 2) To understand parents' communication style and thus promote trust toward parents and a sense of belonging within the family

Learning Targets

- 1) To learn to seek help from different people when encountering different types of problems
- 2) To recognize the potentially positive messages behind parents’ words and actions

Teaching Materials

Group Worksheet: Appendix 1
“Those Were the Days”
Worksheet: Appendix 2
“The Message Behind” (Version A and Version B)
Growth Puzzle: Appendix 3

Teaching Methods

- Group Discussion
- Class Discussion

Implementation Plan (30 Minutes)

Primary Activity
Secondary Activity



Activity	Procedures
I. Warm-up activity (2 minutes)	Begin this unit by asking: 1. Did you come across any problem(s) this week (month)? 2. Was there anyone you can turn to when you were in trouble?
II. Group discussion: Those Were the Days  (15 minutes) Teaching materials <i>Appendix 1</i>	Aim: To learn to seek help from different people when encountering different types of problems 1. Divide students into 8 groups and distribute the Group Worksheets (<i>Appendix 1</i>). 2. Briefly introduce the content. Allow 5 minutes for discussion. 3. Discussion question: “When you have the following problems, who will you talk to or seek help? Write down your reasons.” 4. Ask students to report their responses. 5. Conclude and highlight: i. When one is in trouble, s/he can look for help, rather than facing it alone. ii. There are many options to the same problem. It differs from person to person. iii. Despite the options, students should think carefully and decide who can give the most positive support when they look for help. iv. Students tend to share with others when they are happy but not when they are troubled. Ask them to consider the reasons behind this phenomenon.

Activity	Procedures
III. Class discussion: The Message Behind  (5 minutes) Teaching materials <i>Appendix 2</i>	Aim: To understand parents' way of expression or communication style 1. Distribute the Worksheets (<i>Appendix 2</i>). 2. Some common responses made by parents are shown in the cartoons. By asking students to fill in the answers, they can explore parents' intention and recognize the "real" message. 3. The aim of this exercise is to eliminate any hesitation and uneasiness among students when they ask for help from people of authority (such as parents), and let them realize their parents' concern. Show students the fact that a lack of communication skills and pressure from life may contribute to parents' seemingly harsh attitude. Ask students to try to think in the other's shoes. 4. Ask students to share their experiences briefly.
IV. Conclusion (3 minutes)	1. Encourage to ask for help when they are in trouble. 2. Aim at dissociating students from the thoughts that inhibit them from asking for help. 3. Lead students to consider who they can seek help apart from parents when they are in trouble.
V. Self-reflection (5 minutes) Teaching materials <i>Growth Puzzle</i>	1. Distribute the Growth Puzzle and engage students in self-reflection. 2. Praise students for their participation during the lesson.

Teaching Tips

1. "Those were the days"	- Conduct a poll and write down the answers on the blackboard. - If the choices students made are highly similar, tell them that they can ask for help from different people according to the nature of the problem (e.g., seek help from parents if their problem is related to money; from social worker / counselor if it is related to emotions). - If the person they choose to talk to has big differences, instructors can point out the result is normal due to differences in students' backgrounds and psychological conditions. - Encourage those who always opt to handle problems alone to look for help from others. - If students fail to express themselves in writing, ask them to report verbally. - Put down the reasons on the blackboard that students give as examples, e.g. that the one I talk to always pointing out my problems is sincere; 2) that they are caring and considerate; 3) that they are knowledgeable. - If students are more mature, instructors may modify the worksheet, to use "x" to indicate specific people they would not seek help from. This may lead to an interesting discussion on "why / why not."
2. "The message behind"	- Choose version A (local Chinese-based) or version B (international-based) for <i>Appendix 2</i>, depending on the cultural background of students. - For students with a complicated family background or having a poor relationship with their parents, instructors should pay special attention to their emotional responses. - Encourage students to think from the point of view of their parents. The aim of doing this does not mean that they need to comply with their parents' directions, but focus on understanding parents' difficulties. It also trains students to be more considerate and encourages them to express to parents their feelings in a constructive and helpful way, and talk to teachers and counselors when necessary. - Invite students who are mentally more mature to join in a role-play. It can not only lead to a better participation, but can also allow students to experience their parents' feelings. During the process, instructors should ask students to first think about the intention behind parents' words, and then what they may, as daughters and sons, say in response. Ask students to consider if their response is constructive to a better relationship or not.

Supplementary Activity (Optional)

Activity	Content	Recommendations
Letters of love	Aim: To establish a good relationship with parents and enhance a sense of belonging toward family Ask students to write a letter to their parents after class. Ask them to express their appreciation or gratitude to their parents.	If students have difficulties in expressing themselves, instructors can discuss together with them. Doing so can also promote the relationship between the parties.

A 1.1. Group Worksheet: “Those Were the Days”

Group:

Dear fellow students, when you have the following problems, who will you talk to or seek help? Why?

When I have problems related to...	I will talk to / seek help from: (Can choose more than one)
Study (e.g., fail to catch up with the lesson, having lots of difficulties when doing homework) 	I will talk to / seek help from: (Can choose more than one) ☐ Friends ☐ Social worker / Counselor ☐ Teachers ☐ Parents ☐ Myself ☐ Others: _____ Why? _____
Emotion (e.g., unhappy, angry) 	☐ Friends ☐ Social worker / Counselor ☐ Teachers ☐ Parents ☐ Myself ☐ Others: _____ Why? _____
Money 	☐ Friends ☐ Social worker / Counselor ☐ Teachers ☐ Parents ☐ Myself ☐ Others: _____ Why? _____
Sharing of satisfaction and happiness (e.g., getting a good mark; given an award) 	☐ Friends ☐ Social worker / Counselor ☐ Teachers ☐ Parents ☐ Myself ☐ Others: _____ Why? _____

A 1.2. Worksheet: “The Message Behind” (Version A)

Name: _____

Consider what parents really mean in the following dialogues:

Dialogue 1 	Dialogue 2 
When you are working hard on preparing for an exam... What Mom may really mean: _____ _____	You do not need to go to school the next day, so you want to tell your parents you wish to go out with your friends in the evening... What Mom may really mean: _____ _____
Dialogue 3 	Dialogue 4 
You want to buy an online game, but you don't have enough money... What Dad may really mean: _____ _____	Father comes back every night at around 11:00p.m... What Dad may really mean: _____ _____

A 1.3. Worksheet: “The Message Behind” (Version B)

Name: _____

Consider what parents really mean in the following dialogues:

Dialogue 1	Dialogue 2
	
When you want to join a three-day camp... What Dad may really mean: _____ _____	On Friday evening... What Mom may really mean: _____ _____
Dialogue 3	Dialogue 4
	
You are going out with a friend and plan not to have dinner at home tonight... What Mom may really mean: _____ _____	Father comes back every night at around 10:00pm... What Dad may really mean: _____ _____

A 1.4. Growth Puzzle

Name:

Class:

Date:

Classwork:

1. List out 3 necessary conditions for overcoming difficulties and those functions

2. When you are facing some difficulties, who do you want to ask for help? Why?

3. Recall the experience of your parents helping you to solve problems. Which ways of solving problems have you learned from them?

4. Are there any psychological barriers (e.g. feel embarrassed), which stop you to ask for help? What methods can help you to break the barriers?

5. Do you agree with the assumption that "seeking helps means being weak"? Why?

6. How important does "having hopes" affect you to face the difficulties and solve the problems?

APPENDIX 2: UNIT BO2.1 "WHAT CAN I DO FOR MY FAMILY?"**Construct**

Bonding

Target Participants

Secondary Two students

Unit Aims

To make more contributions at home so as to strengthen relationship with the family

Learning Targets

- 1) To recall the occasions on which students received care from their parents
- 2) To explore the roles play at home and to enhance motivation to contribute to families

Teaching Materials

PowerPoint Slides: Appendix 1
 “Family Album”
 PowerPoint Slides: Appendix 2
 “What Can I Do for My Family?”
 Worksheet: Appendix 3
 “What Can I Do for My Family?”
 Growth Puzzle: Appendix 4

Teaching Methods

- Class Sharing
- Personal Reflection

Implementation Plan (30 Minutes)

Primary Activity
 Secondary Activity



Activity	Procedures
I. Warm-up activity (5 minutes) Teaching materials <i>Appendix 1</i>	1. Begin this unit by playing the PowerPoint Slides (<i>Appendix 1</i>) without instruction. 2. When the slides are finished, ask students: i. What does “family” mean to you? ii. Describe your dream family. iii. What have you received from your family over the years?
II. Class sharing: Family Album  (7 minutes) Teaching materials <i>Appendix 1</i>	Aim: To recall the occasions on which they received care from their parents so as to enhance motivation to contribute to families 1. Play the PowerPoint Slides again. These scenes are from a family life story of a 15-year-old. 2. Ask students to: i. Review whether they have experienced similar occasions in their lives in which they received similar care from their parents; ii. Note down the experiences which have deeply impressed them. 3. When the slides are finished, ask students to share their reflections with classmates sitting next to them. 4. Ask a few students to share with the class their life experiences which have impressed them deeply. It may be the happiest ones or the ones which make them remember the care and love of their parents.
III. Personal reflection: What can I do for my family?  (10 minutes) Teaching materials <i>Appendix 2</i> <i>Appendix 3</i>	Aim: To explore the roles students may play at home and contributions they can make to their families 1. Hand out the Worksheets (<i>Appendix 3</i>) and briefly introduce the content (Play the PowerPoint slides where needed). 2. The pictures are of a building where 8 families live. Ask students to circle the household problems in the family scene with which they think they CAN help. 3. Among the above chosen problems, ask students to use another color to indicate the ones which they HAVE experienced making a contribution in real life. 4. Invite students to think and share about: i. Among those household problems where students think they CAN help, how many of them HAVE actually given a helping hand? ii. Did they circle all objects? Did anyone circle the characters instead? Did anyone suggest that providing care and concern is also a way of contribution to the family?

Activity	Procedures
IV. Conclusion (3 minutes)	1. The family has taken care of us a great deal in a variety of ways since we were born (or even before we were born). 2. Think about what we can contribute, either tangible or intangible, as a member of the family.
V. Self-reflection (5 minutes) Teaching materials <i>Growth puzzle</i>	1. Distribute the Growth Puzzle and engage students in self-reflection. 2. Praise students for their participation during the lesson.

Teaching Tips

1. “Family album”	• If time allows, ask students to bring a memorable family photo and share it with the whole class or the classmates sitting next to them in this session. • Instruct students to share why this photo is important to them. • Some students come from families of special backgrounds in that they have no living father or mother or students do not live with them. Special backgrounds include single-parent families as a result of divorce, separation, death, extended work overseas by one of the parents, separation due to immigration restrictions, etc. Instructors should pay special attention to the emotional response of such students and guide them to think about the care and love their father, mother or guardians have given them. • Invite students who are rather silent in class or have been labeled as “problematic” to share their experiences. This provides students an opportunity to express themselves and their stories are likely to be very moving and sensitive. Should there be negative or highly emotional responses, instructors should listen to their concerns patiently and ask students nearby to comfort them. This helps establish a mutually supportive and caring learning environment. • It was found in the trial-run that students who come from families of special backgrounds can also achieve the intended learning targets. Many of them can even vividly recall childhood experiences.
2. “What can I do for my family?”	• Students who are non-Chinese may think that the setting of this part may not apply to their culture and living environment. Instructors can raise questions like: “Do you notice the differences between your family and your classmates who are from different cultural backgrounds?” or “Have you ever noticed what local families in Hong Kong are like, compared to yours?” Instructors can then lead them to see that building up your family without cultural limitation. • Students can put signs (e.g., square) or ticks to indicate their ideas, should they have no pens of different colors. • Most of the time, students tend to focus only on the objects. Instructors can, therefore, suggest they pay more attention to the characters. This not only encourages them to pay more attention to individual family members, but also establishes a linkage between “people” (family members) and “happenings” (housework), so that students may realize the hardship of their family members and not just focus on the latter. • Ask students to notice the difference between what they “can” do and what they “have already” done. The greater the difference, the more students can potentially contribute to their families. • If students are more mature, instructors can further investigate how one can help the characters, including: (i) tangible tasks such as helping mother / father to prepare the meal, teaching younger brothers / sisters to do homework, helping father by turning off the radio, studying hard so that parents do not have to worry about them, etc.; (ii) intangible tasks such as caring about father’s work, asking if you can offer any help to mother, etc. • For students who have experienced major family difficulties (e.g., one of the family members is chronically ill or died suddenly), they may think that there is nothing they can contribute. In this case, instructors should take care of their emotional response and at the same time, remind students that although there is little that they can do, their intention to help is already a kind of support to their families. Instructors can encourage them to face and overcome difficulties together with the family. • Share some of their memorable family happenings with the class (e.g., the most memorable experience at home and what s/he has done for the family) so as to build a closer relationship with students and to serve as a role model.

Supplementary Activity (Optional)

Activity	Content	Recommendations
I’d love to contribute	Aim: To make contribution to the family in order to improve relationships with families Ask students to act out what they think “CAN” contribute, but “HAVEN’T” contributed to the families as indicated in “What Can I Do for My Family?” (Appendix 3). Ask them to report to the class a week later on issues such as feelings, response from family members to their contribution, or whether there is any improvement of the relationship between them and their families.	Ask students how their family members feel after they have made such contributions. Share the results with the class.

A 2.1. PowerPoint Slides

“Family Album”

**A 2.2. PowerPoint Slides**

“What can I do for my family?”

A 2.3. Worksheet

“What can I do for my family?”

Name: _____



I learned in this lesson that _____

A 2.4. Growth Puzzle

Name:

Class:

Date:

Classwork:

1. What are your duties and responsibilities at home?
2. Do you appreciate your duties and responsibilities at home? Are there any areas of improvement?
3. What is your ideal family like?

Homework:

1. Which family member do you want to thank most? Why?
2. Which family member do you want to learn from most? Why?
3. After this class, how would you contribute to your family in the future?

APPENDIX 3: UNIT BO2.2 (RV) “PARENTS’ MESSAGES”

Construct

Bonding

Target Participants

Secondary Two students

Unit Aims

To learn the skills which lead to a better communication with the parents and to strengthen parent-child relationships

Learning Targets

- 1) To analyze parents' messages from people-oriented and task-oriented points of view
- 2) To demonstrate a proper response to parents' messages and establish a good relationship with the parents

Teaching Materials

Reference materials for Instructors:

Online Polling Content Appendix 1

Group Worksheet: "Parents' Messages" Appendix 2

Video: "Parents' Messages" Appendix 3

Reference Materials for Instructors: Group Worksheet Appendix 4

Reference Materials for Instructors:

"I-message" Online Polling Content Appendix 5

Interactive Learning Platform

Reflective Questions

Teaching Methods

- Group Discussion
- Online Polling

Implementation Plan (30 Minutes)



Primary Activity



Secondary Activity

Activity	Procedures	Teaching Materials
I. Warm-up Activity (5 Minutes)	1. Ask students, "What is your parents' tone of voice when they usually talk to you?" 2. Log in to Interactive Learning Platform (ILP) and let students vote. 3. Students vote "the most frequently used tone by their parents" and "the one they prefer their parents to use" based on different scenarios (<i>Appendix 1</i>). 4. Present the results after the vote. 5. Summarize and conclude: The tone used by parents talking to their children may be different from the one children expect, and sometimes parents' tone may make children feel bad and damage the relationship between parents and children. Today we will try to discuss how to communicate with parents.	Appendix 1 Interactive Learning Platform

Activity	Procedures	Teaching Materials
II. Group Discussion “Parents’ Message”  (9 Minutes)	Aim: To analyze parents’ messages from person- oriented and task- oriented points of view 1. Divide the class into 8 groups and distribute the Worksheets (<i>Appendix 2</i>). 2. Play the video “Parents’ Messages” (<i>Appendix 3</i>). There are 7 scenarios about messages often expressed by parents (<i>Appendix 4</i>). 3. The groups should determine and judge the scenarios one by one and put signs on the appropriate parts of the Worksheets: i. Ratings are given to “people-oriented”: Concern/Apathy (1 refers to the lowest, 10 the highest); ii. Ratings are given to “task-oriented”: Strictness/ Leniency (1 refers to the lowest, 10 the highest); Identify whether the message is an “order,” a “request,” a “suggestion” or a “neglect” by checking the ratings against the graph. 4. Ask the groups to report to the class. 5. Summarize and conclude: i. Most parents care deeply for their children and consider their well-being; ii. Depending on the situation, parents will express messages in different ways. iii. How can children respond to their parents?	Appendix 2 Appendix 3 Appendix 4
III. Students’ Polling “My” Voice  (9 Minutes)	Aim: To learn proper response to parents’ messages to establish a good relationship with the parents 1. Ask students, “We just discussed the tone used by your parents, what kind of tone will you use when you respond to your parents?” 2. Log in to Interactive Learning Platform (ILP) and let students vote. 3. Students vote “the most frequently used tone by themselves” and “the proper one should be used by them” based on different scenarios (<i>Appendix 5</i>). 4. Present the results after the vote. 5. Depending on the situation, the instructor himself/herself or invites some students to read those statements using the tone of “order,” a “request” or a “neglect” for different scenarios: i. Invite students to identify the tone used by the students. ii. Ask students, “If you were parents, how would you feel when you hear your children’s response in such a tone?” and invite students to share their discussion. 6. Invite students to use the tone of “suggestion” to act out the scenarios. 7. Ask students, “If you were parents, how would you feel when you heard your children’s response in the tone of ‘suggestion’?” 8. Encourage students to use “I-message” with “suggestion” tone as a proper response to their parents: i. Feelings; and ii. Views about an issue. 9. Explain to students, “Appropriate response allows students to present their feelings and views calmly and promotes a harmonious atmosphere for effective communication.”	Appendix 5 Interactive Learning Platform
IV. Conclusion (2 Minutes)	1. “Quarreling” and “keeping silent” are two common responses to our parents’ messages. Both responses hide our real thoughts, which prevents communication. We should reveal and share more of our real feelings and thoughts with our parents. 2. “Filial piety” is the core virtue in the Chinese culture and students can practice this by showing sympathy with their parents in responding to their parents’ messages.	
V. Self-reflection (5 Minutes)	1. Distribute the worksheet of Reflective Questions and engage students in self-reflection. 2. Praise students for their participation during the lesson.	Reflective Questions

Teaching Tips

1. Warm-up Activity	Instructors may share their personal experiences to arouse students' interest and increase their involvement.															
2. "Parents' Messages"	- If time allows and if students are mature enough, instructors can direct students to think about the general meanings behind the following types of expressions:<table><tr><td>Type of expression</td><td>Parent-child relationship</td><td>The message suggests ...</td></tr><tr><td>Order</td><td>Parents have a higher status than the children.</td><td>A sense of urgency and seriousness. Children keep ignoring parents' messages.</td></tr><tr><td>Request</td><td>Parents and children have a relatively equal status.</td><td>The situation is not that urgent and the children are willing to follow parents' words.</td></tr><tr><td>Suggestion</td><td>Parents and children share the same status and they get along with each other very well.</td><td>The situation is not urgent at all and there is good communication between the parents and the children.</td></tr><tr><td>Neglect</td><td>Parents and children have an alienating relationship.</td><td>A lack of communication and the parents and children are emotionally distant.</td></tr></table> - Ask students to think what they should do to promote parent-child communication that promotes the "Suggestion" expression in their communication. - Some students may say that their parents "neglect" them most of the time. In this case, instructors should pay special attention to such students and find out whether their family background may have a negative effect on their personal and emotional development. Also ask students to think about what they can do to improve their relationship with their parents. Instructors should look for other support systems where needed, e.g., seeking help from social workers or counselors. - Students who are most often neglected may try to draw attention by engaging in inappropriate or unusual behaviors (e.g., shop-lifting, being rebellious, bullying, etc.). Instructors should pay special attention to such students. Forward the case to social workers or counselors where needed.	Type of expression	Parent-child relationship	The message suggests ...	Order	Parents have a higher status than the children.	A sense of urgency and seriousness. Children keep ignoring parents' messages.	Request	Parents and children have a relatively equal status.	The situation is not that urgent and the children are willing to follow parents' words.	Suggestion	Parents and children share the same status and they get along with each other very well.	The situation is not urgent at all and there is good communication between the parents and the children.	Neglect	Parents and children have an alienating relationship.	A lack of communication and the parents and children are emotionally distant.
Type of expression	Parent-child relationship	The message suggests ...														
Order	Parents have a higher status than the children.	A sense of urgency and seriousness. Children keep ignoring parents' messages.														
Request	Parents and children have a relatively equal status.	The situation is not that urgent and the children are willing to follow parents' words.														
Suggestion	Parents and children share the same status and they get along with each other very well.	The situation is not urgent at all and there is good communication between the parents and the children.														
Neglect	Parents and children have an alienating relationship.	A lack of communication and the parents and children are emotionally distant.														
3. "I-message"	- Instructors can use some of the statements shown in <i>Appendix 5</i> for students' practice; the number of statements used for voice play depends on the class situation. - When instructors teach students to apply the "suggestion" tone to express their personal feelings, ask students to pay attention to the following principles and strategies: - Use active listening and respond slowly in a calm manner, and do not reply in a judgmental way or in a way that leads us into confrontation. - Use appropriate wordings and express your ideas clearly. - If parents ignore you or show no response, try telling them more about your feelings or show them that you are willing to discuss with them to find out ways to solve the problem. - Instructors can highlight that the "suggestion" tone can also be used when facing other people such as teachers and friends - Apart from the examples given in <i>Appendix 5</i>, instructors may also make use of statements appeared in "Warm-up Activity" (<i>Appendix 1</i>) to reinforce students' master of "I-message." - Should instructors wish to engage every student, a further exercise involving students sitting next to each other can be added. Work in pairs, one of them takes on the role of the father / mother, the other being the child and practice responding to parents by using "I-message."															
4. Self-reflection	Use the reflective questions in the Worksheet and in the PPT as appropriate.															

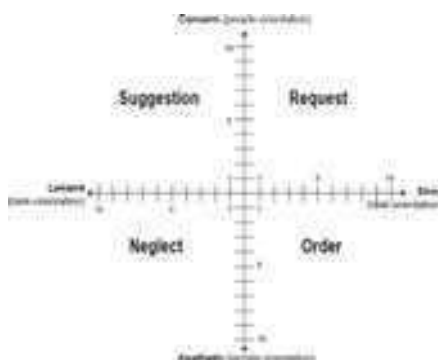
Supplementary Activity

Activity	Content	Recommendations
Thanks-Giving Day	Aim: To express gratitude to parents Ask students to form groups and work on finding ways to express their gratitude to their parents	Organizing a "Thanks-Giving Day" on weekends and invite parents to school. Then ask students to present their gratitude to their parents. Expressions of gratitude can be through to their parents. Expressions of through poetry, songs, pictures, and so on.

A 3.1. Reference Materials for Instructors: Online Polling Content

	Scenarios
(1)	When parents know you are going out, they will: 1) Neglect — “Oh.....Going out again.” 2) Order — “Don’t hang around all day!” 3) Request — “You should stay home.” 4) Suggestion — “Could you stay home? We have not seen you much here. ”
(2)	When parents see you are phubbing, they will: 1) Neglect — “Oh..... Phubbing again. ” 2) Order — “Put down your phone! Do more revisions! ” 3) Request — “Can you put down your phone, please?” 4) Suggestion — “How about putting your phone down, always looking at a bright screen is not good for your eyes.”
(3)	When parents see you are sleeping on bed, they will: 1) Neglect — “Oh.....Still in bed. ” 2) Order — “Wake up, NOW!” 3) Request — “Can you find something to do and not lie on the bed all day?” 4) Suggestion — “It is better to sleep at night. Otherwise, you may be unable to sleep tonight. ”
(4)	When parents think that you are bone idle, they will: 1) Neglect — “Oh.....You are lazy bone. ” 2) Order — “Go to tidy your stuff up, NOW!” 3) Request — “Do something else. I don’t want to see you sitting here.” 4) Suggestion — “Let’s have a walk. It would be better than sitting here. ”
(5)	When parents find you playing games all the time, they will: 1) Neglect — “Gaming again. ” 2) Order — “Turn off the game NOW!” 3) Request — “You should spend less time on playing the game.” 4) Suggestion — “You have played the game for a long time, how about giving your eyes a break now?”
(6)	When you respond to your parents’ blaming on you, your parents will: 1) Neglect — “I don’t care what you said. ” 2) Order — “Shut up!” 3) Request — “You should not talk back.” 4) Suggestion — “Let us know what we blamed you wrongly.”
(7)	During the final exam, your parents notice that you focus on something else rather than doing revision. They will: 1) Neglect — “Oh, you don’t need to revise. ” 2) Order — “Go over your lessons NOW!” 3) Request — “You are still sitting your exams, do your revision, please.” 4) Suggestion — “It would be great if you revise before doing something else.”
(8)	Parents want you to help do some housework, but you are phubbing. They will: 1) Neglect — “Phubbing again.” 2) Order — “Come over and help NOW!” 3) Request — “You should help do some housework in your free time.” 4) Suggestion — “Could you help me wash the dishes? You can play the game after that.”

A 3.2. Reference Materials for Instructors: Group Worksheet



A 3.3. Video: “Parents’ Messages”

A 3.4. Reference Materials for Instructors: “Parents’ Messages”

Category	Father / Mother	Scenarios
(1) Order		“What time is it now? Still playing video games? You have school tomorrow morning! Go to bed now!”
(2) Request		“I’m busy cooking in here and I’m out of cooking oil. Can you go and buy a new bottle for me?”
(3) Neglect		“Don’t bother me!”
(4) Suggestion		“You spent less time playing video games last semester and got better grades. I think we should do the same this semester. Let’s try playing less games this semester like last term. That would be better, right?”
(5) Order		“How many times do I have to repeat it? No matter what, we are going to Grandma’s place for dinner this Saturday.”
(6) Request		“We’ll have an early dinner tonight. Come back before 7:00 “
(7) Suggestion		“These days you stay out so late. Why not stay at home and help your brother with his homework. He is really struggling with his English.”

A 3.5. Reference Materials for Instructors: “i-message”

Online Polling Content

	Scenarios
(1)	When parents said, “What time is it now? Still playing video games? You have school tomorrow morning! Go to bed now!,” you will : Neglect — “I don’t care about that.” and keep playing the game. Order — “Stop annoying me!” Request — “Let me complete this task first.” Suggestion — “I don’t want to waste my effort on this task” (Feeling) “Please give me 10 more minutes and I will go to bed, even I cannot complete it in the end.” (Views about the issue)
(2)	When parents said, “ I’m busy cooking and have run out of cooking oil...can you buy a new bottle for me?,” you will: Neglect — “Don’t bother me.” Order — “You do it by yourself!” Request — “You can do it after finishing the dishes you are cooking.” Suggestion — “I am doing my assignment.” (Feeling) “Give me five minutes. I will buy it after completing my assignment.” (Views about the issue)

	Scenarios
(3)	When parents said, "Don't bother me!" you will: Neglect — "I don't bother anymore." Order — "Fine! Remember what you said." Request — "Let me say it now." Suggestion — "I know you are troubled by something else, but I have something to discuss with you." (Feeling) "Is it okay if we discuss five minutes later?" (Views about the issue)
(4)	When parents said, "You spent less time playing video games and got better grades in last semester. I think we do the same this semester. Try to spend less time playing video games, shall we?," you will: Neglect — "Don't bother me!" Order — "Shut up!" Request — "Let me complete the game first." Suggestion — "I feel much more stressed in this exam and have to relax my mind." (Feeling) "Could you let me play game for half an hour after every two-hour revision?" (Views about the issue)
(5)	When parents said, "How many times do I need to repeat? We are going to have dinner at Grandma's place this Saturday," you will: Neglect — "I didn't hear what you said." Order — "Shut up!" Request — "I don't want to go to grandma's home." Suggestion — "I have promised to attend a gathering on that day and I am not sure what time it will end." (Feeling) "Perhaps I will have dinner with grandmother later." (Views about the issue)
(6)	When parents said, "We'll have an early dinner tonight. You should come back before 7:00 p.m." you will: Neglect — "I don't know." Order — "You can have dinner first!" Request — "Don't wait for me and do it yourselves." Suggestion — "I am not sure when I will finish my work." (Feeling) "I will call you if I cannot come back on time, and you can start first." (Views about the issue)

REFLECTIVE QUESTIONS

Name:

Class:

Date:

1. Are you satisfied with your communication with your parents now? Why?

2. How can you improve your communication with your parents effectively? Please elaborate with examples.

3. Please write down the advantages of using "I-message" as a reply.

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Chapter 315

**ADVANCES IN CHINESE CHILDREN,
ADOLESCENT AND FAMILY RESEARCH**

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ABSTRACT

A survey of the literature showed that most research studies in children, adolescents and families have been conducted in Western contexts, which may not be applicable to non-Western contexts. Hence, research on children, adolescents and families in non-Western contexts is particularly important and we therefore need to enrich human development and family research in the Chinese context. In this book, we included 16 chapters to demonstrate the advances in Chinese children, adolescents, and family

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research. And it is our sincere hope that through this book, we can attempt to conduct more empirical studies that can help to promote the research atmosphere and enrich the knowledge of Chinese children, adolescent, and family research in a larger context.

INTRODUCTION

A survey of the literature showed that most research studies in children, adolescents and families have been conducted in Western contexts. One major limitation is that the related theories and findings may not be applicable to non-Western contexts. Hence, research on children, adolescents and families in non-Western contexts is particularly important. As roughly one-fifth of the world's population are Chinese, the development of research on human development and families in the Chinese context is very important. Although more Chinese research studies have been conducted in the past decades, most of the studies were based on Western theories and tools. Due to cultural differences, it is argued that researchers and practitioners should develop their own theories, programs and measurements [1-3].

There are several areas that require more Chinese research. The first area is the prevention intervention research. For example, by adopting fifteen positive youth development constructs from the West, the first local positive youth development program ("Project P.A.T.H.S.") has been developed for Hong Kong junior secondary students since 2005. Since the implementation, the research team employed multiple evaluation strategies to ensure the quality of the program implementation, such as subjective and outcome evaluation, process evaluation, and focus group and individual interviews. Also, based on the results of the evaluation, the program materials have been updated and revamped based on the results of the evaluations during the 15-year program [4-5].

MAINLAND CHINA

Based on the positive feedback and effectiveness of the Project P.A.T.H.S. in Hong Kong, the program has been introduced into mainland China ("Tin Ka Ping P.A.T.H.S. Project") since 2011 for more than 28 mainland China cities. However, due to the cultural differences between Hong Kong and mainland China, there is a need to have ongoing feedback from different stakeholders. Normally speaking, the teaching style of Hong Kong teachers is more interactive when compared with the style of mainland Chinese teachers. For positive youth development programs, like Project P.A.T.H.S., interaction and students' participation are key factors for promoting students' reflection and learning. Therefore, apart from providing trainings for teachers and program implementers, feedback from both participants and program implementers can not only help researchers to have a full picture of the program effectiveness, but also facilitate program implementers' reflection on their teaching performance and improvement. This example proved that ongoing evaluations and researches are needed for adopted programs for better program effectiveness. In this book, we included some related papers on the Tin Ka Ping Project in China.

EVALUATION

Second, we need more research on the evaluation of holistic adolescent development programs. In order to have a comprehensive picture of the program's effectiveness, it is suggested to collect feedback from both participants and different stakeholders, including program implementers. Besides collecting participants' feedback, it is also important to collect feedback from the program implementers for several reasons: (i) program implementers are more experienced than participants, and they can provide more "accurate" views towards the programs; (ii) it can facilitate reflective practice and to enhance the quality of the programs; (iii) it can provide a better understanding about the implementation process across different settings/schools, especially for those programs which are implemented in different schools; (iv) according to the principle of triangulation, collecting data from different sources can help researchers to generate the same picture and further examine if there are different views among participants and stakeholders. In this book, we included some papers on evaluation based on different evaluation strategies.

Beside intervention research, it is also important to understand adolescent development. As there are few studies on adolescent materialism and egocentrism, there is a need to conduct more studies in this area. Furthermore, there is a need to conduct more longitudinal studies. Although there is an increase of longitudinal studies in adolescents' development, longitudinal studies about late adolescents' well-being (e.g., university students) are still lacking in number, especially in the Chinese context [6]. University life should be regarded as an important transition period from adolescence to adulthood. However, there is a myth in the Chinese society that university students need less support and concern as they are "old" enough to face different challenges. In this book, several papers on adolescent materialism and egocentrism are included. Also, some papers on the development of university students are covered.

FAMILY RESEARCH

Finally, several points should be noted when conducting family research: (i) cultural differences should be taken into consideration, (ii) there is a need to examine the differential paternal and maternal influences when examining a factor on children and adolescent; and (iii) both parents' and children' views should be included in a single study. Because of the unique historical backgrounds between the West and East, cultural differences should always be considered when studying family factors in the Chinese context. Besides, to have a complete understanding of different sides, it would be good to include both parents' and children's views in a single study.

THIS BOOK

Based on the above discussion, there is a need to enrich human development and family research in the Chinese context. In this book, we included 16 chapters to demonstrate the advances in Chinese children, adolescents, and family research. And it is our sincere hope

that through this special issue, we can attempt to conduct more empirical studies that can help to promote the research atmosphere and enrich the knowledge of Chinese children, adolescent, and family research.

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In this book we have gathered single papers published earlier in several of Nova journals with permission relevant to the topic of the book.

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Chapter 316

RELIABILITY AND VALIDITY OF THE CHINESE VERSION OF THE PSYCHO-EDUCATIONAL PROFILE (THIRD EDITION) FOR CHILDREN WITH DEVELOPMENTAL PROBLEMS

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ABSTRACT

The Psycho-Educational Profile-3rd edition (PEP-3) is a popular instrument that assesses the skills and behaviors of children with autism and communicative disabilities, while its application in Chinese population has not been systematically examined. Based on the data collected from a clinical sample of children ($N = 455$) diagnosed as having autism spectrum disorder (ASD) and other pervasive developmental disorders (PPDs) as well as a sample of healthy controls ($N = 281$) in Hong Kong, this study examined the psychometric properties of the Performance Test of the Chinese version of the PEP-3 (CPEP-3). Different types of evidence on the reliability (internal consistency, test-retest reliability and inter-rater reliability) and validity (content validity and criterion-related validity) of the test were examined. It was found that the Performance Test of CPEP-3 possessed sound psychometric properties in assessing the developmental level of Chinese children with autism spectrum disorder in Hong Kong. The translated CPEP-3 Performance Test is a reliable and valid measure for assessing Chinese children with autism.

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INTRODUCTION

Autism spectrum disorder (ASD) refers to a group of developmental disabilities, characterized by unreciprocated interpersonal and emotional interactions, disordered language and communication, and repetitive and stereotypic behaviors [1-3]. Although earlier studies had suggested the prevalence of autism was low, the global prevalence of ASD increased tremendously in the global context in the past decades [4-8]. While children with ASD share similar symptoms, the age of onset, nature and severity of the problems are highly variable, which require different treatment approaches [9]. Hence, psychometrically sound instruments that can help professionals to objectively assess children with ASD are of great importance to ensure accurate diagnosis and appropriate educational programming [10].

According to Shriver, Allen and Mathew [11], assessment is considered as core components in treating children with ASD in terms of three aspects. First, assessment helps to obtain an accurate verification for the diagnosis and special education eligibility. Second, assessment can guide the development of appropriate interventions by providing a descriptive profile on children's development in different areas. Third, assessment enables researchers to establish baselines against which evaluation of different intervention programs could be conducted.

Among different types of assessments measuring children with ASD, the Psycho-Educational Profile-3rd edition (PEP-3) is a standardized observation tool primarily designed for planning educational program for children with ASD from 2 to 7 years of age [12]. It is the revised version of the Psycho-Educational Profile-Revised (PEP-R) which has been widely used in different parts of the world for the assessment of children with ASD in terms of their developmental skills and behaviors [13-17]. Compared with the PEP-R, there are several significant improvements in the PEP-3. First, the measured function domains have been revised by incorporating the most recent research findings, such as the social and communication aspects. Second, normative data from both a sample with autism and a typically developing sample were provided which makes it possible to compare the two groups of children on their developmental profiles. Third, a Caregiver Report, which utilizes information reported by parents and other caregivers about the child's development and behavior in daily lives, has been added to help professionals have a fuller understanding about the child. Fourth, new items and important subtests were added into the PEP-3 while obsolete items were deleted. The validity of the revised instrument has been examined in the West [18].

Specifically, the PEP-3 consists of two complementary parts. The first part is a norm-referenced performance scale (Performance Test) which measures autistic children's development in three areas: communication, motor skills, and maladaptive behaviors. The second part is a parent or caregiver reported form (Caregiver Report). Children's development and performance in communication, motor and social functioning, adaptive behaviors and thinking are rated by their caregivers based on their daily observation. As autistic children's symptoms vary across settings (such as people, places, and things the child interacts with), using both professional observers' ratings on children's performance in the laboratory and caregivers' ratings on children's daily lives helps to obtain a richer and comprehensive developmental profile of the child with reference to the strengths and weaknesses of the child in different environment. This could be very useful for professionals

to design individualized educational and behavioral intervention programs in different settings.

Based on a normative sample of 407 children with ASD and 148 children with typical development in the United States, Schopler et al. [18] reported the reliability and validity of the PEP-3 in its user manual. As far as reliability is concerned, the PEP-3 showed high reliability, with all subtests showing high internal consistency (alphas ranged from 0.84 to 0.90) and temporal stability (test-retest coefficients over a period of two weeks ranged from 0.94 to 0.99). Besides, for the inter-rater reliability for the Caregiver Report, the polychoric correlation coefficients ranged from 0.52 to 1.00. In terms of validity, consistent with the expectations, autistic children's scores on PEP-3 Performance subtests were negatively correlated with their scores on measures of symptom severity in autistic children, including the Childhood Autism Rating Scales (CARS) [19] and the Autism Behavior Checklist-Second Edition (ABC) [20]. For the Caregiver Report, positive correlation coefficients were found between the Vineland Adaptive Behavior Scales (VABS) [21] which assess parent-reported adaptive behavior of children and PEP-3. These findings provide sound support for the good psychometric properties of the PEP-3 when applied to children with ASDs in the United States.

The PEP-R has been translated into several languages and research findings supporting the psychometric properties of the translated measures have been reported [14, 15, 22]. In contrast, there are very few reports on the application of PEP-3 in countries other than the United States [23]. As Chinese people constitute roughly one-fifth of the world's population, translation of PEP-3 to Chinese and establishment of the related psychometric properties should be conducted. Actually, a Chinese version of the PEP-R (CPEP-R) was validated and used in assessing children with ASD in Hong Kong since 2005 which has largely facilitated the diagnoses and treatment of autistic children [14]. Nevertheless, very few reports have been published on the Chinese version of PEP-3 and its psychometric properties. In Taiwan, researchers translated the PEP-3 into Chinese and reported the reliability and validity of the instrument based on Taiwanese children with autism. While the preliminary findings supported the application of PEP-3 in Chinese children, the published studies were mostly based on small samples (ranged from 42 to 64 participants), which makes the generalization of the findings to other Chinese population questionable [22-24].

Against the above background, Heep Hong Society, the biggest organization in Hong Kong that provides professional training and education to children with developmental and learning problems and their families, invited a group of experts consisting of psychologists, occupational therapists, special educators, and special child-care workers to translate the PEP-3 into Chinese [25] and conduct a validation study to examine the psychometric properties of the instrument. Based on a sample of 455 children with ASD and a comparison group of 281 children with typical development, the construct validity of the Chinese version of PEP-3 (CPEP-3) was examined. It was found that older children scored higher than younger children for both groups on different subsets of CPEP-3, while no gender difference was identified within the autistic group. The results of confirmatory factor analysis further showed the three-factor theoretical model of the Performance Test fitted well. These findings provide important evidence for the construct validity of the CPEP-3 [25]. However, besides construct validity, there is a need to further understand the reliability as well as other types of validity of the CPEP-3.

As far as reliability is concerned, three types of reliability are commonly assessed for an assessment tool [26]. First, Cronbach's alphas are usually computed to examine the internal consistency of the scale to see whether the items measure something which is homogenous in nature. Second, temporal stability of the test scores (i.e., test-retest reliability) is typically examined by getting the test scores at two different time points. Finally, if the test is completed by different raters, consistency across raters is examined by inter-rater reliability.

Regarding validity, besides construct validity which was examined in the study of Shek and Yu [25], two additional forms of validity evidence were examined in the present study. First, evidence about content validity was explored, which refers to "the systematic examination of the test content to determine whether it covers a representative sample of the behavior domain to be measured" [27]. Based on the method adopted by the original author of PEP-3 [12], conventional item analyses were performed to provide evidence for content validity, including item discrimination and item difficulty analyses. Second, criterion-related validity was investigated, which was defined as the correlation between a test and an (or a series of) external criterion variable(s) taken as representative of the construct, for example, measures that have previously been validated assessing presumably related constructs [27]. In this study, it was hypothesized that the Performance Test of CPEP-3 should correlate well with previously validated tests that measure developmental skills and behavioral symptoms in children with autistic disorders.

The primary purpose of this paper is to report the reliability and validity of the Performance Test of the Chinese version of PEP-3 (CPEP-3) based on further data collected from the same samples of children as reported in Shek and Yu's [25] paper. Psychometric properties of the Caregiver Report will be presented elsewhere [28]. Specifically, the current study attempted to assess the reliability (internal consistency, test-retest reliability and inter-rater reliability) and validity (content validity and criterion-related validity) of the CPEP-3 Performance Test as a measure to estimate the developmental level among children with ASD in Hong Kong.

OUR STUDY

Prior to the study, approval to conduct the study (including ethics approval) was obtained from the Executive Committee of Heep Hong Society. The primary caregivers of the participated children have given their written informed consents to the research team. Participants were ensured that the data collected in the study would be kept confidential.

Participants

As described in Shek and Yu's [25] paper, 455 children who were diagnosed as having autism or other pervasive developmental disorders (PDDs) in 25 service units in Heep Hong Society including special child care centers, early education and training centers, and parent resource center were recruited to participate in the study. Another sample of 281 children without developmental problems was selected as the "healthy control" from 13 local kindergartens matched for age with the autistic sample for comparison. The diagnoses of the

autistic sample were made based on ICD-10/DSM-IV by consultant psychiatrists and endorsed by a multidisciplinary team consisting of clinical psychologists, special educators, and other helping professionals. Several subgroups of participants were randomly selected for the analyses of test-retest reliability, inter-rater reliability, and criterion-prediction validity.

Table 1. Demographic characteristic of the samples

Age group	2	3	4	5	6	7	
Age range in years	2.0-2.9	3.0-3.9	4.0-4.9	5.0-5.9	6.0-6.9	7.0-7.9	Total
Sample with autism							
No. of participants	32	79	140	161	37	6	455
Percentage	7.0%	17.4%	30.8%	35.4%	8.1%	1.3%	100%
No. of girls	6	11	22	22	5	0	66
No. of boys	26	68	118	139	32	6	389
Typically developing sample							
No. of participants	67	60	60	62	30	2	281
Percentage	23.8%	21.4%	21.4%	22.1%	10.7%	0.7%	100%
No. of girls	34	37	36	30	14	1	152
No. of boys	33	23	24	32	16	1	129

Participants' age ranges from 2.0 to 7.9 years. The characteristics of the two samples in terms of age and gender can be seen in Table 1. For the autistic sample, the ratio of boys to girls is 6:1, which is consistent with the reflecting the fact that boys have a higher risk of autistic disorders than girls. While this figure is higher than the related ratio (4:1); in the sample reported in Schopler et al. [12], it is highly similar to the findings of a large epidemiological study of autistic spectrum disorder in which the male to female ratio was found to be 6.58:1 in Hong Kong children [8]. Scores of the sample with ASD and the typically developing sample were compared as an indication of criterion-related validity.

Procedures

The translation of the CPEP-3 followed standard procedure in questionnaire adaptation, of which the details were reported in Shek and Yu's [25] paper. A group of professionals including speech therapists, occupational therapists, educational psychologists, and preschool teachers administered the tests and rated the participants' performance. All of the raters had experience working with and testing young children. Before the formal launching of the validation study, training sessions were conducted so that the raters worked together to clarify and get familiar with general testing, scoring and interpreting procedures of the CPEP-3 to ensure consistency in the test administration.

To investigate whether the participants' test performance is consistent over time, test-retest reliability was examined on a subsample of 42 children with autism. Six girls and 36 boys between 2.3 and 5.9 years of age were tested twice over a period of time that ranged from 6 weeks to 3 months. The variation of the interval was due to difficulties in the arrangement involved.

Besides, inter-rater reliability was conducted on a subsample of 46 children randomly selected from the autistic group with age ranging from 2 to 5 years (5 girls and 41 boys) to

understand whether the test would be affected by subjective ratings of different raters. Each subject was administered the CPEP-3 Performance Test independently by one administrator and two co-raters as observers. The administrator-co-raters grouping was randomly assigned by a research assistant who was blind to the characteristics of the subjects. In order to keep neutrality throughout the process, testing conditions were similar for all the children and the researchers involved in the case would rate the child's performance independently and handed the protocols to the research assistant directly for data entry.

To test the criterion-related validity of CPEP-3 Performance Test, two established measures related to developmental problems were administered on a subsample of 64 children with autism (56 boys and 8 girls) aged 2 to 6 years. The two measures included the Merrill-Palmer Revised Scales of Development (MPR) [29] and the Childhood Autism Rating Scale (CARS) [18]. Both measures were administered by the raters and the participants were randomly assigned to the researchers. The correlations between the criterion measures and CPEP-3 Performance Test would serve as an index of criterion-related validity.

Instruments

The Chinese Version of Psycho-Educational Profile—3rd Edition (CPEP-3)

The PEP-3 has two major parts: Performance Test and Caregiver Report. The 172-item Performance Test is composed of 10 subtests. Three subtests measure communication ability including Cognitive Verbal/Preverbal (34 items), Expressive Language (25 items), and Receptive Language (19 items). Another three subtests measure motor ability: Fine Motor (20 items), Gross Motor (15 items), and Visual-Motor Imitation (10 items). These six subtests focus on the child's developmental level. The rest four subtests measure maladaptive behaviors, including Affective Expression (11 items), Social Reciprocity (12 items), Characteristic Motor Behaviors (15 items), and Characteristic Verbal Behaviors (11 items). The Caregiver Report consists of 38 items which are combined into three subtests: Problem Behavior (10 items), Personal Self-Care (13 items), and Adaptive Behavior (15 items). The current study focuses on examining the Performance section.

Authorized by the PEP-3 developers, Heep Hong Society organized a working group comprising clinical, developmental and educational psychologists to translate the PEP-3 items into Chinese. The translated draft was then reviewed and modified by the group after discussion. Compared with the English version of PEP-3, changes in the CPEP-3 were made in the areas of language and use of stimuli. Adaptation and modifications were conducted taking into account the cultural and language factors. Chinese words were used to replace the English ones in the items for letter matching, naming and sorting, and a few more culturally suitable pictures were used to replace the original ones. The scoring of items has been quantified as 0, 1, and 2, with "Pass" = 2, "Emerge" = 1, and "Fail" = 0.

To assess the convergent validity of the CPEP-3, the following measures were employed:

Merrill-Palmer Revised Scales of Development (MPR)

The MPR is an individually-administered, norm-referenced measure of children's development in cognitive, language, motor, self-help, and social-emotional domains [29]. It is characterized by a wide range of visual-motor tasks and a few verbal items. This instrument

has been widely used by practitioners in assessing the cognitive functioning of pre-school children with language and cognitive delays, with high scores suggesting high cognitive functioning. There are seven subscales in the MPR: development, cognitive, fine motor, infant language/receptive language, infant memory/memory, speed, and visual motor, measuring different areas of cognitive functioning. It was hypothesized that positive correlation would be found between MPR scores and CPEP-3 Performance subtest scores.

Childhood Autism Rating Scale (CARS)

The CARS is a behavioral rating scale developed by the TEACCH Division [18]. The CARS consists of ratings in 15 different areas of functioning significant for autism: Relating to People, Imitation, Emotional Response, Body Use, Object Use, Adaptation to Change, Visual Response, Listening Response, Taste, Smell, and Touch Response and Use, Fear or Nervousness, Verbal Communication, Nonverbal Communication, Activity Level, Level and Consistency of Intellectual Response and General Impressions. Children's behaviors were observed and rated on a 7-point scale (4 anchor points and 3 half steps) with clear behavioral anchors. High scores on the CARS are considered more maladaptive. Both total score and subscale scores of the CARS were used in the current validity test. It is expected that negative correlation would be found between the CARS and the CPEP-3. On a sample of Hong Kong children with autism, Shek et al. [16] reported a significant correlation coefficient of 0.70 between the Behavioral Scale of CPEP-R and the total score of CARS.

Table 2. Cronbach's alpha coefficients and mean inter-item correlation coefficients for the CPEP-3 performance subtests and composites

Age Group	2	3	4	5	6	7	Average	Mean inter-item correlation coefficients	No. of items
Performance Subtests									
CVP	0.92	0.96	0.96	0.97	0.93	0.60	0.97	0.48	34
EL	0.91	0.96	0.96	0.97	0.94	0.92	0.97	0.53	25
RL	0.92	0.96	0.96	0.97	0.92	0.60	0.97	0.62	19
FM	0.84	0.89	0.88	0.90	0.77	0.52	0.91	0.32	20
GM	0.82	0.88	0.86	0.89	0.62	-	0.90	0.38	15
VMI	0.85	0.90	0.88	0.88	0.71	-	0.90	0.48	10
AE	0.88	0.87	0.91	0.90	0.45	0.72	0.89	0.43	11
SR	0.86	0.86	0.89	0.91	0.81	0.87	0.90	0.45	12
CMB	0.89	0.92	0.91	0.92	0.89	-	0.92	0.41	15
CVB	0.94	0.95	0.93	0.95	0.84	0.64	0.95	0.62	11
Composites									
Communication	0.97	0.98	0.99	0.99	0.97	0.93	0.99	0.51	78
Motor	0.93	0.96	0.95	0.96	0.87	0.82	0.96	0.36	45
Maladaptive Behaviors	0.96	0.97	0.97	0.97	0.93	0.89	0.97	0.40	49

Note. CVP = cognitive verbal/preverbal; EL = expressive language; RL = receptive language; FM = fine motor; GM = gross motor; VMI = visual-motor imitation; AE = affective expression; SR = social reciprocity; CMB = characteristic motor behaviors; CVB = characteristic verbal behaviors.

Data Analyses

Preliminary data screening was performed to verify the suitability of the current data for parametric analyses. The psychometric properties of CPEP-3 were examined at both the subtests and composite levels. First, three types of reliability tests were conducted to examine the consistency of CPEP-3 subtests and composites on the current samples of Hong Kong children. These included internal consistency, test-retest reliability, and inter-rater reliability. Second, conventional item analyses including both item difficulty and item discrimination were performed to provide evidence for the content validity. Third, convergent validity of CPEP-3 was examined by testing the correlation coefficients between CPEP-3 and the two criterion scales, MPR and CARS, which measure similar domains of development as measured by CPEP-3.

FINDINGS

Internal consistency was first examined for the subtests and composites of CPEP-3 Performance Test using the total autistic sample and the subsamples at six age intervals separately. The Cronbach’s alpha coefficients and mean inter-item correlation coefficients are reported in Table 2. For the whole autistic sample, the Cronbach’s alpha coefficients ranged from 0.89 to 0.97 for the Performance subtests, and ranged from 0.96 to 0.99 for the composites. The values of the mean inter-item correlation coefficients were also acceptable (equaled to or exceeded 0.32 and 0.36 for the Performance subtests and the composites, respectively).

Table 3. Test-retest reliability for the CPEP-3 performance subtests

PEP-3 Values	First Testing		Second Testing		r
	M	SD	M	SD	
Performance Subtests					
CVP	38.26	16.89	40.00	17.36	.98
EL	13.07	11.26	13.79	12.30	.99
RL	18.00	11.43	18.76	11.43	.97
FM	31.19	6.46	31.62	6.66	.96
GM	25.38	5.26	26.29	5.20	.92
VMI	12.62	4.70	13.26	5.11	.93
AE	13.43	3.91	14.05	3.40	.84
SR	13.14	4.27	13.74	3.93	.92
CMB	20.71	6.91	21.40	6.69	.95
CVB	7.86	5.99	8.38	5.97	.96

Note. CVP = cognitive verbal/preverbal; EL = expressive language; RL = receptive language; FM = fine motor; GM = gross motor; VMI = visual-motor imitation; AE = affective expression; SR = social reciprocity; CMB = characteristic motor behaviors; CVB = characteristic verbal behaviors.

To investigate the temporal stability of the assessment tools, test-retest reliability was examined on a subsample of 42 randomly selected children with autism. The temporal stability of the CPEP-3 was tested on 6 girls and 36 boys between 2.3 and 5.9 years of age over a period of time ranged from 6 weeks to 3 months. Means and standard deviations of participants’ scores at the two time points are presented in Table 3. Correlation coefficients

between test and retest raw scores for each subtest were computed. Results showed that test-retest correlation coefficients were all above 0.82, indicating a good time sampling reliability of the Chinese version of PEP-3.

Table 4. Polychoric correlation coefficients for CPEP-3 performance subtest items

Performance Subtests	Min	Max	Mean	Median
CVP	0.26	1.00	0.78	0.87
EL	0.41	1.00	0.77	0.81
RL	0.47	0.93	0.71	0.77
FM	0.23	0.96	0.60	0.76
GM	0.14	0.95	0.58	0.62
VMI	0.63	0.91	0.78	0.79
AE	0.11	0.59	0.34	0.34
SR	0.25	0.75	0.46	0.41
CMB	0.47	0.61	0.52	0.48
CVB	0.19	0.71	0.48	0.52

Note. CVP = cognitive verbal/preverbal; EL = expressive language; RL = receptive language; FM = fine motor; GM = gross motor; VMI = visual-motor imitation; AE = affective expression; SR = social reciprocity; CMB = characteristic motor behaviors; CVB = characteristic verbal behaviors.

The reliability between raters was also assessed to understand whether the test would be affected by subjective ratings of different raters. The inter-rater reliability was based on a randomly selected subsample of 46 children with age ranging from 2 to 5 years (5 girls and 41 boys). Two experienced raters evaluated the 46 children independently using the 10 Performance subtests of CPEP-3. Polychoric correlation coefficients for each pair of items rated by different examiners were calculated as an indicator of inter-rater reliability [30]. Descriptive statistics about the correlation coefficients for ten Performance subtests are summarized in Table 4. Because polychoric correlation requires bivariate normality of data, skewness of items was computed initially. Results revealed that 61 out of 344 items skewed greater than the absolute value of 2. Among these items, 12 items (items 42, 120, 155, 3, 70, 97, 56, 62, 69, 135, 137, and 138) yielded polychoric correlation coefficients that appeared to be significantly biased under the condition of bivariate normality. These correlation coefficients were then excluded in the calculation of the range, mean and median of the polychoric correlation coefficients for their corresponding subtests. As can be seen in Table 4, the mean and median polychoric correlation coefficient for each subtest ranged from 0.34 to 0.78 and from 0.34 to 0.87, respectively. According to Hopkin and Stanley [31], these values can be regarded as evidence showing good inter-rater reliability.

Validity of CPEP-3 Performance Test

Regarding the content validity, the rationales underlying the selection of subtest items were established by the test developers in the United States. In fact, an earlier version of PEP-R in Chinese was used in Hong Kong to assess children with autism [14, 32] and showed sufficient clinical validity [33]. The PEP-3 is a modified version of the original PEP-R based on the experience of using this instrument in the United States for more than 20 years. After being translated into Chinese, all test materials and procedures of CPEP-3 were scrutinized by

a steering group consisting of local experts including psychologists, occupational therapists and special teachers in Hong Kong. They generally held the expert view that items of the CPEP-3 are representative and highly relevant to the domains assessed.

Besides content validity supported by expert views, tests of item discrimination and item difficulty were conducted. Item discrimination refers to the extent to which success on an item corresponds to success on the whole test, which can be indexed by the correlation between a specific item and the other items of the questionnaire. Consistent with the method used by the original scale developers, item-total score correlation coefficients were calculated on the current autistic samples of children (age 2 through age 7) to represent for the item discrimination of the CPEP-3 items.

Table 5 shows the median item discrimination coefficients for each subtest of CPEP-3. Using the criterion that discrimination indexes of 0.35 or higher are acceptable [34-35], most items can be regarded as having good item-discrimination ability on both the whole sample and different age groups. For children aged at 7 years or older, item-discrimination indices for several subtests (RL, GM, VMI, CMB, and PSC) are either uninterpretable or less than 0.35, which may be due to the limited number of participants in this age group ($N = 6$).

Table 5. Item discrimination for the CPEP-3 performance subtests

Performance subtests	2	3	4	5	6	7	Overall
CVP	0.54	0.62	0.67	0.74	0.61	0.35	0.72
EL	0.63	0.72	0.77	0.81	0.71	0.85	0.83
RL	0.64	0.81	0.75	0.80	0.65	0.22	0.80
FM	0.46	0.58	0.59	0.63	0.48	0.77	0.61
GM	0.46	0.57	0.52	0.58	0.52	-	0.59
VMI	0.60	0.67	0.61	0.66	0.42	-0.33	0.68
AE	0.60	0.59	0.67	0.71	0.21	0.91	0.66
SR	0.56	0.56	0.61	0.66	0.51	0.72	0.63
CMB	0.61	0.63	0.58	0.61	0.59	0.11	0.64
CVB	0.83	0.78	0.73	0.77	0.52	0.60	0.76

Note. CVP = cognitive verbal/preverbal; EL = expressive language; RL = receptive language; FM = fine motor; GM = gross motor; VMI = visual-motor imitation; AE = affective expression; SR = social reciprocity; CMB = characteristic motor behaviors; CVB = characteristic verbal behaviors.

Table 6. Item difficulty for the CPEP-3 performance subtests

Performance Subtests	2	3	4	5	6	7
CVP	18.8%	42.4%	59.3%	69.9%	89.2%	100%
EL	3.1%	19.0%	36.4%	49.7%	75.7%	83.3%
RL	21.9%	45.6%	62.9%	73.9%	89.2%	100%
FM	48.5%	70.3%	87.2%	91.0%	96.0%	100%
GM	53.1%	75.9%	88.6%	93.8%	100%	100%
VMI	14.1%	40.5%	62.5%	67.1%	82.5%	100%
AE	53.1%	46.8%	57.9%	68.3%	73.0%	83.3%
SR	21.9%	22.8%	44.3%	48.1%	63.6%	83.3%
CMB	43.8%	51.9%	64.3%	67.7%	73.0%	100%
CVB	12.5%	20.5%	35.7%	42.2%	64.9%	66.7%

Note. CVP = cognitive verbal/preverbal; EL = expressive language; RL = receptive language; FM = fine motor; GM = gross motor; VMI = visual-motor imitation; AE = affective expression; SR = social reciprocity; CMB = characteristic motor behaviors; CVB = characteristic verbal behaviors.

Item difficulty refers to the percentage of participants who can pass a given item, which helps to identify whether an item is too difficult or too easy. Anastasi and Urbina [27] suggested an average item difficulty of 50%, with a range of 15% to 85% considered acceptable. Table 6 summarizes the median item difficulty for each subscale of CPEP-3 on the autistic sample of children. For most parts of the test, test items satisfy the requirements. Results showed that as age increased, the percentage of children who passed the item also increased. These results are also consistent with the Western findings [12].

To test the criterion-related validity of CPEP-3, two well-known measures, MPR and CARS were used as criterion measures based on a subsample of 64 randomly selected autistic children. Descriptive information about the two measures and their subscales is reported in table 7. As shown in table 8, MPR subscale scores were positively correlated with the subtest scores of CPEP-3 Performance Test. All correlation coefficients were significant with values being moderate to large. This suggests high convergent validity of the Performance subtests of CPEP-3 when applied to Chinese children. For CARS, both its total score and subscale scores were used in the current validity test. As CARS measures malfunctioning in autistic children, it is expected that negative correlation would be found between the CARS and the CPEP-3 Performance subtests. As can be seen in Table 9, with a few exceptions, most correlation coefficients were significant, with the direction of the correlation coefficients consistent with the hypotheses, providing further evidence for the criterion-prediction validity of the CPEP-3. These findings were also comparable favorably with previous validation studies conducted in the United States using the CARS as one criterion measure for PEP-3 [12].

Table 7. Descriptive information on two criterion measures and their subscales

		Mean	SD	Range
MPR	Development	179.27	54.86	38.00-237.00
	Cognitive	82.20	22.22	24.00-110.00
	Fine motor	47.20	12.27	13.00-64.00
	Infant language/receptive language	49.61	21.80	0.00-71.00
	Infant memory/memory	15.95	8.78	0.00-34.00
	Speed	14.72	4.70	2.00-20.00
	Visual motor	44.84	10.42	10.00-55.00
CARS	Relating to people	2.52	0.53	1.50-4.00
	Imitation	2.16	0.82	1.00-4.00
	Emotional response	1.82	0.68	1.00-3.50
	Body use	2.08	0.54	1.00-3.50
	Object use	2.30	0.50	1.00-3.50
	Adaptation to change	2.03	0.68	1.00-3.50
	Visual response	2.23	0.74	1.00-3.50
	Listening response	2.32	0.51	1.00-3.00
	Taste, smell, and touch response and use	1.78	0.68	1.00-3.00
	Fear or nervousness	1.24	0.62	1.00-4.00
	Verbal communication	2.59	0.75	1.00-4.00
	Nonverbal communication	1.95	0.62	1.00-3.00
	Activity level	1.52	0.65	1.00-3.00
	Level and consistency of intellectual response	1.84	0.62	1.00-4.00
	General impressions	2.69	0.63	1.00-4.00
	Total score	31.05	6.03	21.50-46.00

Table 8. Correlation coefficients between CPEP-3 performance subtests and MPR subscales

		Performance subtests									
		CVP	EL	RL	FM	GM	VMI	AE	SR	CMB	CVB
MPR	Development	.93**	.92**	.91**	.81**	.72**	.79**	.70**	.80**	.73**	.81**
	Cognitive	.88**	.89**	.86**	.75**	.63**	.73**	.68**	.79**	.71**	.80**
	Fine motor	.92**	.87**	.88**	.81**	.75**	.80**	.65**	.72**	.65**	.75**
	Infant language/receptive language	.92**	.91**	.91**	.80**	.74**	.82**	.73**	.81**	.75**	.81**
	Infant memory/memory	.84**	.85**	.81**	.68**	.60**	.68**	.63**	.74**	.65**	.74**
	Speed	.95**	.89**	.90**	.85**	.78**	.80**	.66**	.74**	.66**	.76**
	Visual motor	.92**	.89**	.89**	.83**	.74**	.77**	.64**	.74**	.66**	.76**

Note. CVP = cognitive verbal / preverbal; EL = expressive language; RL = receptive language; FM = fine motor; GM = gross motor; VMI = visual-motor imitation; AE = affective expression; SR = social reciprocity; CMB = characteristic motor behaviors; CVB = characteristic verbal behaviors.

** p < .01

Table 9. Correlation coefficients between CPEP-3 performance subtests and CARS subscales

	Performance subtests									
	CVP	EL	RL	FM	GM	VMI	AE	SR	CMB	CVB
CARS subscales										
Relating to people	-.55**	-.59**	-.65**	-.44**	-.42**	-.62**	-.63**	-.69**	-.74**	-.64**
Imitation	-.72**	-.72**	-.74**	-.66**	-.56**	-.72**	-.65**	-.76**	-.66**	-.73**
Emotional response	-.05	-.01	-.05	-.04	-.03	-.11	-.08	-.11	-.20	-.07
Body use	-.39**	-.44**	-.35**	-.32**	-.28*	-.28*	-.27*	-.43**	-.39**	-.32**
Object use	-.05	-.10	-.07	-.03	-.11	-.16	-.15	-.20	-.36**	-.07
Adaptation to change	.07	.08	.08	.12	.20	.01	-.01	-.07	-.11	.13
Visual response	-.24	-.31*	-.33**	-.17	-.17	-.25*	-.20	-.32**	-.34**	-.39**
Listening response	-.33**	-.36**	-.38**	-.28*	-.30*	-.30*	-.36**	-.43**	-.52**	-.40**
Taste, smell, touch response and use	-.37**	-.45**	-.40**	-.27*	-.23	-.39**	-.48**	-.59**	-.61**	-.50**
Fear or nervousness	.04	.02	.06	.08	.06	.00	.00	.19	.13	-.08
Verbal communication	-.67**	-.72**	-.75**	-.55**	-.47**	-.67**	-.68**	-.72**	-.77**	-.77**
Nonverbal communication	-.63**	-.71**	-.72**	-.49**	-.46**	-.46**	-.66**	-.70**	-.71**	-.76**
Activity level	-.49**	-.50**	-.47**	-.39**	-.31*	-.48**	-.56**	-.65**	-.66**	-.49**
Level& consistency of intellectual response	-.39**	-.43**	-.39**	-.27*	-.20	-.31*	-.53**	-.48**	-.51**	-.51**
General impressions	-.56**	-.62**	-.64**	-.43**	-.38**	-.57**	-.59**	-.70**	-.73**	-.64**
Total score	-.60**	-.65**	-.64**	-.46**	-.39**	-.60**	-.63**	-.77**	-.79**	-.68**

Note. CVP = cognitive verbal/preverbal; EL = expressive language; RL = receptive language; FM = fine motor; GM = gross motor; VMI = visual-motor imitation; AE = affective expression; SR = social reciprocity; CMB = characteristic motor behaviors; CVB = characteristic verbal behaviors. ** p < .01; * p < .05.

Table 10. Comparison of the psychometric findings on CPEP-3 performance subtests and the findings in the PEP-3 manual

Performance subtests	No. of items	Average Cronbach's alpha		Test-retest reliability		Median Inter-rater reliability		Correlation with CARS	
		Chinese (N = 455)	American (N = 407)	Chinese (N = 42)	American (N = 33)	Chinese (N = 46)	American (N.A.)	Chinese (N = 64)	American (N = 68)
CVP	34	0.97	0.97	0.98	0.99	0.87	-	-0.60	-0.75
EL	25	0.97	0.97	0.99	0.99	0.81	-	-0.65	-0.63
RL	19	0.97	0.97	0.97	0.99	0.77	-	-0.64	-0.76
FM	20	0.91	0.93	0.96	0.98	0.76	-	-0.46	-0.78
GM	15	0.90	0.92	0.92	0.99	0.62	-	-0.39	-0.70
VMI	10	0.90	0.95	0.93	0.97	0.79	-	-0.60	-0.78
AE	11	0.89	0.90	0.84	0.94	0.34	-	-0.63	-0.74
SR	12	0.90	0.91	0.92	0.97	0.41	-	-0.77	-0.68
CMB	15	0.92	0.91	0.95	0.98	0.48	-	-0.79	-0.71
CVB	11	0.95	0.93	0.96	0.95	0.52	-	-0.68	-0.65

Note. CVP = cognitive verbal / preverbal; EL = expressive language; RL = receptive language; FM = fine motor; GM = gross motor; VMI = visual-motor imitation; AE = affective expression; SR = social reciprocity; CMB = characteristic motor behaviors; CVB = characteristic verbal behaviors.

Findings of the American sample were excerpted from the PEP-3 manual (Schopler et al., 2005).

Finally, Table 10 summarizes the psychometric findings of CPEP-3 on the present sample of Chinese children and corresponding results of PEP-3 available in the PEP-3 user manual. It can be found that the psychometric properties of CPEP-3 compared favorably with those of PEP-3 reported by the test developers [12].

DISCUSSION

The aim of the present study was to further report evidence on the reliability and validity of the Performance Test of the Chinese version of Psycho-Educational Profile-3rd Edition (CPEP-3) in the assessment of developmental disorders in a Chinese context. The findings showed that the Performance Test of the CPEP-3 has good psychometric properties when applied to Chinese population, which lends support to the cross-cultural applicability and stability of the CPEP-3.

There are several unique features of this study. First, this is a pioneering scientific study of the PEP-3 on a large sample of Chinese children who are under-represented in the scientific literature on ASD. Second, consistent with the approaches adopted in Schopler et al. [12], different types of reliability and validity were examined in this study. Third, the present findings are on par or even better than those reported in the original study. Finally, the sample size of the current study was quite large considering the relatively low incidence of ASD in children.

Three different types of reliability were examined. The internal consistency of each subtest measured by Cronbach's alpha coefficient for the whole sample of children (ranging from 0.89 to 0.97) was high in this study and is comparable with the findings (Cronbach's alpha coefficients ranging from 0.90 to 0.97) reported by Schopler et al. [12] on American samples. The values of the reliability measures appeared to be higher than the previous reports on the Chinese version of PEP-R (ranging from 0.74 to 0.98) in Hong Kong context [14], which suggests that the items of CPEP-3 are more homogeneous than CPEP-R in measuring their latent constructs. For the composites, their internal consistency was also high (ranging from 0.96 to 0.99). When the Cronbach's alpha coefficients were calculated for children at different ages, it was found that all values are high, except for participants of 7 to 7.9 years of age. This may be due to the limited number of cases ($N = 6$) at this age group and the lack of variance for a few items, which make it impossible to calculate any error variance.

For test-retest reliability, a subsample of children with autism was rated twice on the Performance Test of CPEP-3 over six weeks to three months. The correlation coefficients for each subtest at the two time points ranged from 0.84 to 0.99, suggesting high test-retest reliability. In other words, the participants' scores on CPEP-3 are unlikely to be influenced by random factors in the conditions of the participants or the testing environment over time. Inter-rater reliability was assessed for 46 children with ASDs. According to the criterion suggested by Hopkin and Stanley [31] for determining the size of correlation coefficients ($0 < r < 0.1$ means very small correlation; $0.1 < r < 0.3$ means small correlation; $0.3 < r < 0.5$ means moderate correlation; $0.5 < r < 0.7$ means large correlation; and $0.7 < r < 0.9$ means very large correlation), the mean and median polychoric correlation coefficients for each Performance subtest ranged from moderate to very large. This provides support for the inter-

rater reliability of the CPEP-3 Performance subtests. The findings suggest that using the CPEP-3, different examiners rated the items in a consistent way.

Consistent with western findings, traditional item analyses on the CPEP-3 Performance Test showed that both item discrimination and item difficulty were at an acceptable range, and with age increased, the percentage of participants who passed a particular item also increased. These findings support the content validity of the instrument. The evaluation of the criterion-related validity as a measure to estimate the developmental level in comparison with two standardized developmental assessment measures (MPR and CARS) on a subsample of 64 autistic children demonstrated that CPEP-3 can be well used to effectively quantify the developmental level of children with ASDs. Significant correlations were found between CPEP-3 and the two criterion measures, MPR and CARS. These findings echo with the findings reported by Schopler et al. [12] on samples of children in the United States and provide evidence for the criterion-related validity of CPEP-3.

Overall, the above findings support that the CPEP-3 Performance Test had good reliability and validity when applied to Hong Kong samples, which compared favorably with previous findings based on American samples. The summary shown in Table 10 clearly suggests that the translated CPEP-3 Performance Test is a reliable and valid measure for assessing Chinese children with autism and its results can be regarded as consistent.

It should be noted that there are several limitations in the present study. First, the study was conducted in Hong Kong and spoken Cantonese was used as the language for the administration of the test. Therefore, the participants may not be representative of the children with autism in a broader Chinese context, particularly for Mandarin-speaking areas. Further studies must be conducted in other Chinese societies and evaluate the psychometric properties of CPEP-3 when administered in Mandarin. Second, while one significant difference between CPEP-3 and PEP-R is the addition of a Caregiver Report, which rates children's performance based on caregivers' daily observation, the present study only investigated the psychometric properties of the Performance Test. As the adaptive behaviors and symptom severities of children with ASDs vary across different environments, the Caregiver Report would provide important information on children's development in different contexts. To obtain a full picture of the development of children with ASDs in Chinese contexts, the reliability and validity of the Caregiver Report must be investigated. Third, although the group with autism and the control group were matched on participants' age in the present study, other factors that contribute to children's development were not taken into account, such as gender and IQ. Future study shall consider these factors when setting up the inclusion criterion in participants recruitment. Nevertheless, as a promising assessment tool for children with ASD, the psychometric properties of CPEP-3 need to be established before they can be used to guide the development of intervention programs. Researchers and practitioners are most interested in obtaining scores that are accurate, reliable, and can best estimate the child's true level of development. The present study clearly suggests that the Chinese version of the Psycho-Educational Profile-3rd edition (CPEP-3) Performance Test has good reliability and validity when it is used to measure the developmental level of children with autism spectrum disorders in a Chinese context. In future, more evidence on the construct validity of the Performance Test and the psychometric properties of the Caregiver Report of the CPEP-3 need to be further established.

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Chapter 317

THE IMPACTS OF A UNICEF HEALTH PROMOTION PROJECT ON PRIMARY HEALTH CARE IN WESTERN CHINA: A COMPREHENSIVE EVALUATION AT PROVINCIAL LEVEL

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ABSTRACT

In order to improve the health care service in poor rural western region of China, the Ministry of Health of the People's Republic of China and UNICEF had implemented "the Health Management Pilot County Project" in five provinces of western China. The purpose of this article is to evaluate the impacts of the project at provincial level. We collected data through two cross-sectional surveys in 1999, 2000, and used the analytic hierarchy process, the technique for order preference by similarity to ideal solution and linear weighting to analyze the data. The difference of the measurements between the two surveys was tested by paired-samples *t* test. All synthetic values of the five provinces in 2000 were higher than those in 1999 ($t = 6.62$, $P = 0.003$). The ranks of five provinces from highest to lowest were Xinjiang, Gansu, Qinghai, Ningxia and Guizhou. However, we also found disturbing facts that 10-20% of pregnant women had no prenatal care before child delivery. The project significantly improved the health service from shortly point of view, but there is still much to be done.

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INTRODUCTION

Mainland China consists of 31 provincial-level administrative regions under the central government of China, including 22 provinces, five autonomous regions, four municipalities. In general, urban areas are more developed than the rural areas. Villages in the eastern region are generally more developed than the villages in the western region. In rural China, administrative households are nested in villages, which are grouped to form townships, a cluster of townships are governed by a county, tens or even hundreds of counties/cities become a provincial region. The rural health service system of China includes county hospitals such as the main county hospital, maternal and child healthcare hospital, Chinese medicine hospital, township hospitals and village health clinics. We called it “three-tier health service network.” The western region of China is a less developed social and economic area with multi-ethnic culture and diverse geographic conditions, since socio-economic reforms commenced in 1980s, some health service-related issues emerged in this region. For example, most village clinics in the western poor region of China lacked of basic medical facilities [1, 2]. Some village clinics have even used “Three-no” drugs (possibly fake drugs out of the official distribution channel) [3, 4], intravenous injections of antibiotics were overused and the hormone was abused commonly [3-5]. Village doctors were unwilling to provide primary health care for the villagers due to no payment [6, 7].

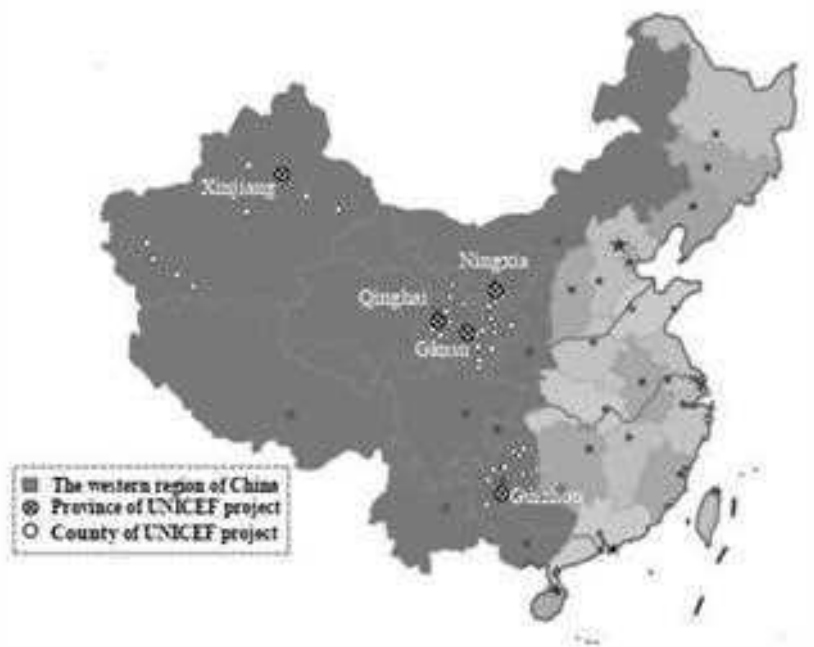


Figure 1. The western region of China and the UNICEF project provinces.

Maternal mortality ratio (MMR) in the western region of China was as high as 200 per 100,000 live births, which was four times the average urban MMR and two times the rural average MMR [8]. Infant mortality rates are nearly five times higher in the poorest rural counties than those in the wealthiest counties [9]. The growth and nutrition of children are in

worrying [9-15]. For children under 5 years of age, the percentages of child stunting and child underweight were 22.6% and 12.6% [15] respectively in rural areas, moreover in western region they were 24.0% and 22.1% [13].

In order to improve the health service especial health care of maternal and children in the poor rural western region of China, the Ministry of Health of the People's Republic of China (MOH) and the United Nations Children's Fund (UNICEF) implemented "the Health Management Pilot County Project" [16] in the forty poor counties of five provinces in the western region of China (Figure 1). In this article, we presented a provincial level analysis on data collected from the project. The counties level analysis was published by Bi, Lai and Yan [17].

OUR STUDY

Two cross-sectional surveys were conducted for the evaluation of the project. A stratified multistage random sampling was used to obtain subjects from each county [17]. The sample size was calculated based on the prevalence of anemia in children under the age of 36 months [17]. A 4-stage sampling design was adopted for the sample in three different strata (county, township and village) [17].

The design of the two surveys was developed by three steps [17]. The study protocol was reviewed and approved by the Human Research Ethics Committee of the Xi'an Jiaotong University College of Medicine. Ten survey teams were created for five provinces; the team's members consisted of the researchers from Xi'an Jiaotong University a prominent academic institute in west China and the staffs from local healthcare sectors. All questionnaires were filled in through face to face interviews by our professional interviewers trained by Xi'an Jiaotong University. We applied a set of quality control techniques during data collection and used double data entry and logical check procedures to input data [17], and employed EpiInfo to establish the database.

Data Analysis

The data in this study came from two surveys. First, in accordance with the objectives of project [16] and the four considerations: purpose, representative, objectivity and comparison [18-22], we selected twenty seven indicators from the questionnaires of the two surveys to evaluate synthetically the effects of the project. These indicators were classified into four aspects: health management, medical treatment condition, maternal health care and child health care [17]. Second, we calculated mean or median values for continuous variables and percentages for categorical variables for summary. Next step was the comprehensive evaluation and comparative analysis.

In the comprehensive evaluation, we used the Analytic Hierarchy Process (AHP) [17-19] to determine the weighting coefficients (W_j) of the four aspects, where j is for the four aspects, $j = 1$ to 4. Then we employed the Technique for Order Preference by Similarity to Ideal Solution (TOPSIS) [17, 20, 21] to compute the D_{ji} values of the four aspects of the difference year surveys ($y = 1999, 2000$) in five provinces ($i = 1$ to 5).

The comprehensive evaluation value was constructed as

$$E_{yi} = \sum_{j=1}^4 W_j \times D_{jyi} .$$

In comparative analysis, paired-samples *t* test was performed to compare the results of the difference of comprehensive evaluation value between two years, the Chi-square test was employed for each categorical indicator between 2000 and 1999. *P*-value < 0.05 was used as the threshold of indicating statistical significance for all tests in this study. SPSS was used for all data analysis and Microsoft Excel was used to draw figures.

FINDINGS

The household sample sizes in five provinces were from 1,083 (Qinghai, 14.7%) to 1,835 (Guizhou, 24.9%). Their household incomes were mainly from agriculture 81.2% (Guizhou) to 98.3% (Ningxia). Among the five provinces, Qinghai had the highest percentage of household drinking boiled water (97.2%) and Guizhou was reported with highest percentage (98.1%) of household using iodized salt for cooking. More detail percentages about each province on source of family income, drinking water, and salt are tabulated in Table 1. On average, mothers' illiteracy rates in each province were higher than fathers', the difference of the illiteracy rates between male and female in four provinces except Xinjiang was statistically significant by Chi-square test (*P* < 0.05). Both highest illiteracy rates were observed in Ningxia. More values and percentages about each province are presented in Table 2. The average birth weight in each province was about 3.13(kg) in Qinghai to 3.37(kg) in Guizhou; we observed that Gansu had highest children immunization record (95.4%); More information of children are presented in Table 3. Table 4 showed us that average percentage of children born at home were from 37.2% in Xinjiang to 82.7% in Qinghai, and Qinghai also had highest of percentage of family person, the relatives and the neighbor as midwives (40.1%). More than 63% of children's families chose the village health clinic for primary care except Xinjiang, there was 46.1% of children's families chose the their village health clinic and 33.9% of children's families chose the township hospital for primary care in Xinjiang (Table 5).

Table 1. General family information

Province	Sample		Source of family Incoming (%)		Drinking water (%)			Cooking salt (%)	
	n	%	Agriculture	others	Not boiled	Sometimes boiled	boiled	Iodine salt	others
Guizhou	1835	24.9	81.2	18.8	25.4	33.5	41.1	98.1	1.9
Gansu	1812	24.6	86.8	13.2	1.5	16.9	81.6	92.0	8.0
Ningxia	1137	15.4	98.3	1.7	2.1	31.8	66.1	56.6	43.4
Qinghai	1083	14.7	95.1	4.9	0.3	2.5	97.2	83.0	17.0
Xinjiang	1497	20.3	95.0	5.0	7.4	42.2	50.4	87.6	12.4

Table 2. Education of parents

Province	Mother (year)				Father (year)			
	mean	median	maximum	Illiteracy rate (%)	mean	median	maximum	Illiteracy rate (%)
Guizhou	3.91	4.00	14	29.5	6.55	7.00	17	5.2
Gansu	4.63	5.00	15	26.5	6.88	8.00	15	7.2
Ningxia	3.62	3.00	16	41.9	5.81	7.00	17	17.4
Qinghai	3.75	3.00	17	40.4	5.84	6.00	16	15.7
Xinjiang	6.27	5.00	16	3.0	6.77	7.00	16	2.0

Table 3. The information on children

Province	Birth weight(kg)		Sex (%)		Immunization records (%)	
	mean	median	male	female	yes	no
Guizhou	3.37	3.40	60.4	39.6	87.6	12.4
Gansu	3.20	3.05	62.1	37.9	95.4	4.6
Ningxia	3.27	3.25	54.6	45.4	83.3	16.7
Qinghai	3.13	3.00	53.0	47.0	93.9	6.1
Xinjiang	3.18	3.00	49.9	50.1	94.2	5.8

Table 4. The information on children's birth site and their midwives

Province	The birth site of children (%)*						Midwives (%) **					
	1	2	3	4	5	6	1	2	3	4	5	6
Guizhou	75.3	6.7	10.4	2.5	2.6	2.2	32.6	13.8	12.7	4.5	2.8	33.3
Gansu	64.9	3.1	16.9	3.9	9.4	1.8	27.5	9.3	19.1	10.2	10.2	23.7
Ningxia	70.9	0.9	6.4	9.3	12.1	0.3	39.4	7.9	10.5	9.7	12.2	20.1
Qinghai	82.7	1.7	1.9	2.5	11.2	0.0	39.5	0.8	2.4	4.3	13.0	40.1
Xinjiang	37.2	10.0	27.8	4.3	19.2	0.8	21.3	5.8	28.6	6.0	19.5	18.8

Table 5. The initial treatment site for childhood illness (%)

Province	Clinic in the same village	Clinic in neighboring village	Township hospital	Hospital of county or above	Maternal and child health center of county or above	Others
Guizhou	69.8	11.5	7.9	1.4	0.5	8.8
Gansu	68.0	9.3	14.1	4.1	0.7	3.8
Ningxia	63.8	5.5	19.4	3.5	0.6	7.2
Qinghai	68.5	17.6	3.4	7.6	1.8	1.2
Xinjiang	46.1	10.6	33.9	2.4	0.9	5.8

The sample proportions of village health clinics in five provinces were from 16.1% to 24.3%. The average distance between villages and the township's administrative center was from 4.28(km) (Qinhai) to 7.06 km (Xinjiang). The average population size of a village in the end of 1998 was 1044.18(Xinjiang) to 1723.25 (Guizhou). The average yearly income per person in 1998 was ¥664.44 (about \$95, Qinhai) to 1432.31 (about \$205, Xinjiang). The villages in the sample were from poor regions. The average number of doctors per village health clinic was less than two and the age of the chief doctor of village health clinic was over 38 years old (38.55 to 44.78). More detail information about each province is tabulated in Table 6. We noticed from Table 7 that over 60% doctors' education level was secondary school or less, only 2.3% of doctors' education level in Xinjiang graduated from colleges or above, no doctors graduated from colleges and above in Guizhou and Gansu. 88.6% of village

doctors in Qinghai were “barefoot doctor,” the lowest percentage in Guizhou was 29.5%. The highest percentage (3.4%) of professional training at college level or above of doctors was in Xinjiang.

Table 6. The information of village

Province	Sample		Distance between village and township (km)		Population of village in 1998		Incoming per person in 1998 (¥)		Number of village doctors		Age of village doctor(year)	
	n	%	Mean	Median	Mean	Median	Mean	Median	Mean	Median	Mean	Median
Guizhou	105	23.8	6.89	5.00	1723.25	1628.00	747.36	700.00	1.81	2.00	38.63	40.00
Gansu	107	24.3	6.08	5.00	1661.01	1350.00	853.89	810.00	1.85	2.00	44.71	46.00
Ningxia	72	16.3	5.14	4.00	1583.26	1356.00	1073.50	602.00	1.25	1.00	44.78	47.00
Qinghai	71	16.1	4.28	3.00	1044.46	1085.00	664.44	589.00	1.17	1.00	43.87	46.50
Xinjiang	86	19.5	7.06	4.00	1299.18	1117.00	1423.31	935.00	1.62	1.00	38.55	40.00

Table 7. Education and professional training of village doctors

Province	Education					Professional Training			
	Less than primary school	primary school	Secondary school	High school	College and above	“barefoot doctor”	County	medical school	Medical college and above
Guizhou	1.9	11.4	48.6	38.1	0.0	29.5	38.4	29.5	2.7
Gansu	4.7	11.2	43.9	40.2	0.0	37.2	51.3	9.7	1.8
Ningxia	5.6	22.2	50.0	20.8	1.4	62.7	17.9	16.4	3.0
Qinghai	1.4	11.3	53.5	32.4	1.4	88.6	2.9	7.1	1.4
Xinjiang	1.2	8.1	51.2	37.2	2.3	69.3	12.5	14.8	3.4

Table 8. The results of evaluation of counties

Province	D values								E values		$E_{2000} - E_{1999}$
	Health management		Medical treatment condition		Maternal health care		Child health care				
	1999	2000	1999	2000	1999	2000	1999	2000	1999	2000	
Guizhou	0.291	0.419	0.531	0.441	0.073	0.300	0.372	0.662	0.379	0.443	0.064
Gansu	0.345	0.323	0.294	0.547	0.345	0.589	0.381	0.470	0.327	0.473	0.146
Ningxia	0.406	0.333	0.195	0.395	0.303	0.485	0.191	0.312	0.273	0.376	0.103
Qinghai	0.329	0.651	0.324	0.293	0.062	0.277	0.436	0.508	0.307	0.429	0.122
Xinjiang	0.285	0.573	0.591	0.727	0.887	0.912	0.657	0.805	0.540	0.711	0.171

Comprehensive Evaluation

Using AHP, we computed the weighting coefficients of the four aspects, they were 0.311 0.440, 0.124 and 0.124, respectively. According to data of two surveys, we used the TOPSIS to calculate the *D* values of the four aspects of five provinces, we calculated the synthetic indicator of *E* via linear weighting, and the all values are listed in Table 8. The results showed that all *E* values in 2000 were higher than those in 1999. The difference of comprehensive values *E* between these two years was statistically significant ($t = 6.62$, $P = 0.003$) by paired *t* test. However, we found that not all of *D* values of the four aspects in five provinces in 2000 were higher than those in 1999; the provinces with higher *D* values in 2000 were Guizhou, Qinghai and Xingjian in health management; Gansu, Ningxia and Xingjian in medical treatment condition; all in maternal health care and in child health care.

The results of comparative analysis of the indicators of four aspects in two surveys were tabulated in the Table 9 to the Table 12. The differences of some indicators of four aspects were exhibited in the Figure 2 to Figure 5. The bars in all figures illustrated by the differences calculated from the values of indicators in 2000 minus the values in 1999. The symbols “*” in each figure denoted the differences of the indicators were statistically significant Chi-square test ($P < 0.05$).

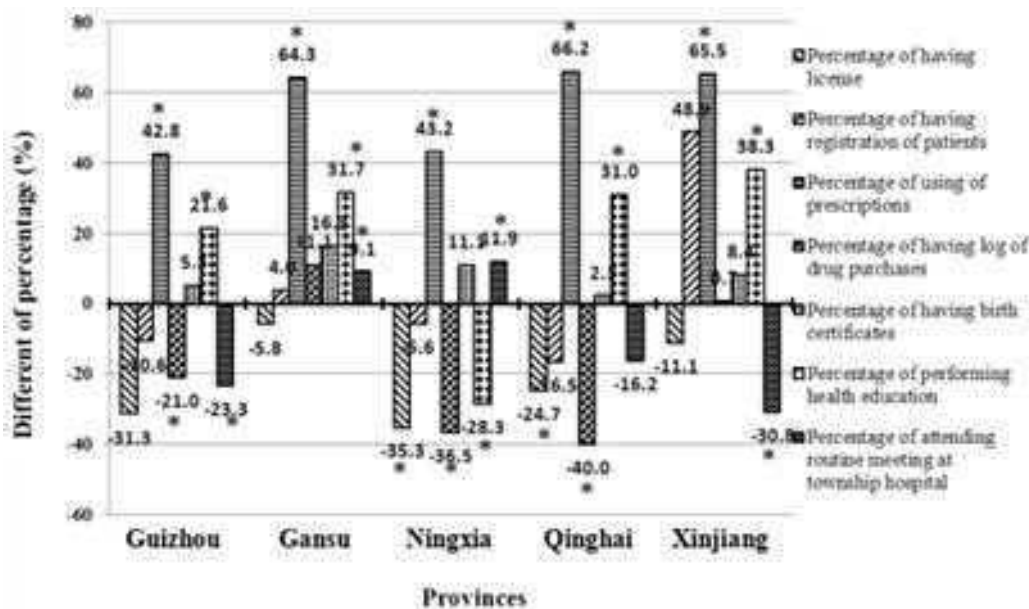


Figure 2. The differences of indicators of health management in 5 provinces.

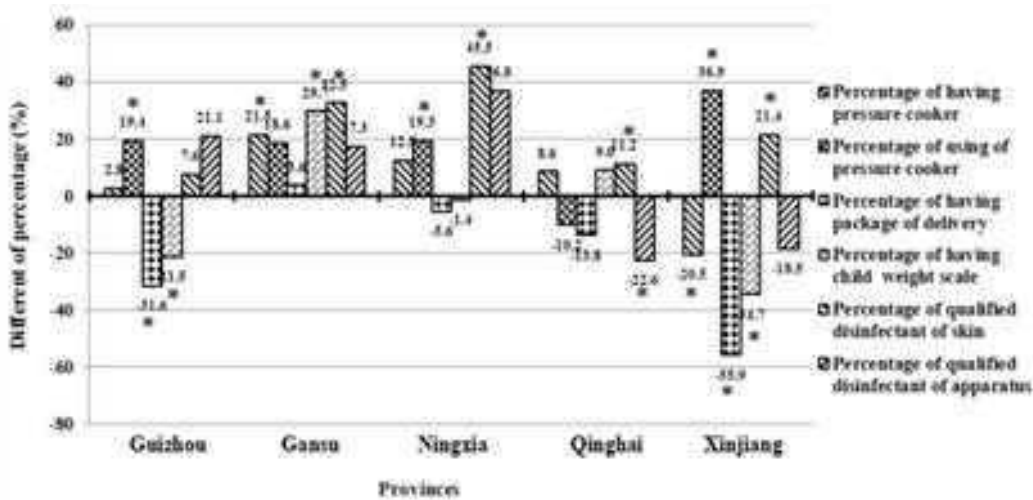


Figure 3. The differences of indicators of medical treatment condition in 5 provinces.

Table 9. Indicators of health management in five provinces in two years

Indicators	Guizhou		Gansu		Ningxia		Qinghai		Xinjiang	
	1999	2000	1999	2000	1999	2000	1999	2000	1999	2000
Percentage of having license (%)	80.39	49.07	96.26	90.43	91.67	56.34	98.60	73.91	55.95	44.83
Percentage of having registration of patients (%)	69.52	58.95	64.49	68.47	38.89	33.33	87.14	70.69	40.00	88.89
Percentage of using of prescriptions (%)	39.42	82.18	30.48	94.74	47.22	90.38	30.43	96.61	32.94	98.48
Percentage of having log of drug purchases (%)	57.14	36.11	41.51	52.63	79.17	42.65	94.37	54.41	36.05	36.76
Percentage of having birth certificates (%)	83.81	89.09	62.26	78.57	77.78	88.89	80.28	82.61	90.48	98.88
Percentage of performing health education (%)	48.08	69.64	40.00	71.68	47.76	19.44	38.57	69.57	58.33	96.63
Percentage of attending routine meeting at township hospital (%)	72.38	49.07	81.31	90.43	44.44	56.34	90.14	73.91	75.58	44.83
The total of charge in thirty prescriptions(yuan)	7572.61	8032.34	5966.7	17480.16	6711.68	6606.44	12867.59	6206.5	9371.13	5558.34
The count of antibiotics in thirty prescriptions	929	1909	545	2164	409	931	1032	925	585	776
The count of hormone drugs in thirty prescriptions	302	102	156	167	151	87	327	14	112	22
The count of intravenous injection in thirty prescriptions	125	51	131	283	106	87	214	95	183	113

Table 10. Indicators of medical treatment condition in five provinces in two years

Indicators (%)	Guizhou		Gansu		Ningxia		Qinghai		Xinjiang	
	1999	2000	1999	2000	1999	2000	1999	2000	1999	2000
Percentage of having pressure cooker	65.71	68.47	68.87	90.35	70.83	83.33	46.48	55.07	75.58	55.07
Percentage of using of pressure cooker	66.18	85.53	51.35	69.90	49.02	68.33	93.94	83.78	46.88	83.78
Percentage of having package of delivery	75.24	43.64	42.45	46.09	27.78	22.22	25.35	11.59	67.44	11.59
Percentage of having child weight scale	32.38	10.91	9.43	39.13	23.61	22.22	9.86	18.84	53.49	18.84
Percentage of qualified disinfectant of skin	77.88	85.45	49.04	81.58	31.94	77.46	71.43	82.61	61.18	82.61
Percentage of qualified disinfectant of apparatus	43.81	64.86	35.85	53.10	15.28	52.11	42.86	20.29	38.82	20.29

Table 11. Indicators of maternal health care in five provinces in two years

Indicators (%)	Guizhou		Gansu		Ningxia		Qinghai		Xinjiang	
	1999	2000	1999	2000	1999	2000	1999	2000	1999	2000
Percentage of prenatal care	57.47	72.60	79.56	89.56	72.25	74.21	64.54	72.47	90.65	91.22
Percentage of hospital birth	15.48	21.00	30.19	39.40	27.79	35.71	15.60	27.22	51.17	56.75
Percentage of postnatal visit	53.01	70.64	47.98	64.28	55.28	63.90	46.30	50.94	84.41	76.27

Table 12. Indicators of child health care in five provinces in two years

Indicators	Guizhou		Gansu		Ningxia		Qinghai		Xinjiang	
	1999	2000	1999	2000	1999	2000	1999	2000	1999	2000
Percentage of breast-feeding (%)	97.49	97.05	96.02	94.84	98.42	97.83	93.8	97.19	98.06	94.73
Score of adding grain food	0.64	0.66	0.63	0.63	0.64	0.65	0.59	0.59	0.62	0.64
Score of adding protein food	0.42	0.55	0.37	0.44	0.33	0.42	0.38	0.45	0.44	0.51
Score of adding vegetable food	0.65	0.72	0.58	0.61	0.58	0.6	0.61	0.63	0.65	0.66
Prevalence of common cold in two weeks (%)	38.71	34.26	34.22	35.04	45.91	43.78	28.24	31.81	17.11	18.96
Prevalence of diarrhea in two weeks (%)	28.07	26.59	17.55	24.40	27.00	33.87	15.88	21.09	20.11	22.71

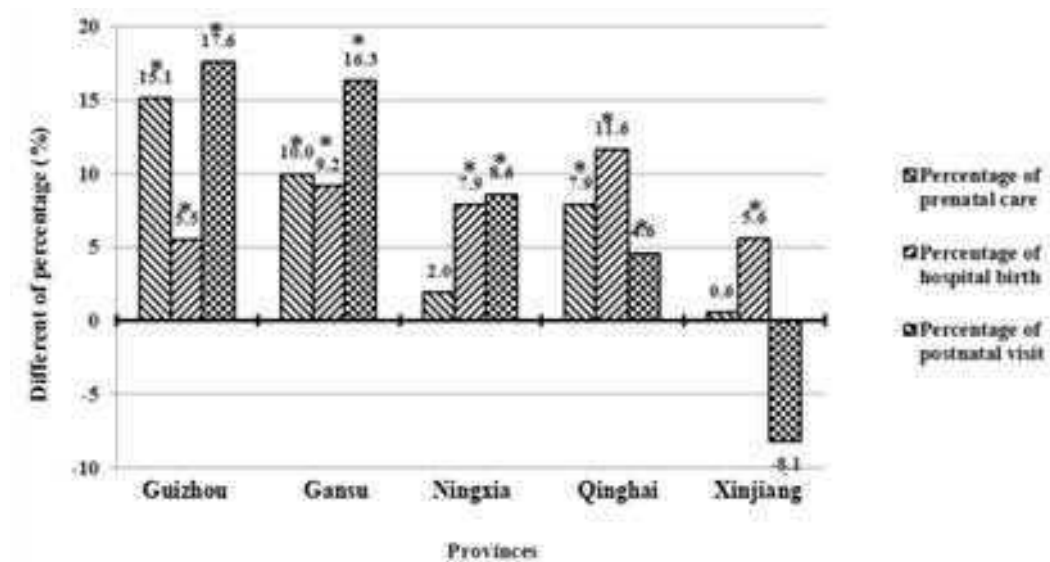


Figure 4. The differences of indicators of maternal health care in 5 provinces.

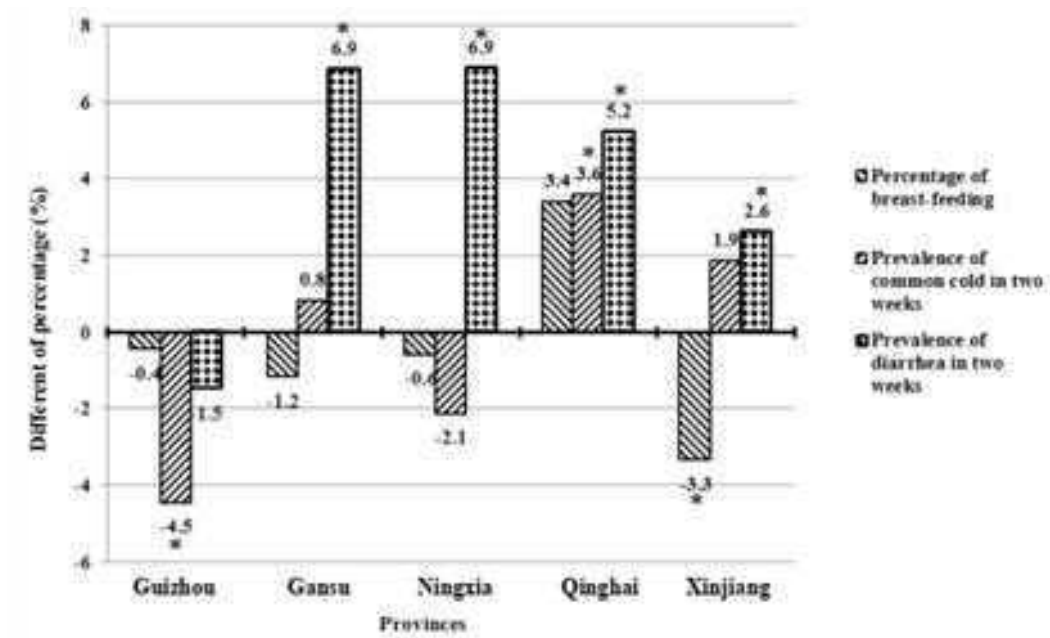


Figure 5. The differences of indicators of child health care in 5 provinces.

DISCUSSION

In this article, we use a hybrid procedure of AHP, TOPSIS, linear weighting to evaluate synthetically the interventional effects of the health promotion project by provinces. One of the major findings from this study is that the *E* values of comprehensive evaluation in 2000 were significantly higher than that in 1999 in each of those five provinces (see Table 5). This

result indicated that the interventional measures of the project in the five provinces in China were effective. Furthermore, we can see the change from the differences of two-year measurement of *E*. the rank of five provinces from highest to lowest were Xinjiang, Gansu Qinghai, Ningxia and Guizhou. This not only shows us the promotion effects of the project but also revealed the quality of conducting the project. Comparing the *D* values in 1999 and 2000, we found that maternal health care and child health care in five provinces had been improved, but health management only in Guizhou, Qinghai and Xinjiang had been improved, medical treatment conditions only in Gansu, Ningxia and Xinjiang have been improved. The experiences of the project provided valuable information to help us to form governmental policies on health service promotion in poor rural western region of China. The promotion measures of the project also can be used by other provinces to find an effective health promotion approaches in China. However, our study also found that some disturbing and conflicting results by comparison of the indicators of four aspects in two surveys (see Tables 9-12 and Figures 2-5).

The figures showed us the changes of four aspects in five provinces before and after promotion, the bars over the X-axis in the figures showed the differences between these two years were positive, the promotion had improved the indicators of each province. Otherwise, the promotion had no effect. We can find clearly identify the issues of these four aspects in five provinces, and lead to a better understand the future improvement. Special attention should be paid to the indicators with negative values (below the X-axis).

Figure 2 shows, among the seven indicators of health management, Guizhou, Ningxia and Qinghai had four indicators under the X-axis, namely No.1, 2, 4 and 7, these four indicators. Gansu and Xinjiang was only one indicator, that is 1 and 7 respectively. In fact, it is not difficult to make improvement with strong leadership. From our experience, as long as we assigned the responsibility to the people with proper management, we should be able to have significant improvement for similar projects in the future.

Figure 3 explicit the five indicators of the medical conditions, Xinjiang, Qinghai, Guizhou, and Ningxia had 4, 3, 2 and 2 indicators respectively below the X-axis. A common issue in the five provinces was the lack of child weight scales. Without weight scale, village doctors cannot measure the weight of children and evaluate their growth. How to raise funds to purchase basic health care equipment is a top priority, it is a challenge for developing western five provinces.

Another issue was the disinfection and sterilization, especially Qinghai and Xinjiang. This two provinces need to pay more attention on the disinfectant of skin and apparatus. If disinfection and sterilization of medical devices do not work properly, medical treatment will lead to cross infection and spread disease, especially in the area with high incidence of hepatitis.

It should be noted that in order to increase percentage of hospital delivery, one of the measures of project was to reclaim package of delivery from the village doctors, so the percentage of having package of delivery should be decline. But Gansu is the only province with percentage increasing.

Figure 4 depicted the changes of difference of three indicators in maternal health care, only the Xinjiang had a negative difference of percentage of postnatal visit. Other indicators of 5 provinces had increase at different level. Table 11 showed there were 10-20% of pregnant women had no prenatal care before child delivery. Hospital births in 5 provinces had

increased significantly, but highest one was only 56.75% in Xinjiang. There is more work to do next for increase percentage of hospital birth.

Figure 5 described the three indicators of child health care. Although the percentages of breast-feeding had kind of decrease, we are pleased to see that they were still up to or above 94% (see Table 12). A common problem was children diarrhea in five provinces. Therefore, we should focus on the prevention of children diarrhea for further health education to reduce risk factors of diarrhea in children.

CONCLUSION

In summary, although our study has some limitations, data were collected through surveys and therefore subjected to biases in recall, There is no doubt that the comprehensive evaluation results of the projects in this study will play an active role in helping us understand the success experience of the project, and find the problems and defects in the process of project implementation. Provincial health administrative departments are the highest level of local administrative units; they played a major role in the supervision and management of the project and play a direct impact on effect of projects. This study can provide valuable reference for the five provinces to carrying out the project more effectively in future. It will also provide valuable reference for other provinces to implement similar project. Since the re-introduction of Chinese rural health care system at the village level in 1985, many progresses have been achieved. A recent review on the development of village doctors in China is given in [22] with an emphasize on health care finance.

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Chapter 318

MATERIALISM IN CHINESE ADOLESCENTS IN HONG KONG: PROFILES AND SOCIO-DEMOGRAPHIC CORRELATES

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ABSTRACT

Although youth development models suggest that materialistic beliefs have a negative impact on adolescent development, empirical studies in this area are scarce. Based on a sample of 2,474 high school students in Hong Kong, this study examined the profiles of materialism and socio-demographic correlates of adolescent materialism. Results showed that more than a quarter of the respondents agreed that earning money is more important than other things. Significant proportions of the respondents also agreed that adolescents in Hong Kong were materialistic. However, the respondents perceived themselves to be less materialistic as compared to adolescents in Hong Kong. Regarding socio-demographic correlates of materialism in adolescents, correlation and regression analyses showed that age, gender, parental education, and family intactness were associated with adolescent materialism. Multiple regression analyses further showed that age, gender, and family intactness were significant predictors of adolescent materialism.

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INTRODUCTION

The quest for material possession is a feature of the contemporary world with several contributing factors. First, under Capitalism, there is a basic emphasis on material possession. Without material possession, the economy will shrink. In order to push up the GDP, people are persuaded and encouraged to buy commodities which essentially leads to the development of the “consumption” culture. Second, with technological advances, there are many new products such as smartphones, personal computers, and fancy electronic devices. Through aggressive marketing strategies, group pressure, and actual needs, possession of such devices is regarded as trendy and a symbol of identity. Hence, many people, particularly young people “chase” after such new products. Third, with the global issue of poverty (i.e., lack of material possession), people tend to develop the mentality that it is better to have more material possession which can give them a sense of security.

How might materialistic mentality influence adolescent development? In different cultures, over-emphasis on materialism has been regarded as problematic for human development. For example, in the Christian and Catholic traditions, spiritual values are upheld while material values are downplayed. With specific reference to the Chinese culture, materialism is also deemphasized in different social philosophies. In Confucianism, focus is placed on non-material virtues than material possession. In Buddhism, material possession is regarded as illusory and the focus is on transcendence of sensory and material urges. In Taoism, the focus is on harmony and non-material experience such as meditation and harmony with nature.

In different youth developmental models [1], there is also an emphasis on the importance of spiritual values. In the model proposed by the Search Institute, there is an emphasis on positive values which are not materialistic in nature. In particular, the value of “restraint” is the contrary of sensory pleasure and material consumption. In the 5C and 6C models [2, 3], character, compassion, and care are developmental ideals which are non-materialistic in nature. In the positive youth development constructs proposed by Catalano et al. [4], spirituality is a PYD construct which can promote the positive development of young people. This construct is in line with the existential approach which focuses on the importance of life meaning and transcendental development in human development. In the “being” approach, spirituality and character are closely related to the process of thriving which represents the healthy and holistic development of adolescents [5, 6].

According to Huta and Ryan [7], there are two motives underlying human happiness. On the one hand, happiness is determined by hedonic motives where a person seeks instant pleasure and comfort through different means, such as physical activities (e.g., shopping and drinking). On the other hand, happiness can be brought forth by eudaimonic motives where happiness is determined by one’s intention to achieve development, excellence, authenticity, and meaning [8, 9, 10, 11]. Based on this framework, materialism can be regarded as hedonic motive which leads to short term happiness only. Similarly, Peterson and colleagues [12] also differentiated hedonic orientation (i.e., life pleasure) from eudaimonic orientation which includes life of engagement and life of meaning. Again, hedonic motives basically underlie materialistic values and behavior.

Materialism is a hallmark of Capitalism. With particular reference to Hong Kong, it is a melting pot of Western influences and traditional Chinese values. Historically, Hong Kong

has also served as an international financial center focusing on business, finance, and trade. Under the Basic Law, the Capitalistic system would continue for 50 years since the handover in 1997. With this backdrop, Shek and Siu [13] argued that materialism is a risk factor for adolescent development in Hong Kong. Developmentally, over-emphasis on materialism would lead to non-holistic development and selective focus on instrumental or utilitarian values.

Although adolescent materialism is an important developmental issue, there are relatively few studies in this area, particularly in the Chinese context [14]. One notable exception is the work by Shek, Ma, and Lin [15] who developed the 21-item Chinese Adolescent Materialism Scale based on the data collected from 1,658 Chinese high school students. Confirmatory factor analyses finally suggest a three-factor model with 19 items (e.g., “unless I can make a lot of money, I won’t respect myself”; “the most important objective in a woman’s life is to marry a rich man”; “possession of money can make people happy”; “no money, no dignity”) underlying three dimensions (including “acquisition centrality,” “materialistic possessions,” and “hedonistic pursuit”). Using five items derived from the Chinese Adolescent Materialism Scale, Shek and Lin [16] examined adolescent development in different domains, including materialism, egocentrism, character strengths, and moral development. The present paper is based on the data collected by this scale.

To understand character and moral development in Chinese high school students in Hong Kong, a series of studies have been conducted by a team of researchers at The Hong Kong Polytechnic University [16-20]. This paper utilized the data collected in the study of Shek and Lin [16]. There are several research objectives in this paper. First, it attempted to examine the materialistic beliefs in Chinese high school students in Hong Kong. Besides perceived materialistic beliefs in high school students, their perception of the materialistic beliefs in Hong Kong adolescents in general was also explored. Second, we compared high school students’ perceptions of their own materialistic attitudes and those of Hong Kong adolescents in general. In the social psychology literature, there are research studies showing that one tends to see oneself as more positive than other people [21]. Hence, we examined this hypothesis in the present study. Finally, as there are few studies examining psychosocial correlates of materialism, we examined how materialistic beliefs in adolescents are related to age, gender, family intactness, and economic disadvantage in Chinese high school students in Hong Kong.

OUR STUDY

The data for the present study were derived from a large-scale study examining their character traits, psychosocial competencies, social behavior, family life, and school life of Chinese high school students in Hong Kong [16]. A total of 20 local secondary schools participated in the study, with seven schools admitting students with high academic performance (i.e., Band 1 schools), nine schools admitting students with average academic performance (i.e., Band 2 schools) and six schools admitting students with low academic performance (i.e., Band 3 schools). According to the school size, three to five classes of students were randomly selected to join the study. We recruited 2,474 students (Mean age = 14.76, SD = 1.82; 1,271 females and 1,123 males) in this study, with 1,336 junior high school

students and 906 senior high school students. Regarding the economic background of the participants, 239 students were on welfare, who could be regarded as experiencing economic disadvantage.

We obtained consent from the school, parents, and students before collecting the data. During data collection, students were requested to complete a questionnaire containing measures of character attributes, psychosocial competencies, social behavior, family life, and school life. Adequate time was provided to the students. A trained research assistant was present throughout the questionnaire administration process.

Instruments

The abridged version of the Chinese Adolescent Materialism Scale [15] was employed in this study to assess the materialistic beliefs of the respondents. Based on theories and research studies on materialism, 21 items assessing adolescent materialism were designed which showed adequate reliability and validity. In this study, five items from the different dimensions of the scale were employed to assess materialistic beliefs in the respondents. These items included: a) “making money is more important than any other things”; b) “I believe that money is everything”; c) “the rich can get respect from others”; d) “I would abandon some principles for the sake of money”; and e) “the amount of money one makes is a fundamental indicator of one’s success”. A 5-point Likert scale was used, with the response options of “strongly disagree = 1”, “disagree = 2”, “neither agree nor disagree = 3,” “agree = 4,” and “strongly agree = 5.”

To assess the respondents’ perceptions of materialism in adolescents in Hong Kong, these five items were used to capture the related views. The items included: a) “Hong Kong adolescents think that making money is more important than any other things”; b) “Hong Kong adolescents believe that money is everything”; c) “Hong Kong adolescents think that the rich can get respect from others”; d) “Hong Kong adolescents would abandon some principles for the sake of money”; and e) “Hong Kong adolescents believe that the amount of money one makes is a fundamental indicator of one’s success”. Five response options were used, including “strongly disagree = 1,” “disagree = 2,” “neither agree nor disagree = 3,” “agree = 4,” and “strongly agree = 5.”

Data Analyses

We used Statistical Package for Social Sciences Version 25 (IBM Corp., Somers, NY, USA) to carry out to answer the questions of the study. First, descriptive statistical analyses based on percentages were performed to understand the responses of the participants to the abridged version of the Chinese Adolescent Materialism Scale. Besides, perceptions of the respondents regarding materialistic beliefs amongst adolescents in Hong Kong in general were examined. Second, respondents’ views of their own materialistic attitudes and perceptions of the materialistic attitudes of Hong Kong adolescents in general would be compared using matched-sample ANOVAs. For the socio-demographic correlates, Pearson correlation analysis, linear regression, and multiple regression analyses were performed.

FINDINGS

For the first research objective, we conducted descriptive statistical analyses to understand the profiles of materialistic beliefs amongst the respondents via percentage responses. In Table 1 to Table 3, the responses of the students to the items in the 5-item abridged scale in the total, junior form, and senior form samples are presented. There are two observations. First, roughly one-third of the respondents believed that earning money is more important than other things. Second, compared to junior high school students, senior high school students held higher levels of materialistic beliefs than did junior high school students. In Table 4 to Table 6, the respondents' perceptions of the materialistic beliefs in general Hong Kong youth population are outlined. Two observations can be highlighted from the findings. First, high proportions of high school students perceived that adolescents in Hong Kong were materialistic. Second, more senior high school students perceived that young people in Hong Kong were materialistic.

To understand whether there were differences between respondents' perception of their materialistic beliefs and those of general adolescents in Hong Kong, several ANOVAs were carried out (Table 7). Results showed that there were statistically significant differences between perceived materialism in the respondents and perceived materialism in Hong Kong adolescents on materialism, $F(5,4887) = 362.900$, $p < .001$, partial eta squared = 0.27. For univariate effects (ANOVA), results similarly showed statistically significant differences between the two perceptions in the scores of each item ($p < 0.001$) and of the composite score ($p < 0.001$). In short, the respondents saw themselves as less materialistic than did Hong Kong adolescents in general.

Table 8 shows the correlations among different variables. While materialistic beliefs in the students were positively correlated with age and family intactness, the related scores were negatively correlated with gender, father education and mother education. However, there was no correlation between student materialism and economic disadvantage. Linear regression analyses were conducted for each predictor separately. As shown in Table 9, except for economic disadvantage, all other variables (age, gender, father education, mother education, and family intactness) significantly predicted student materialism. In short, male students showed higher scores than did female students. Both higher paternal education and higher maternal education predicted lower materialism scores of students. Students from non-intact families (i.e., non-first marriage families) were more materialistic than students from intact families (i.e., first marriage families).

To understand the relative contribution of different predictors to materialistic belief scores, multiple regression analysis was further conducted to predict student materialism from student age, gender, father education, mother education, family intactness, and economic disadvantage (Table 10). Results showed that after controlling other variables, student materialism was positively predicted by age and family intactness and negatively predicted by gender. In other words, older students tended to have higher materialism than did younger students. Male students had higher materialism than did female students. Students from non-intact family had higher materialism than did students from intact family. There was no predicting effect of father and mother education and economic disadvantage on student materialism, when controlling other variables.

Table 1. Perception of materialistic beliefs in the respondents (total sample)

Items	1	2	1+2	3	4	5	4+5	Mean	n
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)		
Making money is more important than any other things.	187 (7.6%)	610 (24.7%)	797 (32.3%)	934 (37.8%)	623 (25.2%)	118 (4.8%)	741 (30.0%)	2.95	2472
I believe that “money is everything”.	587 (23.7%)	857 (34.7%)	1444 (58.4%)	590 (23.9%)	362 (14.6%)	76 (3.1%)	438 (17.7%)	2.39	2472
No money, no dignity.	546 (22.2%)	782 (31.8%)	1328 (54.0%)	664 (27.0%)	383 (15.6%)	86 (3.5%)	469 (19.1%)	2.46	2461
I would abandon some principles for the sake of money.	1298 (52.8%)	729 (29.6%)	2027 (82.4%)	288 (11.7%)	101 (4.1%)	43 (1.7%)	144 (5.8%)	1.72	2459
The amount of money one makes is a fundamental indicator of one’s “success”.	724 (29.3%)	833 (33.8%)	1557 (63.1%)	557 (22.6%)	285 (11.5%)	69 (2.8%)	354 (14.3%)	2.25	2468

Note. 1 = strongly disagree, 2 = disagree, 3 = neither agree nor disagree, 4 = agree, and 5 = strongly agree.

Table 2. Perception of materialistic beliefs in the respondents (junior high school students sample)

Items	1	2	1+2	3	4	5	4+5	Mean	n
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)		
Making money is more important than any other things.	117 (7.9%)	384 (25.9%)	501 (33.7%)	577 (38.9%)	344 (23.2%)	63 (4.2%)	407 (27.4%)	2.90	1485
I believe that “money is everything”.	395 (26.6%)	519 (34.9%)	914 (61.5%)	363 (24.4%)	178 (12.0%)	31 (2.1%)	209 (14.9%)	2.28	1486
No money, no dignity.	387 (26.1%)	500 (33.7%)	887 (59.8%)	364 (24.5 %)	195 (13.1%)	37 (2.5%)	232 (15.6%)	2.32	1483
I would abandon some principles for the sake of money.	856 (57.9%)	404 (27.3%)	1260 (85.3%)	152 (10.3%)	43 (2.9%)	23 (1.6%)	66 (4.5%)	1.63	1478
The amount of money one makes is a fundamental indicator of one’s “success.”	497 (33.6%)	505 (34.1%)	1002 (67.7%)	312 (21.1%)	131 (8.8%)	36 (2.4%)	167 (11.3%)	2.12	1481

Note. 1 = strongly disagree, 2 = disagree, 3 = neither agree nor disagree, 4 = agree, and 5 = strongly agree.

Table 3. Perception of materialistic beliefs in the respondents (senior high school students sample)

Items	1	2	1+2	3	4	5	4+5	Mean	n
	n	n	n	n	n	n	n		
	(%)	(%)	(%)	(%)	(%)	(%)	(%)		
Making money is more important than any other things.	70 (7.1%)	226 (22.9%)	296 (30.0%)	357 (36.2%)	279 (28.3%)	55 (5.6%)	334 (33.8%)	3.02	987
I believe that “money is everything.”	192 (19.5%)	338 (34.3%)	530 (53.8%)	227 (23.0%)	184 (18.7%)	45 (4.6%)	229 (23.2%)	2.55	986
No money, no dignity.	159 (16.3%)	282 (28.8%)	441 (45.1%)	300 (30.7%)	188 (19.2%)	49 (5.0%)	237 (24.2%)	2.68	978
I would abandon some principles for the sake of money.	442 (45.1%)	325 (33.1%)	767 (78.2%)	136 (13.9)	58 (5.9%)	20 (2.0%)	78 (8.0%)	1.87	981
The amount of money one makes is a fundamental indicator of one’s “success.”	227 (23.0%)	328 (33.2%)	555 (56.2%)	245 (24.8%)	154 (15.6%)	33 (3.3%)	187 (18.9%)	2.43	987

Note. 1 = strongly disagree, 2 = disagree, 3 = neither agree nor disagree, 4 = agree, and 5 = strongly agree.

Table 4. Perception of materialistic beliefs in Hong Kong adolescents (total sample)

Items	1	2	1+2	3	4	5	4+5	Mean	n
	n	n	n	n	n	n	n		
	(%)	(%)	(%)	(%)	(%)	(%)	(%)		
Adolescents in HK believe making money is more important than any other things.	109 (4.4%)	456 (18.5%)	565 (22.9%)	792 (32.1%)	914 (37.0%)	199 (8.1%)	1113 (45.1%)	3.26	2470
Adolescents in HK believe “Money is everything.”	152 (6.2%)	479 (19.4%)	631 (25.6%)	748 (30.3%)	864 (35.0%)	225 (9.1%)	1089 (44.1%)	3.22	2468
Adolescents in HK believe “No money, no dignity.”	177 (7.2%)	434 (17.6%)	611 (24.8%)	736 (29.9%)	880 (35.7%)	237 (9.6%)	1117 (45.3%)	3.23	2464
Adolescents in HK believe they would abandon some principles for the sake of money.	332 (13.5%)	566 (23.0%)	898 (36.5%)	756 (30.7%)	645 (26.2%)	166 (6.7%)	811 (32.9%)	2.90	2465
Adolescents in HK believe “The amount of money one makes is a fundamental indicator of one’s “success.”	193 (7.8%)	486 (19.7%)	679 (27.5%)	715 (29.0%)	798 (32.3%)	275 (11.1%)	1073 (43.4%)	3.19	2467

Note. 1 = strongly disagree, 2 = disagree, 3 = neither agree nor disagree, 4 = agree, and 5 = strongly agree.

Table 5. Perception of materialistic beliefs in Hong Kong adolescents (junior high school students sample)

Items	1	2	1+2	3	4	5	4+5	Mean	n
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)		
Adolescents in HK believe making money is more important than any other things.	78 (5.3%)	291 (19.6%)	369 (24.9%)	485 (32.7%)	519 (35.0%)	111 (7.5%)	630 (42.5%)	3.20	1484
Adolescents in HK believe “Money is everything.”	109 (7.4%)	317 (21.4%)	426 (28.8%)	442 (29.8%)	490 (33.1%)	123 (8.3%)	613 (41.4%)	3.14	1481
Adolescents in HK believe “No money, no dignity.”	128 (8.6%)	288 (19.4)	416 (28.1%)	441 (29.8%)	490 (33.1)	134 (9.0%)	624 (42.1%)	3.14	1481
Adolescents in HK believe they would abandon some principles for the sake of money.	235 (15.9%)	352 (23.8%)	587 (39.7%)	443 (29.9%)	351 (23.7%)	99 (6.7%)	450 (30.4%)	2.82	1480
Adolescents in HK believe “The amount of money one makes is a fundamental indicator of one’s “success.”	146 (9.9%)	320 (21.6%)	466 (31.5%)	422 (28.5%)	455 (30.7%)	137 (9.3%)	592 (40.0%)	3.08	1480

Note. 1 = strongly disagree, 2 = disagree, 3 = neither agree nor disagree, 4 = agree, and 5 = strongly agree.

Table 6. Adolescents’ perception of the materialism of their peers in Hong Kong (senior grades)

Items	1	2	1+2	3	4	5	4+5	Mean	n
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)		
Adolescents in HK believe making money is more important than any other things.	31 (3.1%)	165 (16.7%)	196 (19.9%)	307 (31.1%)	395 (40.1%)	88 (8.9%)	483 (49.0%)	3.35	986
Adolescents in HK believe “Money is everything.”	43 (4.4%)	162 (16.4%)	205 (20.8%)	306 (31.0%)	374 (37.9%)	102 (10.3%)	476 (48.2%)	3.33	987
Adolescents in HK believe “No money, no dignity.”	49 (5.0%)	146 (14.9%)	195 (19.8%)	295 (30.0%)	390 (39.7%)	103 (10.5%)	493 (50.2%)	3.36	983
Adolescents in HK believe they would abandon some principles for the sake of money.	97 (9.8%)	214 (21.7%)	311 (31.6%)	313 (31.8%)	294 (29.8%)	67 (6.8%)	361 (36.6%)	3.02	985
Adolescents in HK believe “The amount of money one makes is a fundamental indicator of one’s “success.”	47 (4.8%)	166 (16.8%)	213 (21.6%)	293 (29.7%)	343 (34.8%)	138 (14.0%)	481 (48.7%)	3.36	987

Note. 1 = strongly disagree, 2 = disagree, 3 = neither agree nor disagree, 4 = agree, and 5 = strongly agree.

Table 7. Differences in items and composite scores of materialism between students and HK adolescents (N = 2,441 for students, N = 2,452 for Hong Kong adolescents)

	Students	HK Adolescents	<i>F</i>	partial η^2
	<i>M (SD)</i>	<i>M (SD)</i>	362.900*** [^]	0.27
Making money is more important than any other things	2.95(1.00)	3.26(0.99)	118.798***	0.024
I believe that “money is everything.”	2.39(1.09)	3.22(1.05)	734.150***	0.131
No money, no dignity.	2.47(1.10)	3.23(1.07)	604.468***	0.110
I would abandon some principles for the sake of money.	1.73(0.95)	2.90(1.13)	1553.422***	0.241
The amount of money one makes is a fundamental indicator of one’s “success.”	2.25(1.08)	3.19(1.11)	909.078***	0.157
Composite Score	2.35(0.79)	3.16(0.89)	1125.202***	0.187

Note. *** $p < .001$; [^]Adjusted Bonferroni value = .008.

Table 8. Correlation among variables

Variables	1	2	3	4	5	6
1. Age	-					
2. Gender ^b	0.01	-				
3. Father Education ^c	-0.14***	-0.01	-			
4. Mother Education ^c	-0.13***	-0.00	0.51***	-		
5. Family Intactness ^d	0.10***	0.05*	-0.09***	-0.08 ^a	-	
6. Economic Disadvantage ^e	-0.02	-0.14***	0.21***	0.16***	-0.17***	-
7. Materialism	0.18***	-0.09 ^a	-0.08**	-0.08 ^a	0.10***	-0.03

Note. * $p < .05$, ** $p < .01$, *** $p < .001$, ^a $p = 0.001$;

^bMale = 1, Female = 2;

^cThe 0-9 values of Father and Mother Education were recoded into three categorical values: Primary and below = 1, Secondary = 2, Above secondary = 3. The value “0” (Do not know) was recoded as missing value (999).

^dFamily Intactness was recoded from variable “Parents’ current marital status”: First marriage = 1, Non-first marriage = 2.

^eEconomic Disadvantage was recoded from two variables: “Household on CSSA” and “Results of application of Textbook Assistance Scheme”: On CSSA and/or receiving textbook allowance = 1, other condition = 2.

Table 9. Results of linear regression independently for each predictor

Predictors	Student Materialism			
	β	<i>t</i>	<i>F</i>	<i>R</i> ²
Age	0.19	9.25***	85.596***	0.035
Gender ^b	-0.10	-4.91***	24.117***	0.010
Father Education ^c	-0.06	-2.62**	6.847**	0.004
Mother Education ^c	-0.08	-3.25 ^a	10.565 ^a	0.006
Family Intactness ^d	0.09	4.17***	17.349***	0.007
Economic Disadvantage ^e	-0.01	-0.31	0.098	0.000

Note. * $p < .05$, ** $p < .01$, *** $p < .001$, ^a $p = 0.001$;

^bMale = 1, Female = 2;

^cThe 0-9 values of Father and Mother Education were recoded into three categorical values: Primary and below = 1, Secondary = 2, Above secondary = 3. The value “0” (Do not know) was recoded as missing value (999).

^dFamily Intactness was recoded from variable “Parents’ current marital status”: First marriage = 1, Non-first marriage = 2.

^eEconomic Disadvantage was recoded from two variables: “Household on CSSA” and “Results of application of Textbook Assistance Scheme”: On CSSA and/or receiving textbook allowance = 1, other condition = 2.

Table 10. Results of multiple regression

Predictors	Student Materialism			
	β	t	F	R^2
Age	0.17	6.33***	12.594***	0.052
Gender ^b	-0.09	-3.52***		
Father Education ^c	-0.03	-0.83		
Mother Education ^c	-0.04	-1.33		
Family Intactness ^d	0.08	2.83**		
Economic Disadvantage ^e	-0.01	-0.40		

Note. * $p < .05$, ** $p < .01$, *** $p < .001$, ^a $p = 0.001$;

^bMale = 1, Female = 2;

^cThe 0-9 values of Father and Mother Education were recoded into three categorical values: Primary and below = 1, Secondary = 2, Above secondary = 3. The value "0" (Do not know) was recoded as missing value (999).

^dFamily Intactness was recoded from variable "Parents' current marital status": First marriage = 1, Non-first marriage = 2.

^eEconomic Disadvantage was recoded from two variables: "Household on CSSA" and "Results of application of Textbook Assistance Scheme": On CSSA and/or receiving textbook allowance = 1, other condition = 2.

DISCUSSION

Despite the importance of the topic of materialism in adolescent development, research studies in this area are surprisingly little. As such, the current study was conducted to understand materialistic beliefs in Chinese high school students in Hong Kong. In particular, we assessed students' perceptions of materialistic beliefs in themselves as compared to adolescents in general. Besides, we also explored the socio-demographic correlates of materialistic beliefs in Chinese high school students in Hong Kong. The current study is pioneering in the field of adolescent materialism as no similar studies have been conducted before.

Based on the responses of the participants to the abridged version of the Chinese Adolescent Materialism Scale, we examined the profiles of materialistic beliefs in high school students in Hong Kong. Several observations can be highlighted from the findings. First, amongst junior secondary school students, roughly one-quarter of them (27.4%) agreed that earning money is more important than other things. The related proportion was higher in senior high school students (33.8%). Besides, roughly one-quarter of the senior high school students agreed that owning money can earn the respect of other people. These observations are disturbing because many students employed money or material possession to be a yardstick to define success and personal achievement. In future, studies should be conducted to examine how materialistic beliefs might contribute to the developmental outcomes in adolescents.

Interestingly, when the participants were asked about materialistic attitudes amongst Hong Kong adolescents in general, the participants saw that quite a high proportion of Hong Kong adolescents showed materialistic attitudes: 40% and 49% of junior and senior high school students agreed that Hong Kong adolescents defined success in terms of richness, respectively; 42.1% and 50.2% of junior and senior high school students agreed that Hong Kong adolescents equated money with respect from others, respectively. ANOVAs results also revealed that the participants saw themselves to be less materialistic than adolescents in Hong Kong in general. In other words, students generally perceived that they were less materialistic as compared to adolescents in general. This observation is generally in line with

the social psychology literature that people tend to see themselves as better than others (i.e., social desirability effect).

Regarding sociodemographic correlates of materialistic beliefs in Chinese adolescents, several observations can be highlighted. First, older adolescents showed higher materialism; senior high school students showed stronger endorsement of materialistic beliefs than did junior high school students. There are several factors contributing to this observation. First, when adolescents grow older, their understanding of the importance of money would increase. Second, students in senior forms may actually spend more, hence underscoring the importance of money in the lives of adolescents. Third, older adolescents may be more susceptible to peer influence in material possession which may be used to define their identities.

Regarding gender difference in materialistic beliefs, findings showed that being male was associated with a higher level of materialistic beliefs. There are several possible explanations for this. First, as males are the breadwinners of the family, they would attach higher importance to money and material possession. Second, as males are more instrumental and pragmatic, they would see monetary and material possession to be more important. In future study, we should further examine how such gender differences would be translated into gender differences in other areas, such as psychological well-being and interpersonal relationships.

The present findings also showed that both paternal and maternal education were related to adolescent materialistic beliefs. There are two possible explanations of the findings. First, higher parental education implies higher income for the family, which would reduce the importance of material possession. Second, parents with higher education might nurture their children to develop in a more holistic manner, particularly to look at the world from different angles. Further research is needed to understand how parents would socialize the children, particularly in terms of development of happiness from a hedonic or eudemonic motive.

Finally, materialistic beliefs were higher in high school students in non-intact families than intact families. There are studies showing that parenting and family functioning are less favorable in non-intact families than in intact families. The present study shows that development of materialistic beliefs is adversely affected in non-intact families which is not systematically examined in previous studies. Furthermore, non-intact families might suffer from economic problem which may underscore the importance of material possession. However, as the present findings do not show any relationship between economic disadvantage and materialistic beliefs in adolescents, more research in this area is needed.

Although the present study is a pioneering study in the field, there are several limitations. First, although the sample was large, the students were not randomly selected. Hence, generalizability of the findings should be carefully examined. It is suggested that random samples should be used in future studies. Second, as only five items were used to assess materialistic beliefs, it would be helpful to use more items in future study. Of course, in a survey assessing many constructs, the issue of overloading the respondents should be carefully considered. Finally, regarding the socio-demographics of adolescent materialism, as the effect sizes were not large, there is a need to replicate the findings.

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Chapter 319

MATERIALISM AND EGOCENTRISM IN CHINESE ADOLESCENTS IN HONG KONG: PERCEPTIONS OF TEACHERS

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ABSTRACT

While there are studies on materialism and egocentrism based on self-reports of adolescents, there are very few studies focusing on teachers' perceptions of materialism and egocentrism in their students and adolescents in general. In this study, teachers' perceptions (N = 568) of materialism and egocentrism in Chinese adolescents were examined. Findings showed that many teachers perceived that their students and adolescents in Hong Kong showed materialistic beliefs. A significant proportion of teachers also perceived that their students and adolescents in Hong Kong generally showed worrying signs of egocentrism. While background demographic factors (age, gender, religious orientation and teaching grades) were not related to adolescent materialism, teachers' perceptions of their students' egocentrism were related to teaching grades and teachers' perceptions of egocentrism in adolescents in general were related to age, gender, and teaching grades.

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INTRODUCTION

Adolescence is an important stage where young people develop beliefs and values about themselves and the world. With cognitive maturation and enlargement of the social circle, adolescents form views about themselves, including their own characteristics and unique features. Besides, adolescents also form views about the world, such as ideological beliefs and philosophies. Amongst the beliefs and values formed by adolescents, there are two important areas to be considered. The first belief is on how adolescents view material possession and money (i.e., materialistic beliefs). With more contact with the world (e.g., buying lunch at school and using money at their own discretion) and peer influence (e.g., it is trendy to possess a pair of limited edition of sports shoes), adolescents begin to form beliefs about material possession and money. Obviously, the development of healthy attitude to material possession is important for adolescent thriving behavior. If adolescents hold unhealthy values, they may engage in delinquency behavior such as theft, shoplifting, and compensated dating to earn quick money in order to get material possession.

Shek, Ma and Lin [1] showed that a high level of materialism was related to a higher level of egocentrism but lower levels of morality, spirituality, and empathy. In different youth development models, particularly in the field of positive youth development [2], it is commonly emphasized that “being” (i.e., non-material values) such as character strengths are important to adolescent development. For example, in the developmental assets proposed by the Search Institute, the developmental assets focus on values and virtues which are non-materialistic in nature [3]. In the 5C/6C models on youth development [4, 5], competence, confidence, character, compassion, connection, and contribution are non-materialistic nature. In the existential literature, the theory proposed by Victor Frankl [6] does not focus on “will to sex and aggression” and “will to power”; rather, it focuses on “will to life meaning” which is non-materialistic in nature. In fact, materialism is a by-product of Capitalism which focuses on the importance of material possession and consumption [7].

Another adolescent belief is adolescents’ thoughts and experiences when comparing to others. If one always over-estimates one’s ability and devaluates others’ views, one would develop a “superiority complex”. On the other hand, if one always under-estimates one’s belief and over-emphasizes others’ views, one would develop “inferiority complex”. Furthermore, if one looks at things only from his or her own perspective without considering others’ views, it is a self-centered orientation. On the other hand, if one looks at things from others’ perspectives, it is other-centered orientation. Cognitively speaking, children tend to look at things from one’s perspective without making reference to others’ perspectives. According to Piaget [8], children’s thinking style in late childhood is egocentric. However, with cognitive maturation, adolescents gradually know how to look at the world from one’s perceptive as well as others’ perspectives, although they initially hold distorted views about oneself and others, such as viewing one’s thoughts are superior than others [9-11]. According to Shek, Yu and Siu [12], there are two dimensions of egocentrism, including belief that one’s thought is better than others (i.e., self-conceit) and not considering the views and experiences of other people (i.e., disregard of others). Developmentally speaking, egocentrism is a normal stage in adolescent development; however, if adolescents cannot grow out of it, it would then be developmental problems to the adolescents.

With widening of the social networks during adolescents, self-centered orientation would impair interpersonal relationships. Besides, adolescent egocentrism would lead to engagement in risky behavior because adolescents believe they are exceptional. Shek, Yu, and Siu [12] showed that adolescent egocentrism was negatively related to spirituality and empathy. Conceptually, with reference to different youth development models, it is commonly asserted that taking others' perspective and sensitive to others' feelings are important for adolescent healthy development. Positive values and social competences are emphasized in Benson's developmental assets model [3]. In the 5C/6C model, it is argued that caring and compassion (i.e., consideration of others) are important. In the social-emotional perspective (e.g., CASEL's model), understanding of others' views is an important competence to be acquired by adolescents. In the character strengths perspective [13-15], social intelligence and modesty are emphasized. In the positive youth development models [16], the importance of considering others' views and experiences is highlighted.

The major drawback of the existing studies on adolescent materialism and egocentrism is that the existing studies are primarily based on self-reports of adolescents. There are several limitations of reliance on the self-report data collected from adolescents. First, it can be argued that adolescents may not have an accurate understanding of themselves because of their emerging cognitive maturity. Second, adolescents may have biases in viewing oneself, particularly because of social desirability effects such as "beauty of beholder side". Third, as self-evaluation of one's weaknesses is painful, self-report of adolescents may not be accurate. Hence, it is methodologically desirable to include the perspectives of other stakeholders (i.e., teachers) to look at the related issues. The engagement of teachers is helpful for several reasons. First, as teachers spend much time with students, they have a better understanding of their students and young people in Hong Kong. Second, through intensive interaction with students, teachers would have a good understanding of the students. Third, with professional teacher training, teachers would have a more informed judgment about the situation of their students and adolescents. With reference to Hong Kong, studies on adolescent materialism are few [7, 17, 18]. In the study conducted by Shek and colleagues [7], the finding showed that high school students perceived that adolescents showed worrying signs in materialism and egocentrism. Obviously, it would be illuminating if the views of teachers could be collected.

As there are few studies on the moral character, materialism, egocentrism, and psychosocial development in high school students in Hong Kong, colleagues at The Hong Kong Polytechnic University conducted several studies based on perspectives of adolescents, teachers, and parents [18-22]. In this paper, we used the data collected based on teachers' perceptions of materialism and egocentrism of Chinese adolescents [19] with several objectives. First, we examined the perceptions of teachers on materialism and egocentrism of high school students and adolescents in Hong Kong. Second, we examined whether materialism and egocentrism in high school students and adolescents in general are different based on the perspective of teachers. Based on the social psychology literature, it was hypothesized that teachers would see their students to be less materialistic and egocentric as compared to adolescents in the general adolescent population. Third, as there are not many studies on the psychosocial correlates of teachers' perceptions of materialism and egocentrism in their students and adolescents in Hong Kong, we tested several tentative hypotheses: a) as older people tend to be more conservative, older teachers would see their students or adolescents in general to be more materialistic or egocentric; b) as females focus more on affective relationships and they are more empathetic (i.e., less egocentric), female

teachers would see their students or adolescents to be more materialistic or egocentric as compared to male teachers; c) compared with those without religion, teachers with religious beliefs would see their students and Hong Kong adolescents to be more materialistic or egocentric; and d) as those who teach both junior and senior high school students would have better understanding of high school students, they would see their students to be more egocentric.

OUR STUDY

To understand the views of teachers on adolescent materialism and egocentrism, teachers from 11 secondary schools in Hong Kong were recruited to participate in this study ($N = 568$), with 345 female teachers (60.7%) and 216 male teachers (38%). The sample could be categorized into five age groups: 25 years or below ($n = 36$, 6.3%), 26-35 years ($n = 162$, 28.5%), 36-45 years ($n = 153$, 26.9%), 46-55 years ($n = 160$, 28.2%), and 56 years or above ($n = 49$, 8.2%). A total of 464 teachers were with teaching experiences of more than six years. Consent from the teachers was obtained before data collection.

Prior to data collection, this study was reviewed and approved by the University Institutional Review Board at a public university in Hong Kong. After getting approval from the school principals, data were collected from the teachers. In each school, we distributed the questionnaires to the school coordinator who helped to collect the completed questionnaires in sealed envelopes without revealing the identity of the respondents.

INSTRUMENTS

Teachers' perception of adolescent materialism: To assess teachers' perceptions of adolescent materialism, we modified the abridged 5-item Chinese Adolescent Materialism Scale [1] which was originally developed to assess materialistic beliefs in Chinese adolescents. These items included: a) "My students believe that making money is more important than any other things"; b) "My students believe that money is everything"; c) "My students believe that the rich can get respect from others"; d) "My students would abandon some principles for the sake of money"; and e) "My students believe that the amount of money one makes is a fundamental indicator of one's success". A five-point Likert scale was used, including "strongly disagree", "somewhat disagree", "neither agree nor disagree", "somewhat agree", and "strongly agree", with higher scores indicating higher levels of materialism.

To understand teachers' perceptions of materialism in Hong Kong adolescents in general, the same five items were used with changing perspectives. The items included: a) "Hong Kong adolescents think that making money is more important than any other things"; b) "Hong Kong adolescents believe that money is everything"; c) "Hong Kong adolescents think that the rich can get respect from others"; d) "Hong Kong adolescents would abandon some principles for the sake of money"; and e) "Hong Kong adolescents believe that the amount of money one makes is a fundamental indicator of one's success". We used a five-point Likert scale in which higher egocentrism was reflected by higher scores.

Teachers' perception of adolescent egocentrism: To assess teachers' perceptions of egocentrism in their students, we modified the abridged 5-item Chinese Adolescent Egocentrism Scale [19] which was originally developed to assess egocentrism in Chinese adolescents based on the perspective of adolescents [12]. These items included: a) "My students regard their experiences are more important than those of others"; b) "My students think that their interests are more important than those of others"; c) "My students always find justifications for their behavior"; d) "most of the time, my students think that other people's criticisms about them do not make sense"; e) "even if they make other people unhappy, my students are true to their experience". For each item, there are five response options, including "strongly disagree", "somewhat disagree", "neither agree nor disagree", "somewhat agree", and "strongly agree", with higher scores showing higher levels of egocentrism.

For teachers' perceptions of adolescent egocentrism, we modified the abridged 5-item Chinese Adolescent Egocentrism Scale [19] which was originally developed to assess egocentrism in Chinese adolescents [12]. These items included: a) "Hong Kong adolescents regard their experiences are more important than those of others"; b) "Hong Kong adolescents think that their interests are more important than those of others"; c) "Hong Kong adolescents always find justifications for their behavior"; d) "most of the time, Hong Kong adolescents think that other people's criticisms about them do not make sense"; e) "even if they make other people unhappy, Hong Kong adolescents are true to their experience". For each item, there are five response options. A higher total score means a higher level of perceived egocentrism in Hong Kong adolescents in general.

Data Analyses

The Statistical Package for Social Sciences Version 25 (IBM Corp., Somers, NY, USA) was used to perform the related analyses. First, we examined percentage findings to look at the profiles of responses of teachers to the modified version of the Chinese Adolescent Materialism Scale as well as the modified Chinese Adolescent Egocentrism Scale.

Table 1. Teacher perception of materialistic beliefs in their own students

Items	1 n (%)	2 n (%)	1+2 n (%)	3 n (%)	4 n (%)	5 n (%)	4+5 n (%)	Mean	n
My students believe making money is more important than any other things.	14 (2.5%)	140 (24.7%)	154 (27.2%)	123 (21.7%)	254 (44.8%)	36 (6.3%)	290 (51.1%)	3.28	567
My students believe "Money is everything".	45 (7.9%)	173 (30.5%)	218 (38.4%)	163 (28.7%)	164 (28.9%)	22 (3.9%)	186 (32.8%)	2.90	567
My students believe that the rich can get respect from others .	15 (2.7%)	144 (25.4%)	159 (28.1%)	153 (27.0%)	221 (39.0%)	33 (5.8%)	254 (44.8%)	3.20	566
My students believe they would abandon some principles for the sake of money.	52 (9.2%)	179 (31.8%)	231 (41.0%)	192 (34.1%)	134 (23.8%)	6 (1.1%)	140 (24.9%)	2.76	563
My students believe "The amount of money one makes is a fundamental indicator of one's success".	17 (3.0%)	128 (22.6%)	145 (25.6%)	169 (29.8%)	222 (39.2%)	31 (5.5%)	253 (44.7%)	3.22	567

Besides, teachers' perceptions of materialistic beliefs and egocentric beliefs amongst the general adolescent population in Hong Kong were examined. Second, teachers' views of the materialistic and egocentric beliefs of their students were compared with their perceptions of the materialistic and egocentric beliefs of Hong Kong adolescents in general, respectively. For the socio-demographic correlates, Pearson correlation analysis and regression analyses were performed.

Table 2. Teacher perception of materialistic beliefs in HK adolescents

Items	1 n (%)	2 n (%)	1+2 n (%)	3 n (%)	4 n (%)	5 n (%)	4+5 n (%)	Mean	n
Adolescents in HK believe making money is more important than any other things.	4 (0.7%)	58 (10.2%)	62 (10.9%)	109 (19.2%)	336 (59.3%)	60 (10.6%)	396 (69.9%)	3.69	567
Adolescents in HK believe "Money is everything".	13 (2.3%)	74 (13.1%)	87 (15.4%)	160 (28.2%)	272 (48.0%)	48 (8.5%)	320 (56.5%)	3.47	567
Adolescents in HK believe that the rich can get respect from others".	4 (0.7%)	60 (10.6%)	64 (11.3%)	107 (18.9%)	331 (58.4%)	65 (11.5%)	396 (69.9%)	3.69	567
Adolescents in HK believe they would abandon some principles for the sake of money.	10 (1.8%)	82 (14.5%)	92 (16.3%)	165 (29.1%)	276 (48.7%)	34 (6.0%)	310 (54.7%)	3.43	567
Adolescents in HK believe "The amount of money one makes is a fundamental indicator of one's success".	4 (0.7%)	47 (8.3%)	51 (9.0%)	119 (21.0%)	321 (56.6%)	76 (13.4%)	397 (70.0%)	3.74	567

Table 3. Teacher perception of egocentrism in their own students

Items	1 n (%)	2 n (%)	1+2 n (%)	3 n (%)	4 n (%)	5 n (%)	4+5 n (%)	Mean	n
My students believe their feelings are more important than the feelings of other people.	1 (0.2%)	20 (3.5%)	21 (3.7%)	71 (12.5%)	298 (52.6%)	177 (31.2%)	475 (83.8%)	4.11	567
My students believe their own benefits are more important than the benefits of other people.	4 (0.7%)	19 (3.4%)	23 (4.1%)	107 (18.9%)	335 (59.2%)	101 (17.8%)	436 (77.0%)	3.90	566
My students believe that no matter what happens, they can always justify their behaviors.	3 (0.5%)	19 (3.4%)	22 (3.9%)	83 (14.6%)	291 (51.3%)	171 (30.2%)	462 (81.5%)	4.07	567
My students believe the criticisms on them are usually groundless.	6 (1.1%)	108 (19.1%)	114 (20.2%)	188 (33.2%)	231 (40.8%)	33 (5.8%)	264 (46.6%)	3.31	566
My students are true to their own feelings even if this may upset other people.	1 (0.2%)	52 (9.2%)	53 (9.4%)	178 (31.4%)	270 (47.6%)	66 (11.6%)	336 (59.2%)	3.61	567

FINDINGS

The descriptive profiles based on percentage findings on teachers' perceptions of materialism in students, materialism in Hong Kong adolescents, egocentrism in students, and egocentrism in Hong Kong adolescents are presented in Table 1 to Table 4. First, significant proportions of teachers perceived their students and Hong Kong adolescents showed signs of materialism. For example, 51.1% and 69.9% of the teachers regarded their students and Hong Kong adolescents believed that "making money is more important than any other things", respectively. Second, more than half of the teachers perceived their students and Hong Kong adolescents in general showed signs of egocentrism. For example, the teachers believe that "their feelings are more important than the feelings of other people" (83.8% and 89.9%, respectively). Third, teachers generally perceived that materialism in their own students was lower than that in Hong Kong adolescents. Fourth, teacher perceived egocentrism in their own students to be lower than that in Hong Kong adolescents.

MANOVAs and ANOVAs were further performed to look at the third and fourth observations. Results of the one-way MANOVA analyses showed that there were statistically significant differences in materialistic beliefs between students and Hong Kong adolescents perceived by teachers, $F(5, 1123) = 33.450$, $p < 0.001$, partial eta squared = 0.130. For univariate effects, there were significant differences between teacher perceptions of students and teacher perceptions of Hong Kong adolescents at the item score ($p < 0.001$ in all items) and composite score ($p < 0.001$) levels (see Table 5). Similarly, one-way MANOVA analyses showed that teachers perceived significant difference between egocentrism in their students and Hong Kong adolescents, $F(5, 1124) = 21.379$, $p < 0.001$, partial eta squared = 0.087. For univariate effects, teacher perceptions of students and Hong Kong adolescents were statistically significantly different over Items 2, 4, and 5 ($p < 0.001$) and the composite score ($p < 0.001$) (see Table 6).

Table 4. Teacher perception of egocentrism in HK adolescents

Items	1 n (%)	2 n (%)	1+2 n (%)	3 n (%)	4 n (%)	5 n (%)	4+5 n (%)	Mean	n
Adolescents in HK believe their feelings are more important than the feelings of other people.	2 (0.4%)	10 (1.8%)	12 (2.2%)	45 (8.0%)	351 (62.0%)	158 (27.9%)	509 (89.9%)	4.15	566
Adolescents in HK believe their own benefits are more important than the benefits of other people.	4 (0.7%)	11 (1.9%)	15 (2.6%)	56 (9.9%)	364 (64.3%)	131 (23.1%)	495 (87.4%)	4.07	566
Adolescents in HK believe that no matter what happens, they can always justify their behaviors.	2 (0.4%)	8 (1.4%)	10 (1.8%)	63 (11.2%)	337 (59.6%)	155 (27.4%)	492 (87.0%)	4.12	565
Adolescents in HK believe the criticisms on them are usually groundless.	4 (0.7%)	37 (6.5%)	41 (7.2%)	145 (25.6%)	318 (56.2%)	62 (11.0%)	380 (67.2%)	3.70	566
Adolescents in HK are true to their own feelings even if this may upset other people.	2 (0.4%)	16 (2.8%)	18 (3.2%)	92 (16.3%)	348 (61.5%)	108 (19.1%)	456 (80.6%)	3.96	566

Table 5. Differences in materialistic beliefs between students and HK adolescents perceived by teachers (N = 562 for teacher's perception of students, N = 567 for teacher's perception of Hong Kong adolescents)

	Students	HK Adolescents	<i>F</i>	partial η^2
My students/HK adolescents believe that...	<i>M (SD)</i>	<i>M (SD)</i>	33.450***^	0.13
Making money is more important than any other things	3.28(0.99)	3.69(0.82)	57.662***	0.049
Money is everything.	2.91(1.03)	3.47(0.91)	96.525***	0.079
No money, no dignity.	3.20(0.98)	3.69(0.84)	84.224***	0.070
They would abandon some principles for the sake of money.	2.76(0.95)	3.43(0.87)	151.072***	0.118
The amount of money one makes is a fundamental indicator of one's "success".	3.22(0.96)	3.74(0.82)	96.327***	0.079
Composite Score	3.07(0.79)	3.60(0.71)	141.024***	0.111

Note. ****p* <.001; ^Adjusted Bonferroni value = .008.

Table 6. Differences in egocentrism between students and HK adolescents perceived by teachers (N = 565 for teacher's perception of students, N = 565 for teacher's perception of Hong Kong adolescents)

	Students	HK Adolescents	<i>F</i>	partial η^2
My students/HK adolescents believe that...	<i>M (SD)</i>	<i>M (SD)</i>	21.379***^	0.087
Their feelings are more important than the feelings of other people.	4.11(0.77)	4.15(0.66)	0.996	0.001
Their own benefits are more important than the benefits of other people.	3.90(0.75)	4.07(0.68)	15.925***	0.014
Not matter what happens, they can always justify their behaviors.	4.07(0.79)	4.12(0.68)	1.369	0.001
The criticisms on them are usually groundless.	3.31(0.88)	3.70(0.78)	61.380***	0.052
They are loyal to their own feelings even if this may upset other people.	3.61(0.81)	3.96(0.71)	59.122***	0.050
Composite Score	3.80(0.62)	4.00(0.56)	31.988***	0.028

Note. ****p* <.001; ^Adjusted Bonferroni value = .008.

Pearson correlation analyses showed that teachers' perceptions of materialism in students and materialism in Hong Kong adolescents were not correlated with age, gender, religion, and teaching grade of teachers. In contrast, teachers' perception of egocentrism in their students was related to teaching grade whereas perceived egocentrism in Hong Kong adolescents was correlated with age, gender, and teaching grade (see Table 7).

Table 7. Correlation among variables

Variables	1	2	3	4
Age ^a	-			
Gender ^b	-0.117**	-		
Religion ^c	-0.107**	0.000	-	
Teaching grade ^d	0.031	-0.041	-0.057	-
Materialism in students	-0.023	0.048	0.048	0.020
Materialism in HK adolescents	-0.045	-0.005	0.020	0.066
Egocentrism in students	-0.028	0.062	0.011	0.090*
Egocentrism in HK adolescents	0.125**	0.085*	-0.036	0.147***

Note. **p* <.05, ***p* <.01, ****p* <.001.

^aAged 25 or below = 1, Aged 26-35 = 2, Aged 36-45 = 3, Aged 46-55 = 4; Aged 56 or above = 5.

^bMale = 1, Female = 2; ^cHaving religion = 1, Having no religion = 2.

^dTeaching junior forms (S1-S3) = 1, Teaching senior forms (S4-S6) = 2, Teaching both junior and senior forms (S1-S6) = 3.

Regression analyses were conducted for each predictor separately. Results showed that there were no prediction effects of age, gender, religion, and teaching grade on materialism in students and materialism in Hong Kong adolescents perceived by teachers (Tables 8 and 9). Teachers' perceived egocentrism in students was only predicted by teaching grade ($F(1, 545) = 4.527, p < 0.05$) but not by other predictors (Table 10). Teachers' perceived egocentrism in

Hong Kong adolescents was predicted by age ($F(1, 558) = 7.039, p < 0.01$), gender ($F(1, 559) = 4.482, p < 0.05$) and teaching grade ($F(1, 545) = 12.344, p < 0.001$) but not religion (Table 11).

Table 8. Predicting effects of demographic factors on teacher perceived materialism in their students

Predictors	Materialism in Students			
	β	t	F	R^2
Age ^a	-0.026	-0.604	0.365	0.001
Gender ^b	0.049	1.149	2.320	0.002
Religion ^c	0.051	1.186	1.407	0.003
Teaching Grade ^d	0.044	0.336	1.113	0.0002

Note. ^aAged 25 or below = 1, Aged 26-35 = 2, Aged 36-45 = 3, Aged 46-55 = 4; Aged 56 or above = 5.

^bMale = 1, Female = 2; ^cHaving religion = 1, Having no religion = 2.

^dTeaching junior forms (S1-S3) = 1, Teaching senior forms (S4-S6) = 2, Teaching both junior and senior forms (S1-S6) = 3.

Table 9. Predicting effects of demographic factors on teacher perceived materialism in HK adolescents

Predictors	Materialism in HK Adolescents			
	β	t	F	R^2
Age ^a	-0.056	-1.318	1.738	0.003
Gender ^b	-0.003	-0.080	0.006	0.000011
Religion ^c	0.012	0.274	0.075	0.000137
Teaching Grade ^d	0.065	1.524	2.323	0.004

Note. ^aAged 25 or below = 1, Aged 26-35 = 2, Aged 36-45 = 3, Aged 46-55 = 4; Aged 56 or above = 5.

^bMale = 1, Female = 2; ^cHaving religion = 1, Having no religion = 2.

^dTeaching junior forms (S1-S3) = 1, Teaching senior forms (S4-S6) = 2, Teaching both junior and senior forms (S1-S6) = 3.

Table 10. Predicting effects of demographic factors on teacher perceived egocentrism in their students

Predictors	Egocentrism in Students			
	β	t	F	R^2
Age ^a	-0.037	-0.869	0.755	0.001
Gender ^b	0.066	1.570	2.466	0.004
Religion ^c	0.012	0.270	0.073	0.00013
Teaching Grade ^d	0.091	2.138*	4.527*	0.008

Note. * $p < .05$.

^aAged 25 or below = 1, Aged 26-35 = 2, Aged 36-45 = 3, Aged 46-55 = 4; Aged 56 or above = 5.

^bMale = 1, Female = 2; ^cHaving religion = 1, Having no religion = 2.

^dTeaching junior forms (S1-S3) = 1, Teaching senior forms (S4-S6) = 2, Teaching both junior and senior forms (S1-S6) = 3.

Table 11. Predicting effects of demographic factors on teacher perceived egocentrism in Hong Kong adolescents

Predictors	Egocentrism in HK Adolescents			
	β	t	F	R^2
Age ^a	0.112	2.653**	7.039**	0.012
Gender ^b	0.089	2.117*	4.482*	0.008
Religion ^c	-0.033	-0.768	0.590	0.001
Teaching Grade ^d	0.149	3.513***	12.344***	0.022

Note. * $p < .05$, ** $p < .01$, *** $p < .001$.

^aAged 25 or below = 1, Aged 26-35 = 2, Aged 36-45 = 3, Aged 46-55 = 4; Aged 56 or above = 5.

^bMale = 1, Female = 2; ^cHaving religion = 1, Having no religion = 2; ^dTeaching junior forms (S1-S3) = 1, Teaching senior forms (S4-S6) = 2, Teaching both junior and senior forms (S1-S6) = 3.

DISCUSSION

Although adolescent materialism and egocentrism are important aspects of adolescent development, few Chinese studies have been conducted. In particular, no study has been conducted to look at the related issues from the perspective of significant-others of adolescents, particularly teachers. Against this background, we conducted this study to examine teachers' perceptions of materialism as well as egocentrism in their students and adolescents in Hong Kong. We also compared the perceived differences between students taught by the respondents and Hong Kong adolescents in general on materialism and egocentrism. Furthermore, as there are very few studies on the socio-demographic correlates of perceptions of materialistic and egocentric beliefs in Hong Kong high school students and adolescents in general, we explored several tentative hypotheses in this study. Because there are very few related studies in the field, this is a pioneer attempt in studying adolescent materialism and egocentrism.

Based on the teachers' responses to the modified version of the Chinese Adolescent Materialism Scale, we observed several phenomena. First, around 45% of the teachers perceived their students believe that "no money, no dignity". Similarly, around 45% of the teachers perceived their students believe that "the amount of money one makes is a fundamental indicator of one's success". Second, more than half of the teachers perceived that adolescents in Hong Kong hold materialistic beliefs: around 70% of the teachers perceived that "adolescents in HK believe making money is more important than any other things"; around 70% of the teachers perceived that Hong Kong adolescents equated money with dignity and regarded money as the criteria of success. These findings are worrying because the over-emphasis on material possession would be detrimental to adolescent development. In future, we should further examine how materialistic beliefs influence adolescent development, particularly on the development of character strengths and virtues.

For adolescent egocentrism, the picture is even more worrying. More than two-third of the teachers perceived that their students are egocentric: around 84% of the teachers perceived that their students regarded their feelings to be more important than those of other people; 77% of the teachers perceived that their students regarded their own benefits are more important than the benefits of other people. Furthermore, most of the teachers perceived that adolescents in Hong Kong were egocentric: around 87% of the teachers perceived that Hong Kong adolescents regarded that their benefits are more important than those of others; around 87% of the respondents perceived that adolescents always have justifications for their behavior. These findings suggest that adolescents should be helped to balance the emphasis on superiority of one's views and feelings while respecting the views and experiences of other people.

Regarding perceptions of teachers regarding materialism and egocentrism in their students and Hong Kong adolescents, the findings showed that teachers generally had relatively positive perceptions of their students as compared to adolescents in general – students were seen as less materialistic and less egocentric as compared to adolescents in Hong Kong. This observation is interesting and it is in line with the previous findings that adolescents saw themselves as less materialistic than did adolescents in general [23].

Several observations can be highlighted from the findings on the socio-demographic correlates of teachers' perceived materialism and egocentrism beliefs in Chinese adolescents.

First, socio-demographic correlates were not related to teachers' perceived materialism and egocentrism of their students and Hong Kong adolescents in general. Second, with more teaching exposure (i.e., teaching more grades), teachers tended to perceive that their students were more egocentric. One possible explanation is that teachers might have a more in-depth understanding of their students when they teach junior and senior form students. Third, age, gender, and teaching grades were related to teachers' perceptions of egocentrism of adolescents in Hong Kong. The positive relationship between age and perceived egocentrism is consistent with the conjecture that people with older age are more conservative and they are more critical of young people. Regarding gender, as females attach more emphasis on interpersonal relationship, they would also be more critical of egocentric behavior in adolescents as compared to males. Concerning grade teaching, we can interpret that those with more teaching exposure would understand their students better, hence having a higher level of perceived egocentrism amongst Hong Kong adolescents. However, as the present hypotheses are tentative in nature, there is a need to further refine them in future studies.

Although the present study is a pioneer study in the field, there are several limitations. First, as the sample was not randomly selected, we should be cautious to examine the generalizability of the findings. Further replication of the findings based on random samples is in order. Second, as only abridged scales (i.e., five items) were employed, it would be theoretically and empirically enriching if longer scales could be used. Third, regarding the socio-demographic prediction of teachers' perceived adolescent materialism and egocentrism, the findings are tentative and inconclusive. Hence, there is a need to refine the related hypotheses and theoretical bases. Finally, the origin of materialism and egocentrism in adolescents was not covered in the present study. In the area of materialism, there are studies suggesting that socialization within the family context plays an important role in the development of different motives for happiness in adolescents [24-28]. Hence, it would be exciting to explore how family socialization contributes to the development of materialism and egocentrism in adolescents further.

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Chapter 320

FAMILY MEALTIME ENVIRONMENT AND CHILD BEHAVIOR OUTCOMES IN CHINESE PRESCHOOL CHILDREN

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ABSTRACT

In this chapter we aimed to examine the influence of family mealtime environment on children's behavior, in addition to styles of parenting and family functioning. This study adopted a two-wave longitudinal design. Data was collected over two rounds, 12 months apart, from 470 parents with children aged three to six. Parents completed measures on their parenting style, family functioning, children's behavior, family meal frequency, family feeding practice and mealtime television. Family feeding practice and parenting style were found to be associated with children's behavior. Family feeding practice mediated between parenting style and children's behavior. Family mealtime environment is important on children's behavior.

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INTRODUCTION

Young children under parental care are expected to dine at home as part of the general family routine. It is argued that family mealtime behavior is likely to be consistent with other patterns of family social interaction which are associated with child outcomes [1].

There have been a number of cross-sectional studies on the association between family meal frequency and child behavior in preschool and primary school children. For example, higher family meal frequency was associated with reduced externalizing behavior problems and higher prosocial behavior in preschool/primary school children [2, 3]. Among adolescents aged 11 to 18 years, a cross-sectional study found a negative association between family meal frequency and substance abuse, after controlling for family connectedness [4]. The association between family meal frequency and adolescent problem behavior has also been reported in some longitudinal studies. For example, family meal frequency at baseline was found to be negatively associated with substance use among female adolescents in a 5-year longitudinal study and the mean age of participants was 17.2 at follow-up [5]. More recently, a 3-year longitudinal study found that family meal frequency was negatively associated with substance-use, drinking, physical violence and running away among adolescents [6]. However, there were few longitudinal studies on the association between family meal frequency and child behavior outcomes among preschool/primary school children.

Many scholars theorized about the association between family meal frequency and child psychosocial outcomes. Family mealtimes offer natural “face-to-face sit-together” chances for parent-child communication, parent monitoring of child activities, and sharing of feelings [1]. Parents can be role models for table manners, respect and sharing [5]. Family meals within the context of family routine can provide stability, a developmental protective factor [7].

There are some limitations with previous studies. First, most findings on preschool/primary children were based on cross-sectional studies, and it was not possible to establish causal relationship between family meal frequency and behavior outcomes. Second, many studies failed to consider the roles of family functioning or parenting variables. Family functioning involves cohesion (emotional closeness amongst family members) and communication (sharing of ideas and affect among family members) in the family [8]. Parenting style can be conceived along two dimensions: demandingness (parent acting as socializing agent) and responsiveness (parent recognition of child individuality) [9]. Authoritative parenting is high in demandingness and responsiveness and associated with positive child outcomes. Authoritarian parenting is high in demandingness but low in responsiveness, while permissive parenting is just the opposite [10]. Authoritarian parenting and permissive parenting were associated with poorer child outcomes [11]. Family meal frequency might be confounded with variables like family functioning or parenting style [12]. Third, more frequent family meals might arise from closeness among family members. Family meal frequency might mediate between family relationship and child behavior outcomes, and such role should be examined [12]. Fourth, most studies measured family meal frequency as a composite score for all family members. The contribution of individual family members (e.g., father, mother) should be examined.

Other contextual family mealtime environment variables, including mealtime television viewing and family feeding practice, warrant attention in understanding the association between family meal frequency and child outcomes. Sustained television viewing was found

to be positively associated with child behavior problems in preschool children [13] though mealtime television viewing was not examined specifically in this study. Mealtime routines were related to children's behavior outcomes. For example, parental rigid demands for the child to finish all food served might lead to child behavior problem and conflict with parents. Disorderly mealtime routine was related to neglect and disregard [1]. The impact of these mealtime environment variables on child outcomes should be investigated.

This study addressed the limitations of previous studies. First, it adopted a longitudinal design to provide evidence on causal relationships. Second, it collected data on parenting style and family functioning. The relationship between family mealtime environment variables and family functioning/parenting variables could be investigated. Third, family mealtime environment variables including mealtime television viewing and family feeding practice (type of food served, mealtime behavior management) were investigated. Fourth, to examine the unique contribution of family members, the presence of family members was individually recorded. Finally, to test the cross-cultural applicability of previous findings, the present study targeted Chinese families with preschool children. The results would enable comparison of findings across cultures to map out universal and culture-specific factors.

This study collected two rounds of data from Chinese families with preschool children to examine the influence of family mealtime environment variables (family meal frequency, mealtime television viewing, family feeding practice), parenting style and family functioning on child behavior. Literature review guided this study to examine (i) the direct effect of family mealtime environment variables on child outcomes, in addition to parenting style and family functioning variables; and (ii) family mealtime environment variables as mediators between family functioning/parenting style and child outcomes. The hypotheses were:

- 1) Family mealtime environment, family functioning and parenting style would be associated with child behavior problems.
- 2) Family mealtime environment would mediate between family functioning/parenting style and child behavior problems.

OUR STUDY

This was a longitudinal survey. The two rounds of data collection were 12 months apart. The study only included (i) parents who were Cantonese-speaking (Cantonese being the usual language/dialect used at home for 89.5% of the Hong Kong population) [14]; and (ii) parents whose children were attending preschools at the time of the study. Parents with children with global developmental delay, physical, severe hearing or visual impairment or Autism Spectrum Disorder were excluded. Since there were two rounds of data collection, parents with children in the final year of their preschools were excluded as their children would have left preschools by the second round of data collection.

Two strategies were used to recruit the participants coming from 24 preschools from 15 of the 18 districts in Hong Kong. First, the investigators used their personal network and contacted organizations providing preschool education. Five organizations nominated preschools within their organizations to participate, and 18 preschools participated. Second, a research assistant made phone calls to invite preschools throughout Hong Kong. Six out of

400 participated. In each participating preschool, the number of participating parents ranged from nine to 141.

The ethics committee of The Hong Kong Polytechnic University approved the study. After getting consent from the preschools and parents, the parent questionnaires were distributed through the preschools. At both rounds of data collection, parents completed the questionnaires at a time and place of their own convenience, and returned the completed questionnaires to the preschools in sealed envelopes.

Measures

Parenting Style and Dimension Questionnaire – Short Form (PSDQ-SF) [15] – Parents completed this 32-item 5-point Likert scale with a validated Chinese version for Hong Kong parents [16] measuring authoritative, authoritarian and permissive parenting styles (e.g., emphasizing the reasons for rules, exploding in anger towards child, spoiling child). A total score was calculated for each style. Higher scores indicated more frequent adoption of that particular parenting style.

Chinese Family Assessment Instrument (C-FAI) [17] – This 33-item measure assessed family functioning (e.g., mutual consideration, harmonious family relationship). It yielded five sub-scales, namely, communication, mutuality, conflict and harmony, parental concern and parental control. The parent version was adapted from the original version for completion by adolescents. Parents rated each statement along a 5-point scale (1: *completely agree*; 5: *completely disagree*). The negatively worded-items were reverse scored. Lower scores represented more harmonious family functioning in all sub-scales.

Hong Kong Parent Feeding Questionnaire (HKPFQ) – This 35-item questionnaire assessed parent knowledge, attitude, cooking and feeding practices with regard to their children (e.g., mealtime regularities, diet profile). Parents rated each item on a 3-point scale. A higher score suggested healthier feeding practices. This scale has been used with Hong Kong parents of preschool children in a recent infant and young child feeding survey [18].

Family meal frequency – Parents had to report the frequency of family members present at family dinner over a week. The number of days within a week that mother ate with the target child was summed up to generate a new variable. A similar variable was created for fathers. Another variable on frequency of grandparents eating with the target child was created by summing up all the meals that grandparents (paternal and maternal) ate with the target child.

Frequency of mealtime television viewing – Parents were requested to report the frequency of dinner time television viewing over a week. The total number of nights the television was on was summed up to form a new variable.

Eyberg Child Behavior Inventory (ECBI) [19] – This was a 36-item measure of parental perception of disruptive behavior (e.g., temper tantrums) in children aged two to 16 years. It included two scales, Intensity scale and Problem scale. ECBI-Intensity measured the frequency of problem behavior on a 7-point rating scale. ECBI-Problem measured the extent to which the parents were concerned about the behavior (1: *yes*; 0: *no*). A validated Chinese version was available [20].

Family background - Parents were asked to supply information on their age, family type, education level, employment, family income and social welfare status. Family income was recoded into a dichotomous variable (at/above versus below median household income).

Data Analysis

In this study, the Round 1 and Round 2 variables were measured at the individual level. Owing to the cluster (preschools) nature of the data set, multilevel mediation modelling [21] was used to appropriately model the error structure, treating “preschool” as the random factor. This method allows the testing of mediation effects in clustered datasets. We started by examining the direct effects of Round 1 variables (family mealtime environment, parenting style and family functioning) on Round 2 child behavior outcome. Then, the mediation effect of Round 1 family meal frequency, mealtime television viewing, family feeding practice between Round 1 family functioning/parenting style and Round 2 child behavior outcomes was tested. In the analyses described above, the outcome variables were Round 2 child behavior as measured by ECBI-Intensity and ECBI-Problem. As child gender and family income were found to be associated with child behavior [22, 23], they were controlled for in the analysis.

FINDINGS

The demographic characteristics of the participants and the scale descriptive statistics are shown in Table 1. Table 2 shows the bivariate correlations. As C-FAI mutuality was highly correlated with C-FAI communication ($r = .83$, $p < .001$, $R^2 = .68$) and C-FAI conflict and harmony ($r = .72$, $p < .001$, $R^2 = .52$), C-FAI mutuality was excluded in the following analyses to control for multicollinearity. The direct effects are shown in Table 3.

Table 1. Demographic characteristics of participants and mean and standard deviation scores of scales (N= 470)

	Number	Percentage	
Sex of target child - boy	232	49.40%	
Sex of target child - girl	238	50.60%	
Relationship of participant to target child - mother	372	79.15%	
Relationship of participant to target child - father	94	20.00%	
Relationship of participant to target child - grandparents	4	0.85%	
Target child living with both parents	417	88.72%	
Target child living with mother only	21	4.47%	
Target child living with father only	9	1.91%	
Target child not living with parents	22	4.68%	
Mother's education – junior secondary or below	120	25.53%	
Mother's education – senior secondary or above	347	73.83%	
Father's education – junior secondary or below	133	28.30%	
Father's education – senior secondary or above	327	69.57%	
Mother employed	244	51.91%	
Father employed	442	94.04%	

Table 1. (Continued)

	Number	Percentage	
Family income ^a – HK\$19,999 or below	196	41.70%	
Family income ^a – HK\$20,000 or above	253	53.83%	
Age of target child (in years)	4.48	0.64	NA
Age of mother (in years)	34.50	5.27	NA
Age of father (in years)	38.50	6.82	NA
Mother's length of residence in Hong Kong (in years)	20.72	15.37	NA
Father's length of residence in Hong Kong (in years)	31.86	14.45	NA
Number of children	1.74	0.70	NA
Round 2 ECBI-Intensity	108.93	25.63	.94
Round 2 ECBI-Problem	6.09	6.73	.92
Round 1 authoritative parenting style	58.73	7.51	.89
Round 1 authoritarian parenting style	26.61	5.82	.82
Round 1 permissive parenting style	13.05	2.90	.60
Round 1 C-FAI communication	16.44	6.25	.90
Round 1 C-FAI mutuality	21.56	8.79	.96
Round 1 C-FAI conflict and harmony	11.02	4.23	.73
Round 1 C-FAI parental concern	3.94	1.62	.66
Round 1 C-FAI parental control	6.36	2.36	.67
Round 1 family feeding practice	58.54	7.14	.80
Round 1 frequency of fathers eating with child	4.48	2.67	NA
Round 1 frequency of mothers eating with child	5.79	2.15	NA
Round 1 frequency of grandparents eating with child	5.04	5.09	NA
Round 1 frequency of mealtime television viewing	4.11	2.73	NA

^a Median household income = HK\$20,700.

Table 2. Correlation among variables

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1														
2	.61**													
3	.30**	.23**												
4	.32**	.21**	.83**											
5	.28**	.22**	.60**	.72**										
6	.17**	.16**	.55**	.52**	.41**									
7	.25**	.20**	.25**	.27**	.34**	.19**								
8	-.29**	-.21**	-.42**	-.35**	-.28**	-.27**	-.24**							
9	.40**	.28**	.24**	.27**	.36**	.17**	.53**	-.33**						
10	.36**	.28**	.24**	.22**	.21**	.09	.24**	-.24**	.40**					
11	-.05**	-.03	-.11*	-.07	-.05	.01	.08	.00	.04	-.06				
12	.02	.02	-.13**	-.05	-.10*	-.04	.06	.05	-.00	-.06	.36**			
13	-.36**	-.27**	-.28**	-.27**	-.25**	-.18**	-.21**	.25**	-.33**	-.43**	.05	.01		
14	.14**	.18**	.18**	.18**	.14**	.08	.03	-.12**	.13**	.23**	-.05	-.11*	-.35**	
15	.03	.07	-.01	-.06	-.04	.00	-.10*	-.06	.00	.08	-.13**	-.14**	-.10*	.10*

* $p \leq .05$ ** $p \leq .01$

Legend:

1: Round 2 ECBI-intensity; 2: Round 2 ECBI-problem; 3: Round 1 C-FAI communication; 4: Round 1 C-FAI mutuality; 5: Round 1 C-FAI conflict and harmony; 6: Round 1 C-FAI parental concern; 7: Round 1 C-FAI parental control; 8: Round 1 authoritative parenting style; 9: Round 1 authoritarian parenting style; 10: Round 1 permissive parenting style; 11: Round 1 frequency of fathers eating with child; 12: Round 1 frequency of mothers eating with child; 13: Round 1 family feeding practice; 14: Round 1 frequency of mealtime television viewing; 15: Round 1 frequency of grandparents eating with child

Table 3. Direct effect (b and 95% CI) of round 1 family mealtime environment, parenting style, and family functioning on round 2 child behaviour

Round 1 variables	Round 2 ECBI Intensity	Round 2 ECBI Problem
Family income	-2.61 (-7.02, 1.79), $p = .245$	-0.13 (-1.35, 1.10), $p = .838$
Child gender	-6.39 (-10.43, -2.35), $p = .002$	-1.44 (-2.59, -0.30), $p = .014$
Authoritative parenting style	-0.29 (-0.61, 0.02), $p = .064$	-0.04 (-0.13, 0.05), $p = .393$
Authoritarian parenting style	0.80 (0.36, 1.24), $p < .001$	0.11 (-0.02, 0.23), $p = .102$
Permissive parenting style	1.59 (0.78, 2.39), $p < .001$	0.39 (0.16, 0.62), $p = .001$
C-FAI Communication	0.28 (-0.20, 0.76), $p = .252$	0.05 (-0.09, 0.19), $p = .490$
C-FAI Conflict and harmony	0.27 (-0.37, 0.91), $p = .408$	0.07 (-0.12, 0.25), $p = .481$
C-FAI Parental concern	-0.34 (-1.84, 1.17), $p = .661$	0.17 (-0.26, 0.60), $p = .444$
C-FAI Parental control	0.30 (-0.71, 1.32), $p = .557$	0.17 (-0.12, 0.46), $p = .261$
Frequency of fathers eating with child	-0.16 (-0.98, 0.67), $p = .710$	-0.01 (-0.24, 0.23), $p = .942$
Frequency of mothers eating with child	0.43 (-0.60, 1.47), $p = .413$	0.19 (-0.10, 0.49), $p = .199$
Frequency of grandparents eating with child	0.21 (-0.19, 0.62), $p = .300$	0.10 (-0.02, 0.22), $p = .089$
Frequency of mealtime television viewing	-0.02 (-0.80, 0.77), $p = .970$	0.21 (-0.02, 0.43), $p = .076$
Family feeding practice	-0.58 (-0.92, -0.23), $p = .001$	-0.07 (-0.16, 0.03), $p = .168$

The Sample

In Round 1, among 2,492 consent forms distributed, 923 parents consented to participate. Eleven participants were either outside Hong Kong or had changed schools when data was collected. There were 663 sets of complete data out of 912 data sets collected [24]. In Round 2, there were 676 parents with complete data. There were 470 parents with complete data in both waves, which provided the basis for the reported analysis.

Participants with complete and incomplete data in both rounds differed. Participants with complete data in both rounds attained lower scores on Round 1 C-FAI conflict and harmony, $t(859) = 2.67$, $p = .008$, and Round 1 authoritarian parenting, $t(847) = 2.07$, $p = .043$. Among those with complete data in both rounds, there was a higher proportion of families with monthly income above HK\$20,000, $\chi^2(1) = 8.05$, $p = .005$.

Frequency of Child Behavior Problems (ECBI-Intensity)

Round 2 ECBI-Intensity scores were associated positively with Round 1 authoritarian and permissive parenting and negatively with Round 1 family feeding practice and child gender (Table 3). As Round 1 permissive parenting was negatively associated with Round 1 family feeding practice ($b = -0.78$, $z = -7.01$, $p < .001$), the mediating effect of Round 1 family feeding practice as a mediator between Round 1 permissive parenting and Round 2 ECBI-Intensity scores was tested. The positive indirect ($z = 3.00$, $p = .045$) and total ($z = 5.12$, $p < .001$) effect of Round 1 permissive parenting on Round 2 ECBI-Intensity scores were significant. Round 1 authoritarian parenting was negatively associated with Round 1 family feeding practice ($b = -0.17$, $z = -2.66$, $p = .008$). The mediating effect of Round 1 family feeding practice as a mediator between Round 1 authoritarian parenting and Round 2 ECBI-Intensity scores was tested. The positive indirect ($z = 2.09$, $p = .037$) and total ($z = 3.95$, $p < .001$) effect of Round 1 authoritarian parenting on Round 2 ECBI-Intensity scores were significant.

.001) effect of Round 1 authoritarian parenting on Round 2 ECBI-Intensity scores were significant. In short, higher frequency of child behavior problems was associated with more authoritarian and permissive parenting, less healthy feeding practice, and the child being male. Family feeding practice was a mediator between permissive/authoritarian parenting and frequency of child behavior problems.

Parent Concern over Child Behavior Problems (ECBI-Problem)

Round 2 ECBI-Problem scores were negatively associated with child gender and positively associated with Round 1 permissive parenting (Table 3). More parent concern over child behavior problems was associated with the child being male and more permissive parenting.

DISCUSSION

In terms of Hypothesis 1, the results indicated that family mealtime environment variables had direct contributions to child behavior, after controlling for family functioning, parenting style, and family income. Specifically, healthier feeding practices were associated with lower frequency of child behavior problems. The longitudinal design of the present study provided further support for the causal relationship between family feeding practices and child behavior outcomes. The emphasis on healthy food (rather than the often more appealing unhealthy food) and regular meal routines implies a sense of self-regulation which is conducive to positive behavior outcomes. The results confirmed that mealtime routines were related to children's mental health [1]. The results also concurred with literature and provided support for the negative effect of authoritarian and permissive parenting on child behavior [11].

With regard to Hypothesis 2, the results provided evidence of family mealtime environment variables as mediators of parenting style on child behavior outcomes. Permissive parenting styles negatively influenced child behavior outcomes through family feeding practices. Parents with permissive styles were more likely to allow unhealthy feeding practices (e.g., unhealthy food, lax meal routines), which then predicted more child behavior problems. Authoritarian parenting rigidly demanding the child to finish all food served might lead to parent-child conflict and child problem behavior [1].

The present study illuminated on parenting practices for Hong Kong Chinese families with preschool children. The findings generally concurred with the international literature on the impact of parenting style and family mealtime environment on children's outcomes. Family mealtime environment variables reflected actual parenting practices such as type of food eaten, arrangement of meal routines, and management of mealtime behavior. The results indicated that actual parenting practices and parenting styles were both influential on child developmental outcomes.

Limitations

First, the family and parenting measures were only based on parent reports. Second, the reporting parents were mostly mothers, while views from both parents should be useful to identify possible couple differences in parenting styles or practices, as well as their impact on child and family outcomes. Third, the sample did not include preschools in all administrative districts of Hong Kong, and is not adequately representative of the Hong Kong population. Fourth, participants with incomplete data were more disadvantaged and less positive in parenting practices than those with complete data. These should be fully considered in the interpretation of the data.

CONCLUSION

This study underscores the importance of considering family mealtime environment in understanding family influence on child development. Family mealtime environment variables and parenting style variables contributed directly to child behavior. Family feeding practice was associated with parenting style, and family feeding practice mediated the effect of parenting style on child outcome. This study reinforces the efforts to conduct longitudinal studies in families. Such attempts in this study successfully generated meaningful causative information that can directly enrich health education and the practice of professionals working with young children. The findings allow for evidence-based assertions that parenting styles are associated with child outcomes. It will be helpful for parents to learn to be responsive to their children, harbor realistic expectations on their children and be reasonably demanding on their age-appropriate performance. Parents should try to create more opportunities to cultivate healthy and pleasant family atmosphere. Parents should set limits and rules for appropriate mealtime behavior, provide a variety of food, and let the child decide how much to eat and what to eat [18].

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Chapter 321

FAMILIES IN TRANSITION IN HONG KONG: IMPLICATIONS TO FAMILY RESEARCH AND PRACTICE

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ABSTRACT

Utilizing the life course perspective, historical time and events that have influenced family development, delay of social timing of family development, linked lives that supported families and emergence of different modes of the families in Hong Kong were examined. The analyses showed several changes in the structures and functions of families in Hong Kong during the past few decades, which include: 1) reduced birth rate due to the success of the "birth control" campaign, the change of the conception of childbearing and the rising burden associated with child rearing; 2) delay of social timing of marriage and parenthood as more females participated in the labor force; 3) increased

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involvement of grandparents and foreign domestic helpers in taking care of children; 4) parents are heavily affected by the educational opportunities and achievement of their children, resulting in the mushrooming of “monster parents” (helicopter parents) who “hover” over their children’s lives; 5) emergence of “DINK” (Double Income, No Kids) families; 6) an increase in cross-border marriages; 7) an increasing trend of marital disruption in families; and 8) a growing demand for the recognition of non-traditional forms of families. The implications of these family developments to family research and practice were discussed.

INTRODUCTION

Family is regarded as the “vital component of the society” [1]. It is the basic unit of production, reproduction and perpetuation, protection of members from external forces, socialization, nurturing for the next generations, mutual support and emotional security [2, 3]. However, the socio-economic and cultural transformations in Hong Kong in the past few decades have brought about dramatic changes to families. The reduction of family size, an increasing number of mothers entering into the labour force, the rise of divorce rate, an emergence of “DINK” (double income with no kids) families, the blossoming of “monster parents” (helicopter parents) who “hover” over their children’s lives [4] are examples illustrating the inevitable structural and functional changes that have happened in the families in Hong Kong. While some changes are the result of global transformation of families, some changes are unique to the social, political and economic conditions in Hong Kong. Against such macro social changes, several questions should be asked - What have happened to the cohorts who are now the main actors of the families? What were the historical, social and cultural transformations that have influenced the family structures and functions? What were the changes of the families during this transition?

The generation theorists have offered special labels to different cohorts born after the World War II, namely the “Baby Boomers” (1943-1960), “Generation X” (1961-1981), and “Generation Y” or “The Millennial” (1982-2000) [5, 6]. According to such views, each cohort showed very special characteristics due to the social changes that happened during those eras. The cohort studies provided an insightful lens for scholars and policy makers to understand how social changes affected these generations, and how one generation affected the other generations. However, they did not specifically employ the family as the basic unit of study, and they paid inadequate attention to the changes of the family structures and functions. Moreover, the studies took US as the backstage and the observations might not be applicable to non-American cultures, as culture is an important determinant of the development of families [7]. To understand the changes of families during the transition in Hong Kong, the life course perspective [8, 9] provides an useful angle to examine the historical and social transformations that have influenced Hong Kong family development in the past few decades.

THE LIFE COURSE PERSPECTIVE

As suggested by Bengtson and Allen [10], the life course perspective is a “contextual, processual, and dynamic approach to the study of change in the lives of individual family

members over time, and of families as social units as they change over historical periods” [10]. Elder [8] concretely gave a definition to the life course as “age-graded life patterns embedded in social structures and cultures that are subject to historical change” [8]. Three basic components are intrinsic to this definition: age-graded life patterns, social structure and culture, and historical change. Regarding the age-graded life patterns, they are formulated by the ontogenetic development of individuals as well as the stages of family life cycle. Life span theories, such as Erikson’s [11] psychosocial stages of development, give an account of the ontogenetic development of individuals. A family life cycle portrays the stages of family development by examining different family developmental tasks in response to the development of its members [12]. Concerning the social structure and culture, there are four dimensions: social structural context, social construction of meaning, cultural context and the interplay of macro-micro levels of analysis [10]. Finally, historical time is the “events, periods, or eras dominated by watershed geopolitical or economic events” [10]. In summary, the life course perspective emphasizes the interplay of life span development, historical time and events, as well as the social context. White and Klein [13] regarded the life course perspective to focus on the “sociological meaning of development” [13]. Hence, the evolvement of the life course perspective put the two lines of inquiries, including life span development (i.e., the intra-individual changes) and social development (i.e., the extra-individual changes), together.

PARADIGMATIC THEMES OF THE LIFE COURSE PERSPECTIVE

Elder and his colleagues [8, 9, 14] suggested four paradigmatic themes that are central to the life course perspective, including a) human lives in historical time and place, b) the timing of lives, c) linked or interdependent lives, and d) human agency in the choice making and social constraints. These themes do not only constitute the essential elements of the life course perspective; they also identify important mechanisms through which the history and social contexts influence human development.

Human lives are influenced by the historical events and social contexts. In the life course, people of different ages are exposed to different historical worlds and may have different impacts in their lives. Thus, history brings the “cohort effect” to a particular birth cohort when there are social changes that affect and differentiate their life patterns from other cohorts [8].

The timing of lives emphasizes the concept of “social timing” that defines the start and the termination of social roles, their duration and sequence in respect to the relevant age expectations and beliefs [8]. The social timing of lives is essential as it gives the structure to the life course where age norms, sequences, durations of life events and trajectories are embodied.

Linked or interdependent lives are the social relationships with kin, friends and the significant others across the life span [8]. It is expected that one’s life course would knit with those of the others sharing the significant relationships [9]. Finally, as differentiated from social determinism that human agency is determined by the social environment, the life course theory respects the choices of individuals in determining their live course. However, there are social constraints and age-graded norms that may create restrictions. Individuals

may need to make their own choices with the interpretations of the opportunities and constraints [8].

HONG KONG FAMILIES IN TRANSITION

Hong Kong has undergone rapid demographic and social changes that have strong impacts on the family development during the past few decades. Furthermore, the Government policies also provided structural opportunities and constraints to individuals that may affect their marital and parental trajectories [15]. Thus, identifying the historical development as well as the policies implemented during the past decades would be important for understanding the families in transition.

The Birth Control Campaign in the 1970s: “Two is Enough”

The baby boom in the post-war period as well as the influx of immigrants from mainland China resulted in a rapid increase of the population from 1950s to 1970s in the last century in Hong Kong. There was a need for the Government to control the population growth. Against this background, the Family Planning Association of Hong Kong launched the “Two is enough” campaign to arouse public concern on birth control in 1975. The Association used a series of propaganda and educational means to encourage families to have two children at most, accompanied with other birth control services such as the use of contraceptives, sterilization and pregnancy termination operation. The campaign not only resulted in a sharp decrease in the fertility rate (from 3,459 children per 1,000 women in 1971 to 2,047 in 1980) in Hong Kong; it also altered the Chinese beliefs of “child-bearing” in the Hong Kong society. In the traditional Chinese culture, childbearing was considered as a natural biological imperative in the Chinese families. The Chinese cultural focus of “*chuan zong jie dai*” (continuation of posterity) and “*ji hou xiang deng*” (to have descendants for lighting the joss stick and lantern) was considered as the primary function of the family. Thus, contraception and termination of pregnancy were considered as anti-natural, immoral and anti-familial concepts that were not generally embraced by the Chinese values. The consequences of “*sha sheng*” (killing lives) and “*jue hou*” (prohibiting posterity) were social taboos in the traditional Chinese culture.

However, the “Two is enough” campaign constructed a new conception of childbearing that birth could be “controlled”. Birth control was no longer considered as an anti-natural and anti-familial concept that resulted in “*sha sheng*” or “*jue hou*”, but a new connotation of “family planning”. With the advancement and popularity of contraceptive methods, people are more acceptable to use these methods to “control birth”. The frequent use of contraceptive practice (almost every time of sexual intercourse) was 86%, 79.5% and 74.8% in 2002, 2007 and 2012 respectively. The rate of induced abortion was 26.3%, 20.6% and 14.1% in 2002, 2007 and 2012 respectively [16]. Though there were decreasing trends of frequent use of contraceptive practice and induced abortion during the past decade (probably due to the use of other means of contraception), the figures were still striking. The campaign not only helped to legitimize the use of contraception and termination of pregnancy, but also altered the

Chinese cultural value of “continuation of posterity”. In a survey on understanding the change of family values, it was found that the young generation showed less agreement on “having descendants to carry on the family name is very important” than did their parents [17].

The attitudinal changes on childbearing as well as common practice of contraceptive methods have facilitated the couples to have fewer kids, or even have no kids. From the statistics of the Census and Statistics Department [18, 19], it was found that the average domestic household size has gradually decreased from 4.3 in 1981 to 2.9 in 2014. The total fertility rates also dropped rapidly over the past three decades. There were only 927 children per 1,000 women in 2001, which were far below the replacement level of 2,100 children per 1,000 women [20]. “The small family culture” [21] characterized by very few kids and child-centered family practice was evolving.

Compulsory and Free Education

In 1971, the Government launched the policy of “six-year compulsory and free education” in Hong Kong. The policy was expanded to nine years in 1978 and free education was further expanded to twelve years in 2008. The policies provided dramatic changes on the educational attainment of citizens in Hong Kong. Before that, it was not easy for children to receive education to the secondary level, especially for females. With the traditional cultural discourse of “man is superior to woman” (*nan zun nu bei*) in the Chinese society, the chance for females to receive education was less. However, the implementation of “compulsory and free education” policy became a turning point for educational attainment of women, where women were treated the same as men in receiving free and compulsory education. The policy has three important impacts: higher educational attainment of women, increased women’s participation in the labor force, and rising aspirations for career prospect for women. It was found that female students studying in the programs funded by the University Grants Committee (sub-degrees, undergraduates, postgraduates) had been increased from 15,609 (32.9%) in 1986/1987 to 52,598 (53.9%) in 2014/2015 [22]. The related percentages of females had surpassed the percentages of males from 1996/1997 onwards [19]. In particular, the percentage share of female students enrolled in postgraduate and undergraduate programs were 60.6% and 54.7% respectively, which further exceeded the percentages of males enrolled in these programs [19]. When considering women’s participation into the labor force, there was a steady increase of females entering into the labor force. In the past three decades, the female to male ratio in labor force has increased from 0.58 in 1986 to 0.95 in 2014 [19]. The gap between the labor force participation between males and females was narrowing. Furthermore, there were increasing numbers of women occupying higher positions in the labor market. The numbers of females occupying the posts of managers/administrators and professionals have increased from 403,000 and 377,000 respectively in 1993 to 1,065,000 and 861,000 respectively in 2010 [19]. Women in Hong Kong have been gaining better career prospects.

Open-Door Economic Policy of Mainland China since 1978

The open-door economic policy of mainland China is an important milestone of the changes of the economic structure in Hong Kong. Before that, Hong Kong was dominated by the manufacturing industries which required unskilled or semi-skilled labor. Women were commonly engaged in low-wage factory work which required a low educational standard and skills. With the open-door economic policy of mainland China since 1978, there was a great expansion of tertiary industries such as banking, finance, legal advice and consultation, information technology, etc. A high level of knowledge and professional skills were required. Managerial and professional positions increased and required employees with higher educational attainment and career commitment. As mentioned, this attracted more females to fill the managerial and professional positions [19].

The open-door economic policy of mainland China has also facilitated the emergence of cross-border marriages, extra-marital affairs across the border, and educational problems of children across the border [23].

Engagement of Foreign Domestic Helpers

In the face of the labor policy of the Philippines to encourage and promote export of labor in the form of overseas Filipino workers, the Hong Kong Government has opened up the legal immigration channels for the families to hire foreign domestic helpers (FDH) since 1974. The employer families need to sign up a two-year standard employment contract with the foreign domestic helpers and apply for a visa from the Immigration Department.

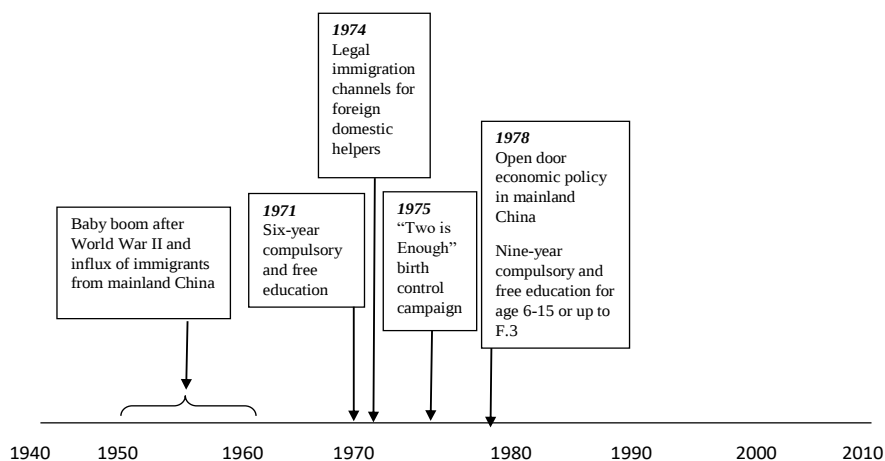


Figure 1. The occurrence of historical events during 1961-1980 in Hong Kong that influenced family development.

With the economic prosperity of Hong Kong in the 1980s and 1990s, the employment of foreign domestic helpers was becoming very popular in Hong Kong. The number of foreign domestic helpers increased from 172,119 in 1998 to 330,650 in 2014. Among them,

Philippino and Indonesian maids accounted for 52.3% and 45.3% of the number of foreign domestic helpers, respectively [19].

In summary, Figure 1 illustrates the occurrence of the historical events during 1961-1980 in Hong Kong that influenced family development.

The Delay of Timing in Different Stages of Family Development

The popularity of education resulted in the delay of school completion age of adults. A crucial effect is that there was a time delay for a person to enter the work force. The labor force participation rate of males and females aged 15-24 dropped significantly from 65.5% and 61.7% respectively in 1986 to 8.0% and 8.6% respectively in 2014 [19]. Obviously, the delay of timing of school completion implies prolonged dependency of adult children to their families.

Besides, women nowadays have a higher chance to hold jobs with better career prospect. To sustain the requirement of their jobs, they need to invest longer working hours, more work commitment, educational advancement and on-job training. According to the human capital theory [24], increased economic opportunities may influence the marriage pattern and decision of women. The career commitment and human capital investment happened early in the life course of adulthood may delay the decision of women to engage in marriage. Wong [25] provided support for this view which showed the relationship between the rising educational attainment and employment opportunities of women and the postponement of timing of marriage in Hong Kong.

During the past three decades, it was found that the median ages of first marriage of males and females have risen from 27.0 and 23.9 respectively in 1981 to 31.2 and 29.1 respectively in 2014 [22]. With the normative sequence that marriage precedes parenthood, the delay of timing of marriage definitely delays the timing of parenthood.

To understand the timing of parenthood, it is important to differentiate the concepts of the biological timing from the social timing. Biological timing of parenthood refers to biological capability of individuals to remain reproductive. Biological capability sets a non-negotiable deadline to parenthood, with the loss of fecundity of women [15]. Normally, the childbearing ages of women are between 15 and 49 years of age [22]. Social timing of parenthood takes into account of the readiness of an individual to enter into the parental role. Marital status, life transition, social expectations and constraints would propose a relative “social timing” [15]. In the past three decades, there was a disparity between biological timing and social timing in marriage and parenthood in Hong Kong. The couples were biologically “fit” to enter marriage and parenthood, but the social timing to enter into the social roles of being married and as parents lagged behind. There are three consequences of the delay of timing of parenthood. First, women gave birth to a child at an older age. The median age of women at the first birth rose from 25.1 in 1981 to 31.3 in 2014 [19]. Second, the couple did not have many children. The changes of cultural beliefs on “child-bearing” resulted from the “birth control” campaign also fascinated the delay of timing of child-bearing. Third, some parents might consider having no children due to the high risk of dystocia and anxiety for bearing an abnormal child in late pregnancy, as well as the anticipated difficulties in finance and effort to rear a child.

Interestingly, there has been a social discourse generated by the mass media that rearing a child lifelong requires HK\$4,000,000 (roughly US\$500,000).

“Linked Lives” --- The Support but Indulgent Care of Grandparents and Foreign Domestic Helpers

In the life course perspective, linked lives are essential for a family to establish significant relationships with others across the life span [9]. Among all, two significant relationships are critical for the Hong Kong families: the family of origin as well as foreign domestic helpers.

The families of origin are important supportive systems of the nuclear families. Grandparents played an important role of taking care of their grandchildren and were often regarded as “substitute parents” [21]. Although grandparents might not live together with their adult children due to the limited space in Hong Kong, the non-cohabitation did not restrict the genuine needs of the adult children as well as the grandparents’ enthusiasm to take care of their grandchildren. In a household survey commissioned by the Family Council in 2013, it was found that 58.3% of the respondents agreed on the high values of roles played by grandparents in family life, and 65.3% agreed that grandparent’s involvement was appreciated by the adult parents [26].

The opening-up of legal immigration channels for foreign domestic helpers from the Asian countries by the Hong Kong Government has facilitated more women to enter into the labor force, while foreign domestic helpers manage the family housework as well as take care of the elderly and the children at home. Though employing foreign domestic helpers in childcare was regarded as the reluctant choice of the working parents, it became an actual reality of many families in Hong Kong [27].

As there was an increasing trend of mothers participating in the labor force, grandparents were more involved in taking care of their grandchildren. However, the parenting style of grandparents might be different from that of the parents [28] and this might result in intergenerational conflicts and disputes [29]. Moreover, the involvement of grandparents might intrude into the family life of the adult child’s family and create power dynamics between the grandparents and adult parents. Intergenerational discrepancies in parenting styles might generate opportunities for the children to manipulate the family members in order to get the most benefits [28].

As a consequence, there was a creation of “4-2-1 indulgence” culture (i.e., four grandparents and two parents spoiling one child) [30]. In addition to the popularity of employing foreign domestic helpers to do housework and take care of the children, there were totally seven adults serving one child. The child becomes the “little emperor” of whom the family adults give superior attention, human and material resources [31]. The adolescents today are labeled as the “spoilt generation” who show signs of narcissist traits [32]. They are also regarded as “Hong Kong Kids” who are “unable to look after themselves, have low emotional quotient and even lower adversity quotient.” [33]. This would make them grow up in a “greenhouse” and become more egocentric [34].

Due to the very few children in the family as well as the “*wang zi cheng long*” (expecting the son to become a dragon) beliefs embedded in the Chinese culture, the parents have high

expectation about their children's future [3]. They were heavily affected by the educational opportunities and achievement of their children, hoping that their children could be competitive in their future. The parents paid great effort and plenty of resources to nurture their children, with the expectation that they could win "at the starting line". As a consequence, they were highly involved and intervened frequently in their children's lives. Different terminologies of "helicopter parenting" [35], "monster parenting", "lawnmower parenting" [36] have been used to describe the over-parenting or over-nurturing phenomenon. The parents have faced much stress in nurturing their children and may further affect the parent-child relationship. In a household survey commissioned by the Family Council in 2013, it was found that 72.0% of the parents felt more tired than before, 63.2% expressed that their large part of life was controlled by the child's needs, and 60.4% suffered from the severe lack of personal time [26].

Choices of the Couples – Emergence of Different Forms of Families

Though there were historical events and social constraints shaping the life course trajectories of the families, the couples could still make their own choice in constructing their families. There were three types of families that are prevalent in Hong Kong: the "DINK" families, cross-border marriages and the divorced families.

"DINK" means "Double income with no kids". "DINK" families are childless or childfree families with the couples participating in the labor force. In the past, the phenomenon was considered as "deviant" and "abnormal", especially in the Chinese culture that continuation of posterity is emphasized. Childlessness was considered as "*jue hou*" (prohibiting posterity) in the traditional Chinese culture which was regarded as a taboo. It was up to 1970s and 1980s that "child-free" was considered as an "alternative lifestyle" that families could have outside the traditional norms of a nuclear family [37]. According to the Family Planning Knowledge, Attitude and Practice in Hong Kong Survey in 2012, it was found that there were 23.4% of the respondent families reported childless (excluding those families with involuntary infertility or sub-fecundity). There were also 7.1% of females and 5.3% of males who preferred to be "child-free" [16].

Besides personal choices, there are social constraints that might affect the couples to choose childlessness. Work is one of the barriers for married couples to have children. Career advancement, employment opportunities, long-hour work culture are considerations of the married couples to remain "childless" [38]. Age is another important factor that the couple would prefer childfree, especially those entering middle adulthood. Rowland [39] highlighted two components for the age-related fertility decline: a reducing probability of conceiving and an increasing risk of spontaneous abortion. Furthermore, the high risk of dystocia as well as anxiety for bearing an abnormal child in late pregnancy would forbid the couples to consider childbearing. In addition, rearing a child requires huge responsibilities and financial costs that have become a social constraint of childbearing. Jones [40] suggested the ideology of having "quality" child and financial costs of childbearing were factors that lower the desire of childbearing among the married couples in Pacific Asia. Among the respondent couples who did not want to have children in the Family Planning Knowledge, Attitude and Practice in

Hong Kong Survey in 2012, 43.3% of females and 42.0% of males suggested that the financial constraint was the main reason for childlessness.

The open-door economic policy of mainland China has facilitated the emergence of the cross-border marriages in Hong Kong. In 2014, there were 26,330 cases of cross-border marriages in Hong Kong, of which 20,698 marriages registered in Hong Kong, occupying 36.7% of the total marriages registered that year [19]. There were some unique features arising from the cross-border marriages, which include the marriages between a young wife and an old husband, split families and pseudo single parent (either children live with father in Hong Kong while mother stays in China, or the children stay with mother in China while father resides in Hong Kong), and cross-border education of children [41, 42]. Though the cross-border marriage has been a common form of marriage in recent years, concerns and problems such as adjustment difficulties of migrant mothers and children, increased risk for marital stability and harmony, accommodation problems in Hong Kong with limited living space, parenting difficulties, problems in children's education, poorer care, nurture and modeling of the children, social isolation and higher risk of spousal violence [23, 42, 43] are emerging.

When looking at the divorce rate figures, the crude divorce rate has been increasing steadily from 0.76 in 1984 to 3.1 in 2013, with the first time of decrease to 2.8 in 2014 [19, 44, 45]. It is worth noting that divorce as a percentage of marriage remained high (33% to 35%) during the past five years. One reason accounting for the change was the direct influence of the Western romantic conception of marriage that has eroded the Chinese cultural values of familism [46]. The conception of marriage in Hong Kong has been moving away from a traditional and patriarchal mode to a modern and egalitarian one [47]. Instead of preserving a long-lasting conjugal relationship based on the Confucian virtues of familism, the couples would consider divorce when they experienced marital dissatisfaction. The temptation of extramarital affairs also constituted the increase of divorce rate [46, 48]. Moreover, the general acceptance of divorce by the public makes divorce become a "means" to solve marital dissatisfaction. In a household survey commissioned by the Family Council, 63.2% of the respondents agreed that if a married couple did not have children, divorce was the best solution for them when they could not live harmoniously. Even if the couple has children, 32.3% still agreed that divorce was the best choice if they could not live together agreeably [26].

Apart from the increase of DINK families, popularity of cross-border marriages and high divorce rate, there is a growing demand for the recognition of non-traditional forms of families. Similar to the Western world, the voice of LGBT (lesbian, gay, bisexual and transgender) communities to recognize their rights for marriage, adoption of children and formation of family was blooming. In 2013, the court ruling on transgender marriage has raised the hopes for sexual minorities to pursue their rights in marriage and family formation [49]. At the same time, it has brought great challenges to the traditional values of marriage and family. As mentioned by the dissenting judge of the court case, to consider a transsexual's marriage a right implies "a radical change to the traditional concept of marriage" [50]. The traditional forms of marriages are confronted with strong pressure, which may bring revolutionary changes to the family forms, values and systems. Table 1 summarizes the family changes in the transition under the paradigmatic themes of the life course perspective.

Table 1. Summary of family changes in Hong Kong under the paradigmatic themes of the life course perspective

Paradigmatic themes	Family changes
Humans live in historical time and place	- The birth control campaign in 1975: “Two is Enough” - Compulsory and free education - Open door economic policy in mainland China - Legal immigration channels for foreign domestic helpers - Reduced birth rate - Change of the conception of childbearing and less emphasis on the Chinese value of “continuation of posterity” - Delay of social timing of marriage and parenthood - More mothers participated in the labor force - The employment of foreign domestic helpers for childcare and family housework
The timing of lives	- Delay of social timing of marriage and parenthood - Reduced birth rate - Emergence of “DINK” (Double Income, No Kids) families
Linked or interdependent lives	- Increased involvement of grandparents and foreign domestic helpers in taking care of the child - Indulgence parenting with seven adults (four grandparents, two parents and one foreign domestic helper) in nurturing one child in a family - Parental stress due to high expectation on education and achievement of their children - The mushrooming of “monster parents” (helicopter parents) who “hover” over their children’s lives
Human agency in choice making and social constraints	- Emergence of “DINK” (Double Income, No Kids) families - Increase in cross-border marriages involving young wives and old husbands - Increasing trend of marital disruption in families - A growing demand for the recognition of non-traditional forms of families

IMPLICATIONS TO FAMILY RESEARCH AND PRACTICE

With reference to the analyses based on the life course perspective, the families in Hong Kong are exhibiting several changes. These included: 1) reduced birth rate due to the success of the “birth control” campaign, the change of the conception of childbearing and the rising burden associated with child rearing; 2) delay of social timing of marriage and parenthood as more females participated in the labor force; 3) increased involvement of grandparents and foreign domestic helpers in taking care of the children; 4) parents are intensely affected by the educational opportunities and achievement of their children, resulting in the mushrooming of “monster parents” (helicopter parents) who “hover” over their children’s lives; 5) emergence of “DINK” (Double Income, No Kids) families; 6) an increase in cross-border marriages involving young wives and old husbands; 7) an increasing trend of marital disruption in families; and 8) a growing demand for the recognition of non-traditional forms of families. The changing family trends draw attention of social scientists, researchers and clinical practitioners on family research and practice.

The life course perspective provides thoughtful ideas in understanding how the historical and social contexts influence the development of family life patterns. This is especially meaningful in the Chinese families, as familism is central in the Chinese culture [51, 52]. It is insightful and important if longitudinal panel studies across cohorts were conducted to

examine how different historical and social contexts influence family beliefs and life patterns in the life course trajectories.

As suggested by Elder and Shanahan [9], the temporal location of reproductive cycle greatly influenced the family life cycle. Early childbearing would hasten the cycle and shorten the distance between generations. In contrast, late childbearing may decelerate the cycle and reduce the age similarities across generations. In Hong Kong, the delay of social timing of marriage and parenthood is salient and affects the family life patterns across adjacent generations. Thus, it is important to examine the influence of temporal location and timing of family life cycle on human development and life patterns.

The life course perspective not only sketches the temporal changes in the patterns of family life cycle, it also portrays the changes of roles within the family. The social contexts have influenced greatly on the roles and division of labor in the family. With more mothers participating in the labor force and grandparents and foreign domestic helpers offer support in childcare and housework, their roles within the family are changing. It is interesting and important to examine the changes in roles and functions of different members in families, as well as the family dynamics such as family boundary, rules, power and interactions, etc. The importance of linked lives across the life span and generations should catch more research attention. Furthermore, timing also matters to the role and identity change of the family members. The implications of marriage and parenthood may vary in accordance with the social timetable, age norms and age-graded sanctions [9]. Ebaugh [53] used the term “role exit” to describe an identity change in response to the transformation of roles in the life span. Indeed, temporality of family roles may be an emerging area that needs to be explored.

The prevalence of divorce and child-free couples has strong impact on the family life development across generations. However, it is criticized that the life cycle which only focuses on reproduction and parenting has “limited value as a way of viewing the lives and developmental trajectories of children and adults because it does not apply to never married, non-parent, or divorced persons, all of whom have become increasingly common” [9]. In fact, divorce may imply multiple families in a person’s life which may lead to interwoven roles and complex kin relationship. Regarding the child-free families, there is a concern about the changes of the family life patterns as well as the developmental life tasks of the couples. “Parenthood” has been expected as an important developmental task in one’s life span, which may result in generativity in the middle age [54]. Thus, the absence of parenthood in the family life cycle may have great impact on their members. The effects of the divorce and DINK to the family members may need to be further researched.

From a macro perspective, the changes of forms and patterns of the families may have significant impact on the social values, structure and functions. For instance, the delay of marriage and parenthood would result in a reduced birth rate of Hong Kong, which may further bring the future risk of the aging population. The cross-border marriages may bring the demographic, cultural and social concerns to the society, as the education, value systems and lifestyles in China may be different from those in Hong Kong. Social scientists need to be sensitive to the changes and explore the impact on the society as a whole. In fact, family research in Hong Kong with respect to these areas is grossly inadequate [55].

Regarding family practice, the “small family culture” characterized by very few kids and child-centered family practice is evolving in Hong Kong. The “seven adults serving one kid” phenomenon (four grandparents, two parents and one foreign domestic helper) has happened in the Hong Kong families, with more resources being allocated for the child development,

but at the same time the children are over-parented and over-protected. Further research to examine the impact of over-parenting on child development in Hong Kong is urged. Besides, it is important for family practitioners to understand the new forms of parenting in the Chinese families and to provide parenting education to the family members. In particular, grand-parenting is becoming more and more popular in Hong Kong when both parents enter the labor force in the recent decades. However, grandparent education programs are not well developed in Hong Kong. Thus, it is important to develop effective training strategies on grandparent education.

Furthermore, the life course perspective suggests that historical events, age-graded experiences and role identity may influence individual's life span and family life development across generations. In the swiftly changing world, grandparents, parents and children may share different cultures and experiences. These may influence the family values, dynamics and interaction among the family members. The discrepancies of perceived roles and expectation among the family members, as well as the differences in parenting styles and practices between the two generations may result in family conflicts [28]. Thus, family practitioners should be sensitive to the intergenerational conflicts that may generate between the grandparents and adult parents, and resolve the conflicts when these arise. It is necessary to explore the collaborative roles between grandparents and adult children of which complementary parenting as well as respectful participation could be nurtured [56].

In view of the prevalence of the cross-border marriages in Hong Kong, there are concerns to the adjustment of the families, educational needs of the children as well as the high risks of family instability. Supportive and counseling services are definitely essential. However, the differences in social welfare policies across the border make the service difficult to be delivered to the cross-border families. Negotiation with the Chinese Government is necessary so that more resources and services can be provided to help the cross-border families. Again, we need more research in this area to illuminate the issues involved.

The rising trend of divorce has set an alarm to the family development in Hong Kong. Family breakdown and dysfunctions has detrimental effects to parental distress and adolescent development. Marital counseling and post-divorced parenting education programs are necessary. Besides, family mediation services are important.

Last but not least, new family forms and patterns challenge the conventional values of the Chinese culture and social expectation to the families. Family practitioners should be sensitive to the cultural changes and work against the social disharmony and stigmatization that may arise. Obviously, we need more research to understand how the public look at these "non-conventional" families and examine the needs, problems and resilience facing by such families. Besides, training family practitioners need to be sensitive to the "macro" social conditions instead of just focusing on the "micro" dyadic or family issues.

CONCLUSION

Hong Kong families have undergone dramatic changes in these few decades. The life course perspective provides a sociocultural lens for social scientists to explore the family life cycle and patterns of the Hong Kong families. The success of birth control campaign, free and compulsory education, increased work opportunities for women in the labor market have

brought forward the delay of social timing of marriage and parenthood. Linked with the support of grandparents and foreign domestic helpers in childcare and family management, the indulgence culture of rearing the children and over-parenting was created. The increase of divorced families, cross-border marriages, DINK families and emergence of non-traditional forms of families also became one of the concerns of family development in Hong Kong. The social account of family life course in Hong Kong is just the beginning of the long journey to explore the family life development in the Chinese communities. More scientific research should be conducted to explore how historical time and socio-cultural contexts influence family life course across generations. With the belief that people can “work out their life course in relation to established, institutionalized pathways and their regulatory constraints” [9, p.706], the studies of family life course in the Chinese communities may open a door for scholars and social scientists to have a better understanding of the Chinese families in the transition.

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Chapter 322

**SUBJECTIVE OUTCOME EVALUATION
OF THE TIN KA PING P.A.T.H.S. PROJECT
IN CHINA: VIEW OF THE STUDENTS**

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ABSTRACT

Utilizing the client satisfaction approach, the present paper reports the program participants' perceptions of a positive youth development program (Tin Ka Ping P.A.T.H.S. Project) in China. Upon the completion of the program, altogether 7,289 Secondary 1 and 2 students completed a valid and reliable questionnaire (Form A) to rate on different aspects including program content, program implementer, and program effectiveness. As anticipated, most students evaluated all the three aspects positively. Grade differences were observed, with Secondary 1 students reporting higher satisfaction on program content, program implementer, and overall satisfaction than did their Secondary 2 counterparts. Furthermore, perceived program content and implementer quality predicted perceived program effectiveness. In short, the findings underscore the effectiveness of the Tin Ka Ping P.A.T.H.S. Project launched in the academic year 2015-2016.

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INTRODUCTION

Since the beginning of the “open-door policy” in the early 1980s, China has developed rapidly. China has become the world’s second largest economy and is forecasted to surpass the United States by 2030 [1]. Such an economic growth goes hand in hand with the urbanization of the contemporary Chinese youth communities. Accordingly, how such an economic transition in China has shaped the psychological development of Chinese adolescents attracts growing interest in the research community. For instance, utilizing the cross-temporal meta-analytic data from thousands of Chinese youth, Xin and associates [2, 3] revealed that urbanization level was a significant positive correlate of adolescents’ anxiety level, depressive symptoms, and mental illness across cohorts, and the mental health of young people in China had deteriorated throughout time.

In view of such a backdrop, the Ministry of Education [4] published “The Outline of Education Guide for Pupil’s Mental Health”. One key strategy entails the permission for primary and secondary schools to hire mental health teachers to implement mental health education and offer counseling service to the students. There is, nonetheless, still a lack of systematic teaching resources for these mental health teachers regarding how psychosocial competencies of the students can be strengthened. As such, there is an urgent need to develop related curriculum materials based on the positive youth development (PYD) approach. According to Damon [5], problem prevention alone is not enough to promote healthy youth development and it is important to discover and nurture adolescents’ strengths, talents, and potentials.

With reference to Hong Kong, adolescents also display problems such as substance abuse, materialism, and bullying [6]. Nonetheless, Shek and Yu [7] highlighted the paucity of robustly evaluated, multi-year PYD programs in Hong Kong. Against such a backdrop, a multi-year project entitled “Positive Adolescent Training through Holistic Social Programs” (Project P.A.T.H.S.), funded by The Hong Kong Jockey Club Charities Trust, was launched in 2005. The Project P.A.T.H.S. which comprises two tiers is a comprehensive PYD program tailored for junior secondary-schoolers in Hong Kong. While the Tier 1 Program represents a curriculum-based intervention targeting the general junior secondary-schooler population, the Tier 2 Program was catered to adolescents with greater psychosocial needs. Results from a multitude of evaluation studies [8] corroborate the effectiveness of the Project P.A.T.H.S. over the years in promoting the holistic youth development alongside eradicating risk behavior in junior secondary students in Hong Kong.

Despite the remarkable achievement of the Project P.A.T.H.S., we have to ask whether the related programs can be successfully applied in other Chinese communities [9]. Funded by the Tin Ka Ping Foundation, the first phase of the program entitled “Tin Ka Ping Positive Adolescent Training through Holistic Social Program” (Tin Ka Ping P.A.T.H.S. Project) was embarked on in four schools in East China (Shanghai, Suzhou, Changzhou, and Yangzhou) since 2011. This pioneer project in China was well-received as evidenced by findings derived from both subjective outcome evaluation [10] and objective outcome evaluation studies [11]. Accordingly, started from the academic year 2015-2016, the second phase of the Tin Ka Ping P.A.T.H.S. Project targeting both junior and senior secondary schoolers was launched in 30 secondary schools in mainland China. Given the geographical socioeconomic differences

across provinces, it is necessary to examine if the second phase, which involves schools from both inside and outside East China, would be similarly effective.

Resembling other PYD programs, the Tin Ka Ping P.A.T.H.S. Project emphasizes program evaluation. Shek and Sun [12] outlined five key elements to a successful PYD program, including program, process, policy, people, and place (i.e., the 5Ps). Particularly, the element “people” which encompasses program participants and implementers was identified as one of the most decisive factors of all [12]. Thus, utilizing the client satisfaction approach, the present paper is primarily concerned with the program participants’ subjective evaluation of the Tin Ka Ping P.A.T.H.S. Project. The client satisfaction approach, which has been adopted cross-culturally in the field of human services [13, 14], permits researchers to examine the participants’ perceptions of program effectiveness in a cost-effective manner. For instance, Walsh and Lord [15] adopted the Client Satisfaction Questionnaire [16] to gather participants’ views on a social work intervention program. Likewise, utilizing the subjective outcome evaluation approach, Shek and Sun [17] assessed students’ perceived effectiveness of a university subject designed to nurture their leadership skills and intrapersonal development.

Nonetheless, Larson and colleagues [18] noted that students, despite being the target recipients of a program, often had their views overlooked when implementers attempted to evaluate program effectiveness. Such a negligence may stem from the stereotype that adolescents are incapable of expressing dissatisfaction in meaningful ways or that they seldom do so because of early dropout [19]. While findings from subjective outcome evaluation studies regarding the Project P.A.T.H.S. in Hong Kong are well-documented [e.g., 20, 21], we could hardly say the same about the Tin Ka Ping P.A.T.H.S. Project in China. Therefore, it is imperative that we scrutinize the views of the participants on the different aspects of the program such as program content and implementers of the project and how these aspects would interrelate with each another.

In short, utilizing the client satisfaction approach, this study examined the following research questions and hypotheses with reference to the Tin Ka Ping P.A.T.H.S. Project launched in the academic year 2015-2016:

- How do the program participants evaluate the curricula-based program (i.e., Tier 1 Program)? Based on the findings from previous evaluation studies [10], we hypothesized that a high proportion of the program participants would be satisfied with the program (Hypothesis 1). Specifically, with reference to the previous Hong Kong findings that around four-fifths of the respondents were positive about Tier 1 Program, we expected that at least four-fifths of the current respondents would show positive responses.
- How do perceived program content, implementer quality, and program effectiveness inter-relate with one another? Results from the evaluation studies of the Project P.A.T.H.S. in Hong Kong [20, 21] suggested a significant inter-correlation among these three program facets (Hypotheses 2a, 2b, and 2c).
- Are satisfaction ratings different across grades? Based on previous studies [22], it was predicted that the three aspects of client satisfaction would be inter-related (Hypotheses 3a, 3b, and 3c)?

- Are perceived program content and perceived implementer quality predictive of perceived program effectiveness? Based on previous findings [21, 22], we hypothesized that these two factors would predict perceived program effectiveness (Hypotheses 4a and 4b).

OUR STUDY

In the academic year 2015-2016, the curricula-based Tin Ka Ping P.A.T.H.S. Project was implemented in 30 secondary schools in mainland China. Amongst them, eighteen junior secondary schools participated in the current evaluation study. Of these schools, all implemented the program at Secondary 1 (S1 hereafter, equivalent to Grade 7), with three implementing the program also at Secondary 2 (S2 hereafter, equivalent to Grade 8).

To examine the effectiveness of the Tin Ka Ping P.A.T.H.S. Project, students were invited to complete the Subjective Outcome Evaluation Form (the Form A) upon the completion of the program. The program implementers who had attended training workshops over evaluation topics were responsible for data collection. An evaluation manual with standardized instructions on data collection was also distributed to each of the schools concerned. The principles of confidentiality, anonymity and voluntary participation were reiterated upon the administration of the survey. All students provided their consent prior to participation. Altogether 7,289 questionnaires were returned to Research Team. Amongst them, 6,222 were S1 students and 1,067 were S2 students.

Instruments

A well-validated and extensively used [20, 22] instrument (Form A) was adopted to solicit participants' feedback on the program. The Form A contains four parts. Part 1 examined students' overall appraisal of Program content, such as program objectives, design, and interaction among classmates (10 items). Part 2 assessed students' perception of qualities exhibited by the program implementers via ten items measuring aspects like preparation for lessons, degree of involvement, and professionalism. Items of Parts 1 and 2 were rated on a six-point Likert scale with 1 representing "strongly disagree" while 6 representing "strongly agree". The sixteen-item Part 3 assessed students' perceived program effectiveness via a five-point Likert scale (1 = unhelpful; 5 = very helpful). Part 4 contains three additional items measuring the likelihood of the respondents recommending the program to others, participating in a similar program in future, and their overall satisfaction with the program. Additionally, Form A consists of four open-ended questions on students' experience of the program (e.g., aspects of the program worthy of their appreciation). The focus of the present paper is on the quantitative data collected from the program participants.

Data Analyses

The individual data of students were adopted as the units of analysis. Reliability analyses were conducted for the present three subscales (i.e., program content, program implementers, and program effectiveness). Descriptive statistical analyses using the percentage of positive responses to each item were conducted to reveal students' perceptions of the various facets of the program (i.e., Hypothesis 1). To test Hypothesis 2, we examined the associations among the three subscales using the Pearson's correlation tests. Additionally, multivariate analysis of variance (MANOVA) was adopted to test whether there were differences in students' subjective program evaluation across grades (i.e., Hypothesis 3). Finally, Hypothesis 4 was examined via several multiple regression analyses.

FINDINGS

Results on the reliability of Form A are detailed in Table 1. All three parts each recorded excellent internal consistency as evidenced by the high alpha values (ranged from 0.93 to 0.96). The Cronbach's alpha for all three parts combined (i.e., 36 items) was 0.97.

Table 1. Mean, standard deviations, Cronbach's alphas, and mean of inter-item correlations

	Secondary 1		Secondary 2		Overall	
	M (SD)	α (Mean [#])	M (SD)	α (Mean [#])	M (SD)	α (Mean [#])
Program content (10 items)	5.04 (.83)	.92 (.55)	4.99 (.97)	.95 (.66)	5.03 (.85)	.93 (.57)
Program implementers (10 items)	5.26 (.81)	.95 (.66)	5.08 (1.05)	.97 (.77)	5.23 (.85)	.96 (.69)
Program effectiveness (16 items)	4.05 (.81)	.96 (.59)	4.07 (.92)	.98 (.72)	4.06 (.83)	.96 (.61)
Total effectiveness (36 items)	4.67 (.70)	.97 (.46)	4.61 (.67)	.95 (.34)	4.66 (.70)	.97 (.44)

Note. [#] Mean inter-item correlations.

Tables 2 to 5 show the numbers and percentages of students having a positive evaluation on the program. As most of the respondents showed positive evaluation of all facets of the program, there was support for Hypothesis 1. Table 2 shows the descriptive statistics on students' evaluation of the program content. Results showed that an overwhelming proportion of the sample responded positively. For instance, 93.1% thought highly of the curriculum design, 93.8% appreciated the clarity of the curriculum objectives, and 92.7% reported that they generally "liked the curriculum very much".

Table 2. Descriptive statistics of the participants' evaluations on the program content

	Respondents with positive responses (Options 4-6)					
	Secondary 1		Secondary 2		Overall	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
The objectives of the curriculum are very clear.	5834	94.2	969	91.2	6803	93.8
The design of the curriculum is very good.	5782	93.5	964	90.7	6746	93.1
The activities were carefully planned.	5695	92.3	951	89.5	6646	91.9
The classroom atmosphere was very pleasant.	5526	89.5	966	90.9	6492	89.7
There was much peer interaction amongst the students.	5581	90.5	947	89.2	6528	90.3
I participated actively during lessons (including discussions, sharing, games, etc.).	5596	90.6	967	91.1	6563	90.7
I was encouraged to do my best.	5575	90.2	921	86.7	6496	89.7
The learning experience I encountered enhanced my interest towards the lessons.	5659	91.6	944	88.8	6603	91.2
Overall speaking, I have a very positive evaluation of the program.	5583	90.4	940	88.4	6523	90.1
On the whole, I like this curriculum very much.	5756	93.2	955	89.8	6711	92.7

Note. All items were rated on a 6-point Likert scale with 1 = strongly disagree, 2 = disagree, 3 = slightly disagree, 4 = slightly agree, 5 = agree, 6 = strongly agree. Only the positive responses (Options 4-6) are shown.

Regarding participants' evaluation of the program implementers, over 92% of the respondents rated positively on all the ten items. Some examples included perceived mastery of the curriculum (93.8%), professionalism exhibited (94.0%), preparation for the lessons (94.9%), and overall satisfaction with the implementers (94.9%).

Table 3. Descriptive statistics of the participants' evaluations of the program implementers

	Respondents with positive responses (Options 4-6)					
	Secondary 1		Secondary 2		Overall	
	<i>n</i>	%	<i>n</i>	%	<i>N</i>	%
The instructor(s) had a good mastery of the curriculum.	5839	94.4	951	90.1	6790	93.8
The instructor(s) was well prepared for the lessons.	5894	95.4	967	91.7	6861	94.9
The instructor(s)' teaching skills were good.	5861	94.9	947	89.8	6808	94.2
The instructor(s) showed good professional attitudes.	5830	94.5	961	91.2	6791	94.0
The instructor(s) was very involved.	5864	95.0	962	91.2	6826	94.5
The instructor(s) encouraged students to participate in the activities.	5880	95.4	983	93.3	6863	95.1
The instructor(s) cared for the students.	5851	94.9	942	89.4	6793	94.1
The instructor(s) was ready to offer help to students when needed.	5902	95.7	960	91.1	6862	95.0
The instructor(s) had much interaction with the students.	5792	93.6	936	88.7	6728	92.9
Overall speaking, I have a very positive evaluation of the instructors.	5901	95.5	966	91.6	6867	94.9

Note. All items are rated on a 6-point Likert scale with 1 = strongly disagree, 2 = disagree, 3 = slightly disagree, 4 = slightly agree, 5 = agree, 6 = strongly agree. Only the positive responses (Options 4-6) are shown.

Table 4 details the descriptive statistics on students' ratings regarding perceived program effectiveness. Over 85% of the respondents showed positive ratings on all the 16 items. For instance, 91.8%, 93.1%, and 92.4% of the students felt that the program had raised their self-confidence, self-awareness, and social competence, respectively. There were 94.4% of them indicating that the program had "enriched my overall development". Table 5 presents students' ratings on the three additional items. Over 90% indicated that they would recommend the program to others (94.5%) and participate in a future similar program (93.2%). Furthermore, 94.3% expressed satisfaction with the program. In short, Hypothesis 1 was supported.

Results of the Pearson correlation analyses showed that the three subscales were significantly and positively correlated with one other. Both program content ($r(6,869) = 0.55$, $p < .001$) and program implementer ($r(6,881) = 0.45$, $p < .001$) were correlated with program effectiveness. The relationship between subscales program content and program implementer was the strongest ($r(6,954) = 0.59$, $p < .001$). Hence, Hypotheses 2a to 2c were supported.

Table 4. Descriptive statistics of the participants' evaluations of the program effectiveness

The extent to which the course (i.e., the program that all students have joined) has helped you:	Respondents with positive responses (Options 3-5)					
	Secondary 1		Secondary 2		Overall	
	<i>n</i>	%	<i>n</i>	%	<i>N</i>	%
It has strengthened my bonding with teachers, classmates and my family.	5496	88.8	933	87.5	6429	88.7
It has strengthened my resilience in adverse conditions.	5610	90.9	984	92.3	6594	91.1
It has enhanced my social competence.	5707	92.5	984	92.3	6691	92.4
It has improved my ability in handling and expressing my emotions.	5675	92.0	978	91.7	6653	92.0
It has enhanced my cognitive competence.	5584	90.6	975	91.5	6559	90.8
My ability to resist harmful influences has been improved.	5778	93.8	971	91.1	6749	93.4
It has strengthened my ability to distinguish between the good and the bad.	5830	94.5	969	90.9	6799	93.9
It has increased my competence in making sensible and wise choices.	5715	92.6	976	91.6	6691	92.4
It has helped me to have life reflections.	5549	89.9	941	88.3	6490	89.7
It has reinforced my self-confidence.	5676	91.9	969	90.9	6645	91.8
It has increased my self-awareness.	5745	93.1	995	93.3	6740	93.1
It has helped me to face the future with a positive attitude.	5715	92.7	993	93.2	6708	92.7
It has helped me to cultivate compassion and care about others.	5647	91.6	970	91.0	6617	91.5
It has encouraged me to care about the community.	5253	85.1	916	85.9	6169	85.2
It has promoted my sense of responsibility in serving the society.	5646	91.4	952	89.3	6598	91.1
It has enriched my overall development.	5846	94.6	995	93.3	6841	94.4

Note. All items are rated on a 5-point Likert scale with 1 = unhelpful, 2 = not very helpful, 3 = slightly helpful, 4 = helpful, 5 = very helpful. Only the positive responses (Options 3-5) are shown.

Table 5. Summary of the participants' positive perceptions toward other aspects

Items	Secondary 1		Secondary 2		Overall	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Willingness to suggest other students to participate in the program*	5856	95.1	974	91.3	6830	94.5
Willingness to participate similar programs in future*	5795	94.1	942	88.3	6737	93.2
The extent to which the participants satisfied with the program [^]	5853	95.5	943	88.5	6796	94.4

Note. *A 4-point Likert scale was used (1 = definitely will not, 2 = will not, 3 = will, 4 = definitely will). Only the positive responses (Options 3–4) are shown in this table.

[^]A 6-point Likert scale was used (1 = very dissatisfied, 2 = moderately dissatisfied, 3 = slightly dissatisfied, 4 = satisfied, 5 = moderately satisfied, 6 = very satisfied). Only the positive responses (Options 4–6) are shown.

Table 6. Comparison of participants' subjective evaluation of the program by grade levels

	S1 (<i>N</i> = 5,719)		S2 (<i>N</i> = 1,047)		MANOVA	
	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>	<i>F</i> -value	<i>p</i> η^2
1) Program content (10 items)	5.05	0.83	4.99	0.97	4.54* [^]	.001
2) Program implementers (10 items)	5.27	0.80	5.08	1.05	48.12*** [^]	.007
3) Program effectiveness (16 items)	4.06	0.81	4.07	0.92	0.29 [^]	.000
4) Overall score (i.e., total of 1 to 3, 36 items)	4.67	0.70	4.61	0.67	7.70*** [^]	.001

Note. * $p < .05$; ** $p < .01$; *** $p < .001$; [^] Adjusted Bonferroni value = .0125; $p\eta^2$ = partial eta-squared.

Table 6 illustrates the findings of the MANOVA. As expected, results showed that Secondary 1 students had significantly more positive evaluation than did their S2 counterparts on program content ($F = 4.54$, $p = .033$, $p\eta^2 = .001$), program implementers ($F = 48.12$, $p < .001$, $p\eta^2 = .007$), and the overall score ($F = 7.70$, $p = .006$, $p\eta^2 = .001$). However, differences across grade levels were not observed in students' evaluation of program effectiveness ($p > .05$). As such, Hypothesis 3c was not supported.

Lastly, results of the multiple regression analyses (see Table 7) demonstrated that students' evaluations of program content (S1: $\beta = 0.42$, $p < .001$; S2: $\beta = 0.32$, $p < .001$; overall: $\beta = 0.43$, $p < .001$) and program implementers (S1: $\beta = 0.25$, $p < .001$; S2: $\beta = 0.07$, $p = .021$; overall: $\beta = 0.20$, $p < .001$) were significant predictors of their perceived program effectiveness. The overall model explained 32.67% of the variance of perceived program effectiveness. In a nutshell, Hypothesis 4 was confirmed at every grade level and for the entire sample.

Table 7. Multiple regression analyses predicting program effectiveness by program content and implementers

	β^a		<i>F</i>	<i>R</i> ²
	Program content	Program implementers		
Secondary 1	0.42***	0.25***	1837.94***	0.39
Secondary 2	0.32***	0.07*	67.91***	0.12
Overall	0.43***	0.20***	1642.14***	0.33

Note. ^a Standardized Beta coefficients. * $p < .05$ (two-tailed). ** $p < .01$ (two-tailed). *** $p < .001$ (two-tailed).

DISCUSSION

Utilizing the subjective outcome evaluation approach, the present study examined the views of students on the Tin Ka Ping P.A.T.H.S. Project in mainland China. Consistent with the previous findings, results showed that the program was well-received by the majority of program participants. This was evidenced by their positive evaluation of the program content, program implementer, program effectiveness, and their eagerness to recommend this program to others and to participate in a similar program in future. The overwhelmingly positive client satisfaction findings strongly supported Hypothesis 1. The findings also replicated those of Shek et al.'s [10] study covering the first phase of the project launched in East China, thus corroborating the evidence which supports the success of the Tin Ka Ping P.A.T.H.S. Project across China.

Echoing previous research findings from both East China and Hong Kong, significant inter-correlations among the three major program dimensions were observed, giving support to Hypotheses 2a to 2c. While no significant difference in program effectiveness was found across grade levels, Secondary 1 participants had a more positive evaluation of program content, program implementers and they also generally felt more satisfied. Nonetheless, judging by the small effect sizes ($p\eta^2 < 0.01$ for all cases) associated with all the significant grade effects (see Table 6) and taking into account the overall high satisfaction of the entire sample (see Table 1), one could legitimately conclude that both Secondary 1 and 2 participants were indeed very satisfied with the program in terms of its content, implementers, and effectiveness.

Regarding Hypothesis 4, results of multiple regression analyses indicated that both perceptions of program content and implementers were significant predictors of perceived program effectiveness. This finding resonates with Shek and Sun's [12] argument that "people" and "process" are vital to successful PYD programs. Nonetheless, the fact that the present model could only explain 32.67% of the variance implies that additional factors such as "policy" or "place" might be worthy areas of investigation in future evaluation studies.

There are several strengths of the present paper. Supplementing Shek et al.'s [10] pioneer subjective evaluation study of the first phase of the Tin Ka Ping P.A.T.H.S. Project, the present study adds to the scanty empirical work utilizing the client satisfaction approach in the mainland China context. Additionally, a valid and reliable subjective outcome evaluation instrument (i.e., the Form A) was presently adopted to comprehensively examine the different facets of the program. Lastly, via scrutinizing various prospective predictors of perceived program effectiveness and satisfaction, this paper could help researchers build models regarding subjective outcome evaluation in the mainland China context. Particularly, our results suggested that the promotion of perceived effectiveness would hinge on the improvement of the quality of both the program content and its implementers.

There are several limitations of this study. First, as the current analyses were predominantly quantitative, it may be insightful to also examine the open-ended responses to gain an understanding of the feelings of the participants. Second, the present findings may not be representative of the entire school sample ($N = 30$) of the Tin Ka Ping P.A.T.H.S. Project as only eighteen of them took part in the current study. Third, impression management [23] may underlie the present overwhelmingly supportive findings. Students may give desirable ratings as to avoid appearing ungrateful for the implementers' hard work. Nevertheless, this

possibility can be conveniently ruled out because of the anonymous nature of the present survey [24]. Finally, although subjective outcome evaluation has been widely used in the human services domain, it is methodologically superior to incorporate other evaluation methods such as the objective outcome and process evaluation as to reinforce the robustness of the findings. Despite these limitations, the present findings suggest that the Tin Ka Ping P.A.T.H.S. Project launched in the academic year 2015-2016 could be regarded as a success.

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Chapter 323

EVALUATION OF THE PROJECT P.A.T.H.S. IN MAINLAND CHINA: VIEWS OF THE PROGRAM IMPLEMENTERS IN SENIOR HIGH SCHOOLS

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ABSTRACT

In this chapter we investigated program implementers' views on the Tin Ka Ping Project P.A.T.H.S. in its first year of implementation in senior high schools in mainland China. After completion of the program, 33 program implementers completed the Subjective Outcome Evaluation Form (Form B). Results showed that over 90% of the implementers had positive views of program content, their self-performance and program effectiveness. In line with previous evaluation studies, perceived worker performance was found to predict perceived program effectiveness. Nevertheless, program content did not predict program effectiveness. Findings of the present study underscore the benefits of implementing the Project P.A.T.H.S. in senior high schools in mainland China.

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INTRODUCTION

While adolescence is often regarded as a period with rapid physical development, it is also a transitional period during which adolescents have to go through many challenges [1]. According to World Health Organization (WHO), adolescents may engage in a range of risk behaviors and health issues, including violent behaviors, alcohol and drug abuse, tobacco use, self-harm, and mental health issues [2]. These health compromising behaviors often have negative impacts on the current and future health of adolescents [3]. Based on the statistics of WHO [2], health compromising behaviors among adolescents are prevalent throughout the world.

The problem of health comprising behaviors among adolescents have also drawn public attention in China. In the study of Hesketh, Ding, and Tomkins [4], it was found that nearly 16% of the junior and senior school students responding to the survey were ever smokers. Alcohol use among Chinese adolescents is another serious problem that more attention should be paid. A meta-analytic study of Feng and Newman [5] indicated that over 35% of male students and over 20% of female students in senior high schools had used alcohol in the last 30 days. Regarding illicit drug use, the prevalence rate was about 4% based on a survey of 15 secondary schools in Wuhan [6]. A large-scale study [7] investigated self-harm behaviors among secondary school students in China, and the findings suggested that 17% of the students had injured themselves deliberately in the past 12 months, which was higher than Western countries [7, 8].

Mental health issue is another leading cause of health problem among adolescents [9]. According to a large-scale survey in China, approximately 10% of Chinese school children had suffered from one or more types of psychiatric disorders [10]. Correspondingly, it was estimated that every trained child psychiatrist has to serve more than 40,000 children with behavioral and emotional problems in mainland China [11]. Thus, prevention of health compromising behaviors and mental health problems among children and adolescents is an urgent and important job in mainland China. Unfortunately, there is a lack of prevention programs designed for Chinese adolescents.

Both individual and contextual factors affect adolescent behavior and shape their development [12]. Turbin et al. [13] suggested that adolescent involvement in health-promoting behaviors were more likely to be affected by protective and risk factors in social context (e.g., family and peers), rather than by their individual-level factors. Therefore, providing prevention in the social context would be effective to reduce the risk of adolescent behavior problems and psychiatric disorders. As school is an important place for adolescents to learn knowledge, develop social skills and build social support [1], it would be appropriate to implement prevention programs in school setting, since Chinese adolescents spend more than 8 hours at school each day [14]. Therefore, school-based positive youth development (PYD) programs for the general adolescent population is a promising approach to promote holistic development in adolescents.

With respect to the above-mentioned issues, a PYD program entitled “P.A.T.H.S. to Adulthood: A Jockey Club Youth Enhancement Scheme” was initiated in Hong Kong in the 2005-2006 academic year and then piloted in mainland China from 2007-2008 academic year to 2009-2010 academic year [15, 16]. The initial version of the Project P.A.T.H.S. was designed by the first author and his collaborators from five universities in Hong Kong and

funded by The Hong Kong Jockey Club Charities Trust. Two tiers of programs were included in the project to help adolescents with different levels of need. The Tier 1 Program provides a series of curricula-based training programs to the general adolescent population in junior secondary schools that students participate in 10 to 20 hours of training on 15 PYD constructs in each school year, whereas the Tier 2 Program is designed for one-fifth of the students who have greater psychosocial needs [17].

Because of the prominent success in the implementation of the project in Hong Kong, a pilot project was funded by Tin Ka Ping Foundation and implemented in four schools in mainland China (including Shanghai, Suzhou, Changzhou and Yangzhou) in 2011-2014. As a transplant of the Project P.A.T.H.S. (i.e., Tin Ka Ping P.A.T.H.S. Project), the pilot project had very good performance. Thus, a second phase of the project was funded to fully implement the project from 2014-2015 academic year [18, 19]. In the academic year of 2015-2016, a total of 30 secondary schools joined the project and the curriculum for senior high schools was also developed. To facilitate program implementation, a series of in-service training programs were provided to school teachers and social workers from participating schools.

Subjective outcome evaluation is a useful approach to gather feedback from stakeholders of programs (e.g., program participants and implementers) and assess their satisfaction. The views of the stakeholders can provide ideas to improve program content and process, which have implications to the application of the program in the general population. Previous evaluation studies using subjective outcome evaluation approach showed that both students and school teachers held very positive views toward the project, which echoes the results of qualitative evaluation and objective outcome evaluation of the project [18-21]. However, the perceptions of program implementers from senior schools are still unknown.

As implementers are an indispensable part of a program, the feedback from these well trained professionals in the field of positive adolescent development could be very helpful to improve program content. Moreover, their first-hand experience of delivering program to students would provide practical data to review the program, as they would not adapt materials which are not fit in their situation [22]. Implementers could review their own practice when they are doing evaluation, and such evaluation could provide them with a sense of respect and fairness [23].

The purpose of the present study was to examine program implementers' perceptions toward the project implemented in senior high schools in China. Subjective outcome evaluation approach was used to collect feedback of implementers who delivered the senior curriculum. As there are very few programs focusing on promoting holistic and positive development for students of senior high schools in mainland China, the evaluation study can provide good insight into the efficacy of the Project P.A.T.H.S. and the factors associated with program success. Three sets of research questions and hypotheses were examined in the present study:

- What are program implementers' perceptions of the project implemented in senior high school? Would the findings be consistent with the findings of previous evaluation studies of programs conducted in junior secondary school? Based on previous studies, it was expected that a majority of the respondents (at least 80%) would have positive view of the program (Hypothesis 1).

- Are there any significant inter-relationships among the three aspects of subjective outcome evaluation? Based on the results of previous findings, we hypothesized that perceived program effectiveness would be significantly associated with program content (Hypothesis 2a) and perceived worker performance (Hypothesis 2b).
- What are the predictors of perceived effectiveness of the program? Based on the findings of previous study, we hypothesized that program content and perceived worker performance would predict the effectiveness of the project (Hypothesis 3a and 3b, respectively).

OUR STUDY

In the academic year of 2015-2016, the Tin Ka Ping P.A.T.H.S. Project was implemented in 30 junior and/or senior high schools in mainland China. To explore program implementers' viewpoints toward the program and their self-performance, and to evaluate program effectiveness, school teachers who taught the senior school programs were invited to complete the Subjective Outcome Evaluation Form for Instructors (Form B) after program curriculum was finished.

A total of 33 implementers from four senior secondary schools in mainland China, with a range from five to twelve teachers in each school, have submitted the Form B after the completion of program. To ensure survey response quality, an evaluation manual with a clear guideline on the completion of Form B was provided to the teachers before they started to fill in the evaluation form. Relevant training on evaluation was also included in different training workshops.

Instruments

The Subjective Outcome Evaluation Form for Instructors (Form B) has been widely applied over the past decade and evaluation studies of the project demonstrate that Form B is a valid and reliable measure gathering feedback from program implementers of the project [24]. Form B consists of both open-ended questions that provide qualitative data and quantitative scales. As shown in Table 1, the three subscales used in Form B have demonstrated very good internal consistency with Cronbach's α s above .90. Due to space limitation, the present study focused on the quantitative data collected from the following items/subscales:

- A 6-point Likert scale assessing implementers' perceptions of program content (10 items);
- A 6-point Likert scale assessing implementers' perceptions of self-performance (10 items);
- A 5-point Likert scale assessing implementers' perceptions of program effectiveness (16 items);
- One item assessing the degree to which implementers would recommend other students to join the program;

- One item assessing the degree to which teachers would teach similar curriculum in the future;
- One item assessing implementers' view toward their professional growth through the program.

Table 1. Mean, standard deviations, Cronbach's alphas, and mean of inter-item correlations

	M	SD	α	Mean [#]
Program content (10 items)	5.17	0.87	.97	.75
Program implementers (10 items)	5.08	0.89	.97	.78
Program effectiveness (16 items)	4.10	0.77	.98	.72
Total effectiveness (36 items)	4.66	0.78	.99	.66

Note: [#] Mean inter-item correlations.

Data Analyses

First, reliability analyses were conducted to examine the internal consistency of the three subscales in Form B and the inter-item correlations among them. Second, descriptive analyses were performed to compute the percentage of positive responses of implementers' perception of program components (program content and implementers' self-performance) and program effectiveness. Third, to examine the correlations between program content, implementers' self-performance and program effectiveness, Pearson correlation analysis was performed. Finally, multiple regression analysis was conducted to test the potential predictors of perceived program effectiveness, including program content and implementers' perceived self-performance. All statistical analysis was performed using SPSS 23.0.

FINDINGS

Program implementers' perceptions of program content, self-performance and program effectiveness are shown in Tables 2-4, respectively. Generally speaking, their views toward the aspects measured in Form B were very positive. Over 96% of the respondents had positive responses on eight out of ten items regarding program content, such as design of the program, program activities, atmosphere in the classroom, student classroom participation, theoretical support and teacher's interest toward the curriculum. Over 90% of the respondents agreed that "the objectives of the curriculum are very clear," and "there was much peer interaction amongst the students." Overall speaking, the respondents perceived positive features of program content (see Table 2). Similarly, the majority of the respondents also had positive perceptions toward their own performance. Seven out of ten questions regarding implementers' perceived self-performance received positive responses from over 96% of the respondents (see Table 3).

Table 2. Summary of the program implementers' perceptions toward the program content

		N	Mean	SD	Respondents with positive responses (Options 4-6)	
					n	%
1.	The objectives of the curriculum are very clear.	32	5.22	1.04	30	93.8
2.	The design of the curriculum is very good.	32	5.06	0.91	31	96.9
3.	The activities were carefully planned.	32	5.19	0.93	31	96.9
4.	The classroom atmosphere was very pleasant.	32	5.19	1.00	31	96.9
5.	There was much peer interaction amongst the students.	32	5.19	1.12	30	93.8
6.	Students participated actively during lessons (including discussions, sharing, games, etc.)	32	5.16	0.95	31	96.9
7.	The program has a strong and sound theoretical support.	32	4.88	0.98	31	96.9
8.	The teaching experience I encountered enhanced my interest towards the lessons.	32	5.16	0.99	31	96.9
9.	Overall speaking, I have very positive evaluation of the program.	32	5.25	1.02	31	96.9
10.	On the whole, students like this curriculum very much.	32	5.41	0.98	31	96.9

Note: All items are on a 6-point Likert scale with 1 = strongly disagree, 2 = disagree, 3 = slightly disagree, 4 = slightly agree, 5 = agree, 6 = strongly agree. Only respondents with positive responses (Options 4-6) are shown in the table.

Table 3. Summary of the program implementers' perceptions toward their own performance

		N	Mean	SD	Respondents with positive responses (Options 4-6)	
					n	%
1.	I have a good mastery of the curriculum	32	4.88	1.07	29	90.6
2.	I prepared well for the lessons.	32	4.94	1.05	30	93.8
3.	My teaching skills were good.	32	4.75	0.98	30	93.8
4.	I have good professional attitudes.	32	5.00	1.02	31	96.9
5.	I was very involved.	32	5.06	0.95	31	96.9
6.	I gained a lot during the course of instruction.	32	5.09	1.00	31	96.9
7.	I cared for the students.	32	5.28	0.99	31	96.9
8.	I was ready to offer help to students when needed.	32	5.41	0.98	31	96.9
9.	I had much interaction with the students.	32	5.19	0.97	31	96.9
10.	Overall speaking, I have very positive evaluation of myself as an instructor.	32	5.19	0.93	31	96.9

Note: All items are on a 6-point Likert scale with 1 = strongly disagree, 2 = disagree, 3 = slightly disagree, 4 = slightly agree, 5 = agree, 6 = strongly agree. Only respondents with positive responses (Options 4-6) are shown in the table.

Results in Table 4 indicated that there were a number of perceived benefits of the project. Over 96% of the respondents agreed that the program could strength students' bonding with their families, teachers and classmates, enhance students' resilience and their competence in regard to social skills, emotion capital and cognitive functioning, and increase students' self-awareness and self-confidence, etc. The great majority (97%) of the respondents agreed that the program enriched students' overall development. From the program implementers' subjective views toward other aspects of the program, all of them (100%) would suggest the students who have similar needs join the program. In addition, 97% of the respondents had intention to teach similar programs again in the future, and over 93% of respondents

perceived the program as helpful in their professional growth (Table 5). In short, the findings supported Hypothesis 1.

Table 4. Summary of the program implementers' perceptions toward the program effectiveness

The extent to which the Tier 1 Program (i.e., the program in which all students have joined) has helped your students:		N	Mean	SD	Respondents with positive responses (Options 3-5)	
					n	%
1.	It has strengthened students' bonding with teachers, classmates and their families.	33	4.18	0.88	32	97.0
2.	It has strengthened students' resilience in adverse conditions.	33	4.03	0.85	32	97.0
3.	It has enhanced students' social competence.	33	4.30	0.85	32	97.0
4.	It has improved students' ability in handling and expressing emotions.	33	4.39	0.83	32	97.0
5.	It has enhanced students' cognitive competence.	33	3.97	0.88	32	97.0
6.	Students' ability to resist harmful influences has been improved.	33	4.03	0.95	31	93.9
7.	It has strengthened students' ability to distinguish between the good and the bad.	33	4.09	0.95	31	93.9
8.	It has increased students' competence in making sensible and wise choices.	33	3.91	0.91	31	93.9
9.	It has helped students to have life reflections.	33	3.94	0.90	32	97.0
10.	It has reinforced students' self-confidence.	32	4.19	0.78	31	96.9
11.	It has increased students' self-awareness.	32	4.31	0.86	31	96.9
12.	It has helped students to face the future with a positive attitude.	33	4.30	0.81	32	97.0
13.	It has helped students to cultivate compassion and care about others.	33	4.06	0.90	32	97.0
14.	It has encouraged students to care about the community.	33	3.55	1.00	30	90.9
15.	It has promoted students' sense of responsibility in serving the society.	33	3.94	1.06	30	90.9
16.	It has enriched the overall development of the students.	33	4.30	0.85	32	97.0

Note: All items are on a 5-point Likert scale with 1 = unhelpful, 2 = not very helpful, 3 = slightly helpful, 4 = helpful, 5 = very helpful. Only respondents with positive responses (Options 3-5) are shown in the table.

Table 5. Other aspects of subjective outcome evaluation based on the program implementers' perceptions

		N	Mean	SD	Respondents with positive responses	
					n	%
Q3	If you have a student/client whose needs and conditions are similar to those of your students who have joined the program, will you suggest him/her to participate in this program?	33	3.58	0.50	33	100
Q4	If there is a chance, will you teach similar programs again in the future?	33	3.58	0.56	32	97.0
Q5	Do you think the implementation of the program has helped you in your professional growth (e.g., enhancement of your skills)?	32	4.28	0.89	30	93.8

Note: For Q3 & Q4, the item is on a 4-point Likert scale with 1 = definitely will not teach, 2 = will not teach, 3 = will teach, 4 = definitely will teach. Only respondents with positive responses (Options 3-4) are shown in the table. For Q5, the item is on a 5-point Likert scale with 1 = unhelpful, 2 = not very helpful, 3 = slightly helpful, 4 = helpful, 5 = very helpful. Only respondents with positive responses (Options 3-5) are shown in the table.

The results of correlation analyses showed that program content, program implementers' perceived worker performance and program effectiveness were significantly associated with each other (r s ranged from .73 to .92, p s < .01; see Table 6). The findings gave support to Hypotheses 2a and 2b. Table 7 presents the results of multiple regression analysis. Consistent with Hypothesis 3b, the overall perception of program implementers' self-performance predicted program effectiveness ($\beta = .65$, $p < .05$). However, Hypothesis 3a was rejected, as program content was not a significant predictor of the benefits of the program based on the data of the present study. This model explained 59% of the variance of program effectiveness.

Table 6. Correlation coefficients on the relationship between program components and program effectiveness

Variable	1	2	3
1. Program content (10 items)	—	—	—
2. Program implementers (10 items)	.92**	—	—
3. Program effectiveness	.73**	.77**	—

** $p < .01$.

Table 7. Multiple regression analyses predicting program effectiveness

	Predictors		Model	
	Program content	Program implementers		
	β^a	β^a	R	R^2
Program effectiveness	.12	.65*	.77	.59

Note: Missing values were replaced with mean ; ^a Standardized coefficients; * $p < .05$.

DISCUSSION

To promote students' whole person development in senior high schools, innovative units and topics based on PYD constructs were developed and incorporated into the senior curriculum of P.A.T.H.S. programs in mainland China. This initiative is groundbreaking in different Chinese communities. Utilizing the subjective outcome evaluation approach, this study examined stakeholder satisfaction of program components (quality of content and implementers) and program effectiveness based on the perceptions of program implementers who taught the senior curriculum of Tier 1 Program in the academic year of 2015-2016. Generally speaking, the great majority of the implementers who responded to the survey were satisfied with the project and recognized its positive influences on adolescent development. The present study replicated the previous evaluation findings in junior secondary schools [24, 25].

As the first subjective evaluation regarding implementers' views of senior school program, several observations can be highlighted. First, approximately 97% of the respondents held positive views toward program content, self-performance and benefits of the program. Second, relatively fewer teachers (90.9%) agreed that the program promoted students' sense of social responsibility and encouraged them to care more about community development, which was consistent with previous evaluation findings [25, 26]. One explanation is that community involvement is more difficult to observe, as activities in the project are mainly conducted within school settings. However, the findings can still be regarded as very positive. Third, this study replicated the relationships among the three aspects of subjective outcome evaluation that both program content and implementers' self-performance had strong and positive relationships with program effectiveness. Fourth, the performance of program implementers was identified as a significant predictor of positive effects of the program. However, in contrast to previous studies based on student participants, program effectiveness was not statistically significant.

There are several reasons why the project was successful and positive feedbacks were received. First, the remarkable success of the junior school programs in Hong Kong and mainland China provides experience and materials for implementing similar programs in senior secondary schools. Second, as implementers in the present study were school teachers who aspired to pass on their knowledge and positive attitude toward life to students, they would have a higher motivation to deliver the program. Third, teaching and learning behavior expected in PYD programs is different from traditional way of education in China. Because different teaching and learning methods are used in the programs, including group discussion, role play, self-reflections, and multimedia teaching, students can be more actively involved [17]. Fourth, in-service training programs for teachers can help strengthen their understanding of PYD constructs and program content [15]. Implementers would be more likely to evaluate their performance and the program positively if they observe that students have positive changes after attending the program [27].

The findings in the present study would be a good reference for similar research and programs in the future, which provide a synthesis of stakeholder satisfaction on program implementation and effectiveness. It is important to collect the views of program implementers, since they play the role of a medium between program participants and program operation. As an indispensable factor contributing to an effective program in the 5P

model (i.e., policy, program, place, process and people), program implementers have crucial influence on program effectiveness [28]. In future studies, researchers may investigate if implementers' perceptions are consistent with students' subjective and objective evaluation of the program.

The present study has several limitations. First, because this is an initial evaluation study of the senior school program of Project P.A.T.H.S., the sample size is relatively small. Hence, the findings could only represent the views of teachers in a few project schools. Second, as few schools joined the evaluation, it is unclear if implementers teaching different grades have different views on the program. Third, only quantitative data were reported in this study. Obviously, a more comprehensive picture of implementers' feedback on the program requires both quantitative and qualitative evaluation. Therefore, it is helpful to include more teachers using different evaluation methods in future evaluation studies.

Despite these limitations, the results of this study demonstrated that the Tier 1 Program of the Tin Ka Ping P.A.T.H.S. Project in mainland senior high schools was positively evaluated by program implementers and they had positive effects on adolescent development, which is pioneer in the Chinese contexts. In view of the limited international and local research on positive youth development programs in China, the present study provides an insight into the initial application of Tin Ka Ping P.A.T.H.S. Project among senior high school students and teachers.

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Chapter 324

EVALUATION OF THE TRAINING PROGRAM OF A POSITIVE YOUTH DEVELOPMENT PROGRAM: TIN KA PING P.A.T.H.S. PROJECT IN CHINA

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ABSTRACT

In this chapter we investigated the participants' perceptions of a training program conducted in Tin Ka Ping P.A.T.H.S. Project in China using the subjective outcome evaluation approach. The participants (N = 151) completed an evaluation form at the end of the training program. Results showed that a very high proportion of the participants were satisfied with the training program in terms of program content, instructors, administrative arrangements, and their own performance. Several significant predictors of effectiveness of the training program were identified, including program quality, instructor quality, administrative arrangement, and participants' perceived self-performance. Perceived program quality also predicted overall satisfaction of the participants. Together with previous evaluation findings, the present study suggests that the Tin Ka Ping P.A.T.H.S. Project training program was effective and well received by colleagues in mainland China.

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INTRODUCTION

With the implementation of one-child policy from 1978 to 2015 and the expanding urban-rural gap in China, adolescent developmental problems have been a critical issue for psychologists, educators, scholars, and the Government in China. Research on the mental health condition of only-child expanded at a remarkable rate in past 10 years. For instance, Hesketh and his colleagues [1] estimated that the suicide rate of adolescents in China was around three times the global average. Xing et al. [2] reported that Chinese adolescents with suicide attempts usually have family problems, such as improper parental rearing behavior, parental divorce, and parental gambling problem. Moreover, it is estimated that over 24 million (14.1%) adolescents in urban cities displayed symptoms of internet addiction [3]. In addition, it also revealed that the adolescents from less developed areas in China have higher prevalence rates of youth internet addiction problem (14.8%) than those from high developed cities (8.4%) [3].

In view of the above observations, it is advocated that effective positive youth development (PYD) programs to strengthen the psychosocial competencies of adolescents are in urgent need in China. The PYD approach emphasizes that “problem-free is not fully prepared” and utilizes the ecological (person-in-environment) and strengths-based principles [4]. It focuses on preventing a wide range of adolescent developmental problems and needs, instead of merely preventing a single adolescent problem.

With particular reference to Hong Kong, adolescents are also facing different types of risk behavior such as substance abuse, materialism, suicide, and bullying [5]. As such, a PYD program entitled “P.A.T.H.S. to Adulthood: A Jockey Club Youth Enhancement Scheme” funded by Hong Kong Jockey Club Charities Trust was launched in 2004. The project comprised of two tiers programs. While the Tier 1 Program was a universal curriculum-based program based on 15 PYD elements identified in the effective programs, such as bonding, social competence, cognitive competence, and behavioral competence [6], the Tier 2 Program was developed for participants who were identified with greater psychosocial needs and tailor-made special programs were constructed. Multiple evaluation studies revealed that project in Hong Kong has received notable success in promoting holistic youth development and preventing problem behavior among junior secondary school students [7-10].

Given the overwhelming success of project in Hong Kong, it is important to ask whether the program can promote the holistic development of adolescents in other Chinese communities. With the financial support from Tin Ka Ping Foundation, a project entitled “Tin Ka Ping P.A.T.H.S. Project” was implemented in four schools in East China, including Shanghai, Suzhou, Changzhou, and Yangzhou from 2011 to 2014, with good outcomes based on subjective and objective outcome evaluation [11, 12].

Despite the encouraging evaluation findings reported in four East China secondary schools [11, 12], we need to further understand the applicability of the program in other parts of China. Hence, a second phase of the Project P.A.T.H.S. designed for the junior secondary school students was implemented in more than 30 secondary schools in mainland China from the 2014-2015 academic year, with the first year as the preparatory year of a full-implementation stage.

Unlike other traditional youth prevention programs, this project emphasizes systematic training through experiential and reflective learning approaches. With respect to the training

programs for the potential implementers of the project in Hong Kong, all potential implementers were expected to actively participate in the training process as students [13]. Participants were given opportunities to reflect on their own values, teaching methods, and attitude towards adolescent development [14]. Such an emphasis was also adopted in the training programs in mainland China. Specifically, four junior form training sessions were offered in Shanghai, Suzhou, and Chongqing in the preparatory year (2014-2015 academic year).

From 2015-2016 to 2016-2017 academic year, the program was launched in over 30 secondary schools in China. In the 2015-2016 academic year, three training workshops targeting potential implementers of the junior and senior secondary programs were held in Zhaoqing, Shaoguan (in Guangdong province), and Changchun (in Jilin province), respectively. The evaluation findings of the training held in Zhaoqing and Shaoguan have been documented [15, 16].

In this chapter, perceptions of the participants joining the training conducted in Changchun were examined. As the training was conducted during the summer holiday, the research team extended the training period from 3 days to 4 days. Therefore, more lesson demonstrations and in-depth sharing sessions from project schools were included. The contents of the third training workshop in Changchun are shown in the Appendix. There were several objectives of this training program: (a) to understand the concepts and rationale of PYD; (b) to understand the features of adolescent development and to develop positive attitudes towards adolescents; (c) to comprehend the rationales, design, implementation, and evaluation of the project; (d) to understand the contents and activities developed for the project; (e) to encourage participants to review and obtain appropriate attitude, knowledge, and teaching skills to facilitate program implementation; and (f) to develop a self-help network among the participants.

Although the importance of prevention programs and PYD programs for adolescents have been highlighted in previous studies, the significance of training programs for implementers tends to be overlooked. Clarke [17] believed that training program should be treated as a key strategy to help trainees familiarize with the program philosophy and content, and strengthen their enthusiasm and support for the program. Fullan [18] also pointed out that the impact of shared meaning and collaboration from the implementers would determine the effectiveness of educational program. Shek and Sun [19] listed five key factors contributing to the success of the PYD program, including program, process, policy, people, and place (i.e., 5 P's). Amongst these factors, "people," which included both program participants and implementers, was identified as the most influential factor affecting the effectiveness of the project [19]. As such, providing systematic and on-site training for the potential program implementers should be taken into account in program delivery. Moreover, since there are very few PYD programs in China, it is important to provide comprehensive support and resources to the project schools and implementers through all-rounded in-service training.

In addition, it is advocated that training evaluation is necessary in every training program. Training evaluation refers to "the process of determining the merit, worth, and value of things, or the product of that process" [20]. In other words, it is a methodological approach for measuring a training program's achievement with regard to program design and content, and changes in trainees. Kirkpatrick's [21] four dimensional training evaluation model (i.e., reactions, learning, behavior, and results) is widely used for understanding the purpose of in-service training evaluation. Training evaluation results can give scientific evidence to explain

how the objectives of training program, content, and methods achieve the expected outcomes or benefits in the training [22]. Furthermore, program developer can identify successful factors through evaluation and then improve program design and implementation in the future.

To date, several training evaluation studies of the project based on subjective outcome evaluation strategy have been conducted in Hong Kong [23-26]. Comparatively speaking, there are still very few training evaluations conducted in Chinese communities. As reviewed by Yang and Guo [27], there were only 86 Chinese studies related to teacher training evaluations published in the last decade in 11 major Chinese or international databases. Besides, most of these studies simply focused on conceptual issues rather than investigating the efficacy of training programs. Most importantly, as the Project P.A.T.H.S. has moved to a full implementation stage, it is worth exploring the influence of its training program on potential implementers and collecting their feedbacks for further improvement.

The current study attempted to examine the effectiveness of the Project P.A.T.H.S. training program conducted in Changchun in August 2016. Similar to other training evaluation studies reported previously [15, 16], there are three research objectives of this paper: 1) to explore potential implementers' viewpoints towards the training program in the areas of training content, instructors' quality, self-performance, and administrative arrangements; 2) to examine the predictors of perceived benefits through the training program from the perspective of the participants; 3) to investigate the predictors of overall satisfaction with the training program amongst the participants.

OUR STUDY

In the academic year of 2015/2016, the third training workshop of the Tin Ka Ping P.A.T.H.S. Project was held in Changchun, China. There were altogether 208 teachers from 35 junior and/or senior secondary schools registering to attend this 4-day workshop.

During the last session of the workshop in Day 4, the participants reflected on their gains through the training, and they were invited to complete an anonymous questionnaire regarding their evaluation on this training workshop. Because of transportation constraints, some participants had to leave earlier upon the completion of the training. Finally, a total of 151 questionnaires were collected, including 70 (46.4%) questionnaires completed by junior secondary school teachers and 81 (53.6%) completed by senior secondary school teachers. Overall speaking, there were more female teachers ($N = 103$, 68.2%) than male teachers ($N = 48$, 31.8%) completing the evaluation after the training. Among all the respondents, 62.9% ($N = 95$) had over 10 years of teaching experience. In addition, the mean years of working experience of the respondents was 12.6 ($SD = 8.42$).

Instruments

The participants' perceptions of the training workshop were measured utilizing the Subjective Outcome Evaluation Questionnaire developed by Shek and his colleagues [24].

The evaluation questionnaire consists of 33 items, including four subscales measured by 31 closed-ended questions and two open-ended questions.

Regarding the four subscales, each respondent is asked to rate the items on a 5-point Likert scale with responses ranging from “strongly disagree” to “strongly agree.” The first subscale, comprising 16 items, measures participants’ overall view of the program training content, including the perceived benefits of the program (9 items), perceived program quality (5 items) and satisfaction degree of participants (2 items). The second subscale investigates participants’ perceptions of the instructors with 5 items. The third subscale, consisting of 4 items, assesses participants’ reflections on their own performance. The fourth subscale focuses on participants’ evaluations of the administrative arrangements of the training. The two open-ended questions examine participants’ most appreciated part of the training and their suggestion for the workshop.

The quantitative part of the questionnaire has demonstrated excellent internal consistency (Cronbach’s $\alpha > .9$) in previous studies evaluating the training programs in Hong Kong [25, 26]. The current study focused on the participants’ perceptions by analyzing the data from the four subscales.

FINDINGS

Table 1 shows that the reliability measures for the total scale (Cronbach’s $\alpha = .95$) and subscales of the Subjective Outcome Evaluation Questionnaire (Cronbach’s alpha ranged from .66 to .93) had good reliability status. Although the alpha value for the overall satisfaction subscale was not high (Cronbach’s $\alpha = .66$), it can be regarded as reasonable because there are only two items in this subscale.

Participants’ perceptions of the program content, program instructors, their own performance and the administrative arrangements of the training are shown in Tables 2-5 respectively. The numbers and percentages of positive responses (scores equal to or above 4) to each item and subscale are presented. In general, the majority (over 80%) of the participants held a positive view regarding program benefits, program quality, program instructors and the administrative arrangements. And taken as a whole, nearly 90% of the participants were satisfied with the workshop. However, relatively fewer participants (74.7%) expressed positive views about their self-performance, although the value was respectable.

Table 1. Means, standard deviations, Cronbach’s alphas, and mean of inter-item correlations

Subjective Outcome Evaluation Scales	<i>M</i>	<i>SD</i>	Cronbach’s α	Mean Inter-item correlation
Perception of the training program (16 items)	4.42	0.43	.93	.47
Perceived benefits (9 items)	4.44	0.44	.89	.49
Program quality (5 items)	4.39	0.48	.81	.47
Overall satisfaction (2 items)	4.33	0.54	.66	.49
Perception of program instructor (5 items)	4.49	0.46	.85	.54
Perception of self-performance (4 items)	4.15	0.53	.81	.52
Perception of administrative arrangements (6 items)	4.44	0.49	.91	.65
Total scale (31 items)	4.41	0.39	.95	.40

Table 2. Summary of the positive views (options 4-5) of the participants towards the training program

Perceptions of the program	N	Agree (4)		Strongly Agree (5)		Positive Response (Options 4-5)		M	SD
		n	%	n	%	n	%		
Perceived benefits ^a									
1. It has strengthened my understanding of the nature of adolescent development.	146					127	87.0	4.44	0.44
2. It has helped me to cultivate positive attitude to adolescent development.	147	71	48.3	71	48.3	142	96.6	4.45	0.56
3. It has strengthened my understanding of positive youth development, including its concept, design and research.	147	55	37.4	90	61.2	145	98.6	4.6	0.52
4. It has helped me to understand the Project P.A.T.H.S., including its basic philosophy, design, implementation, and evaluation.	147	60	40.8	80	54.4	140	95.2	4.5	0.59
5. It has strengthened me to understand the content of the Project P.A.T.H.S..	147	62	42.2	74	50.3	136	92.5	4.43	0.63
6. It has helped me to acquire the attitude, knowledge and skills that are conducive to the successful implementation of the Project P.A.T.H.S..	147	68	46.2	72	49.0	140	95.2	4.44	0.59
7. It has helped me to establish self-help support network and share teaching experiences among the program participants.	147	76	51.7	57	38.8	133	90.5	4.29	0.65
8. It has promoted self-reflection.	147	58	39.5	71	48.3	129	87.8	4.36	0.69
9. It has helped me to recognize factors affecting teaching.	146	65	44.2	78	53.1	143	97.3	4.5	0.55
Program quality ^a	145	71	48.6	67	45.9	138	94.5	4.4	0.59
1. The training methods and activities are appropriate (e.g. lecture, games, group discussion).	145					121	83.4	4.39	0.48
2. Training time is appropriate.	147	64	43.8	80	54.8	144	98.6	4.53	0.53
3. It has met my expectation.	147	74	50.3	45	30.6	119	80.9	4.08	0.77
4. There was much peer interaction amongst participants.	147	73	49.7	54	36.7	127	86.4	4.23	0.67
5. Instructor(s) encouraged participants to do the best.	146	59	40.4	81	55.5	140	95.9	4.51	0.60
Overall satisfaction ^a	147	53	36.1	88	59.9	141	96.0	4.55	0.60
1. Overall speaking, I am satisfied with the training program.	145					130	89.7	4.33	0.54
2. I think participants are satisfied with the training program.	147	73	49.7	67	45.5	140	95.2	4.41	0.58
Perceptions of the program (whole scale) ^a	145	72	49.7	55	37.9	127	87.6	4.25	0.68
	143					116	81.1	4.42	0.43

Note: ^a Scores equal to or higher than 4 were treated as positive views.

Table 3. Summary of the positive views (options 4-5) of the participants towards the program instructor(s)

Perceptions of the program instructor(s)		N	Agree (4)		Strongly Agree (5)		Positive Response (Options 4-5)		M	SD
			n	%	n	%	n	%		
1.	The instructor(s) had good mastery of the curriculum.	147	73	49.7	71	48.3	144	98.0	4.46	0.54
2.	The instructor(s) understood the needs of participants.	147	69	46.9	60	40.8	129	87.7	4.29	0.67
3.	The instructor(s) showed good professional attitude.	147	35	23.8	110	74.8	145	98.6	4.73	0.47
4.	The instructor(s)' teaching was clear and easy to understand.	147	67	45.6	63	42.9	130	88.5	4.31	0.67
5.	Overall speaking, I have positive evaluation of the instructor(s)' teaching performance.	147	46	31.3	98	66.7	144	98.0	4.65	0.52
Total scale ^a		147					134	91.2	4.49	0.46

Note: ^a Scores equal to or higher than 4 were treated as positive views.

Table 4. Summary of the positive views (options 4-5) of participants towards their own performance in training

Perceptions of self-performance		N	Agree (4)		Strongly Agree (5)		Positive Response (Options 4-5)		M	SD
			n	%	n	%	n	%		
1.	I participated actively during discussion.	151	80	53.0	37	24.5	117	77.5	4.01	0.72
2.	I am willing to apply the specific skills and theories learnt from this training program.	151	76	50.3	69	45.7	145	96.0	4.42	0.57
3.	After attending the training program, I have confidence in program implementation.	151	85	56.3	49	32.5	134	88.8	4.21	0.63
4.	Overall speaking, I am satisfied with my performance.	150	85	56.7	33	22.0	118	78.7	3.97	0.74
Total scale ^a		150					112	74.7	4.15	0.53

Note: ^a Scores equal to or higher than 4 were treated as positive views.

Table 5. Summary of the positive views (options 4-5) of participants towards administrative arrangements

Perceptions of the administrative arrangements		N	Satisfied (4)		Very Satisfied (5)		Positive Response (Options 4-5)		M	SD
			n	%	n	%	n	%		
1.	Information obtained before attending the workshop.	151	76	50.3	55	36.4	131	86.7	4.23	0.69
2.	Workshop assigned.	150	74	49.3	64	42.7	138	92.0	4.35	0.62
3.	Location of the workshop.	151	75	49.7	71	47.0	146	97.7	4.44	0.56
4.	Reception provided by training team (e.g. transportation arrangement, refreshments).	151	59	39.1	88	58.3	147	97.4	4.56	0.55
5.	Facilities of the venue.	151	64	42.4	82	54.3	146	96.7	4.51	0.56
6.	Overall speaking, I am satisfied with the administrative arrangement.	151	61	40.4	89	58.9	150	99.3	4.58	0.51
Total scale ^a		150					130	86.7	4.44	0.49

Note: ^a Scores equal to or higher than 4 were treated as positive views.

Regarding perceived benefits, more than 90% of the respondents agreed or strongly agreed that they benefitted from the training, including a better understanding of adolescent development (96.6%) and positive youth development (95.2%), cultivation of positive attitude to adolescent development (98.6%), self-reflection (97.3%), and recognition of factors affecting teaching (94.5%). In addition, through the workshop, the teachers were more familiar with the project (92.5%), understood the content of the Tier 1 Program (95.2%), and acquired knowledge and skills implementing the program (90.5%). Nearly 90% of the respondents agreed that they established a self-help support network in the training.

The teachers in the training were also satisfied with the program quality. Almost all of them (98.6%) agreed that the training methods and activities were appropriate. They also held a positive view about peer interaction amongst teachers during the training (95.9%). Most participants had positive evaluation of program instructors. They agreed that the instructors were a professional team with good mastery of the curriculum (98%), clear understanding of the needs of the participants (87.7%), profession attitude (98.6%) and good teaching skills (88.5%). The participants also showed positive response toward the administrative arrangements of the program. After the training, 96% of the teachers expressed their willingness to use the theories and skills learnt through this training workshop.

To investigate whether there were differences between junior and senior secondary school teachers regarding their perceptions of the training workshop, a MANOVA analysis was performed. As demonstrated in Table 6, based on the omnibus F test, no statistically significant difference was found between the junior form and senior form programs in terms of the overall perception of the training ($F = 1.54, p > .05$).

Table 6. The comparison between junior and senior secondary school participants on the perceptions of the training program

Subjective Outcome Evaluation Scales	Senior			Junior			F
	N	M	SD	N	M	SD	
Program content (16 items)	66	4.48	.40	77	4.36	.45	2.78
Perceived benefits (9 items)	66	4.51	.42	80	4.37	.45	3.81
Program quality (5 items)	67	4.45	.42	78	4.33	.52	2.29
Overall satisfaction (2 items)	67	4.42	.54	78	4.26	.54	2.98
Program instructor (5 items)	67	4.51	.44	80	4.47	.48	.36
Perceived self-performance (4 items)	69	4.30	.49	81	4.02	.54	11.16**
Administrative arrangements (6 items)	70	4.52	.45	80	4.37	.51	3.5
Total scale (31 items)	65	4.47	.36	76	4.34	.40	3.6

Note: ** $p < .01$.

Table 7. Pearson correlations among the key evaluation components

Variable	1	2	3	4	5	6
Perceived benefits (9 items)	-					
Perceived program quality (5 items)	.82***	-				
Instructor quality (5 items)	.64***	.60***	-			
Self-performance (4 items)	.54***	.50***	.38***	-		
Administrative arrangements (6 items)	.65***	.61***	.51***	.51***	-	
Overall satisfaction (2 items)	.69***	.76***	.50***	.44***	.58***	-

Note: *** $p < .001$.

The correlations among participants' perceptions of perceived benefits, program quality, instructor quality, self-performance, administrative arrangements, and overall satisfaction were examined using Pearson correlation analyses. The findings shown in Table 7 demonstrate that all related variables were significantly and positively associated to different extent (r s ranged from .38 to .82, $ps < .001$). In addition, a strong relationship was observed between perceived benefits and program quality ($r = .82$, $p < .001$).

Table 8. Multiple regression analyses predicting perceived benefits and overall satisfaction

Predictors	Perceived Benefits				Overall Satisfaction			
	<i>B</i>	<i>SE</i>	β	R^2	<i>B</i>	<i>SE</i>	β	R^2
Perceived program quality	0.53	.06	.57***	.74	0.64	.11	.55***	.60
Instructor quality	0.15	.06	.15**		0.03	.09	.023	
Self-performance	0.10	.04	.12*		0.04	.07	.03	
Administrative arrangements	0.15	.06	.16**		.16	.09	.14	
Perceived benefits					.13	.13	.11	

Note: * $p < .05$; ** $p < .01$; *** $p < .001$.

To investigate the predictors of perceived benefits of the participants and factors associated with their overall satisfaction, two multiple regression analyses were performed. The findings in Table 8 show that program quality ($\beta = .57$, $p < .001$), instructor quality ($\beta = .15$, $p < .01$), self-performance ($\beta = .12$, $p < .05$) and administrative arrangements ($\beta = .16$, $p < .01$) could significantly predict the perceived effect of the program, with program quality as the strongest predictor of perceived benefits. Program quality also predicted overall satisfaction of the participants ($\beta = .55$, $p < .001$). However, other factors, including instructor quality, self-performance, administrative arrangements and perceived benefits did not significantly contribute to the overall satisfaction.

DISCUSSION

To promote the holistic and positive development in Chinese adolescents, the Project P.A.T.H.S. was transplanted to mainland China and has been implemented in over 30 secondary schools across the country [12, 29]. Obviously, in-service training offered to school teachers is regarded as an indispensable part of this large scale implementation, because teachers usually play a crucial role in implementing the program in the front line [28, 30]. In the training conducted in Changchun, participants showed enthusiasm towards the training by positive registering, learning, discussing, reflecting and sharing. In the present study, subjective outcome evaluation was used to examine the efficacy of this training program.

The present research findings demonstrate an overall success of the training program. Consistent with the previous training programs conducted in Hong Kong and other mainland cities, the training program received very positive feedbacks from the participants [25, 26, 28]. Overall speaking, the quantitative evaluation results showed that a very high percentage of the participants were satisfied with the program content, instructors and administrative arrangement. Besides, majority of the participants agreed that they gained a higher level of

competence in teaching PYD curriculums through this training and optimistic about the implementation of the project in the future. The present study also replicated previous evaluation findings that both junior and senior high school teachers held positive views towards the training program [15]. Thus, we concluded that the training program was well-received in the mainland China. As some studies suggest a positive correlation between subjective outcome and objective outcome evaluation findings [31-33], it is conjectured that the teachers might possibly perform well in their actual teaching. Of course, future studies should examine whether teachers' positive perceptions of the training predict successful objective outcomes of the project in mainland China.

The present study also identified factors that contributed to a successful training program. Participants' perceived program quality as the strongest predictor of their perceived program benefits and their overall satisfaction, which was in line with the findings of previous trainings in mainland China [34-36]. The participants in Changchun training demonstrated an overall satisfaction with the program quality. This finding suggests that in future training programs, training implementers may use Changchun training design as a reference, such as using more interactive training methods and activities, being sensitive to teachers' needs and expectation, and encouraging peer interaction and self-reflection. In addition to the perceived quality of program and instructor, participants' self-performance and administrative arrangements of the training were also found to be important predictors of perceived program benefits. Hence, it is important for the trainers to have a holistic view when designing the training, and to take all these program components, including program quality, instructor quality, self-performance and administrative arrangements, into account [37].

Although the present study provides strong evidence that the training in Changchun is beneficial to the program participants, some limitations should be noted. First, subjective outcome evaluation in the present study was limited to quantitative data only. Although the quantitative approach is cost-effective and it favors objectivity, representativeness and generalization, qualitative approach is an important alternative or complementary evaluation method which can help to develop an in-depth understanding of the program benefits [38]. Thus, qualitative evaluation of subjective outcomes (e.g., in-depth individual interview and focus group interview) should be included in future research to generate an integrated picture of effectiveness. Second, in addition to subjective evaluation, objective outcome evaluation is also recommended which can give a better understanding of training effectiveness in implementing the project in mainland China. Third, other factors that could affect participants' subjective evaluation of training, such as teachers' previous training attendance record and program implementation experiences, should be included in future studies. Despite the limitations above, the favorable evaluation findings suggest that the Changchun training program for the Project P.A.T.H.S. is well received in mainland China.

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APPENDIX. CONTENT OF THE THIRD TRAINING PROGRAM IN THE 2015-2016 ACADEMIC YEAR IN CHANGCHUN, CHINA

Junior Group

Day 1 (6.5 hours)	
Themes and objectives	Activities conducted
Introduce the latest progress of the Tin Ka Ping P.A.T.H.S. Project in the full implementation phase (2015-2016); Offer opportunities for junior and senior school delegates, principals, and teachers to share their experiences; and Familiarize the participants with the teaching units related to the constructs of “Cognitive Competence” (CC).	Introduce the Tin Ka Ping P.A.T.H.S. Project and the professional team; Introduce the training schedules of the Project; Guide the participants how to use the updated teaching materials and other online resources on the website; Introduce the Co-Walker Scheme; Report the results of evaluation of the second training program in Shaoguan; School sharing from Changchun on the implementation progress of senior programs; Warm-up activities; Lecture on the constructs of “Cognitive Competence” (CC) and the contents of units; Sharing session from participatory schools.
Day 2 (6.5 hours)	
Themes and objectives	Activities conducted
Offer opportunities for schools from Changchun and other participatory schools to share their teaching experiences and demonstrate teaching techniques; and Familiarize the participants with teaching method of the Tin Ka Ping P.A.T.H.S. Project.	Warm-up activities; Lesson demonstrations by experienced school teachers from participating schools; Group discussion and Q&A session.
Day 3 (6.5 hours)	
Themes and objectives	Activities conducted
Familiarize the teachers with the constructs and teaching units; Clarify participants’ questions on project implementation; and Familiarize the participants with the teaching units related to the constructs of “Moral Competence” (MC) and “Self-Determination” (SD) Familiarize the participants with teaching method of the Tin Ka Ping P.A.T.H.S. Project.	Warm-up activities; Group discussions on “How to be a good P.A.T.H.S. teacher?”, “How to teach a good lesson of P.A.T.H.S.?”, and “How to implement P.A.T.H.S. much better?” Lecture on the constructs of “Moral Competence” (MC) and the contents of units; Sharing session from participatory schools.
Day 4 (6.5 hours)	
Themes and objectives	Activities conducted
Familiarize the teachers with the constructs and teaching units; Clarify participants’ questions on project implementation; Familiarize the participants with teaching method of the Tin Ka Ping P.A.T.H.S. Project; and Familiarize the participants with the teaching units related to the constructs of “Self-Determination” (SD), “Spirituality” (SP), and “Clear and Positive Identity” (ID).	Warm-up activities; Lecture on the constructs of “Self-Determination” (SD) and the contents of the unit; Lecture on the constructs of “Spirituality” (SP) and the contents of the unit; Lecture on the constructs of “Clear and Positive Identity” (ID) and the contents of the unit; Sharing session from participatory schools; Interactive lecture on the teaching technique (Stress and fatigue for teachers); Introduce the evaluation results of 2015/16 academic year; Wrapping up and self-reflection; and Conclusion.

Appendix (Continued)

Senior Group	
Day 1 (6.5 hours)	
Themes and objectives	Activities conducted
Introduce the latest progress of the Tin Ka Ping P.A.T.H.S. Project during the full implementation phase (2015-2016); Familiarize the teachers with the constructs and teaching units.	Introduce the Tin Ka Ping P.A.T.H.S. Project and the professional team; Warm-up activities; Introduce the training schedules of the Project; Guide the participants how to use the updated teaching materials and other resources of Tin Ka Ping P.A.T.H.S. Project; Introduce the Co-Walker Scheme; Report the results of the second training program evaluation; Lecture on the constructs of “Social Competence (SC)” and the contents of the unit; Lecture on the constructs of “Emotional Competence (EC)” and the contents of the unit; Lecture on the constructs of “Behavioral Competence (BC)” and the contents of the unit; Sharing session from participatory schools; Group discussion and Q&A session
Day 2 (6.5 hours)	
Themes and objectives	Activities conducted
Offer opportunities for school delegates to share their implementation experiences and teaching plans; and Familiarize the participants with teaching method of the Tin Ka Ping P.A.T.H.S. Project.	Lesson demonstration by school teachers from participating schools; Group discussion and Q&A session.
Day 3 (6.5 hours)	
Themes and objectives	Activities conducted
Familiarize the teachers with the constructs and teaching units. Clarify participants’ questions on project implementation; and Familiarize the participants with teaching method of the Tin Ka Ping P.A.T.H.S. Project.	Warm-up activities; Lecture on the constructs of “Cognitive Competence” (CC) and the contents of the unit; Lecture on the constructs of “Self-Efficacy” (SE) and the contents of the unit; Lecture on the constructs of “Moral Competence” (MC) and the contents of the unit; Lecture on the constructs of “Behavioral Competence” (BC) and the contents of the unit; Group discussion on “How to be a good P.A.T.H.S. teacher?”, “How to teach a good lesson of P.A.T.H.S.?” and “How to implement P.A.T.H.S. much better?”
Day 4 (6.5 hours)	
Themes and objectives	Activities conducted
Familiarize the teachers with the constructs and teaching units; Clarify participants’ questions on project implementation; and Familiarize the participants with teaching method of the Tin Ka Ping P.A.T.H.S. Project.	Warm-up activities; Lecture on the constructs of “Behavioral Competence” (BC) and the contents of the unit; Lecture on the constructs of “Social Competence” (SC) and the content of the unit; Lecture on the constructs of “Resilience” (RE) and the contents of the unit; Sharing session from participatory schools; Interactive lecture on the teaching technique (Stress and fatigue for teachers); Introduce the evaluation results of 2015/16 academic year; Wrapping up and self-reflection; and Conclusion.

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Chapter 325

TIN KA PING P.A.T.H.S. PROJECT IN MAINLAND CHINA: PRELIMINARY EVALUATION FINDINGS

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ABSTRACT

The Tin Ka Ping (TKP) P.A.T.H.S. Project is a pioneer positive youth development program implemented in China. In this study, subjective outcome evaluation data from two junior secondary schools in mainland China were used to reach a tentative understanding of students' opinions about program design, program instructors, and benefits of the program. Consistent with previous findings in Hong Kong, the great majority of the students showed positive feelings of the program content, instructors, and program effectiveness. As predicted, program content, instructors, and effectiveness were significantly inter-correlated. Perceived program content and quality of instruction were also identified to be significant predictors of program effectiveness perceived by student participants. The present findings suggest that TKP P.A.T.H.S. program was well received by the students in mainland China.

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INTRODUCTION

In the past few decades, positive youth development (PYD) approach has been widely used to promote holistic development for youths and young adults in Western countries [1, 2]. Additionally, the approach is well adopted in the Chinese contexts [3, 4]. In Hong Kong, the P.A.T.H.S. Project was designed utilizing 15 constructs of positive adolescent development recognized in the scientific literature [5]. Systematic evaluation studies of the programs in the P.A.T.H.S. Project have shown that they have helped promote adolescent well-being and delayed the onset of risk behavior [6-8].

In terms of youth issues, it is noteworthy that adolescents in mainland China show many forms of risk behavior [9, 10]. With a highly competitive education system, young people on the mainland also face very high academic stress. It is important to ask how we can promote holistic development for Chinese students in mainland China. Obviously, with the successful implementation experience of the P.A.T.H.S. Project in Hong Kong, it is expected that the project could be further transplanted to mainland China, where has similar cultural context with Hong Kong. Financially the P.A.T.H. Project was fully supported by Tin Ka Ping (TKP) Foundation. The P.A.T.H.S. Project was preliminary transplanted as a pilot scheme to four schools in Shanghai, Suzhou, Changzhou and Yangzhou in eastern China since 2011. During 2011-2014, teaching materials in simplified Chinese were developed by the Hong Kong Research Team, and teacher training and program evaluation were also implemented in mainland China. Because of the extensive support from TKP schools located throughout the country, the second phase (preparatory phase) of the project was launched in fall 2014, with the objective of providing systematic training and “trial” experience for the school teachers who are the potential instructors of the project [11]. In 2014-15 school year, four training programs had been offered in three different cities in eastern or western China, including Shanghai, Suzhou and Chongqing [12-15]. Besides attending the training programs, some schools also tried out the program.

To facilitate systematic evaluation of the TKP P.A.T.H.S. Project, the Research Team briefed the teachers in the training programs regarding the three major project evaluation strategies: (a) objective outcome evaluation using validated scales; (b) subjective outcome evaluation on the base of the replies in Form A (for the program participants) and Form B (for the program implementers), and (c) qualitative evaluation such as collection of students' diaries. With particular reference to the views of the program participants, the instrument used in evaluation (i.e., Form A) has three primary dimensions (program content, program instructors, and program effectiveness), which had excellent psychometric properties [16]. The adoption of Form A as an evaluation tool has three advantages. First, we can aggregate data from multiple years that can show a general profile of the responses of participants. Second, the tool has been validated with excellent psychometric properties. Finally, subjective outcome evaluation is a relatively economical way to conduct program evaluation [17, 18].

The objective of the present study was to investigate the views of the student participants' on the TKP P.A.T.H.S. program implemented in mainland China. Three sets of research questions were addressed in the study:

- Question 1: What are student participants' perceptions of the program content, program instructors (teachers), and program effectiveness? Based on previous studies conducted in Hong Kong, it was predicted that the participants would be satisfied with the program content, program instructors and program effectiveness (Hypothesis 1).
- Question 2: What are the inter-relationships amongst program content, quality of instruction, and program effectiveness perceived by the participants? Based on the literature, it was expected that there would be a correlation between perceived program content and program instructors (Hypothesis 2a), perceived program content and program effectiveness (Hypothesis 2b), and perceived program instructors and program effectiveness (Hypothesis 2c).
- Question 3: What are the predictors of perceived program effectiveness? Based on previous findings, we predicted that perceived program content and program instructors would predict program effectiveness (Hypothesis 3a and 3b).

OUR STUDY

In the 2014–15 school year, data was collected using the questionnaire Form A from two schools (N = 521). Both schools followed the standardized instructions regarding student data collection and data entry that were given in Form A and provided by the Research Team. Passive informed consent was obtained from the student participating in the program at the beginning of the survey. The students could withdraw from the study if they did not want to participate. All students filled out the survey in a self-administered manner.

Instruments

Form A assesses the subjective views of the program participants. It was widely used in different schools in the Hong Kong P.A.T.H.S. Project. Program participants were invited to use Form A to share their perceptions of program content, program instructors (teachers, social workers, other workers), and program effectiveness after participating in TKP P.A.T.H.S. Project. From the findings in previous evaluation research, it has been found that Form A possesses excellent psychometric properties [16]. Form A includes five parts:

- *Part 1 (participants' evaluations of the program content)*. There are 10 items, which include students' perceptions of the curriculum objectives, course design, interaction with the instructors, and student participation in learning. Details of the items are shown in Table 1.
- *Part 2 (participants' evaluation of the program instructors)*. There are 10 items including students' perception of the teaching, class preparation, the teachers' professional attitude, and the teachers' caring and supportive attitude. Details of the items are shown in Table 2.
- *Part 3 (participants' evaluation of program effectiveness)*. There are 16 items assessing students' perception of the program benefits to their PYD, such as

promotion of bonding, emotional competence, social skills and competence, or moral competence. Details of the items are shown in Table 3.

- *Part 4 (participants' overall satisfaction with the program).* There are three items measuring satisfaction. They inquire whether the students will recommend their friends to join the program, whether the students would like to participate in similar programs again, and the students' global satisfaction with the TKP P.A.T.H.S. program.
- *Part 5 (four open-ended questions).* Students are invited to share their views and feelings on things they learned and appreciated, to give suggestions to the teachers, and recommendations for the program.

Data Analyses

SPSS 23 (IBM SPSS Statistics, IBM Corp, Somers, NY) was used for all the data analyses. Four subscale variables were created: (a) "program content (VC)" was the mean score of the 10 items in Part 1; (b) "program instructors (VI)" was the mean score of the 10 items in Part 2; (c) "program effectiveness (EF)" was the mean score of the 16 items in Part 3; (d) "total effectiveness" was calculated as the overall mean score of all the 36 items in Part 1, 2, and 3. Data analyses in this study only covered the quantitative data in Part 1 to Part 4.

Descriptive analyses were conducted to calculate the mean and standard deviations of each subscale. Reliability analyses were performed to measure the internal consistency of the above subscales and the overall scale. Pearson correlation coefficients were also calculated to examine interrelationships amongst the variables. Lastly, multiple regression analyses were performed to examine whether perceived program content and instructors predict program effectiveness. All the above analyses were conducted for the two schools (School 1 and School 2) separately and aggregately.

FINDINGS

Form A showed good psychometric properties. As the findings shown in Table 4, the scale had good internal consistency in School 1, School 2, and the overall sample. In the overall sample ($N = 521$), the reliability estimates were good: the Cronbach's alpha value for the total effectiveness scale was .96, and the Cronbach's alpha values for the subscales of program content, program instructors, and program effectiveness were .88, .93 and .94 respectively; the mean of inter-item correlation for the scale and subscales above, respectively was .38, .42, .56, and .51.

Descriptive analyses showed that the majority of the student participants evaluated the program positively regarding its content, instructors (teachers, social workers, other workers), as well as its effectiveness. As shown in Table 1, 89.8% of the participants had a positive view on the good design of the curriculum (item 2), 91.9% of the participants agreed that the curriculum objectives were very clear (item 1), and 91.0% of the participants had overall satisfaction of the curriculum (item 10). As shown in Table 2, amongst the top items rating program instructors, 96.0% of the participants agreed that the teachers had encouraged them

to participate in different course activities (item 6), 95.0% of the participants agreed that they received timely help from the teachers (item 8) and 95.4% of the participants had a positive perception of the active involvement of the teachers (item 5).

Table 1. Descriptive statistics of the participants' evaluations of the program content

	Respondents with positive responses (Options 4-6)					
	School 1		School 2		Overall	
	<i>n</i>	%	<i>n</i>	%	<i>N</i>	%
1) The objectives of the curriculum are very clear.	117	95.9	362	90.7	479	91.9
2) The design of the curriculum is very good.	119	97.5	349	87.5	468	89.8
3) The activities were carefully planned.	116	95.1	337	84.5	453	86.9
4) The classroom atmosphere was very pleasant.	110	90.2	325	81.5	435	83.5
5) There was much peer interaction amongst the students.	118	96.7	332	83.2	450	86.4
6) I participated actively during lessons (including discussions, sharing, games, etc.).	117	95.9	334	83.4	451	86.6
7) I was encouraged to do my best.	116	95.9	333	83.5	449	86.3
8) The learning experience I encountered enhanced my interest towards the lessons.	114	94.2	336	84.2	450	86.5
9) Overall speaking, I have a very positive experience of the program.	115	95.0	331	83.0	446	85.8
10) On the whole, I like this curriculum very much.	119	98.3	354	88.7	473	91.0

Note: All items are measured using a 6-point Likert scale where 1 = strongly disagree, 2 = disagree, 3 = slightly disagree, 4 = slightly agree, 5 = agree, 6 = strongly agree. Only respondents with positive responses (Options 4-6) are shown in the table. School 1: Shijiazhuang TKP school, School 2: Shanwei TKP school.

Table 2. Descriptive statistics of the participants' evaluations of the program instructors

	Respondents with positive responses (Options 4-6)					
	School 1		School 2		Overall	
	<i>n</i>	%	<i>n</i>	%	<i>N</i>	%
1) The instructor(s) had a good mastery of the curriculum.	120	98.4	354	88.7	474	91.0
2) The instructor(s) was well prepared for the lessons.	121	99.2	362	90.7	483	92.7
3) The instructor(s)' teaching skills were good.	120	98.4	360	90.2	480	92.1
4) The instructor(s) showed good professional attitudes.	118	96.7	368	92.2	486	93.3
5) The instructor(s) was very involved.	119	98.3	377	94.5	496	95.4
6) The instructor(s) encouraged students to participate in the activities.	121	99.2	379	95.0	500	96.0
7) The instructor(s) cared for the students.	121	99.2	365	91.5	486	93.3
8) The instructor(s) was ready to offer help to students when needed.	121	99.2	374	93.4	495	95.0
9) The instructor(s) had much interaction with the students.	117	95.9	353	88.5	470	90.2
10) Overall speaking, I have a very positive experience of the instructors.	121	99.2	372	93.2	493	94.6

Note: All items are measured using a 6-point Likert scale where 1 = strongly disagree, 2 = disagree, 3 = slightly disagree, 4 = slightly agree, 5 = agree, 6 = strongly agree. Only respondents with positive responses (Options 4-6) are shown in the table. School 1: Shijiazhuang TKP school, School 2: Shanwei TKP school.

Table 3. Descriptive statistics of the participants' evaluations of the program effectiveness

	Respondents with positive responses (Options 3-5)					
	School 1		School 2		Overall	
	<i>n</i>	%	<i>n</i>	%	<i>N</i>	%
1) It has strengthened my bonding with teachers, classmates, and my family.	112	91.8	284	71.2	396	76.0
2) It has strengthened my resilience in adverse conditions.	111	91.0	316	79.2	427	82.0
3) It has enhanced my social competence.	114	93.4	328	82.2	442	84.8
4) It has improved my ability in handling and expressing my emotions.	115	94.3	324	81.2	439	84.3
5) It has enhanced my cognitive competence.	115	94.3	325	81.5	440	84.5
6) My ability to resist harmful influences has been improved.	116	95.1	344	86.2	460	88.3
7) It has strengthened my ability to distinguish between the good and the bad.	118	96.7	346	86.7	464	89.1
8) It has increased my competence in making sensible and wise choices.	115	94.3	333	83.5	448	86.0
9) It has helped me to reflect my life.	113	93.4	310	77.7	423	81.3
10) It has reinforced my self-confidence.	113	92.6	319	79.9	432	82.9
11) It has increased my self-awareness.	117	96.7	344	86.2	461	88.7
12) It has helped me to face the future with a positive attitude.	119	97.5	334	83.7	453	86.9
13) It has helped me to cultivate compassion and care for others.	114	93.4	321	80.5	435	83.5
14) It has encouraged me to care about the community.	101	82.8	256	64.2	357	68.5
15) It has promoted my sense of responsibility in serving the society.	110	90.9	320	80.2	430	82.7
16) It has enriched my overall development.	119	97.5	355	89.2	474	91.2

Note: All items are measured using a 5-point Likert scale where 1 = unhelpful, 2 = not really helpful, 3 = slightly helpful, 4 = helpful, 5 = very helpful. Only respondents with positive responses (Options 3-5) are shown in the table. School 1: Shijiazhuang TKP school, School 2: Shanwei TKP school.

Table 4. Mean, standard deviations, Cronbach's alphas, and the mean of inter-item correlations

	School 1		School 2		Overall	
	M (SD)	α (Mean [#])	M (SD)	α (Mean [#])	M (SD)	α (Mean [#])
Program content (10 items)	5.46 (.66)	.90 (.48)	4.60 (.71)	.83 (.33)	4.80 (.79)	.88 (.42)
Program instructors (10 items)	5.68 (.53)	.93 (.59)	4.90 (.77)	.91 (.50)	5.08 (.79)	.93 (.56)
Program effectiveness (16 items)	4.34 (.76)	.96 (.63)	3.51 (.77)	.92 (.42)	3.70 (.84)	.94 (.51)
Total effectiveness (36 items)	5.02 (.59)	.97 (.45)	4.20 (.62)	.94 (.30)	4.39 (.70)	.96 (.38)

Note: School 1: Shijiazhuang TKP school, School 2: Shanwei TKP school.

[#] Mean inter-item correlations.

Table 5. Other aspects of subjective outcome evaluation based on the participants' perception

If your friends have needs and conditions similar to yours, will you suggest him/her to join this course?

Respondents with positive responses (Options 3-4)					
School 1		School 2		Overall	
<i>n</i>	%	<i>n</i>	%	<i>N</i>	%
121	100.0	365	91.5	486	93.5

Note: The item is measured using a 4-point Likert scale where 1 = definitely will not suggest, 2 = will not suggest, 3 = will suggest, 4 = definitely will suggest. Only respondents with positive responses (Options 3-4) are shown in the table. School 1: Shijiazhuang TKP school, School 2: Shanwei TKP school.

Would you participate in similar courses again in the future?

Respondents with positive responses (Options 3-4)					
School 1		School 2		Overall	
<i>n</i>	%	<i>n</i>	%	<i>N</i>	%
119	98.3	371	93.0	490	94.2

Note: The item is measured using a 4-point Likert scale where 1 = definitely would not participate, 2 = would not participate, 3 = would participate, 4 = definitely would participate. Only respondents with positive responses (Options 3-4) are shown in the table. School 1: Shijiazhuang TKP school, School 2: Shanwei TKP school.

On the whole, are you satisfied with this course?

Respondents with positive responses (Options 4-6)					
School 1		School 2		Overall	
<i>n</i>	%	<i>n</i>	%	<i>N</i>	%
121	100.0	370	92.7	491	94.4

Note: All items are measured using a 6-point Likert scale where 1 = very dissatisfied, 2 = moderately dissatisfied, 3 = slightly dissatisfied, 4 = satisfied, 5 = moderately satisfied, 6 = very satisfied. Only respondents with positive responses (Options 4-6) are shown in the table. School 1: Shijiazhuang TKP school, School 2: Shanwei TKP school.

Table 6. Pearson correlations among program content, instructors, and effectiveness

School 1: Variable	1	2	3
1) Program content (10 items)	-		
2) Program instructors (10 items)	.71**	-	
3) Program effectiveness (16 items)	.59**	.58**	-

** $p < .01$.

School 2: Variable	1	2	3
1) Program content (10 items)	-		
2) Program instructors (10 items)	.60**	-	
3) Program effectiveness (16 items)	.51**	.45**	-

** $p < .01$.

Overall : Variable	1	2	3
1) Program content (10 items)	-		
2) Program instructors (10 items)	.69**	-	
3) Program effectiveness (16 items)	.61**	.56**	-

** $p < .01$.

Regarding students' perception on their personal growth after the program, some items received high ratings. As Table 3 shows, 89.1% of the participants agreed that the program had improved their ability to distinguish between the good and the bad (item 7), 88.7% of the participants had a positive perception of their increased self-awareness (item 11), and 91.2% of the participants agreed that the program had enriched their overall development (item 16). In Table 5 we can see that 93.5% of the students would suggest their friends to join the program, 94.2% would participate in a similar program in the future, and 94.4% were satisfied with the program they participated. These findings provided support to hypothesis 1.

Table 7. Multiple regression analyses predicting program effectiveness by program content and instructors

	Predictors		Model	
	Program content	Program instructors		
	β^a	β^a	R	R ²
School 1	.36**	.33**	.64	.40
School 2	.37***	.23***	.54	.28
Overall	.44***	.26***	.64	.41

a Standardized coefficients.

** $p < .01$, *** $p < .001$.

Pearson correlation analyses (see Table 6) showed that program content (VC), instructors (VI) and effectiveness (EF) were all positively and significantly correlated: VC and VI ($r = .69, p < .01$); VC and EF ($r = .61, p < .01$); VI and EF ($r = .56, p < .01$). This means that hypotheses 2a, 2b, 2c were all supported. Multiple regression analyses (see Table 7) demonstrated that how the students' perceived the program content (VC) and program instructors (VI) significantly predicted their perceived program effectiveness (EF). In the total sample, both VC ($\beta = .44, p < .001$) and VI ($\beta = .26, p < .001$) significantly predicted EF, and accounted for 41% of the total variance of EF. These findings provided support for hypothesis 3a and hypothesis 3b.

DISCUSSION

Similar to previous evaluations in Hong Kong [16, 19-21], Form A was shown to be a reliable evaluation tool of subjective outcome to assess the views of the student participants on the P.A.T.H.S. program implemented in the two middle schools in mainland China. Most important of all, the students had a very positive view on the program content, instructors, and benefits brought to their personal development. The evaluation findings clearly give preliminary support that TKP P.A.T.H.S. Project is an effective and promising program in the two schools which participated in the preparatory phase in 2014-15 school year.

With regard to the inter-relationships amongst the three aspects of subjective outcome evaluation, results of Pearson correlation analyses showed that program content, program instructors (teachers, social workers, other workers), and program effectiveness are the "holy trinity" of the subjective outcome evaluation [22]. Besides, results showed that student participants' perceived program content and instructor quality significantly predicted their perceived program effectiveness, which covered different aspects of PYD. From the student

participants' perspective, the P.A.T.H.S. curriculum was perceived as very beneficial to the development of adolescent.

The present study is a pioneer evaluation study of the project in mainland China. However, it has several limitations. First, common method variance may account for the significant inter-relationships amongst the different components of subjective outcome evaluation. Second, as only two schools were involved in the evaluation, the findings should be treated as tentative in nature. Third, in addition to subjective outcome evaluation, other forms of evaluation (such as qualitative methods) should be included in the evaluation model. Finally, besides students, other major stakeholders should be included to achieve a more comprehensive view of the impact of the program.

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Chapter 326

EVALUATION FINDINGS OF TIN KA PING P.A.T.H.S. PROJECT IMPLEMENTED IN JUNIOR SECONDARY SCHOOLS: IMPLEMENTERS' VIEWS

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ABSTRACT

After the Project P.A.T.H.S. was successfully implemented in the pilot stage in four cities in East China, the project was implemented on a full-scale basis since 2015-2016 academic year. The present paper outlines the evaluation findings of the first year during the full implementation based on the views of the implementers using the subjective outcome evaluation approach. A total of 144 implementers from 13 secondary schools joined the current research. On the whole, results showed that the implementers were highly satisfied with the implementation regarding program content, their own performance, and program benefits. As expected, perceptions of program content and implementers' own performance were positively associated with perceived program benefits. Together with previous evaluation findings in Hong Kong and China mainland, the current study suggests that the Project P.A.T.H.S. has been well received by participants and implementers, and it promotes positive development in adolescents in different Chinese communities.

INTRODUCTION

Positive youth development (PYD) programs are intended to promote all-round development among teenagers by providing them opportunities to recognize, utilize and

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enhance their strengths, which would establish a solid foundation for healthy adjustment which would eventually prevent youth problems, such as substance abuse, juvenile delinquency, and violent crimes [1]. The beneficial influence of PYD programs has been widely recognized globally. For instance, sport camps in the United Kingdom (UK) have been shown to promote competence, confidence, and care amongst students [2]. In South Africa, a narrative-based program was found to promote youth development and it successfully reduced alcohol use and HIV infection among the youngster [3]. In a comprehensive review of efficacious youth programs around the world, researchers concluded that implementing preventive and PYD programs effectively is a promising way to reduce adolescent problem behaviors [4].

Although PYD programs are popular among Western countries, systematic and large-scale PYD programs are rarely developed and implemented in Chinese contexts [5]. To fill this information gap, a curriculum-based PYD program entitled “Positive Adolescent Training through Holistic Social Programmes” (Project P.A.T.H.S.) was developed and carried out in Hong Kong since 2005-2006 academic year with the financial support of The Hong Kong Jockey Club Charities Trust. This is the first large-scale and holistic PYD program in different Chinese communities. During the past decade, this project has achieved a great success in competence building and problem prevention among Hong Kong adolescents. Specifically, empirical findings showed that the project successfully enhanced multiple developmental assets and well-being (e.g., self-confidence, spirituality, prosocial involvement, and social competence) in students while simultaneously reduced adolescents’ engagement in maladaptive behaviors, such as drug abuse, delinquency, and self-harm activities [6-8]. Consistently, the program was positively evaluated and regarded as effective by both adolescent participants and program implementers [9-11]

There is also an urgent need to design and launch evidence-based PYD programs in mainland China because there are growing trends of youth problems in China. For example, with rapid economic growth in the past decades in mainland China, materialism became prevalent among Chinese adolescents. According to a research conducted by Ipsos [12], China is now the most materialistic country among 20 countries including the United States, UK, Japan, Korea, and so on. Under this atmosphere, the younger generation in China is becoming more materialistic when compared to the older generation and their counterparts in other countries [13]. It is noteworthy that materialism was adversely associated with healthy adolescent development, such as self-esteem, mental health, and life satisfaction [14]. Similarly, an orientation of materialism also exerts negative impacts on students’ intrinsic learning motivation, school performance, and developmental outcomes [15]. All these findings take place alongside with the growing trends of external and internal problems among the Chinese youths [16].

To promote health development in Chinese adolescents in mainland China, the Project P.A.T.H.S. was adapted and implemented in mainland China in 2011, with financial support from Tin Ka Ping Foundation. Although the Project P.A.T.H.S. has benefited thousands of secondary students in Hong Kong, its effectiveness in mainland China remains uncertain due to several reasons. First, although the junior secondary school programs adopted in mainland China were based on those implemented in Hong Kong, their applicability is unclear because there are cultural or sub-cultural differences involved.

Second, the pedagogy of Project P.A.T.H.S. was based on experiential learning, which requires teachers to let students learn from their firsthand experience rather than only

passively receiving knowledge from teachers [17]. In particular, it emphasizes reflection since it allows students to introspect challenges and integrate new information to their existing schema [17]. Obviously, such a student-centered pedagogy is quite different from the traditional teacher-centered one adopted in China. This stimulating pedagogy requires both teachers and students to make adaptations to their changing roles in the classroom. In this sense, both teachers and students may have difficulties in adjusting to the new teaching and learning styles, which might also potentially affect the effectiveness of the project.

Third, implementing and participating in such a PYD program might require extra working and schooling hours from teachers and students. Given that academic achievement is morbidly emphasized by schools, parents, and the society in China [18], school teachers and students may still have a mindset that the Project P.A.T.H.S. is competing for resource with other academic courses, which might possibly hinder students' academic achievement. Despite the strong evidence that effective PYD programs can actually enhance adolescents' school performance and academic achievement [19], schools might still have hesitation to devote sufficient effort in implementing the project.

In view of the above issues, a 3-year pilot implementation (i.e., from 2011-2012 to 2013-2014 academic year) was carried out in four secondary schools located in East China and different evaluation strategies were utilized to investigate the implementation effectiveness. Results revealed highly positive findings regarding the program effectiveness in promoting adolescent holistic development [20, 21]. These encouraging findings motivated the Foundation to support the project for three more years (2015-2016 to 2017-2018 school years) after one-year of preparation (i.e., 2014-2015 school year).

Although the pilot implementation showed the benefits of the Tin Ka Ping Project P.A.T.H.S. in China mainland, continuous program evaluation should be carried out, not only for the purpose of providing evidence-based support but also informing directions to improve future implementation. To this end, the present study attempted to evaluate program effectiveness in the first year of full implementation (i.e., 2015-2016 academic year). A subjective outcome evaluation method was used, in which data on the views from the program implementers toward three main aspects (program content, implementer's own performance, and program effectiveness) were collected. Program implementers' views should be considered and understood because they directly deliver the program. Moreover, their direct interactions with students allow them to understand the real need and actual change of students. Based on the previous positive evaluation findings [11, 22, 23], we proposed the following hypotheses:

- A majority of the program implementers would show positive perceptions on program content (Hypothesis 1a), their own performance (Hypothesis 1b), and program effectiveness (Hypothesis 1c). In subjective outcome studies, a program is commonly regarded as positive if more than 80% of the respondents respond in the positive direction. We used the same cutoff point in this study.
- Program implementers' satisfaction of program content (Hypothesis 2a) and self-perceived performance (Hypothesis 2b) would have positive relationships with the perceived program effectiveness.

- Program implementers’ evaluation of program effectiveness would be positively predicted by perceived program content (Hypothesis 3a) and own performance (Hypothesis 3b).

OUR STUDY

Program implementers (e.g., teachers) from 13 participating schools were invited to complete a subjective outcome evaluation form for implementers (i.e., Form B) after the program was implemented in 2015-2016 academic year. A total of 144 implementers completed and returned the Form B. Among all the implementers, 80 implemented the program for Secondary 1, 45 for Secondary 1 and Secondary 2, and 19 for Secondary 1, Secondary 2, and Secondary 3. The number of implementers in each school ranged from 5 to 30, with an average of 11 (*SD* = 6.79). An evaluation manual with detail instructions was given to implementers to guide them to complete the Form B prior to program evaluation. The procedures for collecting data and the related instructions were also covered in the training workshops.

Instruments

The Form B used in the present study has been widely used in prior evaluation studies and proved to be valid and reliable [11, 24]. In Form B, six parts were developed to measure implementers’ subjective perceptions of several aspects of the program.

First, two subscales were included in Part 1. Each subscale adopted 10 items to measure perceptions of the implementers toward the program content (e.g., impression of the program, classroom atmosphere, and students’ participation) and self-performance (e.g., implementers’ understanding of the program, involvement, and teaching skills). For each statement, the implementers gave their response on a 6-point Likert scale (1= strongly disagree, 6 = strongly agree). The higher they rated, the more they agreed with the statement. The two subscales in the first part showed good reliability in the present study (see Table 1).

Table 1. Mean, standard deviation, Cronbach’s alphas, and mean of inter-item correlations among variables

	M	SD	Cronbach’s α	Mean [#]
Program content (10 items)	5.28	.49	.89	.44
Program implementers (10 items)	5.12	.56	.92	.52
Program effectiveness (16 items)	4.23	.59	.96	.59

Note. [#] Mean inter-item correlations

Second, 16 items were employed in Part 2 to evaluate the implementers’ perceived program effectiveness (e.g., improvement in students’ resilience, emotional competence, and social competence). This subscale utilized a 5-point Likert scale (1 = not helpful at all, 5 = very helpful). Similarly, a higher rating in this subscale indicates a higher level of perceived program effectiveness. This subscale also had good reliability as shown in Table 1.

For Part 3 to Part 5, each part only contained one question. The third part asked the implementers to indicate their willingness to recommend the program to students having similar needs on a 4-point Likert scale (1 = definitely will not, 4 = definitely will). Using the same 4-point scale (1 = definitely will not, 4 = definitely will), the fourth part invited the implementers to express their willingness in teaching similar courses in the future. Lastly, the question in the fifth part was designed to assess the implementers' perception of the extent to which the program helped their professional development. Implementers gave their responses on a 5-point Likert scale (1 = not helpful at all, 5 = very helpful).

The sixth part contained three open questions about the most appreciated elements of the program, the areas need improvement, and suggestions for future development. In the present paper, the focus is put on the quantitative data derived from the first five parts.

Data Analyses

A reliability test was done to measure the internal consistency of each subscale. Descriptive analyses were then performed to calculate the percentage of favorable responses of each part. We also examined correlations among respondents' views toward program quality, their own performance, and program effectiveness. Besides, a multiple regression analysis was performed to examine the predictive effect of perceived program qualities and self-perceived performance on the level of perceived program effectiveness.

FINDINGS

Using 80% as a cutoff, positive responses toward the program content were found among all items as shown in Table 2. For example, all implementers agreed that the objectives of the program were very clear and the program activities were carefully designed. Moreover, almost all implementers (99.3%) had a very positive overall evaluation on the program and agreed that their students like this program very much.

Table 2. Summary of the program implementers' perceptions toward the program content

	Positive responses (Options 4-6)	
	N	%
1. The objectives of the curriculum are very clear.	144	100.0
2. The design of the curriculum is very good	143	99.3
3. The activities were carefully planned	144	100.0
4. The classroom atmosphere was very pleasant.	142	98.6
5. There was much peer interaction amongst the students	137	95.1
6. Students participated actively during lessons (including discussions, sharing, games, etc.)	141	97.9
7. The program has a strong and sound theoretical support.	141	97.9
8. The teaching experience I encountered enhanced my interest towards the lessons	142	98.6
9. Overall speaking, I have very positive evaluation of the program	143	99.3
10. On the whole, students like this curriculum very much	143	99.3

Note. All items are on a 6-point Likert scale with 1 = strongly disagree, 2 = disagree, 3 = slightly disagree, 4 = slightly agree, 5 = agree, 6 = strongly agree. Only respondents with positive responses (Options 4-6) are shown in the table.

Similar positive results were found in self-perceived performance (see Table 3). All implementers stated that they were ready to offer help to student when needed. Most of them (99.3%) had a very positive overall evaluation on themselves. Highly positive responses were also found on other items (e.g., professional attitude, involved, and cared for students).

Table 3. Summary of the program implementers' perceptions toward their own performance

	Positive responses (Options 4-6)	
	N	%
1. I have a good mastery of the curriculum.	136	94.4
2. I prepared well for the lessons	138	95.8
3. My teaching skills were good	137	95.1
4. I have professional attitude	142	98.6
5. I was very involved	141	97.9
6. I gained a lot during the course of instruction	142	98.6
7. I cared for the students	142	98.6
8. I was ready to offer help to students when needed	144	100.0
9. I had much interaction with the students	141	97.9
10. Over speaking, I have very positive evaluation of myself as an instructor	143	99.3

Note. All items are on a 6-point Likert scale with 1 = strongly disagree, 2 = disagree, 3 = slightly disagree, 4 = slightly agree, 5 = agree, 6 = strongly agree. Only respondents with positive responses (Options 4-6) are shown in the table.

Table 4. Summary of the program implementers' perceptions toward the program effectiveness

	Positive responses (Options 3-5)	
	N	%
1. It has strengthened students' bonding with teachers, classmates and their families	143	99.3
2. It has strengthened students' resilience in adverse conditions	141	97.9
3. It has enhanced students' social competence	140	97.2
4. It has improved students' ability in handling and expressing emotions	142	98.6
5. It has enhanced students' cognitive competence	141	97.9
6. Students' ability to resist harmful influences has been improved	141	97.9
7. It has strengthened students' ability to distinguish between the good and the bad	142	98.6
8. It has increased students' competence in making sensible and wise choices	141	97.9
9. It has helped students to have life reflections	141	97.9
10. It has reinforced students' self-confidence	142	98.6
11. It has increased students' self-awareness	142	98.6
12. It has helped students to face the future with a positive attitude	143	99.3
13. It has helped students to cultivate compassion and care about others	142	98.6
14. It has encouraged students to care about the community	139	96.5
15. It has promoted students' sense of responsibility in serving the society	142	98.6
16. It has enriched the overall development of the students	138	95.8

Note. All items are on a 5-point Likert scale with 1 = unhelpful, 2 = not very helpful, 3 = slightly helpful, 4 = helpful, 5 = very helpful. Only respondents with positive responses (Options 3-5) are shown in the table.

Table 4 presents the respondents' subjective views on perceived program effectiveness. Overall speaking, respondents gave highly positive responses on all items. More specifically, almost all participants (99.3%) agreed that the program helped their students build a stronger bonding with teachers, classmates and their families, and they perceived their students had a positive attitude to face the future after joining the program. Moreover, nearly 99% of the

implementers indicated that the program strengthened students' ability in expressing emotions, helped students to distinguish between good and bad, and cultivated compassion and care about others.

Table 5. Summary of the program implementers' positive perceptions on other aspects

Items	Positive responses (Options 3-4)	
	N	%
Willingness to suggest other students to participate in the program ^a	143	99.3
Willingness to teach similar programs in future ^a	139	96.5
The extent to which the program helped implementers' professional growth ^b	139	96.5

Note. ^a A 4-point Likert scale was used, with 1 = definitely will not, 2 = will not, 3 = will, 4 = definitely will. Only respondents with positive responses (Options 3–4) are shown in the table.

^b A 5-point Likert scale was used, with 1 = unhelpful, 2 = not very helpful, 3 = slightly helpful, 4 = helpful, 5 = very helpful. Only respondents with positive responses (Options 3–5) are shown in the table.

Table 6 shows the results of Pearson correlation analyses. Both perception of program quality ($r = .58$, $p < .001$) and view toward own performance ($r = .66$, $p < .001$) showed a significant and positive linkage with implementers' perception of program effectiveness. These results provided support for hypotheses 2a and 2b.

Table 6. Correlations among perceptions on program content, implementers, and program effectiveness

Variable	Program effectiveness		
	1	2	3
1. Program content (10 items)	--		
2. Program implementers (10 items)	.74***		
3. Program effectiveness (16 items)	.58***	.66***	--

*** $p < .001$.

To further investigate the relationship between perceived program content, self-perceived performance and perceived program effectiveness, a multiple regression analysis was done and the results are depicted in table 7. Both implementers' self-perceived performance ($\beta = .50$, $p < .001$) and perceived program content ($\beta = .20$, $p < .05$) significantly predicted program effectiveness. The two predictors accounted for 45% of the variance of program effectiveness. In short, both hypotheses 3a and 3b were supported.

Table 7. Multiple regression analysis predicting program effectiveness

Program content	Predictors		Model
	Program implementers		
β^a	β^a	R	R^2
.20*	.50***	.67	.45

Note. ^a Standardized coefficients. *** $p < .001$. * $p < .05$.

DISCUSSION

The present research investigated evaluation findings based on implementers' views toward the Tin Ka Ping P.A.T.H.S. Project implemented in mainland China in 2015-2016 academic year. The current study employed a valid and reliable subjective outcome evaluation measurement (i.e., Form B) to assess the implementers' views toward the program implementation. The Form B mainly included three multi-item subscales that assessed implementers' perceptions of program content, their own performance and program effectiveness, respectively. The information of implementers' willingness to recommend the program to other students, willingness to implement similar programs in future, and the extent the experience promoted teachers' professional growth was also gathered in the present study. The present findings not only demonstrated that the program was effective. It also informed us about the possible factors that contributed to the implementation effectiveness.

Overall speaking, the implementers held positive perceptions of the program implemented in 2015-2016 school year. Notably, over 95% of the respondents gave positive ratings on all aspects of the program content; all of them regarded the curriculum objectives as clear and activities as meticulously designed; over 99% of them perceived that the curriculum was well designed and agreed that students loved the program a lot. In addition, the implementers held favorable views toward their own performance. Nearly or over 95% of them rated themselves as having good performance in all aspects. For instance, over 98% of the respondents perceived that they had professional attitudes, cared for the students, and were willing to offer help to the students.

Regarding perceived program effectiveness, results showed that the implementation of program was effective in cultivating students' myriad positive attributes, such as positive bonding with significant adults and peers, resilience, self-awareness, beliefs in the future, emotional and moral competence, and so on. Implementers' responses to the three questions illustrated in Table 5 reinforced the positive evaluation. Almost all respondents were willing to suggest other students to join the program, and approximately 97% of the implementers wished to teach similar course in future and felt that teaching the program had benefited themselves a lot regarding professional development. All these results coincide with the positive evaluation findings for the P.A.T.H.S. Project implemented in Hong Kong [11, 24], suggesting that the transplanting and adaptation of the project from Hong Kong to mainland China is successful.

Theoretically speaking, the well-designed program content and quality delivery of the content by implementers as well as some supportive external conditions (e.g., policy support) collaboratively ensure the great benefits enjoyed by program participants [25]. In line with this argument, perceptions of program content and program implementers' performance were both significantly correlated with and functioned as two significant predictors of perceived program effectiveness. The existing literature suggests that several factors may contribute to the quality of program content and implementers' good performance in delivering program content.

First of all, the curriculum of the project was developed based on PYD theory that maintains adolescents as "assets to be developed" instead of "problems to be solved" [26]. Based on this positive view of adolescents, course content was carefully selected to fulfill adolescents' developmental needs through promoting a wide range of psychosocial

competencies, including self-efficacy, emotional competence, spirituality, and resilience [27]. In addition to the strong theoretical basis, the curriculum also included a reflective and experiential learning pedagogy, which contends that students can learn by “experiencing, reflecting, thinking, and acting” [17]. In line with the active learning philosophy, the center of teaching shifted from teachers to students; the method of teaching ranged from merely lecturing to a combination of diverse ones, including group work, role play, debate, and reflection. It is noteworthy that an encouraging learning environment as well as a collaborative atmosphere created by such an inspirational and innovative pedagogy are very helpful in promoting students’ positive learning attitude, student engagement, and learning achievement [28, 29]. These two unique features of the program content lay a solid foundation for the success of the program implementation in mainland China.

Besides the solid groundwork linked to program content, the qualified implementer constitutes another indispensable prerequisite of effective program delivery. It was evident that the characteristics of teacher, such as teaching experience and support for students, could significantly affect student learning [30, 31]. Theories and empirical findings in the field of program evaluation also revealed that the quality of program implementers was a significant predictor of program effectiveness [5, 32]. In view of the critical role of program implementers in program implementation, a series of training program was rigorously designed based on a theoretical framework proposed by Shek and Wai [33] and offered to implementers in the preparation year and during the full implementation phase. As expected, these training programs helped implementers better understand the PYD theory and the curriculum design, cultivate the positive and enthusiastic attitude toward program implementation, and master the required teaching skills [34, 35]. Certainly, the comprehensive training enables the implementers to deliver the program effectively, which subsequently guarantees the benefits of the program.

While implementers gained confidence and experience in using experiential teaching method through training programs, positive findings of the present study also demonstrated that adolescents in mainland China can well adapt to the active learning style. In fact, instead of resisting the active pedagogy, students actually favored the student-centered approach and were able to actively participate in in-class activities involving interactions, critical thinking, self-reflections, sharing, and expression of personal views. This encouraging conclusion suggests that implementing PYD programs with active and experiential teaching and learning methods is a very promising way to promote holistic development in Chinese adolescents.

Despite the very positive findings, the present study has several limitations. First, our study only considered the implementers’ views. Besides, the sample size ($N = 144$) was not very large. To provide a full picture of program effectiveness and validate the present findings, future studies should involve other informants such as students and increase the sample size. Second, while acknowledging the advantages of subjective outcome evaluation approach, we also admit its inherent disadvantages. For example, reliability of subjective measures is affected by several factors that are hard, if not impossible, to control, such as item order and social desirability. Therefore, future studies could also include objective measures to offset these shortcomings. Third, although the present quantitative findings are very positive, it will certainly be illuminating to include qualitative methods such as focus group interview in future studies, as qualitative evaluation gives insight into the comprehensive picture of program effectiveness as well as mechanisms that underline the positive quantitative findings.

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Chapter 327

SUBJECTIVE OUTCOME EVALUATION OF THE TIN KA PING P.A.T.H.S. PROJECT: VIEWS OF SENIOR SECONDARY SCHOOL STUDENTS

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ABSTRACT

The Tin Ka Ping P.A.T.H.S. Project is an innovative positive youth development (PYD) program in mainland China with an aim to promote holistic development of Chinese secondary school students. Based on the subjective outcome evaluation approach, this study explored the effectiveness of the Tin Ka Ping P.A.T.H.S. Project in senior secondary schools in the 2015-2016 academic year from the perspective of students. A total of 1,762 senior secondary students from six participating schools completed the evaluation form. Findings suggested that a high proportion of the participants expressed positive attitudes towards the program, instructors' performance, and benefits of the program. Compared with Grade 11, Grade 10 students reported higher levels of satisfaction in all three aspects. In line with previous studies, the three dimensions had significant inter-relationships, and both program quality and instructor performance were found to be significant predictors of perceived program benefits. As a pioneering attempt, this study provides evidence supporting the success of the Tin Ka Ping P.A.T.H.S. Project.

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INTRODUCTION

Adolescence is a unique time of life before teenagers step into adulthood [1]. In this transition period, internalizing and externalizing problems are common [2]. Traditionally, adolescent behavioral problems such as delinquency, substance abuse, and violence have attracted much attention from researchers [1, 3]. With rapid changes in the contemporary world, there is an emergence of new types of adolescent developmental issues such as obesity, eating disorders, unhealthy sexual behaviors, materialization, and low academic motivation [4, 5]. Besides externalizing behaviors, internalizing symptoms also exist [6, 7]. For instance, adolescents' problematic eating behaviors and associated problems (e.g., overweight and obesity) were largely triggered by their weight and body dissatisfaction [8], which in turn probably cause emotional processing difficulties [4]. In the same vein, depressive symptoms, anxiety symptoms, and life stress could also result in unhealthy dietary patterns [9, 10].

Given these rising concerns, prevention and treatment concentrating on one single problem is the common approach in the past to deal with adolescent problematic behaviors and symptoms [11]. However, realizing the co-existence of internalizing and externalizing problems and the overlapping causes, ecological models have been commonly adopted in understanding adolescent developmental issues [12]. Among which, positive youth development (PYD) is an approach that aims to prevent problematic behaviors and symptoms through promoting adolescents' positive development adopting a "whole-person" perspective [13]. PYD contends that adolescents are "resources to be developed" with their strengths in the developmental process [14]. In Western societies, evidence from previous research supported that PYD programs are effective in reducing the probability of adolescent problem behaviors [15, 16].

With particular reference to China, adolescent externalizing behavior continues to rise in the face of complex and ever-changing environment. For example, the latest findings of adolescent sexual behavior study in Hong Kong showed that adolescent sexual behavior and their intention to engage in sexual behavior both gradually increased over time [17]. Similarly, statistics from the National Health and Family Planning Commission in mainland China suggested that the average age for first-time sex behaviors was 15.9, with more than 45 percent of the participants not using contraceptives [18]. Regarding health risk behaviors, findings from China Nationwide Nutrition and Health Survey in 2016 pointed out that adolescent obesity rates are rising dramatically in the last 30 years with prevalence rates of overweight and obese boys increased to 11.1% in 2014 from 0.2% in 1985 [19]. Besides, in the area of unhealthy sleep behavior among adolescents, findings from an eight-year longitudinal study showed that nearly all students experienced at least one type of sleep problems [20]. Another study conducted in southeast China found that the prevalence rate of less-than-5-hours sleep among adolescents (aged 13 to 20) was 5.6% [21]. Meanwhile, short sleep among Chinese adolescents was associated with lower health-related quality of life [22], which are related to defiant attitudes, poor academic performance, and even suicidal ideation and attempts [20, 21]. Although the highly comorbid externalizing and internalizing problems in Chinese adolescents are severe, there are few PYD programs in different Chinese communities, particularly in mainland China.

Utilizing PYD constructs [14] to promote holistic development among Chinese adolescent, Shek and his research team [23] developed a PYD program entitled Project P.A.T.H.S. (Positive Adolescent Training through Holistic Social Programs) for junior secondary students in Hong Kong. Funded by The Hong Kong Jockey Club Charities Trust since 2005, this project has gone through over a decade's implementation [24]. Later on, to benefit adolescents in mainland China, Tin Ka Ping Foundation introduced the Project P.A.T.H.S. in mainland China since 2011 [25], transplanting it into "Tin Ka Ping P.A.T.H.S. Project." With reference to the 15 positive youth development constructs identified by Catalano et al. [7], the research team developed school-based programs attempting to promote adolescent personal qualities (e.g., clear and positive identity, self-efficacy) and various competences (e.g., moral competence, social competence).

With the encouraging outcomes achieved in junior secondary students [26], the Tin Ka Ping P.A.T.H.S. Project was further extended into senior secondary schools since 2014. In response to specific developmental issues in Chinese adolescents, the TKP P.A.T.H.S. Project designed senior curriculum to strengthen the personal abilities and developmental assets among mainland senior secondary students. For example, in Unit EC 5.1 (emotional competence) named "Youth in Full Bloom," through taking part in both individual and group activities, students would learn to recognize different ways of expressing anger and its corresponding consequences, as well as to master effective anger management skills. As the senior curricula-based programs are new to both implementers and participants, the research team is quite concerned about its impact on the students. Thus, it is necessary to test out its effectiveness for further nationwide implementation.

Multiple evaluation methods have been employed to examine the effectiveness of the Project P.A.T.H.S. in Hong Kong since its inception, including objective and subjective outcome evaluation, process evaluation, qualitative assessment, as well as student products that include student reflection diaries and drawings [27]. Longitudinal evaluation findings further confirmed the long-term positive effect of the project in promoting adolescent holistic development. Meanwhile, different stakeholders (e.g., participants, implementers) recognized the effectiveness of the program [24]. Extensive studies have indicated that previous P.A.T.H.S. programs explicitly achieved the whole-person development goals. For example, Shek and Yu [28] found that through participating in Project P.A.T.H.S., adolescents reported a slower rate of increase in sexual behavior. Nevertheless, as the Tin Ka Ping Project is a new project implemented in China, the question of how useful the Tin Ka Ping P.A.T.H.S. Project in nurturing mainland Chinese adolescents needs to be answered. Hence, there is a need to conduct systematic evaluation studies.

Shek et al. [29] pointed out that participants' subjective satisfaction could yield useful information since it is highly associated with the objective PYD attribute scores after program implementation. Therefore, in the present study, subjective outcome evaluation was employed to assess the effectiveness of the Tin Ka Ping P.A.T.H.S. Project. Three dimensions of the program were covered, including perceived program content quality, perceived instructor quality, and perceived benefits of the program. Previous studies have identified factors affecting the effectiveness of school-based programs. Payne and Eckert [30] demonstrated that program structure was the most important factor than program providers and school climate in predicting program implementation quality. However, there is a consensus that teaching quality strongly predicts valued intended learning outcomes [31]. Hence, the importance of factors that predict program effectiveness still needs further investigation.

Against the background mentioned above, several objectives were intrinsic to the current study. First, descriptive profiles on the responses of the participants to the program were presented. Based on past findings, it was predicted that a high proportion (at least 80%) of the respondents would show positive responses (Hypothesis 1). Second, the association among these three dimensions of subjective outcome evaluation was investigated. Based on previous findings, we predicted that there would be significant correlations amongst the three dimensions of subjective outcome evaluation (Hypotheses 2a to 2c). Third, the predictive effects of students' satisfaction with program content and instructor quality on perceived program benefits were examined. It was predicted that both perceived program quality and implementer would predict perceived program effectiveness (Hypotheses 3a and 3b). Finally, grade differences in participants' subjective evaluation on different indicators were also analyzed. Based on previous findings [32], it was expected that Grade 10 students would have more satisfaction than did Grade 11 students (Hypothesis 4).

OUR STUDY

In the 2015-2016 academic year, a total of 20,358 students from 30 schools participated in the Tin Ka Ping P.A.T.H.S. Project. Among which, 5,784 participants were senior secondary students from 17 schools, locating in both developed areas like Shanghai, Jiangsu and underdeveloped area like Gansu, and Guizhou. With encouraging findings in the initial implementation [26], the research team collected feedback from six participating schools. Correspondingly, the current study examined participants' perceptions of the effectiveness of the Tin Ka Ping P.A.T.H.S. senior secondary program in the 2015-2016 academic year.

After one year, all students were invited to respond to a subjective outcome evaluation form. Research findings in previous studies strongly supported the validity and reliability of this assessment tool [25, 29]. Before the data collection process, participants were informed of the evaluation purpose and confidentiality of the data. With clear guidelines and adequate time to complete the assessment form, participants responded in a self-administration format. A total of 1,762 completed questionnaires were collected from senior students, including 1,433 from Grade 10 and 329 from Grade 11.

Instruments

Adopted from the Subjective Outcome Evaluation Form for participants (Form A) of Project P.A.T.H.S. in Hong Kong, the evaluation form employed in this study used the same wording but translated all items into simplified Chinese characters.

This subjective outcome evaluation form is comprised of three parts. The first part contained three rating scales measuring different aspects: participants' perceptions of the program content using 6-point Likert scale (1 = "strongly disagree"; 6 = "strongly agree") with 10 items, the performance of program instructors with same scale structures covering 10 items, and the perceived program benefits using 5-point Likert scale (1 = "unhelpful"; 5 = "very helpful") with 16 items. The second part employed three extra items to understand participants' overall attitudes (e.g. the willingness to participate in similar courses again in the

future). The last part used four open-ended questions to examine participants' gains and opinions (e.g. the most important things that the participants learned from the program).

The present study only analyzed and investigated the quantitative parts (overall 39 items) of this evaluation form, while participants' responses to the open-ended questions will be discussed elsewhere.

Data Analysis

Findings on the percentages of responses to the program content, instructors' performance, and program benefits as well as their overall satisfaction with the program were analyzed by descriptive statistical analyses in this study. By examining the percentages of responses to each response category, we can generate a picture on the satisfaction of the respondents on the different dimensions of the program.

Reliability analysis was conducted to investigate the internal consistency of the total scale and the subscales. Pearson correlation analysis was performed to examine the inter-relationships amongst the three domains of the program. A multivariate Analysis of Variance (MANOVA) was conducted to find out the differences of the three factors between Grade 10 and Grade 11. Lastly, to determine the predictors of the perceived program benefits, multiple regression analyses were employed. All the analyses were performed using SPSS 23.0.

FINDINGS

A total of 1,762 completed subjective evaluation forms were collected. As presented in Table 1, reliability analysis showed that the total scale and subscales had high internal consistency: 10 items on perceived program content ($\alpha = .94$), 10 items on perceived instructor quality ($\alpha = .96$), 16 items on perceived benefits ($\alpha = .97$), and the overall 36 items measuring program effectiveness ($\alpha = .96$).

Table 1. Reliability analyses and correlations among participants' perceptions on program content, instructors and program benefits

Subjective outcome evaluation Scales	M	SD	Cronbach's alphas	Mean of inter-item correlations	Inter-scale correlation		
					Program content	Program instructors	Program benefits
Program Content	5.25	.78	.94	.60	-	-	
Program Instructors	5.45	.72	.96	.71	.58***	-	
Program Benefits	4.23	.79	.97	.66	.36***	.25***	-
Total Effectiveness	4.86	.59	.96	.39	.77***	.70***	.81***

Note: *** $p < .001$.

Several observations based on descriptive statistical analyses can be highlighted from Tables 2 to 5. First, the findings in Table 2 revealed that over 93% of the participants expressed positive attitudes with all items scored 4 or above; 94.7% of the participants liked this program very much (item 10). Specifically, 96.4% participants recognized the "clear objectives of the curriculum" and 96.1% endorsed that the design of the curriculum was good.

Second, Table 3 indicated that almost all students (97.6% of the participants) held positive views of the implementers (item 10) and they agreed that the instructors were well-prepared for class (97.9%). Almost all students also felt that the instructors were ready to help students. Regarding perceived program effectiveness (Table 4), 95.2% of the participants agreed that the program was able to promote their overall development, including improvement in “self-awareness” (95.7%), “ability to distinguish between good and bad” (95.2%), and “ability to face the future with a positive attitude” (95.1%). Table 5 further shows that 95.2% of the participants would potentially “recommend this program to their peers,” 94.4% would consider “to join the similar program again,” and 98.0% were satisfied with this program as a whole. In short, Hypothesis 1 was supported.

Consistent with our prediction, Pearson correlation analyses (Table 1) suggested that there was a strong relationship between perceived program content and perceived instructor quality ($r = .58, p < .001$). Such strong association could also be found in the relationships of these two domains with perceived program benefits (program content: $r = .36, p < .001$; instructor quality: $r = .25, p < .001$). In short, Hypotheses 2a to 2c were supported.

Multiple regression analysis was further performed to examine the predictors of perceived effectiveness. Results in Table 7 revealed that both perceptions of program content ($\beta = .32, p < .001$) and perceived quality of instructors ($\beta = .07, p < .05$) could positively predict perceived program benefits, explaining 8% and 38% of the variance in Grade 10 and Grade 11, respectively. The findings supported Hypotheses 3a and 3b.

Results based on MANOVA (Table 6) showed that significant differences in participants' satisfaction across grades were found for program content, instructor performance, and program benefits ($F = 60.69, 18.86, \text{ and } 56.47, p < .001, \eta^2 = .035, .011, \text{ and } .032$, respectively). In all three dimensions, Grade 10 students reported higher levels of satisfaction ($M = 5.32, 5.49, \text{ and } 4.30$, respectively) compared with Grade 11 students ($M = 4.91, 5.25, \text{ and } 3.90$, respectively). The findings provided support for Hypothesis 4.

Table 2. Descriptive statistics of the participants' evaluations on the program content

Items	Respondents with positive responses (Options 4-6)					
	Grade 10		Grade 11		Overall	
	<i>N</i>	%	<i>n</i>	%	<i>N</i>	%
The objectives of the curriculum are very clear.	1393	97.3	301	92.3	1694	96.4
The design of the curriculum is very good.	1384	96.6	305	93.8	1689	96.1
The activities were carefully planned.	1374	96.0	304	94.1	1678	95.7
The classroom atmosphere was very pleasant.	1367	95.5	300	93.5	1667	95.1
There was much peer interaction amongst the students.	1368	95.5	295	91.0	1663	94.7
I participated actively during lessons (including discussions, sharing, games, etc.).	1372	95.8	289	89.2	1661	94.6
I was encouraged to do my best.	1368	95.5	288	90.0	1656	94.5
The learning experience I encountered enhanced my interest towards the lessons.	1359	94.9	281	86.7	1640	93.4
Overall speaking, I have very positive evaluation of the program.	1363	95.2	291	90.4	1654	94.3
On the whole, I like this curriculum very much.	1372	95.8	292	89.6	1664	94.7

Note: All items are on a 6-point Likert scale with 1 = strongly disagree, 2 = disagree, 3 = slightly disagree, 4 = slightly agree, 5 = agree, 6 = strongly agree. Only respondents with positive responses (Options 4-6) are shown in the table.

Table 3. Descriptive statistics of the participants' evaluations on the program instructors

Items	Respondents with positive responses (Options 4-6)					
	Grade 10		Grade 11		Overall	
	<i>n</i>	%	<i>n</i>	%	<i>N</i>	%
The instructor(s) had a good mastery of the curriculum.	1402	98.0	305	93.6	1707	97.2
The instructor(s) was well prepared for the lessons.	1406	98.2	313	96.6	1719	97.9
The instructor(s)' teaching skills were good.	1393	97.4	308	94.8	1701	96.9
The instructor(s) showed good professional attitudes.	1392	97.3	309	94.8	1701	96.8
The instructor(s) was very involved.	1407	98.3	304	94.4	1711	97.5
The instructor(s) encouraged students to participate in the activities.	1393	97.3	310	95.7	1703	97.0
The instructor(s) cared for the students.	1402	97.9	314	96.6	1716	97.7
The instructor(s) was ready to offer help to students when needed.	1401	97.8	313	96.6	1714	97.6
The instructor(s) had much interaction with the students.	1392	97.2	311	95.4	1703	96.9
Overall speaking, I have very positive evaluation of the instructors.	1400	97.8	315	96.6	1715	97.6

Note: All items are on a 6-point Likert scale with 1 = strongly disagree, 2 = disagree, 3 = slightly disagree, 4 = slightly agree, 5 = agree, 6 = strongly agree. Only respondents with positive responses (Options 4-6) are shown in the table.

Table 4. Descriptive statistics of the participants' evaluations on the program benefits

The extent to which the course (i.e., the program that all students have joined) has helped you:	Respondents with positive responses (Options 3-5)					
	Grade 10		Grade 11		Overall	
	<i>n</i>	%	<i>n</i>	%	<i>N</i>	%
It has strengthened my bonding with teachers, classmates and my family.	1345	94.5	292	90.4	1637	93.8
It has strengthened my resilience in adverse conditions.	1336	93.9	291	90.7	1627	93.3
It has enhanced my social competence.	1345	94.5	294	91.6	1639	94.0
It has improved my ability in handling and expressing my emotions.	1358	95.4	295	92.5	1653	94.9
It has enhanced my cognitive competence.	1353	95.1	286	89.4	1639	94.0
My ability to resist harmful influences has been improved.	1362	95.8	293	91.6	1655	95.0
It has strengthened my ability to distinguish between the good and the bad.	1367	96.1	291	91.5	1658	95.2
It has increased my competence in making sensible and wise choices.	1347	94.7	286	89.4	1633	93.7
It has helped me to have life reflections.	1337	94.0	280	87.2	1617	92.8
It has reinforced my self-confidence.	1354	95.2	288	89.4	1642	94.1
It has increased my self-awareness.	1369	96.3	300	93.2	1669	95.7
It has helped me to face the future with a positive attitude.	1360	95.6	299	92.9	1659	95.1
It has helped me to cultivate compassion and care about others.	1345	94.5	290	90.6	1635	93.8
It has encouraged me to care about the community.	1299	91.3	267	83.2	1566	89.8
It has promoted my sense of responsibility in serving the society.	1341	94.6	293	91.3	1634	94.0
It has enriched my overall development.	1364	95.9	296	92.2	1660	95.2

Note: All items are on a 5-point Likert scale with 1 = unhelpful, 2 = not very helpful, 3 = slightly helpful, 4 = helpful, 5 = very helpful. Only respondents with positive responses (Options 3-5) are shown in the table.

Table 5. Summary of participants' subjective evaluations on other aspects

Items	Respondents with positive responses (Options 3-5)					
	Grade 10		Grade 11		Overall	
	<i>n</i>	%	<i>n</i>	%	<i>N</i>	%
Willingness to suggest friends with similar needs or conditions to participate in the program ^a	1381	96.4	294	90.2	1675	95.2
Willingness to participate in similar courses again in the future ^a	1370	95.6	290	89.0	1660	94.4
Satisfaction with this course on the whole ^b	1412	98.5	312	95.4	1724	98.0

Note: ^a: the item is on a 4-point Likert scale with 1 = definitely will not suggest, 2 = will not suggest, 3 = will suggest, 4 = definitely will suggest. Only respondents with positive responses (Options 3-4) are shown in the table.

^b: the item is on a 6-point Likert scale with 1 = very dissatisfied, 2 = moderately dissatisfied, 3 = slightly dissatisfied, 4 = satisfied, 5 = moderately satisfied, 6 = very satisfied. Only respondents with positive responses (Options 4-6) are shown in the table.

DISCUSSION

The purpose of the current study was to explore senior students' evaluation of the Tin Ka Ping P.A.T.H.S. Project in its pilot extension phase. As there is a lack of PYD programs designed for Chinese adolescents and related evaluation attempts are scarce, this study could be regarded as a pioneering attempt.

The current study adds to the Chinese literature in several important aspects. First, the measuring instrument used in this study is a constructive response to the lack of validated evaluation tools in mainland China. Second, the sample size is sufficiently large to permit generalization to other populations. Third, concerning the externalizing and internalizing problems among adolescents [6], positive perceptions of the perceived benefits of the program indicated that the Tin Ka Ping P.A.T.H.S. Project could serve as a protective factor by promoting the psychosocial competence in adolescents [33]. Furthermore, this study further investigated the predictors of perceived benefits, which could make a contribution to the advancement of the theories and applications of PYD programs in mainland China.

Several positive observations support the above-mentioned contributions. First, high values of Cronbach's coefficient and inter-scale correlation among three subscales gave support to the excellent psychometric properties of this subjective outcome evaluation instrument. Second, consistent with the previous findings from an evaluation of Project P.A.T.H.S. in Hong Kong [24], profiles of responses to all items echoed that the majority of senior secondary students participating in the program were fond of this PYD program. A considerable proportion of participants believed that this program has helped them promote different competencies (e.g., cognitive competence, sense of responsibility in serving the society). In particular, quality of the program instructor was more recognized as revealed by the high endorsement rate (97%). Generally speaking, the findings supported Hypothesis 1. In line with other studies, different dimensions of subjective outcome evaluation were significantly correlated (Hypotheses 2a to 2c) and both perceived program quality and implementers were significant predictors of perceived program effectiveness (Hypotheses 3a and 3b). Similar findings also occurred in the evaluation studies on the Project P.A.T.H.S. in Hong Kong [34].

Similar to previous findings, grade differences existed in all three aspects (i.e., program content, instructor quality, and perceived benefits), with Grade 10 students showing more favorable satisfaction ratings. This finding is consistent with a previous study conducted by Shek and Law [34] that Grade 7 students maintained more positive attitudes compared with Grade 8 students.

Table 6. Comparisons of participants' subjective outcome evaluations on different aspects across grades

Subjective outcome evaluation Scales	Grade 10		Grade 11		MANOVA	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>F</i>	η^2
Program Content	5.32	.75	4.91	.83	60.69 ^a	.035
Program Instructors	5.49	.70	5.25	.74	18.86 ^a	.011
Program Benefits	4.30	.78	3.90	.77	56.47 ^a	.032

Note: ^a: $p < .001$.

Table 7. Multiple regression analyses predicting perceived program benefits by perceived program content and perceived instructors quality

	β^a		Model	
	Program Content	Program Instructors	<i>F</i>	<i>R</i> ²
Grade 10	.23***	.09**	63.80***	.083
Grade 11	.77***	.22***	82.94***	.381
Overall	.32***	.07*	125.13***	.130

Note: ^a Standardized coefficients. * $p < .05$. ** $p < .01$. *** $p < .001$.

Although this paper presents the first study of subjective outcome evaluation of the Tin Ka Ping Project in China, several limitations of this study are worth mentioning. First, the disparity in sample size between different grades deserves serious consideration before making solid conclusions. Second, senior secondary students in Grade 12 were not involved since they were busy with preparation for examination. However, they are also important targets who may encounter intense challenges physically and mentally in the face of the college entrance examination. Third, as subjective outcome evaluation only provides evidence from one perspective, objective outcome evaluation regarding participants' development in real life situations is also required. Despite these limitations, the positive findings in the present study could be interpreted as evidence supporting the effectiveness of the Tin Ka Ping P.A.T.H.S. Project in mainland China.

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Chapter 328

IMPLEMENTATION OF THE TIN KA PIN PROJECT IN TWO CHINESE CITIES: STUDENTS' SUBJECTIVE OUTCOME EVALUATION

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ABSTRACT

In this chapter we investigated the subjective outcome of a positive youth development program, the Tin Ka Ping project, among secondary school students in two relatively underdeveloped cities in China mainland. A total of 1,573 students who participated in the project responded to an evaluative form upon completion of the project. The findings showed that the majority of the participants were highly satisfied with the project. Regardless of their grade, students consistently rated the program content and the instructors positively, and they perceived the project as beneficial to their personal development in multiple areas. Participants' perceptions about the program content and the instructors both significantly predicted their perceived effectiveness of the project. Similar to previous findings based on adolescents living in economically developed Chinese cities, the present study suggests that the Tin Ka Ping project was equally welcomed by youth in underdeveloped areas in China, and provides evidence for the usefulness of the project in promoting Chinese adolescents' holistic development.

INTRODUCTION

The Project P.A.T.H.S. is a curriculum-based positive youth development program designed for Chinese adolescents in Hong Kong [1]. Adopting a strengths-based approach,

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the program focuses on promoting the development of 15 well-established positive youth development attributes among youth, including bonding (BO), social competence (SC), emotional competence (EC), cognitive competence (CC), behavioral competence (BC), moral competence (MC), self-efficacy (SE), Prosocial Norms (PN), Resilience (RE), Self-Determination (SD), Spirituality (SP), clear and positive identity (ID), belief in the future (BF), prosocial involvement (PI) and recognition of positive behaviour (RB) [2]. It is believed that by nurturing these attributes, youth behavioral problems, such as delinquency, alcohol use, and Internet addiction, can be effectively prevented [3, 4]. With the fund by The Hong Kong Jockey Club, the project P.A.T.H.S. has been widely implemented in secondary schools in Hong Kong since 2006, to promote adolescents' holistic development. So far, a total of 280 secondary schools with more than 200,000 students in Hong Kong have participated in the project. To examine the effectiveness of the program, multiple evaluative strategies have been adopted and the findings converged to suggest that the project P.A.T.H.S. was well received by different stakeholders, and had significant impact on Hong Kong adolescents' development [1, 5-7].

The success of the project P.A.T.H.S. in Hong Kong has provided evidence for the applicability and effectiveness of using positive youth development approach to promote Chinese adolescents' development. However, such program is almost non-existent in China mainland, although it has the largest youth population in the world. In particular, the rapid economic and social development that has recently taken place in the country has significant influence on adolescent psychological well-being. A recent review of the current status of youth mental health in China mainland showed that adolescent behavioral problems, mood disorders, substance use, and youth suicide are all on the rise [8]. Besides, similar to Hong Kong youth, adolescents in China mainland are facing a wide range of developmental issues [9, 10], which could lead to various risk behaviors and problems, if not handled well [11]. For example, Chinese parents' high expectation on their children's academic performance and the increased competition have created high academic stress in adolescents. According to a survey by China Youth Social Service Centre, around 70% of secondary school students considered academic stress as their major source of pressure [12]. In another study, perceived academic stress was found to significantly predict high school students' depressive symptoms, while this relationship could be moderated by positive school climate with low level of achievement orientation [9]. This suggests that promoting a healthy school culture or nurturing positive values among students regarding achievement may effectively prevent their mental health problems even the academic stress remains. These findings point to the pressing need of developing and implementing effective prevention and intervention programs to help Chinese young people tackle with the challenges and have healthy holistic development. Positive youth development program, like the Project P.A.T.H.S., may serve this purpose.

Against this background, with the financial support of the Tin Ka Ping foundation, the research team of the project P.A.T.H.S. started to adapt the project for Chinese young people since 2010, collaborating with a university in China mainland. The new project, entitled the Tin Ka Ping (TKP) project, was developed based on the theoretical framework of P.A.T.H.S., whereas took into account the specific cultural context in China Mainland [4]. The project was first piloted in four secondary schools in East China and then further promoted and formally implemented in 30 secondary schools across 27 cities in China [4]. A series of training sessions were provided to school teachers and social workers by the research team before the program implementation to ensure the quality of implementation. To evaluate the

effectiveness of the TKP project, similar evaluative studies were conducted. Both qualitative and quantitative findings supported that the TKP project was highly welcomed by teachers and students, and effectively promoted Chinese secondary school students' positive development [13-17].

While the TKP project has been offered in a number of Chinese cities with different economic backgrounds, evaluative studies were mainly conducted in schools located in relatively developed areas, such as Shanghai, and its nearby cities like Suzhou and Yangzhou [4]. There is a lack of research investigating the implementation quality and outcomes of the project for students in underdeveloped regions where educational resources are relatively limited as compared to big cities. Therefore, the present study aimed to examine the effectiveness of the TKP project for adolescents in two underdeveloped Chinese cities: Baiyin and Shaoguan. Both cities are characterized as “countdown” cities with declined population and economy in recent years. Baiyin used to be a prosperous city with abundant mineral resources, but its development has been slowing down as the mines are exhausted, and the local economy gradually declines. Another city, Shaoguan, had been famous for its steel, non-ferrous metal, electric power, machine, tobacco, pharmaceutical and toy industries. However, since 1980s, the industry development in Shaoguan became tardy and the city has been deindustrialized. These socio-economic changes have inevitably affected local people's life satisfaction, feeling of happiness and mental health [18-20], which may further influence the development of local youth, as well as the implementation and effectiveness of the TKP project in these areas. However, although the TKP project has been implemented in two secondary schools in the two cities for three years, it remains unclear whether the curriculum content of the project is appropriate for local adolescents, whether the project implementers, i.e., school teachers, are able to implement the project with high quality, and to what extent students perceive the project as beneficial to their development.

The present study was designed to address these questions through investigating students' perceptions about the project in two participating schools in Baiyin and Shaoguan. Specifically, we intended to 1) examine participant's subjective outcome evaluation about the TKP project in terms of their views on the program content, instructors and benefits; 2) to compare subjective outcome evaluations among students of different grades and 3), to investigate the predictive effects of students' perceptions about the program quality, the implementers, and benefits of the program on their overall satisfaction of the program.

OUR STUDY

Participants of the present study were recruited from students of two secondary schools in Baiyin (one school) and Shaoguan (one school) who joined the TKP project in the academic years of 2015/16 and 2016/17. Secondary 3 and 6 students (equivalent to Grade 9 and 12) didn't participate because of their heavy workload for the preparation of the entrance exams to high school and university. At the participating school in Baiyin, the program was implemented for senior students at Secondary 4 and 5 only (equivalent to Grade 10 and 11), while at the school in Shaoguan, the program was offered to both junior and senior students in Secondary 1, 2, 4, and 5 (equivalent to Grade 7, 8, 10, and 11).

After obtaining written consents from the school management, students, and their parents, all participating students completed a subjective outcome evaluation form on a voluntary

basis upon completion of the project. The survey was administered by trained program workers in classroom settings with standardized instructions. Students were reassured about the confidentiality and anonymity of their responses. A total of 1,573 participants completed the questionnaires, including 481 students at Secondary 1 (only Shaoguan), 468 students at Secondary 2 (only Shaoguan), 392 students at Secondary 4 (173 from Baiyin, and 219 from Shaoguan), and 232 students at Secondary 5 (142 from Baiyin and 90 from Shaoguan).

Instruments

A validated subjective outcome evaluation form was used to assess students’ perceptions about the TKP project. The form is consisted of six parts. The first subscale contains 10 items measuring participants’ subjective evaluation about the program content. The second part also has 10 items but focusing on participants’ perceptions about the program instructors. Items of both subscales were rated on a 6-point Likert scale (1 = strongly disagree, 6 = strongly agree). The third part measures students’ perceived benefits of the project, consisted of 16 items evaluated on a 5-point rating scale (1 = unhelpful, 5 = very helpful). The fourth part has two questions asking 1) whether the participant would recommend the project program to their friends, and 2) whether the student would like to attend a similar program in the future. The fifth part asks students’ overall satisfaction about the program based on a 6-point rating scale (1 = strongly dissatisfied; 6 = strongly satisfied). The final part is consisted of four open-ended questions about students’ other experiences in the project, and the related findings would be reported elsewhere. The evaluation form shows good internal consistency on the present sample of students. As displayed in Table 1, Cronbach’s alpha coefficients for the three subscales were all above .92, and mean inter-item correlations ranged between .52 and .65.

Table 1. Reliability analyses and correlations among participants’ perceptions on program content, instructors, and program benefits

Subscales	M	SD	Cronbach’s α	Mean inter-item correlations	1	2
Views about program content	4.84	.79	.92	.52	-	-
Views about instructors	5.11	.79	.95	.65	.45***	-
Perceived program benefits	3.84	.79	.94	.57	.36***	.31***

Note: *** $p < .001$.

Data Analyses

Descriptive statistics were used to depict students’ subjective outcome evaluation about the TKP project. Particularly, percentages of students with positive ratings were summarized in terms of their views about program content, program implementers/instructors, and perceived benefits. To compare students’ subjective outcomes across grades, Multivariate Analysis of Variance (MANOVA) was conducted with participants’ perceptions about program, perceptions about instructors, and perceived benefits of the project as three dependent variables, and students’ grade as the independent variable. Lastly, to determine the

predictive effects of students' perceptions of program content and instructors on students' perceived benefits of the program, multiple regression analyses were conducted. In the model, perceived program benefits served as the dependent variable, students' grade, perceptions about the program content, and views about instructors served as three independent variables. All the analyses were performed using SPSS 23.0.

FINDINGS

Means and standard deviations of students' subscale scores were summarized in Table 1. Tables 2 to 5 further report the percentages of students with positive responses to different aspects of the project. First, the majority of students had positive ratings on the program content. As can be seen in Table 2, students of different grades consistently showed favorable evaluation about various aspects of the program content. For instance, 92.3% of students at Secondary 1, 88.5% of students at Secondary 2, 92.6% and 86.6% of the Secondary 4 and 5 students agreed that they liked the curriculum very much. Based on the whole sample, more than 92% of the participants expressed that "the design of the curriculum is very good", and that "the activities were carefully planned"; 89.3% of the participants reported that they participated actively during lessons and "have very positive evaluation of the program". Second, in terms of participants' evaluation about the program instructor, the percentage of students with positive ratings was overwhelmingly high (see Table 3). More than 93% of the students perceived the instructors as having a good mastery of the curriculum (93.8%), being well prepared for the lessons (93.4%), having good teaching skills (93.4%), and showing good professional attitudes (93.6%). Students also appreciate teachers' encouragement and care for the students. Over 95% of the participants agreed that the instructor was ready to offer help when needed, and had very positive evaluation of the instructors.

Table 2. Percentage of participants with positive ratings on program content

Items	Respondents with positive responses (Options 4-6)									
	Secondary 1		Secondary 2		Secondary 4		Secondary 5		Overall	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>N</i>	%
The objectives of the curriculum are very clear.	450	93.6	444	94.9	367	93.6	211	90.9	1472	93.6
The design of the curriculum is very good.	442	91.9	438	93.6	365	93.1	213	91.8	1458	92.7
The activities were carefully planned.	443	92.1	424	90.6	369	94.1	212	91.4	1448	92.1
The classroom atmosphere was very pleasant.	404	84.0	426	91.0	363	92.6	215	92.7	1408	89.5
There was much peer interaction amongst the students.	424	88.1	426	91.0	350	89.3	210	90.5	1410	89.6
I participated actively during lessons (discussions, sharing, games, etc.).	430	89.4	425	90.8	346	88.3	203	87.5	1404	89.3
I was encouraged to do my best.	416	86.5	410	87.6	343	87.5	202	87.1	1371	87.2
The learning experience I encountered enhanced my interest towards the lessons.	435	90.4	412	88.0	358	91.3	196	84.5	1401	89.1
Overall speaking, I have very positive evaluation of the program.	426	88.6	416	88.9	349	89.0	208	89.7	1404	89.3
On the whole, I like this curriculum very much.	444	92.3	414	88.5	363	92.6	201	86.6	1422	90.4

Note: All items are on a 6-point Likert scale with 1 = strongly disagree, 2 = disagree, 3 = slightly disagree, 4 = slightly agree, 5 = agree, 6 = strongly agree. Only respondents with positive responses (options 4-6) are shown in the table.

Table 3. Percentage of participants with positive ratings on program instructors

Items	Respondents with positive responses (Options 4-6)									
	Secondary 1		Secondary 2		Secondary 4		Secondary 5		Overall	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>N</i>	%
The instructor(s) had a good mastery of the curriculum.	446	92.7	446	95.3	370	94.4	213	91.8	1475	93.8
The instructor(s) was well prepared for the lessons.	447	92.9	435	92.9	371	94.6	216	93.1	1469	93.4
The instructor(s)' teaching skills were good.	443	92.1	442	94.4	366	93.4	218	94.0	1469	93.4
The instructor(s) showed good professional attitudes.	447	92.9	441	94.2	368	93.9	217	93.5	1473	93.6
The instructor(s) was very involved.	443	92.1	443	94.7	374	95.4	218	94.0	1478	94.0
The instructor(s) encouraged students to participate in the activities.	456	94.8	442	94.4	366	93.4	221	95.3	1485	94.4
The instructor(s) cared for the students.	453	94.2	448	95.7	369	94.1	223	96.1	1493	94.9
The instructor(s) was ready to offer help to students when needed.	457	95.0	450	96.2	372	94.9	219	94.4	1498	95.2
The instructor(s) had much interaction with the students.	445	92.5	440	94.0	359	91.6	218	94.0	1462	92.9
Overall speaking, I have very positive evaluation of the instructors.	459	95.4	451	96.4	373	95.2	220	94.8	1503	95.5

Note: All items are on a 6-point Likert scale with 1 = strongly disagree, 2 = disagree, 3 = slightly disagree, 4 = slightly agree, 5 = agree, 6 = strongly agree. Only respondents with positive responses (options 4-6) are shown in the table.

Table 4. Percentage of participants with positive ratings on program benefits

Items	Respondents with positive responses (Options 3-5)									
	Secondary 1		Secondary 2		Secondary 4		Secondary 5		Overall	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
The extent to which the course (i.e., the program that all students have joined) has helped you:										
It has strengthened my bonding with teachers, classmates and my family.	406	84.4	405	86.5	359	91.6	211	90.0	1381	87.8
It has strengthened my resilience in adverse conditions.	413	85.9	418	89.3	369	94.1	202	87.1	1402	89.1
It has enhanced my social competence.	424	88.1	418	89.3	366	93.4	214	92.2	1422	90.4
It has improved my ability in handling and expressing my emotions.	427	88.8	421	90.0	368	93.9	214	92.2	1430	90.9
It has enhanced my cognitive competence.	422	87.7	423	90.4	372	94.9	209	90.1	1426	90.7
My ability to resist harmful influences has been improved.	427	88.8	438	93.6	372	94.9	208	89.7	1445	91.9
It has strengthened my ability to distinguish between the good and the bad.	434	90.2	439	93.8	369	94.1	207	89.2	1449	92.1
It has increased my competence in making sensible and wise choices.	430	89.4	411	87.8	365	93.1	206	88.8	1412	89.8
It has helped me to have life reflections.	409	85.0	409	87.4	361	92.1	199	85.8	1378	87.6
It has reinforced my self-confidence.	422	87.7	403	86.1	362	92.3	204	87.9	1391	88.4
It has increased my self-awareness.	420	87.3	419	89.5	371	94.6	210	90.5	1420	90.3
It has helped me to face the future with a positive attitude.	423	87.9	437	93.4	367	93.6	209	90.1	1436	91.3
It has helped me to cultivate compassion and care about others.	422	87.7	416	88.9	365	93.1	210	90.5	1413	89.8
It has encouraged me to care about the community.	374	77.8	375	80.1	356	90.8	200	86.2	1305	83.0
It has promoted my sense of responsibility in serving the society.	413	85.9	418	89.3	368	93.9	212	91.4	1411	89.7
It has enriched my overall development.	436	90.6	442	94.4	371	94.6	206	88.8	1455	92.5

Note: All items are on a 5-point Likert scale with 1 = unhelpful, 2 = not very helpful, 3 = slightly helpful, 4 = helpful, 5 = very helpful. Only respondents with positive responses (options 3-5) are shown in the table.

Third, Table 4 reports students' perceived benefits of the project. As shown in the table, 92.5% of the participants agreed that the program has enriched their overall development, 91.3% of the participants perceived that the program helped them to face the future with a positive attitude, and 92.1% of the participants reported that the programme has strengthened their ability to distinguish between the good and the bad. Moreover, Table 5 indicates that 94.8% of the participants were willing to recommend their friends to participate in this program and 92.9% of the participants would consider joining a similar program in the future. The overall satisfaction was also high, with 95.3% of the participants expressing that they were satisfied or very satisfied with the project as a whole. Overall speaking, these findings suggest that the TKP project has been welcomed by adolescents in Baiyin and Shaoguan, which provide positive evidence for the successful implementation of the project underdeveloped regions.

Table 5. Percentage of participants with positive ratings on other aspects of the program and overall satisfaction

Items	Respondents with positive response (options 3-5)									
	Secondary 1		Secondary 2		Secondary 4		Secondary 5		Overall	
	n	%	n	%	n	%	n	%	N	%
1. Willingness to suggest friends with similar needs or conditions to participate in the program ^a	450	93.6	449	95.9	376	95.9	216	93.1	1491	94.8
2. Willingness to participate in similar courses again in the future ^a	449	93.3	436	93.2	364	92.9	213	91.8	1462	92.9
3. Satisfaction with this course on the whole ^b	449	93.3	451	96.4	381	97.2	218	94.0	1499	95.3

Note: ^aThe two items are rated on a 4-point scale with 1 = definitely will not suggest, 2 = will not suggest, 3 = will suggest, 4 = definitely will suggest. Only respondents with positive responses (options 3-4) are shown in the table.

^bThe item is rated on a 6-point scale with 1 = very dissatisfied, 2 = moderately dissatisfied, 3 = slightly dissatisfied, 4 = satisfied, 5 = moderately satisfied, 6 = very satisfied. Only respondents with positive responses (options 4-6) are shown in the table.

Table 6. Comparisons of participants' subjective outcome evaluations across grades

Subscales	Secondary 1		Secondary 2		Secondary 4		Secondary 5		Tests of Between-Subjects Effects		
	M	SD	M	SD	M	SD	M	SD	F	p	Partial η^2
Views about program content	4.83	.83	4.82	.68	4.86	.84	4.84	.87	0.12	.95	.00
Views about instructors	5.14	.79	5.12	.70	5.05	.86	5.16	.82	1.14	.33	.00
Perceived program benefits	3.84	.84	3.76	.70	3.93	.77	3.84	.89	3.26	.01	.01

Ratings by Students of Different Grades

To compare students' ratings across grades, MANOVA was employed and the results showed a significant multivariate effect for the three dependent variables as a group in relation to students' grade, $F(9, 3765.14) = 2.02$, $p = .03$, Wilk's lambda = 0.99. As seen in Table 6, univariate analyses further suggest that the effect of grade was only significant for students' perceived benefits of the project, but not for their perceptions about program content

and instructors. Post hoc tests revealed that students at Secondary 4 had significantly higher ratings on perceived program benefits than students of Secondary 2 ($p = .01$). No significant differences were detected among students of other grades. It seemed that participants at Secondary 4 level perceived the TKP project as more beneficial to their development than did students of Secondary 2. Overall speaking, the findings suggest that students of different grades had generally consistent ratings about the TKP project.

Prediction of Students' Perceived Benefits

Person correlation coefficients among subscales were reported in Table 1. As expected, participants' views about program content, instructors, and perceived benefits were moderately and positively correlated with each other (r s ranged between .31 and .36, $p < .001$) in expected directions. High ratings of the program content and implementers were significantly associated with high level of perceived benefits of the program. Results of multiple regression analysis further showed that after controlling for the effects of grade ($\beta = .04$, $p = .12$), both students' views about program content ($\beta = .27$, $p < .001$) and their perceptions about the instructors ($\beta = .19$, $p < .001$) significantly predicted project benefits. The two predictors explained 15.9% of the variance in students' perceived benefits of the project, $F(2, 1549)_{\text{change}} = 146.60$, $p < .001$.

DISCUSSION

The aim of this study is to examine whether the TKP project can be well implemented in relatively underdeveloped cities in mainland China to promote positive development of local adolescents, based on subjective outcome evaluation. Using data collected in two years, the findings suggest that the vast majority of the participants perceived the program content positively and had favorable views about the program implementers. Students viewed the project as being beneficial to their development in multiple areas, and expressed their willingness to attend similar programs in the future and to recommend the program to other young people. More than 95% of the participants were satisfied with the project on the whole. These findings support the applicability of positive youth development program in different Chinese contexts [13, 14], and provide preliminary evidence for the effectiveness of the TKP project in promoting adolescents' development in less developed Chinese cities.

Consistent with findings based on secondary school students in Hong Kong and in other Chinese metropolis [15], the current sample of participants showed very positive attitude towards both program content and instructors. Aside from the reason that the TKP project was adapted from a successful youth program with evident outcomes (the project P.A.T.H.S.), the desirable feedbacks from students may also be due to the systematic training conducted by the research team for program implementers [21]. Before each school formally launches the TKP project, the school teaching team is required to attend a series of intensive training workshops in which the theoretical framework of the project, lesson plans for each topic, previous evaluative methods and findings, were introduced by experienced researchers and teachers, through experiential learning and various interactive teaching approaches. The

research team also spent time to discuss with program implementers on the appropriateness of the curriculum content, the pedagogy, and possible difficulties in teaching specific topics. Necessary adaption of the teaching content would be made based on the discussion between researchers and the school teacher. In addition, similar to the project P.A.T.H.S. in Hong Kong, a co-walker scheme has been incorporated in the implementation of the TKP project. For each school, at least one scholar from the research team serves as the co-walker, who keeps constant communication with the school teaching team and provides advice throughout the program implementation in the particular school. All these strategies help the instructors to have extensive preparation and teach the curriculum with confidence, which may contribute to the successful implementation of the project [22]. This also echoes our finding that students' views about the program content and about the instructors significantly predicted their perceived effectiveness of the program.

When we compare students' evaluation across different grades, no significant differences were identified, except that students of Secondary 4 appeared to be more positive when rating the perceived program benefits than did students of Secondary 2. One possible reason may be that Secondary 4 students just successfully passed the entrance exams to high school. These students may have less academic stress and are able to participate in the project more actively than Secondary 2 students who remain facing the problem of entering a high school. It should be noted that as the effect size was quite small (partial $\eta^2 = 0.01$), the finding needs to be further validated in the future based on a larger sample of participants. Generally, students at different grades consistently showed favorable perceptions about the program.

While the findings are encouraging, several limitations of the study must be acknowledged. First, although the sample size of the present study was not small, the participants were from only two schools of the two cities, which may affect the generalizability of the findings. In the future, when the project is implemented on a larger scale, a more representative sample of students from different grade and schools shall be recruited to participate in the evaluation study. Second, this study only gathered student's opinions and did not collect feedbacks from other stakeholders, such as program implementers, other school personnel, and parents. Data provided by other informants on the effectiveness of the project would triangulate the subjective evaluation findings based on students, and offer new insights for researchers to understand the program implementation and its outcomes [23]. Third, apart from the subjective evaluation indicators, more objective outcomes should be measured in the future to evaluate the impact of the program on adolescents' real development [13]. For example, whether students' perceived stress, anxiety, and depression reduced, and their life satisfaction and happiness increased after participating in the program, could be investigated in further studies. Last but not least, other evaluative methods, such as individual interview, focus groups, and reflective journals [16] could be adopted to gain a deeper understanding about how the project plays a role in youth life and helps an adolescent to develop.

To conclude, the present study provides preliminary evidence on the successful implementation of the TKP project in two secondary schools located in less developed regions in China. As there is a lack of evaluation findings focusing on the effectiveness of positive youth development program for Chinese adolescents in these areas [24], the present study makes a useful contribution to the field. The findings suggest that although the positive youth development approach was originally developed in the West [3], it can be well applied in different Chinese contexts to promote the holistic development of adolescents. With the

present evidence, we advocated that more youth programs based on positive youth development approach could be designed and implemented to benefit more Chinese young people.

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Chapter 329

**SUBJECTIVE OUTCOME EVALUATION OF A
SERVICE LEADERSHIP SUBJECT:
FINDINGS BASED ON UNIVERSITY STUDENTS
IN HONG KONG**

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ABSTRACT

In this chapter we assessed the subjective outcome evaluation of a credit-bearing subject entitled “Service Leadership” in a university in Hong Kong. The samples included 64 and 74 students who took the subject offered in the regular semester (Semester 1) and intensive summer semester (Semester 3) in 2016-2017 academic year, respectively. Students’ perceptions of the course content, instructor quality, benefits and global satisfaction of the subject were assessed at the end of the subject. Results indicated that majority of students had positive views toward course content, instructor quality, and benefits from the subject in enhancing their competencies in different aspects, such as social and emotional competence, self-confidence, resilience, and self-leadership. The two delivery modes (i.e., regular semester and intensive summer semester) also showed significant differences in the subjective outcomes, with the course conducted in regular term having higher scores than the course offered in summer term. As predicted, course content, instructor quality, and course benefits were inter-correlated significantly. While course content and instructor quality significantly predicted perceived subject benefits, course content and perceived benefits of the subject were significant predictors of students’ global satisfaction.

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INTRODUCTION

One may ask the question: why does a university teach “service leadership”? There are strong reasons to address the question. First, service-oriented industries are the skeleton of the Hong Kong economy, contributing to 92.4% of Gross Domestic Product (GDP) in 2017 in Hong Kong [1]. Among the service industry components, import/export wholesale and retail trades, finance and insurance, and public administration, social and personal services cover 21.5%, 18.9% and 18.2% of the GDP respectively [1]. As university graduates have potential tendency to be engaged in frontline and supervisory positions in these industries, service leadership education is important for preparing the students to contribute to these service industries. Second, Hong Kong is a metropolitan city where people from all over the world come in and out for business, vacation, education and other matters. Other than acquiring the discipline-related knowledge and skills, university students should build up a global perspective and develop the 21st Century skills to adapt to the dynamic environment in the service industries [2]. Dede [2] highlighted four areas of competence in economic and social ecology of the 21st Century, namely: 1) global awareness; 2) economic and entrepreneurial literacy; 3) awareness of civic rights and responsibilities; and 4) health and wellness sensitivity. Besides, the 21st Century skills cover three sets of competency skills, including: learning and thinking skills (e.g., skills on problem-solving, communication, innovation, critical analyses, collaborative learning), information and communications technology (ICT) literacy, and life skills (e.g., leadership, social responsibility, adaptability, self-direction etc.) [2].

Third, service leadership education serves as a platform for building interpersonal and intrapersonal competencies of university students [3, 4], who are at the developmental transition from adolescence to adulthood. During emerging adulthood, individuals need to develop financial independence, shoulder civic responsibilities, establish connections with peers and romantic partners, and build up engagement with work and education [5]. Service leadership education, which focuses on psychosocial competencies, character strengths and caring disposition, may foster positive youth development of university students in their life transition to adulthood [4].

Fourth, young people nowadays face different developmental and ecological challenges in adapting to the competitive and complex environment [6]. Particularly, millennials growing up in a relatively prosperous and protective era are portrayed as egocentric, narcissistic and unempathetic [7]. Also, the rise of materialism has shifted one’s values from concentrating on intrinsic motives (e.g., purpose in life, satisfaction from helping others) to extrinsic ones (e.g., money, prestige) [8]. Hence, there is a need to reinforce the emphases in service leadership (including moral competence, character strengths, caring disposition) in university education, and give students more opportunities to reflect on their own life expectations and values.

Most importantly, university students are important stakeholders of Hong Kong future. They are expected to lead and contribute to the future social and economic development of Hong Kong. Thus, there is an urgent need to nurture the development of university students via service leadership education.

Table 1. Course content of “Service Leadership” subject

Lecture	Topic	Content
1	Introduction	• Overview of the subject • Definitions and conceptions of service leadership • Importance of service leadership in the global world • Relevance to university students
2	Core beliefs and components	• Core beliefs about service leadership
3	Intrapersonal competences	• IQ, EQ, AQ and SQ
4	Interpersonal competences	• Communication, relationship building, conflict resolution
5	Character strengths	• Moral character; basic character strengths
6	Caring disposition	• Social cognition (warmth and competence); primary elements of care (love, listening, and empathy)
7	Character strengths in Chinese philosophies	• Relevance of Confucian virtues to service leadership, e.g., integrity (lian), loyalty (zhong), filial piety (xiao), benevolence (ren) etc.
8	Contemporary leadership models and the dark side of leadership	• Review of contemporary models of leadership • Dark side of leadership
9	Factors leading to positive social relationship	• Trust, fairness, respect, care, behavioral consistency and loyalty
10	Self-leadership	• Self-monitoring, self-regulation, and self-improvement
11	Developmental assets	• Self-esteem; self-efficacy; purpose in life, and optimism about future
12	Review of Service Leadership qualities	• Comparisons between models of leadership • Potential application
13	Wrap-up; Group presentation	• Group presentation

In 2012, the Victor and William Fung Foundation and the Hong Kong Institute of Service Leadership and Management (HKI-SLAM) initiated the Fung Service Leadership Initiative in eight universities in Hong Kong that were funded by the University Grants Council. The Initiative aims at designing and implementing service leadership education courses and programs to university students. Employing a holistic positive development approach, it is expected that service leadership education can help to enhance leadership mentality, values and competencies among university students [9]. As suggested by Shek and Chung [10], the ultimate goal of service leadership education is to promote students' service leadership attributes in order to “maintain Hong Kong's competitiveness in the global market and to develop leaders with a human face” (p. xix).

Adopting the SLAM framework on the main components of service leadership (i.e., relevant task management capabilities, character strengths and a caring personality) [10, 11], The Hong Kong Polytechnic University has designed and implemented a credit-bearing “Service Leadership” subject for undergraduate students. The program consists of 13 lectures highlighting the important attributes of service leadership (see Table 1). Prior studies showed that participants had positive views on course content, instructors, benefits and global satisfaction [12-14]. To replicate previous findings, this study attempted to evaluate the effectiveness of “Service Leadership” subject offered to undergraduate students in a regular semester (Semester 1) and summer semester (with intensive teaching) of the 2016/17 academic year at The Hong Kong Polytechnic University. A subjective outcome evaluation approach was adopted to examine students' perception of (1) course content, (2) course implementers, (3) course benefits; (4) global satisfaction after completing the subject. There are five research questions:

- 1) What are the perceptions of the students on course content, implementers, benefits and global satisfaction after taking the subject?
- 2) Are there any differences in perceptions of course content, implementers, benefits, total effectiveness (combination of perceived course content, implementers and benefits) and global satisfaction between participants taking the subject in the regular semester (Semester 1) and intensive summer semester (Semester 3)? As the subject schedule offered in intensive summer semester is tight, it was hypothesized that participants taking the subject in the regular semester would have a more positive view on course content, implementers, benefits, total effectiveness and global satisfaction than those taking the subject in summer semester (Hypotheses 2a to 2e).
- 3) What are the interrelationships among perceptions of course content, course implementers, course benefits, total effectiveness and global satisfaction of participants of the subject? Based on the results of previous studies [12-14], it was hypothesized that perceived course content, course implementers, course benefits, total effectiveness and global satisfaction of participants would be interrelated with each other (Hypotheses 3a to 3j).
- 4) Do perceptions of course content and implementers predict perceived benefits of the participants? Based on the findings of previous studies [12-14], it was hypothesized that perceptions of course content and implementers of the participants would positively predict their perceived benefits respectively (Hypotheses 4a and 4b).
- 5) Do perceptions of course content, implementers and benefits predict global satisfaction of the participants? Based on the findings of previous studies [12], it was hypothesized that perceptions of course content, implementers, and benefits of the participants would positively predict their global satisfaction respectively (Hypotheses 5a to 5c).

OUR STUDY

The data was collected from the participants of two classes of “Service Leadership” subject offered in regular semester (Semester 1) and intensive summer semester (Semester 3) of 2016-2017 academic year. There were 64 and 74 university students enrolled into the subject during Semester One and intensive summer term, respectively. Written informed consent from students was obtained at the beginning of the course. The students were invited to fill out the Subjective Outcome Evaluation Scale that contained the measures during the last lecture of the course in an anonymous matter. The students were given adequate time to complete the evaluation form. A trained research assistant was responsible to conduct the evaluation, with the absence of the instructor.

Measures

A validated Subjective Outcome Evaluation Scale (SOES) was employed in the present study. The SOES consists of five parts: program content (PC), program implementer (PI), program benefits (PB), global satisfaction of the course and qualitative feedback of the course for further improvement. The present study focused on the first four parts of the SOES.

- 1) Program Content (PC) consists of 10 items, which assesses perceptions of students on course design, in-class activities, interactions among classmates, students' participation and global satisfaction on program content. The items are rated in a 5-point Likert scale on from 1 = "Strongly disagree" to 5 = "Strongly agree." A higher mean score of PC indicates a more positive view of program content from the students.
- 2) Program Implementer (PI) contains 10 items, which measures the students' perceptions of the attitudes, teaching strategies and skills of the instructors, engagement and interactions with the students, as well as global satisfaction on the instructors' teaching. The items are rated on a 5-point Likert scale on from 1 = "Strongly disagree" to 5 = "Strongly agree." A higher mean score of PI indicates a more positive view of program implementer from the students.
- 3) Program Benefits (PB) consists of 18 items, which assesses the students' perceptions of their changes on relevant task competencies (e.g., problem-solving, cognitive competence), care and compassion towards others, qualities of self-leadership and sense of civic responsibility. The items are rated in a 5-point Likert scale on from 1 = "Strongly disagree" to 5 = "Strongly agree." A higher mean score of PB indicates more benefits perceived by the students after participating in the course.
- 4) Global Satisfaction (GS) includes three questions on whether the participants will recommend their friends to select this course, whether they will enroll in similar course again in the future, and their rating of their global satisfaction of the course. For the first two questions of GS, the respondents are requested to rate in a 5-point Likert scale on from 1 = "Definitely will not" to 5 = "Definitely will." Finally, the last question of GS is rated in a 5-point Likert scale on from 1 = "Very dissatisfied" to 5 = "Very satisfied."

Data Analyses

Descriptive data analyses were performed to assess the perceptions of participants on their comments of program content (PC), program implementer (PI) and benefits from the course (PB). A composite variable of "Total Effectiveness" (TE) was created by averaging the scores of all items of PC, PI and PB. One-way ANOVAs were employed to compare between the participants' responses in two semesters. Correlation analyses were performed to examine the interrelationship of the 5 domains (PC, PI, PB, GS and TE). Finally, multiple regression analyses were conducted to assess the relative importance of different domains in affecting perceived benefits and global satisfaction of the participants respectively.

FINDINGS

Regarding program content, the mean score of perceived program content (PC) of total participants was 4.04 (SD = .46) (see Table 2). Most participants of the two classes showed positive responses (Options 4 and 5) on curriculum design, classroom atmosphere, class activities, peer interaction and their own involvement respectively (Table 3). Particularly, the

clear course objectives, content design, classroom activities and interactions among peers were greatly appreciated by the students, with 91.3%, 87.7%, 88.4% and 87.7% of the participants rated positively on the relative items respectively. Overall, 89.9% of the participants showed very positive evaluation on the course, and 82.6% of the participants liked the course very much (see Table 3).

For students' perceptions of program implementer, the results showed very positive responses (Options 4 and 5) on the qualities of instructors, including their knowledge on service leadership, preparation, professional attitudes and involvement (see Table 4). Besides, the instructors showed positive engagement with the students by expressing their care, offering their help, giving encouragement to them, and facilitating interactions among students (see Table 3). Overall, 97.1% of total students from these two classes expressed a very positive evaluation on the instructors (see Table 4). The mean score of perceived program implementer (PI) of total participants was 4.33 (SD = .42), showing participants' positive responses on the program implementers (see Table 2).

Regarding students' perceptions of their benefits from the course, the participants showed positive views (Options 4 and 5) that the course enhanced their situational task competencies, care and compassion towards others, qualities of self-leadership and sense of responsibility to contribute to the society (see Table 5). 86.2% of the total respondents showed that the course promoted their overall development. Besides, the theories, research and concepts helped majority of students understand (88.4% of the students rated Options 4 or 5) and synthesize (89.1% of the students rated Options 4 or 5) the characteristics of successful service leaders (see Table 5). The mean score of perceived program benefits (PB) of total participants was 4.02 (SD = .47) (see Table 2), showing evidence of positive benefits perceived by the students after participating in the course.

On the whole, 86.3% of the students felt satisfied with the subject (Options 4 and 5; see Table 6). 78.3% of the students would invite their friends to enroll in the course, and 57.2% of the students would attend similar courses in the future (see Table 6). The mean score of global satisfaction (GS) of total participants was 3.90 (SD = .67) (see Table 2).

Table 2. Means, standard deviations, Cronbach's alphas, and mean of inter-item correlations among three samples

Subjective Outcome Evaluation Scales	Semester 1 (n= 64)				Semester 3 (n= 74)				Overall (n= 138)			
	Mean	SD	α	Mean [#]	Mean	SD	α	Mean [#]	Mean	SD	α	Mean [#]
Program Content (PC: 10 items)	4.20	.40	.88	.42	3.90	.47	.90	.50	4.04	.46	.90	.56
Program Implementer (PI: 10 items)	4.48	.42	.92	.54	4.21	.39	.90	.49	4.33	.42	.92	.67
Program Benefits (PB: 18 items)	4.19	.45	.95	.52	3.88	.45	.94	.48	4.02	.47	.95	.50
Total Effectiveness (TE: 38 items)	4.27	.36	.96	.38	3.97	.38	.96	.37	4.11	.40	.96	.45
Global Satisfaction (GS: 3 items)	4.07	.68	.85	.69	3.76	.63	.85	.67	3.90	.67	.86	.73

Note: Mean[#]: inter-item correlation.

Table 3. Summary of the participants' positive responses towards Program Content (PC)

Perceptions of program content ^a	Semester 1 (n = 64)				Semester 3 (n = 74)				Overall (n = 138)			
	M [†]	SD	Positive Responses ^b		M [†]	SD	Positive Responses ^b		M [†]	SD	Positive Responses ^b	
			n	%			n	%			n	%
1. The objectives of the curriculum are very clear.	4.19	.59	60	93.8	3.95	.52	66	89.2	4.06	.56	126	91.3
2. The content design of the curriculum is very good.	4.17	.58	60	93.8	3.89	.54	61	82.4	4.02	.57	121	87.7
3. The activities were carefully arranged.	4.23	.53	61	95.3	3.92	.57	61	82.4	4.07	.57	122	88.4
4. The classroom atmosphere was very pleasant.	4.14	.61	58	90.6	3.84	.74	55	74.3	3.98	.70	113	81.9
5. There was much peer interaction amongst the students.	4.33	.59	60	93.8	3.99	.67	61	82.4	4.14	.66	121	87.7
6. I participated in the class activities actively (including discussions, sharing, games, etc.).	3.98	.55	54	84.4	3.89	.77	55	74.3	3.93	.67	109	79.0
7. I was encouraged to do my best.	4.20	.54	60	93.8	3.95	.62	60	81.1	4.07	.59	120	87.0
8. The learning experience enhanced my interests towards the program.	4.16	.67	56	87.5	3.80	.66	53	71.6	3.96	.69	109	79.0
9. Overall speaking, I have a very positive evaluation on the program.	4.28	.55	61	95.3	3.95	.64	63	85.1	4.10	.62	124	89.9
10. On the whole, I like this program very much.	4.27	.57	60	93.8	3.82	.71	54	73.0	4.03	.68	114	82.6

Note. ^a Scores on the scale/subscale higher than or equal to 4 were treated as positive responses. ^b For every item, respondents with positive responses (options 4-5) are shown in the Table. [†] 1=Strongly Disagree; 2=Disagree; 3=Neutral; 4=Agree; 5=Strongly Agree.

Table 4. Summary of the participants' positive responses towards Program Instructors (PI)

Perceptions of program instructor ^a	Semester 1 (n = 64)				Semester 3 (n = 74)				Overall (n = 138)			
	M [†]	SD	Positive Responses ^b		M [†]	SD	Positive Responses ^b		M [†]	SD	Positive Responses ^b	
			n	%			n	%			n	%
1. The instructor(s) had a good mastery of the program.	4.41	.56	62	96.9	4.15	.54	68	91.9	4.27	.56	130	94.2
2. The instructor(s) was (were) well prepared for the lessons.	4.50	.53	63	98.4	4.19	.49	71	95.9	4.33	.53	134	97.1
3. The teaching skills of the instructor(s) were good.	4.25	.56	60	93.8	3.96	.65	61	82.4	4.09	.63	121	87.7
4. The instructor(s) showed good professional attitudes.	4.47	.53	63	98.4	4.20	.47	72	97.3	4.33	.51	135	97.8
5. The instructor(s) was (were) very involved.	4.61	.52	63	98.4	4.20	.52	70	94.6	4.39	.56	133	96.4
6. The instructor(s) encouraged students to participate in the activities.	4.56	.50	64	100.0	4.39	.54	72	97.3	4.47	.53	136	98.6
7. The instructor(s) cared for the students.	4.41	.58	61	95.3	4.28	.51	72	97.3	4.34	.55	133	96.4
8. The instructor(s) was (were) ready to offer help to students when needed.	4.52	.56	62	96.9	4.32	.50	73	98.6	4.41	.54	135	97.8
9. The instructor(s) had much interaction with the students.	4.50	.62	60	93.8	4.19	.59	67	90.5	4.33	.62	127	92.0
10. Overall speaking, I have a very positive evaluation on the instructor(s).	4.55	.50	64	100.0	4.20	.52	70	94.6	4.36	.54	134	97.1

Note. ^a Scores on the scale/subscale higher than or equal to 4 were treated as positive responses. ^b For every item, respondents with positive responses (options 4-5) are shown in the Table. [†] 1=Strongly Disagree; 2=Disagree; 3=Neutral; 4=Agree; 5=Strongly Agree.

Table 5. Summary of the participants' positive responses towards Program Benefits (PB)

Perceptions of program benefits ^a	Semester 1 (n = 64)				Semester 3 (n = 74)				Overall (n = 138)			
	M [†]	SD	Positive Responses ^b		M [†]	SD	Positive Responses ^b		M [†]	SD	Positive Responses ^b	
			n	%			n	%			n	%
1. It has enhanced my social competence.	4.16	.57	60	93.8	3.99	.54	63	85.1	4.07	.56	123	89.1
2. It has improved my ability in expressing and handling my emotions.	4.11	.59	56	87.5	3.88	.66	57	77.0	3.99	.64	113	81.9
3. It has enhanced my critical thinking.	4.05	.63	55	85.9	3.82	.69	57	77.0	3.93	.67	112	81.2
4. It has increased my competence in making sensible and wise choices.	4.19	.56	59	92.2	3.81	.66	56	75.7	3.99	.64	115	83.3
5. It has helped me make ethical decisions.	4.27	.62	58	90.6	3.95	.72	59	79.7	4.09	.69	117	84.8
6. It has strengthened my resilience in adverse conditions.	4.23	.61	58	90.6	3.78	.67	54	73.0	3.99	.68	112	81.2
7. It has strengthened my self-confidence.	4.13	.65	54	84.4	3.82	.65	55	74.3	3.96	.67	109	79.0
8. It has helped me face the future with a positive attitude.	4.23	.64	57	89.1	3.88	.64	58	78.4	4.04	.66	115	83.3
9. It has enhanced my love for life.	4.03	.67	53	82.8	3.69	.64	46	62.2	3.85	.67	99	71.7
10. It has helped me explore the meaning of life.	4.05	.65	54	84.4	3.69	.60	48	64.9	3.86	.65	102	73.9
11. It has enhanced my ability of self-leadership.	4.33	.56	61	95.3	3.85	.66	54	73.0	4.07	.66	115	83.3
12. It has helped me cultivate compassion and care for others.	4.19	.61	57	89.1	3.89	.61	60	81.1	4.03	.63	117	84.8
13. It has helped me enhance my character strengths comprehensively.	4.30	.58	60	93.8	3.91	.58	62	83.8	4.09	.61	112	88.4
14. It has enabled me to understand the importance of situational task competencies, character strength and caring disposition in successful leadership.	4.22	.55	60	93.8	4.03	.60	64	86.5	4.12	.58	124	89.9
15. It has promoted my sense of responsibility in serving the society.	4.19	.56	59	92.2	3.91	.58	60	81.1	4.04	.58	119	86.2
16. It has promoted my overall development.	4.27	.65	57	89.1	3.97	.64	62	83.8	4.11	.66	119	86.2
17. The theories, research and concepts covered in the program have enabled me to understand the characteristics of successful service leaders.	4.28	.58	60	93.8	3.97	.60	62	83.8	4.12	.60	122	88.4
18. The theories, research and concepts covered in the program have helped me synthesize the characteristics of successful service leaders.	4.22	.60	58	90.6	4.00	.53	65	87.8	4.10	.57	123	89.1

Note. ^a Scores on the scale/subscale higher than or equal to 4 were treated as positive responses. ^b For every item, respondents with positive responses (options 4-5) are shown in the Table. [†] 1=Strongly Disagree; 2=Disagree; 3=Neutral; 4=Agree; 5=Strongly Agree.

Table 6. Summary of the participants' Global Satisfaction with the program

	Satisfaction with the program ^a	Semester 1 (n = 64)				Semester 3 (n = 74)				Overall (n = 138)			
		M	SD	Positive Responses ^b		M	SD	Positive Responses ^b		M	SD	Positive Responses ^b	
				n	%			n	%			n	%
1.	Will you suggest your friends to take this program? ^c	4.11	.72	55	85.9	3.84	.78	53	71.6	3.96	.76	108	78.3
2.	Will you participate in similar programs again in the future? ^c	3.78	1.00	42	65.6	3.53	.80	37	50.0	3.64	.90	79	57.2
3.	On the whole, are you satisfied with this program? ^d	4.31	.53	62	96.9	3.90	.58	57	77.0	4.09	.59	119	86.2

Note. ^a Scores on the scale/subscale higher than or equal to 4 were treated as positive responses. ^b For every item, respondents with positive responses (options 4-5) are shown in the Table. ^c 1 = Definitely will not, 2 = Will not, 3 = Not sure, 4 = Will, 5 = Definitely will. ^d 1 = Very dissatisfied, 2 = Moderately dissatisfied, 3 = Neutral, 4 = Satisfied, 5 = Very satisfied.

The results of one-way ANOVAs showed that there were significant differences on perceptions of program content, program implementer, program benefits, total effectiveness and global satisfaction between students taking service leadership course in regular semester (Semester 1) and intensive summer term (Semester 3) respectively, with students participating in Semester 1 perceived better subjective outcomes than did those participating in intensive summer term (see Table 7). Hypotheses 2a to 2e were supported.

Table 7. One-way ANOVA comparing the evaluations on the program of participants in different semesters

Subjective Outcome Evaluation Scales	Semester 1 (n= 64)		Semester 3 (n= 74)		Comparison	
	Mean	SD	Mean	SD	F	p
Program Content	4.20	.40	3.90	.47	15.54	< .001
Program Implementer	4.48	.42	4.21	.39	15.10	< .001
Program Benefits	4.19	.45	3.88	.45	16.50	< .001
Total Effectiveness	4.27	.36	3.97	.38	21.62	< .001
Global Satisfaction	4.07	.68	3.76	.63	7.74	< .01

Table 8. Correlations coefficients among the variables

	1	2	3	4
1. Program Content	1			
2. Program Implementer	.60***	1		
3. Program Benefits	.71***	.54***	1	
4. Total Effectiveness	.87***	.76***	.93***	1
5. Global Satisfaction	.62***	.43***	.61***	.65***

Note: *** $p < .001$.

Furthermore, correlation analyses showed that all variables (PC, PI, PB, TE, GS) were all correlated with each other, with Pearson's r ranging from .43 to .93 (see table 8). Hypotheses 3a to 3j were supported. Multiple regression analyses further indicated that both program content and program implementer were significant predictors of perceived benefits of the students, with $\beta = .61$ ($p < .001$) and $.17$ ($p < .05$) respectively, explaining 53% of the total variance of perceived benefits (Table 9). Hypotheses 4a and 4b were supported. In addition, among the relationship of program content, program implementer and program benefits on global satisfaction of the students, both program content and program benefits were significant predictors of global satisfaction of the students, with $\beta = .36$ ($p < .001$) and $.34$ ($p < .001$). The predictor variables explained 44% of the total variance of global satisfaction of the participants (see table 9). Hypotheses 5a and 5c were supported.

Table 9. Multiple regression analyses predicting perceived benefits and global satisfaction

Predictors	Program Benefits				Global Satisfaction			
	B	SE	β	R^2	B	SE	β	R^2
Program Content	.68	.08	.61***	.53	.52	.14	.36***	.44
Program Implementer	.19	.08	.17*		.05	.13	.03	
Program Benefits					.48	.13	.34***	

Note: * $p < .05$; *** $p < .001$.

DISCUSSION

This study aimed at assessing the effectiveness of a service leadership subject in a university in Hong Kong. The findings echoed the results of previous studies [12-14], showing that the participants had positive views perceptions on course content, implementers, benefits and global satisfaction after participating in the subject. The findings reveal that the subject was able to introduce the theories and concepts of service leadership to the students and promoted their leadership competencies.

However, participants of subject offered in the regular semester (Semester 1) rated higher on the subjective outcomes in the four aspects (PC, PI, PB and GS) than did those participated in the intensive summer semester (Semester 3). As the summer semester lasted for seven weeks to cover 13 lectures, the students needed to attend two lectures each week. Thus, the students may have difficulties to fully comprehend the concepts and theories, and may exhibit pressure in preparing presentations and assignments. The tight program schedule and stresses may affect their perceptions of course arrangement, instructors, benefits and global satisfaction. As such, there is a need to refine the flow and content of the subject in order to meet the tight program schedule, and provide more support to the students on their preparation of presentations and assignments.

As predicted, course content and quality of implementers are important predictors of perceived benefits of the students. As such, it is important to develop a curriculum that can inspire students on the essential components of service leadership and enhance their competencies and character strengths in becoming a service leader. In particular, program activities and interactions among peers are essential elements for students to acquire the knowledge of service leadership. From the literature [15, 16], experiential learning involves direct experience, reflections and observation, abstract conceptualization, and active experimentation [15], which is a practical pedagogy to engage students in the leadership process, and encourage them to reflect and make meanings through their experiences and reflections [16]. Hence, it is necessary to enrich the curriculum with more experiential activities for the students to experience and reflect on their leadership style. In addition, qualities of instructors are critical in transferring knowledge and practice to university students. In education literature, essential practices of student-teacher contacts, constructive feedback to students, high expectations, and respect for diverse potentials and learning paths of students are evident to facilitate student development and learning [17]. Besides, instructors serve as role-models of a service leader for students. Their attitudes, behaviors and responses to students reflect the attributes of a service leader.

Furthermore, the findings indicated that program content and perceived benefits were predictors of students' global satisfaction, which echo the findings of previous research [12-14]. Obviously, perceived benefits are important predictors in influencing students' global satisfaction, as the strengthening of students' competencies and character strengths fulfils participants' expectations of the course, which increases their satisfaction of the course. Moreover, the program content determines the "what" and "how" of service leadership theories and concepts are conveyed to the students, which affects their global satisfaction. Interestingly, program implementer, relative to program content and perceived benefits, was not a significant predictor of students' global satisfaction. Students felt satisfied with the course only when they acquired the knowledge of service leadership, and perceived changes

of their intrapersonal and interpersonal competence. The performance of program instructors becomes secondary when compared with program content and perceived benefits. These findings are in line with previous findings [18].

There are several implications of the study. First, the findings indicated that students showed positive perceptions on course content, instructors, benefits and global satisfaction of the participants after participating in a service leadership subject. As commented by Eich [16] that “there has been little empirical research on student leadership program quality and program activities that contribute significantly to leadership development and learning” (p. 176), the present study shows empirical support on the effectiveness of a quality service leadership subject conducted in a university. Second, in the urging needs in equipping young people with 21st Century skills to face the present social and economic challenges [2], service leadership is proved to be essential in university education to enhance relevant task competencies, character strengths and a caring composition of the students [10]. Third, while program content and quality of implementer contribute to the perceived benefits of the participants, program content and perceived benefits are predictors of participants’ satisfaction of the course. The findings reaffirm Haworth and Conrad’s [19] comments on the importance of interactive teaching and learning, well-structured curriculum and participatory atmosphere among students are essential attributes of a high-quality leadership education program. Last but not the least, program schedule may contribute to the difference on program effectiveness between subject offered in regular semester and intensive summer semester. Course implementer may need to refine the structure and content of the service leadership program, and provide more flexibility and support to the students to minimize the constraints caused by tight program schedule.

Despite the very positive evaluation findings, there are two main limitations of the study. First, the study employed a subjective outcome evaluation approach to examine the effectiveness of a service leadership subject in Hong Kong. There is a need to conduct objective outcome evaluation [20] to examine the changes of students’ outcomes of task competencies, character strengths and caring attributes before and after participating in the subject. Along with this line, the findings are based on a cross-sectional data collected at the end of the semester, it is suggested to track the changes of students’ outcomes. Actually, we have conducted such studies in the past [21]. Second, qualitative studies can incorporate with subjective outcome evaluation to give a full picture of the experience and changes of the students after taking the subject. Focus group interviews, case study and reflective journals are useful qualitative methods to capture the processes of changes that the students experience [22].

Despite the limitations, this study provides empirical support on the importance of promoting service leadership education to college students in Hong Kong, and identifies key components necessary for designing and implementing a quality leadership subject. As suggested by Shek and Chung [23] that there are “unfinished tasks” of service leadership program evaluation and examination of factors leading to program success, the present study takes a humble step to the quest.

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Chapter 330

STUDENT DEVELOPMENT UNDER A NEW GENERAL EDUCATION PROGRAM IN HONG KONG: A 3-YEAR LONGITUDINAL ASSESSMENT

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ABSTRACT

Universities in Hong Kong have implemented general education programmes since September 2012 when the undergraduate education was formally extended from three years to four years. At The Hong Kong Polytechnic University (PolyU), a new general education curriculum entitled ‘General University Requirements’ (GUR) has been incorporated in its four-year undergraduate education, aiming to cultivate five desired graduate attributes (critical thinking, problem solving, effective communication, ethical leadership, and lifelong learning). To investigate students’ actual learning and development over time under the new general education programme, a yearly online survey was conducted for three consecutive years ($N = 460$). Results showed that students gained significant improvements in their development of the five desired generic competences after two-year university study, despite a slight decrease in some of these attributes in the second year of their university life. These findings suggest that the new general education programme at PolyU is effective in promoting students’ personal development and its intended learning outcomes are largely achieved.

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INTRODUCTION

Higher education system is undergoing changes in face of globalization and emergence of the knowledge economy. In Hong Kong, the University Grants Committee (UGC) mandated the extension of undergraduate education for one additional year (i.e., from 3-year to 4-year) in eight public universities starting from 2012/2013 academic year. The additional year allows the universities to implement their new general education (GE) programs, which aim to help students develop desirable generic attributes such as critical and higher-order thinking, effective communication, leadership, ethical reasoning, and lifelong learning [1], and thus promote students' all-round development. However, little is known about the actual impact of the GE reform on student learning and development. To address this question, the present study investigated how students change pertaining to five desirable generic attributes during their three-year study of one new GE program at The Hong Kong Polytechnic University (PolyU), one of the public universities in Hong Kong.

Educational Changes and Learning Outcomes Assessment

It is believed that higher education adds value to individual development [2]. What university graduates have achieved from university learning has long-term effects of shaping their life and determining their career development [3]. Furthermore, as contemporary economy is primarily based on knowledge and service, competitiveness of citizens is crucial to competitiveness and success of a society [4]. As such, the University Grants Committee of Hong Kong (UGC) [5] believed that Hong Kong's vision to be Asia's world city 'is only possible if it is based upon the platform of a very strong education and higher education sector'. It is this profound worth of higher education that calls for investigations on how university curriculum affects students and to use this information to increase effectiveness of higher education.

In recent years, employers and researchers criticize that what undergraduate students learned in college are falling well short of 21st Century's demands and higher education institutions may not effectively teach foundational skills that promote student success in contemporary knowledge society [6-7]. These concerns prompted a great deal of research especially in North American, Europe, and Australia and the results suggest the importance of a systematic approach to embed a wide range of generic attributes beyond disciplinary expertise or knowledge across curricula in university education [8-10]. In response, more and more higher education institutions have placed higher priority on cultivating students with more generic competences or 'soft skills', by revising teaching practice, implementing 'high-impact' educational programs or integrating General Education (GE) in university curricula. For instance, the Association of American Colleges and Universities [11] has launched a campaign to promote contemporary liberal education and proposed four learning outcomes essential for students to thrive in rapidly changing world, including 'knowledge of human cultures and the physical and natural world', 'intellectual and practical skills', 'personal and social responsibility', and 'integrative and applied learning'.

With these far-reaching educational changes comes research on assessment of actual student accomplishment as a result of university study [12-14]. Particular across the United

States, there has been a great deal of momentum behind student learning outcomes assessment. For example, according to two national surveys conducted by the National Institute for Learning Outcomes Assessment (NILOA) [15], most higher education institutions have applied various assessment approaches such as student surveys and classroom-based assessments to perform learning outcome assessment. Besides, researchers have explored the impacts of contemporary educational practice, especially liberal education on student achievement [13, 16-18]. Basically, these studies suggest that numerous teaching and learning practices (e.g., first-year seminars, reflective learning, learning communities, group project, global learning, service learning, etc.) involved in liberal education are effective to foster essential learning outcomes in college, such as critical and higher-order thinking, moral reasoning, ethical leadership, civic and social responsibility, global looking and multicultural competences.

Education Reform and Emphasis on General Education in Hong Kong

In recent decades, Hong Kong has experienced significant economic and social-cultural changes, including the historical change from a British colony to a Special Administrative Region of China, an increase in economic development and living standards, and the structural shift from a manufacturing-oriented economy to a knowledge- and service-based economy [19]. All these factors make quality higher education particularly important for developing people with a broad knowledge base and multiple competences to sustain Hong Kong's development [20]. However, the 3-year undergraduate education under the British framework in Hong Kong has long been criticized for its over-specialization and emphasis on passive learning [21]. University curricula that concentrate on specialist knowledge upon student enrollment might successfully help students develop intellectual competence, yet they were inadequate to nurture other generic attributes such as critical thinking, leadership, and communication skills. Just as pointed out by Freake [1], Hong Kong university graduates were 'technically knowledgeable upon entry to the workforce, but with limited ability to develop over time and adapt to new situations'. Similar concern was indicated by a market survey which found that over 80% of Hong Kong employers were not confident that Hong Kong students developed sufficient generic attributes such as creativity, analytical thinking, leadership and interpersonal skills [22]. The survey also revealed that approximately 90% of the employers thought that Hong Kong students performed worse than their North American counterparts.

As a result, education reform is in great need to address these concerns and respond to demands of today's society. To this end, Hong Kong Education Commission raised education reform proposals in 2000 and UGC mandated the formal structural change in higher education system in 2012/2013. Specifically, the eight public universities funded by UGC extended the length of their undergraduate education from three to four years and incorporated GE programs in the new curricula. It is expected that the new 4-year undergraduate curricula would contribute to the development of qualified graduates with holistic competences to form a solid foundation for Hong Kong's economy, development of society, and its place in the fast-changing world [23].

As UGC did not mandate a formal structure for GE in Hong Kong, each university independently developed their own GE programs [1, 21]. Despite divergence in some specific common core requirements of GE curricula in different universities, three features were commonly shared [21]. First, a set of intended learning outcomes were emphasized to cultivate desirable graduate attitudes, which focused on multidisciplinary knowledge, multi-perspective, critical thinking, communication, problem-solving, civic responsibility, ethic reasoning, leadership, lifelong learning, and global outlook [1]. Second, to align with the intended learning outcomes, traditional teacher-centered pedagogy emphasizing book learning and rote memorization was altered to a more engaging and student-centered pedagogy, such as individual project and group presentation. Third, more authentic forms of assessment were adopted accordingly to motivate student leaning and support leaning outcomes [21].

Basically, the GE curricula in Hong Kong are based on a US-style general education framework [21]. In fact, most teaching and learning practices involved in Hong Kong GE curricula were similar to that being regarded as ‘good practices’ or ‘high-impact educational practices’ in the United States [13, 24]. As mentioned earlier, these practices adopted in general education have been widely studied in USA and vetted as positively contributing to university students’ holistic development and growth [e.g., 3, 13]. However, whether they are also effective in Hong Kong remains unknown.

Compared with the long history of general education in the United States, Hong Kong GE program represents an entirely new curricular structure and educational philosophy. As a result, it may have ‘less legitimacy as a valued education undertaking and thus will be more difficult to develop as an integral component of undergraduate education’ [21]. On the other hand, Hong Kong students are used to Chinese culture and learning styles, such as didactic training, thus they may have reluctance and difficulties in adapting to the more active mode of pedagogies associated with GE subjects. Just as asked by Jaffee [21]: ‘will the students suddenly be prepared to engage, interact, debate, participate, discuss, and criticize?’. Concerning these challenges, it cannot be taken for granted that GE programs in Hong Kong are effective as they were in USA. As a result, there is a need to investigate the actual changes of students and provide evidence for the effectiveness of general education in Hong Kong.

Assessment of Student Learning Outcomes under General Education in Hong Kong

As GE programs in Hong Kong vary in structure in eight universities, assessment of students’ learning outcomes should accordingly pertain to the specific GE curriculum. Despite the importance of effective assessment of student achievement under the new GE curricula, only a few universities have carried out evaluation projects, among which most were preliminary and focused on pilot courses of new GE curricula. For example, one institution formally evaluated a general education foundation course during its pilot stage, while did not report any evaluation findings in formal implementation [25]. Another university launched a 2-year study to assess the effectiveness of pilot courses of its GE program [26], but no evaluative findings were published.

At The Hong Kong Polytechnic University (PolyU), a five-year longitudinal evaluation project involving multiple evaluation strategies to systematically investigate the effectiveness

of its new GE program has been implemented since 2012/13 academic year [27]. At PolyU, the new GE curriculum entitled 'General University Requirements' (GUR) includes six core components: Freshman Seminar, Language and Communication Requirements, Leadership and Intrapersonal Development, Cluster Area Requirements, Service Learning and Healthy Lifestyle. These GUR components cover a wide range of subjects and intended learning outcomes, which are aligned with five desired graduate attributes defined by PolyU: problem solving, critical thinking, lifelong learning, ethical leadership, and effective communication [28]. Despite the challenges in implementing GE in Hong Kong we mentioned before, the GUR subjects were overall well-received by both students and teaching staff [27, 29-31]. Evaluation findings on one specific subject developed to satisfy the Leadership and Intrapersonal Development requirement also showed that students were not only satisfied with the course [32, 33], but also demonstrated positive changes after taking the course [34].

While the abovementioned findings could support effective implementation of the GUR at PolyU, it is still not clear whether students had significant personal development not just in a single course. To answer this question, the current study sought to assess students' learning and development during GUR study by comparing their ratings on five desired graduate attributes of PolyU across three years. This longitudinal objective outcome evaluation would provide more convincing evidence on students' changes and personal growth over time [35].

OUR STUDY

Participants of the longitudinal study are PolyU undergraduate students under the 4-year curriculum enrolled in 2012-2013 academic year when the GUR was first implemented. Students are invited to complete an online survey every year and their informed consent are obtained before the first wave of data collection. Up to 2014-2015 academic year, three waves of data have been collected.

In the first wave of data collection, a pool including 1,000 students from eight faculties/schools at PolyU was initially selected based on a stratified random sampling method. These 1,000 students were invited through emails and/or phone calls to complete the online survey in November 2012 (i.e., 2012-2013 academic year), and 687 of them responded to the invitation while 543 completed the survey, resulting in a response rate of 54.30%. The second wave of data collection was conducted in November 2013 (i.e., 2013-2014 academic year). Those 687 students who responded to the invitation in first wave were invited again and 643 students completed the survey, resulting in a response rate of 93.59%. In the third wave of data collection conducted in November 2014 (i.e., 2014-2015 academic year), an invitation was sent to 643 students who participated in the second wave of online survey. A total of 566 students completed the online survey in the third wave, indicating a response rate of 88.02%.

In order to investigate longitudinal development of students across three years, data collected in the three waves were matched which resulted in 460 students ($M_{age} = 20.12$, $SD_{age} = .54$) who completed all three waves of online survey. Among these participants, 182 (39.57%) were male, and 278 (60.43%) were female. A total of 333 (72.39%) participants were born in Hong Kong, 113 (24.57%) were born in mainland China, and the remaining 14 (3.04%) were born in other places. Most participants reported that their parental marital status

was first marriage (82.83%). Preliminary analyses showed that there were no significant differences in measures of demographic information including age, gender composition, place of birth and parental marriage status between the matched sample ($N = 460$) and those students who dropped out of the survey after the first wave of data collection ($N = 83$).

Instruments

To measure student development regarding the five desired graduate attributes defined by PolyU, three core instruments were used: a) Chinese Interpersonal Reactivity Index (C-IRI), b) Chinese Positive Youth Development Scale (CPYDS), and c) National Survey of Student Engagement (NESS) which has been updated in 2013. A total of 13 subscales of these instruments were adopted as indicators of the five desired attributes. The alignment of each subscale with corresponding attribute to be measured is shown in Table 1 and Cronbach's alpha for each subscale in each wave is shown in Table 2.

Table 1. Alignments between subscales and desired graduate attributes at PolyU

Desired attributes	Instruments	Indicators
Problem Solving	CPYDS	Problem Solving
Critical Thinking	CPYDS	Critical Thinking
Lifelong Learning	CPYDS NSSE	Life-long Learning Higher Order Learning Reflective and Integrative Learning Learning Strategies Quantitative Reasoning
Ethical Leadership	C-IRI CPYDS	Empathy Ethical Leadership Self-leadership
Effective Communication	CPYDS NSSE	Social Competence Collaborative Learning Discussions with Diverse Others

Note. CPYDS: Chinese Positive Youth Development Scale. C-IRI: Chinese-Interpersonal Reactivity Index. NSSE: National Survey of Student Engagement.

Table 2. Reliabilities of each instrument used in three waves

Instruments	Subscales	# of items	Reliability					
			2012-2013		2013-2014		2014-2015	
			α	mean inter-item correlation	α	mean inter-item correlation	α	mean inter-item correlation
C-IRI	Empathy	11	.72	.19	.69	.17	.71	.19
CPYDS	Problem Solving	3	.67	.42	.65	.38	.76	.51
	Social Competence	3	.84	.65	.86	.68	.86	.68
	Critical Thinking	3	.68	.42	.77	.53	.83	.61
	Ethical Leadership	15	.83	.25	.89	.36	.87	.33
	Self-leadership	5	.68	.30	.71	.33	.72	.35
	Life-long Learning	2	.46	.30	.59	.42	.63	.47
NSSE	Higher Order Learning	4	.77	.45	.77	.46	.82	.54
	Reflective and Integrative Learning	7	.82	.40	.84	.43	.88	.51
	Learning Strategies	3	.70	.43	.75	.50	.78	.54
	Quantitative Reasoning	3	.71	.45	.70	.43	.79	.56
	Collaborative Learning	4	.70	.37	.75	.42	.76	.44
	Discussions with Diverse Others	4	.66	.33	.62	.29	.69	.36

Note. CPYDS: Chinese Positive Youth Development Scale. C-IRI: Chinese-Interpersonal Reactivity Index. NSSE: National Survey of Student Engagement.

Chinese-Interpersonal Reactivity Index (C-IRI)

Since ethical reasoning and empathy are important competences of an ethical leader [36], the present study used the Empathy (EM, 11 items) subscale of the C-IRI that adapted by Siu and Shek [37] as one measure of ethical leadership. Using a 4-point Likert scale, average score across 11 items was computed as one indicator of ethical leadership. The C-IRI has been widely used and demonstrated good reliability in previous studies [e.g., 38, 39]. In the present study, Cronbach's alpha coefficients of the EM subscale in three waves ranged from .68 to .72, indicating good reliability.

Chinese Positive Youth Development Scale (CPYDS)

The Chinese Positive Youth Development Scale (CPYDS) was developed by Shek, Siu, and Lee [40] to measure Chinese adolescents' positive youth development (PYD) attributes. The original scale contains 90 items related to 15 constructs of PYD, and has been found to be valid and reliable as a global measure of PYD in Chinese adolescents in previous studies [34, 41]. In the present study, 6 subscales of the CPYDS including Problem Solving (PS), Social Competence (SC), Critical Thinking (CT), Ethical Leadership (EL), Self-leadership (SL), and Life-long Learning (LL) were adopted to measure student developmental qualities. Using 6-point Likert scale, average scores across items in each subscale were used to form indexes reflecting students' performance in the desired graduate attributes. In the present study, the internal consistencies of the subscales were from acceptable to good as reflected by the medium to large Cronbach's alpha coefficients across three waves.

National Survey of Student Engagement (NSSE)

Another instrument used in the present study was a locally adapted version of the (NSSE which assesses student engagement in high levels of learning and development. The NSSE has been widely used at universities in many countries, including USA, Canada, Australia, and China [42-44]. The NSSE consists of 47 items pertaining to 10 Engagement Indicators (EIs) [45], including Higher-Order Learning (HO), Reflective & Integrative Learning (RI), Learning Strategies (LS), Quantitative Reasoning (QR), Collaborative Learning (CL), Discussions with Diverse Others (DD), Student- Faculty Interaction (SF), Effective Teaching Practices (ET), Quality of Interactions (QI), and Supportive Environment (SE). The present study used 6 EIs (i.e., HO, RI, LS, QR, CL, and DD) to indicate student competence in lifelong learning and effective communication (see Table 1). We adopted a 4-point Likert scale for all items in 6 subscales and calculated average scores in each subscale. In the present study, the Cronbach's alpha coefficients for these subscales ranged from .62 to .88 across three waves, suggesting good internal consistencies of adapted subscales.

FINDINGS

To explore student development over three years, 13 repeated measures analysis of variance (ANOVA) with Bonferroni post hoc tests were performed, each using one indicator of the five desired attributes at PolyU as the dependent variable. The independent variable was time, operationalized as the academic year when the data were collected and extracted (i.e., 2012-2013, 2013-2014 and 2014-2015). Results of ANOVA are summarized in Table 3.

Table 3. Comparisons of students' performance in three waves (N = 460)

Desired Attributes	Indicators	2012-2013		2013-2014		2014-2015		Repeated Measures ANOVA	
		<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>F</i>	η^2_p
Problem Solving	Problem Solving ^a	4.28	.70	4.24	.66	4.47	.64	28.80***	.06
Critical Thinking	Critical Thinking ^b	4.65	.62	4.59	.67	4.67	.69	3.95*	.01
Lifelong Learning	Life-long Learning	4.66	.77	4.59	.73	4.63	.74	1.83	.004
	Higher Order Learning ^{ad}	2.42	.57	2.51	.55	2.77	.57	65.46***	.13
	Reflective and Integrative Learning ^a	2.34	.48	2.28	.47	2.64	.51	120.63***	.21
	Learning Strategies ^a	2.49	.61	2.46	.58	2.60	.61	11.27***	.02
	Quantitative Reasoning ^{ad}	2.06	.57	2.16	.55	2.40	.61	56.54***	.11
Ethical Leadership	Empathy ^c	2.94	.37	2.88	.36	2.92	.36	5.63**	.01
	Ethical Leadership ^c	4.67	.45	4.57	.53	4.63	.49	10.72***	.02
	Self-leadership ^b	3.83	.56	3.79	.56	3.86	.57	3.21*	.01
Effective Communication	Social Competence	4.59	.76	4.58	.73	4.61	.74	.31	.001
	Collaborative Learning ^a	2.43	.54	2.39	.53	2.59	.54	26.27***	.05
	Discussions with Diverse Others ^a	2.27	.54	2.24	.51	2.46	.60	34.67***	.07

Note..^a Post hoc Bonferroni test indicated that rating in Wave 3 was significantly higher than rating in both Wave 1 and Wave 2. ^b Post hoc Bonferroni test indicated that rating in Wave 3 was significantly higher than rating in Wave 2. ^c Post hoc Bonferroni test indicated that rating in Wave 2 was significantly lower than rating in Wave 1. ^d Post hoc Bonferroni test indicated that rating in Wave 2 was significantly higher than rating in Wave 1.

* $p < .05$, ** $p < .01$, *** $p < .001$.

Problem Solving

Students' ability in problem solving was assessed by the CPYDS Problem Solving (PS) subscale. Results of repeated measures ANOVA showed that there were significant differences in participants' scores of PS across three academic years ($F(2, 918) = 28.80$, $p < .001$, $\eta^2_p = .06$). Bonferroni post hoc tests further revealed that the rating in 2014-2015 ($M = 4.47$, $SD = .64$) was significantly higher than the ratings in 2012-2013 ($M = 4.28$, $SD = .70$, $p < .001$) and 2013-2014 ($M = 4.24$, $SD = .66$, $p < .001$). These results suggested that participants had significant growth in their problem solving competence after two years of GUR study.

Critical Thinking

Students' critical thinking was measured by the CPYDS Critical Thinking (CT) subscale. Significant differences in participants' scores of CT across three years were also observed ($F(2, 918) = 3.95, p = .02, \eta^2_p = .02$). Participants had higher CT scores in 2014-2015 ($M = 4.67, SD = .69$) than in 2013-2014 ($M = 4.59, SD = .67, p = .02$). The results provided evidence for positive development in students' critical thinking from their second year to third year of university study.

Lifelong Learning

Students' capacity of lifelong learning was measured by five indicators: Life-long Learning (LL) subscale of CPYDS, and four subscales of NSSE including Higher-Order Learning (HO), Reflective and Integrative Learning (RI), Learning Strategies (LS), and Quantitative Reasoning (QR). While no significant differences were observed in ratings of LL among three waves ($F(2, 918) = 1.83, p = .16, \eta^2_p = .004$), significant differences were found in ratings of HO ($F(2, 918) = 65.46, p < .001, \eta^2_p = .13$), RI ($F(2, 918) = 120.63, p < .001, \eta^2_p = .21$), LS ($F(2, 918) = 11.27, p < .001, \eta^2_p = .02$), and QR ($F(1.97, 905.99) = 56.54, p < .001, \eta^2_p = .11$). For these four indicators, post hoc tests further revealed that student scores in 2014-2015 were significantly higher than their scores in both 2012-2013 and 2013-2014. Besides, for HO and QR, scores in 2013-2014 were also significantly higher than that in 2012-2013. Means and standard deviations for the four indicators are listed in Table 3. These findings suggested that students' competence of lifelong learning has been significantly improved in the third year of their university study.

Ethical Leadership

Three indicators were used to measure ethical leadership: Empathy (EM) subscale of C-IRI, the Ethical Leadership (EL) and Self-leadership (SL) subscales of CPYDS. Results of repeated measures ANOVA indicated that student scores in these three subscales had significant differences in three academic years (see Table 3). Post hoc analyses further indicated that EM score in 2013-2014 ($M = 2.88, SD = .36$) was significantly lower than that in 2012-2013 ($M = 2.94, SD = .37, p = .002$). For EL, the score in the second year ($M = 4.57, SD = .53$) was significantly lower than that in the first year ($M = 4.67, SD = .45, p < .001$) while marginally lower than that in the third year ($M = 4.63, SD = .49, p = .05$). Moreover, student SL score in 2014-2015 ($M = 3.86, SD = .57$) was significantly higher than that in 2013-2014 ($M = 3.79, SD = .56, p = .03$). These findings suggested that students tended to give lower ratings for their empathy and ethical leadership in their second year. Nevertheless, the ratings rebounded in third year of university study.

Effective Communication

Three subscales were adopted to assess students' effective communication including Social Competence (SC) subscale of CPYDS, Collaborative Learning (CL) subscale and Discussions with Diverse Others (DD) subscale of NSSE. Repeated measures ANOVA showed that there was no significant difference in students' scores on SC among three waves ($F(2, 918) = .31, p = .73$). However, students scored higher on CL ($F(1.97, 905.62) = 26.27, p < .001, \eta^2_p = .05$) and DD ($F(1.96, 900.05) = 34.67, p < .001, \eta^2_p = .07$) in 2014-2015 as compared to 2012-2013 and 2013-2014. In other words, in the third year of university study, students had more collaborative learning and were more likely to discuss with diverse others in their study.

DISCUSSION

In Hong Kong, GE curricula usually have two sets of intended learning outcomes [46]. One is 'program intended learning outcomes' which incorporate goals of all general education subjects, such as five desired graduate attributes of PolyU, and the other is 'course intended learning outcomes' which are more specific and should support 'program intended learning outcomes'. The rationale behind two-level design is that it is impossible to achieve all program-level outcomes through one single GE course [47]. Such a framework used in designing intended learning outcomes requires two-level assessment accordingly: course-level and program-level [47-48]. While course-level assessment of student learning outcomes have been carried out in each GE course in all universities in Hong Kong [21], including PolyU [32-34, 49], program-level assessment showing how the students learn and develop as a result of the whole general education curriculum is scanty. In this case, the present study represents a pioneering work in conducting program-level assessment in Hong Kong to reveal how well the students achieve the intended learning outcomes on program-level. Such an attempt would benefit universities and program designers in terms of continuously improving the quality of general education curricula and the whole higher education system [47, 50].

Specifically, the present study investigated learning outcomes of students enrolled in a new general education (GE) curriculum, i.e., the General University Requirements (GUR) at Hong Kong Polytechnic University (PolyU). Based on comparisons of student self-reported ratings on indicators of five desirable generic competences across three academic years, results suggest that students showed significant improvement in most developmental indicators after two-year university study. These findings strongly support previous findings that the implementation of the GUR at PolyU was successful and effective [27, 29]. Furthermore, on top of the positive findings based on subjective outcome evaluations reported in previous studies [e.g., 30, 31], students' actual development and personal growth as measured by the current objective outcome evaluation provide much stronger evidence for the accountability and value of the GUR incorporated in the 4-year undergraduate curriculum.

Regarding students' scores on indicators of the desirable graduate attributes across three years, it seems that most developmental indicators followed a U-shaped trajectory over the period. This distribution features a visible dip on the ratings during the second year of the 4-year curriculum. For example, students tended perceive themselves as having lower level of

capacity in critical thinking, life-long learning, reflective and integrative leaning, empathy, and ethical leadership in the second year (i.e., 2013-2014 academic year) than in the first year, although the tendency was significant in only two indicators (i.e., empathy and ethical leadership). It is possible that such a trend was a result of setbacks encountered in students' first year university life, such as difficulties in adjusting to new educational demands, social environments, and life styles. This reasoning is in line with great challenges revealed in research on university transition in first year [e.g., 51]. These challenges could continue to exist in sophomore year, resulting in identity confusion, low self-evaluation due to academic stress, and other social pressures, which may cause a decline in learning outcomes among sophomores [52].

Nevertheless, ratings on developmental indicators rebounded at the third year. It might be possible that students have already well adapted to university life after two years. For example, students may have developed sufficient skills and supporting networks to deal with academic and other types of stress in the third year of university life, as suggested by students' highest scores in collaborative leaning and higher order leaning strategies in the academic year of 2014-2015. It is noteworthy that students had obtained significant improvement in different aspects of generic competences after two years of university study. The improved areas included problem solving, critical thinking, higher order learning, reflective and integrative learning, learning strategies, quantitative reasoning, self-leadership, collaborative learning, and discussions with diverse other, which cover all five desired graduate attributes of PolyU. Previous research has demonstrated that good practices in general education help students develop desirable generic capacities in Western cultures [e.g., 13, 53]. Findings of the present study indicate that a US-style general education curriculum is also effective in facilitating student development in a holistic manner in Chinese culture.

Taken together, while the present finding suggests that the unique characters of GE program at PolyU help promote student generic competences, for example, more engaging pedagogies are more effective in facilitating student learning than teacher-centered lecturing method [e.g., 54], it should be noted that such a positive effect might be hindered during the first year of students' university life. In other words, students may have difficulties in accepting such a totally new teaching and learning method at the very beginning of their university life. This is consistent with some scholars' concerns that interactive pedagogies might not be readily well received by Chinese students who are largely influenced by cultural traditions [21]. As a result, universities and faculties need to develop more effective approaches to incorporate interactive teaching and learning strategies in GE curricula that take into account Chinese students' characteristics. For example, nurturing student critical thinking through writing assignment may be more easily accepted by Chinese students than asking them to make critical comments in front of all students in the class. Furthermore, more assessment studies should be conducted to reveal strengths and weakness of such approaches in Chinese contexts and use the results to improve the quality of teaching and learning. Besides, additional projects or programs aiming to help freshmen adapt to university life and requirements would help students benefit from general education curricula.

The present study also provides evidence for the effectiveness of using longitudinal self-reported data to assess student learning and personal development during university study. To carry out effective program-level assessment of learning outcomes, balancing efficiency, accuracy and cost in measuring student outcomes is a great challenge. Asking students to report how much they have achieved during a certain period is an inexpensive and efficient

method while students may not always be able to accurately judge their own growth [55]. In contrast, longitudinal assessments of objective outcomes would be more accurate in revealing student achievement during the period. In longitudinal design, objective outcomes can be measured either with actual tests (e.g., some tasks measuring critical thinking) or self-reported questionnaire. Given that the former method should require great financial and human resources (e.g., more standardized and controlled measuring environment), and students are reasonably accurate in estimating their current attributes or skills [55], combining longitudinal design and self-reported measures represents a cost-effective and relatively accurate method to examine student personal development.

Several limitations of the present study should be noted. First, the study only measured student outcomes in three time points and used analysis of variance (ANOVA) to examine changes, which despite of its merits cannot reveal systematic change rates across different waves over time [56]. As a result, future research should follow up student development for a longer time period and using more powerful statistical techniques such as growth curve modeling to identify the developmental trajectory of students [56]. Second, the present study examined student development in one university in Hong Kong. Therefore, the relative advantages and disadvantages of the GUR as compared to other GE curricula in other high education institutions were unknown. Future assessments could conduct comparisons on student learning outcomes across different universities in Hong Kong and abroad (e.g., universities in mainland China). Third, the present study is quantitative research in nature, which is not able to provide students' in-depth perceptions on their experience (i.e., qualitative data) during university study to help researchers interpret and reflect on the findings. To gain a more comprehensive understanding of student learning outcomes and to triangulate the current findings, multiple research methods including qualitative studies should be used in future assessment of student learning outcomes.

Fourth, as no control group was used in this study, it is possible that the change is simply a result of developmental maturation. While it is a logical possibility, it is noteworthy that there is no research suggesting that university students necessarily show a rise in developmental indicators in this study [e.g., 3, 57].

Finally, while we interpret the present findings in terms of the beneficial effect of the GUR at PolyU, the changes may also be due to the beneficial effect of the overall four-year programme (i.e., including the effects of Major Programme). Since both the GUR and the discipline-specific program are offered at the same time, it is difficult, if not impossible, to separate their specific effects. However, two points should be noted when we interpret the findings. Primarily, evaluation of specific GUR subjects, such as leadership subjects, shows their contribution to the development of desired graduate attributes of PolyU students. Besides, as GUR subjects concentrate more in the first two years of the 4-year undergraduate program, it is more likely that the beneficial effect is a result of students' GUR study.

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Chapter 331

**PROMOTION OF SERVICE LEADERSHIP QUALITIES
IN CHINESE UNIVERSITY STUDENTS:
OBJECTIVE OUTCOME EVALUATION BASED
ON SIX WAVES OF DATA**

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ABSTRACT

Economies worldwide are shifting from manufacturing to service economies, resulting in a demand for new leadership qualities. The Hong Kong Institute of Service Leadership & Management (HKI-SLAM) proposed the Service Leadership and Management Model which highlights the importance of leadership competencies, moral character, and caring dispositions as crucial leadership attributes in service economies. The Global Youth Leadership Programme (GYLP) was developed for students from The Hong Kong Polytechnic University and the Peking University, aiming at nurturing students' service leadership qualities. The present paper reports findings based on objective outcome evaluation utilizing six waves of data. Results showed that students had significant improvement over time on different outcome measures, including positive youth development attributes, service leadership competencies, and life satisfaction. The study provides evidence for the effectiveness of service leadership education and GYLP. Implications for nurturing service leaders and promotion of holistic development of students through leadership programmes are discussed.

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INTRODUCTION

One of the most challenging and imperative objectives of tertiary education is to help students develop integrity and strength of character which prepare them for leadership [1]. As future professionals, students should acquire qualities such as, “increased sensitivity and action, responsibility... directness and honesty, and high demands on themselves and others” [2]. Similarly, the Council for the Advancement of Standards in Higher Education asserted that “regardless of differences in academic discipline, organizational affiliation, cultural background, or geographical location, students must be better prepared to serve as citizen leaders in a global community” [3]. Hence, one common expectation is to nurture university students to be leaders. In a recent review of leadership theories over the past two decades, Meuser and colleagues [4] identified 49 leadership approaches/theories. Some of the more popular theories/approaches included transformational leadership, charismatic leadership, participative/shared leadership, and the trait approach to leadership.

Obviously, we have to ask whether existing leadership theories are deemed as effective and relevant in today’s time and age. Satterwhite et al. [5] observed that our understanding of leadership has evolved in the past century as the challenges we face as a global community “have increased in complexity, size, scope, consequence. As a result of this contextual evolution, our definition of effective leadership is evolving as well” [5]. This observation is concurred by Chung [6] in his latest article in the *South China Morning Post* where he spoke of the “economic complexity and challenges we face today”. He argued that “the ones who will succeed in the next 30 years will be those who recognize that the economic growth of the past will not be replicated in the same way again” (para 13). This implies two things: 1) that global economies have changed over the years; and 2) that successful leaders are those who recognize these changes, and are equipped with the skillset that meets the needs of today’s economy.

Indeed, economies worldwide are shifting from manufacturing to service economies. Service sectors are becoming increasingly contributive to nations’ Gross Domestic Product (GDP). In 2014, the service constituted 79.7% in the US, 78.3% in the UK, 71.4% in Japan, 74.7% in Singapore, and 92.7% in Hong Kong [7]. This economic shift poses new demands on the workforce, especially for that of desired leadership qualities. According to Shek and colleagues [8], while traditional manufacturing economies require leaders to be equipped with professional, hands-on knowledge, and skills, leaders are expected to be more “people-oriented” and demonstrate “soft skills” beyond hard skills in service economies. Individuals respect and prefer service leaders who are moral, caring, and willing to serve with empathy and integrity, rather than merely exerting power to exercise manipulation.

Against this background, The Hong Kong Institute of Service Leadership and Management (HKI-SLAM) under the leadership of Dr. Po Chung (co-founder of DHL International, Asia Pacific and Chairman Emeritus of DHL Express (Hong Kong) Ltd.) proposed the Service Leadership and Management Model which highlights the importance of leadership competencies, moral character, and caring dispositions as crucial leadership attributes in contemporary service driven society. According to the model, having leadership competence alone is not enough; moral character and caring dispositions are also vital to successful leadership. Chung [9] further proposed a holistic model which delineated 12 dimensions of an effective service leader. The dimensions are organized into four categories:

Doing (e.g., possessing functional expertise, being physically healthy); *Thinking* (e.g., having emotional and cognitive competencies); *Growing* (i.e., being able to establish and maintain positive relationships with followers, and adopting the attitude of life-long learning); and *Being* (e.g., exercising compassion, morality, and spirituality).

In order to nurture students to become leaders, leadership programmes in tertiary education settings have proliferated since the eve of the 21st century. Binard and Brungardt [10] reported that there were over 600 campuses in the United States providing leadership training. In response to the longstanding question of whether leadership can be “taught”, the authors investigated the impact of leadership programmes on various student outcomes. Findings revealed that students who participated in leadership programmes had improved in leadership behaviours (e.g., inspiring a shared vision, enabling others to act, modelling, encouraging others, and challenging the process), as compared with their counterparts who had never attended such collegiate leadership training.

Although collegiate leadership training has existed for a while, formal leadership programmes are still relatively new. It may be due to two main reasons. First, there is yet to be a consensus on a particular theory or approach about *how* to develop leaders [11]. Second, the differentiation between “leader development” vs. “leadership development” remains clouded. Leader development activities target specifically on nurturing skills and traits of individuals “designated” as a leader or an emerging leader. This notion is somewhat in line with the elitist approach of leadership. In contrast, leadership development refers to nurturing intrapersonal, as well as leader traits and skills that would enable effective interpersonal interactions and facilitate leader-follower exchange [12].

Day et al. [13] pointed out that “leaders do not ‘develop’ in workshops or seminars but rather ‘in the so-called white space between such leader development events’ (p. 80). This “white space” may be certain trigger events that enable individuals to experience and construct a personally meaningful narrative about their own leadership [14]. In line with the above perspectives, the Global Youth Leadership Programme (GYLP) was developed for students from The Hong Kong Polytechnic University and the Peking University, aiming at nurturing students’ service leadership qualities, including leadership competencies, moral competencies, and caring disposition. The GYLP was designed such that students first attended a series of lectures where the concept of service leadership and psychological theoretical underpinnings were introduced. Existing leadership theories were also presented and students were guided to evaluate and compare and contrast different leadership theories while reflecting on the importance and relevance of the service leadership model in the present service economy. During the lectures, students were also given the opportunity to engage in personal reflection on their service leadership competencies (i.e., moral character, leadership competencies, and caring dispositions) and how they can apply these competencies in serving others.

Upon completion of the service leadership lectures, students were given the chance to gain hands-on experience and apply service leadership concepts, and reflect on their competencies through a wide-range of talks, presentations, experiential activities, and service in mainland China, Hong Kong, and Cambodia. For instance, during their initial trip to Beijing and Xi’an, students attended different talks regarding contemporary issues in China such as Chinese Foreign Policy, China’s Five-Year Plan, and Minority Tribes in Western China. Students also engaged in dialogues with renowned community leaders and executives of large corporations.

Students took the self-initiative to conduct research in preparation of presentations during the “Youth Forum on Poverty in Hong Kong and Chinese Mainland” in Hong Kong. Students prepared presentations on the causes and government policies regarding poverty, and looked into what the young generation can do to alleviate poverty. They also engaged in an experiential activity of role-playing as a homeless, sleeping in the streets, and scavenging cardboard boxes to make money to buy food. Students generally reflected that they had positive experience about the programme, such as

“Observing something bad happening around us urges me to think more about how to change the situation. And I felt a greater eagerness to take some actions” and “Leadership should be at the base of the spirit of service, so that one can become a valuable and admirable leader. Though I am still a university student, I will try my best to prepare for the future in my position and serve the society”.

Table 1. Detailed GYLP activities

Beijing and Xi'an Trip
• Opening ceremony • Welcome lunch • Service leadership lecture • Talk: Foreign Policy of China • Visit: Migrant worker community service center • Visit: Organic farm • Visit: African culture project • Visit: Tencent office • Leaders Dialogue Forum • Visit: United Nation Development Programme • Visit: Hong Kong Special Administrative Region Beijing Office • Talk: 125 National Planning • Visit: Museum of Qin Terracotta Warriors and Horses • Talk: Development policy of Western China • Talk: Chinese culture and society • Visit: Deprived village of Shanxi • Talk: Minority tribes in Western China • Visit: Community walk in Muslim district • Group presentation • Visit: Great Wall of China
Hong Kong Trip
• Talk: Social welfare system in Hong Kong • Visit: New Life Psychiatric Organization • Visit: Hong Kong Christian Service Ethnic Minority Services • Practical Dreamers seminar • Talk: Environmental challenges of Hong Kong and Mainland in Global context • Visit: Legislative council • Experiential activity: Role-playing as homeless • Youth Forum on Poverty in Mainland China and Hong Kong • Youth Forum dinner
Cambodia Trip
• Preparation and conducting rural asset survey • Visit: Slum area • Cultural programme at learning village • Talk: Social issues in Cambodia • Orientation with local volunteers • Service at local primary school and orphanage • Visit: Village area • Visit: Killing Fields Museum of Cambodia

Finally, during the Cambodia trip, students provided service to the needy. For instance, some students visited a village where farmers experienced the problem of drought and devised creative ways of irrigation to alleviate the problem. Another group of students visited a primary school where they organized vision screening projects and helped raise awareness of ocular health among the underprivileged in the area. A third group of students served in an orphanage housing children diagnosed with AIDS. The GYLP service leaders developed creative activities such as photography to allow the students to capture and express things in life that they felt grateful towards. Through different services, students demonstrated their service leadership competencies to understand the needs of different parties and applied leadership competencies, care, and moral character, alongside their discipline knowledge to propose solutions to the problems faced by the underprivileged. The detailed programme can be seen in Table 1.

In order to gain a better understanding of the effectiveness of the programme, objective evaluation outcome evaluation data were collected from students at six waves of data during different stages of the Programme. The present paper reports the findings arising from the evaluation study.

OUR STUDY

A total of forty-eight university students (37 females; Mage = 19.65 years, SD = 0.76) participated in the GYLP, in which 24 students were from The Hong Kong Polytechnic University and the other 24 students were from Peking University. The students were enrolled into the programme via application and interview. Besides students from Hong Kong and mainland China ($n = 42$, 87.5%), there were three Koreans (6.25%), one Taiwanese (2.08%), one Thai (2.08%), and one American (2.08%) joining the programme. The numbers of students participated in different trips varied because some students skipped one or two trips and some quitted the programme halfway due to other commitment (see Table 2). Finally, a total of 39 students completed all the assessments.

Table 2. Description of trips of GYLP

Trip	Time	Assessment time	No. of students
Mainland China trip	July 7-27, 2013	Pretest: July 8, 2013	47
		2 nd test: July 12, 2013	48
		3 rd test: July 25, 2013	47
Hong Kong trip	January 13-19, 2014	4 th test: January 19, 2014	44
Cambodia trip	July 27 - August 6, 2014	5 th test: July 24, 2014	41
		6 th test: August 5, 2014	40

Table 3. Descriptive information of the variables of study

	Trip to Mainland China						Trip to Hong Kong			Trip to Cambodia		
	2 nd		3 rd		4 th		5 th		6 th		α	
	Mean (SD)	α	Mean (SD)	α	Mean (SD)	α	Mean (SD)	α	Mean (SD)	α		
Positive youth development total score	4.73(0.45) _a	.90	5.04(0.43) _b	.90	5.09(0.42) _b c	.91	5.02(0.45) _b	.92	4.95(0.54) _b	.95	5.15(0.40) _c	.95
Cognitive-behavioral competence	4.71(0.55) _a	.82	5.04(0.47) _b	.81	5.11(0.49) _b c	.83	5.01(0.60) _b c	.88	4.97(0.63) _b	.93	5.18(0.48) _c	.93
Positive identity	4.78(0.64) _a	.78	5.07(0.68) _b	.83	5.07(0.64) _b	.78	5.16(0.58) _b c	.86	5.23(0.55) _b	.86	5.23(0.55) _c	.86
General positive youth development attributes	4.72(0.45) _a	.80	5.03(0.42) _b d	.80	5.09(0.40) _c	.81	4.97(0.44) _d	.85	5.09(0.43) _b d	.77	5.09(0.43) _c	.87
Life satisfaction	4.17(0.82) _a	.86	4.78(0.82) _b	.86	4.78(0.62) _b	.86	4.76(0.80) _b	.88	4.91(0.66) _b	.83	5.15(0.61) _c	.89
Self-leadership	4.72(0.48) _a	.61	5.03(0.62) _b	.84	5.12(0.44) _b c	.73	5.05(0.57) _b	.80	5.01(0.64) _b	.88	5.26(0.49) _c	.88
Caring disposition	4.98(0.58) _a	.86	5.26(0.52) _b c	.85	5.20(0.51) _b c	.87	5.20(0.55) _b c	.88	5.16(0.60) _b	.94	5.30(0.47) _c	.94
Moral Character	4.66(0.49) _a	.82	4.94(0.42) _b	.79	5.08(0.43) _b c	.87	4.97(0.44) _b	.81	4.97(0.50) _b	.89	5.13(0.46) _c	.90
Service leadership beliefs	5.14(0.65) _a	.91	5.56(0.51) _b	.89	5.49(0.55) _b	.94	5.42(0.60) _b	.94	5.35(0.63) _b	.96	5.43(0.56) _b	.96

Note: same subscript letter indicates no significant difference in mean level.

Instrument

The students were invited to respond to an identical objective outcome evaluation form at six time points, including baseline test before the service leadership class, posttest of service leadership class (i.e., 2nd test), posttest of mainland China trip (i.e., 3rd test), posttest of Hong Kong trip (i.e., 4th), pretest of Cambodian trip (i.e., 5th test), and posttest of Cambodian trip (i.e., 6th test). Due to the short duration, there was no pretest for the Hong Kong trip. This evaluation form includes ten positive youth development attributes, life satisfaction and service leadership qualities and beliefs. It has been repeatedly used in the evaluation of the subject “Service Leadership” with good psychometric properties [15, 16]. Students completed the form in a self-administration manner. The internal consistencies of the scales used in this study were generally good (see Table 3).

Positive Youth Development

The items of positive youth development were selected from the Chinese Positive Youth Development Scale (CPYDS; 17) with modification to fit the context of the programme (31 items). These items assess social competence, cognitive competence, emotional competence, moral competence, behavioral competence, clear and positive identity, belief in the future, self-determination, spirituality, and resilience. According to Shek and Ma [18]’s factor analysis, there are four higher-order factors, including cognitive-behavioral competencies, positive identity, prosocial attributes, general positive youth development qualities. In this study, we tested students’ changes of positive youth development on three higher order factors (i.e., cognitive-behavioral competencies, positive identity, and general positive youth development qualities) and positive youth development total score. Cognitive-behavioral competencies score includes the subscales of cognitive competence, behavioral competence and self-determination; positive identity score includes subscales of clear and positive identity as well as belief in future; general positive youth development qualities score includes the subscales of emotional competence, social competence, moral competence, resilience, and spirituality; positive youth development total score includes all of the subscales of positive youth development attributes. With negative items reverse coded, a higher score denotes a higher level of positive youth development.

Life Satisfaction

Students reported their overall satisfaction with life via the five-item Satisfaction with Life Scale (SWLS) developed by Diener and associates [19]. This scale has been repeatedly used in Chinese population [20]. Mean scores were taken with higher scores indicating higher levels of life satisfaction.

Service Leadership Qualities and Beliefs

Students reported their service leadership qualities and beliefs via a scale developed based on the service leadership model [16, 21]. The scale assesses critical components of service leadership, including self-leadership, caring disposition and character strengths as well as service leadership beliefs. Mean scores were taken with higher scores indicating higher levels of service leadership qualities and stronger endorsement of service leadership beliefs.

FINDINGS

Series of ANOVA analyses with time as repeated measure were conducted on the outcome variables. Time effect was significant on all outcome measures, which indicated that positive youth development, life satisfaction and service leadership qualities and beliefs changed positively during the programme participation. LSD post-hoc analyses were then used to understand the variation across different time points. We focused on the comparison between the baseline test and the subsequent tests, and that between the pretest and the posttest of one trip. The results were presented in table 3.

First, three components of positive youth development all changed positively over time (cognitive-behavioral competence: $F(5,31) = 5.57, p < .001, \eta^2_p = .47$; positive identity: $F(5,31) = 7.12, p < .001, \eta^2_p = .51$; general positive youth development qualities: $F(5,34) = 10.82, p < .001, \eta^2_p = .61$). For cognitive-behavioral competence, compared with the baseline test, the scores of all subsequent tests were higher (1st vs. 2nd: $p < .01$; 1st vs. 3rd: $p < .001$; 1st vs. 4th: $p < .001$; 1st vs. 5th: $p < .01$; 1st vs. 6th: $p < .001$). The score increased from the baseline test to the second test, maintained stable between the second test and the fifth test, and finally increased again from fifth test to the sixth test ($p < .05$). Similar pattern was observed in positive identity. Compared with the baseline test, the scores of all subsequent tests were higher (1st vs. 2nd: $p < .01$; 1st vs. 3rd: $p < .01$; 1st vs. 4th: $p < .001$; 1st vs. 5th: $p < .01$; 1st vs. 6th: $p < .001$). The score increased from the baseline test to the second test, maintained stable between the second test and the fifth test, and finally increased again from fifth test to the sixth test ($p < .01$). For general positive youth development qualities, compared with the baseline test, the scores of all subsequent tests were higher (1st vs. 2nd: $p < .001$; 1st vs. 3rd: $p < .001$; 1st vs. 4th: $p < .001$; 1st vs. 5th: $p < .01$; 1st vs. 6th: $p < .001$). The score kept increasing from the baseline test to the third test (2nd vs. 3rd: $p < .05$), but declined from the third test to the fourth test ($p < .05$). With no difference between the fourth test and the fifth test, the score increased from the fifth test to the sixth test ($p < .001$). Taking all positive youth development attributes as a whole, we found the time change as well ($F(5,34) = 10.72, p < .001, \eta^2_p = .61$). Compared with the baseline test, the scores of all the subsequent tests were higher (1st vs. 2nd: $p < .001$; 1st vs. 3rd: $p < .001$; 1st vs. 4th: $p < .001$; 1st vs. 5th: $p < .01$; 1st vs. 6th: $p < .001$). The total score increased from the baseline test to the second test, maintained stable from the second test to the fifth test, and finally increased again from the fifth test to the sixth test ($p < .01$). All these findings suggested that the programme was effective to promote positive youth development of students. As we found a decline in general positive youth development qualities from the third test to the fourth test, more effort is needed to maintain the programme benefits.

Second, time change occurred in life satisfaction ($F(5,34) = 11.60, p < .001, \eta^2_p = .63$). LSD post hoc analysis revealed that the score of baseline test was lower than all of the subsequent tests ($ps < .001$). In addition, there was no change from the second test to the fifth test, but with an increase from the fifth test to the sixth test ($p < .01$). Students' life satisfaction reached the highest point at the sixth test (6th vs. 4th: $p < .001$; 6th vs. 3rd: $p < .01$; 6th vs. 2nd: $p < .01$). These results suggested the programme was effective to boost students' life satisfaction.

Third, time changes occurred in service leadership qualities (self-leadership: $F(5,34) = 12.84, p < .001, \eta^2_p = .65$; caring disposition: $F(5,34) = 4.55, p < .01, \eta^2_p = .40$; moral

character: $F(5,34) = 14.44$, $p < .001$, $\eta^2_p = .68$) and service leadership beliefs ($F(5,34) = 3.29$, $p < .05$, $\eta^2_p = .33$). For self-leadership, compared with the baseline test, the scores of all subsequent tests were higher (1st vs. 2nd: $p < .01$; 1st vs. 3rd: $p < .01$; 1st vs. 4th: $p < .01$; 1st vs. 5th: $p < .05$; 1st vs. 6th: $p < .001$). Specifically, the score increased from the baseline test to the second test ($p < .001$), maintained stable between the second test and the fifth test, and finally increased again from the fifth test to the sixth test ($p < .05$). Similar pattern was found in caring disposition, in which the score of baseline test was lower than the subsequent tests (1st vs. 2nd: $p < .01$; 1st vs. 3rd: $p < .01$; 1st vs. 4th: $p < .01$; 1st vs. 5th: $p < .05$; 1st vs. 6th: $p < .001$). Specifically, the score increased from the baseline test to the second test ($p < .01$), maintained stable between the second test and the fifth test, and finally increased again from fifth test to the sixth test ($p < .05$). Similarly, for moral character, the score of baseline test was lower than the subsequent tests (1st vs. 2nd: $p < .01$; 1st vs. 3rd: $p < .001$; 1st vs. 4th: $p < .001$; 1st vs. 5th: $p < .001$; 1st vs. 6th: $p < .001$). Specifically, the score increased from the baseline test to the second test, maintained stable between the second test and the fifth test, and finally increased again from fifth test to the sixth test ($p < .01$). Different pattern was observed in service leadership beliefs. Compared with the baseline, only the scores of second, third and sixth tests were higher (1st vs. 2nd: $p < .01$; 1st vs. 3rd: $p < .01$; 1st vs. 6th: $p < .05$). Specifically, the score increased from the baseline test to the second test, but then maintained stable from the second test to the final test. These findings suggested that the programme was effective to enhance service leadership qualities and maintain them at a relatively high level. However, it seems more difficult to boost the level of service leadership beliefs, probably because the baseline was quite high.

DISCUSSION

Student development in tertiary education refers to “the application of human development concepts in postsecondary settings so that everyone involved can master increasingly complex developmental tasks, achieve self-direction, and become interdependent” [22, p. 3]. It is concerned with the development of the whole person and stimulation of positive growth in students [23]. The GYLP is not merely a leadership development programme – it is a programme that targets holistic development among students. As evidenced by the 12 dimensions of an effective service leader, the Service Leadership and Management Model aims to nurture a holistic set of competencies, which would allow students to provide high-quality service in this interdependent world. The service leadership model coincides with existing wellness models targeting to enhance individuals’ wellbeing. For instance, the empirically-based Model of Wellness [24] postulated that individuals’ total wellness comprises of healthy development in five self domains, namely the Creative Self (e.g., being mentally active, emotional awareness and expressivity, control); Coping Self (e.g., stress management, a sense of self-worth, realistic beliefs); Social Self (e.g., connecting with others, having empathy, ability to trust and love); Essential Self (e.g., spirituality, self-care, gender and cultural identity); and Physical Self (e.g., exercising, eating healthily). Taken as a whole, our findings showed that the GYLP influenced the participants positively in many of the aforementioned dimensions and beyond. Students’ positive youth development competencies including cognitive behavioral competencies, positive identity,

and general positive youth development qualities significantly increased when comparing the 1st and 6th wave. Similarly, service leadership competencies, and life satisfaction also improved.

The present findings suggest that more programmes similar to GYLP should be developed which would benefit students in different ways. First, regarding employability and leadership challenges, Clarke [25] reported on the present “soft skills crisis”, referring to the phenomenon where employers believed that young people are ill-prepared for the world of work, and lack soft skills such as communication, resilience, and the ability to work in teams. “Survey after survey is employers saying qualifications are important, but that just as important to us are so-called soft skills, character skills, the ability to get on with different people, to articulate yourself clearly, confidence, grit, self-control. They are saying we are not seeing enough of this in kids coming out of school” [26, para. 6]. Therefore, contemporary leadership theories and development programmes should include components to equip graduates with the very much needed soft skills.

Second, compared with the general population, university students reported higher levels of psychological issues [27]. In the US, suicide is the second lead cause to death of college students [28], and 14.9% of students reported having been diagnosed with a depressive disorder during their college studies [29]. In Hong Kong, worrying trends in suicide have been observed. Since the start of 2015-2016 academic year, an alarming number of 22 young people have taken their lives. Experts have attributed the phenomenon to the high-pressure education system and low levels of resilience against problems and stress [30]. Furthermore, the annual World Happiness report revealed that Hong Kong’s ranking in the United Nations’ global ranking of happiness dropped to its lowest ranking 75th among 156 countries and territories examined. “Hong Kong is losing a lot of competitiveness in terms of social conditions. We are trying our best to develop our economy at the expense of social life” [31]. This further reiterates the dire need and essence of holistic student development. Educators should strive to develop programmes that aim to prepare students to become service leaders in this competitive arena; but not in the expense of the development of intrapersonal and interpersonal competencies, as well as general life satisfaction. The present findings are also consistent with the previous with evidence that Service Leadership education can help students develop effective service leadership qualities based on objective outcome, subjective outcome, and qualitative evaluation [e.g., 8, 32, 33] studies.

While the findings from the objective outcome evaluation of the GYLP provide evidence to support the effectiveness of the programme in nurturing students’ service leadership, positive youth development competencies, and enhancing their life satisfaction, there are some limitations to the study. First, the evaluation was conducted using self-report assessment, which some scholars claimed may be subject to social desirability bias. However, according to Paulhus and Vazire [34], this is seldom a problem in research if well-established instruments are administered as in the case of our present study. The instruments we administered have been validated and widely used among tertiary students with high psychometric credibility. Second, respondents included only the participant themselves, thus providing us with a single source of evidence. Adopting a multi-informant approach to solicit data from participants’ peers or family would provide additional support to corroborate with our findings.

Although there is no consensus within the literature on a particular method that is most effective in leadership development among tertiary students, findings from the objective

outcome evaluation in the present study provide evidence to support the effectiveness of the GYLP, targeted to enhance tertiary students' service leadership, positive youth development competencies, and life satisfaction. Tertiary institutions globally may model after the GYLP in developing leadership programmes to prepare students to meet the challenges and needs in contemporary service economies. Highly autocratic, directive, and transactional leadership styles are dated [35]. Service leaders should be equipped with leadership competencies, caring dispositions, and moral competence. As quoted by Simon Sinek [36], renowned expert in leadership and management:

"The best leaders are those that understand the meaning of service, those who are willing to sacrifice for their own people."

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Chapter 332

**BREAK THE CYCLE OF CHILDREN'S
ENVIRONMENTAL HEALTH DISPARITIES:
14TH ANNUAL REVIEW OF PROGRAM AND
STUDENT PROJECTS**

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ABSTRACT

Break the Cycle of Children's Environmental Health Disparities (Break the Cycle) is an annual collaborative interdisciplinary research and training program involving university students in academic tracks that focus on the impact of adverse social, economic, environmental and political factors on children's health, development, education and prospects for their future. The target populations are communities where there is a substantial measure of poverty associated with social and political marginalization predisposing to environmental degradation and risks to children's health and well-being. Each participating student is required to develop a project that focuses on preventing or reducing adverse environmental factors or their impact, in order to improve the health of the children who live in these communities. At the end of the project, students are required to present their studies and findings at a national conference and write manuscripts on their projects, which are then published in a journal supplement as well as a book. The projects cover a range of social, economic, environmental and political factors that operate over the lifespan, and have an influence on individual, family, community, and societal perspectives with an intergenerational implications. Most importantly, they add to our knowledge about children's environmental health disparities and propose solutions to reduce and eliminate health disparities and promote health equity for all children.

The papers in this publication represent the work of students who participated in the 14th Annual Break the Cycle program. The phrase 'break the cycle' in this context uses the ecological construct of the cycle of environmental health disparities, and represents a framework for projects and programs that reduce health disparities and promote health equity among children who are vulnerable as a consequence of adverse social, economic, environmental and political factors. The student projects are intended to 'break the cycle' and liberate children from the intergenerational cycle of health disparities, so they can grow and develop to their full potential. Through this academic process, the students gain knowledge, insight and skills to enable them to advance in their careers and become future leaders

INTRODUCTION

Children who grow up in poverty are more likely to be exposed to multiple adverse physical, chemical and social elements in their environment and more likely to be emotionally stressed, with multiple elements of insecurity with anxiety and fear [1]. They are more likely to be exposed to poor indoor air quality, which increases the risk for asthma and respiratory disorders, and are more likely to be living in older houses with high lead levels from old paint and plumbing which can result in brain damage [2]. In addition, the children are at risk for a variety of other environmental exposures, because poor neighborhoods are more likely to be located near roadways where the air is more heavily polluted with exhaust from motor vehicles, or near factories and even near toxic waste sites. Their neighborhoods and schools are often characterized by evidence of general degradation, they are more likely to be littered with trash, are poorly lit at night which increases risks of crime with fear of assault and a greater likelihood of having street drugs and drug dealers, with little to no green spaces and suitable facilities for recreation [3]. Furthermore, the emotional toll on the children from multiple stressors, including food insecurity, housing insecurity, and fear of physical injury from neglect and abuse which, cumulatively can result in the physiological phenomenon of chronically elevated cortisol levels and “toxic stress” [4]. The toxic stress syndrome is associated with unfavorable structural and functional changes in the brain, resulting in life-long consequences that can be associated with a reduction in brain volume in white matter, in grey matter, and specifically in the hippocampus and amygdala [5]. As they reach adolescence, these children are more likely to experience school failure and engage in risky behavior, including substance abuse, gang membership, and crime which can result in incarceration or death from drugs or gun violence. The elevated cortisol levels associated with toxic stress also have a metabolic and hemodynamic impact on the cardiovascular, immune and hormonal systems, resulting in an increased likelihood of adverse health outcomes in adulthood including obesity, diabetes, and hypertension, with their associated morbidity and mortality [4].

These risks for children are greater than they are for adults, because children breathe more air, drink more water, and eat more food for their body weight than adults, so their exposure load through polluted air, water and soil is greater. Furthermore, their organs and organ systems as well as physiologic and metabolic processes are still in development, so they are more vulnerable to immediate and long term negative health outcomes [6]. By the same token, the developing embryo and fetus is even more vulnerable to adverse environmental factors because the organs and organ systems are in an earlier stage of development. Therefore, the exposure of pregnant women to environmental toxins as well as emotional stress not only affect the pregnant mother's health and well-being but can also have serious and permanent effects on her fetus [7]. Despite the physiological protective elements in the placenta, many toxins enter the fetal circulation and can affect organ system development, anatomically and physiologically. Many substances can cross the blood-brain barrier and adversely affect the developing brain, resulting in disorders of development and learning with risks for learning disabilities, ADHD, and even autism [8].

Children from low income and minority communities tend to live in poor neighborhoods and attend older, more dilapidated schools, with teachers who are also suffering from the stress of adverse environmental factors. Thus, the combined effects of adverse environmental

and emotional stresses, along with negative educational experiences, compromise learning and even desire for learning or appreciation of the value of learning, which results in high drop-out rates and low graduation rates [9]. Limited education leads to poor employment opportunities, or work with low pay, trapping the young people in the poorer neighborhoods with the older houses in states of disrepair, contributing to exposures to indoor hazards of lead, mold, and other possible contaminants, as well as emotional stress with depression, anxiety about the future with despair and social isolation [10]. Those young people who drop out of school and have limited employment options with a relatively dim view of their future, may resort to drugs to feel better or crime to make money in order to live or support their habits or lifestyles. These behaviors can result in incarceration with the emotional and social consequences for the individual, the family, the community and society [11]. This scenario plays out in too many cities and states in the USA and, along with draconian drug laws, has resulted in the highest incarceration rate in the world with a high percentage of young men of color in prison [12, 13]. On a positive note, the statistics show that since the peak in the 1990s, the number of juvenile justice cases has decreased substantially. Although this positive trend is a result of factors beyond our personal control and reside in the hallways of local, state and federal processes, we can be encouraged to take action and strive to make a positive difference in the lives of vulnerable children, not only in reducing the negative environmental factors, but in promoting resilience through education as well as emotional and social support [14].

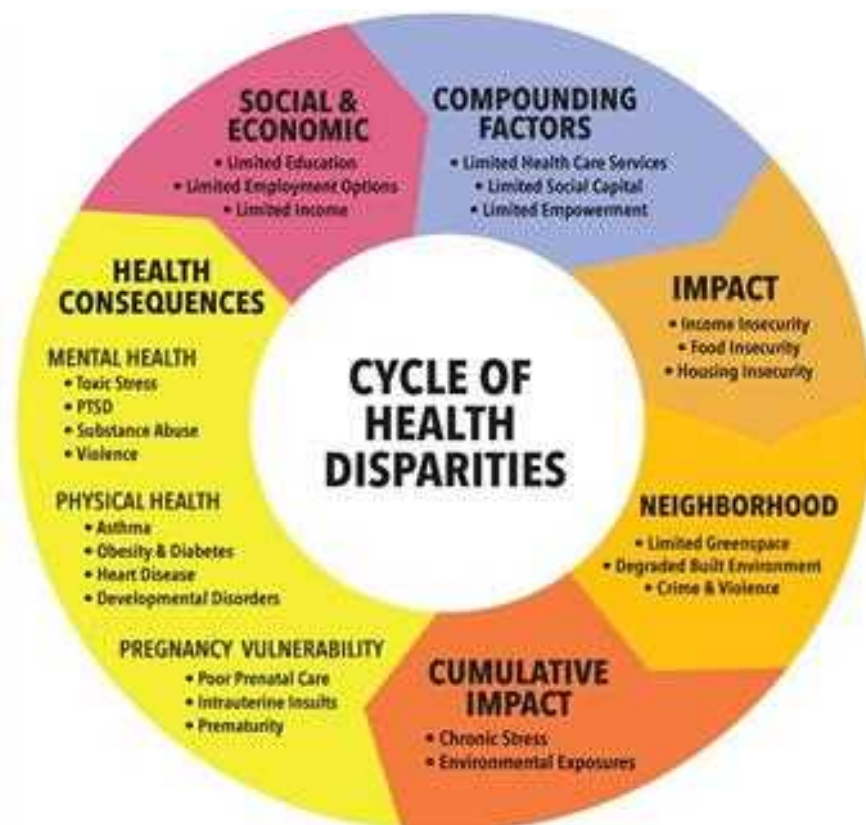


Figure 1. Cycle of environmental health disparities [15].

The assault of adverse social, economic and environmental factors on vulnerable children that results in unfavorable health, developmental, and educational outcomes, and compromises a child's opportunity for economic and social success in life, devolves into the perpetuation of an intergenerational cycle. It is the codification of this ecological construct that embodies the concept of the cycle of children's environmental health disparities (see Figure 1).

BREAK THE CYCLE PROGRAM

"Break the Cycle of Children's Environmental Health Disparities" (Break the Cycle) is an annual, collaborative interdisciplinary research and training program involving university students in academic tracks that focus on the impact of adverse social, economic, and environmental factors on children's health, development, and education. Each participating university student develops a project that focuses on preventing or reducing environment-related disorders for vulnerable children who live in communities where environmental hazards and emotional stresses are related to circumstances of social and economic disadvantage. At the conclusion of the project period, the students present the results of their projects at a national conference and write manuscripts on their projects which are then published in a journal supplement dedicated to the collection of projects from each given year [16]. Each annual program begins with a call for proposals from a wide range of university students. The proposals are then evaluated by a competitive review process for the quality of the proposal, its relevance to children's environmental health disparities, creativity, and feasibility. The 10 best proposals are selected to work with their academic mentors and their home universities and with the Break the Cycle faculty to complete their projects. The students and their mentors are required to participate in monthly conference calls, during which the progress of each project is reviewed, additional perspectives are explored, and constructive guidance is provided. During these conference calls, the students and their mentors also have an opportunity to communicate and collaborate with their counterparts at other universities.

Table 1. Project guidelines

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| <ul style="list-style-type: none"> • University faculty identify students who have an interest in this topic area and support the student in the selection of an idea for projects that explore environmental factors that adversely affect the health of children living in circumstances of social and economic disadvantage. Alternatively, students interested in a specific project can initiate the application process and identify mentors to work with them. • The students submit their proposals which are reviewed by the <i>Break the Cycle</i> faculty. The process is competitive with only 10 projects being selected each year. • During the project period, there are monthly conference calls with all students and mentors to monitor the progress of the projects, share ideas, and assure that the projects are consistent with the spirit of the <i>Break the Cycle</i> concept. • At the end of the project period, the students present the results of their work at the annual Break the Cycle conference. • The students are then required to write papers on their projects, which are submitted for publication in an international journal as a monograph of the <i>Break the Cycle</i> projects. The papers are also published as chapters in a book. • The progress and careers of the participating students are tracked to evaluate the impact of their participation in the <i>Break the Cycle</i> program. |
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When the program was started, the expectation was that the projects would make a positive difference by improving the health and well-being of children, their families, and their communities. It was also envisioned that students would be inspired to pursue careers that focused on reducing health disparities and in becoming leaders for the future. Furthermore, because each student is required to have a mentor at their home university, it was anticipated that the faculty mentors would add to the literature and body of science on the subject into their curricula, and thereby promote further research and academic interest in this field (see Table 1).

Table 2. Desired outcomes

• To inspire students from a variety of academic disciplines to explore the impact of adverse social, economic, environmental and political factors on the health, development and education of children, and to creatively generate strategies to address the challenges. • To collaborate with an interdisciplinary team of academic leaders from a variety of different universities and colleges to get a perspective on the broader issues of this topic area • To encourage faculty at universities who participate in this program to promote academic interest and social awareness in children’s environmental health disparities • To cultivate future leaders among the students

We also expected that the participating students would inspire peers in their academic, social and professional circles, and that the interdisciplinary nature of the program with participation of students at other universities around the world, would be stimulating and inspiring (Table 2). The 2012 survey of alumni of the program showed that the students derived significant benefit from all aspects of their participation in the process, which included the practical aspects of conducting a research project, experience in preparing and delivering a presentation and writing a manuscript. Each student gained knowledge about children’s environmental health and environmental health disparities as well as being exposed to different perspectives from the other student projects [16].

Since its inception in 2004, Break the Cycle has held 14 annual programs and worked with over 120 students representing 30 different university departments in 10 states in the US, as well as students from countries in Latin America, Europe and Africa. To date, 11 monographs have been published in international journals and 11 books in a public health series. In the 2012 survey, the students rated their experience with Break the Cycle as valuable, many reporting that they pursued careers relating to their Break the cycle projects [16].

BREAK THE CYCLE 14 PROJECTS

The papers in this publication represent the interdisciplinary array of creative work by students from universities in six states in the US who participated in the 14th Annual Break the Cycle program in 2019. As usual, the papers in this volume cover a wide range of topic areas including the critical importance of maternal child relationships, adverse childhood experiences, communities, neighborhoods and gentrification, lead in drinking water, disparities in autism and systemic lupus erythematosus (SLE) diagnosis and treatment, and two new topic areas: one on the American Indian experience and the other on Medicaid

coverage. While the projects on the more familiar themes add to our appreciation and understanding of the conditions addressed, the two new topic areas challenge us to think afresh about the complexity and scope of the concept of children's environmental health disparities. In addition, we identified themes across the projects, which are:

- *Cost of care.* Healthcare financing is a critical factor in assuring access to quality diagnostic and therapeutic services. This is the focus of the student project in this series on expansion of Medicaid services and health outcomes, but it also has relevance across other projects, such as access to services for children with autism. There is no question that Medicaid has improved access to healthcare for vulnerable populations in our society, particularly for children from low income families, but there remains room for improvement at a systemic level.
- *Literacy and health literacy.* The importance of speech, language, communication, and understanding of the spoken and written word in health and healthcare is essential. The projects that address this topic area range from the importance of infants being exposed to complex speech and learning vocabulary early in life, to the importance of health literacy of mothers in taking care of their infants, to teenagers with SLE being able to read and interpret the doses of their medication. Ultimately, this speaks to the importance of a good general education as well as being educated about wellness and maintaining good health.
- *Neighborhoods, communities and culture.* Our neighborhoods and the communities are the building blocks of our society. Projects in this series examine the specific communities of American Indian pregnant women and the young mothers of infants from Paraguay, which effectively opened the conversation to exploring cultural identity and how to effect positive change without losing sight of the respect for the importance of cultural history and cultural ties and how these affect health literacy and healthy practices. In addition, there are the African American communities in North Carolina which are geographically isolated from municipal water resources and must rely on well-water which is more likely to be contaminated. Then there are the low-income communities living in degraded neighborhoods which are undergoing transition to an upgraded and more upscale built environment. As a consequence, families in the old neighborhoods are required to adapt to the changing environment and demographics or forced to relocate; either way there is disruption of their communities with adverse social and emotional consequences.
- *Individual vs population or statistics.* The values of science and its practical translation for use in real life are critical to our understanding of ourselves, the environment, and our interaction with the environment. While statistics are the foundational basis of our science today, the appreciation of the findings may not be readily apparent in real life. In several of the papers in this series, most notably in the two on autism disparities and the work on the mothers in Paraguay, there are vignettes of what some of the subjects reported of their experiences. These vignettes help to breathe life into the science and help in conveying an understanding of the findings and their implications.

The following are brief reviews of the Break the Cycle 14 student projects in this volume.

The Development of a Prenatal Care Health Literacy Instrument for American Indian Mothers

This project is the first in the 14 years of Break the Cycle to focus on the American Indian community. As of 2017, there were an estimated 5.6 million people who were classified as American Indian and Alaska Native comprising 1.7 percent of the total US population [17]. American Indians were on American continents for millennia before the European conquerors arrived and decimated the large Native American population with unfamiliar diseases, and with sophisticated weaponry and strategies honed from the frequent and often protracted battles and wars fought on European and Asian soil. After countless battles and wars between the European settlers and the Native Americans, so-called treaties partitioned American Indian land into fragments for each of the remaining tribal groups scattered across the continent, disconnected from one another. This disconnection had some basis in the different identities and cultures of the extant tribes at that time and may have seemed logical, but the dispersion and local tribal affiliations has precluded a cohesive and compelling coalition that, theoretically could, by virtue of a unified voice, become a force to be reckoned with, politically and economically. Furthermore, the conquering armies and immigrant people exerted power over the indigenous population through subjugation with systematic and determined disruption and destruction of the existing cultural norms, languages, practices and beliefs, and through the imposition of the conquerors' culture, language, customs and beliefs.

Consequently, the people who once proudly and powerfully populated and dominated the American continents, effectively became and, even in the 21st Century, remain second class citizens. In the US, they have become a relatively forgotten and neglected people. Apart from the imagery and pageantry, American Indian communities remain in remote and disconnected parcels of land, in situations of social, economic and political isolation. As a result, unemployment, poverty and despair result in the ills of the people and their society, effectively trapped in the cycle of environmental health disparities [17, 18]. However, despite the prevailing poverty, lack of good education and healthcare services, high unemployment, as well as other adverse economic and social factors, there are positive trends with modest individual and group successes. In his book on the resilience of the American Indian Community, David Treuer reviews and revises the history of the people as has been told over time to the present, and builds a picture of a proud and resilient group of people who have survived the genocide and are rebuilding their identity and defining their role on the global stage [19].

There is much work to be done to improve the situation for most people of Native American heritage and to rebuild their communities, their educational institutions, and the provision of healthcare, especially for the children. To this end, the United States Centers for Disease Control and Prevention (CDC) is working with relevant agencies to foster cooperation and promote good health [20].

In her project, Jordyn Gunville, MPH, from the Center for American Indian Community Health, Department of Family Medicine, at the University of Kansas Medical Center, focused on the high infant mortality rate among the American Indian population, which is nearly four times that for white infants. She examined the role of education and health literacy in promoting a healthy attitude towards pregnancy and prenatal care in not only reducing infant

mortality, but also in cultivating a healthier approach to childbearing and childrearing. She makes a very persuasive argument that a focus on literacy and health literacy are crucial to improving awareness of health for the mother, for the child and for the community and for the society at large. The long-term outlook for this approach lies in a positive trans-generational impetus to improved health, improved education, and improved family, community, and societal stability. The next step in the process is to develop strategies to raise awareness in promoting policies and implement practices that will reduce infant mortality and measurably improve child health and education. This student has demonstrated that promoting literacy and health literacy brings substantial benefit in the promise of breaking the cycle of health disparities, particularly for this population.

Barriers and Opportunities for Young Caregivers to Provide Nurturing Care in Low Income Communities in Paraguay

Although we have previously had student projects from Central and South American countries, including Chile, Mexico and Brazil, this is the first from Paraguay. The population profiles of each of the Latin American countries is unique, yet there are themes and patterns common to all [21]. Prior to the European invasion, as in North America, the lands were populated by native tribes, communities with political and economic powers, including great civilizations and empires. The European settlers and conquistadors overpowered and overwhelmed the local peoples with wars, and subjugated them with oppressive policies. At times, there were conflicts and even battles and wars between neighboring countries. Over time, each of the Latin American countries has undergone political changes and upheavals as well as political convulsions and revolutions, cycling through various forms of government, including dictatorships, until eventually settling, for the most part in the 21st century, into relative democracies. The reality in many Latin American Countries is the wide gap between the rich and the poor as measured by the Gini index [22], which is an international measure of economic inequality in a particular country. The lower the score, the more equitable the income distribution. Few regions in the world are as unequal as Latin America [23]. Out of the 20 countries worldwide when measuring high income inequality on the Gini Index, eight are Latin American while the rest are in Sub-Saharan Africa. On a positive note, Latin America is a region to have made the most progress in attenuating wage inequality since the turn of the century, lowering its Gini index by 6 points from 2002 to 2013.

In her project, Jimena Vallejos MPA, studying at Columbia University School of International and Public Affairs in New York, focused on early childhood development and examined child rearing practices in poor neighborhoods in Paraguay using the WHO/UNICEF/World Bank document entitled *Nurturing Care for Early Childhood Development: A Framework for Helping Children Survive and Thrive to Transform Health and Human Potential* [24]. In her project, she interviewed families and catalogued their knowledge, child rearing practices, and the challenges they face.

She also listed the various agencies and policies that have been developed in response to the situation in Paraguay, and made some specific recommendations of her own, most importantly to focus on the families, strengthen the services, monitor progress and keep track

with data to validate the outcomes. This is another strong example of a student project making a difference and offering practical strategies to break the cycle.

Breaking the Cycle of Childhood Adversity through Pediatric Primary Care Screening and Interventions: A Pilot Study

Although the association between chronic disorders and illnesses in adults with early childhood traumas has been documented, it was not until a large study of almost 10,000 subjects from a large health maintenance organization (HMO) in collaboration with the Centers for Disease Control and Prevention (CDC) was published in 1998, that the codification of Adverse Childhood Experiences (ACEs) was clearly linked to adverse health outcomes in adulthood [25].

This study linked a set of 10 ACEs in childhood categorized as reflecting abuse, neglect or household dysfunction and characterized as physical, emotion and sexual abuse or physical and emotional neglect; household dysfunction include mental illness, substance abuse, domestic violence, family disruption, or a family member who is incarcerated. The physical and physiological adverse health outcomes they identified were, metabolic disorders such as obesity and diabetes, cardiac disorders and stroke, chronic lung disease, as well as increased likelihood of broken bones and cancer, all reducing life expectancy. They also had an increased likelihood of patterns of substance abuse, with addictions to tobacco, alcohol, eating, sex, and to drugs such as opioids, all with consequent risks of early death. They also identified a greater likelihood of depression with increased risk for suicide attempts and successes. Furthermore, the patterns of mental and physical disorders make it less likely that they would hold a steady job, resulting in reduced income and increased likelihood of dependence on public welfare. In all, not only did ACEs lead to adverse health, behavioral and social outcomes aggravating the stress on the individual and family, but also on the community and society at large.

Furthermore, the study found a positive correlation between the number of ACEs and the number and severity of adverse health outcomes, especially with those who experienced four or more ACEs compared to those who had experienced none. For example, they found 4- to 12-fold increased risk for alcoholism, drug abuse, depression, and suicide attempt; a 2-to 4-fold increases in smoking, poor self-rated health, having more than 50 sexual intercourse partners, and sexually transmitted disease; as well as a 1.4- to 1.6-fold increase in physical inactivity and severe obesity. The intergenerational consequences are likewise profoundly disturbing – see the cycle of health disparities (see Figure 1).

At the 12th annual Break the Cycle program, there was a symposium on resilience during which one of the presenters, a woman who had a high childhood ACEs score, spoke about her childhood and resultant physical, emotional and social disorders of her adulthood, and how she overcame them to find a job at the CDC working the field of ACEs [14]. The lessons from her life story illustrate how people can overcome ACEs and develop resilience to become successful, functioning and healthy adults.

Importantly, the project by Cristian Quizhpi, MD, a pediatric resident in the Department of Pediatrics at East Tennessee State University, looks at how ACEs and their consequences can be identified at an early age through screening and intervention in primary care pediatric

settings and strategies can be developed to increase the likelihood that the children being seen in infancy and childhood will escape ACEs and grow up will become healthy, competent, functioning and independent adults who make positive contributions to society.



Figure 2. The CDC ACE pyramid [26].

Educating Clinic Stakeholders to Enhance Early Learning Environments through Pediatric Well-Child Visits

The human brain enables sophisticated levels of cognitive and intellectual function, especially with communication and socialization. Most of brain development in the proliferation of numbers of cells, in migration of neurons to their place in the cerebral cortex and with the formation of a network of connections between the neurons, occurs before birth. After birth, the major factor in brain development is in the myelination process, which contributes to brain growth in size as well as physiologically enhancing the speed of neural transmissions facilitating thinking processes and helping to provide the increasing physical, cognitive and social abilities that will serve as a basis for independent functional and social living. The next critical element in brain growth and development is in utilizing the infrastructural elements of the brain in the process of building competence, confidence and independence through enhancing neural connections and networks. While much of the brain development is genetically determined, there are powerful environmental forces at play, prenatally as well as postnatally, that influence all aspects of brain development, especially in the development of neuronal connections directly or indirectly through epigenetic mechanisms [27].

It is during these first three critical years of brain development when environmental factors play the largest role in brain development in positive as well as negative ways. Just as

adverse childhood experiences have a profound negative effect on brain structure and function, positive influences such as maternal-infant bonding, intense mother-child interaction, parental communication around the child and with the child, and reading to the child frequently, have a positive effect on the child though the positive effect on brain function, resulting in greater chances of maturation, independence and success in life [28].

In their project, Cori Walker, a medical student at the University of Chicago, and Asher Liu, a high school student, partnered to raise awareness in pediatric offices of the importance of promoting parent-child interaction towards improving the child's experience of language and promote enhanced language development. This project was supported in part by the Thirty Million Words (TMW) program, which has as its premise that children from high income families will hear 45 million words by three years of age, while the three year-old of a low income or welfare family will only hear about 13 million words, a gap of about 30 million words [29]. The goal of the TMW program is to reduce that gap, and the project by these two students demonstrated that a primary care pediatric office is a good place to start, with the encouragement of stimulation of infant speech development. Similar programs like "Reach Out and Read" also focus on primary care pediatric offices to promote reading among low income children [30]. Each effort at increasing literacy for children, in encouraging children to read and communicate effectively, plays a part in increasing the promise of success in life, thereby contributing towards breaking the cycle of children's environmental health disparities.

Engaging Parents of Children with Autism Spectrum Disorder to Identify Urban and Rural Health Disparities and Factors Related to Delayed Diagnosis and Treatment and Autism Disparities: Structural and Institutional Barriers

Autism spectrum disorder (ASD) is the current term used to diagnose children who have a neurodevelopmental disorder characterized by delays and unusual patterns of speech and language development, and unusual patterns of communication interaction and socialization, along with a need for sameness, with obsessions or repetitive behaviors. An ASD diagnosis manifests in a large range of differences in complexity and severity of the symptoms – hence the use of word "spectrum" in the diagnostic label.

The diagnosis has evolved since the first description in 1943 by Leo Kanner (1894-1981) of infantile autism [31], then, over decades, the less dramatic expressions became characterized as pervasive developmental disorder of childhood, through the inclusion of Asperger syndrome describing children who were verbal and intelligent, sometimes extraordinarily intelligent, often with a singular focus of interest. Interestingly, Hans Asperger (1906-1980) wrote his paper in 1944 [32], but because it was written in German, it only came to clinical attention in the USA after it had been translated into English in the late 1980s [33]. Over the course of the decades since the original description by Kanner in 1943, almost 80 years ago, the number of children who have been diagnosed has grown from one 1 in 10,000 in the early decades to 1 in 150 in the CDC report of 2002, to 1 in 59 in the CDC report of 2018 [34]. Part of the increase in prevalence is certainly the expansion of the diagnostic umbrella, but there may well be a real increase in prevalence, likely related to genetic and

epigenetic factors precipitated by the profusion of chemicals in our environment [35, 36]. Be that as it may, it is critically important to make an early diagnosis and institute therapy as soon as possible, to improve functional outcome and reduce complications [37].

Two student projects this year looked at disparities for children with ASD with delays in diagnosis and limited initiation of therapy related to type of insurance coverage and to geographic location. Alice Hong, a student at Georgia Institute of Technology, School of History and Sociology in Atlanta, Georgia, looked at low-income minority families, often in a single parent household, on public health insurance. Amy Blumling, a student at Emory University Nell Hodgson Woodruff School of Nursing, looked at low income rural populations. In both cases, there were delays in diagnosis and difficulty in accessing necessary services. In both projects, students' methodology reviewed the demographics and other characteristics, but explored individual circumstances of the families, providing not only the statistical information on the situation but delving into the personal and real-life challenges and emotions, as well as coping styles of the families. Both provided a rich insight into the lives of these two groups of families and communities and generated a sympathetic set of recommendations and strategies to reduce these disparities. Since the situation is not uncommon in lower income, often minority, families, a Break the Cycle of Autism Disparities Program was started, which promises a systemic look at how to improve the access to timely diagnosis and appropriate therapies [38].

Water Infrastructure and Childhood Blood Lead Levels: Characterizing the Effects of Exclusion from Municipal Services in Wake County, North Carolina, USA

Water is an essential part of life and access to clean drinking water is at the core of the Sustainable Development Goal #6 of "clean accessible water for all." A driving force of the goal is a call for "increased investment in management of freshwater ecosystems and sanitation facilities on a local level in several developing countries" [39]. In the US, there is substantial pollution of many bodies of water, most notably in the Great Lakes, which was, in the early 1970's, the impetus for the Clean Water Act [40].

Allison C Clonch, a Public Health student at the Gillings School of Global Public Health at the University of North Carolina, Chapel Hill, demonstrated the presence of increased lead in well water in poor African American neighborhoods in North Carolina. Lead is toxic to children and often causes brain damage, placing the children at a disadvantage academically and socially thereby contributing to the cycle of environmental health disparities [41]. The families in these communities use well water because their districts have been excluded from municipal water supply. This is the 2nd project from this academic center looking at the impact of this discriminatory practice in not providing municipal water to a community, thereby putting children at significant risk for the immediate and long-term adverse health outcomes of lower quality than that of the municipal water [42]. Raising awareness of this situation is the first step in breaking the cycle. The next step is to change the situation by restructuring the water supply. The student appropriately asks for "more regulatory oversight and water quality tests of private water systems or facilitating access to municipal supplies in order to mitigate the impacts associated with childhood lead exposure."

Self-Reported Neighborhood Quality and Children's Depression Symptoms in a Gentrifying Northern Manhattan

Gentrification refers to the process of change taking place in an older, low income, often minority and most-likely degraded neighborhood, when relatively wealthier residents and businesses move into the neighborhood because of the lower rent and opportunity to build, restructure and grow [43]. The initial influx is gradual but over the course of time, the trickle becomes a flow and at some point, the neighborhood is transformed from the old, often dilapidated and neglected character, to a modern, often creative one, with desirable amenities such as restaurants and boutiques that attract new, more affluent residents and visitors. Often a large chain business will anchor in the neighborhood, offering the local residents access to more amenities and products with further income generation for the area making it more affluent and desirable for the residents. For those moving into the neighborhoods it is exciting and promising, and for the business it can be lucrative, but for the long-term residents for whom the neighborhood has long been home, and the community a source of support and identity, the change may not be positive and can be disruptive.

The anthropologic history of cities and neighborhoods is one of flux. Cities were often established based on access to transportation routes, or near a sizable waterway for water supply and transportation. As cities grew and flourished, they often became overcrowded and required some strategy to deal with the growth. In the US, as in other parts of the world, the arrival of the automobile altered the patterns of urban living dramatically. When transportation was limited to pedestrian or horse driven vehicles, proximity to the necessities of day-to-day life was a critical determinant of residential location. However, with the advent and increasing availability of the automobile, proximity became less important because people could live some distance from the city and drive to work. Thus, began the suburbanization of society. The migration of people with financial means to purchase homes and cars to the suburbs led to dramatic suburban growth. The resulting vacant urban residential areas provided an opportunity for people of lower income to settle and find work for themselves, schools for their children, and communities of people like themselves to provide the social and emotional support necessary for health and stability [44]. Unfortunately, over time, inner cities became concentrated with low income families and communities, while their more affluent counterparts were living in the suburbs. This situation became informally institutionalized, if not codified and calcified over the course of the early second half of the 20th century [45]. Then, towards the end of the 20th Century, for a variety of social and economic factors, younger people with means began to move back to the cities and started the trend of gentrification, which continues today in many large cities in the US [43].

In her project, Teresa Durham, at the Columbia Center for Children's Environmental Health, Columbia University in New York City, examined the impact on the health and well-being of children in the rapidly gentrifying neighborhoods in Northern Manhattan. The Columbia Center has been working in this neighborhood for many years, tracking the children and families, and has collected data on the impact of gentrification on the community in Northern Manhattan, which their students are now mining. A prior student from the Center who had participated in the Break the Cycle program looked at the impact on children's health focusing on children's nutritional status [46]. In her work, Ms. Dunham focused on the

mental health of the children, particularly anxiety and depression. She found that although anxiety was a common symptom, it was not greater than the baseline level of anxiety of children in the neighborhood under stress. She did, however, find a level of depression greater than baseline among the children. Of interest, her results revealed that the children who exhibited the symptoms of depression were those whose mothers rated their total neighborhood quality as being more stressful over a six-year time period than the children of mothers who reported their neighborhood to be less stressful. This study helps us to recognize the importance of understanding the experience of stress and its manifestation in anxiety and depression in children, and the management of stress as important in promoting health for the children. It is also helpful in determining interventions for the children and their families when a neighborhood is undergoing such dramatic upheaval and the anticipation of a possible move from the familiar and comfortable home and neighborhood environment, to an unknown destination. The question to be asked is whether the measure of stress reported by some of the mothers was a valid reflection of overall neighborhood stress, or the stress was personal and was associated with other factors within the family in terms of coping mechanisms and resilience, which could then affect her children. In addition, communities must consider their collective and individual responsibilities to be aware of the impact of gentrification on children's health and development and to help prevent the inevitable associated health impacts, such as anxiety and depression [47].

The Impact of Childhood Exercise and Socioeconomic Status on Coping Strategies and Resilience in College Students

It is well recognized that children from lower socioeconomic circumstances are less likely to attend college and, if they do, they are less likely to graduate and less likely to attend a post-secondary school of higher education. The statistics are difficult to refute and extremely sobering – see the Figure 3 below [48].

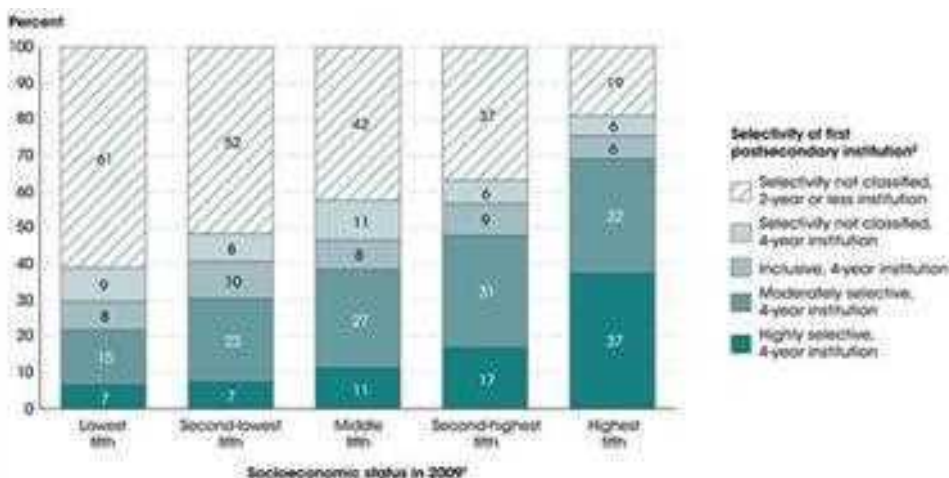


Figure 3. Among 2009 ninth-graders who had enrolled in postsecondary education by 2016, percentage distribution of selectivity of students' first postsecondary institution, by socioeconomic status [48].

Among several reasons given for this phenomenon, one pragmatic reason is that primary education is not as effective or at a level of similar quality in poorer neighborhoods, where the children and their families have less financial resources and the children may need to work to sustain income and pay for college. Other reasons relate to a 'sense of self' or self-esteem and appreciation of one's capability and potential.

In her project, Leah Postilnik, BSN, a student at the College of Nursing, University of Massachusetts, examined the role of exercise and physical activity as a factor in shaping resilience in those students from communities of lower socioeconomic status (SES). Although there are fewer students from lower SES communities who attend college, and, of those who do attend, a significant number who do not complete their courses, there are students with a background of low-SES who do attend college and university and who do thrive and succeed. Students from low-SES background who do succeed do so because of an ability to overcome adversity through resilience. The factors that determine resilience may be genetic and inherent in the personality of the individual, but include environmental and experiential elements as well, most significantly is the presence in their lives of a caring, supportive encouraging, and committed adult, be it a parent, grandparent, other relative, teacher or parent figure in their communities [14]. In addition, social networks of support, positive role models, a good education, intellectual stimulation, self-discipline and positive, physical exercise also contribute significantly to the development of resilience. Ms. Postilnik examined the role of exercise in promoting and reflecting resilience and academic achievement, and found a positive correlation between resilience and exercise frequency. When controlling for other variables, college exercise was the only variable shown to predict resilience, and middle school exercise predicted high school and college exercise. Implications of these results suggest the need for interventions to increase exercise for children from low SES environments, establish exercise habits early in childhood, and use exercise as a tool to promote resilience. Exercise may not be the sole factor, but is a strong and positive force in promoting physical, mental, emotional and social health, which in turn promotes self-esteem and a positive approach to life and its challenges and break the cycle of health disparities.

Health Literacy in Pediatric Onset Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a complex autoimmune disorder. It can affect many organ systems in the body as well as the brain, manifesting in psychiatric disorders. In more severe expressions of the condition, it can result in organ system failure, particularly renal. In all, SLE causes much physical and mental suffering and can shorten life expectancy. Because it affects many organ systems, the person with SLE is likely to need the expertise of a variety of different medical specialists as well as therapists and more often than not, require multiple medications.

This lifestyle of multiple physician and therapy visits, that consume significant hours in any day in travel and waiting in addition to the specific clinic visits, can be physically and emotionally stressful and draining of energy and time for education, recreation and socialization. The combination of the impact of the disease process and the stresses associated with the condition and its management, compound the situation. On a positive note, much research has been done to understand and manage the condition, reducing the likelihood of

complications and mitigating severity. Further, in recognition of the need for close monitoring of the condition and continuity of care, multidisciplinary clinics and centers have been established where people with lupus can go to get their necessary practical help and support that is configured to provide comprehensive, coordinated care to people with lupus, to monitor their progress, assure optimal care, and deliver as good physical, emotional and social health outcomes as possible for each individual.

Catherine Park, MD, a Fellow in the Department of Pediatrics, Division of Nephrology at Emory University School of Medicine, where she serves children with lupus, compared the clinical profiles of children from poor circumstances to those from more affluent backgrounds, and found that the poorer children were more likely to be diagnosed later than their more affluent counterparts, were more likely to be exposed to second hand tobacco smoke (which is known to aggravate the clinical condition), and tended to have more serious complications with more emergency department visits. She administered health literacy tests to the children, and found that the children from the low SES group had lower numeracy literacy than their more affluent counterparts. She postulated that the lower numeracy literacy possibly contributed to their increased rate of medical complications, because of their limited ability to accurately read the instructions on their often multiple bottles of medication, as well as to read the details on food labels. Although her sample size was small, the findings were significant, and reflect the importance of literacy and health literacy. In addition, this speaks to the critical importance of a good education for children, particularly for children from low SES background, with emphasis on fundamental skills such as reading and math, which better prepares them for life and its challenges, and helps them lead healthier lives and break the cycle of health disparities.

Although it is not addressed in this paper, the issue of cost of care and insurance reimbursement with Medicaid is a significant factor in the care of SLE. The condition is often complex and requires frequent, and expensive, specialized medical attention, with multiple medications and increase in emergency department visits, not to mention the incidental costs of transportation and lost hours at school or work for parents. While these costs may be reasonably borne by more affluent families with private health insurance, they are more likely to be burdensome for lower SES families and may seriously affect their livelihood. Fortunately, there is a safety net in publicly funded medical insurance through Medicaid, which helps to secure the necessary medical care, but not necessarily the incidental and collateral costs.

Did Medicaid Expansion Decrease Disparities for Receipt of Preventive Medical Care among Vulnerable Children?

In 14 years of Break the Cycle programs, this is the first student project that examines children's health insurance as a factor in breaking the cycle of children's environmental health disparities. In US society, where access to health care is dependent on the cost of health care and reimbursement to the providers of healthcare, the ability of a family to pay for the care becomes a powerful determinant in access to, and provision of healthcare, be it episodic, routine or long term. In the US, private health insurance is a critical resource to secure necessary healthcare. Families who can afford the cost of insurance premiums have

relatively easier access to quality healthcare. For low income families who do not receive assistance in covering the cost of health insurance premiums, there is Medicaid. Medicaid in the US is a federal and state program that helps cover medical costs for some people with limited income and resources.

The history of American society and government in developing and providing public health insurance through Medicaid, has evolved over the past half century from the establishment of health insurance for the elderly though Medicare established in 1965, based as a policy framework on the social Security Act of 1935. Over the decades, the benefits have been extended to an increasing list of vulnerable populations through the Home and Community Based Services (HCBS) Medicaid waiver programs, and more recently, the Children's Health Insurance Program (CHIP). The most recent evolutionary component of the Medicaid program has been the Affordable Care Act (ACA) of 2010, which expanded the services further (see Figure 4 for details on the evolution of Medicaid services). Of note is that the Medicaid program is a Federal-State partnership, and not all states in the US opted into the ACA.

In her project on whether Medicaid expansion resulted in improved healthcare to vulnerable children, Patricia Daniel, PhD, from the Center for Leadership in Disability, at Georgia State University in Atlanta, Georgia, compared data from those states that opted into the ACA and those that did not. Data suggest that Medicaid does contribute to improvement in health of the populations it serves, and Dr. Daniel was able to demonstrate this in her study. At the time of this writing, national political debate is examining the pros and cons of further Medicaid expansion, with some suggesting a universal coverage model similar to a number of Western European nations and Canada or complete abandonment of the ACA. Whatever the outcome of the debate, the important fact is that Medicaid covers one in five people in the US and is the main sources of coverage and access to healthcare for vulnerable populations. This is especially true for children, the elderly population, people with disabilities, as well as people with low or no income, who cannot afford private insurance; as such, it has been and continues to be of great benefit not only to the individuals and families served, but also to society at large [49].

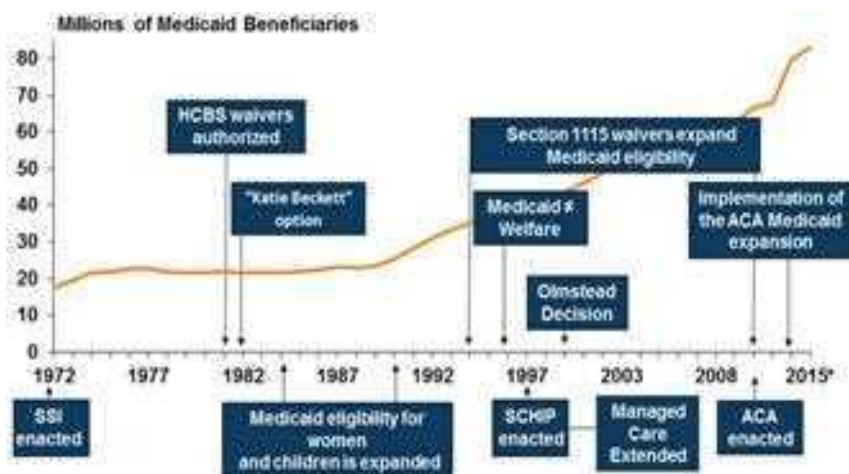


Figure 4. Medicaid has evolved over time 1972-2015 [49].

CONCLUSION

As with our previous Break the Cycle programs, each student had identified a different component of the Cycle of Children's Environmental Health Disparities and highlighted the way in which the cycle can be broken at that point and the health of vulnerable children can be improved. In the process, the students benefited from creatively developing a project, translating it into action, performing the research, presenting the results of their projects at a national conference and now writing manuscripts for publication in this publication. In addition, their mentors, as well as their peers and we, the Break the Cycle Faculty, have also learned and benefitted from this collective experience. Furthermore, our society gains by their work in the present, and will undoubtedly gain in the future when this cohort of students become our leaders.

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Chapter 333

NATURAL DISASTERS AND VULNERABLE POPULATIONS: A COMMENTARY

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ABSTRACT

Every year natural disasters kill around 90,000 people and impact close to 160 million people worldwide. Natural disasters include earthquakes, tsunamis, volcanic eruptions, landslides, tornadoes, hurricanes, floods, wildfires, heat waves and droughts. When a disaster strikes, it has an immediate impact on the physical, biological and social environment with the destruction of property and disruption of human lives. Although a disaster is indiscriminate in whom it affects, poor and medically underserved people, minorities, people with chronic medical problems or disabilities, particularly children and the elderly, bear an unequal burden of the impact. During the initial surge, the health care

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system is immediately overwhelmed with injuries and acute illness needs, resulting in a sudden and dramatic increase in demand for emergency medical services. Following the initial surge, there are long-term consequences of disasters on the population as well as on the natural environment and the built environment, that have economic, social and political implications on health and wellbeing on individuals, their families, communities and societies. We will explore strategies to prepare for and to minimize the impact of the disasters, particularly on vulnerable populations, and advocate to reduce global warming which contributes significantly to the frequency and intensity of natural disasters.

INTRODUCTION

In this commentary we will present an overview of natural disasters and their consequences, and offer examples that serve to illustrate how different countries and different regions, as well as different populations and communities within a country, suffer disproportionately from the disasters. We will offer strategies in responding to disasters as well as disaster preparedness in order to mitigate the effects of the disasters on human populations, particularly the most vulnerable. In this context we will explore strategies to promote resilience for individuals and for systems to deal with the anticipation of disasters and for positive and constructive responses following the event. We will also address the role of climate change in the frequency and intensity of the natural disasters.

DISASTERS

A natural disaster is an act of nature of such magnitude as to create a catastrophic situation in which the day-to-day patterns of life are suddenly disrupted and people are plunged into helplessness and suffering, as a result, there is a need for medical and nursing care, food, clothing, shelter, and protection against unfavorable environmental factors and social conditions. The impact of the disaster takes a toll on the affected population with an increase in death rate, and with acute injuries and health impacts, as well as long-term physical, emotional and financial consequences for the affected individuals, families, communities and society at large. Every year natural disasters kill around 90,000 people and affect close to 160 million people worldwide [1].

Disasters are divided into two categories:

- *Natural disasters:*
 - Geophysical phenomena such as earthquakes, tsunamis, and volcanos,
 - Climatological/Meteorological conditions such as tornadoes, hurricanes, floods, and wildfires, as well as extreme weather events such as blizzards, droughts, and heat waves
- *Technological disasters* occur as a result of structural failures, such as factory explosions, fires, chemical spills, industrial accidents, transportation accidents, and nuclear accidents, as well as acts of terrorism and civil disturbances, with associated humanitarian refugee crises.

In this commentary we will focus on natural disasters although, as will be seen, there are often associated technological elements that complicate and aggravate the impact of the natural disasters. For the geophysical disasters, we will focus on Tsunamis and Earthquakes and for the climatological or meteorological disasters, we will focus mainly on hurricanes.

PREVALENCE AND CONSEQUENCES

In 1988, WHO established the Center for Research on Epidemiology of Disasters (CRED) to maintain an Emergency Events Database (EM-DAT) of disasters, with the objective of informing humanitarian action at national and international levels in order to improve rational decision-making in disaster preparedness, and provide objective data for assessing communities' needs [2].

In order to be recorded as a natural disaster in EM-DAT, an event must meet at least one of the following criteria:

- Ten or more people reported killed
- 100 or more people reported affected
- Declaration of a state of emergency or
- Call for international assistance.

While EM-DAT is the most comprehensive disaster database available worldwide, there may be some underreporting from certain regions such as from Africa. Be that as it may, the database reported that between 1994 and 2013 there were 6,873 disasters, which claimed a total of 1.35 million lives, with an average of 218 million people affected per year, during that 20-year period. Although earthquakes were the deadliest type of disaster accounting for 45% of deaths, flooding affected the highest number of people, accounting for 50% of the total affected [3].

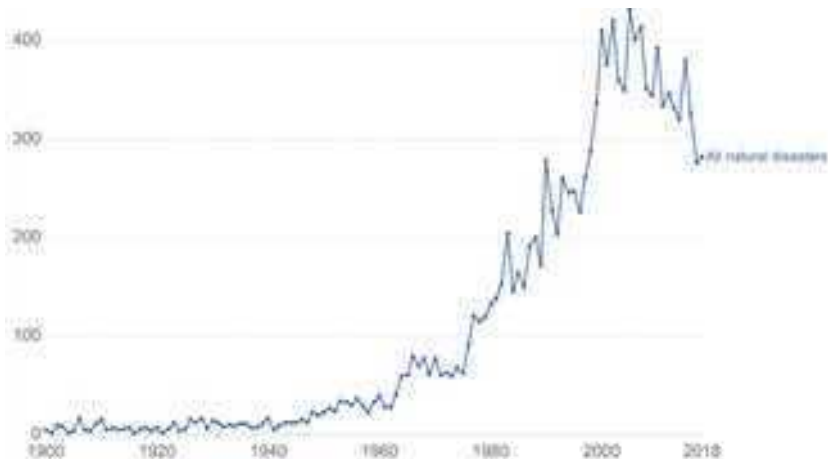


Figure 1. Number of worldwide natural disaster events recorded between 1900 and 2018 [3].

Figure 1 represents the number of disasters per year from 1900-2018 showing the dramatic increase in natural disasters over the past 50 years [3]. This increase in rate and intensity of natural disasters is directly linked to climate change and global warming [4].

Furthermore, there are some areas of the world where particular disasters are more common, for example, along geophysical fault lines such as the Ring of Fire, which is responsible for more than 90% of the world's earthquakes [5]. The concerns around flooding are particularly in low-lying coastal cities such as occurred in New Orleans with Hurricane Katrina [6]. Some areas of the world are so densely populated that a disaster can take its toll on a larger number of people. Other vulnerable populations live in cities and countries considered poor, with limited financial resources and infrastructural services to prepare or manage the disasters. Members of all communities who are particularly vulnerable are children, older people, those with disabilities or chronic medical conditions, as well as minority populations [7].

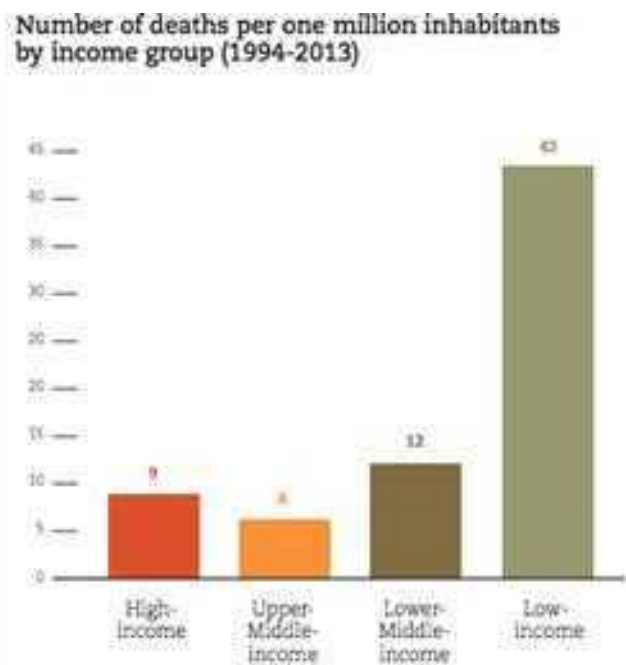


Figure 2. Death rates from disasters in countries with different income levels [8].

Of note is that although the death rates from natural disasters has dropped dramatically because of disaster preparedness strategies, the highest rates of death occur in the poorest populations [3, 8]. Figure 2 shows that the death rates for the low-income countries is substantially greater than for the high and middle-income countries. On average, more than three times the number of people died per disaster in low-income countries than in high-income countries, with 332 deaths for the poorest countries versus 105 deaths on average in the richest countries [8].

COST OF NATURAL DISASTERS

Not only do natural disasters cause much destruction to the natural and built environment with loss of lives and associated physical, emotional and societal disruption, but they come with an economic impact as well. Disasters are very costly – they cause much damage, displace many people and require repairs and restorations to the built environment and community infrastructure, as well as the rebuilding of people's lives and livelihoods. Every year the National Oceanic and Atmospheric Administration of the USA (NOAA) compiles a list of natural disasters around the world that cost a billion dollars or more [9]. The NOAA reports that in 2017, the U.S. experienced a historic year of weather and climate disasters with a total of 16 separate billion-dollar disaster events including: three tropical cyclones, eight severe storms, two inland floods, a crop freeze, drought and wildfire (see Figure 3), with a cumulative cost of over \$300 billion [9].



Figure 3. Natural Disasters in the US in 2017 that cost more than \$1 billion each [9].

GEOPHYSICAL DISASTERS

Tsunamis [10]

The Indian Ocean tsunami of 2004 was a consequence of an undersea earthquake with a magnitude of 9.1 that struck the coast of the Indonesian island of Sumatra devastating coastal areas as far away as East Africa. Some locations reported that the waves had reached a height of 30 feet or more when they hit the shoreline [11]. This tsunami caused massive damage and resulted in more than 225,000 deaths across twelve nations. The lack of food, clean water, and medical treatment, combined with the enormous task faced by relief workers trying to get

supplies into some remote areas where roads had been destroyed or where civil war raged, added to the numbers of casualties. Long-term environmental damage was severe, with villages, tourist resorts, farmland, and fishing grounds demolished or inundated with salt water, debris, and bodies. Displacement and damage to infrastructure are important contributors to the human, social, and economic toll of tsunamis. The damage took a long time to repair and cost billions, but psychological scars remain.

The tsunami that hit Japan in 2011 was the consequence of an earthquake with a magnitude of 9.0 located some 80 miles east of the city of Sendai [12]. It was not as fatal and the Indian Ocean tsunami of 2004, because of the limited impact and lower population density, with an estimated 28,000 deaths (just over 10% of the toll in the 2004 tsunami). While there was much structural damage to buildings, the greatest concern was the damage to the Fukushima Daiichi nuclear power plant, which resulted in the release of ionizing radiation into the air, the soil and the water characterizing it as a Technological Disaster as well, with unexpected and cumulative consequences. The severity level of the nuclear emergency at the Fukushima Daiichi facility was estimated to be from 5 to 7 – the highest level on the scale created by the International Atomic Energy Agency – placing the Fukushima accident in the same category as the Chernobyl accident, which had occurred in the Soviet Union in 1986. The repair and recovery of the plant was expected to take about 10 years, but the fallout is expected to last decades. The impacts on humans physically, emotionally and socially are concerning with increase in mortality among vulnerable populations [13].

Earthquakes [14]

The impact on the built environment and on humans from earthquakes is related not only to the intensity, as measured on the Richter Scale, but also has as much to do with the location of the epicenter and its proximity to population centers, as well as the infrastructure of the built environment. We will examine earthquakes in 2 countries in the same year – approximately 1 month apart from each other that serve as a contrast of the consequences in the 2 countries.

Haiti 2010

On January 12, 2010, Haiti was hit by a magnitude of 7.0 earthquake centered about 15 miles southwest of the Haitian capital of Port-au-Prince with a sizable number of aftershocks [15]. As a result of the location close to the densely populated capital, as well as vulnerable architectural infrastructure, the devastation was great. Furthermore, being a poor country with limited governmental infrastructure, the country was ill-equipped to deal with such a disaster [16]. Buildings collapsed because of lack of building codes, killing or trapping their occupants. Attempts to deal with the disaster by local citizens and organizations, as well as international agencies, including the United Nations, were hampered in their attempts to rescue people who were trapped, and were limited in their ability to provide medical care, food and water because the roads were destroyed or blocked with debris, which further

compromised the already limited transportation services. In addition, the failure of the electric power system and loss of communication lines, seriously limited traditional communication services. As a result of this rather chaotic situation, aid was delayed, and more people suffered and died. On a positive note, the country's computer network was functional, and electronic media emerged as a useful mode for coordinating relief efforts and for connecting family members separated by the quake.

An estimated three million people were affected by the quake—nearly one-third of the country's total population, and an estimated 250,000 people died. Over one million people were left homeless in the immediate aftermath and had to live in tent camps with extremely limited resources. Due to major devastation and disruption of civil society, the physical and mental health needs for children were dire [17]. Infectious diseases were a major cause of morbidity and mortality in children as well traumatic injuries and malnutrition. Children also suffered abuse and violence with symptoms of posttraumatic stress disorder (PTSD), peritraumatic stress, depression, anxiety, and food insecurity [18]. Of particular concern was the situation of children who had lost their parents and were left vulnerable to abuse and human trafficking. Fortunately, many were adopted by families in other countries, particularly in the United States.

To add insult to injury there was an outbreak of cholera, which was apparently brought to Haiti by members of the UN Peacekeeping Force and, with the cramped and unhygienic living circumstances and lack of adequate healthcare, 283,362 cases of cholera had been reported to the national cholera surveillance system, including 152,816 hospitalizations and 4,856 deaths [19].

The sad reality of this disaster is that it was a massive earthquake that devastated one of the poorest countries in the world and, because of the lack of infrastructure at so many levels, even the best efforts of local and international organizations and agencies were unable to effectively manage the situation. This resulted in a high morbidity and mortality with infrastructural impacts that have residual consequences. At 5 years post-disaster, thousands of people remained displaced and to date, now 10 years later, the people of Haiti are still struggling to recover [20].

Chile 2010

One month after the earthquake in Haiti, on February 27, 2010, there was a magnitude-8.8 earthquake off the coast of south-central Chile, causing widespread damage on land and initiating a tsunami that devastated some coastal areas of the country [21]. Although this earthquake was of a much greater magnitude than the one in Haiti, and was associated with a tsunami, the epicenter was about 200 miles southwest of the city and so the impact on the city and its inhabitants was not as devastating. In addition, in stark contrast to the earthquake in Haiti, Chile had experienced previous earthquakes, which prompted the government to institute stringent building codes that significantly limited the damage to buildings. Furthermore, the infrastructure and financial resources of Chile were substantial enough to mobilize more than 10,000 troops to the devastated areas to direct recovery operations and maintain law and order. The Chilean government officials estimated that two million people

had been directly affected by the quake and that the earthquake and tsunami resulted in about 500 deaths, in contrast to the number of people affected and the deaths in Haiti [22].

Although the situation was far from perfect and the Chilean Government requested aid from the UN and the US, recovery efforts resulted in a relatively effective return close to previous functioning status by about the middle of 2014. Furthermore, precautions taken in the wake of the 2010 catastrophe were credited with saving lives during a magnitude-8.2 quake and tsunami that occurred in the northern part of Chile in April 2014 and in the September 2015 earthquake off the coast of Illapel. Not only did the people of Chile focus on the practical approach to disasters, they also examined the psychological impact and approaches to ameliorating associated emotional stresses [23].

METEOROLOGICAL DISASTERS

Tornadoes

Tornadoes are violently rotating columns of air extending from the base of a thunderstorm down to the ground and are capable of completely destroying well-made structures, uprooting trees, and hurling objects through the air like deadly missiles. They can occur anywhere, at any time of the day or year but most commonly in the Central Plains and the southeastern US. If there is warning of a tornado, it is advisable to seek shelter with attention focused on the safest place within home [24]. However, people living in mobile home are uniquely vulnerable. Although some mobile parks have shelters, this is not common. Because of the short time interval between the warning and the landfall, the effectiveness and functionality of local warning sirens and alert systems are paramount. However, these systems do not always reach everyone at risk, either because of inadequate design or malfunction, leaving residents at risk and vulnerable to the devastation the tornadoes wreak on their fragile homes, leaving them effectively homeless [25].

Heat Waves

Heat wave are periods of unusually hot weather that typically last two or more days with temperatures outside the historical averages for a given area. Over the past 5 decades, heat waves, like other natural disasters, have increased in frequency and duration. Typically, the elderly who are socially isolated and living in inner city tenements, which function as 'heat islands' [26], are at greatest risk and those with medical illnesses and taking multiple medications are even more vulnerable. Even brief daily exposure to air conditioning has been found to be effective [27], and public health practice is to establish programs to bring the elderly to air- conditioned malls or other such venues for daily opportunities to cool down [28].

Wildfires

Wildfires are any unplanned fires that burn in forests and other wildlands, such as shrub or grass communities. They can burn millions of acres of land at rapid speeds and can consume everything in their paths, and they are difficult to contain. Concerns about wildfires have increased dramatically with the sharp rise in number and severity of California wildfires (2017-19) and the dramatic events unfolding at this time of writing, in Australia (January 2020) [29]. Consequences result in burn injuries from fires, respiratory distress from the acute dramatic rises in particulate air pollutants as a result of the smoke, and the challenges in recovery for communities devastated by the fires. Vulnerable groups accordingly are low income, low resource populations who were forced to move ever further from high cost urban areas and ever closer to at-risk forests; firefighters, emergency responders, and others caught up within ever shifting flames and vulnerable to burn injuries; and individuals with pre-existing cardio-respiratory diseases such as asthma, COPD, and cardiovascular disease who are most heavily impacted by the acute rises in particulate air pollution. The CDC provides valuable information on how to prepare for and protect from wildfires [30]. However, given the unpredictable vagaries of huge forest fires, even well-to-do and very prosperous communities, such as those adjacent to Los Angeles, can also find themselves at risk, with sudden changes in wind and temperature superimposed on drought conditions. The consequences from the total annihilation of the built environment from wildfires in the losses for individuals and families are great, as are the impacts on the communities and society, financially and ecologically.

Hurricanes [31]

Hurricanes are considered the most violent storms on Earth and are called by other names, such as typhoons or cyclones, depending on where they occur (Figure 4) [32]. The scientific term for all these storms is *tropical cyclone*.

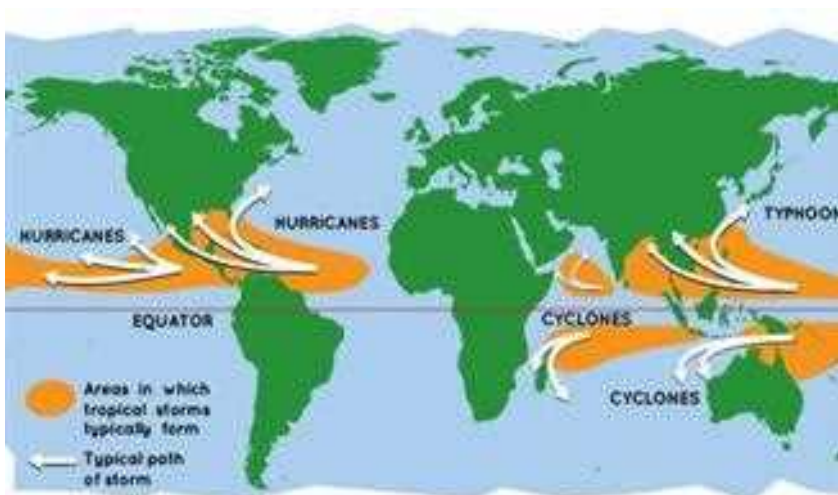


Figure 4. Illustrates the terminology of tropical cyclones depending on where they are located [32].

The classification of hurricanes depends on wind speed, which will determine the consequences on the natural and built environment and on human and animal life (see Table 1) [33].

Table 1. Hurricane categories with associated damage

• Category 1 – winds 74-95 mph - very dangerous winds will produce some damage – storm surge 4-5 feet • Category 2 – winds 96-110 mph - extremely dangerous winds will cause moderate damage– storm surge 6-8 feet • Category 3 – winds (major) 111-129 mph - extremely dangerous winds will cause extensive damage – storm surge 9-12 feet • Category 4 - winds (major) 130-156 mph - extremely dangerous winds will cause extreme damage – storm surge 13-18 feet • Category 5 – winds (major) 157 mph or higher - extremely dangerous winds will cause catastrophic damage – storm surge 19+ feet

According to the Stormfax Weather Almanac 1851-2017 there have been an average of 12 named storms per year with 6.5 per year designated as hurricanes and 2 per year that are classified as major hurricanes of categories 3-5 [34]. Of note is that in 2005, the year of Hurricane Katrina, there was a high of 28 storms, with 15 hurricanes and 7 major hurricanes. In 2017 with hurricanes Harvey, Irma and Maria there were 17 storms, 10 hurricanes and 6 major hurricanes (Figure 3).

Individuals living in flood zones and historically impacted coastal areas are obviously most vulnerable. Over the years, the national system of river levees, and the practices of sheltering and evacuation in hurricane affected coastal areas, has provided significant protection in the US, however, these systems have been coming under increasing stress in recent years, thus increasing vulnerability. At the same time, there have been additional increasing risks, which include:

- more frequent high-category hurricanes leading to greater damage and flooding, and overwhelming protective mechanisms (e.g., Hurricanes Katrina, Sandy, Maria, Harvey);
- inadequate insurance and recovery funds, leaving many with long-term vulnerabilities (e.g., Hurricane Maria in Puerto Rico);
- aging levee systems which in some cases are inadequate (e.g., Hurricane Katrina and New Orleans) or whose design is coming under increasing scrutiny because of concerns about effectiveness (e.g., Midwest and Mississippi floods, 2019), leaving increasing numbers of people at risk;
- the increasing impact of climate change.

Hurricane Katrina

With all the storms and hurricanes over the years, Hurricane Katrina stands out as the most devastating and deadliest hurricane since the Galveston hurricane of 1900, which killed

an estimated 6,000 to 12,000 people [35]. Hurricane Katrina is well recognized as both a natural and technological disaster and demonstrated graphically the triple threat burden: historic health disparities, persistent environmental health risks, and living in a disaster-prone area [36].

Katrina made landfall in southeast Louisiana on August 29, 2005, as a Category 3 hurricane and rapidly became a category 5 hurricane, with sustained winds up to 120 mph making it the third-strongest hurricane ever to affect the United States [37, 38]. The resulting storm surge produced waves that were almost three stories high along with 8 to 10 inches of rain that fell along the coast resulting in extensive flooding all along the U.S. Gulf Coast in the states of Mississippi and Louisiana. With much of New Orleans below sea level, the flooding was compounded by more than 50 breaks in levees and floodwalls which resulted in the flooding of 80% of the city. Neighborhoods were destroyed and reduced to scattered rubble. The flooding affected an estimated 77% of the population of Orleans Parish and nearly all the residents of St. Bernard Parish. To further compound matters, at least four Superfund sites in the New Orleans region were hit by the storm and the flooding also resulted in release of noxious chemicals including 575 reports of petroleum or hazardous chemicals spills that were widely distributed by the floodwaters. There were approximately 1,000 deaths from Katrina with 40% from drowning, 25% from injury and trauma and 11% from heart conditions [39].

The destruction of property and displacement of people as well as the disruption and necessary restoration of neighborhoods came at a significant human and financial cost. While the human cost is difficult to determine, the financial cost as estimated by NOAA was at \$161 billion – the highest of all hurricanes on record [40].

Although a disaster is indiscriminate, the poor and medically underserved bear an inequitable degree of the burden [41]. In Orleans Parish, the mortality rate among black Americans was 1.7 to 4 times higher than whites for all people 18 years old and older [39]. These statistics are not surprising in that thousands of low-income minority people of New Orleans, where 69% of the population is African American and 23% live below the poverty line, were living in substandard housing. These areas were totally inundated with the flood waters destroying the fragile buildings and drowning the residents who had not fled the area. Of the other vulnerable groups of people, those who were 75 years old or greater were significantly more likely to be storm victims [37-39].

There had been warnings of the impending storm urging residents of the threatened areas to evacuate to safer areas. The unfortunate reality was that many of the poorer residents of the city, particularly from the most vulnerable areas, did not respond to the warning. Several reasons are postulated. It is possible that some of the residents did not tune into the news or hear the warning because of lack of connection with media. Some may have heard the warning but did not give it credible consideration. Some have previously voiced suspicion and skepticism of the warning sources, displaying general governmental distrust or any source that may appear to be from government [42]. Others may not have had reliable sources of transportation or funds necessary to purchase transportation. Some may have been concerned about their potential loss of property or possessions. Finally, some may have been too old, too ill, or physically and mentally unable to take advantage of the opportunity to flee from a potential source of danger. Thus, the people who ultimately lost their lives, their livelihoods, their possessions, their loved ones, their health, their well-being and self-

sufficiency were those who were poor, with limited education, limited resources and limited social capital [43].

While more affluent and able citizens heeded the warnings and had sufficient presence of mind and practical resources to leave the threatened areas, thousands of those who remained were herded into the Superdome where they were destined to stay in crowded under-resourced conditions to weather the storm. First-hand reports of the conditions were harrowing with stories of lack of sufficient food, water or medical supplies, lack of sanitation resulting in garbage piling up, and lack of decorum devolving into a dystopian experience [44].

The aftermath for the survivors was dispiriting; with the destruction of homes, loss of possessions and loss of loved ones, they suffered consequences on their physical and mental health with resultant sense of despair and depression affecting children and adults alike. Furthermore, medical resources were limited because hospitals and clinics were also destroyed by the flood, thus taking years to reestablish their lives, their health, their communities, and their sense of well-being.

Another consequence of the widespread damage and destruction was a severe compromise of the public health system in the months after the storm, which, along with substandard living conditions, caused this increased mortality rate, particularly among socially vulnerable groups such as women, children, the elderly, and people with disabilities [38]. During the recovery phase there was a 47% increase in the mortality rate from January to June 2006 for the greater New Orleans area. The monthly mortality rate for this time period averaged 91.4 deaths per 100,000 persons, compared with a monthly average of 62.2 deaths per 100,000 for the years 2002–2004 [45].

Children shared many of the environmental and other ubiquitous hazards in New Orleans following the hurricane, such as widespread exposure to mold and heat, vectors, unsafe food, and poor shelter [46]. Additionally, there were many concerns that applied specifically to children, such as: the hurried mass transport of very sick neonates and children from New Orleans hospitals during the evacuation of the city; the closing of many pediatric practices in the face of the hurricane, many of which did not reopen; and the disruption of necessary pediatric practices such as newborn screening [47]. There were also some unique aspects to the mental health of children caused by the disruption and frenzied evacuation, the fragility of some of the shelters, the separation of thousands of children from their parents and caregivers, the shock of returning to destroyed or heavily damaged homes, and the limited mental health resources for returning or relocated children [48].

Thousands of Gulf Coast families displaced in 2005 by Hurricanes Katrina and Rita were victims of an unprecedented epidemic of chronic medical and mental health problems yet received little appropriate care at the time [49]. Even a year later, over half of the New Orleans population had not returned—perhaps as many as three hundred thousand people, many in FEMA-subsidized trailer parks and many in other parts of the country as climate refugees.

While many families who had fled the disaster returned to their original communities, a sizable number stayed in their new locations. They too needed to rebuild their lives and their livelihoods, settle into new school systems and to begin to belong to a community. After Hurricane Katrina, just over one-half of adults returned to the New Orleans metropolitan area, with only one-third returning to their original dwelling. Among the remainder, Texas was the leading location of displaced residents (18%), followed by other locations in Louisiana

(12%), other southern states (12%), and elsewhere in the United States (5%). Black adults were considerably more likely to be living elsewhere in Louisiana, in Texas, or other cities in the South [50, 51].

Hurricane Katrina made it evident that natural disasters occur in the same social, historical, and political environment in which disparities in health already exist (36,002042). Furthermore, the racial animosity revealed in a *Washington Post*/Kaiser Family Foundation/Harvard University poll of 680 evacuees, 93% of whom were African American, found that 68% believed the response would have been quicker for White and wealthier people and 61% said that the government does not care about “people like them”. These communities experienced social disparities in health before Katrina; their health status was linked to the toxic mix of poverty, poor housing, lack of economic opportunities, and the atmosphere of discrimination in which they lived [52].

The bottom line of the story of Hurricane Katrina and its impact, is that low income, minority people especially the elderly and young children, who live in disaster prone areas of poor neighborhoods, have existing health disparities, or are disproportionately affected by the disaster, are more severely affected by the disaster and have a greater difficulty in recovering from the disaster, if they ever do [36].

Hurricanes in the Caribbean

The vulnerability of the Caribbean islands to natural disasters can be seen in the example of the earthquake in Haiti, referred to earlier in this paper. The islands are small, generally poor and inhabited predominantly by people of African descent. Although some do have agricultural economies, they are heavily reliant on tourism for their main source of revenue. Being in the Caribbean, they are particularly vulnerable to hurricanes. In over 4 consecutive seasons, the Caribbean has experienced several Category 5 Atlantic hurricanes: Matthew (2016), Irma (2017), Maria (2017), Michael (2018) and Dorian (2019). During 2017 alone, 22 of the 29 Caribbean islands were affected by at least one storm, and multiple experienced extreme damage [53]. Furthermore, the devastation caused by the hurricanes is not only on the immediate destruction and death toll, but like the example with Katrina or like the earthquake in Haiti, it is long-term. The devastation of the islands’ infrastructure with their limited resources, can take years to rebuild. The inevitable stress affects the physical and mental health of the people and, with limited health care resources, can result in an increased morbidity and mortality [54].

These storms and their impact on the Caribbean islands further exacerbate the health and wealth divide, contributing to the cycle of health disparities. The irony of the situation is that the Caribbean islands have an economic base in agriculture and tourism, contributing a miniscule amount of greenhouse gases to the atmosphere, yet, they are in the line of fire from the hurricanes that are coming more frequently and fiercely as a result of the global climate changes that are caused by greenhouse gases from the richer industrialized countries [53]. A further example of disparities that play out in the political arena is that of Hurricane Maria that devastated the island of Puerto Rico in 2017. Here, the irony is that in the same year, the Hurricanes that hit the US mainland, Harvey in Texas and Irma in Florida, received substantial federal assistance from the US government through the Federal Emergency

Management Agency (FEMA), while Puerto Rico, effectively also part of the USA, did not receive commensurate assistance. This ultimately contributed significantly to the delayed implementation of emergency and rehabilitation services resulting in a further increase in morbidity and mortality [55].

VULNERABLE POPULATIONS

Vulnerable populations can be divided into two major categories: by geographical location, for example on a seismic fault line predisposing to an earthquake, in the equatorial region predisposing to hurricanes and tropical cyclones, or low-lying area predisposing to flooding; or by population characteristics, such as socioeconomic status, age, ethnicity, physical wellbeing, employment, family structure, and housing condition [7, 38 56]. Social vulnerability is a measure of both the sensitivity of a population to natural hazards and its ability to respond to and recover from the impacts of hazards. It is a multidimensional construct, not easily captured with a single variable. There is ample field-based evidence for understanding the characteristics of people and social groups that make them more sensitive to the effects of natural hazards and reduce their ability to adequately respond and recover [57]. Social vulnerability also refers to the resilience of communities when confronted by external stresses on human health, such as natural or human-caused disasters, or disease outbreaks. CDC's Social Vulnerability Index uses 15 US census variables at tract level to help local officials identify communities that may need support in preparing for hazards, or recovering from disaster (see Figure 5) [7, 38]. The CDC stresses that to mitigate the impact of disasters on at-risk populations, emergency managers must be aware of the social vulnerabilities within their community [58].

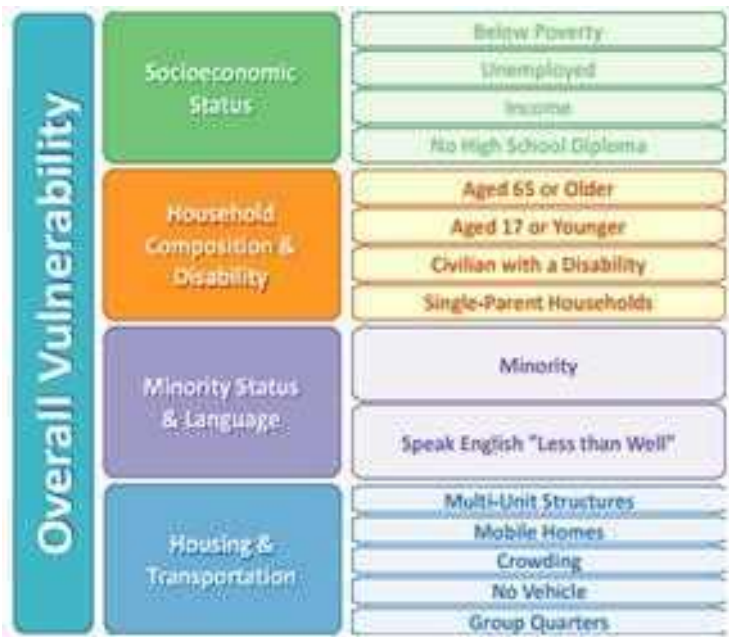


Figure 5. Social Vulnerability Index [7, 38].

DISASTER MANAGEMENT

As seen in the examples of natural disasters presented above, it becomes clear that acute and dramatic devastation to the built environment, the physical environment and the people who are affected, requires an immediate and dramatic response commensurate with the degree and nature of its impact. Furthermore, we need to be cognizant of the vulnerable populations and the long-term consequences. Then follows the steps in rebuilding and restoring a semblance of normality which takes much time. This is particularly the case for vulnerable communities who have limited resources to rebuild or return to their pre-disaster lifestyle. They require a significant level of assistance in recovering their physical and economic security as well as their emotional and social level of wellbeing. This calls for “a holistic community-driven and participatory approach beyond individual survival assistance.” [36]

While the damage cannot be undone, there are opportunities to rebuild the affected areas in creative ways that result in safer, healthier, and more resilient communities to better withstand future dramatic events [59]. The outcome of this process was described above in the situation of case of the earthquake in Chile, where the potential damage of the earthquake was mitigated by the building codes that had been instituted following previous earthquakes [21, 22]. Also, reflected in the reduced death toll from hurricanes [3].



Figure 6. Disaster management cycle [adapted from 60].

Figure 6 represents the elements of the Disaster Management Cycle demonstrating that the way in which we respond to disasters relies upon the crisis management, which informs risk management and disaster preparedness towards mitigation of the impact [60].

STORM DISASTER PREPAREDNESS

In their paper on the impact of hurricanes in the Caribbean, Schultz et al. make the following recommendations [61]:

6. *Communities need to prepare strategically* for the onslaught of stronger storms by revising building codes and redesigning neighborhoods to redress existing socioeconomic inequities in affordable, safe housing and putting in place systems to deal with power outages.
7. *Health care systems need to have emergency response strategies in place* in order to maintain access to lifesaving services and of life-sustaining treatments. This applies to trained personnel as well as hospital facilities.
8. *Enhanced warning systems*, and establishment of available and accessible resources for all citizens with special consideration to vulnerable populations.
9. *Active citizen participation in disaster preparedness and response* can make a big difference in saving lives but also in sharing the burden and working together fosters community cohesion and resilience.
10. *Collaborative conversations and planning process among various segments of society*, including but not limited to health professionals, climate scientists, population health scientists, government agencies and private organizations to advocate for policies that mitigate climate change and develop policies and practices that diminish population health risks and save lives.
11. *Elevate community resilience as an essential public health service* and consequently integrate community resilience measures as performance benchmarks of federal, state, and local health agencies.

Resilience

Resilience is a major factor in surviving a disaster as well as coping with the experiences emotionally, socially and economically in the intermediate aftermath and long-term.

The Composite of Post-Event Well-being (COPEWELL) is a module aiming to support community self-assessments to evaluate factors that influence resilience and incentivize the adoption of interventions that ultimately support National efforts of disaster preparedness, emergency response, and disaster recovery [62]. It insists that effective communication must exist in order for communities to function with resilience when faced with a disastrous event [63]. Because health care providers are inevitably at the frontlines of health management and patient communication during and after the disasters, the CDC has developed a public health training program entitled, “Crisis & Emergency Risk Communication” (CERC) [64]. This multidisciplinary curriculum offers in-person and online instruction for effective disaster communication before, during, and after events. It also offers guidance on handling sensitive topics with special populations and information specific to the type of disaster. It also focuses on the situation of children, who are particularly vulnerable to environmental health risks from disasters and require special attention to effectively address the physical, environmental and biological damage that disasters bring, as well as the emotional trauma that persists long after visible scars have faded.

CONCLUSION

The increasing frequency and severity of natural disasters in the last few decades that is most certainly related to global warming associated with climate change, if unchecked, will undoubtedly continue and become our new reality [4, 65]. The lessons learned over the past 20 years since the technological disaster that was the destruction of the World Trade Centers, and the natural disaster that was hurricane Katrina, have resulted in an ever-increasing set of strategies to anticipate and manage natural and technological disasters as they occur and reduce their impact on the environment and on human populations. Yet, the grave concern is that the frequency and severity of the natural disasters will continue to increase towards catastrophic proportions as we have witnessed in the recent fire in Australia [29]. Again, although a disaster is indiscriminate in whom it affects, the poor and medically underserved bear an inequitable burden [36, 39, 41, 43, 58]. The disastrous storms we have experienced, have not only demonstrated their capacity for destruction of property and impact on human lives, but they come at great cost and have also resulted in an aggravation of injustice with lasting consequences to human health and health disparities.

Our charge, therefore, requires efforts at many different levels involving many difference segments of our global society. We need to confront the imminent threat of global warming [4, 66] we need to continue to focus on the UN Sustainable Development Goals 2030 as a blueprint for action to improve the health of our world [67], all the while preparing for the next disaster wherever it may be and whatever its character [64]. Political leaders, health officials, preparedness and response professionals, and community organizations need to act now to develop a shared vision of optimal health for their community. A long-term plan for health and resilience should be a forethought, rather than an afterthought, when a disaster occurs [68, 69].

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Chapter 334

BARRIERS AND OPPORTUNITIES FOR YOUNG CAREGIVERS TO PROVIDE NURTURING CARE IN LOW-INCOME COMMUNITIES OF PARAGUAY

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ABSTRACT

The United Nations International Children's Fund (UNICEF), the World Bank, and World Health Organization (WHO) suggests a new roadmap for government action and for other programmers and service providers to implement policies and services that help parents and caregivers to provide nurturing care for their children. In Paraguay, despite existing Early Childhood Development (ECD) policies and programs, children, particularly those in poverty, continue to lag behind in many developmental indicators. Young children from low-income households are less likely to have adult members interact with them through stimulation activities, to attend early childhood education centers, or to have three or more books in the home. Furthermore, only 30% of babies are exclusively breastfed for six months, and with limited childcare options, often face greater protection risks from harm. This chapter explores the barriers and opportunities

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that exist for caregivers to provide nurturing care to their children from pregnancy to age three years in low-income families of Paraguay. Based on a literature review, the mapping of existing ECD programs, and seven semi-structured key informant interviews, this paper analyses the current state of nurturing care in Paraguay. It uses the framework to advocate for the integration of interventions thorough a ‘whole child’ approach that takes into consideration the multidimensional nature of supports a child and his or her family need, and provides specific recommendations to break the cycle of health disparities with a focus on ECD for young children in Paraguay.

INTRODUCTION

The science of early childhood development (ECD) draws from multiple disciplines including behavioral and social sciences, neuroscience, biology, epigenetics, among others. Since the late 1990s, with ECD programs expanding across the globe, these disciplines have shaped a strong understanding of what constitutes healthy childhood development as well as the potential detrimental consequences for children and for society of failing to support the full development potential of every child [1]. At the same time, researchers have developed a solid understanding of what programs and support mechanisms best promote positive outcomes for children. We know today that the brain develops more rapidly in the first three years of life than at any other period in a child’s life, and that the architecture of the brain is the result of the interaction between our genetic makeup and the environment, especially our personal experiences early in life [1]. It is estimated that, during the critical period of the first three years, a child forms more than one million neuronal connections every second [1, 2]. During this rapidly growing period, many of the most basic functions that serve as a foundation for later learning and growth are developing. In order to grow, learn and thrive, children need responsive interactions with their main caregivers complemented by positive experiences and environments that help build a strong brain architecture. This translates into better opportunities for learning, improved health, and higher productivity [3]. An additional argument for supporting investment in the early years is evidence favoring that returns on investment for childhood development programs are greater in the early years. Allowing children to build a strong foundation from the very beginning is not only more economical in the long term, but it also promotes a preventive approach instead of an intervention approach, understanding that fixing negative outcomes from disorders of development result in more costly interventions [4].

Along with the growing knowledge of ECD science comes the understanding of factors that can disrupt healthy child development and put children at higher developmental risks. Given that children need nurturing relationships for healthy brain development, experiencing adverse environments and poor interactions puts at-risk children at a further disadvantage and reinforces health and developmental disparities. This may prevent children from developing the skills they need to cope with stress and develop resilience. When children grow up in challenging environments and do not have the support they need, toxic stress may develop as a defense mechanism [1]. Prolonged exposure to this type of stress can weaken the architecture of the developing brain [5]. The consequences of living in extreme poverty often exposes children to higher levels of toxic stress in early childhood and can have cumulative lifetime effects on learning, future earnings, and health [6].

Experiencing poverty early in life hence significantly contributes to health disparities in childhood as well as in the adult population [7]. This is because poverty has profound implications on key life circumstances, such as birth weight, infant mortality, language development, chronic illness, environmental exposure, nutrition, and injury [8]. These and other circumstances of poverty can also impact brain development given its association with a higher degree of stress connected with the need to obtain essential resources (food, housing, income) [9], and other challenges in the environment, such as exposure to violence [10].

Poverty adds further stress to the already challenging task of parenting, including the lack of access to parenting knowledge about the needs of the child for responsive and adequate caregiving and access to support networks to address these needs [3, 8]. The extent of a family's available resources in terms of financial, social and human capital, can influence a child's potential for reaching his or her optimal development [11]. In short, poverty can significantly reduce a caregiver's ability to support, protect, and promote young children's development. This study aims to answer the following question: *What are the barriers for young caregivers to provide nurturing care to their children in low-income communities in Paraguay?* It does so by analyzing the country's ECD landscape under a prominent framework to assess and organize action to promote Nurturing Care to inform future practice and opportunities for integration of programs and policies to achieve optimal development of children [12].

Nurturing Care

As described above, the evidence for investing in the early years has grown exponentially. However, even though increased investment has followed, this continues to be insufficient and insignificant portion of government expenditure in most Latin American countries [13]. In Paraguay, investment in young children ages 0-5 years represent less than 1% of the Gross Domestic Product (GDP), and less than 7% of total social spending. Furthermore, most of this funding corresponds to education expenses for children 3 years old and above (34%) and health (47%) [14].

An added challenge is that investment does not always translate into better development for children, especially when programs aim to operate at scale where maintaining quality becomes more challenging [15, 16]. New evidence is showing the importance of quality implementation in ECD, the fundamental role of multi-sectoral collaboration for its effective implementation, and the need for anchoring any efforts towards improving the development of children under the lens of the domains of the *nurturing care* framework [3].

Nurturing care is what children need for healthy development, and it can be understood as “the conditions created by public policies, programs and services ... (that) enable communities and caregivers to ensure children's good health and nutrition and protect them from threats. Nurturing care also means giving young children opportunities for early learning, through interactions that are responsive and emotionally supportive” [12]. Even though nurturing care can and must be facilitated and promoted at all levels and contexts (family, school, community, local, and national), it is important to emphasize that “the single most powerful context for nurturing care is the immediate home and care settings of young

children often provided by mothers, but also by fathers and other family members, as well as by child-care services” [3].



Figure 1. Nurturing care framework. Adapted from [12].

The Nurturing Care Framework (see Figure 1) developed by United Nations International Children's Fund (UNICEF), the World Bank, and World Health Organization (WHO); provide a roadmap for action which is unique in that it specifically targets the period from pregnancy to the age of three years as the most fundamental period for healthy brain development. The framework calls for a “whole-of-government” and “whole-of-society” approach, outlining principles, strategic actions and guidance for monitoring implementation of progress [12]. It is especially relevant for this research considering its age focus, as well as its emphasis on supporting caregivers with the right set of tools and knowledge that allow them to provide nurturing environments to their children. It reinforces the principle that, when provided with adequate and responsive nurturing care, children are more resilient to even the worst effects of adversity (such as extreme poverty). For this reason, guaranteeing nurturing care with healthy and responsive environments is one of the most important actions to help lower a child's stress level as it encourages his or her emotional and cognitive coping mechanisms [12].

The framework in Figure 1 describes the main domains of nurturing care: (a) good health; (b) adequate nutrition; (c) responsive caregiving; (d) security and safety; and (e) opportunities for early learning. It also shows the support system that needs to be in place to ensure that children receive nurturing care starting with caregivers' capabilities, empowered communities who own and defend child development, supportive services that guide caregivers through the challenging task of parenting in this critical period, and moves up to enabling policies that ensure all of the above and guarantee sustainability and continuity of services [12]. While the framework articulates the importance of integration across sectors, it also calls for the health sector to play a pivotal role as it is usually the main entry point for care and services during the early years.

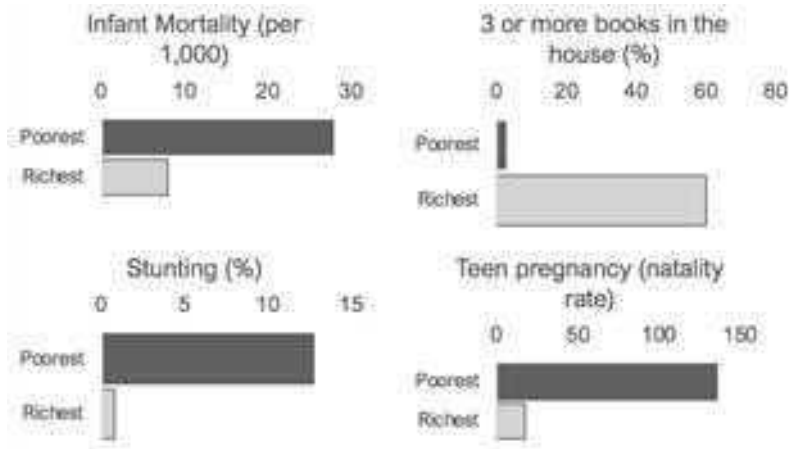


Figure 2. Paraguay ECD indicators by wealth quintiles [17].

In addition to providing guiding principles for policy implementation, the framework for Nurturing Care identifies services and interventions that have proven successful to promote healthy childhood development worldwide under each of the domains presented above [3, 12]. While it is evident that different governmental and non-governmental institutions play different roles for the implementation and delivery of such services, this approach uses a whole child perspective allowing for integration of services based on a child's needs for optimal development rather than based on institutional capacities. This study is unique in that it assesses ECD in Paraguay using the Nurturing Care framework to make a case for integration of services at all levels and provide a series of recommendation for improving opportunities for caregivers in poor households to provide nurturing care to their children.

Early Childhood Development in Paraguay

Despite noticeable progress in health, nutrition and education enrollment in Paraguay, children's developmental outcomes vary significantly depending on where children grow up and their socio-economic status (see Figure 2). Children in the poorest areas are at greater risk for experiencing infant mortality or stunting and malnutrition. They are also much less likely to have adult members interact with them through stimulation activities (only 2 in every 10 children in the poorest households receive stimulation), to attend early childhood education centers, or to have three or more books in the house. Furthermore, they are more likely to be born to an adolescent mother and given that low-income families have limited childcare options children are often at greater risks of needing protection [17].

Paraguay presents an overall 81.9 score in UNICEF's Early Childhood Development Index (ECDI) [17, 18]. Figure 3 shows the distribution of ECDI scores by wealth quintiles in Paraguay. Even though most children are developmentally on track in terms of physical development (97,6%) and approaches to learning (95,8%), the development domains of literacy and numeracy, and socio-emotional development show greater variation and lags in development disproportionately affect children in the lowest wealth quintiles [17].

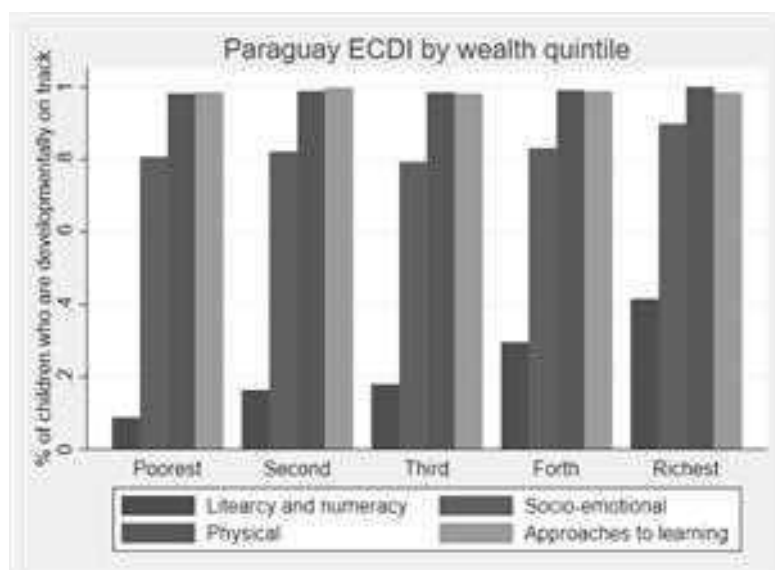


Figure 3. Distribution of ECDI scores in Paraguay by wealth quintiles [17].

In recent years, the increased interest in ECD has led to the development of a national plan for early childhood, the *Plan Nacional de Desarrollo Integral de la Primera Infancia* (PNDIPI) in 2011 and the launching of multiple ECD programs by public, private and civil society sectors. The PNDIPI was pivotal for introducing ECD in the national agenda and for complementing a legal and policy framework with clear action towards young children (see annex 1 for Paraguay's legal and programmatic ECD landscape). It set important targets for putting children at the center for intervention and called for a multi-disciplinary and collaborative approach to address young children's needs. One of its most important components, was the establishment of a national commission on early childhood, known as the *Comisión Nacional de Primera Infancia* (CONPI) as the key promoter agency for the implementation of the plan. This commission is formed by representatives of the Ministry of Health, the Ministry of Education and Science, and the Ministry of Childhood and Adolescence who rotate leadership positions. However, to date CONPI has played primarily a coordination function. As such, it is not an independent body and lacks the autonomy to demand implementation, influence policy and dictate fundamental aspects of the ECD agenda such as demanding funding allocation and monitoring and evaluation of programs.

The PNDPI will undergo an evaluation process at the end of 2019. Importantly, however, reports from key informant interviews, as well as a limited number of publications available on the subject, express important concerns in the translation of the plan from policy to implementation and sustainability [19].

OUR STUDY

A review of the literature was conducted to develop an understanding of the key concepts addressed in the research. The starting point was the recently published document *Nurturing care for early childhood development: A framework for helping children survive and thrive to*

transform health and human potential [11], which serves as the guiding framework for this research. The reference list of this document was reviewed and included to expand the research. In addition, Columbia University Library Database was searched using the terms “brain development,” “early childhood development,” and “nurturing care” “poverty and children health disparities,” “ECD policies in Latin America,” “Early Childhood Development in Paraguay” from 2000 through 2019.

Web searches on local websites of UNICEF Paraguay, Ministry of Childhood and Adolescence, Ministry of Education and Science, Ministry of Health as well as non-profit organizations was conducted to obtain program and policy information specific to Paraguay. Furthermore, the dataset from UNICEF’s Multiple Indicator Cluster Surveys conducted in 2016 was downloaded from UNICEF’s website and used to analyze and report ECD outcome indicators from Paraguay.

Finally, a series of in-person and remote key informant interviews with selected participants working in the ECD sector of Paraguay were conducted. The key informant interviews elicited stakeholder opinions on the relevance, effectiveness, efficiency, sustainability and impact of early childhood development programs in Paraguay, with special emphasis on opportunities and barriers for young caregivers to provide nurturing care. A detailed list of the institutions represented during the interviews as well as the guiding questions are included in annex 2. The names have not been included for confidentiality purposes. Data triangulation was achieved by interviewing a range of stakeholders at different levels from a variety of institutions and reviewing a wide range of documents.

Findings are organized under the main domains of the Nurturing Care framework with the intent of identifying the barriers for young caregivers to provide nurturing environments and highlight opportunities for integration and clear recommendations that can be adopted by policy makers and program implementers [12].

FINDINGS

Barriers for Caregivers to Provide Nurturing Care

This section assesses the main barriers to implementation of nurturing care from the perspective of practitioners and policy makers in Paraguay looking at both household and national level barriers. The end objective is to identify clear opportunities for aligning existing efforts and incorporating recommendations based on the Nurturing Care framework. For reference, findings from key informant interviews are highlighted in bold, and dimensions of the framework are marked in italics.

While it is important to understand the specific needs of children in the different domains of nurturing care, the first finding that became evident is how closely interrelated these domains are. This reinforces the idea that the inability of caregivers to fulfill needs within one domain, puts children at a greater risk in other domains as well [20]. For example, time and caregiver’s availability due to caregivers working 15-18 hours outside of the home was identified as a barrier for *responsive caregiving*. However, having caregivers on such a stressful schedule due to financial need is likely to also affect the caregivers’ capacity to provide *security and safety* as children are often left in someone else’s care because of the

work commitment of the primary caregiver. This may, at the same time, limit the caregivers' ability to seek timely healthcare and appropriate treatment when the child is ill, affecting the caregiver's ability to provide *good health*. What follows is an attempt to organize findings from the interviews under each domain, with the caveat that many of these barriers and challenges affect and relate to each other:

1.1. *Good health*: barriers to good health at the household level include,

- **Large percentage of teen pregnancies** among low-income caregivers put children at greater risk for low-birth weight and, consequently, poor development outcomes [21]. Every day two girls between 10 and 14 years old give birth in Paraguay [22]. These numbers are alarming given that a pregnancy in early adolescence is most often the result of sexual abuse [22]. In addition, the adolescent fertility rate is of 72 births for every 1,000 women ages 15 to 19 years, with adolescent mothers in this age range representing 20% of total births [17]. When disaggregated by region, language spoken at the home and years of study, the adolescent fertility rate goes up ranging from 84 to 164 births every 1,000 women ages 15 to 19 years, showing again a large disparity gap for adolescents in the poorest areas [17, 22].
- **Extreme climate events**: Extreme heat waves and periods of flooding are the largest environmental threats in Paraguay [23]. While flooding has been a challenge throughout history, the problem has exacerbated in recent years with more frequent floods and a larger number of families affected by these extreme weather events. Vulnerable populations are often displaced and face increased exposure to weather related diseases while experiencing additional sources of stress. Paraguay presents a vulnerability index classified as *extreme* and has been ranked as the 8th most vulnerable country to climate change Latin America and the most vulnerable in South America [24]. In 2019, over 49,637 families have been affected by flooding, with at least 11,144 families experiencing displacement [25]. In the context of these emergencies, ECD interventions are challenging to implement and national strategies for dealing with climate change, including Paraguay's, rarely include an intervention approach for the early years [26].
- **Lack of hygiene at the household level**: This barrier is reinforced by an overall lack of awareness and limited education in low income families as addressed in 1.3. below.

1.2. *Nutrition*: barriers to nutrition at the household level include,

- **Limited breastfeeding practices**: only 30% of children are exclusively breastfed until six months [17]. Mothers rarely receive sufficient guidance and support regarding the benefits and importance of breastfeeding for the developing child.
- **Malnutrition**: Paraguay achieved significant progress in reducing the rural-urban gap in nutrition since the mid 1990s until 2012 [27]. However, stunting levels still remain at 6% in children 0-5 years [17]. Today, in line with the global phenomenon, the country is beginning to co-exist with the challenges of eliminating undernutrition while increasingly having to pay attention to the **challenge of childhood obesity** with highly unbalanced diets. This is particularly worrying in vulnerable populations such as indigenous community that migrate to urban areas [28].

1.3. *Responsive caregiving*: barriers to responsive caregiving at the household level include,

- **Time** and caregivers' availability: As mentioned above, low-income caregivers who have to spend a significant portion of their days at work and leave their children under the care of others (often grandmothers or older children) face time constraints for spending quality time with their children.
- Intrusion of **mobile technology** into parental interactions was increasingly recognized as a challenge as parents tend to use technology to keep children entertained [29]. The framework recognizes the added premium that strong cognitive and social abilities that are development in the early years will continue to hold in our increasingly digital world. However, interventions must also stress the importance of human interactions with the main caregivers as the most fundamental factor to ensuring strong development in early childhood.
- **Culture**: Two important components were raised under culture. One is a culture of physical punishment which is addressed further in 1.5., and another commonly shared concern is the idea of **demonstrating affection as a symbol of vulnerability**. Children need love and affection. Boys and girls alike. An important finding at the national level highlights the need for gender sensitivity. Most of the concern was expressed around girls and their vulnerability to sexual abuse (also addressed in 1.5.); however, this finding also calls attention to possible risks regarding the way that children are socialized into different gender roles at a very early age and its possible negative effects on children's development [30]. Culture is also highly linked to opportunities for learning, for example, understanding the role and importance of play. This is addressed in the following point.

1.4. *Opportunities for early learning*: barriers to opportunities to early learning at the household level include,

- **Lack of awareness of the importance of play**: Caregivers often want to play with their children but there is a lack of awareness on the importance of early and responsive interactions, and the role of play in children's development. As it was put in one of the interviews "fathers wait until their child is old enough to play football, at that time, it can be late already." The value play and the implications of spending time playing with children, particularly in ages 0 to 3 years, have for the development of children is not internalized in most caregivers.
- **There is an existing notion that school, and learning, starts in pre-school**. There is a lack of awareness that learning begins at home and not when children enter the education system. In rural areas, children wait to be the same age to go to school together.
- **Location of early childhood education services**: Even if pre-school or early care services for young children are available, 3-year-old children cannot walk a kilometer to school as compared to school-age children.

1.5. *Security and safety*: barriers to safety and security at the household level.

- **Lack of basic income**: extreme poverty was identified as the main barrier to nurturing care in all interviews. Income poverty and extreme poverty affect 24.2% and 4.8% of the population respectively [31]. This barrier significantly affects the

ability of caregivers to provide nurturing care due to higher levels of stress, reduced levels of education, and lack of access to jobs as explained above.

- **Poor housing conditions and overcrowded households:** Paraguay has a household deficit of 50% with housing lacking both in terms of quantity and quality. The demand quantity is concentrated in urban areas due to large populations living in informal settlements whereas quality housing deficit in need of improvements and expansion is higher in rural areas [32]. The housing deficit is further exacerbated by the challenges resulting from flooding and an increase in the number of families and children living in informal, and often insecure, urban settlements.
- **Culture of punishment:** over 50% of children 1 to 14 years of age experience physical punishment or psychological aggression [17]. Families replicate what they know from their own experiences growing up' thus perpetuating the cycle of punishment.

1.6. *System barriers:* In addition to the barriers corresponding to the different domains within the Nurturing Care Framework, several barriers were identified at a systems and policy level. These relate to the implementation, monitoring and scaling up of national programs and policies. They include:

- The PNDIPI policy, which is in its last year of implementation, was identified as an opportunity and barrier at the same time. The policy has been questioned for its **lack of accountability**. While it was important for introducing new early childhood development programs, creating the CONPI, and suggest articulation across government actors, there is no clear evaluation or accountability mechanisms in place to understand how successful the plan has been in advancing and improving ECD.
- More importantly, there is no evidence that this plan **has translated into an integrated approach to child development**. In spite specific language in the plan advocating for interinstitutional collaboration, programs across ministries and institutions have mostly continued to work and develop in silos. Efforts to integrate operate primarily at a pilot stage. Furthermore, programs are often centralized at the ministerial level, leaving little capacity and discretion for implementation at the local level.
- Another important barrier is **institutional weakness**. This is expressed both in **limited multi-sector coordination and implementation** as well as in the limited transition of learning and progress from one administration to the next. While a right-based approach and a multi-sectorial approach is often discussed, programs in the field show little connection to each other.
- Finally, the Nurturing Care framework highlights the importance of funding that is "sustainable, equitably distributed, efficient and flexible" [11]. The last identified barrier to nurturing care is the **sustainability of the current ECD policy**. Financing of ECD occurs primarily through projects, multilateral cooperation, and yearly allocations rather than being embedded as part of the regular national budget.

Parents and other caregivers are the main force and resources for early childhood development in the first three years of life. For this reason, equipping them with the knowledge, capabilities and resources to provide nurturing care for their children in these five domains is essential for ensuring that they reach their full potential. These findings shed light

on the need to strengthen awareness raising services and streamlining information for caregivers in low-income families. Raising awareness is an important way of developing accountability mechanisms so that, in turn, government can become more efficient. Caregivers who know that providing nurturing environments for their children is a clear pathway towards breaking the cycle will be more likely to demand and use ECD services (see Figure 4).

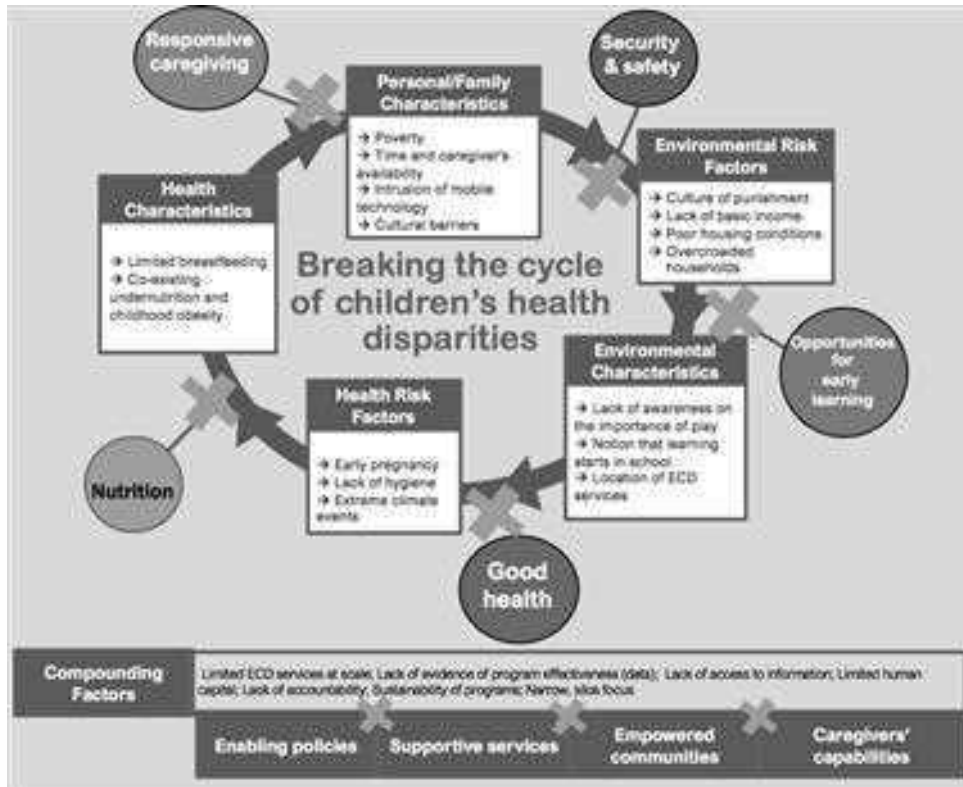


Figure 4. Using the nurturing care framework to break the cycle of health disparities [12].

Opportunities for Caregivers to Provide Nurturing Care

While there are many barriers at the family, community and policy level to promote nurturing care in Paraguay, the literature review and interviews also revealed many opportunities to strengthen nurturing care at all these levels. Using the Nurturing Care Framework to organize and prioritize actions provides an opportunity in and of itself, but additional opportunities were identified and are important to take advantage of the momentum.

In 2018, the government of Paraguay in partnership with the Interamerican Development Bank and UNICEF launched two important initiatives. First, a new program, *Modelo de Atención Integral del Desarrollo Infantil Temprano (MAIDIT)*. The program aims to deliver ECD services through a model based on the public health system. It incorporates important components included as key practices in the Nurturing Care framework such as the

arrangement of programs and policies under a continuum of care with universal, targeted, and intensive services based on individual families' needs [12]. Second, the government of Paraguay launched the *Sistema Nacional de Protección Social ¡Vamos!* (SPS), a national social protection system as its primary platform for organizing its social policy at the end of 2018. The SPS organizes public action by lifecycle with a strong emphasis on early childhood. Both of these platforms present a unique opportunity for this study. Using Nurturing Care can provide further guidance for implementation of the MAIDIT program as it continues to roll out in 10 regions of Paraguay in the next few years [33] and for the SPS as it is rolled out nationally [34]. The PNDIPI and its upcoming evaluation was also highlighted as an opportunity given that it has provided extensive training for the early childhood workforce and put the CONPI in place. While there is much room for improvement, these mechanisms are very adaptable to the Nurturing Care Framework. Finally, it was largely recognized that in the South American region there are examples of best practices related to successful ECD policies that have been widely studied such as national ECD plans of Chile (Chile Crece Contigo), Colombia (De Cero a Siempre) and Uruguay (Uruguay Crece Contigo) that have been successful in improving child development outcomes indicators with a special emphasis on vulnerable populations (See Annex 3). An analysis of best practices of the region and exploring potential partnerships for adaptation and replication provide a unique opportunity for Paraguay to strengthen its current policies and programs.

DISCUSSION

This review presents a comprehensive analysis of the barriers and opportunities for parents and caregivers in Paraguay to provide nurturing care to their children in the first three years of life. It uses key findings from stakeholders' interviews combined with a review of the literature to highlight important gaps in guaranteeing the optimal development of children during this critical period. Below, I present key recommendations that emerged from the research under the five strategic actions recommended for governments in the framework for Nurturing Care [11]:

- 1) Focus on families and their communities:
 - The need to increase the knowledge and awareness of caregivers as well as their capabilities through providing timely information and adequate support systems for everyone must continue to be the primary vision for improving and ensuring the development of services for children in the early years, particularly for the most vulnerable populations.
 - Participatory processes for increased community involvement can bring new ideas not only for increasing awareness on nurturing care but for finding new practices and new ways of engaging in the way we care about children.
- 2) Lead and invest: Take into account regional examples of ECD laws and programs that guarantee long term financing and facilitate the integration of services across sectors. The Social Protection System is an important first step, but quality implementation at scale is key.

- 3) **Strengthen services:** This analysis identifies key barriers at the family, community and system's level. Organizing them under Nurturing Care provides a strong case for the need of improving efforts towards the integration of services as well as the introduction of new tools and mechanisms to facilitate such process. Global experiences show that interinstitutional ECD commissions, such as the CONPI, can play a key part of the coordination for the integration of services. Looking at regional examples can further inform how to improve the implementation capacity of this important unit and support the definition of a strong management model that guarantees access to services through vertical and horizontal coordination across governmental ministries, particularly for policy efforts such as the SPS.
- 4) **Monitor progress:** Integration needs to happen not only at the program level, but also in terms of sharing information around quality monitoring. Finding creative ways to make families accountable and increase their demand for services is an important step in improving the effectiveness of programs.
- 5) **Use data and innovate:** It is important to determine ways in which the data that is collected today at the family level can be used to inform actual needs and promote an ecosystem to nurture innovative solutions from different sectors. Furthermore, the integration of data information systems is an important step in efforts of intersectoral collaboration.

Expanding these lines of actions and taking into account the insights from this study can help overcome the barriers to nurturing care and break the cycle of health and developmental disparities for low-income children in Paraguay as it provides a roadmap for improving the current ECD landscape and transition into a holistic approach with caregivers and children at the center of any intervention (see Figure 4).

CONCLUSION

Placing emphasis on parents and caregivers' capabilities to provide nurturing environments for their children is fundamental for their optimal development. Paraguay has made good progress to establish policies and programs that promote ECD, however, its most vulnerable population continue to lag behind in many indicators of early childhood development. The inability to ensure optimal development of children has negative and long term social and economic implications for the country. For this reason, it is fundamental that current increasing interest in ECD and existing policies be translated into effective and high-quality implementation. The Nurturing Care Framework provides a roadmap to organize public action with a strong emphasis on developing and empowering parents and caregivers' skills and capabilities.

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Chapter 335

THE DEVELOPMENT OF A PRENATAL CARE HEALTH LITERACY INSTRUMENT FOR AMERICAN INDIAN MOTHERS

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ABSTRACT

American Indian (AI) women are nearly four times as likely as white women to experienced delayed prenatal care until the third trimester. Additionally, AI are the only racial/ethnic group that has not had a decline in infant mortality between 2005 and 2014. While these inequities are apparent, little is known about health literacy among AI women of childbearing age. Existing health literacy instruments do not take the cultural context surrounding the prenatal period into account. Method: After a comprehensive review of the literature of health literacy tools and questionnaires, a measure of prenatal care health literacy for AI mothers was developed with four domains. Measure development was iterative. Cognitive interviews, a standard technique to assist validation, were used to verify the face validity of the instrument and to check understanding in the population of interest. Results: The initial instrument had 60 questions. Iterative review by experts in population health and AI health disparity research eliminated 30 duplicative questions. Cognitive interviews were conducted with AI researchers and community members, after which 5 more questions were eliminated. These interviews also help establish the validity of the tool, understanding of the questions, and suggestions for formatting of the instruments. The final instrument consists of 25 questions. Discussion: Health literacy is the ability to obtain, process, and understand health information to make knowledgeable health decisions. There is little information on health literacy specific to prenatal care and infant health among AI. This instrument was developed specifically for this marginalized population.

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INTRODUCTION

American Indian infants are 2.5 times more likely to die before their first birthday than non-Hispanic White infants [1-4]. While trends in maternal and infant health have been improving overall, American Indians are the only racial/ethnic group that did *not* have a decline in infant mortality between 2005 and 2014 [5]. High American Indian infant mortality rates persist, despite national, tribal, and community efforts to eliminate these disparities. The American Indian infant mortality rate is 9.4 per 1,000 live births compared with a non-Hispanic White infant mortality rate of 4.9 per 1,000 live births [1]. The leading causes of death for American Indian infants include congenital malformations, low birth weight, sudden infant death syndrome, and unintentional injuries [4, 6]. These high rates can be attributed to confounding factors of complex interactions of behavioral, social, genetic, environmental, geographic location, economic, and health care access [4, 7, 8].

The geographic isolation of American Indian reservations impacts the quality of life for the population, due to limited access to resources and services [8]. The American Indian population is additionally impacted by harsh environmental conditions, such as uncontrollable seasonal weather, poor road conditions, and inadequate housing [9]. American Indians living on reservations, whether in rural and urban areas, tend to have housing shortages, one aspect that contributes to having multiple families in one household, and poverty is also a continuing problem [10, 11].

American Indian mothers living on a reservation have additional barriers to medical care including limited insurance outside of the Indian Health Service (IHS) and limited access to transportation [12]. Some reservation IHS facilities do not have the capacity to deliver infants, so if a complication arises, a pregnant mother may need to travel 2-4 hours from the reservation to deliver the infant at a better equipped hospital. Often, continuity of care is lost when entering a new health system [8].

The rate of participation for American Indian/Alaska Native women in prenatal care is significantly lower (67%) than all other races in the US (81%), at least among those women using IHS [5]. In 2014, American Indian/Alaska Native mothers were 2.5 times as likely to receive late or no prenatal care as compared to non-Hispanic White mothers [13]. Prenatal care rates among American Indian women who do not use IHS are unknown—another serious gap in our understanding of this complex disparity. It is important to note that the mother may start prenatal care in an IHS clinic and at the time of the delivery must go to an outside health system. This transfer to a facility outside IHS is conflicting and complicated because of the universal coverage the mother gets within the IHS health system. IHS is a health system rather than an insurance plan and federally recognized enrolled tribal members do not pay premiums or co-pays. Non-IHS providers may be paid by IHS for care given to American Indians enrolled in a federally recognized tribe—making some care appear like traditional health insurance. IHS is budgeted on a global level, meaning that all care delivered by IHS and paid for by IHS must fall within a pre-set budget that is approved annually by Congress. This is unlike most of the rest of the health system in the US, which requires insurance with patients paying premiums and copays [14]. When women go outside the IHS system to receive care, their care is very difficult to track, especially if it is not eventually paid for by IHS.



Figure 2. Conceptual model.

Existing studies suggest that good health literacy among pregnant women is associated with better pregnancy outcomes [15-17]. While health literacy is, in some sense, a universal concept, a culturally tailored measure is essential for American Indians given their barriers to care, historical trauma, differing birth practices, and cultural roles [18-20]. The purpose of this study was to create a prenatal care health literacy measure specific to American Indian women to better understand literacy around prenatal care to improve birth outcomes and decrease infant mortality rates. Based on searches of PubMed, we are unaware of existing recent research on prenatal care health literacy among American Indian women. We expect that a Parental Care Health Literacy Instrument for American Indian mothers will help to break the cycle (see Figure 1) of high infant mortality by informing health care providers on providing impactful educational and clinical recommendation that are relative to the American Indian population.

OUR STUDY

The development of the measure began with an assessment of existing health literacy measurement tools. A search in PubMed, Cumulative Index of Nursing and Allied Health Literature (CINAHL) and ScienceDirect was conducted to compile a list of existing health literacy tools. Content coverage and validity information were compiled for the existing tools. Additionally, educational materials that are handed out to pregnant patients from an IHS clinic located near a local university was collected. The additional information was used to further check language and content areas that are important for health education related to pregnancy. After deciding on four topic domains including: awareness (care, warning signs, symptoms), screening (when, where/how, cost), mortality (rates and ranks), and risk

(activities that increase and decrease risk), questions for each domain were extracted from existing instruments to create a draft.

The draft instrument was then reviewed by three American Indian health disparity researchers and one population health expert for relevance, duplication, and content coverage for each domain. After review, certain questions were rewritten for relevance to the American Indian population.

Next, an assessment of the instrument was conducted through cognitive interviewing. Cognitive interviewing is a psychologically oriented method for empirically studying the ways in which individuals mentally process and respond to survey questionnaires [21]. Cognitive interviews can be conducted for the general purpose of enhancing the understanding of how respondents carry out the task of answering survey questions. For this study cognitive interviews were used as a pretesting question and determining how they should be modified making the instrument more understandable or otherwise easier to answer.

The cognitive interviews were completed by two American Indian community members and three American Indian health disparity researchers. None of the five individuals interviewed were involved in the original draft of the instrument.

During the interview one of the study authors (JG) asked the participants to go through each question and talk about what they thought of the questions and how they processed and understood the questions. Cognitive interviews were completed to ensure that the questions had face validity and that understanding was similar across likely respondents.

FINDINGS

Two major scales measuring health literacy in the context of pregnancy were identified in the literature from the literature search described above. The first scale is a psychometrically validated measure of a woman's preferences about a future pregnancy and childbearing (Desire to Avoid Pregnancy-DAP) [22]. The 14 items fit a unidimensional model, with a separation reliability of 0.90 (Cronbach's α : 0.95). The scale met established criteria for internal validity, including appropriately covering the ranges of women's preferences and correspondence between each item's response categories and overall scale scores. There was no important differential item functioning by key sociodemographic characteristics, garnering evidence for external validity [22]. The second scale, the Parental Understanding of Infant Health Information: Health Literacy, Numeracy, and the Parental Health Literacy Activities Test (PHLAT), which is used to assess parental health literacy and numeracy skills in understanding instructions for caring for young children [23]. During the validation of this scale, the authors found that many parents do not understand common health information required to care for their infants. The PHLAT long form and PHLAT-10 short form have good reliability and validity and may be useful tools for identifying parents who need better communication of health-related instructions [23].

After reviewing the two instruments just discussed, the authors created the original draft instrument to measure prenatal health literacy among American Indian women; it was made up of 60 questions. After review by experts in American Indian health disparity, many questions were eliminated because they were either duplicative or misleading, creating a draft long form of 30 questions. The instrument has four domains including: risk (ways to increase

and decrease risk), incidence and mortality (rates and ranks), awareness (care, warning signs, symptoms), and screening (when, where/how, cost). The four domains were chosen based on health outcomes and risk factors among this marginalized population and were agreed upon jointly by three American Indian health disparity researchers who work at the Center for American Indian Community Health at the University of Kansas Medical Center and one population health expert from the Department of Population Health at the University of Kansas Medical Center (JW).

Current health care related readability formulas were used to ensure the understanding of written information in clinical and health care settings [24]. We used two readability formulas, Simple Measure of Gobbledygook (SMOG) Readability formula and FRY readability formula named after developer Edward Fry. The SMOG Readability Formula is a simple method you can use to determine the reading level of your written materials. The FRY graph readability formula is used to determine the interpretation of graphics and numbers. The FRY formula is often used to provide a common standard by which the readability of documents can be measured. The instrument also includes aspects of prose (reading and writing), document (understanding and being able to fill out forms or charts/graphs), and quantitative (math, understanding numbers) literacy into the instrument; ensuring holistic representation of health literacy [25].

Each cognitive interview was around 30 to 45 minutes long and was conducted in-person. The interviewees read each question out loud, after reading the question they described their overall perception of the question including difficulty and readability. Through this interview and feedback, five additional questions were eliminated from the 30-question long form, making the final form 25 questions (see Figure 2).

Modifications of the instruments format was made based off the feedback from the cognitive interviews. If a question had fill in the blank questions, we put a number before the blank spot, making the longer fill-in-the-blank passages easier to follow.

<i>Risk</i>	
	According to the Centers for Disease Control and Prevention, birth defect occurs in the first 3 (1) _____ of pregnancy, when the organs of the baby are forming. However, some birth defects occur later in pregnancy. During the last (2) _____ months of pregnancy, the tissues and organs (3) _____ growing and developing.
	Alcohol in the mother's blood passes to the baby through the (4) _____. Drinking alcohol during pregnancy can cause miscarriage, stillbirth, and a range of lifelong physical, behavioral, and intellectual disabilities. These disabilities are known as (5) _____.
	Toxoplasmosis is a common (6) _____ caused by a parasite that, when contracted by a pregnant woman, can pose serious risks to her unborn baby. To avoid, it is recommended that you do not empty cat litter from outdoor cats, wear gloves when working in the garden, do not eat undercooked (7) _____ and wash produce before consumption.
(8)	Breastfeeding has been shown to decrease the risk of breast cancer.
(9)	Having your child at an early age (under age 35) has been shown to increase the risk of birth defects.
(10)	Smoking is also associated with lower IQ, higher miscarriage rate, higher risk of infant death at term and sudden infant death syndrome (SIDS).
(11)	A miscarriage is often caused by an abnormality with the pregnancy and a result of women's activities or stresses.
(12)	Smoking affects pregnant women by increasing risk for things such as preterm delivery, stillbirth, low birth weight, and _____.
(13)	Nasal congestion and nose bleeds are common throughout pregnancy. They are caused by _____.

Figure 2. (Continued).

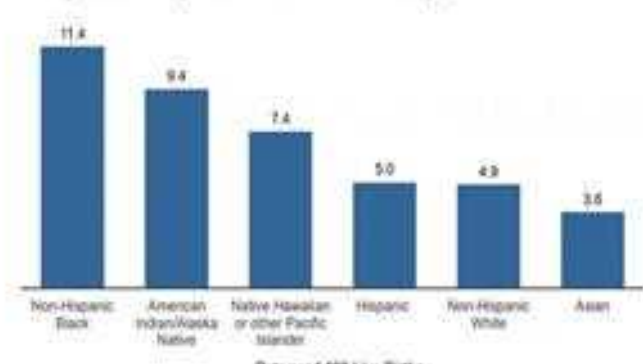
Incidence and Mortality															
Use the graph below to answer questions 14-15.															
Infant Mortality Rates by Race and Ethnicity, 2016  <table border="1"> <thead> <tr> <th>Race and Ethnicity</th> <th>Rate per 1,000 Live Births</th> </tr> </thead> <tbody> <tr> <td>Non-Hispanic Black</td> <td>11.8</td> </tr> <tr> <td>American Indian/Alaska Native</td> <td>9.4</td> </tr> <tr> <td>Native Hawaiian or other Pacific Islander</td> <td>7.4</td> </tr> <tr> <td>Hispanic</td> <td>5.0</td> </tr> <tr> <td>Non-Hispanic White</td> <td>4.9</td> </tr> <tr> <td>Asian</td> <td>3.6</td> </tr> </tbody> </table>		Race and Ethnicity	Rate per 1,000 Live Births	Non-Hispanic Black	11.8	American Indian/Alaska Native	9.4	Native Hawaiian or other Pacific Islander	7.4	Hispanic	5.0	Non-Hispanic White	4.9	Asian	3.6
Race and Ethnicity	Rate per 1,000 Live Births														
Non-Hispanic Black	11.8														
American Indian/Alaska Native	9.4														
Native Hawaiian or other Pacific Islander	7.4														
Hispanic	5.0														
Non-Hispanic White	4.9														
Asian	3.6														
Incidence and Mortality, continued.															
(14)	In 2016, the infant mortality rate for American Indian/Alaska Natives was ____ per 1,000 live births.														
(15)	In 2016, the infant mortality rate was the highest for _____.														
Awareness															
(16)	Signs of miscarriage are usually vaginal bleeding and cramping.														
(17)	When you are pregnant, you need about 300 calories more a day than you usually eat.														
(18)	During pregnancy, you should continue routine dental care including cleanings, extractions, root canal, radiographs, and fillings.														
(19)	The increase hormones of pregnancy make the gums more susceptible to plaque buildup and bacteria causing pregnancy _____.														
Screening															
(20)	A preconception care visit can help women take steps toward a healthy pregnancy before they even get pregnant.														
Prenatal care is the regular visits you will have with your physician during your pregnancy. In the beginning of your pregnancy, you will be seen monthly if everything is progressing well. Starting around week 28, your visits will change to every (21) _____, and then every (22) _____ the last month.															
Taking folic acid daily reduces the risk for neural tube defects by (23) _____. Most prenatal vitamins contain the recommended (24) _____ of folic acid as well as other vitamins that pregnant women and their developing fetus need.															
(25)	It is important to notify your doctor if your baby has not moved ten times in two hours, you have not felt the baby move all day (12 hours) or you notice a significant change in your baby's activity.														

Figure 2. Final questions for prenatal health literacy instrument.

Similarly, further refinement of the instrument was made based on feedback and results from the cognitive interviews, changing wording where appropriate and arranging the instrument in chronological order from preconception to birth. The first section contains 13 questions that gauge knowledge of health, prevention, and risk factors during pregnancy. The second section contains a graph showing infant mortality across race and ethnicity, two questions are based on the graph. The purpose of this section is to understand how the participants interpret information from graphics. The third section, warning signs included four true and false question asking about warning signs during pregnancy. The fourth section includes six questions in the form of multiple choice, reading passages, and true and false questions focusing on development, health, and screening points for the fetus.

DISCUSSION

Infant mortality among American Indians is higher than among whites and is not dropping at the rate seen in other populations [1-4]. While the complex interactions between risk factors such as poverty, housing, and healthcare access are central to reducing infant mortality, adequate prenatal care may address some risk factors directly [4, 9, 18]. American Indian infants are nearly 4 times as likely as non-Hispanic White infants to have mothers who only received prenatal care in the third trimester, or not at all [26]. Prenatal care and health screenings can improve health outcomes for both American Indian mothers and their children by providing health education and knowledge, informing behavior change, and increasing the awareness of necessary interventions [20, 27, 28].

The cycle that creates these poor outcomes can be broken. There are several intervention points. However, due to cultural differences, geographic barriers to access, differences in health policies, and legacy of discrimination, a highly interconnected approach is needed to address the high infant mortality rates among American Indians. [20, 27, 28]. Prenatal health literacy among American Indian mothers has not been measured. We developed a measure of health literacy that is specific to this population to support further efforts in the area.

This measure of prenatal health literacy is a beginning to understanding the needs and desires of this important population. Improving outcomes will only be impactful if the interventions and approaches address the literacy of the population as well as the unique factors affecting outcomes. The Prenatal Care Health Literacy Instrument breaks the cycle of childhood health disparity by improving birth outcomes at the start of pregnancy. This instrument is a tool used to assess the literacy level of the mother to enable her to get the care and information she needs during and after their pregnancy. This instrument also breaks the cycle by providing detail about health literacy in this population.

This instrument is different than other measures both in content and form. It was developed for a specific marginalized population, American Indians. American Indians have their own sovereignty, because of this, policy within different tribal nations and communities may be different than the surrounding areas. Medical training often neglects to cover this special population. Without an understanding of the cultural and contemporary life of tribal nations, as well as their traditional health practices, it is difficult for providers to form bonds with American Indian patients and have barrier-free communication. Future work will use this instrument to understand prenatal care health literacy of American Indian mothers. By understanding the health literacy of prenatal care, the gap can be closed through informing providers on what type of health information is most beneficial for American Indians mother during a prenatal care visit. This may also help bridge the gap between patients and providers, which will 'break the cycle' and improving the care for American Indian mother and reduce poor birth outcomes.

CONCLUSION

Although trends in maternal and infant health have been improving overall, American Indians are the only racial/ethnic group that did not have a decline in infant mortality [5]. The high rates of infant mortality are possibly related to poor health literacy and lack of access.

The development of this prenatal care health literacy instrument for American Indian mothers is a tool to evaluate prenatal care health literacy. We hope that this instrument will be used to assess health literacy so that it can be improved. Increased health literacy has the potential to improve pregnancy and birth outcomes. The next steps include, pilot research of this instrument will be conducted in American Indian communities throughout the US, both on reservations and in rural areas to assess both validity and feasibility.

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Chapter 336

BREAKING THE CYCLE OF CHILDHOOD ADVERSITY THROUGH PEDIATRIC PRIMARY CARE SCREENING AND INTERVENTIONS: A PILOT STUDY

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ABSTRACT

Adverse childhood experiences (ACEs) were defined in the landmark 1998 CDC/Kaiser Permanente Study as traumatic experiences during childhood. These include any form of abuse, neglect, or household dysfunction, such as parental divorce, intra-parental violence, parental addiction, incarceration, and mental illness. ACEs have been shown to substantially contribute to serious health problems in later life, such as mental illness, addictive behaviors, obesity, cardiovascular disease, and other chronic conditions. Numerous epidemiologic studies have demonstrated that exposure to an increased number of ACEs is associated with poorer health outcomes. While ACEs affect all socioeconomic classes, there is a higher prevalence among low-income populations. Interventions that support parenting and address family, social, and economic stressors have been shown to mitigate the impact of ACEs on future health. We sought to develop a process for addressing ACEs in a pediatric primary care office with an existing integrated Behavioral Health and Resource Team. We first assessed baseline knowledge

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and perceptions of ACEs among a sample of our clinic providers and local parents/caregivers. Next, we developed, and pilot tested a screening, brief intervention, and referral protocol to provide parenting resources and other supportive measures that would mitigate ACEs and promote resilience in both the parents/caregivers and children. Finally, we surveyed parents/caregivers of patients to obtain their feedback on feasibility, acceptability, and appropriateness of ACEs screening. Our long-term goals are to identify effective feasible pediatric primary care approaches to addressing trauma, promoting resiliency, and breaking the cycle of trauma and health disparities.

INTRODUCTION

The term *Adverse Childhood Experiences* (ACEs) is used to describe a wide range of traumas experienced during childhood including abuse, neglect, and other stressors. The 1998 study by the Centers for Disease Control (CDC) and Kaiser Permanente assessed 10 types of ACEs: five personal — physical abuse, verbal abuse, sexual abuse, physical neglect, and emotional neglect; and five related to dysfunction in other family members: parent alcohol abuse, domestic violence against the mother, parental incarceration, parental mental illness, or the loss of a parent through divorce, death, or abandonment [1]. In the seminal study published in 1998, data was collected between 1995-1997 from 17,000 Kaiser members who completed surveys on their childhood experiences and current health status and behaviors [2]. This study assessed the association between the 10 ACEs and adult health outcomes including mental health (depression, suicidality), physical health (heart disease, cancer, chronic lung disease, skeletal fractures, liver disease, obesity), and health-related behaviors (alcoholism, drug abuse, smoking, high numbers of sexual partners) [2]. Prior to that survey, there had been no studied association connecting early childhood adverse experiences and adult medical problems and behaviors.

In the 1998 study, the authors aggregated the reported ACEs (each counting as one point) into a total ACE score. For example, a respondent who reported experiencing physical abuse, witnessing a parent being physically abused, losing a parent to incarceration, and experiencing life with a parent who suffered from mental illness during childhood would have an ACEs score of 4. The study concluded that individuals with higher ACE scores had a higher risk of developing the above listed poor health outcomes as adults. Persons who had experienced four or more categories of childhood exposure, compared to those who had experienced none, had 4- to 12-fold increased health risks for alcoholism, drug abuse, depression, and suicide attempt; a 2- to 4-fold increase in smoking, poor self-rated health, ≥ 50 sexual intercourse partners, and sexually transmitted disease; and a 1.4- to 1.6-fold increase in physical inactivity and severe obesity [2]. Additionally, adults with the highest number of ACEs had a life expectancy 20 years less than those with fewer ACEs [1].

Subsequent to the CDC/Kaiser study, there have been many other studies examining the relationship between ACEs and adult health. A meta-analysis of population-based studies published through 2016 included 37 studies with 23,719 participants [3]. The study found strong positive associations between an ACE score of 4+ and all measured negative health outcomes, such as overweight, diabetes, problematic drug use, violence, alcohol abuse, sexual risk taking, and mental illness. Furthermore, other studies have shown that ACEs were positively associated with poor health outcomes in adolescents, such as increased rates of

early sexual debut, teen pregnancy, self-harm, suicidal ideation, and suicide attempts [4]. Furthermore, studies have shown that women who report greater exposure to ACEs have a greater risk of experiencing very early sexual initiation and increased potential exposure to Human Immunodeficiency Virus and Sexually Transmitted Illnesses' [5].

Current research is starting to show that ACEs create a pathological condition called 'toxic stress' that can play a powerful role in disrupting the architecture of the developing brain, thereby negatively influencing behavioral, educational, economic, and health outcomes [6]. Childhood trauma and toxic stress adversely affect and alter a child's physiologic functioning and epigenetic expression, altering the developing immunologic and hormonal systems, further impacting their emotional and cognitive systems [2]. These physiological and developmental changes findings have led the American Academy of Pediatrics (AAP) to acknowledged childhood trauma and toxic stress as foundational causes of morbidity and mortality [3]. In the United States, it was estimated that in 2008 the total lifetime economic burden associated with childhood trauma was approximately \$124 billion. This economic burden rivals the cost of other high-profile public health problems, such as stroke and type 2 diabetes. The lasting effects of childhood trauma and toxic stress have multi-generational consequences due to the perpetuation of the Cycle of Trauma and Health Disparities.

CYCLE OF TRAUMA AND HEALTH DISPARITIES

The Cycle of Trauma and Health Disparities is based on the Break the Cycle model for children's environmental health disparities. Abuse, neglect, and household dysfunction are examples of ACEs that the patient is exposed to during the developing years (single black circle). These events have been shown to disrupt neurological and physical development, as the child's physiological response to stress becomes dysregulated. The ongoing stress leads to both hypertrophy and over activity in the amygdala and a decrease in neural connections between the limbic system and the hippocampus, which is involved in memory function, and medial prefrontal cortex, which is involved in executive functioning and decision-making (double black circle) [7]. These changes in brain development and connectivity lead to impaired memory, disordered mood, and a lack of inhibitory control which can lead to maladaptive behavioral responses such as addictive behaviors or violence. In adulthood, and as parents, the maladaptive behaviors and poor mental and physical health will have a detrimental impact on their provision of a nurturing, resourceful environment for their children and increase the likelihood that their children will also experience ACEs [3], perpetuating what we are calling the "Cycle of trauma and health disparities."

Health care delivery systems and pediatric providers in particular, are in a unique position to identify both risk and resilience factors for the healthy development of the children and their families in their care. In response to the large and devastating burden on individual health as well as the great economic and public health burden caused by childhood trauma, the AAP issued a policy statement urging pediatricians to focus on early screening, prevention, and interventions to manage childhood trauma and toxic stress in their practices [4]. However, in the primary care setting, a major stumbling block to addressing this issue is the availability of efficient ways to identify patients and families at risk for, or experiencing current trauma or the adverse effects of past childhood trauma. Moreover, there are few

evidenced-based trauma-informed interventions that can be implemented in a busy primary care practice. The goal of our project was to develop a process for addressing ACEs in a pediatric primary care clinic with an existing integrated Behavioral Health and Resource team. The clinic Behavioral Health and Resource Team is led by a clinical psychologist and a clinical social worker, and consists of undergraduate and graduate level social workers, as well as doctoral level psychology students [8]. The team was developed to perform assessments, brief interventions, and referrals in response to same-visit concerns identified by the pediatrician, as well as consults to address a variety of concerns [9]. Research included baseline assessment of clinic provider and parent/caregiver knowledge and perceptions of ACEs, development and pilot testing of an ACEs screening, brief intervention, and referral protocol, and collection of parent/caregiver feedback on screening.

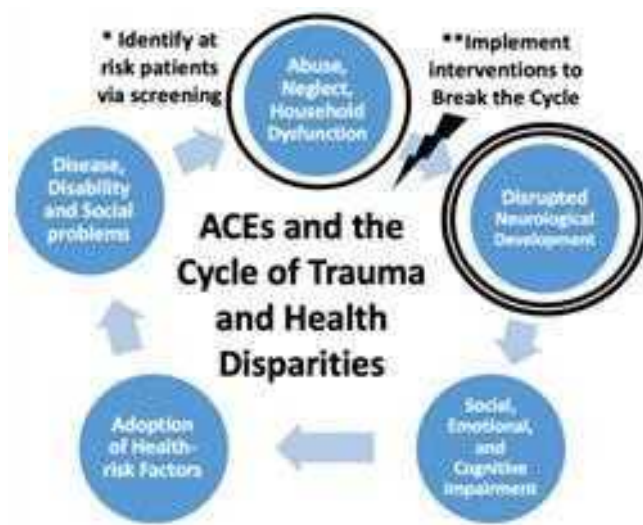


Figure 1. Cycle of trauma and health disparities.

The long-term goal of this work is to inform approaches for the Pediatric Primary Care Setting that will help to break the Cycle of Trauma and Health Disparities. The circled areas are those that are addressed through our screening, brief intervention, and referral program.

OUR STUDY

The setting for this study was an academic pediatric primary care clinic with an existing integrated Behavioral Health and Resource Team located in South Central Appalachia. Eighty-five percent of the children served by the clinic are publicly-insured. In order to qualify for government funded health insurance, a family of four must earn less than \$34,248 per year, which is at 138% of the federal poverty line in 2018. Procedures were reviewed and approved by the East Tennessee State University Institutional Review Board.

Phase I. Knowledge of ACEs

Healthcare providers, who were not previously instructed on ACEs or ACEs screening in the clinic were invited to complete a survey on their knowledge of ACEs and their beliefs about how ACEs affect parents and children. Additionally, parents/caregivers 18 years of age or older visiting a health education table at a local community event were invited to complete the same survey. After being provided with a definition of ACEs, participants were first asked if they had heard of the term “ACEs” before. Next, using a 5-point Likert-type scale, they were asked to rate their knowledge and perceptions of how ACEs impact children’s behavior, adult mental and physical health, and parenting, as well as how support systems may counteract the effects of ACEs. Responses were entered into an Excel spreadsheet and analyzed using IBM SPSS Statistics. Survey collection occurred in July 2017.

Phase II. Screening and Intervention Protocol Development

A “Champion Team” consisting of medical, psychology, social work, nursing, case management, and community home visiting providers developed a new protocol for ACEs screening in the clinic using funding from a State of Tennessee *Building Strong Brains* grant. The team also facilitated training on ACEs and the new protocol for healthcare providers and staff in the clinic using resources from Substance Abuse and Mental Health Services Administration and Tennessee’s Building Strong Brains including discussion of how to communicate about scores with families [10]. The Center for Youth Wellness ACE-Questionnaire (CYW-ACE-Q) was adapted for use as a self-administered parent screener and child screener by parent/caregiver proxy [11]. The CYW ACE-Q is intended for use in pediatric and family practice settings and is available in three age-specific versions and in English and Spanish. It takes approximately two to five minutes to complete the questionnaire.

Screening Questionnaire included a list of ACEs and asked the respondent to simply list the number experienced out of a possible total of ten. Due to concerns about mandatory reporting requirements, a question was added to the child screener asking the respondent to separately indicate if the following two ACEs had been experienced: “Someone pushed, grabbed, slapped, or threw something at your child OR your child was hit so hard that your child was injured or had marks,” and/or “Someone touched your child’s private parts or asked your child to touch their private parts in a sexual way.” Screeners were distributed by the nurse during check-in for their scheduled clinic visit along with an educational resource handout on ACEs and resilience developed by the Champion Team. Education on childhood trauma and resiliency and the proposed screening protocol was provided to all clinicians and staff by the Champion Team. Parent/caregiver screeners were administered at the 1-month well child visit or first visit to the clinic. The child screeners were administered during the 12 month - 5-year annual well-child visits. Scores from the screening questionnaires were documented in the electronic health record (EHR) and discussed by the provider during the encounter. After receiving a brief summary of the clinician’s concerns, also referred to as a “warm handoff,” for a patient’s elevated ACE scores or other behavior/social issues, the

clinic Behavioral Health and Resource Team offered further assessment, resources, and support.

Families with an ACE score of 2 or higher were offered education and resources including *The Incredible Years Well Baby Program* (TIY), during well child visits in the first 9 months of life [11]. TIY is designed to promote emotional and social competence and to prevent, reduce, and treat aggression and emotional problems in young children. The ultimate goal of TIY is to reduce the chance of developing later delinquent or at-risk behaviors [12]. It has also been evaluated as a prevention program with children who are at risk for delinquent or high-risk behaviors because of family or demographic factors such as poverty, parental mental health problems, or poor parenting skills. The Well Baby Program was recently developed for use in the primary care setting. This program consisted of watching and discussing an age-appropriate video of parent-child interactions with a team member during the visit. A summary handout of parenting tips from the program was also provided.

Families with an ACE score of 4 or higher received education and resources from the Behavioral Health and Resource Team and were invited to participate in home or group visits including up to 10 hours of *Nurturing Parenting* (NP) [13]. NP is an evidence-based program shown to improve parenting skills, problem solving, communication, and developmentally-appropriate expectations and to decrease violence in families at high risk of child maltreatment within diverse populations [13, 14].

All families seen during this period for well child visits were provided with locally-developed *ReadNPlay for a Bright Future* materials and *Reach Out and Read* books and were referred to *ReadNPlay* family community events [15]. Care was coordinated for referred patients during bimonthly team conferences.

The number of patients and parents/caregivers with elevated screening results referred to the parenting programs was abstracted from the EHR on a monthly basis during the project period (October 1, 2017-June 30, 2018). Percentages were calculated based on the number of well child visits performed with screener administered during the project period.

Due to funding constraints, the local Nurturing Parenting program referral resource was discontinued during phase three.

Phase III. Parent/Caregiver Feedback on Screening

A survey was constructed to assess parent/caregiver perceptions of acceptability, appropriateness, and feasibility of ACEs screening and interventions. The surveys were developed using the Acceptability of Intervention Measure (AIM), Intervention Appropriateness Measure (IAM), and Feasibility of Intervention Measure framework. Each construct was evaluated with four-item measures of implementation outcomes that are often considered “leading indicators” of implementation success [16]. Each indicator was graded on a 1 to 5 scale, with 1 being completely disagree and 5 being completely agree using the following acceptability, appropriateness and feasibility constructs:

Our team created study flyers containing information about ACEs and ACEs scores, which were offered to parents who completed an ACE-Q screener during their child’s office visit in one of three resident continuity clinics during April-May 2019. Parents who wished to complete a feedback survey did so after the visit before leaving clinic. As compensation for

their time, parents were offered a small toy or book for their child at the completion of feedback survey. Survey data was entered into IBM SPSS Statistics and summarized descriptively using means, standard deviations, and percentages. A summary mean of the four items for acceptability, feasibility, and appropriateness was also calculated.

FINDINGS

During the first phase of the study, 51 parents/caregivers and 16 healthcare providers in the clinic were surveyed in Summer 2017. Results are shown in Table 1 and Figures 1 and 2. The majority of the respondents were white females within the 25-44 years age group. Fewer than one-third of parents/caregivers in this sample had heard of the term “ACEs” prior to receiving this survey. However, after being provided with a definition of ACEs, most respondents agreed that ACEs could affect children's behavior and adult mental health.

Table 1. Demographic and Baseline Characteristics of Study Population in Phase I

	Parents/Caregivers (n = 51)	Healthcare Providers (n = 16)
Gender		
Female	78.4%	93.8%
Male	21.6%	6.3%
Age (Years)		
18-24	5.9%	12.5%
25-34	23.5%	50%
35-44	43.1%	12.5%
45-54	11.8%	12.5%
≥55	15.7%	12.5%
Race/Ethnicity		
White	84.3%	87.5%
Hispanic/Latino	3.9%	0%
Black/African American	7.8%	0%
Asian/Pacific Islander	3.9%	12.5%
Heard of ACEs before	27.5%	50%

Table 2. Demographic characteristics of parent/caregiver ACE-Q screening feedback survey respondents during Phase III

Parent/Caregiver Demographics	# (%)
Age	
18-24 years	7 (41.2%)
25-34 years	6 (35.3%)
35-44 years	1 (5.9%)
45-54 years	2 (11.8%)
55-64 years	0
65 or older	1 (5.9%)
Race/Ethnicity	
Caucasian	15 (88.2%)
Hispanic	2 (11.8%)
Gender	
Female	13 (76.5%)
Male	4 (23.5%)

Agreement was less for perceptions of effects on physical health in adults. Most respondents recognized that a parent’s own ACE exposure could make parenting more difficult and that having a strong support system is helpful in counteracting these negative effects. At the start of the study, it was surprising that only half of healthcare providers were familiar with the term ACEs. After being provided with a definition of ACEs, most healthcare providers agreed that multiple ACEs can have adverse effects on children and adults.

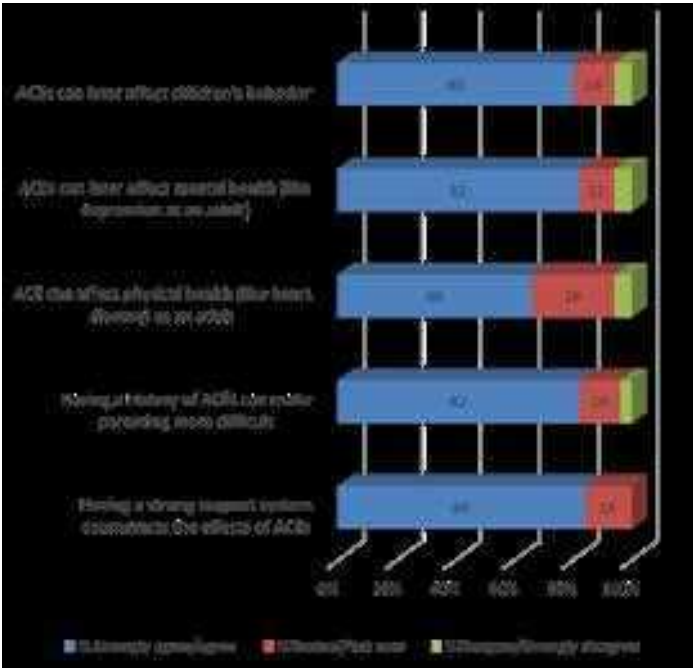


Figure 2. Knowledge and Perceptions of Parents/Caregivers about ACEs (n = 51) Phase I.

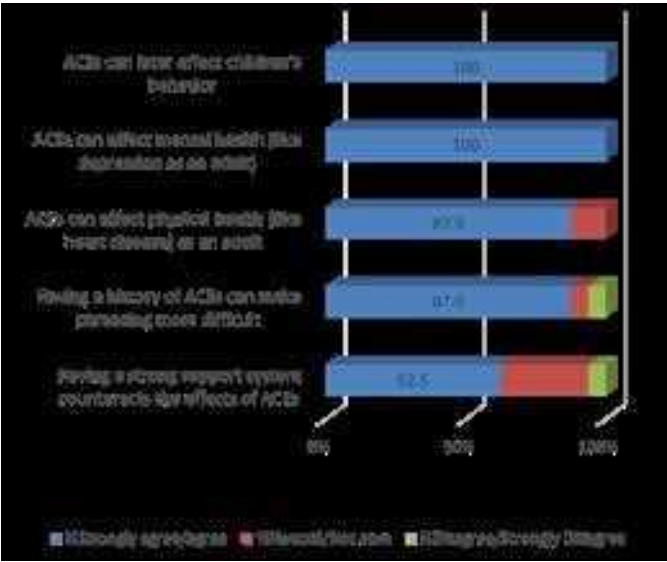


Figure 3. Knowledge and Perceptions of Health Professionals about ACEs (n = 16): Phase I.

Phase II: ACEs Screening and Intervention Protocol Development and Pilot-Testing

Among the 96 parents/caregivers screened, 37.5% reported an ACE score of four or higher and 53.1% reported an ACE score of two or higher for themselves. Out of 66 child screeners completed for children 1-5 years of age, parents/caregivers reported ACEs score of four or higher in 3% of children. Based on our screening protocol, we referred over one third of families for Nurturing Parenting and over one half of patient families with infants 1-9 months of age for TIY.

Table 3. Means and standard deviations for acceptability, feasibility, and appropriateness items (1 = Completely Disagree; 2 = Disagree; 3 = Neutral, 4 = Agree, 5 = Completely Agree)

Question	Mean (standard deviation)
Acceptability	Possible range: 1-5
The ACE-Q screening during my office visit meets my approval	4.89 (0.323)
The ACE-Q screening during my office visit is appealing to me	4.78 (0.428)
I liked the ACE-Q screening during my office visit	4.78 (0.428)
I welcome ACE-Q screening during my office visit	4.78 (0.428)
Feasibility	Possible range 1-5
ACE-Q screening seems fitting during my child's office visit	4.72 (0.575)
ACE-Q screening seems suitable during my child's office visit	4.67 (0.594)
ACE-Q screening seems applicable during my child's office visit	4.33 (1.029)
ACE-Q screening seems like a good match for my child and my family	4.00 (1.085)
Appropriateness	Possible range: 1-5
ACE-Q screening seems implementable during my child's doctor visit	4.28 (0.826)
ACE-Q screening seems possible during my child's doctor visit	4.33 (0.907)
ACE-Q screening seems doable during my child's doctor visit	4.44 (0.784)
ACE-Q screening seems easy to use	4.67 (0.594)

A total of 18 out of 29 parents/caregivers screened for ACEs during the project period completed a feedback survey (62%). Results are shown in Tables 2 and 3. The mean summary scores for acceptability, feasibility, and appropriateness were 4.80, 4.33, and 4.43, respectively. Only two parents/caregivers completed a feedback survey on TIY, but also described it as feasible, acceptable and appropriate. The surveys filled out by both these parents shows that they marked a grade of 5 for each question on the survey provided, thus the parents strongly agreed with the intervention of the TIY. TIY was provided to only three families during the project period due to a small number of infants seen in the continuity clinics.

DISCUSSION

In this study, we assessed the baseline knowledge and perceptions of ACEs among a sample of our clinic providers and local parents/caregivers attending the clinic with their children. We then developed and pilot tested an ACEs screening, brief intervention, and

referral protocol for families with children 5 years of age and younger in a pediatric primary care clinic with an integrated Behavioral Health and Resource Team. Following implementation of the protocol, we assessed parent/caregiver feedback on ACEs screening during well child visits. ACEs screening was imperative to better understand our patient population in hope of providing those at increased risk of negative health outcomes with resources to help build resilience. In order to break the cycle of trauma and health disparities, it is imperative to identify the families experiencing trauma and to intervene as early in the life of the child as possible. Early intervention is protective against the adverse effects of toxic stress on brain development and connectivity, which can lead to impaired memory, disordered mood, and a lack of inhibitory control with regards to impulsive behavior. Thus, early intervention can be preventative against maladaptive behavioral responses such as addictive behaviors or violence [7]. However, prior to our intervention, we found that less than one-third of parents/caregivers and only 50% of healthcare providers in the clinic were familiar with ACEs, suggesting a need for education among families and healthcare providers. Indeed, national data from 302 general pediatricians participating in the 2013 American Academy of Pediatrics Periodic Survey revealed that only 11% were very or somewhat familiar with the ACE study [17]. Thus, our providers were found to have baseline for ACEs awareness greater than that found in a national survey. This finding is likely due to the population that our clinic serves, as 85% of our patients are publicly-insured. Nonetheless, these data suggest additional training of pediatric providers is needed to increase understanding of ACEs and long-term health outcomes.

Multiple research papers have demonstrated a graded dose-response relationship between the number of ACEs a person experienced and their health-risk behaviors [3]. As the strength of the literature and evidence has grown, ACEs scores have now been linked, in the same graded dose-response relationship, to more than 40 health outcomes [18]. An example particularly relevant to the Appalachia due to the opioid drug crisis, involves the graded risk increase for drug use with increasing ACEs scores. In a 2018 research paper, Tilson investigated opioid use and ACEs within the population of North Carolina and found that each ACE increased the likelihood for early initiation of drug use by 2- to 4-fold [19]. Compared with people with no ACEs, people with $>$ or $=$ 5 ACEs were 7- to 10-fold more likely to report drug use problems, addiction, and parenteral drug use [19]. These alarming findings highlight the importance of mitigating the effects of ACEs, and the need for sufficient resources to assist families with high ACE scores and is also a pre-requisite for an effective screening program. We found that the prevalence of ACEs was high in our clinic population with ACE scores of four or higher reported for 37.5% of the parents and 3% of children. An ACE score of two or higher was reported for 53.1% of parents/caregivers. Based on our screening protocol, we referred over one third of families for Nurturing Parenting and over one half of patient families for the IY. Maintaining sufficient resources to meet these needs was a challenge, and funding for Nurturing Parenting was lost during the project period. At the same time, our findings identified a large number of at-risk families, suggesting that development of additional resources should be a priority, for local community clinics such as ours to the state and federal government. The direct cost childhood trauma is measured in the billions, and the downstream effects of improved screening and appropriate and adequate interventions for those affected, has the potential to decrease the rates high cost high burden disease such as obesity, heart disease and diabetes.

Notably, the rate of reported ACEs in our clinic was higher than that found in Tennessee or nationally. In 2014 in Tennessee, 17% of adults reported having experienced four or more ACEs while 42% reported two or more [20]. The high percentage of ACEs among patients and parents/caregivers in our clinic was not unexpected due to the relatively low socioeconomic status of our clinic population and the high rates of maternal opioid use disorder and neonatal abstinence syndrome in Northeast Tennessee [21, 22]. Recent Behavioral Risk Factor Surveillance System (BRFSS) ACE data from 2011-2014 showed that nationally, 15.8% of adults reported 4 or more ACEs, and 38% reported an ACE score of 2 or more [20]. Estimating the magnitude of families affected by ACEs in a pediatric primary care practice can aid in the development and allocation of services and resources.

The ACE-Q screener used in Phase II was suitable for our study population as most parents/caregivers who completed the feedback survey reported the screening as appropriate, feasible, and acceptable to them as part of a well-child visit. Providers in our clinic received training on ACEs prior to initiating screening, including on how to discuss scores with families with sensitivity, and our clinic was equipped with a Behavioral Health and Resource Team to provide support to families experiencing ACEs. Similarly, a study published in 2018 using thematic interviews with parents of children under 6 years of age attending an urban pediatric clinic found consistent support for ACEs screening for the purpose of linking to services as well as recognition of the intergenerational nature of ACEs [23]. Surveys conducted with 152 predominantly Latino adults attending a federally qualified health center found that, following screening, 86% of respondents were comfortable with ACEs screening [24]. In larger study of 480 pregnant women screened at 14-23 weeks gestation, over 90% were somewhat or very comfortable completing screeners and discussing results with their physician [24]. Eighty five percent somewhat or strongly agreed that clinicians should ask prenatal patients about their ACEs [25].

The American Academy of Pediatrics published a policy statement on Toxic Stress, much of which is a result of ACEs [6]. Among their set of recommendations for pediatric practices was to institute screening of families at high risk for ACEs and Toxic Stress and then to provide targeted support for the parents and other caregivers by addressing key social and economic stressors through targeted referrals and by enhancing the caretakers' parenting competence [6]. A potential barrier to ACEs screening is the burden on families and clinic staff at well-child visits. To address this barrier, electronic screening tools can be sent to families via email before the clinic visit. Allowing a family to fill out some of the screeners before they come to the clinic may save time during the visit and reduce the burden on families and staff. However, complete follow up of families with positive screening results reported prior to the visit may be challenging in populations with high "no-show" rates for visits, meaning the patient does not attend their recommended well child visits. Effective screening and intervention often require partnership with external agencies such as early intervention and other social services. In our practice, children have access to a Behavioral Health Resource team which includes a child psychologist and a social worker, who work in close partnerships with local social services such as Tennessee Early Intervention Services, Youth Village, and multiple behavioral therapists. However, most outpatient pediatrics clinics do not have a Behavioral Health Resource team, which can make it more challenging to access local resources or simply are situated in a region that does not have these providers. The lack of availability of expertise and partnerships with community resources to address ACEs is another potential barrier to primary care screening. Integrating professionals who can

provide behavioral health and social services into primary care offices can address this barrier and improve access to needed services and resources.

In this project, we were able to initiate an ACEs screening protocol for a pediatric primary care clinic, which enabled identification of at-risk families. ACEs screening was positively perceived by most parents/caregivers. Approaches to addressing childhood trauma and considerations for ACEs screening in primary care setting has been discussed elsewhere in depth [4, 5, 8, 9]. Our experience suggests that identifying provider training needs, considering parent/caregiver perceptions and preferences, and assessing resource needs are helpful initial steps. The presence of integrated behavioral health and social services in a clinic setting can be invaluable in addressing the needs of families at-risk for experiencing challenges because of their ACE score.

CONCLUSION

Given the high prevalence of ACEs and toxic stress and the high burden of down-stream physical and mental health problems related to these exposures, it is imperative to continue to explore optimal approaches for primary care practices to integrate screening protocols to identify families at risk, to develop sensitive and skilled staff to assist families, and to build partnerships with community organizations that can help support families, prevent ACEs, and break the cycle of trauma and health disparities.

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Chapter 337

EDUCATING CLINIC SUPPORT STAFF TO ENHANCE EARLY LEARNING ENVIRONMENTS THROUGH PEDIATRIC WELL-CHILD VISITS

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ABSTRACT

A rich early language environment in the first years of life is important for optimal language and cognitive development. Socioeconomic disadvantage in a child's early language environment can have long-term impacts on educational attainment, employment opportunities, and health outcomes. In an effort to enhance the early language milieu for children from low-income households, this study aims to 1) improve pediatric clinic support staff's knowledge about early cognitive and language development and 2) positively influence their perceptions of the role they can play in educating parents/caregivers about the importance of early language exposure in the first three years of life. The study was run as a quasi-experimental, One-Group, Pretest-Posttest Design. The participants were pediatric clinic support staff members from four clinics in the Chicago area ($n = 58$). Participants' knowledge and perceptions were assessed one week prior to a curriculum presentation intervention and immediately following the intervention. Analysis showed a significant increase in participants' knowledge of early cognitive and language development post-intervention (infancy: $M = 24.74$ vs. $M = 28.05$, $P = 9.63E-09$; early childhood: $M = 25.78$ vs. $M = 29.90$, $P = 1.39E-11$). Clinic support staff also reported that after attending the presentation, they felt more comfortable and were more likely to discuss these topics with parents/caregivers in clinic. This study highlights the importance of educating clinic staff about early language and cognitive development and informing them of the crucial role they can play in

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helping to enhance early language environments for their young patients, particularly those from low socioeconomic backgrounds.

INTRODUCTION

The first three years of life are said to be the most important for cognitive and language development. During this period, new neural connections are formed at a rate of over 1 million per second [1]. Early social experiences and rich language interactions with nurturing caregivers are critical for this rapid brain development and set the foundation for future learning [2, 3]. A child's early language environment is an important, yet often overlooked, social determinant of health [4]. Research suggests that disparities in the quality of this early language environment exist and disproportionately affect those in poverty [5]. These disparities have been shown to negatively impact brain growth—as well as future educational, occupational, and health outcomes—among socioeconomically disadvantaged children [6-8].

Research shows that the negative impacts of poverty on brain development become apparent well before children enroll in school. In a longitudinal study by Tamara Halle et al. [9], nine-month old infants in families of low socioeconomic status (SES) scored lower on cognitive development assessments than their peers. This disparity tripled in severity by 24 months of age. That being so, programs aimed at supporting children's cognitive development after they begin school may come too late to alter the trajectories of children's neurocognitive development. [10]. Therefore, interventions in the critical first three years of life are necessary to prevent such disparities at their onset.

Parents and caregivers in the home are the key mediators of a child's early learning environment. Disparities in early social interactions and language input among children from differing SES backgrounds have been attributed to differences in parental knowledge of infant development [11, 12]. Further, parental knowledge about the importance of early language exposure has been shown to be predictive of parental behaviors with their children [13]. These behaviors inform the quality of adult-child interactions and a child's early language environment. This environment sets the foundation for a child's brain and language development, which sets the basis for their school readiness and educational attainment. Lower educational attainment has been shown to result in decreased employment opportunities, limited residential options, and ultimately, poor health outcomes [4]. The diagram below represents this cycle of early learning disparities.

Fortunately, studies have shown that well-planned, parent-directed interventions in low-income populations can significantly improve various parenting behaviors with their children [14]. Therefore, interventions to empower all parents with increased knowledge of early brain development and everyday strategies to enrich their children's early language environments represent a promising opportunity to reduce educational inequities and subsequently break the cycle of early learning disparities.

There are 12 recommended routine well-child pediatric visits during the first three years of life [15]. As a result, pediatricians and pediatric clinic staff are uniquely positioned to intervene during this critical period of foundational brain development. In fact, in 2017, the American Academy of Pediatrics established 'early brain and cognitive development' as an integrated child health priority in their "Agenda for children" [16]. However, while studies have shown that parents want more information on early childhood learning at pediatric visits,

they do not regularly receive this desired insight [17]. A recent study surveying 236 parents in Chicago area clinics found that only a minority of parents reported receiving information on cognitive development topics at well-child visits, such as “brain growth” (25.8%), “how babies learn” (13.1%), and “learning to talk” (9.3%) [18].

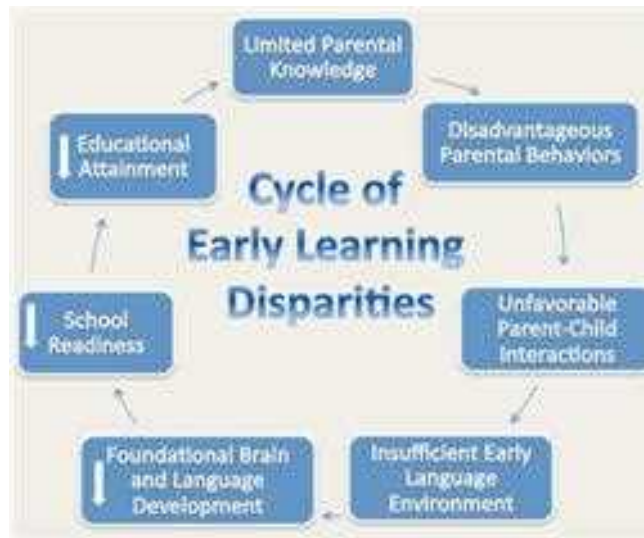


Figure 1. The cycle of early learning disparities.

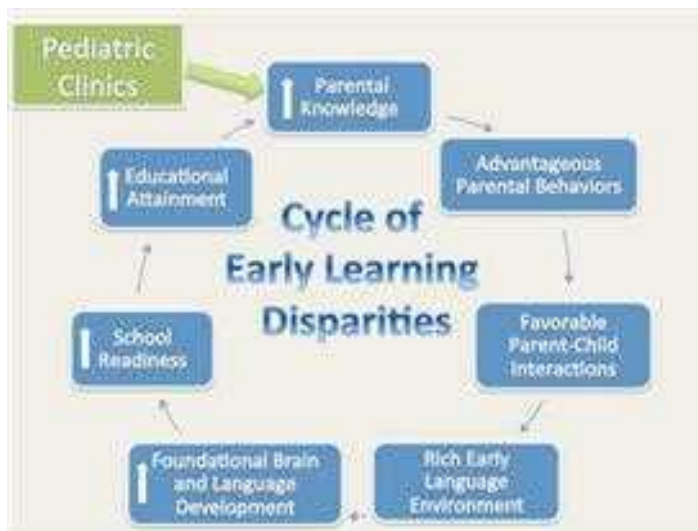


Figure 2. Use of pediatric clinics to break the cycle of early learning disparities.

While pediatricians are often considered the primary source of guidance for parents, they have a large mandate to cover in the relatively brief, well-child visit and may not have the time to engage families and emphasize all anticipatory guidance topics equally [19, 20]. The clinical support staff can play a meaningful role in actively engaging families by providing information about language interactions and enhancing discussions of important topics during clinic visits [21]. Therefore, with the objective to break the cycle of early learning disparities

(see Figure 1), this study intends to use pediatric clinics - and more specifically, the support staff in these clinics - as an access point to positively impact parental knowledge of early brain development (see Figure 2). Our study aimed to create, deliver, and test a curriculum intervention designed to improve pediatric clinic support staff's knowledge about early cognitive and language development, and positively influence their perceptions of the role they can play in educating parents/caregivers about the importance of early language environments during pediatric clinic visits. We hypothesized that after attending our intervention, study participants would exhibit improved knowledge and report increased comfort and likelihood to engage in discussion of these topics with parents during well-child visits. The ultimate goal of this intervention was to see if we could cultivate a pediatric clinic culture that identifies early cognitive and language development as a priority, and considers educating parents on this topic a standard of care.

OUR STUDY

This study was conducted at four pediatric clinics that serve predominantly families with public assistance in the Chicago area. The study began in December 2018 and concluded in February 2019. The clinics were identified through email correspondence with clinic coordinators or directors. All pediatric clinic staff other than the physicians (i.e., nurses, medical assistants, laboratory technicians, receptionists, etc.) were asked to volunteer to participate in the study, including attending an intervention and responding to surveys at their clinic. Staff members were eligible to participate if they were at least 18 years old and English-speaking. Participants were verbally consented prior to the curriculum intervention and received a \$50 gift card as compensation. The Biological Sciences Division Institutional Review Board at the University of Chicago Medicine (IRB#12-1172-CR006) approved this study.

Intervention

A curriculum intervention was developed specifically for pediatric clinic support staff. The multimedia curriculum included an explanation of the science behind early cognitive and language development as well as common misconceptions about these topics and specific strategies and examples for addressing these topics with parents in clinic. The intervention was delivered in the form of an in-person, group presentation at each clinic.

Measures

A demographics questionnaire was administered to study participants about one week prior to the curriculum intervention. Paper versions of the questionnaires were delivered to the clinic for participants to complete at their leisure. The completed questionnaires were collected from the clinic about two days prior to the scheduled intervention date.

Knowledge

Along with the demographics questionnaire, participants completed the Scale of Parent/Provider Expectations and Knowledge (SPEAK) [22]. The SPEAK assesses providers' expectations on developmental milestones and their knowledge about the role of caregiver responsiveness and inputs in children's cognitive and language development during infancy (birth-6 months) and early childhood (birth-5 years). Participants responded to 1 item on a 6-point scale, ranging from 0 (in elementary school, 6 years and up) to 5 (as an infant, 0 to 6 months), and 17 items on a 4-point scale, ranging from 0 (definitely true) to 3 (definitely not true). Two SPEAK sum scores including Infancy ($\alpha = .74$) and Early Childhood ($\alpha = .72$) were calculated. Higher scores represented more knowledge. This questionnaire was administered to participants a second time immediately following the curriculum intervention.

Beliefs

Participants were given qualitative questions to assess their initial beliefs about educating parents on early cognitive development and the importance of early language exposure. Multiple choice questions assessed what role the participants believed they had in educating parents and their comfort level in doing so. Post-intervention questions assessed if participants found the presentation useful and whether or not it made them feel more comfortable discussing topics such as early language and cognitive development with parents during well-child visits.

Reported Behaviors

To assess baseline behaviors, a pre-intervention question asked the participants if they currently discuss early language and brain development with parents/caregivers of infants.

Table 1. Participant demographics

Variable		Category	% (n = 58)
Age		18-24	3.4
		25-34	36.2
		35-44	25.9
		45-54	22.4
		55-64	12.1
		65+	0
Sex		Female	86.2
		Male	8.6
		Prefer not to answer	5.2
Race	Hispanic or Latino	Any race	27.6
	Non-Hispanic	Black or African American	46.6
		White	10.3
		Asian or Pacific Islander	3.5
		Multiracial	1.7
	Prefer not to answer		10.3

Perceived barriers to discussing these topics with parents, along with potential solutions to these barriers, were evaluated with checklist items and free response. Post intervention, participants were asked whether or not the curriculum presentation made them more likely to discuss early language and cognitive development with parents of young children during well-child visits.

Statistical Analysis

Two SPEAK score sums, i.e., infancy (birth-6 months) and early childhood (birth-5 years), for each participant were calculated from the pre- and post-intervention SPEAK surveys. Pre- and post-intervention scores were compared using two-tailed t-tests in Microsoft Excel. In order to investigate whether the intervention had similar effects on participants with varying education, we compared the baseline and post-intervention SPEAK scores among participants with high education (Bachelor's degree or above) and participants with low education (less than Bachelor's degree) separately. Responses to pre- and post-intervention qualitative questions were tallied and the percentages of each response on pre-intervention questions were compared to those from the post-intervention questions.

FINDINGS

The sample included 58 clinic staff members with a 90.6% retention rate among the 64 participants recruited originally. The majority of participants were female (86.2%) mainly in the 25-34 and 35-44 age ranges (36.2% and 25.9%, respectively; see Table 1). Most participants identified as Black or African American (46.6%), followed by English-speaking Hispanic or Latino participants of any race (27.6%, see Table 1). For education level, the majority of study participants had completed some college credit, technical training or an associate's degree, but had not obtained a bachelor's degree (60.3%; see Table 2).

Table 2. Participant education and job title

Variable	Category	% (n = 58)
Education level	High school graduate, or equivalent (GED)	8.6
	Some college credit, no degree	20.7
	Technical training	24.1
	Associate degree	15.5
	Bachelor's degree	17.2
	Postgraduate degree	12.1
	No response	1.7
Job Title	Medical Assistant	37.9
	Registration/Receptionist/Referral Coordinator/PSR	15.5
	Nurse	13.8
	Manager/Clinic Coordinator	6.9
	Lab Tech	5.2
	Social Worker/Case Manager	5.2
	Medical Interpreter	3.4
	Maintenance/Security	3.4
	Nurse Practitioner	1.7
	Lactation Specialist	1.7
	OutReach Manager	1.7
	Healthy Steps Specialist	1.7
	No response	1.7

Participants held a variety of job titles within the clinics. The largest group was Medical Assistants (37.9%) followed by roles that involved assisting patients at the clinic's front desk (i.e., Registration, Receptionist, Referral Coordinator, Patient Service Representative; 15.5%; see Table 2). The third largest group of participants was Nurses (13.8%).

Knowledge

There was a significant increase in Infancy SPEAK scores from baseline ($M = 24.74$, $SD = 4.18$) to post-intervention ($M = 28.05$, $SD = 2.90$; see Table 3). There was also a significant increase in Early Childhood SPEAK scores from baseline ($M = 25.78$, $SD = 4.37$) to post-intervention ($M = 29.90$, $SD = 2.67$; see Table 4). When comparing baseline and post-intervention SPEAK scores by participant education level (less than Bachelor's degree and Bachelor's degree or above), there was a significant increase in SPEAK scores from baseline to post-intervention for both education levels (see Tables 5 and 6).

Table 3. Infancy SPEAK change in knowledge

	Mean	N	SD	SE Mean	t	df	Significance
Baseline	24.74	58	4.18	.549			
Post-Intervention	28.05	58	2.90	.381	-6.711	57	9.63E-09

Table 4. Early childhood SPEAK change in knowledge

	Mean	N	SD	SE Mean	t	df	Significance
Baseline	25.78	58	4.37	.574			
Post-Intervention	29.90	58	2.67	.350	-8.418	57	1.39E-11

Table 5. Infancy SPEAK change in knowledge by education level

Education Level	Time Point	Mean	N	SD	SE Mean	t	df	Significance
Less than Bachelor's Degree	Baseline	24.70	40	4.046	0.640			
	Post-Intervention	27.98	40	3.084	0.488	-5.344	39	0.000
Bachelor's Degree or Higher	Baseline	24.94	17	4.710	1.142			
	Post-Intervention	28.18	17	2.604	0.631	-3.673	16	0.002

Table 6. Early childhood SPEAK change in knowledge by education level

Education Level	Time Point	Mean	N	SD	SE Mean	t	df	Significance
Less than Bachelor's Degree	Baseline	25.85	40	3.718	0.588			
	Post-Intervention	29.83	40	2.735	0.432	-7.493	39	0.000
Bachelor's Degree or Higher	Baseline	25.88	17	5.732	1.390			
	Post-Intervention	29.94	17	2.609	0.633	-3.833	16	0.001

Beliefs

Prior to the curriculum intervention, participants were asked to respond to the statement "In my role, I feel comfortable sharing information about children's language and brain development with parents/caregivers of infants." Responses greatly varied with 10.5%

“Strongly Agree,” 47.4% “Agree,” 31.6% “Disagree,” and 10.5% “Strongly Disagree” (N = 57). Participants were also asked to gauge what role they thought they played “in teaching parents about their child’s early language and brain development.” 35% of study participants felt that they played either a “Significant” or “Moderate Role” in this, while 36.8% responded “Minor Role” and 24.6% responded “No Role” (N = 58).

After the curriculum intervention, 100% of study participants replied “Strongly Agree” or “Agree” to finding the presentation useful. 98.3% reported “Strongly Agree” or “Agree” to the statement: “The strategies presented in this curriculum make me more comfortable discussing topics such as early language and cognitive development with parents during well-child visits” (N = 58).

Reported Behaviors

On the pre-intervention survey, 81% of participants answered “Never” or “Not Often” when asked if they “currently discuss early language and brain development with parents/caregivers of infants” (N = 58). “No expertise in this topic” was the most selected reason for what prevents participants from discussing these topics in their interactions with parents/caregivers. (50%; see Table 7). Participants felt that having pamphlets to provide parents (69%) and more training on the topic (65.5%) would make them more likely to talk about early language and brain development in their interactions with parents/caregivers of infants (see Table 8).

Table 7. Perceived Barriers to discussions. Some themes among free response answers from participants that selected “Other” include limited interactions with parents/ patients, feeling that other professionals in clinic should have these discussions with parents, and not wanting to spread false information

What prevents you from discussing early language and brain development in your interactions with parents/caregivers of infants? (Select all that apply)	%
Time constraints	39.7
No expertise in this topic	50.0
More important topics to discuss with parents	1.7
Difficult topic for parents/caregivers to understand	6.9
Not a part of my job description	37.9
Other	13.8

Table 8. Reported items to increase likelihood of discussions. Free response answers from participants that selected “Other” either reiterated the need for more training on this topic or stated that having these discussions is not a part of their job description

What are some things that would make you more likely to talk about early language and brain development in your interactions with parents/caregivers of infants? (Select all that apply.)	%
More time	43.1
More training on the topic	65.5
Having pamphlets to provide parents	69.0
Making this an EMR checklist item to discuss	15.5
Financial incentive	8.6
Other	15.5

After attending the curriculum intervention, 100% of study participants stated that they “Agree” or “Strongly agree” with the statement: “I am more likely to discuss early language and cognitive development with parents of young children during well-child visits” (N = 58).

DISCUSSION

Rich language environments, shaped by nurturing adult-child interactions, are critical to building children’s brains in the first three years of life. Disparities in early language environments exist and disproportionately affect those in poverty. Not only do these early learning disparities negatively impact children’s cognitive and language development, they also have long-term impacts on educational attainment, future employment and economic security, and health outcomes. Because parents are the key mediators of a child’s learning environment during this early period, impacting parental knowledge of early brain development, and consequently impacting their interactions with their children, is a pivotal step in breaking the cycle of early learning disparities. In an effort to leverage the touchpoints that well-child visits offer, this study aimed to enhance pediatric clinic support staff’s knowledge about early language and cognitive development and impact their beliefs about the critical role they can play in educating parents about the importance of early interactions. The study was conducted in four pediatric clinics, and the intervention included an in-person curriculum presentation focused on the science of early brain development, the role of pediatric clinic support staff, and strategies to discuss brain and language development with parents during well-child visits.

Findings of the present study demonstrate an increase in knowledge of early cognitive and language development among pediatric clinic support staff after attending the educational presentation. The study also reveals that the staff members are more willing to discuss these topics with parents when they feel properly equipped to do so. The commonly reported lack of expertise on early brain and language development, and the need for more training on this topic in order to discuss with parents, can be addressed by providing the support staff with the education they desire, as well as easy-to-implement strategies to promote these discussions with parents in clinic. The findings of our study show that the curriculum intervention we created had an immediate positive impact on knowledge of early cognitive and language development for staff members regardless of their varying levels of education.

This study demonstrates the need for providing ongoing education to the clinic support staff and supporting them with tools and strategies to engage parents. Using their unique access to families, pediatric office staff can promote the importance of early language environments and encourage families to have rich language interactions with their children. Utilizing all pediatric clinic support staff to participate in these discussions with parents and caregivers can directly enhance patient access to important information during clinic visits [23]. It can also improve overall clinic efficiency and ensure providers feel well supported, and clinic support staff feel more empowered to support parents [24, 25]. These discussions with parents may have immediate positive effects on the parent-child relationship, and with continued reinforcement, could potentially contribute to long-term positive educational outcomes for all children.

Limitations

Some limitations of this study should be noted. As a quasi-experimental design, our study lacks a control group and randomization. Although participants reported an increased likelihood to discuss brain and language development with parents in clinic, our study did not include any behavior measures to assess if these discussions did increase post-intervention. A longer study timeline would allow for the addition of these behavior measures and a third SPEAK assessment at a later point in time to measure for retention of the knowledge gained from our intervention. It is also not clear whether changes in clinic staff behavior would have a significant impact on child developmental outcomes, which is the ultimate goal of this effort. Future research might be able to examine this aspect more fully.

CONCLUSION

This study highlights a valuable opportunity for educating pediatric clinic support staff about early language and cognitive development and the important role they may play in enhancing early language environments for their patients. Providing training to pediatric clinic staff may help increase awareness of the importance of early language exposure, but further studies are needed to investigate the true impact of this intervention on the quantity and quality of discussions with parents in clinic. Leveraging the routine well-child visits and all clinic staff members to make these discussions a standard of care has the potential to help break the cycle of early learning disparities experienced by socioeconomically disadvantaged children at their earliest onset.

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Chapter 338

CONTEXTUALIZING THE SOCIAL AND STRUCTURAL CONSTRAINTS OF ACCESSING AUTISM SERVICES AMONG SINGLE BLACK FEMALE CAREGIVERS

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ABSTRACT

Autism spectrum disorder (ASD) affects 1 in 59 children and represent the fastest growing developmental disorder in the United States. However, disparities in ASD evaluation, diagnosis, and services exist based on social factors such as race, ethnicity, and socioeconomic status. To date, limited qualitative research has been conducted that focuses on the experiences of single black female caregivers of children with ASD who live in low-income, minority, and underserved communities in the United States. Objective: This study aimed to understand interrelated social and structural factors that place children and their families with limited resources at risk of delayed ASD diagnostic services and limited therapeutic services. Methods: The study design is based on in-depth interviews conducted with single black female caregivers of children with ASD who rely on state Medicaid health insurance in metro Atlanta, Georgia (N = 21). A grounded theory analysis of the interviews was used to systematically identify themes and multi-level barriers to ASD services. Results: Despite improvements over the past several decades in diagnosing children with ASD, this study identified multiple and interacting social, economic, and residential barriers to accessing ASD services. Two themes were identified that contextualize barriers to ASD services: bureaucratic processes and geographic location of services. These barriers were compounded by the consequences of being a single female parent, including having limited income, employment options, and social capital. Practical recommendations to break the cycle of ASD service disparities are discussed.

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INTRODUCTION

Autism spectrum disorder (ASD) is defined by the American Psychiatric Association as a lifelong neurodevelopmental disorder characterized by persistent challenges in “social communication and social interaction,” and “restricted, repetitive patterns of behavior, interests, or activities” [1]. According to the Centers for Disease Control and Prevention (CDC), ASD affects 1 in 59 children and is the fastest growing developmental disorder in the United States [2]. Recommended treatment for ASD consists of early intensive behavioral and educational interventions [3]. A trained clinician can reliably diagnose ASD in children as early as 2 years old or younger, but most children are not diagnosed with ASD until after age 4 years [2].

ASD is prevalent in all racial and ethnic groups and across all socioeconomic levels; however, disparities exist in the prevalence of ASD associated with social factors, such as by age, sex, race, ethnicity, and geographic area [2]. For example, boys are four times more likely to be identified with ASD than girls [2]. In metropolitan Atlanta, Georgia, which consists of five counties, including Clayton, Cobb, DeKalb, Fulton, and Gwinnett, the prevalence of ASD for both white non-Hispanic and black non-Hispanic children increased from 1996 to 2010 [4]. However, disparities in prevalence of ASD remain evident between white children (18.1 per 1,000) compared to black children (14 per 1,000) diagnosed with ASD in 2010 [4].

In addition to ASD prevalence disparities, population-based quantitative studies have reported that a range of ASD diagnosis and service disparities are associated with race, ethnicity, and social class [5-9]. A quantitative analysis of Medicaid claims of 406 children in Philadelphia found that black children who received specialty mental health services through Medicaid received more time in treatment before obtaining an ASD diagnosis [5] and were 2.6 times less likely than white children to receive a diagnosis on their first specialty care visit [6]. One study that examined racial disparities in identification of ASD in metropolitan Atlanta found that black children were less likely to be identified with milder forms of ASD and more likely to receive the most severe diagnosis compared to white children [7]. Other studies found that there are ASD disparities associated with age of diagnosis, access to therapeutic services, and even racial representation in special education programs at schools [9-11]. Disparities in early evaluation and ASD diagnosis can significantly affect children with ASD and their families mainly because they delay access to early intervention, which is essential for improved developmental outcomes [11]. It is recommended that children with ASD receive twenty or more hours per week of behavioral intervention such as Applied Behavioral Analysis (ABA) therapy [12]. However, several studies have found that children with ASD who are from racial and ethnic minority populations and communities are less likely than white children with ASD to access publicly funded community-based services, including early intervention and ABA therapy, and those who do are less likely to receive the recommended intensity of twenty hours per week [12].

Although population-based quantitative studies offer important knowledge of factors associated with delays and/or barriers related to ASD diagnosis and services, this literature is relatively descriptive in nature and does not typically consider interrelated social or structural factors that place children and their families at risk of delayed assessment, diagnosis, and/or services [13]. Further, quantitative studies on ASD disparities have little to say about the

complex and multi-level challenges faced by caregivers in accessing services for their children after a diagnosis has been made. Knowledge gained from qualitative research offers a more nuanced and contextualized understanding of health disparities based on individual lived experiences situated within the context of social and structural dynamics through which health disparities arise and are sustained, reproduced, and perpetuated [13].

In contrast to quantitative ASD research, there is limited qualitative research based on the experiences of families living in low-income, minority, and underserved communities. A recent review conducted by the second author (JS) found that existing qualitative research on ASD disparities focused on the high cost of ASD services, and lack of competence and training in ASD diagnosis and interventions among healthcare and educational professionals [13]. The same study found limited qualitative research that examined structural inequities related to operations of systems of care and the regulatory and policy climate [13]. Research on the impacts of caring for a child with ASD in alternative family structures is also limited as well as the responsibility taken on by women in general, who are typically the primary caretakers of children, especially children with disabilities [13-14]. Further, the representation of female caregivers of children with ASD in the United States is often uneven, with most voices in qualitative research and mainstream culture being those of married, white, upper-class mothers who have the time, social capital, and financial resources to seek early diagnosis and acquire expertise and knowledge on how to help their children [13-15]. Our research was informed by these gaps in the existing literature on ASD disparities.

The purpose of this study was to investigate and identify structural inequities that are embedded in the process of navigating state Medicaid insurance for ASD services in Georgia. We define structural inequities as customs, practices, or laws that shape health disparities, including healthcare policies and state programs. Medicaid is a federal program that helps with medical costs for low-income individuals, but how it is designed, managed, and implemented differs from state-to-state [16]. There is a long history of the positive impact of Medicaid policy on statewide access to care for low-income and minority adults and children [17]. For example, reliance on Medicaid has been found to be associated with less out-of-pocket medical expenses and reduced financial burden on families [17]. However, an unequal distribution of Medicaid services exists across the United States (e.g., differences in Medicaid reimbursements for each state) and even within individual states (e.g., differences in county-level spending on education versus healthcare resources) [17-18]. Health insurance, including Medicaid, is one factor among many that has an impact on access to services and health outcomes. Thus, we focused on the compounding factors associated with accessing Medicaid ASD services for single black women who rely on state Medicaid insurance. More specifically, this study investigated the constraints of Medicaid that make it difficult for caregivers to access ASD services after children receive an ASD diagnosis.

Conceptually, this paper draws on a model (see Figure 1) adapted from the “Cycle of Environmental Health Disparities framework” that outlines the complex environmental interactions in health disparities by identifying a range of interrelated adverse environmental risk factors at the individual, residential, and community levels [19]. The “Cycle of Autism Disparities” (see Figure 1) centers on compounding factors (e.g., limited social capital and limited educational and healthcare services) since these factors are central to understanding ASD disparities among underserved communities. For our analysis, we focused on relationships between compounding factors, social and economic factors (e.g., limited education, empowerment, and income), and residential options (e.g., limited choice,

infrastructure, and services) portions of the cycle (circled in Figure 1). This model also offered entry points to further expand our understanding of different risk factors associated with ASD service barriers and areas for targeted recommendations to break the cycle of ASD service disparities, which we elaborate in the discussion.

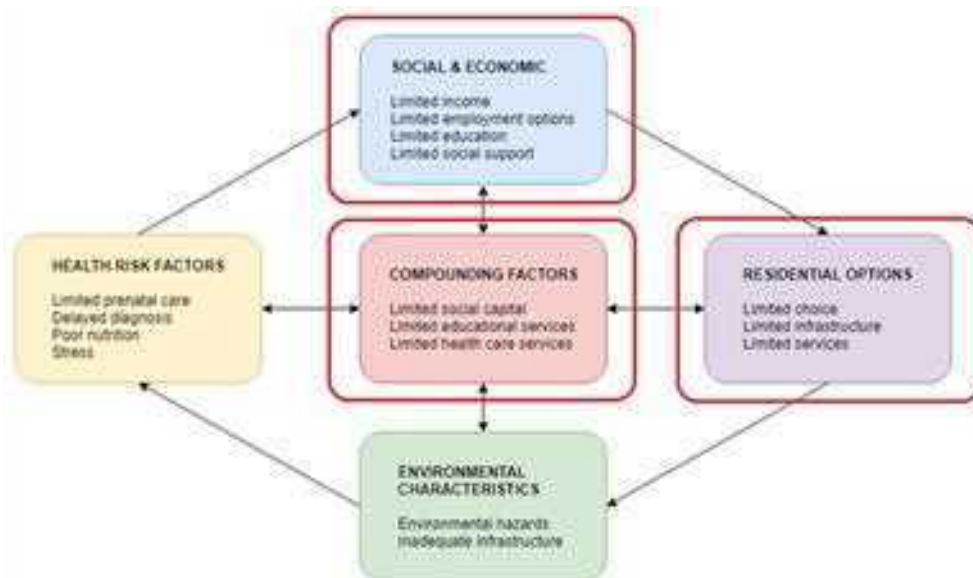


Figure 1. Cycle of autism disparities.

OUR STUDY

This research was approved by Children's Healthcare of Atlanta, Georgia Institute of Technology, and Morehouse School of Medicine Institutional Review Boards, as well as the Grady Research Oversight Committee. Audio-recorded, in-depth interviews were conducted by the second author (JS) with single black female caregivers of children with ASD who rely on state Medicaid health insurance ($N = 21$). These interviews formed the basis of our analysis and were a subset sample of a larger project designed to assess the quality of care of a community-based Autism Clinic and identify barriers to ASD diagnosis and services ($N = 72$). Interviews were conducted with caregivers whose children received services at the Autism Clinic located in a non-profit children's hospital in Atlanta, Georgia, where most of the patients rely on Medicaid. Participants were asked open-ended questions about their experiences before, during, and after receiving a diagnosis. All interviews were recorded, transcribed, and uploaded in HyperRESEARCH, a qualitative data analysis software program [20]. All the participants were given a pseudonym in the presentation of our findings to protect their confidentiality.

This study used a grounded theory analysis of the interviews to systematically identify themes and multi-level barriers to ASD services [21]. This involved using HyperRESEARCH to code segments of qualitative data to specific categories and write detailed memos for categories to capture the data conceptually. Analysis began with open coding of words,

phrases, and passages in the interview transcripts. Open coding is an established analytic method used in studies guided by grounded theory methodology, whereby participants' responses are compared, and conceptual labels are defined in an iterative process [21]. The second author (JS) developed a preliminary codebook, which was refined as we inspected the data multiple times. The codebook was used to identify common themes shared by participants that reflected and further elaborated the Cycle of Autism Disparities framework (see Figure 1).

FINDINGS

The ability of single black female caregivers to access early intervention and appropriate services through Medicaid insurance after receiving an ASD diagnosis were often compromised due to multiple interacting factors apparent in the Cycle of Autism Disparities framework. Of the sample interviewed, all the study participants identified as black or African American, were single, either never married or divorced, and their children relied on state Medicaid insurance (see Table 1). Sixteen of the caregivers were mothers, and five were grandmothers. Fifty-seven percent of the caregivers were unemployed, thirty-eight percent did not have a college degree, eighty-five percent had a household income of less than \$30,000 a year. (Note: the federal poverty level for a four-person household in 2018 was \$25,100 [22]). Previous studies on ASD disparities have shown that lower income and/or parental education are associated with lower ASD prevalence, later diagnosis, and less utilization of ASD-related services [12]. Thus, the demographics alone place these women at higher risk of experiencing disparities in ASD services. Forty-three percent of the women in the sample also resided in the southern part of Fulton County, an area marked by limited healthcare resources, limited services in public schools, and lower median household income [23]. Relatedly, sixty-seven percent of the women in this sample rented an apartment or home or were living in temporary housing (e.g., shelters), and twenty-nine percent took care of more than one child diagnosed with ASD. As we will elaborate below, the interaction of these demographic characteristics is evident in the Cycle of Autism Disparities (see Figure 1), including how limited healthcare resources and educational services (Compounding Factors) available in southern Fulton County (Residential Options) interact with caregivers' educational attainment, income, and employment status (Social and Economic) and their ability to coordinate and access services for their children.

A unique feature about this sample was the fact that these families had access to initial evaluation and diagnosis, which was covered through Medicaid. Most of these families received initial evaluation and diagnosis at the Autism Clinic (69%), while others received initial diagnosis elsewhere (31%). Although access to early evaluation and diagnosis was not the focus of this analysis, caregivers in our sample expressed that "not knowing much about autism," complicated schedule coordination, and long waiting lists were the predominant barriers to early diagnosis. Despite improvements over the last few decades in diagnosing children from racial and ethnic minority communities with ASD in Atlanta, the women in this study continued to experience significant barriers when it came to accessing ASD services such as behavioral, speech, or occupational therapy [2]. Thus, their stories reveal how Medicaid served as an access point to obtain an ASD evaluation, diagnosis, and service

referrals, while at the same time Medicaid served as a barrier in accessing subsequent ASD services especially in certain geographical locations in metro Atlanta. Two themes were identified that contextualize Medicaid as a barrier to ASD services: bureaucratic processes and geographic location of services.

Table 1. Participant demographics (N = 21)

Demographic	Percent of Sample
African American or black	100%
Single Parent or Divorced	100%
Medicaid	100%
Unemployed	57%
Some High School/Diploma/Vocation	62%
Household Income <20K	52%
Household Income 20K – 30K	33%
Live in south Fulton County	43%
Rent Apartment / House or Temporary Housing	67%
More than one child diagnosed with ASD	29%

Bureaucratic Processes

It was clear from the stories told by these mothers and grandmothers (24% of sample) that difficulties in accessing services for their children can be contextualized by the complex and often confusing bureaucracy of acquiring ASD services in Georgia. Many caregivers in our sample voiced their confusion and frustration regarding how Medicaid did not cover some of the recommended services for their children or only covered services for a short period of time. Navigating bureaucratic systems is even more difficult because requests for services are lengthy to process, which can result in delays or long waits for caregivers to acquire the appropriate services for their children. Chantel, the mother of a ten-year-old child diagnosed with ASD and another nine-year-old child who displayed developmental delays and behavioral issues, was no stranger to lengthy wait times and limited services available through Medicaid. After being referred to the Autism Clinic for an initial ASD evaluation, it took almost a year for her to secure an appointment for her older child. It was at this first appointment that this child received a diagnosis of ASD. As part of his recommended treatment, Chantel's ten-year-old child did occupational therapy at a rehabilitation center for three months. Although she found occupational therapy helpful for her child in improving his fine motor skills, she ultimately had to discontinue the therapy after Medicaid stopped covering it after three months. At the time of the interview, Chantel had also been looking for a speech therapist for over a year that accepted Medicaid near her home in south Fulton County. Traveling far distances was not a practical option either because Chantel also had to take care of her younger, nine-year-old child who was scheduled to be evaluated for ASD. Chantel was further discouraged by her inability to follow up on referrals received at subsequent appointments for her ten-year-old son because those referrals "did not take Medicaid."

Another young single mother from south Fulton County named Tianna echoed Chantel's sentiments and had difficulties finding an occupational therapist who would accept Medicaid for her five-year-old son diagnosed with ASD. Tianna was the mother of four children and worked full-time as a janitor. Tianna was frustrated because the Medicaid referrals she received from the Autism Clinic were booked and did not have a wait list. As she explained,

"When I called to schedule an appointment, they said they were booked. There was no waiting list, and they didn't have anyone who could see him because I wanted later hours."

Even though there are other private therapy options available outside Medicaid—which were often located farther away in the northern part of metro Atlanta—Chantel and Tianna could not afford them, and even if they could afford the out-of-pocket cost of these services, they would have to sacrifice their work hours or attention given to their other children. These examples illustrate how limited health care services (Compounding Factors), single parenthood and limited income (Social and Economic), and location of residence (Residential Options) interact with one another in the Cycle of Autism Disparities.

The bureaucratic limitations of Medicaid are compounded when additional institutions are involved. Children with ASD have needs that straddle both healthcare and educational systems. Special educational services for children with ASD are mandated under the Individuals with Disabilities Education Act (IDEA), a federal law that requires a free and appropriate public education be available to children with disabilities in defined age ranges [24]. An Individualized Education Program (IEP), which includes a full evaluation of the child with regards to development, speech, or attention, is required for most children to be eligible for services under IDEA in order to receive special education services in public schools [24]. Several caregivers in this study discussed their frustrations with the bureaucratic process required to receive or change an IEP. Sasha, for example, was the mother of a teenaged daughter diagnosed with ASD. Sasha and her three children relocated to Atlanta from North Carolina and at the time of the interview, she was unemployed, financially dependent on her oldest child's income, and lived in a shelter in south Fulton County. Although Sasha first became concerned with her daughter's development when she was an infant, her daughter did not receive a diagnosis of ASD until she was in the sixth grade (when she was around ten years old), at which time Sasha tried to change her daughter's IEP. Due to the time it took to process the necessary paperwork to amend the IEP, Sasha was not able to get her daughter in the "right class" until she started the seventh grade:

"I had to wait until she graduated sixth grade even though she had a diagnosis of autism."

Sasha went on to say how difficult it was to change her daughter's IEP from a "behavioral intervention class to an autism class," which Sasha believed was more appropriate because the class focused on autism and therefore potentially more beneficial for her daughter.

Another caregiver pointed out an additional complication regarding bureaucratic processes: the educational and medical systems often did not align when it came to

evaluations. This caregiver was the mother of six children, and three of her children were diagnosed with ASD. As this mother elaborated,

“Yeah, [the school] bases [the IEP] on their school system evaluation and not the medical records. Not the doctor’s notes. Nothing dealing with your doctor. You may have a child that has autism or other behavior issues that needs to be in a smaller-setting classroom, but when [the school] tests them, and it’s not to their liking...Dealing with the school system is like dealing with a whole another government. They have their own set of rules, and personally, you know, for me, I think it’s hurting the child to be honest.”

These narratives highlight the complicated bureaucratic processes embedded with both the medical and educational public systems and how navigation of these processes for single women with limited resources shape disparities to ASD services.

Geographic Location of Services

Another salient and recurring theme is how geographic location of services was identified as a constraint to obtaining ASD services. For example, let us consider the experiences of Cynthia, a parent of three children diagnosed with ASD. She resided in south Fulton County, the father of the children was not involved, and she had limited social support from other family members. Alongside the bureaucratic frustrations that came with trying to secure healthcare for her children, Cynthia was frustrated about the limitations of Medicaid coverage and the lack of services around where she lived. Cynthia felt her options were limited because her children were reliant on Medicaid and noted that “there are not many doctors, medical professionals that take the Medicaid.” When asked about her biggest challenges in accessing behavioral therapy for her children, Cynthia answered:

“Well, I can say the area I live... [and] the locations of some of the places that offer the services are...not in my local area, so I have to drive a great distance to get the services. So that’s the biggest challenge. There’s nothing in my area within a twenty-mile radius, so I have to drive to get there.”

Cynthia fortunately had access to the use of a car, which helped her reach therapies that were more than twenty miles away. However, for many of the women in this study, transportation served as a challenge because they relied on public transportation or Medicaid transportation, both of which were not always reliable or practical given these women’s demanding life schedules. Caregivers who utilized Medicaid transportation noted that the van was often time-consuming and unreliable. One mother described an incident where she had to reschedule an appointment for her daughter because the Medicaid van was delayed in picking them up. Another mother noted how she found herself late to several appointments at the Autism Clinic because the van often serviced multiple people:

“You’re not the only one riding that van. They have other clients, other customers they have to pick up, as well as pick you up and drop you off. So, you have to sometimes wait until they pick up those guys, and you might be the second or third or fourth person being dropped off...And sometimes, you might be the last person to get dropped off.”

In addition, the services these women needed to access for their children were often not easily accessible by public transportation. One grandmother, Karen, who resided in south

Fulton County expressed how she was unable to take her three-year-old grandchild diagnosed with ASD to an afterschool learning center that provided services to help children with developmental disabilities:

“A lot of places are too far. We have no way of getting there. Because of transportation issues...Some of the places are just too far and off the bus line, and I don’t have a vehicle, so it makes it harder for me, you know.”

At the time of the interview, Karen was recovering from a stroke which she attributed to stress experienced from raising her grandchildren in addition to her own eleven-year-old daughter. Karen was also in the process of adopting her three-year-old grandchild (as well as two other grandchildren who were not diagnosed with ASD). Karen’s frustration with transportation issues was felt by parents who owned or had access to a car, but it was heightened for those who had to rely on public transportation.



Figure 2. Behavioral therapy services in and around Fulton County.

To add insight into the structural inequities in ASD services in metro Atlanta, a representation of how ASD services are unequally distributed based on geographical location is depicted in Figure 2. The map shows a sample of the places that offer behavioral therapy for ASD. As the map illustrates, there is a lack of behavioral therapy service sites in southern Atlanta, such as south Fulton County (shaded in darker grey area at the bottom in Figure 2) where Cynthia and forty-three percent of the women in this study live. Those sites that offer behavioral therapy were also often difficult to access with public transportation, and not all of the sites represented in Figure 2 accept state Medicaid insurance. The lengthy travel time to therapies further compound the recommended hours of behavioral therapy per week, which is recommended at more than twenty hours per week [12]. In addition, managing work and family life balance for caregivers could be especially challenging if children receive multiple therapies and/or have other healthcare needs in addition to ASD or if parents take care of more than one child with ASD (six parents in our sample had more than one child diagnosed with ASD).

Compounding Factors

The challenges associated with both the complex bureaucracy and limited location of services are compounded with other factors evident in Cycle of Autism Disparities framework (see Figure 1). First, these women's challenges were complicated by limited employment options, low income, and stressful environments they and their families must navigate on a daily basis. For example, having to rely on public transportation with a child diagnosed with ASD compounds the challenges these women experience while navigating ASD services. Some of the women told stories of how public transportation created environments that were often difficult for their children to handle due to strange smells, loud noises, large crowds, and long wait times. Sheila, a single black mother who just moved to Atlanta with her teenaged daughters, reflected on how she and her fifteen-year-old daughter diagnosed with ASD could not reach their appointments because her daughter refused to take public transportation,

"Sometimes I was having trouble with her getting on the train and on the bus...Sometimes she doesn't want to ride. Since the doctor has been helping with the medicine, it's not as bad as before. Before, I couldn't even take her on the bus when there was a whole bunch of people. Because she would have episodes, or she thought people were staring at her."

Also complicating access to care were the barriers related to the consequences of being a single parent, which for this sample was related to navigating ASD services with limited resources and reliance on state services like those supported by Medicaid. Sasha, the previously mentioned mother who encountered problems changing her daughter's IEP, described the difficulties of being a single parent who cares for a child with ASD alongside the multiple responsibilities she faces:

"If you have a child that has a disability it's even more pressure on me because it's like I have to be Superwoman for everybody else. I still have to deal with regular stuff and on top of regular stuff, deal with other stuff. Sometimes it's kind of overwhelming when you don't have that partner there to help you...I have to go every place to take to her therapist appointment, her speech appointment. I have to go to her school for IEPs, you know. I have to do a lot...My other daughter who's younger than her, she still has stuff I have to do with her for her school...Then my oldest daughter, even though she's twenty-seven, I still have to be her momma to her too because she has things that's going on in her job."

Additionally, in many cases parents of children with ASD may find their ability to work during their designated employed work hours periodically constrained, which can be especially challenging for single parents [25]. For example, Janice, a full-time nursing assistant and the mother of a four-year-old child diagnosed with ASD, was asked to leave her previous job due to the demands of taking care of a child and the toll it took on her work life:

"I made a lot of sacrifices. My other job, I really loved my other job, but I had to leave it due to me leaving work early. Like, if [my child] has a big meltdown, nobody could control him, so I had to leave work and go see him. My supervisor sat me down, and she was like, "You've been taking a lot of days off." I told her what was going on, but she said, "You can stay, or you can leave." I had to leave because this is my son, and I left that company. You know, I really loved that company, but I'm the care provider, I'm his mom, I'm his only parent, and I don't want to ever feel like I'm neglecting him because I'm trying to go to work."

This compelling statement highlights the negotiations that single working women have to contemplate to meet the needs of their child with ASD and the limits on what they can do in their jobs and lives. This caregiver, like many others, must balance the needs of her child with a desirable job, not to mention a job that she needs to support her son. Unfortunately, Janice's employer did not offer the flexibility she needed to manage being the primary breadwinner *and* the primary caregiver. These are conflicts single female caregivers must face, which is compounded when caring for a child with special healthcare needs.

Though this paper focused on the shortcomings of autism services offered through public medical and educational systems, several of the women interviewed were able to quickly acquire services for their children with little difficulty. These women often had financial and/or social support from the fathers of their children or other family members. Some women had the education and knowledge resources to navigate different and equally complex bureaucratic systems. For example, Janice had a bachelor's degree and due to her job as a nursing assistant, had extensive knowledge about Medicaid services and how to acquire various therapies for her son. Janice also sought help and information from a coordinator at the Autism Clinic to arrange multiple therapies for her son. Unlike many of the women in our sample, Janice was able to have her child access several different types of therapies and activities through Medicaid, including speech therapy, occupational therapy, physical therapy, swimming lessons, and soccer. These alternative experiences within the sample highlights the heterogeneity of the population under investigation and the importance of having different forms of empowerment and social capital among caregivers in order to navigate complex bureaucratic systems of care. Though public medical and educational programs have enhanced and improved the ability of disadvantaged populations to receive healthcare and related services, ultimately there continues to be areas for improvement.

DISCUSSION

These narratives of single black women negotiating ASD services in metropolitan Atlanta offer firsthand accounts of frustrations that caregivers encounter in dealing with multiple bureaucratic systems of care. These results are in line with a body of research that suggests that when multiple systems are responsible for providing related services to the same child, it can result in considerable gaps and inefficiencies in care [18]. The fragmented systems of care and the amount of work required to gain access to state programs and special education services are constraints that are compounded for low-income single, black, female caregivers who are typically doing all the care coordination with limited assistance and/or resources. One avenue to break the cycle of ASD disparities is to consider how medical and educational state programs can work together in offering complementary services for complex conditions like ASD. For example, some researchers have made the case that social workers and occupational therapists who have contact with families of young children might support in early identification and appropriate referrals [26-27]. Another study found that increased school district funding was correlated with higher proportions of children identified with ASD in schools [28]. Because schools play an important role in identifying children with ASD and other developmental disorders, allocating financial resources and personnel trained

to identify ASD to schools in economically disadvantaged communities may help alleviate ASD disparities [28].

Expanding the location of ASD services also points to areas where we can break the cycle of ASD disparities. The experiences of these families who live in south Fulton County highlight how Residential Options (e.g., limited healthcare services in geographic area) and a range of Social and Economic Factors as indicated above. These interrelated factors also matter with regards to race and social class. For example, according to data generated by the US Census, the racial demographics and median household income in Fulton County are starkly different for north Fulton and south Fulton County. For example, in the East Point subdivision of south Fulton County, Blacks account for 79.1 percent of the population, and the median household income was \$35,974 in 2010 [23]. By contrast in the Roswell-Alpharetta subdivision of north Fulton County, blacks made up only 12 percent of the population (whites composed 61.6 percent of the population here), and the median household income was \$97,291 in 2010 [23]. We know that higher socioeconomic status (SES) correlates with higher ASD prevalence estimates [29]. However, less is known about the effects of compounding factors like living in a lower SES neighborhood that is racially divided. Our data suggests that these are important areas for further investigation. Previous research by Mandell et al. [18] have found that differences in local policies, practices, and resources could result in variation in which children with ASD receive care in the Medicaid system. In our study, difficulties in accessing services can be further contextualized by the lack of services around where these women live and lack of access to reliable transportation if services are farther away. Thus, in addition to addressing the limited ASD services available in low-income and underserved communities, such services should also be made available close to public transportation lines and/or offer transportation services as part of the therapy. The creation of therapy clinics that offer multiple ASD services in one place may also eliminate the constraints placed on caregivers who must travel to multiple locations to acquire different therapies for their children.

As evident by these narratives, the intersecting constraints of trying to access ASD services as a single parent with limited resources highlight how various elements of the Cycle of Autism Disparities framework interact with one another. Several scholars have written about how the accumulation of demands has more consequential effects on populations who have fewer resources to manage their children's ASD [13]. For the women in this study, the knowledge, time, and energy necessary to navigate ASD services were compounded by the various challenges related to being a single parent. For example, single parents carry the burden of both unwaged and waged labor [30-31]. In this case the unwaged labor consists of navigating the bureaucratic processes needed to obtain ASD services in addition all the other caregiving work required to raise a child with special needs. Previous research also found that achieving and maintaining employment was more difficult for parents of children with disabilities than for those without children or without children with disabilities [25, 32]. Cidav et al. [32] found that mothers of children with ASD earn fifty-six percent (\$14,755) less than mothers of children with no health limitations, and they are less likely to be employed and work seven hours less per week, on average, than mothers of children with no health limitations. Given the substantial healthcare expenses associated with ASD, the economic impact of having lower income in addition to these expenses is magnified for caregivers of children with ASD [32].

The intersections of gender and race also matter when considering ASD disparities, especially with regards to income inequalities. For example, various studies have shown there are economic sources of inequity due to persistent gender and race differences with regards to types of work that women do and the income they receive [33-34]. It was found that irrespective of the level of qualification, jobs predominantly done by women pay less on average than jobs predominantly done by men [33]. According to a Pew Research Center analysis of median hourly earnings of both full- and part-time workers in the United States, women earned eighty-three percent of what men earned in 2015 [34]. This same study also found that the hourly earnings of black and Hispanic women (\$13 and \$12, respectively) are lower than those of Asian and white women (\$18 and \$17, respectively) [34]. Our analysis highlights how the challenges of raising a child with ASD was magnified by having limited income, employment options, and social capital (access to knowledge and resources based on one's position in society). These multiple and interrelated factors compounded the difficulties these women experienced in accessing ASD services for their children. While Medicaid coverage lowers financial barriers to accessing healthcare services for low-income uninsured people and improves their health outcomes, the stories these women tell highlight that the program can be further strengthened by addressing recognized shortcomings.

Avenues to break the cycle of ASD disparities must consider these complex and intersecting factors when considering areas of intervention. For example, the development of patient navigation systems designed to provide lay case management specially for families with limited resources early on in ASD evaluation, diagnosis, and services can increase parent empowerment [35]. Such programs can be specifically tailored to address issues more apparent for single parent families, such as lack of social support, time, and job flexibility. ASD service disparities among black communities may also benefit from adaption of culturally tailored ASD interventions like the *promotora de salud* model, or community health worker model, to break the cycle for these communities [36]. The *promotora de salud* model uses a lay health educator from the target community who provides health information to other people in the target community after receiving training in the health topic [36]. For the caregivers of children with ASD in our sample, those with experiences of being single, black, female, and reliant on Medicaid would be the most qualified people to recognize areas of need and areas of strength. For example, a pilot study of parent training for Latinx mothers of children with ASD based on the *promotora de salud* model found that mothers reported improvements in their understanding of ASD, their child's strengths and needs, and how to help their child develop and learn, and knowledge of their child's rights [36]. In addition, the study reported that mothers felt improvements in having support systems, accessing the community and using evidence-based approaches efficiently to enhance social communication skills and manage behaviors for children with ASD [36]. These suggestions and others can be integrated in community-based settings like preschool and elementary school settings [37-38]. Our study supports that it is important to address not only system-level approaches but also the heterogeneity of barriers experienced by under-resourced caregivers of children with ASD [39]. Building social capital through such interventions offers important access points to knowledge, resources, and confidence that parents need to break the cycle of ASD service disparities.

CONCLUSION

The examination of ASD disparities in metro Atlanta provides a lens to a bigger problem regarding lack of services in urban areas that are divided based on racial and social class lines. However, the complex bureaucratic processes, lack of services based on geographic location, and interacting compounding factors are also not unique to ASD. People with other disabilities, chronic health problems, and anyone who relies on Medicaid or other state services often face similar challenges. This research focused on the experiences of single black women, whose ability to seek early intervention and appropriate ASD services were often compromised due to multiple compounding factors in a structurally uneven society. The firsthand accounts of the women in this study point to how different processes (Compounding, Social and Economic, and Residential Options) overlap and are contingent on each other. For example, limited health care services are tied to where people live and the choices available for seeking and accessing services. These women's narratives also add more nuance to the Cycle of Autism Disparities such as the effects of family structure (single parenthood, multiple children with special healthcare needs), the ability to balance work/family life (job flexibility), and transportation options (time, cost, practical considerations)—nuance that opens up and identifies new areas of research and intervention on how to break the cycle of ASD service disparities.

Recent and upcoming changes to Medicaid in the state of Georgia provide avenues for further research as well. In July 2017, the state of Georgia approved a mandate that made it a requirement for Medicaid to cover Adaptive Behavioral Services (ABS) to assess and treat ASD [40]. ABS include behavioral therapy and social skills development, and this policy was designed to improve outcomes for ASD. Because nearly half of the women in the sample for this study were interviewed before this mandate was put into effect, the impacts of this mandate currently remain unknown. One research avenue should investigate whether this mandate improves access to ABS and/or increases (or decreases) the bureaucratic processes needed to access these types of ASD services. Further, would such a mandate increase the number of behavioral services in underserved urban areas? The expansion of Medicaid in Georgia through the Patient Protection and Affordable Care Act also holds potential for recipients of Medicaid [41]. However, since minorities and women are disproportionately more likely to utilize social assistance programs like Medicaid, these programs are politically vulnerable. As such, recipients are particularly likely to be affected by budget cuts and shoulder the various hardships that accompany reliance on such programs [30-31]. Recently in 2019 the Georgia Legislature approved a plan to expand Medicaid, albeit on a limited basis [42-43]. There is value in studying the ramifications of Medicaid expansion on healthcare outcomes for low-income, minority, and underserved communities in Georgia. It remains unknown if the limited expansion Medicaid would address the concerns voiced by the women in this study. There is much value in taking note of how recent and upcoming changes to Medicaid in the state of Georgia would affect ASD disparities.

At the individual level, we also have much to learn from the personal stories of the female caregivers themselves, as they provided recommendations to address some of the daily challenges they faced and practical ideas on how to break the cycle of ASD disparities. One recommendation from a mother who worked full-time and could not find an occupational therapist close to her home that accepted Medicaid suggested the integration of Mobile

Therapy Units that accept Medicaid in areas like south Fulton County. Such easily transportable therapy services would address the problems related to geographic location of services, as well as create options for offering services in the evenings and/or weekends, when working parents are more likely to be available. One parent voiced her concern that community support groups tended to meet up in Gwinnett or north Fulton County, which are more than twenty miles away and not easily accessible by public transportation. Her suggestion was to create community support groups in south Atlanta that were close to public transportation. Southside Support, a community support group based in south Atlanta, was started recently in response to this need [44].

Offering childcare during these sessions (as well as initial therapy sessions) would also allow parents the opportunity to fully engage in these important social support networks. These practical suggestions offer important starting points in breaking the cycle of ASD disparities that may help to alleviate the daunting and often overwhelming task of navigating ASD services among single black women in this study, as well as other families and communities who are situated in similar interacting cycles of health disparities.

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Chapter 339

ENGAGING PARENTS OF CHILDREN WITH AUTISM SPECTRUM DISORDER TO IDENTIFY RURAL HEALTH DISPARITIES AND FACTORS RELATED TO DELAYED DIAGNOSIS AND TREATMENT

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ABSTRACT

Autism spectrum disorder (ASD) is a developmental disability characterized by significant social, communication, and behavioral challenges. Early diagnosis and treatment have shown to improve health outcomes. ASD diagnosis can be achieved by age 2 years, but median age of diagnosis is 4-5 years. The purpose of this project is to identify barriers and facilitators to ASD diagnosis and treatment for families living in rural or Medically Underserved Areas (MUAs). Methods: Two focus groups were conducted online and in-person with parents of children with ASD living in rural and MUAs. Questions examined health disparities and delayed diagnosis or treatment. Sessions were audio-recorded, transcribed, and analyzed. Results: Diagnosis and treatment barriers included distance to healthcare services, limited access to providers, inadequate insurance coverage, and lack of education. Facilitators included school referrals, research studies, ASD research centers, support groups, school-based treatments, and insurance extenders. Analysis revealed decreased parental autonomy, frustration, disappointment, uncertainty, and desire for support. Discussion: Parents of children with ASD living in rural and MUAs discussed several barriers to ASD diagnosis and treatment. Parent-identified ways to improve barriers included increased education,

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enhanced awareness of ASD and needs of rural and MUAs, and improved access to care. Proposed interventions included telehealth and mobile clinics. Conclusion: Families living in rural and MUAs face many barriers related to ASD diagnosis and treatment. Future interventions should address these issues by increasing awareness of ASD, increasing knowledgeable providers, and utilizing electronic technologies to engage individuals in these areas.

INTRODUCTION

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder characterized by communication, social, and behavioral challenges for affected individuals [1]. ASD is associated with a variety of both personal and family-level challenges, including the need for lifelong support and interventions. Families of children with ASD living in rural or medically underserved areas (MUAs) face additional challenges in obtaining a diagnosis and securing ongoing treatment due to a variety of factors, which results in potential healthcare disparities present in these populations [2-4]. There is currently a scarcity of research on families of children with ASD living in rural and MUAs and the role that disparities in services plays in the diagnosis and treatment of ASD. Therefore, the purpose of this project was to identify barriers and facilitators to ASD diagnosis and treatment for families living in rural or MUAs.

AUTISM SPECTRUM DISORDER

Symptoms of ASD emerge in early childhood and include difficulty with communication, difficulty with social-emotional reciprocity, and the presence of restrictive and repetitive behaviors or interests [1]. The current prevalence of ASD is estimated to affect 1 in 59 children [5]. In addition to the primary characteristics of ASD, children with ASD encounter numerous health and behavioral comorbidities (e.g., seizures, gastrointestinal disorders, attention-deficit/hyperactivity disorder [ADHD], sleep disorders), increasing the complex needs of these children [5, 6]. Treatment for ASD includes evidence-based treatments, such as applied behavioral analysis (ABA) therapy, speech language pathology (SLP), occupational therapy (OT), and physical therapy (PT). As a result of the complex nature of ASD and its associated treatment, the lifetime cost of supporting a single individual with ASD in the United States is estimated to be between \$1.4-2.4 million [7]. Despite this costly economic burden on individuals and families, evidence has shown that early diagnosis and intervention for children with ASD can improve long-term health outcomes [7-10].

Given that signs and symptoms of ASD appear in the first year of life, clinicians are currently able to make a valid diagnosis as early as two years of age [1]. According to emerging literature, this age may actually be sooner for some children with ASD. [5, 8, 9, 11]. Despite these facts, the current median age that children receive an ASD diagnosis is between 4-5 years [2, 5, 8-10]. This delay in ASD diagnosis delays the child's ability to receive treatment services, resulting in a significant lag between presentation of symptoms and onset of intervention. This delay has great potential to negatively impact the developmental trajectory of the child, as it occurs during a critical time of early brain development [8-11].

Evidence has shown that a timely ASD diagnosis, coupled with early intervention, increases the likelihood of favorable long-term health outcomes [8, 9, 11].

Rural and Medically Underserved Areas (MUAs)

Geographic health disparities are associated with individuals living in rural or MUAs, where access to care affects their ability to receive necessary healthcare treatments. The United States Health Resources and Service Administration (HRSA) defines rural areas as those that have fewer than 2,500 people [12]. MUAs are defined as areas that have too few primary care providers, high infant mortality, high poverty, and/or a high elderly population [13, 14]. While limited access to healthcare services in rural areas may appear evident, often overlooked are those residing in MUAs who face even higher health adversities and disadvantages given their unique disparities. Research has found that individuals who are part of disadvantaged populations (e.g., geographic, socioeconomic, racial, ethnic) experience comparatively poorer outcomes in health [15-17]. Thus, delayed diagnosis and treatment of any health-related problem are more detrimental to the health outcomes of these disadvantaged populations [2-4, 17-20].

It is currently estimated that nearly one in five Americans live in rural areas and often struggle to meet their healthcare needs due to a lack of providers [21]. As of 2018, there were a total of 4,118 primary care health professional shortage areas identified in rural locations compared to only 1,960 in urban locations, thus increasing the vulnerability of these populations, as they are considered to be both medically underserved and living in a rural area [21]. As a result, life expectancy rates can vary by up to 20 years based on an individual's geographic location [16, 22]. At present, Georgia ranks in the lowest quartile in terms of life expectancy by state [16, 22], where nearly 90% of Georgia counties are designated as rural or MUAs (see Figure 1).



Figure 1. Map of medically underserved areas by county in the state of Georgia.

Cycle of Children's Health Disparities

Health disparities are present in children and families who have limited financial, social, medical, therapeutic, and educational resources. These disparities can be viewed in an intergenerational cycle that includes various geographic, health, environmental, personal, compound risk factors, and environments that can negatively impact a child's health (see Figure 2) [23-28]. This project aims to break the cycle of children's health disparities by exploring factors that impact families of children with ASD living in rural or MUAs, as indicated by the asterisks in Figure 2. As a result of this investigation, we intend to propose strategies to improve the health of children and families (see Figure 2).



Figure 2. Breaking the cycle of autism health disparities in rural and MUAs.

OUR STUDY

The principal study investigators recruited parents of children with ASD living in rural and MUAs of Georgia to explore barriers and facilitators to ASD diagnosis and treatment. The study was deemed exempt by the Emory University Institutional Review Board (IRB). Recruitment took place through flyers sent to local and rural pediatric clinics, social media support groups, and collaborative partners (e.g., Marcus Autism Center, Emory Autism Center, Department of Education Parent Mentors). Two focus groups were held, one in person and one online using remote, Health Insurance Portability and Accountability Act of 1996 (HIPAA)-compliant video-conferencing technology (i.e., Zoom) [29]. The two groups consisted of three to ten participants each, and they included parents of children with ASD and an additional stakeholder, the director of a special education school.

Focus groups utilized open- and closed-ended questions to identify potential barriers and facilitators to delayed ASD diagnosis and treatment. Questions also explored family-centered solutions to mitigate any potential disparities (see Table 1). The focus groups were audio recorded, transcribed, and analyzed using thematic analysis.

Table 1. Focus group guide

Focus group questions
1. Do you think there are any barriers or facilitators to receiving your child’s ASD diagnosis?
2. Tell me more about these barriers or facilitators.
3. Do you think there are any barriers or facilitators to receiving treatment for your child?
4. Tell me more about these barriers or facilitators.
5. What do you think should be done to help families get an earlier diagnosis or treatment?

FINDINGS

Participants represented numerous counties throughout the state of Georgia, some of which were up to 200 miles apart. Because of the interest from counties that were dispersed throughout the state, researchers decided to employ an innovative method for conducting qualitative research: utilizing both in-person and online videoconference focus groups. During the focus groups, participants discussed their perceptions of barriers and facilitators to early ASD diagnosis and treatment.



Figure 3. Georgia county map of interested participants.

Geographic Diversity

Initial participant recruitment resulted in high interest from a variety of geographically diverse locations throughout the state of Georgia. Interested participants spanned nine different counties dispersed throughout Georgia, including Walton, Troup, Fayette, Liberty, Bulloch, Sumter, Columbia, Henry, and Appling Counties (see Figure 3). The geographic diversity and distance in the sample compelled the researchers to conduct one of the focus groups online. This offered participants in a variety of counties a chance to have their voices heard in this study, despite the fact that their distant geographic location would have normally precluded them from participating in traditional in-person focus groups.

Diagnosis

Barriers and facilitators to ASD diagnosis were among the most frequently discussed topics during the focus groups. Parents living in rural and MUAs in Georgia felt that their experiences in receiving an ASD diagnosis differed from individuals living in more heavily populated areas, or areas with more providers.

Barriers

Parents described their journey to receiving an ASD diagnosis as being filled with various barriers that ultimately created a great burden to their family. The main barriers identified were distance to health care providers, provider shortages, inadequate insurance coverage, lengthy wait times, lack of parental and provider education on ASD, and limited ASD awareness of providers (see Table 2). Parents discussed problems with their initial concerns being dismissed by providers, lengthy wait times to see providers capable of making an ASD diagnosis, and limited providers working in their native counties. They also expressed frustration and disappointment in finding a lack of education and awareness about their child’s developmental concerns. Numerous concerns with insurance arose that impeded a child’s ability to receive a timely diagnosis, specifically providers capable of making an

Table 2. List of barriers and facilitators to ASD diagnosis and treatment

	Barriers	Facilitators
Diagnosis	- Distance to health care providers - Provider shortages - Inadequate insurance coverage - Lengthy wait times for providers - Lack of parental and provider education on ASD signs and symptoms - Limited ASD awareness of providers	- School system referrals - Working with ASD research centers - Participating in research studies
Treatment	- Distance to health care providers - Limited providers in immediate area - Inadequate insurance coverage - Cost of treatments - Competing time demands - Lack of follow-up plans for the child	- Social media support groups - Insurance extenders - Access to school-based treatments

ASD diagnosis not accepting certain insurance. Limited providers in the area, combined with dissatisfaction with the available providers, led many parents to seek providers outside their immediate counties. This often required them to travel upwards of two hours roundtrip for a single appointment to discuss their child's signs and symptoms.

Quotes from Parents Related to Diagnosis Barriers

The following quotes from parents represent the variety of barriers that parents living in rural or MUAs in Southern Georgia face in pursuance of an ASD diagnosis for their child:

Lack of ASD Awareness – Participant 1: "...They just kept telling me that my kid's lazy, that boys are lazy, and that's what I was being told the whole time."

Limited Providers & Lengthy Wait Times – Participant 2: "...There is nowhere around here that I knew of, or that at the time, my pediatrician knew of... that could give the autism diagnosis other than [large autism centers], [both] of which at the time was on an extremely long waiting list."

Facilitators

Although parent participants heavily emphasized the barriers to early diagnosis, they also discussed some facilitators that helped the process of diagnosis (see Table 2). Facilitators to diagnosis included school system referrals, working with large ASD centers, and participating in research studies. Parents felt that these facilitators improved early diagnoses. Examples of how these processes facilitated an earlier diagnosis included educators having a developmental concern for a child and making a school-based referral, having access to large ASD centers where professionals are specifically trained in ASD diagnosis and treatment, and opportunities for parents to have their child in research studies that provided ASD diagnosis and/or treatment (e.g., studies that evaluate siblings of children with ASD for developmental delays). Additionally, parents mentioned that their own persistence and determination in pursuing a diagnosis for their child were the most influential facilitators.

Quote from Parent Related to Diagnosis Facilitators

The following quote from a parent represents the facilitators that aided parents in receiving an ASD diagnosis for their child in rural and MUAs:

Parental Perseverance – Participant 3: "...Most of the parents here, we're the go-getters, we're the advocates. I had learned at an early, younger year, like, I have to fight, fight, fight and not take 'no' [as an answer]..."

Treatment Services

Upon receiving an ASD diagnosis, parents discussed factors that impacted receiving treatment services for their child. Accessing follow-up care after the ASD diagnosis and receiving ongoing treatment were often problematic for parents living in rural and MUAs.

Barriers

When identifying barriers to ASD treatments for their child, parents discussed many of the same problems associated with barriers to diagnosis (see Table 2). These treatment barriers included distance, limited providers, insurance, cost, competing demands, and lack of follow-up. Similar to diagnosis barriers, treatment barriers centered around the lack of

providers in the immediate area who were able or willing to provide ongoing treatments to children with ASD. Parents also mentioned that the state-wide early intervention programs were not necessarily helpful, as there appeared to be a severe provider shortage for these programs in their rural and MUAs. Of the limited providers available, parents often mentioned that they once again had problems with providers taking certain types of insurance for the treatments. When insurance was unwilling to cover these expenditures, it caused parents to pay out-of-pocket for often expensive interventions. This led to parents seeking providers outside their native counties who would be willing to treat children with ASD, as well as accept their insurance. This ultimately led to problems with competing demands requiring extended time commitments, such as missed school or work days.

Finally, a large problem identified was the lack of follow-up care for parents once they received an ASD diagnosis for their child. Parents expressed that they were relieved once they received the ASD diagnosis, but then felt unsure as to how they were supposed to follow-up or with whom in their native counties for treatment services. Parents described a lack of coordination and clear direction for parents regarding treatments, services, or facilities to seek out after receiving their child's ASD diagnosis.

Quotes from Parents Related to Treatment Barriers

The following quotes from parents represent the barriers to treatment and follow-up care for their child with ASD in rural and MUAs in Georgia:

Limited Providers – Participant 4: “Two different problems...Getting the diagnosis, but then even when you get the diagnosis, that doesn't solve everything [because] then there's not [any] treatments [in rural areas].”

Distance – Participant 5: “I have to drive an hour east or two hours west to go to an appointment. So, he misses school, and it happens because we live in a rural area.”

Lack of Follow-Up – Participant 1: “I thought...I was there getting a diagnosis and you're going to help me fix him. And I remember saying, ‘well, what next?’”

Facilitators

Aside from the overwhelming barriers to accessing evidence-based treatments, parents identified certain facilitators that enhanced this process (see Table 2). Social media support groups (e.g., Facebook), insurance extenders and access to school-based treatments were identified as facilitators to ASD treatment. Social media groups allowed them to find both helpful resources and support for their experiences. Parents expressed that these social groups helped with the processes involved in applying for services, such as specific treatments or insurance extenders. The insurance extenders, or medical Deeming Waivers (previously known as the Katie Beckett Waiver) [30], allowed families of children with disabilities to apply for Medicaid coverage services without their family income being taken into consideration. Lastly, school-based therapies or school systems that offered evidence-based therapies were found to be facilitators to treatment. Unfortunately, few school systems in Southern Georgia were reported to offer such services.

Quotes from Parents Related to Treatment Facilitators

The following quotes from parents demonstrate how social media support groups and insurance extenders facilitated treatment for their children:

Social Groups & Insurance Extenders – Participant 3: “...[Social media groups] ... had people talking about the Katie Beckett and trying to...apply for the Katie Beckett was very overwhelming, frustrating. So, they said, you know, hey, there's a specific group that helps you, that does that, so you can post questions in there, or you can search to see if your question's already been asked. And so that group was very helpful.”

Social Groups – Participant 6: “I wouldn't have found out about the ABA (Applied Behavioral Analysis) group, the ABA place that opened up in [local location] if it wasn't for the [social media] group.”

Parental Suggestions for Improvement

In addition to identifying the barriers and facilitators to ASD diagnosis and treatment in rural and MUAs in Georgia, parents were asked what should be done going forward to improve ASD diagnosis and treatment for those living in rural and MUAs. Parental suggestions to improve issues of health disparities when navigating the healthcare system for children with ASD included: increased education for parents and healthcare providers on early signs and symptoms of ASD, enhanced public and healthcare awareness of the disorder, increased training of new ASD diagnosticians or treatment providers, better hand-off from diagnosis to treatment, and better access to care in rural and MUAs. While these are strategies that will be universally helpful and facilitative for all children and families with ASD, these ideas are particularly important for families in rural or MUAs who, by virtue of their distance from resources, must take a more informed and active role in the early development of their children and advocacy for their children's health.

One of the most significant problems reportedly faced by parents in rural and MUAs to receiving an ASD diagnosis and treatment was the lack of education and awareness about ASD in the community, schools, and healthcare. Specifically, they felt that their concerns over early red flags in their children's development were ignored by certain professionals, leading to delays in diagnosis and treatment. They also discussed how other physiological, psychological, or social disorders of childhood received more public attention and awareness compared to ASD. In order to address these concerns, parents suggested increased education, awareness, and training for professionals interacting with children on a daily basis, such as those working in the education system and pediatric-focused medical fields.

In addition to these potential solutions, parents also described how better transitions from diagnosis to treatment and access to care in their native areas would greatly ease the burden of ASD treatments in rural and MUAs. One participant suggested that after leaving an appointment with a provider who could make the ASD diagnosis, that same provider could also specify next steps and contact information to treatment providers. This parent also suggested a document list of providers in their native areas and the insurances these individuals accepted. Other suggestions for increasing access to care in these underserved areas included the following interventions: telehealth, mobile clinics, encouraging other providers to come to the area, and having healthcare students train in rural and MUAs. To implement these ideas, parents suggested the use of telehealth and mobile clinics. They also proposed that healthcare organizations offer incentives to increase the number of providers willing to work in rural and MUAs, as well as partnering with nearby schools to train students in rural areas.

Quotes from Parents Related to Ideas for Improvement

The following quotes from parents identified ways to address ASD disparities in diagnosis and treatment in rural and MUAs:

Mobile Clinics – Participant 7: “I think it will help if they brought like...mini clinics. Even, you know, something a little closer so we don't always have to drive so far out.”

Increasing Providers – Participant 8: “I think that, well, there needs to be more developmental pediatricians and...diagnosticians. So, whether it's a psychiatrist, psychologist... that can make the diagnosis.”

Training Providers – Participant 2: “...a lot of the schools like [local University] have really big [therapy programs]. In order for students to get their...ABA clinic hours, [they practice delivering ABA therapy to children with ASD]. That's why parents are able to afford it, because now these are college kids doing it for clinic hours.”

DISCUSSION

Timely diagnosis and treatment is crucial for the long-term health outcomes of children with ASD. This process can be impeded by a variety of factors, but the challenges are compounded for individuals living in rural or MUAs. Individuals in these areas face a disproportionate number of unique health disparities and barriers related to acquiring a diagnosis and accessing treatment for ASD, when compared to their urban peers [4, 17, 19].

Focus groups with parents of children with ASD living in rural and MUAs revealed a number of barriers related to both ASD diagnosis and treatment. Parents described a variety of diagnosis and treatment challenges, including limited providers in their area, excessive distance to providers, lengthy wait times for appointments, inadequate insurance coverage, lack of parental and provider education, and overall lack of awareness of ASD diagnoses and treatment in both families and clinicians. In addition, parents also mentioned the lack of follow-up care, leaving them feeling unsure of what the next steps were supposed to be after receiving their child's ASD diagnosis. Thematic analysis of parents' responses revealed perceived limited parental autonomy over their child's healthcare, frustration and disappointment with the healthcare system, and a desire for more support and education. The impact of these disparities and barriers weighs emotionally and financially on parents and families in the form of lost jobs due to time away from work to attend appointments, lost time in school for affected children and siblings, and a general sense of confusion and abandonment by the healthcare system. One parent specifically mentioned that due to the distance and necessary time-off that she had to take from her job, she ended up being fired and becoming unemployed, thus creating the cycle of poverty and perpetuating the cycle of health disparities. These barriers not only affect parents and families, but also could potentially influence the affected child's developmental and social health trajectory if not addressed appropriately.

Many rural and MUA areas are underserved, and families of children with ASD in these populations suffer disproportionately compared to their peers; however, little is known in terms of specific barriers and facilitators to diagnosis and treatment, as well as family-based interventions. This study has demonstrated the needs of underserved children and families with ASD residing in rural and MUAs in Georgia, and it addresses them specifically with a desire to know the barriers and facilitators, to engage the community, and to offer partnership in community-based pragmatic solutions. It has also drawn attention to the difficulties in recruitment and engagement of rural communities. Members of these areas are potentially vulnerable families with past negative experiences with healthcare and research, and they may be hesitant to participate in studies without rapport and understanding being built first. They also face challenges with numerous obligations of running a home and family, which

renders them unable to participate in-person in studies. However, there are ways to ensure that the voices of individuals from rural and MUAs are heard and are present in ASD research, despite any challenges that arise from their geographic locations and socioeconomic and cultural circumstances.

The use of online focus groups to engage parents living in rural allows the consideration of the pros and cons of conducting non-traditional (i.e., online) focus group research and service in these areas. Positive aspects of these nontraditional focus groups can include the chance for participants who live in distant areas to share their stories and have their voices heard when they might not be able to participate in person otherwise, enabling them to be more empowered. However, potential problems with online focus groups may involve technical difficulties when conducting them or the possibility of missing out on a more personalized, in-person interaction. Despite these challenges, research and medical care utilizing telehealth, mobile clinics, or online resources could potentially mitigate the geographic health disparities in vulnerable communities dealing with access to care difficulties. These solutions offer viable alternatives to traditional diagnostic and therapeutic services in rural and MUAs.

Future Directions

Future directions for this study, and for studying ASD disparities in MUAs, involve continuing to engage more parents, especially those living in rural and MUAs in different areas of the state, and in other states with large rural or MUA populations. Research would also benefit from engaging other stakeholders, including providers, educators, parent mentors, and policymakers, to better understand their perspective and experiences with these healthcare disparities. Finally, future research should focus on interventions to minimize these health disparities in MUAs, potentially through the use of telehealth or mobile clinics. Additional interventions, as suggested by the parents, should involve increasing ASD awareness and education to pediatric providers and individuals who work with children, such as those in the school sector. This would likely help to recognize early signs and symptoms of ASD in children and potentially aid in earlier diagnoses. Finally, statewide early interventions may consider leveraging their existing outreach, increasing visibility through social media or other shared programs, and improving existing programs to increase ASD diagnosis.

Limitations

The scope of this project was a pilot project. Thus, the sample size was limited. However, the experience and frustrations expressed by participants in this study are mirrored with other populations. Additionally, given that this population is understudied in the ASD community, the small sample size works as a pilot project for assessing the feasibility for reaching these groups, whether it be via in-person or online focus groups, as many of the families are unable to travel long distances to meet in person. Despite the small sample size, results of this study are an important first step to conducting future research in rural and MUAs, as well as

determining feasibility of tele-focus groups. This will increase the generalizability to different populations, and it could potentially lead to the development of evidence-based interventions.

CONCLUSION

Parents of children with ASD living in rural and MUAs face health disparities in the forms of barriers to accessing ASD diagnosis and treatment. A majority of barriers are centered around the lack of access to providers and challenges associated with access to care, such as limited providers in the area providing ASD specific services and issues with insurance providers not covering treatments. Potential interventions to address these barriers must be focused on patient- and family-centered care, where patients and families identify their specific needs and possible solutions to address them. According to the parents in this study, decreasing health disparities in MUAs in Georgia may be accomplished through increased education, enhanced awareness, and increasing the number of providers that are available to meet the needs of these underserved, vulnerable populations. Given that there are many states throughout the United States that have rural and MUAs similar to Georgia, this early research is key to developing interventions for many children and families affected by ASD healthcare disparities throughout the country. Such interventions could include innovative methods of delivering care, such as through the use of telehealth and mobile clinics, as well as increasing awareness of ASD for parents, providers, and educators of young children. These interventions address the factors of limited access to healthcare and educational services, inadequate infrastructure, and limited parental empowerment and stress, thus helping to break the cycle of ASD health disparities in rural and MUAs.

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Chapter 340

EVALUATION OF HEALTH LITERACY IN CHILDHOOD-ONSET SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS AND ITS EFFECT ON HEALTHCARE UTILIZATION

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ABSTRACT

We enrolled 22 SLE patients (8-19 years old) over three months during clinic visits. Demographic information and medical history were self-reported and collected from medical records. Health and numeracy literacy were assessed using short test of functional health literacy (S-TOFHLA) and Newest Vital Signs (NVS), respectively. Results: Out of the 22 patients, 19 (86%) were female. The greatest percentage by race was Black (45%), and 32% of patients identified as Hispanic. The median age of the participants at the time of the study was 15 years while the median age at diagnosis was 13.5 years. All of the patients surveyed had an adequate score on the S-TOFHLA while only 36% (95% CI: 17.2%-59.3%) scored adequate on the NVS. 27% of the patients

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surveyed stated that they have been exposed to secondhand smoke, and 9% had tried cigarettes and/or other tobacco products. Conclusion: Although all of the patients surveyed scored adequate levels on the S-TOFHLA, the majority scored in the limited/inadequate range on the numeracy test. This is concerning, as numeracy skills are critical for patients to optimally take medications and follow recommendations including dietary guidelines. Based on these results, going forward, we would like to provide patient recommendations that take into account their numeracy and health literacy levels. One potential way to do this is to create patient education material for easier identification of pills and pill dosages as a first step towards increasing adherence and improving patient outcomes.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multifactorial autoimmune disease that has the potential to affect multiple organ systems. It affects people of all ages and races, but racial and ethnic minority groups are disproportionately affected with almost double in Black women when compared to White [1-3]. Childhood-onset SLE (cSLE) is commonly defined as being diagnosed at <18 years of age, and about 20% of SLE cases present in this age group. Involvement of some organ systems, such as kidneys, have been found to be more common and with higher disease severity in cSLE when compared to adult-onset SLE [4]. As of yet, the etiology of SLE is not fully understood. The presumed pathophysiology is that one has a genetic predisposition and then potential factors including environmental stresses, such as smoking, diet, drugs, and hormones trigger the development of SLE [5]. Given the variability of symptoms with the common symptoms being nonspecific, such as fatigue, weakness, and joint pains, along with symptom severity ranging from mild to severe, the diagnosis of SLE can be quite challenging. This generally results in a delay in diagnosis of about two years from the onset of symptoms [6, 7]. Additionally, achieving favorable long-term outcomes in a disease process that has a severe impact on quality of life can prove to be challenging. Successful long-term outcomes in chronic conditions depend largely on education, awareness, and developing self-management skills, which include administering medications appropriately and consistently, managing symptoms, and navigating the life style changes along with the psychosocial components of one's condition [8, 9].

A major barrier to managing chronic conditions today is non-adherence to medications and other management recommendations [10-12]. There is a high prevalence of medication non-adherence in adolescents, which puts them at higher risk for worse outcomes [13]. For SLE specifically, medication non-adherence is as high as 40% with a recent study specifically looking at cSLE showing medication non-adherence at 19.7% [14-16]. One proposed tool to improve medication adherence is to individualize patient education by focusing on health literacy and providing patient instructions based on health literacy levels. Health literacy is defined as "the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions" [17]. The 2003 National Assessment of Adult Literacy, which was a seminal study looking at adult literacy levels in the United States, was administered to more than 19,000 individuals aged 16 years and older. This study found that approximately 36% had limited health literacy levels defined as scoring at basic or below basic levels. This study along with several additional analyses of the study showed that factors, such as poverty, race/ethnicity, disability, age, and education, can all influence health

literacy levels (HLL) [18, 19]. In particular, low HLL along with low literacy in general are associated with lower income and racial/ethnic minority groups [17, 20]. This makes it crucial that HLL in disease processes that affect racial/ethnic minority groups more, such as SLE, are assessed. There is growing evidence to suggest that addressing health literacy will have significant benefits in chronic pediatric illness [20, 21].

In addition to reading, numeracy skills are an important variable when it comes to health literacy. Studies have shown that although numeracy skills can be equivalent to literacy skills, many patients actually tend to have poorer quantitative skills [18, 22]. A 2018 study done at a single pediatric center looked at health literacy, including numeracy, in pediatric kidney transplant recipients and found that 95% of the patients had adequate literacy skills but only 27% had adequate numeracy skills [23]. An adequate functional HLL is crucial to comprehend information provided by healthcare providers and develop lifelong behaviors needed for successful adherence and ultimately favorable long-term outcomes [21, 24-26].

Integrated with traditional health literacy skills is the emerging and evolving field of environmental health literacy, which is defined as “an understanding of the connection between environmental exposures and human health” and its impact on patient outcomes [27]. The 2018 data from the National Youth Tobacco Survey showed that the prevalence of tobacco product use was 27.1% in high school students, and 7.2% in middle school students; both were increased when compared to 2017 data [28]. Data on secondhand smoke exposure in children showed that the prevalence was more than 37% in 2016 [29-31], and the exposure was highest among those living in poverty as well as among non-Hispanic blacks. Several studies have shown that environmental cigarette smoke is associated with an increased risk of the development of SLE in individuals with a genetic predisposition [32-34]. Therefore, in children of a younger age with cSLE, secondhand smoke exposure also needs to be considered as a risk factor for SLE. In a disease process where environmental triggers can potentially worsen outcomes or lead to flares, it is crucial to also increase awareness of environmental health literacy.

The primary aim of this study was to determine the functional HLL, which included literacy, numeracy, and environmental, of cSLE patients in a pediatric center in Atlanta, Georgia where there are about 400 cSLE patients under the combined care of Rheumatology and Nephrology services. We determined if lower HLL were associated with increased healthcare utilization defined as number of Emergency Room (ER) visits and hospitalizations per year. Given previous results for pediatric patients with kidney transplants in the same geographic region, we hypothesize that cSLE patients in this study will have lower HLL, particularly with numeracy literacy. Since understanding of prescriptions is essential in accurately taking medications at home, lower numeracy skills may prove to be a barrier in optimal self-management leading to poorer outcomes, hence we also hypothesize that lower HLL will be associated with increased medical complications and increased healthcare utilization. A secondary aim was to estimate smoking and exposure to secondhand smoke. We hypothesize that the prevalence of secondhand smoke exposure in cSLE patients will be at the least the same or higher than the general population.

OUR STUDY

Approval for this study was obtained through the Institutional Internal Review Board. This was a cross-sectional study and a retrospective chart review over the span of 2 months (2/1/2019-3/31/2019), enrolling 22 SLE patients ranging from 8 to 19 years of age. Demographic information and medical history were collected at the time of scheduled clinic visits. Our primary outcome measures were hospitalizations and ER visits related to SLE.

Inclusion and Exclusion Criteria

Inclusion criteria for this study were cSLE patients between the ages of 8 and 21 years who speak and understand English. Parents/caretakers/guardians of cSLE patients were also able to participate if they were able to speak, read, and/or understand English. Exclusion criteria were those who could not speak, read, and/or understand English, had cognitive delay, were unable to provide informed consent, and were outside the age range of 8 to 21 years.

Survey Design

The Short Test of Functional Health Literacy (S-TOFHLA), a validated measure assessing health literacy [35], and the Newest Vital Signs (NVS), a validated measure assessing numeracy skills [36, 37], were administered during the clinic visit and the results were used to determine baseline functional HLL. Patients were also asked to fill out a secondhand smoke exposure survey, which is adapted from the CDC Youth Tobacco survey, to assess exposure [38]. Clinical information was obtained from patient's medical records from the time of SLE diagnosis to the end of the study period (3/31/2019). We used this information to determine a healthcare utilization rate defined as the total number of ER visits and hospitalizations per patient-year.

Data Analysis

Based on the results of the S-TOFHLA and NVS, individuals were classified as either having adequate HLL or inadequate HLL with adequate being a score of 23-36 on S-TOFHLA and 4-6 on NVS [35-37]. Participants were placed in the inadequate group if they scored in the inadequate/marginal range for the S-TOFHLA (0-16 and 17-22 respectively) or in the inadequate/limited range on the NVS (0-1 and 2-3 respectively). Proportions of adequate/inadequate literacy were calculated with the 95% confidence interval (CI) using the Clopper-Pearson exact method. Fisher's exact test was used for categorical data while Wilcoxon rank sum was used for testing continuous data by adequate vs inadequate groups. Poisson test was used to analyze healthcare utilization between the adequate and inadequate HLL groups. Exact confidence intervals for healthcare utilization were calculated, which is based on the binomial distribution given the small sample size.

FINDINGS

Of the 22 individuals who participated, 86% were female. The greatest percentage in race were Black (45%), while 32% identified themselves as White-Hispanic. The median age of the participants at recruitment was 15 years while the median age at diagnosis was 13.5 years (see Table 1). All of the individuals who participated scored in the adequate range for the S-TOFHLA (see Figure 1). However, for the NVS, only eight patients (36%) scored in the adequate range while the remaining 14 (64%) scored in the inadequate range (combination of high likelihood of limited numeracy skills and possibility of limited numeracy skills) (see figure 2). Of note, we attempted to assess the parents’ functional health literacy as well, but due to the scarcity of the responses, found that the data could not be analyzed meaningfully.

Table 1. Baseline characteristics of the 22 p-SLE participants

Demographics	p-SLE Patients N = 22
Gender, n (%)	
Female	19 (86%)
Male	3 (14%)
Race, n (%)	
White	9 (41%)
Black	10 (45%)
Asian	3 (14%)
Ethnicity, n (%)	
Hispanic	7 (32%)
Non-Hispanic	15 (68%)
Age at diagnosis (years), median (Q1,Q3)	13.48 (11.94, 14.56)
Duration of disease (months), median (Q1,Q3)	23 (11.04, 46.09)

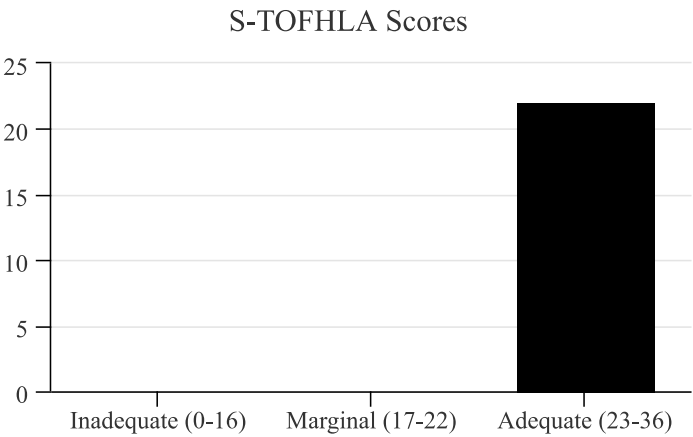


Figure 1. S-TOFHLA scores.

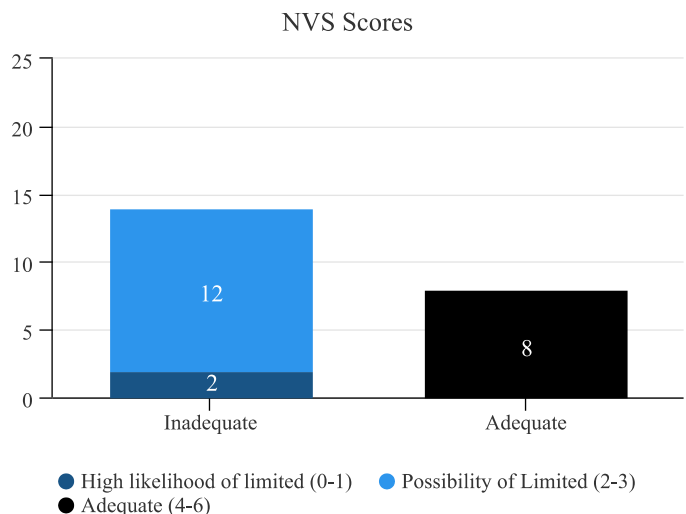


Figure 2. NVS scores.

Table 2. Patient characteristics compared by inadequate and adequate HLL based on scores from newest vital signs (numeracy test)

Variable	Overall (n = 22)	Inadequate HLL (n = 14)	Adequate HLL (n = 8)	p-value
Age, mean (SD)	15.4 (2.3)	15.4 (2.2)	15.3 (2.7)	0.97
Age at diagnosis, mean (SD)	13.0 (2.0)	13.5 (1.8)	12.1 (2.2)	0.15
Gender, n (%)				0.53
Female	19 (86.4)	13 (92.9)	6 (75.0)	
Male	3 (13.6)	1 (7.1)	2 (25.0)	
Race, n (%)				0.69
White	9 (40.9)	6 (42.9)	3 (37.5)	
Black	10 (45.5)	7 (50.0)	3 (37.5)	
Asian	3 (13.6)	1 (7.1)	2 (25.0)	
Ethnicity, n (%)				1.00
Hispanic or Latino	7 (31.8)	4 (28.6)	3 (37.5)	
Non-Hispanic	15 (68.2)	10 (71.4)	5 (62.5)	

Table 3. Healthcare utilization rates compared by inadequate and adequate Hll based on scores from newest vital signs (numeracy test)

	Overall (n = 22)	Inadequate HLL (n = 14)	Adequate HLL (n = 8)	p-value
Duration of illness calculated (yrs), mean (SD)	2.38 (2.19)	1.89 (1.54)	3.24 (2.95)	0.27
Number of hospitalizations or ER visits, mean (SD)	5.55 (6.64)	5.71 (6.35)	5.25 (7.55)	
Healthcare utilization, ER visits/hospitalizations per yr (95% CI)		3.02 (0.63 – 8.80)	1.62 (0.14 – 6.61)	0.0011*

Since all participants scored in the adequate range under S-TOFHLA, the individuals were divided into an adequate and inadequate health literacy group based on their NVS scores. Baseline characteristics were compared by health literacy group. There were no statistically significant differences in age, gender, race, ethnicity, and duration of disease between the groups. The mean (SD) age in years was 15.4 (2.2) for the inadequate group and 15.3 (2.7) for the adequate group. The mean (SD) age in years at diagnosis for the adequate HLL group was 12.1 (2.2) and 13.5 (1.8) for the inadequate HLL group although this difference was not statistically significant (Table 2). The inadequate HLL group had an average (SD) of 5.71 (6.35) number of hospitalizations/ER visits for the individuals' disease course compared to 5.25 (7.55) per disease course for the adequate HLL group. However, if we take into account the actual duration of illness/follow-up, a significant difference was present between the groups. The eight adequate HLL individuals had a healthcare utilization rate of 1.62 (95% CI 0.14 – 6.61) per patient-year, while the 14 inadequate HLL individuals had a healthcare utilization rate of 3.0 (95% CI 0.63 – 8.80) per patient-year. Therefore, using a Poisson test, a significant difference was detected in healthcare utilization by group (Table 3).

In regard to the secondhand smoke survey, 27% of the individuals surveyed stated that they have been exposed, and 9% reported trying cigarette and/or other tobacco products. Those who reported trying tobacco products stated that they were not exposed to secondhand smoke.

DISCUSSION

To our knowledge, there are a lack of studies looking at functional health literacy in cSLE patients and its effect on clinical outcomes. A few small studies on adult SLE patients show that a low HLL was present in about 20-50% of the population and was associated with worse chronic organ damage and patient reported outcomes [39, 40]. Generally, assessing pediatric health literacy can be more complex given the developing literacy skills of pediatric patients along with the need for adequate parent or caregiver's literacy levels. Therefore, health literacy in both the pediatric patients and their caregivers need to be carefully assessed and addressed [41]. This is imperative for a disease process that is known to be more prevalent in lower socioeconomic groups since low health literacy is an important underlying factor in further widening the gap in healthcare disparities [42].

The results of this study show that the demographics of our small sample size are similar to previous cSLE studies with the majority of the sample being female and from a racial or ethnic minority group. Although 100% of the individuals surveyed scored at adequate levels on the S-TOFHLA, the majority scored in the limited/inadequate range for their numeracy skills based on the NVS. In an age group where medication adherence is already problematic, these results are concerning. Since SLE is known to affect multiple organ systems, the majority of patients are responsible for managing multiple prescriptions, and numeracy skills are vital in accurately interpreting and optimally adhering to these prescriptions. If an individual also has renal involvement, it is critical to be able to read food labels and determine how much sodium, potassium, and phosphorous are in the foods, which requires adequate numeracy skills.

A recent study in 2018 looked at health literacy disparity and its effect on adolescents and young adults with chronic or end-stage kidney disease [43]. Results from this study did not show major differences between low and adequate health literacy groups on healthcare utilization defined as preventable hospitalizations, total hospitalizations, length of hospital stay, and ER visits [43]. For the cSLE patients surveyed in our study though the results did indicate that healthcare utilization, defined as ER visits and hospitalizations pertaining to SLE, differed between low and adequate health literacy groups. According to patient reports, SLE has a tremendous impact on the quality of life of patients, caretakers, family members, employment, financial status, and work productivity [44]. Therefore, the ultimate goal in SLE management is to get patients on an effective maintenance medication regimen to prevent flares/relapse and eventually improve quality of life for both the child and the family. Our results indicate that the group with inadequate HLL had increased utilization of healthcare services, which suggests an increased risk for worse outcomes.

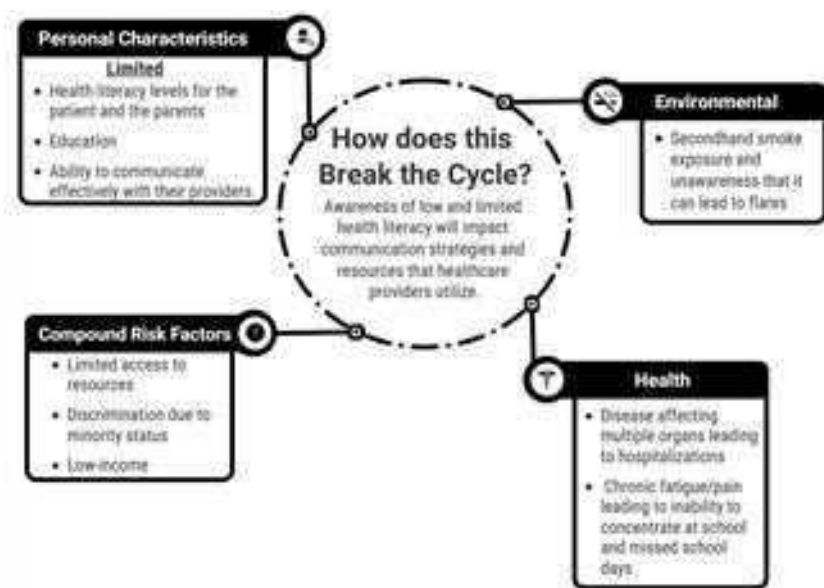


Figure 3. Breaking the cycle of health disparities related to health literacy including numeracy skills and environmental health literacy.

The estimate of health literacy was the primary focus of this study. Although the utilization rates were not compared for all possible confounders due to small sample size, these results still indicate that the need for counseling and instruction based on one's health literacy level may be an optimal point of intervention to break the cycle of health disparities for children with SLE (see Figure 3). In particular, health literacy interventions targeting high-risk groups, such as cSLE patients, may improve outcomes and ultimately break the cycle of health disparities. Given SLE affects minority groups more often and a lower socioeconomic status is associated with more severe disease, the cycle of health disparities is perpetuated by resources that may not be appropriate for those with limited education and/or lower HLL. Several resources are available to these patients, either in the form of online material, written pamphlets, or written instructions from the providers, but resources are of limited value if the individual is not able to read, understand, remember, and adequately act

on the instructions at home. A recent randomized controlled trial showed a statistically significant and clinically meaningful effect on medication decision making in patients with lupus nephritis when using a computerized decision aid that is individualized and culturally tailored compared to an American College of Rheumatology lupus pamphlet [45]. One possible indicator of poor health literacy is identification of pills by the color and size and not by their names. One way to combat misidentification of medications due to the inability to identify them by name is to provide patients with pictures of commonly used SLE medications and demonstrate which pills and how many of them to take [46-48]. Studies done in pediatric diabetic patients and parents have shown that hands-on demonstration of how to dose medications have been helpful particularly for individuals with low HLL [49]. Another key intervention is the teach-back/show-back method, which has been confirmed in several studies to be highly effective in improving communication and confirming understanding [50-52]. Ultimately, our recommendation would be to individualize the education process based on each individual's education status as well as health literacy level.

This study also revealed that about a quarter of the cSLE patients were exposed to secondhand smoke, which is less than the prevalence for the general population. This is interesting given that the cSLE patients tend to have the demographics of individuals with higher risk for secondhand smoke exposure. What the smoking survey was not able to adequately ascertain though was the difficulty that participants had in not fully understanding the concept of secondhand smoke exposure. This observation suggests that, although this was not formally tested, environmental health literacy may be inadequate in this patient population as well as not discussed adequately by the providers. Further evaluation of this along with increased awareness for our patients are needed.

Limitations

One of the major limitations to this study is the small sample size. The majority of the individuals with cSLE were recruited in the general nephrology or rheumatology clinic setting as opposed to in the end-stage renal disease clinics, such as chronic kidney disease, dialysis, and transplant clinics. This could potentially represent a selection bias since the individuals with more significant disease and potentially lower HLL and limited transportation resources may not come to clinic as often. There is also a chance that patients with perceived lower HLL declined to participate due to fear of taking a literacy test although only two patients declined to participate. Another limitation is that this data analysis did not take into account any potential confounders, such as income, education level, minority status, which could affect our results. Furthermore, the ER visits and hospitalizations counted in this study were only those that occurred at our single center so if patients went to other ER's or were hospitalized at other hospitals, they were not counted, which could skew results. Of note, the hospital assessed in this study is the main hospital that provides pediatric rheumatology and nephrology care to the majority of Georgia. Therefore, most of the patients with cSLE in Georgia are likely to attend the clinic at this hospital and are likely to visit this specific hospital's ER, be admitted to this particular hospital, or at least contact the clinic when there is a concern. At this age, some of the medical management is still done by parents, which was not asked in the surveys. If the medical care is strictly managed by the parents or other

caregivers, then it is crucial to determine their HLL as well. One of the exclusion criteria in this study was not being able to speak, read, and/or write English; however, the subjects were not asked what the primary language was spoken at home, which could potentially affect literacy levels.

Future Directions

Results of this preliminary study were suggestive that HLL can potentially affect one's outcomes. Therefore, the next steps would be to recruit more caregivers if they are doing the majority of the medical management as well as do further data analyses to account for the aforementioned limitations. The take-home message is to focus the efforts on individualizing the education process, and in turn, improve communication between the providers and the patients with lower HLL. One plan for the future is two-tiered. The goal is to increase awareness amongst the providers about the potential for patients to have limited HLL as well as create optimal educational materials for our cSLE patients for easier identification of medications so that they can successfully demonstrate the teach-back method. These interventions can ultimately improve home management and aide patients in decreasing medical complications and potentially achieving better quality of life and thus break the cycle of health disparities for children with SLE.

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Chapter 341

DID MEDICAID EXPANSION DECREASE DISPARITIES FOR RECEIPT OF PREVENTIVE MEDICAL CARE AMONG VULNERABLE CHILDREN?

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ABSTRACT

In this chapter we investigate differences in receipt of pediatric preventive medical visits (PMV) among racial/ethnic groups between the states that did and did not expand Medicaid as a part of the 2010 Affordable Care Act. Differences were investigated using hierarchical linear modeling. Tested models included whether respondents were first generation immigrant families, if English was spoken in the home, whether the child had special health care needs, if there was an insurance gap, and race/ethnicity of the child as level-1 variables and residence state as a level-2 variable to predict odds ratios of PMV, with cross-level interactions between race/ethnicity and Medicaid expansion. All groups of children living in states with Medicaid expansion had increased log-odds of receiving a PMV. When the interactions between race/ethnicity and Medicaid expansion were considered, the odds of PMV among Whites, Hispanics, Black, and other race/ethnicity children was greater in Medicaid expansion states; however, the strongest effect was for White children. If the interaction term was not considered, children of Hispanic and Other ethnicity had significantly lower odds of receiving PMV in both expansion and non-expansion states. Children who did not speak English in the home, were first generation immigrant families, and/or experienced a gap in insurance had reduced odds ratios for receiving PMV compared to other children.

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INTRODUCTION

The Affordable Care Act of 2010 (ACA) was introduced to improve health care coverage for United States citizens. The ACA included a goal to expand Medicaid to cover all families below 138% of the poverty level [1], but not all states opted to expand Medicaid coverage. Medicaid is a public health insurance program, funded by a combination of federal and state monies. Both federal and state funds are managed by the states, resulting in many different approaches to administering Medicaid [1]. Prior to 2014 the median income to qualify for Medicaid was \$15,000 for a family of four, with wide variation from state to state. Children's health benefits were mandated by the federal government through the Children's Health Insurance Program (CHIP) program for children whose family income fell below 100% federal poverty level, \$23,842 for a family of four [1]. After 2014 the median income for a family of four qualifying for Medicaid rose to \$33,465. All states lost federal funding for uncompensated healthcare as part of the ACA, but these losses were expected to be balanced with a greater proportion of healthcare costs paid through Medicaid [1, 2]. As funds for uncompensated care were reduced--in all states--the number of people covered by Medicaid did not increase, but decreased in non-expanded states, due to changes in waiver legislation. The states that did not expand lost a large portion of their federal funding for healthcare [2]. The monies that had been flowing to uncompensated health care were diverted to Medicaid, so if a state did not expand Medicaid, it generally lost funding.

While the ACA expansion was primarily aimed at adults, the fact that children follow their caretakers into insurance coverage suggests that children should reap benefits as well [3]. It is reasonable to expect that the Medicaid expansion increased children's access to health care. One important outcome of Medicaid expansion is whether children have increased access to a preventive medical visit (PMV), an indicator of children's access to preventive health care [4]. Preventive health care is important for connecting children to health care providers who promote health, teach caretakers and children to make better health decisions, and help prevent and/or detect disease early [5]. During a preventive health visit children and caretakers receive guidance in promoting physical, emotional, and intellectual development. This help includes guidance to choose appropriate nutrition, exercise, and safety habits such as car seat and helmet usage [6]; talking and reading to promote intellectual development [7]; education and interventions to prevent or reduce adverse childhood events [8], and screening for developmental delays and behavior [5]. Further, during these visits children receive vaccinations to prevent disease and reduce health care costs over time [9].



Figure 1. Breaking the cycle of children's environmental health disparities.

Thus, children who receive preventive health care are also less likely to experience preventable illness and more likely to receive timely intervention for health conditions that are not preventable [5]. Timely intervention often reduces morbidity and mortality, allowing children longer life spans [5]. Thus, PMVs are an important outcome to consider in relation to the ACA Medicaid expansion. Reducing disparities in PMV can break the cycle of environmental health disparities by reducing the disproportionately negative effects of both social and physical determinants of health to which vulnerable children are exposed (see Figure 1).

Medicaid Expansion and Health Disparities

Health disparities among children in the USA are well documented [10]. Children of minority race or ethnicity had less desirable health outcomes on many measures including less access to care, lower quality care, and greater morbidity and mortality from disease [11, 12]. These inequities existed in preventive health care [10] even as preventive care was being promoted to reduce health disparities and reduce health care cost in the US [13].

The ACA is seen as successful in certain respects, as large disparities in healthcare insurance coverage found prior to the ACA were reduced after Medicaid expansion among all racial and ethnic groups, although not equally among all groups [14]. Research concerning children's healthcare outcomes in states with Medicaid expansion includes findings of decreased infant mortality [15], reduced disparities in trauma care in adolescents [16], increased school readiness [17], and increased access to mental health care for youth [18]. Studies indicate that Medicaid expansion is associated with increased adult preventive care [19] and that there is an increased likelihood of a well child visit among children of low income parents in states with increased eligibility for Medicaid, i.e., as the threshold for Medicaid eligibility is reduced by increasing percent of federal poverty level for eligibility, the probability of a well child visit increases [20]. In the study by Venkataramani et al [20] the data source was 2001-2009 Medical Expenditure Panel Surveys, thus it does not address differences related to ACA Medicaid expansion.

Factors Affecting Pediatric Health Care Utilization

There are many factors affecting health care utilization. For example, Anderson's Model of Health Care Consumption [21] suggests that health care consumption is predicted by need, access, and predisposing variables. Predisposing variables include demographics such as age, race, language, income, caretakers' education, family structure, and beliefs; need variables include children with special health care needs (CSHCN) that are more than the health care needs of typically developing children; access variables include health insurance, prior use of the healthcare system, and geographic location [22]. Researchers suggest that language can influence a caretaker's assessment of care quality and trust, informing their decision to take a child to a well care provider [23]. Also immigrants use less preventive health services than natives [24]. Furthermore, community poverty is associated with the emergence of health

service “deserts”, medically underserved areas or populations, where there are limited healthcare services [25].

Research Questions

In the current climate of debate concerning the efficacy of the ACA and Medicaid expansion it is important to determine what, if any, impact Medicaid expansion had on the health care outcomes of US citizens. Our study’s goal is to compare the receipt of preventive medical visits among children who lived in states that did, and did not, expand Medicaid.

Table 1. Number of children sampled in each state

State	N	State	N	State	N	State	N
AL	830	IL	1115	MT	1018	RI	893
AK	823	IN	942	NE	1073	SC	885
AZ	887	IO	1132	NV	774	SD	1133
AR	829	KS	1007	NH	995	TN	885
CA	942	KY	879	NJ	1081	TX	813
CO	1101	LA	687	NM	792	UT	1148
CT	1090	MA	986	NY	950	VT	1117
DE	918	MD	1095	NC	951	VA	1158
DC	1001	MA	1185	ND	1051	WA	1141
FL	905	MI	1127	OH	1027	WV	785
GA	795	MN	1351	OK	764	WI	1267
HI	1122	MS	638	OR	1107	WY	835
ID	1068	MO	1015	PA	1099		

Total sample size of individuals = 50,212.
Total number of clusters = 51.

This study focused on the question: Are children of all races and ethnicities living in Medicaid expansion states more likely to receive preventive health care than in non-expansion states? This study aimed to determine if (a) there are differences among states in the likelihood of receiving a preventive medical visit, (b) if these differences can be attributed to Medicaid expansion, and (c) if disparities among groups of racial and ethnic children’s receipt of PMV persist after Medicaid expansion.

OUR STUDY

The data source was the 2016 National Survey of Children’s Health (NSCH), a cross-sectional survey conducted by the US Census Bureau [4]. This survey is used to assess the physical and mental well-being of US children ages 0-17 years. A caregiver responded to inquiries focused on the health and health care of one child living in the household in 50,212 randomly selected households [4]. Table 1 contains the distribution of the sampled children among the states. Most questions required either a yes/no or a categorical response. The data source for statewide policies was the National Council of State Legislators’ database of state legislation [26]. The measurement was whether the state did or did not participate in Medicaid expansion before 2016.



Figure 2. Anderson's model of health care consumption. Anderson (Andersen RM. Revisiting the behavioral model and access to medical care: Does it matter? *J Health Soc Behav* 1995;36(1):1–10) suggested three types of variables predict health care consumption, predisposing, need based, and access. Our model is focused on the interaction between predisposing variables of race/ethnicity and access increased by living in a Medicaid expanded state.

Outcome and Predictors

The outcome variable PMV was the caregiver's yes or no response to the question "Did the child receive one or more PMV in the last 12 months". 433 children (0.8%) were missing the outcome variable, PMV, and their data was deleted from the analysis during model building.

Andersen's model of health care utilization [21] was used to select predictor variables, illustrated in figure 2. The predisposing variables included were speaking English in the home, first generation immigrant families, and race/ethnicity. These choices were based on the research question connecting persistent disparities to Medicaid expansion. The need variable was CSHCN, this is the 2016 NSCH indicator for children who need more healthcare than typical children. Caretakers responded to a series of questions that screened the child as CSHCN or not according to the criteria estimated by the Maternal Child Health Bureau [4]. Access variables were insurance gap and state of residence, insurance gap indicating if the child was insured the full 12 months prior to the survey, and state of residence indicating if the child was living in a state that did or did not expand Medicaid.

Immigration and language have been identified in other studies as predictors of PMV [11, 23] suggesting that first generation (family) and English speaking in the home might be significant predictors for this study. The focus of this research was on disparities among race/ethnic groups. Prior studies have shown that poverty level, family structure and parental education are correlated to race/ethnicity and these are important demographic factors associated with the impact of the ACA [27]. We chose race/ethnicity as predictors over the other characteristics as recent research on adults indicates that the ACA expansion has benefited White populations to a greater degree than other minority groups [14]. We included insurance gap in the prior year because Medicaid expansion is aimed at increasing health insurance coverage within the states' populations. Medicaid expansion, the only level-2 (state level) predictor, is a state level policy that may help determine the child's access to health insurance.

The outcome and predictor variables were coded as follows: Children who received PMV were coded PMV = 1, children who did not receive PMV were coded PMV = 0; children who spoke English in the home were coded English = 0, children who did not were coded English = 1; children who were not first generation were coded FirstGen = 0, children who were first

generation were coded FirstGen =1. The race/ethnicity indicator in the 2016 NSCH has four categories: Black, Hispanic, Other, and White. Each child is assigned to only one of these categories in the survey. Children who were categorized as Hispanic were coded Hispanic = 1, all other children were coded Hispanic =0; children who were categorized as Black were coded Black = 1, all other children were coded Black = 0; children who were categorized as Other were coded Other =1, all other children were coded Other =0; children who were categorized as White were coded Hispanic =0, Black =0, and Other = 0, making White the reference group for the race/ethnicity variable. Children identified as CSHCN in the survey were coded CSHCN = 1, other children were coded CSHCN =0. Children who experienced an insurance gap in the prior 12 months were coded Gap = 1, other children were coded gap =0. The states that expanded Medicaid were coded Exp = 1, the other states were coded Exp =0.

A cross-level interaction was included in the final model to study the interaction between race and Medicaid expansion among the states. The cross-level interaction was added to the level-2 model for Hispanic, Black, and Other.

Analysis

A Hierarchical Generalized Linear Regression (HGLM) model was built using HLM 7.03 [28]. HLM software uses a Bernoulli link function and penalized quasi-likelihood estimation method to produce log-odds of PMV. The unconditional model, predicting the log-odds of an average child in the study receiving PMV with no predictor other than state, separated the model variance into individual variance within the states and state level variance between the states. This model produced an intraclass correlation coefficient of .04, suggesting that 4% of variance was related to state differences, and that a hierarchical modeling approach was appropriate for this study.

Variables in the model were uncentered and all slopes fixed because 51 clusters were too few to allow for random slopes. The model was constructed without interaction terms, and then with cross-level interaction terms for the variables first generation, non-English in the home, Black, Hispanic and other. The interaction terms for first generation and non-English in the home were not significant. The interaction terms for Black, Hispanic, and Other were significant. The final model was built including only interaction terms for the set of race/ethnicity variables, Black, Hispanic, and Other. The final fully conditional model was:

$$\ln \left(\frac{\Pr(PMV_{ij}=1)}{1-\Pr(PMV_{ij}=1)} \right) = \beta_{0j} + \beta_{1j}(English) + \beta_{2j}(FirstGen) + \beta_{3j}(Gap) + \beta_{4j}Hispanic_{ij} + \beta_{5j}Black_{ij} + \beta_{6j}Other_{ij} + \beta_{7j}CSHCN_{ij}$$

$$\beta_{0j} = \gamma_{00} + \gamma_{01}Exp_j + u_{0j}; u_{0j} \sim N(0, \tau_{00})$$

$$\beta_{1j} = \gamma_{10}$$

$$\beta_{2j} = \gamma_{20}$$

$$\beta_{3j} = \gamma_{30}$$

$$\beta_{4j} = \gamma_{40} + \gamma_{41}(Exp_j)$$

$$\beta_{5j} = \gamma_{50} + \gamma_{51}(Exp_j)$$

$$\beta_{6j} = \gamma_{60} + \gamma_{61}(Exp_j)$$

$$\beta_{7j} = \gamma_{70};$$

In this model γ_{00} was the expected log-odds of having a PMV for a referent child described as one who: (a) speaks English in the home, (b) is not first generation, (c) had no insurance gap, (d) is White race, (e) does not have special health care needs and (f) lives in a state without Medicaid expansion. γ_{01} represents the expected log-odds of having a PMV in a state that has Medicaid expansion compared to the log-odds in a state that does not, holding all other variables constant. The $\gamma_{10, 20, 30, 40, 50, 60, \text{ and } 70}$ estimates represent changes in log-odds--controlling for other variables in the model—among children different from the reference group in each predictor category, that is a child who (a) does not speak English in the home, and/or (b) is first generation, and/or (c) had an insurance gap, and/or (d) is of Black, Hispanic, and/or Other race/ethnicity, and/or (e) has special health care needs.

Assumption Checking

Assumptions underpinning the use of a 2-level binomial model were checked to determine if this set of predictors and outcome were appropriate for use in HGLM. Pearson correlations among the level-1 predictors and level-1 residuals were calculated and the level-1 predictors were determined to be independent of the level-1 residuals. Pearson correlations among the level-1 predictors were determined and the only highly correlated pair was not speaking English in the home and Hispanic. Not speaking English in the home and Hispanic had a .46 correlation, but both predictors were included because the literature search suggested parental language as an important predictor of PMV [11], and race/ethnicity form the research questions. The level-2 residuals were reasonably normal. There was no correlation between level-2 residuals and level-2 predictors, suggesting independence. There was no correlation between level-1 residuals and level-2 residuals, suggesting they were also independent. The omitted level-1 predictors of poverty level, sex, age, and family structure were not correlated to the level-2 residual.

Table 2. Characteristics of population estimated by the sample

Variable	Sample N	Level	Estimated Population N	Proportion	SE
Preventive Medical Visit	42344	Outcome	59647331	0.81	0.001
No Preventive Medical Visit	7435	Outcome	12858597	0.18	0.001
Medicaid Expansion States	27	2	27	0.54	0.07
Non-Medicaid Expansion States	23	2	23	0.46	0.07
English Speaking in the home	46687	1	6216651	.86	0.001
Not English Speaking in the home	3148	1	695454	.10	0.001
First Generation	8486	1	1876126	0.03	0.001
Not First Generation	39273	1	64749922	.89	0.001
Insurance Gap	2504	1	5882311	0.08	0.001
No Insurance Gap	47708	1	66670823	0.91	0.001
Hispanic ethnicity*	5523	1	18000627	0.25	0.001
Not Hispanic ethnicity	44689	1	55349413	0.75	0.001
Black race*	2871	1	9324320	0.13	0.001
Not Black race	47341	1	64025720	0.87	0.001
Other race*	6501	1	7965888	0.11	0.001
Not Other race	43711	1	65384152	0.89	0.001
Special Health Care Needs	11392	1	14196961	0.19	0.001
No Special Health Care Needs	38820	1	59153079	0.81	0.001

FINDINGS

Population estimates, shown in table 2, were found for the proportions of children with the outcome and predictor variables included in the model. The questions concerning first generation and language spoken in the home had a higher rate of missing responses than other predictors, eight percent and four percent, respectively. All other variables had less than one percent missing responses. 81% of all children were estimated to have received a preventive medical visit in the previous 12 months. An estimated 86% of children spoke English in the home, 10% did not speak English in the home and 4% of respondents did not answer this question. An estimated 89% of respondents said the child being surveyed was not first-generation, 3% of caregivers responded that the child in the survey was first-generation, and 8% of the caregivers did not answer this question. An estimated 91% of children did not experience an insurance gap in the 12 months preceding the survey, 8% did experience an insurance gap. 19% of children were estimated to have a special health care need, 81% did not have a special health care need. Twenty-six of the states included in the 2016 NSCH states expanded Medicaid prior to data collection in 2016.

Table 3. HLM model predicting primary medical visit in the last year of children 0-17 in National Survey of Children's Health (2016)

Fixed Effect	Coefficient	Odds Ratio Ratio	Confidence Interval Interval
For Intercept 1, β_0			
INTRCPT2, γ_{00}	1.62	5.05	(4.48,5.69)
EXP, γ_{01}	0.42	1.53	(1.24,1.88)
For CSHCN slope β_6			
INTRCPT2, γ_{70}	0.54	1.72	(1.59,1.86)
For FIRSTGEN slope, β_1			
INTRCPT2, γ_{10}	-0.45	0.64	(0.45,0.89)
For ENGLISH slope, β_7			
INTRCPT2, γ_{70}	-0.48	0.62	(0.50,0.75)
For GAP slope, β_2			
INTRCPT2, γ_{20}	-0.46	0.63	(0.53,0.75)
For HISPANIC slope, β_3			
INTRCPT2, γ_{30}	-0.07	0.93	(0.80,1.09)
EXP, γ_{31}	-0.19	0.83	(0.68,1.01)
For BLACK slope, β_4			
INTRCPT2, γ_{40}	-0.01	0.98	(0.77,1.25)
EXP, γ_{41}	-0.31	0.73	(0.54,1.03)
For OTHER slope, β_5			
INTRCPT2, γ_{50}	0.05	1.05	(0.91,1.21)
EXP, γ_{51}	-0.26	0.77	(0.64,0.94)

Only fixed effects are reported in this table because there are no random slopes in the final model.

Results of Model Building

Results of HGLM analysis suggested that children living in Medicaid Expansion states and children with special health care needs were more likely to receive PMV than children who did not live in expanded states and/or who did not have special health care needs, as

shown in table 3. The odds ratio for PMV among children in expanded states was 1.53, 95% CI = [1.26, 1.86] times those of children in non-Medicaid expansion states. The odds ratio for PMV among children with special health care needs was 1.72, 95% CI = [1.59, 1.86] times those of children who did not have special health care needs.

Several predictors in the model reduced children's odds ratios for PMV. These were first generation, insurance gap, and not speaking English in the home. Odds of PMV among first generation children were 0.64, 95% CI = [0.45, 0.89] times those who were not first generation, odds of PMV among children who experienced an insurance gap in the prior 12 months were 0.63, 95% CI [0.53, 0.75] times those of children who did not experience an insurance gap, and odds of PMV among children who did not speak English in the home were 0.62, 95% CI [0.25, 0.75] times those of children who spoke English in the home.

The race/ethnicity variables were analyzed with cross-level interaction terms added to the final model. The coefficient for cross-level interaction for other was -.26, p-value = .009; the cross-level interaction coefficient for Hispanic was -0.19, p-value = .06, and the cross level interaction coefficient for Black was -0.30, p-value = .05.

Figure 3 is a chart showing the odds ratios for all four race/ethnicity categories in Medicaid expansion states and non-Medicaid expansion states including the interaction between Medicaid expansion and race/ethnicity. The negative interaction coefficients in table 3 suggested that non-White children in Medicaid expansion states had lower odds of PMV than children who were White, but children in all four race/ethnicity categories had increased odds of PMV in Medicaid expansion states versus non-Medicaid expansion states.

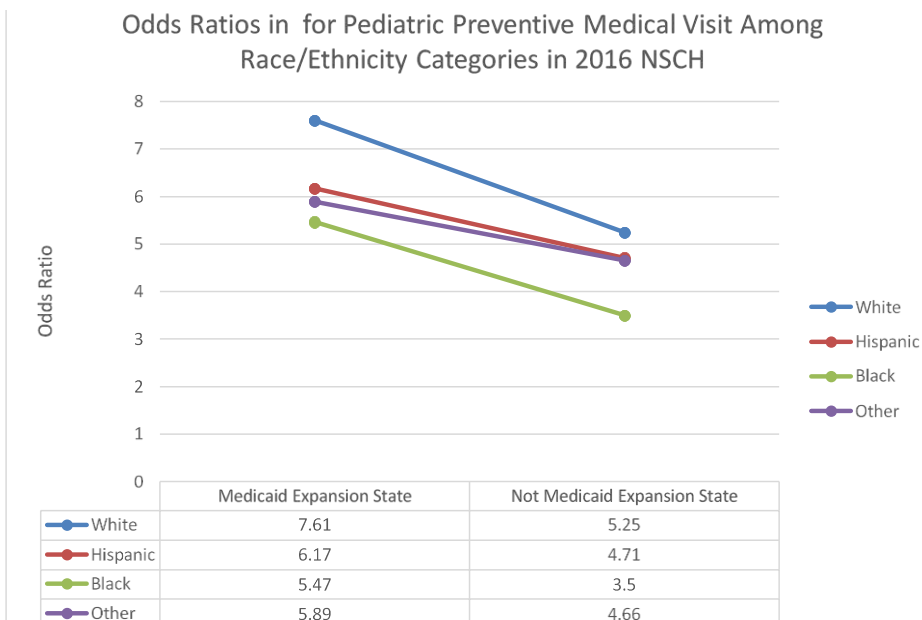


Figure 3. Odds Ratios for PMV produced by the model including interactions between Medicaid expansion and race/ethnicity. The graph illustrates the negative interaction between Hispanic, Black, and Other race/ethnicities in Medicaid expansion states—the odds ratio for White children are noticeably higher than the other three. The coefficients for the Hispanic and Black race/ethnicity are not statistically significant, the coefficient for Other is statistically significant. The slopes for White and Black are greater than Other and Hispanic, suggesting that Medicaid expansion had a greater impact on White and Black children's receipt of PMV.

Holding all other variables constant, the equation for determining the effects of Medicaid expansion among the race/ethnic groups is:

$$\ln \left(\frac{\Pr(PMV_{ij}=1)}{1-\Pr(PMV_{ij}=1)} \right) = \gamma_{00} + \gamma_{30}(\text{Hispanic}) + \gamma_{40}(\text{Black}) + \gamma_{50}(\text{Other}) + \gamma_{01}(\text{Exp}) + \gamma_{31}(\text{Hispanic}) * (\text{Exp}) + \gamma_{41}(\text{Black}) * (\text{Exp}) + \gamma_{51}(\text{Other}) * (\text{Exp})$$

The race/ethnicities were dummy coded, with White as a reference group. Substituting ones for the desired race and zeros for the other races determined the log-odds for PMV among the group of interest. The log-odds for White children is simply $\gamma_{00} + \gamma_{01}(\text{Exp})$. In this equation the odds ratio of White children receiving PMV in Medicaid expansion states was 7.61, in non-expansion states it was 5.25. The odds ratio of Hispanic children receiving PMV in Medicaid expansion states was 6.17, in non-expansion states it was 4.48. The odds ratio of Black children receiving PMV in expansion states was 5.47, in non-expansion states it was 4.50. The odds ratio of Other children receiving PMV in expansion states was 5.89, in non-expansion states it was 4.85.

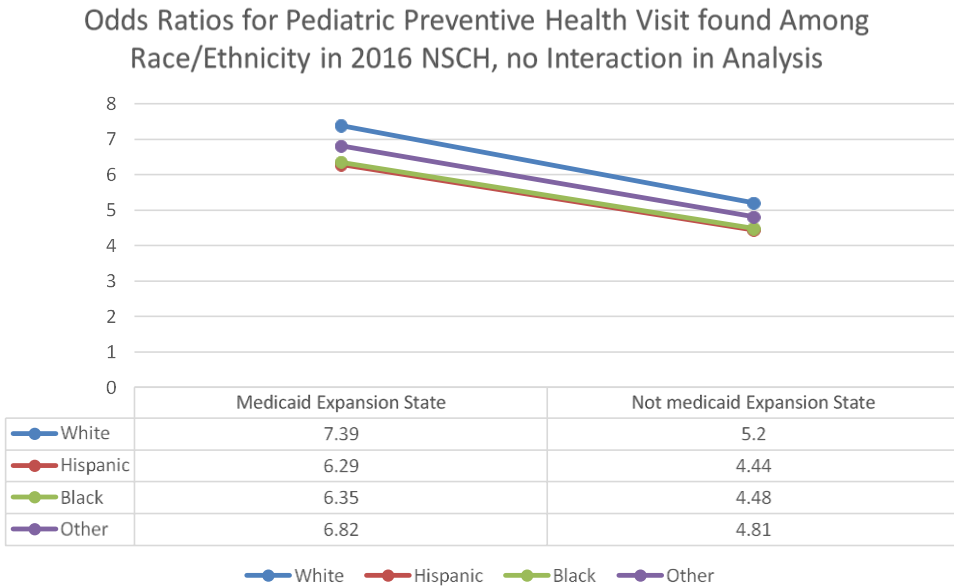


Figure 4. Odds ratios produced from the model that did not include a cross-level interaction between race/ethnicity and Medicaid expansion. In this chart the interaction term is not used in the model. Black and Hispanic have similar odds ratios, Hispanic is obscured by Black. Hispanic is statistically significantly different from White, but Black and other are not.

Figure 4 is a chart comparing odds ratios among the racial/ethnic groups ignoring the interactions between Medicaid and PMV. In this model the odds ratio for PMV among children in expansion states is 1.42 times the odds ratio for children in non-expansion states 95% CI= [1.17, 1.72]. In this chart the slopes between Medicaid expansion and non-expansion states are equal because the interaction term is missing. All four race/ethnic categories of children in Medicaid Expansion states had greater odds ratios for PMV than children in the same categories in non-expansion states.

DISCUSSION

These findings suggest that children in Medicaid expansion states had a higher probability of receiving a PMV than children in non-Medicaid expansion states. The results from the models with and without interaction terms both suggest that Medicaid expansion potentially had a positive effect on children's receipt of PMV, regardless of race or ethnicity. The reduced log-odds for children who are Black or Hispanic echo findings of disparities in insurance coverage among racial/ethnic groups after passage of the ACA [14]. Disparities among the races and ethnicities remain in both expansion and non-expansion states and appear to be amplified in expansion states. This finding, which seemed counter-intuitive, appears to fit a pattern of exaggerated disparities that occur when health systems undergo reform [29]. The 2013 annual report from the Agency for Healthcare Research and Quality suggested that states with higher health care quality scores also tended to have higher disparities among racial and ethnic groups, while states with lower health care quality scores tended to show lower disparities in care among racial and ethnic groups [30, 31].

Historic and systemic inequities (for example, the Home Owners Loan Corporation's "redlining", or color-coding, of neighborhoods by race and associating lending risk with the color coding) removed vulnerable populations to less desirable and less served areas, making it harder to physically get to healthcare providers. Systemic inequity reduced vulnerable populations' ability to receive and understand information (for example, by 2014 sixteen states had passed laws regulating navigators—assistants who help vulnerable populations in understanding and purchasing insurance in the ACA marketplace [30, 32]) and created disparities in the ways that vulnerable populations were able to take advantage of healthcare reform. Although all groups in the expanded states are receiving PMV at higher rates than their corresponding groups in non-expanded states, our results suggest that White children seem better positioned to take advantage of the changes in healthcare.

PMVs are considered critical components of children's health and wellbeing, particularly in relationship to ongoing surveillance of physical and developmental health concerns. That children in Medicaid expansion states have an increased probability of receiving PMV resonates with the well-known impact that having affordable insurance can have on accessing healthcare. That said, while the expansion of ACA creates an opportunity for affordable healthcare, it does not completely relieve populations from the ongoing effects of other social determinants of healthcare access.

It is notable that disparities continue to exist in ACA expansion states, and potentially speaks to the greater realities of accessing healthcare for many minority families, particularly those experiencing poverty [10]. The ACA makes health insurance more affordable for more families, but it does not alleviate all barriers to healthcare. Impoverished children's caregivers are more likely to have caretakers working multiple jobs in order to make ends meet and may have less flexible schedules available to coordinate healthcare visits. Furthermore, transportation concerns may be more frequent in minority populations who may have less reliable sources of transportation, forcing parents to cancel appointments because of transportation issues. Lack of transportation could be compounded by the fact that minority populations are also more likely to live in a "medical desert," an area where few or no health care providers are available [25]. While the ACA has had beneficial effects, it is one policy aimed at eliminating disparities painted on a canvas of 150 years of policy that created

disparities [30]. Even as Medicaid expansion accentuated disparities in children's receipt of PMV it simultaneously reduced barriers to PMV and is helping break the cycle of disadvantaged populations who have carried a disproportionate burden of morbidity and mortality in the US.

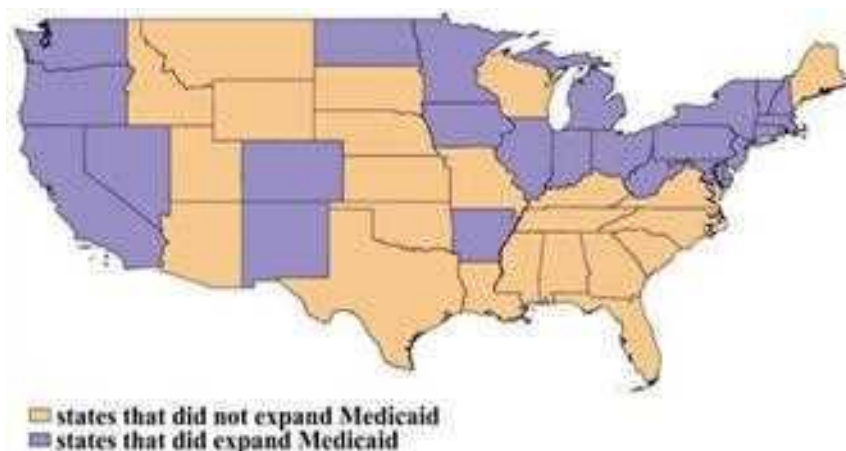


Figure 5. States that expanded Medicaid prior to data collection for the 2016 NSCH. This map illustrates the geographic clustering of states that did and did not expand Medicaid before 2016 NSCH data collection.

Ultimately, the data presented here indicate that ACA expansion is associated with some degree of improvement in healthcare access for all children; however, being in an ACA expansion state does not necessarily ensure ready access for all. The issues of poverty, transportation, medical deserts, and other social maladies more likely to be faced by minority populations continue to exacerbate unequal healthcare access, even in ACA expanded states. To be sure, a key to open the door to a healthcare office is a good thing, but if there is no road to the door, or a reliable means of transportation, then some citizens will still not have access to affordable healthcare.

Limitations

The current analysis is largely framed as a consideration of healthcare access in relation to ACA expansion with an emphasis of ongoing racial and ethnic discrepancies in PMV receipt. The differences between receipt of PMV among the race/ethnic categories in this study might be attributable to other predictors not included in our models, including the demographics of the states. Perhaps differences in the racial/ethnic makeup, rurality, poverty, or other political policies of the states that expanded and did not expand may account for the differences we found. Another study might be strengthened by including state level variables that measure these differences. Prior research [27] suggests that there is spatial autocorrelation among the states that expanded and did not expand Medicaid. Figure 5 is a map of the states that expanded Medicaid in the time period before data collection for the 2016 NSCH illustrating their geographic clustering. The states that chose to expand Medicaid may share similar demographic and political characteristics, and the states that did not chose

to expand may share different demographic and political characteristics. Another limitation is that the study does not include individual level predictors that could account for health care consumption. The inclusion of such predictors might improve the model, but with a cost of increased multicollinearity and potential model misspecification.

Future Work

The next step for this inquiry is to apply a similar analysis to the 2017 NSCH [4]. Since Medicaid has continued to expand; the newer survey would include more states that have expanded and may paint a different picture of the impact of Medicaid expansion on pediatric PMV. It may also be informative to compare older versions of the NSCH from 2007 and 2012 to consider how these relationships have changed over time, though changes in the NSCH design will prevent firm comparison. Further investigation into differences in state policy regarding how providers interact with Medicaid would also provide beneficial information. Additionally, there may be subtle factors influencing the provider's willingness to accept Medicaid patients and that may have an impact on pediatric PMV.

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Chapter 342

SELF-PERCEIVED NEIGHBORHOOD QUALITY AND CHILDREN'S DEPRESSION SYMPTOMS IN A GENTRIFYING NORTHERN MANHATTAN

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ABSTRACT

Poor neighborhood quality (NQ) is associated with social withdrawal and low self-esteem, as well as increased symptoms of anxiety and depression. The majority of reports assessing the association between NQ and child mental health use Census data, which rely on objective components of neighborhood composition and cannot capture a resident's perception of the neighborhood environment. This study used longitudinal measures of maternal self-reported NQ to assess the impact of NQ patterns in middle childhood on children's mental health, in a low-income, minority population that largely resides in gentrifying Northern Manhattan neighborhoods. When children were 5, 7, 9 and 11 years old, self-reported neighborhood information was collected, and neighborhood stress was used as the metric for NQ. Symptoms of anxiety and depression were assessed using the Revised Children's Manifest Anxiety Scale (RCMAS) and the Children's Depression Rating Scale (CDRS) in early adolescence at age 9-12 years. Children of mothers who rated their total NQ as "stressed" in middle childhood had significantly more symptoms of depression than children of mothers who reported their NQ as "non-stressed" ($p = 0.046$). Additionally, there was an observable difference in the number of individuals who reported clinically significant counts of depressive symptoms between mothers who reported stressed versus non-stressed NQ (10% vs. 6%, $p = 0.20$). There was, however, no association between NQ and total anxiety. Unlike Census data, self-report NQ assessments can be used as a tool to gauge residents' subjective experience in the neighborhood and to highlight how gentrification may benefit some child residents disproportionately.

INTRODUCTION

Over the past 20 years, the relationship between neighborhood composition and children's health has become increasingly well-established. Depending on the quality and frequency of a child's interactions with his or her neighborhood, environmental context can shape youth developmental outcomes. Variations in neighborhood quality (NQ) have been associated with childhood and adolescent cognitive differences in educational achievement, verbal ability, and working memory [1-8]. With regard to socioemotional outcomes, stronger neighborhood economic resources, increased resident involvement, and increased resident employment are associated with better parent report of children's mental health and fewer parent-reported internalizing behaviors, such as social withdrawal and low self-esteem [9-11]. Conversely, both living in a low socioeconomic status (SES) neighborhood and exposure to violence have been associated with increased levels of child and adolescent symptoms of depression and anxiety, as measured through parent and self-report [11-14].

In the field of children's health, this body of research emphasizes that investigations into environmental influences on children's mental development cannot be fully complete without considering the neighborhoods in which they live and grow. Despite robust NQ examinations, there remains a gap between analyses utilizing Census data and those that use residents' self-

reported NQ assessments. Most studies observing a significant relationship between neighborhood makeup and children's health use area-level measures (e.g., Census), which rely on sociodemographic measurements of income, racial and ethnic composition, residential instability, and unemployment [15]. While Census collections can be thorough, they are entirely objective, and some researchers argue they have the potential to weaken the observed linkage between place of residence and health [16]. The systematically collected material does not measure neighborhood context and how individuals subjectively perceive their environment, in turn silencing elements of neighborhood satisfaction, structural and institutional problems in the neighborhood, relations with neighbors, and feelings of safety, all of which have been associated with resident well-being [17].

Furthermore, the use of Census data in children's environmental health studies is insufficient when trying to capture quickly changing neighborhood characteristics and how these might impact NQ perception and children's health, as a Census is only collected once every 10 years. This limitation, in addition to the Census' inability to capture an individual's perception of the neighborhood, is particularly relevant when monitoring how low-income, minority children are affected by the rapid gentrification of urban American cities. Importantly, this growing and often neglected demographic is more likely to live in disadvantaged, urban neighborhoods, due to the historical social and economic isolation of poor communities of color [1, 18–20]. Many of such neighborhoods, including the neighborhood of participants in the present study, are quickly being gentrified [20, 21]; however, how this phenomenon is impacting the health of existing child residents is largely unexplored.

Gentrification refers to the transformation of low-income, divested communities through the influx of investment and new residents with high SES [22, 23]. Resulting increases in taxes and property value often raise the community's cost of living, creating a significant financial burden for long-time residents [24]. While Census data can measure long-term socioeconomic differences in NQ following reinvestment, it cannot measure how some residents may benefit from gentrification disproportionately and how this may influence perception of the neighborhood. This is an important distinction, as research suggests parent perception of NQ can act as a mediator between neighborhood environment and children's health [3, 25].

Thus, a gap in children's environmental health literature is evidenced by the shortage of analyses exploring the impact of longitudinal self-perceived NQ on children's mental health. This gap is especially relevant as researchers begin to analyze the health consequences of low-income, minority children residing in gentrifying communities. The goal of this study was to strengthen the relationship between longitudinal self-perceived NQ and differences in children's mental health (see Figure 1). We believe that after this relationship is established, future studies should connect individual NQ differences with indicators of neighborhood gentrification. Combined, this research can reveal the disproportionate benefits to children of reinvestment in a community and, ultimately, identify levers that can help all children living in gentrifying neighborhoods benefit from reinvestment, thereby breaking the cycle between self-perceived stressed NQ and children's mental health (see Figure 2).

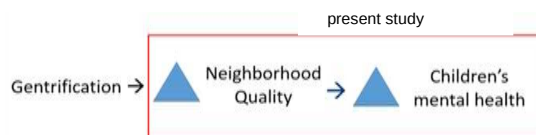


Figure 1. Conceptual framework for analysis of impacts of neighborhood quality on children's anxiety and depression symptoms.

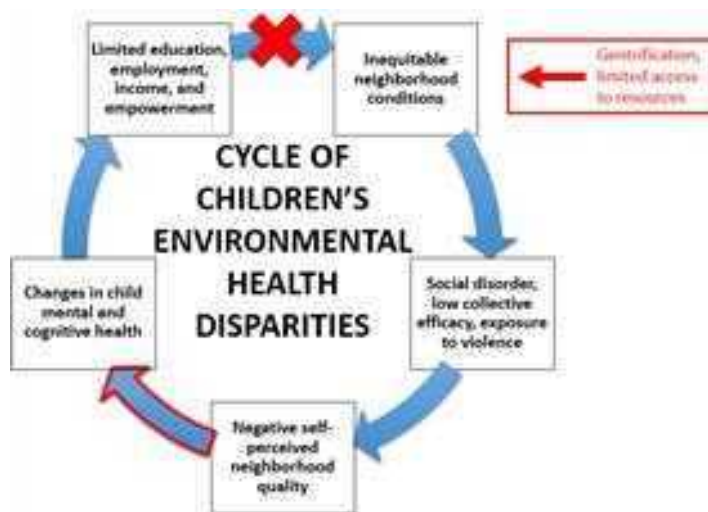


Figure 2. Breaking the cycle of environmental health disparities related to neighborhood quality and children's mental health.

OUR STUDY

Study subjects were participants in the Mothers and Newborns Study, a prospective longitudinal birth cohort at the Columbia Center for Children's Environmental Health (CCCEH). Between 1998 and 2006, CCCEH recruited 727 women ages 18-35 years into the study from the prenatal clinics of New York Presbyterian Medical Center, Harlem Hospital, or their satellite clinics [26]. Subjects were Dominican and African American women residing in Northern Manhattan (Washington Heights, Central Harlem) or the South Bronx. Enrollment exclusion criteria included smoking or use of other tobacco products during pregnancy, illicit drug use, first prenatal visit after 20th week of pregnancy, and the following pre-existing conditions: diabetes, hypertension, or known HIV infection. All study protocols were approved by the Institutional Review Board of Columbia University. Before each visit, mothers were informed about all study procedures and provided written informed consent to participate.

Neighborhood Quality (NQ) Assessment

When children were 5, 7, 9, and 11 years old, mothers were given a 32-question self-reported NQ assessment. The repeated administration of the questionnaire was intended to

evaluate patterns of NQ over time across middle childhood. The questionnaire was adapted from existing measures of NQ [27–29], and consisted of three subscales, each used to assess different subjective aspects of neighborhood composition. Subscales included social order/disorder (12 questions), safety and violence (seven questions), and social cohesion and neighborhood stability (13 questions). Content in the social order/disorder and safety and violence subscales was rated based on level of agreement (0-4), while components of the social cohesion and neighborhood stability subscale were evaluated through yes/no responses. Examples from each include “Homeless/unemployed people are hanging around” (social order/disorder), worried about “Letting children go outside during the day/night” (safety and violence), and “My neighborhood is a good place to live” (social cohesion and neighborhood stability). The full questionnaire can be found in the Supplemental File.

Anxiety and Depression Assessments

Anxiety and depression symptoms were assessed once in early adolescence when children were between 9-12 years.

RCMAS – Revised Children’s Manifest Anxiety Scale

The level and nature of anxiety symptoms in children were measured using the Revised Children’s Manifest Anxiety Scale (RCMAS), a self-administered 37-item assessment completed by the child. RCMAS is divided into three subscales including physiological anxiety, worry and oversensitivity, and social concerns and concentration. Answering “yes” indicates that the item is descriptive of the child’s feelings; higher scores on the assessment indicate increased levels of anxiety. Raw scores above 18 signal significant levels of anxiety that warrant further clinical assessment.

CDRS – Children’s Depression Rating Scale

Level and severity of depressive symptoms were measured using the Children’s Depression Rating Scale (CDRS) in a semi-structured interview administered by a trained research worker to the child. The CDRS includes 17 symptom areas encompassing cognitive, somatic, affective, and psychomotor symptoms. Examples include depressed feelings, difficulty having fun, depressed facial affect, and self-esteem. For 14 items, children rate on a 7-point scale, while the remaining three items are rated on a 5-point scale. Possible total scores range from 17-113. Any score above or equal to 40 signals significant levels of depression, whereas any score below or equal to 28 is often used to define minimal or no symptoms.

Statistical Analysis

There were $n = 727$ mother and child pairs with available data on self-perceived NQ gathered at any one of the assessing time points: child ages 5, 7, 9, and 11 years. Of 727, 379 children had available data on anxiety symptoms measured through the RCMAS, and 372 children had available data on depression symptoms measured through the CDRS (see Figure 3).

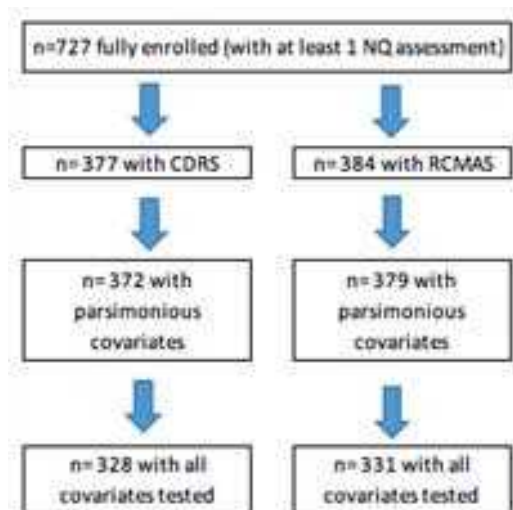


Figure 3. Flow Chart of Inclusion detailing how participants were selected for inclusion; parsimonious covariates include age at testing, sex, and ethnicity.

To analyze NQ, each participant's total NQ score and three individual subscale scores were standardized and scaled for the presence of stress. Items assessed through the 0-4 Likert scale were standardized such that all scores could be equally weighted and interpreted on a scale between 0-1 (0 = absence of stress, 1 = presence of stress). Subscale scores and total scores were found by taking the mean across all items. To analyze participants' patterns of NQ in middle childhood, group-based trajectory models using a latent class growth curve (LCGC) analysis were applied. Group-based trajectory models aim to identify clusters of individuals having similar NQ trajectories over the six-year period using finite mixture models [30]. We modeled total and individual subscale scores, varying numbers of groups (1–4) and shapes (linear, quadratic, cubic). We selected the best fitting model for each NQ outcome (total NQ, social order/disorder, safety and violence, and social cohesion and neighborhood stability) using the Bayesian Information Criterion (BIC), as well as the magnitude of group membership posterior probabilities. We evaluated change in BIC ($\Delta BIC \approx \log_e(B_{10})$) to compare increasingly complex models vs. the simpler (null) models and selected the final model based on the inflection point at which the ΔBIC leveled off [30, 31]. These analyses were conducted using the SAS Proc TRAJ macro [31]. Proc TRAJ will use any data provided to include the individual in the model that best fits them; individuals need not have all data points to be included.

To assess the association between patterns of NQ in middle childhood and symptoms of anxiety and depression in early adolescence, we examined eight multiple linear regression models, focusing on total NQ as our main exposure of interest. Prior to modeling, we assessed the distribution of RCMAS and CDRS to confirm that they were approximately normally distributed. NQ trajectory group was used as the independent variable, where separate models were fit to assess the association between total NQ, neighborhood social order/disorder, neighborhood safety and violence, and social cohesion and neighborhood stability and symptoms of anxiety (from RCMAS) and symptoms of depression (from CDRS) as the dependent variables. To isolate the effect of NQ on the presentation of anxiety and depression symptoms, we evaluated the inclusion of known or suspected risk factors for anxiety or depression symptoms based on the literature and our previous research [32]. These included sex, age (in months) of child at testing, ethnicity, mother's intelligence (measured by the Test of Nonverbal Intelligence 3rd Edition, TONI-3) [33], maternal education (completion of high school prior to birth of this child vs. no completion), and maternal demoralization (measured by the Psychiatric Epidemiology Research Instrument–Demoralization (PERI-D) scale) [34]. Final models included child sex, ethnicity, and age at testing, based on their statistically significant (at $p = 0.10$) association with either or both RCMAS and CDRS. Additionally, we explored stratified sex-specific associations between NQ and symptoms of anxiety and depression.

FINDINGS

A breakdown of participant characteristics is listed in Table 1. While there were no statistically significant differences among children included and excluded from this analysis, those included were slightly more likely to be female, African American, have lower maternal IQ and have mothers who were less likely to complete high school. At the time of enrollment, a majority of the participants resided in Northern Manhattan, a residential, non-tourist region of New York City that has been quickly gentrifying for the past 20 years [21, 35].

Table 1. Characteristics of subjects included (n = 386) and excluded (n = 342) from this analysis among 727 fully enrolled participants

Characteristic	Included in final model for CDRS or RCMAS (n = 386)	Excluded from final models (n = 342)	p-value
Sex (Female)	209 (54.1%)	167 (49.0%)	0.16
Race (African American)	146 (37.8%)	108 (31.7%)	0.08
Maternal Education (Completed High School)	233 (61.5%)	223 (66.8%)	0.14
Maternal TONI score ¹	20.0 (SD 8.6)	21.4 (8.8)	0.07
Maternal demoralization score ^{1,2}	1.16 (SD 0.64)	1.14 (SD 0.62)	0.68

¹ mean $\pm$ SD

² Range of demoralization: 0-3.3, where higher scores indicate more demoralization.

After total and subscale NQ data were standardized and scaled for the presence of stress, the best fitting group-based trajectory model yielded a binary separation of maternal self-reported NQ over the six-year assessment period in middle childhood. This result is shown in Table 2, where, for all four NQ outcomes, the two-group model showed the greatest change in

BIC when comparing between models with different number of trajectory groups. Thus, NQ results suggested two distinct groups of NQ patterns across middle childhood, namely persistently “stressed” over time and persistently “non-stressed” over time. Participant characteristics by total NQ group assignment are presented in Table 1. It is noteworthy that mothers who were categorized as living in more stressed neighborhoods are less likely to have completed high school ($p = 0.02$), have a lower TONI score ($p = 0.003$) and have more demoralization ($p = 0.009$) than participants in the non-stressed neighborhoods. Raw individual trajectories for total NQ are shown in Figure 4A, while mean total NQ values at each time point are presented in Figure 4B. Figure 4B also shows percent breakdown of the two groups, with 41% of mothers ($n = 158$) persistently rating their total neighborhood composition as stressed, and 59% of mothers ($n = 228$) rating their neighborhood as being non-stressed. While all subscales were correlated, the trajectory pattern of the neighborhood safety and violence subscale was most similar to that of overall NQ (see Figure 5).

Table 2. BIC and BIC change between different number of NQ trajectory groups

Number of Groups	BIC	Null Model	ΔBIC*
NQ (total)			
1	470.19		
2	726.79	1	256.6
3	768.84	2	42.05
4	787.28	3	18.44
NQ (social order/disorder)			
1	153.12		
2	369.11	1	215.99
3	421.81	2	52.7
4	429.92	3	8.11
NQ (safety and violence)			
1	-175.84		
2	21.83	1	197.67
3	32.93	2	11.1
4	44.76	3	11.83
NQ (social cohesion & neighborhood stability)			
1	-642.46		
2	-512.8	1	129.66
3	-485.84	2	26.96
4	-484.46	3	1.38

*BIC = Bayesian Information Criterion.

*ΔBIC: BIC change between a more complex model and null model.

We found that stressed NQ across middle childhood was not associated with any observable difference in anxiety symptoms in early adolescence (see Table 3). However, persistently stressed NQ was associated with higher levels of depression symptoms in this age group (see Table 3). After controlling for sex, ethnicity, and child age at testing, Figure 6 shows that children of mothers in the stressed NQ trajectory group scored, on average, 1.5 points higher on the CDRS than those in the non-stressed trajectory group—and this difference was statistically significant with $p = 0.046$ ($\beta = 1.56$, 95% CI: 0.03, 3.08). Although not statistically significant, it is notable that more individuals obtained CDRS scores greater than 40 (clinical cutoff) in the stressed versus non-stressed NQ trajectory group (10% vs. 6%, $p = 0.20$; Figure 6). None of the three NQ subscale trajectories were

individually predictive of children’s depression scores (data not shown), and we found no significant sex-specific associations between NQ and either anxiety or depression symptoms (data not shown).

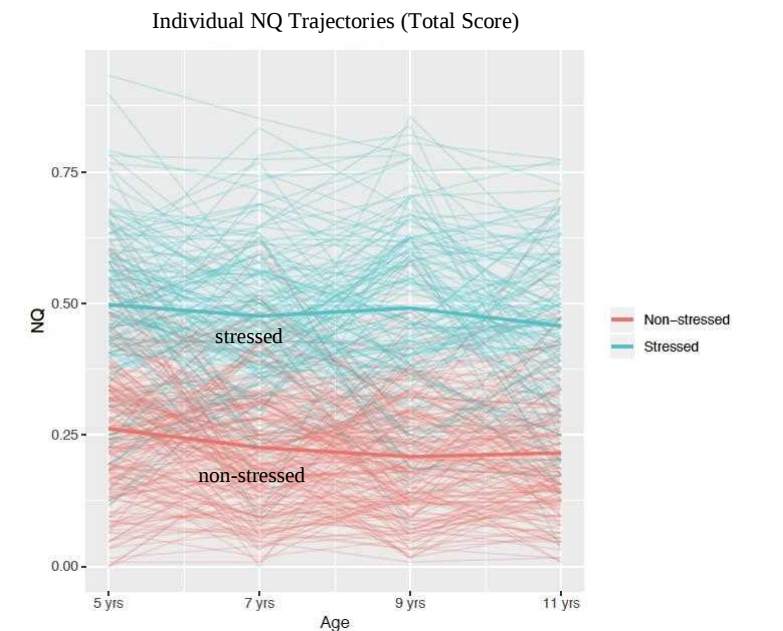


Figure 4A. All individual total NQ trajectories across middle childhood revealing distinct separation between stressed and non-stressed trajectory groups.

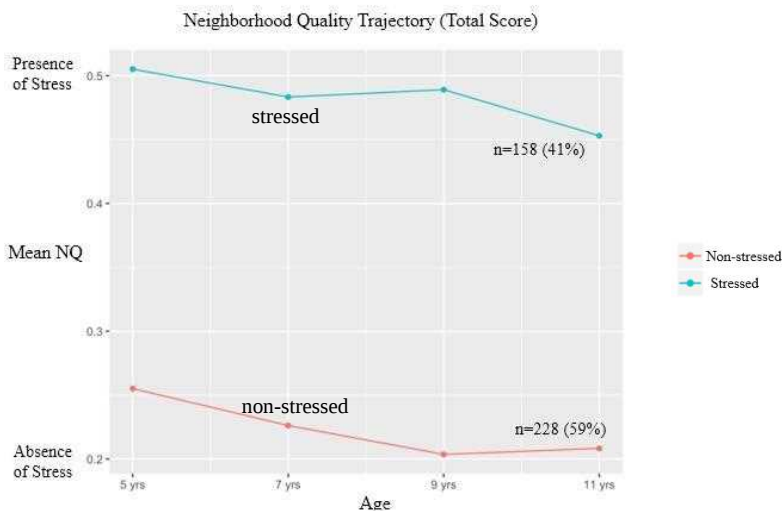


Figure 4B. Total NQ trajectory grouping by mean showing percent breakdown between stressed and non-stressed trajectory groups.

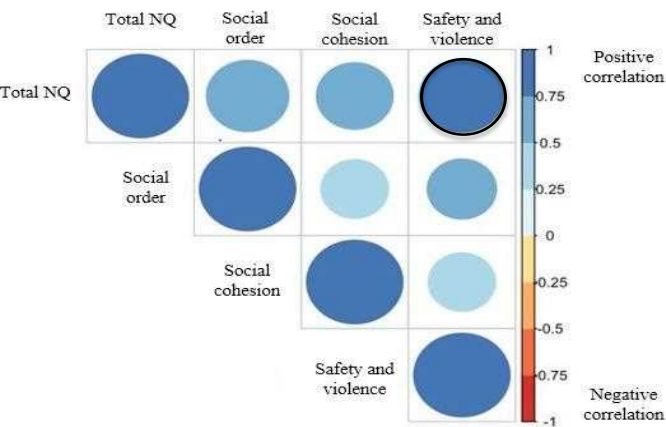
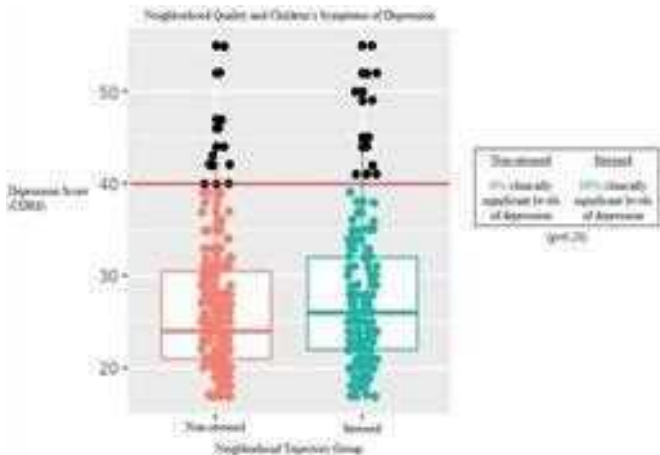


Figure 5. Correlations between total and subscale neighborhood quality trajectories showing strongest correlation between total NQ and safety and violence subscale.

Table 3. Association between NQ trajectories (stressed vs. non-stressed) and anxiety and depression symptoms measured by the CDRS and RCMAS

	CDRS (beta, 95% CI)		RCMAS (beta, 95% CI)	
	Univariate	Adjusted*	Univariate	Adjusted*
N	372	372	379	379
Stressed NQ	1.53 (0.004, 3.06)	1.56 (0.03, 3.08)	0.09 (-1.14, 1.32)	0.13 (-1.10, 1.36)
Not stressed NQ	ref	ref	ref	ref
Age at assessment	-0.14 (-0.78, 0.51)	-0.08 (-0.72, 0.56)	-0.87 (-1.39, -0.35)	-0.86 (-1.38, -0.34)
Dominican	--	-0.78 (-1.55, -0.001)	--	-0.39 (-1.01, 0.24)
African American	--	ref	--	ref
Female	--	-0.23 (-1.73, 1.28)	--	-0.75 (-1.96, 0.47)
Male	--	ref	--	ref

* Adjusted models include sex, child age at testing and ethnicity.



* red line marks cutoff for clinically significant levels of depression.

Figure 6. Difference in child report of depression symptoms between self-perceived stressed and non-stressed NQ as reported by mother.

DISCUSSION

In this study, we examined the association between longitudinal maternal self-reported NQ and children's self-report of symptoms of anxiety and depression. After controlling for other factors which may influence report of children's levels of symptoms of anxiety or depression, we observed that as mothers reported increasing levels of neighborhood stress, children reported increasing levels of symptoms of depression. Interestingly, while a number of sociodemographic factors were associated with NQ trajectory (e.g., education, IQ, demoralization), these were not significant predictors of child's report of depressive symptoms while self-perceived NQ trajectory was. Thus, maternal assessment of NQ may be an important predictor of childhood depression symptoms. Although we did not formally perform statistical tests of mediation, our findings support existing literature which suggests parent perception of NQ may act as a mediator between neighborhood environment and changes in children's mental health.

This research is relevant for the health and success of children living in stressed neighborhood environments. Depressive symptoms in childhood have been inversely associated with a child's ability to build social relationships, concentrate academically, and be self-reliant [36–38]. Understanding the environmental factors that drive children's symptoms of depression, including those related to NQ, is important as researchers continue to direct effort towards breaking the cycle of children's mental illness, particularly for those low-income and minority children who are more likely to live in disadvantaged neighborhood environments and more susceptible to poor mental health (see Figure 2). In order for such efforts to be best targeted, researchers must be able to acquire the most informative measurement of NQ as a predictor of children's mental health. The growing body of research proposing neighborhoods as a source inequality relies heavily on SES and its association with children's development [3]. Given the weaknesses inherent to Census collection data, these analyses might overlook important influences of neighborhood environment on children's health.

Rather than measuring objective neighborhood characteristics through Census, the self-reported NQ evaluation allows researchers to gauge neighborhood context and record how residents subjectively experience their surrounding environment. This is a useful tool considering that outside observation and resident perception of environmental stressors may not always converge [17]. Furthermore, the repeated, longitudinal administration of the self-report assessment allows researchers to capture the effect of quickly changing neighborhood characteristics on perception of NQ, which contrasts most NQ research based on neighborhood residence at a single point in time [12]. Thus, a subjective, long-term NQ assessment is more descriptive of the mechanisms through which a disadvantaged neighborhood environment may be linked to decreased mental health, and also better illustrates the mental, physical, and social dimensions that are known to shape a child's wellbeing [39].

These strengths of the self-report are particularly relevant as researchers analyze how gentrification impacts the health of existing low-income minority youth living in the neighborhood. This demographic is not only more likely to live in socially and economically

under-resourced urban neighborhoods, it may also be more vulnerable to inequitable neighborhood conditions due to ongoing transformation of urban communities [40, 41]. While direct effects of gentrification were not measured in this study, gentrification and its community health implications are interlaced in the context of our analysis. The children in this study live in Northern Manhattan, a neighborhood of New York City that has experienced rapid reinvestment. However, not all individuals residing in gentrifying neighborhoods, similar to this one, benefit from incoming resources. Using Census material to measure the benefits of reinvestment in a community may lead to the conclusion that gentrification is net positive for new and existing residents, as the data could reveal increases in median income and neighborhood diversity. Despite such socioeconomic changes, perceived neighborhood quality can remain constant for residents without access to the neighborhood's new amenities (e.g., upscale restaurants, commercial shopping districts), and also for residents displaced due to cost of living increase. In order to evaluate how certain children may benefit from gentrification disproportionately, a longitudinal, self-perceived NQ assessment is necessary. In future research, it may also be important to consider the role of large-scale public housing near or adjacent to gentrifying neighborhoods.

Study Limitations

There are a number of noteworthy limitations to this analysis, mainly related to our inability to control for all possible stressors that may contribute to a child's presentation of anxiety and depression symptoms, leading to residual confounding. While the children included in this analysis were not statistically different than those who were excluded due to missing data, there were slight differences that might have influenced the results (see Table 1). Additionally, some researchers have suggested differential effects on child behavior from two-parent and single-parent households [25], which leads us to believe that variances in family structure may also have affected children's symptoms of depression. Previous research conducted among this same cohort has shown that housing instability, as defined by more than three residential moves in a seven year time frame, is related to behavioral differences in childhood [42]. This provides an additional route for variance in children's mental development, one that can potentially be connected with gentrification and residential displacement in the future. Lastly, we recognize that we tested the effects of difference in NQ against two discrete endpoints—anxiety symptoms and depression symptoms. We did not adjust for multiple comparisons because there is independent literature suggesting investigation into both domains. Had we adjusted for multiple comparisons, our findings would not reach statistical significance with $p = 0.05$ due to the small sample size. Should researchers interpret this study as an exploratory, combined analysis between NQ and anxiety and depression symptoms, an adjustment for multiple comparisons would be necessary.

CONCLUSION

Through this study, we have shown that a mother's longitudinal assessment of her NQ is associated with her child's self-reported symptoms of depression in early adolescence. To

more closely connect gentrification to children's mental health outcomes, future research should connect gentrification indicators and precise resident location directly with changes in self-reported NQ. Through this linkage, researchers can document the disproportionate impacts to children that reinvestment can bring to urban communities. Furthermore, this information can be used to identify levers that can be used to develop health-based policy interventions designed to help all children living in gentrifying neighborhoods benefit from reinvestment.

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Chapter 343

WATER INFRASTRUCTURE AND CHILDHOOD BLOOD LEAD LEVELS: CHARACTERIZING THE EFFECTS OF EXCLUSION FROM MUNICIPAL SERVICES IN WAKE COUNTY (NC, USA)

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ABSTRACT

Childhood lead exposure is associated with impaired cognitive development, decreased IQ levels, and increased rates of juvenile delinquency. Lack of access to municipal water services, which in some communities disproportionately affects Black neighborhoods, is associated with higher levels of lead in drinking water. Objectives: This study aims to characterize the effects of exclusion from municipal water infrastructure on childhood blood lead levels. Methods: We created a novel 16-year database of 34,314 children, with which we examined the effects of municipal water access on childhood blood lead levels in Wake County, NC. Using childhood blood lead data from 2002 to 2017, we used ordinary-least squares and logistic regression models with childhood blood lead levels as the primary outcome of interest and municipal water access at time of birth as the primary exposure of interest. Results: Our results suggest that a lack of access to municipal water is significantly associated with elevated blood lead levels. Children without municipal water service at birth had blood lead concentrations that were 0.12 µg/dL higher than children with municipal water. Children with access to municipal water service had significantly lower odds of having blood lead above the ‘level of concern’ as defined by the Centers for Disease Control than children with municipal water service (OR = 0.82). Conclusion: These findings support the need

for more regulatory oversight and water quality tests of private water systems or facilitating access to municipal supplies in order to mitigate the impacts associated with childhood lead exposure.

INTRODUCTION

Approximately 535,000 children ages 1 to 5 years in the United States had a blood lead level above 5 $\mu\text{g}/\text{dL}$ in 2018 [1]. There is no safe concentration of blood lead in children, and lead exposure in childhood has long been known to impair intellectual and behavioral development [2]. Young children are particularly susceptible to lead toxicity. Infants absorb 4 to 5 times more lead than older children and adults, and early childhood is a critical period of vulnerability to lead toxicity [3].

A lack of access to municipal water services is associated with elevated levels of lead in drinking water [4], especially among low-income and African-American neighborhoods [5]. “Municipal underbounding” is the phenomenon whereby communities of color living adjacent to majority white municipalities are systematically excluded from incorporation [6–9]. In the state of North Carolina, individuals outside of municipal service areas live in areas called extraterritorial jurisdictions (ETJs), and many of these households rely on private wells for water [10, 11]. It has been demonstrated that land use planning and policy, at least in some jurisdictions, has discriminatorily excluded low-income and minority neighborhoods from municipal boundaries [6, 8, 9, 12–14]. It has also been shown that race significantly predicts whether a community within an extraterritorial jurisdiction has municipal water services in North Carolina and Wake County, with predominantly Black neighborhoods being the least likely to have municipal water access [10, 11]. The Safe Drinking Water Act in the United States sets an action level for lead in drinking water at 15 $\mu\text{g}/\text{L}$. However, the Safe Drinking Water Act only applies to community water systems, which are defined as those serving at least 15 service connections or 25 people year-round [15]. Private wells, which are not protected by the Safe Drinking Water Act, are often overlooked as a source of lead exposure [4, 16].

The purpose of this project is to quantify the relationship between a lack of access to municipal water and childhood blood lead levels in Wake County, North Carolina, USA.

OUR STUDY

We created a database of 34,314 observations at the level of the individual child spanning from 2002 to 2017 with data including children’s blood lead, water access, location within an ETJ, demographic data, and other variables. Using this database, we used statistical models to estimate the effect of exclusion from municipal water services on childhood blood lead levels. Figure 1 illustrates the conceptual model used to create our statistical models.

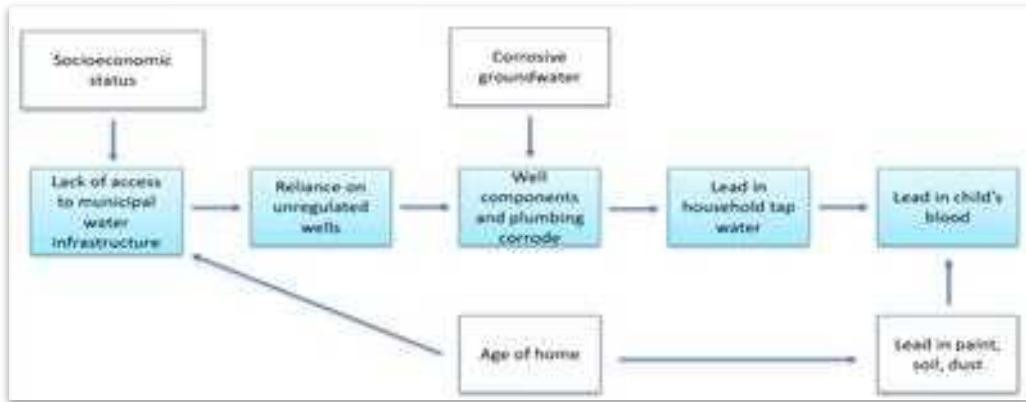


Figure 1. Conceptual model detailing the causal pathway between lack of access to municipal water and a child's observed blood lead with key covariates which may also affect either water access or lead exposure, such as socioeconomic status or age of the home.

Database Development

Our retrospective database included tax parcel data from Wake County GIS Services, childhood blood lead data from North Carolina's Childhood Lead Poisoning Prevention Program (NC LEAD), and 2010 census data and 2017 American Community Survey (ACS) 5-year estimates data. NC LEAD provided all blood lead test results for children screened in Wake County between 2002 and 2017. The NC LEAD program requires health care providers across the state to report results of children's blood lead tests for surveillance purposes. While health care providers are encouraged to test blood lead for all children between the ages of 12 and 24 months, screening is mandatory for children enrolled in federal and state assistance programs (women, infants, and children; Medicaid; or Health Choice). The tax parcel data included in this study were for all residential parcels in Wake County from 2002 to 2018. All data cleaning and analysis was completed in STATA 15.1 (Statacorp, College Station, TX).

Merging all the yearly tax parcel files was the first step of creating the database. After acquiring the data, which is publicly available, we merged the yearly datasets using the unique PIN ID assigned to each parcel. If a parcel existed in multiple years of data, we kept the data for the first occurrence of the parcel, while incorporating all new parcel information that appeared in later years. Additionally, utility status and extraterritorial jurisdiction status were captured for each individual year for each parcel to determine when or if a parcel received municipal water access or if a parcel was incorporated into municipal boundaries. Utility data from Wake County GIS services, which indicated municipal water access, were only reported from 2002-2010. To capture data timepoints after this, we supplemented our data set with tax parcel data from Wake County's revenue services department from 2013 and 2018; additional years of data were not available. Therefore, municipal water access data were incorporated from 2002-2010, 2013, and 2018. After this, all non-residential parcels were dropped from the dataset, leaving only parcels identified as dwellings.

Next, childhood blood lead data from the NC LEAD database were merged with the tax parcel data using the addresses from both datasets. The addresses were disaggregated into their parts (i.e. street name and number, city, zip) and cleaned for any possible variations

between the two datasets (for example, RD versus road). We used an exact match on the datasets based on addresses, then STATA's DTALink function, which uses probabilistic linkage methods to score each potential pair of records on the probability the two records match, so that pairs with higher overall scores indicate a better match than pairs with lower scores. The merge parameters were iteratively revised and results reviewed until the parameters yielded results that included only exact matches and plausible inexact matches as determined from inspection of subsets of 100 matched entries.

Geocoding and Spatial Join

We used ArcMap (Version 10.6, ESRI, Redlands, CA) to geocode the data and perform a spatial join in order to merge ACS data to each observation. We geocoded the data in ArcMap using a stand-alone geocoding program created from ESRI's StreetMap Premium data for the year 2017 (StreetMap™ Premium for ArcGIS, ESRI, Redlands, CA). Fewer than 1% of the addresses were not matched; these were dropped from the dataset. We downloaded population demographics from the 2010 census and income data from the 2017 ACS 5-year estimates. We used a shapefile of Wake County to perform a spatial join to assign each observation from our dataset to a census block along with the corresponding census and ACS data.

Statistical Models

For the analysis of the database, the primary outcome of interest was childhood blood lead concentration, and the primary exposure of interest was municipal water access at time of birth. We built an ordinary least squares regression model and two logistic regression models using blood lead benchmarks of 5 µg/dL and 2 µg/dL. For all models, we controlled for age in intervals of 18 months, gender, municipal status at time of birth, year of blood draw, home value in logarithmic form, year the home was built, median household income at the census block group, percent Black population at the census block, and percent Hispanic population at the census block.

FINDINGS

A total of 34,314 children from Wake County, NC, were included in the analyses. The mean blood lead level for the population was 1.7 µg/dL, and the mean age of the child at time of testing was 550 days (see Table 1). Males and females were evenly represented at 51% and 49% of the study population, respectively. Approximately 5.5% of individuals in the study population lived in extraterritorial jurisdictions, and 14.7% of individuals did not have municipal water access at time of birth (see Table 2).

Table 1. Summary statistics for key continuous variables included in the models

Variables	Mean	Min	Max
Lead	1.65	1	35
Black, Percent	0.25	0.0022	0.93
Hispanic, Percent	0.1	0.0056	0.69
Year Tested		2002	2017
Year Built		1803	2017
Median Household Income	78600	17900	210000
Home Value (Log)	12.2	9.91	16.9
Age (Days)	550	0	2190

Table 2. Brief summary of dichotomous variables from the model. Summary statistics for key binomial variables included in the models

Variable		N	%
Water	Y	29,279	85.3
	N	5,035	14.7
ETJ	Y	1,871	5.5
	N	32,443	94.5
Gender	F	16,827	49
	M	17,487	51

Variables Influencing Blood Lead Levels in the Study Population

Access to municipal water and Black race were associated with children's blood lead levels (see Table 3). Children without municipal water service at birth had blood lead concentrations that were 0.12 $\mu\text{g}/\text{dL}$ higher than children with municipal water. Blood lead levels increased, on average, by 0.023 $\mu\text{g}/\text{dL}$, for every 10% increase in the Black population proportion in the child's census block. In contrast, Hispanic population was not associated with blood lead levels. Year the child was tested was highly significant ($p < 0.0001$), with each additional year of time being associated with a decrease in blood lead levels of -0.092 $\mu\text{g}/\text{dL}$.

Similarly, the age of the child being between 18 to 36 months was highly significantly associated with an average increase in blood lead of 0.13 $\mu\text{g}/\text{dL}$ from the referent (less than 18 months, $p < 0.0001$), and the age of the child being between 36 to 54 months was also significantly associated with an average increase in blood lead of 0.095 $\mu\text{g}/\text{dL}$ ($p < 0.05$). Year the house was built was also highly significant at all levels when compared to the referent (built before 1950), with houses built between 2000 and 2005 being associated with the lowest level, a decrease of 0.55 $\mu\text{g}/\text{dL}$ blood lead ($p < 0.0001$). Finally, home value in logarithmic form was highly significantly associated with a decrease of 0.22 $\mu\text{g}/\text{dL}$ in blood lead level on average for every log-10 increase in home value ($p < 0.0001$). Thus, a two-fold increase in home value is associated with a decrease in blood lead levels of -0.066 $\mu\text{g}/\text{dL}$.

Table 3. Results of ordinary least squares regression model using blood lead levels as primary endpoint

R ² = 0.1053		
Variables	B	p-value
Water Access at Birth	-0.12	<0.0001
Year Tested	-0.092	<0.0001
Black Population fraction	0.23	<0.0001
Home Value (Log)	-0.22	<0.0001
Gender	0.037	0.0059
Municipal Status	0.038	0.24
Hispanic Population, percent	-0.085	0.44
Median Household Income	<0.0001	0.6
Age		
18 to 36 Months	0.13	<0.0001
36 to 54 Months	0.095	0.01
Over 54 Months	0.053	0.73
Year Household Built		
1970 to 1950	-0.33	<0.0001
1970 to 1990	-0.41	<0.0001
1990 to 2000	-0.5	<0.0001
2000 to 2005	-0.55	<0.0001
After 2005	-0.44	<0.0001
N	34314	

Table 4. Results of a logistic regression model of dichotomized blood lead level (above or below 5µg/dL)

Pseudo R ² = 0.0875		
Variables	OR	p-value
Water Access at Birth	0.82	0.021
Year Tested	0.81	<0.0001
Black Population Fraction	1.5	0.02
Hispanic Population Fraction	0.58	0.23
Home Value (Log)	0.65	<0.0001
Gender	1.1	0.26
Municipal Status	0.98	0.9
Median Household Income	1.0	0.9
Age		
18 to 36 Months	1.4	<0.0001
36 to 54 Months	1.3	0.01
Over 54 Months	2.8	0.17
Year Household Built		
1950 to 1970	0.48	<0.0001
1970 to 1990	0.43	<0.0001
1990 to 2000	0.33	<0.0001
2000 to 2005	0.29	<0.0001
After 2005	0.44	<0.0001
N	34314	

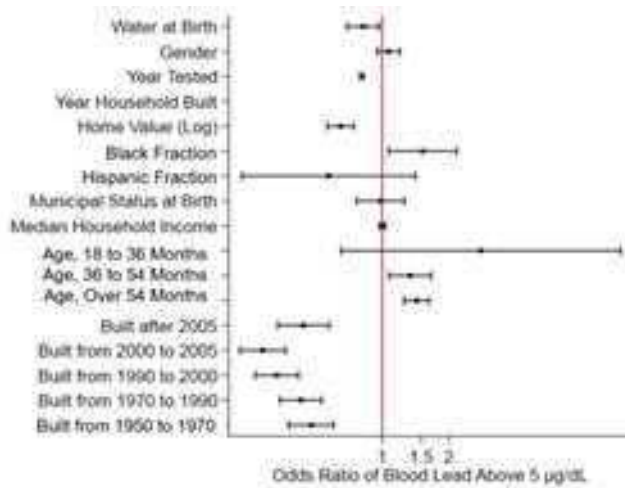


Figure 2. Graphical representation of the 5 µg/dL logistic model with odds ratios, confidence intervals, and all variables included in model. Each point represents the odds ratio, and the lines extending left and right from each point represent the lower and upper confidence intervals, respectively.

Variables Influencing the Odds of Elevated Blood Lead Levels in the Study Population

Children with access to municipal water service had significantly lower odds of having elevated blood lead above the 'level of concern' as defined by the Centers for Disease Control than children with municipal water service (see Table 4, Figure 2: OR = 0.82, $p < 0.05$). Similarly, these children had decreased odds of having blood lead concentrations above 2 µg/dL than children without water service (see Table 5, Figure 3: OR = 0.73, $p < 0.0001$). Year in which the child was tested was highly significantly associated with the odds of elevated blood lead levels when dichotomized at 5 µg/dL (see Table 4, Figure 2, OR = 0.81, $p < 0.0001$). The same effect was observed when blood lead was dichotomized at 2 µg/dL (see Table 5, Figure 3, OR = 0.78, $p < 0.0001$). Children living in census blocks with increasing fraction of Black population had significantly higher odds of elevated blood lead levels when dichotomized at 5 µg/dL (see Table 4, Figure 2, OR = 1.5, $p < 0.05$). Similarly, children living in census Blocks with increasing fraction of Black population had highly significantly increased odds of blood lead levels above 2 µg/dL (see Table 5, Figure 3, OR = 1.8, $p < 0.0001$).

Children living in census blocks with increasing percentage of Hispanic population did not have significantly increased odds of having elevated blood lead levels above 5 µg/dL (see Table 4, Figure 2, OR = 0.58, $p = 0.23$). However, when dichotomized at 2 µg/dL, children living in census blocks with an increasing fraction of Hispanic population did have significantly increased odds of having blood lead levels above 2 µg/dL (see Table 5, Figure 3: OR = 1.5, $p < 0.05$).

Table 5. Results of a logistic regression model of dichotomized blood lead level (above or below 2µg/dL).

Pseudo R ² = 0.1687		
Variables	OR	p-value
Water Access at Birth	0.73	<0.0001
Year Tested	0.78	<0.0001
Black Population Fraction	1.81	<0.0001
Home Value (Log)	0.63	<0.0001
Gender	1.07	0.0063
Municipal Status	1.07	0.21
Hispanic Population Fraction	1.47	0.047
Median Household Income	1.00	0.30
Age		
18 to 36 Months	1.3	<0.0001
36 to 54 Months	1.1	0.03
Over 54 Months	1.3	0.43
Year Household Built		
1950 to 1970	0.64	<0.0001
1970 to 1990	0.54	<0.0001
1990 to 2000	0.44	<0.0001
2000 to 2005	0.39	<0.0001
After 2005	0.48	<0.0001
N	34314	

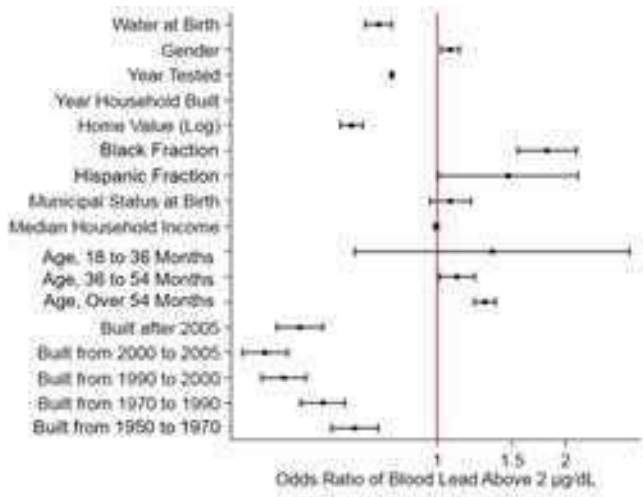


Figure 3. Graphical representation of the 2 µg/dL logistic model with odds ratios, confidence intervals, and all variables included in model. Each point represents the odds ratio, and the lines extending left and right from each point represent the lower and upper confidence intervals, respectively.

DISCUSSION

The objective of this study was to characterize the effects of exclusion from municipal water infrastructure on childhood blood lead levels in the community studied. We found that

municipal water access and childhood blood lead levels are significantly associated across all models in this dataset. Children without municipal water access were more likely to have elevated blood lead levels as compared to children with municipal water access in the area studied. These findings support our hypothesis that a lack of access to municipal water is associated with elevated blood lead levels in our study population.

The findings of this study lend support to the hypothesis that private well water in underserved communities may contribute to the risk of elevated blood lead. Studies have found significant amounts of lead from private well water in neighborhoods without municipal water access in North Carolina [5]. To date, this is the first study seeking to determine the relationship between a lack of municipal water access and childhood blood lead levels. Multiple studies have described racial disparities in municipal water access in North Carolina [8, 11, 13, 17, 18] and Wake County specifically [10]. Predominantly Black communities in this area are significantly less likely to have municipal water access [10]. Our results further these studies' findings by providing evidence that Black communities are also more likely to have elevated blood lead levels.

It is also important to consider the historical context of race in drawing municipal boundaries and providing municipal services in some communities. Predominantly Black communities have been historically excluded from municipal boundaries in some jurisdictions [6, 8, 13, 18]. The results of this study suggest potential health risks associated with being excluded from municipal boundaries by increased blood lead levels due to unregulated private wells, especially for predominantly Black communities. Health effects from lead exposure in childhood include decreased IQ, poor school performance, and increased risk of delinquent behavior [2]. The severe and pointed effects of childhood lead exposure are still an issue today, and drinking water constitutes a major source of lead exposure in some communities.

The findings of this study have many implications for public health and urban planning policy. Our results demonstrate a clear relationship between childhood blood lead levels and municipal water access. The results of this study demonstrate a clear relationship between demographics at the census block level and childhood blood lead levels. This demonstrated relationship in Wake County, while not generalizable to other locations, could be used by municipalities to determine which neighborhoods are most likely to benefit greatly from municipal water extensions.

Cycle of Childhood Environmental Health Disparities

Lead exposure in childhood is one example of persistent environmental health disparities experienced more frequently by communities of color. Figure 4 shows the cycle of childhood environmental health disparities experienced by communities without access to municipal water infrastructure. Children living in underbounded communities without access to public drinking water infrastructure rely on private wells, which are unregulated under the Safe Drinking Water Act. Public water systems governed by the Safe Drinking Water Act are required to implement corrosion controls to prevent the leaching of lead into the water supply, but private wells do not have these protections [15]. Corrosive ground water from private wells can cause lead to leach from well and plumbing components [19].



Figure 4. The cycle of childhood environmental health disparities experienced by individuals excluded from municipal water services due to racial underbouding of their community.

Households that rely on private wells are likely to neither have the knowledge nor the means to monitor water quality and/or to maintain their water systems should an issue be discovered [20–23]. Thus, children living in these communities without access to municipal water infrastructure are at a greater risk for elevated blood lead levels, as demonstrated in this study’s results. A report published by the CDC found blood lead levels of Black and Hispanic children were elevated compared to the blood lead levels of white children [1]. Lead exposure in childhood results in negative health outcomes such as neurotoxicity, learning disorders, and behavioral problems, even at low levels of exposure [24–26]. To break this cycle of childhood environmental health disparities, targeted interventions must be implemented to better educate private well owners on the importance of testing water quality regularly and implementing corrosion controls. Additionally, policy makers should work with historically underbouded communities to facilitate the extension of municipal water infrastructure.

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Chapter 344

THE IMPACT OF CHILDHOOD EXERCISE AND HOUSEHOLD INCOME ON RESILIENCE IN COLLEGE STUDENTS

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ABSTRACT

Living in poverty has detrimental effects on children's health. Children who are resilient may be protected from the damaging health effects of a low-income environment. There is a moderate amount of literature suggesting exercise behaviors can increase resilience. In this study, we investigate whether college students from low-income environments with established childhood exercise habits are more resilient than students who exercised less. An electronic survey sent to students at the University of Massachusetts, Amherst included the Brief Resilience Scale[®] to measure students' resilience levels and the Godin Leisure-Time Exercise Questionnaire[®] to measure current and past exercise habits. The final analysis included 269 responses. Across income brackets, participants exercise most frequently in high school and least frequently in college. Students in the lowest household income bracket exercise the least while students from the highest household income bracket exercise the most. Students in the high-medium income bracket had the lowest mean resilience scores, and students in the highest income bracket had the highest resilience scores. When controlling for other variables, college exercise was shown to predict increased resilience scores. Additionally, middle school exercise was shown to predict high school and college exercise. These results demonstrate the necessity of interventions to increase exercise in children from

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low-income environments, establish exercise habits early in childhood, and use exercise as a strategy to promote resilience. Such interventions may enable children to protect themselves from developing chronic diseases caused by their environmental circumstances and thus break the cycle of environmental health disparities.

INTRODUCTION

Living in poverty has detrimental effects on children's health – children from low-income households have an increased risk of developing behavioral disorders [1] and developing a chronic disease later in life compared to children from higher income families [2]. The list of possible underlying causes of these conditions is extensive – studies identify pollution [3], food insecurity [4], poor housing quality [5], lack of access to recreational space [6] and healthcare providers [7]. These factors highlight the environmental health disparity between children from low-income households compared to average or high-income households. In order to mitigate the potential damaging health effects of poverty and break the cycle of health disparities, children need to have tools to manage increased stressors of their environment and cope with the adverse effects.

Frequent exercise has been shown to be one method that allows children to manage stress and improve their mental health [8]. Since children in low-income environments experience higher stress levels [9] they may greatly benefit from using exercise to overcome the challenges of their harsh surroundings. Unfortunately, children from low-income households exercise significantly less than their wealthier peers [10]. Research has identified a lack of access to recreational spaces [11], inadequate sports facilities [12] and unsafe neighborhood conditions [13] as possible causes of this disparity. The impact of children's physical environment on physical and mental health has become a highly researched subject, and the relationship may be more complicated than previously thought. For example, Huynh et al. [14] showed that children who reside near highways have a two-fold increased risk of uncontrolled asthma compared to children living more than two miles from a highway.

Developing resilience to the harsh environmental conditions associated with living in a low-income household would allow children to protect themselves the long-term damaging effects of asthma and other environmentally triggered conditions. The American Psychological Association [15] defines resilience as “the process of adapting well in the face of adversity, trauma, tragedy, threats or significant sources of stress.” In a 2014 review of literature on the subject of resilience, Southwick et al. [16] describe psychological resilience as complex construct with determinants that include “a host of biological, psychological, social and cultural factors that interact with one another to determine how one responds to stressful experiences.” Studies have shown these factors to include emotional intelligence [17], self-esteem, number of adverse life experiences, and quality of parental relationships [18].

In this study, we measure the resilience of college students from different backgrounds and examine the role of past and present exercise habits as a factor in their resilience level. Based on literature that demonstrates the role of exercise in reducing stress and the protective nature of resilience [19, 20], we hypothesize that established exercise habits will increase the resilience levels of children from low-income environments and bring them closer to breaking the cycle of health disparities (see Figure 1). We decided to measure exercise habits over time

in addition to current exercise patterns because we felt measuring long-term habits would yield an understanding of when interventions focused on exercise would be most effective in increasing resilience. Additionally, none of the previous literature on this subject explores the impact of long-term exercise habits and family income on resilience in college students specifically. Thus, our study will address this gap in the literature and yield a better understanding of how long-standing exercise habits impact college students' resilience levels and how family income impacts this relationship.



Figure 1. Hypothesis of the role of established exercise habits in breaking the cycle of health disparities.

OUR STUDY

This study was conducted at the University of Massachusetts (UMass), Amherst, a large four-year public institution. UMass Amherst is an appropriate setting for conducting this research due to the diverse student population; approximately one out of five students in the 2018 entering class are first generation college students and 15% of students are from underrepresented minority groups [21]. After approval by the University's Institutional Review Board, a 23-question, five-minute, online electronic survey was developed using RedCap®, a HIPPA-compliant survey software. To recruit participants, the survey link was sent to 13 professors to forward to their class lists, posted on two class Facebook® pages, and verbally presented to students in three lectures halls at the beginning of that day's lecture.

Questionnaire

A single electronic survey was developed by combining the Brief Resilience Scale®, three iterations of the Godin-Shephard Leisure-Time Exercise Questionnaire® and participant demographic questions. Results from the Brief Resilience Scale allow researchers to assess respondents' resilience as "ability to bounce back from stress" and assign a unitary construct to resilience with as few queries as possible [22]. This scale was chosen because it is a

concise yet reliable method of quantifying resilience [22]. The Godin-Shephard Leisure-Time Exercise Questionnaire[®] is a self-reported survey of weekly instances of mild, moderate, and strenuous leisure time exercise [23]. In order to examine how exercise habits change over time, researchers included the survey three times, asking students about their exercise frequency in middle school, high school, and college. In addition to its high reliability and validity [24], the Godin-Shephard Leisure-Time Exercise Questionnaire[®] was chosen because it can be used to calculate a weighted exercise score based on the type of exercise. Researchers agree with the creator of the scale who states that the ability to weigh exercise by type provides a more comprehensive description of participants' exercise habits than scales that do not account for the type of exercise [23]. Additionally, both questionnaires produce numerical results which were used for quantitative analysis.

Demographics

Demographic questions included age, gender, academic grade level, family household income, financial aid status, parental education level, and ability to cover household expenses. Yearly family household income was broken into four brackets: high (\$200,000 or more), high-medium (\$150,000-\$199,999), low-medium (\$60,000-\$149,999), and low (less than \$60,000). These brackets were created to straddle the average family household income of a UMass Amherst student, which is \$120,000 [25]. Each of these income brackets is significantly above the national poverty level; researchers chose the income brackets so the sample would be evenly distributed in order to make reliable conclusions about exercise and resilience for each group of respondents.

Resilience

Resilience was measured using the Brief Resilience Scale[®] developed by Smith et al. [22] in 2008 (Cronbach's alpha from .80 - .91 over four samples). This scale was chosen over the more extensive resilience scales in order to promote completion of the entire survey and increase the number of valid responses. The scale includes three positively worded statements such as "I tend to bounce back quickly after hard times" and three negatively worded statements such as "I have a hard time making it through stressful events" [22]. Students respond to these statements on a Likert scale from Strongly Disagree to Strongly Agree. Based on responses to these statements, a resilience score was assigned to each participant on a scale from one to five.

Exercise Habits

Long-term exercise habits were measured using a modified version of the Godin-Shephard Leisure-Time Exercise Questionnaire[®] [23]. Independent evaluations of the scale have shown it to have satisfactory validity and reliability checks against gold-standard measures of physical activity [24]. The original scale asks how many times per week

participants perform mild, moderate and strenuous exercise at one point in time. The scale was modified and repeated three times, asking students about their exercise habits in middle school, high school, and college. To calculate a weighted exercise score for each time period, moderate exercise weekly instances were multiplied by two, and strenuous exercise weekly instances were multiplied by three and added to the other types of exercise. Additionally, a total exercise score was calculated by adding the weighted sums from the three time periods.

Data Analysis

After the data collection period, quantitative statistical analysis with multiple regression was performed on SPSS software version 25[®] [26]. A total of 300 surveys were submitted by participants. 31 surveys were not included in the analysis because respondents did not fill out the survey to completion. Resilience and exercise scores were averaged for participants in each of the four income brackets to examine correlations with income. For multiple regression analysis, a *p*-value of 0.05 was used to determine the statistical significance of relationships between demographic variables, resilience score, and exercise at each time period.

FINDINGS

Of the 269 surveys included in the final analysis, 73.2% percent of participants were female and 26.8% percent were male (see Table 1). Most participants (70.6%) reported receiving some form of financial aid. The largest group of participants (38.8%) were college juniors. Additionally, the largest group of respondents (42.8%) was in the low-medium income bracket. Most participants (71.4%) reported that one parent had at least a bachelor's degree (see Table 1 for demographic information).

The distribution of mean exercise scores in middle school, high school, and college by income bracket is displayed in the graph titled *Exercise by household income level in middle school, high school and college* (see Figure 2).

Across all income brackets, participants exercise most frequently in high school and least frequently in college. Exercise frequency was positively correlated with income level in all three time periods. Students in the lowest income bracket exercise the least in middle school, high school, and college, while students from the highest income bracket exercise the most. In addition to exercise, resilience was also lower among students in the lowest income bracket than the resilience of students in the highest bracket, but overall the relationship between income and resilience was not linear. Students in the high-medium income bracket had the lowest resilience scores. Mean resilience scores by income are displayed in the graph titled *Mean Resilience Score by Income level* (see Figure 3). The graph titled *Sum of individual exercise scores compared to individual mean resilience scores* shows participants' total exercise score (the sum of their weighted scores in middle school, high school, and college) compared to their resilience score (see Figure 4). While there is a large amount of variability in the results, there is a slight positive relationship between exercise and resilience. Multiple linear regression analysis showed that, when controlling for all other variables, exercise in

college correlated with students' resilience score. Additionally, middle school exercise was shown to strongly predict high school exercise and moderately predict college exercise.

Table 1. Participant demographics

Variable Label	N	Percent
Gender		
Female	197	73.2
Male	72	26.8
Age		
19	45	16.7
20	95	35.3
21	76	28.3
Older than 21	53	19.7
Year		
Freshman	16	5.9
Sophomore	76	28.3
Junior	109	38.3
Senior	69	25.7
Other	5	1.9
Race		
American Indian or Native American	3	1.1
Asian or Pacific Islander	29	10.8
Black or African American	9	3.3
Caucasian (Non-Hispanic)	225	83.6
Hispanic	11	4.1
Other	9	3.3
Household Income		
Less than \$60,000	31	11.5
\$60,000 to \$149,999	115	41.8
\$150,000 to \$199,999	66	24.5
\$200,000 or more	17	21.2
Ability to Cover Expenses		
Yes	232	86.2
No	14	5.2
Sometimes	23	8.6
Financial Aid Recipient		
Yes	190	70.6
No	79	29.4
Highest Parent Education		
Less than a high school diploma	1	0.4
High school degree or equivalent	22	8.3
Some college	27	10
Bachelor's degree	88	36.4
Master's degree or Doctorate degree	121	45

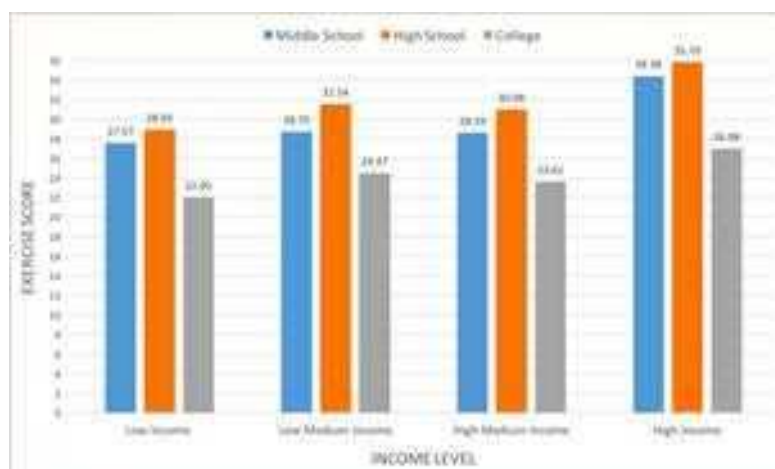


Figure 2. Exercise by household income level in middle school, high school and college.

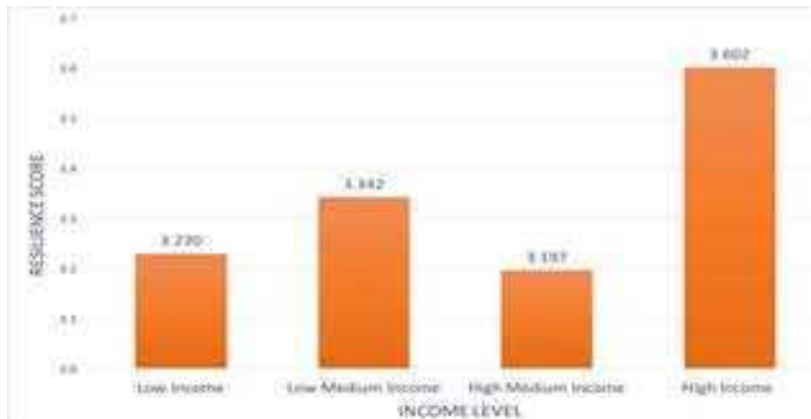


Figure 3. Mean resilience score by income level.

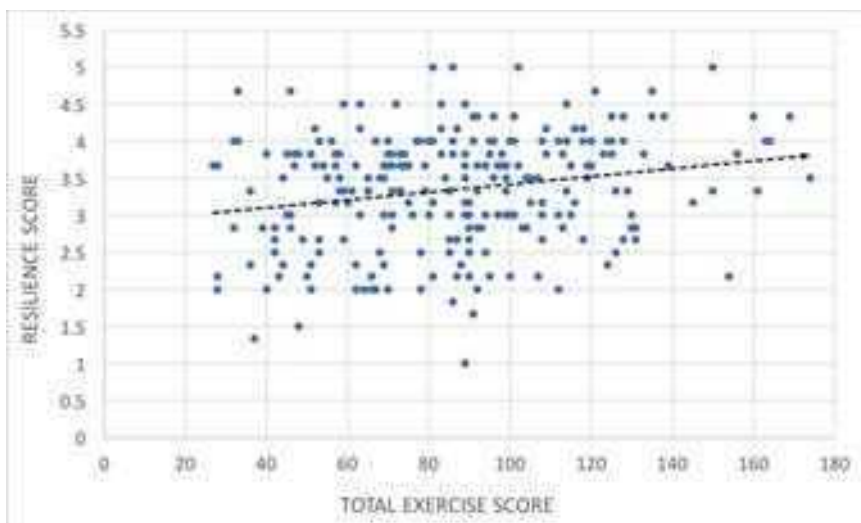


Figure 4. Sum of individual exercise scores compared to individual mean resilience scores.

DISCUSSION

The purpose of this study was to measure whether childhood exercise habits impact the resilience of college students from different income levels. Respondents were divided into four income brackets. Students' resilience scores and weekly frequency of mild, moderate, and vigorous exercise levels in middle school, high school and college were analyzed. Trends and positive correlations in student's resilience and exercise seen in this study are consistent with current literature and can be used to make recommendations to increase resilience through exercise. The primary finding that college exercise was predictor of resilience in this dataset adds weight to the existing literature demonstrating a connection between exercise and resilience. The significance of this finding is increased by the fact that the largest percentage of participants were college juniors, who, by the third year of college, may have more

consistent habits than freshmen. Although some students may have left the university by Junior year, 86.6% of UMass Amherst Juniors were retained from the original freshman class [27]. The relationship between frequent exercise and increased resilience can be used to support the implementation of exercise programs targeted towards increasing resilience and improving mental health of college students. The finding that students who exercise in middle school continue to exercise in high school and college reveals exercise habits are established early in life and is consistent with literature on the subject. Thus, we recommend interventions for children across income levels should begin with introducing exercise at a young age since the habit will likely be maintained in young adulthood and beyond.

While individual interventions are important, local and national governments should also recognize the impact of environmental improvements on exercise outcomes of entire communities. A greenway built in Knoxville, Tennessee significantly increased the amount of time community members spent walking and biking [28], although other studies show that trail users are most likely to be white adult males [29]. Among children from low-income households in Chicago, perceived neighborhood safety was associated with the amount of unstructured play while access to neighborhood exercise facilities predicted organized sport participation [30]. Healthcare policy advocates should refer to case studies and literature that demonstrates the impact of green space, recreational facilities and safe neighborhoods on children's health to promote policies that improve the built environment.

When controlling for other variables with multiple regression analysis, family income and other socioeconomic variables did not significantly predict resilience or exercise. Although student demographics did not predict exercise habits in the data, there was a positive correlation between exercise and income level. This finding is consistent with the robust literature demonstrating the disparity in exercise habits of children in low and high-income environments [31]. Trends in resilience by income were less linear – students in the high-medium income bracket had lower resilience scores than students in the two lower income brackets. Studies of childhood development and stress have shown that experiences of severe adversity, called ACEs (Adverse Childhood Experiences), have long-term destructive effects on children's physical and mental health [32]. However, experiencing a moderate amount of adversity (as the students in the lower income levels most likely have) can contribute to the development of resilience [33]. In a longitudinal survey of 1,994 participants, Seery et al. [33] found that respondents with a history of some lifetime adversity were less affected by adverse experiences than individuals with an extensive history of adversity or no history of adversity. Seery et al. [33] hypothesized that experiencing some adversity could “teach effective coping skills, help engage social support networks, create a sense of mastery over past adversity, foster beliefs in the ability to cope successfully in the future, and generate psychophysiological toughness” [33]. The beneficial effect of moderate adversity can be compared to the common belief that strenuous exercise and sports “build character” [34]. The literature on exercise and adversity suggests exercise may be a form of intentionally induced moderate adversity that creates a similar effect to the moderate stress described by Seery et al. [33]. Further research should be conducted to compare the impact of experiencing purposeful, positive adversity through exercise to the impact of experiencing unfortunate adversity such as ACE's. Exercise may provide an opportunity for children to safely experience hardship and failure to develop psychological resilience that becomes vital when more serious challenges arise.

At the Mindfulness-Based Stress Reduction Clinic, located a short drive away from the UMass Amherst campus, students can learn resilience not only on the sports field, but also in a classroom. Participants practice mindfulness techniques which demonstrate that "paying attention on purpose, in the present moment, and nonjudgmentally, to the unfolding of experience moment to moment" can even help to manage physical conditions such as asthma, fibromyalgia, skin disorders and heart disease [35]. This approach stresses the relationship between physiological habits and mental health. This mind-body relationship suggests that both physical and psychological training through exercise, meditation, and mindfulness, are important elements in fostering resilience for individuals of all ages.

Limitations

Limitations of this study include the fact that the sample ($n = 269$) was relatively small, and from only one public university. The ethnic distribution of participants was representative of the UMass student population (see Figure 5), but due to the sample size the number of participants from minority groups was too small to be able to make conclusions about exercise and resilience of different ethnic groups. Additionally, students were mostly recruited from traditional lectures in disciplines such as computer science, business administration, nursing, biology, and engineering. Including students studying art, dance, or agricultural studies may be underrepresented because they do not attend traditional lectures and were therefore harder to recruit for this study. The unequal gender distribution of the sample (73.2% female) is likely due to the fact that one of the lectures researchers attended to recruit participants was a Nursing lecture and included mostly female students. In order to encourage completion of the entire survey, demographic questions were kept as concise and simple as possible, which may have resulted in loss of detail about students' backgrounds.

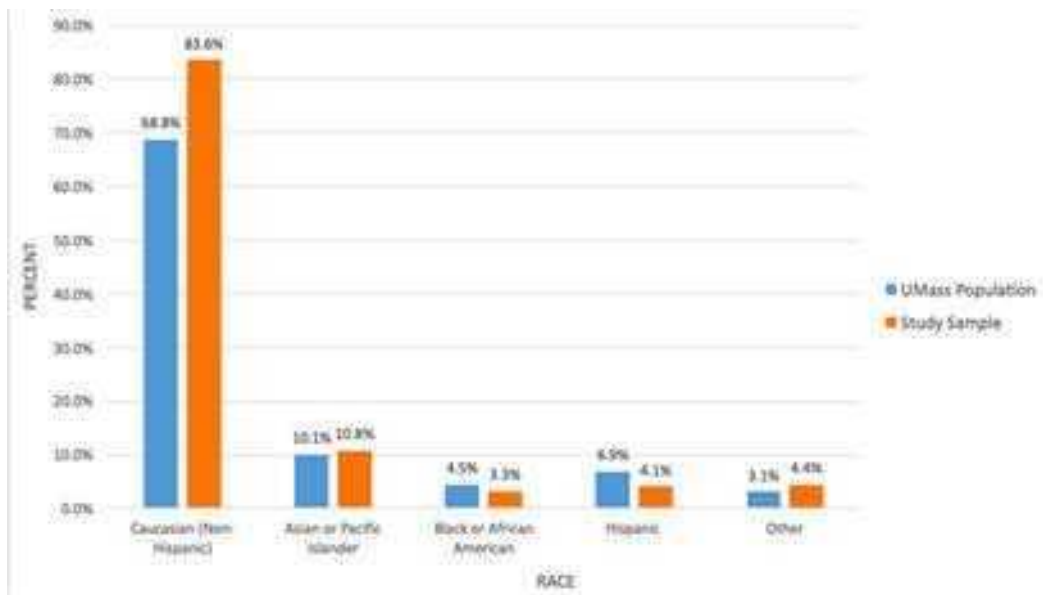


Figure 5. Race distribution of UMass student population versus study sample.

Because participation was optional, the study population was self selecting, so results do not necessarily reflect information about other college students. The relatively high household income of the study population limits the study's generalizability. Future surveys should include an analysis of a more diverse sample as well as other socioeconomic variables in addition to income. A deeper exploration of students' lifestyle would be valuable – one suggestion is to ask students if they have to work to finance their education or pay back large student loans. Additionally, a longitudinal study that follows a cohort over time would be more accurate than retrospective responses. Finally, different methods of quantifying exercise habits, including real-time activity monitors such as watches or chest straps, would be useful to remove the inaccuracies of the self-reports used in this study.

CONCLUSION

Through a self-selected survey of college students, psychological resilience levels, family household income, and past and present exercise habits, student's exercise frequency was determined to predict students' resilience and that students who start exercising in middle school are likely to continue exercising in high school and in college. Results also showed household income level is directly related to how much a student exercises. The finding of a correlation between the low resilience and the poor exercise habits of children from low-income households shown in this study suggests exercise interventions should be targeted towards children in low-income environments to help them build resilience to the health risk factors that are prevalent in these environments. Furthermore, the relationship between exercise and resilience shown in this study should prompt health policy changes to improve children's environments making exercise accessible and safe in the critical middle school years, thereby promoting protective resilience against environmental stressors. Resilience built through holistic interventions that include consistent physical and psychological training will enable children to disrupt the cycle of health disparities resulting in improved health, educational achievement and success in life.

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Chapter 345

GAME-BASED LEARNING FOR POSITIVE YOUTH DEVELOPMENT: A PREVENTIVE APPROACH

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INTRODUCTION

Adolescents grow up in a digital environment which promotes and at the same time threatens the development of their bio-psycho-social well-being [1]. Teens in the United States in 2015 on average spent one hour and twenty minutes playing video, computer, or mobile games [2]. Another study found that they spent about 6 hours a day in 2016 on digital media and social media [3]. New media, including computer games and social media, is an important part of adolescents' daily experiences. From a positive view, we need to develop more digital game-based learning (DGBL) materials to promote the wellbeing of young people through self-help and peer influence. However, a majority of adolescents' favorite

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commercial games usually involve violence and pornographic content. Moreover, there are concerns that computer game use puts adolescents at risk of addiction, violence, sexual exploitation, exposure to hateful or discriminatory contents, online and offline victimization, social isolation, and so on.

Game-Based Learning for Positive Youth Development: A Preventive Approach

Games have a long history as they can promote bio-psycho-social well-being for all ages. Parents, teachers, social workers, and mental health practitioners may use different types of games, including chess, board, card, physical, mental and spiritual activities, and video/digital games for educational purposes. The design and use of digital games in education developed together with the rise of home computers. Prensky [4] first coined the term digital game-based learning (DGBL). Since then developers have produced educational games according to educational theories to enhance engagement and learning outcomes. However, the number of educational digital games can hardly compare to that for entertainment purposes. While the controversy of possible ill-effects of many digital games is still on-going, the rapid development of new technologies facilitates the design and production of digital games that hold potential for education, medical and health, humanities and social sciences, and many more disciplines. Charities and non-profit making organizations that support bio-psycho-social-cultural well-being are becoming aware of the effectiveness, efficiency, and potential contributions of digital games to their causes and social impact. They contributed to supplementing the gap left behind by commercial companies. As part of the effort in promoting positive youth development (PYD) among early adolescents, seven digital games were designed and developed to support the Project P.A.T.H.S. which has been recognized as an evidence-based intervention by World Health Organization for ending violence against children [5] and promoting life and social skills in adolescents [6]. These games will strengthen the intervention strategies in prevention at primary, secondary, and tertiary levels. This special issue will focus on theory, practice, and initial evaluation of these digital games designed for the enhancement of PYD (hereafter referred to as DPYD games).

Prevention

As an interdisciplinary field to address the need for prevention-related research, numerous studies in prevention science have demonstrated with increasing evidence that many antecedents of risk behaviors can be prevented. They also support that primary and secondary prevention is much better than tertiary prevention because they save lives, minimize harms of different kinds, reduce public expenditure on expensive remedial treatment of risk behaviors, promote positive development, and build a better environment for children and adolescents. The latest development in prevention science witnesses the development and evaluation of DGBL.

Digital Game-Based Learning (DGBL)

This trend suggests that DGBL will become one of the major teaching and learning strategies in prevention, particularly in education [7-9], health fields [10-12], social-emotional learning [13-14], and treatment, for example, of children with attention-deficit/hyperactivity disorder [15]. The presence of digital games in promoting social-emotional learning (SEL) and positive youth development (PYD) is spreading due to their favorable results in terms of intended learning outcomes and users' engagement [16].

Many studies have examined the negative impact of playing video games, such as addiction, aggression, interruption of sleep habits, and parent-child conflict. Only a few studies have investigated potential positive outcomes [17-18]. However, very few studies demonstrate a link between playing video games and enhanced well-being, problem-solving skills, intergroup relations, and physical activity [10, 19-21]. This special issue is an effort to explore further the impact of DGBL on PYD.

ADOLESCENT ISSUES AND DIGITAL POSITIVE YOUTH DEVELOPMENT GAME: A CONCEPTUAL FRAMEWORK

We are now living in a digital age. Many children and adolescents and their parents keep using their smartphones and computers day and night. It is very difficult, if not impossible, to trace the effects of smartphones and social media on adolescents although it seems that the effects are potentially profound [1]. Rapid changes in the contexts of varied exposure to media contents, playing on-line games, connection with different on-line groups, post challenges and create opportunities for adolescents. From developmental and preventive perspectives, we are concerned about how adolescents handle their developmental tasks in the digital era with regard to the fact that their bio-psycho-social-cultural-behavioral interactions with family and peers have been changed drastically as compared to that of their parents. We may even agree that with the rapid development of information and communication technology (ICT), substantial contextual changes in the environment of adolescents could take place in months, based on Moore's law [22] that the speed of the central processing unit of a computer will double while the price will go down about every two years.

The uses and gratification approach in explaining how adolescents use and are affected by the use of smartphones and new media is far from adequate because its assumption on individual characteristics and decisions are convincingly confronted by Kahneman's Nobel Prize winning study on irrational judgment and decision-making in times of uncertainty [23]. Bronfenbrenner's [24] perspective on interactions between different social spheres is well-accepted to guide studies on media effects on adolescents. Based on Bandura's social learning theory and Gerbner's cultivation theory, Steele and Brown's [25] media practice model which covers personal identity, characteristics, daily practices, and the environment is a more specific approach to examine the factors for the media to induce various effects on adolescents.

Why These Games?

When focusing on early adolescents (aged 12-15 years), we witness changes in the following ways:

1. disrespecting others, engaging in dishonest, criminal on-line behaviors, and cyberbullying partly due to a wrong conception of anonymity in the cyber world;
2. being confused in building one's own identity partly because of premature decisions based on irrational judgment and decision-making [23] as well as information explosion;
3. experiencing difficulties in bonding with parents partly due to the use of "electronic pacifier", the lack of parental attention and quality parent-child time as a result of over-use of smartphone and social media [26], and in relating to peers as a result of weakened communication skills and emotional development [27];
4. having gender stereotypes and biases partly due to the biased advertisements and media contents; and
5. emphasizing money and success in cultivating their value systems partly because of media exposure.

As a prevention measure, seven digital positive youth development (DPYD) games were designed and developed. By strengthening relevant PYD constructs, these games target at enhancing the players' competencies.

SEVEN DIGITAL GAMES FOR PYD: A BRIEF DESCRIPTION

With the support by the sponsor, the seven DPYD games introduced in this special issue were designed mainly for the promotion of five core competencies among the 15 PYD constructs identified in successful programs by Catalano et al. [28], namely, social (SC),

Table 1. Adolescent issue addressed and targeted PYD constructs of each game

	Name of the Game	Adolescent Issue Addressed	Core PYD Constructs	Related PYD Constructs
1	The Digital Age	Respect for privacy	Moral Competence, Social Competence	Resilience
2	The Integrity Crisis	Integrity	Moral Competence, Social Competence	Resilience
3	The Bullying Storm	Bullying and cyber-bullying	Moral Competence, Social Competence	Resilience
4	The Male-Female Dichotomy	Gender stereo-types and biases	Clear and Positive Identity	Self-determination, Prosocial Norms, Social Competence, Moral Competence
5	The Great Thinking Adventure	Cognitive traps	Cognitive Competence	
6	A Journey to Somewhere, to Someone	Friendship and love affair	Bonding, Social Competence, Behavioral Competence, Emotional Competence	Self-Determination, Clear and Positive Identity, Prosocial Norm
7	Live a Meaningful Life	Money and success	Spirituality	Self-efficacy

cognitive (CC), emotional (EC), moral (MC), and behavioral competencies (BC) as well as the following seven constructs, namely, clear and positive identity (ID), self-determination (SD), self-efficacy (SE), bonding (BO), resilience (RE), spirituality (SP), and prosocial norms (PN) among adolescent users of these games. Only three constructs were not included—promotion of beliefs in the future (BF), providing opportunities for prosocial involvement (PI), and recognition for positive behavior (RP). Although DPYD game design must provide immediate positive feedback and reinforcement of RP and PI at the cognitive and intention levels, responses in playing DPYD games are not actual behaviors. Table 1 shows the name, adolescent issues addressed, and targeted PYD constructs of each game.

OVERALL AIMS

This book covers a collection of seven digital games as a demonstration of the state-of-the-art non-commercial “serious games” [9, 29] for promotion of PYD among adolescents. The design of each game and how it can be creatively used by teachers and professionals to achieve the purposes of primary, secondary, and to a smaller extent, tertiary prevention are presented. An early female adolescent studying in an international school in Shanghai and a 19-year-old male college student in the United States were invited to play all the games and provide detailed comments on their learning experiences. Their insightful comments and feedbacks are presented. Difficulties in the use of DGBL technologies will also be discussed, although technical issues in game development are omitted. Some chapters also address implications for ongoing research that will further our knowledge of how DPYD games affect youth development. The use of distinctive game design principles and elements (e.g. rules of play, point scoring, competition with others, immediate feedback) in promoting PYD are discussed in chapter 2.

This book has demonstrated the design and development of DPYD games which show the practice of permeation of gamification [10] and the application of game design principles into positive youth development through e-learning and as a supplement to the conventional learning procedure as a future emergence.

Theory and Practice of Using DPYD Games for Prevention

In this book, chapter 2 offers a thorough discussion on theory and practice of design, development, and use of digital games for the enhancement of PYD constructs. Education theories, concepts and knowledge of gamification, GBL, game principles, and DGBL are reviewed to provide theoretical underpinnings to support the development of these seven games. It also discusses the importance of enabling young people with relevant knowledge and skills to handle commonly found issues properly.

Furthermore, this introductory chapter discusses how and why the creative use of these games will serve the purposes of prevention. For primary prevention, it is to protect adolescents from engagement in risk behavior and harm. These DPYD games are designed for early adolescents (S1 to S3, Grades 7-9) in English, traditional Chinese and simplified Chinese. For secondary prevention, the DPYD games provide guidance and feedbacks

according to users' responses to some relevant and valid psychosocial measures. Adolescents who experience some problems in one or more of these common issues could benefit from the feedback generated according to their choices in a number of carefully selected psychosocial tests. It is particularly useful when students are encouraged to use the print-screen function to keep the feedback and reply to the game using different strategies or available options. Learning can be consolidated when students compare and contrast different outcomes or results with their choices during different stages and at the end of the game. For tertiary prevention, adolescents who suffered from problems in these common issues could be helped by using selected parts of the game as initial engagement, assessment, and part of the intervention efforts to be jointly discussed and determined by the target user and the professional. Although the games do not keep any personal or psych-social test data on the computer in order to protect users, users can use the print-screen function to capture the results and feedback generated. With the consent from users, the print-outs can be used for engagement, raising target users' awareness of the issues and their responses to difficult situations, conducting initial diagnosis, and serving as topics for discussion on the use of knowledge and skills provided in the game to handle similar situations or crises.

Finally, chapter 2 contributes to the development of a practice model named "STREAM" to promote PYD through digital games for prevention.

The Design of Three Games on the Same Theme

Chapter 3 discusses how game design knowledge is applied in the first three games and how they can help adolescents who face difficulties with on-and-off-line interpersonal relationship difficulties, including intruding into someone's privacy, following peers' dishonest behavior, and engaging in bullying and cyber-bullying with peers. The three short DPYD games, each runs for about 15-20 minutes, serve as a series of games on the same theme using three different stories.

Seven Chapters on Seven Games

The following seven chapters each offers a review of a specific and current adolescent issue. Each chapter demonstrates how teachers and professionals can use the specially designed game to promote core competence and related PYD constructs. Concrete suggestions on how to use the game creatively and effectively are presented. Each chapter is supported by theory and users' critical comments as initial qualitative evidence. Theoretical and practical issues are discussed, and limitations and future research suggestions are presented.

The Use of Literature in a DPYD Game

Chapter 11 contributes to cross-disciplinary methodology in illustrating the use of literature in the design and development of a DPYD game. It provides a significant reflection

on the nature and function of literature and its importance in promoting PYD constructs among adolescents.

SPECIFIC OBJECTIVES

The chapters in this book tackle questions related to GBL and PYD. The newly developed games target knowledge acquisition and the development of qualities that are PYD friendly. In this issue, we explore how these games can be used to help adolescents acquire knowledge and skills such as self-awareness, moral decision making, perspective-taking, empathetic understanding, acceptance and respect of gender difference, avoidance of cognitive fallacies, effective communication, personal reflection, relationship building and maintenance, handling intimate relationships, and in managing their own finances as part of their game playing experiences. Moreover, we try to explore how these games can be used to support greater insight into the process and effectiveness of PYD and how they can be effectively used for the prevention of problems encountered by adolescents. In this collection of papers, we seek to

- review the literature on a range of contemporary developmental challenges and relationship issues;
- review the literature on game-based learning for PYD with an intention of preventive intervention;
- describe how these games can serve as additional resources to support the existing teaching and learning materials of the project P.A.T.H.S. to enhance its effectiveness;
- provide users' qualitative reviews on each game to identify their strengths and weaknesses;
- discuss issues related to gamification of PYD, in particular, to consider how user agency, gamification, transportation theory, learning theories, perspective-taking, communication, the use of literature, the integration of in-person individual and group counseling, and other factors that may affect the intended outcomes of these games; and
- develop further questions, practice guidelines, and recommendations for establishing preventive programs around using digital games to enhance PYD.

To achieve these objectives, the seven chapters on each game contain four parts. First, it presents a review of relevant literature on selected contemporary adolescent developmental issues. Second, it gives a description of the game design, contents, objectives, and its relation to the project P.A.T.H.S. by detailing concrete teaching points with relevant concept maps. Third, it offers a discussion on identifying critical success factors after a presentation of the users' feedback and the viewpoints of implementers. Finally, a discussion on intervention strategies via the digital game is included to offer insights and direction for future game development and research.

METHODOLOGY

A significant portion of the chapter on each game is devoted to the implementation and initial evaluation. To demonstrate the effectiveness of the games, the qualitative approach was adopted according to five dimensions that were used in the literature review:

- *Participants*: Convenient samples were used. Two participants, a 15-year old female student from Shanghai and a 19-year old male college student from the United States were invited. For the female participant, parental consent was secured.
- *Intervention*: Participants played the games in their leisure at home.
- *Methods*: For all games, no time limit and number of testing moments were set.
- *Outcome measures*: Free expression in written format. No word limit was set.
- *Data-analysis*. Reflective writings of participants were used for illustration.

CONCLUSION

On the whole, this special issue furnishes a rich description and discussion on the theory and practice of DPYD games, in particular, design, implementation, and initial evaluation. Chapters in this book show a concerted and creative effort in providing preventive measures on commonly found adolescent developmental issues. They also demonstrate that the newly developed and specially designed games are in general efficient and effective measures to promote PYD and prevent some common adolescent problems from deteriorating in contemporary urban societies. Initial users' qualitative feedback supports their effectiveness. Findings related to motivational variables such as self-efficacy, situational interest, goal orientation, and engagement variables are discussed. It is noteworthy that the game on interpersonal relationship has a special feature of promoting cross-cultural understanding of the values behind Chinese and Western (English-speaking only) cultures.

Future effort is needed to improve the measurement of DPYD game use as well as conduct longitudinal research on the effects of DPYD games to identify if and how cumulative effects could result from the use in the presence of a multitude of important variables, under what circumstances and in what developmental stages.

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Chapter 346

THE ‘STREAM’ MODEL OF DIGITAL GAME-BASED LEARNING FOR ENHANCING POSITIVE YOUTH DEVELOPMENT AMONG ADOLESCENTS

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ABSTRACT

To help adolescents develop 21st century skills, digital game-based learning (DGBL) is an effective option. Supported by learning theories and game elements in designing DGBL, more and more “serious educational games” (SEGs) have been produced. Results of evaluation studies provide evidence of the effectiveness of DGBL and expand the literature to cover new areas such as positive youth development (PYD), and peaceful and sustainable societies. To promote PYD, digital positive youth development (DPYD) games could be a cost-effective option. This chapter offers a review of learning theories and digital game design elements that show the design and development of DPYD games as effective learning resources. Guided by learning theories and game elements, this chapter describes how seven newly developed games can help promote relevant PYD constructs among adolescents, clarify their values, and enhance their knowledge and skills to handle properly difficulties commonly encountered, and to protect them from being harmed and engaging in risky behaviors. Finally, based on theories and initial users’ feedback, this chapter attempts to enhance the literature through the development of a practice model from the prevention science perspective to guide future practice.

INTRODUCTION

The aim of this chapter is three-fold. First, it provides a brief review of literature on the theory and practice of design, development, and the use of digital game-based learning

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(DGBL) for the enhancement of positive youth development (PYD) constructs. Educational theories, concepts, and principles of DGBL were reviewed to provide theoretical underpinnings to support the design and development of seven digital positive youth development (DPYD) games.

Second, it briefly describes the design of these seven games and how they can be used as electronic learning materials for the prevention of common adolescent issues. They are intrusion of privacy in digital and real-life environments, participation in dishonest behaviors due to peer pressure, engagement in bullying and cyberbullying (BCB) in on-and-off-line situations, demonstration of gender biases and stereotypes, confinement in cognitive fallacies, having difficulties in friendship and romantic relationships (FRRs) as well as improper attitude towards money and success.

Third, it presents a model to guide the practice of prevention through the creative use of these DPYD games among early adolescents at three levels – primary, secondary, and tertiary. Specifically, this chapter

- reviews the literature on DGBL for enhancement of PYD as prevention;
- describes a range of contemporary developmental challenges and relationship issues;
- describes how the games can serve as digital resources to promote PYD;
- discusses issues related to DGBL of PYD constructs, in particular, gamification, game-based learning, learning theories, perspective-taking, communication, the use of literature, the integration of individual and group counselling, and other factors that may affect the intended learning outcomes (ILOs) of these games; and
- presents a practice model of using DPYD games for prevention purposes.

LITERATURE REVIEW

Games play an important role in human history as they are essential parts of being alive [1-6]. Educational games have a long history as they can promote bio-psycho-social-spiritual well-being. Parents, teachers, social workers, and mental health practitioners may use different types of games, including chess, board, card, physical activities, and video/digital games for educational purposes. Gamification is the application of game-design elements in different contexts including education [7, 8]. It aims at improving user engagement, learning, feedback to users, and more. Game-based learning has huge market potentials [9].

Computer Game

Prensky [10] classified eight “genres” of digital games—action, adventure, fighting, puzzle, role-play, simulation, sports, and strategy games. Recently, Bean [11] classified eleven genres of digital games—action, action-adventure, adventure, horrors, racing, shoot-’em-ups, simulations, sports simulations, strategy, role-playing, and others. Although there is a wide range of cultural genre of computer games, Martin [12] summarized five communities through co-citation analysis. They are education, humanities/social sciences, computer science, communication, and health. The rapid advancement in information and

communication technology (ICT) proliferates the production of computer games mainly for entertainment purposes. Unfortunately, many of them have various degrees of violence and pornographic content.

Digital Game

After Prensky [10] published the first book on digital game-based learning (DGBL), increasing efforts have been made in developing digital games or “serious games” for education, medical and health, and bio-psycho-social-cognitive-behavioral rehabilitation that fit roughly into the framework of prevention science. From 2006, thousands of research studies on digital games were published every year [12, 13].

Digital Game-Based Learning (DGBL)

Digital game-based learning (DGBL) refers to achieving an educational purpose through the use of fun/entertainment means [10, 14, 15]. The range of research on DGBL covers all ages of learners [16], examination of its relationship with 21st century skills [1], identification of best practices [17], development of educational games [1], building up models [18, 19], and assessment of its effectiveness of interventions for prevention, treatment and rehabilitation purposes [20-23]. Recent efforts have been devoted to the establishment of a comprehensive methodology [24] and platforms for the interdisciplinary design of games in education [25, 26].

Types of DGBL

Two types of games can be distinguished in DGBL: special-purpose games that have been developed with an educational purpose and commercial-off-the-shelf games that have been developed for entertainment purposes but deployed in an educational context [27]. This chapter focuses on purpose-built educational games that strike a balance between gaming elements and learning for non-commercial purposes [28]. On the commercial side, the latest products of popular digital games show a trend of combining different genres, for example, *League of Legends*, *Minecraft*, *Counter-Strike: Global Offensive*, *Tom Clancy's Rainbow Six: Siege*, *World of Warcraft*, and *Hearthstone: Heroes of Warcraft*. New technologies including 5G, artificial intelligence (AI) and virtual reality (VR) will enlarge the functions, create more opportunities, and enhance the attractiveness of DGBL. For educational purposes, they are usually called “serious games” or “serious educational games” (SEGs) [14, 21, 24, 29].

Examples of Game-Based Prevention Programs

Some GBL programs are designed for prevention. Examples include preventing child sexual abuse among children aged 8 to 10 years [30], obesity among children [31], fire

prevention education among children [32], phishing prevention among regular computer users [33], and car accident prevention for drivers [34]. The newly developed DPYD games are the latest examples of such intent.

Merits and Demerits of DGBL

An increasing number of studies has demonstrated positive outcomes of DGBL which include enhancing students' enthusiasm in learning [35], providing an exciting avenue for learning [36], meeting students' emotional needs [37], and enhancing their problem-solving skills [38]. However, DGBL may contribute to other forms of addiction which include gambling, addiction to technology [39], and prolonged screen time [40, 41].

Learning Theories and Successful Game Designs

While commercial digital games employ “every single worthwhile learning theory in existence” [42], studies on GBL point out a lack of theory support [43, 44]. For example, a review of 567 published studies found a close connection between the use of learning theories and positive outcomes but most studies fail to discuss the application of learning theories [44].

Learning theories have been enriched by anthropology, communication, psychology, socio-linguistics, and sociology. Classical learning theories include behavioral theory [45] and social learning theory [46]. Experiential learning theory [47] and self-determination theory [48] belong to the humanistic approach which stresses that each student should be respected as a unique individual who is capable of learning in his/her own style and pace. Cognitivism emphasizes that learning depends on mental capacity and stresses that a free environment for decision-making is vital. Distributed cognition [49] and cognitive theory [50] are the most relevant to GBL.

The constructivist perspective which includes social constructionism [51] and social constructivism [52] theorizes how human beings construct their knowledge through active processes. While social constructivism emphasizes an individual's learning from his or her interactions in a group, social constructionism [51] focuses on the products that are co-created through social interactions in the group. Constructivism theories that are highly related to GBL include cognitive apprenticeship [53], communities of practice [54], activity theory [55, 56], and situated learning theory [23].

Contemporary learning theories that can also explain DGBL include generative learning [19, 57], flow theory [23, 56], and narrative centered learning [58]. Last but not least, uses and gratification theory [59] helps to design and use digital games as prevention tools because no GBL can happen without engagement or motivation.

Theories for Digital Game-Based Learning

This section will briefly describe how these theories support DGBL. When playing DPYD games, students learn by doing tasks and are benefited through *experiential learning*.

If learners fulfill their innate psychological needs of competence, relatedness, and autonomy, they will function and develop at an optimal level according to *self-determination theory* [48, 60].

Although stand-alone and collaboration games require different strategies, the former removes the pressure of social comparison to reduce or eliminate social stigma and sanction during the learning process. Collaboration games require social interaction. Through *distributed cognition*, i.e., sharing cognitive resources, players can achieve learning outcomes that an individual learner cannot achieve alone [49, 61]. When engaging or sharing the tasks or strategies of a game with peers, they form a community of practice through which they interact regularly to improve their performance [54].

Activity theory helps explain the achievement of intended learning outcomes (ILOs) because digital games allow players to participate and experiment in non-threatening situations and learn through the game repeatedly to maximize learning effects [55, 56]. The theory provides a framework that explains a hierarchical analysis of motivated human activity [62]. To achieve pre-determined ILOs, game-based learning is designed in a given context or setting, providing specific information and knowledge, and requiring special skills. In this connection, *situated learning theory* provides substantial support as it emphasizes that an individual learns, sees, and behaves in his/her role within society [63]. The game provides game-based learning environments that integrate educational information and interactive scenarios with gameplay dynamics to boost players' motivation. This is what *narrative-centered learning* refers to [64]. From the players' point of view, *uses and gratification theory* suggests that students control their media usage instead of just being influenced by the games or media [65].

When designing a DPYD game, *cognitive apprenticeship* is helpful as it stresses the importance of turning the tacit processes into an open-mode, through which students can learn with the help from the "master of skill" [53]. Flow theory helps us understand the mental state of the game-player who fully concentrates and engages in the activity when doing something that challenges his/her skills [66].

Game Design Elements for Digital Game-Based Learning

DGBL and gamification are similar in that they both promote engagement and sustain intrinsic and extrinsic motivations in learning. They can be distinguished in that DGBL involves applying game elements in designing new learning activities that are intrinsically game-like to achieve learning outcomes whereas gamification applies game design elements to existing learning activities. A review of the literature identifies 22 digital game design elements. The summary presented below draws on the extensive analysis by Qian and Clark [1]. Table 1 shows the simplified definitions of game design elements. These 22 elements are used to evaluate the seven DPYD games and the results are presented after an introduction of the games.

Table 1. Definitions of game design elements

	Game Element	Definition
1	Challenge	An element which enhances the difficulty of the game [50], for the purpose of providing active learning experiences to players [67]
2	Collaboration	Providing players with a situation to work together with others in handling a challenge [68] through which players learn and internalize knowledge when they respond to others during the discussion [69]
3	Competition	As an interactive feature of the game which allows a player to play against the computer, another player or his/her own records [19, 70]
4	Complexity	The situation that balances the features of games and simulations of real-life conditions [57] and provides different pathways for players toward the goal [58]
5	Control	The power to influence or direct the learning and thinking of players [71]
6	Exploration & Discovery	An inquiry-based learning activity in which players think and explore the situation so as to boost their critical thinking abilities [72]
7	Goals	A desired result of the game which requires players to try a variety of methods for reaching it [23] and a crucial element for efficient learning games since it enhances the motivation among players [50, 56]
8	Interactivity	Providing interactive learning opportunities for players [73] so as to boost their development of scientifically appropriate responses to different situations [58]
9	Low Stakes Failure	Allowing players to improve technique and decisions by trial-and-error through pleasantly frustrating experiences [70]
10	Narrative	Referring to the storylines, conditions and characters of the game [74] which help attract the players to devote their full attention and experience situations and emotions brought by the interactions with the characters of the game [58]
11	Realism	The imitation of a realistic situation in the game [19]
12	Role Play	Assigning each player to be a character in the dramatic interactive story with the responsibility to complete the tasks by choosing how the story can go on [75, 76]
13	Rules	Providing players with a rule-based environment for the purpose of making the game engaging and fun [23, 50]
14	Scaffolds	Acting as supporting equipment for the balance of the game contents and educational contents [77]
15	Self-Expression	Providing chances for players to control their learning process so as to enhance their learning confidence and motivation [78]
16	Strategy	A detailed plan which requires players' communication, strategic thinking, and problem-solving skills [67, 68] for achieving the final goal of becoming competent at playing games [79]
17	Surprise & Uncertainty	The situation when an unexpected condition happens which raises the comprehension of the game by requiring players to reevaluate the preconceptions of the game [80]
18	Immediate feedback	Improving players' problem-solving skills and enhancing their sense of achievement [55] by determining whether the players' solution in the game is correct [81]
19	Augmented reality (AR)	A three-dimensional interactive experience of the real-world environment and computer-generated objects, in which players can interact with each other in real-time [69]
20	Curiosity	Acting as an element that raises players' motivation in engaging in the game [82]
21	Explanation	The interpretation of the social flow experience [50, 56]
22	Rewards	Providing the scores and ranking of the game, which boosts players to accomplish the tasks set in the game [69]

USING DIGITAL GAMES FOR PROMOTING POSITIVE YOUTH DEVELOPMENT (PYD)

The rapid development of new technologies facilitates the design and production of digital games with potentials for educational purposes in disciplines such as education,

medical and health, humanities and social sciences, and many more. The use of digital games in education has a long history. However, the number can hardly compare with that of commercial games for entertainment purposes.

With the support of a funder, the seven games introduced in this special issue were designed mainly for the promotion of five major PYD constructs, namely, social (SC), cognitive (CC), emotional (EC), moral (MC), and behavioral competencies (BC). They can also enhance clear and positive identity (ID), self-determination (SD), self-efficacy (SE), bonding (BO), spirituality (SP), and prosocial norms (PN) among adolescent users of these games. Table 2 shows the name, the adolescent issue addressed, and targeted PYD constructs of each game.

Table 2. Adolescent issues and PYD constructs addressed by the seven DPYD games

	Name of the Game	Adolescent Issue Addressed	PYD Core Competence	Related PYD constructs
1	The Digital Age	Respect for privacy	MC, SC	RE
2	The Integrity Crisis	Integrity	MC, SC	RE
3	The Bullying Storm	BCB	MC, SC	RE
4	The Male-Female Dichotomy	Gender stereotype and biases	BC	ID
5	The Great Thinking Adventure	Think critically and discern wisely	CC	
6	A Journey to Somewhere, to Someone	FRR	SC, BC, EC	SD, ID, BO, PN
7	Live a Meaningful Life	Money and success	BC	SP, SE

Five Themes

The major contents of the seven games can be grouped into five themes, namely, “online and offline interpersonal relationship” (three games); “gender stereotypes and biases” which covers appearance, behavior, occupation, and trait; “think critically and discern wisely” which focuses on cognitive fallacies; “friendship and romantic relationship” (FRR) as well as “money and success.” These themes are chosen because of their relevance to the lives of adolescents in most urban cities. Figure 1 shows the relationships between the issues and the games.



Figure 1. The relationships between adolescent issues and the DPYD games.

Table 3. The intended learning outcomes and related PYD constructs of each game

Name & Issue	Intended Learning Outcomes			PYD Constructs
	Cognitive	Emotional	Behavioral	
1. The Digital Age: Respect for privacy	- understand: - the boundary of privacy; - the need to deal with privacy issues in an honest and careful manner; - the need to respect the privacy of others; - the different ways to tackle bullying - reflect on the choice between friendship and honesty; - understand the necessity of sincere confession; - be aware of different ways of handling threats from classmates	Change from understanding the victim's plight (pity), to caring for the victim (sympathy), and to showing compassion for (empathy) the victim's pain and negative emotions.	- consciously practice honest behaviors; - take appropriate actions to deal with interpersonal conflicts; - reduce the behaviours of escalating bullying incidents; - prevent the worsening of bullying incidents	MC, SC, RE
2. The Integrity Crisis: Integrity	- reflect on the choice between friendship and honesty; - understand the necessity of sincere confession; - be aware of different ways of handling threats from classmates	Change from understanding the victim's plight (pity), to caring for the victim (sympathy), and to showing compassion for (empathy) the victim's pain and negative emotions.	- consciously practice honest behaviors - refuse to perform inappropriate behaviors - take appropriate actions in face of frauds or extortions - do good deeds to their friends - proactively admit one's fault - forgive a friend's wrong doings	MC, SC, RE
3. The Bullying Storm: Bullying and cyber-bullying	- understand - school bullying; - the need of adherence to important personal principles; - the need to seek assistance actively if necessary; - various ways of dealing with bullying - understand their own gender stereotypes and biases in "appearance", "behaviour", "occupation" and "traits"	Change from understanding the victim's plight (pity), to caring for the victim (sympathy), and to showing compassion for (empathy) the victim's pain and negative emotions.	- take appropriate action to deal with interpersonal conflicts; - seek help proactively from the teacher or good friends in face of bullying; - reduce the behaviors of escalating bullying incidents; - prevent the worsening of bullying incidents	MC, SC, RE
4. The Male-Female Dichotomy: Gender stereotype and biases	- understand the 51 cognitive traps; - understand the principles of rational thinking; - enhance the capacity for identifying the cognitive traps; - understand the effective use of thinking ability - understand the personal traits and characteristics of oneself; - learn gender equality and beware of gender issues; - differentiate the levels of friendship and identify features of good friends; - distinguish like from love; - understand the 14 important elements of building, maintaining, and enhancing friendship; - understand the seven stages of love affair	enhance their acceptance of the opposite gender in four areas	- reduce discrimination against people with a distinctive gender profile; - get along harmoniously with the opposite gender as a result of an increased acceptance level	BC, ID
5. The Great Thinking Adventure: Cognitive traps	- understand the 51 cognitive traps; - understand the principles of rational thinking; - enhance the capacity for identifying the cognitive traps; - understand the effective use of thinking ability - understand the personal traits and characteristics of oneself; - learn gender equality and beware of gender issues; - differentiate the levels of friendship and identify features of good friends; - distinguish like from love; - understand the 14 important elements of building, maintaining, and enhancing friendship; - understand the seven stages of love affair	reduce emotional distress in daily life caused by mistakes made	use thinking ability to help others	CC
6. A Journey to Somewhere, to Someone: Friendship and romantic relationships	- understand the 51 cognitive traps; - understand the principles of rational thinking; - enhance the capacity for identifying the cognitive traps; - understand the effective use of thinking ability - understand the personal traits and characteristics of oneself; - learn gender equality and beware of gender issues; - differentiate the levels of friendship and identify features of good friends; - distinguish like from love; - understand the 14 important elements of building, maintaining, and enhancing friendship; - understand the seven stages of love affair	- feel the joy of a reciprocal relationship with friends or partners - reduce negative emotions resulting from relationship problems with peers and partners	- increase desirable behaviors related to strengths of one's personal traits; - reduce undesirable behaviors related to weaknesses of one's personal traits; - get along harmoniously with the opposite gender; - identify and make desirable friends; - practice empathy; - learn active listening; - understand and try effective ways to deal with conflicts; - apply knowledge and skills to handle issues arising from a love relationship	BO, SC, BC, EC, SD, ID, PN
7. Live a Meaningful Life: Money and success	- understand their own view and practice of financial management; - reflect on the values and meaning of life	- enhance their EC in facing life issues beyond their control; - enhance their levels of empathetic competence and care for the community through experiencing the lives of different social classes	apply prudent financial management skills	BC, SP, SE

Intended Learning Outcomes

The cognitive, emotional, and behavioral ILOs of these seven games are described in Table 3.

USING GAME ELEMENTS IN DESIGNING DPYD GAMES

Different game elements were used in designing the seven games. Table 4 shows an initial assessment of the use of 22 game design elements in each of the game. It only represents the views of the author and the main designer of these seven DPYD games. High (H), Medium (M), Low (L), and None (0) were used to indicate the relative strengths.

Table 4. The level of game design elements used in each game

Game Design Element		Use of Game Element in the 7 Games						
		1	2	3	4	5	6	7
1	Challenge	M	M	M	M	H	H	M
2	Collaboration	M	M	M	0	M	H	H
3	Competition	0	0	0	0	H	M	H
4	Complexity	H	H	H	L	M	H	L
5	Control	M	M	M	M	H	H	M
6	Exploration & Discovery	H	H	H	M	H	H	M
7	Goals	H	H	H	M	H	M	H
8	Interactivity	H	H	H	M	M	H	H
9	Low Stakes Failure	H	H	H	H	M	H	L
10	Narrative	H	H	H	0	M	H	M
11	Realism	H	H	H	L	M	H	M
12	Role Play	H	H	H	0	0	H	H
13	Rules	M	M	M	M	H	H	H
14	Scaffolds	L	L	L	H	H	H	L
15	Self-Expression	M	M	M	H	0	H	L
16	Strategy	L	L	L	M	H	M	H
17	Surprise & Uncertainty	H	H	H	0	L	M	H
18	Immediate feedback	H	H	H	H	H	H	H
19	Augmented reality	H	H	H	0	0	H	L
20	Curiosity	M	M	M	L	M	H	M
21	Explanation	M	M	M	H	H	M	M
22	Rewards	0	0	0	0	M	H	H

TOWARDS A PRACTICE MODEL OF USING DPYD GAMES FOR PREVENTION

Effectiveness studies on DGBL focus on two core elements – player engagement/motivation and achievement of ILOs [14], which are also the two major issues – theory and practice – that inform the design and application of DPYD games. The first issue

emphasizes the need for the application of learning theories and game design elements. To achieve ILOs, purpose-built DPYD games must be underpinned by learning theories and game design elements. This chapter gives a brief description of why and how traditional and contemporary learning theories can be applied in designing DPYD games. Moreover, this chapter reviews and provides precise and concise definitions of game design elements which are then used to assess how well these elements are adopted in the seven newly-developed DPYD games. As a necessary condition for effectiveness, these games must motivate students to use the game preferably more than once and they must be more than fun to engage users. As described above, 22 game design elements have been used to engage and motivate target users. The effectiveness of these elements in motivating and engaging target users remains unknown. Future research is needed in this area.

The second issue is the development of a practice model that guides the appropriate use of these seven purpose-built DPYD games for effective prevention. To help teachers and mental health practitioners to make good use of these games, a practice model is presented below. Supported by learning theories, the model is named 'STREAM,' an acronym which is the abbreviation of the following components:

- (1) Scope: Using the games for prevention at primary, secondary, and tertiary levels;
- (2) Tool: Selection of appropriate DPYD games/relevant parts of a game;
- (3) Reward systems: Creation and maintenance of reward systems to promote the appropriate use of the feedback generated according to players' choices and responses;
- (4) Educational processes: Enhancement of players' independent, collaborative, and supportive learning in an environment conducive to deep learning;
- (5) Assessment of learning outcomes: Collection of users' formative and summative feedback;
- (6) Mixed methods of research for innovation: Creating prospects for transformational advance in DGBL to promote PYD.

The STREAM model offers professionals a framework for helping adolescents address common issues and prevent problems by changing their attitudes, knowledge, skills, and behaviors through DGBL. It offers prevention strategies for adolescents, who may encounter intra- and inter-personal problems, with two main pillars of education – learning to be and learning to live together [83]. This model incorporates educational principles and knowledge into strategies to help adolescents prevent problems by promoting relevant PYD constructs. It is believed that this model is equally applicable to other DPYD games. The contents of the practice model are presented below.

The Scope: Enhancement of PYD for Prevention at Different Levels

This set of DPYD games is useful for prevention in primary, secondary, and tertiary levels. For primary level, it aims at preventing users from involving in risky behaviors or getting harmed. For secondary level, these games can benefit adolescents who have experienced mild challenges for some common adolescent problems by providing them with

feedback based on their responses. Regarding tertiary level, students who have these problems can be helped by being encouraged to play relevant games or using specific parts of a game for engagement, initial assessment, and as part of the intervention plan.

Although the games will not save any personal or test data to safeguard privacy, students can be invited to use the print-screen function to keep the feedbacks. The feedbacks can be used for conducting an initial assessment, promoting self-understanding, monitoring their reactions to different conditions, equipping them with skills in handling similar situations in real-life, and documenting changes. For example, to prevent BCB, the first three games can be used. At the primary level, the games can be used in class in which students are asked to choose one of the responses either by casting a vote or inviting one representative to make the choice. To enhance learning, the games can be available for students who have gone through the debriefing after the demonstration. In secondary level, the game can be introduced to a group of selected students who experienced BCB problems in different roles – the bully, the victim, and the bystander. The game helps the professional build up trust and a working relationship with group members, diagnose, and change members' beliefs and behaviors. For tertiary level, the professional may use the game for helping the target students practice assertive behaviors (SC and BC), enhance empathetic understanding (BO and MC), promote self-understanding (SE), and foster resilience (RE).

The Tool: Selection of Appropriate DPYD Games/Relevant Parts of a Game

Most of the seven DPYD games provide branch-out stories that promote curiosity and replay modular [84]. Students can try alternate routes to create an atmosphere for discussion to promote curiosity and maximize learning. The game 'A Journey to Somewhere, to Someone' also allows for multiple entry points at secondary and tertiary levels. Careful selections of the most appropriate entry points which meet the needs of the target players to facilitate learning are important.

Reward Systems: Creation and Maintenance

Reward systems foster intrinsic motivation, promote players' positive and appropriate behaviors, and engage players in learning through the PDYD game [85]. Aside from the built-in reward systems in the game, the creation and maintenance of reward systems to promote the appropriate use of the feedback generated from the game according to players' choices and responses are also important. For example, the games about on-and-offline interpersonal relationships provide six choices that affect how the game story develops and the feedbacks the player receives. Instructors can create a new reward system by making use of the feedback to encourage the player to replay in order to compare the results of different strategies or choices. Alternatively, after reflecting on the contents of 'Character trait' through discussion, instructors may encourage students to set goals for improving the scores of some desirable traits. They can compare and contrast different results by using the print-screen function to boost their learning. Besides, students can try different roles in each scenario to understand the consequences of different choices at the end of the game. This may facilitate students to

put themselves in others' positions. Furthermore, choices are crucial for adolescents according to self-determination theory of motivation [48]. The variety of DPYD games is, in fact, a motivator as they provide choices. Furthermore, the availability of choices during the game serves to engage the player. For example, the design of the first three games about on-and-offline interpersonal relationships provides six choices based on the five communication modes [86].

Educational Processes: Independent, Collaborative, Supportive, and Proactive Learning

For *independent* learning, students are given a DPYD game to play on their own. Motivation and engagement are crucial for self-learning. For *collaborative* learning, students can be encouraged to join a discussion with their peers after playing the game. Instructors may also encourage them to play together with peers to stimulate interactions and discussion to maximize the achievement of the ILOs. For *supportive* learning, instructors can guide students to discuss their experiences so as to consolidate their learning. Instructors can also encourage students to play DPYD games more than once. Moreover, learning is highly effective when learners are motivated, capable of mastering the content knowledge, and practice what they have learned. Instructors may use the 4F techniques (facts, feelings, findings, future) [87] to engage students, promote curiosity as well as encourage a change in strategies and choices when replaying the game. For example, when using the game 'The Great Thinking Adventure,' to facilitate *proactive learning*, instructors may encourage capable students and help them organize competitions or even design the contents for the 51 cognitive traps according to the definitions and examples provided. This approach can benefit more students by updating the contents of the game and create an ethos for the school to enlarge the impact.

It must be added that the learning environment is also vital for learning processes to take place effectively. To enhance PYD among adolescents through adopting purpose-built digital games, a relaxing environment should be provided when instructors introduce and demonstrate how to play the games before students work on their own. It helps raise students' interests and motivations.

Assessment of Learning Outcomes

While DGBL can primarily aim to achieve specific ILOs, it could also achieve secondary learning outcomes [88]. For example, the game 'A Journey to Somewhere, to Someone' with a primary aim to promote FRRs (social-emotional-moral-behavioral outcomes) can also result in a more accepting attitude towards taking literature as a subject (cognitive learning outcomes).

Although the potential for using DPYD games for targeted, curriculum-driven teaching and learning and self-directed learning is enormous, many well-intentioned games have failed to achieve their ILOs [89]. A systematic collection of users' feedback on how well ILOs have been achieved is necessary.

Mixed Methods of Research for Innovation

It is important to create prospects for transformational advance in DGBL to promote PYD through the use of mixed methods of research for innovation. While teachers and practitioners must involve in collecting users' evaluative feedback, researchers should also involve them in conducting quantitative research to test hypotheses and collect formative feedback to improve the game design.

CONCLUSION

This chapter is an attempt to deal with the practice of prevention with the adoption of DGBL. It briefly reviews learning theories and game design elements to illuminate the learning processes and the linkage of theory and practice. Its contribution lies in explaining how DPYD games can be used in the prevention of some commonly-found adolescent issues. Application of DGBL technology and innovation can play an important role to promote PYD. This chapter also makes an initial attempt to generalize some aspects of the theory and practice of DPYD games. It provides a practice model that attempts to integrate learning theories and game elements in the design and application of DPYD games for prevention. Readers will find revised definitions of game design principles (Table 1) that are necessary for further development of the DPYD games.

While this chapter provides initial answers to some application questions by proposing a practice model, some issues need more attention. First, we need to find more resources to develop DPYD games. Second, most professionals who help adolescents are not well-informed of the available DPYD games and their potentials. Some may never have a chance to play such games [89]. Promotion of the efficacy of DGBL and how it can enhance PYD for prevention is needed. Third, we need more research to inform the development of DPYD games and support further game-enhanced prevention. At the same time, we need to know the limitations [90].

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Chapter 347

DESIGNING DIGITAL POSITIVE YOUTH DEVELOPMENT GAMES FOR THE ENHANCEMENT OF ON-AND-OFFLINE INTERPERSONAL RELATIONSHIPS AMONG ADOLESCENTS

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ABSTRACT

To prevent conflicts in peer relationships (PRs) which are commonly found among adolescents, a set of three digital positive youth development (DPYD) games has been developed and made available free of charge for non-commercial and educational use. These games aim to enhance the core competencies of adolescents in handling PRs so as to prevent bullying and cyberbullying (BCB). This chapter describes the design and functions of these three games - 'The Digital Age', 'The Integrity Crisis', and 'The Bullying Storm' which share the same game structure. In these games, students follow different storylines, encounter difficult online and offline situations, and have to choose a response out of six choices in each scenario. Based on students' responses, their patterns of the use of conflict management strategy and their relative strengths on each of the twenty positive psychological constructs will be presented in the form of a percentage at the end of the game. With proper guidance by instructors, these games can help students learn how to handle on-and-offline PRs and BCB. Finally, this chapter discusses issues related to the use of game principles in designing DPYD games and using them for prevention.

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INTRODUCTION

Adolescents often encounter problems with on-and-offline peer relationships (PRs) partly due to the high penetration rate and the inappropriate use of smartphones [1-3] and the internet. In many cases, such problems may end up in bullying and cyberbullying (BCB). Besides, many adolescents grow up in families with few or even without siblings. This means that children and adolescents are in lack of appropriate experiences in interacting, playing, giving and receiving social and emotional support, arguing, fighting and resolving conflicts with siblings. The lack of effective parental supervision and guidance is also a risk factor for adolescents having troubles in their PRs. In 2013, *the Time Magazine* first coined the term the “*Me Me Me Generation*”, which is characterized as over-protected, overly-recognized, and narcissistic adolescents [4]. A reason leading to this phenomenon may be that people starting in the 1970s wished to boost children’s chances of success through enhancing self-esteem, but they accidentally raised their narcissism [4].

The rapid development of information and communication technology (ICT) facilitates a round-the-clock interaction among adolescents. The explosive increase in online connection has shaken their growth and development bio-psycho-social-moral-behaviorly and changed the traditional socialization processes. Adolescents use online communication more often than offline means [5]. As heavy-users of ICT, adolescents enter to an ever-changing cyber-environment, which on one hand promotes opportunities and threatens established social relationships on the other. Compared to their parents when they were young, adolescents nowadays have a much wider connection with people of different background, age, ethnicity, nationality, classes, and from different places. At the same time, they share somewhat similar experiences with their parents in terms of engagement with others physically [6]. The growth of smartphone and social media not only allows people to share information but also provides a platform to induce bullying and harassment [7]. The misuse of social media causes discourses such as bullying, offensive content and hate speech [8]. It was also found that cyberbullying is associated with smartphone addiction among university students [9]. Against this background, evidence-based positive youth development (PYD) programs are designed to help prevent problems facing adolescents. The project P.A.T.H.S., which finances the design and development of these DPYD games, is one of them [10-13].

LITERATURE REVIEW

Many studies report that adolescents encounter problems with PRs. One study found that 57% of adolescents experienced different kinds of offline interpersonal victimization such as bullying or sexual abuse, while 23% of the respondents, aged 10-17 years, experienced online interpersonal victimization like sexual solicitation or harassment [14]. The same study also found that 73% of the respondents who were victimized online also reported offline victimization [14]. Besides, it is reported that adolescents who experienced online sexual solicitation were two times more likely to suffer from substance abuse or depressive symptomatology [14]. Another study found that 42% of college students experienced online interpersonal victimization [15, 16].

Positive Psychological Constructs

Twenty positive psychological constructs, also called character traits were used for providing feedback to promote PYD. They came from the book “Character strengths and virtues: A handbook and classification” by Peterson and Seligman [2]. It describes the VIA classification of character strengths and virtues, where VIA stands for ‘the way’ or ‘the path’ in Latin. It is used as a measurement tool to assess 24 character strengths which are grouped into six areas. In the three DPYD games, we have chosen 20 character traits out of 24, which are appropriate according to the contents and scenarios of the games to help students understand their character strengths and work towards improving their desirable traits while playing the games. A percentage of each positive trait is displayed to illustrate the degree of strength. The strengths of curiosity, love of learning, zest, as well as the appreciation of beauty and excellence are not measured in the games because the stories do not cover these elements. The contents of the 20 character traits are described below [17].

Group A: Transcendence (Gratitude, Hope, Humour, and Spirituality)

Group B: Temperance (Forgiveness, Humility, Prudence, and Self-regulation)

Group C: Justice (Teamwork, Fairness, and Leadership)

Group D: Humanity (Kindness, Love, and Social Intelligence)

Group E: Courage (Bravery, Perseverance, and Honesty)

Group F: Wisdom (Creativity, Judgment, and Perspective)

Definitions of the 20 Traits

The definitions of four traits with an asterisk have been amended because the main theme of these games is only about on-and-offline PRs.

A1 Gratitude*: Know how to get along with others and treat them with respect; appreciate their qualities.

A2 Hope: Be positive; work hard to achieve goals; believe that one can work towards a brighter future.

A3 Humor: Remain calm and undisturbed even when faced with adverse situations; express in an innovative and hopeful way; avoid being awkward; solve interpersonal conflicts

A4 Spirituality*: Have a positive faith in life; work hard at personal growth; and have a realistic plan to achieve goals.

B1 Forgiveness: Be willing to forgive others and give them another chance instead of getting revenge.

B2 Humility: Remain humble of achievements; does not seek attention from others.

B3 Prudence: Be very cautious, never does anything that will be regretted later.

B4 Self-regulation: Do not engage in any unlawful acts; able to think about others, and control emotions.

C1 Teamwork*: Be able to be a good friend, and candidly point out the faults of others.

C2 Fairness: Treat everyone the same way, and not let feelings affect judgment.

C3 Leadership*: Value and maintain good friendships.

D1 Kindness: Care for and get along well with others; value good relationships with others.

D2 Love: Treat others in a friendly way, willing to assist and care for others.

D3 Social Intelligence: Be able to see things from others' perspectives; able to control emotions when with others.

E1 Bravery: Will not back out when facing difficulties; able to speak out even if it might make one unpopular; act accordingly to what one believes in.

E2 Perseverance: Adopt appropriate means to deal with difficulties; persevere and take pleasure in completing tasks.

E3 Honesty: Express candidly, with no pretenses; be responsible for one's own actions and feelings.

F1 Creativity: Able to come up with new methods when dealing with others.

F2 Judgement: Able to consider things from multiple perspectives; objectively make judgments and not be affected by feelings. Change views when presented with new evidence.

F3 Perspective: Very observant; able to suggest valuable views and good advice.

A positive association is found between a person's positive psychological constructs and his/her well-being [18]. Besides, such constructs are suggested to act as one of the sources of positive emotions [18]. Moreover, a significant correlation between the positive psychological construct and the health outcome is reported [19].

Conflict Resolution Strategy

The Thomas-Kilmann Model [20] is adopted in the game design to illustrate the options we have when handling interpersonal conflicts. There are two dimensions in the model. First, the vertical axis, which includes assertive options, represents conflict responses based on our attempt to get what we want. Second, the horizontal axis shows the co-operative options and is concerned with responses based on helping others get what they want. As a result, it creates five basic types of response – competing, accommodating, avoiding, compromising, and collaborating.

First, “competing” is an assertive and un-cooperative approach to resolve conflict. For example, one is standing up for his/her rights, defending a position which one thinks is correct or simply trying to beat the opponent. Second, “accommodating” is an unassertive and co-operative approach. This might take the form of selfless generosity, giving in to another person's orders or yielding to another's point of view. Third, “avoiding” takes an unassertive and un-cooperative approach to conflict by simply not dealing with it. It might take the form of diplomatically sidestepping an issue, postponing it, or withdrawing from a threatening situation. Fourth, “compromising,” which is located at the centre of the model because of

both of its assertive and co-operating approach to a certain extent. Both sides get something but not everything. Lastly, “collaborating,” is the opposite extreme of avoiding, where both parties can come together, reach a consensus, and get what they want if they join hands. It requires developed conflict resolution skills based on mutual respect, a willingness to listen to others, and creativity in finding solutions.

Rahim’s Meta-Model of Conflict Management

Rahim and colleagues [1] pointed out that there is no single best approach when it comes to decision making or managing conflict as agreed among management scholars. Rather than having a specific model for managing conflict, Rahim created a meta-model, which focuses on the conflict styles based on two dimensions: concern for self and concern for others. There are five conflict management strategies or communication modes according to this framework. They are:

Dominating: One party primarily focuses on winning over the other party regarding the subject of concern. He/she often ignores the needs or expectations of the other party in the process.

Avoiding: One ignores and fails to acknowledge or find solutions for a concern that affects him/her and the other party.

Compromising: It involves thinking for the other party when dealing with a conflict, and both parties often give up something to reach a mutually agreed decision where give-and-take occurs in the process.

Obliging: It involves minimizing the differences while highlighting the common grounds to appeal to the other party of concern.

Integrating: It involves being open-minded, exchanging information, seeking alternatives, and studying differences when trying to resolve an issue in a manner that is acceptable to both parties.

In these three games, students face different storylines, scenarios and they have to choose a response from six choices in each scene. These choices represent five different communication styles namely aggressive, passive, submissive, passive-aggressive, and assertive. Students get feedback about their communication modes during a conflict and their personality traits at the end of the game. Instructors can make use of the opportunity to discuss these different modes and how they work in different scenarios. Students can always play the game again and try to choose a different communication style to observe the different outcomes.

GAME DESIGN

Each game has a unique story-line and provides twelve scenarios for students as the story develops. In each scenario, students are given six different responses to choose, and the choice will affect the development of the story accordingly. At the end of the game,

Third, based on the choices, the relative strengths on each of the twenty positive psychological constructs [2] in percentage format will be shown (This will be discussed in details in the next section). Even though some behaviors seem undesirable, they also have positive implications from the perspective of positive psychology. For example, fighting requires a sense of courage without rational thinking while avoidance implies self-restraint which may reduce the chance of deepening a conflict. Students pick their preferred choices in each scenario of the simulation game, where different feedback and scores on the personal traits will be given accordingly.



Figure 3. A typical feedback on the player's twenty positive psychology traits based on their use of different communication modes in the game.

Calculation of the Percentage of the Positive Psychology Constructs

There are 12 scenarios in the games as the story goes on. The player has to make a choice among six options. Two responses are from the competing mode while the other four from avoiding, accommodating, compromising, and collaborating modes. The idea of using animals to represent different communication modes was considered [21]. For example, shark for competing, turtle for avoiding, teddy bear for accommodating, fox for compromising, and owl for collaborating. Using animals as gimmicks may be attractive but it may be confusing and distorting because different cultures may attribute different meanings to animals. For example, a fox may be interpreted as cunning and dishonest and a turtle may have an insulting connotation.

In assigning weightings to different responses for players to choose, the research team first worked on the definitions of all the constructs from positive psychology. After reaching a consensus of the definitions, two team members were assigned to use a 6-point scale (5 being the highest and zero the lowest) to rate each of the response in the game according to the level of the twenty positive psychology constructs. For example, the response "You guys peek on others' private life? Why did you act so despicable?" is given zero marks for the construct of "social intelligence." In the end, each response will be given a score based on how the player responds according to the communication mode used in each scenario. After obtaining all the scores, the constructs with a huge difference of scores between the two members were

reviewed and the scores were adjusted accordingly after discussion. Finally, if there were still differences, the mean scores would be used. Table 1 shows the assigned ratings for each positive trait on each response in one scenario.

Table 1. An example of assigning weighting for each positive trait on each response

Positive Trait	Transcendence				Temperance				Justice			Humanity			Courage			Wisdom		
	A1	A2	A3	A4	B1	B2	B3	B4	C1	C2	C3	D1	D2	D3	E1	E2	E3	F1	F2	F3
Choices																				
I won't do such immoral things! (Competing)	3	3	1	3	1	1	3	3	3	3	2	1	1	2	3	0	3	2	3	3
You are so despicable, going through other's private things! (Competing)	0	2	0	1	0	0	2	2	2	2	0	0	0	0	2	0	2	0	1	1
You're going through other's private things? Why are you so despicable? (Competing)	0	2	0	1	0	0	2	2	2	2	0	0	0	0	2	0	2	0	1	1
I won't join you on such an immoral thing! (Competing)	2	3	1	3	1	1	3	3	3	3	1	1	1	1	3	0	3	2	2	2
Thanks, but I'm not that despicable, snooping through other people's private stuff. (Competing)	0	2	0	1	0	0	2	2	2	2	0	0	0	0	2	0	2	0	1	1
Silently join them. (Avoiding)	1	0	0	1	1	1	0	0	0	0	1	1	1	1	0	0	0	0	1	1
Go closer to take a look, but keep silent. (Avoiding)	1	0	0	1	1	1	0	0	0	0	1	1	1	1	0	0	0	0	1	1
Excitedly join Lilith by her side, and look at the photos together. (Accommodating)	2	1	2	1	2	2	0	0	0	0	2	2	2	2	1	1	1	1	1	1
Reply happily, "Yeah definitely!" (Accommodating)	2	1	2	1	2	2	0	0	0	0	2	2	2	2	1	1	1	1	1	1
"I don't think there's much to see on there, let's watch this crazy video online instead!" (Compromising)	2	3	2	3	3	3	3	3	3	3	3	3	3	3	3	2	3	3	3	3
"Nah, I'm not that interested in him, I didn't know you guys were, till now! Haha!" (Compromising)	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	2	3	3	3	3
His photos must be very interesting, or else you guys wouldn't be this happy. I want to join you guys, but I won't look at other's private things without their permission, isn't that right guys? Class is almost starting, let's just go back to our seats. (Collaborating)	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5

Note: Please refer to the section "definitions of the 20 traits" for the name of each trait.

The Calculation Method in the Game

The game will randomly draw two from the five competing responses and one from the two for the other four communication modes for the player. This will facilitate students to replay the game for better outcomes. A player has to make twelve choices in the game and each choice may include some or all the twenty constructs in the background. Each construct has to be calculated independently in the 12 choices to obtain a cumulative score. For example, if a player obtains the score of 1 (minimum is zero, maximum is 5) in all the 12 scenarios on the construct of “social intelligence” which is relevant in all responses, the calculation using the percentage as a representation will be: $(1 \times 12) / (12 \times 5) \times 100\% = 20\%$. The formula will be adjusted if a specific construct is not relevant in certain situations. It has to be noted that this percentage is calculated according to the choices of the player. Depending on the attitude of the player, the calculation could represent the player’s character. This statement has been included in the instruction manual.

An Illustration

The second scene of the first game is presented below for illustration. The story goes: “During recess time on Monday, Lilith and another classmate are whispering in a corner of the classroom, and there are sounds of laughter from time to time. You get curious, and approach them. You find out that they are secretly browsing another classmate’s phone, looking at the photos on it. At this time, Lilith asks you to join them, how will you react?”



Figure 4. An image captured from the screen on the second scene of the game.



Figure 5. Players are offered six randomly generated choices for the five communication modes.

TEACHING TIPS

Instructors can remind students that the percentages as shown in the personal traits are only calculated based on their choices and the percentages should be used as reference points only. For example, if the percentage of a trait is below 20%, it requires much attention and thoughtful discussion with the students; and if the percentage is 60% and above, it shows that the performance of that trait is excellent and instructors can encourage students to examine what leads to such feedback and reflect on the different responses adopted during the game. More importantly, the scores on different traits vary among students and should not be seen as a representation of students' conduct. Instead, they can only be served as a reference point to help students be aware of the availability of different choices which may affect the overall analysis of one's traits in a simulation game of BCB incidents. Having a higher or lower percentage on different traits does not imply that one is a better person or not. Instructors can clearly explain to students that although achieving a higher percentage is desirable, all traits are positive, and students can play again getting a lower score in certain traits to find what makes the difference. Moreover, instructors may stress that everyone has different personalities and predispositions. Students should be mindful of this and take the result as an opportunity to further understand themselves and reflect on which areas they would want to improve on. Instructors must strongly emphasize that points and scores should not be treated as a means of competition among students, which defeats the purpose of the games.

DISCUSSION

These DPYD games boost several PYD constructs including moral competence, resilience, and prosocial norms. According to Green and Norrish [22], school-based positive psychology interventions are programs which hope to boost students' well-being or build competence within the school context. It is proved that positive psychology is effective in raising students' holistic well-being [22].

Besides, the use of game-based learning is an effective intervention in therapeutic intervention. It is found that the therapeutic board game is proved to help patients to talk about their personal experiences, feelings in a creative way and a comfortable situation [23]. Moreover, an interactive multimedia game called *Lucity* is proved to engage adolescents and facilitate communication regarding sexual violence and other sexual health issues, and thus it proved that game-based interaction is a feasible method for students to acquire new knowledge [24]. Furthermore, Van Lippevelde et al. [25] found that a gamified app is effective to change adolescents' snack intake. It shows that the game-based intervention is an effective behavior change strategy which is attractive for youngsters [25].

There are two issues that deserve our attention. First, in design level, how the design motivates students to learn through playing the game. Second, in practice level, how teachers and human services personnel can maximize the intended learning outcomes.

The following table summarizes the game elements used.

Table 2. Illustration of game elements in the game “The digital age”

Game element	Illustration
Story	A simple matter turns out to be a complicated one because of the misuse of ICT, disrespect for others, and intrusion of privacy
Choices	Players are given 6 Choices at each decision point
Attractive	Use of cartoons and illustrations
Curiosity	The story develops with around 12 scenarios
Real life	The story is based on real-life cases
Adaptive learning	Receive individual feedback at three levels

The game elements are the major components in the application of gamification [26]. Story-telling is proved to be an essential component in gamification applications since it helps enrich barely stimulating contexts, and thus raise people’s interest [27]. There are three story forms which include linear, branching, and modular [28].

Moreover, choices are important for adolescents according to self-determination theory of motivation [29]. A research revealed that the satisfaction of autonomy is positively associated with the intrinsic motivation of respondents [26]. If the options are relevant to players’ interests and goals, manageable, and consistent with the values of the students’ culture, the motivational effect will be enlarged [30]. Since different choices of reaction in online and offline interpersonal encounters may result in different consequences, the game can send important messages which include “You have choices!” or “You can make a difference!”

Aside from it, attractiveness is a crucial game element in motivating students to learn. It is proved that the use of cartoons positively influenced constructive learning, cooperative learning and collaborative learning among students [31].

Furthermore, curiosity is one of the underlying forces for a person to learn [32]. It is found that an individual’s curiosity is positively related to his/her knowledge acquisition [33]. Thus, it is an essential game element during the application of gamification.

Besides, adaptive learning applies computer algorithms to organise the interaction with the learner. It is an educational method which uses computer algorithms to organise the interaction with the learner and deliver customized resources and learning activities to address the unique needs of each learner. A research found that adaptive and interactive digital learning enhances students’ perceived competency and their learning satisfaction [34].

Recommendations for Teaching

The games aim at arousing students’ interests and motivation to learn how to handle online and offline interpersonal relationships. First, instructors choose one of the games to give a brief introduction and demonstrate how to play the games in classes or an assembly. They could draw students’ attention to the different choices available in each scenario which will lead to different endings. The first level of feedback - ‘Reflection and Learning’, displays the result or consequences of their choices. Second, instructors could encourage students to play the games more than once. Students could play different roles such as bullies (i.e., player could choose to threaten to take revenge, edit pictures of the bullied and post it on social media, or hurt the bullies), victims (feeling helpless, keeping quiet, pretending not seeing, and

crying when bullied), or bystanders (watching silently your classmates peeking at the pictures of another classmate's phone without permission) in each scenario and observe different results. Instructors could encourage students to try putting themselves in the shoes of the victim and experience the pain while playing that role. Discussion among students relating to that aspect can arouse more empathy when students are sharing the experiences and their feelings with each other. Besides, students should be encouraged to discuss the strategies to resolve on-and-offline interpersonal conflicts according to the second level feedback, which is an analysis of communication mode according to students' responses in the game with five categories: dominating, integrating, compromising, avoiding, and obliging. Explanations of each term will be given; what the player is like in communicating with others in terms of attitudes, actions taken, and thought processes will be displayed as a percentage under each category. Third, instructors could encourage students to examine and reflect on the contents of the third level feedback, which is 'Character Trait' and set goals to get higher scores on specific desirable positive traits by adjusting their choices in the game. The game makes use of twenty character traits and is presented in the form of percentages. Explanation of each trait is given so that students can understand the meaning of each trait and reflect on their own traits accordingly using the percentage as a reference. Relative strengths on each of the constructs in percentage format based on the choices of students will be shown. It is hoped that students can experience compassion or even empathy in the simulated game settings if they treat the materials as a learning tool rather than merely a game.

The Roles of Instructors, Social Workers, and Students

Instructors play the roles of teaching and facilitating in the learning process. They need to familiarise themselves with the content of the game materials and the relevant teaching units for the particular class (Grade 7 to Grade 9) to fully utilise the teaching materials and achieve the purpose of the game. This will be further elaborated in the individual game section in later sections. Instructors need to be aware of the technical aspects involved in the operation of the games and thus, provide support to students if they come up with issues relating to those aspects. Therefore, instructors need to know how to use basic ICT tools and media to guide students through the teaching materials. They could explain the teaching and learning methods and strategies with the whole class, demonstrate part of the games, and allow students to use the teaching materials on their own after class.

The role of the instructor includes not only planning the lessons, but also facilitating learning and discussion in class, answering students' questions, and managing the class time to fully utilize the lesson to achieve the goals of each class. When time is a concern, instructors can encourage students to participate and work on the games on their own so that they can have their feedback and questions ready for discussion in school. Also, those topics and scenarios which are of more interests to students can be allocated more time for students to express their areas of concerns and opinions for further discussion in class i.e., cyberbullying. Instructors can have students discuss the game in groups, and pay attention to any concerns and disagreement they have in responding to certain scenarios. Thus, they can then facilitate discussion and provide guidance for students to engage their thinking processes from different perspectives.

Social workers and counsellors can use the game materials when working with students who have been facing those issues in their daily lives. Of course, there is no way we can look at students' responses in the scenarios due to confidentiality and the software design. However, social workers can invite students to play the games and discuss with them about their responses, and issues they are facing in their lives regarding bullying for example. Students can be encouraged to compare different outcomes of the ending in the game by choosing different responses. It can be done by saving the feedback of each stage in the game using the saving screen function or printing out the page of feedback. Also, counsellors can make use of the teaching materials for individual or group counselling.

Students have a high degree of autonomy in the learning process. They should take full responsibilities of their learning by playing the games in their spare time after school, deciding on what aspects they want to learn and which areas they want to improve, as well as engage in meaningful discussion with their peers on issues raised in the games. The goal is to achieve peer learning; students understand each other's different responses in certain scenarios in the games, and be ready to engage in meaningful and purposeful conversations of the topics.

All these three games are targeting the constructs of moral competence, social competence, and resilience. Apart from some universal points shared by the three games categorised under theme 1, each game has its unique characteristics, story-lines, and objectives to achieve. They will be displayed in the following sections one by one to help schools and organisations make better use of each game on its own.

Teaching Points

Some adolescents use cyberbullying to humiliate, threaten and harass others. In the process, it always causes harm to the victims psychologically and mentally in their daily life [35]. Instructors could discuss with students how to distinguish right from wrong when faced with cyberbullying incidents. There is always the option of reporting the incident to teachers or social workers. More importantly, students should be reminded to stay firm and refuse to participate in any cyberbullying activities.

Instructors could encourage students not to publish anything that is not in accordance with facts to avoid hurting others; do not be an instigator; never gather others to participate in cyberbullying; advise others who participate in cyberbullying to stop their bullying behaviors; do not take revenge for others who are being bullied, but immediately seek help from teachers and social workers; and maintain an objective and neutral attitude in handling information on the internet.

The games arouse students' attention to properly handle BCB which are common phenomena on and off campus. Most students have experienced being one of those roles as the bully, the victim or the bystander, and it is not difficult to recall what those scenes are like and how they felt. Instructors are in a good position to bring out the importance of choice, and how different responses may lead to a more desirable and fairer outcome to all parties. It does not help by avoiding, arguing, or fighting with the bully, and students need to take actions such as seeking help from social workers or discipline masters when a bullying incident occurs.

CONCLUSION

To summarize, this set of three games has four major contributions. First, they provide knowledge and skills for adolescents in handling peer pressure properly. Second, they offer choices so that players can learn vicariously and use the trial-and-error strategy in a simulation game. As there are male and female versions, the principle of gender-sensitivity has been observed. This will also attract adolescents to try the two versions for better learning outcomes. Third, they create chances of cooperative learning that encourages support and open discussion rather than didactical communication and competition. The game design maximizes the positive effects of the reciprocal relationship among peers. Fourth, they demonstrate how to use game elements to design DPYD games in preventing fragile PRs from turning into BCB incidents. By helping adolescents review their communication modes and positive traits critically and substantially, it helps promote PRs.

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Chapter 348

A DIGITAL POSITIVE YOUTH DEVELOPMENT GAME TO PREVENT INTRUSION OF PRIVACY

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ABSTRACT

This chapter presents a brief literature review on the issue of intrusion of privacy among adolescents followed by a description of the project P.A.T.H.S. which sponsored the design and production of a digital positive youth development (DPYD) game to strength moral competence, social competence, and pro-social norms among early adolescents. It then describes how it can be used to promote respect of privacy in the use of information and communication technology (ICT) as an important component of media literacy. A detailed description on how to make the best use of the game together with the use of related teaching units of the project P.A.T.H.S. for primary prevention is given. To demonstrate the potential impact, a male and a female young users from China and the United States were invited to play and comment on the game design and give feedback in terms of perceived effectiveness. A discussion of how to use the game for secondary prevention is also presented.

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INTRODUCTION

Early adolescents have entered the digital age since early childhood. Their experiences of interaction and connection with others have been transformed by the frequent use of information and communication technology (ICT). The face-to-face physical contact meet one another has reduced drastically to texting or video calling due to the advancement and availability of ICT. This phenomenon is particularly evident in our youth population, not only locally but globally as well. The number of social media platforms and messaging applications is rising at an alarming rate considering the high number of young people using those platforms. Online social groups have become a part of their identity. The inadequate media literacy for children and early adolescents is one of the major concerns for both parents and educators. Teens are easily attracted by the new technology and the search for identity and belonging in their peer groups. It could put them at risk of disclosing their personal information to others and even strangers, who might have bad intentions. Information such as their names, age, gender, home address, school attended, as well as pictures of themselves and family and friends they posed could be obtained by others if they are not careful in the process of sharing information. The consequences can be severe – misuse of personal data, stolen identity, financial loss, harassment, or victims of sexual crime.

This chapter first outlines the change of mode of communication and interaction, and we can easily connect to someone thousands of miles away with a click on the phone. It is exceptionally true for our adolescents, who spend a great deal of their time on social media on a daily basis. The literature on the issues of privacy invasion revealed insufficient awareness of privacy protection as well as media literacy. The research team has, therefore, designed the game, ‘The digital age’, to bridge the gap of this inadequacy. The pilot of the game was locally and elsewhere welcoming. Positive feedback and constructive recommendations were received to help improve the game features. It is hoped that more PYD games will be used to educate students on the importance of this matter and prevent the intrusion of privacy and misuse of personal data.

LITERATURE REVIEW

The means of communication and maintaining friendship has changed drastically over the past fifteen years to devices with internet connectivity. We are now able to interact with millions of people with different backgrounds all over the world and receive instant information behind the screens. However, it also decreased the quality of interaction that led some of us completely incapable of carrying out a normal and meaningful conversation or interacting with other people in person. It is because of the growing inability to read social cues and body language, as well as the increased dependency of using more simplified written language. The increased use of social media and messaging service in recent years has also taken us to the hidden risk that can endanger our personal safety and well-being – privacy concerns. People are getting more used to meeting new friends and sharing their everyday activities through social media networks. They may also upload their sensitive information to their personal profile, which is often required for online service usage, with the massive data and messages stored online in the cloud of the social media network and messaging

companies. Choi, Park and Jung [1] conceptualized a phenomenon called privacy fatigue, a sense of weariness toward privacy issue for users who believe that there is no effective means of managing their personal information on the internet. In 2014, 500 million Yahoo user accounts were compromised with an involvement of more than 1 billion users [2]. The unguarded practice of diminishing the potential risk to information privacy can lead to the violation of privacy boundaries or privacy security breach by our friends and anyone on the internet.

The influx of social media networks and messaging services have been fully embraced by adolescents for their own social purposes and the exploration of their identity. In a report published by Common Sense Media, the percentage of adolescents checking their social media networks for more than once a day has increased from 34% in 2012 to 70% in 2018 [3]. With more than 81% of adolescents aged 13 to 17 reported that social media makes them feel more connected to what is going on in their friends' lives, they often associate their social media use with positive rather than negative emotions [4]. This age group is particularly linked with a higher risk of exposing their personal and sensitive information due to the insufficient awareness of the management of privacy. For example, there was a television interview of a female student concerning about revealing personal information on Facebook reported by Barnes [5]. When the student was asked to show her personal Facebook page, it contained all the information about her home address and phone numbers. It is clear that she already revealed too much personal information, whether or not she was attentive to her level of privacy protection of the social media networks. However, in a study that examines the tendency of adolescents sharing their personal information on social media networks in public or private profiles, females were 1.5 times more likely than males to have their profile set to private, while age did not indicate any significant difference. The decision in keeping their information public or private can bring negative impact to students as schools, college officers, and future employers are reportedly checking these social media networks to learn more about the potential background of future students and employees. Personal and sensitive information and pictures revealed online can negatively impact the perception of students.

The frequent use of online media platforms can also lead to other psychological issues that have been widely discussed in recent years. "Fear of missing out" (FoMO) originates from social psychological deficits in people's competence and relatedness needs. It is a pervasive apprehension that others might be having rewarding experiences from which one is absent, and characterized by one's desire to stay continually connected with what others are doing [6]. It was found that adolescents with a high level of FoMO used Facebook more intensely and had the feeling of stress when not connected on Facebook [7]. The frequent presence on Facebook and FoMO was related to problematic Facebook use severity [8].

Tension and conflicts among friends may happen on many occasions involving the misuse of ICT. When adolescents found that they were not being invited to activities or events by their close friends, they are likely to experience some hard times, and perhaps, believed that they are being left out on purpose. Sometimes fabricated information, pictures, or even videos of someone would be sent to different groups in social media networks without the awareness and consent of the person involved. Furthermore, they may get bullied for revealing their personal information online and being teased for an act that was supposed to be personal and private. The inconsistency with the common norms in school or social circles can lead to social bullying. It appears to be a matter of weighing of perceived benefits between committing to online social networking and risks of disclosing personal information

[9]. The common strategy of safeguarding personal and sensitive information in private is to decrease profile visibility by restricting limited access to friends only and block access to strangers [9, 10]. Improving their awareness of the underlying risk of mismanaging their privacy protection is a good strategy to warn students of its potential harm. It could lead to the misuse of personal data and harassment by other parties.

The need for protection and respect of privacy is an important issue for all, especially for children and teens. It is an important part of media literacy which is considered as one of the 21st century skills. For this purpose, a digital positive youth development (DPYD) game was developed.

GAME DESCRIPTION

This is the first game of a series of three closely related games that share the same theme of on-and-off-line interpersonal relationships. They are designed to support the P.A.T.H.S. project as electronic teaching and learning resources.

The P.A.T.H.S. to Adulthood

Sponsored by the Hong Kong Jockey Club Charities Trust and co-organized by the Social Welfare Department, the Education Bureau, and a research team comprising academics from five universities in Hong Kong, the “P.A.T.H.S. to Adulthood: A Jockey Club Youth Enhancement Scheme” project was initiated in 2004 to provide primary and secondary prevention through enhancing of positive youth development constructs. The project was a curricula-based intervention program focusing on fostering adolescents’ psychosocial competencies, developmental assets, healthy relationships, and their well-being. Throughout the program, holistic development is promoted among adolescents to better prepare them to meet various challenges in their paths to adulthood. Up to 2018, more than 284,400 students in 320 secondary schools have participated in the project. More than 7,000 teachers and social workers have benefitted from the training.

Research showed that the program was efficacious in addressing peer and individual risk during adolescence [11]. Supported by evidence, positive feedback has been received since the launching of the P.A.T.H.S. Participating schools appreciated that the program’s invaluable experience brought meaningful and positive changes to the development of youths [12]. It is clear that the reference materials of the project would continue to give precious contributions to the education and social welfare sectors incessantly. The project was recognized by the World Health Organization as an evidence-based program in one of the seven strategies for ending violence against children [13] and one of the three evidence-based programs for promoting life and social skills in adolescents [14].

Game Story

Players are given an incident of disrespect of personal privacy by a classmate on a social media platform. They have to choose a response out of six different options as the storyline

develops. Feedbacks on three levels are provided to the player at the end of the game for self-reflection and evaluation.

Targeted Participants: S3 Students

The related teaching units and constructs of the game (will be elaborated later in this section) especially the foundation and knowledge of the issues of the modern digital age can start at S1 (Grade 7). It is essential to instil the concepts and the content gradually so that students can further build their knowledge on previous learning when they advance through the junior high school years. Using selected teaching units on targeted participants serve the purpose of preventive education. For this game 'The digital age', a teaching unit of 'Lying or Not' is designed for S1 (Grade 7) students. Two other units, 'Unresolved' and 'A blog post a day' are designed for S3 (Grade 9) students. It not only consolidates the information they received previously but also introduces related subject matters under the same theme to help students see the bigger picture of the complexity of the digital age. The time needed for demonstrating the game is about 10 to 15 minutes.

Game Contents

The game highlights the issues created through the misuse of technology and the invasion of privacy, which is a common phenomenon in today's world. It examines the importance of honesty in the context of cyberbullying. Advanced technology allows us to take and share photos or messages with others through social media instantly. However, as efficient and convenient as it is, misuse of information and communication technology (ICT) could easily lead to abuse, dishonest and criminal behaviors, such as infringement of rights, social media fraud, bullying, online dating traps and technology crimes related to online games. Therefore, honesty is a very important principle in this game. Instructors should this point out. Students can pick either the male or female version in the game.



Figure 1. An image captured from the screen of the game.

Objectives of the Game

There are various objectives of the game. First, on the cognitive aspect, it aims at helping students understand the boundary of privacy, the need to deal with privacy issues in an honest and careful manner, the need to respect the privacy of others, and that there are different ways to tackle bullying. Second, on the emotional aspect, students can change from understanding the victim's plight to caring for the victim (sympathy), and to showing compassion (empathy) for the victim's pain and negative emotions. Third, on the behavioral aspect, students can consciously practice honest behaviors, take appropriate actions to deal with interpersonal conflicts, reduce the behaviors of escalating bullying incidents, and prevent the worsening of those incidents. Instructors should encourage students to use the game repeatedly and observe the results generated from different responses. In this way, it stimulates their thinking processes and makes them aware that they have choices, and it will lead to a different outcome accordingly. That is when learning a new way of response or changing a behavior starts to emerge.

Game Design

Based on a campus story, students play the role as the main character, who has to handle interpersonal conflicts when his/her privacy is invaded by classmates. The story consists of different scenarios and develops differently according to the responses of the player. Players have six responses to choose from in each scene.

The first level feedback is based on students' choices during the early stage of the story when a classmate sneaks a peek at another student's mobile phone and the ending (the tenth episode of facing the bullying). The second level feedback presents the player's pattern of handling interpersonal conflicts. The third level feedback presents the calculated scores of the twenty positive psychological constructs that reflect the choices of the students.

For detailed description of the game design, please refer to chapter 3.

Game's Storyline

Regarding the learning process, students are given a situation where he/she is bullied by a classmate on a social media platform at the beginning of the game. Rocky and Lilith (the male/female main characters) are very popular in class but often abuse the use of ICT and invade others' privacy. As a player, students are tempted to join them and have to make a difficult choice on whether to maintain their friendship with the bullies or stick with their integrity and honesty. Students are given six different responses to choose from in various scenarios as the story continues, such as peeking on other's phone and social media site, posting other's photo with no permission, and bullying and teasing friends on a group chat. Different scenarios and options are presented for students to choose, and the story develops according to the choices they make. In other words, their choices directly affect the outcome and the ending of the story. For feedback, the first level feedback will be given according to an early stage of the story when a classmate sneaks a peek at another student's mobile phone.

The ending is around the tenth episode when students face the bullying incident directly. The second and third level feedback will be provided at the end of the game on the players' pattern of handling interpersonal conflicts and their personal traits.

Tips for Instructors

Instructor needs to familiarize himself/herself with the storyline, the teaching points, and the plot of the game. They can remind students to pay special attention to the issues surrounding violating others' privacy and disrespecting others throughout the game. There are plenty of places in the game where instructors can pause the game/game demonstration to dig deeper about the issues with the students in the form of class or small group discussion if time allows. For example, the instructor may inspire discussion about making difficult choices between maintaining a relationship and being honest in Scenario 2 (when the player was asked to join Luke/Lucy to browse through the photos of another classmate's phone without consent). Questions that can be used to generate discussion throughout the game include: As a friend, would you dissuade your friend from the dishonest behavior? If your friend tried to dissuade you from dishonest behavior, would you stop the behavior and admit to your faults? Did your final decision effectively protect your personal rights to privacy as well as resolve conflicts with others? If not, how could you improve the situation?

PYD Constructs and Related Teaching Units of the Game

This game is suitable for use together with one or more of the three units listed in Table 1. The PYD constructs behind are moral competence (MC), resilience (RE), and social competence (SC), prosocial involvement (PI) and prosocial norm (PN). Table 1 summarizes the constructs and their related teaching units in various classes.

Table 1. PYD constructs and the names of the related teaching units

Game	Adolescent Issue	PYD Construct	Curriculum Unit Code and Name	Grade
Digital Age	Disrespect of privacy; Inappropriate use of ICT	Moral Competence (MC)	MC1.2 / IT1.1 'Lying or Not'	7
		Resilience (RE)	RE3.3 / IT3.1 'Unresolved'	9
		Social Competence (SC)	SC3.4 'A Blog Post a Day'	9

The curriculum of the P.A.T.H.S. Project has been revamped twice since 2009. The constructs and their illustrations in different teaching units are displayed in a set of concept maps. A total of 289 concept maps for all the teaching units and constructs can be found at <http://www.cityu.edu.hk/ss/pltr/ty/new/en/enter.html>. After the second revamping, five themes of adolescent issues were developed. They are Anti-bullying Education (AB), Anti-Drug Education (AD), Internet Use Education (IT), Money and Success Education (MS), and Sex Education (SX). All the teaching materials in the revamped teaching units can be accessed on the P.A.T.H.S. website (<https://www.P.A.T.H.S..hk/en/>).

In this section, the construct of moral competence, resilience, and social competence are displayed with different sets of concept maps to further explain how the concept works in relation to the theme and scenarios in the games.

Construct: Moral Competence

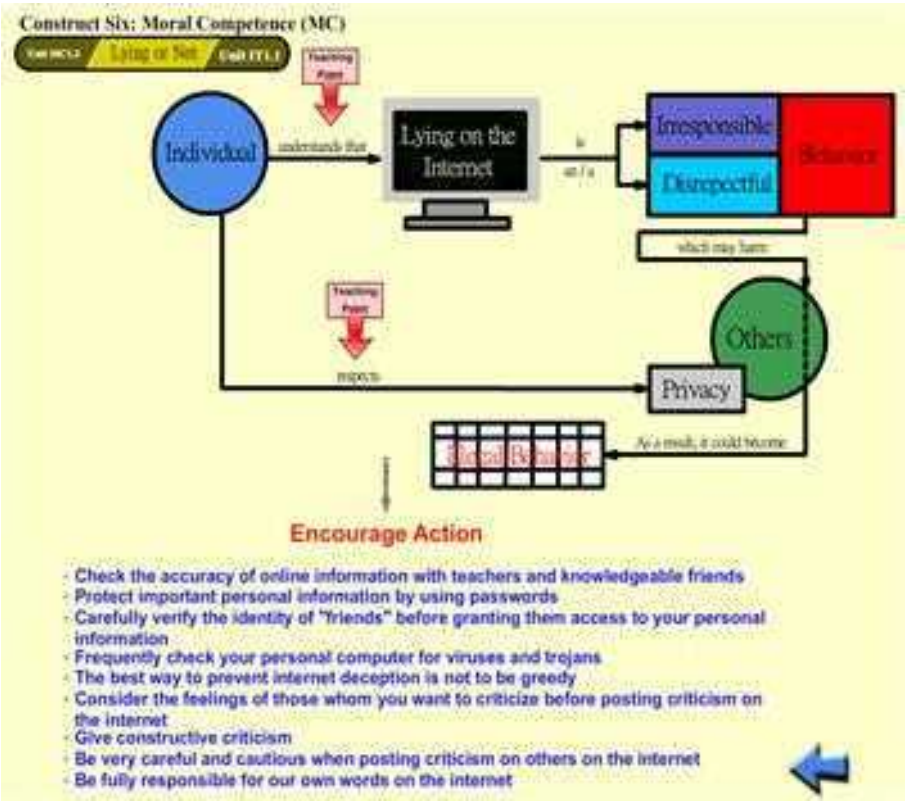


Figure 2. The concept map of Unit MC 1.2 (IT 1.1) ‘Lying or not’.

Teaching Points

Living in the era of technology, individuals can easily use the internet in a reciprocal manner. At the same time, issues of honesty when surfing the net arises. It is of dire importance for individuals to understand that lying on the internet is an irresponsible and disrespectful behavior. If it is not handled carefully, it may even harm the privacy of others and lead to the commitment of illegal behaviors. Knowing such adverse consequences, preventive measures should be taken so that individuals will learn to respect privacy.

Instructors should encourage individuals to check the accuracy of online information with teachers and knowledgeable friends. To further protect personal information, individuals should protect important personal information by using passwords, carefully verify the identity of ‘friends’ before granting them access to personal information and frequently check

their personal computers for viruses and Trojans. Finally, we ought to develop a positive mindset for individuals when using the internet. This includes having a non-greedy attitude and an empathetic mindset when posting criticisms. Individuals must carefully and cautiously consider the feelings of those being criticized before posting the criticism online, which is preferred to be constructive. Lastly, instructors should remind individuals that they are fully responsible for their own words on the internet.

Construct: Resilience

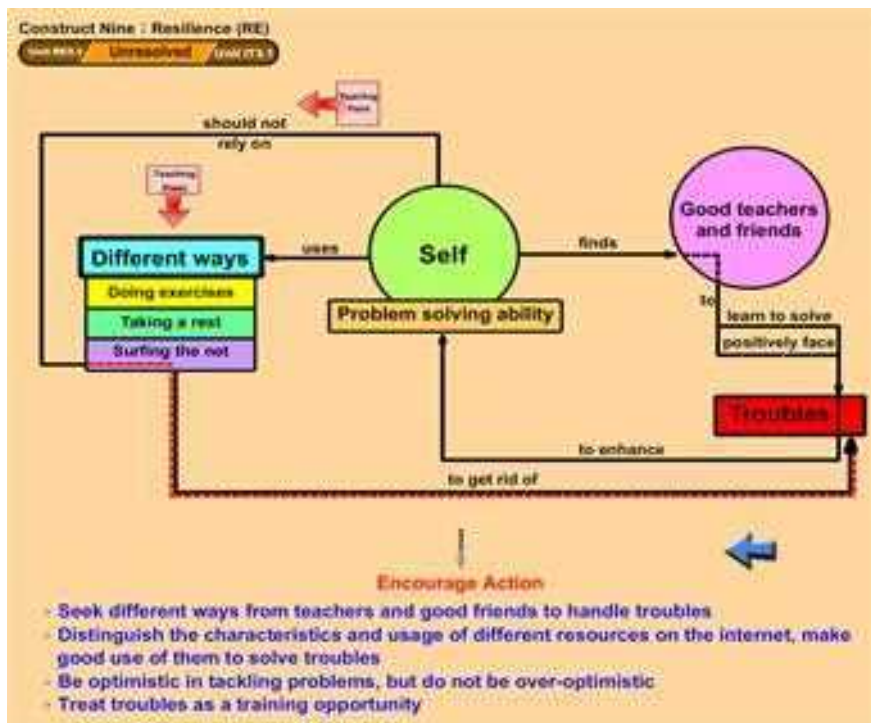


Figure 3. The concept map of teaching Unit RE3.3 (IT3.1) 'Unresolved'.

Teaching Points

The appropriate use of self is an important element when tackling issues of ICT. Individuals should not purely rely on surfing the net to get rid of all troubles. Instead, they are advised to use adaptive ways to solve problems, such as doing exercises and taking a rest. The problem solving ability could be enhanced by making use of individuals' social circles. In face of a problem, they are encouraged to seek help from teachers and good friends. Through interacting with them, individuals will gain insights, thus gradually learn to solve and positively face their troubles. Instructors should motivate students to distinguish the characteristics and usage of different resources on the internet and make good use of them to solve problems. Students should be optimistic in tackling their problems and treat them as a learning opportunity.

Construct: Social Competence

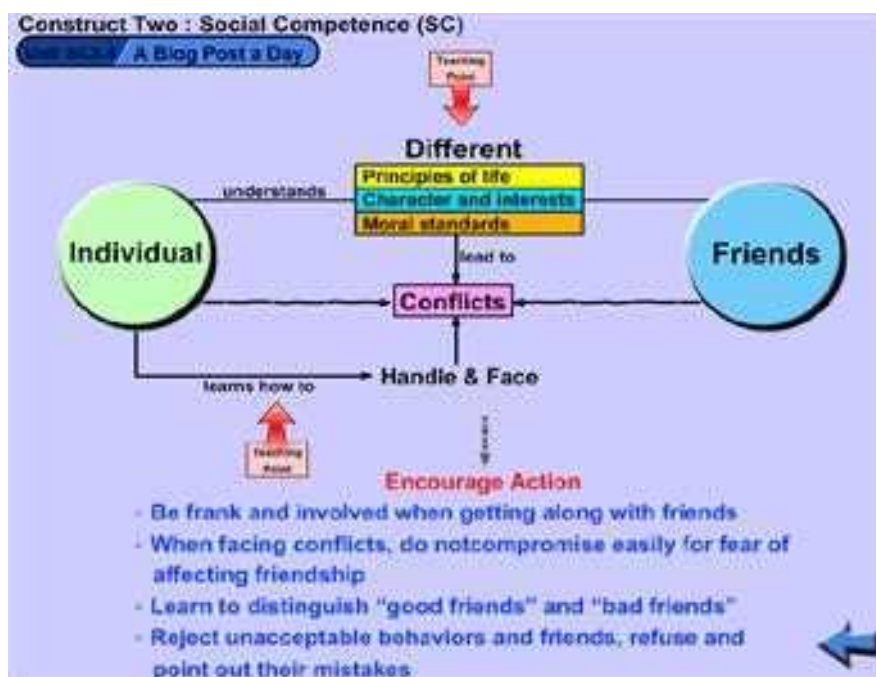


Figure 4. The concept map of teaching Unit SC3.4 'A Blog Post a Day'.

Teaching Points

Because of individual differences in principles of life, characters, traits and interests, and moral standards, there are conflicts in our inter-personal relationships with others. In the above teaching unit, students are guided by the instructor in class to discuss how to face and handle those conflicts and more importantly, to prevent intrusion of privacy. Students are reminded to maintain an honest relationship with their friends. When conflicts occur, students should never compromise their integrity and personal private information for fear of affecting the relationship. Through practising with the guidance of an instructor, it is hoped that students can learn to distinguish good friends from bad friends, and choose the appropriate action to protect one's privacy as well as others.

USER FEEDBACK – PERSONAL REFLECTION

After playing the game, a Chinese girl aged 15 studying in an international school in Shanghai wrote the following reflection. Parental consent to play the game and publish her views were obtained.

"I think that what I learned from this game is that there are multiple ways to deal with social problems regarding cyberbullying or in-person bullying, and most of them are not always 100% good or bad. Before playing this game, I thought that I would be able to make a clear distinction between what would be the most 'perfect' solution, but throughout the game, I had to really consider the pros and cons of all the answer choices because many of them seemed to be good solutions initially. Another thing I learned was that even if you pick what seems like the better solution in your eyes, it may not work immediately. In this case, you can reevaluate whether or not the solution is effective, then change it or use it again. In my case, I clicked on several solutions that had the same kind of 'attitude' in the answer, and that eventually led to the conflict being resolved." (Case No: 25)

The following is written by a male young adult aged 19 studying at college in the United States.

"I think the takeaway that I got from this game is that bullying can happen both in real life interactions and in digital environments. However, my first impression was that the game was on just bullying. However, I realize this might be a result of the environment that I have grown up in and technology is an integral part of my life. The intended audience probably has even more exposure to tech than me. Therefore, an improvement would be to emphasize that knowing how to interact online and in person are very different skills. The game should explicitly state the direct consequences and responses of the characters as a result of the player's individual choices. Maybe state at the end that there are different social norms in these environments." (Case No.: 27).

DISCUSSION

Adopting PYD games in the school curriculum has been proven effective and constructive according to our findings. Issues such as invasion of privacy and cyberbullying have been the subject of research interests for a long time. Literature has documented those issues and interventions in different parts of the world. As internet usage is on the rise in our youth population, so does the chances of potential risks they expose to daily. The consequences can be grave if they are not educated on those risks. The attributes of the PYD approach and the characteristics of the prevention science approach are compatible and could supplement each other [15].

DPYD games could be included in primary prevention programs to tackle issues that students, parents, and educators have been facing, such as respect of privacy and proper use of ICT. DPYD games in the Asian context have been limited as Shek and Yu [16] found only 14 programs out of 63 targeted the Asian youth population. Project P.A.T.H.S. has been leading the progress in continuing to develop games that serve as primary prevention to cater to both the local and international needs. Users have commented positively about the game, 'The Digital Age' and its benefits to them. Scenarios in the game provide a safe place for students to try out different responses to a potential situation they could face in real life circumstances. They receive different feedback according to their choices of response, and instructors and students are encouraged to discuss the outcomes of various choices, such as the pros and cons of them.

The pairing up of positive youth development constructs and their related teaching units give instructors further support in terms of resources and materials to consolidate the lessons learned in the game according to the students' levels (S1, S2 or S3). For example, different constructs of the game, such as resilience, social competence, and moral competence can be grouped under the subject of anti-bullying and internet use at a different level. The illustration

of concept maps makes those relationship visual and easy to comprehend, and thus, facilitates the teaching of those inter-related constructs at the cognitive level. The call for actions in each teaching unit serves as a conclusion for students to ponder on ways that they can practice what they have learned in the unit and the game to prevent intrusion of privacy.

CONCLUSION

This chapter demonstrates how school instructors can utilize the game to promote the respect of privacy and introduce media literacy in secondary school classrooms (Grade 7 – Grade 9). User feedback was received and analyzed for evaluating the outcomes of the game. A brief introduction of the topic, a description of the game, and its relationship to the P.A.T.H.S. project (Hong Kong) were laid out in this chapter. Users' qualitative comments were included, followed by a discussion on how to best adopt the game for secondary prevention. This chapter shares the process of designing and adopting a game, derived from theories, with the academic world to denote the effectiveness of gamification in the curriculum.

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Chapter 349

A DIGITAL POSITIVE YOUTH DEVELOPMENT GAME FOR PROMOTION OF INTEGRITY IN A DIGITAL WORLD

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ABSTRACT

Early adolescents are often influenced by their peers to engage in risky behaviors which include deceptive behavior in families and schools. Lying has been studied for centuries and is usually seen not a serious problem unless it becomes habitual, compulsive, remorseless, or when it is complicated by the co-occurrence of other risky behaviors such as skipping school or forgery. From the preventive perspective, we can strengthen adolescents' moral and social competences through game-based learning (GBL) and positive youth development (PYD). A digital PYD game is designed to attract and engage adolescents in examining and experimenting consequences of deceptive behavior in a non-threatening and manner. It aims at promoting moral decision making through simulations and extensive feedback. It is available for free use as an electronic

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teaching and learning resource. This chapter reviews relevant literature, followed by a brief description on the game design, and its relationship to the Project P.A.T.H.S. which is recognized as an evidence-based prevention program by the World Health Organization [1]. Two respondents from different gender, age, education, and cultural backgrounds were invited to play the game and give comments on their experiences. Based on the users' feedback and the literature, a discussion on how to make the best use of the game together with the related curriculum units for primary and secondary prevention is presented.

INTRODUCTION

Lying is common misbehavior for students. Most parents think that their children lie to get or avoid something they want or do not want to do. Children may develop an unfavorable mindset and attitude when telling lies becomes habitual through reinforcement and observations of the consequences of lying [2, 3]. In schools, students sometimes tell lies to their teachers and school prefects [4, 5]. The issue is getting more serious in the digital era [6]. According to a survey in 2009 [7], lying about being ill to skip school or work is one of the ten most common forms of misbehavior of youths in Hong Kong. Lying behavior becomes a major concern when it is accompanied with other risky behaviors such as skipping school or forgery. In a digital world when most adolescents are connected through digital means, the issue of lying will easily become complicated as the problem may magnify as it goes on-line. The issue may even lead to bullying and cyberbullying (BCB) because skipping school and forgery are considered as major deviant behaviors and could become excuses for blackmail. Importantly, however, making use of the very same social learning process to reinforce normative and prosocial behavior among early adolescents should be promoted. Against this background, a digital positive youth development game is designed and developed.

LITERATURE REVIEW

Lying refers to a person making a false statement with the intention to deceive others [8, 9]. When toddlers (ages 2 to 3) engage in pretend play, they start to develop the ability to make factually untrue statements [10]. As children grow older (3-8 years), making a false statement involves executive functioning and conceptual moral understanding abilities. Recent theory-of-mind research postulates that there are first- and second-order belief understandings [11]. The initial false denials of a child are associated with his/her inhibitory control and the first-order belief understanding, while the maintenance of false statements is associated with his/her second-order belief understanding [12]. On top of executive functioning, conceptual moral understanding and theory-of-mind understanding, other social and cognitive correlates of young children's lying behavior include age, intellectual and language abilities, parenting and disciplinary styles, as well as cultural contexts [3, 13-15].

During middle childhood (ages 9-12 years), children tend to lie more than those in early childhood [16]. Since the lying behaviors are more cognitively demanding than telling the truth, the lie error rate for children declined with age [16].

Adolescents have the highest lying frequency among all age groups [16]. The sophistication of lies is closely associated with adolescents' executive functioning skills [17]. Deception is moderately correlated with parenting styles, parent-child relationship, and behavioral and emotional problems of adolescents [5, 18]. Early adolescents usually lie to their parents but seldom to their friends [5]. According to Cumsille and colleagues [19], parental warmth is negatively correlated with adolescents' lying. It was found that a better parent-adolescent relationship is associated with less lying as youths with close relationships with their parents will have less need to lie [20]. Moreover, poor relationships with parents may reinforce adolescents to involve with peers who tend to engage in deviant behaviors and increase the propensity to tell lies [21].

Peer Cluster Theory

Numerous studies have identified contributions of friendship to a child's social, moral, emotional and cognitive development through perspective-taking, cognitive flexibility, conformity to desirable social norms, resistance to peer group pressure, making close friends, as well as learning through vicarious experiences and verbal persuasion. The processes of peer influence and peer pressure are not easy to delineate and more often confusing and ambiguous [22]. Many youth work experts suggested studying peer pressure and peer influence by peer cluster theory [23]. The theory examines the interactive process that affects youth decision making, conformity to norms, and acquisition of deviant values. When a teenager is asked by a friend to do some inappropriate things, he or she may conform in order to maintain the friendship and thereby making mistakes together. Therefore, the conflict between maintaining friendship and integrity is worthy of reflection and learning. Peer pressure happens when an individual or a peer group encourages others to change their values, attitudes, or behaviors in order to conform to those of the influencing individual or group. Peer pressure may become a sufficient condition for the onset of bullying behavior if an individual refuses to follow.

Integrity

In order to obtain the acceptance by peers and to maintain a social position within the peer group, adolescents are often influenced by their peers to engage in behaviors that were reinforced to conform to the expectation of a social group [24]. When adolescents were asked to do inappropriate things that contradict with their personal values and beliefs, the decisions and adjustment of following their moral integrity are vital in maintaining their interpersonal relationships, and as a result of self-awareness in response to the circumstances. Taking responsibility and maintaining honesty to oneself allows the person to understand and view the full picture of the situation that untangle the misunderstanding and promote strong moral principles.

From a positive view, usually, adolescents can differentiate socially desirable and undesirable behaviors. In a study, some vignettes showing internalizing and externalizing behavior problems were shown to adolescents for them to rate. It was found that adolescents

could recognize the behavior problems of vignette characters and they are likely to approach and like those who did not reveal any problem than those who showed externalized behavior problems. [25].

From Isolation to Victimization

To be independent honest to oneself requires lots of competencies and support. Being isolated is an important risk factor for being bullied. Despite the fact that all bullies were disliked, social status and feelings of rejection and humiliation are strongly related to aggressive behavior, suggesting an adolescent's social status may affect his/her tendency in doing aggressive and bullying perpetration behavior [26-28]. Bullying perpetration is constant aggressive behavior towards a person or a group of people. Olweus [29] defined bullying perpetration as, 1) repetition – it occurs repeatedly, and 2) a power imbalance happened so that the victim cannot protect him/herself. Stein, Dukes, and Warren [30] later added a criterion, 3) negative or malicious behavior intended to harm or distress. For adolescents who are bullies, Salmivalli [31] revealed a dominance hypothesis for the occurrence of bullying, in which they are driven by a desire for dominant status in the peer group. The leader can feel rewarded when their followers and reinforcers support their actions, especially when the majority of bystanders remain in a passive state. A similar pattern of the reaction was observed among children in Canadian playgrounds [32]. The prevalence of misbehavior was elevated among adolescents who reported one negative life event and more markedly elevated for those reported more than one negative event [33]. Another reason that can be attributed to taking the side of bullies is concerns of peer rejection, which is known to peak during the adolescent years [34]. For victims of bullying, research has found that the youth of ethnic minority backgrounds were more likely to get picked up due to the fact that they didn't have any distinct group to join, and for the same reason, they seldom have a group for their identity [30]. Both bullies and victims scored lower on subjective well-being than those not involved in any bullying perpetration events [35]. They are also positively related to internalizing problems across culture and time [36].

When facing risks and threats from social circles, support from family members often plays a critical role in protecting adolescents from bullying experiences. Family relationships were found to be mediated through adolescents' susceptibility to peer pressure, including school misbehavior [37]. Parental support and warmth showed significant negative associations with adolescents' misbehavior, which suggested adolescent attachment to parents is able to influence children's behavior when parents are physically absent [33]. The overall misbehavior was also four times less prevalent among adolescents in the quartile of reporting most teacher support compared to the quartile reporting least teacher support. Talking to friends for quality communication and perceived peer support were also negatively correlated with bullying perpetration or bullying victimization experiences [36], particularly for adolescent girls that are more likely than boys to turn to peers for support.

From a study that focused on coping strategies to bullying experiences, the five most frequently used strategies were to confide in somebody, ignore the behaviors, to support yourself, to get away from the bullies, and build up your social circles [38]. Some non-assertive strategies, such as crying, were commonly less efficient in tackling the issue than

actively seeking help behaviors. The most frequent solution suggested was seeking support from the school, and it is often recommended in schools [39].

For prevention and intervention strategies, it is important to understand that even research findings have shown social support from teachers, parents, and peers have negative relationships with adolescents' misbehavior at school, there is always limitations and capacity for each side to support and respond proactively. Each party should bear equal responsibility in bringing quality communication and interdisciplinary networking to support adolescents in responding to crises and implanting appropriate reactions to threats that bought by their social circles.

Positive Youth Development

Adolescents may find that some peer expectations conflict with their personal needs and values. However, in order not to lose their friends in a rather favorable cluster, they may feel uneasy to refuse which is a very important life skill of social competence. They may conform to inappropriate acts and even join risky behaviors. To resist peer pressure, adolescents need to be equipped with positive youth development (PYD) constructs [40] which include social, emotional, moral, cognitive, and behavioral competencies, clear and positive identity, self-determination, self-efficacy, beliefs in the future, bonding, resilience, spirituality, prosocial norms, and pros-social involvement. These 14 PYD constructs, together with recognition for positive behavior, are recognized as crucial constructs for any PYD programs.

Friendship

Friendship is an important part of the social and emotional developmental stage for adolescents during the period of transition between childhood and adulthood. A perceived higher level of friendship quality can bring adolescents to have a higher level of self-worth and social competence [41]. Patterson, Bettini, and Nussbaum [42] identified nine definitional clusters of friendship conceptualization across the life-span, including devotion, commonality, reciprocity, relational stratification, frequent contact, positive attributions, positive impact, understanding, and familial comparison. Friendships allow adolescents to gain social support, learn to get along with others, acquire knowledge and self-esteem, and strengthen social competence [43]. In adolescence, agreeableness, which is characterized by traits as cooperative, friendly, considerate, and helpful, is associated with better interpersonal adjustment and more harmonious conflict resolution.

Promotion of Bonding

There are many ways to build up bonding with good friends at school. They include the promotion of physical and psychological safety, the establishment of appropriate structure that promotes bonding, cultivation of supportive and intimate relationships, creating

opportunities to belong, promotion of positive social norms, support for efficacy, and provision of opportunities for skill-building [44].

The Structural Cognitive Theories of Morality

The structural cognitive theories of morality denoted the process of how individuals reason and judge their own behaviors when faced with moral dilemma issues during their active participation in engaging activities. Following the tradition of structural-developmental theorists [e.g., 45-48], Bredemeier and Shields [49] posited the example of sportspersons were actively interpreting their morality by interacting with others and making judgments on appropriate behaviors. Moral constructs, reasoning, and judgments became some of the important learning in sports participation and the same as in many engaging interactive games.

Another important concept “Ethos” [50] denotes the nature and characteristic of every unique participation that may govern the behavioral and cognitive aspects of all participants differently. Friendship, acceptance by peers and risks facing among peers are some of the vivid examples that will generate different ethos for adolescents to construe with when their integrity, honesty, and moral reasoning are being challenged. These processes of active construing the meaning of their own unique physical and mental participation echo the way for an agentic understanding [51] of the social cognitive theory of morality. The following examples illustrate adolescents are not passive recipients of their situations; they are actively interpreting how to exercise their moral will and desire. The dilemmas of making fair decisions, maintaining honesty, and upholding integrity will engender consequences, be it intentional or accidental.

Digital Game-Based Learning (DGBL)

Prensky [52] observed that people respond more effectively to fun, speed, and graphics and wrote the first book of digital game-based learning. He defined digital game-based learning as the combination of serious learning with fast-paced video-games that provides interactive entertainment. Since then, there is a growing interest in the use of digital game-based learning (DGBL) [53] in formal education [54], socio-emotional learning (SEL), mental health [55], and PYD [56]. Moreover, educational games facilitate the acquisition of procedural knowledge and the occurrence of a higher level of cognitive process [57].

From the preventive perspective, we can strengthen adolescents’ moral and social competences through digital game-based learning (DGBL). A positive youth development (PYD) electronic educational game is designed to attract and engage adolescents in examining and experimenting with the consequences of dishonest behavior in a non-threatening and manner.

This digital positive youth development (DPYD) game is designed to allow players to experience the natural consequences of being invited to engage in dishonest behaviors. Simulating the reality, players face temptations of breaking school rules as lured by peers

through new media via smartphone in a school setting and through online connections. The issues reflect a need for strengthening moral competence and media literacy.

In this game, honesty is regarded as good behaviors consistent with one's own inner consciousness, resulted from a full self-awareness which is not copied or being forced from outside. Players are given choices to conform or to refuse in different scenarios when the story develops. Players make choices that represent their perceptions of the importance of honesty and sincere confession as well as their willingness to conform to peer pressure. Players experience the consequence of their choices as the game continues. Moreover, it also introduces solutions when facing threats from classmates and simulation scenarios relating to forgiveness.

A Digital Game

The game, "The integrity crisis," was designed for Secondary 1 to 3 (Grades 7-9) students. The story develops in and outside of campus. It describes how the character handles interpersonal conflicts when her or his privacy is invaded by classmates. The story has different scenarios in which the player is required to make a choice from six responses representing various ways of handling the conflict. The story will end differently according to the players' choices. The game takes about 10 to 15 minutes to complete, depending on the reading ability and attitude of the player. Both the male and female versions are available.

The teaching material mainly explores the choice between friendship and honesty, emphasizing the importance of honest and sincere confessions, and it allows students to experience the consequences of dishonesty. Honesty is defined as behaving consistently with one's own inner consciousness, where one is fully self-aware, and the resulting behaviors are not copied nor being forced from the outside. In addition, it also allows students to decide on different solutions or reactions when facing threats from classmates, which highlights the issues of forgiveness. Both male and female versions are available.



Figure 1. An image captured from the screen of the game.



Figure 2. An image captured from the screen of the game.

Friendship is an important element in the lives of adolescents. When a teenager is asked by a friend to do inappropriate things, he or she may blindly follow in order to maintain the friendship and possibly making mistakes together. Hence, the choice between friendship and integrity is worthy of reflection and learning, which is the key message of this game.

OBJECTIVES OF THE GAME

The purposes of this game can be separated into three different aspects: cognitive, emotional, and behavioral. On the “cognitive” aspect, the game allows students to reflect on the choice between friendship and honesty. Is maintaining a friendship more important or confessing one’s faults with the possibility of putting a tear in the friendship? It helps students understand the necessity of a sincere confession. Confessing allows one or more parties to understand the full picture of the situation, which can clear out any misunderstandings and apologize, so all parties can analyze the situation rationally to work out the best solution. The game can also increase students’ awareness of the different ways of handling threats from classmates through the choices they personally make in the game, as well as the different options they can choose from. It is important to stress that students always have a choice, and the outcome of the situation changes according to their response.

On the “emotional” aspect, the game allows students to put themselves in the character’s shoes as if what they are experiencing is happening in real life. Students can change from understanding the victim’s plight, to caring for the victim, and to showing compassion for the victim’s pain and negative emotions. This enables students to feel pity, sympathy, and empathy respectively in those situations described above.

On the “behavioral” aspect, the game allows students to perform drills through different scenarios, to prepare them for real-life if similar situations were to arise and to find out what actions they would potentially take. This enables students to consciously practice honest behaviors, refuse to perform inappropriate behaviors, and take appropriate actions in the face of frauds or extortions. On top of that, they can also do good deeds for their friends, proactively admit one’s fault, and forgive a friend’s wrongdoings.

GAME DESIGN

The first level feedback provides general guidance on the incident based on students' choices during the early phase of the story (the player hesitates to follow a friend's idea of modifying a school notice) and toward the ending (10th, 11th, episodes where the character faces the unreasonable threat of the class representative). The second level feedback targets students' strategies in handling conflicts while the third level feedback shows the calculated scores of the 20 positive psychological constructs of the player. They are discussed in chapter 3.

Storyline

A classmate Bruce/Carol invites the player to forge a school notice together in order to skip participating in a two-day life planning camp and join other classmates for other leisure activities. The character hesitates at first but eventually joins the forgery and faces the risk to be punished for violations of school rules. The forgery is discovered by the class representative who later keeps asking for money to cover up. The theme of the game is related to how the player makes his/her decision when facing the pressures from the classmates in various scenarios as the story develops.

Tips for Instructors

Instructors need to familiarize themselves with the objectives, design, and storyline of the game. One of the key teaching points is making choices and maintaining one's integrity. Class discussion on how students make a choice and their sharing of the experiences could illicit interests for the topic. Discussions on following rules and do the right thing versus breaking rules to fulfill one's desires or wishes, act or remain silent when threatened, agreeing with friends to do mischievous things or follow one's conscience could, on one hand, stimulate students' discussion, and on the other hand, gives the instructors some ideas of what students have experienced in real lives regarding those issues. Instructors should be sensitive about students' disclosure of their personal experiences, which can cause upsetting emotions. Reminding students to respect one another's disclosure for the sake of learning from one another, and students should not tease or tell others what their classmates have said in the sharing.

RELATED TEACHING UNITS FOR THIS GAME

Prosocial involvement (PI), resilience (RE), moral (MC) and social competences (SC) are the core PYD constructs for this game. Anti-bullying (AB) is a major developmental issue. There are five related teaching units in the original and revamped program of the Project P.A.T.H.S. launched in 2006 and 2009 respectively – MC3.4 "The Stolen PIN," SC3.4/AB3.2 "Alien," PI1.2/AB1.2 "Behind the Mask of Bullying," RE1.3/AB1.3 "A Secret Book of

Bullying Prevention,” and PN2.4/AB2.1: “I can make a Difference.” The last two units will be presented in chapter 6 on the game to prevent bullying and cyberbullying. The concept maps of all teaching units can be accessed through the P.A.T.H.S. website <https://www.P.A.T.H.S..hk/en/>. Table 1 shows the three most relevant units which will be described in detail below.

Concept maps of all teaching units can be found in the special teaching units except for MC3.4, which are updated teaching units of the teaching materials of the Project P.A.T.H.S. This game and the other game “the Bullying Storm” share some of the teaching units under the theme of anti-bullying (AB). They are summarized in the following table. For all concept maps, please visit <http://www.cityu.edu.hk/ss/pltr/ty/new/en/enter.html> (Flash Player required).

Table 1. The three most relevant teaching units

Game	Issue	Construct(s)	Unit(s)
The Integrity Crisis	Honesty, isolation caused by bullying	Moral Competence (MC)	MC 3.4: “The Stolen PIN”
		Social Competence (SC)	SC3.4/AB3.2: “Alien”
		Prosocial Involvement (PI)	PI1.2/AB1.2: “Behind the mask of bullying”

Unit MC3.4 “The Stolen PIN”

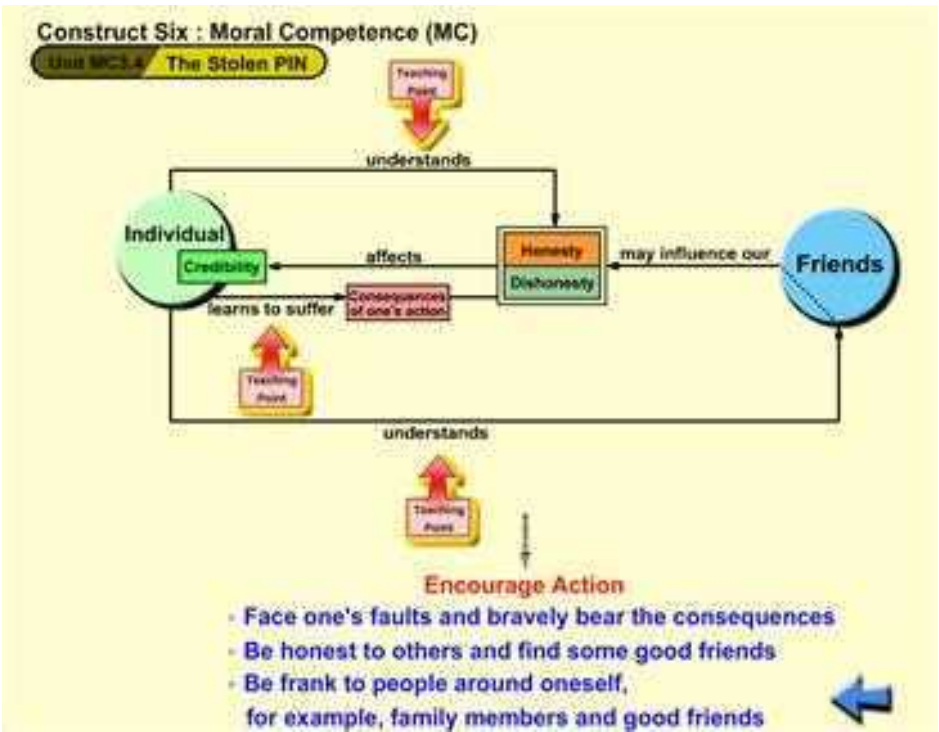


Figure 3. The concept map of the teaching unit MC3.4.

Teaching Points

The construct for this unit is resilience (RE). In this unit, individuals understand that the interrelationship between honesty and credibility. The more honest one behaves, the more credible he or she is, vice versa. Individuals also realize that peers play an important role in influencing their behaviors of honesty and dishonesty, which indirectly affects their level of credibility as well. Lastly, they learn to suffer the consequences when performing actions of dishonesty.

Instructors should encourage individuals to be honest with others and find some good friends. Having friends with a positive and upright character, they would eventually develop these characteristics, such as being frank to people around themselves. In the face of issues on being dishonest, they are confident to face their faults and bravely bear the consequences.

Unit SC3.4/AB3.2 “Alien?”

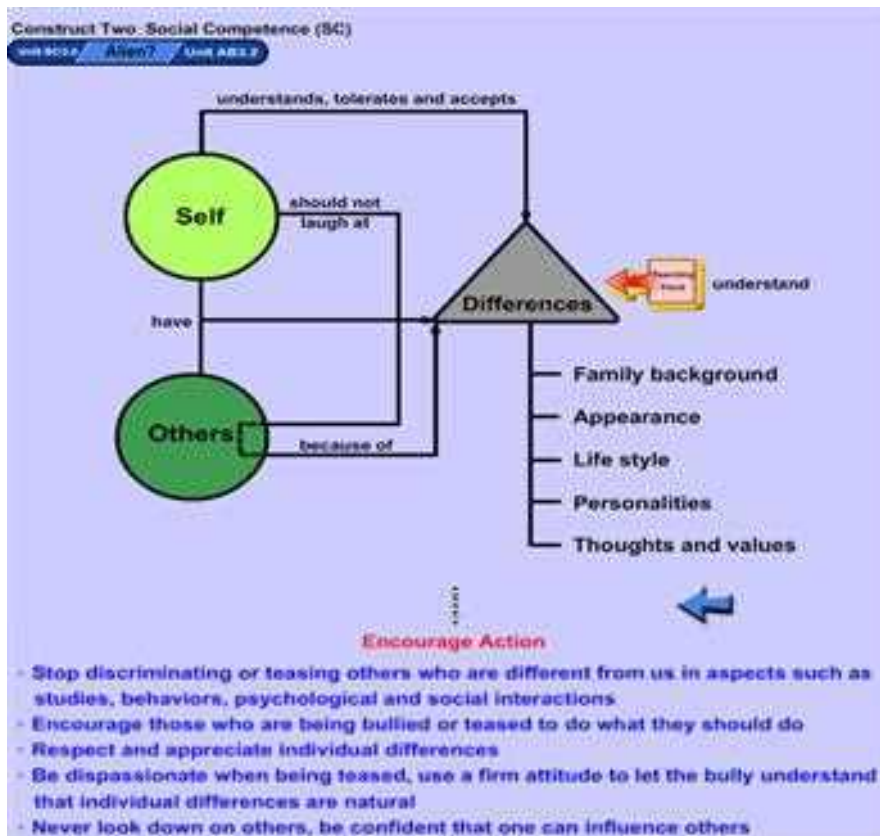


Figure 4. The concept map of the teaching unit SC3.4/AB3.2.

Teaching Points

The construct for this unit is social competence (SC). Everyone is unique and we need to realize the difference between each other. Many factors contribute to those differences such as family background, appearance, lifestyle, personalities, and individual's thoughts and values. Thus, one should not tease or make fun of others because of those differences. Instead, we should try to understand the differences, and learn to tolerate and accept others as different from us. Instructors should focus on discussing the differences and what makes everyone unique with students.

We should encourage respect, understanding, and tolerance; and condemn discrimination, teasing behaviors, bullying incidents. There are lots of differences one can pick from their classmates such as behaviors, studies, and how one interacts with others, but we need to learn to respect and appreciate individual differences. When faced with bullies, one should be dispassionate when being teased and use a firm attitude to let the bully understand that individual differences are part of nature. We should never look down on others because of our differences. Instead, instructors should remind students that they can make a difference and influence others to take proper actions.

Unit PI1.2/AB1.2 “Behind the Mask of Bullying”

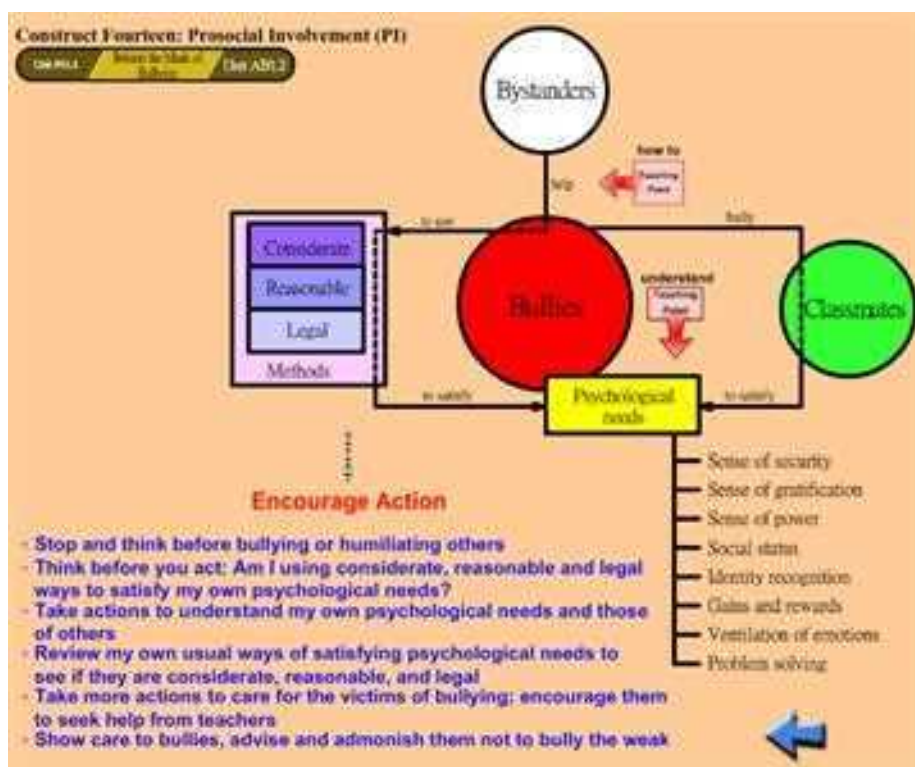


Figure 5. The concept map of the teaching unit PI1.2/AB1.2.

Teaching Points

The construct for this unit is prosocial involvement (PI). This unit explores the mindset of bullies in a bullying incident. Usually, bullies bully their classmates in order to satisfy their psychological needs, including having a sense of security, sense of gratification, sense of power, a higher social status, better recognition of identity, a favor of gains and rewards, ventilating their emotions, as well as solving their own problems. It's crucial for bullies to understand that their actions initially do not intend to hurt others, but it's a maladaptive approach in response to their inner issues. Besides, bystanders can help bullies by using considerate, responsible and legal methods to respond to their psychological needs. From time to time, bullies learn to express themselves in an appropriate and acceptable way.

Instructors should encourage individuals to think before performing bullying or humiliating actions, again stressing the use of considerate, responsible and legal measures to satisfy individuals' psychological needs. Moreover, concrete actions ought to be taken to understand the psychological needs of bullies and those of others, such as doing personal reflection and review on their interpersonal skills, caring for victims and bullies' inner needs, fostering help-seeking behaviors from trust-worthy people (e.g., teachers), advising and admonishing bullies not to bully the weak.

CONCLUSION

Everyone treasures friendship in our lives and students need to be careful when handling the relationship with friends. It is understandable that peer pressure is not easy to resist. During the adolescence stage, peer plays an elevated role and occupies a large proportion of their lives. Informed by the peer cluster theory, we come to figure out why many prevention and educational programs failed to compete with the youth's original environment, in which the norming influences of peer clusters eliminate the gainful learning experiences [22, 58-59]. This interactive game shows how peer influences challenge adolescents' honesty and integrity. The lively issues engender thought-provoking process; given appropriate time to think and experience the possibility of alternative decisions. They are real-life examples of viable solutions which are seldom available in their own peer interaction. The process of provision of proper guidance, coaching, and accurate information may be able to elevate certain alternatives way to counter-influence peer cluster pressure. It is hoped that participants could be well equipped and informed to choose wisely when faced with situations they have to make a choice, bearing in mind the importance of honesty and integrity.

USER FEEDBACK - PERSONAL REFLECTION

Below is the written feedback of a female aged 15 who studies in an international school in Shanghai, China. Parental consent to play the game and publish her views was obtained.

“After playing this game, I realized how difficult it might be to say no to friends. It is one case to disagree with what someone you dislike is doing, but it is much harder to say no to friends because you value their opinion of you. Additionally, after trying out different options for the ending, I also learned that how you choose to communicate with your friend will have a large impact on how long the friendship will last. If you really value a person’s integrity and loyalty, Carol’s betrayal of you may not mean that you want her as a friend. However, you can still try to keep things neutral and avoid an altercation or fight. Overall, this game/simulation also reinforced the idea that breaking the rules has consequences, but if the main ‘rule-breaking’ has happened already, consequences can be minimized by acting responsibly and contacting an adult when no previous strategies have worked.”

A 19-year old student studying at a college in the U.S. wrote:

“There was no option in the game to reject Bruce’s idea in early stages. Personally, I would have firmly said no. I believe the expectation was that it was very hard to say no to Bruce. I liked there were different endings, depending on how you resolved your disputes with Bruce. You would either be able to mend or destroy your relationship with Bruce. However, it should be emphasized that how to approach friendships and relationships are nuanced. There could be a middle ground between different options. There is no one right answer.”

DISCUSSION

The peer cluster theory has helped us understand the operationalization of peer influence and the pressure a favored peer cluster will have on youth’s non-conforming behaviors. Young people are prone to be influenced by peers. The theory sheds light on the understanding of why providing information alone is ineffective for treating adolescent misbehavior. For primary prevention, the learning gained from educational programs cannot withstand the peer influence engendering from their favor clusters. The complexity of many integrity issues and moral developmental examples of violation of school rules, like fraudulence and victimization, and having secondary deviance because of differential association and being further labeled are just many vivid challenges in adolescents’ daily life.

The game has several contributions. First, it provides knowledge and skills in handling peer pressure. Second, it offers choices that players can learn vicariously. Third, it creates chances of cooperative learning that encourages open discussion and support rather than competition and didactical communication. The game design may maximize the positive effects of the reciprocal relationship among peers which is the essence of secondary prevention.

Cooperative learning provides the quintessential way to counter-influence peer cluster pressure since the adult facilitator will remain neutral and distant, not providing the orthodox answer, nor responding with reckless comments. This facilitative stance may facilitate adolescents to seek their own answers from an active learning process. The other major contribution to cooperative learning is the notion of awaiting and motivating the readiness of adolescents. Adults often look for quick measures and are easily losing the patience to allow young people the time of contemplation, deliberation, and making fair decisions. This helps explain why the learning processes in sharing of ideas and viewpoints may help explore identity and encourage adolescents to exchange diversified interactions to curtail some risk factors for engaging in cyberbullying [60]. The elements among this gaming cooperative learning consists of considering individual accountability during challenging situations, face-to-face interaction (internet communication) to reveal one’s own decision making, positive

interdependence thinking through the empathetic reflection to the plight of others, and finally, the essential social skills acquisition, which will be crucial for moral decision making and integrity building [61, 62]. Applying these games in cooperative learning can make the gaming process a tool for engagement, initial diagnosis, reflective discussion, skills acquisitions to relate to peers in difficult situations where students are lured to engage in deviant behaviors [22].

Here a DPYD game is designed to enhance motivation and engagement in positive youth development. Whether or not it has a positive impact on the learning outcomes is of prime concern. Empirical evidence supports that playing serious educational games (SEGs) facilitates users to learn the content and boost knowledge acquisition [63]. Cheng and associates' study results are informative to science educators, game designers, instructional designers, and SEG advocates. The results offer empirical evidence that SEGs allow students to understand the confusing and difficult concepts of the human immune system in an easier way [57].

Even though some evidence supports the use of SEGs, there is still substantial controversy about the actual effectiveness [64]. SEGs help students gain procedural knowledge and facilitate a higher-level cognitive process [57]. They allow students to gain positive learning experiences that are useful, clear, attractive, interesting, and satisfying [57, 64]. Many scholars still believed that playfulness was negatively associated with the learning outcomes of users. The playfulness of SEGs can be a double-edged sword since excessive playfulness may generate some issues which instructors have to consider when using SEGs in facilitating student science's learning [57]. On the other hand, many scholars maintained that playfulness is one of the major attractions in motivating adolescents' participation [64-66] especially in serious issues such as morality in computer game learning.

Implications for Practice and/or Policy

As in many emerging methodologies in social science programs, many practical problems come up before answers can be provided. There is much to be discussed not just in the fun versus learning dichotomy. Experienced practitioners often think about how much games will contribute to intervention. Here comes the contention of active versus the laid-back style of game program facilitation. It is not appropriate to provide direct answers in the process of cooperative learning while a more carefree learning atmosphere might as well not be desirable for evaluating what the participants have learned in the process. Here we stand in the crossroad of pushing for a result or allowing participants to contemplate. In experiential learning, a concrete experience gained through the participation in a game can be used and tested in new scenarios, to verify and to apply in daily life [66]. Substantial follow up and facilitations by experienced practitioners are essential. Here comes the challenge of limited resources vs. the intensity of learning and growth. The most challenging situation is how to allow for the maturity of discussion in important value clarification issues such as cheating/lying, integrity, freedom, and liberty to help learners be better able to comprehend the desired educational targets while the facilitators might need to advocate for certain morality direction from the funders and donors.

The above discussions have implications on practice and policy to be implemented in serious game learning. The know-how of game program design should address the issue of balance fun to attract with the seriousness of the contents. For example, how to engage adolescents with the free spirit of discussion in a scenario of integrity is a matter of program design and process facilitation.

The multi-level of value self-examination of funders, designers, and practitioners are quintessential, as the serious computer game might have generated moral discussion and reflection to question the above stakeholders' position before adolescents come to re-examine theirs. If life integrity issue should go beyond cognition to practice, the application issue of game learning reserves more resources and energy to handle with. The second part of the evaluation of effectiveness should be focused on the impact of learning on daily life. This helps to answer the prime concern of the effectiveness of DPYD, not only for investigating the results but also for its impact on the life-changing capacity for participants.

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Chapter 350

A DIGITAL POSITIVE YOUTH DEVELOPMENT GAME FOR PREVENTION OF BULLYING AND CYBERBULLYING

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ABSTRACT

This chapter presents a brief literature review on the issue of bullying and cyberbullying (BCB) among adolescents. It then introduces the project P.A.T.H.S. which sponsored the design and production of this digital positive youth development (DPYD) game to strengthen three positive youth development (PYD) constructs - social competence, moral competence, and pro-social norms among early adolescents. It then describes how it can be used to enhance media literacy to prevent BCB which are very often intermingled as a result of prevalent use of information and communication technology (ICT). A description on how to use the game in conjunction with related teaching units of the project P.A.T.H.S. for primary prevention is presented. Teaching points and tips of related units are also provided. To demonstrate the potential effectiveness, two young users – a 15-year-old female from China and a 21-year-old male

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from the United States were invited to play the digital game and provide comments on the game design and perceived effectiveness. How the game can be used for secondary and tertiary prevention is also discussed.

INTRODUCTION

The availability and use of electronic devices, particularly mobile phones, has been exponentially growing over the years. This widespread behavioral change in excessive use on screens has given us a new online platform in exchanging instant information and connecting with people that we may or may not have known in life. Meanwhile, it has also created many issues that may have brought from offline to online, such as bullying, which is typically named as cyberbullying, electronic bullying, or internet bullying. Cyberbullying is among the most commonly exposed and unidentified risk for children and adolescents on the internet.

Over the years, scholars have proposed different approaches to tackle the issue of bullying. However, the problem of bullying has been worsening in the digital era. In 2018, it was found that 59% of the American youngsters experienced cyberbullying or harassment. In Britain, 54% of the teenagers aged 12-20 reported that they experienced bullying, while 33% of them cyberbullying [1]. A study conducted by the UNESCO [2] reflected that Hong Kong's cyber victimization is as serious as in western countries, proven by an overall victimization rate of 30.9% and a testing and blaming rate of 18.9%. These results correspond with the research by the Organization for Economic Co-operation and Development (OECD) in 2018 [3], which focused on the mental well-being of students aged 15. It is found that Hong Kong has the most serious bullying situation in schools. More than 32% of the respondents reported having experienced bullying from peers, which is more serious than Canada (20.3%), Taiwan (10.7%) and America (18.9%). On average, around one student in each class reported they were beaten or pushed several times in one month. Furthermore, one in three Primary 4 to Secondary 3 students experiences internet victimization [4]. These figures highlight the seriousness of the issue.

The impact of cyberbullying may affect a much larger number of people at a faster rate than bullying. The Hong Kong Family Welfare Society [4] found that one-third of the children and early adolescents in primary and secondary schools were victims of cyberbullying. Inadequate parental support and skills may undermine parents' role in protecting their children. In addition, parents working long hours may also compromise parent-child relationship. Research shows that the tendency of bullying cases decreases if students' relationship with their teachers is positive [3]. In contrast, if the victims receive limited support from classmates or teachers, they will have a higher tendency to become victims in cyberbullying [4]. These findings indicate the importance of bonding, a PYD construct which promotes positive interpersonal relationships, as an effective element to curb bullying.

There is a growing concern on the prevention of BCB, and an interest in the use of digital games to promote PYD among adolescents for successful adaptation to challenges they face in and out of school. This chapter discusses how to apply game-based learning (GBL) to tackle the BCB problems. We will also study how a newly-developed DPYD game can be effectively used as a preventive measure for BCB encountered by adolescents. In this chapter, we seek to:

- review briefly the literature on bullying and cyberbullying;
- outline the design of the digital game and its relationship with the project P.A.T.H.S.;
- provide users' review on the game to identify its strengths and weaknesses; and,
- discuss issues related to DPYD game for prevention of bullying and cyberbullying.

LITERATURE REVIEW

Cyberbullying in adolescence often comes in the form of voluntary and repeated assaults against a person through offensive emails or text messages, instant messaging, or inappropriate act on social networks/social media [5]. In a study of 4,477 elementary, middle, and high school students in Israel, the results revealed that approximately 30% of the participants experienced personal victimization from cyberbullying in their WhatsApp classmate groups [6]. Children and adolescents exposed to cyberbullying, whether as cyberbullies, cyber-victims, or both cyberbullies and cyber-victims, are strongly related to the use of social networking sites. The risk of victimization increases with the time spent online [7, 8].

Cyberbullying and Traditional Bullying

A major theme in the literature is the linkage between traditional bullying and cyberbullying. While adolescents mainly use the internet to maintain pre-existing friendships, some make close friendships online. Although there are legal and behavioral definitions of cyberbullying, some victims do not perceive all such behaviors as cyberbullying [9]. Moreover, they perceived aggression online and at school differently. Cyberbullying is generally perceived as less problematic than traditional bullying partly because the online environment lacks clearly established rules, physical presence, body language, authority figures, and formal reporting mechanisms [9].

Recent studies have identified the potential risks of cyberbullying in using social media platforms for children and youths. The insensitivity to information privacy threats will also increase the exposed risk [10]. Fogel and Nehmad [11] conducted a study on privacy concerns in the social network communities and found that on "Facebook" social media platform, 75% of the sample population have no restrictions on who viewed their profiles and about 10% showed their phone numbers and home addresses on their profiles publicly. Another study showed that some adolescents who are heavy social media users are less likely than their peers to be victims of cyberbullying and less likely to bully others [12]. The characteristics of cyberbully-victims and cyberbullies are different. Cyberbully-victims are typically similar to one another in that they have low self-control, offline aggression, low level of empathy, and heavy consumption of violent media [13, 14]. Media violence exposure was a risk factor leading to both cyberbullying and cyber-victimization [15].

Regarding the bystander effect in cyberbullying, adolescents' relationship with both the perpetrator and the target may affect whether they would intervene when witnessing cyberbullying. The relationship may also affect their ability to understand the context of the situation and the perceived severity of the effect of the incident on the victims [9, 16].

Impact of Cyberbullying on Victims

Cyberbullying poses severe threat to the overall wellbeing on cyber-victims in terms of their emotional and psychological health. Cyber-victimization in adolescents was found to be associated with greater internalizing problems, such as feelings of loneliness, anxiety, and poor psychosocial well-being [17]. Among the problems, cyber victimization and depression have the strongest relationship. It was reported that suicidality is also linked to victimization [18]. Moreover, the exposed risk on the use of multiple social media platforms had substantially put users at greater odds of having higher levels of both depression and anxiety symptoms [19, 20]. Primack and colleagues [19] argued that depression and anxiety symptoms may be related more to participation in multiple social media platforms than to the amount of time spent on social media. Plausible reasons include multitasking among platforms which may lead to poor cognitive and mental health outcomes [19, 21], difficulties in adjusting to unwritten rules, cultural assumptions, and idiosyncrasies of different platforms [19], and a higher risk of insensitive language being misinterpreted and magnified. All these could further aggravate the problem and lead to severe distress and even self-harm in extreme cases [22].

Age and Gender Differences

The high penetration rate of smartphone and the internet may facilitate wider age permeability of cyberbullying among children and adolescents. For gender differences, Festl and Quandt [23] found that females' cyberbullying involvement in both perpetration and victimization could be traced back to more intensive online social activities and a higher amount of online contact with strangers. For males, only higher exposure to antisocial media content predicted higher levels of victimization over time. Moreover, males were also found to be more likely to engage in sexual cyberbullying perpetration, yet females were more likely to engage in psychological cyberbullying perpetration [14]. This information is useful when designing DPYD games and one must consider potential players' age and gender and use gender-appropriate contents to yield the best outcomes.

Preventive Measures

There is an urgency for intervention for BCB through a holistic approach. Ttofi and Farrington's [24] meta-analytic review showed the positive impact of school-based anti-bullying programs with an overall 20-23% decrease in bullying and 17-20% reduction in victimization. A recent systematic review on prevention and intervention on cyberbullying among adolescents reported that the most frequently used intervention components include coping skills training, empathy training, parent education, and enhancement of communication and social skills [25]. Specifically, an intervention program with eleven sessions over a period of 3-month focusing on enhancement of emotional skills reduced victimization and assault. It also enhanced emotional perception and regulation skills and life satisfaction [26]. Recent efforts have been made in adopting program elements originally

designed for traditional bullying in dealing with cyberbullying [27]. Interestingly, programs focused at the school level were found to have the strongest effects against cyberbullying [28]. Slonje, Smith, and Erisen [29] also found evidence to support components, such as a whole-school anti-bullying policy, activities to promote awareness, curriculum-based and classroom intervention and prevention efforts, as well as support for victims from capable peers.

Issues regarding BCB are real challenges for human services and mental health professionals. It was evident that intervention strategies can be successful in reducing the problem, thus, more efforts should be put in prevention of the problem. Literature review supports a holistic approach to tackle the issues from the ecological perspective. Specific educational strategies are adopted to strengthen students' empathy and effective decision-making ability [30]. For example, the Project P.A.T.H.S. [31], which adopted a holistic PYD approach to enhance psychosocial competencies among early adolescents (Grades 7-9) through a universal school-based curriculum and a secondary prevention targeting students with greater psychosocial needs, was demonstrated to be effective in reducing risky behaviors [32-34]. The project, adopting 15 constructs identified as core components of PYD, has been recognized by the World Health Organization as an evidence-based program in one of the seven strategies for ending violence against children [35] and one of the three evidence-based programs for promoting life and social skills in adolescents [36].

A total of 120 30-minute curriculum units were designed with reference to 15 positive youth development constructs identified in the successful PYD programs [37]. Specifically, the Project P.A.T.H.S. developed seven units to help students enhance five PYD constructs which include moral and social competencies, resilience, prosocial norms, and prosocial involvement. These units aim to promote general awareness on bullying, space for self-reflection and opportunities to rehearse new behavior. Students learn how BCB harm themselves and others, and they practice skills to help protect themselves when being bullied. They also learn bystanders' role and learn skills to be responsible bystanders in school bullying and cyberbullying [38].

A Digital Game for the Project P.A.T.H.S.

The game, "The bullying storm," was designed for Secondary 1 to 3 (Grades 7-9) students. The story mainly focuses on the theme of bullying. It is relatively simple, and it develops according to the choices of the player. Both male and female versions are available. Learning in a safe environment is one of the basic rights of students. However, bullying occurs from time to time on school campus or outside, where victims often suffer from physical and mental harm. Therefore, learning to adhere to personal principles, protecting oneself properly and seeking assistance actively are important issues when facing bullying. The game takes about 10 to 15 minutes to complete, depending on the reading ability and attitude of the player.



Figure 1. An image captured from the game (female version) illustrating choices available.



Figure 2. An image captured from the game (male version) illustrating choices available.

OBJECTIVES OF THE GAME

The game targets three different aspects: cognitive, emotional, and behavioral. On the “cognitive” aspect, students can develop a deeper understanding of school bullying, the need to adhere to important personal principles, the need to seek assistance actively if necessary, and the various ways of dealing with different types of bullying.

On the “emotional” aspect, the game allows students to put themselves in the character’s shoes as if they were experiencing the issues in real life. Students can change from understanding the victim’s plight to caring for the victim and showing compassion for the

victim's pain and negative emotions. This enables the player to feel pity, sympathy, and empathy respectively in those situations described above.

On the “behavioral” aspect, students can learn to take appropriate action to deal with interpersonal conflicts, seek help proactively from teachers or good friends in the face of bullying, reduce behaviors that escalate bullying incidents, and prevent bullying from worsening.

This game makes use of a story line and provides various scenarios for users to choose as the story develops. In each scenario, users are given six different responses to choose from, and it will affect the development of the story accordingly. Corresponding feedback and guidance on three aspects will be provided based on user's responses to all scenarios at the end of the game. First, comments according to the end of the story will be shown. Second, based on students' responses, their patterns of conflict resolution strategies in terms of communication mode, including competing, avoiding, accommodating, compromising, and collaborating will be presented in the form of percentage. Third, the relative strengths on each of the twenty positive psychological constructs in percentage format based on the choices will be shown. They are discussed in chapter 3.

Game Design

The story develops in the school campus, and it describes how the character handles bullying. The story has different scenarios in which the player is required to make a choice from six different responses representing various ways of handling the bullying. The first level feedback is based on the ending (the 11th episodes when the character is facing the bullying incident), and there will be guidance provided according to the user's choices. The second level feedback targets users' strategies in handling conflicts. The third level feedback shows the calculated scores of the twenty positive psychological constructs of the player.

Storyline

A student, Bruce/Carol (depending on the gender of the character), who is an active key figure in class. Bruce/Carol is the captain and coach of the basketball team and he/she plays the role of a bully in the story. He/She has many followers, but he/she often bullies others and abuses his/her power. Unfortunately, the player becomes his/her target. Facing the mockery and exclusion of the classmates, how will the player escape from this predicament?

Tips for Instructors

Instructors need to familiarize themselves with the story line, the teaching points and the plot of the game. They can remind students to pay special attention to the issues surrounding bullying and being threatened by others throughout the game. There are plenty of places in the game where instructors can pause the game/game demonstration to dig deeper into issues with students in the form of class or small group discussion if time allows. Instructors can

remind students to apply the knowledge of making choices in the previous game to the scenarios when facing bullying - Bruce/Carol snatches the player's pen, which is the player's birthday present or when Bruce/Carol wants the player to take a picture of a completed assignment and send it to him/her. Having the class to discuss what they will do in a few scenarios can motivate students to continue with the game on their own. More importantly, the class may apply knowledge and skills which include self-awareness, moral decision making, perspective-taking, empathetic understanding, effective communication, and relationship building and maintenance in real life situations.

Related Teaching Units for This Game

Anti-bullying (AB) and internet use (IT) are two of the five developmental issues of the revamped program of the Project P.A.T.H.S. launched in 2009. There are seven teaching units on the theme of anti-bullying. Among them, five are directly related to the game which were designed as intervention to address the issues of BCB. They are AB1.1 (Incidents of Bullying), AB1.2 (Behind the Mask of Bullying), AB1.3 (A Secret Book of Bullying Prevention), AB2.1 (I Can Make a Difference), AB2.2 (Make a Smart Move), AB3.1 (Online Buddies), AB3.2 (Alien?), and MC3.4 (The Digital Age). Table 1 shows the four most relevant units which will be described in detail.

Table 1. The four most relevant teaching units

Game	Issue	Construct(s)	Unit(s)
The Bullying Storm	Bullying, cyberbullying	Resilience (RE)	RE1.3/AB1.3: "A Secret Book of Bullying Prevention"
		Resilience (RE)	RE1.4/AB1.1: "Incidents of Bullying"
		Prosocial Norms (PN)	PN2.4/AB2.1: "I can make a Difference"
		Moral Competence (MC)	MC2.2/AB2.2: "Make a Smart Move"

Unit RE1.3/AB1.3 'A Secret Book of Bullying Prevention'

The construct for this unit is resilience (RE). When faced with bullying, students can choose different ways to respond in the situation. Staying calm can be helpful, and they should never use the method of "an eye for an eye" because it would only make things worse as it causes more harm to more people. Instructors can remind students to weigh the circumstances and make wise decisions. Instructors should also encourage students to seek help from teachers or social workers and not to provoke the bully. Responding with the "I" message approach in the face of bullying can be effective to bring across the message. It conveys the feeling of the speaker and explains the needs of the speaker, and it does not imply any criticism of others.

Instructors can help students understand the characteristics of bullies fully and deeply to avoid intensifying or further provoking the act of bullying. These methods can help students

to stop others from bullying them, and they learn to stand their ground. Instructors should discuss the methods with students and encourage them to learn these methods by heart to stop others from bullying them.

Students should never tolerate any bullying behaviors. Instructors can remind students to stay calm when being bullied or in the face of bullying. Students can find suitable ways to respond and use the methods they have learned from this unit. Instructors should also remind students that the approach to tackling bullying varies according to the environment, situation, type of bullying, and reactions of the bullies. Students should consider the environment and make wise decisions accordingly.

The following concept map shows the contents and teaching points of the unit. Further pointers are provided for instructors to encourage students to take appropriate actions.

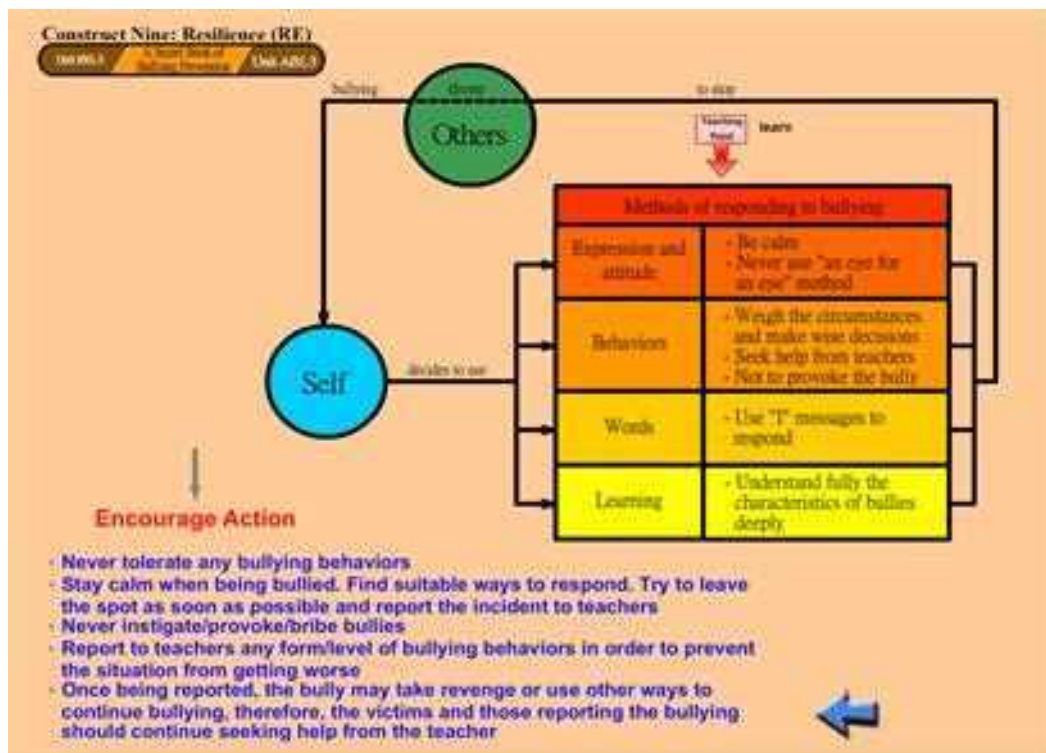


Figure 3. The concept map of Unit RE1.3/AB1.3 'A secret book of bullying prevention.'

UNIT RE1.4/AB1.1 'INCIDENTS OF BULLYING'

The PYD construct for this unit is resilience (RE). There are many forms and ways of bullying. They can be physical, verbal, social or extortive. Bullying are often physical or psychological attacks involving a wide disparity in strength between the bully and the victim, and it is often done repeatedly. Victims who are bullied most suffer from negative consequences psychologically, and/or physically, which can have a short term, long term, or even a permanent effect on the victims.

Instructors are encouraged to analyze the thoughts of bullying and explore the negative consequences on victims. Also, we should encourage students to stop all bullying behaviors and not to provoke bullying behaviors. Students should learn to be wise and brave rescuers, but they should ensure one's safety before seeking help from teachers when facing bullying. They should treat others with kindness and understanding and participate in activities to build a harmonious campus. The following concept map shows the contents and teaching points of the unit. Further pointers are provided for the instructor to encourage and guide students to take appropriate actions.

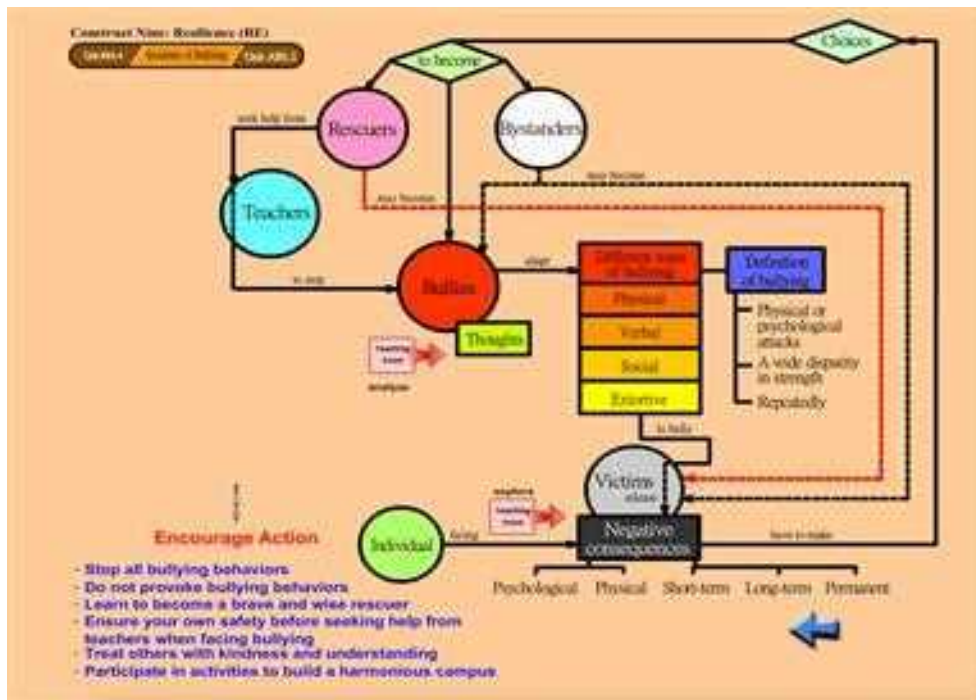


Figure 4. Concept map of Unit RE1.4/AB1.1 ‘Incidents of bullying.’

UNIT PN2.4/AB2.1 'I CAN MAKE A DIFFERENCE'

In the face of a bullying event, one should consider some personal factors, such as responsibility, safety, and benefits in order to decide if one should intervene in the midst of a bullying incident. The more people take the stance of a bystander, the less the likelihood of a

person in the bystander group to take action. In a school bullying incident, most students are bystanders. Instructors should discuss the bystander effect with students and how the attitudes and responses of the bystanders affect the bullying incident.

Instructors, therefore, can encourage students to reflect on one's actions and responses when witnessing a bullying incident, such as seeking help from teachers immediately when it is safe to do so. Also, if possible and under safe circumstances, students can provide help to victims and encourage others to provide help and reduce the "bystander effect."

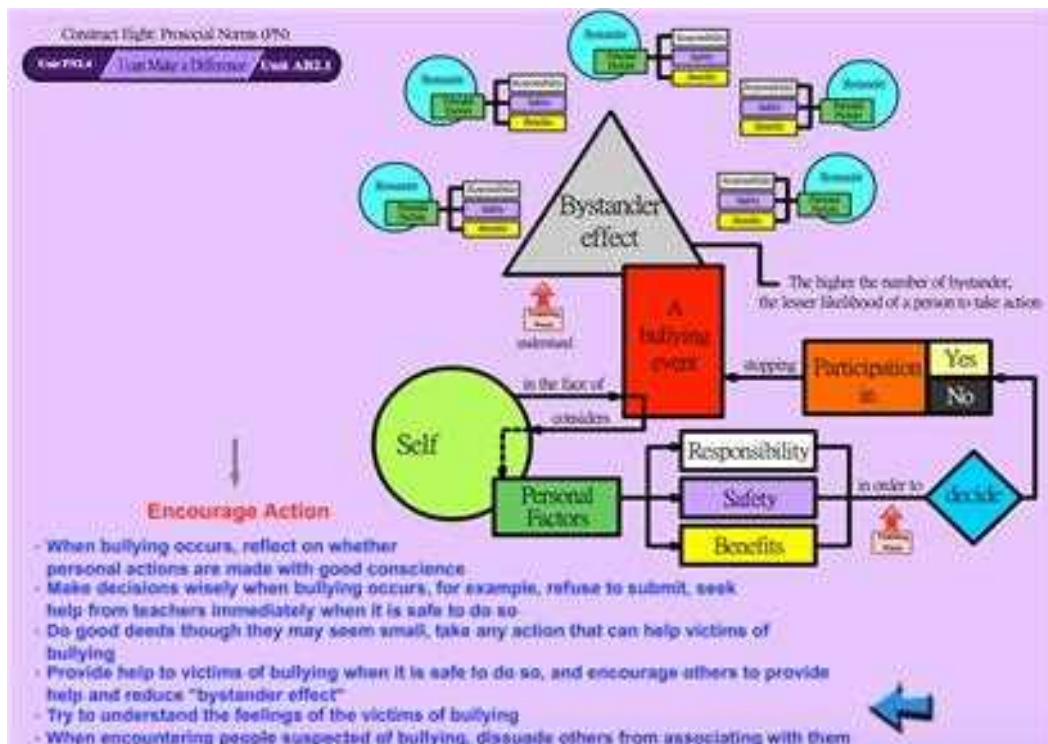


Figure 5. Concept map of Unit PN2.4/AB2.1 'I can make a difference.'

Besides, instructors can make use of other methods, such as role play and group discussion to help students understand the feelings of the victims. They can guide students to reflect on circumstances, such as if other people turn a blind eye when they are the victims, and how they will feel if others watch with folding arms and do not offer any help. When students suspect any bullying incidents, they should try to dissuade others from associating with them. The bottom line is that bullying should never be tolerated or encouraged.

Bullying violates the rights of others and no one deserves to be bullied. Schools should help students acquire proper values and skills so that they become alert of such incidents and know what actions to take when they encounter any bullying incidents.

Figure 5 shows the concept map.

UNIT MC2.2/AB2.2 ‘MAKE A SMART MOVE’

There are personal factors for us to consider, such as power, safety, and friendship when we have to decide what to do in times of bullying. We can intervene wisely, choose to neglect, be a bystander or instigate when faced with bullying. Instructors can discuss some of the personal factors with students and let them share with one another what those factors look like for them.

To conclude, instructors should encourage students to avoid direct conflicts with bullies and their allies. Students should ally themselves with reliable friends and learn to be very discreet in reporting any bullying to teachers in details. Also, instructors need to remind students to keep the matter confidential after reporting the incident to teachers. Students can befriend victims of bullying, show their support, concern and encourage them to stay strong, to seek help from teachers or social workers when being bullied. We all have to learn to take our stance: “Say no to bully and stay strong in the face of evil.”

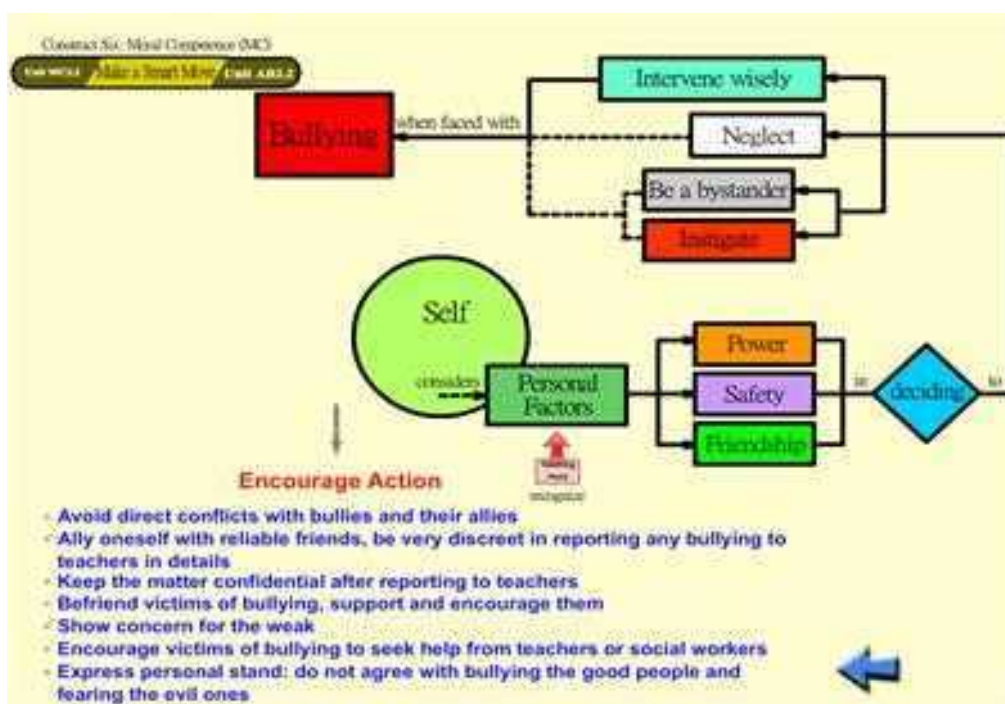


Figure 6. Concept map of Unit MC2.2/AB2.2 “Make a smart move.”

UNIT MC 3.4/AB 3.1 ‘ONLINE BUDDIES’

Some people use cyberbullying to humiliate, threaten and harass others. In the process, it always causes harm to the victims psychologically and mentally in their daily life. Instructors should discuss with students how to distinguish right from wrong when faced with cyberbullying incidents. There is always the option of reporting the incident to teachers or

social workers. More importantly, students should be reminded to stay firm and refuse to participate in any cyberbullying activities.

Instructors should encourage students not to disseminate anything that is not in accordance with facts to avoid hurting others. Students should not be an instigator and never gather others to participate in cyberbullying. They should advise others who participate in cyberbullying to stop their bullying behaviors. Students should not take revenge for others who are being bullied, but immediately seek help from teachers and social workers and maintain an objective and neutral attitude in handling information on the internet.

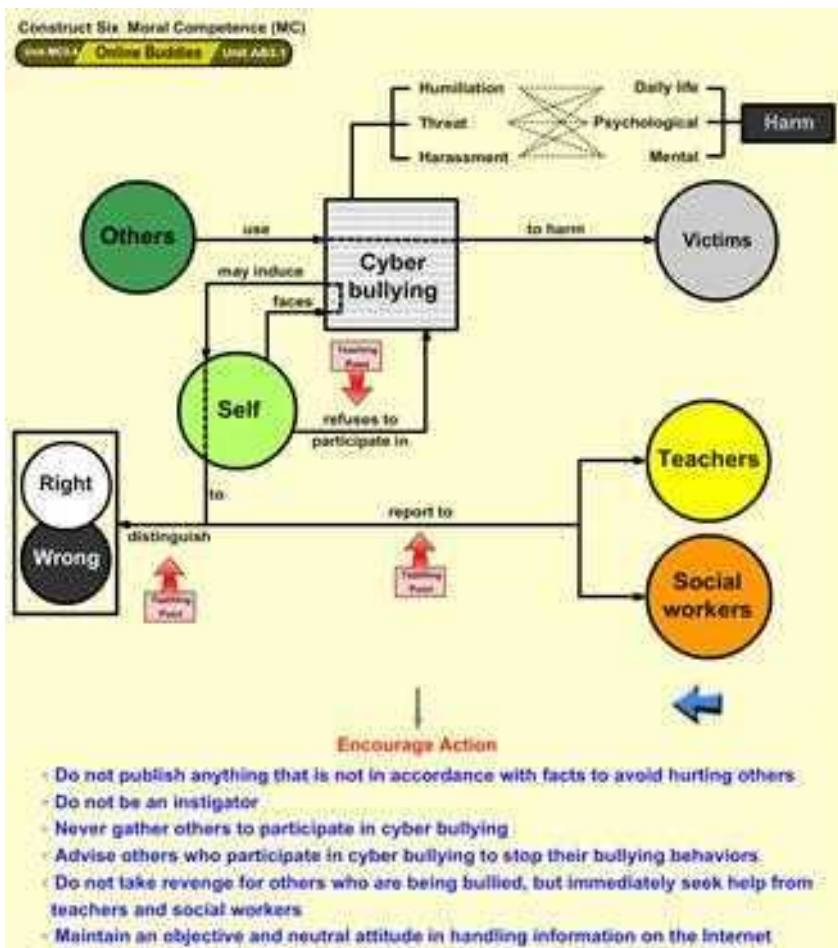


Figure 7. Unit MC 3.4/AB 3.1 'Online buddies.'

CONCLUSION

The teaching materials will arouse students' attention as bullying is a common phenomenon on and off campus. Most students have experienced being one of the roles as the bully, the victim or the bystander, and it is not difficult to recall what those scenes are like and how they felt. Instructors are in a good position to bring out the importance of choice, and

how different responses can lead to a more desirable and fair outcome to all parties. It does not help by avoiding, arguing or fighting with the bully, and students need to take actions, such as seeking help from social workers or discipline masters when bullying incidents occur.

User Feedback -- Personal Reflection

Below is the personal reflection of a female aged 15 who attends an international school in Shanghai, China. Parental consent to play the digital game and publish her own views were obtained. She wrote: “What I learned from this game was that there are many strategies for dealing with bullies in a class. A lot of responses to a bully will probably be related to how you feel and your personality type. For example, if you are a naturally shy person, when a popular girl like Carol bullies you, you may feel embarrassed and be more inclined to just ignore the problem at hand. This usually does not do anything to stop the bully from making fun of you; not speaking up for yourself may even make the situation worse. On the other hand, if you get angry too quickly and your responses are too harsh, the situation may also escalate quickly and end with punishments for everyone involved. Most of the more “successful” answer choices seemed to be answers where the narrator character was open about feelings and wanting change.”

A young adult man aged 19 studying in a college in the United States wrote:

“This game conveys the message that if you are getting bullied and do not respond, the problem does not necessarily go away. You have to respond to it and stand for yourself. However, I am not sure that it is necessarily true. Every situation is different. Sometimes, it is necessary to escalate things, and punishments for everyone are the most beneficial solution. Maybe it should still be stressed that every situation is different. There is no single right way, just do not end up bullying others as well because that will make you a bully too.”

DISCUSSION

BCB are complicated issues that require prevention at primary, secondary, and tertiary levels. A significant number of students are victims; some are intentional or unintentional bullies while many who have witnessed BCB remain to be bystanders. The high prevalence rate justifies continuous and concerted efforts in primary prevention for all to enhance students’ empathy, knowledge, and skills to handle the problems. This chapter attempts to contribute to the development of knowledge and practice of prevention of BCB through the development of a DPYD game, which can be used together with relevant PYD curriculum units, which are the foundation of the evidence-based program – the Project P.A.T.H.S. [32, 35, 36]. Qualitative evaluation comments from two users provide initial but encouraging support to the potentials of the game in helping adolescents. There are several issues that deserve attention.

First, there is a growing interest in the use of GBL [39] and gamification [40] in education and prevention of adolescent issues. The availability of a DPYD game presented in the context of on-and-off-line relationship targeting on BCB serves as an electronic resource for enhancing some specific PYD constructs which include moral competence, resilience, and prosocial norms. The game is intended to enable players for successful adaptations to

challenges in and out of school. With the generous support from the funding body, the digital game can be used with only little to no cost. It is hoped that a wide adoption of the game may contribute to a further reduction of the problem worldwide.

Second, the design of this DPYD game is based on theories of BCB as well as GBL. School social workers who work with secondary school students were consulted during the design stage. Their frontline experiences were adopted to develop the storyline. By adopting game elements, such as curiosity, attractiveness, different story endings for different choices, immediate and extensive feedback, the game has an attractive outlook. Following different storylines in the game, players' curiosity will be sustained. Different choices allow players to experience different endings and thus, obtain different feedbacks. The design can serve the functions of maintaining players' engagement and encouraging their repetitive use which will enhance the achievement of intended learning outcomes. Moreover, the use of cartoons/illustrations can help reduce the cultural barrier. The availability of gender-specific versions of the game may also increase the attractiveness and reduce the possible gender-bias problem.

Third, to prevent BCB, students need to learn knowledge and skills, such as self-awareness, moral decision making, perspective-taking, empathetic understanding, effective communication, personal reflection, and relationship building and maintenance. These outcomes can be achieved through conscientious discussions facilitated by well-informed instructors. This chapter illustrates how a well-designed, evidence-based prevention program helps reduce multiple forms of BCB and echoes the argument that there is no need for specific programs for different forms of BCB [41]. Recent research supports the development of empathetic understanding through digital games [42] and in-game empathy can predict interest in learning more about the game topic [43]. Providing information alone is not effective for preventive interventions [44]. In prevention of BCB, provision of legal knowledge and information on consequences for stakeholders do not change their attitude and behavior. Even though adolescents possess the knowledge and self-efficacy in not engaging in BCB behaviors, many victims may engage in cyberbullying for the sake of retaliation.

This chapter has several "practice" implications. The first implication is that this DPYD game could serve as a supplementary teaching and learning strategy in order to produce the best possible results in prevention. The literature supports offering school-based programs [24].

From the ecological perspective, an effective preventive program must reach all groups involved. A primary prevention program targeting all stakeholders is more likely to be effective. It may be practical for schools to implement primary prevention program for all students. The DPYD game can reach all students. With the support and guidance from instructors, students may become self-motivated learners.

The second implication is that schools can provide ongoing support for students with greater psychosocial needs and victims [45]. When most students are highly aware of the issues through a universal program and constructive ways of handling BCB incidents are introduced to all students, including victims, bullies, and bystanders, the dynamics and the processes of BCB are changed according to systems theory.

The third practice implication is for the helping professionals to use the game for secondary prevention. When most students are aware of the issues and ways to tackle the problem after playing the game, asking victims about their experiences in an open manner may become easier because the story in the game resembles their own experiences which may

be difficult for some to describe clearly. It may be easier for the helping professionals to build a working relationship with bullies, victims, or bystanders when they start by sharing and discussing similar matters albeit different perceptions. The issue of how to make good use of the DPYD game is important. The game is designed for primary prevention. It can be used for secondary prevention. It may be valuable for the helping professions, such as social workers, psychologists, mental health professionals to use the game for engagement, initial assessment, and discussion on the foci of intervention for individual intervention and for restorative and peer mediation on interpersonal conflicts between bullies-victims [46]. Although the digital game does not keep any personal data, with client consent, the use of print-screen function can facilitate the intervention process.

The fourth implication is on the implementation of evidence-based programs. Literature on the quality of program implementation supports the adoption of the 5 “P”s model which includes policy, people, program, process, and place [47, 48]. As a primary prevention effort to reduce BCB among adolescents, the Project P.A.T.H.S. is an evidence-informed and school-based program. Although the program aims at promoting holistic development, there is evidence to support that participants are better prepared to meet various challenges in their paths to adulthood [32, 35, 36]. Apart from the program and place aspects, the Project provided training to over 7,000 teachers and social workers to support the implementation of the program to promote PYD. Moreover, since the Project was supported by the Education Bureau and the Social Welfare Department, the policy aspect received proper support at the central and local levels. Furthermore, an average high rate of over 90% of adherence to the original design was recorded [49]. The adoption of the 5-P model explains partly why the program succeeded. The design and development of DPYD game serves as a supporting and reinforcement electronic learning resource to further enhance the effect of prevention.

The fifth implication is related to cultural issue. The attitude of adults in engaging adolescents’ participation in prevention and intervention to find a quick fix of BCB could be a challenge. It is particularly relevant to Asian societies in which authoritarianism still prevails. Joining in a game with real-life situations is much easier for adolescents to engage in non-threatening discussions and develop reflective thinking. Game-based learning facilitates in a dialogue among stakeholders without the guise of intolerance, exclusion, and rigidity. In a digital era, realizing youth’s potentials in shared leadership to create thoughtful, peaceful and inclusive interactive relationships are more viable than right or wrong responses to the legal and policy challenge of the daunting BCB issues [50].

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Chapter 351

REDUCING GENDER STEREOTYPES THROUGH A DIGITAL POSITIVE YOUTH DEVELOPMENT GAME

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ABSTRACT

The purpose of this chapter is to describe a newly developed digital positive youth development (PYD) game and discuss its effectiveness in understanding and reducing gender stereotypes and biases among junior secondary school students. The game, “male and female dichotomy,” allows students to explore gender stereotypes on “appearance,” “behavior,” “occupation,” and “traits” (ABOT) based on Deaux and Lewis’ gender stereotyping model. The design of the game is described after a review of relevant literature. The game guides students to examine the social demands and expectations of men and women in today’s world, and it enables them to reflect on how gender norms and their perceived gender stereotypes affect their perception on both genders. The game has been piloted in secondary schools in Hong Kong and is available free of charge upon request for non-commercial purposes. Two users who study in Shanghai and the United States were invited to review the game. Initial findings revealed that the section on “occupation” and “traits” were beneficial in the learning process, and the users became more aware of their gender biases. More research is needed to investigate the effectiveness of electronic game-based learning (GBL) in reducing gender stereotypes and biases among children and early adolescents.

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INTRODUCTION

The problem of gender bias is global. Gender bias affects people in academics, career choices, and mixed-gender relationships, and to certain extent personalities. According to the ISSP Research group, women from more than 20 countries have reported issues of the family posing a challenge for their careers and women reported a higher level of family interference with work than men [1, 2]. The formation of gender identity starts at an early age. A study in Hong Kong suggested that boys prefer masculine toys while girls prefer feminine ones. Thus, this shapes children into certain personalities in that girls are found to be more empathic and less aggressive [3]. Furthermore, the awareness of a person's gender can harm his/her relationship with the opposite sex. Single-sex schooling is practiced in some schools. Wong, Shi, and Chen [4] suggested that single-sex school students are more prone to having mixed-gender anxiety and less mixed-sex friendship. As gender bias is a global issue, it is crucial to investigate this problem in search of prevention and intervention plans.

LITERATURE REVIEW

Gender stereotype is defined as the social standard perception of how males and females should think and behave in different situations [5]. Traditionally, men and women were assumed to be responsible for particular roles, appropriate behaviors, and duties in society. The social-political-economic-cultural opportunities for women in most cultures have been restricted, even though the situation has been improved noticeably nowadays in some economically advanced societies [6]. Furthermore, sometimes women are highly involved in the labor market. At the same time, they are still very often the major carer at home in most societies. Yet, the dual role of women has led to conflicts and concerns [7]. Caring for children and doing household chores are tasks usually taken up by working women. The notion of gender role difference, the practice of dual role, and the societal norms may have reinforced the stereotypical concept and the dual role. More importantly, this stereotype is found in children and adolescents in one way or another.

Gender Differences in Activities and Games

A study in Australia reported that teenage boys prefer spending time in physical activities or video games, whereas teenage girls rather spend their time on social activities, studying and household chores [8]. In fact, gender role learning starts at an early age, and this process continues in children's development [9]. Children can differentiate gender differences by 18 months old through their ability in associating gender-stereotyped toys (girls with dolls and boys with toy trucks) [10]. By the end of childhood, those who have a stronger gender identity reported to have pressure to conform to their gender role [11]. To behave according to the gender identity becomes a norm.

The Formation of Gender Stereotype

The development of gender stereotype involves children's interpretation of the information in their surrounding sociocultural environment. Based on this process, they form a representation of gender called "gender schema" [12]. A schema is a cognitive structure that guides an individual's perception through an association network [13]. The gender schema theory proposed that gender schema contributes to sex typing by individuals due to the readiness of processing information based on the sex-linked associations [13]. Ultimately, sex typing turns into a standard guide for one's perception and behavior, which also influences the concept of self-identity [12]. Self-identity is inseparable with gender as identity is the adoption of specific traits or groups [14]. By identifying the self with female or male, this identity becomes part of the self that increases the motivation to behave similarly to the identified group, attention to information of their own sex, and increases one's own interests in the activities that belong to one's own sex group [15].

The formation of gender stereotypes is complex and often derives from the sociocultural environment and cognitive development. According to social learning theory, people learn from observing others' behaviors and their consequences to avoid negative outcomes and gain benefits [16]. Leaper and Farkas [12] suggested that the development of gender identity involves four distinguished processes including the 1) social-structural process, 2) social-interactive process, 3) cognitive-motivational processes and 4) biological process. The social-structural process is the perspective on gender roles in society; the social-interactive process refers to the experience children interacting with others such as parents and peers; the cognitive-motivational process helps shape children's perception and interpretation on the world, usually related to self-esteem and self-identification; and finally, the biological process that children recognize from the physical differences with their opposite sex.

Media Influence

As part of socialization agents, mass media shape gender stereotype as they are the major source for children and adolescents to acquire an enormous amount of gender information. Even products for preschoolers are embedded with gender-specific messages such as bedsheets, furniture, toys and clothes [17]. The marketing of products for young children is also specific to gender, creating a differentiation between boys and girls [18]. Young children utilize the information they learn from popular culture and media to shape the way they dress, talk and play [19]. For example, media has been portraying females as a subordinate figure such as associating women with housewives and homemakers [20] and promoting a specific body shape [21]. With the constant exposure of this in-balanced or even biased information, adolescents form their perception of gender.

Parental Influence

Parents and significant others play a crucial role in the development of gender stereotype. Parents influence their child's perception of gender identity when they reinforce or discourage

certain behavior in play [18]. For instance, fathers react negatively to their children's cross-gendered behavior, particularly with their sons [22]. From that, children develop their gender identity on how they should behave according to their genders. Parents' contributions to their children's gender stereotype continue to the adolescence period [23]. A study showed that parents' distorted perception of their children's ability and interest based on gender stereotype affect children's performance in gender-role stereotypical activities such as sports and mathematics [24].

Peer Influence

Peer influence is powerful in adolescent development [25]. According to social identity theory, people naturally seek positive identification with social groups [26]. Adolescents learn to avoid behaviors that are inconsistent with their social group. Friends contribute to gender stereotype via peer pressure on how they interact with their friends. Children are aware of cross-gender behavior. For example, boys find their peers who display feminine behaviors and qualities less acceptable [27]. Boiché and colleagues [28] have proven that adolescents' sports performance, especially in girls, depends on their social environment. Moreover, if girls perceive sports-gender stereotype in their social environment, they are likely to drop out from physical activities.

To summarize, young children start to form their gender stereotypes while they are actively searching for gender cues in their environment [15]. Young children demonstrate their gender-stereotypical behavior through play [18]. For example, girls are likely to select family roles while boys prefer action-oriented roles in dramatic play [29].

Effects of Gender Stereotype

During adolescence, the effects of gender stereotype extend to appearance, behavior and personality traits. Young boys and girls have a certain perception of how men and women should look like. One interesting finding is that both boys and girls hold a perception bias in women's body size, underestimating the average body size of women with a slim-female thin ideal [30]. Such a perception is encouraged through advertisements in mass media promoting slim females, resulting in a decrease in body satisfaction and self-esteem in young girls [21]. In terms of behavior, young males are associated with verbal and physical aggression [31], a tendency to be engaged in risky behaviors [32], and a tendency to risk driving as the characteristic of risk-taking is associated with masculinity [33]. Moreover, girls show a less risk taking and more self-less characteristic compared to boys [6]. Females are also perceived to score higher in certain personality traits such as openness, conscientiousness, and agreeableness [34], while males are associated with instrumental traits including aggressiveness and competitiveness [35].

Consequences

Gender stereotyping does not only affect adolescent academic performance but also in physical activities and occupational choices. Numerous studies confirmed its effect on academic performance, in particular, mathematics. Research showed that adolescent girls are less likely to participate in a mathematic task under competition circumstances, while no gender difference is observed in verbal tasks [6]. In addition, it is found that girls perceive themselves to have better literacy ability, while they rated the boys lower in literacy [36]. Girls also feel less comfort and a sense of belonging to computer science due to the negative stereotypical concerns [37]. In terms of physical health, a study showed that adolescents are likely to hold stronger sports gender stereotype if they perceive their social environment to do so [28]. Additionally, personal endorsement of stereotypes can lead to dropout behavior when adolescents' perceived gender plays a significant role in the success of playing a certain type of sports [28]. In fact, boys adopt such a stereotype. They are more likely to participate in invasion game and reported invasive ball games to be enjoyable, while girls prefer to be a bystander and take an observer role, demonstrating gender differences in physical education [38]. Exercise is beneficial to young people's cognitive development [39] and reduces depressive symptoms [40]. With girls being less physically active due to the stereotypical effect, it could adversely affect their mental health.

While occupation aspiration will develop in children at an early age [41], early gender bias in occupational choice has been observed in boys that they tend to pursue a traditionally male career [42]. Adolescent boys usually have a science and mathematics career aspiration, especially if their male peers also hold the same career aspiration [43]. When asking both young boys and girls about their expectations on future occupation, young girls reported to value helping people, whereas boys preferred science-related jobs and valued variables such as becoming famous, earning lots of money and controlling others [44]. Interestingly, female adolescents exhibit struggles between their commitment to their future family and their future careers. Their career aspiration is also associated with their mother's occupation [45] and they tend to select a career that matches with their gender role [44].

Apart from affecting academic performance, limiting the choices of physical activities and occupation, gender stereotyping could have more severe consequences such as peer victimization which include physical, verbal, and relational aggression [46], social exclusion, and social isolation [47] for both genders. They can lead to a devastating outcome if a child was isolated or excluded from his/her social group because of exhibiting behaviors deviated from the gender norms. Interestingly, there has been little research that specifically examines the impact of gender stereotyping that focuses on how children think about the issue - what they understand about gender stereotyping and the consequences that bring forth by it [48].

Deaux and Lewis [1] identified a gender stereotyping model with four components to explain how people differentiate males from females, including physical appearance, traits, behaviors, and occupations. The model posits that information about physical features seems to be in the central position which strongly affects judgments about the other three components whereas the other three components affect one another mutually. Moreover, stereotyping is a cognitive process which is a necessary antecedent for a negative evaluation of any individuals or groups. As an attitude, prejudice is a necessary condition for discrimination behaviors.

PREVENTION STRATEGIES

Andreoletti, Leszczynski and Disch's [49] study on compound stereotypes (gender, race, age) suggested that gender stereotypes about agency and communion tend to remain across the life span and that people usually hold a unique stereotypical belief based on multiple social categories. For prevention, work should start as early as possible. Children's potentials and development are limited by gender stereotype and sexism [18].

Awareness and Reflection

To facilitate positive development in adolescents, it is important for adolescents to recognize and to be aware of gender stereotype in order to reflect on their own perception and behavior.

Role-Model and Workshops

One possible way is to provide a role model that overcomes gender-stereotype barriers [50]. Alternatively, educational workshops on gender stereotypes with teacher participation are found to be effective to facilitate students to make less gender bias decisions and behavior [51]. Given that, we expect teacher's involvement in the learning process as a moderator and guidance.

Classification and Game-Based Learning

Classification training has been shown in research to be helpful to resist gender stereotype information in young people [52]. The newly developed game adopts this idea with a final product of classification game highlighting the gender stereotype perception. We aim to help players identify gender stereotypes in order to reduce them.

Video games have been proved to have educational value, especially in this modern age where computer and video games thrive [53]. Students are more engaged when they learn from playing video games [54]. However, Weber and Custer's study [55] suggested that digital game-based learning (DGBL) might be more suitable for middle school students compared to high school students partly because middle school students showed a keen interest in contemporary technological learning activities and they may have less been exposed to such learning experiences. Thus, this supports why the digital games are specifically designed for middle school age students who start to develop their gender identity at this stage of their development with an aim to minimize the effect of gender stereotype.

DESIGN OF THE GAME

It is inevitable that we experienced a certain degree of social indoctrinations such as different views on women and men, and their respective demands and expectations from society when we grow up. In modern societies, many traditional gender roles or images have changed. For example, the number of husbands taking care of household chores has been increasing. Can we maintain an open attitude? Respect and acceptance are important elements of gender issues. Students may have already had their unique opinion on both genders growing up in their family, community and social environment. They might have a set of criteria regarding gender roles, which have been deep-rooted in their minds. To intervene, the game enables students to explore gender stereotypes on “appearance,” “behavior,” “occupation” and “traits” (ABOT). The aim is to examine the perception of gender stereotypes in contemporary society. It guides students to examine the social demands and expectations of men and women in today’s world. It enables them to reflect on those perceived gender stereotypes, and how they affect their personal perceptions of both genders.

This game targets participants of Secondary 3 level, the equivalent of Grade 8 in North America. There are four sections of the game to choose from, and instructors can choose selectively according to the needs of the students. Games range from 15-minute long to about half an hour.



Figure 1. The front page of the game.

Game Objectives

The objectives of this game can be separated into three different aspects: cognitive, emotional, and behavioral. On the “cognitive” aspect, students can develop a deeper understanding of their own gender stereotypes and biases in ABOT. On the “emotional” aspect, students can enhance their acceptance of the opposite gender in the four areas. On the “behavioral” aspect, students can reduce discrimination against people with a distinctive gender profile, and get along harmoniously with the opposite gender as a result of an increased acceptance level.

The games are designed for students to understand gender stereotypes as well as their views and values on gender roles. Besides, students can learn and understand how stereotyping affects career decisions and reflect on the importance of gender equality.

Teaching and Learning Method

Through the use of gender stereotype awareness games, feedback and guidance are provided for students according to their responses to help them reduce gender stereotypes and biases. Besides, instructors can make use of the supplementary teaching materials and encourage small group and class discussion on the topic of gender. Ideas of “Male Superiority, Female Inferiority” and “Men Focus on the Outside World, Women Focus on the Home” and their respective impacts on our society can be used for discussion to help students understand the traditional views on the two genders and the reasons behind those thoughts. Through the exploration of the differences in social status, values, and responsibilities between men and women, we can invite students to share their thoughts and opinions, and instructors would get a sense of how students perceive gender and its respective role.

Learning effectiveness can be enhanced through discussions among mixed-gender groups. Specifically, such discussions provide an opportunity for students to clarify their own values about gender norms. Through discussing with an open mind, where students can face each other as equals, students can learn to respect different views while reflecting on their own values.

Game Design

Students are required to answer questions to indicate their acceptance of different gender images. All questions are presented together with graphics. The whole game is composed of four sections. The first two games test students’ gender stereotypes and biases in “appearance” and “behavior” by their acceptance levels. Students are invited to ponder if appearance affects their attitude and perception of others, i.e., their preferences regarding making friends with people of particular features or style such as an untidy person, a fat or thin person, a girl with short hair; and if they accept them, to what extent they want to be associated with them such as becoming their spouse or good friends.

The Guttman scale [56] is used in measuring the attitude of each user in the first two games on appearance and behavior. Users are given an artwork which shows a certain appearance or behavior. They are asked whether they accept it from a list of 7 people who have varying levels of relationships. These 7 choices are arranged in a hierarchical order: the future spouse, a family member, a good friend, a friend, an acquaintance, an on-line-follower, and unacceptable. If a respondent can accept a certain appearance or behavior from his/her future spouse, it can be inferred that this respondent will accept all other people who have the same appearance or behavior. This reflects that the respondent has the highest acceptance level. At the end of each of these two games, a quantitative analysis on the acceptance level of the player will be presented. Instructors can encourage students to discuss two questions: Is people’s appearance or behavior a factor to consider before students form a certain

relationship with a person? What level of relationship will students be willing to have with someone who shows unconventional appearance or behavior, for example, a man who cooks or learns ballet?

In the last two games, students are invited to indicate whether an “occupation” or a “trait” is gender-neutral to test their gender stereotypes. In the game on occupation, students need to think if certain occupations are generally more suitable for females, males or both in the contemporary society. They might conform to social norms and traditional gender roles, and thus form an impression that particular occupations should be held by a particular gender but not both. For the game on trait, students are asked to determine if the features are suitable to describe a particular gender or both. This will test how they perceive the differences in personality traits between the two genders.

After they finish one of these two games, a qualitative analysis based on students’ choices will be provided in terms of gender stereotypes. For the game on occupation, instructors can make use of that opportunity to discuss with students that choices of career are influenced by many aspects such as income, social status, social expectations, and significant others, and that gender-specific traits are stereotypes. For the game on trait, students will have opportunities to review their degree of tolerance and acceptance of others as well as the level of respect for others and the tendency towards gender stereotyping. Instructors can encourage students to reflect on how they describe females, males or both genders, whether they have gender biases, and whether there are gender-specific traits.

The qualitative analysis presents the views and beliefs of students, which to a large extent are influenced by social requirements and views and expectations. To promote further discussion, instructors may suggest students to use the print-screen function to print out the analysis as the game does not record any data once the player exits the game. Suggestions can be given to encourage students to be more courageous and open-minded about the choice of career and views on gender-specific traits. Constructive suggestions might be given to encourage students to adopt a more open-minded approach to human diversity and equality. They are encouraged to reflect on the reasons why they believe certain occupations/traits are more suitable for a specific gender.

Tips for Instructors

Instructors may demonstrate the game in a class or an assembly and remind students to have an open mind when reading the feedback provided by the game. The feedback and guidance help students reflect on the issues of gender biases, look in-depth into these issues through discussions in or outside of the class, and try to summarize the different views. Instructors may encourage students to re-play the game so that they can observe any changes in their acceptance level of different gender images after discussion. As our impression and perception of women and men are largely influenced by our socialization through life experiences and interactions with others in our circle, instructors may encourage students to try to see how our society projects the images of gender and how it treats the two different genders. Moreover, our stereotypes and biases on ABOT are reinforced through our social interactions and expectations. We have to help those who might be confused, feel

uncomfortable or unable to accept. Instructors may encourage students to try to see gender disparity in a different way - the bottom line is to treat one another with respect and tolerance.

In terms of occupations, instructors can remind students to be respectful and tolerant of others in terms of career choices based on one's interests, abilities, and adaptive development. Students can explore the possibilities of certain occupations, which traditionally are dominated by one gender, from a different angle. Will they accept themselves to take up the work which is normally performed by the opposite gender such as a male nurse and a female electrician?

Instructors can bring in their personal experiences and other real-life examples to broaden student's thinking on the issue. Discussions between female and male students should be encouraged to help students understand what the other gender think or experience in their daily life. In cases such as single-gender schools, instructors can encourage students to use the teaching material after class and discuss with their family members. Social workers or counselors can use the teaching material for individual or group counseling.

POSITIVE YOUTH DEVELOPMENT CONSTRUCTS

The game was specially designed to contribute to one of the 15 positive youth development (PYD) constructs, i.e., "Clear and positive identity." They have been identified as effective components of PYD programs [57]. Incorporating all the 15 constructs, the project P.A.T.H.S. is an evidence-based and multi-years universal PYD program [58, 59]. The objectives of the project are to promote a holistic development of adolescents in Hong Kong by providing opportunities and recognition to develop competence and skills which are conducive to PYD. The program aims at promoting bonding and resilience among adolescents, enhancing core competencies, training critical thinking skills, and cultivating healthy beliefs and values. The project provides a primary prevention program through 20 hours in Secondary 1 to 3 (Grades 7-9). A total of 120 teaching units (each 30 minutes) covering 15 PYD constructs. It also provides a tier-two program to meet the needs of students with greater psycho-social needs. Evaluation studies showed that the project was efficacious in addressing psychosocial risk factors during adolescence [58]. In an effort to revamp the content by adding a DPYD game, a new curriculum unit was designed. It can be used independently or to support two existing teaching units. A brief description of these two related units is provided below.

Related Teaching Units: Concept Maps, Learning Targets, and Teaching Tips

The two related teaching units are named SX2.2 "Men...Women...Not" and SX2.3 "You Can' be Good at this." They were designed to promote sex education for S2 (Grade 8). For SX2.2, the learning targets are to understand gender stereotypes and understand students' views and values on the gender roles. It focuses on the construct of "Prosocial Norms" and "Social Competence." The concept map is presented in Figure 2.



Figure 2. Concept map for teaching unit SX2.2.

Teaching Points for the Teaching Unit SX2.2

There are a set of expectations towards the two genders in our daily life, schooling, choice of career and family. It is often affected by gender stereotypes and has a direct impact on an individual from different people such as parents at home and teachers from schools. Those gender stereotypes on the two genders also have an impact on people's behaviors, characters, and values. Instructors should understand those gender stereotypes and share with students what they are and how they affect our perceptions of gender consciously and unconsciously.

In the teaching unit, students could reflect on one's own personal views toward gender roles, and be encouraged to treat the opposite sex with a fair and open attitude. Instructors can guide students to reflect on the reasons for having different expectations on people of different gender and remind students to respect others even when our behaviors, character, and values are different.

For SX2.3, the learning targets are to understand how stereotyping affects career decisions and help students to learn about the importance of gender equality. It focuses on the construct of "Self-determination" and "Moral Competence."

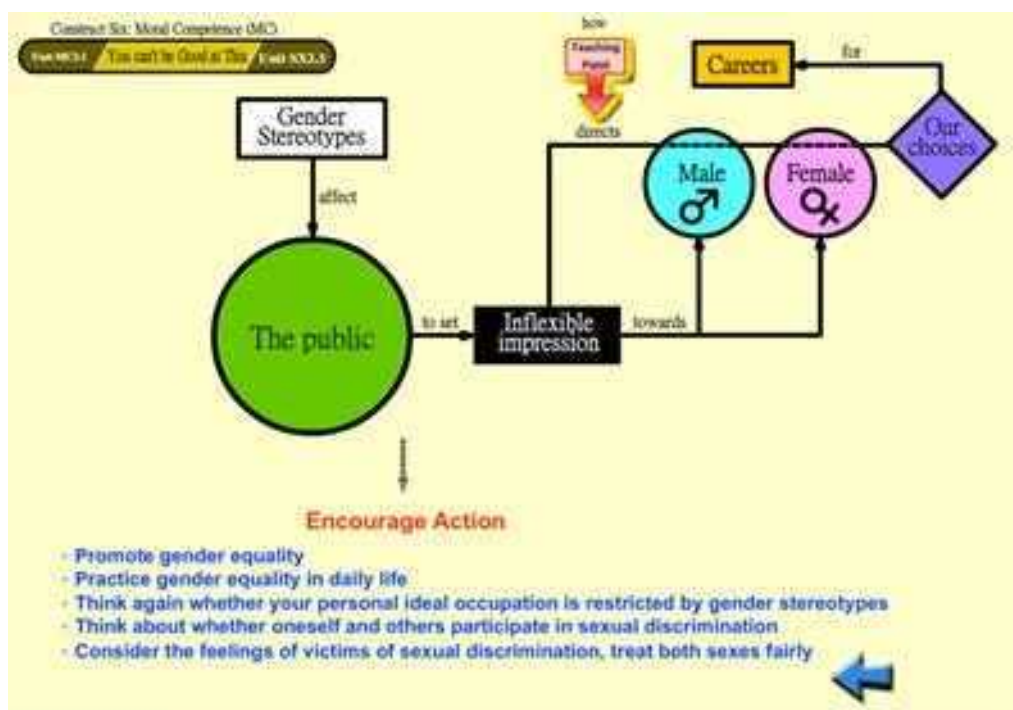


Figure 3. Concept map for teaching unit SX2.3.

Teaching Points for the Teaching Unit SX2.3

Gender stereotypes affect everyone in the public domain as our society often sets inflexible impression towards both male and female. Those impressions and ideas directly affect our choices for careers and people might see certain careers exclusively for male or female without questioning the rationale behind. In the theory of planned behavior, it links one's beliefs and behaviors. Our attitude toward others' behaviors, the subjective norms, and perceived behavioral control, all combined to shape our behavioral intentions and behaviors [60]. Instructors should discuss those impressions and ideas with students and listen and understand where students are coming from when they share their thoughts on the topic.

Instructors may make the best use of this unit to promote gender equality and suggest ways for students to practice gender equality in daily life. Encourage students to think thoroughly if their personal ideal occupation is restricted by gender stereotypes through class discussion. Besides, it is a good opportunity to help students reflect on whether they or others in the community have engaged in sexual discrimination behavior. If so, discuss some of the ways students can do to minimize that from happening again. We can increase students' empathy towards the victims of sexual discrimination by inviting them to consider victims' feelings so that they realize that they should treat both genders in a fair way.

Instructors can make use of the reference materials provided to supplement their teaching of this unit when using the game with students. The materials can be found in unit ID3.2 "The male-female dichotomy?" There are reflection questions available for instructors to use with students at the end of the teaching section.

In the game, students were given the opportunity to think about how our attitude and perception toward someone are affected by his/her appearance which affects their relationship with others. They can reflect on their preference regarding making friends with a person with particular features or style i.e., a fat person, an untidy person, a very thin person or a girl with short hair, etc. Students can be invited to actively engage in self-reflection on their own personal values towards gender roles and how that affects their behaviors. Also, students are invited to think if certain occupations are generally more suitable for females, males or both currently in society.

To sum up, the games support the teaching units to help promote and practice gender equality, increase awareness of gender stereotypes, and cultivate empathy for victims of sexual discrimination among students.

USERS' FEEDBACK

To collect feedback from users, convenient samples of adolescents and young adults were invited to use the game. Participants were invited to reflect on their experiences and comment on the game design.

The following comments came from a 15-year old Chinese female student studying in an international school in Shanghai. Parental and participant's consents were obtained to use the game and her comments on her experience.

Appearance

"For me personally, this exercise was not extremely eye-opening because I think that in my upbringing in an international school, I've been exposed to a range of students and friends from many different countries and with different physical appearances. Thus, my responses for most of the categories remained unchanged throughout the game."

Behavior

"For the behavior game, I was entirely sure what the main learning aim was when playing. Based on my understanding, the game was set up in such a way that typical assumptions about girls and boys were provided, and I would pick what type of relationship I would be willing to be in. However, I think that one aspect that this game overlooks is the player's personal values. For the traits that are stereotyped as non-feminine, such as "behaving violently with others" and "fights with others physically," by clicking not acceptable does not necessarily mean that the player is against females specifically doing this, it may be that the behavior overall is something that people should not have. To account for players' personal values, it may be useful to ask players to pick whether or not they would accept a relationship with a certain behavior for females and males separately. For example, "What relationships can you accept to form with a young lady who does not know how to

cook?” and “What relationships can you accept to form with a young man who does not know how to cook?” could both be asked in the game.”

Occupation

“I found this game interesting because there were a lot of occupation options offered. It helped reinforced ideas supporting career gender equality, such as how males can also be home-carers, and females can be engineers or programmers. However, I felt like the game was a bit repetitive.

Towards the end of the game, it was easy to fall into the trap of just putting all the occupation blocks into the “both” category without thinking or reflecting on what my opinion really was.”

Traits

“Throughout the first run-through this game, I found that there were definitely some biases I held towards what traits are considered feminine or masculine. After playing the game, I think that I was more self-aware of these biases. Similar to the occupation game, I think that due to the repetitive nature of just placing traits into different categories, it was less effective in self-reflection towards the end of the game.”

A 19-year old college student from the United States wrote on one of the games ‘Behavior’:

“I do not think there is much that needs improvement here. It is fine as it is. I believe this section was well done. It conveys the message of breaking down stereotypes and being more accepting clearly to the player.”

DISCUSSION

Different times impose different demands and expectations on either gender, which play a crucial role in maintaining social stability and harmony. As we grow up, the external world including families, schools, communities, and societies instill into us identities of what men and women should be and what is expected of each gender. This teaching unit helps students examine in depth the positive and negative implications of these notions with regard to gender equality. The instructors can lead students to think of examples of heroes/heroines of all times from around the world and talk about their achievements. As a basic principle for human relationships in any modern society, individuality should be respected. Women and men develop their own distinct qualities such as physical appearance, physique and thought pattern through socialization since birth. On one hand, we should treat one another with respect, acceptance, and tolerance, and on the other, we must help keep this principle through primary prevention to provide early education, clarification of values, and treatment if necessary when it comes to the issues of gender inequality. Our society should strive to recognize and rectify inequality should gender prejudice and discrimination happen. Students should be reminded

that people should not be limited by gender, and they are free to follow their passion and fulfill their dreams regardless of society's perception of gender roles.

From the users' feedbacks, it was suggested that the games successfully evoked adolescents to rethink about gender roles and their perception of gender. Particularly, the two users found the occupation and trait modules inspiring and interesting. They reported that the game in the occupation module helped to reinforce gender equality in occupation choice, especially in this modern society, man could be a home carer, whereas women could work in the science and engineering industry. It seems that this game can help students understand the constraint by gender stereotypes and gender norms [61] and expand their options in their future career choices [62]. For the trait module, it was reported to have a similar effect with the occupational module. Users reported to be more self-aware of their gender-biased traits, which they have formed unconsciously in the past. However, whether they will adopt a higher level of acceptance remains unknown. This calls for further research.

The feedback on the appearance and behavioral modules were not as positive as the occupation and trait modules. Users expressed that the appearance game did not offer a surprising experience because they were used to the diversity in people. One further explained that she had many opportunities in life encountering people from different countries with different physical appearances properly because she studied in an international school. Further studies are recommended to include players of different backgrounds. The behavioral module was reported to be confusing that the user had difficulties understanding the learning purpose of the game. One user pointed out that the cause of his confusion could be design-related as it disregarded the personal value of the participants. This issue deserves further examination.

The initial findings from users' feedback were partially consistent with previous research that education on gender stereotype helps the young ones to be less gender-biased [51]. Participants suggested 2 out of the 4 modules of the game could be further improved in order to clearly deliver the game content to address gender stereotype. The qualitative comments were also supported by the study of Bigler and Liben [52] that classification trainings such as occupational sorting were crucial for counter-stereotypic information, potentially reducing gender stereotype in young people. In addition, utilizing computer games in the education context suggested by Squire [53] is supported in the current study. Junior secondary school students generally enjoyed learning through playing computer games, echoing the study by Weber and Custer [55] that early adolescents benefit from DGBL. This study provided a background for testing the effectiveness of the game.

To sum up, the use of GBL materials do have benefits over traditional teaching and learning format such as learning from textbooks. In this game, designers have considered the principles of attractiveness of the pictures and characters, the background of the screens, the engagement and responses of the participants in the activities and the feature of repeated use when putting the games together. With the help and guidance of the instructors and peer interactions, students were motivated to participate in the activities and learn in a fun and educational atmosphere on gender equity and stereotypes at the pace of the class and at home as well.

LIMITATIONS

A problem with the current study was the generalizability of its results. Compared to quantitative research studies, the findings of a qualitative study cannot be extended to the greater population as the data from a qualitative study are not examined to ascertain whether the findings are statistically significant or due to chance [63]. The qualitative data should be interpreted with caution.

Testing the Effectiveness

This study did not obtain any quantitative data on the level of gender stereotype of the middle school students. In the future, a thorough quantitative research can be conducted to test the effectiveness of the game in minimizing gender stereotype among adolescents. Many well-established scales have been developed to measure the level of stereotype including the Gender Role Attitude Scale (GRAS), the Bem Sex Role Inventory (BSRI), the Personal Endorsement of Gender Stereotypes Scale, and IAT (implicit association test). These measurements have been validated in Asian countries including Japan [64], Taiwan [65], and China [66]. Adopting these measurements to examine gender stereotype would be suitable for future research. To test the effectiveness of the game, a pre-test and post-test design is recommended. Basically, the study could first examine the level of gender stereotype in secondary school students using the above measurements before introducing the electronic game. After students have completed their learning, the same set of questionnaires could be done by the same group of students in order to find out if there are changes in their level of gender stereotype by comparing the scores before and after introducing the materials. From that, the effectiveness of the materials could be concluded in our target group. It is also worth investigating whether the games could be utilized for children aged between 8 to 11 using the suggested design above as evidence has proven that children as young as aged 8 can develop gender stereotype in academic and occupation preference [67]. Apart from examining the gender stereotype, other factors that are affected by gender stereotype such as self-esteem, body shapes, and subjective wellbeing could be explored in addition to the effectiveness of the games.

After testing the effectiveness of the study, future studies can focus on the impact of teacher involvement in maximizing the effect of the game. The role of teachers in educational activities that minimize gender stereotype has been confirmed in a study [51]. Even though we have assumed the involvement of teachers in delivering the materials, future exploratory study could be conducted to examine the teaching and learning processes of our DPYD games. A cross-sectional study comparing the level of gender stereotype between the group of students with teachers as guidance and the group of students without teacher involvement would be ideal. This could further inform the teaching and learning processes to maximize the effect.

CONCLUSION

The key finding is that the game seems to be beneficial for secondary school students in terms of enhancing their awareness and reducing the effect of gender stereotypes and biases. A few issues are raised in this study that required further research on the issue. Some adjustments are needed on the use of the game for different levels of prevention. The results suggested a need to conduct exploratory and quantitative studies to gain a better understanding of the effectiveness of the materials and its utilization among students.

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Chapter 352

PREVENTION OF COGNITIVE BIASES THROUGH A DIGITAL POSITIVE YOUTH DEVELOPMENT GAME

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ABSTRACT

This chapter presents a brief literature review on cognitive biases among early adolescents who grow up in the digital age. It then describes the design and production of a digital positive youth development (DPYD) game to strengthen cognitive competence. A description of how to make the best use of the game together with the use of related teaching units of the project P.A.T.H.S. for primary prevention is given. To demonstrate the potential impact, users' feedback of an adult male college student from the United States and a female early adolescent from China are presented. A discussion of how to use the game for promoting positive youth development is presented.

INTRODUCTION

Living in a digital age implies processing large amounts of information daily for almost every young person. To verify the truthfulness of information requires much time, effort, and know-how. To check the accuracy of every piece of information received is literally impossible. Children and adolescents may not be adequately prepared for an environment in

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which information overwhelms. A famous technology and social media scholar, danah boyd [1] raised an important issue that many people asked students not to trust Wikipedia, but failed to teach them critical research skills to discover the trustworthiness of any one piece of information. She argued that distrust of media and selective research to reaffirm one's own selective exposure, interpretation, and retention of information cannot help strengthen media literacy of anyone, including young people [1]. However, young people are heavy users of social media, which might contain dis-ordered information including hate speech, slander, rumors, and offending, discrediting, badmouthing and misleading narratives. Using deep-fakes is also commonly found [2-4].

In this day and age, the media landscape is developing rapidly. An individual's web search experience is tailored specifically to his/her interests or needs. Due to independent journalism and press freedom, the amount of news people produce on the internet every day is mind-boggling. At the same time, the phenomena of fake news, biased news, and content farms are rife in society.

Recently, many places in the world, including Hong Kong, have been deluged with rumors, where inconceivable rumors spread on social networking sites and apps rapidly. These rumors might come from an edited video, a misleading report, or simply fake news. Rumors without any evidence are dangerous as they would amplify collective fear, confusion, and conflict in society.

On an individual level, people are likely to choose or read the information that supports their stands or worldview. Furthermore, different social networking sites like Facebook or Twitter are able to filter information it presents to its users which corresponds to their political beliefs, leading to the formation of echo chambers [5]. Many people stare at their smartphone all day for updating the latest news and it may lead to various health problems. It is found that using social media during the weekday is correlated with lower sleeping quality [6]. Moreover, social media addiction is negatively correlated with adolescents' academic performance [7]. For the psychological aspect, it is reported that social media addiction is associated with mental health disorders [7, 8]. People may suffer from stress, anxiety, and depression when they spend a long time reading similar kinds of depressing news through social media.

Since people tend to read and share information that is one-sided due to echo chamber effects, it may lead to the distortion of the truth or moral choices [9]. It has even caused more negative consequences. For instance, social media addiction was significantly correlated with hyperactivity, conduct problems and sedentary behavior [10].

As a result, it is crucial to understand the viewpoints from different stakeholders. Due to the ubiquity of fake news nowadays, adolescents should be trained to make a rational judgement and counter fake news or rumors. It can be done by equipping them with independent thinking skills and social conscience.

LITERATURE REVIEW

Since Nielsen [11] coined the term "information pollution" in 2003, the information ecosystems in different countries have gone through drastic changes according to intertwined factors which include history, culture, politics, economy, education, adoption of information

and communication technology (ICT), media law, and press systems [12]. Global concerns have increased over the precarious nature, polarized content, the instantaneous process, and harmful impact of “information disorder” which include mis-, dis-, and mal-information. The intention, truthfulness, and whether harmful or not are the criteria to differentiate these three types of “disorder” [13]. Information disorder and manipulation have become global issues of prime concern as these phenomena are found in almost every aspect of life for everyone. Table 1 shows the differences.

Table 1. Compare and Contrast Mis-, Dis-, and Mal-information

	Intention to harm	Truthfulness	Harmfulness	Example
Mis-information	N	N	Depends	To spread, without knowing it is false, information in attempt to offer help, e.g., rumors, insults, and pranks.
Dis-information	Y	N	Y	To produce and spread false information with political, financial, psychological, or social intentions, e.g., captioned photos or GIFs, manipulated or fabricated images.
Mal-information	Y	Y	Y	To harm a person or his/her reputation by sharing genuine information, e.g., doxing and trolling (deliberately posting inflammatory or offensive content).

Mis-information is false information disseminated without harmful intent. Dis-information is false information created and shared by people with harmful intent. Mal-information is the sharing of “genuine” information with the intent to harm a person or group. Wardle [13] classified seven types of mis- and dis-information which include 1) satire or parody; 2) false connection; 3) misleading content; 4) false context; 5) imposter content; 6) manipulated content and 7) fabricated content. Adolescents need to enhance media literacy skills to handle information disorder and manipulation.

Negative Impacts

For early adolescents, knowing how to ascertain the credibility of any one piece of information received may be necessary but certainly not sufficient for getting rid of troubles in the digital world [14]. Examples include harming others, being cheated, making wrong decisions, wasting time and money, etc., through spreading hate speech, making statements that are misleading or untrue, or claims based on unverified messages being circulated online, and further spreading of debunked rumor.

For young adults who have the right to vote, the negative impact may be a challenge to democracies [15]. In the political aspect, the coordinated campaign could be an orchestrated activity which aims at spreading incorrect content on different social media. The result could possibly undermine the legitimacy of an election, negatively influencing the prestige of a foreign company, or construct a hateful relationship that drives a military operation [15]. Exposure to biased media contents, the inability to discern the credibility of information, the

influence of reference groups, and even the algorithm used by search engines are factors related to the failure of making correct decisions.

According to MIT news [16], an analysis of posts on Twitter by three million people between 2006 and 2017 shows that false information spread six times faster than facts since it takes time to determine the correctness of a piece of news, while the false information could have already been widely spread. The research project also finds that it was people, not robots, who spread misleading information.

Cognitive Biases

Cognitive biases refer to the systematic thinking errors that influence the decision-making of a person when he/she is handling information [17]. It is observed that a higher level of approach bias was correlated with higher alcohol use among male adolescents [18]. The correlation was also found between attentional bias and alcohol use among adolescents [18]. Moreover, previous research found that cognitive biases including interpretation, self-referential memory and facial expression recognition are significantly associated with an adolescent's well-being, depression and anxiety symptoms [19, 20]. Besides, it is reported that cognitive biases play a mediating role between shyness and society anxiety among early adolescents [21]. These show that cognitive biases affect adolescents in different aspects of their lives.

Cognitive traps are everywhere. Biased and false information which include clickbait, fabricated journalism, and sponsored content are commonly found in digital communication. With rapid advancement in information and communication technology (ICT), the cost of spreading such false information and biased views has been largely reduced. Social media offers an opportunity that allows information to be spread widely and instantly which may influence decision making [22]. Fake news is defined as make-up information aimed to deceive readers [23], and has shaped many economic-political-cultural issues which include hate speech, biased views, and misinformed citizens. From the psycho-social-moral perspectives, the sensational and provocative fake news provokes readers emotionally and appeals to irrationality, and as a result misinforms the public [24]. The spreading of false claims potentially facilitates identity and emotional debates and struggles among people, resulting in a polarized society, and "losers" in the situation lose their confidence in society due to the misinformation [24]. This is partly because individuals tend to support pre-conceived stances or preferred explanations even though information might be conflicting [25]. Selective exposure theories [26] and cognitive dissonance theory [27] are useful in explaining such a phenomenon.

It is undeniable that social media and smartphone have brought huge influence among adolescents. One reason is that a large number of adolescents and their parents spend more than two hours on their smartphones daily. The uses and gratification approach is still adopted to understand why and how people use social media. Nevertheless, Tversky and Kahneman [28] challenged the assumption of individual characteristics and decisions under the uses and gratification approach. Besides, Brofenbrenner [29] emphasized a person's relationships within communities and the wider society instead of individual relationships. In order to handle the challenges, the adolescents' identity, characteristics, personal habits, and

environment are proved to have different kinds of influence on adolescents in the Media Practice Model by Steele and Brown [30]. The model is an initial integration of Bandura's social learning theory and Gerbner's cultivation theory, which are two significant theories about media influence. More attention is still required to enhance the measurement of media use. Besides, more longitudinal research can be done to understand the influences of new media so as to find whether and how the large number of essential variables can lead to the cumulative effects.

Rumor

Another frequently occurring information error in society nowadays is rumors. Based on the rumor theory, rumor is a collective behavior in which people offer, interpret and evaluate information in an event or situation under ambiguity and relative collective ignorance [31]. Anxiety and uncertainty occur in ambiguous situations, especially when horrible events happen [32]. Extreme situations such as natural disasters stimulate people's anxiety and stress, and from that they start making up rumors and false information, creating more anxiety in the public [31]. It was found that social media such as Twitter are used to spread information about crises and the reliability of the information is questionable [33]. Rumors also frequently occur in organisations and institutions. A study which investigated rumors within a hospital undergoing changes found that employees who heard of negative rumors reported higher level of stress compared to those who heard of positive rumors [34].

At an individual level, indirect bullying among young adolescent boys and girls such as spreading rumors predicts anxiety, depression and withdrawal behaviors [35]. Besides rumors, gossip can also be categorically sensitive and very difficult if not impossible to ignore, and teens are particularly susceptible to it. These spread quickly on social media, and as frequent users, the social lives of young people can be heavily affected. Gossip and rumors targeting individuals can result in damaging teenagers' self-confidence, and as a result affect their self-esteem with possible negative consequences such as depression, suicidal thoughts, eating disorders, anxiety, and many other issues [36]. Reliable information from creditable resources is the key to suppress groundless rumors and false information, resulting in a decrease in anxiety [31]. This process requires decision making, which can be rational, irrational or non-rational [37]. However, the process of obtaining reliable information is not simple, as it requires multiple efforts from an individual.

Cognitive Illusions

Cognitive illusions are often the barrier that prevents people from making a rational judgment on information they receive. These so-called cognitive "errors" include overconfidence bias, which means people having strong belief that the information or answer they have chosen is correct; conjunction fallacy, defined as the misconception to assume a specific condition being more possible than a general one, and base-rated fallacy, which describes when people ignore the original data and rely heavily on the current information

[38]. From that, we can conclude that our judgement is not always rational, and people fall into cognitive traps.

Through recognising and understanding the cognitive illusions, people can avoid cognitive errors and deceptions with their own judgement [38]. Judgement or decision making is a type of cognitive process, which can be carried out in a critical or uncritical manner [39]. Critical thinking, which is the ability to think logically, is proven to be effective in preventing biases [40].

Critical Thinking

Critical thinking is crucial in people's lives due to a few reasons. According to Vieira, Tenreiro-Vieira and Martins [41], critical thinking should be taught to students, as individuals are wrongly assumed to be able to think critically and make rational decisions, avoid egocentric attitude, and living, working and functioning efficiently in this modern complex society. People constantly have to assess and obtain different information. In fact, educators are promoting critical thinking as it is related to personal disposition, academic performance and leadership [42]. Cognitive competence including critical thinking and creative thinking also contributes to adolescent's positive development, especially in learning and wellbeing [43].

Therefore, training adolescent critical thinking is beneficial to their development. Utilising the problem-based learning approach, which simulates ill-structured and complicated situations in an online environment, is found to be effective in enhancing critical thinking skills in young people [44]. In addition, critical thinking also includes the ability to justify statements and ideas with adequate information and examples in early adolescents [45]. Carmichael and Farrell [46] reported that with the use of modern technology, an online critical thinking blackboard site is created for the young ones to practice critical thinking. However, its effectiveness depends on the students' level of development, their knowledge in technology, and their levels of engagement. In fact, students with better computing skills score higher in critical thinking tasks, indicating a technology-rich environment is associated with the development of critical thinking ability [47]. Information literacy also promotes critical thinking skills in young people which can be developed via skills training [48].

To avoid falling prey to cognitive traps and false information, the development of critical thinking is crucial and beneficial to young people's development. Digital game-based learning has been proven to be effective for junior secondary school students [49]. Digital games, especially "dialogue games" that adopt the features of "building blocks game" with instructional goals alone support the development of critical thinking and reasoning skills [50]. The learning materials are designed based on these previous findings, incorporating digital games and training for critical thinking skills. The materials simulate cognitive traps that people encounter in daily life in a game format in order to allow students to learn and train in a fun and interactive way.

To summarize, while part of the solution may rest on enabling adolescents to enhance their media literacy skills, it has to be noted that young people might believe in something not because of the information itself, but because it came from their peers. Against this

background, a DPYD game which adopts the game-based learning approach could be an efficient and effective teaching and learning strategy.

GAME DESIGN

The theme of this digital game is “Think critically, discern wisely” and the name is “The great thinking adventure -- 51 cognitive traps.” In our daily life, thinking is a basic function of the mind. For children and early adolescents who have yet to develop their cognitive competence, it is easy for them to fall into cognitive traps. The consequence may be undesirable if not harmful – it may lead them to adverse results such as using false information or making decisions based on wrong judgements. In order to be able to identify and avoid fallacies, they have to learn critical thinking skills which are of paramount importance in the process of positive youth development (PYD). Educators need to try to incorporate the cultivation and practice of critical thinking in the curriculum as much as possible so that students get the opportunity to develop their skills in thinking critically in their daily life. The education systems in some parts of the world put more priority on the academic achievements than other areas. In places where the tradition of rote learning is emphasized, students might be less likely to practice critical thinking skills in and outside of classrooms. This game is an effective tool to engage students in pondering on thinking principles and recognizing the traps that anyone may fall into if he/she does not pay close attention to the thinking processes. The cognitive traps categories and definitions are referenced mainly from the book by Dobelli [51]. The majority of the contents in the game (over 90%) is original.

It challenges students to question their assumptions and cognition of cause-effect relationships, rational and logical thinking, prejudice, and biases, and learn to become an independent, logical, and rational thinker. The game introduces 51 cognitive traps and asks questions related to common phenomena. It analyses students’ mistakes based on calculated scores, and it provides feedback on difficulties that arise during the game.

Objectives

The game is designed for Grade 9 students to help them recognize the 51 types of cognitive traps, to learn about the primary thinking principles and to distinguish the authenticity of information encountered in everyday life. On the cognitive aspect, the game aims to help students understand the 51 cognitive traps and the principles of rational thinking, enhance the capacity for identifying the cognitive traps, and understand the use of thinking ability effectively. On the emotional aspect, students can reduce emotional distress in daily life caused by making mistakes due to not being able to think critically. Additionally, on the behavioral aspect, it is hoped that students can not only utilize the thinking ability to assist themselves to achieve better outcomes, but also be able to help others recognize their irrational thinking and beliefs, and thus develop a chain effect in the process.

Teaching and Learning Methods

The teaching material in the game provides feedback and guidance according to students' different responses to the cognitive trap test. It also provides learning contents at three levels. First, it provides performance tests on thinking principles. The results are shown as numeric scores which reflect the degree of mastery of the five major thinking principles. Students can always replay the game if they wish to obtain a higher score. Second, there are four challenge areas. Each area is composed of three levels, from easy to difficult. After the completion of each area, accumulated scores in each of the five thinking principles are displayed in a pentagram. Finally, detailed feedback for each principle will be provided upon clicking the appropriate places in the pentagram.

Storyline

At the beginning of the game, the player is shopping in the supermarket and he/she notices a sale at half price of a certain brand of orange juice. He/she then buys the item thinking it is a good deal. Upon returning home, his/her mother points out that it is in fact not a good deal because the usual price is lower than the price it was offered at the sale price. At that moment, the player becomes very upset and he/she decides to study the secret book of 51 cognitive traps to gain more knowledge about thinking skills in order to avoid being captured by the **"SPIDER,"** which is the acronym for **S**elf-recognition Bias, **P**robability and Statistic Error, **L**ack of **I**ndependent Thinking, **E**motional Bias and **R**esult-Oriented Bias. By answering questions in the game, students will deepen their understanding of cognitive fallacies and strengthen their ability to avoid such fallacies.

Breakdown and Procedures

The game is divided into four challenge areas, and each of the first three areas shows 17 types of cognitive traps and randomly presents 15 test items. In the final area, items covering all the 51 traps will be randomly shown, increasing the difficulty level of the game. Each area has three different sections with varying levels of difficulty. In the first level, students are asked to choose between two options, and two wrong attempts are allowed. In the second level, three options are given, allowing three wrong attempts. In the third section, students have to choose the right one from four options, and they are also allowed four wrong attempts to continue the game.

Instructors can play the storyline of the game (10 minutes) with the class to introduce the game. Students can play the game in groups. It will take about 15 to 30 minutes to complete each challenge area depending on how much time students need to review the definitions and examples. To maximize the learning outcomes, it is recommended that instructors encourage students to aim at achieving error-free answers but not shortening the time for completing the game. Instructors can also allocate some time for class discussion subsequent to game completion. Students should be encouraged to continue playing the game repeatedly and at home individually because test items are randomly drawn from a pool of 459 items. The

completion of the four challenge areas will total to only 150 items, about one-third from the pool. Thus, students will have the opportunity to tackle different questions when they replay the game.

TIPS FOR INSTRUCTORS AND TEACHING HIGHLIGHTS

There are plenty of ways to classify cognitive traps, and “SPIDER” represents one of the many ways. The purpose of this classification is to facilitate students’ identification of different cognitive traps. However, instructors have to be mindful that we must be open in grouping cognitive traps as a single trap which can be classified into different categories to avoid unnecessary debates.

To facilitate students’ memorization and understanding of the cognitive traps, they are named by corresponding Chinese idioms. However, the definitions of the traps may be slightly different from the original meanings of the idioms. Therefore, instructors should encourage students to read each definition of the trap carefully before starting the game. Students are also able to review such definitions during the game if needed. Students may encounter some neutral descriptions in the tests. For example, “The Nazis triggered the Second World War.” This sentence implies the “simplification” cognitive trap, i.e., accepting an easily understood phenomenon as historical truth. Hence, the focus of the test is NOT on differentiating between right and wrong, but on learning to identify the possibility of falling into different cognitive traps. As a result, students can think independently and make decisions carefully.

In the feedback section, “Do not avoid thinking”, “Understanding thinking principles,” “Beware of bias,” “Comply with logic” and “Open mind, open heart” are the five basic thinking principles. In fact, there is the sixth principle “Putting oneself in the place of another person” which is not frequently found in this game. Mastering these principles helps students identify and avoid cognitive traps. Instructors should encourage students to read the feedback generated carefully according to their responses to the test items so that they can know their capabilities and pay attention to the areas for improvement.

Even if students get high scores on the tests, they should still be reminded not to become complacent over the test performance. Instead, they should use their cognitive ability modestly to help others. Instructors should remind students that there is no need to compare their own results with others. The scores are for reference only and they are just indicators reflecting their performance in this game. Therefore, students should not be upset when they get low scores. Instructors may encourage them to play the game repeatedly and read carefully the definitions and examples of each cognitive trap to deepen their understanding.

SUGGESTIONS ON USAGE FOR INSTRUCTORS

Instructors can arouse students’ interest in using the material and enhance their motivation of improving their cognitive ability through demonstration in classes or an assembly. Instructors can explain the teaching and learning method in classes and ask

students to use the teaching materials on their own after class. They should also encourage students to refer to the feedback, set goals, and then replay the game.

When students get to the hardest level of the game, where there are four options available to choose from, they might lack motivation to think clearly. Discussion in class can make the game more interesting as students can talk about which option they will pick and the reasons behind. Instructors can facilitate a lively discussion and challenge students' thinking processes accordingly. Nonetheless, it can be frustrating if students cannot pass the level once or for a few times. They might find the games tedious and time-consuming, and thus lose interest in playing at a more difficult level. Strategies like working in pairs and groups can help motivate students to understand the teaching materials and work on the game together. Real-life examples can be used to stimulate students' interest, for example, finishing up the whole pack of snack that tastes bad because one has paid for it already, or keep pressing the button of the lift thinking it will come sooner. Encouraging students to look at the tips for the question and to check if they understand the trap accurately will help.

Finally, instructors and social workers may use the material for competitions or group games. It is recommended to complete the first level of the first three challenge areas initially. Students can try the first round as it is easier because there are only two choices. To maintain students' interest, test questions will be presented randomly in the game. Test items shown in the most difficult area, the fourth challenge area, are randomly drawn from all the 51 traps. Lively discussion can stimulate students' critical thinking skills and allow instructors to understand their thinking processes, making it easier to find strategies to help them improve their capacities to think critically.

CONSTRUCT: COGNITIVE COMPETENCE

Besides the electronic game, there are some supplementary teaching materials such as worksheets and reflection questions available for instructors to use when introducing this game to the class. For example, instructors can make use of the worksheet "The five major cognitive traps categories" once the "SPIDER" is introduced. Instructors can explain what SPIDER stands for and how they associate with cognitive traps so that students can remember the various categories more easily. In the worksheet, instructors may identify some common scenarios experienced in everyday life situations, and remind students to be aware of inadvertently falling into those traps. One or two examples from each category can be used to open up the discussion in class before playing the game.

An example of each category will be given here for instructors' reference (taken from Appendix 3 of the teaching unit CC3.1). In the "Self-recognition bias" category, it is common to think that "I won the game because my skills were better, but I lost the game because I did not have enough sleep the previous night."

In the probability and statistic error category, a statement goes: "Since the successive terrorist attacks in Europe in recent years, the number of people of Hong Kong visiting Europe has decreased." However, our interpretation of it as "The people of Hong Kong are worried that terrorist attacks might take place and therefore they do not want to go to Europe" might not be accurate because people neglect the fact that the chance of terrorist attacks is much lower when compared to traffic accidents.

In the category of “Lack of independent thinking”, it is often assumed that experts know best that “the theory of scientist must be correct.” In fact, being a scientist with professional knowledge does not mean that their theory must be correct. Instructors can make use of more examples to illustrate the point especially in the field of the medical profession. People might trust and follow the advice of doctors and other medical professionals without doubt simply because they are the experts of the field.

In the emotional bias category, students are challenged to think rationally rather than emotionally. For example, “Someone asked me to donate after she gave me a small gift. I agreed to donate because I did not feel good to refuse.” This happens in real life where we would do something reluctantly because we would feel bad to refuse so, or the person has helped us before. Others give us a small gift, and we feel like we owe them a favor. Nonetheless, it does not mean that we must agree to the request of others. We should consider if that is something we truly want to do and the right thing to do rather than simply agree to return a favor.

For the “result-oriented bias” category, instructors can share an example of “Plenty of people smoke and live a long life. Therefore, smoking should not have much impact on my health and my life expectancy.” Although cases of smoking and longevity may look appealing, we should not ignore the dangers of smoking or overestimate chances of living a long life with smoking. It is easy for us to spot and emphasize the positive outcome when justifying certain behaviors. For example, students sometimes overemphasize individuals who do not study hard but get promoted or admitted to universities. Instructors could remind them to look into the facts and see the full picture rather than a small portion of the odds.

It is very easy for us to fall into cognitive traps in our daily lives, which could lead to self-induced deception and ignorance, self-blame, missed opportunities or misjudgment and the like. Instructors can lead a reflection session with students and encourage them to list out some examples that show how someone falls into any cognitive traps from their experiences, and invite the class to discuss those examples and try to analyse which category the example falls into. A reflection worksheet accompanies the unit.

THE SIX PRIMARY THINKING PRINCIPLES

There is another supplementary worksheet on this theme. Instructors can introduce students to the six primary thinking principles summarized by Tsui [52], which can assist them to think critically and discern wisely. They are as follows:

1. Do not avoid thinking: think independently, do not appeal to authority, and do not blindly follow conventional beliefs
2. Understand thinking principle I: be rational, be objective, and be less emotional
3. Understand thinking principle II: treat others as you want to be treated
4. Beware of bias: be aware of all kinds of prejudice and bias
5. Comply with logic: be logical in reasoning, do not generalize, and base judgment on facts
6. Keep an open mind, open heart: learn to question, keep an open mind and respect others’ beliefs

Instructors can make use of the principles creatively and discuss with students how they can memorize them and put them to good use in their lives. Students can be encouraged to call out others' thinking fallacies in a constructive and respectful manner, for example, to help one another practice thinking more critically day by day.

Learning to think critically and independently is very important especially for our young people, who face an overwhelming amount of data and information on a daily basis. Being able to understand and recognize one's own thinking when falling into a cognitive trap will be a great asset for everyone. We are all susceptible to thinking fallacies and we have to learn to accept the fact, have the integrity to admit mistakes and be open-minded to others' perspectives. On the other hand, knowing all the cognitive traps does not give us a right to be arrogant or dominate others with our own thinking. It is hoped that students can learn these important skills in the teaching unit and be kind and logical when attempting to point out others' thinking fallacies to avoid denigration.

REFLECTION AND FEEDBACK

After playing the game, a Chinese girl aged 15 studying in an international school in Shanghai wrote the following reflection. Parental consent to play the game and publish her views was obtained.

"I really enjoyed reading about the different types of biases because I think that they are very applicable to life, whether it's through conducting scientific research or having small talk with someone. I also liked playing this game because previously, I had not been taught much about biases. So it was very eye-opening to me when I realized that my line of reasoning or logic would be considered biased. For example, I have definitely fallen into the trap of buying over-priced items because they were on 'sale' and marked down (the contrast effect). The game itself was fun to play around with. The rules were easy to understand, and the animation was entertaining. Overall, I think that this game has given me the knowledge and tools to think in a more objective way regarding stories and scenarios."

The following is written by a male young adult aged 19 studying at a university in the United States:

"I really enjoyed this game since I definitely learned a lot about the biases that I have from my day to day life and how to use my knowledge of them to make better decisions. The quizzes definitely solidified my understanding of the biases. I have actually learned a lot from this game and believe I can reduce a lot of my logical fallacies in my day to day life from now on."

DISCUSSION

In this digital age, there are large amounts of information daily that require much time, effort, and know-how to verify their accuracy. In this chapter, a DPYD game which can be used with the relevant teaching units of the Project P.A.T.H.S. is introduced so as to strengthen the cognitive competence of adolescents. Some practical and design issues which deserve our concern will be illustrated step by step.

For the preparation of materials, the instructor may read and familiarize themselves with the cognitive traps categories and the corresponding examples. It is believed that providing

some real-life examples for each category may help make the class discussion more interesting.

In order to motivate students, the instructor may initiate the thinking process by asking the class, “What is the purpose of identifying the cognitive traps? How do cognitive traps relate to our daily lives?” On top of that, the instructor may guide the class to first expand their understanding of cognitive traps before answering the questions.

In introducing the game and in discussion, the six primary thinking principles which help students think critically will be introduced. Students are encouraged to recite the principles to each other. After that, the instructor may explain to the students: There are 51 cognitive traps in the entire game, which includes 17 traps in each of the Challenge Zone 1, 2 and 3. During the beginner stage (Zone 1), only the first 17 cognitive traps will be discussed and tested. There are three checkpoints within each challenge zone, being 1-Star (Easy), 2-Star (Normal), and 3-Star (Hard). All the topics in 1-Star are to be completed during class; students are advised to thoroughly familiarize themselves with the definition of the cognitive traps in order to complete the remaining topics in 2-Star and 3-Star after class. To maximize the benefit of the game, it is advisable for students to continue playing the game in their free time in order to understand and be able to recognize the 51 types of traps in their daily lives.

For the purpose of creating interest and involvement, the instructor may add, “Would the protagonist eventually come to his senses? How would the story end? Find it out by completing the game!” Students may devote their full efforts into the game and maximize their learning when they find it interesting.

Upon completion of the game, the instructor may inspire discussion by asking the class, “What did the protagonist use to banish the spider in the game?”, “Is being good at thinking equivalent to putting the thinking ability in good use?” A relaxing and interactive learning environment should be provided for students for personal reflection.

Furthermore, the attitude of learning cognitive traps can be discussed. At the end of the game, the protagonist is pleased with himself for comprehending the Thinking Principles as he waves the “Thinking sword” in the air to flaunt his proficiency in thinking. Regarding this scenario, the instructor can ask “Do you agree with the protagonist’s attitude? What sort of problems would surface if one simply has the “technicality” of thinking without “sensibility” and a sense of justice? Is it important to use thinking skills well? Are you willing to help others with your thinking skills?” It helps students understand that using the “Thinking Sword” as a weapon to humiliate others’ thinking fallacies or misjudgments taints the beauty of thinking.

Besides, other reflection questions about their learning for future application can be discussed. For instance, “How can the computer game be of use to you in recognizing cognitive traps in the future in your daily life? How will you utilize the knowledge and skills you have learnt in class in your daily life? Why should we beware of cognitive traps in our daily lives?” These questions help conceptualize students’ learning for their actual application.

In the following part, several supplementary activity suggestions will be provided. First, the instructor can invite students to share their learning and feelings for the day. The instructor may respond according to students’ sharing and offer encouragement so as to strengthen their learning outcome.

Second, a “Cognitive Traps Questionnaire Design Competition” can be held. Instructors may co-host the competition with the Student Council in order to devise new questions on cognitive traps that are not mentioned in the game. Since most cognitive traps categories and

definitions are referenced from a book called “The Art of Thinking Clearly” by Dobelli [51], instructors are suggested to refer to the book when devising new questions on cognitive traps.

Third, it is suggested to organize an event called “Name the Cognitive Traps.” Instructors can co-host this activity with the Chinese Society, for the purpose of amending the names of the existing 51 cognitive traps and/or naming new ones that are not mentioned in the game. Participants are asked to refer to and name the cognitive traps that are mentioned in the book *Why do we always believe we are right? 101 Common types of unconscious cognitive traps*. It allows participants to understand the differences between the actual proverbs and their respective definition as cognitive traps.

Fourth, it is proposed to hold a “Thinking Sword Competition.” The competition can be co-hosted with the Student Council or other student bodies (e.g., The Debate Society) to assess students’ abilities to recognize cognitive traps and expand their existing knowledge. Students are allowed to devise the rules for the competition. Besides, they may use the submissions from the “Cognitive Traps Questionnaire Design Competition” as the theme of the competition.

During the learning process, it is crucial for students to acknowledge that being able to identify cognitive traps do not give them a right to be arrogant or dominate others with their thinking. Besides, they should be kind and logical when attempting to point out others’ thinking fallacies to avoid denigration. They need to learn to accept that they are susceptible to thinking fallacies, have the integrity to admit mistakes, and be open-minded to others’ perspectives. Moreover, they should not judge others mindlessly, or disagree for the sake of disagreeing, but learn to respect others’ beliefs and values. Furthermore, they should be empathetic, and be considerate to other’s difficulties with thinking fallacies. A sense of “chivalry” should be cultivated, which means that they should not be boastful, give more, expect less, and use their thinking skills to be of service to others.

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Chapter 353

**A JOURNEY TO SOMEWHERE, TO SOMEONE:
A DIGITAL POSITIVE YOUTH DEVELOPMENT GAME
ON FRIENDSHIP AND ROMANTIC RELATIONSHIP
FOR ADOLESCENTS**

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ABSTRACT

Growing up through adolescence is like travelling in a journey which is full of wonder, excitement, fun, and often frustrations, sadness and sometimes adversities. With this analogy, a digital positive youth development game, targeting users aged 12-17 to promote self-understanding, gender- awareness and equality, friendship, and romantic relationship is designed and developed in English, Traditional and Simplified Chinese. It is free for non-commercial purposes and can be used as an electronic learning resource for psycho-social sex education. This chapter presents the design and functions of the different components of the game after a brief review of the literature on the core positive youth development constructs and their connections with friendship and romantic relationship. Practical issues are discussed.

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INTRODUCTION

The psycho-social approach of human development postulates individuals must go through the developmental struggle between their capacities and own traits and various demands of the environment. This approach has solid linkages to theories of evolution, psychosexual development, cognitive development, learning, social role, as well as cultural theory and systems theory which explain and predict adolescent development. Recent efforts in the advancement of human development theories are shown partly in the integration of the fulfilment theories into the field of positive psychology [1]. Recent trends of research in positive youth development (PYD) inform prevention programs for adolescents. Based on research findings on evaluations of PYD programs, Catalano et al. identified 15 PYD constructs among successful programs. They are social (SC), emotional (EC), moral (MC), cognitive (CC), behavioral competencies (BC) which can be regarded as core competences. Moreover, they also include clear and positive identity (ID), beliefs in the future (BF), self-determination (SD), and self-efficacy (SE) [2]. These four constructs require a solid foundation of the five core competences. Furthermore, to facilitate positive development, adolescents need to strengthen their capacities on bonding (BO), resilience (RE), spirituality (SP), prosocial norms (PN), and engage in prosocial involvement (PI). Last but not least, recognition for positive behavior (RB) helps to reinforce the development of all other constructs. The Project P.A.T.H.S., designed to strengthen these constructs, has demonstrated encouraging evidence and been recognized as an effective preventive program [2-6]. The Project received support to revamp its program by providing themes to tackle common adolescent issues which include education for anti-drug (AD), anti-bullying (AB), Internet use (IT), money and success (MS), and sex education (SX).

In Hong Kong, most secondary students do not have many opportunities to receive sex education, particularly from the psycho-social perspective [7]. To fill this gap, a total of 15 curriculum units (five for each year for grade 7 to grade 9) on sex education are included in the extension phase of Project P.A.T.H.S. Sex education is intended for personal growth in which students have the chance to reflect on self, gender differences, relationships, love, dating, and diversity. With the support from the sponsor, a digital positive youth development (DPYD) game is designed to promote friendship and romantic relationship (FRR) to support sex education. In this game, all constructs are included except three—promotion of beliefs in the future, providing opportunities for prosocial involvement (PI), and recognition for positive behavior (RP).

LITERATURE REVIEW

Strengthening of Social Competence

Baron [8] defined social competence as an individual's capacity to interact with others appropriately and effectively. Reed [9] proposed that social competence contains two major components, which include 1) organizing cognitions and behaviors into actions according to a socially acceptable aim, and 2) assessing and modifying one's social behavior in a socially acceptable way. According to Agir [10], the level of social competence is positively

associated with an individual's emotional management skills. Aside from these, perceived social competence is negatively related to social exclusion [10]. These show that a high level of social competence will bring positive outcomes to adolescents which are essential for them to build harmonious and mutually-constructive FRRs. This game is designed to promote social competence through many short stories from Chinese and Western cultures. Short quizzes are provided to ensure players to clarify their own values, and to master knowledge and skills necessary for building up and maintaining FRRs.

Enhancement of Cognitive Competence

There are two essential elements for constructing cognitive competence. The first form is "the ability to develop and apply the cognitive skills of self-talk, the reading and interpretation of social cues, using steps for problem-solving and decision-making, understanding the perspective of others, understanding behavioral norms, a positive attitude toward life, and self-awareness" and the second aspect is "the ability to use logical and analytical thinking, and abstract reasoning which directly contribute to academic and intellectual achievement" [11, p. 136]. Resonating with the "cognitive processes" proposed by Fry [12] in which one would be able to think critically and apply the knowledge learnt into practice, cognitive competence supports individual's "overt behaviors" such as problem-solving skills and decision-making [13]. High level of cognitive competence is found to bring a number of positive outcomes to youth development: 1) prediction of better academic performance at school, 2) improvement in physical health due to outstanding problem-solving skills, 3) lower tendency of aversive behavioral problems, including bullying, violence and drug abuse, 4) reduction of mental or emotional illness, such as depression and anxiety, 5) cultivation of leadership skills, and 6) stimulation of critical and creative thinking [14, 15]. Owing to the fact that cognitive competence is the core stone of all action and behaviors, it is of utmost importance for adolescents to develop such competence from a young age. The game is designed to enhance players' FRRs via the enhancement of cognitive competence through the teaching of literature.

Fostering Emotional Competence

Boyatzis, Goleman and Rhee [16] defined emotional competence (EC) as "a person demonstrates the competencies that constitute self-awareness, self-management, social awareness, and social skills at appropriate times and ways in sufficient frequency to be effective in the situation" [17, p. 2], which could be acquired through social interaction and cultural experiences with others [17]. Lau [18], quoted from Saarni [19], concludes three core elements in the construction of emotional competence, which are "the skills for identifying personal feelings and those of others, the skills for communicating emotions with others, and the skills for coping with negative emotions and adversities" (p. 357). Adolescents with good emotional competence showcase a positive relationship with their well-being and development. Proper emotional management has a higher chance in preventing adolescents' alcohol, drugs, and mental problems such as depression, stress and anxiety [17]. College

students who score high in emotional intelligence are more likely to report positive relationships with parents and friends [20]. Young people's ability to handle negative emotions and pressure would be strengthened through proper expression and coping strategies [17, 21]. The game design makes use of a large amount of Chinese and English literature to enhance players' empathy and stimulate perspective-taking to enable them to be absorbed into the stories and understand others' emotions to enhance their emotional competence and subsequently their FRRs.

Building Behavioral Competence

Ma [22] proposed that behavioral competence is determined by four components. 1) Moral and social knowledge: imitation and the following of the learnt "social norms, common manners and rituals, social laws, rules, and regulations in an organization or group"; 2) Social skills: manipulation of verbal (oral expression and writing) and non-verbal strategies (facial expression, gesture, tone of voice and eye contact); 3) Positive characters and traits: positive character qualities such as endurance, patience and conscience help promote one's well-being and moral behavior, for instance, respect, responsibility and reciprocity; and 4) Behavioral decision process and action taking: involving the identification and interpretation of the problem, formulation of a moral and ideal plan, evaluation and assessment of the consequences of the action, and implementation [22, p. 88]. Behavioral competence is the result of all other forms of competence, in which cognitive competence enhances students' intelligence, providing sufficient information for one to identify problems and think of possible solutions; emotional competence reminds them to think twice and avoid being impulsive before the actual implementation. This ensures youngsters to make the correct decision, which would generate positive and proper outcomes. The game provides clear guidance and suggestions for players when encountering a range of dilemma or difficulties – from the appropriate physical boundaries for getting along with the opposite sex to the proper ways to end an intimate relationship.

Enhancement of Moral Competence

Moral judgment competence is defined by Kohlberg [23] as "the capacity to make decisions and judgments which are moral (i.e., based on internal principles) and to act in accordance with such judgments" [23, p. 425]. It means that people show their moral competence by only considering if the arguments are in line with their moral principles instead of their personal desires [24]. Thus, it is expected that students with a higher level of moral competence will be less influenced by the unconscious biases in moral judgement based on peer norms, and hence moral competence is negatively associated with the likelihood of a student's conforming the bullying behavior of his/her peers [24]. Besides, Lajčiaková [25] found that the level of moral competence is positively correlated with both cognitive and affective empathy. The game provides rich contents and many scenarios to encourage players to apply knowledge and skills in making rational and moral decisions when handling FRR issues.

From the holistic perspective, the other 10 PYD constructs identified by Catalano [2] among successful programs are also closely related to how well adolescents build and maintain FRRs. For instance, bonding (BO) with friends and adults in society [26] such as school and church is a protective factor for sex behavior among male adolescents [27]. Prosocial activities (PN) and peer values are protective factors for adolescents against sexual behavior [28].

The Project P.A.T.H.S. which aims to bring positive changes in all PYD constructs has produced promising results by a longitudinal study [25]. It is found that significant differences were shown in clear and positive identity (ID), self-determination (SD), self-efficacy (SE), resilience (RE) and spirituality (SP) among students who joined the program, indicating that they had great improvement in these constructs [6]. Besides, improvement is also shown in bonding (BO) and prosocial norms (PN) among students who participated in the program even though the differences were not significant [6]. During the second phase of its implementation in 2009-2012, the research team revamped some of the curriculum units to offer sex education as one of the six adolescent issues. The research team added some electronic materials to meet the needs of teachers and students in 2018. The DPYD game introduced in this chapter is one example.

Learning about Romantic Relationships in Sex Education

In most modern urban cities around the globe, adolescents have resources and capacities to learn about romantic relationships. In some extreme cases, children at the age of 10 might have experienced intimate sexual behaviors and breakups. Many sex education programs have been developed to address related issues. From the psycho-social perspective, it is advisable to help early adolescents to build up and maintain good friendships before they engage in romantic relationships.

From the preventive perspective, a comprehensive school-based sex education program which aims at boosting protective factors instead of only dealing with the problematic students or weakening the risk factors is more convincing [7]. To facilitate the achievement of the goal of prevention through PYD, a digital PYD game is developed to help adolescents to learn their developmental needs from various aspects such as friendship, and boost their social, moral, cognitive, emotional, behavioral skills, and related PYD constructs [7]. Throughout the game, a life-skills-based education is adopted and players are given sufficient opportunities to express their views in a relaxing way so as to encourage their personal thinking and boosting their strengths. Thus, it can facilitate adolescents to enhance their protective factors and prevent them from committing risky behaviors in FRRs. Table 1 shows the aims and learning targets of the original teaching units for the promotion of bonding with peers and relevant contents in the digital game.

Specifically, the contents of the digital game are closely related to 8 out of 15 revamped units. Table 2 shows the aims and learning targets of these 8 units.

Game Design and Function: Station 1

This DPYD game is designed for adolescents aged 12-17 to foster self-understanding, gender-awareness, friendship, and romantic relationship. It started with enhancing students' self-awareness and self-image by providing positive feedback to their responses. Then, the game enhances students' awareness of gender equality and gender sensitivity before they are introduced to rich educational contents on FRRs.

Self-Understanding

Self-understanding, a composite of different aspects in regulating oneself, leads to the development of emotional intelligence [29]. Self-awareness, defined as being aware of the internal states and their interactions or relationships to others [30], is generally associated with positive psychological well-being and is crucial for one's healthy psychosocial development. If one feels inadequate compared with peers, they may avoid learning new things or stepping out of the comfort zone [31]. Moreover, a weak self-concept may lead to difficulties in peer relations [32].

Game Design and Function: Station 2

One hundred pieces of artwork on traits are used -- 43 positive, 43 negative, and 14 neutral images. Traits include lively, stupid, fair, proud, friendly, idealistic, filial piety, reliable, depressed, kind-hearted, serious, principled, intelligent, hypocritical, feeling inferior, unruly, shy, contented, cynical, timorous, bored, naïve, going with the flow, ambitious, witty, impatient, desired to advance, nit-picking, passionate, nervous, greedy, etc. [33]. A five-point Likert scale is used (exactly like me, very similar to me, quite similar to me, not quite like me, completely different from me). Feedback will be given according to responses. This part of the game can serve the purposes of engagement, initial assessment, and treatment planning for enhancing players' self-awareness and self-image that are necessary for the promotion of a positive identity [34]. This DPYD game provides positive feedback or encouragement to those who choose a positive or a negative trait respectively. A side game is provided to ask the players to select some from among the negative traits for a change. Instructors may use this part of the game to help adolescents who encounter difficulties in FRRs for secondary prevention.

Gender Awareness

A gender stereotype is composed of beliefs about traits and characteristics of, and role appropriate behaviors of men or women. It forms one's prejudiced attitude and as a result discriminative behavior [35]. Even the two genders have their specific roles, the differences have become blurred as time changes, and the traditional stereotypical roles have evolved towards equality. Socialization to a large extent determines one's awareness of gender equality [36]. Bandura's social cognitive theory is used to explain gender development and functioning [37]. Gender-sensitivity is vital for clarifying confusing gender expectations as well as building and maintaining reasonable and stable heterosexual intimate relationships [35].

Table 1. Aims and learning targets of the original teaching units

Teaching Unit Code and Name	Unit Aim	Learning Targets	PYD	Relevant contents in the Game
BO1.2 “The Power of Personality”	To enhance students’ understanding of their own personality and to investigate the effect of personality on interpersonal relationships	1. To learn about three major types of personality 2. To understand the effect of personality on interpersonal relationships	BO	Station 1: Self-understanding; Station 6: Enneagram
BO1.3 “Looking for Friends at the Crossroads”	1. How to recognize desirable friends from undesirable ones and encourage students to choose the right friends and establish a healthy relationship 2. To show the required skills to resist temptation	1. To identify the determinants for desirable and undesirable friends 2. To practice refusal principles and skills	BO, SC	Station 3: Desirable and undesirable friends; becoming a good friend; Station 4: Seven levels of friendship;
BO1.4 “Sail on Together”	To establish trust among students	1. To understand the importance of trust in friendships 2. To practice skills that establish or promote trust between classmates	BO	Station 4: Seven levels of friendship; Station 6: 14 core friendship components
BO3.1 “Modern Love Stories”	To understand qualities of a healthy love relationship	1. To examine one’s attitude toward love relationship 2. To identify the essential elements of love	BO	Station 6: Core components of FRR
BO3.2 “What is Freedom of Love?”	To construct the proper attitude toward love relationships	1. To differentiate the proper and improper attitudes that appear during the initial stage of love relationships 2. To generalize the do’s and don’ts of dating	BO	Station 2: Gender biases; Station 5: love or like? Station 7: “The Love Institute”

Table 2. Special teaching units for sex education and relevant contents in the game

Unit Code and Name	Unit Aim	Learning Targets	PYD	Relevant game contents
ID1.3/SX1.1 “Golden Youth”	To understand and to learn how to go through the physical and psychological changes of adolescence	1. To understand that adolescent development varies from person to person, and that we should not make comparisons or ridicule others for how they are changing 2. To understand what leads to these changes and learn to face them positively	ID, SC, EC	Station 1: Self-understanding Station 3: gender biases;
BC1.1/SX1.2 “Close Relation-ships?”	To understand that opposite-sex and same-sex friendships require different attitudes	1. To understand that excessive intimacy with the opposite sex may lead to misunderstandings 2. To learn about appropriate physical boundaries for getting along with the opposite-sex	BC, BO, EC	Station 2: gender biases; Station 5: love or like? Station 7: “The Love Institute”
PN1.1/SX1.3 “Sex and love”	To understand the meaning of sex and love	1. To understand the definition of sex and how it is related to everyday living; 2. To learn to respect and consider other people’s feelings before deciding sexual behavior 3. To understand the consequences and responsibilities after sexual behavior	PN, BC, SD	Respect; legal and moral consequences of intimate behaviors; Station 7: “The Love Institute”
ID 1.2/SX1.4 “Sex and Peer Pressure”	To understand how friends affect our decision making and behavior	1. To know how peer pressure affects our decisions and behavior 2. To think about the motives and attitudes before we face sexual behavior	ID, BO	Station 1: Enhancement of self-understanding Station 3: Peer pressure
SC2.1/SX2.2 “Men...Women...Not”	To understand gender roles	1. To understand gender stereotypes 2. To understand views and values on gender roles	SC, PN	Station 2: Clarification of gender stereotypes
MC2.1/SX2.3 “You can’t be good at this”	To understand sex equality and discrimination	1. To understand how stereotyping affects career decisions 2. To learn the importance of gender equality	MC, SD	Station 2: Promotion of gender equality
BO3.1/SX3.4 “Marriage... before and after”	To examine the relationships among family, marriage and sex	1. To understand the similarities and differences between dating relationship and marriage 2. To clarify one’s values on sexual relationship in dating or before marriage	BO	Station 7: “The Love Institute” -- dating relationship
RE3.4/SX3.5 “Happy ‘Never’ After”	To cultivate positive views on marriage	1. To know the factors contributing to happy marriages and those to divorces 2. To find out how one could be affected by the marriage of parents or close family members	RE	Station 7: “The Love Institute” -- 7 stages of love relationship

Game Design and Function: Station 3

To test players' awareness of gender equality, a twenty-six item scale was used [38]. Sample items include "The gender division of labor at home should be 'men are breadwinners, women are homemakers'"; "Boys are careless, casual, and sloppy. They do not like tidiness or dressing up"; "Girls are always narrow-minded and easy to lose their temper." Immediate feedback is provided to promote gender awareness, clarify gender biases, and promote gender equality. To encourage replaying the game for better learning outcomes, only 10 items are randomly generated. Players are encouraged to be aware of some gender stereotypes and prejudices.

Beneficial and Harmful Friends

There are different kinds of friendships. Children experience different interactions with their peers which include peer acceptance and rejection [39]. A friend can be unique and irreplaceable. However, adolescents may encounter harmful friends. Some friendships can be sustained even when the interactions between both parties cannot generate reward for their development [40]. In other words, friendships, ordinarily speaking, should not be calculative on the cost to the relationship, and people may not expect the other party reciprocate equal effort or favors given. Moreover, young adults differentiate best friends, ordinary friends, and acquaintance by intenseness and intimacy [41].

Game Design and Function: Station 4

Ten interesting questions on how well players treat their friends are adopted to stimulate players' awareness of the quality of interactions and relationships with their friends [33]. Subsequently, short stories on five themes about friendship from Chinese literature are presented with short quizzes to enhance their knowledge. They are "learning alone without friends," "friendship in the East and West," "three types of beneficial friends and three types of harmful friends," "emphasis on loyalty and faithfulness," and "acquaintances all over the world but few bosom friends." Two questions will be randomly generated from a pool of five questions in each theme. Players will have to answer the two questions correctly at the same time before they are allowed to move on to the next stage of the game.

Friendship

The term "friend" has many different meanings when it is referred to a range of relationships. Friendship can be classified into 4 levels which include acquaintance, casual friends, close friends, and intimate friends. Acquaintance and casual friends are friendships, in which both parties do not engage deeply. Both parties may have little knowledge about each other. The difference between an acquaintance and a casual friend may be the number of interactions. Close and intimate friendships can only be formed when both parties make an effort to know each other. People regarded that there are different behavioral strategies for maintaining close and good friends [42]. A good friendship is regarded as more self-maintaining, more dependent on affection, which in turn is less reliant on proximity than casual friendships [40, 43].

Game Design and Function: Station 5

Using the analogy of mountaineering with a close friend, the game design adopts a more sophisticated classification system to differentiate friends into seven levels: massive crowds, followers, acquaintances, casual friends, good friends, fraternity, and confidant. The following table shows the details.

In the first part, players are asked to respond to a questionnaire [44] and feedback on how the player performs in groups, according to the “System for the Multiple Level observation of groups (SYMLOG)” [44] which will help players understand leadership, group dynamics and working with people in groups. Players will take a short quiz after reading a short article on communication modes. Then, players will be given tips for improving communication. To continue with the game, players will have to take a quiz on each of the six levels after reading short passages from Chinese and Western literature. Having gone through these seven levels, players are enabled to have a deeper understanding on the meanings of friendship.

Table 3. The contents of station 4 “Friendship Mountain”

Checkpoint	Contents	Equipment for Climbers
Massive Crowds Peak	Knowing the characteristics of personality	Peak-climbing guide
Followers Peak	A sincere heart/ Based on interests	Tent
Acquaintance Peak	Helpful friends, harmful friends	Eye mask
Knowing Peak	Four attitudes towards friendship: Empathy, Acceptance of diversity among individuals, Acceptance of diversity in individual intuitions, Adjustment of attitude based on the situation of the other side	Gloves, backpack, hiking boots, chisel
Good Friends Peak	Caring skills	Walkie-talkie
Fraternity Peak	Forming a literary circle	Altimeter
Confidant Peak	A friend until death	Ropes

Love or Like?

Adolescents may not be able to differentiate love from like. However, friendship comes before love. Players are encouraged to reflect on their friendship with a good friend of the opposite gender, and complete Rubin’s Love and Liking Scale [45, 46]. It helps players know more about their feelings and differentiate between romantic love and friendship-based love.

Game Design and Function: Station 6

The story goes like this. Players have arrived at Hazy Moon Station, which is near Hazy Moon Walled Village. Villagers attach great importance to friendship and respect love and marriage. They generally respect young people’s choices for their lovers. However, they still stress family values and attach great importance to the faithfulness of love and relationship in marriage. Villagers disagree that love is a game. They also oppose to learning about love from mistakes. People come to visit this village because of its fame and are attracted by the village’s love education. The game design requires players to take a quiz on their choices of famous Chinese love poems.

Being Watchful

Friendships differ in quality and in intimacy level. Although it is difficult to judge friendship quality by behavior, Davis [47] assesses the quality of FRRs by seven global characteristics. They are (1) viability (including acceptance, tolerance, respect, and trust), (2) intimacy (including confiding and understanding), (3) care (including giving the utmost, championing, and assistance), (4) passion (more in romantic relationship), (5) commitment, (6) satisfaction, and (7) conflict and ambivalence. In this game, the subscales on passion and conflict/ambivalence, the constructs of success, conflict and ambivalence are not adopted due to the age of the game-players. Three facets from the satisfaction subscale, namely enjoyment, reciprocity, and esteem as well as two single facets, maintenance and equality are also used. These 14 constructs are conceptualized as core components of FRRs.

Table 4. The core components of FRRs and the major contents of station 6

Name of Scenic Spot	Core Component of FRR	Major Contents of Station 6
Meditation Sea	Understanding of self and friends	Enneagram
Tianping (Balance) Village	Equality	Discussing gender equality in ancient poems
Comfort Forest	Pleasure	Confucius' three types of harmful and disadvantageous pleasures
Patience Mountain	Acceptance/ tolerance	Foundations for maintaining a relationship
Dedication Spring	Devotion	Respect, understanding, caring, and being responsible are 'giving' behaviors.
Thousand-hand Cliff	Assistance	Active and passive helping; rejecting unreasonable requests
Heart-to-heart Lake	Trust	Keeping one's promises is the first step for building up trust.
Respect Lake	Respect	Benevolent people love others while polite people respect others.
Fidelity Rock	Loyalty	With the freedom to love, 'whom do I love the most' is a difficult question.
Awakening Rock	Self-esteem	Building up one's confidence and personality
Symbiotic Wood	Reciprocity	FRR depends partly on mutual benefit.
Jintang (Golden hot water) Brook	Championing	Love is harder than gold.
Xique (Magpie) Bridge	Maintenance	Maintenance of FRRs
Echo Valley	Confiding	Confiding to others and active listening

Game Design and Function: Station 7

Using the analogy of a journey, scenic spots are named after the 14 core components. Each spot provides both Chinese and English short stories with short quizzes. Some side games are also provided to attract players. One example is to compose melodies through choosing from four musical instruments and using just three notes (Do Re Me) to create different pieces of music. Immediate playback is available.

The Love Institute

A number of questions are raised to motivate students to play this game.

- Do you believe that real love is not momentary, but long-lasting instead?

- Have you ever witnessed your friend feel frustrated due to the failure of first love?
- Have you ever found the frustrations from first love in books or movies?
- Have you ever experienced failure in your first love?
- Have you ever questioned why the simplest, yet the most captivating and mesmerizing first love is frequently fragile and temporary?
- Is experiencing obstacles in one's first love a necessary stage in life?
- Are the frustrations experienced in one's first love related to one's behavioral and emotional characteristics? Is it inevitable?

As an introduction, students are guided to read the following statement: "This Institute has always emphasized the importance of social and emotional education for families, friends and couples. In light of the current over-emphasis on academic results, we started this Institute to provide short-term courses for people interested in more fulfilling relationships. We believe you are attracted to this place because you may want to have a deeper understanding of love and gender equality in Balance Village and to know the reasons for the zero separation/divorce rate among villagers."

The material goes on to provide further guidance: "When we are nourished by love, we feel sweet and happy. However, differences between people begin to surface as we gradually enter into each other's lives. Differences in lifestyle habits, needs, beliefs, and values may catalyze conflicts, making them an integral part of the path to love. Learning to work with each other while going through conflicts allows the relationship to become more intimate so that both parties may travel on the path of love together!"

Students are given a full list of choices in a chart. It states "The Institute offers two majors, being (A) To Commit; (B) To Breakup. You must first make a choice. The prerequisites for both majors are three compulsory subjects, being (1) Observation; (2) Gestation; (3) Disclosure. After that, students may choose one elective in Stage 4 (Romantic Period) and Stage 5 (Conflict Period). Finally, a student may choose one major from two (either to commit or to breakup) and go through Stages 6 and 7. A total of seven subjects must be completed to graduate."

After Stage 5 (Conflict Period), students are required to make a choice of either to commit or to break up. No matter which direction students choose, they are offered two more stages. Courses offered in Stages 6 and 7 represent two separate routes. For commitment, there will be Stage 6A – The Understanding Period, and Stage 7A – Recommitment. For breakup, there will be Stage 6B – The Breakup Struggle, and Stage 7B – The Breakup.

Contents of the Love Institute

The courses comprise of both compulsory and elective parts, classified into seven stages summarized by Fok [48] who is a very experienced family therapist. Students must commence from Stage 1. Users are required to go through the seven stages of romantic love with two different endings (majors) – to commit or to separate. As a gimmick, they are told that there is no course exemption or credit transfer.

Different educational and motivational strategies are used to increase the attractiveness of the lengthy contents. Some are presented through short passages, questions and answers. Case

discussions are used to stimulate further thinking. Validated psychological tests and interactive tests are used to provide individual feedback. Short tests with feedback based on knowledge of social sciences are also offered.

The courses in the first three stages are compulsory. Users are not offered choices.

1. **Observation period:** Developing feelings for each other -- a case discussion on developing a relationship with an Internet “friend” [49].
2. **Gestation period:** Increasing the frequency of contact with each other -- an adaptive interactive test with only 7 questions named “Will my relationship with her/him be fruitful?” [50, pp. 31-32]. Three different types of feedback will be provided according to the responses of students.
3. **Disclosure period:** Directly revealing feelings to each other -- a short passage reminding students of respect, equality, responsibility, allowing each other space, putting in effort and dedication in the relationship as well as to minimize misunderstanding and hurtful feelings.

Stages 4 and 5 offer “common electives” representing different experiences everyone may go through. Students can choose one among the three (Stage 4) and six (Stage 5) courses.

4. **Romantic period:** Missing each other day and night; being together like the honey and the bee; trying hard to show one’s best side; mutual attraction. A sweet romantic period makes people radiant and energetic. A turbulent conflict diminishes people’s passion. The vast contrast between the two makes it difficult for people to adapt. Students may even doubt love and fabricate illusions – causing irrational thinking. Students may choose one from the following three common electives.
 - a. **Interesting tests for male and female students**

Checking honesty, respect, integrity, and unselfishness. For male students: Am I a frog or a prince? [50, pp. 74-75]. For female students: Is he a frog or a prince? [50, pp. 92-93]. Before taking the test, 12 commonly found lies by males are presented and they remind students that these words (lies) are usually used by men to take advantage of women. It serves as a starting point to go through the quiz.
 - b. **Does love equal a yearning for passion?**

It provides a short passage to help students differentiate yearning for passion and love [48]. On the other hand, lyrics from a popular song are used to remind students that physical distance entails anticipation and surprise.
 - c. **Love language**

Chapman’s [51] conceptualization of five love languages, i.e., affirmation, quality time, receiving gifts, acts of service, and physical touch is introduced. Thirty pairs of sentences are given to test participants’ choices in order to calculate and show their comparative reliance on certain types of expression of love. Definitions and guidance notes on each love language are provided.
5. **Conflict period:** As important and commonly found experiences among lovers, this stage introduces issues of decreasing in passion and resolving discrepancies with each other. Six choices in the name of common elective courses are provided.

a. **You love me, don't you?**

It is about emotional blackmail between adolescents in a love relationship. Pathological and suffocating ways of getting along are presented [52]. They are important contents which are seldom found in formal educational curriculum. They are provided to help prevent adolescent relationship issues from deteriorating to pathological problems.

b. **I have feelings for another person, am I a fool?**

The major difference between romantic love and friendship is the excludability in romantic relationships. Clarifications are made between the two. Reasons are provided [48, p. 178].

c. **A fine line between love and hate?**

Talking about love, one often thinks of positive, beautiful and warm scenes. People often quote the book of 1 Corinthians Chapter 13 Verses 4-8 from the Bible in describing love. However, what is commonly found is the opposite. Tao [53] offers an interesting reversed version which serves as a good reminder for all people in love relationships.

d. **Sources of conflicts**

e. Five types of conflict resolution proposed by Kilmann and Thomas [54] are used to design a short test with eight questions to differentiate one's commonly used ways of handling conflicts. Advantages and disadvantages of each type are provided [33, pp. 104-109].

f. **Ten commandments of conflicts**

Wong's [33, pp. 110-111] ten inappropriate behaviors to avoid are presented to remind lovers how to behave in conflict with people they love.

g. **Ten ways to intensify conflicts**

Adapted from Osborn, Hunt, and Jauch [55], Lee's [56] ten ways of heightening conflicts serve as another interesting way to remind them how to behave in conflict.

By now users are required to choose either "to commit" or "to separate." Each choice offers two stages. For commitment, they are 6A "understanding" and 7A "recommitment." For separation, they are 6B "struggling to break up" and 7B "breaking up."

6B3. Understanding period: It covers how to get a deeper understanding and be more caring and intimate with each other during and/or after conflicts. Four choices, each on one key issue, are provided. They are:

6A1. The fragility of first love – Philosophical notes on "The Little Prince"!

Originally written by Antoine de Saint-Exupery, Katherine Woods' [57] translated version of *The Little Prince* and Chow's [58] philosophical notes are chosen to provide an in-depth understanding of the complicated issues around romantic love. To enhance users' comprehensive understanding of related issues, lengthy contents are provided through questions and answers. Interesting and inspiring questions are raised and thoughtful answers are given. Ten major questions include: Is this the so-called "happiness" we are striving for in our romantic relationship? Why was the Little Prince so determined to leave the rose

and let his beloved rose live on the asteroid alone? What problems arose between the Little Prince and the rose that contributed to his departure? At the moment of farewell, what was deep inside rose's heart? Why did the Little Prince have this kind of reaction after seeing the 5000 roses? What does "taming" mean according to the fox? What did the fox want to tell the Little Prince? If the Little Prince did not leave the planet, would he have had such an insight? Are we the rose? How do we find a person to tame in our lives, and how do we live out a tamed relationship?

The book is chosen because of its relevance of its contents to the message we want to get across. It is also the most-translated book (into over 250 languages) among all French novels. Chow's [58] philosophical notes provide an insightful and fruitful discussion on issues of romantic love relationship as well as a sensible guide for everyone who wants to understand romantic love. This section is the lengthiest among all in this educational material. It has about 3,500 words and 10 important questions.

6A4. Love and forgiveness

A short passage by Wu [59] on forgiveness in love relationship is given. Users from different cultural backgrounds may have difficulties in forgiving or have been socialized to be gentle and suppressive in power relationships. The message is that forgiveness does not mean staying silent to avoid conflicts, bowing to please others continuously, or hiding discontent or even feeling guilty of being angry. Disregarding the problems not only prolongs the underlying issues in relationships but intensify them as well. When both parties are fed up with each other, conflicts explode. In contrast, expressing feelings to each other assertively can improve mutual understanding.

6A3. Who's right and who's wrong?

To protect one's own pride, when conflict explodes in a couple's relationship, one would often say to the other, "It's all your fault!" A short passage on how to handle interpersonal conflict in words with appropriate attitude is provided [60].

6A4. How to handle temporary separation?

Separation is rather common in many love stories. Failing to deal with it appropriately may cause guilt and regret that can last a lifetime. One common scenario is when the two are still students, and one party is sent abroad to continue with her/his studies after they have been dating for a while, which usually leaves them feeling helpless despite the availability of instant message and social media. According to Fok [48], there is an important reminder for young people in romantic relationships: when the relationship is not fully developed yet and the pair is in separation for over two to three years, this would definitely hinder the development of their relationship. Therefore, before separation, they must have enough time to communicate with each other in order to avoid traumatic feelings, such as abandonment, betrayal, deception and suspicion, or the sense of being stuck in a dilemma.

- 6A. **The breakup struggle:** If conflicts cannot be resolved, there will be much pressure within the relationship. Struggling on the decision to break up may not be difficult for some but how to break up sensibly and responsibly?

6B1. Breaking up with your partner

A case on a pair of young lovers struggling to break up is described [49, pp. 164-169]. Questions include: How do you interpret her behavior and motives? How would you use the information you have read to analyze the development of their relationship? If you know her, how would you help her? If you know her 'boyfriend', what advice would you give him?

6B2. Are people who broke off all fools?

Intimate relationships make people feel cherished and sweet. Yet it is the most vulnerable at the same time. An intimate relationship is an expression of valued importance and love. When couples break up, they believe they are not loved anymore, which makes them doubt if there will ever be anyone else to love them again. They are afraid of being abandoned and rejected, and the feeling of not being important anymore is the most terrifying thought that leaves many people perplexed and confused. Furthermore, separation elicits fears in human beings. Young people and particularly those who are serious in an intimate relationship often get hurt in breaking up.

A short passage by Fok [48] is provided to guide users on how to handle the complicated and very often hurtful feelings arising from separation. When breaking up, adolescents need to learn to respect others and at the same time protect themselves in order to continue one's journey separately.

7A. **Recommitment:** Three choices, each on one key issue, are given. They are:

7A1. What are regular reviews and assessments?

A love relationship has its own big and small cycles, ups and downs. Adapting and accommodating to each other in down periods does not necessarily imply the sacrifice of love. On the contrary, if both continue to hide the potential difficulties, the relationship will be at stake and the subjective satisfaction would fluctuate or decline. When the romantic relationship has developed for several years, and there are no apparent or concrete reasons not to get married, many people ambiguously and half-heartedly get married. Because of that, the emotions are set apart upon the marriage. This poses a potential threat to their future relationship. That is why a love relationship needs regular review and evaluation [48, pp. 202-204]. The material provides concrete guidelines on how to review and reflect.

7A2. To recommit or not?

A relationship is a kind of art that is difficult to understand. Marriage throughout the rest of life is significant and precious because it is based on the freedom of choice and voluntary commitment. Based on years of experience with family therapy, Fok [48] offers insightful materials for all – those who are in, or out of, and not yet in an intimate romantic love relationship.

7A3. A mature and intimate relationship

In her book "Intimacy forever," Fok [61] offers insightful discussion on a mature and intimate relationship. To Fok, an intimate relationship is like wrestling. All valuable things have great costs; there is no love without cost. In a romantic relationship, when people still choose to live in this stage, which they can make choices, they should ask themselves seriously: are they willing to bear the responsibility for this person for forty or fifty years? The message in this

section is that love does not necessarily engulf individuals and destroy freedom. On the contrary, genuine love and its richness help us mature.

- 7B. **The breakup:** Preventive and therapeutic guidelines are given in the following three key issues – the pain, the art, and how to prevent emotional harms.

7B1. The pain of breakups

Feelings of being an outcast and abandoned are very difficult to bear. One's self-worth disintegrates as the partner criticizes, judges, and insults. Cultivating inner peace, broad-mindedness and remaining to be calm at all times are all critical factors for attaining spiritual purity. On the other hand, re-evaluating one's values to re-establish his/her faith in humanity that fits the value priorities of objective facts is another important way to reach spiritual serenity. A short passage of Fok [48, pp. 179-182] offers spiritual education that provides food for thought for all users. It serves as value clarification and offers guidance for promoting spiritual serenity.

7B2. The art of breaking-up

This is perhaps the most difficult part. Fok [48, p. 210, pp. 207-208] offers concrete and step-by-step guidelines on how to differentiate clearly with details seven proper ways and five poor treatments.

7B3. How to face emotional harms?

Users are invited to recall an incident that has made them feel very sad and hurt in a relationship. Then, the following questions are raised [62, p. 29]:

1. What adjectives would you use to describe the feelings you had in this incident?
2. What life beliefs have been changed? How did it affect your self-evaluation?
3. How did it affect your relationships with your family members, friends, or even future partners whom you haven't met yet?
4. What have you learned from this incident? How did it help you understand yourself?
5. Did you discover any more important values in your reflection or ways to adjust some life values in an appropriate manner?
6. What was the meaning of this incident to you?
7. After this incident, what are your changes?

On top of these personal questions, a general discussion on why we get emotional harms easily and deeply is simulated. Sensible answers from different perspectives are offered as group discussion results for users' reference. To promote positive development, five tools for improving one's self-image are offered [33].

DISCUSSION

For early adolescents, they experiment to build and make initial and later essential commitments to relationships, from friendship to courtship and then to romantic relationships. All these require their virtue and capabilities to form and maintain effective and constructive

interpersonal relationships. This chapter aims at contributing to the development of psycho-social sex education through introducing a DPYD game that can be used together with the corresponding PYD curriculum of the Project P.A.T.H.S. The effectiveness of the P.A.T.H.S. program in Hong Kong has been recognized by the World Health Organization [4, 5]. Two issues regarding sex education deserve our concern.

Firstly, educators should help adolescents understand FRRs through adopting a positive and holistic view instead of pathological concepts [63]. Many prevention programs on sex education were criticized as focusing only on the biological aspect to reduce teenage pregnancy [7]. Instead, the game can be adopted in the prevention program through PYD.

Second, prevention programs based on a holistic approach have received increasing attention and been generating evidence [2]. It is suggested that the program has to adopt a positive approach to sexuality, create a comfortable atmosphere for interactions and participation, and use a tailor-made syllabus for students and encourage them to express how they think and understand their rights and responsibilities [7]. By using the above measures, students' knowledge about intimacy, love and sex will be enhanced. They will better understand the concepts of gender differences and stereotypes as well as build a positive attitude regarding sex-related issues. According to Fok [64], biological knowledge is one of the protective factors for youth sexual behavior, while having insufficient sex-related psycho-social-legal-cultural knowledge is a risk factor. Providing such knowledge to youth through the above ways is crucial to equip students with a proper attitude towards a romantic relationship. DPYD games have potentials in prevention from a holistic approach of the psycho-social-legal-cultural perspective.

From the practice viewpoint, using different parts of the game can serve the purposes of engagement, initial assessment, and treatment planning for prevention. It can be adopted as a primary prevention program by targeting all adolescents. Besides, the game can be used in secondary prevention for students with some negative self-evaluation or difficulties in FRRs. It acts as a means to strengthen their self-awareness and self-image which are necessary for the promotion of a positive identity. Moreover, the game can be adopted as tertiary prevention which aims at providing intervention to students with serious problems on self-image, gender biases, and serious conflicts in FRRs. At this level, mental health professionals can use relevant parts of the game as an intervention means for individual or group counselling. It helps identify, get an initial assessment, engage with the potential client, and with the player's consent, discuss plans of intervention.

Another practice implication is on the coverage of PYD constructs. It is worth noticing that although the DPYD game design must provide immediate positive feedback and reinforcement of positive responses at the cognitive and intention levels, responses in playing DPYD games are not actual behaviors.

The third practice implication is that young adults can also be the target users. As the contents cover FRRs, the game can be used without adaptation by late adolescents and young adults who experience relationship problems or those who have never gone through formal/informal education on romantic love.

The fourth practice implication is about the special use of the game by students or users in need. This game is designed for use by both adolescents and helping professionals who offer help to students with problems in different stages of romantic love. There are different points of entry. The direct entry to the "Love Institute" can facilitate social and emotional learning on romantic relationships.

For all students, the design encourages them to go through the whole game by visiting all stations one by one. It attracts and encourages students to play the game again as attractive and relevant contents are offered on different routes by having different choices. If students want to learn more about the other choices, or they are keen to know more about romantic love, they may have to go through again from Station 1 to Station 6 in which they explore self-awareness, gender characteristics, ways of getting along with friends, improvement of friendship, identification of love, and guarding their loved one.

The feeling of boredom in reusing this material is largely reduced for two reasons. First, the interactive design provides different feedback according to the responses. Using it repeatedly may enable users to learn more and see the differences resulting from different responses. Second, choices are offered throughout the game, particularly in the “Love Institute.” Users who want to learn more are motivated. Making the best use of a DPYD game depends very much on instructors’ creativity.

With students’ consent, feedback of interactive tests can be copied by using the print-screen key on the keyboard and users may print out the results and/or feedback for discussion between the user in need and the helping professional. The game could be used as an initial assessment tool and it provides comprehensive coverage of key issues for further deliberation.

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Chapter 354

A DIGITAL GAME FOR THE ENHANCEMENT OF REFLECTION ON MATERIALISTIC AND NON-MATERIALISTIC VALUES

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ABSTRACT

This chapter offers a brief review of literature on materialism among adolescents and game-based learning on the promotion of one specific positive youth development construct, namely spirituality as a preventive measure. It then describes the design of the digital game and how it can be used as an electronic resource to enhance learning on reflection of materialistic and non-materialistic values and the development of spirituality and enhancement of self-efficacy in financial management. It also provides suggestions on how to use the game effectively. The discussion is supported by in-depth qualitative and critical comments of two users from different cultures and educational levels. Theoretical and practical issues are discussed. Limitations and future research suggestions are presented.

INTRODUCTION

Overemphasis on materialism and high rates of narcissism and overconfidence are some of the common concerns for young people in many developed countries. Most Asian parents believe that their children must enter into a good university so that they will get a good job with high salary. The notion of “hover parents” has been widely accepted by Asian parents. In

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China, where collectivism is more highly recognized than individualism, similar patterns are observed. In Hong Kong, emphasis on children's high academic achievement seems to have gone to an extreme that parents "should never let their children lose at the starting point" [1-3]. The notion of success held by these parents is rather instrumental and often materialistic. Commission on Youth [4] found that 20-30% of youths would consider using unethical means to achieve what they want which are material orientations based on hedonism, wealth, and sensual stimulation.

When young people value possession and judge success and others by materialistic values, they would consider less on other significant elements of a meaningful life such as moral character and spirituality. They value less in the areas of universalism, benevolence, righteousness, honesty, responsibility, diligence, conformity to norms, cultural tradition, and show less commitment to family, friendship, as well as the community. One plausible explanation is that Hong Kong is a city with strong international connections of finance and trading [5]. However, it is disturbing when a significant number of young people would consider using unethical means to achieve their wealth. Against this background, the promotion of a positive concept of money and success as well as material possession is needed and the production of educational resources for educators, teachers and parents are desirable. With the financial support from The Hong Kong Jockey Club Charities Trust, a digital game designed to enhance adolescents' reflection on materialistic and non-materialistic values was produced.

LITERATURE REVIEW

Materialism is a complex concept with various definitions. From the consumers' perspective, materialism is defined as the desire to pursue goods [6]. Belk [7] equated it with three personality traits which include envy, non-generosity and possessiveness. Shek, Ma and Lin [8] further conceptualized it along three dimensions which include, materialistic possessions, acquisition centrality and hedonistic pursuit and developed a test on materialism in the Chinese culture.

The development of materialism in children and teenagers is complicated. Models are constructed to predict materialism including the consumer socialization model of children [9], materialistic value orientation model and the concept of social comparison [10]. According to John [9], the desire for material goods starts at the early age where pre-schoolers request certain type of products and demonstrate their desires through behaviors such as grabbing and begging. Throughout children's development process, they acquire consumer skills, knowledge, and values that are related to their function as a consumer in the market [9]. The model of materialistic value orientation based on the concept of socialization suggests that materialistic values are derived from experiences with the feelings of insecurity and real life examples of materialistic values, beliefs, and behaviors in children's life [10]. When children's psychological needs are not met, they tend to use material goods to compensate for their negative feelings and sense of insecurity [10]. In addition, the emergence of material possessions among young people is due to a decline in self-esteem when they enter adolescence at the ages of 12 to 13, giving them a strong motivation to obtain material possession to enhance their self-esteem [11]. Chan and Prendergast [12] adjusted the model of

materialistic value orientation and the concept of social comparison by replacing insecurity and materialism exposure with social comparison variables such as family communication, peer influence, peer communication and television viewing as an effort to adapt the model into the Chinese context. The authors further concluded that media figures and social comparison are positive predictors of materialism in the Chinese youth population [12].

Concerns for materialism in adolescent are increasing. Youth materialism, meaning owning luxury goods and the importance of money, has increased over generations of 12th graders in America between 1976 and 2007 due to the popularity of advertising [13]. 95% of adults in American agreed that children are attracted to shopping and about 80% of adults believed that regulations on advertising to children are needed [14]. In the United Kingdom, a phenomenon that parents frequently buy goods for themselves and their children is observed, while such a phenomenon is not found in Spain and Sweden [15]. Interestingly, it was observed that the levels of materialism among children to early adolescence are at the highest and then they decrease afterwards [11]. Comparing children and adolescents with poor and affluent backgrounds, underprivileged children aged between 8 to 10 years old exhibit similar level of materialism as compared to their wealthier peers, but the impoverished teens are more materialistic than their rich fellows when they enter inter adolescence [13].

The perception of materialism is not only found in the west, but also in the east. A study of young consumers in both the United States and China concluded that materialism is cross-cultural as both samples demonstrated similar results in the questionnaire items related to materialism [16]. In another study, Chinese youth tend to be more materialistic when they grow up because of high parental material success expectations due to the one child policy [17], whereas young people in the U.S. reduce their levels of materialism after the peak at early adolescence [11]. Unlike the situation in western countries, television programs have no effect on materialism in children and teenagers because China has restricted rules on media contents [17]. In Hong Kong, adolescents are living in an environment that emphasizes money and material possession. In a metropolitan that focuses on economics and finance, adolescents in Hong Kong develop and maintain their materialistic values [5]. Although Children in Hong Kong do not show an excessive level of materialism, they understand the value of possession as young as six years old [18]. Chan [18] further found that younger children with more pocket money are more materialistic, and the effect of television on materialism depends on the perception on advertisements of children and adolescents.

The concept of materialism is associated with individual's physical and psychological well-being as well as academic performance. A study found that young adults who focus on money, popularity and reputation are more likely to be depressed and report to have experienced physical symptoms such as headaches, sore muscles and backaches [19]. Focusing on money drives individuals to spend more time at work and less time with friends and family, negatively affecting the level of happiness [20]. Psychological needs satisfaction is undermined by materialism, leading to a decrease in psychological well-being and an increase in depressive symptoms [20]. Moreover, those reported with strong materialistic value experience more negative emotions, and thus distanced themselves with positive life constructs which include competence, autonomy, gratitude, and meaning in life [21]. Materialistic youth who have a habit of spending and saving little are more likely to be excited by new products in advertising. They report school as less enjoyable, and have poor academic performance [22].

In order to facilitate positive development in children and adolescents, minimizing the influence of materialism is crucial. In fact, materialism has become a major concern in both developing and developed countries. Scholars suggest some intervention directions to reduce the level of materialism in children and adolescents as improvement in their well-being is observed if the degree of significance of materialistic value and goals decreases [23]. Self-esteem has been proved to be associated with materialism. A study by Liang et al. [24] found that increasing self-esteem results in a low level of materialism and reduced corrupted intention. Meaning in life and psychological well-being are highly correlated in adolescents that meaning in life is a potentially protective factor of materialism [25]. Similarly, another study demonstrated a positive association between meaning in life with well-being, academic adjustment, self-esteem, ethnic belonging and exploration [26]. A normative developmental characteristic during the adolescence period helps the development of spirituality in teenagers, building resilience to challenges in puberty [27]. Chaplin et al. [28] suggested promoting a sense of gratitude in adolescents and children to reduce materialism as those who are grateful with what they have are less materialistic. Based on the previous findings, the design of the digital positive youth development (DPYD) game tackles the aspect of meaning in life to enhance spirituality and promote resilience in adolescents towards materialism.

With increasing recognition of the importance of well-being, many schools promote positive well-being among students on top of the acquisition of skills and knowledge [29]. The digital game described in this chapter is designed to promote one of the positive youth development constructs, namely spirituality. It is intended to promote early adolescents' well-being through reflection on both materialistic and non-materialistic values with game-based learning (GBL). Gaming environment promotes both learning and motivation to learn, allowing students to participate actively in the learning process [30].

As part of the effort in updating teaching and learning materials for the project P.A.T.H.S. [31], a digital game named "Live a meaningful life" was designed and produced in 2015 to support teaching on the construct of spirituality through prudent financial management and reflection on the meaning of life. Digital GBL on financial literacy is popular nowadays due to rapid advancement in information and communication technology (ICT). A study on digital learning game and financial literacy education has found that well-designed and instructionally integrated digital games can motivate players to learn financial management knowledge [32]. In the United States, an online financial game named *Gen i Revolution* (Council for Economic Education) was developed to educate students the importance of personal finance skills [33] for high school students. Over 120,000 students have played the game to acquire knowledge [33]. Other games such as Financial Football and the Visa's Practical Money Skills platform were designed to serve a similar purpose, i.e., teaching children and adolescents about money concept [34]. Our game is designed with a similar purpose for students in Hong Kong, adopting the idea of "Edutainment".

THEORETICAL UNDERPINNINGS OF THE GAME

The name of the game is "Live a meaningful life." It is targeted at Secondary 2 (Grade 7) students. Its design is based on the framework on money literacy for children and adolescents [35] which was inspired by Potter [36] effort on media literacy and research on education on

personal finance and economics as well as the developmental and cultural characteristics of children and adolescents. The framework is built on two levels: foundation and advanced. The former is composed of three components, namely, narrative acquisition, cultivation of traditional value, and developing scepticism. The advanced level consists of experiential exploring, critical appreciation, and social responsibility. The six-stage model [35] covers from developing an awareness of differences between needs and wants to disputing beliefs about materialism and hedonism for the foundation level; and for the advanced level, from searching for gratification and fulfilment from new experiences, which include emotional, moral, aesthetic, and sports activities to recognizing what one can do to contribute to society positively.

Based on the framework, cognitive, affective, value judgement, and behavioral dimensions are covered in the game. For the cognitive dimension, the game covers “desire to gain money”, “money as a symbolic meaning of power”, “cautions in using money”, “money is not the only criterion to determine success or failure”. For the value judgment domain, it includes reflections on whether “money has a symbolic meaning of good or bad” and “personal spending”. On the affective dimension, the game encourages making contributions to support family and society through donations”. Finally, on the behavioral dimension, the game requires players to conduct monthly personal financial management which will, to a large extent, determine whether the player will win one of the four awards, namely, the “Individual Award” (the largest positive balance of good moral character cards); the “Family Award” (who has the largest amount of money by adding savings, remainder of investment, the total amount of family expenses times two, and cash-on-hand together); the “Donation Award” (the highest donation ratio); and the “Social Contribution Award” (long-term social benefits generated from personal donations). The game is designed to help students examine such elements in their lives.



Figure 1. The front page of the game “Live a meaningful life” (2015).

The time needed to finish the game is around 10 to 30 minutes depending on the number of rounds chosen by students. Throughout the game, students experience randomly different life circumstances, which are mostly uncontrollable. In this way, the game shows what real life can be and it is hoped that students can reflect on the meaning of life with the help of the instructors. They are also encouraged to learn to make personal financial decisions wisely in order to stay on the game and get awards in the end. Feedback is provided for players at the end of the game so that they can learn how to make better decisions and come up with other effective strategies to compete for the awards in the next round of the game.

Objectives

The game is designed to enhance students' reflection on personal values through discussing materialistic and non-materialistic values as well as the definition of a meaningful life. The objectives of the game are three-folded. First, on the cognitive aspect, students can understand their own view on financial management and have chances to practice it in the game. They can reflect on the values and meaning of life when making the decisions of how to allocate their salary in different categories such as family expenses and donation. Second, on the affective aspect, students can enhance their emotional competence in facing life issues beyond their control; and enhance their levels of empathetic competence and care for their community through experiencing the lives of different social classes. Finally, on the behavioral aspect, students can apply prudent financial management skills in the virtual reality. This will be a great learning experience for students, who may not have experience on how to manage their money on the whole in real life situations.

The purpose of the game is to help students understand that some things are beyond our control in life, such as one's origin and a financial tsunami. However, students could develop good moral character, learn prudent financial management skills, engage in careful decision-making processes, show more concerns toward society, and make donations, which are the crucial elements of a decent and meaningful life. This teaching material is designed for a teaching unit, MS 2.3 'A meaningful life'. The objectives are to help students to understand that good moral character is essential in leading a meaningful life; and sensible and smart financial management is important skills for managing life. The unit focuses on the construct of spirituality and self-efficacy.

Game Design

The physical design of the game is very similar to the board game 'Monopoly'. Players are allowed to choose their gender and the number of rounds at the beginning of the game. They will be assigned a social class with a fixed amount of monthly salaries randomly by the game. Lower class with \$10,000; middle-class with \$20,000; and upper class with \$30,000. The game will also generate three virtual players with different genders and social classes to join the game simultaneously. Players can see them at the lower right corner of the screen. At the beginning of the game, a fixed amount of rent will be automatically deducted from the salary. The player has to decide how to distribute his/her remaining salary to the following

items: personal consumption, savings, investments, family expenses, and donations. The remaining amount of cash-on-hand will be shown, and it is a crucial factor to determine if the player can carry on with the game. The player starts the game by throwing a dice and the icon of the player will move according to the number of steps shown on the dice. He/she has to decide how to use the salary every time when passing through the starting point on the board. The game is over when the amount of cash-on-hand is in deficit or the player has completed the number of rounds she/he chooses to play at the start of the game.

Throughout the game, players will have the opportunities to get good or bad moral character cards, which include kind-heartedness, diligence, contentment, health, family warmth, craving for knowledge, selfishness, laziness, greediness, criminal record, jealousy, arrogance, etc. Players will be given an award when the number of good moral character cards are more than the bad ones. In addition, there are four awards: The Individual Award will be given to the player who has the largest positive balance of good moral character cards; The Family Award to the one who has the largest amount of money by adding savings, remainder of investment, the total amount of family expenses times two, and cash-on-hand together; the Donation Award to the player who has the highest donation ratio; and lastly the Social Contribution Award to the one who has long-term social benefits generated from his/her personal donations.

Teaching and Learning Method

The teaching material is designed for a single user. It randomly assigns a social class to the player, who will virtually experience different life circumstances and unexpected changes that are mostly beyond their control such as accidents, change of economic environment, etc. On one hand, the players learn to use their monthly salaries through careful budgeting and planning. On the other hand, they are introduced to the significance of non-materialistic elements of life which include moral character, care for others, and contribute to society through donations. The game provides feedback to students on how to use money wisely and encourage them to search for the meaning of life at the same time.

Teaching and Learning Strategy

Instructors can introduce and demonstrate the game in class or during an assembly to arouse curiosity and interest in playing the game. Students can play the game in class or at home depending on the availability of time during lessons in school. Instructors are encouraged to focus on the reflection of the meaning of life, money and success, personal financial management, and the feedback provided at the end of the game with students. Social workers and counsellors can also use the game for group or individual counselling, especially for those who are weak in financial management or who over-emphasize materialistic values.

Besides, instructors can make good use of students' curiosity and interest in organising competitions in order to enhance the learning outcomes. In this way, students become more engaged and they can discuss as a group to win certain awards in the game. Since students will be assigned a different status at the beginning of the game, they have to employ different

strategies in personal financial management. Students might complain it is not fair that they are given the low social status most of the time while others are often lucky to have a high salary. Instructors can make use of some post-activities discussion on issues related to money and success, and the meaning of “being a winner” with students as they have gained some learning experiences through the game. Instructors should encourage students to try to get non-monetary awards such as the Individual, Donation, and Social Contribution Awards. This could provide food for thought to help students reflect on their own values and encourage a reflection on the meaning of life for students. Finally, instructors may remind students to use the print-screen function to save their personal financial management table for review purposes. In that way, they can review and analyze their practice of personal financial management, and initiate some discussion with their peers regarding strategies to win awards.

Tips for Instructors

Instructors need to explain to students about each item of expenditure and what are supposed to be included in the item. Most students lack the concept of running a family and do not understand much about budgeting within a household. For example, family expenses usually include all the bills like rent, water, electricity, internet fees, food, transportation, medical bills, etc. Activities such as donation to support a good cause and assist the less fortunate groups in the community is encouraged by giving two awards to players who regularly donate. If students have allocated an amount of donation, they will get a Card of Kind-heartedness automatically when they pick a surprise card that praises their willingness to help. On the contrary, overspending on shopping can cause 50% of one’s salary if one picks a surprise card. All these can be used for teaching points at the end of the game with students. They need to be careful about making purchases and instructors can bring up the possible “traps” of using credit cards and the high interest rate it incurs if one cannot repay the amount owed. There are plenty of areas instructors can discuss with the class such as the topic of “Spiritual Wealth” and its meaning. Positive behaviors will be rewarded like the value of hard work with a bonus of one-month salary when players land on the “work hard” square; and a card of arrogance is given when students land on the square of being overconfident. Instructors can encourage students to discuss the values and meaning of life using the materials provided in the game.

A Digital Game for the Project P.A.T.H.S.

To promote the holistic development of junior secondary school students in Hong Kong, the project titled “P.A.T.H.S. to Adulthood: A Jockey Club Youth Enhancement Scheme” was launched in the 2005/2006 school year. It is a collaboration with the research team involving scholars from five universities, the Social Welfare Department, and the Education Bureau (formerly the Education and Manpower Bureau). The project P.A.T.H.S. has been recognized as one of the evidence-based programs that apply prevention science [37] using 15 constructs identified as core components of positive youth development (PYD) [38].

Figure 2. The concept map of MS 1.1 “I Believe I Can”.

Teaching Points for MS 1.1

Instructors can lead students in the process of understanding and believing that we cannot develop many of the essential abilities with money, and we cannot rely only on money to deal with things properly in our daily lives such as our academic study and cultivation of friendship. Instead, we need to recognize one's self-efficacy in social, living habits, academic study, appearance, and financial management, and use one's capabilities to cope with one's day to day issues. When students have good performance, their confidence and self-efficacy will be enhanced. Thus, it will reinforce our coping capabilities when we are dealing with different issues in life.

Students are encouraged to believe in their talents, trusting that they are capable of doing many things well. Instructors can discuss with the class about the value of money, and list out things that money cannot buy, such as a warm family, sufficient sleep and good health. We can use considerate, reasonable and legal ways to obtain things that we deem important, but these are the things that cannot be purchased such as good friends and affection from others. Instructors can encourage students to discuss the value of money and other things with teachers, family and good friends to generate more constructive discussion on the issue.

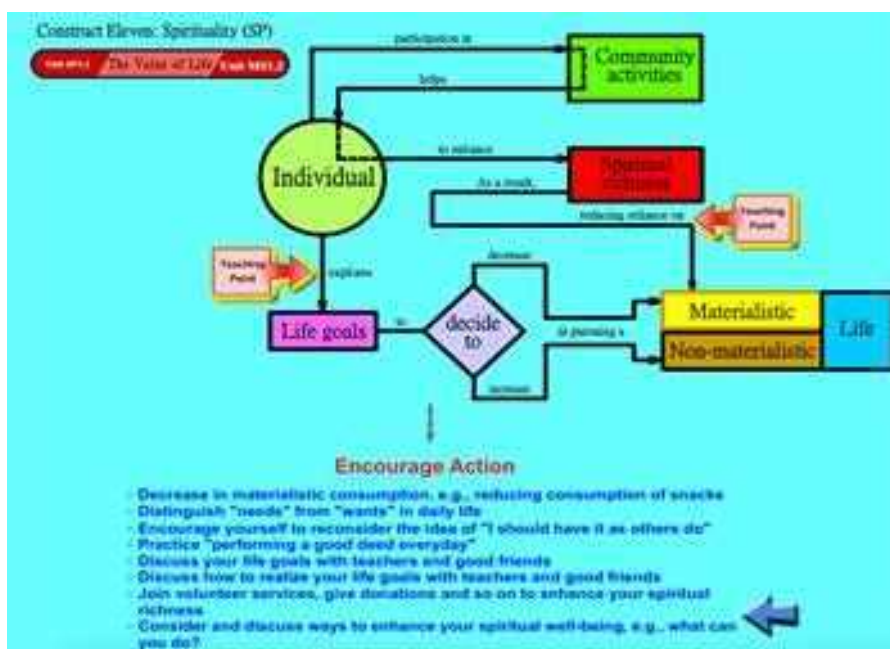


Figure 3: The concept map of MS 1.2 "The Value of Life".

Teaching Points for MS 1.2

The unit targets at students who are at the age of exploring the meaning of life and their life goals. Some might start exploring different kinds of lifestyle which will lead to a different outcome. Should they pursue a more materialistic or non-materialistic life? Instructors can highlight the importance of participation in community activities such as volunteering in

community projects, shelters for homeless or senior centres. It helps enhance a sense of spiritual richness in students and as a result, it reduces their reliance on material goods for satisfaction, fulfilment or accomplishment. In fact, those feelings are short-lived and instructors can draw on personal experiences and real life examples to illustrate the point.

Students are encouraged to discuss what their life goals are with their teachers and classmates, and think about how they can achieve those goals. At the same time, instructors should help students to distinguish “needs” from “wants” in their daily lives, and encourage them to rethink the idea of “getting things because others have them”. Students can form into groups and debate about the reasons for and against the practice of purchasing something because “I should have things as others do”. This can stimulate students’ thinking of the logic behind the idea and come up with a plan to deal with the situation when they want to have something as others do. At the same time, instructors can discuss the value of life with students and remind them of the importance to have a balanced life. For example, students can try to reduce the consumption of materialistic goods such as snacks, clothes and games. Instructors can also encourage students to try practicing a good deed a day, serving voluntary in the community, and finding ways to enhance their spiritual richness. Having a walk in the park, going hiking and cycling with close friends and family or just helping a senior to carry his/her grocery will be a good start for students’ experience in this area.

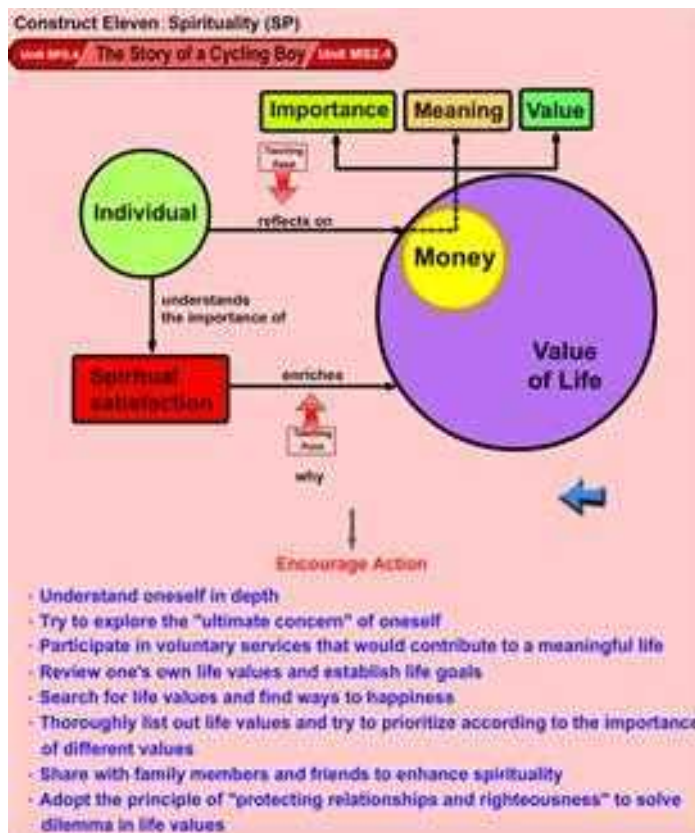


Figure 4. Concept map of MS 2.4 “The Story of a Cycling Boy”.

Teaching Points for MS 2.4

At the beginning of the story, a person who loved cycling developed a passion for cycling and set a goal of touring around the world. What is the meaning and value of life, and where does money stand in the equation? Instructors can guide students to discuss those questions and reflect on the meaning of money and other values in our lives. Students will be helped to think about the differences between “Material satisfaction” and “Spiritual satisfaction”. Instructors can ask students to share their experiences of both satisfaction and give them feedback accordingly. On the whole, the unit teaches how spiritual satisfaction enriches our lives and helps students understand the value of life which include a broad spectrum other than just money.

It is a golden opportunity for instructors to encourage certain actions in this teaching unit. We need to first understand ourselves in depth and try to explore what our “ultimate concern” is. Instructors can discuss with the class and review their own life values and establish life goals with them. This will facilitate students’ search for their life values and ways of happiness. Another exercise they can do is to list out students’ life values. Both instructors and students work together to prioritize according to the importance of different values. Students will be encouraged to participate in voluntary services that would contribute to a meaningful life; share their goals with family members and friends and spend more quality time with them to enhance spirituality. They will adopt the principle of “protecting relationships and righteousness” to solve dilemma in life issues.

Remarks

This game is designed to help students learn some important skills of managing finances, and understand there are circumstances in life where we have no control over. The happiness of life can be achieved by a lot of non-monetary values such as seeking and reaching one’s dreams, helping out in the community, or simply enjoying a quiet afternoon reading on a beach. Everyone has his or her own standard of happiness, students should learn to strike a balance between “Material Satisfaction” and “Spiritual Satisfaction” and should not rely too much on using material goods for happiness. The principles of “Helping others is the origin of happiness” and “Giving is more blessed than receiving” as well as the fact that “Maintaining fairness and promoting equality” can help students themselves and others happy.

User Feedback

The following comments were from a 15-year old girl attending an international school in Shanghai. Informed parental consent to play the game and publish her critical comments on the game was secured.

“The game resembles the popular board game Monopoly. Players use an electronic dice to move ahead but have free choices in gender, duration of the game of three, five, or seven rounds, and most importantly managing their monthly income. They will lose the game

whenever their accounts (money-on-hand) are in deficit. The game will end when players complete the number of rounds selected.

Positive Side

The game embodies a lot of elements in real life such as family, social organization, cultural practices, society, financial management, moral values, and value judgments.

First, the users have a free choice in distributing their salary in how much they are going to use in each aspect (personal consumption, savings, family expenses, and donation). The money remains will be the cash-on-hand. When the cash-on-hand is in deficit, the game ends. Each round, they have a choice to change their decision on how to distribute their monthly salary. This gives the users a good experience in managing their money. Users throw a dice to see how many steps they will move. Therefore, the players have minimal influence on where their chess will stand on. On some places, negative things will happen such as loss of money in investment, sickness, hospitalization and things that will use up money unexpectedly. These resemble the real-life situation that sometimes we need to use money in situations that we do not expect. In this case, students can learn to reserve a slightly higher amount of money for unexpected use. Most importantly, when players find that their money at a round is very close to zero, they will learn to prepare more money for cash-on-hand next time so that they will not lose easily. In this case, students can learn how to save money for unexpected things in real life situation and may not overspend.

Secondly, although the game focuses on how to manage money, it also promotes moral values. The players with the most money in hand can get an award but players who donate a great proportion of their salary, or who have the most good moral character cards, or who contribute the most to society can also get awards. This brings out the idea that not only is earning money important, other aspects such as family, personal warmth, moral values are also important elements in life.

Thirdly, this game is interesting as players may engage in some ups and downs in emotion when they step on rewarding squares and unfavorable squares.

Negative Side

First, as cash-on-hand is a crucial factor of the game, once a player's cash-on-hand is in deficit, he/she will lose the game. It is possible that after a few times the players played the game, they may put all or most of the money to cash-on-hand rather than putting them to personal consumption, savings, family expenses, and donation, in the hope of not losing the game rather than thinking of how to distribute the money in a real-life sense. Therefore, an experienced teacher and instructor may help players clarify their aims and targets when they play this game.

Secondly, it is possible that the game cannot promote the correct way of how to enhance familial relationship. Family award is given to the player who has the largest amount of money by adding savings, remainder of investment, the total amount of family expenses times two, and cash-on-hand together. Usually, players who were given the upper-class role will

spend more money (not in ratio) in family expenses than the middle-class and the lower-class because they have more money. There are a lot of reasons and ways to achieve a harmonious family relationship. Money is only one of the important factors. Although the aim of the game is not to bring out the idea that money is the most important factor in maintaining familial relationship, the game somehow works in this sense. It is possible that students may neglect other crucial factors which could promote good familial relationship such as time spent with family, tolerance, and understanding.

Thirdly, it is better if some small games that could promote correct values judgment can be added to some squares on the board. If players stop on some certain squares, they will be given some positive or negative moral value cards (e.g. greedy, jealous, hard-working, and healthy). Students may not have a deep impression of those values. It is possible to add some small games or some short questions about the corresponding values on those squares. So if students answered them correctly, they can avoid getting bad cards and get good cards. In this case, students may find it more fun as they have to work or discuss to get good cards and avoid getting bad cards, instead of getting them without doing anything. In addition, the game designer can also instill correct value judgments and moral values to students in those questions.

To conclude, the game is interesting enough to arouse students' motivation to play it more than one time. And, the frame of the game was nicely structured. However, some small changes may be needed to improve the game."

The following comments were from a Chinese female young adult (21 years old), a university student from Hong Kong.

Pictures

There are a clear starting page and a clean and clear image of male and female characters for players to choose. The colorful checkerboard is eye-catching and therefore, it is able to arouse my interest in playing the game. The artworks match the description of different life situations with clear instructions.

Game Design

The rules were clearly stated. The important rules that describe different points counting system are highlighted in different colors. However, it may be better to specify the use of remaining cash in the game. The use of dice was good in the game as the randomness of the dice resembles the unpredictability of life. The quote in the end can let me reflect on the meaning of life and daily life decisions.

Content

There are four awards in the game which are individual, family, donation and social contribution. This helps me know that there are different values in life. It is good that the cards are written with different kinds of attitudes and feelings. So it can concretize some abstract description. The reasons given when I get a particular card (attitudes and characteristics) can let me know what specific behaviors are classified as certain characteristics. The game also includes different kinds of situation that adolescents and young adults may encounter when they start work. Lastly, the personal financial management table

helps me think about how I would spend my money meaningfully. The financial management table can reflect a player's spending pattern and his/her value towards money and success.

Effect

Different situations can impress me and help me think deeper (e.g. work hard so that I can get a card of diligence and bonus of one-month salary; you will get what you deserve; once you work hard, how much effort you make, how much you get)."

DISCUSSION

Our findings suggest potential effectiveness of the electronic learning material. From the feedbacks of the users, the design of the learning material is easy to understand and interesting as it is similar to a popular board game named Monopoly. Most importantly, users agreed that the game helps students acquire money management skills and understand moral values, which is the primary goal of designing the game. The feedbacks are consistent with a previous study that a well-designed and clear instructions digital games is beneficial to adolescents in terms of learning financial literacy, supporting the game-based learning phenomenon in schools [32]. The feedbacks have provided some insights to a well-designed DPYD game for young people. For instance, colorful pictures and gorgeous animation attract young people to play the game, increasing their motivation to learn. Moreover, the game has clear learning objectives which are extremely crucial.

Secondly, the effect of teachers' involvement in the process of learning is not ascertained as this is not the focus in this study. However, from the feedbacks of the users, teachers or instructors play an important role in clarifying the learning objectives of the game and indicating a positive effect to enhance the effectiveness of the game. Besides, as pointed out by Kim, Lee [39], teacher support significantly influences youth people who display maladaptive behaviors. Franklin, Kim [40] showcased the effectiveness of school-based psychological intervention delivered by teachers. Teachers not only assist adolescents to learn but also play a therapeutic role which requires further studies to confirm their influence. In addition to their role, teachers can also act as a facilitator to assist in the discussion amongst adolescents on the topic, and getting feedbacks from their fellows. If players receive feedbacks regularly during their learning process, the game is more than just entertainment but a deep learning process for the players [30]. To tackle materialism in youth, it is no doubt that educators should be involved.

Thirdly, a previous study has found that Chinese adolescents from different age groups exhibit different levels of materialism, which reveals materialism increases with age [41]. Impulsive buying behaviors increase with age and female shows more impulsive buying compared to male [42]. In response to the gender and age differences, game designers might have to provide a guideline to teachers or instructors to ensure the learning materials are applicable in adolescents with all age range.

Finally, adjustments on the content of the learning materials are suggested. One user shows concerns that the game might be over-emphasizing on money to maintain family relationship while money is just one of the factors that can promote family harmony. Also,

some mini games can be added into the game in order to help players to make correct moral judgements and understand correct moral values.

Limitations

First of all, the feedbacks in this study do not represent the effectiveness of the learning material. The feedbacks are the fundamental ground for further studies. They are purely opinions of the users that cannot be generalized to a greater population. This is because qualitative method is not designed to test whether the result is statistically significant or due to chance [43]. In fact, the utilization of game-based learning on financial literacy is a relatively new concept that almost no research has been done in Hong Kong. With limited knowledge in this area, it is difficult to make an in-depth conclusion on the effectiveness of the game. Further research on this area is recommended, especially testing the effectiveness of game-based learning on money management using quantitative method with rigorous methodology and validated measurements. In addition, the data in this study is collected only from two individuals. Thus the result in this study should be interpreted with caution.

Apart from that, the game does not cover other protective factors of materialism such as promotion of gratitude [28], social comparison with friends and media influence [12]. These factors should not be ignored in the interpretation of the effectiveness of the game. Financial education is one of the possible solutions to tackle the problem of materialism in youth people.

Finally, it is also worth mentioning that the game design itself is limited to money literacy in young people to reflect on materialistic and non-materialistic values. Other factors that contribute to materialism such as parental influence cannot be addressed. Based on the model by Chan and Prendergast [12], social learning from family members on materialistic values contributes to the development of materialism. For those who are strongly influenced by their parents' materialistic value, this learning materialism might not be as effective. Special training in teaching skills is needed to help this group of young people to deal with their conflicting values [35].

Testing the Effectiveness

This study did not obtain any quantitative data on the level of materialism of the students. Future studies can conduct a thorough quantitative research to test the effectiveness of the game with regard to minimizing materialism among adolescents. Studies have been done in Hong Kong or with Chinese population to explore materialism in adolescents with translated measurements with validation [12, 17, 18]. The Chinese Adolescent Materialism Scale (CAMS) is also ideal to be administrated to test young people's level of materialism as it measures materialistic beliefs through several aspects related to materialism which include morality, spirituality, egocentrism and empathy [8]. To test the effectiveness of the game, a pre-test and post-test design is recommended. The study could first examine the level of materialism using Richins and Dawson [44] Material Values Scale before introducing the learning material. After students have completed the game, the same set of questionnaires

could be done by the same group of students in order to find out if there are changes in their level of materialism by comparing the scores before and after introducing the learning materials. Hieftje, Edelman [45] believed successful electronic media interventions should promote behavior change. Future studies could also measure behavior changes of the students who have played the game. From that, the effectiveness of the game could be concluded.

Apart from testing the effectiveness of the game, it is also worth investigating the contribution of teacher's participation. From the feedbacks, teacher seems to play an important role in students' learning process. Therefore, a cross-sectional study comparing the level of materialism between the group of students with teacher's guidance and the group of students without could provide an insight on the effective implementation of the learning materials.

CONCLUSION

To conclude, the learning materials can educate young people on money literacy. Some adjustments are needed on the game for students to understand the concepts of financial management. Further investigation on the effectiveness of the materials through quantitative method is needed to reach an accurate conclusion on the effectiveness of the game. Overall speaking, the game is a form of "Edutainment" for the promotion of positive youth development among adolescents.

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Chapter 355

USING CHINESE AND WESTERN LITERATURE IN A DIGITAL GAME TO ENHANCE CORE COMPETENCIES FOR PEER AND ROMANTIC RELATIONSHIPS AMONG ADOLESCENTS

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ABSTRACT

Research supports that evidence-based positive youth development (PYD) programs assist adolescents in dealing with developmental problems. One major adolescent issue is relationship, particularly friendship and courtship. Deterioration in bonding with parents and inadequate support from psycho-socially mature adults are commonly found in urban cities around the world. High divorce rate is an indicator. Many adolescents grow up in families with insecurity, lacking proper social and emotional support. The lack of appropriate role models and parental guidance are risk factors for adolescents having troubles in their peer and romantic relationships (PRR). A digital positive youth development (DPYD) game with an aim to enhance the core competencies of adolescents in building and maintaining PRR, which incorporates literature as learning materials, has been developed and made available for free educational use. The game employs both Chinese and Western literature in a bilingual context to provide examples to engross the players' attention and facilitate their understanding of the concepts through stories and practice tasks. Not only does it help promote proper attitude and enhance necessary knowledge and skills, but it also helps foster players' self-awareness and self-reflection through literary references. This paper contributes to cross-disciplinary methodology in using literature in the design and development of DPYD games, as well as providing a

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significant reflection on the nature and function of literature and its importance in promoting PYD among adolescents.

INTRODUCTION

In Hong Kong, only three out of one hundred students took the subject Chinese literature in the post-secondary examination in 2018 [1]. Moreover, in 2017 only 33.6% of secondary schools offered the subject, which is a 23% decrease compared with that of 43.7% in 2012 [2]. Apart from students' heavy study load, another reason is students' perception of literature as difficult and dull. Moreover, literature is regarded as an impractical subject which does not guarantee students a good career prospect in a business and technology-oriented society. Nevertheless, literature is vital to the cultivation of an individual's morality and virtue and the understanding of the root of culture and history. With financial support, a digital positive youth development (DPYD) game to promote proper attitude and enhance knowledge and skills about peer and romantic relationships (PRR) is developed. The game is also designed to enhance exposure to traditional Chinese values and classics from Chinese and Western literature. Through appreciating the beauty of literature, students' perception towards literature might gradually change and they might find literature useful and intriguing, helping them build the habit of reading literature.

A JOURNEY TO SOMEWHERE, TO SOMEONE

The game, 'A journey to somewhere, to someone', simulates taking a journey with friends who might become intimate friends, exploring different landscapes and examining the meanings and principles behind. It aims to help players learn core elements of social interaction with peers, crucial qualities of friendship, and important knowledge and skills for engaging in PRR. The Growth Road Railway has seven stations which include Pingjin Lake Station, Pingshui Station, Hundred-year-old Trees Station, Friendship Mountain Station, Hazy Moon Station, Watchful Station, and the terminal station, Love Road Station. Each station has different contents and game elements through which players learn PYD constructs and related knowledge and skills.

Pingjin Lake Station aims to deepen students' self-understanding; Pingshui Station helps one understand the opposite gender and reduce gender stereotypes and biases; Hundred-year-old Trees Station serves as an examination of friendship; Friendship Mountain Station helps differentiate desirable from undesirable friends; Hazy Moon Station aims to deepen learners' understanding of the differences between like and love; Watchful Station enables the learning of the fourteen crucial elements of building, maintaining, and enhancing PRR; and Love Road Station introduces players to the seven stages of romantic relationship. The design helps students learn step by step. Each part is equally important, and the topics are interrelated. Therefore, students are encouraged to play the game repeatedly and thoroughly in order to achieve more in-depth learning outcomes.

The game provides short stories from Chinese and Western cultures. It also uses Chinese poetry, essays, and literary knowledge. To engage players, short quizzes, psychological tests with feedback, and small games are included. Players will be attracted by the journey to reach the final destination, Love Road Station, which stimulates engagement and motivates them to continue playing the game.

With the examination of the values behind human affairs and self-reflection, students are given opportunities to improve their self-awareness, learn to get along with good friends, change their behaviors, maintain and enhance friendship, and finally obtain necessary knowledge, attitude and skills required at different stages of romantic relationship.

LITERATURE REVIEW

Bonding is defined as “the emotional attachment and commitment an individual makes to social relationships with parents, caregivers, siblings, peers, schoolmates, teachers, romantic partners, and other members of the community throughout the whole life circle” [3, p. 1]. This paper focuses on students’ bonding with friends. Peers play an important role in providing physical and mental support, intimacy and guidance, which are the key foundation of adolescents’ self-worth and self-esteem [4]. Companionship of friends is found to help one cope with alienation and adversities that favors the construction of a sense of belonging and higher level of social acceptance, enabling a smooth integration into the community and society [4]. Positive bonding with peers also correlates with students’ psychological health and whole-person development. On the contrary, negative peer pressure could result in the imitation of friends’ aversive behaviors, such as smoking or drug abuse. Hence, the game aims to teach students to distinguish between helpful and harmful friends and ways to build and maintain friendship in order to enlarge their social circle and have a fruitful social life.

Literature in Game-Based Learning

Literature is not used in the first two stations as the game adopts a step-by-step approach to avoid teaching difficult concepts at the beginning, which might hinder students’ incentives to continue playing the game. According to Nor and Wong’s [5] report on the design of history digital game-based learning software, it is recommended that “design must be immersive, motivating, engaging and playability high” (p. 12). Literature is often perceived by students as difficult and boring. Hence, the incorporation of small games, short quizzes, and psychological tests with feedback would be effective in the formation of new concepts and the development of cognitive thinking and skills [6]. This would alter students’ prejudice against literature and could strengthen their interest and motivation to read more Chinese and Western classical literature. Conceivably, students could develop a long-term reading habit, favoring the enrichment of knowledge and the cultivation of good virtues.

STATION 1: PINGJIN LAKE STATION

Students can enhance self-understanding of their personality traits, including strengths and weaknesses. Through determining the described features, such as lively, stupid, fair, and proud, on the scale of ‘completely different from me’ to ‘exactly like me’, students could obtain feedback on their self-image. This not only increases learners’ engagement but also fulfills the objective of self-understanding, enabling them to reflect on their bad habits and encourage them to acquire more positive traits. Moreover, the game is tailor-made for students of various personalities. If they demonstrate a very positive self-image, they could directly head to the third or fourth station. For those who have room for improvement, they are asked either to select some of the personality traits they want to improve or to choose positive qualities they desire to have. Self-understanding is fundamental for building and maintaining PRR, paving their way to latter stations of seven levels of friendship and fourteen essential qualities [7].

STATION 2: PINGSHUI STATION

One’s first impression to an unacquainted person is largely determined by their appearance. Gender stereotype and prejudice shaped by social norms might obstruct one’s relationship with others and even hinder human interaction. The game offers a test which checks players’ attitude towards males and females. Despite the fact that no absolute right or wrong answers are given in the game, students would be asked to rethink whether common expectation of both gender is reasonable. Girls are often perceived as narrow-minded and temperamental, while boys should be brave, independent, resolute, rational and active. The game would then remind players that these are groundless gender stereotypes and that girls and boys can have various traits. Youngsters after completing the tests could have a conceptual change, freeing them from traditional/subjective bias and encouraging them to strive for gender equality through actions. Positive identity and social competence are thus enhanced as they learn to accept differences and respect diversity. For students who are not fully familiar with the concept or could have improvement, they are recommended to read a short passage and complete a yes or no question, ensuring an awareness of gender stereotype before moving to the next station.

STATION 3: CENTURY-OLD TREES STATION

Students have to reflect on whether they are a good friend to others by selecting the most suitable answers to the questions relating to their friends and they would be given feedback afterward. Based on an individual’s response, if one is confirmed as a helpful friend and a wise companion of others, one is qualified to speed up the pace and directly proceed to the fourth peak ‘Acquaintance Peak’ of Friendship Mountain Station. This reveals the customized-nature of the game with corresponding adjustment according to the students’ character and ability.

First, learners start by understanding the cultural differences of friendship in Chinese and Western cultures. There is a saying in *The Analects of Confucius – Wei Zheng* that goes, “Show your kindness towards your friends as they are like your brothers” [8]. In traditional Chinese society, real friends can even swear to live or die together, implying the intimacy between friends is only second to that of filial relationships. On the contrary, western culture emphasizes individualism, which implies that people sharing similar thoughts would gather together but they will go separate ways if they hold different views. To conclude, Asians are relatively more “interdependent and relationship-oriented” compared with westerners [9, p. 1476]. Hence, Westerners might have difficulties understanding the Chinese ways of hospitality. Students would learn to respect one another’s diversity and the cultural differences between east and west, cultivating the spirit of embracing those who hold different opinions. This lays a solid foundation for the construction of one’s social competence and bonding with others.

Second, students have to develop the ability to distinguish between beneficial and harmful friends. According to *The Analects of Confucius – Ji Shi*, there are three types of desirable and undesirable friends respectively. One should make friends with those who are upstanding, honest and knowledgeable, and stay away from people who are obsequious, good at tempting and using dishonest rhetoric. Adolescents are hugely influenced by their peers which could lead to “peer contagion”, referring to the “influence among peers that results in the spread of shared behaviors” [10, p. 249]. The quote in *The Analects of Confucius – Wei Zheng*, “I do not see how a man who is untrustworthy in words can be acceptable” introduces the two moral values, integrity and uprightness, that are indispensable in helping students get along with others in society [11]. Learners will gradually find literature useful and applicable even in modern society.

Third, loyalty and faithfulness are necessary in the maintenance of friendship. To cultivate the mentioned virtues, one could learn from Zeng Zi, who examined himself on three things every day. “In what I have undertaken on others’ behalf, have I failed to do my best? In my dealings with my friends, have I failed to be trustworthy in what I say? Have I failed to practice repeatedly what has been passed onto me?” [12] Constant reflection on oneself would remind one to be honest and loyal to one’s responsibilities. Moreover, youngsters should not look down on anybody as everyone has his/her own strengths. They are advised to hold a humble attitude to learn from others’ merits and rectify their shortcomings as Confucius instructed in *The Analects of Confucius – Wei Xue*, “Do not make friends with anyone who is not as good as you. When you make a mistake, do not be afraid of mending your ways” [12, p. 34]. Undoubtedly, literature serves as a good model for one to follow the skills of pursuing good virtue and self-reflection.

Literature can guide one to look for bosom friends with whom the friendship would last long. According to *The Analects of Confucius – Yan Yuan*, “Use writings and knowledge to meet one’s friends, and through ones’ friends to develop ones’ benevolence. Form a literary circle and make friendship as a help to right conduct” [12, p. 509]. Through the reading of orthodox literature, one’s cognitive knowledge is enriched and one is able to better express one’s opinion. This fosters the communication and exchange of thoughts with like-minded people, which could enhance one’s temperament and benevolence [12]. Bosom friends are like mirrors, who would kindly point out all demerits of one another for the sake of helping them. Selfishness and self-centeredness are replaced by mutual trust. With the support of one another, both would together proceed on a correct path to success. Realizing the importance

and benefits of reading literature, students would be motivated to study more Chinese classics.

Quotes from Chinese classics are integrated into this station which acts as a warm-up activity for students to get prepared for literary stories in Hazy Moon Station. Concepts introduced in this station will further be elaborated in the next station and applied in actual practice, which is the seven levels of friendship that provide guidance for students to build and maintain intimate relationships with peers.

STATION 4: FRIENDSHIP MOUNTAIN STATION

Station 4 lays out seven levels of friendship and outlines a stepwise and systematic guidance for students to build and maintain friendships.

Massive Crowd Peak

Students could learn to identify the characteristics of their personalities and reflect on their way of getting along with others, which favors the improvement of the modes of communication with others. The test of identifying the best descriptions that match oneself provides a personalized learning approach which could cater for students of different personalities and backgrounds, enabling them to understand their role in the relationship, attitude when treating people, and way of dealing with matters based on their responses. Suggestions are also given for one to learn to get along with people of different personalities. For example, one is advised to respect others' opinions and reach a consensus through communication with people who are dominant and proactive. This lays the foundation of building friendships as researchers found that the most explicit strategy in maintaining friendships as well as romantic and familial relationships was "direct discussions and listening to one another" in a large sample of undergraduates [13, p. 207]. Acknowledging one's shortcomings and acquiring communication skills would improve their social and behavioral competencies of maintaining a relationship.

Followers Peak

Students could get exposed to the four levels of friendship in Chinese literature, ascending from 'friends of wine and meat', 'friends with common interests', 'friends with righteousness' to 'sworn friends for life and death'. To elevate one's friendship and become confidant of one another, sincerity is the most crucial principle. Confucius and Zuo-qiu Ming once mentioned in *The Analects of Confucius - Gongye Chang* that one should directly speak one's thoughts to one another if resentment and problems arose, instead of pretending nothing has happened and keep getting along with them. As a true friend, one has the responsibility to advise one another on the basis of equal status [14]. On the other hand, Western culture recognized the importance of sincerity in friendship as evidenced in the saying, 'When getting along with friends, your personality should be exposed thoroughly to one another' [14].

Literature contributes to the facilitation of implicitly maintaining friendship by highlighting the significance of self-disclosure and providing mental support [13]. Understanding the wisdom of maintaining friendship through reading classical literature, students' cognitive knowledge would be further enriched, and they would be reminded to treat friends with a sincere heart.

Acquaintance Peak

Through *The Analects of Confucius*, students could understand and identify the determinants for desirable and undesirable friends. Students are recommended to make friends with those who have a firm stance, are fair and honest, are willing to assist others to go forward and be responsible, and dare to admonish their friends directly. They are also reminded to stay away from those who are ingratiating in action and place too much importance on pleasant appearance and plausible speeches [14]. Friendship quality is featured as "the nature of friendship interactions" which would be influenced by the factors of "pro-social behavior, loyalty and intimacy, and few conflicts" [15, p. 517]. Having quality friendships has been proven to have a positive association with one's psychological well-being [4, 15], which contributes to adolescents' behavioral regulation and cognitive and emotional competences [15].

Owing to the fact that helpful friends are good listeners and advisers, providing "guidance, reassurance, acceptance, sympathetic listening, encouragement, feedback and a sense of belonging" [4, p. 666], they are key socializing agent of youngsters to adjust their behaviors and communication skills. Social support provided by friends could boost the feelings of self-worth and self-esteem of youngsters, enhancing their psychological health development and bonding with peers [3]. In contrast, social learning theory and primary socialization theory are used by Kobus [16] to explain that adolescents might go astray if they imitate deviant behaviors from peers such as smoking and doping [3]. Knowing the importance of making worthy friends, adolescents could make right decisions when making new friends, maintaining a close relationship with those who are credible and knowledgeable, and distancing from harmful friends.

Knowing Peak

When getting along with friends who have different characteristics, one has to adjust his/her attitude based on the situation or characters of the other party in order to avoid clashes or confrontations. One should consider raising their demands when working with those who are lazy, indifferent or disrespectful. One is advised to make requests when facing those who are sensitive, short-tempered or experienced but lack enthusiasm. Remembering the suggestions, students would be able to make the correct judgement and decisions when encountering similar situations. This strengthens one's ability to handle matters and cope with adversity, promoting PYD [3]. Besides, provision of material and mental support to friends are essential in maintaining an intimate relationship [13], for instance, lending a helping hand to them when they have to complete a particularly difficult or annoying task. The knowledge

acquired paves the way for students to proceed to the next station, enabling them to have a more in-depth understanding of the literature and the qualities, which are assistance, devotion and reciprocity.

Good Friends Peak

Establishing and maintaining mutually trusting relationships with friends require time and joint effort from both parties. This station serves as a warm-up activity for students to have a glimpse of the qualities one should possess to enhance an intimate relationship with others, which correlates to the fourteen elements in Watchful Station. Students are reminded to respect friends' freedom of expression, accept unconditionally and trust everything about them, and keep the conversation confidential. Self-disclosure, which is the revelation of private and sensitive personal information to others, would be effective to build trust and foster intimacy in a relationship as it indicates commitment and the willingness to expose one's weakness [9]. One would be emotionally involved with peers' disclosure, implying that they are starting to be aware of and understand others' emotions [17]. The ability to express empathy demonstrates their awareness of catering to the needs of others and putting themselves into others' shoes, favoring the development of "interpersonal priming, self-awareness, mental flexibility, and emotional regulation" [18, p. 248]. Having a basic understanding of the above important qualities helps youngsters build a solid foundation, ensuring a smooth transition to Watchful Station, in which large amounts of Chinese and Western literature are included. They could thus better immerse in classics and have an in-depth knowledge of the fourteen core components, and integrate theory into overt behaviors. As Tillman and Prazak [19] proposed, "developmentally important skills include those related to communication, conflict resolution, developing and maintaining trust and intimacy, which in turn facilitate friendships that may serve as basic building blocks for adult relationships of an intimate nature" (p. 158). Students are encouraged to practice skills that establish or promote trust among classmates, which strengthen their bonding with peers.

Fraternity Peak

It is essential to form literary circle as literature not only cultivates one's well-being and virtue, but also helps one make friends with those who share similar hobbies and visions. *The Analects of Confucius* - Yan Yuan states, "Gentlemen gather together with friends to talk about literature and art. They develop benevolence through the support of friends" [14]. Through the reading of Chinese and Western literature, students could savor the words and appreciate the content, through which their vision would be broadened by exploring ancient people's social lives and emotions [20]. The reflection on the connotation and the value of life fosters the gradual formation of their own ideals and codes of conduct, helping them become a person with great virtue and a strong sense of social responsibility [20]. Moreover, one's passion in reading literature and pursuing knowledge would draw us to those who share similar aspirations. Hence, talking about literature and art with friends promotes a common language and genuine exchanges of opinion. Echoing with the saying in *The Analects of*

Confucius - Zi Lu, “Friends should encourage one another and exchange views with one another.” This suggests the significance of literature in assisting one to look for long-lasting friendships where peers could always support one another and enable one to learn from their strengths, striving together on the rightful path in life [14].

Confidant Peak

The supreme level of friendship is to be friends until or even after death. One of the examples in Chinese classics is if a friend of Confucius passed away and nobody undertook his funeral, Confucius would take care of it [14]. This implies that friendship persists no matter in life or death. Even after the death of one’s closest friend, one should still treat them benevolently. Ancient people’s emphasis on confidant would move youngsters’ heart, making them rethink whether they are willing to go through trials and tribulations with one another and determine whom one’s real friends are. The real-life stories of Confucius may enhance students’ social and moral competencies. For example, Confucius’ student Zi Lu always shared his carriage, horses and clothes with his friends, without caring about the objects’ wear and tear [14]. This sets a perfect model to educate youngsters that the amiable relationship between friends outweighs the value of possessions. Besides urging adolescents to reject materialism, classical literature reminds youngsters of traditional Chinese values where group intimacy and altruism are emphasized. As Confucius once mentioned, “the teaching of respect to one’s elder brothers is a preparation for serving all the elders of the country” [21, p. 69]. By reinforcing a sense of social altruism, people are reminded to be generous not only to family members, friends, and lovers, but also to less closely related individuals in society [22]. When understanding that sharing is more blessed than receiving, one would be eager to help those in need, which helps enhance one’s moral and social competencies.

STATION 5: HAZY MOON STATION

Social, moral and emotional competencies could be enhanced from classical literature and poetry, for instance, the Chinese ancient classic *Book of Poetry*. Confucius proclaimed, “the verses of *Book of Poetry* can be concluded in a single phrase - Don’t think in an evil way”, which is to guide people on the right path through the provision of correct knowledge on morality and romantic relationship [23]. In Station 5, six poems are provided to students as a warm-up activity to have a taste of the three core components of love, namely passion, commitment, and intimacy.

Firstly, commitment refers to “a short-term decision to love someone and a long-term commitment to a loving relationship” [24, p. 330]. This could be manifested in two poems: *Guan-guan* (‘The Osprey’) edited by Confucius and *Sheng Zha Zi* by Ouyang Xiu. *Guan-guan* expresses the yearning and pursuit of pure love by ordinary ancient people and reflects the healthy and sincere thoughts/feelings of the youth [23]. While students are free to fall in love with another person, just like the author in the poem, they are responsible to commit in the relationship when encountering true love and see marriage as the ultimate form of love [25].

Sheng Zha Zi describes the feelings of breakup and separation of a couple, and one would be moved by the sorrow and commitment of the author. “Tears soaked the sleeves of my spring gown” manifests the difficulty to part and how deeply the man once loved his partner [26].

Secondly, passion is defined as the “internal forces that lead to romance, physical attraction, and sexual satisfaction” [24, p. 330]. One could experience the passion of ancient people in the poem *Flower? Not Flower* written by Bai Juyi which expresses the author’s longing for love. Scholars generally agreed that the background of the poem is the poet’s affair with a lady, allegedly a prostitute. Just as short-lived as the flower and the haze in the poem, his love may be intense, but lasting no longer than flowers and haze [27].

Another poem is *Butterflies Love Flowers* by Su Shi, expressing delicate feelings of vacancy and loss. A passer-by was attracted to stay and listen for a while by the sounds of swings and laughter from a fair lady within the garden wall, but after her laughter faded away, the passer-by could only take a deep sigh for his ‘sensation being disturbed by the reality’ [26]. In spite of encountering failure in love, teenagers are encouraged to continue to seek true love.

Thirdly, the two poems by Liu Yuxi in *Song of Bamboo* convey the feeling of intimacy in love which includes “such qualities as experienced happiness with the loved one, mutual understanding, intimate communication, and emotional support” [24, p. 330]. The first poem demonstrates intimacy through dating activities. Referring to nature in the background, the persona portrays her feelings towards entering a romantic relationship [28].

The other poem portrays the worries of a woman that the love of her lover would be fleeting like peach blossoms. Then, an infinite gloominess came upon her like endless river currents [26]. It is common for one to feel anxious and nervous in a love relationship, for fear of not being loved by their partner. However, one should be honest and try to communicate with their partner in order to eliminate the uneasiness to maintain intimacy [29].

Distinguishing between Love and Like

The exposure to literature and poems could enrich youngsters’ understanding of love and help them develop the ability to distinguish between ‘love’ and ‘like’. Different from ‘like’ which could be merely out of physical attraction or similarity of personality, ‘love’ consists of three core components: passion, intimacy, and commitment, resulting in the desire to possess and the exclusion of others [24]. The story of Su Shi is a good example to determine whether one has found their true love. Su Shi, one of the greatest writers in Chinese literature, expresses his deep feeling of grief and remembrance towards his dead wife, Wang Fu, through the poem *Jiang Cheng Zi*, revealing the highest level of love: love would never perish due to death [26]. In the ten years after his wife’s death, Su Shi tried very hard to forget her, but she was forever in his mind. His deep sorrow and affection touch the hearts of many readers and invite youngsters to reflect on what is meant by true love. A precious lesson is taught to adolescents, reminding them not only to be the only one for each other, but also to love one’s partner even after their death. Absorbing new knowledge of love, students would think twice before starting a romantic relationship or devote their time and effort only after having a deep understanding of their partner, which resonates with the “cognitive processes”

that enables them to use a reasoning process of deciding what to believe and critically examine one's own thinking in order to make appropriate judgement and action [30].

STATION 6: WATCHFUL STATION

Maintaining a stable and harmonious relationship with both same and opposite-gender friends and furthermore, partners, requires both parties' contribution and sacrifice of their time and effort. One would be motivated to improve his/her personality, cultivate a sense of responsibility and even the selfless sacrificing spirit. To achieve the above goal, one has to possess fourteen essential elements: understanding, equality, pleasure, acceptance, devotion, assistance, trust, respect, loyalty, self-esteem, reciprocity, defense, maintenance, and confiding.

Mediation Sea (Theme: Understanding)

The ideal personality traits in Chinese and Western cultures are listed respectively, which share great similarities, for instance, advocating the complete morality of benevolence, righteousness and wisdom, and the maintenance of an honest and sincere attitude towards others [31]. Understanding the qualities could help one set up goals and motivate one to pursue them in life.

Balance Village (Theme: Equality)

The need to go on a business trip separated Qin Jia from his wife Xu Shu, so they could only express sorrow, remembrance and deep love through letters [32]. This Chinese love story demonstrates the ideal of mutual love and respect between spouses, where one should always be courteous to their partner and be devoted to them.

Comfort Forest (Theme: Pleasure)

Yu Boya became bosom friend with Zhong Ziqi as they appreciate each other's musical attainment and find connection in the pleasure of music. This is similar to the western story of Robert and Clara Schumann, who fell in love due to their shared passion in music. Even after Robert's death, Clara continued to promote his work as they were not merely partners, but also each other's bosom friends, who shared pleasure in their musical journeys. Students would learn to reinforce friendships through spiritual pleasure.

Patience Mountain (Theme: Acceptance)

The Chinese short story of Lin Xiangru and Lian Po shows two high-ranking officials willing to put aside rancor and forgive each other. On the other hand, the Western short story uses a bag as a metaphor of hatred. The more attention you pay to it, the more the hatred expands [33]. Both ask players to be mindful of hatred and be forgiving.

Dedication Spring (Theme: Devotion)

The friendship of Guan Zhong and Bao Shuya and the story of Samuel Walton who founded Wal-Mart Stores teach students a lesson about devotion. The former manifests the importance of trust and willingness to sacrifice and devote oneself to another without demanding return; while the latter demonstrates Walton's great sense of sincerity, responsibility, and devotion [33]. Devotion decides a person's mental and moral nobility, which not only helps improve a person's well-being, but also one's relationships with others.

Thousand-Hand Cliff (Theme: Assistance)

Assistance is not just about material or emotional support, but also spiritual help. Guan Ning ended his friendship with Hua Xin due to his friend's inattentive attitude, but his act was to assist Hua Xin to reflect on the value judgments behind his behaviors, hoping that he would make improvements. Former US President Barack Obama's considerate, humble and straightforward personality won the support of his wife, the public and even his opponents [33]. A spiritual level of help with deep spiritual connection enables one to extend the meaning of life and improve one's shortcomings.

Heart-to-Heart Lake (Theme: Trust)

The two Chinese short stories, the friendship of Fan Shi and Zhang Shao, and the trustworthiness of Jin Wengong, emphasize trust and the importance of keeping one's promise, from a promise for a meeting to a promise to citizens by a high-ranking official. Similarly, in a western story, Damon was willing to trust his friend Pythias in face of an imminent death penalty. Trust is the basic condition of getting along with friends, and keeping one's promises is the first step for building trust.

Respect Lake (Theme: Respect)

Mencius mentioned one should "look humble outside and be respectful inside", implying that respect to parents, friends, and lovers has to come from the heart [34]. Saying and teachings from Confucius reveal the emphasis of filial piety and respect in traditional Chinese society, which are the basic qualities of one's well-being.

Fidelity Rock (Theme: Loyalty)

Loyalty is of utmost importance in a romantic relationship. Take the modern story in the game as an example, one should not hang out alone with a friend of the opposite gender simply because one's boy/girlfriend is not available. A romantic relationship is extremely fragile and has strong exclusivity where the intervention of other parties is not allowed [34].

Awakening Rock (Theme: Self-Esteem)

One would sometimes be depressed or feel helpless when facing difficult tasks and adversities in life, but one must not lose the belief of self-respect [12]. The two Chinese short stories describe two persons having great ambition and open-minded confidence respectively even after being relegated. This motivates students to have confidence and determination for making improvements, which would favor their building of positive self-esteem.

Symbiotic Wood (Theme: Reciprocity)

Confucius advocated a person's positive character is the most important consideration in choosing friends, instead of their social status or wealth [14]. Relationship built on mutual development, for example, the exchange of opinions and thoughts, is more long lasting than that of materialistic interests [14].

Jintang Brook (Theme: Defense)

The forced divorce case of Lu Yu and his wife is used to teach students that 'love is more solid than gold' and one is obliged to defend theirs and others' rights. Bounded by the traditional customs and the rejection of his mother, Lu Yu was unable to defend the marriage between him and his wife, and they were ultimately forced to separate. Nowadays, with every person having the same rights, when an individual executes his/her own rights, he/she should never invade or damage others' rights, and should defend against injustice.

Magpie Bridge (Theme: Maintenance)

A poem written based on the renowned Chinese mythology - the cowherd and the weaving girl who could only reunify once a year - describes the grief at their separation and joy in reunion [26]. This resonates with another poem written by Su Shi, in which he expressed his deep nostalgia towards parting with his younger brother [26]. Both poems urge youngsters to treasure the time with their beloved and maintain an intimate relationship with them.

Echo Valley (Theme: Confiding)

Students could acquire the skills of confiding and listening to others through ‘self-inspection’. Confucius admonished that “be strict with oneself and be lenient with others”, underscoring the need to constantly review our behavior and words in order to correct one’s mistake. Improvement in confiding skills ensures a harmonious relationship with peers.

Discussion: Enrichment of Knowledge through Literature and Games

It would be a challenge for students who do not have adequate knowledge regarding the historical background and social context of the authors to grasp the underlying meanings of their work. Therefore, to help students attain a better understanding on the fourteen core components, detailed explanation of the classics and poems are provided in the game. The provision of additional information - such as the feature, origin, and structure of parallel prose - is a precious opportunity for foreigners to be exposed to classical Chinese poetry which is different from western forms. Chinese poetry emphasizes “consistency in the number of words” and “neatness of lines”, fulfilling visual aesthetics and antithesis; whereas Western poems fail to achieve the same length of lines owing to the alphabetical constraint [35, p. 25]. The exposure of new knowledge might stimulate their interest and willingness to read more poetry and literature to build a long-term reading habit [36, p. 87]. Moreover, students could better understand the differences between Chinese and Western cultures and values. In terms of gender equality, traditional Chinese society defines equality as “always [being] courteous to each other like guests”, as being polite is the result of one’s self-respect and love to others [37]. Thus, one is reminded to treat their friends and loved ones wholeheartedly and respectfully. In contrast, western countries emphasize philanthropism, meaning the caring and respect for all individuals, not only one’s friends and loved ones [37]. Hence, they advocate everyone should enjoy equal rights and equality and offer help to the poor and the needy. Understanding the cultural differences could narrow the gap between people with different backgrounds, encouraging them to respect and build bonding with one another. After digesting huge amounts of Chinese and Western literature, mini-games are effective ways for youngsters to contemplate and put knowledge into practice, for instance, distinguishing between desirable and undesirable behaviors.

Favoring Personal Development

Literature encourages students to think from others’ perspectives, fostering the development of empathy and understanding which enable them to build strong bonding with others. Scholars agree fiction strengthens audience’s abilities to substitute themselves in another’s situation, bringing changes to their thoughts and emotions [38, p. 2]. Engagement with fiction stimulates the development of “Theory of Mind” [39], “the ability to detect and understand others’ emotions and the inference and representation of others’ beliefs and intentions”, leading to the cultivation of a sense of empathy and understanding (p. 377). Chiariello [40] also proposes encouraging of empathy and perspective taking, along with facilitating impersonal (thus rational) discussion, and providing models for character as the three social functions of fiction.

Table 1. Chinese and Western literature used for the fourteen core components

Station	Chinese literature	Western literature	Game element	Core quality of friendship
Mediation Sea	The characteristics of ideal personality affirmed by traditional Chinese culture	The characteristics of ideal personality affirmed by Western culture	Psychological test	Understanding self and a close friend
Tianping (Balance) Village	The amount of love given to your loved one should be mutually equal; Qin Jia felt sorry for not giving enough love to his wife, and instead he gave physical goods to his wife as recompense.	The true essence of love according to book of Corinthians from the Bible	Mini quiz on gender equality	Equality (Law-abiding / courteous)
Comfort Forest	Yu Boya became bosom friend with Zhong Ziqi as they appreciated each other's musical attainment and found connection in the pleasure of music.	Robert and Clara Schumann fell in love with each other due to their passion in music. Even after Robert's death, Clara continued to promote his work.	Making friends through arts and literature: A mini game on music production	Pleasure
Patience Mountain	Two high-ranking officials, Lin Xiangru and Lian Po, demonstrated willingness to put aside rancor and forgive each other.	A bag is used as a metaphor of hatred, implying the more attention Hercules pays on it, the greater the hatred expands. This shows the importance of forgiveness.	A short message on acceptance	Acceptance
Dedication Spring	The friendship of Guan Zhong and Bao Shuya manifests the importance of trust and willingness to sacrifice and devote oneself to another without demanding return.	Samuel Walton's unacceptance of any imperfection in his work demonstrated his great sense of sincerity, responsibility, and devotion.	A mini game on devotion to your loved ones	Devotion

Table 1. (Continued)

Station	Chinese literature	Western literature	Game element	Core quality of friendship
Thousand-hand cliff	Guan Ning ended the friendship with Hua Xin due to his inattentive attitude, but Guan's act was to assist Hua to reflect on the value behind his behaviors, hoping that he would make improvements.	Former American President Obama's considerate, humble and straightforward personality won the support of his wife, the mass and even his opponents.	A mini game testing how helpful the player is, with immediate feedback	Assistance
Heart-to-heart lake	The two short stories emphasize trust and the importance of keeping one's promise, including a high-ranking official's promise to citizens.	Damon was willing to trust his friend Pythias despite of impending death.	A metaphor of mathematics induction method to illustrate whether a person is trustworthy	Trust
Respect Lake	Confucius teaching stressed one should "look humble outside and be respectful inside", implying that respect to parents, friends and lovers has to come from the heart.	Norms of respect in Western societies such as attitude, respecting others' rights, courtesy towards teachers, seniors, classmates, at home, in public places, and maintaining personal appearance	Mini quiz on 90 randomly selected items on respect from 112 items in 1.5 minutes	Respect
Fidelity Rock	Study the lyrics of a Cantonese song	Read a modern short story on the companionship of two young lovers	Discussion questions provided	Loyalty
Awakening Rock	Two Chinese poems describing individuals having great ambition and open-minded confidence even after being relegated	A Western short story on the building blocks of self-esteem	Nil	Self-esteem
Symbiotic Wood	Confucius advocated a person's positive character is the most important consideration in choosing friends, instead of their social status or wealth.	A modern short story on mutual recognition and respect	A test on reciprocity with immediate feedback	Reciprocity
Jintang (Golden hot water) Brook	The forced divorce case of Lu Yu and his wife manifested that 'love is more solid than gold' and one is obliged to defend theirs and others' rights.	A passage to encourage the adoption of different perspectives to make moral decisions	Illustrations of moral decision making	Defense
Xique (Magpie) Bridge	A poem based on the renowned mythology - the cowherd and the weaving girl who could only reunify once a year - describes the grief at their separation and joy in reunion. Another poem written by Su Shi expresses his deep nostalgia towards parting with his younger brother.	A modern short story: Unable to accompany	Scenario-based questions	Maintenance
Echo Valley	Confucius teaching mentioned one should "be strict with oneself and be lenient with others", underscoring the need to constantly review our behavior and words in order to correct one's mistake.	Ancient and modern mottos are suggested, for instance, Jesus said, "There is no greater love than this: to lay down one's life for one's friends."	Scenario-based questions	Confiding

Through self-reflection on their ways of treating their friends, readers are reminded to self-modify their behaviors in order to become a considerate person, which would bring positive influences on their self-development and interpersonal relationship [38]. This echoes the findings of the Dutch Institute for Curriculum Development that literature education “has an important value for developing citizenship, broadening social and cultural horizons and developing empathic capabilities” [38, p. 2], in which readers would have a change in their inner self and attitude towards others. In addition, the fourteen essential elements are good examples of strategies to strengthen students’ bonding, “providing clear and consistent guidelines and expectations for adolescents to follow and maintain an intimate bonding with peers” [3, p. 6]. For instance, one should keep their promises faithfully to gain friends’ trust and respect, which is also the core for youngsters to become a person with great virtue and good reputation.

Enhancing Language Skills and the Expression of Emotions

Literature enhances youngsters’ emotional and behavioral competencies. Through the enlargement of readers’ vocabulary, their ability to express emotions and thoughts would be strengthened [17]. Confucius believed that, “Poetry serves to stimulate the mind. They may be used for purposes of self-contemplation. They teach the art of sociability. They show how to regulate feelings of resentment” [35, pp. 4-5]. Indeed, one could learn to cope with aversive emotions and distressing circumstances from literature, which could be illustrated with the story of Lin Xiangru and Lian Po (from Patience Mountain). When having conflicts, one should restrain his/her temper and show sincerity to communicate with one another in order to solve the crisis, as only understanding would bring forgiveness and foster a deeper relationship with peers [41].

STATION 7: LOVE ROAD STATION

To motivate students to use the material, the contents are delivered in the “Love Institute” where players can choose their majors and elective courses on the seven stages of a romantic relationship. *The Little Prince* is used to help students reflect on their own values and encourage a critical examination of their beliefs when encountering difficulties in the sixth stage – to decide whether to commit or to breakup. The book is one of the classics of all time that covers seven stages of a romantic relationship. It is on the list of The 10th Secondary School’s Best Ten Books Election in Hong Kong. Having a basic understanding of the storyline in mind, players would be able to develop an in-depth analysis and grasp the underlying meaning.

The Differences between Literature and Literature in Game

In literature, “the author’s intention’ and ‘the perspicacity of the ‘audience’” are both indispensable [42]. Yet the author’s intention, otherwise known as literary implications/

assertion, would often not be explicitly stated, which is called ‘secondary meanings’ or ‘depth meanings’. This leaves room for readers’ own interpretation and subjectivity, resulting in the varying understanding of the author’s intention [43]. Moreover, according to McDuffie [44], “literary authors are not letter-writers”, meaning they are not addressing a specific person but a wider spectrum of audience (p. 108). Thus, they have to adopt a rather universal expression and representation. As our target audience is mainly youngsters, it is possible that they might misread the stories, or be unable to grasp the underlying meanings and in turn the moral lesson owing to the lack of experience or knowledge. From the perspective of educators, there is a need to guide students to acknowledge the assertion that the author is trying to proclaim, and to emphasize those that align with our teaching goals. Take *The Little Prince* as an illustration: the question “why was the Little Prince so determined to leave the rose and let his beloved rose live on the asteroid alone” is first raised to stimulate discussion among teenagers [45, pp. 49-50]. One of the possible reasons is “the rose is not beautiful enough”, but the book actually mentions that “her beauty made it difficult for him to calm down, and he believed that the rose was the most stunning and unique flower in the universe”, meaning that it would not be the answer [45, pp. 49-50]. Another possibility is that “the Little Prince got bored”; yet it is unconvincing as “the Little Prince took care of the rose attentively and patiently until his departure”, implying that the rose meant a lot to him [45, pp. 49-50]. Indeed, the truth is “the Little Prince could not face the rose or himself”. They both loved each other deeply, but misunderstanding tore them apart [45, pp. 49-50]. Consequently, it is essential to list out all possible interpretations along with evidence and explanation in the game in order to help youngsters differentiate between right and wrong interpretations (in this case, right and wrong interpretations towards the one you love). By revealing the characters’ inner feelings, readers would be aware of the need to put themselves in others’ shoes and view an issue from multiple perspectives. They would be able to cultivate a sense of empathy towards friends and family and become a considerate individual [46].

The Function of Literature in Promoting PYD

Literature is believed to carry cognitive values through the communication of propositional knowledge, which puts the focus on conveying the actual knowledge and experience to readers. Mikkonen sees literature as a carrier of human knowledge and experience, and suggests that the knowledge obtained from literature is believed to be “knowledge of concepts, modal knowledge or knowledge of possibilities, knowledge of human nature or emotions” [46, p. 9]. Readers’ own knowledge and experience overlap with the author’s to various extents, helping them explore new experiences, broaden their horizons, and stimulate their imagination [46]. Mary Sirridge further elaborates on this point that literature has an educational function which “clarifies our knowledge of the actual world” [46, p. 10].

Literary truth is arguably different from scientific truth, which presents facts explicitly [46]. Therefore, readers are demanded to think thoroughly and even think from the author’s perspective to extract literary truth, since the moral lessons are hidden in between words [43]. For example, in *The Little Prince*, readers have to look for the meaning of love from the conversation between the fox and the boy. With the help of the explanation provided in the

game, one understands love “comes from one’s internal emotions” and the willingness to be another’s “the one and the only one” [45, pp. 67-69]. Through an in-depth reflection, students would foster a desirable cognitive change in their mind regarding the topic of love, which could not be learnt from ordinary textbooks or lessons in schools.

Educational Purposes of Literature (Behavioral Influence on Teenagers)

Pulido-Mantas and Ruiz-Seisdedos [47] quoted Soriano’s definition of children’s literature as “a literary and historical communication ... located in time and space between an adult speaker or writer, the sender, and a recipient child, being the receiver, and who by definition, only experiences part of the reality and the linguistic, intellectual, emotional, etc. structures that are characteristic of adulthood” [47, p. 33]. Text is described as a vehicle of communication, which serves as the bridge between readers and authors. Authors not only intend to “communicate a message”, but more importantly to “convey a sweep of experiences as they are lived, in every facet of their vivid, concrete, and unmediated complexity” [44, p. 108]. Literature is the accumulation of past knowledge and experience, enriching and guiding audience towards the correct path. For instance, ‘taming’ is one of the core topics in *The Little Prince*, in which the fox taught the boy ‘taming’ is to be the one and the only one in each other’s world and needing each other [45]. Therefore, one ought to be loyal and attentive to one’s partner, and be willing to spend time in caring and listening to their beloved’s needs. It is a precious lesson for teenagers to be prepared for starting a romantic relationship and learn the way of building harmonious relationships with others. Di Girolamo offers a good conclusion: “The social function of literature becomes fully manifest only where the reader’s literary experience enters into the horizon of expectations of his real life, shapes his understanding of the world, and therefore influences his social behavior” [48, p. 41]. Literature, like other educational activities, possesses the social function to guide youngsters to be a better person. In addition, literature has the power to encourage the audience to continue craving for knowledge, driving them to delve into other relevant literary texts/publications regarding the historical and social context of the fiction, which is in favor of the enrichment of knowledge [36].

Promote an Interactive Relationship between the Author and Readers

Instead of applying a top-down teaching approach, literature cultivates the audience’s response on an issue or hypothesis raised by the author, which fosters contemplation and verification [46]. From intrinsic to extrinsic, readers would relate back to their daily lives or own experience [46]. For example, in *The Little Prince*, the depiction of the breakup of the boy and the rose is not just meant to arouse sympathy, but also urges readers to ponder on the reasons behind which cause the tragedy, granting them the opportunity to contemplate and reflect on their behaviors. Recalling what they have learnt in the previous stations, for instance, the fourteen essential elements for building, maintaining and enhancing relationships would help them gradually apply knowledge into daily lives, such as cultivating

good qualities and dropping bad habits, and thus improve their well-being in order to be prepared for a new relationship.

Mental and Emotional Sensation/Resonance

Moral values and messages are conveyed through fables and stories as “tale is essential for gaining knowledge in a dynamic and playful way” [47, p. 35]. Stories stimulate readers’ imagination, helping readers visualize text into images, which is similar to a “cartoon story” [42]. According to Palmer [42], audience are “encouraged to ‘dwell in the experience’” which “conveys both the involvement and the detachment of our response to imagined situations” [42, p. 203]. With the aid of game-based learning, ‘transportation theory’ is applied where players are mentally transported into the fictional world [49]. This would potentially induce their empathy and engagement with the characters, as students might have been through similar situations [36]. For those who had experienced failure in relationships, they might understand the heartbreaking feeling when the Little Prince broke up with the rose. However, they could also find mental support and concrete suggestions in the game on ways of getting over the pain and moving on. Other than looking for another person to ‘tame’, a new way is to expand the conception of ‘tamelessness’, as the meaning of life is not restricted to romantic relationships. Youngsters are encouraged to pursue dreams or dedicate themselves to other meaningful activities [45].

CONCLUSION

To nurture adolescents on all the core components of building and maintaining PRR, self-understanding and empathetic understanding of others through values clarification and perspective taking are crucial. This game provides an effective means to achieve these through incorporating learning materials taken from Chinese and Western literature, with a higher proportion of the former due to the cultural background of the game designer. However, English translations are provided, which enables players from different cultural backgrounds to access the game. Although the game includes only Chinese and Western literature, it represents a thoughtful effort in promoting PYD among adolescents through integrating Chinese and Western ideas.

In a world of multi-ethnicity and cultural diversity, the game represents a small step in promoting mutual understanding and cross-cultural learning. Literature that reflects traditional Chinese cultural characteristics regarding the core components of peer and intimate relations are chosen. Selected from a vast range of literature in classical Chinese across different historical periods, this game also helps students explore the rich educational heritage and heterogeneous complexity of Chinese literature. English-speaking players may find it interesting to be exposed to many different forms of Chinese literacy and the values in traditional Chinese culture. This game can act both as a simulation of a PYD journey and an introduction to Chinese culture and literature.

The game can be incorporated into the curriculum of language, literature or translation studies for secondary school students from Chinese and Western cultural backgrounds or in a

cross-cultural classroom. By going through the game twice, following Chinese and Western literature respectively, students will be able to 1) understand the meaning of literature, especially the exploration of PRR; 2) be exposed to different literary styles, genres, and techniques of Chinese literature; and 3) learn core components of PRR through values of different cultures from various perspectives.

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Chapter 356

ELECTRONIC CIGARETTES: WHAT’S THE BOTTOM LINE?*

U.S. Department of Health and Human Services

- E-cigarettes have the potential to benefit adult smokers who are not pregnant if used as a complete substitute for regular cigarettes and other smoked tobacco products.
- E-cigarettes are not safe for youth, young adults, pregnant women, or adults who do not currently use tobacco products.
- While e-cigarettes have the potential to benefit some people and harm others, scientists still have a lot to learn about whether e-cigarettes are effective for quitting smoking.
- If you’ve never smoked or used other tobacco products or e-cigarettes, don’t start.

WHAT ARE E-CIGARETTES?

- E-cigarettes are known by many different names. They are sometimes called “e-cigs,” “e-hookahs,” “mods,” “vape pens,” “vapes,” “tank systems,” and “electronic nicotine delivery systems.”
- Some e-cigarettes are made to look like regular cigarettes, cigars, or pipes. Some resemble pens, USB sticks, and other everyday items.
- E-cigarettes produce an aerosol by heating a liquid that usually contains nicotine—the addictive drug in regular cigarettes, cigars, and other tobacco products—flavorings, and other chemicals that help to make the aerosol. Users inhale this aerosol into their lungs. Bystanders can also breathe in this aerosol when the user exhales into the air.
- E-cigarettes can be used to deliver marijuana and other drugs.

* This is an edited, reformatted and augmented version of the U.S. Department of Health and Human Services publication.



WHAT IS IN E-CIGARETTE AEROSOL?

The e-cigarette aerosol that users breathe from the device and exhale can contain harmful and potentially harmful substances:



It is difficult for consumers to know what e-cigarette products contain. For example, some e-cigarettes marketed as containing zero percent nicotine have been found to contain nicotine.

ARE E-CIGARETTES LESS HARMFUL THAN REGULAR CIGARETTES?

E-cigarette aerosol generally contains fewer toxic chemicals than the deadly mix of 7,000 chemicals in smoke from regular cigarettes. However, e-cigarette aerosol is not harmless. It can contain harmful and potentially harmful substances, including nicotine, heavy metals like lead, volatile organic compounds, and cancer-causing agents.



SCIENTISTS ARE STILL LEARNING ABOUT THE LONG-TERM HEALTH EFFECTS OF E-CIGARETTES. HERE IS WHAT WE KNOW NOW

Most e-cigarettes contain nicotine, which has known health effects.

- Nicotine is highly addictive.
- Nicotine is toxic to developing fetuses.
- Nicotine can harm adolescent brain development, which continues into the early to mid-20s.
- Nicotine is a health danger for pregnant women and their developing babies.



Besides nicotine, e-cigarette aerosol can contain substances that harm the body.

- This includes cancer-causing chemicals and tiny particles that reach deep into lungs. However, e-cigarette aerosol generally contains fewer harmful chemicals than smoke from burned tobacco products.



E-cigarettes can cause unintended injuries.

- Defective e-cigarette batteries have caused fires and explosions, some of which have resulted in serious injuries.

- In addition, acute nicotine exposure can be toxic. Children and adults have been poisoned by swallowing, breathing, or absorbing e-cigarette liquid.



CAN E-CIGARETTES HELP ADULTS QUIT SMOKING CIGARETTES?



E-CIGARETTES ARE NOT CURRENTLY APPROVED BY THE FDA AS A QUIT SMOKING AID

The U.S. Preventive Services Task Force, a group of health experts that makes recommendations about preventive health care, concluded that the evidence is insufficient to recommend e-cigarettes for smoking cessation in adults, including pregnant women.



HOWEVER, e-cigarettes may help non-pregnant adult smokers if used as a complete substitute for all cigarettes and other smoked tobacco products.

TO DATE, THE FEW STUDIES ON THE ISSUE ARE MIXED

Evidence from two randomized controlled trials found that e-cigarettes with nicotine can help smokers stop smoking in the long term compared with placebo (non-nicotine) e-cigarettes.

A recent CDC study found that many adults are using e-cigarettes in an attempt to quit smoking. However, most adult e-cigarette users do not stop smoking cigarettes and are instead continuing to use both products (“dual use”). Because smoking even a few cigarettes a day can be dangerous, quitting smoking completely is very important to protect your health.

WHO IS USING E-CIGARETTES?



Chapter 357

E-CIGARETTE USE AMONG YOUTH AND YOUNG ADULTS*

U.S. Department of Health and Human Services

MESSAGE FROM SYLVIA BURWELL

Secretary, U.S. Department of Health and Human Services

The mission of the Department of Health and Human Services is to enhance and protect the health and well-being of all Americans. This report confirms that the use of electronic cigarettes (or e-cigarettes) is growing rapidly among American youth and young adults. While these products are novel, we know they contain harmful ingredients that are dangerous to youth. Important strides have been made over the past several decades in reducing conventional cigarette smoking among youth and young adults. We must make sure this progress is not compromised by the initiation and use of new tobacco products, such as e-cigarettes. That work is already underway.

To protect young people from initiating or continuing the use of e-cigarettes, actions must be taken at the federal, state, and local levels. At the federal level, the U.S. Food and Drug Administration (FDA)—under authority granted to it by Congress under the Family Smoking Prevention and Tobacco Control Act of 2009—took a historic step to protect America’s youth from the harmful effects of using e-cigarettes by extending its regulatory authority over the manufacturing, distribution, and marketing of e-cigarettes. Through such action, FDA now requires minimum age restrictions to prevent sales to minors and prohibits sales through vending machines (in any facility that admits youth), and will require products to carry a nicotine warning.

We have more to do to help protect Americans from the dangers of tobacco and nicotine, especially our youth. As cigarette smoking among those under 18 has fallen, the use of other nicotine products, including e-cigarettes, has taken a drastic leap. All of this is creating a new generation of Americans who are at risk of nicotine addiction.

* This is an edited, reformatted and augmented version of U.S. Department of Health and Human Services, dated 2016.

The findings from this report reinforce the need to support evidence-based programs to prevent youth and young adults from using tobacco in any form, including e-cigarettes. The health and well-being of our nation's young people depend on it.

FOREWORD

Tobacco use among youth and young adults in any form, including e-cigarettes, is not safe. In recent years, e-cigarette use by youth and young adults has increased at an alarming rate. E-cigarettes are now the most commonly used tobacco product among youth in the United States. This timely report highlights the rapidly changing patterns of e-cigarette use among youth and young adults, assesses what we know about the health effects of using these products, and describes strategies that tobacco companies use to recruit our nation's youth and young adults to try and continue using e-cigarettes. The report also outlines interventions that can be adopted to minimize the harm these products cause to our nation's youth.

E-cigarettes are tobacco products that deliver nicotine. Nicotine is a highly addictive substance, and many of today's youth who are using e-cigarettes could become tomorrow's cigarette smokers. Nicotine exposure can also harm brain development in ways that may affect the health and mental health of our kids.

E-cigarette use among youth and young adults is associated with the use of other tobacco products, including conventional cigarettes. Because most tobacco use is established during adolescence, actions to prevent our nation's young people from the potential of a lifetime of nicotine addiction are critical.

E-cigarette companies appear to be using many of the advertising tactics the tobacco industry used to persuade a new generation of young people to use their products. Companies are promoting their products through television and radio advertisements that use celebrities, sexual content, and claims of independence to glamorize these addictive products and make them appealing to young people.

Comprehensive tobacco control and prevention strategies for youth and young adults should address all tobacco products, including e-cigarettes. Further reductions in tobacco use and initiation among youth and young adults are achievable by regulating the manufacturing, distribution, marketing, and sales of all tobacco products—including e-cigarettes, and particularly to children—and combining those approaches with other proven strategies. These strategies include funding tobacco control programs at levels recommended by the Centers for Disease Control and Prevention (CDC); increasing prices of tobacco products; implementing and enforcing comprehensive smokefree laws; and sustaining hard-hitting media campaigns, such as CDC's *Tips from Former Smokers* that encourages smokers to quit for good, and FDA's *Real Cost* that is aimed at preventing youth from trying tobacco and reducing the number of youth who move from experimenting to regular use. We can implement these cost-effective, evidence-based, life-saving strategies now. Together with additional effort and support, we can protect the health of our nation's young people.

Thomas R. Frieden, M.D., M.P.H.

Director

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PREFACE

From the Surgeon General

E-cigarette use among U.S. youth and young adults is now a major public health concern. E-cigarette use has increased considerably in recent years, growing an astounding 900% among high school students from 2011 to 2015. These products are now the most commonly used form of tobacco among youth in the United States, surpassing conventional tobacco products, including cigarettes, cigars, chewing tobacco, and hookahs. Most e-cigarettes contain nicotine, which can cause addiction and can harm the developing adolescent brain.

Compared with older adults, the brain of youth and young adults is more vulnerable to the negative consequences of nicotine exposure. The effects include addiction, priming for use of other addictive substances, reduced impulse control, deficits in attention and cognition, and mood disorders. Furthermore, fetal exposure to nicotine during pregnancy can result in multiple adverse consequences, including sudden infant death syndrome, altered corpus callosum, auditory processing deficits, effects on behaviors and obesity, and deficits in attention and cognition. Ingestion of e-cigarette liquids containing nicotine can also cause acute toxicity and possibly death if the contents of refill cartridges or bottles containing nicotine are consumed.

This report highlights what we know and do not know about e-cigarettes. Gaps in scientific evidence do exist, and this report is being issued while these products and their patterns of use continue to change quickly. For example, the health effects and potentially harmful doses of heated and aerosolized constituents of e-cigarette liquids—including solvents, flavorants, and toxicants—are not completely understood. However, although e-cigarettes generally emit fewer toxicants than combustible tobacco products, we know that aerosol from e-cigarettes is not harmless.

Although we continue to learn more about e-cigarettes with each passing day, we currently know enough to take action to protect our nation's young people from being harmed by these products. Previous reports of the Surgeon General have established that nearly all habitual tobacco use begins during youth and young adulthood. To prevent and reduce the use of e-cigarettes by youth and young adults, we must work together as a society. We must implement proven prevention and education strategies. Health care providers, parents, teachers, and other caregivers should advise youth about the dangers of nicotine and discourage tobacco use in any form, including e-cigarettes. They can set a positive example by being tobacco-free and encouraging those who already use these products to quit. Free help is available at 1-800-QUIT-NOW or <http://www.smokefree.gov>. Preventing tobacco use in any form among youth and young adults is critical to ending the tobacco epidemic in the United States.

Vivek H. Murthy, M.D., M.B.A.
U.S. Surgeon General

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SECTION 1. INTRODUCTION, CONCLUSIONS, AND HISTORICAL BACKGROUND RELATIVE TO E-CIGARETTES

Introduction

Although conventional cigarette smoking has declined markedly over the past several decades among youth and young adults in the United States (U.S. Department of Health and Human Services [USDHHS] 2012), there have been substantial increases in the use of emerging tobacco products among these populations in recent years (Centers for Disease Control and Prevention [CDC] 2015c). Among these increases has been a dramatic rise in electronic cigarette (e-cigarette) use among youth and young adults. It is crucial that the progress made in reducing cigarette smoking among youth and young adults not be compromised by the initiation and use of e-cigarettes. This Surgeon General's report focuses on the history, epidemiology, and health effects of e-cigarette use among youth and young adults; the companies involved with marketing and promoting these products; and existing and proposed public health policies regarding the use of these products by youth and young adults.



Source: Photo by Mandie Mills, CDC.

Figure 1.1. Diversity of e-cigarette products.

E-cigarettes include a diverse group of devices that allow users to inhale an aerosol, which typically contains nicotine, flavorings, and other additives. E-cigarettes vary widely in design and appearance, but generally operate in a similar manner and are composed of similar components (Figure 1.1). A key challenge for surveillance of the products and understanding their patterns of use is the diverse and nonstandard nomenclature for the devices (Alexander et al. 2016). These devices are referred to, by the companies themselves, and by consumers, as “e-cigarettes,” “e-cigs,” “cigalikes,” “e-hookahs,” “mods,” “vape pens,” “vapes,” and “tank systems.” In this report, the term “e-cigarette” is used to represent all of the various products in this rapidly diversifying product category. The terms may differ by geographic region or simply by the prevailing preferences among young users. For example, some refer to all cigarette-shaped products as “e-cigarettes” or as “cigalikes,” and some may refer to the pen-style e-cigarettes as “hookah pens” or “vape pens” (Richtel 2014; Lempert et al. 2016).

This report focuses on research conducted among youth and young adults because of the implications of e-cigarette use in this population, particularly the potential for future public health problems. Understanding e-cigarette use among young persons is critical because previous research suggests that about 9 in 10 adult smokers first try conventional cigarettes during adolescence (USDHHS 2012). Similarly, youth e-cigarette experimentation and use could also extend into adulthood; however, e-cigarette use in this population has not been examined in previous reports of the Surgeon General. The first Surgeon General’s report on the health consequences of smoking was published in 1964; of the subsequent reports, those published in 1994 and 2012 focused solely on youth and young adults (USDHHS 1994, 2012). More recently, the 2012 report documented the evidence regarding tobacco use among youth and young adults, concluding that declines in cigarette smoking had slowed and that decreases in the use of smokeless tobacco had stalled. That report also found that the tobacco

industry's advertising and promotional activities are causal to the onset of smoking in youth and young adults and the continuation of such use as adults (USDHHS 2012). However, the 2012 report was prepared before e-cigarettes were as widely promoted and used in the United States as they are now. Therefore, this 2016 report documents the scientific literature on these new products and their marketing, within the context of youth and young adults. This report also looks to the future by examining the potential impact of e-cigarette use among youth and young adults, while also summarizing the research on current use, health consequences, and marketing as it applies to youth and young adults.

Evidence for this report was gathered from studies that included one or more of three age groups. We defined these age groups to be young adolescents (11–13 years of age), adolescents (14–17 years of age), and young adults (18–24 years of age). Some studies refer to the younger groups more generally as *youth*. Despite important issues related to e-cigarette use in adult populations, clinical and otherwise (e.g., their potential for use in conventional smoking cessation), that literature will generally not be included in this report unless it also discusses youth and young adults (Farsalinos and Polosa 2014; Franck et al. 2014; Grana et al. 2014).

Given the recency of the research that pertains to e-cigarettes, compared with the decades of research on cigarette smoking, the “precautionary principle” is used to guide actions to address e-cigarette use among youth and young adults. This principle supports intervention to avoid possible health risks when the potential risks remain uncertain and have been as yet partially undefined (Bialous and Sarma 2014; Saitta et al. 2014; Hagopian et al. 2015). Still, the report underscores and draws its conclusions from the known health risks of e-cigarette use in this age group.

Organization of the Report

This chapter presents a brief introduction to this report and includes its major conclusions followed by the conclusions of the chapters, the historical background of e-cigarettes, descriptions of the products, a review of the marketing and promotional activities of e-cigarette companies, and the current status of regulations from the U.S. Food and Drug Administration (FDA). Chapter 2 (“Patterns of E-Cigarette Use Among U.S. Youth and Young Adults”) describes the epidemiology of e-cigarette use, including current use (i.e., past 30 day); ever use; co-occurrence of using e-cigarettes with other tobacco products, like cigarettes; and psychosocial factors associated with using e-cigarettes, relying on data from the most recent nationally representative studies available at the time this report was prepared. Chapter 3 (“Health Effects of E-Cigarette Use Among U.S. Youth and Young Adults”) documents the evidence related to the health effects of e-cigarette use, including those that are associated with direct aerosol inhalation by users, the indirect health effects of e-cigarette use, other non-aerosol health effects of e-cigarette use, and secondhand exposure to constituents of the aerosol. Chapter 4 (“Activities of the E-Cigarette Companies”) describes e-cigarette companies’ influences on e-cigarette use and considers manufacturing and price; the impact of price on sales and use; the rapid changes in the industry, particularly the e-cigarette companies; and the marketing and promotion of e-cigarettes. Chapter 5 (“E-Cigarette Policy and Practice Implications”) discusses the implications for policy and practice at the national, state, and local levels. The report ends with a Call to Action to stakeholders—including policymakers, public health practitioners and clinicians, researchers, and the public—to work

to prevent harms from e-cigarette use and secondhand aerosol exposure among youth and young adults.

Preparation of This Report

This Surgeon General's report was prepared by the Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, CDC, which is part of USDHHS. The initial drafts of the chapters were written by 27 experts who were selected for their knowledge of the topics addressed. These contributions are summarized in five chapters that were evaluated by approximately 30 peer reviewers. After peer review, the entire manuscript was sent to more than 20 scientists and other experts, who examined it for its scientific integrity. After each review cycle, the drafts were revised by the report's scientific editors on the basis of reviewers' comments. Subsequently, the report was reviewed by various institutes and agencies within USDHHS.

Scientific Basis of the Report

The statements and conclusions throughout this report are documented by the citation of studies published in the scientific literature. Publication lags have prevented an up-to-the-minute inclusion of all recently published articles and data. This overall report primarily cites peer-reviewed journal articles, including reviews that integrate findings from numerous studies and books that were published through December 2015. However, selected studies from 2016 have been added during the review process that provide further support for the conclusions in this report. When a cited study has been accepted for publication, but the publication has not yet occurred because of the delay between acceptance and final publication, the study is referred to as "in press." This report also refers, on occasion, to unpublished research, such as presentations at a professional meeting, personal communications from a researcher, or information available in various media. These references are employed when acknowledged by the editors and reviewers as being from reliable sources, which add to the emerging literature on a topic.

Major Conclusions

- 1) E-cigarettes are a rapidly emerging and diversified product class. These devices typically deliver nicotine, flavorings, and other additives to users via an inhaled aerosol. These devices are referred to by a variety of names, including "e-cigs," "e-hookahs," "mods," "vape pens," "vapes," and "tank systems."
- 2) E-cigarette use among youth and young adults has become a public health concern. In 2014, current use of e-cigarettes by young adults 18–24 years of age surpassed that of adults 25 years of age and older.
- 3) E-cigarettes are now the most commonly used tobacco product among youth, surpassing conventional cigarettes in 2014. E-cigarette use is strongly associated with the use of other tobacco products among youth and young adults, including combustible tobacco products.

- 4) The use of products containing nicotine poses dangers to youth, pregnant women, and fetuses. The use of products containing nicotine in any form among youth, including in e-cigarettes, is unsafe.
- 5) E-cigarette aerosol is not harmless. It can contain harmful and potentially harmful constituents, including nicotine. Nicotine exposure during adolescence can cause addiction and can harm the developing adolescent brain.
- 6) E-cigarettes are marketed by promoting flavors and using a wide variety of media channels and approaches that have been used in the past for marketing conventional tobacco products to youth and young adults.
- 7) Action can be taken at the national, state, local, tribal, and territorial levels to address e-cigarette use among youth and young adults. Actions could include incorporating e-cigarettes into smokefree policies, preventing access to e-cigarettes by youth, price and tax policies, retail licensure, regulation of e-cigarette marketing likely to attract youth, and educational initiatives targeting youth and young adults.

Chapter Conclusions

Chapter 1. Introduction, Conclusions, and Historical Background Relative to E-Cigarettes

- 1) E-cigarettes are devices that typically deliver nicotine, flavorings, and other additives to users via an inhaled aerosol. These devices are referred to by a variety of names, including “e-cigs,” “e-hookahs,” “mods,” “vape pens,” “vapes,” and “tank systems.”
- 2) E-cigarettes represent an evolution in a long history of tobacco products in the United States, including conventional cigarettes.
- 3) In May 2016, the Food and Drug Administration issued the deeming rule, exercising its regulatory authority over e-cigarettes as a tobacco product.

Chapter 2. Patterns of E-Cigarette Use among U.S. Youth and Young Adults

- 1) Among middle and high school students, both ever and past-30-day e-cigarette use have more than tripled since 2011. Among young adults 18–24 years of age, ever e-cigarette use more than doubled from 2013 to 2014 following a period of relative stability from 2011 to 2013.
- 2) The most recent data available show that the prevalence of past-30-day use of e-cigarettes is similar among high school students (16% in 2015, 13.4% in 2014) and young adults 18–24 years of age (13.6% in 2013–2014) compared to middle school students (5.3% in 2015, 3.9% in 2014) and adults 25 years of age and older (5.7% in 2013–2014).
- 3) Exclusive, past-30-day use of e-cigarettes among 8th-, 10th-, and 12th-grade students (6.8%, 10.4%, and 10.4%, respectively) exceeded exclusive, past-30-day use of conventional cigarettes in 2015 (1.4%, 2.2%, and 5.3%, respectively). In contrast—in 2013–2014 among young adults 18–24 years of age—exclusive, past-30-day use of conventional cigarettes (9.6%) exceeded exclusive, past-30-day use of e-cigarettes (6.1%). For both age groups, dual use of these products is common.

- 4) E-cigarette use is strongly associated with the use of other tobacco products among youth and young adults, particularly the use of combustible tobacco products. For example, in 2015, 58.8% of high school students who were current users of combustible tobacco products were also current users of e-cigarettes.
- 5) Among youth—older students, Hispanics, and Whites are more likely to use e-cigarettes than younger students and Blacks. Among young adults—males, Hispanics, Whites, and those with lower levels of education are more likely to use e-cigarettes than females, Blacks, and those with higher levels of education.
- 6) The most commonly cited reasons for using e-cigarettes among both youth and young adults are curiosity, flavoring/taste, and low perceived harm compared to other tobacco products. The use of e-cigarettes as an aid to quit conventional cigarettes is not reported as a primary reason for use among youth and young adults.
- 7) Flavored e-cigarette use among young adult current users (18–24 years of age) exceeds that of older adult current users (25 years of age and older). Moreover, among youth who have ever tried an e-cigarette, a majority used a flavored product the first time they tried an e-cigarette.
- 8) E-cigarette products can be used as a delivery system for cannabinoids and potentially for other illicit drugs. More specific surveillance measures are needed to assess the use of drugs other than nicotine in e-cigarettes.

Chapter 3. Health Effects of E-Cigarette Use among U.S. Youth and Young Adults

- 1) Nicotine exposure during adolescence can cause addiction and can harm the developing adolescent brain.
- 2) Nicotine can cross the placenta and has known effects on fetal and postnatal development. Therefore, nicotine delivered by e-cigarettes during pregnancy can result in multiple adverse consequences, including sudden infant death syndrome, and could result in altered corpus callosum, deficits in auditory processing, and obesity.
- 3) E-cigarettes can expose users to several chemicals, including nicotine, carbonyl compounds, and volatile organic compounds, known to have adverse health effects. The health effects and potentially harmful doses of heated and aerosolized constituents of e-cigarette liquids, including solvents, flavorants, and toxicants, are not completely understood.
- 4) E-cigarette aerosol is not harmless “water vapor,” although it generally contains fewer toxicants than combustible tobacco products.
- 5) Ingestion of e-cigarette liquids containing nicotine can cause acute toxicity and possibly death if the contents of refill cartridges or bottles containing nicotine are consumed.

Chapter 4. Activities of the E-Cigarette Companies

- 1) The e-cigarette market has grown and changed rapidly, with notable increases in total sales of e-cigarette products, types of products, consolidation of companies, marketing expenses, and sales channels.
- 2) Prices of e-cigarette products are inversely related to sales volume: as prices have declined, sales have sharply increased.

- 3) E-cigarette products are marketed in a wide variety of channels that have broad reach among youth and young adults, including television, point-of-sale, magazines, promotional activities, radio, and the Internet.
- 4) Themes in e-cigarette marketing, including sexual content and customer satisfaction, are parallel to themes and techniques that have been found to be appealing to youth and young adults in conventional cigarette advertising and promotion.

Chapter 5. E-Cigarette Policy and Practice Implications

- 1) The dynamic nature of the e-cigarette landscape calls for expansion and enhancement of tobacco-related surveillance to include (a) tracking patterns of use in priority populations; (b) monitoring the characteristics of the retail market; (c) examining policies at the national, state, local, tribal, and territorial levels; (d) examining the channels and messaging for marketing e-cigarettes in order to more fully understand the impact future regulations could have; and (e) searching for sentinel health events in youth and young adult e-cigarette users, while longer-term health consequences are tracked.
- 2) Strategic, comprehensive research is critical to identify and characterize the potential health risks from e-cigarette use, particularly among youth and young adults.
- 3) The adoption of public health strategies that are pre-cautionary to protect youth and young adults from adverse effects related to e-cigarettes is justified.
- 4) A broad program of behavioral, communications, and educational research is crucial to assess how youth perceive e-cigarettes and associated marketing messages, and to determine what kinds of tobacco control communication strategies and channels are most effective.
- 5) Health professionals represent an important channel for education about e-cigarettes, particularly for youth and young adults.
- 6) Diverse actions, modeled after evidence-based tobacco control strategies, can be taken at the state, local, tribal, and territorial levels to address e-cigarette use among youth and young adults, including incorporating e-cigarettes into smoke-free policies; preventing the access of youth to e-cigarettes; price and tax policies; retail licensure; regulation of e-cigarette marketing that is likely to attract youth and young adults, to the extent feasible under the law; and educational initiatives targeting youth and young adults. Among others, research focused on policy, economics, and the e-cigarette industry will aid in the development and implementation of evidence-based strategies and best practices.

Historical Background

Understanding the role of e-cigarettes requires understanding the long history of tobacco use in the United States, including the role of nicotine delivery, the multiple examples of “reduced-harm” products and associated health claims, and the impact of using tobacco products on the public’s health. Since the late nineteenth century, when the “modern” cigarette came into use, scientists and public health officials have linked cigarette smoking to a remarkable number of adverse effects, and it is now recognized as the primary cause of

premature death in the United States (USDHHS 2014). Correspondingly, for a century, manufacturers, scientists, entrepreneurs, and public health leaders have promoted or recommended product changes that might remove some of the harmful elements in cigarette smoke. E-cigarettes are among the latest products.

E-cigarettes are designed for users to inhale nicotine, flavorings, and other additives through an aerosol. The claims and marketing strategies employed by the e-cigarette companies, and the efforts made by others to develop scientific and regulatory tools to deal with these new products, both contribute to the current discourse on e-cigarettes. Many lessons for assessing the potential (and future) consequences of these products can be learned from examining the relevant experiences of the past century, especially the introduction of novel products (including e-cigarettes as well as other tobacco and nicotine products) and the claims of reduced exposure to toxins made by the industry and elsewhere.

Early Efforts to Modify Cigarettes

In the 1880s and 1890s, entrepreneurs promoted novel products that allegedly blocked nicotine and other constituents of conventional cigarettes believed to be poisonous. Dr. Scott's Electric Cigarettes, advertised in *Harper's Weekly*, claimed not only to light without matches but also to contain a cotton filter that "strains and eliminates the injurious qualities from the smoke," including nicotine (*Harper's Weekly* 1887). Nicotine delivery was essential to the development of the modern cigarette in the twentieth century; early on, this substance was thought to be addicting and thus vital to retaining customers. In 1913, the Camel brand was a new kind of cigarette that introduced high-nicotine content by using burley tobacco, which was generally too harsh to inhale into the lungs, but was made more inhalable through the addition of casings (e.g., sugars, licorice) (Tindall 1992; Proctor 2011). In 1916, American Tobacco introduced its Lucky Strike blended cigarette, and in 1918 Liggett & Myers (L&M) reformulated its Chesterfield brand to make it more palatable to users. As the market grew, advertisements for major brands routinely included health-related statements and testimonials from physicians. During the 1930s and 1940s, prominent advertising campaigns included claims like "Not a cough in a carload" (Old Gold) (Federal Trade Commission [FTC] 1964, p. LBA-5); "We removed from the tobacco harmful corrosive ACRIDS (pungent irritants) present in cigarettes manufactured in the old-fashioned way" (Lucky Strike) (FTC 1964, p. LBA-2); and "Smoking Camels stimulates the natural flow of digestive fluids ... increases alkalinity" (Camel) (FTC 1964, p. LBA-1a). Thus, early modifications to the cigarette were made so that it was more palatable, had a higher nicotine delivery and uptake, and could be marketed as "safe" (FTC 1964; Calfee 1985).

Filters, Tar Reduction, and Light and Low-Tar Cigarettes

The landmark 1964 Surgeon General's report on smoking and health concluded that cigarette smoking contributed substantially to mortality from certain specific diseases, including lung cancer (U.S. Department of Health, Education, and Welfare 1964). Although the 1964 report considered the topic, it found the evidence insufficient to assess the potential health benefits of cigarette filters. Cigarettes with filters became the norm by the 1960s, and marketing them with an overt message about harm reduction became the standard (National Cancer Institute [NCI] 1996). However, the Surgeon General convened another group of experts on June 1, 1966, to review the evidence on the role played by the tar and nicotine content in health. The group concluded that "[t]he preponderance of scientific evidence

strongly suggests that the lower the ‘tar’ and nicotine content of cigarette smoke, the less harmful are the effects” (Horn 1966, p. 16,168). Subsequent studies have repeatedly failed to demonstrate health benefits of smoking light and low-tar cigarettes versus full-flavor cigarettes (Herning et al. 1981; Russell et al. 1982; Benowitz et al. 1983, NCI 2001).

Over the years, the tobacco industry used multiple methods to reduce the machine-tested yields of tar and nicotine in cigarettes as a way to claim “healthier” cigarettes. Beginning in the 1970s, tobacco companies advertised the tar and nicotine levels for their cigarettes, which encouraged smokers to believe, without substantiation, they could reduce their risk of exposure to these constituents (Cummings et al. 2002; Pollay and Dewhirst 2002). In 1996, the FTC issued a statement that it would allow cigarette companies to include statements about tar and nicotine content in their advertising as long as they used a standardized machine-testing method (Peeler 1996).

The Role of Nicotine and Nicotine Delivery

Although the public health community understood early on that nicotine was the primary psychoactive ingredient in cigarette smoke, before the 1980s, little was known about the importance of nicotine in the addiction process beyond what the cigarette manufacturers had learned from their own research. Some scientists warned that due to nicotine addiction, a reduction in nicotine yields, along with decreases in tar, could lead smokers to change their smoking behavior, such as by smoking a greater number of cigarettes to maintain their nicotine intake or changing their behavior in more subtle ways, such as varying the depth of inhalation or smoking more of the cigarette (Jarvis et al. 2001; National Cancer Institute 2001; Thun and Burns 2001). Not until the 1970s and 1980s, as researchers studying other forms of drug abuse began to apply their research methods to cigarette smoking, did it become apparent that nicotine was similar in its addictive capability to other drugs of abuse, such as heroin and cocaine (USDHHS 1981, 1988). As described in the 1988 Surgeon General’s report and in subsequent research, symptoms associated with nicotine addiction include craving, withdrawal, and unconscious behaviors to ensure consistent intake of nicotine (USDHHS 1988; al’Absi et al. 2002; Hughes 2007).

Although the tobacco industry has long understood the importance of nicotine to maintain long-term cigarette smokers through addiction, public health officials did not fully appreciate this in a broad sense until the 1988 Surgeon General’s report, *The Health Consequences of Smoking: Nicotine Addiction* (USDHHS 1988).

FDA and Nicotine Regulation

In 1988 (and again in 1994), the Coalition on Smoking OR Health and other public-interest organizations petitioned FDA to classify low-tar and nicotine products as drugs and to classify Premier, the short-lived “smokeless cigarette product” from R.J. Reynolds, as an alternative nicotine-delivery system (Stratton et al. 2001). The Coalition on Smoking OR Health cited indirect claims made through advertising and marketing as evidence of R. J. Reynolds’s intent to have the product used for the mitigation or prevention of disease (Slade and Ballin 1993). Meanwhile, FDA launched an investigation into the practices of the tobacco industry, including the manipulation of nicotine delivery. FDA asserted its jurisdiction over cigarettes and smokeless tobacco and issued certain rules governing access to and promotion of these products (*Federal Register* 1996). On March 21, 2000, the U.S. Supreme Court ruled 5-4 that Congress had not yet given FDA the necessary statutory authority to issue any rules

pertaining to tobacco products (Gottlieb 2000; *FDA v. Brown & Williamson Tobacco Corp.* 2000). The subsequent debate over control of nicotine products, including their potential impact on youth, ultimately led to the passage of the 2009 *Family Smoking Prevention and Tobacco Control Act*, which gave FDA authority to regulate tobacco products. Thus, discussions about the introduction of novel nicotine-containing tobacco products in the market during the 1980s and 1990s helped shape the current regulation of tobacco and nicotine products.

New products introduced in the 1990s or later included modified tobacco cigarettes (e.g., Advance, Omni); cigarette-like products, also called cigalikes (e.g., Eclipse, Accord); and smokeless tobacco products (e.g., Ariva, Exalt, Revel, snus). Advance, made by Brown and Williamson, was test-marketed with the slogan “All of the taste ... Less of the toxins.” Vector launched a national advertising campaign for its Omni cigarette with the slogan “Reduced carcinogens. Premium taste.” In addition to the question of whether the claims were supported by sufficient evidence, scientists and tobacco control leaders raised concerns about the potential for adverse consequences associated with novel nicotine and tobacco products marketed for harm reduction, such as a reduction in cessation rates or increased experimentation by children (Warner and Martin 2003; Joseph et al. 2004; Caraballo et al. 2006). Studies have shown that smokers are interested in trying novel “reduced-exposure” products and perceive them to have lower health risks, even when advertising messages do not make explicit health claims (Hamilton et al. 2004; O’Connor et al. 2005; Caraballo et al. 2006; Choi et al. 2012; Pearson et al. 2012).

At FDA’s request, the Institute of Medicine (IOM [now the National Academy of Medicine]) convened a committee of experts to formulate scientific methods and standards by which potentially reduced-exposure products (PREPs), whether the purported reduction was pharmaceutical or tobacco related, could be assessed. The committee concluded that “[f]or many diseases attributable to tobacco use, reducing risk of disease by reducing exposure to tobacco toxicants is feasible” (Stratton et al. 2001, p. 232). However, it also cautioned that “PREPs have not yet been evaluated comprehensively enough (including for a sufficient time) to provide a scientific basis for concluding that they are associated with a reduced risk of disease compared to conventional tobacco use” (Stratton et al. 2001, p. 232). The committee added that “the major concern for public health is that tobacco users who might otherwise quit will use PREPs instead, or others may initiate smoking, feeling that PREPs are safe. That will lead to less harm reduction for a population (as well as less risk reduction for that individual) than would occur without the PREP, and possibly to an adverse effect on the population” (Stratton et al. 2001, p. 235). Subsequently, in 2006, Judge Kessler cited these findings in her decision which demanded the removal of light and low-tar labeling due to the misleading nature of these claims (*United States v. Philip Morris* 2006).

The E-Cigarette

Invention of the E-Cigarette

An early approximation of the current e-cigarette appeared in a U.S. patent application submitted in 1963 by Herbert A. Gilbert and was patented in August 1965 (U.S. Patent No. 3,200,819) (Gilbert 1965). The application was for a “smokeless nontobacco cigarette,” with the aim of providing “a safe and harmless means for and method of smoking” by replacing

burning tobacco and paper with heated, moist, flavored air. A battery-powered heating element would heat the flavor elements without combustion (Gilbert 1965). The Favor cigarette, introduced in 1986, was another early noncombustible product promoted as an alternative nicotine-containing tobacco product (United Press International 1986; Ling and Glantz 2005).

The first device in the recent innovation in e-cigarettes was developed in 2003 by the Chinese pharmacist Hon Lik, a former deputy director of the Institute of Chinese Medicine in Liaoning Province. Lik's patent application described a kind of electronic atomizing cigarette (Hon 2013). With support from Chinese investors, in 2004 the product was introduced on the Chinese market under the company name Ruyan (Sanford and Goebel 2014). The product gained some attention among Chinese smokers early on as a potential cessation device or an alternative cigarette product.

The e-cigarette was part of the U.S. market by the mid-2000s, and by 2010 additional brands started to appear in the nation's marketplace, including Ruyan and Janty (Regan et al. 2013). Ruyan gained a U.S. patent for its product with the application stating that the product is "an electronic atomization cigarette that functions as substitutes (sic) for quitting smoking and cigarette substitutes." (U.S. Patent No. 8,490,628 B2, 2013). In August 2013, Imperial Tobacco Group purchased the intellectual property behind the Ruyan e-cigarette for \$75 million. As of 2014 an estimated 90% of the world's production of e-cigarette technology and products came from mainland China, mainly Guangdong Province and Zhejiang Province (Barboza 2014).

Sales of e-cigarettes in the United States have risen rapidly since 2007. Widespread advertising via television commercials and through print advertisements for popular brands, often featuring celebrities, has contributed to a large increase in e-cigarette use by both adults and youth since 2010 (Felberbaum 2013; King et al. 2013; Regan et al. 2013). Additionally, marketing through social media, as well as other forms of Internet marketing, has been employed to market these devices (Huang et al. 2014; Kim et al. 2014).

In 2013, an estimated 13.1 million middle school and high school students were aware of e-cigarettes (Wang et al. 2014). According to data from the National Youth Tobacco Survey, in 2011 the prevalence of current e-cigarette use (defined as use during at least 1 day in the past 30 days) among high school students was 1.5%; prevalence increased dramatically, however, to 16% by 2015, surpassing the rate of conventional-cigarette use among high school students (CDC 2016b; see Chapter 2). This equates to 2.4 million high school students and 620,000 middle school students having used an e-cigarette at least one time in the past 30 days in 2015 (CDC 2016b).

These trends have led to substantial concern and discussion within public health communities, including state and national public health agencies, professional organizations, and school administrators and teachers. A primary concern is the potential for nicotine addiction among nonsmokers, especially youth and young adults, and that this exposure to nicotine among youth and young adults is harmful. The diversity and novelty of e-cigarette products on the market and ongoing product innovations make assessments of the biological effects of current e-cigarettes under actual conditions of use—such as their long-term harmfulness—difficult to measure. Unanswered questions remain about the risk profile of these devices, their potential use by young people as a first step to other nicotine products, and their total impact on public health. There are diverging opinions about the potential public health impact of these new products. Some public health scientists have highlighted the

potential for alternative nicotine products to serve as a substitute for conventional cigarettes and thus a harm reduction tool (Henningfield et al. 2003; Abrams 2014). Others have cautioned that the use of alternative nicotine products might become a bridge that may lead to greater tobacco product use—including dual or multiple-product use—or initiate nicotine addiction among nonsmokers, especially youth (Cobb et al. 2010; Wagener et al. 2012; Benowitz and Goniewicz 2013; Britton 2013; Chapman 2013; Etter 2013; USDHHS 2014). Current evidence is insufficient to reject either of these hypotheses.

E-Cigarette Products

Components and Devices

E-cigarette devices are composed of a battery, a reservoir for holding a solution that typically contains nicotine, a heating element or an atomizer, and a mouthpiece through which the user puffs (Figure 1.2). The device heats a liquid solution (often called e-liquid or e-juice) into an aerosol that is inhaled by the user. E-liquid typically uses propylene glycol and/or glycerin as a solvent for the nicotine and flavoring chemicals.

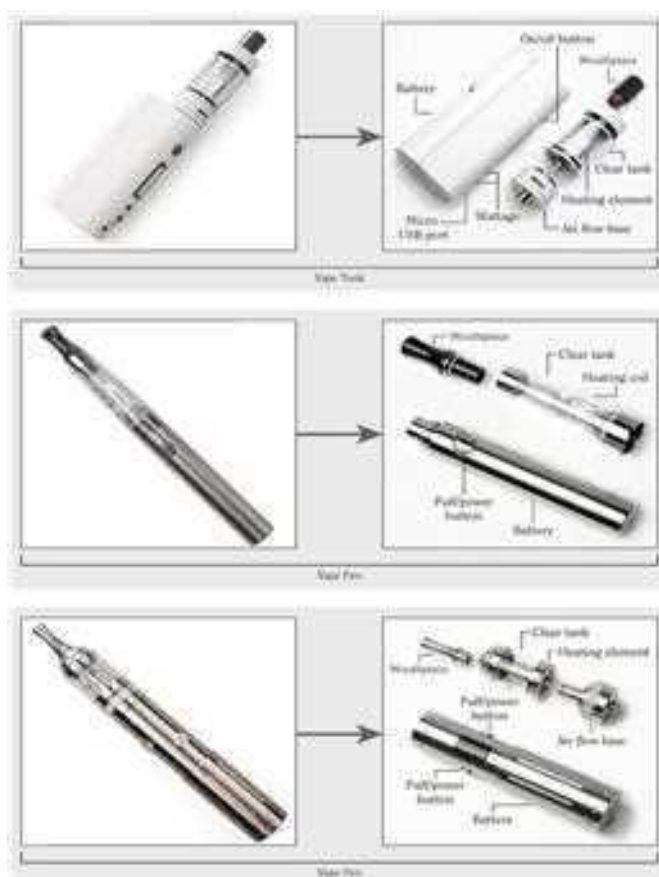
Flavors and E-Cigarettes

The e-liquids in e-cigarettes are most often flavored; a study estimated that 7,700 unique flavors exist (Zhu et al. 2014) and that most of them are fruit or candy flavors (Figure 1.3). A content analysis of the products available via online retail websites documented that tobacco, mint, coffee, and fruit flavors were most common, followed by candy (e.g., bubble gum), unique flavors (e.g., Belgian waffle), and alcoholic drink flavors (e.g., strawberry daiquiri) (Grana and Ling 2014). Some retail stores are also manufacturers that create custom flavors, which increases the variety of flavors available.

The widespread availability and popularity of flavored e-cigarettes is a key concern regarding the potential public health implications of the products. The concern, among youth, is that the availability of e-cigarettes with sweet flavors will facilitate nicotine addiction and simulated smoking behavior—which will lead to the use of conventional tobacco products (Kong et al. 2015; Krishnan-Sarin et al. 2015). Flavors have been used for decades to attract youth to tobacco products and to mask the flavor and harshness of tobacco (USDHHS 2012). Industry documents show that tobacco companies marketed flavored little cigars and cigarillos to youth and to African Americans to facilitate their uptake of cigarettes (Kostygina et al. 2014). Companies also intended flavored smokeless tobacco products to facilitate “graduation” to unflavored products that more easily deliver more nicotine to the user (USDHHS 2012). Various studies have shown that youth are more likely than adults to choose flavored cigarettes and cigars (CDC 2015b). Concern over these findings led Congress to include a ban on characterizing flavors for cigarettes, other than tobacco or menthol, in the Tobacco Control Act. A similar concern exists about e-cigarettes, and this concern is supported by studies indicating that youth and young adults who have ever used e-cigarettes begin their use with sweet flavors rather than tobacco flavors (Kong et al. 2015; Krishnan-Sarin et al. 2015). Notably, 81.5% of current youth e-cigarette users said they used e-cigarettes “because they come in flavors I like” (Ambrose et al. 2015).

E-Cigarette Devices

First-generation e-cigarettes were often similar in size and shape to conventional cigarettes, with a design that also simulated a traditional cigarette in terms of the colors used (e.g., a white body with tan mouthpiece). These devices were often called cigalikes, but there were other products designed to simulate a cigar or pipe. Other cigalikes were slightly longer or narrower than a cigarette; they may combine white with tan or may be black or colored brightly. These newer models use a cartridge design for the part of the device that holds the e-liquid, which is either prefilled with the liquid or empty and ready to be filled. The user then squeezes drops of the e-liquid onto a wick (or bit of cotton or polyfil) connected to the heating element and atomizer (Figure 1.4). As e-cigarettes have become more popular, their designs have become more diverse, as have the types of venues where they are sold (Noel et al. 2011; Zhu et al. 2014).



Source: Photo by Mandie Mills, CDC.

Figure 1.2. Parts of an e-cigarette device.

Second-generation devices include products that are shaped like pens, are comparatively larger and cylindrical, and are often referred to as “tank systems” in a nod to the transparent reservoir that holds larger amounts of e-liquid than previous cartridge-containing models. Third- and fourth-generation devices represent a diverse set of products and, aesthetically, constitute the greatest departure from the traditional cigarette shape, as many are square or

rectangular and feature customizable and rebuildable atomizers and batteries. In addition, since the beginning of the availability of e-cigarettes and their component parts, users have been modifying the devices or building their own devices, which are often referred to as “mods.” The differences in design and engineering of the products are key factors in the size, distribution, and amount of aerosol particles and the variability in levels of chemicals and nicotine present in the e-liquid/aerosol and delivered to the user (Brown and Cheng 2014).



Source: Photo by Mandie Mills, CDC.

Figure 1.3. Examples of e-liquid flavors.



Source: Photo by Mandie Mills, CDC.

Figure 1.4. E-liquids being poured into an e-cigarette device.

E-Cigarette Product Components and Risks

One of the primary features of the more recent generation of devices is that they contain larger batteries and are capable of heating the liquid to a higher temperature, potentially releasing more nicotine, forming additional toxicants, and creating larger clouds of particulate matter (Bhatnagar et al. 2014; Kosmider et al. 2014). For instance, one study demonstrated that, at high temperatures (150°C), exceedingly high levels of formaldehyde—a carcinogen (found to be 10 times higher than at ambient temperatures)—are present that are formed through the heating of the e-liquid solvents (propylene glycol and glycerin), although the level of tolerance of actual users to the taste of the aerosol heated to this temperature is debated (Kosmider et al. 2014; CDC 2015a; Flavor and Extract Manufacturers Association of the United States 2015; Pankow et al. 2015). There is also concern regarding the safety of inhaling e-cigarette flavorings. Although some manufacturers have claimed their flavorants are generally recognized as safe for food additives (i.e., to be used in preparing foods for eating), little is known about the long-term health effects of inhaling these substances into the lungs (CDC 2015a).

Many devices can be readily customized by their users, which is also leading to the concern that these devices are often being used to deliver drugs other than nicotine (Brown and Cheng 2014). Most commonly reported in the news media, on blogs, and by user anecdote is the use of certain types of e-cigarette-related products for delivering different forms of marijuana (Morean et al. 2015; Schauer et al. 2016). The tank systems, for example, have been used with liquid tetrahydrocannabinol (THC) or hash oil. Some personal vaporizer devices can be used with marijuana plant material or a concentrated resin form of marijuana called “wax.” One study describes the use, in Europe, of e-cigarette devices to smoke marijuana (Etter 2015).

The various e-cigarette products, viewed as a group, lack standardization in terms of design, capacity for safely holding e-liquid, packaging of the e-liquid, and features designed to minimize hazards with use (Yang et al. 2014). All of these design features may have implications for the health impact of e-cigarette use. Notably, from 2010 to 2014, calls to poison control centers in the United States about exposures related to e-cigarettes increased dramatically. According to the American Association of Poison Control Centers (2015), 271 cases were reported in 2011, but 3,783 calls were reported in 2014. Among all calls, 51% involved exposure among children younger than 5 years of age (CDC 2014). Most poisonings appear to have been caused by exposure to nicotine-containing liquid (CDC 2014). The lack of a requirement for child-resistant packaging for e-liquid containers may have contributed to these poisonings. Since these data were released, one death in the United States has been confirmed in a child who drank e-liquid containing nicotine (Mohney 2014). Additionally, serious adverse reactions, including at least two deaths, have been reported to FDA in cases that could be attributed to the use of e-cigarettes (FDA 2013). This increase in poisonings prompted the *Child Nicotine Poisoning Prevention Act of 2015* (2016), which was enacted in January 2016. This law requires any container of liquid nicotine that is sold, manufactured, distributed, or imported into the United States to be placed in packaging that is difficult to open by children under 5 years of age.

Secondary risks are also of concern regarding e-cigarettes, including passive exposure to nicotine and other chemicals, and adverse events due to device malfunction. Nicotine is a neuroteratogen, and its use by pregnant women exposes a developing fetus to risks that are well documented in the 50th-anniversary Surgeon General’s report on smoking (USDHHS 2014) and include impaired brain development (England et al. 2015) and other serious consequences. Finally, another consequence of the lack of device regulation is the occurrence of battery failures and subsequent explosions. Explosions have typically occurred during charging, resulting in house and car fires, and sometimes causing injuries to those involved. From 2009 to late 2014, 25 incidents of explosions and fires involving e-cigarettes occurred in the United States (Chen 2013; U.S. Fire Administration 2014; FDA 2013).

E-Cigarette Companies

E-cigarette companies include manufacturers, wholesalers, importers, retailers, distributors, and some other groups that overlap with these entities (Barboza 2014; Whelan 2015). Currently, most of the products are manufactured in Shenzhen, Guangdong Province, China (Cobb et al. 2010; Grana et al. 2014; Zhu et al. 2014). One study placed the number of

brands at 466 in January 2014 and found a net increase of 10.5 brands per month (Zhu et al. 2014). All the major tobacco companies (e.g., Reynolds American, Altria; Table 1.1) and many smaller, independent companies are now in the business. When e-cigarettes first entered the U.S. market, they were sold primarily by independent companies via the Internet and in shopping malls at kiosks where those interested could sample the products. A unique feature of the e-cigarette industry, compared to other tobacco and nicotine products, is the recruitment of visitors to their websites as “affiliates” or distributors to help market the products and, in turn, receive commissions on sales (Grana and Ling 2014; Cobb et al. 2015). For example, some companies offer a way for users to earn a commission by advertising the products (e.g., a banner ad is placed on one’s website, and when someone clicks on the link and subsequently purchases a product, the website owner gets a percentage commission). Some companies also offer rewards programs for recruiting new customers or for brand loyalty, with web-site users earning points for free or reduced-price products (Richardson et al. 2015).

E-cigarettes are now in widespread national distribution through convenience stores, tobacco stores, pharmacies, “big box” retail chains such as Costco, online retailers, and shops devoted to e-cigarette products (often called “vape shops”) (Giovenco et al. 2015; Public Health Law Center 2015). The “vape shops” offer a place to buy customizable devices and e-liquid solutions in many flavors and sometimes include a café or other elements that promote socializing, essentially making such places like a lounge. With the rapid increase in distribution and marketing in the industry, sales have increased rapidly and were projected to reach \$2.5 billion in 2014 and \$3.5 billion in 2015, including projections for retail and online channels, as well as “vape shops” (Wells Fargo Securities 2015).

Table 1.1. Multinational tobacco companies with e-cigarette brands

Company	E-cigarette brand
Altria (NuMark)	MarkTen, Green Smoke
Philip Morris International	Heat-not-burn, IQOS brand (Vape Ranks 2014) E-cigs, Nicolites by Nicocigs (Philip Morris International 2014)
Reynolds (Reynolds Vapor Company)	VUSE
Lorillard (Lorillard Vapor Company)	blu (until 2015)
Imperial Tobacco (Fontem Ventures)	Puritane (formerly Ruyan) blu (acquired in 2015)
British American Tobacco	Vype
Swisher	E-swisher
Japan Tobacco International (JTI)	E-Lites, offered in the United Kingdom by Zandera Ltd., which was acquired by Japan Tobacco Inc. in 2014 (Japan Tobacco Inc. 2014) Ploom (tobacco pods in heat-not-burn) and Ploom PAX (used for vaporizing marijuana) (Japan Tobacco Inc. 2015)

The advertising and marketing of e-cigarette products has engendered skepticism among public health professionals and legislators, who have noted many similarities to the advertising claims and promotional tactics used for decades by the tobacco industry to sell conventional tobacco products (Campaign for Tobacco-Free Kids 2013; CDC 2016a). Indeed, several of the e-cigarette marketing themes have been reprised from the most memorable cigarette advertising, including those focused on freedom, rebellion, and glamor (Grana and Ling 2014). E-cigarette products are marketed with a variety of unsubstantiated health and cessation messages, with some websites featuring videos of endorsements by physicians

(another reprisal of old tobacco industry advertising) (Grana and Ling 2014; Zhu et al. 2014). Unlike conventional cigarettes, for which advertising has been prohibited from radio and television since 1971, e-cigarette products are advertised on both radio and television, with many ads featuring celebrities. E-cigarettes also are promoted through sports and music festival sponsorships, in contrast to conventional cigarettes and smokeless tobacco products, which have been prohibited from such sponsorships since the Master Settlement Agreement in 1998. E-cigarettes also appear as product placements in television shows and movies (Grana et al. 2011; Grana and Ling 2014).

Another key avenue for e-cigarette promotion is social media, such as Twitter, Facebook, YouTube, and Instagram. As is true in the tobacco industry, the e-cigarette industry organizes users through advocacy groups (Noel et al. 2011; Harris et al. 2014; Saitta et al. 2014; Caponnetto et al. 2015). The extensive marketing and advocacy through various channels broadens exposure to e-cigarette marketing messages and products; such activity may encourage nonsmokers, particularly youth and young adults, to perceive e-cigarette use as socially normative. The plethora of unregulated advertising is of particular concern, as exposure to advertising for tobacco products among youth is associated with cigarette smoking in a dose-response fashion (USDHHS 2012).

Federal Regulation of E-Cigarettes

A “Two-Pronged” Approach to Comprehensive Tobacco Control

Since the passage of the Tobacco Control Act in 2009, FDA has had the authority to regulate the manufacturing, distribution, and marketing of tobacco products sold in the United States. FDA had immediate jurisdiction over cigarettes, roll-your-own cigarette tobacco, and smokeless tobacco. In May 2016, FDA asserted jurisdiction over products that meet the statutory definition of a tobacco product, including e-cigarettes, except accessories of these products (*Federal Register* 2016). That regulation is currently under litigation.

The IOM’s 2007 report, *Ending the Tobacco Problem: A Blueprint for the Nation*, established a “two-pronged” strategy for comprehensive tobacco control: (1) full implementation of proven, traditional tobacco control measures such as clean indoor air laws, taxation, and countermarketing campaigns; and (2) “strong federal regulation of tobacco products and their marketing and distribution” (Bonnie et al. 2007, p. 1).

Included in FDA’s broad authority are the restriction of marketing and sales to youth, requiring disclosure of ingredients and harmful and potentially harmful constituents, setting product standards (e.g., requiring the reduction or elimination of ingredients or constituents), requiring premarket approval of new tobacco products and review of modified-risk tobacco products, and requiring health warnings. The standard for FDA to use many of its regulatory authorities is whether such an action is appropriate for the protection of public health (*Federal Food, Drug, and Cosmetic Act*, § 907(a)(3)(A)). The public health standard in the Tobacco Control Act also requires FDA to consider the health impact of certain regulatory actions at both the individual and population levels, including their impact on nonusers, and on initiation and cessation (*Federal Food, Drug, and Cosmetic Act*, § 907(a)(3)(B)).

Importantly, the Tobacco Control Act preserves the authority of state, local, tribal, and territorial governments to enact any policy “in addition to, or more stringent than”

requirements established under the Tobacco Control Act “relating to or prohibiting the sale, distribution, possession, exposure to, access to, advertising and promotion of, or use of tobacco products by individuals of any age” (*Federal Food, Drug, and Cosmetic Act*, § 916(a)(1)). This preservation of state and local authority ensures the continuation of more local-level, comprehensive tobacco control. However, the statute expressly preempts states and localities from establishing or continuing requirements that are different from or in addition to FDA requirements regarding standards for tobacco products, premarket review, adulteration, misbranding, labeling, registration, good manufacturing practices, or modified-risk tobacco products (*Federal Food, Drug, and Cosmetic Act*, § 916(a)(2)(A)). But this express preemption provision does not apply to state and local authority to impose requirements relating to the “sale, distribution, possession, information reporting to the State, exposure to, access to, the advertising and promotion of, or use of, tobacco products by individuals of any age . . .” (*Federal Food, Drug, and Cosmetic Act*, § 916(a)(2)(b)). The interaction of these complex provisions related to federal preemption of state law has been the subject of challenges by the tobacco industry to state and local laws. Thus far, courts have upheld certain local ordinances restricting the sale of flavored tobacco products (*National Association of Tobacco Outlets, Inc. v. City of Providence* 2013; *U.S. Smokeless Tobacco Manufacturing Co. v. City of New York* 2013).

Legal Basis for Regulating E-Cigarettes as Tobacco Products

In the United States, e-cigarettes can be regulated either as products marketed for therapeutic purposes or as tobacco products. Since the advent of e-cigarettes in the United States around 2007, manufacturers have had the option to apply to FDA’s Center for Drug Evaluation and Research (CDER) or Center for Devices and Radiological Health (CDRH) for approval to market e-cigarettes for therapeutic purposes; as of August 2016, no e-cigarette manufacturers have received approval through this avenue.

In 2008 and early 2009, FDA detained multiple shipments of e-cigarettes from overseas manufacturers and denied them entry into the United States on the grounds that e-cigarettes were unapproved drug-device combination products (FDA 2011). Sottera, Inc., which now does business as NJOY, challenged that determination (*Smoking Everywhere, Inc. and Sottera, Inc., d/b/a NJOY v. U.S. Food and Drug Administration, et al.* 2010; Bloomberg Business 2015). Between the filing of the lawsuit and a decision on the motion for preliminary injunction, Congress passed the Tobacco Control Act and the President signed it into law. The Tobacco Control Act defines the term “tobacco product,” in part, as any product, including component parts or accessories, “made or derived from tobacco” that is not a “drug,” “device,” or “combination product” as defined by the *Federal Food, Drug, and Cosmetic Act* (21 U.S.C. 321(rr)) (*Family Smoking Prevention and Tobacco Control Act* 2009, § 101(a)). The District Court subsequently granted a preliminary injunction relying on the Supreme Court’s decision in *Brown and Williamson* (1996) and the recently enacted Tobacco Control Act. FDA appealed the decision and the U.S. Court of Appeals for the D.C. Circuit held that e-cigarettes and, therefore, other products “made or derived from tobacco” are not drug/device combinations unless they are marketed for therapeutic purposes, but can be regulated by FDA as tobacco products under the Tobacco Control Act (*Sottera, Inc. v. Food & Drug Administration* 2010).

On September 25, 2015, FDA proposed regulations to describe the circumstances in which a product made or derived from tobacco that is intended for human consumption will

be subject to regulation as a drug, device, or a combination product. The comment period for this proposed regulation closed on November 24, 2015.

Most e-cigarettes marketed and sold in the United States today contain nicotine made or derived from tobacco. Although some e-cigarettes claim that they contain nicotine not derived from tobacco, or that they contain no nicotine at all (Lempert et al. 2016), there may be reason to doubt some of these claims. Currently, synthetic nicotine and nicotine derived from genetically modified, nontobacco plants are cost-prohibitive for e-cigarette manufacturers, although technological advances could eventually increase the cost-effectiveness of using nicotine that was not derived from tobacco (Lempert et al. 2016). The health effects of passive exposure to e-cigarettes with no nicotine, as well as their actual use and the extent of exposure to these products, have just begun to be studied (Hall et al. 2014; Marini et al. 2014; Schweitzer et al. 2015) and some states and localities are taking steps to regulate e-cigarettes that do not contain nicotine or tobacco (Lempert et al. 2016).

Deeming Rule

The Tobacco Control Act added a new chapter to the *Federal Food, Drug, and Cosmetic Act*, which provides FDA with authority over tobacco products. The new chapter applied immediately to all cigarettes, cigarette tobacco, roll-your-own tobacco, and smokeless tobacco; and the law included “any other tobacco products that the Secretary of Health and Human Services by regulation deems to be subject to this chapter” (*Federal Food, Drug, and Cosmetic Act*, §901 (b)). Therefore, to regulate e-cigarettes as tobacco products, FDA was required to undertake a rulemaking process to extend its regulatory authority to include e-cigarettes.

Consequently, in May 2016, through its Center for Tobacco Products (CTP), FDA issued a rule—often referred to as the “deeming rule”—to extend its authority over all products meeting the definition of a tobacco product, except accessories of the newly deemed products. This rule extended FDA’s tobacco product authorities to include e-cigarettes and their components and parts (e.g., nicotine cartridges), but also to such products as cigars, pipe tobacco, nicotine gels, waterpipe/hookah tobacco, and dissolvables not already regulated as smokeless tobacco products (*Federal Register* 2016). This regulation is currently under litigation. The deeming rule subjects e-cigarettes to Tobacco Control Act provisions, including:

- Prohibitions on adulterated and misbranded products;
- Required disclosure of existing health information, including lists of ingredients and documents on health effects;
- Required registration of manufacturers;
- Required disclosure of a list of all tobacco products, including information related to labeling and advertising;
- Premarket review of new tobacco products (i.e., those not on the market on February 15, 2007);
- Restrictions on products marketed with claims about modified risk.

In addition to the aforementioned Tobacco Control Act provisions applicable to all deemed tobacco products, the Tobacco Control Act grants FDA authority to undertake a

broad range of other actions on specific classes of products. In its deeming rule, FDA included the following additional actions for tobacco products, including e-cigarettes:

- Minimum age restrictions to prevent sales to minors;
- Requirements to include a nicotine warning; and
- Prohibitions on vending machine sales, unless in a facility that never admits youth.

Future Regulatory Options

E-cigarette manufacturers have the option to apply to FDA to authorize the marketing of their products or to be able to manufacture and sell tobacco products marketed with modified-risk claims, in addition to the existing option to apply to FDA's CDER or CDRH for approval to market their products for therapeutic purposes. FDA also has authority to undertake a number of actions if the Secretary of USDHHS finds such actions to be appropriate for the protection of public health, including:

- Product standards, including restrictions on flavors;
- Restrictions on promotion, marketing, and advertising, and prohibitions on brand-name sponsorship of events;
- Minimum package sizes;
- Prohibitions on self-service displays;
- Child-resistant packaging and the inclusion of health warnings; and
- Regulation of nicotine levels in products.

Despite this broad authority, FDA is prohibited from certain regulatory actions, even if those actions may be appropriate for the protection of public health. Specifically, FDA generally cannot restrict tobacco use in public places, levy taxes on tobacco products, prohibit sales by a specific category of retail outlet (e.g., pharmacies), completely eliminate nicotine in tobacco products, require prescriptions for tobacco products unless it is marketed for therapeutic purposes, or establish a federal minimum age of sale for tobacco products above 18 years of age. Thus, even if FDA fully exercises all of its existing authority over e-cigarettes, regulation will still need to be complemented at the state and local levels, including efforts previously shown to be effective for conventional tobacco products, such as comprehensive smokefree laws at the state and local levels, pricing strategies, raising the minimum age of sales to minors to 21, and high-impact countermarketing campaigns. In the current context of rising rates of use by youth, localities and states can also implement policies and programs that minimize the individual- and population-level harms of e-cigarettes (see Chapter 5).

Summary

This chapter presents the major conclusions of this Surgeon General's report and the conclusions of each chapter. E-cigarettes are presented within their historical context, with an overview of the components of these devices and the types of products. In 2016, FDA announced its final rule to regulate e-cigarettes under the *Family Smoking Prevention and*

Tobacco Control Act. The chapter outlines options for the regulation of e-cigarettes, particularly as they relate to youth and young adults, based on successful smoking policies. The need to protect youth and young adults from initiating or continuing the use of nicotine-containing products forms a strong basis for the need to regulate e-cigarettes at the local, state, and national levels in the future.

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SECTION 2. PATTERNS OF E-CIGARETTE USE AMONG U.S. YOUTH AND YOUNG ADULTS

Introduction

This chapter documents patterns and trends in awareness of electronic cigarettes (e-cigarettes), their use, and perceptions about these devices among youth and young adults in the United States. Both the awareness of e-cigarettes and levels of their use have increased rapidly throughout the U.S. population. Understanding young people’s patterns of e-cigarette

use is essential to determining the scope of potential benefits or harms that these products may have from a public health perspective. This chapter summarizes the patterns of use of e-cigarettes, identifies subgroups at higher risk for using them, highlights the ways in which e-cigarettes are used with other tobacco products, and identifies correlates of e-cigarette use, including knowledge, attitudes, beliefs, and sociodemographic characteristics. In most cases, the term “e-cigarette(s)” is used, but when needed to accord with usage in the cited literature, the acronym “ENDS” (electronic nicotine delivery systems) is employed.

Sources of Data

Data summarized in this chapter come from nationally representative datasets that were federally funded and peer-reviewed literature of subnational and international surveillance studies of e-cigarette use that were mostly cross-sectional in design. Appendix 2.1. and Table A2.1-1 in that appendix¹ describe all the years of data available for these data sources, but only selected years are used for this report. For youth, this report relies on data from the National Youth Tobacco Survey (NYTS) and the Monitoring the Future Study (MTF), as measures of e-cigarette use were available for at least two or more time points. For this reason, the report also relies on data from the National Adult Tobacco Survey (NATS) for young adults. More recently, the Youth Risk Behavior Surveillance System and other surveys from the National Center for Health Statistics have added measures of e-cigarette use to their surveys, but only one data point was available at the time this report was prepared. Only five longitudinal studies were available on this topic at the time this report was prepared (Leventhal et al. 2015; Primack et al. 2015; Barrington-Trimis et al. 2016; Unger et al. 2016; Wills et al. 2016). Because e-cigarettes only became prevalent in the tobacco product marketplace in recent years, minimal data are available on their use before 2011. Given the paucity of surveillance information on e-cigarettes and the low prevalence of their use in the early years of their availability in the United States, peer-reviewed studies with smaller subnational samples are used in this chapter to complement national surveillance data. Surveillance of e-cigarette use presents a unique set of challenges, given the emerging and dynamic market specific to these products (see Chapter 4 for more on the latter topic). Appendix 2.1 and Tables A2.2-1 and A2.2-2 in Appendix 2.2 summarize the key terms and measures used in this chapter.

Other Literature

This chapter also summarizes findings from peer-reviewed literature on e-cigarettes that were identified through a systematic review of studies of these products from the United States and abroad. A literature search was conducted in April 2015 (Glasser et al. 2015) using the National Library of Medicine’s PubMed database and the following keywords: “e-cigarette*” OR “electronic cigarette” OR “electronic cigarettes” OR “electronic nicotine delivery” OR “vape” OR “vaping.” Articles were excluded from this review for any of five reasons: (1) the article was not available in English; (2) the article was not relevant to e-cigarettes; (3) the study included nonhuman subjects; (4) the study did not include original data; or (5) the study did not include findings specific to adolescents or young adults. More details about this review’s methodology are available in Glasser and colleagues’ (2015)

¹ All appendixes and appendix tables that are cross-referenced in this chapter are available only online at <http://www.surgeongeneral.gov/library/reports/>.

report. The search was subsequently updated in November 2015, January 2016, and March 2016 during continued development of the report. For consistency, the same search strategy and databases were employed at all times. Studies on patterns of e-cigarette use behaviors for both youth and young adults are reviewed in the text and tables that follow. All other studies not explicitly described in the text are summarized in Appendix 2.3 and Tables A2.3-1 through A2.3-3.

Key Findings

Youth

Current Prevalence

Ever Use

According to the 2015 National Youth Tobacco Survey (NYTS), an estimated 27.1% of U.S. adolescents, representing approximately 7,260,500 persons, had ever tried e-cigarettes (Centers for Disease Control and Prevention [CDC], unpublished data [NYTS 2015]). This included 13.5% of middle school students and 37.7% of high school students (Tables 2.1a and 2.1b). Among middle school students, use was comparable between boys and girls, but it was higher among Hispanics compared with other racial/ethnic groups (Table 2.1a). For high school students, use was also comparable between boys and girls, but higher among both White and Hispanic youth compared with Black youth (Table 2.1b). According to data from the 2015 Youth Risk Behavior Survey (YRBS), a larger percentage of high school students (44.9%) had ever used e-cigarettes (Kann et al. 2016), while the Monitoring the Future (MTF) survey does not collect data on ever use of e-cigarettes (Johnston et al. 2016).

Past-30-Day Use

According to the 2015 NYTS, an estimated 620,000 middle school students and 2,390,000 high school students had used e-cigarettes at least once in the past 30 days (CDC 2016). This was an increase from the 2014 NYTS, which reported 450,000 middle school students and 2,010,000 high school students had used e-cigarettes in the past 30 days (CDC 2015c). Levels of past-30-day use were 5.3% for middle school students and 16% for high school students in 2015 (Tables 2.2a and 2.2b), compared with 3.9% for middle school students and 13.4% for high school students in 2014. Sociodemographic differences in past-30-day use for middle and high school students had the same patterns as those for ever use (Tables 2.2a and 2.2b). In 2015, according to the YRBS, 24.1% of high school students had used e-cigarettes at least once in the past 30 days (Kann et al. 2016). The 2015 MTF shows past-30-day prevalence of e-cigarette use among adolescents was 9.5% among 8th graders, 14% among 10th graders, and 16% among 12th graders (Johnston et al. 2016). Notably, data from NYTS, YRBS, and MTF show that in 2014 exclusive past-30-day use of e-cigarettes exceeded exclusive past-30-day use of conventional cigarettes for the first time since these types of data were collected (University of Michigan 2014; CDC 2015c).

Frequency of Use

Among middle school students, according to the 2015 NYTS, 5.3% were current users of e-cigarettes, and 0.6% used e-cigarettes frequently (defined as using an e-cigarette 20 or more days in the past 30 days preceding the survey) (Table 2.1a). Among high school students, these estimates were 15.5% and 2.5%, respectively (Table 2.1b). Due to smaller sample sizes, confidence intervals were too wide to determine sociodemographic differences in these measures. These estimates are consistent with a report by CDC (2015b).

A recent analysis of 2014 MTF data, specific to high school seniors, showed the frequency of e-cigarette use (defined as the number of days in the past 30 days a student used an e-cigarette) increases with ever cigarette smoking (Warner et al. 2016). Among high school seniors who used at least 1 e-cigarette in the past 30 days, the frequency of e-cigarette use was almost twice as high (10.2 days) among those who regularly smoke conventional cigarettes, compared to those who had never smoked a conventional cigarette (5.8 days). However, the frequency of e-cigarette use did not vary substantially among current cigarette smokers. Among high school seniors who used at least 1 e-cigarette in the past 30 days, the frequency of e-cigarette use averaged 8–10 days for “heavy cigarette smokers” (those who smoked more than a half pack of cigarettes per day), “light cigarette smokers” (those who smoked 1–5 cigarettes per day), and “very light cigarette smokers” (those who smoked fewer than 1 cigarette per day) (Warner et al. 2016).

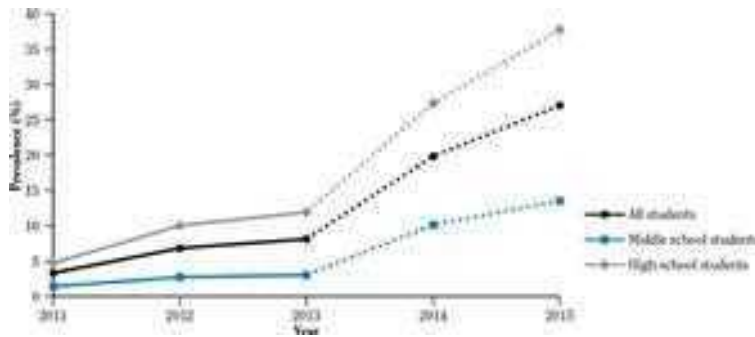
Susceptibility to Use

Among those who had never used an e-cigarette, 32.1% of middle school students and 38.4% of high school students were susceptible to using e-cigarettes in the future. That is, these students did not have a firm resolve not to use e-cigarettes in the future. This is according to the 2015 NYTS (Tables 2.1a and 2.1b). No differences in susceptibility to use e-cigarettes were observed by gender or race/ethnicity for either middle school or high school students.

Trends in Prevalence

Ever Use

Overall, according to the NYTS, ever use of e-cigarettes among students in grades 6–12 increased from 3.3% in 2011, to 6.8% in 2012, to 8.1% in 2013, to 19.8% in 2014, and then to 27% in 2015 (Figure 2.1). As discussed in Appendix 2.2 (see NYTS Measures—Special Issues), measures of e-cigarette use were changed for the 2014 NYTS, as signaled by the dotted line in the figure. Research conducted using the New Jersey Youth Tobacco Survey suggests that the NYTS measures used in 2011–2013 may potentially underestimate use, compared with the 2014 measure (Delnevo et al. 2016). For the 2011–2015 period, use of e-cigarettes was higher in each year among high school students than among middle school students (Tables 2.3a and 2.3b).



Source: Centers for Disease Control and Prevention 2013a, 2014b; unpublished data (data: NYTS 2015).

Note: In 2014, modifications were made to the e-cigarette measure to enhance its accuracy, which may limit the comparability of this estimate to those collected in previous years. The dotted lines from 2013 to 2015 represent these differences.

^aIncludes those who responded “1 or more” to the following question: *During the last 30 days, on how many days did you use electronic cigarettes or e-cigarettes?*

Figure 2.1. Trends in ever e-cigarette use^a among U.S. middle and high school students; National Youth Tobacco Survey (NYTS) 2011–2015.

Middle School Students

Trends in ever use of e-cigarettes among U.S. middle school students are presented in Table 2.3a and Figure 2.1, using data from the 2011–2015 NYTS. The prevalence of ever use increased from 1.4% in 2011 to 2.7% in 2012, to 3.0% in 2013, to 10.1% in 2014, and then to 13.5% in 2015. The jump in prevalence between 2013 and 2014 may be an artifact of a change in how the use item was asked (see Appendix 2.2. Key Measures of Use). Nonetheless, prevalence of use would be expected to be minimal prior to 2011, suggesting that a considerable increase in use was still observed during this relatively short 4-year period. In 2015, among middle school students, an estimated 1,595,481 had ever tried e-cigarettes (CDC, unpublished data [NYTS 2015]). From 2011 to 2013, the prevalence of ever use did not differ significantly by gender or race/ethnicity. There remained no significant difference in ever use by gender in the 2014 or 2015 NYTS, but by 2014 and still in 2015, a greater percentage of Hispanic middle school students (18.6%) had tried e-cigarettes than White (12.2%) or Black (11.7%) students or students of other races/ethnicities (11.9%) (Table 2.3a).

High School Students

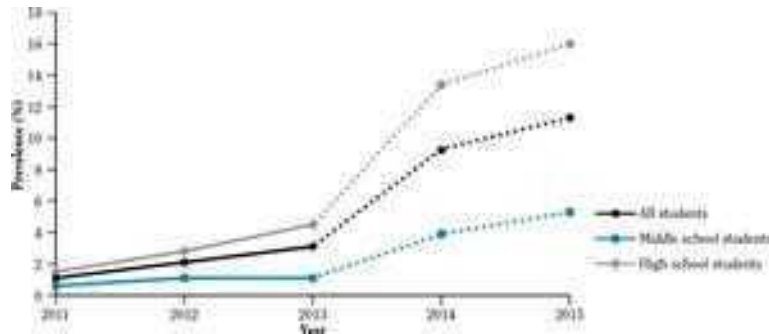
Trends in ever use of e-cigarettes among U.S. high school students are presented in Tables 2.3b and Figure 2.1, using data from the 2011–2015 NYTS. The prevalence of ever use increased from 4.7% in 2011 to 10% in 2012, to 11.9% in 2013, to 27.3% in 2014, and then to 37.7% in 2015. In that year, an estimated 5,624,876 high school students had ever used e-cigarettes (CDC, unpublished data [NYTS 2015]). In 2011–2013, male high school students had a higher rate of ever use each year compared with female students, but in 2014 the genders did not differ significantly in their rates. From 2011 to 2015, White and Hispanic high school students were more likely each year to be ever users than were Black students: In 2015, these figures were 38% and 43%, respectively, for White and Hispanic students compared with 28.5% for Black students.

Middle School Students

Trends in past-30-day use of e-cigarettes among middle school students in the United States are presented in Table 2.2a and Figure 2.2, again using data from the 2011–2015 NYTS. The prevalence of such use in this population increased from 0.6% in 2011 to 1.1% in 2012 and 2013, to 3.9% in 2014, and then to 5.3% in 2015 (Table 2.2a) (CDC 2016). Between 2011 and 2015, there were no significant differences in prevalence by gender; unstable estimates (see notes to the table) precluded an examination of differences in past-30-day e-cigarette use by race/ethnicity for 2011–2013. In 2014, the prevalence of past-30-day use was higher among Hispanics (6.2%) than Whites (3.1%), a trend that was also seen in 2015 with 8.3% of Hispanics and 4.4% of Whites reporting past-30-day use. From 2011 to 2015, increases were seen among females (0.4% to 4.8%), males (0.7% to 5.9%), Whites (0.6% to 4.4%), Hispanics (0.6% to 8.3%), and Blacks (1.1% in 2012 to 4.1%) (Table 2.2a) (CDC 2013b; CDC 2015c; CDC 2016).

Past-30-Day Use

According to the NYTS, past-30-day use of e-cigarettes among students in grades 6–12 in the United States increased from 1.1% in 2011 to 2.1% in 2012, to 3.1% in 2013, to 9.3% in 2014, and then 11.3% in 2015 (CDC 2013b; Ambrose et al. 2014; Lippert 2015; CDC, unpublished data) (Figure 2.2). In 2015, approximately 3,038,000 middle and high school students were past-30-day users of e-cigarettes (CDC, unpublished data [NYTS 2015]). Across all years, past-30-day use of e-cigarettes was higher among high school students than middle school students (Figure 2.2; Tables 2.2a and 2.2b). In the MTF, estimates were stable from 2014 to 2015; among 8th, 10th, and 12th graders, past-30-day use went from 8.7% to 9.5%, 16.2% to 14%, and 17.1% to 16.2%, respectively (University of Michigan, Institute for Social Research, unpublished data). Differences in trends in past-30-day use between the NYTS and MTF may be due to differences in age groups (e.g., the NYTS includes all grades in middle school and all grades in high schools) and the way in which these measures were asked on the instruments (see Table A2.2-1 in Appendix 2.2).



Source: Centers for Disease Control and Prevention 2013a, 2014b; unpublished data (data: NYTS 2015).
Note: In 2014, modifications were made to the e-cigarette measure to enhance its accuracy, which may limit the comparability of this estimate to those collected in previous years. The dotted lines from 2013 to 2015 represent these differences.

^aIncludes those who responded “1 or more” for the following question: “During the last 30 days, on how many days did you use electronic cigarettes or e-cigarettes?”

Figure 2.2. Trends in past-30-day e-cigarette use^a among U.S. middle and high school students; National Youth Tobacco Survey (NYTS) 2011–2015.

Table 2.1a. Percentage of middle school students who have used e-cigarettes, by gender and race/ethnicity;
National Youth Tobacco Survey (NYTS) 2015

Characteristic	Ever use ^a		Current use ^b		Frequent use ^c ; Among current users		Frequent use ^c ; Among all students		Susceptibility to use ^d ; Among never users		Susceptibility to use ^d ; Among all students	
	% (95% CI)	SE	% (95% CI)	SE	% (95% CI)	SE	% (95% CI)	SE	% (95% CI)	SE	% (95% CI)	SE
Overall	13.5 (11.8–15.5)	0.9	5.3 (4.6–6.2)	0.4	11.7 (8.6–15.8)	1.8	0.6 (0.4–0.9)	0.1	32.1 (29.7–34.7)	1.3	41.4 (38.3–44.5)	1.5
Gender												
Female	12.2 (10.5–14.1)	0.9	4.8 (4.0–5.6)	0.4	11.0 (6.9–17.0)	2.5	0.5 (0.3–0.8)	0.1	33.1 (30.2–36.2)	1.5	41.4 (38.0–44.8)	1.7
Male	14.9 (12.9–17.2)	1.1	5.9 (4.7–7.2)	0.6	11.8 (8.3–16.5)	2.0	0.7 (0.5–1.0)	0.1	31.3 (28.2–34.6)	1.6	41.6 (37.9–45.4)	1.9
Race/ethnicity												
White	12.2 (10.1–14.5)	1.1	4.4 (3.6–5.5)	0.5	10.8 (6.5–17.5)	2.7	0.5 (0.3–0.8)	0.1	29.7 (26.1–33.6)	1.9	38.0 (33.7–42.5)	2.2
Black or African American	11.7 (9.5–14.3)	1.2	4.1 (3.1–5.3)	0.6	14.0 (5.9–29.6)	5.7	—	—	34.7 (30.7–39.0)	2.1	42.5 (39.0–46.2)	1.8
Hispanic or Latino	18.6 (15.9–21.5)	1.4	8.3 (6.8–10.0)	0.8	12.1 (7.5–18.9)	2.8	1.0 (0.6–1.6)	0.2	38.0 (35.2–40.8)	1.4	49.8 (46.9–52.7)	1.5
Other ^e	11.9 (8.2–17.1)	2.2	4.6 (2.7–7.7)	1.2	—	—	—	—	30.4 (24.7–36.8)	3.1	39.5 (33.2–46.2)	3.3

Source: Centers for Disease Control and Prevention, unpublished data (data: NYTS 2015).

Notes: CI = confidence interval; SE = standard error. An em dash (—) indicates that data are statistically unstable because of a relative standard error >40%.

^aIncludes those who reported using an e-cigarette, even once or twice.

^bIncludes those who reported using e-cigarettes on 1 or more days in the past 30 days.

^cIncludes those who responded “≥20 days” to the following question: “During the past 30 days, on how many days did you use electronic cigarettes or e-cigarettes?” See CDC (2015b).

^dIncludes those who failed to respond “definitely not” to any of the following questions: (a) “Do you think that you will try an electronic cigarette or e-cigarette soon?”; (b) “If one of your best friends

were to offer you an electronic cigarette or e-cigarette, would you use it?”; or (c) “Have you ever been curious about using an electronic cigarette or e-cigarette, even once or twice?”

^eIncludes non-Hispanic Asian, non-Hispanic Native Hawaiian/Other Pacific Islander, and non-Hispanic American Indian/Alaska Native.

Table 2.1b. Percentage of high school students who have used e-cigarettes, by gender and race/ethnicity;
National Youth Tobacco Survey (NYTS) 2015

Characteristic	Ever use ^a		Current use ^b		Frequent use ^c ; Among current users		Frequent use ^c ; Among all students		Susceptibility to use ^d ; Among never users		Susceptibility to use ^d ; Among all students	
	% (95% CI)	SE	% (95% CI)	SE	% (95% CI)	SE	% (95% CI)	SE	% (95% CI)	SE	% (95% CI)	SE
Overall	37.7 (35.3–40.2)	1.2	16.0 (14.1–18.0)	1.0	15.5 (12.9–18.4)	1.4	2.5 (1.9–3.2)	0.3	38.4 (36.5–40.4)	1.0	61.1 (59.0–63.2)	1.0
Gender												
Female	34.6 (31.9–37.3)	1.4	12.8 (11.0–15.0)	1.0	10.1 (7.2–14.0)	1.7	1.3 (0.9–1.8)	0.2	39.8 (37.4–42.2)	1.2	60.3 (58.1–62.5)	1.1
Male	40.7 (37.7–43.7)	1.5	19.0 (16.5–21.7)	1.3	19.1 (15.6–23.1)	1.9	3.6 (2.7–4.8)	0.5	36.9 (34.3–39.5)	1.3	61.8 (59.2–64.4)	1.3
Race/ethnicity												
White	38.0 (35.1–41.0)	1.5	17.2 (14.7–19.9)	1.3	16.8 (13.4–20.8)	1.9	2.9 (2.1–3.9)	0.4	36.3 (33.4–39.4)	1.5	60.1 (57.4–62.7)	1.3
Black or African American	28.5 (25.5–31.8)	1.6	8.9 (7.4–10.8)	0.8	8.5 (3.9–17.4)	3.2	0.8 (0.3–1.7)	0.3	37.2 (32.2–42.5)	2.6	54.5 (51.0–57.9)	1.7

**Table 2.2b. Percentage of high school students who used e-cigarettes in the past 30 days^a, by gender and race/ethnicity;
National Youth Tobacco Survey (NYTS) 2011–2015**

	2011	2012	2013	2014	2015
Characteristic	% (95% CI)	SE	% (95% CI)	SE	% (95% CI)
Overall	1.5 (1.2–2.0)	0.2	2.8 (2.3–3.5)	0.3	4.5 (3.8–5.3)
Gender					
Female	0.7 (0.5–1.0)	0.1	1.9 (1.5–2.4)	0.2	3.5 (2.8–4.3)
Male	2.3 (1.7–3.2)	0.4	3.7 (2.9–4.8)	0.5	5.5 (4.5–6.8)
Race/ethnicity					
White	1.8 (1.3–2.4)	0.3	3.4 (2.7–4.2)	0.4	4.8 (3.8–6.1)
Black or African American	—	—	1.1 (0.7–1.9)	0.3	2.7 (1.9–3.9)
Hispanic or Latino	1.3 (0.8–2.1)	0.3	2.7 (1.9–3.8)	0.5	5.3 (4.2–6.6)
Other ^b	—	—	—	—	4.0 (2.3–6.9)

Source: Centers for Disease Control and Prevention, unpublished data (data: NYTS 2011–2015).

Notes: CI = confidence interval; SE = standard error. An em dash (—) indicates that data are statistically unstable because of a relative standard error >40%. Wording of questions used to measure e-cigarette use varied from 2011 to 2015.

^a Includes those who reported using e-cigarettes on 1 or more of the past 30 days. This is also considered “current use” in this survey.

^b Includes non-Hispanic Asian, non-Hispanic Native Hawaiian/Other Pacific Islander, and non-Hispanic American Indian/Alaska Native.

**Table 2.3a. Percentage of middle school students who have ever used e-cigarettes^a, by gender and race/ethnicity;
National Youth Tobacco Survey (NYTS) 2011–2015**

	2011	2012	2013	2014	2015
Characteristic	% (95% CI)	SE	% (95% CI)	SE	% (95% CI)
Overall	1.4 (1.0–2.0)	0.2	2.7 (2.2–3.2)	0.2	3.0 (2.5–3.5)
Gender					
Female	1.2 (0.8–1.6)	0.2	2.4 (1.9–3.0)	0.3	2.8 (2.3–3.5)
Male	1.7 (1.1–2.7)	0.4	3.0 (2.4–3.6)	0.3	3.1 (2.5–3.9)
Race/ethnicity					
White	1.5 (0.9–2.3)	0.3	2.6 (2.1–3.3)	0.3	3.0 (2.4–3.7)
Black or African American	1.2 (0.7–2.0)	0.3	2.3 (1.3–4.2)	0.7	2.7 (1.9–3.7)
Hispanic or Latino	1.6 (1.1–2.3)	0.3	3.3 (2.3–4.6)	0.6	3.9 (2.9–5.2)
Other ^b	—	—	1.0 (0.5–2.2)	0.4	—

Source: Centers for Disease Control and Prevention, unpublished data (data: NYTS 2011–2015).

Notes: CI = confidence interval; SE = standard error. An em dash (—) indicates that data are statistically unstable because of a relative standard error >40%. Wording of questions used to measure e-cigarette use varied from 2011 to 2015.

^aIncludes those who reported ever trying e-cigarettes.

^bIncludes non-Hispanic Asian, non-Hispanic Native Hawaiian/Other Pacific Islander, and non-Hispanic American Indian/Alaska Native.

**Table 2.3b. Percentage of high school students who have ever used e-cigarettes^a, by gender and race/ethnicity;
National Youth Tobacco Survey (NYTS) 2011–2015**

Characteristic	2011		2012		2013		2014		2015	
	% (95% CI)	SE	% (95% CI)	SE	% (95% CI)	SE	% (95% CI)	SE	% (95% CI)	SE
Overall	4.7 (3.8–5.7)	0.5	10.0 (8.6–11.6)	0.7	11.9 (10.5–13.5)	0.8	27.3 (24.4–30.5)	1.5	37.7 (35.3–40.2)	1.2
Gender										
Female	3.5 (2.7–4.4)	0.4	8.0 (6.7–9.5)	0.7	9.9 (8.3–11.7)	0.8	24.5 (21.4–27.9)	1.6	34.6 (31.9–37.3)	1.4
Male	5.9 (4.7–7.3)	0.7	12.0 (10.2–14.1)	1.0	13.8 (12.1–15.8)	0.9	30.1 (27.2–33.3)	1.5	40.7 (37.7–43.7)	1.5
Race/ethnicity										
White	5.8 (4.6–7.4)	0.7	12.3 (10.5–14.4)	1.0	14.7 (12.8–16.9)	1.0	29.7 (26.2–33.4)	1.8	38.0 (35.1–41.0)	1.5
Black or African American	1.5 (0.9–2.4)	0.4	4.0 (3.1–5.1)	0.5	4.9 (3.6–6.6)	0.7	17.6 (14.1–21.8)	1.9	28.5 (25.5–31.8)	1.6
Hispanic or Latino	3.7 (2.5–5.5)	0.7	8.5 (6.6–10.8)	1.0	10.4 (8.6–12.5)	1.0	29.9 (25.4–34.9)	2.4	43.0 (38.9–47.2)	2.1
Other ^b	2.8 (1.7–4.6)	0.7	6.0 (3.3–10.8)	1.8	8.3 (5.3–12.8)	1.8	18.7 (14–24.5)	2.6	37.4 (24.8–52.1)	7.0

Source: Centers for Disease Control and Prevention, unpublished data (data: NYTS 2011–2015).

Notes: CI = confidence interval; SE = standard error. Wording of questions used to measure e-cigarette use varied from 2011 to 2015.

^aIncludes those who reported ever trying e-cigarettes.

^bIncludes non-Hispanic Asian, non-Hispanic Native Hawaiian/Other Pacific Islander, and non-Hispanic American Indian/Alaska Native.

High School Students

Trends in past-30-day use of e-cigarettes among high school students are also presented in Table 2.2b and Figure 2.2, again using data from the 2011–2015 NYTS. The prevalence of such use in this population increased from 1.5% in 2011 to 2.8% in 2012, to 4.5% in 2013, to 13.4% in 2014, and then to 16% in 2015. From 2011 to 2013 and in 2015, males were significantly more likely each year to be past-30-day users than were females, but this difference was not significant in 2014 (Table 2.2b). From 2012 to 2015, Black high school students were less likely each year to be past-30-day users than were White or Hispanic high school students (Table 2.2b). During 2011–2015, large increases in past-30-day use were seen among females (0.7% to 12.8%), males (2.3% to 19%), Whites (1.8% to 17.2%), and Hispanics (1.3% to 16.4%) (Table 2.2b) (CDC 2013b, 2015c, 2016).

Young Adults

Current Prevalence

According to the 2013–2014 National Adult Tobacco Survey (NATS), among young U.S. adults aged 18–24 years, the prevalence of ever use and current use of e-cigarettes was 35.8% and 13.6%, respectively (Table 2.4a). These percentages were significantly higher than for the same measures among adults aged 25 years or over (16.4% and 5.7%, respectively) (Table 2.4b). Among young adults, ever and current use were both higher among males than females and for Whites than in other racial/ethnic groups (Table 2.4a). By educational attainment, among young adults, both ever and current use were lowest among those with a college degree (Table 2.4a). Among all young adults, 2% reported using e-cigarettes “every day”; while among current users in this age group, 15% reported this frequency (Table 2.4a). Use of e-cigarettes “every day” among older adults (≥ 25 years of age) was 1.3% overall and 22% among current users (Table 2.4b). Among young adults, sociodemographic differences in frequent use followed the same pattern as those for ever and current use (Table 2.4a).

Trends in Prevalence

According to the Styles (also known as HealthStyles or Summer Styles) survey, the prevalence of ever use of e-cigarettes among young adults aged 18–24 years was 6.9% in 2011, 4.1% in 2012, 7.8% in 2013, and 14.3% in 2014, a year that saw the addition of other products to this measure, including e-hookahs and e-pipes or e-cigars (Figure 2.3). Although the prevalence of ever use of e-cigarettes among young adults remained consistent from 2010 to 2013, it doubled from 2013 to 2014, presumably reflecting in part the addition of new products to the definition of e-cigarettes. In 2010, young adults (18–24 years) were more likely than older adults (25–44 and 45–64 years of age) to be ever users of e-cigarettes (King et al. 2015). In 2014, ever use of e-cigarettes or similar products was statistically equivalent between young adults (18–24 years old) at 14.3%, adults 25–44 years old at 15%, and adults 45–64 years old at 11.9% ($p > 0.05$) (CDC, unpublished data [Styles 2014]).

E-Cigarette Use and Use of Other Tobacco Products

Evidence from both national and regional studies suggests that e-cigarette use is strongly associated with other tobacco use, especially the use of combustible products (including conventional cigarettes, cigar products, and hookahs). However, many youth and young adults use e-cigarettes exclusively, too. Estimates from cross-sectional surveys such as the NYTS, MTF, and NATS are presented below for youth and young adults, followed by longitudinal studies that examine whether e-cigarette use precedes the use of other tobacco products (Leventhal et al. 2015; Primack et al. 2015; Barrington-Trimis et al. 2016; Unger et al. 2016; Wills et al. 2016).

Cross-Sectional Studies

Youth

Current Prevalence

Using data from the 2015 MTF survey, Figure 2.4 and Table 2.5 show past-30-day use of e-cigarettes and conventional cigarettes, including both exclusive and combined use of these products, among 8th-, 10th-, and 12th-grade students. In the 2015 MTF survey, 10.4% of 12th graders used e-cigarettes only, 5.3% used conventional cigarettes only, and 5.8% used both e-cigarettes and conventional cigarettes at least once in the past 30 days (Table 2.5) (MTF 2015a,b). For all grade levels, exclusive use of e-cigarettes was more prevalent (6.8%, 10.4%, and 10.4% of 8th, 10th, and 12th graders, respectively) than exclusive use of conventional cigarettes alone (1.4%, 2.2%, 5.3%, respectively). In the 8th and 10th grades, the combined or dual use of e-cigarettes and conventional cigarettes was also more prevalent than the use of conventional cigarettes alone (2.4% vs. 1.4%, and 3.5% vs. 2.2% for 8th and 10th graders, respectively); while in the 12th grade, the prevalence in the two categories was nearly identical (5.8% vs. 5.3%). As grade level increases, the ratio of any e-cigarette use to any conventional cigarette use decreases. Among 12th graders, dual use of these products was higher among boys than girls and among Whites than Blacks. In all grade levels, dual use was much higher among students who planned to attend fewer than 4 years of college compared to those who planned to attend 4 years of college. No other sociodemographic differences were observed among dual users (Table 2.5). For 10th and 12th graders, exclusive use of e-cigarettes was higher among boys than girls.

Tables 2.6a and 2.6b present data from the 2015 NYTS for middle and high school students. These data represent the percentages of tobacco users who were either lifetime or past-30-day users of e-cigarettes, by tobacco-use category (e.g., cigarettes only, other combustibles only). In these data, a correlation among the increasing levels of tobacco use, increasing complexity of poly-tobacco use, and e-cigarette use is apparent, with ever use and past-30-day use of e-cigarettes emerging as least prevalent among never tobacco users and most prevalent among the highest category of poly-tobacco users (conventional cigarettes plus other combustibles and noncombustibles) for both age groups. As an example, past-30-day e-cigarette use was rare (2.8%) among middle school students who did not use other

Table 2.4a. Percentage of young adults (18–24 years of age) who have used e-cigarettes, by gender, race/ethnicity, and education; National Adult Tobacco Survey (NATS) 2013–2014

Characteristic	Ever use ^a		Current use ^b		Frequent use ^c : Among current users		Frequent use ^c : Among all young adults	
	% (95% CI)	SE	% (95% CI)	SE	% (95% CI)	SE	% (95% CI)	SE
Overall	35.8 (34.1–37.6)	0.9	13.6 (12.5–14.8)	0.6	15.0 (12.1–18.5)	1.6	2.0 (1.6–2.6)	0.2
Gender								
Female	28.4 (26.1–30.8)	1.2	9.8 (8.3–11.5)	0.8	10.0 (6.5–15.1)	2.2	1.0 (0.6–1.5)	0.2
Male	42.9 (40.4–45.3)	1.2	17.1 (15.4–19.0)	0.9	17.8 (13.9–22.5)	2.2	3.0 (2.3–4.0)	0.4
Race/ethnicity								
White	39.7 (37.4–41.9)	1.2	16.1 (14.5–17.8)	0.9	15.3 (11.7–19.7)	2.0	2.5 (1.9–3.2)	0.4
Black or African American	23.1 (19.0–27.8)	2.3	5.4 (3.7–7.9)	1.1	—	—	—	—
Hispanic or Latino	36.6 (32.6–40.7)	2.1	13.4 (10.9–16.4)	1.4	12.0 (6.8–20.2)	3.3	1.6 (0.9–2.8)	0.5
Other ^d	30.8 (25.8–36.3)	2.7	10.8 (8.1–14.2)	1.6	21.5 (11.6–36.4)	6.3	2.3 (1.2–4.4)	0.8
Education								
< High school	44.8 (38.9–50.9)	3.1	15.2 (11.5–19.7)	2.1	9.8 (4.8–18.8)	3.4	1.5 (0.7–3.0)	0.5
High school	39.4 (36.7–42.2)	1.4	14.9 (13.1–17.0)	1.0	17.6 (13.0–23.4)	2.6	2.6 (1.9–3.6)	0.4
Some college ^e	34.3 (31.6–37.0)	1.4	14.7 (12.8–16.8)	1.0	14.8 (10.2–21.0)	2.7	2.2 (1.5–3.2)	0.4
College degree ^f	16.9 (14.2–20.0)	1.5	4.5 (3.1–6.4)	0.8	—	—	—	—

Source: Centers for Disease Control and Prevention, unpublished data (data: NATS 2013–2014).

Notes: **CI** = confidence interval; **SE** = standard error. An em dash (—) indicates that data are statistically unstable because of a relative standard error >40%.

^aIncludes those who reported they had heard of e-cigarettes and tried e-cigarettes.

^bIncludes those who reported they had heard of, tried, and used e-cigarettes every day, some days, or rarely at the time of the interview.

^cIncludes those who reported they had heard of e-cigarettes, tried e-cigarettes, and reported using e-cigarettes every day at the time of the interview.

^dIncludes non-Hispanic Asian, non-Hispanic Native Hawaiian/Other Pacific Islander, non-Hispanic American Indian/Alaska Native, and multiracial.

^eIncludes some college, no degree; associate's degree, academic program; associate's degree, unspecified; certificate; diploma; or associate's degree.

^fIncludes bachelor's degree, master's/professional school degree, or doctoral degree.

Table 2.4b. Percentage of adults (≥25 years of age) who have used e-cigarettes, by gender, race/ethnicity, and education; National Adult Tobacco Survey (NATS) 2013–2014

Characteristic	Ever use ^a		Current use ^b		Frequent use ^c : Among current users		Frequent use ^c : Among all adults	
	% (95% CI)	SE	% (95% CI)	SE	% (95% CI)	SE	% (95% CI)	SE
Overall	16.4 (15.9–16.8)	0.2	5.7 (5.5–6.0)	0.1	22.0 (20.1–24.0)	1.0	1.3 (1.1–1.4)	0.1

Table 2.4b. (Continued)

	Ever use ^a	Current use ^b	Frequent use ^c : Among current users	Frequent use ^c : Among all adults
Gender				
Female	14.7 (14.2–15.3)	5.0 (4.7–5.4)	20.6 (18.1–23.3)	1.3
Male	18.3 (17.6–18.9)	6.6 (6.1–7.0)	23.0 (20.2–25.9)	1.5
Race/ethnicity				
White	16.2 (15.8–16.7)	6.0 (5.7–6.4)	23.9 (21.7–26.3)	1.2
Characteristic	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
Black or African American	15.1 (13.9–16.5)	3.8 (3.2–4.5)	15.2 (10.2–22.2)	3.0
Hispanic or Latino	15.6 (14.3–17.0)	4.9 (4.1–5.8)	15.8 (10.4–23.4)	3.3
Other ^d	21.0 (19.2–22.9)	8.0 (6.7–9.4)	19.4 (14.0–26.2)	3.1
Education				
<High school	18.2 (16.8–19.7)	5.2 (4.4–6.1)	20.8 (15.2–27.7)	3.2
High school	20.6 (19.7–21.6)	7.6 (7.0–8.3)	19.2 (16.1–22.7)	1.7
Some college ^e	19.7 (18.9–20.5)	7.4 (6.8–7.9)	24.5 (21.4–27.8)	1.6
College degree ^f	8.7 (8.2–9.1)	2.8 (2.5–3.1)	22.0 (18.1–26.4)	2.1

Source: Centers for Disease Control and Prevention, unpublished data (data: NATS 2013–2014).

Note: CI = confidence interval; SE = standard error.

^aIncludes those who reported they had heard of and tried e-cigarettes.

^bIncludes those who reported they had heard, tried, and used e-cigarettes every day, some days, or rarely at the time of the interview.

^cIncludes those who reported they had heard of, tried, and reported using e-cigarettes every day at the time of the interview.

^dIncludes non-Hispanic Asian, non-Hispanic Native Hawaiian/Other Pacific Islander, non-Hispanic American Indian/Alaska Native, and multiracial.

^eIncludes some college, no degree; associate's degree, academic program; associate's degree, unspecified; certificate; diploma; or associate's degree.

^fIncludes bachelor's degree, master's/professional school degree, or doctoral degree.

Table 2.5. Percentage of students in grades 8, 10, and 12 who used e-cigarettes, cigarettes, or both products in the past 30 days, by sociodemographic characteristics; Monitoring the Future (MTF) 2015

8th grade											
Neither: % (95% CI)		E-cigarettes only: % (95% CI)		Cigarettes only: % (95% CI)		Both: % (95% CI)		Neither: % (95% CI)		E-cigarettes only: % (95% CI)	
Overall		89.4 (88.4–90.5)	6.8 (5.8–7.8)	1.4 (0.9–1.8)	2.4 (1.9–2.9)	83.9 (81.9–85.9)	10.4 (9.0–11.8)	2.2 (1.7–2.7)	3.5 (2.8–4.3)	78.5 (76.7–80.3)	10.4 (9.1–11.8)

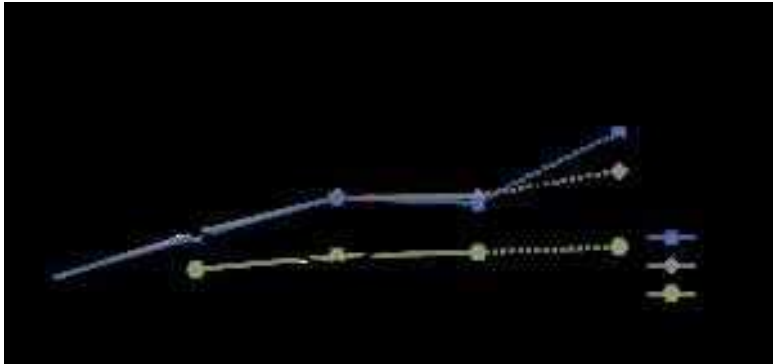
8th grade								10th grade				12th grade		
Gender														
Female	90.2 (88.7–91.7)	6.2 (4.9–7.5)	1.4 (0.7–2.0)	2.2 (1.6–2.9)	85.6 (83.6–87.6)	8.6 (7.2–10.1)	2.4 (1.6–3.1)	3.4 (2.5–4.3)	84.4 (82.8–86.0)	7.1 (6.2–8.0)	4.7 (3.6–5.7)	3.8 (3.1–4.6)		
Male	88.9 (87.3–90.4)	7.2 (6.0–8.5)	1.4 (0.7–2.0)	2.5 (1.7–3.3)	82.2 (79.6–84.7)	12.2 (10.2–14.2)	2.0 (1.3–2.7)	3.6 (2.6–4.7)	72.9 (70.2–75.6)	14.1 (11.8–16.3)	5.6 (4.6–6.6)	7.5 (6.1–8.9)		
Race/ethnicity														
White	90.1 (88.6–91.6)	6.2 (4.9–7.4)	1.2 (0.6–1.8)	2.6 (1.7–3.4)	82.1 (79.5–84.7)	11.2 (9.2–13.2)	2.3 (1.6–2.9)	4.4 (3.4–5.4)	75.2 (72.7–77.7)	12.0 (10.4–13.6)	5.8 (4.7–6.9)	7.1 (5.9–8.3)		
African American	91.2 (88.7–94.1)	5.3 (2.7–7.8)	2.1 (0.6–3.7)	1.5 (0.0–2.9)	89.9 (85.7–94.1)	6.6 (3.6–9.5)	1.8 (0.4–3.1)	1.7 (0.4–3.1)	87.7 (85.1–90.3)	5.2 (3.8–6.6)	5.1 (3.3–6.8)	2.0 (1.1–3.0)		
Hispanic	88.7 (85.8–91.5)	8.2 (6.1–10.4)	0.9 (0.2–1.6)	2.2 (1.2–3.2)	84.6 (81.5–87.6)	10.5 (7.6–13.4)	2.4 (0.9–4.0)	2.5 (0.8–4.2)	80.9 (78.0–83.7)	10.3 (8.0–12.5)	4.4 (3.2–5.5)	4.5 (3.1–6.0)		
	Neither: % (95% CI)	E-cigarettes only: % (95% CI)	Cigarettes only: % (95% CI)	Both: % (95% CI)	Neither: % (95% CI)	E-cigarettes only: % (95% CI)	Cigarettes only: % (95% CI)	Both: % (95% CI)	Neither: % (95% CI)	E-cigarettes only: % (95% CI)	Cigarettes only: % (95% CI)	Both: % (95% CI)		
College plans														
None or <4 years	76.8 (71.0–82.5)	10.1 (6.1–14.0)	4.9 (1.7–8.1)	8.3 (4.8–11.8)	66.3 (61.1–71.5)	15.4 (11.3–19.4)	7.0 (3.8–10.2)	11.3 (7.6–15.1)	65.1 (61.2–68.9)	13.0 (9.7–16.3)	10.2 (8.2–12.3)	11.7 (9.5–13.9)		
Complete 4 years	90.5 (89.4–91.5)	6.5 (5.5–7.4)	1.1 (0.7–1.5)	2.0 (1.5–2.5)	85.7 (83.6–87.7)	9.8 (8.3–11.4)	1.7 (1.3–2.2)	2.8 (2.1–3.5)	81.6 (79.9–83.2)	9.9 (8.6–11.1)	4.1 (3.4–4.8)	4.5 (3.8–5.2)		
Parental education ^a														
1–2 (Low)	88.1 (83.9–92.2)	5.9 (3.3–8.4)	1.8 (0.3–3.2)	4.3 (2.1–6.6)	77.2 (72.0–82.4)	12.6 (9.0–16.2)	4.8 (1.5–8.0)	5.4 (3.1–7.8)	77.3 (73.4–81.2)	10.1 (7.3–13.0)	7.9 (5.4–10.4)	4.7 (3.1–6.3)		
2.5–3	86.2 (83.3–89.1)	9.4 (6.7–12.1)	1.8 (0.6–3.1)	2.6 (1.2–3.9)	81.7 (78.3–85.2)	10.6 (8.1–13.0)	2.5 (1.3–3.7)	5.2 (3.2–7.1)	75.2 (72.4–78.1)	11.1 (9.0–13.3)	7.2 (5.5–8.8)	6.5 (5.0–7.9)		
	Neither: % (95% CI)	E-cigarettes only: % (95% CI)	Cigarettes only: % (95% CI)	Both: % (95% CI)	Neither: % (95% CI)	E-cigarettes only: % (95% CI)	Cigarettes only: % (95% CI)	Both: % (95% CI)	Neither: % (95% CI)	E-cigarettes only: % (95% CI)	Cigarettes only: % (95% CI)	Both: % (95% CI)		
3.5–4	89.6 (87.5–91.8)	7.3 (5.5–9.2)	1.3 (0.3–2.3)	0.8 (1.7–2.7)	83.5 (80.3–86.7)	10.0 (7.7–12.3)	2.8 (1.7–3.9)	3.7 (2.5–5.0)	78.7 (75.9–81.5)	9.9 (7.9–11.8)	4.6 (3.6–5.6)	6.8 (5.3–8.4)		
4.5–5	91.0 (89.1–92.8)	6.2 (4.5–7.9)	1.3 (0.4–2.1)	1.5 (0.6–2.5)	86.1 (83.5–88.8)	9.7 (7.5–11.8)	1.4 (0.7–2.0)	2.9 (1.7–4.1)	78.6 (75.7–81.5)	11.2 (9.1–13.2)	4.4 (3.3–5.5)	5.8 (4.4–7.2)		
5.5–6 (High)	91.9 (89.4–94.5)	5.2 (3.3–7.0)	1.0 (0.0–2.1)	1.9 (0.4–3.4)	87.6 (83.6–91.6)	9.2 (6.3–12.2)	1.0 (0.2–1.8)	2.2 (0.7–3.7)	82.7 (79.7–85.7)	10.4 (8.1–12.7)	3.2 (2.1–4.3)	3.7 (2.2–5.2)		

Source: University of Michigan, Institute for Social Research, unpublished data (data: MTF 2015).

Notes: Questions on e-cigarette use were asked on four of six questionnaire forms. Data presented here are based on those four forms only.

^aParental education is an average score of mother's education and father's education.

tobacco products in that time period. However, using the standard of past-30-day-use for each category, the level of such use grew from 44.9% among those who had used cigarettes only; to 61.3% among those who had used cigarettes and other combustibles only; to 74.6% among those who had used cigarettes, other combustibles, and other noncombustibles only (Table 2.6a). These data are consistent with results from the 2013–2014 PATH study (n = 13,651 youth, 12–17 years old), which showed that 52.6% of past-30-day tobacco users also used e-cigarettes (Kasza et al. 2016).

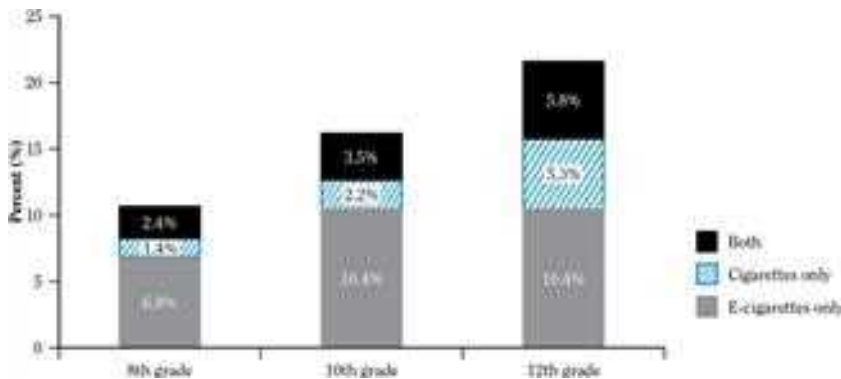


Source: King et al. (2015) (data: HealthStyles 2010–2013); Centers for Disease Control and Prevention, unpublished data (data: HealthStyles 2014).

Note: In 2014, modifications were made to the e-cigarette measure to enhance its accuracy, which may limit the comparability of this estimate to those collected in previous years. The dotted lines from 2013 to 2014 represent these differences.

^aIncludes those who responded “electronic cigarettes or e-cigarettes” to the following question, “Have you ever tried any of the following products, even just one time? Electronic cigarettes or e-cigarettes, such as Ruyan or NJOY?”

Figure 2.3. Trends in ever e-cigarette use^a among U.S. adults by age group; Styles 2010–2014.



Source: University of Michigan, Institute for Social Research, unpublished data (data: MTF 2015).

Note: Questions on e-cigarette use were asked on four of six questionnaire forms. Data presented here are based on those four forms only.

Figure 2.4. Percentage of students in grades 8, 10, and 12 who used e-cigarettes and cigarettes in the past 30 days; Monitoring the Future (MTF) 2015.

According to the 2015 NYTS, among high school students, past-30-day use of e-cigarettes was also rare (3.4%) among never users of other tobacco products (Table 2.6b). In

contrast, 18.4% of ever smokers of cigarettes only; 36.3% of ever smokers of cigarettes and other combustible products only; and 55% of ever users of cigarettes, other combustibles, and other noncombustible products only had used e-cigarettes in the past 30 days. Although the survey found that just 7.3% of high school students were past-30-day exclusive users of e-cigarettes, many types of tobacco product users in the past 30 days were found to have used e-cigarettes in that period: 41.1% of cigarette-only smokers; 58.8% of cigarette smokers and smokers of other combustible tobacco products only; and 77% of cigarette, other combustible, and noncombustible product users only. Similarly, 27.4% of high school students who had not used tobacco products in the past 30 days had ever tried e-cigarettes, as had 80.8% of past-30-day cigarette-only smokers and 95.5% of those who had used cigarettes, other combustible, and other noncombustible tobacco products only (Table 2.6b).

Figure 2.5 presents data from the 2015 NYTS on the prevalence of past-30-day use of various tobacco products among middle and high school students. Although the overall level of tobacco use was lower in middle school, the patterns of poly-tobacco use were similar between the two groups, albeit with a larger proportion of poly-tobacco use in high school. An estimated 6.6% of high school students and 1.8% of middle school students were dual users of combustible tobacco products and e-cigarettes in 2015. Combined use of combustible tobacco, noncombustible tobacco, and e-cigarettes in the past 30 days was rare, with this pattern found for just 0.7% of middle school and 2.6% of high school students in 2015 (Figure 2.5). Longitudinal data are needed to follow individuals over time, ideally for several years, to more precisely examine both the trajectories into and out of cigarette and e-cigarette use and to determine if dual use is a steady state or a pathway-to-persistent-use-of-combustible-tobacco state (Cobb et al. 2015). The small number of such studies that currently exist are discussed below.

Trends in Prevalence

Tables 2.7a and 2.7b and Figures 2.6 and 2.7 present patterns of ever e-cigarette and poly-tobacco use over time, using the NYTS data from 2011 to 2015. Among both middle school and high school students, the exclusive use of combustible products declined over time, while both the exclusive use of e-cigarettes and the dual use of e-cigarettes with combustible products increased, especially from 2013 to 2015.

Middle School Students

In 2011, an estimated 21% of middle school students had ever used some form of tobacco in their lifetimes, compared to just 1.4% of middle school students who had ever used e-cigarettes (Table 2.7a). By 2015, 13.5% of middle school students had ever tried a tobacco product, while 3.5% had tried e-cigarettes. In that year, 4.5% of middle school students were ever users of e-cigarettes only; 6.2% were ever users of e-cigarettes and combustible products only; and 2.2% were ever users of combustible products, noncombustible products, and e-cigarettes. This means that 70% of middle school students who had ever used e-cigarettes had also experimented with a combustible tobacco product, although which came first is unknown. In 2015, for past-30-day use, exclusive e-cigarette use was 2.6% and exclusive combustible tobacco use was 1.2%. Also in 2015, the prevalence of past-30-day dual use of e-cigarettes and any other combustible or noncombustible product was similar to those estimates, at 2.7% (1.8% for e-cigarettes plus combustibles only, 0.2% for noncombustibles

and e-cigarettes only, and 0.7% for e-cigarettes plus combustibles and noncombustibles only). In 2015, ever use of cigarettes in combination with combustibles (6.2%) was equal to or higher than ever use of e-cigarettes only (4.5%) or combustibles only (4.4%) (Table 2.7a).

High School Students

In 2011, an estimated 47.2% of high school students had ever used other tobacco products in their lifetimes, compared to 4.7% who had ever used e-cigarettes (Table 2.7b). By 2015, 50.4% of high school students had ever tried a tobacco product, and 37.7% had ever used an e-cigarette. In 2015, 7.4% of high school students had ever used e-cigarettes exclusively; 20% were ever dual users of e-cigarettes and combustible products; 0.6% were

Table 2.6a. Lifetime and past-30-day e-cigarette use among U.S. middle school students, by other tobacco product use; National Youth Tobacco Survey (NYTS) 2015

	N ^c	Lifetime e-cigarette use ^a		Past-30-day e-cigarette use ^b	
		% (95% CI)	SE	% (95% CI)	SE
Ever other tobacco use ^d (n = 1,757)	8,162				
Never	6,942	5.3 (4.5–6.2)	0.4	1.6 (1.3–2.0)	0.2
Cigarettes only	343	54.3 (46.7–61.7)	3.8	20.8 (15.7–27.0)	2.8
Other combustibles only	261	59.0 (51.5–66.1)	3.7	24.8 (19.0–31.7)	3.2
Noncombustibles only	89	30.7 (23.2–39.3)	4.1	—	—
Cigarettes + other combustibles only	300	70.6 (62.9–77.3)	3.6	35.0 (27.5–43.3)	4.0
Cigarettes + noncombustibles only	67	69.5 (54.5–81.3)	6.9	21.7 (12.7–34.6)	5.5
Other combustibles + noncombustibles only	27	80.3 (56.1–92.9)	9.2	39.4 (20.3–62.3)	11.2
Cigarettes + other combustibles + noncombustibles only	133	84.1 (73.3–91.1)	4.4	45.0 (34.7–55.7)	5.3
Past-30-day other tobacco use ^e (n = 417)	8,145				
No	7,728	10.5 (9.1–12.0)	0.7	2.8 (2.3–3.4)	0.3
Cigarettes only	70	80.6 (68.3–89.0)	5.2	44.9 (32.0–58.6)	6.8
Other combustibles only	153	82.8 (74.0–89.1)	3.8	69.2 (59.1–77.8)	4.7
Noncombustibles only	50	49.0 (34.9–63.3)	7.3	23.1 (12.7–38.2)	6.4
Cigarettes + other combustibles only	63	77.3 (58.8–89.0)	7.6	61.3 (43.9–76.2)	8.4
Cigarettes + noncombustibles only	18	87.2 (65.2–96.1)	7.2	67.8 (40.0–87.0)	12.6
Other combustibles + noncombustibles only	20	87.5 (63.2–96.6)	7.7	64.8 (42.2–82.3)	10.6
Cigarettes + other combustibles + noncombustibles only	43	85.8 (67.5–94.6)	6.5	74.6 (43.4–91.8)	12.7

Source: Centers for Disease Control and Prevention, unpublished data (data: NYTS 2015).

Notes: CI = confidence interval; SE = standard error. *Cigarettes Only* includes those who reported trying cigarettes but not any other tobacco product. *Other combustibles* includes cigars, pipes, and hookah or bidis. *Noncombustibles* includes smokeless tobacco, dissolvables, or snus. *Other Combustibles Only* includes those who reported trying other combustibles but not cigarettes nor noncombustibles. *Noncombustibles Only* includes those who reported trying noncombustibles but not cigarettes nor other combustibles. *Cigarettes and Other Combustibles Only* includes those who reported trying cigarettes and other combustibles but not noncombustibles. *Cigarettes and Noncombustibles Only* includes those who reported trying cigarettes and noncombustibles but not other combustibles. *Other Combustibles and Noncombustibles Only* includes those who reported trying other combustibles and noncombustibles but not cigarettes.

Cigarettes, Other Combustibles, and Noncombustibles includes those who reported trying a product from each group.

^aIncludes those who responded “yes” to the following question, “Have you ever used an electronic cigarette or e-cigarette, even once or twice?”

^bIncludes those who responded “1 or more days” to the following question, “During the past 30 days, on how many days did you use electronic cigarettes or e-cigarettes?”

^cIncludes all respondents categorized into each group. It does not exclude those missing for e-cigarette status.

^dIncludes those who reported trying at least one of the following products (e-cigarettes not included in the definitions): *Cigarettes Only*; *Other Combustibles Only*; *Noncombustibles Only*; *Cigarettes and Other Combustibles Only*; *Cigarettes and Noncombustibles Only*; *Other Combustibles and Noncombustibles Only*; and *Cigarettes, Other Combustibles, and Noncombustibles*.

^eIncludes those who reported using at least one of the following products on 1 of the past 30 days (e-cigarettes were not included in the definitions): *Cigarettes Only*; *Other Combustibles Only*; *Noncombustibles Only*; *Cigarettes and Other Combustibles Only*; *Cigarettes and Noncombustibles Only*; *Other Combustibles and Noncombustibles Only*; and *Cigarettes, Other Combustibles, and Noncombustibles*.

ever dual users of noncombustible products and e-cigarettes only; and 9.1% were ever poly users of combustibles, noncombustibles, and e-cigarettes. However, the order of the use (i.e., which product came first) remains unknown. In 2015, 5.9% of high school students were exclusive past-30-day users of e-cigarettes; 6.6% were past-30-day dual users of e-cigarettes and combustible tobacco products; 0.7% were past-30-day dual users of e-cigarettes and noncombustible tobacco products only; and 2.6% were past-30-day poly users of e-cigarettes, combustible, and noncombustible tobacco products. Exclusive use of combustible products (6.8%) remained as prevalent as past-30-day dual use of e-cigarettes and combustible products (6.6%) among high school students (Table 2.7b).

Table 2.6b. Lifetime and past-30-day e-cigarette use among U.S. high school students, by other tobacco product use; National Youth Tobacco Survey (NYTS) 2015

	N ^c	Lifetime e-cigarette use ^a		Past-30-day e-cigarette use ^b	
		% (95% CI)	SE	% (95% CI)	SE
Ever other tobacco use ^d (n = 5,094)	9,422				
Never	5,326	13.1 (11.7–14.8)	0.8	3.4 (2.5–4.4)	0.5
Cigarettes only	675	54.7 (48.5–60.6)	3.0	18.4 (13.7–24.4)	2.7
Other combustibles only	947	60.0 (54.4–65.3)	2.7	21.7 (18.0–25.9)	2.0
Noncombustibles only	137	39.8 (30.8–49.6)	4.7	20.2 (12.5–31.0)	4.6
Cigarettes + other combustibles only	1,307	79.6 (74.7–83.8)	2.3	36.3 (31.5–41.3)	2.5
Cigarettes + noncombustibles only	131	61.5 (48.7–72.9)	6.2	25.5 (18.5–34.0)	3.9
Other combustibles + noncombustibles only	171	69.5 (57.1–79.6)	5.7	35.3 (26.1–45.8)	5.0
Cigarettes + other combustibles + noncombustibles only	728	89.2 (82.6–93.5)	2.7	55.0 (47.5–62.4)	3.8
Past-30-day other tobacco use ^e (n = 2,389)	9,416				
No	7,542	27.4 (25.2–29.7)	1.1	7.3 (6.1–8.8)	0.7
Cigarettes only	288	80.8 (74.2–86.0)	2.9	41.1 (32.2–50.6)	4.7
Other combustibles only	701	77.2 (71.2–82.3)	2.8	50.4 (45.0–55.8)	2.7
Noncombustibles only	192	69.6 (54.6–81.4)	6.8	31.2 (23.0–40.9)	4.5
Cigarettes + other combustibles only	353	87.1 (77.5–93.0)	3.8	58.8 (49.1–67.8)	4.7
Cigarettes + noncombustibles only	62	76.9 (59.8–88.2)	7.2	50.8 (27.9–73.5)	12.3
Other combustibles + noncombustibles only	108	88.7 (78.8–94.3)	3.8	74.1 (61.3–83.9)	5.7
Cigarettes + other combustibles + noncombustibles only	170	95.9 (87.2–98.8)	2.4	77.0 (66.6–84.8)	4.6

Source: Centers for Disease Control and Prevention, unpublished data (data: NYTS 2015).

Notes: CI = confidence interval; SE = standard error. *Cigarettes Only* includes those who reported trying cigarettes but not any other tobacco product. *Other combustibles* includes cigars, pipes, and hookah or bidis. *Noncombustibles* includes smokeless tobacco, dissolvables, or snus. *Other Combustibles Only* includes those who reported trying other combustibles but not cigarettes nor noncombustibles. *Noncombustibles Only* includes those who reported trying noncombustibles but not cigarettes nor other combustibles. *Cigarettes and Other Combustibles Only* includes those who reported trying cigarettes and other combustibles but not noncombustibles. *Cigarettes and Noncombustibles Only* includes those who reported trying cigarettes and noncombustibles but not other combustibles. *Other Combustibles and Noncombustibles Only* includes those who reported trying other combustibles and noncombustibles but not cigarettes.

Cigarettes, Other Combustibles, and Noncombustibles includes those who reported trying a product from each group.

^aIncludes those who responded “yes” to the following question, “Have you ever used an electronic cigarette or e-cigarette, even once or twice?”

^bIncludes those who responded “1 or more days” to the following question, “During the past 30 days, on how many days did you use electronic cigarettes or e-cigarettes?”

^cIncludes all respondents categorized into each group. It does not exclude those missing for e-cigarette status.

^dIncludes those who reported trying at least one of the following products (*e-cigarettes not included in the definitions*): *Cigarettes Only*; *Other Combustibles Only*; *Noncombustibles Only*; *Cigarettes and Other Combustibles Only*; *Cigarettes and Noncombustibles Only*; *Other Combustibles and Noncombustibles Only*; and *Cigarettes, Other Combustibles, and Noncombustibles*.

^eIncludes those who reported using at least one of the following products on 1 of the past 30 days (*e-cigarettes were not included in the definitions*): *Cigarettes Only*; *Other Combustibles Only*; *Noncombustibles Only*; *Cigarettes and Other Combustibles Only*; *Cigarettes and Noncombustibles Only*; *Other Combustibles and Noncombustibles Only*; and *Cigarettes, Other Combustibles, and Noncombustibles*.

**Table 2.7a. Percentage of middle school students who have ever used tobacco, by type of product;
National Youth Tobacco Survey (NYTS) 2011–2015**

	2011		2012		2013		2014		2015	
Characteristic	% (95% CI)	SE	% (95% CI)	SE	% (95% CI)	SE	% (95% CI)	SE	% (95% CI)	SE
Any lifetime ^a tobacco use	21.0 (19.2–22.9)	0.9	17.9 (15.9–20.0)	1.0	17.6 (15.6–19.9)	1.1	19.1 (16.7–21.8)	1.3	19.4 (17.0–22.0)	1.2
Any lifetime e-cigarette use ^b	1.4 (1.0–2.0)	0.2	2.7 (2.2–3.2)	0.2	3.0 (2.5–3.5)	0.2	10.1 (8.5–11.9)	0.8	13.5 (11.8–15.5)	0.9
Ever tobacco use ^c										
E-cigarettes only	0.3 (0.2–0.6)	0.1	0.4 (0.3–0.5)	0.1	0.5 (0.3–0.9)	0.1	2.9 (2.3–3.5)	0.3	4.5 (3.9–5.2)	0.3
Combustibles and e-cigarettes only	0.4 (0.3–0.6)	0.1	1.1 (0.9–1.4)	0.1	1.5 (1.1–1.9)	0.2	4.5 (3.9–5.3)	0.4	6.2 (5.4–7.2)	0.5
Noncombustibles and e-cigarettes only	ND	ND	—	—	—	—	0.3 (0.1–0.6)	0.1	0.4 (0.2–0.7)	0.1
Combustibles, noncombustibles, and e-cigarettes	0.5 (0.3–0.9)	0.1	1.1 (0.8–1.4)	0.1	0.8 (0.6–1.2)	0.1	2.2 (1.45–3.2)	0.4	2.2 (1.7–2.9)	0.3
Combustibles only	13.9 (12.5–15.4)	0.7	10.7 (9.5–12.1)	0.7	11.6 (10.1–13.3)	0.8	6.9 (5.6–8.4)	0.7	4.4 (3.7–5.2)	0.4
Noncombustibles only	1.5 (1.1–1.9)	0.2	1.2 (0.9–1.6)	0.2	0.8 (0.6–1.1)	0.1	0.8 (0.5–1.2)	0.2	1.0 (0.7–1.4)	0.2
Combustibles and noncombustibles only	4.3 (3.5–5.1)	0.4	3.4 (2.8–4.0)	0.3	2.4 (1.8–3.2)	0.3	1.5 (1.1–2.1)	0.2	0.7 (0.4–1.1)	0.2
Any past-30-day tobacco use ^d	7.5 (6.4–8.8)	0.6	6.7 (5.8–7.7)	0.5	6.5 (5.43–7.8)	0.6	7.7 (6.7–8.9)	0.6	7.4 (6.3–8.7)	0.6
Any past-30-day e-cigarette use ^e	0.6 (0.4–0.9)	0.1	1.1 (0.9–1.5)	0.1	1.1 (0.8–1.5)	0.2	3.9 (3.0–5.0)	0.5	5.3 (4.6–6.2)	0.4
Past-30-day tobacco use										
E-cigarettes only ^f	0.2 (0.1–0.4)	0.1	0.3 (0.2–0.4)	0.1	0.4 (0.2–0.8)	0.1	1.9 (1.4–2.5)	0.3	2.6 (2.2–3.2)	0.3
Combustibles and e-cigarettes only	0.1 (0.1–0.3)	0.0	0.5 (0.3–0.7)	0.1	0.4 (0.3–0.6)	0.1	1.3 (1.0–1.7)	0.2	1.8 (1.4–2.2)	0.2
Noncombustibles and e-cigarettes only	—	—	—	—	—	—	0.1 (0.1–0.2)	0.0	0.2 (0.1–0.3)	0.0
Combustibles, noncombustibles, and e-cigarettes	0.2 (0.1–0.3)	0.1	0.4 (0.2–0.5)	0.1	0.2 (0.1–0.4)	0.1	0.6 (0.4–0.8)	0.1	0.7 (0.4–1.1)	0.1
Combustibles only	4.5 (3.7–5.5)	0.4	3.7 (3.2–4.3)	0.3	4.0 (3.3–4.9)	0.4	2.7 (2.1–3.3)	0.3	1.2 (0.9–1.6)	0.2
Noncombustibles only	0.9 (0.6–1.3)	0.2	0.7 (0.5–1.0)	0.1	0.6 (0.3–0.9)	0.2	0.7 (0.4–1.2)	0.2	0.6 (0.3–1.2)	0.2
Combustibles and noncombustibles only	1.6 (1.3–2.0)	0.2	1.2 (0.9–1.5)	0.2	0.8 (0.5–1.1)	0.1	0.5 (0.4–0.8)	0.1	0.3 (0.1–0.6)	0.1

Source: Centers for Disease Control and Prevention, unpublished data (data: NYTS 2011–2015).

Notes: CI = confidence interval; ND = no data for this cell; SE = standard error. An em dash (—) indicates that data are statistically unstable because of a relative standard error >40%. Wording of questions used to measure e-cigarette use varied from 2011 to 2015. Cigarettes were not included in this analysis. *Combustibles* includes cigars, pipes, hookahs, or bidis. *Noncombustibles* includes smokeless tobacco, dissolvables, or snus. *Combustibles and E-Cigarettes Only* includes those who reported trying e-cigarettes and combustibles but not noncombustibles. *Noncombustibles and E-Cigarettes Only* includes those who reported trying e-cigarettes and noncombustibles but not combustibles.

Combustibles, Noncombustibles, and E-Cigarettes includes those who reported trying e-cigarettes, noncombustibles, and combustibles. *Combustibles Only* includes those who reported trying combustibles but not noncombustibles or e-cigarettes. *Noncombustibles Only* includes those who reported trying noncombustibles but not combustibles or e-cigarettes. *Combustibles and*

Noncombustibles Only includes those who reported trying noncombustibles and combustibles but not e-cigarettes.

^aIncludes those who reported having tried at least one tobacco product in their lives (e-cigarettes, combustibles, and noncombustibles).

^bIncludes those who reported having tried e-cigarettes in their lives.

^cIncludes those who reported having tried at least one tobacco product in their lives.

^dIncludes those who reported using at least one other tobacco product on at least 1 of the past 30 days.

^eIncludes those who reported using e-cigarettes on at least 1 of the past 30 days.

^fIncludes those who reported using e-cigarettes only on at least 1 of the past 30 days.

**Table 2.7b. Percentage of high school students who have ever used tobacco, by type of product;
National Youth Tobacco Survey (NYTS) 2011–2015**

	2011		2012		2013		2014		2015	
Characteristic	% (95% CI)	SE	% (95% CI)	SE	% (95% CI)	SE	% (95% CI)	SE	% (95% CI)	SE
Any lifetime ^c tobacco use	47.2 (44.0–50.4)	1.6	45.7 (43.0–48.5)	1.4	46.0 (43.3–48.7)	1.4	47.1 (44.5–49.8)	1.3	50.4 (47.9–52.9)	1.3
Any lifetime e-cigarette use ^b	4.7 (3.8–5.7)	0.5	10.0 (8.6–11.6)	0.7	11.9 (10.5–13.5)	0.8	27.3 (24.4–30.5)	1.5	37.7 (35.3–40.2)	1.2
Ever tobacco use ^d										
E-cigarettes only	0.1 (0.1–0.2)	0.0	0.2 (0.2–0.4)	0.0	0.3 (0.2–0.6)	0.1	3.7 (2.9–4.8)	0.5	7.4 (6.6–8.4)	0.5
Combustibles and e-cigarettes only	1.6 (1.3–2.0)	0.2	4.2 (3.5–5.0)	0.4	6.0 (5.2–6.9)	0.4	14.5 (13.2–16.0)	0.7	20.0 (18.6–21.6)	0.8
Noncombustibles and e-cigarettes only	—	—	—	—	—	—	0.3 (0.1–0.4)	0.1	0.6 (0.4–0.8)	0.1
Combustibles, noncombustibles, and e-cigarettes	2.8 (2.2–3.6)	0.4	5.2 (4.3–6.2)	0.5	5.2 (4.2–6.3)	0.5	8.3 (7.0–9.7)	0.7	9.1 (7.6–10.9)	0.8
Combustibles only	29.1 (27.3–30.9)	0.9	25.1 (23.1–27.1)	1.0	25.2 (22.7–27.8)	1.3	15.8 (14.3–17.5)	0.8	10.2 (8.8–11.8)	0.8
Noncombustibles only	1.8 (1.3–2.4)	0.3	1.3 (1.0–1.8)	0.2	1.5 (1.1–1.9)	0.2	1.2 (0.9–1.7)	0.2	0.9 (0.7–1.2)	0.1
Combustibles and noncombustibles only	11.8 (9.8–13.9)	1.1	9.7 (8.6–10.9)	0.6	7.8 (6.6–9.3)	0.7	3.3 (2.6–4.2)	0.4	2.2 (1.6–3.0)	0.4
Any past-30-day tobacco use ^d	24.0 (22.0–26.5)	1.2	23 (21.5–25.2)	0.9	22.9 (21.1–24.9)	0.9	24.6 (22.6–26.7)	1.0	25.3 (23.1–27.6)	1.1
Any past-30-day e-cigarette use ^e	1.5 (1.2–2.0)	0.2	2.8 (2.3–3.5)	0.3	4.5 (3.8–5.3)	0.4	13.4 (11.2–16.1)	1.2	16.0 (14.1–18.0)	1.0
Past-30-day tobacco use										
E-cigarettes only ^f	0.1 (0.1–0.2)	0.0	0.3 (0.2–0.4)	0.1	0.7 (0.5–0.9)	0.1	4.4 (3.4–5.7)	0.6	5.9 (4.9–7.0)	0.5
Combustibles and e-cigarettes only	0.7 (0.5–0.9)	0.1	1.4 (1.1–1.8)	0.2	2.6 (2.1–3.2)	0.3	5.8 (4.9–6.8)	0.5	6.6 (5.7–7.7)	0.5
Noncombustibles and e-cigarettes only	ND	ND	—	—	—	—	0.6 (0.4–0.8)	0.1	0.7 (0.5–0.9)	0.1
Combustibles, noncombustibles, and e-cigarettes	0.6 (0.4–0.9)	0.1	1.1 (0.8–1.4)	0.1	1.1 (0.8–1.4)	0.1	2.5 (2.0–3.2)	0.3	2.6 (2.1–3.3)	0.3
Combustibles only	15.6 (14.5–16.8)	0.6	14.4 (13.2–15.6)	0.6	13.5 (12.4–14.8)	0.6	8.1 (7.2–9.2)	0.5	6.8 (5.9–7.8)	0.5
Noncombustibles only	2.3 (1.7–3.0)	0.3	1.9 (1.4–2.4)	0.2	1.6 (1.2–2.2)	0.3	1.5 (1.1–2.0)	0.2	1.5 (1.0–2.2)	0.3
Combustibles and noncombustibles only	4.9 (4.0–6.1)	0.5	4.3 (3.7–5.2)	0.4	3.4 (2.7–4.3)	0.4	1.6 (1.2–2.2)	0.2	1.1 (0.7–1.8)	0.2

Source: Centers for Disease Control and Prevention, unpublished data (data: NYTS 2011–2015).

Notes: CI = confidence interval; ND = no data for this cell; SE = standard error. An em dash (—) indicates that data are statistically unstable because of a relative standard error >40%. Wording of questions used to measure e-cigarette use varied from 2011 to 2015. Cigarettes were not included in this analysis. *Combustibles* includes cigars, pipes, hookahs, or bidis. *Noncombustibles* includes smokeless tobacco, dissolvables, or snus. *Combustibles and E-Cigarettes Only* includes those who reported trying e-cigarettes and combustibles but not noncombustibles. *Noncombustibles and E-Cigarettes Only* includes those who reported trying e-cigarettes and noncombustibles but not combustibles.

Combustibles, Noncombustibles, and E-Cigarettes includes those who reported trying e-cigarettes, noncombustibles, and combustibles. *Combustibles Only* includes those who reported trying combustibles but not noncombustibles or e-cigarettes. *Noncombustibles Only* includes those who reported trying noncombustibles but not combustibles or e-cigarettes. *Combustibles and Noncombustibles Only* includes those who reported trying noncombustibles and combustibles but not e-cigarettes.

^aIncludes those who reported having tried at least one tobacco product in their lives (e-cigarettes, combustibles, and noncombustibles).

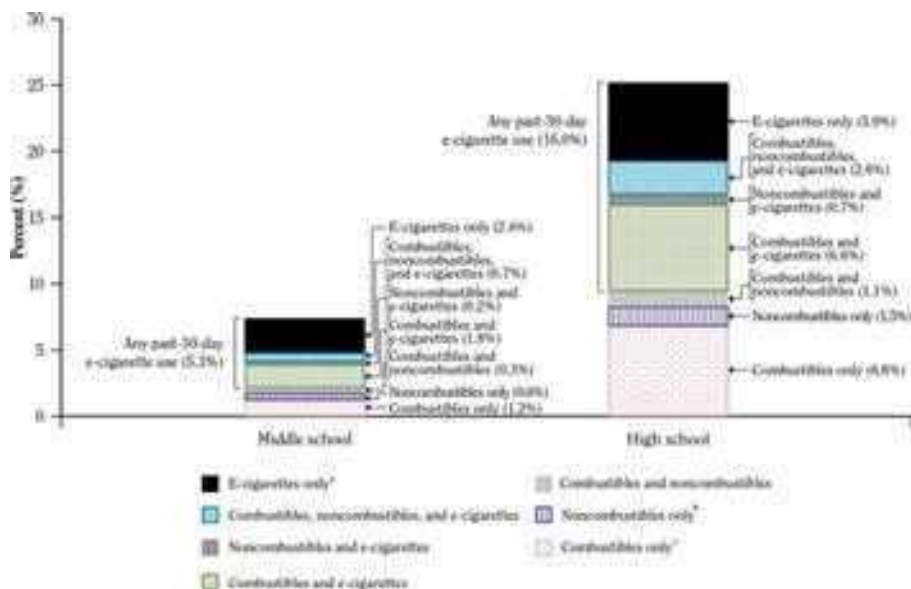
^bIncludes those who reported having tried e-cigarettes in their lives.

^cIncludes those who reported having tried at least one tobacco product in their lives.

^dIncludes those who reported using at least one other tobacco product on at least 1 of the past 30 days.

^eIncludes those who reported using e-cigarettes on at least 1 of the past 30 days.

^fIncludes those who reported using e-cigarettes only on at least 1 of the past 30 days.



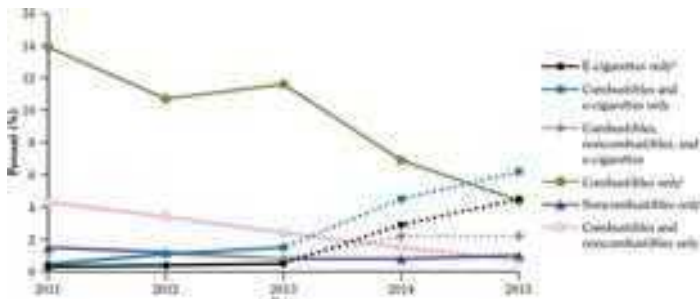
Source: Centers for Disease Control and Prevention 2015b; unpublished data (data: NYTS 2015).

^aIncludes exclusive use of e-cigarettes. It does not include use of any other product.

^bIncludes exclusive use of smokeless tobacco, snus, and/or dissolvable tobacco. It does not include use of combustible products or e-cigarettes.

^cIncludes the use of cigarettes, cigars, pipes, bidis, kreteks, and/or hookahs. It includes participants who reported use of combustible and noncombustible products but not e-cigarettes.

Figure 2.5. Past-30-day use of various tobacco products among U.S. middle and high school students; National Youth Tobacco Survey (NYTS) 2015.



Source: Centers for Disease Control and Prevention, unpublished data (data: NYTS 2011–2015).

Notes: For more information see Table 2.10a. In 2014, modifications were made to the e-cigarette measure to enhance its accuracy, which may limit the comparability of this estimate to those collected in previous years. The dotted lines from 2013 to 2015 represent these differences.

^aIncludes those who reported having tried at least one other tobacco product in their lives.

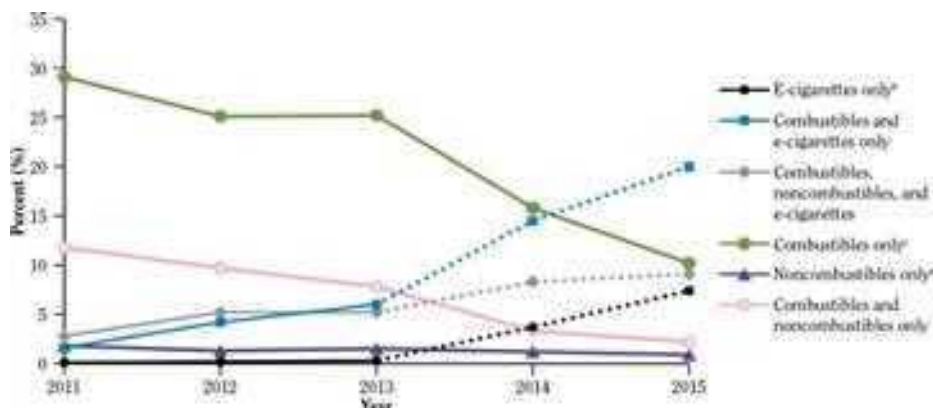
^bIncludes exclusive use of only e-cigarettes. It does not include use of any other product. Ever e-cigarette use includes those who responded “electronic cigarettes or e-cigarettes, such as Ruyan or NJOY” to the following question: “Which of the following tobacco products have you ever tried, even just one time?”

^cIncludes exclusive use of only cigarettes, cigars, pipes, bidis, kreteks, and/or hookahs. It does not include use of noncombustible products or e-cigarettes. They were defined using the following questions: Conventional cigarettes: “Have you ever tried cigarette smoking, even one or two puffs?” and “During the past 30 days, on how many days did you smoke cigarettes?”; cigars: “Have you ever tried smoking cigars, cigarillos, or little cigars, such as Black and Milds, Swisher Sweets, Dutch Masters, White Owl, or Phillies Blunts, even one or two puffs?” and “During the past 30 days, on how many days did you smoke cigars, cigarillos, or little cigars?”; pipes: “Have you ever tried smoking tobacco in a pipe, even one or two puffs?” and “During the past 30 days, on how many days did you smoke tobacco in a pipe?”; and hookahs, kreteks, and bidis: “Which of the following tobacco products have you ever tried, even just one time? (CHOOSE ALL THAT APPLY)” and “During the past 30 days, which of the following products have you used on at least 1 day? (CHOOSE ALL THAT APPLY).”

Figure 2.6. (Continued).

^dIncludes exclusive use of only smokeless tobacco, snus, and/or dissolvable tobacco. It does not include use of combustible products or e-cigarettes. They were defined using the following questions: Smokeless tobacco: “Have you ever used chewing tobacco, snuff, or dip, such as Red Man, Levi Garrett, Beechnut, Skoal, Skoal Bandits, or Copenhagen, even just a small amount?” and “During the past 30 days, on how many days did you use chewing tobacco, snuff, or dip?”; and dissolvables and snus: “Which of the following tobacco products have you ever tried, even just one time? (CHOOSE ALL THAT APPLY)” and “During the past 30 days, which of the following products have you used on at least 1 day? (CHOOSE ALL THAT APPLY).”

Figure 2.6. Percentage of U.S. middle school students who have ever used tobacco^a, by type of product; National Youth Tobacco Survey (NYTS) 2011–2015.



Source: Centers for Disease Control and Prevention, unpublished data (data: NYTS 2011–2015).

Notes: For more information see Table 2.10b. In 2014, modifications were made to the e-cigarette measure to enhance its accuracy, which may limit the comparability of this estimate to those collected in previous years. The dotted lines from 2013 to 2015 represent these differences.

^aIncludes those who reported having tried at least one other tobacco product in their lives.

^bIncludes exclusive use of only e-cigarettes. It does not include use of any other product. Ever e-cigarette use includes those who selected “electronic cigarettes or e-cigarettes, such as Ruyan or NJOY” for the following question: “Which of the following tobacco products have you ever tried, even just one time?”

^cIncludes exclusive use of only cigarettes, cigars, pipes, bidis, kreteks, and/or hookahs. It does not include use of noncombustible products or e-cigarettes. They were defined using the following questions: Conventional cigarettes: “Have you ever tried cigarette smoking, even one or two puffs?” and “During the past 30 days, on how many days did you smoke cigarettes?”; cigars: “Have you ever tried smoking cigars, cigarillos, or little cigars, such as Black and Milds, Swisher Sweets, Dutch Masters, White Owl, or Phillies Blunts, even one or two puffs?” and “During the past 30 days, on how many days did you smoke cigars, cigarillos, or little cigars?”; pipes: “Have you ever tried smoking tobacco in a pipe, even one or two puffs?” and “During the past 30 days, on how many days did you smoke tobacco in a pipe?”; and hookahs, kreteks, and bidis: “Which of the following tobacco products have you ever tried, even just one time? (CHOOSE ALL THAT APPLY)” and “During the past 30 days, which of the following products have you used on at least 1 day? (CHOOSE ALL THAT APPLY).”

^dIncludes exclusive use of only smokeless tobacco, snus, and/or dissolvable tobacco. It does not include use of combustible products or e-cigarettes. They were defined using the following questions: Smokeless tobacco: “Have you ever used chewing tobacco, snuff, or dip, such as Red Man, Levi Garrett, Beechnut, Skoal, Skoal Bandits, or Copenhagen, even just a small amount?” and “During the past 30 days, on how many days did you use chewing tobacco, snuff, or dip?”; and dissolvables and snus: “Which of the following tobacco products have you ever tried, even just one time? (CHOOSE ALL THAT APPLY)” and “During the past 30 days, which of the following products have you used on at least 1 day? (CHOOSE ALL THAT APPLY).”

Figure 2.7. Percentage of U.S. high school students who have ever used tobacco^a, by type of product; National Youth Tobacco Survey (NYTS) 2011–2015.

Young Adults²

Current Prevalence

Using data from the 2013–2014 NATS, current exclusive and combined use of e-cigarettes and cigarettes are presented in Figure 2.8 and Table 2.8a for young adults (18–24 years old), and in Figure 2.8 and Table 2.8b for adults 25 years of age and older. For both age groups, exclusive use of regular cigarettes was the most prevalent pattern of behavior (9.6%, young adults; 13%, adults), followed by dual use of cigarettes and e-cigarettes (7.5%, young adults; 4.2%, adults), and exclusive use of e-cigarettes (6.1%, young adults; 1.6%, adults). Among young adults, combined use of the two products and exclusive use of e-cigarettes were both higher among males than females; combined use was higher among Whites than in Hispanics or Blacks; and both combined use of the two products and exclusive use of e-cigarettes were lowest among those with a college degree.

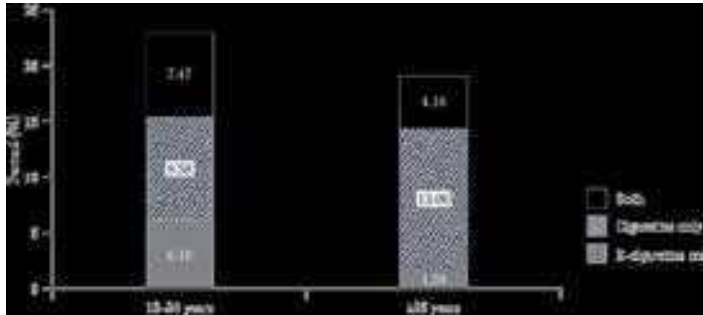
Longitudinal Studies

Understanding the role that e-cigarettes play in the initiation of tobacco product use, especially conventional cigarettes and other combustible tobacco products, such as cigars and hookahs, is extremely important for informing public health policy, planning, and practice. It is unclear what impact e-cigarette use will have on the overall toll of tobacco use on public health (Cobb et al. 2015). Some researchers and policymakers are concerned about the order in which the initiation of tobacco products takes place, positing that the use of e-cigarettes could increase the likelihood that adolescents and young adults who have never used any tobacco products, but initiate e-cigarettes, will become lifetime users of conventional cigarettes or other tobacco products in sufficiently large numbers, resulting in a net harm to public health (USDHHS 2012). Other researchers suggest that the order of product initiation for tobacco products is unimportant and that experimentation with a variety of substances may be a marker of a common vulnerability to tobacco, alcohol, marijuana, and other substance-use behaviors (Vanyukov et al. 2012). Regardless, both of these perspectives on the effect of e-cigarette use on youth and young adults require longitudinal data to understand how current behaviors may affect health outcomes.

Five longitudinal studies to date suggest that e-cigarette use among youth (Leventhal et al. 2015; Barrington-Trimis et al. 2016; Wills et al. 2016) and youth and young adults (Primack et al. 2015; Unger et al. 2016) might lead to initiation of the use of combustible tobacco products in the future. The first study to appear was by Leventhal and colleagues (2015). In this study, a cohort of 9th graders in Los Angeles, California, was followed up at both 6 and 12 months, into 10th grade. Those who at base-line had never used combustible tobacco, but were ever users of an e-cigarette, were more likely to use combustible tobacco products at both follow-up points (odds ratio [OR] = 4.27, 95% confidence interval [CI], 3.19–5.71). Product-specific analyses showed that e-cigarette use in 9th grade was associated with the use of cigars (OR = 4.85, 95% CI, 3.38–6.96), hookahs (OR = 3.25, 95% CI, 2.29–4.62), and cigarettes (OR = 2.65, 95% CI, 1.73–4.05) in 10th grade. It was also associated with the number of different combustible products used in 10th grade (OR = 4.26, 95% CI, 3.16–5.74) (all ORs presented here were averaged across the two time points). In these

² As opposed to the situation in youth, cigarettes are the most commonly used tobacco product among young adults. Therefore, this chapter does not assess co-use of e-cigarettes and other tobacco products among young adults.

analyses, Leventhal and colleagues (2015) adjusted for demographic characteristics (age, gender, race/ethnicity, highest parental education), social factors (peer smoking, parental smoking), and intrapersonal factors (depression, impulsivity, delinquent behaviors) linked with cigarette smoking in previous research.



Source: Centers for Disease Control and Prevention, unpublished data (data: NATS 2013–2014).

^aCurrent e-cigarette use was defined as those who reported they had heard of e-cigarettes and had tried e-cigarettes, and reported using e-cigarettes every day, some days, or rarely at the time of the interview.

Figure 2.8. Percentage of young adults who currently use e-cigarettes^a and conventional cigarettes; National Adult Tobacco Survey (NATS) 2013–2014.

Table 2.8a. Percentage of young adults (18–24 years of age) who currently use e-cigarettes^a, cigarettes^b, or both^c products, by gender, race/ethnicity, and education: National Adult Tobacco Survey (NATS) 2013–2014

	Neither ^d		E-cigarettes only ^e		Cigarettes only ^f		Both ^c	
Characteristic	% (95% CI)	SE	% (95% CI)	SE	% (95% CI)	SE	% (95% CI)	SE
Overall	76.8 (75.3–78.3)	0.8	6.1 (5.3–7.0)	0.4	9.6 (8.6–10.7)	0.5	7.5 (6.6–8.4)	0.5
Gender								
Female	81.8 (79.7–83.7)	1.0	4.0 (3.1–5.2)	0.5	8.4 (7.1–9.9)	0.7	5.8 (4.7–7.2)	0.6
Male	72.3 (70.1–74.4)	1.1	8.1 (6.9–9.4)	0.6	10.6 (9.2–12.2)	0.8	9.0 (7.7–10.4)	0.7
Race/ethnicity								
White	72.8 (70.7–74.8)	1.1	6.3 (5.3–7.5)	0.6	11.2 (9.8–12.8)	0.8	9.7 (8.4–11.2)	0.7
Black or African American	84.8 (80.8–88.2)	1.9	2.9 (1.7–4.9)	0.8	9.8 (7.0–13.5)	1.6	2.5 (1.4–4.4)	0.7
Hispanic or Latino	80.5 (77.0–83.6)	1.7	7.5 (5.7–9.7)	1.0	6.1 (4.3–8.5)	1.1	5.9 (4.2–8.3)	1.1
Other ^g	79.8 (75.5–83.5)	2.1	5.7 (3.8–8.6)	1.2	9.4 (6.9–12.5)	1.4	5.1 (3.4–7.6)	1.0
Education								
<High school	67.4 (61.7–72.6)	2.8	5.8 (3.7–9.1)	1.3	17.3 (13.4–22.1)	2.2	9.4 (6.6–13.3)	1.7
High school	74.4 (71.9–76.7)	1.2	6.5 (5.3–7.8)	0.6	10.7 (9.2–12.5)	0.8	8.5 (7.0–10.1)	0.8
Some college ^h	78.2 (75.8–80.4)	1.2	7.3 (5.9–9.0)	0.8	7.2 (5.9–8.7)	0.7	7.3 (6.1–8.8)	0.7
College degree ⁱ	92.5 (90.2–94.4)	1.1	2.3 (1.4–3.9)	0.6	3.1 (2.0–4.7)	0.7	2.1 (1.2–3.5)	0.6

Source: Centers for Disease Control and Prevention, unpublished data (data: NATS 2013–2014).

Note: CI = confidence interval; SE = standard error.

^aIncludes those who reported they had heard of, tried, and used e-cigarettes every day, some days, or rarely at the time of the interview.

^bIncludes those who smoked at least 100 cigarettes and reported using cigarettes every day or some days at the time of the interview.

^cIncludes those who reported currently using both e-cigarettes and conventional cigarettes.

^dIncludes those who reported currently using neither conventional cigarettes nor e-cigarettes.

^eIncludes those who reported currently using e-cigarettes but not conventional cigarettes.

^fIncludes those who reported currently using conventional cigarettes but not electronic e-cigarettes.

^gIncludes non-Hispanic Asian, non-Hispanic Native Hawaiian/Other Pacific Islander, non-Hispanic American Indian/ Alaska Native, and multiracial.

^hIncludes some college, no degree; associate's degree, academic program; associate's degree, unspecified; certificate; diploma; or associate's degree.

ⁱIncludes bachelor's degree, master's/professional school degree, or doctoral degree.

**Table 2.8b. Percentage of adults (≥ 25 years of age) who currently use e-cigarettes^a, cigarettes^b, or both^c products, by gender, race/ethnicity, and education:
National Adult Tobacco Survey (NATS) 2013–2014**

	Neither ^d		E-cigarettes only ^e		Cigarettes only ^f		Both ^c	
Characteristic	% (95% CI)	SE	% (95% CI)	SE	% (95% CI)	SE	% (95% CI)	SE
Overall	81.3 (80.8–81.7)	0.2	1.6 (1.5–1.7)	0.1	13.0 (12.6–13.4)	0.2	4.2 (3.9–4.4)	0.1
Gender								
Female	83.4 (82.8–84.0)	0.3	1.3 (1.1–1.4)	0.1	11.5 (11.0–12.0)	0.3	3.8 (3.5–4.1)	0.2
Male	78.8 (78.1–79.5)	0.4	2.0 (1.7–2.2)	0.1	14.6 (14.0–15.3)	0.3	4.6 (4.2–5.0)	0.2
Race/ethnicity								
White	82.1 (81.6–82.6)	0.3	1.6 (1.5–1.8)	0.1	11.9 (11.5–12.3)	0.2	4.4 (4.1–4.7)	0.1
Black or African American	76.2 (74.6–77.7)	0.8	0.9 (0.7–1.3)	0.2	20.0 (18.6–21.5)	0.7	2.9 (2.4–3.5)	0.3
Hispanic or Latino	83.2 (81.6–84.6)	0.8	1.5 (1.1–2.0)	0.2	12.0 (10.7–13.3)	0.7	3.4 (2.7–4.2)	0.4
Other ^g	77.5 (75.6–79.4)	1.0	2.5 (1.9–3.3)	0.4	14.5 (13.0–16.1)	0.8	5.5 (4.4–6.7)	0.6
Education								
<High school	71.3 (69.5–73.1)	0.9	1.0 (0.7–1.4)	0.2	23.5 (21.8–25.2)	0.9	4.2 (3.5–5.1)	0.4
High school	75.4 (74.4–76.4)	0.5	1.8 (1.5–2.2)	0.2	16.9 (16.1–17.8)	0.4	5.9 (5.3–6.5)	0.3
Some college ^h	79.2 (78.4–80.0)	0.4	2.0 (1.8–2.3)	0.1	13.4 (12.7–14.1)	0.3	5.3 (4.9–5.8)	0.2
College degree ⁱ	92.5 (92.1–93.0)	0.2	1.2 (1.0–1.4)	0.1	4.7 (4.3–5.0)	0.2	1.6 (1.4–1.8)	0.1

Source: Centers for Disease Control and Prevention, unpublished data (data: NATS 2013–2014).

Note: CI = confidence interval; SE = standard error.

^aIncludes those who reported they had heard of, tried, and used e-cigarettes every day, some days, or rarely at the time of the interview.

^bIncludes those who smoked at least 100 cigarettes and reported using cigarettes every day or some days at the time of the interview.

^cIncludes those who reported currently using both e-cigarettes and conventional cigarettes.

^dIncludes those who reported currently using neither conventional cigarettes nor e-cigarettes.

^eIncludes those who reported currently using e-cigarettes but not conventional cigarettes.

^fIncludes those who reported currently using conventional cigarettes but not e-cigarettes.

^gIncludes non-Hispanic Asian, non-Hispanic Native Hawaiian/Other Pacific Islander, non-Hispanic American Indian/Alaska Native, and multiracial.

^hIncludes some college, no degree; associate's degree: academic program; associate's degree, unspecified; certificate; diploma; or associate's degree.

ⁱIncludes bachelor's degree, master's/professional school degree, or doctoral degree.

Primack and colleagues (2015), in a national cohort study, followed youth and young adults, 16–26 years of age, for 1 year. At baseline, only 16 participants (2.3%) had ever used e-cigarettes. In adjusted models that included only those who did not use conventional cigarettes at base-line and adjusted for gender, age, race/ethnicity, maternal educational level, sensation seeking, parental cigarette smoking, and peer cigarette smoking, baseline e-cigarette use was independently associated with progression to cigarette smoking (OR = 8.3, 95% CI, 1.2–58.6) and susceptibility to cigarette smoking (OR = 8.5, 95% CI, 1.3–57.2). Susceptibility was defined as a lack of a firm commitment not to smoke using established measures of this construct (Evans et al. 1995; Pierce et al. 1996).

Wills and colleagues (2016) followed a cohort of 2,338 students in grades 9 and 10 in Hawaii for 1 year. At baseline, 31% of the sample had ever used an e-cigarette, and 15% had ever used a conventional cigarette. One year later, these increased to 38% and 21%, respectively. Of those who had not used either of these products at baseline, 10% initiated exclusive e-cigarette use 1 year later; 2% initiated exclusive conventional cigarette use; and 4% initiated use of both products. Students who had never smoked a conventional cigarette at baseline but had used an e-cigarette at baseline were three times more likely to smoke

conventional cigarettes 1 year later (adjusted OR = 2.87, $p < 0.001$). By comparison, among those who smoked conventional cigarettes at baseline, use of e-cigarettes at that same point in time was not related to any reduction in the use of conventional cigarettes 1 year later ($p > 0.05$). Moreover, students were more likely to transition from never use to dual use of both products 1 year later if they were older, Caucasian or Native Hawaiian (compared with Asian-American), more rebellious, and perceived e-cigarettes as healthier (adjusted OR = 2.05, 2.15, 3.10, 3.32, 2.59, respectively, all $p < 0.001$).

Barrington-Trimis and colleagues (2016) followed a cohort of 11th and 12th grade students in California for more than 1 year (median 15.6 months). In this cohort, at baseline, 146 were ever e-cigarette users and 152 were never e-cigarette users; none had ever smoked a cigarette. Among never e-cigarette users at baseline, 16 participants (10.5%) reported using cigarettes at follow-up; among ever e-cigarette users at baseline, 59 participants (40.4%) reported the same (OR = 6.17; 95% CI, 3.30–11.60). After adjusting for cigar, pipe, or hookah use at baseline, the relationship attenuated only somewhat (OR = 5.48; 95% CI, 2.69–11.20). When stratified by susceptibility to cigarette smoking at baseline (defined, like Primack and colleagues [2015], as the lack of a firm commitment not to smoke using established measures of this construct [Evans et al. 1995; Pierce et al. 1996]), the relationship was actually stronger among those who were not susceptible (OR = 9.69; 95% CI, 4.02–23.40) compared to those who were susceptible (OR = 2.12; 95% CI, 0.79–5.74). The latter relationship was not statistically significant. In additional analyses that were restricted to those who reported no use of any combustible tobacco product at baseline, e-cigarette users were more likely to initiate use of any combustible tobacco product at follow-up (OR = 4.98; 95% CI, 2.37–10.4), including the use of cigarettes (OR = 4.29; 95% CI, 1.84–10.0), hookahs (OR = 2.86; 95% CI, 1.21–6.78), cigars (OR = 4.39; 95% CI, 1.72–11.2), and pipes (OR = 8.21; 95% CI, 1.20–56.2). The models used by Barrington-Trimis and colleagues (2016) adjusted for a variety of demographic characteristics (grade, gender, race/ethnicity, highest parental education) and social factors (peer and parental smoking). Additionally, gender, race/ethnicity (Hispanic White, non-Hispanic White, other), grade (11th or 12th), and ever use of hookahs were tested as potential effect modifiers of these associations, but no evidence was found for the same.

Unger and colleagues (2016) followed a cohort of 1,332 Hispanic young adults in California who provided survey data in 2014 and 2015. At baseline, these participants were an average of 22.7 years old. E-cigarette use at baseline was significantly associated with cigarette smoking (OR = 3.32; 95% CI, 1.55–7.10, among non-cigarette smokers at baseline) and marijuana use (OR = 1.97; 95% CI, 1.01–3.86, among non-marijuana users at baseline) at follow-up. Among those who did not smoke cigarettes at baseline ($n = 1,056$), 42 reported past month e-cigarette use in 2014; 26% of those who smoked e-cigarettes at baseline became cigarette smokers in 2015, compared to 7% of those who did not smoke e-cigarettes. Further, among those who did not smoke marijuana at baseline ($n = 1,028$), 68 reported past month e-cigarette use in 2014; 24% of those who smoked e-cigarettes at baseline became marijuana smokers in 2015, compared to 12% of those who did not smoke e-cigarettes. Moreover, in this study, e-cigarette use at baseline was *not* associated with cessation of cigarette smoking (OR = 1.31; 95% CI, 0.73–2.36) or marijuana use (OR = 1.05; 95% CI, 0.54–2.01) at follow-up. Among those who did smoke cigarettes at baseline ($n = 276$), 76% reported past month e-cigarette use in 2014; and 63% of those who smoked e-cigarettes at baseline were still smoking cigarettes at follow-up, compared to 58% of those who did not smoke e-cigarettes.

Covariates in these regression models included age, gender, past month use of alcohol, and past month use of other tobacco products (hookah, cigars, little cigars, smokeless tobacco).

Despite the several strengths of these studies, including their longitudinal nature, they had weaknesses as well. Rigotti (2015) notes, for example, that the study by Leventhal and colleagues (2015) could not distinguish between those who merely began experimenting with a combustible product and those who became regular smokers at follow-up. The same could be said for the studies by Barrington-Trimis and colleagues (2016), Primack and colleagues (2015), and Wills and colleagues (2016). Similarly, the single exposure measure of the independent variable (i.e., any e-cigarette use) in these studies did not allow the authors to assess whether there was a dose–response relationship between the extent of prior e-cigarette use and subsequent use of combustible tobacco products. In addition, the studies by Primack and colleagues (2015) and Wills and colleagues (2016) did not assess prior use at baseline of other tobacco products, marijuana, or alcohol. Though it is not highlighted prominently in their article, Leventhal and colleagues (2015) showed a bidirectional relationship between e-cigarette use and other combustible tobacco product use in their study: Use of other combustible tobacco products at baseline was significantly associated with the onset of e-cigarette use in two follow-ups. This hypothesis was not tested by Barrington-Trimis and colleagues (2016), Wills and colleagues (2016), or Primack and colleagues (2015). However, at the 1-year follow-up, Wills and colleagues (2016) did consider other demographics, personality, and psychosocial predictors of exclusive e-cigarette use and dual use of conventional cigarettes and e-cigarettes.

Concerns about the samples for the two studies can be raised as well. The samples in the studies by Barrington-Trimis and colleagues (2016) and Leventhal and colleagues (2015) were limited to youth in California; the study by Primack and colleagues (2015) suffered from a small sample size, with only 16 e-cigarette users at baseline (Leventhal et al. 2015; Primack et al. 2015); and the study by Wills and colleagues (2016) was limited to 9th- and 10th-grade students in Hawaii. Additional studies are still needed in the future to further elucidate any causal relationship in either direction between the use of e-cigarettes and other types of tobacco products, such as combustibles.

E-Cigarette Use and Other Substance Use

Few studies have investigated the co-occurrence of e-cigarette use and other risk behaviors in adolescents and young adults. The available evidence suggests that e-cigarette use is associated not only with the use of other tobacco products, but also with alcohol and other substance use, such as marijuana. This is consistent with the common liability model for substance use and other risky behaviors (Vanyukov et al. 2012). Because nearly all currently available studies on this topic focus on regional, international, and at-risk samples, the conclusions from most studies cannot be generalized to the U.S. population as a whole, however.

In the only nationally representative study examining the associations between e-cigarettes, alcohol, and other drug use in young adults 18–24 years of age, the odds of alcohol use were nine times as high and the odds of everyday/some-day marijuana use were three-and-a-half times as high among past-30-day e-cigarette users as they were for those who had not used these products in that period (Cohn et al. 2015). Elsewhere, in a nonprobability sample of college students 17–25 years of age, 66% of current e-cigarette users and 67% of current dual users were heavy drinkers, defined as consuming at least once, five or more

drinks (men) or four or more drinks (women) in a single sitting during the course of 1 month (Littlefield et al. 2015). In another study, this one of college students in New York, past-30-day use of e-cigarettes was positively associated with current binge drinking and tobacco product use, and it was less common among those 20–23 years of age (versus those 18 years of age), females, non-Hispanic non-Whites (compared with non-Hispanic Whites), and those reporting better-than-average school performance (Saddleson et al. 2015).

Data from a longitudinal cohort study of children with alcoholic parents found that adolescents (both middle and late adolescence) who used cigarettes, marijuana, or alcohol were significantly more likely to have ever used e-cigarettes. Among those who had used marijuana, e-cigarette use was associated with greater use of marijuana during the previous 30 days (Lessard et al. 2014). In a cross-sectional pilot study of seventh-grade students in Southern California, ever use of e-cigarettes was 11%, compared to 6.8% for cigarettes, 38.1% for alcohol, and 39% for cigarettes or alcohol. In this study, 80% of ever users of e-cigarettes had used alcohol, and 42.2% had used conventional cigarettes (Pentz et al. 2015).

In a 2013 sample of students ($n = 2,002$) in two states in the southeastern United States, 53.4% of e-cigarette users also used marijuana (Berg et al. 2015). Elsewhere, in a sample of young adults (18–23 years of age) at colleges and universities that was taken in 2013 in upstate New York ($n = 1,437$), 54.2% of past-30-day marijuana users, 23.9% of past-30-day alcohol users, and 40.3% of past-30-day binge drinkers had ever used e-cigarettes (Saddleson et al. 2015). In Switzerland, among a sample of eighth graders, nearly 60% of regular e-cigarette users “had been drunk” at least once in the past 30 days (defined as an affirmative response to the question, “have you been drunk in the previous 30 days”), and 44.8% had used marijuana at least once during that period (Suris et al. 2015).

There are several limitations to these observational studies. For example, when considering the associations derived from these observational studies, the order of initiation of the products of interest cannot be inferred. In addition, some biases cannot be ruled out because of the nature of the samples, and patterns of associations may reflect an underlying common liability to use substances and take part in other risky behaviors. Some studies adjusted for risk taking, sensation seeking, and impulsivity, while others did not.

E-Cigarettes and Marijuana

Because of their design, e-cigarettes may facilitate drug use among youth and young adults, as these products can be used as a delivery system for cannabinoids and other illicit drugs (Giroud et al. 2015; Morean et al. 2015; Schauer et al. 2016). The aerosolization of cannabis is a relatively new technology used to deliver inhaled tetrahydrocannabinol (THC) and other cannabinoids while reducing the toxic byproducts of smoked cannabis, which are primarily caused by combustion (Abrams et al. 2007). Laboratory studies of prototype aerosolizers have demonstrated that they can provide a relatively effective mode of delivering THC, with plasma THC concentrations similar to those obtained from smoking a standard marijuana cigarette (Abrams et al. 2007; Giroud et al. 2015). In addition, thermal metered-dose cannabis inhalers have been developed for medical applications; their technology is similar to that of e-cigarettes (Eisenberg et al. 2014). While the first generation of cannabis aerosolizers was developed to aerosolize dry cannabis, the widespread availability of e-cigarettes and rapid advances in their technology have led to the development of liquid/oil forms of cannabis/THC that can be used with e-cigarettes in a fashion similar to that employed when they are filled with nicotine (Giroud et al. 2015). Articles explaining how to

acquire and use THC-containing liquid using e-cigarette technology are accessible on the Internet and are strongly suggestive of relatively widespread awareness and use (Gray 2013).

The actual prevalence of users of marijuana aerosolizers and their experiences remain unclear and understudied (Van Dam and Earleywine 2010; Malouff et al. 2014). In one of the few published studies on this issue specific to youth, Morean and colleagues (2015) found that, among high school students in Connecticut, vaporizing cannabis was common among ever e-cigarette users (18%), ever cannabis users (18.4%), and ever dual users (26.5%). This finding suggests a need for more specific surveillance measures that take into account the use of drugs other than nicotine in e-cigarettes.

Use of Flavored E-Cigarettes

The liquid that is vaporized in an e-cigarette is available to consumers in a wide variety of flavors, including tobacco, mint/menthol, and fruit flavors. Although characterizing “flavors” are prohibited in cigarettes (with the exception of menthol and tobacco) by the *Family Smoking Prevention and Tobacco Control Act of 2009*, this practice is not currently prohibited in other tobacco products, like e-cigarettes. Retail sales data suggest that the consumption of flavored e-cigarettes and tobacco products, such as flavored cigars, has increased in recent years (Delnevo et al. 2015; Giovenco et al. 2015), and recent studies show that youth and young adults may find these flavored products more appealing than their unflavored counterparts (Table 2.9) (Ambrose et al. 2015; Krishnan-Sarin et al. 2015; McDonald and Ling 2015).

Data on the use of flavored e-cigarettes among youth and young adults is presented in Table 2.9. In the 2015 NYTS, participants were asked about any current use of e-cigarettes that were “flavored to taste like menthol (mint), alcohol (wine, cognac), candy, fruit, chocolate, or other sweets” (CDC 2015a, 1066). Among middle and high school students who were past-30-day users of e-cigarettes, 44.6%, had used a flavored e-cigarette in that timeframe (CDC, unpublished data [NYTS 2015]); this included 42.6% of middle school students and 45.1% of high school students (Table 2.9) (CDC 2015a). The use of flavored e-cigarettes did not differ by gender and was lowest among Blacks (Table 2.9) (CDC 2015a). The use of flavored e-cigarettes was highest among young adults, according to the 2013–2014 NATS (Table 2.9): among those who reported using e-cigarettes every day or some days, 91.6% of young adults (18–24 years old) reported using an e-cigarette flavored to taste like menthol, mint, clover, spice, candy, fruit, chocolate, or other sweets. On the other hand, 66.6% of adults (≥ 25 years of age) who reported using e-cigarettes every day or some days had used flavored e-cigarettes. No gender differences were noted for young adults, but Blacks, as with middle and high school students, reported the lowest rate of using flavored e-cigarette products.

Data from the 2013–2014 wave of the PATH study revealed that a majority of adolescents who used e-cigarettes use flavors. Of those who had ever tried e-cigarettes, 81% used flavors the first time they tried an e-cigarette; of past-30-day users, 85.3% regularly used flavored e-cigarettes (Ambrose et al. 2015). Ambrose and colleagues (2015) also reported that 81.5% of respondents aged 12–17 reported that they used e-cigarettes because “they come in flavors I like.” Elsewhere, among 8th, 10th, and 12th graders in the 2015 MTF study, about 40% said that the primary reason they used e-cigarettes was “because they tasted good.” In contrast, about 10% said they used e-cigarettes to quit smoking conventional cigarettes (University of Michigan 2015). In the 2015 MTF study, about two-thirds of 8th-, 10th-, and

12th-grade students said that they used “just flavouring” in their vaporizer when they “last used” a vaporizer, while only 20% reported that they used nicotine (Miech et al. 2016). While the findings specific to nicotine are unexpected, it is important to note that these data are self-reported. It is questionable whether youth know what nicotine is, let alone whether it is contained in the e-cigarette products that they are using. Moreover, even if youth were accurately reporting nicotine strength according to the label on the package, a study by Buettner-Schmidt and colleagues (2016) found that more than half of the labels on assessed e-cigarette products did not accurately reflect actual nicotine content in the product. Therefore, further research on nicotine content using objective measures (e.g., retail sales data) is warranted. Both the PATH and MTF studies, however, reinforce that flavorings may play an important role in the initiation of e-cigarette use.

Table 2.9. Percentage of youth (middle and high school students), young adults (18–24 years of age), and adults (≥25 years of age) using tobacco products who reported using flavored e-cigarette products, by gender and race/ethnicity; National Youth Tobacco Survey (NYTS)^a and National Adult Tobacco Survey (NATS)^b

	NYTS 2015 ^a (youth): Middle school students		NYTS 2015 ^a (youth): High school students		NATS 2013–2014 ^b (young adults): 18–24 years of age		NATS 2013–2014 ^b (adults): ≥25 years of age	
Characteristic	% (95% CI)	SE	% (95% CI)	SE	% (95% CI)	SE	% (95% CI)	SE
Overall	42.6 (36.1–49.3)	3.3	45.1 (40.4–49.9)	2.4	91.6 (87.0–94.6)	1.9	66.6 (63.4–69.5)	1.6
Gender								
Female	45.5 (36.2–55.2)	4.8	46.8 (40.5–53.2)	3.2	90.1 (78.6–95.7)	4.1	68.2 (63.7–72.3)	2.2
Male	40.2 (32.2–48.7)	4.2	44.0 (39.3–48.8)	2.4	92.2 (87.0–95.4)	2.1	65.2 (60.7–69.4)	2.2
Race/ethnicity								
White	52.5 (42.0–62.8)	5.3	51.4 (45.7–57.0)	2.9	90.9 (84.7–94.7)	2.5	61.2 (57.5–64.8)	1.9
Black or African American	32.9 (18.5–51.6)	8.6	20.4 (12.8–31.0)	4.5	100 (100–100) ^c	0.0 ^c	92.0 (82.1–96.6)	3.5
Hispanic or Latino	28.5 (20.5–38.1)	4.4	38.8 (32.7–45.3)	3.2	89.8 (75.3–96.2) ^c	5.0 ^c	85.9 (76.6–91.9)	3.8
Other ^d	57.3 (39.4–73.5)	8.9	34.1 (24.8–44.9)	5.1	94.4 (82.1–98.4) ^c	3.5 ^c	67.4 (57.0–76.3)	5.0

Source: Centers for Disease Control and Prevention, unpublished data (data: NYTS 2015; NATS 2013–2014).

Note: CI = confidence interval; SE = standard error.

^aFlavored e-cigarette product use in NYTS was determined by the response to the question, “Which of the following tobacco products that you used in the past 30 days were flavored to taste like menthol (mint), alcohol (wine, cognac), candy, fruit, chocolate, or other sweets?” Participants could select from a list of options to designate the flavored tobacco product(s) they used. (Among those who reported any use of e-cigarettes in the preceding 30 days.) Those who selected e-cigarettes were coded as “yes” for flavored e-cigarettes. Those who did not select e-cigarettes were categorized as “no” for flavored e-cigarettes. Excludes 82 current e-cigarette users whose answers were missing for all flavored tobacco response options.

^bFlavored e-cigarette product use in NATS was determined by the response to the question, “Were any of the electronic cigarettes that you used in the past 30 days flavored to taste like menthol, mint, clover, spice, candy, fruit, chocolate, or other sweets?” (Among those who reported using e-cigarettes every day or some days.) Those who selected “yes” were categorized as “yes” for flavored e-cigarettes. Those who selected “no” were categorized as “no” for flavored e-cigarettes. Excludes five every-day or some-day users who reported not using any noncigarette tobacco product in the past 30 days.

^cSample size <50. No estimates had a relative SE >.40.

^dIncludes non-Hispanic Asian, non-Hispanic Native Hawaiian/Other Pacific Islander, and non-Hispanic American Indian/Alaska Native. For young adults and adults, this group also includes multiracial.

Other regional studies have reinforced the popularity of flavored e-cigarette use among youth. Table 2.10 summarizes these data on the use of flavored e-cigarettes among youth and young adults. Krishnan-Sarin and colleagues (2015), for example, found that sweet-flavored

e-cigarettes were popular among middle and high school students. In another study, which examined nonsmoking middle and high school students and college-aged adults in New Haven County, Connecticut, Kong and colleagues (2015) found that “appealing flavors” was the second most common reason cited for experimenting with e-cigarettes, and in a qualitative study of young adults living in New York City, flavors were identified as an attractive aspect of e-cigarettes (McDonald and Ling 2015). In a study examining nonsmoking teens and adult smokers, the e-cigarette flavors tested appealed more to adults than to teens; non-smoking teens demonstrated equally low levels of interest in tobacco, fruit, and candy flavors (Shiffman et al. 2015). It should be noted, however, that this study was funded by NJOY, an e-cigarette company and, therefore, may have suffered from commercial bias. Additional concerns about this study concerning selection bias, validity of the survey measures, and reliability of the findings have been raised (Glantz 2015).

Consumer Perceptions of E-Cigarettes

Perceived Harm of E-Cigarettes

In the general population of U.S. adults, e-cigarettes have been perceived to be generally less harmful (Pearson et al. 2012; Czoli et al. 2014; Gallus et al. 2014; Richardson et al. 2014; Berg et al. 2015; Pokhrel et al. 2015) and less addictive (Dockrell et al. 2013; Li et al. 2013; Brown et al. 2014; Farsalinos et al. 2015; Harrell et al. 2015; Hendricks et al. 2015; Kadimpati et al. 2015; Wackowski and Delnevo 2015) than conventional cigarettes. The perceived harm of e-cigarettes relative to conventional cigarettes was lowest among those who were current smokers, followed by former smokers and then nonsmokers (Pearson et al. 2012; Richardson et al. 2014). In a nationally representative sample of U.S. adults, young adults 18–34 years of age were more likely than their older counterparts to perceive e-cigarettes as being less harmful than conventional cigarettes (Tan and Bigman 2014).

Table 2.10. Summary of studies on e-cigarette flavors among youth and young adults

Study	Design/population	Measures	Outcomes/findings
Ambrose et al. (2015)	• Cross-sectional • Wave 1 of PATH study • Household-based, nationally representative survey of 13,651 youth 12–17 years of age	• For each product ever used, youth were asked if it was flavored to taste like menthol, mint, clove, spice, candy, fruit, chocolate, alcohol (such as wine or cognac), or other sweets	• 81% of e-cigarette ever users used a flavored product at first use • 85.3% of past-30-day e-cigarette users used a flavored product • 81.5% of past-30-day users cited “because they come in flavors I like” as a reason for using e-cigarettes
Berg et al. (2015)	• Cross-sectional • Recruitment through Facebook targeting of tobacco and marijuana users and nonusers • 2014 • 1,567 participants, 18–34 years of age, living in the United States	• E-cigarette use (ever tried, number of days in past 30 days) • Flavors used or of interest	• Most commonly used flavor was fruit flavors (67%), which was most commonly reported by never cigarette smokers. • Current smokers were most likely to report using tobacco flavors, but least likely to report using caramel, vanilla, chocolate, cream, or candy flavors.
CDC (2015a)	• Cross-sectional • 2014 NYTS data • Three-stage cluster sampling procedure • Nationally representative sample of 22,007 U.S. middle and high school students	• Participants were asked about any current use of tobacco products that were “flavored to taste like menthol (mint), alcohol (wine, cognac), candy, fruit, chocolate, or other sweets” • Participants could select from a list of options	• Among current e-cigarette users, 63.3% used a flavored product

Study	Design/population	Measures	Outcomes/findings
Kong et al. (2015)	• Cross-sectional • 18 focus groups, schoolwide survey • Recruitment by flyers and active recruitment sessions • Years sample drawn: 2012–2013 • New Haven County, Connecticut • Youth: Middle and high school students; focus group n = 127 (youth); survey n = 4,780 • Young adults: New Haven County, Connecticut, college students; focus group n = 127 (young adults); survey n = 625	• Why did you try an e-cigarette?	• 43.8% of e-cigarette ever users experimented with e-cigarettes for the availability of appealing flavors School-level differences: $\chi^2(2, N = 1,157) = 18.63$, $p \leq 0.001$ • Compared with college students, high school students were more likely to experiment with e-cigarettes because of flavors (47% vs. 32.8%): $\chi^2(1, N = 1,116) = 13.61$, $p \leq 0.001$
Krishnan-Sarin et al. (2015)	• Cross-sectional • School-based survey • Recruitment by selected district reference groups • Year sample drawn: 2013 • Youth: Connecticut middle (n = 1,166) and high school (n = 3,614) students • Young adults: n/a	• Which of the following flavors of e-cigarettes have you tried?	• Most e-cigarette ever users preferred sweet flavors: • Sweet flavors: 56.8% • Menthol: 8.7% • Combos: 7.7% • Tobacco: 3% • Other: 2.8% • Menthol and tobacco flavors used mostly by e-cigarette users who were also cigarette smokers. • Menthol preference: • 3.5% (never smokers) • 5.5% (ever smokers) • 18.6 (current smokers) • Tobacco preference: • 0.5% (never smokers) • 2.4% (ever smokers) • 7.1% (current smokers)
McDonald and Ling (2015)	• Focus groups and semistructured interviews • Recruitment from bars through screener surveys • Years sample drawn: 2012–2013 • Youth: n/a • Young adults: 87 young adults, 18–27 years of age, in the boroughs of Manhattan, Brooklyn, and Queens in New York City	• Attraction to flavors	• Flavors were an attractive e-cigarette characteristic
Shiffman et al. (2015)	• Cross-sectional • Participants drawn from online research panel • Year sample drawn: 2014 • Youth: Nonsmoking teenagers, 13–17 years of age • Young adults: n/a	• Interest in e-cigarettes paired with various flavor descriptors	• Nonsmoking teens' interest in e-cigarettes was very low • (mean = 0.41 ± 0.14 [SE] on 0–10 scale). • Teen interest did not vary by flavor ($p = .75$)
Ford et al. (2016)	• Cross-sectional in-home survey • Wave 7 of the Youth Tobacco Policy Survey (YTPS) • Random location quota sampling • 1,205 youth, 11–16 years of age, in the United Kingdom	• Awareness of e-cigarettes • E-cigarette use • E-cigarette flavor awareness • Perceptions of harm	• 12% had tried e-cigarettes • 2% were regular users (confined to adolescents who had also smoked tobacco) • 82% were aware of at least one promotional channel (82%) • 69% were aware that e-cigarettes came in different flavours • Brand awareness was low • E-cigarettes were perceived as harmful (mean = 3.54, SD = 1.19)
Vasiljevic et al. (2016)	• Randomized controlled trial • Participants exposed to advertisements of candy-like flavored e-cigarettes, non-flavoured e-cigarettes, or control • Youth: 598 English children, 11–16 years of age	• Appeal of using e-cigarettes • Appeal of e-cigarette ads • Interest in buying and trying e-cigarettes following ad exposure	• Exposure to e-cigarette ads did not seem to increase the appeal of tobacco smoking in children. • Exposure to flavoured e-cigarette ads (compared with non-flavoured ads) increased the appeal and interest in buying and trying e-cigarettes in children.

Note: NYTS = National Youth Tobacco Survey; PATH = Population Assessment of Tobacco and Health Study; SD = standard deviation; SE = standard error.

Common theories of health behavior, such as the Theory of Reasoned Action and the Health Belief Model, posit that perceptions of harm influence tobacco-use behavior, with lower perceived harm encouraging higher levels of experimentation and current tobacco use (Primack et al. 2008). Monitoring both absolute perceived harm and perceived harm relative to conventional cigarettes could be an indicator of later product adoption. Table 2.11 presents studies of the perceived harm of e-cigarettes among adolescents and young adults that are included in this chapter.

Youth

Table 2.12a presents NYTS data from middle school and high school students on the perceived harm of using e-cigarettes on some days but not every day. In 2015, 61.9% of these students, overall, believed that e-cigarettes caused “little or some harm” under such conditions; 14.5%, “no harm”; and 23.6%, “a lot of harm.” However, when these data are stratified by students’ history of e-cigarette use, important differences become clear. Notably, 34.2% of past-30-day e-cigarette users believed e-cigarettes cause “no harm,” compared with 22.4% of ever e-cigarette users and only 9.5% of never e-cigarette users. Conversely, 29.4% of never e-cigarette users believed that e-cigarettes cause “a lot of harm,” compared with 8.3% of ever e-cigarette users and 6.8% of past-30-day e-cigarette users. These important differences by e-cigarette use status, which suggest perceptions of no harm related to e-cigarette use, were consistent for both middle school students and high school students (Tables 2.12b and 2.12c).

Three studies that used data from the 2012 NYTS examined the correlates of U.S. adolescents’ opinions about the perceived harm of e-cigarettes relative to the harm of conventional cigarettes. Non-Hispanic Whites, students who lived with a smoker (Cardenas et al. 2015) or had a family member who used tobacco (Amrock et al. 2015), and past-30-day users of tobacco products other than cigarettes were more likely to believe that e-cigarettes were safer than conventional cigarettes (Amrock et al. 2015). Conversely, girls and students 17 years of age or older were more likely to believe that e-cigarettes were more harmful than regular cigarettes (Amrock et al. 2015). The perceived harm of e-cigarettes decreased with increasing levels of cigarette smoking, such that in 2012, 25% of adolescent never smokers, 41.3% of adolescent ever smokers, and 54.2% of adolescent past-30-day smokers believed that e-cigarettes were less harmful than cigarettes (Ambrose et al. 2014). Prior use of e-cigarettes was also associated with perceived harm of that product. Among students who had ever tried e-cigarettes in 2012, 71.8% believed that they were less harmful than cigarettes, 12.1% equally harmful, and 5% more harmful. These estimates were similar to those for students who had used e-cigarettes in the past 30 days (Amrock et al. 2015). In addition, susceptibility to cigarette smoking among never smokers was associated with perceptions of low harm for e-cigarettes (Ambrose et al. 2014).

Although not all studies reviewed in this section included “don’t know” as a response option for questions on the harms of e-cigarettes, those that did, found that a large number of students were unsure of the relative harmfulness of e-cigarettes compared to conventional cigarettes (Ambrose et al. 2014; Amrock et al. 2015). In fact, among U.S. adolescents responding to the 2012 NYTS, “don’t know” was the most common response (41.1–53.3%) across all the demographic subgroups examined (gender, age, and race/ethnicity) (Amrock et al. 2015). In this sample, more never smokers (57.4%) than ever smokers (37.5%) or past-30-day smokers (24%) had not heard of or did not know enough about e-cigarettes to make a

judgment of harm (Ambrose et al. 2014). Future studies will benefit from examining the effect of harm perception on the use of e-cigarettes and other tobacco-use behaviors among adolescents.

Young Adults

Table 2.12d presents data from the 2013–2014 NATS on beliefs about harm from e-cigarettes among young adults (18–24 years old). Just over half (53.8%) of young adults believed that e-cigarettes were “moderately harmful,” 26.8% believed they were “very harmful,” and 19.4% believed they caused “no harm.” Levels of belief in moderate harm were quite similar by type of e-cigarette use: 52.8% of never users, 56.8% of ever (but not current) users, and 53.6% of current users. Ever and current users were more likely than never users to report that e-cigarettes were “not at all harmful,” while never users were more likely than the other two groups to report that e-cigarettes were “very harmful.”

Published studies on perceived harm of e-cigarettes from regional samples, primarily of college and university students, are presented in Table 2.11. A large survey ($n = 4,444$) of college students in North Carolina conducted in 2009 found that, as with adolescents, perceived harm of e-cigarettes, compared with conventional cigarettes, was lower among college students who had ever used e-cigarettes (45%) than among those who had never used e-cigarettes (22%) (Sutfin et al. 2013). Just over half of the participants in this study who had never tried e-cigarettes, however, said that they did not know enough to judge the relative harm of e-cigarettes compared to conventional cigarettes. In this study and another study, lack of knowledge about the perceived harm of e-cigarettes relative to conventional cigarettes was associated with lower odds of using e-cigarettes (Sutfin et al. 2013; Choi and Forster 2014b). In the study by Choi and Forster (2014b), lower perceived harm of e-cigarettes and the belief at baseline that e-cigarettes can help people quit smoking were both associated at follow-up with a higher likelihood of having tried e-cigarettes.

Table 2.11. Summary of studies on perceptions of e-cigarette harm among youth and young adults

Study	Design/population	Measures	Outcomes/findings	Comments
Choi et al. (2012)	- Focus groups - Recruitment by (1) online advertisements, (2) flyers on one 4-year and two 2-year college campuses, (3) announcements in student life newsletter at a 2-year college, and (4) recruitment booth on a 2-year college campus - Year sample drawn: 2010 - Youth: n/a - Young adults: Individuals in Minneapolis-St. Paul, MN, enrolled in or who had graduated from 4-year colleges, or those who were enrolled in or had graduated from 2-year colleges, or those who had not enrolled in postsecondary education; $N = 66$	Perceived harmfulness relative to cigarettes	- No consensus among participants - Lack of information on ingredients, (2) health impact, and (3) mechanism used to vaporize nicotine - Some noted e-cigarettes to be as harmful as cigarettes (“all one product, in different forms”)	- Generalizability - Limited sample size

Table 2.11. (Continued)

Study	Design/population	Measures	Outcomes/findings	Comments
Adkison et al. (2013)	- Parallel prospective cohort - Telephone interview and web-based surveys - Probability sampling methods (random-digit dialing) - Years sample drawn: 2010–2011 (Wave 8), 2008–2009 (Wave 7, where available) - Youth: n/a - Young adults: current smokers, ≥18 years of age; N = 5,939 (Canada: n = 1,581; United States: n = 1,520; United Kingdom: n = 1,325; Australia: n = 1,513)	Are electronic cigarettes more harmful than, less harmful than, or equally harmful as regular cigarettes to one's health?	Not explicitly reported for young adults	- Inclusion of only current and former cigarette smokers - Limited set of questions
Faletau et al. (2013)	- Qualitative exploratory - Structured focus groups and individual interviews - Recruited from two low socioeconomic primary schools in East and South Auckland, New Zealand - Year sample drawn: 2011 - Youth: Maori, Tongan, Samoan, Cook Island, and Niuean children, 6–10 years of age; N = 20 - Young adults: n/a	Viewed tobacco cigarette and electronic cigarette videos	Still allows smokers to smoke, despite its function as a cessation aid	- Generalizability - Unknown if saturation was reached in children between focus groups - and individual interviews
Sutfin et al. (2013)	- Cross-sectional - Web-based survey (part of a randomized group trial) - Stratified random sample - Year sample drawn: 2009 - Youth: n/a - Young adults: undergraduate students attending eight universities in North Carolina; N = 4,857 (completers of e-cigarette question, n = 4,444).	- Compared with a regular cigarette, how harmful do you think e-cigarettes are? - Less harmful - As harmful - More harmful - Do not know	- Among the overall sample: 17% indicated “as harmful” 23% indicated “less harmful” 2% indicated “more harmful” 50% indicated “do not know” - Among ever e-cigarette users: 17% indicated “as harmful” 45% indicated “less harmful” 3% indicated “more harmful” 23% indicated “do not know” - Among never e-cigarette users: 16% indicated “as harmful” 22% indicated “less harmful” 2% indicated “more harmful”	- Low response rate - Generalizability - Inability to differentiate former smokers from experimenters - Cross-sectional analysis

Study	Design/population	Measures	Outcomes/findings	Comments
Sutfin et al. (2013)			51% indicated “do not know” - Ever e-cigarette use significantly associated with harm perceptions ($p < 0.001$)	
Ambrose et al. (2014)	- NYTS - Cross-sectional - School-based survey - Three-stage cluster sampling - Year sample drawn: 2012 - Youth: U.S. middle and high school students (grades 6–12); $N = 24,658$ - Young adults: n/a	Do you believe that electronic cigarettes or e-cigarettes, such as Ruyan or NJOY, are less harmful, equally harmful, or more harmful than regular cigarettes?	30.6% (CI, 29.3–31.9%) of respondents believed - e-cigarettes are less harmful than cigarettes: never smokers: 25% (CI, 23.9–26.2%); ever smokers: 41.3% (CI, 39.1–43.6%); current smokers: 54.2% (CI, 51.0–57.4%) - Female and Hispanics were less likely to perceive e-cigarettes as less harmful than cigarettes compared with males and Whites, across all smoking statuses - Current smokers that had ever used e-cigarettes were more than twice as likely to perceive e-cigarettes as less harmful, compared with smokers who had never used e-cigarettes (AOR = 2.48; CI, 1.87–3.29) - Never smokers who had ever used e-cigarettes were almost six times as likely to perceive e-cigarettes as less harmful, compared with - never smokers who had never used e-cigarettes (AOR = 5.88; CI, 3.07–11.25)	- Perceived graduated risk - Self-reported items - Social desirability bias - Generalizability
Czoli et al. (2014)	- Cross-sectional - Survey - Recruitment through online panel of commercial market research company - Year sample drawn: 2012 - Youth: Canadian youth recruited from online panel, 16–30 years of age; $n = 1,188$	- Is this product harmful to your health? - Have you ever experienced any side-effects or adverse outcome(s) while using e-cigarettes?	- Mean score for agreement with e-cigarettes as harmful to your health (higher score indicates greater agreement): - Among cigarette nonsmokers: 5.5 (e-cigarette nonuser) vs. 4.4 (e-cigarette ever user)	- Cross-sectional analysis - Generalizability

Table 2.11. (Continued)

Study	Design/population	Measures	Outcomes/findings	Comments
	Young adults: Canadian young adults recruited from same online panel (see above)		- Among former smokers: 5.2 (e-cigarette nonuser) vs. 3.6 (e-cigarette ever user) - Among current smokers: 2.6 (e-cigarette nonuser) vs. 3.5 (e-cigarette ever user)	
Gallus et al. (2014)	- Cross-sectional - In-person survey - Representative multistage sampling - Year sample drawn: 2013 - Youth: n/a - Young adults: Italians ≥ 15 years of age; N = 3,000	- Indicate your opinion (true/ false) concerning e-cigarettes on the following: (1) Are not harmful for health (2) Are less harmful than traditional cigarettes because they do not contain nicotine (3) Are less harmful because there is no tobacco combustion (4) Are less harmful because they contain only nicotine (5) Are more harmful than traditional cigarettes (6) Are an efficient tool to quit smoking (7) Allow smoking even where it is forbidden	Findings not explicitly reported for young adults	- Unstable estimates due to small sample of e-cigarette users - Unvalidated survey
Tan and Bigman (2014)	- Cross-sectional - Health Information National Trends Survey 4 Cycle 2 - Collected between October 2012 and January 2013 - U.S. adults ≥ 18 years of age - N = 3,630, 29.8% 18–34 years of age	- Compared to smoking cigarettes, would you say that electronic cigarettes are: - Much less harmful - Less harmful - Just as harmful - More harmful - Much more harmful - I've never heard of electronic cigarettes	Compared with younger respondents (18–34 years of age), older respondents had 38%–72% lower odds of believing that e-cigarettes are less harmful than regular cigarettes	—
Tucker et al. (2014)	- Cross-sectional - Paper-based survey - Probability-based sampling - Year sample drawn: not reported - Youth: n/a - Young adults: homeless young adults,	Rate whether they perceive e-cigarettes to be less harmful, more harmful, or just as harmful as smoking cigarettes	44.9% viewed e-cigarettes as less harmful than conventional cigarettes 26.6% viewed e-cigarettes as just as harmful as conventional cigarettes	Did not collect information on youth's attitudes about alternate tobacco products besides e-cigarettes

Study	Design/population	Measures	Outcomes/findings	Comments
	17–25 years of age; N = 292 (subset of lifetime e-cigarette users, n = 83)		3.7% viewed e-cigarettes as more harmful than conventional cigarettes 24.8% did not know the relative harm	Did not collect information on the conditions under which they used various products
Amrock et al. (2015)	- NYTS - Cross-sectional - School-based survey - Three-stage cluster sampling - Year sample drawn: 2012 - Youth: U.S. middle and high school - students (grades 6–12); N = 24,658 - Young adults: n/a	Do you believe that electronic cigarettes or e-cigarettes, such as Ruyan or NJOY, are less harmful, equally harmful, or more harmful than regular cigarettes?	34.2% (CI, 32.8–35.6%) of adolescents considered e-cigarettes to be less harmful than cigarettes - Females were less likely than males to perceive e-cigarettes as less harmful than cigarettes - Lifetime e-cigarette users were more likely than never users to report e-cigarettes as less harmful than cigarettes (71.8% vs. 31%) - Past-30-day e-cigarette users were more likely than nonrecent users to report e-cigarettes as less harmful than cigarettes (73.8% vs. 33.1%)	- Missingness - Perceived graduated risk - Self-reported items - Social desirability bias - Generalizability
Berg et al. (2015)	- Cross-sectional - Online-based survey - Recruitment by random selection - Year sample drawn: 2013 - Youth: n/a - Young adults: U.S. university students; n = 2,002	- How harmful to your health do you think electronic cigarettes are? - How addictive do you think electronic cigarettes are? - How socially acceptable among your peers do you think electronic cigarettes are?	- Respondents considered e-cigarettes among the least harmful (4.26 ± 1.95), addictive (4.29 ± 2.08), and socially acceptable (4.12 ± 2.03) of the products considered - Electronic cigarettes were among the most positively perceived products (11.56 ± 4.22) - Predictors of more favorable perceptions included: - Being male ($p = 0.03$) - Parental tobacco smoking ($p = 0.02$) - More friends who smoke cigarettes ($p < 0.001$) - More friends who use hookah ($p < 0.001$) - More friends who use electronic cigarettes ($p = 0.04$) - Recent cigarette smoking ($p < 0.001$).	- Generalizability - Responder bias - Cross-sectional analysis

Table 2.11. (Continued)

Study	Design/population	Measures	Outcomes/findings	Comments
Camenga et al. (2015)	• Focus groups • Purposive sampling • Years sample drawn: 2012–2013 • Youth: middle and high school students in Connecticut; n = 68 • Young adults: college students in Connecticut; n = 59	• Discuss the comparison between e-cigarettes and cigarettes.	• Compared with nonsmokers, college and high school smokers were more likely to believe the use of e-cigarettes could lead to a persistent “craving” that would prevent successful smoking cessation • Compared with nonsmokers, college and high school smokers were more likely to believe that e-cigarette use would maintain nicotine addiction	• Transferability • Generalizability • Limited definition of e-cigarettes
Cardenas et al. (2015)	• Cross-sectional • School-based survey • Three-stage cluster sampling • Year sample drawn: 2012 • Youth: U.S. middle and high school students; full sample size not reported; subsample of children who • never tried smoking cigarettes, n = 14,861 • Young adults: n/a	• Do you believe that electronic cigarettes or e-cigarettes, such as Ruyan or NJOY, are less harmful, equally harmful, or more harmful than regular cigarettes?	• Participants who lived with a smoker were more likely to report e-cigarettes are less harmful than regular cigarettes (16.2% vs. 24.8%) • E-cigarette users were more likely to believe e-cigarettes are less harmful than regular cigarettes (70.9% vs. 27.5%)	• No limitations reported
Chaffee et al. (2015)	• Cross-sectional • Year sample drawn: 2014 • Youth: male high school students • from San Francisco; n = 104	• Participants were asked to estimate the probability (0–100%) that specific health or social outcomes would happen to them as a result of e-cigarette use (e.g., heart attack, lung cancer, get into trouble, upset family, etc.)	• Ever use of electronic cigarettes was associated with lower perceived probabilities that unfavorable outcomes would happen	—
Lotrean (2015)	• Cross-sectional • 2013 • Students 19–24 years of age from Cluj-Napoca, Romania; n = 480	• Belief that e-cigarettes are less dangerous than cigarettes: agree, partially agree, disagree, partially disagree, don’t know	• 55.9% of the total sample agreed or partially agreed that e-cigarettes are less dangerous, 35.8% did not know, and 8.3% disagreed or partially disagreed • More smokers than nonsmokers or ex-smokers agreed or partially agreed that e-cigarettes are less dangerous (62.3% vs. 58.7% and 33.3%, respectively)	• Very small sample • Measures not clearly defined

Study	Design/population	Measures	Outcomes/findings	Comments
McDonald and Ling (2015)	- Focus groups and semistructured interviews - Recruitment from bars through screener surveys - Years sample drawn: 2012–2013 - Youth: n/a - Young adults: young adults in the boroughs of Manhattan, Brooklyn, and Queens in New York City, 18–27 years of age; N = 87	Perceived risks	- Little knowledge of the devices - Belief that e-cigarettes contain harmless “water vapor” rather than smoke - Belief that “water vapor” is less harmful or even “good” for users	No limitations reported
Roditis and Halpern-Felsher (2015)	- Focus groups - Recruitment from after-school programs in urban Northern California 2–6 participants in each group 24 adolescents: 9 female, 15 male	Perceived risks and benefits associated with conventional cigarettes versus e-cigarettes	- Little knowledge of risks of e-cigarette use - Belief that e-cigarettes have no nicotine	—
Cooper et al. (2016)	- Cross-sectional - Drawn from 2014 Texas Youth Tobacco Survey, a school-based survey - Youth: students in grades 6–12 from 27 counties in Texas; N = 13,602	“How dangerous do you think it is for a person your age to use electronic cigarettes?”	- Those in the e-cigarette-only group viewed conventional cigarettes as more harmful than did those in the dual user group - No differences in how harmful those in the e-cigarette-only group and the dual user group rated e-cigarettes - Those in the cigarette-only group rated e-cigarettes as more harmful than did those in the dual user group	—

Note: Studies in this table are sorted by year of publication and then alphabetically. AOR = adjusted odds ratio; CI = confidence interval; NYTS = National Youth Tobacco Survey.

Table 2.12a. Percentage of middle school and high school students who reported that using e-cigarettes on some days but not every day caused no harm, little/some harm, or a lot of harm^a, by e-cigarette smoking status; National Youth Tobacco Survey (NYTS) 2015

No harm			Little/some harm		A lot of harm	
Characteristic	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Overall	2,511	14.5 (13.4–15.8)	10,471	61.9 (60.3–63.5)	4,070	23.6 (22.2–25.0)
E-cigarette use						
Never ^b	1,200	9.5 (8.4–10.8)	7,528	61.0 (59.4–62.6)	3,653	29.4 (28.0–30.9)
Ever, but not past 30 days ^c	601	22.4 (20.3–24.6)	1,748	69.3 (66.4–72.1)	249	8.3 (7.0–9.9)
Past 30 days ^d	641	34.2 (31.2–37.3)	1,089	59.0 (55.9–62.0)	126	6.8 (5.4–8.7)

Source: Centers for Disease Control and Prevention, unpublished data (data: NYTS 2015).

Notes: CI = confidence interval. There were 325 youth excluded due to missing responses for e-cigarette use.

^aIncludes responses to the question, “How much do you think people harm themselves when they use e-cigarettes some days but not every day?” Responses for “little harm” and “some harm” were combined.

^bIncludes those who reported never trying e-cigarettes.

^cIncludes those who reported trying e-cigarettes but not using e-cigarettes on 1 or more days in the past 30 days.

^dIncludes those who reported using e-cigarettes on 1 or more days in the past 30 days.

Table 2.12b. Percentage of middle school students who reported that using e-cigarettes on some days but not every day caused no harm, little/some harm, or a lot of harm^a, by e-cigarette smoking status; National Youth Tobacco Survey (NYTS) 2015

No harm			Little/some harm		A lot of harm	
Characteristic	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Overall	1,089	13.5 (11.9–15.4)	4,579	57.6 (56.1–59.2)	2,260	28.8 (27.1–30.6)
E-cigarette use						
Never ^b	658	9.9 (8.3–11.6)	3,927	58.0 (56.5–59.4)	2,141	32.2 (30.5–33.9)
Ever, but not past 30 days ^c	211	31.9 (27.7–36.3)	383	60.6 (55.7–65.4)	60	7.5 (5.4–10.4)
Past 30 days ^d	193	41.5 (35.6–47.6)	220	50.0 (44.3–55.7)	38	8.5 (6.0–12.0)

Source: Centers for Disease Control and Prevention, unpublished data (data: NYTS 2015).

Notes: CI = confidence interval. There were 132 middle students excluded due to missing responses for e-cigarette use.

^aIncludes responses to the question, “How much do you think people harm themselves when they use e-cigarettes some days but not every day?” Responses for “little harm” and “some harm” were combined.

^bIncludes those who reported never trying e-cigarettes.

^cIncludes those who reported trying e-cigarettes but not using e-cigarettes on 1 or more days in the past 30 days.

^dIncludes those who reported using e-cigarettes, on 1 or more days in the past 30 days.

Table 2.12c. Percentage of high school students who reported that using e-cigarettes on some days but not every day caused no harm, little/some harm, or a lot of harm^a, by e-cigarette smoking status; National Youth Tobacco Survey (NYTS) 2015

No harm			Little/some harm		A lot of harm	
Characteristic	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Overall	1,422	15.3 (14.0–16.7)	5,892	65.3 (63.2–67.3)	1,810	19.4 (18.0–20.9)
E-cigarette use						
Never ^b	542	9.2 (7.8–10.9)	3,601	64.3 (62.0–66.7)	1,512	26.4 (24.6–28.3)
Ever, but not past 30 days ^c	390	19.5 (17.5–21.8)	1,365	71.9 (68.6–74.9)	189	8.6 (6.9–10.6)
Past 30 days ^d	448	32.3 (28.8–35.9)	869	61.3 (57.8–64.8)	88	6.4 (4.8–8.4)

Source: Centers for Disease Control and Prevention, unpublished data (data: NYTS 2015).

Notes: CI = confidence interval. There were 166 high school students excluded due to missing responses for e-cigarette use.

^aIncludes responses to the question, “How much do you think people harm themselves when they use e-cigarettes some days but not every day?” Responses for “little harm” and “some harm” were combined.

^bIncludes those who reported never trying e-cigarettes.

^cIncludes those who reported trying e-cigarettes but not using electronic cigarettes on 1 or more days in the past 30 days.

^dIncludes those who reported using e-cigarettes, on 1 or more days in the past 30 days.

Table 2.12d. Percentage of young adults (18–24 years of age) who reported that e-cigarettes were not at all harmful, moderately harmful, or very harmful^a, by e-cigarette smoking status; National Adult Tobacco Study (NATS) 2013–2014

Not at all harmful			Moderately harmful		Very harmful	
Characteristic	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Overall	796	19.4 (17.9–20.9)	2,260	53.8 (51.9–55.7)	1,053	26.8 (25.1–28.6)
E-cigarette use						
Never ^b	359	14.3 (12.7–16.2)	1,423	52.8 (50.4–55.2)	814	32.9 (30.6–35.2)
Ever, but not current ^c	210	22.9 (19.7–26.4)	520	56.8 (52.7–60.8)	186	20.3 (17.2–23.8)
Current ^d	227	36.4 (31.8–41.2)	317	53.6 (48.6–58.5)	53	10.0 (7.2–13.9)

Source: Centers for Disease Control and Prevention, unpublished data (data: NATS 2013–2014).

Notes: CI = confidence interval. There were three young adults who were excluded because of missing responses for both ECIGEVER and ECIGNOW.

^aIncludes responses to the question, “How harmful do you think using e-cigarettes are to a person’s health?”

^bIncludes those who reported having never tried e-cigarettes or having never heard of them.

^cIncludes those who reported having heard of e-cigarettes and tried e-cigarettes but reported using them “not at all” at the time of the interview.

^dIncludes those who reported having heard of e-cigarettes, tried e-cigarettes, and using e-cigarettes some days, every day, or rarely at the time of the interview.

*Reasons for Use and Discontinuation***Reasons for Use**

Table 2.13 summarizes studies of reasons for using and discontinuing e-cigarettes. The most commonly cited reasons for use by adolescent and young adult e-cigarette users included curiosity (Schmidt et al. 2014; Biener and Hargraves 2015; Biener et al. 2015; Kong et al. 2015; McDonald and Ling 2015; Suris et al. 2015; Sutfin et al. 2015), flavorings/taste (Ambrose et al. 2015; University of Michigan 2015), use as a less harmful/less toxic alternative to conventional cigarettes (Peters et al. 2013; Tucker et al. 2014; Ambrose et al. 2015; Kong et al. 2015; McDonald and Ling 2015; Sutfin et al. 2015), and avoidance of indoor smoking restrictions or disturbing people with second-hand smoke from conventional cigarettes (Tucker et al. 2014; Ambrose et al. 2015; Kong et al. 2015; McDonald and Ling 2015; Suris et al. 2015; Sutfin et al. 2015). Other reasons youth and young adults reported trying or using e-cigarettes included affordability and lower cost than conventional cigarettes (Tucker et al. 2014; Ambrose et al. 2015); accessibility and convenience (Choi et al. 2012; Kong et al. 2015); social approval and/or offer from a family member or friend (Peters et al. 2013; Kong et al. 2015; Suris et al. 2015; Sutfin et al. 2015); perception that e-cigarettes are “cool,” “modern,” or “high-tech” (Choi et al. 2012; Kong et al. 2015); avoidance of smelling cigarette smoke (Peters et al. 2013; Tucker et al. 2014; Ambrose et al. 2015; Kong et al. 2015; Sutfin et al. 2015); ease of keeping hidden from parents/teachers (Peters et al. 2013; Kong et al. 2015); and weight control (Tucker et al. 2014). Young adults also perceived that e-cigarettes were more socially acceptable than smoking conventional cigarettes in public (Trumbo and Harper 2013).

Some youth and young adults also reported using e-cigarettes as an aid to reducing and/or quitting their use of conventional cigarettes (Li et al. 2013; Schmidt et al. 2014; Tucker et al. 2014; Suris et al. 2015; Sutfin et al. 2015; Bold et al. 2016). Data from the 2012 NYTS, however, suggest that while e-cigarette use among U.S. youth may be associated with intentions to smoke conventional cigarettes, it is not associated with intentions to quit conventional cigarette smoking (Park et al. 2016). This is further reinforced by a study of young adults from Switzerland, which found that after 15 months of follow-up, e-cigarette use was not associated with either cessation or reduction in the use of conventional cigarettes (Gmel et al. 2016). There is some evidence to suggest that curiosity was a stronger driver of an e-cigarette trial among young adults than smoking cessation, and that smoking cessation was a stronger driver of such a trial among older adults (Schmidt et al. 2014). Other evidence suggests that reasons for use were driven by tobacco-use status, with regular adolescent e-cigarette users much more likely than adolescents who had used e-cigarettes just once to give the reason for use as smoking cessation, smoking reduction, or avoidance of smoke-free air regulations (Suris et al. 2015). Nationwide, according to the 2015 MTF (University of Michigan 2015), “because they tasted good” was cited as a reason to use e-cigarettes among 40% of 8th-, 10th-, and 12th-grade users, versus just 10% who reported they used them in an attempt to quit smoking conventional cigarettes. In a New Zealand study, interest in using e-cigarettes to quit using conventional cigarettes was higher among young adults than older adults (Li et al. 2013). Finally, another study, this one conducted among high school, middle school, and college students in Connecticut in 2012–2013, found that although the students were aware that e-cigarettes could be used to aid in smoking cessation, they thought that few smokers had successfully used e-cigarettes to quit smoking (Camenga et al. 2015). However,

in an article published by this group (Bold et al. 2016), trying e-cigarettes to quit smoking was the most robust predictor of continued e-cigarette use 6 months later, using a multivariable model that included all reasons simultaneously, though this reason was only endorsed at baseline by 5.9% of youth. Low cost was the most robust predictor of more frequent use 6 months later, though only 10% of students endorsed this reason at baseline (Bold et al. 2016). Therefore, the reasons to experiment with e-cigarettes are likely different from the reasons to continue using them, over time.

No randomized controlled trials specific to the efficacy of using e-cigarettes for quitting conventional cigarette smoking for young adults have been conducted to date. Although use of e-cigarettes as a potential cessation device for conventional cigarette smoking among adults is important to examine (e.g., McRobbie et al. 2014; McNeill et al. 2015), none of this evidence is included here, as it does not directly discuss youth and young adults. Three observational studies specific to this issue, however, have been conducted among young adults to date. Data from a population-based cohort study of U.S. young adults in the Midwest suggest that e-cigarettes are not effective as a technique for quitting the use of conventional cigarettes. In that study, 11% of cigarette smokers who had used e-cigarettes in the past 30 days at baseline quit smoking at the 1-year follow-up, compared with 17% of cigarette smokers who had never used e-cigarettes (OR = 0.93, $p = 0.93$) (Choi and Forster 2014a). Another cohort study of Swiss young adult men concluded that there were no beneficial effects of vaping for conventional cigarette smoking cessation or smoking reduction (Gmel et al. 2016). In this study, e-cigarette users reported lower cigarette smoking cessation rates at follow-up among those who were occasional cigarette smokers at baseline (OR = 0.43; 95% CI, 0.19–0.96). No differences between e-cigarette users and nonusers were noted among those who were daily cigarette smokers at baseline (OR = 0.42; 95% CI, 0.15–1.18). No differential changes between e-cigarette users and nonusers in the number of conventional cigarettes smoked per week were noted at follow-up, either (Gmel et al. 2016). In a study by Unger and colleagues (2016), which focused on Hispanic young adults in California, e-cigarette use at baseline (2014) was *not* associated with cessation of cigarette smoking (OR = 1.31; 95% CI, 0.73–2.36) or marijuana use (OR = 1.05; 95% CI, 0.54–2.01) at follow-up (2015), though e-cigarette use at baseline did increase the likelihood of transitioning from nonuser to user of cigarettes (OR = 3.32; 95% CI, 1.55–7.10) and marijuana (OR = 1.97; 95% CI, 1.01–3.86) (Unger et al. 2016). Additional research is required to determine any potential efficacy of e-cigarette use for conventional cigarette smoking cessation in young adults.

Reason for Discontinuation

In the small number of published studies on reasons for discontinuation of e-cigarette use in young users, adolescent and young adult smokers have cited lack of satisfaction and e-cigarettes' poor taste and cost (Kong et al. 2015) as reasons for discontinuing. Additional reasons have included negative physical effects (e.g., feeling light-headed) (Kong et al. 2015) and loss of interest. In one study of young adults aged 18–35, former and never smokers of conventional cigarettes also cited the idea that e-cigarettes were “bad for their health” as a reason for discontinuation (Biener and Hargraves 2015; Biener et al. 2015).

Table 2.13. Summary of studies on reasons for use and discontinuation of e-cigarettes among youth and young adults

Study	Design/population	Measures	Outcomes/findings
Adkison et al. (2013)	- Parallel prospective cohort - Telephone interview and web-based surveys - Probability sampling methods (random-digit dialing) - Years sample drawn: 2010–2011 (Wave 8), 2008–2009 (Wave 7; where available) - Youth: n/a - Young adults: current smokers, ≥ 18 years of age; N = 5,939 (Canada, n = 1,581; U.S., n = 1,520; United Kingdom, n = 1,325; Australia, n = 1,513)	- Four questions were asked regarding reasons for use (yes/no): - Electronic cigarettes may not be as bad as cigarettes for your health - Easier to cut down on the number of cigarettes you smoke - Can smoke in places where smoking conventional cigarettes is prohibited - Might help you quit	Not explicitly reported for young adults
Choi et al. (2012)	- Focus groups - Recruitment by (1) online advertisements, (2) flyers on one 4-year and two 2-year college campuses, announcements in student life newsletter at a 2-year college, and recruitment booth on a 2-year college campus - Year sample drawn: 2010 - Youth: n/a - Young adults: Individuals in Minneapolis-St. Paul, MN, enrolled in or who had graduated from 4-year colleges, or those who were enrolled in or had graduated from 2-year colleges, or those who had not enrolled in postsecondary education; N = 66	Potential as quit aids	- Ineffective as quit aids because: - Contain nicotine - Potential to be addicted to e-cigarettes - Eliminate social interaction aspect - Potential to help quit smoking because: - Potential for gradual reduction in nicotine
Choi and Forster (2013)	- Population-based prospective cohort study - Interview - Cluster random sampling - Years sample drawn: 2010–2011 - Youth: n/a - Young adults: U.S. midwestern adults, 20–28 years of age; n = 2,624 (sample from Minnesota)	- Indicate your level of agreement: - E-cigarettes can help people quit smoking - E-cigarettes are less harmful than cigarettes - E-cigarettes are less addictive than cigarettes	44.5% agreed e-cigarettes can help quit smoking; associated with the following characteristics: - Not being non-Hispanic White (AOR = 0.60; CI, 0.44–0.84) - Enrolled/graduated from 2-year college (AOR = 1.47; CI, 1.09–1.98) - Current smoker (AOR = 1.35; CI, 1.05–1.73) - At least one close friend who smokes (AOR = 1.27; CI, 1.03–1.57) 52.9% agreed e-cigarettes are less harmful than cigarettes; associated with the following characteristics: - Not being non-Hispanic White (AOR = 0.73; CI, 0.53–0.99) - Male (AOR = 1.39; CI, 1.15–1.67) - Current smoker (AOR = 1.42; CI, 1.11–1.83)

Table 2.13. (Continued)

Study	Design/population	Measures	Outcomes/findings
Choi and Forster (2013)			• 26.4% agreed e-cigarettes are less addictive than cigarettes; associated with the following characteristics: • Current smoker (AOR = 1.51; CI, 1.15–1.99) • Former smoker (AOR = 1.64; CI, 1.19–2.25) • At least one close friend who smokes (AOR = 1.28; CI, 1.00–1.63)
Faletau et al. (2013)	• Qualitative exploratory • Structured focus groups and individual interviews • Recruited from two low socioeconomic primary schools in East and South Auckland, New Zealand • Year sample drawn: 2011 • Youth: Maori, Tongan, Samoan, Cook Island, and Niuean children, 6–10 years of age; N = 20 • Young adults: n/a	• Viewed tobacco cigarette and electronic cigarette videos	• Stops people from smoking • People won't die • Protects those around e-cigarette users from sickness
Li et al. (2013)	• Cross-sectional • Telephone-based survey • Random-digit-dial sampling • Years sample drawn: 2011–2012 • Youth: n/a • Young adults: current smokers and recent quitters, ≥18 years of age, in New Zealand; N = 840	• Indicate your level of agreement: 1. E-cigarettes are safer to use than tobacco cigarettes (n = 317) 2. E-cigarettes can help people quit smoking tobacco (n = 313)	• OR = 1.81 (.78–4.18) among participants 18–24 years of age for perceived safety of e-cigarettes compared with participants ≥45 years of age • OR = 0.50 (0.21–1.17) among participants 18–24 years of age for perceived efficacy of e-cigarettes compared with participants ≥45 years of age
Pepper et al. (2013)	• Cross-sectional • Web-based survey • Recruited through parents who were members of an online panel assembled by random-digit dialing and address-based sampling. • Year sample drawn: 2011 • Youth: U.S. males, 11–17 years of age; N = 228 • Young adults: n/a	• If one of your best friends were to offer you an e-cigarette, would you try it? • If one of your best friends were to offer you a flavored e-cigarette (chocolate, mint, apple, etc.), would you try it?	• Overall, 18% were willing to try an e-cigarette if offered by a best friend: – 13% willing to try a plain e-cigarette – 5% willing to try flavored e-cigarettes or both kinds • Willingness to try e-cigarettes by age: – 11–13: 11% – 14–16: 15% – 17–19: 29% • OR = 3.26 (CI, 1.27–8.35) among those 17–19 years of age for willingness to try an e-cigarette, compared with those 11–13 years of age • Willingness to try e-cigarettes by smoking status: – Nonsmoker: 13% – Smoker: 74% • OR = 18.67 (6.22–55.98) among smokers for willingness to try an e-cigarette, compared with nonsmokers

Study	Design/population	Measures	Outcomes/findings
Peters et al. (2013)	• Focus groups • Recruitment through large, diverse high school in southwestern United States • Year sample drawn: 2012 • Youth: U.S. teenage boys; N = 47 • Young adults: n/a	• Why do youth use electronic cigarettes? • What do your friends think about electronic cigarettes? • Why are electronic cigarettes so popular?	• Reported reasons for use among youth: • Expeditionary consumption and concealment: 40% • High school approval: 26% • Healthier than cigarettes: 19% • Odorless: 15% • Reported perceptions of friends: • High school approval: 49% • Healthier than cigarettes: 36% • Safe high: 15% • Reported reasons for popularity: • Accessibility: 43% • Healthier than cigarettes: 30% • Aesthetics: 23% • Don't know: 4%
Trumbo and Harper (2013)	• Cross-sectional • Web-based survey • Recruitment by offer of extra credit to students in a 100-level course • Year sample drawn: 2011 • Youth: n/a • Young adults: freshmen and sophomores in a 100-level mass media in society course; n = 244	• Indicate your level of agreement with relative advantage: 1. I think e-cigarettes are safer in terms of "secondhand" smoke compared to tobacco cigarettes 2. I think e-cigarettes are not as harmful to users as tobacco cigarettes • Indicate your level of agreement with compatibility: 1. I think e-cigarette users can easily make use of existing smoking areas 2. I believe using e-cigarettes would fit in well with the lifestyle of most smokers • Indicate your level of agreement with complexity: 1. I believe it will not be difficult for smoker to learn how to use e-cigarettes 2. Overall, e-cigarettes are no more complicated to use than ordinary tobacco cigarettes • Indicate your level of agreement with "trialability": 1. I think it will be easy for people to purchase e-cigarettes 2. Smokers could easily give e-cigarettes a try to see if they like them better than tobacco	• Mean score (SD) of innovation items: 36.0 (4.7)
Zhu et al. (2013)	• Population • Online-based surveys • National probability sample • Year sample drawn: 2012 • Youth: n/a • Young adults: U.S. adults, >18 years of age; N = 10,041	• Why did you use e-cigarettes (yes/no)? 1. Safer than cigarettes 2. Cheaper than cigarettes 3. Easy to use when I can't smoke 4. To try to quit smoking cigarettes 5. Just because	• Not explicitly reported for young adults

Table 2.13. (Continued)

Study	Design/population	Measures	Outcomes/findings
Choi and Forster (2014b)	- Population-based prospective cohort study - Survey - Cluster random sampling - Years sample drawn: 2011–2012 - Youth: n/a - Young adults: participants in Minnesota Adolescent Community Cohort; n = 1,379	- Indicate your level of agreement with the following: - Using e-cigarettes can help people quit smoking - Using e-cigarettes is less harmful to health of the user than smoking cigarettes - E-cigarettes are less addictive than cigarettes	10% agreed that e-cigarettes can help people quit smoking; associated with e-cigarette experimentation at follow-up (AOR = 1.98; CI, 1.29–3.04) 10.1% agreed that e-cigarettes are less harmful than cigarettes; associated with e-cigarette experimentation at follow-up (AOR = 2.34; CI, 1.49–3.69) 9.3% agreed that e-cigarettes are less addictive than cigarettes
Czoli et al. (2014)	- Cross-sectional - Survey - Recruitment through online panel of commercial market research company - Year sample drawn: 2012 - Youth: Canadian youth recruited from online panel, 16–30 years of age; n = 1,188 - Young adults: Canadian young adults recruited from same online panel	- Indicate your agreement with the following reasons for trying e-cigarettes: - In places where you can't smoke cigarettes - For times when you don't want to smoke around others - To help you cut back on the amount you smoke - To help you while you are trying to quit smoking - As a long-term replacement for cigarettes - As a cheaper alternative to cigarettes	- Reasons for trying e-cigarettes among current cigarette smokers: –To help cut back on the amount they smoked (77.7%) –As a long-term replacement for cigarettes (77.8%) –For the times when they don't want to smoke around others (78.8%) –To help them while they are trying to quit smoking (80.4%) –As a cheaper alternative to cigarettes (80.7%) –In places where they can't smoke cigarettes (80.9%)
Li et al. (2014)	- Cross-sectional - Telephone-based survey - Recruitment by telephone-based omnibus survey and quitline client database - Year sample drawn: 2013 - Youth: n/a - Young adults: current smokers and recent quitters, ≥18 years of age, in New Zealand; N = 267	- Indicate your level of agreement: - Electronic cigarettes are for people who want to stop smoking completely - Electronic cigarettes are for people who want to cut down on their smoking - Electronic cigarettes are for people who want to still smoke in restricted public places such as inside a cafe, restaurant, or pub	- OR = 1.99 (CI, 0.99–3.97) among those 18–34 years of age for agreeing that “electronic cigarettes are for people who want to stop smoking completely,” compared with individuals ≥35 years of age - OR = 0.72 (CI, 0.24–2.21) among those 18–34 years of age for agreeing that “electronic cigarettes are for people who want to cut down on their smoking,” compared with individuals ≥35 years of age - OR = 0.93 (0.47–1.85) among those 18–34 years of age for agreeing that “electronic cigarettes are for people who want to still smoke in restricted public places such as inside a cafe, restaurant or pub,” compared with individuals ≥35 years of age
Schmidt et al. (2014)	- Cross-sectional - Telephone-based survey - Random-digit-dial sampling - Year sample drawn: 2013 - Youth: n/a - Young adults: noninstitutionalized adults in Montana; n = 5,000	- Select all of the reasons you initiated use of e-cigarettes: - To quit smoking cigarettes - To reduce cigarette consumption - To try something new (curiosity)	- Among those 18–34 years of age, approximately 50% reported trying e-cigarettes to quit or reduce cigarette use - Among those 18–34 years of age, approximately 70% reported trying e-cigarettes to try something new (curiosity)

Study	Design/population	Measures	Outcomes/findings
		4. To not disturb other people with smoke 5. To smoke in a place where cigarette smoking is prohibited 6. To save money 7. E-cigarettes might be less harmful than cigarettes 8. E-cigarettes taste better 9. Other	
Tucker et al. (2014)	• Cross-sectional • Paper-based survey • Probability-based sampling • Year sample drawn: not reported • Youth: n/a • Young adults: homeless young adults, 17–25 years of age; N = 292 (subset of lifetime e-cigarette users, n = 83)	• 18-item measure of reasons for using e-cigarettes, rating each reason on a 4-point scale (1 = not at all true, 4 = very true)	• Most common reasons for use included: Not having to go outside to smoke cigarettes (38%) – To deal with situations or places where they cannot smoke (36%) – To avoid bothering other people with tobacco smoke (31%) – Less common to report using e-cigarettes was to quit smoking (17–18%)
Ambrose et al. (2015)	• Cross-sectional • Wave 1 of PATH study • Household-based, nationally representative survey • Youth: 12–17 years of age; n = 13,651 • Young adults: n/a	• Past 30-day e-cigarette users were asked to report reasons for product use, including “it comes in flavors I like”	• 81.5% of past-30-day users cited “because they come in flavors I like” as a reason for using e-cigarettes • Other common reasons for use were “they might be less harmful to me than cigarettes” (79.1%); “they might be less harmful to people around me than cigarettes” (78.1%); and “I can smoke/use them at times when or in places where smoking cigarettes isn’t allowed” (58.9%)
Biener et al. (2015)	• Cross-sectional • Population-based mail survey • Dual-frame sample • Youth: n/a • Young adults: 18–25 years of age; n = 4,740	• Reasons for trying: curiosity, use by friends, health risks relative to cigarettes, absence of smell, for use where smoking is prohibited, and to quit or cut down on smoking • Reasons for stopping e-cigarette use: health concerns, negative reactions to taste and feeling sick, inferiority to other forms of tobacco, expense, lack of availability, and social disapproval	• Most common reason cited was curiosity, with never smokers more likely to cite this (77.3%) than former or current cigarette smokers (59% and 61%)
Camenga et al. (2015)	• Focus groups • Purposive sampling • Years sample drawn: 2012–2013 • Youth: middle and high school students in Connecticut; n = 68 • Young adults: college students in Connecticut; n = 59	• Discuss your motivations to use e-cigarettes	• Maintain smoking actions while allowing individuals to use a “healthier” nicotine product • Maintain tactile sensations to help with conditioned-smoking cues • College students believed e-cigarettes to be healthier than cigarettes

Table 2.13. (Continued)

Study	Design/population	Measures	Outcomes/findings
Kong et al. (2015)	• Cross-sectional • Focus groups, schoolwide survey • Recruitment by flyers and active recruitment sessions • Years sample drawn: 2012–2013 • Youth: New Haven County, Connecticut, middle and high school students; focus group n = 127 (youth and young adults); survey n = 4,780 • Young adults: New Haven County, Connecticut, college students; focus group n = 127 (youth and young adults); survey n = 625	• Focus group: – Why do you think people your age would use e-cigarettes? • Survey: – Why did you try an e-cigarette? – If you tried an e-cigarette but stopped using it, why did you stop?	• Focus group responses: – Reasons for use: • Influence of family and friends • To be “cool” • Curiosity • Readily available • Flavors – Comparison to cigarettes: • Healthier • Less harsh • Cheaper • Smells better • More convenient • Can hide it • Use it indoors – Reasons for discontinuation: • Losing interest • Negative physical effects (e.g., light-headed) • Bad taste • High cost • Less satisfying than cigarettes • Survey responses: – Reasons for experimentation (among lifetime e-cigarette users): • Curiosity (54.4%) • Friends’ influence (31.6%) – Reasons for discontinuation: • Uncool (16.3%) • Health risks (12.1%)
Li et al. (2015)	• Cross-sectional • 2014 • Nationwide, in-home survey in New Zealand • Multistage, stratified, clustered, and random probability sampling method (oversampling of Maori and Pacific peoples) • Participants ≥15 years of age; n = 2,594: – Youth: 15–17 years of age, 3.8% of sample – Young adults: 18–24 years of age, 13.4% of sample	• Why did you try using an electronic cigarette? (Multiple responses allowed— wanted to quit smoking cigarettes completely/wanted to replace smoking cigarettes some of the time/wanted to smoke in places where cigarette smoking is not allowed/cheaper than tobacco cigarettes/ safer than tobacco cigarettes/curiosity/ recommendation/other)	• 57.1% of ever users cited curiosity as a reason for first trying, followed by 31.3% of ever users who cited wanting to quit smoking completely • Current e-cigarette users were more likely than noncurrent users to report wanting to quit smoking completely as a reason for using e-cigarettes
McDonald and Ling (2015)	• Focus groups and semistructured interviews • Recruitment from bars through screener surveys • Years sample drawn: 2012–2013 • Youth: n/a • Young adults: young adults in the boroughs of Manhattan, Brooklyn, and Queens in New York City, 18–27 years of age; N = 87	• Bodily sensations • Use in response to clean air laws	• Vapor described as “harsh” or “burning” • Discontinued use because believed it would cause one to smoke more • Discontinued use due to fear of nicotine hangover • Use to smoke in places where conventional smoking is not allowed

Study	Design/population	Measures	Outcomes/findings
Pokhrel et al. (2015)	• Cross-sectional • Web-based survey • Recruitment by flyers across three college campuses • Year sample drawn: 2013 • Youth: n/a • Young adults: U.S. students from a 4-year university and two 2-year • community colleges in Oahu, Hawaii; n = 307	• Fourteen items, scored on a scale of 1 (do not agree) to 7 (agree), address three main beliefs. E-cigarettes: – Are less harmful than cigarettes – Improve the health of current smokers – May be used to quit smoking	• Participants generally scored harm-reduction items higher • Among health benefit items, “e-cigarettes improve breathing and reduce coughing” received the highest average score: mean (SD) = 3.9 (1.6) • Among smoking-cessation items, “e-cigarettes are a good compromise for people trying to quit smoking” received the highest average score: mean (SD) = 4.6 (1.8) • Across all items, “e-cigarettes cut down on the harmful effects of secondhand smoke” was scored the highest: mean (SD) = 5.3 (1.7) • 69% of participants agreed with the above item
Suris (2015)	• Cross-sectional • Data drawn from spring 2014 wave of <i>ado @ internet.ch</i>, a longitudinal study on Internet use • Representative sample of students in French-speaking part of Switzerland • Sample of 621 students included never e-cigarette users (n = 353), experimenters (n = 120), and users (n = 148); mean age = 16.2 years	• Reason for having used e-cigarettes? – Curiosity – To smoke where it is forbidden – To reduce smoking – To do like my friends – To quit smoking – Other	• Experimenters were significantly more likely to have used e-cigarettes for curiosity while users were more likely to use them where it is forbidden to smoke (p<.01)
Sutfin (2015)	• Longitudinal cohort study • Data from the Smokeless Tobacco Use in College Students Study • College students from North Carolina and Virginia • Reasons for e-cigarette use were evaluated at Wave 6 of the study, n = 271	• Why did you try e-cigarettes? (check all that apply): – “I was curious about the product” – “It might be better for my health than smoking cigarettes” – “My friends use e-cigarettes” – “I can use it in places where cigarette smoking is not allowed” – “To help me quit smoking” – “To cut down on smoking” – “It doesn’t smell bad”	• The majority (91.6%) reported curiosity as a reason for trying e-cigarettes • More than 70% tried e-cigarettes because their friends used them • About 70% tried e-cigarettes because they believed them to be better for their health than cigarettes • Fifty percent cited, “It doesn’t smell bad,” and “I can use it where cigarette smoking is not allowed” • About 31% said that they used e-cigarettes to cut down on smoking • Twenty percent said that they tried e-cigarettes to help them quit smoking
University of Michigan (2015)	• Cross-sectional • Data from the Monitoring the Future Study	• “What have been the most important reasons for your using an electronic vaporizer, such as an e-cigarette?” – To help me quit regular cigarettes	• More than half of all students in 8th, 10th, and 12th grades reported that curiosity to see what they were like was a primary reason for use

Table 2.13. (Continued)

Study	Design/population	Measures	Outcomes/findings
University of Michigan (2015)	- School-based, self-administered, paper-and-pencil questionnaire with cross-sectional and longitudinal components - Students from 8th, 10th, and 12th grades - Weighted sample of students responding to the “reasons for use of electronic vaporizer” question: 603 (8th grade), 846 (10th grade), and 1,449 (12th grade)	- Because regular cigarette use is not permitted - To experiment to see what it’s like - To relax or relieve tension - To feel good or get high - Because it looks cool - To have a good time with my friends - Because of boredom—nothing else to do - Because it tastes good - Because I am “hooked”—I have to have it	- Forty percent said that they used e-cigarettes because they tasted good - About 10% said they used them in an attempt to quit smoking regular cigarettes
Berg (2016)	- Cross-sectional - Recruitment through Facebook targeting of tobacco and marijuana users and nonusers 2014 - Youth: n/a - Young adults: 18–34 years of age, living in the United States; N = 1,567	- Reasons for use: For what reasons do you/ might you use e-cigarettes? - Reasons for discontinued use: Why have you not used recently?	- Reasons for use among current e-cigarette users: “They might be less harmful than cigarettes” (77%) “They do not smell” (77%) “They help people quit smoking” (66%) “They cost less than other forms of tobacco” (62%) - Reasons for use among nonusers: “They might be less harmful than cigarettes” (41%) “They don’t smell” (34%) - Reasons for discontinuation: “Using other tobacco products instead” (43%) “They are too expensive” (35%) “I just don’t think about it” (31%)
Bold (2016)	- Longitudinal - Youth: New Haven County, Connecticut, middle and high school students 2013–2014 340 e-cigarette users at baseline	- Reasons for first trying e-cigarettes: - Curiosity - It is cool - Good flavors - Does not smell bad - Can hide it from adults - Low cost - My friends use it - My parents/family use it - Can use it anywhere - To quit smoking regular cigarettes - It is healthier than regular cigarettes	- In multivariable model, including all reasons simultaneously, trying e-cigarettes to quit smoking was the most robust predictor of current (i.e., past 30 days) e-cigarette use 6 months later; however, this reason was endorsed by very few youth (5.9%) - In multivariable model, including all reasons simultaneously, trying e-cigarettes because of low cost was the most robust predictor of more frequent e-cigarette use (i.e., more days/month) 6 months later; this reason was endorsed by few youth (10%)

Note: Studies in this table are sorted by year of publication and then alphabetically. AOR = adjusted odds ratio; OR = odds ratio; PATH = Population Assessment of Tobacco and Health Study; SD = standard deviation.

Evidence Summary

The most recent estimates available show that 13.5% of middle school students (2015), 37.7% of high school students (2015), and 35.8% of young adults (2013–2014) had ever used an e-cigarette (Tables 2.1a, 2.1b, and 2.4a). The most recent data also show that past-30-day use of e-cigarettes is higher among high school students (16% in 2015) and young adults (13.6% in 2013–2014) than among middle school students (5.3% in 2015) and adults (25 years of age and older) (5.7% in 2013–2014) (Tables 2.1b, 2.4a, and 2.4b). Among youth and young adults, rates of ever and past-30-day use of e-cigarettes have increased greatly since the earliest e-cigarette surveillance efforts began in 2011. The increases among adults 25 years of age and older, by comparison, have been less steep. Among middle school and high school students, both ever use and past-30-day use of e-cigarettes more than tripled from 2011 to 2015 (NYTS 2011–2015; Figures 2.1 and 2.2) (CDC 2013a; Ambrose et al. 2014; Lippert 2015), and among young adults (18–24 years of age), the prevalence of ever use more than doubled from 2013 to 2014 (Styles 2013–2014; Figure 2.3).

Among youth, past-30-day exclusive use of e-cigarettes among 8th, 10th, and 12 graders (6.8%, 10.4%, and 10.4%, respectively) was more common than exclusive use of conventional cigarettes (1.4%, 2.2%, and 5.3% in those grades) or dual use of e-cigarettes and conventional cigarettes (2.4%, 3.5%, and 5.8% in those grades) (Table 2.5; Figure 2.4). However, among young adults 18–24 years of age, the patterns were different. In that group, exclusive use of conventional cigarettes surpassed exclusive use of e-cigarettes and use of both types of products (Figure 2.8). For example, in 2013–2014, 9.6% of young adults smoked conventional cigarettes exclusively, 6.1% were current users of e-cigarettes, and 7.5% currently used both. The use of e-cigarettes and other tobacco products, such as combustibles, appeared to co-vary among youth and young adults (Figures 2.6, 2.7, and 2.8). Although five longitudinal studies suggest that e-cigarette use is related to the onset of other tobacco product and marijuana use among youth and young adults (Leventhal et al. 2015; Primack et al. 2015; Barrington-Trimis et al. 2016; Unger et al. 2016; Wills et al. 2016), some studies had limitations in their ability to distinguish experimental smokers from regular smokers at follow-up (Leventhal et al. 2015; Primack et al. 2015; Barrington-Trimis et al. 2016; Wills et al. 2016). Therefore, more studies are needed to elucidate the nature of any true causal relationship between e-cigarette use and combustible tobacco products. Investigation of whether e-cigarette use is related to other types of substance abuse (e.g., marijuana, alcohol) might help distinguish the extent to which e-cigarette use may precede or follow other forms of substance use in the context of the common liability/vulnerability model (Vanyukov et al. 2012).

Although use of other tobacco products has been the strongest correlate of ever and past-30-day e-cigarette use among youth and young adults, sociodemographic characteristics have also been associated with the use of these products. Across both ever use and past-30-day use measures, e-cigarette use has been more common among high school than middle school students, a pattern similar to trends seen in other categories of tobacco products (CDC 2015c). Among middle school students in 2014 and 2015 (CDC 2016), ever e-cigarette use was highest for Hispanics (Table 2.1a); among high school students, ever use was highest among Hispanics and Whites (Table 2.1b). No differences between boys and girls were observed among middle school students in 2015 (Tables 2.1a, 2.1b). However, in 2015 male high

school students were significantly more likely to report past-30-day use than their female counterparts (Table 2.2b) (CDC 2016). For young adults, ever and past-30-day use of e-cigarettes were significantly higher among males than females (Table 2.4a). Current e-cigarette use was significantly lower among Blacks than in other racial/ethnic groups (Table 2.4a). Ever and past-30-day e-cigarette use was also significantly lower among those with a college education. Continued research is warranted to monitor patterns of e-cigarette use across population groups by gender, age, race/ethnicity, and education, as well as by sociodemographic characteristics for which disparities in tobacco use have been noted. Availability of data on e-cigarette use among youth and young adults is currently limited, including geography (e.g., subnational data at the state or local levels), sexual orientation and gender identity (e.g., lesbian, gay, bisexual, transgender), and socioeco-nomic status (e.g., household income, poverty status) (CDC 2014a; Johnson et al. 2016).

Research on youth and young adults' e-cigarette-related knowledge, attitudes, and beliefs is still developing and remains relatively sparse. Perceived harm is the most developed area of research. Most youth and young adults believe e-cigarettes are "less harmful" than conventional cigarettes (Table 2.11). However, up to 50% of respondents in some of these studies felt they did not know enough about the potential dangers associated with e-cigarettes to answer questions about perceived harm (Ambrose et al. 2014; Amrock et al. 2015). Although relative harm compared with cigarettes is important to assess, equally important is determining young people's perception of the absolute harm from e-cigarettes. National data show that only 23.6% of middle and high school students combined believed that e-cigarettes cause "a lot of harm" (Table 2.12a), and only 26.8% of young adults believed e-cigarettes are "very harmful" (Table 2.12d). However, significant differences emerge in these perceptions of harm when examined by whether or not youth and young adults use e-cigarettes. Among both middle and high school students and young adults, perceptions of "no harm" were much more prevalent among those with prior experience with e-cigarettes (Tables 2.12b–2.12d). Current e-cigarette users were two to three times more likely to report that e-cigarettes convey "no harm" compared to never e-cigarette users, for both age groups (Tables 2.12a and 2.12d).

The most commonly cited reasons that youth and young adults reported using e-cigarettes included curiosity (Schmidt et al. 2014; Biener and Hargraves 2015; Biener et al. 2015; Kong et al. 2015; McDonald and Ling 2015; Suris et al. 2015; Sutfin et al. 2015), flavorings/taste (Ambrose et al. 2015; University of Michigan 2015), use as a less harmful/less toxic alternative to conventional cigarettes (Peters et al. 2013; Tucker et al. 2014; Ambrose et al. 2015; Kong et al. 2015; McDonald and Ling 2015; Sutfin et al. 2015), and avoidance of indoor smoking restrictions or disturbing people with secondhand smoke from conventional cigarettes (Tucker et al. 2014; Ambrose et al. 2015; Kong et al. 2015; McDonald and Ling 2015; Suris et al. 2015; Sutfin et al. 2015). Using e-cigarettes as an aid to conventional cigarette smoking reduction/cessation (Li et al. 2013; Schmidt et al. 2014; Tucker et al. 2014) was not a primary motivator among youth and young adults. Youth and young adult smokers cited lack of satisfaction, poor taste, and cost (Kong et al. 2015) as reasons for discontinuing e-cigarette use. Additional research is needed to examine how reasons for use, including the appeal of flavored e-cigarettes, are causally related to the onset and progression of e-cigarette use among youth and young adults. Data from the first wave of the PATH study suggest that flavors may play an important role in the initiation of e-cigarette use among youth (Ambrose et al. 2015), while data from the 2014 NYTS (Corey et al. 2015) and 2013–2014 NATS

(Table 2.9) underscore that use of flavored e-cigarettes remains prevalent among youth and young adults who currently use e-cigarettes.

Conclusion

- 1) Among middle and high school students, both ever and past-30-day e-cigarette use have more than tripled since 2011. Among young adults 18–24 years of age, ever e-cigarette use more than doubled from 2013 to 2014 following a period of relative stability from 2011 to 2013.
- 2) The most recent data available show that the prevalence of past-30-day use of e-cigarettes is similar among high school students (16% in 2015, 13.4% in 2014) and young adults 18–24 years of age (13.6% in 2013–2014) compared to middle school students (5.3% in 2015, 3.9% in 2014) and adults 25 years of age and older (5.7% in 2013–2014).
- 3) Exclusive, past-30-day use of e-cigarettes among 8th-, 10th-, and 12th-grade students (6.8%, 10.4%, and 10.4%, respectively) exceeded exclusive, past-30-day use of conventional cigarettes in 2015 (1.4%, 2.2%, and 5.3%, respectively). In contrast—in 2013–2014 among young adults 18–24 years of age—exclusive, past-30-day use of conventional cigarettes (9.6%) exceeded exclusive, past-30-day use of e-cigarettes (6.1%). For both age groups, dual use of these products is common.
- 4) E-cigarette use is strongly associated with the use of other tobacco products among youth and young adults, particularly the use of combustible tobacco products. For example, in 2015, 58.8% of high school students who were current users of combustible tobacco products were also current users of e-cigarettes.
- 5) Among youth—older students, Hispanics, and Whites are more likely to use e-cigarettes than younger students and Blacks. Among young adults—males, Hispanics, Whites, and those with lower levels of education are more likely to use e-cigarettes than females, Blacks, and those with higher levels of education.
- 6) The most commonly cited reasons for using e-cigarettes among both youth and young adults are curiosity, flavoring/taste, and low perceived harm compared to other tobacco products. The use of e-cigarettes as an aid to quit conventional cigarettes is not reported as a primary reason for use among youth and young adults.
- 7) Flavored e-cigarette use among young adult current users (18–24 years of age) exceeds that of older adult current users (25 years of age and older). Moreover, among youth who have ever tried an e-cigarette, a majority used a flavored product the first time they tried an e-cigarette.
- 8) E-cigarette products can be used as a delivery system for cannabinoids and potentially for other illicit drugs. More specific surveillance measures are needed to assess the use of drugs other than nicotine in e-cigarettes.

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SECTION 3. HEALTH EFFECTS OF E-CIGARETTE USE AMONG U.S. YOUTH AND YOUNG ADULTS

Introduction

This chapter focuses on the short-term and potential long-term health effects related to the incidence and continued use of electronic cigarettes (e-cigarettes) by youth and young adults. The sharp increase in the prevalence of e-cigarette use among youth and young adults, especially from 2011 to 2015 (Centers for Disease Control and Prevention [CDC] 2015, 2016), highlights the compelling need to learn more about this evolving class of products. This chapter highlights the scientific literature that addresses potential adverse health effects caused by direct exposure to aerosolized nicotine, flavorants, chemicals, and other particulates of e-cigarettes; secondhand exposure to e-cigarette aerosol; and exposure to the surface-deposited aerosol contaminants. Literature regarding harmful consequences of close contact with malfunctioning e-cigarette devices and ingestion of the nicotine-containing liquids (e-liquids) are also explored. This chapter examines available data on e-cigarettes and youth, reviews established human and animal data on harmful developmental effects of nicotine (prenatal and adolescent), and reviews data on e-cigarettes among adults when data on youth are not available. Of note, given the relatively recent emergence of e-cigarettes, data are not yet available that address the long-term health effects of use or exposure over several years compared with nonuse or exposure to air free from secondhand tobacco smoke and aerosol from e-cigarettes; thus, the discussion is limited in that regard.

Conclusions from Previous Surgeon General's Reports

This chapter comprehensively reviews a new and emerging body of scientific evidence related to the use of e-cigarettes by youth and young adults. The enormous knowledge base on tobacco smoking and human health is also relevant to this discussion. That literature, which has been accumulating for more than 50 years, provides incontrovertible evidence that smoking is a cause of disease in almost every organ of the body (U.S. Department of Health and Human Services [USDHHS] 2004, 2014). Laboratory research has characterized the components of tobacco smoke and probed the mechanisms by which these constituents cause addiction and injury to cells, tissues, organs, and the developing fetus.

The evidence on the harmful consequences of nicotine exposure in conventional cigarettes, including addiction, and other adverse effects, is particularly relevant to e-cigarettes. Nicotine doses from e-cigarettes vary tremendously depending on characteristics of the user (experience with smoking conventional cigarettes or e-cigarettes), technical aspects of the e-cigarette, and levels of nicotine in the e-liquid. Although studies of nicotine doses in youth and young adults are lacking, studies of adults have found delivery of nicotine from e-cigarettes in doses ranging from negligible to as large as (Lopez et al. 2016; Vansickel and Eissenberg 2013; Spindle et al. 2015; St. Helen et al. 2016) or larger than (Ramôa et al.

2016) conventional cigarettes. Similarly, passive exposure to secondhand nicotine from e-cigarettes is just as large (Flouris et al. 2013) or lower than (Czogala et al. 2014) conventional cigarettes.

The findings of scientific research on smoking and involuntary exposure to tobacco smoke have been reviewed thoroughly in the 32 reports on smoking and health produced by the Surgeon General to date (there is one report on smokeless tobacco) (Table 3.1). The landmark first report was published in 1964 (U.S. Department of Health, Education, and Welfare [USDHEW] 1964), and the 50th-anniversary report, released in January 2014, comprehensively covered multiple aspects of cigarette smoking and health and lengthened the list of diseases caused by smoking and involuntary exposure to tobacco smoke (USDHHS 2014). Other Surgeon General's reports that are particularly relevant to the present report include reports on the health consequences of smoking and involuntary exposure to tobacco smoke (USDHHS 2004, 2006), on the mechanisms by which smoking causes disease (USDHHS 2010), and on the health consequences of smoking on youth and young adults (USDHHS 1994, 2012). The Surgeon General's reports on smoking and health have provided powerful conclusions on the dangers of nicotine. The 1988 report, released by Surgeon General C. Everett Koop, was the first to characterize smoking as addictive, and it identified nicotine as "...the drug in tobacco that causes addiction" (Appendix 3.1)³ (USDHHS 1988, p. 9).

Subsequent reports expanded on the conclusions in the 1988 report related to nicotine—reaffirming that nicotine causes addiction, describing nicotine's effects on key brain receptors (USDHHS 2010), and emphasizing that youth are more sensitive to nicotine than adults and can become dependent to nicotine much faster than adults (USDHHS 2012). This is of particular concern in the context of e-cigarettes because blood nicotine levels in e-cigarette users have been reported as being comparable to or higher than levels in smokers of conventional cigarettes (Lopez et al. 2016; Spindle et al. 2015), and serum cotinine (a nicotine metabolite) levels have been reported as being equal to that found in conventional cigarette users (Etter 2016; Marsot and Simon 2016). Because of their sensitivity to nicotine and subsequent addiction, about 3 out of 14 young smokers end up smoking into adulthood, even if they intend to quit after a few years; among youth who continue to smoke as adults, one-half will die prematurely from smoking (Peto et al. 1994; CDC 1996; Hahn et al. 2002; Doll et al. 2004). Surgeon General's reports have also emphasized the critical role of environmental determinants of tobacco use, including the causal roles of the tobacco industry's advertising and promotional activities and of the peer social environment (USDHHS 2012).

The 2014 Surgeon General's report included a chapter that addressed the numerous adverse consequences of nicotine other than addiction (USDHHS 2014).

The review documented the broad biological activity of nicotine, which can activate multiple biological pathways, and the adverse effects of nicotine exposure during pregnancy on fetal development and during adolescence on brain development. Of concern with regard to current trends in e-cigarette use among youth and young adults, the evidence suggests that exposure to nicotine during this period of life may have lasting deleterious consequences for brain development, including detrimental effects on cognition (USDHHS 2014).

³ All appendixes and appendix tables that are cross-referenced in this chapter are available only online at <http://www.surgeongeneral.gov/library/reports/>.

Table 3.1. Relevant conclusions from previous Surgeon General's reports on smoking and health

Report	Year	Conclusions
<i>The Health Consequences of Smoking: Nicotine Addiction</i> (USDHHS 1988, p. 9)	1988	Major Conclusions 1. Cigarettes and other forms of tobacco are addicting. 2. Nicotine is the drug in tobacco that causes addiction. 3. The pharmacologic and behavioral processes that determine tobacco addiction are similar to those that determine addiction to drugs such as heroin and cocaine.
<i>How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease</i> (USDHHS 2010, p. 183)	2010	Chapter 4. Nicotine Addiction: Past and Present 1. Nicotine is the key chemical compound that causes and sustains the powerful addicting effects of commercial tobacco products. 2. The powerful addicting effects of commercial tobacco products are mediated by diverse actions of nicotine at multiple types of nicotinic receptors in the brain. 3. Evidence is suggestive that there may be psychosocial, biologic, and genetic determinants associated with different trajectories observed among population subgroups as they move from experimentation to heavy smoking. 4. Inherited genetic variation in genes such as <i>CYP2A6</i> contributes to the differing patterns of smoking behavior and smoking cessation. 5. Evidence is consistent that individual differences in smoking histories and severity of withdrawal symptoms are related to successful recovery from nicotine addiction.
<i>Preventing Tobacco Use Among Youth and Young Adults</i> (USDHHS 2012, pp. 8, 460)	2012	Major Conclusions 1. Cigarette smoking by youth and young adults has immediate adverse health consequences, including addiction, and accelerates the development of chronic diseases across the full life course. 2. Prevention efforts must focus on both adolescents and young adults because among adults who become daily smokers, nearly all first use of cigarettes occurs by 18 years of age (88%), with 99% of first use by 26 years of age. 3. Advertising and promotional activities by tobacco companies have been shown to cause the onset and continuation of smoking among adolescents and young adults. 4. After years of steady progress, declines in the use of tobacco by youth and young adults have slowed for cigarette smoking and stalled for smokeless tobacco use. 5. Coordinated, multicomponent interventions that combine mass media campaigns, price increases including those that result from tax increases, school-based policies and programs, and statewide or community-wide changes in smokefree policies and norms are effective in reducing the initiation, prevalence, and intensity of smoking among youth and young adults. Chapter 4. Social, Environmental, Cognitive, and Genetic Influences on the Use of Tobacco among Youth 1. Given their developmental stage, adolescents and young adults are uniquely susceptible to social and environmental influences to use tobacco. 2. Socioeconomic factors and educational attainment influence the development of youth smoking behavior. The adolescents most likely to begin to use tobacco and progress to regular use are those who have lower academic achievement. 3. The evidence is sufficient to conclude that there is a causal relationship between peer group social influences and the initiation and maintenance of smoking behaviors during adolescence. 4. Affective processes play an important role in youth smoking behavior, with a strong association between youth smoking and negative affect. 5. The evidence is suggestive that tobacco use is a heritable trait, more so for regular use than for onset. The expression of genetic risk for smoking among young people may be moderated by small-group and larger social-environmental factors.
<i>The Health Consequences of Smoking—50 Years of Progress</i> (USDHHS 2014, p. 126)	2014	Chapter 5: Nicotine 1. The evidence is sufficient to infer that at high-enough doses nicotine has acute toxicity. 2. The evidence is sufficient to infer that nicotine activates multiple biological pathways through which smoking increases risk for disease. 3. The evidence is sufficient to infer that nicotine exposure during fetal development, a critical window for brain development, has lasting adverse consequences for brain development. 4. The evidence is sufficient to infer that nicotine adversely affects maternal and fetal health during pregnancy, contributing to multiple adverse outcomes such as preterm delivery and stillbirth. 5. The evidence is suggestive that nicotine exposure during adolescence, a critical window for brain development, may have lasting adverse consequences for brain development. 6. The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to nicotine and risk for cancer.

Note: USDHHS = U.S. Department of Health and Human Services.

Finally, the aerosol from e-cigarettes may include other components that have been addressed in previous Surgeon General's reports, such as tobacco-specific nitrosamines (TSNAs), acrolein, and formaldehyde (USDHEW 1979; USDHHS 2010). Aerosols generated with vaporizers contain up to 31 compounds, including nicotine, nicotyrine, formaldehyde, acetaldehyde glycidol, acrolein, acetol, and diacetyl (Sleiman et al. 2016). Glycidol is a probable carcinogen not previously identified in the vapor, and acrolein is a powerful irritant (Sleiman et al. 2016). Although these constituents have been identified in e-cigarette aerosol, current evidence is unclear on whether typical user dosages achieve levels as high as conventional cigarettes, or at harmful or potentially harmful levels. More information will be available in the coming years as e-cigarette manufacturers begin reporting harmful or potential harmful constituents in compliance with the Tobacco Control Act.

Health Effects of E-Cigarette Use

The potential adverse health effects for youth who inhale e-cigarette aerosol include those on the body from acute administration of nicotine, flavorants, chemicals, other particulates, and additional effects, such as (1) nicotine addiction; (2) developmental effects on the brain from nicotine exposure, which may have implications for cognition, attention, and mood; (3) e-cigarette influence initiating or supporting the use of conventional cigarettes and dual use of conventional cigarettes and e-cigarettes; (4) e-cigarette influence on subsequent illicit drug use; (5) e-cigarette effects on psychosocial health, particularly among youth with one or more comorbid mental health disorders; and (6) battery explosion and accidental overdose of nicotine.

Effects of Aerosol Inhalation by the E-Cigarette User

Determining the potential health effects of inhaling e-cigarette aerosol is challenging due to the number of possible combinations of customizable options (Seidenberg et al. 2016), including battery power, nicotine concentration, e-liquids (Goniewicz et al. 2015; Buettner-Schmidt et al. 2016), and use behaviors and puff topography (Dawkins et al. 2016; Lopez et al. 2016). The amount of nicotine, flavorants, and other e-liquid constituents in e-cigarettes available for consumers to purchase varies widely, and the aerosolized constituents delivered vary by the type and voltage of the e-cigarette device being used (Cobb et al. 2015). Studies of commercial products have shown that e-liquids can contain as little as 0 milligrams/milliliter (mg/mL) to as much as 36.6 mg/mL of nicotine (Goniewicz et al. 2015); can be mislabeled (Peace et al. 2016); can vary by propylene glycol (PG)/vegetable glycerin (VG) ratio; and can contain one or more of several thousand available flavorants (Zhu et al. 2014b). Some liquids intended for use in e-cigarettes contain adulterants not named on ingredient lists (Varlet et al. 2015), and under at least some user conditions, the aerosolization process, which involves heating, produces additional toxicants that may present health risks (Talih et al. 2015). The sections that follow comprehensively cover the effects of inhaling aerosolized nicotine and then consider what is known about solvents (i.e., PG and VG, flavorants, and other chemicals) added to e-cigarettes, adulterants in e-liquids formed in the nicotine extraction process (e.g., *N*-nitrosonornicotine), and toxicants formed during the heating and aerosolization process (e.g., acrolein and formaldehyde) (Sleiman et al. 2016).

Dose and Effects of Inhaling Aerosolized Nicotine

Nicotine addiction via e-cigarette use is a primary public health concern due to the exponential growth in e-cigarette use among youth. The potential for widespread nicotine addiction among youth is high, as are the harmful consequences of nicotine on fetal development and the developing adolescent brain (USDHHS 2014). Nicotine, a psychomotor stimulant drug, is the primary psychoactive and addictive constituent in the smoke of conventional cigarettes and an important determinant in maintaining smoking dependence (e.g., USDHHS 2014). E-liquids typically contain nicotine, although in more widely variable concentrations than those found in conventional cigarettes (Trehy et al. 2011; Cameron et al. 2014; Cheng 2014; Goniewicz et al. 2015; Marsot and Simon 2016). The concentration of liquid nicotine is only one factor that influences the amount of aerosolized nicotine available for inhalation (Lopez et al. 2016); other factors include the power of the device being used (e.g., battery voltage, heater resistance) and user behavior (e.g., puff duration, interpuff interval) (Shihadeh and Eissenberg 2015; Talih et al. 2016; Etter 2016). The interplay of these factors may help to explain the variability in plasma nicotine concentration when adults use e-cigarettes under controlled conditions which can be higher (Ramôa et al. 2016), lower (Bullen et al. 2010; Vansickel et al. 2010, 2012; Farsalinos et al. 2014b; Nides et al. 2014; Oncken et al. 2015; Yan and D’Ruiz 2015), or similar to those obtained by smoking conventional cigarettes (Vansickel and Eissenberg 2013; Spindle et al. 2015; St. Helen et al. 2016; see Figure 3.1). Generalization across studies is difficult due to variations in devices, e-liquids, and e-cigarette use behavior within the study sample. As demonstrated in Figure 3.1, in studies where a variety of products were used under similar laboratory conditions (i.e., blood sampling before and immediately after a 10-puff episode), there was wide variability in nicotine delivery between devices, with “cigalike” products (cigarette-like products) delivering less nicotine than “tank” products (Farsalinos et al. 2014b; Yan and D’Ruiz 2015), and low-resistance, dual-coil “cartomizer” products having the capacity to deliver less or more nicotine than a conventional cigarette, depending on the concentration of liquid nicotine (Ramôa et al. 2016).

When the device type and liquid dose were held constant in a controlled session in one study, plasma nicotine concentrations (in this case in nanograms [ng]/mL) varied considerably across participants (0.8 to 8.5 ng/mL) (Nides et al. 2014). This variation was likely attributable to the manner in which the users puffed when using e-cigarettes, or that person’s “puff topography,” which includes the number of puffs, the intake volume and duration, the interpuff interval, and the flow rate (Zacny and Stitzer 1988; Blank et al. 2009).

Available data suggest that puff durations among adult cigarette smokers who are new e-cigarette users are comparable to those observed with conventional cigarettes (at least about 2 seconds [sec]) (Farsalinos et al. 2013b; Hua et al. 2013; Norton et al. 2014). However, puff durations during e-cigarette use among experienced e-cigarette users may be twice as long (~4 sec) (Farsalinos et al. 2013b; Hua et al. 2013; Spindle et al. 2015) as puff duration during conventional cigarette use. Puff duration is directly related to the nicotine content of the e-cigarette aerosol (i.e., the yield or dose) (Talih et al. 2016), suggesting that smokers of conventional cigarettes who switch to e-cigarettes may increase the duration of their puffs when using the new product in an attempt to extract more nicotine. Research also suggests that cigarette smokers may learn to alter other aspects of their puffing behavior when using an e-cigarette (Spindle et al. 2015). Relative to smokers of conventional cigarettes (Kleykamp et al. 2008), experienced e-cigarette users were found to have puff volumes that were

significantly higher (101.4 mL vs. 51.3 mL) and puff flow rates that were significantly lower (24.2 mL/sec vs. 37.9 mL/sec) (Spindle et al. 2015). In a different study, adult cigarette smokers who had never used e-cigarettes but switched to e-cigarettes showed significantly increased puff durations and decreased puff flow rates within 1 week (Lee et al. 2015). Elsewhere, adult cigarette smokers given an e-cigarette appeared to show an enhanced ability to extract nicotine from their device after 4 weeks of use (Hajek et al. 2015). Thus, the health effects of aerosolized nicotine in e-cigarette users may depend on a variety of factors, including the e-liquid used, the user's behavior, and the user's experience with the product.

Aerosolized Nicotine and Cardiovascular Function

Smoking is a major cause of death from cardiovascular disease (USDHHS 2014), and exposure to nicotine has been identified as a potential initiating factor in the atherogenic process (Lee et al. 2011; Santanam et al. 2012; Benowitz and Burbank 2016). Acute administration of nicotine causes a variety of well-characterized, dose- and route-dependent effects in adults, including cardiovascular effects, such as increases in heart rate and blood pressure (BP) and greater cardiac output, leading to an increase in myocardial oxygen demand (Rosenberg et al. 1980; USDHHS 2014). Reports from cell biology and animal studies have established biologic plausibility between nicotine alone and negative cardiovascular effects (Hanna 2006; Santanam et al. 2012). These studies have shown that nicotine induces the production of various inflammatory mediators involved with atherosclerotic pathogenesis (Lau and Baldus 2006), and that at the cellular level, nicotine induces C-reactive protein (CRP) expression in macrophages that contribute pro-inflammatory and pro-atherosclerotic effects (Mao et al. 2012).

Long-term studies on the safety of nicotine-only exposure (e.g., as with using e-cigarettes rather than smoking conventional cigarettes) among youth have not been conducted, and little is known about the cardiovascular effects of e-cigarette use among adults. However, when e-cigarettes are accompanied by a measurable increase in plasma nicotine concentration, it increases heart rate (Vansickel et al. 2012; Vansickel and Eissenberg 2013; Nides et al. 2014; Yan and D'Ruiz 2015), and diastolic BP rises.

Given the paucity of long-term data on the impact of e-cigarette smoking in relation to cardiovascular disease, other nicotine products offer a useful analogy. A meta-analysis reported that replacing the consumption of conventional cigarettes with nicotine replacement therapy (NRT) reduces cardiovascular risk among former smokers without significant adverse consequences (compared with current smokers) (Greenland et al. 1998; Moore et al. 2009). However, most NRT use is temporary (<26 months), and the adverse consequences of longer term NRT therapy are unknown.

Elsewhere, investigators examined the relationship between the use of Swedish-type moist snuff (or "snus"), which contains high levels of nicotine and low levels of TSNA, and the incidence of acute myocardial infarction among men with a mean age of 35 years who had never smoked cigarettes. The researchers, who pooled data from eight prospective cohort studies, found no support for any association between the use of snus and the development of acute myocardial infarction (Hansson et al. 2012), regardless of timing, intensity, duration, or period of use among the men who were followed for 4–29 years.

In summary, despite overwhelming epidemiologic evidence linking the use of conventional cigarettes with cardiovascular disease, the precise components of cigarette smoke responsible for this relationship and the mechanisms by which they exert their effects

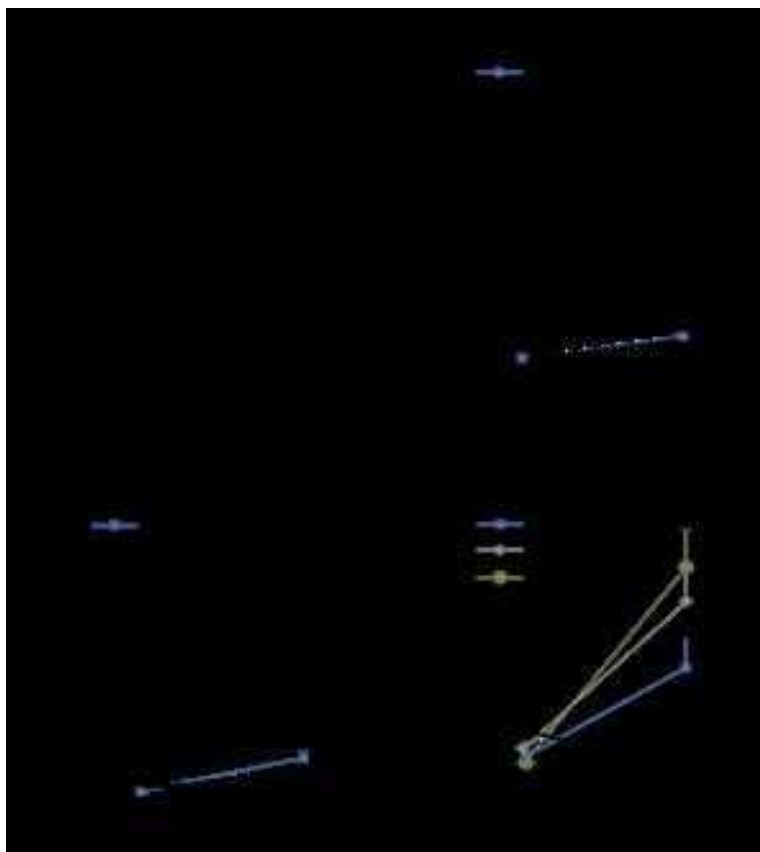
have not yet been fully explained (Hanna 2006). For e-cigarettes, biological data support a potential association with cardiovascular disease, and short-term use of these products is accompanied by a measurable increase in plasma nicotine concentrations in adults as well as increases in heart rate and blood pressure. Much more research is needed, but the limited data available suggest the typical cardiovascular effects exerted by nicotine are also exerted by e-cigarettes (Benowitz and Burbank 2016; Bhatnagar 2016).

Aerosolized Nicotine and Dependence

Although a great deal is known about self-administration of nicotine and the development of nicotine dependence among adults (USDHHS 2014) and youth (Colby et al. 2000; USDHHS 2012; O’Loughlin et al. 2014; Yuan et al. 2015), more research is needed on nicotine dependence in youth and young adults as a result of using e-cigarettes. Nicotine dependence, also referred to as nicotine addiction (USDHHS 2010) or tobacco use disorder (American Psychiatric Association [APA] 2013), is defined as a neurobiological adaptation to repeated drug exposure that is manifested behaviorally by highly controlled or compulsive use; psychoactive effects such as tolerance, physical dependence, and pleasant effect; and nicotine-reinforced behavior, including an inability to quit despite harmful effects, a desire to quit, and repeated cessation attempts (USDHHS 1988; APA 2013). In tobacco-dependent users of conventional cigarettes, a predictable consequence of short-term abstinence (e.g., for more than a few hours) is the onset of withdrawal symptoms indicated by self-reported behavioral, cognitive, and physiological symptoms and by clinical signs (USDHHS 2010). Subjective withdrawal symptoms are manifested by affective disturbance, including irritability and anger, anxiety, and depressed mood. The behavioral symptoms include restlessness, sleep disturbance, and increased appetite. Cognitive disturbances usually center on difficulty in concentrating (USDHHS 2010).

Early studies of conventional cigarette smokers using e-cigarettes reported poor nicotine delivery with little to no increase in blood nicotine levels after puffing (Eissenberg 2010; Vansickel et al. 2010). Later studies reported that the effect on serum cotinine levels among new e-cigarette users can be similar to that generated by conventional cigarettes (Flouris et al. 2013; Lopez et al. 2016). Studies examining this discrepancy found that e-cigarette users require longer puffs to deliver equivalent nicotine doses (Lee et al. 2015), and within a week, inexperienced e-cigarette users adjust their puffing patterns after switching (Hua et al. 2013b; Lee et al. 2015; Talih et al. 2015).

In more experienced e-cigarette users, blood nicotine levels appear to be influenced by puffing patterns, such as puff length. Volume and frequency and plasma nicotine levels ranging from 2.50 to 13.4 ng/mL have been observed after 10 puffs of an e-cigarette (Dawkins and Corcoran 2014). Dawkins and colleagues (2016) used 24 mg/mL nicotine strength liquid and observed high blood nicotine levels that were achieved very quickly, matching and even exceeding those reported in conventional cigarette smokers. St. Helen and colleagues (2016) conducted a similar study and reported that e-cigarettes can deliver levels of nicotine that are comparable to or higher than conventional cigarettes. Finally, Etter (2016) reported cotinine levels among experienced e-cigarette users similar to levels usually observed in conventional cigarette smokers. Figure 3.1 and Table A3.1-1 in Appendix 3.1 summarize studies on aerosolized nicotine from e-cigarettes and dependence using dependency criteria.



Source: Vansickel et al. (2010); Farsalinos et al. (2014b); Yan and D’Ruiz (2015); and Ramôa et al. (2016).

Notes: Data for conventional cigarettes are from 32 tobacco cigarette smokers using their usual brand of cigarette (Vansickel et al. 2010). E-cigarette A is a cigalike called “blu” loaded with two different concentrations of liquid nicotine (16 or 24 mg/mL, both containing 20% propylene glycol and 50% vegetable glycerin). Data are from 23 smokers of tobacco cigarettes with 7 days of experience with the e-cigarette product (Yan and D’Ruiz 2015). E-cigarette B is a cigalike called “V2cigs,” and E-cigarette C is a “tank” product called “EVIC” with an “Evod” heating element; both were loaded with an 18 mg/mL liquid containing 34% propylene glycol and 66% vegetable glycerin. Data are from 23 experienced users of e-cigarettes (Farsalinos et al. 2014b). E-cigarette D uses a 3.3-volt “Ego” battery fitted with a 1.5-Ohm dual coil cartomizer (“Smoktech”) and filled with ~1 mL of a 70% propylene glycol, 30% vegetable glycerin liquid that varied by liquid nicotine concentration (0, 8, 18, or 36 mg/mL). Data are from 16 experienced users of e-cigarettes (Ramôa et al. 2016).

Figure 3.1. Plasma nicotine concentration from different human laboratory studies and four different products with blood sampled before and immediately after a 10-puff bout with the products.

The ability of e-cigarettes to deliver comparable or higher amounts of nicotine compared to conventional cigarettes raises concerns about e-cigarette use generating nicotine dependence among young people (Dawkins et al. 2016; Etter 2016; St. Helen et al. 2016). The reported blood levels of nicotine, or cotinine, in e-cigarette users is likely to cause physiological changes in nicotinic acetylcholine receptors in the brain that would sustain nicotine addiction (Kandel and Kandel 2014; Yuan et al. 2015). This is particularly

concerning for adolescents and young adults, given that early exposure to nicotine increases the severity of future nicotine dependence (St. Helen et al. 2016; USDHHS 2014).

Symptoms of nicotine dependence can occur soon after the initiation of conventional smoking, and even before established use, among adolescents and young adults (DiFranza et al. 2002; O'Loughlin et al. 2003; Dierker et al. 2007; Ramôa et al. 2016). Furthermore, some adolescents have reported nicotine dependence symptoms while using tobacco as little as 1–3 days per month (Rose et al. 2010). Using the National Comorbidity Survey-Adolescent dataset, Dierker and colleagues (2012) reported that nicotine dependence in adolescents was likely to occur within 1 year of the initiation of weekly or daily smoking, regardless of sociodemographic variables. Importantly, when smoking onset began at a younger age, the transition to weekly and daily smoking was more rapid, indicating a youthful neurobiological sensitivity to nicotine (Dierker et al. 2012). Zhan and colleagues (2012) found that symptoms of nicotine dependence could be detected among teenagers before they had smoked even 100 cigarettes.

Because few validated measures exist for assessing dependence on e-cigarette use, some researchers have adapted those originally developed to measure dependence in smokers of conventional cigarettes. Among adults, scores on these measures have been consistently lower in e-cigarette users than in smokers of conventional cigarettes (Farsalinos et al. 2013a; Etter and Eissenberg 2015; Foulds et al. 2015). Still, scores for e-cigarette dependence among former cigarette smokers were positively associated with the nicotine concentration of the e-cigarette liquid and the type of device used (Etter 2015; Etter and Eissenberg 2015; Foulds et al. 2015). Research in this area is challenging to interpret because measurement of youth e-cigarette dependence has not been standardized and there is a wide variation in device/e-liquid combinations, which allow for adjustable nicotine delivery among study participants. Regardless, among 766 adults, who were daily users of e-cigarettes (with nicotine) and who were either former cigarette smokers (83%) or current cigarette smokers (17%), 30.7% indicated that they would likely be unable to stop using e-cigarettes, 28.2% that they would find it “very difficult” or “impossible” to stop using e-cigarettes, and 27.5% that they were unable to stop e-cigarette use (Etter and Eissenberg 2015). However, it is important to note that e-cigarettes were less addictive than conventional cigarettes in this sample (Etter and Eissenberg 2015).

In summary, the addictive liability of e-cigarettes has the potential to be at least equivalent to that of conventional cigarettes, given nicotine dose levels produced by these products, particularly among experienced users operating new-generation devices (Ramôa et al. 2016). More generally, the delivery of nicotine in sufficient doses and blood concentration would be expected to produce and maintain dependence in e-cigarette users. Further work would be useful to determine the natural course and history of e-cigarette use among smokers of conventional cigarettes, former smokers, and never smokers and to more accurately determine the nicotine addiction liability of e-cigarette use. Unfortunately, these issues have not been explored in adolescents, although the prevalence of e-cigarette use has increased considerably in that population since 2011 (see Chapter 2).

Effects of Nicotine in Youth Users

Nicotine is the prime psychoactive substance in conventional cigarettes (Yuan et al. 2015), and given that the developing adolescent brain is immature and vulnerable to neurobiological insults (Bernheim et al. 2013; Lydon et al. 2014), it is important to

understand how nicotine delivered by e-cigarette use affects adolescent brain development and how responses to nicotine in adolescents differ from those seen in adults. Substantial evidence suggests that nicotine can negatively influence both adolescent and prenatal brain development (USDHHS 2014). For example, Weiss and colleagues (2008) reported a strong mechanistic link among early nicotine exposure (younger than 16 years of age), common genes related to the severity of nicotine addiction (CHRNA5-A3-B4 haplotypes), and adult nicotine addiction in three independent populations of European origins. Although much of the literature on nicotine addiction arises from studies of nicotine exposure among adults, and with combustible tobacco products (see Table A3.1-2 in Appendix 3.1), there is a growing body of biological mechanistic literature from animal studies that model the effects of nicotine in doses equivalent to those for humans (see Table A3.1-3 in Appendix 3.1). These animal and human studies, taken together with studies of rising e-cigarette prevalence in youth (see Chapter 2), point to an age-dependent susceptibility to nicotine as a neurobiological insult.

Limited direct human experimental data exist on the effects of nicotine exposure from e-cigarettes on the developing adolescent brain, but experimental laboratory data have been found to be relevant in animal models to contextualize effects in humans (Stevens and Vaccarino 2015). Even if the full complexity of human brain development and behavioral function during adolescence cannot be completely modeled in other species, the similarities across adolescents of different species support the use of animal models of adolescence when examining neural and environmental contributors to adolescent-characteristic functioning (Spear 2010).

Animal studies provide an effective method to examine the persistent effects of prenatal, child, and adolescent nicotine exposure, in addition to human epidemiologic data. When considering an epidemiologic causal argument of exposure (risk factor) to health outcome (disease), one should note that animal models lend biological plausibility when experimentation with humans is not possible (or ethical) (Rothman et al. 2008). Furthermore, animal studies offer significant advantages compared to human studies—with the ability to control for many confounding factors, to limit nicotine exposure to differing levels of physical and neural development—and are pivotal for understanding the neural substrates associated with adolescence. The validity of any causal argument when examining animal models requires careful consideration, and yet in combination with epidemiologic data—such as prevalence, incidence, and strength of association between exposure and outcome—a causal argument can be constructed with literature from animal models representing biologic plausibility. Using a variety of study designs and research paradigms including humans and animals, research in this area provides evidence for neuroteratogenic and neurotoxic effects on the developing adolescent brain (Lydon et al. 2014; England et al. 2015).

The brain undergoes significant neurobiological development during adolescence and young adulthood, which are critical periods of sensitivity to neurobiological insults (such as nicotine) and experience-induced plasticity (Spear 2000; Dahl 2004; Gulley and Juraska 2013). Although maturation occurs in different regions of the brain at different rates, a similar progression occurs in all areas characterized by a rapid formation of synaptic connections in early childhood, followed by a loss of redundant or unnecessary synapses (called pruning) and the formation of myelin. Myelination is the process by which a fatty layer, called myelin, accumulates around nerve cells (neurons). Because of myelin, nerve cells can transmit information faster, allowing for more complex brain processes. Pruning allows for more

focused concentration, and myelination allows for faster electrical and neural signaling; both allow for more efficient cognitive processing. During adolescence and into young adulthood, myelination occurs rapidly in the frontal lobe, a place in the brain that controls executive functioning, reasoning, decision-making skills, self-discipline, and impulse control. Plasticity refers to the current understanding that the brain continues to change throughout life, not only because of normal, maturational neural growth and development but also because of changes in environmental neurobiological exposures (such as nicotine), injuries, behaviors, thinking, and emotions (Mills and Tamnes 2014).

Across species, and in humans, adolescence is a key period of increased plasticity and rapid growth of brain circuits that regulate social, emotional, and motivational processes and decision making (Spear 2000, 2011; Nelson et al. 2005; Ernst and Fudge 2009; Counotte et al. 2011). The prefrontal cortex, which is involved in higher level regulatory control of complex behaviors (such as planning, impulse control, and working memory), continues normal structural and functional development into young adulthood, to about 25 years of age (Giedd and Rapoport 2010; Somerville and Casey 2010). Because of the immaturity and rapid growth of the prefrontal cortex, adolescents and young adults normally exhibit moody, risk-taking, and unpredictable impulsive behaviors. The combination of delayed maturation of frontal cognitive control and increased reactivity of subcortical reward-related and emotion-processing systems may lead to increased risk-taking behavior and a greater susceptibility to initiating substance use and the development of dependence (Steinberg 2008; Ernst and Fudge 2009; Counotte et al. 2011; Spear 2011). Thus, myelination is vitally important to the healthy functioning of the central nervous system, and any exposure that significantly interferes with the myelination process can cause mild-to-severe cognitive and learning problems (Brady et al. 2012).

Brain development in juvenile rodents has been reported to display patterns that resemble those of human beings, suggesting that the rodent model might be relevant to studying the neurobiological underpinnings of brain maturation in teenagers (Spear 2000). Studies across species have revealed unique characteristics of adolescent nonhuman brain structure, mechanisms, and function that provide biological plausibility to the hypothesis that human adolescents are particularly vulnerable to nicotine uptake (O'Loughlin et al. 2015; Yuan et al. 2015). There is evidence for rapid growth of gray matter, followed by activity-dependent synaptic pruning (the process of synapse elimination that occurs between early childhood and the onset of puberty) and increasing myelination throughout the brain (Casey et al. 2005; Lenroot and Giedd 2006; Giedd and Rapoport 2010; Counotte et al. 2011).

Nicotine has more significant and durable damaging effects on adolescent brains compared to adult brains, the former suffering more harmful effects. Preclinical animal studies have shown that in rodent models, nicotinic acetylcholine receptor (nAChR) signaling is still actively changing during adolescence, with higher expression and functional activity of nAChRs in the forebrain of adolescent rodents compared to their adult counterparts (Britton et al. 2007; Kota et al. 2007; Doura et al. 2008). Furthermore, in rodent models, nicotine actually enhances neuronal activity in several reward-related regions and does so more robustly in adolescents than in adults (Schochet et al. 2005; Shram et al. 2007; Dao et al. 2011). This increased sensitivity to nicotine in the reward pathways of adolescent rats is associated with enhanced behavioral responses, such as strengthening the stimulus-response reward for administration of nicotine. In conditioned place-preference tests—where reward is measured by the amount of time animals spend in an environment where they receive nicotine

compared to an environment where nicotine is not administered—adolescent rodents have shown an increased sensitivity to the rewarding effects of nicotine at very low doses (0.03 mg/kg) (Vastola et al. 2002; Belluzzi et al. 2004; Brielmaier et al. 2007; Kota et al. 2007; Natarajan et al. 2011) and exhibited a unique vulnerability to oral self-administration during the early-adolescent period (Adriani et al. 2002). Adolescent rodents also have shown higher levels of nicotine self-administration than adults (Levin et al. 2003; Chen et al. 2007; Natividad et al. 2013), decreased sensitivity to the aversive effects of nicotine (Adriani et al. 2002; Shram et al. 2006; Torres et al. 2008), and less prominent withdrawal symptoms following chronic nicotine exposure (O'Dell et al. 2006). This characteristic in rodent models of increased positive and decreased negative short-term effects of nicotine during adolescence (versus adulthood) highlights the possibility that human adolescents might be particularly vulnerable to developing dependency to and continuing to use e-cigarettes. These biological mechanisms are of great public health importance as exposure to nicotine grows among nonsmoking youth through the increasing prevalence of e-cigarette use.

Beyond their unique vulnerability to nicotine use, and thus smoking uptake, human adolescents may be particularly vulnerable to the detrimental consequences of nicotine exposure, including an increase in drug-seeking behaviors (Kandel and Kandel 2014), deficits in attention and cognition, and mood disorders (Yuan et al. 2015). In animal models, chronic nicotine exposure during adolescence has been shown to produce long-lasting, unique effects that are not observed in mature adult animals. Moreover, animal models have provided substantial evidence that the limbic system—which controls cognition, emotion, and drug-reward—is actively maturing during adolescence and during this age is vulnerable to long-term modification by nicotine.

Reward-Seeking Behaviors

A very strong argument can be made about the association between adolescent exposure to nicotine by smoking conventional cigarettes and the subsequent onset of using other dependence-producing substances. Strong, temporal, and dose-dependent associations have been reported (Isensee et al. 2003; John et al. 2004b; Bronisch et al. 2008; Kandel and Kandel 2015), and a plausible biological mechanism (via rodent and human modeling) suggests that long-term changes in the neural reward system take place as a result of adolescent smoking (Lewinsohn et al. 1999; Huang et al. 2013; Kandel and Kandel 2014). Adolescent smokers of conventional cigarettes have disproportionately high rates of comorbid substance abuse (Kandel et al. 1992; Lai et al. 2000; Hanna et al. 2001), and longitudinal studies have suggested that early adolescent smoking may be a starting point or “gateway” for substance abuse later in life (Kandel et al. 1992; Lewinsohn et al. 1999; Wagner and Anthony 2002; Brook et al. 2007), with this effect more likely for persons with attention deficit hyperactivity disorder (ADHD) (Biederman et al. 2006; Wilens et al. 2008). Although factors such as genetic comorbidity, innate propensity for risk taking, and social influences may underlie these findings (Lindsay and Rainey 1997; Smith et al. 2015), both human neuroimaging and animal studies suggest a neurobiological mechanism also plays a role. In addition, behavioral studies in adolescent and young adult smokers have revealed an increased propensity for risk taking, both generally and in the presence of peers, and neuroimaging studies have shown altered frontal neural activation during a risk-taking task as compared with nonsmokers (Lejuez et al. 2005; Cavalca et al. 2013; Galvan et al. 2013). Rubinstein and colleagues (2011b) used neuroimaging to show decreased brain response to a natural reinforcer

(pleasurable food cues) in adolescent light smokers (1–5 cigarettes per day), with their results highlighting the possibility of neural alterations consistent with nicotine dependence and altered brain response to reward even in adolescent low-level smokers.

Nicotine exposure in rodents at an age of physical development corresponding to human adolescence has been found to increase the reinforcing effects of other drugs of abuse, including cocaine, methamphetamine, and alcohol, without having a major impact on responding for other rewards, thus providing further evidence in support of nicotine as an initiation toward other substance use and abuse (McQuown et al. 2007; Dao et al. 2011; Dickson et al. 2014; Pipkin et al. 2014; Kandel and Kandel 2014). In several rodent studies, treatment with very low doses of nicotine for a few days during early adolescence, but not in late adolescence or adulthood, produced lasting changes in D2 and D3 dopamine receptors and in the selfadministration of other abused drugs (McQuown et al. 2007; Dao et al. 2011; Mojica et al. 2014). Nicotine exposure in adolescent rats also induced rapid and long-lasting dendritic remodeling in the nucleus accumbens shell, a critical component of reward learning and addiction, via a D1 dopamine receptor-mediated mechanism (Ehlinger et al. 2016). This persistent form of nicotine-induced neuroplasticity has the potential to alter synaptic connectivity within reward-processing centers and enhance the addictive effects of drugs of abuse.

Attention and Cognition

Both cognitive improvements (Jasinska et al. 2014) and cognitive deficits (Hall et al. 2014) have been reported after nicotine exposure in healthy human adults, while smoking during adolescence impairs cognition and attention processes. Results of a genetically sensitive, longitudinal “concordant” and “discordant” twin study from the Netherlands Twin Registry indicated a larger increase in attention problems from adolescence to adulthood in twins who smoked than in their never-smoking co-twins (Treur et al. 2015). In another study, adolescent smokers were found to have chronic impairments in the accuracy of their working memory (e.g., in processing information from two sensory modalities simultaneously), which were more severe with an earlier age of onset of smoking (Jacobsen et al. 2005). Functional imaging studies have shown that 24-hour smoking abstinence in adolescent smokers causes acute impairments of verbal memory and working memory, along with chronic decrements in cognitive performance (Jacobsen et al. 2007a). In another study, adolescent users of conventional cigarettes showed decreased prefrontal cortex activation (versus never smokers) during attention tasks, and duration of smoking (in years) was directly correlated with the extent of reduction in prefrontal cortical activity (Musso et al. 2007).

Thus, longitudinal and imaging studies in humans provide support for the hypothesis that adolescent use of conventional cigarettes has both acute and long-term effects on attention and memory. Although nicotine exposure cannot be cited as the sole cause of cognitive defects (or even one of several combined effects in humans), other studies have shown that adolescent nicotine exposure in rats induces lasting synaptic changes in the prefrontal cortical regions critical for normal attention, memory, and cognition that likely underlie observed impairments in attentional and cognitive function (Bergstrom et al. 2008). Adolescent nicotine exposure in rats has induced impairments in stimulus-response-discrimination-learning processes but not in abstract rule-learning processes, which are dependent on dissociable cognitive systems, thus showing the selective effects of nicotine (Pickens et al. 2013). In addition, adolescent, but not postadolescent, treatment of rats with nicotine resulted

in diminished attention span and enhanced impulsivity in adulthood (Counotte et al. 2009, 2011). The biological causes of these cognitive disturbances (reduced attention span and impulse control) were associated with reduced regulation of prefrontal cortex excitatory synapses function in metabotropic glutamate receptor 2 (mGluR2) (Counotte et al. 2011; Goriounova and Mansvelder 2012). In addition, hippocampal function, which is critical for memory, was altered in adult mice by nicotine exposure during adolescence. Contextual fear conditioning—a hippocampus-dependent task in which animals learn and remember to associate a fearful stimulus (e.g., a foot shock) with a particular context—was disrupted in adult mice that had been treated during adolescence with chronic nicotine but not following chronic treatment with nicotine in adulthood (Portugal et al. 2012). Rodent studies have implications for human adolescents, suggesting that exposure to tobacco during youth may lead to long-lasting changes in behavioral and neuronal plasticity into adulthood.

Mood Disorders

Adolescents with symptoms of mental health disorders (e.g., anxiety, aggressive and disruptive behaviors, mood disorders) are at increased risk for initiation of conventional cigarette use and long-term nicotine dependence compared with those without such disorders (Gehricke et al. 2007; Morris et al. 2011). Although this risk may reflect a common genetic predisposition, or the use of nicotine to self-medicate in the hope of improving mental health symptoms, the question arises of whether the smoking of conventional cigarettes by adolescents contributes to the development of mood disorders. A meta-analysis of existing studies showed consistent evidence that both tobacco use and dependence on tobacco products among adolescents indeed increased their risk of anxiety disorders (Moylan et al. 2012). Other studies have shown that an early onset of smoking is associated with a shorter time to first onset of an anxiety disorder (Jamal et al. 2011), and there is a positive association between adolescent smoking, particularly through a nicotine pathway, and anxiety in early adulthood (Moylan et al. 2013). Bidirectional relationships between adolescent smoking and disruptive disorders (e.g., ADHD; oppositional defiant disorder [ODD] [Griesler et al. 2011]) as well as depression (Tjora et al. 2014) also have been reported, while a longitudinal birth cohort found evidence to support a causal relationship between teen smoking and onset of depression (Boden et al. 2010). Although these findings are complex and warrant further study using comparisons of genetic polymorphisms associated with smoking or twin and sibling discordant/concordant studies (Munafo and Araya 2010; Leventhal and Zvolensky 2015), they do suggest that nicotine exposure during adolescence could contribute to long-term mental health disorders.

Findings of animal studies support the theory that adolescent nicotine exposure results in long-term alterations in emotional response, specifically enhanced anxiety and fear (Slawecki et al. 2003; Smith et al. 2006), and in persistent alterations in serotonin systems involved in mediating mood disorders by reprogramming the future response of 5-HT systems to nicotine (Slotkin and Seidler 2009). Even a single day of nicotine treatment in adolescent rats can enhance sensitivity to aversive stimuli later in life and result in a depression-like state in adulthood that is normalized by treatment with nicotine or antidepressants (Iniguez et al. 2009).

In summary, given the existing evidence from human and animal studies of the detrimental impact of nicotine exposure on adolescent brain development, the use of e-cigarettes by youth should be avoided and actively discouraged. Both preadolescence and

adolescence are developmental periods associated with increased vulnerability to nicotine addiction, and exposure to nicotine during these periods may lead to long-lasting changes in behavioral and neuronal plasticity. Studies reveal that for most tobacco users, initial use begins before 18 years of age. Moreover, in some adolescents, symptoms of nicotine dependence can develop after exposure to very low levels of nicotine—less than 100 cigarettes. Cross-species studies have identified characteristics of the adolescent brain that may render it vulnerable at this age to nicotine uptake in the form of equivalent doses via nonsmoking administration mechanisms. In addition, animal models of nicotine exposure in adolescence reveal neural and behavioral alterations consistent with an increased likelihood of future nicotine use, increased activation of reward pathways and, unlike in adult animals, decreased aversive effects. Regarding e-cigarettes, data demonstrate adolescent use of these devices is associated with use of tobacco, alcohol, and other drugs (Dutra and Glantz 2014; Kristjansson et al. 2015; Wills et al. 2015a, b; Schneider and Diehl 2016). Finally, animal and human studies suggest a bidirectional relationship between the smoking of conventional cigarettes and exposure to nicotine during adolescence and factors related to disruptive disorders, such as ADHD and ODD that impair academic performance, as well as to depression. Because the adolescent brain is still developing, nicotine use during adolescence can disrupt the formation of brain circuits that control attention, learning, and susceptibility to addiction. Further research is warranted to more fully understand the effects of e-cigarette use on youth.

Nicotine Exposure from Maternal Nicotine Consumption: Prenatal and Postnatal Health Outcomes

Prenatal nicotine exposure through maternal cigarette use during pregnancy is one of the most widespread perinatal insults in the world (Levin and Slotkin 1998; Xiao et al. 2008; USDHHS 2014). Despite medical and societal sanctions and ongoing public health campaigns, the prevalence of maternal cigarette use during pregnancy in the United States was estimated to be 11–15% in 2013 (Tong et al. 2013). Smoking rates were even higher among women who were poor, young, or less educated, with rates as high as 25–30%, indicating that infants born to mothers who are poor have disproportionately higher exposure to nicotine (Dietz et al. 2011; Hamilton et al. 2012; Tong et al. 2013). Despite these adverse consequences, an estimated one-half of pregnant smokers continue to smoke into the third trimester (Osterman et al. 2013; Tong et al. 2013).

Because adults who use e-cigarettes can achieve plasma nicotine concentrations similar to those found among smokers of equivalent amounts of conventional cigarettes (Vansickel et al. 2010; Lopez et al. 2016; St. Helen et al. 2016), it is important that research continues in this area. Nicotine has been shown to cross the placenta and has been found in placental tissue as early as 7 weeks of embryonic gestation, and nicotine concentrations are higher in fetal fluids than in maternal fluids (Luck et al. 1985; Jauniaux et al. 1999). nAChRs are widely distributed in the fetal brain. As has been clearly demonstrated in animal models, acetylcholine acts on nAChRs to modulate functional connections during critical periods of development when regions are most sensitive to environmental input (Dwyer et al. 2008). When nicotine in the maternal bloodstream crosses the placental barrier, it binds to these receptors (Pentel et al. 2006; Wong et al. 2015), and in rodents this can result in long-term changes in neural structure and function. Results from animal studies show consistent associations between prenatal nicotine exposure and upregulation of nAChRs associated with

disruption of fetal brain cell replication and differentiation (Slotkin 1998). Highlighting the role of nicotine in the effects of maternal smoking during pregnancy, nAChRs have been shown to be present in the human embryonic brain from 5 weeks of gestation (Hellstrom-Lindahl et al. 1998), and their normal maturation is altered in a region- and receptor subtype-dependent fashion by maternal cigarette smoking during pregnancy (Falk et al. 2005; Duncan et al. 2008). In those brainstem nuclei important for arousal, prenatal nicotine exposure decreases [3H]-nicotine binding (Duncan et al. 2008) and prevents normal age-related increases in $\alpha 4$ and $\alpha 7$ mRNA (Falk et al. 2005).

Prenatal nicotine exposure also has been associated with dysregulation of catecholaminergic, serotonergic, and other neurotransmitter systems. In addition, animal work suggests significant adverse effects of nicotine alone at levels commensurate with exposure to secondhand smoke (10-fold below those seen in active smokers), and that the non-nicotine components of tobacco smoke can exacerbate nicotine's teratogenic effects (Slotkin et al. 2015). Offermann (2015) concluded that e-cigarettes emit many harmful chemicals into the air and that indirect exposure to nicotine exceeded exposure-level standards for noncarcinogenic health effects established by the California Environmental Protection Agency. No safe level of prenatal nicotine exposure has been established (England et al. 2015).

Airborne nicotine exposure through secondhand aerosol from e-cigarettes has been observed, as has salivary cotinine concentrations of nonsmokers in the homes of e-cigarette users (Ballbe et al. 2014; Czogala et al. 2014). Ballbe and colleagues (2014) reported the geometric means of airborne nicotine were 0.74 $\mu\text{g}/\text{m}^3$ in the homes of smokers, 0.13 $\mu\text{g}/\text{m}^3$ in the homes of e-cigarette users, and 0.02 $\mu\text{g}/\text{m}^3$ in the homes of nonsmoking controls. While airborne nicotine exposure from combustible cigarette smoke was 5.7 (Ballbe et al. 2014) to 10 times higher (Czogala et al. 2014) than e-cigarette aerosol, one study reported only a twofold increase in salivary cotinine (0.38 ng/ml in the homes of smokers versus 0.19 ng/ml in the homes of e-cigarette users) (Ballbe et al. 2014), and another study found that exposure to cigarette smoke and exposure to e-cigarette aerosol had similar effects on the serum cotinine levels of bystanders (Flouris et al. 2013). Thus, the passive exposure to nicotine from e-cigarette smoking has been reported to be just as large (Flouris et al. 2013; Grana et al. 2013) or lower than (Czogala et al. 2014) conventional cigarettes, but exposure to nicotine from e-cigarette smoking is not negligible and is higher than in nonsmoking environments. This evidence suggests the importance of avoiding secondhand exposure of e-cigarette vapor and secondhand smoke during pregnancy (Flouris et al. 2013; Grana et al. 2013; Czogala et al. 2014).

Of the components of tobacco smoke, nicotine has been cited as the most important toxicant in terms of interfering with fetal development. Because of the health risks to the developing fetus associated with nicotine exposure during pregnancy, the U.S. Food and Drug Administration (FDA) (2015) recommends that pregnant women seek medical approval before using NRT, and the American College of Obstetricians and Gynecologists (2011) recommends consideration of NRT only if a woman fails behavioral interventions to quit smoking conventional cigarettes and has discussed the potential harms and benefits of NRT with her physician. NRT is most often used during pregnancy as a last resort to avoid exposing the fetus to the other toxic ingredients found in conventional tobacco smoke (Fiore et al. 2008). A Cochrane Database systematic review concluded that both the effectiveness and safety of NRT during pregnancy are unclear (Coleman et al. 2012). Table A3.1-4 in

Appendix 3.1 presents a summary of studies in humans on the effects of tobacco exposure on fetal brain development.

Even with a firm understanding of the negative health consequences of nicotine on the developing fetus (Fiore et al. 2008; USDHHS 2014; Ekblad et al. 2015), little is known about the prevalence of e-cigarette use among pregnant women or the direct harmful effects on their fetus by other toxicants delivered by the aerosol from e-cigarettes (England et al. 2015; Suter et al. 2015). In one of the few studies identified, a survey of 316 pregnant women in a Maryland clinic found that the majority had heard of e-cigarettes, 13% had ever used them, and 0.6% were current daily users (Mark et al. 2015). These findings are of concern because the dose of nicotine delivered by e-cigarettes can be as high or higher than that delivered by conventional cigarettes. Therefore, plasma nicotine concentrations delivered while using e-cigarettes have the potential to harm the developing fetus. Furthermore, in 2013 in the United States, there were 26.5 births for every 1,000 adolescent females (15–19 years of age), or 273,105 babies born to females in this age group (Hamilton et al. 2013). Currently, the rate of e-cigarette use among pregnant adolescents is unknown, but the effects of nicotine and the potential for harm by other e-cigarette toxicants indicate that the use of e-cigarettes is a fetal risk factor among pregnant adolescent girls.

As outlined below, the specific effects of nicotine on prenatal development and postnatal outcomes include sudden infant death syndrome (SIDS) and may include altered development of the corpus callosum, deficits in auditory processing, and alterations in appetitive behavior, attention, and cognition.

SIDS

SIDS is the sudden and unexplained death of an infant younger than 1 year of age (Krous 2014). Maternal smoking and infant exposure to secondhand smoke have been causally associated with SIDS, with 20–29% of deaths from SIDS attributable to maternal smoking of conventional cigarettes during pregnancy (Dietz et al. 2010; Zhang and Wang 2013; USDHHS 2014). Prenatal exposure to cigarettes and to smokeless tobacco have been associated with increased risk for apnea events, which have been linked to increased risk for SIDS (Gunnerbeck et al. 2011; Zhang and Wang 2013; Inamdar et al. 2015).

Although the mechanistic pathways underlying SIDS remain largely unknown, nicotine has effects on pathways that could be related to SIDS and is related to known risk factors, particularly lung and respiratory development (England et al. 2015; Holbrook 2016; Spindel and McEvoy 2016). Evidence from animal models supports the hypothesis that prenatal nicotine exposure alters both fetal autonomic function and arousal, which could increase the risk of SIDS (Slotkin 1998; Task Force on Sudden Infant Death Syndrome and Moon 2011). In humans, a dose–response relationship between cotinine (the major nicotine metabolite) and altered arousal patterns has been shown in preterm infants (Richardson et al. 2009), and this relationship is suggestive of nicotine’s role in arousal deficits that could be linked to SIDS. There is widespread distribution of nAChRs in the brainstem nuclei in both humans and animals that control cardiopulmonary integration and arousal in the newborn (Dwyer et al. 2008). In some animal studies, prenatal exposure to nicotine has increased mortality in newborns that were exposed to reduced oxygen (Slotkin et al. 1995; Fewell and Smith 1998). Prenatal exposure to nicotine is also associated with altered serotonin signaling in the brainstem in the rat model, leading to an exaggerated trigeminocardiac reflex and resulting in bradycardia, hypotension, and apnea (Gorini et al. 2013).

Altered Development of the Corpus callosum

The corpus callosum, the largest white matter structure in the brain, facilitates communication between the left and right cerebral hemispheres. Several human studies have revealed alterations in the structure of the corpus callosum in offspring following their exposure to maternal cigarette use during pregnancy (Jacobsen et al. 2007b; Paus et al. 2008). In animal models, prenatal exposure to nicotine has been shown to result in widespread alterations in gene expression in the brains of adolescent offspring (Cao et al. 2011, 2013; Wei et al. 2011). In particular, the expression of a number of genes involved in myelination—the formation of white matter via the addition of protective myelin sheaths to axons—is altered in a sex-dependent manner, with upregulation in males and downregulation in females (Cao et al. 2013). Such changes in the expression profiles of myelin-related genes may influence the structure and function of white matter, and both hypermyelination and hypomyelination have been associated with cognitive deficits (Quaranta et al. 2002; Sokolov 2007).

Deficits in Auditory Processing

A number of human studies, using a variety of methods, have investigated the effects of maternal cigarette smoking during pregnancy on auditory processing from the fetal period through childhood (Jacobson and Morehouse 1984; Kristjansson et al. 1989; McCartney et al. 1994; Franco et al. 1999; Leech et al. 1999; Cowperthwaite et al. 2007). Deficits in auditory processing in fetuses are of concern because they affect later language development (Kisilevsky and Davies 2007; Kisilevsky et al. 2014). Various studies in infants have investigated the brain's physiological activity response to auditory stimuli (the cochlea translates sound into nerve impulses to be sent to the brain), neuroelectric activity of the auditory nerve, and cochlear response (Key et al. 2007; Korres et al. 2007; Kable et al. 2009; Peck et al. 2010; Katbamna et al. 2013). Key and colleagues (2007) reported prenatal exposure to cigarette use (compared with nonexposed infants) to be associated with alterations in hemispheric asymmetry and suboptimal brain activity related to speech processing in otherwise healthy newborns at least 2 days of age. Korres and associates (2007) found altered cochlear responses to auditory stimuli in newborns that were exposed to maternal cigarette smoking (n = 200) compared with those that were unexposed (n = 200), regardless of degree of cigarette exposure. Similar findings were reported by Durante and colleagues (2011) in two case-control studies.

Two additional studies investigated effects of maternal cigarette use during pregnancy on auditory brainstem responses in newborns (≤ 2 days old) (Peck et al. 2010) and infants (6 months old) (Kable et al. 2009). Both studies found greater neuroelectric response to sound stimuli, a phenomenon that may disrupt an infant's ability to encode auditory information, potentially leading to deficits in language development. Furthermore, both studies demonstrated dose-response relationships between altered auditory processing and maternal cotinine levels. Finally, in a study of a small sample of newborns that sought to understand the direct biological pathway, maternal smoking during pregnancy produced changes in newborn cochlear and auditory brainstem functions and changes in placental gene expression in genes that appear to modulate the motility of cochlear hair cells (Katbamna et al. 2013). Thus, all three studies indicate effects based on consumption of conventional cigarettes, and they highlight the possibility of a mediating role of maternal nicotine use in altered infant

auditory processing, although further work must rule out confounding effects and effect modification by other constituents (e.g., arsenic, benzene, and cadmium).

A study using functional magnetic resonance imaging (fMRI) in older offspring exposed to tobacco in utero assessed response to auditory and visual attention tasks in adolescent smokers (Jacobsen et al. 2007a). Teens whose mothers smoked during pregnancy exhibited decreased accuracy in the tasks, with greater activation of both the temporal lobe and the occipital lobe, regions of the brain that are critical for auditory and visual processing. Additive effects of maternal cigarette use during pregnancy and of adolescent smoking on activation of the temporal and occipital lobes also emerged, indicative of reduced coordination among brain regions during auditory attention tasks.

Animal studies have shown that nAChRs play a critical developmental role in establishing synaptic connections between sensory thalamic afferents and those cortical targets that are necessary for normal sensory processing (Table A3.1-5 in Appendix 3.1). Brief nicotine exposure during this critical postnatal period of sensory cortex development disrupts glutamate transmission (Aramakis et al. 2000) and eliminates nAChR regulation of signal processing in the adult auditory cortex, inhibiting normal auditory learning (Liang et al. 2006). Animals that are prenatally exposed to nicotine also exhibit deficits in cognitive processing in response to an auditory cue, which appears to be mediated by a loss of function of the nAChR $\beta 2$ subunit (Liang et al. 2006; Horst et al. 2012).

Appetitive and Consummatory Behaviors

Clinical studies and animal studies have linked prenatal exposure to nicotine to subsequent appetitive behaviors (an active searching process that is performed consciously) and consummatory behaviors (such as ingestion of food or drugs) in offspring. Associations have been demonstrated in humans between maternal cigarette use during pregnancy and risk to the child of smoking uptake/nicotine dependence, drug abuse, and obesity; parallel relationships have been shown in animal models between prenatal exposure to nicotine and similar appetitive behaviors of offspring.

Parental use of tobacco is one of many well-known risk factors for offspring initiation of tobacco, progression to heavy use, and nicotine dependence. Tobacco use by parents influences their children through social, environmental, cognitive, and genetic mechanisms (USDHHS 2012). As a subset of these influences, mothers' use of tobacco during pregnancy has been studied as an independent risk factor and has been associated with offspring susceptibility, initiation, regular use, and dependence (Kandel et al. 1994; Griesler et al. 1998; Kandel and Udry 1999; Buka et al. 2003; Lieb et al. 2003; Oncken et al. 2004; Al Mamun et al. 2006; O'Callaghan et al. 2009; Tehranifar et al. 2009; Agrawal et al. 2010; Rydell et al. 2012; Weden and Miles 2012; Stroud et al. 2014; Shenassa et al. 2015). Wakschlag and colleagues (2010, 2011) suggest that maternal smoking during pregnancy has a teratologic effect with abnormalities stemming from the in utero environment which disrupt neural (Kandel et al. 1994; Jacobsen et al. 2006) and dopamine systems that promote sensitivity to nicotine dependence (Kandel et al. 1994; Selya et al. 2013). For example, nicotinic receptors of laboratory animals exposed to nicotine in utero are upregulated, suggesting a latent vulnerability to nicotine dependence among animals exposed to nicotine in utero (Slotkin et al. 2006, 2015).

At issue with all human studies investigating maternal use of tobacco during pregnancy and offspring use of tobacco is isolating the independent effect on the fetus in relation to the

other social, environmental, and cognitive factors that also predict offspring tobacco use. After controlling for maternal smoking during the offspring's childhood, several studies have reported that maternal smoking during pregnancy is associated with higher nicotine dependence in offspring (Kardia et al. 2003; Lieb et al. 2003; Selya et al. 2013; Shenassa et al. 2015), increased or earlier smoking initiation, and heavier smoking among adolescent girls and adult offspring (Kandel et al. 1994; Cornelius et al. 2005). However, the association was attenuated and nonsignificant among several studies that controlled for a variety of environmental, social, and cognitive confounders between maternal cigarette use during pregnancy and initiation of offspring smoking (but not nicotine dependence) (Cornelius et al. 2005; Roberts et al. 2005; Munafo et al. 2006; Kandel et al. 2007; D'Onofrio et al. 2012; Rydell et al. 2014; Taylor et al. 2014), leaving speculation for the independent effect. In summary, evidence from animal models offers a biologic mechanism for, and human evidence is suggestive of, an association between maternal tobacco use during pregnancy with offspring smoking and nicotine dependence, but is insufficient to infer causation. Further research and longitudinal studies that examine these outcomes while assessing the full spectrum of environmental, social, and cognitive mediating pathways are needed to disentangle these issues.

A smaller set of literature has documented associations between maternal cigarette smoking during pregnancy and use of other substances by the child (Fergusson et al. 1998; Weissman et al. 1999; Porath and Fried 2005; Nomura et al. 2011). In utero exposure to nicotine also affects behavioral responses for drug rewards in both adolescent and adult experimental animals. Prenatal exposure to nicotine increases the preference of adolescents for a saccharin solution containing nicotine compared with saccharin alone (Klein et al. 2003), and it results in self-administration of nicotine either during acquisition of the task (Chistyakov et al. 2010) or after forced abstinence (Levin et al. 2006). Prenatal exposure to nicotine also increases subsequent oral intake of alcohol (Chang et al. 2013), and intravenous self-administration of both cocaine and methamphetamine is enhanced in a dose-dependent manner in adolescent rats (Franke et al. 2008) and adult rats (Lacy et al. 2014).

In contrast, in a study that used a discordant sibling pair design to reduce confounding by genetic and environmental factors, initial associations between prenatal smoking and alcohol use disorder were attenuated and were no longer statistically significant (D'Onofrio et al. 2012). In a large longitudinal study that spanned 40 years, Shenassa and colleagues (2015) found evidence to support effects on nicotine dependence among children of mothers who smoked during pregnancy, but no effects on their progression to marijuana dependence were observed. A possible explanation for these discordant findings is suggested by a study that found significant effects from prenatal smoking of conventional cigarettes on drug use among adolescents, but showed that these effects were restricted to a genetic subpopulation of carriers of a specific $\alpha 6$ nAChR gene (*rs2304297*) polymorphism (Lotfipour et al. 2010). In sum, a number of studies have documented associations between cigarette use by the mother during pregnancy and smoking initiation, heavy use, and nicotine dependence among her children, although control of confounding reduces this association. In addition, the literature is sparse and inconsistent regarding a connection between maternal cigarette use during pregnancy and the use of nontobacco substances by the child.

A large body of literature has demonstrated effects of maternal cigarette use during pregnancy on weight levels and obesity in childhood. For example, three meta-analytic reviews found a 47–64% increased risk of obesity in children following exposure to maternal

cigarette smoking during pregnancy (Oken et al. 2008; Ino 2010; Weng et al. 2012; Behl et al. 2013). Additional systematic reviews (Bruin et al. 2010) and other studies (Harrod et al. 2015; La Merrill et al. 2015; Mourtakos et al. 2015; Bao et al. 2016) have all concluded that prenatal exposure to nicotine likely acts as a developmental obesogen in humans. However, unmeasured residual confounding or confounding by familial factors, which have not been fully explored, could attenuate the observed associations (Gilman et al. 2008; Iliadou et al. 2010). Animal studies support the epidemiologic literature suggesting a potentially causal relationship here by defining biologic pathways (Wong et al. 2015). Fetal and neonatal exposure to nicotine in rodents has resulted in neurochemical, neurobehavioral, and metabolic changes in the children that are consistent with obesity and type 2 diabetes (Williams and Kanagasabai 1984; Newman et al. 1999; Grove et al. 2001; Chen and Kelly 2005; Gao et al. 2005; Holloway et al. 2005).

In humans, studies involving structural MRI and fMRI have shown alterations in the size and sensitivity of brain reward centers in the teenage offspring of maternal smokers. Several of these studies revealed a thinning of the orbitofrontal cortex among persons who were prenatally exposed to maternal cigarette smoking, a thinning that was associated with drug use and experimentation during adolescence (Toro et al. 2008; Lotfipour et al. 2009); decreased amygdalar volume, which is associated with increased fat intake (Haghighi et al. 2013); and altered response to reward anticipation in the ventral striatum, an area associated with risk taking and drug use (Muller et al. 2013). In addition, highlighting the role of altered nicotinic pathways in the disruption of neural circuits from prenatal tobacco exposure, changes in striatal volume, and a propensity for drug use in adolescent offspring have been linked to interactions between prenatal exposure to cigarette smoking and a polymorphism in the gene encoding the $\alpha 6$ nAChR (Lotfipour et al. 2010). Structural alterations in the orbital frontal cortex have also been shown to result from interactions between maternal cigarette smoking during pregnancy and polymorphisms of brain-derived neurotrophic factor, a growth factor that regulates growth and differentiation of new neurons and supports existing neurons (Lotfipour et al. 2009). Although these clinical findings are specific to conventional cigarettes, they converge with results of animal studies of the effects of prenatal nicotine on brain reward centers and thus highlight the potential pernicious effects of e-cigarettes in pregnant women.

Animal studies have shown that the dopamine system, which is critically involved in satisfaction-seeking or appetitive behaviors, is modulated by nAChRs from the fetal period to adulthood (Azam et al. 2007). Prenatal nicotine exposure alters dopamine's content, turnover, release, and receptor expression in forebrain regions, which are important for motor and cognitive functions (Navarro et al. 1988; Richardson and Tizabi 1994; Muneoka et al. 1999; Zhu et al. 2012) and for assigning motivational value to natural and drug rewards (Kohlmeier 2015; McNair and Kohlmeier 2015). Prenatal exposure to nicotine also modifies the structure of dendritic targets of dopamine innervations in the nucleus accumbens (a critical component of reward learning and addiction) (Mychasiuk et al. 2013) and alters neuronal signaling that affects dopamine function (Chang et al. 2013; Morgan et al. 2013).

Prenatal exposure to nicotine has been shown in a variety of animal studies to induce complex effects on behavioral response to natural rewards. Although adolescent offspring of nicotine-exposed mothers show an initial decrease in motivation to work for sucrose reward (Franke et al. 2008), they exhibit enhanced sensitivity to the rewarding effects as the task

becomes harder (Lacy et al. 2012). Prenatal exposure to nicotine also results in enhanced intake of fatty foods, with no change in the intake of normal chow (Chang et al. 2013).

Attention and Cognition

Numerous human studies have investigated the effects of maternal cigarette use during pregnancy on disruptive behavior and attention deficits in the child. The 2014 Surgeon General's report included results of a systematic review of effects of maternal cigarette use during pregnancy on disruptive-behavior disorders—including ADHD, conduct disorder, and ODD—in offspring (USDHHS 2014). The evidence for effects of maternal cigarette use during pregnancy on disruptive-behavior disorders, and ADHD in particular, was suggestive but not sufficient to infer a causal relationship. Several systematic reviews using meta-analyses have found evidence for associations between exposure to maternal cigarette use during pregnancy and ADHD in offspring, including dose-response relationships between number of cigarettes smoked per day and ADHD symptoms (Linnet et al. 2003; Langley et al. 2005; Latimer et al. 2012; Massey et al. 2016). However, similar to effects on nicotine dependence and obesity in offspring, the possibility of unmeasured confounding remains (D'Onofrio et al. 2008; Thapar et al. 2009; Langley et al. 2012). Evidence for associations with maternal cigarette use during pregnancy is perhaps more consistent for offspring conduct disorders than it is for ADHD. In particular, although some studies that used a gene-environment interaction design or a propensity score-matching approach to exposure to control for confounding, they found no effect of maternal cigarette smoking during pregnancy on conduct disorders (D'Onofrio et al. 2008; Gilman et al. 2008; Boutwell and Beaver 2010; Lavigne et al. 2011). However, several other studies—including a meta-analytic review across three studies using “genetically sensitive”⁴ research designs—have suggested a direct causal relationship between maternal smoking during pregnancy and conduct disorders in offspring (McCrory and Layte 2012; Gaysina et al. 2013; Kuja-Halkola et al. 2014; Estabrook et al. 2015; Paus and Pausova 2015).

To explore the potential role of nicotine exposure in these associations, a small number of studies have included a prospective measure of confirmed tobacco exposure, maternal cotinine levels, in addition to maternal report of smoking, to study relationships with disruptive behaviors among offspring (Wakschlag et al. 2011; O'Brien et al. 2013; Massey et al. 2016). Wakschlag and colleagues (2011) found associations between maternal cigarette smoking and aggression and noncompliance among offspring. Studies have also shown alterations in the structure and function of the orbital frontal cortex, a region important for emotional regulation and cognition, in relation to maternal cigarette smoking during pregnancy (Toro et al. 2008; Bennett et al. 2009). Consistent with animal models of altered dopamine regulation, two studies have shown interactions of maternal cigarette smoking during pregnancy with dopamine regulation genotype (DAT1) in influencing disruptive-behavior phenotypes in offspring (Wakschlag et al. 2011; O'Brien et al. 2013). In another study, Wakschlag and colleagues (2010) demonstrated a sex-dependent interaction of maternal smoking during pregnancy with monoamine oxidase A (MAOA) genotype, which is associated with the development of antisocial behavior. In this study, maternal smoking

⁴ Genetically sensitive designs typically include monozygotic and dizygotic twins and a broader inclusion of sibling pairs, mother-child pairs, and grandparent-grandchild pairs. Genetically sensitive multigroup designs allow for simultaneous testing of additive and nonadditive genetic, common, and specific environmental effects, including cultural transmission and twin-specific environmental influences.

during pregnancy further increased the risk for conduct disorder. In sum, although issues of confounding remain, much evidence from human studies is suggestive of a causal association between maternal cigarette smoking during pregnancy and disruptive behaviors among offspring. This was confirmed by the 2014 Surgeon General's report on tobacco (USDHHS 2014). Since then, newer studies, controlling for personal and genetic confounders, have reported significant associations as well as nonsignificant, attenuated associations. Biologic evidence of nicotine-induced alterations in dopamine regulation also provides a possible mechanism for the role of nicotine in these outcomes.

Animal studies have shown that cholinergic modulation of prefrontal cortex function, via nAChRs, is essential for attention and cognition (Poorthuis and Mansvelder 2013; Proulx et al. 2014). Prenatal exposure to nicotine alters the morphology and nAChR functional response of prefrontal cortical neurons (Mychasiuk et al. 2013; Bailey et al. 2014). When tested as adolescents, animals that were exposed prenatally to nicotine show some behaviors characteristic of ADHD. For example, exposed offspring were found in two studies to show less impulse control and/or slower learning acquisition on two cognitive tests that tax attentional processes (Sorenson et al. 1991; Schneider et al. 2012). In addition, some studies have found hyperactivity in exposed offspring (Pauly et al. 2004; Schneider et al. 2012; Zhu et al. 2012), which was found in another study to be transmitted via maternal lineage from one generation to the next and to be ameliorated by methylphenidate treatment across all generations, showcasing the long-term impact of prenatal nicotine exposure (Zhu et al. 2014a). This transgenerational transmission of prenatal nicotine-induced hyperactivity must reflect longterm changes to the epigenome (Leslie 2013). Finally, emerging animal studies suggest that prenatal exposure to nicotine affects the proliferation and maturation of progenitor cells to glutamatergic neurons during neurodevelopment in the medial prefrontal cortex, resulting in behavioral impairments in attentional function and behavioral flexibility in adulthood (Aoyama et al. 2016; Poon and Leibowitz 2016; Powell et al. 2016).

Summary

Because of the rising prevalence of e-cigarette use, there is potential for widespread nicotine exposure to youth and young adults, resulting in nicotine addiction and related harmful consequences associated with exposure to nicotine. During pregnancy, there is neural sensitivity to the number and volume of substances, including nicotine, transported through the placenta. From prenatal development through adolescence and early adulthood, exposure to nicotine poses a serious threat, because these are critical times for brain development and brain plasticity. Furthermore, youth and young adults are more vulnerable than adults to the long-term consequences of nicotine exposure, including susceptibility to nicotine addiction and potentially reduced impulse control, deficits in attention and cognition, and mood disorders. An additional public health concern is exposure to e-cigarettes among persons who have never used conventional tobacco products. If the prevalence of e-cigarette use continues to rise among those who do not use conventional tobacco products, the harmful consequences of exposure to nicotine will rise accordingly.

The 2014 Surgeon General's report (USDHHS 2014) states there is sufficient evidence to infer that: (a) nicotine activates multiple biological pathways through which smoking increases risk for disease; (b) nicotine exposure during fetal development, a critical window for brain development, has lasting adverse consequences for brain development; (c) nicotine adversely affects maternal and fetal health during pregnancy, contributing to multiple adverse

outcomes such as preterm delivery and stillbirth; and (d) nicotine exposure during adolescence, a critical window for brain development, may have lasting adverse consequences for brain development and cognition. The literature presented in this section attempts to differentiate the risks to fetal and child health associated with nicotine in tobacco versus nicotine alone or in e-cigarettes. Evidence is sufficient to conclude tobacco use increases the risk of SIDS (USDHHS 2014), but further research is necessary with regard to nicotine alone or nicotine in e-cigarettes. The review finds evidence that tobacco is associated with structural brain changes and alterations in cognition, attention, and appetitive behaviors in human offspring. Less well known is the role that nicotine plays in mediating these associations, although animal models provide support for a role for nicotine in these outcomes. nAChRs, the chief receptor targets for nicotine, are widely expressed in the fetal brain, and their normal functioning is negatively affected by smoking and, in animals, by prenatal exposure to nicotine through experimental treatment. Furthermore, both human genetic studies and animal studies implicate a neurotoxic effect of fetal nicotine exposure. Pregnant women and women intending to become pregnant should be cautioned against using e-cigarettes to avoid unnecessary nicotine exposure to their baby.

Effects of the Inhalation of Aerosol Constituents Other Than Nicotine

The scientific literature on the health effects of exposure to constituents other than nicotine in the e-cigarette aerosol is still developing. One study found that after 5 minutes of ad lib e-cigarette use, healthy adult cigarette smokers showed an increase in airway resistance, but no effect on other spirometry parameters such as forced vital capacity (FVC), forced expiratory volume in 1 second FEV1, and ratios of these values (FEV1/FVC) (Vardavas et al. 2012).

A noninvasive marker of airway inflammation is the fraction of exhaled nitric oxide (FeNO) (Taylor et al. 2006; Munakata 2012). NO is a gaseous molecule that produces vasodilation and bronchodilation (decreasing resistance in the respiratory airway and increasing airflow to the lungs). FeNO is reduced by acute and chronic cigarette smoking (resulting in poorer vasodilation and bronchodilation) and is increased among smokers following cessation (see Vleeming et al. 2002 for a review). Studies examining current adult cigarette smokers revealed a reduction in FeNO after use of an e-cigarette with and without nicotine (Vardavas et al. 2012; Marini et al. 2014; Ferrari et al. 2015). One study found that these reductions did not differ significantly between e-cigarettes containing nicotine and those without nicotine (Marini et al. 2014), suggesting non-nicotine factors mediated the effect.

However, a study of occasional smokers (<10 cigarettes per week), but non-e-cigarette users, found an increase in FeNO after use of an e-cigarette containing nicotine (Schober et al. 2014). Furthermore, this study found no statistical difference in FeNO after use of an e-cigarette not containing nicotine. This variation in findings suggests the impact of e-cigarette use on FeNO may vary based on smoking history, nicotine content of e-liquid, or other environmental or biological factors.

Limited studies have examined chronic exposure on the potential inhalation toxicity of PG and VG. Prior to e-cigarettes, consumer products containing these chemicals were almost exclusively liquids or creams, or the substance was contained in a matrix. Animal models have shown few toxicological effects resulting from nose-only exposure to VG aerosol, with the exception of minimal or mild squamous metaplasia in rats exposed to the highest concentration (0.662 mg glycerol) for 13 weeks (Anderson et al. 1950; Renne et al. 1992).

Other inhalation studies testing PG in rats and monkeys did not observe treatment-related effects on respiratory physiology, clinical chemistry, hematology, gross pathology, or respiratory tract histology (Robertson et al. 1947). However, neither of these studies examined potential inhalation toxicity of PG and VG in humans using e-cigarette devices. In summary, other than nicotine, very little is known from human studies about the long-term health effects of inhaling PG and VG from e-cigarette aerosol, although adverse effects have been detected in animal models. Further investigation would improve our understanding of the effects of nicotine-related compounds, aerosolized solvents (PG and VG), aerosolized flavorants, aerosolized adulterants in e-liquids, and toxicants produced during the aerosolization process—or a combination of these chemicals.

Aerosolized Nicotine-Related Compounds

The nicotine used in e-liquids is extracted from tobacco. The extraction process may produce some potentially harmful tobacco-specific impurities, including minor alkaloids like nornicotine, anatabine, anabasine, myosmine, cotinine, nicotine-N-oxides (cis and trans isomers), β -nicotyrine, and β -nornicotyrine (Etter et al. 2013; Farsalinos et al. 2015a; Lisko et al. 2015; Oh and Shin 2015).

The correlation between nicotine and the concentrations of minor alkaloids is much stronger in conventional tobacco products (Jacob et al. 1999) than in e-cigarettes (Lisko et al. 2015). While the cause of these differing concentrations of minor alkaloids is unknown, Lisko and colleagues (2015) speculated potential reasons may derive from the e-liquid extraction process (i.e., purification and manufacturing) used to obtain nicotine from tobacco, as well as poor quality control of e-liquid products.

The American E-Liquid Manufacturing Standards Association (2014), an industry group with no regulatory authority, has called for the use of U.S. Pharmacopeia (USP)-grade nicotine in its e-cigarette products. USP specifications for nicotine allow for a maximum of 0.5% (5 mg/g) of a single impurity and 1% (10 mg/g) of total impurities (U.S. Pharmacopeia n.d.). Although the health implications of nicotine-related impurities are not known, toxicology studies are needed to demonstrate the effects of high levels of these products.

Aerosolized Solvents

Although e-cigarettes produce PG aerosols at levels known to cause eye and respiratory irritation to both users and nonusers (Offermann 2015), only mild effects (e.g., upper respiratory irritation) have been described in humans exposed to PG mist for 1 minute (Wieslander et al. 2001), and little is known about long-term effects. Inhaling PG can increase the risk of developing asthma (Choi et al. 2010). Animal studies of PG and VG aerosolizing agents not produced by e-cigarettes concluded that these substances are relatively safe when inhaled by animals for up to 28 days (Werley et al. 2011) or 18 months (Robertson et al. 1947).

Particles emitted from e-cigarettes are assumed to be formed from supersaturated PG (i.e., concentration beyond the point of saturation) in e-liquids (Schripp et al. 2013). Several studies designed to characterize the aerosol generated by e-cigarettes examined the chemical composition of the particles and their concentrations as measured by their number and distribution by size (Trehy et al. 2011; Ingebrethsen et al. 2012; Schripp et al. 2013; Zhang et al. 2013; Fuoco et al. 2014; Ruprecht et al. 2014; Saffari et al. 2014; Mikheev et al. 2016). E-cigarettes are recognized as a new source of submicron-sized particles, leading to possible

high exposure to these particles in users. Concentrations in the range of 10^9 particles $\times$ cm⁻³ were measured in the mainstream of e-cigarette aerosols (Fuoco et al. 2014). An in vitro study by Zhang and colleagues (2013) found that under the conditions of a single-puff experiment, an e-cigarette generated an aerosol having particle sizes in the range of 100–600 nm (nanometers), similar to that of conventional cigarettes. Mikheev and colleagues (2016) reported that the size distribution of e-cigarette aerosol differs from that of combustible tobacco smoke and that e-cigarettes normally exhibit a bimodal particle size distribution: nanoparticles (11–25 nm count median diameter) and submicron particles (96–175 nm count median diameter). Each mode has comparable number concentrations (107–108 particles/cm³). Goel and colleagues (2015) detected radicals in aerosols from all e-cigarettes and e-liquids tested ($2.5\text{--}10.3 \times 10^{13}$ radicals per puff at 3.3 V [voltage]), from e-liquid solvents PG and VG, and from “dry puffing” (overheating of e-liquid) (Farsalinos et al. 2015c).

Because the aerosols deriving from e-liquids are mainly made of droplets that are expected to dissolve as they reach the lung’s epithelium, not only the number but also the volume (size) of particles needs to be considered. Manigrasso and colleagues (2015) found that e-cigarettes are a source of extremely high doses of particles in the human respiratory system. On average, 6.25×10^{10} particles were deposited in the respiratory tree after a single 2-second puff, an estimated 30% of the daily doses of particles for a nonsmoking person. After 10 puffs, the relevant mean-layer thickness of the e-liquid on the lung epithelium was comparable to the thickness of surfactant layer covering the alveolar and bronchial regions, suggesting a higher susceptibility to irritant endpoints (Manigrasso et al. 2015). These results demonstrate that e-cigarettes produce submicron-sized particles and highly oxidizing free radicals that may present a potential toxicologic risk to e-cigarette users.

Aerosolized Flavorants

Little is known about the flavorants used in e-cigarettes, and more than 7,700 unique flavors are on the market (Zhu et al. 2014b). Flavored e-cigarette products are popular with adult users, and sweet and candylike flavors may make these products attractive to children and adolescents (Villanti et al. 2013; Farley et al. 2014; King et al. 2014). Many of the chemicals used in e-liquid flavorings are “generally recognized as safe” for ingesting (e.g., in food). However, these substances have not been tested adequately for safety when heated at various temperatures when inhaled in aerosolized form (Barrington-Trimis et al. 2014). The Flavor and Extract Manufacturers Association of the United States (2015), in an official statement, notes that ingredients in flavors are evaluated for exposure through ingestion only; thus, any results cannot be extrapolated to use through inhalation. Further, flavoring compounds often remain undeclared on e-cigarette and e-liquid packaging (Tierney et al. 2016).

CDC tested 36 e-cigarette products for 10 flavor compounds commonly used as additives in tobacco products (Lisko et al. 2015). Measurable levels of eucalyptol and pulegone were found in the menthol-flavored varieties for all manufacturers. Menthol concentrations ranged from 3,700 to 12,000 μ g/g in flavored e-liquids, levels similar to those found in the filler of conventional cigarettes. Interestingly, menthol was found at low concentrations in 40% of the tobacco-flavored nonmenthol products tested. Other flavor compounds found were camphor, methyl, salicylate, pulegone, cinnamaldehyde (CAD), and eugenol (Lisko et al. 2015).

Tierney and colleagues (2016) analyzed 30 e-cigarette products on the U.S. market and found 13 products contained more than 1% flavor chemicals by weight. Among the chemicals identified were aldehydes (e.g., benzaldehyde and vanillin), which are categorized as primary irritants of the respiratory tract (Roberts et al. 2015). Tierney and colleagues (2016) also found that tobacco-flavored e-liquids were derived from confection-flavored chemicals (e.g., bubble gum and cotton candy flavoring) rather than tobacco extract.

Some chemicals in e-cigarettes, although approved for ingestion, have established adverse health effects when inhaled. In vitro studies of cytotoxicity suggest that different flavored e-cigarette products may vary in their potential to adversely affect health. Bahl and colleagues (2012) reported cytotoxic effects of the solutions used in e-cigarettes that were not attributable to the nicotine but to the concentration of chemicals employed as flavors. These effects were most pronounced on mouse neural stem cells and human embryonic stem cells compared to human pulmonary fibroblast (Bahl et al. 2012).

Similar findings were reported by Behar and colleagues (2014) who found a greater cytotoxic effect of flavored e-liquid solutions on human embryonic stem cells compared to human pulmonary fibroblast. Further, two cinnamon-related chemicals, CAD and 2-methoxycinnamaldehyde, were particularly cytotoxic at doses found in the refill liquids (Behar et al. 2014). CAD, which is derived from the essential oil of cinnamon bark, is a highly bioactive compound (Jayaprakasha and Rao 2011). It has been used as an anticancer agent (Nagle et al. 2012), an insecticide (Cheng et al. 2009), and a bactericide (Nostro et al. 2012), and it is employed commercially as an additive in many foods and fragrances (Cocchiara et al. 2005).

Farsalinos and colleagues (2014a) analyzed 159 e-liquids obtained from a variety of manufacturers and retailers in Europe and the United States for the presence of two flavorings: diacetyl (DA) and acetyl propionyl (AP). The study revealed that these substances were present in the majority of the samples tested, with a significant proportion containing both chemicals. Furthermore, Allen and colleagues (2016) detected DA above the laboratory limit of detection in 39 of 51 flavors tested. DA, also known as 2, 3-butanedione, is a member of a general class of organic compounds referred to as diketones, α -diketones, or α -dicarbonyls. It provides a characteristic buttery flavor, is naturally found in various foods, and is used as a synthetic flavoring agent in food products such as butter, caramel, cocoa, coffee, dairy products, and alcoholic beverages. Although it is generally recognized as safe when ingested, it has been associated with a decline in respiratory function in persons exposed to it through inhalation (Egilman et al. 2011; Clark and Winter 2015). Inhaling DA and artificial butter-flavored powders and aerosols can cause fixed obstructive lung disease in exposed workers (Chaisson et al. 2010). In addition, it has been implicated in the development of bronchiolitis obliterans, an irreversible respiratory disease also called "popcorn lung disease" (Harber et al. 2006). AP, also called 2, 3-pentanedione, is a α -diketone that is chemically and structurally similar to DA. Although it has become a popular replacement for DA, acute inhalation exposure to AP has been shown to cause airway epithelial damage similar to DA (Hubbs et al. 2012).

The analysis by Farsalinos and colleagues (2014a) found that 74.2% of the sample contained one or both of these chemicals, with 69.2% of the sample containing DA. Both DA and AP were found in 28.3% of the sample e-liquids. These chemicals were detected even in samples coming from manufacturers that stated these flavorings were not present in their products. However, exposure to DA and AP was 100 and 10 times lower, respectively, than

exposure to these chemicals from cigarette smoking. Few studies have examined safe levels of DA and AP via tobacco product; however, 47.3% of DA- and 41.5% of AP-containing samples exposed consumers to levels higher than the safety limits outlined by the National Institute for Occupational Safety (NIOSH) for occupational exposure. This exposure threshold outlined by NIOSH is not intended to suggest exposure at or below that limit should be considered sufficiently safe (Hubbs et al. 2015).

Aerosolized Adulterants

TSNAs, potent carcinogens identified in tobacco and tobacco smoke, include N-nitrosornicotine (NNN), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), N-nitrosoanabasine (NAB), and N-nitrosoanatabine (NAT) (Hecht 1998, 1999; USDHHS 2010, 2014). NNN and NNK are classified by the International Agency for Research on Cancer (IARC) as Group 1 human carcinogens (IARC 2004). Their presence in e-liquids is mostly attributable to the processes used in extracting nicotine from tobacco leaves or the addition of tobacco flavorings (Kim and Shin 2013; Cheng 2014). These compounds are formed from their alkaloid precursors and from nitrite or nitrate, predominantly during tobacco curing, fermentation, and aging. NNN, NAB, and NAT are formed primarily from their corresponding secondary amines (nornicotine, anatabine, and anabasine) in the early stages of tobacco curing and processing, while the majority of NNK is formed from the tertiary amine nicotine at the later stages of tobacco curing and fermentation (Hecht 1998). Nitrosation reactions of corresponding amines can occur in e-liquids, especially during inadequate storage or manufacturing processes; inadequate storage is believed to increase the levels of NNN as a consequence of the nitrosation of nornicotine converted from nicotine in liquids (Kim and Shin 2013).

Some studies have identified traces of TSNAs in e-liquids, but at levels far below those seen in combustible tobacco (Trehly et al. 2011; Farsalinos et al. 2015a). Further, Goniewicz and colleagues (2014b) found that the aerosol of some e-cigarettes contains traces of the carcinogenic nitrosamines NNN and NNK, but neither was detected in aerosol from the Nicorette inhalator (an NRT product).

Several studies have reported the presence of other hazardous compounds in e-liquids or in the aerosol produced by e-cigarettes (Exponent Inc. 2009; Hadwiger et al. 2010; Lim and Shin 2013; Uchiyama et al. 2013; Williams et al. 2013; Bekki et al. 2014; Goniewicz et al. 2014a,b; Kosmider et al. 2014; Jensen et al. 2015; Kavvalakis et al. 2015; Laugesen 2015; Oh and Shin 2015; Varlet et al. 2015; Khlystov and Samburova 2016). For example, an FDA study detected the presence of amino-tadalafil and rimonabant in e-liquids (Hadwiger et al. 2010); amino-tadalafil is a structural analogue of tadalafil, the active pharmaceutical ingredient in Cialis, a prescription drug approved in the United States for treatment of erectile dysfunction. Rimonabant (trade name Zimulti) was approved in Europe for the treatment of obesity, but its marketing authorization was withdrawn by the European Medicines Agency in 2009. FDA approval of this drug has been withheld because of unresolved issues involving rimonabant therapy and increased frequencies of psychiatric adverse events, including suicide and an ill-defined constellation of neurologic symptoms and seizures (FDA 2007). The presence of unapproved active pharmaceutical ingredients suggests that some e-cigarettes may expose users to pharmacologically active substances with undocumented and unknown effects.

Oh and Shin (2015) conducted a study to identify and quantify the presence of diethyl phthalate (DEP) and diethylhexyl phthalate (DEHP) in e-liquids. DEP is used as a solvent to bind cosmetics and fragrances and in various industrial applications, including plasticizers, detergent bases, and aerosol sprays. DEHP is used widely as a plasticizer in the manufacture of articles made of polyvinylchloride. DEP and DEHP were detected in 47.6% and 79.1% of e-liquids, respectively, with concentration ranges of 0.01–1745.20 mg/L and 0.06–81.89 mg/L (Oh and Shin 2015). Both DEP and DEHP have estrogenic and antiandrogenic activity that cause premature breast development in girls. DEHP is classified by IARC as a possible carcinogen in humans (IARC 2000). Although the amounts of the two phthalates detected in this study were lower than the safety levels, the source of these toxicants is unknown, perhaps coming from packaging materials and the production procedure.

Carbonyls are present in e-cigarettes, and levels increase with device voltage (Kosmider et al. 2014; Jensen et al. 2015). Long-term exposure to carbonyl compounds, such as formaldehyde, acetaldehyde, and acrolein, increases the risk of cancer. IARC and the U.S. Environmental Protection Agency (EPA) have classified formaldehyde as “carcinogenic to humans” (USDHHS 1999; IARC 2009). EPA has set the acceptable daily intake (ADI) of formaldehyde as 0.2 mg/kg (kilograms) body weight and has warned of the potential adverse health effects of exceeding ADI. Acetaldehyde is also toxic, an irritant, and a probable carcinogen (USDHHS 1999). Acrolein is toxic through all routes of administration and may cause respiratory and ocular irritation (Faroon et al. 2008; Bein and Leikauf 2011). Acrolein in cigarette smoke has been linked to several pulmonary diseases, including increased risk of lung cancer (Feng et al. 2006), as well as asthma and chronic obstructive pulmonary disease (Bein and Leikauf 2011). One study found an association between acrolein exposure and risk of cardiovascular disease (DeJarnett et al. 2014).

Lim and Shin (2013) detected formaldehyde and acetaldehyde in 225 replacement liquids for e-cigarettes purchased in Korea, with ranges of 0.02–10.09 mg/L (mean 2.16 mg/L) and 0.10–15.63 mg/L (mean = 4.98 mg/L). Although the amounts of formaldehyde and acetaldehyde detected in replacement liquids for e-cigarettes are relatively low compared to conventional cigarettes, they should be controlled to the lowest possible concentrations in raw materials, as they may be formed when e-liquids are heated. Furthermore, as larger capacity batteries and heating mechanisms are developed (Farsalinos et al. 2014b; Sleiman et al. 2016), users will be exposed to higher concentrations of formaldehyde, acetaldehyde, acrolein, and other carbonyls (Kosmider et al. 2014). Jensen and colleagues (2015) reported formaldehyde concentrations higher than conventional cigarettes in high-voltage e-cigarettes. Havel and colleagues (2016) reported acetaldehyde, acrolein, and formaldehyde generation increased markedly at voltages at or above 5 volts. Geiss and colleagues (2016) reported that formaldehyde exceeded safety levels at the lowest wattage (5 watts), which is the wattage applied in most second generation e-cigarettes.

Summary

Although some typical constituents of the e-cigarette aerosol have been identified, the potential short- and long-term health consequences of inhalation of the heated and aerosolized constituents of the e-liquids, including solvents, flavorants, and toxicants, still require further investigation to quantify health effects. Commercial and custom-mixed e-liquids are produced with undisclosed manufacturing procedures, packaging materials, and purity standards for their constituents, increasing the risks of potential health consequences. E-cigarettes are a

source of extremely high doses of fine particles (e.g., aerosol) in the human respiratory system. Fine particles are emitted when the solvents PG and VG are aerosolized, and mild respiratory effects have been documented, but adequate assessments are lacking. An additional concern is the aerosolization and inhalation of flavor additives in e-liquids. While some of the chemicals used may be generally recognized as safe for use in foods, they have not been thoroughly tested for their potential sensitizing, toxic, or irritating characteristics when inhaled. Further, given the extent of possible variations in the ratio of flavor additives, with up to 7,700 unique e-liquid varieties available (Zhu et al. 2014b), these chemicals may be toxic in the concentrations present in manufactured or do-it-yourself e-liquids. Finally, other hazardous compounds and carcinogens have been detected in e-liquids, or in the heated aerosol produced by e-cigarettes, including formaldehyde, acetaldehyde, and acrolein.

Effects of Toxicants Produced during Aerosolization

A primary reason for investigating the health effects of heated and aerosolized e-liquids is that, under such conditions, chemical reactions may result in the formation of new compounds (Sleiman et al. 2016). In some devices, the temperature in the center of a heating coil can exceed 350°C, causing changes in the chemical components of the e-liquid. When carbonyl compounds are present in the refill liquids, heating can enhance their concentrations in the aerosol (Talib et al. 2015). Carbonyl compounds result from dehydration and fragmentation of VG and PG, which can be oxidized to formaldehyde and acetaldehyde during heating. Hutzler and colleagues (2014) applied headspace gas chromatography-mass spectrometry to enable incubation of liquids at various temperatures. At 150°C, the levels of acetaldehyde and formaldehyde were found to be up to 10-fold higher than they were at ambient temperatures for samples in which PG was a main component. The generation of carbonyl compounds seems to increase when liquids touch the heating element inside an e-cigarette, which is indicated by a color change around the wire, as has been reported in some devices (Uchiyama et al. 2013). Evidence suggests when e-liquid touches the heating element (heated nichrome wire), it is oxidized to formaldehyde, acetaldehyde, acrolein, glyoxal, and methylglyoxal in the presence of oxygen (Bekki et al. 2014; Goniewicz et al. 2014b; Kosmider et al. 2014).

Several studies have reported that short-chain aldehydes, such as formaldehyde, acetaldehyde, or acrolein, are produced during heating. Uchiyama and colleagues (2013) measured carbonyl compounds in e-cigarette aerosols generated according to the Canadian “intense regimen” (55mL puff volume, 2-second puff duration, 30 seconds between puffs, and a total of 10 puffs). Thirteen brands of e-cigarettes were assessed, and investigators detected several carbonyl compounds, such as formaldehyde, acetaldehyde, acetone, acrolein, propanol, crotonaldehyde, and butanol. They also detected two other harmful carbonyl compounds that had not been detected in the mainstream smoke from conventional cigarettes: glyoxal and methyl-glyoxal. Jensen and colleagues (2015) observed that formaldehyde-containing hemiacetals can be formed during the aerosolization process. These molecules are known to release formaldehyde and are used as industrial biocides, but it is not currently known how formaldehyde-releasing agents affect the respiratory tract.

The amount of carbonyl compounds in e-cigarette aerosols varies substantially, not only among different brands but also among different samples of the same products (Ohta et al. 2011; Bekki et al. 2014; Kosmider et al. 2014; Jensen et al. 2015), from 100-fold less than tobacco to nearly equivalent values. Notably, the amount of voltage the battery puts out

affects the concentration of the carbonyl compounds in the emission. Some e-cigarettes allow users to increase aerosol production and nicotine delivery by raising the battery's output voltage. In addition, some users elect to directly drip e-liquid onto an exposed heater coil, reportedly for greater aerosol production and "throat hit." Talih and colleagues (2015) showed that use of such direct-drip atomizers may involve greater exposure to toxic carbonyls, including formaldehyde, because of the potentially higher temperatures reached by the coil. The adverse effects of acrolein (2-propenal), an unsaturated aldehyde, depend on dose and cell type and are influenced by experimental conditions (Bein and Leikauf 2011). In vitro studies found that acrolein inhibits DNA repair and forms acrolein-deoxyguanosine DNA adducts that are mutagenic (Wang et al. 2009, 2012; Tang et al. 2011). Despite the known DNA-damaging effects of acrolein, its mutagenicity in mammalian cells remains uncertain, and according to an evaluation by the IARC, there is inadequate evidence for carcinogenicity in humans or animals (IARC 1995). Because of its extreme toxicity, acrolein has been difficult to characterize in standard animal carcinogenicity tests. Animal experiments showed that acrolein can have a range of adverse effects, including a role in carcinogenesis (Cohen et al. 1992); excessive mucus production and macrophage and neutrophil accumulation with consequent production of proinflammatory cytokines and proteases (Moretto et al. 2012); damage to neurons and myelin disruption (Shi et al. 2011); and it may play a role in the progression of atherosclerosis and cardiovascular disease (Park and Taniguchi 2008; DeJarnett et al. 2014).

Other volatile organic compounds (VOCs) found in e-cigarette aerosol include a variety of chemicals (e.g., aliphatic and aromatic hydrocarbons), some of which may have short- or long-term adverse health effects. Benzene (classified as group 1 by IARC) and other solvents (toluene, xylenes, and styrene) could be present in e-cigarettes because of their use in the extraction of nicotine from tobacco leaves. Goniewicz and colleagues (2014b) detected both toluene and m- and p-xylene in e-cigarette aerosols. A wide variety of other VOCs in e-cigarette liquids produce aromas and flavor through heating (Tierney et al. 2016).

Heavy metals such as tin, lead, and nickel were discovered by Williams and colleagues (2013) in a brand of e-liquids and the resulting aerosols. Those researchers analyzed the contents of e-cigarette cartomizers (a polyfill wrapped heating coil capable of longer puff durations than an atomizer) and the aerosols by using light and electron microscopy, x-ray microanalysis, particle counting, and inductively coupled plasma optical emission spectrometry. The aerosol contained particles $>1\ \mu\text{m}$ that were composed of tin, silver, iron, nickel, aluminum, and silicate, and nanoparticles ($<100\ \text{nm}$) of tin, chromium, and nickel. Small particles composed of various elements (tin, other metals, semimetals, and silicates) passed through the cartomizer fibers and were present in aerosols. These particles likely originated from parts of the device (i.e., atomizer/cartomizer) (Williams et al. 2013).

Concentrations of 9 of the 11 elements in e-cigarette aerosol identified by Williams and colleagues (2013) were higher than or equal to concentrations in conventional cigarette smoke. Many of the metals identified in e-cigarette aerosol, such as lead and cadmium (Farsalinos et al. 2015b), are known to cause respiratory distress and disease (Zalups and Ahmad 2003). These metals are produced by the aerosolization of e-liquids (Farsalinos et al. 2015b) and by flaws in e-cigarette heating mechanisms and poor quality control (Williams et al. 2013; Farsalinos et al. 2015b; Mikheev et al. 2016). While these initial analyses indicate potential exposures, additional measures are needed because of challenges in measuring trace levels of metals.

Summary

E-liquids produce chemical reactions that may result in the formation of new, harmful compounds. Carcinogens (e.g., formaldehyde, acetaldehyde, and acrolein) and toxic heavy metals (e.g., lead and cadmium) have been found in e-cigarette aerosols in laboratory tests conducted at temperatures within the range of most e-cigarette products. These chemicals and metals have been detected in e-liquids and e-cigarette aerosols, signifying the need for further study on the potential short- and long-term health ramifications.

A limitation to understanding the health impact of chemical reactions is the heterogeneity of e-cigarette devices (e.g., voltage), e-liquids (e.g., quality, content), and use behaviors (e.g., puff duration), as emissions may be altered by any combination of these mechanical and behavioral differences. Further, it is difficult to fully contextualize the carcinogenic emissions of e-cigarette aerosol given the diversity of products currently available, as well as those that may become available as the devices continue to evolve (Farsalinos et al. 2014b).

Effects Not Involving Inhalation of Aerosol by the E-Cigarette User

Health effects not attributable to direct inhalation of e-cigarette aerosol include explosion or fire associated with malfunctioned devices, poisoning through contact exposure or intentional or unintentional ingestion of e-liquid, and exposure to secondhand aerosol or its condensate.

Health Effects Attributable to Explosions and Fires Caused by E-Cigarettes

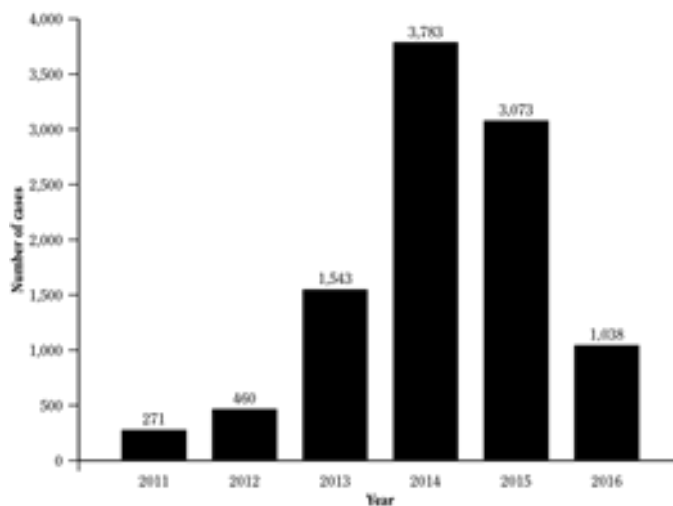
Most reports of explosions and fires caused by e-cigarettes have appeared in print and online media and on televised programs. From August 2009 to March 2014, a search of U.S. media by the U.S. Fire Administration (2014) found 25 reports of e-cigarette explosions or fires. These data suggest that the number of such events is small when compared with the number of e-cigarette users. Of the 25 incidents found in the search, 2 caused serious harm, and there were no deaths attributable to explosions. In most cases, the resulting fires did not spread far from the site of the explosion. However, in one case an entire bedroom was lost to fire (U.S. Fire Administration 2014). As for explosions, several have occurred during an e-cigarette's use, causing severe facial damage or injuries to bodies and hands (Brennan 2015; Corona and Marcus 2015; Duranty 2015; Fox 5 Digital Team 2015; Goff and Schwartz 2015; Jablow and Sexton 2015; Shastry and Langdorf 2016), but most occurred while the device's batteries were being charged. Overcharging lithium batteries can lead to thermal runaway, causing the e-cigarette battery or container to be propelled, often with portions catching fire (U.S. Fire Administration 2014; Bohr et al. in press).

Health Effects Caused by Ingestion of E-Cigarette Liquids

The liquids in both e-cigarettes and the containers used to refill them can cause nicotine poisoning. Consequences of nicotine intoxication in the e-liquid include nausea, vomiting, headaches, dizziness, and diarrhea at low doses; seizures; tachycardia; abdominal pain; confusion; and even death (Cervellin et al. 2013). The amount of nicotine needed to cause death in humans is uncertain and, according to a reevaluation, may be higher than previously thought (Mayer 2014). The total amount of nicotine in refill liquids varies and can be as high as 1,000 mg/10 mL in do-it-yourself bottles (Davis et al. 2015), which could be lethal if consumed (Mayer 2014).

The increase in poisonings prompted enactment of the *Child Nicotine Poisoning Prevention Act of 2015* (2016) in January 2016. This law requires any container of liquid nicotine sold, manufactured, distributed, or imported into the United States be placed in special packaging that is difficult to open by children under 5 years of age. Although labels may indicate the concentrations of nicotine, such labels can be incomplete, confusing, or inaccurate (Tritchounian and Talbot 2011; Cameron et al. 2014), and some bottles have not been labeled at all (Davis et al. 2015). Of most concern, some bottles of e-cigarette refill liquids labeled “no nicotine” have been found to contain significant amounts of that substance (e.g., 25.6 mg/mL; Trehy et al. 2011). Regardless, many e-cigarette users may not be aware of the toxic effects of nicotine and may not know that refill liquids should be kept away from toddlers and children. These liquids are often sold in colorful bottles with flavors that are attractive to children (Bahl et al. 2012). The liquids usually come in small dropper bottles that can be mistaken for bottles containing food dye or eye drops. Finally, many refill liquids are made in local “vape shops,” which have only recently come under FDA regulation (*Federal Register* 2016), with no uniform training process for mixers, a lack of standards and protections, and unknown concentrations of nicotine.

The rapid growth in popularity of e-cigarettes and the ease with which refill liquids can be purchased have made e-cigarettes an increasingly common item in many households, thereby elevating the possibility of accidental nicotine poisoning. Instances of related case reports, often involving children or infants, are increasing. For example, an 18-month-old girl was treated at an emergency room for hypertension and tachycardia after drinking about 2 mL of refill liquid from a bottle on a nightstand (Shawn and Nelson 2013). Unintentional exposure to nicotine can occur through ingestion, absorption through the skin, inhalation, or dropping refill liquids into one’s eyes (Cantrell 2014).



Source: American Association of Poison Control Centers (2016).

Note: These numbers reflect the closed human exposures to e-cigarettes and liquid nicotine reported to poison centers as of July 31, 2016. The numbers may change as cases are closed and additional information is received.

Figure 3.2. Data showing exponential increase in the number of cases of human exposure to e-cigarette products and liquid nicotine between 2011 and 2016.

Figure 3.2 shows data from 2011 to 2016 on exposures to e-cigarettes or liquid nicotine (i.e., any contact with e-cigarettes or liquid nicotine, not necessarily resulting in any health effects) (American Association of Poison Control Centers 2016). These data show a dramatic increase in exposures through 2014 with a slight reduction of exposures in 2015. Fifty-one percent of the calls to poison control centers regarding exposures to e-cigarettes involved children 5 years of age or younger (CDC 2014). Increased e-cigarette exposures have also been reported by state and local poison centers (Banerji et al. 2014; Cantrell 2014; Guttentburg et al. 2014; Lee et al. 2014; California Department of Public Health 2015).

Secondhand Exposure to the Constituents of E-Cigarette Aerosol

Exposure to secondhand smoke from combustible tobacco products is a known cause of morbidity and mortality (USDHHS 2006). Secondhand smoke, a mixture of the sidestream smoke from a smoldering cigarette and the mainstream smoke exhaled by a smoker, is known to contaminate both indoor and outdoor environments. In addition, when the constituents of smoke deposit on surfaces, nonsmokers can be exposed to them via touch, ingestion, or inhalation. These deposited constituents of combustible smoke are known as “thirdhand smoke” (Matt et al. 2011; Protano and Vitali 2011). E-cigarettes represent another potential source of exposure to toxicants for nonusers, via secondhand or thirdhand exposure to aerosol.

Exposure to Nonusers

In contrast to combustible tobacco products, e-cigarettes do not produce sidestream emissions; aerosol is produced during activation of the device. Some of this aerosol is subsequently exhaled into the environment where nonusers may be exposed through inhalation, ingestion, or dermal contact. As previously described in this chapter, constituents of the emissions may include nicotine, carbonyl compounds, VOCs, polyaromatic hydrocarbons, TSNA, heavy metals, and glycols. It is not clear how much of inhaled e-cigarette aerosol is exhaled into the environment where nonusers can be exposed. Some studies have used machines to produce e-cigarette aerosols and measured the pollutants emitted (McAuley et al. 2012; Czogala et al. 2014; Geiss et al. 2015); others have involved the use by one or more persons of an e-cigarette and measured the change in pollutants in either a room or a test chamber after use (Schripp et al. 2013; Schober et al. 2014). One study measured airborne nicotine in the homes of e-cigarette users (Ballbe et al. 2014). The concentration of e-cigarette aerosol in a given microenvironment depends primarily on the strength of the source or the number of e-cigarettes used and the emission rate of the aerosol for that device. E-cigarettes, however, are heterogeneous in their design and in the liquids used, and the specific product combination significantly affects the secondhand emissions (Kosmider et al. 2014; Geiss et al. 2015). The number of puffs and depth of inhalation may be particularly relevant to the amount exhaled by the user and may also affect e-cigarette emissions (Talih et al. 2016).

Movement of E-Cigarette Aerosol

Similar to the case with secondhand tobacco smoke, e-cigarette aerosol is an inherently dynamic mixture that changes over time in terms of constituents and concentrations. Czogala and colleagues (2014) demonstrated a significant signal from a laser photometer indicating

the presence of ambient aerosol in a room after e-cigarette use. However, this aerosol disappeared in just seconds to a few minutes as it either evaporated to the gas phase or deposited on surfaces in the room. In contrast, in the same study, secondhand cigarette smoke exhibited a particulate phase that stayed suspended in the room at high concentrations for more than 30 minutes. For the VOCs in e-cigarette aerosol, such as formaldehyde, acrolein, and acetaldehyde, the source strength and ventilation rate will largely determine their concentration in indoor air. Semi-VOCs, such as nicotine and TSNAs, are also largely affected by sorption on and subsequent desorption from surfaces and dust in a room (Singer et al. 2002, 2003; Goniewicz and Lee 2015). The extent of this type of thirdhand contamination from e-cigarettes in real-world settings has not been established but would be of particular concern for children living in homes of e-cigarette users, as they spend more time indoors, are in proximity to and engage in greater activity in areas where dust collects and may be resuspended (e.g., carpets on the floor), and insert nonfood items in their mouths more frequently (EPA 2008; Matt et al. 2011).

Exposure to E-Cigarette Aerosol and Considerations of Dose

A large body of studies has measured exposure to secondhand and thirdhand smoke from conventional cigarettes using personal or area air monitoring, surface testing, and dust testing. Studies of the exposure of e-cigarette aerosol to nonusers, however, are limited. Schripp and colleagues (2013) observed small increases of fine and ultrafine particles and some VOCs, including PG, flavoring substances, and nicotine, indicating passive inhalation of e-cigarette aerosols by nonusers in the presence of e-cigarette users. Those authors demonstrated that the distribution in the sizes of the aerosol's component particles changes in the lungs and results in the exhalation of smaller particles, likely caused by the evaporation of the liquid particles in the lungs and in the environment after exhalation. Schober and colleagues (2014) found substantially higher amounts of PG, VG, particulate matter (PM), and nicotine in a 45-m³ chamber during e-cigarette use sessions with volunteers compared to controlled sessions. They also found a 20% increase in the level of polycyclic aromatic hydrocarbons (PAHs) and a 2.4-fold increase in aluminum concentrations.

Williams and colleagues (2013) demonstrated contamination by metal and silicate particles in e-liquid and its aerosol using scanning electron microscopy. In a different study measuring machine-generated secondhand e-cigarette aerosol in an emission chamber, Geiss and colleagues (2015) found significant levels of PG, VG, and nicotine in the chamber's air. Carbonyl compounds of concern (e.g., formaldehyde, acetaldehyde, acrolein, and acetone) were below the limits of detection in this study. O'Connell and colleagues (2015), who assessed secondhand e-cigarette emissions in a small meeting room (12.8 m²) with three e-cigarette users during a 165-minute session, found a significant increase in PG but did not see the expected increase in VG or nicotine. This study reported no increase in PAHs, trace metals, TSNAs, or acrolein, but did find an increase in total VOCs, formaldehyde, and acetaldehyde. However, the compounds were found at levels below guidelines for the quality of indoor air from the World Health Organization or European Union. Ruprecht and colleagues (2014) found significantly lower concentrations and counts for particles from an e-cigarette used in a 50-m³ room compared with conventional cigarettes. Interestingly, they also found that nicotine-free e-cigarettes produced higher particle levels than e-cigarettes containing nicotine. Saffari and colleagues (2014) found that total particulate exposure was 10-fold lower in e-cigarettes than it was in conventional cigarettes. Emissions of heavy metals

from e-cigarettes were also dramatically less, with the exception of nickel, zinc sulfide, and silver, which showed higher emission rates from e-cigarettes. PAH levels were not elevated by e-cigarette use in this study.

Concentrations of PM, especially PM_{2.5}, which is fine PM, and nicotine are the two most common markers used to measure exposure to secondhand smoke (Avila-Tang et al. 2010; Apelberg et al. 2013). Indirect measures of the mass concentration of PM from secondhand smoke using real-time particle monitors are well validated in terms of the accuracy of these measurements in relation to other constituents of secondhand smoke and to health effects (Hyland et al. 2008; Apelberg et al. 2013). These same types of particle monitors are often used in studies of e-cigarette aerosol to compare PM levels from conventional cigarettes with those from e-cigarettes, though PM findings may not directly relate to the short- and long-term health effects of each product (Czogala et al. 2014; Schober et al. 2014).

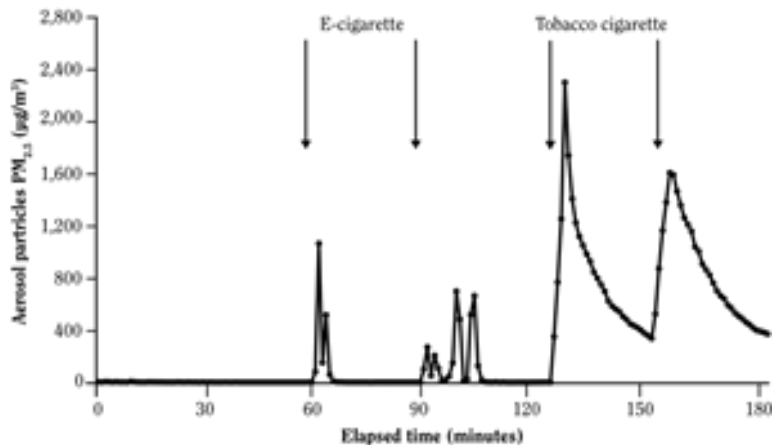
Caution is warranted when interpreting the results of PM measurements comparing e-cigarettes with conventional cigarettes. The aerosols produced are fundamentally different, with the former resulting from aerosolization of liquid and the latter resulting from combustion of organic matter. The true PM_{2.5} mass concentration of e-cigarette aerosol from commonly used light-scattering instruments (Czogala et al. 2014) cannot be determined without calibrating the device to a reference standard for the aerosol in question. Even this calibration would be questionable given the highly volatile nature of e-cigarette aerosol, making it difficult to capture and accurately determine the mass. Real-time PM_{2.5} measurements such as this are useful, however, to determine the presence of an aerosol and to see the *relative* changes in this aerosol over time and under various conditions, such as changing source strength. Figure 3.3 shows the significant increase in aerosol concentration from e-cigarettes after about 1 hour and the subsequent rapid decline, presumably from initial aerosolization and deposition of this aerosol. There may still be significant amounts of this e-cigarette aerosol in the environment, but the particle monitor can no longer measure it, as it is either in the aerosol phase or deposited on surfaces. For these reasons, it is important not to rely solely on PM mass concentrations for determining exposure to e-cigarette aerosol and for making comparisons with conventional cigarettes. Measurement of the individual toxicants of concern in the aerosol phase and on surfaces is warranted.

Health Effects of Secondhand Exposure to E-Cigarette Aerosols

Flouris and colleagues (2012, 2013) conducted two clinical studies of the health effects of secondhand exposure to e-cigarette aerosol. The researchers found no short-term change in markers of complete blood count after 1 hour of exposure to e-cigarette aerosol in a group of 15 nonsmokers (Flouris et al. 2012). Similarly, the same exposure caused no significant change in short-term lung function, although the results were of borderline statistical significance (Flouris et al. 2013). However, these studies demonstrated that passive exposure to e-cigarettes causes an increase in serum cotinine that is similar to that from passive exposure to cigarette smoke, suggesting the need to examine the impact of passive aerosolized nicotine inhalation on long-term lung function. Furthermore, limited effects would likely occur in the short exposure observed through the methodologies used by Flouris and colleagues (2012, 2013), as these studies did not account for prolonged and persistent passive exposure to e-cigarette aerosols.

Several researchers have modeled the health risks of passive exposure to e-cigarettes (Colard et al. 2015) on the basis of the limited exposure data available and have come to

various conclusions. Offermann (2015) concluded that, for indirect exposure, two chemicals—nicotine and PG—exceeded California EPA exposure level standards for noncarcinogenic health effects. Burstyn (2014), who compared e-cigarette aerosol exposure to workplace exposure standards, concluded that only PG and VG warrant attention in e-cigarette users while, for bystanders, none of the constituents of e-cigarette aerosol pose apparent concern. It is important to note that standards for workplace exposure are typically not appropriate to apply to the population as a whole, as they are intended for a healthy working population during a typical work day, not accounting for the risks to children, pregnant women, or those with preexisting health conditions. Further, standards for workplace exposure are very different in concentration and duration than what is to be expected from e-cigarette use.



Source: Czogala et al. (2014).

Note: PM = particulate matter.

Figure 3.3. Changes in aerosol particle PM_{2.5} concentrations during experiment of e-cigarette use and tobacco cigarette smoking in an exposure chamber.

An additional consideration for regulating e-cigarettes in indoor environments is the potential for allergic reactions in nonusers. Dermal and oral PG exposures are known causes of dermatitis and allergic sensitization (Warshaw et al. 2009; Al Jasser et al. 2011). Several e-liquids contain flavorants derived from nuts and in fact have labels cautioning persons who have nut allergies not to use these products. Research has not evaluated whether nonusers can have allergic reactions from these potential allergens in e-cigarette aerosol, but this is a risk that should be explored as 8% of U.S. children have food allergies (Gupta et al. 2011).

Evidence Summary

E-cigarette use among youth and young adults in the United States has increased considerably in recent years (see Chapter 2). There is little doubt that the use of e-cigarettes by youth and young adults represents self-administration of the drug nicotine, and this self-administration of nicotine puts youth at risk for addiction and many related harmful consequences. Animal research indicates adolescent brains are particularly sensitive to

nicotine's effects, such that subsequent self-administration is more likely, and that same literature indicates that this age group is at risk for a constellation of nicotine-induced neural and behavioral alterations. Studies of the effects of maternal smoking of conventional cigarettes during pregnancy, coupled with preclinical literature examining the effects of maternal self-administration of nicotine during pregnancy, suggest that e-cigarette use by mothers during pregnancy presents a wide variety of risks to fetal, infant, and child brain development.

Users of e-cigarettes risk respiratory exposure to a variety of aerosolized chemicals, including solvents and flavorants added intentionally to e-liquids, adulterants added unintentionally, and other toxicants produced during the heating/aerosolization process. The health impacts of frequent exposure to the toxicants in e-cigarette aerosol are not well understood, though several are known carcinogens. As highlighted previously in this chapter, the detection and level of these carcinogens depend on several factors, including the concentration of the e-liquid and the strength of the heating device. Although e-cigarettes have been used as a cessation device, the evidence supporting the effectiveness of e-cigarettes as an aid for quitting conventional cigarettes remains extremely weak for adults (Bullen et al. 2013; Caponnetto et al. 2013; Grana et al. 2014; Kalkhoran and Glantz 2016) and untested and nonexistent among youth.

Further research is warranted to focus on the characteristics of e-cigarette devices, the constituents of e-liquids, and the user behaviors that can influence the yield of nicotine and other toxicants (Shihadeh and Eissenberg 2015). This close focus includes providing details of devices (e.g., voltage of the power supply, heating element resistance) and components of e-liquids (e.g., propylene glycol, vegetable glycerin, other additives), and measuring user puff topography. Standardization of procedures for producing and delivering the aerosol is likely a necessary component of at least some in vivo and in vitro work. Preclinical work examining the effects of e-cigarette aerosols is a clear research need and, again, the standardization of procedures for production and delivery of the aerosol is necessary. To enhance relevance, the parameters of aerosol production should span the range of those seen with humans (Shihadeh and Eissenberg 2011).

The huge variety of products of different origin and design, the rapid emergence of new products, and the varied ways in which consumers use these products make the development of standard measurement conditions challenging (Famele et al. 2015). Accordingly, research is needed to understand how different design features relate to potential toxicity—for example, if the compounds in e-cigarettes are affected by heating, changes in chemical composition, or pH; if these compounds are absorbed into the bloodstream; and how additives to the e-liquid affect the bioavailability of these compounds, among other considerations. Research is also needed to understand whether potential health risks may be ameliorated by changes in product engineering.

Conclusion

- 1) Nicotine exposure during adolescence can cause addiction and can harm the developing adolescent brain.

- 2) Nicotine can cross the placenta and has known effects on fetal and postnatal development. Therefore, nicotine delivered by e-cigarettes during pregnancy can result in multiple adverse consequences, including sudden infant death syndrome, and could result in altered corpus callosum, deficits in auditory processing, and obesity.
- 3) E-cigarettes can expose users to several chemicals, including nicotine, carbonyl compounds, and volatile organic compounds, known to have adverse health effects. The health effects and potentially harmful doses of heated and aerosolized constituents of e-cigarette liquids, including solvents, flavorants, and toxicants, are not completely understood.
- 4) E-cigarette aerosol is not harmless “water vapor,” although it generally contains fewer toxicants than combustible tobacco products.
- 5) Ingestion of e-cigarette liquids containing nicotine can cause acute toxicity and possibly death if the contents of refill cartridges or bottles containing nicotine are consumed.

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SECTION 4. ACTIVITIES OF THE E-CIGARETTE COMPANIES

Introduction

This chapter focuses on the companies that are active in the production, distribution, or marketing of e-cigarettes in the United States and examines the potential influence of these companies on the use of e-cigarettes, particularly among youth and young adults. The e-cigarette marketplace is complicated by the fact that some brands and devices are owned by tobacco companies, while others are independently owned. This chapter will refer to the e-cigarette companies as a whole but, when necessary, will distinguish between the e-cigarette brands that are owned by tobacco companies and others that are independently owned. The chapter covers manufacturing and price, marketing and promotional activities, the retail environments for e-cigarette products, exposure to marketing and receptivity to such activity, and the effects of e-cigarette marketing activities on consumer behavior.

Manufacturing and Price

As discussed in Chapter 1, although the concept of e-cigarettes was initially introduced in the 1960s, the first-generation version of e-cigarettes was not developed and commercialized until the mid-2000s (Grana and Ling 2014). In the short period since the first appearance of e-cigarettes, the exponential growth in awareness and use of these products (Centers for Disease Control and Prevention [CDC] 2015), the rapid product development (Zhu et al. 2014), and the rapid evolution of both the e-cigarette market and the industry itself (Huang and Chaloupka in press) have been unprecedented. E-cigarettes were recently named a “disruptive innovation” that may change the existing tobacco market and displace conventional (combustible) cigarettes in a fore-seeable timeframe (Spielman and Azer 2013).

Consumer demand for a less harmful alternative to conventional cigarettes and the implementation of macro policies, such as those that restrict cigarette use or mandate clean indoor air, may influence the use of e-cigarettes (Pepper et al. 2014b; Rose et al. 2014). However, e-cigarette companies may play a critical role in shaping the market, affecting everything from the development and innovation of new products and brands to the manufacture, distribution, marketing, promotion, and pricing of the product— activities that parallel those in the cigarette industry.

This section describes and summarizes both the rapidly changing e-cigarette market and the activities of e-cigarette companies in the United States, providing a broad overview of the

major players. These participants include the major tobacco companies and other manufacturers. The chapter also addresses how the companies influence the e-cigarette market in the United States, focusing on the impact of product development and innovation, distribution channels, product availability, and pricing strategies, as well as the role of e-cigarette trade organizations and partnerships.

Overview of the E-Cigarette Market in the United States

For 2014, the value of the e-cigarette market in the United States was estimated at \$2.5 billion: 40% (\$1.0 billion) was for cigarette-like e-cigarettes (cigalikes), and 60% (\$1.5 billion) was for tank-style e-cigarettes, mods, and other types of “vaporizers” (Wells Fargo Securities 2015a) (Table 4.1). The market was projected to grow to \$3.5 billion, a rise of 40%, in 2015 (Rose et al. 2014) (Table 4.2). Total sales of e-cigarettes in convenience, food, drug, and big-box stores (such as Walmart), which are tracked by commercial market research companies (such as Nielsen), were estimated to be \$900 million in 2014. There was an additional estimated \$500 million in online sales, and \$1.1 billion in sales in “vape shops” and other channels, which are not currently tracked by commercial market research companies (Table 4.1) (Wells Fargo Securities 2015b).

Distribution and Purchase Channels

E-cigarettes entered the U.S. market around 2006–2007, and since that time the distribution and purchase channels for these products have evolved greatly. Initially they were sold exclusively by Internet retailers, but then selling activity expanded to shopping mall kiosks and conventional retail outlets and, more recently, to “vape shops” and some pharmacies (Rose et al. 2014; Lee and Kim 2015).

Some companies operating in the U.S. market have their own manufacturing facilities in this country, but companies generally import parts or even complete products from abroad, almost exclusively from China (Barboza 2014). Manufacturers and importers distribute their products via a wide number of channels, such as the companies’ own e-commerce websites and/or retail outlets. In 2010, the most popular channels for selling e-cigarettes and their accessories directly to consumers were websites and third parties, such as retail outlets (Linarch Information Solutions 2012). Many e-cigarette manufacturers and importers, including the big-brand companies and those supplying products to “vape shops,” rely on distributors and retailers to deliver the products to the consumer (Linarch Information Solutions 2012).

The emergence of e-cigarette devices and products resulted from the endeavors of a few entrepreneurs and widespread Internet and television advertising (Grana et al. 2013; Rose et al. 2014). It is noteworthy that the product class took hold when e-commerce was rapidly expanding in the United States, and major social media platforms—such as Facebook (founded in 2004), YouTube (2005), and Twitter (2006)—were emerging. In such an environment, information about a new product like e-cigarettes could be rapidly disseminated across geographic boundaries, and new products and technologies could be speedily adopted. This process is partly reflected by the Google search volume of queries related to e-cigarettes; the volume of queries surpassed those for nicotine replacement therapy products and snus by 2008 (Ayers et al. 2011).

Table 4.1. Estimated e-cigarette market size in 2014 (\$ billion)

	Convenience, food, drug, and big-box stores	Online	Other channels (“vape shops” and other untracked retail channels)	Total
E-cigarettes	0.6	0.2	0.2	1.0
Vapors/tanks/mods	0.3	0.3	0.9	1.5
Total	0.9	0.5	1.1	2.5

Source: Wells Fargo Securities (2015a).

Table 4.2. Estimated e-cigarette market size in 2015 (\$ billion)

	Convenience, food, drug, and big-box stores	Online	Other channels (“vape shops” and other untracked retail channels)	Total
E-cigarettes	0.7	0.4	0.4	1.5
Vapors/tanks/mods	0.4	0.4	1.2	2.0
Total	1.1	0.8	1.6	3.5

Source: Wells Fargo Securities (2015a).

Manufacturers noticed the fast rise in consumer interest in e-cigarettes, so they quickly pushed to expand the sale of their products to brick-and-mortar retail stores. Sales of cigalikes and related products were first observed in Nielsen’s store-scanner database in 2007, and between 2009 and 2012, retail sales of e-cigarettes expanded to all major markets in the United States (Huang and Chaloupka in press). This growth coincided with a surge in marketing expenditures by the e-cigarette companies across all media platforms (Kim et al. 2014; Kornfield et al. 2015). The products sold in these conventional channels were predominantly disposable and rechargeable cigalikes (Giovenco et al. 2015; Huang and Chaloupka in press), but retail stores started to carry tank-style e-cigarette devices as well (CSP Daily News 2014; Giovenco et al. 2015).

Today, e-cigarette brands, such as MarkTen (manufactured by Altria) and VUSE (manufactured by Reynolds American Inc.), are available in more than 70,000 retail stores across the country, and their availability is expanding rapidly (Wells Fargo Securities 2014b). E-cigarettes were more likely to be available in retail locations in neighborhoods with a higher median household income and a lower percentage of African American and Hispanic residents; these sales patterns are consistent with patterns of use of these products observed among youth, young adults, and adults more generally (see Chapter 2). Notably, the price of conventional cigarettes and the existence of comprehensive smokefree laws were inversely associated with the availability of e-cigarettes (Rose et al. 2014).

Through growth in their sales, tank-style e-cigarettes (also known as mods) and advanced personal vaporizers (APVs) have begun to play an increasingly important role in the e-cigarette market (Wells Fargo Securities 2015a). “Vape shops,” which provide a range of e-cigarette devices and products, have emerged as the primary retail channel for consumers seeking such products (Lee and Kim 2015). Unlike conventional retail outlets, “vape shops” sell a wide range of more complex and powerful tank-style e-cigarettes and many different types of liquids for e-cigarette devices (e-liquids or e-juices) (Sussman et al. 2016).

The rise of “vape shops” can be attributed to a number of factors. First, in the past, most of these establishments offered a wide range of e-cigarettes and e-liquids, allowed users to sample different types of flavored e-liquids at no cost, and permitted the trial use of various types of e-cigarettes. Most of these establishments sell products made by independent

companies, as opposed to products manufactured by the major conventional tobacco companies (Kamerow 2014; Sussman et al. 2016). As a result, “vape shops” can serve as an information hub where consumers can easily obtain knowledge about (and gain experience with) a wide range of e-cigarettes and related products (Sussman et al. 2016). However, the information provided may be misleading or misinterpreted (Cheney et al. 2016). Second, unlike traditional retail outlets, “vape shops” are usually equipped to provide consumers with individualized information about how e-cigarette products can be used to best satisfy the user’s preferences; this capability may be important as e-cigarette products become more diversified and sophisticated. Because of the diversity of these products, some of these establishments provided free samples of different flavored e-liquids and allowed trial use of different e-cigarettes before actual purchase in an attempt to compete with traditional retail outlets. Under the deeming rule published in May 2016, free samples of e-liquids containing nicotine were banned (*Federal Register* 2016). Third, “vape shops” serve as a place for e-cigarette users to socialize.

Some “vape shops” also host various events, including competitions (also known as cloud chasing), that build loyal customer bases by creating a sense of community and camaraderie among customers (Sussman et al. 2014; Cheney et al. 2015; Lee and Kim 2015). Additionally, a 2015 study of “vape shop” owners found that customers view the owners as important sources of health information, which could include information related to cessation (Cheney et al. 2016). However, the owners reported (a) obtaining their information from YouTube or industry sources but finding the research hard to understand and (b) looking for government sources but not finding them. Estimates of the number of “vape shops” in the United States have varied greatly due to the lack of a clear definition of what constitutes such an establishment. The low end of these estimates puts the number around 3,500 (Klein 2013; Lee and Kim 2015), while intermediate estimates indicate that there are about 6,000–15,000 “vape shops” in this country (Bour 2015; Wells Fargo Securities 2015b). One high estimate is that in 2014 there were as many as 35,000 such shops in the United States (Kamerow 2014).

Product Evolution

E-cigarette products have evolved and diversified rapidly since they entered the U.S. market (see Chapter 1). Detailed information about different types of e-cigarette products has been presented elsewhere (Grana et al. 2014). Over time, with consolidation of e-cigarette companies and technological improvements, the manufacturing process has become more standardized, enabling the production of e-cigarette products with a more effective and more consistent dose and delivery of nicotine and flavorings, and a more consistent generation of aerosol (Goniewicz et al. 2013a,b; Farsalinos and Polosa 2014; Saitta et al. 2014).

Many e-cigarette manufacturers make multiple types of e-cigarette products. For example, the NJOY brand has not only disposable and rechargeable cigalikes but also tank-style e-cigarette devices, which are larger than cigalikes and include options for refills and batteries. In addition, NJOY sells a variety of flavored e-liquids, although in California, flavors appealing to minors (e.g., strawberry and cookies and cream) are prohibited (*State of California v. Sottera, Inc.* 2010). Within each product type, there are many different brands, albeit the brands are often very similar. For example, NJOY, blu, Logic, Mystic, and many other brands of rechargeable e-cigarettes differ very little from each other with regard to the flavors and types of products offered (e.g., cigalike, tank style) (Zhu et al. 2014). A study examining the growth of brands and flavors between 2012 and 2014 found that older brands

were more likely to involve cigalikes, while newer brands were more likely to offer tank-style devices and mods (Zhu et al. 2014). As tank systems and mods become more popular, the distinction between a closed system and an open system becomes more important. In a closed system, components cannot be customized. In this case, the e-liquid is “locked in”; the amounts of e-liquid, level of nicotine, and flavors are dictated by the manufacturer. Because users cannot mix their own e-liquids or refill the cartridges or tanks, there is less risk of spillage, nicotine overdose, and accidental ingestion. In addition, users cannot change the power source, adjust the voltage, or customize the atomizers. Many brands offer only closed-system devices (e.g., Vype, Vapestick, and FIN). Most cigalikes are closed systems, sold primarily online or in conventional retail outlets, and are favored by the larger e-cigarette companies, likely because of the high profit margins from the e-liquid refill cartridges and the nature of the distribution paths.

Open systems, in contrast, allow for personalization and customization: Users can mix their own e-liquid, choosing different e-liquid bases, flavors, and nicotine concentration levels. Users can also adjust the voltage, customize the atomizers, and/or modify the aesthetics and shapes/sizes of their devices (Popken 2014; Richtel 2014c; Lee and Kim 2015). Tanks and mods/APVs are open systems sold primarily in “vape shops” or online. While research has demonstrated that more-experienced e-cigarette users prefer open system mods (Farsalinos et al. 2014), one analyst has suggested that closed systems may better facilitate consistent and enforceable product and manufacturing standards (Wells Fargo Securities 2014a).

Beyond the increased variety over time of products, their components, and related products (including accessories such as carriers, lanyards, stickers, and sleeves), the products continue to appeal to consumers through the incorporation of increasingly complex technologies—including location tracking; Bluetooth connectivity; social networking functions and integration with users’ social media accounts; and entertainment functions, such as playing music and videos (Bauld et al. 2014; Brown and Cheng 2014; Honig 2014).

The terminology for e-cigarettes has also expanded. Terms such as e-cigars, e-hookahs, vaping pens, hookah pens, and personal vaporizers are used interchangeably (or preferentially) by some users (Richtel 2014b). In addition, the spectrum of use has broadened, as some e-cigarettes that involve open systems are also used for the aerosolization of marijuana and cannabis oil (Bryan 2014; Morean et al. 2015) and could be adapted for other illicit substances (see Chapter 2).

Worldwide, more than 95% of e-cigarettes sold are thought to have been manufactured in China (Jourdan 2014), most in one city—Shenzhen (Barboza 2014). A few large manufacturers (e.g., Joyetech, Kimree, and First Union) dominate the market (see Appendix 4.1 for descriptions of the major e-cigarette manufacturers).⁵ Most of these manufacturers provide supplies to many different e-cigarette companies, including American companies marketing conventional cigarettes, as well as independent e-cigarette companies. Some companies (e.g., Gamucci) have an exclusive manufacturer in Shenzhen.

Some e-cigarette companies have begun to locate their manufacturing base in the United States. Reynolds American, for example, has a factory in Tobaccoville, North Carolina, to manufacture its VUSE brand and strongly emphasizes this location as part of its marketing

⁵ All appendixes and appendix tables that are cross-referenced in this chapter are available only online at <http://www.surgeongeneral.gov/library/reports/>.

strategy (CSP Daily News 2015). White Cloud, another U.S.-based company, moved its cartridge-filling production from China to Tarpon Springs, Florida, in May 2014 (McConnell 2014), and the U.S.-based brand Mistic has announced plans to move its manufacturing from China to Greenville, North Carolina (Bettis 2014).

Evolution of Market Share in the E-Cigarette Market

Although the e-cigarette market in the United States has changed significantly since its emergence, these changes have not been studied extensively. This section documents market share by brand for e-cigarette sales in retail outlets tracked by Nielsen, using data from the forthcoming study by Huang and Chaloupka (in press) and supplemented with data from industry reports issued by a number of investment banks. These data, available in Appendix 4.5, clearly show the dynamic changes in the e-cigarette market, and these changes are important to understand in terms of access to and marketing of these products to youth and young adults.

E-Cigarette Sales in Tracked Retail Outlets

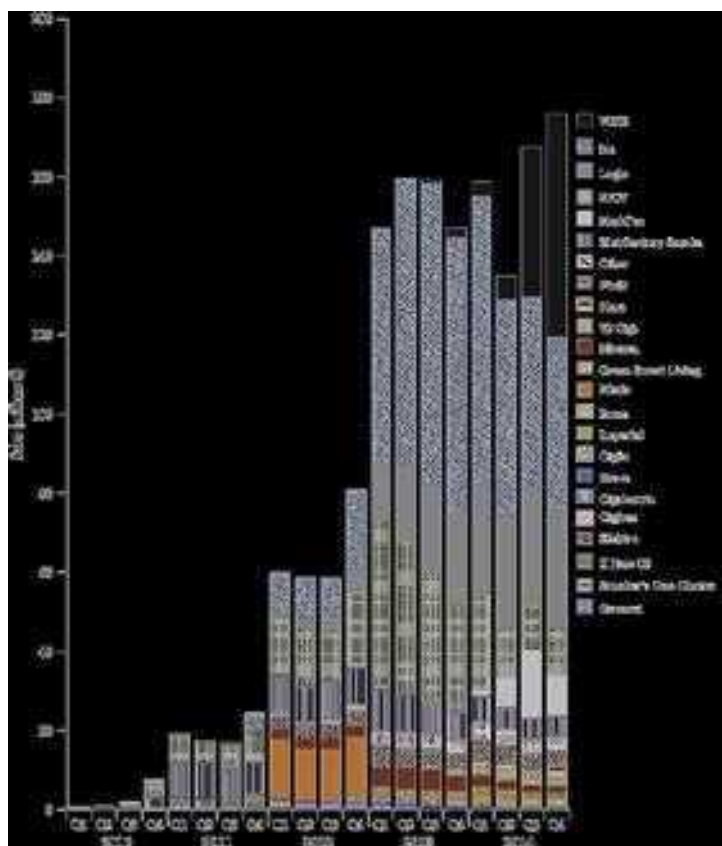
Total sales of e-cigarettes in tracked retail channels have surged exponentially since 2010, increasing from only a few million dollars per quarter in 2010 to more than \$170 million in the last quarter of 2014 (Figure 4.1). Although Reynolds American's VUSE brand did not enter the market until late 2013, its sales climbed rapidly in 2014 because of heavy promotion and price discounts. At the end of 2014, VUSE had become the market leader with the highest quarterly sales at \$56 million. Blu (owned by Lorillard and thus now by Imperial Tobacco) was the market leader for most of 2013 and 2014, with an average \$60 million in quarterly sales. During this time the number of its distribution points rose from 60,000 to more than 150,000 because of its acquisition by Lorillard and subsequent marketing and promotion efforts.

After doubling every year between 2010 and 2013 (Figure 4.2) in the tracked retail channels, rates of increase in the sales of e-cigarettes decelerated significantly, with total sales actually declining in the second quarter of 2014. The deceleration may reflect, in part, the shift away from cigalikes to tank-style devices, mods, and other e-cigarette products among users; the sales of these devices are not tracked as well, which makes it difficult to know the true trends in sales (see Tables 4.1 and 4.2).

Figure 4.2 presents sales data by product type. Sales of disposable e-cigarettes trended upward from 2010 to 2013, increasing from a minimal amount in 2010 to almost \$100 million in the second quarter of 2013, but 2014 showed a substantial decline, with the value only about \$50 million for the final quarter of that year. The figure shows a clear pattern of seasonality in sales for disposables: sales usually rose in the first quarter of the year—potentially reflecting the effect of New Year's resolutions among smokers who seek to use rechargeable e-cigarettes as a way to quit conventional cigarettes—but had subsequently declined during the rest of the year. Sales of e-liquid refills increased steadily over the 4-year period between 2010 and 2014 and reached \$80 million in the final quarter of 2014, representing approximately half of the total e-cigarette sales in the tracked retail channels.

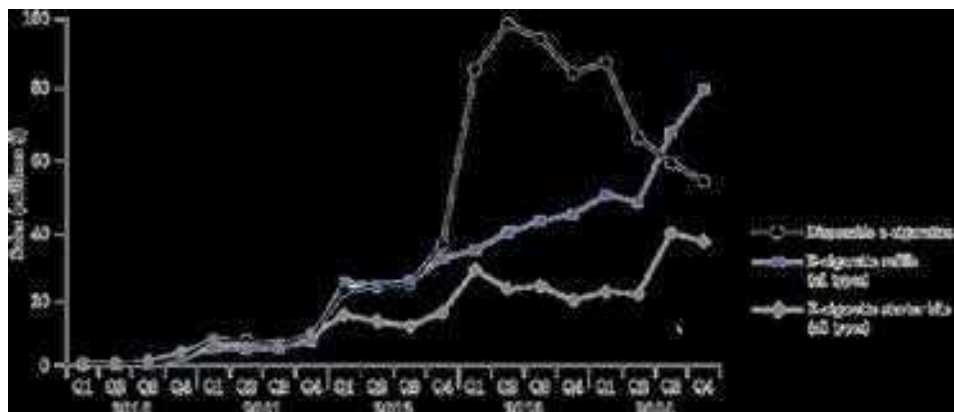
In 2014, more than 85% of e-cigarette sales occurred in the tracked retail and online channels, including certain convenience stores and food, drug, and big-box stores (Wells Fargo Securities 2015a; see Table 4.1). It was estimated that 20% of *all* e-cigarette sales (including e-cigarettes and tanks/mods) in 2014 occurred online, while 44% of *all* e-cigarette

sales occurred in “vape shops” and other untracked retail channels (Wells Fargo Securities 2015a; see Table 4.1).



Source: Huang and Chaloupka (in press).
Note: Data points for this figure are shown in Table A4.4-1 in Appendix 4.4.

Figure 4.1. E-cigarette sales in tracked channels by brand, 2010–2014.



Source: Huang and Chaloupka (in press).
Figure 4.2. E-cigarette sales in tracked channels by product type, 2010–2014.

Another important trend in e-cigarette sales is the growth of flavored products. Although some brands, such as NJOY, initially did not sell flavored e-cigarette products, most companies now offer some form of flavored varieties. Giovenco and colleagues (2015) found that sales of menthol-flavored e-cigarettes in traditional U.S. retail channels (e.g., convenience stores, grocery stores, pharmacies, and mass merchandisers) more than doubled between 2012 and 2013, increasing from \$96.4 million in 2012 to \$215.7 million in 2013. Sales of fruit-flavored e-cigarettes more than tripled during the same period, from \$4.9 million to \$16.7 million.

Sales of different types and brands of e-cigarettes likely differ by demographic group. For example, anecdotal evidence suggests that youth and young adults prefer pen-style devices, those that come in various shapes and styles, and devices that may be used interchangeably with e-hookahs (Richtel 2014b). Research also suggests that users may eventually graduate to more complex systems; more specifically, experienced users may be more likely to use tanks and mods (Farsalinos et al. 2014). Unfortunately, sales data by demographics are very limited, and studies have not yet examined how sales of e-cigarette products differ by demographic classification.

Production of E-Liquids

E-liquids used in closed-system devices usually are produced in the United States and then shipped to China to be included in the assembly process. For example, MarkTen, blu, and NJOY manufacture their own e-liquids in the United States, which then are sent to China before the final product is assembled there.

In the United States, one of the biggest players in the premixed e-liquid market for refillable e-cigarettes is Johnson Creek Vapor Company (2011), which claims to be the world's leading manufacturer of e-liquid and the first company to produce and manufacture e-liquid in the United States. Johnson Creek has not disclosed the suppliers of its nicotine solution.

Impact of E-Cigarette Price on Sales and Use of These Products

This section summarizes the limited evidence on the impact of e-cigarette prices on the sales and consumption of these products. The sizable body of research examining the effects of taxes and prices on the sale and use of conventional cigarettes (Chaloupka and Tauras 2011; International Agency for Research on Cancer 2011) leads to the conclusion that price increases resulting from higher excise taxes are effective tools for reducing cigarette consumption, especially among youth.

Trends in E-Cigarette Prices over Time

A study by Huang and Chaloupka (in press) documented and analyzed the relationship between real price and sales volume for both disposable and rechargeable e-cigarettes by using Nielsen data, which reflected the e-cigarette (predominantly cigalikes) sales and prices in retail stores tracked by Nielsen.

Figure 4.3 presents U.S. data on real price (determined by adjusting the prices to the value of the U.S. dollar in the fourth quarter of 2014) and sales volume for disposable e-cigarettes between 2010 and 2014 based on data from Huang and Chaloupka (in press). The average price for a single disposable e-cigarette declined from approximately \$17 in the first

quarter of 2010 to less than \$9 in 2014. In terms of volume, the estimate for disposables increased from far below 100,000 in the first quarter of 2010 to almost 11 million in the first quarter of 2014, before dropping to about 6.3 million in the final quarter of 2014. This graph reveals an association between real price and the sales volume for disposable e-cigarettes from 2010 to the second quarter of 2013: As real price declined over time, sales volume increased. Looking back, the rapid decline in the price of disposable e-cigarettes between 2007 and 2011 (Huang and Chaloupka in press) may have occurred because of improvements in product technology and industry promotion, which significantly cut the costs of producing such products (Bhatnagar et al. 2014; Wells Fargo Securities 2015c). The rather modest declines in prices since 2011 may reflect the fact that further technological improvements became less feasible (Wells Fargo Securities 2015c).

In terms of volume, the substantial decrease in 2014 may be partly attributable to consumers shifting away from cigalikes to tanks, mods, and other more powerful devices, for which sales were not tracked well.



Source: Huang and Chaloupka (in press).

Figure 4.3. Sales volume and price of disposable e-cigarettes, U.S. market, 2010–2014.

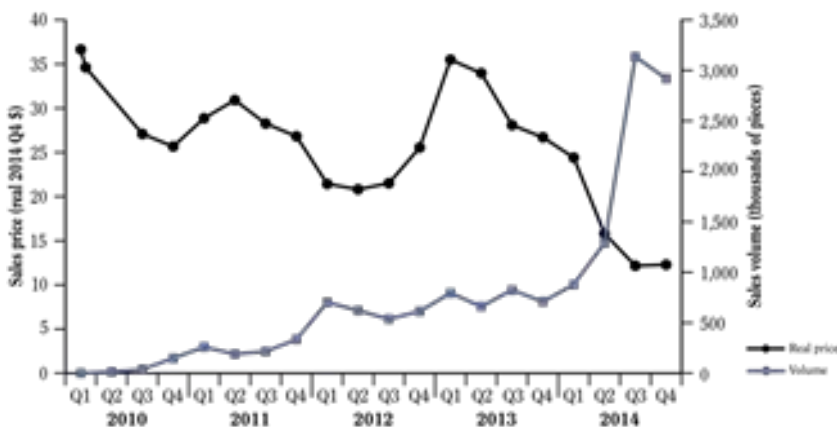
An inverse relationship is also evident between real price and sales volume for rechargeable e-cigarettes. Figure 4.4 demonstrates that when the real price went down, the sales volume increased, particularly after 2012. Between 2010 and 2014, the average unit price for rechargeables decreased markedly, dropping from \$37 in the first quarter of 2010 to \$12 at the end of 2014. However, there were more price fluctuations than were found for disposable e-cigarettes (Figure 4.3). The price fluctuations for rechargeables were likely because of the change in product mix and the influx of various new types and brands of these devices during this period (Bhatnagar et al. 2014; Wells Fargo Securities 2015c). Sales volume increased dramatically between 2010 and 2014, rising from a minimal amount at the beginning of 2010 to about 3 million units in the last quarter of 2014.

Impact of E-Cigarette Prices on E-Cigarette Sales

In one of the first studies to explore the effects of e-cigarette prices on the sales of these products, Huang and colleagues (2014b) estimated, from Nielsen data, both the own-price elasticity and the cross-price elasticity of demand for e-cigarettes (disposable or rechargeable)

and studied the impact of conventional cigarette prices and smokefree policies on e-cigarette sales. Own-price elasticity is a measure showing how much demand for a product will change given a change in its price, while cross-price elasticity is a measure showing how much demand for a product will change given a change in another product's price. Using data from Nielsen's commercial retail store scanning service, this study employed fixed-effects models to estimate elasticity of demand and associations between e-cigarette sales and either the prices of conventional cigarettes or smokefree policies from 2009 to 2012. Results demonstrated (a) that e-cigarette sales were quite responsive to own-price changes (estimated own-price elasticities for disposable e-cigarettes centered around -1.2 [a 10% increase in price would decrease sales by 12%], while those for rechargeable e-cigarettes were approximately -1.9 [a 10% increase in price would decrease sales by 19%]) and (b) that disposable e-cigarettes appeared to be emerging as substitutes for rechargeables (a 10% increase in rechargeable e-cigarette prices increased sales of disposable e-cigarettes by about 5%). This study concluded that policies increasing the retail prices of e-cigarettes—such as imposing taxes or limiting rebates, coupons, and discounts—could potentially lead to significant reductions in e-cigarette sales and that variations in tax policy by product type could lead to substitution between product categories. It is important to note that “vape shops” were not included in these data, as Nielsen collects data only from convenience, food, drug, and big-box stores.

Although these results provide evidence that changing the price of e-cigarettes affects the number sold, the potential effects of the price of conventional cigarettes on the purchase of e-cigarettes are less clear. Huang and colleagues (2014b) found no consistent or statistically significant relationship between the price of conventional cigarettes and the sale of e-cigarettes. In contrast, Grace and colleagues (2015), who measured the cross-price elasticity of e-cigarettes and conventional cigarettes using simulated demand for the latter in a sample of New Zealand smokers, found that the cross-price elasticity of e-cigarettes was significantly positive, suggesting that e-cigarettes may be partially substitutable for conventional cigarettes. Thus, the use of e-cigarettes may increase as the price of conventional cigarettes increases.



Source: Huang and Chaloupka (in press).

Figure 4.4. Sales volume and price of rechargeable e-cigarettes, U.S. market, 2010–2014.

Other evidence suggests that the potential impact of price changes on the use of e-cigarettes may differ by demographic characteristics. Relationships between the smoking of conventional cigarettes and socioeconomic status (SES) are well documented in the literature, and additional evidence has demonstrated that youth and young adults, and those with low SES, tend to exhibit higher sensitivity to changes in the price of conventional cigarettes (International Agency for Research on Cancer 2011; U.S. Department of Health and Human Services [USDHHS] 2012). Therefore, youth and young adults, as well as low-SES persons, may be more price-sensitive in the purchase of e-cigarette products, and thus they may be more likely to stop using e-cigarettes as their price increases. These potential connections between the price of e-cigarettes and their use should be examined carefully as more data become available.

Marketing and Promotion of E-Cigarettes

Marketing is an important tool for industries to use in influencing consumer preferences, and the potential for marketing to influence smoking behaviors has been a source of public health concern for many years (DiFranza et al. 1991; USDHHS 2000, 2012; National Cancer Institute [NCI] 2008). Research has demonstrated a causal relationship between tobacco marketing and smoking, with the majority of research focusing on the impact of tobacco marketing on the initiation of smoking by youth (Biener and Siegel 2000; USDHHS 2012). For adolescents, studies have found cross-sectional and longitudinal associations between the intensity of cigarette marketing and initiation of smoking, brand awareness, brand preferences, attitudes toward smoking, susceptibility to smoking, and smoking behaviors (O’Connell et al. 1981; Chapman and Fitzgerald 1982; McNeill et al. 1985; Charlton 1986; Potts et al. 1986; Aitken et al. 1987; Goldstein et al. 1987; Aitken and Eadie 1990; Botvin et al. 1991; DiFranza et al. 1991; Klitzner et al. 1991; Pierce et al. 1991; Botvin et al. 1993; Hastings et al. 1994; Pierce et al. 1994; Coeytaux et al. 1995; Evans et al. 1995; Pierce and Gilpin 1995; Richards et al. 1995; Slade et al. 1995; Unger et al. 1995; Pollay et al. 1996; Schooler et al. 1996; Gilpin and Pierce 1997; Lam et al. 1998; Feighery et al. 2006). A review of these and other studies led the 2012 Surgeon General’s report to conclude that exposure to advertising causes the initiation of smoking (USDHHS 2012).

In general, product marketing is designed to inform people about the products being offered (and thus develop brand “awareness”) and to persuade people to buy particular brands (i.e., develop brand “preference”). Branding is particularly important for products considered to be “commodities,” such as conventional cigarettes and e-cigarettes, where the offerings are similar and branding differentiates the products (Rossiter and Bellman 2005; NCI 2008). Marketing is particularly critical for e-cigarettes, as new products must be introduced to potential users (Sethuraman et al. 2011).

Like marketers of conventional cigarettes, marketers of e-cigarettes use a number of channels and tactics to advertise and promote their products. These channels have included extensive marketing on the Internet and advertising in mainstream media, including popular magazines, retailer point-of-sale ads, product placement on popular media, and even television commercials—an advertising option unavailable to cigarette manufacturers because of regulatory policies (Legacy for Health 2014; Ganz et al. 2015). E-cigarette brands

also use web-sites to interact directly with their customers through direct-to-consumer marketing (e.g., direct mail and direct e-mail) and social media channels, such as Facebook, Twitter, and Instagram (Huang et al. 2014a; Richardson et al. 2014; Ganz et al. 2015).

Marketing Expenditures

E-cigarette manufacturers currently are not required to report marketing expenditures to any regulatory agency (Boxer et al. 2013; *Federal Register* 2015). Using proprietary data from Kantar Media, however, Kornfield and colleagues (2015) tracked marketing expenditures (television, print, radio, and Internet) back to 2008 for approximately 130 e-cigarette brands (note that many e-cigarette products are not branded, and thus these data are not complete). Kornfield and colleagues (2015) found minimal spending through 2010, followed by an acceleration in spending from \$12 million in 2011 to \$125 million in 2014 (Figure 4.5). Not shown in the figure is that in 2012, more than 60% of advertising expenditures were for blu (then owned by Lorillard, now Imperial Tobacco), which was the market leader (Kornfield et al. 2015). The trajectory for spending was consistent with the pattern for product sales, particularly for the most dominant brands (Figures 4.1 and 4.5).

Annual marketing expenditures for conventional cigarettes (\$9.2 billion in 2012) dwarf the \$125 million in 2014 for e-cigarettes (Federal Trade Commission 2015a,b; Kornfield et al. 2015). However, the available data about e-cigarette marketing also underestimate total marketing expenditures. Not included are expenditures for retail marketing, social media, and sponsored events, all of which are essential components of the industry's integrated marketing strategy. In the absence of regulation, television advertising for e-cigarettes will continue, as the two largest tobacco companies moved promotions of MarkTen (Altria) and VUSE (Reynolds American) from test markets to national distribution in 2014 (Kornfield et al. 2015; Truth Initiative 2015; Cantrell et al. 2016).

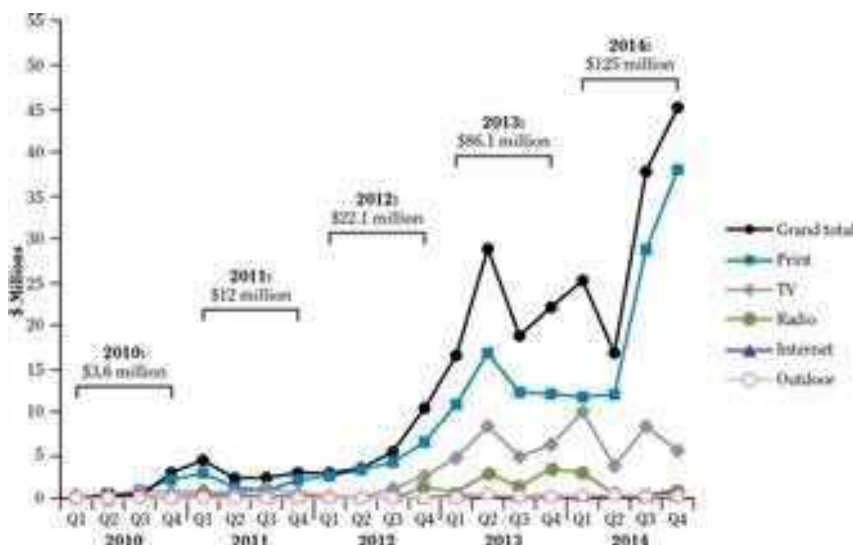
Tobacco marketing and surveillance systems—including the Trinkets & Trash archive maintained by the Rutgers University School of Public Health and the Stanford Research into the Impact of Tobacco Advertising (SRITA) research group—collect examples of e-cigarette advertising and promotions and make these available to users through image-rich websites (see Trinkets & Trash [<http://www.trinketsandtrash.org>] and Stanford Research into the Impact of Tobacco Advertising [http://tobacco.stanford.edu/tobacco_main/index.php]).

Magazine and Print Advertising

Print has been the dominant channel for tracked expenditures of traditional e-cigarette advertising, representing 84% of annual expenditures in 2014 (Kornfield et al. 2015; Figure 4.5). A study by Richardson and colleagues (2014) collected U.S. advertisements for all noncombustible tobacco products (i.e., e-cigarettes, snus, dissolvables, and chew/dip/snuff) for a 3-month period in 2012 through Mintel, which tracks direct mail and opt-in e-mail ads, and Competitrack, which monitors 21 other media sources. Metadata for identified ads showed advertising for e-cigarettes in print, television, radio, online, direct mail, and e-mail. The three most common media were print, television, and e-mail, and spending was highest for print ads (Richardson et al. 2014). An analysis of industry marketing data by the American Legacy Foundation (now called Truth Initiative) reported that 47% of U.S. teens (12–17 years of age) and 82% of young adults (18–21 years of age) were exposed to magazine advertising for e-cigarettes in 2014; popular venues included tabloids, entertainment weeklies, and men's life-style magazines (Truth Initiative 2015).

Research indicates that e-cigarette advertising in magazines with high teen readership is on the rise (U.S. Congress 2014). From 2012 to 2013, the number of e-cigarette advertisements in magazines with high youth readership was four times the number in magazines with high adult readership (U.S. Congress 2014). Recent studies using data from Kantar Media and GfK MRI (the latter measures media audiences and consumer insights; see <http://www.mri.gfk.com>) on e-cigarette advertisements show that blu led all e-cigarette brands in magazine advertising and that respondents had the highest recall of blu advertisements (Legacy for Health 2014).

A content analysis by Banerjee and colleagues (2015) of print magazine tobacco ads for 2012–2013, using data collected from Kantar Media, identified 171 e-cigarette ads over this period, 27 of which were unique. Ads were found in 24 magazines, 11 of which had been identified in prior studies as having youth and young adult readerships greater than 2 million per year or for which the teen portion of the audience was more than 10%. By number, ads for e-cigarettes were second only to those for conventional cigarettes and higher than the numbers for moist snuff, cigars, and snus. Eighty-five percent of the content in e-cigarette ads focused more on a theme of logos (i.e., logic or facts to support a position) than on a theme of emotional appeal.



Source: Data for 2010–2013 (Q2) from Kornfield and colleagues (2015, p. 110) and adapted with permission from BMJ Publishing Group Limited. Data for 2013 (Q3)–2014 from Kantar Media (unpublished data).

Figure 4.5. Quarterly promotional spending for e-cigarettes, 2010–2014.

In examining persuasive themes, the study found that ads used several approaches, including highlighting the conventional advantages of the product—such as a focus on customer satisfaction—and emphasizing the quality of the product or price (85.2%) (Banerjee et al. 2015). The ads also used the comparative approach, such as portraying the product as being different from other products, being smokefree, or being exempt from use in areas where conventional cigarettes are prohibited. Figure 4.6 shows examples of the claims in e-cigarette marketing. In terms of images, 100% of the ads included the brand name and an

image of the product. In addition, ads were most frequently full-page advertisements (89.9%), usually placed the product in a way that drew attention to it (92.6%), and most often used six or more colors (85.2%), which the authors noted increases the attention-grabbing ability of the ads (Banerjee et al. 2015).

A different content analysis of magazine ads for e-cigarettes, this one for a 3-month period in 2012 (Richardson et al. 2014), found health-related themes and non-health-related attributes—such as romantic, sexual, or sociability content, with the highlighting of taste as the most frequent selling proposition (see Figure 4.6, parts B–D for examples). All ads in this analysis were found to contain links to a product’s website. When examined by readership, e-cigarette ads were found to have run in magazines with mostly White-male readers and, to a lesser extent, magazines targeting White women. The analysis noted that ads were targeted to a magazine’s readership, with different ads shown in the White, male-oriented *Rolling Stone* publication as compared with the female-dominated *Us Weekly*.

Television Advertising to Youth and Young Adults

The increasing frequency and reach of advertising on television raises concerns about the potential impact of promoting nicotine products and renormalizing smoking through that medium, particularly for youth (Hodge Jr 2013; Duke et al. 2014; Grana and Ling 2014). At least 40 unique advertisements for e-cigarettes appeared on U.S. television in 2013 and early 2014 (Farrelly et al. 2015). For example, e-cigarette ads were featured in the Super Bowl broadcast, which reached an estimated audience of more than 100 million persons in 2012 (Deans 2012). The Truth Initiative (formerly the American Legacy Foundation) found that in 2014, television advertising reached similar proportions of youth (62% of 12- to 17-year-olds) and young adults (64% of 18- to 24-year-olds) (Truth Initiative 2015). Using proprietary data from Nielsen, Duke and colleagues (2014) estimated that 50% of U.S. youth were exposed to e-cigarette ads on television in 2013 and that 80% of this advertising was for blu (Lorillard, now Reynolds American). On average, those exposed saw 21 ads between October 2012 and September 2013. Between 2011 and 2013, exposure to e-cigarette advertising on television increased dramatically, by 321% for young adults (18–24 years of age) and 256% for adolescents (12–17 years of age) (Duke et al. 2014).

The same study (Duke et al. 2014) found that more than 75% of the exposure of youth to e-cigarette ads occurred on cable networks. The study found television ads for several different brands—including blu, FIN, Starfire, and NJOY—during a 9-month period in 2013. The most widely aired ad was for blu, featuring a celebrity and closing with the tagline “we’re all adults here. It’s time to take back your freedom” (Duke et al. 2014, p. 6).

Sponsorships

After the Master Settlement Agreement in 1998, sponsorship of events with a significant youth audience, such as concerts and athletic events, was banned for conventional cigarettes. However, e-cigarettes do not fall under these parameters, and recalling the early marketing of conventional cigarettes, e-cigarette brands have used sponsorships to increase the awareness and appeal of their label and product. For example, in 2011 blu sponsored a NASCAR driver and had its own car in some races (PRNewswire 2011). Additionally, blu has handed out free samples during large events and has even sponsored events at music festivals (PRNewswire 2013; blu eCigs 2014). Further, conservative estimates indicate that in 2012 and 2013, free samples were provided by six companies at 348 events, most of these events having high

participation by youth (Durbin et al. 2014). Under the deeming rule published in May 2016 (currently under litigation), free samples were banned (*Federal Register* 2016).

Digital Landscape for E-Cigarettes

The Internet has been widely used to promote cigarettes, cigars, and smokeless products (Ribisl 2003; Freeman and Chapman 2007; USDHHS 2012). This medium—through websites, message forums, and social media—has been heavily used to sell and glamorize e-cigarettes and their use. Nearly all teens 13–17 years of age (92%) use the Internet daily, and 73% of teens access the Internet via smartphones (Lenhart 2015). In 2015, a study conducted by the Truth Initiative indicated that 40% of youth (13–17 years of age) and 57% of young adults (18–21 years of age) had seen e-cigarette advertising online (Truth Initiative 2015).

A. Freedom



Source: *Esquire* (2014).

B. Health



Source: Stanford Research into the Impact of Tobacco Advertising (n.d.b.).

C. Romance, sexuality, or sociability



Source: (Left) *Maxim* (2012), (middle) *Men's Journal* (2014), and (right) *Sports Illustrated* (2014).

Figure 4.6. (Continued).

D. Taste



Source: Soap Opera Digest (2013).

E. Smoking cessation



Source: Rolling Stone (2013).

F. Use in smokefree environments



Source: Rolling Stone (2012).

G. Product engineering



Source: Rolling Stone (2015).

Figure 4.6. (Continued).

Price promotions are not just involved in sales at brick-and-mortar stores; they are also offered by online stores and through social media. Grana and Ling (2014) found that 80% of websites indicated a sale price or discount, while Huang and colleagues (2014a) found that 34% of commercial tweets mentioned the words “price” or “discount.” Both Facebook and Twitter provide opportunities for brands and companies to offer online coupons and discounts (Discount Coupons for blu n.d.; Vapor4Life n.d.). In a study of online e-cigarette retailers, 28% of the web-sites offered a promotion, such as a discount, other free items, or a loyalty program (Williams et al. in press). Without age restrictions or age verification, youth can access these websites easily and thus obtain the discount or coupon (Williams et al. in press).

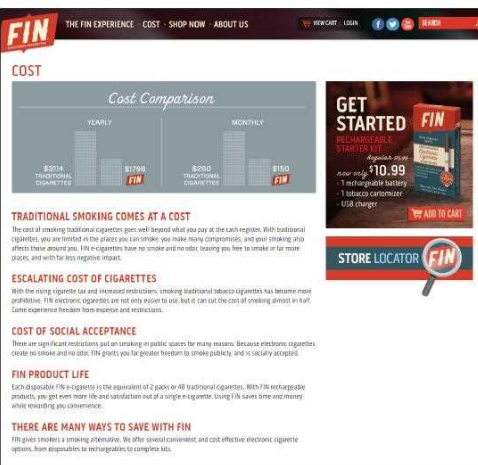
H. Cleaner than cigarettes


**ADULT SMOKERS:
IF YOUR CAR COULD TALK...**

It would insist you try blu™ electronic cigarettes. Smoke-free, ash-free, and odor-free means blu eCigs® electronic cigarettes give you complete freedom. Imagine smoking satisfaction without rolling down the car windows! No more offensive, lingering odors in your car's upholstery. No more fuss over messy ashes that missed the ashtray. Since your car can't talk, it won't ask you to try blu eCigs e-cigarettes. So we will... take back your freedom: have a blu e-cigarette.

Visit www.blucigs.com for more information.

Source: *Car and Driver* (2014).

I. Save money


FIN THE FIN EXPERIENCE COST SHOP NOW ABOUT US

COST

Cost Comparison

YEARLY	MONTHLY
\$2014 TRADITIONAL CIGARETTES	\$2014 TRADITIONAL CIGARETTES
\$1799 FIN	\$150 FIN

TRADITIONAL SMOKING COMES AT A COST

The cost of smoking traditional cigarettes goes well beyond what you pay at the cash register. With traditional cigarettes, you are limited in the places you can smoke, you make many compromises, and your smoking often affects those around you. FIN e-cigarettes have no smoke and no odor, leaving you free to smoke in far more places, and with far less negative impact.

ESCALATING COST OF CIGARETTES

With the rising cigarette tax and increased restrictions, smoking traditional tobacco cigarettes has become more profitable. FIN electronic cigarettes are not only easier to use, but it can cut the cost of smoking almost in half. Come experience freedom from expense and restrictions.

COST OF SOCIAL ACCEPTANCE

There are significant restrictions and an smoking in public spaces for many reasons. Because electronic cigarettes, create no smoke and no odor, FIN grants you far greater freedom to smoke publicly, and is socially accepted.

FIN PRODUCT LIFE

Each disposable FIN e-cigarette is the equivalent of 2 packs or 40 traditional cigarettes. With FIN rechargeable products, you get even more life and satisfaction out of a single e-cigarette. Using FIN saves time and money while resupplying you conveniently.

THERE ARE MANY WAYS TO SAVE WITH FIN

FIN gives smokers a smoking alternative, the often unmet convenient and cost effective electronic cigarette options, from disposables to rechargeables to complete kits.

GET STARTED

RECHARGEABLE STARTER KIT

Rechargeable kit \$10.99

- 1 rechargeable battery
- 1 tobacco cartomizer
- USB charger

STORE LOCATOR

Source: FIN Electronic Cigarettes (n.d.).

J. Circumvent smokefree policies


DEAR SMOKING BAN,

blu ELECTRONIC CIGARETTE

Take back your freedom to smoke anywhere with blu electronic cigarettes. blu produces no smoke and no ash, only vapor, making it the smarter alternative to regular cigarettes. It's the most satisfying way to tell the smoking bans to kiss off. Cissy, maybe the second-most satisfying way.

From blu Smart Pack

blucigs.com

18+ only. CALIFORNIA PROPOSITION 65 Warning: This product contains nicotine, a chemical known to the state of California to cause birth defects or other reproductive harm.

Source: *Spin* (2012).

Figure 4.6. E-cigarette marketing claims.

However, under the deeming rule, websites cannot sell e-cigarettes to youth under the age of 18, so access will likely be curtailed as a result (*Federal Register* 2016). The following sections review three basic categories of online e-cigarette content: websites that sell e-cigarettes, manufacturer-sponsored brand name websites, and e-cigarette promotions on social media websites (including Facebook, Twitter, and YouTube).

Websites Selling E-Cigarettes

Tobacco industry analysts estimate that online sales accounted for approximately 30% of e-cigarette sales volume in the first quarter of 2015 (Wells Fargo Securities 2015a). Some Internet vendors sell their own brands exclusively (e.g., Mystic, Green Smoke), while a large

number are online stores that sell many brands and varieties of products (Zhu et al. 2014; Williams et al. in press).

Although the marketers of e-cigarettes have made claims that differ from those made for conventional cigarettes (such as use for smoking cessation, which is illegal without being an approved cessation drug or device), a content analysis of e-cigarette marketing (Grana and Ling 2014) and the observations of tobacco marketing surveillance systems point to several similarities, including the use of young, attractive models; lifestyle claims; and celebrities. Other claims made in e-cigarette advertising have been used in the past by conventional cigarette brands (such as having fewer carcinogens, lower risk of tobacco-related disease) or by smokeless tobacco products (such as the ability to use them where smoking is prohibited) (Grana and Ling 2014). However, under the deeming rule that was published in May 2016, after August 8, 2016, e-cigarette manufacturers cannot make modified risk claims (*Federal Register* 2016) (although this provision has been challenged in pending lawsuits).

Formal analyses of marketing claims of branded e-cigarette sites that both promote and sell e-cigarettes provide details on the types of claims made in these channels. The study by Grana and Ling (2014) analyzed claims from 59 English-language websites over a 2-month period in 2011 and found four major thematic content areas: health- and cessation-related benefits, avoiding smokefree policies, lifestyle benefits, and product-engineering claims. Ninety-five percent of websites made explicit or implicit health-related claims, and 64% made claims related to cessation, often through the use of testimonials. Almost all (98%) included a comparison of the risks and benefits of e-cigarettes and conventional cigarettes; 95% included claims that e-cigarettes are cleaner; and 93% said they were cheaper. Claims regarding where e-cigarettes could be used were also common—with 88% claiming e-cigarettes can be used anywhere, and 71% pointing to e-cigarette use as a means of circumventing clean air policies. Figure 4.6 shows advertising that exemplifies these marketing claims for e-cigarettes.

Grana and Ling's (2014) analysis also points to the common use of lifestyle-related claims, a hallmark of traditional tobacco marketing: 73% of websites contained images or claims of being modern or glamorous. Websites also pointed to social advantages for users of their particular brand: 44% of claims pointed to increased social status and 32% to enhanced social activity, 31% suggested romantic advantages, and 22% used celebrities. Claims of increased social status, opportunity, and romance as well as the use of celebrities may resonate especially with youth and young adults (Grana et al. 2011).

A different content analysis, this one of the marketing messages of English-language branded e-cigarette retail sites, examined and compared websites for two different time periods (May–August 2012 and December 2013–January 2014) and found differences in claims between the two timeframes (Zhu et al. 2014). In comparing claims for brands available during both time periods with those that were newly available in 2013–2014, the authors found that products and advertising messages varied between the two samples. Brands analyzed from 2012 were significantly more likely than those in the later period to (a) claim that their products were healthier and less expensive than conventional cigarettes and could be used where smoking is prohibited and (b) indirectly claim their products were effective for smoking cessation through testimonials and other methods (Zhu et al. 2014). The study also found an increase from one period to the next in the number of branded retail websites and the number of flavors per brand advertised on a website, as well as the likelihood of a web-site offering e-cigarette hardware and such other products as e-liquids and

e-hookahs or other products that did not resemble cigalikes (Zhu et al. 2014). The study's findings suggested that the emphasis for newer brands had shifted from comparing them with conventional cigarettes to a focus on their role as new nicotine delivery systems.

Williams and colleagues (in press) used a standardized search strategy employed in their earlier study of websites selling cigarettes (Ribisl 2003) to identify 995 English-language websites selling e-cigarettes in 2014. The authors performed a content analysis on the 281 most popular websites, as judged by data on traffic. Most of the websites were based in the United States (71.9%), the United Kingdom (16.7%), and China (5.3%), and they offered a variety of products, but more sold e-cigarette starter kits (92.5%) than disposables (55.2%). Most offered flavors, with the most popular being fruit (79.4%), candy (75.2%), coffee (68.0%), and alcohol (45.6%). Although 71.5% featured some type of health warning, 69.4% claimed health advantages over other tobacco products, and 32.7% claimed that the product helped people to quit smoking conventional cigarettes. The sites also featured endorsements or mentions of celebrities using the products (Stanford Research into the Impact of Tobacco Advertising n.d.a.). Physicians and other health professionals provided endorsements as well.

Elsewhere, Cobb and colleagues (2015) conducted a forensic analysis of websites that sold e-cigarettes and participated in affiliate advertising on the Internet. In addition to identifying multiple layers of redirection between online advertising by affiliates and websites selling e-cigarettes, the authors found that online advertisements and affiliate websites included cessation claims.

Research suggests Internet e-cigarette vendors have not routinely verified the age and identity of website visitors or blocked sales to minors. However, after August 8, 2016, due to the deeming rule, it has become illegal for online retailers to sell e-cigarettes to those under 18 (*Federal Register* 2016). In a survey of purchasing by youth, Williams and colleagues (2015) identified 98 web-sites selling e-cigarettes on which youth, 14–17 years of age, made purchase attempts using prepaid credit cards. In all, 18 (of 98) order attempts failed because of technical problems with the website or the payment system, all of which were unrelated to age verification. Of the remaining 80 orders, 75 (93.8%) were filled. Five vendors claimed to use a service offered by shipping companies to verify age at delivery, but none actually did. Although data are not available on the proportion of youth who purchase their e-cigarettes online versus buying them at retail outlets, this study suggests that youth would have ready access if they tried to purchase e-cigarettes online. The *Prevent All Cigarette Trafficking Act of 2009* requires Internet sellers of cigarettes and smokeless tobacco to, among other provisions, verify age of customers at the time of purchase and ensure that the deliverer checks identification at the time of delivery; stop Internet sales to minors; and pay applicable local, state, federal, and territorial taxes to reduce the price advantage of online sales. FDA regulation now prohibits the Internet sales of e-cigarettes to minors. However, there are currently no federal requirements for Internet vendors of e-cigarettes to check identification upon delivery or pay applicable taxes (Campaign for Tobacco Free Kids 2016).

The marketing of candy and fruit flavors may be one of the reasons that e-cigarettes appeal to youth (Grana and Ling 2014; Richtel 2014a; Zhu et al. 2014). Young adults (18–24 years of age) are more likely to use flavored tobacco products than are adults in the next age group (25–34 years of age) (Villanti et al. 2013). Zhu and colleagues (2014), who used three search engines (Google, Yahoo!, and Bing) and various keywords from May 2012 to January 2014 to identify a wide variety of e-cigarette brands and flavors, found 466 brands and 7,764 unique flavors, with 242 new flavors appearing each month. Other than tobacco flavor, the

most popular flavors were menthol (92.1%), fruit (84.2%), dessert/candy (79.9%), and alcohol/ drinks (77.5%). Additionally, in their content analysis of e-cigarette retail websites, Grana and Ling (2014) found that such flavors as coffee, fruit, and candy were offered on most sites. Further, flavors were being sold under brand names similar to cereal and candy products that appeal to youth, such as Wrigley's Big Red Gum (Daniels 2015).

Tobacco Industry Corporate and Brand Websites

Three categories of e-cigarette brands have emerged within the U.S. market: brands developed by cigarette manufacturers (i.e., MarkTen, VUSE), brands acquired by cigarette manufacturers (i.e., blu, Green Smoke) (Table 4.3), and brands that have no affiliation with a cigarette manufacturer (e.g., NJOY, FIN). A content analysis of websites for these three types of brands suggested that those *developed* by cigarette manufacturers may be marketed more cautiously than brands *acquired* by cigarette manufacturers or brands that have no affiliation with a cigarette manufacturer (Seidenberg et al. 2016). Table 4.4 compares and contrasts some key features of the web-sites by manufacturer affiliation. It shows, for example, that access to websites of brands developed by cigarette manufacturers (or a subsidiary) was restricted to users 21 years of age and older (MarkTen), and user registration was required (i.e., the user needed to input personal information such as name, address, and birthdate) for VUSE. In contrast, websites for brands with no affiliation with a cigarette manufacturer and those acquired by cigarette manufacturers were accessible to users 18 years of age and older via self-reporting of age, with the exception of 21st Century Smoke. In addition, VUSE e-cigarettes were not sold online (they were sold only in retail outlets), and they were available in a single nicotine level with limited flavor options (except for forthcoming tank versions), while MarkTen could be purchased online. The websites for both MarkTen and VUSE mentioned selling flavored e-cigarettes. As far as e-cigarette brands not having an affiliation with a cigarette manufacturer or that were acquired by a cigarette manufacturer, all brands except Logic offered fruit, candy, or other flavors. Further, all of the unaffiliated brand websites sold e-cigarettes online and offered multiple nicotine levels. Most websites offered nicotine-free options and flavored e-cigarettes as well (Seidenberg et al. 2016). The Green Smoke website even provided a link to guide customers in finding the proper nicotine level for their cartridges (Green Smoke E-Vapor n.d.).

Social Media Promoting E-Cigarettes

E-cigarettes have been widely promoted on social media platforms such as YouTube, Twitter, Instagram, and Facebook; most of these social media sites do not require age verification. YouTube is the most popular video-sharing website globally and features many e-cigarette videos. Luo and colleagues (2014) used various search terms to identify 196 unique videos in February 2013 that were portraying e-cigarettes and found that 94% of the videos were "pro" e-cigarettes, 4% were neutral, and 2% were "anti" e-cigarettes. Those authors found that the three most common genres were advertising of products, user sharing, and product reviews. Of the "pro" e-cigarette videos, 84.3% featured links to websites selling e-cigarettes, and 71.4% claimed that e-cigarettes were a healthier alternative to conventional cigarettes. Finally, the "pro" videos received more visits and were rated more favorably than were the small number of "anti" videos.

Table 4.3. Mergers, acquisitions, partnerships, and other agreements in the e-cigarette industry

Date	Purchaser	Acquisition target	Partnerships and other agreements	Deal size ^a	Geography ^b
December 2011	Japan Tobacco	—	Ploom (partnership)	Not disclosed	United States
December 2012	BAT	CN Creative	—	£40 million	United Kingdom
April 2012	Lorillard	blu	—	\$135 million	United States
April 2013	National Tobacco	—	V2 Cigs (partnership)	Not disclosed	United States
August 2013	Imperial	Dragonite	—	\$75 million	China
October 2013	Lorillard	SKYCIG	—	£60 million	United Kingdom
January 2014	ECIG	VAPESTICK	—	\$70 million	United Kingdom
January 2014	Gilla	Drinan	—	Not disclosed	Ireland
February 2014	Altria	Green Smoke	—	\$110 million	United States
March 2014	ECIG	FIN	—	\$170 million	United States
April 2014	ECIG	VIP	—	\$58 million	United Kingdom
June 2014	ECIG	Ten Motives	—	\$104 million	United Kingdom
June 2014	PMI	Nicocigs	—	Not disclosed	United Kingdom
July 2014	ECIG	Hardwire	—	\$30 million	Internet
November 2014	Japan Tobacco	E-Lites	—	Not disclosed	United Kingdom
January 2015	BreatheEcigs/DNA	Breathe LLC	—	Not disclosed	United States
February 2015	Japan Tobacco	—	Ploom (purchased the intellectual rights to some Ploom technology)	Not disclosed	United States
March 2015	Gilla	An undisclosed Florida e-liquid company	—	\$1.5 million	United States
April 2015	Japan Tobacco	Logic	—	Not disclosed	United States
June 2015	Imperial	blu	—	\$7.1 billion	United States and United Kingdom
December 2015	Gilla	The Mad Alchemist	—	\$500,000	United States, Canada, Europe, and United Arab Emirates

Source: Various news sources and companies' websites, SEC (Securities and Exchange Commission) reports, and press releases as of January 25, 2016.

^aDeal size refers to prices at the time of the announcement, not necessarily the final transaction price.

^bGeography refers to the country in which the acquisition target was registered.

The authors of another study, this one a content analysis of 365 e-cigarette videos on YouTube that ran at some time from June 2007 to June 2011, estimated that more than 1.2 million youth and a total of 15.5 million people worldwide were exposed to these videos (Paek et al. 2014). In addition to looking at viewership, the content analysis examined the type, sponsorship, and health claims of the videos. Just 16% of the videos were formal advertisements or news clips, and 79.2% of the content was coded as appearing to have been generated by users. Videos emphasized economic, psychological, and social benefits, and health claims included e-cigarettes being less harmful than conventional cigarettes, healthy, and providing help in quitting smoking. Most (85.2%) videos in the sample were sponsored by e-cigarette companies or their associates, with an additional 10% coming from individuals who did not mention a specific website or company. Interestingly, videos sponsored by marketers contained a significantly lower level of health claims than did those from laypeople

(users) and, not surprisingly, contained a higher level of information cues (e.g., product contents, price, distribution channel).

Table 4.4. Comparison of website access restrictions, online sales, nicotine levels, and flavors among e-cigarette brands with no cigarette manufacturer affiliation, brands acquired by cigarette manufacturers, and brands developed by cigarette manufacturers

		E-cigarette brands (10)	
	Not affiliated with a cigarette manufacturer: NJOY, Logic, 21st Century Smoke, FIN, Nicotek, and Mystic (6)	Acquired by a cigarette manufacturer: blu and Green Smoke (2)	Developed by a cigarette manufacturer (or subsidiary): MarkTen and VUSE (2)
Website access	All websites (except 21st Century Smoke) have one-click access ^a or age verification to restrict initial access to people 18 years of age and older; 21st Century Smoke does not have any website restrictions for initial access.	Both sites have one-click access or age verification to restrict initial access to people 18 years of age and older (blu) and 21 years of age and older (Green Smoke).	MarkTen has age verification to restrict initial access to people 21 years of age and older. Before initial access, VUSE requires people 21 years of age and older to register first with the website.
Online sales	All brands can be purchased online.	Both brands can be purchased online.	MarkTen can be purchased online; VUSE cannot.
Multiple levels of nicotine	Among all brands, the level of nicotine varies by product. Some (e.g., blu, Logic Zero, 21st Century Smoke, Nicotek) offer products with 0% nicotine (by volume).	Among both brands, the level of nicotine varies by product.	For MarkTen, the level of nicotine varies by product. VUSE e-cigarettes contain 4.8% nicotine (by weight). VUSE tanks, set to come out in February 2016, will have different levels of nicotine (Kress 2015).
	Not affiliated with a cigarette manufacturer: NJOY, Logic, 21st Century Smoke, FIN, Nicotek, and Mystic (6)	Acquired by a cigarette manufacturer: blu and Green Smoke (2)	Developed by a cigarette manufacturer (or subsidiary): MarkTen and VUSE (2)
Flavors (other than tobacco and/or menthol)	All brands offer a variety of flavors, such as fruit and candy.	Both brands offer a variety of flavors.	MarkTen offers two flavors: fusion and wintermint. VUSE offers four flavors: crema, chai, berry, and mint (Kress 2015).

Source: Unless cited otherwise, information was obtained from the companies' websites (January 2016): <https://www.njoy.com/>; <http://store.logiccig.com/>; <https://www.21stcenturysmoke.com/>; <https://www.fincigs.com/>; <http://www.nicotekecigs.com/>; <http://www.misticcigs.com/>; <http://www.blucigs.com/>; <https://www.greensmoke.com/>; <https://www.markten.com/>; and <https://vusevapor.com/>.

^aWith "one-click access," visitors to a website self-report on their age by identifying their age from a clickable pop-up box. For example, persons 18 years of age and older can browse the website, but those younger than 18 cannot.

A cross-sectional study of Twitter, a microblogging platform, that examined more than 74,000 tweets accessed through a licensed Twitter data provider over a 2-month period in 2012, found extensive marketing of e-cigarettes (Huang et al. 2014a). The majority of e-cigarette content during this period was advertising and promotion. In fact, 89.6% of the tweets contained commercial content (e.g., presence of branded promotional messages or hyperlinks to commercial websites), and only 11% identified as being non-sponsored or independent, reflecting individual opinions or experiences, or being linked to non-promotional content. Commercial tweets most commonly contained price promotions and

discounts (34.3%), with cessation-related claims included in 10.8% and lower percentages for health or safety (Huang et al. 2014a).

Jo and colleagues (2016), in a study of 2,847 tobacco-related tweets about price promotions and coupons, found that e-cigarettes, not conventional cigarettes, were the most frequently mentioned product (90.1%), and about one-third of all e-cigarette-related tweets included a discount code. The tweets also touted the relatively low price of e-cigarettes and made comparative claims about the health risks of the product.

Sponsored Online and Video Advertising

The study by Richardson and colleagues (2015) used information from the monitoring service Competitrack to analyze the volume and characteristics of industry-sponsored tobacco and e-cigarette online banner/ video advertisements in the United States and Canada in 2012–2013. This study found that online banner/video advertising—which embeds an ad or video on a web-site—was more commonly used for e-cigarettes than for conventional cigarettes. E-cigarette ads were often placed on music or entertainment (39.1%) sites, which the authors noted attract a sizeable number of youth and young adults. The most frequent theme for the 24 online banner or video e-cigarette ads (promoting five e-cigarette brands) analyzed was that the product was more “green” or environmentally friendly than conventional cigarettes (54.2%), followed by less harmful than cigarettes (37.5%), and being an alternative to conventional cigarettes when someone could not smoke (33.3%).

E-Cigarettes in the Retail Environment

Conventional Tobacco Retailers (Convenience Stores, Pharmacies, Tobacco Shops)

As of December 2015, 48 of the 50 states prohibited sales of e-cigarettes to minors (National Conference of State Legislatures 2015), but compliance of retailers with youth-access laws has not yet been studied. FDA is actively enforcing the federal minimum age requirements. As of August 8, 2016, the federal deeming rule bans the sale of e-cigarettes to minors under the age of 18 and requires photo identification for those under age 27 (*Federal Register* 2016). In the past few years, brick-and-mortar retailers have surpassed the Internet as the dominant distribution channel for e-cigarettes. For example, after Lorillard acquired blu in 2012, the number of retailers selling this brand increased from 13,000 to 127,000 in just 1 year (Esterl 2012; Bannon 2013). In California, the proportion of licensed tobacco retailers that sold e-cigarettes increased from 12% in 2011 to 67% in 2014 (Chapman 2015).

E-cigarettes are widely available in convenience stores, a type of establishment that 4.1 million U.S. teenagers visit at least once per week (Rose et al. 2014; Sanders-Jackson et al. 2015a). According to a 2013 state-sponsored survey that included a sample of approximately 7,300 licensed tobacco retailers in California, e-cigarettes were sold in more than half of convenience stores, pharmacies, and liquor stores and in nearly all tobacco shops (California Department of Public Health and California Tobacco Control Program 2014).

Only three studies have examined the retail availability of e-cigarettes near schools. In a 2012 nationally representative sample of tobacco retailers, the presence of a public school within 1,000 feet was not related to the availability of e-cigarettes (Rose et al. 2014). In a study that examined a much larger buffer zone in Kentucky, 88% of schools in two counties were located within 1 mile of a retailer that sold e-cigarettes (Hahn et al. 2015). As for

colleges, disposable and/or rechargeable e-cigarettes were available at 60% of tobacco retailers near campuses in North Carolina and Virginia in 2013, a more than two-fold increase from the previous year (Wagoner et al. 2014). A pilot study examining tobacco point-of-sale advertising and promotion in the central Harlem neighborhood of New York City found that 26% of stores had e-cigarette advertising on the building's exterior (Ganz et al. 2015). External ads included those located less than 3 feet above the ground at the eye level of children—a placement that was outlawed for conventional cigarettes by the Master Settlement Agreement—and featured flavored products (Ganz et al. 2015).

Unlike conventional cigarettes, e-cigarettes appear to be relatively less prevalent at stores in economically disadvantaged communities. In an analysis that examined data from two studies that had used representative samples of U.S. tobacco retailers, e-cigarettes were less likely to be sold than conventional cigarettes at stores located in economically disadvantaged neighborhoods and in neighborhoods with a higher proportion of African American residents (Rose et al. 2014). These patterns are consistent with evidence that e-cigarette marketing in other channels targets higher income non-Hispanic White males (Emery et al. 2014). However, the retail availability of e-cigarettes has changed at different rates in different neighborhoods. In a study of U.S. food stores, only 3% of stores located in non-Hispanic White and Hispanic neighborhoods sold e-cigarettes in 2010; none of the stores in predominantly African American neighborhoods sold them (Khan et al. 2014). Three years later, the figures were 36% in pre-dominantly non-Hispanic White neighborhoods, 18% in Hispanic-majority neighborhoods, and 19% in African American-majority neighborhoods. Notably, these data were collected before the two largest U.S. tobacco companies launched MarkTen (Altria) and VUSE (Reynolds American) in late 2013. Thus, the industry's current influence on disparities in the retail availability and marketing of e-cigarettes cannot be readily estimated from the studies reviewed.

Two studies examined retail data about e-cigarettes as a function of state and/or county smokefree air laws (Huang et al. 2014b; Rose et al. 2014). In one of the studies, which used data collected in two studies that used independent samples of U.S. tobacco retailers, the odds of selling e-cigarettes were greater for retailers in states with weaker smokefree air policies, even after controlling for store type, price of conventional cigarettes, and neighborhood demographics (Rose et al. 2014). A similar inverse relationship was found between sales of disposable e-cigarettes (as measured by retail scanner data in 52 U.S. markets from 2009 to 2012) and the proportion of the population protected by 100% smokefree policies covering all indoor areas of bars, restaurants, and work-places (Huang et al. 2014b). Taken together, these results suggest that e-cigarettes are, at least initially, more likely to be sold in communities with weaker smokefree policies. Few retail surveillance studies have characterized promotion, placement, or price for e-cigarettes (Hsu et al. 2013; Wagoner et al. 2014; Ganz et al. 2015). In a study of licensed tobacco retailers in Florida, advertising for e-cigarettes was more prevalent on the exterior than the interior (50% vs. 11%) (Kim et al. 2015). In the study by Wagoner and colleagues (2014), the presence of e-cigarette advertising near college campuses in North Carolina and Virginia tripled on store exteriors and quadrupled in store interiors in just 1 year. Although the price of rechargeable units decreased significantly, there was little evidence of price discounting for any e-cigarettes (Wagoner et al. 2014). The low visibility of price discounts at the point of sale suggests that marketing for e-cigarettes favors a "pull" strategy, relying on direct mail and e-mail coupons and special offers to entice customers to retail locations.

“Vape Shops”

“Vape shops” specialize in the sale of refillable devices and tank systems, typically offer a tasting menu of flavors, and sometimes feature a lounge area where customers can “vape” while socializing (Lee and Kim 2015; Sussman et al. 2016). “Vape shops” have been excluded from most studies about the retail marketing of e-cigarettes, in part because the environment is so different from that of conventional tobacco retailers (Lee and Kim 2015) and because so few states require these establishments to obtain a tobacco retailer license, effectively keeping them out of the sampling frame for many studies and making the monitoring and enforcement of laws difficult (Lee et al. 2014).

Anecdotal evidence suggests that “vape shops” currently do not have readily visible branded signs and displays that characterize the retail marketing of other tobacco products. Even though the relationship between the “vape shop” industry and the tobacco industry can be adversarial (Sussman et al. 2016), one study found that the marketing practices of these establishments closely resemble the current and former strategies that tobacco companies have used to market other tobacco products (Cheney et al. 2015). According to this study, “vape shop” owners and managers in Oklahoma used free samples, loyalty programs, sponsored events, direct mail, advertising through social media, and price promotions targeted at particular consumers, such as college students (Cheney et al. 2015). No other study about marketing by “vape shops” has been published. Numerous gaps exist in research about “vape shops,” including information on consumer behavior, the use of tracking systems for sales data, marketing surveillance, purchases by youth, and the opinions of retailers and the general public about regulations. Spatial analyses are needed to determine whether “vape shops” are clustered near schools or college campuses, whether other neighborhood demographics are correlated with the location of these establishments, and how such associations, if present, have changed over time and in response to state and local policy interventions. The proportion of “vape shops” where workers mix solutions of liquid nicotine on site is not known, and the absence of uniform safety pre-cautions regarding handling and spills poses additional concern for regulation (ChangeLab Solutions 2014). Under the deeming rule that was published in May 2016, “vape shops” that mix and sell e-liquids are both retailers and manufacturers and, therefore, are subject to the provisions in the deeming rule and the Tobacco Control Act that apply to both (*Federal Register* 2016).

Exposure and Receptivity to Advertising for E-Cigarettes

Exposure

Given industry data about increasing expenditures for e-cigarette advertising and extending its reach, the high levels of advertising awareness reported in studies of youth and/or young adults are not surprising. An online panel of U.S. youth (13–17 years of age) and young adults (18–21 years of age) conducted in February 2014 found that awareness of e-cigarette advertising was greatest for retail advertising, followed by awareness of advertising on television and online (Truth Initiative 2015). In this study, and compared with the entire population, awareness among current smokers of e-cigarette advertising was higher across all channels and higher for online ads than for television ads (Legacy for Health 2014).

In school-based surveys of middle and high school students in Connecticut, gas stations and television were the dominant channels in which students reported recently seeing e-

cigarettes advertised or sold (Krishnan-Sarin et al. 2015). A different pattern was observed in a convenience sample of college students in Hawaii, where the figures for seeing ads were 59%, online; 58%, television; 71%, malls; 41%, gas stations; and 47%, convenience stores (Pokhrel et al. 2015). Elsewhere, in an online experiment, 56% of adolescents (13–17 years of age) who had never used e-cigarettes reported seeing at least one televised advertisement previously, and there were modest, but statistically insignificant differences in exposure by smoking status and race/ethnicity ($p < .10$) (Farrelly et al. 2015).

The National Youth Tobacco Survey reported that in 2014, 18.3 million middle and high school students were exposed to e-cigarette advertising from at least one source (CDC 2016b). In this nationally representative sample of U.S. middle and high school students, nearly 7 out of 10 reported seeing an e-cigarette advertisement in that year. The most common places for exposure among middle school students were retail stores (52.8%), the Internet (35.8%), television and movies (34.1%), and newspapers and magazines (25.0%). Similarly, high school students reported the highest exposure at retail stores (56.3%) and then the Internet (42.9%), television and movies (38.4%), and newspapers and magazines (34.6%). Among both middle school and high school students, exposure through retail stores was higher among non-Hispanic Whites than non-Hispanic Blacks. However, non-Hispanic Blacks had higher exposure to e-cigarette advertisements on television and in movies than non-Hispanic Whites. Females had higher exposure than males to advertisements on the Internet and in newspapers and magazines.

Receptivity to Advertising

Receptivity to tobacco marketing is a well-established risk factor for tobacco use by adolescents and young adults (NCI 2008; USDHHS 2012), and two studies adapted measures of receptivity to the marketing of tobacco in research on e-cigarettes. In one study, college students from a southwestern state who watched three advertisements for different brands of e-cigarettes in an online survey used a 7-point scale to rate how enjoyable, likable, and appealing the ads were; results suggested moderate receptivity (mean of 51 on a scale ranging from 7 to 126) and significant differences between brands (Trumbo and Kim 2015). In the other study, Pokhrel and colleagues (2015), using a sample of college students from Hawaii, adapted a multi-item scale of liking advertisements from studies about alcohol (Unger et al. 2003) and two items from the most commonly used measure of receptivity to tobacco marketing (Pierce et al. 1998). This study observed low levels of liking advertisements (all below the scale mid-point) (Pokhrel et al. 2015). The extent to which youth and young adults who are receptive to e-cigarette marketing are also receptive to tobacco marketing has not been studied. However, the extent to which advertising strategies for e-cigarettes mimic strategies used by tobacco companies suggests that the two measures of receptivity could be highly correlated.

Effect of E-Cigarette Advertising on Behavior

Associations with E-Cigarette Use and Intentions to Use

Evidence that advertising for conventional cigarettes increases product initiation among never users, discourages quit attempts in current users, and encourages relapse in those trying to quit is well established (NCI 2008; USDHHS 2012). However, while fewer studies have

focused on e-cigarette advertising in particular, the available evidence suggests that e-cigarette advertising has similar effects, although additional research is recommended. A search for studies of youth or adults that either (a) manipulated exposure to e-cigarette advertising or measured self-reported recall of advertisements, (b) assessed the frequency of exposure to advertising in one or more channels, or (c) measured receptivity to e-cigarette advertising yielded 10 studies that addressed the impact of advertising on the use of or intentions to use e-cigarettes. One experiment tested whether seeing television advertising for e-cigarettes predisposed adolescents to try these products (Farrelly et al. 2015). Among adolescents (13–17 years of age) who had never used e-cigarettes, a single exposure to a set of four televised advertisements for popular brands resulted in significantly greater intention to try e-cigarettes—more than 50% higher in the treatment group than the control group (Farrelly et al. 2015). Another study examined responses to e-cigarette advertisements among young adults (Trumbo and Kim 2015); among a convenience sample of college students who watched three television ads for e-cigarettes, greater receptivity to e-cigarette advertising was associated with significantly higher odds of intending to use e-cigarettes in the future, but the analysis did not adjust for prior use or individual demographics (Trumbo and Kim 2015).

Very few cross-sectional or longitudinal surveys have examined associations between adolescents' exposure to e-cigarette advertising and either trial or regular use of such products. An analysis of the 2011 National Youth Tobacco Survey found that adolescents who reported frequent exposure to protobacco advertising at the point of sale and on the Internet (e.g., seeing ads most of the time or always) had significantly higher odds of ever using e-cigarettes, and there was a dose-response association between the number of marketing channels to which they were exposed and ever use (Agaku and Ayo-Yusuf 2014).

Surveillance research that differentiates exposure to advertising for e-cigarettes from exposure to ads for conventional tobacco products would be useful to establish whether exposure to e-cigarette advertising is correlated with product use and contributes to product initiation and product use among young people who were not tobacco users to start. It bears mentioning here that a generation of U.S. youth has grown up without any television or billboard ads for conventional cigarettes. In this context, research is needed to understand at what age young people understand that e-cigarette advertising depicts the use of e-cigarettes rather than the smoking of conventional cigarettes and to examine whether there are spillover effects of marketing for e-cigarettes on the use of conventional tobacco products.

In the study from Hawaii (Pokhrel et al. 2015), researchers examined the association between exposure to e-cigarette advertising and product use using a convenience sample of approximately 300 college students in that state. The study found that more frequent exposure to e-cigarette advertising—as measured by exposure in any of multiple channels (e.g., newspapers, magazines, Internet, television billboards, sporting/cultural events, convenience stores, gas stations, grocery stores, and malls)—was associated with significantly higher odds of ever using e-cigarettes, and receptivity to e-cigarette advertising was associated with higher odds of past-month use, even after adjustments for smoking status and individual demographics.

Two studies strongly support the association between exposure to e-cigarette advertising and youth susceptibility to and use of e-cigarettes (CDC 2016a; Mantey et al. 2016). Both studies examined data from the 2014 National Youth Tobacco Survey, a survey of more than 20,000 U.S. middle and high school students. The studies assessed self-reported levels of exposure to e-cigarette ads on the Internet, in newspapers and magazines, at retail stores, and

on television or in movies, and used multivariate logistic regression models to examine the relationships between marketing exposure and e-cigarette susceptibility and use. Exposure to each type of e-cigarette marketing was significantly associated with increased likelihood of ever having used and current use of e-cigarettes among middle and high school students (CDC 2016a; Mantey et al. 2016). Exposure was also associated with susceptibility to use e-cigarettes among current nonusers. In multivariate models, as the number of channels of e-cigarette marketing exposure increased, the likelihood of use and susceptibility also increased (Mantey et al. 2016).

One concern is that e-cigarette advertising may perpetuate dual use of conventional cigarettes and e-cigarettes, a concern that comes from the visual depictions of e-cigarette use that may serve as smoking cues to current and former smokers of conventional cigarettes, increasing the urge to smoke and decreasing intentions and efficacy to quit or abstain from smoking (Glynn 2014; Grana and Ling 2014; Maloney and Cappella 2016). Consistent with cue-reactivity studies about conventional cigarettes, exposure to e-cigarette use in a laboratory was associated with increased urge to smoke conventional cigarettes among smokers and an urge to use e-cigarettes among users of that product (King et al. 2015). Whether exposure to depictions in advertising of the use of e-cigarettes triggers urges to begin or continue to smoke conventional cigarettes or weakens users' resolve to quit has received little attention. This is particularly important because rates of cigarette smoking among youth in the United States are at an historic low (CDC 2014).

Associations with Knowledge, Risk Perceptions, and Other Attitudes

Advertising is an important source of information about e-cigarettes for youth and adults (de Andrade et al. 2013; Pepper et al. 2014a), and there is emerging evidence about how unregulated advertising for e-cigarettes may influence consumer perceptions about product safety. One study of adolescents (Farrelly et al. 2015) and three studies of adults (Pokhrel et al. 2015; Sanders-Jackson et al. 2015b; Tan et al. 2015a) examined the associations between exposure to e-cigarette advertising and knowledge or perceptions of these products.

Among U.S. adolescents (13–17 years of age) who had never used e-cigarettes, a single exposure to a set of four televised advertisements was associated with significantly higher odds of agreeing that the products can be used without affecting those around you and with lower odds of agreeing that the products are harmful (Farrelly et al. 2015). Compared with the control group, the treatment group reported significantly more positive attitudes about the benefits of using e-cigarettes. Elsewhere, in an online survey representative of U.S. households, 57% of young adults (18–34 years of age) were aware that some e-cigarettes contain nicotine, but more frequent exposure to e-cigarette advertising at point of sale, in mass media, and in social media (the three variables combined) was associated with a significantly higher likelihood of answering this question incorrectly (Sanders-Jackson et al. 2015b).

In the previously cited study of college students in Hawaii (Pokhrel et al. 2015), greater receptivity to e-cigarette marketing—but not more frequent exposure to the advertising of these products—was associated with significantly greater endorsement of beliefs about harm reduction for e-cigarettes (e.g., safer, improves health, helps to quit). A different study referred to an online survey of U.S. adults (the Annenberg National Health Communication Survey [ANHCS]) in which surveyors measured the frequency of exposure to e-cigarette advertising (point of sale, mass media, and social media) and the degree to which participants

perceived those messages as negative or positive (Tan et al. 2015a). Compared with those who reported no exposure to advertising, those who held negative perceptions of these messages reported significantly greater perceptions of harm from breathing e-cigarette vapor. Taken together, the available evidence suggests that continued exposure to unregulated advertising likely promotes reduced perceptions of harm and toxicity and increased perceptions of the efficacy of e-cigarettes for quitting conventional cigarettes.

Whether the increasing amount of advertising and promotional activities for e-cigarettes serves to renormalize the smoking of conventional cigarettes—that is, to shift public norms back to acceptance of cigarette smoking—is also not known. In focus groups of adult smokers 45 years of age and older, participants expressed almost unanimous agreement, after seeing selected ads, that e-cigarette advertisements promote smoking as a socially desirable behavior (Cataldo et al. 2015). The analysis by Farrelly and colleagues (2015) also looked at outcomes for conventional cigarettes. After exposure to e-cigarette advertising, there were no significant differences between the treatment and control groups on intentions to smoke conventional cigarettes, attitudes toward those products, or perceived harm from cigarettes (even though there were differences between groups on their perceptions of e-cigarettes, as noted previously).

The study that used data from the ANHCS also tested the hypothesis that greater exposure to e-cigarette advertising was associated with weaker support for restricting cigarette smoking in public spaces (Tan et al. 2015b). Both more frequent exposure to e-cigarette advertising and the degree to which participants perceived those messages as positive correlated negatively with support for smoking restrictions. However, in models adjusted for demographic variables, neither measure predicted support for restricting smoking. Further research is needed to address whether the large amount of advertising for e-cigarettes weakens support for smokefree air laws and other tobacco control policies or supports other potential indicators of renormalizing smoking, particularly those indicators that are known risk factors for tobacco use by adolescents and young adults, such as descriptive norms (e.g., perceived prevalence), injunctive norms (e.g., peer acceptance or social acceptability), outcome expectations (e.g., perceived benefits), and attitudes toward the tobacco industry. Additional research is also needed to assess whether e-cigarette advertising that draws comparisons to conventional cigarettes could serve to undermine antismoking messages.

Evidence Summary

Although the e-cigarette marketplace is complicated by the differences in brands that are owned by tobacco companies versus independent brands, e-cigarette companies continue to change and to influence the manufacturing, price, marketing and promotion, and distribution of e-cigarette products and accessories. The e-cigarette market continues to grow, with projected sales of \$3.5 billion in 2015. Consolidation of e-cigarette companies has been rapid, with the first major merger taking place in 2012. These mergers and acquisitions are likely to continue, but the rate of consolidation may slow down as sales of cigalikes decelerate, and “vape shops” could have the potential to influence the e-cigarette marketplace based on the current structure of the marketplace and a regulatory landscape where federal regulation is

just beginning to be implemented. All of these factors create additional uncertainties and risks for both the existing independent e-cigarette companies and the large cigarette companies. This chapter has shown that many of the marketing techniques used by e-cigarette companies are similar to those used by the tobacco industry for conventional cigarettes, and that awareness by youth and young adults of this marketing, and their levels of exposure to it, is high. Further, tracking marketing expenditures and product sales is difficult because of the rapidly changing venues, including “vape shops,” use of social media, and online advertising.

Conclusion

- 1) The e-cigarette market has grown and changed rapidly, with notable increases in total sales of e-cigarette products, types of products, consolidation of companies, marketing expenses, and sales channels.
- 2) Prices of e-cigarette products are inversely related to sales volume: as prices have declined, sales have sharply increased.
- 3) E-cigarette products are marketed in a wide variety of channels that have broad reach among youth and young adults, including television, point-of-sale, magazines, promotional activities, radio, and the Internet.
- 4) Themes in e-cigarette marketing, including sexual content and customer satisfaction, are parallel to themes and techniques that have been found to be appealing to youth and young adults in conventional cigarette advertising and promotion.

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SECTION 5. E-CIGARETTE POLICY AND PRACTICE IMPLICATIONS

Introduction

The previous chapters have set out what is currently known and not known about e-cigarettes. Despite the identified gaps in evidence and the dynamic, evolving patterns of the use of e-cigarettes, policy options are needed. These policy options are particularly important as they affect the use of e-cigarettes by youth and young adults. As this report has demonstrated, e-cigarettes are widely used by youth and young adults and are particularly risky for these age groups, and efforts to prevent their use by young people are needed. This chapter explores the policy landscape of e-cigarettes and sets forth recommendations that should protect the public's health, particularly as these policies relate to the short- and long-term health of youth and young adults.

The *Family Smoking Prevention and Tobacco Control Act of 2009* (or Tobacco Control Act) (2009) is meant to protect the health of the public, including young people. As previously discussed, on May 10, 2016, FDA published a final rule which deemed all other products, including e-cigarettes, meeting the definition of a tobacco product, except accessories of such products, to be subject to the *Federal Food, Drug, and Cosmetic Act*. This rule went into effect on August 8, 2016 (Federal Register 2016). Under the Tobacco Control Act, FDA likely will be required to consider the consequences of e-cigarette use for those who do not use tobacco products (as well as for those who do).

It can be stated that public health will be harmed *if* the availability of e-cigarettes:

- Increases exposure to nicotine among youth and young adults;
- Leads to the initiation of combustible tobacco smoking;
- Slows or prevents cessation of combustible products by nicotine-addicted smokers; or
- Increases the likelihood that former smokers will again become addicted to nicotine and/or use combustible products after being reintroduced to nicotine by e-cigarettes.

Potential harm also comes from secondhand exposure to the vapor or aerosol expelled from e-cigarette users. Secondhand exposure comes from inhaling the aerosol or contacting vapor-contaminated surfaces. Each of the potential negative consequences of the availability of e-cigarettes could lead to additional disease and premature mortality (Chapter 3).

Relative to efforts in cigarette and smokeless tobacco use prevention and control, a polarized debate has been in progress for several years over the role of e-cigarettes. There is general agreement that exclusive use of e-cigarettes poses a lower health risk to the individual than the extremely high health risks of using conventional, combustible tobacco products (Farsalinos and Polosa 2014; Grana et al. 2014a,b), although more research is needed on this as more becomes known about the harmful constituents of e-cigarettes (Sleiman et al. 2016). The controversy reflects the relative degree of emphasis given to the potential harm to adolescents and young adults from using e-cigarettes at one pole compared with the potential for reduced risk for established adult users of conventional cigarettes at the other (if they transition completely to e-cigarettes). Although this characterization does not reflect the complexity of the situation, it is useful in defining the potential tradeoffs that are implicit:

increased numbers of young people who are exposed to nicotine (and who may go on to conventional tobacco products) versus reduced health risks to individuals who completely switch from conventional, combustible tobacco products with their extremely high health risks. The discussion has become increasingly complicated as e-cigarette use has increased, and still-incomplete evidence potentially supports the views of those holding to both poles of the argument about reducing harm for the overall population. However, the majority of currently available scientific evidence does not support the recommendation to use e-cigarettes for the cessation of cigarette smoking (Hartmann-Boyce et al. 2016). Additionally, the use of e-cigarettes does not pose benefits to youth and young adults, and some data suggest that use of e-cigarettes could lead to the more harmful use of conventional cigarettes. In the context of young people, the precautionary principle should apply. The precautionary principle is defined by the United Nations Educational, Scientific and Cultural Organization (2005) as appropriate “when human activities may lead to morally unacceptable harm that is scientifically plausible but uncertain, actions shall be taken to avoid or diminish that harm” (p.14).

Critical Issues Related to Policies on E-Cigarettes in 2016

The E-Cigarette Landscape Is Dynamic and Evolving

Considerations of policy approaches to e-cigarettes offered in this report are made in the context of a rapidly changing marketplace for nicotine-containing products that now includes primarily conventional cigarettes, cigars, smokeless products, hookahs, and e-cigarettes (see Chapter 2). The manufacture and sales of nicotine-containing products, once dominated by a few large companies selling conventional cigarettes, have been transformed and now include many smaller companies that manufacture and sell through stores and “vape shops.” E-cigarettes are also sold through websites and in places where conventional cigarettes have long been available— convenience stores, pharmacies, gas stations, and grocery stores. Currently, hundreds of different e-cigarette products are on the market: designs are evolving rapidly, and major tobacco companies have their own lines of e-cigarette products. However, unlike the situation in the past in which the marketing of conventional tobacco products changed relatively slowly and there were limited media outlets, information about e-cigarettes is now promoted quickly through new media, as well as television, in part to reach key target groups, including youth and young adults.

As documented in Chapter 2, patterns of use are rapidly changing among adolescents and young adults, and likely among other groups within the population. For some of the most critical issues related to e-cigarettes, longitudinal data are not yet available because the use of these products is recent and constantly changing, and whether and when the patterns of use will stabilize is uncertain. Additionally, surveillance data and research on the wide-ranging consequences of e-cigarette use, including such key issues as the likelihood of addiction and other health problems for users and those passively exposed, are lagging behind the highly dynamic changes in the nicotine-product marketplace and the impact of these changes on the use of tobacco products, including e-cigarettes.

With regard to the potential health consequences of using e-cigarettes, estimates can be made based on knowledge of the characteristics and components of the aerosols that are then

inhaled. Unfortunately, evidence on short-term risks is limited, and long-term risks have not yet been identified because this would require monitoring users for years. For example, the impact of long-term inhalation of flavorings is not yet known. While some of the flavorings used in e-cigarettes are generally recognized as safe for ingestion as food, the health effects of their inhalation are generally unknown, and some flavorings have been shown to cause a serious lung disease, bronchiolitis obliterans, when inhaled (Kreiss et al. 2002; Barrington-Trimis et al. 2014). Whether the risk of lung disease or other disorders is truly substantial will require longer term epidemiologic and other research (Allen et al. 2016).

Thus, policy approaches must support control measures that (a) are as dynamic as the rapidly changing marketplace for e-cigarettes; (b) are supported by surveillance data; and (c) document in timely fashion the current status of the use of multiple types of tobacco products (including e-cigarettes); the emergence of state, local, tribal, and territorial policies; and the strategies being used to market these products.

Risk Tradeoffs Are Inherent for E-Cigarettes

Policy discussions about e-cigarettes have highlighted the potential tradeoffs in risk that could occur, particularly if e-cigarettes are positioned as a harm-reducing alternative to combustible tobacco products. Some have characterized these products as new technologies that might lead to a dramatic decline in the use of more dangerous forms of nicotine delivery, particularly conventional cigarettes and other combustible tobacco products (Abrams 2014; Cobb and Abrams 2014; Fagerström and Bridgman 2014; Grana et al. 2014a; Hajek et al. 2014; Henningfield 2014; Schraufnagel et al. 2014; West and Brown 2014; Lindblom 2015). Correspondingly, e-cigarettes have been proposed by some as a harm-reduction strategy and as a tool for smoking cessation, but the data to date do not support e-cigarettes for harm reduction or cessation (Siegel et al. 2011; Abrams 2014). By contrast, others are concerned that the availability of these new products will expand the number of youth and young adults who are exposed to nicotine and will eventually lead to exclusive use of other conventional tobacco products or dual use of both (e-cigarettes and conventional cigarettes) (Leventhal et al. 2015; Primack et al. 2015). Early longitudinal evidence provides some support for these concerns, although further research on this issue is still warranted.

As reviewed in Chapter 3, uncertainty remains about the health effects of e-cigarettes, particularly in the long term. Such effects will remain unknown until sufficient observations can be made over time. However, current knowledge of the characteristics of the inhaled aerosol from e-cigarettes suggests that if a current adult smoker of conventional cigarettes or other combustible tobacco products would use e-cigarettes exclusively instead of combustibles as a substitute nicotine delivery system, either en route to quitting tobacco completely or even as a long-term alternative, the risks of tobacco-related diseases would be reduced substantially compared with the risk imparted by continued smoking of conventional cigarettes (Fiore et al. 2014; USDHHS 2014; McNeill et al. 2015).

Still, as documented in Chapter 3, immediate and future health risks for youth and young adults who use e-cigarettes can be anticipated from exposure to nicotine, including addiction and harmful effects on brain development. Research must continue to characterize and quantify the full spectrum of potential health risks. Thus, in formulating policies related to the role of e-cigarettes in tobacco control and reducing the burden of tobacco-related disease, particularly among youth and young adults, e-cigarette products that deliver nicotine cannot

be considered a risk-free alternative to conventional cigarettes or other combustible tobacco products.

Any analysis of the potential increased risks and reduced harms of e-cigarette use also needs to consider data on the actual patterns of use because more of the risks affect youth and young adults and most of the potential benefits from reduced risk to health largely accrue to older cigarette smokers (Chapter 2). However, the reports of the tobacco industry to investors indicate the industry's interest in maintaining a broad pattern of use of nicotine-containing products, including conventional cigarettes, for decades to come (Calantzopoulos 2015). When considered in the context of the tobacco industry's past changes to product design (e.g., the creation of so-called "low-tar" cigarettes), the broader array of tobacco products now being discussed within the tobacco industry's plans (e.g., "Heat-Not-Burn" products) could slow cessation (because smokers have historically been drawn to reduced-harm products) and thus the overall decline of tobacco-related diseases (USDHHS 2014).

The dynamic balancing between risks and potential benefits of e-cigarette use will be swayed by the impact of such use on the use of other tobacco products by youth and young adults over time. The availability of e-cigarettes could adversely affect the use of tobacco products in this group by slowing the decline of smoking because this population will be exposed to nicotine and possibly become addicted to that substance. Indeed, data reviewed in Chapter 2 show evidence of such trends. Although the decline in rates of smoking conventional cigarettes and other combustible tobacco products is viewed universally as positive, the increasing number of youth and young adults who use e-cigarettes is a serious concern for all the reasons cited above. West and Brown (2014) and McNeill and colleagues (2015) suggest that the limited evidence from the United Kingdom does not support the concern that using e-cigarettes leads to the use of other tobacco products, and they maintain that the new adolescent users of these e-cigarette products include very few never smokers. However, the marketing of e-cigarettes is quite different between the United Kingdom and the United States, and the patterns of use, particularly among youth, are also quite different (European Parliament and Council 2014; England et al. 2015; Klein 2015; Leventhal et al. 2015; Primack et al. 2015; Barrington-Trimis et al. 2016; Wills et al. 2016; Institute for Global Tobacco Control n.d.). This pattern is also evident in some U.S. survey data from early in the era of e-cigarette use (as reviewed in Chapter 2), but not in more recent data, which indicate that e-cigarette products may contribute to nicotine addiction in a new generation of young people and thereby lead to increased use of a variety of nicotine delivery products, including combustible tobacco (Bauld et al. 2016; CDC 2016).

Fundamentally, the public health challenge and the charge to policy development can be framed as balancing the potential use of e-cigarettes as a new technology to reduce the use of combustible tobacco products against the possibility of expanding tobacco use among non-using youth and young adults, long-term former smokers, and other vulnerable populations (e.g., women of reproductive age and individuals with significant comorbidities, including those with mental health problems). Already, the e-cigarette companies are increasing the appeal of their offerings by enhancing the efficiency of nicotine delivery and using flavorings while they continue to advertise and promote their products aggressively.

Additional Evidence Suggested for Future Research

To characterize the critical balance for public health between the harms and potential benefits of e-cigarettes, more evidence on each of the elements that determine that balance

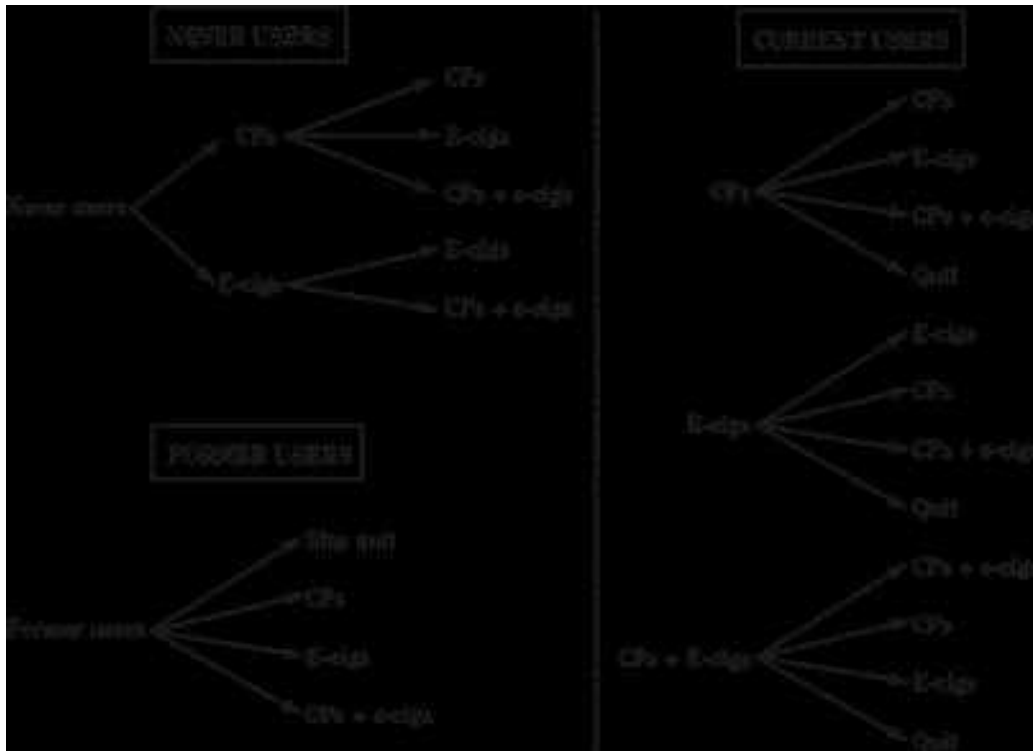
would be useful (Table 5.1). The needed data would come from surveillance of patterns of adoption of e-cigarettes and their use among the population generally, and particularly among the most critical populations for uptake: youth and young adults, former smokers, smokers, and other populations that are particularly at risk for adverse outcomes. Few studies have been done on the health risks posed by e-cigarettes and their potential effectiveness for smoking cessation (Hartmann-Boyce et al. 2016). However, as discussed in Chapter 2, there are still no standardized questions for research on e-cigarettes, and there is a need for further testing and development of e-cigarette questions and measurements.

Table 5.1. Comparative risk assessment: Potential harms and benefits of e-cigarettes

Harms	Benefits
Increased youth exposure to nicotine and potentially greater initiation of conventional cigarettes	Reduced disease risk for current smokers who completely switch to e-cigarettes
Slowing cessation by smokers due to nicotine addiction	Reduced disease morbidity for smokers with existing heart or lung disease who switch to e-cigarettes
Nicotine addiction in former smokers who begin to use e-cigarettes and possibly transition back to smoking	Potential for cessation of combustible products
Renormalization of nicotine use and smoking as acceptable	Fewer users of combustible products in the entire population
Future disease risks for youth who are exposed to nicotine	
Increasing the dual use of e-cigarettes with combustible products	
Serving as a “gateway” to the initiation of tobacco smoking	
Increased disease risk vs. complete cessation among those who use both e-cigarettes and combustible products	
Exposure to secondhand aerosol and lack of clean air	

To characterize the harms and benefits of e-cigarettes to public health, models are used to project their overall impact on public health (Levy et al. 2016). The use of modeling was described in detail in the 2014 Surgeon General’s report (USDHHS 2014). Conceptual models are needed to define the potential scenarios of changes in patterns of use among youth, young adults, adult smokers, former smokers, and other significant vulnerable populations. Figure 5.1 displays the range of patterns that are emerging with the wider adoption of e-cigarettes (Cobb et al. 2015; Vugrin et al. 2015). Researchers and public health officials can use dynamic population models (Mejia et al. 2010; Kalkhoran and Glantz 2015; Vugrin et al. 2015; Levy et al. 2016) to analyze the potential impact on population health of the relative probabilities of these various paths. Initial modeling has shown that the potential population health benefits are very sensitive to several factors: the levels of product risk, particularly those of e-cigarettes; patterns of initiation and switching; and the extent of dual use (Mejia et al. 2010; Cobb et al. 2015; Kalkhoran and Glantz 2015; Vugrin et al. 2015). The benefits of smoking cessation, particularly as early in life as possible, are well documented, but the epidemiologic evidence that reducing (but not quitting) cigarette consumption can lower the risk of all-cause mortality, or mortality from cardiovascular diseases, remains inconclusive (USDHHS 2014). Thus, more research is needed to better characterize the health consequences of dual use, in particular, in comparison to the recognized health benefits of complete smoking cessation (or potentially only e-cigarette use). Similarly, the health risks to former smokers who become exposed again to nicotine through e-cigarettes are uncertain.

Data are still limited on the risk of starting (or not starting) to smoke conventional cigarettes again (after successful cessation) following exposure to nicotine via e-cigarettes.



Source: USDHHS (2014). Adapted for this report.

Figure 5.1. Potential patterns of use of combustible products (CPs) and e-cigarettes (e-cigs).

As reviewed in Chapter 3, the long-term health risks of e-cigarettes will not be known for decades, although evidence to date suggests that they are generally less harmful than combustible products. However, less harmful is not the same as harmless. A substantial amount of evidence is available on some components of the aerosols inhaled by e-cigarette users. For many people, exposure to aerosol could occur across much of the life span, beginning in adolescence and even in childhood, when the lungs and brain are still developing. Flavorings are of particular concern with regard to pulmonary toxicity, as are the various effects of nicotine on the brain. Although the National Institutes of Health is now supporting a growing program of research on e-cigarettes, critical questions have not yet been answered. Given experiences with conventional cigarettes, long-term studies will be needed to identify the full health consequences of using e-cigarettes.

Thus, policies related to e-cigarettes will necessarily be made in the context of accumulating but incomplete evidence. The landscape is changing rapidly and, inevitably, research cannot keep pace. Quoting Sir Austin Bradford Hill's landmark paper on environment and disease: "All scientific work is incomplete—whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer on us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time" (Hill 1965, p. 300).

Potential Public Policy Approaches

In formulating public policies related to e-cigarettes, the context and possibilities vary across the national, state, local, tribal, and territorial governments and public entities. At the national level, progressive steps are being taken by FDA under the Tobacco Control Act. In 2010, the U.S. Court of Appeals for the D.C. Circuit determined that e-cigarettes and other products made or derived from tobacco may be regulated by FDA as tobacco products under the Tobacco Control Act and are not drugs or devices unless marketed for therapeutic purposes, such as being an aid to smoking cessation (*Sottera, Inc. v. Food and Drug Administration* 2010). In May 2016, FDA released its deeming rule to regulate the sale and distribution of e-cigarettes as a tobacco product (see Chapter 1) (*Federal Register* 2016). The rule is currently under litigation. The rule restricts the age of sale to those 18 years of age and older and requires retailers to check the age identification of young people under age 27, restricts vending machines to adult-only facilities, prohibits free samples, requires a health-warning statement about nicotine on packaging and in advertisements, requires domestic manufacturers to register their products and disclose the ingredients of their products, requires the reporting of the levels of harmful and potentially harmful constituents to FDA, allows FDA to review any new or changed products before being sold, and requires manufacturers to show scientific evidence that demonstrates the overall public health benefit of any product before it can be marketed as a modified risk tobacco product (*Federal Register* 2016). The Tobacco Control Act does not provide FDA with authority to impose taxes on tobacco products (Bhatnagar et al. 2014; Huang et al. 2014; Tobacco Control Legal Consortium 2015) or regulate indoor air quality (Schripp et al. 2013; Bam et al. 2014; Bhatnagar et al. 2014; Brandon et al. 2015a), occupational health and safety (USDHHS 2015; Whitsel et al. 2015), or hazardous waste disposal (Chang 2014; Krause and Townsend 2015).

FDA is not the only federal agency with potential jurisdiction over some aspect of e-cigarettes (Table 5.2). For example, the U.S. Department of Defense and U.S. Department of Veterans Affairs relate to specific populations, and other agencies relate to regulatory activities, such as the U.S. Federal Trade Commission, U.S. Department of Transportation, and the U.S. Environmental Protection Agency. Some agencies have coverage over specific areas, such as the General Services Administration and the National Park Service.

State, local, tribal, and territorial governments, as well as private entities, may also address these and other matters that are covered by the Tobacco Control Act (Freiberg 2012), and since 2010 many actions have been taken at the nonfederal level. State and local governments may utilize effective interventions that would also be expected to apply to e-cigarettes: increasing the price of tobacco products through taxation (Community Preventive Services Task Force 2012); creating and enforcing clean air policies (Hopkins et al. 2010); and passing comprehensive laws prohibiting sales to minors, combined with active enforcement (Community Preventive Services Task Force 2001). In addition, based on evidence that new e-cigarette products may addict a generation of young people to nicotine (Bunnell et al. 2015; CDC 2015b) and on mounting indications about potential harm from the use of these products in this population (Flouris et al. 2013; Barrington-Trimis et al. 2014; Goniewicz et al. 2014; Grana et al. 2014a; Pisinger and Dossing 2014; Goniewicz and Lee 2015), numerous health organizations have called for the extension of smoking-related policies to e-cigarettes (Association of State and Territorial Health Officials 2014; Bam et al.

2014; Bhatnagar et al. 2014; Offermann 2014; Schraufnagel et al. 2014; World Health Organization 2014a; Brandon et al. 2015a; USDHHS 2015). In the absence of causal findings that have guided evidence-based tobacco control for decades, the “precautionary principle” is relevant to decision makers as a guide to action to address e-cigarettes among youth and young adults. This principle supports intervention to avoid possible health risks when the potential risks remain uncertain and have been as yet partially undefined (Bialous and Sarma 2014; Saitta et al. 2014; Hagopian et al. 2015). However, the interventions should be appropriate to the currently perceived risk for future health consequences, in this case from e-cigarette use by youth, young adults, and pregnant women, as well as from the secondhand exposure of non-users to e-cigarette vapor.

Clean Indoor Air Policies

Clean indoor air or smokefree policies prohibit the use of conventional tobacco products in indoor public places, such as worksites, restaurants, bars, and casinos. Because most of these policies predate the rise of e-cigarettes, their language does not necessarily cover emissions from these products. To protect the public from both secondhand smoke and secondhand aerosol, smokefree air policies should be modernized to include e-cigarettes. Such policies will maintain current standards for clean indoor air, reduce the potential for renormalization of tobacco product use, and prevent involuntary exposure to nicotine and other aerosolized emissions from e-cigarettes (Ingebrethsen et al. 2012; Schripp et al. 2013; Goniewicz et al. 2014; Offermann 2014; Schober et al. 2014). Updating existing policies to cover e-cigarettes (and all electronic nicotine delivery systems) will eliminate the introduction of airborne toxins into enclosed spaces and establish a uniform standard for preventing the use of both combustible and electronic tobacco products in public and private spaces, including schools, offices, restaurants, bars, casinos, and airplanes.

Prohibiting the use of e-cigarettes in enclosed spaces eliminates potential health risks to nonusers and ensures their right to clean air; may discourage the dual use of electronic and combustible tobacco products; simplifies public compliance with and enforcement of existing clean indoor air laws; facilitates reduced consumption of these products; and maintains clear, comprehensive non-smoking norms (Richardson et al. 2014; World Health Organization 2014a). As of January 1, 2016, six states (Delaware, Hawaii, New Jersey, North Dakota, Oregon, and Utah) had passed comprehensive smokefree indoor air laws that include e-cigarettes (CDC 2015a). These laws prohibit smoking and the use of e-cigarettes in indoor areas of private worksites, restaurants, and bars. Sixteen additional states had prohibited the use of e-cigarettes on some or all state property, and 475 local laws restricted e-cigarette use in 100% smokefree venues (Americans for Nonsmokers’ Rights Foundation 2015). Nationwide, more than 400 local jurisdictions prohibit e-cigarette use in 100%-smokefree workplaces (Americans for Nonsmokers’ Rights Foundation 2015). Major cities that have addressed e-cigarettes include Austin, Boston, El Paso, Chicago, Los Angeles, Minneapolis, San Francisco, and New York City.

Prevent Youth Access

Ensuring that laws on youth access include e-cigarettes is intended to protect youth from exposure to nicotine, which can lead to addiction and other health problems. Additionally, ensuring that these laws include e-cigarettes helps to capture the full diversity of the tobacco product landscape, including combustible, non-combustible, and electronic tobacco products.

Effective strategies to deter access to e-cigarettes by youth and the use of these products in this population include restricting sales of e-cigarettes to minors, requiring verification of age, mandating clear signage about minimum age where sales take place, prohibiting the sale of e-cigarettes from vending machines, eliminating self-service displays of e-cigarettes, and actively enforcing existing laws with a focus on retailers. Compliance with laws that regulate the sale and distribution of e-cigarettes is facilitated by requiring retailers to be licensed. To date, 46 states have prohibited the sale of e-cigarettes to minors younger than a specified age (National Conference of State Legislatures 2015; The Council of State Governments 2015). Federally, aligning youth tobacco access control regulations with the statutory definition of tobacco products in the Tobacco Control Act, which includes e-cigarettes, could provide consistent framework to help ensure that restrictions on youth access to e-cigarettes are prioritized and enforced (*Federal Register* 2016). This could include modifications to the Synar regulation, which requires states, U.S. territories, and jurisdictions to enact and enforce laws prohibiting the sale or distribution of tobacco products to youth. Substance Abuse Prevention and Treatment Block Grant recipients must comply with the Synar amendment and implement regulations in order to receive their full awards (U.S. Food and Drug Administration, Center for Tobacco Products n.d.).

Licensing

Licensing is used to regulate professional practice and business operations and represents one strategy to control the rising use of e-cigarettes among youth. In general, in the case of tobacco-related licensing, a business is authorized to manufacture, distribute, or sell tobacco products as long as it complies with all relevant laws (McLaughlin 2010). Typically, tobacco-related licensing requirements for retailers and/or manufacturers help to prevent evasion of excise taxes, ensure that licensees comply with tobacco-related laws, and promote safe manufacturing practices (ChangeLab Solutions 2012). Repeat violators of relevant laws may be subject to suspension or permanent revocation of their license, an outcome that provides a strong incentive to comply with existing requirements. As in the conventional cigarette industry, licensing of e-cigarette retailers and manufacturers is designed in part to prevent the use of these products by youth and to facilitate safe manufacturing practices. Unlike traditional tobacco products, for which retailers sell prepackaged products and the number of manufacturers is limited, a growing number of businesses engage in both the retail sale and manufacturing of devices and liquids used in the devices (e-liquids). Stores devoted exclusively to the sale of e-cigarettes are known as “vape shops.” These shops frequently offer a social environment for using products, and they may also sell food and beverages (Sussman et al. 2014).

As of April 2015, 99 cities and counties in California required a retailer to obtain a license to sell e-cigarettes. The majority of these jurisdictions did so by broadening the definition of tobacco products to include “electronic smoking devices” (ChangeLab Solutions 2015a). The definition was purposely broadened to include products that do not include nicotine to decrease the complexity of enforcement and in recognition of the fact that e-cigarette devices are sometimes used with liquids that do not contain nicotine but may contain marijuana oil (The Center for Tobacco Policy & Organizing 2015a). Licensing requirements also may be used to restrict the sale of flavored products or to address issues of consumer and worker safety relative to the mixing of e-liquids.

Imposing a moratorium is another potential approach that has been used in some communities to stop new “vape shops” from entering the market while a more comprehensive approach was being considered. A moratorium is a land-use law that takes effect immediately to stop temporarily the issuance of a business license, building permit, or use permit. Typically, a moratorium is enacted to provide a jurisdiction with time to research and study how to regulate a type of business (ChangeLab Solutions 2015b). In California, several communities enacted moratoria that are initially 45 days but can be extended for up to 2 years (ChangeLab Solutions 2014, 2015b). A four-fifths vote, however, is required to establish a moratorium in California. Hayward and Union City, California, are examples of cities that have enacted moratoria and later adopted both retail licensing requirements for existing e-cigarette retailers and zoning restrictions to prohibit new vapor and hookah bars and lounges from opening within city limits (ChangeLab Solutions 2014; The Center for Tobacco Policy & Organizing 2015b).

Taxation and Other Price Policies

Taxation and other price policies directed at making e-cigarettes more expensive may be implemented at multiple levels of government, from local to federal. Increasing the price of conventional cigarettes, including those increases resulting from excise taxes, significantly prevents and reduces tobacco use, particularly among youth and young adults (USDHHS 2014), and has potentially more impact on prevalence of current use in this population than on first use (Bader et al. 2011). Similarly, price policies are likely to reduce the use of e-cigarettes: a 10% increase in the price of e-cigarettes has been estimated to reduce sales of disposable e-cigarettes by approximately 12% and reusable products by about 19% (Bader et al. 2011; Huang et al. 2014). Data are currently lacking on the potential effects that taxing e-cigarettes might have on conventional cigarettes. Tobacco products are taxed in two main ways:

- 1) A “specific” excise tax is levied based on the quantity of the product sold (e.g., as measured by number of cigarettes, weight, or volume). This type of mechanism applies the same tax across low-end and premium brands and is generally simple to administer. The disadvantages to specific excise taxes are that the real value of the tax declines over time with inflation, making products more affordable, and that super-lightweight products—such as snus, orbs, sticks, and dissolvables—are grossly under-taxed if the tax is based on weight (Freiberg 2012; Boonn 2013; Shang et al. 2015).
- 2) The second tax mechanism is an ad valorem excise tax, which is levied on a percentage of the value of the tobacco product (e.g., the retailer’s, wholesaler’s, or manufacturer’s price). This type of tax keeps up with inflation and establishes a flat tax rate across all brands, product types, weights, and packaging. The disadvantages to this kind of tax include the potential for tax evasion through predatory (below-cost) or anticompetitive pricing; increasing the price differential between products with different pretax prices, leading to greater price variability and more opportunity for tax avoidance; a government-provided subsidy for manufacturers’ price cuts; and more expensive brands being subjected to a larger tax (Freiberg 2012; Boonn 2013; Shang et al. 2015).

Table 5.2. Principle federal policies and regulations of tobacco that emphasize e-cigarettes

Agency	Authority and description	Current	Potential
Executive Office of the President (EOP) and Office of Management and Budget (OMB)	—	Executive Order 13058, issued on August 9, 1997 (EOP 1997), generally prohibits the smoking of tobacco products in all interior space owned, rented, or leased by the executive branch of the federal government, and in any outdoor areas under executive branch control in front of air intake ducts. The Executive Order carves out an exception to its smoking prohibition for any residential accommodation for persons voluntarily or involuntarily residing, on a temporary or long-term basis, in a building owned, leased, or rented by the federal government.	—
Executive Office of the President (EOP) and Office of the U.S. Trade Representative (USTR)	—	Executive Order 13193, issued January 18, 2001 (EOP 2001), prohibits all U.S. executive branch agencies from promoting the sale or export of tobacco. It also prohibits using U.S. trade initiatives to restrict tobacco marketing and advertising regulations in other countries, unless those regulations discriminate against U.S. tobacco products in favor of that country's domestic tobacco products.	—
Federal Communications Commission (FCC)	Has broad regulatory power over commercial communication, including television, radio, and the Internet.	15 U.S.C. § 1335 (the “Broadcast Ban”); 15 U.S.C. § 4402(f); Prohibits advertising for cigarettes, little cigars, smokeless tobacco, and chewing tobacco on radio, TV, or any other medium of electronic communication under FCC’s jurisdiction.	Prohibit the advertising of smoking accessories, cigars, pipes, pipe tobacco, or cigarette-making machines on television; prohibit the advertising of e-cigarettes on television; and regulate the advertising of tobacco products on the Internet.
General Services Administration (GSA)	In its role as an independent agency, GSA manages and maintains more than 1,550 federally owned buildings and leases space in an additional 7,100 buildings in the United States. GSA manages the federal government’s automobile fleet and is the acquisition arm of the federal government.	GSA Order ADM, 5800, 1C: Smoking in GSA-occupied space and government-owned or -leased vehicles assigned to GSA is prohibited “to protect GSA employees, GSA contractors, and the visiting public from exposure to tobacco smoke in the Federal workplace.” The Order prohibits smoking in or on all “interior GSA-occupied space, exterior GSA-occupied space, including courtyards, garages, loading docks, stairwells, rooftops and balconies, and other outdoor areas under GSA control within 25 feet of doorways and building air intake ducts; and government-owned or leased vehicles assigned to GSA” (U.S. General Services Administration 2009).	Clarify that existing policies include e-cigarettes. Implement a tobacco-free campus policy in GSA-occupied space.

Agency	Authority and description	Current	Potential
Office of Personnel Management (OPM)	—	While not regulatory in nature, OPM and GSA coordinate standard responses to frequently asked questions about the use of e-cigarettes in government facilities.	—
U.S. Department of Agriculture (USDA)	Commodity and inspection standards for agricultural products. Administers SNAP and WIC programs.	7 U.S.C. § 30: USDA provides commodity standards for tobacco. 7 U.S.C. § 2012: Under the <i>Food and Nutrition Act of 2008</i>, tobacco products cannot be purchased with SNAP benefits. ENDS are included in the policy because the USDA interprets ENDS to be tobacco products. 7 CFR 246.10: USDA identifies requirements for WIC-eligible foods.	—
U.S. Department of Defense (DoD)	May issue general instructions and restrictions in regulating the sale and/or use of tobacco products. Individual service branches may expand these regulations. Individual bases may also draft regulations. These typically are based on DoD instructions, directives, or service policies. DoD has authority over TRICARE.	DoD follows the smoking policy in federal facilities covered in 41 CFR 102-74.315, which states, “pursuant to Executive Order 13058, ‘Protecting Federal Employees and the Public From Exposure to Tobacco Smoke in the Federal Workplace’ it is the policy of the Executive Branch to establish a smokefree environment for federal employees and members of the public visiting or using federal facilities. The smoking of tobacco products is prohibited in all interior space owned, rented or leased by the Executive Branch of the federal government” (<i>Federal Register</i> 2008, p. 77518). Each of the armed services has issued statements clarifying that the prohibition on smoking tobacco products extends to the use of e-cigarettes. The 2015 NDAA directs the sale of cigarettes, cigars, and chewing tobacco at military commissaries. These items cannot be sold on military bases at prices lower than the most competitive prices in the local community. The NDAA replaced Directive 1330.09 (U.S. Department of Defense 2005), which established that tobacco prices on U.S. military bases should be no lower than 5% below the most competitive commercial price in the local community. Branches of the armed services have tobacco policies:	DoD-unified regulations on tobacco use in common housing. Increased restrictions on commissary sales.

Table 5.2. (Continued)

Agency	Authority and description	Current	Potential
		• U.S. Navy and Marines, Instruction 5100.13E (U.S. Navy 2002) • U.S. Army, Army Health Promotion Policy Regulation 600–63 (U.S. Army 1996) • U.S. Air Force, Instruction 40–102, Air Force Tobacco Policy (U.S. Air Force 2013) TRICARE covers limited tobacco cessation counseling from any TRICARE-authorized provider in the United States. This coverage includes up to 18 counseling sessions per quit attempt, with up to 4 individual counseling sessions per quit attempt. Two quit attempts per fiscal year are automatically covered, with coverage extending to a third with a doctor's justification and pre-authorization. TRICARE also covers tobacco cessation products, including prescriptions and over-the-counter products, with 120 days' use of a tobacco cessation product per quit attempt.	
U.S. Department of Education (ED)	Funding for tobacco control programs	In FY 2014, pursuant to 20 U.S.C. § 7131, <i>Safe and Drug-Free Schools and Communities Act</i>, ED awarded the first round of 5-year grant awards under the School Climate Transformation Grant—Local Educational Agency Grants program. These FY 2014, Year 1 grant awards provided more than \$35.8 million to 71 school districts in 23 states; Washington, DC; and the U.S. Virgin Islands. The funds should be used to develop, enhance, or expand systems of support for implementing evidence-based, multitiered behavioral frameworks for improving behavioral outcomes and learning conditions among students. The goals of the program are to connect children, youth, and families to appropriate services and supports; improve conditions for learning and behavioral outcomes for school-aged youth; and increase awareness of mental health issues and the ability to respond to such issues among school-aged youth. School districts can also use the funds to implement models for reform and evidence-based practices.	—

Agency	Authority and description	Current	Potential
		Drug prevention, including preventing tobacco use by youth, is an allowable activity. Grantees are encouraged, as part of their local needs assessment, to measure drug use among students along with other relevant issues and problems. This assessment of local needs will also be used by grantees to help identify and select the most appropriate evidence-based programs and practices. If the needs assessment indicates that drug abuse is an issue for students, prevention of drug abuse should be addressed by a multitiered behavioral framework.	
U.S. Department of Education (ED)	Restrictions on tobacco use	20 U.S.C. § 7181: <i>The Pro-Children Act of 2001</i> prohibits smoking in any indoor facility that provides routine or regular kindergarten, elementary, or secondary education and library, health, or day care services to children, if such services and/or facilities are funded by the federal government, whether directly or through state or local governments, by federal grant, loan, loan guarantee, or contract programs.	—
U.S. Department of Health and Human Services, Centers for Medicare & Medicaid Services (CMS)	Sets policies regarding Medicaid coverage for tobacco cessation products and counseling.	42 U.S.C. § 1396r-8(d)(7): Tobacco cessation medications cannot be excluded from coverage under Medicaid prescription drug benefits. Section 2502 of the <i>Affordable Care Act</i> amends section 1927(d)(2) of the <i>Social Security Act</i> by removing barbiturates, benzodiazepines, and agents used to promote smoking cessation from the list of drugs that a state Medicaid program may exclude from coverage or otherwise restrict.	—
U.S. Department of Health and Human Services, Centers for Medicare & Medicaid Services (CMS)	Sets policies regarding Medicaid coverage for tobacco cessation products and counseling.	42 U.S.C. §§ 18021(a)(1)(B), 18022(b)(1): Tobacco use screening and cessation must be provided at no cost as an essential health benefit and a preventive benefit. This includes Medicaid expansion plans, plans sold on insurance exchanges, and private plans. For youth: Tobacco cessation services are coverable as part of EPSDT, the Medicaid benefit for children and adolescents. EPSDT provides a comprehensive array of prevention, diagnostic, and treatment services for low-income infants, children, and adolescents under age 21, as specified in Section 19051 of the <i>Social</i>	

Table 5.2. (Continued)

Agency	Authority and description	Current	Potential
		<i>Security Act.</i> For pregnant women: Section 4107 of the <i>Affordable Care Act</i> amends section 1905 of the <i>Social Security Act</i> to require coverage of counseling and pharmacotherapy for cessation of tobacco use by pregnant women. Section 1905(bb)(2) of the <i>Social Security Act</i> defines the new tobacco cessation coverage services for pregnant women as services recommended in the 2008 PHS Guideline, or any subsequent modification of this Guideline, and such other services that the Secretary recognizes to be effective for cessation of tobacco use by pregnant women. <i>Affordable Care Act</i>, Section 4108, Medicaid Incentives for Chronic Disease Prevention Program: This is a grant program in which states apply for funds to incentivize Medicaid recipients to prevent chronic disease, including through tobacco cessation.	
U.S. Department of Health and Human Services, Centers for Medicare & Medicaid Services (CMS)	—	42 U.S.C. § 1395x (ddd): Medicare covers tobacco cessation programs (Centers for Medicare & Medicaid Services 2010); Effective for claims with dates of service on or after August 25, 2010, CMS will cover tobacco cessation counseling for outpatient and hospitalized Medicare beneficiaries: • Who use tobacco, regardless of whether they have signs or symptoms of tobacco-related disease; • Who are competent and alert at the time that counseling is provided; and • Whose counseling is furnished by a qualified physician or other Medicare-recognized practitioner.	—
U.S. Department of Health and Human Services, Centers for Medicare & Medicaid Services (CMS)		Intermediate and intensive tobacco cessation counseling services are covered under Medicare Parts A and B when the above conditions of coverage are met, subject to frequency and other limitations. Medicare covers two individual tobacco cessation counseling attempts per 12-month period. Each attempt may include a maximum of four intermediate or intensive sessions, with a total benefit covering up to eight sessions per 12-month period per Medicare beneficiary who uses tobacco. The practitioner	

Agency	Authority and description	Current	Potential
		and patient have the flexibility to choose between intermediate (more than 3 minutes, up to 10 minutes) and intensive (more than 10 minutes) cessation counseling sessions for each attempt. Medicare beneficiaries also have access to smoking cessation prescription medication through Medicare Part D.	
U.S. Department of Health and Human Services, Centers for Medicare & Medicaid Services (CMS)	Sets policies regarding private and marketplace health plan coverage of tobacco cessation products and counseling.	42 U.S.C. §§ 18021(a)(1)(B), 18022(b)(1): Tobacco cessation must be provided at no cost as an essential health benefit. This includes Medicaid expansion plans, plans sold on insurance exchanges, and private plans. 42 U.S.C. § 300gg-6 (Public Law 114-38): Tobacco cessation must be covered in employer plans. Plans should cover two cessation attempts per year, including (1) all FDA-approved cessation medications (both prescription and over-the-counter) and (2) four tobacco cessation counseling sessions, including telephone, group, and individual counseling. 42 U.S.C. § 300gg(a)(1)(iv): Tobacco users may be charged 50% more for insurance than nonusers of tobacco. 42 U.S.C. § 300gg-4(j)-(k): Employers may reward or penalize employees by up to 50% of the cost of health care coverage based on their tobacco use, if the employer offers a health-contingent wellness program designed to prevent or reduce tobacco use.	—
U.S. Department of Health and Human Services, National Institutes of Health (NIH)	NIH is a tobacco-free campus.	NIH's policy specifically includes e-cigarettes. In accordance with the tobacco-free initiative from HHS, the use of cigarettes, e-cigarettes, cigars, pipes, smokeless tobacco ("snuff"), and any other tobacco product is prohibited on the NIH campus in Bethesda, MD (NIH 2016).	—
U.S. Department of Health and Human Services, National Institutes of Health, National Institute on Drug Abuse (NIDA), National Advisory Council on Drug Abuse (NACDA)	The mission of NIDA is to advance science on the causes and consequences of drug use and addiction and to apply that knowledge to improve individual and public health. NACDA serves crucial roles in advising NIDA on research priorities and policy and in providing a secondary level of review for applications under consideration for federal funding.	NIDA (2016) urges grantees to recognize that: Receiving funding from the tobacco industry may compromise the perceived objectivity of their research results, which in turn could impact the overall credibility of their research findings, including its interpretation, acceptance, and implementation;	—

Table 5.2. (Continued)

Agency	Authority and description	Current	Potential
U.S. Department of Health and Human Services, Substance Abuse and Mental Health Services Administration (SAMHSA)		- Acceptance of tobacco industry funds is viewed by many as contributing directly or indirectly to the industry's interests, and thus harmful to the public health; and - Any connection between tobacco industry-supported research (or tobacco industry scientists) and NIDA could negatively impact NIDA's credibility and the public's trust in NIDA-funded research.	
U.S. Department of Homeland Security (DHS)	Implements the Synar Amendment, which requires states, in order to receive their full Substance Abuse Prevention and Treatment Block Grant awards, to enact and enforce laws that prohibit the sale or distribution of tobacco products to individuals under the age of 18. Sales and use restrictions for the U.S. Coast Guard. DHS Management Directorate-Directive No. 06603 Smoking Policy.	More information about the Synar Program is available online: http://www.samhsa.gov/synar/ about	SAMHSA is exploring opportunities to align the Synar regulation with the federal statutory definition of tobacco products, which includes e-cigarettes.
U.S. Department of Homeland Security (DHS), Bureau of Immigration and Customs Enforcement (ICE)	Issues standards for facilities housing immigration detainees	COMDTINST M6200.1B limits smoking to designated outdoor areas, prohibits use of tobacco by recruits, and prohibits tobacco use in any Coast Guard-controlled living quarters, including common areas. This policy includes extensive sales and advertising restrictions, but it does not consider NRT to be a tobacco product. Detainee smoking is prohibited in all buildings, including detainee-housing units. If smoking is permitted at a particular facility, the only designated smoking areas are outside of all buildings (Immigration and Naturalization Service 2000).	Implement a policy to enforce a ban on e-cigarette use on federal property.
U.S. Department of Housing and Urban Development (HUD)	Resident health in assisted housing	Public and Indian Housing (PIH) Notice 2009-21 strongly encourages HUD-funded public housing agencies to adopt smokefree policies in some or all of their public housing units. Housing Notice 2010-21 encourages owners and management agents of HUD-assisted multifamily housing to implement smokefree housing policies in	HUD's Office of PIH published its proposed rule on Instituting Smoke-Free Public Housing (80 FR 71762) on November 17, 2015, accepting comments through January 19, 2016 (<i>Federal Register</i> 2015). In addition to inviting comments on all aspects of the

Agency	Authority and description	Current	Potential
		one or all of the properties they own or manage. Both notices focus on cigarettes that “burn” as their mechanism for generating smoke, and so their applicability to e-cigarettes is uncertain. Regarding its Weaver Building headquarters (the only building for which GSA has designated HUD as the facility management authority), HUD follows GSA Order ADM 5800.1C: GSA’s smoking policy for federal offices (U.S. General Services Administration 2009). This GSA policy permits smoking in exterior space under GSA control that is beyond “25 feet of doorways and building air intake ducts,” except for “courtyards, garages, loading docks, stairwells, rooftops, and balconies.” The management of HUD’s other facilities, federally owned or leased, is not delegated to the Department, and so GSA makes the decision on smoking policy for those campuses.	proposed rule, the notice specifically solicited public comments on nine questions (e.g., should the policy extend to electronic nicotine delivery systems, such as e-cigarettes, and/or to waterpipe tobacco smoking?). Based on responses to HUD’s Request for Information on Adopting Smoke-Free Policies in PHAs and Multifamily Housing (77 FR 60712) (Federal Register 2012), HUD may consider drafting a regulation or notice that could prohibit smoking in some or all HUD-assisted multifamily housing. Such a proposal could cover e-cigarettes. HUD is beginning to prepare for the adoption and implementation of a campus-wide tobacco-free policy, which would include e-cigarette use, at the Weaver Building headquarters by January 1, 2017.
U.S. Department of Justice, Bureau of Alcohol, Tobacco, Firearms and Explosives (ATF)	ATF is given primary jurisdiction to combat cigarette trafficking and administration (via the CCTA) and to stop tobacco diversion (via the PACT).	18 U.S.C. § 2342: Under the CCTA, it is illegal to possess more than 10,000 unstamped cigarettes in a state that requires a tax stamp. 18 U.S.C. § 2343: Any person who distributes more than 10,000 cigarettes must keep accurate records pertaining to the shipment, receipt, sale, and distribution of cigarettes. 18 U.S.C § 2320: Trafficking in counterfeit cigarettes. 15 U.S.C. § 375: It is illegal to ship cigarettes to a non-licensee in a state without notifying the state taxation authority. 15 U.S.C. § 375–377: Requires online retailers to check the identification of customers at purchase and delivery: section 375 covers definitions; section 376 covers reports to state tobacco administrators; and section 377 covers penalties. The <i>Smuggled Tobacco Prevention (STOP) Act</i> amends the IRC to restrict the sale, lease, export or import, or delivery of tobacco production machines to persons lawfully engaged in (1) the sale, lease, export or import, or delivery of such machines; (2) the manufacture or packaging of tobacco products or processed tobacco; or (3) the application of unique identification markings onto tobacco products or processed tobacco packages.	—

Table 5.2. (Continued)

Agency	Authority and description	Current	Potential
U.S. Department of Justice, Bureau of Prisons (BOP)	BOP has authority to govern the control and management of federal penal and correctional institutions.	28 C.F.R. § 551.162: Smoking is generally prohibited in and on the grounds of BOP institutions and offices, with exceptions for smoking as part of an authorized inmate religious activity, and for smoking only in smoking areas designated by the warden, for BOP staff and official visitors. 28 C.F.R. § 551.163: Possession of smoking apparatus and tobacco in any form is prohibited for inmates, unless as part of an authorized inmate religious activity.	BOP Operations Memorandum 006-2015 (BOP 2015) sets out guidelines for e-cigarette use. (Guidelines state that e-cigarette use is to be limited to designated outdoor areas that are reasonably accessible to employees and provide a measure of protection from the elements. These areas may only be used by employees, but must be separate from the areas presently designated as “smoking areas” for use of tobacco products. Indoor use of e-cigarettes shall not be permitted in BOP facilities, except in perimeter towers and perimeter patrol vehicles when occupied by one person.
U.S. Department of Labor, Occupational Safety and Health Administration (OSHA)	Sets standards for indoor air quality.	29 CFR 1910.1000, Air Contaminants: This policy restricts employee exposure to several of the main chemical components found in tobacco smoke. OSHA rules apply to tobacco smoke only in rare and extreme circumstances, such as when contaminants created by a manufacturing process combine with tobacco smoke to create a dangerous air supply that fails OSHA standards for the workplace. In normal situations, exposures would not exceed permissible exposure limits and, as a matter of prosecutorial discretion, OSHA will not apply the General Duty Clause to environmental tobacco smoke.	Have smokefree workplaces. In the 1990s, OSHA proposed a regulation setting indoor air quality standards for environmental tobacco smoke, but this rulemaking was terminated (<i>Federal Register</i> 2001).
U.S. Department of Transportation (DOT)	Sets restrictions on tobacco use on commercial and personal aircraft.	49 U.S.C. § 41706: Prohibits smoking on passenger flights. 14 CFR Part 252: DOT rule implementing 49 U.S.C. § 41706, and prohibiting smoking on most passenger flights. DOT interprets current Part 252 to include e-cigarettes in smokefree policies. Note: FAA regulations also prohibit smoking on most aircraft from an aircraft safety perspective, not from a health perspective (see notes to 14 CFR Part 252).	In early 2016, DOT issued a final rule (RIN 2105-AE06). In keeping with section 41706, the rule amends Part 252 to prohibit smoking on charter flights where a flight attendant is a required crew member. The rule also makes explicit the determination that the use of e-cigarettes falls within the definition of smoking. DOT’s Pipeline and Hazardous Materials Safety Administration has proposed a rule to prohibit the carrying of e-cigarettes in an aircraft cabin, and to prohibit stowage of e-cigarettes in the cargo hold of an aircraft (this is a hazardous material/safety rule, not a health/tobacco rule).

Agency	Authority and description	Current	Potential
U.S. Department of Treasury, Alcohol and Tobacco Tax and Trade Bureau (TTB)	TTB administers the provisions of the Internal Revenue Code (IRC) of 1986, as amended, that impose federal excise taxes on tobacco products and cigarette papers and tubes, and it establishes a comprehensive civil and criminal framework to protect the revenue. Among other issues, TTB investigates illegal production, underreporting of production, smuggling or unlawful importation, and diversion of domestic tobacco products intended for export.	26 U.S.C. 26 § 5701–5763, Tobacco Products and Cigarette Papers and Tubes: Under the IRC, the tobacco products that are subject to tax and TTB regulation are cigars, cigarettes, smokeless tobacco (chewing tobacco and snuff), pipe tobacco, and roll-your-own tobacco. Each of these tobacco products is defined with reference to “tobacco.” TTB also has regulatory authority over processed tobacco, which is not subject to tax. TTB regulations define processed tobacco to mean any tobacco that has undergone processing but that does not include tobacco products. The processing of tobacco includes, but is not limited to, stemming (i.e., removing the stem from the tobacco leaf); fermenting, threshing, cutting, or flavoring the tobacco; or otherwise combining the tobacco with nontobacco ingredients. To protect revenue, the IRC and its implementing regulations establish qualification criteria to engage in businesses related to manufacturing, importing, or exporting tobacco products or in manufacturing or importing processed tobacco, and they require that persons obtain permits to engage in these activities.	TTB will collaborate with foreign-counterpart tax administrators to share information and best practices in the administration of tobacco excise taxes and their enforcement. Areas of possible technical assistance include setting up an auditing system and permitting regimen and conducting investigations. TTB’s tobacco laboratory provides technical assistance to TTB program offices on tobacco products for regulatory compliance and enforcement purposes. TTB’s tobacco laboratory develops and validates analytical methods and protocols on tobacco products. It also collaborates with national and international tobacco regulatory federal agencies and has established a collaborative partnership with the World Health Organization’s Tobacco Laboratory Network and the North America Tobacco Regulatory Laboratory Network.
U.S. Department of Treasury, Alcohol and Tobacco Tax and Trade Bureau (TTB)		Under the IRC, manufacturers of tobacco products and export warehouse proprietors must file a bond that relates to the tax liability for the tobacco products on the premises covered by the permit. The IRC and implementing regulations also include recordkeeping and reporting requirements designed to ensure that TTB can verify that the tax on tobacco products is paid or determined or that adequate documentation exists to confirm that a tax exemption applies. The IRC also provides TTB with certain enforced-collection options (e.g., liens and levies), civil and criminal penalties, permit suspension and revocation procedures, and forfeiture provisions to ensure that the tax is collected. ENDS that do not contain nicotine derived from tobacco are not tobacco products under the IRC and are not subject to taxation or TTB regulation. ENDS containing nicotine derived from tobacco may meet the definition of a tobacco product under the IRC, in which case they would be regulated by TTB and taxed accordingly.	

Table 5.2. (Continued)

Agency	Authority and description	Current	Potential
U.S. Department of Veterans Affairs (VA)	Can restrict the use of e-cigarettes and combustible cigarettes on facility grounds of the Veterans Health Administration to designated outdoor smoking areas only.	Public Law 102-585: Requires medical centers, nursing homes, and domiciliary care facilities of the Veterans Health Administration to establish smoking areas for patients and residents in a way that is consistent with medical requirements and limitations.	Include language about restrictions on the use of e-cigarettes in local and national guidance regarding smokefree policies.
U.S. Department of Veterans Affairs (VA)	Provides evidence-based tobacco cessation treatment to veterans receiving care in the VA health care system.	38 CFR Part 17: Eliminated in 2006 the copayment for smoking cessation counseling for veterans in care facilities of the Veterans Health Administration (<i>Federal Register</i> 2006).	Continue to provide clinical guidance for the health care professionals and patients in facilities of the Veterans Health Administration on the evidence base of (a) potential health effects of e-cigarettes and (b) comparisons to FDA-approved NRT for cessation treatment.
U.S. Environmental Protection Agency (EPA)	Sets policies regarding the hazardous waste status of e-cigarettes under the RCRA.	Nicotine is a commercial chemical product listed in 40 CFR 261.33(e) and is an acute hazardous waste (EPA waste code P075) when disposed. EPA has concluded that nicotine is the sole active ingredient of the e-liquid in e-cigarettes and thus a commercial chemical product, that e-cigarettes are not manufactured articles, and that e-cigarette cartridges are considered containers of nicotine. Therefore, e-cigarettes may be regulated as acute hazardous waste code P075 when disposed.	—
U.S. Environmental Protection Agency (EPA)		If the nicotine e-liquid is legitimately recycled, it is not considered a solid waste under 261.2 because it is considered a commercial chemical product, and therefore it is not subject to hazardous waste regulation. E-cigarettes that are disposed of by consumers at their residences are considered exempt household hazardous waste under 261.4(b)(1) and are not subject to regulation as hazardous waste under the federal RCRA regulations. - Regulatory Citation(s): 261.2, 261.4(b)(1), 261.33. - Statutory Citation(s): 3006 Read U.S. Code 42, Chapter 82.	

Note: ATF = Bureau of Alcohol, Tobacco, Firearms and Explosives; BOP = Bureau of Prisons; CCTA = *Contraband Cigarette Trafficking Act*; CFR = Code of Federal Regulations; CMS = Centers for Medicare & Medicaid Services; DHS = U.S. Department of Homeland Security; DoD = U.S. Department of Defense; DOT = U.S. Department of Transportation; ED = U.S. Department of Education; ENDS = electronic nicotine delivery systems; EOP = Executive Office of the President; EPA = U.S. Environmental Protection Agency; EPSDT = Early and Periodic Screening, Diagnosis and Treatment; FAA = Federal Aviation Administration; FCC = Federal Communications Commission; FDA = Food and Drug Administration; FTC = U.S. Federal Trade Commission; FY = fiscal year; GSA = General Services Administration; HUD = U.S. Department of Housing and Urban Development; ICE = Bureau of Immigration and Customs Enforcement; IRC = Internal Revenue Code; NACDA = National Advisory Council on Drug Abuse; NDAA = *National Defense Authorization Act*; NIDA = National Institute on Drug Abuse; NRT = nicotine replacement therapy; OMB = Office of Management and Budget; OPM = Office of Personnel Management; OSHA = Occupational Safety and Health Administration; PACT = *Prevent All Cigarette Trafficking Act*; PHS = Public Health Service; PIH = Public and Indian Housing; RCRA = *Resource Conservation and Recovery Act*; SAMHSA = Substance Abuse and Mental Health Services Administration; SNAP = Special Supplemental Nutrition Program; TTB = Alcohol and Tobacco Tax and Trade Bureau; U.S.C. = United States Code; USDA = U.S. Department of Agriculture; USTR = U.S. Trade Representative; VA = U.S. Department of Veterans Affairs; WIC = Women, Infants, and Children.

Governments use uniform, tiered, and mixed-tax approaches to implement specific and ad valorem tobacco excise taxes. Uniform systems apply the same tax rate across all products; tiered systems levy taxes based on such product characteristics as toxicity, nicotine content, type of production (handmade versus machine made), sales volume, packaging, or whether the products are domestic or imported; and mixed systems use a combination of uniform and tiered-tax approaches (Shang et al. 2015). Tiered-tax approaches, such as those based on nicotine content, could steer consumers to a less toxic product or one with lower nicotine (Benowitz 2014). Tiered-tax approaches are more complex to administer and may provide greater opportunity for tax evasion as a result of manipulation of the product or its packaging by the manufacturer (Shang et al. 2015). In recognition of nicotine's toxicity, particularly to youth, several health groups have endorsed imposing excise taxes on e-cigarettes to discourage their use by youth (American Thoracic Society 2013; Association of State and Territorial Health Officials 2014; Bhatnagar et al. 2014; Brandon et al. 2015a; Crowley and Health Public Policy Committee of the American College of Physicians 2015; National Association of County and City Health Officials 2014). E-cigarettes are likely less toxic than combustible products (such as conventional cigarettes), and therefore, some contend should be taxed at a lower rate (Benowitz 2014; Bhatnagar et al. 2014). Yet others argue that e-cigarettes should be taxed at the same rate as other tobacco products (Freiberg 2012; American Thoracic Society 2013; National Association of County and City Health Officials April 2014).

As of January 2016, four states (Kansas, Louisiana, Minnesota, and North Carolina) and six localities (Juneau, Matanuska-Susitna, Petersburg, and Sitka, Alaska; Montgomery County, Maryland; and Chicago, Illinois) had enacted e-cigarette taxation policies. Minnesota's ad valorem tobacco tax equates to 95% of the wholesale cost of any product containing or derived from tobacco (Minnesota Revenue 2014; Tobacco Control Legal Consortium 2015). It taxes e-liquids and e-cigarettes sold with nicotine cartridges that cannot be removed (i.e., disposables). In Minnesota, devices without a nicotine cartridge are not taxed as a tobacco product. On the other hand, North Carolina applies a specific excise tax, taxing e-liquids based on volume at 5 cents per milliliter (National Conference of State Legislatures 2015).

The Tobacco Control Legal Consortium, which is based at William Mitchell College of Law in St. Paul, Minnesota, recommends using an ad valorem tax for e-cigarettes applied at the retail level to the "essential" components of these devices. The tax is simple, captures both disposable and refillable devices, and could exclude accessories and universal parts sold separately, such as batteries or charging cords (Tobacco Control Legal Consortium 2015).

Numerous major health organizations support raising the price of e-cigarettes through non-tax options, such as limiting rebates, discounts, and coupons (Freiberg 2012; Association of State and Territorial Health Officials 2014; Bhatnagar et al. 2014; Huang et al. 2014; Brandon et al. 2015a).

Finally, Chaloupka and colleagues (2015) have proposed that differential taxation of tobacco products can be used to incentivize a move away from combustible products to less hazardous noncombustible products, including e-cigarettes. They have argued that taxation could be part of a harm-reduction system. In their view, future determinations by FDA as to whether a product poses a substantially reduced risk would be one criterion in determining the relative rate of taxation.

Restrictions on Marketing

As described in Chapter 4, the marketing of e-cigarettes drives consumer demand for these products. Such marketing also may promote misperceptions about the safety and efficacy of these products for use as cessation devices (Choi and Forster 2014; Mark et al. 2015; Pokhrel et al. 2015). For some populations—such as pregnant women, adolescents, former smokers, and young adults—the adverse health consequences of nicotine intake are substantial. Several groups have supported extending marketing restrictions that apply to conventional cigarettes and other tobacco products to e-cigarettes (Association of State and Territorial Health Officials 2014; Bam et al. 2014; Bhatnagar et al. 2014; Partnership for Prevention 2014; Brandon et al. 2015a). Significant barriers still exist to regulating commercial speech, including the First Amendment rights of the e-cigarette companies (Laird-Metke 2010).

Additionally, for traditional tobacco products, partial advertising bans and voluntary agreements have generally been ineffective in reducing consumption because the tobacco industry circumvents the restrictions by shifting the marketing platforms used to unregulated platforms (National Cancer Institute 2008). This response would be expected to be similar with regard to e-cigarettes. Therefore, despite the numerous barriers, public health groups and state, local, tribal, and territorial governments should take steps to stem the proliferation of e-cigarette marketing likely to appeal to young people by using tools designed to curb youth-oriented tobacco marketing and expanding evidence to inform future restrictions on the marketing of e-cigarettes to youth and young adults.

Surveillance of e-cigarette marketing, performing content analyses of the messages used, and conducting studies to assess the link between exposure to e-cigarette marketing and the use of e-cigarette products, particularly among youth and young adults, will facilitate the development of an evidence base of the type that informed prior federal and Master Settlement Agreement restrictions on tobacco advertising. Observations of retailers' practices, assessments of outdoor advertising, and identification of event sponsorships and promotional activities at bars and community events are actions that state, local, tribal, and territorial public health agencies have taken related to traditional tobacco products. Many of these actions can be adapted to monitor and document the presence of e-cigarette marketing in communities (Pucci et al. 1998; Feighery et al. 2001; Rigotti et al. 2005; Roeseler et al. 2010; Rose et al. 2014).

In the absence of legal restrictions on e-cigarette marketing, and apart from the issue of the previous promulgation by some companies of unsubstantiated health and cessation claims, public health groups can advocate for television and radio broadcasters, print and outdoor media companies, the management of event venues and sports events, digital media outlets, retailers, and others to voluntarily refuse to air or place e-cigarette advertising, offer sponsorships, or give out free samples at fairs and festivals. Although the impact of a voluntary approach may be low, such actions raise awareness, build concern, and help to denormalize the proliferation of e-cigarette marketing. In California, surveillance plus voluntary efforts to promote restrictions on sponsorship of events by the tobacco industry facilitated a modest decline in tobacco industry-sponsored events and youth-oriented activities at those events that promoted the interests of the tobacco companies, and it led to a productive partnership with the tobacco litigation unit of the California attorney general's office that resulted in several settlements with tobacco companies (Roeseler et al. 2010).

State, local, tribal, and territorial public health agencies may be able to contribute to the stimulation of enforcement and compliance with existing rules that constrain marketing. Some states have brought lawsuits against e-cigarette companies, alleging that distributors of these products violated state law by selling to minors or making unsubstantiated health claims; some of those lawsuits resulted in financial damages and agreements to stop making claims that e-cigarettes are safer than conventional cigarettes unless confirmed by rigorous science (Center for Public Health and Tobacco Policy 2013).

Finally, another area to address is the use of “advertorials” employed by e-cigarette retailers to promote cessation and health claims. Advertorials are paid advertisements designed to look like an independent editorial. Although there are no specific rules for how a publisher should distinguish actual editorial content from paid editorial content in terms of their appearance, the Federal Trade Commission (FTC) stated in an advisory opinion that disclosure of the source is necessary when content “uses the format and has the general appearance of a news feature and/or article for public information which purports to give an independent, impartial and unbiased view” (*Federal Register* 1972, p. 154). Additionally, paid advertising must be disclosed clearly and conspicuously in a manner that is understandable to consumers (FTC 1984). State and local public health agencies can play an important role by monitoring and providing substantiation to their state attorney general or FTC regarding advertising that makes improper claims or is not clearly identified as advertising.

Educational Initiatives

The extensive data reviewed in Chapter 2 highlighted the limited knowledge that members of the general public, particularly adolescents and young adults, have about e-cigarettes and their potential for nicotine addiction and other adverse health consequences. FDA has jurisdiction for product warnings that can reach users, but that agency, along with other federal entities and state and local governmental and nongovernmental organizations, can also carry out educational campaigns to enhance such limited knowledge levels. Potentially effective initiatives with youth and young adults to prevent smoking were reviewed in the 2012 Surgeon General’s report and may be applicable to preventing e-cigarette use. That report concluded that sufficient evidence exists to conclude that mass media campaigns, comprehensive community programs, comprehensive statewide tobacco control programs, and school-based programs that have shown evidence of effectiveness, if they contain specific components, can produce at least short-term effects and reduce the prevalence of tobacco use among school-aged youth (USDHHS 2012).

Implications for Health Care Practice

Although the issues are not well documented, health care practitioners face questions about e-cigarettes from their patients and their communities, including what are the risks of using e-cigarettes, how do these risks compare with those of cigarettes or other combustible products, and is e-cigarette use an effective way to quit smoking? Chapter 3 set out the limited evidence base related to these questions. Clinicians need to respond to these questions and guide their patients in the context of considerable uncertainty. At this time, practitioners can turn to the various statements from medical organizations, which generally urge caution regarding e-cigarettes and do not find the evidence to be supportive of their use for cessation or for formal harm-reduction strategies (Table 5.3). In fact, any recommendation to use

Table 5.3. Medical organizations
A. Positions of professional organizations

Organization	Organizational position on cessation	Organizational position on harm	Organizational position on regulation	General comments
American Academy of Pediatrics (2015b)	—	• “Concentrated nicotine solution for electronic nicotine delivery systems should be sold in child-resistant containers with amounts limited to that which would not be lethal to a young child if ingested.” • “Prohibitions on smoking and use of tobacco products should include prohibitions on use of electronic delivery systems.”	• “The promotion and sale of electronic nicotine delivery systems to youth should be prohibited by federal, state, and local regulations.” • “Prohibitions on promotion should include all media that can be viewed by youth, including broadcast, print, and electronic (Web- or Internet-based) media.” • “Prohibitions on promotion should include prohibitions on sponsorships, such as sports, cultural event, and entertainment sponsorships. Any promotional activities that can be accessed by children and/or adolescents should be considered promoting to children.” • “Electronic nicotine delivery systems should be subject to the same restrictions on advertising and promotion at least as restrictive as that on combustible cigarettes. Until government agencies institute these prohibitions, media companies, entertainment companies, sports teams, and promoters should voluntarily institute these prohibitions.” • “Celebrities should not use their privileged position to model tobacco product use, including electronic nicotine delivery systems and other existing or emerging tobacco products.”	—

Organization	Organizational position on cessation	Organizational position on harm	Organizational position on regulation	General comments
American Association for Cancer Research (AACR) and the American Society of Clinical Oncology (2015)	- FDA has not approved e-cigarettes as smoking cessation aids, and current data are inconclusive with regard to their efficacy as quit-smoking products. “Oncologists would be wise to refrain from recommending e-cigarettes to patients as a first-line therapy for smoking cessation.”	“The evidence regarding the risks and benefits of e-cigarettes is difficult to interpret, and data on the long-term consequences of e-cigarette use are not yet available.” “Chemicals and ultrafine particles known to be toxic and carcinogenic and/or to cause respiratory and heart distress have been identified in e-cigarettes.” “Studies find the levels of the toxicants in e-cigarette aerosol to be significantly lower than in cigarette smoke and, in many cases, comparable with trace amounts found in a medicinal nicotine inhaler. It is unclear what effects these toxicants might have on e-cigarette users after chronic and frequent use.” “The vast majority of e-cigarette users use products containing nicotine.” - Nicotine is an addictive chemical, adversely affects maternal and fetal health during pregnancy, has adverse consequences for fetal brain development, and may adversely affect the adolescent brain. It is unclear what effect nicotine intake via e-cigarettes has on health or on the addictiveness of these products.” “Data from the [CDC] showed a significant increase in e-cigarette-related calls to poison centers between 2010 and 2014 as a result of accidental ingestion or absorption of e-cigarette liquid.”	“The FDA CTP should regulate all ENDS that meet the statutory definition of tobacco products and their component parts. ENDS delivery systems and e-liquids containing tobacco-derived nicotine should be regulated whether they are sold together or separately.” “ENDS manufacturers should be required to register with FDA and report all product and ingredient listings, as well as the nicotine concentration in the ENDS solution.” “ENDS packaging and advertising should be required to carry health warnings and safety labels—including a warning regarding nicotine addiction.” “Youth-oriented ENDS advertising and marketing should be prohibited, including: self-service ENDS displays, the provision of gifts and other giveaways with purchase of ENDS, the sale and distribution of items such as hats or t-shirts with ENDS brand logos, brand name sponsorship of social or cultural events, or of any team entry into those events, and youth-oriented advertising of tobacco products.” “Internet and other mail-order sellers of ENDS should be required to check the age and identification of customers at the point of purchase and delivery; to comply with all laws in the purchaser’s state or local jurisdiction; and pay all applicable federal, state, and local taxes.”	“There are insufficient data on health consequences of e-cigarette use, their value as tobacco cessation aids, and their effects on the use of combustible tobacco products by smokers and nonsmokers. “Oncologists should advise all smokers to quit smoking combustible cigarettes, encourage use of FDA-approved cessation medications, refer patients for smoking cessation counseling, and provide education about the potential risks and lack of known benefits of long-term e-cigarette use.”

Table 5.3. (A. Continued)

Organization	Organizational position on cessation	Organizational position on harm	Organizational position on regulation	General comments
(Continued)		• “Secondhand exposure to toxicants and nicotine from e-cigarette aerosol has been documented, though there are not current data suggesting that exposure to the aerosol has adverse health effects.” • “There are no published studies evaluating thirdhand (i.e., residue that builds up on surfaces over time) exposure to e-cigarette aerosol in indoor environments, although preliminary data suggest that nicotine from e-cigarettes can stick to surfaces.”	• “Childproof caps should be required for all e-liquid containers.” • “ENDS and ENDS liquid containing candy and other youth-friendly flavors should be banned unless there is evidence demonstrating that these products do not encourage youth uptake.” • “ENDS use should be prohibited in places where combustible tobacco product use is prohibited by federal, state, or local law until the safety of second- and thirdhand aerosol exposure is established.” • “Funding generated through tobacco product taxes, including any potential taxes levied on ENDS, should be used to help support research on ENDS and other tobacco products, but should not preclude the allocation of federal funding for this research.” • “All data related to ENDS composition, use, and health effects should be disclosed for dissemination and independent review as well as to enhance policy decisions for ENDS product regulation.” • “Tobacco products should be taxed proportionate to their harm; therefore, ENDS should not be taxed at equal or higher rates than combustible cigarettes.” • “State and local governments should implement ENDS regulations within their authorities that are appropriate for protecting the public health, including restricting the sale, distribution, marketing, and advertising of ENDS to youth.” • “International cooperation is needed to develop standards for the regulation of ENDS, and these regulations should prioritize protection of the public’s health and draw upon the best available scientific evidence whenever possible.”	—

Organization	Organizational position on cessation	Organizational position on harm	Organizational position on regulation	General comments
American Association for Respiratory Care (AARC) (2015)	“Even though the concept of using the e-cigarettes for smoking cessation is attractive, they have not been fully studied and the use among middle school children is increasing year after year.”	“There is no evidence as to the amount of nicotine or other potentially harmful chemicals being inhaled during use or if there are any benefits associated with using these products.”	—	- Date effective: April 2014 “The [AARC] opposes the use of the electronic cigarette (e-cigarette).”
American College of Physicians (ACP) (Crowley and Health Public Policy Committee of the ACP 2015)	“ENDS, which include electronic cigarettes, or e-cigarettes, are growing in popularity, but their safety and efficacy as a smoking cessation aid are not well understood.”	“[There is concern] that the health effects of ENDS use are unknown, that they may appeal to young people, and that they may encourage dual use of ENDS and traditional tobacco products.”	“The Food and Drug Administration [should] extend its regulatory authority granted through the <i>Family Smoking Prevention and Tobacco Control Act</i> to cover electronic nicotine delivery systems (ENDS).” “Characterizing flavors should be banned from all tobacco products, including ENDS.” “The [ACP] supports taxing tobacco products, including ENDS devices and nicotine liquids, to discourage use among children and adolescents. Local governments should be permitted to establish higher tax rates for ENDS and related products than state levels.” “The [ACP] supports legislative or regulatory efforts to restrict promotion, advertising, and marketing for ENDS products in the same manner as for combustible cigarettes, including a prohibition on television advertising.” “Youth tobacco prevention efforts, such as antismoking media campaigns and school-based interventions, should include information about the potential risks of ENDS use.” “The federal, state, and local regulators should take action to extend indoor and public place clean air laws that prohibit smoking in public places, places of employment, commercial aircraft, and other areas to ENDS products.”	“The [ACP] supports strong regulations to ensure product safety and transparency, policies that prevent use among young people, increased research to better determine their health effects, strong limits on marketing and promotion to discourage interest among young people, and application of indoor air laws to protect the health of bystanders.” “This paper is not intended to offer clinical guidance or serve as an exhaustive literature review of existing ENDS-related evidence but to help direct the [ACP], policymakers, and regulators on how to address these products.”

Table 5.3. (A. Continued)

Organization	Organizational position on cessation	Organizational position on harm	Organizational position on regulation	General comments
(continued)			“The federal government should authorize and appropriate funding to rigorously research the health effects of ENDS use, chemical content, and toxicity; effects of ENDS vapor exposure; dual-use rates; and effects of ENDS-derived nicotine on human health.”	
American Thoracic Society (2013, 2015)	“The new CDC data show that Big Tobacco is once again peddling a new product intended to get youth hooked on nicotine, and that e-cigarettes are not about harm reduction or smoking cessation, but about addiction.”	“The short- and long-term health risks of these nicotine-delivery devices are largely unknown.”	“States should regulate e-cigarettes as tobacco products. - E-cigarettes should not be sold to those younger than 18, and regulations requiring identification and proof of age at the time of purchase should apply. Internet sales of e-cigarettes should be strictly regulated.” “E-cigarettes should be taxed at rates equivalent with traditional cigarettes and other tobacco products.” “E-cigarettes should be subject to the same restrictions regarding public use as combustible tobacco products, and e-cigarettes should not be used in smoke-free areas.” “The FDA should deem regulatory authority over e-cigarettes.” “Candy and menthol flavored e-cigarettes should be banned.” “E-cigarette packaging should include warning labels, similar in size and scope to those required of combustible tobacco packaging. Where risks are known, the consumer should be informed of those risks in clear and direct language. Where data regarding risk is [sic] unavailable or inconclusive, the consumer should be informed of the lack of reliable safety testing data.”	“[E]-cigarettes need to be subject to the same marketing and manufacturing restrictions as tobacco products.” “For the first time, e-cigarette use among young people is higher than for any other tobacco product.”

Organization	Organizational position on cessation	Organizational position on harm	Organizational position on regulation	General comments
(continued)			• “The FDA should regulate the form and content of e-cigarette advertising.” • “Both direct and implied health and safety claims by e-cigarette manufacturers should be subject to the same evidentiary review process currently required for other products making such claims.” • “The FDA should require e-cigarette manufacturers to adopt Good Manufacturing Processes similar to those that exist for other regulated products, including lot numbers, securing packaging, etc.” • “Given that nicotine is an addictive drug, with the dependence liability related to the pharmacokinetic characteristics of the delivery device, delivery characteristics of the e-cigarette should be evaluated and disclosed, and periodically monitored to ensure consistency of the product’s dependence potential over time.”	
American Thoracic Society (2013, 2015)	—	—	• Content of e-cigarette cartridges should be disclosed and regulated. • “The nicotine content of the e-cigarette cartridge should not exceed that of similar user volume of combustible tobacco.” • “Deliverable nicotine levels should be consistent between cartridges.” • “Researchers and clinicians, along with scientific societies and publications, receiving funding from e-cigarette manufacturers should disclose this relationship and the potential for conflict of interest in a manner equivalent to disclosures required for funding from the remainder of the tobacco industry.”	—

Table 5.3. (A. Continued)

Organization	Organizational position on cessation	Organizational position on harm	Organizational position on regulation	General comments
European Respiratory Society (ERS) (2014)	“Electronic cigarettes are designed for the purpose of direct nicotine delivery to the respiratory system, and they fall into a regulatory gap in most countries, escaping regulation as medicinal products and avoiding the controls applicable to tobacco products.”	“For ERS, the priority of the Revision of the Tobacco Products Directive is to protect children and youth from becoming smokers by preventing them from picking up their first cigarette.” “There is no adequate scientific research available on the overall health risk or the long-term effects of electronic cigarette use on humans.”	“Mandatory reporting system of ingredients used in tobacco products.” “Harmonised regulation of the ingredients of tobacco products.” “80% pictorial health warnings, covering the front and back of packages. Based on evidence, the larger the pictorial health warnings are, the more effective they are.” “Plain/standardised packaging of tobacco products.” “Introduction of both visible and invisible security features on tobacco packaging and ensuring that the storage and access to such data is [sic] independent from tobacco companies.” “Prohibition on the cross-border distance sale of tobacco products.” “Strong regulatory framework and independent research for electronic cigarettes. Any regulation of electronic nicotine delivery systems should be science based.” “Ensuring the adoption of delegated acts is not exposed to the interests of the tobacco industry, which would jeopardise the achievement of high level of health protection.”	“ERS supports the European Commission’s Proposal for the Tobacco Products Directive and Rapporteur Linda McAvan’s efforts to improve it.” “Introduction of standard packs with increased health warnings.” “Prohibition of characterizing flavours.” “Strengthening of traceability and security features for combating illicit trade.” “Prohibiting misleading features, including slim cigarettes.” “Approximately 700,000 EU citizens die prematurely every year because of tobacco consumption.”
Forum of International Respiratory Societies (American College of Chest Physicians 2014; Schraufnagel et al. 2014)	“Studies looking at whether electronic cigarettes can aid smoking cessation have had inconsistent results.”	“The safety of electronic cigarettes has not been adequately demonstrated.” “The addictive power of nicotine and its untoward effects should not be underestimated. “Potential benefits to an individual smoker should be weighed against harm to the population of increased social acceptability of smoking and use of nicotine.” “Adverse health effects for third parties exposed to the emissions of electronic cigarettes cannot be excluded.”	“Health and safety claims regarding electronic nicotine delivery devices should be subject to evidentiary review.” “If ENDS devices are permitted, they should be regulated as tobacco products.” “Research, supported by sources other than the tobacco or electronic cigarette industry, should be carried out to determine the impact of electronic nicotine delivery devices on health in a wide variety of settings.” “The use and population effects of END devices should be monitored.” “All information derived from this research should be conveyed to the public in a clear manner.”	“ENDS should be restricted or banned, at least until more information about their safety is available.”

Table 5.3. (Continued)
B. Voluntary Health Organizations

Organization	Organizational position on cessation	Organizational position on harm	Organizational position on regulation	General comments
American Cancer Society (ACS) (2014)	“Because the American Cancer Society doesn’t yet know whether e-cigarettes are safe and effective, we cannot recommend them to help people quit smoking.” “There are proven methods available to help people quit, including pure forms of inhalable nicotine as well as nasal sprays, gums, and patches.”	“[E]-cigarettes are not labeled with their ingredients, so the user doesn’t know what’s in them.” “Inhaling a substance is not the same as swallowing it.” “Studies have shown that e-cigarettes can cause short-term lung changes that are much like those caused by regular cigarettes.”	“E-cigarettes need to be researched and regulated.”	“Until electronic cigarettes are scientifically proven to be safe and effective, ACS will support the regulation of e-cigarettes and laws that treat them like all other tobacco products.”
American Heart Association (AHA) (Bhatnagar et al. 2014)	“Current evidence evaluating the efficacy of these products as a cessation aid is sparse, confined to 2 randomized controlled trials and 1 large cross-sectional study, anecdotal reports, and Internet-based surveys.” “[R]eports are confounded by a self-selection bias in that the respondents are often e-cigarette enthusiasts.” “The AHA maintains that e-cigarette use should be part of tobacco screening questions incorporated into clinical visits and worksite/community health screenings that are tied into healthcare delivery.” “Clinicians should be educated about e-cigarettes and should be prepared to counsel their patients who are using combustible tobacco products to use e-cigarettes as a primary cessation aid.” “For patients with existing cardiovascular disease and stroke, or at risk of a cardiovascular disease event, intensive cessation counseling should be offered as soon as possible.”	“Low levels of harmful or potentially harmful metals such as lead, nickel, and chromium are listed as having been detected.” “Trace levels of tobacco-specific N-nitrosamines, polycyclic aromatic hydrocarbons, and volatile organic compounds in the e-liquid and vapor have been reported.” “The FDA has issued warnings to several e-cigarette companies for selling e-cartridges with [diethylene glycol, weight-loss chemical rimonabant (Zimulti), and the erectile dysfunction medication tadalafil (active ingredient in Cialis)] contaminants.” “There are no reports of e-cigarette safety in patients with known cardiovascular disease.”	“The regulation should allow for quality-controlled products for adults who want to transition from conventional cigarettes to e-cigarettes or to quit or reduce smoking.” “Bottles containing nicotine refill liquids can be toxic if swallowed, so cartridges and bottles should have proper warning labeling and child-proofing packaging.” “It is important that the relevant government agency monitor whether these devices are used for delivery of other drugs and medications.”	“The [AHA] supports effective regulation that addresses marketing, labeling, quality control of manufacturing, and standards for contaminants.” “[It] also supports including e-cigarettes in smoke-free air laws and prohibiting the sales of e-cigarettes to youth.”
			“Companies should not be able to claim that e-cigarettes are a cessation aid unless they are approved by the FDA for that purpose.”	

Table 5.3. (B. Continued)

Organization	Organizational position on cessation	Organizational position on harm	Organizational position on regulation	General comments
American Lung Association (2014, 2015)	“Until and unless the FDA approves a specific e-cigarette for use as a tobacco cessation aid, the American Lung Association does not support any direct or implied claims that e-cigarettes help smokers quit.”	“There is currently no scientific evidence establishing the safety of e-cigarettes.” “FDA found detectable levels of toxic cancer-causing chemicals, including an ingredient used in anti-freeze, in two leading brands of e-cigarettes and 18 various cartridges.” “The lab tests also found that cartridges labeled as nicotine-free had traceable levels of nicotine.” “Nicotine is believed to contribute to increased incidence of premature birth, and low birth weight.” “Research has also shown a negative impact on pulmonary function in newborns.”	“The FDA has not approved any e-cigarettes as a safe or effective method to help smokers quit.”	“Including e-cigarettes in smokefree laws and ordinances.” “State laws that would prohibit the sale of any flavored e-cigarette product.” “Taxing e-cigarettes at a rate equivalent with all tobacco products, including cigarettes.” “Eliminating e-cigarette sales to youth, otherwise restricting youth access to e-cigarettes and requiring e-cigarette retailers to be licensed.” “E-cigarettes should be defined as tobacco products.” “Opposes creating new definitions for ‘vapor products’ and/or ‘alternative nicotine products’ in state laws.”
Americans for Nonsmokers’ Rights (ANR) (n.d.a; n.d.b)	“ESDs are not proven cessation devices.” “Many people become ‘stable dual-users’ who use both cigarettes and ESDs.”	“Americans for Nonsmokers’ Rights recommends that e-cigarettes not be used in areas where people will be exposed to the vapors they emit.” “Electronic smoking device aerosol is not water vapor...” - The aerosol (incorrectly called vapor) contains nicotine, hazardous ultrafine particles that lodge deeply in the lungs and toxins known to cause cancer.”	“Electronic smoking devices are currently unregulated products.” “[ANR] . . . encourages municipalities and states to prohibit the use of ESDs in all smokefree venues.”	“Electronic cigarettes are not a safe alternative!”

Table 5.3. (Continued)
C. World Health Organization

Organization	Organizational position on cessation	Organizational position on harm	Organizational position on regulation	General comments
World Health Organization (WHO) (Bates 2014; WHO 2014b)	“Prohibit manufacturers and third parties from making health claims for ENDS, including that ENDS are smoking cessation aids.” “The regulatory standard for cessation claims and approval as cessation aids should remain an appropriate body of evidence, based on well-controlled clinical trials.”	“ENDS users should be legally requested not to use ENDS indoors, especially where smoking is banned until exhaled vapour is proven to be not harmful to bystanders and reasonable evidence exists that smoke-free policy enforcement is not undermined. If smoke-free legislation is not fully developed according to Article 8 of the WHO FCTC and the guidelines for its implementation, this should be done as soon as possible.” “Health warnings should be commensurate with proven health risks.”	“Parties should contemplate putting in place an effective restriction on ENDS advertising, promotion and sponsorship.” “Protection from vested commercial interests.” “Governments are recommended to use or strengthen their existing tobacco surveillance and monitoring systems to assess developments in ENDS and nicotine use by sex and age.”	“Overall, in its public communication WHO portrays e-cigarettes as a threat to public health.” “Encourage smoking cessation and provide a quitline number if one exists.”
World Health Organization (WHO) (Bates 2014; WHO 2014b)	“For ENDS products to be approved for smoking cessation by the suitable regulatory agency, the appropriate balance should be reached between providing accurate scientific information to the public about the risk of ENDS use and its potential benefits as compared with smoking.”	—	—	—
European Union (EU) (European Parliament and Council 2014; WHO Framework Convention on Tobacco Control 2014)	—	“Certain additives used to create the impression that tobacco products have health benefits, as well as those with [carcinogenic, mutagenic, or reprotoxic] properties in unburnt form, should be prohibited in order to ensure uniform rules throughout the Union and a high level of protection of human health.”	“The prohibition of tobacco products with characterizing flavours does not preclude the use of individual additives outright, but it does oblige manufacturers to reduce the additive or the combination of additives.” “Electronic cigarettes and refill containers should be regulated by this Directive.”	- New directive: May 2014. - New rules applied: First half of 2016. “Aims at ensuring equal treatment across the EU for nicotine-containing e-cigarettes (products that do not contain nicotine are not covered by the Directive).”

Table 5.3. (C. Continued)

Organization	Organizational position on cessation	Organizational position on harm	Organizational position on regulation	General comments
(Continued)	—	“Electronic cigarettes and refill containers could create a health risk when in the hands of children—it is necessary to ensure products are child and tamperproof.” “Nicotine-containing liquid should only be placed on the market in electronic cigarettes or in refill containers that meet certain safety and quality requirements.”	“Where the manufacturer of the relevant product is not established in the Union, the importer of that product should bear the responsibilities relating to the compliance of those products with this Directive.” “Nicotine-containing liquid should only be allowed to be placed on the market, where the nicotine concentration does not exceed 20 mg/ml.” “Only electronic cigarettes that deliver nicotine doses at consistent levels should be allowed to be placed on the market.” “The labeling and packaging of [e-cigarettes] should display sufficient and appropriate information on their safe use.”	“Electronic cigarettes can develop into a gateway to nicotine addiction and ultimately traditional tobacco consumption, as they mimic and normalize the action of smoking. - For this reason, it is appropriate to adopt a restrictive approach to advertising electronic cigarettes and refill containers.”
CAP/BCAP (UK) (2014)	—	“Ads cannot convey health benefits or claim that they are safer or healthier than smoking tobacco.”	“Ads must not be likely to appeal particularly to people under 18, especially by reflecting or being associated with youth culture.” “People shown using e-cigarettes or playing a significant role must neither be, nor seem to be, under 25.” “Ads must not be directed at people under 18 through the selection of media or the context in which they appear.” “Ads must not encourage nonsmokers or nonnicotine users to use e-cigarettes.” “Ads must make clear that the product is an e-cigarette and not a tobacco product.” “Ads on TV and radio will be subject to scheduling restrictions to reduce the chance of e-cigarette advertisements being seen or heard by children.”	- Effective date: November 10, 2014. “The rules place an emphasis on the protection of young people and ads must avoid containing anything that promotes the use of a tobacco product or that shows the use of a tobacco product in a positive light.” - CAP: Write and maintain the UK advertising codes.
Public Health England (UK) (Britton and Bogdanovica 2014; CAMQUIT n.d.)	—	—	“Under the terms of the new Tobacco Product Directive (TPD) . . . advertising of nicotine-containing devices that are not licensed as medicines will be prohibited, products will be required to carry health warnings, meet purity and emission standards that are yet to be defined.”	- Effective date: 2016. “The UK [Medicines and Healthcare products Regulatory Agency] announced that from 2016, it intended to regulate electronic cigarettes and other nicotine-containing products as medicines by function, and

Organization	Organizational position on cessation	Organizational position on harm	Organizational position on regulation	General comments
(Continued)			“Under the terms of the new Tobacco Product Directive (TPD) . . . advertising of nicotine-containing devices that are not licensed as medicines will be prohibited, products will be required to carry health warnings, meet purity and emission standards that are yet to be defined.”	thus require manufacture to medicinal purity and delivery standards, and proactive controls on advertising.”
International Union Against Tuberculosis and Lung Cancer (2013)	“The benefits of e-cigarettes have not been scientifically proven.” “Very few studies have assessed ECs/ ENDS as a harm reduction and cessation aid and with conflicting findings.”	“The safety of ECs or ENDS has not been scientifically demonstrated.”^{xxx} “Adverse health effects for [secondhand smoke] cannot be excluded because the use of electronic cigarettes leads to emission of fine and ultrafine inhalable liquid particles, nicotine and cancer-causing substances into indoor air.”	“A range of current and proposed legislative and regulatory options exists.” “Brazil, Norway, and Singapore have banned ECs/ENDS completely.” “ENDS could undermine the implementation of WHO FCTC Article 12 (de-normalisation of tobacco use).” “Use of ENDS could also hamper the implementation of Article 8 (protection from exposure to tobacco smoke).”	“The Union strongly supports the regulation of the manufacture, marketing and sale of Electronic cigarettes (ECs) or electronic nicotine delivery systems (ENDS); - the preferred option is to regulate ECs or ENDS as medicines.” “The Union is concerned that the marketing, awareness and use of ECs or ENDS is growing rapidly.”

Note: AARC = American Association for Respiratory Care; ACP = American College of Physicians; ACS = American Cancer Society; AHA = American Heart Association; ANR = Americans for Nonsmokers’ Rights; CAP/BCAP = Committees of Advertising Practice/Broadcast Committee of Advertising Practice; CDC = Centers for Disease Control and Prevention; CTP = Center for Tobacco Products; ECs = electronic cigarettes; ENDS = electronic nicotine delivery systems; ERS = European Respiratory Society; ESDs = electronic smoking devices; EU = European Union; FCTC = Framework Convention for Tobacco Control; FDA = U.S. Food and Drug Administration; UK = United Kingdom; WHO = World Health Organization.

e-cigarettes for the cessation of smoking is not supported by the bulk of the available scientific evidence (Hartmann-Boyce et al. 2016). Both the American Association of Cancer Research and the American Society of Clinical Oncology recommend against advising the use of e-cigarettes for cessation (Brandon et al. 2015b). The U.S. Preventive Services Task Force found that there is insufficient evidence that e-cigarettes are an effective smoking cessation tool in adults, including pregnant women (Agency for Healthcare Research and Quality 2015).

The clinical care setting is a critical venue for taking evidence-based approaches for enhancing smoking cessation and increasing the protection of susceptible groups against exposure to secondhand smoke (USDHHS 2014). However, research on e-cigarettes in relation to this set of venues is lacking and urgently needed. Regardless, some pragmatic approaches have been proposed. For example, the American Academy of Pediatrics (AAP) gives advice on how pediatricians can approach questioning about the use of e-cigarettes. As of October 2015, the AAP's position on e-cigarettes is that sales to minors should be prohibited; flavors that appeal to youth should be prohibited; and measures against the use of e-cigarette products need to be included in requirements for maintaining smoke-free environments, such as in restaurants and workplaces (AAP 2015a).

Case Studies

Case studies in California and North Dakota demonstrate how e-cigarette policies have been enacted at the local and state levels, and they provide potential models of how cities, counties, and other states might address e-cigarettes in their jurisdictions.

City of Hayward Takes Bold Steps to Address Tobacco Products Aimed at Kids

In response to the “D” grade that the city of Hayward received in 2011 from the American Lung Association in California for its efforts to protect youth from tobacco sales, the city council directed its staff to develop regulations to address the problem of youth tobacco sales. Draft regulations were presented at a city planning meeting in 2012, followed by a series of community meetings and hearings that culminated in the Hayward city council's adoption of a 45-day moratorium to begin in January 2014 on the issuance of business licenses or building permits for any new tobacco retailers. The following month, the moratorium was extended another 15 months to provide more time to research and consider the issue (City of Hayward 2014).

On July 1, 2014, the Hayward city council unanimously adopted an ordinance that requires sellers of tobacco products and “electronic smoking devices” to obtain annually a \$400 tobacco retailer license that covers the cost of an annual inspection for compliance with federal, state, local, tribal, and territorial tobacco control laws. The ordinance allowed the city's existing 142 tobacco retailers, 8 e-cigarette retailers, and 2 hookah lounges to continue operating at their current locations; however, new sellers must obtain a conditional use permit, are restricted to special commercial zones, and may not locate within 500 feet of residential areas or child-sensitive areas (e.g., schools and parks) or within 500 feet of an existing tobacco seller. It also prohibits new hookah lounges or vaping lounges from opening within the city.

The ordinance also contains provisions to prohibit self-service displays of tobacco products and e-cigarettes and to regulate the sales of cigars, flavored products, and imitation tobacco products. Cigars selling for less than \$5 each are required to be sold in pack sizes of five or more, and the sale of flavored traditional tobacco products, e-cigarettes, and imitation tobacco products (e.g., candy cigarettes, bubble gum chew) is prohibited within 500 feet of schools for any business not selling these products before July 1, 2014.

Penalties range from \$1,500 for a first violation and possible suspension to a complete revocation of a license after three violations within a 3-year period (City of Hayward 2014; n.d.a.). Active enforcement of the ordinance began in April 2015 (City of Hayward n.d.b.).

Throughout the process, Hayward officials and staff relied heavily on materials from the American Lung Association, the Center for Tobacco Policy and Organizing, and ChangeLab Solutions to provide the public health and legal rationale for supporting the provisions. Hayward's tobacco retail licensing effort was also supported by the tobacco control program of the Alameda County public health department, which used monies from its Master Settlement Agreement to fund the Hayward police department to conduct youth decoy operations and local community and youth organizations to conduct educational outreach (City of Hayward 2014). Collectively, these resources informed the Hayward city council's decision-making process.

North Dakota's Statewide Clean Indoor Air Law Prohibits Conventional Tobacco Products and E-Cigarettes

In November 2012, North Dakota achieved a remarkable victory for statewide clean indoor air (BreatheND n.d.a.) despite major obstacles, including a harsh winter climate, an adult smoking rate of 21.9% (CDC 2013), and several prior failed legislative attempts to close exemptions in the state's 2005 clean indoor air law (CDC 2014). Despite these impediments, two-thirds of the state voted to prohibit both the smoking of conventional tobacco products and use of e-cigarettes in all non-hospitality workplaces; restaurants; bars; hotel guest rooms and communal areas; health care facilities; assisted living facilities; all licensed child and adult day care facilities; gaming facilities; indoor areas of sports arenas; and within 20 feet of entrances, exits, operable windows, air intakes, and ventilation systems of enclosed areas where smoking is not allowed (BreatheND n.d.b.). Additionally, the law provided no exemptions for tobacco-only retail or "vape shops" (Americans for Nonsmokers' Rights Foundation 2015, n.d.).

The 2012 ballot initiative on statewide clean indoor air resulted from the lack of progress in working with the legislature to try to close smoking exemptions in the state law. The initiative's sponsors, Tobacco Free North Dakota and the American Lung Association in North Dakota, worked closely with the Tobacco Control Legal Consortium to draft policy language, which included prohibiting the use of e-cigarettes anywhere smoking was prohibited. The sponsors approached stakeholders and assessed public support. Little opposition was encountered to prohibiting the use of e-cigarettes indoors. In addition to the sponsors' efforts, the North Dakota Center for Tobacco Prevention and Control Policy conducted a media campaign and worked with local partners to educate their communities, resulting in 11 smokefree ordinances prior to the issuing of the statewide ballot initiative. The landslide victory (66% vs. 33%) in favor of clean indoor air, with the initiative successfully carried in every one of North Dakota's 53 counties, demonstrated widespread public support for clean indoor air (Ballotpedia 2012).

Only a few years later, the law continues to enjoy strong public support from nonsmokers (84.4%) and smokers (58%) alike. Compliance with the law is comparable to cigarette smoking; just 16.8% of North Dakotans reported having observed smoking indoors in areas where it was prohibited, and 23.2% reported having seen e-cigarettes used indoors in such places. Local enforcement personnel confirm a high level of compliance, reporting violations primarily related to smoking within 20 feet of entrances. To date, the only prosecuted violation of the law involved the sampling of an e-cigarette product inside a "vape shop" (BreatheND 2014). In hindsight, the decision to include e-cigarettes in North Dakota's smokefree law was helpful, given increasing concerns about involuntary exposure to nicotine and other aerosolized e-cigarette emissions.

Summary and Recommendations

The Surgeon General has long played a leading role in identifying the harms of tobacco use and documenting the most effective ways to reduce them. This report comes amid the

rising use of e-cigarettes among the nation's youth and young adults. It calls attention to this problem and the need to implement immediately a comprehensive strategy to minimize any negative public health impact now and in the future, giving consideration to the potential for youth to be harmed from e-cigarettes while, simultaneously, acknowledging that gains might be made if the use of combustible tobacco products fell among adult smokers. Chapters 1–4 documented the particular challenges posed by the rapid emergence and dynamic nature of e-cigarette use among youth and young adults. The marketplace is diverse, and although it includes the large tobacco companies, e-cigarettes are sold in thousands of “vape shops” and other small commercial locations and on the Internet. Marketing strategies exploit social media, reaching widely and with tailored targeting to consumers.

The differences notwithstanding, the principles and strategies articulated in the 2014 Surgeon General's report and prior reports remain relevant to e-cigarettes. The 2014 report was written not long after the use of e-cigarettes began to surge dramatically; that report commented on the need for rapid elimination of conventional cigarettes and other combustible tobacco products but did not specify a role for e-cigarettes or discuss strategies to minimize adverse effects among youth and young adults (USDHHS 2014). The report's final chapter, however, set out an evidence-based strategy for the future. The present report builds on this foundation, adding recommendations related to e-cigarettes.

Conclusion

- 1) The dynamic nature of the e-cigarette landscape calls for expansion and enhancement of tobacco-related surveillance to include (a) tracking patterns of use in priority populations; (b) monitoring the characteristics of the retail market; (c) examining policies at the national, state, local, tribal, and territorial levels; (d) examining the channels and messaging for marketing e-cigarettes in order to more fully understand the impact future regulations could have; and (e) searching for sentinel health events in youth and young adult e-cigarette users, while longer-term health consequences are tracked.
- 2) Strategic, comprehensive research is critical to identify and characterize the potential health risks from e-cigarette use, particularly among youth and young adults.
- 3) The adoption of public health strategies that are pre-cautionary to protect youth and young adults from adverse effects related to e-cigarettes is justified.
- 4) A broad program of behavioral, communications, and educational research is crucial to assess how youth perceive e-cigarettes and associated marketing messages, and to determine what kinds of tobacco control communication strategies and channels are most effective.
- 5) Health professionals represent an important channel for education about e-cigarettes, particularly for youth and young adults.
- 6) Diverse actions, modeled after evidence-based tobacco control strategies, can be taken at the state, local, tribal, and territorial levels to address e-cigarette use among youth and young adults, including incorporating e-cigarettes into smoke-free policies; preventing the access of youth to e-cigarettes; price and tax policies; retail licensure; regulation of e-cigarette marketing that is likely to attract youth and young

adults, to the extent feasible under the law; and educational initiatives targeting youth and young adults. Among others, research focused on policy, economics, and the e-cigarette industry will aid in the development and implementation of evidence-based strategies and best practices.

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THE CALL TO ACTION

The Call to Action on E-Cigarette Use among Youth and Young Adults

The Surgeon General issues this Call to Action on e-cigarettes, specifically focusing on youth and young adults, to accelerate policies and programs that can reduce e-cigarette use among young people. This Call to Action comes amid the dramatic increase in e-cigarette use among our nation's youth and young adults. It highlights the need to implement proven strategies that will prevent potentially harmful effects of e-cigarette use among young people. The previous chapters explained what we know and do not know about e-cigarettes and reviewed policy options. Gaps in scientific evidence still exist, and this Call to Action is being issued while these products and their patterns of use are changing quickly. However,

policies and strategies are available that can clearly reduce the public health threat posed by e-cigarette use among young people.

Use of e-cigarettes is increasing rapidly among young people, even among those who have never smoked cigarettes.

This Call to Action presents six goals and related strategies that should guide efforts to reduce e-cigarette use among youth and young adults. To achieve these goals, we must work together, which means working with individuals and families; civic and community leaders; public health and health care professionals; e-cigarette manufacturers and retailers; voluntary health agencies; researchers; and other stakeholders.

Stakeholders Who Can Take Action

- Individuals, parents, and families
- Teachers, coaches, and other youth influencers
- Civic and community leaders
- Public health and health care professionals
- Researchers
- Federal government
- State, local, tribal, and territorial governments
- E-cigarette manufacturers, distributors, and retailers
- Voluntary health agencies, non-governmental organizations, and other community- and faith-based organizations

Goal 1. First, Do No Harm

Since 1964, reports from the U.S. Surgeon General have led the way in identifying the harms of tobacco use and detailing the most effective ways to reduce the dangerous effects of tobacco use. For example, reports from 1994 and 2012 outlined proven strategies to prevent and reduce tobacco use among youth and young adults (U.S. Department of Health and Human Services [USDHHS] 1994, 2012). Building on these and other past reports, this Call to Action considers the harms of e-cigarette use among youth and young adults and stresses the importance of strategies that will protect young people from the adverse consequences of these new products.



Strategy 1A.

Implement a comprehensive strategy to address e-cigarettes that will avoid adverse consequences and give careful consideration to the risks for youth and young adults. This can be done by including e-cigarettes in policies and programs related to conventional cigarette smoking at the national, state, local, tribal, and territorial levels.

We have many effective strategies to prevent tobacco use among youth and young adults (USDHHS 2012), and many of these strategies can also be applied to e-cigarettes. A strategy to address e-cigarette use among young people should be precautionary. A precautionary approach urges action to prevent harm when there is scientific uncertainty. That is, when there is inadequate or early knowledge, public health decisions should be made on the basis of precaution to prevent harm, rather than on certain risk. This approach requires proof that a product *is not* harmful—especially for youth—rather than proof that it *is* harmful. The burden of proof regarding product safety should be placed on those who wish to market and sell such tobacco products, rather than the public health community charged with protecting the public's health. The harms of nicotine exposure in youth and young adults are well-documented in this report and warrant this Call to Action (see Chapter 3). We must protect the health of our nation's young people by assuring that there will be no harm to youth from e-cigarettes. The stakeholders identified on the previous page should work together to prevent and reduce the use of all forms of tobacco products, including e-cigarettes, among our nation's youth and young adults. A comprehensive strategy includes:

- Implementing the U.S. Food and Drug Administration's (FDA's) authority to regulate tobacco products in order to provide oversight of the manufacturing, distribution, and marketing of e-cigarettes, particularly as they relate to youth and young adults;
- Funding comprehensive statewide tobacco control programs at levels recommended by the Centers for Disease Control and Prevention (CDC);
- Implementing comprehensive clean indoor air policies that protect people from exposure to secondhand tobacco smoke and the aerosol emitted from e-cigarettes;
- Raising and strongly enforcing minimum age-of-sale laws for all tobacco products, including e-cigarettes, to prevent initiation at young ages;

Use of e-cigarettes can expose young people to nicotine. Nicotine can be highly addictive and can harm brain development. Nicotine use may also lead to the use of other tobacco or nicotine-containing products.

- Setting price policies for e-cigarettes, which could include taxation policies;
- Restricting advertising and marketing that encourages youth and young adults to use e-cigarettes;
- Sponsoring high-impact media campaigns to educate the public using evidence-based information about the consequences of e-cigarette use among youth and young adults, including the harms of nicotine on the developing brain; and
- Expanding tobacco control and prevention research efforts to increase our understanding of the evolving landscape of e-cigarettes.

These components make up an evidence-based strategy. However, the e-cigarette marketplace is diverse and continues to evolve. Thus, ongoing efforts should rapidly and effectively track and adapt to such changes, thereby protecting our nation's young people from the consequences of e-cigarette use and exposure to secondhand aerosol.



Strategy 1B.

Provide consistent and evidence-based messages about the health risks of e-cigarette use and exposure to secondhand aerosol from e-cigarettes.

Research on e-cigarettes is ongoing, and the e-cigarette marketplace continues to evolve. Even so, a sufficient body of evidence justifies actions taken now to prevent and reduce the use of e-cigarettes and exposure to secondhand aerosol from e-cigarettes, particularly among youth and young adults. Most important, many health risks are already known, and sufficient information exists to take action to minimize potential harms. The evidence is most compelling for nicotine. As part of comprehensive reviews, previous Surgeon General's reports have provided causal findings on the development of addiction and other health consequences of exposure to nicotine (USDHHS 1988, 2014). Beyond addiction, intake of nicotine by young people can harm brain development (Chapter 3).

Additionally, aerosol from e-cigarettes contains toxins that can harm the body, and the flavorings used in these products cannot be considered safe for inhalation, either firsthand or secondhand (Chapter 3). For example, some flavorings have been known to be associated with pulmonary toxicity (Allen et al. 2016).

Messaging about the potential role of e-cigarettes in reducing the burden of tobacco-related diseases should note that e-cigarette products that deliver nicotine are not considered safe, particularly for youth and young adults, even before researchers fully characterize and quantify all of their health risks, including possible permanent changes to the adolescent brain and lungs.

The use of any tobacco product, including e-cigarettes, among young people is unsafe.

Goal 2. Provide Information about the Dangers of E-Cigarette Use among Youth and Young Adults

Once youth and young adults start using products that contain nicotine, including e-cigarettes, they can become addicted. Such addiction has the potential to lead to long-term use of products that contain nicotine, such as cigarettes. Most adolescents who use tobacco already use more than one nicotine-containing product and are not just using e-cigarettes alone (Chapter 2). The majority of tobacco users start before they are 18 years of age, and almost no one starts after age 25 (USDHHS 2012). Therefore, the best way to protect young people from the harms of tobacco use, including e-cigarettes, is to prevent the use of these products altogether. Prevention should start with robust public policies that make it easy for youth not to use tobacco and harder for them to use any tobacco products. Parents, teachers, health professionals, and other influencers of youth should be educated about the risks of e-cigarette use. They can then help educate their own children as well as other young people about the harms of e-cigarettes and the risk of a potential lifetime of nicotine addiction.

Use of e-cigarettes and exposure to nicotine is particularly dangerous for pregnant women. Nicotine is toxic to the fetus and impairs fetal brain and lung development.

Strategy 2A.

Educate parents, teachers, coaches, and other influencers of youth about the risks of e-cigarette use among youth and young adults.

Parents, guardians, teachers, coaches, health professionals, faith leaders, and other persons whose advice and behavior influence youth play critical roles in protecting youth and young adults from the harms of e-cigarette use and exposure to the secondhand aerosol emitted from these devices. Most adults are familiar with some of the dangers of using tobacco products, especially conventional cigarettes, and of exposure to secondhand tobacco smoke. Because of these dangers, many adults have taken steps to keep children safe. However, most adults are not aware of the potential risks of using e-cigarettes and exposure to secondhand aerosol, and e-cigarette marketing often promotes these products as safe alternatives to smoking conventional cigarettes. But messaging about the dangers is essential. For example, the use of these products can lead to nicotine addiction, harm brain development, and lead to continued tobacco use.



Parents, teachers, coaches, and others can protect their children and other young people by educating them about e-cigarettes:

- Talk openly about the harms of nicotine and tobacco use.
- Express firmly the idea that young people should not use any tobacco products, including e-cigarettes.
- Do not let any individuals use e-cigarettes or other tobacco products around children.
- Ask health care providers, adults, and parents to discuss with children the health risks of using e-cigarettes, such as nicotine addiction.
- Patronize restaurants and other places that do not allow the use of e-cigarettes indoors, and let business owners that allow e-cigarette use indoors know that it is not as safe as clean air or even legal in many places.
- Make sure children's day care centers, schools, and universities are completely tobacco-free, including being free of e-cigarettes. A comprehensive tobacco-free campus policy prohibits any tobacco use, including e-cigarettes, on school property by anyone at any time. These policies should be expanded to include school events that are held off campus.
- Prohibit tobacco and e-cigarette company sponsorship of teams or events, promotional activities, and offers of educational materials for preventing tobacco use among youth.
- Make homes and cars completely tobacco-free, including the use of e-cigarettes. This means no use by family members, friends, or guests. Opening a window does not fully protect against exposure to secondhand cigarette smoke or from the secondhand aerosol from e-cigarettes. For youth and young adults to be fully protected from indoor exposure, all indoor environments must be 100% free from tobacco smoke and e-cigarette aerosol.
- Set an example by being tobacco-free.
- Provide positive support and encouragement to anyone who is trying to quit tobacco.

E-cigarettes are now the most common form of tobacco used by young people. High school students use e-cigarettes more than adults.



Research suggests that youth and young adults are not as aware of the health consequences of e-cigarette use as they are with the consequences of cigarette smoking (Chapter 2) (Pearson et al. 2012; Richardson et al. 2014; Tan and Bigman 2014). FDA has the authority to require health warnings on tobacco products and tobacco advertising. In addition, FDA and other federal entities, along with state and local organizations, can carry out educational campaigns to better inform the public, especially parents, and increase their understanding of the harms of e-cigarette use.

Strategy 2B.

Educate health professionals about the risks of e-cigarette use among youth and young adults.

The health care setting is an ideal place to educate people of all ages on the potential risks of e-cigarette use and exposure to secondhand aerosol from e-cigarettes. Because e-cigarettes are a relatively new product, health care professionals frequently face a lot of questions about them. These often include questions related to the risks of using e-cigarettes and whether these products can help people to quit smoking. No e-cigarettes have been approved as safe and effective cessation aids.

For youth, in particular, sufficient evidence shows that the use of nicotine is not safe regardless of the delivery device: combustible, non-combustible, or electronic (USDHHS 2014; see also Chapter 3). Thus, health care professionals should warn youth and youth influencers, such as parents, about the health risks of using any product that contains nicotine, including e-cigarettes. They should also warn youth about the dangers of using other substances, such as marijuana, in e-cigarette devices (American Academy of Pediatrics 2015).



Goal 3. Continue to Regulate E-Cigarettes at the Federal Level to Protect Public Health

In 2009, the *Family Smoking Prevention and Tobacco Control Act* (Tobacco Control Act) provided FDA with authority to regulate tobacco products in a manner that is “appropriate for the protection of public health” (e.g., §§ 906(d)(1), 907(a)(3)(A) & (a)(4)(A), and § 910(c)(2)(A) of the *Federal Food, Drug, and Cosmetic Act*, as amended by the Tobacco Control Act) (*Family Smoking Prevention and Tobacco Control Act* 2009, p. 1786). The Tobacco Control Act also requires FDA to consider in regulatory actions the health effects at the individual and population levels, including the impacts on the initiation of measures taken to quit tobacco use as well as effects on relapse among former tobacco users. But FDA is not the only federal agency that can address certain aspects of e-cigarettes (see Chapter 5, Table 5.2).

**Strategy 3A.**

Implement FDA regulatory authority over the manufacturing, marketing, and distribution of e-cigarettes.

A federal appellate court decision titled *Sottera, Inc. v. Food & Drug Administration* (2010) determined that FDA can regulate e-cigarettes and other products made or derived from tobacco under the Tobacco Control Act, and that these products are not drugs or devices under the *Food, Drug, and Cosmetic Act* unless marketed as therapeutic or smoking cessation products. In May 2016, FDA finalized a rule deeming most products meeting the definition of a tobacco product, including e-cigarettes, subject to regulation under the Tobacco Control Act. The regulation went into effect on August 8, 2016 (but is under litigation) (FDA 2016).

FDA's rule for e-cigarettes includes several provisions that can help protect youth and young adults from the harms of e-cigarettes, such as the following:

- Prohibiting the sale of e-cigarettes to youth who are under 18 years of age (both in person and online);
- Requiring proof of age at the point of purchase;
- Prohibiting vending machine sales in all facilities where children are allowed to enter;
- Prohibiting the distribution of free samples;
- Requiring health warnings about nicotine on packaging and in advertisements;
- Requiring manufacturers to register their e-cigarette products with FDA and disclose the ingredients and levels of harmful and potentially harmful constituents in those products to that agency;
- Requiring premarket review of new or changed tobacco products and authorization by FDA before they can be introduced into the marketplace; and
- Requiring manufacturers that intend to market e-cigarettes for use to reduce harm or risk of tobacco-related disease to receive authorization from FDA based on scientific evidence that the product is less harmful or presents less risk to the public.

This authority allows FDA to undertake future regulatory actions, if determined appropriate for the protection of public health, including:

- Within constitutional limitations, restricting promotion, marketing, and advertising of e-cigarettes;
- Restricting Internet sales and requiring age verification on websites and upon delivery;
- Prohibiting characterizing flavors;
- Promulgating product standards to reduce the toxicity, addictiveness, or appeal of tobacco products;
- Regulating packaging, including requiring minimum package sizes, mandating child-resistant packaging, and requiring health warnings; and
- Prohibiting self-service displays.

Despite gaining this broad authority, FDA does not have specific authority for certain regulatory actions. For example, FDA generally does not restrict tobacco use in public places, levy taxes on tobacco products, or restrict sales to only certain types of retailers (e.g., pharmacies); and FDA cannot completely eliminate nicotine in tobacco products, require prescriptions for tobacco products, or raise the minimum age for sale of tobacco products above 18.



Other complementary comprehensive tobacco control strategies at the state, local, tribal, and territorial levels include:

- Implementing comprehensive clean indoor air laws;
- Prohibiting sales to those under 21 years of age;
- Increasing prices of tobacco products; and
- Developing high-impact countermarketing campaigns.

Effective action at the state and local levels is critical to fully protecting young people from the harms of e-cigarettes.

Strategy 3B.

Reinforce other federal agencies as they implement programs and policies to address e-cigarettes.

Of the other federal agencies that play a role in implementing strategies to address e-cigarettes (see Chapter 5, Table 5.2), some target specific populations (e.g., the Department of Defense and the U.S. Department of Veterans Affairs); others cover specific areas (e.g., the General Services Administration, National Park Service); and some focus on certain aspects of e-cigarettes (e.g., the Federal Trade Commission, the U.S. Department of Transportation, and the U.S. Environmental Protection Agency). Specific strategies to address e-cigarettes could include those that protect employees, customers, and visitors from exposure to secondhand aerosol, support and encourage tobacco cessation, and curb youth-targeted or false advertising. For example, the National Park Service (2015) implemented a policy to protect employees and visitors from exposure to secondhand aerosol from e-cigarettes.

Goal 4. Programs and Policies to Prevent E-Cigarette Use among Youth and Young Adults

Subject to certain exceptions, the Tobacco Control Act does not limit the authority of state, local, tribal, and territorial governments to enact any tobacco-related policies related to the sale, distribution, or possession of tobacco products; exposure to these products; or access to them. This broad preservation of authority enables states and localities to adopt many comprehensive tobacco control strategies that have been proven to prevent and reduce tobacco use among youth and young adults. That means that state, local, tribal, and territorial governments could act first in developing regulations, policies, and programs that minimize any individual- and population-level harms of e-cigarettes. The strongest, most innovative tobacco control policies typically have originated at the local level before eventually being adopted at the state level. However, it is important that these strategies are developed with evaluators and epidemiologists that can collect robust data to inform the implementation and sustainment of such strategies.

Strategy 4A.

State, local, tribal, and territorial governments should implement population-level strategies to reduce e-cigarette use among youth and young adults, such as including e-cigarettes in smokefree indoor air policies, restricting youth access to e-cigarettes in retail settings, licensing retailers, and establishing specific package requirements.



Over 50 years of research offers a strong body of evidence on the effectiveness of certain tobacco prevention and control measures. Much of this evidence can also be applied to e-cigarettes. And from this evidence, state, local, tribal, and territorial entities can take a variety of actions to address e-cigarettes, such as:

- Including e-cigarettes in smokefree indoor air policies;
- Restricting youth access to e-cigarettes in retail settings;
- Licensing retailers; and
- Establishing specific package requirements.

Including E-Cigarettes in Smokefree Indoor Air Policies

Most smokefree indoor air policies were put in place before the great rise in e-cigarette use. Because of that, these policies may not cover e-cigarettes or exposure to the aerosol they produce. Aerosol from e-cigarettes is not harmless (CDC 2014). Smokefree indoor air policies should be updated to prohibit the use of both conventional cigarettes and e-cigarettes, thereby preserving standards for clean indoor air. Efforts to include e-cigarettes in smokefree laws should also uphold or strengthen, not weaken, existing protections against exposure to secondhand smoke.

Including e-cigarettes in smokefree indoor air policies can:

- Eliminate health risks from exposure to secondhand aerosol from e-cigarettes;
- Discourage people from using both combustible and electronic tobacco products (dual use);
- Simplify compliance with and enforcement of existing smokefree laws;
- Help to reduce the use of e-cigarettes among youth and young adults; and
- Maintain tobacco-free norms.

Aerosol from e-cigarettes is not harmless.
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To date, several states and several hundred communities include e-cigarettes in comprehensive smoke-free laws that prohibit smoking in all indoor areas of public places,

including worksites, restaurants, bars, and gambling facilities (Americans for Nonsmokers' Rights Foundation 2015; CDC n.d.).



Restricting Youth Access to E-Cigarettes

When laws prohibiting tobacco sales to youth are strong and actively enforced with the education of retailers, they successfully reduce tobacco use among youth (Task Force on Community Preventive Services 2001; Zaza et al. 2005). To date, all 50 states and the District of Columbia restrict the sale of tobacco products to minors (CDC n.d.). Extending such laws to include e-cigarettes can further protect youth from exposure to nicotine, which nearly all states have done. Specific strategies can be implemented to deter the access of youth to e-cigarettes and their use in this population:

- Restricting the sale of e-cigarettes to minors;
- Placing restrictions on Internet sales of all tobacco products and e-cigarettes, including requirements for verifying age and providing identification at the time of purchase and upon delivery;
- Requiring age verification at the point of purchase;
- Displaying clear signage in retail locations about required age for sale;
- Prohibiting the sale of e-cigarettes from vending machines;
- Eliminating self-service displays of e-cigarettes; and
- Enforcing laws on the retail sale of e-cigarettes to minors.

Nearly all states prohibit the sale of e-cigarettes to youth under 18 years of age. Some states have a higher minimum age for purchase (e.g., 19 or 21 years of age) (CDC 2014). Some e-cigarette manufacturers have supported state legislation to prevent minors from purchasing e-cigarettes (Healy 2014). Their actions may, to some extent, be responsible for why these age-of-sale laws have been adopted more quickly than laws that prohibit e-cigarette use in public indoor spaces. However, industry-supported, youth-access bills have contained provisions that undermine prevention efforts for youth, including preemption of stricter local policies and weak requirements for enforcement (USDHHS 2012). Additionally, laws prohibiting sales to minors are likely to have limited effectiveness as a prevention

strategy if they are not aggressively enforced and are not coupled with proven interventions, such as comprehensive smoke-free laws, pricing strategies, or public health campaigns (USDHHS 2012, 2014). Ensuring that e-cigarettes are regulated at the state and local levels can facilitate the application of additional tobacco control policies regarding e-cigarettes.

Many actions can help to protect young people from the harms of e-cigarettes, such as including e-cigarettes in smokefree indoor air policies, restricting youth access to e-cigarettes *in retail settings*, *licensing retailers*, and *setting specific package requirements*.

Licensing Retailers

Licensing is another strategy to control access to e-cigarettes among youth and young adults. A tobacco-related license can authorize a business to manufacture, distribute, or sell tobacco products (McLaughlin 2010). Licensing requirements help to prevent sales to minors, prevent evasion of tobacco excise taxes, ensure that licensees comply with tobacco-related laws, and promote safe manufacturing practices (ChangeLab Solutions 2012). Businesses that repeatedly violate these laws can have their right to engage in commercial activity suspended or their licenses permanently removed. The possibility of these outcomes provides a strong incentive to comply with license requirements. Licensing may also be used to restrict the sale of flavored products or to address consumer and worker safety issues involved with the mixing of liquids for e-cigarette products (e-liquids).



Establishing Specific Packaging Requirements

Federal, state, local, tribal, and territorial governments are actively considering the potential harms of e-liquids. Exposure to these liquids may lead to nicotine and other types of poisoning. Calls to poison control centers about e-cigarettes and e-liquids have been on the rise, and about half of these calls are for incidents involving young children (American Association of Poison Control Centers 2015). The most common adverse health effects of poisoning are vomiting, nausea, and eye irritation, but some deaths have occurred as well. Developing strategies to monitor and prevent future poisonings is critical.

Calls to poison control centers about e-cigarettes are on the rise. A large portion of these calls are for incidents involving young children.

Enacting laws that require e-liquids to be labeled and sold in childproof packaging is one way to reduce the incidence of poisonings, particularly among children. To date, in addition to the federal *Child Nicotine Poisoning Prevention Act of 2015* (2016) enacted in January 2016, more than a dozen states have enacted laws requiring childproof packaging for e-liquids (Tobacco Control Legal Consortium n.d.). Health care providers, the public health community, e-cigarette manufacturers and retailers, and the public should be aware that e-liquids pose a serious public health concern, particularly among young children.

Strategy 4B.

Coordinate, evaluate, and share best practices from state and local entities that have implemented programs and policies to address e-cigarette use among youth and young adults.

Many governments at the national, state, local, tribal, and territorial levels are involved in the regulation of e-cigarettes. To have the biggest impact on reducing the use and exposure of e-cigarettes among youth and young adults, it is integral for these governments to share best practices and coordinate and evaluate efforts as part of a comprehensive tobacco prevention and control strategy. FDA has asserted regulatory authority over e-cigarettes, and other agencies and governments, as discussed previously and in Chapter 5, also have relevant authorities.

Goal 5. Curb Advertising and Marketing That Encourages Youth and Young Adults to Use E-Cigarettes

Unconstrained marketing of e-cigarettes drives consumer demand for these products. E-cigarette manufacturers are using tactics similar to those used to market conventional cigarettes to youth, including offering candy-flavored products; employing youth-minded themes, such as rebellion, glamour, and sex; getting celebrity endorsements; and obtaining sports and music sponsorships (Chapter 4). Some groups have called for extending to e-cigarettes the same marketing restrictions that already apply to conventional cigarettes and other tobacco products (Association of State and Territorial Health Officials 2014; Partnership for Prevention 2014). But regulating commercial speech is typically met with significant barriers and complex legal issues (Laird-Metke 2010), and partial advertising bans and voluntary agreements generally have not been fully effective at reducing consumption because the tobacco industry adapts by shifting to other types of advertising that are not regulated (National Cancer Institute 2008). Despite these obstacles, public health organizations and state and local governments must take action to control the marketing of e-cigarettes to youth and young adults, including (a) seeking legally feasible interventions that are proven to curb youth-oriented tobacco marketing, including removing advertising from television; and (b) continuing to help build an evidence base that informs future potential restrictions on e-cigarette marketing.

Strategy 5A.

Curb e-cigarette advertising and marketing that are likely to attract youth and young adults.

In the absence or delayed implementation of government restrictions on the marketing of e-cigarettes, media outlets, the management staff of special event and sports venues, and retailers can voluntarily refuse to air or place youth- and young adult-oriented e-cigarette advertising; avoid sponsorships; and not offer free samples of these products at fairs, festivals, and other events.

E-cigarettes are aggressively marketed using tactics similar to those proven to lead to cigarette smoking among youth.

Finally, state and local public health agencies can stimulate enforcement of and compliance with existing rules that limit marketing. For example, they can monitor advertising and notify their state's attorney general or the Federal Trade Commission about improper claims or marketing that is not clearly identified as advertising (*Federal Register* 1972; FTC 1984; Center for Public Health and Tobacco Policy 2013).

Strategy 5B.

Urge the e-cigarette companies to stop advertising and marketing that encourages and glamorizes e-cigarette use among youth and young adults.

E-cigarette advertising has increased considerably over the years in multiple venues (Legacy for Health 2014; Ganz et al. 2015; see also Chapter 4), while the advertising for conventional cigarettes on television has been prohibited in the United States since 1971. But e-cigarettes are now marketed on television and other mainstream media channels, such as radio and magazines, which are main sources of information for youth and young adults. Emerging research suggests that exposure to television advertisements for e-cigarettes increases the likelihood that young people will use e-cigarettes in the future and will believe that e-cigarettes can be used in places where conventional cigarette smoking is not allowed (Farrelly et al. 2015). This is not surprising because e-cigarette marketing has previously included unproven claims about safety and smoking cessation, as well as statements that e-cigarettes are exempt from clean air policies that restrict smoking (USDHHS 2014). Visual depictions of e-cigarette use in advertisements may also serve as smoking cues to both current and former smokers, increasing their urges to smoke and undermining their efforts to quit (Maloney and Cappella 2015). Advertising for e-cigarettes that encourages and glamorizes the use of e-cigarettes among youth and young adults can harm public health by undermining:

- Clean indoor air standards;
- Enforcement of smokefree policies;
- Tobacco-free social norms; and
- Marketing restrictions that prohibit the advertising of cigarettes and smokeless tobacco on television and radio.

Discontinuing advertising and marketing by e-cigarette companies that intentionally or unintentionally encourages or glamorizes e-cigarette use among youth and young adults is essential. Responsible advertising by the e-cigarette companies is needed, including advertising that focuses directly on established adult smokers and features adults (not young adults), does not depict active use of e-cigarettes, does not use themes proven to appeal to youth and young adults, avoids media channels with high youth access, and does not undermine cessation efforts involving traditional tobacco products.

Goal 6. Expand Surveillance, Research, and Evaluation Related to E-Cigarettes

Tobacco control research focused on e-cigarettes has grown considerably in the past few years. Certainly, more detailed information is needed to better understand the use of e-cigarettes and its relationship to the use of other types of tobacco products. A comprehensive and evolving approach to research, surveillance, and evaluation is needed.

Strategy 6A.

Improve the quality, timeliness, and scope of e-cigarette surveillance, research, and evaluation.



Present surveillance systems show that e-cigarette use is increasing rapidly and that most regular e-cigarette users also use conventional tobacco products (see Chapter 2). Thus, further study can inform strategies that minimize harms and maximize the potential health benefits of these products at the individual and population levels. Data should be timely and focus on the patterns of e-cigarette initiation and use among the general public—including youth, young adults, and former smokers. Strategic and comprehensive research and evaluation must further characterize the health risks of e-cigarette use. A comprehensive package of surveillance, research, and evaluation should:

- Track patterns of e-cigarette use through cross-sectional surveys and through panels that follow the same people, including youth and young adults, over time;
- Monitor trends in the e-cigarette retail market by type of product;
- Examine the channels and messaging in the e-cigarette marketplace to inform proactive countermarketing strategies;

- Assess the short- and medium-term health effects of e-cigarette use by youth and young adults and track long-term consequences;
- Examine the risk factors and other risk behaviors that may be associated with using e-cigarettes; and
- Create a model to develop and track the public health impact of e-cigarettes.

The rapidly changing nature of the e-cigarette landscape calls for a comprehensive and evolving approach to research, surveillance, and evaluation.

For such a package, researchers, the public health community, and other key stakeholders must work together to address and overcome many challenges:

- The rapidly changing e-cigarette landscape and terminology;
- Limited resources for collecting timely information;
- The cross-sectional nature of existing surveys and their limited space for questions;
- The different populations that need to be studied;
- A lack of validated questions; and
- Different measures and definitions across surveys.

Strategy 6B.

Address surveillance, research, and evaluation gaps related to e-cigarettes.

Patterns of e-cigarette use are rapidly changing among youth and young adults, as well as among other groups in the population. Longitudinal data are not yet available to address some of the most critical issues related to e-cigarettes. The e-cigarette marketplace is changing so fast that surveillance data and research on the harms of e-cigarette use and the impact of these changes on traditional tobacco products are lagging behind. As they look to fill in gaps in scientific research, it is important for researchers to continue to seek more current and complete answers to many critical questions, such as:

- What are the risks of progressing to traditional tobacco use among youth and young adults who have used e-cigarettes?
- What are the health risks posed by e-cigarettes?
- Are e-cigarettes safer and more effective than current products at helping smokers with smoking cessation?
- What are the health consequences for youth and young adults of initiation of e-cigarettes and of dual use (conventional cigarettes plus e-cigarettes) compared with the health benefits of completely quitting smoking (or not starting at all)?
- What are the health risks to former smokers who are exposed to nicotine from e-cigarette use? Will these persons be more likely to resume smoking?

Additionally, surveillance of e-cigarette marketing and the advertising messages and strategies used is critical, as is the carrying out of more studies assessing the link between exposure to e-cigarette marketing and use of these products. With traditional tobacco

products, state and local public health agencies have monitored retail settings, assessed outdoor advertising, and identified sponsorships of events by tobacco companies. These efforts should be adapted to e-cigarettes.

The health care setting has always been an important venue for exchanging information about evidence-based approaches to smoking cessation and for protecting susceptible groups from exposure to secondhand smoke. More research is needed on the role of e-cigarettes in facilitating or hindering cessation of conventional cigarettes and the potential hazards of exposure to secondhand aerosol from e-cigarettes so that e-cigarettes can also be a part of this exchange. But even without this research, there is sufficient evidence about the dangers that nicotine-containing cigarettes pose for youth and young adults that health care providers and professionals can act now to prevent the use of such products among their young patients.

Finally, existing research and surveillance efforts should include more detailed measures than just general use of e-cigarettes, including:

- Frequency and patterns of e-cigarette use;
- Type of e-cigarette and/or other tobacco product used;
- The natural history of e-cigarette use, including initiation, co-use with other tobacco products, and flavoring;
- Ingredients, such as nicotine and flavors;
- Brand;
- Reasons for using and quitting e-cigarettes;
- Exposure to e-cigarette advertising;
- Methods of obtaining e-cigarettes; and
- Exposure to secondhand aerosol from e-cigarettes.

Additionally, evaluation is critical to further assess the impact of policies on e-cigarette initiation, use, and other patterns of tobacco use.

Conclusion

E-cigarette use, particularly among youth and young adults, has become a public health concern that warrants immediate and coordinated action. The increase in e-cigarette use among youth and young adults in the past few years is cause for great concern. Many questions remain about e-cigarettes and their long-term impact, even as evidence on patterns of use and risks to health continue to emerge. But we know enough about these health risks to take action now to protect the health of our nation's young people. We cannot wait. Strategies to prevent and control the harms of e-cigarettes among youth and young adults need to be precautionary. Therefore, we must take a precautionary approach by implementing these strategies and protecting the health of our nation's young people.



We know what works to effectively prevent tobacco use among young people. Now we must apply these strategies to e-cigarettes—and continue to apply them to other tobacco products. To achieve success, we must work together, aligning and coordinating efforts across a wide range of stakeholders. We must protect our nation’s young people from a lifetime of nicotine addiction and associated problems by immediately addressing e-cigarettes as an urgent public health problem. Now is the time to take action.

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APPENDIX: LIST OF ABBREVIATIONS

[125I]A-85380 binding	measurement of binding at $\alpha 4\beta 2$ nAChRs using the agonist A-85380
[125I] α -CtxMII binding	measurement of binding at $\alpha 6$ nAChRs using the antagonist alpha-conotoxin MII
5AP tLTP protocol	5 action potential timing-dependent long-term potentiation protocol
5-CSRTT	5-choice serial reaction time task
5-HIAA	5-hydroxyindole acetic acid, the primary metabolite of serotonin
5-HT1AR	serotonin (5-hydroxytryptamine) receptor 1A
5-HT2A/C	serotonin (5-hydroxytryptamine) receptor 2 A/C
86Rb ⁺ efflux assay	measure of nicotinic acetylcholine receptor function via rubidium-86 ion efflux [125-I] α -Btx binding measurement of binding at $\alpha 7$ nAChRs using the antagonist alpha-bungarotoxin
$\alpha 4\beta 2$	alpha 4 beta 2-nicotinic acetylcholine receptor subtype
$\alpha 6$	alpha 6 nicotinic acetylcholine receptor subtype
$\alpha 7$	alpha 7 nicotinic acetylcholine receptor subtype
μ g	microgram
A1	primary auditory cortex
AAP	American Academy of Pediatrics
AARC	American Association for Respiratory Care
ACP	American College of Physicians
ACR	American Association of Cancer Research
ACS	American Cancer Society
ADHD	attention deficit hyperactivity disorder
ADI	acceptable daily intake
AEMSA	American E-Liquid Manufacturing Standards Association
AHA	American Heart Association
AMPA	α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AMPA	AMPA receptor
ANHCS	Annenberg National Health Communication Survey
ANR	Americans for Nonsmokers' Rights
AOR	adjusted odds ratio
AP	acetyl propionyl
APA	American Psychiatric Association
APV	advanced personal vaporizers
Arc	activity-regulated cytoskeleton-associated protein
ATF	U.S. Department of Justice, Bureau of Alcohol, Tobacco, Firearms and Explosives
A-V	atrial-ventricular
AVA	American Vaping Association
BART	Balloon Analogue Risk Task
BCAP/CAP	Committees of Advertising Practice (UK)
BLA	basolateral amygdala
BNST	bed nucleus of the stria terminalis
BOP	Bureau of Prisons
BP	blood pressure
CAD	cinnamaldehyde
CAM	cell-adhesion molecule
cAMP-PKA	cyclic AMP-protein kinase A, signaling cascade

CARDIA	Coronary Artery Risk Development in Young Adults
CASAA	Consumer Advocates for Smoke-free Alternatives Association
CCTA	Contraband Cigarette Trafficking Act
CDC	Centers for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
C-DISC-IV	Diagnostic Interview for Children—Version 4
<i>cFos</i>	protooncogene and immediate early gene used as a marker of neuronal activity
CFR	Code of Federal Regulations
CI	confidence interval
CMS	Centers for Medicare & Medicaid Services
CO ₂	carbon dioxide
COMDTINST	Commandant Instruction
CPP	conditioned place preference
CPu	caudate putamen
CREB	cAMP response element-binding protein
CRF	corticotropin-releasing factor
CRP	C-reactive protein
CSI	Child Symptom Inventory
CTA	conditioned taste aversion
CTP	Center for Tobacco Products
D1R	dopamine D1 receptor
DA	diacetyl
DA	dopamine
DAT1	dopamine regulation genotype
DEHP	diethylhexyl phthalate
DEP	diethyl phthalate
DHS	U.S. Department of Homeland Security
DISC-YC	Diagnostic Interview Schedule for Children-Parent Scale-Young Child
DoD	U.S. Department of Defense
DOPAC	3,4-dihydroxyphenylacetic acid, metabolite of dopamine
DOT	U.S. Department of Transportation
DSM-III	Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
EC	electronic cigarette
ECIG Inc.	Electronic Cigarette Industry Group, Inc.
ECIG Ltd.	Electronic Cigarettes International Group, Ltd.
ED	U.S. Department of Education
ENDS	electronic nicotine delivery systems
ENNDS	electronic non-nicotine delivery systems
EOP	Executive Office of the President
EPA	U.S. Environmental Protection Agency
EPSC	excitatory postsynaptic current
EPSDT	Early and Periodic Screening, Diagnosis and Treatment
EPSP	excitatory postsynaptic potential
ERS	European Respiratory Society
ESD	electronic smoking device
EU	European Union
F1	first filial generation (and similar)
FAA	Federal Aviation Administration

FCC	Federal Communications Commission
FCLAA	Federal Cigarette Labeling and Advertising Act
FCTC	Framework Convention on Tobacco Control
FD&C Act	Federal Food, Drug, and Cosmetic Act
FDA	U.S. Food and Drug Administration
FEF	forced expiratory flow
FeNO	exhaled nitric oxide
FEV1	forced expiratory volume in 1 second
fMRI	functional magnetic resonance imaging
FR	fixed ratio
FST	forced swim test
FTC	U.S. Federal Trade Commission
FVC	forced vital capacity
FY	fiscal year
g	gram
G20	gestational day 20 (and similar)
GABA	gamma-aminobutyric acid
GABAergic	any cell, especially any neuron, that releases GABA
GPCR	G-protein-coupled-receptor
GSA	General Services Administration
GTP	guanosine triphosphate
GTPase	large family of hydrolase enzymes that can bind and hydrolyze GTP
HONC	Hooked on Nicotine Checklist
HPLC-ECD	high-performance liquid chromatography electrochemical detection
HUD	U.S. Department of Housing and Urban Development
HVA	homovanillic acid
i.p.	intraperitoneal
i.v.	intravenous
IARC	International Agency for Research on Cancer
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th revision
ICE	Bureau of Immigration and Customs Enforcement
ICR mice	Institute for Cancer Research strain of mice
ICSS	intracranial self-stimulation
IOM	Institute of Medicine
IQ	intelligence quotient
IRC	Internal Revenue Code
kg	kilogram
KO	knockout
L	liter
L&M	Liggett & Myers
LC-MS/MS	liquid chromatography-tandem mass spectrometry
LH	lateral hypothalamus
M&As	mergers, formations of partnerships, and acquisitions
m ²	square meter
m ³	cubic meter
MAOA	monoamine oxidase A
MAPK	mitogen-activated protein kinase
MCH	melanin-concentrating hormone
mFTQ	modified Fagerström Tolerance Questionnaire

mg	milligram
mGluR2	metabotropic glutamate receptor 2
mL	milliliter
mPFC	medial prefrontal cortex
mRNA	messenger ribonucleic acid
MSN	medium spiny neuron
MTF	Monitoring the Future
N ₂	nitrogen
NAB	N-nitrosoanabasine
NAc	nucleus accumbens
NACDA	National Advisory Council on Drug Abuse
nAChR	nicotinic acetylcholine receptor
NAc-shell	nucleus accumbens shell
NAT	N-nitrosoanatabine
NATS	National Adult Tobacco Survey
NCI	National Cancer Institute
NDAA	National Defense Authorization Act
NDSS	Nicotine Dependence Syndrome Scale
NE	norepinephrine
ng	nanogram
NGFI-B	nerve growth factor-induced gene-B
NHANES III	Third National Health and Nutrition Examination Survey
NHSDA	National Household Survey on Drug Abuse
NIDA	National Institute on Drug Abuse
NIH	National Institutes of Health
NIOSH	National Institute for Occupational Safety
NJYTS	New Jersey Youth Tobacco Survey
NLSY	National Longitudinal Survey of Youth
nm	nanometer
NMDAR	N-methyl-d-aspartate receptor
NNK	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
NNN	N-nitrosornicotine
NRT	nicotine replacement therapy
NYS	New York State Follow-Up
NYTS	National Youth Tobacco Survey
O ₂	oxygen
ODD	oppositional defiant disorder
OMB	Office of Management and Budget
OPM	Office of Personnel Management
OR	odds ratio
OSH	Office on Smoking and Health
OSHA	U.S. Department of Labor, Occupational Safety and Health Administration
p.o.	per os (by mouth)
P3 (and similar)	postnatal day number
PACT	Prevent All Cigarette Trafficking Act
PAH	polycyclic aromatic hydrocarbon
PATH	Population Assessment of Tobacco and Health
PDAY	Pathological Determinants of Atherosclerosis in Youth
PFC	prefrontal cortex
PG	propylene glycol

PHS	Public Health Service
PIH	Public and Indian Housing
PM	particulate matter
PM _{2.5}	fine particulate matter
PNE	prenatal nicotine exposure
Postn	periostin, osteoblast-specific factor
PR	progressive ratio
PREP	potential reduced-exposure product
PVN	paraventricular nucleus of the thalamus
PVN	paraventricular nucleus of the thalamus
qRT-PCR	quantitative real-time polymerase chain reaction
RCRA	Resource Conservation and Recovery Act
s.c.	subcutaneous
SAC	saccharin
SAMHSA	Substance Abuse and Mental Health Services Administration
SCAN	Screening test for Auditory Processing Disorders
SD	standard deviation
SE	standard error
sec	seconds
SEC	Securities and Exchange Commission
SES	socioeconomic status
SFATA	Smoke Free Alternatives Trade Association
SIDS	sudden infant death syndrome
SMC	serial multiple choice
SNAP	Special Supplemental Nutrition Program
SNP	single-nucleotide polymorphism
SRITA	Stanford Research into the Impact of Tobacco Advertising
STOP	Smuggled Tobacco Prevention Act
TCR	trigeminocardiac reflex
TEOAEs	transient evoked otoacoustic emissions
TH	tyrosine hydroxylase
THC	tetrahydrocannabinol
TSNA	tobacco-specific nitrosamine
TTB	U.S. Department of Treasury, Alcohol and Tobacco Tax and Trade Bureau
TVECA	Tobacco Vapor Electronic Cigarette Association
U.S.C.	U.S. Code
UK	United Kingdom
USDA	U.S. Department of Agriculture
USDHEW	U.S. Department of Health, Education, and Welfare
USDHHS	U.S. Department of Health and Human Services
USP	U.S. Pharmacopeia
USTR	U.S. Trade Representative
V	voltage
VA	U.S. Department of Veterans Affairs
VG	vegetable glycerin
VOC	volatile organic compound
VTA	ventral tegmental area
w/v	weight/volume
WHO	World Health Organization
WIC	Women, Infants, and Children

Wnt	Wingless-Type MMTV Integration Site Family, member 1, intracellular signaling factors
WT	wild type
YRBSS	Youth Risk Behavior Surveillance System

Chapter 358

ELECTRONIC CIGARETTES: U.S. IMPORTS IN 2016*

United States Government Accountability Office

The Honorable Ron Wyden
Ranking Member Committee on Finance
United States Senate

Dear Senator Wyden:

Over the last decade, use of electronic cigarettes, known as e-cigarettes, in the United States has grown rapidly as use of traditional cigarettes declined among both adolescents and adults. As we reported in May 2015, most e-cigarettes sold in the United States were thought to be imported, but e-cigarette import volume and tariff revenue were unknown because the Harmonized Tariff Schedule of the United States (HTS) did not contain separate statistical reporting numbers (also known as 10-digit HTS numbers or codes) specific to e-cigarettes.¹ Instead, imports of e-cigarette devices, e-cigarette parts, and e-cigarette liquid were entered under HTS statistical reporting numbers that the U.S. International Trade Commission (USITC) calls basket categories, which cover a range of goods.

An e-cigarette device typically contains a battery, a heating element, and a cartridge or tank that can be empty or filled with liquid. Major e-cigarette parts include heating elements and cartridges, which can be imported separately from devices. E-cigarette liquid—which can contain nicotine in different concentrations or have no nicotine—can also be imported separately from both devices and cartridges.

* This is an edited, reformatted and augmented accessible version of the United States Government Accountability Office Publication No. GAO-17-515R, dated April 24, 2017.

¹ GAO, *Electronic Cigarettes: Imports, Tariffs, and Data Collection*, GAO-15-491R (Washington, D.C.: May 7, 2015). All goods imported into the United States are classified by U.S. Customs and Border Protection according to the HTS. The HTS, published and maintained by the U.S. International Trade Commission, provides the legal basis for the classification of every product that enters the United States and the corresponding tariff rate the importer must pay for each product. The HTS contains numbered provisions at the 2-, 4-, 6-, 8-, and 10-digit level. The 10-digit provision is known as a statistical reporting number that can be used for tracking and reporting trade statistics.

In the fall of 2015, the Committee for Statistical Annotation of Tariff Schedules—comprising representatives from USITC, U.S. Customs and Border Protection (CBP), and the U.S. Census Bureau (Census)—established six new statistical reporting numbers for e-cigarette devices, parts, and liquid in the HTS. The six new statistical reporting numbers went into effect on January 1, 2016, and covered

- e-cigarette liquid that contains 5 percent or more by weight of nicotine (3824.90.2840) or less than 5 percent by weight of nicotine (3824.90.9280),²
- e-cigarette devices with cartridges that contain liquid with nicotine (8543.70.9630) or without nicotine (8543.70.9640),³ and
- e-cigarette parts, including cartridges imported separately from devices that contain liquid with nicotine (8543.90.8850) or without nicotine (8543.90.8860).

You requested that we report on e-cigarettes imported into the United States in 2016. We analyzed the e-cigarette import data for calendar year 2016, the first year such data were collected by the U.S. government. To analyze U.S. e-cigarette imports, we used 2016 data that were available in February 2017 from the public Interactive Tariff and Trade DataWeb database maintained by USITC, which incorporates U.S. trade statistics published by Census.⁴ We analyzed import data for the six statistical reporting numbers that covered e-cigarette devices, parts, and liquid in calendar year 2016. For each statistical reporting number, we analyzed customs value, dutiable customs value, tariff revenue, country of origin, and port of entry. We also analyzed data on quantities for the four e-cigarette statistical reporting numbers for which quantity is tracked.

U.S. import data are collected by CBP from records submitted by importers. These data are then incorporated into the official trade statistics published by Census. We used unrevised 2016 trade data. Census revises trade data periodically, and its first official revisions of 2016 trade data will be available in the summer of 2017.

To assess the reliability of the data, we reviewed agency documents about U.S. foreign trade statistics and interviewed CBP and Census officials about how the data were collected, how they were checked, and any limitations of the data. According to the officials we interviewed, the quality of trade data associated with new statistical reporting numbers improves over time both because the trade community learns to use them correctly and because Census is able to develop checks tailored for specific commodities or statistical reporting numbers. We determined that the 2016 data on U.S. e-cigarette imports that were available in February 2017 were sufficiently reliable for the purposes of presenting annual descriptive statistics but not for reporting monthly import data. We do not present monthly data in this report for the following reasons:

² Presidential Proclamation 9549 implementing international changes to the HTS, which took effect on January 1, 2017, resulted in the renumbering of HTS statistical categories 3824.90.2840 and 3824.90.9280 to 3824.99.2840 and 3824.99.9280, respectively.

³ Presidential Proclamation 9466, which took effect on July 1, 2016, resulted in the renumbering of HTS statistical categories 8543.70.9630 and 8543.70.9640 to 8543.70.9930 and 8543.70.9940, respectively. The units of quantity used for the new statistical categories were changed, enabling the tracking of the number of imported e-cigarette devices.

⁴ See <https://dataweb.usitc.gov/>.

- We observed an upward trend in overall customs value for U.S. e-cigarette imports in 2016. Based on our interviews with agency officials, we concluded that it is not yet known if the data reflect an actual trend or the importers' improved use of the new e-cigarette statistical reporting numbers over the course of 2016.
- We observed considerable monthly fluctuations in unit values (customs value divided by quantity) for e-cigarette liquid and devices. It is not yet known if these values are accurate or reflect data errors.
- We identified a notable error in the monthly data for one statistical reporting number. The 2016 data show a quantity for January 2016 for e-cigarette liquid containing less than 5 percent of nicotine by weight (classified under HTS number 3824.90.9280) that is more than 30 times the average value for the remaining months: 338,178 kilograms compared to the monthly average of 10,090 kilograms for February through December 2016. In response to our inquiries, CBP officials determined that this quantity was incorrect because of importer misclassification of some goods. According to Census officials, the corrected January 2016 data for HTS number 3824.90.9280 will be reflected in the revised 2016 data that will be released in the summer of 2017. The annual descriptive statistics we report for that e-cigarette product, and totals across all imported e-cigarette products, contain a value of zero for January, which we note in presenting the data.

We conducted this performance audit from January 2017 to April 2017 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

In summary we found the following:

- In calendar year 2016, customs value of U.S. e-cigarette imports was about \$342 million; of that amount, \$323 million was dutiable value resulting in about \$9 million in tariff revenue (see table 1). E-cigarette devices accounted for \$204 million (or almost 60 percent), parts for \$108 million (almost 32 percent), and liquid for \$30 million (almost 9 percent) of total customs value. Customs value is defined as the price actually paid or payable for merchandise when sold for exportation to the United States, excluding U.S. import tariffs (also known as duties), freight, insurance, and other charges incurred in bringing the merchandise to the United States. Dutiable value is defined as the customs value of foreign merchandise imported into the United States that is subject to tariff. In some cases, the dutiable value can be zero, if goods imported from a particular country are not subject to tariff.
- Although e-cigarettes, parts, and liquid were imported from 41 countries in 2016, e-cigarette imports from China accounted for about 91 percent of U.S. e-cigarette imports by customs value (see table 2). Imports from China also accounted for at least 98 percent of customs value for devices with nicotine and parts with and without nicotine (see table 3).

- In 2016, importers brought in 481,400 kilograms of e-cigarette liquid with higher nicotine content compared to 110,994 kilograms of liquid with lower nicotine content. From July through December 2016, importers brought in about 5.6 million e-cigarette devices with nicotine-containing liquid and about 5.3 million devices with nicotine-free liquid (see table 4).⁵
- U.S. e-cigarette imports cleared customs at 34 ports of entry; the top five ports of entry—Cleveland, Los Angeles, Savannah, Norfolk, and Seattle—accounted for 81 percent of customs value of U.S. e-cigarette imports in 2016 (see table 5).⁶

More detailed information is included in tables 1 through 5.

Table 1. Data Summary for U.S. e-cigarette imports in 2016

	E-cigarette product, Harmonized Tariff Schedule (HTS) number, and tariff rate	Customs value (dollars)	Dutiable customs value (dollars)	Tariff revenue (dollars)
Liquid ^a	E-liquid (nicotine content of 5 percent or more) HTS 3824.90.2840 Tariff rate: 6.5 percent of dutiable customs value	26,617,601	26,005,531	1,690,364
	E-liquid (nicotine content of less than 5 percent) ^b HTS 3824.90.9280 Tariff rate: 5 percent	2,888,820	2,684,570	134,249
	Subtotal for liquid	29,506,421	28,690,101	1,824,613
Devices ^c	Devices (imported with nicotine) HTS 8543.70.9630 (January–June 2016) HTS 8543.70.9930 (July–December 2016) Tariff rate: 2.6 percent	54,031,562	54,028,197	1,404,745
	Devices (imported without nicotine) HTS 8543.70.9640 (January–June 2016) HTS 8543.70.9940 (July–December 2016) Tariff rate: 2.6 percent	150,339,057	131,854,876	3,428,330
	Subtotal for devices	204,370,619	185,883,073	4,833,075
Parts ^d	Parts (imported with nicotine) HTS 8543.90.8850 Tariff rate: 2.6 percent (January–June 2016) 1.9 percent (July–December 2016)	26,302,044	26,275,168	584,030
	Parts (imported without nicotine) HTS 8543.90.8860 Tariff rate: 2.6 percent (January–June 2016) 1.9 percent (July–December 2016)	82,078,224	81,888,575	1,648,097
	Subtotal for parts	108,380,268	108,163,743	2,232,127
Total	Total	342,257,308	322,736,917	8,889,815

Source: GAO analysis of U.S. Census Bureau data as retrieved from the U.S. International Trade Commission's Interactive Trade DataWeb (accessed Feb. 9, 2017). | GAO-17-515R.

Notes: Customs value is defined as the price actually paid or payable for merchandise when sold for exportation to the United States, excluding U.S. import tariffs (also known as duties), freight, insurance, and other charges incurred in bringing the merchandise to the United States. Dutiable value is defined as the customs value of foreign merchandise imported into the United States that is subject to tariff.

^a According to the HTS, “mixtures for use in personal electric or electronic vaporizing devices means a formulated liquid, whether or not containing nicotine, and whether or not packaged for retail sale in cartridges or tanks adaptable to such devices” (see HTS ch. 38, statistical note 3). Ten-digit HTS number (also known as statistical reporting number) 3824.90.2840 covered e-cigarette liquid containing 5 percent or more by weight of nicotine; HTS number 3824.90.9280 covered liquid containing less than 5 percent by weight of nicotine. Presidential Proclamation 9549, which took effect on January 1, 2017, resulted in the renumbering of 3824.90.2840 and 3824.90.9280 to 3824.99.2840 and 3824.99.9280, respectively. Liquid quantity is tracked in kilograms.

^b In this table, the summary data for customs value, dutiable value, and tariff revenue for HTS number 3824.90.9280 cover the period from February through December 2016 because of an error in the January 2016 data. According to U.S. Census Bureau officials, the corrected January 2016 data for HTS number 3824.90.9280 will be reflected in the revised 2016 data that will be released in the

^c HTS numbers for devices cover both closed-system and open-system e-cigarettes if they are imported as functional devices with or without cartridges. The difference between the two sets of HTS numbers for devices is nicotine content. Presidential Proclamation 9466, which took effect on July 1, 2016, resulted in the renumbering of 8543.70.9630 and 8543.70.9640 to 8543.70.9930 and 8543.70.9940, respectively. The units of quantity used for the new HTS numbers were changed, enabling the tracking of the number of imported e-cigarette devices.

⁵ Quantities were tracked for e-cigarette liquid from January 1, 2016, and began to be tracked for e-cigarette devices on July 1, 2016.

⁶ The port of entry is where imported goods clear U.S. customs and may differ from the port of unloading where goods are unloaded from the importing vessel or aircraft.

Table 1. (continued)

^d HTS numbers for e-cigarette parts cover major parts, such as heating elements and cartridges containing heating elements, that are imported separately from e-cigarette devices. Smaller e-cigarette components—such as microprocessors, batteries, tubes containing batteries, or light-emitting diode lights—that may be used for other products in addition to e-cigarettes are classified under other applicable HTS provisions. The difference between the two statistical reporting numbers for e-cigarette parts is nicotine content of substances in cartridges. The tariff rate for e-cigarette parts was 2.6 percent of dutiable customs value from January 1 through June 30, 2016. The lower tariff rate of 1.9 percent took effect on July 1, 2016, as a result of Presidential Proclamation 9466. Quantity of e-cigarette parts is not tracked.

Table 2. Customs value of U.S. e-cigarette imports by country of origin in 2016

41 countries, in actual dollars

Country	Customs value ^a	
	Dollars	Percentage
China	313,009,762	91.45
Canada	11,555,599	3.38
Mexico	9,434,594	2.76
Germany	1,998,540	0.58
United Kingdom	1,621,301	0.47
Israel	856,402	0.25
France	653,978	0.19
Austria	620,404	0.18
Japan	487,278	0.14
Switzerland	392,636	0.11
Italy	300,315	0.09
South Korea	225,664	0.07
Taiwan ^b	146,639	0.04
Denmark	133,761	0.04
Poland	121,811	0.04
Panama	109,968	0.03
Netherlands	82,164	0.02
India	73,132	0.02
Hungary	55,626	0.02
Malaysia	51,317	0.01
Singapore	47,694	0.01
Australia	39,093	0.01
Ireland	35,176	0.01
New Zealand	32,823	0.01
Slovak Republic	28,730	0.01
Sweden	28,187	0.01
Russia	26,712	0.01
Vietnam	14,960	0.00
Romania	14,010	0.00
Croatia	10,000	0.00
Spain	8,901	0.00
Costa Rica	8,393	0.00
Philippines	7,020	0.00
Indonesia	5,000	0.00
Jordan	3,721	0.00
Bulgaria	3,215	0.00
Lithuania	2,791	0.00
Norway	2,744	0.00
Slovenia	2,448	0.00
Czech Republic	2,400	0.00
Thailand	2,399	0.00
Total	342,257,308	100.00

Source: GAO analysis of U.S. Census Bureau data as retrieved from the U.S. International Trade Commission's Interactive Trade DataWeb (accessed Feb. 9, 2017). | GAO-17-515R.

^a Country totals for customs value cover the entire calendar year 2016 for all e-cigarette Harmonized Tariff Schedule (HTS) numbers except HTS number 3824.90.9280. Customs value for HTS number 3824.90.9280 covers the period from February through December 2016 because of an error in the January 2016 data. According to U.S. Census Bureau officials, the corrected January 2016 data for HTS number 3824.90.9280 will be reflected in the revised 2016 data that will be released in the summer of 2017. The top 10 countries—China (including Hong Kong) through Switzerland—account for 99.5 percent of the total customs value of U.S. e-cigarette imports.

^b The United States does not have diplomatic relations with Taiwan; the data we used list Taiwan as a country and break out imports from Taiwan separately.

Table 3. Customs value of U.S. e-cigarette imports by country of origin and product in 2016

41 countries, in millions of dollars

Country	Liquid		Devices		Parts		Total by country
	With 5 percent or more of nicotine ^a	With less than 5 percent of nicotine ^b	With nicotine ^c	Without nicotine ^d	With nicotine ^e	Without nicotine ^f	
China	24.671	1.581	53.865	125.987	26.157	80.750	313.010
Canada	0.139	0.084	-	11.214	0.016	0.103	11.556
Mexico	-	-	-	9.403	-	0.032	9.435
Germany	-	0.191	0.017	1.612	0.006	0.174	1.999
United Kingdom	0.744	0.110	0.030	0.605	0.009	0.124	1.621
Israel	0.453	-	-	0.246	-	0.158	0.856
France	0.153	0.241	0.003	0.176	0.008	0.073	0.654
Austria	0.100	0.115	0.055	0.136	0.025	0.191	0.620
Japan	0.197	0.112	0.005	0.148	-	0.025	0.487
Switzerland	-	0.104	-	0.104	0.003	0.183	0.393
Other (31 countries)	0.161	0.353	0.057	0.710	0.077	0.268	1.627
Total by product	26.618	2.889	54.032	150.339	26.302	82.078	342.257

Source: GAO analysis of U.S. Census Bureau data as retrieved from the U.S. International Trade Commission Interactive Trade DataWeb (accessed Feb. 9, 2017). | GAO-17-515R.

Notes: The top 10 countries—China (including Hong Kong) through Switzerland—account for 99.5 percent of the total customs value of U.S. e-cigarette imports. See table 2 for a complete list of countries. The numbers may not add up precisely because of rounding.

^a Harmonized Tariff Schedule (HTS) number 3824.90.2840—replaced with 3824.99.2840 on January 1, 2017—covered e-cigarette liquid containing 5 percent or more by weight of nicotine.

^b HTS number 3824.90.9280—replaced with 3824.99.9280 on January 1, 2017—covered e-cigarette liquid containing less than 5 percent by weight of nicotine. In this table, customs value for HTS number 3824.90.9280 covers the period from February through December 2016 because of an error in the January 2016 data. According to U.S. Census Bureau officials, the corrected January 2016 data for HTS number 3824.90.9280 will be reflected in the revised 2016 data that will be released in the summer of 2017.

^c HTS number 8543.70.9930—which replaced 8543.70.9630 on July 1, 2016—covers e-cigarette devices imported with cartridges filled with liquid containing nicotine.

^d HTS number 8543.70.9940—which replaced 8543.70.9640 on July 1, 2016—covers e-cigarette devices imported with cartridges filled with nicotine-free liquid.

^e HTS number 8543.90.8850 covers major e-cigarette parts, including cartridges containing heating elements and filled with liquid containing nicotine, that are imported separately from devices.

^f HTS number 8543.90.8860 covers major e-cigarette parts, including cartridges containing heating elements and filled with nicotine-free liquid, that are imported separately from devices.

Table 4. Quantity and customs value of e-cigarette liquid and devices imported into the United States in 2016

Liquid	Quantity (kg)	Customs value (dollars)
Liquid with 5 percent or more of nicotine (January–December) ^a	481,400	26,617,601
Liquid with less than 5 percent of nicotine (February–December) ^b	110,994	2,888,820
Devices	Quantity (number)	Customs value (dollars)
Devices with nicotine (July–December) ^c	5,637,744	26,066,916
Devices without nicotine (July–December) ^d	5,311,204	97,867,572

Source: GAO analysis of U.S. Census Bureau data as retrieved from the U.S. International Trade Commission's Interactive Trade DataWeb (accessed Feb. 9, 2017). | GAO-17-515R

Notes: Tracking of quantity of imported e-cigarette liquid took effect on January 1, 2016; tracking of quantity of imported e-cigarette devices began on July 1, 2016.

^a Harmonized Tariff Schedule (HTS) number 3824.90.2840—replaced with 3824.99.2840 on January 1, 2017—covered e-cigarette liquid containing 5 percent or more by weight of nicotine.

^b HTS number 3824.90.9280—replaced with 3824.99.9280 on January 1, 2017—covered e-cigarette liquid containing less than 5 percent by weight of nicotine. In this table, quantity and customs value for HTS number 3824.90.9280 cover the period from February through December 2016 because of an error in the January 2016 data. According to U.S. Census Bureau officials, the corrected January 2016 data for HTS number 3824.90.9280 will be reflected in the revised 2016 data that will be released in the summer of 2017.

^c HTS number 8543.70.9930—which replaced 8543.70.9630 on July 1, 2016—covers e-cigarette devices imported with cartridges filled with liquid containing nicotine.

^d HTS number 8543.70.9940—which replaced 8543.70.9640 on July 1, 2016—covers e-cigarette devices imported with cartridges filled with nicotine-free liquid.

Table 5. Customs value of U.S. e-cigarette imports by port of entry in 2016

34 ports of entry, in actual dollars

Port of entry	Customs value ^a	
	Dollars	Percentage
Cleveland, OH	83,828,226	24.49
Los Angeles, CA	79,065,697	23.10
Savannah, GA	48,324,446	14.12
Norfolk, VA	33,524,990	9.80
Seattle, WA	32,532,897	9.51
Miami, FL	11,033,970	3.22
Detroit, MI	10,146,590	2.96
Laredo, TX	6,661,991	1.95
Charlotte, NC	6,465,758	1.89
Chicago, IL	5,820,868	1.70
San Francisco, CA	5,807,383	1.70
New York, NY	5,240,342	1.53
New Orleans, LA	3,112,414	0.91
El Paso, TX	1,814,928	0.53
Nogales, AZ	1,688,568	0.49
Buffalo, NY	1,378,946	0.40
Boston, MA	995,126	0.29
San Diego, CA	882,153	0.26
Dallas-Fort Worth, TX	826,516	0.24
Tampa, FL	618,252	0.18
Great Falls, MT	598,996	0.18
Philadelphia, PA	531,016	0.16
Anchorage, AK	439,289	0.13
St. Louis, MO	352,094	0.10
Charleston, SC	156,941	0.05
Houston-Galveston, TX	144,425	0.04
Columbia-Snake, OR	87,672	0.03
Ogdensburg, NY	65,006	0.02
Baltimore, MD	52,500	0.02
Washington, DC	31,565	0.01
Portland, ME	14,153	0.00
Minneapolis, MN	6,920	0.00
St. Albans, VT	4,129	0.00
Honolulu, HI	2,541	0.00
Total	342,257,308	100.00

Source: GAO analysis of U.S. Census Bureau data as retrieved from the U.S. International Trade Commission's Interactive Trade DataWeb (accessed Feb. 9, 2017). | GAO-17-515R.

Notes: The port of entry is where imported goods clear U.S. customs and may differ from the port of unloading where goods are unloaded from the importing vessel or aircraft.

^a Port-of-entry totals for customs value cover the entire calendar year 2016 for all e-cigarette Harmonized Tariff Schedule (HTS) numbers except HTS number 3824.90.9280. Customs value for HTS number 3824.90.9280 covers the period from February through December 2016 because of an error in the January 2016 data. According to U.S. Census Bureau officials, the corrected January 2016 data for HTS number 3824.90.9280 will be reflected in the revised 2016 data that will be released in the summer of 2017.

Chapter 359

ELECTRONIC CIGARETTES: U.S. IMPORTS, 2016-2018*

United States Government Accountability Office

The Honorable Ron Wyden Ranking Member
Committee on Finance United States Senate

Dear Senator Wyden:

Over the last 15 years, use of electronic cigarettes, known as e-cigarettes, in the United States has grown rapidly as use of traditional cigarettes declined among both adolescents and adults. As we reported previously, most e-cigarettes sold in the United States are thought to be imported.¹ The U.S. government began collecting data specific to e-cigarette imports in January 2016, after the Committee for Statistical Annotation of Tariff Schedules established six new statistical reporting numbers for e-cigarette devices, parts, and liquid in the Harmonized Tariff Schedule of the United States (HTS).² In April 2017, we reported, on the basis of the first year of data, that the customs value of U.S. e-cigarette imports in 2016 was

* This is an edited, reformatted and augmented version of United States Government Accountability Office, Accessible Version, Publication No. GAO-19-619R, dated July 12, 2019.

¹ GAO, *Electronic Cigarettes: U.S. Imports in 2016*, GAO-17-515R (Washington, D.C.: Apr. 24, 2017).

² The committee comprises representatives from the U.S. International Trade Commission (USITC), U.S. Customs and Border Protection (CBP), and the U.S. Census Bureau. All goods imported into the United States are classified by CBP according to the HTS. The HTS, published and maintained by USITC, provides the legal basis for the classification of every product that enters the United States and the corresponding tariff rate the importer must pay for each product. The HTS contains numbered provisions at the 2-, 4-, 6-, 8-, and 10-digit level. The 10-digit provision is known as a statistical reporting number that can be used for tracking and reporting trade statistics. For more information about the committee and process for establishing new statistical reporting numbers, see GAO, *Electronic Cigarettes: Imports, Tariffs, and Data Collection*, GAO-15-491R (Washington, D.C.: May 7, 2015).

about \$342 million and that 91 percent of those imports, by customs value, came from China.³

You requested that we report on e-cigarettes imported into the United States from 2016 through 2018. This report examines the customs value, tariff revenue, countries of origin, and ports of entry for e-cigarette devices, parts, and liquid imported during those years. We analyzed the data that were available in April 2019 from the Interactive Tariff and Trade DataWeb maintained by the U.S. International Trade Commission (USITC), which incorporates U.S. trade statistics published by the U.S. Census Bureau (Census).⁴ We analyzed import data for the six statistical reporting numbers that covered e-cigarette devices, parts, and liquid in 2016 through 2018.⁵ For each reporting number, we analyzed customs value, tariff revenue, country of origin, and port of entry.⁶ We also analyzed data on import quantities for four e-cigarette reporting numbers—covering e-cigarette devices and liquid—for which the federal government tracked quantity in 2016 through 2018.⁷

To understand trends in the data and assess the data's reliability, we reviewed agency documents about U.S. foreign trade statistics and interviewed U.S. Customs and Border Protection (CBP) and Census officials about how the data were collected, how they were checked, and any limitations of the data. We determined that the data were sufficiently reliable for the purposes of presenting annual descriptive statistics.

We conducted this performance audit from April to July 2019 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence we obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

An e-cigarette device typically contains a battery, a heating element, and a cartridge or tank that may be empty or filled with liquid. Major e-cigarette parts include heating elements and cartridges, which can be imported separately from devices. E-cigarette liquid—which may contain nicotine in different concentrations or no nicotine—can also be imported separately from both devices and cartridges.

As Table 1 in the enclosure shows, the six statistical reporting numbers in the HTS for U.S. e-cigarette imports cover devices with and without nicotine; parts with and without nicotine; and two types of nicotine-containing e-cigarette liquid: (1) liquid mixtures containing 5 percent or more by weight of one or more aromatic or modified aromatic

³ GAO-17-515R. Customs value is defined as the price actually paid or payable for merchandise when sold for exportation to the United States, excluding U.S. import tariffs (also known as duties), freight, insurance, and other charges incurred in bringing the merchandise to the United States.

⁴ See <https://dataweb.usitc.gov/>.

⁵ All years cited in this report are calendar years (January–December). U.S. import data are collected by CBP from records submitted by importers. These data are then incorporated into the official trade statistics published by Census. We used unrevised 2018 trade data. Census revises trade data periodically, and its first official revisions of 2018 trade data became available in June 2019, after we completed our analysis. Throughout this report, our analysis is based on consumption import data, which measure the total of merchandise that has physically cleared U.S. customs, either entering consumption channels immediately or entering after withdrawal for consumption from bonded warehouses or foreign trade zones under CBP custody.

⁶ To report tariff revenue, we used the “calculated duty” variable, which represents the estimated import duties collected. Estimated duties are calculated on the basis of the applicable rate(s) of duty (or tariff) as shown in the HTS.

⁷ Tracking of the quantity of imported e-cigarette liquid began in January 2016 and of e-cigarette devices in July 2016. Tracking of the quantity of imported e-cigarette parts began in January 2019.

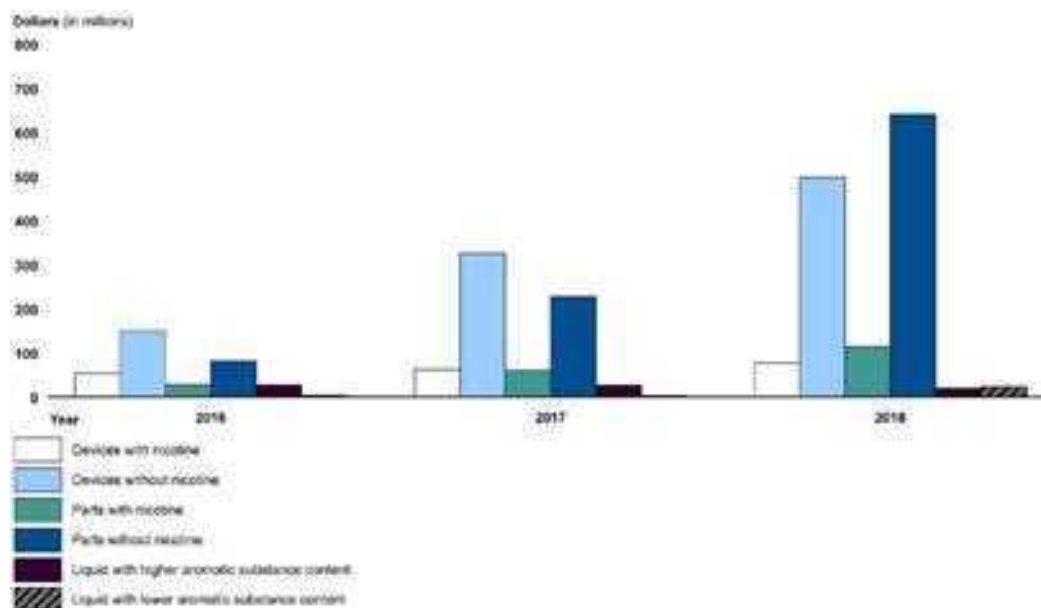
substances, including nicotine (liquid with higher aromatic substance content), and (2) liquid mixtures containing less than 5 percent by weight of one or more aromatic or modified aromatic substances, including nicotine (liquid with lower aromatic substance content).⁸ Devices with and without nicotine are subject to the same general tariff rate, and parts with and without nicotine are subject to the same general tariff rate. However, liquid with higher aromatic substance content is subject to a higher general tariff rate (6.5 percent of customs value) than liquid with lower aromatic substance content (5 percent of customs value).⁹

In summary, our analysis of U.S. e-cigarette import data for 2016 through 2018 found the following:

- **Customs value and tariff revenue for all U.S. e-cigarette imports.** The customs value of e-cigarette devices, parts, and liquid imported into the United States from 2016 through 2018 was \$2.4 billion (see Table 2 in the enclosure). Devices and parts each accounted for about \$1.2 billion of total customs value (48 percent for each, or 96 percent for both) and liquid accounted for \$101.5 million (4 percent). The federal government collected \$120 million in total tariff revenue from these imports during this period.
- **Changes in customs value, tariff revenue, and quantities of U.S. e-cigarette imports from 2016 to 2018.** The customs value of all U.S. e-cigarette imports increased by 300 percent from 2016 to 2018 (see Table 3 in the enclosure). The customs value of five of the six imported e-cigarette products—devices with and without nicotine, parts with and without nicotine, and liquid with lower aromatic substance content—increased from the 2016 level to the 2018 level. Tariff revenue from these products also increased (see Table 4 in the enclosure). In addition, quantities of imported devices with and without nicotine and of liquid with lower aromatic substance content increased (see Table 5 in the enclosure). Only imported e-cigarette liquid with higher aromatic substance content decreased in customs value, tariff revenue, and quantity from the 2016 level to the 2018 level.

⁸ These descriptions for the two types of e-cigarette liquid, corresponding to statistical reporting numbers 3824.99.2840 and 3824.99.9280, reflect recent discussions with U.S. International Trade Commission and U.S. Customs and Border Protection officials and differ from the descriptions presented in our prior related report (GAO-17-515R). In that report, the descriptions for e-cigarette liquid, developed in consultation with officials from the same agencies, distinguished between the two statistical reporting numbers on the basis of nicotine content. The two statistical reporting numbers each cover nicotine-containing formulated liquid mixtures and are distinguished from each other by the percentage of aromatic or modified aromatic substances, including nicotine, and not by the percentage of nicotine alone. Formulated liquid mixtures imported under 3824.99.2840 and 3824.99.9280 may also contain other substances in addition to aromatic and modified aromatic substances. For more information, see table 1 in the enclosure.

⁹ General tariff rates are applied to imported goods from countries with which the United States has normal trade relations.



Source: GAO analysis of U.S. Census Bureau data retrieved from the U.S. International Trade Commission's Interactive Trade DataWeb (accessed Apr. 29, 2019). | GAO-19-619R.

Notes: See Table 3 in GAO-19-619R for a more detailed presentation of the data for these imports.

The descriptions for the two types of nicotine-containing e-cigarette liquid, corresponding to statistical reporting numbers 3824.99.2840 and 3824.99.9280, reflect recent discussions with U.S. International Trade Commission and U.S. Customs and Border Protection officials and differ from the descriptions presented in our prior related report (GAO-17-515R). In that report, the descriptions for e-cigarette liquid, developed in consultation with officials from the same agencies, distinguished between the two statistical reporting numbers on the basis of the percentage of nicotine content. The two statistical reporting numbers each cover nicotine-containing formulated liquid mixtures; are distinguished from each other by the percentage of aromatic or modified aromatic substances, including nicotine; and may also contain other substances.

Figure 1. Customs value of e-cigarette devices, parts, and liquid imported into the United States, 2016-2018.

As Figure 1 and Table 3 in the enclosure show, the highest increases in customs value from the 2016 level to the 2018 level were associated with imported parts without nicotine (684 percent), liquid with lower aromatic substance content (582 percent), and parts with nicotine (322 percent). In addition, the customs value of imported devices without nicotine increased by 231 percent during this period. By comparison, the customs value of imported liquid with higher aromatic substance content decreased by 28 percent from 2016 to 2018.

- U.S. e-cigarette imports by country.** The customs value of e-cigarette imports from China accounted for 97 percent of the customs value of all e-cigarette imports from 65 countries from 2016 through 2018 (see Table 6 in the enclosure). Imports from China accounted for almost 100 percent of the customs value of all devices with nicotine and 95 percent of the customs value of all devices without nicotine (see Table 7 in the enclosure) and for about 99 percent of the customs value of all parts with and without nicotine (see Table 8 in the enclosure). Devices and parts without

nicotine were imported from a larger number of countries than devices and parts with nicotine. In contrast to devices and parts, e-cigarette liquid imported from China represented a smaller percentage of the customs value of the two types of imported e-cigarette liquid: 90 percent for liquid with higher aromatic substance content and 69 percent for liquid with lower aromatic substance content (see Table 9 in the enclosure).

Our analysis of quantities of e-cigarette devices and liquid imported from 2016 through 2018 shows similar patterns. From July 2016 through December 2018, e-cigarette importers brought 271 million e-cigarette devices with and without nicotine into the United States. Almost all imported devices with and without nicotine, or just under 100 percent by quantity, came from China (see Table 10 in the enclosure). From January 2016 through December 2018, e-cigarette importers brought 2 million kilograms of nicotine-containing e-cigarette liquid into the United States. Liquid with higher aromatic substance content imported from China accounted for 55 percent of all such imported liquid by quantity, and liquid with lower aromatic substance content imported from China accounted for 45 percent (see Table 11 in the enclosure).

- **Ports of entry.** The top five ports of entry—Los Angeles, Cleveland, Chicago, Savannah, and Norfolk—accounted for 81 percent of the customs value of U.S. e-cigarette imports in 2016 through 2018 (see Table 12 in the enclosure).¹⁰ Notably, the value of e-cigarette imports that cleared customs at the Chicago port of entry increased 80-fold, from about \$6 million in 2016 to \$468 million in 2018.

ENCLOSURE – 1

Table 1. HTS classification summary for U.S. e-cigarette imports, January 2016–June 2019

E-cigarette product and statistical reporting number	General tariff rate (percentage of customs value)	Unit of quantity	Date when tracking of quantity began
Devices ^a			
Devices with nicotine 8543.70.9930 ^b	2.6 percent	Number	July 2016
Devices without nicotine 8543.70.9940 ^b	[+25 percent additional tariff rate since August 23, 2018, for products from Chinac]		
Parts ^a			
Parts with nicotine 8543.90.8850 ^d	2.6 percent (Jan. 2016–June 2016) 1.9 percent (July 2016–June 2017) 1.3 percent (July 2017–June 2018) 0.6 percent (July 2018–June 2019) ^e	Number	January 2019
Parts without nicotine 8543.90.8860 ^d	[+10 percent additional tariff rate since September 24, 2018, for products from China that increased to 25 percent on May 10, 2019 ^c]		

¹⁰ The port of entry is the location where imported goods clear U.S. customs and may differ from the port of unloading, where goods are unloaded from the importing vessel or aircraft.

Table 1. (Continued)

E-cigarette product and statistical reporting number	General tariff rate (percentage of customs value)	Unit of quantity	Date when tracking of quantity began
Liquid^f			
Liquid mixtures containing 5 percent or more by weight of one or more aromatic or modified aromatic substances, including nicotine (liquid with higher aromatic substance content) 3824.99.2840 ^g	6.5 percent [+10 percent additional tariff rate since September 24, 2018, for products from China that increased to 25 percent on May 10, 2019 ^c]	Kilogram	January 2016
Liquid mixtures containing less than 5 percent by weight of one or more aromatic or modified aromatic substances, including nicotine (liquid with lower aromatic substance content) 3824.99.9280 ^g	5 percent [+10 percent additional tariff rate since September 24, 2018, for products from China that increased to 25 percent on May 10, 2019 ^c]		

Source: GAO presentation of information from the Harmonized Tariff Schedule of the United States (HTS) and U.S. International Trade Commission. | GAO-19-619R.

Notes: General tariff rates are applied to imported goods from countries with which the United States has normal trade relations. The HTS also enumerates tariff rates for goods from some of these countries that qualify for preferential tariff rates under a variety of special trade agreements as well as rates for a specific list of countries. The HTS additionally lists special tariff rates for products that fit technical specifications enumerated in notes to the HTS. See the HTS for these other rates.

Customs value is defined as the price actually paid or payable for merchandise when sold for exportation to the United States, excluding U.S. import tariffs (also known as duties), freight, insurance, and other charges incurred in bringing the merchandise to the United States.

^aAccording to the HTS (chapter 85, statistical note 7), for the purposes of statistical reporting numbers 8543.70.9930, 8543.70.9940, 8543.90.8850, and 8543.90.8860, personal electric or electronic vaporizing devices are devices that electrically heat or atomize liquids or other substances, whether or not containing nicotine, producing a vapor to be inhaled through the mouthpiece.

^bStatistical reporting numbers 8543.70.9930 and 8543.70.9940 replaced 8543.70.9630 and 8543.70.9640, respectively, on July 1, 2016. These reporting numbers cover closed-system and open-system e-cigarettes if they are imported as functional devices with or without cartridges.

^cThe additional tariffs were imposed by the U.S. Trade Representative (USTR) in accordance with the direction of the President. On August 18, 2017, following a Memorandum from the President, USTR initiated an investigation under Section 301 of the Trade Act of 1974 into the government of China's acts, policies, and practices related to technology transfer, intellectual property, and innovation. 82 *Fed. Reg.* 40,213 (Aug. 24, 2017). As a result of the investigation and at the direction of the President, USTR imposed tariffs on a range of products from China in three separate actions in 2018. See, 83 *Fed. Reg.* 28,710 (June 20, 2018); 83 *Fed. Reg.* 40,823 (Aug. 16, 2018); and 83 *Fed. Reg.* 47,974 (Sept. 21, 2018). Additionally, effective May 10, 2019, USTR increased the tariff rate imposed on products covered by its third action from 10 percent to 25 percent. The additional tariffs are effective until suspended or terminated.

^dStatistical reporting numbers 8543.90.8850 and 8543.90.8860 cover major parts, such as heating elements and cartridges containing heating elements, that are imported separately from e-cigarette devices. Smaller e-cigarette components—such as microprocessors, batteries, tubes containing batteries, or light-emitting diode lights—that may be used for other products in addition to e-cigarettes are classified under other applicable HTS provisions.

^eThe general tariff rate of 0.6 percent was reduced to zero on July 1, 2019.

^fAccording to the HTS (chapter 38, statistical note 3), for the purposes of statistical reporting numbers 3824.99.2840 and 3824.99.9280, “mixtures for use in personal electric or electronic vaporizing devices” means a formulated liquid containing nicotine, whether or not packaged for retail sale in cartridges or tanks adaptable to such devices.

^gIn this report, the descriptions of the two types of e-cigarette liquid, corresponding to statistical reporting numbers 3824.99.2840 and 3824.99.9280, reflect recent discussions with U.S. International Trade Commission and U.S. Customs and Border Protection officials and differs from the descriptions presented in our prior related report (GAO-17-515R). In that report, the descriptions for e-cigarette liquid, developed in consultation with officials from the same agencies, distinguished between the two reporting numbers on the basis of nicotine content. The two statistical reporting numbers each cover nicotine-containing formulated liquid mixtures and are distinguished from each other by the percentage of aromatic or modified aromatic substances, including nicotine, and not by the percentage of nicotine alone. Formulated liquid mixtures imported under 3824.99.2840 and 3824.99.9280 may also contain other substances—such as, for example, glycol or glycerin—in addition to aromatic and modified aromatic substances. Statistical reporting numbers 3824.99.2840 and 3824.99.9280 replaced 3824.90.2840 and 3824.90.9280, respectively, on January 1, 2017.

Table 2. Total customs value and tariff revenue for U.S. E-cigarette imports, 2016-2018

E-cigarette product	Customs value in dollars	Tariff revenue in dollars
Devices		
Devices with nicotine	192,997,202	14,513,280
Devices without nicotine	971,789,973	56,949,466
Subtotal for devices	1,164,787,175	71,462,746
Parts		
Parts with nicotine	201,284,194	6,118,656
Parts without nicotine	949,522,430	35,508,317
Subtotal for parts	1,150,806,624	41,626,973
Liquida		
Liquid with higher aromatic substance content	71,942,536	4,825,617
Liquid with lower aromatic substance content	29,572,706	2,541,831
Subtotal for liquid	101,515,242	7,367,448
Total	2,417,109,041	120,457,167

Source: GAO analysis of U.S. Census Bureau data retrieved from the U.S. International Trade Commission's Interactive Trade DataWeb (accessed Apr. 29, 2019). | GAO-19-619R.

^aThe descriptions for the two types of nicotine-containing e-cigarette liquid, corresponding to statistical reporting numbers 3824.99.2840 and 3824.99.9280, reflect recent discussions with U.S. International Trade Commission and U.S. Customs and Border Protection officials and differ from the descriptions presented in our prior related report (GAO-17-515R). In that report, the descriptions for e-cigarette liquid, developed in consultation with officials from the same agencies, distinguished between the two statistical reporting numbers on the basis of the percentage of nicotine content. The two statistical reporting numbers each cover nicotine-containing formulated liquid mixtures; are distinguished from each other by the percentage of aromatic or modified aromatic substances, including nicotine; and may also contain other substances.

Table 3. Customs value of U.S. E-cigarette imports, by product and year, 2016-2018

E-cigarette product	Customs value in dollars			Percentage change, 2016–2018
	2016	2017	2018	
Devices with nicotine	53,946,173	62,053,635	76,997,394	43
Devices without nicotine	150,155,638	324,592,277	497,042,058	231
Subtotal for devices	204,101,811	386,645,912	574,039,452	181
Parts with nicotine	26,996,229	60,462,520	113,825,445	322
Parts without nicotine	81,745,233	227,116,550	640,660,647	684
Subtotal for parts	108,741,462	287,579,070	754,486,092	594
Liquid with higher aromatic substance content	26,675,683	26,088,221	19,178,632	-28
Liquid with lower aromatic substance content	3,412,746	2,871,712	23,288,248	582
Subtotal for liquid ^a	30,088,429	28,959,933	42,466,880	41
Total	342,931,702	703,184,915	1,370,992,424	300

Source: GAO analysis of U.S. Census Bureau data retrieved from the U.S. International Trade Commission's Interactive Trade DataWeb, (accessed Apr. 29, 2019). | GAO-19-619R.

^aThe descriptions for the two types of nicotine-containing e-cigarette liquid, corresponding to statistical reporting numbers 3824.99.2840 and 3824.99.9280, reflect recent discussions with U.S. International Trade Commission and U.S. Customs and Border Protection officials and differ from the descriptions presented in our prior related report (GAO-17-515R). In that report, the descriptions for e-cigarette liquid, developed in consultation with officials from the same agencies, distinguished between the two statistical reporting numbers on the basis of the percentage of nicotine content. The two statistical reporting numbers each cover nicotine-containing formulated liquid mixtures; are distinguished from each other by the percentage of aromatic or modified aromatic substances, including nicotine; and may also contain other substances.

Table 4. Tariff revenue from U.S. E-cigarette imports, by product and year, 2016-2018

E-cigarette product	Tariff revenue in dollars		2018	Percentage change, 2016–2018
	2016	2017		
Devices with nicotine	1,402,525	1,613,409	11,497,346	720
Devices without nicotine	3,423,424	8,150,814	45,375,228	1,225
Subtotal for devices	4,825,949	9,764,223	56,872,574	1,078
Parts with nicotine	602,086	919,833	4,596,737	663
Parts without nicotine	1,638,998	3,528,174	30,341,145	1,751
Subtotal for parts	2,241,084	4,448,007	34,937,882	1,459
Liquid with higher aromatic substance content	1,693,349	1,671,372	1,460,896	-14
Liquid with lower aromatic substance content	159,221	134,535	2,248,075	1,312
Subtotal for liquid ^a	1,852,570	1,805,907	3,708,971	100
Total	8,919,603	16,018,137	95,519,427	971

Source: GAO analysis of U.S. Census Bureau data retrieved from the U.S. International Trade Commission's Interactive Trade DataWeb (accessed Apr. 29, 2019). | GAO-19-619R.

^aThe descriptions for the two types of nicotine-containing e-cigarette liquid, corresponding to statistical reporting numbers 3824.99.2840 and 3824.99.9280, reflect recent discussions with U.S. International Trade Commission and U.S. Customs and Border Protection officials and differ from the descriptions presented in our prior related report (GAO-17-515R). In that report, the descriptions for e-cigarette liquid, developed in consultation with officials from the same agencies, distinguished between the two statistical reporting numbers on the basis of the percentage of nicotine content. The two statistical reporting numbers each cover nicotine-containing formulated liquid mixtures; are distinguished from each other by the percentage of aromatic or modified aromatic substances, including nicotine; and may also contain other substances.

Table 5. Quantities of imported e-cigarette devices and liquid, by product and year, 2016-2018

Devices (July 2016–Dec. 2018), Number

E-cigarette product	2016	2017	2018	Percentage change, 2016–2018
Devices with nicotine	5,629,456	30,222,777	30,601,891	444
Devices without nicotine	5,310,938	91,265,598	108,301,027	1,939
Total for devices	10,940,394	121,488,375	138,902,918	1,170

Liquid (Jan. 2016–Dec. 2018)/a/, Kilograms

E-cigarette product	2016	2017	2018	Percentage change, 2016–2018
Liquid with higher aromatic substance content	486,313	399,744	407,864	-16
Liquid with lower aromatic substance content	123,608	157,044	462,214	274
Total for liquid	609,921	556,788	870,078	43

Source: GAO analysis of U.S. Census Bureau data retrieved from the U.S. International Trade Commission's Interactive Trade DataWeb (accessed Apr. 29, 2019). | GAO-19-619R.

Notes: Tracking of the quantity of imported e-cigarette liquid began in January 2016 and of e-cigarette devices in July 2016. Tracking of the quantity of imported e-cigarette parts began in January 2019.

^aThe descriptions for the two types of nicotine-containing e-cigarette liquid, corresponding to statistical reporting numbers 3824.99.2840 and 3824.99.9280, reflect recent discussions with U.S. International Trade Commission and U.S. Customs and Border Protection officials and differ from the descriptions presented in our prior related report (GAO-17-515R). In that report, the descriptions for e-cigarette liquid, developed in consultation with officials from the same agencies, distinguished between the two statistical reporting numbers on the basis of the percentage of nicotine content. The two statistical reporting numbers each cover nicotine-containing formulated liquid mixtures; are distinguished from each other by the percentage of aromatic or modified aromatic substances, including nicotine; and may also contain other substances.

**Table 6. Customs value of U.S. e-cigarette imports,
by country of origin and year, 2016-2018**

65 countries, customs value in dollars

Country	2016	2017	2018	Total	Percentage
China	313,521,695	680,648,542	1,352,922,732	2,347,092,969	97.1
Canada	11,573,095	11,275,241	3,388,247	26,236,583	1.1
Mexico	9,423,067	1,649,546	1,509,108	12,581,721	0.5
Germany	1,998,540	2,990,635	2,971,204	7,960,379	0.3
United Kingdom	1,635,250	1,852,016	2,504,044	5,991,310	0.2
Italy	318,437	167,385	1,492,978	1,978,800	0.1
France	656,008	92,681	1,080,753	1,829,442	0.1
Malaysia	51,317	605,196	1,048,329	1,704,842	0.1
Israel	856,402	348,484	254,742	1,459,628	0.1
Czech Republic	2,400	738,486	550,685	1,291,571	0.1
Austria	620,404	548,841	55,538	1,224,783	0.1
Switzerland	392,636	291,780	423,578	1,107,994	0.0
South Korea	225,664	408,383	435,626	1,069,673	0.0
Singapore	47,694	125,677	769,258	942,629	0.0
Poland	137,664	318,502	398,338	854,504	0.0
Japan	587,374	115,097	128,031	830,502	0.0
Taiwan ^a	146,639	124,253	201,957	472,849	0.0
New Zealand	32,823	105,831	159,366	298,020	0.0
India	86,472	123,765	77,825	288,062	0.0
Malta	-	-	201,250	201,250	0.0
Vietnam	14,960	173,880	4,924	193,764	0.0
Denmark	133,761	11,250	12,145	157,156	0.0
Hungary	48,728	102,010	2,906	153,644	0.0
Panama	109,968	8,029	-	117,997	0.0
Netherlands	82,164	21,769	7,415	111,348	0.0
Other (40 countries)	228,540	337,636	391,445	957,621	0.0
Total	342,931,702	703,184,915	1,370,992,424	2,417,109,041	100.0

Source: GAO analysis of U.S. Census Bureau data retrieved from the U.S. International Trade Commission's Interactive Trade DataWeb (accessed Apr. 29, 2019). | GAO-19-619R.

^aAlthough the United States does not have diplomatic relations with Taiwan, we have listed it as a separate country because whenever the laws of the United States refer or relate to foreign countries, nations, states, governments, or similar entities, such terms shall include and shall apply to Taiwan. Taiwan Relations Act, Pub. L. No. 96-8, § 4(b)(1), 93 Stat. 14 (1979). Furthermore, the data we used list Taiwan as a country and show imports from Taiwan separately.

**Table 7. Customs value of e-cigarette devices imported into
the United States, by country of origin and year, 2016-2018**

In dollars						
	Country	2016	2017	2018	Total	Percentage
Devices with nicotine	China	53,779,326	61,841,443	76,828,711	192,449,480	99.7
	Austria	54,680	107,273	-	161,953	0.1
	Japan	4,763	85,545	36,797	127,105	0.1
	Singapore	-	-	120,000	120,000	0.1
	United Kingdom	30,412	5,135	-	35,547	0.0
	Netherlands	32,239	-	-	32,239	0.0
	Germany	16,650	-	9,873	26,523	0.0
	Australia	12,951	-	-	12,951	0.0
	Taiwan	8,712	-	-	8,712	0.0
	Poland	-	6,542	-	6,542	0.0
	Other (5 countries)	6,440	7,697	2,013	16,150	0.0
	Subtotal Devices without nicotine	53,946,173	62,053,635	76,997,394	192,997,202	100.0

Table 7. (Continued)

In dollars						
	Country	2016	2017	2018	Total	Percentage
Devices without nicotine	China	125,801,030	308,481,870	490,251,421	924,534,321	95.1
	Canada	11,213,774	10,676,729	315,967	22,206,470	2.3
	Mexico	9,390,998	1,578,933	1,484,036	12,453,967	1.3
	Germany	1,611,568	2,509,892	2,616,927	6,738,387	0.7
	United Kingdom	618,628	136,885	484,797	1,240,310	0.1
	France	175,887	37,046	882,474	1,095,407	0.1
	South Korea	171,555	295,911	155,584	623,050	0.1
	Switzerland	103,704	153,322	182,933	439,959	0.0
	Austria	135,656	182,000	9,576	327,232	0.0
	Israel	245,872	30,000	41,700	317,572	0.0
	Other (42 countries)	686,966	509,689	616,643	1,813,298	0.2
	Subtotal Devices without nicotine	150,155,638	324,592,277	497,042,058	971,789,973	100.0
Total	All	204,101,811	386,645,912	574,039,452	1,164,787,175	

Source: GAO analysis of U.S. Census Bureau data retrieved from the U.S. International Trade Commission's Interactive Trade DataWeb (accessed Apr. 29, 2019). | GAO-19-619R.

Table 8. Customs value of e-cigarette parts imported into the United States, by country of origin and year, 2016-2018 (in dollars)

	Country	2016	2017	2018	Total	Percentage
Parts with nicotine	China	26,851,401	60,316,602	113,749,046	200,917,049	99.8
	Italy	7,048	74,015	-	81,063	0.0
	Austria	25,142	37,500	-	62,642	0.0
	United Kingdom	8,696	-	46,441	55,137	0.0
	Mexico	-	24,003	-	24,003	0.0
	Netherlands	22,635	-	-	22,635	0.0
	Denmark	21,258	-	-	21,258	0.0
	South Korea	21,000	-	-	21,000	0.0
	Canada	16,345	-	4,505	20,850	0.0
	Japan	-	-	16,008	16,008	0.0
	Other (5 countries)	22,704	10,400	9,445	42,549	0.0
	Subtotal	26,996,229	60,462,520	113,825,445	201,284,194	100.0
Parts without nicotine	China	80,420,948	225,072,922	638,782,709	944,276,579	99.4
	Germany	173,569	352,187	300,619	826,375	0.1
	Israel	157,729	318,484	213,042	689,255	0.1
	Switzerland	182,552	132,239	229,347	544,138	0.1
	United Kingdom	123,884	136,548	121,457	381,889	0.0
	Singapore	7,103	112,722	230,928	350,753	0.0
	Malaysia	51,317	90,380	149,223	290,920	0.0
	Taiwan ^a	67,111	108,357	110,959	286,427	0.0
	Austria	190,522	58,163	23,276	271,961	0.0
	Canada	102,867	113,683	53,160	269,710	0.0
	Other (27 countries)	267,631	620,865	445,927	1,334,423	0.1
	Subtotal	81,745,233	227,116,550	640,660,647	949,522,430	100.0
Total	All	108,741,462	287,579,070	754,486,092	1,150,806,624	

Source: GAO analysis of U.S. Census Bureau data retrieved from the U.S. International Trade Commission's Interactive Trade DataWeb (accessed Apr. 29, 2019). | GAO-19-619R.

^aAlthough the United States does not have diplomatic relations with Taiwan, we have listed it as a separate country because whenever the laws of the United States refer or relate to foreign countries, nations, states, governments, or similar entities, such terms shall include and shall apply to Taiwan. Taiwan Relations Act, Pub. L. No. 96-8, § 4(b)(1), 93 Stat. 14 (1979). Furthermore, the data we used list Taiwan as a country and show imports from Taiwan separately.

Table 9. Customs value of e-cigarette liquid imported into the United States, by country of origin and year, 2016-2018 (In dollars)

	Country	2016	2017	2018	Total	Percentage
Liquid with higher aromatic substance content	China	24,728,648	23,730,184	16,032,933	64,491,765	89.6
	United Kingdom	743,995	754,607	543,922	2,042,524	2.8
	Czech Republic	-	738,486	492,570	1,231,056	1.7
	Malaysia	-	172,571	765,933	938,504	1.3
	Canada	138,512	368,411	321,853	828,776	1.2
	Israel	452,801	-	-	452,801	0.6
	Singapore	-	-	401,730	401,730	0.6
	France	153,153	-	182,853	336,006	0.5
	Austria	99,831	163,905	22,686	286,422	0.4
	Malta	-	-	201,250	201,250	0.3
	Other (15 countries)	358,743	160,057	212,902	731,702	1.0
	Subtotal	26,675,683	26,088,221	19,178,632	71,942,536	100.0
Liquid with lower aromatic substance content	China	1,940,342	1,205,521	17,277,912	20,423,775	69.1
	Canada	101,597	116,418	2,690,749	2,908,764	9.8
	United Kingdom	109,635	818,841	1,307,427	2,235,903	7.6
	Italy	172,071	11,349	1,414,563	1,597,983	5.4
	Malaysia	-	278,644	121,489	400,133	1.4
	Poland	56,936	84,414	222,952	364,302	1.2
	Germany	190,513	100,960	32,519	323,992	1.1
	France	242,799	5,402	13,425	261,626	0.9
	Japan	216,671	3,057	-	219,728	0.7
	South Korea	-	90,002	101,790	191,792	0.6
	Other (17 countries)	382,182	157,104	105,422	644,708	2.2
	Subtotal	3,412,746	2,871,712	23,288,248	29,572,706	100.0
Total	All	30,088,429	28,959,933	42,466,880	101,515,242	

Source: GAO analysis of U.S. Census Bureau data retrieved from the U.S. International Trade Commission's Interactive Trade DataWeb (accessed Apr. 29, 2019). | GAO-19-619R.

Note: The descriptions for the two types of nicotine-containing e-cigarette liquid, corresponding to statistical reporting numbers 3824.99.2840 and 3824.99.9280, reflect recent discussions with U.S. International Trade Commission and U.S. Customs and Border Protection officials and differ from the descriptions presented in our prior related report (GAO-17-515R). In that report, the descriptions for e-cigarette liquid, developed in consultation with officials from the same agencies, distinguished between the two statistical reporting numbers on the basis of the percentage of nicotine content. The two statistical reporting numbers each cover nicotine-containing formulated liquid mixtures; are distinguished from each other by the percentage of aromatic or modified aromatic substances, including nicotine; and may also contain other substances.

Table 10. Quantities of e-cigarette devices imported into the United States, by country of origin and year, 2016-2018 (number of devices)

	Country	2016 (July-Dec.)	2017	2018	Total	Percentage
Devices with nicotine	China	5,624,706	30,000,323	30,482,228	66,107,257	99.5
	Japan	100	213,600	79,263	292,963	0.4
	Singapore	-	-	40,000	40,000	0.1
	Austria	3,822	8,132	-	11,954	0.0
	United Kingdom	-	545	-	545	0.0
	Germany	320	-	100	420	0.0
	Canada	-	-	300	300	0.0
	Australia	249	-	-	249	0.0
	France	154	-	-	154	0.0
	Poland	-	101	-	101	0.0
	Other (4 countries)	105	76	-	181	0.0
	Subtotal	5,629,456	30,222,777	30,601,891	66,454,124	100.0

Table 10. (Continued)

	Country	2016 (July-Dec.)	2017	2018	Total	Percentage
Devices without nicotine	China	4,848,766	89,758,820	107,597,974	202,205,560	98.7
	Canada	313,710	927,250	4,108	1,245,068	0.6
	Germany	36,641	243,884	225,129	505,654	0.2
	Mexico	85,331	169,200	167,886	422,417	0.2
	Taiwan	1,146	1,718	106,884	109,748	0.1
	France	43	2,162	79,736	81,941	0.0
	Hungary	233	72,700	-	72,933	0.0
	United Kingdom	8,433	17,218	45,038	70,689	0.0
	Switzerland	788	9,511	32,786	43,085	0.0
	Austria	4,414	16,256	5	20,675	0.0
	Other (35 countries)	11,433	46,879	41,481	99,793	0.0
	Subtotal	5,310,938	91,265,598	108,301,027	204,877,563	100.0
Total	All	10,940,394	121,488,375	138,902,918	271,331,687	

Source: GAO analysis of U.S. Census Bureau data retrieved from the U.S. International Trade Commission's Interactive Trade DataWeb (accessed Apr. 29, 2019). | GAO-19-619R.

Note: Tracking of the quantity of imported e-cigarette devices began on July 1, 2016.

Table 11. Quantities of e-cigarette liquid imported into the United States, by country of origin and year, 2016-2018 (quantity of liquid in kilograms)

	Country	2016	2017	2018	Total	Percentage
Liquid with higher aromatic substance content	China	261,435	279,386	174,998	715,819	55.3
	Malaysia	-	15,126	105,411	120,537	9.3
	Canada	38,118	51,475	14,900	104,493	8.1
	United Kingdom	32,778	29,427	34,449	96,654	7.5
	Israel	92,880	-	-	92,880	7.2
	France	36,188	-	39,491	75,679	5.8
	Czech Republic	-	20,344	14,953	35,297	2.7
	Japan	20,200	-	-	20,200	1.6
	Singapore	-	-	12,738	12,738	1.0
	Malta	-	-	5,665	5,665	0.4
	Other (15 countries)	4,714	3,986	5,259	13,959	1.1
	Subtotal	486,313	399,744	407,864	1,293,921	100.0
Liquid with lower aromatic substance content	China	67,435	47,070	215,805	330,310	44.5
	Canada	22,229	45,822	101,836	169,887	22.9
	United Kingdom	2,586	32,120	69,914	104,620	14.1
	Italy	6,403	115	40,280	46,798	6.3
	Malaysia	-	24,354	6,186	30,540	4.1
	Poland	3,208	308	24,393	27,909	3.8
	Germany	6,384	4,231	1,140	11,755	1.6
	Panama	4,371	-	-	4,371	0.6
	France	3,049	1	33	3,083	0.4
	Austria	2,788	-	-	2,788	0.4
	Other (18 countries)	5,155	3,023	2,627	10,805	1.5
	Subtotal	123,608	157,044	462,214	742,866	100.0
Total	All	609,921	556,788	870,078	2,036,787	

Source: GAO analysis of U.S. Census Bureau data retrieved from the U.S. International Trade Commission's Interactive Trade DataWeb (accessed Apr. 29, 2019). | GAO-19-619R.

Note: The descriptions for the two types of nicotine-containing e-cigarette liquid, corresponding to statistical reporting numbers 3824.99.2840 and 3824.99.9280, reflect recent discussions with U.S. International Trade Commission and U.S. Customs and Border Protection officials and differ from the descriptions presented in our prior related report (GAO-17-515R). In that report, the descriptions for e-cigarette liquid, developed in consultation with officials from the same agencies, distinguished between the two statistical reporting numbers on the basis of the percentage of nicotine content. The two statistical reporting numbers each cover nicotine-containing formulated liquid mixtures; are distinguished from each other by the percentage of aromatic or modified aromatic substances, including nicotine; and may also contain other substances.

Table 12. Customs value of U.S. e-cigarette imports, by port of entry and year, 2016- 2018

36 ports of entry, customs value in dollars

Port of entry	2016	2017	2018	Total	Percentage
Los Angeles, CA	79,171,965	178,761,131	306,788,945	564,722,041	23.4
Cleveland, OH	84,092,569	214,004,915	252,378,553	550,476,037	22.8
Chicago, IL	5,820,868	52,950,725	467,881,234	526,652,827	21.8
Savannah, GA	48,324,446	45,613,837	72,523,855	166,462,138	6.9
Norfolk, VA	33,524,990	63,303,574	59,790,878	156,619,442	6.5
Seattle, WA	32,532,897	39,625,364	39,303,053	111,461,314	4.6
San Francisco, CA	5,906,883	22,656,333	48,134,246	76,697,462	3.2
Miami, FL	11,223,418	22,246,446	12,764,027	46,233,891	1.9
New Orleans, LA	3,114,444	14,001,187	26,028,167	43,143,798	1.8
New York, NY	5,235,341	7,056,619	18,485,298	30,777,258	1.3
Anchorage, AK	439,289	3,607,200	21,843,253	25,889,742	1.1
Detroit, MI	10,164,086	10,759,924	2,101,735	23,025,745	1.0
Charlotte, NC	6,465,758	7,977,892	2,980,260	17,423,910	0.7
Tampa, FL	618,252	2,679,239	9,473,451	12,770,942	0.5
Dallas-Fort Worth, TX	835,266	5,314,062	4,606,733	10,756,061	0.4
Charleston, SC	156,941	2,666,136	5,601,859	8,424,936	0.3
Washington, DC	31,565	63,210	8,153,177	8,247,952	0.3
Buffalo, NY	1,382,033	1,567,954	4,102,601	7,052,588	0.3
Laredo, TX	6,661,991	47,848	-	6,709,839	0.3
Boston, MA	995,126	1,868,237	1,212,431	4,075,794	0.2
San Diego, CA	870,626	1,296,155	1,426,746	3,593,527	0.1
Great Falls, MT	598,996	1,331,986	1,144,239	3,075,221	0.1
Nogales, AZ	1,688,568	150,670	985,896	2,825,134	0.1
Houston-Galveston, TX	144,425	1,745,494	931,110	2,821,029	0.1
St. Louis, MO	352,094	1,165,900	813,923	2,331,917	0.1
Other (11 ports of entry)	2,578,865	722,877	1,536,754	4,838,496	0.2
Total	342,931,702	703,184,915	1,370,992,424	2,417,109,041	100.0

Source: GAO analysis of U.S. Census Bureau data retrieved from the U.S. International Trade Commission's Interactive Trade DataWeb (accessed Apr. 29, 2019). | GAO-19-619R.

Note: The port of entry is the location where imported goods clear U.S. customs and may differ from the port of unloading, where goods are unloaded from the importing vessel or aircraft.

Chapter 360

ELECTRONIC CIGARETTE FIRES AND EXPLOSIONS IN THE UNITED STATES 2009 - 2016*

Lawrence A. McKenna Jr.

MISSION STATEMENT

We provide national leadership to foster a solid foundation for our fire and emergency services stakeholders in prevention, preparedness and response.

Key Points

- The combination of an electronic cigarette and a lithium-ion battery is a new and unique hazard. There is no analogy among consumer products to the risk of a severe, acute injury presented by an e-cigarette.
- Fires or explosions caused by the batteries used in electronic cigarette are uncommon; however the consequences can be devastating and life-altering for the victims.
- It is likely that the number of incidents and injuries will continue to increase.
- Since the current generation of lithium-ion batteries is the root cause of these incidents, it is clear that these batteries are not a safe source of energy for these devices.
- Between January 2009 and December 31, 2016, 195 separate incidents of explosion and fire involving an electronic cigarette were reported by the U.S. media. These incidents resulted in 133 acute injuries. Of these injuries, 38 (29 percent) were severe.
- To date, there have been no deaths in the United States caused by electronic cigarette fires or explosions.
- One hundred and twenty-one (62 percent) of the incidents of explosion and fire involving an electronic cigarette or its battery occurred when the device was either in a pocket or actively in use.
- The shape and construction of electronic cigarettes can make them (more likely than other products with lithium-ion batteries) behave like “flaming rockets” when a battery fails.
- Lithium-ion batteries must be charged in accordance with the manufacturer’s instructions.

* This is an edited, reformatted and augmented version of U.S. Fire Administration, dated July 2017.

UPDATED REPORT

This report is an update to the report “Electronic Cigarette Fires and Explosions” published by the U.S. Fire Administration (USFA) in October 2014. Data on electronic cigarette incidents that occurred in the U.S. between September 2014 and December 2016 have been added to the data reported in the previous report for this analysis. Any additional incidents that occurred prior to September 2014 and discovered during this literature survey were included in the data reported herein.

A considerable number of incidents and severe injuries is reported, as well as the revelation of a previously unrecognized hazardous condition — electronic cigarette and battery explosions in pockets.

WHAT IS AN E-CIGARETTE

The term “electronic cigarette” encompasses a whole class of devices with many different shapes and configurations. In this report, the term “e-cigarette” will be used generically to refer to any or all e-cigarettes, e-cigs, personal vaporizers (PVs), electronic nicotine delivery systems (ENDS), mods, or similar devices.

E-cigarettes are battery-powered devices which simulate tobacco smoking by producing a heated vapor that resembles smoke. These devices have become very popular as an alternative to smoking, including with a growing number of individuals who have never been smokers, but who enjoy the many flavors and/or the experience of using e-cigarettes.

Development

E-cigarettes were first patented in 2003, and have been available for sale in the U.S. since 2007. E-cigs have been rapidly growing in popularity as the number and selection of products expand at an extremely rapid pace. Zhu, et al. (2014) report that by January 2014, there were 466 brands of e-cigarettes and 7,764 unique flavors available for sale. They also state that the number of products has been increasing at a rate of 10.5 brands and 242 new flavors per month. StatisticBrain¹ reports that there were 2,750,000 e-cigarette smokers in America and sales of e-cigarette devices and accessories in America exceeded \$2.8 billion in 2015. Indicators point to continued dynamic growth in the industry.

What Do They Look Like? How Much Do They Cost?

E-cigarette designs vary greatly. Some resemble a traditional cigarette, cigar or pipe, while others resemble a flashlight, or a small pack of cigarettes with a protruding tube. Cell phone cases with built-in e-cigarettes are also available. Figure 1 shows three common, commercially available devices.

¹ <http://www.statisticbrain.com/electronic-cigarette-statistics>.



Figure 1. Three of the many e-cigarette styles available.

Prices for the devices range from \$30 to over \$300, with a corresponding range in battery size, liquid capacity, and vapor output. The most basic device is an electronic cigarette, which looks like a traditional cigarette. Moving up the line, devices designed to make larger quantities of vapor are often called PVs or mods. Users can purchase a wide variety of commercially available devices or can make their own. Homemade vaporizers and e-liquids are common.

How Do They Work?

The devices have an electric heating element (an atomizer or cartomizer) to vaporize a liquid solution. Solutions (also called juice) usually contain a mixture of propylene glycol (increases flavor), vegetable glycerin (increases vapor), nicotine, and flavorings. Some juices provide flavored vapor without nicotine. Figure 2 shows the principal parts that are found in every e-cigarette or vaporizer.



Figure 2. Parts of an electronic cigarette.

“Automatic” e-cigarettes activate the heating coil when a user takes a drag from the device. Manual e-cigarettes have a switch that the user depresses to energize the heating element to make the heated vapor. Most manufactured devices have built-in timeout features that prevent overheating, and many have locking features to prevent the switch from being activated in a pocket or purse. An LED light to simulate cigarette glow on the end is present in some e-cigarettes, but is not common in PVs or mods.

Alternate Uses

E-cigarettes are sometimes used to smoke hash oil or “honey oil,” a cannabis product derived by separating the resins from marijuana. Separating hash oil from marijuana is a hazardous process, sometimes done illegally in hotels and homes. First responders should be aware that this practice exists and the hazards that it presents.²

Health and Safety

The health effects of the vapor and the danger of nicotine overdose by ingestion or dermal contact with the juice are the subject of ongoing review by various agencies (Cressey, 2014, World Health Organization (WHO), 2014). The regulatory situation related to e-cigarettes varies by jurisdiction and is rapidly changing. At the time of publication of this report, the following facts were known:

- On May 10, 2016, the U.S. Food and Drug Administration (FDA) issued a final rule that brought e-cigarettes under the FDA’s tobacco product authority. With this rule making, FDA now regulates the manufacture, import, packaging, labeling, advertising, promotion, sale, and distribution of e-cigarettes. At the time this report was prepared, the FDA had extended the compliance deadline until August 10, 2017.
- The WHO has proposed that member states adopt stringent controls on e-cigarettes (2014). The proposal is limited to the potential health effects of e-cigarettes, and does not include language addressing the electronics.
- American Nonsmoker’s Rights Foundation (2017) reports that 12 states and 615 local jurisdictions have laws restricting e-cigarette use in smoke-free venues; 15 states and 503 local jurisdictions have laws that restrict e-cigarette use in other venues.
- Underwriters Laboratories (UL) has developed standards that relate to lithium-ion battery safety. These standards are applied to products containing batteries that undergo UL safety testing. In early 2017, UL promulgated UL Standard 8139, Electrical Systems of Electronic Cigarettes, which evaluates only the battery and electrical controls of an electronic cigarette.
- No current regulation, code, or law applies to the safety of the electronics or batteries in e-cigarettes. While many consumer products are required to be tested by a

² For more information see: <http://www.rmhidta.org/default.aspx/MenuItemID/691/MenuGroup/RMHIDTAHome.htm>.

Nationally Recognized Test Laboratory, such as UL, there are no requirements that e-cigarettes be subjected to product safety testing. The FDA is considering regulations of the battery or electronics used in/with the devices (FDA, 2014; Ledford, 2014).

METHODOLOGY

Why Did We Look at E-Cigarettes?

A number of explosions and fires have been attributed to e-cigarettes, causing some concern within the fire service community. We conducted this review to gather information to inform first responders and other interested parties about the scope and nature of the problem.

Data Sources

Authoritative data on the occurrence of e-cigarette fires and explosions is not easy to find. The National Fire Incident Reporting System (NFIRS) does not include specific data fields on e-cigarettes that will permit the typical analysis of the frequency or impact of these incidents. Concurrent with the publication of the 2014 edition of this report, the USFA issued an advisory on how to code an e-cigarette incident in an NFIRS report³. The data cited in this report includes e-cigarette incidents reported in the NFIRS.

It has been recognized that many fires are never reported to the fire department. Fires that self-extinguish, or those that are easily extinguished by persons nearby, are frequently not reported. The 2014 report showed that the majority of e-cigarette fires fall into this category of self- or easily-extinguished. As such, few are reported in the NFIRS database.

As was done in the previous study, media reports were used to collect information on e-cigarette incidents. The internet was searched using a variety of relevant terms and multiple search engines to locate media reports on incidents of interest. Incidents were logged, and the reports were carefully reviewed to eliminate duplicate reports and to extract data of interest. Due to the newsworthy nature of the more severe incidents, there were often multiple reports on a single incident, with occasionally conflicting information. Every effort was made to eliminate duplication and redundancy.

There may be other data sources that could shed additional light on the topic. Data from emergency-room visits and/or hospital admissions could be informative. Similarly, we are aware of emergency medical system databases that could be mined for relevant data. Due to time constraints and other factors, these data sources were not queried for the present analysis.

In light of these constraints on the availability of data, and in light of the quality of that data, the information presented herein is qualitative rather than quantitative. Readers are advised to use the results appropriately.

³ USFA, NFIRSGram: Coding an electronic cigarette fire, https://www.usfa.fema.gov/data/nfirs/support/nfirsgrams/nfirsgram_electronic_cigarettes.html.

FINDINGS

Overview

Reports of 195 separate e-cigarette fire and explosion incidents in the U.S. were found, dating from January 2009 to Dec 31, 2016. In 68 percent of these incidents, 133 acute injuries were reported. No deaths were reported during the study period. A summary spreadsheet of the incidents reported is included in Appendix 2 for reference.

Figure 3 shows the status of the e-cigarettes at the time the incidents occurred.

- Sixty-one incidents occurred when either the device or spare batteries for the device were in a pocket.
- Sixty incidents occurred while the device was being used.
- Forty-eight incidents occurred while the battery in the device was being charged.
- Eighteen incidents occurred while the device or battery was stored.
- In seven incidents, it is not reported whether the e-cigarette was in use, stored, or being charged.
- One incident occurred during transportation on a cargo aircraft.

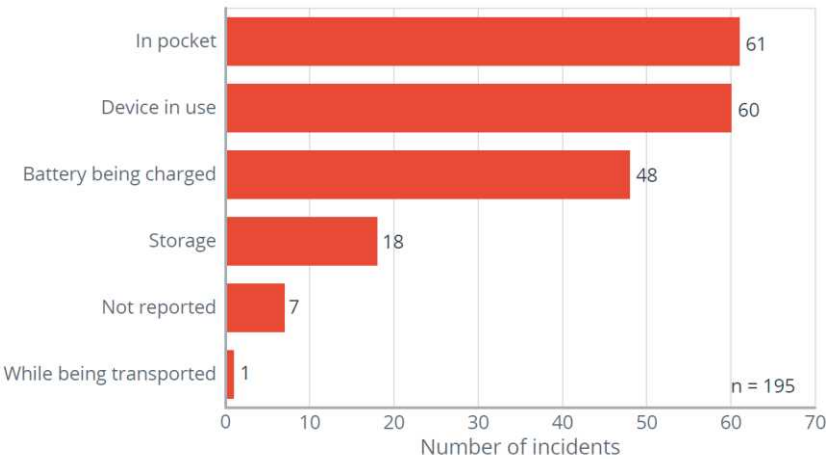


Figure 3. Status of e-cigarette when the incident occurred.

Media reports generally characterize these incidents as explosions. While there is generally a brief period of overheating and off-gassing at the onset of the event, the events tend to occur suddenly, and are accompanied by loud noise, a flash of light, smoke, flames, and often vigorous ejection of the battery and other parts. A number of the media reports state that the battery or other components of the device were ejected under pressure and “flew across the room,” often igniting combustible items where they landed.

Injuries

In 133 (68 percent) of the reported fire and explosion incidents involving e-cigarettes, a single individual was injured.⁴ Figure 4 illustrates the number and severity of injuries in e-cigarette fires and explosions.

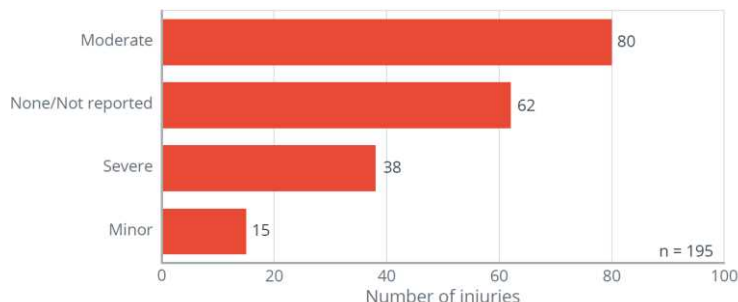


Figure 4. Injuries reported in e-cigarette incidents.

- Thirty-eight of the incidents resulted in severe injury to an individual, meaning that the victim required hospitalization, and may have suffered loss of a body part, 3rd degree burns, or facial injuries.
- Eighty victims suffered moderate injuries, which were defined as persons requiring treatment in the emergency room for smoke inhalation, 2nd degree burns, or lacerations requiring stitches. Typically, incidents reported as moderate injuries did not require admission to the hospital.
- Fifteen individuals suffered minor injuries, including smoke inhalation, minor lacerations, or 1st degree burns. Emergency room treatment may or may not have been provided.
- No injuries were reported in 62 (32 percent) of the incidents.

The incidents involving severe injuries occurred while the e-cigarette device was in the victim's mouth, in very close proximity to their face, on in a pocket. This inherent intimacy with the device is what makes the e-cigarette hazard unique among consumer products. No other consumer product that is typically used so close to the human body contains the lithium-ion battery that is the root cause of the incidents.

Did the Fires Spread?

Of the reported fire and explosion incidents involving e-cigarettes, 128 (66 percent) resulted in ignition of nearby contents such as clothing, carpets, drapes, bedding, couches, or vehicle seats. Users were generally nearby when the incident occurred, were alerted by the sound of the explosion, and were able to take action to extinguish the fires while they were still small. Figure 5 shows the distribution of fire spread due to e-cigarette incidents.

⁴ Press in the United Kingdom has reported one death in an August 2014 incident where an e-cigarette that was being charged in a non-manufacturer approved device exploded and ignited nearby oxygen equipment.

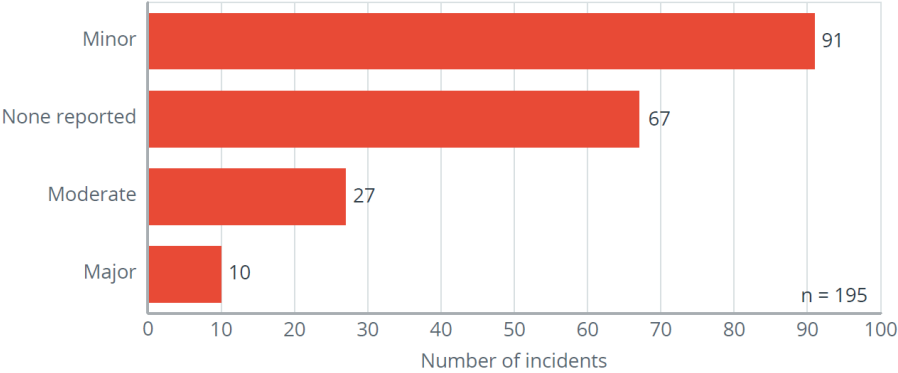


Figure 5. Fire spread in e-cigarette fire and explosion incidents.

- In 91 incidents, the fire spread was minor, meaning that the scorching or flames either self-extinguished or were extinguished very quickly by persons nearby. Typically, in these incidents, the burned areas were 6 inches or less in diameter.
- In 27 incidents, the fire spread was moderate, where the burned area was larger than 6 inches in diameter, but the fire was extinguished by occupants before the fire department arrived.
- In 10 incidents, the fire spread was major and involved significant portions of a building, and required suppression by the fire department. Typically, these incidents are what the fire service refers to as “room and contents” type fires, or larger.
- In 67 of the incidents (34 percent), there was no fire spread, or fire spread was not evident in the reports reviewed.

How the Fires Were Suppressed

The battery in the e-cigarette contains a limited amount of combustible material. If the burning battery and/or e-cigarette comes into contact with a material that is easily ignited, such as bedding or clothing, a fire can easily spread and grow. The media reports were reviewed to determine how the ensuing fires were suppressed; the results are shown in Figure 6.

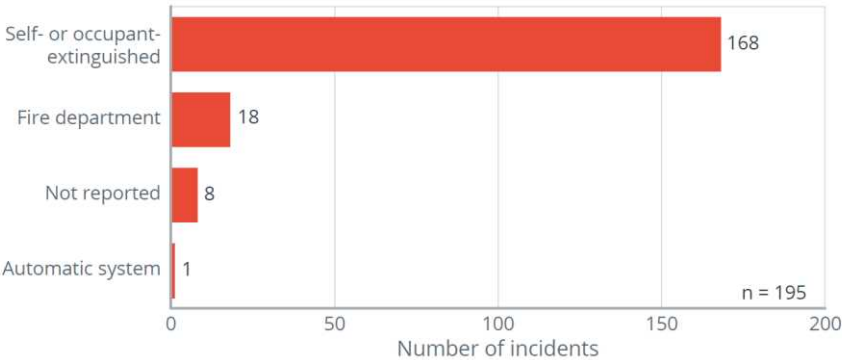


Figure 6. How e-cigarette fire incidents were suppressed.

- In 168 incidents, the fires either self-extinguished or were extinguished very quickly by persons nearby.
- In 18 incidents, the fire department performed final suppression of the fire.
- In 8 incidents, the mode of fire suppression was not reported.
- In 1 incident, an automatic fire suppression system extinguished the fire.

Trends

Figure 7 and Figure 8 show that the number of e-cigarette fires and explosions is increasing over time. An increase in the number of e-cigarette fires and explosions was postulated in the 2014 report and appears to correlate well with the increase in sales of e-cigarettes.

Figure 9 illustrates the increasing number of severe and moderate injuries resulting from e-cigarette explosions and fires. Note the increase in number of severe injuries since 2014. This appears to correlate well with the e-cigarette sales trend shown in Figure 8.

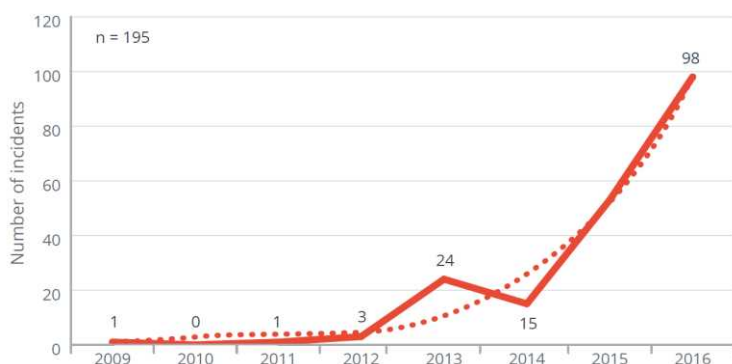
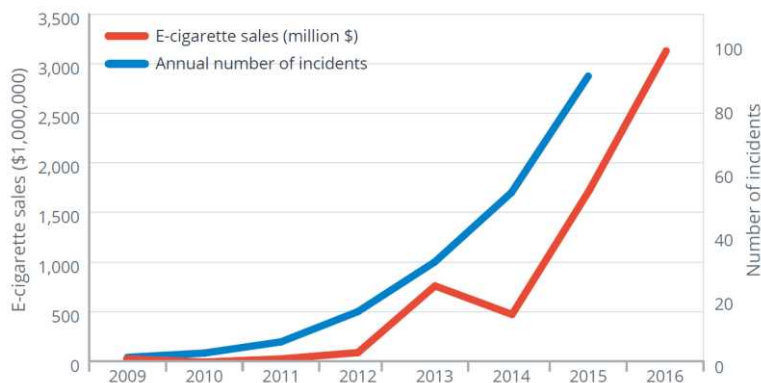


Figure 7. Number of e-cigarette fires and explosions.



E-cigarette sales data from <http://www.statisticbrain.com/electronic-cigarette-statistics/> on 3/27/2017.

Figure 8. E-Cigarette fires and explosions compared to sales.



Figure 9. Incidence of severe and moderate injuries from e-cigarette explosions and fires.

Always use the charging appliance that comes with the unit, and follow the manufacturer’s instructions. Plugging an e-cigarette into a “standard” USB port to recharge may result in an explosion and/or fire.

A NEW AND UNIQUE HAZARD TO CONSUMERS

The e-cigarette/lithium-ion battery combination presents a new and unique hazard to consumers. No other consumer product places a battery with a known explosion hazard such as this in such close proximity to the human body. It is this intimate contact between the body and the battery that is most responsible for the severity of the injuries that have been seen. While the failure rate of the lithium-ion batteries is very small, the consequences of a failure, as we have seen, can be severe and life-altering for the consumer.

Responsible battery and e-cigarette manufacturers are working hard to develop remedies for the known lithium-ion battery failures. Indeed, good and successful solutions have been put into production by responsible manufacturers. Unfortunately, the manufacturers cannot control what modifications are made by the consumer, or what replacement battery is installed into the e-cigarette by the consumer. The impact of safety features on consumer safety can be dampened by consumer behavior.

Spare Batteries

Many consumers purchase spare batteries so they can vape through the day without having to recharge batteries. Many vape shops sell plastic cases to store and carry the spare batteries; these are intended to prevent a battery short-circuit (and the ensuing explosion) if the terminals of the battery come into contact with keys or spare change in a pocket. As noted above, the device or battery in a pocket was the leading status of the e-cigarette at the time of the incident (Figure 3).

Users procure spare batteries from a number of sources. Some purchase spare batteries with their device in the anticipation that the battery will be compatible with the protection circuitry in the device. Others will salvage lithium-ion batteries from old laptop computers or power tool battery packs. While salvaged batteries can be essentially free, few users

understand that such batteries rarely have protective circuitry built in, since robust protective circuitry is typically integrated into the battery pack and/or the original device. Still other users purchase spare batteries from a variety of sources.

A quick search of online sales or auction sites will show thousands of listings for 18650 batteries, a lithium-ion battery frequently used in e-cigarettes and many other consumer devices. Most of the listings will highlight the energy capacity in milli-amp hours (mAh) of the battery being offered; typical listings vary from 2,500 mAh to 6,000 mAh. Many consumers will gravitate to the higher capacity batteries to gain the longest use. Unfortunately, many of these claims are unsubstantiated or misleading. The space inside the case of every 18650 battery for the battery components is the same, and the capacity varies considerably depending on the current draw.

Similarly, many of the online listings will claim that a battery is “protected” or “has protection,” implying protection against overcharging, overheating, or other deleterious events. While the manufacturer may (or may not) be placing a protection circuit in the battery, there is generally little technical information available about this “protection” that even an advanced user could access.

Do It Yourself

Further compounding the safety situation is the fact that a substantial number of e-cigarette users either construct their own devices from widely available parts or modify commercial products to suit their desires. Since the data reviewed in preparing this report do not provide sufficient information to permit any conclusion about how many of the incidents reported involved homemade or modified devices, it is not possible to draw valid conclusions about how these practices could be impacting the incidence of fires.

There are a number of sites on the internet that provide instructional material on how to safely construct or modify a device. Many vape shops also offer advice and instruction for the do-it-yourself vaper. The quality of the instruction and advice available varies widely, and even the best of those that were reviewed in the preparation of this report are incomplete in that they overlook elements of battery/system safety or rely on poorly-documented system components. Without a proper engineering analysis, neither purchasing a battery that has “protection,” nor adding a generic “protection circuit” to a device, can be a guarantee that the desired level of protection will be provided.

Safety Standards

UL has recently promulgated UL Standard 8139, *Electrical Systems of Electronic Cigarettes*. This new test standard will evaluate the safety of the electrical and battery systems of e-cigarettes, in the hope that fires and explosions resulting from the battery and electrical system can be eliminated.



It is important to understand what UL8139 will not do. UL advises that,

“These requirements do not cover the consumable of the electronic cigarette, such as e-Liquids and other inhaled vapor substances, wicks, and other particulate matter inhaled during use. These requirements do not consider the physiological effects of any consumable used with the product.”

Most Americans are familiar with the UL listing mark and look for this certification when purchasing electrical products. E-cigarettes that are UL-listed using this new test standard should provide a level of assurance of safety to consumers that has not been available before. However, this assurance is not absolute, since manufacturing defects and damage to the product can still occur.

This new UL standard is an important development in the safety of these devices and should serve to reduce the number of e-cigarette fires and explosions, as well as the number of injuries that American consumers have experienced from these products.

CONCLUSION

E-cigarettes using lithium-ion batteries present a new and unique hazard to consumers. No other consumer product places a battery with a known explosion hazard such as this in such close proximity to vital areas of the human body. In order to reduce the frequency of e-cigarette fires and explosions, the following recommendations should be considered:

- Consumers should look for and demand e-cigarette products that have been evaluated for safety and that are listed by UL. Look for the UL mark on the product and packaging.
- The long-term effects of the new UL safety standard cannot be determined at this time. Even with improved protection circuitry in an e-cigarette device, and with 100 percent compliance in providing such protection, there remains a possibility of battery failure and severe injury. Manufacturing defects and damage to the device or battery simply cannot be eliminated.
- Lithium-ion batteries should not be used in e-cigarettes. While the number of batteries that explode and catch fire is statistically small, the catastrophic nature of the injuries that can occur warrants the use of another battery technology for e-cigarettes.
- As long as lithium-ion batteries continue to be used in e-cigarettes, severe injuries will continue to occur. As the number of e-cigarettes in use increases, the number of

severe injuries from lithium-ion battery explosions and fires will likely continue to increase.

- Suppliers, industry associations, user groups, and fire prevention educators should all stress the importance of using UL-listed devices and proper charging practices to reduce the number of incidents. Stronger warnings in the literature and user manuals may be helpful.

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APPENDIX 1: A PRIMER ON LITHIUM-ION BATTERY FAILURE IN E-CIGARETTES

Lithium-ion-polymer (Li-ion) batteries are excellent power supplies for portable devices and are widely used by consumers, industry, and the emergency services. Li-ion batteries are known to experience statistically rare failure events, including fire and explosions (Mikolajczak, Kahn, White & Long, 2011). Indeed, there are multiple reports of fires caused

by failures of Li-ion batteries in cell phones, laptop computers, medical devices, electric cars, power tools, hoverboards, and a myriad of other electronic devices.

Why Do Li-Ion Batteries Catch Fire?

A cylindrical Li-ion battery is made by winding alternating layers of metallic anode and cathode material separated by a porous film. The porous separator film holds a liquid electrolyte made of an organic solvent and dissolved lithium salts. This core is placed into a cylindrical metal can through the open end, and the can is then sealed tightly closed so that the liquid electrolyte cannot escape or evaporate.



All of the electrolytes currently used in Li-ion batteries are either flammable or combustible liquids. It is this flammable electrolyte that causes the fire and explosion when the Li-ion battery overheats.⁵ Scientists are working to develop nonflammable electrolytes for Li-ion batteries, but these are not yet available in the market.

During the typical failure mode for a Li-ion battery, the electrolyte is heated to its boiling point.⁶ The internal pressure in the battery builds to a point where the seal at the end of the battery ruptures, and the pressure is abruptly released through the sealed end of the battery case. Usually, the electrolyte then ignites, and expanding gas from the rapid combustion will further increase the pressure. The fire is sustained briefly after initial ignition by the porous separator film, which is made of plastic. Mikolajczak, et al. (2011) provide detailed descriptions and explanations of the various failure modes that Li-ion batteries can experience. A number of videos showing Li-ion battery ignition can be easily found on the internet.

Why Is the Impact of Battery Failure Different in E-Cigarettes?

E-cigarettes are different from other electronic consumer devices because the battery is installed in a cylindrical device (the e-cigarette) that has its weakest (structural) point at the ends. When the battery seal (at the end of the battery) ruptures, the pressure within the e-

⁵ A variety of organic solvents are used, alone or in combinations. The boiling points of the electrolytes range from 200°F to 500°F, and ignition temperatures range from 60°F to 300°F.

⁶ Overheating of the battery (thermal runaway) can be caused by: puncture, overcharge, external heat, short circuit, or internal cell fault.

cigarette cylinder builds quickly until it ruptures, usually at the end. As a result of the battery and container failure, one or the other, or both, can be propelled across the room like a bullet or small rocket.

In contrast to e-cigarettes, the cylindrical Li-ion batteries used in laptop computers and portable tools are contained in rigid plastic cases that are generally strong enough to prevent the failing battery from rocketing away. Fires do occur as a result of battery failure, but most fires initially involve only the device that the battery pack is installed in.⁷

Cell phones, tablets, and other devices use pouch-type Li-ion batteries that are flat, rather than cylindrical in shape, and are encased in a sealed flexible plastic pouch or rigid plastic case instead of a metal can. These pouch-type batteries will not build up much pressure when they overheat and do not explode violently when they fail. Pouch batteries can, and have, overheated to the point where the pouch bursts, the electrolyte ignites and a fire spreads beyond the device.⁸



What Safeguards Are Used to Prevent Fires in Li-Ion Batteries?

Several different approaches to protecting Li-ion batteries against explosion or fire have been developed. Protection can be built into the battery, into the charging appliance, or into the electronics that control the charging cycle and/or the current draw. Often, a combination of these approaches is used in a product. Amon, Andersson, Karlson, and Sahlin (2012) conclude that the risk of fire depends heavily on the type and effectiveness of the protection system used.

The protection appropriate for a particular device or appliance is determined by the device manufacturer, and/or by regulations or standards that apply to that product. Since there are no regulatory standards directly applicable to e-cigarettes, the selection of protection for the Li-ion battery is left to the manufacturers' best judgment. The fact that, statistically, so few of these devices are failing in the ways described in the media reports suggests that e-cigarette manufacturers have been largely successful in preventing battery fires.

⁷ A laboratory experiment showing worst-case Li-ion battery failures in a laptop computer can be seen at <https://www.youtube.com/watch?v=pizFsY0yjs#t=250>.

⁸ Failure of an intentionally overloaded pouch-type Li-ion battery can be seen at https://www.youtube.com/watch?v=SMY2_qNO2Y0&index=8&list=PLkLKD6x5giq2LyjhKbJt-OYR8kiAN8_UW.

APPENDIX 2: E-CIGARETTE FIRES AND EXPLOSION INCIDENTS

E-cigarette incidents reviewed						
Date	Location	Status	Fire beyond e-cig?	Injuries?	Extinguished	Notes
Aug 2009	Minneapolis, MN	Transport	Moderate	None	System	Fire in a cargo container on a FedEx® jet discovered during approach to landing. Fire suppression system activated. Fire was linked to lithium-ion batteries in box of Ruyan inhalers, model RappE-Mystick.
Nov 2011	Greeley, CO	Use	No	Severe	Self or occupant	A man was hospitalized for eight days after an electronic cigarette exploded in his face, sending burning debris and battery acid into his mouth, face and eyes. Prodigy V3.1 e-cig cited, as well as Radio Shack Energell battery.
Feb 2012	Niceville, FL	Use	No	Severe	Self or occupant	E-cigarette explodes in mouth causing severe burns, lost teeth and part of tongue. Lots of press coverage on this one. Some stories report that the device may have been modified by the user.
Apr 2012	Muskogee, OK	Use	No	None	Self or occupant	New e-cig exploded when withdrawn from packaging.
Nov 2012	Sherman, TX	Charge	No	Moderate	Not reported	Battery into two-hour charge exploded in users hand. Second and third degree burns on hand and smoke inhalation.
Apr 2013	Glendale, AZ	Charge	Moderate	None	Self or occupant	Exploded while charging from USB adaptor in car. Hot fragments ignited back seat upholstery.
Apr 2013	Oklahoma City, OK	Storage	Moderate	Minor	Not reported	Explosion of lithium-ion battery in e-cig in office. Occupant treated for inhalation.
Jul 2013	Corona, CA	Charge	Minor	Moderate	Self or occupant	Charging in car led to "blowtorch" fire and explosion. Debris flew into occupant's lap, resulting in second degree burns on upper thighs and lower buttocks. Driver used coffee to extinguish the fire.
						Source URL
						https://www.consumeraffairs.com/news/04/2012/04/e-cigarette-exploded-in-mans-face-suit-charges.html
						http://www.cbsnews.com/news/electronic-cigarette-explodes-in-mans-mouth-causes-serious-injuries/
						http://www.mothejones.com/environment/2014/04/e-cigarettes-explode-fda-timeline
						http://www.kxii.com/news/headlines/E-cigarette-explodes-in-Texas-mans-home-215771641.html
						http://www.kpho.com/story/22066822/unattended-electronic-cigarette-charger-explodes-car-catches-fire
						http://www.koco.com/news/oklahomaews/okc/Police-Explosion-at-apartment-complex-came-from-e-cigarette/19768650#!T8hDI
						http://losangeles.cbslocal.com/2013/07/11/corona-couple-sues-after-e-cigarette-battery-explodes-in-car/

E-cigarette incidents reviewed						
Date	Location	Status	Fire beyond e-cig?	Injuries?	Extinguished	Notes
Jul 2013	Oklahoma City, OK	Charge	Minor	None	Self or occupant	Device exploded and shot across the room 15 minutes after being plugged into charger. Bum marks on carpet and wall.
Jul 2013	Tulsa, OK	Charge	Minor	Not Reported	Not reported	Fire while charging off laptop.
Jul 2013	Claremont, CA	Storage	Moderate	Moderate	Self or occupant	E-cigarette charging in car overheated and exploded. Parts landed in female occupant's lap and caused burns. Reported second degree burns on back of upper thighs and lower buttocks.
Aug 2013	Oklahoma City, OK	Charge	Minor	None	Self or occupant	Device exploded while being charged.
Aug 2013	Phoenix, AZ	Charge	Minor	None	Self or occupant	This one ignited carpet, was put out by resident. Video shows plugging into white laptop for charge.
Aug 2013	Phoenix, AZ	Charge	Major	Minor	Fire department	Resident states in article that e-cig started two fires in their bedroom in recent days. They just exploded. Charging for about 20 minutes. First incident scorched carpet, second gutted the bedroom. Resident treated for smoke inhalation. (Smokin Time brand cited.)
Sep 2013	Grant Park, GA	Charge	Minor	None	Self or occupant	Device exploded during charging, shooting flame across the room. Scorch mark on couch, hole burned in carpet. Occupant used a rag to control.
Sep 2013	Binghamton, NY	Charge	Moderate	None	Fire department	Fire in home caused by charging e-cig.
Sep 2013	Provo, UT	Charge	Moderate	Moderate	Self or occupant	Explosion while charging in car. Hot fragments ignited baby's car seat in back seat resulting in first and second degree burns to 3 year old. Driver used iced coffee to extinguish fire.

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Appendix 2. (Continued)

E-cigarette incidents reviewed						
Date	Location	Status	Fire beyond e-cig?	Injuries?	Extinguished	Notes
Oct 2013	La Crosse, WI	Charge	Minor	Not Reported	Self or occupant	Story highlights several incidents during charging. Lack of overcurrent/ overhear circuitry implicated.
Oct 2013	Valparaiso, FL	Charge	Moderate	None	Self or occupant	Explosion while charging from USB port, igniting curtains. Occurred after 10 minutes charging.
Oct 2013	Blaine, MN	Charge	Minor	None	Self or occupant	Exploded and shot across the room while charging on USB plugged into computer. Carpet burned in several spots.
Nov 2013	Kootenai County, ID	Charge	Moderate	None	Self or occupant	Explosion while charging from USB port of laptop. Ignited couch. Smoke alarm alerted the sleeping family of four.
Nov 2013	Warren, MI	Charge	Minor	None	Self or occupant	Device blew out of wall socket in ball of fire. Scorched hardwood flooring before occupant extinguished it. TV video report shows a USB wall charger that does not match those supplied by the manufacturer (Bulldog brand cited).
Nov 2013	Eugene, OR	Charge	Moderate	None	Not reported	Device failed after about two hours charging. Fragments flew to back seat, igniting seat of truck.
Nov 2013	Queen Creek, AZ	Charge	Minor	None	Self or occupant	Exploded while charging, shooting across the room. Impacted window, fell to floor and ignited carpet.
Nov 2013	Colorado Springs, CO	Charge	Moderate	Moderate	Self or occupant	Unattended while charging on floor. Ignited bed. Home occupant burned arms, hands and face while using blanket to smother flames.
Dec 2013	Salt Lake City, UT	Charge	Minor	None	Self or occupant	E-cig exploded while being charged through USB port on a computer.
						Source URL
						http://www.dailymail.co.uk/news/article-2442715/E-cigarette-explosion-causes-Wisconsin-home.html
						http://www.nwfdailynews.com/1.214335
						Original story accessed October 2014 from www.fox9.com (KMSP, Eden Prairie, MN) has been removed.
						http://www.wptv.com/news/local-news/water-cooler/e-cigarette-blamed-for-house-fire-in-idaho-electronic-cigarette-battery-overcharged-and-exploded
						http://www.wxyz.com/news/warren-woman-says-electronic-cigarette-caused-small-explosion-and-fire
						http://www.kval.com/news/local/e-cigarette-explodes-damaging-truck
						http://www.motherjones.com/environment/2014/04/e-cigarettes-explode-fda-timeline
						http://www.azfamily.com/story/28374147/exploding-electronic-cigarette-blamed-for-fire
						http://www.krdo.com/news/local-news/e-cigarette-blamed-for-mattress-fire/34229451
						http://fox13now.com/2013/12/09/e-cigarette-explodes-while-charging/

E-cigarette incidents reviewed							
Date	Location	Status	Fire beyond e-cig?	Injuries?	Extinguished	Notes	Source URL
Dec 2013	Springfield, MO	Charge	Moderate	Moderate	Self or occupant	Failure while charging on laptop USB port. Ignited bedding, second degree burns on leg and foot. User quoted as saying he likely used the wrong charger.	Original story accessed October 2014 from www.ky3.com (Springfield MO) has been removed.
Dec 2013	Salt Lake City, UT	Charge	Minor	None	Self or occupant	Device exploded while being charged. Shot across the room; minor burn marks.	http://fox13now.com/2013/12/09/e-cigarette-explodes-while-charging/
Dec 2013	Phoenix, AZ	Charge	Major	None	Fire department	E-cig being charged exploded on bed, igniting room and contents.	http://www.abc15.com/news/local-news/investigations/ phoenix-fire-department- officials-wam-electronic-cigarette-users-about-fire-danger
Jan 2014	Sneads Ferry, NC	Use	No	Minor	Self or occupant	Device erupted in his face. Temporary blindness, minor burns to face.	http://www.jdnews.com/20140111/man-injured-after-e-cig-blows-up/301119030
Mar 2014	Medford, OR	Charge	Minor	None	Self or occupant	Exploded while being charged, sending bits of burning battery flying into the ceiling and walls. One hot piece of battery landed on a pillow, causing it to smolder and filling the house with smoke.	http://www.katu.com/news/ local/Fire-marshal-e-cigarette- batteries-cause-fires-in- Medford-248274331.html
Mar 2014	Medford, OR	Charge	Minor	None	Self or occupant	The lithium batteries that power the vaporizers in electronic cigarettes caused two recent fires in Medford. In this second case, a mattress caught fire, but a resident put it out.	http://www.katu.com/news/ local/Fire-marshal-e-cigarette- batteries-cause-fires-in- Medford-248274331.html
Mar 2014	Lompoc, CA	Charge	Moderate	None	Self or occupant	Started kitchen fire while charging unattended.	Original story accessed October 2014 from www.ksby.com (San Louis Obispo, CA) has been removed.
Mar 2014	Syracuse, NY	Not reported	Moderate	Severe	Self or occupant	Patient on oxygen in a hospital suffered first and second degree burns. Patient had e-cig, but investigation has not yet tied e-cig to the ignition. Hospital has banned e-cigs out of caution. Patient transferred to area burn unit.	http://www.foxnews.com/us/2014/04/22/ny-hospital- reinforces-ban-after-e-cigarette- fire/

Appendix 2. (Continued)

E-cigarette incidents reviewed						
Date	Location	Status	Fire beyond e-cig?	Injuries?	Extinguished	Notes
Apr 2014	Goffstown, NH	Charge	Minor	None	Self or occupant	Resident reported to fire department that e-cigarette was left in bedroom to charge. Shortly thereafter, resident heard a loud bang and on investigating discovered a small fire in the carpet of the bedroom. Resident extinguished the fire and found e-cigarette pieces on the carpet.
Apr 2014	Destin, FL	Use	No	Severe	Self or occupant	Vape blew up in his face. Dime-sized hole in the roof of his mouth. Burns to hand, fractured neck and finger, burns to cornea, damaged teeth.
May 2014	Orlando, FL	Charge	Minor	None	Self or occupant	Resident heard a loud bang in bedroom where e-cigarette was charging and discovered carpet on fire when she investigated. Resident extinguished the fire.
Jul 2014	Oklahoma City, OK	Charge	Major	None	Fire department	Device exploded while being charged. Ignited home fire.
Jul 2014	Lawrenceville, NJ	Charge	Major	None	Self or occupant	E-cigarette left unattended for two plus hours in an aftermarket charger in a vehicle failed and started fire in rear seats. Windows were closed, so fire self-extinguished; sedan interior was extensively damaged.
Aug 2014	Boston, MA	Storage	Minor	None	Self or occupant	E-cigarette packed in checked luggage ignited in the baggage hold of a commercial airliner before takeoff. Burned a "small hole" in the bag.
Sep 2014	Honolulu, HI	Charge	Minor	None	Fire department	Unattended charging via typical AC USB adaptor. Occupant returned to find kitchen counter and contents burning. Occupant extinguished the fire and called fire department.
Nov 2014	College Park, MD	Use	inor	None	Fire department	A sparking e-cigarette was discarded into a university trash can, igniting the contents. Fire department responded and extinguished the fire. No damage beyond the trash.
						Source URL
						Direct report from Lt. Bill Connor, EFO, Goffstown Fire Department.
						http://www.fox5dc.com/news/national/17391566-story
						http://www.wftv.com/news/news/local/Action-9-investigates-electronic-cigarette-charger/ngwJM/
						http://www.news9.com/story/25939272/e-cigarette-charger-explodes-causes-house-fire
						http://hijaii.org/electronic-cigarette-was-overcharged-causing-a-fire/
						http://www.nytimes.com/2014/08/14/business/e-cigarettes-under-scrutiny-for-listing-as-flight-hazard.html?_r=0
						http://www.hawaiinewsnow.com/story/26659072/explosion-at-honolulu-apartment-blamed-on-e-cigarette
						http://www.diamondbackonline.com/news/campus/article_dfebfb78-6ac9-11e4-86ee-97c41f1e0c8e.html

Appendix 2. (Continued)

E-cigarette incidents reviewed						
Date	Location	Status	Fire beyond e-cig?	Injuries?	Extinguished	Notes
Feb 2015	Ramona, CA	Use	No	Severe	Fire department	Authorities responded to the Stage Stop Liquor Store in Ramona Sunday evening after an e-cigarette exploded, burning an employee and damaging the store. Materials from the e-cigarette cut the man's face and shattered a glass display inside the store, the captain said. Victim was hospitalized with facial burns.
Feb 2015	Anaheim, CA	Use	No	Minor	Not reported	Witnesses told police that the 17-year-old boy was holding an electronic cigarette in the moments before the explosion. Victim suffered cuts and burns to his hand.
Feb 2015	CA	Use	No	Severe	Self or occupant	When victim brought the device up to his face to see if it was making the hissing sound, it exploded. The tank hit him in the face, the mouth piece blasted through his cheek leaving a ragged hole, and the bottom of the tank blew off and caught fire. A nearby curtain, blanket and chair caught fire. Second degree burns to face, ear and neck, also broken cheekbone and concussion.
Mar 2015	Gates, NY	Use	Minor	Moderate	Not reported	MOD failed 30 seconds after battery was inserted. Victim required about six stitches to close hand laceration.
Mar 2015	Santa Ana, CA	Use	No	Minor	Not reported	Victim was smoking a MOD e-cigarette about 1:45 a.m. Treated for flash burns to face and hand, and lacerations to the hand.
						http://fox5sandiego.com/2015/02/09/e-cigarette-explodes-in-mans-face/ http://www.latimes.com/local/lanow/la-me-ln-e-cigarette-explosion-oc-teen-20150210-story.html http://abc7.com/news/e-cigarettes-may-lead-to-explosions-fires/513968/ http://www.dailymail.co.uk/news/article-3327374/Former-LA-Galaxy-star-suffers-hole-cheek-e-cigarette-exploded-face-industry-faces-string-lawsuits-victims-say-suffered-burns-lost-FINGERS.html https://www.youtube.com/watch?v=03ilX9nln2E http://www.latimes.com/local/lanow/la-me-ln-man-e-cigarette-explodes-santa-ana-20150309-story.html http://losangeles.cbslocal.com/2015/03/09/e-cigarette-explosion-burns-oc-mans-face-and-sets-fire-to-bed/

E-cigarette incidents reviewed							
Date	Location	Status	Fire beyond e-cig?	Injuries?	Extinguished	Notes	Source URL
Apr 2015	Little Egg Harbor, NJ	Charge	Minor	None	Not reported	Consumer using cellphone wall charger instead of e-cig charger (USB cord). Char marks in kitchen.	http://www.pressofatlanticcity.com/news/breaking/little-egg-harbor-knows-e-cigarettes-can-explode/article_6f7693d0-ed4b-11e4-b70f-a3cb9214b370.html
Apr 2015	Jupiter, FL	Pocket	No	Moderate	Self or occupant	Battery exploded in pants pocket. Severe burns to leg.	http://palmbeachhealthbeat.blog.palmbeachpost.com/2015/05/27/jupiter-schoolteacher-claims-vape-battery-exploded-in-pants/
Apr 2015	N. Myrtle Beach, SC	Charge	Minor	None	Self or occupant	The event occurred April 8, 2015. The device was being charged; a loud noise was heard. After which, a fire was found in a suitcase which was open. A dry chemical extinguisher was used to extinguish. Products cited: AC Adapter Eleaf Model: DEK-OC-001 Output 5.0 V. Battery pack: Brand VaVaVape	Direct report from Keith Williams, Fire Marshal, Fire Prevention Division, City of North Myrtle Beach, 1018 Second Ave. South, North Myrtle Beach, S.C. 29582. (843) 280-5614 Office. kwilliams@nmb.us
Jun 2015	Coeur D'Alene, ID	Charge	Minor	None	Self or occupant	Device in wall charger not provided with the e-cig. Battery failed, igniting carpet. Extinguished by hotel manager with extinguisher.	http://www.krem.com/story/news/local/kootenai-county/2015/06/18/e-cigarette-in-wrong-charger-sparks-coeur-dalene-fire/28961587/
Jun 2015	Austin, TX	Pocket	No	Moderate	Self or occupant	Extra battery exploded in pocket, causing first and second degree burns on leg.	http://www.theblaze.com/stories/2015/07/22/e-cigarette-blows-up-like-a-firecracker-in-mans-pocket/
Jul 2015	Miramar Beach, FL	Use	No	Severe	Self or occupant	Device exploded in mouth. Severe injuries reported.	http://www.waltonsun.com/1.498698
Jul 2015	Las Vegas, NV	Pocket	Minor	Moderate	Self or occupant	Device exploded in pocket. Burns to leg.	http://www.reviewjournal.com/news/las-vegas/las-vegas-man-files-lawsuit-over-exploding-e-cigarette-battery
Aug 2015	Wyandotte, MI	Use	No	Moderate	Self or occupant	The pen was in victim's hand when it exploded. "The thing just fired up out of my hands, hit the wall," he said. His arm was scorched; he may have lasting nerve damage to his thumb and a part of his abdomen is black from burns, according to the report.	http://patch.com/michigan/dearborn/man-injured-exploding-e-cigarette-congresswoman-wants-fda-regulate-0

Appendix 2. (Continued)

E-cigarette incidents reviewed							
Date	Location	Status	Fire beyond e-cig?	Injuries?	Extinguished	Notes	Source URL
Sep 2015	CA	Pocket	No	Severe	Self or occupant	Second degree burns to left leg. Two skin grafts.	http://www.dailymail.co.uk/news/article-3327374/Former-LA-Galaxy-star-suffers-hole-cheek-e-cigarette-exploded-face-industry-faces-string-lawsuits-victims-say-suffered-burns-lost-FINGERS.html
Sep 2015	White House, TN	Pocket	Minor	Moderate	Self or occupant	Device overheated and caught fire in pocket. Second and third degree burn to upper thigh and stomach.	http://kval.com/news/nation-world/white-house-teen-burned-by-exploding-vape-warns-of-potential-dangers
Oct 2015	Wichita, KS	Use	No	Minor	Self or occupant	Battery exploded when e-cig was taken off charger to use. Minor burns to hand. Parts of the e-cig flew in separate directions, parts embedded into sheet rock walls on opposite side of the room.	Original story accessed November 2016 from www.ky3.com (Wichita, KS) has been removed.
Oct 2015	Omaha, NE	Use	No	Moderate	Self or occupant	Device exploded, burning his face, knocking out several teeth, and breaking the roof of mouth.	http://www.ketv.com/article/vaporizer-explodes-in-mans-mouth/8302383
Oct 2015	Cape Coral, FL	Pocket	Minor	Moderate	Self or occupant	Device exploded in man's pocket. Second and third degree burns to thigh.	http://www.nbc-2.com/story/30387843/cape-man-is-latest-to-suffer-from-e-cigarette-malfunction#VjORmfVhrM https://www.youtube.com/watch?v=blcL-w2stp8&feature=youtu.be
Oct 2015	Seattle, WA	Use	Minor	Severe	Self or occupant	Device exploded in mouth. Lost eight teeth, lacerations to lips and gums, burns to right eye.	http://www.seattletimes.com/seattle-news/health/exploding-e-cigarettes-send-vapers-to-harborview-with-groesome-injuries/
Oct 2015	Bakersfield, CA	Use	No	Severe	Self or occupant	Device exploded near his face, badly burning his mouth, tongue, and left hand, which was holding the device. Doctors amputated his left index finger.	http://ktla.com/2015/11/19/lawsuits-filed-after-exploding-e-cigarettes-leave-3-injured/ http://www.mercurynews.com/2015/11/20/los-angeles-exploding-e-cigarettes-prompt-lawsuits-one-user-lost-half-a-finger/

		E-cigarette incidents reviewed					
Date	Location	Status	Fire beyond e-cig?	Injuries?	Extinguished	Notes	Source URL
Oct 2015	North Naples, FL	Use	No	Severe	Self or occupant	Twenty-one year old man critically injured when e-cig exploded in his mouth during use. Reports include claims that part of the device went down his throat and exploded again.	http://www.foxnews.com/health/2015/10/28/florida-man-placed-in-coma-after-e-cigarette-explosion.html http://www.winknews.com/2015/10/26/e-cigarette-explosion-leaves-man-in-medically-induced-coma/ http://www.keameyhub.com/news/regional/columbus-man-almost-loses-an-ear-in-e-cigarette-explosion/article_6496bd6e-8d6e-11e5-aff1-3fabf4c602ba.html
Nov 2015	Columbus, NE	Use	No	Moderate	Self or occupant	First-degree burns to his eye, and first and second-degree burns to his face. Nearly lost ear. Device exploded near head.	http://www.arkansasmaters.com/news/local-news/e-cigarette-explodes-in-bentonville-mans-face
Nov 2015	Bentonville, AK	Use	No	Severe	Self or occupant	User reported, "I put it to my mouth, and as soon as I pressed the button on the bottom, the device exploded." User suffered burns to mouth, throat, and hand, shattered teeth, and severed lips.	NFIRS 0035805
Nov 2015	Aloha, OR	Charge	Moderate	None	Self or occupant	Device exploded when charging. Ignited wicker shelving unit.	NFIRS 1536089
Nov 2015	Shreveport, LA	Pocket	Moderate	None	Self or occupant	He stated that he was looking for his keys when something sparked coming out of his pocket. The charger was flung into the right rear of the passenger compartment, causing clothing and other materials behind the seat to catch fire.	http://mynews1a.com/uncategorized/2016/01/11/did-e-cigarette-explode-in-his-pocket-user-sues-manufacturer-seller/ http://www.wpxi.com/news/local/e-cigarette-explodes-sets-washington-cou/26982472
Nov 2015	CA	Pocket	Minor	Moderate	Self or occupant	Device burned and then flashed inside pants pocket. Second and third degree burns on thumbs and left leg.	http://www.seattletimes.com/seattle-news/health/exploding-e-cigarettes-send-vapers-to-harborview-with-gruesome-injuries/
Nov 2015	Washington County, PA	Storage	Minor	Minor	Self or occupant	Mod-type device exploded while driving car. First degree burns to two occupants. Minor burns to car seat and floor carpet.	
Nov 2015	Seattle, WA	Use	No	Severe	Self or occupant	Device exploded near mouth. Lacerations to nose and upper lip; ripped out nose ring.	

Appendix 2. (Continued)

E-cigarette incidents reviewed						
Date	Location	Status	Fire beyond e-cig?	Injuries?	Extinguished	Notes
Nov 2015	Colorado Springs, CO	Use	No	Severe	Self or occupant	Device exploded near 29 year old user's face. Reports included fractured neck vertebrae, facial fractures, fractured teeth and other injuries.
Nov 2015	Hollywood, FL	Charge	Minor	None	Self or occupant	E-cig exploded on bed while being charged. Ignited mattress and bed clothes.
Nov 2015	Brenerton, WA	Charge	Major	None	Fire department	Charging e-cig ignited hotel room contents. Room and contents fire.
Nov 2015	Newport Beach, C.A	Use	No	Moderate	Self or occupant	Device exploded in hand. Third degree burns to hand.
Dec 2015	Gulfport, FL	Pocket	No	Moderate	Self or occupant	Device exploded in pants pocket. Second and third degree burns to leg.
Dec 2015	Oklahoma City, OK	Use	No	Moderate	Self or occupant	Device exploded while being refilled. Laceration to head; burns to carpet.
Dec 2015	Grand Rapids, MI	Pocket	Minor	Moderate	Self or occupant	E-cigarette battery exploded in his pocket; second and third degree burns on his leg.
Dec 2015	Pittsburg, PA	Pocket	Minor	Moderate	Self or occupant	Spare battery ignited inside pants pocket. Second and third degree burns to leg.

E-cigarette incidents reviewed						
Date	Location	Status	Fire beyond e-cig?	Injuries?	Extinguished	Notes
Dec 2015	Clovis, CA	Pocket	Minor	Moderate	Self or occupant	E-cigarette in his pocket exploded and caught fire. "He's got pretty serious burns on his hand as he reached into his pocket to pull the cigarette out, and on his leg," Stirrup said. "It burned straight through his pants."
Dec 2015	Cashmere, WA	Use	Minor	Severe	Self or occupant	Ignited in hand while driving. Third degree burns forearm and elbow.
Dec 2015	Huntsville, AL	Pocket	No	Moderate	Self or occupant	Second and third degree burns to his legs and hands.
Dec 2015	Chesterfield, VA	Charge	Moderate	None	Self or occupant	Six plug charging unit for vapor smoking devices caught fire on the floor in the office/storage area. The unit had five of the six ports in the charging unit being used. The charging device was melted and charred with minor charring/burned area in the carpet approximately 2 feet by 2 feet where the device was sitting. The manager/employees extinguished the fire prior to our arrival.
Dec 2015	Kelso, WA	Use	No	Severe	Self or occupant	Device exploded at mouth. Lost eight teeth and portion of lower palate. Burns to face, neck, chest and mouth.
Dec 2015	Pismo Beach, CA	Use	No	Moderate	Self or occupant	The e-cig exploded, igniting his right hand, and sending hot metal shrapnel and debris toward his face and hands. Multiple lacerations, a flash burn to his right eye, and experienced pain in his lungs from inhaling fumes and debris from the e-cigarette's exploded battery.

Source URL

<http://abc7news.com/news/explosive-lawsuit-could-light-up-e-cigarette-industry/1224224/>

<http://www.seattletimes.com/seattle-news/health/exploding-e-cigarettes-send-vapers-to-harborview-with-gnuesome-injuries/>

<http://www.wsfa.com/story/34066138/huntsville-man-sues-after-e-cigarette-battery-explodes>

NFIRS 0036595

http://tdn.com/news/local/kelso-man-sues-over-exploding-e-cigarette/article_91e46836-8146-5667-93bd-bb317e1441ce.html

<http://www.newtimeslo.com/news/13377/pismo-man-sues-after-hes-injured-by-exploding-e-cigarette/>

Appendix 2. (Continued)

E-cigarette incidents reviewed						
Date	Location	Status	Fire beyond e-cig?	Injuries?	Extinguished	Notes
Dec 2015	Seattle, WA	Use	No	Severe	Self or occupant	Device exploded in hand. Burns and lacerations to hand and arm.
Dec 2015	Pittsburg, PA	Pocket	Minor	Moderate	Self or occupant	Spare battery ignited inside pants pocket. Second and third degree burns to leg.
Dec 2015	Cowlitz County, WA	Use	No	Severe	Self or occupant	Device exploded at mouth. Lost teeth, burns to face, mouth.
Dec 2015	Ogden, UT	Use	Major	Minor	Fire department	Device exploded in hand; user dropped the device and ran to sink to cool bum. Device ignited room fire. Fire department extinguished.
Jan 2016	Orange, CA	Pocket	No	Moderate	Self or occupant	Battery exploded in pants pocket, causing second and third degree burns to leg.
Jan 2016	Ladera Ranch, CA	Pocket	No	Moderate	Self or occupant	Battery exploded in pants pocket. First and second degree burns to leg.
Jan 2016	Jackson, IN	Use	No	Moderate	Self or occupant	E-cig exploded while driving. Burns to face and hands. Lost control and crashed truck.
Jan 2016	Round Rock, TX	Use	Moderate	Severe	Self or occupant	Device exploded in hand. Severe burns on hand.
Jan 2016	Dallas, TX	Pocket	Minor	Moderate	Self or occupant	Device overheated and caught fire in pocket. Second and third degree burns to thigh.
Jan 2016	Seattle, WA	Use	No	Moderate	Self or occupant	Device exploded and burned face and hand.
						http://www.seattletimes.com/ seattle-news/health/exploding- e-cigarettes-send-vapers-to- harborview-with-gruesome-injuries/
						https://www.ems1.com/weird-news/articles/72121048-3- men-suffer-serious-burns-from-e-cigarette-battery-fires/
						http://www.seattletimes.com/ seattle-news/vapers-sue-e- cigarette-makers-sellers-after-explosions-burns/
						http://www.standard.net/ fire/2015/12/25/christmas- house-fire-ogden-exploding-e- cigarette
						http://www.nbcdosangeles.com/ news/local/e-cigarette-explode- law-suit-battery-los-angeles.html
						http://www.cbsnews.com/ news/e-cigarette-explodes-in-teens-pocket-at-work/
						http://www.wbiw.com/local/archive/2016/01/e-cigarette- explodes-causing-crash-on-i-65.php
						NFIRS 0107009
						http://dfw.cbslocal.com/2016/01/11/man-suffers-third-degree-burns-when-e-cigarette-battery-bursts/
						http://www.seattletimes.com/ seattle-news/health/exploding- e-cigarettes-send-vapers-to- harborview-with-gruesome-injuries/

E-cigarette incidents reviewed							
Date	Location	Status	Fire beyond e-cig?	Injuries?	Extinguished	Notes	Source URL
Feb 2016	Cecil County, MD	Use	No	None	Self or occupant	User reported the battery was ejected from the e-cig and struck him in the cheek.	http://www.abc2news.com/news/in-focus/cecil-county-man-says-e-cigarette-exploded-in-his-face
Feb 2016	Missoula, MT	Use	Minor	Severe	Self or occupant	"E-cigarette recently exploded while he was using it, causing massive damage to his mouth. Lost four front teeth, top front teeth, and his lower front teeth are all going to need root canals, because there was just so much damage. Not only to the teeth, but it also blew out large chunks of jaw bone," said his dentist. "It blew a tooth out, an upper tooth out, and all the way through the mouth, and it took 22 stitches. It was like a bullet hole in the young man's face."	http://www.ktrh.com/2016/02/missoula-teenager-loses-teeth-to-exploding-e-cigarette
Feb 2016	Splendora, TX	Pocket	Moderate	Moderate	Self or occupant	Battery exploded in pocket while driving. Burns to leg. Car fire.	http://www.fox4news.com/news/texas/84728658-story
Feb 2016	UT	Pocket	Minor	Moderate	Self or occupant	Ignited in pocket; second and third degree burns to leg and hand.	http://fox13now.com/2016/02/19/utah-man-burned-by-exploding-battery-urges-other-e-cigarette-users-to-be-cautious/
Feb 2016	Owensboro, KY	Pocket	Minor	Minor	Self or occupant	Device ignited in pants pocket. Second degree burns on leg.	http://www.valleynewslive.com/home/headlines/VIDEO-e-cigarette-explodes-in-mans-pants-369968501.html
Feb 2016	Rising Sun, MD	Use	No	Minor	Self or occupant	Device ignited while driving. Battery hit driver in face.	http://www.abc2news.com/news/in-focus/cecil-county-man-says-e-cigarette-exploded-in-his-face
Feb 2016	Surprise, AZ	Pocket	Minor	Moderate	Self or occupant	Batteries in pocket exploded while driving. Second and third degree burns on leg and hand.	http://fox13now.com/2016/02/19/utah-man-burned-by-exploding-battery-urges-other-e-cigarette-users-to-be-cautious/
Feb 2016	Southern UT	Pocket	No	Moderate	Self or occupant	Ignited in pocket; second and third degree burns in leg.	http://fox13now.com/2016/02/17/utah-man-says-he-suffered-third-degree-burns-after-e-cigarette-exploded-in-his-pocket/

E-cigarette incidents reviewed							
Date	Location	Status	Fire beyond e-cig?	Injuries?	Extinguished	Notes	Source URL
Feb 2016	Lyndhurst, OH	Pocket	No	None	Self or occupant	Device exploded in pocket of lab coat.	http://www.newsnet5.com/news/local-news/cleveland-metro/e-cigarette-blows-up-at-lyndhurst-plastic-surgery-office
Feb 2016	Naples, FL	Use	Major	Moderate	Self or occupant	First and second degree burns on her face, neck and hands when she says her e-cigarette exploded in her face. Damage to teeth and gums. Fire ignited contents of car.	http://www.winknews.com/2016/02/26/woman-severely-burned-in-e-cigarette-explosion/
Feb 2016	Phoenix, AZ	Pocket	Minor	Moderate	Self or occupant	Device exploded in his pocket while driving. Second and third degree burns to legs and hands.	http://www.fox10phoenix.com/news/arizona-news/98062903-story
Feb 2016	Rochester, NH	Charge	Minor	None	Self or occupant	Device exploded while charging. Not using the proper charger.	http://www.wmur.com/article/electronic-cigarette-explodes-while-charging-in-rochester-apartment/5208926
Feb 2016	Scappoose, OR	Pocket	No	Moderate	Self or occupant	Battery exploded in pocket. Burned legs.	http://www.seattletimes.com/seattle-news/vapers-sue-e-cigarette-makers-sellers-after-explosions-burns/
Feb 2016	Castle Rock, CO	Pocket	Minor	Moderate	Self or occupant	Device ignited in pants pocket. Second and third degree burns on leg and hands.	http://kdvr.com/2016/02/28/castle-rock-teen-suffers-third-degree-burns-after-vaporizer-battery-explodes-in-his-pocket/
Mar 2016	Aurora, CO	Use	Minor	Severe	Self or occupant	Device exploded in face. Second and third degree burns to chest, neck, face, eyes.	http://denver.cbslocal.com/2016/03/03/vape-pen-explosion-victim-suffered-severe-burns/
Mar 2016	Fulton, MD	Pocket	Minor	Moderate	Self or occupant	Device ignited in pants pocket. Second and third degree burns on leg and hands.	http://www.abcn2news.com/news/in-focus/howard-county-man-suffers-burns-after-e-cigarette-explodes-in-his-pocket
Mar 2016	New Orleans, LA	Use	Minor	None	Self or occupant	Device exploded and burned face and hand. Rocketed around room, burning wall and floor at impact sites.	http://www.wvtl.com/news/local-mansays-e-cigarette-charger-exploded-on-him-caught-on-fire/66623741
Mar 2016	Arroyo Grande, CA	Use	No	Severe	Self or occupant	Device exploded near face. Burns to face.	http://www.sanluisobispo.com/news/local/article88047182.html

Appendix 2. (Continued)

E-cigarette incidents reviewed							Source URL
Date	Location	Status	Fire beyond e-cig?	Injuries?	Extinguished	Notes	
Mar 2016	Atlanta, GA	Storage	Minor	None	Self or occupant	Device ignited inside a carry-on bag on a Delta flight headed to St. Louis. Aircraft was still on the ground.	http://abcnews.go.com/US/delta-flight-delayed-cigarette-ignites-passengers-carry/story?id=37710018
Mar 2016	Costa Mesa, CA	Pocket	Minor	Moderate	Self or occupant	Upper leg and groin — first and second degree burns when spare battery exploded in pants pocket.	http://www.ocregister.com/articles/batteries-709292-coates-fire.html
Mar 2016	Kalamazoo, MI	Use	No	Moderate	Self or occupant	E-cig exploded in hand. Third degree burns on hand.	http://wwmt.com/news/local/kalamazoo-man-says-e-cig-exploded-in-his-hand-causing-burns
Mar 2016	Chico, CA	Not reported	Moderate	None	Self or occupant	Vape was cited as cause of accidental fire in bathroom of college dorm.	http://theorion.com/54656/news/students-evacuate-university-village/
Mar 2016	Keene, NH	Storage	Minor	None	Self or occupant	Device exploded on restaurant table and rocketed about hitting two customers and causing minor burns to clothing and door.	http://www.sentinel-source.com/news/local/e-cigarette-explodes-in-keene-restaurant/article_fa81c331-fba6-5e7d-9988-4042c7f9bf18.html
Apr 2016	NC	Charge	Moderate	None	Fire department	E-cig on charge exploded, flew across room, and ignited carpet and night stand.	NFIRS 0758
Apr 2016	Brooklyn, NY	Use	No	Severe	Self or occupant	A 14-year-old was blinded in one eye and burned on the face when a vape shop clerk in a Brooklyn mall foolishly plugged an e-cigarette into the wrong battery and it exploded.	http://www.nydailynews.com/new-york/boy-14-partially-blinded-exploding-e-cigarette-battery-article-1.2601552
Apr 2016	Phoenix, AZ	Pocket	Minor	Moderate	Self or occupant	Device ignited in pants pocket. Second and third degree burns on leg and hands.	http://www.fox10phoenix.com/news/arizona-news/118366996-story
Apr 2016	Queens, NY	Pocket	Minor	Moderate	Self or occupant	Spare battery ignited inside pants pocket. Second and third degree burns to leg.	http://www.nydailynews.com/new-york/e-cigarette-violently-explodes-pocket-queens-woman-article-1.2607505

E-cigarette incidents reviewed							
Date	Location	Status	Fire beyond e-cig?	Injuries?	Extinguished	Notes	Source URL
Apr 2016	Spokane, WA	Pocket	No	Severe	Self or occupant	Device exploded in pocket. Burns to leg.	http://www.seattletimes.com/ seattle-news/vapers-sue-e- cigarette-makers-sellers-after-explosions-burns/
Apr 2016	Idaho Falls, ID	Pocket	Minor	Moderate	Self or occupant	Device exploded in pocket. Burns to leg and hand.	http://www.localnews8.com/ news/kifitop-story/local-man- injured-from-e-cigarette_20160825070832821/58580069
Apr 2016	Brooklyn, NY	Use	No	Moderate	Self or occupant	Device exploded in hands. Burns to hands, face and eyes.	http://www.cbsnews.com/news/ new-york-teen-badly-injured-by-exploding-e-cigarette/
Apr 2016	Oklahoma City, OK	Pocket	Minor	Moderate	Self or occupant	Spare battery ignited inside pants pocket (coins reported in pocket). Second and third degree burns to leg.	http://ksn.com/2016/04/20/ exploding-e-cigarette-injures-teen/
Apr 2016	Paso Robles, CA	Use	No	Severe	Self or occupant	Victim lost many of his bottom teeth and blew a small hole through his tongue.	https://pasoroblesdailynews.com/local-teen-hospitalized- after-e-cig-reportedly-explodes-during-use/53099/
Apr 2016	Oswego, IL	Storage	Major	None	Fire department	Device exploded in SUV center console while unattended. SUV and adjacent car destroyed in fire.	http://wgnrtv.com/2016/04/19/e-cigarette-may-be-to-blame-for- car-fire-in-suburban-wal-mart- parking-lot/
Apr 2016	Colorado Springs, CO	Pocket	Minor	Moderate	Self or occupant	Spare battery ignited inside pants pocket (keys and coins reported in pocket). Second and third degree burns to leg.	http://www.koaa.com/story/31801206/burned-man- shares-safety-warning-after-battery-explosion-caught-on-camera
Apr 2016	Chattahoochee Hills, GA	Pocket	Minor	Moderate	Self or occupant	Spare battery ignited inside pants pocket. Second and third degree burns to leg and hands.	http://www.fox5atlanta.com/news/132595190-story
Apr 2016	Chesterfield, VA	Storage	Minor	Minor	Self or occupant	Device exploded and rocketed across room. Second and third degree burns to hand. Burns to mattress and carpet.	http://www.nbc12.com/story/31850463/lithium-ion- battery-explosions-on-the-rise
May 2016	St. Joseph, KS	Pocket	Minor	Minor	Self or occupant	Device ignited in pants pocket. First and second degree burns on leg and hands.	http://www.newspressnow.com/news/local_news/article_f60d5ddc-5f4e-5253-8eb0-84504e546ac2.html

E-cigarette incidents reviewed							
Date	Location	Status	Fire beyond e-cig?	Injuries?	Extinguished	Notes	Source URL
May 2016	Hesperia, CA	Use	No	Moderate	Self or occupant	Device blew up causing "moderate facial burns."	http://www.vvng.com/man-airlifted-after-vaping-product-explodes-in-face/
May 2016	Albertville, AL	Pocket	Minor	Moderate	Self or occupant	Student was carrying e-cig in his pants pocket when the battery started heating up and burning him. This burning got so bad the student took it from his pocket and put in on a nearby desk. The e-cigarette battery then reportedly exploded, hit the wall and struck another student, burning him on the face and neck.	http://www.al.com/news/index.ssf/2016/05/albertville_high_school_student.html
May 2016	Ogden, NY	Use	Minor	Moderate	Self or occupant	Device exploded when activated near mouth. Injuries to throat, face and hand.	http://www.wfaa.com/news/nation-now/ny-teen-hospitalized-after-his-e-cigarette-explodes/170912533
May 2016	Albuquerque, NM	Pocket	Minor	Moderate	Self or occupant	Mod and two batteries in pocket ignited while driving. Second and third degree burns to left leg, thighs and buttocks.	Original story accessed November 2016 on www.kob.com (KOB4, Albuquerque, NM) has been removed or moved.
May 2016	Maricopa, AZ	Use	Moderate	Moderate	Self or occupant	Device exploded in user's hands. Second and third degree burn injuries to hands, side and chest.	http://www.abc15.com/news/region-central-southern-az/maricopa-valley-teenager-injured-after-e-cig-explodes-faces-surgery-to-morrow-to-repair-burns
May 2016	Longboat Key, FL	Pocket	Minor	Moderate	Self or occupant	Spare battery for e-cig exploded in pocket causing second degree burns to thigh.	http://www.fox13news.com/news/local-news/139722872-story
May 2016	Irvine, CA	Storage	Moderate	Severe	Self or occupant	Device exploded after being placed on desk. Victim Device and debris shot toward his face. Victim lost left eye. Burn injuries to hand and chest. Started a fire on the computer on the desk.	http://www.nbcdosangeles.com/news/local/Orange-County-Man-Loses-Eye-in-E-Cig-Explosion-378894001.html
May 2016	Wentzville, MO	Pocket	Minor	Severe	Self or occupant	Spare battery for e-cig exploded in pocket causing second and third degree burns to thigh.	http://fox2now.com/2016/05/12/e-cig-users-report-severe-burns-after-devices-explode/
May 2016	Albany, NY	Use	Minor	Severe	Self or occupant	The e-cig exploded, went into his mouth and burned everything. Hands burned, some teeth knocked out, burned and lacerated tongue.	http://ktla.com/2016/05/19/vaporizer-explodes-in-ny-mans-face-rips-hole-in-his-tongue/

E-cigarette incidents reviewed							
Date	Location	Status	Fire beyond e-cig?	Injuries?	Extinguished	Notes	Source URL
May 2016	Manomet, MA	Use	No	Moderate	Self or occupant	Burns to hands and fingers. No other information.	http://plymouth.wickedlocal.com/article/20160524/NEWS/160528120
Jun 2016	Tulsa, OK	Pocket	Minor	Moderate	Self or occupant	E-cig exploded in pocket. Third degree burns on thigh.	http://www.kjrh.com/news/local-news/doctors-at-hillcrest-medical-center-have-treated-four-patients-for-third-degree-burns-due-to-e-cigs
Jun 2016	Tustin, CA	Use	Minor	Severe	Self or occupant	E-cig exploded near face. Burns and cuts to face.	http://laist.com/2016/06/04/man_burned_after_e_cig_blow_up_in.php
Jun 2016	Kirkland, WA	Pocket	Minor	Moderate	Self or occupant	Battery exploded in pants pocket causing second degree burns to back of leg.	http://www.kiro7.com/news/local/kirkland-mans-vape-pen-battery-explodes/373773562
Jun 2016	Fairfield, OH	Use	No	Moderate	Self or occupant	E-cig exploded in hand. Lacerations and burns to hand. Ten stitches.	http://www.fox19.com/story/32179819/fairfield-man-says-e-cigarette-exploded-in-his-hand
Jun 2016	Muskogee, OK	Use	No	Moderate	Self or occupant	E-cig exploded near mouth. Disfigurement, temporary vision damage. This story is a report on a lawsuit; details and date not specified.	http://www.muskogeephenix.com/news/man-sues-after-e-cigarette-allegedly-explodes-in-his-mouth/article_3751be1e-320c-5757-96b3-0d3c0bb13de6.html
Jun 2016	Mobile, AL	Not reported	Unknown	Severe	Unknown	Story quotes medical center stating there have been seven incidents of battery burns in last six months.	http://wkrg.com/2016/06/08/e-cigarette-batteries-exploding/
Jun 2016	Lava Hot Springs, ID	Not reported	Minor	Moderate	Self or occupant	Device exploded causing lacerations to leg and foot, and burns to carpet.	http://idahostatejournal.com/news/local-teen-injured-when-vape-explodes/article_56bd34ac-543b-5648-9002-82a6c247c8f5.html
Jun 2016	Chicago, IL	Storage	Minor	None	Self or occupant	Occupant noticed e-cig smoking on bed, picked it up and then dropped it on the floor because it was too hot. It then blew up and started a small fire that she extinguished with a bottle of water.	NFIRS 0429762

Appendix 2. (Continued)

E-cigarette incidents reviewed							Source URL
Date	Location	Status	Fire beyond e-cig?	Injuries?	Extinguished	Notes	
Jun 2016	Victor Valley, CA	Storage	Moderate	None	Fire department	Device exploded in parked car, setting interior on fire.	http://www.vvng.com/exploding-vape-blamed-for-victorville-car-fire/
Jun 2016	Carrollton, TX	Use	Large	Minor	Fire department	Occupant was using an e-cigarette and it started to spark and explode in his hand. The occupant threw the e-cigarette away to avoid getting more injured. The occupant stated that he went the bathroom to put cold water on his hand. When he returned to the room, a large part of the room was on fire. The e-cigarette was believed to have landed on a blanket and first ignited the blanket. Extinguishment by fire service personnel.	NFIRS 0005544
Jun 2016	Arlington, TX	Pocket	Minor	Moderate	Self or occupant	Battery exploded in pocket. Second and third degree burns to leg and hands.	http://dfw.cbslocal.com/2016/09/13/faulty-lithium-ion-batteries-raise-concerns-for-electronics-users/
Jul 2016	Chelmsford, MA	Charge	Minor	Minor	Self or occupant	Battery exploded while being charged.	http://www.lowellsun.com/news/ci_30088610/man-burned-when-battery-e-cigarette-explodes
Jul 2016	Bay City, MI	Pocket	Minor	Moderate	Self or occupant	Device exploded in pocket. Burns to leg.	http://www.mlive.com/news/bay-city/index.ssf/2016/07/man_suffers_bum_when_vaporize.html
Jul 2016	Atlanta, GA	Pocket	No	Moderate	Self or occupant	Battery exploded in pocket. Second and third degree burns to leg and hand.	http://www.ajc.com/news/local/cigarette-battery-explodes-like-hand-grenade-pocket/LvP3W9w5xYyTZhSPyF0TO/
Jul 2016	Bear, DE	Pocket	Minor	Moderate	Self or occupant	Device exploded in pocket. Burns to leg.	http://6abc.com/news/del-man-suing-over-e-cigarette-fire-/1435239/
Aug 2016	Idaho Falls, ID	Pocket	No	Moderate	Self or occupant	Device exploded in pocket. Burns to leg.	http://www.localhews8.com/news/kfiftop-story/local-man-injured-from-e-cigarette_20160825070832821/58580069
Sep 2016	Monmouth, NJ	Storage	Minor	None	Self or occupant	Device exploded in purse.	http://www.ij.com/monmouth/index.ssf/2016/09/watch_vape_battery_explodes_in_womans_purse_at_fire.html

Appendix 2. (Continued)

E-cigarette incidents reviewed							
Date	Location	Status	Fire beyond e-cig?	Injuries?	Extinguished	Notes	Source URL
Nov 2016	New York, NY	Pocket	No	Moderate	Self or occupant	Device exploded in pocket. Second and third degree burns on leg and hand.	http://www.aol.com/article/news/2016/11/25/horrific-video-shows-e-cigarette-burst-into-flames-in-mans-pocket/21614390/
Dec 2016	Little Rock, AR	Storage	No	None	Self or occupant	Device ignited inside a carry-on bag on American flight. Aircraft diverted to Little Rock. Flight crew extinguished with water and extinguisher.	http://www.star-telegram.com/news/local/community/fort-worth/article121150273.html
Dec 2016	Petoskey, MI	Charge	Minor	None	Self or occupant	Device ignited while charging in bedroom. No other information reported. Fire department responded, but out on arrival.	http://www.9and10news.com/story/34065155/overheating-e-cigarette-prompts-firefighters-to-respond-to-emmet-co-condo
Dec 2016	Fresno, CA	Pocket	No	Moderate	Self or occupant	Device exploded in pocket. Second and third degree burns on leg and hand.	http://www.aol.com/article/news/2016/12/22/e-cigarette-explosion-on-bus-leaves-man-with-third-degree-burns/21633284/
Dec 2016	Putnam, NY	Pocket	Minor	Moderate	Self or occupant	Device exploded in pocket. Second and third degree burns to right thigh.	http://newyork.cbslocal.com/2016/12/22/latest-e-cigarette-explosion/
Dec 2016	Lyndhurst, NJ	Charge	Minor	None	Fire department	Device exploded while being charged with improper charger.	http://www.northjersey.com/story/news/bergen/lyndhurst/2017/01/18/e-cigarette-explosions-prompt-reminder-lyndhurst-officials/96689642/

Chapter 361

CHARACTERIZATION AND ABUSE OF ELECTRONIC CIGARETTES: THE EFFICACY OF “PERSONAL VAPORIZERS” AS AN ILLICIT DRUG DELIVERY SYSTEM*

Michelle Peace, PhD and Joseph Turner, PhD

STATEMENT OF PROBLEM

Electronic cigarettes (e-cigarettes or e-cigs), known as “personal vaporizers” (PV) by avid users or electronic nicotine delivery systems (ENDS) by industry, have experienced a significant increase in popularity for those seeking an alternative to smoking traditional tobacco products. These products are comprised of a battery-powered atomizer and a cartridge filled with a pharmaceutical (nicotine), flavorings, and water dissolved in glycerol products. E-cigarette are manufactured in a variety of options: from off-the-shelf non-customizable devices to customizable, including self-wrapping of the element, homemade wicks, self-preparation of the e-cigarette liquid formulation (e-liquids), cups to hold plant material, dripping vs wicking, and wattage adjusters to administer the desired drug.

The lack of enforced regulation prior to May 2016 has resulted in easy accesses to e-cigarettes and has shepherded their nefarious uses. The use of the e-cigarettes as an illicit drug delivery device is touted on websites, forums, blogs, and videos describing how best to use them for specific illicit drugs such as tetrahydrocannabinol, methamphetamine, fentanyl, and heroin. These sites explain at length the benefits of “vaping” illicit drugs as it can conceivably be done in public without attracting notice. While some individuals and communities have begun to legislate where users can vape, vaping is not just acceptable, it is considered “cool” by many and often has the added benefit of no odor.

Analyzing paraphernalia for drug usage uses straightforward methodology established in controlled substance laboratories nationwide. E-cigarettes were largely uncharacterized at the

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beginning of this research. In forensic science laboratories, little is known or understood about their construction, let alone how they are used to deliver illicit drugs. From a general toxicological perspective, little is documented regarding the delivery of nicotine, particularly as a function of power, for e-cigarettes. Even less is known regarding the adulteration of e-cigarettes and how the e-cigarettes are used or modified to optimize the delivery of an adulterant and/or alternative drug.

Problems can arise with using electronic cigarettes to deliver illicit drugs. According to the vaping community, the dosing can be increased by turning up the wattage/voltage on the device. This method to increase dosage alone, or combined with increasing the volume of the “puff,” could easily lead to overdoses. Increasing temperatures could lead to pyrolysis products which can potentially be used as biomarkers that could identify the use of e-cigarettes in biological tissues and which may have unknown biological effects. Drug forums are providing cautionary tales to users, however, these are overshadowed by the clear benefits these devices bring to drug users.

Few peer-reviewed published manuscripts in the literature describe, define, and/or illustrate the use of e-cigarettes. The overarching purpose for this study was to characterize the use and efficacy of electronic cigarettes to deliver pharmaceutical products. E-cigarettes were functionally described, methods were developed to analyze the pharmaceutical products (e-liquids and aerosol), truth in advertising was described for commercially available products, adulterations to the products were assessed, and potential biomarkers were evaluated.

IMPLICATIONS FOR CRIMINAL JUSTICE POLICY AND PRACTICE

What Is the Impact of the Project on the Criminal Justice System?

Significant efforts have been made to educate law enforcement, medical examiners, toxicologists, and crime lab practitioners about drug use and abuse employing e-cigarettes. Public awareness has increased as to the potential dangers, and crime scene investigators and death investigators have reported collecting these and sending them to crime labs. Ultimately, this study has provided greater understanding in the court systems nationwide as to the nature of drug usage, abuse, and overdose cases in which e-cigarettes were used to deliver an illicit drug.

We believe that the impact to the criminal justice system is slowly unfolding. However, the research group has been asked to speak at national and international conferences to continue to educate scientists and crime scene investigators as to the potential impact of using e-cigarettes illicitly. Dr. Peace, the PI, has been invited to numerous conferences to present our findings, and will be providing information directly to the DEA who now has significant interest in the adoption of e-cigarettes. Additionally, the research group has been interviewed for news outlets such as *New Scientist* and NPR's *With Good Reason*. This kind of broader exposure will benefit the criminal justice system from an immediate general awareness perspective to, hopefully, programmatic/systemic changes.

How Has It Contributed to Crime Laboratories?

Given that one role of the forensic toxicologist is to define and characterize drug usage trends, this publicly funded research posed an important, relevant, and critically timed study to address an identified threat to public health and criminal justice. This research supported the analytical efforts in controlled substances units and will support the findings and opinions of scientists, medical examiners, death investigators, and forensic toxicologists as they present analytical results.

As of April 24, 2017, the research group has been consulted on seven e-cigarette cases. One case involved a professional athlete who submitted to a urine drug test and tested positive for a banned substance. He reported that he vaped from someone else's e-cigarettes, that contained an e-liquid purchased from a retail shop that was not labeled as having contained that substance. The laboratory who conducted the testing called to inquire about the feasibility of this claim. Based on our analyses of dozens of samples of e-liquids purchased from multiple vendors, the story was plausible. Three cases involved samples submitted through emergency room departments. One sample was determined to contain apomorphine and nuciferine, found in blue lotus flowers. Two cases involved potential overdose deaths. In the first, witnesses claimed that the victim vaped from an e-cigarette and died shortly thereafter. Analysis of the e-cigarette and e-liquid revealed no drug besides nicotine. One case involved a family-based litigation case in which someone claimed to be "just vaping" while illicit substances were found in the e-cigarette. And lastly, a "smoke easy" raid was conducted in a Philadelphia warehouse in which 22 people were arrested for marijuana possession and distribution. According to an analyst in the crime laboratory, the evidence collected included dozens of cartridges presumably containing cannabinoids. The analyst had attended the two webinars produced by the Center of Excellence on our research, and, as a result, was assigned the e-cigarette evidence. The research group will collaborate with that crime laboratory to analyze the products seized.

What Is the Impact on Technology Transfer?

In addition to providing critical information at an important time in the emergence of these products, the study has supported the efforts to understand the e-cigarette industry by regulatory agencies such as the FDA. Given that most of the knowledge of "puff topography," or the volume of cloud, duration of the inhale, and the concentration of drug in the cloud, is promulgated by users, this research has contributed to the scientific foundation for electronic e-cigarette usage.

Recently, the research group was asked to provide presentations and our list of publications to the U.S. Food and Drug Administration and to U.S. Department of the Navy, which is evaluating whether or not to ban e-cigarettes on submarines. So, while the impact on the criminal justice system is evolving, significant implications exist in other forums.

DESIGN METHODS AND RESULTS

The following aims and experiments were identified within the proposal. Within each, specific experimental goals and results are described.

In addition to pursuing these aims, we also monitor the current state of e-cigarette usage, messaging in the media, and legislation and regulation.

Goal: The goal was to identify information and resources to assist ongoing research to understand the forensic impact and implications of e-cigarettes. Information gleaned in the process of this study will assist decision-making regarding criminal justice and public education.

- Modifications and adulterations to electronic cigarettes and e-liquids, including illicit drug delivery, are described and promulgated by experienced users through videos, social media, and user blogs.
- All fifty states have developed policy in at least one of these five areas: sales to minors, defining e-cigarettes as tobacco products, bans on use in public, taxes, or other regulations.
- Media has reported deaths due to e-liquid consumption.
- Over the course of the 2+ year project, drug forum conversations evolved rapidly to discuss modifications and adulterations to e-cigarettes and e-liquids.
 - Recent conversations have included drugs such as Kratom (mitragynine), synthetic cannabinoids, synthetic opioids, and blue lotus (apomorphine and nuciferine)
 - Natural products in addition to illicit substances continue in the threads.
 - New e-cigarettes models emerged for the specific use of waxes, dabs, and dry natural products.
 - Modifications to the atomizers, mostly with regards to coil configurations, escalated as e-cigs became more technologically advanced.
 - Users continued to advocate regularly, despite prohibitions to public vaping, that the ease of transporting illicit substances and vaping illicit substances in public was a bonus for adopting the method.
- After the FDA banned the sale of products, websites had to stand-up a screening process to make sure that people were >18 years old. We monitored the complexity of this and have been challenged by more reputable websites who have questioned the identity of the purchaser. Since the credit card had the university address, the vendor was unable to “confirm” identity and age of the purchaser. Vendors with questionable e-liquid products have had no problem with the disconnect between the address of the credit card and our identity. While there is no way to know without further investigation, the difference between the two types of vendors has been observed.
- An evaluation of historical patents was performed to create a timeline of e-cigarettes and their mechanisms for operation, particularly as their construction evolves.

Aim 1

Develop reliable, validated analytical methods to support the efficient and thorough analysis of e-cigarette devices, device components, and aerosol for pharmaceuticals in adulterated, unadulterated, and self-prepared formulations.

Experiment 1. Develop method for capturing vapor product from electronic cigarettes by water trap and solid-phase micro-extraction (SPME).

Experiment 2. Develop validated method for the qualitative assessment of electronic cigarettes artifacts using Direct Analysis in Real Time Accu-TOF™ Mass Spectrometry (DART). A quantitative method will also be assessed.

Goal: To develop a simple trap to analyze the aerosol from e-cigarettes.

Results: A simple trap was developed and validated to analyze aerosol via SPME and to trap ingredients/drugs in water. Erlenmeyer flasks were connected to a vacuum with tubing and glass wool filters in between for capture. Corks were drilled to accommodate the tubing attached to the e-cigarette and a septum for the SPME sampling (Figure 1). Briefly, two Erlenmeyer flasks were connected in tandem to a vacuum with a flow rate of 2.3 L/min. DI-water was added to each trap and a gas dispersion tube bubbled the aerosol into the water. Glass wool was placed in between the two traps to contain the aerosol in the first trap. Results are reported in Aim 2.

Goal: To develop a sampling protocol in order to use solid-phase microextraction (SPME) to capture aerosol produced by an e-cigarette for analysis by a SPME GC-MS and SPME-DARTMS methods in order to both qualitatively and quantitatively assess the amount of nicotine and flavoring agents found in e-cigarette aerosol.

Results: Polydimethylsiloxane (PDMS) SPME fibers were demonstrated to successfully capture nicotine and flavoring agents in concentrations that were analyzed by GC-MS and DART-MS. The aerosol produced by the e-cigarette was trapped with the apparatus described above. A 7µm or 10 µm PDMS SPME fiber was inserted through a stopper in the first trap, depending on the molecular weight of the drug. The fiber was introduced into the trap while the e-cigarette was activated for four seconds, aerosolizing 7-10 µL and the aerosol filled the trap. The SPME fiber was held in the trap for five minutes, after which the fiber was removed.

The SPME fiber was then inserted into the injection port of an Agilent GC-MS 6890N/5973 Mass Selective Detector with an HP-5MS column 30 m × 0.25 mm id × 0.25 µm. The injection port was set to 315°C and the run was made in splitless mode with a 15-minute thermal desorption time. The initial temperature was set to 120°C, with a ramp to 300°C at 10°C/min, with a hold time of 12 min at 300°C, for a total run time of 30 min. The fibers were thermally cleaned between runs to ensure no carryover occurred between samples. (Figure 2).

Alternatively, the SPME fiber was waved in the helium stream of the DART-MS following previously validated methods. The analysis was performed in positive-ion mode with a helium stream temperature of 300°C. The ion guide peak voltage was 400 V, reflectron voltage was 900 V, orifice 2 was set to 5 V, and the ring lens was set to 3 V with orifice 1

operated in function switching mode at 20, 60, or 90 V with a single data file created for all three voltages. The range of masses measured was from 40 to 1100 Da. (Figure 3).

The general analytical scheme adopted in the laboratory was that all e-liquids were screened by DART-MS. Samples were then quantitated by GC-MS or LC-MS/MS. Samples were aerosolized and active ingredients were extracted by SPME for analysis by DART-MS and GC-MS in order to demonstrate that pharmacologically active ingredients were in the vapor. See Figure 4 for examples.

Experiment 3. Quantify nicotine and adulterant pharmaceuticals by LCMS³.

Goal: Validated method for nicotine and Drugs Other Than Nicotine (DOTNs) by LCMS³.

Results: The nicotine concentrations of the e-liquids were determined using HPLC-MS/MS with a Hypersil® Gold 3x50 mm, 5 μ m column and a method previously published. The mobile phase consisted of 1:9 DI water with 10 mmol ammonium acetate and 0.1% formic acid: methanol, and was run at an isocratic flow rate of 0.5 mL/min. The injection volume was 10 μ L. The ion spray voltage was 5000 V and the source temperature was 600°C with 30 mL/min curtain gas flow. The instrument was operated in multiple reaction monitoring mode (MRM) monitoring the following m/z transitions: nicotine, 163 > 130 and 163 > 117; and nicotine-d4, 167 > 134. A linear regression was plotted of peak area ratio of nicotine to internal standard versus nicotine concentration.

A method for quantitation of methamphetamine was validated using an Agilent 6890N Gas Chromatograph coupled to a 5973 Mass Selective Detector per SWGTOX guidelines. Chromatographic separation was performed on a HP-5MS column 30 m x 0.25 mm id x 0.25 mm (Agilent, Santa Clara, CA). The GC/MS was operated in a split mode at a ratio of 6:1, with 1 μ L injection volume. The carrier gas was helium at a linear velocity of 35 cm/s. The GC had an oven temperature of 120°C-200°C at a rate of 10°C/min then ramped to 280°C at a rate of 30°C/min. The MSD was operated in SIM mode with 58, 64, 91, 96, 134 m/z as the selected ions. Quantification was performed using 58 and 64 m/z as the quantitative ions for methamphetamine and methamphetamine-d11, respectively. The qualitative ions for methamphetamine were 91 and 64 m/z and 91 m/z for methamphetamine-d11. The total run time of 10.67 minutes. A six-point calibration curve was constructed with methamphetamine concentrations of 100, 200, 500, 750, 1000, and 2000 ng/mL with 500 ng/mL of methamphetamine-d11 as internal standard. The calibration curve was matrix-matched and was extracted from water using the method previously described. A linear regression was generated using the peak area ratio counts of methamphetamine and internal standard versus the theoretical calibrator concentrations, and $r^2 > 0.9981$ for all curves. The limit of quantitation was administratively set to 100 ng/mL. Six sets of controls were included with each analytical batch: Limit of Detection QC (100 ng/mL), Low QC (150 ng/mL), Mid QC (600 ng/mL), High QC (1500 ng/mL), a blank, and a double blank. Intraday precision and bias were determined by the largest percent coefficient of variation (% CV) and by the largest percent difference of the five runs (N = 5). Carryover was assessed by injecting the lowest quality control (150 ng/mL) following the injection of the high-quality control (1500 ng/mL). (Figure 5).

A method for the quantitation of methadone was validated using an Agilent 6890N Gas Chromatograph coupled to a 5973 Mass Selective Detector per SWGTOX guidelines.

Chromatographic separation was performed on a HP-5MS column 30 m x 0.25 mm id x 0.25 mm (Agilent, Santa Clara, CA). The GC/MS was operated in a split mode at a ratio of 20:1, with 1 μ L injection volume. The carrier gas was helium at a linear velocity of 20 mL/min. The GC had a front inlet temperature of 275°C. The temperature program began with the oven temperature of 225°C, and then programmed at a rate of 15°C/min to 285°C. The MSD was operated in SIM mode with 72, 223, 294, and 309 m/z as the selected ions for methadone and 78, 226, 303, and 318 m/z for methadone-d9. A seven-point calibration curve ranging from 100-5000 ng/mL of methadone was prepared along with a blank, a double blank control, and controls containing methadone and its internal standard were analyzed. The controls were run in triplicate with Limit of Detection/Quantitation control at 100 ng/mL; a low-control at 150 ng/mL; a mid-control at 1000 ng/mL; and a high-control at 4500 ng/mL. The limit of detection was arbitrarily set to match the limit of quantitation at 100 ng/mL. An internal standard (500 ng/mL methadone-d9) was added to each calibrator, blank, controls, and sample. The coefficient of determination (r^2) was $\geq$ 0.9985 for all calibration curves. The bias for all the controls ($n = 3$) for methadone ranged from 5-15% with coefficient of variance (% CV) of 20%. Carryover was assessed by injecting the lowest quality control following the injection of the high-quality control.

Experiment 4. Develop a dynamic headspace GCMS (DHS GCMS) method for the direct analysis of e-cigarette components.

Challenge: The DHS GC-MS had significant equipment failures over many months. A method for headspace analysis used in the analysis of fire debris evidence was concept tested to analyze atomizers on e-cigarettes. It was demonstrated that this method could be adopted for nicotine analysis. However, this method did not work for the analysis of methamphetamine. Static headspace with the charcoal strip used in nicotine analysis was evaluated a number of times with a number of extraction time periods and temperature parameters for methamphetamine analysis. Methamphetamine was demonstrated to aerosolize; however, it was not extracted from the aerosol onto the charcoal test strip or it was not possible to extract it from the charcoal test strip. The conclusion is that the charcoal test strip was not suitable for some drugs.

Aim 2

Characterize representative electronic cigarettes available for consumers to purchase, to include efficacy of drug delivery.

Experiment 1. Characterize major classes of e-cigarette devices available for consumers to purchase and describe the function of each component.

Goal: The three major types of e-cigarettes were characterized (Figure 6-9). In order to understand the relationship between voltage, resistance, heat, and concentration of drugs in the aerosol, coil temperatures were assessed at various voltages and various gauges.

Method: Two popular types of wire used within the e-cigarette community are Kanthal A-1 and Nichrome 80:20. Coils can be either contact or non-contact. Contact coils are tightly wrapped and the wire touches each wrap. Non-contact coils do not touch and typically have the wraps evenly spaced apart from one another. The temperature of the coils for the dry burns and wet burns when the coil is wrapped to the same resistance and burned at the same voltages were assessed. Both metal types will be evaluated at the same resistance ($1.8\ \Omega$), wet and dry, contact and non-contact, with wire gauge ranging from 26 to 36 and at 3.5, 3.7, 4.2, 4.5, 5.0, 5.5, and 6.0 volts, with replicates of at least 3 for each variable. The atomizer was a Kayfun Lite Close Atomizer. The type of atomizer is less important than the assessment of the coils as the atomizer was attached to a constant power supply instead of a battery. Center coil temperatures of two wire types, each in three gauges, wrapped in both contact and non-contact, fired at four voltages, and wet with 100% VG or kept dry were measured. All coils were hand-built to $1.8\ \Omega$ resistance. Temperatures were measured using a Micro-Epsilon IR sensor with a laser sighting.

To complicate this single coil model, users have begun to use dual coils in parallel for a technique called “sub-ohming” ($<1\ \Omega$). As opposed to a single coil being wrapped to a resistance of $1.8\ \Omega$, 2 coils are each wrapped to about $1.2\ \Omega$ and are aligned in parallel to create a resistance of $0.6\ \Omega$ (Figure 10). In order to explore if there was potentially a significant difference between the 2 types of atomizers, a short study was conducted.

Results: In the dry configuration, Kanthal is the hotter wire, meaning it is able to sustain hotter temperatures. This is not surprising since it is an alloy composed of iron, chromium, and aluminum and has a melting point of 1400°C . Nichrome is a nickel and chromium alloy with a melting point of 1200°C . Not surprisingly, contact is hotter than non-contact.

When coils had a wick wet with 100% vegetable glycerin (VG), no statistically significant difference was seen between wire gauge, wire type, and wire configuration. Hence, VG is a limiting factor to coil temperature (Figures 11-12).

These findings are significant because they provide some basis for understanding the vaporization of drugs into the aerosols. More importantly, the temperature of the wet coils disproves user claims that the wet coils get hotter with Kanthal. The real value of using Kanthal is that the melting temperature is higher for those who are vaping off dry coils. While temperature may be the same, it is unknown as to if the wire type and size may be impacting the particle size of the aerosols.

When the coils are in contact with 100% propylene glycol (PG), the temperature output between the two mediums differed significantly. The PG medium had lower temperature outputs than VG, reaching temperatures as low as 160°C and as high as 360°C . The type of coil, Kanthal A-1 or nichrome 80:20 did not have a significant difference in temperature nor did differing coil configurations. There was a trend of temperature increase with decreasing wire thickness. These results contradict what most e-cigarettes users claim: That wire type and configuration have an impact on the temperature outputs of the coils and how they vaporize the e-liquid. It appears that the medium that the coils are submerged in have a more significant impact in the temperature outputs of the coils, which may also lead to an impact in the particle size produced.

The temperature profile of the dual dry 26 gauge Kanthal coils wrapped in contact from 3.5 to 5.0 V showed minor temperature variations between the two coils. This is predominantly due to the nature of how much wire is touching the contacts. Microns of metal length can impact resistance enough to change the temperature profile between the two coils

in the same atomizer. The temperature profile for the 26 gauge Kanthal dual coil sub-Ohm at 3.7 V is significantly higher than what was found with the 26 gauge Kanthal single coil 1.8 Ω at 3.7 V wire (951°C and 793°C, respectively), both wrapped in contact and dry, due to the difference between resistances of the coils. By holding the voltage constant between the two e-cigarette models, the current running through the lower resistance dual coil model is higher, leading to higher wattage and higher temperatures.

Experiment 2. Characterize the delivery of nicotine in e-cigarettes, based upon device type and voltage, in terms of concentration of nicotine in the liquid and concentration of nicotine in the vapor. After this is characterized, adulterant illicit drugs will also be evaluated (THC, methamphetamine, opiates, and other drugs as necessary and time permits).

Goal: Characterize the concentration of nicotine in aerosol based on the performance of the device, including varying the voltage to manipulate the heat produced by the heating element.

Results: Studies showed that the yield of nicotine in the aerosolized e-liquid consisting of 50:50 propylene glycol:vegetable glycerin (PG:VG) with 12 mg/L nicotine (delivered by a KangerTech AeroTank, 1.8 Ω preassembled atomizer with eGo-V2 variable voltage battery e-cigarette, Nichrome, 34 gauge, non-contact coil) increased with increasing voltage (3.9, 4.3, and 4.7 V), from 89 μg to 125 μg (based on weight difference of the tank) (see figure). The concentration of nicotine recovered from the traps, as determined by LC-MS³, averaged 378 ng/ml (+/- 64). As seen with the nicotine yield, the aerosol concentration increased from 322 to 374 to 432 ng/ml, at 3.9, 4.3, and 4.7 V, but had moderately high SD. The average recovery of nicotine in the trap across the voltages was 101%, ranging from 82-113% (Figure 13).

See Aim 1 for analysis of methamphetamine in e-liquids. A study was conducted to determine if increasing voltage of the e-cigarette yielded higher dosing in the aerosol. The study concluded that there was no significant difference in the concentration of methamphetamine as the voltage of the e-cigarette increased, serving to contradict the users' myth. Three concentrations of methamphetamine were prepared in 50:50 PG:VG (v:v) and aerosolized at 3.9, 4.3, and 4.7 V for 4 seconds at 2.3 ml/minute. Five replicates were analyzed at each voltage. The change in voltage did not significantly alter the dose of methamphetamine contained in the aerosol (Figure 14).

For methadone, the theoretical dose capture concentrations were determined from the gravimetric difference of the e-cigarette tank before and after aerosolization into the trap. At 10 mg/mL of methadone in the e-liquid, the dose per puff was expected to from 38 to 46 μg with increasing voltage. For the 30 mg/mL e-liquid, the predicted concentrations ranged from 170 to 221 μg and the 60 mg/mL e-liquid from 234 to 549 μg . GC/MS results showed that at 10 mg/mL, the average dose per puff at 3.9 and 4.7 V was 8 and 4 μg respectively with a 19 and 8% recovery. At 30 mg/mL the average doses were 37 and 17 μg with 16 and 10% recovery, and at 60 mg/mL, the average doses were 30 and 417 μg with 12 and 79% recovery. Statistical analysis of ANOVAs comparing the dose capture results by voltage showed that there was not a difference between the dosage at 3.9 and 4.3 V ($P = 0.76$), but that there was a difference in the dosage between 3.9 and 4.7 V and 4.3 and 4.7 V ($P < 0.001$). The hypothesis regarding the low recovery of methadone from the aerosol is that the boiling point for methadone is higher than the temperature of the coil in the electronic cigarette.

Experiment 3. Characterize the formation of potential biomarkers formed during pyrolysis based on the wattage of the e-cigarette.

Goal: Characterization of coil temperature studies have revealed that the coils, after multiple burns begin to deteriorate. A study to characterize the degradation of the coils by SEM-EDX was conducted.

Results: Nichrome and Kanthal wires at 30, 32, and 34 gauges were triggered 1, 50, and 150 times in both contact, and non-contact coil configurations. The voltage used was dependent on the gauge and coil configuration and can be found in Table 1. All coils were triggered dry for 10 seconds, and SEX-EDX analysis was completed at 2000x magnification. Two metals for each wire type showed a significant decrease at 1, 50, and 150 burns as compared to a pristine (unburned) coil. Kanthal wires showed a significant decrease in iron and chromium, while nichrome wires showed a significant decrease in iron and nickel. Statistical analysis shows that there is no significant difference in iron or nickel loss between gauges for nichrome wires, while Kanthal wires were found to have significantly less loss of iron and chromium with 30 gauge wire as compared to 32 and 34 gauge wire. The data also suggests that Kanthal coils wrapped in a contact configuration lead to a significantly higher loss of iron and chromium when compared to the non-contact configuration. Nichrome wires, however, show a general trend of no difference in nickel and iron loss when comparing final metal percentage of contact and non-contact configurations. Overall, the data has shown that the metal composition of both nichrome and Kanthal wires decreases significantly after 1 burn and progressively deteriorates as the number of burns increases. This effect is independent of wire type, gauge, and configuration (Figures 15-17).

A method is being validated on the Agilent 7700 ICP-Mass Spectrometer to analyze metals in the aerosol. A filter system had to be developed to capture the aerosol. Using the e-cigarette system as previously described, ten 30 gauge Kanthal and Nichrome wires were heated for 10 seconds and the aerosol was each trapped onto a single 0.1 micron Teflon hydrophobic filter. This was repeated 10 times. They were digested in aqua regia, diluted, and analyzed by ICP-MS. Samples were run to eliminate the potential that metal would be in the aerosol from the wick, PG, and VG. Preliminary data demonstrates that the metal is contained in the aerosol and does not condense in the mouthpiece of the atomizer. Average ppb of chromium-53, iron-57, and nickel-60 for Kanthal was 11.0 (± 15.4), 41.9 (± 58.7), and 4.04 (± 5.60), respectively.

Aim 3

Characterize the liquid refill products for electronic cigarettes, to include nicotine and adulterant pharmaceuticals.

Experiment 1. Characterize variation in supplies purchased by consumers:

Goal: Characterize the e-liquids for e-cigarettes, to include nicotine and adulterant pharmaceuticals (THC, methamphetamine, heroin).

Results: A stability study was conducted to understand the quality of e-liquids and how they might impact nicotine concentration. Samples were stored in three types of containers in three conditions: 24 hours light at room temperature (RT), 24 hours dark at room temperature, and 24 hours dark at 40 °C. They were samples periodically and analyzed by LC-MS/MS. The concentration of nicotine decreased significantly from time 0 through time 12 weeks, and then plateaued for the remaining time when exposed to light conditions. For example, the 36 mg/mL sample kept in 24 hour light at room temperature decreased to 27.8 mg/mL in 12 weeks. The container type (glass, plastic, and amber glass) did not impact the concentration of nicotine in the sample. The concentration of nicotine in commercial samples deteriorated from 20.5 mg/mL to 13.2 mg/mL in 12 weeks and then plateaued. However, no statistically significant difference exists between light and RT, dark and RT, and dark and refrigerated (Figure 18).

Goal: Characterize e-liquids purchased online for “truth in advertising”

Results: Nicotine concentrations of 27 commercial e-liquids were compared to advertised nicotine concentration (Table 1). Actual concentrations varied 53-139% from advertised. Glycol ratios in the 27 commercial e-liquids were compared to advertised label concentration and found to be in general agreement.

A sample of e-liquid was received in the laboratory labeled as a cannabinoid-based products. The concentrations of the THC, 42.6% (v:v), and CBD, 0.5% (v:v), were different then the labeled content, THC at 69% and CBD at 1%. Four additional unlabeled cannabinoids were identified and quantitated. Fourteen terpene compounds were identified: α -pinene, 3-myrcene, 3-pinene, limonene, (1R)-endo-(+)-fenchyl alcohol, linalool, α -terpineol, 3-caryophyllene, α -humulene, cis/trans nerolidol, guaiol, (+)-cedrol, and α -bisabolol. The identification of these unlabeled cannabinoids and marijuana terpenes indicated the e-liquid was produced by extraction of marijuana.

Cannabidiol (CBD) was listed as the active ingredient in e-liquids found online. Two e-liquids were acquired that claim to be infused with CBD and contained 3.3 mg/mL CBD. They screened positive by DART-MS and CBD was quantitated by LC-MS³ at 6.53 and 7.61 mg/mL. The website (cloud9hemp.com) has an FDA Disclosure statement that reads “... FDA considers non-THC based hemp products to be “food based” and therefore legal...CBD Rich Hemp Oil is legal in all 50 states.” They also state that the products are “not intended to diagnose, treat, or cure any disease.”

Ethanol was determined in 53 of the 56 e-liquids by HS GC-FID. Only one e-liquid included ethanol as a labeled component. Thirty of 42 e-liquid samples were reported as positive for ethanol with concentrations > 3.70 g/mL. Once it was determined that commercial e-liquids contain ethanol, coil temperatures were evaluated for any significant change from the original temperature studies conducted without ethanol in lab-prepared e-liquids. Temperatures were significantly lower in some cases and higher in others. Therefore, it could be said that the temperature the coils were unpredictable with ethanol in the e-liquid (Figure 19).

PROJECT FINDINGS

Aim 1

Develop reliable, validated analytical methods to support the efficient and thorough analysis of e-cigarette devices, device components, and aerosol for pharmaceuticals in adulterated, unadulterated, and self-prepared formulations.

1. DART-MS, LC-MS³, and GC-MS methods were successfully validated to screen, confirm, and quantitate pharmacologically active ingredients in e-liquids and the aerosol.
 - a. A trap and SPME extraction method were developed and validated to successfully capture the aerosol produced by an e-cigarette.

Aim 2

Characterize representative electronic cigarettes available for consumers to purchase, to include efficacy of drug delivery.

1. Increases in voltage do not increase the temperature of the coil significantly and do not yield significantly higher concentrations of the pharmacologically active ingredient (nicotine or methamphetamine) in the aerosol.
2. Metal composition of both nichrome and Kanthal wires decreases significantly after 1 burn and progressively deteriorates as the number of burns increases. This effect is independent of wire type, gauge, and configuration.

Aim 3

Characterize the liquid refill products for electronic cigarettes, to include nicotine and adulterant pharmaceuticals.

1. Given that the e-cigarette industry is un-regulated, it should not be unexpected to find nicotine or glycol concentrations different than the labeled concentrations on e-cigarette liquid formulations.
2. Poor QA/QC in facilities producing e-liquid products result in products that have significantly less or significantly more than what is indicated on the bottle.
3. Some e-liquids are not labeled as to the pharmacologically active component, nor are they advertised by the vendor. Indicators that a product contains a DOTN is that it is 2-10 times more expensive than a nicotine-based e-liquid.
4. Ethanol was a major component in most e-liquids and was only labeled in one product.

FUTURE STUDIES

1. It is imperative to evaluate how vaping alcohol impacts field sobriety tests and BAC.
2. It is important to continue to monitor how the technology for e cigs continues to evolve. In the 2.5 years of this study, the types of e cigarettes have grown significantly in order to vape dry herb, waxes, dabs, oils, and other types of tinctures.
3. Eutectic mixtures should be explored to assess improving the aerosolization of high molecule weight molecules, such as opioids, particularly since user blogs indicate recommendations for cutting these drugs with caffeine before putting into e liquids.

DISSEMINATION/PRODUCTS/ACCOMPLISHMENTS

This research group has aggressively presented and published its finding. Twenty scientific presentations have been made (Table 2). Two traditional workshops and two webinars were conducted. Six peer-reviewed manuscripts have been published, and three more are in preparation and on-track for submission by June.

Findings from this study were also disseminated in China, but NIJ provided no funding for this travel.

Presentations Workshops and Webinars

Peace MR. "Characterization and Abuse of Electronic Cigarettes: The Efficacy of Personal Vaporizers as an Illicit Drug Delivery System." Forensic Technology Center of Excellence Live Webinar, August 2016.

Peace MR, Butler KE, Stone JW. "Characterization and Abuse of Electronic Cigarettes: The Efficacy of Personal Vaporizers as an Illicit Drug Delivery System." NIJ Research Symposium, February 2016.

"Vaping: What you don't know about electronic cigarettes and why you should care"

- Society of Forensic Toxicologists Annual Meeting, Dallas, TX, 2016, Chair: Michelle Peace, Co-Chair: Justin Poklis
- American Academy of Forensic Scientists, Las Vegas, NV, 2016, Chair: Michelle Peace, Co-Chair: Justin Poklis

Invited Talks, Media Engagements, Miscellaneous

- Eastern Analytical Symposium. "New Marijuana Products" in a workshop titled "Marijuana: From Research and Use to Abuse," Princeton, NJ, November 2017.
- Peace MR, Poklis JL. "Chasing the E Cigarette Dragon: Overview of Research Findings." DEA, July 2017.

- Peace MR. “Current Trends in Drug Addiction and Trafficking in the United States” and “Electronic Cigarettes and the Threat to Criminal Justice and Public Health” International Conference on Forensic Science, University of Public Safety, Beijing, China, and Northwest Law University, Xi’An, China, September 2016 (NOT FUNDED BY NIJ).
- Peace MR. “Characterization and Abuse of Electronic Cigarettes: The Efficacy of Personal Vaporizers as an Illicit Drug Delivery System.” Tobacco Product Analysis Technology Summit, Research Triangle Park, Raleigh, NC, July 2016.
- Interview with New Scientist Magazine published December 14, 2016.
- Interview with National Public Radio with Good Reason” in December, to air in January.

Manuscripts

1. Poklis JL, Wolf CE, Peace MR. Ethanol Concentration in 56 Refillable Electronic Cigarettes Liquid Formulations Determined by Headspace Gas Chromatography with Flame Ionization Detector (HS-GCFID). *Drug Testing and Analysis* doi: 10.1002/dta.2193.
2. Poklis JL, Mulder HA, Halquist MS, Wolf CE, Poklis A, Peace MR. The Blue Lotus Flower (*Nymphaea Caerulea*) Resin Used in a New Type of Electronic Cigarette, the Re-buildable Dripping Atomizer. *Journal of Psychotropic Drugs* (2017). DOI: 10.1080/02791072.2017.1290304.
3. Peace MR, Krakowiak RI, Wolf CE, Poklis A, Poklis JL. Identification of MDMB-FUBINACA in Commercially Available E-liquid Formulations for Use in Electronic Cigarettes. *Forensic Science International* (2016), doi.org/10.1016/j.forsciint.2016.12.031.
4. Peace MR, Butler KE, Wolf CE, Poklis JL, Poklis A. *Evaluation of Two Commercially Available Cannabidiol Formulations for use in Electronic Cigarettes*, *Frontiers in Pharmacology*, August 29, 2016. doi: 10.3389/fphar.2016.00279.
5. Peace MR, Stone J, Poklis JL, Turner JBM, Poklis A. Analysis of a Commercial Marijuana E-cigarette Formulation. *Journal of Analytical Toxicology*, 40(3); April 2016. doi: 10.1093/jat/bkw021.
6. Peace MR, Baird T, Poklis JL, Wolf CE, Smith N, Turner JBM, Poklis A. Concentration of Nicotine and Glycols in 27 E-Cigarette Formulations. *Journal of Analytical Toxicology*, 40(6); May 2016. doi: 10.1093/jat/bkw037.
7. Peace MR, Baird TR, Stone JW, Butler KE, Poklis JL, Poklis A. *Capture and Quantification of Nicotine Generated by an Electronic Cigarette by SPME-GC-MS and HPLC-MS/MS*. In preparation.
8. Peace MR, Stewart JB, Mulder HA, Dupont A, Royals J, Forsythe K, Poklis JL, Turner JBM. *Assessment of Temperature and Metals Loss from Electronic Cigarette Coils with Changing Voltages*. In preparation.
9. Peace MR, Mulder HA, Poklis JL. *The History and Evolution of Electronic Cigarettes*. In preparation.

APPENDIX

Figures and Tables

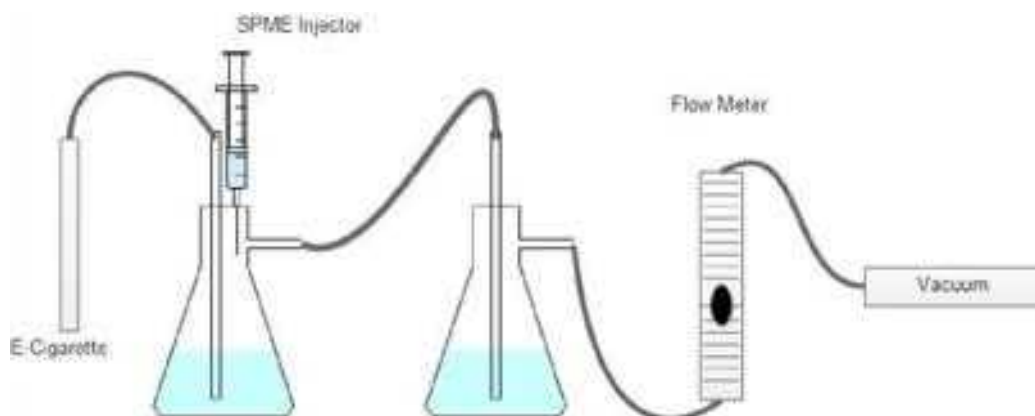


Figure 1. Diagram of trap to capture aerosol from electronic cigarette.

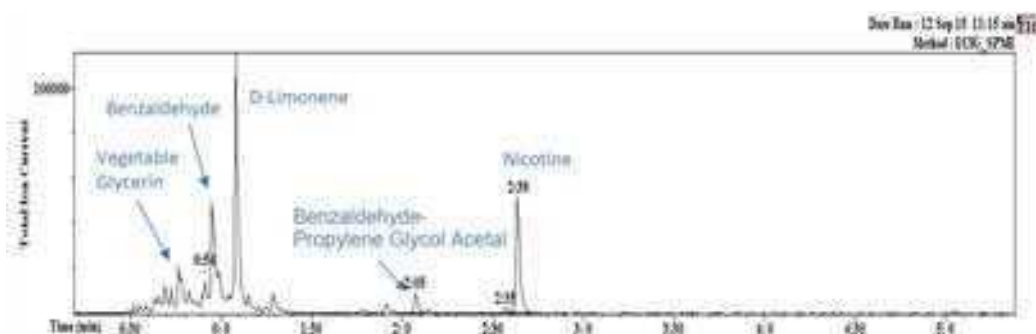


Figure 2. Gas Chromatograph of commercial e-liquid VapeWell Cheery. Major components of the vapor detected were benzaldehyde, d-limonene, and nicotine.

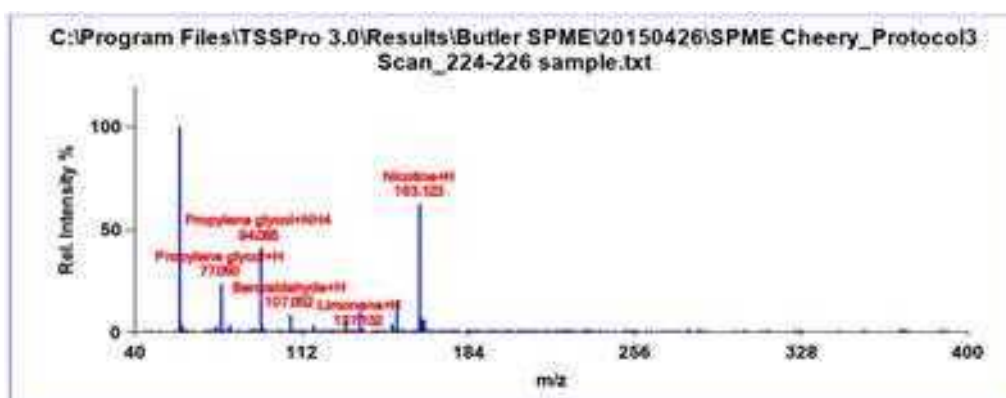


Figure 3. Mass Spectrum of SPME-DART analysis of VapeWell Cherry. The components detected were propylene glycol, benzaldehyde, limonene, and nicotine.

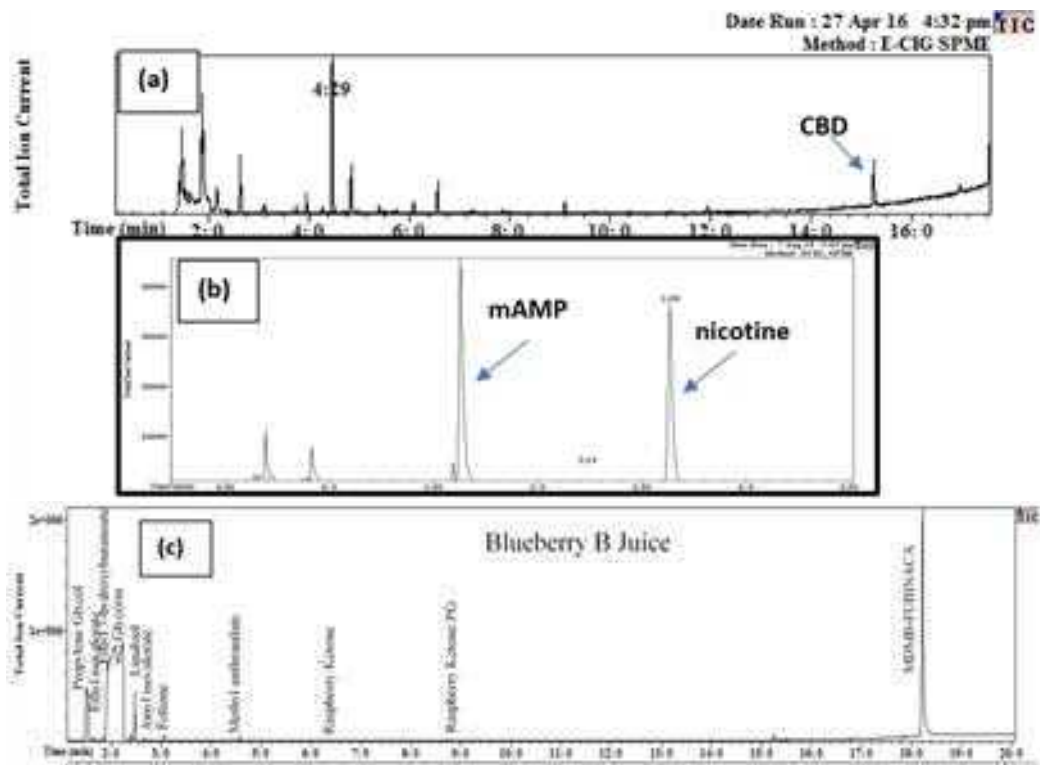


Figure 4. SPME GC-MS results for aerosolized (a) CBD, (b) methamphetamine and nicotine, and (c) MDMBFubinaca.

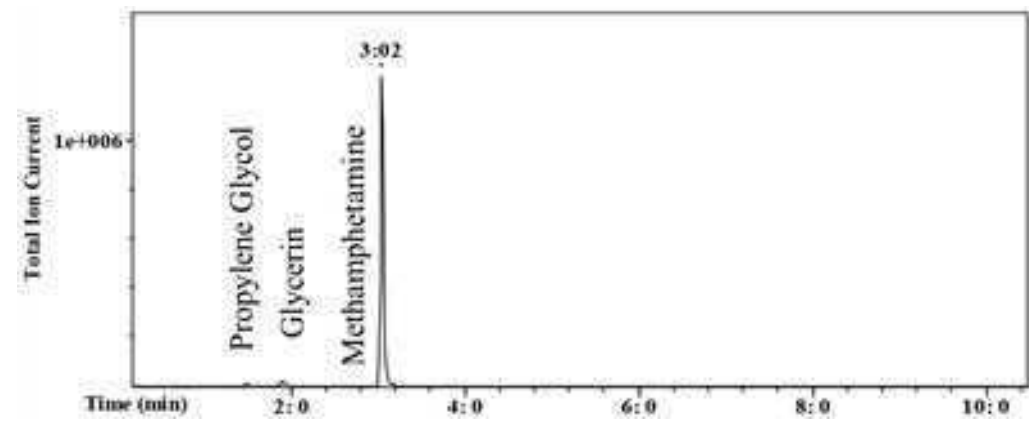


Figure 5. GC-MS SIM method for quantitation of methamphetamine.



Figure 6. Cig-a-like electronic cigarette. Electronic cigarette is not customizable and have a self-contained non-modifiable e-liquid.

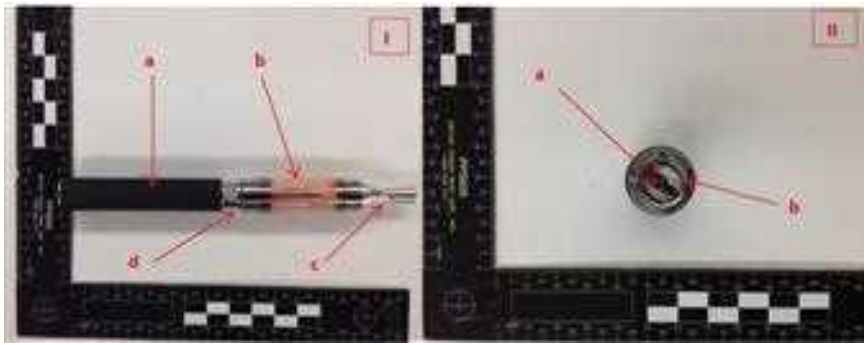


Figure 7. Clearomizer electronic cigarette components. I. (a) Battery power supply (b) Clearomizer tank (c) Mouthpiece (d) Atomizer base. II. (a) Heating element (b) Wick.

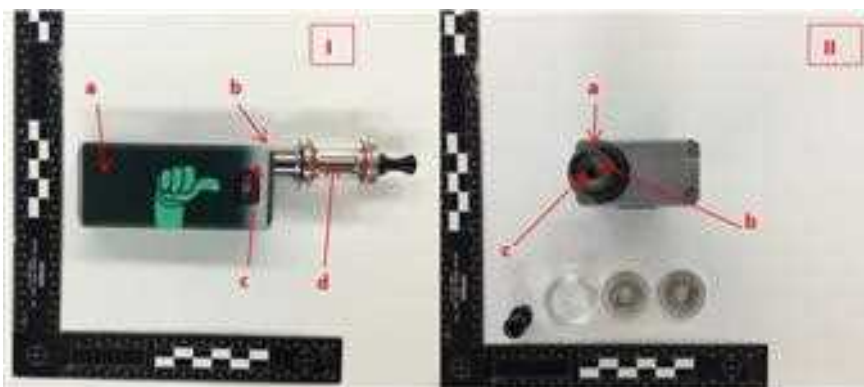


Figure 8. Cartomizer tank electronic cigarette. I. (a) Variable voltage power supply (b) cartomizer tank (c) Steel cartomizer (d) Mouthpiece. II. (a) Steel cartomizer, (b) Wicking material, (c) heating element.

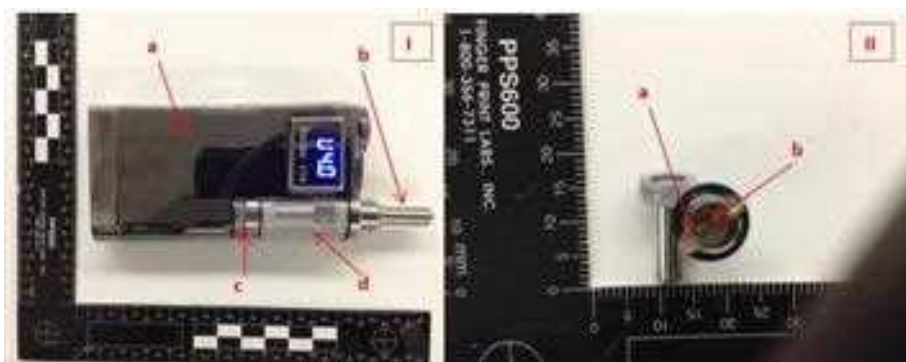


Figure 9. Rebuildable atomizer electronic cigarette. I. (a) Variable voltage power supply (b) Mouthpiece, (c) Base containing heating element and wick, (d) Tank. II. (a) wicking material (b) heating element.

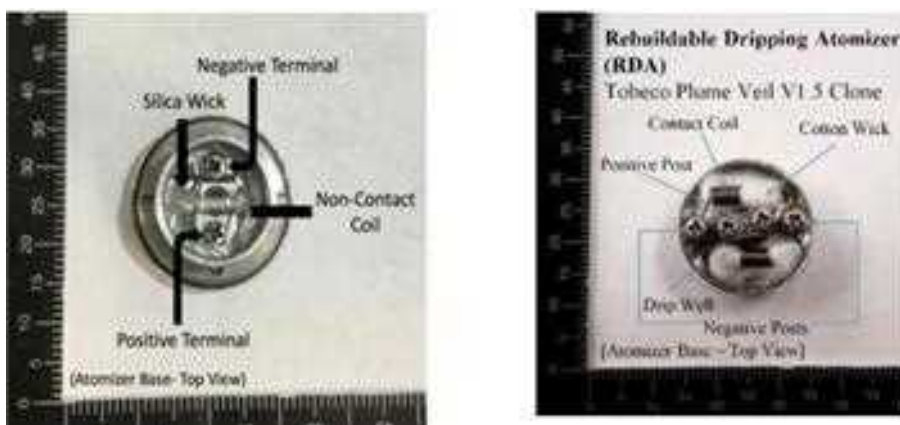


Figure 10. Single coil atomizer (on left) versus the Rebuildable Dropper Atomizer (RDA) with 2 coils wrapped in parallel for “sub-ohming” technique.

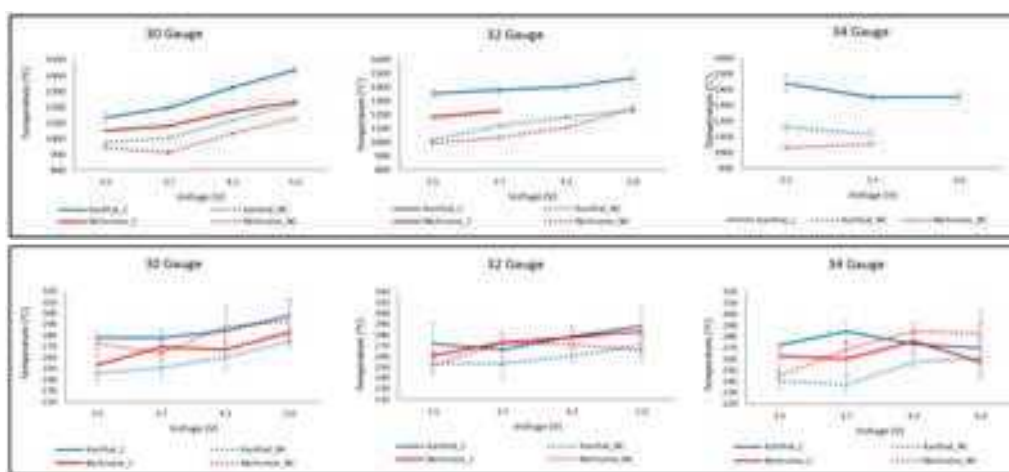


Figure 11. Temperature of center coil of 3 gauges of wire that were dry (top) or wet with 100% VG (bottom).

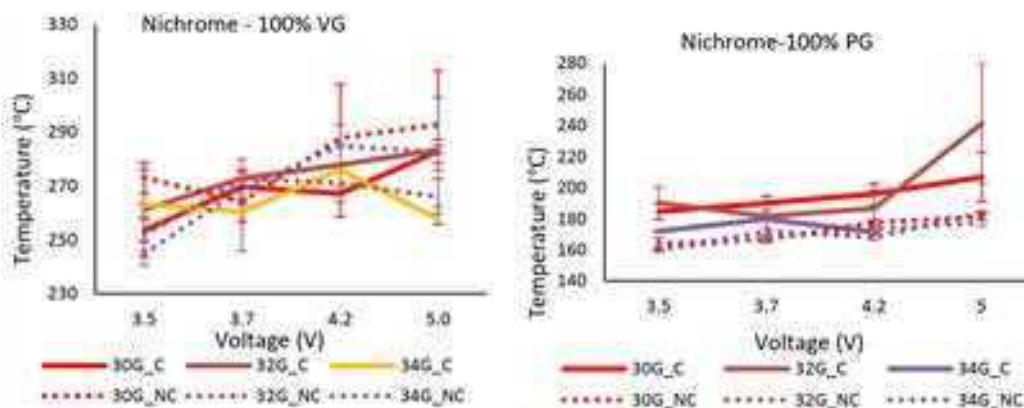


Figure 12. Comparison of temperature output of Nichrome wires in 100% VG (left) and 100% PG (right).

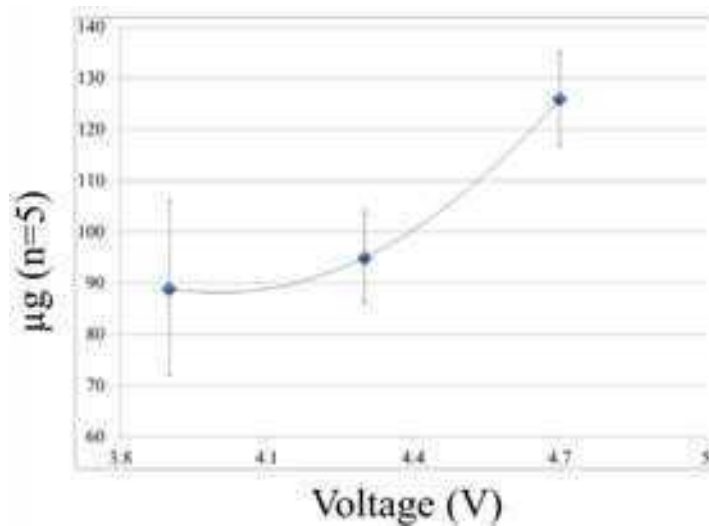


Figure 13. Nicotine yield as a function of voltage of the KangerTech AeroTank, 1.8 Ω .

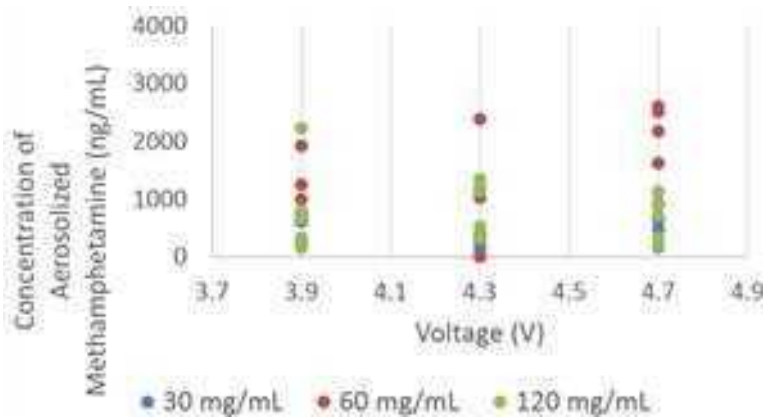


Figure 14. Quantitation of methamphetamine at three voltages.

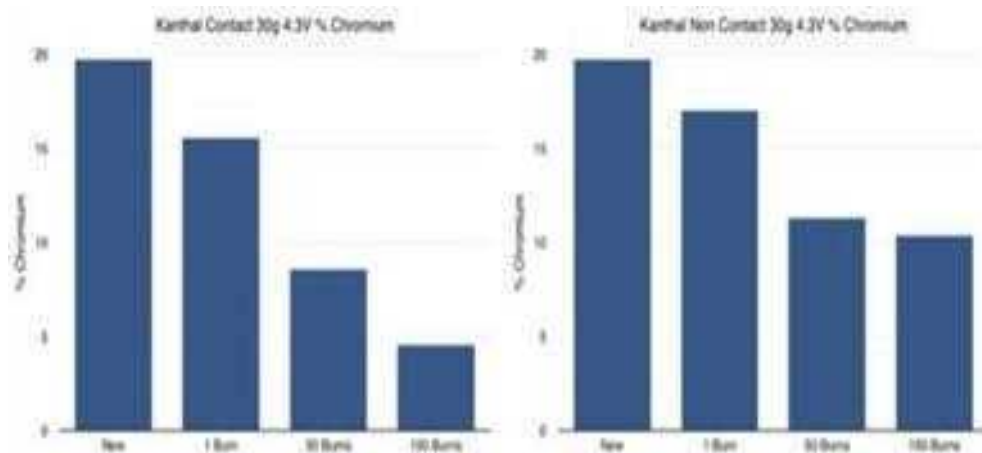


Figure 15. (Continued).

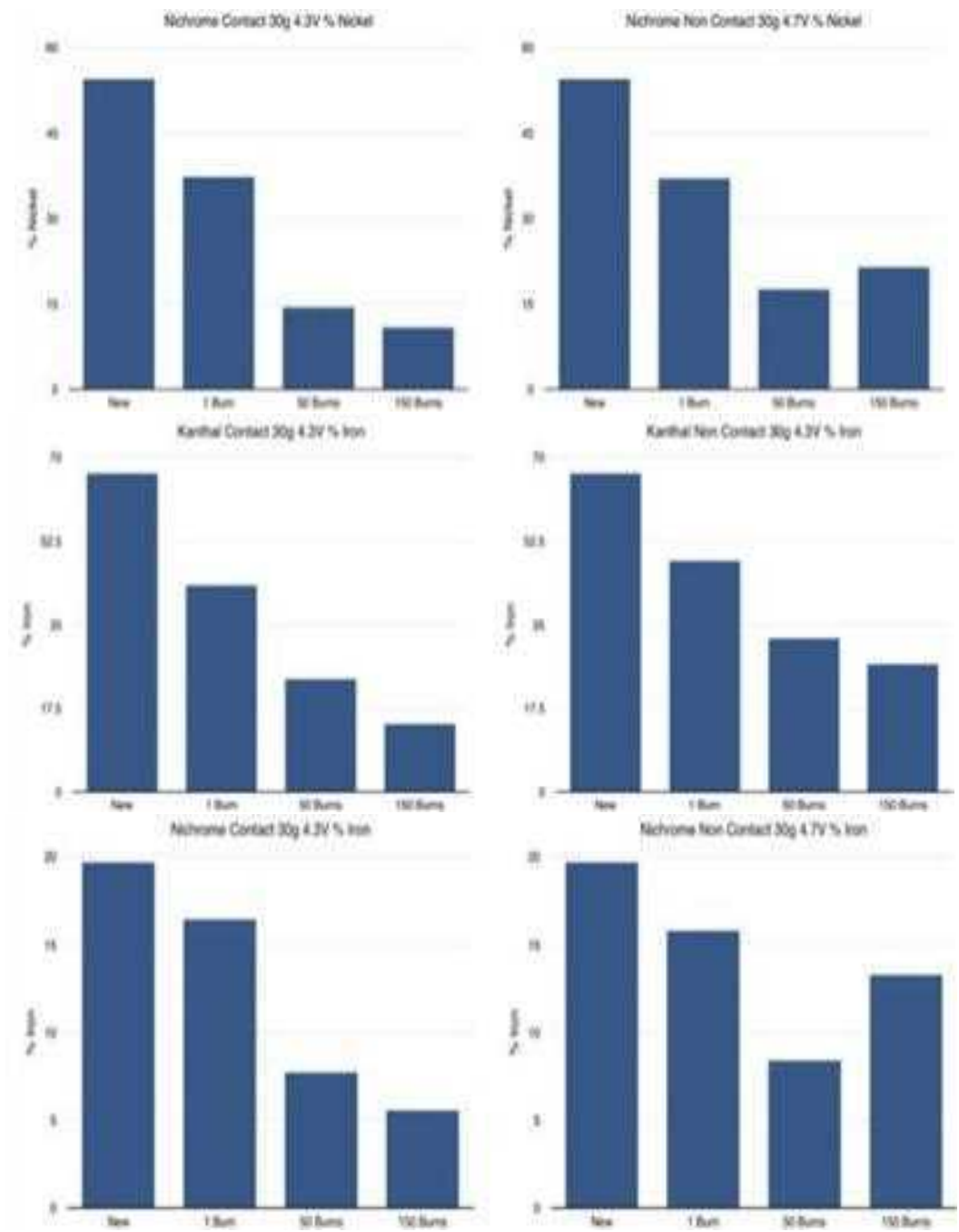


Figure 15. Percent weight of metals lost following 0, 1, 50, and 150 burns.

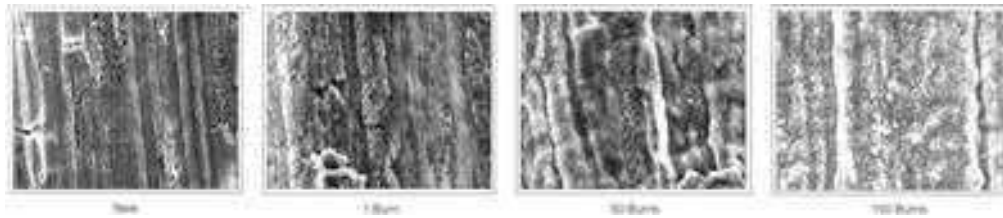


Figure 16. Kanthal contact 30 AWG surface features at 2000x magnification on the SEM following 0, 1, 50, and 150 burns.

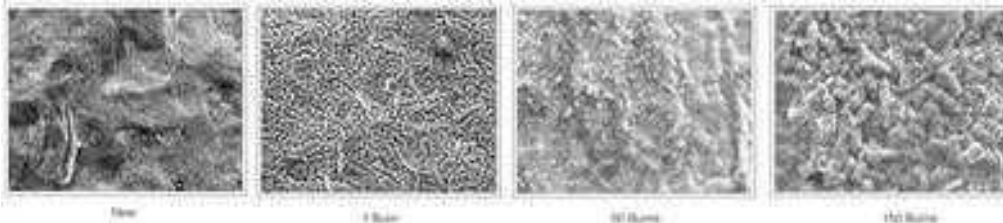


Figure 17. Nichrome contact 30 AWG surface features at 2000x magnification on the SEM following 0, 1, 50, and 150 burns.

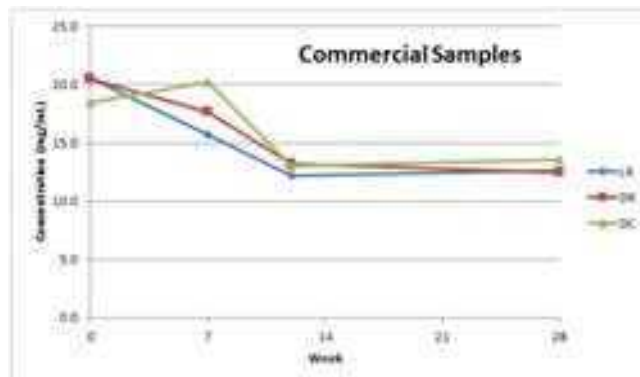


Figure 18. Concentration of nicotine in eliquids stored at 3 conditions: Light + Room Temperature (LR), Dark + Room Temperature (DR), and Dark + Cold (DC).



Figure 19. (Continued).

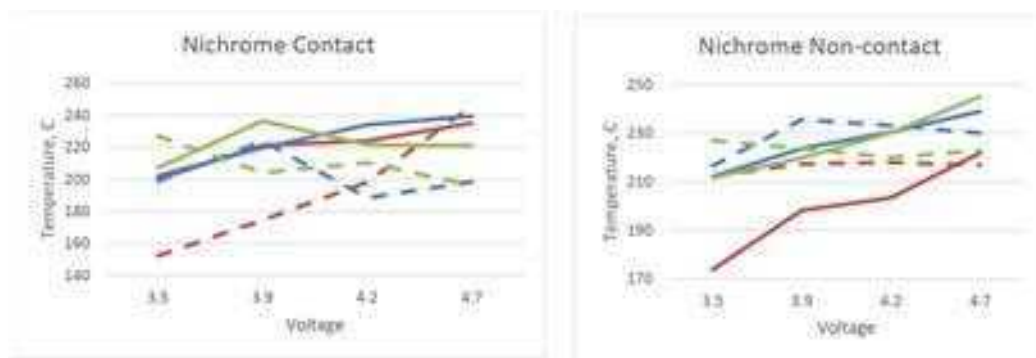


Figure 19. Comparison of e-cigarette coil temperatures with 10% ethanol and without ethanol in the e-liquids.

Table 1. Nicotine Quantitation by HPLC-MS³

Brand/Flavor	Label (mg/mL)	Mean (mg/mL)	S.D. (mg/mL)	%CV	Accuracy
258 Rally Squirrel	16	10.3	0.1	1	64
Captain Ron	12	11	0.2	2	92
Cheery	18	14.7	0.9	6	82
Delta	12	7.7	1.1	14	64
El Kamino	12	8.7	0.7	8	73
FennetHIGH	12	12.4	0.2	2	103
Grandmaster	6	7.8	0.4	5	131
Gremlin Juice Birthday Cake	12	13.8	3.1	23	115
Grumpy's Hooch	12	10	1.9	19	84
GWAR Spew	12	14.6	2.4	16	122
Indigo Birthday Cake	12	10.8	1.1	10	90
Jango	12	12.6	1.2	10	105
Kentucky Mint Julip	6	6.3	0.7	11	105
Mayflower	6	4.9	1.1	22	82
Peach Tobacco	12	8.9	0.7	8	74
Pharaoh	12	10.7	0.9	9	89
Snake Eyes	12	10.1	1.1	11	84
Snake Oil	12	10.5	1.5	14	87
Spearmint	22	11.6	2.7	23	53
Sunset	6	6	0.5	9	100
Turkish Tobacco	12	11.2	1.2	11	93
Unflavored PG	6	8.3	1.3	16	139
Vanilla Cream Custard	6	6	1.2	20	99
Vanilla Custard	12	10.7	2.7	25	89
Vanilla Tobacco	6	7.8	2.3	30	130
VG (12 mg/mL)	12	10.3	0.2	2	85
White Gummy Bear	6	5	0.4	8	83

Table 2. Scientific presentations over life of funding

1.	Royals JM (presenter), Poklis JL, Turner JBM, Wolf CE, Peace MR. Ethanol in E-liquids: Concentration in 35 Formulations by Headspace Gas Chromatography with Flame Ionization Detector (HS-GC-FID) and the Impact on the Temperature of the E-Cigarette Coils. Poster Presentation, Society of Forensic Toxicologists, Boca Raton, FL, 2017.
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Chapter 362

OUTBREAK OF LUNG INJURY ASSOCIATED WITH E-CIGARETTE USE, OR VAPING

Centers for Disease Control and Prevention

Posted October 3, 2019 at 4:00pm ET

CDC, the U.S. Food and Drug Administration (FDA), state and local health departments, and other clinical and public health partners are investigating a multistate outbreak of lung injury associated with use of e-cigarette, or vaping, products.

WHAT WE KNOW

- As of October 1, 2019, 1,080* lung injury cases associated with using e-cigarette, or vaping, products have been reported to CDC from 48 states and 1 U.S. territory.
- Eighteen deaths have been confirmed in 15 states.
- All patients have reported a history of using e-cigarette, or vaping, products.
- Most patients report a history of using THC-containing products. The latest national and regional findings suggest products containing THC play a role in the outbreak.
- Approximately 70% of patients are male.
- Approximately 80% of patients are under 35 years old.
 - 16% of patients are under 18 years old
 - 21% of patients are 18 to 20 years old

WHAT WE DON'T KNOW

- The specific chemical exposure(s) causing lung injuries associated with e-cigarette use, or vaping, remains unknown at this time.
- No single product or substance has been linked to all lung injury cases.

- The outbreak is occurring in the context of a dynamic marketplace for e-cigarette, or vaping, products, which may have a mix of ingredients, complex packaging and supply chains, and include potentially illicit substances.
- Users may not know what is in their e-cigarette or e-liquid solutions. Many of the products and substances can be modified by suppliers or users. They can be obtained from stores, online retailers, from informal sources (e.g. friends, family members), or “off the street.”
- More information is needed to know whether one or more e-cigarette or vaping products, substances, or brands is responsible for the outbreak.

WHAT CDC RECOMMENDS

- While this investigation is ongoing, CDC recommends that you consider refraining from using e-cigarette, or vaping, products, particularly those containing THC.
- If you are an adult who used e-cigarettes containing nicotine to quit cigarette smoking, do not return to smoking cigarettes.
- If you have recently used an e-cigarette or vaping product and you have symptoms like those reported in this outbreak, see a healthcare provider.
- Regardless of the ongoing investigation:
 - Anyone who uses e-cigarette, or vaping, products should not buy these products (e.g., e-cigarette or vaping products with THC or CBD oils) from informal sources (e.g. friends, family members) or “off the street,” and should not modify or add any substances to these products that are not intended by the manufacturer.
 - Youth and young adults should not use e-cigarette, or vaping, products.
 - Women who are pregnant should not use e-cigarette, or vaping, products.
 - Adults who do not currently use tobacco products should not start using e-cigarette, or vaping, products.
 - THC use has been associated with a wide range of health effects, particularly with prolonged heavy use. The best way to avoid potentially harmful effects is to not use THC, including through e-cigarette, or vaping, products. Persons with marijuana use disorder should seek evidence-based treatment by a health care provider.

KEY FACTS ABOUT E-CIGARETTE USE, OR VAPING

- Electronic cigarettes – or e-cigarettes — are also called vapes, e-hookahs, vape pens, tank systems, mods, and electronic nicotine delivery systems (ENDS).
- Using an e-cigarette product is commonly called vaping.
- E-cigarettes work by heating a liquid to produce an aerosol that users inhale into their lungs.
- The liquid can contain: nicotine, tetrahydrocannabinol (THC) and cannabinoid (CBD) oils, and other substances and additives. THC is the psychoactive mind-altering compound of marijuana that produces the “high”.

LATEST OUTBREAK INFORMATION

- As of October 1, 2019, 1,080 lung injury cases associated with the use of e-cigarette, or vaping, products have been reported to CDC from the following states and 1 U.S. territory: AL, AR, AZ, CA, CO, CT, DE, FL, GA, HI, IA, ID, IL, IN, KS, KY, LA, MA, ME, MD, MI, MN, MO, MT, MS, NC, ND, NE, NJ, NM, NV, NY, OH, OK, OR, PA, RI, SC, SD, TN, TX, UT, VA, VT, WA, WI, WV, WY, and USVI.
- Eighteen deaths have been confirmed in 15 states: Alabama, California (2), Delaware, Florida, Georgia, Illinois, Indiana, Kansas (2), Minnesota, Mississippi, Missouri, Nebraska, New Jersey, Oregon (2), and Virginia. More deaths are under investigation.
 - The median age of deceased patients was 49.5 years and ranged from 27-71 years.
- Among 889 patients with data on age and sex:
 - 70% of patients are male.
 - The median age of patients is 23 years and ranges from 13-75 years.
 - 81% of patients are under 35 years old.
 - By age group category:
 - 16% of patients are under 18 years old;
 - 21% of patients are 18 to 20 years old;
 - 18% of patients are 21 to 24 years old;
 - 26% of patients are 25 to 34 years old; and
 - 19% of patients are 35 years or older.
- The latest findings from the investigation into lung injuries associated with e-cigarette use, or vaping, suggest products containing THC play a role in the outbreak.
- All patients have a reported history of e-cigarette product use, or vaping, and no consistent evidence of an infectious cause has been discovered. Therefore, the suspected cause is a chemical exposure.
- The specific chemical exposure(s) causing lung injuries associated with e-cigarette product use, or vaping, remains unknown at this time.
- No single product or substance has been linked to all lung injury cases. More information is needed to know whether a single product, substance, brand, or method of use is responsible for the outbreak.
- Among 578 patients with information on substances used in e-cigarette, or vaping, products in the 3 months prior to symptom onset:
 - About 78% reported using THC-containing products; 37% reported exclusive use of THC-containing products.
 - About 58% reported using nicotine-containing products; 17% reported exclusive use of nicotine-containing products.
- This complex investigation spans many states, involves hundreds of patients, and involves a wide variety of substances and e-cigarette, or vaping, products.

WHAT CDC IS DOING

- CDC is working 24/7 to identify the cause or causes of this outbreak through partnerships with states and other federal agencies.
- CDC has activated the Emergency Operations Center (EOC) to coordinate activities and provide assistance to states, public health partners and clinicians around the nation.
- CDC's Lung Injury response efforts are committed to:
 - Identify and define the risk factors and the source for lung disease associated with e-cigarette product use, or vaping.
 - Detect and track confirmed and probable cases in the US.
 - Communicate actionable recommendations to state, local, and clinical audiences.
 - Establish lab procedures that can assist with the public health investigation and patient care.
- CDC continues to work closely with FDA, states, public health partners, and clinicians on this investigation by providing consultation and technical assistance to states on communication, health alerts, public outreach, and surveillance.
- CDC is maintaining an outbreak webpage with key messages and weekly updates on case counts, deaths, and resources.
- CDC is holding congressional briefings, media telebriefings, and regular calls with health departments, clinicians to provide timely updates.
- CDC worked with states to create a case definition to classify confirmed and probable cases in a consistent way. States are in the process of classifying patients. We expect that states and clinicians may look back for past lung injury cases based on CDC's case definition CDC will report numbers of confirmed and probable lung injury cases once states have finalized their classification of cases.
- By invitation, CDC has deployed Epidemic Intelligence Service (EIS) officers to states to conduct Epi-Aids.
- CDC has started collecting and testing clinical lab specimens to learn more about this lung injury.
- CDC developed guidance documents for were created to assist public health laboratories, healthcare providers, and pathologists, and others, with specimen collection, storage, and submission.

FOR THE PUBLIC: WHAT YOU NEED TO KNOW

Symptoms of Lung Injury Reported by Some Patients in This Outbreak

- Patients in this investigation have reported symptoms such as:
 - cough, shortness of breath, or chest pain
 - nausea, vomiting, or diarrhea
 - fatigue, fever, or abdominal pain

- Some patients have reported that their symptoms developed over a few days, while others have reported that their symptoms developed over several weeks. A lung infection does not appear to be causing the symptoms.

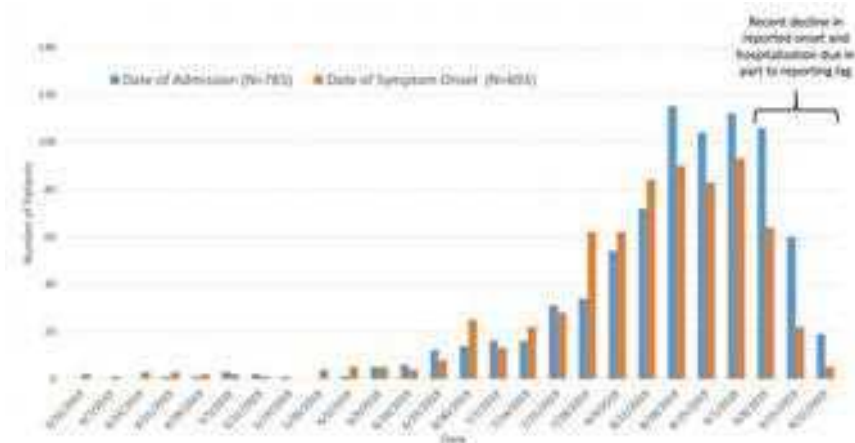


Figure 1. Dates of symptom onset and hospital admission for patients with lung injury associated with e-cigarette use, or vaping — United States, March 31–September 28, 2019.

Recommendations

You should consider refraining from using e-cigarette, or vaping, products, particularly those containing THC.

If you have recently used an e-cigarette, or vaping, product and you have symptoms like those reported in this outbreak, see a healthcare provider.

If you use e-cigarette, or vaping, products, you should:

- Not buy these products (e.g., e-cigarette or vaping products with THC or CBD oils) off the street, and not modify or add any substances to these products that are not intended by the manufacturer.
- See a healthcare provider right away if you have symptoms like those reported in this outbreak.

If you are an adult who uses e-cigarettes because you have quit cigarette smoking:

- Do not return to smoking cigarettes.
- If you continue to use e-cigarettes, carefully monitor yourself for symptoms and see a healthcare provider right away if you have symptoms like those reported in this outbreak.

If you are an adult who is trying to quit smoking:

- Contact your healthcare provider if you need help quitting tobacco products, including e-cigarettes.

- Use evidence-based treatments, including counseling and FDA-approved medication[external icon](#).

If you are an adult who is addicted to marijuana:

- Effective treatments are available and recovery is possible.
- A number of therapy-based treatments such as cognitive-behavioral therapy, contingency management, motivational enhancement therapy, and multi-dimensional family therapy have been shown to help people who are addicted to marijuana.
- Visit the Substance Abuse and Mental Health Services Administration's treatment locator[external icon](#) to find treatment in your area, or call 1-800-662-HELP (4357).

If you are a teen or young adult who is trying to quit nicotine or marijuana:

- Visit the Substance Abuse and Mental Health Services Administration's treatment locator[external icon](#) to locate treatment in your area, or call 1-800-662-HELP (4357).
- Visit the National Institute on Drug Abuse for Teens' What to Do If You Have a Problem with Drugs: For Teens and Young Adults[external icon](#).
- Get resources and support at Smokefree Teen[external icon](#) and Truth Initiative[external icon](#).

If you are concerned about your health after using an e-cigarette, or vaping, product, contact your health care provider, or you can also call your local poison control center at 1-800-222-1222.

Regardless of this investigation, CDC recommends:

- Youth and young adults should not use e-cigarette, or vaping, products.
- Women who are pregnant should not use e-cigarette, or vaping, products.
- Adults who do not currently use tobacco products should not start using e-cigarette, or vaping, products.
- THC use has been associated with a wide range of health effects, particularly with prolonged heavy use. The best way to avoid potentially harmful effects is to not use THC, including through e-cigarette, or vaping, products. Persons with marijuana use disorder should seek evidence-based treatment by a health care provider.

QUESTIONS ABOUT E-CIGARETTE USE, OR VAPING

What Is an E-Cigarette?

- Electronic cigarettes – or e-cigarettes – work by heating a liquid to produce an aerosol that users inhale into their lungs.
- The liquid can contain: nicotine, tetrahydrocannabinol (THC) and cannabinoid (CBD) oils, and other substances, flavorings, and additives.

- E-cigarettes are also called vapes, e-hookahs, vape pens, tank systems, mods, and electronic nicotine delivery systems (ENDS).

What Is Vaping?

- Using an e-cigarette is commonly called vaping.
- Vaping can refer to using e-cigarettes to inhale many substances, including nicotine, and THC or CBD oils.

What Is Causing This Outbreak of Lung Injury?

- The specific chemical exposure(s) causing lung injuries associated with e-cigarette use, or vaping, remains unknown at this time.
- No single product or substance has been linked to all lung injury cases. The outbreak is occurring in the context of a dynamic marketplace for e-cigarette or vaping products, which may have a mix of ingredients, complex packaging and supply chains, and include potentially illicit substances. Users may not know what is in their e-cigarette or e-liquid solutions. Many of the products and substances can be modified by suppliers or users. They can be obtained from stores, online retailers, from informal sources (e.g. friends, family members), or “off the street.”
- More information is needed to know whether one or more e-cigarette or vaping products, substances, or brand is responsible for the outbreak.

How Can I Protect Myself?

- While this investigation is ongoing, CDC recommends that you consider refraining from using e-cigarette, or vaping, products, particularly those containing THC.
- Anyone who uses an e-cigarette or vaping product should not buy these products (e.g., e-cigarette or vaping products with THC or CBD oils) off the street, and should not modify or add any substances to these products that are not intended by the manufacturer.
- If you are an adult who uses e-cigarettes because you have quit cigarette smoking, you should not return to smoking cigarettes.

What Should I Do If I Have Used E-Cigarettes and Have Symptoms?

- See a healthcare provider right away if you have symptoms like those reported in this outbreak.
- You can also call your local poison control center at 1-800-222-1222.

- You can also submit a detailed report of any unexpected health or product issues related to tobacco or e-cigarette products to the FDA via the online Safety Reporting Portal [external icon](#).

What If I'm an Adult Who Quit Cigarette Smoking and Now Uses E-Cigarettes?

- If you are an adult who uses e-cigarettes because you have quit cigarette smoking, do not return to smoking cigarettes.
- If you continue to use e-cigarettes, carefully monitor yourself for symptoms and see a healthcare provider right away if you have symptoms like those reported in this outbreak.

What Is Marijuana (THC)?

- Marijuana, which can also be called weed, pot, dope, or cannabis, is the dried flowers and leaves of the cannabis plant.
- Marijuana contains mind-altering (e.g., psychoactive) compounds like tetrahydrocannabinol, or THC, as well as other active compounds like cannabidiol, or CBD, that are not mind-altering.
- For more information visit the CDC web page [Marijuana and Public Health](#)

What Are the Health Risks of Marijuana (THC)?

- Marijuana use has been associated with a wide range of health effects, particularly with prolonged heavy use.
- These effects range from short-term problems with attention, memory, learning, to longer-term problems such as psychosis, anxiety, suicidal ideation and attempts, depression, and substance use disorder. It is not known whether these are causal relationships or simply associations.
- The best way to avoid potentially harmful effects is to not use marijuana.

How Does Marijuana Use during Adolescence Affect Youth?

- Marijuana use, including in e-cigarettes or through vaping, is associated with a broad range of health effects. Marijuana use can harm the developing adolescent brain and impact attention, learning, and memory. Starting to use marijuana at a younger age increases the likelihood of frequent and problematic use later in life.
- Youth marijuana use has also been associated with antisocial and oppositional behaviors, nicotine use, poor school performance, use of other illicit substances and

the development of substance use disorders, and impairments in social relationships. See the recent Surgeon General's Advisory: Marijuana Use and the Developing Brain [external icon](#).

- Regardless of the substance used, e-cigarette or vaping products should never be used by youth or pregnant women. It is important for parents to communicate with their child about the risks of nicotine, THC, or other substance use. CDC offers a [Talk With Your Teen About E-cigarettespdf iconexternal icon](#) tip sheet to help parents talk with their children about why e-cigarettes are harmful for them.

What Should I Do if I Am Currently Vaping Marijuana/THC for Medical Use?

- While this investigation is ongoing, CDC recommends that persons consider refraining from using e-cigarette or vaping products, particularly those containing THC. Until we have more information, this includes THC-containing products obtained from any source but in particular, individuals should not purchase from informal sources (e.g. friends, family members), or “off the street.”
- If you have recently used a THC-containing product in an e-cigarette or vaping product and you have symptoms like those reported in this outbreak see a healthcare provider.
- We do not know if there are different health effects of using different forms of marijuana, such as smoking, vaping, and edibles, to recommend transitioning from one mode of use to another to reduce harm. Talk with your healthcare provider about other available treatment options for the conditions).

How Are States Regulating THC-Containing Vaping Products?

- Some states have legalized the use of THC-containing vaping products for nonmedical and/or medical purposes.
- State regulations vary with regard to product pre-approval processes, ingredient requirements and/or limitations, packaging and labeling, and testing requirements and methods. States typically conduct various levels of testing of products, including testing for potency, contaminants, metals, pesticides, and/or pathogens.
- Both THC-containing and nicotine-containing e-cigarette, or vaping, products purchased legally within states might also contain harmful substances. It is difficult to know what is in these products, and full ingredient lists are typically not available. It is difficult to know what substances the products contain and potential for harm.

RECOMMENDATIONS FOR CLINICIANS

1. Report cases of lung injury of unclear etiology and a history of e-cigarette or vaping product use within the past 90 days to your state or local health department.

Reporting of lung injury cases may help CDC and state health departments determine the cause of these lung injuries.

2. Ask all patients who report e-cigarette, or vaping, product use within the last 90 days about signs and symptoms of respiratory illness.
3. If e-cigarette, or vaping, product use is suspected as a possible etiology of a patient's lung injury, obtain detailed history regarding:
 - Substance(s) used: nicotine, cannabinoids (e.g., marijuana, THC, THC concentrates, CBD, CBD oil, synthetic cannabinoids [e.g., K2 or spice], hash oil, Dank vapes), flavors, or other substances
 - Substance source(s): commercially available liquids (i.e., bottles, cartridges, or pods), homemade liquids, and re-use of old cartridges or pods with homemade or commercially bought liquids
 - Device(s) used: manufacturer; brand name; product name; model; serial number of the product, device, or e-liquid; if the device can be customized by the user; and any product modifications by the user (e.g., exposure of the atomizer or heating coil)
 - Where the product(s) were purchased
 - Method of substance use: aerosolization, dabbing, or dripping
 - Other potential cases: sharing e-cigarette or vaping products (devices, liquids, refill pods, or cartridges) with others
6. Determine if any remaining product, including devices and liquids, are available for testing. Testing can be coordinated with the local or state health departments.
7. Consider all possible causes of illness in patients reporting respiratory and gastrointestinal symptoms. Evaluate and treat for other possible causes of illness (e.g., infectious, rheumatologic, neoplastic) as clinically indicated. Consider consultation with specialists (pulmonary, infectious disease, critical care, medical toxicology) as appropriate.
8. Clinical improvement of patients with lung injury associated with e-cigarette use has been reported with the use of corticosteroids. The decision to use corticosteroids should be made on a case-by-case basis based on risks and benefits and the likelihood of other etiologies.
9. Lipoid pneumonia associated with inhalation of lipids in aerosols generated by e-cigarettes or vaping products has been reported based on the detection of lipid-laden alveolar macrophages obtained by bronchoalveolar lavage (BAL) and lipid staining (e.g., Oil Red O, Sudan Black). The decision about whether to perform a BAL should be based on individual clinical circumstances.
10. Lung biopsies have been performed on some patients. If a lung biopsy is obtained, lipid staining may be considered during pathologic examination, and is best performed on fresh tissue. Routine pathology tissue processing (including formalin-fixation and paraffin-embedding) can remove lipids. Conducting routine tissue processing and histopathologic evaluation is still important. Consider consultation with specialists in pulmonary medicine and pathology to help inform any evaluation plan.
11. Patients who have received treatment for lung injury related to e-cigarette or vaping product use should undergo follow-up evaluation as clinically indicated to monitor pulmonary function.

12. Consider asking the medical examiner or coroner's office and hospital pathologists to report possible deaths, especially those without an alternative, likely diagnosis. If individuals are identified after death or at autopsy who showed signs of lung injury as described above, medical examiners and coroners are encouraged to report the cases to their local or state health department.

If a lung biopsy or autopsy is performed on a patient suspected of lung injury related to e-cigarette, or vaping, product use, consider submission of fixed lung biopsy tissues or autopsy tissues to CDC for evaluation. Testing can include evaluation for lipids on formalin-fixed (wet) lung tissues that have not undergone routine processing. Routine microscopic examination will be performed, as well as infectious disease testing, if indicated, on formalin-fixed (wet) tissues, or formalin-fixed, paraffin-embedded tissue specimens.

OTHER CONSIDERATIONS

Clinicians routinely consider multiple possible etiologies when evaluating and treating patients presenting with respiratory symptoms. In some cases, treatment directed at one or more of these etiologies must be initiated before the results of diagnostic testing, or other clinical features enable the list of possibilities to be narrowed.

- For the coming flu season, CDC recommends that clinicians strongly consider respiratory infections such as influenza, as well as lung injury associated with e-cigarette use, or vaping, in all patients presenting with respiratory symptoms and a history of e-cigarette use, or vaping.
- Clinicians are further advised that it may not be possible to definitively distinguish between respiratory infection and lung injury associated with use of e-cigarettes, or vaping, using available testing. Therefore, therapy directed at both may be necessary. Decisions on the initiation or discontinuation of treatment should be based on specific clinical features and, when appropriate, in consultation with specialists.

Chapter 363

OUTBREAK OF LUNG INJURY ASSOCIATED WITH E-CIGARETTE PRODUCT USE OR VAPING: INFORMATION FOR CLINICIANS*

Centers for Disease Control and Prevention

CDC 2019 Lung Injury Response

BACKGROUND

- As of September 17, 2019, 530 cases of lung injury associated with the use of e-cigarette products or vaping have been reported to CDC
 - data updated weekly at CDC's outbreak website
 - 38 states, 1 U.S. territory; 7 deaths have been confirmed
- No specific etiology has been identified, but all patients have reported using e-cigarette products, or vaping
 - Most have reported using products containing THC
 - Many have reported using THC and nicotine; some only nicotine
- CDC issued recommendations for clinicians, public health officials, and the public through its health advisory network (HAN) on August 30, 2019
- Initial clinical experience summarized in recent publications in *Morbidity & Mortality Weekly Report (MMWR)* and *New England Journal of Medicine (NEJM)*

* This is an edited, reformatted and augmented version of Centers for Disease Control and Prevention, dated September 16, 2019.

Patient Exposures in the Lung Injury Outbreak

- All have reported use of e-cigarette products, or vaping, within 90 days of illness
 - Most have reported using cannabinoids such as Δ -9-tetrahydrocannabinol (THC) or cannabidiol (CBD)
 - Some have reported nicotine use alone
- No single device type has been reported consistently (though device types have not yet been well-characterized)
- No single e-cigarette product or substance (including cannabis products) has been reported consistently

CDC Confirmed Case Definition (September 18, 2019)

- Using an e-cigarette ("vaping") or dabbing* in 90 days prior to symptom onset
- AND**
- Pulmonary infiltrate, such as opacities, on plain film chest radiograph or ground-glass opacities on chest CT
- AND**
- Absence of pulmonary infection on initial work-up. **Minimum criteria** are
 - A negative respiratory viral panel **and**
 - A negative influenza PCR or rapid test, if local epidemiology supports influenza testing; **and**
 - All other clinically-indicated respiratory ID testing (e.g., urine Antigen for *Streptococcus pneumoniae* and *Legionella*, sputum culture if productive cough, bronchoalveolar lavage (BAL) culture if done, blood culture, HIV-related opportunistic respiratory infections if appropriate) are negative
- AND**
- No evidence in medical record of alternative plausible diagnoses (e.g., cardiac, rheumatologic, or neoplastic process)

CDC Probable Case Definition (September 18, 2019)

- Using an e-cigarette ("vaping") or dabbing* in 90 days prior to symptom onset
- AND**
- Pulmonary infiltrate, such as opacities, on plain film chest radiograph or ground-glass opacities on chest CT
- AND**
- Infection identified via culture or PCR, but clinical team** believes this infection is not the sole cause of the underlying lung injury **OR Minimum criteria** to rule out pulmonary infection not met (testing not performed) and clinical team** believes this infection is not the sole cause of the underlying lung injury

** Clinical team caring for the patient.

AND

- No evidence in medical record of alternative plausible diagnoses (e.g., cardiac, rheumatologic, or neoplastic process)

Patient Exposures in the Lung Injury Outbreak

- Series of 53 cases from Illinois and Wisconsin*
 - All had history of e-cigarette use and related products
 - 41 extensively interviewed
 - 61% reported nicotine use; 80% reported THC use; 7% reported CBD use
 - 37% reported THC use alone; 17% reported nicotine use alone
 - 44% reporting both nicotine and THC product use
 - Various brands and flavors
- Among patients with additional data, 94% used within week before symptom onset; 88% reported daily use

E-CIGARETTE OR VAPING PRODUCTS



E-Cigarette or Vaping Products: The Basics

- E-cigarette products include devices, liquids, flavorings, refill pods, and cartridges
- Devices heat liquid to produce an aerosol that is inhaled by the user
- E-cigarette **aerosol** can contain harmful or potentially harmful substances

* Layden J, et al. Pulmonary illness related to e-cigarette use in Illinois and Wisconsin—preliminary report. *NEJM* 2019.

- Nicotine
- Heavy metals (e.g., lead, nickel, tin)
- Volatile organic compounds
- Ultrafine particles
- Cancer-causing chemicals
- Flavoring (e.g., diacetyl)



E-Cigarette Products: Devices

- Devices vary in shape, size, type, and manufacturer
- Common names
 - E-cigs
 - Vapes
 - E-hookahs
 - Vape pens
 - Mods
 - Tanks
 - Electronic nicotine delivery systems



E-Cigarette Products: Liquids, Cartridges, and Pods

- E-cigarette **liquid** can contain
 - Nicotine
 - Flavorings
 - Propylene glycol and vegetable glycerin used in varying proportions as carriers
 - Other chemicals also present
 - Cannabinoids: Δ -9-tetrahydrocannabinol (THC), cannabidiol (CBD), butane hash oil (BHO)
 - Other substances
- E-cigarette liquid types
 - Commercial refillable e-liquid
 - Commercial non-refillable e-liquid
 - Homemade or street sources

E-CIGARETTE PRODUCTS: BEHAVIORS

- Hacking: modifying device in a way not intended by the manufacturer
 - Refilling single-use cartridges (e.g., with homemade or illicit substances)
 - Dripping: dropping liquid directly onto device heating coil to attain higher compound concentrations in the aerosol
- Dabbing: superheating substances containing high concentrations of THC or other cannabinoids (e.g., budder, BHO, 710, CBD)

CLINICAL FEATURES: FREQUENT CLINICAL, LABORATORY, RADIOGRAPHIC, AND PATHOLOGIC FINDINGS AND OUTCOMES

Information Sources on Clinical Features

- Anecdotal and verified reports from health departments
- Formal and informal discussions between CDC, clinicians, and medical professional societies
- Recent publications in *Morbidity and Mortality Weekly Report* and *New England Journal of Medicine* (published September 6, 2019)
 - Schier JG, et al. Severe Pulmonary Disease Associated with Electronic-Cigarette-Product Use — Interim Guidance. *MMWR* 2019;68(36).
 - Layden J, et al. Pulmonary illness related to e-cigarette use in Illinois and Wisconsin—preliminary report. *NEJM* 2019.
 - Davidson K, et al. Outbreak of e-cigarette-associated acute lipoid pneumonia—North Carolina, July–August 2019. *MMWR* 2019;68(36).
 - Maddock S, et al. Pulmonary lipid-laden macrophages and vaping. *NEJM* 2019.
 - Henry TS, et al. Imaging of vaping-associated lung disease. *NEJM* 2019

FREQUENT CLINICAL SYMPTOMS

- Most patients have been young and otherwise healthy
- Report gradual onset of various symptoms over days to weeks
 - Respiratory (cough, chest pain, shortness of breath)
 - Gastrointestinal (GI) (abdominal pain, nausea, vomiting, diarrhea)
 - Systemic symptoms (fatigue, fever, weight loss)
- GI symptoms sometimes precede respiratory symptoms
 - Tend to resolve quickly after admission
 - Evaluation for GI-related illness unrevealing
- Almost all published cases have been hospitalized
 - Many with ≥ 1 antecedent evaluation in ambulatory settings

Frequent Presenting Signs upon Hospital Admission

- Fever
- Tachycardia
- Tachypnea
- Hypoxemia (even in patients without respiratory symptoms upon presentation)
 - One of 53 patients in the recently published 53-case series in *New England Journal of Medicine** did not report respiratory symptoms, but had oxygen saturation of 91% on room air on admission

FREQUENT LABORATORY AND RADIOGRAPHIC FINDINGS

- Laboratory
 - Serum leukocytosis with neutrophil predominance
 - Elevated serum markers of inflammation (e.g., ESR, CRP)
 - Transient, mild elevation in serum transaminases
- Chest imaging
 - Abnormal findings may or may not be present on initial imaging, but develop eventually
 - Bilateral opacities on plain radiograph or ground-glass opacities on chest computed tomography (CT), often with sub-pleural sparing
- Imaging of abdomen/pelvis usually unremarkable except for bilateral opacities in cuts of lower lung fields included on CT

* Layden J, et al. Pulmonary illness related to e-cigarette use in Illinois and Wisconsin—preliminary report. *NEJM* 2019.

Clinical Course

- Initial therapies focused on presumed infectious etiologies
 - Empiric antibiotics with or without steroids
 - Observation with supportive therapy other than antibiotics or steroids
- Many patients have experienced sub-acute or acute hypoxemic respiratory failure requiring supplemental oxygenation and at times ventilatory support, including with intubation and mechanical ventilation or extracorporeal membrane oxygenation
- Patients who did not respond to antibiotics alone have tended to respond to systemic corticosteroids (either alone or concurrent with antibiotics)

Frequently Performed Diagnostic Evaluations

- Appropriate extensive evaluations for infectious etiologies often completed without an identified cause
- Use of pulmonary function testing has been highly variable, mostly depending upon institutional practices
- Some patients evaluated for lung injury with bronchoscopy with bronchoalveolar lavage or lung biopsy (either transbronchial or surgical via video-assisted thoracoscopic surgery [VATS] or thoracotomy)
 - Additional patients considered for these procedures but were too ill
 - Roles and frequencies of biopsy methods remain unknown

Evaluation of Pathologic Specimens

- Both routine histopathologic and special evaluations of specimens have been performed
- Routine processing of tissues includes the application of alcohol, which removes lipids
- Therefore, as a special evaluation, lipid-staining (e.g., Oil Red O, Sudan Black) has been performed on fresh tissues and bronchoalveolar lavage fluid

Spectrum of Clinical and Pathologic Diagnoses

- Acute lung injury and adult respiratory distress syndrome (ARDS)
- Diffuse alveolar damage
- Lipoid pneumonia
- Acute necrotizing pneumonitis
- Organizing pneumonia with lipid-laden macrophages
- Non-specific inflammation
- Hypersensitivity pneumonitis
- Eosinophilic pneumonia

Outcomes

- Specialists in pulmonary medicine, critical care, infectious diseases, pathology, or toxicology frequently involved in patients' care
- Despite illness severity, most patients have survived to hospital discharge
 - Most patients have been young and healthy pre-illness
 - Some patients who have not recovered to pre-illness pulmonary function at time of discharge, demonstrated improvement during post-hospitalization evaluation
 - Other patients still had reduced pulmonary function during post-hospitalization evaluation
 - 7 patients died in the hospital (as of September 17, 2019)

RECOMMENDATIONS FOR CLINICIANS

Overview

- History
- Diagnosis
- Clinical Management
- Evaluation of Pathologic Specimens at CDC
- Autopsy
- What to Tell Patients
- Case Reporting to Public Health Authorities
- CDC will provide updates as more information becomes available

History

- Ask patients who report e-cigarette product use, or vaping, within the last 90 days about signs and symptoms of respiratory illness
- Ask patients who present with signs and symptoms of respiratory illness about e-cigarette use, or vaping, within the last 90 days
- If e-cigarette product use is suspected as a possible etiology of a patient's respiratory illness, obtain a detailed history about e-cigarette product use, or vaping

E-Cigarette Product Use

- Substances used: nicotine, cannabinoids (e.g., marijuana, THC, THC concentrates, CBD, CBD oil, synthetic cannabinoids [e.g., K2 or spice], hash oil, Dank vapes), flavors, or other substances
- Substance sources: commercially refillable e-liquids (e.g., bottles, cartridges, or pods), commercial non-refillable e-liquids, homemade or street sources

- Devices used: manufacturer; brand name; product name; model; serial number of the product, device, or e-liquid; if the device can be customized by the user; and any product modifications by the user (e.g., exposure of the atomizer or heating coil)
 - Where the devices were purchased
 - Method of use: aerosolization, dabbing, dripping, or re-use of old cartridges or pods with homemade or commercially bought e-liquids
 - Sharing e-cigarette products (devices, liquids, refill pods, or cartridges) with others (to identify other cases)

Diagnosis

- Consider all possible causes of illness (e.g., infectious, rheumatologic, neoplastic) in patients reporting respiratory with or without GI symptoms and e-cigarette product use
- Consider consultation with specialists (pulmonary, infectious disease, critical care, medical toxicology, pathology) as clinically indicated
- Lipoid pneumonia associated with inhalation of lipids in aerosols generated by e-cigarettes, or vaping, has been reported based on the detection of lipid-laden alveolar macrophages obtained by bronchoalveolar lavage and lipid staining (e.g., Oil Red O, Sudan Black)
 - The decision about whether to perform bronchoalveolar lavage, with or without transbronchial biopsy, should be based on the overall clinical picture
- Lung biopsies have been performed on some patients
 - The decision about whether to perform biopsy (whether transbronchial or surgical) should be based on the overall clinical picture.
 - If a lung biopsy is obtained, consider lipid-staining during pathologic examination.* Because routine tissue processing involves the application of alcohols, which remove lipids, lipid-staining is best performed on fresh tissue.
 - Before the procedure consider consultation with pulmonary, critical care, pathology, or other specialties to inform any evaluation plan
 - However, conducting routine tissue processing and histopathologic evaluation is still important.
- Contact public health officials as needed for technical assistance with laboratory testing, including for guidance regarding whether to retain specimens, storage instructions in the event of long-term storage, and collection of specimens for indications other than clinical care
- If retaining of specimens is anticipated, contact your facility's laboratory since routine practice might result in discarding of specimens before desired

* Additional information on lipid-staining is available at: https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease/healthcare-providers/index.html.

Clinical Management

- Decisions regarding outpatient versus inpatient management should be based on individual clinical circumstances
- Evaluate and treat as appropriate for other possible causes of illness (e.g., infectious, rheumatologic, neoplastic)
- Consider consultation with specialists (pulmonary, infectious disease, critical care, medical toxicology)
- Clinical improvement of patients with lung injury associated with e-cigarette use, or vaping, has been reported with the use of corticosteroids
 - Dosing, route of administration, duration, and timing have varied
 - The decision to use corticosteroids should be made on a case-by-case basis based on risks and benefits and the likelihood of other etiologies
- Patients who have received treatment for lung injury related to e-cigarette product use, or vaping, should undergo follow-up evaluation as clinically indicated to monitor pulmonary function

Evaluation of Pathologic Specimens at CDC*

- If feasible, submission of formalin-fixed (wet) lung tissues is encouraged
- CDC's Infectious Disease Pathology Branch can perform lipid-staining on formalin-fixed (wet) lung tissues using osmium tetroxide before routine tissue processing and paraffin embedding
 - However, lipid staining cannot be performed on formalin-fixed, paraffin-embedded lung tissue blocks, because they have undergone processing that removes lipids
- CDC's Infectious Disease Pathology Branch will also review tissue histopathology and perform additional testing, including testing for possible infectious etiologies
- Please first report any possible cases of lung injury associated with e-cigarette product use, or vaping, to your state, territorial, tribal, or local health department
- Pre-approval is required prior to submission of any tissue specimens. For pre-approval, health departments should contact pathology@cdc.gov and [Vaping AssocIllness@cdc.gov](mailto:VapingAssocIllness@cdc.gov).

Autopsy

- In the event of a fatal outcome, autopsies can be considered
 - Collection of fresh lung tissue for staining of lipids, formalin-fixed (wet) lung tissue, and submission of lung and other tissues for routine tissue processing, paraffin-embedding, and evaluation of histopathology should be considered

* Additional information on lipid-staining is available at: https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease/healthcare-providers/index.html.

- Infectious disease testing, including postmortem microbiology and molecular testing, should also be considered if indicated by patient history or autopsy findings
- Contact public health officials as needed for technical assistance with laboratory testing

What to Tell Patients

- Regardless of the ongoing investigation, e-cigarette products should not be used by
 - Youth and young adults
 - Pregnant women
 - Adults who do not currently use tobacco products
- Regardless of the ongoing investigation, anyone who uses e-cigarette products should
 - Not buy these products off the street (e.g., e-cigarette products with THC, other cannabinoids)
 - Not modify e-cigarette products or add any substances to these products that are not intended by the manufacturer
 - Monitor yourself for symptoms (e.g., abdominal pain, nausea, vomiting, diarrhea, cough, shortness of breath, chest pain)
 - Promptly seek medical attention if you have concerns about your health
- For adults trying to quit tobacco product use, including e-cigarettes
 - Use evidence-based treatments, including counseling from a healthcare provider and FDA-approved medications
- During the current investigation of lung injury associated with e-cigarettes, or vaping, if you are concerned about these specific health risks
 - Consider refraining from using e-cigarette or vaping products
 - If you are an adult who uses e-cigarettes because you have quit cigarette smoking, do not return to smoking cigarettes
 - If you continue to use e-cigarettes, carefully monitor yourself for symptoms and see a healthcare provider right away if you have symptoms like those reported in this outbreak
- If you are concerned about harmful effects from e-cigarette products, call your local poison control center at: 1-800-222-1222
- Submit detailed reports of any unexpected tobacco or e-cigarette-related health or product issues to the FDA via the online Safety Reporting Portal: <https://www.safetyreporting.hhs.gov> external icon

Case Reporting to Public Health Authorities

- Report cases of lung injury of unclear etiology and a history of e-cigarette product use, or vaping, within the past 90 days to your state or local health department

- Reporting of cases may help CDC and state health departments determine the cause or causes of these pulmonary illnesses
- Determine if any remaining product, including devices and liquids, are available for testing
 - Coordinate testing with the local or state health departments

Additional Resources

- CDC will provide updates as more information becomes available
- CDC website with updates for the ongoing investigation of lung injury associated with e-cigarette products use, or vaping: https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html.

LIMITATIONS AND KNOWLEDGE GAPS

- Information sources have included both confirmed and unconfirmed reports and small case series
 - Anecdotal data can generate hypotheses but alone are insufficient; clinical information to support range of diagnoses has been lacking
 - As of September 17, 2019, of 530 reported cases, <20% have been described in published literature; representativeness of published cases is unknown
- Outbreak surveillance case definitions are intended for public health data collection purposes and not intended for use as a clinical diagnostic tool or replacement for individual clinical judgment
 - No diagnostic criteria exist
- Most cases have been severe illness resulting in hospitalization, but true spectrum of illnesses (including less severe illness) could be unrecognized
- Investigations in affected states have been ongoing, but national efforts to coordinate, centralize, and standardize data collection efforts have been underway since August 16, 2019
- No systematic data yet for exposure (including products, quantities, sources) or clinical information
- Available data point away from a purely infectious etiology, but this does not exclude the possibility of concurrent processes
 - No decision-making tools to distinguish infection versus non-infection at presentation, so important to rule out and empirically treat infectious etiologies as appropriate, even in patients with exposure history
 - Patterns of illness could change with the approaching respiratory virus season
- Remains unclear whether this is a new syndrome or a newly recognized one previously thought to be pneumonia or pneumonitis of unclear etiology

- Although most patients have survived to hospital discharge, whether there are post-illness sequelae (e.g., reduced pulmonary function) after hospital discharge is not yet known for most patients
- Age-related differences in illness have not been assessed
 - Outbreak predominantly has affected younger, healthy patients, possibly reflecting different use patterns conferring increased risk compared with older patients
 - Alternatively, diagnosis could be more complicated in adults who are more likely to have chronic lung disease or other medical comorbidities, leading to under-recognition of illness in adults
 - Unclear whether adults have more severe illness more likely to result in death
- Lipoid pneumonia has been reported in historical and recent case reports and series, but important caveats remain
 - Clinical significance of lipid-laden macrophages remains undetermined— are these markers of disease or markers of exposure?
 - Bronchoalveolar lavage has not been obtained universally on bronchoscope evaluation, and in turn nor has lipid-staining (a non-routine procedure), so frequency of finding is uncertain
 - Characteristics of cellularity of bronchoalveolar lavage fluid are uncertain because they could be altered by antibiotics or steroids and influenced by timing of therapies and interventions
- Autopsy has not been performed for all cases resulting in death, and results have not been reported for all cases when performed

Summary

- CDC's investigation has not yet identified any specific substance or e-cigarette product linked to all cases
 - Most patients have reported using cannabinoids such as THC or CBD
 - Some have reported nicotine use alone
- Most patients have been hospitalized with respiratory illness and received treatment for presumed infectious etiologies; some have responded to steroids with or without antibiotics
- Report possible cases to and coordinate product testing with your health department
- CDC will provide updates as information becomes available
https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease/healthcare-providers/index.html

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348;
www.cdc.gov

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

APPENDIX: REVIEW OF RECENT AND HISTORICAL LITERATURE

Recent Publications on Pulmonary Disease Associated with E-Cigarette Product Use, or Vaping

Recent Publications with Case Findings

Reference	Number of patients	Brief Description
Layden J, et al. Pulmonary illness related to- e cigarette use in Illinois and Wisconsin— preliminary report. <i>NEJM</i> 2019	53	Summary of clinical characteristics and use of e-cigarette products reported among initial reported cases in Wisconsin and Illinois
Davidson K, et al. Outbreak of e-cigarette-associated acute lipoid pneumonia—North Carolina, July–August 2019. <i>MMWR</i> 2019;68(36).	5	Description of patients with lipoid pneumonia diagnosed at 2 hospitals in North Carolina
Maddock S, et al. Pulmonary lipid-laden macrophages and vaping. <i>NEJM</i> 2019.	6	Summary of clinical characteristics and bronchoalveolar lavage findings for patients in Utah
Henry TS, et al. Imaging of vaping-associated lung disease. <i>NEJM</i> 2019	19 (+15 in literature)	Review of imaging findings

Comparison of Patients in North Carolina and Illinois/Wisconsin

Patient Characteristics in North Carolina, Illinois, and Wisconsin

Characteristic	NC (n=5)	IL/WI (n=53)
Ages (years)	18–35	16–53 (median:19)
Male	Not reported	44/53 (83%)
Hospitalized	5/5	50/53 (94%)

Reported Symptoms in North Carolina, Illinois, and Wisconsin

Symptom	NC (n=5)	IL/WI (n=53)
Shortness of breath	5/5	46/53 (87%)
Nausea or vomiting	5/5	37/53 (70%)
Abdominal pain or discomfort	5/5	23/53 (43%)
Diarrhea	Not reported	23/53 (43%)
Subjective fever	5/5	43/53 (81%)
Any systemic symptoms*	Not reported	53/53 (100%)

* Subjective fever, chills, weight loss, fatigue or malaise.

Presentation Findings in North Carolina, Illinois, and Wisconsin

Finding	NC (n=5)	IL/WI (n=53)
Fever	Not reported	15/51 (29%)
Hypoxemia	5/5 with sat <90% on room air (RA)	20/52 (38%) with sat <95% on RA; 16/52 (31%) with sat <89% on RA
CXR with bilateral infiltrates	5/5 on initial	48/53 (91%) on initial
CT chest with bilateral opacities	5/5 (timing not specified)	48/48 (100%) on initial
Elevated white-cell count	5/5, all with neutrophil predominance; none with eosinophils	45/52 (87%); 34/36 (94%) with neutrophil predominance; none with eosinophils

Clinical Course in North Carolina, Illinois, and Wisconsin

Finding	NC (n=5)	IL/WI (n=53)
Received empiric antibiotics	5/5	45/50 (90%)
Worsened on antibiotics	5/5	Not reported
Received steroids	5/5	46/50 (92%)
Improved on steroids (with or without antibiotics)	5/5	30/46 (65%)
Negative workup for infectious etiologies	5/5	"Nearly all"
Required ICU care	3/5	31/53 (58% overall, 62% of hospitalized)
Diagnosed with ARDS	3/5	15/53 (28%)
Required intubation and mechanical ventilation	1/5	17/53 (32% overall, 35% of hospitalized)
Received extracorporeal membrane oxygenation	0/5	2 (1 died)
Survived to discharge	5/5	52/53 (98%)

Comparison of Bronchoalveolar Lavage Findings for Patients in North Carolina, Illinois/Wisconsin, and Utah

Bronchoscopy Alveolar Lavage Findings in North Carolina, Illinois, Wisconsin, and Utah

Characteristic	NC (n=3)	IL/WI (n=24)	UT (n=6)
Lipid staining performed	3/3	Not specified	6/6
Lipid-laden macrophages identified	3/3	7/14 with cell counts reported	6/6
>5% eosinophils*	0/3	0/3	1/6

Review of Imaging Studies for 19 Patients and Review of Literature

Henry TS, et al. Imaging of vaping-associated lung disease. *NEJM* 2019

Review of Imaging Studies (Correspondence from Henry et al.)

- Based on review of imaging for 19 patients and 15 patients reported in literature

* Timing of steroids or other interventions not specified.

- No information provided regarding exposure other than “*all met the case definition of vaping-associated lung injury*”
- Most imaging patterns have basilar-predominant consolidation and ground-glass opacity, often with areas of lobular or subpleural sparing
- Authors noted that fat attenuation (highly suggestive of lipoid pneumonia) has not been frequently observed on CT

Additional Data from Wisconsin and Illinois

Layden J, et al. Pulmonary illness related to e-cigarette use in Illinois and Wisconsin—preliminary report. *NEJM* 2019

Experience in Illinois and Wisconsin (n=53 patients)



- Patient demographics
 - Median age 19 years (range: 16–53 years)
 - 83% male
 - 30% with asthma; otherwise no underlying chronic lung disease
- Clinical presentations
 - Median symptom duration before admission 6 days (range: 0–61 days)
 - 94% of patients hospitalized; 72% evaluated as outpatient before admission
 - 45% of those evaluated as outpatients received outpatient antibiotic treatment, however all reported progression of symptoms

Clinical Presentation

- Respiratory symptoms (98% of cases)
 - Shortness of breath (87%)
 - No report of upper respiratory symptoms (e.g., rhinorrhea, sneezing, congestion)
- GI symptoms (81% of cases)
 - Nausea (70%)

- Vomiting (66%)
- Diarrhea (43%)
- Systemic symptoms (100% of cases)
 - Subjective fever (81%)
- Initial recorded vital signs
 - 64% with tachycardia (range 55–146 BPM)
 - 43% with tachypnea (range: 15–48 breaths/min)
 - 69% with SpO₂ <95% on room air
 - 31% with SpO₂ <89% on room air
 - 29% with fever
- Initial laboratory findings
 - 87% with leukocytosis (median: 15.9K/ml, range 12.3–18.1K/ml); 94% with neutrophil predominance; no eosinophilia >2%
 - 50% with mild transient transaminase elevations
 - Acute kidney injury reported in 1 patient who responded to intravenous fluid (IVF) hydration

Imaging

- 91% with abnormal findings on chest radiograph at presentation
- All 48 patients who had CT chest had abnormal findings
- Characteristic finding: bilateral ground-glass opacities with subpleural sparing
- All patients had bilateral lung opacities

Biopsy Findings

- 3 patients underwent lung biopsy
 - 2 patients transbronchial only, 1 patient also had open lung biopsy
 - 2 on antibiotics/corticosteroids, 1 on neither before biopsy
 - Lipid staining not performed
 - Findings: mild and non-specific damage, acute diffuse alveolar damage and foamy macrophages suggesting inhalation toxin exposure, interstitial and peribronchiolar granulomatous pneumonitis

Dosing of Corticosteroids in Recent Outbreak Reports

Publication	Dosages and medications
Davidson K, et al. Outbreak of e-cigarette-associated acute lipid pneumonia—North Carolina, July–August 2019. <i>MMWR</i> 2019;68(36).	5/5 patients received intravenous methylprednisone (120 mg–500 mg daily); all discharged home on taper of oral prednisone (dose and duration not specified)
Maddock S, et al. Pulmonary lipid-laden macrophages and vaping. <i>NEJM</i> 2019.	2/6 patients received “high-dose glucocorticoids” (dose, duration, and discharge regimen not specified); 2 other patients received “short-course of prednisone” before hospitalization (dose and duration not specified)
Layden J, et al. Pulmonary illness related to e-cigarette use in Illinois and Wisconsin—preliminary report. <i>NEJM</i> 2019	“majority of patients have received prolonged courses” of systemic glucocorticoid therapy

Chapter 364

HEALTH AND THE NIGERIAN SOCIETY: AN OVERVIEW

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ABSTRACT

Nigeria – a pluralistic society – is a sub-Saharan Africa country, home to about 200 million people from 371 cultural tribes. All tribes in Nigeria have their specific cultural beliefs and practices. As a matter of fact, many of these practices had been in existence for hundreds of years, even before British colonization (1800-1960). There exists a strong interrelationship between the society and health. Some practices in the society have negative health implications while some do not. Unfortunately, many of the traditional or cultural practices in the Nigerian society have more associated harms than benefits. In

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this book we have gathered research that describes health and health aspects of modern Nigeria, which we hope will be of interest to the reader.

INTRODUCTION

It is a popular saying that health is wealth. This statement is actually true. The health of a person goes far a long way in determining their wealth. Similarly, a healthy society is a wealthy society.



Figure 1. Map of Nigeria showing all the 36 states with the federal capital territory.

A society, according to the Cambridge dictionary is “a large group of people who live together in an organized way, making decisions about how to do things and sharing the work that needs to be done” [1]. All the people in a country, or in several similar countries, can be referred to as a society [1].

NIGERIAN SOCIETY

There are 36 states in Nigeria, excluding the Federal Capital Territory (FCT) which is situated in Abuja (see figure 1) [2]. These 36 states spread across the six geopolitical zones of the country (see Table 1). The Nigerian political system is democracy, adopting the United States presidential structure of governance [3].

Nigeria – a pluralistic society – is a sub-Saharan Africa country, home to about 200 million people from 371 cultural tribes [4, 5]. Amongst all the cultural tribes in Nigeria, Yoruba, Hausa/Fulani and Igbo are the three major tribes [5]. The northern part of Nigeria is

predominantly occupied by the Hausa/Fulani ethnic group while the southern part of Nigeria is predominantly occupied by the Yoruba and the Igbo ethnic groups [5].

Table 1. Geopolitical zones of Nigeria

Geopolitical zone	State
South-west	Osun, Oyo, Ondo, Ogun, Ekiti, Lagos
South-east	Abia, Anambra, Ebonyi, Enugu, Imo
South-south	Akwa Ibom, Bayelsa, Cross River, Edo, Delta, Rivers
North-central	Benue, Kogi, Nasarawa, Plateau, Niger, Kwara, Federal Capital Territory
North-east	Borno, Bauchi, Gombe, Taraba, Yobe, Adamawa
North-west	Sokoto, Kebbi, Zamfara, Katsina, Kaduna, Jigawa, Kano

CULTURAL BELIEFS AND PRACTICES IN NIGERIA

All tribes in Nigeria have their specific cultural beliefs and practices. As a matter of fact, many of these practices had been in existence for hundreds of years, even before British colonization (1800-1960) [6]. Health-wise, some beliefs and practices are favorable, while some are not [6, 7]. In this chapter, we shall briefly mention some popular cultural beliefs and practices and their health implications in the Nigerian society (see Table 2).

Table 2. Examples of popular cultural beliefs and practices in Nigeria

Part of Nigeria	Beliefs/practice	Purpose/understanding	Health implication
Northern	Sakkiya	To cure body swelling	Negative; controversial
Northern	Kawo	To cure body swelling	Negative; controversial
Northern	Kamun wuta	To cure severe burns	Negative; controversial
Northern	Dauri	To treat limb fracture	Negative; controversial
Southern	Te Magun	To punish women who are not faithful in their marriage	Negative
Southern	Eji beauty	Epitome of feminine beauty	Nil

In the Hausa culture, for instance, there is a popular traditional practice called Sakkiya [8]. Sakkiya is an act of using a hot pointed metallic tip to puncture a body swelling with the hope of achieving a curative effect [8]. This procedure is widely practiced in rural villages in northern Nigeria commonly by the blacksmith (called Makera) and traditional barbers (called wanzami) [9]. Scientific investigations has shown that this traditional practice can be lethal due to its queried safety profile and associated complications that may arise from it [7, 10]. Also, there exist some other traditional practices in this region such as Kawo, Kamun wuta, Dauri, etc. The Kawo practice involves the use of the human mouth to suck out the fluid content in a body swelling via horn of a ram (the horn of the ram serves as a straw to suck the fluid). Kamun wuta is a spiritual procedure that involves the use of special ritual and the application of locally prepared special powder on severe burns; this procedure is being done by Malams (spiritualists), it is not hygienic and it is done with the purpose of curing burns. Dauri is known as traditional bone setting and it involves the use of sticks and bandages to

support fractured limbs. Dauri is being done by Malams. These cultural practices towards are crude and harmful to human health.

In the Yoruba culture, there is a popular practice called “te Magun”(“te” means placing while Magun refers to “thunderbolt”). This practice the placing of magical thread on door threshold for a woman to inadvertently walk over it and be under the spell; if any woman walks over it and she fails to have penetrative vaginal intercourse with any man within seven days after, she will emaciate and dry; however, if she does, the man will die after the intercourse. For the men that fell victim of such, they may crow or somersault three times, and die immediately. The “te Magun” is used in the Yoruba culture to punish married women who are not faithful to their spouse. Also, there is a belief that midline diastema (called “Eji” in Yoruba language) is a mark of epitome of beauty. Women with “Eji” are more appealing to the men in the Yoruba society than those without “Eji”. Due to this societal perception on “Eji”, some women do patronize quacks who are parading themselves as dentist to have a gap created in-between their upper central incisors. In the course of getting a gap tooth, some women sustain/develop dental traumas and/or odontogenic infections.

In the Igbo culture, the midline diastema (“Eji” belief in Yoruba culture) is also believed to be a mark of magnificent beauty among Igbo women. Some Igbo women do seek quacks for gap creation in between their teeth; unfortunately, this practice has negative oral health implications (such as tooth fracture, dentinal hypersensitivity) that can be incurred.

CONCLUSION

There exists a strong interrelationship between the society and health. Some practices in the society have negative health implications while some do not. Unfortunately, many of the traditional or cultural practices in the Nigerian society have more associated harms than benefits.

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Chapter 365

OPINIONS OF NIGERIAN RELIGIOUS LEADERS AND SEMINARIANS ON WHAT CAUSES CANCER

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ABSTRACT

Many cancer patients in Nigeria present very late at hospitals for treatment. Studies have shown that the delay is due to the belief that their cancer disease is of a spiritual cause. In this chapter we explore the opinions of religious leaders and seminarians in Ibadan City, Oyo State, Nigeria, on the top five aetiology/risk factors of cancer. Methods: A cross-sectional study was done among 302 religious leaders and seminarians in Ibadan. Study tool was an anonymous questionnaire. Data collected was analysed using SPSS version 16 software. Results: The top five cancer aetiology/risk factors, as indicated by the respondents, were as follows: toxic drugs (58.9%); genetic factors (53.6%); radiation exposure (52%); poison (42.4%); poverty (34.8%). Conclusion: The opinion of the majority of the surveyed religious leaders and seminarians favoured biological, physical and chemical factors as the commonest cancer aetiology/risk factors, although the minority were of the opinion that cancer can also be caused by socioeconomic factors and supernatural forces.

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INTRODUCTION

The prevalence of cancer disease is on the increase among Nigerians, and also among the inhabitants of other developing nations [1, 2]. As far back as 2008, about 12.7 million cancer cases and 7.6 million cancer deaths have been reported worldwide, of which 56% of these cases and 64% of these deaths occurred in the developing countries, Nigeria inclusive [3].

It is so unfortunate that many cancer patients in Nigeria do delay their presentation at hospitals, unlike those in the developed world [4-8]. Many of these patients do present at the hospital when their cancer disease is already at its advanced stage [4, 6-8]. As a matter of fact, one of the main reasons for their delay in seeking hospital care is that many of them ascribed their cancer disease to spiritual causes [4, 6, 7] and many of these patients had first sought spiritual healing by visiting prayer houses, traditional healers, and spiritualists, before eventually presenting at the hospital after their attempts towards achieving spiritual healing of the cancer disease proved abortive [4-6].

In Nigeria, the religious leaders have a strong influence on their followers. In many cases, they are being referred to as someone next to God. At times, people consult them for healing prayers, blessings, and counselling. Similarly, the seminarians who are the future religious leaders, usually occupy leadership positions in the religious institutions where they find themselves. The seminarians are also, though to a lesser extent, consulted for prayers and counselling too.

Since the religious leaders and seminarians are visited for healing prayers, it will be of importance to conduct a study to explore their opinions on the common risk factors of cancer, as the information obtained will determine their level of awareness on the evidence-based cancer aetiology and risk factors. Based on the above, we aim to write a short report on the opinions of a sample of religious leaders and seminarians in Ibadan City, Nigeria, on the most common causes of cancer in the Nigerian society.

OUR STUDY

This study was a descriptive cross-sectional study. This study also forms part of a bigger study conducted among religious leaders and seminarians in Ibadan, Nigeria [9], which adopted the use of same methodology.

However, the study tool used in this present study was a paper semi-structured questionnaire which obtained information on the socio-demographic characteristics of the participants, and the five commonest causes of cancer in the Nigerian society.

A total of 350 participants were recruited for this study. Each of the participants was given a questionnaire to fill and return. After the retrieval of the administered questionnaires, only 311 questionnaires were found filled. Out of the 311 filled questionnaires, only 9 were discarded because they were not filled properly, so we finally worked on the data from 302 respondents. Research data were entered into the SPSS version 16 software for analysis. The frequency distributions of all variables were determined, and test of association between two non-continuous variables were done using the Chi-square test. A significant p-value was recorded as <0.05 .

This study was conducted under strict compliance with the 1964 Helsinki Declaration on health research involving human subjects.

FINDINGS

The demographic characteristics of the respondents had been presented earlier in a paper by Badru and Kanmodi [9]. Table 1 depicts the opinions of the respondents on the causes of cancer in the Nigerian society. The top five cancer aetiology/risk factors, as indicated by the respondents, are as follows: toxic drugs (58.9%); genetic factors (53.6%); radiation exposure (52%); poison (42.4%) and poverty (34.8%).

Table 1. Association between gender of respondents and their opinion on the commonest cancer causes

Cancer causes	Frequency (%) [N = 302]
Sin	79 (26.2)
Evil spirit	85 (28.1)
God	17 (5.6)
Radiation exposure	157 (52.0)
Toxic drugs	178 (58.9)
Genetic factor	162 (53.6)
Generational curses	66 (21.9)
Witchcraft	58 (19.2)
Poison	128 (42.4)
Wealth	57 (18.9)
Poverty	105 (34.8)

DISCUSSION

The Nigerian religious leaders are known to have strong influence over their followers; these leaders bear different religious titles such as Pastor, Reverend, Evangelist, Imam, Alfas, among others. The pastors, evangelists, reverends, and missionaries are of the Christian faith, while the Imams and Alfas are of the Islamic faith. These religious leaders see to the social and spiritual welfare of their followers. On many occasions, they organize sessions of healing prayers for their sick followers. The seminarians, on the other hand, are trainees hoping to become a religious leader someday. As a matter of fact, some seminarians are likewise actively engaged in religious leadership positions in the Nigerian society.

This study was conducted to explore the opinions of religious leaders and seminarians in the metropolitan city of Ibadan, Nigeria, on the five most common causes of cancer in the Nigerian society. The findings made from this study revealed diverse opinions on this issue of concern, and these opinions are noteworthy. It is interesting to note that roughly one-quarter believed that sin can cause cancer disease. The Merriam-Webster Dictionary defines sin as: an offense against religious or moral law; an action that is or is felt to be highly reprehensible;

an often serious shortcoming; a transgression of the law of God; or a vitiated state of human nature in which the self is estranged from God [10]. This, by interpretation, suggests that many believed that many cancer diseases in the Nigerian society are afflictions from God.

Furthermore, the opinion of the surveyed religious leaders and seminarians on socioeconomic factors being responsible for having cancer is also insightful. Some of them believed that poverty and wealth can make one to develop cancer diseases. However, and fortunately, the evidenced-based medical risk factors of cancer (such as genetic factors, radiation exposure, poison, toxic drugs, etc.) were known by many of the respondents in this study; this shows that many of them acknowledged that cancers can be caused by biological, physical and chemical factors.

CONCLUSION

In conclusion, many of the surveyed religious leaders and seminarians were of the opinion that cancer is mainly caused by biological, physical and chemical factors; however, some of them still have the belief that socioeconomic and supernatural factors are the causes of cancers in the Nigerian society.

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Chapter 366

AWARENESS AND PERCEIVED NEED OF NIGERIANS ON THE RESTORATIVE TREATMENT FOR A DEFECTIVE TOOTH: A SCHOOL SURVEY

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ABSTRACT

In this chapter we try to determine the awareness rate of students in the University of Ibadan campus on restorative dental treatment and also explore their perceived needs for a dental restoration. Methods: Data of surveyed 668 University of Ibadan students was used in this study. Study tool was a well-structured self-administered questionnaire. Analysis was done using the SPSS version 16 software. Results: The majority (55.2%) of the respondents were within the age range of 21-25 years, 51.3% were females, and 76.8% were Yorubas. The majority (96.9%) were aware of a dentist, while only 34.1% had ever visited a dentist in their life time. Only 14.22% had missing teeth, 17.7% had broken teeth, while 19.5% had discolored teeth. The majority (82.3%) were aware that a missing tooth can be restored. Only 47 out of the 130 respondents who had a discolored tooth felt the need to get a dental restoration. Only 115 out of 415 respondents who had a broken tooth felt the need to get a dental restoration. Removable denture is the most popularly known (36.7%) dental restorative device among the respondents. Conclusions: This study revealed a very high awareness rate of a dentist among students of the University of Ibadan. Many of these students had defective teeth that needed restoration; however many did not perceive the need to get them restored. The authors recommend the need for education and awareness on the benefits of good oral health status.

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INTRODUCTION

The teeth constitute an important part of the human body that aids in mastication, phonation, and aesthetics [1]. Deviation from the normal state of health of a tooth can result into a diseased state and pain [2-5]. This could arise from insults to the tooth [2, 3], like trauma, bacterial action, erosive chemicals, heat, among others [4, 5], causing dental diseases like tooth wear lesions, pulpitis, pulpal necrosis, periapical abscess, pain and ultimately tooth loss [2, 6].

The literature had reported a significant prevalence of dental diseases among different Nigerian populations and across different age groups and socio-economic strata [7-10]; thus making it a public health problem in Nigeria. Public awareness on oral health had also been well documented, and had been found to be increasing over the years [9-11]. Despite this gradual increase in the awareness rate on oral health in Nigeria, a high prevalence of dental disease is still seen among Nigerians [10, 12]. This has been attributed to a number of contributing factors including ignorance, anxiety of getting dental treatments, poverty, unperceived need for dental care, and extremely high population – dentist ratio [13-19].

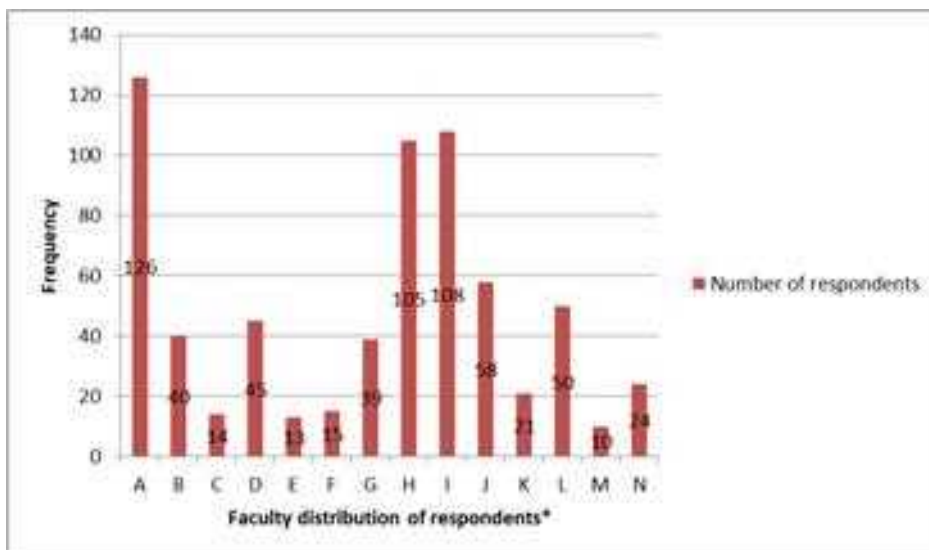
Ignorance about the possibility of restorative treatment for a diseased tooth has been found to be high among lay people [13, 14], causing many of them to suffer intractable tooth ache, poor quality of life, and anodontia [14]. Inability to perceive and attend to dental health needs early had also been found to be low among the lay Nigerian adult populations [15], making many of them to present late at the dental clinic when their dental diseases had already developed complications requiring higher treatment costs [15]. Anxiety for dental treatment also had been well studied among different populations [16]. As a matter of fact, some dentally anxious individuals often delay visiting a dental surgery for a long period of time, causing detrimental effects on their dental health conditions which in turn make their dental treatment needs more complex due to the complications that would have arisen [16]. All these problems – ignorance, anxiety of dental treatment, and unperceived needs, are psychosocial factors that could be solved through oral health education [13, 20, 21].

The problems of the socio-economic deprived population – dentist ratio and high poverty rate in the country are demographic and economic problems that could be solved by the government [13, 22]. Research has shown that a number of fruitful efforts, over the years, had been made by the government in this regard, to reduce the intensity of these two problems [23, 24]. However, more still needs to be done in making comprehensive dental health care more accessible for the Nigerian masses [13, 22].

After thorough search of the literature, the authors observed scanty literature on the awareness of Nigerian adults on the restorative treatment options for a defective tooth, and also on their perceived need for a dental restoration [9, 25]. Also, the majority of the available studies in this area were conducted amongst the health professionals and their trainees [9, 25, 26]. To the best of the authors' knowledge, no published research data exist on the awareness rate and perceived needs of the University of Ibadan students on restorative dental treatment. This study aims to determine the level of awareness of the students on the University of Ibadan campus on restorative dental treatment and also to explore their perceived needs for a dental restoration.

OUR STUDY

This cross-sectional study was conducted in accordance with the Helsinki Declaration. Ethical clearance to carry out this study was officially obtained from the Ministry of Education, Ibadan, Nigeria. The study was conducted among students of the University of Ibadan. This tertiary institution is the premier university of the country and she is situated within the city of Ibadan, Nigeria. This school had a total of twelve [12] academic faculties (see Figure 1), with each faculty running both undergraduate and postgraduate academic program.



Keywords: A= Faculty of Veterinary Medicine; B= Faculty of Pharmacy; C= Faculty of Law; C= Faculty of Science; D= Faculty of Arts; E= Faculty of Public Health; F= Faculty of Agriculture; G= Faculty of Social Sciences; H= Faculty of Basic Medical Sciences; I= Faculty of Clinical Sciences; J= Faculty of Dentistry; K= Faculty of Technology; L= Faculty of Education; N= Faculty not indicated.

Figure 1. Faculty distribution of respondents.

The study tool for this present study was a well-structured four-sectioned pre-tested questionnaire, which was adapted from a similar study [9]. The first section obtained information on the socio-economic attributes of the participants. The second section obtained information about participants' awareness of a dental surgeon, and the possibility of restoration of a defective or missing tooth. The third section obtained information about participants' awareness of common dental restorations. The fourth section obtained information about participants' knowledge of the use of the dental restorations mentioned earlier in the third section.

Participant's selection was based on lack of exposure to clinical training in dentistry. Based on this criterion, all bona fide students of the University of Ibadan were considered eligible, except for those dental students that have started the clinical phase of their training in dentistry and the senior medical students (i.e., those medical students in the clinical phase of their study program) who had rotated through clinical postings in dentistry.

A sample of 700 students was interviewed in this study via our study tool (i.e., a self-administered questionnaire). Study participants were approached in their classrooms and dormitories. The aims and objectives of the study were clearly explained to them, and they were also informed about the confidentiality of their participation. Verbal informed consent was sought from each participant before being issued a questionnaire to fill. Only 676 participants returned their questionnaires filled, of which 8 were discarded during data cleaning process. Data collection process was done from October to December, 2014.

Data analysis was done using the SPSS version 16 software. Frequencies of variables were illustrated using tables and a chart. Tests of association between variables were done using the Chi-square test and a p-value of <0.05 was considered to be of statistical significance.

FINDINGS

Out of the 700 persons recruited for this study, only 676 responded, giving a response rate of 96.6%. Table 1 shows the socio-demographic attributes of the participants. The majority (55.2%) were within the age range of 21-25 years, 51.3% were females, 81.6% were Christians, while 76.8% were from the Yoruba tribe. Figure 1 illustrates the faculty distribution of the respondents. About one-fifth (18.9%) of our respondents were students from the Faculty of Veterinary Medicine.

Table 1. Socio-demographic attributes of respondents

Characteristics (n=668)	N	%
Age*		
16 – 20	205	30.7
21 – 25	369	55.2
26 – 30	64	9.6
31 – 35	6	0.9
>35	8	1.2
Not specified	16	2.4
Gender		
Male	319	47.8
Female	343	51.3
Not specified	6	0.9
Religion		
Islam	110	16.5
Christianity	545	81.6
Traditional	2	0.3
Others	5	0.7
Not specified	6	0.9
Tribe		
Yoruba	513	76.8
Igbo	84	12.6
Hausa	5	0.7
Others	58	8.7
Not specified	8	1.2

n=total number of respondents in this study; N= total number of respondents in each category; *Age was reported in years.

Table 2 shows the rate of awareness of the dentist and the possibility of restoration of a defective tooth among our respondents. The majority (96.9%) of them were aware of a dentist, however only 34.1% had never visited a dentist in their life time. Only 14.22% had a missing tooth, 17.7% had a broken tooth, while 19.5% had a discoloured tooth. The majority (82.3%) were aware that a missing tooth can be restored.

Table 2. Awareness of respondents about a dentist and the possibility of the restoration of a defective tooth

Variables	Yes (%)	No (%)	NR (%)
Do you know who a dentist is?	647 (96.9)	19 (2.8)	2 (0.3)
Have you ever visited a dentist before?	228 (34.1)	428 (64.1)	9 (0.13)
Have you had any restoration placed on your tooth before?	76 (11.4)	588 (88.0)	4 (0.6)
Do you have a missing tooth?	95 (14.2)	569 (85.2)	4 (0.6)
Are you aware of replacement of a missing tooth in the mouth?	550 (82.3)	111 (16.6)	7 (1.0)
Do you have a broken tooth?	118 (17.7)	547 (81.9)	3 (0.4)
Do you know if a broken tooth can be restored?	412 (61.7)	192 (28.7)	62 (9.3)
Do you have a discoloured tooth?	130 (19.5)	521 (78.0)	17 (2.5)
Do you know if a discoloured tooth can be restored?	328 (49.1)	286 (42.8)	54 (8.1)
Has anybody advised you to restore/replace a tooth before?	115 (17.2)	530 (79.3)	23 (3.4)

NR= No response.

Table 3 shows statistically significant relationships between respondents' dental problems, and perceived need for a dental restoration. Only 47 out of the 130 respondents who had a discoloured tooth felt the need to get a dental restoration (see Tables 2-3). Only 115 out of 415 respondents who had a broken tooth felt the need to get a dental restoration (see Tables 2-3.)

Table 3. Comparison between respondents' dental problems, and perceived need for a dental restoration

		Have you ever felt the need to restore/replace a tooth at any time? **			
		Yes	No	Total	p – value (X ²)
Do you have a discoloured tooth? **	Yes	47	81	128	<0.0001
	No	67	437	504	
	Total	114	518	632	
Do you have a broken tooth? **	Yes	50	68	118	<0.0001
	No	85	460	525	
	Total	115	528	643	
Do you have a missing tooth? **	Yes	45	50	95	<0.0001
	No	68	479	547	
	Total	113	529	642	

**Not all respondents gave a response to this variable, hence missing values were not computed in this statistics.

Table 4 shows the comparison between the awareness and the knowledge of respondents on the specific use of the common restorative devices. Only 245 out of the 283 respondents who had heard of a removable denture knew its use. Removable denture is the most popularly known (36.7%) dental restorative device among our respondents.

Table 4. Comparison between the awareness and knowledge of respondents on the specific use of the common dental restorative devices

Restorative devices	Awareness*			Knowledge of use*			p – value (X^2)
	Yes	No	NS	Yes	No	IDK	
Removable denture	283	301	63	245	42	360	<0.0001
Bridge	237	324	84	123	108	414	<0.0001
Crown	333	241	72	198	64	384	<0.0001

NS= Not sure; IDK= I don't know; *Missing values were not computed in this analysis.

DISCUSSION

Dental health can be described as the state of freedom from diseases affecting the teeth [27]. Whenever there is a significant insult to a tooth, dental disease sets in. Dental diseases, such as tooth loss, tooth discolouration, and pathologic tooth fracture, can negatively affect an individual's quality of life [28, 29].

Individuals with dental diseases tend to suffer from social inequalities [29]. Unfortunately, many of those with dental diseases have been found to carry these problems along with their day-to-day activities while being ignorant of the possibility of having restorations done on these defective teeth [9, 12, 14]. Furthermore, some of them suffer from speech and masticatory difficulties of varying degree of severity, depending on the stage of the dental disease progression [30-32].

A way to nib the progression of dental diseases and its complications is to seek for a professional dental care [15]. The aspect of dentistry that deals with the restoration of diseased tooth is called restorative dentistry. The various possible restorative treatment options for a diseased tooth include dental filling, crown, veneer, denture, bridge, dental implant, among others.

Quite a number of studies had been published on the awareness rate of oral health and the prevalence of perceived oral health needs among different Nigerian populations [9-11, 13-15]. However, to the best of the authors' knowledge, no published article had reported data on these subject areas amongst the population of the University of Ibadan students. The need for relevant research data on the prevalence of perceived restorative dental needs and the level of awareness of University of Ibadan students on restorative dental treatment options informed the authors to conduct this present study.

In this present study, the authors observed that the majority (96.9%) of the respondents were aware of the dentist (see Table 2). Unfortunately, many (64.1%) of them had never visited a dentist in their life time. This finding is slightly similar to that reported by Sulaiman and Kanmodi [9] in a study where they reported an awareness rate of 99.0% among some surveyed nursing students in Ibadan. In their study, they observed that the majority (78.5%) of their respondents had never visited a dentist in their life time; however this rate was higher than the one observed (64.1%) in this study. Overall, this shows that many tertiary students in Ibadan do not visit a dentist for regular dental check-ups, despite the high awareness rate of the dentist among them. Many of the respondents in this study had missing, fractured, and discoloured teeth; however not all of them have had them restored/replaced. This may be due

to many factors, some of which may include ignorance, stress of visiting a dentist, anxiety, and financial limitations [13, 14, 17, 19, 33].

Some of the respondents who had fractured teeth did not see any need to get those teeth restored. This may be due to ignorance of the possible complications associated with tooth fracture. The complications that could arise from a fractured tooth include pulpal necrosis, periapical abscess, periapical cyst, dentoalveolar abscess, tissue space infections, cavernous sinus thrombophlebitis, amongst others. This finding reveals a necessitating need to appropriately educate this population group on the socioeconomic and health benefits of seeking early treatment of a fractured tooth.

This study also showed that removable denture is the most popularly known restorative device among the respondents in this study. This finding is similar to that reported among a population of surveyed nursing students in Ibadan [9]. Authors suggest that the relatively low cost of removable dentures, amongst other restorations, may be the most likely reason why removable denture is the most popular dental restoration among this study population.

Quite a lot of the respondents in this study did not know about the use of the common types of dental restorative devices. This suggests that many of them had limited knowledge of the different restorative options they could seek for regarding their defective teeth. This calls for the need to educate them on this area.

This study has its limitations. It did not explore the reasons why some study participants had not visited a dentist in their life time. It also did not enquire into the purpose of the past dental visits of the respondents. This study surveyed a single institution; hence data of students in other tertiary institutions were not captured.

CONCLUSION

To the best of the authors' knowledge, this study is the first study that ever determined and explored awareness rate and perceived needs for restorative dental treatment amongst the University of Ibadan students, respectively. Most of the available published studies that had been conducted in this area only surveyed Nigerian health professionals and trainees [9, 25, 26]. In this study, we observed a very high awareness rate of a dentist amongst students of the University of Ibadan. Furthermore, many of them had never visited a dentist in their life time; hence they lacked adequate knowledge about their oral health status. Some of them had fractured, discoloured, and/or missing teeth that need restoration, but had not got them restored. This shows the need to educate and encourage them to get those teeth restored before complications develop from them. Educating them about this issue is very important because many of the individuals in our environment do present late to the dentist when complications had already occurred [15].

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Chapter 367

THE ROLE OF FEAR OF MENTAL ILLNESS ON ACADEMIC PERFORMANCE OF NIGERIAN MEDICAL STUDENTS

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ABSTRACT

There is a popular belief in the Nigerian society that reading too much can result in mental illness. Interestingly, virtually no research literature had recorded any relationship between this belief and academic performance of Nigerian students. *Objectives:* To evaluate the impact of the belief that reading too much can cause mental illness on the academic performance of Nigerian students. *Study group:* The final year medical students of the Usmanu Danfodiyo University, Sokoto, Nigeria. *Methods:* A cross-section of 60 final year medical students was interviewed using a self-administered anonymous questionnaire. The questionnaire obtained information from the participants on their socio-demographic characteristics, academic records, and beliefs on reading too much to be a cause of mental illness. Data obtained were analyzed using the SPSS version 16 software. *Results:* The mean ($\pm$ SD) age of the respondents was 26.05 ($\pm$ 4.34) years, and the majority (83.3%) of them were males. Less than one-tenth (6.7%) of them reported that they had excellent performance in their current study programme. A higher proportion of the females, when compared to the males, were of the mind-set that too much reading is dangerous to the brain (6/10 (60%) versus 16/50 (32%), p -value = 0.533). Also, a higher proportion of those that did not believe that reading too much could cause mental illness had a very good to excellent academic record in their current academic program, when compared to those with such belief (12/39 (30.8%) versus 3/13 (23.1%), p -value = 0.409). *Conclusion:* Students who did not believe that they can develop mental illness as a result of reading too much generally had better academic performance than those that had such belief.

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INTRODUCTION

Education is a powerful tool for the attainment and sustenance of development of any nation. For any nation to develop, her citizens need to be properly educated and well informed. More importantly, it is not sufficient for the citizens of a nation to just attend school, but getting the best from school education should be the main focus. In Nigeria, a lot of individuals are in school, however only a small fraction of them are getting the best from school education [1]. There are many factors that limit Nigerian students from getting the best from school education. Some of these factors include poverty, terrorism, and socio-cultural beliefs, among others [2-5].

If we focus on socio-cultural beliefs, we will find many factors limiting the proper utilization of educational opportunities among Nigerian students. For example, it is a popular belief in some Nigerian societies that educating a girl-child is a sheer waste of time, because a girl child is presumed to end up as a housewife when married [3]. This belief had hindered many girls from getting the best from school education [3]. From our observation, there is also a popular societal belief that reading too much can cause mental illness; this belief had made many people to embrace academic mediocrity on account of fears of developing mental illnesses that may arise from rigorous pursuit of academic prowess. After extensive literature search, we found that virtually no literature had recorded any relationship between this belief and academic performance of Nigerian students.

It will be of many benefits to the Nigerian society if the impact of the fear of developing mental illness from reading too much can be measured among Nigerian students. This study aims to evaluate the impact of this belief on the academic performance of Nigerian students, using the final year medical students in Sokoto State, Nigeria, as a case study. Conducting this kind of study among this peculiar population group (i.e., medical students) is of high significance, being that this population group is expected to be more medically knowledgeable about the medical causes of mental illness than the lay populations. Hence, the findings made from this study will give a projection of what may obtain of such among the lay populations.

OUR STUDY

This study was a cross-sectional study conducted under the guidelines of the Helsinki declaration on research involving human subjects. The study population was the medical students studying at the medical school of the Usmanu Danfodiyo University (UDU), Sokoto Metropolis, Sokoto State, Nigeria. This university (i.e., UDU) is the home to the one and only medical school in the entire Sokoto State. This school runs a six-year medical degree program. This program has two phases, which are the pre-clinical and the clinical phases; those students in the 1st, 2nd, and 3rd undergraduate years (UGYs) are in the pre-clinical phase while those in the 4th, 5th, and 6th UGYs are in the clinical phase. Those medical students that are in the clinical phase of their medical program are domiciled within the Usmanu Danfodiyo University Teaching Hospital (UDUTH), while those in the preclinical phase are domiciled within the university campuses. This hospital is a tertiary hospital affiliated to the UDU. Both the hospital and the university campuses are situated within Sokoto metropolis.

The study instrument was a well-structured questionnaire designed by the authors. The questionnaire had three sections:

- The 1st section obtained information on the socio-demographic characteristics of the participants;
- The 2nd section obtained information on the participants' beliefs regarding reading too much to be a cause of mental illness;
- And the 3rd section obtained information on the participants' academic records

Authors developed some two criteria for the participants' selection. Below are those criteria:

- Willingness to participate in the study
- Completion of clinical postings in Psychiatry

The justification for including the completion of postings in Psychiatry as part of the eligibility criteria was that Psychiatry is a medical specialty that deals with the management of mental illnesses; hence, this will ensure that all subjects are averagely knowledgeable about the causes and risk factors of mental illnesses before participating.

Based on these eligibility criteria highlighted above, only those medical students in their 6th UGY (n = 98) could participate in this study.

The eligible medical students (i.e., those in their 6th UGY) were approached at their lecture hall and dormitories. They were informed about the purpose of the study, and that their participation is strictly voluntary and confidential. Only those that gave verbal informed consent to participate in the study were given an anonymous questionnaire to fill and return. Participants' selection was done using simple random sampling technique. Out of the 65 questionnaires administered, only 60 were returned filled.

All the returned questionnaires (n = 60) were used for this study; none was discarded because they were all appropriately filled. Data was analyzed using the SPSS version 16 software. Frequency distributions of all variables were determined and Chi-square test was used to compare relationships between the qualitative variables with a p-value of <0.005 considered to be of statistical significance. The results obtained from the analysis were presented using tables and charts.

FINDINGS

The mean ($\pm$ SD) age of the respondents was 26.05 ($\pm$ 4.34) years. The majority of them were single (86.7%), and in the male gender (83.3%) category (see Table 1).

The majority (66.7%) of the respondents made a minimum of credit pass in all the 5 compulsory subjects needed to secure their admission into their current medical programme in a sitting (see Table 2). Also, less than one-tenth (6.7%) of the respondents reported that they had excellent performance in their current study programme (see Table 3).

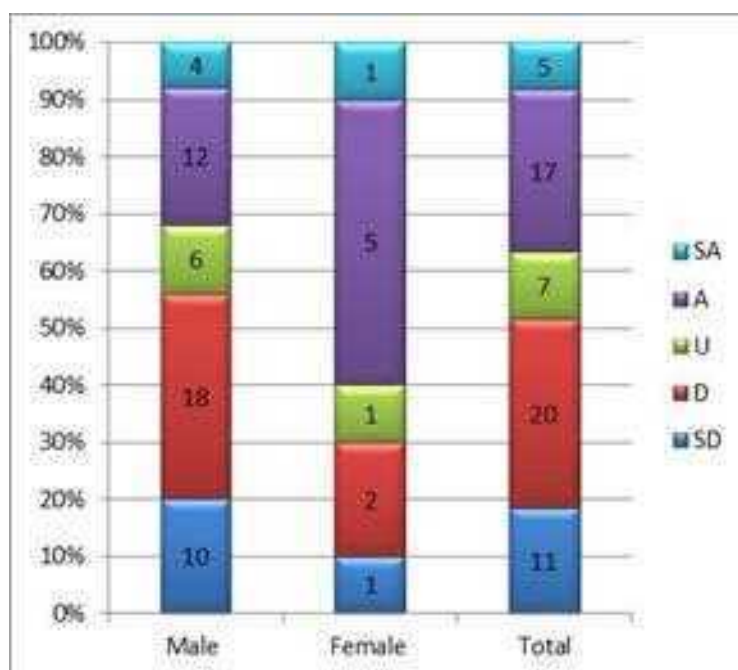
A higher proportion of the females, when compared to the males, were of the mind-set that too much of reading is dangerous to the brain (6/10 (60%) versus 16/50 (32%), p-value =

0.533) (see figure 1). Furthermore, a higher proportion of those respondents that did not believe that reading too much is dangerous to the brain passed their O' level entrance examination to the university at one sitting when compared to those that believed the opposite (20/21 (95.2%) versus 17/23 (73.9%)) (see Table 2).

Table 1. Socio-demographic characteristics of respondents

Characteristics	N (%)
Gender	
Male	50 (83.3)
Female	10 (16.7)
Mean ($\pm$ SD) age*	26.05 ($\pm$ 4.34)
Tribe	
Yoruba	11 (18.3)
Hausa	39 (65.0)
Igbo	1 (1.7)
Others	8 (13.3)
Not mentioned	1 (1.7)
Marital status	
Single	52 (86.7)
Married	8 (13.3)
Religion	
Christianity	9 (15.0)
Islam	61 (85.0)

*Age was recorded in years; N = Total number of respondents in each category.



p-value = 0.533, df = 4 (X^2).

SD = Strongly disagree; D = Disagree; U = Undecided; A = Agree; SA = Strongly agree.

Figure 1. Response of the respondents to the statement: Too much reading is dangerous to the brain.

Table 2. Comparison between the depths of belief of the respondents on “reading too much” to be dangerous to the brain with the frequency of sitting attempts for their O’ level examination

Variable	Too much reading is dangerous for the brain (n = 60)						X2
	SD	D	U	A	SA	Total	
How many times did you sit for your O’ level examination before you passed all the 5 compulsory subjects you needed to secure admission for your current study programme?	Once	6 (10.0)	14 (23.3)	3 (5.0)	14 (23.3)	3 (5.0)	0.730, df = 20
	Twice	3 (5.0)	4 (6.7)	3 (5.0)	2 (3.3)	1 (1.7)	
	Thrice	1 (1.7)	0 (0.0)	1 (1.7)	1 (1.7)	4 (6.7)	
	Four times	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	1 (1.7)	
	Five times	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	1 (1.7)	
	>5 times	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	
	Total	11 (18.3)	20 (33.3)	7 (11.7)	17 (28.3)	5 (8.3)	

SD = Strongly disagree; D = Disagree; U = Undecided; A = Agree; SA = Strongly agree.

Table 3. Comparison between the beliefs of the respondents on “reading too much” to be a mental illness risk factor with their academic performance

Variable	Reading too much can make me run mad (n = 60)*						X2
	SD	D	U	A	SA	Total	
So far in your current academic program, what is the rating of your academic performance?	Average	5 (83.3)	6 (10.0)	2 (3.3)	2 (3.3)	17 (28.3)	0.409, df = 12
	Good	7 (11.7)	9 (15.0)	4 (6.7)	6 (10.0)	26 (43.3)	
	Very good	6 (10.0)	3 (5.0)	0 (0.0)	2 (3.3)	11 (18.3)	
	Excellent	2 (3.3)	1 (1.7)	0 (0.0)	0 (0.0)	4 (6.7)	
	Total	20 (33.3)	19 (31.7)	6 (10.0)	10 (16.7)	58 (96.7)	

*Data of two respondents were not computed because they gave no complete response to the variables cross-tabulated.

SD = Strongly disagree; D = Disagree; U = Undecided; A = Agree; SA = Strongly agree.

Lastly, a higher proportion of those that did not believe that reading too much could cause mental illness had a very good to excellent academic record in their current academic program, when compared to those with such belief (12/39 (30.8%) versus 3/13 (23.1%), p -value = 0.409) (see Table 3).

DISCUSSION

Madness can be defined as a state of severe mental illness [6]. Mental illness can be described as a health condition involving changes in thinking, emotion or behaviour (or a combination of these) [7]. The risk factors for mental illness among school-age individuals are diverse [8]. However, some school-related risk factors that could cause mental illnesses among these individuals include adverse learning environment, difficulties at school, and lack of educational opportunities [8].

It is noteworthy that the impact of Nigerian socio-cultural beliefs on mental illness on formal education had been under-explored. For instance, and to the best of the authors' knowledge, no available study had reported the impacts of such beliefs on the academic performance of tertiary school students. The rationale for conducting this study was to explore the impact of the fear of developing mental illness as a result of reading too much.

In this study, it is alarming that despite the level of medical knowledge of the respondents on the aetiology and risk factors of mental illness, yet a significant proportion of them still believed that reading too much could cause mental illness. If this kind of belief was found to be as this common among final year medical students, how much more the medical students in lower classes as well as those students in the non-medical disciplines. Furthermore, this belief was found to tell negatively on the academic performance of those medical students that believed in such. By implication, it could be said that quite many of them had not benefitted maximally from medical education due to this belief.

In the nearest future, the respondents in this present study will hopefully graduate as a medical doctor, and start working as clinicians. Clinical practice requires continual medical education. A clinician who desires to be of relevance in the society needs to keep updating his/her medical knowledge from time to time. To be up to date in the current trends of patient management, a clinician has to passionately embrace lifetime studying. From this juncture, it is good to recall that many of the surveyed medical students believed that reading too much could make them develop mental illness. This may suggest that some of them may possibly not want to further their medical education after concluding their medical programme, due to the heavier academic workload in postgraduate studies, which will demand more intensive studying of books.

For a nation to be strong, the factors limiting the maximal utilization of her citizens on educational pursuits need to be successfully eradicated. In this study, we found out that the fear of developing mental illness from reading too much is a factor limiting the surveyed medical students from having better academic performance in their current study program. Based on this finding, it could be said further that students in other academic disciplines will most likely be experiencing similar problems, telling negatively on their academic performance likewise.

However, this study has its limitation. This study did not survey the medical students in lower classes as well as those in other Nigerian medical schools; this informs the need to conduct a bigger study on this subject matter. Also, this study did not enquire into the reasons why the respondents believed that reading too much could cause mental illness; hence, conducting a qualitative study to explore the reasons behind this belief among medical students will be of benefit. From the findings made in this research, authors would like to recommend the following:

- Proper education and counselling of medical students, as well as the entire public, on the evidence-based causes of mental illness
- A need for research to explore the degree of impact of the belief that reading too much could cause mental illness on the academic performance of Nigerian students from the secondary to the tertiary level of education
- Disabusing the minds of Nigerian youths from the beliefs that reading too much could make them develop mental illness

In conclusion, the wrong belief that reading too much is dangerous to the brain had contributed negatively to the academic performance of the surveyed Nigerian doctors-to-be. Academic diligence is not a risk factor for mental illness; rather it boosts one's memory status, and help to reduce one's risk of developing neurodegenerative diseases like Alzheimer's diseases [9]. Proper public education needs to be done on the proven risk factors of mental illness. It will also be very helpful to the Nigerian society if a survey could be conducted to assess the extent of the damage made by this popularly observed belief among Nigerian youths.

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Chapter 368

DO EXPECTANT MOTHERS IN SOKOTO CITY ACTUALLY WANT THE HBV VACCINE?

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ABSTRACT

Hepatitis B viral infection is a killer disease that can be prevented through proper vaccination. This study aims to determine the awareness and acceptance rates of hepatitis B vaccination by pregnant women in Sokoto City, Nigeria. Methods: A cross-section of 330 pregnant women was surveyed in this study using an interviewer-administered questionnaire. The questionnaire obtained information on the demographic profile, hepatitis B vaccine awareness, vaccination status, and attitudes of the subjects towards hepatitis B vaccination. Data collected was analyzed using the SPSS version 20 software. Results: All the respondents were married, 40.3% of them were within the age range of 20 to 25 years, 74.8% had no source of income, and 38.5% had no formal education. Only 3.9% of the respondents were aware of hepatitis B vaccine, of which none of them had ever received the vaccine. However, more than 90% of the respondents would like to get the vaccine. Conclusions: The findings made from this study revealed a very low awareness rate on hepatitis B vaccine amongst pregnant women in Sokoto City, Nigeria. However, many of them would like to get vaccinated against HB infection.

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INTRODUCTION

Hepatitis B (HB) viral infection is a potentially life-threatening liver infection that is chronically affecting about 370 million individuals globally; unfortunately, about 2 million people die of complications arising from the disease yearly [1]. Hepatitis B viral infection is known to be caused by the hepatitis B virus (HBV). This virus is a double stranded DNA virus which belongs to the hepadnaviridae family. The mature HBV is spherical in shape and it has 4 different genes; these genes include the HBsAg, HBcAg, HBeAg, and the nucleocapsid which encloses the viral DNA [2-4].

In Nigeria, pregnant women constitute one of the population groups that are highly predisposed to hepatitis B infection [5]. Furthermore, statistics had shown that about 14.1% of pregnant women in Nigeria are living with hepatitis B infection [5]. One of the major problems associated with hepatitis B infection among pregnant women is mother-to-child transmission (MTCT) of the virus [6]. Sadly, about 1 out of 10 Nigerian children are infected with hepatitis B, of which the majority of them acquired the infection through MTCT of the virus [5-7]. In order to eradicate MTCT of HBV in Nigeria, the Nigerian government began HB vaccination programs in the year 2004 [2, 8]; fortunately these programs are still active till date. Furthermore, impressive success rates had been recorded through these vaccination programs [9-12]. However, there are still some stumbling blocks hindering the holistic success of these vaccination programs. Some of these stumbling blocks include: low awareness rate on the disease; lack of reliable cold chain in storing the vaccine; illiteracy; limited health personnel; poverty; and ignorance [7, 13].

From our literature search, we observed that different studies have determined the awareness and acceptance rates of HB vaccination among people in different geographical areas in Nigeria [14-23]. Interestingly, the majority of those studies were found to have been conducted among health workers. However, we observed that only very scanty literatures were available on the awareness and acceptance rates of HB vaccination among pregnant women in Nigeria.

This study aims to: determine the awareness rate on HB vaccination; determine the acceptance rate of HB vaccination; and also explore the factors that might have influenced the choice of pregnant women in Sokoto City, northwestern Nigeria, on accepting hepatitis B vaccine. This study is of high significance, as the study will provide the first literature exploring the factors influencing the choice of acceptance of HB vaccine among pregnant women in Sokoto City, northwestern Nigeria.

OUR STUDY

This study was a cross-sectional survey of pregnant women attending the antenatal clinics of two public hospitals situated within Sokoto City, Nigeria. The names of the two surveyed hospitals were: Maryam Abacha Women and Children Hospital; and Specialist Hospital. These hospitals are owned by the Sokoto State Government, Sokoto State, Nigeria.

This study was done in accordance with the Helsinki Declaration on health research involving human subjects. Approval to conduct the study was officially obtained from the State Health Research Ethics Committee, Ministry of Health, Sokoto State, Nigeria (Ref. No:

SKHREC/081/017). Permission to collect research data was also sought from the management of the participating hospitals. The identity of the study subjects were kept with strict confidentiality, during and after the study. The subjects were also given the right to decline participating in the study at any stage should they find it uncomfortable to continue. Only those that gave informed consents were recruited for the study.

The study tool was a 14-item paper questionnaire developed through literature review [24-26]. The questionnaire obtained information on the demographic profile, hepatitis B vaccine awareness, vaccination status, and attitudes of each subjects toward hepatitis B vaccination. Before the above information was obtained from the subjects, the subjects were first informed about the meaning of hepatitis B in lay man terms. Also, the questionnaire was first drafted in English before being translated into Hausa: the most widely spoken local language in the study area. The translation was done by an experienced translator who is a native speaker of Hausa. The questionnaire was then back-translated into English by another translator and comparison was made for similarity, of which was found satisfactory. The questionnaire was then pretested and all necessary adjustments were made in the questionnaire to suit the purpose of the study.

The minimum sample size for this study ($n=280$) was determined using the Leslie formula for study population $<10,000$ at a HBV awareness rate of 24% derived from a previous study conducted among pregnant women in Punjab, Pakistan [24].

Within the month of December, 2017, a total of 340 pregnant women attending the antenatal clinics of the above-mentioned hospitals were approached and invited to participate in the study; only 330 women gave their consent to participate. All subjects' data were collected with the questionnaire, via face-to-face interviews. Data was analyzed using the SPSS version 20 software. The frequency distribution of all variables were determine, and comparisons between variables were done using the Chi-square test with a p-value of <0.05 set to be the level of statistical significance. Results obtained were presented using tables.

FINDINGS

Response rate was 97.1% (330/340). Four-tenth (40.3%) of the respondents were within the age range of 20 to 25 years, 44.2% had been pregnant for 1 to 3 times (aside their current pregnancy as of the time of the interview), and all (100.0%) were married. Furthermore, about two-fifth (38.5%) of the respondents had no formal education, 74.8% had no source of income, and 68.5% were married in a monogamous setting (see Table 1).

Only 3.9% of the respondents were aware of the hepatitis B vaccine. From comparisons between educational levels and awareness of respondents on the vaccine, we found that the majority (61.5%) of those that were aware of the vaccine had tertiary school education ($p\text{-value}<0.0001$) (see Table 2). None of the respondents had ever been vaccinated against HBV (see Table 3).

Table 4 provides information on the attitudes of the respondents towards HB vaccination. The majority (94.8%) of the respondents had never been vaccinated against HB infection due to unawareness. However, more than 90% of them reported that: they would like to get the vaccine; and their husband would allow them to get vaccinated against the disease. Interestingly, the cost of HB vaccine was found to be a factor limiting the majority (63.0%) of the respondents in enrolling for HB vaccination.

Table 1. Characteristics of the respondents

Characteristic	Frequency (%)
Age (in years)	
<20	56 (17.0)
20 – 25	133 (40.3)
26 – 30	91 (27.6))
31 – 35	26 (7.9)
35 – 40	19 (5.8)
>40	4 (1.2)
I do not know my age	1 (0.3)
Total number of pregnancies	
None	64 (19.4)
1 – 3	146 (44.2)
4 – 7	97 (29.4)
>7	23 (7.0)
Marital status	
Married	330 (100.0)
Educational level	
No formal education	127 (38.5)
Primary	56 (17.0)
Secondary	120 (36.4)
Tertiary	27 (8.2)
Total	330 (100.0)
Average monthly income (in Naira)	
No income	247 (74.8)
1000 – 10,000	73 (22.1)
>10,000	10 (3.0)
Family setting	
Monogamy	226 (68.5)
Polygamy	104 (31.5)

Table 2. Comparison between awareness on hepatitis B vaccine and educational level of respondents

Question	Response	Educational level of respondents					p-value (X ²)
		No formal education (N=127)	Primary (N=56)	Secondary (N=120)	Tertiary (N=27)	Total (N=330)	
Before now, have you ever heard about hepatitis B vaccine?	Yes	3 (2.4)	0 (0.0)	2 (1.7)	8 (29.6)	13 (3.9)	<0.0001, df=3
	No	124(97.6)	56(100.0)	118(98.3)	19 (70.4)	317(96.1)	
Total		127(100.0)	56(100.0)	120(100.0)	27(100.0)	330(100.0)	

N=Total number of respondents in each category; X²=Chi square; df=Degree of freedom.

Table 3. Comparison between hepatitis B vaccination history and educational level of respondents

Question	Response	Educational level of respondents					p-value (X ²)
		No formal education (N=127)	Primary (N=56)	Secondary (N=120)	Tertiary (N=27)	Total (N=330)	X ²
Have you ever been vaccinated against HBV?	Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	***
	No	127(100.0)	56(100.0)	120(100.0)	27(100.0)	330(100.0)	
Total		127(100.0)	56(100.0)	120(100.0)	27(100.0)	330(100.0)	

N=Total number of respondents in each category; X²=Chi square; df=Degree of freedom; ***No statistics were computed because "HAVE YOU EVER BEEN VACCINATED AGAINST HEPATITIS B BEFORE" was a constant.

Table 4. Attitudes of respondents toward hepatitis B vaccination

Question	Response	Frequency (%)
Why have you not been vaccinated against HBV?	Unaware that hepatitis B vaccine exist	313 (94.8)
	Unaware that the vaccine was important	14 (4.2)
	Do not believe that the vaccine is effective	1 (0.3)
	Do not believe that the vaccine is safe	1 (0.3)
	Religion does not permit vaccination	1 (0.3)
Would your husband allow you to be vaccinated against hepatitis B infection?	Yes	308 (93.3)
	No	18 (5.5)
	Not sure	4 (1.2)
Would the cost of the vaccine be a determinant to you been vaccinated?	Yes	208 (63.0)
	No	122 (37.0)
Do you like to be vaccinated against hepatitis B infection?	Yes	322 (97.6)
	No	5 (1.5)
	Not sure	3 (0.9)
Assuming you have hepatitis B infection, would you still allow your baby to receive anti-HBV antibodies?	Yes	325 (98.5)
	No	4 (1.2)
	Not sure	1 (0.3)
Assuming you are diagnosed to have HBV infection, would you be willing to take the drugs, which are safe, given to you by your doctor in order to prevent HBV transmission to your baby?	Yes	325 (98.5)
	No	3 (0.9)
	Not sure	2 (0.6)

HBV=Hepatitis B virus.

DISCUSSION

With the findings made in this study, it is glaring that the Nigerian government still has a long way to go for her to achieve her set goals of eradicating MTCT of HBV in Nigeria. In this study, a very low (3.9%) awareness rate on hepatitis B vaccine was recorded among the pregnant women that took part in the questionnaire; this rate is much more lower than that reported among pregnant women in other international cities [24, 26]. Also, none of the respondents in this present study had ever received HB vaccination. This reveals that all of the respondents are at risk of getting infected with HB if exposed to the virus. For those among them who might have been already infected with the virus, their babies stand at high risk of contracting the viral infection through MTCT.

Interestingly, only very few respondents were aware of the HB vaccine, and none of these few had got themselves vaccinated against HBV. The reasons for non-vaccination were: vaccination against the virus was not important; the safety profile of the vaccine could not be guaranteed; and the efficacy of the vaccine could not be guaranteed. Hence, it could be assumed that some of them had been misinformed about the importance of HB vaccination.

Aside the above-mentioned factors (such as unawareness, fear of safety of HB vaccine, and doubt of efficacy of HB vaccine) hindering the respondents from getting vaccinated against HBV, objection of spouses towards enrollment for HB vaccination, religious beliefs, lack of personal income, as well as the cost of the vaccine were also considerable limiting factors.

Based on our findings, many of the respondents in this study were at high risk of contracting hepatitis B infection. This observation was made based on the socio-demographic attributes of the respondents, as many of them fell into the categories of those that were:

illiterate; married in a polygamous setting; and multiparous are at risk of contracting hepatitis B infection [6]. However, many of them demonstrated positive attitudes toward receiving the HB vaccine. In fact, many of them would like to get their baby protected against HB viral infection, to the extent that they are ready to allow their baby take anti-HBV antibodies and/or also take drugs, themselves, to prevent the transmission of HBV to their baby, if infected with HBV. This shows that the respondents were very receptive to getting vaccinated against HBV.

However, this study has its limitations. First of all, this study did not objectively determine the HB sero-positivity and vaccination status of the respondents. Secondly, this study is a hospital-based study; only those that presented at the antenatal clinics of the surveyed public hospitals were recruited for the study. Based on the limitations and findings made in this study, authors would like to suggest the following:

- Conduction of a big community-based study among pregnant women in the various communities situated within Sokoto City, Nigeria. This kind of study will be able to cover the population of women who do not visit antenatal clinics during pregnancy.
- Proper education of pregnant women and their spouses on MTCT of HBV as well as the benefits of HB vaccination.
- More efforts need to be put by local and international governmental and non-governmental in supporting the HBV vaccination programs in Nigeria, so that Nigeria can achieve her set goal of eradicating MTCT of HBV.

CONCLUSION

The findings made from this study had established that there is a very low awareness rate on hepatitis B vaccine amongst pregnant women in Sokoto City, Nigeria; however, many of them would be glad to get themselves and their babies protected against HB infection through the vaccine.

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Chapter 369

PREVALENCE OF SHISHA SMOKING AND AWARENESS OF HEAD AND NECK CANCER AMONG SECONDARY SCHOOL STUDENTS IN IBOKUN TOWN

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ABSTRACT

Shisha smoking is a known risk factor for head and neck cancer (HNC). Objectives: To determine the rate of shisha smoking among secondary school students in Ibokun Town, Nigeria. Methods: This was a pilot questionnaire-based study conducted among

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grades 7 to 12 students in two secondary schools in Ibokun Town, Nigeria. Questionnaire obtained information from the subjects on their biodata, history of shisha smoking, awareness of HNC, and attitudes toward receiving HNC education. Results: More than half (54.0%) of the subjects were ≤ 14 years old, 56.6% of them were females, 97.5% were Yorubas, 50.5% were in a private school, and 82.8% were in grades 10 to 12. Only 11 (5.6%) subjects had ever smoked shisha, and 54.5% (6/11) of them were females. Only 3, out of these 11 subjects, smoked shisha for the first time at the age of 10 years or younger. Also, 7 subjects (5 females, and 2 males) reported that they smoked shisha on all the 30 days prior to their participation in the study. Lastly, less than half (47.5%) of the subjects had never heard of HNC; however, the majority (81.8%) of them showed interest in being educated on HNC. Conclusion: This study recorded a low prevalence rate of shisha smoking among the surveyed students. Many of the subjects had never heard of HNC before; however majority of them loved to be educated on HNC. Authors recommend early HNC education for secondary school students, with emphasis placed on tobacco cessation.

INTRODUCTION

Shisha smoking, according to the British Heart Foundation, is a way of smoking tobacco, sometimes mixed with fruit or molasses sugar, through a bowl hose or tube [1]. Shisha smoking is also called hookah, narghile, waterpipe, or hubble bubble smoking [1, 2]. Shisha smoking took its history from Asia [1, 2]. In some parts of the world, shisha smoking has surpassed cigarette smoking, with its rate of use increasingly growing among children and young adults [1, 2, 3].

According to the World Health Organization, shisha smoking is an addictive behavior [2], and it has been reported that shisha smokers do take shisha in the company of relatives and friends [4-7]. This reflects that shisha smoking is an acceptable social behavior in many societies.

Unlike cigarettes where their packs have warning labels about the negative health implications associated with tobacco smoking, shisha bottles do not have such warning labels [8]. Shisha has tobacco as part of its constituents; hence shisha smoking is a risk factor for life-threatening diseases like cancer [2, 8]. Furthermore, most of the anti-smoking policies in different nations of the world are focused on cigarette, while policies discouraging shisha smoking were not in focus [9-12]. As a matter of fact, virtually no shisha-specific policy exists in many nations [2, 11, 12]. In many developed countries for instance, shisha smoking venues and shisha products are exempted from tobacco control policies [9, 10].

In Nigeria, shisha is gaining its popularity and more shisha smoking venues are erected in some Nigerian discos and restaurants [2, 13]. Interestingly, little or no empirical study is available on shisha smoking in Nigeria [13]. This preliminary study aims to determine the prevalence of shisha smoking and also explore the awareness of head and neck cancer (HNC) among a pilot sample of school-going adolescents and young adults in Ibokun Town, Nigeria.

OUR STUDY

This preliminary study forms part of the research projects conducted during the 2016 Campaign for Head and Neck Cancer Education (CHANCE) Program [14, 15]. This program was an initiative of the Cephas Health Research Initiative Inc., a non-profit indigenous non-governmental organization based in Nigeria. Permission to conduct this study was officially obtained from the authorities of the participating schools, and all subjects' participation was completely voluntary and anonymous.

Two conveniently selected secondary schools were surveyed in this study: one public school and one private school. Being a preliminary study, authors used a convenient sample of 198 students. Multistage sampling technique was used in the selection of the participating classes, while simple random sampling technique was used in the selection of the subjects from the participating classes. Prior to questionnaire administration, authors approached the students and the teachers of the selected classes in their respective classrooms; they were informed about the purpose of the study and that their participation is voluntary and confidential. Informed consent was also obtained from all that took part in the study. All questionnaires were self-administered. The questionnaire obtained information from each participant about their demographic profile, history of smoking shisha, and awareness of tobacco as a risk factor for head and neck cancer.

The collected data were cross-checked and none was discarded because they all were appropriately filled. Data was analyzed using the SPSS version 16 Software. The outcomes of the analysis were presented in tables.

FINDINGS

More than half (54.0%) of the subjects were ≤ 14 years old, 56.6% of them were females, 97.5% were Yorubas, 50.5% were in a private school, 82.8% were in grades 10 to 12, and 74.2% were Christians (see Table 1).

Only 11 (5.6%) subjects had ever smoked shisha, of which 54.5% (6/11) of them were females (see Table 2). Only 3, out of these 11 subjects, smoked shisha for the first time at the age of 10 years or younger (see Table 3). Also, 7 subjects (5 females, and 2 males) reported that they smoked shisha on all the 30 days prior to their participation in the study (see Table 4). Lastly, less than half (47.5%) of the subjects had never heard of HNC (see Table 5); however, the majority (81.8%) of them showed interest in being educated on HNC (See Table 6).

DISCUSSION

This study surveyed a pilot sample of 198 secondary school students in Ibokun Town, Nigeria, on the prevalence of shisha smoking and awareness of HNC. In this study, we observed a very low prevalence of shisha smoking among the study subjects. Also, we found that many of the subjects had never heard of HNC and the majority of them would like to be educated on the killer disease.

Table 1. Demographic profile of subjects

Characteristics (n = 198)	Frequency (%)
Gender	
Female	112 (56.6)
Male	81 (40.9)
Not specified	5 (2.5)
School grade	
Grades 7 – 9	37 (17.2)
Grades 10 – 12	161 (82.8)
Age (in years)	
≤14	107 (54.0)
15 – 18	83 (41.9)
19 – 24	3 (1.5)
Not specified	5 (2.5)
School	
Public	98 (49.5)
Private	100 (50.5)
Tribe	
Yoruba	193 (97.5)
Igbo	1 (0.5)
Others	1 (0.5)
Not specified	3 (1.5)
Religion	
Islam	47 (23.7)
Christianity	147 (74.2)
Traditional	1 (0.5)
Others	1 (0.5)
Not specified	2 (1.0)

n = Total number of the subjects.

Table 2. Comparison between gender of subjects and experimentation of waterpipe (shisha) smoking

	Response	Gender		Total	X ² (p-value)
		Female	Male		
Have you ever tried or experimented with waterpipe smoking even one or two puffs?	Yes	6	5	11	0.521
	No	105	75	180	
Total		111	80	191	

Response	Frequency (%)
Yes	94 (47.5)
No	83 (41.9)
Not sure	11 (5.6)
No response	10 (5.1)
Total	198 (100.0)

Shisha smoking is an addictive behavior, also its smokes has detrimental effects on the body [2, 8]. The likelihood of developing smoking habit have been reported to be very high among adolescents due to some influencing factors like peer influence, parental smoking, and poor academic performance [2, 16, 17]. The age at which smoking habit is developed goes a long way in predicting an individual’s level of risk of developing tobacco-associated chronic

diseases; individuals with early exposure to tobacco smoking tends to have higher risk of developing such health problems when compared to those who started smoking at latter ages [18-21]. It is worthy of note that some of the subjects in this study experimented shisha smoking at age 10 or younger. This suggests that some of the subjects are at risk of developing tobacco-associated chronic diseases if they continue to smoke shisha.

Table 3. Comparison between gender of subjects and age at first waterpipe (shisha) smoking experience

	Response	Gender		Total	X ² (p-value)
		Female	Male		
How old were you when you first tried smoking waterpipe (shisha)?	I have never smoked water-pipe	104	76	180	0.422
	Age 10 or younger	1	2	3	
	Age 16 to 17	1	0	1	
	Age 18 or older	0	1	1	
Total		106	79	185	

Table 4. Comparison between gender of subjects and history of recent waterpipe (shisha) smoking

	Response	Gender		Total	X ² (p-value)
		Female	Male		
During the past 30 days, on how many days did you smoke waterpipe (shisha)?	0 day	96	71	167	0.207
	1 or 2 days	0	2	2	
	3 to 5 days	0	1	1	
	6 to 9 days	0	1	1	
	10 to 19 days	0	1	1	
	All 30 days	5	2	7	
Total		101	78	179	

Table 5. Response of subjects to the question: Have you ever heard of head and neck cancer before?

Response	Frequency (%)
Yes	94 (47.5)
No	83 (41.9)
Not sure	11 (5.6)
No response	10 (5.1)
Total	198 (100.0)

Table 6. Response of subjects to the question: Do you like to receive a comprehensive education on how to prevent head and neck cancer in future?

Response	Frequency (%)
Yes	162 (81.8)
No	30 (15.2)
No response	6 (3.0)
Total	198 (100.0)

In this study, the lifetime prevalence of shisha use among the subjects was 5.6%. Furthermore, some few subjects were found to be active shisha smokers. Some of these few subjects smoked shisha in all the recent 30 days prior to the day of participation in the questionnaire. However, the prevalence rate of shisha smoking recorded among the subjects in this present study is very low when compared to that recorded among Pakistani and German adolescents [22, 23]. The low prevalence rate recorded in this study may be because of the setting where this study was conducted, as the study area was a semi-urban area unlike the other studies which were conducted in a more developed setting.

Furthermore, we observed that the majority of the subjects had never heard of HNC. Head and neck cancer is a notorious disease which claims 300,000 lives every year [24]; hence the need for public education on its risk factors, symptoms, and HNC self-examination. In this study, the majority of the subjects showed interest in getting a comprehensive education on HNC prevention. Based on their level of motivation, authors predict that the surveyed students will benefit immensely from HNC education.

However, this study has its limitations. First of all, this study can only give an estimated prevalence rate of shisha smoking among the surveyed students, because it is difficult to ascertain if all information provided by the subjects was true. Secondly, this study did not explore how and why some subjects are active shisha smokers. Hence, there is a need for qualitative study, preferably a mixed study, to explore shisha smoking habits among secondary school students in this study area. Also, this study was a preliminary survey with small sample size; authors recommend that bigger studies should be conducted on shisha smoking in Nigeria.

CONCLUSION

To the best of authors' knowledge, this is the first study to report shisha smoking among Nigerian adolescents. This study recorded a low prevalence rate of shisha smoking among the surveyed secondary school students in Ibokun Town. Many of the subjects had never heard of HNC before; however majority of them loved to be educated on HNC. Authors recommend that such programs should be conducted for the secondary school students in Ibokun Town.

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Chapter 370

HEALTHCARE PROVIDER ATTITUDE TOWARDS PERSONS WITH DISABILITIES IN NIGERIA

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ABSTRACT

In this chapter we investigate healthcare providers' attitudes towards persons with disabilities (PWDs) at the University College Hospital (UCH), Ibadan, Nigeria. The investigators utilised the Interaction with Disabled Persons (IDP) Scale to measure the attitudes of direct and indirect healthcare providers at UCH. In all, 203 workers fully completed a questionnaire containing demographic and experiential questions and the IDP. Scores on three scale factors were analysed. The mean Discomfort score was lower for direct- versus indirect-care providers ($t=-2.537$; $p=0.012$). A higher Discomfort score was associated with a lower level of confidence in treating PWDs ($r=-0.221$; $p=0.003$). Similarly, a higher Information score was associated with lower confidence ($r=-0.300$; $p<0.001$), a lower level of training on treating PWDs ($r=-0.170$; $p=0.018$), and a lower knowledge of legislation and policies pertaining to PWDs ($r=-0.180$; $p=0.013$). The mean cubed Vulnerability score was lower for healthcare providers reporting less confidence ($t=-2.201$; $p=0.029$) and higher for older providers ($t=2.073$; $p=0.039$). Three-quarters of participants were direct-care providers, which is suggestive of physicians' willingness to deliver services to specialised populations. Recommendations are made to increase providers' confidence through in-service training, and to facilitate direct and indirect healthcare providers' organisational and individual capacities to sustain quality healthcare for PWDs.

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INTRODUCTION

In numerous countries throughout the world, some factors have been identified in healthcare providers' attitudes towards persons with disabilities (PWDs). These factors, inter alia, include lack of disability-specific knowledge, discomfort with working with PWDs, fear of disability and misperceptions about disability [1-6]. These challenges are so pervasive that PWDs themselves have cited poor attitudes of physicians as the most formidable obstacle to accessing healthcare services [7, 8]. For the purpose of this study, we define attitudes as positive or negative dispositions towards a person, concept or situation. Our conviction is that a healthcare provider's attitude towards a patient is fundamental because existing misconceptions can potentially hinder diagnosis and treatment [9, 10].

Furthermore, a provider's disposition is particularly important when tending to patients with disabilities. This is because the healthcare professional may view an individual's disability as a negative trait, and such perception may prevent resources from effective utilizations [6, 11]. The assumption that a person with a disability has a baseline quality of life at a low threshold may lead the provider to avoid caring for the patient. Thus, adverse outcomes may be compounded and services available to patients may be limited if these subtle attitudes unduly affect the provider's actions.

PRIOR RESEARCH IN NIGERIA

A Nigerian study [3] found that more than half of 134 sampled healthcare workers noted that facilities and legislation related to the human rights of children with developmental disabilities are nonexistent in the country. In order to ameliorate the situation, the researchers advocated for inclusion of topics on developmental disorders in the curricula of nurses and allied medical practitioners.

Ayanniyi et al. [2] explored the knowledge and attitudes of 330 physiotherapists towards people with leprosy in the six geopolitical regions of Nigeria. The leprologists found that a significant number of participants exhibited fair knowledge, but poor attitudes towards leprosy. According to the investigators, the institution of training seems to influence the respondents' knowledge and attitudes. They advocated that educational and training programmes on leprosy should be emphasised at the basic training institutions for physiotherapists. Earlier, Awofeso [12] investigated the knowledge of nurses regarding leprosy, and reported that these healthcare workers not only lacked disability-specific knowledge, but also had a fear of leprosy. As a way of combatting such apprehensions, the author recommended that leprosy information be infused into the basic nursing curriculum in order to heighten awareness and minimise the stigma of leprosy throughout Nigeria.

Reis et al. [13], in the first population-based assessment of discrimination against people living with HIV/AIDS in four states in Nigeria, found that nine percent of professionals reported avoiding to care for an HIV/AIDS patient, and nine percent indicated that they had refused an HIV/AIDS patient admission to a hospital. Twelve percent of participants agreed that treatment of opportunistic infections in HIV/AIDS patients depletes resources, and eight percent indicated that treating an individual with HIV/AIDS is a waste of valuable resources. The researchers concluded that while most of the healthcare professionals reported being in

compliance with ethical obligations, despite the lack of resources, discriminatory behaviour and attitudes towards patients with HIV/AIDS prevail among a significant number of healthcare professionals. They identified inadequate education and absence of treatment materials as contributing to these negative practices and attitudes.

NEED FOR CURRENT STUDY

The issues discussed in the preceding paragraphs attest to the need to investigate further healthcare professionals' attitudes towards PWDs in Nigeria. Nigeria is the most populous and ethnically diverse African country, comprising 182 million people [14]. Using the World Health Organisation [15] disability threshold of 15% to determine the number of PWDs in the population, Nigeria now has 27,300,000 PWDs. This figure is expected to rise significantly in the future, given the increase in the causal factors of disabilities such as illnesses, road accidents, birth defects, collapsed buildings, poverty, environmental toxins, natural disasters, communal and religious conflict, lead poisoning, Boko Haram insurgency, and superstitions [16]. These complex variables point to the need for each country to evaluate its own attitudes towards PWDs, since these factors are powerful, yet invisible obstacles to rehabilitation and integration. The current research was therefore conceived as a way to assess healthcare providers' dispositions towards their patients with disabilities in the country.

OUR STUDY

University College Hospital (UCH), the setting for this investigation, is strategically located in Ibadan, the largest city in West Africa. Established in 1959 as a teaching hospital to service the College of Medicine, it now has over 1,000 beds, with current occupancy rates of 55-60%, and includes 60 service and clinical departments. UCH is primarily a tertiary institution with appendages of community-based outreach. Given its location in a major urban centre and its dominant role in the country, UCH caters annually to thousands of patients with varying disabilities [17].

PROCEDURES

The research protocol was approved by the Institutional Review Boards of Missouri State University, United States and the College of Medicine, Ibadan, Nigeria. Having secured approval from the two institutions, the second author distributed a total of 500 questionnaires (described below) to workers in the hospital's 20 clinics. The distribution of the questionnaires occurred during the last quarter of 2015, and the first quarter of 2016 at monthly departmental meetings.

Two hundred and fifty completed questionnaires were returned to the secretary in the office of the second author. Thereafter, the second author mailed all completed questionnaires to the first author in the United States for data entry. All data were entered into an excel

spreadsheet and imported to SPSS for analysis. In all, 203 questionnaires were found to be complete and analyzable.

Study Questionnaire

The questionnaire was prefaced by a cover letter to the participants explaining the purpose of the study and defining key terms. Disability was defined as "... an impairment in body functions that imposes limitations in activity or restricts how an individual participates in the society." Categories of disabilities were described to include those who experience orthopedic, intellectual (mental), seeing, hearing, emotional/behavioural, speaking, breathing, and other problems, including birth defects, genetic disorders and skeletal deformities. Participants were assured of confidentiality of all responses in accordance with the ethical guidelines of the two approving universities.

The questionnaire was delineated into three sections. Section one addressed basic participants' demographics, including age, gender, job title, education, and time in present position at UCH, along with experiential questions, including level of prior contact with PWDs, level of training on treating PWDs, level of confidence in treating PWDs, and knowledge of policies and legislation pertaining to PWDs in Nigeria. The second section comprised the 20-item IDP Scale developed by Gething [18]. The final section of the questionnaire was open-ended, and enabled the participants to share personalised comments.

Interaction with Disabled Persons (IDP) Scale

In her 1994 paper summarising the development and validation of the IDP since its origins in 1980, Gething [19] provides the following operational definition: "The Interaction with Disabled Persons (IDP) Scale measures attitudes in terms of level of discomfort reported by nondisabled people during interaction with people with disabilities" [19]. It consists of a 6-point Likert-type response scale ranging from "I agree very much," to "I disagree very much." Representative items include: "I admire the ability of a person with a disability to cope," and "It is rewarding when I am able to help a person with a disability." Individual items are scored from six for high agreement to one for high disagreement, with the exception of items 10, 14, and 15, which are intentionally reversed. A total score is computed by summing the item scores, excluding item 19, per Gething's instructions [18]. A higher score is interpreted as indicating a greater degree of social discomfort in interacting with PWDs.

Gething [19] confirmed a six-factor model derived from the IDP Scale. These factors and their associated proportion of the total variance are as follows: Discomfort in Social Interaction (23.3%); Coping/Succumbing Framework (12.3%); Perceived Level of Information (6.1%); Vulnerability-1st (6.0%); Coping (5.2%); and Vulnerability-2nd (5.0%).

Statistical Methods

Statistical analyses were conducted using IBM SPSS Statistics version 24. Scale and sub-scale reliabilities were assessed using Cronbach's alpha, corrected item-to-total correlations,

and inter-item correlations. A cubic transformation was applied to one factor based on Tukey's Ladder of Transformation [20] to rectify a negative skew. The correlations between ordinal-level demographic and experiential variables and factor scores were assessed with Spearman's rank correlation coefficient. The differences in mean factor scores between 2-class demographic variables were assessed using the Student's *t* test for independent samples and Levene's test for equality of variances. For 3- or 4-level demographic or experiential variables, the overall differences in mean factor scores were assessed using the F-test from a one-way analysis of variance (ANOVA) and Levene's test for homogeneity of variances. Inter-class mean differences were further assessed using the Scheffe test for simultaneous pairwise joint comparisons, with a simultaneous type I error of 5%.

FINDINGS

Table 1 summarizes the characteristics of the study participants. Relatively small response categories were combined with adjacent categories as appropriate for this table. Two-thirds of the participants were female, and their ages ranged from 18 to 60 years. Half of participants had been in their current position from 1 to 5 years. Based on their stated job title, participants were classified as either direct- or indirect- care providers (see footnote for Table 1). Nearly 80 percent of participants were engaged in direct-care, based on this classification. Over half of participants stated that they had either daily or weekly contact with PWDs. While only 11 percent reported having received at least 40 hours of training on treating PWDs, 31 percent of participants reported having either a high or very high level of confidence in treating PWDs. One-third of participants reported that their knowledge of legislation pertaining to PWDs was either none or poor.

Table 1. Characteristics of study participants

	N	%
Gender		
Female	134	66.3
Male	68	33.7
(missing)	1	-
Age		
18-33 years	60	30.5
34-43 years	96	48.7
44-60 years	41	20.8
(missing)	6	-
Direct/indirect care provider		
Direct ^a	154	78.6
Indirect	42	21.4
(missing)	7	-
Time in present position		
1-5 years	104	52.3
6-10 years	45	22.6
11-31 or more years	50	25.1
(missing)	4	-

Table 1. (Continued)

	N	%
Prior contact with PWDs		
Daily	61	30.2
Weekly	49	24.3
At least once/month or once/3 months	31	15.3
Less frequently	61	30.2
(missing)	1	-
Training on treating PWDs		
None	64	31.8
Some	115	57.2
High (at least 40 hours)	22	10.9
(missing)	1	-
Confidence in treating PWDs		
Very low or low	25	12.3
Average	115	56.7
High or very high	63	31.0
Knowledge of legislation and policies pertaining to PWDs		
None or poor	69	34.5
Average	89	44.5
Good or very good	42	21.0
(missing)	3	-

^a Includes physicians or surgeons, medical interns or residents, nurses, audiologists, clinical psychologists, dentists, and physiotherapists.

Abbreviations: PWDs persons with disabilities.

Interactions with Disabled Persons (IDP) Scale

A reliability analysis was performed using items comprising the total IDP Scale and coded following instructions by Gething [18, 19]. Additional reliability analyses were performed using the items comprising each of the six factors identified by Gething [19]. Reliability analysis for the total IDP Scale yielded a Cronbach's alpha of 0.614. It was observed that many of the corrected item-to-total correlations were very small (<0.3), and many of the inter-item correlations were negative. These observations suggest that the total IDP Scale does not form a reliable indicator for this study population. Reliability analyses for the second, fourth, and fifth factors were similarly problematic and yielded very low Cronbach's alphas of 0.180, 0.264, and 0.246, respectively. Therefore, only three factor scores were computed and retained for further analysis. Characteristics of these three factors: Discomfort in social interaction, perceived level of information and vulnerability are shown in Table 2.

Table 2. Characteristics of selected IDP scale factors

Factor	N	# items	Range	Mean	Standard deviation	Cronbach's alpha
Discomfort ^a	184	6	6-30	16.15	5.54	0.70
Information ^b	195	5	5-25	13.67	4.28	0.57
Vulnerability ^c	200	2	2-12	9.65	1.91	0.57

^a Includes items 9, 11, 12, 16, 17, and 18

^b Includes items 3, 6, 9, 10 (reversed), and 12

^c Includes items 4 and 5; this is Gething's second Vulnerability factor

Abbreviations: IDP Interaction with Disabled Persons.

A histogram of vulnerability scores revealed a moderately negatively skewed distribution. A cubic transformation was applied following Tukey [20]. The univariate distribution of the cubed factor value was more symmetrical and depicted no outliers.

IDP Factors by Participant Characteristics

A Spearman rank correlation coefficient was computed for each combination of the three IDP factors and each ordinal or interval level participant characteristic. These results are displayed in Table 3. Discomfort was significantly negatively correlated with the level of confidence in treating PWDs ($r = -0.221$). Information was negatively correlated with level of training on treating PWDs ($r = -0.170$), confidence ($r = -0.300$), and knowledge of legislation and policies pertaining to PWDs ($r = -0.180$).

Table 3. Spearman Rank correlation coefficients for selected IDP factors by study participants' characteristics

	Discomfort	Information	Vulnerability
Age (years)	-0.065 (0.389)	-0.139 (0.056)	0.136 (0.058)
Time in present position	0.034 (0.646)	-0.033 (0.651)	0.003 (0.969)
Prior contact with PWDs	-0.077 (0.303)	0.005 (0.948)	0.056 (0.434)
Training on treating PWDs	-0.090 (0.225)	-0.170 (0.018)	0.033 (0.649)
Confidence in treating PWDs	-0.221 (0.003)	-0.300 (<0.001)	-0.028 (0.693)
Knowledge of legislation and policies pertaining to PWDs	0.007 (0.928)	-0.180 (0.013)	0.006 (0.935)

Data expressed as r (p).

Abbreviations: IDP Interaction with Disabled Persons; PWDs persons with disabilities.

The differences in mean scores for each of the three factors by gender and direct/indirect care provider were assessed using the t-test. For all other participant characteristics, relatively small response categories were combined with adjacent categories as appropriate to form three classes. These classes are the same as those shown in Table 1. The presence of an overall difference in mean scores by characteristics with three classes was examined for each of the three factors and was assessed by the F-test from one-way ANOVA. Inter-class mean score differences were measured using the Scheffe test.

The first factor "discomfort in social interaction" differed significantly by classes of two characteristics. The t-test statistic for direct/indirect care provider was -2.537 (176 degrees of freedom-df; $p = 0.012$). The mean (standard deviation-sd) discomfort score was 15.57 (5.22) for direct- versus 18.05 (5.64) for indirect-care providers. The F-test statistic for level of confidence in treating PWDs was 4.964 (2, 81 df; $p = 0.008$). The mean (sd) discomfort scores for very low/low, average, and high/very high level of confidence were 19.05 (5.64), 16.31 (5.32), and 14.70 (5.55), respectively. This association was negative and nearly linear. The mean difference between classes very low/low and high/very high was statistically significant ($p = 0.009$).

The second factor "perceived level of information" differed significantly by classes of two characteristics. The F-test statistic for level of confidence was 10.994 (2, 192 df; $p < 0.001$). The mean (sd) Information scores were 16.28 (3.52), 14.00 (4.20) and 11.90 (4.05) for very low/low, average, and high/very high level of confidence. This association was again

negative and linear. The mean differences between classes very low/low and average, very low/low and high/very high, and average and high/very high were all statistically significant ($p=0.043$; $p<0.001$; and $p=0.007$, respectively).

Similarly, the F-test for level of training on treating PWDs was statistically significant ($F=4.557$; 2, 190 df; $p=0.012$). The mean (sd) Information scores for none, some, and high level of training were 14.24 (3.96), 13.84 (4.42), and 11.10 (3.87), respectively. This association was negative, but not linear. The mean differences between classes none and high and some and high were statistically significant ($p=0.014$ and $p=0.026$, respectively). The F-test for a third characteristic, knowledge of legislation and policies about PWDs, approached the 0.05 level of significance ($F=2.828$; 2, 189 df; $p=0.062$). The mean (sd) Information scores were 14.57 (4.12), 13.40 (4.23), and 12.65 (4.44) for none/poor, average, and good/very good knowledge. This association was negative and nearly linear. The mean differences between classes were not significant at the 0.05 level.

The re-expressed third factor “vulnerability” differed significantly by level of confidence ($F=3.049$; 2, 197 df; $p=0.050$). The mean (sd) cubed vulnerability scores for very low/low, average, and high/very high level of confidence were 1178 (443), 942 (424), and 1021 (479), respectively. The mean vulnerability score was higher among healthcare providers who reported very low or low confidence in treating PWDs than for providers reporting a higher level of confidence. However, the mean differences between classes were not significant at the 0.05 level. The classes were recombined to compare very low/low versus average/high/very high means; a t-test was computed and was statistically significant ($t=-2.201$, 198 df, $p=0.029$).

The F-test for age group was marginally significant ($F=2.363$; 2, 191 df; $p=0.097$). The mean (sd) cubed Vulnerability scores were 991 (414), 942 (466), and 1124 (442) for age groups 18-33, 34-43, and 44-60, respectively. The mean vulnerability score was higher among the oldest healthcare providers (ages 44-60 years) than for younger providers. The mean differences between classes were not significant at the 0.05 level. The classes were recombined to compare age 18-43 versus 44-60 means; a t-test was computed and was statistically significant ($t=2.073$, 192 df, $p=0.039$).

In order to better explain the finding of a lower mean Discomfort score for workers classified as direct- versus indirect-care providers, the distributions of other participant characteristics were examined by direct/indirect care status. Direct care providers did not differ from indirect care workers by gender, age, prior contact, or knowledge of legislation/policies. However, direct-care providers had lower representation in the mid-range [6-10] of years in current position at UCH (Chi-square =7.912, 2 df, $p=0.019$), were more likely to report having had a high (at least 40 hours) level of training on treating PWDs (Chi-square =12.437, 2 df, $p=0.002$), and were less likely to report a very low or low level of confidence in treating PWDs (Chi-square =13.359, 2 df, $p=0.001$) as compared to indirect - care providers.

Similarly, the finding of a higher mean vulnerability score for the oldest healthcare workers (44-60) versus younger workers was explored further by examining the distributions of other participant characteristics by two age groups (18-43 versus 44-60). Older workers did not differ from younger workers by direct/indirect care status, training, confidence, or knowledge of legislation/policies. Older workers were more likely to be female (Chi-square =4.849, 1 df, $p=0.028$) and had lower representation in the weekly contact class for level of prior contact with PWDs (Chi-square =8.507, 3 df, $p=0.037$) as compared to younger

workers. As expected intuitively, older workers were more likely to have been employed in their current position in the highest class of 11 or more years (Chi-square =81.803, 2 df, $p<0.001$) than younger workers.

DISCUSSION

In this study, healthcare workers in direct patient care positions had lower scores, on average, on the IDP factor Discomfort in Social Interactions with PWDs as compared to workers whose positions connote indirect care. We found a significant negative correspondence between the IDP factor Discomfort and confidence in treating PWDs, and between the IDP factor Information and confidence, level of training on treating PWDs, and knowledge of legislation pertaining to PWDs. Additionally, workers reporting a lower level of confidence had higher scores, on average, on the IDP factor Vulnerability-2nd than their colleagues reporting more confidence, and likewise for older versus younger workers.

The findings noted above are similar to results obtained elsewhere [1, 4, 21, 22]. In California, McNeal and colleagues [4] found that majority of primary care physicians have at least some difficulty in examining patients with physical disabilities and many are uncomfortable in managing their care. Similarly, a Nepalese study by Devkota et al. [21] found provider's attitude towards pregnant women with disability to be negative with poor knowledge and skills about service provision. In a Canadian investigation, Aragon et al. [1] noted that six percent of their respondents did not think they could safely treat a patient with epilepsy, because they lacked knowledge of people living with the disability. Along the same vein, Al-Adawi et al. [22] stated that the majority of their study participants in Oman thought that people with epilepsy have more predispositions towards dysfunctional personality and behavioural characteristics than do "normal" people. They suggested that a developing country like Oman must inculcate in their physicians more realistic attitudes towards individuals with epilepsy.

Our extensive search of the literature indicates that this is the first time in Nigeria the IDP Scale has been used to measure the attitudes of practicing healthcare providers towards PWDs. Healthcare providers are likely to be among the first individuals with whom a newly disabled person has contact, so their dispositions towards PWDs can have significant implications for implementing treatment, rehabilitation, and reintegration into the community. Yet, as has been shown in our review of previous studies, the literature is generally inconclusive about the attitudes of these professionals.

Our study findings indicate that healthcare workers who provide direct patient care are more comfortable when interacting with their patients with disabilities as compared to workers providing indirect care. Direct/indirect care provider status was not associated with the experiential variables level of prior contact with PWDs and knowledge of legislation regarding PWDs in this sample, but level of training specific to PWDs and confidence in treating PWDs were. Hence, it may be that a larger amount of specialised training leads to greater confidence in treating PWDs.

We found that older (age 44-60 years) healthcare workers express more feelings of vulnerability about becoming disabled. Age was not associated with the experiential variables with the exception of level of prior contact, for which there was no uniform trend. Hence, it

may be that we are simply capturing the recognition that, as one ages, the likelihood of experiencing a significant disabling condition is increasing, resulting in one's feelings of vulnerability.

The negative association that we observed between each of the three factor scores, discomfort, information and vulnerability, with level of confidence in treating PWDs provides support for the multi-dimensionality of the IDP Scale. Forlin, Fogarty and Carroll [23] preferred to label the factor Information as Uncertainty. Our findings indicate that less training specific to PWDs and less knowledge of legislation and policies result in more uncertainty in dealing with patients with disabilities.

A major take-away from this study is the need for healthcare providers to be adequately trained in disability-related topics while in residency or medical, nursing, or allied health professional training. Oredugba and Sanu [11], in their survey of dentists in Nigeria, alluded to this salient point when they commented that improved training would help the dentists better manage patient behaviour and utilise time effectively. Given the pervasive nature of disabilities in the Nigerian society today, proactive measures should be embarked upon so healthcare practitioners are sufficiently prepared to deal with existing and emerging disabling conditions [16]. We believe healthcare providers' attitudes can influence their behaviour towards their patients. Therefore, it is critical periodically to examine their attitudes towards their patients with disabilities who come to the hospital for treatment and care.

Recommendations

From the insights gained in this study, we recommend a number of measures to develop and sustain practitioners' attitudes towards PWDs and their families. First, there should be regular in-service training sessions where healthcare providers participate in structured role-plays to experience the use of the wheelchair around the premises, wearing ear plugs and using a blindfold with a human guide to simulate walking difficulty, deafness and blindness, respectively. Second, hospital management and staff could collaborate with the Joint National Association of Persons with Disabilities, an umbrella organisation of PWDs in Nigeria, to recruit competent guest speakers with disabilities and their families to share their experiences during in-service training sessions. Third, hospital management could organise healthcare providers' visits to special education schools and rehabilitation centres for PWDs to gain authentic insights into issues that impact the special populations.

Surveys at participating institutions before and after such educational interventions (including a scale such as the IDP) could be conducted to assess changes in attitudes towards persons with disability. Further and ongoing research on the attitudes, knowledge and practices of the providers would also help to determine, over a sustained period, if health-related government policies are being implemented to promote inclusive, quality healthcare for all PWDs.

Limitations of the Study

Because data for this project were gathered from one hospital, the nature of the sample limits the generalisability of the results. Therefore, we recommend expanded investigations to include selected hospitals in the six geopolitical regions of the country, including the Federal Capital Territory, Abuja. This would enable the researchers to capture responses from healthcare providers with a wider range of exposure to, and experience with, individuals with disabilities. This could result in a sample for which the total IDP Scale would prove to be a reliable indicator, as was shown for healthcare providers in other countries [24].

CONCLUSION

One notable aspect of our study is that three-quarters of participants were direct care providers, which is suggestive of the willingness of workers at UCH to implement specialized services. Significantly, over half of respondents indicated they had either daily or weekly interactions with patients with disabilities. However, only 11% reported having acquired at least 40 hours of disability-related training, and only 31% stated having either a high or very high level of confidence in treating PWDs. As members of the caring profession, direct- and indirect- healthcare providers have critical roles to play in the provision of quality health services. Therefore, it will behoove providers to be cognizant of the needs, wants and choices of PWDs. Furthermore, these healthcare providers must engage in frequent contact with PWDs in order to develop providers' confidence and foster organisational and individual capacities that will empower PWDs to live fully inclusive lives in their communities.

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Chapter 371

FACTORS INFLUENCING THE CHOICE OF GRADUATING MEDICS IN PURSUING A MEDICAL CAREER WITH THE NIGERIA DEFENCE FORCES

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ABSTRACT

In this chapter we explore the interest of graduating medical students in the Usmanu Danfodiyo University (UDU), Sokoto, Nigeria, on taking up medical jobs in the Nigeria defence sector. Methods: This study was a cross-sectional questionnaire survey of 63 graduating medical students of UDU, Sokoto, Nigeria. Collected data was analysed using the SPSS version 16 software. Results: The mean ($\pm$ SD) age of the 63 respondents was 24.87 ($\pm$ 2.17) years, and the majority (73.0%) of them were males. Only 26 (41.3%) out of the 63 respondents showed interest in taking up a medical job position in the Nigeria defence sector, and the majority (22/26, 84.6%) of them were men. The majority (57.7%) of those respondents who desired working in this sector would like to work with the Nigeria Armed Forces (NAF), and their most desired arm of the NAF was the Nigeria Navy. Personal interest (65.4%), prestige (57.7%), and job security/advancement prospects (38.5%) were the top three motivating factors among those respondents that desired a medical job in the Nigeria defence sector. Conclusions: This study shows that only the minority of the surveyed graduating medics would like to take up a medical job

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position in the Nigeria defence sector. Personal interest, prestige, and job security/advancement prospects were the predominant motivating factors among those that desired medical job positions in the Nigeria defence sector.

INTRODUCTION

There are diverse career paths to choose from after bagging a degree in human medicine. The work of a medical doctor goes beyond clinical and as a matter of fact, a medical doctor can also work as an administrator, a policy maker, an educator, or a scientist. For instance, if we focus on the Nigeria defence sector, we will observe that the services of medical doctors are seriously needed in the Nigerian defence sector. Some of the roles played by medical doctors in the establishments under the Nigeria defence sector includes provision of medical care to defence personnel and their family, provision of medical care to civilians at warring places and other conflict zones home and abroad, planning and execution of emergency medical care and services to victims of natural disasters, amidst other duties.

Globally, career choice of medical students in the defence sector had been sparsely reported. However, from the few studies available, it was found that career in the defence sector was very appealing to medical students in Pakistan and the United States of America [1, 2], and many factors had been documented to influence the career choice of these students in the defence sector. Some of these factors include national patriotism, high income, and attractiveness of the uniform [1, 2]. However, to the best of the authors' knowledge, no literature had particularly explored Nigerian medical students' choice of career with the Nigeria defence sector. Hence, authors aim to conduct this study to determine the level of interest of the graduating medics of the Usmanu Danfodiyo University (UDU), Sokoto, Nigeria, in pursuing a medical career in the Nigeria defence sector, and to also explore the factors that influence their career choice in this sector.

OUR STUDY

This research was a cross-sectional study conducted among the final year medical students of the UDU, under the ethical guidelines of the Helsinki Declaration. This institution is a public university situated within the metropolitan city of Sokoto, Nigeria. The instrument adopted for the study was a well-structured 27-item questionnaire developed through review of literatures [1, 3]. The questionnaire obtained information on the bio-data, interest of participants in taking up medical jobs in the defence sector, and the factors that influenced their choice of career in these job positions.

The study population comprises 98 graduating medical students. These students were approached at their classroom and dormitories. The aims and objectives of the study were clearly explained to them before obtaining verbal informed consents for participation. However, only 63 students volunteered to participate in this study. For the sake of confidentiality, an anonymous questionnaire was used for data collection. Data collection was done in November, 2017. Collected data was entered into the SPSS version 16 software for analysis. Frequency distributions of all variables were determined, and comparisons between

qualitative variables was done using Chi-square with the level of significance set to a p -value <0.05 .

Table 1. Demographic profile of respondents

Attributes (n=63)	Frequency (%)
Mean age in years ($\pm$ SD)	24.87 ($\pm$ 2.17)
Gender	
Male	46 (73.0)
Female	17 (27.0)

n=Total number of respondents.

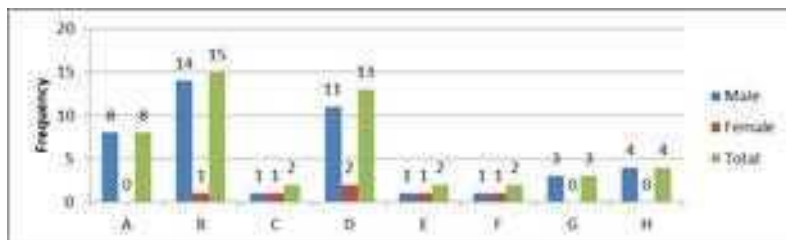
Table 2. Comparison between gender of respondents and their interest of taking up a medical job in the Nigeria defence sector

		Gender		Total (N=63)	X^2
		Male (N=46)	Female (N=17)		
Can you take up a medical job in the Nigeria defence sector?	Yes	22 (47.8)	4 (23.5)	26 (41.3)	0.173, df=2
	No	16 (34.8)	10 (58.8)	26 (41.3)	
	Yet to decide	8 (17.4)	3 (17.6)	11 (17.5)	
	Total	46 (100.0)	17 (100.0)	63 (100.0)	

FINDINGS

The mean ($\pm$ SD) age of the respondents was 24.87 ($\pm$ 2.17) years. Gender distribution of the respondents was skewed with the majority (73.0%) of them being males (see Table 1). Only 26 (41.3%) out of the 63 respondents showed interest in taking up a medical job in the Nigeria defence sector, of which the majority (84.6%) of them (i.e., those who desired a career in the Nigeria defence sector) were men (see Table 2).

The majority (57.7%) of those respondents who desired working in the Nigeria defence sector would like to work in the Nigeria Armed Forces (NAF), and the most desired arm of the NAF was the Nigeria Navy (see Figure 1). Personal interest (65.4%), prestige (57.7%), and job security/advancement prospects (38.5%) were the top three motivating factors among those respondents that desired a medical job in the Nigeria defence sector (see Table 3).



Keywords: A=Nigeria Army; B=Nigeria Navy; C=Nigeria Prisons Service; D=Nigeria Air Force; E=Nigeria Police Force; F=Nigeria Security and Civil Defence Corps; G=Nigeria Customs Service; H=National Drug Law Enforcement Agency.

Figure 1. Places where those respondents who showed interest in working with the Nigeria defence forces desired (N=26).

Table 3. Factors influencing the career choice of those respondents that showed interest in taking up a medical job position in the Nigeria defence sector

Influencing factors	Gender*		Total (N=26)
	Male (N=22)	Female (N=4)	
Personal interest	16 (72.7)	1 (25.0)	17 (65.4)
Job security/advancement prospects	8 (36.3)	2 (50.0)	10 (38.5)
Lifestyle and the job description	9 (40.9)	0 (0.0)	9 (34.6)
Prestige	13 (59.1)	2 (50.0)	15 (57.7)
Flexibility of the profession	3 (13.6)	0 (0.0)	3 (11.5)
High wages	6 (27.3)	1 (25.5)	7 (26.9)
Easily compatible with having a family	5 (22.7)	1 (25.5)	6 (23.1)
Influence from a mentor	7 (31.8)	1 (25.5)	8 (30.8)
Enough time for leisure activity	3 (13.6)	0 (0.0)	3 (11.5)
Influence from a family or relative	3 (13.6)	1 (25.5)	4 (15.4)
Gender distribution in the job	6 (27.3)	1 (25.5)	7 (26.9)

N=Total number of respondents in each category.

DISCUSSION

Doctors-in-training in foreign countries like Pakistan and United States of America had been reported to show keen interest in taking up medical job positions with their homeland defence forces, after graduation from medical school [1, 2]; national patriotism, high income, and attraction for uniform, were the predominant motivating factors that were found to have influenced their choice of career with the defence forces of their country [1, 2]. Interestingly, to the best of the authors' knowledge, no similar study is available from a similar study population in Nigeria. The rationale for conducting this present study was to provide the first literature that explores Nigerian medical students' choice of medical career with the Nigerian defence forces.

In this study, it was observed that less than half of the respondents would like to take up a medical job position in the Nigerian defence sector (see Table 1). Most of those respondents that showed positive interest in working in the Nigerian defence sector preferred to work within the arms of the NAF (i.e., the Nigeria Army, Nigeria Navy, and Nigeria Air Force); this may be because the NAF is the most prestigious and powerful arm of the defence sector of Nigeria.

Interestingly, none of the female respondents in this present study would like to take up a medical career with the Nigerian Army, Nigerian Customs Service, and the National Drug Law Enforcement Agency. Unfortunately, the precise reasons why the female folks showed no interest in this study were not given in the scope of this study. However, this finding has generated research questions that need to be answered through further studies.

It is also noteworthy that the factors that informed the respondents' choice of career with the Nigeria defence forces are diverse and numerous. The top three influencing factors, among all, were personal interest, prestige, and job security/advancement prospects; interestingly, these top three factors were put into consideration by both genders. However, we observed that there were some other motivating factors that were not put into consideration by both genders. For instance, factors like job flexibility, lifestyle and job description, and enough time for leisure activities were not considered by any of the female

respondents; this finding is dissimilar with other existing studies on career choice among Nigerian students in clinical professions [3, 4], as the females in those studies considered these aforementioned factors.

Our findings have its implications. First of all, the majority of the surveyed medical students had no interest in working with the Nigeria defence forces; this may pose a problem to the holistic healthcare of the Nigerian security personnel if similar disinterest is recorded among medical students in other Nigerian medical schools. There also exists skewed distribution in the choices of the medical students, as many of them preferred to work in the Nigeria Armed Forces, while a scanty few would like to work in the paramilitary and police forces. This shows that some security agencies/forces may find it very difficult to recruit medical personnel into their setting as such agencies are not appealing to medical students, as demonstrated in this study.

Lastly, this study has its limitations. Firstly, this study did not enquire into reasons why the respondents showed no interest in medical careers in the Nigeria defence sector. Secondly, this study was a single centre study and it did not survey other graduating medics in other Nigerian medical schools; hence the need for multi-centre studies that will capture a larger population.

CONCLUSION

This study shows that many medical students would not want to take up a medical job positions in the Nigerian defence sector. However, the majority of those that would like to work in this sector preferred the NAF. Motivating factors like personal interest, prestige, and job security/advancement prospects were the most predominant factors that were found to influence medical students' decision in taking up a medical job positions in the Nigeria defence sector.

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Chapter 372

AFTER MEDICAL SCHOOL, WHAT NEXT?

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ABSTRACT

Not all medical students want to further their education after bagging a medical degree. Even among those who want to further, not all of them want to pursue postgraduate disciplines in clinical medicine. This study aims to explore the postgraduate disciplines desired by the graduating medical students of the Usmanu Danfodiyo University (UDU), Sokoto, Nigeria, and also explore the factors that influenced their choice of a postgraduate study program. Methods: This study surveyed a cross section of 63 graduating medical students of the UDU using a well-structured anonymous questionnaire. Data obtained was analyzed using the SPSS version 16 software. Results: The mean age ($\pm$ SD) of the 63 respondents was 24.87 ($\pm$ 2.17) years, with the majority (73.0%) of them being males. Only 44 (69.8%), out of a total of 63, respondents desired to go for postgraduate studies after finishing medical school, of which the majority (89.2%) of them desired to pursue a medical residency program. Also, not up to half (39.5%) of those respondents who desired postgraduate study intended to have it done in an institution within Africa. The disciplines chosen by those respondents who desired postgraduate studies were diverse, however the majority (70.5%) of them prefer postgraduate programs in clinical sciences. Personal interest (75.0%) and research opportunities were the top two factors influencing the respondents' choice of a postgraduate study program. Conclusions: Not all medical students desired to further

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their education after medical school. Also, the choices of postgraduate study programs among the surveyed students were diverse.

INTRODUCTION

After the completion of a medical degree program, a fresh medical doctor is born. As a fresh medical graduate, the next question to be asked is “What is the next task to embark upon?” Interestingly, different studies had shown that medical students have diverse preference for what to do after graduation [1-4]. Those studies showed that: some medical students prefer to go into general medical practice; some prefer to pursue further educational qualifications; while some prefer to pursue other career paths that may or may not be related to medicine, after graduation [1-4].

In actual fact, there are many postgraduate disciplines that could be explored by a medical doctor, if considering further studies. As a matter of fact, specialization in disciplines within the borders of clinical sciences is just an option, amongst a gamut of options. Some of the other disciplines that could be explored include some, if not all, disciplines in social sciences, humanities, law, basic medical sciences, and public health, among others.

However, many factors had been found to influence medical students’ choice of a postgraduate study program, some of which includes personal interest, ease of admission into the program, and prestige [1-4]. Also, many studies had elaborately explored medical students’ interest in residency training in the clinical specialties; however only scanty studies had been done on medical students’ interests in disciplines outside medical sciences [1-5].

This study aims to explore the interest of graduating medical students of the Usmanu Danfodiyo University (UDU), Sokoto, Nigeria, on various postgraduate study programs, and also explore the factors that influence their choice of the proposed area of postgraduate study.

OUR STUDY

This was a cross-sectional study undertaken among graduating medical students of the Usmanu Danfodiyo University (UDU). This institution is a public university situated within the metropolitan city of Sokoto, Sokoto State, Nigeria. This institution is also the home to the only medical school within Sokoto State. A total of 98 medical students were in the graduating class during the period this study was conducted.

Study tool was a well-structured 34-item anonymous questionnaire designed by the authors through the review of literatures [1-4]. Questionnaire obtained information on the: bio-data; interest of the participants in pursuing postgraduate studies after graduation; the postgraduate disciplines they would like to pursue; the continent where they would like to have the study program done; and the factors that influenced their choice of a postgraduate study program.

The participants were approached at their classroom and dormitories. The aims and objectives of the study were clearly explained to them before obtaining verbal informed consents. Only 63 students volunteered to participate in this study. Data collection was done in November, 2017.

A total of 63 questionnaires were analyzed for this study; no questionnaire was discarded because all were properly filled. Collected data was entered into the SPSS version 16 software for analysis. Frequency distributions of all variables were determined, and comparisons between qualitative variables was done using Chi-square with the level of significance set to a p-value <0.05.

FINDINGS

The mean age ($\pm$ SD) of the 63 respondents was 24.87 ($\pm$ 2.17) years and majority (73.0%) of them were males (see Table 1).

Only 44 (69.8%), out of a total of 63, respondents desired to go for postgraduate studies after finishing their undergraduate medical program (see Table 2), of which the majority (89.2%) of them desired to pursue a residency program (see Table 3). In addition, a higher proportion (80.4%) of the men, when compared to the women (41.2%) intended to further; this comparison was found to be statistically significant ($p = 0.005$, $df = 2$).

Table 1. Demographic profile of respondents

Attributes (n = 63)	Frequency (%)
Mean age in years ($\pm$ SD)	24.87 ($\pm$ 2.17)
Gender	
Male	46 (73.0)
Female	17 (27.0)

n = Total number of respondents.

Table 2. Comparison between gender of respondents and intention for postgraduate studies

		Gender of respondents			p-value (X^2), df
Do you intend to		Male (N = 46)	Female (N = 17)	Total (N = 63)	
further your	Yes	37 (80.4)	7 (41.2)	44 (69.8)	0.005, df = 2
education after	No	5 (10.9)	8 (47.0)	13 (20.6)	
having your medical	Yet to decide	4 (8.7)	2 (11.8)	6 (9.5)	
degree?	Total	46 (100.0)	17 (100.0)	63 (100.0)	

N = total number of respondents in each category, X^2 = Chi-square, df = degree of freedom.

Table 3. Postgraduate programs intended to be pursued by the respondents that showed interest in further studies

Postgraduate program	Male* (N = 37)	Female* (N = 7)	Total* (N = 44)
Masters	26 (70.3)	4 (57.1)	30 (68.2)
Doctorate	24 (64.9)	3 (42.9)	27 (61.4)
Residency program	33 (89.2)	5 (71.4)	38 (86.4)

*Only those that had the intention for postgraduate studies were analyzed here.

Not up to half (39.5%) of those respondents who desired postgraduate study intended to have it done in an institution within Africa (see Figure 1). Furthermore, disciplines in clinical sciences was the highest (70.5%) chosen discipline among those respondents who desired postgraduate studies (see Table 4).

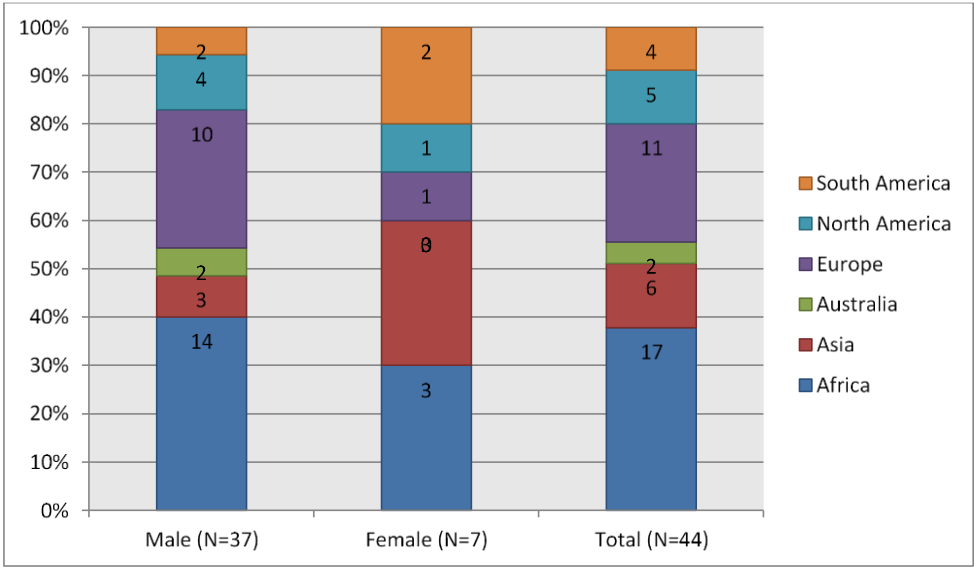


Figure 1. Continental distribution of places where respondents desired to have their postgraduate education.

Table 4. Educational disciplines desired to be pursued by those respondents that desired postgraduate education

Discipline	Gender	
	Male (N = 37)	Female (N = 7)
Social sciences	2 (5.4)	0 (0.0)
Biological sciences	1 (2.7)	0 (0.0)
Public health	20 (54.0)	7 (100.0)
Basic medical sciences	10 (27.0)	4 (57.1)
Clinical sciences	26 (70.2)	5 (71.4)
Physical sciences	3 (8.1)	0 (0.0)
Humanities	2 (5.4)	0 (0.0)
Arts	1 (2.7)	0 (0.0)
Engineering	2 (5.4)	0 (0.0)
Law	3 (8.1)	0 (0.0)

Of all other influencing factors, personal interest was found to be the most popular (75.0%) influencing factor on the respondents’ choice of a postgraduate study program. However, factors such as gender distribution in a study program, and other people’s perception of the qualification obtained from the study program were the least popular (6.8%) influencing factors among them (see Table 5).

Table 5. Factors influencing respondents' choice of a postgraduate discipline

Influencing factors	Gender*	
	Male (N = 37)	Female (N = 7)
Personal interest in the study program	27 (73.0)	6 (85.7)
Job security/advancement prospects	14 (37.8)	1 (14.3)
Ease of entry into the study program	9 (24.3)	1 (14.3)
Lifestyle and the job description	16 (43.2)	2 (28.6)
Prestige	11 (29.7)	0 (0.0)
Opportunity to conduct research	16 (43.2)	3 (42.9)
Flexibility of the study program	8 (21.6)	3 (42.9)
Contact with patient and clinical samples	15 (40.5)	2 (28.6)
High wages	9 (24.3)	1 (14.3)
Easily compatible with having a family	9 (24.3)	2 (28.6)
Inclination of the study program before entering medical school	4 (10.8)	0 (0.0)
Influence from a mentor	9 (24.3)	2 (28.6)
Enough time for leisure activity	12 (32.4)	4 (57.1)
Influence from a family or relative	5 (13.5)	1 (14.3)
Other people's perception of the qualification obtained from the study program	3 (8.1)	0 (0.0)
Low risk of litigation	8 (21.6)	1 (14.3)
Gender distribution in the study program	3 (8.1)	0 (0.0)

N = Total number of respondents in each category, *only those that indicated interest in pursuing postgraduate studies were analyzed here.

DISCUSSION

Studies had shown that not all medical students wish to further their education after bagging a medical degree [4, 6]. Furthermore, among those medical students who intended to further their education, not all of them want to go for residency training [4]. In this present study, only 69.8% of the surveyed graduating medical students had the intent to further their studies, of which only 86.4% of them desired to go for residency training. This finding is lower than that reported in a previous Nigerian study, where 89.5% of the respondents in that study desired to go for residency training [7].

It is noteworthy that lack of intent to pursue a postgraduate study program was found to be more common among the female respondents when compared to their male counterparts. In fact, many female medical students do want to get married as soon as possible, after graduation, and start giving birth to children [6]. Hence, the challenge of combining family responsibilities with studying may be a major reason why many of the female respondents showed no interest in postgraduate studies [8].

Furthermore, not all of the respondents considered going for postgraduate study in disciplines within medical sciences, as some of them prefer pursuing postgraduate degree programs in arts, biological sciences, engineering, law, humanities, physical sciences, public health, and social sciences. This finding corroborates with that reported among medical students in Korea [4, 5].

It is interesting to note that less than four-tenth of the study respondents who desired to pursue postgraduate studies desired to have it done in Africa. This may suggest that postgraduate qualifications from institutions domiciled in Africa are less appealing to the majority of these medical students.

The factors that influence the respondents' choice of a postgraduate study program are diverse. Personal interest was found to be the most popular influencing factors among the respondents. Similar attribute had also been demonstrated among students in other clinical disciplines [9, 10]. Opportunity to conduct research, contact with patients and clinical samples, study program's flexibility, high wages, easy compatibility with having one's family, and ease of entry into a study program, were also factors that jointly influenced both the participating men and women.

We also observed that prestige, inclination of the study program before entering medical school, other peoples' perception of the qualification obtained from such study program, and gender distribution in such study program were the motivating factors that informed the women's choice of a postgraduate study program; however these factors did not inform the men's choice.

CONCLUSION

This study had shown that not all medical students desired to further their education after obtaining a medical degree. Among those that intended to further, not all of them want to go residency training, rather some wish to pursue degrees in fields outside medicine.

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Chapter 373

BARRIERS TO UPTAKE OF LOW VISION AIDS AMONG VISUALLY IMPAIRED ELDERLY NIGERIAN PATIENTS

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ABSTRACT

While low vision aids enhance possibilities of reading, performing daily tasks and distant viewing for visually impaired individuals, there is paucity of research on their usage and adoption among Nigerians with low vision. Objective: This study attempts to bridge the knowledge gap about non-use of low vision aids among visually impaired older adults. Methods: Data concerning visually impaired older adults non-use of Low Vision Aids (LVAs) was collected and analysed through a cross-sectional survey in a Southwest city in Nigeria. Participants were 230 visually impaired non-users of LVAs aged 60 years and over. Results: Findings show that most non-users who were not aware of LVAs were less likely to be males, more likely to be aged over 71 years, and less likely to be middle and high educated compared to lower educated older adults. Participants aged 71 years and over were also less likely to consider future use of LVAs compared to other participants aged between 60 and 70 years. Visually impaired older adults with low levels of education were also significantly less likely to have intentions of using LVAs. Conclusion: The differences identified were mainly related to socio-demographic variables such as age, gender, household composition, and severity of vision impairment. This study highlights the importance of understanding how groups of visually impaired older adults will most likely benefit from interventions aimed at promoting uptake of LVAs and facilitating independent living among this population.

INTRODUCTION

Low vision refers to irreversible loss of vision which makes activities of daily living difficult for a person to perform [1]. It is defined as visual acuity ranging from light perception to $<6/18$ (0.3 logMAR), or a visual field smaller than 10 degrees from the point of fixation even after treatment and/or standard refractive correction [1]. However, low vision taken together with blindness represents all visual impairment [1, 2]. People with low vision are, however, capable of using their residual vision and if given appropriate low vision aids and training, they do not typically need to function with additional or complementary support. In principle, many patients with low vision are not technically considered blind, although they might be classified as such. With increasing global population, the prevalence of visual impairment is increasing [2].

However, the provision and uptake of low vision services and low vision aids (LVAs) continues to be relatively low particularly in the developing countries [3, 4]. In some developing countries, such as India, research focus is shifting towards identifying avenues for effective provision and uptake of low vision services [5, 6]. In this context, efforts are increasingly channelled towards having data on the knowledge and awareness of low vision services among patients and eye care practitioners, and to improve quality of low vision care in the developing world [5-9].

The aim of this study was to investigate barriers to the uptake of low vision aids among visually impaired older adults in Nigeria in order to create understanding of how they can be encouraged to embrace the use of LVAs. Our focus is on older adults because it is estimated that 80 per cent of all people who need low vision care in are aged over 60 years [10]. The research question explores the extent to which major barriers to accessing low vision aids hinder visually impaired older people in Nigeria from adopting LVAs. It also seeks to provide explanations on associated key factors for low uptake of low vision aids.

Low vision aids and products include a wide variety of devices designed to help those with vision disabilities live independently and make the best use of their residual vision. There are a variety of talking products that can help alleviate eye strain and improve daily living, including talking calculators, compasses, scales, cooking items, clocks, money identifiers, scales, medication reminders, talking watches, books and much more. These simple-to-use and sometimes, technology driven aids enable visually impaired individuals to take care of themselves and not have to rely on others for support. Low vision aids are frequently categorized as optical, non-optical, and electronic aids. Optical aids are useful for people with low vision as they have optical properties capable of promoting better distance and near visual performance through lenses, e.g., Telescopes (hand-held, monocular and/or binocular telescopes), High-plus spectacles (microscopes), Hand-held magnifiers, and Stand magnifiers. As optical aids require use of residual vision, they are usually more useful for individuals with low vision than for totally blind persons [11]. Non-optical aids do not use magnifying lenses to improve visual function, e.g.,; typoscope used as a guide to reading, writing, and signature in cases of large defects of visual field, polarizing lenses used to control the reflection of light such as visors, and side shields. Electronic aids include computer and high-tech aids such as video magnifier systems, closed-circuit televisions, Bluetooth connections to smart projectors, large-print computer programs such as Zoom Text,

screen readers such as Virtual Vision, Jaws, and electronic-based aids for daily living, e.g., talking clocks/wristwatches are aids with computer sound systems.

While low vision aids are essential products for low vision rehabilitation, there is scarcity of data on their use and adoption among visually impaired persons in Nigeria, as well as many developing countries. Evidence suggests that some individuals with vision impairment are, however, unaware of the myriad of low vision devices that are available and applicable to them, and others may be aware but chose not to use them [11]. This is particularly a significant concern; considering that the prevalence of blindness in developing countries, is higher than developed countries. Based on figures from the Nigerian National Blindness and Visual impairment survey, it is estimated that over 2.3 million individuals suffer low vision in Nigeria [12, 13]. There is a huge challenge of providing low vision services and rehabilitation for such a large population and it is important to create understanding about handy devices that can ameliorate the day-to-day challenges of living with vision impairment. In addition, the dearth of facilities and/or skilled personnels for low vision rehabilitation in Nigeria underscores the importance of interventions focusing on restoring the blind individuals' functional capacity pending other treatment alternatives. There are evidences suggesting that effective use of low vision aids promotes successful adjustment to challenges of living with vision impairment [14, 15].

In a review of existing literature regarding barriers that hinder access to low-vision (LV) care from the perspective of individuals with vision impairment, a Canadian study showed that lack of understanding about low vision services, inadequate information and miscommunication by eye care professionals, low levels of awareness about low vision care, and the need to appear independent were major barriers to accessing low vision services [16]. Other factors identified by the study include negative societal views and stigma associated with use of low vision aids. However, the existence of low vision services is not synonymous to use and uptake of low vision aids. Detailed surveys in some rural communities in Nigeria have found very low uptake of public healthcare facilities despite being, in principle, within geographic proximity and free of charges [17]. Understanding access to low vision services could foster knowledge, awareness, professional recommendation and use of low vision aids.

A study conducted among ophthalmologists in Nigeria cited non-availability of low vision devices within the country, lack of public awareness of low vision care, lack of training in low vision care, and practitioners (ophthalmologists' and optometrists') preoccupation with general ophthalmic practice as the major barriers in clinical low vision provision [18]. Although the study focused on ophthalmologists in Nigeria, there has not been any study exploring perceptions of the end-users; i.e., the visually impaired patients, to understand the challenges of non-use from their perspective. This study therefore, attempts to bridge the knowledge gap about non-use of low vision aids from the views of intended end-users.

OUR STUDY

The study employed a cross-sectional survey method. This study adhered to the tenets of the Declaration of Helsinki and ethical approval was obtained from the Research and Ethics Committee of the School of health. Participants were aged 60 years and over. The eligibility criteria for the study included best corrected visual acuity of $<6/18$ in the better eye, 60 years

of age and over, and the ability to read and converse in English. Participants were recruited during their routine follow-up visits in 14 registered eye clinics in the metropolitan cities of Lagos state and Delta state in Nigeria. A total of 323 visually impaired older people were contacted from 14 private eye clinics in Delta-state and Lagos state, Nigeria. The private clinics were randomly selected from five local government areas in Delta state and nine local governments in Lagos state. The study typically gathered data from surveys of views or opinions of participants as well as past clinical records of routine eye examinations. It was conducted in accordance with institutional and national guidelines for conduct of research with human subjects. The investigation was carried out in accordance with the Declaration of Helsinki of 1975 (As revised in Tokyo in 2004). Informed consent was obtained from all participants as they were briefed about the study and their verbal consent obtained before participation. Consecutive consenting respondents visiting the registered private clinics in the two states were recruited for the study. A structured interview questionnaire to ascertain socio-demographic details of participants was read out to participants and their responses recorded. Participants' low-vision case files were accessed, with their consent, to obtain relevant data on vision impairment. Of the 323 participants contacted over a period of eight months during the sampling phase of the study, 281 participants (86.99%) indicated that they did not use LVAs and were recruited to participate in the survey. However, a total of 230 participants (81.85%) participants completed the survey. Measures including: Age, gender, and vision acuity were considered as independent variables in analyses concerning non-use of LVA (see Table 1). Vision Acuity (VA) was measured using computerized Snellen chart and corresponding LogMAR values of the Snellen ratio were recorded.

Table 1. Demographic profile of participants

	N	%
Gender		
Male	92	40.00
Female	138	60.00
Age		
60-65	55	23.91
66-70	52	22.61
71-75	60	26.09
76+	63	27.39
Education		
Low	143	62.17
Medium	64	27.83
High	23	10.00
Household composition		
Single	43	18.70
Living with others	187	81.30

In the survey, participants were asked about how much they relied on others to perform daily tasks (also referred hereafter as activities of daily living). Questionnaires were printed in large fonts for partially sighted participants and read aloud for participants with severe low vision and totally blind. Appropriate boxes corresponding to their responses were ticked on the questionnaires. Dependent variables were Lack of knowledge or awareness of LVAs, Asking others for help (relying on others to perform daily living tasks), and Intended future use of LVAs. The question about Lack of awareness and Intended future use of LVAs

allowed respondents to answer with yes or no. Yes was coded as 1 and no = 0. Sample questions on asking others for help included, 'I have difficulties telling the time on the clock, but I do not need a LVA because I rely on others to tell me what time of the day it is', 'I find it difficult to read, but I do not need a LVA because I rely on others to read out any printed document to me'. The question on asking others for help allowed respondents to answer on a 4-point scale: 1 (strongly agree), 2 (agree), 3 (disagree), and 4 (strongly disagree). All scores were recoded and lower scores corresponded to higher levels of reliance on others to perform tasks of daily living and therefore, not needing a LVA. Dichotomous key variables of reasons for non-use of LVAs were included. We conducted a Hierarchical logistic regression analyses using IBM SPSS statistics version 18. We initially used two-step models to investigate whether the effects of gender, education, and household composition changed with vision acuity, but as these variables did not affect the original model, we report only the final regression analysis.

FINDINGS

Among the participants, 61 percent indicated not being aware of LVAs (Mean score (M) = 0.21, and Standard Deviation (SD) = 0.41). Table 2 shows that, the non-users who were not aware of LVAs were less likely to be males, more likely to be aged over 71 years than aged between 60 and 70 years, and less likely to be middle and high educated compared to lower educated older adults. However, among this group, participants who live with others were more likely to have knowledge of LVAs than those living alone and respondents with lower vision acuity seemed to have higher knowledge and awareness of LVAs.

Table 2. Logistic regressions non-users of LVAs, alternative and future use

	Knowledge or Awareness of LVAs	Asking Others for help	Intended future use of LVAs
Constant	0.15	0.15	0.00***
Gender			
Male	0.54*	0.49*	0.78
Age (Reference: 60 – 65)			
66 - 70	0.40	0.47*	0.74
71 - 75	0.29***	0.55	0.28**
76+	0.21***	0.56	0.34**
Educational Level (Reference: Low)			
Medium	0.35	1.16	4.81***
High	0.28	1.23	4.97**
Household Composition (Ref: Single)			
Living with others	2.69**	2.65*	0.05
Vision Acuity	1.50	1.64*	4.54**
Chi-Square test	38.65***	18.94**	35.46***
Nagelkerke R^2	0.15	0.001	0.29

* Significant at $p < 0.05$, ** Significant at $p < 0.01$, *** Significant at $p < 0.001$.

Approximately 58 percent of participants reported having asked someone else for help on a task requiring vision. Mean scores (M) and Standard Deviation (SD) for the variables are: M = 1.62, SD = 0.41). Men were less likely to request for help. Similarly, participants aged

between 66 and 70 were more likely to request for such help compared to other age groups of visually impaired older adults. Participants living with others were significantly more likely to ask someone for help while participants with lower vision acuity were less likely to request for help. Only 23 percent of the participants indicated intentions to use LVAs in the future ($M = 0.78$, $SD = 0.42$). Participants aged 71 years and over were less likely to consider future use of LVAs compared to other participants aged between 60 and 70 years. Visually impaired older adults with low levels of education were also significantly less likely to have intentions of using LVAs. A lower visual acuity also suggested a higher likelihood of intention to use LVA in the future.

Table 3. Reasons for non-use of LVAs analysed using logistic regression

Explanatory variable	No need	Cost of LVAs	Stigma	Too old to use LVAs
Constant	7.20*	0.10	0.15	0.19
Gender (Reference: Female)				
Male	2.63*	1.02	1.03	1.15
Age (Reference: 60 – 65)				
66 - 70	0.27	1.13	10.41**	1.47
71 - 75	1.11	1.45	1.20	2.68
76+	0.96	0.86	0.60	7.68**
Educational Level (Reference: Low)				
Medium	1.16	1.39	1.21	1.13
High	0.36**	1.28	1.45	1.21
Household Composition (Ref: Single)				
Living with others	2.41*	0.98	1.43	1.56
Vision Acuity	1.17	1.19	2.13	1.35
Chi-Square test	2.42	7.67	11.17	25.62***
Nagelkerke R^2	0.04	0.33	0.36	0.45

* Significant at $p < 0.05$, **Significant at $p < 0.01$, ***Significant at $p < 0.001$.

Explanations for non-use were also investigated. Table 3 shows tests of significance in differences for most important reasons for not adopting use of LVAs. The results showed that among visually impaired older adult men and women, a majority of men are more likely to not see the need for use of a LVA. Older adults aged 60-70 years were significantly more likely to report stigma as a discouraging factor for use of LVAs while older adults aged 76 years and over were significantly more likely to mention being too old to use LVAs. However, while participants with more education were significantly less likely to mention that there was ‘no need’ for LVAs, those who lived with others were significantly more likely to mention that there was no need for LVAs.

DISCUSSION

This study set-out to investigate non-use of LVAs among visually impaired older people aged 60 years and over and important reasons for non-use. A majority of our participants reported not being aware of LVAs. This finding echoes the report from previous (and similar) studies that lack of public awareness about low vision care is a significant impediment to uptake of low vision aids and related services [4, 18]. Findings suggest that, the non-users

who were not aware of LVAs were less likely to be males, more likely to be aged over 71 years, and less likely to be middle and high educated compared to lower educated older adults. While findings echo a previous report that highly educated individuals are more aware of the existence of LVAs and much older participants - less technologically inclined [12], there is paucity of evidence that knowledge and awareness of LVAs is gender based. The use of LVAs might not be a male-dominated activity but stereotypically, males have been considered good with use of gadgets and historically reported as being more ICT-inclined than females [19] because women underestimate themselves in this regard [20].

Our findings also showed that a lower vision acuity was significantly related to higher knowledge or awareness of LVAs. Arguably, more severely low vision patients could be keener and more enthusiastic about exploring solutions that would remedy their sight loss in order to avoid total blindness [21]. Conversely, patients with mild and moderate vision impairment are usually hopeful that their sight loss is reversible, and as such, more likely to be complacent with seeking low vision aid [4]. This is further underscored in findings from this study showing that a lower visual acuity indicated a higher likelihood of intention to use LVA in the future.

Some participants reported having asked someone else for help on a task requiring vision. Findings from this study showed that when considering gender, men were less likely to request for help. This finding is consistent with previous studies showing that men are less likely to admit weakness and seek medical attention [22]. It is therefore not surprising that in the investigated explanations for non-use conducted within this study, men were more likely than women to not see the need for use of a LVA.

Our participants who lived with others were more likely to report that there was no need for LVAs. This is not surprising as living with others could enhance access to alternative assistance to performing daily activities and living alone could possibly steer a compelling need for independent living aids. Similarly, participants aged between 66 and 70 years were more likely to request for help compared with other age groups of visually impaired older adults. It is possible that older participants with vision impairment have learnt ways to adapt to sight loss. As suggested by some authors, people who have lived with severely low vision for long periods are more likely to have learnt to lead independent lives than others in their early stages of mild or moderate vision impairment [23]. Similarly, participants aged 71 years and over were less likely to consider future use of LVAs compared to other participants aged between 60 and 70 years. This could perhaps be so because they considered themselves too old to use LVAs and seem not to see any point in adopting use of LVAs at old ages when they have already learnt to make adjustments to cope with sight loss. Findings also showed that visually impaired older adults with low levels of education were also less likely to have intentions of using LVAs. This is not surprising given that those with higher levels of education might still see the need for use of LVAs for reading and other activities related to accessing printed materials.

From our findings, older adults aged 60-70 years were more likely to report stigma as a discouraging factor for use of LVAs while older adults aged 76 years and over did not see this as an issue. There are on-going debates that use of assistive technologies could be stigmatizing [24, 25]. In some societies, social stigma still surrounds blind people due to misconceptions about blindness [16, 26]. It is, however, yet to be reported that younger age groups are more cautious of the potential for stigmatising identities than older age groups. It could be argued from this aspect of the study finding that the younger age groups might be a

potentially challenging group for interventions to promote adoption of LVAs among people with vision impairment. This finding adds novel understandings to the issue of social stigma and other factors impairing adoption of LVAs among visually impaired groups.

This study has some limitations. Due to the low sample size, our sample may not be fully representative of older adults' non-LVA users. Although the explored explanatory variables for non-use of LVAs among participants are moderate and consistent with previous studies of older adults' adoption of assistive technologies, it is not necessarily exhaustive. Future research should make investigate additional explanatory factors that can provide more robust explanations for visually impaired older adults' non-use of LVAs. This study investigated LVA non-use among older people in Nigeria – an emerging economy country with relatively lower availability of LVAs when compared to many first world countries. It would be insightful to replicate this study in other developing countries with similar levels of LVA and low vision services availability.

CONCLUSION

This study looked at visually impaired older adults' non-use of LVAs and other socio-psychological variables that may account for poor uptake of LVAs in Nigeria. The results showed that visually impaired older adults are likely to have different reasons for (dis)engagement with LVAs. The differences identified were mainly related to socio-demographic variables such as age, gender, household composition, and severity of vision impairment. This study highlights the importance of understanding how groups of visually impaired older adults will most likely benefit from interventions aimed at promoting uptake of LVAs and facilitating independent living among this population. However, more research is needed to understand attitudes of this population towards LVAs as vision impairment is not a homogenous concept and refers to a broad spectrum of needs with different levels of complexity

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Chapter 374

**ATTITUDES OF A SNOWBALLED SAMPLE
OF NIGERIAN HOOKAH (SHISHA) SMOKERS
TOWARD TOBACCO BAN**

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ABSTRACT

Secondhand shisha smoke exposure is a cause of tobacco-induced diseases. There is a need to for the enforcement of law against shisha smoking in public places. This study aims to explore the attitudes of active shisha smokers towards the ban of shisha smoking in public places in Nigeria. Methods: A snowballed sample of 45 active shisha smokers

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in Birnin Kebbi was interviewed using a self-administered questionnaire. Data collected was analyzed using the SPSS version 20 software. Results: The mean ($\pm$ SD) age of the surveyed active shisha smokers was 25.8 ($\pm$ 5.5) years, and 32 were males. Less than a third (11/45) had ever heard of the Nigeria tobacco ban law, while only a little above half were in support of tobacco ban. Conclusion: The Nigeria tobacco ban law is not popular. Despite the fact that the surveyed subjects were active shisha smokers, a majority still supported the ban of shisha smoking in public places.

INTRODUCTION

Secondhand tobacco smoke exposure is one of the major causes of tobacco-induced diseases [1-3]. Unfortunately, a lot of Nigerians are exposed to these smokes [4, 5]. As a matter of fact, about 14.5-55.8% of the youth living in major Nigerian cities had been exposed to this dangerous smoke in public places [4, 6, 7], making exposure to tobacco smoke an issue of public health concern in Nigeria.

In the month of May, 2015, the Federal Government of Nigeria passed the tobacco control bill into law, prohibiting smoking of tobacco in public places (such as gardens, amusement parks, schools, restaurants, healthcare centers, stadia, public transportation parks and plazas) [4]. However, the enforcement of the ban was focused on cigarettes and not shisha, as more and more public shisha smoking places are being erected in the major cities in Nigeria [6-9]. As a matter of fact, shisha is generally considered by the public to be a fairly harmless product, while in the actual sense shisha use is very harmful due to its tobacco content [10-14]. Unfortunately, more and more people in Nigeria are now using shisha, day by day [8, 9]. With the weak enforcement of tobacco ban law in Nigeria, which does not restrict the public use of shisha, many more people will continue to be active, and even passive, shisha smokers [8, 9].

Research in Nigeria had reported negative attitudes among cigarette smokers (a sub-population of smoked tobacco users) toward the Nigeria tobacco ban law [15]. However, to the best of our knowledge, no published study had ever been conducted among shisha smokers in Nigeria concerning their attitudes towards this ban law. Therefore, this study aims to explore the attitudes of a sample of active shisha smokers in Birnin Kebbi metropolis, Nigeria, on the tobacco ban law in Nigeria. The significance of this study is that the outcome of this study will add new information to the body of existing knowledge on smokers' attitudes toward the tobacco ban law.

OUR SURVEY

This was a survey of 45 young active shisha smokers in Birnin Kebbi City, Kebbi State, Nigeria, which was conducted under compliance with the 1964 Helsinki Declaration on health research involving human subjects. This study forms a part of the Campaign for Head and Neck Cancer Education (CHANCE) Program organized under the aegis of the Cephas Health Research Initiative Inc, Ibadan, Nigeria [7-9, 16-17].

The sampling method and the data collection procedure used in this present study had been elaborately discussed in another article [9]. Study tool was a structured anonymous

questionnaire developed from a similar study [7]. The questionnaire obtained information about the socio-demographic characteristics of the subjects as well as their attitudes toward tobacco ban law. Data was collected from 45 active shisha smokers. Collected data was analyzed using the SPSS version 20 software.

FINDINGS

The mean ($\pm$ SD) age of the surveyed active shisha smokers was 25.8 ($\pm$ 5.5) years. The majority (32/45) were males, 16 had secondary school education, 27 had tertiary school education, 33 were Muslims, and 28 were from the Hausa ethnic group.

Only 11 respondents knew that there is a ban on tobacco smoking in public places in Nigeria. However, only 27 agreed that shisha sales to adolescents should be banned, 23 agreed that the advertisement of shisha and shisha products should be banned, 30 agreed that shisha smoking should be banned in restaurants, 25 agreed that shisha smoking should be banned in bars/discos/pubs, and 20 agreed that shisha smoking in all enclosed public places should be banned.

DISCUSSION

The issue of tobacco smoking in public places continues to be an issue of public health concern in Nigeria. Due to the weak enforcement of the tobacco ban law in Nigeria, many cigarette smokers in Nigeria still engage in public smoking [4-6]. Due to this, more and more people have become passive tobacco smokers due to their frequent exposures to second-hand tobacco smokes [4-6]. Due to the issue of weak law enforcement of the tobacco ban law in Nigeria, more and more shisha smoking places (such as discos, restaurants, hubs, etc.) had been erected in some Nigerian major cities [8, 9]. Hence, this issue needs to be considered as a public health emergency.

Furthermore, the peculiarities of shisha smoking make public shisha smoking more dangerous than cigarette smoking. First, shisha is naively perceived by the many lay people, and even among its active smokers, to be a harmless product [10-14]. Second, shisha smoking is widely considered as a socially acceptable behavior, unlike cigarette smoking [18-21]. Third, many shisha smokers smoke shisha in enclosed public areas (such as restaurants, discos, hubs, etc.) unlike cigarette smokers, where a huge number of cigarette smokers smoke in the open air (e.g., along the street) [9]. Fourth, shisha smokers often smoke shisha for a long duration, especially at social gatherings [22]; hence they have the high possibility of inhaling more tobacco smokes in one sitting.

In this study, we surveyed a snowballed sample of shisha smokers on their attitudes towards banning shisha smoking in public places and interesting findings were recorded from our data analyses. We found that the majority of the surveyed shisha smokers were not aware about the tobacco ban law in Nigeria. This current finding is similar to that reported in a Nigerian study conducted among cigarette smokers by Olowookere et al. [15], where a very low awareness rate of tobacco ban was reported. This suggests the need to educate smokers, and as well the entire public on the Nigeria tobacco ban law.

However, the majority (although, averagely above half) of the shisha smokers surveyed in this study supported that shisha smoking in public places should be banned. This finding is dissimilar to that reported among a surveyed sub-population of cigarette smokers in Osun State, Southwest Nigeria, where only the minority of them were in support of tobacco ban. Nevertheless, the findings made from our study and that of Olowookere et al. [15] reveals that not all smokers (be it shisha or cigarette) are against the implementation of the tobacco ban law in Nigeria. In conclusion, the Nigeria tobacco ban law is not popular and it is also weakly enforced in Nigeria [15]. Despite the fact that the surveyed subjects were active shisha smokers, majority of them still supported the ban of shisha smoking in public places.

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Chapter 375

**THE KNOWLEDGE OF DRUG PRESCRIBERS,
DISPENSERS, AND ADMINISTERS IN SOKOTO
METROPOLIS, NIGERIA, ON NON-OPIOID
ANALGESICS: ANY NEED FOR A
REFRESHER COURSE?**

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ABSTRACT

Pain management is a very important aspect in the holistic care of patients. The clinical practitioner's knowledge of the pharmacology of pain killers goes a long way in the effective control of pain. Objectives: To assess the level of knowledge of clinical practitioners in Sokoto metropolis, Nigeria, on the pharmacology of non-opioid analgesics (NOAs). Methods: This study utilized the primary data obtained from a cross-section of 175 clinical practitioners working in five randomly selected hospitals situated within the metropolitan city of Sokoto, Nigeria. The study tool was a 17-item questionnaire. Data analysis was done using the SPSS version 16 Software. Results: Less

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than four-tenth (36.5%) of the subjects were within the age bracket of 26 to 30 years. 62.3% were males, 45% were nursing officers, and 36% had less than six years of experience in clinical practice. None of the surveyed pharmacists strongly disagreed that they were knowledgeable about the metabolism of NOAs, unlike the subjects in other occupational categories ($p < 0.0001$, $df = 12$). All of the surveyed dentists knew of the World Health Organization (WHO) analgesic ladder, unlike the other subjects in the other occupational categories ($p = 0.001$, $df = 12$). A range of 30 to 40% of the nurses, medical doctors, and pharmacists surveyed in this study considered tramadol to be a NOA. Paracetamol, ibuprofen, and diclofenac were the top three commonly prescribed NOAs among the subjects. The most common side effects of NOAs known to the subjects were nausea, vomiting, and peptic ulcer disease (PUD). Conclusion: Many of the surveyed subjects had inadequate knowledge of NOAs. This study population will highly benefit from educational programs that are focused on the clinical use of NOAs.

INTRODUCTION

The knowledge of a clinical practitioner on the pharmacology of pain killers is very important in patient management. In fact, it is virtually impossible for a practicing clinical practitioner not to prescribe, administer or dispense analgesic medications in his/her entire lifetime of clinical practice; hence this reflects the need for a clinical practitioner to have a very sound knowledge on pain management.

Pain can be managed pharmacologically and/or non-pharmacologically [1-5]. The pharmacological management of pain involves the use of drugs [1, 2], while the non-pharmacological management involves the use of other means, such as acupuncture, acupressure, behavioral therapy, and physical therapy [3-5].

One of the main groups of drugs used in the pharmacological management of pain is known as analgesics [1, 2]. The analgesics are broadly classified into the opioid analgesics (OAs) and the non-opioid analgesics (NOAs). The OAs are known to be more potent in pain control than the NOAs [6]; however one of the major problems associated with the use of OAs is the risk of dependence or tolerance [7].

It is an unbeatable fact that the NOAs still remain as the most commonly prescribed analgesics globally. After thorough literature search, authors noticed that the majority of the available literatures assessing clinicians' knowledge of analgesics were focused on OAs while only few literatures assessed clinicians' knowledge of NOAs. This study aims to assess the level of knowledge of doctors, nurses, and pharmacists in Sokoto metropolis, Nigeria, on the pharmacology of NOAs. Conducting this kind of study among this population group is of high significance as the outcome of the study will provide information on how knowledgeable they are on the pharmacology of NOAs.

OUR STUDY

This was a cross-sectional study conducted under the ethical guidelines of the Helsinki Declaration on health research involving human subjects. Approval to conduct this study was officially obtained from the Ethical Clearance Committee, Ministry of Health, Sokoto State,

Nigeria (Ref. No: SKHREC/068/017). All subject participation was absolutely voluntary, and all identities were kept strictly confidential.

The instrument used for data collection was an anonymous well-structured 17-item questionnaire. This questionnaire had three sections. The first section obtained information on the bio-data of the participants. The second section obtained information from the participants on their knowledge of the: pharmacology (route of administration, dosage, and, adverse effects) of NOAs; and management of complications associated with NOA overdose. The third section obtained information from the participants on the frequency at which they prescribe NOAs to patients.

This study was a survey of nurses, medical doctors, pharmacists, and dentists working in five hospitals situated within the metropolitan city of Sokoto, Nigeria. A total of 188 consenting participants were recruited for this study using simple random sampling technique. Each of the participants was issued a paper questionnaire to fill and return. Only 175 (93.1%) out of the 188 participants returned their questionnaires filled. None of the returned questionnaires was discarded, because all were properly filled.

Data analysis was done using the SPSS version 20 software. The frequency distributions of all variables were determined, and tests of associations between variables were done using the Chi-square test with a p -value of < 0.05 considered to be of statistical significance. The statistical results obtained were presented using tables.

FINDINGS

About four-tenth (36.5%) of the 175 subjects were within the age bracket of 26 to 30 years. 62.3% were males, 45% were nursing officers, and 36% of them had less than six years of experience in clinical practice (see Table 1). None of the surveyed pharmacists strongly disagreed that they were knowledgeable about the metabolism of NOAs, unlike the subjects in other occupational categories ($p < 0.0001$, $df = 12$). Furthermore, less than 40% of all the subjects in each occupational category strongly agreed that they knew the dosage of NOAs ($p = 0.066$, $df = 12$). It is also noteworthy that all of the surveyed dentists knew of the World Health Organization (WHO) analgesic ladder, unlike other subjects in the other occupational categories ($p = 0.001$, $df = 12$) (see Table 2). Interestingly, a range of 30 to 40% of the nurses, medical doctors, and pharmacists surveyed in this study considered tramadol to be a NOA (see Table 3).

Amidst other findings presented in Table 4, it is noteworthy that just only 9.0% and 7.1% of the surveyed nurses and pharmacists, respectively, did not prescribe NOAs to patients (see Table 4).

Paracetamol, ibuprofen, and diclofenac were the top three commonly prescribed NOAs among the subjects (see Table 5). The three most common side effects of NOAs known to the subjects were nausea, vomiting, and peptic ulcer disease (PUD) (see Table 6).

Lastly, the three most common route of administration of NOAs known by the subjects were intramuscular, intravenous, and the oral routes (see Table 7).

Table 1. Bio-data of the subjects (n = 175)

Characteristics	Frequency (%)
Gender	
Male	109 (62.3)
Female	66 (37.7)
Age (in years)	
< 21	1 (0.6)
21 – 25	20 (11.4)
26 – 30	64 (36.5)
31 – 35	51 (29.1)
36 – 40	25 (14.3)
41 – 45	7 (4.0)
>46	6 (3.4)
Not specified	1 (0.6)
Year(s) of practice	
< 1	45 (25.7)
1 – 5	63 (36.0)
6 – 10	47 (26.9)
11 – 15	11 (6.3)
16 – 20	3 (1.7)
>20	5 (2.9)
Not specified	1 (0.6)
Profession	
Nurse	78 (45.0)
Medical doctor	62 (35.0)
Dentist	7 (4)
Pharmacist	28 (16)

Table 2. Knowledge of the subjects about the pharmacology of NOAs and the clinical management of NOA overdose

Questions	Profession of respondents					
	Response	Nurse (N = 78)*	Medical doctor (N = 62)*	Dentist (N = 7)*	Pharmacist (N = 28)*	X2
I am knowledgeable about the metabolism of NOAs	SD	5 (6.4)	3 (4.8)	1 (14.3)	0 (0.0)	< 0.0001, df = 12
	D	11 (14.1)	3(4.8)	0(0.0)	0(0.0)	
	U	21 (26.9)	5(7.7)	0(0.0)	2(7.1)	
	A	40 (51.3)	33 (53.2)	5 (71.4)	17 (60.7)	
	SA	1 (1.3)	18 (29.0)	1 (14.3)	9 (32.1)	
I am knowledgeable about the dosage of NOAs	Total	78 (100.0)	62(100.0)	7(100.0)	28(100.0)	0.066, df = 12
	SD	6(7.7)	3(4.8)	1(14.3)	1(3.6)	
	D	5(6.4)	0(0.0)	0(0.0)	0(0.0)	
	U	11(14.1)	2(3.2)	0(0.0)	1(3.6)	
	A	42(53.8)	36(58.1)	3(0.0)	15(53.6)	
I am knowledgeable about the WHO analgesic ladder	SA	14(17.9)	21(33.9)	3(0.0)	11(39.3)	0.001, df = 12
	Total	78(100.0)	62(100.0)	7(100.0)	28(100.0)	
	Yes	34(43.6)	46(74.2)	7(100.0)	22(78.6)	
	No	27(34.6)	12(19.4)	0(0.0)	3(10.7)	
	Not sure	17(21.8)	4(6.5)	0(0.0)	3(10.7)	
I know how to manage the complications of NOA overdose	Total	78(100.0)	62(100.0)	7(100.0)	28(100.0)	0.251, df = 12
	SD	5(6.4)	2(0.0)	0(0.0)	0(0.0)	
	D	7(9.0)	1(1.6)	0(0.0)	0(0.0)	
	U	14(17.9)	10(16.1)	0(0.0)	5(0.0)	
	A	45(57.7)	36(58.1)	5(71.4)	19(23.2)	
	SA	7(9.0)	13(21.0)	2(28.6)	4(14.3)	28(100.0)
	Total	78(100.0)	62(100.0)	7(100.0)	28(100.0)	

N = Total number of respondents in each category; SD = Strongly disagree; D = Disagree; U = Undecided; A = agree; SA = Strongly agree; X² = Chi square; df = Degree of freedom.

Table 3. Knowledge of the subjects on the drug class of tramadol

Question	Profession of respondents					X2
	Nurse (N = 78)	Medical doctor (N = 62)	Dentist (N = 7)	Pharmacist (N = 28)	Total (N = 175)	
Tramadol is a NOA	Yes	19 (30.6)	0 (0.0)	4 (14.3)	53 (30.3)	< 0.0001, df = 6
	No	40 (64.5)	7 (100.0)	22 (78.6)	96 (54.9)	
	Not sure	3 (4.8)	0 (0.0)	2 (7.1)	26 (14.9)	
	Total	78 (100.0)	7 (100.0)	28 (100.0)	175 (100.0)	

N = Total number of respondents in each category; X2 = Chi square; df = Degree of freedom.

Table 4. Comparison between the frequency of NOA prescription and the profession of the subjects

Question		Profession of respondents					X2
		Nurse (N = 78)	Medical doctor	Dentist	Pharmacist	Total	
How often do you prescribe NOA to patients?	Never	7(9.0)	0(0.0)	0(0.0)	2(7.1)	9(5.1)	0.018, df = 12
	Rare	12(15.4)	1(1.6)	0(0.0)	5(17.9)	18(10.3)	
	Sometimes	33(42.3)	25(40.3)	2(28.6)	9(32.1)	69(39.4)	
	Usually	17(21.8)	25(40.3)	2(28.6)	9(32.1)	53(30.3)	
	Always	9(11.5)	11(17.7)	3(42.9)	3(10.7)	26(14.9)	
	Total	78(100.0)	62(100.0)	7(100.0)	28(100.0)	175(100.0)	

**Table 5. Response of the subjects to the question:
Can you mention three NOA you commonly prescribe to patients?**

Drugs indicated	Profession of respondents				
	Nurse	Medical doctor	Dentist	Pharmacist	Total
Dihydrocodeine	1	1	0	0	2
Morphine	2	0	0	0	2
Paraldehyde	1	0	0	0	1
Tramadol	11	7	0	0	18
Tenoxicam	0	1	0	2	3
Diclofenac	36	44	7	22	109
Mefenamic acid	0	2	0	0	2
Hyoscine hydrobromide	0	2	0	0	2
Pentazocine	4	1	0	0	5
Indomethacin	2	1	0	0	3
Ibuprofen	46	35	5	23	109
Dipyrene	1	0	0	0	1
Piroxicam	18	17	0	6	41
Paracetamol	52	37	5	17	111
Aceclofenac	0	4	1	4	9
Naproxen	0	4	0	1	5
Meloxicam	0	3	1	0	4
Celecoxib	2	2	0	1	5
Ketorolac	0	2	0	0	2
Aspirin	17	10	2	2	31

**Table 6. Response of the subjects to the question:
Can you list six (6) adverse effects of NOAs?**

Side effects	Profession of respondents				
	Nurse	Medical doctors	Dentist	Pharmacist	Total
General					
Fatigue	3	0	0	0	3
Hypothermia	2	0	0	0	2
Malaise	0	0	0	1	1
Weakness	11	0	0	0	11
Edema	0	0	0	2	2
Restlessness	1	0	0	0	1
Hyperactivity	1	0	0	0	1
Cardiovascular					
Cardiac toxicity	0	1	0	0	1
Hypertension	2	6	0	4	12
Heart failure	1	0	0	0	1
Premature closure of PDA	0	4	0	1	5
Abnormal heart rate	0	0	0	1	1
Gastrointestinal					
Indigestion	1	0	0	0	1
Heart burn	7	2	1	1	11
Nausea	35	27	4	13	79
Anorexia	4	0	1	1	6
Vomiting	36	20	3	10	69
Abdominal discomfort	14	7	0	9	30
Abdominal pain	5	4	1	2	12
Dyspepsia	3	2	1	1	7
Melena	0	1	0	0	1

Table 6. (Continued)

Side effects	Profession of respondents				
	Nurse	Medical doctors	Dentist	Pharmacist	Total
Oesophagitis	0	1	0	0	1
Esophageal ulcer	0	1	0	0	1
Constipation	15	6	0	2	23
Diarrhea	10	3	1	4	18
Gastritis	0	13	0	0	13
Gastric cancer	0	1	0	0	1
Hyperacidity	4	0	0	0	4
PUD	6	32	4	15	57
Xerostomia	6	1	0	0	7
Urogenital					
Chronic kidney disease	0	1	0	0	1
Fluid retention	0	0	1	0	1
Urinary intention	1	1	0	1	3
Renal tubular necrosis	0	1	0	0	1
Nephropathy	0	4	0	0	4
Nephrotoxicity	1	11	3	5	20
Acute kidney injury	0	4	0	0	4
Hematological					
Acidosis	1	0	0	0	1
Blood intoxication	1	0	0	0	1
Hemorrhage	9	25	3	12	49
Coagulopathy	0	2	0	0	2
Pancytopenia	0	1	0	0	1
Platelet dysfunction	0	6	0	0	6
Neutropenia	0	1	0	0	1
Blood dyscrasia	1	0	0	0	1
Neurological					
Confusion	2	0	0	1	3
Headache	9	5	1	5	20
Raised ICP	1	0	0	0	1
Insomnia	2	0	0	0	2
Light-headedness	0	0	0	2	2
Loss of consciousness	2	0	0	0	2
Reye syndrome	0	3	0	1	4
Irritability	1	0	0	0	1
Drowsiness	16	3	0	0	19
Vertigo	0	0	0	1	1
Dizziness	18	8	1	9	36
Convulsion	1	1	0	0	2
Nervous disorder	0	1	0	0	1
Cognitive impairment	4	1	0	0	5
Sedation	1	0	0	0	1
Ophthalmologic					
Blurred vision	2	0	0	0	2
Behavioral					
Hallucination	2	0	0	0	2
Euphoria	1	0	0	0	1
Addiction	4	9	1	0	14
Tolerance	1	1	0	0	2
Irrational talk	2	0	0	0	2
Anxiety	2	0	0	2	4
Dermatological					
Angioedema	0	1	0	0	1

Side effects	Profession of respondents				
	Nurse	Medical doctors	Dentist	Pharmacist	Total
Pruritus	6	1	1	0	8
Urticaria	0	6	1	3	10
Itching	4	0	1	0	5
Otorhinolaryngological					
Tinnitus	1	1	1	0	3
Immunological					
Steven-Johnson syndrome	0	3	1	3	7
Allergy	1	5	2	1	9
Hypersensitivity reaction	1	2	0	1	4
Anaphylactic reaction	1	1	0	0	2
Respiratory					
Asthma	0	8	0	4	12
Respiratory depression	3	1	0	0	4
Others					
Tissue necrosis	1	0	0	0	1
Drug interaction	0	1	0	0	1
Metabolic disorders	1	0	0	0	1

PDA = Patent ductus arteriosus; GERD = Gastroesophageal reflux disease; ICP = Intracranial pressure; PUD = Peptic ulcer disease.

**Table 7. Response of the subjects to the question:
Can you list seven (7) routes of administration of NOAs?**

Routes of administration indicated by respondents	Profession of respondents				
	Nurse	Medical doctor	Dentist	Pharmacist	Total
Intravenous	65	53	7	26	151
Intramuscular	61	55	7	27	150
Intra-articular	0	2	1	0	3
Intra-mucosal	2	1	0	0	3
Buccal	0	0	1	0	1
Oral	71	55	7	27	160
Intra-capsular	0	1	0	0	1
Superficial	3	0	0	0	3
Drop	0	1	0	0	1
Sublingual	7	15	2	2	26
Intra-vaginal	3	0	0	0	3
Intra-peritoneal	0	1	0	0	1
Rectal	38	30	3	20	91
Topical	21	26	1	9	57
Intra-theal	9	9	0	2	20
Intra-nasal	1	3	0	0	4
Otic route	1	0	0	0	1
Transdermal	16	10	4	9	39
Intra-cordal	1	0	0	1	2
Subcutaneous	17	8	3	5	33
Inhalational	8	1	0	1	10
Epidural	0	1	0	1	2
Intra-osseus	0	0	1	0	1
Spray	5	2	0	0	7
Aerosol	2	0	0	0	2
Intra-lesional	0	1	0	0	1
Intra-ocular	1	2	5	0	8

DISCUSSION

This study surveyed a sample of nurses, dentists, medical doctors, and pharmacists working in five major hospitals situated within the metropolitan city of Sokoto, Nigeria, on their knowledge of the pharmacology of NOAs. The significance of this study was that it provided information on subjects' level of knowledge on NOAs (the NOAs are the first line of drugs in pain management [8]).

Pain is a common symptom in many disease conditions. In patient management, pain control is a very important aspect that needs to be put into consideration. Pain management in a hospital setting involves a multidisciplinary approach. Starting from the doctor, after clinical diagnosis has been made, analgesics are prescribed to the patient in a prescription note. Thereafter, the drugs are dispensed by the pharmacist before being finally administered by the nurse.

Based on the above, a clinical practitioner needs to have a very sound knowledge of the pharmacology of NOAs. From the findings made in this study, it can be said that the knowledge of many of the subjects was inadequate. First of all, not all of them had sound knowledge of the metabolism and dosage of NOAs. This is noteworthy because these individuals are actively involved in patient management; hence their knowledge deficits in pain management may tell negatively on the proper management of their patient.

Secondly, some of the subjects did not know the class of analgesics where tramadol belongs to, as many of them considered tramadol to be a NOA. Tramadol is an OA which is known to cause dependence [9, 10]; it is also one of the abused drugs in the environment where this study was carried out [11]. Unfortunately, the wrong understanding of tramadol as a NOA among the subjects might have made some of them prescribed this drug irrationally to patients increasing such patients' level of risk of developing drug addiction to tramadol.

Thirdly, some of the subjects demonstrated poor knowledge of the adverse effects of NOAs. For instance, some of them mentioned addiction, tolerance, euphoria, and hallucination as adverse effects of NOA, meanwhile NOAs are not known to have addictive or psychedelic effect [12, 13]. Furthermore, the most commonly prescribed drugs among the respondents were ibuprofen, diclofenac, and paracetamol. Diclofenac and Ibuprofen are popularly known to cause drug-induced peptic ulcer [14]; possibly, some of these respondents may not know of this adverse effect.

Fourthly, some of the subjects in this present study had poor knowledge about the route of administration of NOAs. It is noteworthy that some of them highlighted some wrong routes of administration such as "spray," "epidural," "intra-vaginal," and "intra-capsular," to mention a few.

Based on the above findings, authors conclude that the surveyed clinical practitioners in this present study demonstrated inadequate knowledge of the pharmacology of NOAs. Authors would like to recommend that continual medical education (CME) programs (such as workshops, and seminars) on the use of NOAs should be organized for this population group. By doing so, their knowledge will be updated on the use of these drugs in patient management; hence improving the quality of services they render to the sick.

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Authors declare that they have no competing interest regarding this study.

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Chapter 376

NECK CIRCUMFERENCE AS A SCREENING INSTRUMENT FOR OVERWEIGHT AND OBESITY IN NIGERIAN SECONDARY SCHOOL ADOLESCENTS IN AN URBAN AREA

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ABSTRACT

Overweight and obesity are on the increase worldwide and the adolescent population is of special concern. Methods of assessing overweight and obesity are being explored but neck circumference has not been widely investigated in adolescents. Objective: This study aimed at assessing neck circumference as a simple screening tool for overweight and obesity among Nigerian adolescents. Study group and Methods: A cross sectional survey was conducted among 897 adolescents aged 10-19 years in urban Lagos, using a stratified, multistage sampling method. Overweight and obesity were defined using the criteria by the United States Center for Disease Control. Student t test was used for continuous data and Pearson correlation coefficient for exploring the relationship

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between neck circumference and other variables. Receiver operating characteristic analysis was used to evaluate optimal neck circumference cutoffs for overweight or obesity. Results: 64 adolescents (7.1%) were overweight while those with obesity were 33 (3.7%). Neck circumference was positively correlated with age and Body Mass Index. There were significant differences in the neck circumferences of those that were overweight or with obesity compared to those with normal weight. The cutoff ranges for overweight/obesity per adolescent period were 33.95 to 36.95cm in males and 31.05 to 33.40cm in females. Sensitivities were 70-96.6% while specificities were 60.2-87.7%. Conclusions: Neck circumference is a simple and reliable tool which could be used to screen for overweight and obesity in Nigerian adolescents.

INTRODUCTION

Overweight and obesity have become major public concerns worldwide [1] as they are being reported increasingly in developed and recently in developing countries [2] including Nigeria [3]. The adolescent population is of special concern because the health and mortality risks of these phenomena are higher when developed during this period compared to development in adulthood [4]. Therefore, screening and detection of adolescent overweight and obesity are important as there are strategies to manage them [4]. Furthermore, a preliminary step towards curtailing the obesity epidemic is to provide monitoring tools that are cost effective, quick, easy to use, and acceptable to both recipients and health care practitioners [1].

Weight status is currently being described using the body mass index (BMI) [5], which in children and adolescents, varies with age and gender [5]. It has however been criticized for its reduced ability to describe central fat with which the greater health risks of overweight and obesity are associated [6] and for its time consuming derivation [7], amongst other things. Hence, simple, acceptable, quick and reliable methods of assessing overweight and obesity are being explored [7].

The neck is an easily accessible part of the body and its measurement is simple, quick and inexpensive [1, 7]. Limited studies have been documented on the use of neck circumference (NC), to identify overweight and obesity [1, 7, 8]. However, NC has not been investigated as a screening tool for overweight and obesity in Nigerian adolescents. The aim of this study is to determine the usefulness of neck circumference as a screening tool for overweight and obesity among Nigerian adolescents.

OUR SURVEY

A cross sectional survey was conducted from March to July 2013, among a representative sample of 897 adolescents aged 10-19 years in urban Lagos, using a stratified, multistage sampling method. Metropolitan Lagos is said to have captured 36.8% of Nigeria's urban population [9] making it the nation's largest urban population. The multistage sampling method included simple random, stratified random, systematic random and probability proportional-to-size (PPS) sampling techniques employed in the different stages.

Ethical and administrative approvals were obtained from the Health Research and Ethics Committee of the Lagos University Teaching Hospital and the Lagos State Ministry of Education, respectively.

Only those who satisfied the inclusion criteria were enrolled for the study. These criteria included subjects in the age group 10-19 years, consent from parents or guardians, assent from subjects and completed questionnaires. Exclusion criteria applied were possession of neck masses or deformities and history of or features suggestive of chronic ill health such as sickle cell disease and poorly controlled bronchial asthma.

Measurements

The selected study participants had their anthropometries determined. Trained volunteer measurers took the anthropometric measurements which included weight, height and neck circumference. These three measurements were taken using standard methods, according to the protocols recommended in the International Standards for Anthropometric Assessment published [10].

Body Mass Index (BMI)

BMI was calculated using a standard formula:

$$\text{BMI} = \text{Weight (kg)} / \text{height}^2 (\text{m}^2) \text{ in kg/m}^2$$

This was done with the aid of the Children's BMI Tool for Schools [11], a software produced by the United States Centre for Disease Control. Adolescents with BMI at 85th to just below the 95th percentile were said to be with overweight while those with BMI at 95th percentile and above were with obesity.

Data Analysis

The data was analyzed using the statistical software package SPSS Version 17.0. Mean with standard deviation were generated as necessary for age and gender specific anthropometric indices. Tests of statistical significance included Student's t test for continuous data and chi-square test for discrete data. Pearson correlation coefficient was used to explore the association between neck circumference and other continuous variables.

Receiver operating characteristic (ROC) analyses were used to determine the predictive validity of neck circumference and also evaluate optimal cut off values for adolescents with overweight and obesity in the different age categories. ROC curves assess the ability of a screening test to diagnose an outcome correctly, with reference to a gold standard.

The essentials of ROC analysis include [12] the sensitivity, specificity, the positive (PPV) or negative predictive value (NPV) of the test, the likelihood ratio for a positive (LR+) or a negative (LR-) test, the ROC curve and its area under the curve (AUC). Sensitivity and

specificity are usefully combined in likelihood ratios. A high likelihood ratio for a positive result and a low likelihood ratio for a negative result indicate that a test is useful [12]. The ideal test would have an AUC of 1 while a random guess would have an AUC of 0.5. Hence, AUC values closer to 1 indicate a test is useful. Probability values less than 0.05 were accepted as statistically significant.

FINDINGS

Eight hundred and ninety-seven students, selected from public and private schools, participated in the study. Of these, ninety seven were either overweight or obese based on defined BMI criteria [11], making the overall prevalence of overweight and obesity 10.8%. Prevalence of obesity was 3.7% (thirty-three) while that of overweight was 7.1% (sixty-four).

Body Mass Index Categories in Relation to Gender (See Table 1)

This shows the overall prevalence of overweight and obesity along gender lines.

Table 1. Body mass index categories in relation to gender

Gender	BMI Percentile		Total
	<85 th Percentile	≥85 th Percentile	
Female	474 (87.13%)	70 (12.87%)	544 (100%)
Male	326 (92.35%)	27 (7.65%)	353 (100%)
Total	800 (89.2%)	97 (10.8%)	897 (100%)

Chi-square test (χ^2): 6.046, p value = 0.014.

Table 2. The neck circumference of study participants in relation to age and gender

Age (years)	Male		Female		t	p
	n	Mean ($\pm$ SD) cm	n	Mean ($\pm$ SD)cm		
10	12	30.49 (2.50)	12	30.50 (1.76)	-0.021	0.98
11	23	29.68 (2.86)	39	30.15 (2.81)	0.436	0.67
12	48	30.80 (2.34)	83	30.80 (2.58)	-1.014	0.316
13	48	31.68 (2.87)	88	30.86 (2.18)	-1.046	0.301
14	44	32.19 (2.78)	84	30.48 (2.09)	-3.306	0.002
15	60	33.30 (2.80)	109	31.34 (2.33)	-4.042	<0.001
16	51	34.11 (2.58)	66	31.17 (2.23)	-6.454	<0.001
17	37	35.09 (2.55)	34	31.37 (2.14)	-7.496	<0.001
18	20	34.87 (2.04)	20	31.32 (2.22)	-6.697	<0.001
19	10	36.85 (3.83)	9	31.94 (3.27)	-2.708	0.027
All	353	32.77 (3.17)	544	30.93 (2.35)		

Neck Circumference Range in Relation to Age and Gender (See Table 2)

The mean NC ($\pm$ S.D) for all males 32.77(3.17) cm while that for all females was 30.93(2.35) cm. From the ages of 10 to 13 years, the mean NC values in males and females were not significantly different. However, from the age of 14 to 19 years, the mean NC values of males were significantly higher than those of females ($p < 0.001$ to $p = 0.027$).

Neck Circumference Range in Relation to Age, Gender and Body Mass Index Categories (See Table 3)

Table 3 shows that the mean NC ($\pm$ S.D) of all adolescent males with BMI <85th percentile was 30.05(2.03) cm while in those with BMI $\geq$ 85th percentile it was 35.5(3.09) cm ($p = <0.001$). For the adolescent females, these were 29.23(1.95) cm and 33.76(2.54) cm respectively ($p = <0.001$). Thus, there was a significant difference in the NC of subjects in the two BMI categories in both genders.

Table 3. Neck circumference of study participants in relation to age, gender and body mass index categories

Age (years)	Males				Females			
	<85 th percentile		$\geq$ 85 th percentile		<85 th percentile		$\geq$ 85 th percentile	
	Mean ($\pm$ SD)cm n		Mean ($\pm$ SD)cm n		Mean ($\pm$ SD)cm n		Mean ($\pm$ SD)cm n	
10	30.10 (1.49)	10	32.55 (2.05)	2	29.26 (1.72)	8	32.95 (1.98)	4
11	29.50 (2.92)	21	31.60 (0.42)	2	29.28 (2.06)	31	33.61 (2.59)	8
12	30.56 (2.13)	45	34.46 (2.75)	3	30.18 (1.83)	72	34.84 (3.07)	11
13	31.34 (2.63)	42	34.10 (3.58)	6	30.73 (2.19)	82	32.72 (1.45)	6
14	31.94 (2.56)	42	37.45 (2.19)	2	30.13 (1.79)	75	33.23 (2.46)	9
15	33.02 (2.69)	55	36.40 (2.31)	5	30.96 (1.99)	94	33.69 (2.88)	15
16	33.89 (2.39)	49	39.35 (1.06)	2	30.75 (1.81)	59	34.71 (2.45)	7
17	34.73 (2.46)	32	37.34 (1.98)	5	30.72 (1.48)	26	33.48 (2.68)	8
18	34.86 (2.04)	20	--		31.04 (2.17)	18	33.75 (0.35)	2
19	36.85 (3.83)	10	--		31.94 (3.27)	9	--	
All	30.05 (2.03)	326	35.50 (3.09)	27	29.23 (1.95)	474	33.76 (2.54)	70

t test: -7.328, $p < 0.001$ (Males)

t test: -10.824, $p < 0.001$ (Females)

Correlation Studies

There was significant positive correlation between neck circumference and BMI ($r = 0.538$, $p < 0.001$). When split along gender lines and adolescent periods the correlation is shown in Table 4.

Table 4. Correlation between neck circumference and body mass index in relation to gender and period of adolescence

Age group	Male r	p value	Female r	p value
10 – 13 years	0.556	<0.001	0.673	<0.001
14 – 16 years	0.698	<0.001	0.650	<0.001
17 – 19 years	0.515	<0.001	0.554	<0.001

Optimal Cutoff Values of Neck Circumference For Overweight/Obesity

Table 5 shows the AUC and NC cutoff values with their corresponding sensitivities and specificities in the males per adolescent period. Using the ROC statistical maneuvers, the optimal NC cutoff for overweight and obesity in a boy in middle adolescence is 35.85cm with a sensitivity of 77.8% and specificity of 87.7%. The positive likelihood ratio (LR+) of 6.3, indicates that a boy of 14-16 years with a NC greater than 35.85cm is 6.3 times more likely to be with overweight or obesity than a boy of the same age with NC value less than or equal to 35.85cm. A negative likelihood ratio (LR-) of 0.2 means that a negative result (≤ 35.85 cm) is 0.2 times as likely for a 14-16 year old boy who is overweight or obese as one who is normal weight. Table 6 shows the AUC and NC cutoff values with their corresponding sensitivities and specificities in the females per adolescent period. As was done in the males, the optimal NC cutoff for overweight and obesity in a girl in early adolescence is 31.05cm with a sensitivity of 96.6% and specificity of 65.8%. Also, the LR+ of a girl of in this group (10-13 years) with a NC of > 31.05 cm is 2.8 while LR- is 0.05. Furthermore, though the sensitivities of the proposed cutoff values decrease as age increases, their LR+ are almost the same or increase with a corresponding decrease in LR-, indicating their usefulness.

Table 5. Optimal neck circumference cutoff values for high body mass index in males, their sensitivities and specificities per adolescent period

Age group n(n ⁰) (years)	AUC (95% CI)	Cutoff (cm)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+	LR-
10 – 13 131(13)	0.786 (0.660-0.911)	31.05	84.6	60.2	19.1	97.4	2.1	0.49
14 – 16 155(9)	0.888 (0.786-0.990)	35.85	77.8	87.7	28.1	98.5	6.3	0.25
17 – 19 67(5)	0.774 (0.623-0.926)	36.05	80	69.4	16.7	97.8	2.6	0.29

n(n⁰): total number (number with overweight/obesity), CI: Confidence Interval.

Table 6. Optimal neck circumference cutoff values for high body mass index in females, their sensitivities and specificities per adolescent period

Age group n(n ⁰) (years)	AUC (95% CI)	Cutoff (cm)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+	LR-
10 – 13 222(29)	0.877 (0.825-0.929)	31.05	96.6	65.8	29.8	99.2	2.8	0.05
14 – 16 259(31)	0.834 (0.760-0.908)	31.35	80.6	67.1	25.0	96.2	2.4	0.28
17 – 19 63(10)	0.802 (0.650-0.959)	32.90	70	84.9	46.9	93.7	4.6	0.35

n (n⁰): total number (number of adolescents with overweight/obesity), CI: Confidence Interval.

DISCUSSION

There has been a rising trend in the prevalence of adolescent overweight and obesity globally [13]. This poses major public health concerns because of the adverse associated outcomes such as psychosocial [14], health and socioeconomic consequences [15]. Therefore,

the importance of providing tools that screen and detect these epidemics cannot be over emphasized [1].

Various methods are available to assess body fat and thereby detect overweight or obesity, but for epidemiological purposes, body mass index (BMI) skin-fold thickness measurement, bioelectrical impedance analysis (BIA), waste circumference and waist-hip ratio are some which have been recommended [5, 16 17].

BMI, derived from weight and height, is currently the best available anthropometric estimate of fatness for public health purposes [18] and was used as the gold standard for overweight and obesity in this study. It has the advantages of being simple, easily available, inexpensive, with a high degree of reproducibility but limited because it does not discriminate between fat and muscle, does not correlate with central fat (the index of obesity related health risks) [18] and its derivation is time consuming [7].

BIA, a non-anthropometric tool, is relatively inexpensive (when compared with other non-anthropometric methods) and easy to use [16], but its results are influenced by the environment, ethnicity, phase of menstrual cycle and underlying medical conditions. Hence its measurements should be validated for specific ethnic groups, populations and conditions prior to its use [19].

Waist circumference (WC), an index of central fat distribution, also said to be the best simple anthropometric measure of total body fat and more sensitive than BMI [17] has limited wide-spread acceptance because there is no agreement about landmarks, when to measure it, and what it means [20]. Furthermore, it could be culturally or environmentally problematic as clothes have to be removed for it to be measured accurately [1].

Neck circumference (NC), an index of central fat distribution, was found to be independently related to cardiovascular risk factors in obese adults [21], reported to be a simple and time-saving tool for screening and identifying overweight and obese adults [7] and children [1]. Though said to correlate less with BMI than WC [1, 8], NC, unlike WC, has agreed land marks, is easily accessible in the neck, and clothes don't need to be removed for it to be measured accurately. Lastly, in adolescents, NC was found to show very good inter and intra-rater reliability [22]. Multiple measurements are not required for precision and reliability.

In Nigeria, there's a dearth of studies on indices of central fat in the adolescent population and none has explored the usefulness of NC as a screening tool for overweight and obesity in adolescents, hence the relevance of this study.

This study confirms the presence of adolescent overweight and obesity in Nigeria, albeit at lower rates when compared with the western world and Mediterranean region, consistent with the review stating that countries in sub-Saharan Africa have the lowest prevalent rates of adolescent overweight and obesity [13]. This is because the speed of this epidemic is said to be slower in less economically developed countries predominant in sub-Saharan Africa as a result of the less rapid changes in diet and activity associated with the lower income in these countries [13].

In this study, the mean NC of males and females aged 10 to 13 years were not significantly different, but from the age of 14 to 19 years, the mean NC of males was significantly higher than that of the females. This is consistent with similar studies in children and adolescents in the United States of America [1] and Turkey [8] and may be explained by the fact that male sex hormones (androgens) are associated with deposition of fat in the upper body, of which the neck region is a part of [6]. Female sex hormones on the other hand are

associated with an increase in lower body fat which includes the thighs and gluteal region [6]. Also, pubertal changes in boys, marked by the appearance of secondary sexual characteristics, are usually as a result of increased androgenic secretion from the gonads which begin to be seen at about 11 to 12 years of age [23]. These androgens also cause laryngeal and pharyngeal enlargement in males [24]. As the androgenic secretions continue to increase in the latter adolescent years, it is not surprising that its effect on the neck was evident in the increasing neck circumference of the male subjects in this study, throughout their mid- and late adolescent years.

BMI was found to significantly correlate positively with NC, as was seen in other studies [1, 8]. The fact that NC was significantly different in the two BMI categories studied in both genders (normal and high BMI) indicates that it would do well as marker for overweight and obesity.

This study proposed NC cutoff values for overweight and obesity per period of adolescence, and not per singular age group, as were seen in similar studies carried out in areas of higher overweight/obesity prevalence [1, 8]. This may be useful in places with relatively low prevalence of overweight and obesity so that larger numbers of overweight or obese people are available to evaluate optimal cutoff values, as opposed to the fewer numbers or none that may be available when evaluated per singular age. Secondly, the larger groupings per adolescent period means that fewer cutoff values need to be remembered by a busy clinician who may not have time to refer to a chart which would be a necessity if the cutoff values were provided per singular age group.

ROC analysis routinely provides predictive values for the diagnostic test being evaluated, being NC in this instance. The positive predictive values of NC were low, while the negative predictive values were high. These values depend on disease prevalence and are not unwavering characteristics of the diagnostic test that is being evaluated [25]. Hence, they could be misleading in an area of relatively low prevalence such as Nigeria. A more clinically useful measure is the Likelihood Ratio which is independent of prevalence [25].

With the high sensitivities and less remarkable specificities of the proposed NC cutoff values, along with their high positive likelihood ratios and low negative likelihood ratios, NC can serve as a good screening tool for overweight and obesity in Nigerian adolescents. Further evaluation of those with a positive test based on the NC value can then be carried out with more specific tests of overweight and obesity.

A limitation of this study is that its findings may not be extended to adolescents outside the school community like those already employed or in other institutions of learning.

CONCLUSION

This study has demonstrated that neck circumference is a useful screening tool for obese and overweight adolescents. It is simple and cost effective and so envisaged to be beneficial in primary health care settings. Hopefully this picks-up potential candidates for the two morbidities and avert the more sinister associated complications.

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Chapter 377

SERUM TRIGLYCERIDE-TO-HIGH-DENSITY LIPOPROTEIN CHOLESTEROL RATIO: PROFILE AND ITS USE AS SURROGATE FOR INSULIN RESISTANCE PREVALENCE IN OVERWEIGHT/OBESE ADOLESCENTS

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ABSTRACT

Triglyceride-to-high-density lipoprotein cholesterol (TG/HDL-C) ratio is a cost-effective tool to predict and identify insulin resistance and cardiometabolic risk in overweight/obese children and adolescents. The present study described the pattern and distribution of TG/HDL-C ratio as well as its use in determining the prevalence of insulin resistance in overweight/obese adolescents. *Methods:* In this school-based cross-sectional study, the serum lipid levels (total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), triglyceride (TG), and low density lipoprotein cholesterol (LDL-C) of overweight/obese and normal weight adolescents were measured. The TG/HDL-C ratio was calculated for subjects and controls. Insulin resistance was defined by serum TG/HDL-C ratio greater than 2.27. *Results:* In the overweight/obese participants, 53.1% and 38.8% were in middle and upper tertiles of TG/HDL-C concentration ratios, respectively. The mean TG/HDL-C ratios was higher in overweight/obese than normal weight participants; 1.92 ± 0.64 (95% CI = 1.74-2.10) versus 1.68 ± 0.31 (95% CI =

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1.59-1.77); p-value < 0.05. The prevalence of insulin resistance as defined by TG/HDL-C > 2.27 was significantly higher in overweight/obese than normal weight adolescents; 35.4% (95% CI = 28.6-42.2) versus 12.2% (95% CI = 7.5-16.9); Odds ratio (OR) = 4.0. *Conclusion:* Clinicians can apply TG/HDL-C ratio to the standard lipid screening in order to identify overweight/obese adolescents with increased risk of insulin resistance and cardiometabolic disorders.

INTRODUCTION

The triglyceride-to-high-density lipoprotein cholesterol (TG/HDL-C) ratio reflects the association between triglyceride (TG) and high density lipoprotein cholesterol (HDL-C), depicting the balance between atherogenic and protective lipoproteins [1]. TG/HDL-C ratio has a good correlation with LDL particle size in children and adolescents [2]. This lipid ratio has been found to be a useful marker in detection of early functional and morphological vascular changes as well as nonalcoholic fatty liver disease (NAFLD) in paediatric population [3, 4]. The results of some studies indicate that elevated TG/HDL-C ratio in children and adolescents is associated with increased risk of insulin resistance, high blood pressure, metabolic syndrome and NAFLD [4-7]. In a study in China, it was concluded that TG/HDL-C ratio has a discriminatory power in detecting potential metabolic syndrome in the paediatric age group [8]. In the same study, the authors stated in their conclusion that TG/HDL-C ratio was a better index than homeostasis model assessment insulin resistance (HOMA-IR) for screening for metabolic syndrome in obese children and adolescents. Urbina et al. [9] demonstrated that elevated TG/HDL-C ratio was an independent determinant of arterial stiffness in adolescents and young adults, suggesting that the use of TG/HDL-C ratio may also be helpful in identifying young adults requiring intervention to prevent arteriosclerotic cardiovascular disease. In a study involving Spanish children, aged 2-17 years, it was demonstrated that TG/HDL-C ratio > 2 is an effective and relatively cheap biomarker to identify the early stage of potential metabolic syndrome in overweight/obese paediatric population at any age and pubertal status [10]. Therefore, some researcher have recommended that TG/HDL-C ratio should be routinely determined from traditional serum lipid levels to assess atherogeneity of dyslipidaemias which is critical for prevention of cardiometabolic diseases [4, 5].

The results of several studies have demonstrated that TG/HDL-C ratio is a useful surrogate for insulin resistance in the paediatric age group [3, 6, 11, 12]. The interest in TG/HDL-C ratio as a tool for estimating insulin resistance was because of ease of measurement in routine clinical settings and cost-effectiveness. Within this context, other components of insulin sensitivity indices such as insulin, C-peptide, leptin, cytokines and free fatty acids are more expensive to measure. In resource-limited countries, simple affordable screening tool is an attractive option. There are lines of evidence showing that TG/HDL-C ratio is a relatively simple cost-effective way to identify apparently healthy insulin-resistance children and adolescents with increased cardiometabolic risk [5, 13]. Various cutoff points of serum TG/HDL-C ratio have been used as a surrogate in different studies to define insulin resistance in children and adolescents. In this regard, Pacifico et al. [4] used ≥ 1.98 and Hannon et al. [15] used ≥ 3.0 as definitions, respectively. In two separate studies, serum TG/HDL-C ratio greater than 2.27 was used in identifying overweight/obese children and

adolescents with insulin resistance [7, 14]. The results of a study in Malaysian children, aged 9 to 16 years, revealed that children with insulin resistance had a significantly higher TG/HDL-C ratio than those without insulin resistance [16]. In the same report, the authors stated that the odds of having insulin resistance was about 2.5 times higher for those in the upper tertile of TG/HDL-C ratio compared with those in the two lower tertiles. Di Bonito et al. [5] demonstrated that TG/HDL-C ratio ≥ 2.0 is associated with several cardiometabolic risk factors and preclinical signs of cardiac abnormalities in a group of Caucasian children and adolescents, suggesting that this lipid ratio may also predict insulin-resistance-mediated organ damage. Inter-ethnic differences in muscle, liver and abdominal fat partitioning has been demonstrated, suggesting that the degree of insulin resistance may be different for the same body mass index, depending on ethnicity [17, 18]. It has been reported that TG/HDL-C ratio ≥ 2.2 was significantly associated with impaired glucose tolerance (IGT) in children and adolescents, reflecting its usefulness in identifying overweight/obese individuals at risk of IGT [19] and future type 2 diabetes [20, 21]. To the best of our knowledge, there is no published report on the pattern, distribution and use of TG/HDL-C ratio as a surrogate for identifying insulin resistance in overweight/obese Nigerian children and adolescents. The aim of the present study is to describe the pattern and distribution of TG/HDL-C ratio as well as its use in determining the prevalence of insulin resistance in overweight/obese adolescents.

OUR STUDY

This was a school-based cross-sectional study involving an urban secondary school in Egor Local Government Area (LGA) of Edo State, Nigeria. The study was conducted over one-month period, 1st to 30th June, 2016. Ethical clearance certificate was obtained from Research and Ethics Committee of the College of Medical Sciences, University of Benin, Benin City. The administrative head of the school and the ministry of education gave permission for the conduct of the study. Written informed consent was obtained from the parent(s)/caregiver of each of the study subjects. We obtained verbal consent from each of the participants and emphasized to them that their participation was entirely voluntary.

Study Group and Sampling Technique

In this study, the first secondary school in a list of alphabetically arranged private secondary schools in Egor LGA was selected. The list of private secondary schools was obtained from the Edo State Ministry of Education [22]. Thereafter, students within the age group of 10-16 years were randomly selected. Each of the selected students was given a written note explaining the nature of the study as well as a questionnaire to be completed by their parent(s). The subjects (high BMI, $\geq 85^{\text{th}}$ percentile) and controls (normal BMI, 5^{th} to $< 85^{\text{th}}$ percentile) were matched for age and gender. The socio-economic status and ethnicity of the subjects and controls were largely similar. Excluded from the study were students with positive history or obvious clinical evidence of hypothyroidism, liver disease, chronic kidney disease, Cushing syndrome, diabetes mellitus or who are on drugs such as corticosteroids or oral contraceptives.

Anthropometric Measurements

Following a standard procedure [23] the height was measured to the nearest 0.1 cm, using a Holtian portable anthropometer and the weight was measured to the nearest 0.1 kg, using a Seca Scale Balance with the subject in light clothing and bare foot. If a duplicate measurement differed by > 0.5 cm or > 0.5 kg respectively, a third measurement was performed and the average of the two closest measurements was recorded as the final value. To eliminate inter-observer error, all the anthropometric measurements were performed by one of the authors. The body mass index of each of the subjects was computed, using the standard formula [23]. The blood pressure of the participants was measured by one of the authors and steps were taken to minimize errors.

Blood Sample Collection and Serum Lipid Profile Analysis

Venous blood sample was collected after the details of the intended procedure was explained to the participants. The participants maintained their usual dietary pattern within the past three days preceding the study. Following an overnight fast (at least 12-hour fast), 5ml of venous blood was collected into appropriate sample container without anticoagulant and stored at 8°C. After one hour, all samples were centrifuged at 3000rpm for 15 minutes and the serum aliquots were stored at -20°C until assayed. The serum concentrations of total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C) and triglycerides (TG) and low-density lipoprotein-cholesterol (LDL-C) were determined, using automated analyzer with commercially available kits and following strictly the manufacturer's instructions throughout the assay procedures.

Definitions

TG/HDL-C ratio was calculated as TG(mg/dl) divided by HDL-C (mg/dl). The participants were grouped into tertiles based on their serum TG/HDL-C concentration ratios as follows: lower tertile < 1.2; middle tertile 1.2 to < 2.0; and upper tertile ≥ 2.0 [6]. Participants with TG/HDL-C ratio in the upper tertile were considered as having high TG/HDL-C ratio [5, 6]. Serum TG/HDL-C ratio greater than 2.27 defined insulin resistance [7, 14]. High serum triglyceride concentrations was defined as triglyceride ≥ 130 mg/dl (for children ≥ 10 years old) and low HDL-C concentration as < 40mg/dl, according the criteria proposed by National Heart, Lung and Blood Institute (NHLBI) in 2011 [24]. Normal weight, overweight and obesity were defined as BMI between 5th to < 85th, 85th to < 95th and $\geq 95^{\text{th}}$ percentiles, respectively.

Table 1. Characteristics of the subjects (overweight/obese) and controls (normal weight) according to gender

Characteristics	Subjects Male	Controls Male	t-statistic (p-value)	Subjects Female	Controls Female	t-statistic (p-value)
Mean weight (kg)	52.3 ± 6.4	39.1 ± 7.8	9.158 (< 0.001)	40.6 ± 5.2	36.3 ± 8.4	3.047 (< 0.01)
Mean height (cm)	149.3 ± 6.8	142.4 ± 6.6	5.097 (< 0.01)	146.8 ± 7.3	140.3 ± 5.6	4.945 (< 0.01)
Mean BMI(kg/m ²)	27.32 ± 72	16.8 ± 2.15	9.800 (< 0.001)	28.7 ± 3.3	17.5 ± 3.50	16.300 (< 0.001)
Mean WC (cm)	83.2 ± 4.9	68.8 ± 4.1	15.777 (< 0.001)	88.9 ± 5.2	69.1 ± 6.7	16.342 (< 0.001)
Mean HC (cm)	90.3 ± 10.6	70.8 ± 8.8	9.908 (< 0.001)	102.3 ± 8.7	72.5 ± 8.6	17.052 (< 0.001)
Mean WC/HC ratio	0.90 ± 0.08	0.85 ± 0.05	3.710 (< 0.001)	0.86 ± 0.05	0.80 ± 0.06	5.378 (< 0.001)
Mean SBP (mmHg)	107.3 ± 10.2	103.5 ± 9.9	1.871 (> 0.05)	105.0 ± 9.4	101.5 ± 9.3	1.853 (> 0.05)
Mean DBP(mmHg)	70.0 ± 6.7	63.6 ± 8.8	4.051 (< 0.001)	65.7 ± 9.1	62.1 ± 9.6	1.905 (> 0.05)
Mean TC (mg/dl)	136.3 ± 26.6	124.2 ± 23.8	1.652 (> 0.05)	141.0 ± 25.8	133.2 ± 20.9	1.243 (> 0.05)
Mean HDL-C(mg/dl)	37.0 ± 5.2	37.2 ± 4.6	0.132 (> 0.05)	38.1 ± 6.1	37.1 ± 5.3	0.655 (> 0.05)
Mean TG (mg/dl)	101.8 ± 27.2	90.3 ± 25.6	1.414 (> 0.05)	102.5 ± 23.7	95.5 ± 22.7	1.129 (> 0.05)
Mean LDL-C(mg/dl)	68.5 ± 24.2	65.7 ± 25.8	0.363 (> 0.05)	76.7 ± 20.2	73.1 ± 18.8	0.690 (> 0.05)

WC = Waist circumference; HC = Hip circumference; SBP = Systolic blood pressure; DBP = Diastolic blood pressure.

Statistical Analysis

The data were collated and entered into an Excel spread sheet. Accuracy of the data entered was double checked. Subsequently, data were analysed, using Microsoft Excel and SPSS (Statistical Package for Social Sciences) version 20.0. The descriptive statistics reported are mean, standard deviation, confidence intervals, tertiles and percentages. Differences between means were tested with t-test and proportions were tested using Z-test. Significant p-values were set at < 0.05.

FINDINGS

A total of 98 (49 subjects and 49 controls) students were investigated. There were 29 girls and 20 boys in each of the two groups. The mean age of the participants was 12.1 ± 1.2 years. The characteristics of subjects and controls are displayed in Table 1. Overweight/obese participants had a significantly higher mean BMI and waist circumference.

As shown in Table 2, 38.8% of overweight/obese participants were in the upper tertiles of TG/HDL-C concentration ratio. The mean TG/HDL-C ratio was higher in overweight/obese than in normal weight adolescents; 1.92 ± 0.64 (95% Confidence Interval, CI = 1.74-2.10) versus 1.68 ± 0.31 (95% CI = 1.59-1.77); t-statistic 2.362, $p < 0.05$. Table 3 shows that the prevalence of insulin resistance (TG/HDL-C ratio > 2.27) was 35.4% (95% CI = 28.6-42.2) and 12.2% (95% CI = 7.5-16.9) in overweight/obese and normal weight adolescents, respectively; Odds ratio (OR) = 4.0. When TG/HDL-C ratio ≥ 3.0 was applied as cutoff point for insulin resistance, only two (4.1%) overweight/obese but none in normal weight group demonstrated insulin resistance. In both overweight/obese and normal weight groups none had serum triglyceride level equal or greater than 130 mg/dl.

Table 2. Frequency of tertiles of TG/HDL-C concentration ratios in overweight/obese and normal weight subjects

Tertiles of TG/HDL-C Ratio	Normal weight (n = 49) No (%)	Overweight/obese (n = 49) No (%)	Z-statistic (p-value)
Lower (< 1.2)	9(18.4)	4(8.2)	1.504(>0.05)
Middle (1.2 to < 2.0)	23(46.9)	26(53.1)	0.615(>0.05)
Upper (≥ 2.0)	17(34.7)	19(38.8)	0.421(>0.05)

TG = Triglyceride; HDL-C = High density lipoprotein cholesterol.

Table 3. Prevalence of insulin resistance in overweight/obese and normal weight participants based on TG/HDL-C ratio greater than 2.27

Category of participant	Prevalence of insulin resistance (TG/HDL-C ratio > 2.27) Number Percent	Z-statistic (p-value)
Normal weight (n = 49)	6 12.2	
Overweight/obese (n = 49)	17 35.4	2.802(<0.01)
Total (N = 98)	23 23.5	

TG = Triglyceride; HDL-C = High density lipoprotein cholesterol.

DISCUSSION

Nearly every four out of ten of our overweight/obese adolescents demonstrated upper tertile TG/HDL-C concentration ratios (≥ 2.0) which is considered elevated. Other investigators have reported a similar finding [6]. Considering the report of Di Bonito et al. [5], this finding is worrisome. Di Bonito et al. [5] demonstrated that TG/HDL-C ratio ≥ 2.0 is associated with increased risk of cardiometabolic disorders in a group of Caucasian children and adolescents. In the same study, they found an association with preclinical signs of cardiac abnormalities. The public health implication is that TG/HDL-C ratio in upper tertile constitutes a non-communicable healthcare burden because it may also predict insulin-resistance-mediated organ damage [5]. In addition, some studies have shown that an elevated TG/HDL-C ratio (≥ 2.0) identified the onset of metabolic alterations related to metabolic syndrome (MetS), such as decreased insulin sensitivity and altered lipid profile [5, 10, 25]. The elevated TG/HDL-C ratio found in the present study was mainly due to low serum HDL-C concentrations as none of the participants, in both subjects and controls, had serum triglyceride level in the abnormal range (i.e., ≥ 130 mg/dl in individuals ≥ 10 years old), using the criteria proposed by National Heart, Lung and Blood Institute (NHLBI) in 2011 [24]. The public health implication is that specific dietary modification capable of increasing serum HDL-C level is indicated in our adolescent population.

As in other reports [6], the mean TG/HDL-C concentration ratio was statistically significantly higher in overweight/obese than normal weight adolescents in this study. Further confirming that overweight/obesity is a risk factor for abnormal TG/HDL-C ratio in adolescents.

We found a 4-fold greater odd of elevated TG/HDL-C ratio (>2.27) for overweight/obese than normal weight adolescents. In the present study, as in others [7, 14], TG/HDL-C ratio greater than 2.27 was considered a surrogate for insulin resistance. Based on this criteria, prevalence of insulin resistance was statistically significantly higher in overweight/obese than in normal weight group. Our finding is in consonance with previous reports [6, 13, 19]. Adolescents with such abnormal lipid ratio profile are at increased risk of exhibiting impaired glucose tolerance and may develop type 2 diabetes in future [20, 21]. It has been documented that when insulin sensitivity is impaired, compensatory hyperinsulinaemia is produced. Over time, pancreatic beta cell dysfunction occurs, promoting development of type 2 diabetes [25]. Within this context, TG/HDL-C ratio is a useful clinical tool for identifying adolescents at risk of MetS and low insulin sensitivity [5, 26]. Some pathophysiologic mechanisms have been proposed to explain the link between obesity and insulin resistance. Obesity results in proinflammatory state, starting in metabolic cells (adipocyte, hepatocyte, or myocyte). This is followed by recruitment of macrophages with subsequent release of inflammatory cytokines that predispose toward insulin resistance [27]. Chen et al. [28] have demonstrated that myostatin, a novel skeletal muscle-derived secretory factor has a strong relationship with obesity-associated insulin resistance. A higher ratio of TG/HDL-C implies a poor health status not only because the amount of fat in circulation is larger but also because the amount of healthy cholesterol in circulation is lower. Cardiometabolic risk factors tend to precede the development of atherosclerosis in obese children and adolescents [29]. Therefore, lifestyle modification is required in adolescents with TG/HDL-C concentration ratio > 2.27 . When a higher cutoff point of TG/HDL-C ratio of ≥ 3.0 was applied, the frequency of insulin

resistance was nearly 9 times lower in overweight/obese adolescents, suggesting that TG/HDL-C ratio > 2.27 was a more appropriate cutoff point in the paediatric age group.

Strengths and Weaknesses of the Study

The strength of the study is that the subjects and controls were derived from a single well defined source population. In addition, matching increased the statistical precision of estimates, thereby allowing smaller sample size. The weakness of the study was that the study population was derived from a single school, making it possible that the sample was not representative of adolescents in the source population. Despite this limitation, it provided baseline epidemiological data (the first among Nigerian adolescents) on the subject and could serve as an initial point for future study.

CONCLUSION

In conclusion, clinicians can apply TG/HDL-C ratio to the standard lipid screening in order to identify overweight/obese adolescents with increased risk of insulin resistance and cardiometabolic disorders.

CONFLICT OF INTEREST

We have no conflict of interest in this study.

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Chapter 378

PSEUDOHYPOPARATHYROIDISM: A RARE CAUSE OF HYPOCALCAEMIA

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ABSTRACT

Pseudohypoparathyroidism (PHP) is a rare heterogeneous group of disorders due to genetic defects in the hormone receptor adenylate cyclase system and whose common feature is end-organ unresponsiveness to parathyroid hormone. In all its forms, it is biochemically characterized by hypocalcaemia, hyperphosphataemia and elevated level of serum parathyroid hormone. In this report, we present a case of a 15-year-old Nigerian boy who had symptoms of both acute and chronic hypocalcaemia. He was referred to our hospital because of chest pain. Prior to his referral, he has had an episode of generalized tonic-clonic seizure. Further inquiry revealed history of muscle cramps and pain in the bones and joints. Anthropometric measurements revealed that weight, height and body mass index were all below the 5th percentile for age and gender. Trousseau's sign was positive in the patient. The laboratory findings include hypocalcaemia (serum calcium 0.18 mmol/L), hyperphosphataemia (serum phosphate 11.2 mmol/L), elevated parathyroid hormone (serum parathyroid hormone 7.8 pmol/L) level and normal serum magnesium (serum magnesium 0.72 mmol/L) level. Results of both the renal and thyroid function tests were normal. The diagnosis of PHP was delayed probably because of the rarity and heterogeneity of this clinical entity. Conclusion: Pseudohypoparathyroidism should be considered in any child or adolescent with persistent hypocalcaemia in the presence of elevated serum parathyroid hormone level, particularly if renal function tests and serum magnesium level are normal.

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INTRODUCTION

Pseudohypoparathyroidism (PHP) is a rare heterogeneous group of disorders whose common feature is end-organ unresponsiveness to parathyroid hormone due to receptor or post-receptor defect [1]. In all its forms, it is biochemically characterized by hypocalcaemia, hyperphosphataemia and elevated serum parathyroid hormone (PTH) level [1]. The classification of PHP is based on the phenotype and cellular cyclic adenosine monophosphate (cAMP) response to exogenous parathyroid hormone administration. Phenotypically, some patients have the constellation of features of Albright Hereditary Osteodystrophy (AHO) which includes short stature, obesity, round face, shortened metacarpals and metatarsals and multiple hormonal resistances [1]. PHP is divided into two major groups, types I and II based on renal response to exogenous PTH administration [1]. Type I PHP is further subdivided into types Ia, Ib, Ic [1]. In patients with PHP types Ia and Ic features of AHO and multiple hormonal resistance are present. In contrast, patients with PHP types Ib and type II features of AHO and multiple hormonal resistance are absent [1]. Very recently, the EuroPHP Network proposed a novel nomenclature/classification from PHP to “inactivating PTH/PTHrP signalling disorder (iPPSD)” [2]. According to EuroPHP Network, the merits of the new terminology include (i) defines the common mechanism responsible for all diseases (ii) does not require a confirmed genetic defect (iii) avoids ambiguous terms like ‘pseudo’ and (iv) eliminates the clinical or molecular overlap between diseases. The authors concluded that the use of this nomenclature and classification will facilitate the development of rationale and comprehensive international guidelines for the diagnosis and treatment of iPPSDs [2].

The prevalence of PHP is largely unknown. The reported prevalence rates are 3.4 and 11 per million population in Japan and Denmark, respectively [3, 4]. An extensive search of the literature did not reveal any report on the subject from Nigeria. Thus, emphasizing the rare nature of this clinical entity.

A CASE STORY

A 15-year-old Nigerian boy referred to the Endocrinology and Metabolism unit, University of Benin Teaching Hospital (UBTH), because of persistent symptomatic hypocalcaemia despite treatment with oral calcium and vitamin D3. The patient was referred to UBTH from a private hospital because of recurrent chest pain of two years duration. The chest pain was sharp and retrosternal. In addition, he has recurrent muscle cramps, bone and joint pain which are aggravated by strenuous exercise and writing. In the past one month, the frequency of the muscle cramps, bone and joint pain has increased (coupled with the persistent hypocalcaemia) warranting referral to a paediatric endocrinologist. There is no history of disturbances of taste, smell, vision or hearing. Developmental milestones including pubertal development appear normal. He had an episode of seizure (probably hypocalcaemic) three years ago and no repeats since then. There was no history suggestive of chronic kidney or liver disease. The index patient is the second of three children (all boys) in the family. No family history of similar symptoms. He had an average academic performance. Physical examination revealed an apparently healthy-looking boy with weight 35.5 kg (<5th percentile), height 147 cm (<5th percentile) and body mass index 16.4 kgm⁻² (<5th percentile).

He had a positive Trousseau's sign and no shortening of metacarpals or metatarsals. He has no evidence of dental anomaly or subcutaneous calcification or cataract or moniliasis. His blood pressure was 80/60 mmHg. Examination of the body systems was unremarkable. The results of laboratory investigations showed that serum urea, electrolytes, creatinine as well as urinalysis were all normal. The results of his thyroid function tests were normal. Echocardiogram did not reveal any structural anomaly of the heart. His haemoglobin phenotype is AS. The initial laboratory findings are summarized in Table 1.

Table 1. Summary of initial biochemical results initial

Parameter	Results	Comments
Serum total calcium	0.18 mmol/L	Very low
Serum corrected calcium	0.13 mmol/L	Very low
Serum phosphate	11.2 mmol/L	Very high
Parathyroid hormone	7.8 pmol/L	High
Serum magnesium	0.72 mmol/L	Within normal limits
Serum albumin	4.2 g/L	Within normal limits
Serum alkaline phosphatase	411 μ U/L	Within normal limits
24-hour-urine calcium	1.92 mmol/24hrs	Low
Random blood glucose	5.1 mmol/L	Within normal limits

Table 2. Serial serum calcium and phosphate concentrations

Serial no	Serum total calcium mmol/L	Comments	Serum phosphate mmol/L	Comments
Test 1	0.93	Very low	1.87	High
Test 2	1.33	Low	2.00	High
Test 3	1.70	Low	2.84	Very high
Test 4	1.93	Low	2.13	High
Test 5	1.13	Very low	2.62	Very high
Test 6	1.86	Low	2.17	High

He had correction of the symptomatic hypocalcaemia using intravenous 10% calcium gluconate, followed by maintenance oral calcium but the hypocalcaemia persisted as shown in Table 2. In addition, his serum phosphate levels remained high.

We considered a clinical diagnosis of pseudohypoparathyroidism. Based on this diagnosis, we planned further laboratory investigation. In this regard, the Parathyroid Hormone Response Test with assay of urinary phosphate and cyclic adenosine monophosphate (cAMP) was planned. We were unable to perform this investigation because of inadequate laboratory facility in our hospital and financial constraint prevented using commercial medical laboratories outside. Oral calcium supplement was continued and the vitamin D was changed to oral 1 α -vitamin D (calcitriol).

DISCUSSION

In the index case, the presence of hypocalcaemia, hyperphosphataemia, elevated level of serum parathyroid hormone and normal serum magnesium level without evidence of underlying systemic disorder, such as chronic kidney disease suggested a diagnosis of pseudohypoparathyroidism. In addition, the absence of the phenotypic features of Albright Hereditary Osteodystrophy suggests a subtype diagnosis of PHP type Ib or type II [1]. The

clinical manifestations in our patient included an episode of seizure and recurrent episodes of muscle cramps, pain in the chest, bone and joints. The single episode of seizure may be related to severe hypocalcaemia at that time. His hypocalcaemic condition may have become clinically evident following the pubertal growth spurt, which is known to be associated with a relatively higher calcium requirements [5]. This clinical scenario in our patient is not surprising as Kabicek et al. [6] reported two cases of PHP in two adolescent boys; one with low back pain and the other with seizure. Although vitamin D deficiency with biochemical findings resembling PHP types I and II has been described [7], alone it is unlikely to cause significant hypocalcaemia as observed in our patient without a rise in alkaline phosphatase level. Our patient's serum alkaline phosphatase level was normal, thereby negating the diagnosis of vitamin D deficiency.

The etiologic diagnosis of the persistent hypocalcaemia was delayed for 2 to 3 years in our patient despite several medical consultations. This is not surprising as similar observation has been reported from Italy [5] and India [9]. In the case reported from India, the patient had symptoms of chronic hypocalcaemia for 10 years before diagnosis [9]. The difficulty in diagnosing PHP is due to its rarity as well as the varying phenotypic aspects. The clinical implication is that full biochemical investigation of calcium-phosphate metabolism is required in any child or adolescent with signs and symptoms of hypocalcaemia to avoid missed aetiological diagnosis. In this regard, it is imperative to always measure serum levels of calcium, phosphate, magnesium and parathyroid hormone. In addition, assessment of the renal function is required to exclude hyperphosphataemia secondary to chronic kidney disease [10]. Measurement of serum magnesium is important because low serum magnesium is known to impair both the secretion and function of parathyroid hormone [1].

We encountered some challenges in evaluation and management of the index case. Inadequate laboratory facility prevented us from performing the Parathyroid Hormone Response Test with assay of urinary phosphate and cAMP to distinguish between PHP types I and II and molecular studies (demonstration of the mutated G-protein) to confirm our diagnosis of PHP. The parents of the patient were experiencing difficulties procuring oral calcitriol, which is the preferred form of vitamin D for therapy. Despite this limitation, we are reasonably certain that the patient has PHP (with either types Ib or II being the likely subtype). It is possible that in future, if the novel classification proposed by EuroPHP Network [2] is adopted, more appropriate diagnosis could be achieved with less sophisticated laboratory investigations, particularly in resource-limited countries with inadequate laboratory facilities.

CONCLUSION

In conclusion, the learning point is that full biochemical investigation of calcium-phosphate metabolism is required in any child or adolescent with signs and symptoms of hypocalcaemia to avoid missed aetiological diagnosis. Pseudohypoparathyroidism should be considered in any child or adolescent with persistent hypocalcaemia associated with elevated parathyroid hormone level, particularly if serum magnesium level and renal function are normal.

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Chapter 379

DETECTING AND PREVENTING WHEAT STRIPE RUST EPIDEMICS IN ARGENTINA

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ABSTRACT

Wheat stripe rust (SR), caused by the fungus *Puccinia striiformis* f. sp. *tritici* (*Pst*), is one of the most aggressive crop diseases worldwide that threatens global food security. In Argentina, the disease caused the worst epidemics in 2017 affecting about three million hectares. The occurrence of the epidemics was anomalous, as for 87 years there had not been disease outbreaks of this magnitude. We were able to relate the epidemics to the incursion of new exotic strains of *Pst* into the Argentine wheat-growing regions, where the majority of wheat varieties are susceptible to the disease. In addition, we estimated the impact and chemical control of the disease in the region. Average wheat yield losses were estimated at 3,700 kg ha⁻¹ (53%) in field trials conducted in the epidemic area with a maximum of up to 4,700 kg ha⁻¹ (70%) in the seven most susceptible varieties. This scenario represents a challenge for plant breeders, since the vast majority of wheat varieties are susceptible to the new *Pst* races. Fungicides showed to be highly effective in reducing SR intensity and yield losses, thus they have become the only tool for managing SR when planting SR-susceptible wheat varieties. In this work, we analyze the importance of detection and prevention of SR epidemics in Argentina under the described scenario and within the context of an integrated management of the disease.

Keywords: yellow rust, *Puccinia striiformis* f. sp. *tritici*, epidemiology, fungicides

INTRODUCTION

Importance of Wheat Stripe Rust

Wheat stripe rust (SR), caused by *Puccinia striiformis* Westend. f. sp. *tritici* Erikss (*Pst*), was first described by Gadd and Bjerkander in Europe in 1777 (Eriksson and Henning, 1896) and is widespread in all the wheat- growing regions of the world. Currently, SR is one of the most important and destructive diseases of wheat worldwide. The disease can cause up to 70% yield losses in highly susceptible wheat varieties (Chen and Kang, 2017a). Global yield losses were estimated at more than 5 million tons and annual economic losses at USD 1 billion (Beddow et al., 2015). Historically, wheat stem rust, caused by *Puccinia graminis* Pers. f. sp. *tritici* Eriks. & E. Henn. (*Pgt*), was considered the rust that caused the greatest losses in wheat crops (Beddow et al., 2015). However, in recent years, SR became the disease causing the greatest losses due to the recent epidemics registered around the world (Chen and Kang, 2017a). The SR causal agent, *Pst*, is an obligate biotrophic parasite that has a high variability and adaptability, continuously mutating into new races or pathotypes. This phenomenon is the main cause of the different wheat varieties genetic resistance breakdown by *Pst*. It is estimated that 88% of the world's wheat production is currently vulnerable to the pathogen (Beddow et al., 2015; Schwessinger, 2016). Because of all of the aforementioned characteristics, SR may be considered as the main phytosanitary challenge of wheat cultivation worldwide at present (Hovmøller et al., 2010, Chen et al., 2014, Beddow et al., 2015, Schwessinger, 2016).

The species of rust fungus *P. striiformis* is divided into several formae speciales (special forms) based on host specialization, i.e., varieties within this species (based on host specificity and/or morphological characteristics). It can infect different cereals such as wheat (*P. striiformis* f. sp. *tritici*), barley (*P. striiformis* f. sp. *hordei*), rye (*P. striiformis* f. sp. *secalis*), and different grasses such as *Agropyron* spp. (*P. striiformis* f. sp. *agropyri*) and *Elymus* spp. (*P. striiformis* f. sp. *elymi*) (Chen and Kang, 2017a; Huang et al., 2019). *Pst* is classified as a typical heteroecious, macrocyclic rust since the alternate hosts (*Berberis* spp. and *Mahonia* spp.) were recently identified (Jin et al., 2010; Wang and Chen, 2013). This discovery allows to ponder the impact of potential sexual recombination in generating new and more aggressive strains of the pathogen (Zhao et al., 2016; Mehmood et al., 2020a,b). For the case of Argentina, however, this aspect is unknown and there is no evidence to support that the sexual cycle of *Pst* actually occurs in nature in the Southern Cone of South America. Future research will be key in elucidating this unknown. The urediniospores (asexual spores of the pathogen) can be dispersed by wind over long distances and are responsible for severe epidemics that develop on wheat crops (Hovmøller et al., 2002). Therefore, it is believed that survival and initial inocula of wheat rusts occur on self-sown (voluntary) wheat plants in Argentina and neighbour countries at latitudes where frost does not occur during the off-season.

The SR epidemics that occurred in Argentina during the 2017/2018 growing season, coupled with the resulting yield losses, situate SR as one of the most economically important diseases of wheat in the country. This stems from the fact that wheat is the main cereal crop in the country, with a cultivated area of 6.7 million hectares and a total production of 18.5 million tons, per year (MINAGRI, 2018). This chapter describes how SR became the most

important disease in Argentina upon the incursion of new (exotic) pathogenic *Pst* races into the country. The chapter also addresses how detection and prevention of epidemics play a crucial role in SR integrated management.

Detection and Diagnosis of SR

In general, the geographic location and prevalence of rusts that attack cereals largely depend on the average temperature, the susceptibility of the wheat genotypes that are planted and the races of the pathogen present in each particular growing season. In Argentina, the three rusts that infect wheat are present. The most important is SR (Figures 1 to 6). The second in importance is leaf rust, caused by *Puccinia triticina* Eriks., which is common and endemic to South America (Figures 7 and 8) (Lindquist, 1982; Carmona et al., 2000, German et al., 2007). Finally, not less important is the stem rust, caused by *Pgt*, which can cause devastating epidemics in few days when infecting susceptible varieties (Figures 9 and 10) (Carmona et al., 2020). Leaf rust occurs more frequently than stem rust, but the prevalence and severity of the latter has increased in the last growing seasons in the Argentine Pampas region.

Wheat rusts are easy to distinguish between each other and from other wheat diseases, particularly when the pustules are young. The differences between the three rusts are summarized in Table 1. SR pustules are yellow orange arranged in stripes on leaves (Figure 1). When the disease becomes severe in susceptible varieties, SR can develop on glumes, lemma, palea and awns. The characteristic yellow color can be more easily distinguished during the morning because most spores are produced overnight (Stubbs, 1985; Chen, 2005). Generally, pustules are arranged in lines between leaf veins (Figure 2). However, sometimes uredinia do not appear in linear arrangement, especially in the seedling stage of some cultivars, and could cause the diagnosis to be difficult when trying to distinguish between SR from leaf rust (Figure 3). The same happens when the infection is very severe on the leaves of adult plants where the density of pustules does not allow to clearly distinguish the stripes (Figure 4) (Cheng, 2020). Dead stripes without pustules can often be observed on some leaves, especially after a late fungicide application or in varieties that show some type of resistance (Figure 5). Later, the teleutosoric pustules appear with black teleutospores that are also arranged in the form of stripes. These pustules tend to be more frequently arranged on the upper side of the leaves.

The interaction between the host plant (wheat), the pathogenic organism (causative agents of rusts) and the environment is visibly expressed through signs (pustules) and symptoms (chlorosis). These vary from its absence (immune wheat variety) to its maximum manifestation (susceptible cultivars). Symptoms and signs, therefore, are used to quantify these diseases. The number of pustules per leaf or the percentage of covered leaf area expresses the severity of the disease, while the percentage of plants or leaves attacked represents the incidence. The intensity of the disease is a function of the incidence and severity. The more susceptible the cultivar, the more virulent the rust races will be and if the environmental conditions are optimal for the development of the disease, then the maximum values of severity and incidence will be reached (Reis and Carmona, 2000).



Figure 1. Signs (uredosoric pustules) of stripe rust (SR), caused by *Puccinia striiformis* f. sp. *triticea* (Pst). Author: Di Nubila S., Carmona M.



Figure 2. Signs and symptoms (chlorosis) of SR in a highly susceptible wheat variety in Argentina. Author: Di Nubila S., Carmona M.



Figure 3. Pustules of SR in early vegetative stages of wheat in Argentina. Author: Vettorello L.



Figure 4. Pustules of SR are arranged in lines between leaf veins. Author: Carmona M.



Figure 5. Necrotic stretch marks of SR after fungicide application in Argentina. Author: Carmona M.



Figure 6. Hot spot of SR in the field in Argentina. Author: Vettorello L.



Figure 7. Leaf rust pustules caused by *Puccinia triticina* in Brasil. Author: Reis E. M.



Figure 8. Leaf rust pustules caused by *Puccinia triticina* in a highly susceptible wheat variety in Argentina. Author: Vettorello L.



Figure 9. Stem rust pustules, caused by *Puccinia graminis* f. sp. *tritici*, in Argentina. Author: Carmona M.



Figure 10. Stem rust pustules in a highly susceptible wheat variety in Argentina. Author: Carmona M.

In the particular case of SR, unlike other wheat rusts, at the beginning of the epidemics it is common to observe the symptoms and signs of the disease distributed in groups of few plants in the field, developing the typical infected patches known as “foci” or hot-spots (Figure 6). They can be seen in the distance as islands of yellowish spots or patches, up to 10 meters in diameter, in the middle of a wheat field. The foci pattern in hot spots would appear to be due to a combination of spore biology and morphology, moisture in the atmosphere and to greater susceptibility of upper leaves (Farber et al., 2017). If there is a high relative humidity, as it is frequent in winters of Argentina, most of the urediniospores are grouped together and remain in the air in small groups: they are relatively heavy and quickly fall out of the air, so their propagation takes place mainly over very short distances, generating so-called “hot spots” or foci. These hot-spots or patches can often be mistaken for nutrient deficiencies, waterlogging, or soil defects. Therefore, it is essential that when scouting, disease scouting be directed specifically at those spots. Because of the SR latent period (the time it takes for a spore to penetrate and infect until new pustules with urediniospores are produced), which usually takes between 10 to 14 days, it is very likely that after observing hot-spots, most plants in a whole field plot are infected. On the contrary, if there is not high relative humidity in the air, spores are dispersed in the air in an ungrouped manner and can travel considerably longer distances. This can give a uniform infection or generalized disease pattern development and not patches. SR spreads rapidly in the field and readily to other leaves and plants as infection of susceptible wheat varieties by *Pst* is highly effective. The proximity between wheat plants at normal planting densities (200-300 plants m²) facilitates natural infection and consequently increases the epidemic rate of development.

Table 1. Hosts and symptoms of leaf, stem and stripe rusts

Disease	Pathogen	Primary (uredinal/telial) hosts	Alternate (pycnial/aecial) hosts	Uredospores on primary host ⁽⁶⁾	Teliospores on primary host ⁽⁶⁾	Symptoms
Leaf rust	<i>Puccinia triticina</i> (Pt)	Common wheat (<i>Triticum aestivum</i> L.), durum wheat (<i>T. turgidum</i> L. var. <i>durum</i>), cultivated emmer wheat (<i>T. dicoccon</i>) and wild emmer wheat (<i>T. dicoccoides</i>), <i>Aegilops speltioides</i> , goatgrass (<i>Ae. cylindrica</i>), and triticale (X Triticosecale) ⁽¹⁾	<i>Thalictrum speciosissimum</i> (= <i>T. flavum glaucum</i>), <i>Isopyrum fumarioides</i> ⁽¹⁾	20-28 x 18-22 µm and have a diameter of 15 to 30 µm, subglobose and orange or reddish brown in color, with three to eight germinating pores distributed in their thick equimulate walls.	36-65 x 11-22 µm, bicellular, ellipsoidal, clavulate and pointed.	Typical leaf rust. Isolated or scattered uredinia on upper leaf surface.
Stem rust	<i>Puccinia graminis</i> f. sp. <i>tritici</i> (Pgt)	Common wheat (<i>Triticum aestivum</i> L.), durum wheat (<i>T. turgidum</i> L. var. <i>durum</i>), cultivated barleys (<i>Hordeum vulgare</i> L.), triticale (X Triticosecale) ⁽²⁾	Barberry (<i>Berberis</i> spp.), Oregon grape (<i>Mahonia</i> spp.), and their hybrids (× <i>Mahoberberis</i>) ⁽⁴⁾	17-25 x 18-22 µm, reddish orange, dehiscient and oblong oval.	39-57 X 15 X 18 µm, rounded and flattened at their apices, transversely septate into two cells, the lower one shortly pedicellate	Frequently on stem and spikes (glume and awns). Isolated uredinia on upper and lower leaf surfaces.
Stripe rust	<i>Puccinia striiformis</i> f. sp. <i>tritici</i> (Pst)	Common wheat (<i>Triticum aestivum</i> L.), durum wheat (<i>T. turgidum</i> var. <i>durum</i> L.), cultivated emmer wheat (<i>T. dicoccum</i> Schrank), wild emmer wheat (<i>T. dicoccoides</i> Kom), triticale (X Triticosecale), cultivated barleys (<i>Hordeum vulgare</i> L.), rye (<i>Secale cereale</i> L.), naturalized and improved pasture grass species (<i>Elymus canadensis</i> L., <i>Leymus secalinus</i> Hochst, <i>Agropyron</i> spp. Garetn, <i>Hordeum</i> spp. L., <i>Phalaris</i> spp. L., <i>Bromus unioloides</i> Kunth) ⁽³⁾	Barberry (<i>Berberis chinensis</i> , <i>B. koreana</i> , <i>B. holstii</i> , <i>B. vulgaris</i> , <i>B. shensiiana</i> , <i>B. potaninii</i> , <i>B. dolichobotrys</i> , <i>B. heteropoda</i> , etc.) and Oregon grape (<i>Mahonia aquifolium</i> , <i>Mahonia</i> spp., etc.) ^(3,5)	23-35 x 20-31 µm and have a diameter of 20 to 30 µm, yellowish orange, with thick walls equimulated with 6 to 12 germinative pores.	35-63 x 12-20 µm, subepidermal, frequently on sheaths, clavulate, with rounded apex, similar to those of <i>P. triticina</i>	Systemic uredinia on leaves (stripes) and spikes (glumes and awns)

Source: modified from Roelfs et al., 1992.⁽¹⁾ Bolton et al., 2008.⁽²⁾ Pgt was shown to infect 74 species in 34 genera in artificial inoculations of seedlings, but only 28 of those species belonging to eight genera were known to be natural hosts of the fungus (Leonard and Szabo, 2005).⁽³⁾ Chen et al., 2014.⁽⁴⁾ More than 90 species or varieties of *Berberis*, *Mahonia*, and their hybrids (× *Mahoberberis*) have been found to be susceptible to *P. graminis*; being *Berberis vulgaris* the most important species in North America and Europe (Roelfs, 1985).⁽⁵⁾ At present, 33 species of *Berberis* and *Mahonia* have been reported to be susceptible to *Pst* (Zhao et al., 2016).⁽⁶⁾ Indquist, 1982; Bushnell and Roelfs, 1984; Carmona et al., 2000.

The dispersal of urediniospores can be attributed to wind and rainsplash. Rains can favor the disease not because of its gravitational impact, but because they can guarantee humid hours to facilitate germination. However, excessive or intense rains could eliminate the spore stock in the air (Geagea et al., 1999). Urediniospores of SR can be spread by the wind from a few meters to more than 8000 km in the same growing season (Chen and Kang, 2017a; (Brown and Hovmøller, 2002). They have an adherent mucilaginous membrane and therefore can be dispersed mainly as groups of 2 to 10 spores (Rapilly et al., 1970). In contrast, spores of *Pgt* and *Pt* are mainly removed and dispersed as single spores (Geagea et al., 1997). According to Geagea et al. (1997), wind speed is very efficient at removing *Pst* urediniospores from diseased leaves at a speed of between 3 and 5 m s⁻¹. This dispersal ability causes fields to turn “yellow” in a few days, showing a large number of infected and sporulated wheat leaves. However, viable urediniospores are frequently dispersed within a certain region but may not be successful in initiating an epidemic. This is because wheat cultivars from that region may be resistant to the predominant genotype of the pathogen, environmental conditions after dissemination may be unfavorable or spores may arrive late with no time for the development of the epidemic.

Spore transport through human travel by aircraft can also contribute to the spread of the pathogen between countries. A clearly example was carried out by Wellings (2007) who demonstrated the introduction of *Pst* into Australia in 1979 from Europe, through contaminated passenger clothing.

Occurrence and Development Epidemics of SR in Argentina

According to available historical records, *Pst* was first reported in South America in the early 20th century, with an unknown origin (Rudorf and Job, 1934; Stubbs, 1985). Nevertheless, according to recent multilocus microsatellite genotyping studies, it is hypothesized that *Pst* migrated to South America from northwestern Europe in the early 1900s, probably through human intervention and not by wind (Ali et al., 2014). In Argentina, SR first appeared in 1929 attacking almost 80% of the total wheat grown area (Humphrey and Crowell, 1930). The following year the disease caused severe epidemics causing losses estimated at 2 million tons, representing 30% of the total production of that year (Fernández Valiela, 1979; Lindquist, 1982). At that time, Humphrey and Crowell (1930) suggested the possibility of SR being brought into the country from Europe in shipments containing wheat plant material with urediniospores. According to these authors, the disease was registered in an area of about 10 million hectares. The Tres Arroyos area located southeast of the province of Buenos Aires was one of the most attacked wheat regions at that time. In that location, there were two periods of disease attack: at the beginning of flowering (Zadocks 6.1 stage), by initial infections on lower leaves, and a more severe attack at the milky grain stage (Zadocks 7.5 stage). The spread of the epidemic was favored by the susceptibility of the varieties planted at that time (examples are Klein Record and Klein San Martín). High grain losses caused by SR forced growers to replace the most susceptible (and most planted) wheat varieties to the least susceptible (Fernández Valiela, 1979). Since 1930, the disease had only been sporadic and especially confined to regions with cooler temperatures in the southern wheat growing area of Buenos Aires province (German et al., 2007). Thus, Argentina was

historically considered marginally favorable for the epidemic development of SR due to its climate, except for the southern region of the Buenos Aires province with cooler average temperatures.

After almost 90 years of no epidemic occurrence, the agronomic scenario changed due to the introduction into the country of new races, virulent to the majority of Argentine wheat varieties. It was during the 2017/2018 and 2018/2019 growing seasons that SR was observed in regions with higher mean temperatures than those in south of the Buenos Aires province, where it had not been previously reported. The disease caused serious and widespread epidemics in many wheat growing regions of Argentina, specially in fields with high-water content soils and frequent dew formation. In total, more than 3 million hectares were affected including warmer areas of the Argentine Pampas for the first time. Unusual and early infections of SR were detected at several locations in the Entre Rios, Córdoba, Santa Fe, and Buenos Aires provinces. Typical “foci” or hot-spots were observed at the beginning of epidemics. The disease spread rapidly throughout most wheat-growing areas of the country and the SR was observed on almost all wheat cultivars (Carmona et al., 2019). During these two growing seasons, the Plant Pathology Department of the FAUBA coordinated a *Pst* survey in the Argentine Pampas region. During the first year of sampling, the SR foliar severity ranged from 5% to 50% depending on the particular crop environment and wheat variety. The maximum was registered in Pergamino, Buenos Aires (33°54'59.15"S; 60°27'30.92"W), and the minimum in Landeta, Santa Fe (31°59'00"S; 62°01'36"W). In the second year of sampling, SR foliar severity ranged from <1% in Alejo Ledesma (33°40'51.36"S, 62°37'49.48"W), Ordoñez (32°55'05.36"S, 62°53'59.71"W) and Oro Verde (31°51'24", 60°38'22"), to 80% in Famailá, Tucumán (27°03'14"S; 65°24'11"W). Likewise, samples of Triticale and Candeal wheat affected by SR were detected with a severity range of 1 to 5%.

Argentine *Pst* genetic lineages were analyzed by the Global Rust Reference Center (Aarhus University, Denmark). Annually, the GRRC elaborates a yellow rust genotyping and race analyses report based on a large number of samples being shipped from around the world. Genotyping was based on single sequence repeat (SSR) analysis and race phenotyping was based on bioassays of differential wheat lines using spore samples of recovered, pure isolates grown under strict experimental conditions (Hovmøller et al., 2019). A clear connection between the unusual epidemics and the incursion of new exotic SR strains into Argentina was evidenced. Genotyping results showed that a single genetic lineage named as *PstS13* was prevalent (80% of the sampled localities) in 2017 (Hovmøller et al., 2018). The testing of additional samples from 2018 confirmed the widespread of *PstS13* as it was completely dominating the composition of genetic lineages determined (100% of the sampled localities in Argentina) (Figure 11). Isolates of *PstS13* were first detected on Triticale giving rise to significant epidemics in Northern Europe in 2015. Later it was detected in Italy, Ukraine, Spain, Poland, Netherlands and three Scandinavian countries. Only a single race has been detected in the *PstS13* lineage in 2017 causing severe epidemics on bread wheat and durum wheat in Italy. Significant yield losses caused by highly aggressive *PstS13* isolates on multiple spring wheat (Carmona et al., 2019) and durum wheat (southern Europe) varieties and multiple triticale varieties (northern Europe and South America) were reported so far (Hovmøller et al., 2019). In 2019, a new *Yr10*-virulent variant in *PstS13* was detected in Europe. In Argentina, although only a single race (virulence phenotype: -,2,-,-,6,7,8,9,-,-,-

,-, -, -, -, AvS, -) has been detected irrespective of sampling origin, the determination of the particular race of *PstS13* is pending.



Figure 11a. Location of Argentinean wheat fields in South America sampled for SR epidemic monitoring.



Figure 11b. (Continued).



Figure 11b. Location of wheat fields sampled in 2017 (squares) and 2018 (black dots) in Argentina for SR epidemic monitoring.

A different genetic lineage, *PstS14*, first detected in Europe in 2016 and Morocco, Africa in 2017, was also detected in Argentina in 2017 epidemics with a prevalence of 13% (Hovmøller et al., 2018). Further, another genetic lineage harboring the ‘Warrior’ race, *PstS7*, was detected in only one sample (2.6% prevalence) in Argentina in 2017. The first confirmation of the detection of this lineage in Argentina in a non-epidemic situation was in 2015. The *PstS7* isolates from Argentina (both 2015 and 2017) were unique, diverging by 1-2 alleles from the *PstS7* isolates in Europe and West Asia (Hovmøller et al., 2018). These findings are in agreement with the hypothesis proposed by Ali et al. (2014) that Europe could be the source of origin of the SR populations infecting wheat in South America. Isolates of the *PstS13* lineage were detected in 2017 both in Italy and Argentina causing severe epidemics on wheat. The about 12,000 km separation distance between these geographic regions suggests a high global dispersal capacity of *Pst*. However, this hypothesis has yet to

be demonstrated at least with dispersion prediction models according to the prevailing global circulation patterns.

An important component in the onset and development of rust epidemics is the role of alternate hosts of *Pst*. To date, however, for the case of SR there is no evidence or relationship that secondary hosts may play a key roll in the epidemiology of the disease in Argentina (Carmona et al., 2020), even though SR has been detected in triticale (X Triticosecale), rye (*Secale cereale*) and tricepiro (hexaploid Triticale x octoploid Trigopyre).

Although the information available is not sufficient to fully clarify the epidemiology of the disease in Argentina, we hypothesize that: (i) the recent widespread SR epidemics caused by new aggressive *Pst* strains in Argentina were the result of direct introductions of airborne urediniospores from inoculum source areas in southern Africa, and (ii) the spatio-temporal progress of disease in the wheat growing regions of the country was the result of intermittent spore reintroductions in air parcels or land bridge inoculum accumulation in host areas resulted from short-distance dispersal of spores by surface winds. Research exploring these areas is underway. This analysis paves the way to new studies on control and understanding of the biology of this pathogen.

Preventing SR Epidemics

Wheat SR epidemiology has changed dramatically in Argentina since 2017 in terms of cultivar susceptibility and disease severity. Unlike other regions of the world where SR occurrence has increased during the last 20 years, recent SR epidemics in Argentina were built up over three years and have been the most severe since 1930. It is expected that SR epidemics will continue to occur due to the presence of new SR strains virulent on wheat varieties and because most of the high yield potential wheat cultivars that are planted in the country are highly susceptible to SR. For all this, the risks of SR epidemics and susceptibility response of wheat cultivars to the pathogen strains has become unpredictable for wheat producers and plant breeders.

Integrated management of SR should combine control strategies such as planting SR-resistant wheat varieties, development of local or regional infection risk models to predict SR epidemics, frequent scouting, balanced fertilization, appropriate use of efficacious fungicides (seed and foliar treatment) and development of local or regional decision support tools for timing fungicide applications. It is likely that SR-resistant wheat varieties with appropriate level of durable resistance be developed in the near future. Planting of such varieties should be promoted or encouraged to avoid planting a few varieties with high-yield potential but highly SR-susceptible in the largest proportion of the wheat area. Additionally, it is highly recommended to scout not only SR-susceptible cultivars but also SR-resistant varieties that can be broken down within a few years after their release. Some cultural practices can contribute to the increase of an epidemic if they contribute to create a greater number of infected volunteer plants, vegetating during the period between wheat crops.

The use of fungicides has become one of the most important tools for SR control worldwide, especially when susceptible genotypes are planted. Numerous fungicides formulations are available for SR control in the different wheat growing regions of the world (Carmona et al., 2020). The combination choice of fungicide active ingredients (a.i.), time

and rate of application must be defined for each field depending on the level of genetic resistance to SR of the planted wheat variety, the level of disease intensity and the forecast of weather variables conducive to disease development. One of the most important points is the optimal timing for fungicide application according to scientific criteria. Late fungicide applications are ineffective and have a reduced yield economic response. We proposed the development of a local or regional economic damage threshold (EDT). For example, 10–20% of SR foliar incidence from the Z3.0 wheat growth stage is a preliminary guideline in Argentina (Carmona et al., 2019). Following this recommendation, several field trials with fungicides were carried out. During the 2017/2018 growing season, trials were conducted in Landeta, Santa Fe province, with yield responses to fungicide as high as 3091 kg ha⁻¹ and 4743 kg ha⁻¹ for one and two sprays in susceptible wheat genotypes, respectively. The results indicated that one or two fungicide applications significantly decreased SR intensity and increased the wheat grain yield. In 2019, a field trial was conducted in Bigand, Santa Fe (-35.5963 S, -62.9838 W), in order to determine the effect of different fungicide a.i. efficiency on SR control and its impact on wheat grain yield. Significant differences occurred between treated and untreated plots. One application of Allegro® (kresoxim-methyl 12.5% + epoxiconazole 12.5%) at Z3.1 resulted in 1,323 kg ha⁻¹ yield increase. Treatments with two fungicide applications of Allegro® (kresoxim-methyl 12.5% + epoxiconazole 12.5%) + Opera® (pyraclostrobin 13.3% + epoxiconazole 5%) in Z3.1 and Allegro® (kresoxim-methyl 12.5% + epoxiconazole 12.5%) + Orquesta Ultra® (fluxapiroxad 5% + pyraclostrobin 8.1% + epoxiconazole 5%) in Z3.9 controlled > 90% of the SR severity, with a significant yield increase of 2373 and 2217 kg ha⁻¹, respectively, compared to the untreated control. These data confirm the potentially damaging effects of SR in susceptible wheat varieties in Argentina and the high efficacy of different fungicidal active ingredients for its control. Carmona et al. (2020) recently published a comprehensive review of the impact and role of fungicides in the integrated management of SR. This review further summarizes the registered fungicides and timing of foliar spray that are recommended worldwide.

CONCLUSION

Despite the potential damage that SR can cause in wheat crops in Argentina and elsewhere, and the relatively low cost of fungicides to control the disease effectively, it is likely that Argentina growers will continue to plant high-yield potential, yet highly SR susceptible wheat varieties. Our analysis suggests that to achieve an efficient and complementary management of SR, regional disease early warning system and government programs should be implemented. Efforts must include early monitoring in the growing season, starting in the fields with the highest epidemiological risk, using sentinel plots and weather monitoring. It is emphasized that the quantitative monitoring and image processing of urediniospores efficiently captured from wheat fields could provide critical information for SR prediction (Lei et al., 2018). Further, the need for SR scouting and monitoring for emergence of fungicide resistance are key points to assist growers.

In this review, we have outlined a detailed description of the morphological characteristics that must be recognized for an early diagnosis of SR. Diagnosis should couple visual disease monitoring in wheat crops as well as in volunteer wheat plants where inoculum

could cause primary infections early in the growing season. Our extensive work on chemical control of SR and assessments of economic losses indicate that timing detection of SR and weather monitoring are paramount for fungicide application decisions, which are conducive to prevention of disease or reduction of the amount of initial inoculum.

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Chapter 380

GLYCOENGINEERING OF VACCINES THAT HARNESSING THE NATURAL ANTI-GAL ANTIBODY INCREASES IMMUNE PROTECTION IN VIRAL EPIDEMICS

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ABSTRACT

The main protective mechanism in humans against viral epidemics is the activity of the immune system which produces neutralizing antibodies that prevent the virus from infecting cells and destroy it. The immune system also produces T lymphocytes that kill cells infected by the virus and thus prevent further replication of the virus. In each infected individual there is a “race” between the replicating virus damaging various tissues and the immune system preventing infecting viruses from reaching a lethal mass. In some epidemics or pandemics, the immune system of many individuals fails to “catch up” with the expanding virus populations, resulting in death of the infected person. The development of vaccines prepared of inactivated virus, attenuated virus, or of isolated viral proteins (subunit vaccines) has enabled the “education” of the immune system to fight effectively the infectious virus by inducing expansion of lymphocyte populations that react rapidly against the antigens of the virus. Thus, upon infection, these expanded virus specific lymphocyte populations are activated to neutralize and destroy the virus thereby stopping its replication and preventing its deleterious effects. However, some vaccines are suboptimal and do not elicit a sufficiently protective immune response in many of the vaccinated individuals (in particular in elderly populations). In a number of viral vaccines the low immunogenicity (i.e., efficacy) is caused by the masking (i.e., camouflaging) of vaccinating viral antigens by multiple carbohydrate chains (glycans) forming “glycan shields” that are not recognized by the immune system as foreign antigens (e.g., HIV and SARS-CoV-2 causing the COVID-19 pandemic).

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Immunogenicity of such viral vaccines may be markedly amplified by a novel immunotherapeutic approach which harnesses a natural antibody that is produced in large amounts in all humans who are not severely immunosuppressed. This antibody is called the “natural anti-Gal antibody” and the carbohydrate antigen it binds is the “ α -gal epitope” with the structure Gal α 1-3Gal β 1-4GlcNAc-R. This chapter describes amplification of anti-viral vaccines immunogenicity by modifying the glycans on the glycan shield of the virus, referred to as “glycoengineering.” Such amplification of vaccine immunogenicity is achieved by glycoengineering the vaccinating inactivated virus or its subunit vaccine to present α -gal epitopes. Upon vaccination with these vaccines (called “ α -gal vaccines”), the natural anti-Gal antibody binds to the multiple α -gal epitopes presented on the α -gal vaccine and forms immune complexes with it. The Fc portion of anti-Gal in these immune complexes binds to Fc receptors on antigen presenting cells (APC) and induces extensive uptake of the vaccine by APC, mediated by active endocytosis. In the absence of immune complexes, the uptake is suboptimal due to random pinocytosis. The ensuing extensive transport of these immune complexes to regional lymph nodes by the APC results in 10-200 fold higher antibody and T cell immune response than with vaccines that are not immunocomplexed. This is shown in this chapter with influenza inactivated whole virus and with gp120 envelope glycoprotein of HIV vaccines. Studies in anti-Gal producing mouse experimental model demonstrated a much higher survival of animals immunized with influenza α -gal vaccine and challenged with a lethal dose of the virus, than following immunization with vaccine presenting unmodified glycan shield. This chapter further describes a number of methods for glycoengineering of COVID-19 virus to present multiple α -gal epitopes for amplification of α -gal vaccine efficacy against SARS-CoV-2 infections.

Keywords: viral vaccines, influenza, HIV, COVID-19, SARS-CoV-2, S protein, glycan shield, anti-Gal, α -gal epitopes, glycoengineering, vaccine efficacy

INTRODUCTION

The key prophylactic protective method against infection by epidemic causing viruses which are transmitted from mammalian reservoirs (zoonotic virus) or from infected humans is immunization with a vaccine that elicits an immune response against the virus. Such a protective immune response is mediated by antibodies that neutralize and destroy the virus thus preventing the virus from penetrating into host cells. This protective immune response also includes T cells that identify and kill virus infected cells, thereby preventing further infection of cells and replication of the virus. Viruses causing epidemics usually display poor immunogenicity, i.e., the ability of the immune system to mount a rapid protective immune response is limited. This is because the immune system fails to recognize fast enough the virus as an invading microbial agent that should be destroyed. In each infected individual there is a “race” between the replicating virus damaging various tissues and the immune system preventing infecting viruses from reaching a lethal mass. In lethal epidemics, the immune system of many individuals fails to “catch up” with the expanding virus population, resulting in death of the infected person. Vaccination of populations in danger of being infected by the harmful virus introduces into the vaccinated individual harmless viral proteins (or genes coding for these proteins), thus “fooling” the immune system to sense a viral attack. This enables the “education” of the immune system to fight effectively the infectious virus by

inducing expansion of the lymphocyte populations that react rapidly and specifically against the proteins of the virus (i.e., viral antigens). Thus, upon infection by the lethal virus during an epidemic, the expanded populations of virus specific lymphocytes are rapidly activated to produce antibodies that neutralize (i.e., prevent the virus from attaching to cells and infecting them) and destroy the virus by activation of the complement system to forms “holes” in the envelope of the virus. In addition, virus specific T lymphocytes kill cells infected by the virus, thereby stopping its replication and expansion and preventing further viral deleterious effects.

Some vaccines are not effective enough in eliciting a protective immune response in a significant proportion of the vaccinated individuals (in particular in elderly populations). Among the reasons for this suboptimal efficacy are:

- 1) *Seasonal epidemics* – Changes in viral antigens in some seasonal epidemics (e.g., influenza) which prevent recognition of the infectious virus by the immune system of individuals immunized with vaccines prepared from a previous season virus.
- 2) *Low immune response to new antigens in the elderly*- Some vaccines are less effective in the elderly in eliciting long lasting anti-viral protective immune response than in young populations, as demonstrated with influenza vaccines (Webster, 2000; Katz et al., 2004; Chang et al., 2012). Because of these differences, mortality among the elderly infected during the seasonal outbreak of influenza virus is much higher than among young patients. Moreover, the lower immune response to SARS-CoV-2 infection makes the elderly much more susceptible to the detrimental effects of the virus, as indicated by the much higher mortality rate of COVID-19 among elderly than in young individuals (CDC, 2020; Liu et al., 2020). Among the many reasons for the significantly lower immune response in the elderly are the near complete to complete elimination of the thymus (main site for T cell differentiation) in individuals 65 year old or older (Kendal et al. 1980), telomere erosion in lymphocytes, damaged DNA and mitochondrial disfunction (Akwbar & Gilroy 2020). A common clinical example which demonstrates the differences between the potent immune response in young vs. lesser immune response in the elderly is the replacement of impaired heart valves with porcine heart valve in the two age groups. Because of the extensive immune response against the porcine antigens in young recipients, the porcine heart valve function is impaired in 100% of <35 year old young recipients within <5 years. Therefore, young patients are implanted with mechanical heart valve that requires constant anticoagulation therapy (Wang et al. 2017). In contrast, the very weak immune response against the porcine implant antigens in elderly recipients (>70 year old) enables appropriate function of porcine heart valve implants for 10-20 years.
- 3) *Glycan shields on viruses* – Enveloped viruses usually have carbohydrate chains (glycans) linked to their envelope proteins. In a large proportion of these viruses, the multiple glycans “camouflage” the virus by forming a “glycan shield” that “hides” immunogenic peptides of envelope glycoproteins (Walls et al. 2016; Yang et al. 2020; Watanabe et al. 2020). This camouflaging results in low immunogenicity of vaccines made of such viruses, or of their envelope glycoproteins, leading to low efficacy of the protective immune response elicited by the vaccine. Suboptimal efficacy of viral vaccines was attributed to the glycan shield masking antigens in vaccines of enveloped viruses such as hepatitis C virus vaccine (Ahlén & Frelin

2016), HIV vaccine (Goulder & Watkins 2004; Lewis et al. 2014) and influenza virus vaccine (Wei et al. 2003; Chang et al. 2012; Wei et al. 2010).

All these shortcomings of some viral vaccines raise the need for developing methods that increase immunogenicity and efficacy of vaccines. This chapter describes a method for achieving this objective by altering (called here glycoengineering) the structure of the glycan shield on enveloped virus vaccines, thereby harnessing the immunologic potential of an abundant antibody in humans, called the natural anti-Gal antibody which constitutes ~1% of circulating immunoglobulins. Experimental studies in mice with vaccines described in this chapter, were found to increase immunogenicity of viral vaccines by 10-200 fold. Thus, it is suggested that the proposed glycoengineering may also markedly increase the efficacy of vaccines protecting humans against viral epidemics.

Viral vaccines are usually of three kinds: 1. Vaccines prepared from the inactivated (killed) virus (called inactivated whole virus vaccine), from its proteins (split or subunit vaccine) or from recombinant viral proteins produced in eukaryote or prokaryote expression systems. 2. Gene based vaccines made of gene(s) of viral proteins that are injected into tissues (usually muscles) of the vaccinated individuals for production of the vaccinating protein by the individual's own cells. 3. Attenuated virus vaccines which consists of virus that does not cause the disease but has proteins that immunize the vaccinated individual against the epidemic causing virus. This chapter discusses methods for increasing the efficacy of vaccines included in the first group above and which are prepared against enveloped viruses. The glycoengineering of the vaccine aims to manipulate the glycans on the envelope glycoproteins to present a carbohydrate antigen called the " α -gal epitope," which is the antigen binding the natural anti-Gal antibody. This epitope is illustrated on the right glycan in Figure 1.

Following the injection of virus vaccines (e.g., influenza virus vaccine) into the arm muscle, nothing happens at the injection site other than internalization of the vaccinating envelope proteins or of the inactivated whole virus by antigen presenting cells (APC), such dendritic cells and macrophages. This uptake of the vaccine is mediated by random internalization of small droplets (pinocytosis) of the suspension of vaccinating proteins or inactivate virus that are in the vicinity of the APC. This uptake is nonspecific and the efficacy of internalizing vaccines into APC is moderate. The vaccinating proteins are transported by APC to regional lymph nodes. The APC further process the vaccinating proteins into small peptides which are presented on MHC molecules. These presented peptides interact with the corresponding T cell receptors (TCR) and activate the peptide specific CD4⁺ and CD8⁺ T cells (Banchereau & Steinman, 1998; Zinkernagel et al. 1997). The activated CD8⁺ T cells proliferate, then leave the lymph nodes, circulate in the body, detect and kill cells containing replicating virus. Activated CD4⁺ T cells proliferate and function as helper T cells which help B cells to produce antibodies against the infecting virus, as well as secrete cytokines helping proliferation of CD8⁺ T cells and their maturation into cytotoxic T cells (CTL) that kill host cells infected by the virus.

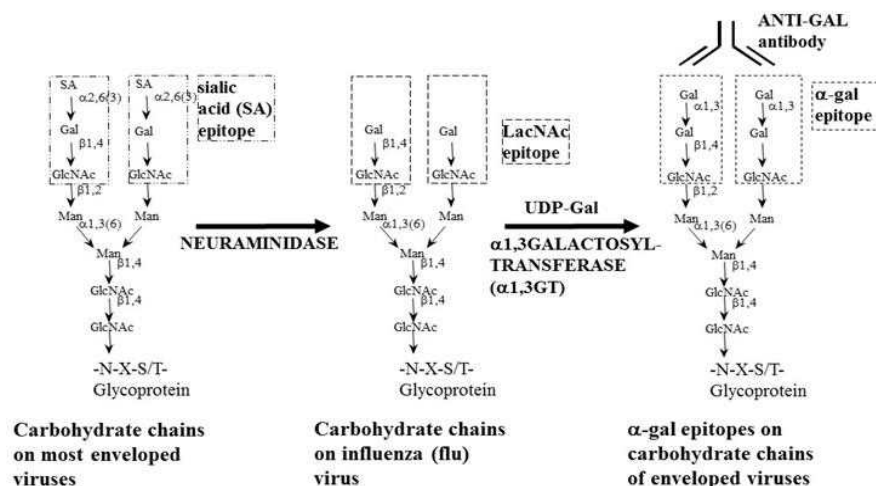


Figure 1. Structure of N-linked glycans on viral envelope glycoproteins and synthesis of α -gal epitopes on these glycans. Left glycan- Carbohydrate chains of the complex type are synthesized on asparagine (N) in the sequon N-X-S/T (asparagine-any amino acid-serine or threonine). Many of these glycans are capped by sialic acid (SA). Center glycan- Sialic acid capping the glycan is removed by neuraminidase to expose the penultimate Gal $\beta 1$ -4GlcNAc-R (N-acetylglucosamine- LacNAc). In glycans of influenza virus the SA is absent because it is eliminated by the viral neuraminidase. Right glycan- Incubation of inactivated virus or soluble envelope glycoproteins carrying the desialylated glycans, with recombinant (r) $\alpha 1,3GT$ and with the sugar donor uridine diphosphate galactose (UDP-Gal), in the presence of Mn^{++} , results in synthesis of α -gal epitopes (Gal $\alpha 1$ -3Gal $\beta 1$ -(3)4GlcNAc-R) on the glycan. These epitopes readily bind the natural anti-Gal antibody, thereby forming immune complexes with viral vaccines presenting α -gal epitopes. From Galili U. *The natural anti-Gal antibody as foe turned friend in medicine*. Academic Press/Elsevier, Publishers, London (2018), page 152.

One of the critical factors in the process inducing a protective anti-viral immune response by vaccination is the extent of vaccine uptake by the APC. As indicated above, one reason for the suboptimal uptake of vaccines by APC is the random pinocytosis which occurs in many cells and results in internalization of vaccinating virus or proteins that accidentally are near the cell membrane. Another reason for suboptimal uptake by APC is the negative charges on viral vaccines. Enveloped virus vaccines usually present multiple sialic acid residues on their glycan shield (with the exception of influenza virus). Examples for such envelope glycoproteins are the spike (S) protein of the SARS-CoV-2 virus causing the COVID-19 pandemic and gp120 of HIV. The sialic acid has a negative electrostatic charge. When approaching the cell membrane of APC, negative charges on the vaccinating virus or viral glycoproteins and those on the cell surface of APC create electrostatic repulsion (zeta (ζ) potential) that deflects the virus or viral glycoprotein and thus decreases uptake of vaccines (Galili, 2018). Increased uptake of vaccines, which results in increased vaccine immunogenicity, can be achieved by formation of immune complexes between the vaccine and the corresponding IgG antibody. The high affinity interaction between the Fc portion of the immunocomplexed IgG molecule and Fc γ receptors (Fc γ R) on the cell membrane of dendritic cells and macrophages results in effective targeting of the immunocomplexed vaccine to APC. Binding of the Fc portion of the immunocomplexed antibody to Fc γ R on the APC generates a signal that stimulates APC to internalize the immunocomplexed vaccine by active endocytosis (Clynes et al. 1998; Schuurhuis et al., 2002; Regnault et al., 1999). The

result of this extensive endocytosis is a marked increase in uptake, processing and presentation of vaccine peptides by APC that leads to increased immunogenicity of the vaccine, thus amplifying its efficacy.

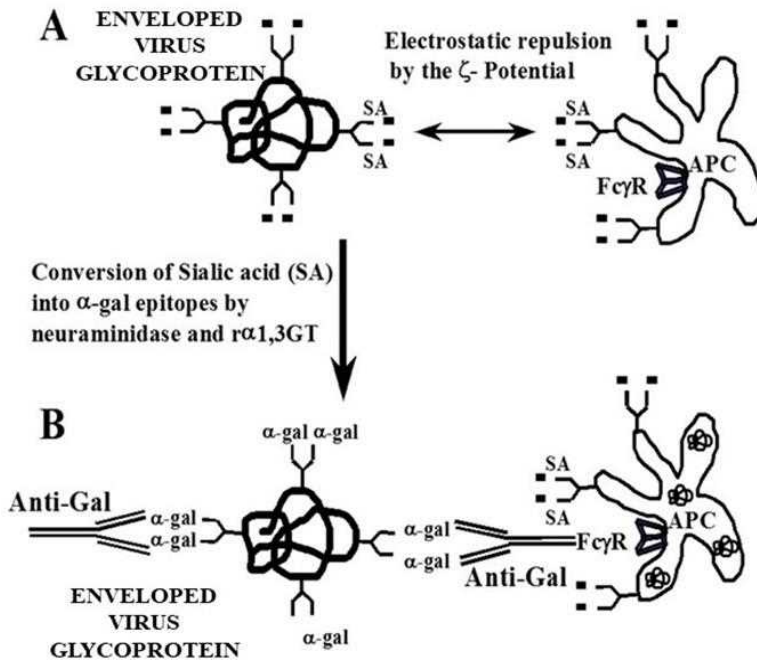


Figure 2. Anti-Gal mediated targeting of vaccinating viral envelope glycoproteins to APC. (A) The negative charges of sialic acid (SA) on the glycan shield of viruses and on the APC surface glycans generate electrostatic repulsion (ζ (zeta)-potential) between the inactivated virus or the virus glycoproteins vaccines and the APC. This electrostatic repulsion decreases the uptake of vaccines by random pinocytosis into the APC. (B) Glycoengineering of the viral glycan shield by replacing SA with α -gal epitopes, eliminates the electrostatic repulsion and enables binding of the natural anti-Gal IgG antibody to the glycoprotein and formation of immune complexes. The binding of the Fc portion of anti-Gal in the immune complexes to Fc γ receptors (Fc γ R) on APC induces extensive uptake of the vaccine by endocytosis into APC thus greatly increasing immunogenicity of vaccines. Modified from Galili U. *The natural anti-Gal antibody as foe turned friend in medicine*. Academic Press/Elsevier, Publishers, London (2018), page 160.

Amplification of the immune response following vaccination with immunocomplexed vaccines in comparison to vaccines delivered without an immunocomplexed antibody has been known for ~60 years. Among the vaccines shown to increase the immune response when immunocomplexed with their corresponding antibodies were tetanus toxoid (Stoner and Terres, 1963; Manca et al. 1991; Gosselin et al. 1992; Fanger et al. 1996), hepatitis B envelope antigen (Celis and Chang, 1984), Venezuelan equine encephalitis virus (Houston et al. 1977), simian immunodeficiency virus (SIV) (Villinger et al., 2003) and *Trypanosoma* (Stäger et al. 2003). The immune response against these vaccines immunocomplexed with the corresponding antibody was reported to be 10-1000-fold higher than with the same vaccine in the absence of immunocomplexing antibody. With the understanding of APC role as cells internalizing vaccines, transporting the internalized vaccines to regional lymph nodes, processing them and presenting the immunogenic peptides to T cells with the corresponding

TCR, it became evident that the Fc portion of the antibody immunocomplexed to vaccines targets the vaccine for effective binding to Fc receptors of APC, induction of extensive endocytosis into APC and maturation of these cells to professional APC (Clynes et al. 1998; Regnault et al. 1999; Schuurhuis et al. 2002).

The use of vaccines immunocomplexed with their specific antibodies has not resulted in their extensive use in the clinic for several reasons: 1. The antibodies for each of these vaccines have to be purified and complexed *in vitro* with the vaccine. Preparation of standardized immune complexes and the preservation of such immune complexes without inactivation of the antibody are difficult. 2. The immunocomplexing antibodies may be available from non-human species (including monoclonal antibodies) which may elicit an anti-antibody immune response in vaccinated individuals. 3. The immunocomplexed antibodies may mask immunodominant peptide epitopes on the vaccinating antigen within the immune complexes, thereby decreasing the efficacy of the vaccine. The present chapter describes a method for targeting immunocomplexed enveloped virus vaccines and avoiding the difficulties listed above by harnessing the natural anti-Gal antibody. Immune complexes are formed at the vaccination site between the endogenous natural anti-Gal antibody of the vaccinated individual and viral vaccines glycoengineered to present the carbohydrate antigen binding anti-Gal, i.e., the α -gal epitope (right glycan in Figure 1). This chapter describes an experimental model that demonstrates the mechanism and efficacy of this method and the marked increase in the immunogenicity of influenza virus and gp120 of HIV vaccines glycoengineered to present α -gal epitopes. Such vaccines are referred to as “ α -gal vaccines.” Since this chapter is written ~10 months into the COVID-19 pandemic, the chapter further describes possible preparation of future α -gal COVID-19 vaccines that harness the natural anti-Gal antibody for the formation of immune complexes targeted to APC.

The method for enhancing immunogenicity of vaccines by glycoengineering them to present α -gal epitopes was originally used for conversion of tumors into vaccines that amplify the immunogenicity of autologous tumor antigens (Galili & LaTemple, 1997; LaTemple et al. 1999; Rossi et al. 2005; Galili et al. 2007; Abdel-Motal et al. 2009a). This chapter demonstrates the use of the same principle in amplifying viral vaccine immunogenicity. Viral α -gal vaccines have not been studied yet in humans. Thus, this chapter includes several figures associated with the studies of α -gal viral vaccines in murine experimental models. The presented results strongly suggest that a similar increased efficacy may be feasible with human viral vaccines glycoengineered to present multiple α -gal epitopes.

THE NATURAL ANTI-GAL ANTIBODY SIGNIFICANCE IN AMPLIFYING α -GAL VACCINE IMMUNOGENICITY

The Natural Anti-Gal Antibody and the α -Gal Epitope

The human immune system constantly produces natural antibodies without active vaccination. The antigens (ligands) of many of the natural antibodies in humans are various carbohydrate antigens (Blixt et al. 2004; Bovin, 2013; Stowell et al. 2014). Many of these antibodies are produced in response to antigenic stimulation by carbohydrate antigens on bacteria of the natural gastrointestinal (GI) flora (Wiener, 1951; Springer, 1971; Hooper &

Macpherson, 2010). Fortuitously, a number of these antibodies, although produced against bacterial carbohydrate antigens, also bind to mammalian carbohydrate antigens produced in species other than humans. These antibodies function as an important immune barrier against zoonotic viruses carrying carbohydrate antigens produce in various mammalian hosts (Galili 2020a). One of the major natural anti-carbohydrate antibodies in humans is the natural anti-Gal antibody (also known as anti- α -galactosyl and anti-Gal α 1-3Gal). Anti-Gal is abundant in human, constituting ~1% of serum IgG, IgM, and IgA immunoglobulins (Galili et al. 1984, Galili, 2013; Hamadeh et al. 1995; McMorro et al. 1997; Parker et al. 1999). Anti-Gal is also found as IgA and IgG antibodies in a variety of body secretions including milk, colostrum, saliva, and bile (Hamadeh et al. 1995). Anti-Gal is found in the blood of individuals of all ages (Wang, 1995) and is produced as the result of continuous antigenic stimulation by carbohydrate antigens on GI bacteria such as *Serratia*, *Klebsiella* and *E. coli* (Galili et al. 1988a; Mañez et al. 2001; Posekany et al. 2002). When human circulating B cells are stimulated to produce antibodies, as many as 1% of these cells produce anti-Gal (Galili et al. 1993). Anti-Gal is a polyclonal antibody (Galili et al. 1984). In blood-group A and O individuals, anti-Gal also comprises >80% of the anti-blood-group B activity (Galili et al. 1987a).

Anti-Gal binds specifically to a carbohydrate antigen called the α -gal epitope, with the structure Gal α 1-3Gal β 1-(3)4GlcNAc-R on glycans linked to mammalian glycoproteins, glycolipids, and proteoglycans (Galili et al. 1985; 1987b; Towbin et al. 1987; Teneberg et al. 1996) (Figures 1 and 2B). The α -gal epitope is abundantly found on cells and on secreted glycoproteins of all mammals that are not monkeys or apes (non-primate mammals including both marsupials and placentals), in lemurs (prosimians that evolved in Madagascar), and in monkeys of South America (New World monkeys) (Table 1) (Galili et al. 1987b, 1988b). In all these mammals the α -gal epitope is synthesized by a glycosylation enzyme called α 1,3galactosyltransferase (α 1,3GT), which catalyzes the synthesis of α -gal epitopes by the second enzymatic the reaction illustrated in Figure 1 (Basu & Basu, 1973; Blake & Goldstein, 1981; Blanken & Van den Eijnden, 1985; Galili et al. 1988b). The α -gal epitope is absent in vertebrates which are not mammals, including birds, reptiles, amphibians and fish, implying that this enzyme appeared early in mammalian evolution before marsupials and placentals diverged from a common ancestor (Galili, 1988b). In contrast to New World monkeys, lemurs and non-primate mammals, the Old World monkeys (monkeys of Asia and Africa), apes, and humans completely lack α -gal epitopes because of inactivation of the α 1,3galactosyltransferase gene (also called α 1,3GT gene, or *GGTA1*) in ancestral Old World primates 20-30 million years ago (Galili et al. 1987b, 1988b; Larsen et al. 1990; Galili & Swanson, 1991; Koike et al. 2002; Lanterni et al. 2002). Instead, humans, apes and Old World monkeys, all produce the natural anti-Gal antibody in large amounts (Table 1) (Galili et al. 1984; 1987b; Teranishi et al. 2002). Because of this distribution of anti-Gal and the α -gal epitope, transplantation of porcine xenografts into Old World monkeys or humans results in rapid (hyperacute) anti-Gal mediated rejection of the graft (Galili, 1993; Good et al. 1992; Cooper et al. 1993; Sandrin et al. 1993). As discussed below, a plausible cause for the evolutionary elimination of the α -gal epitope in ancestral Old World primates could be a virus mediated pandemic which eliminated α -gal epitopes synthesizing primates and survival of few progeny in which the α 1,3GT gene was accidentally inactivated, resulting in production of protective natural anti-Gal antibody.

Table 1. Reciprocal distribution of the natural anti-Gal antibody (Ab) and its ligand the α -gal epitope in mammals

Animal group	α 1,3galactosyl-transferase	α -gal epitope (Gal α 1-3Gal β 1-4GlcNAc-R)	Natural anti-Gal Ab
Nonprimate mammals	+	+	-
Prosimians (lemurs)	+	+	-
New World monkeys	+	+	-
Old World monkeys	-	-	+
Apes	-	-	+
Humans	-	-	+

Evolutionary Causes for the Appearance of the Natural Anti-Gal Antibody

Mammals synthesizing α -gal epitopes are immunotolerant to this carbohydrate antigens which is a self-antigen in them and thus, do not produce the natural anti-Gal antibody. Since New World monkeys and nonprimate mammals synthesize the α -gal epitope, it is probable that ancestral Old World primates also synthesized this antigen. The complete lack of α 1,3GT activity in Old World monkeys, apes and humans (Table 1) implies that the α 1,3GT gene was inactivated and thus the α -gal epitope was eliminated in ancestral Old World primates after they were geographically separated from New World monkeys. A plausible scenario for this evolutionary event is the elimination of Old World primates synthesizing the α -gal epitope in the course of an epidemic occurring in the Africa-Eurasia land mass, mediated by a virus that was lethal to primates. However, few primate progeny in which the α 1,3GT gene (*GGTA1*) was accidentally inactivated by one or few base deletion mutations, survived this putative epidemic. In the absence of α -gal epitopes, these progeny lost the immune tolerance to the α -gal epitope and produced the natural anti-Gal antibody due to antigenic stimulation by GI bacteria. Synthesis of glycans on viral glycoproteins is mediated by the host cell glycosylation machinery. Therefore, virus replicating in the ancestral primates synthesizing α -gal epitopes and killing them also presented this epitope on its envelope glycoproteins. This resulted in neutralization and destruction of such viruses by anti-Gal following infection of progeny lacking α -gal epitopes and producing this antibody. Ultimately, this evolutionary process resulted in complete replacement of α -gal epitope producing Old World primates with primates lacking this epitope and producing the natural anti-Gal antibody (Galili, 2019). New World monkeys evolving in the continent of South America and lemurs evolving in the island of Madagascar were not subjected to this selective process because of the oceanic barriers between them and the primates in Eurasia-Africa. Anti-Gal was also found to bind and kill some protozoa such as *Plasmodium* (Yilmaz et al. 2014), *Trypanosoma* (Portillo et al. 2019) and *Leishmania* (Iniguez et al. 2017). Thus, such pathogens may also be considered as a theoretical cause for the elimination of ancestral Old World primates synthesizing the α -gal epitope and survival of the few progeny producing natural anti-Gal antibody. However, the complete elimination of primates synthesizing α -gal epitopes in all geographic and climate zones of Eurasia-Africa suggests that a virus with very high capacity of spreading throughout populations, is a more likely candidate for a pathogen mediating this selection process this land mass.

Hypothesis on Anti-Gal Mediated Amplification of Viral Vaccine Immunogenicity

The observations above on increased immunogenicity of vaccines administered as immune complexes with their corresponding antibodies suggest that amplification of vaccine immunogenicity may be achieved by formation of immune complexes also with the natural anti-Gal antibody, provided that the vaccines include glycoproteins that carry multiple α -gal epitopes on their glycans. Such an α -gal vaccine in the form of inactivated whole virus may be used as an example. It could be hypothesized that immunization with inactivated virus glycoengineered to present α -gal epitopes will result in the formation of immune complexes between anti-Gal and the α -gal vaccine at the vaccination site. The immunization process by α -gal vaccines is hypothesized to occur in several steps which are illustrated below in Figure 3.

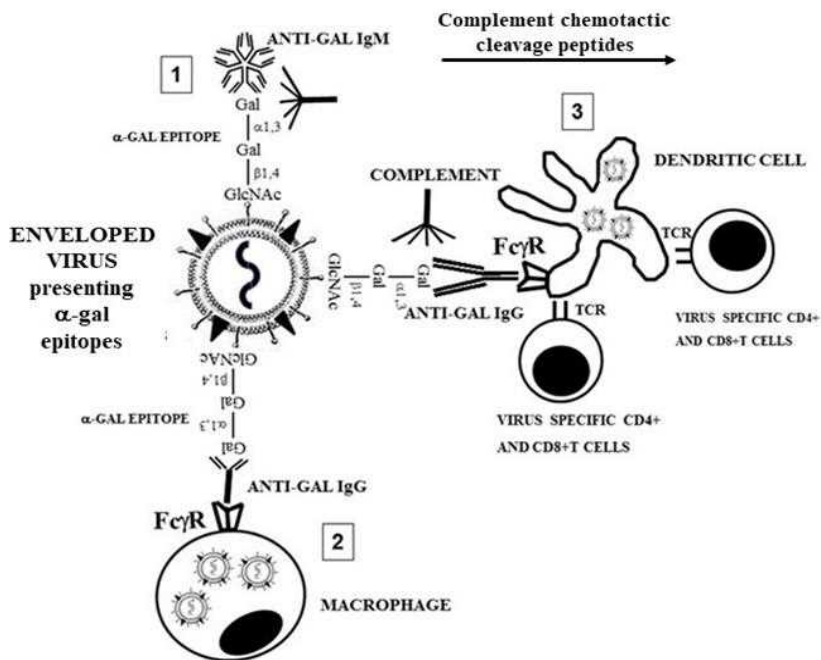


Figure 3. Suggested mechanism for amplification of α -gal vaccine immunogenicity by anti-Gal mediated targeting to APC. Inactivated whole virus vaccine presenting multiple α -gal epitopes is used as a vaccine example. Step 1- The injected virus vaccine forms immune complexes with anti-Gal IgM and IgG molecules thereby activating the complement system to generated complement cleavage peptides C5a and C3a. These chemotactic peptides recruit dendritic cells and macrophages that function as APC. Step 2- Anti-Gal IgG coating the virus targets it for extensive uptake by the recruited APC, mediated by Fc/Fc γ receptors (Fc γ R) interaction between the immunocomplexed vaccine and the APC. Step 3- APC transport the internalized virus vaccine to the regional lymph nodes and process the virus antigens. Within the lymph nodes, APC present the immunogenic viral peptides on MHC molecules. These peptides engage CD4⁺ and CD8⁺ T cells with the corresponding TCR and activate these lymphocytes which proliferate and leave the lymph nodes. TCR- T cell receptor. Modified from “*The natural anti-Gal antibody as foe turned friend in medicine*” by U. Galili, 2018, Elsevier/Academic Press, p. 153.

Step 1

Formation of immune complexes between anti-Gal IgM and IgG molecules and the α -gal vaccine will activate the complement system and generate chemotactic complement cleavage peptides such as C5a and C3a which recruit APC, including macrophages and dendritic cells, to the vaccination site.

Step 2

Anti-Gal IgG molecules bound to α -gal epitopes of the vaccinating virus glycoproteins will target the vaccine for extensive uptake by the recruited APC as a result of the interaction between the Fc portion of anti-Gal IgG molecules bound to α -gal epitopes on the vaccinating virus and Fc γ receptors (Fc γ R) of the recruited APC. This interaction generates a signal that induces active and extensive endocytosis of the immunocomplexed vaccine. In addition, C3b complement molecules formed by the complement activation process and which are attached to the immunocomplexed anti-Gal, further bind to C3b receptors (also called CR1) on APC and generate additional signals that increase endocytosis of the vaccine by APC (not shown).

Step 3

The vaccine internalized within endosomes of the APC is subjected to proteolytic activity of proteases that generate peptides of the viral proteins. These APC further migrate to the regional lymph nodes, process and present the vaccinating peptides in association with MHC molecules for effective activation of CD4⁺ and CD8⁺ T cells. The activated CD8⁺ T cells proliferate, leave the lymph nodes and circulate in order to detect and kill host cells containing the replicating virus. Activated CD4⁺ T cells proliferate and function as helper T cells that assist B cells in proliferation, isotype switching and maturation into antibody producing plasma cells. Activated CD4⁺ T cells also function as helper cells to CD8⁺ T cells maturing into CTL. In the absence of α -gal epitopes on the vaccinating virus, uptake by APC is likely to be suboptimal as it is mediated only by random pinocytosis.

This scenario is applicable to enveloped viruses and to their isolated viral envelope glycoproteins (including split or subunit vaccines or produced as recombinant glycoproteins) which can be glycoengineered to present α -gal epitopes on their glycans. In addition to the enzymatic method described below for *in vitro* synthesizing α -gal epitopes on vaccines, other methods for glycoengineering inactivated whole virus or viral glycoprotein vaccines to present α -gal epitopes are described at the end of this chapter.

Synthesis of α -Gal Epitopes on Viruses

The basic principle in the method of amplifying immunogenicity of viral vaccines presented in this chapter is the glycoengineering of the viral glycan shield for conversion of the multiple sialic acid epitopes into α -gal epitopes in order to prepare viral α -gal vaccines. Many of the glycans on envelope glycoproteins of viruses are asparagine (N)-linked glycans, synthesized on asparagines in amino acid sequences (sequon) asparagine-any amino acid-serine or threonine (N-X-S/T) (Vigerust & Shepherd, 2007). These glycans are synthesized by glycosylation enzymes (glycosyltransferases), mostly in the Golgi apparatus, in a sequential manner resembling an assembly line in a car plant. Part of the glycans are of the high-

mannose type having multiple mannose units and the rest are of the complex-type in which many the terminal carbohydrate units are “capped” with sialic acid (SA) as the left glycan in Figure 1. The enzyme neuraminidase (also called sialidase) in the first step (left reaction in Figure 1) cleaves the terminal SA from the SA-Gal β 1-4GlcNAc-R (sialyl-N-acetyllactosamine) carbohydrate sequence and exposes the penultimate N-acetyllactosamine (Gal β 1-4GlcNAc-R). The N-acetyllactosamine serves as acceptor for the α 1,3GT which links a galactose α 1-3 to the N-acetyllactosamine to form the α -gal epitope (second [right] reaction in Figure 1). The galactose is provided by the high energy sugar donor UDP-Gal. The second reaction, which is similar to the one in the Golgi apparatus of cells, is performed *in vitro* by recombinant (r) α 1,3GT (Chen et al. 2001). UDP-Gal may be purchased from commercial sources. In the case of inactivated influenza virus vaccine preparation, the envelope glycoprotein hemagglutinin (HA) does not have SA on its glycans. The SA of influenza virus is removed by the viral neuraminidase, thus the glycans of the complex type on HA have the center glycan structure in Figure 1. SA serves as a cellular docking receptor for the HA on influenza virus, and the removal of the autologous SA of the virus by neuraminidase has evolved in order to prevent the binding of HA on one virus to SA on the envelope of another virus. Thus, synthesis of α -gal epitopes on HA of influenza virus does not require the first reaction in Figure 1 (Henion et al. 1997).

Experimental Animal Model for Production of Anti-Gal and Amplification of Viral Vaccine Immunogenicity by This Antibody

The study of the hypothesis illustrated in Figure 3 requires the use of an experimental animal model that does not synthesize α -gal epitopes and thus, can produce the natural anti-Gal antibody. As indicated above, nonprimate mammals including lab animals such as mice, rats, guinea pigs and rabbits synthesize the α -gal epitope and thus are immunotolerant to it and cannot produce the anti-Gal antibody. However, mice suitable for this purpose are the GT-KO mice which lack α -gal epitopes because of the disruption (i.e., knockout [KO]) of the α 1,3GT gene (Thall et al. 1995; Tearle et al. 1995). Since these mice are usually kept in sterile environment, they lack the GI bacteria which provide the carbohydrate antigens that stimulate the immune system to produce anti-Gal. Induction of these mice to produce anti-Gal is feasible by repeated immunization with xeno-glycoproteins presenting multiple α -gal epitopes, such as pig kidney membrane homogenate (Tanemura et al. 2000), or with rabbit red blood cell membranes (LaTemple et al. 1999). In addition to the use of anti-Gal producing GT-KO mice, GT-KO pigs may be used as a large animal model (size close to that of humans) for studying α -gal vaccines. These pigs lack α -gal epitopes because of disruption of their α 1,3GT gene (Lai et al. 2002; Phelps et al. 2003) and they naturally produce the anti-Gal antibody with characteristics similar to those of human anti-Gal (Dor et al. 2004; Fang et al. 2012; Galili, 2013b). No other nonprimate mammals have yet been engineered to lack α -gal epitopes. Thus, all other nonprimate mammals cannot produce anti-Gal and are not suitable for studying α -gal vaccines. However, α -gal vaccines may be studied also in Old World monkeys such as baboon, rhesus, and cynomolgus monkeys, all lacking α -gal epitopes and producing the natural anti-Gal antibody (Galili et al. 1987b, 1988b; Teranishi et al. 2002).

OVA CONTAINING α -GAL LIPOSOMES AS A MODEL FOR VIRAL α -GAL VACCINE

The study of the hypothesis presented in Figure 3 required the use of a vaccinating antigen that can be detected following endocytosis into APC and which includes an immunogenic peptide of known structure. Such a peptide should be detected by activation of T cells with the corresponding TCR that can engage the presented immunogenic peptide. These requirements could be fulfilled by studying the amplification of immunogenicity of chicken ovalbumin (OVA) as a vaccine model in anti-Gal producing GT-KO mice (Abdel-Motal et al. 2009b). OVA is a suitable antigen for detection of APC internalizing it and for identification of T cells activated by it because the most immunogenic peptide of OVA for CD8⁺ T cells in mice is the 8-amino acid peptide SIINFEKL (Rötzschke et al. 1991). A CD8⁺ T hybridoma cell line called B3Z with a TCR specific for SIINFEKL was generated (Shastri & Gonzalez, 1993). These B3Z cells are activated when they engage APC presenting SIINFEKL. B3Z cell activation can be detected by the subsequent activation of a β -galactosidase transgene *LacZ* under IL2 promoter. Since T cells secrete IL2 as a result of their activation, in activated B3Z cells the IL2 promoter of the *LacZ* transgene activates this gene to produce β -galactosidase. These intracellular activation events occur following binding of SIINFEKL presented on MHC class I of H-2bK^b (called here H-2b) of APC to the TCR on B3Z cells. The β -galactosidase produced following such activation hydrolyzes FITC-di- β -D-galactopyranoside (FDG) introduced into B3Z cells, resulting in labeling the cells by the released fluorescein. This labeling of activated B3Z cells can be detected by flow cytometry.

OVA is a protein that lacks N-linked glycans and thus, it cannot be glycoengineered to carry α -gal epitopes. Simulation of a virus presenting α -gal epitopes, having OVA as a major protein antigen that is targeted to APC by anti-Gal, was achieved by use of OVA encapsulated within liposomes that present multiple α -gal epitopes (Abdel-Motal et al. 2009b). These α -gal liposomes are prepared from phospholipids, cholesterol and glycolipids extracted from rabbit red blood cell membranes. They present $\sim 10^{15}$ α -gal epitopes/mg liposomes and thus, readily bind the anti-Gal antibody (Wigglesworth et al. 2011). Following the immunocomplexing with anti-Gal these liposomes were effectively internalized by dendritic cells and macrophages. Moreover, 24 hours following such *in vitro* uptake of the α -gal liposomes containing OVA (called OVA-liposomes) by dendritic cells, these APC readily activated B3Z hybridoma T cells (Abdel-Motal et al. 2009b). This indicated that within 24 hours, the internalized OVA in OVA-liposomes was processed and SIINFEKL presented on the APC in association with MHC class I.

The *in vivo* uptake and transport of OVA-liposomes to regional lymph nodes by APC could be studied by subcutaneous injection of OVA-liposomes into GT-KO mice, in the right thigh. A week later the inguinal lymph nodes (the right regional lymph nodes of the injection site) were harvested, minced and the cells within them were co-incubated for 24 hours with B3Z cells. APC processing and presenting SIINFEKL within these lymph nodes were expected to activate the B3Z cells. Such activated B3Z cells could be detected by flow cytometry, following gating for the hybridoma cell size. The activated B3Z cells were detected as cells double stained, green for hydrolyzed FDG and red for anti-CD8 antibody-PerCP labeling all the B3Z cells since they are CD8⁺ T hybridoma cells (Figure 4A).

Lymph nodes draining the vaccination site in three anti-Gal producing GT-KO mice that were injected with OVA-liposomes displayed high numbers of SIINFEKL presenting APC, as indicated by the activation of 14-24% B3Z cells. In contrast, whereas the opposite (left) inguinal lymph node cells, displayed activation of only 2.5-3.7% B3Z cells (Figure 4A). The presence of multiple APC presenting SIINFEKL in lymph nodes draining the vaccination site area depended on the presence of the anti-Gal antibody in the injected mouse. This was shown with wild-type (WT) mice. As indicated above, WT mice are incapable of producing the anti-Gal antibody, as they synthesize α -gal epitopes and thus they are immunotolerant to this carbohydrate antigen. Cells from lymph nodes draining the vaccination site in WT mice injected with OVA-liposomes activated only 2.2-3.1% B3Z cells. This activation level was only slightly higher than that measured in the opposite leg inguinal lymph nodes (Figure 4B).

The data on B3Z cell activation by APC in lymph nodes draining the vaccination site suggest that anti-Gal mediated targeting of the vaccine to APC greatly increases uptake and transport of the vaccine to regional lymph nodes, as well as the processing and presentation of vaccinating antigens by APC. This, in turn, amplifies the activation of T cells specific for the immunogenic vaccine peptides. The increased activation of T cells could be further demonstrated by ELISPOT with spleen lymphocytes from the immunized mice that were co-incubated with dendritic cells pulsed with SIINFEKL. In this assay, individual activated T cells are detected by their secretion of interferon- γ (IFN γ) which is captured as a spot on membranes lining cell culture wells and identified by staining with labeled anti-IFN γ antibodies.

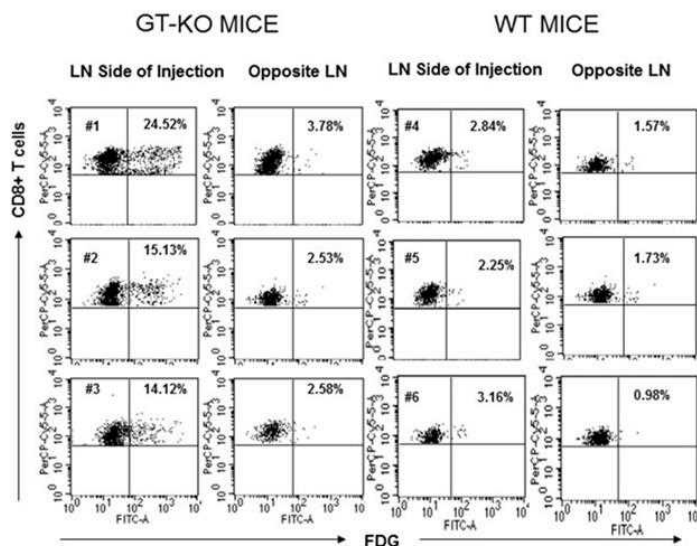


Figure 4. *In vitro* quantification of APC internalizing anti-Gal opsonized OVA liposome vaccine by subsequent evaluation of B3Z hybridoma T cell activation with APC from regional lymph nodes. APC internalizing the OVA liposomes present SIINFEKL on class I MHC molecules and activate B3Z cells. Cells from inguinal lymph nodes (LN) draining the immunization site in the right thigh (side of injection) and in left thigh (opposite LN) were obtained from anti-Gal producing GT-KO mice and from wild type (WT) C57BL/6 mice. Activation by SIINFEKL was detected by flow cytometry of B3Z cells with hydrolyzed FDG. Inguinal lymph node cells were harvested 7 days after vaccination with 10 mg OVA-liposomes in the right thigh. From “*The natural anti-Gal antibody as foe turned friend in medicine*” by U. Galili, 2018, Elsevier/Academic Press, p. 164, after (Abdel-Motal et al. 2009b).

There were on average 20-fold more SIINFEKL specific T cells among splenocytes of GT-KO mice immunized with OVA-liposomes than among splenocytes obtained from WT mice receiving similar immunization (Abdel-Motal et al. 2009b). Accordingly, the proportion of CD8⁺ T cells binding pentamers of H-2b carrying SIINFEKL was higher in the immunized GT-KO mice than in immunized WT mice.

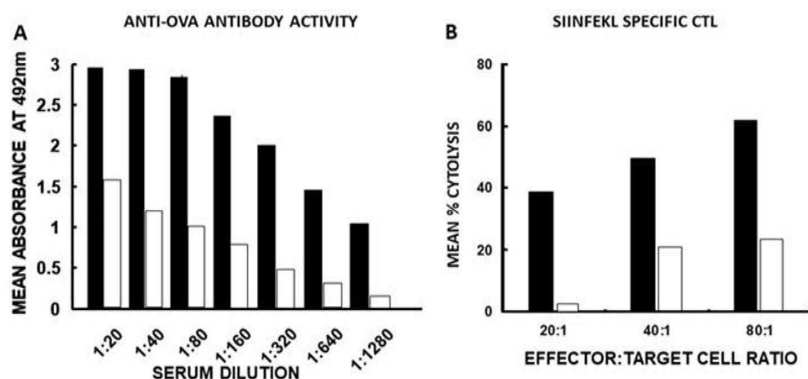


Figure 5. Anti-Gal mediated amplification of antibody (A) and CTL immune response (B) following immunization with OVA-liposomes in anti-Gal producing GT-KO mice (■) and WT mice (□). (A) Production of anti-OVA IgG antibodies was assayed by ELISA, (n=6 per group). (B) Anti-SIINFEKL CTL activity with EL4 cells pulsed with SIINFEKL as target cells. Cell cytotoxicity was assessed by chromium release assay. Results represent the mean of data from six mice per group). Modified from (Abdel-Motal et al. 2009b).

Functional B cell and CTL activities were markedly higher in anti-Gal producing GT-KO mice immunized with the OVA-liposomes than in immunized WT mice that lack this antibody. As shown in Figure 5A, the titer of anti-OVA antibodies (measured by ELISA with OVA as solid-phase antigen) was found to be ~30-fold higher in GT-KO mice immunized with OVA-liposomes than in WT mice after similar immunization. Furthermore, cytotoxicity of target cells pulsed with SIINFEKL by CTL obtained from GT-KO mice immunized with OVA liposomes was >4 fold higher than cytotoxicity by CTL from WT mice (Figure 5B). These observations indicate that the elevated uptake of OVA-liposomes opsonized by anti-Gal and the increased transport of the internalized OVA by APC to regional lymph nodes, ultimately result in amplification of both cellular and humoral immune responses against the vaccinating protein. In sections below, the amplification of vaccine immunogenicity is further demonstrated with α -gal vaccines consisting of inactivated whole virus and vaccines containing recombinant enveloped virus glycoprotein.

INCREASED EFFICACY OF INFLUENZA VIRUS α -GAL VACCINE

Influenza virus appears around the world in yearly outbreaks that lead to 3-5 million cases of severe infections and >290,000 deaths (Iuliano et al. 2018). The major glycoprotein on the virus envelope is hemagglutinin (HA). The core of the virus contains 8 segments of negative sense RNA, each containing at least one gene. The virus spreads fast by human to human transmission. The HA glycoprotein on this virus mediates adhesion of the virus to

sialic acid on cell surface glycans. Based on the annual number of individuals displaying infection by the virus despite vaccination, it seems that presently used influenza vaccines fail to protect as many as 50% of vaccinated individuals from infection by the virus (Couch et al., 1997; Webster, 2000; Katz et al., 2004; Chang et al. 2012). Thus, more effective influenza vaccines are needed to be developed, in particularly for elderly individuals. Development of more effective vaccines is also needed in view of the risk of occasional appearance of influenza virus strains presenting new antigens on the viral envelope HA and neuraminidase. Pandemics caused by new influenza virus strains require the production of highly immunogenic vaccines that will protect individuals of all ages because all humans lack previous exposure to the new viral antigens. This section describes experiments demonstrating as much as 100 fold increase in immunogenicity of influenza inactivated whole virus vaccine glycoengineered to present multiple α -gal epitopes and studied in anti-Gal producing GT-KO mice. The influenza virus A/Puerto Rico/8/34- H1N1 (PR8 virus- adapted to work with mice) was used for these studies.

The HA glycoprotein of influenza virus has 6-8 glycans capped with N-acetyllactosamine (Gal β 1-4GlcNAc-R) as the center glycan in Figure 1 (Matsumoto et al. 1983; Kiel et al. 1985). This is the structure of the viral glycans when the virus is propagated in embryonated chicken eggs (lacking α 1,3GT). The glycans lack sialic acid because the viral neuraminidase on the virus envelope cleaves the terminal sialic acid off the HA glycans. However, when the PR8 virus was propagated in bovine cells (Madin-Darby bovine kidney (MDBK) cells) or in canine cells (Madin-Darby canine kidney (MDCK) cells), some of its HA glycans were capped with the α -gal epitopes as in the right glycan in Figure 1 (Galili et al. 1996). These epitopes were synthesized on the HA glycans because both cell types have active α 1,3GT enzyme (Galili et al. 1988b). Inactivated viruses produced in chicken, bovine and canine cells were studied for anti-Gal mediated uptake by APC according to the hypothesis illustrated in Figure 3. The uptake was assessed by activation of an HA specific T cell clone which has TCR specifically recognizing processed HA peptides presented on the APC. *In vitro* immunocomplexing of human anti-Gal with inactivated PR8 virus presenting α -gal epitopes resulted in increased uptake by APC. This was demonstrated by the ~10-fold increase in subsequent activation of the HA specific T cell clone by processed peptides presented on the APC, in comparison with activation of these HA specific T cells in the absence of anti-Gal (Galili et al., 1996). However, incubation of inactivated influenza virus produced in embryonated chicken eggs, with anti-Gal and APC resulted in subsequent uptake, processing and presentation of viral peptides by APC which was similar to that observed in the absence of anti-Gal. These findings indicated that presence of α -gal epitopes on vaccinating influenza virus enables formation of immune complexes with anti-Gal, resulting in more effective uptake of the vaccine by APC than the random pinocytosis of the vaccine in the absence of α -gal epitopes.

It could be argued that producing influenza virus for vaccine preparation in MDCK or MDBK may suffice for preparation of a vaccine presenting α -gal epitopes that will be effectively targeted by anti-Gal to APC. However, the number of α -gal epitopes on influenza virus replicating in these cells seems to be far from optimal for effective *in vivo* targeting to APC. The number of such epitopes on MDCK cells is ~10 fold lower than that on MDBK cells and may be less than one per glycan (Galili et al. 1996). This low presentation of α -gal epitopes may explain why the efficacy of MDCK produced vaccine is not significantly

different from that of vaccine produced in chicken cells (Ambrozaitis et al. 2009; Szymczakiewicz-Multanowska et al. 2009).

Propagation of influenza virus (as well as other enveloped viruses) in available cell lines cannot reach a maximum number of α -gal epitopes (i.e., on each of the 2-4 branches (antennae) of the glycan), because of competition between α 1,3GT and other glycosyltransferases (in particular sialyltransferases) in the Golgi apparatus. The last step in the glycosylation process of cellular and viral glycans occurs in the trans-Golgi compartment where in nonprimate mammalian cells α 1,3GT and other glycosyltransferases (mostly sialyltransferases) compete for capping the nascent glycan with Gal α 1-3 to form α -gal epitopes, as in the right glycan of Figure 1, or with sialic acid to form the left glycan in Figure 1 (Smith et al. 1990). The final makeup (profile) of glycans on host cells and on viruses replicating in them depends on the concentration and relative activities of α 1,3GT and sialyltransferases (as well as other glycosyltransferases) in the trans-Golgi. Sections at the end of this chapter describes several glycoengineering methods which can maximize the number of α -gal epitopes on vaccinating viruses. One of the methods which has been tried and shown to markedly increase immunogenicity of influenza virus vaccine due to extensive targeting of α -gal vaccines by anti-Gal to APC, uses recombinant α 1,3GT (α 1,3GT) for *in vitro* synthesis of α -gal epitopes on the vaccinating virus (Abdel-Motal et al. 2007). The α 1,3GT was cloned from New World monkey cDNA as a truncated gene lacking the cytoplasmic and trans-membrane domains and was produced first in mosquito SF9 cell line expression system (Henion et al. 1994) and later in the yeast *Pichia pastoris* expression system (Chen et al. 2001).

The PR8 virus was precipitated from the allantoic fluid of embryonated chicken eggs by polyethyleneglycol and purified on a continuous sucrose gradient (Galili et al., 1996). The virus was inactivated by incubation for 45 min in 65°C and confirmed for complete inactivation by the loss of hemagglutinating activity with chicken red blood cells (RBC). The virus was subjected to *de novo* synthesis of α -gal epitopes according to the second enzymatic reaction in Figure 1 in which PR8 virus (100 μ g/ml) was incubated with α 1,3GT (30 μ g/ml) and UDP-Gal (1mM) in the presence of Mn⁺⁺ for 2 hours at 37°C. Control PR8 virus was incubated under similar conditions with inactivated α 1,3GT (10 min incubation in boiling water) and with 1mM UDP-Gal (Henion et al. 1997; Abdel-Motal et al. 2007). The enzymatic reaction resulted in the synthesis of ~3000 α -gal epitopes on the inactivated PR8 virus (referred to as PR8 _{α gal}), but not on the control PR8 virus. Western blot analysis of the α -galactosylated glycoproteins separated by SDS-PAGE electrophoresis under reducing conditions indicated that the synthesis of α -gal epitopes was mainly on the glycans of the HA₁ molecule, which is the distal portion of the HA molecule (Figure 6). The α -gal epitopes on HA₁ bound both serum anti-Gal produced in GT-KO mice and monoclonal anti-Gal M86 (Abdel-Motal et al. 2007).

In order to determine whether the immunogenicity of PR8 _{α gal} differs from that of PR8, anti-Gal producing GT-KO mice received two immunizations in two-week interval of either 1 μ g of inactivated PR8 _{α gal}, or a similar amount of inactivated PR8 virus. The Ribi adjuvant was administered with the vaccine. The immune response to the vaccine was determined two weeks after the second vaccination. The number of T cells activated by the vaccination was determined by production of interferon- γ (IFN γ) into two types of assays: 1. ELISPOT

measuring secretion of IFN γ from individual cells, and 2. Intracellular staining (ICS) measuring by flow cytometry the proportion of cells that are positively stained for production of IFN γ , characteristic to activated CD4 $^{+}$ and CD8 $^{+}$ T cells. In the ELISPOT assay, four of the six mice immunized with PR8 $_{\alpha\text{gal}}$ inactivated virus displayed ~ 2200 T cells secreting IFN γ per 10^6 spleen cells, whereas mice immunized with PR8 inactivated virus displayed only ~ 600 IFN γ secreting T cells per 10^6 cells (Abdel-Motal et al. 2007).

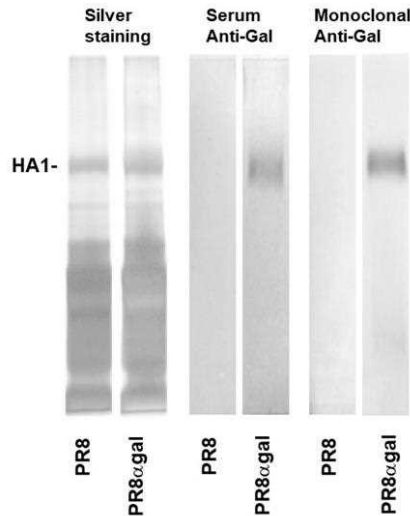


Figure 6. Glycoengineering of PR8 influenza virus to present α -gal epitopes. α -Gal epitopes on PR8 $_{\alpha\text{gal}}$ were demonstrated by Western blots stained with anti-Gal antibody purified from GT-KO mouse serum and with monoclonal anti-Gal M86 (Galili et al. 1998). Note that both anti-Gal antibodies bind to HA1 from PR8 $_{\alpha\text{gal}}$ and not to the HA1 from unprocessed PR8. A representative study of three independent studies with similar results. From (Abdel-Motal et al. 2007).

ICS evaluation of IFN γ production demonstrated on average $\sim 21\%$ of cells with positive staining among CD8 $^{+}$ T cells of the four out of six PR8 $_{\alpha\text{gal}}$ immunized mice vs. $\sim 3.5\%$ of CD8 $^{+}$ cells in PR8 immunized mice (Figure 7A). Similarly, $\sim 13\%$ of the CD4 $^{+}$ T cells from PR8 $_{\alpha\text{gal}}$ immunized mice stained positively for intracellular IFN γ vs. $\sim 0.1\%$ of CD4 $^{+}$ cells in PR8 immunized mice (Figure 7B). The remaining two mice immunized with PR8 $_{\alpha\text{gal}}$ (#5 and #6) assayed in both ELISPOT and ICS analyses displayed similar numbers of IFN γ producing T cells as those in PR8 immunized mice (#11 and #12).

The immunization of anti-Gal producing GT-KO mice with PR8 $_{\alpha\text{gal}}$ inactivated virus also resulted in a much higher production of anti-PR8 antibodies in comparison to mice immunized with inactivated PR8 virus lacking α -gal epitopes (i.e., virus serving as an antigenic source for some of the present day used vaccines). The activity of anti-PR8 antibodies was measured by ELISA in which PR8 virus served as solid-phase antigen attached to ELISA wells by drying aliquots of virus suspension. The titer of anti-PR8 IgG antibodies (defined as serum dilution yielding 1.0 O.D. in ELISA) was ~ 100 -fold higher in PR8 $_{\alpha\text{gal}}$ immunized GT-KO mice than in the mice immunized with inactivated PR8 virus (Figure 8A). In four of the PR8 $_{\alpha\text{gal}}$ immunized mice, anti-PR8 production was much higher than in the remaining two mice which also displayed low T cell response in Figure 7.

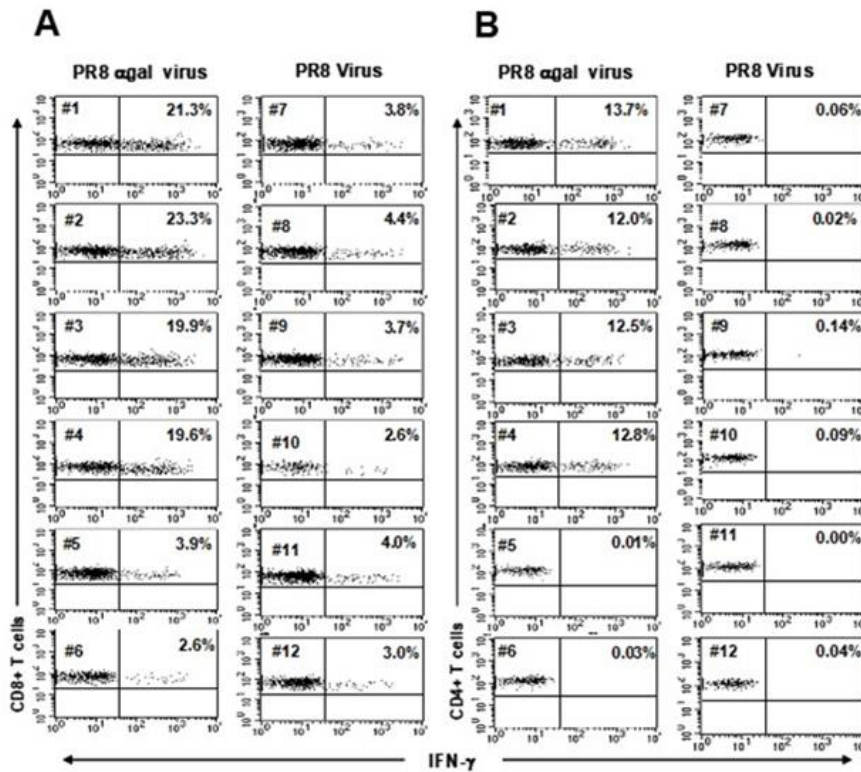


Figure 7. Intracellular staining (ICS) of IFN γ in CD8 $^{+}$ (A) and CD4 $^{+}$ T cells (B) in PR8 $_{\text{agal}}$ or PR8 immunized, anti-Gal producing GT-KO mice. ICS analysis in CD8 $^{+}$ T cells (A including two left panels) and CD4 $^{+}$ T cells (B including two right panels) in PR8 $_{\text{agal}}$, or PR8 immunized mice (n=6 per group). Lymphocytes were gated in (A) for CD8 $^{+}$ and in (B) for CD4 $^{+}$ membrane markers and analyzed for IFN γ production. Lymphocytes were obtained 14 days after the second immunization and incubated overnight with dendritic cells prepulsed with inactivated PR8. From (Abdel-Motal et al. 2007).

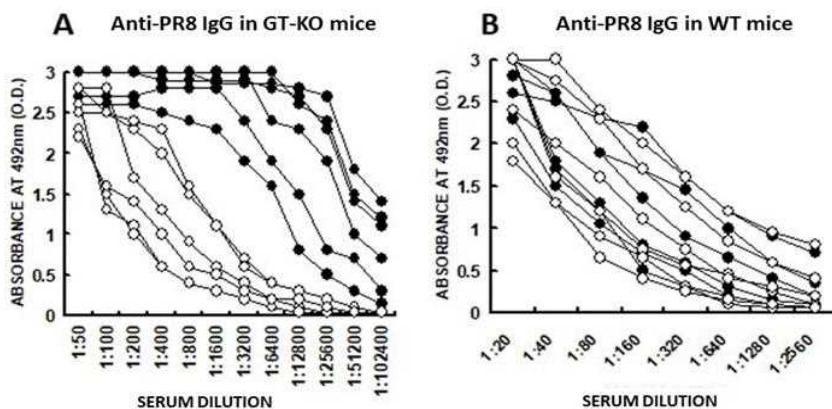


Figure 8. Production of anti-PR8 antibodies in immunized mice. Mice were immunized twice with 1 μ g inactivated PR8 $_{\text{agal}}$ (●), or with 1 μ g inactivated PR8 (○). Both vaccines also included Ribi adjuvant. Production of anti-PR8 antibodies was measured by ELISA with PR8 virus as solid phase antigen. (A) Anti-PR8 IgG antibodies in anti-Gal producing GT-KO mice. (B) Anti-PR8 IgG response in wild type (WT) mice. (n=6 per group). From (Abdel-Motal et al. 2007).

The importance of anti-Gal as the antibody targeting the immunocomplexed virus to APC could be evaluated by repeating the experiment of Figure 8A in wild type (WT) C57BL/6 mice. These mice lack anti-Gal despite immunization with pig kidney membranes because the α -gal epitope is a self-antigen in them. No difference in anti-PR8 titer was observed between PR8 $_{\alpha\text{gal}}$ immunized and PR8 immunized mice. In both groups, anti-PR8 antibodies were produced at a similar low titer that was 80-100 fold lower than that in PR8 $_{\alpha\text{gal}}$ immunized GT-KO mice (Figure 8B).

The anti-viral activity of these antibodies was further studied by determining the ability of the antibodies to block binding of HA on the virus to its docking receptor, the sialic acid on cell surface glycans. This is performed by studying the inhibition of hemagglutination of chicken RBC by the PR8 virus. The virus was incubated with serum at serial two fold dilutions of the serum. The RBC (1%) were added to the virus incubated in the serum and hemagglutination inhibition was determined after 30 min. Sera of PR8 $_{\alpha\text{gal}}$ immunized mice that displayed high anti-PR8 IgG antibody activity were found to be >10 fold more potent in inhibiting hemagglutination than sera from PR8 immunized mice (Abdel-Motal et al. 2007). This implies that a significant proportion of the anti-PR8 antibodies produced in PR8 $_{\alpha\text{gal}}$ immunized mice bind to HA and inhibit its biological activity that enables infection of cells.

The secretory IgA antibody against influenza virus is considered to be the primary antibody involved in protecting mucosal surfaces of the respiratory tract against infection by this virus (Kiyono et al. 2008). Therefore, it was of interest to determine if there is a difference in anti-PR8 IgA antibody production in PR8 $_{\alpha\text{gal}}$ vs. PR8 immunized mice. ELISA studies for anti-PR8 IgA antibodies in the serum of vaccinated mice were performed by the same method as that presented in Figure 8 for anti-PR8 IgG, using anti-mouse IgA-HRP as a secondary antibody (Figure 9A). These studies demonstrated high titers of anti-PR8 IgA (1:800 to 1:6400) in four of the six mice immunized with PR8 $_{\alpha\text{gal}}$ that also displayed high T cell response to PR8 antigens in Figure 7 and high anti-PR8 IgG antibodies in Figure 8A. In contrast, mice immunized with PR8 displayed anti-PR8 IgA titers of <1:50.

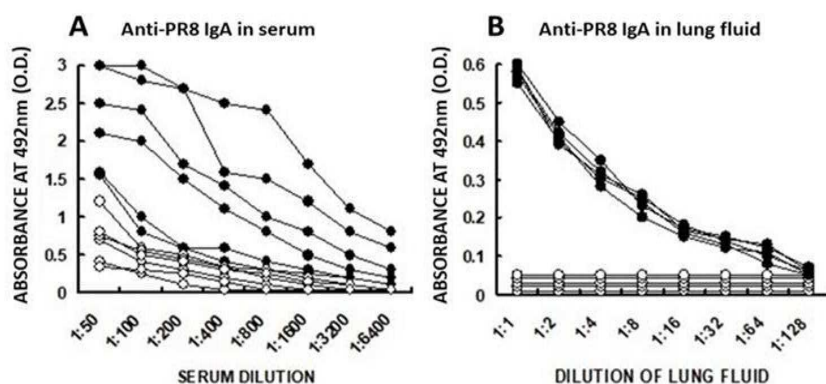


Figure 9. Anti-PR8 IgA antibodies in serum (A) and in lungs (B) of mice immunized with PR8 $_{\alpha\text{gal}}$ (●) vs. PR8 vaccine (○). (A) Antibody production in the serum of anti-Gal producing GT-KO mice. The two lowest PR8 $_{\alpha\text{gal}}$ immunized GT-KO mice producing anti-PR8 IgA are the same as mice #5 and #6 in Figure 7 and also producing the lowest anti-PR8 IgG. (B) Anti-PR8 IgA antibodies in lungs of immunized mice (n=6 per group). From (Abdel-Motal et al. 2007).

Study of anti-PR8 IgA antibodies in supernatants prepared from homogenates of lungs obtained from the immunized mice demonstrated the presence of these antibodies in lungs of PR8_{αgal} immunized mice, whereas lungs of mice immunized with PR8 lacked detectable amounts of these IgA antibodies (Figure 9B) (Abdel-Motal et al. 2007). This finding indicated that in addition to amplification of the immune response against the virus within the serum of mice vaccinated with whole virus α-gal vaccine, this vaccination enables the production of anti-virus IgA antibodies that are secreted into the respiratory tract of vaccinated mice. As further shown below, these secreted antibodies are likely to protect the cells lining the respiratory tract from infection by inhaled influenza virus. These observations suggest that the use of viral α-gal vaccines may be of similar significance in prophylactic immunization of individuals against other viruses capable of infecting the respiratory tract such as SARS-CoV-2 that is the pathogen causing COVID-19 respiratory disease (Galili 2020b).

In order to determine whether the antibodies produced following immunization with PR8_{αgal} affect the replication of the virus in the respiratory tract, immunized mice were challenged by intranasal application of 2000 plaque forming units (PFU) of infectious PR8 virus, 14 days after the second immunization. This challenge dose is lethal for 100% of non-immunized infected mice. The mice were euthanized three days post intranasal challenge, lungs harvested and homogenized in PBS in a total volume of 1ml. The virus was quantified in the suspension by measuring the tissue culture infectious dose (TCID) in MDCK cell monolayers at serial dilutions of the supernatant and determining the reciprocal of the highest dilution displaying cytopathic effect. The TCID of lung homogenate in two PR8_{αgal} immunized mice was 100 and the remaining 3 mice had TCID of 10, i.e., lung supernatant dilution of 1:10 was the highest dilution displaying a cytopathic effect on MDCK cells (Figure 10A). In contrast, in PR8 immunized mice, four of the five mice displayed TCID of 1000 and the fifth displayed TCID of 100. The average TCID among PR8_{αgal} immunized mice was ~18 fold lower than that among PR8 immunized mice. Thus, the number of virus particles in the lungs of PR8_{αgal} immunized mice was ~5% of that in PR8 immunized mice, suggesting that the majority of the virus in the challenge was neutralized and destroyed in the former group (Abdel-Motal et al. 2007). A second method of measurement PR8 presence in the lungs was hemagglutination of chicken RBC at various dilutions of the supernatant. The hemagglutination titers (reciprocal of end point dilution displaying hemagglutination) in four PR8_{αgal} immunized mice was 50 and in the fifth it was 100 (Figure 10B). In contrast, in PR8 immunized mice the titer in lungs of three mice was 1000 and in the remaining two mice it was 10,000, thus supporting the TCID observations on the much lower viral load in the lungs of the PR8_{αgal} immunized mice than in the PR8 immunized mice.

The ultimate test for evaluating the efficacy of PR8_{αgal} vs. PR8 vaccines is the protection in preventing death of the immunized mice following intranasal challenge by a lethal dose (2000 PFU) of infectious PR8 virus. Survival was monitored for 30 days following that challenge of mice (n=25 per group). Most mice (88%) immunized with inactivated PR8 virus succumbed to the PR8 infection and died by Day 10 post challenge (Figure 11). The survival of three out of 25 mice immunized with PR8 vaccine, vs. the death of all nonimmunized mice infected with the infectious virus implies that this vaccine has suboptimal efficacy, protecting only ~12% of the immunized mice. In contrast to PR8 immunized mice, mice immunized with inactivated PR8_{αgal} virus were much more resistant to the challenge. Only 12% of the

mice died following the viral infection and the remaining 88% survived. Survival data on Day 30 were the same as on Day 15 in Figure 11.

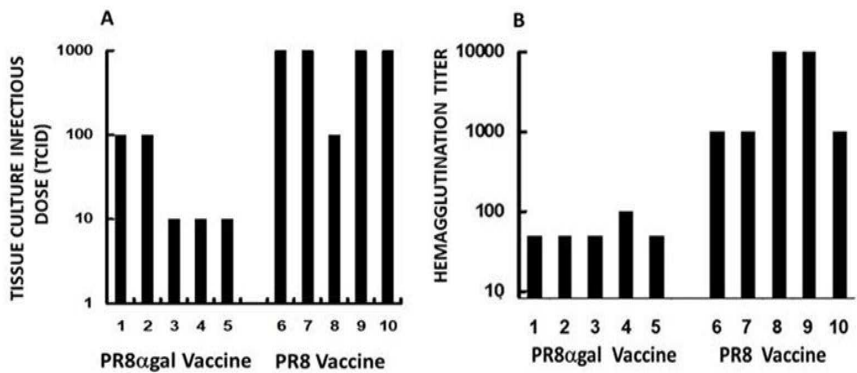


Figure 10. Virus quantification following intranasal challenge by a lethal dose of PR8 influenza virus in anti-Gal producing GT-KO mice immunized with inactivated PR8 α gal or PR8 virus. (A) Analysis of virus titer as tissue culture infectious dose (TCID) in lungs of the challenged mice, 3 days post challenge (n=5 per group). Supernatants of lung homogenates were incubated in serial 10 fold dilutions in 96 well plates with MDCK cell monolayers. Cytopathic effects were scored after 96 hours. (B) PR8 virus titers in lungs of GT-KO mice, 3 days post challenges as assessed by hemagglutination of chicken RBC. The virus titers were assayed in supernatants of lung homogenates (n=5 per group). From (Abdel-Motal et al. 2007).

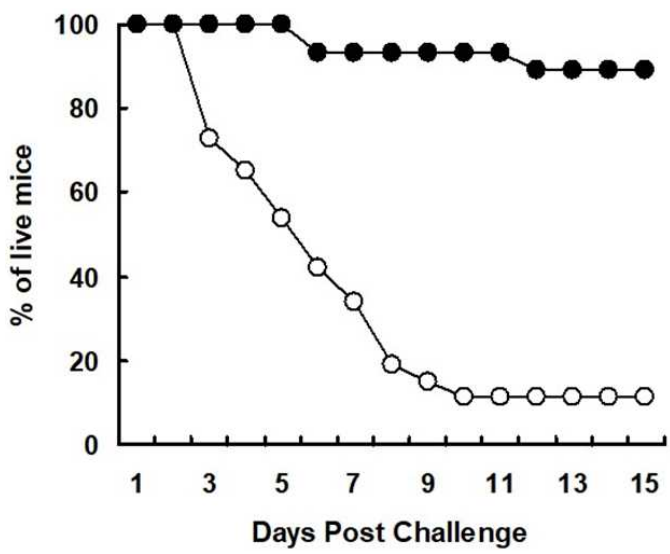


Figure 11. Survival of mice immunized with inactivated PR8 or PR8 α gal virus, following intranasal challenge with lethal dose of fresh infectious PR8 influenza virus. Anti-Gal producing GT-KO mice were immunized twice with 1 μ g inactivated PR8 (O), or with PR8 α gal (●) whole virus vaccines. Mice were subsequently challenged with 2000 PFU of infectious PR8 virus, 14 days after the second immunization (n=25 per group). Data presented as % of infected mice at various days. Survival data on Day 30 were the same as on Day 15 post challenge. From (Abdel-Motal et al. 2007).

Overall, the studies with the PR8 virus provide a proof of principle for the hypothesis illustrated in Figure 3, as they demonstrate a much higher protection from a lethal dose virus infection in mice immunized with a glycoengineered whole virus α -gal vaccine than in mice immunized with vaccine of the original virus lacking α -gal epitopes. This higher protection is associated with a higher activation of virus specific T cells and a much higher production anti-viral IgG and IgA antibodies. A recent study has demonstrated increased resistance to challenge by infectious influenza virus in GT-KO mice that were immunized with attenuated influenza virus containing the α 1,3GT transgene and thus presenting α -gal epitopes synthesized by α 1,3GT coded by this gene (Yan et al. 2020). All these studies suggest that vaccination of humans with virus presenting α -gal epitopes (i.e., α -gal vaccine) may confer a much higher protection upon exposure to infectious virus than virus vaccines that present the original unmodified glycan shield. In view of the current use of several viral envelope glycoprotein vaccines in the form of split, subunit or recombinant proteins, the studies with the inactivated PR8 _{α gal} whole virus vaccines raised the question whether a similar anti-Gal mediated amplification of vaccine immunogenicity can be achieved with the isolated envelope glycoprotein or with recombinant viral glycoprotein vaccines. Studies on this issue are described in the section below. with recombinant gp120 of HIV as vaccine.

INCREASED IMMUNOGENICITY OF HIV-GP120 PRESENTING α -GAL EPI- TOPES AS A RECOMBINANT GLYCOPROTEIN VACCINE MODEL

Immunogenicity analysis of an α -gal vaccine consisting of a viral glycoprotein was performed with the major envelope glycoprotein gp120 of human immunodeficiency virus (HIV). This glycoprotein produced as recombinant gp120 of the HIV_{BAL} strain in Chinese Hamster Ovary (CHO) cells that were transformed with the corresponding codon optimized *env* gene. The interest in this glycoprotein stems from the fact that recombinant HIV vaccines trials in primate models and in clinical trials were found to display only suboptimal efficacy in eliciting a sterilizing protective immune response against infection with HIV or with simian immunodeficiency virus (SIV) (Berzofsky et al. 2004; Goulder & Watkins, 2004; Pantaleo & Koup, 2004; Letvin, 2005; Munier et al. 2011). It is expected that an effective prophylactic HIV vaccine should induce a strong protective memory immune response that produces neutralizing antibodies and cytotoxic T-lymphocyte (CTL) response. Combination of these two types of immune response should prevent binding of HIV to its receptors on cells, thereby inhibit infection of cells by neutralizing anti-gp120 antibodies and induce effective detection of infected host cells for their destruction by CTL. Such an immune response should be effective in early stages following transmission of the virus, when the number of infected cells is relatively low, in order to prevent the virus from expanding and reaching a lethal mass. In addition to prevention of extensive virus replication within host cells of the infected individual, a rapid immune response will prevent the virus from undergoing mutations in envelope glycoproteins that enable HIV to evade the neutralizing antibodies without losing receptor binding activity (Wei et al. 2003; Crooks et al. 2015).

Gp120 of HIV mediates binding of the virus to specific receptors. This glycoprotein has 479 amino acids and carries a glycan shield of 24 N-linked glycans of which 13-16 are of the complex type capped with sialic acid (SA) (left chain in Figure 1), and the rest are of the high-mannose type (Geyer et al. 1988; Mizuochi et al. 1988; 1990; Leonard et al. 1990). The glycans of gp120 have a size of approximately ~ 60 Å, which is $\sim 30\%$ of the diameter of the protein portion of the gp120 molecule in its globular form. Because of the relatively large size of the glycan, the glycan shield comprised of 24 glycans can mask a significant proportion of the immunogenic gp120 peptides, thus resulting in decreased efficacy of gp120 vaccine (Wei et al. 2003). In addition, multiple negative charges surrounding the gp120 vaccine are provided by many SA units capping the N-linked glycan of the complex type. These negative charges induce electrostatic repulsion (ζ -potential) which decreases the uptake of vaccinating glycoprotein molecules, as illustrated in Figure 2A. The protective effects of the multiple glycans of the glycan shield in evasion of HIV from the immune response can be inferred from isolate clones of HIV type 1 (HIV-1) in AIDS patients, where at least half of the mutations in gp120 (i.e., the *env* gene) form new N-glycosylation sites (i.e., Asn-X-Ser/Thr sequon) which increase the size of the glycan shield that protects the virus from neutralizing antibodies (Wei et al. 2003).

All these considerations on the role of the glycan shield in minimizing the immunogenicity of gp120 led to the assumption that glycoengineering this glycoprotein by synthesizing α -gal epitopes on its glycans may increase its immunogenicity according the hypothesis illustrated in Figure 3. It was hypothesized that immunization with gp120 _{α gal} will elicit a much stronger anti-gp120 immune response than immunization with the original gp120 lacking α -gal epitopes, as the result of effective anti-Gal mediated targeting of the immunizing glycoprotein to APC.

Synthesis of α -Gal Epitopes on gp120

Glycoengineering gp120 into gp120 _{α gal} is achieved by a two-step enzymatic reaction combining the activities of neuraminidase and $\alpha 1,3$ GT, as describe in Figure 1. For performing these studies, recombinant gp120 of the HIV_{BAL} strain was produced in CHO cells and provided as a generous gift from the NIH AIDS Research and Reference Reagent Program. It should be stressed that CHO cells lack active $\alpha 1,3$ GT (Smith et al. 1990), although they originate in hamster, which like other nonprimate mammals, has active $\alpha 1,3$ GT synthesizing α -gal epitopes (Galili et al. 1988b). It is possible that CHO cells were grown in the 1950s in culture medium containing human serum and the anti-Gal in the human serum selected for growth of CHO cells devoid of α -gal epitopes. Neuraminidase was purified from *Vibrio cholerae* and recombinant $\alpha 1,3$ GT was produced in the *Pichia pastoris* expression system (Chen et al. 2001).

The glycans on gp120 differ from those on HA of influenza virus in that gp120 has SA capping the glycan (left carbohydrate chain in Figure 1). In contrast the influenza virus HA lacks SA because SA that caps the glycan in the Golgi apparatus is cleaved off the glycan by viral neuraminidase. The absence of SA (center glycan in Figure 1) enables synthesis of α -gal epitopes by $\alpha 1,3$ GT on the desialylated glycans to generated gp120 _{α gal} (second enzymatic

reaction in Figure 1). These two enzymatic reactions of SA cleaving and synthesis of α -gal epitopes on gp120 could be performed in one solution containing neuraminidase, α 1,3GT and UDP-Gal, as well as Mn^{++} cations that are required for α 1,3GT catalytic activity (Abdel-Motal et al. 2006). Isolation of gp120 _{α gal} from the rest of reaction mixture components is feasible by the use of an affinity agarose column with coupled *Bandeiraea (Griffonia) simplicifolia* IB4 (BS lectin). This lectin binds α -gal epitopes (Wood et al., 1979) and thus specifically binds only gp120 _{α gal} and no other molecules or ions in the reaction mixture. After washing the column, the bound gp120 _{α gal} can be eluted by galactose, α -methyl galactoside, or melibiose solution passed through the column. The specific binding of both human anti-Gal and mouse anti-Gal to the gp120 _{α gal} and not to the original gp120 is shown in Figure 16 in the section discussing the similarities between human and mouse anti-Gal antibodies regarding their ability to bind to α -gal viral vaccines.

Amplification of Anti-HIV Immune Response Following Immunization with gp120 _{α gal} vs. gp120 Vaccines

As in the studies above on PR8 _{α gal} and α -gal OVA-liposomes, the analysis of gp120 _{α gal} immunogenicity vs. that of gp120 was performed in anti-Gal producing GT-KO mice. These mice were immunized subcutaneously twice with 5 μ g gp120 or gp120 _{α gal} and Ribi adjuvant, in 2 week interval (Abdel-Motal et al. 2006). The immune response was evaluated 17 days after the second immunization. Assessment of the gp120 specific T cell response in the immunized mice was determined by quantification of IFN γ secreting activated T cells among splenocytes co-incubated with dendritic cells pulsed with gp120 in a 24 hour ELISPOT assay. Each T cell secreting IFN γ is detected as a spot in this assay since the secreted IFN γ binds to anti-IFN γ coating membranes lining the wells and is subsequently identified by a labeled anti-IFN γ -peroxidase antibody. The clear visual difference in the number of spots generated by this T cell activation is demonstrated in Figure 12A which shows the triplicate wells with splenocytes from three representative mice per each group.

Practically, no spots indicating spontaneous secretion of IFN γ were observed in the absence of pulsing gp120 as the *in vitro* stimulatory antigen. However, in the presence of gp120 as the activating antigen in the ELISPOT wells, the numbers of IFN γ secreting T cells in gp120 _{α gal} immunized mice were visually much higher than those in gp120 immunized mice (Figure 12A). Figure 12B describes the average number of spots representing activated T cells secreting IFN γ in the 6 mice evaluated in each group. Whereas mice immunized with gp120 displayed on average 23 spots (i.e., 23 gp120 specific activated T cells per 10⁶ cells incubated in each well in the presence of gp120), mice immunized with gp120 _{α gal} displayed ~15 fold higher number of gp120 specific activated T cells, i.e., 332 spots per 10⁶ cells (Abdel-Motal et al. 2006).

In addition to the higher gp120 specific T cell activation following immunization with gp120 _{α gal}, the antibody production against gp120 was much higher post immunization with gp120 _{α gal} than post immunization with the original gp120 lacking α -gal epitopes. Production of anti-gp120 antibody was measured in 5 mice in each group by ELISA with gp120 as solid-

phase antigen. The vast difference in production of anti-gp120 IgG antibodies is clearly observed in Figure 13A.

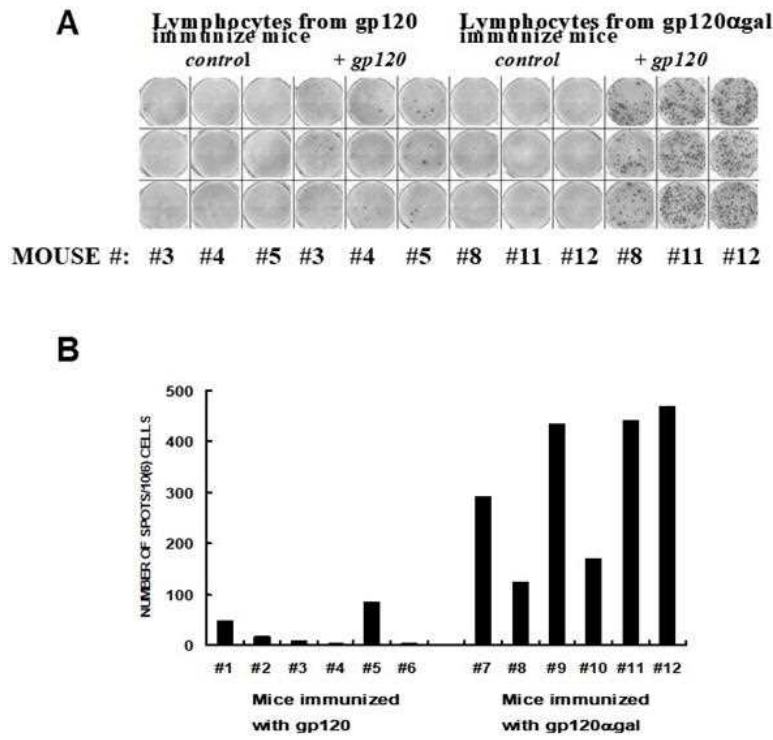


Figure 12. Identification of gp120 specific T cells in anti-Gal producing GT-KO mice immunized with gp120, or gp120_{gal} as assessed by ELISPOT analysis for IFN γ secretion. (A) Photos of spots in wells with splenocytes from three mice, each tested in triplicates wells (vertical lanes) which lacked (control wells) or contained gp120 pulsed dendritic cells. (B) Mean number of spots per well from six individual mice in each of the two groups (mean of spots in triplicate wells for each mouse). Modified from (Abdel-Motal et al. 2006).

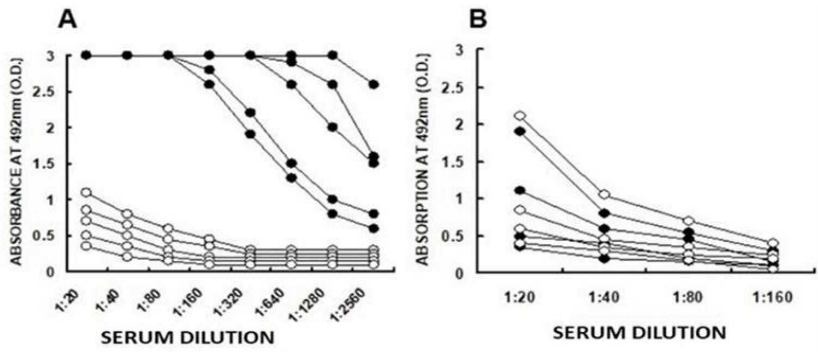


Figure 13. Anti-gp120 IgG production in mice following immunization with gp120 (O) or gp120_{gal} (●). (A) Anti-gp120 antibody production in anti-Gal producing GT-KO mice immunized twice with either 5 μ g gp120 vaccine, or with 5 μ g gp120_{gal} vaccine. (B) Anti-gp120 antibody production in wild type mice (WT) immunized as in Figure 13A. From (Abdel-Motal et al. 2006).

Anti-gp120 antibody activity in mice immunized with gp120 _{α gal} was 100-200 fold higher than in mice immunized with gp120 (Abdel-Motal et al. 2006). The much higher production of anti-gp120 antibodies was dependent on the presence of the anti-Gal antibody which forms immune complexes with gp120 _{α gal} and not with gp120. This is demonstrated in Figure 13B in which the same vaccination as in Figure 13A was performed in wild-type (WT) mice which lack the anti-Gal antibody despite repeated immunizations with pig kidney membranes. All groups received a similar number of immunizations with pig kidney membranes homogenate for eliciting anti-Gal production. Anti-gp120 antibody production in WT mice was low and similar in both groups of mice indicating that the presence of α -gal epitopes on the immunizing gp120 _{α gal} vaccine resulted in no amplification of the antibody response in the absence of anti-Gal. A similar marked increase in antibody and T cell response was observed with antibodies to bovine serum albumin (BSA) in GT-KO mice immunized with BSA _{α gal} in comparison to those immunized with BSA, as well as with CTL killing tumor cells presenting viral antigens (Benatuil et al. 2005).

The ultimate objective of vaccination for production of anti-gp120 antibodies is protection of the vaccinated individuals by antibodies that can neutralize HIV, thus preventing HIV infection of host cells. The neutralizing potential of anti-gp120 antibodies produced in mice immunized with gp120 _{α gal} was determined in comparison to antibodies produced in gp120 immunized mice. For this study, the HIV-1 lab strain MN was tested for infectivity of cells following incubation with sera from the two groups, at serial dilutions of the sera. The extent of neutralization was measured by the prevention of T cell killing by the HIV_{MN} in a killing assay of the human T-cell lymphoma line MT-2 infected by the virus (Montefiori et al. 1996; Wang et al. 2005). The HIV_{MN} virus used for mediating killing of the infected T cells is a strain which is convenient for work in the lab and its gp120 amino acid sequence differs by only few amino acids from that of gp120 of HIV_{BAL} (the source for the vaccinating gp120). Thus, it is assumed that anti-gp120 antibodies mediated prevention of MT-2 cell killing by HIV_{MN} would serve as a positive conservative result on even higher neutralizing effect of the anti-gp120 antibodies on HIV_{BAL} infecting T cells.

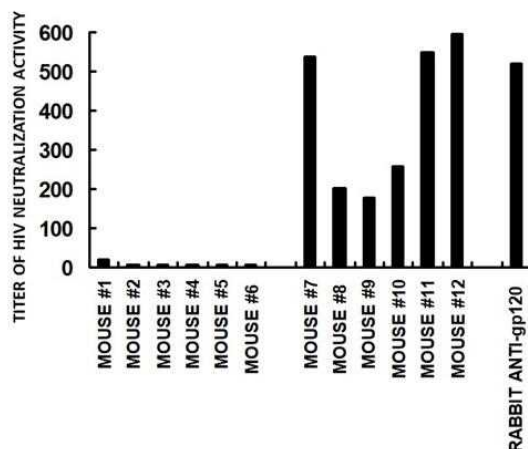


Figure 14. Evaluation of neutralizing antibody activity in anti-Gal producing GT-KO mice. Mice were immunized with gp120 (mice #1-#6), or with gp120 _{α gal} (mice #7-#12). Titer is defined as reciprocal of serum dilution displaying 50% neutralization. From (Abdel-Motal et al. 2006).

In accord with the low titers of anti-gp120 antibodies in sera of mice immunized with gp120 (Figure 13A), these sera displayed no neutralizing activity above that of the nonimmunized mice (mice #1 to #6 in Figure 14). In contrast, antibodies in sera of mice immunized with gp120_{αgal} (mice #7 to #12 in Figure 14) were found to display very effective neutralization activities, which were similar to that observed in the positive control of rabbit serum containing anti-HIV neutralizing antibodies (originating from a rabbit receiving multiple immunizations with gp120) (Wang et al., 2005).

These results demonstrate a correlation between the high titer of anti-gp120 antibody production as a result of immunization with gp120_{αgal} and the neutralizing activity of the elicited antibodies. Overall, the findings on the immune response in mice immunized with gp120_{αgal} vs. mice immunized with gp120 suggest that both T cell activation against the gp120 peptides and antibody production against gp120 are much higher in mice that were immunized with recombinant envelope glycoprotein α-gal vaccine than in mice immunized with recombinant envelope glycoprotein vaccine lacking α-gal epitopes. These findings are in line with the vaccine studies using a whole inactivated influenza virus vaccine glycoengineered to present α-gal epitopes. These results raise the possibility that glycoengineering of inactivated whole virus, subunit glycoprotein, and of recombinant viral glycoprotein vaccines for their conversion into α-gal vaccines may serve as a general method for increasing viral vaccine immunogenicity by altering their glycan shield from part of the envelope glycoprotein that protects the virus against the immune system to a component of the vaccine that effectively targets it to APC by immunocomplexing with the natural anti-Gal antibody.

TARGETING OF LOW IMMUNOGENICITY HIV PROTEINS TO APC BY FUSION WITH GP120_{αGAL}

Studies on possible changes in HIV in the course of infection in humans demonstrated the occurrence of mutations in the envelope glycoprotein gp120 which enable the virus to evade the neutralizing and destructive effects of antibodies produced against the virus replicating in the patients (Wei et al. 2003; Crooks et al. 2015). Therefore, it is assumed that vaccination only with gp120 may not elicit an immune response against HIV infections that is effective enough to protect large populations against human to human transmission of this virus (Goulder and Watkins, 2004; Lewis et al. 2014). In contrast, the internal proteins of HIV, such as tat, rev, p17 or p24, do not mutate in course of HIV infection, probably because of functional constraints that prevent viruses with such mutations from further replication. Thus, these internal proteins may serve as effective vaccines that elicit a cellular immune response which can destroy HIV infected cells by CTL. It has been assumed that increased immunogenicity of vaccinating internal HIV proteins may be achieved by effective targeting of such vaccines to APC. These proteins cannot be glycoengineered to present α-gal epitopes because they carry no glycans. Thus, it was hypothesized that fusion of such internal proteins with gp120 and subsequent glycoengineering of the gp120 glycans to present α-gal epitopes may result in increased targeting to APC of internal protein fused to glycoengineered gp120 (Abdel-Motal et al. 2010). In order to test this assumption, the core (capsid) protein p24 was

chosen as a model protein and was fused with gp120. The fused gp120/p24 protein was produced as a recombinant protein in a mammalian cell expression system and the glycan shield of the gp120 portion of the fused protein was engineered into presenting α -gal epitopes by the use of neuraminidase and α 1,3GT, as described above and in Figure 1, thus generating gp120 _{α gal}/p24 vaccine.

Production and Immunogenicity of gp120 _{α gal}/p24 Vaccine

In order to produce a fusion protein between gp120 and p24, the gene regions of *env* coding for gp120 and of *gag* coding for p24 were ligated as shown in Figure 15A (Abdel-Motal et al., 2010). The fused gene was inserted into a plasmid downstream from the strong CMV promoter. The fused gp120/p24 gene within the plasmid underwent transient transfection in human 293 cells which produced the gp120/p24 fusion protein in a secreted form. Following the isolation of the fusion protein from the culture medium by precipitation with ammonium sulfate, gp120/p24 was subjected to the two step enzymatic reaction with neuraminidase and α 1,3GT as illustrated in Figure 1. This synthesizes α -gal epitopes on the glycan shield of the fusion protein, thereby converting it into gp120 _{α gal}/p24. As indicated above, the p24 portion of the fusion protein lacks N-linked glycans and thus it lacks α -gal epitopes.

The immunogenicity of gp120 _{α gal}/p24 was compared to that of gp120/p24 by immunizing two groups of anti-Gal producing GT-KO mice with each of these two vaccines. Mice received two subcutaneous immunizations of gp120/p24 or gp120 _{α gal}/p24 in two-week interval. The vaccines were delivered at 5 μ g per injection with Ribi adjuvant. Two weeks after the second immunization the spleens of the mice were harvested and the splenocytes isolated from these spleens. The presence of T cells specific to p24 was determined by incubation with the p24 immunodominant peptide p24₁₈₉₋₂₀₇ (Qiu et al. 1999) which pulsed APC among the splenocytes. T cells with TCR specific to this peptide were activated within 24 hour coincubation with the APC pulsed with p24₁₈₉₋₂₀₇ and secreted IFN γ that could be detected for individual activated T cells by the ELISPOT assay. The number of T cells secreting IFN γ among lymphocytes from gp120 _{α gal}/p24 immunized mice was ~12 fold higher than the number of these cells in gp120/p24 immunized mice (Abdel-Motal et al., 2010). The proportion of p24 specific CD8⁺ T cells (T cells becoming CTL) was determined by double staining of cells binding anti-CD8 antibody and displaying intracellular staining of IFN γ . As shown in Figure 15B, mice immunized with gp120 _{α gal}/p24 displayed 5-20-fold higher number of CD8⁺ T cells with detectable production of IFN γ than mice immunized with gp120/p24 lacking α -gal epitopes. These findings imply that anti-Gal immunocomplexed with gp120 _{α gal}/p24 indeed markedly increased the immunogenicity of p24 in comparison to immunogenicity of p24 in the gp120/p24 fusion protein, probably because of the effective targeting to APC of the fused protein via Fc/Fc receptor interaction.

Studies above demonstrated increased immunogenicity of gp120 _{α gal} in comparison to gp120 (Figure 13A). Accordingly, immunization of anti-Gal producing mice with gp120 _{α gal}/p24 vaccine also resulted in marked increase in the antibody response against the gp120 portion of this fusion molecule in comparison to anti-gp120 antibody production in

mice immunized with gp120/p24 vaccine. This could be demonstrated by ELISA with gp120 as solid-phase antigen in which anti-gp120 antibody titer in mice immunized with gp120_{αgal}/p24 was ~30-fold higher than that measured in mice immunized with gp120/p24 vaccine (Figure 15C). These observations strongly suggest that the use of a fusion protein as α-gal vaccine in which only gp120 portion has α-gal epitopes, results in anti-Gal mediated increase in immunogenicity of both gp120 and p24, despite the lack of glycans on p24. The studies with the gp120/p24 fusion protein further suggest that in addition to increasing the immunogenicity of gp120 by converting it into gp120_{αgal}, this envelope glycoprotein of HIV may also serve as an effective platform for targeting to APC other internal virus matrix or core proteins thereby amplifying their immunogenicity.

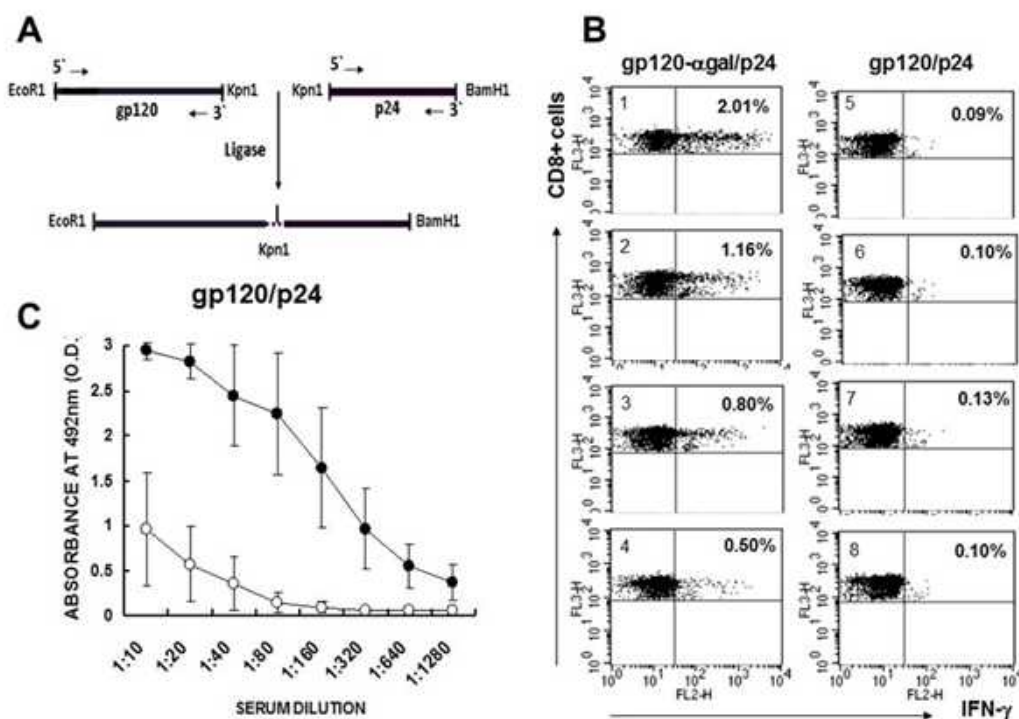


Figure 15. Studies on gp120/p24 fusion protein as vaccine in anti-Gal producing GT-KO mice. (A) Illustration of fusion of the genes used for production of gp120/p24. (B) Analysis of intracellular staining (ICS) by flow cytometry of IFN γ production in CD8⁺ T cells specific for p24 among splenocytes of mice immunized with gp120_{αgal}/p24 (left panels, mice #1 - #4) and mice immunized with gp120/p24 (right panels, mice #5 - #8). The splenocytes were co-incubated for 6 hours with APC pulsed with p24 peptides. (C) Production of anti-gp120 IgG antibodies in GT-KO mice immunized with gp120_{αgal}/p24 (●), or with gp120/p24 (○), as measured by ELISA with gp120 solid-phase antigen. Mean $\pm$ SD of results from 5 mice per group. From “The natural anti-Gal antibody as foe turned friend in medicine” by U. Galili, 2018, Elsevier/Academic Press, p. 164, after (Abdel-Motal et al. 2010).

Based on the presence of 13-16 complex type glycans on gp120 and the 2-4 antennae on each glycan, it is estimated that glycoengineering of gp120 by the enzymatic reactions described in Figure 1 could result in synthesis of 30-40 α-gal epitopes per molecule. This number of α-gal epitopes is likely to ensure effective immunocomplexing of anti-Gal with the fusion protein and targeting of the fusion α-gal vaccine to APC. This method for generating

fusion proteins between an envelope glycoprotein and a non-glycosylated viral internal protein may serve as a general method for preparation of recombinant vaccinating fusion glycoproteins that elicit effective protective antibody response against envelope glycoproteins and T cell response against both envelope glycoproteins and non-mutating proteins in other viral infections. One example which may be considered is production of influenza virus vaccines containing a fusion protein between HA and the M2 proton channel, since M2 is nearly invariant in all influenza A strains (Fiers et al. 2004; Estrada LD & Schultz-Cherry, 2019). A fusion vaccine of HA_{αgal}/M2 may be protective even against infections with influenza virus in which the HA is mutated, because of the anti-M2 effective immune response due to effective targeting of M2 to APC by the HA_{αgal} portion of such α-gal fusion vaccine. Another plausible example is COVID-19 fusion α-gal vaccines comprised of the S protein envelope glycoprotein of SARS-CoV-2 fused with other envelope or internal proteins and glycoengineering the fusion protein to present multiple α-gal epitopes. Suggested methods for preparation of α-gal SARS-CoV-2 vaccines are discussed in sections below.

SIMILARITIES BETWEEN MOUSE AND HUMAN ANTI-GAL ANTIBODIES

In order to determine whether the studies in GT-KO mice described in this chapter are applicable to humans, it is important to examine the question of similarities between the anti-Gal antibody naturally produced in humans and the anti-Gal antibody elicited in GT-KO mice as a result for several immunizations with wild type pig kidney membrane homogenate. The similarities between human and mouse anti-Gal are as follows:

- *Similarity in anti-Gal titers* – Anti-Gal IgG activity was measured in parallel in human sera and in sera of GT-KO mice immunized with pig kidney membrane homogenate. The analysis was performed by ELISA in which synthetic α-gal epitopes linked to bovine serum albumin (BSA) served as solid phase antigen. Sera from both sources displayed similar anti-Gal binding to α-gal-BSA with half maximum binding at serum dilutions of 1:160-1:320 (Figure 16A) (Abdel-Motal et al. 2006).
- *Binding to glycoengineered vaccine* – Human and mouse anti-Gal were studied for binding to gp120_{αgal} of HIV in order to determine whether both antibodies bind to α-gal epitopes. As shown in Figure 16B, both original recombinant gp120 and gp120_{αgal} display the same size since the replacement of SA on the original gp120 with galactose linked α1-3 to the glycan in gp120_{αgal} does not significantly alter the size of this HIV glycoprotein.

Both human and mouse anti-Gal bind to the α-gal epitopes on gp120_{αgal} but do not bind to glycans on gp120 as demonstrated in Western blot staining with these antibodies (Figure 16B). The presence of α-gal epitopes on gp120_{αgal} but not on gp120 is further validated by binding of the lectin *Bandeiraea simplicifolia* IB4 to the α-gal epitopes on gp120_{αgal} (Abdel-Motal et al. 2006; Wood et al. 1979).

- *Destruction of enveloped viruses by human anti-Gal antibody* – The demonstration of human anti-Gal binding to viral glycoproteins presenting α -gal epitopes is further supported by several studies demonstrating binding of anti-Gal in human serum to a variety of viruses presenting α -gal epitopes and induction of complement dependent virolysis as a result of this binding. Such binding followed by virolysis was demonstrated in Friend Murine Leukemia Virus (Rother et al. 1995), porcine endogenous retrovirus (PERV) (Takeuchi et al. 1996; Hayashi et al. 2004), HIV (Niel et al. 2005), pseudo-rabies virus, rhabdo-, lenti-, and spumaviruses (Takeuchi et al. 1997), Newcastle disease virus, Sindbis virus and vesicular stomatitis virus (Welsh et al. 1998; Pipperger et al. 2020), measles virus (Preece et al. 2002; Dürrbach et al. 2007) and vaccinia virus (Kim et al.). In all these examples, the viruses replicated in cells containing active α 1,3GT, whereas replication of these viruses in human cells lacking α 1,3GT resulted in no binding of human anti-Gal and no virolysis following incubation in human serum.
- *Targeting to APC by human anti-Gal* – The similarity between the GT-KO mouse and human anti-Gal can be further demonstrated by their ability to target anti-Gal immunocomplexed vaccines to APC, such as dendritic cells and macrophages via Fc/Fc receptor interaction. The ability of mouse anti-Gal to mediate such extensive uptake by opsonization was demonstrated above in the studies on OVA-liposomes vaccine (Figure 4). Such targeting was further visualized by the extensive uptake by mouse macrophages of rabbit RBC immunocomplexed with mouse anti-Gal, and no uptake without anti-Gal (LaTemple et al. 1999). The ability of human anti-Gal to opsonize particles and thus perform targeting to APC could be visualized with freshly obtained human lymphoma cells that were glycoengineered to present α -gal epitopes (as in Figure 1). The autologous anti-Gal of the studied patient bound to the glycoengineered lymphoma cells but not to the original lymphoma cells lacking α -gal epitope (Manches et al. 2005). Incubation for 2 hours at 37°C of the original and of glycoengineered lymphoma cells with autologous anti-Gal and with the APC of the patient resulted in extensive uptake of the tumor cells by macrophages and to a lesser extent into dendritic cells, whereas no such uptake was observed with the original lymphoma cells lacking α -gal epitopes (Figure 17). This uptake was inhibited in the presence of anti-CD64 antibody but not by anti-CD32 or anti-CD16 antibodies, implying that the uptake is mediate by high affinity Fc γ I receptors (Manches et al. 2005) which are present also on dendritic cells (Fanger et al. 1996).

All these studies strongly suggest that human anti-Gal and GT-KO mouse anti-Gal display great similarity in their characteristics, including their ability to form immune complexes with vaccinating viruses or virus envelope glycoproteins that are glycoengineered to present multiple α -gal epitopes. Thus, use of α -gal viral vaccines may be further evaluated in studies on safety and efficacy in primate and human trials.

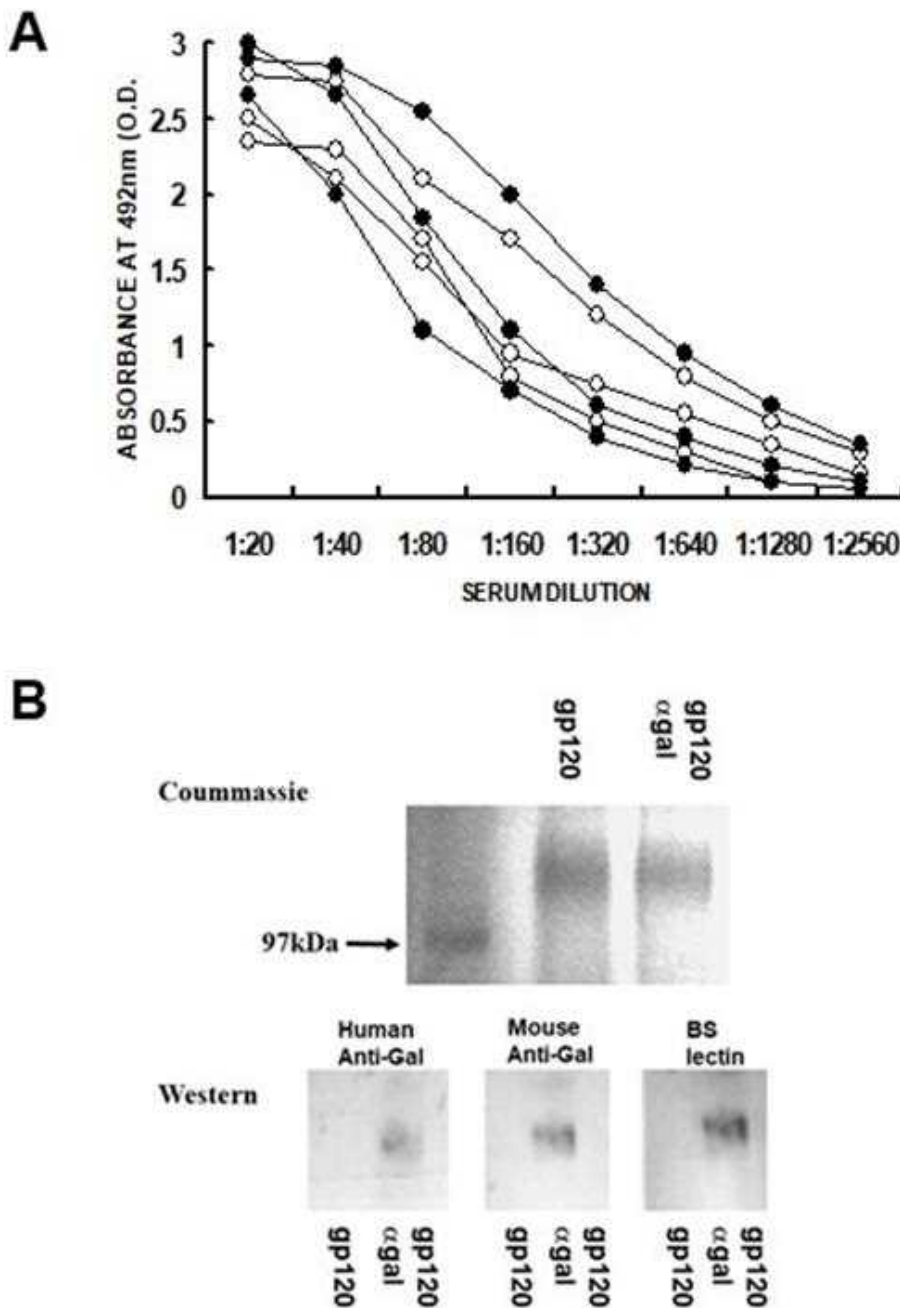


Figure 16. Similarities in activity of GT-KO mouse and human anti-Gal antibodies. (A) Comparison of anti-Gal IgG activity in human sera (●) and sera of mice immunized with pig kidney membrane homogenate (○). Data are of 3 out of 30 humans and 30 GT-KO mice with similar results. (B) Similarity in binding of both antibodies to *do novo* synthesized α -gal epitopes on gp120 by recombinant α 1,3GT. The glycoproteins were subjected to SDS-PAGE electrophoresis followed and Western blotting. Upper gel: Coomassie staining of SDS-PAGE gel. Lower gels: Western blot stained with human anti-Gal, mouse anti-Gal, and the α -gal epitope specific *Bandeiraea simplicifolia* IB4 (BS) lectin. Note that the antibodies and the lectin bind to gp120 $_{\alpha gal}$ and not to gp120. Modified from (Abdel-Motal et al. 2006).

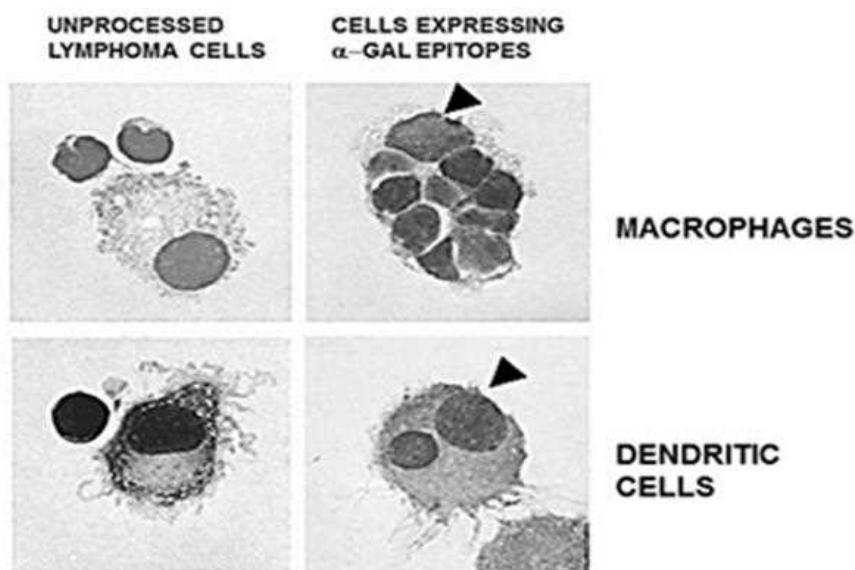


Figure 17. *In vitro* demonstration of anti-Gal mediated uptake of human B lymphoma cells by autologous APC. Human fresh lymphoma cells (B cell lymphoma) were subjected to the reactions in Figure 1 for the synthesis of α -Gal epitopes on the cell surface glycans. Lymphoma cells presenting α -gal epitopes or lacking them (i.e., original cells) were incubated with autologous anti-Gal for 30 min and subsequently, for 2 hours at 37°C with autologous macrophages or dendritic cells. At the end of incubation, the cells were placed on slides and stained. Arrowheads mark nuclei of the APC. Note the uptake of multiple glycoengineered lymphoma cells by the representative macrophage and of one lymphoma cell by the dendritic cell. No uptake of original lymphoma cells lacking α -gal epitopes was observed (x1000). Modified from (Manches et al. 2005).

METHODS FOR INCREASING EFFICACY OF COVID-19 VACCINES BY THEIR ANTI-GAL MEDIATED TARGETING TO APC

While writing this chapter, the world has been coping for 10 months with the COVID-19 pandemic with >35 million known infected individuals and an estimate of >1 million deaths associated with COVID-19 infection. There is an extensive effort for development of prophylactic vaccines against SARS-CoV-2 virus which causes the COVID-19 pandemic. As discussed below, there is a theoretical possibility that presently developed vaccines may be suboptimal for inducing immune protection against SARS-CoV-2 in many elderly individuals. This section discusses possible reasons for suboptimal future vaccine immunogenicity among the elderly and describes methods for converting COVID-19 vaccines into α -gal vaccines, thereby amplifying their immunogenicity.

SARS-CoV-2 is an enveloped, single-stranded, positive-sense RNA virus that belongs to the Coronaviridae family (Zhou et al. 2020.) . The main target for vaccine development against SARS-CoV-2 infection is considered to be the spike (S) protein which is the major envelope glycoprotein of the virus. The notion that S protein may serve as a vaccine has been supported by studies demonstrating both neutralizing anti-S protein antibodies (Cao et al. 2020; Ju et. 2020) and memory T cells specific for the S protein in sera of convalescent

COVID-19 patients (Grifoni et al. 2020; Ni et al. 2020). The S protein is present on the virus envelope as a trimer transmembrane protein that mediates attachment of SARS-CoV-2 to cells, fusion and entry into host cells (Wrapp et al. 2020). The S protein monomer is of the size of ~180 kDa and contains ~1300 aa comprised of two functional subunits. The S1 subunit (~700 aa) mediates viral attachment to its cell surface “docking” receptor, the angiotensin converting enzyme 2 (ACE-2), and the S2 subunit (~600 aa) enables fusion of the virus with the cell membrane and penetration of the virus into the infected cell (Li et al. 2003; Letko et al. 2020; Wan et al. 2020). The S protein has 22 N-glycans forming the glycan shield of SARS-CoV-2. Several of these glycans are of the high mannose type and the rest are of the complex type, as the left glycan in Figure 1.

The two main types of vaccines being developed against COVID-19 are: 1. Vaccines prepared of virus replicating in cell lines, including attenuated viruses, inactivated viruses, split vaccines, subunit vaccines prepared of the virus replicating in cell lines or produced as a recombinant protein in various expression systems, and virus-like particles. 2. Gene based vaccines prepared of nucleic acid (DNA or mRNA) containing the S protein gene. These gene based vaccines introduce the S protein gene into cells of the vaccinated individual and the transfected cells produce the vaccinating S protein which induces the generation of a protective immune response against the virus. The methods discussed in this section for increasing immunogenicity of S protein or of the whole SARS-CoV-2 virus, can be used only with the vaccines generated in the first group. The reason for this limitation is that glycoproteins produced in the vaccinated individual cannot be glycoengineered by the methods discussed below. In contrast, the inactivated whole virus, or the S protein as a subunit vaccine or as a recombinant protein are amenable to glycoengineering of the glycan shield, for converting glycans capped by sialic acid (left chain in Figure 1) into those presenting α -gal epitopes (right chain in Figure 1).

Initial clinical trials with gene base vaccines of SARS-CoV-2 S protein suggest that one vaccine injection does not suffice for inducing significant neutralizing antibody production in vaccinated individuals (Pedro et al. 2020; Jackson et al. 2020). A relatively low immunogenicity may be suggested by the great variability and modest levels of anti-S protein antibody production, observed in COVID-19 patients studied for post symptom detection onset (Xiao et al. 2020; Luchsinger et al. 2020). Taken together with the much higher proportion of elderly patients infected by and dying of COVID-19 compared to young patients (Cobos-Siles et al. 2020; Xie et al. 2020), it is possible that S protein vaccines may require amplification of their immunogenicity in order to increase the range of vaccinated individual benefiting from COVID-19 vaccines. Moreover, the need for providing COVID-19 vaccines worldwide to billions of individuals may require generation of vaccines that elicit a protective immune response with relatively low amounts of vaccinating material, i.e., vaccines with high immunogenicity.

As suggested in the Introduction section, the glycan shield of S protein is likely to negatively affect the immunogenicity of this glycoprotein. Two of the reasons for the low immunogenicity are: 1. The multiple sialic acid units on the glycans on the S protein generate an electrostatic negative charge that surrounds this glycoprotein and thus is likely to induce electrostatic repulsion with the sialic acid units on APC cell membrane glycans. This repulsion decreases the amount of vaccinating S protein molecules internalized by the APC due to random pinocytosis (Figure 2A). 2. The multiple glycans “camouflage” many of the immunogenic peptides of the S protein as they cover ~65% of S protein surface (Walls et al.

2016; Yang et al. 2020; Watanabe et al. 2020). This camouflage and the negative charge it generates further prevent many of the immunogenic peptides from engaging the corresponding B cell receptors in order to effectively activate B cells producing anti-S protein antibodies. The studies described in this chapter on the amplification of the immune response to influenza virus and to gp120 of HIV suggest that glycoengineering of the inactivated SARS-CoV-2 or of its S protein to present α -gal epitopes is likely to increase their immunogenicity, as well (Galili 2020b). In addition to the elimination of the negative electrostatic charges surrounding the S protein (Figure 2), anti-Gal will form immune complexes with the vaccinating inactivated SARS-CoV-2 _{α gal} or with S protein _{α gal} and target these vaccines for effective uptake by APC via Fc/Fc receptor interaction (Figures 2B and 3). This extensive uptake of COVID-19 α -gal vaccines by APC will be followed by increased transport, processing and presentation of immunogenic S protein peptides within the lymph nodes, thereby increasing the probability of activation of the corresponding naive T and B cells in the elderly.

Glycoengineering of α -Gal Epitopes on COVID-19 Vaccines

Glycoengineering COVID-19 vaccines to present multiple α -gal epitopes may be achieved by a variety of methods. Some of these methods are described in this section:

- 1) *Neuraminidase and recombinant α 1,3galactosyltransferase synthesizing α -gal epitopes on whole virus or on S protein* – The method for synthesis of α -gal epitopes on the inactivated SARS-CoV-2 or on subunit and recombinant S protein is illustrated in Figure 1. Neuraminidase, α 1,3GT and UDP-Gal are available from commercial sources. In the studies on the glycoengineering of influenza virus or of gp120, the α 1,3GT was produced by cloning truncated New World monkey (marmoset) α 1,3GT cDNA lacking the cytoplasmic and transmembrane domains thereby allowing for secretion of the recombinant enzyme (Henion et al. 1994). The enzyme also had a (His)₆ tag which enabled its purification. The production of α 1,3GT was performed in *Pichia pastoris* expression system stably transfected with this cDNA in a plasmid used for this expression system (Chen et al. 2001). The secreted enzyme was isolated by passing the medium through a nickel-Sepharose column which attaches the enzyme via a (His)₆ tag, followed by elution with imidazole. In addition to synthesis of multiple α -gal epitopes on influenza virus and on gp120, this α 1,3GT was found to effectively synthesize α -gal epitopes on human tumor cells by the two step enzymatic reaction illustrated in Figure 1 (Chen et al. 2001; Galili et al. 2003; Furukawa et al. 2017) and on a variety of mammalian RBC and nucleated cells (Ogawa & Galili, 2006). Thus, it is probable that inactivated SARS-CoV-2 or its S protein, subjected to the enzymatic reactions in Figure 1, will effectively undergo a similar conversion of the SA carrying glycan shield to multiple α -gal epitopes presented on the glycans. Whereas the resulting inactivated SARS-CoV-2 _{α gal} can be isolated from the reaction mixture by precipitation or washing methods, the S protein _{α gal} can be purified by passing the reaction mixture through a

column of the lectin *Bandeiraea simplicifolia* IB4 linked to Sepharose or to other porous beads. This lectin binds specifically α -gal epitopes (Wood et al. 1979), thus it would bind the S protein _{α gal} and no other components of the reaction mixture. The bound S protein _{α gal} may be eluted from the washed column by free galactose, melibiose or α -methyl galactoside, which subsequently may be removed by dialysis. It is not known whether chemical linking of α -gal epitope to the S protein (e.g., linking of the trisaccharide via a spacer to lysins) is a suitable method because such linking may affect the specificity of the immune response against the native protein.

2) *Synthesizing α -gal epitopes on replicating SARS-CoV-2 virus-*

SARS-CoV-2 _{α gal} is by engineering the host cells to effectively synthesized α -gal epitopes on the S protein of the virus envelope. As discussed above, complex type glycans on the S protein, as those on other viral and cellular glycoproteins, are synthesized within compartments of the Golgi apparatus by a series of glycosyltransferases that add in a sequential manner carbohydrate units to the nascent carbohydrate chain on glycoproteins and glycolipids. Many of the glycans are “capped” with sialic acid which is linked to the glycan by sialyltransferases (SiaT), whereas the terminal galactose of the α -gal epitope is linked to the same glycan by α 1,3GT. Both glycosyltransferases reside within the trans-Golgi compartment and compete with each other for capping the glycan (Smith et al. 1990). The ultimate number of α -gal epitopes vs. sialic acid epitopes on a virus depends on the relative activity of α 1,3GT vs. that of SiaT. As shown in studies on activation of influenza virus specific T cells following anti-Gal mediated targeting of inactivated virus to APC, there is a correlation between the number of α -gal epitopes per vaccinating virus and the extent of T cell activation by peptides processed and presented by the APC (Galili et al. 1996). This suggests that by increasing the activity of α 1,3GT within the trans-Golgi of host cells, more α -gal epitopes will be synthesized on the glycan shield of the replicating virus. Thus, it is possible that stable transfection of the host cell line in which SARS-CoV-2 is propagated, with several copies of the α 1,3GT gene (*GGTA1*) will result increased activity of α 1,3GT. A high number of copies of this gene will elevate the amount of α 1,3GT thereby increasing the number of synthesized α -gal epitopes on the S protein of the replicating virus. This assumption is supported by studies demonstrating that measles virus replicating in human host cells transfected with the α 1,3GT gene present α -gal epitopes binding anti-Gal on their envelope glycoproteins (Preece et al. 2002; Dürrbach et al. 2007). A similar effect of increased number of α -gal epitopes on the virus may be achieved by disruption (i.e., knockout) of SiaT genes in host cells which will result in decreased competition of SiaT capping the glycans with SA and α 1,3GT thus, enabling α 1,3GT capping more glycans with α -gal epitopes. Since part of the glycans on the S protein are of the high mannose type, it is further possible that by disrupting genes associated with synthesis of high mannose glycans, more glycans will be synthesized as complex type glycans which enable additional synthesis of α -gal epitopes. Thus, an optimal host cell for production of SARS-CoV-2 with multiple α -gal epitopes may be a cell with several copies of the α 1,3GT gene, with reduced SiaT activity and possibly with reduced proportion of glycans of the high mannose type. It should be

noted that the glycans on SARS-CoV-2 also may affect the extent of replication of the virus in the host cell. Thus, following each genetic manipulation step of the host cells, the extent of virus replication should be determined in order to confirm that it was not affected. A similar approach may be considered for cell expression systems producing recombinant S protein and for cells producing SARS-CoV-2 virus like particles. All these vaccine materials may be produced with a large number of α -gal epitopes on the glycan shield in cells that have several copies of the α 1,3GT gene, disrupted SiaT genes and possibly disrupted genes of enzymes synthesizing high mannose glycans.

- 3) *Transduction with replication defective adenovirus containing the α 1,3GT gene for synthesis of α -gal epitopes on vaccinating viruses* – Multiple copies of the α 1,3GT gene may be introduced into host cells also by transduction with replication defective adenovirus containing the α 1,3GT gene (Deriy et al. 2002), prior to infection of the cells with SARS-CoV-2. Mouse α 1,3GT cDNA was inserted into a replication-defective adenovirus vector which lacks the E1 and E2 genes (Gao et al. 1996). This viral vector, designated Ad α GT, could be propagated in human 293 cells that have the viral E1 complementing gene. Transduction of human HeLa cells with Ad α GT resulted in immediate penetration of ~ 20 Ad α GT copies into each cell and the appearance of α 1,3GT mRNA after 4 hours (Deriy et al. 2002). Analysis of the appearance of α 1,3GT catalytic activity within the transduced cells at various time points demonstrated activity of this enzyme 6 hours post transduction. The α -gal epitopes were first detected on the cell surface glycans 10 hours post transduction. After 24 hours, each cell expressed $\sim 2 \times 10^6$ epitopes and after 48 hours the cells expressed a maximum number of 4×10^6 epitopes per cell. Thus, it is suggested that transduction of host cells with Ad α GT 12-24 hours prior to the infection of the cells with SARS-CoV-2 may result in effective synthesis of α -gal epitopes on the replicating virus. Since the number of complex type glycans vs. that of high mannose glycans may vary from one cell line to the other, a cell line producing virus with the highest number of glycans of the complex type may be preferable for intracellular synthesis of α -gal epitopes on SARS-CoV-2. Alternatively, glycoengineering the optimal cell line for decrease or elimination of high mannose glycans may require the inactivation of gene(s) associated with synthesis of such glycans. Glycoengineering of cells producing the S protein by methods suggested above for host cells producing replicating virus with maximum α -gal epitopes may also be applicable to the S protein producing cells.
- 4) *Production of S protein _{α gal} in glycoengineered yeasts*– Production of relatively large amounts of recombinant S protein _{α gal} may be achieved in yeast expression systems by stable transfection of the yeast cells with the S protein. However, in order to achieve synthesis of α -gal epitopes on the S protein product, yeast need to undergo additional glycoengineering manipulation since naturally, yeast have glycosyltransferases that can synthesize N-linked glycans only of the high mannose type. Glycoproteins which carry only the high mannose N-linked glycans have short half-life in humans. For production of glycoproteins with complex type glycans, yeasts such as *Pichia pastoris* have been glycoengineered to synthesize humanized

glycans with the terminal structure of complex type by introducing the corresponding glycosyltransferase genes (Choi et al. 2003; Wildt & Gerngross, 2005). In order to produce S protein with glycan shield presenting multiple α -gal epitopes, the *SiaT* gene in these yeasts may be replaced by the $\alpha 1,3GT$ gene (*GGTA1*). It remains to be determined whether such a manipulation is feasible and to what extent this expression system can produce sufficiently large amounts of S protein _{α gal} for preparation of a high number of vaccines.

- 5) *Production of S protein _{α gal} in glycoengineered bacteria* – Bacteria such as *E. coli* may also be engineered to produce S protein _{α gal}. Production of recombinant proteins in bacteria has been limited because of the difficulties in secretion of recombinant proteins beyond the periplasmic space into the culture medium. Secretion of such recombinant proteins has been achieved by the use of a nonionic detergent such as Triton X-100 (Fu, 2010). Secretion of a recombinant protein also could be achieved by modifying the protein for targeting it to the outer membrane and further into the extracellular medium (Fisher et al. 2011). Other studies have demonstrated biosynthesis of α -gal epitope oligosaccharides in *E. coli* by introducing into this bacterium genes coding for the sequence of mammalian glycosyltransferases including $\alpha 1,3GT$, required for α -gal epitope synthesis (Chen et al. 2000; Gebus et al. 2012). Moreover, *E. coli* was engineered to synthesize N-linked glycans by transfer into it an N-linked glycosylation system found in *Campylobacter jejuni* (Wacker et al. 2002; Fisher et al. 2011). It is suggested that combining these characteristics by introducing the genes coding for the above enzymes into one bacterial strain may lead to the production of an expression system that effectively produces S protein _{α gal} in quality and amounts suitable for vaccine preparation.

Potential Safety Issues with Future α -Gal Vaccines in Humans

Humans are regularly exposed to α -gal epitopes in meat such as beef, pork and lamb. However, relatively few individuals have been exposed to this epitope administered in the form of injection. This raises the question whether administration of vaccines presenting α -gal epitopes is safe in humans. The most common example of α -gal epitopes administration into humans in a form that is constantly exposed to the blood circulation is the replacement of impaired heart valves with bioprostheses of porcine heart valves or of bovine pericardium crosslinked by glutaraldehyde. Like other porcine and bovine tissues, these valves present multiple α -gal epitopes (Tanemura et al. 2000). No toxicity or other deleterious effects have been observed in association with this treatment which is widely used for replacement of impaired heart valves in elderly and young patients, respectively. Phase I clinical trials in which α -gal glycolipids are injected into solid tumors of cancer patients, in order to convert the tumor into autologous anti-tumor vaccines, also were found to be safe and demonstrated no adverse effects (Whalen et al. 2012; Albertini et al. 2016). Similarly, synthesis of α -gal epitopes on autologous tumor cell membranes followed by their incubation with anti-Gal and autologous dendritic cells, was performed for converting autologous tumors into vaccines.

Injection of such mixtures into patients was reported to be safe with no adverse effects, as well (Qiu et al. 2011; 2013; 2016).

A small proportion of individuals in various populations was found to produce anti-Gal IgE antibodies following the bite of several kinds of ticks including *Ambliomma Americanum* (Lone Star tick) in USA (Commins & Platts-Mills, 2013), *Ixodes ricinus* in Europe (Hamsten et al. 2013), *Haemaphysalis longicornis* in Japan (Chinuki et al. 2016) and *Ixodes holocyclus* in Australia (van Nunen, 2015). This IgE mediates allergic response to α -gal epitopes in meat is referred to as “ α -gal syndrome” (Wilson et al. 2017; Pollack et al. 2019). If viral vaccines presenting α -gal epitopes are developed for use in humans, it remains to be determined whether individuals with α -gal syndrome display adverse effects following administration of α -gal vaccine. In addition, vaccination of such individuals with α -gal vaccine will enable determining whether they require anti-allergy treatment prior to vaccination.

CONCLUSION

Production of the natural anti-Gal antibody in large amounts in all humans who are not severely immunocompromised, enables development of several novel immunotherapies. In these immunotherapies, the interaction between anti-Gal and the carbohydrate antigen it recognizes- the “ α -gal epitope,” may be applied for generating a variety of immune responses that can be beneficial to treated patients (Galili, 2013a; 2018). One of these applications is the amplification of viral vaccines efficacy by glycoengineering the glycan shield of glycoproteins on enveloped viruses to present multiple α -gal epitope and thus produce α -gal vaccines. Administration of viral α -gal vaccines in the form of inactivated whole virus vaccine, or of envelope glycoprotein vaccine results in formation of immune complexes with the natural anti-Gal antibody. This antibody is released from capillaries ruptured by the syringe needle at the vaccination site. The complement activation by such immune complexes results in generation of chemotactic peptides that recruit APC to the injected vaccine suspension or solution. This is followed by extensive endocytosis of the vaccine/anti-Gal immune complexes into the APC, instead of random suboptimal uptake by pinocytosis of standard non-immunocomplexed vaccines. The endocytosis is induced by interaction between the Fc portion of immunocomplexed anti-Gal and Fc receptors on APC and possibly between C3b attached to the immune complexes and C3b receptors (CR1) on APC. The internalized vaccines are processed within the APC and their immunogenic peptides are presented on cell surface MHC molecules. Transport of these vaccines by APC to regional lymph nodes results in activation of many virus specific helper and cytotoxic T cells which may effectively prevent the subsequent detrimental infection by the corresponding infectious virus. Studies in anti-Gal producing mice on the efficacy of α -gal vaccines, including inactivated whole influenza virus and recombinant gp120 of HIV, demonstrated 10-200 fold increase in the immune response with α -gal vaccines vs. vaccine lacking α -gal epitopes. Studies of challenge with a lethal dose of infectious influenza virus demonstrated 8 fold higher resistance to challenge of a lethal infection dose in mice immunized with α -gal vaccine than in the absence of α -gal epitopes on the vaccine. The α -gal vaccine method can further enable increasing immunity of internal viral proteins of low immunity by formation of fusion α -gal vaccines

between virus envelope glycoprotein and virus internal protein such as gp120_{αgal}/p24 of HIV which was found to greatly increase immunogenicity of both gp120 and p24.

The studies of influenza virus and gp120 α -gal vaccines strongly suggest that glycoengineering of SARS-CoV-2 inactivated whole virus and of this virus envelope S protein vaccines to present α -gal epitopes will markedly increase the immunogenicity and efficacy of these COVID-19 vaccines. This is because the number of N-linked glycans on the S protein is high, thereby ensuring the synthesis of many α -gal epitopes on the glycan shield of this envelope glycoprotein. Synthesis of multiple α -gal epitopes on SARS-CoV-2 or on S protein vaccines may be feasible by several methods. These include: *In vitro* enzymatic synthesis; propagating the virus in host cells engineered to contain many copies of the α 1,3GT gene (*GGTA1*) by stable transfection; transduction of host cells with replication defective Ad α GT virus; production of S protein_{αgal} in mammalian cell, yeast, or bacterial expression systems engineered to contain the glycosyltransferase transgenes required for the synthesis of α -gal epitopes.

Introduction of α -gal epitopes into humans, on glycans porcine heart valve or as glycolipids in cancer immunotherapy suggest that α -gal vaccines may be safe in humans. However, since a small proportion of humans display delayed allergic response to α -gal epitopes in meat (" α -gal syndrome"), it should be determined whether individuals with α -gal syndrome require anti-allergy treatment prior to receiving α -gal vaccines.

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Chapter 381

THE MYOPIA EPIDEMIC - A WORLDWIDE VISUAL CONCERN

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ABSTRACT

Myopia is the most common ocular disorder worldwide. It is the leading cause of visual impairment in children, and the incidence is increasing rapidly. In 2010, an estimated 1.9 billion people (27% of the world's population) had myopia, 70 million of whom (2.8%) had high myopia, commonly defined as refractive error $\geq -6D$. These numbers are projected to rise to 52% and 10%, respectively, by 2050. Vision impairment related to myopia has significant effects on a patient's quality of life, including physical, emotional, and social functioning. Pathologic myopia (prevalence 0.9%–3.1%), which confers an increased risk of cataract development, retinal detachment, glaucoma, and even blindness, is particularly devastating.

Major economic impact has resulted from the increasing prevalence of myopia. Experts have estimated the loss in world productivity caused by uncorrected myopia in 2004 to have been 268.8 billion international dollars and the cost of addressing this problem to be US \$28 billion over 5 years.

Myopia is a particular public health concern in many East Asian countries, where the condition affects 80% to 90% of high school graduates. Of these individuals, 10% to 20% have sight threatening pathologic myopia. There appears to be not only environmental but also genetic factors that play a part in development and progression of myopia.

Initial research has shown that outdoor activity, sun light exposure, and low dose atropine all seem to help slow down the rate of myopia. It is theorized that visual input to the peripheral retina regulates adjacent scleral growth, and the relative peripheral hyperopic defocus in myopic eyes that remains despite wearing corrective myopic spectacles may be associated with elongation of the globe. Some have proposed using contact lenses that emphasize peripheral myopic defocus—and thus minimize hyperopic defocus—to help decrease progression of myopia. Similarly, there have been promising developments in technologies of lens spectacles to help slow down the rate of myopia. Perhaps the most exciting advancements have been in establishing efficacious dosing and

drug delivery of low dose atropine to the pediatric population. The concern for this global epidemic of myopia has spurred intense research efforts, and there are a number of promising avenues for prevention and treatment.

INTRODUCTION

Epidemiology

The global myopia epidemic and its attendant visual consequences have been well established. There is a race to ameliorate that rise as incidence across the globe continues to increase at an alarming rate. Myopia is the most common disorder of the eye as well as the leading cause of visual impairment in children [1, 2]. Patients with myopia experience difficulty with focus on distance objects without appropriate corrective eyewear, which can interfere with daily activities such as learning in school or driving safely.

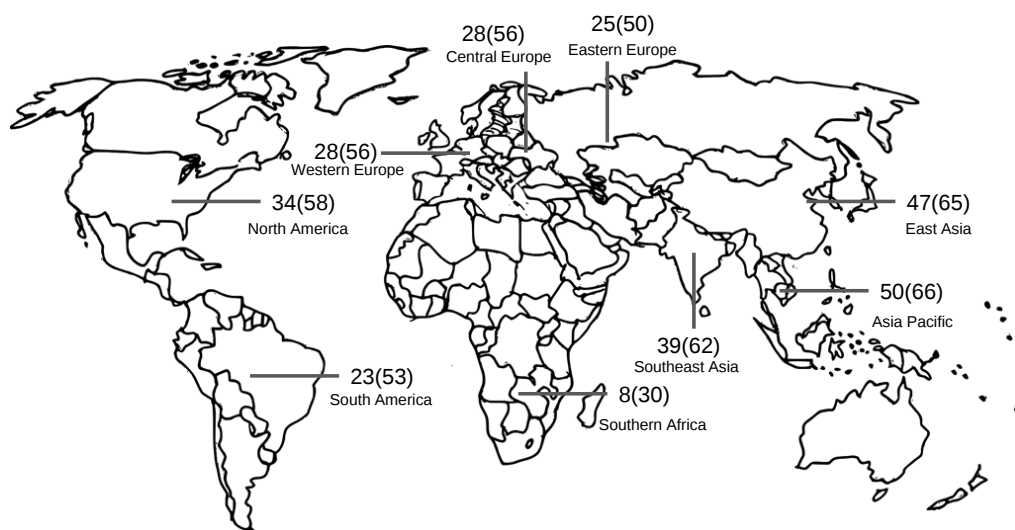


Figure 1. The prevalence of myopia current % (projected % in 2050).

The World Health Organization (WHO) defines myopia as spherical equivalent objective refractive error of ≤ -0.50 diopter in either eye, high myopia as ≥ -5.00 D in either eye, and myopic macular degeneration as refractive error ≥ -5.00 D with specific retinal changes, or refractive error ≥ -10.00 D with or without retinal changes [3].

According to data compiled from 145 studies including 2.1 million subjects, an estimated 22.9% of the world population had myopia and 2.7% had high myopia in the year 2000, with the largest cohort between 10-39 years old [1]. In addition, by the year 2050 it is projected that a staggering 49.8% of the world population will be myopic, with 9.8% of them high myopes [1] (see Figure).

The myopia epidemic is of particular concern in certain East Asian countries. For instance, in China and Taiwan, the disorder is estimated to affect 80-90% of high school graduates, 10-20% of whom have vision threatening pathologic myopia [2, 4]. According to

Lam et al. the prevalence of myopia and high myopia in children age 6 was 18.3% and 0.7% respectively, and for those at age 12 was 61.5% and 3.8% [4].

In North America, the prevalence of myopia among high income families was estimated to be 28.3% in 2000 and projected to be 58.4% in 2050 [1]. In the United States, analysis of the IRIS (Intelligent Research in Sight) Data registry and the NHANES (National Health and Nutrition Examination Survey) data revealed diopter-adjusted prevalence of high myopia in 2014 to be 3.92% in 2014 with prevalence of pathologic myopia of 0.33% [5]. A cross sectional study of pediatric patients in Southern California by Theophanous shed light on the breakdown of myopia among age groups and race/ethnic background. Myopia was found to be more common in older children (59% in ages 17-19 versus 14.8% in those between 5 and 7 years of age) [6]. Household income was found to play a role as median households with income of \$25,000 -\$40,000 had lower rates of myopia compared to households with incomes less than 25,000 [6]. In addition, patients of Asian/Pacific Islander descent had an increased rate of myopia compared to their Caucasian and African American counterparts [6].

Wen et al. looked at the prevalence of myopia in a multi-ethnic pediatric eye disease study and found that non-Hispanic white children had the lowest overall prevalence of myopia compared to the other four racial/ethnic groups studied, whereas children of Asian descent had the highest prevalence [7]. However, no difference was found between gender in the children included in the study.

Sequelae of Myopia

There are significant visual complications associated with myopia, in particular pathologic myopia, which has an estimated prevalence of 0.9%-3.1% [3, 8]. Among the many sequelae are cataract, retinal damage including choroidal neovascularization and retinal detachment, glaucoma, and blindness. The WHO notes that the most common cause of vision impairment is undercorrected myopia likely from lack of access to providers and resources for corrective eyewear [3]. While corrective eyewear can remedy simple myopia and cataracts can be removed with surgery, the peripheral vision loss that occurs with glaucomatous optic nerve damage and the central vision loss that occurs with Myopic Macular Degeneration [MMD] of the retina is unfortunately permanent. Glaucoma involves progressive damage to the optic nerve fiber layer and loss of peripheral vision that can eventually affect central vision if left untreated. MMD can be seen clinically as either patchy or diffuse chorioretinal atrophy. In advanced cases, abnormal blood vessel development, known as choroidal neovascularization (CNV), can develop in the fovea of the retina, which is responsible for central vision [3]. These abnormal blood vessels leak blood and proteins into the surrounding retina and can cause vision loss and distortion. The prevalence of CNV in individuals with MMD is estimated to be 5.2% to 11.3%, and can be bilateral in 30% of patients. Macular holes, which can be particularly damaging to central vision, can occur in 6% to 8% of these cases [8, 9].

As previously mentioned, the burden of disease is increased in patients of Asian descent. An estimated 1% of Caucasian compared to 1-3% of Asians counterparts have pathologic myopia [3, 8]. Furthermore, pathologic myopia in Asians leads to more visual impairment and blindness compared to Caucasians [3, 8].

Financial Burden of Myopia

The myopia epidemic also has significant global economic consequences. Poor vision resulting from myopia leads to loss of work force and inefficiencies in the work and home environment. According to Fricke, uncorrected refractive error contributes to a loss of \$202 billion of the global gross domestic product [10]. In addition, it is estimated that there was a loss in world productivity of 268.8 billion international dollars in 2004, and it cost 28 billion US dollars to address the issue [11]. The astounding burden disproportionately affects people from low-income families [12]. Additionally, a study by Ma et al. in China suggests that providing access to refractive correction in low socioeconomic areas would improve educational outcomes in children [13].

In Singapore the direct cost attributed to remedy myopia per child per year is estimated to be \$148 US dollars [14]. Zheng et al. looked at 125 myopic patients and found the mean cost per person per year was \$709 US dollars and a lifetime per capita cost of \$17,020 for those with an 80-year lifespan. A breakdown of the cost estimate includes such services as glasses, contact lenses, refractive surgery, and overall ophthalmologic services [15].

PATHOGENESIS

Onset/Progression

The onset of myopia seems to increase significantly after the age of 6. This increase has previously been linked in studies to the beginning of school and attendant increase in near work and hours spent studying [16, 17]. The prevalence rate of myopia in subjects less than 6 years of age tends to be less than 5% even in areas of high burden such as East Asia [18-21]. However, the incidence in even this very young population is increasing as well. Fa et al. found an estimated increase in myopia of 6.3% from 2.3% over 10 years among Hong Kong preschoolers [22].

In Chinese populations the annual incidence of myopia between the ages of 7-15 years has been relatively constant with up to 80% of certain subpopulations suffering from myopia [23]. Studies show comparable patterns in other East Asian countries, with increased incidence at even younger ages suggested in Singapore, Taiwan, and Hong Kong [24-26]. Western countries seem to fare better, with meta-analyses showing a much lower childhood incidence of myopia with a later age onset as well [27]. Rahi et al. reported that most cases of myopia identified in the United Kingdom were in children 16 years of age or older [28].

The meta-analysis performed by Rudnicka et al. reported that populations in South Asia, black populations in Africa, and Hispanics tended to have lower prevalence of myopia than Western white populations, whereas black populations outside of Africa, South-East Asians, Middle Eastern/North African populations, Native Hawaiians, and American Indians have a higher prevalence [27]. All these groups still have significantly lower incidence of myopia compared with East Asian populations [27].

Environment

The alarming rise of myopia has led investigators to work to uncover modifiable risk factors for myopia in order to engage in early prevention. Multiple risk factors contributing to the development of myopia have been postulated. Among those explored are time spent outdoors, near work, and a societal shift to dependence on phones, tablets, and computers.

At the current time, the predominant protective environmental factor seems to be time spent outdoors. A potential dose dependent relationship has been researched between the amount of time spent outdoors and the risk of myopia [29, 30]. In a systematic review Xiong et al. looked at the relationship between outdoor time with the incidence of myopia as well as progression in already myopic eyes. There was a protective effect against myopia *onset* with increased time spent outdoors. Unfortunately, there was no effect on slowing progression in patients *already* myopic [29]. The study elucidated the need for further investigation on the subject including optimal time outdoors and strategies for implementing this protective environmental factor. The authors acknowledged multiple limitations of the study including retrospective nature and high heterogeneity among the studies analyzed.

The hypothesized mechanism of protection of time spent outdoors include biochemical activity, a uniform dioptric space, relaxed accommodation and increased pupil constriction, as well as physical activity [30]. Light stimulated retinal release of dopamine and other neurotransmitters that inhibit increased axial length may serve as the biochemical mechanism for decreased myopia with outdoor activity [30, 31]. This has been supported to some degree in certain animal studies while other mechanisms explaining outdoor time protection have had less of an impact [30, 31]. Outdoor sports and other physical activity have been theorized to contribute to decreased incidence of myopia. Interestingly, a study by Rose et al. found that there was no association between participating in indoor sports and myopia [32]. Further studies attempting to separate the factors of increased light exposure and outdoor/indoor activity would be of great interest in guiding recommendations for children and physical education classes in school.

Near Work

Another environmental factor highly investigated in association with myopia is near work. The definition of and means of measurement of near work has been highly variable among different studies. This included level of education, duration of sustained study time, duration of leisure reading, books read per certain amount of time, font size, and screen use [33].

Near work as a cause of myopia is especially problematic given that over the last two decades, daily routine in many developed countries has shifted exponentially towards the reliance on digital formats for work, leisure, and activities of daily living. Much of this digital content is consumed on screens at arm's length, such as on smartphones and desktop or tablet computers. Communication has transitioned heavily to texting, emails, and video usage, all which require sustained near work activity. This dependence on screen time contributes to increased cumulative near work hours. Huang et al. found in a systematic review and meta-analysis of 12 cohort studies and 15 cross-sectional studies that increased time spent

participating in near work activity was associated with higher odds of myopia, and that the odds of developing myopia increased by 2% for every additional diopter-hour of near work performed per week [34].

Even more worrisome is the fact that children are introduced to screen time via phones and tablets at a younger and younger age as forms of early education and entertainment. The Sydney Vascular and Eye Study (SAVES) was a 5 to 6 year follow up study of 2103 children that showed an increased odds of incidence of myopia by age 12 for those children with short periods of time outdoors and longer duration and frequency of near work [30]. A Study in Shanghai by You examined the relationship between various near work activities among 6-to-10-year-old children and myopia over a one year follow up [35]. In the study, the participants and their parents filled out a questionnaire together on nine different near work factors in addition to baseline eye exams which included measurements such as axial length and cycloplegic refraction at baseline and one year follow up. They reported on various factors that were associated with increased myopia as measured by both cycloplegic refraction and axial length biometry. These included use of an inappropriate distance with the eye while reading, writing, or engaging in TV screen time, poor lighting while reading or writing, and continuous near work greater than 30-40 minutes without an eye break [35].

The Covid19 pandemic and the attendant recommendations for social distancing have resulted in a shift to working from home for many adults, and remote learning for children, resulting in an exponential increase in screen time for both groups. There is great concern that a semi-permanent switch to digital classrooms can have a devastating acceleration in the rise of myopia in young children. Currently, the WHO and the American Academy of Pediatrics recommend no screen time at all for children younger than 2 years of age, and less than 1 hour a day for children 2 to 5 years old [36]. More studies are required in the future to study the effects of digital near work on children and adolescents, especially those of handheld devices.

Genetics

Genetic factors and heritability have also been explored in the development of myopia. More than 150 gene loci associated with myopia have been identified in genome-wide association studies [37]. A study by Chen reported nine gene loci that were associated with axial length *RSPO1*, *C3orf26*, *LAMA2*, *GJD2*, *ZNRF3*, *CD55*, *MIP*, *ALPPL2*, and *ZC3H11B* [38]. The researchers organized the mentioned loci into two groups. The first group includes loci involved in the Wnt signaling pathway related to the regulation of axial length (*RSPO1* and *ZNRF3*). The other group includes 5 loci that were found to be associated with common refractive error variation *LAMA2*, *GJD2*, *CD55*, *ALPPL2*, and *ZC3H11B*.

A meta-analysis by Sanfilippo reported that heritability for refractive error was 0.71 [39]. Other heritability estimates from studies have ranged from 0.11 to 0.98, the higher estimate coming from a study of Finnish female twins [40]. Although many gene loci have been identified, genetic risk scores estimate they only explain 0.6% of the variance in refractive error at age 7 and only 2.3% at age 15 [43].

Family history of myopia has also been investigated. Zhang et al. summarized in a meta-analysis an association between the number of myopic parents and incident myopia [43]. The

odds ratios calculated in this analysis ranged from 1.44 to 2.96 for having a myopic child depending on the number of myopic parents [43]. Another study of Chinese students found that there were 26-fold higher odds for prevalent myopia in students with close reading distances and two parents with myopia [44]. However, family history as a risk factor has further indications, particularly in light of increased myopic prevalence. Xiang comments that the odds of a child becoming myopic with two myopic parents is different than the odds of a myopic child having parents that are both myopic because there are likely more children than parents with myopia [45]. Thus, the sensitivity of parental myopia in predicting childhood myopia remains weak [46].

TREATMENT

Contact Lenses

It is theorized that input to the peripheral retina regulates adjacent scleral growth, and in turn the peripheral hyperopic defocus associated with globe elongation and thus myopia [47, 48]. Consequently, there is interest in using contact lenses that emphasize peripheral myopic defocus to help counteract hyperopic defocus and to decrease myopic progression. Early studies have been promising, with Lam of Hong Kong finding a 25% slower progression of myopia with specialty bifocal defocus-incorporated soft contact lenses compared with single-vision soft contact lenses. This treatment effect had a positive correlation with length of time the defocus-incorporated soft contact lenses were used [49].

A review by Bullimore looked at multiple treatment methods researched in the prevention of myopia, including soft contact lenses that alter central distance zone and provide increased peripheral retina positive power [50]. Variables manipulated among studies included lens design, amount of power provided by the lens periphery, spherical area of positive power, multiple concentric treatment zones, and spherical aberration. They concluded that while single vision soft contact lenses were not recommended in myopic children, multifocal and orthokeratology lenses could potentially become the standard of care for preventing myopic progression in children and adolescents.

A study by Walline looked at progression of axial length and myopia among eight-to-eleven-year old children fitted with distance center soft multifocal contact lenses over a two year period [51]. It was found that myopia and axial length progression were decreased in participants by 50% and 29% respectively. Another study found similar progression reduction in dual-focus soft contact lenses among participants eleven to fourteen years of age. It was reported that in 70% of the children enrolled in the study, myopic progression was reduced by 30% in those assigned to dual focus lenses [52].

A study among Chinese children ranging from ages seven to fourteen by Sankaridurg found that reducing relative peripheral hyperopia with contact lenses can slow progression of axial length and myopia as well [53]. They reported that the spherical equivalent at 12 months was 34% less (-0.57D in contact lenses versus -0.86 D glasses) and that axial length was 33% less in those in the contact lens group.

Orthokeratology

Orthokeratology involves the placement of a hard gas permeable contact lens overnight to temporarily alter the cornea curvature to improve visual acuity throughout the day. Previous studies have shown temporary improvement of visual acuity, though there is expected regression of the majority of the effects during the day when the lens is not worn. Current research focus has turned to the potential of orthokeratology in reducing myopic progression. A randomized trial of 78 participants by Cho and Cheung over a two year period found a reduced increase in axial length by 43% in those assigned to orthokeratology compared to those wearing single-vision glasses over time [54]. In addition, it was reported that younger participants had faster rates of axial elongation suggesting earlier initiation of treatment. A study by Li estimated the two year reduction in axial length progression to be around 0.28mm [55].

A study by Santodomingo-Rubido looked at the increase in axial length over a seven year period in a group of subjects wearing orthokeratology lenses compared to controls. Rate of change in axial length was reported to be 33% less in those patients using orthokeratology lenses [56]. Another prospective study over five years found a statistically significant difference in axial length between orthokeratology versus control groups [57]. Axial length during the 5 years was 0.99 ± 0.47 for the orthokeratology group and 1.41 ± 0.68 mm for the control group. It must be noted that there are considerable safety concerns associated with orthokeratology including but not limited to the potential for blinding microbial keratitis associated with overnight contact lens wear, and thus the use of orthokeratology at all is still considered controversial in many medical ophthalmologists [58, 59].

MiSight

MiSight dual-focused optical design soft contact lenses by Cooper Vision (USA) are the first contact lenses approved by the FDA for reducing myopia in November 2019. The study performed in 2018 showed a significant slowing of the progression of myopia and axial length over a four year time period including in children starting use at later ages [60].

A three year multicenter randomized clinical trial of MiSight lenses was conducted by Chamberlain comparing the dual-focus MiSight lens with a single-vision contact lens of the same material and general geometry. Overall, it was reported that MiSight was effective in slowing the progression of spherical equivalence and axial length in the participants ages eight to twelve years old. Spherical equivalent refraction was found to be 59% less in the MiSight group than the control group (-0.51 ± 0.64 vs. -1.24 ± 0.61 D, $P < .001$) [61]. In addition, mean change in axial length was also found to be 52% less in the MiSight group (0.30 ± 0.27 vs. 0.62 ± 0.30 mm, $P < .001$). A two year study performed in Spain by Ruiz-Pomeda looked at MiSight compared to single vision contact lenses, and reported similar findings that the MiSight group had a slower progression of myopia and decreased axial elongation compared to the control single-vision contact lens wearers [62].

Spectacles

Glasses have also been an area of interest in efforts to slow the myopia epidemic, though many studies have not found clinically significant reductions. The COMET (Correction of Myopia Evaluation Trial) was a landmark study that compared progression of myopia in subjects using progressive addition lenses (PALs) and single vision lenses. PALs are lenses that have a blended bifocal design with the top segment of the lens used for distance focus, and progressively positive lens power towards the bottom of the lens with corresponding shorter and shorter focal points. It was found that myopia progression was slowed in subjects in the PALs group compared to the group with single vision lenses. A 5 year follow up of the COMET study found only a small statistically significant difference between the groups that was present only during the first year [63]. Edwards reported a similar disappointing finding in progressive addition lenses versus single vision lenses. After two years they found that there was no difference in axial length or myopic progression between the two groups [64].

Bifocal glasses have also been evaluated in reducing accommodative lag and hyperopic focus to reduce myopia. In a three year randomized control trial by Cheng et al. subjects were assigned to one of three groups, single vision glasses, +1.50 D bifocals, or +1.50 bifocals with 3 D base down prism in the near segment. It was reported that both bifocals and prismatic bifocals significantly slowed myopia progression compared to single-vision lenses during the study time period [65]. Average spherical equivalents reported over the three years were -2.06 D for single-vision lens, -1.25 D for bifocal, and -1.01 D for the bifocal plus prism group.

Other research in spectacles is ongoing, many through innovative biotech companies. SightGlass Vision (USA) is currently working on developing novel spectacles aimed at slowing myopia progression in children. The CYPRESS (Control of Myopia Using Peripheral Diffusion Lenses: Efficacy and Safety Study) trial is an ongoing multicenter, double-masked, randomized controlled clinical trial that is looking to measure myopia progression over the course of 36 months using novel lens designs [66].

The Defocus Incorporated Multiple Segments (DIMS) spectacle lens (Hoya Vision, Japan) is a specialized lens that features a central optical zone that corrects refractive error and includes multiple microlenses around the central zone and extending to the midperiphery that produce constant myopic defocus. A 2 year double masked randomized controlled trial by Lam et al. looked at 160 Chinese children aged 8 to 13 years who had between -1.00 and -5.00 D of myopia and 1.50 D or less of astigmatism. The results showed that children wearing DIMS lenses myopia progressed 52% slower and had 62% less axial length elongation compared to the single vision glasses group over the two year period [67]. Furthermore, seventeen of the 79 children (21.5%) in the DIMS group and six of the 81 children (7%) in the single vision group had no myopia progression during the 2-year study.

Atropine

Medical therapy has been at the forefront of myopia prevention, with the antimuscarinic agent atropine being an especially promising medication under investigation. Atropine is a cycloplegic agent that dilates the pupil and restricts accommodation. Accommodation is the

process by which the eye changes from distance focus to near focus, and involves changes in the natural eye lens shape and contraction and relaxation of the ciliary muscle. Although the exact mechanism of action of slowing myopic progression is unclear, some postulate an anti-muscarinic impact on receptors in scleral fibroblasts that slow axial length elongation [68, 69].

A study by Shih from 2001 was important in showing that atropine had a greater therapeutic effect for myopic progression than glasses. In this randomized clinical trial, the results from 188 myopic children assigned to three groups 0.5% atropine with multi-focal glasses, multifocal glasses, and single vision spectacles over an 18 month period were provided. Main conclusions from the study were that myopia progression was significantly correlated with increased axial length, those assigned to the 0.5% atropine and multifocal lens group had a significant reduction in myopia progression, and that multi-focal lenses failed to show difference in effect compared to control [70].

The ATOM1 (Atropine for Treatment of Childhood Myopia study) by Chu et al. looked at 346 children aged 6 to 12 over two years who were randomly assigned to 1% atropine drops or control vehicle drops. There was a reduction in progression of myopia of -0.92D and reduction in axial length elongation of 0.40mm in groups treated with atropine 1% compared with control [68]. ATOM2, a follow-up study, further investigated the effective dose-dependence of atropine in preventing myopia progression [69]. 400 children were randomly assigned in a 2:2:1 ratio to 0.5%, 0.1%, and 0.01% atropine drops. Mean myopia progression at 2 years was found to be -0.30 ± 0.60 , -0.38 ± 0.60 , and -0.49 ± 0.63 D in the atropine 0.5%, 0.1%, and 0.01% groups, respectively, and the mean increase in axial length was 0.27 ± 0.25 , 0.28 ± 0.28 , and 0.41 ± 0.32 mm respectively [69]. Differences in myopia progression and axial length between groups however were not found to be clinically significant. Furthermore, it was found that there was a rapid rebound increase in myopia when atropine was stopped for 12 months after the 24 months of study treatment. The group receiving atropine 0.01%, had the least rebound effect and had minimal side effects compared to the 0.1% and 0.5% groups, suggesting extended efficacy of a low-dose of atropine [69] (see Table).

Study	Year/Authors	Key Findings
An intervention trial on efficacy of atropine and multi-focal glasses in controlling myopic progression	2001/Shih et al.	0.5% atropine with multi-focal lenses can slow down the progression rate of myopia Multi-focal lenses alone showed no difference in effect compared to single vision lenses (control)
Atropine for Treatment of Childhood Myopia study (ATOM1)	2006/Chua et al.	Reduction in progression of myopia of -0.92D and reduction in axial length elongation of 0.40mm in groups treated with atropine 1% compared with control
Atropine for the treatment of childhood myopia: safety and efficacy of 0.5%, 0.1%, and 0.01% doses (Atropine for the Treatment of Myopia 2) (ATOM2)	2012/Chia et al.	Differences in myopia progression and axial length change between groups were small and clinically insignificant Atropine 0.01% has minimal side effects compared with atropine at 0.1% and 0.5
Five-Year Clinical Trial on Atropine for the Treatment of Myopia 2: Myopia Control with Atropine 0.01% Eyedrop	2016/Chia et al.	Medications were stopped for 12 months after the initial 24 months of study treatment, and the group receiving atropine 0.01%, had the least rebound effect and had minimal side effects compared to the 0.1% and 0.5% groups
The Low-Concentration Atropine for Myopia Progression (LAMP) Study: Phase 2 Report	2020/Yam et al.	0.05%, 0.025%, and 0.01% atropine eye drops were all well tolerated and reduced myopia progression along a concentration-dependent response 0.05% atropine was most effective in controlling spherical equivalent progression and axial elongation

The more recent LAMP (The Low-Concentration Atropine for Myopia Progression) study took a closer look at even lower doses of atropine, investigating safety and efficacy of atropine at 0.05%, 0.025%, and 0.01% concentrations compared to placebo over a 1-year period [71]. Subjects were randomly assigned in a 1:1:1:1 ratio to receive 0.05%, 0.025%, 0.01%, or placebo nightly. All atropine concentrations were found to slow myopic progression, with the 0.05% being the most effective in reducing progression of both spherical equivalent and axial length elongation [71].

A recent randomized clinical trial conducted by Wei et al. in published in October 2020 sought to determine the safety and efficacy of atropine 0.01%. 220 Chinese children aged 6 to 12 were randomly assigned in a 1:1 ration to atropine 0.01% or placebo groups. Results after 1 year showed a relative reduction of myopic progression of 34.2% and 22.0% in axial elongation in the group receiving 0.01% atropine [72].

Since the ideal window for treatment for myopia prevention appears to be in the pediatric age group, there is also a push to research novel methods of medication administration to make it more tolerable for children, who often find eyedrop application uncomfortable. The Optejet dispenser by EyeNovia (USA) uses piezo-print technology to allow children to self-administer 8 μ L of atropine in order to minimize dose-related side effects [73]. Their ongoing CHAPARONE study, a US-based phase 3 multicenter, randomized, double-masked study, seeks to investigate the safety and efficacy of the Optejet dispenser, enrolling more than 400 children.

Pirenzepine

Another drug being investigated for myopia prevention is pirenzepine, a relatively selective antimuscarinic M1- receptor antagonist. Atropine is a nonselective antimuscarinic agent. A study by Siatkowski randomized children aged 8 to 12 years in a 2:1 ratio to receive 2% pirenzepine ophthalmic gel or placebo twice daily. At 1 year, the mean increase in myopia om the pirenzepine group compared to control was 0.26 D and 0.53 D respectively. At 2 years, the mean increase in myopia was 0.58 D and 0.99 for the pirenzepine group and the placebo group respectively [74].

CONCLUSION

The myopia epidemic is sweeping the globe at an alarming rate with potential visual consequences that impact productivity and individual quality of life. With such profound visual, social, and economic consequences, the importance of mitigating progression has never been greater. Further research needs to be conducted on modifiable environmental risk factors, genomics, and medical therapy. Higher near work demands in our increasingly digital world threatens to accelerate the rise in prevalence of myopia. Dual zone contact lenses and other specialty contact lenses and spectacles seem to be promising treatments. Atropine in particular is a major focus of pharmacological treatment. In addition, continued innovation in providing therapy and reaching those communities most at risk must be implemented.

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Chapter 382

WHICH DEMOGRAPHIC QUINTILE BENEFITS FROM PUBLIC HEALTH EXPENDITURE IN NIGERIA: A MARGINAL BENEFIT ANALYSIS*

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ABSTRACT

In the last twenty years, policy makers have come to an understanding that for poverty reduction to be sustainable and welfare benefits distributed evenly, social investments must act as a catalyst. Thus, no meaningful progress in sustainable development can be made when the level of inequality level is continuously rising and benefits of government expenditure unevenly shared. At the moment, Nigeria is one of the twenty poorest, most unequal societies in the world, with just half of the population controlling 5 percent of national resources. Productive sectors in Nigeria have considerably shrunk in size since the 1980s, to the extent that about 70 per cent of the population lives below the poverty line, which is deep, severe and pervasive. This raises concerns and questions on demographic dividends from investments in the social sector. Data for research was obtained from ministries of health as well as private service-providers in the SE region of Nigeria. Marginal Benefit Incidence Analysis was used in estimating the benefits of various quintiles by combining information about unit costs of providing services with information on the use of these services. Thus, this chapter focused on the distribution of beneficiaries across different demographic groups from services rather than measuring the exact value to recipients of government-sponsored services. Results indicate that the states in the South East (SE) Nigeria subsidized the rich in the society. The chapter recommends effective discretionary targeting of expenditure, and the less privileged in government expenditure programmes. This is a potent strategy for curtailing poverty and inequality in the system and would serve as a means of sustaining societal growth and economic progress.

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1. SOCIAL INVESTMENTS AND POVERTY REDUCTION

In most developing countries, Nigeria inclusive, government forms a large bulk of economic activity (Agu and Aldo, 2013) and one major challenge to government at all levels is the decision they make in organizing and distributing resources. However, the nexus between government expenditure and economic growth has been debated constantly among scholars. This includes protection and security of lives and properties and the provision of public and social goods such as defense, good roads, education, and health. Thus, government allocates resources to perform these basic functions, while some scholars argue that an increase in government expenditure promote growth (Al-Yousif, 2000; Ranjan and Sharma, 2008; Cooray, 2009), others argue that government expenditure undermines economic growth (Laudua, 1986; Engen and Skinner, 1992; Folster and Henrekson, 2001). For the last two decades, poverty reduction and public expenditure nexus have taken the center stage (Aigbokhan, 2000), with no agreeable framework on the dynamics.

Over time, economists and demographers have come in agreement that for even benefits across population groups, poverty reduction to be sustainable, social investments in education and health sector should be given high priority. Furthermore, Addison and Cornia (2001) suggest that no meaningful progress in sustainable development can be made when the level of inequality level is continuously rising, which is in contradiction with earlier development theories that inequality is good for growth and poverty reduction. This dichotomy is calling attention to the actual role of health infrastructure in economic growth vis-à-vis poverty reduction. However, much of contemporary debate on the nexus between public expenditure and demographic dynamics has been on what is the right size for a population and implications for standards of living and no emphasis on who gets what, when and how. No doubt, that the efforts by most populous countries to provide an acceptable living condition in terms of social services are constantly frustrated with rapid population growth, without a commensurate increase in economic growth. Therefore, the benefit incidence amongst the different quintiles becomes very pertinent.

The relationship between inequality, poverty and demographic dividends from public health expenditure is part of a larger cycle, where inequality and poverty leads to ill health and ill health due to lack of any substantial benefits sustains the twin evils. Available statistics suggest that people in emerging and transition countries tend to have less access to health services than those in better-off countries, and within countries, the poor have less access to health services. Although a lack of financial resources or information can create barriers to accessing services in developing countries, the causal relationship between benefits to health services and poverty also runs in the other direction. When health care is needed, but is delayed or not obtained, people's health worsens, which in turn leads to lost income and

higher health care costs, both of which contribute to negative outcomes. Lack of health care dividends by the vulnerable could lead to ill health, and worsened poverty levels¹.

Nonetheless, Nigeria has become a reference point for high inequality, economic growth and poverty levels. This has become so, more especially since the oil boom of the 1970s and the current rebasing (2014) of the Nigerian Economy, making it the biggest in Africa. This development paradox stands out when compared with similar comparable countries in Africa and Asia based on their collective history. The current per capita income in Nigeria is still very minimal in real terms and less than the 1975 estimate, despite the receipt of about two hundred and eighty-eight million dollars (USD288) in total oil revenue from 1975 to 2010². Adejuwon and Adekunle (2012)³ sums it up that about 70 per cent of the population lives below the poverty line and poverty is deep, severe and pervasive in the country. At the moment, Nigeria is one of the twenty poorest, most unequal societies in the world, with just half of the population controlling 5percent of national resources (Temitope, 2008). This raises the question of what has happened to all the investments in the social sector and who is benefiting from government expenditure.

Bridging the income margin between the rich and the poor as well as the efficient allocation of resources is necessary as part of a larger strategy to design and implement a sustainable developmental framework. Ogundipe and Lawal (2013) maintain that such a design would reduce poverty to some extent, especially if funds are well targeted towards health and education. Nonetheless, households in Nigeria are divergent in their ability to access and utilize services provided by the government (Diejomaoh and Eboh 2010). Most often, it is households in the upper income group which may reap larger benefits from public spending (health and education) programs (Suberu 2001). As a palliative to expenditure cutback, Ravallion (2002) argues positively for safety net measures, which would reduce the negative effects on expenditure, more especially on the vulnerable. One of such could be an effective targeting of health expenditure across different population groups.

According to Obansa et al. (2013) and retrieved from www.mcer.org, basic life-saving commodities are in short supply in lower income health systems. In these countries, provision of health related services depends on the availability of relevant equipment, drugs and infrastructure. Therefore, in the light of this, a constant and fundamental component of health management is an effective and accountable framework for procurement. In most states of Nigeria, several health facilities are without portable drinking water, electricity, dysfunctional equipment, etc. Health system is grossly inadequate, most especially at the Primary Health-care level (Obansa and Orimisan, 2013). Furthermore, poor state of infrastructure such as buildings, materials, equipment, and supplies and inequitable distribution of available facilities is the norm in many places in Nigeria.

Furthermore, uncertainty of drug supplies, which is common across the country and lack of basic amenities, has been traced to importation dependency of the health system in the country. The lack of updating of the pharmaceutical regulations could also be responsible for this ambivalence which has resulted in a complete chaotic drug distribution framework in the country. A clear negative fall-out of this scenario is the observed resistance to some drugs by

¹ The vulnerable in most of sub-Saharan Africa is particularly at risk.

² Furthermore, the productive sectors of the economy have considerably shrunk in size since the 1980s.

³ Poverty is also becoming *dynastic* in Nigeria—with the threat that the children of the poor are also likely to end up poor (Ehigiene 2007).

the disease pathogens in some patients (HERFON, 2006, FMOH, 2004, Travis et al., 2004). Nonetheless, without functional health facilities and qualified personnel, the availability of drugs alone would not improve the quality of health service. Vital to the provision of a functional health system is the former. However, it is common knowledge that in most communities in Nigeria, people travel several kilometers for basic health care services and in some case if not most, some these facilities are based on political expediency rather than economic rationality because they lack adequate professionals. Poor services at public health institutions in Nigeria have prompted the use of unorthodox medicines by most people, and for the privileged rich, the use of private health facilities (Ravi Rannan-Eliya, 2008), in addition to government hospitals.

The Nigerian government has been resorting to social spending discretions to alleviate poverty, thus it has become imperative for the government to understand the distributional outcomes from such expenditure. Marginal Benefit Incidence Analysis has assumed a center stage in most policy evaluations. The technique is normally used in assessing the distributional impact of government expenditure in addition to determining which demographic group benefits from the government (cash or in-kind). The underlying framework is that benefits derived from government expenditure should be shared disproportionately so that the lowest strata benefits more than those on a higher quintile. This implies that government spending according to the Keynesian model, should correct failures in the system, while promoting efficiency and equitable distribution of resources.

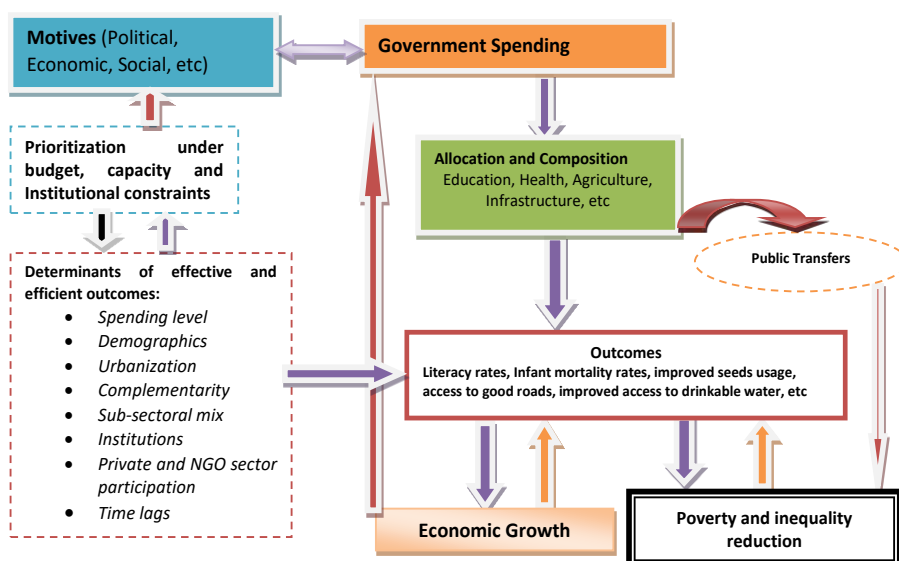
2. CONCEPTUAL FRAMEWORK

Fan, Zhang, and Zhang (2002) report that social expenditure reduced the rural poverty rate effectively. Jung and Thorbecke (2003) study also confirms that government social sector spending contributes to economic growth and supports poverty reduction. According to Lipton and Ravallion (1995), the poor that had less access to the infrastructure in the past can have larger benefits from new investment in health infrastructure. They came to this conclusion from their study on the effects of government expenditure on poverty. Also, in a study by Jung, et al. (2009) the marginal effects of government expenditures on poverty alleviation has generally weakened over time. Their analysis stands out in two ways: (1) contributes to the expanding literature on effects of government expenditure on poverty reduction by determining how the effects on poverty of four categories government expenditures have changed over time and compared these changes among categories; and (2) the study analyzed spatial variation in the effects of government expenditure on poverty across counties using GWR and LISA clustering. Their analysis further examined marginal effects of government expenditure on poverty reduction in each of the identified poverty clusters including the identification of poverty 'hot-spots'.

There are divided opinions and findings on the relationship between public sector spending and economic performance though most scholars are in agreement that there are circumstances in which decreased government spending would enhance economic growth and other circumstances in which increased government spending would be sought-after. Therefore, the connection between economic growth and government spending is bi-directional, particularly with growth and sectoral outcomes, in that higher growth leads to

improved sectoral outcomes (better schools, health indicators, road access, etc.) while enhanced sectoral outcomes will correspondingly lead to superior growth (in particular investment in health education and infrastructure is associated with higher growth rates). Looking at the theoretical underpinnings of public spending effects, it becomes imperative to look at the motive and its linkages with economic growth, poverty and inequality reduction for it to have the desired effect on distributional outcome.

Available literature suggests that exceptional variables which could hamper or effect positively public spending outcome are the roles of regulatory framework and private sector interventions because of their multiplier effect on service provision to the poor. According to Wilhelm and Fiestas (2005) government spending is driven by the objective to positively affect growth and poverty reduction through improved provision of social services. However, achieving this objective depends to a great extent on specific issues and initial conditions within a country.



Source: Adapted from Wilhelm and Fiestas 2005.

Figure 1. Public spending motives, determinants and linkage with growth and poverty reduction.

Figure 1 above shows the linkage which indicates that motives (political, economic, social, etc.) have effects on public spending while capacity and institutional constraints do affect motives behind public spending. The diagram also shows that effective and efficient outcomes could be determined by spending level; demographics; level of urbanization; complementarity; sub-sectoral mix; strength of institutions; the level of participation for private and NGO sector as well as time lags.

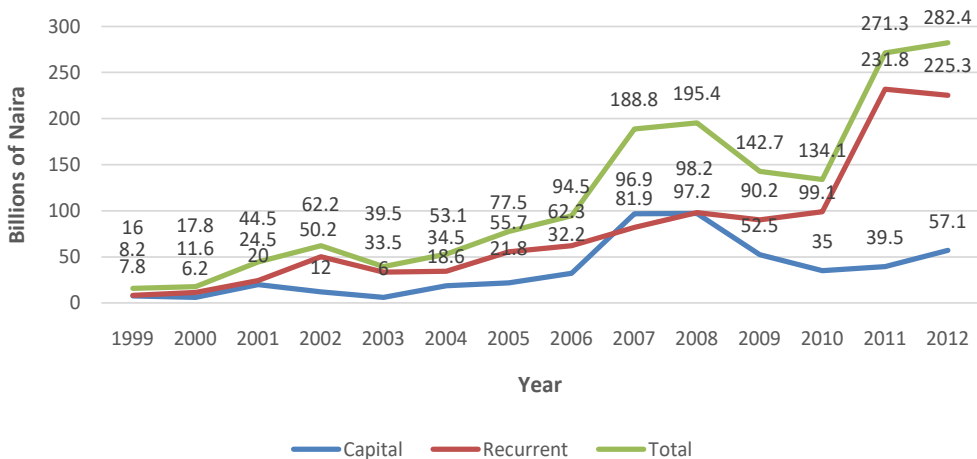
The relationship between public spending and poverty has gained sufficient attention in the literature and Economists are in agreement that expenditure on growth drivers has the capacity to reduce poverty and increase human capabilities. Asghar, et al. (2012) posits that economic growth and poverty reduction could occur with government spending on the social sector which would positively affect economic development. Nonetheless, investments in health, education and generally on the social sector were the mantra in the 1990s for the World Bank in its poverty Reduction Strategies Programmes. They argued that boosting

human capital formation reduces the level of poverty. Human resources according to the World Bank enrich human capabilities and productivity level of the people, which has the capacity to reduce poverty and increase income level through improved opportunities. Their results imply a positive reduction of poverty as expenditure is focused on social issues and the opposite when expenditure is focused on deficit financing, economic and community services in Pakistan.

Nonetheless, the relationship between public spending and poverty has gained sufficient attention in the literature. Demographers are in agreement that expenditure on growth drivers has the capacity to reduce poverty and increase human capabilities which is depicted in Figure 1. Asghar, et al. (2012) posits that economic growth and poverty reduction could occur with government spending on the social sector which would positively affect economic development. Also, according to Fan, Hazell, and Thorat (2000) expenditures on roads, research, and development have the largest impacts on poverty reduction in their study using India. Howbeit results from Gomanee et al. (2005) show the need for new strategies in combating poverty rates, because spending on social services is not as effective as it should be in poverty reduction. This has generated a lot of debate on how effective, the targeting mechanism of government of Nigeria is.

2.1. Federal Government Expenditure on Health in Nigeria

Public expenditure on health has not followed a definitive pattern between 1999 and 2012. The percentage increased from 1.7 in 1999 to 2.7 per cent in 2000, 4.4 per cent in 2001 and 6.2 per cent in 2002 respectively. In 2003, the share reduced to 3.2 percent. Though, health expenditure was 4.2 percent in 2004 and declined slightly to 4.1 percent in 2005. In 2006, the percentage increased to 5.7 percent. Between 2008 and 2010, it declined consistently with 3.7 percent in 2008, and 3.1 percent in 2009 and 2010, respectively. The percentage, however, climbed to 5.8 percent in 2011 and decreased slightly to 5.6 per cent in 2012.



Source: Authors'

Figure 2. Federal government expenditure on health (N' billion) 1999 – 2012.

Table 1. Federal government expenditure on health (N' billion)

	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Recurrent	8.2	11.6	24.5	50.2	33.5	34.5	55.7	62.3	81.9	98.2	90.2	99.1	231.8	225.3
Capital	7.8	6.2	20.0	12.0	6.0	18.6	21.8	32.2	96.9	97.2	52.5	35.0	39.5	57.1
Total	16.0	17.8	44.5	62.2	39.5	53.1	77.5	94.5	188.8	195.4	142.7	134.1	271.3	282.4
FGN Total	947.0	701.1	1,018.0	1,018.2	1,226.0	1,384.0.	1,743.2	1,842.6	2,450.9	3,240.8	3,453.0	4,194.6	4,712.1	4,987.0
% of FGN Total Exp.	1.7	2.7	4.4	6.2	3.2	4.2	4.1	5.7	5.2	3.7	3.1	3.1	5.8	5.6

Sources: NBS, CBN (Statistical Bulletin) and Federal Ministry of Finance, 2004, 2008, 2011.

Comparatively, data from selected countries in 2009, shows Haiti as 29.8 percent, Rwanda 27.3 percent, Nauru 25.0 percent, Norway 17.9 percent, Australia 17.2 percent, United Kingdom 16.5 percent, Gabon 13.9 percent, Cameroon 8.6 percent, Niger 10.6 percent and Ghana 6.8 percent (WHO, 2009). The statistics of other countries implies that Nigeria's health spending is weak and needs to be strengthened. Health care indicators also show that public spending on health is a source of concern in Nigeria. The WHO recommends the population to doctor ratio standard at 600: 1. In Nigeria, ratio of population to doctor which stood at 4,529:1 in 2000 further decreased to 5,075:1 in 2007. Between 2009 and 2010 it increased paltry to 3,967:1 and the negative trend is still unbaiting. Available data suggests an annual increase in the number of persons per physicians implying declined access of citizens to the services of physicians. Furthermore, the annual increase in the population to nurse ratio is also worrisome. This indicates reduced access of the citizens to the services of nurses. For example, the ratio stood at 920:1 in 2000 and increased negatively to 1,405:1 in 2007 and has remained high since then. The analysis suggests a higher growth rate of population than the number of nurses. In-addition, most citizens are not aware of the available services and their constitutional rights in relation to the health care.

3. DATA AND METHODS

Most analysis of benefit incidence are derived from the pioneered works of Meerman (1979) and Selowsky (1979) which provides estimates of the distribution of public expenditures. Benefit Incidence Analysis (BIA) normally reveals who is benefiting from public services, and describes the welfare impact on different groups or individual households of government spending. This is achieved by combining information about unit costs of providing those services. In this case, this was obtained from ministries of health as well as private service-providers with information on the use of these services, which was obtained from the households - the 2010 Nigerian Living Standard Survey report (NLSS). Thus, the method could be said to be a measure of how pro-poor government fiscal programme is.

For example, spending on (health), can be formally written as:

$$X_j = \sum_{i=1}^3 E_{ij} \frac{S_i}{E_i} = \sum_{i=1}^3 \frac{E_{ij}}{E_i} S_i \quad (1)$$

As cited in Amakom (2012) where X_j is the amount of the social service (health) subsidy that benefits group j (j is the economic group and for the purpose of this paper, all households have been grouped into 5 quintiles representing their economic status - from the lowest income to the highest income group). S and E refer respectively to the government social sector (health) subsidy and the number that is expected to benefit from the (the number of people that uses the health facility for the health sector), and the subscript i denotes the level of social service (health in Nigeria - healthcare in both private and public are categorized into primary, secondary and tertiary hence $i = 1$ to 3). The benefit incidence of total health imputed to group j is given by the number of primary access from the group (E_{pj}) multiplied by the unit cost of a primary health facility added to the number of secondary

access multiplied by the secondary unit cost of secondary health, plus the number of tertiary access multiplied by the unit cost of tertiary health.

The benefit incidence of total health imputed according to Amakom (2012) to group j is given by the number of users of primary healthcare from the group (E_{pj}) multiplied by the unit cost of providing primary health care and added to the number of users of secondary healthcare which is multiplied by the unit cost of providing secondary healthcare, plus the number of users of tertiary healthcare multiplied by the unit cost of providing tertiary healthcare.

The share of total health spending imputed to group (X_j) is then given by:

$$X_j = \sum_{i=1}^3 \frac{E_{ij}}{E_i} \left(\frac{S_i}{S} \right) = \sum_{i=1}^3 e_{ij} s_i \quad (2)$$

Equation (2) above depends on two major determinants:

1. The e_{ij} 's which are the shares of the group in total service use (number that uses a health facility for health sector) reflect household behaviour.
2. The s_i which is the shares of public spending across the different types of service, reflect government behaviour.

This paper followed a variant procedure, where behavioural information does not determine the monetary valuation of the benefits an individual receives from using public services, rather same monetary value of benefits are assigned to all those who used the services, which is the value of the unit cost of providing the service. The paper is focused on the distribution of beneficiaries from services rather than measuring the exact value to recipients of government-sponsored services (Heltberg, Simler and Tarp 2003). This is the marginal odds of benefits that would accrue to a group for every subsidy or expenditure by government. Given the poor quality of data on public expenditure as well as budget estimates at highly aggregated level, the binary approach proposed by Sahn and Younger (1998) is introduced in our analysis. This bypasses the need for estimating the unit subsidy (S/S_i), which then disappears in equations (1) and (2). Focus is made on only whether a service is used or not with users of public services counted and given the benefit of one, while non-users get zero. Secondly, the above assessment of how the health budget is distributed across the population is based on the observed use of government funded health facilities. This is called current accounting. Thus, it may not give an accurate notion of how changes in the health budget will be distributed across the quintiles.

However, Ajwad and Wodon (2001) and Lanjouw and Ravallion (1999) proposed methodologies that use a single cross-section of data to identify the distribution of increases, at the margin, in access rates to public services. Both studies assumed that the distribution of new access in lagging regions will follow the pattern observed in regions where access rates are higher and used the variation in access rates across regions in a country to capture the expected evolution of access over time. However, the techniques by Ajwad and Wodon (2001) and Lanjouw and Ravallion (1999) differ in the method used for ranking individuals. Furthermore, Lanjouw and Ravallion classify individuals as poor or rich according to their rank in the national distribution of income while Ajwad and Wodon classify individuals

according to their rank in the local distribution of income. This presupposes two differences between the works of Ajwad and Wodon (2000) and Lanjouw and Ravallion (1999). They are as follows:

1. The first concerns the manner in which the endogeneity bias in the estimation of the marginal benefit incidence analysis is handled. Both papers regressed access rate in a given quintile against the mean access rate. The mean access rate, however, includes information from the access rates in each quintile. To purge the mean from this endogeneity, Ajwad and Wodon use the leave-out mean as their right-hand side variable. That is, the access rate in any given quintile is regressed against the average of the access rates across all quintiles, except for the quintile for which the regression is performed. Lanjouw and Ravallion, on the other hand, use an instrumental technique, whereby the actual mean is instrumented by the leave-out mean.
2. The second is that Ajwad and Wodon constrain the estimates of the marginal benefit incidence analysis to sum to one, and show that without such a constraint, the estimates will be biased downward, while Lanjouw and Ravallion does not.

Furthermore, Lanjouw and Ravallion provide the following econometric method which has been used in a few studies (Ajwad and Wodon, 2001; Kamgnia et al., 2008; Demery and Gaddis, 2009), given as:

$$\rho_{i,j,q} = \alpha_q + \beta \rho_k + \mu_q \quad (3)$$

Where i index a small geographical unit, k indexes a larger one, and q indexes the welfare quantile. The left-hand variable is the program participation rate for the division and quantile. The regressor is the program participation rate for the region in which the division is located. q , then is the marginal effect of an increase in the program participation rates of people in a given region and quantile. According to Lanjouw and Ravallion (1999), the average participation rate is defined as the proportion of the population of a particular quintile that participates in a government sponsored program. The regressor is run separately for each quantile. In addition, because ijk is included in k , there is an upward bias in the estimation. As mentioned earlier, Lanjouw and Ravallion resolved this problem by instrumenting k with the left-out mean. The intuition behind the regression is that by observing variations in participation, it is possible to understand how increased coverage affects the participation of different population groups. If q is greater than one, it indicates that a general expansion in coverage is correlated with a disproportionately large increase in participation for that division and quantile. An important assumption in our model is that across locations the same political process determines the correlation between program discretion and incidence. Also, the margin that this model estimates is the incidence of an increase in program participation.

3.1. Justification of Method (Previous Studies)

According to Demery et al. (1995); Castro-Leal et al. (1996); Sahn and Younger (2000); Van de Walle (2003), the World Bank have conducted studies in low and middle income

countries using the method. O'Donnell et al. (2007) in their analysis used the technique and justified it because of its application in recent years. Also, Reinikka (2002) posits that employing BIA is most deserving because of evidence of limited impact of public spending on growth and human development outcomes which is the case in Nigeria. Nonetheless, who benefits from government spending is same as judging public policy efficiency in addressing issues on poverty and inequality. Younger (2002) considered a variety of options for analyzing the marginal benefit incidence of policy change and argued that despite the reality that each approach measures, marginal incidence, they neither in reality measure the same thing nor propose to do. Empirically, the accuracy of the approaches varies considerably with those relying on the dissimilarity data or aggregations of household into groups yielding normal errors that are fairly large relative to the expected shares.

Demery (1995) and the World Bank (1995a) used the Benefit Incidence Analysis (BIA) methodology for Ghana, Bulgaria and Vietnam and their results showed that women gained more in terms of an in-kind transfer of about 4,321 cedis per-capita as against 3,576 cedis per-capita in Ghana. Also, their results showed that the Bulgarian Turks¹ were the most disadvantaged when compared to the Gypsies. On the average, the Turks and Gypsies represent Thirteen percent of the population, but they received only six per cent of health subsidy. In Vietnam, the results showed that the mean subsidy for hospital inpatient and outpatient care was used for the benefit incidence estimates. Furthermore, Ghana results showed that a major source of inequality in the benefit incidence of health spending in Ghana was the gender dimension. Females benefited more than males in terms of health subsidy and there was a wide disparity in racial access to health. However, targeting health services to the poor have an ethnic undertone in Bulgaria, but there was no conclusion for Vietnam in the study.

Castro-Leal et al. (1999) examined health and education spending using comparative benefit incidence analysis. He finds that on average, the amount of overall government health spending going to the top twenty 20 per cent of the population was about two and a half times the amount benefiting the bottom 20 per cent. The highest 20 per cent of the population received more financial gains than the lowest 20 per cent in five of the seven countries; overall, the richest 20 per cent gained about one and a half times from primary care expenditure as much as the poorest 20 per cent. The study concluded that public spending in all the countries was found to be reverting.

Ajay et al. (2000) in their study employs BIA in appraising the distributional impacts of health spending in India and its principal states and uncovers that public health spending benefited the richer than the deprived. The financial gains from primary and outpatient service were less unequally allocated than those from hospital care. Overall, the pro-rich favoritism was larger in rural than in urban areas and greatly in poor than in richer states. Also, the gains connected with hospital services were less improving than other health facilities according to findings. Generally, the survey concluded that social services were poorly targeted while concentration curves are helpful method to sum up details on the gains of public spending, statistical examination of disparities in curves is imperative.

¹ The Turks and Gypsy are the two minority groups in Bulgaria comprising 13% of the total population, 25% of the poorest quintile and very few are found among the better off (only about 3% in the richest quintile).

Heltberg et al. (2001) and (2003) estimated the spread of government expenditure by socio-economic status in Mozambique. They used the non-behavioral method and found that outcomes from the method is that post-primary education crosses the Lorenz curve at 0.1 on the horizontal axis, and lies below the Lorenz curve for the rest of the allocation. Results indicate that the poorest 50 per cent of school children constitute about 50 per cent of students enrolled in lower primary and 32 per cent of students in upper primary. The poorest half of the sample accounted for about 19 per cent and 11 percent of students in post-primary education and intermediate post-primary education respectively. Their results confirmed earlier positions that services in Mozambique² were more equal than most African countries and a progressive distribution for services in health and public infrastructure is in place. Amakom (2012 and 2011) in separate studies for Nigeria using the Nigerian Living Standard Survey of 2004 evaluates public spending efforts in reducing inequality and poverty at all levels of both education and health sectors using the benefit incidence analysis (BIA). Results suggest that primary education and primary healthcare were more pro-poor than tertiary education and tertiary healthcare in absolute terms. Furthermore, secondary education and secondary healthcare showed varied results while findings suggest state, region, location and gender partiality influence benefits from government expenditure for education and health services. In conclusion, the study posits that income redistribution may be achieved through subsidies, and not through direct consumption transfers.

However, Soares et al. (2006) developed an approach that separated out the income of different cash transfers. Evaluating the incidence of the programmes using concentration curves indexes and decomposing the Gini indexes. Soares et al. (2006) found that the old age pension and disability grant programmes were targeted properly. Study indicates that the analysis of distributive effects of these programmes contributes to the correction of existing deficiencies; thus implying that the planning of future expansion of the programmes in eradicating poverty and inequality could be achieved within a reasonable time frame. Furthermore, Soares (2006) in his health and the evolution of welfare across Brazilian municipalities study compensates differentials method in estimating the value of the observed reductions in mortality. The results suggest that benefits in life expectancy are responsible for about 28 per cent of the improvement in welfare with a welfare value equivalent to 39 per cent of the growth in income per capita. The study concluded that initial income disparity across Brazilian municipalities was very high and life expectancy benefits were more or less uniform.

² Except for Upper Secondary and University Education.

4. RESULTS

Beneficiaries' of Health Expenditure across Quintiles in South East Nigeria

Table 2. Primary health care (benefit spread using 2010 HNLSS)

States	Abia	Anambra	Ebonyi	Enugu	Imo
Quintile 1	0.964	1.385	1.113	1.453	0.988
T - Stat	2.515	2.335	2.449	2.262	1.558
Quintile 2	0.997	1.520	1.063	1.480	1.088
T - Stat	1.644	2.521	2.277	1.734	1.785
Quintile 3	1.112	1.393	1.067	1.327	1.063
T - Stat	2.559	3.060	2.446	1.555	2.466
Quintile 4	1.014	0.514	0.957	0.449	1.039
T - Stat	1.875	1.768	1.788	2.150	1.908
Quintile 5	0.923	0.200	0.822	0.300	0.837
T - Stat	6.619	1.997	5.992	3.908	8.282
Total	5.010	5.012	5.021	5.008	5.015

Source: Author's Computations.

Table 3. Secondary health care (benefit spread using 2010 HNLSS)

States	Abia	Anambra	Ebonyi	Enugu	Imo
Quintile 1	1.015	1.068	0.964	1.074	0.995
T - Stat	3.747	3.156	2.246	3.622	3.889
Quintile 2	0.927	1.117	1.016	1.076	1.015
T - Stat	6.721	2.458	7.400	2.142	3.556
Quintile 3	1.115	0.979	1.015	1.065	1.023
T - Stat	4.832	2.152	2.720	2.663	5.956
Quintile 4	0.879	0.973	0.891	0.993	1.057
T - Stat	1.445	1.591	1.958	1.163	1.727
Quintile 5	1.066	0.863	1.117	0.793	0.913
T - Stat	3.887	3.519	2.847	2.649	3.483
Total	5.002	5.000	5.003	5.001	5.002

Source: Author's Computations.

Table 4. Tertiary health care (benefit spread using 2010 HNLSS)

States	Abia	Anambra	Ebonyi	Enugu	Imo
Quintile 1	0.633	0.700	0.670	0.760	0.803
T - Stat	2.246	2.934	1.705	2.450	3.177
Quintile 2	0.814	0.850	0.788	0.882	0.699
T - Stat	3.208	1.776	2.012	1.499	2.803
Quintile 3	1.082	0.974	1.019	1.070	0.975
T - Stat	4.525	2.167	2.456	2.886	3.850
Quintile 4	1.207	1.132	1.113	1.067	1.186
T - Stat	4.648	2.360	2.829	1.996	4.485
Quintile 5	1.264	1.344	1.411	1.223	1.338
T - Stat	4.613	3.926	3.258	4.165	3.615
Total	5.001	5.001	5.002	5.001	5.001

Source: Author's Computations.

N/b:

1. Tables 2 – 4 gives the instrumental variables estimate of the regression coefficient of the quintile specific service rates on the average rate for the South-East Region, based on the 2010 HNLSS.
2. The leave-out mean region service rate is the instrument for the actual mean.
3. The numbers in parentheses are the t-ratios.
4. Quintile 1(Very Poor); Quintile 2(Poor); Quintile 3(Moderate); Quintile 4(Rich); Quintile 5(Very Rich)

4.1. Discussion

A major measurement of success, progress of poverty reduction has been the trend and allocation of resources. This propelled structural adjustment programmes across many countries and according to Geoff et al. (2009), many recorded positive growth rates. It should be noted that in the 1970s, 1980s and 1990s the focus was on growing economies and incomes. This strategy took a new dimension in the 2000s. Thus, financing of social sectors was seen as a strategy to propel growth. In addition, during 1990s, a dominant view in development literature was that growth is the end game for every poverty reduction strategy. Several studies indicated that countries with fast and high growths made progress on poverty reduction via health and education (World Bank, 2000; Dollar and Kraay 2000). Ravallion and Datt (1996) and Mellor (1999) modified this view and argued that it is not growth per se, but the structure of benefits across population groups is fundamental in poverty reduction.

Table 2 above gives the estimated benefits and marginal odds of using public primary health services obtained by regressing participation rates of each quintile across average participation rate. The estimated numbers in the table can be interpreted as the gain in subsidy incidence per capita for each quintile from a one Naira increase in aggregate spending on primary healthcare. A cursory look at the table 2 indicates a pro-poor target for only three states (Anambra, Ebonyi and Enugu) out of five SE States regarding primary healthcare. Quintiles (1, 2 and 3) for the states showed that more benefits from the allocations were received by the vulnerable group. They received a benefit of more than N1 expenditure from government. This is in-tune with MDG Goal 4: Reducing Child Mortality and MDG Goal 5: Improving Maternal Health. However, this supposed improvement would not show an improved average because the other states are still far off from the expected mark. The other three states to a great extent subsidized the rich in the society, which obviously would lead to further poverty and weakness in overall health structure. In- as much as Ebonyi State showed some targeting, resources devoted to the rich was on the high side. These resources could have been re-channeled towards the weak and vulnerable in the society. Out of a 100 per cent scale, Anambra and Enugu states subsidized Quintile 5 with 3.9 per cent and 5.9 percent respectively while Ebonyi, Imo and Abia states gave 16.4 per cent, 16.7 per cent and 18.4 per cent respectively to the same group. The scenario suggests that the scourge of poverty at the minimum would still be felt by the people who do not have access to primary health care.

Health data from developing countries invariably indicates higher-than-average instances of disease, premature mortality, maternal mortality, or HIV/AIDS infection rates. A preliminary conclusion would be that poverty is increasing the vulnerability of the poor to health-related problems in these countries, as well as exacerbating ill-health and whether poverty in itself is proving an impediment to the capacity of the poor to seek adequate health care when sick. A comparative study of Demographic and Health Surveys in over 25 countries suggests that the health status of children is closely linked to poverty, thus suggesting the need for a proper targeting of resources to the vulnerable to abate this scenario.

Table 3 and 4 above gives the estimated benefits and marginal odds of using public secondary health services obtained by regressing participation rates of each quintile across average participation rate. The estimated numbers in the table can be interpreted as the gain in subsidy incidence per capita for each quintile from a one Naira increase in aggregate spending on secondary and tertiary healthcare. At the secondary healthcare level, three states from the

South East showed an incidence of more than 1 which is good for population group in quintile 1. However, population group under quintile 4 and quintile 5 still had the largest benefits from the discretionary spending by the respective state governments. Results from Table 3 shows that targeting for quintiles 1, 2 and 3 were better than quintiles 4 and 5. They collected over 60%. Nonetheless, quintile 5 collected about 20% of the resources which is not pro-poor. The same trajectory was observed at the tertiary level. Table 4 indicates high significant values for quintile 4 and 5 across the five (5) states. These group, benefited about 50% of the public resources. However, this pattern is believed to be occurring across all the states in Nigeria. The structure suggests a total exclusion of the poor from development decisions. There was poor targeting for quintile 1 and quintile 2. The vulnerable group (quintile 1 and 2) in this case, did not benefit at this level. They only had about 155 of total resources. This situation is an aberration of development. Furthermore, tertiary health care is designed to benefit the poor who cannot afford the cost of overseas specialist treatment, but the reverse is the case here. The very rich and the rich across the five eastern states of Nigeria benefited more than the poor. This situation can only support the widening inequality in the system. Our results are supported by Foster et al. (2002). Key findings from other work in five Sub-Saharan African countries, specifically Ghana, Malawi, Mozambique, Tanzania and Uganda, indicated the existing relationships between poverty reduction approach and public social spending management in each country. They established that the efficiency and effectiveness of public spending were very low and benefited largely the wealthy.

Furthermore, the work of Sahn and Younger (1999) using a benefit incidence approach focused on Ghana, Cote d'Ivoire, Guinea, Madagascar, South Africa, Uganda, Tanzania, and Mauritania, concluded that social services were poorly targeted in these countries. This confirms the ambivalence observed in Nigeria. Evidence in Nigeria from different studies (Ichoku 2008) indicates that in the health sector, the nature of the tertiary health-care which includes tertiary facilities like teaching hospitals, medical colleges and specialist hospitals are in shambles and hence has been a boost for health tourism in favour of other countries with better health facilities. Despite this trend, the upper class are still being subsidized by government going by our results. In the health sector, for example, poorer households across some states are already incurring catastrophic expenditure as they spend 40% or more of their discretionary (non-food) on health-care. Amakom and Ezenekwe (2012) analyzed whether there is a positive association between a household's poverty shortfall and its health out-of-pocket budget share from two standpoints. Their study found that high out of pocket (OOP) in healthcare has succeeded in changing the poverty situation (pushing households below poverty line) even households who were originally on or above the poverty line including some of the households that were originally in the 4th and 5th quintiles. Statistical data from WDI seem to concur with the above findings, as it suggests that out-of-pocket health expenditure (per cent of private expenditure on health) was 95.34 per cent in 2010 while the Nigerian Medical Association (NMA) in 2012 opined that over 5,000 Nigerians travel to India and other countries monthly for medical treatment implying that the country spends between \$1bn and \$2bn in medical tourism annually. A total mis-alignment is observed with the health expenditure in the SE region of Nigeria. Households that need the services don't get it, whereas richer individuals are greatly subsidized.

CONCLUSION AND RECOMMENDATION

Two recent surveys in Nigeria have shown a low index for health. Firstly, the Nigerian Living Standard Survey (NLSS) of 2004 estimated on the average, an annual per capita for health (out of pocket expenditure) to be equivalent to twenty-two dollars (US\$ 22). The 2004 Survey collected data on household health expenditures from a representative sample of 19,159 households. The estimate from these data of average annual per capita out-of-pocket spending on health is Naira 2,999, equivalent to around US\$ 22. Out-of-pocket health expenditure by households constituted over 8 percent and was mostly on out-patient care, transportation to facilities and medication, showing that government expenditure on health sector is not effective. This represents one of the largest shares of health expenditure out of total family spending for developing countries. Secondly, the 2009/2010³ survey which is the follow-up to the 2004 survey showed similar trends. The total health expenditure share of Household for 2009/10 decreased to 7.51 from 7.78 in 2004. Statistics suggests that fewer households visited a health provider in comparison with the 2004 survey results, indicating a lack of confidence on the services provided by the government. Also, the 2009/2010 survey results show that poverty and inequality have been on the increase since the last survey of 2004. Unfortunately, available records suggest, that this trend is still unabated at the moment and indicative that health services payment in Nigeria is still from out-of-pocket expenses. This scenario equally shows that the middle and upper class that benefit from local health facilities are still not satisfied with the health system. This has inadvertently, skewed health benefits to urban areas and for the middle and upper class mostly.

Lack of access and uneven benefits to healthcare services makes the poor vulnerable. Furthermore, the lack of healthcare access contributes to marginalization of the poor and widening inequality. Focusing on re-balancing of expenditure benefits as well as raising health standards by the authorities in Nigeria could enhance empowerment, which represents the expansion of assets and capabilities which will allow households in Quintiles 1 and 2 participate fully; negotiate and hold accountable institutions that affect their lives. Access and benefits to healthcare services not only imparts specific knowledge and develops general reasoning skills, but leads to changes in beliefs and values, as well as attitudes toward work and society. For the Government of Nigeria to meet the challenge of initiating an inclusive rapid growth and social transformation, spending options must be derived from evidence based analysis and evaluation of “who gets what, when and how”.

Summarily, poverty and inequality reduction strategies in Nigeria, therefore, have to incorporate effective benefit distributive features and high level of inclusiveness. There are glaring indications that in the SE region of Nigeria, those living in poverty do not enjoy the same levels of care and treatment as other people on a higher income level. Some may not access any health care at all because of poor targeting of resources by the government as a result of absence of a counter-factual framework by the government. This means that poor people are less able to enjoy protection against ill-health that is beneficial for higher income

³ The 2009/2010 Survey is an enlarged survey compared to that of 2004. The questionnaire included Demographics; Health; and Fertility behaviour, Education and Skills/Training; Employment and Time-use; Housing and Housing Condition; Social Capital, Agriculture; Social Capital, Agriculture; Household Income, consumption and Expenditure.

groups and consequently, most children of poor households may not benefit from immunization programmes by the government.

In this chapter, we analyzed which demographic quintile benefits from discretionary government spending. However, the methodological and framework in this chapter, does not address the policies that might bring about program expansion for health. Rather, it makes a more general appeal to the political economy behind the policies to argue that, whatever policies are used, the outcome must respect the political constraints implied by each group's cost, benefits, and political power.

From the foregoing, a maximum impact in targeting poverty in Nigeria would be achieved if all the states in Nigeria focus on social sector resources exclusively on the households within Quintiles 1(very poor) and 2 (poor) across the country. This would support poverty reduction via productivity increase of able-bodied men and women. Furthermore, households and communities should be enlightened and their consciousness increased in understanding how best to access health care in their various jurisdictions for maximum positive impact on their socioeconomic status. We, therefore, recommend the subsidization of health services for the poor by the use of local government financing, and similar tools in the engagement of communities in their health care programmes. Effective inclusion and targeting of the poor and less privileged in sustaining societal growth and economic progress may be a potent strategy for curtailing poverty and inequality. Health care services are a prominent social good that is very much needed by the citizenry; hence efforts at providing these services should be a national priority. Government should invest more on social services and enhance access to primary health care with a focus on outcomes and not outputs.

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Chapter 383

OVERVIEW OF U.S. DOMESTIC RESPONSE TO CORONAVIRUS DISEASE 2019 (COVID-19)*

***Sarah A. Lister, Kavya Sekar, Agata Dabrowska,
Frank Gottron, Audrey Singer and Amanda K. Sarata***

BACKGROUND

On December 31, 2019, the World Health Organization (WHO) was informed of a cluster of pneumonia cases in Wuhan City, Hubei Province of China. Illnesses have since been linked to a disease caused by a previously unidentified strain of coronavirus, designated Coronavirus Disease 2019, or COVID-19. The disease has spread to several other countries, including the United States. As of March 2, 2020, tens of thousands of people have been infected and over 2,500 have died. Both WHO and the U.S. Centers for Disease Control and Prevention (CDC) post frequent updates on the outbreak.¹

On January 30, 2020, the Emergency Committee convened by the WHO Director-General declared the COVID-19 outbreak to be a Public Health Emergency of International Concern (PHEIC).² The next day, on January 31, 2020, U.S. Department of Health and Human Services (HHS) Secretary Alex Azar declared the outbreak to be a Public Health

* This is an edited, reformatted and augmented version of Congressional Research Service, Publication No. R46219, dated March 2, 2020.

¹ WHO, "Novel Coronavirus (COVID-19) Situation Reports," <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports>; and U.S. Centers for Disease Control and Prevention (CDC), "Coronavirus Disease 2019 (COVID-19) Situation Summary," <https://www.cdc.gov/coronavirus/COVID-19/summary.html>.

² WHO, "Statement on the second meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus (COVID-19)," January 30, 2020, <https://www.who.int/news-room/statements>. The definition of and procedures for a PHEIC are at <https://www.who.int/ihr/procedures/pheic/en/>. See also CRS In Focus IF10022, *The Global Health Security Agenda and International Health Regulations*.

Emergency pursuant to Public Health Service Act (PHSA) Section 319, retroactively dated to January 27, 2020.³

Despite containment efforts in China, the United States, and elsewhere, by late February there were indications that the COVID-19 outbreak may have entered a new phase, with community spread occurring or suspected in several countries other than China, and in at least two U.S. states. According to federal health officials, the COVID-19 outbreak currently meets two of three criteria needed to be considered a pandemic, namely that the disease has caused illness, including illness resulting in death, and that there is sustained person-to-person spread. They note that as community spread is detected in more and more countries, “the world moves closer toward meeting the third criteria, worldwide spread of the new virus.”⁴ In addition, they say

...we should be prepared for COVID-19 to gain a foothold throughout the world, including in the United States. Community spread in the United States could require a shift from containment to mitigation strategies such as social distancing in order to reduce transmission. Such strategies could include isolating ill persons (including voluntary isolation at home), school closures, and telecommuting where possible.⁵

This report discusses selected actions taken by the U.S. federal government to quell the introduction and spread of COVID-19 in the United States. The President, the HHS Secretary, and other federal officials have taken several specific actions to address this threat. While some of these actions are based in generally applicable authorities, others may be contingent upon the Secretary or another federal official making a determination or declaration, specific to that action, regarding the existence of a public health emergency or threat. Key actions and their legal basis are discussed in this report.

Additional CRS products about this outbreak include

- CRS Report R46209, 2019 Novel Coronavirus (2019-nCoV) Outbreak: CRS Experts;
- CRS In Focus IF11421, COVID-2019: Global Implications and Responses;
- CRS In Focus IF11434, The Coronavirus: U.S.-China Economic Considerations;
- CRS Insight IN11228, COVID-19: Federal Economic Development Tools and Potential Responses.

A Snapshot of the Domestic Response to COVID-19, as of March 3, 2020 Note: All dates below are in 2020.

International

<https://www.who.int/emergencies/diseases/novel-coronavirus-2019>

- WHO declared the COVID-19 outbreak to be a PHEIC on January 30.
- WHO announced the official name for the disease, COVID-19 on February 11.
- WHO raised its global risk assessment for the outbreak to “very high,” its highest risk level, on February 28.
- Globally, almost 90,000 cases have been confirmed, including almost 3,000 deaths. Cases have been reported in 58 countries.

United States

<https://www.hhs.gov/about/news/index.html>; <https://www.cdc.gov/coronavirus/COVID-19/summary.html>;

³ U.S. Department of Health and Human Services (HHS), “Secretary Azar Declares Public Health Emergency for United States for Coronavirus Disease 2019,” press release, January 31, 2020, <https://www.hhs.gov/about/news/2020/01/31/secretary-azar-declares-public-health-emergency-us-2019-novel-coronavirus.html>.

⁴ CDC, “Coronavirus Disease 2019 (COVID-19) Situation Summary,” updated February 25, 2020, <https://www.cdc.gov/coronavirus/2019-ncov/summary.html#risk-assessment>.

⁵ Anthony S. Fauci, H. Clifford Lane, and Robert R. Redfield, “COVID-19—Navigating the Uncharted,” *New England Journal of Medicine*, online editorial, February 28, 2020, <https://www.nejm.org/doi/full/10.1056/NEJMe.2002387>.

<https://travel.state.gov/content/travel/en/traveladvisories/ea/novel-coronavirus-hubei-province—china.html>; and <https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/novel-coronavirus-COVID-19>.

- A Public Health Emergency is in effect under Section 319 of the Public Health Service Act.
- President Donald Trump has announced the formation of the President’s Coronavirus Task Force, and appointed Vice President Mike Pence as the coordinator for the U.S. COVID-19 response.
- For response efforts, the HHS Secretary has allowed for the allotment of \$105 million in funding from the Infectious Diseases Rapid Response Reserve Fund, and also requested an appropriations transfer of up to \$136 million. The Administration has submitted to Congress a request for \$1.25 billion in emergency supplemental appropriations, and asked for authority to re-allocate another \$1.25 billion. Congress has begun discussions of supplemental funding, likely in amounts to exceed the Administration request.
- CDC has developed a diagnostic test for the virus and distributed it to certain public health laboratories at the state and local level, pursuant to an Emergency Use Authorization (EUA) issued by FDA on February 4. Problems with test performance have limited access to testing at a local level.
- FDA issued guidance on February 29 to authorize certain certified labs, including non-government hospital labs, to use their own COVID-19 laboratory-developed tests for clinical diagnosis before EUA is granted.
- Travel restrictions and quarantine requirements are in effect for certain travelers who have been in mainland China or the Islamic Republic of Iran within 14 days prior to arrival, pursuant to Proclamations issued by President Trump.
- U.S. Department of State and other agencies have ordered or facilitated the repatriation of certain federal employees from China.
- Travel warnings by CDC and State Department are in effect for several countries including China, South Korea, Italy, and Iran.
- CDC has issued guidance for the general public, health care providers, health departments, pregnant women and children, travelers, and others.
- CDC reports 43 U.S. cases identified through public health surveillance, and an additional 48 cases among persons repatriated to the United States. CDC reported the first instance of possible community spread on February 26.
- Outbreaks have been reported in California, Oregon, and Washington State. Nine deaths have been reported in Washington State, four of them associated with a nursing home outbreak.

EPIDEMIOLOGY OF COVID-19

Coronaviruses (see Figure 1) are common respiratory pathogens, usually causing mild illnesses such as the common cold; however, several strains that cause serious illness have emerged in recent years. COVID-19 is the third serious outbreak caused by a novel coronavirus in modern times, following severe acute respiratory syndrome (SARS) in 2002 and Middle East Respiratory Syndrome (MERS) in 2012.⁶ The global health community is closely monitoring COVID-19 because of the severity of symptoms (including death) among those infected and the speed of its spread worldwide. Experts do not know the origin of COVID-19, though genetic analysis and other features suggest an animal source.⁷

Health officials and researchers are still learning about COVID-19 (see text box on “What We Know About COVID-19”). COVID-19 is a respiratory infection characterized by a fever, cough, and sometimes breathing difficulty—a suite of symptoms that is common during influenza season.⁸ Although initial COVID-19 cases likely resulted from animal

⁶ CDC, “Human Coronavirus Types,” accessed February 4, 2020, <https://www.cdc.gov/coronavirus/types.html>.

⁷ Kristian G. Andersen, Andrew Rambaut, and W. Ian Lipkin, “The Proximal Origin of SARS-CoV-2,” *Virological*, pre-print, February 2020, virological.org/t/the-proximal-origin-of-sars-cov-2/398; and CDC, “Coronavirus Disease 2019 (COVID-19) Situation Summary,” updated February 16, 2020, <https://www.cdc.gov/coronavirus/COVID-19/summary.html>.

⁸ CDC, “Symptoms—Coronavirus Disease 2019,” accessed February 18, 2020, <https://www.cdc.gov/coronavirus/COVID-19/about/symptoms.html>.

contact, Chinese officials confirmed person-to-person transmission on January 21, 2020.⁹ While health officials and researchers are still learning about the disease, CDC has concluded the following about COVID19:

- **Routes of transmission.** Based on how similar viruses spread, the virus is thought to spread via respiratory droplets and between people who are in close contact with one another (within about six feet). The virus may also spread via infected surfaces or objects, but according to CDC, this is not thought to be a primary means of transmission.¹⁰
- **Incubation period.** Health officials and researchers are still determining the virus's incubation period, or time between infection and onset of symptoms.¹¹ CDC is using 14 days as the outer bound for the incubation period, meaning that the agency expects someone who has been infected to show symptoms at some point during those 14 days.¹²
- **Transmission from asymptomatic patients.** CDC has confirmed that some transmission may occur before people show symptoms, based on a few reports and general characteristics of respiratory viruses.¹³ However, the agency, WHO, and other health experts agree that asymptomatic spread is unlikely to be a main driver of the outbreak.¹⁴

At this time, no specific treatment or preventive vaccine exists for COVID-19. Care for patients is supportive: maintaining hydration, preventing secondary infections, and providing respiratory support, such as use of a ventilator, if needed.¹⁵



Source: National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID).

Notes: Scanning electron microscope image of SARS-CoV-2 (yellow)—also known as 2019-nCoV, the virus that causes COVID-19—isolated from a patient in the United States, emerging from the surface of cells (blue/pink) cultured in the lab.

Figure 1. Coronaviruses infecting cells.

⁹ Matthew Walsh and Han Wei, "Wuhan Virus Update: China Confirms Human-to-Human Transmission," *Caixin Global*, January 21, 2020, <https://www.caixinglobal.com/2020-01-21/wuhan-virus-update-china-confirms-human-tohuman-transmission-101506555.html>.

¹⁰ CDC, "How COVID-19 Spreads," accessed February 18, 2020, <https://www.cdc.gov/coronavirus/2019-ncov/about/transmission.html>.

¹¹ WHO states that "Current estimates of the incubation period range from 1-12.5 days with median estimates of 5-6 days. These estimates will be refined as more data become available. Based on information from other coronavirus diseases, such as MERS and SARS, the incubation period of 2019-nCoV could be up to 14 days. WHO recommends that the follow-up of contacts of confirmed cases is 14 days." from WHO, "Q&A on Coronaviruses," February 11, 2020, <https://www.who.int/news-room/q-a-detail/q-a-coronaviruses>.

¹² CDC, "Transcript for CDC Media Telebriefing: Update on COVID-19," February 14, 2020, <https://www.cdc.gov/media/releases/2020/t0214-covid-19-update.html.html>.

¹³ Ibid.

¹⁴ Ibid, and WHO, "Q&A on Coronaviruses," February 11, 2020, <https://www.who.int/news-room/q-a-detail/q-a-coronaviruses>.

¹⁵ CDC, "Coronavirus Disease 2019: Information for Healthcare Professionals," <https://www.cdc.gov/coronavirus/COVID-19/hcp/index.html>.

What We Know About COVID-19

As the outbreak has progressed, researchers and health officials have been learning about the disease and its epidemiology. Initially, data and reporting from China, the epicenter from the outbreak, was limited and uncertain. With the recent WHO mission to China and more data coming from other countries, experts have a better understanding of the clinical features of the disease and how it spreads. Some of the key findings include:

- Data from China suggests that serious illness occurs in about 16% of people.
- Older people and people with underlying health conditions, like heart disease, lung disease and diabetes, for example, were about twice as likely to develop serious outcomes versus otherwise younger, healthier people.
- Disease in children appears to be relatively rare and mild with approximately 2.4% of the total reported cases reported amongst individuals aged under 19 years.

Experts are still understanding the exact fatality rate and attack rate (how easily the virus transmits), among other epidemiological characteristics. There is still uncertainty if the full spectrum of disease (including all mild cases) has been captured in the data from other countries, which affects our understanding of severity and transmission. Regardless, estimates suggest that the disease has a higher case fatality rate than the annual flu. Given the uncertainty, CRS presents conclusions that have been made by CDC and/or WHO.

See WHO, “Report of the WHO-China Joint Mission on Coronavirus Disease (COVID-19),” February 16-24, 2020, <https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf>.

DOMESTIC RESPONSE

The nation has both planning and real-world experience with pandemic infectious diseases, most notably the influenza pandemic of 2009.¹⁶ Although COVID-19 is from a different family of viruses, its similarity to influenza—the route of spread, respiratory system effects, and the possible role of antiviral drugs and vaccines, for example—allow the body of influenza experience and plans across government and the private sector to be applied to the COVID-19 response, with modest adjustments.¹⁷

Domestic communicable disease control involves collaboration among federal agencies, state health departments, and international partners. Many public health authorities are based in state law, such as authority to compel isolation (for sick patients), quarantine (for healthy exposed persons), and disease reporting.¹⁸ The HHS Secretary and, by delegation, CDC have broad authority to assist in the control of communicable diseases through international cooperation, federal-state cooperation, and public health emergency response activities.¹⁹ CDC (by delegation) also has explicit authority to detain, examine, and release persons arriving into the United States, and traveling between states, who are suspected of having a communicable disease.²⁰ Other authorities, such as those in the Immigration and Nationality Act of 1952 (INA, P.L. 82-414), allow for other actions relevant to communicable disease control, such as travel restrictions.²¹

¹⁶ CRS Report R40554, *The 2009 Influenza Pandemic: An Overview*.

¹⁷ CDC, “Pandemic Preparedness Resources,” February 15, 2020, <https://www.cdc.gov/coronavirus/2019-ncov/php/pandemic-preparedness-resources.html>.

¹⁸ CDC, “Legal Authorities for Isolation and Quarantine,” <https://www.cdc.gov/quarantine/aboutlawsregulation/quarantineisolation.html>.

¹⁹ CDC, “Selected Federal Legal Authorities Pertinent to Public Health Emergencies,” August 2017, <https://www.cdc.gov/php/docs/ph-emergencies.pdf>.

²⁰ Interstate Quarantine regulations: 42 C.F.R. Part 70, and Foreign Quarantine regulations: 42 C.F.R. Part 71.

²¹ 8 U.S.C. Chapter 12.

The use of federal and state disease control authorities and other key actions taken in response to the COVID-19 outbreak are discussed below. These activities of federal agencies in collaboration with state and local governments include, among others (1) investigation of COVID-19 cases and infection control measures in the community, (2) travel restrictions and/or quarantine requirements on certain travelers who have recently visited China, (3) medical countermeasure development, and (4) health system preparedness. Federal agencies involved include several HHS agencies, such as CDC, the Assistant Secretary for Preparedness and Response (ASPR), the National Institutes of Health (NIH), and the U.S. Food and Drug Administration (FDA), in collaboration with other agencies such as the U.S. Department of State and the Department of Homeland Security (DHS).

Investigation and Control of COVID-19 Cases in the Community

To curb the spread of COVID-19 cases in the community, state, tribal, local, and territorial health departments, with support from CDC, work to identify cases, investigate the possible spread of disease, and take infection control measures.

Case identification begins with diagnostic testing for COVID-19. As of February 27, CDC guidance urges clinicians to consider a patient's travel and/or contact history, as well as symptoms when deciding to test for COVID-19. CDC recommends COVID-19 testing for patients without known travel and/or contact history if clinical features include, "fever with severe acute lower respiratory illness ... requiring hospitalization and without alternative explanatory diagnosis (e.g., influenza)." ²² (See the next section, "The Role of Laboratories in Testing" for more information about the CDC-developed test.) Health care providers are urged to report possible cases to jurisdictional health departments, which then report to CDC. ²³

Once a patient is reported and in the process of having specimens tested, he or she is considered a *patient under investigation* (PUI) for COVID-19. CDC has developed guidelines for isolation and other precautions for PUIs (including potential PUIs) or those receiving supportive care for COVID-19 infection in health care settings. ²⁴ A key goal of the guidelines is the prevention of disease transmission to health care workers, who may be exposed through high-risk procedures, such as maintaining an ill patient on a ventilator. ²⁵

Disease investigation for confirmed cases involves *contact tracing*—identifying and evaluating individuals who had contact with the patient to determine if transmission has occurred. These investigations are generally conducted by jurisdictional health officials, often with support and technical assistance from CDC. ²⁶ CDC has reported community spread in

²² CDC, "Evaluating and Reporting Persons under Investigation (PUI)," updated February 27, 2020.

²³ Anita Patel, Daniel B. Jernigan, and 2019 n-CoV CDC Response Team, "Initial Public Health Response and Interim Clinical Guidance for the Coronavirus Disease 2019 Outbreak—United States, December 31, 2019–February 4, 2020," *Morbidity and Mortality Weekly Report (MMWR)*, vol. 69 (February 5, 2020).

²⁴ Current guidance is compiled at CDC, "Information for Healthcare Professionals," <https://www.cdc.gov/coronavirus/2019-ncov/hcp/index.html>; and "Resources for State, Local, Territorial and Tribal Health Departments," <https://www.cdc.gov/coronavirus/2019-ncov/php/index.html>.

²⁵ Chaolin Huang, Yeming Wang, Xingwang Li, et al., "Clinical Features of Patients Infected with Coronavirus Disease 2019 in Wuhan, China," *The Lancet*, January 24, 2020.

²⁶ CDC, "Transcript of Coronavirus Disease 2019 (COVID-19) Update," January 27, 2020, <https://www.cdc.gov/media/releases/2020/t0127-coronavirus-update.html>.

three states during the week of February 23, including a potential outbreak in a long-term care facility.²⁷

Jurisdictional health departments may take actions at a local level to control the spread of COVID-19. For example, the government of Washington State declared a state of emergency on February 29.²⁸ In addition, schools in the states of Washington and Oregon have had temporary closures due to presumptive positive COVID-19 cases.²⁹ If and when outbreaks continue, jurisdictions may consider actions such as cancellation of events and encouraging telecommuting for workers. Such actions would be based in state and local level authorities.

As of February 29, 2020, CDC reported that it had “deployed multidisciplinary teams to support health departments with clinical management, contact tracing, and communications.”³⁰ In addition, the Public Health Emergency declaration by Secretary Azar, pursuant to PHS Act Section 319, gives jurisdictional health departments more flexibility to reassign personnel to respond to COVID-19.

The Role of Laboratories in Testing

Every state, territory, and the District of Columbia has a central public health laboratory. These laboratories play many roles, including specialized testing for the detection and identification of infectious disease.³¹ Depending on the structure of their respective public health systems, states may also operate local public health laboratories.³² Health care facilities and businesses also separately operate laboratories outside of the public health laboratory system and are regulated by the FDA.

Typically, in emergency situations involving novel pathogens, diagnostic testing is initially centralized under CDC because CDC has the equipment, trained personnel, and facilities to provide the containment necessary to safely carry out the testing. Once a CDC-developed test is ready and meets any related regulatory requirements, the test may be distributed to state and local public health laboratories to expand testing capacity.

Initially, CDC performed all domestic COVID-19 testing, using a diagnostic test it developed, and continues to confirm presumptive positive cases.³³ The CDC test, 2019-nCoV Real-Time RTPCR Diagnostic Panel, is a molecular diagnostic test that requires specialized equipment and laboratory expertise.³⁴ It is intended for use only by laboratories designated by CDC as qualified and certified to perform high-complexity testing under the CLIA (Clinical Laboratory Improvement Amendments of 1988) program, administered by the HHS Centers

²⁷ CDC, “Coronavirus Disease 2019 (COVID-19) Situation Summary,” updated February 29, 2020, <https://www.cdc.gov/coronavirus/COVID-19/summary.html>.

²⁸ Andrew Selsky, “Washington Governor Declares State of Emergency Over Virus,” February 29, 2020, <https://abcnews.go.com/US/wireStory/coronavirus-cases-unknown-origin-found-west-coast-69301250>.

²⁹ Alex Horton and William Wan, “Coronavirus Shuts Down Two Public Schools as Districts Race to Contain the Spread,” *Washington Post*, February 29, 2020.

³⁰ CDC, “Coronavirus Disease 2019 (COVID-19) Situation Summary,” updated February 20, 2020, <https://www.cdc.gov/coronavirus/COVID-19/summary.html>.

³¹ Stanley L. Inhorn, J. Rex Astiles, and Vanessa A. White, “The State Public Health Laboratory System,” *Public Health Reports*, vol. 125, no. Suppl 2 (2010), pp. 4-17.

³² Association of Public Health Laboratories, “About Public Health Laboratories,” <https://www.aphl.org/aboutAPHL/Pages/aboutphls.aspx>.

³³ CDC, “Coronavirus Disease 2019 (COVID-2019) Situation Summary,” updated February 3, 2020, <https://www.cdc.gov/coronavirus/COVID-2019/summary.html>.

³⁴ Reverse transcriptase-polymerase chain reaction (RT-PCR) is a very sensitive technique that, in this use, allows the detection of otherwise undetectably low amounts of biological components specific to coronavirus.

for Medicare & Medicaid Services (CMS).³⁵ In the national Laboratory Response Network (LRN) supported by CDC, approximately 130 laboratories, mostly governmental, have the capability to perform specialized testing for high-risk clinical samples, such as those for COVID-2019.³⁶

On February 5, 2020, CDC announced that it would begin distributing test kits to jurisdictional laboratories, following an Emergency Use Authorization from FDA (see the “Medical Countermeasures” section for more details).³⁷ After distribution began, problems with one of the reagents (i.e., test chemicals), later reported to be linked to manufacturing, led to inconclusive test results in many laboratories.³⁸ Performance problems with the CDC test persisted throughout the month of February.

On February 27, 2020, CDC and FDA reported that the problem of inconclusive test results was resolved and that newly manufactured tests were again being distributed to state and local public health laboratories.³⁹ CDC reported that 40 laboratories in 32 states and the District of Columbia had received test kits, with additional kits to be made available to public health laboratories through the International Reagent Resource (IRR), a repository established by CDC.⁴⁰ Domestic laboratories are not charged for reagents or shipping from the IRR.

For more information on U.S. diagnostic testing, see CRS Report R46261, *Development and Regulation of Domestic Diagnostic Testing for Novel Coronavirus (COVID-19): Frequently Asked Questions*, by Amanda K. Sarata.

Travel-Related Policies and Restrictions

Given that initially the spread of COVID-19 cases was linked to travel, particularly to mainland China, several policies have been implemented to curb travel-related cases. These have included CDC and State Department advisories to avoid travel to certain countries, and specific restrictions and quarantine requirements on travelers returning from mainland China or Iran pursuant to presidential proclamations (further explained below). In addition, screening programs have been implemented at U.S. airports and other ports of entry to evaluate the health of returning travelers. As COVID-19 continues to spread globally, screening and entry policies may continue to evolve.

³⁵ CDC, “CDC Tests for COVID-19,” accessed February 18, 2020, <https://www.cdc.gov/coronavirus/2019-ncov/about/testing.html>; and Centers for Medicare & Medicaid Services (CMS), Clinical Laboratory Improvement Amendments (CLIA), <https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA>.

³⁶ CDC, “Laboratory Response Network for Biological Threats (LRN-B),” accessed February 18, 2020, <https://emergency.cdc.gov/lrn/biological.asp>.

³⁷ CDC “Media Telebriefing: Update on Coronavirus Disease 2019 (COVID-2019),” February 5, 2020, <https://www.cdc.gov/media/releases/2020/a0205-cdc-telebriefing-coronavirus-update.html>.

³⁸ CDC, “CDC Tests for COVID-19,” accessed February 18, 2020, <https://www.cdc.gov/coronavirus/2019-ncov/about/testing.html>; and CDC, “Transcript for CDC Telebriefing: CDC Update on Novel Coronavirus,” February 12, 2020, <https://www.cdc.gov/media/releases/2020/t0212-cdc-telebriefing-transcript.html>.

³⁹ CDC, “COVID-19 Situation Summary,” February 29, 2020, <https://www.cdc.gov/coronavirus/2019-ncov/summary.html>; and Rob Stein, “CDC Has Fixed Issue Delaying Coronavirus Testing In U.S., Health Officials Say,” *National Public Radio*, February 27, 2020, <https://www.npr.org/sections/health-shots/2020/02/27/809936132/cdc-fixes-issue-delaying-coronavirus-testing-in-u-s>.

⁴⁰ International Reagent Resource, <https://www.internationalreagentresource.org/>.

COVID-19 Travel Restrictions and Quarantine Requirements: Legal Basis

The Trump Administration has imposed two types of movement restrictions to prevent the entry and/or spread of COVID-19 in the United States. First, an immigration restriction generally suspends the entry of foreign nationals who have been in mainland China or in the Islamic Republic of Iran (Iran) within the prior 14 days.⁴¹ Second, quarantine requirements have been imposed on persons entering the United States if they have been in mainland China within the prior 14 days.⁴² Persons entering the United States who have been in Iran within the prior 14 days are subject to health monitoring.⁴³

Entry Restriction

President Trump issued a Proclamation on January 31, 2020, that suspends the entry of any foreign national who has been in mainland China within the prior 14 days, subject to some exceptions.⁴⁴ Hong Kong and Macau, both Special Administrative Regions of the People's Republic of China, are explicitly exempted. The China Proclamation directs the U.S. Department of State and the Department of Homeland Security (DHS) to establish procedures for implementing and enforcing the entry restrictions, which by the Proclamation's terms took effect on February 2, 2020. On February 29, 2020, President Trump issued another Proclamation with similar restrictions and exceptions for foreign nationals who had been in Iran within the prior 14 days.⁴⁵ In similar fashion, the Iran Proclamation's terms took effect on March 2, 2020. Both proclamations excepted lawful permanent residents (LPRs), most immediate relatives of U.S. citizens and LPRs, and some other groups such as some airplane and ship crew members.⁴⁶

For statutory authority, the Proclamations rely principally upon Section 212(f) of the Immigration and Nationality Act (INA).⁴⁷ That statute authorizes the President to "suspend the entry of all aliens or any class of aliens" whose entry he "finds ... would be detrimental to the interests of the United States."⁴⁸ The Supreme Court has held that Section 212(f) "exudes deference to the President in every clause" and gives him mostly unfettered discretion to

⁴¹ The travel restrictions for China became effective on February 2, 2020, and for Iran, March 2, 2020. The White House, *Remarks by President Trump, Vice President Pence, and Members of the Coronavirus Task Force in Press Conference*, February 29, 2020, <https://www.whitehouse.gov/briefings-statements/remarks-president-trump-vice-president-pence-members-coronavirus-task-force-press-conference-2/>.

⁴² Although the incubation period for COVID-19 has not yet been established, the U.S. Centers for Disease Control and Prevention (CDC) advises that "[f]or COVID-19, the period of quarantine is 14 days from the last date of exposure because 14 days is the longest incubation period seen for similar coronaviruses." Centers for Disease Control and Prevention, "Coronavirus Disease 2019 (COVID-19)," updated February 15, 2020, <https://www.cdc.gov/coronavirus/2019-ncov/faq.html>.

⁴³ Centers for Disease Control and Prevention, *Travelers from Countries with Widespread Sustained (Ongoing) Transmission Arriving in the United States*, accessed March 4, 2020, <https://www.cdc.gov/coronavirus/2019-ncov/travelers/after-travel-precautions.html>.

⁴⁴ The White House, "Proclamation on Suspension of Entry as Immigrants and Nonimmigrants of Persons Who Pose a Risk of Transmitting 2019 Novel Coronavirus," January 31, 2020, <https://www.whitehouse.gov/presidential-actions/proclamation-suspension-entry-immigrants-nonimmigrants-persons-pose-risk-transmitting-2019-novel-coronavirus/> [hereinafter *China Proclamation*].

⁴⁵ The White House, "Proclamation on Suspension of Entry as Immigrants and Nonimmigrants of Persons Who Pose a Risk of Transmitting 2019 Novel Coronavirus," February 29, 2020, <https://www.whitehouse.gov/presidential-actions/proclamation-suspension-entry-immigrants-nonimmigrants-certain-additional-persons-pose-risk-transmitting-coronavirus/> [hereinafter *Iran Proclamation*].

⁴⁶ *Id.*

⁴⁷ 8 U.S.C. §1182(f).

⁴⁸ *Id.*

decide “when to suspend entry,” “whose entry to suspend,” “for how long,” and “on what conditions.”⁴⁹ The Proclamations are in effect until terminated by the President.⁵⁰ The Proclamations also direct the Secretary of Health and Human Services (HHS) to “recommend that the President continue, modify, or terminate this proclamation and any other proclamation suspending or limiting the entry of foreign nationals into the United States as immigrants or nonimmigrants because of the threat posed by the virus.”⁵¹ Such recommendation is required “no more than 15 days after the date of this order and every 15 days thereafter.”⁵²

Although the Supreme Court has affirmed broad presidential discretion in the application of Section 212(f), the travel restriction applied in response to COVID-19 is the first such use of this authority to control the spread of a communicable disease.

Quarantine Requirements

DHS announced quarantine requirements, for arrivals on and after February 2, 2020 from China, and for arrivals from Iran, as of March 2, 2020.⁵³ Travelers who arrive in the United States within 14 days after having been in mainland China, are to be screened at one of 11 designated airports (see text box). Such persons may also be subject to mandatory quarantine, pursuant to the standing quarantine authorities of the HHS Secretary under Section 361 of the Public Health Service Act (PHSA).⁵⁴ These authorities are generally implemented by the CDC through its Division of Global Migration and Quarantine.⁵⁵ Persons showing symptoms of illness are to be evaluated by CDC staff to determine if they should be taken to a hospital for medical evaluation and to get care as needed.⁵⁶ Asymptomatic persons are generally to be held under federal quarantine for 14 days from the time they left China if they have recently visited China’s Hubei Province. However, asymptomatic persons whose recent travels have not included Hubei Province, are asked to self-quarantine for 14 days.⁵⁷ Persons entering the United States who have been in Iran within the prior 14 days are subject to health monitoring.⁵⁸

⁴⁹ *Trump v. Hawaii*, 138 S. Ct. 2392, 2408 (2018).

⁵⁰ *China Proclamation*, *supra* note 43, §5; *Iran Proclamation*, *supra* note 44, §5.

⁵¹ *China Proclamation*, *supra* note 43, §5, as amended by *Iran Proclamation*, *supra* note 44, §4(c).

⁵² *Id.*

⁵³ U.S. Department of Homeland Security (DHS), “DHS Issues Supplemental Instructions for Inbound Flights with Individuals Who Have Been in China,” press release, February 2, 2020, <https://www.dhs.gov/news/2020/02/02/dhsissues-supplemental-instructions-inbound-flights-individuals-who-have-been-china>, and U.S. Customs and Border Protection, “Notification of Arrival Restrictions Applicable to Flights Carrying Persons Who Have Recently Traveled From or Were Otherwise Present Within the People’s Republic of China or the Islamic Republic of Iran,” 85 *Federal Register* 12731-12733, March 4, 2020.

⁵⁴ 42 U.S.C. §264. See “Domestic Quarantine and Isolation: Legal Authority and Policies,” in CRS Report R43809, *Preventing the Introduction and Spread of Ebola in the United States: Frequently Asked Questions*; and CDC, “Legal Authorities for Isolation and Quarantine,” updated February 20, 2020, <https://www.cdc.gov/quarantine/aboutlawsregulations/quarantineisolation.html>.

⁵⁵ CDC, Division of Global Migration and Quarantine (DGMQ), <https://www.cdc.gov/nczid/dgmq/index.html>.

⁵⁶ CDC, “2019 Novel Coronavirus: Travelers from China Arriving in the United States,” <https://www.cdc.gov/coronavirus/2019ncov/travelers/from-china.html>.

⁵⁷ DHS, “DHS Issues Supplemental Instructions for Inbound Flights with Individuals Who Have Been in China,” press release, February 2, 2020, <https://www.dhs.gov/news/2020/02/02/dhs-issues-supplemental-instructions-inboundflights-individuals-who-have-been-china>.

⁵⁸ Centers for Disease Control and Prevention, *Travelers from Countries with Widespread Sustained (Ongoing) Transmission Arriving in the United States*, accessed March 4, 2020, <https://www.cdc.gov/coronavirus/2019-ncov/travelers/after-travel-precautions.html>.

Prior to the COVID-19 response, the HHS/CDC federal quarantine authority had not been used to restrict the movement of people since the early 1960s.⁵⁹ The CDC, however, regularly applies its quarantine authorities to assure that imports of animals, animal products, and other goods are free from diseases that could be transmitted to humans.⁶⁰ Authority to compel isolation (for sick human patients) and quarantine (for healthy exposed persons) has generally been exercised under state law.⁶¹

(Of note, in addition to announcing the United States' use of entry restrictions and quarantine authority on January 31, 2020, HHS Secretary Azar declared the COVID-19 outbreak to be a Public Health Emergency, pursuant to PHS Section 319.⁶² This declaration was not statutorily required for the abovementioned entry restrictions and quarantine requirements to go into effect, as each of these legal authorities is independent of the others. However, this declaration allows other actions, such as permitting states to reassign personnel on federal grants in order to respond to the emergency).

COVID-19 Travel Restrictions and Quarantine Requirements: Implementation

In large part, the exclusion of foreign nationals who have been in mainland China within the past 14 days has been carried out by commercial airlines, who are working with DHS to comply with new requirements, and many carriers have cancelled flights from mainland China.⁶³ Expanded exit screening of travelers in South Korea, Italy, and other countries, in addition to those traveling from China, are being put in place.⁶⁴

In addition, personnel from DHS components—namely Customs and Border Protection (CBP) and the Transportation Security Administration (TSA)—are involved in excluding foreign nationals from entry once travelers arrive at a port of entry in the United States, whether due to the January 31 and February 29 Presidential Proclamations or for unrelated reasons under immigration law. These flights are arriving in one of 11 U.S. airports (see text box).⁶⁵

Entry Restriction

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⁵⁹ Stephanie Soucheray, "CDC Quarantines 195 Passengers; U.S. Declares nCoV Public Health Emergency," *CIDRAP News*, January 31, 2020, <http://www.cidrap.umn.edu/news-perspective/2020/01/cdc-quarantines-195-passengers-usdeclares-ncov-public-health-emergency>.

⁶⁰ CDC, "Importation," <https://www.cdc.gov/importation/index.html>.

⁶¹ For a discussion, see "Domestic Quarantine and Isolation: Legal Authority and Policies" in CRS Report R43809, *Preventing the Introduction and Spread of Ebola in the United States: Frequently Asked Questions*.

⁶² HHS, "Secretary Azar Declares Public Health Emergency for United States for 2019 Novel Coronavirus," press release, January 31, 2020.

⁶³ Department of Homeland Security, "Notification of Arrival Restrictions Applicable to Flights Carrying Persons Who Have Recently Traveled From or Were Otherwise Present within the People's Republic of China," 85 *Federal Register* 7214-7215, February 7, 2020. [hereinafter *Notification of Arrival Restrictions*].

⁶⁴ Hollie Silverman, "Travelers Will Face New Restrictions and Cancellations as Coronavirus Cases Grow in the US," *CNN*, March 2, 2020.

⁶⁵ *Notification of Arrival Restrictions*, February 7, 2020.

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U.S. Airports Accepting Passengers Who Have Been in Mainland China within 14 Days

John F. Kennedy International Airport (JFK), New York Chicago O'Hare International Airport (ORD), Illinois San Francisco International Airport (SFO), California Seattle-Tacoma International Airport (SEA), Washington Daniel K. Inouye International Airport (HNL), Hawaii Los Angeles International Airport, (LAX), California Hartsfield-Jackson Atlanta International Airport (ATL), Georgia Washington-Dulles International Airport (IAD), Virginia Newark Liberty International Airport (EWR), New Jersey Dallas/Fort Worth International Airport (DFW), Texas Detroit Metropolitan Airport (DTW), Michigan.

Quarantine Requirements for Travelers Arriving from China

Upon arrival at one of the designated U.S. airports, the health status and travel history of individuals who have been in mainland China within the prior 14 days are evaluated to determine the need for mandatory quarantine (if they have been in Hubei Province within the prior 14 days); isolation (if they are symptomatic and/or test positive for coronavirus infection); or education and self-quarantine (if they have been elsewhere in mainland China within the prior 14 days). These passenger screenings have been conducted by personnel from CDC with assistance from CBP. The Department of State has also assisted American citizens, LPRs, and other persons who are permitted to return to the United States, by providing a number of repatriation airline flights, among other assistance.⁶⁹ According to CDC, as of February 23, “A total of 46,016 air travelers had been screened at the 11 U.S. airports to which all flights from China are being directed.”⁷⁰

Travelers designated for mandatory quarantine have generally been housed on military bases for a 14-day period. While in quarantine, the individuals are monitored and their care and basic needs attended to by personnel from CDC, the office of the HHS Assistant Secretary for Preparedness and Response (ASPR), officers of the U.S. Public Health Service

⁶⁶ Department of Homeland Security, “Notification of Arrival Restrictions Applicable to Flights Carrying Persons Who Have Recently Traveled From or Were Otherwise Present within the People’s Republic of China,” 85 *Federal Register* 7214-7215, February 7, 2020. [hereinafter *Notification of Arrival Restrictions*].

⁶⁷ Hollie Silverman, “Travelers Will Face New Restrictions and Cancellations as Coronavirus Cases Grow in the US,” *CNN*, March 2, 2020.

⁶⁸ *Id.*

⁶⁹ U.S. Department of State, “Evacuation of Americans from Wuhan, China,” Press Statement, February 8, 2020, <https://www.state.gov/evacuation-of-americans-from-wuhan-china-2/>. See also Department of State, “On the Repatriation of U.S. Citizens from the Princess Diamond Cruise Ship,” Special Briefing, February 17, 2020, <https://www.state.gov/on-the-repatriation-of-u-s-citizens-from-the-princess-diamond-cruise-ship/>.

⁷⁰ Daniel B. Jernigan, MD and CDC COVID-19 Response Team, “Update: Public Health Response to Coronavirus Disease 2019 Outbreak—United States, February 24, 2020,” *Morbidity and Mortality Weekly Report*, vol. 69, no. 8 (February 25, 2020), <https://www.cdc.gov/mmwr/volumes/69/wr/mm6908e1.htm>.

Commissioned Corps, and deployed teams from the National Disaster Medical System (see Figure 2).⁷¹



Source: HHS Assistant Secretary for Preparedness and Response (ASPR), Flickr photostream, <https://www.flickr.com/photos/phgov/with/49531565831/>.

Notes: “When evacuees from Wuhan arrived at Travis Air Force Base on February 5, responders from the National Disaster Medical System (NDMS) and the U.S. Public Health Service Commissioned Corps were there to evaluate evacuees for symptoms of COVID19 and stood ready to help. The U.S. Department of Health and Human Services (HHS) is continuing to take steps to fight COVID-19 and keep Americans healthy.” Wuhan is the capital of Hubei Province in mainland China.

Figure 2. HHS Responders at Travis Air Force Base Taken February 5, 2020.

Individuals who self-quarantine are directed to monitor their health and remain away from public places where close contact may occur (e.g., workplaces) for 14 days from the time the person was possibly exposed. State or local health departments are to provide oversight for individuals who self-quarantine.⁷²

Potential Health Effects of Travel Restrictions and Quarantines

Proposals to restrict the movement of people from affected regions or countries are part of early discussions when novel communicable diseases arise. The World Health Organization (WHO) generally advises against nations imposing travel restrictions on other nations, citing limited evidence of the effectiveness of such measures in controlling outbreaks and the harmful economic effects they have on nations struggling with outbreaks.⁷³ On January 27, 2020, WHO stated, with respect to COVID-19, that it “advises against the application of any restrictions of international traffic based on the information currently

⁷¹ The U.S. Public Health Service Commissioned Corps and the National Disaster Medical System are described in CRS Report R43560, *Deployable Federal Assets Supporting Domestic Disaster Response Operations: Summary and Considerations for Congress*.

⁷² CDC, “Coronavirus Disease 2019 (COVID-19), Travel: Frequently Asked Questions and Answers,” accessed February 21, 2020, <https://www.cdc.gov/coronavirus/2019-ncov/travelers/faqs.html>.

⁷³ See, for example, World Health Organization (WHO), “No Rationale for Travel Restrictions,” May 1, 2009, in the context of the 2009 H1N1 influenza pandemic, https://www.who.int/csr/disease/swineflu/guidance/public_health/travel_advice/en/.

available on this event.”⁷⁴ However, on February 11, WHO issued more nuanced guidance, saying

Evidence on travel measures that significantly interfere with international traffic for more than 24 hours shows that such measures may have a public health rationale at the beginning of the containment phase of an outbreak, as they may allow affected countries to implement sustained response measures, and non-affected countries to gain time to initiate and implement effective preparedness measures. Such restrictions, however, need to be short in duration, proportionate to the public health risks, and be reconsidered regularly as the situation evolves.⁷⁵

WHO’s guidance then discusses the measures it recommends be taken in managing travelers before embarkation, en route, upon arrival and, if indicated, while in quarantine.

The effect of movement restrictions on the spread of communicable diseases is generally considered poorly understood for several reasons, including (1) limited contemporary examples for study; (2) the inherent variability in the natural progression of global disease outbreaks, even those caused by the same pathogen; (3) variation in actions taken by affected countries and restrictions imposed by other countries; and (4) difficulty in accounting for the effects of nongovernmental actions such as event cancellations and airline flight adjustments. In response to the emergence of COVID-19, China imposed sweeping internal movement restrictions,⁷⁶ a measure that is likely, in later analyses, to obscure or confound any additional transmission-damping effects that the U.S.-imposed travel restrictions may achieve.

Several studies have examined the potential effects of travel restrictions on disease spread, particularly looking at the global spread of influenza and at the outbreak of Severe Acute Respiratory Syndrome (SARS) in 2002-2003. Of note, these analyses sometimes indicated delays in the speed of spread of an outbreak. However, the effect of travel restrictions on the ultimate geographic spread of the outbreak—or on the reduction of overall morbidity or mortality—is unclear, and the evidence base is limited. Some studies have found no effect of travel restrictions on overall morbidity and mortality of infectious disease.⁷⁷ Others have found that very strict travel restrictions may effectively prevent the spread of disease (i.e., complete border closure) or that travel restrictions might be more effective when combined with other infection control measures, such as quarantine and isolation.⁷⁸ In particular, compulsory movement restrictions may rely on public support in order to be effective, as well as to avoid discrimination and loss of public trust. Many suggest that if

⁷⁴ WHO, “Updated WHO Advice for International Traffic in Relation to the Outbreak of the Novel Coronavirus 2019-nCoV,” January 27, 2020, https://www.who.int/ith/2019-nCoV_advice_for_international_traffic/en/.

⁷⁵ WHO, “Key Considerations for Repatriation and Quarantine of Travellers in Relation to the Outbreak of Novel Coronavirus 2019-nCoV,” February 11, 2020, <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/travel-advice>.

⁷⁶ Michael Levenson, “Scale of China’s Wuhan Shutdown Is Believed to Be without Precedent,” *The New York Times*, January 22, 2020. Wuhan is the capital of Hubei Province in mainland China.

⁷⁷ Several such studies are discussed in Julia Belluz and Steven Hoffman, “The evidence on travel bans for diseases like coronavirus is clear: They don’t work,” *Vox*, January 23, 2020, <https://www.vox.com/2020/1/23/21078325/wuhanchina-coronavirus-travel-ban>.

⁷⁸ Sukhyun Ryu, Huizhi Gao, Jessica Y. Wong, et al., “Nonpharmaceutical Measures for Pandemic Influenza in Nonhealthcare Settings—International Travel-Related Measures,” *Emerging Infectious Diseases*, vol. 26, no. 5 (May 2020).

public support and trust are essential in any case, enlisting movement restriction through voluntary measures may be just as effective, with less societal disruption.⁷⁹

Quarantine has a long history as a disease control measure, substantially predating the “germ theory” of infectious disease embraced in the late 19th century. According to CDC,

The practice of quarantine, as we know it, began during the 14th century in an effort to protect coastal cities from plague epidemics. Ships arriving in Venice from infected ports were required to sit at anchor for 40 days before landing. This practice, called quarantine, was derived from the Italian words *quaranta giorni* which mean 40 days.⁸⁰

Quarantine is considered a social distancing measure in public health, along with isolation, contact tracing, and measures to avoid crowding (i.e., school closures). Similar to the studies on movement restrictions, the precise effect of social distancing measures on the spread of infectious disease can be difficult to measure and the evidence base is limited.⁸¹ Yet, social distancing measures were some of the primary means by which the 2003 SARS outbreak in China was contained and are generally considered fundamental tools of infection control in public health.

Medical Countermeasures

Potential Products for Use in the COVID-19 Response

Medical countermeasures (MCMs) are medical products that may be used to treat, prevent, or diagnose conditions associated with emerging infectious diseases or chemical, biological, radiological, or nuclear (CBRN) threats. Examples of MCMs include biologics (e.g., vaccines, monoclonal antibodies), drugs (e.g., antimicrobials, antivirals), and devices (e.g., diagnostic tests and general personal protective equipment such as gloves, respirators/masks, and gowns).⁸² FDA regulates MCMs domestically. Currently, there are no FDA-approved MCMs specifically for COVID-19, although FDA has authorized the use of *unapproved* diagnostic tests, including via Emergency Use Authorization (EUA).⁸³ Federal agencies, pharmaceutical and biotech companies, nongovernmental organizations, and global regulators have been working to expedite the development and availability of MCMs for 2019-nCoV. Examples of such efforts include the following:

⁷⁹ Francesca Matthews Pillemer et al., “Predicting Support for Non-pharmaceutical Interventions during Infectious Outbreaks: A Four Region Analysis,” *Disasters*, vol. 39, no. 1, pp. 125-145, January 2015, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4355939/>.

⁸⁰ CDC, “History of Quarantine,” <https://www.cdc.gov/quarantine/historyquarantine.html>.

⁸¹ Min W. Fong, Huizhi Gao, and Jessica Y. Wong, “Nonpharmaceutical Measures for Pandemic Influenza in Nonhealthcare Settings—Social Distancing Measures,” *Emerging Infectious Diseases*, pre-print, vol. 26, no. 5 (May 2020).

⁸² FDA, “What Are Medical Countermeasures?” accessed February 4, 2020, <https://www.fda.gov/emergency-preparedness-and-response/about-mcm/what-are-medical-countermeasures>.

⁸³ FDA, “Novel coronavirus (2019-nCoV),” accessed February 4, 2020, <https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/novel-coronavirus-2019-ncov>; and FDA, “Coronavirus (COVID-19) Update: FDA Issues New Policy to Help Expedite Availability of Diagnostics,” press release with link to guidance, February 29, 2020, <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-issues-new-policy-helpexpedite-availability-diagnostics>.

Diagnostics

As summarized earlier, CDC developed the 2019-nCoV Real-Time RT-PCR Diagnostic Panel for which FDA issued an EUA on February 4, 2020 (EUAs are described in more detail below).⁸⁴ The CDC test is a “test kit,” meaning it is manufactured, assembled, and then may be shipped for use by multiple laboratories. In contrast, many diagnostic tests are “laboratory-developed tests,” meaning that they are developed, validated, and used in a single laboratory. Generally, the FDA waives most regulatory requirements (e.g., premarket review) for LDTs, but nevertheless, LDTs may only be used with authorization (an EUA) during an emergency declaration pursuant to FFDCA Section 564.

On February 29, 2020, as problems with the roll-out of the CDC-developed diagnostic test continued, FDA announced a new policy to immediately leverage LDTs developed in high-complexity commercial, reference, and clinical laboratories nationwide to expand testing capacity. Specifically, the new guidance from the agency allows the nation’s CLIA-certified high-complexity laboratories that have developed and validated their own COVID-19 diagnostics to begin to use the tests while the laboratory is preparing, and FDA is reviewing, their EUA submissions.⁸⁵ The FDA guidance recommends that laboratories have 15 days after validating their test to submit their EUA application to the FDA, and recommends confirming the test’s first five negative and positive results against an EUA-authorized diagnostic. According to FDA, it “does not intend to object to the use of these tests for clinical testing while the laboratories are pursuing an EUA with the FDA. Importantly, this policy only applies to laboratories that are certified to perform high-complexity testing consistent with requirements under Clinical Laboratory Improvement Amendments.”⁸⁶

Several federal agencies are working with industry partners to develop rapid diagnostic point-of care tests for COVID-19, including NIH, particularly through the National Institute of Allergy and Infectious Diseases (NIAID); ASPR, through the Biomedical Advanced Research and Development Authority (BARDA); and the Department of Defense (DOD).⁸⁷ On February 5, 2020, BARDA announced an Easy Broad Agency Announcement (EZ-BAA) to solicit applications for development funding of COVID-19 molecular diagnostics. The submissions must have a viable plan to meet requirements for the FDA to consider EUA within 12 weeks of an award.⁸⁸

⁸⁴ FDA, “FDA Takes Significant Step in Coronavirus Response Efforts, Issues Emergency Use Authorization for the First 2019 Novel Coronavirus Diagnostic,” February 4, 2020, <https://www.fda.gov/news-events/press-announcements/fda-takes-significant-step-coronavirus-response-efforts-issues-emergency-use-authorization-first>.

⁸⁵ GenomeWeb, “FDA Provides SARS-CoV-2 Test Validation Guidance for High-Complexity Labs Seeking EUA,” March 3, 2020, <https://www.genomeweb.com/pcr/fda-provides-sars-cov-2-test-validation-guidance-high-complexitylabs-seeking-eua#.Xl7JFqhKiUk>; and FDA, “Policy for Diagnostics Testing in Laboratories Certified to Perform High Complexity Testing under CLIA prior to Emergency Use Authorization for Coronavirus Disease-2019 during the Public Health Emergency,” February 29, 2020, <https://www.fda.gov/media/135659/download>.

⁸⁶ FDA, “Coronavirus (COVID-19) Update: FDA Issues New Policy to Help Expedite Availability of Diagnostics,” press release with link to guidance, February 29, 2020, <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-issues-new-policy-help-expedite-availability-diagnostics>. See also CRS In Focus IF11389, *FDA Regulation of Laboratory-Developed Tests (LDTs)*.

⁸⁷ HHS Representative, White House Coronavirus Task Force news conference, January 31, 2020, <https://plus.cq.com/doc/newsmakertranscripts-5826415>.

⁸⁸ HHS, “HHS Seeks Abstract Submissions for 2019-nCoV Diagnostics Development,” press release, February 5, 2020, <https://www.hhs.gov/about/news/2020/02/05/hhs-seeks-abstract-submissions-for-2019-ncov-diagnostics-development.html>.

Therapeutics

Research and development into several treatment strategies for COVID-19 are underway by federal agencies, international partners, and industry. Drawing from research on the SARS and MERS coronaviruses, NIAID is assessing potential treatment strategies such as antiviral drugs and animal models that can be used to test potential MCMs. In addition, NIAID is developing assays and other research tools to study COVID-19.⁸⁹ In February 2020, BARDA announced that it would expand existing collaborations with Regeneron Pharmaceuticals Inc. and Janssen Research and Development to develop COVID-19 therapeutics.⁹⁰

Scientists in China are testing drugs currently approved for treatment of HIV, influenza (flu), and malaria for potential effectiveness against COVID-19.⁹¹ For example, Chinese authorities have reportedly recommended AbbVie's HIV drug Kaletra to treat patients, while the drug undergoes clinical testing.⁹² Johnson & Johnson has reportedly provided its HIV drug Prezcoibix to China to test as a potential treatment as well.⁹³ Scientists are also testing many experimental treatments in the research pipeline.⁹⁴ For example, Gilead is working with health authorities in China to determine whether its experimental antiviral drug Remdesivir can safely and effectively treat COVID-19.⁹⁵ In the United States, a clinical trial evaluating the safety and effectiveness of Remdesivir has begun at the University of Nebraska Medical Center (UNMC) in Omaha. The trial is sponsored by NIAID.⁹⁶

Vaccines

At least eight different COVID-19 vaccine development initiatives among federal agencies, industry, research institutions, and philanthropies have been announced.⁹⁷ Of note, the NIAID Vaccine Research Center (VRC) is collaborating with the drug company Moderna and the Coalition for Epidemic Preparedness Innovations (CEPI) to advance a vaccine candidate. Moderna expects this vaccine to enter phase 1 clinical testing in the spring of 2020.⁹⁸ CEPI is also supporting vaccine development by the University of Queensland

⁸⁹ Hilary Marston, NIAID, "2019 Novel Coronavirus Stakeholder Listening Session Transcript," January 30, 2020, <https://www.phe.gov/Preparedness/nCoV/Documents/2019nCoV-Listening-Session-Transcript.pdf>.

⁹⁰ HHS, "HHS, Regeneron Collaborate to Develop 2019-nCoV Treatment," February 4, 2020, <https://www.hhs.gov/about/news/2020/02/04/hhs-regeneron-collaborate-to-develop-2019-ncov-treatment.html>; and HHS, "HHS, Janssen Collaborate to Develop Coronavirus Therapeutics," February 18, 2020, <https://www.hhs.gov/about/news/2020/02/18/hhs-janssen-collaborate-to-develop-coronavirus-therapeutics.html>.

⁹¹ Guangdi Li and Erik De Clercq, "Therapeutic options for the 2019 novel coronavirus (2019-nCoV)," *Nature Reviews: Drug Discovery*, February 10, 2020, <https://www.nature.com/articles/d41573-020-00016-0>.

⁹² Jared Hopkins, "U.S. Drugmakers Ship Therapies to China, Seeking to Treat Coronavirus," *Wall Street Journal*, January 27, 2020.

⁹³ Ibid.

⁹⁴ Guangdi Li and Erik De Clercq, "Therapeutic options for the 2019 novel coronavirus (2019-nCoV)," *Nature Reviews: Drug Discovery*, February 10, 2020, <https://www.nature.com/articles/d41573-020-00016-0>.

⁹⁵ Gilead, "Gilead Sciences Statement on the Company's Ongoing Response to the 2019 Novel Coronavirus (2019-nCoV)," January 31, 2020, <https://www.gilead.com/news-and-press/company-statements/gilead-sciences-statement-on-the-company-ongoing-response-to-the-2019-new-coronavirus>.

⁹⁶ NIH, "NIH clinical trial of remdesivir to treat COVID-19 begins," February 25, 2020, <https://www.nih.gov/news-events/news-releases/nih-clinical-trial-remdesivir-treat-covid-19-begins>.

⁹⁷ Steve Usdin and Karen Tkach Tuzman, "The Race Is on to Develop Therapies and Vaccines for the Coronavirus Outbreak," *Biocentury*, January 24, 2020, <https://www.biocentury.com/article/304290/the-coronavirus-outbreak-is-creating-a-testbed-for-new-vaccine-and-therapeutic-technologies>.

⁹⁸ Moderna, "Moderna Announces Funding Award from CEPI to Accelerate Development of Messenger RNA (mRNA) Vaccine Against Novel Coronavirus," January 23, 2020, <https://investors.modernatx.com/news-releases/news-release-details/moderna-announces-funding-award-cepi-accelerate-development>.

(Australia) and the drug companies GlaxoSmithKline and Inovio.⁹⁹ BARDA has announced vaccine development partnerships with Sanofi and Johnson & Johnson.¹⁰⁰

Status of MCM Development

MCM development for COVID-19 has exceeded the pace of MCM development for previous infectious disease outbreaks; however, it is still uncertain if the products will be available in time to curb spread of the virus. Diagnostic tests for COVID-19 were developed by CDC and other global public health laboratories in a few weeks after COVID-19 was first reported, compared to almost six months for the 2002-2003 SARS outbreak.¹⁰¹ The NIAID supported Moderna vaccine is expected to begin phase 1 clinical trials in late April. In comparison, it took 20 months for NIAID to get a SARS vaccine into phase 1 clinical trials.¹⁰² However, vaccine development is difficult and only a handful of new vaccines have been licensed in recent decades, despite ongoing efforts to develop vaccines for infectious diseases such as MERS and HIV.¹⁰³ Additionally, the NIAID and Moderna vaccine relies on a new technology that no FDA-approved vaccine has ever used.¹⁰⁴ An FDA official has reportedly asserted that therapeutics for COVID2019 are likely to be available more quickly than a vaccine.¹⁰⁵

FDA Emergency Use Authorization (EUA)

Clinical testing and the FDA review process typically take several years, so it will take time for MCMs in development to reach the commercial market. However, experimental products may become available in the United States prior to FDA approval pursuant to an EUA. FDA encourages industry and government sponsors (e.g., CDC) to engage with FDA prior to submitting a formal request for an EUA, if possible.

Under most circumstances, drugs, medical devices, and biologics may be introduced into interstate commerce only if they have been approved, cleared, or licensed by FDA. Under certain circumstances, however, FDA may permit a medical product to be provided to patients outside the standard regulatory framework, including through issuance of an EUA. In the absence of an approved MCM for COVID-19, FDA may enable access to investigational

⁹⁹ Coalition for Epidemic Preparedness Innovations, “CEPI and GSK announce collaboration to strengthen the global effort to develop a vaccine for the 2019-nCoV virus,” February 3, 2020, https://cepi.net/news_cepi/cepi-and-gskannounce-collaboration-to-strengthen-the-global-effort-to-develop-a-vaccine-for-the-2019-ncov-virus/.

¹⁰⁰ HHS, “HHS Engages Sanofi’s Recombinant Technology for 2019 Novel Coronavirus Vaccine,” February 18, 2020, <https://www.hhs.gov/about/news/2020/02/18/hhs-engages-sanofis-recombinant-technology-for-2019-novel-coronavirus-vaccine.html>; and HHS, “HHS, Janssen Join Forces On Coronavirus Vaccine,” February 11, 2020, <https://www.hhs.gov/about/news/2020/02/11/hhs-janssen-join-forces-on-coronavirus-vaccine.html>.

¹⁰¹ Cormac Sheridan, “Coronavirus and the Race to Distribute Reliable Diagnostics,” *Nature Biotechnology*, February 21, 2020.

¹⁰² Peter Loftus, “Drugmaker Moderna Delivers First Experimental Coronavirus Vaccine for Human Testing,” *Wall Street Journal*, February 24, 2020.

¹⁰³ HHS, Encouraging Vaccine Innovation: Promoting the Development of Vaccines that Minimize the Burden of Infectious Diseases in the 21st Century, Report to Congress, December 2017, https://www.hhs.gov/sites/default/files/encouraging_vaccine_innovation_2018_final_report.pdf.

¹⁰⁴ Hanna Ziad, “Biotech Company Moderna Says its Coronavirus Vaccine is Ready for First Tests,” *CNN Business*, February 26, 2020, <https://www.cnn.com/2020/02/25/business/moderna-coronavirus-vaccine/index.html>.

¹⁰⁵ Matthew Herper and Damien Garde, “Coronavirus Vaccines Are Far Off, FDA Official Says, But Drugs to Treat Patients Could Come Sooner,” *STAT*, February 26, 2020, <https://www.statnews.com/2020/02/26/coronavirus-vaccines-are-far-off-fda-official-says-but-drugs-to-treat-patients-could-come-sooner/>.

MCMs by issuing an EUA, if the HHS Secretary declares that circumstances exist to justify the emergency use of an *unapproved product* or an *unapproved use of an approved medical product*.¹⁰⁶ The HHS Secretary's declaration must be based on one of four determinations; for example, a determination that there is an actual or significant potential for a public health emergency that affects or has significant potential to affect national security or the health and security of U.S. citizens living abroad.¹⁰⁷ Following the HHS Secretary's declaration, FDA, in consultation with ASPR, NIH, and CDC, may issue an EUA authorizing the emergency use of a specific drug, device, or biologic, provided that certain criteria are met (e.g., that there is no adequate, approved, and available alternative to the product).¹⁰⁸

On February 4, 2020, the HHS Secretary determined that there is a public health emergency that has a significant potential to affect national security or the health and security of U.S. citizens living abroad, and that involves the COVID-2019.¹⁰⁹ This emergency determination by the HHS Secretary is distinct from the Public Health Emergency declaration made pursuant to PHSA Section 319. On the basis of this determination, on February 4, 2020, the HHS Secretary declared that circumstances exist justifying the authorization of emergency use of in vitro diagnostics for the detection and/or diagnosis of COVID-2019. This declaration allowed FDA to issue an EUA authorizing the emergency use of the CDC-developed diagnostic test for COVID-2019. Pursuant to the same February 4, 2020 determination, on March 2, 2020, the HHS Secretary declared that circumstance exist justifying the emergency use of personal respiratory protective devices during the COVID-19 outbreak. This declaration allowed FDA to issue a second EUA—this one authorizing the emergency use of certain respirators in health care settings by health care personnel “to prevent wearer exposure to pathogenic biological airborne particulates during FFR [filtering facepiece respirator] shortages resulting from the COVID-19 outbreak.”¹¹⁰

Health System Preparedness

Health Care Capability and Capacity

There is concern that if COVID-19 spreads widely in the community, it will overwhelm the health care system's ability to care for patients and prevent further spread of the disease.

¹⁰⁶ 21 U.S.C. §360bbb-3. For additional information, see CRS In Focus IF10745, *Emergency Use Authorization and FDA's Related Authorities*.

¹⁰⁷ 21 U.S.C. §360bbb-3(b)(1).

¹⁰⁸ 21 U.S.C. §360bbb-3(c).

¹⁰⁹ This determination, made pursuant to Section 564(b)(1)(C) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. §360bbb-3(b)(1)(C)), is noted on page 1 of the letter of authorization from FDA to CDC, advising of the authorization for emergency use of the CDC-developed diagnostic test. This letter is available at “Novel coronavirus (COVID-2019) EUA Information” on the FDA web page “Emergency Use Authorization,” <https://www.fda.gov/emergencypreparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization>. See also footnote 84.

¹¹⁰ FDA, “Coronavirus (COVID-19) Update: FDA and CDC take action to increase access to respirators, including N95s, for health care personnel,” March 2, 2020, <https://www.fda.gov/news-events/press-announcements/coronaviruscovid-19-update-fda-and-cdc-take-action-increase-access-respirators-including-n95s>. The letter of authorization from FDA to CDC, advising of the authorization for emergency use of certain eligible respirators is available at “Novel coronavirus (COVID-2019) EUA Information” on the FDA web page “Emergency Use Authorization,” <https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization>.

Given that it is currently flu season, many health care facilities are already at or near patient capacity.

The ASPR is the principal advisor to the HHS Secretary on the public health and medical preparedness and response for public health emergencies.¹¹¹ CDC is the nation's leading public health agency. Since 2002, the ASPR and CDC have funded grants to states for health system and public health preparedness, respectively.¹¹² These grants have fostered nationwide development of several response capabilities that would be called upon for a successful response to the COVID19 threat, including the following:

- **Medical surge:** "...the ability to provide adequate medical evaluation and care during events that exceed the limits of the normal medical infrastructure of an affected community. It encompasses the ability of the health care system to endure a hazard impact, maintain or rapidly recover operations that were compromised, and support the delivery of medical care and associated public health services, including disease surveillance, epidemiological inquiry, laboratory diagnostic services, and environmental health assessments."¹¹³ ASPR and CDC are projecting the potential long-term impact of COVID-19 and assessing the capacity of the health care system to respond to a larger outbreak. A sustained response could engage the Regional Treatment Network for Ebola and Other Special Pathogens, a tiered health system response network developed with funding provided by Congress for response to the Ebola outbreak in 2015.¹¹⁴
- **Nonpharmaceutical interventions (NPI):** "...actions that people and communities can take to help slow the spread of illness or reduce the adverse impact of public health emergencies. This capability focuses on communities, community partners, and stakeholders recommending and implementing [NPI] in response to the needs of an incident, event, or threat."¹¹⁵ Interventions may include isolation, quarantine, restrictions on movement and travel advisories or warnings, social distancing, external decontamination, hygiene, and precautionary protective behaviors.
- **Medical countermeasure dispensing and administration:** "...the ability to provide medical countermeasures to targeted population(s) to prevent, mitigate, or treat the adverse health effects of a public health incident. This capability focuses on dispensing and administering medical countermeasures, such as vaccines, antiviral drugs, antibiotics..."¹¹⁶ The Strategic National Stockpile (SNS), managed by ASPR, provides select medicines and medical supplies during public health emergencies when local supply chains are disrupted.¹¹⁷

¹¹¹ HHS, "Coronavirus Disease 2019," <https://www.phe.gov/Preparedness/nCoV/Pages/default.aspx>. See also CRS Insight IN11038, *U.S. National Health Security: Homeland Security Issues in the 116th Congress*.

¹¹² CDC, Public Health Emergency Preparedness (PHEP) Cooperative Agreement, <https://www.cdc.gov/cpr/readiness/phep.htm>; and HHS, Assistant Secretary for Preparedness and Response (ASPR), Hospital Preparedness Program (HPP), <https://www.phe.gov/Preparedness/planning/hpp/Pages/default.aspx>.

¹¹³ CDC, "Public Health Emergency Preparedness and Response Capabilities," p. 103, October 2018, Updated January 2019, <https://www.cdc.gov/cpr/readiness/capabilities.htm>, hereinafter "CDC Capabilities 2019."

¹¹⁴ HHS, "HPP Funds Regional Treatment Network for Ebola and Other Special Pathogens," <https://www.phe.gov/Preparedness/planning/hpp/Pages/hpp-pathogens.aspx>.

¹¹⁵ CDC Capabilities 2019, p. 112.

¹¹⁶ *Ibid.*, p. 80.

¹¹⁷ HHS, "Strategic National Stockpile," <https://www.phe.gov/about/sns/Pages/default.aspx>.

The National Health Security Preparedness Index (NHSPI, or the Index), a public-private partnership begun in 2013, currently assesses preparedness, using 140 measures, across all 50 states and the District of Columbia.¹¹⁸ In its latest comprehensive report, for 2017, NHSPI found overall incremental improvements over earlier years in capabilities such as disease surveillance and medical countermeasures management. However, the report highlighted differing preparedness levels among states, stating

Large geographic areas in the Deep South and Mountain West trail the rest of the nation in health security, leaving many low-income populations and rural residents at elevated risk.¹¹⁹

In addition, measures of health care delivery—for example, the number of certain types of health care providers (including mental health providers) per unit of population, access to trauma centers, the extent of preparedness planning in long-term care facilities, and uptake of electronic health record systems—and of community planning and engagement—for example, the degree of coordination between public health authorities and the health care system—continued to yield the lowest scores among the indicators across the United States.

Supply Chain Management

ASPR, CDC, and FDA play roles in protecting against and preparing for the potential impact of the COVID-19 virus on the medical product supply chain, including shortages of critical drugs and medical devices such as personal protective equipment (PPE). ASPR, FDA, and CDC have indicated that they are working with health care and/or industry partners to ensure an adequate supply of medical products needed to contain the outbreak and to identify potential disruptions or shortages.¹²⁰ A chief concern in supply chain management is that many medical products or drugs are manufactured, at least in part, in China, the epicenter of the current outbreak.¹²¹

By law, drug manufacturers are required to notify FDA of a permanent discontinuance of or interruption in the manufacture of a drug that is likely to lead to a disruption in its supply.¹²² Based on the reported information, FDA may take various actions to mitigate or prevent a drug shortage from occurring, such as expediting applications for approval from other manufacturers and allowing for the temporary importation of unapproved drugs.¹²³ Currently, there are no parallel reporting requirements for medical devices.

Some have concerns with respect to FDA's ability to inspect and monitor compliance of FDA-regulated products manufactured overseas and particularly in China. As of February 24,

¹¹⁸ National Health Security Preparedness Index (NHSPI), <https://nhspi.org/>.

¹¹⁹ NHSPI Frequently Asked Questions, 2019, <https://nhspi.org/?s=FAQs>.

¹²⁰ Robert Kadlec, HHS Assistant Secretary for Preparedness and Response (ASPR), "Coronavirus Disease 2019 Stakeholder Listening Session Transcript," January 30, 2020, <https://www.phe.gov/Preparedness/nCoV/Documents/2019nCoV-Listening-Session-Transcript.pdf>; CDC, "CDC Update on Novel Coronavirus," February 5, 2020, <https://www.cdc.gov/media/releases/2020/t0205-coronavirus-update.html>; and FDA, "FDA's Actions in Response to 2019 Novel Coronavirus at Home and Abroad," February 14, 2020, <https://www.fda.gov/news-events/pressannouncements/fdas-actions-response-2019-novel-coronavirus-home-and-abroad>.

¹²¹ Robert Kadlec, HHS Assistant Secretary for Preparedness and Response (ASPR), "Coronavirus Disease 2019 Stakeholder Listening Session Transcript," January 30, 2020, <https://www.phe.gov/Preparedness/nCoV/Documents/2019nCoV-Listening-Session-Transcript.pdf>; and CDC, "CDC Update on Novel Coronavirus," February 5, 2020, <https://www.cdc.gov/media/releases/2020/t0205-coronavirus-update.html>.

¹²² 21 U.S.C. §356c(a).

¹²³ 21 U.S.C. §356c(g), 21 U.S.C. §381(d).

2020, FDA is not conducting inspections in China due to the State Department travel advisory. Inspections in China scheduled for February 2020 have been either postponed, or the agency is using different means to obtain information to inform regulatory decisions about FDA-regulated products manufactured in these facilities.¹²⁴ While there are no FDA-licensed vaccines, gene therapies, or blood derivatives manufactured in China, the raw materials used to produce these biologics are manufactured in China and other countries in Southeast Asia.¹²⁵ In addition, according to FDA data, 72% of facilities that manufacture active pharmaceutical ingredients (APIs) for drugs are located outside of the United States, with 13% of facilities in China; 53% of facilities manufacturing finished drugs are located outside of the United States, with 7% of facilities in China.¹²⁶ These numbers are not reflective of product volume. FDA is not able to determine what volume of APIs being used for the U.S. market is from China, as manufacturers are not required to report this information to the agency.

Response Funding

CDC and other federal agencies may have the authority needed to respond to the COVID-19 epidemic, but their ability to act may be affected by the availability of appropriations. Annual appropriations and standing transfer authority provide the HHS Secretary with some flexibility.¹²⁷ Upon a declaration of a Public Health Emergency pursuant to PHSA Section 319—which HHS Secretary Azar made on January 31, 2020—HHS may access a Public Health Emergency Fund,¹²⁸ but the fund does not have an available balance at this time. Separately, funding has generally not been available under the Robert T. Stafford Disaster Relief and Emergency Assistance Act (the Stafford Act) for the response to infectious disease outbreaks. As a result, Congress and the President provided supplemental appropriations for the response to the recent Ebola and Zika virus outbreaks in FY2015 and FY2016.¹²⁹

¹²⁴ FDA, “Coronavirus Update: FDA steps to ensure quality of foreign products,” February 24, 2020, <https://www.fda.gov/news-events/press-announcements/coronavirus-update-fda-steps-ensure-quality-foreign-products>.

¹²⁵ FDA, “FDA’s Actions in Response to 2019 Novel Coronavirus at Home and Abroad,” February 14, 2020, <https://www.fda.gov/news-events/press-announcements/fdas-actions-response-2019-novel-coronavirus-home-andabroad>.

¹²⁶ FDA, Testimony of Dr. Janet Woodcock, Director the Center for Drug Evaluation and Research, “Securing the U.S. Drug Supply Chain: Oversight of FDA’s Foreign Inspection Program,” December 10, 2019, <https://www.fda.gov/newsevents/congressional-testimony/securing-us-drug-supply-chain-oversight-fdas-foreign-inspection-program-12102019>.

¹²⁷ Annual appropriations acts give the HHS Secretary limited authority to transfer funds from one budget account to another within the department. For instance, a provision in the FY2020 HHS appropriations act (P.L. 116-94, Division A, Title II, §205) generally allows the Secretary to transfer up to 1% of the funds from any given account. However, in general, a recipient account may not be increased by more than 3%. Congressional appropriators must be notified in advance of any transfer. Another FY2020 appropriations provision (P.L. 116-94, Division A, Title V, §514) addresses the Secretary’s authority to reprogram funds from one program, project, or activity in a given budget account to a different program, project, or activity within the same budget account. This provision places certain limits on such actions and clarifies the circumstances in which appropriations committees must be consulted in advance. (See P.L. 115-245).

¹²⁸ See HHS, “Legal Authority with Declaration of Public Health Emergency,” <https://www.phe.gov/Preparedness/support/secauthority/Pages/default.aspx#phe>.

¹²⁹ Rebecca Katz, Aurelia Attal-Juncqua, and Julie E. Fischer, “Funding Public Health Emergency Preparedness in the United States,” *American Journal of Public Health*, vol. 107, suppl. 2, pp. S148-S152, September, 2017, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5594396/>.

In 2018, Congress established an Infectious Diseases Rapid Response Reserve Fund (IDRRRF) for CDC, providing appropriations of \$50 million for FY2019 (P.L. 115-245) and \$85 million for FY2020 (P.L. 116-94), available until expended.¹³⁰ These funds may be made available for an infectious disease emergency if the HHS Secretary either (1) declares a Public Health Emergency pursuant PHSA Section 319, or (2) determines that the infectious disease outbreak has significant potential to occur and, if it occurs, the potential to affect national security or the health and security of U.S. citizens, both domestically and abroad.

Before HHS Secretary Azar declared the COVID-19 outbreak to be a Public Health Emergency under PHSA Section 319, he issued a determination on January 25, 2020, allowing the allotment of \$105 million from the IDRRRF for the COVID-19 response.¹³¹ Secretary Azar had previously determined that the U.S. response to the Ebola outbreak in the Democratic Republic of Congo allowed the use of up to \$30 million from the IDRRRF. If both the Ebola and COVID-19 amounts are fully used, all funds currently in the IDRRRF would be exhausted.¹³² On February 2, 2020, HHS reportedly notified Congress of its intention to use the Secretary's standing authority to transfer up to \$136 million for COVID-19 response efforts, of which \$75 million would be made available to CDC, \$52 million for ASPR, and \$8 million for the HHS Office of Global Affairs.¹³³ Since then, Secretary Azar has reportedly "told lawmakers that the administration has now spent or obligated the entirety of \$105 million [from the IDRRRF] and is now moving into previously announced transfers of \$136 million from other programs."¹³⁴

CDC has an additional source of emergency support through the CDC Foundation, a 501(c)(3) public charity established by Congress "to support and carry out activities for the prevention and control of diseases, disorders, injuries, and disabilities, and for promotion of public health."¹³⁵ The CDC Foundation activated its Emergency Response Fund (ERF) to support COVID-19 response on January 27, 2020, as requested by CDC.¹³⁶ Funds have been donated to the ERF for this response by the Robert Wood Johnson Foundation, among others. Although the support provided by the foundation for outbreak response has been modest compared with supplemental appropriations, the foundation has greater spending flexibility and can sometimes procure response supplies and services more quickly than CDC through federal procurement processes.¹³⁷

On February 24, 2020, the Administration asked Congress for an emergency supplemental appropriation of \$1.25 billion for COVID-19 response efforts. The Administration also asked Congress to allow re-purposing of another \$1.25 billion in existing

¹³⁰ The IDRRRF authority is codified at 42 U.S.C. §247d-4a.

¹³¹ CQ Newsmaker Transcripts, "Health and Human Services Secretary Azar Holds News Conference on Coronavirus," January 28, 2020, https://plus.cq.com/doc/newsmaker_transcripts-5822133?8&searchId=XGVQS7c5.

¹³² Communication with CDC, January 28, 2020.

¹³³ Yasmeen Abutaleb and Erica Werner, "HHS Notifies Congress that it May Tap Millions of Additional Dollars for Coronavirus Response," *Washington Post*, February 3, 2020. Likely the authority described in footnote 127.

¹³⁴ Erica Werner and Yasmeen Abutaleb, "Congressional Leaders Launch Emergency Spending Talks for Coronavirus Response," *Washington Post*, February 26, 2020.

¹³⁵ Public Health Service Act Section 399G, 42 U.S.C. §280e-11. See "National Foundation for the Centers for Disease Control and Prevention" in CRS Report R46109, *Agency-Related Nonprofit Research Foundations and Corporations*.

¹³⁶ CDC Foundation, "Responding to Coronavirus," <https://www.cdcfoundation.org/coronavirus>.

¹³⁷ See, for example, CDC Foundation, "2018 Ebola Outbreak," <https://www.cdcfoundation.org/2018-ebola-outbreak>.

funds from across the government, including HHS funds for current Ebola response activities.¹³⁸ It is reported that “House and Senate appropriators are discussing a package in the range of \$6 billion to \$8 billion ... [for] the departments of Health and Human Services, State, Homeland Security, Defense and possibly other agencies....”¹³⁹

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¹³⁸ Russell T. Vought, Acting Director, White House Office of Management and Budget, letter to the Honorable Michael R. Pence, President of the Senate, February 24, 2020.

¹³⁹ Paul M. Krawzak, “Lawmakers Zeroing in on \$6B to \$8B Coronavirus Aid Package,” *CQ News*, February 27, 2020.

Chapter 384

GLOBAL ECONOMIC EFFECTS OF COVID-19: IN BRIEF*

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OVERVIEW

Since the World Health Organization (WHO) first declared COVID-19 a world health emergency in January 2020, the virus has been detected in over 150 countries and almost all U.S. states.¹ The infection has sickened more than 200,000 people, with thousands of fatalities.

On March 11, the WHO announced that the outbreak was officially a pandemic, the highest level of health emergency.² During that time, it has become clear that the outbreak is negatively impacting global economic growth.³ The virus is affecting a broad swath of economic activities, from tourism, medical supplies and other global value chains, consumer electronics, and financial markets to energy, food, and a range of social activities, to name a few. Without a clear understanding of when the health and economic effects may peak economic forecasts must necessarily be considered preliminary. Efforts to reduce social interaction to contain the spread of the virus are disrupting the daily lives of most Americans.

On March 2, 2020, the Organization for Economic Cooperation and Development (OECD) released its revised economic outlook and suggested that global economic growth could decline by 0.5% in 2020 to 2.4% if the economic effects of the virus peak in the first

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¹ Mapping the Spread of the Coronavirus in the U.S. and Worldwide, Washington Post Staff, *The Washington Post*, March 4, 2020. <https://www.washingtonpost.com/world/2020/01/22/mapping-spread-new-coronavirus/?arc404=true>.

² Bill Chappell, "Coronavirus: COVID-19 Is Now Officially A Pandemic, WHO Says," *National Public Radio*, March 11, 2020, <https://www.npr.org/sections/goatsandsoda/2020/03/11/814474930/coronavirus-covid-19-is-now-officially-a-pandemic-who-says>.

³ Mapping the Spread of the Coronavirus.

quarter of 2020⁴ (see Table 1). If the effects of the virus do not peak in the first quarter, which now seems unlikely, the OECD estimates that global economic growth in 2020 could be reduced by half, or 1.5%.

Concerns over economic and financial risks have pushed investors to search out safe-haven investments such as the benchmark U.S. Treasury 10-year security, which experienced a historic drop in yield to below 1% on March 3, 2020 (the price and yield of a bond are inversely related).⁵ The yield dropped again to historic levels on March 6, 2020, and March 9, 2020, as investors moved out of stocks and into bonds due to concerns over declines in major stock indices and expectations that the Federal Reserve would lower interest rates for a second time in March 2020.⁶ In overnight trading on March 8, 2020, and again on March 11, 2020, March 13, 2020, and March 15, 2020, U.S. stock market indices moved sharply, triggering automatic circuit breakers designed to halt trading if the indices rise or fall by more than 5% when markets are closed.⁷ Financial markets from the United States to Asia and Europe are volatile as investors are concerned that the virus is creating a global issue with few metrics to indicate how prolonged and expansive the economic effects may be.⁸ Similar to the 2008-2009 global financial crisis, central banks are finding themselves put in the position of being the lender of last resort. During the financial crisis, central banks intervened to restart credit and spending. In the current environment, however, central banks are attempting to address financial market volatility that reflects the underlying economic uncertainty caused by the viral outbreak. The virus is also affecting global politics as world leaders are cancelling international meetings⁹ and some nations reportedly are stoking conspiracy theories that shift blame to other countries.¹⁰

The challenge for policymakers is to implement targeted policies that address what are expected to be short-term problems without creating distortions in economies that can outlast the impact of the virus itself. Policymakers are being overwhelmed by the quickly changing nature of the crisis that has compounded a health issue with what could become a global trade and economic crisis whose potential effects on the global economy are rapidly growing. In addition, many policymakers are constrained in their response to the crisis, with little flexibility for monetary and fiscal support, given the broad-based synchronized slowdown in global economic growth, especially in manufacturing and trade, which had developed prior to the viral outbreak.

⁴ OECD *Interim Economic Assessment: Coronavirus: The World Economy at Risk*, Organization for Economic Cooperation and Development, March 2, 2020. <http://www.oecd.org/economic-outlook/#resources>.

⁵ Levisohn, Ben, The 10-Year Treasury Yield Fell Below 1% for the First Time Ever. What That Means, *Barrons*, March 3, 2020. <https://www.barrons.com/articles/the-10-year-treasury-yield-fell-below-1-for-the-first-time-ever-what-that-means-51583267310>.

⁶ Smith, Colby, Richard Henderson, Philip Georgiadis, and Hudson Lockett, Stocks Tumble and Government Bonds Hit Highs on Virus Fears, *The Financial Times*, March 6, 2020. <https://www.ft.com/content/9f94d6f8-5f51-11ea-b0ab-339c2307bcd4>.

⁷ Georgiadis, Philip, Adam Samson, and Hudson Lockett, Stocks Plummet as Oil Crash Shakes Financial Markets, *The Financial Times*, March 9, 2020. <https://www.ft.com/content/8273a32a-61e4-11ea-a6cd-df28cc3c6a68>.

⁸ Samson, Adam and Hudson Lockett, Stocks Fall Again in Worst Week Since 2008 Crisis, *The Financial Times*, February 28. <https://www.ft.com/content/4b23a140-59d3-11ea-a528-dd0f971feb9c>.

⁹ Taylor, Adam, Teo Armus, and Rick Noak, Live updates: Coronavirus Turmoil Widens as U.S. Death Toll Mounts; Xi Cancels Japan Trip. *The Washington Post*, March 5, 2020, <https://www.washingtonpost.com/world/2020/03/05/coronavirus-live-updates/>.

¹⁰ Shih, Gerry, China is Subtly Stoking Coronavirus Conspiracy Theories That Blame the U.S. for Outbreak, *The Washington Post*, March 5, 2020. <https://www.washingtonpost.com/world/2020/03/05/coronavirus-live-updates/>.

Table 1. OECD economic outlook forecast, March 2020

Percent change in Real GDP Growth					
	2019	2020			2021
		November projections	Difference from November	November projections	Difference from November
World	2.9	2.4	-0.5	3.3	0.3
G20	3.1	2.7	-0.5	3.5	0.2
Australia	1.7	1.8	-0.5	2.6	0.3
Canada	1.6	1.3	-0.3	1.9	0.2
Euro area	1.2	0.8	-0.3	1.2	0.0
Germany	0.6	0.3	-0.1	0.9	0.0
France	1.3	0.9	-0.3	1.4	0.2
Italy	0.2	0.0	-0.4	0.5	0.0
Japan	0.7	0.2	-0.4	0.7	0.0
Korea	2.0	2.0	-0.3	2.3	0.0
Mexico	-0.1	0.7	-0.5	1.4	-0.2
Turkey	0.9	2.7	-0.3	3.3	0.1
United Kingdom	1.4	0.8	-0.2	0.8	-0.4
United States	2.3	1.9	-0.1	2.1	0.1
Argentina	-2.7	-2.0	-0.3	0.7	0.0
Brazil	1.1	1.7	0.0	1.8	0.0
China	6.1	4.9	-0.8	6.4	0.9
India	4.9	5.1	-1.1	5.6	-0.8
Indonesia	5.0	4.8	-0.2	5.1	0.0
Russia	1.0	1.2	-0.4	1.3	-0.1
Saudi Arabia	0.0	1.4	0.0	1.9	0.5
South Africa	0.3	0.6	-0.6	1.0	-0.3

Source: *OECD Interim Economic Assessment: Coronavirus: The World Economy at Risk*, Organization for Economic Cooperation and Development. March 2, 2020, p. 2.

ESTIMATED ECONOMIC EFFECTS

The economic situation remains highly fluid. Uncertainty about the length and depth of the virus-related economic effects are fueling perceptions of risk and volatility in financial markets and corporate decisionmaking. In addition, uncertainties concerning the virus and the effectiveness of public policies intended to curtail its spread are adding to market volatility.

The OECD also estimates that increased direct and indirect economic costs through global supply chains reduced demand for goods and services, and that declines in tourism and business travel mean that, “the adverse consequences of these developments for other countries (non-OECD) are significant.”¹¹ Global trade, measured by trade volumes, slowed in the last quarter of 2019 and was expected to decline further in 2020 as a result of weaker global economic activity associated with the viral outbreak, which is reducing economic activity in various sectors, including ports and the shipping industry.¹²

¹¹ Ibid., p. 2.

¹² Ibid., p. 4.

COMPARING THE CURRENT CRISIS AND THE 2008 CRISIS

Sharp declines in the stock market and broader financial sector turbulence; interest rate cuts and large-scale Federal Reserve intervention; and discussions of massive government stimulus packages have led some observers to compare the current market reaction to that experienced a little over a decade ago. There are similarities and important differences between the current economic crisis and the global financial crisis of 2008/2009. Foremost, the earlier crisis was rooted in structural weakness in the U.S. financial sector. Following the collapse of the U.S. housing bubble, it became impossible for firms to identify demand and hold inventories (across many sectors (construction, retail, etc.)). This led to massive oversupply and sharp retail losses which extended to other sectors of the U.S. economy and eventually the global economy. Moreover, financial markets across countries were linked together by credit default swaps. As the crisis unfolded, large numbers of banks and other financial institutions were negatively affected, raising questions about capital sufficiency and reserves. The crisis, then quickly engulfed credit-rating agencies, mortgage lending companies and the real estate industry broadly. Market resolution came gradually with a range of monetary and fiscal policy measures that were closely coordinated at the global level. These were focused on putting a floor under the falling markets, stabilizing banks, and shoring up investor confidence to get spending started again. Starting in September 2007, The Federal Reserve cut interest rates from over 5% in September 2007 to between 0 and 0.25% before the end of the 2008.

Once interest rates approached zero, the Fed turned to other so-called “unconventional measures” including targeted assistance to financial institutions, including encouraging Congress to pass the Troubled Asset Relief Program (TARP) and the Term Asset Backed Security Loan Facility (TALF) to prevent the collapse of the financial sector and boost consumer spending. Other measures included forced bank capitalizations (or bank nationalizations in other countries), swap arrangements between the Federal Reserve and the European Central Bank and smaller central banks, and so-called “quantitative easing” to boost the money supply. On a global level, the United States and other countries tripled the resources of the IMF (from \$250 billion to \$750 billion) and coordinated domestic stimulus efforts.

Unlike the 2008 crisis, the current crisis began as a supply shock. As the global economy has become more interdependent in recent decades, most products are produced as part of a global value chain (GVC), where an item such as a car or mobile device consists of parts manufactured all over the world, and involving multiple border crossings before final assembly. The earliest implications of the current crisis came in January as plant closures in China and other parts of Asia led to interruptions in the supply chain and concerns about dwindling inventories. As the virus spread from Asia to Europe, the crisis switched from supply concerns to a broader demand crisis as the measures being introduced to contain the spread of the virus (social distancing, travel restrictions, cancelling sporting events, closing shops and restaurants, and mandatory quarantine measures) prevent most forms of economic activity from occurring. Thus, unlike the 2008 crisis response, which involved liquidity and solvency-related policy measures to get people spending again, the current crisis is related to the amount of operating capital in the economy. While larger firms may have sufficient capital to wait out a crisis, many aspects of the economy (such as restaurants or retail operations) operate on very tight margins and would likely not be able to pay employees after closures lasting more than a few days. Many people will also need to balance child care and work during quarantine or social distancing measures.

During this type of crisis, while monetary policy measures play a part -- and the Federal Reserve has once again cut rates to near zero -- they cannot compensate for the physical interaction that the global economy is dependent upon. As a result, fiscal stimulus will likely play a relatively larger role in this crisis in order to prevent personal and corporate bankruptcies during the peak crisis period. Efforts to coordinate U.S. and foreign economic policy measures will also have an important role in mitigating the scale and length of any global economic downturn.

In addition, the OECD argues that China’s emergence as a global economic actor marks a significant departure from previous global health episodes. China’s growth in combination with globalization and the interconnected nature of economies through supply chains and foreign investment magnify the cost of containing the spread of the virus through quarantines

and restrictions on labor mobility and travel.¹³ China's global economic role and globalization more broadly mean that trade is playing a role in spreading the economic effects of COVID-19 through three channels: directly through supply chains as reduced economic activity is spread from intermediate goods producers to finished goods producers; as a result of a drop in economic activity, which reduces demand for goods in general, including imports; and through reduced trade with commodity exporters that supply producers, which, in turn, reduces their imports and negatively affects trade and economic activity of exporters.

Initially, the economic effects of the virus were expected to be a short-term supply issue as factory output fell because workers were quarantined to reduce the spread of the virus through social interaction. The drop in economic activity, initially in China, created larger supply issues as firms experienced delays in supplies in intermediate and finished goods through supply chains. Concerns have grown, however, that the virus-related supply shock is creating a more prolonged demand shock as reduced activity by consumers and businesses lead to a lower rate of economic growth. As demand shocks unfold, businesses experience a decline in activity, reduced profits, and potentially escalating and binding credit and liquidity constraints. While manufacturing firms are experiencing supply shocks through their supply chains, reduced consumer activity through social distancing is affecting the services sector of the economy, which accounts for two-thirds of U.S. economic output. In this environment, manufacturing and service firms are hoarding cash, which affects market liquidity. In response central banks have taken measures to provide financial markets with liquidity.

If the economic effects persist, contagion issues can spread the economic effects widely and affect an ever-broadening group of firms and households. This potentially can increase liquidity constraints and credit market tightening in global financial markets as firms hoard cash, with negative fallout effects on economic growth. In some financial markets, fund managers have started selling government securities to increase their cash reserves, pushing down government bond prices. At the same time, financial markets are factoring in an increase in government bond issuance in the United States and Europe as government debt levels rise to meet spending obligations during an expected slowdown in economic activity and efforts to fight the effects of COVID-19. Unlike the 2008 financial crisis, reduced demand by consumers, labor market issues, and a reduced level of activity among businesses, rather than risky trading by global banks, has led to corporate credit issues. The market dynamics have led some observers to question if these events mark the beginning of a full-scale global financial crisis.¹⁴

Liquidity and credit market issues present policymakers with a different set of challenges than addressing supply-side constraints. As a result, the focus of government policy has expanded from a health issue to macroeconomic and financial market issues that are being addressed through a combination of monetary, fiscal, and other policies. Essentially, while businesses are attempting to address worker and output issues at the firm level, national leaders are attempting to implement fiscal policies to assist workers and businesses that are facing financial strains, and central bankers are adjusting monetary policies to address mounting credit market issues. So far, households have been affected primarily through a loss of income, compared with the 2008-2009 financial crisis in which households experienced a

¹³ Goldin, Ian. Coronavirus Shows How Globalization Spreads Contagion of All Kinds, *The Financial Times*, March 2, 2020. <https://www.ft.com/content/70300682-5d33-11ea-ac5e-df00963c20e6>.

¹⁴ Foroohar, Rana, How Coronavirus Became a Corporate Credit Run, *The Financial Times*, March 15, 2020. <https://www.ft.com/content/f1ea5096-6531-11ea-a6cd-df28cc3c6a68>.

sudden and large loss in the value of their assets, largely through a decline in the market value of their primary residence.

In many cases, national fiscal policies that might be employed to address demand issues are already constrained by high government debt levels; similarly, recent monetary policies have generally been accommodative, which leaves central banks little room for additional cuts in interest rates. In addition, in the current environment, even traditional policy tools, such as monetary accommodation, apparently are not being processed by markets in a traditional manner, with equity market indices displaying heightened, rather than lower, levels of uncertainty following the Federal Reserve's cut in interest rates. Such volatility is adding to uncertainties about what governments can do to address weaknesses in the global economy.

Before the COVID-19 outbreak, the global economy was struggling to regain a broad-based recovery as a result of the lingering impact of growing trade protectionism, trade disputes among major trading partners, falling commodity and energy prices, and economic uncertainties in Europe over the impact of the UK withdrawal from the European Union. Individually, each of these issues presented a solvable challenge for the global economy. Collectively, however, the issues weakened the global economy and reduced the available policy flexibility of many countries, especially among the leading developed economies. In this environment, COVID-19 could have an outsized impact. While the level of economic effects will eventually become clearer, the response to the virus could have a significant and enduring impact on the way businesses organize their work forces, global supply chains, and how governments respond to a global health crisis.¹⁵

POLICY RESPONSE

In response to growing concerns over the global economic impact of the virus, G-7 finance ministers and central bankers released a statement on March 3, 2020, indicating they will “use all appropriate policy tools” to sustain economic growth.¹⁶ The Finance Ministers also pledged fiscal support to ensure health systems could sustain efforts to fight the outbreak.¹⁷ Following the G-7 statement, the U.S. Federal Reserve (Fed) lowered its federal funds rate by 50 basis points, or 0.5%, to a range of 1.0% to 1.25% due to concerns about the “evolving risks to economic activity of the coronavirus.”¹⁸ At the time, the cut was the largest one-time reduction in the interest rate by the Fed since the financial crisis of 2008.

¹⁵ Rowland, Christopher and Peter Whoriskey, U.S. Health System is Showing Why it's Not Ready for a Coronavirus Pandemic, *The Washington Post*, March 4, 2020. https://www.washingtonpost.com/business/economy/the-us-health-system-is-showing-why-its-not-ready-for-a-coronavirus-pandemic/2020/03/04/7c307bb4-5d61-11ea-b29b-9db42f7803a7_story.html.

¹⁶ the G-7 is comprised of Canada, France, Germany, Italy, Japan, the United Kingdom, and the United States. *Statement of G-7 Finance Ministers and Central Bank Governors*, March 3, 2020, <https://home.treasury.gov/news/press-releases/sm927>, Long, Heather, G-7 Leaders Promise to Help Economy as Coronavirus Spreads, But They Don't Announce Any New Action, *The Washington Post*, March 3, 2020. <https://www.washingtonpost.com/business/2020/03/03/economy-coronavirus-rate-cuts/>.

¹⁷ Giles, et, al, Finance Ministers Ready to Take Action.

¹⁸ CRS Insight IN11235, *COVID-19: Potential Economic Federal Reserve Releases FOMC Statement*, March 3, 2020, <https://www.federalreserve.gov/newsevents/pressreleases/monetary20200303a.htm>.

The United States

In a sign of growing concern over strains in financial markets, on March 12, 2020, the Federal Reserve announced it will supply liquidity to the financial system by providing \$5 trillion through a series of funding operations that will add to current monthly funding operations targeted at increasing reserves in the banking system and reducing stress in short-term funding market and in trading U.S. Treasury securities. Corporate bond markets halted activity on March 11, 2020, as companies drew on revolving credit facilities from banks to ensure they had enough cash on hand to sustain their operations during a prolonged slump in economic activity and potential credit tightening by banks.

In addition, banks and financial institutions that deal in trading U.S. Treasury securities had begun to pull back from facilitating trades to protect themselves from market volatility, increasing costs to traders who profit from the difference between buying Treasury securities and then selling futures contracts.¹⁹ The Federal Reserve reportedly will provide \$1 trillion in short-term lending to banks to sustain lending between banks, because credit markets had begun to freeze up. In addition, the Federal Reserve opened a financial crisis-era facility to acquire corporate bonds in the commercial paper (CP) market, which is used by firms to raise cash by selling short-term debt.²⁰ Banks have become reluctant to acquire the securities over concerns that markets that trade in CP will be frozen.²¹ The Fed also indicated that it will provide a series of \$500 billion injections of funds into the repo (repurchase) market, where investors borrow cash in exchange for high-quality collateral like Treasury securities.²²

In an additional step, the Federal Reserve cut interest rates by 100 basis points (1.0%) on March 15, 2020, to a range of 0% to 0.25%, because it determined that “....The coronavirus outbreak has harmed communities and disrupted economic activity in many countries, including the United States. Global financial conditions have also been significantly affected.”²³ The Federal Reserve announced that it was providing an additional \$700 billion in asset purchases (Treasury securities and mortgage-backed securities), expanding repurchase operations, extending dollar swap lines with foreign banks (Canada, the UK, Japan and Europe, including the Swiss National Bank), and opened its discount window to commercial banks and urged banks to use their own capital and liquidity buffers to ease household and business lending. In its statement, the Federal Reserve announced that it was prepared to use its “full range of tools to support the flow of credit to households and businesses....” The coordinated central bank actions were intended to calm global financial markets after a week of greater than usual volatility. On March 17, 2020, the Federal Reserve opened a new financing facility for the 24 primary dealers in U.S. Treasury securities that allows them to borrow cash secured against some stocks, municipal debt and higher-rated corporate bonds.

¹⁹ Rennison, Joe, and Colby Smith, What is Causing Such Fear in the U.S. Treasuries Market?, *The Financial Times*, March 13, 2020. <https://www.ft.com/content/efa431c8-6471-11ea-b3f3-fe4680ea68b5>.

²⁰ Politi, James, Brendan Greeley, Colby Smith, and Joe Rennison, Fed to Lend Against Stocks and Bonds in Bid to Stabilize Markets, *The Financial Times*, March 17, 2020. <https://www.ft.com/content/cf485398-689d-11ea-800d-da70cff6e4d3>.

²¹ Rennison, Joe and Colby Smith, Investors Call for Fed Help in ‘Frozen’ Commercial Paper Market, *The Financial Times*, March 16, 2020. <https://www.ft.com/content/34213560-677b-11ea-a3c9-1fe6fedcca75>.

²² Smith, Colby, and Brendan Greeley, Fed to Pump Trillions of Dollars into Financial Markets, *The Financial Times*, March 12, 2020. <https://www.ft.com/content/7b231b2c-6483-11ea-a6cd-df28cc3c6a68>.

²³ *Federal Reserve Issues FOMC Statement*, March 15, 2020. <https://www.federalreserve.gov/newsevents/pressreleases/monetary20200315a.htm>.

In terms of a fiscal stimulus, the House passed H.R. 6074 on March 5, 2020, to appropriate \$8.3 billion in emergency funding to support efforts to fight COVID-19; President Trump signed the measure on March 6, 2020. Other countries have indicated they will also provide assistance. Congress also is considering other possible measures, including contingency plans for agencies to implement offsite telework for employees, financial assistance to the shale oil industry, paid sick leave, a reduction in the payroll tax,²⁴ and an extension of the tax filing deadline.²⁵ On March 11, 2020, President Trump announced a restriction on all travel from Europe to the United States for 30 days, directed the Small Business Administration (SBA) to offer low-interest loans to small businesses, and directed the Treasury Department to defer tax payments penalty-free for affected businesses.²⁶

On March 13, President Trump declared a state of emergency, freeing up disaster relief funding to assist state and local governments in addressing the effects of the virus. The President also announced additional testing for the virus, a website to help individuals identify symptoms of the virus, increased oil purchases for the Strategic Oil Reserve, and a waiver on interest payments on student loans.²⁷ The White House and House Democrats announced they had reached agreement on a package of measures that is intended to provide tens of billions of dollars for paid sick leave, unemployment insurance, food stamps, and other measures.²⁸

On March 17, 2020, President Trump announced that he intended to ask Congress for an additional \$1.2 trillion in funds to support the economy.²⁹ This amount reportedly would include loans to support cargo and passenger air carriers and loans and guarantees to other affected industries, loans to small businesses, and direct payments to individual taxpayers.³⁰ For additional information about the impact of COVID-19 on the U.S. economy see CRS Insight IN11235, *COVID-19: Potential Economic Effects*.³¹

²⁴ Armus, Theo, Federal, State Officials Attempt to Fight Virus Through Social Distancing, Stimulus Package, *The Washington Post*, <https://www.washingtonpost.com/world/2020/03/11/coronavirus-live-updates/>.

²⁵ Sevastopulo, Demetri, US Treasury Considers Tax Filing Extension to Ease Virus Impact, *The Financial Times*, March 11, 2020. <https://www.ft.com/content/c65a6e40-639f-11ea-b3f3-fe4680ea68b5>.

²⁶ McAuley, James, and Michael Birnbaum, Europe Blindsided by Trump's Travel Restrictions, With Many Seeing Political Motive, *The Washington Post*, March 12, 2020. https://www.washingtonpost.com/world/europe/europe-blindsided-by-trumps-travel-restrictions-with-many-seeing-political-motive/2020/03/12/42a279d0-6412-11ea-8a8e-5c5336b32760_story.html.

²⁷ Fritz, Angela and Meryl Kornfield, President Trump Declares a National Emergency, Freeing \$50 Billion in Funding, *The Washington Post*, March 13, 2020. <https://www.washingtonpost.com/world/2020/03/13/coronavirus-latest-news/>.

²⁸ Werner, Erica, Mike DeBonis, Paul Kane, and Jeff Stein, White House, House Democrats Reach Deal on Coronavirus Economic Relief Package, Pelosi Announces, *The Washington Post*, March 13, 2020. <https://www.washingtonpost.com/us-policy/2020/03/13/paid-leave-democrats-trump-deal-coronavirus/>.

²⁹ Werner, Eric and Jeff Stein, Trump Administration Seeks Roughly \$850 Billion in Emergency Stimulus to Confront Coronavirus Economic Fallout, *The Washington Post*, March 17, 2020. <https://www.washingtonpost.com/us-policy/2020/03/17/trump-coronavirus-stimulus-package/>.

³⁰ *Stage Three Proposal*, U.S. Department of the Treasury, March 17, 2020. https://www.washingtonpost.com/context/department-of-treasury-proposal-for-coronavirus-response/6c2d2ed5-a18b-43d2-8124-28d394fa51ff/?itid=lk_inline_manual_3.

³¹ CRS Insight IN11235, *COVID-19: Potential Economic Effects*, by Marc Labonte.

Europe

To date, European countries have not had the kind of synchronized policy response they developed during the global financial crisis of 2008-2009. Instead, they have used a combination of tax holidays for businesses and extensions of certain payments and loan guarantees and subsidies for workers. The European Commission announced that it was relaxing rules on government debt to allow countries more flexibility in using fiscal policies. The European Central Bank (ECB) announced that it was ready to take “appropriate and targeted measures,” if needed. With interest rates already low, however, it indicated that it could expand its program of providing loans to EU banks, or buying debt from EU firms, and possibly lowering its deposit rate further into negative territory in an attempt to shore up the Euro’s exchange rate.³² ECB President-designate Christine Lagarde called on EU leaders to take more urgent action to avoid the spread of coronavirus triggering a serious economic slowdown. The European Commission indicated that it was creating a nearly \$30 billion investment fund to address COVID-19 issues.³³ On March 12, 2020, the ECB decided to: (1) expand its longer-term refinance operations (LTRO) to provide low-cost loans to Eurozone banks to increase bank liquidity; (2) extend targeted longer-term refinance operations (TLTRO) to provide loans at below-market rates to businesses, especially small and medium-sized businesses, directly affected by COVID-19; (3) provide an additional €120 billion (about \$130 billion) for the Bank’s asset purchase program to provide liquidity to firms.³⁴ On March 13, 2020, financial market regulators in the UK, Italy, and Spain intervened in stock and bond markets to stabilize prices after historic swings in indexes on March 12, 2020.³⁵ In addition, the ECB announced that it would do more to assist financial markets in distress, including altering self-imposed rules on purchases of sovereign debt.³⁶ Germany’s Economic Minister announced on March 13, 2020, that Germany would provide unlimited loans to businesses experiencing negative economic activity (initially providing \$555 billion), tax breaks for businesses,³⁷ and export credits and guarantees.³⁸ Recent forecasts indicate that the economic effect of COVID-19 could push the Eurozone into an economic recession in 2020.³⁹

³² US Fed’s Coronavirus Rate Cut is First Move in a Dance With Markets, *The Financial Times*, March 4, 2020. <https://www.ft.com/content/83c07594-5e3a-11ea-b0ab-339c2307bcd4>, Giles, Chris, Martin Arnold, Sam Jones, and Jamie Smyth, Finance Ministers ‘Ready to Take Action’ on Coronavirus, *The Financial Times*, March 3, 2020. <https://www.ft.com/content/b86f7d92-5d38-11ea-b0ab-339c2307bcd4>.

³³ Arnold, Martin and Guy Chazan, Christine Lagarde Calls on EU Leaders to Ramp up Coronavirus Response, *The Financial Times*, March 11, 2020. <https://www.ft.com/content/44eac1f2-6386-11ea-a6cd-df28cc3c6a68>.

³⁴ *Monetary Policy Decisions*, The European Central Bank, March 12, 2020. <https://www.ecb.europa.eu/press/pr/date/2020/html/ecb.mp200312~8d3aec3ff2.en.htm>.

³⁵ Stafford, Philip and Adam Samson, European Regulators Intervene in Bid to Stabilize Stock and Bond Prices, *The Financial Times*, March 13, 2020. <https://www.ft.com/content/77f57d4c-6509-11ea-a6cd-df28cc3c6a68>.

³⁶ Arnold, Martin, ECB Enters Damage-Limitation Mode With Pledge of More Action, *The Financial Times*, March 13, 2020. <https://www.ft.com/content/f1cbd4f8-650f-11ea-b3f3-fe4680ea68b5>.

³⁷ Loveday, Morris and Louisa Beck, Germany Announces “Bazooka” Economic Plan to Mitigate Coronavirus Hit, *The Washington Post*, March 13, 2020. <https://www.washingtonpost.com/world/2020/03/13/coronavirus-latest-news/>.

³⁸ Arnold, Martin, Guy Chazan, Victor Mallet, Miles Johnson, and Daniel Dombey, How European economies are trying to mitigate the coronavirus shock, *The Financial Times*, March 17, 2020. <https://www.ft.com/content/26af5520-6793-11ea-800d-da70cff6e4d3>.

³⁹ Lagarde to Confront Coronavirus Crisis at ECB Policy Meeting, *The Financial Times*, March 8, 2020. <https://www.ft.com/content/79a280c6-5fb5-11ea-b0ab-339c2307bcd4>.

The United Kingdom

The Bank of England announced on March 11, 2020, that it would adopt a package of four measures to deal with any economic disruptions associated with COVID-19. The measures include: an unscheduled cut in the benchmark interest rate by 50 basis points (0.5%) to a historic low of 0.25%; reintroduce the Term Funding scheme for Small and Medium-sized Enterprises (TFSME) that provides banks with over \$110 billion for loans at low interest rates; lower banks' countercyclical capital buffer to zero percent, which is estimated to support over \$200 billion of bank lending to businesses; and freeze banks' dividend payments.⁴⁰ The UK Chancellor of the Exchequer proposed a national budget on March 11, 2020, that includes nearly \$35 billion in fiscal spending to counter adverse economic effects of the viral crisis and proposes that statutory sick leave be boosted by about \$2.5 billion in funds to small and medium businesses to provide up to 14 days of sick leave for affected employees. Part of the fiscal spending package includes open-ended funding for the National Health Service (NHS), \$6 billion in emergency funds to the NHS, \$600 million hardship fund to assist vulnerable people, and tax cuts and tax holidays for small businesses in certain affected sectors.⁴¹

Japan

The Bank of Japan, with already-low interest rates, interjected \$4.6 billion in liquidity into Japanese banks to provide short-term loans and twice that amount into exchange traded funds to aid Japanese businesses. The Japanese government also pledged to provide wage subsidies for parents forced to take time off due to school closures.⁴²

China

According to a recent CRS In Focus,⁴³ China's economic growth could go negative in the first quarter of 2020 and fall below 5% for the year, with more serious effects if the outbreak continues. In early February, China's central bank pumped \$57 billion into the banking system, capped banks' interest rates on loans for major firms, and extended deadlines for banks to curb shadow lending. The central bank has been setting the reference rate for China's currency stronger than its official close rate to keep it stable. On March 13, 2020, The People's Bank of China announced that it would provide \$78.8 billion in funding, primarily to small businesses, by reducing bank's reserve requirements.⁴⁴

⁴⁰ Romei, Valentina, Coronavirus fallout: Bank of England launches 4 key measures, *The Financial Times*, <https://www.ft.com/content/4e60c08e-6380-11ea-b3f3-fe4680ea68b5>.

⁴¹ Payne, Sebastian and Chris Giles, Budget 2020: Sunak Unveils £30bn Stimulus to Counter UK Coronavirus Shock, *The Financial Times*, <https://www.ft.com/content/f7b27264-6384-11ea-a6cd-df28cc3c6a68>.

⁴² Harding, Robin and Hudson Lockett, BoJ Spurs Asia Markets Rebound With Vow to Fight Coronavirus, *The Financial Times*, March 2, 2020. <https://www.ft.com/content/9fa91e06-5c3b-11ea-b0ab-339c2307bcd4>.

⁴³ For additional information about China's response, see: CRS In Focus IF11434, *COVID-19: U.S.-China Economic Considerations*, by Karen M. Sutter and Michael D. Sutherland.

⁴⁴ Weinland, Don, China's Central Bank Launches \$79bn Stimulus for Virus-hit Companies, *The Financial Times*, March 13, 2020. <https://www.ft.com/content/deb56f86-6515-11ea-b3f3-fe4680ea68b5>.

The International Monetary Fund (IMF) is providing funding to poor and emerging market economies that are short on financial resources.⁴⁵ If the economic effects of the virus persist, countries may need to be proactive in coordinating fiscal and monetary policy responses, similar to actions taken by of the G-20 following the 2008-2009 global financial crisis.

MULTILATERAL RESPONSE

International Monetary Fund

The IMF announced that it is making available about \$50 billion for the global crisis response.⁴⁶ For low-income countries, the IMF is providing rapid-disbursing emergency financing of up to \$10 billion (50% of quota of eligible members) that can be accessed without a full-fledged IMF program. Other IMF members can access emergency financing through the Fund's Rapid Financing Instrument (RFI). This facility could provide about \$40 billion for emerging markets facing fiscal pressures from COVID-19. Separate from these resources, the IMF has a Catastrophe Containment and Relief Trust (CCRT), which provides eligible countries with up-front grants for relief on IMF debt service falling due. The CCRT was used during the 2014 Ebola outbreak, but is now underfunded, according to IMF Managing Director Kristolina Georgieva with just over \$200 million available against possible needs of over \$1 billion.⁴⁷ On March 11, 2020, the United Kingdom announced that it will contribute £150 million (about \$170 million) to the CCRT. To date, the United States has not contributed to the CCRT.⁴⁸

World Bank and Regional Development Banks

The World Bank announced that it is making up to \$12 billion in financing (\$8 billion of which is new) immediately available to help impacted developing countries.⁴⁹ This support comprises up to \$2.7 billion in new financing from the International Bank for Reconstruction and Development (IBRD), the World Bank's market-rate lending facility for middle-income developing countries and \$1.3 billion from the International Development Association (IDA), the World Bank's concessional facility for low-income countries. In addition, the Bank is reprioritizing \$2 billion of the Bank's existing portfolio. The International Finance Corporation (IFC), the Bank's private-sector lending arm is making available up to \$6 billion. According to the Bank, support will cover a wide range of activities including strengthening health services and primary health care, bolstering disease monitoring and reporting, training

⁴⁵ Politi, James, IMF Sets Aside \$50bn for Coronavirus-hit Countries, *The Financial Times*, March 4, 2020, <https://www.ft.com/content/83c07594-5e3a-11ea-b0ab-339c2307bcd4>.

⁴⁶ International Monetary Fund, IMF Makes Available \$50 Billion to Help Address Coronavirus, March 4, 2020.

⁴⁷ International Monetary Fund, *United Kingdom Boosts IMF's Catastrophe Relief Fund with £150 million*, March 11, 2020.

⁴⁸ Ibid.

⁴⁹ World Bank, *World Bank Group Announces Up to \$12 Billion Immediate Support for COVID-19 Country Response*, March 3, 2020.

front line health workers, encouraging community engagement to maintain public trust, and improving access to treatment for the poorest patients.

Several years ago, the World Bank introduced pandemic bonds, a novel form of catastrophe financing.⁵⁰ The Bank sold two classes of bonds worth \$320 million in a program designed to provide financing to developing countries facing an acute epidemic crisis if certain triggers are met. Once these conditions are met, bondholders no longer receive interest payments on their investments, the money is no longer repaid in full, and funds are used to support the particular crisis. In the case of COVID-19, for the bonds to be triggered, the epidemic must be continuing to grow 12 weeks after the first day of the outbreak. Critics have raised a range of concerns about the bonds, arguing that the terms are too restrictive and that the length of time needs to be shortened before triggering the bonds.⁵¹ Others stress that the proposal remains valid – shifting the cost of pandemic assistance from governments to the private sector, especially in light of the failure of past efforts to rally donor support to establish multilateral pandemic funds.

The Asian Development Bank (ADB) has approved a total of \$4 million to help developing countries in Asia and the Pacific.⁵² Of the total, \$2 million is for improving the immediate response capacity in Cambodia, China, Laos, Myanmar, Thailand, and Vietnam; \$2 million will be available to all ADB developing member countries in updating and implementing their pandemic response plans. The ADB also provided a private sector loan of up to \$18.6 million to Wuhan-based Jointown Pharmaceutical Group Co. Ltd. to enhance the distribution and supply of essential medicines and protective equipment.

International Economic Cooperation

On March 16, 2020, the leaders of the G-7 countries (Canada, France, Germany, Italy, Japan, the United Kingdom, and the United States) held an emergency summit by teleconference to discuss and coordinate their policy responses to the economic fallout from the global spread of COVID-19. In the joint statement released by the G-7 leaders after the emergency teleconference summit, the leaders stressed they are committed to doing “whatever is necessary to ensure a strong global response through closer cooperation and enhanced cooperation of efforts.”⁵³ The countries pledged to coordinate research efforts, increase the availability of medical equipment; mobilize “the full range” of policy instruments, including monetary and fiscal measures as well as targeted actions, to support workers, companies, and sectors most affected by the spread of COVID-19; task the finance ministers to coordinate on a weekly basis, and direct the IMF and the World Bank Group, as well as other international organizations, to support countries worldwide as part of a coordinated global response.⁵⁴

⁵⁰ Anna Gross, “Critics take aim at ‘failure’ of bond designed to fight disease,” *Financial Times*, March 10, 2020, <https://www.ft.com/content/a6239e12-5ec7-11ea-b0ab-339c2307bcd4>.

⁵¹ Ibid.

⁵² Asian Development Bank, *ADB Approves Another \$2 Million to Help Asia and the Pacific Tackle Coronavirus*, February 26, 2020.

⁵³ White House, G-7 Leaders’ Statement, March 16, 2020, <https://www.whitehouse.gov/briefings-statements/g7-leaders-statement/>.

⁵⁴ Ibid.

News reports indicate that Saudi Arabia, the 2020 chair of the G-20, intends to call an emergency G-20 summit in coming days.⁵⁵ The G-20 is a broader group of economies, including the G-7 countries and several major emerging markets.⁵⁶ During the global financial crisis, world leaders decided that henceforth the G-20 would be the premiere forum for international economic cooperation. Some analysts have been surprised that the G-7 has been in front of the G-20 in responding to COVID-19, while other analysts have questioned whether the larger size and diversity of economies in the G-20 can make coordination more difficult.⁵⁷

Analysts are hopeful that the recent G-7 summit, and movement towards a G-20 summit, will mark a shift towards greater international cooperation at the highest (leader) levels in combatting the economic fallout from the spread of COVID-19.⁵⁸ An emergency of G-7 finance ministers on March 3, 2020, fell short of the aggressive and concrete coordinated action that investors and economists had been hoping for, and U.S. and European stock markets fell after the meeting.⁵⁹ More generally, governments have been divided over the appropriate response and in some cases have acted unilaterally, particularly when closing borders and imposing export restrictions on medical equipment and medicine. Meanwhile, international organizations including the IMF and multilateral development banks have tried to forge ahead with economic support given their current resources

ESTIMATED EFFECTS ON DEVELOPED AND MAJOR ECONOMIES

Among most developed and major developing economies, economic growth at the beginning of 2020 was tepid, but still was estimated to be positive. Countries highly dependent on trade—Canada, Germany, Italy, Japan, Mexico, and South Korea—and commodity exporters are now projected to be the most negatively affected by the slowdown in economic activity associated with the virus.⁶⁰ In addition, travel bans and quarantines are taking an especially heavy economic toll on China, South Korea, and Italy, where viral outbreaks have so far been most prevalent. The OECD notes that production declines in China have spillover effects around the world given China's role in producing computers, electronics, pharmaceuticals and transport equipment, and as a primary source of demand for many commodities.⁶¹

In early January 2020, before the coronavirus outbreak, economic growth in developing economies as a whole was projected by the International Monetary Fund (IMF) to be slightly more positive than in 2019. This outlook was based on progress being made in U.S.-China trade talks that were expected to roll back some tariffs and an increase in India's rate of growth. Growth rates in Latin America and the Middle East were also projected to be positive

⁵⁵ "Spain Says Saudi Arabia to Call G-20 to Meet on Coronavirus in Coming Days," *Reuters*, March 16, 2020.

⁵⁶ The G-20 includes the G-7 countries plus Argentina, Australia, Brazil, China, India, Indonesia, Mexico, Russia, Saudi Arabia, South Africa, South Korea, Turkey, and the European Union (EU).

⁵⁷ For more information about the G-20, see CRS Report R40977, *The G-20 and International Economic Cooperation: Background and Implications for Congress*, by Rebecca M. Nelson.

⁵⁸ See for example, Jennifer Rankin, "EU Leaders Divided on How to Protect Economies after Coronavirus," *The Guardian*, March 14, 2020.

⁵⁹ Jack Ewing and Jeanna Smialek, "Economic Powers Vow to Fight Crisis," *New York Times*, March 3, 2020.

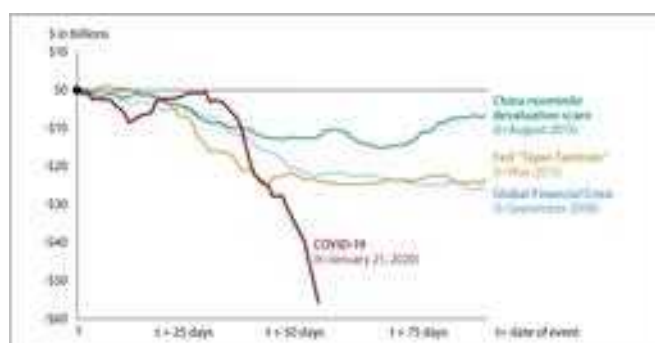
⁶⁰ *OECD Interim Economic Assessment*, p. 7.

⁶¹ *Ibid.*, p. 5.

in 2020.⁶² These projections likely will be revised downward due to the slowdown in global trade associated with COVID-19, lower energy and commodity prices, and other secondary effects that could curtail growth. Commodity exporting countries, in particular, likely will experience a greater slowdown in growth than forecasted in earlier projections as a result of a slowdown on trade with China and lower commodity prices.

EMERGING MARKETS

The combined impact of COVID-19 and an oil price war between Saudi Arabia and Russia are hitting developing and emerging economies hard. Not all of these countries have the resources or policy flexibility to respond effectively. According to figures compiled by the Institute for International Finance (IIF), cumulative capital outflows from developing countries since January 2020 are double the level experienced during the 2008/2009 crisis and substantially higher than recent market events (Figure 1).⁶³



Source: Original graphic and data from International Institute for Finance using data from Haver. Edited by CRS for clarification.

Figure 1. Capital flows to emerging markets in global shocks.

The impact of the price war and lower energy demand associated with a COVID-19-related economic slowdown is especially hard on oil and gas exporters, some of whose currencies are at record lows (Figure 2). Oil importers, such as South Africa and Turkey, have also been hit hard; South Africa's rand has fallen 18%⁶⁴ against the dollar since the beginning of 2020 and the Turkish lira has lost 8.5%.⁶⁵

⁶² *Tentative Stabilization, Sluggish Recovery? World Economic Outlook Update*, January 20, 2020, The International Monetary Fund. <https://www.imf.org/en/Publications/WEO/Issues/2020/01/20/weo-update-january2020>.

⁶³ These include concerns in 2015 over China's renminbi devaluation and the so-called "Taper Tantrum" in 2013 when the Federal Reserve announced that it would slow down the pace of its post global financial crisis asset purchases. Sergei Lanau and Jonathan Fortun, "Economic Views –The COVID-19 Shock to EM Flows," Institute for International Finance, March 17, 2020.

⁶⁴ Paul Wallace, "Here's How the Oil Crash is Hitting Emerging Market Currencies," *Bloomberg*, March 17, 2020, <https://www.bloomberg.com/news/articles/2020-03-17/here-s-how-the-oil-crash-is-hitting-emerging-market-currencies>.

⁶⁵ Nevzat Devranoglu, "Turkish lira hits weakest level since 2018 currency crisis due to coronavirus," *Nasdaq*, March 17, 2020, <https://www.nasdaq.com/articles/turkish-lira-hits-weakest-level-since-2018-currency-crisis-due-to-coronavirus-2020-03-17>.

Depending on individual levels of foreign exchange reserves and the duration of the capital flow slowdown, some countries may have sufficient buffers to weather the slowdown, while others will likely need to make some form of current account adjustment (reduce spending, raise taxes, etc.). Several countries, such as Iran and Venezuela, have already asked the IMF for financial assistance and others are likely to follow.⁶⁶ (Venezuela's request was quickly rebuffed due to disagreement among the IMF membership over who is recognized as Venezuela's legitimate leader: Nicolás Maduro or Juan Guaidó.⁶⁷)

OTHER AFFECTED SECTORS

Public concerns over the spread of the virus have led to self-quarantines, reductions in airline and cruise liner travel, the closing of such institutions as the Louvre, and the rescheduling of theatrical releases of movies, including the sequel in the iconic James Bond series (titled, "No Time to Die").⁶⁸ School closures, so far in China, Japan, South Korea, Italy, India, and some U.S. States are affecting at least 290 million children worldwide, challenging parental leave policies.⁶⁹ Other countries are limiting the size of public gatherings.

Some businesses are considering new approaches to managing their workforces and work methods. These techniques build on, or in some places replace, such standard techniques as self-quarantines and travel bans. Some firms are adopting an open-leave policy to ensure employees receive sick pay if they are, or suspect they are, sick. Other firms are adopting paid sick leave policies to encourage sick employees to stay home and are adopting remote working policies.⁷⁰ Concerns remain, however, that some U.S. workers will continue going to work when they are sick, since not all U.S. employers provide paid sick leave. Microsoft and Amazon have instructed all of their Seattle-based employees to work from home until the end of March 2020.⁷¹

The drop in business and tourist travel is causing a sharp drop in scheduled airline flights by as much as 10%; airlines are estimating they could lose \$113 billion in 2020 (an estimate that could prove optimistic given the Trump Administration's announced restrictions on

⁶⁶ COVID-19-hit Iran asks IMF for aid amid US sanctions, *Deutsche Welle*, March 13, 2020, <https://www.dw.com/en/covid-19-hit-iran-asks-imf-for-aid-amid-us-sanctions/a-52763114>. Iran is currently under U.S. sanctions, which include, among other things, prohibitions on the ability of the United States to vote in favor of lending IMF or World Bank assistance to Iran. The United States, however, cannot unilaterally block lending to a particular country. Approving an IMF or World Bank loan requires a majority of the total voting power and the U.S. voting power is 16.5% of the total voting power at the IMF and 15.4% at the World Bank. Iran has not borrowed from the IMF since 1962, but did borrow from the World Bank between 2003 and 2005 over U.S. opposition.

⁶⁷ Joshua Goodman, "IMF rejects Maduro's bid for emergency loan to fight virus," *StarTribune*, <http://www.startribune.com/venezuela-seeks-emergency-5-billion-imf-loan-to-fight-virus/568868442/>.

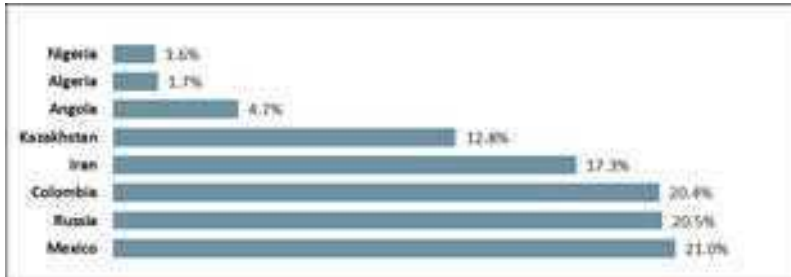
⁶⁸ Rosenberg, Alyssa, Coronavirus Shut Down Mona Lisa and James Bond. We Can't Let it Isolate Us, *The Washington Post*, March 4, 2020. <https://www.washingtonpost.com/opinions/2020/03/04/coronavirus-shut-down-mona-lisa-james-bond-we-cant-let-it-isolate-us/>.

⁶⁹ Taylor, Adam, Teo Armus, Rick Noak, Coronavirus Turmoil Widens as U.S. Death Toll Mounts; Xi Cancels Japan Trip, *The Washington Post*, March 5, 2020.

⁷⁰ Hill, Andrew and Emma Jacobs, Coronavirus May Create Lasting Workplace Change, *The Financial Times*, February 27, 2020. <https://www.ft.com/content/5801a710-597c-11ea-abe5-8e03987b7b20>.

⁷¹ Armus, Teo, Live updates: Coronavirus Turmoil Widens as U.S. Death Toll Mounts; Xi Cancels Japan Trip, *The Washington Post*, March 5, 2020, <https://www.washingtonpost.com/world/2020/03/05/coronavirus-live-updates/>.

flights from Europe to the United States),⁷² while airports in Europe estimate they could lose \$4.3 billion in revenue due to fewer flights.⁷³ Industry experts estimate that many airlines will be in bankruptcy by May 2020 under current conditions as a result of travel restrictions imposed by a growing number of countries.⁷⁴ The loss of Chinese tourists is another economic blow to countries in Asia and elsewhere that have benefitted from the growing market for Chinese tourists and the stimulus such tourism has provided.



Source: Created by CRS. Data from Bloomberg.

Figure 2. Depreciation against the dollar since Jan. 1, 2020.

The decline in industrial activity has reduced demand for energy products such as crude oil, causing prices to drop sharply, which negatively affects energy producers, renewable energy producers, and electric vehicle manufacturers, but generally is positive for consumers and businesses. Saudi Arabia is pushing other OPEC (Organization of the Petroleum Exporting Countries) members collectively to reduce output by 1.5 million barrels a day to raise market prices. U.S. shale oil producers, who are not represented by OPEC, support the move to raise prices.⁷⁵ An unwillingness by Russia to agree to output reductions added to other downward pressures on oil prices and caused Saudi Arabia to engage in a price war with Russia that has driven oil prices below \$50 per barrel, the estimated break-even point for most oil producing countries.⁷⁶ In 2019, low energy prices combined with high debt levels reportedly caused U.S. energy producers to reduce their spending on capital equipment, reduced their profits and, in some cases, led to bankruptcies.⁷⁷ Reportedly, in late 2019 and early 2020, bond and equity investors, as well as banks, reduced their lending to shale oil producers and other energy producers that typically use oil and gas reserves as collateral.⁷⁸

⁷² Taylor, Adam, Airlines Could Suffer up to \$113 Billion in Lost Revenue Due to Coronavirus Crisis, IATA Says, *The Washington Post*, March 5, 2020. <https://www.washingtonpost.com/world/2020/03/05/coronavirus-live-updates/>.

⁷³ Airlines Slash Flights to Cut Costs as Coronavirus Hits Travel Demand, *The Financial Times*. <https://www.ft.com/content/c28b5790-62c6-11ea-a6cd-df28cc3c6a68>.

⁷⁴ Smyth, Jamie Smyth, Andrew Edgecliffe-Johnson, Peggy Hollinger, Myles McCormick, David Keohane, and Richard Milne, Most Airlines Face Bankruptcy by End of May, Industry Body Warns, *The Financial Times*, March 16, 2020.

⁷⁵ Brower, Derek, Cash-Strapped US Shale Producers Pray for OPEC Aid, *The Financial Times*, March 3, 2020. <https://www.ft.com/content/9161e62c-5cb1-11ea-b0ab-339c2307bcd4>.

⁷⁶ Strauss, Delphine, Why There Are no Winners From the Oil Price Plunge This Time, *The Financial Times*, March 10, 2020. <https://www.ft.com/content/da2b0700-622c-11ea-b3f3-fe4680ea68b5>; Mufson, Steve and Will Englund, Oil Price War Threatens Widespread Collateral Damage, *The Washington Post*, March 10, 2020. https://www.washingtonpost.com/climate-environment/oil-price-war-threatens-widespread-collateral-damage/2020/03/09/3e42c9e2-6207-11ea-acca-80c22bbe96f_story.html.

⁷⁷ Texas Oil Groups: Panhandling Ahead, *The Financial Times*, January 20, 2020.

⁷⁸ *Ibid.*

Disruptions to industrial activity in China reportedly are causing delays in shipments of computers, cell phones, toys, and medical equipment.⁷⁹ Factory output in China, the United States, Japan, and South Korea all declined in the first months of 2020.⁸⁰ Reduced Chinese agricultural exports, including to Japan, are leading to shortages in some commodities. In addition, numerous auto producers are facing shortages in parts and other supplies that have been sourced in China. Reductions in international trade have also affected ocean freight prices. Some freight companies argue that they could be forced to shutter if prices do not rebound quickly.⁸¹ Disruptions in the movements of goods and people reportedly are causing some companies to reassess how international they want their supply chains to be.⁸² According to some estimates, nearly every member of the Fortune 1000 is being affected by disruptions in production in China.⁸³

CONCLUSION

The quickly evolving nature of the COVID-19 crisis creates a number of issues that make it difficult to estimate the full cost to global economic activity. These issues include, but are not limited to:

- How long will the crisis last?
- How many workers will be affected both temporarily and permanently?
- How many countries will be infected and how much economic activity will be reduced?
- When will the economic effects peak?
- How much economic activity will be lost as a result of the viral outbreak?
- What are the most effective monetary and fiscal policies at the national and global level to address the crisis?
- What temporary and permanent effects will the crisis have on how businesses organize their work forces?
- Many of the public health measures taken by Italy, Taiwan, South Korea, Hong Kong, China, etc. have sharply impacted their economies (plant closures, travel restrictions, etc.). How are the tradeoffs between public health and the economic impact of policies to contain the spread of the virus being weighed?

⁷⁹ Hille, Kathrin, Alistair Gray, and Patrick McGee, Coronavirus delays PC and smartphone shipments for weeks, *The Financial Times*, March 3, 2020. <https://www.ft.com/content/72742872-5c31-11ea-b0ab-339c2307bcd4>.

⁸⁰ Newmyer, Tory, The Finance 202: Stocks Stage Major Comeback, but Manufacturing Report Points to Continued Coronavirus Pain, *The Washington Post*, March 3, 2020. https://www.washingtonpost.com/news/powerpost/paloma/the-finance-202/2020/03/03/the-finance-202-stocks-stage-major-comeback-but-manufacturing-report-points-to-continued-coronavirus-pain/5e5d84a6602ff10d49ac081f/?itid=hp_hp-cards_hp-card-politics%3Ahomepage%2Fcard-ans.

⁸¹ Lynch, David J., Economic Fallout From China's Coronavirus Mounts Around the World, *The Washington Post*, February 13, 2020. https://www.washingtonpost.com/business/economy/economic-fallout-from-chinas-coronavirus-mounts-across-the-globe/2020/02/13/7bb69a12-4e8c-11ea-9b5c-eac5b16dafa_story.html?itid=lk_inline_manual_12.

⁸² Ibid.

⁸³ Ibid.

APPENDIX. SELECT MEASURES IMPLEMENTED OR ANNOUNCED BY MAJOR ECONOMIES IN RESPONSE TO COVID-19

United States	<i>U.S. Federal Reserve</i> March 3: Cut the target range for the federal funds rate by 0.5 percentage point. March 12: Expanded reverse repo operations, adding \$1.5 trillion of liquidity to the banking system. March 15: Cut the target range for the federal funds rate by a full percentage point to a range of 0.00% to 0.25% and restarted quantitative easing with the purchase of at least \$500 billion in Treasury securities and \$200 billion in mortgage-backed securities.
	<i>U.S. Congress</i> March 5: Passed, and the President signed, a bill providing \$8.3 billion in emergency funding for federal agencies to respond to the coronavirus outbreak (H.R. 6074: Coronavirus Preparedness and Response Supplemental Appropriations Act 2020). March 13: The House of Representatives passed a coronavirus response package (H.R. 6201: Families First Coronavirus Response Act). The Senate is expected to follow this week. <i>Trump Administration</i> March 13: President Trump declared a state of emergency, allowing the Federal Government to distribute up to \$50 billion in aid to states, cities, and territories. March 17: The Internal Revenue Service postponed the April 15 tax-payment deadline for 90 days and will waive interest and penalties. (The extension and waiver is available only to individuals and corporations that owe \$1 million or \$10 million or less, respectively.) March 17: Administration officials begin negotiations with Members of Congress on a third stimulus package of \$850 billion.
Australia	March 12: The government announced a AU\$17.6 billion (\$11.4 billion) stimulus package that includes support for business investment, cash flow assistance for small and medium sized business and employees, and household stimulus payments. March 16: The Australian Securities and Investments Commission ordered large equity market participants to reduce their number of executed trades by 25% from the levels executed on March 13, 2020, until further notice.
Canada	<i>Bank of Canada</i> March 13: Lowered its benchmark overnight rate to 1.25% from 1.75% in response to the epidemic.
	<i>Canadian Government</i> March 11: Unveiled CA\$1 billion (\$750 million) in funding for vaccine research and health measures. March 13: Announced CA\$10 billion (\$7.5 billion) credit package to help businesses, particularly small and medium-sized enterprises, struggling due to the pandemic.
Chile	March 16: The Central Bank of Chile cut its benchmark rate by 75 basis points to 1% on Monday and announced measures to inject liquidity, including allocating \$4 billion to purchase inflation-linked bank bonds and providing additional credit to banks.
China	<i>People's Bank of China (PBOC)</i> February 3: Expanded reverse repo operations by \$174 billion; added another \$71 billion on February 4. February 16: Cut the one-year medium-term lending facility rate by 10 basis points. February 20: Cut the one-year and five-year prime rates by 10 and 5 basis points, respectively. March 13: Lowered bank reserve requirements, freeing up about \$79 billion to be lent out.

	<i>PRC Government</i> February: Asked banks to extend the terms of business loans and commercial landlords to reduce rents. March: Earmarked \$15.9 billion to fight the epidemic.
Czech Republic	March 16: The Czech National Bank lowered its main two-week repo rate by 50 basis points to 1.75%, reversing its February rate hike to combat the hit from the virus outbreak. It also raised the number of repo operations that provide liquidity to banks to three times a week from once, noting that bids would be met with zero spread to the repo rate.
Egypt	<i>Central Bank of Egypt</i> March 16: Cut by 300 basis points both the overnight lending rate (from 13.25% to 10.25%) and the overnight deposit rate (from 12.25% to 9.25%) in what it described as a “preemptive” move to support the economy in the face of the COVID-19 outbreak. <i>Government of Egypt</i> March 14: The President indicated that the government will allocate 100 billion Egyptian pounds (\$6.4 billion) to finance a “comprehensive” state plan for combating the coronavirus outbreak.
European Union	<i>European Commission</i> March 11: Announced a 37 billion euro (\$41 billion) “Corona Investment Fund” that would use “spare” money from the EU budget to help businesses, health-care systems, and sectors in need; additionally, the EU’s own investment fund will guarantee 8 billion euros (\$8.9 billion) of loans to 100,000 small- and medium-sized enterprises and affected companies may be able to delay the payment of their existing loans. <i>European Central Bank (ECB)</i> March 12: Announced that it would provide banks with loans at a rate as low as minus 0.75%, below the -0.5% deposit rate, increase bond purchases by 120 billion euros (\$135.28 billion) this year (with a focus on corporate debt), and allow euro zone banks to fall short of some key capital and cash requirements (in order to keep credit flowing to the economy).
France	March 12: The government pledged more generous guarantees on loans made to small businesses, more cash for firms struggling to hold on to workers, and a solidarity fund to help companies cushion the blow from the coronavirus outbreak; it also announced that the government would be ready to increase funds available to help companies reduce workers’ hours, instead of laying them off. March 16: The president announced that the government would guarantee 300 billion euros in bank loans for small and medium-sized businesses. March 17: The Autorité des Marchés Financiers (AMF), France’s financial-markets authority, stated that it would forbid short selling of stock in 92 companies during the March 17 session. March 17: The government announced that it would spend 45 billion euros (\$50 billion) to help small businesses and employees struggling with the coronavirus outbreak, including through an expanded partial-unemployment package in which the state pays the salaries of employees who are not needed during the crisis.
Germany	March 13: Pledged to provide unlimited liquidity assistance to German companies hit by the pandemic. (The measure envisages a massive expansion of loans provided by KfW, the state development bank, and will allow companies to defer billions of euros in tax payments.) The Bundestag also expanded the <i>Kurzarbeit</i> or short-time work scheme, under which companies that put their workers on reduced hours can receive state support. The government also indicated that it would boost investments by €3.1 billion per year between 2021 and 2024.
Hong Kong	February 26: The government announced a HK\$120 billion (\$15.4 billion) relief package as part of its 2020–2021 budget, including a payment of HK\$10,000 (\$1,200) to each permanent resident of the city 18 or older, paying one month’s rent for people living in public housing, cutting payroll, income, property, and business taxes, low-interest, government-guaranteed loans for businesses, and an extra month’s worth of payments to people collecting old-age or disability benefits

India	<i>Reserve Bank of India</i> March 12: Announced a \$2 billion injection into the foreign-exchange market to support the rupee. March 13: Announced a plan to add liquidity through short-term repurchase operations. <i>Government of India</i> March 15: Pledged \$10 million towards South Asian Association for Regional Cooperation (SAARC) “coronavirus emergency fund.” March 11: The government announced two packages worth 25 billion euros (\$28.3 billion): A package worth 12 billion euros will provide extra funding for the health system as well as a mix of measures to help companies and households, including freezing tax and loan payments and boosting unemployment benefits to ensure no jobs were lost. The remainder will be a reserve to pay for any further measures. The government also indicated that payments on mortgages will be suspended across Italy. ABI, Italy’s banking lobby, said lenders would offer debt moratoriums to small firms and households grappling with the economic fallout from the virus.
Italy	
Japan	<i>Bank of Japan</i> March 16: Announced that it would (1) double its upper limit of annual purchases of exchange traded funds to 12 trillion yen (\$112.46 billion) and of real-estate investment trusts to 180 billion yen (\$1.7 billion) per year, (2) expand its upper limit of its corporate bond balance and commercial paper balance by 1 trillion yen (\$9.5 billion) each, and (3) start a lending program for commercial banks, providing them with one-year loans in exchange for corporate collateral worth 8 trillion yen (\$75.6 billion). <i>Japanese Government</i> February 13: Unveiled a set of measures worth 15.3 billion yen (\$140 million) to fight the spread of coronavirus; secured 500 billion yen (\$4.7 billion) for emergency lending and loan guarantees at the Japan Finance Corporation and other institutions for small businesses hit hard by the virus outbreak. March 10: Unveiled a second package of measures totaling 430.8 billion yen (\$4.1 billion) in spending to cope with the fallout of the coronavirus outbreak (focusing on support to small and mid-sized firms) and boosted to 1.6 trillion yen (\$15.1 billion) its special financing for small- and mid-size firms hit by the virus, up from 500 billion yen. March 16: The Central Bank of Kuwait cut by 100 basis points its deposit rate to 1.5% and its overnight, one-week, and one-month repo rates to 1%, 1.25%, and 1.75%, respectively.
Kuwait	
Mexico	February 13: The Bank of Mexico cut its key rate by 25 basis points to 7.0%. <i>Government of New Zealand</i> March 16: Announced a spending package of NZ\$12.1 billion (\$7.3 billion), equivalent to 4% of GDP in an attempt to fight the effects of COVID-19 on the economy; approximately NZ\$5 billion will go toward wage subsidies for businesses, NZ\$2.8 billion toward income support, NZ\$2.8 billion in business tax relief, and NZ\$600 million toward the airline industry. <i>Reserve Bank of New Zealand</i> March 16: Cut the official cash rate by 75 basis points to a record low of 0.25%, and pledged to keep it at this level for at least 12 months.
New Zealand	
Norway	March 13: The Norges Bank, Norway’s central bank, cut its key interest rate to 1% from 1.5%, as it seeks to counter the economic impact of the coronavirus pandemic. It indicated that it would offer funding to banks to help counter the volatility in financial markets and announced that banks’ countercyclical capital buffer would be reduced from 2.5% to 1%, to help banks continue to lend money.
Philippines	March 13: The government instructed the Government Service Insurance System and the Social Security System “to take advantage of the low stock prices” and “support the stock market by at least doubling their daily average purchase volumes” from 2019. March 17: The Philippine Stock Exchange halted all stock, bond and currency trading until further notice, after President Rodrigo Duterte placed Luzon, the country’s economic powerhouse, under “enhanced community quarantine”.

Qatar	<i>Qatar Central Bank</i> March 16: Cut the deposit rate by 50 basis points to 1%, lending rate by 100 basis points to 2.50%, and repurchase rate (repo) by 50 basis points to 1%.	<i>Government of Qatar</i> March 15: The Emir of Qatar announced several measures to shield the economic and financial sectors in the country from the impact of the coronavirus, including: (1) allocating 75 billion Qatari riyals (\$20.6 billion) to support and provide financial and economic incentives in the private sector, (2) directing the Central Bank of Qatar to provide additional liquidity to banks operating in the country and putting in place the appropriate mechanism to encourage banks to postpone loan installments and obligations of the private sector with a grace period of six months, (3) directing the Qatar Development Bank to postpone the installments for all borrowers for a period of six months, (4) directing the government to increase its investments in the stock exchange by 10 billion Qatari riyals (\$2.75 billion), (5) exempting food and medical goods from customs duties for a period of six months, and (6) exempting the various sectors of the economy from electricity and water fees for a period of 6 months.
	Saudi Arabia	March 15: The Saudi Arabian Monetary Authority announced that it had prepared a 50 billion riyal (\$13.32 billion) package to help small and medium-sized enterprises cope with the economic impacts of coronavirus; it also lowered by 75 basis points both its repo rate to 1% and its reverse repo rate to 0.5%.
Singapore	February 18: The government announced around \$4.5 billion in financial packages to help contain the coronavirus outbreak, including \$575 million to fight and contain the disease, mainly through healthcare funding, and 4 billion in economic stimulus measures to manage its impact on businesses, jobs and households.	
South Korea	March 3: Announced a 11.7 trillion won (\$9.8 billion) stimulus package that includes funding for medical institutions and quarantine efforts, assistance to small- to medium-sized businesses struggling to pay wages to their workers, and subsidies for child care.	
Spain	March 12: The government announced additional support for the health system and a 14 billion euro (\$15.6 billion) stimulus package for the economy.	
Sri Lanka	March 16: The Central Bank of Sri Lanka cut the Standing Deposit Facility Rate (SDFR) and the Standing Lending Facility Rate (SLFR) by 25 basis points to 6.25% and 7.25%, respectively, and the Statutory Reserve Ratio (SRR) on all rupee deposit liabilities of licensed commercial banks was reduced by 1 percentage point to 4% March 16: The Colombo Stock Exchange was closed until March 19, as the government extended the public holiday in a bid to halt the spread of coronavirus in the country.	
Sweden	<i>Sveriges Riksbank</i> March 13: Stated that it would lend up to 500 billion crowns (\$51 billion) to Swedish companies via banks to shore up credit flows as the epidemic wreaks havoc on financial markets. March 16: Announced that it would buy securities for up to an additional 300 billion Swedish crowns (\$31 billion) in 2020 to facilitate credit supply and mitigate the downturn in the economy caused by the coronavirus, reduced the overnight lending rate to banks to 0.2 percentage point above its repo rate (from 0.75 percentage point), and indicated that it would be flexible with the collateral banks can use when they borrow money from the Riksbank, giving lenders more scope to use mortgage bonds as collateral.	
	<i>Government of Sweden</i> March 16: Presented a package worth more than 300 billion Swedish crowns (\$31 billion) to support the economy in the face of the coronavirus pandemic. It included measures such as the central government assuming the full cost for sick leave from companies through the months of April and May 2020 and for temporary redundancies due to the crisis, and allowing companies to put off paying tax and VAT for up to a year (retroactive to the start of 2020).	

Taiwan	February 25: The government approved a T\$60 billion (\$2 billion) package to help cushion the impact of the coronavirus outbreak on its export-reliant economy, including loans for small businesses, subsidies for hard-hit tour agencies, tax cuts for tour bus drivers, and vouchers to spend on food in night markets. March 12: The president announced that an additional T\$40 billion (\$1.33 billion) from the Employment Stabilization Fund and the Tourism Development Fund would be available to stimulate Taiwanese economy. March 15: The Central Bank of the UAE announced a 100 billion dirham (\$27 billion) stimulus package to deal with the economic effects of the coronavirus pandemic; it cut the rate on one-week certificates of deposit by 75 basis points and will also ease regulatory limits on loans.
United Arab Emirates (UAE)	
United Kingdom	<i>Bank of England</i> March 11: Cut its benchmark interest rate by half a percentage point, to 0.25%, revived a program to support lending to small and midsize businesses, and reduced bank capital requirements to further boost credit. <i>UK Government</i> March 11: Announced a stimulus package totaling 30 billion pounds (\$39 billion). It will include 7 billion pounds (\$8.6 billion) available to support the labor market, 5 billion pounds (\$6.1 billion) to help the health-care system, and 18 billion pounds (\$22 billion) to support the UK economy, bringing the total fiscal stimulus to 30 billion pounds (\$39 billion). (Among the specific measures, there will be a tax cut for retailers, cash grants to small businesses, a mandate to provide sick pay for people who need to self-isolate, subsidies to cover the costs of sick pay for small businesses, and expanded access to government benefits for the self-employed and unemployed.)
Vietnam	March 16: The State Bank of Vietnam cut by 100 basis points both its refinance rate (to 5%) and the overnight lending rate in the inter-bank market (to 6%), and by 50 basis points its discount rate (to 3.5%).

Chapter 385

COVID-19: POTENTIAL ECONOMIC EFFECTS*

Marc Labonte

ABSTRACT

This Insight discusses the potential economic effects of the coronavirus (COVID-19) on the U.S. economy. For background on the coronavirus, see CRS In Focus IF11421, *COVID-19: Global Implications and Responses*, by Sara M. Tharakan et al.

CHANNELS THROUGH WHICH THE VIRUS COULD AFFECT THE ECONOMY

Although the COVID-19 outbreak presently is most widespread abroad, it will directly affect foreign demand for U.S. exports of goods and services. As discussed in this CRS In Focus, the coronavirus could also disrupt U.S. companies' international supply chains. If COVID-19 becomes widespread in the United States, it could directly reduce domestic economic activity by reducing both supply and demand. On the supply side, hours worked would be reduced by illnesses and fatalities and any work stoppages to prevent the virus from spreading. On the demand side, spending could be reduced by quarantines and other attempts to avoid crowds, such as public event cancellations. In addition, fear and uncertainty could reduce business and consumer confidence, leading to a reduction in spending. A reduction in investor confidence could also tighten financial conditions. For example, the sharp decline in the stock market since late February 2020 was widely perceived to be in response to worsening news about the virus. In general, these macroeconomic effects would be expected to eventually reverse once conditions return to normal, except to the extent COVID-19 causes worker fatalities.

* This is an edited, reformatted and augmented version of Congressional Research Service, Publication No. IN11235, dated March 11, 2020.

UNKNOWNNS IN EVALUATING THE ECONOMIC IMPACT

How large could the economic effects of the coronavirus ultimately be? At this stage, uncertainty is so great that a very wide range of economic outcomes—from little effect on the U.S. economy to a severe downturn—is plausible. The unknowns include the following questions:

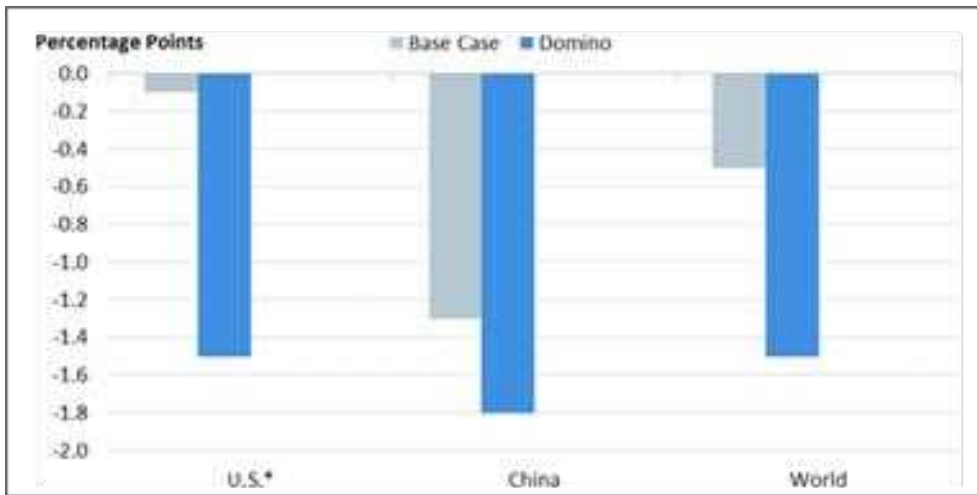
- How many people will become infected over the course of the outbreak in the United States and abroad?
- How long will the outbreak last?
- What public and private measures will ultimately be taken that disrupt normal economic activity (e.g., travel restrictions, closures, shutdowns, cancellations)?
- How easily can businesses find substitutes for supply chain disruptions?
- How many businesses will fail before the outbreak ends?
- How will consumer and investor confidence be affected?
- What fiscal or monetary policy actions will ultimately be taken to offset the economic effects, and how effective would they be in a pandemic? To date, an emergency supplemental appropriation has been enacted (P.L. 116-123), and the Federal Reserve has reduced interest rates by 0.5 percentage points.

ECONOMIC ESTIMATES

Two recent studies attempt to quantify the potential economic effects of the outbreak. The purpose of these studies is to illustrate how the economy would be affected under different outbreak scenarios rather than to provide the best projection of the outbreak's scope.

OECD

In its base-case scenario—a contained outbreak centered in China—the Organisation for Economic Co-operation and Development (OECD) stated “global GDP growth is projected to slow from 2.9% in 2019 to 2.4% this year, before picking up to around 3¼ per cent in 2021 as the effects of the coronavirus fade and output gradually recovers.” In this scenario, U.S. growth is only 0.1 percentage points lower in 2020 and is 0.1 percentage points higher in 2021. Despite the negative impact of COVID- 19, the OECD projects a global recession is averted as growth remains positive in all the major economies—including China—except Italy. The base-case scenario assumes the outbreak peaks in the first quarter of 2020 and gradually fades thereafter. (The OECD did not report specific estimates on the number of illnesses or fatalities.) The base-case scenario also incorporates an assumption that monetary stimulus is used around the world to offset the negative effects.



Source: Organization for Economic Co-operation and Development (OECD).

Notes: *For the domino scenario, “U.S.” is for North America.

Figure 1. Projected decline in 2020 GDP growth under two scenarios OECD.

The OECD also presents a “domino scenario” where the virus “spread much more intensively ... through the wider Asia-Pacific region and the major advanced economies in the northern hemisphere.” In this scenario, “the level of world GDP is reduced by up to 1¾ per cent (relative to baseline) at the peak of the shock in the latter half of 2020, with the full year impact on global GDP growth in 2020 being close to 1½ per cent.” The OECD does not present an estimate for the effect on U.S. growth in the domino scenario, but growth in North America would decline by 1.5 percentage points. Figure 1 illustrates both scenarios presented by the OECD.

McKibbin and Fernando

A Brookings Institution working paper by Warwick McKibbin and Roshen Fernando used a long-standing economic forecasting model developed by one of the authors to simulate economic effects under seven different outbreak scenarios—three that limit the outbreak to China and four in which the outbreak is worldwide. (The paper does not provide the relative likelihood of the various scenarios.) The model projects that “even a low-end pandemic modeled on the Hong Kong Flu is expected to reduce global GDP by around \$2.4 trillion and a more serious outbreak similar to the Spanish flu reduces global GDP by over \$9 trillion in 2020.” The loss in U.S. GDP relative to the 2020 baseline varies between 0.1%-8.4% across the scenarios. The scenarios assume a decline in the labor supply of 0.1%-3.44% in China and 0%-1.3% in the United States.

**Table 1. Projected decrease in 2020 GDP under various scenarios
McKibbin and Fernando**

Decrease in 2020 GDP Relative to Baseline			
Scenario	COVID-19 Deaths	United States	China
Scenario 1	China: 279	-0.1	-0.4
Scenario 2	China: 3,493	-0.1	-1.9
Scenario 3	China: 12,573	-0.2	-6.0
Scenario 4	China: 2,794; U.S.: 236	-2.0	-1.6
Scenario 5	China: 6,985; U.S.: 589	-4.8	-3.6
Scenario 6	China: 12,573; U.S.: 1,060	-8.4	-6.2
Scenario 7	China: 2,794; U.S.: 236	-1.5	-2.2

Source: McKibbin and Fernando.

Notes: In Scenarios 1-3, the mortality rate for the rest of the world is negligible. In Scenario 7, the outbreak recurs annually; in the other scenarios, it is a one-time outbreak.

U.S. and global growth had been projected to be moderate before the outbreak. Therefore, the economic effects of COVID-19 could result in a growth slowdown but would have to be large for the economy to contract, as the forecasts above illustrate. The estimated effects presented above are for the whole year; it is expected, however, that the economic effects will be larger in the first half of the year.

Chapter 386

DOMESTIC PUBLIC HEALTH RESPONSE TO COVID-19: CURRENT STATUS AND RESOURCES GUIDE*

Kavya Sekar and Ada S. Cornell

ABSTRACT

The global outbreak of Coronavirus Disease 2019, COVID-19, is affecting communities throughout the United States, with case counts growing daily. Containment and mitigation efforts by federal, state, and local governments have been undertaken to “flatten the curve”—that is, to curb widespread transmission that could overwhelm the nation’s health care system.

This CRS Insight presents selected international and U.S. government actions and related events, CRS products, and federal websites relevant to the *domestic public health response* to COVID-19. As the situation evolves, CRS will continue to publish and update products relevant to the current needs of Congress. This Insight will be updated accordingly.

This Insight does not provide information on the international response to COVID-19, nor on economic or other non-health policy issues related to COVID-19. This Insight also does not address issues related to health insurance and financing. For further information on those issues, see the CRS Coronavirus Disease 2019 homepage.

A Snapshot of the Domestic Public Health Response to COVID-19, as of March 18, 2020

Note: All dates below are in 2020.

International Events and World Health Organization (WHO) Actions

<https://www.who.int/emergencies/diseases/novel-coronavirus-2019>

* This is an edited, reformatted and augmented version of Congressional Research Service, Publication No. IN11253, dated March 18, 2020.

- WHO declared the COVID-19 outbreak to be a Public Health Emergency of International Concern (PHEIC) on January 30.
- WHO announced the official name for the disease, COVID-19, on February 11.
- WHO raised its global risk assessment for the outbreak to “very high,” its highest risk level, on February 28.
- WHO declared the global COVID-19 outbreak a “pandemic” on March 11.
- Globally, over 200,000 cases have been confirmed in over 150 countries, with over 8,500 deaths reported.

United States Actions and Status

<https://www.hhs.gov/about/news/index.html>;

<https://www.cdc.gov/coronavirus/COVID-19/summary.html>; and

<https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/novel-coronavirus->
COVID-19.

- Several emergency declarations are in effect, including a Public Health Emergency under Section 319 of the Public Health Service Act; an Emergency Declaration pursuant to Section 501(b) of the Stafford Act; and a National Emergency declaration pursuant to the National Emergencies Act. Waivers are in effect under Section 1135 of the Social Security Act to aid the health care system with surge capacity.
- President Donald Trump announced the formation of the President’s Coronavirus Task Force, and appointed Vice President Mike Pence as the coordinator and Dr. Deborah Brix as response coordinator.
- Congress and the President enacted the Coronavirus Preparedness and Response Supplemental Appropriations Act (P.L. 116-123) on March 6, which provides a total of \$7.767 billion in appropriations: \$6.497 billion for HHS (including contingent amount), \$20 million for the Small Business Administration, and \$1.250 billion for foreign operations. Expanded telehealth services in Division B of the act additionally have a cost estimate of \$490 million over the course of FY2020 through FY2022. Prior to enactment, health response efforts were primarily supported by the Centers for Disease Control and Prevention (CDC) Infectious Diseases Rapid Response Reserve Fund allotment of \$105 million and HHS transfers of \$136 million.
- The House and Senate passed The Families First Coronavirus Response Act, H.R. 6201, which includes several provisions related to health care coverage and delivery. Discussions about additional measures to provide response assistance are underway.
- CDC has developed a diagnostic test kit for the virus and distributed it to public health laboratories pursuant to an Emergency Use Authorization (EUA) issued by the U.S. Food and Drug Administration (FDA) on February 4. Issues with test performance have limited access to testing at a local level. FDA has issued several EUAs for COVID-19 diagnostic tests (including for both commercial test kits and laboratory-developed tests, or LDTs) and personal protective equipment.
- FDA issued guidance on February 29 to authorize certain CLIA (Clinical Laboratory Improvement Amendments) certified labs to validate and use their own COVID-19 laboratory-developed tests for clinical diagnosis before EUA is granted. On March 16, FDA expanded this policy to cover the manufacture, distribution and use of commercial test kits prior to EUA authorization. In this guidance, FDA also authorizes states to further authorize laboratories within their own state to develop and perform tests for COVID-19 pursuant to state law and without the objection of the FDA.
- Medical countermeasures (diagnostics, vaccines, and therapeutics) are in development, including those supported by the National Institutes of Health (NIH) and the Biomedical Advanced Research and Development Authority (BARDA). An NIH-supported Moderna vaccine is in Phase 1 clinical trials (early-stage testing in humans). Gilead’s Remdesivir antiviral therapy is in Phase 3 clinical

trials and available under expanded access (also known as compassionate use). Widespread availability of a vaccine is projected to be at least a year away, while initial results of clinical trials of potential treatments are said to be expected by May.

- Travel restrictions and quarantine requirements are in effect for certain travelers who have been in mainland China, the Islamic Republic of Iran, Schengen area of the European Union, the United Kingdom and the Republic of Ireland within 14 days prior to arrival, pursuant to proclamations issued by President Trump.
- Enhanced health screenings are in place at 13 major U.S. airports. Health screenings and referrals are in place at all air, land, and sea ports of entry by DHS.
- CDC has issued guidance for the general public, schools, health care providers, health departments, pregnant women and children, travelers, and others.
- Containment and mitigation efforts are underway in several state and local jurisdictions. Several states have mandated cancellation of events, closures of schools, bars, and/or restaurants, among other actions. Several counties in Northern California are under a shelter-in-place order.
- The White House has advised Americans to avoid gatherings of 10 or more people, discretionary travel, and restaurants, food courts, and bars.
- Over 7,500 cases have been reported in 50 states, the District of Columbia, Puerto Rico, Guam, and the U.S. Virgin Islands, with over 100 deaths reported. Given limitations with testing, these are likely to be underestimates of disease spread.

FEDERAL AGENCY WEBSITES

General

- The White House, <https://www.whitehouse.gov/>.
- USA.gov, “Government Response to Coronavirus, COVID-19,” <https://www.usa.gov/coronavirus>.

Department of Health and Human Services

- Administration for Community Living (ACL): “Coronavirus Disease 2019 (COVID-19),” <https://acl.gov/COVID-19>.
- Assistant Secretary for Preparedness and Response (ASPR): “COVID-19: Coronavirus Disease 2019,” <https://www.phe.gov/emergency/events/COVID19/Pages/default.aspx>.
- Centers for Disease Control and Prevention (CDC): “Coronavirus Disease 2019 (COVID-19),” <https://www.cdc.gov/coronavirus/2019-ncov/index.html>; and “CDC Newsroom,” <https://www.cdc.gov/media/index.html>.
- Centers for Medicare and Medicaid Services (CMS), “Current Emergencies,” <https://www.cms.gov/About-CMS/Agency-Information/Emergency/EPRO/Current-Emergencies/Current-Emergencies-page>; “Coronavirus Disease 2019 (COVID-19).”
- Food and Drug Administration (FDA): “Coronavirus Disease 2019 (COVID-19),” <https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/coronavirus-disease-2019-covid-19>.

- Health Resources and Services Administration (HRSA): “Emergency Preparedness and Recovery Resources for Health Centers,” <https://bphc.hrsa.gov/emergency-response>.
- Indian Health Service (IHS), “COVID-19 Update as of March 16, 2020,” <https://www.ihs.gov/newsroom/announcements/2020-announcements/covid-19-update-as-of-march-16-2020/>.
- National Institutes of Health (NIH): “Coronavirus Disease 2019 (COVID-19),” <https://www.nih.gov/health-information/coronavirus>.

Other Relevant Agencies

- Department of Homeland Security (DHS): “Coronavirus (COVID-19)” <https://www.dhs.gov/coronavirus>.
- Department of Veterans Affairs (VA), “Novel Coronavirus Disease (COVID-19),” <https://www.publichealth.va.gov/n-coronavirus/>.
- Transportation Security Administration (TSA), “Coronavirus (COVID-19) information,” <https://www.tsa.gov/coronavirus>.

Chapter 387

COVID-19 MEDICAL COUNTERMEASURES: INTELLECTUAL PROPERTY AND AFFORDABILITY*

Kevin J. Hickey

ABSTRACT

Federal agencies and private industry have begun efforts to develop and test medical countermeasures (such as antiviral treatments and vaccines) to combat COVID-19, the disease caused by the novel coronavirus SARS-CoV-2. For example, Gilead Sciences has begun clinical trials, both in China and in the United States, to test whether its experimental antiviral drug remdesivir is safe and effective against COVID-19. In February 2020, the Biomedical Advanced Research and Development Authority (BARDA), a division of the Department of Health and Human Services (HHS), entered into agreements with two pharmaceutical companies—Johnson & Johnson and Sanofi—to develop vaccines for COVID-19. BARDA has also partnered with Regeneron Pharmaceuticals to develop a monoclonal antibody treatment for COVID-19. (See this CRS report for further detail on these and other potential countermeasures against COVID-19.)

Some Members of Congress have raised concerns about whether these medical countermeasures, if shown to be safe and effective, will be affordable and accessible to the public—especially if federal funds contribute to their development. The Coronavirus Preparedness and Response Supplemental Appropriations Act (CPRSA), enacted into law on March 6, 2020, contains two provisions relating to affordability of COVID-19 countermeasures. First, products purchased by the federal government using funds appropriated by CPRSA, including vaccines, therapeutics, and diagnostics for COVID-19, “shall be purchased in accordance with Federal Acquisition Regulation guidance on fair and reasonable pricing.”

Second, CPRSA states that the Secretary of HHS “may take such measures authorized under current law to ensure that vaccines, therapeutics, and diagnostics developed from funds provided in this Act will be affordable in the commercial market.”

* This is an edited, reformatted and augmented version of Congressional Research Service, Publication No. LSB10422, dated March 18, 2020.

This Sidebar reviews several intellectual property (IP) rights provisions under current law that the federal government could use to try to ensure that COVID-19 countermeasures are accessible and affordable. Other actions that the federal government might hypothetically take—such as additional spending, production by federal agencies, governmental negotiation, or direct price controls—are beyond the scope of this Sidebar, in that such measures do not implicate IP rights and may require additional legislative action beyond the “current law” referenced in CPRSA.

PATENT RIGHTS IN INVENTIONS MADE WITH FEDERAL ASSISTANCE

Patent Basics

Under the Patent Act, any person who “invents or discovers any new and useful process, machine, manufacture, or composition of matter” may apply for a patent on the invention with the U.S. Patent and Trademark Office (PTO). PTO patent examiners evaluate the application to ensure it meets all the applicable legal requirements to merit the grant of a patent. If the patent examiner concludes that the claimed invention is new, nonobvious, useful, directed at patentable subject matter, and adequately disclosed and claimed, PTO will issue the patent. If granted, patents typically expire twenty years after the initial patent application is filed.

Patents are available for almost every field of technology, including biotechnology, chemistry, computer hardware, electrical engineering, mechanical engineering, and manufacturing processes. In the pharmaceutical context, if an inventor is the first to synthesize a particular chemical that is useful in treating disease, she may seek a patent claiming the chemical itself. That said, patents on a pharmaceutical’s active ingredient are only a subset of patents relating to pharmaceuticals and other medical treatments. Particular drug formulations, methods of using the pharmaceutical to treat a particular disease, methods and technologies to administer a pharmaceutical, methods and technologies to manufacture a pharmaceutical, as well as methods and technologies for testing for and diagnosing disease, are all patentable if they meet Patent Act’s requirements.

To encourage innovation, a valid patent holder has the exclusive right to make, use, sell, and import (collectively, “practice”) the patented invention in the United States. Patents are thus said to confer a “temporary monopoly” on the patent holder: anyone else who wishes to practice the invention needs to obtain permission from the patent holder to do so (and, typically, pays for that permission). In some situations, patent rights can confer substantial market power on patent holders, enabling them to charge higher-than-competitive prices for the patented product, as a monopolist would. Some empirical studies have found patent rights are among the most important factors driving high prices for pharmaceuticals. At least to some extent, higher prices are part of the patent system’s design, in that they enable inventors to recoup the costs of research and development necessary to produce the invention in the first place. Fundamentally, IP law seeks to balance the importance of providing incentives to innovate against the costs that IP rights impose on the public in the form of higher prices and reduced competition.

Inventions Made with Federal Assistance

Patent rights initially vest in the individual inventor or inventors, as a general rule. Commonly, however, employees agree by contract to assign their patent rights to inventions made in the course of their employment to their employer, who may seek a patent on an employee's behalf.

When private parties rely on federal assistance to develop an invention, any resulting patent rights will typically be owned by either the U.S. government or the federal contractor, depending on the nature of federal involvement. For inventions made by federal employees during their official duties, the federal government will typically obtain title to the patent. The federal government's general policy for federally owned inventions, under the Stevenson-Wydler Technology Innovation Act and the Federal Technology Transfer Act of 1986, is to encourage their commercialization by licensing the federally owned patent rights to private parties—a process called “technology transfer.” Under technology transfer agreements, federal agencies grant private parties the exclusive or nonexclusive right to practice the invention, while the U.S. government retains: (1) a “nontransferable, irrevocable, paid-up license . . . to practice the invention or . . . by or on behalf of” the United States (the “government-use license”); and (2) the power “to terminate the license in whole or in part” based on grounds similar to the conditions for “march-in rights” (discussed below).

The Bayh-Dole Act of 1980 (Bayh-Dole), as amended, applies to inventions that a federal contractor conceives or first reduces to practice during the performance of a funding agreement with a federal agency. Under Bayh-Dole, the federal contractor may elect to retain the patent rights for a federally funded invention. In exchange, however, the contractor provides the federal agency with a government-use license, and the United States retains the authority to grant compulsory licenses to third parties in certain circumstances (“march-in rights”). Although Bayh-Dole, by its terms, only applies to federal contractors that are nonprofit organizations or small businesses, longstanding executive practice (codified by regulation) has applied Bayh-Dole to all federal contractors, regardless of size.

Finally, federal laboratories and private parties may enter into cooperative research and development agreements (CRADAs) in which both parties agree to provide services, facilities, equipment, IP, or other resources, but the federal government does not provide federal funding to the non-federal party. In this situation, ownership of IP rights may depend on the terms of the agreement. However, the federal laboratory generally has the authority to license existing federally owned IP to a private party as part of a CRADA, as well as to license or assign inventions made in whole or part by a federal employee working under a CRADA. In return, the federal government retains a government-use license and compulsory-licensing authority similar to Bayh-Dole march-in rights.

These general rules for patent ownership are subject to various exceptions and waivers, depending on the agency and circumstances. For example, some agencies (including BARDA and the National Institutes of Health) have the authority to enter into transactions that are *not* contracts, grants, or cooperative agreements, known as “other transaction” authority. “Other transactions” are exempt from many statutory provisions and procurement regulations, including Bayh-Dole's requirements. BARDA's template for other transactions includes contractual patent provisions much like those of Bayh-Dole, including march-in rights provisions. These patent provisions are “fluid and negotiable,” however, and may be different

for particular transactions. In addition, both Stevenson-Wydler's and Bayh-Dole's requirements contain specific exceptions. For example, Bayh-Dole's patent provisions do not apply to contractors located outside the United States, nor in "exceptional circumstances," including if necessary "to meet the needs of the Government and protect the public against nonuse or unreasonable use of inventions."

GOVERNMENTAL COMPULSORY PATENT LICENSES

As explained above, a patent holder generally has the exclusive right to make, use, sell, and import an invention. Thus, any other person who wishes to practice that invention will ordinarily need a license (i.e., permission) from the patent holder, or else be exposed to legal liability. In certain cases, however, patents may be subject to a "compulsory license," which allows another person to practice the invention *without* the consent of the patent holder. Compulsory licenses require the sanction of a governmental entity and the payment of compensation to the patent holder. Compulsory licenses differ from ordinary licenses in two important respects. First, the person seeking to use the invention need not obtain permission from the patent holder. Second, the compensation paid to the patent holder is determined by operation of law, not by private contractual negotiations between the licensee and the patent holder.

March-in Rights under the Bayh-Dole Act (35 U.S.C. 203)

Although Bayh-Dole generally allows federal contractors to take title to patents on inventions created with federal funding, the federal government retains the authority to "march in" and grant compulsory licenses to third parties in some circumstances. Specifically, the federal agency that provided the funding may require the federal contractor to grant a patent license to a third party if the agency determines that either:

- 1) action is necessary because the contractor or assignee has not taken, or is not expected to take within a reasonable time, effective steps to achieve practical application of the subject invention in such field of use;
- 2) action is *necessary to alleviate health or safety needs* which are not reasonably satisfied by the contractor, assignee, or their licensees;
- 3) action is necessary to meet requirements for public use specified by Federal regulations and such requirements are not reasonably satisfied by the contractor, assignee, or licensees; or
- 4) action is necessary because the agreement [to prefer U.S. manufacturing of the invention by any of the contractor's exclusive licensees] has not been obtained or waived or because a licensee of the exclusive right to use or sell any subject invention in the United States is in breach of its agreement [to prefer U.S. manufacturing].

A license granted under Bayh-Dole's march-in provisions must be "upon terms that are reasonable under the circumstances," which may require that the licensee pay compensation to the patent holder (i.e., the federal contractor or its assignee).

The federal government has never exercised march-in rights under Bayh-Dole. Advocacy groups have petitioned the National Institute of Health (NIH) several times to exercise march-in rights based on the high prices of certain drugs developed with federal funding, such as treatments for HIV/AIDS. NIH has rejected these petitions, contending that pricing concerns alone are insufficient to exercise march-in rights—so long as the invention is on the market and available to patients. In the context of a pandemic like COVID-19, the "health or safety needs" language would appear to provide a possible basis for the exercise of march-in rights, should the federal agency determine that compulsory licensing is necessary to address public health needs unmet by a federal contractor.

Governmental Use Rights (28 U.S.C. § 1498)

A broader statutory authority than march-in rights, 28 U.S.C. § 1498 (section 1498), applies to any patented invention—not just inventions made with federal funding. Under section 1498, sometimes described as an "eminent domain" provision for patents, the U.S. government has the authority to use or manufacture any patented invention "without license." In practice, this means that if the U.S. government determines that it needs to practice an invention, it need not ask permission from the patent holder to do so, and—despite the existence of the patent—courts will not order the government to cease infringing activity. The patent holder, however, has the right to sue in the U.S. Court of Federal Claims for "reasonable and entire compensation" for the government's use of the patented invention. In effect, then, section 1498 allows the United States to issue itself a compulsory license to make and use any patented invention without obtaining the permission of the patent holder, in exchange for consenting to liability in a suit seeking reasonable compensation for the government's use.

In the context of COVID-19 medical countermeasures, the U.S. government could rely on section 1498 to make and use any patented invention without the consent of the patent holder. Because section 1498 extends to infringement "by a contractor, a subcontractor, or any person, firm, or corporation for the [U.S.] Government and with the authorization or consent of the [U.S.] Government," the federal government could also extend its section 1498 authority to the actions of private entities by authorizing them to practice a patented invention on behalf of the government.

TARGETED LEGISLATION AND THE TAKINGS CLAUSE

U.S. patent rights were created by an act of Congress. Thus, should patent rights inhibit access to or affordability of COVID-19 countermeasures and should Congress conclude that existing legal authorities are insufficient, targeted legislation is a possible option. Although the U.S. Constitution grants Congress the authority to create a patent system, it does not require Congress to do so. Congress therefore has wide discretion in designing the patent

system's scope and operation. So long as it operates prospectively (and consistent with its international treaty obligations), Congress may exclude certain technologies from patent protection. For example, a provision in the 2011 Leahy-Smith America Invents Act prohibits the PTO from issuing a patent on inventions "directed to or encompassing a human organism."

When legislation operates retroactively to invalidate a patent or diminish patent rights, however, it raises issues under the Takings Clause of the Fifth Amendment to the U.S. Constitution. The Takings Clause states that if "private property [is] taken for public use" by the U.S. government, it must provide "just compensation." The Supreme Court has suggested several times that patents are private property under the Takings Clause, but it has never held so explicitly. Presuming that patents are private property under the Fifth Amendment, legislation that retroactively impairs patent rights could give rise to a constitutional claim for just compensation. Recognizing this, Congress has often provided for compensation in past legislation that has retroactively invalidated patents. For example, the Atomic Energy Act of 1954 "revoked" existing patents on "any invention or discovery which is useful solely in the utilization of special nuclear material or atomic energy in an atomic weapon," while providing a process to provide just compensation to any such patent holder.

If Congress seeks to preclude the exercise of exclusive patent rights over COVID-19 medical countermeasures, it could pass legislation preventing the PTO from issuing such patents, or invalidating already-issued patents relating to countermeasures. In the latter case, some mechanism for compensation to the patent holder might be required under the Takings Clause. In either case, such legislation could raise issues under the United States' treaty obligations, including the treaty on Trade-Related Aspects of Intellectual Property Rights of the Marrakesh Agreement establishing the World Trade Organization (WTO), in which WTO members agree to make patents available in "all fields of technology," with some exceptions. In addition, preclusion of patent rights could reduce incentives to create and develop medical countermeasures against COVID-19.

Chapter 388

CORONAVIRUS DISEASE 2019 (COVID-19) POSES CHALLENGES FOR THE U.S. BLOOD SUPPLY*

Jared S. Sussman

The current Coronavirus Disease 2019 (COVID-19) outbreak may pose significant challenges for the United States' blood supply. Mitigation strategies to prevent the spread of COVID-19, such as closures of schools and workplaces, have led to blood drive cancellations, resulting in a critical blood supply shortage in the Pacific Northwest (specifically, western Washington and Oregon). School closures, event cancellations, and other mitigation strategies in other areas of the country may provide challenges for maintaining a sufficient blood supply. The management and distribution of the U.S. blood supply is largely coordinated by private organizations, with some oversight by the Department of Health and Human Services (HHS). Congress may consider how best to address critical storages, such as through HHS or the U.S. Food and Drug Administration's (FDA) authority over blood safety and donation guidance.

INDUSTRY AND BLOOD CENTER RESPONSE

The nation's blood supply is managed by a network of independent blood centers and the American Red Cross. On March 9, 2020, one blood center, Bloodworks Northwest, headquartered in Seattle, Washington, issued a press release warning that the Pacific Northwest blood supply is at the risk of collapse in coming days due to COVID-19 concerns. The release notes that the closure of schools, businesses, and events has led to the cancellation of blood drives in the area.

Immediate risk of blood supply collapse due to the COVID-19 outbreak is currently limited to the Pacific Northwest. However, blood drives may potentially be cancelled in other areas of the country as containment and mitigation strategies increase, which may lead to

* This is an edited, reformatted and augmented version of Congressional Research Service Publication No. IN11238, dated March 13, 2020.

blood supply shortages in additional areas. Blood centers are also concerned that potential donors may choose not to donate over fears of contracting COVID-19 while at the blood center. Blood centers throughout the country and organizations representing the industry are urging individuals to donate blood to mitigate potential shortages. (For examples, see Kentucky Blood Center, New York Blood Center, and LifeServe Blood Center.)

Blood products have a limited shelf-life, and therefore ongoing donations are necessary. Blood can be mobilized and distributed regionally by blood center networks when a shortage exists at a blood center, but only to a certain extent given the limited shelf-life. HHS supports blood availability preparedness and response coordination through a number of roles and responsibilities.

BLOOD DONATION AND TRANSFUSION SAFETY

The industry is reinforcing the notion that blood donation is a safe activity. Bloodworks Northwest, for instance, relayed in its press release on the outbreak that it routinely sanitizes its facilities and equipment, and staff regularly implement infection control precautions. Furthermore, staff, donors, and volunteers are encouraged to stay home if they feel unwell. Other blood centers are including similar reassurances in their calls to donate.

On the day of donation, donors must have a normal temperature and present other signs of good health (21 C.F.R. § 630.10(f)). Blood centers are asking donors to follow-up after donating if diagnosed with COVID-19, as recommended by FDA.

FDA reports that there are no known cases of respiratory virus transmission by blood transfusion and there have been no reported cases of transfusion-transmitted COVID-19, but has issued recommendations to guide the blood donation activities of persons who may have been exposed.

FDA RECOMMENDATIONS ON BLOOD DONATION

On March 11, 2020, FDA published updated information for blood establishments regarding donation during the outbreak. The March 11 information suggests that some blood establishments may want to consider donor education, encourage self-deferral, and manage post-donation information about COVID-19. The March 11 information recommends that individuals self-defer from donating blood for 28 days after either (1) resolution of symptoms after a diagnosis of COVID-19 or (2) the last possible contact exposure to a person with a COVID-19 infection. Donors are also directed to report a subsequent diagnosis after donation.

Previous, now-outdated FDA information published on February 4, 2020, also recommended that individuals self-defer from donating blood for 28 days following travel to a location with a COVID-19 outbreak. However, some blood centers are still instructing potential donors to self-defer from donating if they recently traveled to areas with COVID-19 cases (for examples, see LifeServe Blood Center and Bloodworks Northwest). If these instructions remain in effect, they could potentially limit supply in areas that have the most critical need as many potential donors may meet the self-deferral criteria.

The March 11 information also recommends that blood centers “prepare and evaluate emergency plans to address challenges, such as effects on the availability of blood donors and staff.” FDA did not provide any specific guidance for the preparation of emergency plans for blood centers.

IMPLICATIONS FOR CONGRESS

Congress may direct FDA to issue more specific information to help blood centers educate potential donors as the outbreak evolves, to prevent travel deferrals, and to guide the development of emergency plans. Congress may also direct HHS to ensure that measures are in place to mobilize and distribute blood to blood centers, as needed. In addition, individual members of Congress may wish to communicate the safety of blood donation to constituents and to encourage donations at the local level.

Chapter 389

COVID-19: AN OVERVIEW OF TRADE-RELATED MEASURES TO ADDRESS ACCESS TO MEDICAL GOODS*

Nina M. Hart

ABSTRACT

As the coronavirus (COVID-19) pandemic continues, government officials around the world have raised questions and concerns about how to ensure that their countries have adequate access to, and supplies of, medical goods, including personal protective equipment (e.g., masks, gloves, garments), medical equipment (e.g., ventilators), and pharmaceuticals. This Sidebar presents an overview of some of the trade-related measures taken by the United States and its trading partners in their efforts to address these concerns, including: (1) introducing export restrictions; (2) reducing or eliminating tariffs; (3) revising import procedures; and (4) prioritizing domestic production. It then discusses possible legal challenges to each of these measures, as well as avenues for congressional action or oversight.

METHOD ONE: INTRODUCING EXPORT RESTRICTIONS

Several of the United States' trading partners have imposed export restrictions on certain medical goods to meet their domestic supply needs. For example, the European Union (EU) introduced export authorization measures that prohibit the export of personal protective equipment (e.g., masks, protective glasses, and garments) from the EU without prior regulatory approval. India restricted exports of twenty-six pharmaceutical components, as well as medicines and vitamins made from them, accounting for approximately ten percent of

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India's pharmaceutical exports. To date, the United States has not supported its trading partners' use of export restrictions to address potential supply shortages.

The World Trade Organization's (WTO's) international trade regime generally prohibits quantitative restrictions on the export of goods, whether in the form of export bans, licensing requirements, or other measures having similar restrictive effects. In light of this general rule, the export restrictions described above may arguably cause some to raise concerns. At the same time, however, three exceptions may apply. First, the general prohibition does not cover export restrictions "temporarily applied to prevent or relieve critical shortages of ... products essential to the exporting contracting party." Second, the WTO regime permits its Members to implement measures contrary to their general obligations if the measures are "necessary to protect human, animal or plant life or health" or "essential to the acquisition or distribution of products in general or local short supply." Any potentially WTO-inconsistent measures must also meet other conditions, including that their application not create "arbitrary or unjustifiable discrimination between countries where the same conditions prevail." Measures taken to address the acquisition or distribution of products in short supply must also be time-limited and conform to the principle that all WTO Members "are entitled to an equitable share of the international supply of such products." Third, the WTO does not prevent any Member from implementing measures "that it considers necessary for the protection of its essential security interests ... in time of war or other emergency in international relations."

It is uncertain whether the export restrictions imposed by WTO Members (or any future restrictions that may be imposed by other WTO Members, including the United States) to address concerns about shortages of medical supplies are WTO-inconsistent and, if so, fall within one of the exceptions, as this precise issue has not yet been litigated before the WTO's Dispute Settlement Body. However, in a joint study, the WTO and World Health Organization (WHO) indicated that some trade-restrictive measures used to address widespread infectious diseases are "unlikely to conflict with WTO rules," provided that they are time-limited and crafted to minimize trade disruptions. Nonetheless, the WHO has advised against export restrictions to address COVID-19, instead recommending that countries incentivize increased domestic production of the needed products (discussed below). The WTO Director-General has also stressed that "maintaining open trade and investment flows will be critical to protect jobs, prevent supply chain breakdown, and ensure that vital products do not become unaffordable for consumers."

METHOD TWO: REDUCING OR ELIMINATING TARIFFS

Since the onset of the COVID-19 pandemic, the cost of a number of medical goods has increased dramatically. For example, the cost of surgical masks has increased 600% and the cost of medical gowns has doubled.

To alleviate the financial pressure on firms and other entities that must buy these products, the United States has removed some tariffs on certain medical goods from China imposed under Section 301 of the Trade Act of 1974. However, some commentators remain concerned that the remaining Section 301 tariffs imposed by the Trump Administration may impair the United States' ability to respond to COVID-19. Some Members of Congress have urged the Administration to remove or suspend tariffs on a number of products from China to

alleviate the economic impact from COVID-19, including by reducing the cost for firms to purchase medical supplies.

Congress could potentially remove or eliminate tariffs, as it possesses constitutional authority to “lay and collect ... Duties” (i.e., tariffs). Alternatively, the President could “authorize the Secretary of the Treasury to permit ... the importation free of duty of food, clothing, and medical, surgical, and other supplies for use in emergency relief work” under Section 318 of the Tariff Act of 1930, after a declaration that “an emergency ... exist[s] by reason of a state of war, or otherwise.” The scope of Section 318 may raise the question of whether its broad delegation of authority may violate the non-delegation doctrine, which prohibits the transfer of legislative functions to the Executive without an “intelligible principle” to limit the Executive’s discretion when implementing such functions. However, a recent challenge to another trade statute that grants the President broad authority to restrict imports may suggest otherwise. Specifically, the U.S. Court of Appeals for the Federal Circuit upheld the constitutionality of Section 232 of the Trade Expansion Act of 1962, which permits the President to restrict imports if he determines they are entering the United States “in such quantities or under such circumstances as to threaten the national security.” As of the time of writing, no court has considered the legality of Section 318.

The impact of tariffs on access to medical goods has long been of interest to WTO Members, even in the absence of immediate public health crises. In 2006, they committed to negotiating the elimination of tariffs and non-tariff barriers on a number of healthcare-related goods. These negotiations remain ongoing.

METHOD THREE: REVISING IMPORT PROCEDURES

Most countries regulate the importation of medical goods for public health and safety reasons. For instance, in the United States, U.S. Customs and Border Protection (CBP) would need to approve the importation of medical devices and pharmaceutical products. CBP may assess, at the port of entry, whether the products to be imported satisfy customs rules, such as entry documentation, and comply with other U.S. laws and regulations, including the U.S. Food and Drug Administration’s governing statutes. Failure to satisfy these requirements can lead to delays in processing and release of products into the United States, or in some circumstances, to seizure of the goods.

To address procedural issues that could potentially delay access to medical goods, some countries have taken steps to streamline their customs procedures. China created a “green lane” system, which prioritizes the inspection and review of imported medical goods with the goal of reducing regulatory processing time before the goods may be released for use. Similarly, the EU recently introduced guidelines, instructing its Member States to create “green lanes” for freight transport to ensure access to “essential products,” including medicines and medical equipment.

Thus far, the United States has seemingly not publicly proposed amending its customs or other regulatory procedures in response to the COVID-19 pandemic. However, CBP has congressional authorization to “develop and implement screening and targeting capabilities, including ... prioritizing of passengers and cargo.” Thus, CBP may be able to create a “green lane” system, similar to those described above, to reduce processing times for medical goods.

Given that the creation of such a system may require CBP to complete a rulemaking process, it may not be feasible to implement this type of system to address COVID-19 (although CBP may be able to create a new regulation that would apply to any future emergencies). Congress could, however, consider using its constitutional authority to “regulate Commerce with foreign Nations” to more quickly implement new customs prioritization procedures.

METHOD FOUR: PRIORITIZING DOMESTIC PRODUCTION

As an alternative to reliance on cross-border supply chains, the United States and some of its trading partners have sought to prioritize domestic production of necessary goods, either by requiring manufacturers to complete orders of medical goods before orders of non-medical goods, or by imposing increased production requirements on these manufacturers. This reflects, at least in part, growing concern about supply chain security, as many countries import more health-related products than they export—as of 2010, only 24 countries out of 139 surveyed were net exporters of such products.

On March 18, 2020, President Trump issued an Executive Order authorizing the Secretary of Health and Human Services to use the Executive Branch’s authority under the Defense Production Act to address potential shortages in health and medical resources needed to respond to COVID-19. This Act permits the President, or agency to whom he delegates responsibility, to require that certain contracts or orders “take priority” over others, as well as to require companies to fulfill production orders “necessary or appropriate to promote the national defense.” The Act also allows the President to incentivize domestic production and ensure that essential products and their components “are available from reliable sources,” such as by restricting the suppliers, whether foreign or domestic, from whom manufacturers can obtain materials. While the Act does not envision a large role for Congress in its implementation (except with regard to wage and price controls), Congress may consider enhancing its oversight or authorization role. Additionally, to the extent that some Members of Congress may have questions as to the scope of “national defense,” Congress could consider amending the Act to clarify whether it applies to COVID-19 or any other future public health emergencies.

Other countries have also implemented or are considering similar measures. For example, Germany and Italy placed additional orders for ventilators and other health-related products, and Italy has directed its military to assist the country’s only domestic producer of ventilators to quadruple production. The United Kingdom is also assessing options for increasing domestic production of medical supplies. Such measures seemingly align with the WHO’s suggestion that “Governments should develop incentives for industry to ramp up production.” Such measures may be permitted under the WTO regime, provided they are not unlawful subsidies (e.g., subsidies that harm the industries of other WTO Members) under the WTO’s Agreement on Subsidies and Countervailing Measures, or, if the measures are potentially WTOinconsistent, provided that they fall within an exception (e.g., the public health or essential security exceptions described above).

Chapter 390

DEVELOPMENT AND REGULATION OF DOMESTIC DIAGNOSTIC TESTING FOR NOVEL CORONAVIRUS (COVID-19): FREQUENTLY ASKED QUESTIONS*

Amanda K. Sarata

ABSTRACT

On December 31, 2019, the World Health Organization (WHO) was informed of a cluster of pneumonia cases in Wuhan City, Hubei Province of China. Illnesses have since been linked to a disease caused by a previously unidentified strain of coronavirus, designated Coronavirus Disease 2019, or COVID-19. Despite containment efforts in China, the United States, and elsewhere, by late February there were indications that the COVID-19 outbreak may have entered a new phase, with community spread occurring or suspected in several countries other than China, including in the United States.

Diagnostic testing is a critical part of the public health response to and clinical management of COVID-19, caused by the SARS-CoV-2 virus. Efforts in the United States to develop and disseminate a test for COVID-19 have faced challenges. Manufacturing and quality issues with the nation's test—developed by the Centers for Disease Control and Prevention (CDC)—resulted in significant delay in access to testing throughout the country. In this context, on February 29, 2020, in an effort to facilitate the expansion of testing capacity as the first cases of community spread were confirmed in the United States, the Food and Drug Administration (FDA) announced a new policy, issued via agency guidance and effective immediately, that would allow certain laboratories—principally clinical and large commercial and reference laboratories—that have developed and validated their own COVID-19 diagnostic to begin to use the test prior to it receiving an Emergency Use Authorization (EUA) from the agency.

FDA's February 29 guidance aims to facilitate the expansion of diagnostic testing from the public health setting into the clinical health care and commercial settings. Doing so may help the country meet the increasing and substantial demand for testing generated by community spread of the disease and expanded clinical testing guidelines issued by

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the CDC. This report does not address financing or coverage of diagnostic testing for COVID-19.

On December 31, 2019, the World Health Organization (WHO) was informed of a cluster of pneumonia cases in Wuhan City, Hubei Province of China. Illnesses have since been linked to a disease caused by a previously unidentified strain of coronavirus, designated Coronavirus Disease 2019, or COVID-19. Despite containment efforts in China, the United States, and elsewhere, by late February there were indications that the COVID-19 outbreak may have entered a new phase, with community spread occurring or suspected in several countries other than China, including in the United States.¹

Diagnostic testing is a critical part of the public health response to and clinical management of the COVID-19 caused by the SARS-CoV-2 virus. Efforts in the United States to develop and disseminate a test for COVID-19 have faced challenges. Manufacturing and quality issues with the nation's test—developed by the Centers for Disease Control and Prevention (CDC)—resulted in essentially all testing going through CDC's laboratory facility in Atlanta through early March, despite distribution of test kits to state and local public health labs beginning in early February.

CDC's initial test kits had to be remanufactured and redistributed, which, along with other factors, has significantly delayed access to testing throughout the country. It has been reported that the CDC's Atlanta laboratory is currently under investigation by the Department of Health and Human Services (HHS) for possible quality issues related to its manufacture of the test kits, which may have led to the contamination of one reagent and thus to the quality issues with the test.²

In this context, on February 29, 2020, in an effort to facilitate the expansion of testing capacity as the first cases of community spread were confirmed in the United States, the Food and Drug Administration (FDA) announced a significant new policy. This policy, issued via agency guidance and effective immediately, allows certain laboratories—principally clinical and commercial laboratories—that have developed and validated their own COVID-19 diagnostics to begin to use the tests prior to the test receiving an Emergency Use Authorization (EUA) from the agency.³

Diagnostic testing for COVID-19, in part because it is caused by a novel pathogen, has been led and carried out to date through the country's public health infrastructure. This includes primarily the CDC and the country's network of state and local public health laboratories. In contrast, in most situations, diagnostic testing is carried out by a number of facilities, including private commercial laboratories (e.g., Quest, LabCorp), hospital and other clinical laboratories, and laboratories in academic medical centers, among others.

FDA's February 29 guidance aims to facilitate the expansion of diagnostic testing from the public health setting into the clinical health care and commercial settings, leveraging

¹ For more information about the domestic response to the novel coronavirus, see CRS Report R46219, *Overview of U.S. Domestic Response to Coronavirus Disease 2019 (COVID-19)*.

² "U.S. agency investigating production of faulty coronavirus test kits," March 1, 2020, <https://www.reuters.com/article/us-china-health-test-kits/u-s-agency-investigating-production-of-faulty-coronavirus-test-kits-idUSKBN20P09Y>.

³ See generally FDA, "Policy for Diagnostics Testing in Laboratories Certified to Perform High Complexity Testing under CLIA prior to Emergency Use Authorization for Coronavirus Disease-2019 during the Public Health Emergency," February 29, 2020, <https://www.fda.gov/media/135659/download>.

significant standing resources throughout the country, including facilities, trained personnel, expertise, materials, and equipment. It is FDA's intention that this expansion will help the country meet the increasing and substantial demand for testing generated by community spread of the disease and expanded clinical testing guidelines issued by the CDC. In addition, because many cases of COVID-19 are reportedly mild or asymptomatic, widespread access to testing—which informs development of important metrics such as the case fatality rate—is critical to understanding the scope and extent of the disease in the United States, and to efficiently directing resources to mitigate its impact in the broader community.

Diagnostic tests—formally called *in vitro* diagnostic (IVD) devices—may be commercially developed and distributed as “kits” or developed, validated, and carried out by a single laboratory. This second type of test—known as a laboratory-developed test, or an LDT—is the more commonly used type of test because of its flexibility and differing federal regulatory requirements, among other reasons. Although the CDC's test is being manufactured as a test kit and initially has been distributed to specific CDC-qualified labs, the FDA guidance targets LDTs that are generally carried out in clinical and academic settings or private commercial laboratories. All clinical laboratories in the United States, regardless of whether they are part of the country's public health infrastructure or part of the health care delivery system, are regulated by the Clinical Laboratory Improvement Amendments of 1988 (CLIA) program, administered by the Centers for Medicare & Medicaid Services (CMS).

Federal agencies involved in the regulation of IVDs include FDA and CMS. FDA derives its authority to regulate the sale and distribution of medical devices, such as IVDs, from the Federal Food, Drug, and Cosmetics Act (FFDCA) and the Public Health Service Act (PHSA). CMS's authority to regulate IVDs is through CLIA (P.L. 100-578). FDA regulates the safety and effectiveness of diagnostic tests, as well as the quality of the design and manufacture of the diagnostic test. CMS regulates the quality of clinical laboratories and the clinical testing process.

DIAGNOSTIC TESTS

What Are IVD Tests?

In vitro diagnostic devices are defined in FDA regulation as a specific subset of medical devices that include “reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions ... in order to cure, mitigate, treat, or prevent disease ... [s]uch products are intended for use in the collection, preparation, and examination of specimens taken from the human body.” As indicated by this definition, an IVD may also include components of tests, which can include both non-diagnostic ingredients, called general purpose reagents (GPRs), and the active ingredient in a diagnostic test, referred to as the analyte specific reagent (ASR).

In general, an IVD device may be a “commercial test kit” (a product developed, produced, and sold by a manufacturer for distribution to multiple laboratories) or a “laboratory developed test” (a product developed by and used in a single laboratory). LDTs may use components (e.g., general purpose reagents like a buffer) that are either manufactured in-house by the laboratory or commercially developed and distributed.

What Is an LDT?

A laboratory-developed test is a class of IVD that is designed, manufactured, and used within a single laboratory. LDTs are often used to test for conditions or diseases that are either rapidly changing (e.g., new strains of known infectious diseases) or the subject of quickly advancing scientific research (e.g., genomic testing for cancer). The majority of genetic tests—a type of IVD that analyzes various aspects of an individual's genetic material (e.g., DNA, RNA)—are LDTs.

How Are IVD Tests Regulated?

In general, oversight of in vitro diagnostic devices focuses on ensuring their safety and effectiveness; their accuracy and reliability; the quality of clinical laboratories that carry out IVD testing; the utility of the information generated by IVDs in clinician and patient decision-making; and the truthfulness of claims made about IVDs that are marketed directly to consumers. As with other medical devices, the application of FDA regulatory requirements to IVDs depends on the IVD's risk classification according to its intended use. Classification is based, in turn, on the risk the device poses to the patient. For IVDs, which are informational tests, the risk to the patient is that of an incorrect test result, either a false positive or a false negative result, either of which may cause serious harm to the individual. In the case of infectious diseases—for example, COVID-19—the risk of a false negative test extends beyond the individual patient into the community at large. The FDA has three classes of medical device: Class I (low risk), Class II (moderate risk), and Class III (high risk). Regulatory controls are dependent on the class of a given medical device. COVID-19 diagnostics would most likely fall in Class III, as they would be considered to be high-risk devices.

How Are LDTs Regulated?

The regulation of laboratory-developed tests has been the subject of ongoing debate over the past 20 years, driven in large part by an increase in the number and complexity of genetic tests over this time. In general, the FDA has maintained that it has clear regulatory authority over LDTs, as it does with all IVDs that meet the definition of medical device in the FFDCA.⁴ However, the FDA traditionally exercised enforcement discretion over LDTs—choosing not to enforce applicable statutory and regulatory requirements with respect to such tests—meaning that most of these tests have neither undergone premarket review nor received FDA clearance or approval for marketing. To date, FDA has instead focused its enforcement efforts on commercial IVD kits, which are broadly commercially marketed. In recent years, despite the absence of specific agency guidance on the regulation of LDTs, FDA has nevertheless begun to assert authority over LDTs, and specifically over some direct-to-consumer (DTC) genetic tests, that it considers to be higher-risk tests.

⁴ The term *medical device* is defined in FFDCA §201(h) [21 U.S.C. §321(h)].

What Is CLIA and How Is It Involved in LDT Regulation?

CLIA of 1988 provides CMS with authority to regulate clinical laboratories.⁵ CLIA establishes quality standards for clinical laboratory testing and a certification program for clinical laboratories that perform testing using IVD devices. All laboratories that perform diagnostic testing for health-related reasons (i.e., with results returned to the patient or a health care practitioner) are regulated by CMS under the authority of CLIA. For CLIA to apply, testing must be carried out on a human specimen. CLIA certification is based on the level of complexity of testing that the laboratory performs, specifically (1) low (therefore, waived) complexity, (2) moderate complexity, and (3) high complexity. FDA is responsible for categorizing tests according to their level of complexity. CLIA requirements are used to evaluate a test's *analytical validity*, defined as the ability of a test to detect or measure the analyte it is intended to detect or measure. Laboratories that perform moderate- and high-complexity testing must meet specific standards and requirements as a condition of certification, including proficiency testing (PT), patient test management, quality control, personnel qualifications, and quality assurance. All LDTs, including genetic tests offered as LDTs, are considered high-complexity tests under CLIA. All COVID-19 diagnostics would be considered to be high complexity tests under CLIA.

How Are IVDs Regulated by the FDA during an Emergency Such as the Outbreak of COVID-19?

In certain public health or other emergency situations, the HHS Secretary may declare that existing circumstances justify the use of unapproved medical products for certain uses, or approved medical products for unapproved uses.⁶ This declaration facilitates access to not-yet- approved medical products in an expedited manner during certain emergency situations. In the case of the COVID-19 disease, HHS Secretary Azar determined that “there is a public health emergency and [declared] that circumstances exist justifying the authorization of emergency use of in vitro diagnostics for detection and/or diagnosis of the novel coronavirus.”⁷ On the basis of this declaration, FDA issued an Emergency Use Authorization authorizing the emergency use of the CDC-developed diagnostic test for COVID-19.⁸ The FDA also issued an EUA to the state of New York for an LDT developed by the state public health labs. To date, these are the only two EUAs for coronavirus diagnostics that the FDA has issued.⁹

⁵ PHS 353; 42 U.S.C. §263a.

⁶ FFDCA §564 [21 U.S.C. §360bbb-3].

⁷ FDA, “Policy for Diagnostics Testing in Laboratories Certified to Perform High Complexity Testing under CLIA prior to Emergency Use Authorization for Coronavirus Disease-2019 during the Public Health Emergency,” February 29, 2020, <https://www.fda.gov/media/135659/download>, page 1.

⁸ Letter of authorization from FDA to CDC, advising of the authorization for emergency use of the CDC-developed diagnostic test, available at “Novel coronavirus (COVID-2019) EUA Information” on the FDA web page “Emergency Use Authorization,” <https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization>.

⁹ FDA, Emergency Use Authorization, <https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization>.

How Does the Emergency Use Authority Apply to LDTs if They Are Generally Exempted from Premarket Requirements?

During an emergency, all laboratory-developed tests testing for the relevant pathogen (in this case, SARS-CoV-2) must either be approved, cleared, or authorized under an EUA to be legally carried out. As noted above, FDA generally waives most regulatory requirements (e.g., premarket review) for LDTs in normal situations; nevertheless, LDTs may only be used with authorization (e.g., an EUA) during an emergency declaration pursuant to FFDCa Section 564.¹⁰ That is, statutory requirements under FFDCa Section 564 apply to LDTs as they do to other medical products, and they apply to both commercial test kits—which are normally subject to FDA regulatory requirements—and to LDTs.

The EUA process is usually used to expedite access to medical products that would otherwise need premarket approval or clearance in emergency situations. However, because premarket approval requirements for LDTs are generally waived through enforcement discretion by the agency, the EUA represents additional regulatory requirements for the use of an LDT in emergency situations. This is because, among other things, in the case of a communicable disease, the test result has implications beyond the individual being tested, and so a false negative result could have serious consequences for the community.¹¹ Therefore, FDA states that these tests need an EUA in an emergency prior to clinical use as do other medical products. In contrast, for commercial test kits, the EUA represents an abbreviated mechanism that allows the unapproved product to be used without undergoing the FDA premarket review typically required (for a complex molecular test for a novel pathogen, that review would generally be a Premarket Approval, or PMA, for high-risk medical devices).

Despite a request from the Association of Public Health Laboratories (APHL) to FDA, the agency declined to exercise enforcement discretion with respect to LDTs that detect SARS-CoV-2 and diagnose COVID-19 and the requirement that they receive an EUA prior to use. APHL maintains that these labs are regulated by CLIA, and that this regulatory oversight is sufficient.¹² However, on February 29, 2020, FDA announced a new policy allowing certain laboratories that have developed and validated COVID-19 LDTs to begin to use the test clinically *prior* to it receiving an EUA from the agency but *after* validation of the test and notification of the agency (see “What Steps Did FDA Take to Expand Testing Capacity in Response to the Problems with CDC’s Test?”).¹³

¹⁰ 21 U.S.C. §360bbb-3.

¹¹ FDA, “Information for Laboratories Implementing IVD Tests Under an EUA,” <https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/information-laboratories-implementing-ivd-tests-under-eua>.

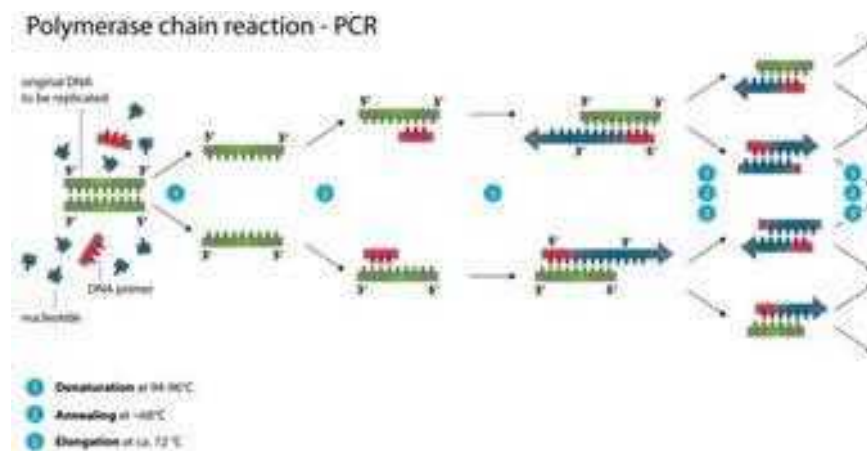
¹² 360dx, “APHL Asks FDA to Make Own Tests as CDC Struggles to Provide SARS-CoV-2 Test Kits,” February 25, 2020, https://www.360dx.com/clinical-lab-management/aphl-asks-fda-make-own-tests-cdc-struggles-provide-sars-cov-2-test-kits?trendmd-shared=0&utm_medium=TrendMD&utm_campaign=0&utm_source=TrendMD#.XmKIwqhKiUm.

¹³ See generally FDA, “Policy for Diagnostics Testing in Laboratories Certified to Perform High Complexity Testing under CLIA prior to Emergency Use Authorization for Coronavirus Disease-2019 during the Public Health Emergency,” February 29, 2020, <https://www.fda.gov/media/135659/download>.

THE CDC 2019-NOVEL CORONAVIRUS (2019-nCoV) REAL-TIME REVERSE TRANSCRIPTASE (RT)-PCR DIAGNOSTIC PANEL

How Does the CDC's COVID-19 Diagnostic Test Work?

The diagnostic test developed by the CDC, called the 2019-Novel Coronavirus (2019-nCoV) Real-Time Reverse Transcriptase (RT)-PCR Diagnostic Panel, is a complex molecular diagnostic test that relies on generally standard molecular biology laboratory techniques. Specifically, the test uses a technique called Polymerase Chain Reaction (PCR), a standard *in vitro* technique for amplification of DNA. Because the SARS-CoV-2 virus—the virus that causes COVID-19—is an RNA¹⁴ virus, the RNA must be first reverse transcribed to generate copy DNA, or cDNA, which is then amplified (multiple copies are generated) using PCR. PCR relies on primers—very short single stranded pieces of DNA that are complementary to and bind with specific regions of the viral genome and thus define the specific genomic region to be amplified. The test then relies on a probe, or a single-stranded piece of DNA that is chemically or radioactively labelled, that can bind to and thus detect the amplified target portion of the viral genetic material.



Source:

https://upload.wikimedia.org/wikipedia/commons/thumb/9/96/Polymerase_chain_reaction.svg/835px-Polymerase_chain_reaction.svg.png, accessed March 3, 2020.

Figure 1. Polymerase chain reaction overview.

CDC's original test used three sets of primers and probes: two to target specific regions of a designated gene within the SARS-CoV-2 viral genome, and a third that was specific to all SARS-like coronaviruses (see "What Quality Problems Did the CDC's Test Experience on Rollout to the State and Local Public Health Laboratories?"). The test also includes a number of authorized control samples, including a positive control for SARS-CoV-2 and a "no template control" to test for system contamination. Together, these controls help ensure that the test is functioning properly.

¹⁴ RNA stands for ribonucleic acid. RNA is genetic material with a slightly different chemical composition from DNA, or deoxyribonucleic acid.

What Type of IVD Is the CDC's Test and Who May Carry It Out?

The CDC's test is being developed by the agency as a test kit and is generally authorized to be distributed to state and local public health laboratories to augment public health testing capacity. The test received an EUA from the FDA on February 4, 2020, under which "authorized laboratories" may receive and carry out the test despite the fact that it is not FDA-approved or FDA-cleared, and that it does not meet all related regulatory requirements for marketing.¹⁵ The EUA notes that "[t]esting is limited to qualified laboratories designated by CDC and, in the United States, certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), (42 U.S.C. §263a), to perform high complexity tests."¹⁶ CDC-qualified laboratories with a CLIA certification for high-complexity testing able to receive the test kits include U.S. state and local public health laboratories, Department of Defense (DOD) laboratories, and select international laboratories. The public health laboratories must verify the test themselves prior to using it, and are currently required to send presumptive positive cases back to the CDC in Atlanta for confirmatory testing by the agency.

What Is the Role of the Commercial Manufacturer IDT in the Development and Distribution of the CDC's Test Kit?

The Trump Administration had estimated that approximately 1 million tests would be broadly available imminently, facilitated by leveraging manufacturing of the CDC test kit by a private company, Integrated DNA Technologies (IDT), a manufacturer that has been working with CDC.¹⁷ According to HHS Secretary Azar on March 5, 2020, IDT will send the CDC test kit to "hospitals, other labs around the country, commercial, public health ... labs" by the end of the week of March 2.¹⁸ The test kit being manufactured by IDT, identical to the CDC test kit and referred to as "IDT 2019-novel coronavirus kit," is being qualified by CDC in lots, and FDA reports that these CDC-qualified, IDT-manufactured test kits are covered by the CDC's EUA authorization of February 4, 2020.¹⁹

FDA notes that if a lab purchases a test kit from IDT, the laboratory does not need its own EUA to carry it out, but that "[t]esting using CDC's EUA-authorized protocol and CDC qualified lots of reagents is considered to be testing done under the CDC's EUA. Labs performing such testing should follow any applicable conditions set forth in the EUA."²⁰ LabCorp, a large commercial laboratory, is already reporting that it can perform the CDC test "if needed to meet testing demand" and that the test is only for use with "authorized

¹⁵ EUA Letter from FDA to CDC, dated February 4, 2020, <https://www.fda.gov/media/134919/download>.

¹⁶ *Ibid.*

¹⁷ RAPS, "FDA's Hahn Addresses Coronavirus Test Capacity, Drug Shortages at Senate Hearing," March 3, 2020, <https://www.raps.org/news-and-articles/news-articles/2020/3/fdas-hahn-addresses-coronavirus-test-capacity-dr>.

¹⁸ Secretary of HHS Alex Azar, Coronavirus Press Briefing, March 5, 2020, <https://www.c-span.org/video/?470068-2/secretary-azar-federal-health-officials-coronavirus-briefing>.

¹⁹ Stenzel, Timothy, FDA Office of In Vitro Diagnostics Webinar, "Policy for Diagnostics Testing in Laboratories Certified to Perform High Complexity Testing under CLIA prior to Emergency Use Authorization for Coronavirus Disease-2019 during the Public Health Emergency" Immediately in Effect Guidance," March 2, 2020; see slide 13, <https://www.fda.gov/media/135707/download>.

²⁰ FDA, "FAQs on Diagnostic Testing for SARS-CoV-2," <https://www.fda.gov/medical-devices/emergency-situations-medical-devices/faqs-diagnostic-testing-sars-cov-2>.

specimens collected from individuals who meet CDC criteria for COVID-19 testing.”²¹ IDT is manufacturing test kits in two sizes, with the largest having a capacity of 500 reactions (approximately 250 individual patients).²²

What Quality Problems Did the CDC’s Test Experience on Rollout to the State and Local Public Health Laboratories?

As noted above, the CDC’s test kit used three sets of probes and primers—or reagents—to detect and identify viral DNA beyond that specific to COVID-19. One of these reagents, the one meant to detect any SARS-like coronavirus including SARS-CoV-2, was returning inconclusive results. In response, the CDC validated a new protocol for their test that allows it to be run excluding the faulty reagent, running the test with only the other two diagnostic components. CDC has the authority to modify the test through enforcement discretion granted by FDA.²³ The agency determined that the exclusion of this reagent does not affect the accuracy or the sensitivity and specificity of the test.

Certain laboratories have continued to experience problems running the test, even when using the modified protocol, with at least one laboratory reporting that the first reagent was also returning inconclusive results. This problem severely limited the state and local public health laboratories’ ability to carry out the CDC’s test.

In response to these issues, the New York State Department of Health requested and was granted the FDA’s second EUA for its own laboratory-developed test, the New York SARS-CoV-2 Real-time RT-PCR Diagnostic Panel.²⁴ Testing is limited under the EUA to two laboratories in New York—the Wadsworth Center, New York State Department of Public Health, and the New York City Department of Health and Mental Hygiene, Public Health Laboratories. New York was one of the states that had continued difficulty implementing CDC’s original test kit, even with the modified protocol.

In response, CDC is also manufacturing new test kits after reportedly resolving the manufacturing issue that affected the original test kit. This time, however, CDC is manufacturing test kits with only the two reagents that were unaffected by the quality issue—that are specific to SARS-CoV-2—and those kits are being made available to qualified CDC labs through the International Reagent Resource.^{25,26} These test kits are expected to result in the public health laboratories having capacity to test up to 75,000 patients.²⁷

²¹ LabCorp, “Information from LabCorp about Coronavirus Disease 2019 (COVID-19),” March 5, 2020, <https://www.labcorp.com/information-labcorp-about-coronavirus-disease-2019-covid-19>.

²² IDT, <https://www.idtdna.com/pages/landing/coronavirus-research-reagents>.

²³ CDC, “Revision to Test Instructions: CDC 2019 Novel Coronavirus (nCoV) Real-Time RT-PCR Diagnostic Panel (EUA200001),” February 26, 2020, https://www.aphl.org/Materials/Signed_CDC_Letter_to_PHLs-N3_Removal_Instructions_26Feb2020.pdf.

²⁴ FDA Letter to NYSDOH, February 29, 2020, <https://www.fda.gov/media/135661/download>.

²⁵ GenomeWeb, Johnson, Madeline, “CDC Revises SARS-CoV-2 Assay Protocol; Surveillance Testing on Track to Start Next Week,” February 28, 2020, <https://www.genomeweb.com/pcr/cdc-revises-sars-cov-2-assay-protocol-surveillance-testing-track-start-next-week#.Xl63kqhKiUk>.

²⁶ “The International Reagent Resource (IRR) was established by the Centers for Disease Control and Prevention (CDC) to provide registered users with reagents, tools and information for studying and detection of Influenza Virus,” see <https://www.internationalreagentresource.org/About/IRR.aspx>.

²⁷ CDC, “Coronavirus Disease 2019 (COVID-19) Situation Summary,” Updated March 3, 2020, <https://www.cdc.gov/coronavirus/2019-ncov/summary.html>.

Some believe that the CDC's choice to develop and mitigate quality problems with its own COVID-19 diagnostic when an accepted diagnostic was available through the World Health Organization (WHO), which was efficiently distributing a German-developed test globally early in the outbreak, was a decision that cost the United States time in its response to the virus's introduction and spread in the country.²⁸ Some speculated about the use of the third reagent—that was to detect SARS-like coronaviruses—and whether it had been strictly necessary if the test was still accurate at diagnosing COVID-19 without that reagent included in the test at all, or if it had instead overcomplicated the test.²⁹ In general, there have been questions raised about the CDC's handling of the development and distribution of its test, and its response to the quality problems that occurred, and the impact this may have had on the country's ability to detect community spread of the disease before it occurred more widely.³⁰

What Steps Did FDA Take to Expand Testing Capacity in Response to the Problems with CDC's Test?

On February 29, 2020, as problems with the rollout of the CDC-developed diagnostic test continued, FDA announced a new policy to immediately leverage LDTs developed in high-complexity commercial, reference, and clinical laboratories nationwide to expand testing capacity. Specifically, the new agency guidance allows CLIA-certified high-complexity laboratories that have developed and validated their own COVID-19 diagnostics to use the tests while the laboratory is preparing, and FDA is reviewing, their EUA submission.^{31,32}

The FDA guidance states that laboratories have 15 days after validating their test to submit an EUA application to FDA, and the guidance recommends confirming the test's first five negative and positive results against an EUA-authorized diagnostic. According to FDA, it “does not intend to object to the use of these tests for clinical testing while the laboratories are pursuing an EUA with the FDA. Importantly, this policy only applies to laboratories that are certified to perform high-complexity testing consistent with requirements under Clinical Laboratory Improvement Amendments.”³³ The guidance includes detailed information about FDA's expected methods for test validation.

Pursuant to this FDA guidance, on March 5, 2020, LabCorp announced that it had begun offering its LDT, the LabCorp 2019 Novel Coronavirus (COVID-19), NAA test “for ordering

²⁸ Sheridan, Cormac, “Coronavirus and the Race to Distribute Reliable Diagnostics,” *Nature*, February 19, 2020, <https://www.nature.com/articles/d41587-020-00002-2>.

²⁹ ProPublica, “Key Missteps at the CDC Have Set Back its Ability to Detect the Potential Spread of Coronavirus,” February 28, 2020, <https://www.propublica.org/article/cdc-coronavirus-covid-19-test>.

³⁰ Politico, “How testing failures allowed the coronavirus to sweep the United States,” March 6, 2020, <https://www.politico.com/news/2020/03/06/coronavirus-testing-failure-123166>.

³¹ GenomeWeb, “FDA Provides SARS-CoV-2 Test Validation Guidance for High-Complexity Labs Seeking EUA,” March 3, 2020, <https://www.genomeweb.com/pcr/fda-provides-sars-cov-2-test-validation-guidance-high-complexity-labs-seeking-eua#.Xl7JFqhKiUk>.

³² FDA, “Policy for Diagnostics Testing in Laboratories Certified to Perform High Complexity Testing under CLIA prior to Emergency Use Authorization for Coronavirus Disease-2019 during the Public Health Emergency,” February 29, 2020, <https://www.fda.gov/media/135659/download>.

³³ FDA, “Coronavirus (COVID-19) Update: FDA Issues New Policy to Help Expedite Availability of Diagnostics,” press release with link to guidance, February 29, 2020, <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-issues-new-policy-help-expedite-availability-diagnostics>. See also CRS In Focus IF11389, *FDA Regulation of Laboratory-Developed Tests (LDTs)*.

by physicians or other authorized healthcare providers anywhere in the U.S.,” and that it is currently pursuing an EUA with the agency for the test.³⁴ This test is to take between three to four days to return results, and a health care provider must order and authorize it, and obtain the required specimen from the patient. Under the FDA’s new guidance, Quest has also announced that it will begin testing for coronavirus with its own LDT, beginning March 9, 2020, and that it plans to pursue an EUA with the agency within 15 days, as required by the guidance.³⁵

³⁴ LabCorp, “Information from LabCorp about Coronavirus Disease 2019 (COVID-19),” March 5, 2020, <https://www.labcorp.com/information-labcorp-about-coronavirus-disease-2019-covid-19>.

³⁵ QuestDiagnostics, “Quest Diagnostics to Launch Coronavirus Disease 2019 (COVID19) Test,” March 5, 2020, <https://newsroom.questdiagnostics.com/2020-03-05-Quest-Diagnostics-to-Launch-Coronavirus-Disease-2019-COVID-19-Test>.

Chapter 391

THE STAFFORD ACT EMERGENCY DECLARATION FOR COVID-19*

Erica A. Lee, Elizabeth M. Webster and Bruce R. Lindsay

This Insight provides an overview of emergency declarations under the Robert T. Stafford Disaster Relief and Emergency Assistance Act (hereinafter the Stafford Act, P.L. 93-288, as amended; 42 U.S.C. §§5121 et seq.). It describes the forms of assistance authorized pursuant to President Donald J. Trump's March 13, 2020 emergency declaration under the Stafford Act in all U.S. states and territories in response to the coronavirus disease 2019 (COVID-19) pandemic.

STAFFORD ACT EMERGENCY DECLARATION FOR COVID-19

The President's emergency declaration, pursuant to Stafford Act Section 501(b), authorized assistance for COVID-19 response efforts for all U.S. states, territories, and the District of Columbia. There was no precedent for a nationwide Stafford Act declaration. Generally, the governor of an affected state/territory or tribal chief executive of an affected Indian tribal government requests the President approve a Stafford Act declaration for specific jurisdictions and types of needed assistance, and the President makes the determination in consultation with FEMA. It is rare for the President to declare an emergency without a governor or chief executive's request; examples include the explosion at the federal courthouse in Oklahoma City and the loss of the Space Shuttle Columbia. Like the COVID-19 emergency declaration, these declarations were authorized under Stafford Act Section 501(b), for certain emergencies involving federal primary responsibility (42 U.S.C. §5191).

The Department of Health and Human Services (HHS) remains the lead agency for the federal response to COVID-19 (see also 42 U.S.C. 300hh(a)). Assistance authorized through the Stafford Act is to supplement and support the efforts of HHS and state, territorial, tribal,

* This is an edited, reformatted and augmented version of a Congressional Research Service publication IN11251, prepared for Members and Committees of Congress dated March 13, 2020.

and local governments. The Stafford Act does not supplant or supersede other federal authorities, including public health authorities exercised by the Secretary of HHS.

COMPARING STAFFORD ACT DECLARATIONS

The Stafford Act authorizes the President to issue either “emergency” or “major disaster” declarations. An emergency is broadly defined, and may include public health incidents. Although infectious disease events are not listed in the definition of a major disaster, President Trump stated that he “believe[s] that the disaster is of such severity and magnitude nationwide that requests for a declaration of a major disaster ... may be appropriate.”

Table 1 lists the forms of assistance available pursuant to each type of declaration.

Table 1. Assistance available under Stafford Act Declarations

	Emergency Declaration	Major Disaster Declaration
Public Assistance (PA)	Emergency Work Category A – Debris Removal Category B – Emergency Protective Measures	Emergency Work Category A – Debris Removal Category B – Emergency Protective Measures Permanent Work Categories C-G – Restoration of damaged facilities
Individual Assistance (IA)	Individuals and Households Program (IHP)	IHP Crisis Counseling Program Disaster Case Management Disaster Unemployment Assistance Disaster Legal Services Disaster Supplemental Nutrition Assistance Program
Hazard Mitigation Assistance (HMA)	Not Available	Hazard Mitigation Grant Program

Source: FEMA, “The Disaster Declaration Process.”

PUBLIC ASSISTANCE

Emergency declarations typically authorize certain types of Public Assistance (PA), which provides financial assistance to supplement a state, territorial, or tribal government’s ability to respond to an incident. Emergency declarations may authorize PA “emergency work” undertaken to save lives, protect property and public health and safety, and lessen or avert the threat of a catastrophe. The two forms of PA “emergency work” are debris removal (authorized under Stafford Act Sections 403, 407, and 502) and emergency protective measures (authorized under Stafford Act Sections 403, 418, 419, and 502).

When PA is authorized, a state, territory, or tribe becomes the PA grant recipient. Local governments and certain nonprofit entities may apply for grant funds through the recipient. The Stafford Act authorizes FEMA to reimburse not less than 75% of the eligible costs of specific types of work undertaken by eligible PA applicants.

Aside from eligibility restrictions, the amount of money that can be awarded for any single applicant or declaration through the PA program is not limited. However, the President must notify Congress when assistance provided for an emergency declaration exceeds \$5 million (42 U.S.C. §5193).

PUBLIC ASSISTANCE FOR COVID-19 EMERGENCY DECLARATION

The Stafford Act emergency declaration for COVID-19 authorized only one form of assistance: PA emergency protective measures. Applicants are to be reimbursed for 75% of eligible costs incurred while performing emergency protective measures. FEMA will not reimburse work supported by the authorities of another federal agency (42 U.S.C. §5155).

Emergency protective measures encompass a wide range of activities. According to a FEMA news release on the COVID-19 emergency declaration, reimbursable activities may include “activation of State Emergency Operations Centers, National Guard costs, law enforcement and other measures necessary to protect public health and safety.” Additionally, FEMA may reimburse costs for overtime labor performed by applicants’ budgeted employees and for overtime and regular-time labor performed by unbudgeted employees engaged in eligible work, per 44 C.F.R. §206.228. General FEMA guidance includes the following activities that may be relevant to a pandemic in a non-exclusive list of eligible emergency protective measures. FEMA has not yet specifically authorized these activities for COVID-19 response. Disaster-specific guidance may provide more information.

- Transporting and pre-positioning equipment and resources for response;
- Emergency Operation Center (EOC)-related costs;
- Supplies and commodities;
- Limited, uninsured emergency medical care and transport up to 30 days from the declaration date, unless extended by FEMA. Eligible care includes uninsured vaccinations, durable and consumable medical equipment and supplies, temporary medical facilities, and medical waste disposal;
- Evacuation and sheltering. Generally, FEMA only provides assistance for congregate sheltering, though non-congregate sheltering may be authorized upon request;
- Limited child care;
- Security, including law enforcement;
- Use or lease of temporary generators for facilities that provide essential services;
- Public dissemination of hazard information; and
- Mass mortuary services.

INDIVIDUAL ASSISTANCE

The FEMA Individuals and Households Program (IHP) may be available following a Stafford Act emergency declaration. IA was not authorized pursuant to the initial emergency declaration for COVID-19. An amended emergency declaration or a major disaster declaration could authorize different forms of IA.

Chapter 392

DIVISION B OF THE CORONAVIRUS AID, RELIEF, AND ECONOMIC SECURITY (CARES) ACT—RELIEF FOR INDIVIDUALS, FAMILIES, AND BUSINESSES*

*Molly F. Sherlock, Jane G. Gravelle, Margot L. Crandall-Hollick,
Donald J. Marples and Grant A. Driessen*

Congress is considering a number of proposals that seek to mitigate the economic effects of the COVID-19 pandemic. One such proposal, the Coronavirus Aid, Relief, and Economic Security (CARES) Act (S. 3548), was introduced in the Senate on March 19, 2020. Division B of S. 3548 includes tax relief for individuals and businesses, including

- a one-time rebate to taxpayers;
- a delay of the individual tax filing deadline for tax year 2019;
- modification of the tax treatment of certain retirement fund withdrawals and charitable contributions;
- a delay of employer payroll taxes and taxes paid by certain corporations; and
- a variety of changes to the tax treatment of business income and net operating losses.

This is the latest in a series of legislative packages addressing the COVID-19 pandemic. Two bills have already been enacted into law: the Coronavirus Preparedness and Response Supplemental Appropriations Act, 2020 (P.L. 116-123) and the Families First Coronavirus Response Act (P.L. 116-127).

* This is an edited, reformatted and augmented version of Congressional Research Service, Publication No. R46279, dated March 20, 2020.

This report briefly summarizes the major provisions in Division B of S. 3548 (Table 1).¹ Links to CRS resources that offer additional information are provided. Provision summaries reflect the language in S. 3548 as introduced; legislative discussions concerning S. 3548 and other stimulus proposals are ongoing.

Table 1. Provisions in Division B of the CARES Act (S. 3548)

Provision	Description	CRS Resources
<i>Title I—Rebates and Other Individual Provisions</i>		
2020 recovery rebates for individuals	Credit against 2020 income taxes, but advanced, generally based on 2018 income tax returns. Credit equals the greater of (1) taxpayer's <i>net income tax liability</i> up to \$1,200 (\$2,400 for married joint filers). Net income tax liability is income tax liability <i>before</i> the child tax credit and refundable tax credits (like the EITC); or (2) \$600 (\$1,200 for married joint filers) if the taxpayer has <i>qualifying income</i> . To have qualifying income, taxpayer must have either (a) at least \$2,500 in total of earned income, social security income, or veterans' benefits, or (b) gross income above the taxpayer's standard deduction and \$1 of net income tax liability. Taxpayers eligible for the credit can also receive \$500 for each child eligible for the child credit. The total credit phases out at a rate of 5% of adjusted gross income (AGI) above \$75,000 (\$150,000 for married joint returns). All individuals must have social security numbers. Taxpayers must have filed a 2018 return (or file a 2019 return if they did not file a 2018 return) in order to get a rebate in 2020. Otherwise, it can be claimed on a 2020 income tax return.	For more, see • CRS Insight IN11255, <i>COVID-19 and Stimulus Payments to Individuals: How Did the 2008 Recovery Rebates Work?</i>, by Margot L. Crandall-Hollick. • CRS Insight IN11247, <i>COVID-19 and Stimulus Payments to Individuals: Considerations on Using Advanced Refundable Credits as Economic Stimulus</i>, by Margot L. Crandall-Hollick. • CRS Insight IN11256, <i>COVID-19 and Direct Payments to Individuals: Historical Precedents</i>, by Gene Falk. • CRS Insight IN11234, <i>Tax Cuts as Fiscal Stimulus: Comparing a Payroll Tax Cut to a One-Time Tax Rebate</i>, by Molly F. Sherlock and Donald J. Marples. • CRS Report RS21126, <i>Tax Cuts and Economic Stimulus: How Effective Are the Alternatives?</i>, by Jane G. Gravelle.
Delay of certain deadlines	Tax filing deadline extended from April 15, 2020, to July 15, 2020, to align with the extended payment deadline. a Allows individuals required to make estimated tax payments to postpone such payments until October 15, 2020.	For more on IRS administrative relief for tax filing deadlines following disasters, see • CRS Report R45864, <i>Tax Policy and Disaster Recovery</i>, by Molly F. Sherlock and Jennifer Teefy.
Special rules for use of retirement funds	For retirement plan distributions, the provision provides an exception to the 10% early withdrawal penalty for distributions up to \$100,000 for coronavirus-related purposes. Income from such distributions would be recognized over three years, and taxpayers can recontribute funds to an eligible retirement plan within three years without regard to the year's contribution cap. Loan limits from retirement plans are increased from \$50,000 to \$100,000 and repayment deadline is delayed.	For more on disaster-related special retirement fund access, see • CRS Report R45864, <i>Tax Policy and Disaster Recovery</i>, by Molly F. Sherlock and Jennifer Teefy. • CRS In Focus IF11447, <i>COVID-19: Social Insurance and Other Income-Support Options for Those Unable to Work</i>, coordinated by Laura Haltzel.

¹ Other tax-related provisions included in other divisions of the CARES Act, and not discussed in this report, include changes that would temporarily suspend excise taxes related to aviation; provide a temporary tax exemption for certain telehealth services; temporarily include certain over-the-counter medical costs as qualified medical expenses for tax purposes; extend the sequestration on direct spending by one year, to 2030; and temporarily provide advance refunding of payroll tax credits for sick leave and paid family leave. For more on the sick and family leave payroll tax credits, see CRS Insight IN11243, *Tax Credit for Paid Sick and Family Leave in the Families First Coronavirus Response Act (H.R. 6201) (Updated)*, by Molly F. Sherlock.

Provision	Description	CRS Resources
<i>Title I—Rebates and Other Individual Provisions</i>		
Allowance of partial above-the-line deduction for charitable contributions	An above-the-line deduction for cash contributions of up to \$300 is made available for taxpayers not itemizing deductions. This deduction would be allowed to taxpayers who do not itemize deductions.	For more on the tax treatment of charitable contributions, see - CRS Report R45922, <i>Tax Issues Relating to Charitable Contributions and Organizations</i>, by Jane G. Gravelle, Donald J. Marples, and Molly F. Sherlock. - CRS In Focus IF11022, <i>The Charitable Deduction for Individuals</i>, by Margot L. Crandall-Hollick and Molly F. Sherlock.
Modification of limitations on charitable contributions during 2020	Income limits apply to both individual and charitable contribution deductions. This provision would suspend the 50% of AGI limit on cash contributions for individuals for 2020. The corporate deduction limit would be increased from 10% of taxable income to 25% for cash contributions. The limit on the deduction of food inventory would be increased from 15% to 25%. The increased limits do not apply to contributions to private foundations and donor-advised funds.	For more on disaster-related changes in charitable giving limits, see - CRS Report R45864, <i>Tax Policy and Disaster Recovery</i>, by Molly F. Sherlock and Jennifer Teefy. For more on the tax treatment of charitable contributions, see - CRS Report R45922, <i>Tax Issues Relating to Charitable Contributions and Organizations</i>, by Jane G. Gravelle, Donald J. Marples, and Molly F. Sherlock. - CRS In Focus IF11022, <i>The Charitable Deduction for Individuals</i>, by Margot L. Crandall-Hollick and Molly F. Sherlock.
<i>Title II—Business Provisions</i>		
Delay of estimated tax payments for corporations	Corporations would be allowed to postpone estimated tax payments to October 15, 2020.	
Delay of payment of employer payroll taxes	Employers and self-employed individuals would be able to defer, or postpone, the employer share of the Social Security payroll tax. Deferred tax liability would be paid in two installments: one due by December 31, 2021, and the second by December 31, 2022. The Social Security trust funds would not be affected.	For more, see CRS Insight IN11260, <i>COVID-19 Economic Stimulus: Business Payroll Tax Cuts</i>, by Molly F. Sherlock and Donald J. Marples.
Modifications for net operating losses	The provision would allow carrybacks for up to five years for net operating losses (NOLs) recorded in tax years 2018, 2019, and 2020. NOL carryback capabilities were repealed by the 2017 tax revision (P.L. 115-97), and were previously allowed for up to two years. This provision would also temporarily lift the income limitation applicable to the corporate income tax treatment of NOLs under current law.	For more, see CRS Insight IN11240, <i>COVID-19: Potential Role of Net Operating Loss (NOL) Carrybacks in Addressing the Economic Effects</i>, by Mark P. Keightley.
Modification of limitation on losses for taxpayers other than corporations	This provision allows taxpayers not subject to the corporate income tax that incur NOLs, including pass-through businesses and sole proprietorships, to receive the temporary NOL carryback capabilities provided to corporations, as described above.	For more, see CRS Insight IN11240, <i>COVID-19: Potential Role of Net Operating Loss (NOL) Carrybacks in Addressing the Economic Effects</i>, by Mark P. Keightley.
Modification of credit for prior year minimum tax liability of corporations	The corporate alternative minimum tax (AMT) was repealed by the 2017 tax revision (P.L. 115-97). Corporations having AMT credits (for prior year AMT payments) were allowed to claim the credits against regular tax liability for tax years through 2021. This provision makes these credits refundable.	For more on the corporate AMT before its repeal, see CRS In Focus IF10705, <i>Tax Reform: The Alternative Minimum Tax</i>, by Donald J. Marples.

Table 1. (Continued)

Provision	Description	CRS Resources
<i>Title II—Business Provisions</i>		
Modification of limitation on business interest	The 2017 tax revision (P.L. 115-97) reduced the limit on the deduction for net interest from 50% to 30% of adjusted taxable income (income before taxes, interest deductions, and depreciation, amortization or depletion deductions). P.L. 115-97 also eliminated the rule that restricted net interest deduction limits to firms with a debt-to-equity ratio above 1.5. These revisions were adopted, in part, to reduce profit-shifting by multinational corporations (by borrowing in the United States). This provision increases the limit to 50% for 2019 and 2020.	For more, see CRS Report R45186, Issues in International Corporate Taxation: The 2017 Revision (P.L. 115-97), by Jane G. Gravelle and Donald J. Marples.
Technical amendments regarding qualified improvement property	The 2017 tax revision (P.L. 115-97) increased the period for deducting the cost of qualified improvement property (leasehold, restaurant, and retail property improvements) from 15 years to 39 years. This change was apparently a technical error that also prevented these investments from being expensed immediately (sometimes referred to as bonus depreciation). This provision allows these investments to be expensed.	For more, see CRS In Focus IF11187, Qualified Improvement Property and the 2017 Tax Revision (P.L. 115-97), by Gary Guenther.
Installments not to prevent credit or refund of overpayments or increase estimated taxes	As part of the transition to a new international tax regime under the 2017 tax revision (P.L. 115-97), firms were required to pay taxes on their prior untaxed foreign earnings (the repatriation tax). Firms could elect to pay these taxes in eight annual installments. Due to what was apparently a technical error, firms that overpaid their regular taxes in 2017 could not receive a refund if they owed taxes on repatriations. This provision allows firms to receive refunds for 2017.	For more, see CRS Report R45186, Issues in International Corporate Taxation: The 2017 Revision (P.L. 115-97), by Jane G. Gravelle and Donald J. Marples.
Restoration of limitation on downward attribution of stock ownership in applying constructive ownership rules	The 2017 tax revision (P.L. 115-97) treats stock owned by a foreign person as attributable to a U.S. entity owned by the foreign person (“downward attribution”). As a result, stock owned by a foreign person may generally be attributed to (1) a U.S. corporation, 10% of the value of the stock of which is owned, directly or indirectly, by the foreign person; (2) a U.S. partnership in which the foreign person is a partner; and (3) certain U.S. trusts if the foreign person is a beneficiary or, in certain circumstances, a grantor or a substantial owner. Downward attribution rules can result in additional tax to the U.S. entity under rules taxing certain income of controlled foreign corporations. This provision limits the application of the downward application rules to a U.S. corporation owning, directly or indirectly, 50% of the value of stock.	For more, see CRS Report R45186, Issues in International Corporate Taxation: The 2017 Revision (P.L. 115-97), by Jane G. Gravelle and Donald J. Marples.

Source: CRS analysis of the CARES Act (S. 3548, as Introduced).

- a. In guidance released on March 18, 2020, the U.S. Department of the Treasury announced that the tax payment deadline had been extended from April 15, 2020, to July 15, 2020. This guidance did not extend the April 15, 2020, filing deadline. See the U.S. Department of the Treasury’s March 18, 2020, press release, “Treasury and IRS Issue Guidance on Deferring Tax Payments Due to COVID-19 Outbreak,” at <https://home.treasury.gov/news/press-releases/sm948>. Subsequently, the Treasury announced via tweet that the tax filing deadline would also be moved to July 15, 2020.

Chapter 393

**OVERVIEW OF INITIAL RESPONSES TO COVID-19
BY THE ADMINISTRATIVE OFFICE OF U.S. COURTS
AND BY SELECT COURTS WITHIN THE
FEDERAL JUDICIARY***

Barry J. McMillion

This CRS Insight provides information related to initial responses to Coronavirus disease 2019, or COVID-19, by the Administrative Office of U.S. Courts and select courts within the federal judiciary. Consequently, this Insight is not intended to provide a comprehensive overview of the policies and practices adopted by each federal court or judicial entity. Additionally, given the rapidly changing situation surrounding COVID-19, the information provided in this Insight may be superseded by new information from that which is described in the text below. If there are any questions regarding whether such changes have occurred, congressional staff may contact the author of this Insight. The author can also be contacted for information related to responses to COVID-19 by other federal judicial entities or courts not specifically addressed below.

ADMINISTRATIVE OFFICE OF U.S. COURTS

The Administrative Office of U.S. Courts (AO) is the agency within the federal judiciary that provides, in part, administrative services and program support to federal courts. On March 12, 2020, the AO issued a statement indicating that federal courts were “individually coordinating with state and local health officials to obtain local information about the coronavirus (COVID-19).” The flexibility provided to federal courts to adapt to local

* This is an edited, reformatted and augmented version of Congressional Research Service Publication No. IN11252, dated March 18, 2020.

conditions is reflective of past practices during other recent emergencies (see, for example, the response by some courts to Hurricane Sandy in 2012).

The AO also created a task force to serve “as a single point of contact to share information and guidance related to the coronavirus outbreak as it relates to the Judiciary.” The taskforce includes, in part, representatives from the General Services Administration (GSA), the U.S. Marshals Service, and Federal Occupational Health (FOH).

UNITED STATES SUPREME COURT

On March 16, 2020, the Supreme Court announced that it is postponing all oral arguments scheduled for its March session (March 23-25 and March 30-April 1). The Court also announced that the building itself will continue to be open for official business but that it is “expanding remote working capabilities” to reduce the number of on-site Court employees. Previously, on March 12, 2020, the Court announced that its building was closed to the public until further notice.

U.S. DISTRICT COURTS IN WASHINGTON STATE

The first case of COVID-19 in the United States was identified in Washington State on January 21, 2020. At present, the state has the second-highest number of confirmed cases of COVID-19 in the United States, as well as the most deaths attributable to the virus. The Western District of Washington—with courthouses in Seattle and Tacoma—announced on March 6, 2020, that most in-court civil and criminal proceedings, including jury trials, are postponed until further court order. The Eastern District of Washington (with its headquarters in Spokane) announced on March 16, 2020, that it is cancelling naturalization ceremonies through April 30, 2020.

U.S. DISTRICT COURTS IN THE FIVE MOST POPULOUS JUDICIAL DISTRICTS

According to data compiled by CRS, the five most populous federal judicial districts are, in ascending order, the Central District of California, the Middle District of Florida, the Southern District of Texas, the Northern District of Illinois, and the District of New Jersey. These five judicial districts have a combined population of approximately 59.9 million, representing approximately 18.3% of the U.S. population (based on 2018 estimates by the Census Bureau).

Some of the initial responses by these five courts are highlighted below (the [hypertext link](#) for a particular court provides additional information regarding the court’s response). The actions taken by these courts are presented as illustrative examples, and may not be representative of actions taken by other courts.

- *Central District of California* (Los Angeles, Riverside, Santa Ana): The court has restricted entry to courthouses in the district, as well as access to its probation and pretrial services offices, for any individuals who have travelled to certain countries within the past 14 days. Additionally, the court has also issued an order that no jurors would be called for criminal or civil trials until April 13, 2020.
- *Middle District of Florida* (Orlando, Tampa, Jacksonville, Fort Myers, Ocala): The court has restricted entry to courthouses in the district for certain individuals, including those who have traveled within 14 days to or from certain countries. The bankruptcy court (a unit of the district court) has announced several changes, including that all non- evidentiary hearings will be conducted by telephone.
- *Southern District of Texas* (Houston, Galveston, Laredo, Corpus Christi, Brownsville, Victoria, McAllen): The court announced that civil and criminal jury trials in two of its seven divisions (covering the Houston and Galveston areas) are deferred through May 1, 2020. The court has otherwise emphasized that “other deadlines and settings remain in place pending further order by each judge in specific cases or by standing order.”
- *Northern District of Illinois* (Chicago, Rockford): The court has postponed all civil jury trials that were scheduled to begin before April 3, 2020, and extended deadlines in all federal civil cases in the district by 21 days from their current deadline. Additionally, criminal case proceedings that cannot be postponed will be conducted in Chicago only (not Rockford) by emergency district judges. Grand juries will continue to meet during the week of March 16, 2020, but “reasonable limits” will be placed on future meetings.
- *District of New Jersey* (entire state): On March 16, 2020, the court announced visitor restrictions covering individuals who have been diagnosed with COVID-19, asked to self-quarantine, or who have had close contact with someone who has been asked to self-quarantine. Additionally, on the same date, the court announced that all civil and criminal jury selections and jury trials scheduled to begin before April 30, 2020, are postponed pending further notice. The court has also encouraged all judicial officers to conduct proceedings by telephone or videoconferencing where practicable and permitted by law.

Chapter 394

OVERSIGHT PROVISIONS IN H.R. 6074, THE CORONAVIRUS PREPAREDNESS AND RESPONSE SUPPLEMENTAL APPROPRIATIONS ACT*

Ben Wilhelm

President Donald Trump signed H.R. 6074, the Coronavirus Preparedness and Response Supplemental Appropriations Act, on March 6, 2020. It provides a total of \$8.3 billion in supplemental funding to support the response of the United States to Coronavirus Disease 2019 (COVID-19).

Prior to the passage of H.R. 6074, Congress had already begun to oversee the federal government's response to COVID-19 with committee hearings in both the House and the Senate. Other committees are planning additional hearings in the coming weeks, and the Trump Administration has also been providing regular briefings.

This voluntary flow of information among Congress, senior Administration leaders, and frontline experts will facilitate Congress's response to COVID-19. If lines of communication remain open, voluntary information sharing may prove to be sufficient to meet Congress's needs and expectations for oversight. However, H.R. 6074 makes explicit a number of requirements regarding both the type and frequency of information Congress will receive.

H.R. 6074 appropriates significant funding for specific responses to COVID-19 and sets explicit requirements regarding how funds may be spent. The specificity of these conditions, as well as ongoing development of the outbreak, make it particularly important that Congress receive information in a timely manner. Even relatively short delays may prevent Congress from ensuring that the executive branch is following its instructions. The reporting requirements in H.R. 6074 are designed to improve the executive branch's ability to provide timely information to Congress.

This Insight details the oversight provisions included in H.R. 6074. CRS has produced several other written products related to COVID-19, some of which are linked at the bottom of this Insight. All CRS materials on the subject are available on CRS.gov.

* This is an edited, reformatted and augmented version of Congressional Research Service Publication No. IN11236, dated March 12, 2020.

CONSULTATION AND REPORTING REQUIREMENTS IN H.R. 6074

H.R. 6074 creates the following reporting requirements for entities receiving supplemental appropriations:

- Title III appropriates \$300 million to be transferred into the Infectious Disease Rapid Response Reserve Fund. If the Secretary of the Department of Health and Human Services (HHS) declares an infectious disease emergency and seeks to use the fund (as authorized by the third proviso of Section 231 of Division B of P.L. 115-245), the Secretary must, in consultation with the director of the Centers for Disease Control and Prevention, report to the Appropriations Committees every 14 days for one year from the date of the declaration “as long as such report[s] would detail obligations in excess of \$5,000,000” or upon the request of either committee.
- Title III also appropriates \$300 million to the HHS Public Health and Social Services Emergency Fund for the purchase of “vaccines, therapeutics, and diagnostics” to respond to COVID-19. In order to access these funds, the HHS Secretary must certify to the Appropriations Committees that the funds are necessary in addition to other funds appropriated in the bill.
- Section 302 authorizes the HHS Secretary to enter into personal services contracts to respond to COVID-19 following notification to the Appropriations Committees.
- Section 305 requires that the HHS Secretary provide to the Appropriations Committees a detailed spend plan for the funds appropriated to HHS no later than 30 days after enactment of the act (i.e., April 6). HHS is required to update the plan every 60 days until September 30, 2024. Each spend plan submission must also include a listing of all new contract obligations in excess of \$5 million and the amount of each of those obligations.
- Section 401 establishes that funds appropriated under Title IV of the act to the Department of State and United States Agency for International Development (USAID) are subject to the “regular notification procedures” of the Appropriations Committees. This requirement does not apply to \$300 million appropriated for International Disaster Assistance.
- Section 404 allows funds appropriated in the act for Global Health Programs and the Economic Support Fund to be contributed to international organizations following consultation with the Appropriations Committees.
- Section 406(a) requires the Secretary of State and the USAID administrator to submit a strategy to “prevent, prepare for, and respond to coronavirus abroad” to the Appropriations Committees within 15 days of the enactment of the act (i.e., March 21).
- Section 406(b) requires the Secretary of State and the USAID administrator to provide the Appropriations Committees a report on the proposed uses of appropriated funds by country and project no later than 30 days after enactment (i.e., April 6). It also requires updates every 60 days until September 30, 2022, and then every 180 days until all funds have been expended.

- Section 505 requires the comptroller general of United States to consult with the Appropriations Committees on the “oversight of activities supported with funds appropriated by this Act.”
- H.R. 6074 also includes several provisions amending existing transfer authorities and authorizing the transfer of funds between specified accounts, subject to notification of the Appropriations Committees.

SUPPLEMENTAL FUNDING FOR SELECT INSPECTORS GENERAL

A portion of the supplemental funding appropriated in H.R. 6074 is directed to the Offices of the Inspectors General for HHS and USAID. Section 306 provides for the transfer of up to \$2 million from the Public Health and Social Services Emergency Fund to the Office of the Inspector General for HHS.

The inspector general is required to consult with the Appropriations Committees prior to the obligation of funds regarding how such funds will be used.

H.R. 6074 also appropriates \$1 million to the Office of the Inspector General for USAID for the oversight of USAID activities funded by the act.

Chapter 395

H.R. 6201: PAID LEAVE AND UNEMPLOYMENT INSURANCE RESPONSES TO COVID-19*

Sarah A. Donovan, Julie M. Whittaker and Katelin P. Isaacs

ABSTRACT

This Insight provides summary information on the paid leave and unemployment insurance (UI) provisions in the House-passed version of H.R. 6201, the Families First Coronavirus Response Act, including the technical corrections made by H.Res. 904. For a general discussion of current workplace leave policies and UI programs and benefits, including considerations related to COVID-19, see CRS Insight IN11233, *Workplace Leave and Unemployment Insurance for Individuals Affected by COVID-19*. For additional legislation introduced related to UI and COVID-19, see CRS Report R45478, *Unemployment Insurance: Legislative Issues in the 116th Congress*.

PAID LEAVE PROVISIONS IN H.R. 6201

H.R. 6201, as amended by H.Res. 904 contains two paid leave provisions: (1) providing for paid family and medical leave in certain instances for needs related to a COVID-19 public health emergency and (2) providing for paid sick leave for a similar but more expansive set of needs. In terms of private-sector coverage, the provisions apply only to eligible employees who are employed by employers with fewer than 500 employees. The bill also includes tax credit provisions to help employers cover costs related to paid leave requirements; self-employed individuals, including gig workers, are similarly eligible for tax credits if they are unable to perform services in their trade or business for reasons discussed below.

Both provisions allow employers of health care providers and emergency responders to exclude such employees from the application of the leave provisions. Further, both provisions would allow the Secretary of Labor to issue regulations that (1) exclude certain health care

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workers and emergency responders from the leave provisions and (2) exempt employers with fewer than 50 employees from the requirement to provide leave when an employee's child's school or care facility is unavailable if it "would jeopardize the viability of the business as a going concern."

Both paid leave provisions would take effect no later than 15 days after the bill's enactment and expire on December 31, 2020.

DIVISION C — EMERGENCY FAMILY AND MEDICAL LEAVE EXPANSION ACT

H.R. 6201, as amended by H.Res. 904, proposes to temporarily extend Family and Medical Leave Act (FMLA) leave to include leave needed to care for the employee's minor child whose school or care provider is unavailable due to a COVID-19 public health emergency. Such FMLA-leave may be used by employees who have been employed by their current employer for at least 30 calendar days and work for a covered employer. Covered employers are private-sector employers employing fewer than 500 employees, and certain public agencies, including state and local governments.

The first 10 days of the new FMLA leave may be unpaid; although the employee may elect to use other paid leave during that period. Employers would be required to compensate employees for the remainder of FMLA-leave taken for qualifying public health emergencies (i.e., up to 10 work weeks) at two-thirds of their regular rate of pay. Such paid leave is capped at \$200 per day and \$10,000 total per employee.

FMLA leave is generally job-protected, but this requirement would not apply to employers with fewer than 25 employees if the employee used FMLA-leave for public health needs and certain conditions are met. Whereas FMLA provides that employees may seek damages or equitable relief for FMLA violations, 6201 provides that such liability would not apply to employers with fewer than 50 employees for violations related to FMLA-leave for a public health emergency.

DIVISION E — EMERGENCY PAID SICK LEAVE ACT

The bill would require covered employers to temporarily provide paid sick leave to employees to attend to certain COVID-19-related medical and caregiving needs if the employee is unable to work (including telework). Such needs include (1) the employee's self-isolation or quarantine in compliance with an official order or as advised by a health care provider due to concerns related to COVID-19; (2) to care for an individual subject to such an order or medical advice to self-isolation or quarantine; (3) to seek a medical diagnosis when the employee is experiencing COVID-19 symptoms; (4) to care for the employee's child, generally a minor child, whose school or care provider is unavailable due to a COVID-19 public health emergency; and (5) any other substantially similar condition specified by the Secretary of Health and Human Services in consultation with the Secretary of the Treasury and the Secretary of Labor.

Full-time employees would be entitled to 80 hours of paid sick leave, and part-time employees the equivalent of 2 weeks of leave. For leave taken for the employee's quarantine, self-isolation, or medical diagnosis, sick leave is compensated at the greater of the employee's regular rate of pay, the federal minimum wage, or the minimum wage rate in the applicable state or locality of employment; such paid leave is capped at \$511 per day and \$5,110 total per employee. For caregiving and other needs, the employer must compensate the employee at two-thirds of such a rate; such paid leave is capped at \$200 per day and \$2,000 total per employee. The provisions apply broadly to public-sector employers and to private-sector employers with fewer than 500 employees.

UNEMPLOYMENT INSURANCE PROVISIONS IN H.R. 6201

The UI provisions in Division D of H.R. 6201, which were not amended by H.Res. 904, would give states more flexibility to address COVID-19 through expanded benefit eligibility as well as additional administrative funding, among other UI measures. Unlike workplace leave policies, the UI system generally treats public-sector workers similarly to private-sector workers. UI benefits replace a proportion of wages for those workers who are temporarily or permanently separated from their jobs, but are otherwise able, available, and searching for work. Depending on state law, UI benefits may replace up to 60%-66% of total wages and are often subject to a benefit cap of half of the state's average weekly wage, although some states have lower benefit caps.

DIVISION D — EMERGENCY UNEMPLOYMENT INSURANCE STABILITY AND ACCESS ACT OF 2020

The UI provisions in Division D of H.R. 6201 would

- Provide \$1 billion in “emergency administrative grants” to states in calendar year 2020 for administrative purposes. Half of this amount would be available to all states who meet certain requirements related to Unemployment Compensation eligibility notifications and claims access. The second half of this amount would be available to states that experience at least a 10% increase in UC claims over the previous calendar year and meet certain other requirements related to easing UC eligibility requirements for individuals affected by COVID-19. There would be reporting requirements to U.S. Department of Labor (DOL) and committees of jurisdiction within one year for states that receive these grants.
- Waive any federal UI requirements related to work search, one-week waiting periods, quits for good cause, and employer tax assessments for state programs (i.e., under Section 303 of the Social Security Act and Federal Unemployment Tax Act [FUTA] Section 3304) if a state modifies its UC laws “on an emergency temporary basis as needed to respond to the spread of COVID-19.”

- Temporarily waive interest payments and the accrual of interest on federal advances (loans) to states to pay UC benefits through December 2020. However, these provisions would not reduce any underlying loan principal.
- Require DOL to provide assistance to states in establishing, implementing, and improving Short-Time Compensation (work sharing) programs.
- Temporarily make Extended Benefits (EB) 100% federally financed (under permanent law: 50% state, 50% federal) from enactment until the end of December 2020, but only for states that receive emergency administrative grants. This bill would also temporarily remove the current incentive in EB law for states to have a waiting week for their regular UC programs through December 2020.

Chapter 396

TAX CREDIT FOR PAID SICK AND FAMILY LEAVE IN THE FAMILIES FIRST CORONAVIRUS RESPONSE ACT (H.R. 6201) (UPDATED)*

Molly F. Sherlock

ABSTRACT

The Families First Coronavirus Response Act (H.R. 6201) includes an employer tax credit for the paid sick and family leave required as part of this legislation. This tax credit is intended to cover the cost to businesses of providing paid leave to address the coronavirus disease (COVID-19) pandemic. This Insight provides an overview of the tax credits, including the corrections included in H.Res. 904, as passed by the House on March 16, 2020.

TAX CREDITS FOR PAID LEAVE

The employer payroll tax credit is for wages paid to fulfill the new leave requirements. The Emergency Paid Sick Leave Act, Division E of H.R. 6201 as modified by H.Res. 904, generally requires private employers with fewer than 500 employees, and all government employers, to provide employees with two workweeks of paid sick leave for certain coronavirus-related leave purposes. The Emergency Family and Medical Leave Expansion Act, Division C of H.R. 6201, as modified by H.Res. 904, generally provides employees of private employers with fewer than 500 employees, state and local government employees, and some federal employees expanded job-protected Family and Medical Leave Act (FMLA) leave for certain caregiving responsibilities. Under certain conditions, this expanded family leave must be partially compensated by employers. For both sick and family leave, the bill

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includes provisions that may exclude health care providers, emergency responders, and employees in certain small businesses from leave requirements.

The legislation expands access to paid sick and family leave for employees at many small- and mid-sized businesses. Employees of large businesses, however, would not have guaranteed access to paid sick or family leave under this proposal.

Employer Payroll Tax Credit

The employer payroll tax credit is computed using wages paid, and claimed against the employer's share of the Social Security or railroad retirement payroll tax in each calendar quarter. The Social Security payroll tax rate is generally 12.4% of wages, with 6.2% paid by employers and 6.2% paid by employees. The Social Security payroll tax applies to workers' earnings up to an annual limit, \$137,700 in 2020.

Similar taxes are withheld for railroad employees. The Social Security trust fund will not be affected by the tax credit. A general fund transfer to the trust fund will offset the reduction in federal revenues from the tax credit.

The tax credit is refundable. If an employer's tax credits exceed its payroll tax liability, the excess can be received as a payment from the Treasury. Employers that claim this credit are required to include the amount claimed in gross income, for income tax purposes, offsetting the reduction in gross income from deducting wages paid (preventing a double benefit). Additionally, employers cannot claim this credit for any wages taken into account for the purposes of calculating the employer tax credit for paid family and medical leave. Employers may also elect not to have the credit apply. The credit does not apply to state or local governments. The tax credits can be claimed for a period to begin within 15 days following enactment, and ending December 31, 2020.

Sick Leave

Employers can claim a tax credit for 100% of the amount required to be paid in sick leave wages. Sick leave wages must be paid for up to 10 workdays for a full-time employee (prorated for part-time employees). The maximum amount that must be paid in sick leave depends on the purpose for which the sick leave is taken.

Sick leave wages cannot exceed \$511 per day for employees if they are taking leave because (1) the employee is subject to a federal, state, or local quarantine or isolation order related to COVID-19; (2) the employee has been advised by a health care provider to self-quarantine due to COVID-19; or (3) the employee is experiencing symptoms of COVID-19 and is seeking a medical diagnosis.

Sick leave wages cannot exceed \$200 per day for employees if they are taking leave because (A) the employee is caring for an individual described in number (1) or (2) above; (B) the employee is caring for their own minor child whose school, place of care, or caregiver is closed or unavailable due to COVID- 19; or (C) the employee is experiencing any other to-be-specified "substantially similar condition." The tax credit amounts for paid sick leave can be increased by the amount employers pay for an employee's health care plan while they are on leave.

Family Leave

The employer tax credit is for paid family leave, required for employees who take leave (are unable to work) because they must care for their own minor child whose school or place of care has been closed due to a COVID-19-related public health emergency.

The paid leave period for the purposes of the tax credit begins once an individual has taken 10 days of leave for the family leave purpose described above. These 10 days of leave may consist of unpaid leave, or an employee may elect to use paid vacation, personal, or another form of paid leave. After this 10-day period, employees will receive a benefit from their employers that is at least two-thirds of the employee's usual pay, but not more than \$200 per day. The tax credit for family leave wages is limited to \$200 per day, and \$10,000 total per employee. The tax credit amounts for paid family leave can be increased by the amount employers pay for an employee's health care plan while they are on leave.

TAX CREDIT FOR SELF-EMPLOYED INDIVIDUALS

Self-employed individuals, including gig workers, are eligible for tax credits similar to above. If individuals are unable to perform services in their trade or business for the sick leave purposes described above, the individual may qualify for an income tax credit equal to 100% of average daily self-employment income. Like the employer credits, this credit is limited to \$511 per day for certain qualifying sick leave purposes, and \$200 for other sick and qualified family leave purposes. The sick leave credit is limited to a maximum of 10 days. The family leave credit is limited to 50 days. For self-employed individuals, the income tax credit is refundable (meaning that if the tax credit amount exceeds the individual's income tax liability, the excess is received as a refund, or payment, from the Treasury). Like the employer tax credit, the tax credits for self-employed taxpayers can be claimed for a period to begin within 15 days of enactment, and ending December 31, 2020.

ISSUES AND CONSIDERATIONS FOR CONGRESS

The tax credit for required paid sick and family leave will largely offset the cost of providing such required leave in the Families First Coronavirus Response Act. The legislation mandates leave for employees of private-sector firms that employ fewer than 500 individuals. In 2019, 47.6% of employees worked in firms with fewer than 500 employees. The other 52.4% of employees worked in large firms, or firms with 500 or more employees. This legislation does not mandate sick leave for employees of these firms who may not have access to paid sick or family leave. Nor does it provide tax credits for these larger firms for providing leave. Some experts have expressed concern about this potential gap in coverage.

A refundable payroll tax credit will likely reduce the financial burden of providing required paid sick and family leave. The credit, however, does not necessarily encourage businesses to provide additional leave beyond what is required. Employees of large businesses in particular may be left without coverage.

Additionally, this credit is not designed to help businesses who have suffered lost business as a result of COVID-19.

Chapter 397

WORKPLACE LEAVE AND UNEMPLOYMENT INSURANCE FOR INDIVIDUALS AFFECTED BY COVID-19*

Julie M. Whittaker, Sarah A. Donovan and Katelin P. Isaacs

ABSTRACT

This Insight provides a brief overview of the current availability of job-connected assistance to individuals, which may be relevant to the outbreak of coronavirus disease 2019 (COVID-19).

Specifically, this product discusses workplace leave, paid and unpaid, that may be available to workers affected by the virus, as well as unemployment insurance (UI) benefits. It also discusses policy options to amend or expand existing UI programs to be more responsive to the effects of COVID-19.

WORKPLACE LEAVE

Workers affected by COVID-19 may seek to use paid or unpaid workplace leave for their own medical needs or to care for family members. Leave, even if unpaid, may be preferable to a complete separation from employment if it allows for continuation of health care benefits and facilitates the employee's return to work following recovery. Most federal civil service employees are entitled to paid sick and annual leave, but no federal law requires private-sector employers to provide paid leave of any kind.

* This is an edited, reformatted and augmented version of Congressional Research Service, Publication No. IN11233, dated March 16, 2020.

Family and Medical Leave Act

The Family and Medical Leave Act (FMLA) provides an entitlement to eligible workers to unpaid, job-protected leave for a limited set of family caregiving and medical needs, with continued group health plan coverage; eligible employees may use up to 12-workweeks of leave in a 12-month period. FMLA coverage and eligibility is not universal. Federal, state, and local governments are covered employers, but private-sector employers employing fewer than 50 employees are not. Employees of covered employers must also meet tenure, hours-of-service, and work-site coverage requirements before using FMLA-leave. No other federal law creates a leave entitlement for private-sector workers.

FMLA and COVID-19 Considerations

A key consideration is whether FMLA-leave can be claimed for COVID-19-related needs, such as testing, quarantine, treatment, and caregiving. In most instances, FMLA-leave for medical needs (the employee's own or a family member's) is limited to *serious health conditions*, which require overnight inpatient care or *continuing treatment* by a health care provider. Continuing treatment generally constitutes several days of incapacitation and multiple in-person treatments by a health care provider; a single in-person treatment may suffice if the employee is prescribed a regimen of continuing treatment (e.g., prescription medication). As such, hospitalization and, potentially, testing for COVID-19 may be FMLA-qualifying needs. However, a worker who tests positive for the virus and is sent home to rest and take over-the-counter medications is unlikely to qualify for FMLA-leave for the period of home recovery. Federal law and regulations do not provide for FMLA-leave to address general needs related to public health emergencies (e.g., school closures).

State Leave and Leave Insurance Laws

Some states have enacted family and medical leave laws (similar to FMLA) that entitle workers to unpaid leave in certain instances. In addition, five states currently operate state leave insurance programs, which provide cash benefits (a percentage of the employee's usual earnings, up to a maximum amount) to eligible workers who are absent from work for certain medical and caregiving reasons. As with FMLA, the extent to which state leave entitlements and leave insurance benefits may be claimed by COVID-19-affected workers will depend upon the worker meeting the criteria set out in state law.

Some states have paid sick leave or paid time-off laws that require covered employers to allow employees to accrue and use several days of leave per year. Paid sick leave can generally be used for the employee's own medical needs or to attend to the medical needs of certain family members. Some states, like New Jersey, allow that accrued sick leave may be used for workplace or school closures due to a public health emergency or because a public health official has determined that the employee should be quarantined.

Policy Options

As noted, the extent to which employees may use FMLA-leave for COVID-19 related needs is limited and must be assessed on a case-by-case basis. Congress may consider expanding FMLA-qualifying needs to include those related to a declared public health emergency or expanding the act's employer coverage (e.g., including some employers with fewer than 50 employees). Given the likelihood that such changes will complicate employers' scheduling and otherwise disrupt business activity, Congress may also consider pairing them with employer assistance (e.g., through state grants or tax credits to help cover the costs of hiring replacements for workers on leave).

THE FEDERAL-STATE UNEMPLOYMENT INSURANCE SYSTEM

Two programs within the federal-state unemployment insurance (UI) system may either respond to some types of unemployment caused by COVID-19 or could be modified to respond more broadly to provide weekly income replacement for individuals unavailable to work or unemployed as a result of COVID-19. Unlike workplace leave, the UI system generally treats public-sector workers similarly to private-sector workers. The National Association of State Workforce Agencies (NASWA) has published information provided by states on how they are dealing with workforce issues related to the impact of COVID-19 on their daily operations.

Unemployment Compensation

The joint federal-state Unemployment Compensation (UC) program provides income support through weekly UC benefit payments. Although there are broad requirements under federal law regarding UC benefits and financing, the specifics are set out under each state's laws. States administer state-funded UC benefits with U.S. Department of Labor (DOL) oversight, resulting in 53 different UC programs operated in the states, the District of Columbia, Puerto Rico, and the Virgin Islands.

To receive UC benefits, claimants must generally have been laid off through no fault of their own; have enough recent earnings (distributed over a specified period) to meet their state's requirements; and be able, available, and actively searching for work. The UC program generally does not provide UC benefits to the self-employed, those who are unable or unavailable to work, or those who do not have a recent earnings history.

UC and COVID-19 Considerations

Individuals who are laid off for COVID-19-related reasons would be subject to UC laws regarding benefit eligibility in the state where the previous work was performed. As described above, some categories of workers would not meet state eligibility requirements for UC benefits. Additionally, individuals who are unavailable for work due to COVID-19—whether they are quarantined or caregiving for sick or quarantined family members—may be ineligible for UC benefits because they may not meet state requirements regarding being able

and available for work. The DOL has recently issued guidance to states on how states may be able to interpret or alter state UC eligibility requirements to broaden these definitions if they choose to do so.

Disaster Unemployment Assistance

Disaster Unemployment Assistance (DUA), which is authorized under the Robert T. Stafford Disaster Relief and Emergency Assistance Act (the Stafford Act), provides federally funded unemployment benefits to individuals unable to work as a result of a federally declared major disaster and otherwise ineligible for regular UC benefits. For example, DUA benefits may be available to the self-employed and workers unable to reach their place of employment as a direct result of a major disaster, among other categories of DUA eligible employees.

DUA and COVID-19 Considerations

The current law definition of *major disaster* for the purposes of DUA, however, does not include a disease outbreak or other public health emergency. (No public health incident has ever been declared as “major disaster” under the Stafford Act.) Therefore, DUA benefits would not be available in response to unemployment or unavailability for employment related to COVID-19.

UI POLICY OPTIONS TO RESPOND TO COVID-19

Unlike some other federal or state programs, UC and DUA have the ability to rapidly respond and provide immediate income support. Thus, Congress may consider amending or expanding current unemployment benefits for individuals affected by COVID-19. For example, the DUA authority under the Stafford Act could be a model for responding to public health emergencies. More generally, in response to the 2007-2009 recession, UC benefits were temporarily augmented and extended, with some costs temporarily assumed by the federal government. For summaries of introduced COVID-19 UI legislation, see CRS Report R45478, *Unemployment Insurance: Legislative Issues in the 116th Congress*.

Chapter 398

COVID-19: SOCIAL INSURANCE AND OTHER INCOME-SUPPORT OPTIONS FOR THOSE UNABLE TO WORK*

***Laura Haltzel, Katelin P. Isaacs, William R. Morton,
Elizabeth A. Myers, Scott D. Szymendera and Julie M. Whittaker***

OVERVIEW

There is uncertainty about how the Coronavirus Disease 2019 (COVID-19) may spread in the United States; what measures federal, state, or local governments may take to mitigate the spread; and the possible effect on individual income security from both. This In Focus provides an overview of existing federal and state government social insurance programs or options that may be implemented relatively quickly to provide financial assistance for those unable to work due to COVID-19 from (1) their own illness; (2) exposure leading to quarantine; (3) illness of a close family member or school closures that may require long-term caregiving; or (4) unemployment resulting from business closures.

EXISTING SOCIAL INSURANCE PROGRAMS

Unemployment Compensation and Disaster Unemployment Assistance

The joint federal-state Unemployment Compensation (UC) program provides income support through UC benefit payments. Although there are broad requirements under federal law regarding UC benefits and financing, the specifics are set out under each state's laws. States administer state-funded UC benefits with U.S. Department of Labor (DOL) oversight,

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resulting in 53 different UC programs operated in the states, the District of Columbia, Puerto Rico, and the Virgin Islands. To receive UC benefits, claimants must generally have been laid off through no fault of their own; have enough recent earnings (distributed over a specified period) to meet their state's earnings requirements; and be able, available, and actively searching for work. The UC program generally does not provide UC benefits to the self-employed, those who are unable or unavailable to work, or those who do not have a recent earnings history. Individuals who are laid off for reasons related to COVID-19 would be subject to UC laws regarding benefit eligibility in the state where the previous work was performed. Individuals who are unavailable for work due to COVID-19 (e.g., because of a quarantine, or caregiving for sick or quarantined family members) may not meet state requirements regarding being able and available for work.

Disaster Unemployment Assistance (DUA) provides federally funded unemployment benefits to individuals who are unable to work as a result of a federally declared disaster and are otherwise ineligible for regular UC benefits; however, the current statutory definition of "major disaster" (42 U.S.C. § 5122[2]) for the purposes of DUA does not include a disease outbreak. Thus, DUA will not be available under current law in response to COVID-19.

Unlike some federal or state programs, UC and DUA have the ability to rapidly respond and provide immediate income support. Thus, Congress may consider amending or expanding current unemployment benefits for individuals unemployed due to COVID-19. For example, the DUA authority could be a model for responding to public health emergencies. More generally, in response to the 2007-2009 recession, UC benefits were temporarily augmented and extended, with some costs temporarily assumed by the federal government.

Workers' Compensation

Every state has a workers' compensation system that provides wage-replacement and medical benefits to persons who are injured, become ill, or die in the course of employment. There is no federal requirement that states have workers' compensation systems and no federal oversight of state workers' compensation systems. The federal government administers workers' compensation for federal employees under the Federal Employees' Compensation Act (FECA) and for longshore and harbor workers and several other groups of private-sector employees, such as overseas federal contractors, under the Longshore and Harbor Workers' Compensation Act (LHWCA).

Although the state programs and the FECA and LHWCA programs share similar features, each program operates under its own laws and regulations. However, nearly all private-sector workers in the United States are covered by some form of workers' compensation. Coverage of self-employed individuals and certain other classes of workers varies by program. The diffuse nature of workers' compensation makes it difficult to provide general information on how any given program would respond to cases of workers contracting COVID-19 in the workplace.

A worker who contracts COVID-19 as a direct result of his or her job, such as a healthcare worker who contracts COVID-19 after treating a patient, would likely be covered by workers' compensation and eligible for benefits.

However, a person who contracts COVID-19 through casual contact with a coworker or other person that happens to occur in the workplace may not be covered, as it could be argued that the risk of this person being exposed to COVID-19 was not related to, or peculiar to, the individual's job. Ultimately, such compensation decisions would have to be made by the specific workers' compensation programs and may vary across programs. Workers' compensation would not generally be expected to provide any benefits to a person who is unable to work because of a quarantine order unrelated to his or her employment.

State Temporary Disability Insurance and Medical Leave Insurance

Temporary Disability Insurance (TDI) and Medical Leave Insurance (MLI) are state-mandated insurance programs that provide time-limited cash benefits to qualified workers who generally are unable to work due to *nonoccupational* illnesses or injuries. Workers qualify for benefits by meeting minimum work or earnings requirements and, in most cases, by serving a nonpayable waiting period (usually one week). Benefits replace between 50% and 90% of a worker's pre-disability earnings (up to a maximum amount) and are provided for up to 12-52 weeks. Where available, state TDI/MLI programs cover nearly all private-sector workers and, in some cases, state and local government workers. Federal workers are not covered by TDI/MLI, and self-employed individuals may elect coverage in some states. Currently, TDI/MLI programs operate only in California, Hawaii, New Jersey, New York, Puerto Rico, Rhode Island, and Washington State.

In general, covered workers who meet the state's minimum work or earnings requirements (i.e., insured workers) qualify for TDI/MLI benefits if they become unable to work due to COVID-19 illness and satisfy the waiting period requirement (if any). However, insured workers who are quarantined due to COVID-19 but who are not ill may not qualify for TDI/MLI benefits unless the state specifically permits them to do so. Historically, the federal government has played no direct role in the operation of TDI/MLI programs, which are established and funded via state laws. That said, federal law permits states to withdraw *employee* contributions (if any) from the state's unemployment fund to finance TDI/MLI benefits. Congress could permit states to use *employer* UC contributions to finance benefits; however, this option would likely assist only those states with existing TDI/MLI programs.

OTHER INCOME SUPPORT OPTIONS

Access to Individual Retirement Accounts and Employer-Sponsored Defined Contribution Pensions

The Internal Revenue Code generally imposes a 10% penalty on retirement savings account withdrawals, including those from individual retirement accounts (IRAs) and employer-sponsored defined contribution plans (such as 401[k]s and the federal government's Thrift Savings Plan), that occur before the account owner reaches age 59½.

Under current law, certain circumstances that warrant withdrawals are exempted from the penalty, including unreimbursed medical expenses in excess of 7.5% of adjusted gross income (10% if under age 65).

While individuals may withdraw amounts from their IRAs for any reason, individuals with employer-sponsored plans are generally not permitted to withdraw funds except in the case of hardship. Plans may, but are not required to, offer hardship distributions and may choose which situations qualify. Safe harbor regulations automatically deem certain expenses as being due to hardship, or immediate and heavy financial need (26 C.F.R. §1.401[k]-1[d][3][B]), including certain medical expenses and expenses and losses incurred by the employee on account of a federally declared disaster.

Internal Revenue Service guidance could clarify whether COVID-19-related expenses (outside of direct health expenses) would be included as being withdrawn on account of hardship. Hardship distributions are subject to the 10% penalty unless they qualify for an exemption. In addition, some employer-sponsored plans permit employees to take out loans (up to a statutory maximum) from their retirement accounts.

In response to certain past federally declared disasters, Congress has waived the 10% penalty for withdrawals for disaster-related expenses. For example, a provision in Division Q of the Further Consolidated Appropriations Act, 2020 (P.L. 116-94) allowed for penalty-free distributions up to \$100,000 for individuals who lived in an area that had a major federally declared disaster from January 1, 2018, to 60 days after the enactment of the legislation on December 20, 2019. Congress could enact a similar penalty waiver provision, providing penalty relief for COVID-19-related retirement account withdrawals. In 2019, 36% of U.S. households had an IRA and 43% of civilian workers participated in an employer-sponsored defined contribution retirement plan.

Chapter 399

COVID-19 ECONOMIC STIMULUS: BUSINESS PAYROLL TAX CUTS*

Molly F. Sherlock and Donald J. Marples

The economic fallout from coronavirus disease (COVID-19) has accelerated rapidly. Policymakers continue to evaluate tax policy economic relief options. Payroll tax cuts for businesses are one option that would provide economic assistance to business activities.

BUSINESS PAYROLL TAXES

Payroll taxes are collected to finance certain entitlement programs, including Social Security, parts of Medicare, and Unemployment Compensation (UC). Social Security's old age, survivors, and disability insurance (OASDI) payroll tax is paid by both employers and employees, and it finances the Social Security trust funds. The tax equals 6.2% of wages on the taxable earnings base (\$137,700 in 2020). This tax is paid by both employers and employees (with self-employed individuals paying both the employer and the employee share, or 12.4%). The primary source of funding for Medicare Part A is a separate payroll tax paid by employers and employees. Each pays a tax of 1.45% on the employee's earnings; the self-employed pay 2.9%.

Employers typically deposit payroll taxes with the Internal Revenue Service semiweekly or monthly, and report employment taxes paid on quarterly federal tax returns filed no later than 30 days after the end of the calendar quarter. Some employers with small payrolls may file annually.

Employment payroll taxes generally are paid by all types of employers: businesses, nonprofits, and government employers. Thus, tax relief that is provided through payroll tax reductions may be available to nonprofits, which generally do not benefit from income tax reductions.

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If maintaining Social Security or Medicare Part A trust fund balances is a policy objective, these funds can be made whole through a transfer of general revenue. In this case, the revenue loss from a payroll tax cut would add to the deficit, but not decrease amounts available for Social Security or Medicare benefits. Temporary cuts to payroll taxes enacted in past recessions have protected trust funds from any impact in such a manner.

OPTIONS FOR PAYROLL TAX CUTS

There are a number of options for how to structure and implement payroll tax reductions. The Relief for Individuals, Families, and Businesses portion (i.e., Division B) of the Coronavirus Aid, Relief, and Economic Security (CARES) Act (S. 3548) proposes a payroll tax deferral for employers. Employers and self-employed individuals would be able to defer, or postpone, the employer share of the Social Security payroll tax. Deferred tax liability would be paid in two installments: one due by December 31, 2021, and the second by December 31, 2022. The Social Security trust funds would not be affected.

Another option is to provide a payroll tax rebate. This option would return 2020 payroll taxes already paid by employers. It could be targeted to small businesses, with small businesses identified using an employee threshold, a gross receipts threshold, or some other measure. A rebate could be capped at a fixed amount per employee, or given for a certain number of employees. A payroll tax rebate could also apply only to businesses who have been ordered by federal, state, or local government officials to cease operations due to COVID-19, or these types of businesses could be given a larger rebate. A payroll tax rebate payment could improve cash flow, helping businesses with limited financial resources. Depending on how the policy was designed, a portion of the lost federal revenue may also support employers whose business activities were unaffected by the COVID-19 economic shock.

A third option is to suspend business payroll taxes (provide a payroll tax holiday). The Trump Administration has expressed interest in this option. The business community has also expressed support for a payroll tax suspension. How long the payroll tax would be suspended is one policy choice. It could be suspended for three months, for the rest of the year, or for some other period of time. There is also the question of whether employee payroll tax collections would be suspended entirely or instead reduced by some amount (e.g., reduced by two percentage points). Suspending payroll taxes would reduce the cost of keeping employees on the payroll, and thus could promote worker retention. A payroll tax suspension only helps employers with paid employees; if an employer has already been forced to lay off its workforce, a payroll tax suspension will not provide financial assistance.

PAST EXPERIENCE AND POTENTIAL EFFECTIVENESS

Employer payroll tax cuts have been enacted in the past. The Hiring Incentives to Restore Employment (HIRE) Act of 2010 (P.L. 111-147), enacted during the Great Recession, suspended the employer's share of the 2010 payroll tax (6.2% of the worker's earnings) for qualified workers (generally unemployed individuals) hired between February 3, 2010, and January 1, 2011. The policy was estimated to reduce federal revenue by \$7.6 billion. One

difference between the past policy and the current proposals is that the past policy was intended to spur hiring; current proposals have the goal of preventing layoffs.

The provision's effectiveness will depend on how the additional cash flow is utilized. According to CBO models run during the Great Recession, an employer payroll tax reduction would provide a small incentive to increase employment or hours worked. The empirical literature generally agrees with the results from the CBO model, finding that during economic turmoil businesses are prone to favor holding cash or reducing debt over making investments (Eisfeldt and Muir 2016, Bolton, Chen and Wang 2013, and Dobridge 2016). The last study also found that the use of refunds to improve a firm's cash flow reduced the firm's bankruptcy risk and the probability of a future credit-ratings downgrade. One caveat to this empirical literature is that those studies examined a different cash flow incentive—net operating loss carrybacks—that would be equivalent to a payroll tax refund.

Chapter 400

TAX CUTS AND ECONOMIC STIMULUS: HOW EFFECTIVE ARE THE ALTERNATIVES?*

Jane G. Gravelle

SUMMARY

The economic effects of the COVID-19 pandemic may lead Congress to consider a general fiscal stimulus in the form of tax cuts. This report discusses tax cuts enacted during the previous recessions and their potential effectiveness.

In response to the Great Recession several types of tax cuts were debated as possible fiscal stimulus bills—with fiscal stimulus legislation enacted in February, 2008 (P.L. 110-185) and a much larger one in February 2009 (P.L. 111-5). Both bills included individual tax cuts aimed at lower- and middle-income individuals, along with business tax cuts. In December 2010, along with an extension of expiring tax cuts, a temporary payroll tax cut was adopted. Many, but not all, tax cuts that were expiring after 2012 were extended permanently.

A tax cut is more effective the greater the fraction of it that is spent. Empirical evidence suggests individual tax cuts will be more likely to be spent if they go to lower-income individuals, making the tax rebate for lower-income individuals likely more effective than several other tax cuts. There is some weak evidence that tax cuts received in a lump sum will have a smaller stimulative effect than those reflected in paychecks, but this evidence is uncertain. However, studies of the 2001 rebate found that a significant amount of that rebate was spent. While temporary individual tax cuts likely have smaller effects than permanent ones, temporary cuts contingent on spending (such as temporary investment subsidies or a sales tax holiday) are likely more effective than permanent cuts. (Sales tax holidays may, however, be very difficult to implement.) The effect of business tax cuts is uncertain, but likely small for tax cuts whose main effects are through cash flow.

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The economic effects of the COVID-19 pandemic may lead Congress to consider a general fiscal stimulus in the form of tax cuts. This report discusses tax cuts enacted during the previous recessions and their potential effectiveness.

Several tax cuts were discussed during consideration of fiscal stimulus in response to the Great Recession, and the specific proposal (the American Recovery and Reinvestment Act of 2009, P.L. 111-5). This stimulus as enacted included individual tax cuts directed at lower- and middle-income individuals and also included business tax cuts.

An earlier fiscal stimulus (P.L. 110-185) adopted in February 2008 included rebates and accelerated depreciation (bonus depreciation) for businesses. Some of these types of provisions were included in stimulus tax cut legislation in 2001-2003 and some of the debate centered on the effectiveness of alternatives. Among the tax cuts discussed in 2001 were tax rebates targeted towards lower-income individuals, a speed-up tax rate reductions for higher income individuals, a temporary sales tax holiday, a temporary payroll tax holiday, a temporary investment stimulus, corporate tax cuts (primarily repealing the alternative minimum tax), and dividend reductions. The 2001 tax cut included a rebate and the final version of the 2002 tax cut bill included a temporary investment stimulus. President Bush proposed accelerated rate cuts and dividend relief in his stimulus package for 2003. Proposals such as rebates were made by Democratic leaders. Although the economy recovered from the recession, issues of fiscal stimulus arose again in the 109th Congress in the wake of Hurricane Katrina. The tax stimulus enacted in response included rebates for both low and middle income individuals and temporary bonus depreciation for businesses.

In February of 2009, Congress passed a much larger package (P.L. 111-5), which included spending and tax cuts. Among tax cuts the single largest provision was a two-year refundable earnings credit, the making-work-pay credit, with a dollar cap that was provided through a change in withholding rather than a rebate. Other tax components target lower-income individuals and businesses. The business provisions included a bonus depreciation extension and a carryback of net operating losses. The legislation also extended the Alternative Minimum Tax, which tends to go to higher-income individuals.

In December of 2010, along with extending expiring tax cuts (which tended to benefit middle- and higher-income individuals) and unemployment benefits, P.L. 111-312 adopted a temporary two-percentage-point reduction in the payroll tax. As with the making-work-pay credit, its benefits were received in paychecks over time, and unlike the rebate or making-work-pay credit, was not targeted to lower- and middle-income families. Many, but not all, tax cuts that were expiring after 2012 were extended permanently. The payroll tax was not extended, and bonus depreciation was extended for a year.

Effectiveness of a tax cut for short run stimulus purposes is judged by the extent to which the tax cut increases private demand (either consumption or investment spending). A tax cut that is saved will have no short term stimulative economic effect (or long term one, if the cut is financed by a deficit, since increased private saving would be offset by decreased government saving). Thus, in general, tax cuts received by individuals will not be successful as a short run stimulus if they lead to additional saving, and tax cuts received by firms will not be successful unless they lead to spending on investment (or lead quickly to spending on consumption by shareholders).

The following four propositions can generally be supported by economic theory and empirical evidence:

- (1) Individual income tax cuts directed at lower-income individuals will likely have a larger effect than cuts directed at higher income individuals, other things equal. This distributional effect suggests that the most effective tax cut would be a rebate which is not only a flat amount but specifically directed at lower-income individuals (who did not have tax liability). While payroll and sales taxes are more concentrated among lower- and moderate-income individuals than the normal income tax, they are largely proportional taxes and the bulk of them will still go to middle- and higher-income individuals. Most income tax cuts actually exclude the bottom 44% of the population who do not pay income tax unless they are refundable (as with the February 2008 cut). Similarly, payroll tax cuts exclude 16% of the population who do not pay payroll taxes.¹ Tax reductions enacted in 2001 were concentrated among the upper part of the income distribution as are dividend and capital gains tax reduction. A flat dollar reduction, if refundable, would be more concentrated on lower and middle incomes than tax cuts that reduce rates or allow deductions.
- (2) There is weak empirical evidence that a lump sum tax cut is less likely to be spent than one received in small increments (e.g. through withholding). This effect could make a rebate less effective than alternative individual tax cuts if it were not for the distributional evidence. However, the distributional effect is more solidly grounded in economic theory, and is based on more concrete and extensive empirical evidence.
- (3) Certain types of temporary tax cuts are likely to be more effective than permanent ones while, in other cases, they are less effective. The most important illustration of this effect is a temporary investment subsidy, but it could also apply to a temporary sales tax holiday or any design where spending is required to obtain the subsidy and is for a limited duration. Otherwise, temporary cuts are likely to be less effective than permanent ones.
- (4) Corporate tax cuts that do not make new investments more profitable are unlikely to have much effect on investment or consumer spending, especially when the economy is in a recession, and the effect of corporate rate cuts is likely small.

The remainder of this report provides a summary of the evidence and economic reasoning supporting these propositions. Before discussing these propositions, however, it is important to note the differences between a model where individuals consume based primarily on current income compared to those where individuals consume primarily out of permanent (lifetime) income, because much of the empirical analysis focuses on this issue. Optimal lifetime consumption models imply that consumption is based on permanent income and suggest very little will be spent out of transitory income (because it has little effect on permanent income). Thus, a temporary tax cut, which is the normal mode of a fiscal stimulus, would be ineffective. Extensive empirical investigation has rejected this permanent income model in its pure form and suggests that consumption responds to permanent and current income.

¹ Philip Stallworth and Daniel Berger, "The TCJA Is Increasing The Share Of Households Paying No Federal Income Tax, Tax Policy Center," September 5, 2018, <https://www.taxpolicycenter.org/taxvox/tcja-increasing-share-households-paying-no-federal-income-tax>.

Proposition 1: A tax cut directed at lower-income individuals should have a larger effect on spending than one directed at higher-income individuals.

Data show that the fraction of income saved rises as income rises.² One study found that the savings rate for the top 1% was at least 300 times the average.³ Arraying families by wealth, another study found that the top 1% saved 37%, the next 9% saved 15%, and the bottom 90% saved 0%.⁴

This pattern is far too pronounced to be accounted for by business cycle reasons and cannot be explained by life cycle patterns and thus, itself implies a departure from the permanent income model of consumption.⁵ A saving rate that rises across incomes could be expected even in a permanent income model if each individual has the same permanent saving rate. At any time, some individuals may be earning lower than average amounts and others higher than average amounts. Thus the transitory income would understate permanent income in some cases and overstate it in others. Since more individuals with unusually low incomes would fall into the lower groups (and more with higher incomes into the high groups), some pattern of rising saving rates is expected. But empirically the effect is far too large to be explained by this phenomenon (which can be examined by looking at variations over time for an individual). A rising saving share with income could also arise from life cycle reasons. Typically income is low in the early years of life, rises during the working career and falls at retirement. If individuals want consumption to be smoother than income, they will save less when they are young and old and have lower incomes, and save more in the middle when they have higher incomes. However, when examining the data, we find that age does very little to explain saving behavior and the patterns of rising saving rates with income persist within age groups.

Aside from these empirical observations, there are theoretical reasons to expect that lower income individuals are likely to spend more of an additional dollar of income than do higher income individuals, especially in the case of a temporary tax cut, which is the kind of cut normally associated with fiscal stimulus. They may have a lower-lifetime saving rate because social welfare programs are likely to have a higher wage replacement rate during instances of bad luck (e.g. disability) or old age and because they are less likely to wish to leave bequests. Indeed, for some means-tested programs, assets can disqualify an individual from coverage. They may have less information with which to optimize over time and, if they save at all, simply have a target amount (at least in the short run), so that additional income is spent (including temporary income increases). Finally, they are more likely to be subject to

² This pattern can be found in data from the Bureau of Labor Statistics, Consumer Expenditure Survey, <https://www.bls.gov/cex/2018/combined/decile.pdf>, although there are a number of concerns about measurement in this survey, especially with respect to capturing high incomes or capturing all income. The bottom 10% had a negative savings rate of 4.3% and the second 10% had a 2.8% saving rate, whereas the top 10% had a 24.6% saving rate.

³ Rishabh Kumar, "Personal Savings from Top Incomes and Household Wealth Accumulation," *International Journal of Political Economy*, vol. 45, 2016, pp. 224-240.

⁴ Emmanuel Saez and Gabriel Zucman, "Wealth Inequality in the United States Since 1913," *Quarterly Journal of Economics*, vol. 131, iss. 2, May 2016, pp. 516-538.

⁵ See Martin Browning and Annamaria Lusardi, "Household Savings: Micro Theories and Micro Facts," *Journal of Economic Literature*, vol. 34 (December 1996); and John Sabelhaus and Jeff Groen, *Can Permanent Income Theory Explain Cross Section Consumption Patterns?*, Congressional Budget Office, Technical Paper 1997-3, July 1997. The general view that incentives directed at low-income individuals are more effective is reflected in different multipliers used by macroeconomic forecasters, as discussed in CRS Report R45780, *Fiscal Policy Considerations for the Next Recession*, by Mark P. Keightley.

liquidity constraints; that is, to prefer to spend more than their earnings and not be able to because they cannot borrow and have no assets. Indeed, permanent income theories suggest that for a temporary tax cut, tax cuts for non-liquidity constrained individuals may have virtually no effect, while tax cuts for liquidity constrained individuals will be largely spent.⁶

Proposition 2. A tax cut provided through a lump sum payment may be less likely to be spent than one which shows up in withholding, but the evidence is weak.

This differential effect (which would not occur in a permanent income model) was pointed out by the Congressional Budget Office (CBO) in its studies of the effectiveness of alternative tax cuts.⁷ CBO referred to a comparison of results from two studies that examined the effect of income tax refunds, and of expected rate cuts from pre-announced tax cuts of the early 1980s.⁸ Both studies rejected the permanent income model (suggesting some spending effects from a transitory tax cut), but larger effects were found for the rate reductions.

There are, however, two reservations about comparing these two events to gain insight into the effects of lump-sum tax cuts versus tax cuts reflected in paychecks over time. First, to the extent that individuals use over-withholding as a means of forcing themselves to save, one

⁶ An extensive literature has addressed these issues. They are related to the empirical rejection, by and large, that consumption is solely determined by permanent income, as occurs with rational, optimizing models of consumer behavior in perfect capital markets (as reviewed in Browning and Lusardi, cited above). These empirical tests generally find a smaller marginal propensity to consume than is indicated by long run, economy-wide savings rates, but nevertheless one far above zero. Some economists have suggested that heterogeneity among consumers is responsible, that is, that some individuals behave according to the rational optimizing model, while the consumption of others is closely affected by current income. There is evidence that liquidity constraints play an important role. In addition to the review in Brown and Lusardi, above, see N. Gregory Mankiw, "The Savers-Spenders Theory of Fiscal Policy," *American Economic Review*, vol. 90 (May 2000), pp. 120-125 for a review and an additional paper that finds support for liquidity constraint effects: Jonathan McCarthy, "Imperfect Insurance and Differing Propensities to Consume Across Individuals," *Journal of Monetary Economics*, vol. 36 (November 1995), pp. 301-327. However, positive results are not universally found including results in several recent studies (Nicholas Souleles, "The Response of Household Consumption to Income Tax Refunds," and Jonathan Parker, "The Reaction of Household Consumption to Predictable Changes in Social Security Taxes," both in the *American Economic Review*, vol. 89 (September 1999), pp. 947-958, and 959-973; Nicholas Souleles, "Consumer Response to the Reagan Tax Cuts," *Journal of Public Economics*, vol. 85, 2002, pp. 99-120). Studies that have not found effects, however, have generally excluded or under-represented low income individuals who are most likely to be liquidity constrained. In addition, the Souleles study may be flawed if overwithholding is used as a form of forced savings by low and moderate income individuals and the Parker study may be flawed if there are unmeasured seasonal differences in spending by wealth. In addition, in two studies examining individual responses to rebates (provided in 2001 and in 2008) evidence suggested that lower-income households spent more of their income. See David S. Johnson, Jonathan A. Parker, and Nicholas S. Souleles, "Household Expenditures and the Income Tax Rebate of 2001," *American Economic Review*, vol. 96, December 2006, pp. 1589-1610 and Jonathan Parker, Nicholas Souleles, David S. Johnson, and Robert McClelland, "Consumer Spending and the Economic Stimulus Payment of 2008," *American Economic Review*, vol. 103, no. 6, 2013, pp. 2530-2553. A study of the 2011 payroll tax cut using survey data that asked respondents about how they spent the tax cut found no differences between spending shares by income. See Grant Graziani, Wilbert van der Klaauw, and Basit Zadar, "Spending Response to the 2011 Payroll Tax Cuts," *American Economic Review*, vol. 8, no. 4, 2016, pp. 124-159. Parker and Souleles find, in their study of the 2008 rebate, that while answers to survey questions do not show a difference across incomes, inferences about actual spending do show a difference. See Jonathan A. Parker and Nicholas S. Souleles, "Reported Effects vs. Revealed Preference Estimates: Evidence from the Propensity to Spend Tax Rebates," *American Economic Review: Insights*, vol. 1, no. 3, pp. 273-290.

⁷ Congressional Budget Office, *Economic Stimulus: Evaluating Proposed Changes in Tax Policy, January 2002 and Options for Responding to Short-Term Economic Weakness*, January 2008.

⁸ See Nicholas Souleles, "The Response of Household Consumption to Income Tax Refunds," *American Economic Review*, vol. 89 (September 1999), pp. 947-958; and Nicholas Souleles, "Consumer Response to the Reagan Tax Cuts," forthcoming, *Journal of Public Economics*.

would not expect spending to rise when the refund is received, even though it might rise when an unplanned rebate is received. Thus, finding a smaller amount of spending out of a refund than out of tax cuts reflected in paychecks may not be very meaningful. Secondly, the model assumes that individuals were certain that the later phases of the Reagan tax cuts would be received. If there was some uncertainty, however, the fact that spending did not increase until the tax cut was actually received may partially reflect not the failure of the permanent income model, but the lack of certainty about receipt of the cut. If a differential does indeed exist, this effect could make the payroll tax cut (and sales tax holidays) more effective than a rebate. However, these “lump sum” effects would have to be offset by the distributional effects discussed in proposition I and supported by considerable empirical evidence. For that reason, it would be difficult to conclude that a payroll tax holiday would be more effective than a rebate directed at low income individuals. In addition, some evidence on the 2001 and 2008 tax rebates suggested that a large fraction of that rebate was spent.⁹ Evidence on the payroll tax cut in 2011 found a smaller share of that tax cut spent than the rebate, but that difference may reflect methodological and distributional differences or differences in economic conditions.¹⁰

Proposition 3. Certain types of temporary tax cuts may be more effective than permanent ones.

In general, the permanent income modeling of consumption, even when it does not hold in a pure form, suggests that temporary tax cuts will be less effective than permanent ones, presenting something of a dilemma because, tax cuts motivated for fiscal policy reasons need to be temporary (if they are not to hamper long term growth). However, temporary tax cuts that depend on spending (rather than receiving income) are likely to be more effective in the short run than permanent ones. During a period of slack employment, a payroll or individual income tax cut is simply a temporary windfall which can be spent at any time without any further consequence for the size of the tax cut. But if the tax benefit is triggered by spending, a temporary tax cut will be more effective (just as a temporary sale tends to induce a large response). The most common example is the investment tax credit or a similar subsidy, such as temporary partial expensing of investment, but the same would be true of a temporary sales

⁹ David Johnson, Jonathan Parker, and Nicholas S. Souleles, “Household Expenditures and the Income Tax Rebates of 2001,” *American Economic Review*, vol. 96, no. 5 (December 2006), pp. 1589-1610; Sumit Agarwal, Chunlin Liu, and Nicholas S. Souleles, “The Reaction of Consumer Spending and Debt to Tax Rebates: Evidence from Consumer Credit Data,” *Journal of Political Economy*, vol. 115, no. 6 (December 2007), pp. 986-1019; and Jonathan Parker, Nicholas Souleles, David S. Johnson, and Robert McClelland, “Consumer Spending and the Economic Stimulus Payment of 2008.” A recent survey of study of the 2009 income tax cut that would lead economists to predict a larger spending rate actually showed a smaller one on surveys. See Claudia R. Sahm, Matthew D. Shapiro, and Joel B. Slemrod, *Check in the Mail or More in the Paycheck: Does the Effectiveness of Fiscal Stimulus Depend on How it is Delivered?*, National Bureau of Economic Research Working paper 16246, July 2010, Joel B. Slemrod at <http://www-personal.umich.edu/~shapiro/papers/w16246.pdf>. This finding may simply reflect the lack of reliability of survey results, however. Parker, Souleles, Johnson and McClelland (cited above) found answers to survey questions to be poor predictors of response. In a subsequent study of the 2008 rebate, Parker and Souleles found survey responses related to statistical estimates of spending, but with higher responses from statistical evidence. They generally found a large fraction of the 2008 rebate to be spent with somewhat higher spending by lower-income households. See Jonathan A. Parker, Nicholas S. Souleles, “Reported Effects vs. Revealed Preference Estimates: Evidence from the Propensity to Spend Tax Rebates,” *American Economic Review: Insights*, vol. 1, no. 3, pp. 273-290.

¹⁰ Grant Graziani, Wilbert van der Klaauw, and Basit Zadar, “Spending Response to the 2011 Payroll Tax Cuts,” *American Economic Review*, vol. 8, no. 4, 2016, pp. 124-159. This study relied on survey data.

tax holiday. Although expensing of equipment is no longer an option (as 100% is currently allowed following the 2017 tax cut), investment credits would still be a possible investment incentive.

Note that while this feature may make a temporary tax cut more effective than a permanent one, it does not mean that the stimulus is more effective than other alternatives when all factors are considered. Most evidence suggests that investment subsidies have a small effect on investment and that the temporary investment subsidy enacted in 2006 was not very effective.¹¹ And, it may be particularly difficult to induce investment (even with a temporary subsidy) when excess capacity exists. While firms benefit from the temporary subsidy, they lose the benefit of delaying cash outlays. If investment is insensitive to these cost effects, a subsidy directed at increasing consumption may be more effective even if the latter is not the type where the temporary nature provides a benefit. In the case of the sales tax holiday versus other individual cuts, there may be a substantial implementation lag in arranging the sales tax holiday since sales taxes are imposed by the states, and fiscal stimulus may be applied at the wrong time. Moreover, the anticipation of the holiday should be contractionary. That is, a pre-announced future temporary spending subsidy is initially contractionary.

Proposition 4. Corporate tax cuts that do not make new investments more profitable would not have much effect; corporate rate cuts are less effective than investment subsidies.

One proposal considered in the past was a repeal of the corporate alternative minimum tax with a refund of existing credits. Such a change does not necessarily make new investment more profitable; indeed, it is possible that new investment may be subject to higher tax burdens under the regular rates than under the lower rates in the AMT. The corporate AMT was permanently repealed after the 2017 tax cut, but other measures of a similar nature might be considered. An extension of net operating loss (NOL) carrybacks was proposed in the 2009 stimulus package and would likely not make investments more profitable although a restoration of NOLs (which were eliminated in the 2017 tax cut, might be considered to aid businesses severely affected by COVID-19).¹²

Economic theory suggests that the investment decision should be driven by its expected profitability. A tax decrease not associated with that profitability should have no effect on investment. Rather, a tax decrease (which increases a firm's cash flow) is more likely to be spent on reducing debt, or paying out dividends. Both choices would not expand aggregate demand.¹³ Similarly, a corporate rate reduction, which largely benefits existing capital, would have modest effect compared to a stimulus directed at new investment. An extension of net

¹¹ See CRS Report RS22790, *Tax Cuts for Short-Run Economic Stimulus: Recent Experiences with Rebates and Bonus Depreciation*, coordinated by Jane G. Gravelle and CRS Report R43432, *Bonus Depreciation: Economic and Budgetary Issues*, by Jane G. Gravelle for a review of the evidence indicating that this investment incentive was not very effective. See also CRS Report R41034, *Business Investment and Employment Tax Incentives to Stimulate the Economy*, by Thomas L. Hungerford and Jane G. Gravelle (available upon request) for a broader comparison of business incentives.

¹² See CRS Insight IN11240, *COVID-19: Potential Role of Net Operating Loss (NOL) Carrybacks in Addressing the Economic Effects*, by Mark P. Keightley.

¹³ It is possible that knowledge of a tax cut could induce stockholder's consumption, or that cash flow translated into dividends would do so, but this effect is delayed and less certain than a direct tax benefit, as well as accruing to higher income individuals who are less likely to spend it.

operating loss carrybacks as proposed in the 2009 stimulus package would likely not make investments more profitable (although such a measure might be considered to aid businesses severely affected by COVID-19).

There is a potential constraint, however: if the firm does not have access to outside capital or finds outside capital excessively costly, cash flow might have an effect on investment. This effect would be likely, however, to be focused on small firms. There is some empirical evidence of a positive relationship between firm investment and cash flow. However, interpreting this evidence with respect to the effectiveness of a corporate cash flow as a stimulus to investment spending during an economic contraction is hampered by two important reservations. First, in most cases, cash flow is correlated with the productivity of investment and investment growth, and investment may be responding not to cash flow but to investment outlook. Secondly, even if there is some independent effect of cash flow in normal circumstances, then whether an increase in cash flow would induce a firm to make new investments during periods of excess capacity is doubtful.¹⁴ In any case, a choice that is more focused on investment (such as an investment subsidy) would have a more pronounced effect than one that is not. During the period of tight credit now being experienced a net operating loss carryback may have more effect because distressed firms are finding it more difficult to borrow.

General corporate rate cuts are less likely to be effective than investment subsidies because they have a smaller “bang-for-the-buck” because much of their cost is a windfall that only affects cash flow and not the return to new investment. Since even temporary investment subsidies do not appear to have worked effectively, a corporate rate cut or other provision that primarily affects cash flow would be expected to have a small effect.

¹⁴ For a survey of this issue, see R. Glenn Hubbard, “Capital Market Imperfections and Investment,” *Journal of Economic Literature*, vol. 36 (March 1998), pp. 193-225.

Chapter 401

PAYROLL TAX CUTS AS AN ECONOMIC STIMULUS RESPONSE TO CORONAVIRUS DISEASE (COVID-19)*

Donald J. Marples and Molly F. Sherlock

The current coronavirus disease (COVID-19) outbreak has increased concerns that the U.S. economy could be affected as part of a global economic downturn. A range of fiscal and monetary policy tools have been used to address prior times of economic weakness. One option for fiscal stimulus is a temporary payroll tax cut for employees. This option was used to address economic weakness in 2011 and 2012. On March 2, 2020, President Trump and others expressed interest in a one-year payroll tax cut to help bolster the economy.

WHAT ARE PAYROLL TAXES?

Payroll taxes are collected to finance certain entitlement programs, including Social Security, parts of Medicare, and Unemployment Compensation (UC). Social Security's old age, survivors, and disability insurance (OASDI) payroll tax is paid by eligible workers and their employers, and it finances the Social Security trust funds. The tax equals 6.2% of wages on the taxable earnings base (\$137,700 in 2020). This tax is paid by both employers and employees (with self-employed individuals paying both the employer and the employee share, or 12.4%).

STIMULUS EFFECTS OF A TEMPORARY REDUCTION IN PAYROLL TAXES

Short-term fiscal stimulus measures aim to boost economic activity primarily through increases in the demand for goods and services. The Congressional Budget Office (CBO), in

* This is an edited, reformatted and augmented version of Congressional Research Service Publication No. IN11230, dated March 5, 2020.

testimony before Congress, previously identified three key criteria commonly used to assess the stimulating effects of policy proposals: (1) timing, (2) cost-effectiveness, and (3) consistency with long-term fiscal objectives. The following sections evaluate a payroll tax rate reduction using these criteria.

Timing

To be effective, short-term stimulus should affect the economy while it is in a period of economic weakness. Although there is general agreement that the coronavirus will have dampening effects on the U.S. economy, there is substantial uncertainty regarding the magnitude of these effects. The Federal Reserve Federal Open Market Committee decision to lower the federal funds rate by half a percentage point is indicative of the risk the coronavirus poses to the economy. Many fundamentals of the U.S. economy, however, remain strong. Unemployment is at its lowest level since the 1960s, consumer spending is strong, and the economy remains in its longest period of economic expansion. Some Members of Congress and other commentators have expressed skepticism regarding fiscal stimulus in the form of a payroll tax cut as a coronavirus response. Others believe the situation warrants an immediate response that includes some form of fiscal stimulus. Relative to most other forms of fiscal stimulus, a payroll tax cut could be implemented relatively quickly. It could also be designed to expire as the economy strengthens.

Cost-Effectiveness

Effective short-term stimulus maximizes the increase in output and employment per dollar of budgetary cost. This is often colloquially referred to as the policy's "bang for the buck." Economists more often use the term *multiplier effect*. The multiplier effect of a fiscal policy depends on the fraction of additional income spent, as opposed to saved, on goods and services relative to the lost federal revenue. Provisions targeted at low-income individuals or the unemployed often are expected to be more cost-effective—have larger multiplier effects—than broad tax rate reductions, as those facing financial constraints are more likely to fully spend any additional disposable income.

Considering the source of the economic weakness can inform analysis of the likely effectiveness of a payroll tax cut. A payroll tax cut does not address supply-chain disruptions and might have limited effectiveness if the economy were positioned to snap back on its own after the shock—referred to as a "V-shaped" economic disruption. If, however, the coronavirus-induced economic slowdown leads to layoffs, reduced hours, or reduced consumer spending, a payroll tax cut could help offset reduced demand.

A 2015 CBO working paper presented data suggesting that multipliers vary according to the strength of the economy—with the smallest multipliers occurring when the economy is at or near full employment. A payroll tax cut enacted in a strong economy likely would have less "bang for the buck." Currently, the coronavirus does not appear to have caused widespread economic damage, and a statement from the G7 Finance Ministers and Central Bank Governors affirmed a readiness to respond if economic conditions deteriorate. As noted above, however, the situation is evolving.

Consistency with Long-Term Fiscal Objectives

Effective short-term stimulus should not hinder long-term fiscal sustainability. Any reduction in payroll taxes, by itself, adds to short-term budget deficits and could be at odds with the long-term goal of debt sustainability. This is a consideration given that the budget deficit and federal debt are higher than their historical averages, relative to the size of the economy.

To address long-term fiscal objectives, a temporary reduction in payroll taxes could include offsets to reduce or eliminate the net budgetary cost of the proposals. Offsets are, by definition, contractionary, as they either cut spending or raise taxes—though the timing of the offsets could be designed to apply their contractionary effects in later years.

In the past, the effect of payroll tax cuts on federal tax revenue has been substantial. The temporary payroll tax cut effective for 2011 reduced federal tax revenue by \$111.7 billion. The two-month extension for early 2012 reduced federal revenue by \$20.8 billion, and extending the payroll tax cut through the remainder of 2012 reduced federal revenue by \$93.2 billion. When payroll tax cuts were used as economic stimulus in 2011 and 2012, the Social Security trust fund was “made whole” by a transfer of general revenue.

Chapter 402

FEDERAL EXECUTIVE AGENCIES: HIRING FLEXIBILITIES FOR EMERGENCY SITUATIONS*

Barbara L. Schwemle

On January 31, 2020, Secretary of Health and Human Services Alex Azar declared a public health emergency for the United States in response to Coronavirus Disease 2019 (COVID-19). To assist the federal government in responding to the emergency, Congress passed legislation that provides Direct-Hire Authority (DHA) to the Department of Health and Human Services (HHS). The U.S. Office of Personnel Management (OPM) has also reiterated long-standing guidance on flexibilities for hiring in executive agencies that are codified in Title 5 of the *United States Code* and Title 5 of the *Code of Federal Regulations*.

DIRECT-HIRE AUTHORITY

Section 302 of P.L. 116-123 (H.R. 6074), the Coronavirus Preparedness and Response Supplemental Appropriations Act, 2020, as enacted on March 6, 2020, provides the HHS Secretary with DHA to appoint individuals to positions that perform critical work related to coronavirus. The law states that appointments may be made without regard to Title 5, Sections 3309-3319, of the *U.S. Code*, which prescribe veterans' preference requirements, requirements for rating and ranking applicants, and category rating procedures that increase the number of eligible candidates a selecting official may choose from. Still, public notice of positions the department seeks to fill would need to be given. And, the Secretary would need to determine that a public health threat exists.

Under Section 3304(a)(3), OPM may also authorize an agency to appoint candidates directly to positions without regard to Sections 3309-3318. The statute provides that public notice must be given for positions the agency seeks to fill. OPM would need to determine that there exists a severe shortage of candidates (for the Department of Veterans Affairs, there

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must be a severe shortage of highly qualified candidates) or that there is a critical hiring need. OPM regulations indicate that there is a severe shortage of candidates when “an agency is having difficulty identifying candidates possessing the competencies or the knowledge, skills, and abilities required to perform the job requirements despite extensive recruitment, extended announcement periods, and the use, as applicable, of hiring flexibilities such as recruitment or relocation incentives or special salary rates.” A critical hiring need occurs when “an agency has a need to fill the position(s) to meet mission requirements brought about by circumstances such as, but not limited to, a national emergency, threat, potential threat, environmental disaster, or unanticipated or unusual event or mission requirement, or to conform to the requirements of law, a Presidential directive or Administration initiative.”

The regulations also provide that OPM may decide independently that a severe shortage exists or that there is a critical hiring need or may make a decision about granting DHA in response to an agency’s written request. An agency with delegated examining authority may request DHA for a position or group of positions in the competitive service at pay grade GS-15 (or equivalent) and below. OPM determines the length of the authority. The regulations specify the evidence that must support an agency’s request. Periodically, OPM reviews DHAs and may extend them if the conditions justifying their use are continuing. DHAs may be terminated or modified when changes occur in the justifying conditions or when an agency does not use them properly. An agency must also report to OPM when there are adequate numbers of qualified candidates for positions filled by direct hire. (5 C.F.R. Part 337, Subpart B) OPM maintains a webpage with information on DHA, including templates for submitting direct-hire requests based on a severe shortage of candidates and critical hiring need.

GUIDANCE ON HIRING FLEXIBILITIES

On February 7, 2020, OPM issued guidance on human resources flexibilities for COVID-19 that included policies related to hiring. With regard to DHA authorities, OPM reminded agencies that direct hire is authorized government-wide for certain positions, including the following:

- Medical officers, nurses, diagnostic radiologic technicians, and pharmacists for all grade levels and locations;
- Information technology management (information security) for GS-9 and above at all locations;
- Veterinary medical officers for GS-11 through GS-15 nationwide, including overseas territories and commonwealths, indefinitely, until terminated;
- Scientific, technical, engineering and mathematics for GS-11 through GS-15 nationwide through October 10, 2023; and
- Cybersecurity-related positions for GS-12 through GS-15 nationwide, indefinitely, until terminated.

Individuals in the positions listed above may be appointed as competitive service career, career-conditional, term, or temporary employees. The guidance advised an agency to contact OPM “if it believes it has one or more occupations for which an agency-specific direct hire authority may be appropriate in support of relief and recovery efforts.”

Competitive service positions are civil service positions in the executive branch that are not specifically excepted from the competitive service by or under statute, positions to which appointments are made by nomination for confirmation by the Senate (unless the Senate otherwise directs), and positions in the Senior Executive Service (SES) (5 U.S.C. §2102(a)). Competitive service positions require applicants to compete against one another in open competition based on job-related criteria to obtain employment (5 C.F.R. Parts 212, 330, and 332).

Several long-standing hiring flexibilities available to federal agencies were identified by OPM in reiterating its guidance:

Excepted Service Appointment—Temporary Emergency Need (5 C.F.R. §213.3102(i)(3)). Agencies may appoint individuals for 30 days and may extend the appointment for up to an additional 30 days if continued employment is essential to the agency's operations. The same individual may not be employed for more than 60 days in a 12-month period. The agency determines the qualification requirements. The authority may be used to fill senior-level and lower-level positions. Excepted service positions are civil service positions that are not in the competitive service or the SES (5 U.S.C. §2103(a)). Qualification standards and requirements for these positions are established by the individual agencies. The Title 5 rules on appointment (except for veterans' preference), pay, and classification do not apply (5 C.F.R. Parts 213 and 302).

SES—Limited Appointments (5 C.F.R. Part 317, Subpart F). Agencies may appoint career employees to limited term or limited emergency appointments provided such appointments are within the space allocations limit previously authorized by OPM. If an appointment would not be within that limit, an agency may request a temporary space allocation. Agencies may request authority from OPM to appoint non-career employees to limited term or limited emergency appointments. A limited term appointee is an individual appointed under a nonrenewable appointment for a term of three years or less to an SES position the duties of which will expire at the end of such term. A limited emergency appointee is an individual appointed under a nonrenewable appointment, not to exceed 18 months, to an SES position established to meet a bona fide, unanticipated, urgent need (5 U.S.C. §3132(a)(5)(6)).

SES positions are classified above GS-15 or in level IV or V of the Executive Schedule, or an equivalent position, and are not filled by presidential appointment with the advice and consent of the Senate. SES members, among other duties, direct the work of an organizational unit and exercise important policymaking, policy-determining, or other executive functions (5 U.S.C. §3132(a)(2)) service firms to quickly provide specific services (but not for SES, managerial, or supervisory positions). A contract may be extended for an additional 120 workdays.

Individuals provided by temporary help service firms are not considered or treated as federal employees for any purpose.

Competitive Service Appointment—Temporary Appointments, 120 Days or Less (5 C.F.R. §330.609(c) and 5 C.F.R. §330.707(e)). Agencies may make appointments of 120 days or less without first selecting a surplus or displaced employee who is eligible for appointment under an Agency Career Transition Assistance Plan (CTAP) or an Interagency Career Transition Assistance Plan (ICTAP).

For appointments of longer duration, the CTAP and the ICTAP may be used to identify well-qualified displaced federal employees who are available for immediate employment (5 C.F.R. Part 330, Subparts F and G).

Reemployment Priority List (RPL) (5 C.F.R. Part 330, Subpart B). The RPL is used by agencies to give reemployment consideration to their current and former competitive service employees who will be, or were, separated by reduction in force or who are fully recovered from a compensable injury after more than one year (5C.F.R. §330.201). Agencies may use the RPL as a source of qualified individuals who are available for temporary appointments (generally, one year with up to one additional year), term appointments (more than one year but not more than four years), or permanent appointments in the competitive service. An agency may apply an exception to choosing someone from the RPL from the list of exceptions at Title 5, Section 330.211, of the *Code of Federal Regulations*.

Reemployed Annuitants [5 U.S.C. §8344(i), §8468(i)]. Agencies, without OPM approval, may reemploy retirees without applying the dual compensation salary offset, which prohibits federal retirees from getting the full combined value of their salary and annuity upon reemployment. Appointments are for one year or less.

Reemployed annuitants may work 520 hours during the first six months of retirement, 1,040 hours during any 12-month period, and 3,120 total hours during any period.

Authorization for a longer time period requires OPM approval. Reemployment may not exceed 2.5% of the full- time workforce at any time. An agency must explain and justify the reemployment if it exceeds 1% of the full-time workforce.

Reemploying Recipients of Voluntary Separation Incentives (commonly referred to as buyouts) (5 U.S.C. §5597 note). Upon agency request, OPM may authorize agencies to rehire federal employees who retired or separated with buyouts. Laws authorizing buyouts may have included a requirement that the buyout be repaid upon government reemployment. Agencies may request that OPM grant a waiver of any buyout repayment.

Chapter 403

SBA ECONOMIC INJURY DISASTER LOANS FOR COVID-19*

Bruce R. Lindsay

The current COVID-19 pandemic may have significant economic implications for businesses and nonprofit organizations, including negative impacts on imports, global supply chains, and tourism. Furthermore, if COVID-19 becomes increasingly widespread or prolonged it may slow global growth, and some businesses may be forced to furlough or lay off workers. One potential form of assistance to small businesses is Small Business Administration (SBA) economic injury disaster loans (EIDLs).

EIDL OVERVIEW

EIDLs provide eligible small businesses and nonprofit organizations up to \$2 million to help meet financial obligations and operating expenses that could have been met had the disaster not occurred. Loan proceeds can only be used for working capital necessary to enable the business or organization to alleviate the specific economic injury and resume normal operations. Interest rates for EIDLs are statutorily set at 4% per annum or less and can have maturities up to 30 years. Collateral is generally required for loans over \$25,000 if it is available, though SBA will not decline loans for a lack of collateral.

EIDLs are available only to businesses and private and nonprofit organizations that are located in a declared disaster area, have suffered substantial economic injury, are unable to obtain credit elsewhere, and are defined as small by SBA size regulations. Small businesses in declared counties (and contiguous counties) apply directly to the SBA for EIDLs.

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SBA DECLARATION ACTIVITY

On March 6, 2020, Congress signed into law P.L. 116-123. In addition to providing supplemental funding to several agencies, the act deemed the coronavirus disease (COVID-19) outbreak a declarable disaster under the Small Business Act. The amendment allows the Small Business Administrator to issue disaster declarations that make SBA EIDLs available to eligible small businesses.

On March 16, 2020, the SBA Administrator began issuing declarations for SBA EIDLs in response to states seeking SBA disaster assistance for small businesses. SBA EIDL declarations are not automatic, they must be requested by a state governor. Historically, to be eligible SBA has required a state or territory to “provide documentation certifying that at least five small businesses have suffered substantial economic injury as a result of the disaster, with at least one business located in each declared county/parish.” Under new criteria issued by the SBA, states/territories now “are only required to certify that at least five small businesses within the state/territory have suffered substantial economic injury, regardless of where the businesses are located.”

ADDITIONAL DECLARATIONS THAT TRIGGER SBA EIDLs

EIDLs may also be made available pursuant to a disaster declaration authorized by the SBA, based on a notification from the Secretary of Agriculture or the Secretary of Commerce, if a governor certifies that eligible small businesses have suffered substantial economic injury as a result of commercial fishery failures or fishery resource disasters.

The third type of declaration authorizing EIDLs is a major disaster declaration issued by the President under the Robert T. Stafford Disaster Relief and Emergency Assistance Act that authorizes both Individual Assistance (IA) and Public Assistance (PA). There is some debate whether an infectious disease outbreak could be considered a major disaster given that the list of incidents that explicitly qualify as a major disaster under the Stafford Act does not include outbreaks of infectious diseases. In the past some incidents were considered ineligible due to definitional reasons (such as the major disaster denial for the Flint water contamination incident). Moreover, the thresholds used to determine whether to provide IA and PA are based on damages to homes and public infrastructure. It is unclear how COVID-19 damages would be evaluated to determine whether a state warranted a major disaster declaration. The President, however, has stated that COVID-19 is of “such severity and magnitude nationwide that requests for a declaration of a major disaster ... may be appropriate” if requested by a state governor or tribal chief (tribal nations under the Stafford are entitled to the same types of assistance as a state).

It is important to note that the COVID19 emergency declarations issued on March 13, 2020, by the President, including the emergency declared under the Stafford Act, did not trigger SBA EIDLs.

Chapter 404

COVID-19 AND THE CRUISE SHIP INDUSTRY*

John Frittelli

The cruise ship industry has been heavily impacted by coronavirus disease 2019 (COVID-19). Major cruise lines have canceled trips from U.S. ports over the next month. In recent weeks, several cruise ships have been quarantined offshore and U.S. government health officials have advised against cruise ship travel for the time being. These events have raised questions about government oversight over the cruise industry, the potential economic harm the coronavirus could have on the industry, and whether the industry is largely America- or foreign-based.

EMPLOYMENT IN THE CRUISE SHIP INDUSTRY

While most of the major cruise lines are incorporated or otherwise domiciled in foreign countries, they have headquarters in the United States, with office staff who handle advertising, sales, bookings, and vessel planning. According to federal government data, Miami has the largest contingent of workers employed by the cruise industry (North American Industry Classification System code 483112), with Los Angeles and Washington State as secondary centers of employment. In terms of number of cruise ship port calls in 2018, Florida was the leading state with over 3,000 port calls, followed by Alaska with nearly 2,000, and California with over 500. Puerto Rico also had over 500 cruise ship port calls, and the U.S. Virgin Islands nearly 500. Ship chandlers are another significant employer in port areas, as they supply navigation-related parts and equipment as well as food, beverages, linens, and other passenger-related supplies.

Although U.S. nationals are employed in the “onshore” business segment of the cruise industry, in the offshore segment (aboard ships), foreign workers fill most positions. Almost all oceangoing cruise ships calling at U.S. ports are “foreign-flagged,” meaning they are registered in foreign countries, and particularly in “open-registry” countries such as Panama,

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Bermuda, Malta, the Bahamas, and the Marshall Islands. While U.S. law requires that passengers being transported from one U.S. point to another U.S. point be carried in only U.S.-built, -owned, and -crewed vessels, this law does not apply to cruise ship voyages that include foreign port calls or that embark and disembark passengers at the same dock. Plus, Puerto Rico and the U.S. Virgin Islands are exempt from this law. Open registries allow cruise ships to crew and staff their vessels with citizens other than from the registering country, and these registries generally assess lower fees and taxes. The Philippines is a popular home country for many ship crews, particularly sailors, engine room mechanics, and hotel and food service workers. U.S. nationals are more likely to be hired as entertainers on ships catering to American passengers. A cruise ship with thousands of passengers can have a staff and crew of several hundred or more on board.

FEDERAL OVERSIGHT OF CRUISE SHIPS

Three federal agencies have the most direct interaction with cruise ships when they call at a U.S. port: the Coast Guard, Customs and Border Protection (CBP), and the Centers for Disease Control and Prevention (CDC). The Coast Guard's authority is largely in the areas of safety, security, and pollution prevention with respect to the ships and their harbor transits. CBP's authority comes into play mostly once a ship is docked, and is centered around screening the arriving passengers. The CDC focuses on the sanitary condition of the ship.

Ships must report to the Coast Guard four days prior to arriving at a U.S. harbor. The Coast Guard can board and inspect a ship before entering the harbor, but usually inspections and boarding take place at the dock. Ship anchorage areas are designated in or outside harbors for ships ordered into quarantine (42U.S.C. 267, 33 C.F.R. §109.05(b)). For security reasons, the Coast Guard may escort a cruise ship in and out of a harbor, typically with a patrol boat (or boats). The Coast Guard "Captain of the Port" is the most senior Coast Guard official in a local port area, and has considerable discretion in making decisions related to the safety and security of harbor operations.

The Coast Guard inspects cruise ships for compliance with international safety, security, and pollution prevention standards established by the United Nations' International Maritime Organization (IMO), as well as those laws specific to the United States. Relevant IMO standards for safety and security include the Safety of Life at Sea (SOLAS) convention, the Standards of Training, Certification, and Watchkeeping for Seafarers (SCTW), and the International Ship and Port Facility Security (ISPS) Code. While the SCTW includes minimal requirements for medical-related training for some of the crew, the convention mostly concerns the training and qualifications of the navigation crew.

U.S.-specific law includes the Cruise Vessel Security and Safety Act of 2010 (P.L. 111-207). In response to concern over sexual assaults on cruise ships, this law requires cruise ships to have medical staff on board, to include either a physician or registered nurse, to attend to a victim of sexual assault (46 U.S.C. §3507(d)(3)(A)). The Coast Guard checks the qualifications of the medical staff during its boarding examinations. The cruise industry has issued medical staffing guidance that exceeds current U.S. law. Bills introduced in the 116th Congress would expand the medical staffing requirements for cruise ships (H.R. 5096, S. 3124).

Ships entering and departing U.S. ports must report to CBP before doing so. CBP screens cruise ship passengers essentially in the same manner that it does for arriving international air travelers.

CDC conducts sanitary inspections of cruise ships seeking to prevent gastrointestinal and other illnesses pursuant to the Public Health Service Act (42 U.S.C. §269). This inspection program began in the early 1970s. Cruise ships are subject to two unannounced CDC inspections per year. Cruise ships must report to CDC any sicknesses or deaths of crew or passengers that have occurred in the 15 days prior to a U.S. port arrival (42 C.F.R. §71.21). In their annual reports, cruise lines typically note disease outbreaks and concerns for the risk of illness as a risk factor for potential investors.

Chapter 405

THE FINANCIAL INDUSTRY AND CONSUMERS STRUGGLING TO PAY BILLS DURING THE COVID-19 (CORONAVIRUS) OUTBREAK*

Cheryl R. Cooper

A growing number of cases of Coronavirus Disease 2019 (COVID-19) have been identified in the United States, significantly impacting many communities. For background on the coronavirus, see CRS In Focus IF11421, *COVID-19: Global Implications and Responses*, by Sara M. Tharakan et al.

This outbreak may continue to cause disruptions as federal, state, and local governments limit public gatherings, close schools, and encourage workers to telework to contain the coronavirus's spread. While this situation is evolving rapidly, the economic impact may be large due to illnesses, quarantines, and other business disruptions.

Consequently, many Americans may lose income and face financial hardship due to the coronavirus outbreak. Some workers may need to take time off work if they or their families fall ill. In addition, layoffs or reduced hours may impact workers in particular industries affected by the outbreak, such as the travel, restaurant, and entertainment industries. To address these concerns, on Saturday, March 14, the House passed H.R. 6201, which, among other things, expands sick leave access, unemployment insurance, and food assistance benefits. Even if this bill is enacted, some families may continue to feel the economic impact. This Insight focuses on possible policy options relating to the financial services industry for consumers who may have trouble paying their bills due to the outbreak.

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PAYMENT RELIEF FOR CONSUMER LOANS

On Monday, March 9, federal and state financial regulators coordinated a statement to the financial industry, encouraging it to help meet the needs of consumers impacted by the coronavirus outbreak. They stated that “financial institutions should work constructively with borrowers and other consumers in affected communities,” and that “prudent efforts that are consistent with safe and sound lending practices” would not be criticized by regulators. This statement was similar to past statements by financial regulators during events such as natural disasters and government shutdowns. On Friday, March 13, the Office of the Comptroller of the Currency (OCC) and the Federal Deposit Insurance Corporation (FDIC) expanded on this statement with more detailed guidance for the institutions they regulate.

In addition, on Wednesday, March 11, the chairwoman and other members of the House Financial Services Committee sent a letter to financial services organizations “[urging them] to proactively help [their] customers who may be experiencing temporary financial hardship in making payments on their existing credit obligations as a result of this crisis.”

During past responses to natural disasters, government shutdowns, or other similar events, the financial industry has provided financial assistance to some impacted consumers. For example, they sometimes help consumers having trouble paying their mortgages, credit cards, or other loans due to temporary financial problems through forbearance plans, which are agreements that allow extended time for consumers to become current on their payments. Financial institutions also may agree to limit late or other fees and extend credit to ease consumer financial struggles amid the outbreak. However, some of these efforts may be more difficult for some institutions if they require changes in credit contracts.

Financial regulatory agencies might also consider employing other policy tools to encourage banks to provide this type of financial assistance. For example, bank regulators may award Community Reinvestment Act (CRA) credits after major disasters in adversely affected communities, even those where the bank does not primarily collect deposits. Regulator guidance under the CRA encourages banks during major disasters to meet customer cash and financial needs by waiving fees and penalties, deferring or skipping loan payments, or other related activities. In order to qualify, the federal government, through the Federal Emergency Management Agency (FEMA), must declare a “designated disaster area” (Category A or B). FEMA’s national emergency declaration on Friday, March 13, does not trigger this statute.

Although the coronavirus outbreak may be similar to these other events, making it consistent for the financial industry to provide assistance, it is also possible that this current outbreak may be more widespread than past events. Therefore, it might be more challenging for institutions to provide support alone. Some banks have recently announced measures they are taking to help assist impacted consumers. However, it remains unclear whether these efforts will be sufficient, particularly depending on how large the financial consequences of the outbreak become in the United States. For example, in Italy, which is currently one of the hardest hit countries in the world, mortgage payments generally have been suspended to help people during the crisis. However, this type of action may require direct government support to the financial industry, and other types of government policies outside of the financial industry might better target impacted Americans and be more appropriate given the economic situation.

OTHER POTENTIAL RESPONSES TO HELP CONSUMERS

Other policy options may be available to help consumers having trouble paying their bills during the coronavirus outbreak. For example, consumers can harm their credit scores when they miss consumer loan payments, which can impact their access to credit in the future. In this way, the credit reporting industry may be in a position to help affected consumers. During natural disasters, lenders have the ability to flag affected borrowers by using special comment codes when reporting to credit bureaus. A similar approach might be appropriate during the coronavirus outbreak. Encouraging lenders to furnish this information to credit bureaus could allow the credit reporting industry to limit the impact on affected consumers' credit scores and their future access to credit. Moreover, legislation could be considered to help prevent declining credit scores. However, it may be difficult to target this type of policy to the most impacted people, and, if the policy is too widespread, it may potentially harm the predictiveness of credit scores in the future.

Communication and financial education may also play an important role. Many consumers having trouble paying their bills may not realize that their financial institutions can provide loan forbearance, access to credit, or other assistance under extenuating circumstances. Financial institutions and government agencies such as the Bureau of Consumer Financial Protection (CFPB) may be able to conduct outreach to consumers to let them know about their possible options.

Chapter 406

FEDERAL RESERVE: RECENT ACTIONS IN RESPONSE TO COVID-19*

Marc Labonte

Coronavirus (COVID-19) has created significant economic disruption. In response, the Federal Reserve (Fed) has taken a number of steps to promote economic and financial stability involving the Fed's monetary policy and "lender of last resort" roles. Some of these actions are intended to stimulate economic activity by reducing interest rates and others are intended to provide liquidity to financial markets so that firms have access to needed funding.

ACTIONS TO LOWER INTEREST RATES

Federal Funds Rate

Traditionally, the Fed conducts monetary policy by changing the federal funds rate, the overnight interbank lending rate. In response to COVID-19, on March 3, the Fed reduced the federal funds rate from a range of 1.5%-1.75% to a range of 1%-1.25% to stimulate economic activity. On March 15, it reduced the range to 0%-0.25%. Economists refer to this as the "zero lower bound" to signify that the Fed's traditional monetary policy tool has been exhausted at this point, and cannot be used to provide additional stimulus. This is the second time this interest rate has ever hit the zero lower bound—the first time was in 2008, during the financial crisis.

At that time, the Fed developed two other tools to provide stimulus at the zero lower bound—forward guidance and quantitative easing. Both aim to reduce long-term interest rates which, unlike short-term rates, are not directly determined by the Fed, but are important for stimulating economic activity. These tools are being revived in response to COVID-19.

* This is an edited, reformatted and augmented version of a Congressional Research Service publication IN11259, prepared for Members and Committees of Congress dated March 20, 2020.

Forward Guidance

Forward guidance refers to Fed public communications on its future plans for short-term interest rates, and it took many forms following the 2008 financial crisis. As monetary policy returned to normal in recent years, forward guidance was phased out. It is being used again today. For example, when the Fed reduced short-term rates to zero on March 15, it announced that it “expects to maintain this target range until it is confident that the economy has weathered recent events and is on track to achieve its maximum employment and price stability goals.”

Quantitative Easing

Large-scale asset purchases, popularly referred to as *quantitative easing* or *QE*, were also used during the financial crisis. Under QE, the Fed expanded its balance sheet by purchasing Treasury securities and government-backed mortgage-related securities. Three rounds of QE from 2009 to 2014 increased the Fed’s securities holdings by \$3.7 trillion.

On March 15, the Fed announced that it would increase its Treasury securities holdings by at least \$500 billion and its mortgage-backed securities holdings by at least \$200 billion “over the coming months.” As a result, the value of the Fed’s balance sheet is projected to exceed its post-financial crisis peak of \$4.5 trillion. One notable difference from previous rounds of QE is that the Fed is purchasing securities of different maturities, so the effect likely will not be concentrated on long-term rates.

ACTIONS TO PROVIDE LIQUIDITY

Reserve Requirements

On March 15, the Fed announced that it was reducing reserve requirements—the amount of vault cash or deposits at the Fed that banks must hold against deposits—to zero for the first time ever. As the Fed noted in its announcement, because bank reserves are currently so abundant, reserve requirements “do not play a significant role” in monetary policy.

Term Repos

The Fed can temporarily provide liquidity to financial markets by lending cash through repurchase agreements (repos) with primary dealers (i.e., large government securities dealers who are market makers). Before the financial crisis, this was the Fed’s routine method for targeting the federal funds rate. Following the financial crisis, the Fed’s large balance sheet meant that repos were no longer needed, until they were revived in September 2019. On March 12, the Fed announced it would offer a three-month repo of \$500 billion and a one-month repo of \$500 billion on a weekly basis through the end of the month in addition to the

shorter-term repos it had already been offering. These repos would be larger and longer than those offered since September.

Discount Window

In its March 15 announcement, the Fed encouraged banks (insured depository institutions) to borrow from the Fed's discount window to meet their liquidity needs. This is the Fed's traditional tool in its "lender of last resort" function. The Fed also encouraged banks to use intraday credit available through the Fed's payment systems as a source of liquidity.

Foreign Central Bank Swap Lines

Both domestic and foreign commercial banks rely on short-term borrowing markets to access U.S. dollars needed to fund their operations and meet their cash flow needs. But in an environment of strained liquidity, only banks operating in the United States can access the discount window. Therefore, the Fed has standing "swap lines" with major foreign central banks to provide central banks with U.S. dollar funding that they can in turn lend to private banks in their jurisdictions. On March 15, the Fed reduced the cost of using those swap lines and on March 19 it extended swap lines to nine more central banks.

Emergency Credit Facilities for Nonbanks

In 2008, the Fed created a series of emergency credit facilities to support liquidity in the nonbank financial system. This extended the Fed's traditional role as lender of last resort from the banking system to the overall financial system for the first time since the Great Depression. To create these facilities, the Fed relied on its emergency lending authority (Section 13(3) of the Federal Reserve Act). To date, the Fed has resurrected three of those facilities in response to COVID-19.

- The commercial paper market is another important source of short-term credit for financial and nonfinancial companies. On March 17, the Fed revived the commercial paper funding facility (CPFF) to purchase commercial paper, offsetting a drop in private demand.
- Like banks, primary dealers are heavily reliant on short-term lending markets in their role as securities market makers. Unlike banks, they cannot access the discount window. On March 17, the Fed revived the primary dealer credit facility (PDCF), which is akin to a discount window for primary dealers. Like the discount window, it provides short-term, fully collateralized loans to primary dealers.
- On March 19, the Fed created the Money Market Mutual Fund Liquidity Facility (MMLF), similar to a facility created during the 2008 financial crisis. The MMLF makes loans to financial institutions to purchase assets that money market funds are selling to meet redemptions.

Although there were no losses from these facilities during the financial crisis, assets of the Treasury's Exchange Stabilization Fund have been pledged to backstop any losses on the CPFF and MMLF today.

Chapter 407

COVID-19 AND STIMULUS PAYMENTS TO INDIVIDUALS: CONSIDERATIONS ON USING ADVANCED REFUNDABLE CREDITS AS ECONOMIC STIMULUS*

Margot L. Crandall-Hollick

In response to concerns about an economic slowdown stemming from the COVID-19 pandemic, policymakers have been considering a broad array of policy options. Some are targeted directly toward the individuals and industries that may be most affected. Others would more broadly seek to stimulate the economy. Among this latter category of policies, some have suggested a payroll tax cut, while others have proposed direct cash payments—“recovery rebates”—to virtually all households. One mechanism to provide cash payments relatively quickly is to create a new refundable tax credit and then advance it to households before they would otherwise claim it on their income tax returns. A similar policy was enacted most recently in 2008. This Insight addresses some common questions about advanced refundable tax credits.

WHAT IS A REFUNDABLE TAX CREDIT?

Tax credits reduce income taxes owed dollar for dollar; each dollar in tax credit is a one-dollar subtraction from income tax liability. Nonrefundable credits are limited by the taxpayer’s income tax liability, while refundable credits are not. Hence, taxpayers with little to no income tax liability—including many low-income taxpayers—can benefit from refundable tax credits. Refundable tax credits targeted toward low-income individuals and families are estimated to have relatively large stimulative effects compared to other policies—

* This is an edited, reformatted and augmented version of Congressional Research Service Publication No. IN11247, dated March 17, 2020.

a large “bang for the buck”—because low-income populations tend to spend these amounts quickly. Some economists were concerned that the 2008 credit would not be effective because a lump-sum payment might be saved rather than spent. Empirical evidence based on studying a prior rebate found, however, that the rebate was largely spent.

Current refundable tax credits—the earned income tax credit (EITC) and the refundable portion of the child credit—benefit low-income families that include workers and children. These tax credits are received once a year when federal income tax returns are filed. Tax credit amounts are primarily based on the taxpayer’s earned income and number of qualifying children in the prior year (e.g., an EITC received in 2020 when 2019 tax returns are filed is based on 2019 income and family composition).

WHAT DOES “ADVANCING” A TAX CREDIT MEAN?

Advancing a tax credit effectively means issuing a tax credit for a given year before the tax return for that year has been filed (and before income taxes for that year have been calculated). The 2008 recovery rebates for individuals included in P.L. 110-185 were refundable tax credits against 2008 income taxes.

However, taxpayers did not need to wait to file their 2008 income tax returns in early 2009 to receive these credits. Instead, the law allowed the IRS to advance these credits in 2008, basing the advanced amount on income and family structure information from tax returns filed for the 2007 tax year. The credit equaled up to \$600 per person (\$1,200 for joint filers), with an additional \$300 per dependent child. Lower-income taxpayers tended to receive a smaller credit, while the credit phased out for taxpayers with incomes over \$75,000 (\$150,000 for married joint filers).

Advancing tax credits based on prior data can pose challenges if any of the parameters used to calculate the credit—like income and number of children—change from these prior values. For example, if a taxpayer’s 2019 income is significantly greater than their income at the end of 2020, an advanced credit estimated based on 2019 income may be larger than what a taxpayer is ultimately eligible for in 2020. (Even if an advanced payment is a fixed amount per person [does not vary by income], the final amount can still vary if family structure changes during the year.) This could result in taxpayers having to pay back the excess credit when they file their 2020 income tax returns (in early 2021). Insofar as this is a concern, policymakers can limit how much taxpayers have to pay back (for example, as is done with the advanced premium assistance tax credit), or they can bar repayments of excess advanced payments entirely, as was done with the 2008 recovery rebates.

HOW LONG WOULD IT TAKE FOR THE IRS TO BEGIN ISSUING ADVANCED CREDITS?

Past experiences with the IRS issuing advanced refundable tax credits may provide some guide on how long these policies take to implement. On January 28, 2008, H.R. 5140, which included the 2008 recovery rebates for individuals, was introduced in the House. Two weeks

later, on February 13, 2008, it was enacted as P.L. 110-185. Sixty-two days later, the IRS began issuing the first one-time rebate checks.

More than 120 million taxpayers received their payments by mid-July 2008. Taxpayers who had filed their 2007 tax returns and received a refund via direct deposit also received the 2008 recovery rebates via direct deposit. Otherwise, paper checks were mailed out to taxpayers using address information from 2007 income tax returns. A 2007 tax return had to be filed to receive a recovery rebate check. Those who did not receive a recovery rebate check could claim the benefit when filing a 2008 income tax return.

HOW MANY INDIVIDUALS COULD RECEIVE AN ADVANCED REFUNDABLE TAX CREDIT?

One concern that some have about using the federal tax system to administer direct cash payments to households is that not all individuals in the United States file income tax returns—either because their income is below the filing threshold or because they are not complying with federal tax laws. A 2017 CBO analysis estimated that of 292.6 million individuals who could be included on a federal income tax return (as the taxpayer, spouse, or dependent), 251.9 million were actually included—or 86%. The study estimated that the greatest share of nonfilers were lower-income individuals, especially those 65 years or older. As was noted above, the 2008 recovery rebate could be claimed by taxpayers who did not file a 2007 tax return. These nonfilers—which included many low-income individuals and seniors—could claim the credit on their 2008 returns when they filed them in 2009. The federal income tax system is limited in its ability to provide cash assistance to individuals quickly, particularly when those individuals are nonfilers.

Chapter 408

COVID-19 AND STIMULUS PAYMENTS TO INDIVIDUALS: SUMMARY OF THE 2020 RECOVERY REBATES IN THE CARES ACT (S. 3548)*

Margot L. Crandall-Hollick

ABSTRACT

The Coronavirus Aid, Relief, and Economic Security (CARES) Act (S. 3548) proposes direct payments of up to \$1,200 per person (\$2,400 for married taxpayers filing a joint tax return) and \$500 per child—“2020 recovery rebates.” Similar to the 2008 recovery rebates, these payments are structured as tax credits advanced to households that file an income tax return. Taxpayers that filed a 2018 income tax return would have this credit advanced to them in 2020, generally in the form of a direct deposit or check by mail. Thus, these taxpayers do not need to wait until 2020 tax returns are filed in 2021 to claim the credit. If they did not file a 2018 return, information from a 2019 return can be used for the advanced credit.

These payments are intended to broadly stimulate the economy in response to concerns about an economic slowdown stemming from the COVID-19 pandemic.

This Insight provides a brief overview of the proposed 2020 recovery rebates, with several simplified examples to illustrate payment amounts for different families.

CALCULATING THE CREDIT AMOUNT

The credit equals the *greater* of

1. the taxpayer’s *net income tax liability* up to \$1,200 (\$2,400 for married joint filers). Net income tax liability is the taxpayer’s income tax liability *before* the child tax credit and refundable tax credits (like the EITC); or

* This is an edited, reformatted and augmented version of Congressional Research Service, Publication No. IN11262, dated March 20, 2020.

2. \$600 (\$1,200 for married joint filers) if the taxpayer has *qualifying income*. For the purposes of the basic credit, qualifying income is either
 - a. at least \$2,500 of earned income, social security income, or veterans' benefits; or
 - b. gross income above the standard deduction and \$1 of net income tax liability.

All eligible taxpayers would receive the minimum basic credit of \$600 (\$1,200 married joint filers).

Taxpayers eligible for the credit can receive an additional \$500 for each child that qualifies for the child tax credit.

The total credit phases out at a rate of 5% of adjusted gross income (AGI) above \$75,000 (\$150,000 for married joint returns).

As with any tax refund, these payments would not count as income or resources in determining eligibility for, or the amount of, any federally funded public benefit program.

Lower-income taxpayers with little or no income tax liability would tend to receive a smaller credit, on average. Tax credit amounts rise for higher-income taxpayers, until the tax credit phases out at the upper end of the distribution. The distribution of the 2020 recovery rebates may be similar to that of the 2008 recovery rebates.

OTHER FEATURES OF THE PROPOSED 2020 RECOVERY REBATES

- **SSN requirement:** Taxpayers must provide social security numbers (SSNs) for themselves, their spouse (if married filing jointly), and any child for whom they claim the \$500 child credit. Adoption taxpayer ID numbers (ATINs) are also acceptable for adopted children. Taxpayers who provide an individual taxpayer identification number (ITIN) are ineligible for the credit. Hence, married couples in which one spouse has an SSN and another has an ITIN are ineligible for the credit.
- **Nonresident aliens:** The credit is not available to nonresident aliens.
- **Territories:** The law includes a provision requiring the U.S. Treasury to make payments to territories (mirror code and non-mirror code) equal to the aggregate amount of credits claimed by their residents.
- **Past-Due debts:** The credit cannot be reduced for certain unpaid debts, including debts owed to a federal agency (excluding child support), past-due state income taxes, and unemployment compensation debts.
- **Appropriations:** The bill appropriates \$396.45 million in FY2020 for the administration of these payments.

ADVANCING THE PROPOSED 2020 RECOVERY REBATES

The bill would advance the credit, which would be received as a direct deposit or a check by mail. Without this advancing provision, taxpayers would have to wait until they file their 2020 income tax returns in early 2021 to claim this credit.

The advanced credit amount is estimated using the same formula as the 2020 recovery rebates, but based on taxpayers' 2018 income tax return information (if the taxpayer did not file a 2018 income tax return, 2019 income tax return information could be used instead).

If, when taxpayers file their 2020 income tax returns in 2021, they find that the advanced credit is greater than the actual credit, they *would not* be required to repay the excess credit. In contrast, if the advanced credit is less than the actual credit, the taxpayer would be able to claim the difference on their 2020 income tax return.

SIMPLIFIED EXAMPLES OF 2020 REBATE AMOUNTS

The following examples illustrate the rebate amount received in 2020 using the taxpayer's 2018 tax return. These are simplified examples and assume the taxpayer files a 2018 return, meets all the eligibility criteria of the credit, and only claims the standard deduction and child credit and EITC (if eligible).

Income tax liabilities are estimated using TAXSIM.

Low-Income Disabled Individual with Only Supplemental Security Income (SSI)

In general, cash public assistance for low-income populations, such as SSI, is not considered gross income and is excludable from gross income under a limited general welfare exclusion. In addition—excluding social security retirement benefits (§ 86(d)) and veterans' benefits—cash public assistance for low-income populations would not be considered qualifying income as defined in this bill. So if SSI is the individual's only source of income, they would be ineligible for the rebate.

Low-Income Single Worker with \$10,000 of Earned Income

This individual has \$0 of net income tax liability prior to applying the EITC (actual liability after the EITC is -\$403). Because they have qualifying income (earned income above \$2,500), they would receive a \$600 rebate.

Low-Income Senior with \$15,000 of Social Security Income

This individual has \$0 net income tax liability (and \$0 in actual liability). Because they have qualifying income (social security benefits above \$2,500) they would receive a \$600 rebate.

Married Couple with Two Children and \$50,000 of Earned Income

The couple has \$2,739 in net income tax liability prior to applying the child credit and EITC (actual liability after these credits is \$1,575). They would receive a \$3,400 rebate (\$2,400 basic credit and \$500 for each child).

Married Couple with Two Children and \$200,000 of Earned Income

The couple has \$30,819 in net income tax liability prior to applying the child credit (actual liability after this credit is \$26,819). Before applying the phaseout, the rebate would be \$3,400. As a result of the phaseout, they would receive a rebate of \$900.

Chapter 409

COVID-19 AND STIMULUS PAYMENTS TO INDIVIDUALS: HOW THE 2009 ECONOMIC RECOVERY PAYMENT WORKED*

William R. Morton

In response to concerns about an economic slowdown due to the Coronavirus Disease 2019 (COVID-19) outbreak, some lawmakers have expressed interest in providing direct cash payments to Americans. One option to provide such payments would be to establish a new advanced refundable tax credit, as was done in 2008 with “recovery rebates.” Although this option would disburse payments to the vast majority of Americans relatively quickly, it would not directly help those who do not file a federal income tax return. A 2017 study found that “nonfilers” were more likely to be seniors or recipients of public assistance than those who filed a tax return.

To provide direct cash payments to nonfilers, lawmakers could consider providing such payments through existing programs for certain vulnerable populations. To assist lawmakers in assessing the merits of such a proposal, this Insight examines the 2009 Economic Recovery Payment (ERP), which was a one-time \$250 payment made to most individuals who received recurring cash benefits from the Social Security Administration (SSA), the Railroad Retirement Board (RRB), or the Department of Veterans Affairs (VA).

OVERVIEW

The ERP was established as part of the American Recovery and Reinvestment Act of 2009 (ARRA; P.L. 111-5). Section 2201 of ARRA provided a one-time payment of \$250 to the following groups:

* This is an edited, reformatted and augmented version of Congressional Research Service Publication No. IN11254, dated March 18, 2020.

- Adult Social Security beneficiaries;
- Supplemental Security Income (SSI) recipients of all ages;
- Adult railroad retirement annuitants; and
- Adult VA disability compensation or pension recipients.

The ERP was not available to dependent minor or student children who might otherwise receive benefits under Social Security, railroad retirement, or VA's programs, nor was it available to SSI recipients who received a personal needs allowance.

To qualify, an individual must have been eligible for benefits under one of the aforementioned programs for at least one month during the three-month period prior to ARRA's enactment (i.e., eligible for benefits between November 2008 and January 2009). Individuals were ineligible for the ERP if they resided outside of the United States or had their benefits suspended during the qualifying month prior to ARRA's enactment because they were (1) incarcerated, (2) a fugitive felon, (3) a probation or parole violator, (4) not lawfully present in the United States, or (5) found to have committed fraud.

Each eligible individual received the ERP. Thus, a married couple composed of two eligible individuals received \$500 in combined payments (\$250 each). However, ARRA specified that no eligible individual could receive more than one payment, even if he or she were eligible for benefits under multiple programs (e.g., Social Security and VA disability compensation). In addition, the ERP reduced the amount of the Making Work Pay tax credit, which was another stimulus measure in ARRA.

ARRA specified that the ERP was not subject to federal income tax, and it provided the ERP with certain garnishment protections, although the ERP was still subject to the Treasury Offset Program. ARRA also provided that the ERP could not be treated as income, or as a resource for the month of receipt and the following nine months, in determining the individual's eligibility or assistance amount under any federally funded public program. ERPs and administrative costs were financed by general revenues.

LEGISLATIVE HISTORY AND RATIONALE

The House version of ARRA would have provided for a one-time payment to SSI recipients equal to the average monthly SSI payment. In justifying the payment, Representative Carolyn Kilpatrick noted that ARRA "focuses on addressing the needs of those who need assistance most" and SSI recipients would be more likely to spend the payment quickly because they have "very low incomes."

The Senate version of ARRA would have set the one-time payment equal to \$300 and extended it to Social Security, RRB, and VA beneficiaries. Then-Senate Finance Committee chairman Max Baucus said the provisions in ARRA (including the one-time payment) were designed to "counteract weak consumer demand and spending slowdowns."

The conference agreement followed the Senate version but set the payment level at \$250. Representative Paul Kanjorski remarked that by providing the ERP to retirees and disabled individuals, the payment was designed to "help more people without jobs." Meanwhile, Senator Sheldon Whitehouse noted that the ERP provided "extra help from the Federal Government" for vulnerable seniors.

IMPLEMENTATION

ARRA required SSA, RRB, and VA to work with Treasury to coordinate and certify the eligibility of each ERP recipient. Administering agencies sent out notices to identified individuals in advance of receiving the ERP, as well as provided FAQs on their websites.

Treasury was required to start disbursing ERPs no later than 120 days (4 months) after enactment of ARRA (February 17, 2009), and no payments were to be made after 2010. Treasury disbursed most ERPs in May 2009, as well as a “catch-up” payment in December 2010 for individuals identified as eligible after the initial disbursement date (*Table 1*). SSA considered the May 2009 timeframe to be “a major accomplishment,” given the short statutory deadline for initial payments. Treasury ultimately issued more than 55.2 million ERPs, totaling over \$13.8 billion.

Table 1. Economic Recovery Payment (ERP) schedule

Milestone	Completion Date	Days Since Enactment of ARRA (Feb. 17, 2009)
First Social Security payments	05/07/2009	79
SSI payments	05/18/2009	90
Last Social Security payments	05/28/2009	100
RRB payments	05/29/2009	101
VA payments	06/30/2009	133
“Catch-up” payments	12/31/2010	682

Source: U.S. Department of the Treasury.

DISCUSSION

The congressional rationale for the ERP was twofold: (1) to provide assistance to certain vulnerable populations and (2) to stimulate economic activity through consumer spending. A 2012 study analyzed the answers to a 2009 household survey on certain stimulus measures created in 2008 and 2009. It found that most ERP recipients were aged 65 or older, had household income at or below \$35,000, and had little or no wealth in stocks. With respect to how recipients used the ERP, the study found that 30% mostly spent it, 29% mostly saved it, and 41% mostly paid down debt with it.

Chapter 410

COVID-19 AND STIMULUS PAYMENTS TO INDIVIDUALS: HOW DID THE 2008 RECOVERY REBATES WORK?*

Margot L. Crandall-Hollick

In response to concerns about an economic slowdown stemming from the COVID-19 pandemic, policymakers have been considering a broad array of policy options. Some are targeted directly toward individuals and industries that may be most affected. Others would more broadly seek to stimulate the economy. Among this latter category of policies, some have proposed direct cash payments sent to virtually all U.S. households.

In 2008 Congress enacted direct cash payments—the 2008 recovery rebates—that were tax credits advanced to households that had filed an income tax return. A portion of these credits were refundable and hence available to taxpayers with little to no income tax liability, including many low-income filers. (For answers to some common questions about advanced refundable tax credits, see CRS Insight IN11247).

This Insight provides a brief overview of how those 2008 recovery rebates worked.

2008 RECOVERY REBATES

On January 28, 2008, the House introduced H.R. 5140, which was enacted into law as P.L. 110-185 two weeks later. The law included 2008 recovery rebates for individuals that were credits against 2008 income taxes. The recovery rebate for a given taxpayer was equal to (1) a \$300-\$600 basic credit amount per individual, plus (2) an additional \$300 per-child credit amount. These credit amounts were phased out for higher-income taxpayers.

* This is an edited, reformatted and augmented version of Congressional Research Service Publication No. IN11255, dated March 19, 2020.

CALCULATING THE CREDIT AMOUNT

The basic credit was equal to the greater of the following:

- the taxpayer's *net income tax liability* up to \$600 (\$1,200 for married joint filers). Net income tax liability was effectively pre-EITC and pre-child tax credit income tax liability—or
- \$300 (\$600 for married joint filers) if the taxpayer had *qualifying income*. For the purposes of the basic credit, qualifying income was either (a) at least \$3,000 in total of some combination of earned income, social security income, or veterans' benefits, or (b) gross income above the taxpayer's standard deduction plus a personal exemption (two personal exemptions for married joint filers) and \$1 of net income tax liability.

The child credit was \$300 for each of the taxpayer's children that qualified for the permanent child tax credit. Taxpayers could only receive the supplementary child credit if they were eligible to receive the basic credit.

The total credit—basic credit plus child credit—was phased out at a rate of 5% of adjusted gross income (AGI) above \$75,000 (\$150,000 for married joint returns). Higher-income taxpayers not subject to the phaseout would tend to receive a larger basic credit, while lower-income taxpayers would tend to receive a smaller basic credit.

OTHER PROVISIONS OF THE 2008 RECOVERY REBATES

- *SSN Requirement*: Taxpayers had to provide social security numbers (SSN) for themselves, their spouse (if married filing jointly), and any child for whom they claimed the supplementary child credit. Taxpayers who provided an individual taxpayer identification number (ITIN) were ineligible for the credit.
- *Nonresident Aliens*: The credit was not available to nonresident aliens.
- *Territories*: The law included a provision requiring the U.S. Treasury to make payments to territories (mirror code and non-mirror code) equal to the aggregate amount of credits claimed by their residents.
- *Interaction with Means-Tested Programs*: 2008 recovery rebates were not included in income (for the month they were received and the following two months) in determining eligibility for, or the amount of, any federally funded public benefit program. (A similar provision is now permanent law for all refundable credits.)
- *Subject to Offset for Past-Due Debts*: All or part of an economic stimulus payment could be applied to back taxes or certain other debts of the taxpayer, such as delinquent child support and student loans.

ADVANCING THE 2008 RECOVERY REBATES

The law also included a provision to advance the credit during 2008. Without this advancing provision, taxpayers would have received the recovery rebates when they filed their 2008 income tax returns in early 2009.

The advanced credit amount was estimated using the same formula as the 2008 recovery rebates, but based on taxpayers' 2007 income tax return information. Hence, the IRS evaluated information on taxpayers' 2007 returns, determined the credit amount as described above, and began to advance the recovery rebate by the end of April 2008. Taxpayers that had filed their 2007 tax returns and received a refund via direct deposit also received the 2008 recovery rebates via direct deposit. (They also generally received their advanced recovery rebate within two weeks of payments going out.) Otherwise, paper checks were mailed out to taxpayers using address information collected from their 2007 income tax returns. In other words, taxpayers had to file a 2007 income tax return in order to receive the recovery rebate check in 2008.

However, taxpayers that did not receive the advanced credit, perhaps because they did not file a 2007 income tax return, could receive it when they filed their 2008 income tax return at the beginning of 2009.

According to the Treasury Inspector General for Tax Administration (TIGTA), "The IRS issued more than \$96 billion in advanced economic stimulus payments to more than 119 million individuals in Calendar Year 2008 and approximately \$8.5 billion in recovery rebate credits to almost 21 million taxpayers as of April 17, 2009."

If taxpayers received a larger advanced credit in 2008 than they were eligible for, they *were not* required to repay the excess credit. For example, if a single parent had \$600 in net income tax liability and one qualifying child in 2007, the IRS would advance the taxpayer a \$900 recovery rebate (\$600 basic credit plus the \$300 supplemental child credit). If, in 2008, the taxpayer's income tax liability remained the same, but their child actually ended up living with their ex-spouse—and therefore was not the taxpayer's qualifying child for the \$300 supplementary child credit in 2008—their actual recovery rebate would have been \$600, a \$300 difference. However, under the law, the taxpayer would not need to pay back this excess amount.

Chapter 411

COVID-19 AND STIMULUS PAYMENTS TO INDIVIDUALS: POTENTIAL IMPACTS OF DIRECT PAYMENTS ON FAMILY INCOMES*

Conor F. Boyle and Jameson A. Carter

Several Members of Congress and the Trump Administration have proposed direct cash payments as part of a fiscal response to the economic impacts of the COVID-19 pandemic. Direct cash payments have previously been part of the federal government's response to economic downturns, most recently in 2001 and 2008. In general, the purpose of direct payments is twofold: (1) they allow families to spend more, and through a multiplier effect help to stimulate the economy; and (2) they provide resources to help meet basic needs for those whose income has decreased due to COVID-19 infection or potential job loss. This Insight discusses several current direct payment proposals and their impact on family incomes.

WHAT DIRECT PAYMENT PROPOSALS ARE CURRENTLY BEING DISCUSSED?

Members of both parties, as well as the Trump Administration, have proposed some form of direct payments. These proposals vary in terms of who is eligible to receive a payment, the per-person amount to be paid, and whether payments would be one-time or recurring. Selected direct payment proposals include the following:

- a one-time payment of \$1,000 per adult proposed by Senator Romney,
- up to two payments of \$1,000 per adult and \$500 per child proposed by the Trump Administration, and

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- a proposal from Senators Bennet, Brown, Booker, King, Murphy, and Schatz to provide recurring payments of \$2,000 per individual (adult and child) that would gradually phase down as economic conditions improve.

When considering direct payment proposals, one question is how payments would be delivered to eligible Americans. In both 2001 and 2008, direct payments were provided as advance refundable tax credits received as a direct deposit or a check in the U.S. mail. Because these payments were made through the tax system, eligible individuals who did not file an income tax return the previous year did not receive a payment. In the past, the federal government has also provided additional direct payments to individuals who receive recurring benefits such as Social Security or pensions through the Department of Veterans Affairs. (Note that while some proposals may provide payments to taxpayers, this analysis is of families, which may include more than one taxpayer.)

HOW MUCH WOULD FAMILY INCOMES INCREASE DUE TO A DIRECT PAYMENT?

Policymakers may wish to consider the extent to which a direct payment could increase family income. To estimate the potential impact of a direct payment, CRS calculated the amount that families would receive under each of the three proposals noted above. CRS then compared the estimated benefit a family would receive to their estimated monthly income. *Table 1* presents families' median estimated monthly income and the median percentage of monthly income that families would receive under the direct payment proposals. These estimates are broken down by the ratio of family income to the poverty threshold in order to show the impacts of direct payment proposals across the income distribution.

The estimates presented in *Table 1* suggest that all three of the direct payment proposals would provide families with a substantial amount of their prior estimated monthly income. This effect is particularly strong for lower-income families. *Table 1* presents estimates at a high level, and does not convey variations in the impact of direct payments based on factors such as family size, family structure, and age.

These estimates should be considered with a number of caveats in mind. This analysis (1) assumes that every eligible family would receive exactly the benefit to which it is entitled, (2) does not phase down payments to higher-income families, (3) estimates monthly income using an annual measure and does not reflect potential month-to-month fluctuations in family income, and (4) does not estimate decreases in income that families may experience as a result of COVID-19.

Other analysis of direct payment proposals returns estimates that are similar to the ones presented in this analysis, but are methodologically different in several important ways. First, this analysis uses a broader definition of family income that includes additional sources of income and benefits. Second, this analysis breaks families into groups based on the ratio of family income to poverty rather than using deciles of taxable income. Finally, this analysis estimates *median* increases rather than average (or mean) increases in income.

Table 1. Median percentage of estimated monthly income families would receive under three proposed direct payments

Ratio of Family Income to Poverty	Median Estimated Monthly Income (current law)	Median Percentage of Estimated Monthly Income Families Would Receive if Payment is \$1,000 per Adult	Median Percentage of Estimated Monthly Income Families Would Receive if Payment is \$1,000 per Adult and \$500 per Child	Median Percentage of Estimated Monthly Income Families Would Receive if Payment is \$2,000 per Individual
Under 100% (below poverty)	\$850	137%	153%	337%
100%-199%	\$2,100	69%	80%	177%
200%-299%	\$3,570	44%	49%	105%
300%-399%	\$4,930	32%	36%	77%
400%-499%	\$6,240	26%	29%	60%
500% and above	\$10,440	16%	17%	36%
Total	\$3,600	42%	48%	104%

Source: CRS calculations via the TRIM3 microsimulation model using 2016 data.

Notes: Median estimated monthly income rounded to the nearest ten. Estimated monthly income was calculated by dividing families' annual income by 12. Income reported in this analysis reflects the Supplemental Poverty Measure (SPM) definition of income, and includes a family's after-tax wage income, self-employment income, the value of refundable tax credits, Social Security, Supplemental Security Income (SSI), Supplemental Nutrition Assistance Program (SNAP), assisted housing benefits, child care subsidies, and more. SPM poverty thresholds were used to calculate the ratios of family income to poverty.

WHAT ARE THE ALTERNATIVES TO DIRECT PAYMENTS?

Some commentators have noted that direct payments are not necessarily targeted at the families most impacted by COVID-19. Social insurance programs such as unemployment compensation, workers' compensation, and disability insurance are well established and may be more effective at targeting benefits to families impacted by the virus or an associated economic downturn. The Temporary Assistance for Needy Families (TANF) program has also been used in previous economic downturns to provide short-term benefits to families with immediate needs.

Chapter 412

COVID-19 AND DIRECT PAYMENTS TO INDIVIDUALS: HISTORICAL PRECEDENTS*

Gene Falk

ABSTRACT

Members of Congress and the Trump Administration have signaled their support for making direct payments to individuals to address the economic fallout from the COVID-19 outbreak. In current discussions, these payments are sometimes framed in terms of “universal basic income” or UBI proposals. In the past when these proposals were made—and sometimes enacted—they were framed in terms of providing economic stimulus.

HISTORICAL PRECEDENTS

There are historical precedents for such payments; most of these were done through the federal income tax code. The Internal Revenue Service (IRS) sent checks to taxpayers in 1975, 2001, and 2008. An issue with using the IRS to make payments to individuals is that payments generally have been restricted to those who file federal income tax returns. Those who do not file tax returns generally include populations such as retirees, disabled individuals, and low-income individuals who have no earnings. The 1975 legislation included direct payments to retirees receiving Social Security and Railroad Retirement. In 2009, direct payments were also made to retirees, recipients of Supplemental Security Income (SSI), and recipients of certain veterans’ benefits.

Table 1 provides an overview of laws enacted since 1975 that provided for one-time payments to individuals to address economic downturns.

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Table 1. Selected law providing direct payments to individuals: 1975 to present

Law	Description	CRS Products
Tax Reduction Act of 1975 (P.L. 94-12)	Tax rebate: 10% of taxes paid in 1974. Maximum payment of \$200 (phased down to \$100 for higher income taxpayers). Direct payment: \$50 for Social Security and Railroad Retirees and recipients of Supplemental Security Income (SSI).	CRS Report 92-20E (available to congressional clients upon request).
The Economic Growth and Tax Relief Reconciliation Act of 2001 (P.L. 107-16)	Advance payment of a tax rate reduction. Maximum credit of \$600 for married couples filing jointly and \$300 for others.	CRS Report RS21171, <i>The Rate Reduction Tax Credit - "The Tax Rebate" - in the Economic Growth and Tax Relief Reconciliation Act of 2001: A Brief Explanation</i>
Economic Stimulus Act of 2008 (P.L. 110-185)	Advance payment of a refundable tax credit. Maximum credit of \$1,200 for joint filers, \$600 for others, and an additional \$300 per dependent. Credits phased out for higher income taxpayers.	CRS Insight IN11255, <i>COVID-19 and Stimulus Payments to Individuals: How Did the 2008 Recovery Rebates Work?</i>
American Recovery and Reinvestment Act of 2009 (P.L. 111-5)	Payment of \$250 for certain recipients of Social Security, Supplemental Security Income (SSI), Railroad Retirement, and veterans' compensation or pensions.	CRS Insight IN11254, <i>COVID-19 and Stimulus Payments to Individuals: How the 2009 Economic Recovery Payment Worked.</i>

Source: Congressional Research Service (CRS).

The economic effects of past direct tax payments have been studied (see summaries here and here). Also see here for a discussion of how direct payments may compare with an alternative to provide payroll tax relief.

RELATIONSHIP TO UNIVERSAL BASIC INCOME AND AUTOMATIC PAYMENTS

The current discussions about these payments are sometimes framed as a “universal basic income” or UBI. UBI is a form of guaranteed income that would provide a payment to individuals or families at regular intervals. The United States does not have an income guarantee other than the Supplemental Security Income program (SSI), which is restricted to the needy aged, blind, and disabled. SSI was created in 1972 in legislation related to President Nixon’s proposal to create a guaranteed income for families with children, his Family Assistance Plan (FAP).

Social insurance benefits—particularly unemployment compensation—provides partial wage replacement for some workers who lose their jobs. Need-tested programs provide benefits to low-income individuals and families, though benefits are restricted to certain categories of low-income persons, and not all persons who are eligible receive aid. The programs that aid the largest number of low-income persons— the Supplemental Nutrition Assistance Program (SNAP) and Medicaid—provide in-kind rather than cash aid. Cash aid provides families and individuals with the greatest flexibility to address their individual circumstances, whether that is paying rent, bills, child care, or other necessities.

Prior to the current situation, Claudia Sahm, formerly an economist at the Federal Reserve Board, proposed in May 2019 automatic direct payment in the event of a recession. She proposed that direct payments be triggered by a rise in the unemployment rate by a sufficient amount.

Chapter 413

COVID-19: CYBERCRIME OPPORTUNITIES AND LAW ENFORCEMENT RESPONSE*

Kristin Finklea

Opportunistic criminals and other malicious actors exploit the internet and rapidly evolving technology to their advantage. Criminals can compromise financial assets; hacktivists can flood websites with traffic, effectively shutting them down; and spies can steal intellectual property and government secrets. And, they capitalize on ever changing world events. Federal officials have cautioned about scams relating to the outbreak of disease caused by a previously unidentified strain of coronavirus, designated Coronavirus Disease 2019, or COVID-19. They have noted that “[c]yber actors may send emails with malicious attachments or links to fraudulent websites to trick victims into revealing sensitive information or donating to fraudulent charities or causes.”

Indeed, analysts and officials have reported criminals using public interest in COVID-19 to their advantage. For instance, the Department of Justice (DOJ) cites “reports of individuals and businesses selling fake cures for COVID-19 online and engaging in other forms of fraud, reports of phishing emails from entities posing as the World Health Organization or the Centers for Disease Control and Prevention, and reports of malware being inserted onto mobile apps designed to track the spread of the virus.” In one scheme reported by security experts, hackers sold a malware infection kit that used an interactive map of coronavirus infections produced by Johns Hopkins University. The kit was designed to spread malware to steal passwords.

CYBERCRIME INVESTIGATIONS

Federal law enforcement has the principal role in investigating and attributing cyber incidents, including those that may take advantage of heightened public interest in the

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COVID-19 pandemic, to specific perpetrators, and this responsibility has been codified within the broader framework of federal cyber incident response. Specifically, DOJ—through the Federal Bureau of Investigation (FBI) and National Cyber Investigative Joint Task Force (NCIJTF)—is the designated lead in responding to these threats.

FBI Cyber Investigations

The FBI pursues cybercrime cases ranging from computer hacking and intellectual property rights violations to child exploitation, fraud, and identity theft. Its top cyber priorities involve combating computer and network intrusions and investigating ransomware. The FBI's cyber efforts are focused on “high-level intrusions by state-sponsored hackers, global organized crime syndicates, and other technically sophisticated and dangerous actors.”

One key challenge involves moving away from reacting to malicious cyber events and toward preventing them. As such, the FBI has focused resources on enhancing cyber capabilities in a number of ways, including bolstering the FBI's cyber workforce, strengthening the NCIJTF, expanding Cyber Task Forces (CTFs) and focusing their efforts on computer/network intrusion investigations, and increasing information sharing and coordination with the private sector.

Task Forces and Partnerships

The NCIJTF was established by National Security Presidential Directive-54/Homeland Security Presidential Directive-23 in January 2008. The NCIJTF's mission is to “serve as a multi-agency national focal point for coordinating, integrating, and sharing pertinent information related to cyber threat investigations.” Led by the FBI, the NCIJTF coordinates over 20 federal agencies, including law enforcement, intelligence, and the military. It also collaborates with the private sector and international partners. Early on, there were concerns that “the NCIJTF was not always sharing information about cyber threats among the partner agencies.” There were also criticisms that the NCIJTF was perceived as an extension of the FBI's Cyber Division instead of as a multiagency effort. However, DOJ's Inspector General has since noted that these issues have improved.

The FBI leads several other task forces and partnerships focused on cyber threat response. For instance, there is a CTF at each field office. CTFs focus on local cybersecurity threats, respond to incidents, and maintain relationships with companies and institutions. CTFs also support the national effort to combat cybercrime by participating in national virtual teams on certain cyber issues and providing cyber subject matter experts or enhanced capability outside of their assigned areas, when needed. Additionally, the FBI has established and maintained Cyber Action Teams of agents and computer scientists that can be rapidly deployed around the world to assist in computer intrusion investigations. In addition to domestic field offices pursuing international leads in investigations, the FBI has positioned cyber assistant legal attachés (ALATs) in some foreign countries. ALATs work with law enforcement in host countries to share information, collaborate on investigations, and enhance

relationships with partner agencies. ALATs focus on “identifying, disrupting, and dismantling cyber threat actors and organizations.”

GOING FORWARD: DOJ CYBER PRIORITIES

Countering cyber threats is among DOJ’s top priorities, and countering threats related to the COVID-19 pandemic is receiving heightened attention. On March 16, 2020, Attorney General William Barr issued a memorandum to the U.S. Attorneys regarding DOJ’s COVID-19 priorities. Noting that criminals may take advantage of the COVID-19 pandemic, the memorandum stated that “[e]very U.S. Attorney’s Office is thus hereby directed to prioritize the detection, investigation, and prosecution of all criminal conduct related to the current pandemic.” Congress, in examining DOJ’s cyber priorities going forward, may look to the resources DOJ has placed toward countering cyber threats broadly as well as specific nefarious activity capitalizing on the COVID-19 pandemic.

DOJ has highlighted a number of challenges that law enforcement faces in countering cybercrime, and Congress may continue to conduct oversight and debate legislation in these arenas, including the following:

- **Transnational Crime.** Cybercriminals have specialized their activities and, because they can operate anywhere in the world, networks of expert cybercriminals—and digital evidence of their activity—may exist in various countries. There are sometimes investigative challenges in gathering evidence, working with international law enforcement, and bringing perpetrators to justice in the United States.
- **Evolving Technology.** While some note that law enforcement may have access to more digital information than ever before, others contend that law enforcement is “going dark” as some investigative capabilities are outpaced by the speed of technological change. These hurdles for law enforcement reportedly include strong, end-to-end (or what law enforcement has sometimes called “warrant-proof”) encryption, which can prevent access to certain communications and information. The tension between privacy of electronic communications and law enforcement’s ability to investigate crimes remains of congressional interest.

Chapter 414

COVID-19 AND BROADBAND: POTENTIAL IMPLICATIONS FOR THE DIGITAL DIVIDE*

Colby Leigh Rachfal

ABSTRACT

According to the Federal Communications Commission's (FCC) 2019 Broadband Deployment Report, approximately 21.3 million Americans lack a broadband connection speed of at least 25 megabits per second (Mbps) download/3 Mbps upload, which is the FCC's benchmark for high-speed broadband. In the midst of the coronavirus (COVID-19) pandemic, federal, local, and state governments, in addition to large and small businesses, are considering remote working or distance learning options to help abate the spread of the virus. As these decisions are made, some portion of the population will likely have the option and the capability to shift activities online, while others will not. COVID-19 mitigation efforts will likely reveal discrepancies in broadband availability and accessibility—termed the digital divide—across the United States.

THE DIGITAL DIVIDE

The term digital divide refers to the gap between those Americans who use or have access to telecommunications and information technologies and those who do not. Several factors contribute to the digital divide disparity, including terrain, population density, demography, and market factors. Even in areas with broadband penetration, factors such as income can inhibit the ability of individuals to access broadband. For example, according to a 2019 Pew Research Center study, 44% of adults with household incomes below \$30,000 a year do not have home broadband services. Although broadband access in the United States

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has steadily increased over the last 10 years, the digital divide persists. For background on the digital divide, see CRS Report RL30719, *Broadband Internet Access and the Digital Divide: Federal Assistance Programs*, by Colby Leigh Rachfal and Angele A. Gilroy.

REMOTE WORKFORCE CHALLENGES

Moving an entire workforce from an onsite environment to a remote environment may present some challenges; including the ability to connect to broadband in the home and the inability of all jobs to be done remotely. While those who have access to broadband may be able to work remotely and continue operations uninterrupted, there are many people who cannot perform their work functions from home, such as those in the restaurant, construction, or hospitality industries. According to the Department of Labor, approximately 29% of workers in the United States may be able to work from home. Another challenge may be capacity issues and whether a network can support a remote workforce.

DISTANCE LEARNING AND THE HOMEWORK GAP

Internet use has increased in schools, with a growing number of schools issuing homework assignments online. In response to the coronavirus, some schools are not just assigning homework online, but temporarily moving all instruction online. The move to online instruction on a massive scale will likely encounter various challenges, especially if students do not have access to broadband at home or access to service with sufficient speed to support live features such as video conferencing. The divide between students that have access to adequate broadband at home and those that do not is known as the *Homework Gap*. While some schools may have the option to shift classes online, many cannot due in part to the varying levels of access to broadband. Some schools may have the resources to lend devices, such as laptops or tablets, along with hotspots to provide broadband to students; however, some schools may not—which may place those students at a potential disadvantage to their peers who do have connectivity.

TELEMEDICINE

As the coronavirus continues to spread in the United States, the Centers for Disease Control and Prevention (CDC) have advised the best way to prevent catching the coronavirus is to avoid being exposed to the virus; namely avoiding close contact with people who may be carrying the virus (also known as social distancing). Visiting a doctor's office may increase the chance of encountering people who are contagious, and an option of seeing a doctor virtually, known as telemedicine, may be an effective method of reducing the spread of the coronavirus. In addition, the coronavirus may constrain resources at hospitals and telemedicine could be an efficient and safe way for doctors to diagnose patients. By using the telemedicine option, a patient may be able to video teleconference with a doctor from the comfort of their home; however, telemedicine requires connection to high-speed broadband.

For background on telemedicine, see CRS Report R46239, *Telehealth and Telemedicine: Frequently Asked Questions*, by Victoria L. Elliott.

BROADBAND MAPPING

Although the FCC's 2019 Broadband Deployment Report indicates approximately 21.3 million Americans lack a broadband connection, the number may be higher due to potential inaccuracies in broadband mapping data. Pinpointing where broadband is and is not available in the United States has been an ongoing challenge. Current data on national broadband availability is provided by private telecommunications providers, collected by the FCC, and displayed on the FCC's Fixed Broadband Deployment Map. Difficulty in accurately mapping broadband availability has been attributed to a number of factors, including the adequacy of census block data, the lack of independent data validation outside the FCC, and the absence of a challenge process for consumers and other entities that believe the Fixed Broadband Deployment Map may overstate availability in their area. This can be particularly challenging for decision-making on whether to move classes online or move a workforce to telework, as there is no accurate basis for determining who would have access to broadband and who would not. For additional information on broadband data and mapping, see CRS Report R45962, *Broadband Data and Mapping: Background and Issues for the 116th Congress*, by Colby Leigh Rachfal.

Chapter 415

COVID-19: POTENTIAL ROLE OF NET OPERATING LOSS (NOL) CARRYBACKS IN ADDRESSING THE ECONOMIC EFFECTS*

Mark P. Keightley

ABSTRACT

A number of industries may suffer losses in 2020 as a result of the coronavirus disease 2019 (COVID-19) outbreak. The travel and tourism industry, and restaurant industry, appear particularly susceptible at the moment due to an uptick in canceled reservations and a reduction in bookings. Other industries are likely to be impacted as well by a drop-off in consumer spending and a resulting reduction in profits, with the impacts likely increasing if COVID-19 continues to spread.

Before 2018, businesses with losses could “carry back” net operating losses (NOL) and use them to receive a refund for past taxes paid. On several occasions, Congress temporarily extended or enhanced the carryback rules to assist businesses in times of general economic weakness, or in response to natural disasters. Recent changes enacted in the 2017 tax revision (P.L. 115-97), commonly referred to as the Tax Cuts and Jobs Act (TCJA), however, eliminated the ability to carry back losses. This Insight discusses how allowing NOL carrybacks could potentially assist businesses impacted by economic weakness associated with COVID-19.

CARRYBACKS AND CARRYFORWARDS

When a business experiences a loss (or NOL, in tax jargon) it owes no tax in that year. Currently, a business may use a loss to reduce future taxes by claiming it as a deduction against income earned in some future year. This process is known as carrying forward a loss, and a business may carry a loss forward indefinitely. Prior to the TCJA, businesses were able

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to use losses to obtain a refund for taxes paid in the past two years, a process known as carrying back a loss. TCJA, however, eliminated the two- year carryback. Businesses generally prefer to carry losses back rather than carry them forward because carrybacks produce a benefit sooner and with certainty, whereas carryforwards reduce taxes at some uncertain time in the future.

An example may help demonstrate the mechanics of carrying back a loss. Suppose that a business earned profits of \$100 last year and paid taxes of \$21 (i.e., the tax rate was 21%). This year the business incurred a loss of \$40 and thus owes nothing in taxes. If the business is allowed to carry back this \$40 loss it can receive a partial refund for taxes paid last year. It does this by recalculating its tax liability last year, subtracting the \$40 loss from its \$100 in income and applying the 21% tax rate. The business would find its recalculated tax liability for last year to be \$12.60 ($\$60 \times 21\%$). It would then receive as a refund the difference between what it originally paid in taxes last year and its recalculated tax liability, or \$8.40 ($\$21 - \12.60).

EXPANDED NOL CARRYBACKS: PAST EXPERIENCE

At various times, the NOL carryback period was modified to provide temporary or targeted tax relief. For example, during the Great Recession, the American Recovery and Reinvestment Act of 2009 (P.L. 111-5) and Worker, Homeownership, and Business Assistance Act of 2009 (P.L. 111-92) temporarily extended the two-year carryback period to up to five years. In response to the destruction caused by Hurricanes Katrina, Rita, and Wilma, Congress passed the Gulf Opportunity Zone Act of 2005 (P.L. 109-135), which extended the carryback period from two to five years for qualified losses occurring in the Gulf Opportunity Zone (or GO Zone). The Job Creation and Worker Assistance Act of 2002 (P.L. 107-147) temporarily extended the NOL carryback period from two to five years for losses incurred in 2001 and 2002 to assist in the economic recovery.

STIMULATIVE EFFECT OF LOSS CARRYBACKS

One feature of effective fiscal stimulus is the speed with which it can impact the economy. Loss carrybacks suffer from one fundamental issue in this aspect: losses cannot be carried back until after the end of the tax year. The reason is that tax losses are computed over a tax year, and not over a month or a quarter. Additionally, some businesses suffering from short-term economic disruption may not benefit from a NOL carryback if they earn a profit over their full year. Businesses that are reasonably confident that they will be in a loss position at the end of the tax year, and that have (or have access to) technical tax accounting expertise, may be able to adjust required estimated tax payments to reflect an expected loss carryback and experience some relief. These will most likely be larger corporate taxpayers, and not smaller businesses.

Still, because it is notoriously difficult to predict the economy's performance, and because there is a great deal of uncertainty about COVID-19, providing the ability to carry back losses may help support businesses if economic weakness is prolonged. Businesses that

ultimately incur losses at the end of the tax year would be able to amend previous years' tax returns and receive a partial refund. This could assist businesses that struggled to make payroll or cover operating expenses, as well as those that took loans that need to be repaid.

Another aspect of effective fiscal stimulus is the “bang for the buck” a given tax reduction or spending increase produces. Economists quantify this notion with the use of fiscal “multipliers.” Fiscal policy multipliers measure the change in economic output in response to a dollar change in taxes or a dollar change in spending. Past estimates by the Congressional Budget Office (CBO) and Moody's Analytics suggest that the multiplier effects associated with NOL carrybacks are small when compared to other policy options. CRS Report R45780, *Fiscal Policy Considerations for the Next Recession*, contains the CBO's and Moody's estimates, and also reviews the potential effectiveness of a number of fiscal stimulus options that have been considered in response to recent economic slowdowns, including NOL carryback modifications.

Separate from the stimulative effects of NOL carrybacks is the issue of whether carrybacks should be part of the tax system's underlying structure. Many economists would argue that allowing businesses to carry back losses increases economic efficiency by reducing the distorting effect taxation has on investment.

Chapter 416

USDA DOMESTIC FOOD ASSISTANCE PROGRAMS’ RESPONSE TO COVID-19: HOUSE-PASSED H.R. 6201 AND RELATED EFFORTS*

Randy Alison Aussenberg and Kara Clifford

ABSTRACT

U.S. Department of Agriculture (USDA) Food and Nutrition Service (FNS) programs are often part of emergency response efforts, providing program flexibilities, foods for distribution, and benefits for redemption. Emergencies generate different FNS responses and vary with states’ requests. During the COVID-19 pandemic, access to food—particularly in light of school closures—has been a concern for many. Some also view the Supplemental Nutrition Assistance Program (SNAP) as a force for economic stimulus. This Insight discusses House-passed H.R. 6201’s food assistance provisions, which supplement FNS’s existing COVID-19 response with new funds and authorities.

USDA-FNS RESPONSES TO-DATE

FNS maintains a COVID-19 response website.

During unanticipated school closures, school districts or “school food authorities” that normally operate the National School Lunch Program and School Breakfast Program may transition to serving meals through the Summer Food Service Program (SFSP) or Seamless Summer Option (SSO) if they are approved as summer meal sponsors. Nonprofit and other public agency sponsors may also operate meal sites, and states may approve new sponsors, during unanticipated school closures.

Normally, SFSP/SSO meals must be served at non-school sites and consumed onsite (“congregate feeding”). As of March 15, 2020, USDA-FNS had granted waivers to all 50

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states, DC, and Puerto Rico, allowing SFSP/SSO operators to serve meals in non-congregate settings (e.g., meal pick-up or delivery) and at school sites during COVID-19-related school closures.

For SNAP's Quality Control system, FNS is allowing telephone interviews instead of face-to-face interviews in 16 states as of March 15, 2020.

SUPPLEMENTAL APPROPRIATIONS FOR WIC AND TEFAP (DIVISION A)

H.R. 6201 provides a \$500 million supplemental appropriation for the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC). It also provides a \$400 million supplemental appropriation for The Emergency Food Assistance Program (TEFAP), of which \$100 million can be used for food distribution costs.

CHILD NUTRITION PROGRAMS (§§2102, 2202)

Under §12(l) of the Richard B. Russell National School Lunch Act (42 U.S.C. §1760(l)), states and service providers may request, and USDA may grant, waivers of child nutrition program requirements. Division B of H.R. 6201 expands these authorities.

§2102 newly allows USDA to grant waivers that increase federal costs. Such waivers must be requested by a state or service provider and be aimed at providing meals and snacks during a COVID-19-related school closure.

§2202 newly allows USDA to issue a single waiver to all states. States may opt-in without USDA's approval. §2202 also specifies that USDA may grant waivers to allow non-congregate feeding in the Child and Adult Care Food Program. Both waivers must be for the purpose of providing meals and snacks "with appropriate safety measures with respect to COVID-19."

§2202 also newly allows USDA to grant waivers related to the nutritional content of meals served in child nutrition programs if USDA determines the waiver is necessary to provide meals and snacks and there is a food "supply chain disruption" due to COVID-19.

The waiver authority under §2202 expires on September 30, 2020.

SNAP

SNAP Benefits during School Closures (§1101)

H.R. 6201 includes what has been called "P-SNAP" (Pandemic Supplemental Nutrition Assistance Program), an option allowing USDA approval of state plans to provide SNAP benefits, when a school is closed five or more days, to households with children who would normally receive free or reduced-price school meals (in an amount equal to at least five days' of free meal reimbursements).

This option was last available in FY2010 (during the H1N1 flu epidemic), enacted in an FY2010 appropriations law (P.L. 111-80, §746). In 2009, FNS issued detailed guidance. However, no SNAP state agencies ever administered P-SNAP.

Work-Related Requirements (§2301)

SNAP has work-related eligibility requirements, the strictest being a time limit for nondisabled adults (ages 18 to 49) without dependents (“ABAWDs”) who work less than 80 hours per month. §2301 suspends this time limit nationwide during the period of the Secretary of Health and Human Services’ public health emergency declaration, allowing participants who would have lost eligibility due to the time limit to continue to receive benefits.

Separately, on March 13, 2020, a federal court blocked enforcement of the part of a USDA final rule that would make it more difficult for states to use labor statistics to waive the time limit, changes that were to go into effect April 1. The court “determined that aspects of the Final Rule are likely unlawful ... [and]

USDA will be enjoined from implementing those aspects of the Final Rule nationwide pending final judicial review.” Part of the court’s rationale was the global pandemic.

Benefit Increases, Administrative Requirements (§2302)

§2302 provides for temporary SNAP benefit increases during the public health emergency. It requires USDA to grant SNAP state agencies’ requests that are supported “with sufficient data (as determined by [USDA]).” The increases are “to address temporary food needs not greater than the applicable maximum monthly allotment for the household size.” Previously, a nationwide increase to SNAP benefits was included in the American Recovery and Reinvestment Act of 2009 (P.L. 111-5).

The bill also allows USDA to adjust (through guidance and based on states’ requests) administrative requirements like issuance methods and reporting requirements.

WIC (§§2203, 2204)

In addition to the aforementioned supplemental funding provided, H.R. 6201 gives USDA further authority to grant waivers allowing WIC participants to get certified (or recertified) without being physically present at the WIC clinic (normally required). Waiver requests are to be made by state agencies to USDA.

Also, the bill authorizes USDA to grant waivers from program administrative requirements that a state determines “cannot be met due to COVID-19” and is “necessary to provide assistance” under WIC.

GRANTS FOR NUTRITION ASSISTANCE FUNDING FOR CERTAIN TERRITORIES (§1102)

The Northern Mariana Islands, Puerto Rico, and American Samoa do not operate a SNAP program; instead, they operate programs funded by Nutrition Assistance Program block grants in lieu of SNAP. §1102 provides \$100 million for grants to these territories for nutrition assistance “in response to a COVID-19 public health emergency,” as presumably they would not have the authority to operate P-SNAP or other options in the bill that increase SNAP benefits.

Chapter 417

COVID-19: THE POTENTIAL ROLE OF TANF IN ADDRESSING THE ECONOMIC EFFECTS*

Gene Falk

The Temporary Assistance for Needy Families (TANF) block grant provides grants to the 50 states, District of Columbia, American Indian tribes, and certain territories with the broad purpose of ameliorating and addressing root causes of childhood economic disadvantage. Some of the flexibility the block grant affords to states has been used, and augmented by federal legislation, to address the fallout from Hurricane Katrina and the deep economic recession of 2007-2009. TANF is currently funded on a short-term basis, with funding set to expire on May 22, 2020.

OVERVIEW OF TANF

TANF was created by the Personal Responsibility and Work Opportunity Reconciliation Act of 1996 (PRWORA, P.L. 104-193) and is best known as funding for state programs that provide monthly assistance to needy families with children. PRWORA placed work requirements on states and time limits on families that receive this assistance. TANF funds a wide range of benefits and services—including what are known as “non-recurrent short-term benefits,” which are defined as aid that addresses a specific episode of need and does not exceed four months. The receipt of a nonrecurrent short-term benefit does not count toward a family’s time limit, nor other requirements such as those related to work, assigning child support to the state, and state reporting of detailed characteristics. In crafting a response to Hurricane Katrina in 2005, Congress enacted special rules to permit states to tap an existing fund to pay nonrecurrent short-term benefits to families evacuated from their homes because of Hurricane Katrina.

* This is an edited, reformatted and augmented version of a Congressional Research Service publication IN11241, prepared for Members and Committees of Congress dated March 16, 2020.

In terms of addressing unemployment related to a recession, TANF can also fund employment services and subsidized employment. If an individual is in subsidized employment, the requirements of assistance (e.g., time limits) also do not count.

TANF FUNDING

The basic TANF block grant provided to states was established in PRWORA in 1996, based on spending in its predecessor programs in the early 1990s. The basic block grant has not been adjusted for inflation or changes in other circumstances (e.g., population growths and shifts among the states). It represents the bulk of funding available to the states under TANF. Nationally, the assistance caseload is about 25% of what it was in the 1990s, and states have shifted TANF funds to a wide range of activities.

PRWORA also contained a \$2 billion contingency fund for economic downturns. However, that fund was exhausted in the last recession; in recent years, Congress has provided appropriations of \$608 million per year to it. The fund is spent each year regardless of economic conditions. It is expected to be exhausted in April of this year. Thus, there is little in the way of additional federal funding for states to meet unexpected costs related to COVID-19.

States also have the ability to “reserve” (save) TANF funding. Some states have relatively large reserves, others have no reserves.

POTENTIAL LEGISLATION TO ADDRESS THE EFFECTS OF THE COVID-19 OUTBREAK

The flexibility of states’ use of TANF make it a possible source of funding for them to address the unknown and evolving needs of families resulting from the COVID-19 pandemic. However, states may not have funds to meet *unexpected* costs. Moreover, the fund that was tapped to provide states with help to address Hurricane Katrina is in the process of being exhausted for the current fiscal year.

Congress responded to the economic downturn of 2007-2009 by creating a separate emergency fund. Such a fund to provide for increased short-term benefits would be an option to address the immediate economic needs of families resulting from the COVID-19 pandemic. Further, Congress might consider addressing not only these emergency needs, but also the lack of a counter-cyclical funding mechanism for states under TANF. That is, if the economy does go into recession, there is no automatic TANF funding to address it. The emergency fund created for the 2007-2009 recession might be considered a model for such a fund.

Additionally, Congress might consider addressing TANF work participation standards. These standards are rules for *states*, not individuals, and states are penalized if they do not have a sufficient number of families participating for a minimum number of hours per week. Thus, they do help guide how states set work requirements for individual recipients.

TANF regulations require that all hours that an individual is in paid employment—including paid sick leave—count toward meeting the hourly requirement. However, the

regulations limit to 16 hours per month excused absences from non-paid activities because of illness. States may excuse hours for individual recipients, providing “good cause” exemptions for those who are sick or caring for family members. However, this could disadvantage states in meeting their work participation standards. The U.S. Secretary of Health and Human Services may, but is not required to, provide a “reasonable cause” waiver of the penalty imposed on a state for failure to meet the TANF work requirements.

Chapter 418

COVID-19 AT A GLANCE: FROM HEALTH, EDUCATION, ECONOMIC, TO SCIENCE AND TECHNOLOGY IN SOUTH EAST ASIA AND INDIA

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ABSTRACT

Corona virus disease 2019 (COVID19) emerged in December 2019 in China and has been a viral disease as it continues to spread in almost all the countries of the world. It has put us in unprecedented situation and has changed our daily activities. It has also forced us to find different ways in conducting our plans. There have been many researches on the COVID-19 conducted around the globe. Among of the many conducted research, we compiled some in this book. The aim of this book, therefore, is to share information and scientific evidence and to provide an overview of the COVID-19 in South East Asia and India.

Keywords: COVID-19

INTRODUCTION

On 11 February 2020, World Health Organization (WHO) announced a disease caused by a new coronavirus was a COVID-19, which is the acronym of corona virus disease 2019. This COVID-19 was first identified in Wuhan province, China in December 2019. According to the WHO, viral diseases continue to emerge and represent a serious issue to public health and

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COVID-19 is one of them because it has claimed hundred thousands of lives worldwide (Anggraeni et al., 2020).

COVID-19 has put us the unprecedented situation where isolation has to be taken to lower the infection. People have to stay indoors and do the activities inside as much as possible. As a result, almost all aspects of our life have been affected from the economy, health, education, information and technology to social condition. At the time, we are working on book chapters, the COVID-19 is still haunting us, while throughout the world, scientists, government, and health authorities are working and making incredible efforts to find the cure for this virus. Others have been working to find ways to adapt to the new life. In Indonesia, in some areas, the government even imposed stricter social restrictions for the so-called “red zones” (Zuhairroh and Rosadi 2020). It also affects the economy which is shown by the potential for shocks in the demand and supply of goods and services (Machmud and Minghat 2020).

There was a significant increase in the number of publications on COVID-19 from 2019 to 2020 (Hamidah, Sriyono and Hudha 2020) such as its effects on vocational education (Ana 2020; Mulyanti, Purnama, and Pawinanto 2020). In the midst of this crisis, the authors of this book have chosen to make use of our time to do our part to contribute to the research world. This book provides us with information from South East Asia and India during the COVID-19 pandemic outbreak. How the COVID-19 has infected countries like India, Indonesia, Malaysia, Thailand, and The Philippines. This book has given opportunities to researchers from those countries to contribute their research. It represents a collaboration between researchers from different fields and also from different countries. We collected the information and did our researches regarding the COVID-19 effects to the society, education, economy, information, and technology and also provide some insights about COVID-19 from the medical perspectives.

The aim of this book, therefore, is to share information and scientific evidence and to provide an overview of the topic. This book covers general condition of COVID-19, Health State, Social Condition, Education, and Economy during COVID-19 pandemic, as well as Science and Information Technology in Handling COVID-19.

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Chapter 419

A GLIMPSE OF THE PANDEMIC COVID-19 OUTBREAK AROUND THE GLOBE

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ABSTRACT

A new epidemic emerged as severe acute respiratory syndrome corona virus (SARS-CoV-2) intensely shook the world. The disease is caused by the infection from this deadly virus, known as COVID-19. The number of cases infected by this virus are increasing day by day. Despite all the control measures taken by all healthcare authorities, the number of death toll is not halting. The crown-shaped RNA virus is reported to be transmitted from animal to human and human to human within 14 days of incubation period. The clinical manifestation of the disease ranges from mild symptoms, including fever, dry cough with sore throat, nasal congestion leading to difficulties in breathing, severe continuous headache, unbearable pain in muscle, as well severe respiratory failure and septic shock. Most of the deaths are observed in old patients or in those with comorbidities. Healthcare regulatory authorities including World Health Organization (WHO) and national Center for Drug Control (CDC) are closely monitoring the situation and are continuously giving the necessary guidelines to avoid further transmission of COVID-19.

Keywords: coronaviruses, COVID-19, outbreak, pandemic, SARS-CoV-2

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1. INTRODUCTION

Combating viral diseases has always been a serious challenge for health authorities throughout the world (Mulyanti, Purnama and Parwinanto 2020). In last two decades, the world has already been threatened by two highly infectious viruses including severe acute respiratory syndrome coronavirus (SARS-CoV), H1N1 influenza and Middle East respiratory syndrome coronavirus (MERS-CoV). The world has not forgotten the damage caused by two of the members of coronavirus family, a novel virus SARS-CoV-2 from the same family has emerged as a biological disaster to mankind.

The second SARS-CoV (known as SARS-CoV-2) infection was first reported in Wuhan, China on 31 December 2019, and the related literature henceforth published can help tracing the origin of the symptomatic individuals back to the early December 2019 (Anggraeni et al., 2020). This virus affects the lower respiratory tract and has some of the symptoms related to pneumonia. Due to unidentifiable etiology of this virus, it was classified as “pneumonia of unknown etiology.”

On February 11, 2020, the WHO named the disease as “COVID-19,” an acronym of “coronavirus disease 2019” (Razon 2020). The earlier infections caused by SARS-CoV that began in China has caused more than 800 casualties with infection spreading to two dozen states, and MERS-CoV that began in Saudi Arabia was equally threatening.

This new virus has been reported as more contagious and having a higher human to human transmission potential. On February 26, 2020, as the first SARS-CoV-2 positive case was reported in United States without having a travel history to China. SARS-CoV-2 is a member of family of single-stranded RNA viruses (+ssRNA) that can infect multiple animal species, especially mammals (Perlman and Netland 2009). Although mechanism of infection is not completely understood, the illness can range from mild common cold to more serious respiratory depression. Origin of coronavirus is linked to bats, Himalayan palm civet, and dromedary camel. Scientists around the world are working day and night to gather the information on the transmission, virus-host interaction, diagnosis, spectrum of disease, and prevention strategies.

2. CAUSE FOR CORONAVIRUS

SARS-CoV-2, like other members of the family, has a crown-like appearance which is due to the presence of spiked glycoproteins on the outer surface. *Coronam* is the Latin term for crown. It is classified under *Coronaviridae* family, *Orthocoronavirinae* sub-family and order *Nidovirales*. Table 1. lists different types of Coronaviruses with their probable hosts (Schoeman and Fielding 2020), (Wang et al., 2020).

HCoV-OC43, and HCoV-HKU1 (betaCoVs of the A lineage); HCoV-229E, and HCoV-NL63 (alphaCoVs) are common human coronaviruses with a viral lineage, and they are potential to infect an individual, causing common cold and self-limiting upper respiratory infections especially in people with a weak immune system (Chan et al., 2013) (Chen, Liu, and Guo 2020). SARS-CoV, SARS-CoV-2, and MERS-CoV are other human betaCoVs with B and C viral lineage have the potential and one of the root causes of severe respiratory and extra-respiratory dysfunctions (Table 1). Multiple reported documents have shown high rates

of deaths up to 10-35%. Although SARS-CoV-2 has a lower mortality rate, which is around 2.3%, the reproduction number is higher than SARS-CoV and MERS (Petrosillo et al., 2020).

Table 1. Types of coronaviruses and their respective hosts

Types	Species of Coronaviruses
Type 1 Alpha Coronavirus	Transmissible gastroenteritis coronavirus (TGEV)
	Canine coronavirus (CCoV)
	Porcine respiratory coronavirus (PRCoV)
	Feline coronavirus (FeCoV)
	Porcine epidemic diarrhea coronavirus (PEDV)
	Human coronavirus 229E (HCoV-229E)
Type 2 Beta Coronavirus	Human coronavirus NL63 (HCoV-NL63)
	Bat coronavirus (BCoV)
	Porcine hemagglutinating encephalomyelitis virus (HEV)
	Murine hepatitis virus (MHV)
	Human coronavirus 4408 (HVoV-4408)
	Human coronavirus OC43 (HVoV-OC43)
	Human coronavirus HKU1 (HVoV-HKU1)
	Severe acute respiratory syndrome coronavirus (SARS-CoV)
Type 3 Gamma Coronavirus	Middle Eastern respiratory syndrome coronavirus (MERS-CoV)
	Avian infectious bronchitis virus (IBV)
Type 4 Delta Coronavirus	Turkey coronavirus (TCoV)
	Bulbul coronavirus HKU11
	Thrush coronavirus HKU12
	Munia coronavirus HKU13

SARS-CoV-2 is a round or elliptic shaped virus with an approximately 60-140 nm in diameter. It is sensitive to heat and UV rays. It can be made inert with the use of lipid-dissolving solvents, which includes commonly used ethanol, isopropanol, chloroform, and chlorhexidine. It has around 80% genetic similarity with human SARS-CoV, making it named as SARS-CoV-2 (Chan et al., 2020). It has a single stranded RNA containing 29891 nucleotides, which encodes for 9860 amino acids.

3. TRANSMISSION OF THE DISEASE

The first case of COVID-19 is linked to Seafood Wholesale Market of Wuhan, China. The transmission of virus has been reported to be from the droplets released from the infected person, which is similar to other viruses attacking the respiratory organs such as the rhinovirus and the influenza. The transmission has been thought to be from symptomatic as well as asymptomatic patients. Reports showed that the infection spreads because of close contact with the infected people. The incubation time of this virus is expected to be 3 to 7 days and can go up to 14 days (Li et al., 2020), (Bauch et al., 2005).

4. EPIDEMIOLOGY

WHO (March 03, 10.00 am CET) reported 87,137 confirmed cases in worldwide. Out of which 2977 cases (3.42%) have been found to be deceased. Nearly 92% (79,968 cases) of the total confirmed cases, and 2,873 cases (96.5%) resulted deaths in China. Outside of the People's Republic of China in March 2020, there are approximately 7,169 reported cases, spanning 59 countries which includes the Republic of Korea with 3,736 cases followed by Italy (1,128), international conveyance (Diamond Princess, 705 cases), the Islamic Republic of Iran (593), Japan (239), Singapore (102), France (100), United States of America (62), Germany (57), Kuwait (45), Spain (45), Thailand (42), Bahrain (40), Australia (25), Malaysia (24), United Kingdom (23), Canada (19), United Arab Emirates (19), Switzerland (18), Viet Nam (16), Norway (15), Iraq (13), Sweden (13), Austria (10), Croatia (7), Israel (7), Netherlands (7), Oman (6), Pakistan (4), Azerbaijan (3), Denmark (3), Georgia (3), Greece (3), India (3), Philippines (3), Romania (3). Moreover, two lawsuits were recorded in Brazil, Finland, Lebanon, Mexico, the Russian Federation, and a single event each in Afghanistan, Algeria, Belarus, Belgium, Cambodia, Ecuador, Egypt, Estonia, Ireland, Lithuania, Monaco, Nepal, New Zealand, Nigeria, North Macedonia, Qatar, San Marino, and Sri Lanka.

In India, the death was reported in a 76-year-old male from Karnataka and 68-year-old female from Delhi, and 63-year old man from Maharashtra. All three with co-morbidities (WHO 2020). Data showed correlation of Age and % Case Fatality Rate in China (Table 2) (The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team 2020).

Table 2. Percentage of fatality rates for different age groups

Age (in years)	% Case Fatality Rate
10 to 19	0.2
20 to 29	0.2
30 to 39	0.2
40 to 49	0.4
50 to 59	1.3
60 to 69	3.6
70 to 79	8
80 and above	14.8

Both South Korea and Italy have high number of patients positively diagnosed with COVID-19 but in Italy the percentage fatality rate is higher as 90% of deaths occur in those 70 years old or older. On contrary, in South Korea the percentage fatality rate is significantly low as most of the positively diagnosed population is young (less than 40 years old). The morbidity rates are higher in men as compared to women (Sepkowitz 2020). Although WHO have stated that people irrespective of any certain age-groups can be potentially infected by new corona virus (2019-nCoV), certain population is more vulnerable, which include (WHO 2020):

- a. Elderly people over 65 years old
- b. Healthcare workers including the doctors, nurses and other staffs
- c. People with following medical health conditions:
 1. Asthmatic or people suffering from any kind of chronic lung disease

2. People with artery blockage conditions and weaker heart
 3. Individuals with high blood glucose levels, otherwise known as diabetic
 4. People with neurological conditions and weaker ability to cough
 5. Individuals going through chemotherapy sessions for the treatment of cancer (currently or in recent past)
 6. Individuals suffering from chronic kidney disease requiring dialysis
 7. Individuals with infections in liver
 8. Individuals with lack of spleen
 9. Extremely obese individuals with BMI > 40.
- d. People who are pregnant* (CDC 2020). Present data shows that there is no transmission of COVID-19 from maternal-fetal (Stower 2020). No maternal morbidity has been observed so far (Mullins et al., 2020).

5. MANAGEMENT OF COVID-19

Although repurposing of several drugs is being done along with the screening of herbal remedies, still health regulatory is continuously advising to take necessary precautions. These preventive steps help to reduce the risk factor, including:

- a. Remaining update with the latest information on COVID-19 available on WHO website or nation and local public health agency.
- b. Maintaining hygiene is an utmost priority. This includes washing or sanitizing hands after regular interval of time.
- c. Maintaining social distancing i.e., at least distance of 1 meter between two persons.
- d. Avoiding in touching the face especially eyes, mouth, and nose.
- e. Wearing a mask at public places.
- f. Practicing good respiratory hygiene by covering the mouth while sneezing or coughing with an elbow.
- g. Seeking medical health when symptoms arise. Not following the practice of self-medication.
- h. Avoiding spreading false claims which comes without strong justifications.
- i. Avoiding public gatherings.

CONCLUSION

It is not the first time that the world has faced an epidemic, but this is certainly one of the most threatening phenomena, at least one in past 100 years. It took few weeks to rise from regional crisis to global threat. To reduce the jeopardy caused by COVID-19, WHO, CDCs, and other organizations are working together to make stringent policies and guidelines to curb the virus transmission.

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Chapter 420

THE COVID-19 PANDEMIC IN INDONESIA

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ABSTRACT

Since the first case of coronavirus disease 2019 (COVID-19) was reported in Wuhan, China, as of 12 June 2020, the total number of confirmed cases of COVID-19 was 7,648,823 cases in 215 countries and regions. In Indonesia, the first confirmed case was reported on 2 March 2020, and since then, the number of cases is rising exponentially on a daily basis. As the largest country in South East Asia, Indonesia is the second-largest number of confirmed cases in South East Asia (36,406 cases) after Singapore (39,850 cases). This situation brings Indonesia like other Asian countries into a catastrophe condition. This report described epidemiologic and clinical features, as well as the management of COVID-19 patients in Indonesia.

Keywords: COVID-19, pandemic, Indonesia

1. INTRODUCTION

Since 31 December 2019, coronavirus disease or known as COVID-19 was firstly found in Wuhan, China. It has spread all over the world causing the pandemic (Mulyanti, Purnama, and Parwinanto 2020; Anggraeni et al., 2020; Razon 2020). This virus was previously named 2019 novel Coronaviruses or known as 2019-nCoV, but then World Health Organization (WHO) changed its name into COVID-19 on 11 February 2020. COVID-19 is a severe acute respiratory syndrome caused by SARS-CoV2, a new virus that thought of as zoonotic and mutated so that it can infect human (Sun et al., 2020). It has the closest similarity to

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coronaviruses found in bat, so it is thought to be the primary source. SARS-CoV-2 belongs to betacoronavirus, the same subgenus as Severe Acute Respiratory Syndrome (SARS), and Middle East Respiratory Syndrome (MERS). WHO declared COVID-19 as a Public Health Emergency of International Concern on 30 January 2020, and declared the pandemic on 11 March 2020 (WHO 2020). The first case in Indonesia was on 2 March 2020, and since then, the cases increase exponentially (Indonesia. Kementerian Kesehatan Republik Indonesia 2020).

2. EPIDEMIOLOGY

COVID-19 has a higher rate transmission compared to SARS and MERS. Its basic reproductive number is 2-3, which means one patient can transmit to 2-3 other people. COVID-19 transmission is five times at the early phase. A study in China showed that at an early phase, many patients transmitted a large amount of virus, while the conditions were asymptomatic or mild pneumonia. This caused the virus spread more easily (Wang et al., 2020; Zhou et al. 2020).

COVID-19 is linked to wild animal market in Wuhan, China, pangolins, and snakes. They are linked as the intermediate host. COVID-19 has the closest similarity to coronaviruses found in bat, so it is thought to be the primary source (Sun et al., 2020; Wang et al., 2020; CDC 2020). In China, the majority of patients was men with a median age of 56 years, shown by the fact that patients who need Intensive Care Unit (ICU) were 26% (Zhou et.al., 2020). According to other reports in the US, a total patient reaches 5,700 cases, in which 60.30% of them were male and 39.70% were female. Patients with comorbidities are more vulnerable to get COVID-19. The most common comorbidities were hypertension (55.60%), obesity (41.70%), and diabetes (41.70%). Other conditions were cancer (6%), asthma (9%), chronic obstructive disease (5.40%), history of transplant (1%), chronic kidney disease (5%), and others. Patients with no comorbid reach 6.10%, with one comorbid 6.30%, and more than 1 comorbid were 88%. Patients come into emergency with fever (30.70%), shortness of breath (17.30%), and 27.80% of them received oxygenation. Patients who treated in ICU were 14.20%, and 12.20% received invasive mechanical ventilation, and 3.20% receive kidney replacement therapy (WHO 2020).

Until April 2020, WHO reported 3,090,445 positive cases and 217,669 deaths globally. It has spread in all the continents, except Antarctica (WHO 2020). The case for fatality rate among diagnosed cases is about 2-3%, but it varies by countries (Oke and Heneghan 2020). Chinese Center for Disease Control has reported mortality rate of about 3.46%, which is lower than SARS (9.60%) and MERS (34.50%) (Wu, Leung, and Leung 2020). However, the true mortality rate cannot be ascertained because the total positive cases are still unknown. Furthermore, the average incubation day is about 6.40 days but it varies between 0 and 24 days (Wang et al., 2020).

In Indonesia, since the first announced case on 2 March until April 2020, there are 9,771 positive cases and 784 deaths. COVID-19 has been reported in all 34 provinces but it varies depending on demographic and density (Indonesia. Kementerian Kesehatan Republik Indonesia 2020). The highest rate is found in Jakarta (the highest population density), in which mid-May 2020, it has 34.40% of the cases in Indonesia (Indonesia. Dinas Kesehatan

DKI Jakarta 2020). Based on the latest data from the COVID-19 task force of the Indonesian government, the susceptible sex was male with a mortality increase in age group ≥ 60 years old. SARS-CoV-2 is also more likely to infect people with chronic comorbidities such as hypertension (55.6%), diabetes (35.2%), cardiovascular disease (20.7%), chronic obstructive pulmonary diseases (COPD) (12.6%) and other respiratory problem (5.6%). Among them, the highest proportion for mortality was COVID-19 with hypertension (14.6%) (Indonesia. Kementerian Kesehatan Republik Indonesia 2020). Among 34 provinces in Indonesia (on 12 June 2020) the capital city of Jakarta and the second-largest city of Surabaya are the higher proportion for COVID-19 patients (Figure 1).



Figure 1. Map of the COVID-19 spread in Indonesia. Size of red circle related with proportion of COVID-19 positive cases. (Source from <https://covid19.go.id/peta-sebaran>).

3. CLINICAL MANIFESTATIONS

The clinical manifestations vary from asymptomatic to severe conditions such as respiratory distress syndrome, septic condition, or multiple organ dysfunction. Chinese Center Disease Control and Prevention (CDC) divided into mild pneumonia, severe, and critical disease. About 1% of positive cases did not have any symptoms. 81% of patients with positive cases are mild or non-pneumonia. Severe disease is defined by respiratory rate ≥ 30 times/minutes, oxygen saturation $\leq 93\%$, $\text{PaO}_2/\text{FiO}_2$, and percentage of oxygen supplied < 300 , lung infiltrate in radiograph $> 50\%$ in 24 to 48 hours. The severe disease occurred in 14% cases and the critical disease occurred in 5% cases is patient with respiratory failure, septic shock, and/or multiple organ dysfunction syndromes (MODS).

- a. Moderate pneumonia. Usually patients come with dyspnea and dry cough but without any sign of severe disease
- b. Severe disease. Patients come with fever and sign of severe dyspnea, saturation $< 90\%$, and respiratory rate $> 30\text{x/minutes}$. But in severe disease, the fever could be absent or slightly increased.

- c. Acute Respiratory Distress Syndrome (ARDS). Patients with respiratory failure are divided into (i) Mild ($\text{PaO}_2/\text{FiO}_2$ between 201-300 mmHg. Patients with no ventilator or non-invasive ventilation by Positive end-expiratory pressure (PEEP) or continuous positive airway pressure (CPAP) ≥ 5 cmH₂O; (ii) Moderate ($\text{PaO}_2/\text{FiO}_2$ 101-200 mmHg), and (iii) Severe ($\text{PaO}_2/\text{FiO}_2 \leq 100$ mmHg). Chest radiograph with bilateral opacities not followed by effusions, lung collapses, or lobar also suggested ARDS.
- d. Septic. Sign of shock includes dyspnea, hypoxemia, hypotension, tachycardia, prolonged capillary refill, hyperthermia or hypothermia, and sign of multi organ dysfunction such as oliguria (decreased kidney function), altered mental status, coagulopathy, hyperbilirubinemia, acidosis, high lactate and others. MODS can be evaluated by sequential organ failure assessment (SOFA) which can predict mortality score on ICU based on clinical and lab data.

4. MANAGEMENT OF COVID-19 IN INDONESIA

During the COVID-19 pandemic several specialty societies have published treatment guidance and management related to COVID-19, which is divided into two factors: non pharmacology treatment and pharmacology treatment.

Non pharmacology treatment is explained as

1. Patient should use face mask to reduce the aerosol spread to healthcare and place patient in isolation room with negative pressure (Centers for Diseases Control and Prevention 2020).
2. Oxygenation and ventilation (WHO 2020), (National Institutes of Health 2020).
 - a. Use oxygen when saturation falls below 90-92% (Alhazzani et al., 2020)
 - b. Use nasal cannula 5 lpm or reservoir bag 10-15 lpm with initial target saturation more than 94% (Alhazzani et al., 2020)
 - If the patient is stable, target saturation more than 90% in nonpregnant adults, and 92% in pregnant patients.
 - Saturation target in children is 90% or higher, for children who need urgent resuscitation (apnea or obstructed, distress respiratory syndrome, central cyanosis, shock, seizures, or coma) SpO_2 minimal 94% or higher
 - c. High-flow nasal oxygen or Non-invasive ventilation has been used to achieve adequate oxygenation (Murthy, Gomersall and Fowler 2020).
 - High flow nasal oxygen is recommended for patients with hypoxemic respiratory failure despite using conventional oxygen therapy. There is evidence that this can reduce the need for intubation and mechanical ventilation (Murthy, Gomersall and Fowler 2020; Huang et.al 2020). However, using this technique can result in higher risk of aerosolization virus and still need emergent intubation if the saturation drops suddenly which can risk providers and put patients in more dangerous condition.
 - d. Mechanical ventilation is an option for patient with less saturation who received less invasive measures or patient that cannot maintain breath.

- Tidal volume settings around 4-8 ml/kg (predicted body weight) and inspiratory pressure < 30 cmH₂O.
 - Set tidal volume for children 5-8 ml/kg (predicted body weight) for preserved lung compliance and inspiratory pressure < 28 cmH₂O.
 - PEEP recommended for patient who develop respiratory distress syndrome with higher pressure (>10 cmH₂O) better than lower pressure (Alhazzani 2020; Huang et.al 2020).
 - Patient with moderate to severe respiratory distress syndrome recommend with prone position in 12-18 hours per day, and for pregnant patient in lateral decubitus.
- e. Extracorporeal membrane oxygenation also can be used for severely ill patients if expertise and resources are available (Huang et.al 2020).
3. Fluid therapy
- a. Do not give overhydration because it can precipitate respiratory distress syndrome.
- b. Patient with shock:
- Crystalloids is recommended (balanced more preferred, example: ringer lactate solution) than colloid fluids such as hydroxyethyl starches, gelatin or albumin for patient critically ill with COVID-19 (Huang et.al 2020).
 - Administer within 15-30 minutes 250-500 ml fluid, with target mean arterial pressure (MAP) 60-65 mmHg for adults' patient.
 - For children administered 10-20 cc/kg bolus within 30 minutes.
 - If there are signs of overhydration or no response then discontinue or reduce the fluid.
 - After initial bolus check the clinical signs (CRT, heart rate, the tactile temperature of extremities, palpable pulse), urinary output (0,5 ml/kg/hour in adult and 1 ml/kg/hour in children), and hemodynamic (MAP > 65 mmHg in adults). If the response is good then titrate continues the fluid (Alhazzani 2020).

Pharmacology treatment is explained in the following. COVID-19 patients are divided into asymptomatic, mild, moderate, and severe pneumonia. They are treated according to their conditions. (Protokol Tatalaksana COVID-19 2020).

1. Asymptomatic:
 - a. Self-isolation at home for 14 days.
 - b. Education for patients (for example: given a leaflet to take home).
 - c. Vitamin C 3x500 mg (for 14 days).
 - d. Check the temperature twice a day, every morning and night.
 - e. Surveillance by medical center officer by phone.
 - f. Control in medical center after 14 days surveillance.
2. Mild symptoms
 - a. Self-isolation at home for 14 days.
 - b. Education for patients (for example: given a leaflet to take home).

- c. Vitamin C 3x500 mg (for 14 days).
 - d. Chloroquine 2x 500 mg (for 5 days) or hydroxychloroquine 1x400 mg for 5 days.
 - e. Azithromycin 1x 500 mg (for 3 days).
 - f. Symptomatic therapy (for example: paracetamol for fever)
 - g. Antiviral drug if needed, oseltamivir 2x75 mg or favipiravir 2x .600 mg for 5 days.
 - h. Control in medical center after 14 days surveillance.
3. Moderate
- a. Refer to hospital or emergency hospital.
 - b. Isolation in hospital for 14 days.
 - c. Intravena vitamin C.
 - d. Chloroquine 2x 500 mg (for 5 days) or hydroxychloroquine 1x400 mg for 5 days.
 - e. Azithromycin 1x 500 mg (for 3 days).
 - f. Antiviral drug if needed, oseltamivir 2x 75 mg (for 5 days) or favipiravir loading dose 2x1600 mg for day 1 and then continue with 2x600 mg (day 2-5).
4. Severe
- a. Refer to hospital with facility for COVID-19
 - b. Regimen for COVID-19:
 - Chloroquine 2x500 mg (day 1-3) and continue with 2x250 mg (day 4-19) or hydroxychloroquine 1x400 mg (day 1-5).
 - Azithromycin 1x500 mg (for 3 days).
 - Antiviral drug: oseltamivir 2x75 mg or favipiravir loading dose 2x1600 mg for day 1 and continue with 2x600 mg (day 2-5).
 - Intravenous drip of vitamin C 200-400 mg in NaCl 0,9% 100 cc.
 - a. Supportive therapy (example paracetamol for fever).
 - b. Comorbid therapy (if present).
 - c. Strictly monitor the patient to prevent respiratory failure.

There are no specific drugs approved for the treatment of COVID-19, but there are some drugs being used under clinical trial and compassionate use protocol based on in vitro study:

1. Remdesivir is antiviral therapy recommended for COVID-19 in severe condition ($\text{SpO}_2 \leq 94\%$ ambient air, need supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation). Although this drug has not been approved by the Food and Drug Administration (FDA). It is issued by the FDA for emergency use as IV remdesivir to treat the severe conditions. According to one placebo-controlled randomized trial, the use of remdesivir is significant in improving recovery time yet does not do any differences for mortality (Gilead 2020). However, remdesivir is not recommended for mild to moderate COVID-19 patients outside the setting of the clinical trial.
2. Chloroquine and hydroxychloroquine have been used in some countries, but the guideline does not recommend high dose chloroquine (2x600 mg for 10 days) because of higher serious effect than the lower dose. It is associated with prolonged QT and risk of arrhythmia (Simpson, Kovacs and Stecker 2020). They can be combined with azithromycin in some protocols, but this also can increase the risk of

arrythmia. Infectious Diseases Society of America recommends using this combination only for the clinical trial. NIH guidelines noted when using this combination, patients must be monitored to see the side effects (Clinical Pharmacology 2020).

3. Lopinavir-ritonavir is currently being used to treat HIV. It was used for treating COVID-19 patients but the results are not good.
 - a. A study comparing lopinavir-ritonavir with standard treatment shows no difference between improvement time or mortality in 28 days (Cao et al., 2020).
 - b. NIH does not recommend using this for treating COVID-19 patients.
4. Immunomodulator is expected to reduce cytokine storm which is estimated to be a factor contributing to respiratory distress syndrome in COVID-19 patients (example: tocilizumab or sarilumab are monoclonal antibodies against interleukin-6).
 - a. Convalescent plasma is still uncertain in safety and efficacy for treating COVID-19.
 - b. Recently the panel recommends the use of antithrombotic agents to prevent thromboembolic event in COVID-19 patients because COVID-19 has been associated with proinflammation and thrombotic state, increasing fibrin and d-dimers (Han et al., 2020). But the patient who gets antithrombotic drugs should be monitored and evaluated carefully, so this prevention can only be given to inpatients. outpatients are not allowed to get tested hematology and get prophylaxis except with underlying conditions. This reduces mortality for inpatients with COVID-19.
 - c. COVID-19 patients with suspected thromboembolism should get anticoagulant therapy with therapeutic doses like the standard dose for patients without COVID-19. Patient with extracorporeal membrane or kidney replacement therapy or thrombosis in catheters or extracorporeal filters should get anticoagulant therapy like the standard care for patients without COVID-19.
 - d. Low molecular weight heparin or unfractionated heparin is preferred for critically ill COVID-19 patients because of their short-lived duration (American Society of Hematology 2020).
5. If the patient falls into septic shock condition, the panel recommends fluid administration first and if the condition persists, adding vasopressin is more recommended (Alhazzani et al., 2020; Murthy, Gomersall and Fowler 2020; Huang et al., 2020).
6. Treatment is started with norepinephrine as the first line. Epinephrine or vasopressin as the second line if norepinephrine is unavailable. The target of mean arterial pressure is 60-65 mmHg.
 - a. If the patient is not responding to the usual dose of norepinephrine, adding vasopressin is more recommended than titrating norepinephrine.
 - b. If the patient is not responding to norepinephrine and has cardiac dysfunction, adding dobutamine is more recommended than titrating norepinephrine.
 - c. Epinephrine is recommended for children and norepinephrine is the second line.

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Chapter 421

WHAT WE LEARN WHEN WE ARE FACING COVID-19 IN INDONESIA

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ABSTRACT

As the world is facing a new threat through virus which was found in early December 2019 in Wuhan, China, the changes are happening rapidly. On 2 March 2020, Indonesian government officially announced that the outbreak had finally reached Indonesia. This study conducted to examine and analyze the COVID-19 pandemic outbreak in Indonesia. The main focus of this study was to investigate the challenges Indonesia encountered and how we combat it. Using the existing and evolving information to provide comprehensive picture of the society. The data was taken using the existing data from the current researches on COVID-19 and the reliable mass media. Our research found three major challenges we encountered namely the physical distancing policy, the increasing of the fake news and messages spreading, rising number of unemployment, which eventually bring new changes in our society. The challenges have made us rethinking about our cultural greeting, our news consumption, and its spreading. Also, it made us thinking creatively to change the way we generate our income. On the other hand, it has been a 'blessing in disguise' where the '*gotong royong*' as our cultural heritage has encouraged us to collaborate to help each other, and it has definitely created an opportunity for nature to reclaim itself, and lastly it also lowers the crime rate.

Keywords: COVID-19, education, Indonesia, social humanities

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1. INTRODUCTION

In December 2019, when we read the news about the coronavirus disease 2019 (COVID-19) which had emerged in Wuhan province, China, we did not think that the epidemic would cause global shock. The coronavirus is a type of virus that comes from animals. This virus has a very small size and can infect the human body (Maryanti et al. 2020a). The COVID-19 virus is transmitted through droplets, either directly or indirectly. Viruses enter the human body through the nose or mouth. As the death tolls kept increasing, on 30 January 2020, the World Health Organization (WHO) declared it as a Public Health Emergency of International Concern (Anggraeni et al. 2020). The common signs and symptoms of COVID-19 infection include symptoms of acute respiratory disorders such as fever, coughing, and shortness of breath. In severe cases, COVID-19 can cause pneumonia, acute respiratory syndrome, kidney failure, and even death (Tosepu et al. 2020). However, some patients have not shown those symptoms prior to the test. Currently, there has not been any clinical treatments or prevention strategies available for any human coronavirus (Cui, Li and Shi 2019). Even so, there are some simple steps that can be taken in an effort to prevent contracting the COVID-19 virus. We can prevent this virus transmission in several ways by maintaining physical distance (maintaining a minimum distance of 1 meter from other people), using a mask when we leave the house, diligently washing hands with soap, applying hand sanitizer, body booster, be immune to consuming vitamins and a balanced diet, avoid contact with patients, maintain cleanliness, cover mouth and nose when sneezing and coughing, and do not touch nose and mouth before washing hands (Maryanti et al. 2020b).

Elderly patients are having high mortality rates from COVID-19 infection compared to younger patients (Lake 2020). They have weak immune system. Most human coronaviruses are transmitted mainly by the respiratory route or via contact with infected secretions (Chatterjee 2020).

The lock-down in Wuhan has increased the apprehension including the Indonesian citizens who were staying there (Ana 2020). They requested the Indonesian government to evacuate them. As a result, on 30 January 2020, Indonesian government evacuated 238 Indonesian citizens from Wuhan and later quarantined them for 14 days in Natuna Regency, Riau Islands. Two weeks after the quarantine on 15 February 2020, Indonesian Ministry of Health announced to public that all the 238 citizens were all healthy and could continue doing their daily activities (Garnesia 2020).

Prior to that, Indonesian people had been concerned because cases of COVID-19 had been found in other countries. However, Indonesian government had not taken any prevention action although the WHO had announced it as an international concern. On 2 March 2020, Indonesian government officially announced that the outbreak had finally reached Indonesia after two suspected patients were identified. The number of affected people has been rising since the first announcement. On 28 April 2020, Indonesia reported 9,056 laboratories confirmed COVID-19 cases with 765 deaths (WHO 2020). Although the first case had been found in March 2020, the government was reluctant to enforce a complete nationwide lockdown. However, city mayor of Tegal (a city in Central Java) decided to do local lockdown, regardless of resentment that he might receive from the citizens against his decision (Dzulfaroh and Hardiyanto 2020).

The official announcement affected many sectors. School closures started, most of offices decided to apply work-from-home policy, and religious activities were encouraged to be performed at home. No crowds are allowed. Immediately after the declaration, Indonesian risk communication team COVID-19 or also known as *Gugus Tugas Percepatan Penanganan COVID-19* launched with the goal of communicating relevant information across different target audiences. The objectives of the Task Force on Acceleration of Handling COVID-19 are to improve national resilience in the health sector, to accelerate the handling of COVID-19 through synergy between ministries or institutions and local governments, to enhance anticipation of the escalation developments spread of COVID-19, to develop the synergy of policy making operational, as well as to increase the readiness and proficiency in the prevention, detection and response to COVID-19 (Indonesia. Keppres no.7 tahun 2020).

2. METHOD

The main focus of this study was to investigate the challenges happening during the COVID-19 pandemic outbreak and how we deal with the challenges. All information was obtained from the news mostly covered by *kompas.com*; *tirto.id*; *tempo.com*; and *bbc.indonesia.com*. The data was also taken also from the published papers by typing COVID-19 in Indonesia as well as *virus corona di Indonesia* as the key words search. This study is limited; therefore, several considerations should be taken into account when interpreting the findings.

3. RESULTS AND DISCUSSION

3.1. Indonesia at Glance

Indonesia has 34 provinces, approximately 16,056 islands spreading over with five main islands namely Sumatra, Java, Kalimantan, Sulawesi, and Papua, and 268 million people (Indonesia. Badan Pusat Statistik 2020). Indonesia has been well-known for its diverse culture, which makes it unique. It is a democratic country and has been independent since 17 August 1945. Indonesia adopts the presidential government system. However, the political and administrative system consists of four levels of government such as the central, the provincial level, the district, the urban municipalities, and the villages (Krishnamohan 2016). Thus, the local government has the right to regulate, allocate, and utilize national resource and intergovernmental fiscal relations between central and local government (Hidayat 2017).

3.2. Challenges during COVID-19 Pandemic Outbreak

The consequences of COVID-19 pandemic outbreak have been affected most of our activities. The situation has been challenging for both government and society. According to us, these three topics are the main challenges that Indonesian encountered besides the economy, health, security, information and technology, and other areas. The three challenges

below have been a challenge, however, at the same time enforce us to make a change regardless of our willingness to.

3.3. Physical Distancing

During this COVID-19, local lock down is implemented. We have experienced changes, shifted rapidly after the official announcement. As more information about COVID-19 published on mass media, the more people started to worry because the COVID-19 diseases transfer through droplets (Anggraeni et al. 2020). Maintaining physical distance, improving personal hygiene, including washing hands using soap, and applying hand sanitizers are one of the best preventions that people can take because this virus gives serious threat.

Consequently, people started to panic. Hand sanitizers and masks were two important items that people bought. As a result, the price of these two items rocketed for few weeks after the announcement. Hospitals, clinics and government-mandated community health clinics encountered shortage of Personal Protective Equipment (PPE). This shortage affected the healthcare workers as the frontline because they have to wear PPE in order to prevent the transmission of the virus. However, the shortage has caused a few of the health workers infected.

The physical distancing method has also been affected the way we greet each other. People commonly greet each other in Indonesia by shaking hands. After the COVID-19 case found in Indonesia, it is suggested to avoid this greeting gesture. Shaking hands has been a part of Indonesian culture, however, the virus has forced us to change the greeting into healthier way by clasping hands in front of our chest or simply giving a slight nod.

3.4. Spreading of Fake News and Messages

At the era of social media, misinformation and the spreading of fake news or messages is inevitable. Misinformation and conspiracy theories spread on social media have generated panic and mistrust among the general public, diverted attention away from the outbreak response, and impeded the activities of health-care workers (Cui, Li, and Si 2019). The global pandemic is not only on COVID-19 but also a global epidemic of misinformation—spreading rapidly through social media platforms and other outlets—poses a serious problem for public health (Zarocostas 2020). By 23 March, 2020, there were 44 cases on fake news in Indonesia (Halim and Rastika 2020).

The cases have caused some suspects being charged under the 2016 Electronic Information and Transactions (ITE) Law. The fake news and messages including the death of two volunteers at the Jakarta's makeshift hospital for COVID-19 in the Kemayoran athletes village (Oktaviani 2020), message about prevention of the virus by using UNICEF where one of the statements mentioned that at 26-27°C the coronavirus would die because the viruses cannot live in a hot temperature (Arnani and Wedhaswary 2020).

The spreading of the fake news and messages has made Indonesian police department to conduct round-the-clock cyber patrols, implemented the law enforcement, and continued to educate the public and fight hoaxes with counter-narratives (Antara and Bhwana 2020). It has

also made The Indonesian Ulama Council to urge Muslims not to spread hoaxes and false information regarding the disease, as the council had issued a fatwa on declaring such wrongdoing as *haram* (News Desk The Jakarta Post 2020).

3.5. Unemployment Creates New Ways of Generating Revenue

The COVID-19 pandemic has many major consequences not only for one area but also in whole aspects. It has obviously increased the numbers of unemployed citizens as companies were forced to do massive layoffs. The number is predicted to reach 2.9 to 5.2 million unemployed people if the situation is getting worse (Fauzia and Setiawan 2020). In 2019, there were 5.28% of unemployed people in Indonesia which approximately about 7.05 million. In order to prevent the spread of the virus, government is controlling the transmission by lockdowns and travel bans to “flatten the pandemic curve.” The lockdown has caused financial challenges and uncertainty. The tourism industry in Bali potentially experience the loss for almost 1 trillion IDR each month because most of the tourists coming are from Australia and China (Gamar and Belarminus 2020). The flight blocking has surely been challenging for the people who work in the tourism industry. Needless to say, the massive layoffs have enforced people to think of new ways to support their families during the pandemic. Due to restrictions, lockdown, and the physical distance policy, many have tried to start their small businesses from home by selling some home-made food and offering the service-based jobs such as courier service and in-home haircut service. Restaurants have changed their services, some have changed their system, where they now open online orders, and some shops have conducted the same approaches by encouraging the staff to sell their products online and to get direct contact with their customers.

The changes had been experienced before. We had online applications where we could order food from restaurants; however, there were some restaurants unwilling to apply the same marketing approaches. The pandemic has obviously changed them.

4. A SILVER LINING

Besides the changes aforementioned, there are many other areas that have improved. COVID-19 is a global pandemic and serious threat to human health which halt the economic activities, however it is also considered as a “Blessing in Disguise,” where pollution is reducing and nature is reclaiming itself (Muhammad, Long and Salman 2020). Additionally, the criminal cases have been decreased as reported in Papua during March 2020 the cases have been lower to 277% comparing to crime cases in February 2020 (Aditra and Agriesta 2020).

Ultimately, during this pandemic, we also see how the cultural heritage is emerging. In Wonosari, one of the villages in Yogyakarta, the people collaborated to help families that isolated due to the COVID-19. People provided the food supplies for the families. In Bali, the governor worked with local security officers known as *pecalang* to ensure the lockdown is implemented and people maintain the social distancing. Furthermore, as the health care workers are in the shortage of the PPE, this situation emerged solidarity from some citizens

including celebrities (CNNIndonesia.com) by organizing the funding to buy more PPE and distribute it to hospitals, clinics, and to government-mandated community health clinics in need.

CONCLUSION

COVID-19 has affected most of our activities. It has also caused us to encounter unprecedented time and enforced us to start thinking about the ‘new normal.’ It has caused us to experience new changes at the same time. The challenges have made us rethinking about our cultural greeting, our news consumption and its spreading, as well as also made us thinking creatively to change the way we generate our income. On the other hand, it has been a ‘blessing in disguise’ where the ‘*gotong royong*’ as our cultural heritage has encouraged us to collaborate to help each other, and it has definitely created an opportunity for nature to reclaim itself, and lastly it lowers the crime rate.

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Chapter 422

COVID-19 OUTBREAK AND THE STEPS TAKEN BY INDIA

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ABSTRACT

The COVID-19 outbreak is now a global pandemic as announced by the World Health Organization. Countries like China and Italy are completely locked down in an attempt to control the situation. Countries like India with vast population density have taken multiple major decisions in order to flatten the curve of epidemic outbreak. Multiple states have announced complete lockdown of major cities and even states. The central government has decided to even halt the passenger trains of Indian Railway services. State government have stopped transport services in their respective states. Some cities even have announced curfews in major areas. Private companies have ordered their employees to work from home. Major government services like banks, medical shops, and vegetable shops are permitted to be kept open. The citizens are encouraged to socially distance themselves at the stores for purchasing the daily needed products. Thermal scanners are installed at airports, railway stations, and at the entry gates of government institutions. Multiple isolated wards are being made at major hospitals to provide medical facilities to the affected people.

Keywords: COVID-19, India

1. INTRODUCTION

At the beginning of 2020, a new transmission of a virus is found in more than 200 countries in the world started as we experience the Corona Virus Disease 2019 (COVID-19) pandemic outbreak. On 11 February, 2020, the World Health Organization (WHO) named the disease from the corona virus as “COVID-19,” an acronym of “coronavirus disease 2019” (Razon 2020). The WHO has officially declared the COVID-19 condition to be a global pandemic and the whole world should pay serious attention to it. Thus, all public activities, including educational institutions with a large number of masses, must be halted to reduce the amount of COVID-19 virus transmission and spread.

The deadly virus had infected the humankind after the consumption of some wild animals/birds which was being sold at the Chinese city of Wuhan (Anggraeni et al. 2020). The infected animal/bird from where the virus originated is yet unknown (WHO 2020). From a small province of Wuhan, China, it is now a global epidemic (WHO 2020), (Hamidah, Sriyono and Hudha 2020).

The World Health Organization (WHO) labelled this outbreak as pandemic (a disease that is spreading in multiple countries around the world at the same time). The appearance of severe acute respiratory syndrome coronavirus 2 (SARS-CoV 2) is also known as novel coronavirus (2019-nCoV) or coronavirus disease 2019 (COVID-19) during the end of 2019 year in the Chinese province of Wuhan is now spreading uncontrollably throughout the world.

Apart from China, European countries like Italy, Spain, and UK are facing huge crisis when it comes to provide proper healthcare and medical facilities to the infected citizens and have lost more lives than China did at the similar stage (Financial Times 2020). The outbreak has taken more than 190 countries into its grip till 22 March 2020 with more than 0.33 million people affected worldwide.

‘Quarantine’ is one of the most effective strategy to control the outbreak-like situation of epidemics and communicable disease (Wilder-Smith and Freedman 2020). And, ‘Social distancing’ is a way to reduce contact with the infected to the non-infected individuals. Many countries have failed to contain this deadly virus and now the situation have gone out of control. Developed nations have failed miserably in order to control the outbreak. Scientists and researchers from about 35 leading companies and research institutions are racing hard to come up with vaccines which seem to be a distant dream (Gallagher 2020). Citizens of the countries where the outbreak happened are advised to stay inside and take proper self-care by regularly washing hands with soap and water. The use of sanitizers with more than 50% alcohol content are promoted. People are also advised to use masks and keep social distance from people coughing nearby.

2. AFFECTED COUNTRIES

The major countries which have been an epicenter of this COVID-19 pandemic are China where the outbreak happened, followed by European countries like Italy, France, Spain, Switzerland and the UK, the USA and the Asian nations of South Korea and Iran (Figure 1).

It is also spreading to other countries of the world spanning over 190 countries and territories, in which there are more than 70 countries with over 100 reported cases as on 23 March 2020. From these 70 countries, San Marino has the highest rate of individuals affected per million people which is 5,158 individuals per million, followed by the countries of Iceland (1,665), Andorra (1,462) and Luxembourg (1,275). On the other hand, India has the lowest rate of affected individuals per million people which is about 0.33 individuals per million. Other countries on the list in Figure 1 with lowest per million affected people are Vietnam (1), Indonesia, and Mexico at two people per million. Highest deaths due to the COVID-19 outbreak are reported in Italy which is about 5,476 although it has the world's second-best healthcare facilities. China, from where the deadly coronavirus originated, has reported a total death toll of 3,270 individuals, followed by the countries of Spain (1,813) and Iran (1,685) (Table 1).

Indian Council of Medical Research (ICMR), the apex body of India responsible for formulating, coordinating, and promoting the biomedical research has freshly revised its strategies for the containment of the spread of COVID-19 in order to deliver dependable diagnosis to the individuals suspected of being infected by COVID-19. The government has asked the relevant authorities to check every suspected individual who has international travel history within last two weeks; And, as a precautionary measurement, the government has advised the individuals along with their respective families to strictly follow 14-days quarantine.



Figure 1. Top 10 countries of coronavirus pandemic outbreak.

Furthermore, the government has asked for the COVID-19 test of the individuals suffering from relatable symptoms such as fever, cough, difficulty in breathing, and sore throat. The test should also be done on asymptomatic individuals from day 5 to day 14 if they have come in contact with the infected individuals.

Table 1. Top 50 countries of the world to be affected from to outbreak of COVID-19 pandemic

No	Country	Total Cases	Total Deaths	Total Recovered	Cases per 1 M population	Reported 1 st case
	World	862,574	42,528	179,127	110.7	Jan-10
1	US	188,592	4,056	7,251	570	Jan-20
2	Italy	105,792	12,428	15,729	1,750	Jan-29
3	Spain	95,923	8,464	19,259	2,052	Jan-30
4	China	81,554	3,312	76,238	57	Jan-10
5	Germany	71,808	775	16,100	857	Jan-26
6	France	52,128	3,523	9,444	799	Jan-23
7	Iran	44,605	2,898	14,656	531	Feb-18
8	UK	25,150	1,789	135	370	Jan-30
9	Switzerland	16,605	433	1,823	1,919	Feb-24
10	Belgium	13,964	828	2,132	1,205	Feb-03
11	Turkey	13,531	214	243	160	Mar-09
12	Netherlands	12,595	1,039	250	735	Feb-26
13	Austria	10,366	146	1,095	1,151	Feb-24
14	South Korea	9,887	165	5,567	193	Jan-19
15	Canada	8,612	101	1,242	228	Jan-24
16	Portugal	7,443	160	43	730	Mar-01
17	Brazil	5,812	202	127	27	Feb-24
18	Israel	5,591	21	226	646	Feb-20
19	Australia	4,862	21	345	191	Jan-24
20	Norway	4,651	39	13	858	Feb-25
21	Sweden	4,435	180	16	439	Jan-30
22	Czechia	3,330	32	45	311	Feb-29
23	Ireland	3,235	71	5	655	Feb-28
24	Malaysia	2,908	45	645	90	Jan-24
25	Denmark	2,860	90	1	494	Feb-26
26	Russia	2,777	24	190	19	Jan-30
27	Chile	2,738	12	156	143	Mar-02
28	Poland	2,347	35	7	62	Mar-03
29	Philippines	2,311	96	50	21	Jan-29
30	Ecuador	2,302	79	58	130	Feb-28
31	Romania	2,245	85	220	117	Feb-25
32	Japan	2,178	57	424	17	Jan-14
33	Luxembourg	2,178	23	80	3,479	Feb-28
34	Pakistan	2,042	26	82	9	Feb-25
35	Thailand	1,771	12	416	25	Jan-12
36	Indonesia	1,677	157	103	6	Mar-01
37	India	1,590	45	148	1	Jan-29
38	Saudi Arabia	1,563	10	165	45	Mar-01
39	Finland	1,418	17	10	256	Jan-28
40	South Africa	1,353	5	50	23	Mar-04
41	Greece	1,314	49	52	126	Feb-25
42	Mexico	1,215	29	35	9	Feb-27
43	Panama	1,181	30	9	274	Mar-09
44	Iceland	1,135	2	198	3,326	Feb-27
45	Dominican Rep.	1,109	51	5	102	Feb-29
46	Peru	1,065	30	394	32	Mar-05
47	Argentina	1,054	27	240	23	Mar-02
48	Singapore	926	3	240	158	Jan-22
49	Colombia	906	16	31	18	Mar-05
50	Serbia	900	23	42	103	Mar-02

Source: <https://www.worldometers.info/coronavirus/> (as on 1 April 2020).

3. INDIAN SCENARIO AND AFFECTED AREAS

Below are scenarios that Indian government conducted:

- ‘Stay in whichever city you are,’ PM Modi urged people; as the number of cases crossed 1700 mark in India (Business Today India 2020).
- Coronavirus cases in India: Several cities across India, including the national capital Delhi and Mumbai were declared to be completely lockdown as cases of COVID-19 infection continued to surge (Chandrashekhkar 2020).
- PM Modi announced a country-wide lockdown for 21 days up to 14 April 2020. For general public (Chandrashekhkar 2020). Inter-state travel was completely banned throughout the country and was allowed only with official government documents under special permissions granted by respective state governments (The Hindu Business Line 2020)
- Only the medical staffers and journalists with proper documentation were being permitted to move out during the lockdown (Bloomberg Quint 2020).

**Table 2. Indian states affected from to outbreak of COVID-19 pandemic
(as on 1 April 2020)**

State/Union Territory	Confirmed	Active	Recovered	Deceased
Maharashtra	325	274	39	12
Kerala	241	215	24	2
Tamil Nadu	124	117	6	1
Delhi	123	115	6	2
Rajasthan	106	103	3	-
Karnataka	105	93	9	3
Uttar Pradesh	104	86	17	1
Telangana	97	77	14	6
Andhra Pradesh	87	85	2	-
Madhya Pradesh	86	80	-	6
Gujarat	82	71	5	6
Jammu And Kashmir	55	52	1	2
Punjab	45	40	1	4
Haryana	43	26	17	-
West Bengal	27	18	3	6
Bihar	23	22	-	1
Chandigarh	15	15	-	-
Ladakh	13	10	3	-
Andaman And Nicobar Islands	10	10	-	-
Chhattisgarh	9	7	2	-
Uttarakhand	7	5	2	-
Assam	5	5	-	-
Goa	5	5	-	-
Odisha	4	4	-	-
Himachal Pradesh	3	1	1	1
Puducherry	3	3	-	-
Jharkhand	1	1	-	-
Manipur	1	1	-	-
Mizoram	1	1	-	-
Total	1750	1542	155	53

Source: <https://www.covid19india.org/>.

- Coronavirus cases in India crossed 1900 on 1 April 2020 with thousands of people testing positive for the infection. Maharashtra and Kerala with 325 and 241 cases respectively were recorded making them worst affecting states of India (India Today Web Desk 2020).
- Followed by the above-mentioned states, southern Indian state of Tamil Nadu had witnessed a rise of 124 corona virus cases, while the national capital Delhi had 123 on-record positive cases.
- Union territories of Jammu and Kashmir, Chandigarh, Ladakh, Andaman and Nicobar Islands and Puducherry were also heavily affected due to the outbreak of the COVID-19 pandemic.

4. STEPS TAKEN BY INDIA TO FLATTEN THE CURVE

India with the world's second highest population is now facing a challenge to secure the lives of its citizens from the deadly virus. If the spread of this COVID-19 pandemic spreads like in the US and the European nations, then the country may witness massive loss of human lives as well as severe economic losses. The PM of India has urged people to stay indoors for the restricting the outspread of this disease. For flattening the curve of the reported cases, 21-day country-wide lockdown is announced from 24 March 2020. During the lockdown, the police forces are deployed to ensure public stays inside their houses. The daily necessities and food items are made available to public via home-delivery service. The medical stores are also been ordered to be opened. Indian railways are closed completely to stop people to travel in masses. The railway coaches are being transformed into healthcare bogies to make medical facilities available to distant places in the country. Indian airline companies too are playing a major role in controlling the spread of virus. Indigo has said that it will be operational on only 60% of its routes while Vistara and GoAir have also announced curtailment of their service to help the government in checking the spread of highly infectious COVID-19 (SNS Web 2020). The curfew has been declared basically to break down the chain of spreading the virus between the infected people and others. As a learning from the mistakes of Italy, UK, France, and Iran to prevent the stage 2 to stage 3. If people of India used to go for a minimum quarantine time, in the 3rd and 4th weeks of the crucial time of spreading the virus, India could save its people.

Apart from the central government, respective state governments played their part to control the situation as well. Delhi CM Arvind Kejriwal has ordered the closure of all shops, malls, and other places that are prone to contagion with exceptions given to pharmacies and grocery stores. Delhi CM Arvind Kejriwal announced to even lockdown the national capital to prevent the outbreak of COVID-19 if the situation worsens.

Establishments in the state not to terminate the services of its employees even if they go on leave in view of the COVID-19 outbreak. It also asked these establishments not to deduct the wages of their employees. In his directive, State Labor commissioner Mahendra Kalyankar said that if any worker goes on leave, he should be deemed to be on duty without consequential deduction in wages for this period (The Economic Times 2020). Furthermore, Bihar shutdowns bus services, restaurants, and banquet halls to prevent the spread of COVID-19. However, home-delivery and take-home services of restaurants will remain functional,

PTI quoted a health department order (Patna 2020). Odisha lockdowns 40% of the state to knockdown COVID-19, including state capital for a week, 5 districts, and 8 major towns. 70% of the total 3,200 foreign returnees belong to these districts. Airport, railways, bus-stand, and essential services were exempted. All service providers, including private sector, engaged in COVID-19 relief services, to be declared Emergency Workers: Naveen Patnaik, Chief Minister of Odisha (Mohanty 2020).

The West Bengal government ordered all restaurants, bars, pubs, nightclubs, amusement parks, museums, and zoos to be shut down as a precautionary measure in wake of the COVID-19 pandemic. It aims to prevent all non-essential social gatherings. The strict action would be taken in case of any violation (Deccan Herald 2020). UP government under CM Yogi Adityanath announced to provide financial help to labor (about Rs. 1,000 per month) for meeting their daily requirements due to non-availability of work (India Today Web Desk 2020).

Kerala government under the leadership of CM P. Vijayan announced Rs. 20,000 as a special economic package, for disbursing two-month of advance payment of pension. Those without any welfare pension will be provided Rs. 1,000 each along with free ration for all. Additionally, Rs 500 for health package also being announced (The New Indian Express 2020). Karnataka CM B. S. Yedurappa has stated to release fund of amount 200 crores to fight against the COVID-19 pandemic outbreak. In addition, foreign returning individuals are being stamped to ensure the complete safety of all the residents of Karnataka, and must be quarantine for 15 days (Pinto 2020).

The ministry of health and family welfare have started training for critical care management at 1,000 places through video conference. Health ministry joint secretary Lav Agarwal told reporters that guidelines for coronavirus tests have been revised, directing that asymptomatic direct, and high-risk contacts of confirmed cases should be tested once between day 5 and day 14 of coming in contact with an infected person.

Some initiatives from other institutes for the control of COVID-19 outbreak are:

1. *Teachers to work from home.* Teachers and non-teaching staff of universities, colleges and schools permitted to work from home: Amit Khare, Secretary, Ministry of Human Resource Development (Hindustan Times 2020).
2. *Using of Hand Sanitizer.* In each and every shopping complex are providing sanitizer to each and every customer during the entry to the shopping mall and the exit of the mall. The ministry has also informed to sanitizer maker/provider to provide hand sanitizer under Rs. 100/- for 200 ml (Niyogy 2020).
3. 111 labs to test COVID-19 across the country will be functional from today to test coronavirus (The Economic Times 2020).
4. All restaurants, pubs, bars to remain shut across the country. The restaurants are being allowed to provide home-delivery facilities of food to ensure no citizen goes hungry in the difficult time (Deccan Herald 2020).

CONCLUSION

The government of India was keeping a watch on the situation around the globe and has made efficient strategies to combat this COVID-19 threat, including lockdown whole country, reduce the prices of sanitizers, give fund, increase the testing of sample, disinfect the suspected areas. The statistics showed that the action taken by Indian government has slowed down the spread of COVID-19 infection. Albeit, the number of cases is rising but the rate is not very high as compared to the other countries. The preparedness of India can be shared with other nations as all other nations have been sharing their strategies, experiences, and precautions to reduce the number of positive cases. This COVID-19 pandemic threat faced by the world could be stated as an unpredictable the third world war.

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Chapter 423

BAYANIHAN VALUES DURING COVID-19

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ABSTRACT

The Coronavirus Disease in December 2019 (COVID-19) pandemic continued to spread to the whole world. On 12 March 2020, President Rodrigo Duterte announced the month-long lockdown of the entire Metro Manila from 15 March to 14 April 2020. Within this period, vehicles traveling include land, air and sea to and from Metro Manila were suspended, followed by social and religious events involving mass gatherings. Conferences, seminars, and related events were also postponed and people were told to stay home. The government was merely following the usual procedure, such as the implementation of thermal screening at airports to detect arrivals with flu. The COVID-19 was not of great importance for most ordinary people in the Philippines, but the lockdown has both the downsides and the upsides. It has affected the economic, social, and psychological aspects. Needless to say, a tragedy or misfortune to a place or individual may be an advantage for others. Therefore, the economic, social, and ecological aspects have been seen as favorable and beneficial opportunity during this lockdown. We have also learned the value of compassion and empathy during this crisis. This COVID-19 prompted the Philippines to unite to resolve the crisis. '*Bayanihan*' value encourages people to fight the negative and undesirable things in the community and finding the opportunity which can be used and developed.

Keywords: Bayanihan, COVID-19 virus, Filipino

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1. INTRODUCTION

Since December 2019, an increasing number of cases of novel coronavirus (2019-nCoV)-infected pneumonia (NCIP) have been identified in Wuhan (Li et al., 2020). The outbreak of serious acute respiratory syndrome coronavirus (SARS-CoV-2) has now reached pandemic proportions, affecting more than 100 countries in just weeks (Remuzzi and Remuzzi 2020). On 11 February 2020, WHO announced the name for the coronavirus disease as COVID-19. The virus transmitted between humans via respiratory droplets and also with other possibilities that it can be transmitted through direct or indirect contact with mucous membranes in the eyes, mouth, or nose (Li et al., 2020). This shows the reasons why people are aware of COVID-19 since it can attack several organs in the human body. The impact of COVID-19 is a catastrophe because as of 14 April 2020 it has infected no less than 1.9 million people in the world and kills thousands (Corona 24 news 2020).

However, the COVID-19 was not of great importance for most ordinary people in the Philippines. The news about this virus originated from China can be heard in both local and international television networks. It made us recalled the unpleasant experience as we feared the influenza virus (known as H1N1) in 2009. As we heard the news on TV, airports were fitted with a thermal scanner to identify arriving passengers and were instructed to quarantine as detected (Razon 2020). People traveling from countries with H1N1 cases were also advised to do home quarantine to prevent the virus from spreading. It was a monumental experience yet unpleasant. People who took a flight to Osaka, Japan were out on masks uncomfortably as they disembarked. At that period, most ordinary citizens in the Philippines were not affected by the H1N1 pandemic.

Therefore, for Filipinos the coronavirus was just similar to those previously known viruses and was not of big importance. Additionally, most ordinary people including those educated but without scientific inclination do not know what a virus is. Virus is a borderline between living and non-living things, not capable of reproduction but only do this process utilizing the machineries of a living cell. Virus infections are often experienced by most people regardless of status in life such as viruses that cause chickenpox, mumps, sore eyes, and many other illnesses. Some viral infections last for only a short period of time while others serious might last for a longer period and can have a serious impact on the person such as the poliomyelitis virus and many others. International Health organizations such as the World Health Organization (WHO) is making efforts to stop the spread of these viral infections in some ways such as developing vaccines and ensuring the availability of medicines and antiviral agents.

Consequently, countries are working on giving clear and concise information about the symptoms, the transmission, the preventive measures, and the socioeconomical impacts. The continued spread of the virus is the reason why mass media still disseminate awareness through print, television, and other methods to educate people about the best way to wash hands, the proper strategies to sneeze in public and many other acceptable hygiene practices to avoid the widespread. However, cases of confirmed coronavirus positive continued to rise almost exponentially.

Although the outbreak is likely to have started from a zoonotic transmission event associated with a large seafood market which also traded in live wild animals, it soon became clear that efficient transmission from person to person was also happening (Zhou et al., 2020)

and consequently the discrimination of the Chinese nationals is also occurring. As an example, in the northern part of the Philippines, before a research conference, the Chinese researcher who supposed to be one of the plenary speakers cancelled the agenda for fear of creating panic to the participants. Another case, when Filipinos encountered Chinese-speaking tourists wearing a mask in the plaza and indeed, they refrain from getting near to them. This was the start where the face masks in the drug stores were out of stock and it was very difficult to find one.

Initially, people did not think this virus would have any significant impacts. However, as the number of people infected by COVID-19 was increasing, at the same time, the fear of getting the virus was also increasing. As a result, some students from the Philippine Science High School in Korondal City commented on the slow action the president took. At that time, airport was still remained open and flights from other countries which considered to increase the spread of the virus were still run. As the death toll was rising, the government became more concerned about the issue of coronavirus. On 12 March 2020, President Rodrigo Duterte announced a month-long lockdown of the entire Metro Manila from 15 March to 14 April 2020. Within this period, vehicles traveling include land, air, and sea to and from Metro Manila were suspended, followed by social and religious events involving mass gathering and also conferences, seminars, and related events were postponed. People were told to stay home. President Rodrigo Duterte announced the effect of the lockdown by on 11 March 2020, night live on ABS CBN (US News 2020).

Regardless of the lockdown, the virus continued to spread rapidly and some Filipinos started to fear the virus since death cases were increasing as it continued to spread. People did not think this virus would have any significant impacts in the Philippines. Due to its simple transmission, the spread of the virus is vast and rapid. Most sick people in the Philippines are those with a travel history outside the country and it spreads to other people in the provinces who also have travel history to the capital city. As the lockdown started, intensive distribution of information and ongoing education to the public was also started. People were given information on the “dos” and “don’ts” while fighting on the COVID-19.

This rapid change is not easy for many people. There were some challenges at the initial stage of the lockdown. There was chaos on the checkpoints, and some people could not stand on the situation. All citizen was encouraged to wear masks, did handwashing as often as possible with soap and water, put on hand sanitizers, and maintained social distancing. The change is inevitable and all Filipinos have been affected. Although the infection is not common among economically challenged people but the effect of the lockdown experience by all citizens regardless of the social status.

Therefore, this study aimed to scrutinize the *Bayanihan* values among Filipino because we believe the values encourage people to fight the negative and undesirable things in the community and finding the opportunity which can be used and developed. As much as the COVID-19 has affected the economic, social, and psychological aspects, however, at the same time we have also learned the values of compassion and empathy during this crisis.

2. LOCKDOWN EFFECTS TOWARDS THE LOCAL COMMUNITY

COVID-19 has devastated the income of the people. It affects economic activities, such as disruption in the manufacturing, transport, tourism, and other works sectors, which leads to financial distress among those who are on the status of ‘no job no pay.’ The lockdown as a way of enforcing group quarantine has clearly resulted in both negative and positive issues for the government and people.

2.1. The Negative Impact

The negative aspects could fall into economic, social, and psychological aspects as commonly observed scenario in our place.

2.1.1. *Psychological Effect*

As stated earlier that the number of the death toll during the COVID-19 pandemic has infected the mental stated of the people. People are worried that their family might be the victims of this virus. Due to the increasing fear, the panic buying for masks, rubbing alcohols, and hand sanitizers happened. As a result, these items were out of stocks. This can imply that people buy such products to avoid infection or some could hoard supplies, and eventually sell them for higher price.

Additionally, people who are sick or unwell choose not to visit the hospitals for fear of being infected. Although they have different types of sickness, they are reluctant to go for medication. Besides, the fear of running out of food supplies and money during the lockdown has also contributed to their psychological condition. This fear eventually might contribute to depression that people might encounter during this uncertain time.

2.1.2. *Economic Effect*

COVID-19 has added to the immense economic costs not only for the vulnerable but also for the country as a whole (Mahmud and Minghat 2020). In the Philippines, 50% of the population are poor people (Zoleta 2020). Therefore, it is not easy for the government to solve this issue. The government made a scheme of providing cash amelioration in the amount of Php 5.000 (± 100 USD) to this economically challenged family (Colcol 2020). The Department of Social Welfare and Development (DSWD) was assigned to arrange the distribution. A food package consisting of five kilograms of rice, three packages of instant noodles, and three canned sardines were also distributed. Needless to say, that the most affected people are the poor people who only have a budget for one-day consumption and with the lock down, these groups of people cannot go working. They are also still worried about the insufficient supplies during the lockdown. However, few families have started planting easy to grow vegetables in the prevention of the extended and continued lockdown.

2.1.3. *Social Effect*

As mentioned earlier, vehicles traveling include land, air, and sea to and from Metro Manila were suspended. This has affected the lower-income families the most. So, many people could not go home and could not be with their families during the lockdown. The

COVID-19 crisis has a social dimension (Hasanah et al., 2020, Sangsawang 2020). At the beginning, the upper and middle-income classes are specifically affected as they are the ones who have traveled or are acquainted with others who have traveled (National Economic and Development Authority 2020). Government also told people to maintain social distancing and avoid involving mass gathering including social and religious events and also conferences, seminars, and related events were postponed and people were told to stay home. As a result, academia has to reschedule and reconstruct schedules. Socializing outside the house is forbidden and drinking liquor outside the house is also banned. Unfortunately, healthcare front liners have encountered discrimination due to the fear of them carrying the virus.

2.2. The Positive Impact

Undoubtedly, COVID-19 has disrupted our life. However, a tragedy or misfortune to a place or individuals may be an advantage for others. Currently there are plenty of issues that are positive and helpful to many people during the lockdown.

2.2.1. Ecological Aspect

According to the Philippine Department of Environment and Natural Resources, the air pollution in the capital city, Manila, was remarkably reduced since most people stay at home. The burning of fossil fuels is also decreasing as the streets are mostly silent and we do not have both domestic and international flights. Garbage piles are also reducing as most hotels, restaurants, and tourist destinations are closed. Mother Nature is taking its time to recover.

2.2.2. Social Aspect

The social aspect seems not only having a negative impact but also beneficial effects. During this COVID-19 pandemic outbreak, Filipinos have shown the “*Bayanihan*” culture that we have. *Bayanihan* is also called the ‘community spirit’ where people help out neighbors in order to make the job easier and to ease the burden through collaboration. It is commonly observed during disaster and hardship. Fortunately, it is happening during the COVID-19 pandemic.

Although healthcare workers initially encountered discrimination but realizing the *Bayanihan* value, people stated showing support to them by giving food, water, masks, and other personal protective equipment they need. Some people sing for the healthcare staff and the patients by keeping maintaining the distance, and some send encouragement notes.

Additionally, many families in the Philippines are intact families. The lockdown has given more opportunities for families to devote longer times with their loved ones and do more family bonding activities. This, undoubtedly, has contributed to their immune system as people also promote health practices by taking a balanced diet. People have also learned to affirm their faith and loyalty to God as they show more concern for their fellows. For some Christians, the coronavirus is God’s will to make people repent and make them believe that God is still in control above all.

2.2.3. Economic Aspect

As aforementioned that COVID-19 has affected the economic condition adversely (Dirgantari et al. 2020). However, it has also encouraged people to be creative. Due to the lockdown and the social distancing policy, people are not allowed to go out unless they go by motorcycle. Even so, only one person is allowed on the motorcycle. Therefore, people find it difficult to buy their daily needs. But some people came up with the idea of “mobile market.” Although the price is higher than the market, but online selling has been more popular. For the seller, they get bigger return than usual and for the buyer it is more practical and less risky than sending one member of the family to go out. In addition, the government-owned employees have been given two months of loan deduction from the Government System Insurance Service in order to help them with their needs during the lockdown.

CONCLUSION

COVID-19 is and has seriously destroyed human lives and disrupted economic development in all nations. It gives pain to the families and relatives of the victims. It challenges all the world leaders to find solutions. However, there are also good things that evolved from this pandemic effect. It can give good results and impact to communities and countries. The lockdown in all parts of the Philippines has brought solidarity between family members and people in the society. In times of crisis, the lesson from the current situation is the importance of compassion and empathy. One of the most significant results of this pandemic is its ability to move the people in the Philippines to reinforce the Filipino importance of *bayanihan* or “community spirits” and to combat this pandemic together as one. The whole world will overcome this crisis, together we heal as one.

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Chapter 424

STRESS OF THE CHANGES IN THE LIFE AND CONDITIONS OF PATIENTS

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ABSTRACT

This article analyzed the narratives of patients as one of the most productive methods of psychotherapeutic work with adults, particularly work aimed at the development of man, his manhood. The authors paid special attention to the problems of the metaphors of the signals and triggers a psychological transformation. The aim of the study was to analyze the problems of anticipating and minimizing the stress of changes in the life of a person (patient). The research method was theoretically understanding of the problems of anticipating and minimizing the stress of changes in the life of a person (patient). The main results of the study showed the patient overcame estrangement from himself and the world, liminality. A metaphor in a person's life acts as a signal and a trigger for change: its use, one way or another, reveals zones that are subject to changes and stimulates changes themselves. Metaphors manifest themselves in various archetypal structures and in specific metaphors of role models. They allow you to evaluate the direction of the patient's internal movement towards the realization of a particular motivation, intention, support upward and/or slow down downward intentions, as well as comprehend how the patient perceives external changes, how he experiences stress of changes.

Keywords: narrative psychotherapy, markers of change, stress of change, the archetypes, triggers for change

1. INTRODUCTION

Stress and change are an integral part of the human life. The stresses of change (a concept introduced by M.R. Arpentieva in 2020) can be smoothed out and transformed by anticipating and understanding them. One approach is to study the precursors of change and transformation by analyzing life scenarios and narratives. This moment is especially relevant in working with people mentally and somatically ill, patients (Arpentieva 2015; Arpentieva and Terentiev 2016; Mindell 1997; Minigalieva 1999).

In working with narratives, special attention should be paid to combining diachronic and synchronous analysis: changing patterns of behavior and the essence of participants' actions at different stages of their life paths, in different worlds and times. Particularly great attention in this context should be given to metaphors - denoting worlds and times, as well as - accomplished or emerging transitions between worlds and times. Metaphors act as bright signals and triggers of change. Each metaphor is a germ or designation of intention, which the heroes follow on their way to themselves, to each other and to God, to happiness and the resolution of the crisis.

The purpose of the study was to analyze the problems of anticipating and minimizing the stress of changes in the life of a person (patient). The research method was a theoretical understanding of the problems of anticipating and minimizing the stress of changes in the life of a person (patient).

2. RESULTS AND DISCUSSIONS

2.1. Transderivational Search and Understanding of Changes

On the way to resolution, the patient overcomes estrangement from himself and the world, liminality. He learns to comprehend changes in himself and the world, recognizing their being and the right to change. Recognizing oneself and other patients in a particular narrative, recognizing themselves and each other as heroes of the narrative, their self-understanding and understanding of other people are processes that can be almost parallel. The condition is semantic resonance: in the process of studying a narrative in the inner world of a person, a search for similar content between the composing narrative and his life world takes place. The fragment of the world' image resonates with a fragment of a fairytale world, a semantic (semantic) resonance arises, due to which it is "unpacked", a new one is updated, productive and more accurate understanding of what is happening (Arpentieva and Terentiev 2016; Bazhov 1993; Hilborn 2004, Meadows 1999. "Transderivational search" - the search for correspondence to the current situation of the patient and fragments of the experience of stress of change, given in the form of a metaphor, story/narrative, script (fabulous or relational).

In order to overcome the non-constructive methods of self-defense associated with this process, to make the structure-schemes and processes-strategies for understanding oneself and the world developed during previous professional and general life experiences, a metaphorical language that integrates the value relationship of a person to himself and the world becomes necessary. As well as ways to translate this relationship into real life - in the process of understanding what is happening and communicating with another person. Metaphors eventually become markers and triggers of change: sometimes nothing acts as strongly as a metaphor applied and/or captured by those who communicate. Moreover, her understanding is the deconstruction of the polylogue of “weak” and “strong” voices (Arpentieva 2015; Packard 2001; Pekar 2010; Ufimstev 2009).

Each of the possible strategies of understanding - based on strong and/or weak signals or voices - acts as a set of ways to understand yourself and another person, the world. Generally speaking, markers and triggers of change can be very intense, explicit, related and declared values and goals of the patient and/or his relationship system. Moreover, they are formed in the form of concepts that have more or less fixed social meanings and personal meanings. They can be weak, hidden, including those associated with implicitly existing, but up to a certain point, not manifested system characteristics. They take shape and arise in dialogue with the therapist and other people in the form of metaphors. Their peculiarity lies in the fact that even minimal changes in the parameters lead to disproportionately significant changes in the behavior of the entire system: these supersensitive zones are usually called “chaos boundaries” (Lewin 2000; Prigozhin and Stengers 1986).

2.2. Between Worlds: Transformations at the Border of Spaces and Times

It is difficult to find “pure chaos” in the surrounding world, and just as it is difficult to find the absolute order. Instead of a limited complex adaptive system surrounded by chaos, the researchers have in front of them an unlimited complex heterogeneous and adaptive environment that looks like an endless “patchwork quilt”. There is “relatively pure” chaos as complete uncertainty: the ordering forces here do not act or act differently, including in the direction of increasing chaos. The “boundaries of chaos” can be called the “boundaries of orders”: they are located at the junction of the flaps, at the junctions and interactions of the regions of orderliness and homeostatic stability (Beytson 2000; Packard 2001; Prigozhin and Stengers 1986; Ufimtsev 2009). In these junctions there is a conflict and interaction of two (or more) neighboring orders. The “points” of personal or social reality located in them fall under the conflicting influence of two or several homeostatic systems at the same time. This creates a special “tension” in them comparable to the border transition between two hostile countries. One order is contrary, hostile to the other. Where two orders are in contact, tension arises and close mutual attention develops disproportionate sensitivity even to minor events (“provocations”). Here, nonlinear, recursive characteristics appear, which one of the creators of the theory of complex systems Ed pointed out. Lorentz: their ability to be hypersensitive in certain areas, striving for “strange attractors” instead of “logically explainable” (Hilborn 2004; Lorenz 1995; Prigozhin and Stengers 1986). These zones can be called borderline or shimmering, obeying the described the concept of butterfly effect. The butterfly impact

denotes the property of some chaotic systems: a slight effect on the system can have large and unpredictable consequences elsewhere and at another time.

The general characteristics of the areas of order are: adaptability; sustainability; the desire for expansion as the development of accessible space; susceptibility to phases of the life cycle, the duration of the phases of which varies depending on the scale and content of the structure (Ufimtsev 2009). Usually it including the phases: the phase of the emergence of “key ideas”, the “core”, the rapid development and capture of new areas as a result of adaptation to a wide range of conditions (phase of active expansion), a phase of defense against competing structures and a phase of collision with changing external conditions and decay (Ufimtsev 2009).

Common characteristics of “flickering zones” or “areas of collision of orders” are maladaptation, instability/variability, life cycle instability, and the ability to enhance or weaken the expansion of “zones of order”. In the border zones or “seams” between the “flaps” of social reality, areas of order are actively clashing, and unique properties of “flickering zones” arise. For example, the “hypersensitivity” of cognitive structures to its periphery, the “sensitivity to problems” of this periphery, and, therefore, the entire “flap” — the concepts, concepts, percentages and (re) constructed by them of social phenomena and objects (Bakurova 2015; Ufimtsev 2009; Van Raj 2012).

Metaphors indicate the presence of “flickering zones”. They, like strict concepts, can denote the same fragments of reality - the same “flickering zones”. Moreover, they have different “indicator value”, revealing the meaning of the tension of relations between concepts and concepts in the border zone, the “between” zone. The general signs of “indicator value” and the separation of metaphors are as follows: repeated repetition of a metaphor in various circumstances by different people; the metaphor is not repeated literally, but modified with the preservation of meaning; a metaphor is spread socially (Leskov 1981; Ufimtsev 2009).

However, in addition to the artificial metaphors generated by people, there are also natural metaphors created by a stream of socially significant events and pointing to “flickering zones”, the existence of which is not yet recognized and which manifest themselves as “strange coincidences”. “Irony of fate”, “jokers”, in practice events that are not connected both in space and in time with each other - synchronisms as manifestations of the collective unconscious: the plots of events are metaphorically identical (Hilborn 2004; Howe and Strauss 1997; Jung 1996; Khlebnikova 2013; Meadows 1999; Van Raj 2012; Zinkevich-Evstigneeva 2013). Through synchrony of apparently unrelated events, the collective unconscious “indicates” the appearance of “flickering zones” of social reality in which significant events occur (Frants 1998; Jung 2003).

2.3. Identification of Markers of Change and the Transformation of Reality

At the junction of reality, borderline or “flickering zones” there are points that are most effective and productive from the point of view of understanding the essence of development difficulties and the productive transformation of reality: influences can be produced with more or less purposeful directing of events and facts that have metaphorical significance. To increase the likelihood and intensity of the desired effect of interventions in these zones, one

can resort to methods of increasing their “indicator value”. We can resort to repeated use of a language or event metaphor, its variation while preserving the essence, and widespread use of language - artificial or event - natural metaphors in social space. For example, we can resort to “sowing” as repeated use of event and language metaphors along the “target” “flickering zone”.

D. Meadows, a student of J. Forrester (Forrester et al. 1977; Meadows 1999; Meadows 1999) examines the limits of the cybernetic approach to the study of complex social systems. J. Forrester already in the 60s of the XX century began to model and study complex social systems (“system dynamics” - the study and prediction of complex systems using computer simulation methods based on cybernetic schematizations). He wrote about the presence of “sensitive points” in these systems, which are the preferred targets for interventions in complex systems. These targets allow you to purposefully change the behavior and condition of large and complex systems with minimal loss of strength and means (Forrester et al. 1977). D. Meadows used the term that is used by system analysts - “leverage points”, which can also be translated as “sensitive points” - places in complex systems in which even a small shift can lead to big changes in the whole system. She believed that people often intuitively know where sensitive points are located, but either do not pay attention to it, or try to put pressure on it in a direction that is not productive for the individual or group: errors of intuition arise. Therefore, J. Forrester called these points “counter-intuitive”: everyday life and its intuition suggest incorrect movements, leading to a systemic deterioration of the problem (Forrester et al. 1977; Meadows 1999; Meadows 1999; Sangsawang 2020; Hasanah et al. 2020). In terms of the metacognitive approach, we are talking about the fact that the use of everyday heuristics without reflection of the areas of their application often leads to errors (Arpentieva 2015; Arpentieva and Terentiev 2016; Minigalieva 1999).

In the work of D. Harris and St. Zeisler on weak signals as “signs of big changes” (Harris and Zeisler 2002) disclosed one of the approaches to forecasting, based on the representation of social reality as a complex adaptive system in which the so-called weak signals appear and the development of “weak signal amplifiers” to help understand them. The richest source of weak signals is the periphery of culture: 1) interdisciplinary, inter-traditional; 2) kitsch and simulated, pseudo-art and pseudoscience; 3) extra-traditional, cultural, anti-science and anti-art. That is, rejected and forbidden, unusual and rare, devoid of price - worthless and priceless, and also magical, fabulous, which is why narrative therapy has the most significant psychotherapeutic potential among other types of psychotherapy.

According to the theory of “amplification of weak signals”, a targeted search for weak signals at the boundary of chaos is the first step in their search. The second step is to understand weak signals, which should not be carried out by methods that understand strong trends: statistics and sorting are unproductive here. An intermediate procedure for understanding them is the “weak signal amplifier” - which helps to filter out weak signals from noise by their ability to cause changes in a complex adaptive system (Ufimtsev 2009).

However, the future makes itself felt not in one weak signal, but in their series distributed in various parts of the “flickering zones”. A weak signal, unlike noise, combines (often unusual and incomprehensible) a number of cognitively significant factors that are pointless to “sort through” individually and logically and linearly calculate their potential. Therefore, the “fishing” and the “breadcrumb road” described by E. Mindell are more productive: simply waiting for a “weak signal” without the intention to typologize it and create a space/study of its self-realization space (Mindell 1997). Closest to him is the “integrating impression”

regarding the methods and strategies of understanding. All the “crumbs” of the picture are important. They are all transferred from the “background - periphery” to the “center-figure”. All of them find their gestalt: where the gestalt is destined to be acquired. In addition, in order to use the weak signal amplifier and other techniques for working with metaphors that serve as indicators (markers) of changes, it is necessary to identify the perspective that helps to search for weak signals. If this is impossible, then you just need to adopt the idea of the need to develop “sensitivity to problems/signals”, being in a state of “active listening”, including:

1. The irregularities of the “psychological texture”, errors and holes (gaps) in a complex system and its manifestations;
2. “Information leaks”, blocks - resistances and facades - interaction barriers;
3. Repeating and ignored zones, concepts and concepts;
4. Ordinary and unusual forms and contents of interaction,
5. Discovering both problems and methods of solving problems in the functioning and development of the system.

Instability zones (“flicker zones”) are the boundaries of chaos that arise at the junction of stable zones. At these points, control signals come from a number of stable regions and enter into non-linear interactions, “quasi-chaos”. It is at these points that the system is very sensitive and variable (Ufimtsev 2009). Areas of sustainability are areas of established and self-sustaining collective representations (values) of oneself and the world, unstable areas are areas of “cognitive flicker”, conflict, and the transformation of various meanings. To find weak signals, you need to find significant things/events in the border areas - seams and joints - stable areas that are characterized by unusual and asymmetric, strange coincidences and repetitions.

M. Scheffer et al. also consider the topic of “early warning signals” of critical transitions to models from catastrophe theory: they call the point when the system is between two possible equilibrium states, jumping from one to the other under the action of even minimal influences, a bifurcation point or a phase or critical transition point (Scheffer et al. 2009). In their opinion, there are signs of approaching this point. Decrease in system resistance and its “critical slowdown” - the system is long restored from various fluctuations and perturbations, in contrast to the equilibrium system, which immediately returns to the state of homeostasis and relative isolation).

The critical state of a complex system can be more precisely related to the scale invariance (fractality) of the system structures: when the system structures acquire the property of “scale invariance”, they become self-similar, then the system is in a critical/transition state, and the fact that designated self-similarity and there is a “weak signal.” A fractal is a typically recursive model, each part of which repeats in its development the development of the entire model as a whole and is reproduced at various scales without major changes. The erosion of the characteristic spatial and temporal relationships in the system and the general drop in energy are common signals of approaching a critical transition (Scheffer et al. 2009; Ufimtsev 2009).

In metaphors, the unity of diachronic and synchronous, dialectics of life, the difficulties of life “grasp” especially easily and harmoniously: a person gains access to understanding the value of his experience - both for himself and for those around him. In psychotherapeutic communication, where the unconscious is almost inevitably involved, the metaphorical

language of the narrative is valuable for a number of reasons (Arpentieva 2015; Arpentieva and Terentiev 2016; Bakurova 2015; Zinkevich-Evstegneeva 2012; Zinkevich-Evstegneeva 1998). It is more open to analysis and understanding; it is more powerful in terms of psychotherapeutic intervention, it gives the consciousness the opportunity to relax, and activates the awareness that are ignored by the patient in everyday life, also it reveals “weak signals” or markers of change and it can be used to create change as a trigger.

Metaphors allow us to comprehend the most complex, incomplete or ambivalent aspects of problem relations for a patient and a psychotherapist, including, in the context of the theory of archetypes/archetypal structures, to form on the basis of their analysis more productive in relation to a particular period of a person’s life in one or another community, and more conscious role models that underlie the “paradigm” of understanding oneself and the world (Briggs-Myers 1998; Chernyshov 2011; Fromm 2010). In technical terms, this means the use of techniques such as “fishing” and “the road of their breadcrumbs” by E. Mindell (Mindell 1997) “an amplifier of weak signals” or the analysis and transformation of archetypal and role structures of a person’s relationship to himself and the world. For these aims we the use of techniques similar to the analysis of projective techniques, including those developed by us to optimize the processing of TAT, “Self-attitude test”, “Rules of the three” test and other projective techniques (Arpentieva 2015; Harris and Zeisler St 2002; Mindell 1997; Ufimtsev 2009). In addition, the idea of “weak”, intertext signals formed the basis of our tales (Arpentieva and Terentiev 2016; Leskov 1981).

CONCLUSION

A metaphor in a person’s life acts as a signal and a trigger for change: its use, one way or another, reveals zones that are subject to changes and stimulates changes themselves. Metaphors manifest themselves in various archetypal structures and in specific metaphors of role models. They allow you to evaluate the direction of the patient’s internal movement towards the realization of a particular motivation, intention, support upward and/or slow down downward intentions, as well as comprehend how the patient perceives external changes, how he experiences stress of changes.

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Chapter 425

COVID-19 POSSIBLE TREATMENT THROUGH EXERCISE AND NUTRITION

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ABSTRACT

In December 2019, a public health emergency was induced by an outbreak of novel beta coronavirus termed 2019-novel coronavirus (SARS-CoV-2) in Wuhan City, Hubei Province, China. Since May 20, 2020, in Indonesia, there were 20.162 cases confirmed as positive for COVID-19. COVID-19 prevention and mitigation actions are the keys to implementation in health and community services. This paper aimed to provide some possibilities treatment through exercise and nutrition in order to improve immune system as a prevention to COVID-19. A weak immune response will occur due to fewer nutrients. If the nutrients with sufficient energy and micronutrients are adequate then the body's immune system will be strong. A home exercise program using different safe, simple, and easily implementable exercises is suitable to avoid the airborne coronavirus and preserve fitness levels due to the high risk of spread (by a person to person or contaminated surfaces).

Keywords: COVID-19, exercise, nutrition, prevention and mitigation actions.

1. INTRODUCTION

Virus disease is still emerging and is a serious public health problem. Several virus diseases include the severe acute respiratory syndrome coronavirus (SARS-CoV) from 2002 to 2003, and H1N1 influenza in 2009 was recorded. In December 2019, a public health

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emergency was induced by an outbreak of novel beta coronavirus termed 2019-novel coronavirus (SARS-CoV-2) in Wuhan City, Hubei Province, China, which is going to be a worldwide epidemic with high mortality and morbidity (Pradhan et al., 2020) and the World Health Organization (WHO) declared an official name for the new coronavirus disease as COVID-19 (Hamidah, Sriyono and Hudha 2020; Anggraeni et al., 2020).

Since May 20, 2020, in Indonesia, there were as many as 20,162 cases confirmed as positive for COVID-19. The numbers of fatalities are 1,278, while the number of recovered patients is 4,838 and these cases still increases until now. Based on scientific evidence, COVID-19 can be transmitted from human to human through coughing/sneezing (droplets). The people at the highest risk of developing this disease are people in direct contact with patients with COVID-19, including those who treat patients with COVID-19. Standard recommendations for preventing the spread of infection are regular hand washing with soap and clean water, applying the ethics of coughing and sneezing, avoiding direct contact with livestock and wild animals, and avoiding close contact with anyone who shows symptoms of respiratory illnesses such as coughing and sneezing. Also, implementing Prevention and Control Infection while in health care facilities, especially at the emergency departments.

COVID-19 prevention and mitigation actions are the keys to implementation in health and community services. The most effective preventive measures in the community include maintaining hand hygiene by washing hands with soap and using running water or with a hand sanitizer; avoiding touching eyes, nose and mouth; applying the ethics of coughing or sneezing by covering the nose and mouth with the inner upper arm or tissue, then throwing the tissue in the trash; wearing a medical mask if you have respiratory symptoms and doing hand hygiene after removing the mask; maintaining a distance (at least 1 meter) from people who experience symptoms of respiratory distress.

2. PREVENTION OF COVID-19 THROUGH PHYSICAL ACTIVITY

Keeping your physical condition fit is an important thing to do, especially for people who are at risk of non-communicable diseases. However, on the COVID-19 pandemic like this, physical activity and space are limited. How could we work around this? Previous studies have shown that moderate-intensity physical activity has positive enhancing effects on immune system responses against viral respiratory infections (Halabchi, Ahmadinejad, Selk-Ghaffari 2020; Martin, Pence, Woods 2009; Harris 2011).

People who exercise with moderate-intensity physical activity suggested to increase in neutrophil. Furthermore, natural killer (NK) cell counts are detected and salivary IgA concentrations are enhanced (Halabchi, Ahmadinejad, Selk-Ghaffari 2020; Martin, Pence, Woods 2009). Moderate-intensity physical activity increases stress hormones, which leads to a reduction in excessive inflammation (Harris 2011). This leads to a boost in immunity in order to against viral infections via a change in Th1/Th2 cell responses (Pradhan et al., 2020). Twenty to thirty percent reduction of upper respiratory tract infections is reported in individuals performing on moderate levels of physical activity in their daily life. However, prolonged high-intensity physical activity leads to immunosuppression (Pradhan et al., 2020; Ahmadinejad 2014). Moderate intensity physical activity boosts the immune system and the risk of respiratory track viral infections is reduced. However, high-intensity physical activity

with long durations weakens the immune system for several hours following the exercise, and the risk of inspiratory track infection is increased in this period (Rondanelli, 2018).

3. SPORT HEALTH CHARACTERISTIC TO PREVENT COVID-19

Sports Health is a form of sports activities for health purposes. As a sporting activity, it is clear that it is working on the body or the body - (physical aspects). General characteristics of sports health are:

1. Easy: the movements are easy, so that it can be followed by ordinary people, which can enrich and enhance the ability and basic movement skills, for example the motion needed for the implementation of daily living activities.
2. Cheap: very minimal equipment or even no equipment at all.
3. Festive: able to arouse excitement and not boring.
4. Beneficial and Safe:
 - The benefits can clearly be felt, and it is safe to be implemented by each participant with different age levels and dynamic healthy levels.
 - The intensity is sub-maximal and homogeneous, not maximal movements or maximal explosive movements (safety factor).

Terms of the benefits and safety of health sports require special technical-physiological characteristics, namely:

1. Homogeneous and submaximal in intensity or sports load:
 - Sports are carried out with $\pm$ flat / homogeneous intensity
 - There are no movements with a load / intensity that is maximal,
 - No deployment of maximal capabilities.

A homogeneous intensity is needed to make it easier to regulate exercise dosages appropriately, while submaximal intensity is needed as a safety factor. In health sports, people are not required to make a maximum appearance, except when undergoing physical fitness tests. Health sports consist of units of motion that can (deliberately) be made to reach all joints and muscles and can be assembled to become a continuous movement (non-stop), which is an important factor to be able to regulate the dose and intensity of health sports.

1. A unity of measure (dosage): - can be regulated both in intensity (by adjusting the load/strength and/or the speed of repetition/contraction repetition), as well as the duration (duration) of its implementation (by adjusting the number of repetitions).
2. Adequate:
 - There are certain minimum limits for the intensity and timing of the exercise of health to produce benefits, in particular, to increase the functional ability of the Supporting Motion Equipment, held 3-5x/week (minimum 2x/week).

- It can reach intensities between 60-80% maximum pulse rate (Maximal Heart Rate / MHR) according to age. MHR according to age = $220 - \text{age}$. It is good for each participant to know how to set and calculate the pulse of each exercise.
- 3. No Stress Conditions: done with ease, without emotional burden, not competing with each other

4. SPORTS HEALTH TARGETS

There are three stages of health sports goals.

1. *Goal 1 - MINIMUM Targets*: In this first goal, the main goal is to at least maintain the ability of motion that is still there, and if possible try to improve the ability of motion by seeking an increase in area movement of all joints to achieve flexibility, through stretching and relaxation training as much as possible, without any jerks or snaps, which means mobilizing all joints. For example, people who are attached to a wheelchair must maintain and improve the ability of movement that still exists in all their joints, as well as maintaining flexibility and coordination ability, through movements such as Aerobic Gymnastics. Basic abilities (physical abilities) and coordination skills can be improved by requiring participants/students to follow the movements exemplified by the instructor as intensely and accurately as possible following their abilities.
2. *Goal 2 - Goal BETWEEN*: The goal of health exercise at this stage is to maintain and enhance the ability of muscles to maintain and improve their mobility further. The exercise is conducted dynamically and statically. Training in a dynamic way is to perform movements that are fast, repetitive, and antagonistic accompanied by a jolt to further “fill” the movement (the plyometric principle). The exercise of health sports must always be gradual and not exceed the capabilities at that time. Static training is by performing isometric contractions, but breathing must continue as usual (may not suppress breathing/straining), because it should be done part by part. As an example, first, an isometric contraction is done both the upper extremity and then the two lower extremities. Isometric contractions are maintained for 4-6 seconds repeated 3-5 times with active breaks in between. Active rest is intended as an auto-massage. A mistake that can be dangerous is when an isometric contraction is carried out at the same time for the whole body so that there is a kind of Valsalva maneuver (= straining), which will increase blood pressure so that it can be dangerous for health sport participants who have high blood pressure or have heart disease. Health sports training which has reached the Goal 2 stage will naturally include the Gold 1 stage because to train the strength and endurance of the muscles it must always go through joint movements. Therefore, the dynamic way is the most physiological.
3. *Goal 3 - MAIN Targets*: The main objective of health sports is to maintain adequate aerobic abilities or increase aerobic capacity to achieve a “medium” minimum category.

5. BODY IMMUNE FUNCTION AND MICRONUTRIENTS REQUIREMENT

The immune system is a system that works naturally in one's body. Immune system function is protecting the body against microorganisms, infections and harmful substances from outside the body. This self-protection system consists of three layers, namely:

- Physical (for example skin, epithelial layer along the airways and gastrointestinal tract) and biochemical (for example mucus and stomach acid),
- Various immune cells: granulocytes, CD4/CD8 T cells and B cells,
- Antibodies, e.g., immunoglobulin.

This first line of defense system is commonly referred to as innate immunity, which is a combination of physical and biochemical protection (Castelo-Branco and Soveral 2014). In the case of the COVID-19 which enters through the skin from a handshake, the body will respond by activating this first layer of self-protection system. When COVID-19 successfully passes this first tier, then will face various components of the second layer of T cell and B cell. In the case of the above there are two consequences that will occur, depending on the functioning condition of the immune system of the person, namely:

- First, when the immune system function is strong then the individual will be painless and there are no symptoms, or mild pain such as mild cold symptoms, muscle aches, bloating and diarrhea, but a few days later back healthy.
- Secondly, if the immune system function is weak then the individual will experience the symptoms of COVID-19, even one to death.

Both systems also protect against cancerous or precancerous cells. The immune system function is also influenced by the age factor. In infants and children, the system is newly developed and has not been functioning. In adulthood, the body's immune system is already functioning maturely. In elderly people, the system will gradually experience a decline in function (Rondanelli et al., 2018). Common symptoms that are perceived when the immune system decreases are fever, colds, and diarrhea. Even in the age of adulthood, the function of the body's immune system is mature, its strong or weak condition is strongly influenced by the adequacy of energy and micronutrients, or nutrients, derived from food. If the nutrients with sufficient energy and micronutrients are adequate then the body's immune system will be strong, and conversely if less it will be weak. Energy supply can be obtained from foods with adequate carbohydrates, protein, and fat content. Whereas micronutrients that are important to enhance the body's immune system are vitamins A, C, D, E, B2, B6, and B12, folic acid, beta carotene, iron, selenium and zinc (Alpert 2017).

Aside from the adequacy of energy and micronutrients, other factors are also important for the immune system. This factor is emotional stress, which will increase cortisol (a type of stress hormone). Heavy stress and stress that occurs for a long time, will weaken the immune system. In this condition, the body will also need a micronutrient substance above in larger quantities, so that the immune system can function optimally. Emotional stress occurs as a result of a person's mindset that is fraught with fear, excessive anxiety, and often negative thinking. The COVID-19 pandemic condition is at risk of triggering the negative flavors

above which ultimately cause emotional stress which is the consequence of weakening the body's immune system. This condition will cause a person's body to be a high risk for contracting and suffering from the symptoms of COVID-19.

There is a close relationship between nutrients, infections, and the body's immune system. A weak immune response will occur due to fewer nutrients. There is a contact history with infections, and a malnourished physical condition (Calder 2013). It is clear that optimal immunocompetence depends upon nutritional status (Watson, Zibadi, and Preedy 2010). It has been reported by researchers that micronutrient deficiency is a common factor in the world (Biebinger, Hurrell, and Ottaway 2008). Micronutrients are often not noticed by the layman, even by medical personnel, because of the enormous amount and need to be consumed in the long term, and the given effect is not realized in the improvement. For example, if we are rarely sick this is an extraordinary blessing of life, but many people are unaware of it. The use of micronutrients as primary therapy has not been a standardized medical procedure, whereas there have been some reports stating that therapy with micronutrients can provide a corrective effect on the health of a person, even in those who are experiencing certain diseases.

In one case, X, experiencing similar symptoms to that of autoimmune sufferers: weak muscles, bloating, and digestive tract body often not fit. Apparently, after being checked, X has a deficiency in blood levels of vitamin D. After being administered vitamin D for three months, the blood vitamin D levels gradually increased to normal, increased muscle strength significantly, bloating becomes rare and the body is more fit, becoming less flu pain. It is an example of a good case, to see the relationship between vitamins and the immune system. Until now, X is still a consume vitamin D and still performs a vitamin D blood test regularly and health conditions are better than before.

The following will display some types of micronutrients that are beneficial to the function of the immune system and various food sources. And it will be explained which micronutrients are somewhat difficult to digest and are processed by the body, so it needs to be considered obtained through the supplement.

Vitamin A, stand out from the color aspects of the food, is colorful. This colorful food source contains carotenoids. Food sources with high carotenoid content: carrots, yam, pumpkin, egg, and deep-sea fish. Our body can convert carotenoids into vitamin A which serves as an antioxidant and strengthens the immune system function of the body against infections. Vitamin B12 is a vitamin that helps the formation of energy in the body. Food source with vitamin B12 content: Red meat, clams, oysters, and eggs. The body needs carbohydrates, proteins and fats to form energy so that energy production can be optimal, hence this is the role of vitamin B12. If the body is deficient in vitamin B12, then the body will feel less energy and tired quickly.

Vitamin C is the most popular and well-known vitamins in society. It is known that vitamin C is essential for the functioning of the immune system. Food sources with high vitamin C levels are papaya, strawberry, orange, lemon, broccoli, kale, spinach, and green leaves. Furthermore, vitamin D is a vitamin commonly referred to as the sun's vitamin. It is generally known that sunbathing at 9 a.m. will increase vitamin D in the blood. Although it increases, not necessarily the level of vitamin D blood is sufficient to support the function of the immune system. This is because vitamin D obtained from the food and the sunbathing process should still be processed in the liver organ to be vitamin D active. Most Indonesians have problems digesting vitamin D food sources and also process problems in the liver

organs, so it is necessary to check the blood level of vitamin D and consult the doctor. Food sources with high vitamin D content are deep-sea fish, salmon, sardines, tuna, fish oil, and krill shrimp oil.

Vitamin E is a vitamin that is already known for the health of our skin. It also works to help the body fight infections. Food sources with high vitamin E content spinach, broccoli, almonds, peanuts, cashews, and sunflower seeds. Folic acid, a vitamin that helps the formation of new cells, is essential for cells involved in the immune system. Food sources for folic acid are kidney beans, black beans, white beans, peas, and other foods added folic acid supplements. Iron is a blood-enhancer vitamin that has been well known by the people of Indonesia. Blood will bring oxygen and distributed to all parts of the body. Food sources for iron are chicken, duck, turkey, red meat, liver, kidney beans, black beans, broccoli, kale, and various seafood.

Additionally, selenium is an important vitamin in enhancing the functioning of the immune system. It includes for its effect on lowering the over-active response of the body in the case of terrorism, therefore selenium is also known as a vitamin for cancer. High-feeding sources of Selenium are Brazilian beans, broccoli, garlic, sardines, tuna, and barley. Zinc, a vitamin that helps the body's immune response and also lowers the inflammation that occurs in various diseases. Food sources are high in Zinc levels: oysters, clams, crabs, low-fat meats, chickens, ducks, red beans, and Arabic beans.

CONCLUSION

As a conclusion, moderate-intensity (and not high-intensity) exercise may be helpful for healthy asymptomatic people and should be recommended. However, as mentioned earlier, due to the high risk of spread (by a person to person or contaminated surfaces), an exercise in private environments (at home) with good ventilation and use of personal equipment may be more reasonable. A home exercise program using different safe, simple, and easily implementable exercises is suitable to avoid the airborne coronavirus and preserve fitness levels. This program may include aerobic (walking in the house), strengthening, stretching, and balance exercises, or a combination of these (Chen et al., 2020).

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Chapter 426

CHANGES AND TRANSFORMATIONS IN HUMAN AND SOCIAL LIFE: ANTICIPATION AND UNDERSTANDING OF EVENTS AND STRESSES

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ABSTRACT

The stress of change is comprehended, experienced, and passed by a person depending on the sociocultural situation, especially facing corona virus disease 2019 (COVID-19) pandemic. This pandemic influence how people lives, changing traditions and stage of development of society. Scenarios and human life stories in the COVID-19 pandemic include many points of change and transformation, including changes associated with external and internal deformations and dangers, such as bodily somatic and other diseases and disorders. These points form narratives - a multidimensional and multicomponent phenomenon. The aim of the study was an integrative analysis of anticipation and minimization of the stress of changes in the life of a person (patient) in the context of the analysis of sociocultural changes. The research method was a systematic theoretical understanding of the problems of anticipating and minimizing the stress of changes in the life of a person (patient) in the context of the analysis of sociocultural changes. The main results of the study showed that archetypes and role

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models are of great importance in the analysis of the sociocultural aspects of understanding, experiencing and undergoing the stresses of change. Moreover, role models, unlike archetypes, according to researchers, can be classified based on a comparison with the basic motives of life. In addition, human communities go through developmental levels, which manifest themselves as different approaches to solving the problems that reality poses for them.

Keywords: archetypes, narrative psychotherapy, markers of change, stress of change, triggers for change, weak signals

1. INTRODUCTION

Scenarios and human life stories include many points of change and transformation, including changes associated with external and internal deformations and dangers, such as bodily somatic and other diseases and disorders. These points form narratives a multidimensional and multicomponent phenomenon. Participants or heroes of narratives (narratives of change or narratives of stress of change) live in a number of spaces and times, a number of worlds intersecting with each other, changing their understanding of themselves, others and situations of interaction (Arpentieva 2015; Jung 2003; Khlebnikova 2013; Meadows 1999; Meadows 1999). Therefore, in working with stresses of changes) and narratives describing them, aimed at understanding and anticipating (“foresight”) stresses of changes in order to minimize them, special attention should be paid to combinations of diachronic and synchronous analysis. One of the incidents currently occurring is the Corona Viruses Diseases 2019 (COVID-19) pandemic (Anggraeni et al. 2020), which made online learning popular in the education system worldwide; it is discussed that not all teachers were ready to provide online lessons during this COVID-19 pandemic time (Arlinwibowo et al, 2020). However, online education has certain advantages for both teachers and students. Teachers should focus on its benefits in order to develop educational process and students' competences (Asnul Dahar Minghat et al., 2020; Kassymova et al, 2019).

COVID-19 is a disease caused by the corona virus. This virus first hit China in the city of Wuhan. This virus can infect the human body and cause death (Maryanti et al. 2020a, Maryanti et al. 2020b). Currently, the COVID-19 virus pandemic is hitting various countries in the world. The spread of COVID-19 does not only have an impact on health problems (Machmud and Mighat 2020). The spread of this virus has implications for problems in other aspects of human life and the country (for example, education, economy and social). The government has made various policies on preventing the transmission of COVID-19. The community limits various social activities outside the home (Putra and Abidin 2020). The danger of COVID-19 has made a large part of the community experience fear. In addition, the education process creates tangible level of stress by itself. Especially, when academic assignments are too much to be completed in a short period of time (Kassymova, 2018). However, there are different stress management techniques for students to cope (Kassymova et al., 2018). In fact, most people experience stress with the various changes that are made. This results in most of the illnesses suffered by them because of the suggestion of fear they have. They need an understanding of how to deal with and respond to various problems caused by this pandemic.

Changing patterns of behavior and the essence of the actions of participants at different stages of their life paths, in different worlds and times. Particularly great attention in this context should be given to metaphors - denoting worlds and times, as well as - accomplished or emerging transitions between worlds and times. Metaphors act as bright signals and triggers of change (Forrester et al. 1977; Loveridge 2009; Van Ray 2011). Each metaphor is a germ or designation of intention, which the heroes follow on their way to themselves, to each other and to God, to happiness and the resolution of the crisis.

2. PURPOSE AND METHOD

The aim of the study was an integrative analysis of anticipation and minimization of the stress of changes in the life of a person (patient) in the context of the analysis of sociocultural changes. The research method was a systematic theoretical understanding of the problems of anticipating and minimizing the stress of changes in the life of a person (patient) in the context of the analysis of sociocultural changes.

3. RESULTS OF THE STUDY

The stress of change is comprehended, experienced and passed by a person depending on the sociocultural situation in which he lives, on traditions and stage of development of society.

Archetypal Metaphors in the Work of a Narrative Therapist

Despite the huge variety of narratives, they highlight the main stages and moments inherent in any life narrative and form an algorithm (Zinkevich-Evstegneeva 2012; Zinkevich-Evstegneeva 1998; Zinkevich-Evstegneeva 2013).

The algorithm of life stresses or changes usually includes:

- Life in the “father’s home” (appropriation of parental experience, understanding the world, building relationships with worlds, people - life support),
- Parting with the home (voluntary or forced start of the path),
- Choice of road (crossroads and a choice corresponding to the goal of the path),
- Verification (for “good” or “evil heart” - selfishness or mutual assistance),
- Meeting with future helpers (friends who can help),
- Struggle and victory (achieving the goal of the path and fighting with personified evil, as a result which man becomes stronger and wiser or, on the contrary, succumbs to evil, weakens),
- Returning home (difficulties of going back, meeting a hidden evil, death when applying the old experience),

- Rebirth (death of the past, illusions, infantilism, discovering new creative abilities, strength and wisdom, help from friends, victory inside and out),
- Arrival home (a changed home, changed relationships, help from friends and the last trials, restoration of justice and roots that will serve as a support for him in further adulthood), a new image (change about Faces - Transformation: forgiveness, acceptance of the world, the path to a new future with an “open heart”),
- A wedding or a coronation (victory celebration, new social status, objectives, greater responsibility).

Each stage is important, meaning, forming stages, each of which has its own meaning, which can be revealed by asking the patient a series of questions (Beytson 2000; Zinkevich-Evstegneeva 2012, Zinkevich-Evstegneeva 1998). The description and problems of choosing behaviors are well demonstrated by archetypal and other typologies of personality development and its relations. These personal models describe the development of a person and human communities in terms of their belonging to certain generations, their social myths and archetypal figures and scenarios (narratives). The theory of archetypes, created by K. G. Jung on the basis of mythological narratives, was abroad. It developed in the typologies of J. Myers-Briggs, E. Schwartz, E. Bern, and others (Beck and Cowan 2005; Beck and Cowan 2010; Graves, Cowan and Todorovic 2005; Frants 1998; Fromm 2010; Jung 1996). Currently, the theory of archetypes is an effective and efficient tool for creating successful brands and advertising, as well as developing innovative areas of psychotherapeutic care. Based on their work, practitioners and theorists often distinguish a number of basic models of behavior and archetypes as systems of partially conflicting basic needs (intentions), as well as combinations that implement them. Often distinguished archetypal figures and scenarios can also be classified (Briggs-Myers 1998; Jung 2003; Lewin 2000; Meadows 1999; Jung 2003).

In Russia, a detailed typology of the archetypes of A. V. Chernyshov deserves special attention. Studying and analyzing fairy narratives, he revealed a number of characters corresponding to archetypes: Mother (Stepmother), Bogatyr, Lefty/Craftsman, Tsar/King, Koschey, Goldfish, Soldier, “Beautiful Vasilisa”, “Fool Ivan”, Prince Ivan, Damn, Baba Yag/ Witch (Chernyshov 2011). Many of these archetypes are similar to the archetypes of C. Jung et al. A. V. Chernyshov analyzes the ancient Russian folk tales and myths. However, he did not find complete coincidences of all archetypes and names; in particular, he did not find a clearly defined archetype (ideal image) that would correspond to the archetype of Creativity. The archetypes of the Goldfish and the magical qualities of Beautiful Vasilisa, creating the world and wonders, are somewhat similar to him.

Creativity acts as a process of implementing a project, a dream, a representation, the process of transforming an unstable imaginary object into some materials. This is reflected in a much later fairy tale tradition, in an author’s fairy tale. This is personifying in such images of Russian craftsmen from the people as Levsha/Craftsman of the N.S. Leskov (Jung 1996 or Master Danila of P. P. Bazhov (Bazhov1993). When analyzing narratives, “fabulous” archetypes help to expand identity and balance different intentions in the patient’s relationship with himself and the world. However, not all archetypes are combined, which sometimes causes an internal go or even an external conflict, a misunderstanding of the need for a particular type of behavior/attitude, and the need for change (Chernyshov, 2011). The archetype can become a design, a way of realizing significant or probably significant for the

subject of intentions: changes, attitudes or understanding (Chernyshov, 2011, Jung 1996; Jung 2003).

At the very beginning of their research, K. G. Jung wrote that the field of archetypes is not limited, archetypes pass into each other, and the archetype itself is a definite “tendency to form a representation of motive” (Jung 2003). At the same time, archetypal structures include both positive and negative traits, which is quite consistent with the reality of human life, but can form obstacles for people to understand each other, for changes, making what is happening between patients and the therapist, patient and other people ambiguous and blurred. Moreover, the archetype as a super cultural concept is characteristic of all humankind, for each person in one way or another. Therefore, appeal to archetypes does not guarantee that their use will be effective, and the use of archetypes in themselves in psychotherapy is sufficiently motivating to transformations.

However, it is impossible and unproductive to ignore the cultural context. Narrative therapy can be quite successful, productive, and effective if you use not so much the archetypes as support and transformation, but role models — some reference (unambiguous) sets of behavioral patterns that have typical characteristics and act as role models. The role model, like the archetype, has super cultural significance, however, it is not necessarily addressed to the collective unconscious and is included in the process of socialization of a person to one degree or another fully and intensively, depending on the characteristics of the cultural context.

In each culture, role models have special and common features. The main thing in them is the possibility of forming a reference sample and an important, from the point of view of the psychotherapeutic process, design of the stereotype of the carrier of other role-playing behavior. The role model is significant as a specific way of implementing a motive, and, more broadly, of a person's self-expression, designation of his life beliefs in a specific context of life. The role model applicable in psychotherapy can be considered as a potential image that a person may have a desire to play, that is, demonstrate to people around. And it can become the basis of a new way of life. Moreover, role models, unlike archetypes, according to researchers, can be classified based on a comparison with the basic motives of life. Role models correspond to different situations of life and, importantly, do not have conflicts with the cultural context, as they can be used as specific, and as super cultural, but with a specific embodiment in a specific cultural environment.

The Development of Metaphors - Models for the Development of Archetypes

The archetype or role model, with all its “timelessness” and “super culturalism,” is more or less specific, representing in the conscious and unconscious patient certain aspects depending on the time and space of his life. One of the interesting approaches to taking into account the diachronic and synchronous aspects of role models, understanding the cultural and historical features of their forms and contents, their relevance and realization, is provided by the so-called “spiral dynamics”, which is based on the work of the American psychologist and philosopher of the 60s of the XX century Cl. W. Graves (Beck and Cowan 2005; Beck and Cowan 2010; Graves, Cowan and Todorovic 2005; Ufimtsev 2009). He investigated the “emergent cyclical levels of existence” that “adult biopsychosocial systems” are subject to,

believing that human communities go through developmental levels, which manifest themselves as different approaches to solving the problems that reality poses to them.

At the same time, the models of behavior described by him change depending on the cultural and historical space into which a person falls (Hamidah et al. 2020; Dirgantari et al 2020). Each stage of its development in this space is characterized by a specific system of values, different cognitive attitudes (“cognitive points” or strategies for understanding oneself and the world) and different behaviors. At the same time, each next level is not so much crowding out the previous one as it is superimposed on it: all previous levels of development continue to exist along with the most recent one. Cl. Graves argued that in usually societies one or another paradigm prevails, which is the “cognitive glasses” through which society looks at the world. It is subject to change, because, helping society to solve some problems, it raises others before it, the solution of which requires a paradigm shift. This process is not accidental and the following paradigm is in certain dialectical relations with the previous one, hypothetically described as a spiral of two turns, on which there are a number of nodal points. Each paradigm does not completely replace the other; it only supplants it from a dominant position. This transition is not just “rebranding”, but the process of changing identities that are not related to each other as levels of development (Graves, Cowan and Todorovic 2005).

Later D. Beck and Cl. Cowan (Beck and Cowan 2005; Beck and Cowan 2010; Graves, Cowan and Todorovic 2005) noted that communities of people are carriers of memes (cognitive structures), among which a special, decisive role is played by “valuememes” - in their designation, v-memes (values-memes). Value memes or “supermemes” attract lower-order memes that define cognitive habits, as well as actions as methods for solving life tasks and problems accepted in a given community, at a given age, etc. (that is, in fact, role-playing models). The prevailing supermem gives rise to a new supermem, which gradually replaces the previous one, moving to the “shadow” or marginal areas of mass and individual consciousness. Usually a movement is realized from one level to the next, located higher on a spiral, but a downward movement, “degradation” to lower-level values is also possible. Each level is associated with its own supermem, endowing a person with its worldview and values. Each level is characterized by its own understanding of itself and the world, which affects more or less conscious aspirations (intentions) and the choice of behavior patterns (response to problems) (Ufimtsev 2009; Van Ray 2010).

A change of levels occurs when a person or society accumulates tasks that cannot be solved within the framework of the current level (Graves, Cowan and Todorovic 2005; Pekar 2010; Scheffer et al. 2009). D. Beck and C. Wilber introduced the concept of “spiral masters” - people and communities who have reached the “highest level” of the spiral and have the ability to control all other communities. However, still Cl. Graves warned that his levels are no more advanced among less developed people and groups, but simply different value systems and ways to solve problems. That is, “spiral masters”, including in psychotherapy, are people who are able to reflect and use the potential of each stage and changes in the community for the development of man, his relations with himself and the world (Beck and Cowan 2005; Graves, Cowan and Todorovic 2005; Wilber 2013). Described by Cl. Graves and colleagues, the particulars of understanding the world and the intentions of changes at each level, as well as the theory of generations, can serve as the direct basis for the development of role models.

4. DISCUSSION

A similar model of the behavior patterns of different types of people, their development over time, in different historical and political periods, is presented in the theory of generations developed by W. Strauss and N. Howe (Howe and Strauss 1997). They believe that there are “generational cycles” that reflect a repeating pattern of behavior of different types of generations in which one or another “age identity” dominates. People of each separate age group (cohort) tend to share a special set of relationships and values, perceptions (“cognitive points”) and patterns of behavior and communication, insofar as they grew up in the same historical conditions.

At the same time, representatives of each generation experience a sense of belonging to their generation and subjectively share one historical era: they are faced with the same historical events and social trends, being in the same phases of life; they share certain general ideas and relationships, as well as patterns of behavior and communication. Since each generational period lasts 20–25 years, four periods make up a complete cycle lasting approximately 80–90 years: it is called *sakuala* (saeculum) - the “natural age”. According to the survey of centenarians, a new cycle or “natural age” begins at the age of 90: the cycles tend to repeat, reproducing in the individual development the stages of youth-adulthood-old age. In addition, in some cultures, people predominate whose psychological age does not rise above that of children (many “primitive” cultures“), and in some (Tibet, India) there are many psychologically” old “people. Therefore, the result of various processes and layers of a person’s relationship with the world is very diverse, although it is not devoid of trends, the consideration of which can help resolve development crises, intergenerational conflicts and development crises of civilization as a whole.

In general, researchers identify a number of generational archetypes that are repeated sequentially, creating and maintaining the rhythms of the crisis/awakening cycle: idealist, responsive, civic and adaptive (Howe and Strauss 1997). Work with people of different generations, therefore, must take into account generational intentions and models, those problems that are associated with the birth, life and death of a person in certain periods of time. At each moment in time in the inner space - the time of man - there are several alternative “paradigms” or models at the same time. In turn, each of them gives rise to a family of templates, which together form an understanding and attitude to various life problems. During the life cycle of each model or paradigm, it gives rise to several other models and paradigms that go through their shorter life cycle - from the stages of ascension to the stages of decline. The psychotherapist’s task is to connect the patient with the myths or models that are at the apogee stage and regularly “transplant” it with the “descending” one, which has demonstrated its limitations and errors, the paradigm on another, “upward”, giving a more developed, complete and accurate understanding of oneself and the world.

Understanding archetypal and more specific metaphors, including role models implemented by a person in his life, allows us to evaluate the direction of the patient’s internal movement towards the realization of a particular motivation, intention, support upward and/or slow down downward intentions, reduce the level of negative impact of stress of changes (Arpentieva 2015; Meadows 1999; Meadows 1999; Ufimtsev 2009). Turning to the study of patient’s narratives and metaphors, with all its external simplicity, requires a specialist to have a good knowledge of himself, highly qualified: an individual approach,

empathy and intelligence of the psychotherapist himself, his willingness and ability to see the “truth” of a person, life, himself (Arpentieva and Terentiev 2006). In addition, the idea of “weak”, intertextual and intertextual signals can be laid in the basis of psychotherapeutic stories/fairy tales (Arpentieva 2015; Arpentieva and Terentiev 2006). In them, “weak signals” take on their own names (Bakurova 2015; Harris and Zeisler 2002; Hilborn 2004). The simplest and most common concept becomes a metaphor for another concept or a whole group of concepts. These are metaphors of Path, Light, Love, Change, etc. they are fill the space of fairy tales in such a way that, in fact, they act, along with the main characters. Thanks to such stories, the patient, as a reader or even as the author of the story, tunes in to the fact that the story he will study has much more meanings than it might seem he himself becomes a seeker and conceptualizer of the metaphors with which he resonates in the process narrative psychotherapy.

CONCLUSION

Classical predictions of a person’s development, changes in his life, including changes in psychotherapy, are based on the quite logical idea that small, weak changes usually produce small results. They underestimate or simply ignore weak signals, focusing on indicators of the strength of trends and probabilities. However, many phenomena do not fit into statistical trends. Oscillations on the border of chaos is a rich environment in which weak signals can most often be detected (Minigalieva 1999; Minigalieva 1999). If you teach a person or group to recognize the border and balance between areas of order, structure and randomness, uncertainty, they gain the advantage of understanding to see and take into account weak signals and those trends that stand behind them. The richest source of weak signals is the periphery of culture: 1) interdisciplinary, inter-traditional; 2) kitsch and simulated, pseudo-art and pseudoscience; 3) extra-traditional, cultural, anti-science and anti-art. That is, rejected and forbidden, unusual and rare, devoid of price - worthless and priceless, and magical, fabulous, which is why narrative therapy has the most significant psychotherapeutic potential among other types of psychotherapy.

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Chapter 427

ADJUSTMENT OF THAI CURRICULUM AND INSTRUCTION IN THE COVID-19 CRISIS

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ABSTRACT

The crisis from COVID-19 has a big impact on the education sector both in Thailand and abroad. Educational institutions, including tutoring schools and various skill schools, were closed. During this stage, both the schools and many universities have begun to consider postponing the entrance exam, changing the curriculum, and making the online examination to reduce the risk of student gatherings. This includes the graduation ceremony as well.

Therefore, educators or educational policy administrators under the emergency situation of COVID-19 should consider not only accessing to online teaching but also changing other teaching methods during the COVID-19 crisis. Traditional methods might be used to support local areas that cannot access online education effectively. The person responsible for Thai education must also concern the context of inequality and disadvantaged children in society. Thailand is not the only country in the world that has this problem. Many countries face with this problem together and are able to learn lessons and solutions together.

Keywords: COVID-19, education adjustment, Thai curriculum

1. INTRODUCTION

A crisis happens from the COVID-19 pandemic after the World Health Organization (WHO) declared it a serious pandemic (Anggraeni et al. 2020).

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One way to deal with an outbreak is through social distancing or maintains physical distance in society in order to break the chain of COVID-19 spread from person to person.



Figure 1. Online teachers meeting and instructions in the COVID-19 crisis.

The social distancing has a significant impact on all levels or sectors (Hashim et al. 2020). Adaptation to survive has been happening both in Thailand and abroad. The pandemic has influenced the education sector as well. Online teaching system has been adopted in order to conduct teaching and learning (Figure 10.1). Schools and universities have started to consider postponing the exam and switching regular to online classes to reduce the risk of student gatherings on the test day. It also includes the adjournment of the graduation ceremony as well. The state declared tutoring schools and vocational schools to also start providing online education (Bangkok Busyness 2020).

Activities to promote skills and knowledge such as a science camp and summer camps in foreign countries are also affected. Postponing travel is also considered to be the safest under unprecedented situation and to reduce the risk of virus infection.

2. ADAPTATION OF THE THAI EDUCATION SEGMENT

As mentioned earlier that COVID-19 has affected education sector, therefore, the Ministry of Higher Education, Science, Research, and Innovation (MHESRI) of Thailand announced the request for cooperation with educational institutions affiliated with MHESRI. The cooperation includes (Marketingoop 2020):

1. Reducing the rental fee for small business operators in the university.
2. Reducing student tuition in this upcoming semester.
3. Reducing other expenses which is not urgent in order to increase the employment of students and general personnel.
4. Preparing online learning and teaching (Mulyanti et al. 2020).
5. Reducing various service fees charged by Small-Medium-Sized- Enterprises, startup, and the general public as special case.
6. Higher education institutions consider and assess suitable steps to support those impacted by the additional incidents.

In addition, Thai universities have released different initiatives to respond to the COVID-19 crisis. As an example, "Srinakharinwirot University" has announced guidelines for teaching and learning to prevent the spread of COVID-19. At the end of the announcement stated that:

1. Teaching and learning management help teachers to adapt the assessment and evaluation of teaching styles as necessary.
2. Final examination allows teachers to adapt appropriate and effective methods of measurement and evaluation that can use the original format test or other methods.
3. Examination at the graduate level can be adjusted using the online examination or teleconference program.
4. All non-urgent tasks should be postponed, but, if a justification is required, the faculty should plan the screening/prevention/control of infectious diseases (COVID-19).
5. Implementation of the teaching and learning model adjustment and final exams to avoid the spread of COVID-19 are exempted from checking the number of courses attended by at least 80%.
6. Implementation of the teaching and learning model adjustment and graduation final exam and other activities.

Therefore, teaching and learning in the COVID-19 era is one of the challenges for teachers encountered. They have to find ways to transfer knowledge through new channels as the traditional lecture in the classroom is no longer available (Sangsawang 2020). One approach is to build online lessons using internet technologies and different software, but the key issue is the infrastructure. In some countries, as we know, the digital basics are not quite excellently-supported to all teachers. According to the 'Teacher Tapp' survey, which surveyed the teaching of more than 6,000 teachers in the UK, it is found that teachers in public schools can publish less online lessons than that in private schools.

Taking into account for 40 to 69% of respondents indicates that the availability of tools in public schools is much slower than in private schools (Thanalerdsomboon 2020).

In addition, some teachers do not have enough knowledge or expertise to use technology. Some subjects, such as physical education, are not familiar with tools which are not suitable for online teaching. Therefore, it is difficult to adjust the design of new teaching methods to keep things up to date. In regards, some students are not able to access online lessons effectively due to the lack of equipment and the quality of the network signals. Furthermore, it is still found that most students continue to show less ability when studying online, so

learning online may not be the best option for long-term studies. Unless, the curriculum designed for this type of teaching approach has been prepared from the outset. However, problem-solving strategies for changing educational problems will have to consider important issues such as the World Economic Forum projected that the world of education will change in the future schools (Thanalerdsomboon 2020).

1. We will see educational development and changes in the lifestyle of learning
In the past, almost all educational structures around the world stayed in the classroom and had schools was the main center. However, many educational institutions will continue to implement new technologies in the future to replace classroom teaching. Within a short time, there will be several developments for education, and there will be different types of access to information. Resulting in a learning lifestyle outside the classroom, we do not adhere to the conventional school hour schedule which may mean that 'Learn Anywhere, Anytime' is one of the everyday practices.
2. We will see cooperation from many parties to improve education.
COVID-19 crisis phenomenon allows us to see cooperation in developing educational systems from many sections. In addition to teachers and educational stakeholders, there are governments, media, scholars, and various service providers of communication networks, technology developers, in which they help build a platform database system. Many interactive learning platforms considered a positive indication that the education system would be able to progress much far from brainstorming and collaboration like this condition in the future.
3. We must reduce the inequality of access to digital technology for equal education.
In the future, online classrooms (that play a greater role in the classroom) create a secure comprehensive infrastructure, and enhance access to technology. All aspects of innovations that the education system is currently using such as 5G will help all groups of children to have equal education or at the very least causing most children to have a better education.

3. CONCLUSIONS TO BE CONSIDERED FOR EDUCATION MANAGEMENT TO SUPPORT THE COVID-19 CRISIS

According to data collected in 2018 by The Organization for Economic Co-operation and Development (OECD) (Margetingoop 2020), it is found that Thailand still has an inequality access online learning, such as in-house study sites, computer, notebook, and tablet. Particularly, it happens when comparing between rich and poor families. In terms of digital divide, there may be exceptions for accessing television, mobile phones, and smartphones. It seems that all families can access these digital devices. This information can be used as sources of knowledge for educators or policy executives regarding the emergency COVID-19 crisis in order to address the online access to make teaching and learning (Margetingoop 2020).

However, Thailand is not the only country in this world facing the same problems. Many countries also encounter a similar problem, so each country should learn from each other and

work together to find solutions. Therefore, the conclusions that could be considered in order to handle education during the COVID-19 crisis (Tongliemna 2020) are written as follows.

The Use of Radio and Newspapers

The use of radio and newspapers are the most traditional method in the United States. Schools were closed because of the polio outbreak in 1937, causing 325,000 elementary school students to leave the school. In that era, the use of broadcasting on the radio with homework questions sent to the newspaper every morning. There were qualified teachers to check the lesson contents, and experts were invited to broadcast and used the hotline system so parents could call for consultations. There were about 20 teachers waiting to answer the call with parents interested in calling on all the time to make comments. Parents were given support to help children to do homework by taking lessons with children. However, there were also problems. As an example, some houses did not have a good radio signal, so they had to move from outside the city where radio signals. Another problem was uneven learning speeds that are not much different from the era of Internet use. Despite being more convenient, unequal access has problems.

In countries where students have difficult situations for accessing communication devices as during the Ebola crisis in 2014. During that time, West African region shut down schools and delivered the education via radio. They also used text messaging where they shared educational news via mobile phone using Short Message System or short video transmission that uses less internet signals.

Television Use

During school holidays, China has a television program for students at different levels to learn on the screen by dividing the channel, channel schedule, date, time by grade level and by different subjects. It is considered the most accessible method for students without internet or computers. Although it is one-way communication, many countries use television as one of the educational channels, such as Greece, New Zealand, Educational TV channels in some U.S. states and British BBC television Discovery television station that focused on education. In Thailand, the teaching system via satellite television (DLTV) has long been used, and there is a fairly complete database and operating system.

Using a Document System (Learning Box Set)

Using the learning document method by using a series of books or lessons and various activities are the traditional way. Students can study on their own or combining it with other methods, such as providing homework and then having time to ask questions or discuss online. In Portugal, the documents are sent to students by mail including the homework. In China, parents who worry their children spend too much time on the screen could learn to

read or work by typing documents. In New Zealand, when the school is closed the printing and distribution on educational materials has increased because they send it to students.

The Context of Inequality and Disadvantaged Children in Society

Regardless of the method used in the teaching and learning during the COVID-19, it is important to choose the appropriate approach according to the context and readiness of the learners and instructors. Apart from academic concerns, the main concern is that school should be cautious and helpful to the students who might be absent for a long time due to the closure of the school. In times of COVID-19 crisis, school should be giving importance to the mental, emotional, and social conditions of the students as well. Teachers and schools should make students feel comfortable, feel they are not abandoned by the teacher, and in times of crisis, they are still part of the school.

Furthermore, Thai education should continue to think about students in special education classes, people with disabilities, people with learning disabilities, students whose parents or guardians cannot support them because they must work to earn money, students in a poor environment, and students live in domestic violence. How are the government and schools going to better assist those students? This is because children need special support in these communities and simply cannot wait for such a long crisis.

CONCLUSION

The crisis from COVID-19 has a big impact on the education sector. Therefore, educators or educational policy administrators under the emergency situation of COVID-19 should consider not only access to online teaching but also other teaching methods during the COVID-19 crisis. Traditional methods might be used to support local areas that cannot access online education effectively. The person responsible for Thai education must also consider the context of inequality and disadvantaged children in society. Thailand is not the only country in the world that has this problem. Many countries faced with this problem together and are able to learn lessons and solutions together.

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Chapter 428

EDUCATION AND INFORMATION ABOUT COVID-19 FOR IMPROVING STUDENTS WITH SPECIAL NEEDS KNOWLEDGE IN INDONESIA

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ABSTRACT

Students with special needs have several challenges in various developments and academics aspects. They need special treatments and ways to understand realistic conditions. At the time this research conducted, an outbreak of the coronavirus diseases 2019 (COVID-19) is spreading in Indonesia. Providing information and education about the COVID-19 is very important, especially for students with special needs in Indonesia. It is very crucial since special needs students are easily infected with the COVID-19. Most of them have low self-development skills (for example, rarely washing their hands, weak immune system, and not keeping the body and the environment clean). They need guidance on how to against the COVID-19 and how to improve their awareness, as well as how to avoid and reduce virus transmission. They can get education and information about the COVID-19 from the family, school, and community. Various questions were asked to students to find out the level of student knowledge about the COVID-19. Most students with special needs can understand COVID-19 through education and getting information from their environment. They understand COVID-19 through habituation, appropriate methods, and media, as well as simple and concrete explanations.

Keywords: COVID-19, education, information, knowledge, students with special needs

1. INTRODUCTION

COVID-19 stands for Coronavirus Diseases 19, and this pandemic was first discovered in 2019 (Ana 2020, 246-260). At the time this research conducted, Indonesia is experiencing problems because COVID-19 outbreak has hit people in Indonesia. Patients infected by COVID-19 in Indonesia continue to grow (Martina et al. 2020). We need efforts to prevent the spread of COVID-19. Giving education and information about COVID-19 is very important to students, especially for students with special needs. Students with special needs are students who have problems in both developmental and academic aspects. They need teaching, guidance, and special services. Students with special needs have difficulties in understanding information (Maryanti et al. 2020). They need methods and media that suit their needs. Students with special needs have difficulties understanding abstract phenomena (Maryanti et al. 2020, 1909-1920). They need concrete media to understand.

COVID-19 is a virus that can infect the human body. This virus has a very small size and invisible (Maryanti et al. 2020). We need an electron microscope to observe this virus. The small form of the virus makes it easy for viruses to enter the human body (Li et al. 2020). For students with special needs having knowledge of COVID-19 is very important. They have a greater potential for being infected with the COVID-19 virus compared to normal students. That is because they have a weak immune system, low awareness of hygiene (Giust and Valle Riestra 2017), and limited knowledge about the dangers of COVID-19.

At present, there are many papers or news that contain information (Hashim et al. 2020), the form (Sahin et al. 2020), the size (Yunus and Rezki 2020), the transmission (Windhiyana 2020), symptoms (Razon 2020), the impact (Putra and Abidin 2020), and the efforts to prevent the COVID-19 (Telaumbanua 2020). However, until now there has been no paper or book that explains education and information about COVID-19 knowledge for students with special needs.

Students with special needs can get education and information from their environment (Kurniawan 2017). Education and information about the COVID-19 are not only obtained through education from teachers in the formal environment. However, students can obtain education and information from the family and the community. Students understand information through habituation, appropriate methods, and media, as well as simple and concrete explanations. This study was one of the efforts to prevent the spread of the COVID-19 in Indonesia.

2. THEORY

COVID-19

The COVID-19 is a virus originated from animals (Maryanti et al. 2020). This virus first spreads in the city of Wuhan, China. The virus can infect the human body through the nose, mouth, and eyes, causing shortness of breath as it damages the lung organs. This virus is very dangerous and even causing death (Angraeni et al. 2020).

The small size of the virus makes it easy to enter the human body (Hamidah et al. 2020). We can prevent the spread of this virus in several ways, including keeping a distance,

maintaining the cleanliness of the body, washing hands, and wearing a mask when leaving the house. COVID-19 pandemic does not only affect public health problems but also economic, social, and educational fields, especially in Indonesia.

Students with Special Needs in Indonesia

Students with special needs are students who have problems in their developments and it affects their academic performance (Hermawan et al. 2020). There are several categories of students with special needs including visual impairment, hearing impairment, intellectual disabilities, physical impairment, autism, and down syndrome. The classifications are simply explained as follows:

- 1) Students with visual impairments known as blind people are students who have problems in their visual senses (Purwati et al. 2020).
- 2) Students with hearing impairments have problems with hearing organs or nerves resulting in hearing disability (Hidayat et al. 2020). They usually have difficulties in understanding and communicating verbally.
- 3) Students with intellectual disabilities are often referred to mentally disabled (Sari and Kustiawan 2020). They have below-average intelligence, problems in adaptive behavior, and independence.
- 4) Students with physical disabilities in Indonesia are called *tunadaksa* (Munir and Aljauhari 2020). Students with physical disabilities have problems in their physical aspects, one of which relates to gross and fine motor movements.
- 5) Students with autism are students who have problems with interaction and communication (Ayunungtyas et al. 2020). They have difficulties in establishing eye contact and communicating their needs.
- 6) Students with down syndrome are students who have the same facial characteristics, short thick tongue, and short fingers (Keen et al. 2020). They have problems in the aspect of intelligence, usually included in the classification of mentally retarded children.

Education for Students with Special Needs

Education for children with special needs is different with the education in general (Hernawati 2007). Educating children with special needs requires special methods, strategies, media, and services based on their needs that impacted by their conditions. There are several principles of educational services that must be considered in an effort to educate children with special needs such as compassion, individual service, readiness, advocacy, motivation, learning, working in groups, skills, and the cultivation and refinement of attitudes (Abdullah 2017).

3. METHOD

This research used descriptive qualitative method. The subjects in this study were students with special needs (visually impaired, deaf, intellectually impaired, physically impaired, autistic, down syndrome) in special schools in Indonesia. We obtained data through a number of questions given to students. The aim was to determine the level of students' understanding of the COVID-19. We made 15 polar questions, and the analysis of a score of 0 (no) and 1 (yes) with a total score of 100 for all questions answered with 'yes'. We made questions through Google Form and distributed the questions through social media. Parents and teachers played an important role in helping the process of obtaining data in the field. Table 1 shows the 15 polar questions given to students.

4. STUDENTS DEMOGRAPHIC

Figure 1 displays student data about the types of challenges they encountered. 7% of students were students with visual impairments. Students had obstacles in orientation and mobility, understanding abstracts, and auditory learning. 18% of students had hearing impairments resulting challenges in language, speech, and communication. They also had visual learning characteristics and difficulties in socializing and behaving. Furthermore, 45% of students were children with intellectual disabilities. They had problems with concentration, adaptive behavior, and intelligence. Students with intellectual disabilities generally are easy to forget, easily bored, difficult to focus, difficult to understand abstract concepts, and problems in independence. 8% of students were children with physical disabilities. They had problems in the perception of motion, gross motor, and fine motor.

Table 1. COVID-19 knowledge question instrument for students with special needs

No	List of questions	Answer	
		Yes	No
1	Do you know what COVID-19 is?		
2	Do you know the size of the COVID-19?		
3	Do you know the form of the COVID-19?		
4	Do you know that the COVID-19 originated from animals?		
5	Do you know how the COVID-19 is transmitted?		
6	Do you know how COVID-19 enters the human body?		
7	Do you know the symptoms of COVID-19 infection?		
8	Do you know the danger of the COVID-19?		
9	Are you aware of the efforts to prevent the transmission of the COVID-19?		
10	Do you know that physical distancing can prevent COVID-19 transmission?		
11	Do you know that washing your hands can prevent COVID-19 transmission?		
12	Do you know that social distancing can prevent COVID-19 transmission?		
13	Do you know that wearing a mask can prevent COVID-19 transmission?		
14	Do you get information about the COVID-19 from your parents?		
15	Do you get information about the COVID-19 from the teacher?		

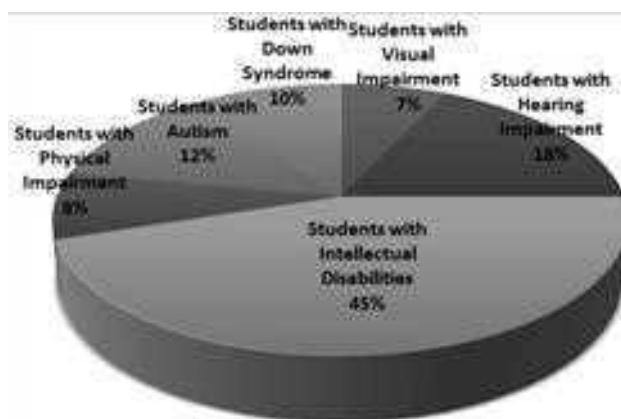


Figure 1. Types of Disabilities that Subjects have.

In the cognitive aspect, some of students did not experience obstacles and were able to participate in learning like children in general. 12% of students were students with autism who had obstacles in interaction and communication. They had difficulties in making eye contact, interacting, and often raging. 10% of students were students with down syndrome. Students with down syndrome have characteristics of unclear pronunciation, thick short tongue, and fingers, motor resistance, lack of concentration, and have below-average intelligence.

5. EDUCATIONAL PROCESS AND PROVISION OF INFORMATION ABOUT COVID-19 FOR STUDENTS WITH SPECIAL NEEDS

For students with special needs, it is very important to obtain education and information about COVID-19 and how it is transmitted because they have difficulties when studying the COVID-19 (Maryanti et al. 2020). Providing education and information about the virus for students with special needs can increase their knowledge.

In providing knowledge and support, we must pay attention to many issues including students' challenges, the opportunities, and students' needs. They have difficulties in understanding complicated and abstract concepts. As for students with visual impairments, they need learning media that can optimize their hearing and tactile capacities. Furthermore, children with hearing impairments need visual learning media and students with intellectual disabilities, autism, and down syndrome need interesting and fun media.

Basically, providing education and information about COVID-19 for students with special needs requires simple explanations and concrete examples. The role of family is also essential to increase students' knowledge. Collaboration between parents, families, teachers, and the community is needed in educating students with special needs. They can learn through habituation in daily life. As they often get education and information about the COVID-19 from the surrounding environment, their level of knowledge will improve (Abdullah 2017). In an effort to find students' improvement in understanding COVID-19, several questions about the virus were given to students with special needs from easy to difficult questions.

6. DATA ANALYSIS

Table 2 shows the percentage data analysis of students knowledge about COVID-19 before and after given education and information. A few students with special needs knew COVID-19. After given information and education, their knowledge increased.

Table 2. Subject knowledge before and after the provision of education and information about COVID-19

No	Subject	Total	Before Providing Education and Information		After Providing Education and Information		COVID-19 Knowledge Enhancement
			K	NK	K	NK	
1	Students with Visual Impairment	7%	2%	5%	5%	2%	3%
2	Students with Hearing Impairment	18%	6%	12%	15%	3%	9%
3	Students with Intellectual Disabilities	45%	10%	35%	30%	15%	20%
4	Students with Physical Impairment	8%	3%	5%	6%	2%	3%
5	Students with Autism	12%	2%	10%	7%	5%	5%
6	Students with Down Syndrome	10%	2%	8%	7%	3%	5%
Percentage Amount		100%	26%	74%	70%	30%	44%

Note: K= know; NK= Not Know

Students with special needs require education and information to improve their knowledge. They get the knowledge and information from their families, teachers, and community. However, a few students with special needs only receive education from one party. This is one of the reasons why the level of student understanding is low. Environmental factors greatly affect students' knowledge improvement besides the obstacles they have. Building good collaboration between various parties to provide education and information will increase the level of student knowledge.

Figure 2 explains the percentage of efforts made by parents and teachers in providing education and information about COVID-19. About 35% of parents and 65% of teachers gave education about COVID-19 to students with special needs.

Students with special needs are also vulnerable towards COVID-19. Most of them have low self-development skills (rarely washing hands, weak immune system, and poor hygiene). The education and information provided must be adjusted to their needs and conditions. Habituation, simple explanations, and concrete examples help students to understand education and information about the COVID-19. The balanced participation among parents and teachers makes students' knowledge increase.

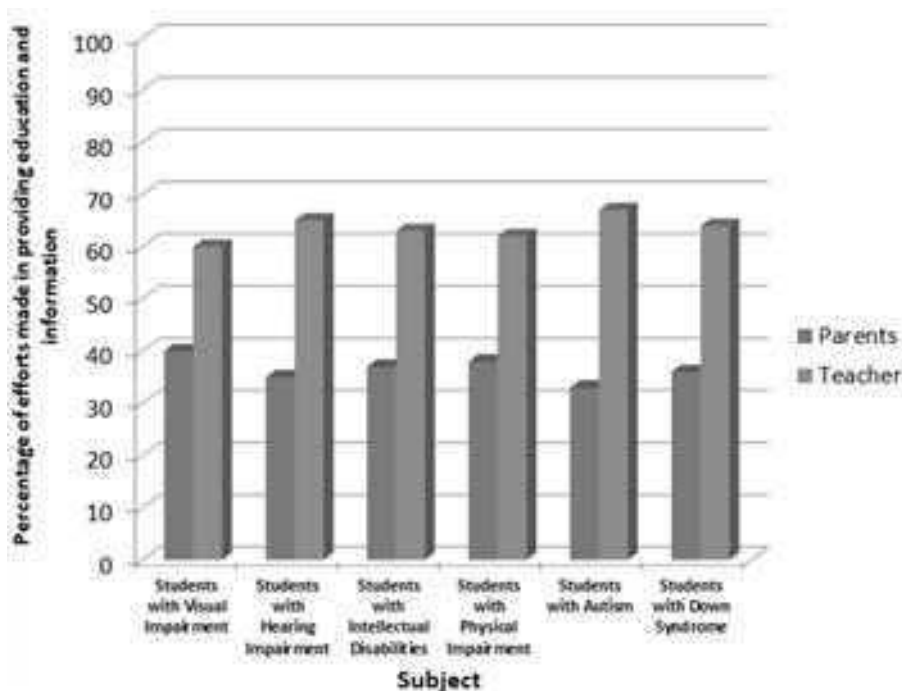


Figure 2. Efforts made in providing education and information about COVID-19.

CONCLUSION

Providing information and education about the COVID-19 is essential to students with special needs in Indonesia. It is important because students with special needs are very much easily infected by the COVID-19. They need education and information about the virus so their knowledge increases. They can get education and information about the virus from the family, school, and community. 70% of students with special needs can understand COVID-19 through education and information they get from their environment. They understand the concepts through habituation, appropriate methods and media, simple explanations, and concrete examples.

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Chapter 429

INCREASING THE SCIENCE PROCESS SKILLS USING VIRTUAL SCIENCE LABORATORY DURING THE COVID-19 PANDEMIC

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ABSTRACT

One of the science learning's main goals is to provide students with skills in the science process. Typically, these skills are acquired when students do an experiment in the laboratory. However, laboratory experiments have become difficult to conduct in the current corona virus disease 2019 (COVID-19) pandemic. This study aimed to examine all forms of learning that could be applied to improve the science process skills of the students. Types of learning that could be performed for this purpose include virtual science laboratory, problem-based gaming, open-ended science experiment, mobile scientific inquiry, and project-based learning. Based on the characteristics of each learning, it is suggested that the most effective learning during this pandemic is virtual science laboratory. This learning has features that offer students the ability to analyze, describe, anticipate, collect, prepare and answer questions.

Keywords: COVID-19 pandemic, science process skills, virtual science laboratory, problem-based gaming, open-ended science experiment, mobile scientific inquiry, project-based learning

1. INTRODUCTION

The corona virus disease 2019 (COVID-19) pandemic has now spread across the world since it first emerged in Wuhan, China in December 2019 (Hamidah, Sriyono, and Hudha 2020). On 11 February 2020, the WHO named the disease as “COVID-19,” an acronym of “coronavirus disease 2019” (Razon 2020). This pandemic naturally affects all sectors of

human life, from the manufacturing, health, transport, government, maritime affairs, to education (Ng and Peggy 2020). Education plays a key role in shaping people into being resilient people to face the changing challenges of real life. By education, we will prepare students to have certain skills that are aligned with the demands of the workforce. Scientific process skills are one of the skills they need.

Scientific process skills are skills that allow students to observe, explain, predict, pose questions, plan, and communicate (Harlen 1999). Typically, these skills are incorporated into the curriculum when performing laboratory experiments. Students are divided into different groups, then work together to accomplish an experiment with a particular topic, discuss data analysis and report results. It can be identified that there are additional benefits to the students during the experimental activities. Students feel inspired and enjoy doing it, because these practices help students grasp a concept in the same way as a scientist discovers the theory (Elfeky, Masadeh and Elbyaly 2020). Unfortunately, this practice could not be performed during this pandemic because almost all countries implement lockdown to prevent wider spread of coronavirus. The implementation of quarantine is also supported by the findings of scientists by conducting analysis based on Reduced-Space Gaussian Process Regression, which states that new quarantine measures with more restrictions for the implemented containment strategy can be successful, but in a late period (Arias Velásquez and Mejía Lara 2020).

However, learning must continue. There is no way we can let students go through the day without a lesson. During this pandemic, various ways can be taken to keep students involved in learning, including virtual science laboratory, problem-based gaming, open-ended science experiment, mobile scientific inquiry, and project-based learning.

Among the learning models listed above, it is prudent for a teacher to be able to choose one that is in line with the characteristics of science learning. In Indonesia, the fourth core competency of the 2013 curriculum notes that students must be able to process, view, and reason in the concrete realm (use, interpret, organize, modify, and make) and the abstract realm (writing, reading, counting, drawing, and composing) according to what is learned from the same perspective or theory in school and other sources (Kemendikbud 2014). These core competencies are consistent with the scientific method, namely the acquisition of knowledge through observation, questioning, testing, reasoning, analysis, presentation and creation, which are carried out in deep discussion or group practice through classical activities.

Acquiring knowledge through practicum group activities will train critical thinking and problem-solving skills as one of the skills of the 21st century. Therefore, there are several ways to improve science process skills. It can be obtained through virtual science laboratory, problem-based gaming, open-ended science experiment, mobile scientific inquiry, and project-based learning.

2. SCIENCE PROCESS SKILLS

Practicum group activities, as described previously, may provide students with skills in the science process. Science process skills are a wide range of transferable skills, applicable for many disciplines and representing the scientists' behavior. Science process skills can be divided into two levels as basic and integrated. Basic science process skills consist of

observation, communication, classification, measuring with numbers, inference, prediction, and using the space-and-time relationship. Integrated process skills consist of interpreting data, controlling variables, defining operationally, making hypotheses, and experimenting. Those two science process skills are essential cognitive skills for the success of primary school science learning, specifically at the pre-school or early childhood level because children do not have sufficient cognitive competence. Therefore, science processing skills for them do not need to be overemphasized. Nonetheless, the teaching of basic skills that will lead them to higher-order skills should also be guided. The active role of students to play, discover, solve problems and conduct research needs to be explored in the learning curriculum developed by the teacher. (Bati, Ertürk and Kaptan 2010).

Experts recommend that each stage be evaluated through a series of questionnaires to ensure the effectiveness of providing students with any measure of science process skills. The questions can include the students' findings related to their initial questions, the comparison to their findings with their earlier predictions, the associations between changes in one variable and another, the patterns or trends against all the evidence, the conclusion that students summarize and also students' recognition that any conclusions may have to be changed in the light of new evidence (Harlen and Jelly 1997; Harlen 1999). To provide science process skills with each indicator, the following describes several learning models or strategies that correspond to its characteristics.

3. VIRTUAL SCIENCE LABORATORY

Initially, the virtual science laboratory was intended to improve students' understanding of science concepts that have abstract phenomena (for example, the concept of electric fields, electricity flow and fluid flow) or to overcome the limitations of experimental equipment in schools that lack complete practical tools. However nowadays, in accordance with the rapid advancement of information and communication technology (ICT), virtual science laboratories can be applied to various subjects outside of science, for example mathematics, engineering, and languages. In general, the virtual science laboratory module must provide various information or instructions before students carry out a science experiment project, namely:

1. Course and content introduction
2. Problem or question introduction
3. Discussion and Collaborative Learning
4. Links to other learning resources and case studies
5. In-house three-dimensional virtual laboratory
6. Online scaffolding (Klentien and Wannasawade 2016)

Virtual science laboratory is a term used to refer to a digital environment designed to meet research needs. A significant contribution to many research domains, facilitating more efficient, open and reproducible research in new ways possible through virtual laboratories (Barker et al., 2019). Specifically, virtual science laboratories refer to integrated access to a variety of resources including software, databases, collaboration tools, workflows,

instrumentation, and high-performance computing, usually via websites and mobile applications. Thus, the virtual science laboratory requires an internet connection when operating it. However, during difficult times like we experiencing nowadays, every virtual science laboratory developer is required to produce programs that can also be accessed offline.

There is a wide variety of applications available on the market for building virtual laboratories, from basic to complex, from free to purchased applications (Bilgehan, et al., 2016). All of this software is useful for producing various kinds of simple simulations to more sophisticated virtual laboratories. The subject matter can be presented to students in an integrated way with its web-based and mobile application-based characteristics. Virtual science laboratories can be used effectively in the classroom as well as outside the classroom, even at home if some further work may be required. What needs to be addressed when developing content in a virtual science laboratory is the pedagogical aspect that is integrated with the content that enables students to construct an easy-to-understand learning environment (Esquembre 2015).

A more sophisticated virtual laboratory model, for example, can be created with unique characteristics into a 3-dimensional interactive virtual laboratory. Due to its design, this model is the first of its kind which allows multi-admin, multi-user, special software compatible to run on iPad, iPhone, android and other smartphone platforms. This 3-dimensional virtual laboratory is ideal for the use of all student-centered active learning models (problem-based learning, cooperative learning, project-based learning, inquiry-based learning, research-based learning, invention-based learning and structuralist learning), due to its multi-user nature and accessible through the Internet (İnce et al., 2015).

Several research findings have shown the acceptance of the virtual science laboratory, including that student acceptance of this technology is focused on levels of performance, enjoyment and student satisfaction. Efficiency and fun are factors that positively influence student adoption of this technology. As a result, virtual activities and practices must be well designed to provide a successful educational environment for students. Additionally, virtual tools should be built with a playful approach, since fun and enjoyment are essential to involve students in the subject matter and learning process, as well as to increase the motivation and acceptance of these tools (Estriegana, Medina-merodio and Barchino 2019).

In contrast to science subjects, in the engineering field, virtual laboratory applications are less meaningful if the students' desired skills are hands-on especially if it is applied to distance or online learning. The reason for this difference lies in the fact that engineering often requires laboratory training to provide effective skill acquisition and hands-on experience. Real laboratory still needs to be activated or replicated as a virtual laboratory that is completely software-based (Potkonjak et al., 2016). In line with the virtual science laboratory, virtual learning is also being promoted in various countries (Almarzooq, Lopes, and Kochar 2020; Jowsey, Foster, Cooper-Ioelu, and Jacobs 2020) because during pandemic like this time, face-to-face learning is less likely to be implemented.

4. PROBLEM BASED-GAMING

Teachers often have to think that learning must be enjoyable for students, so that they can acquire knowledge in a more meaningful way. Games are a medium that can be used for this purpose, like puzzles or simulations. Games could become simple solution games or complex multi-solution paths that require inquiry skill and all dimensions of science process skills to complete. Games are proven to be able to meet the challenges of strategic and logical thinking as well as challenges to win the game (Rahmani and Abbas 2014). Other researchers also mentioned that problem-based gaming can improve student programming skills (Topalli and Cagiltay 2018). This is because problem-based gaming can increase student motivation to introduce programming concepts. In addition, because they can see the big picture of the software development cycle and the place of coding in that cycle, their understanding of programming concepts can most likely be conceptualized thereby enabling them to better integrate other concepts in their programs. Specifically, for increasing learning motivation, the same thing is also revealed that with problem-based gaming in the English course, student learning motivation can be further improved compared to conventional learning. (Hwang et al., 2017).

5. OPEN-ENDED SCIENCE EXPERIMENTS

The open-ended experiments are designed to enable students to explore and create. This method allows students to select experimental equipment, obtain and interpret data, and to determine results. Therefore, with the open experimental method it is hoped that students can develop psychomotor skills and behaviors such as thinking, deciding, making original implementations according to their decisions, and deducing the results obtained (Aydoğdu, Buldur, and Kartal 2013). The results of other studies show that with an open-ended experiment, students are able to better design and carry out experiments, analyze and interpret experimental results and work in groups (Haron et al., 2013). They are also able to design their own procedures, analyze and interpret experimental results, and work in teams (Mahmoud, Hashim and Sunarso 2020).

6. MOBILE SCIENTIFIC INQUIRY

Mobile scientific inquiry is defined as a scientific investigation application that is supported by mobile devices in the science process skills. The development of mobile scientific inquiry is based on the fact that the use of mobile devices has become an integral part of our daily lives, and this has great potential for educational applications. With a storage unit, camera, sensors, and internet connection, it allows students to use their cellphones for more meaningful learning. Regarding science process skills, technology-based inquiry activities need to be designed. Developing better science process skills, which are not only related to science but also with problem solving and critical thinking, will help students to develop higher order thinking skills that can be generalized for the life of students (Ekici and Erdem 2020). Learning using mobile scientific inquiry is also suitable for fostering student

curiosity and motivation. It helps learners to develop their ability to work in complex and unpredictable environments that can make them critical thinkers and agentic learners (Suárez et al., 2018).

7. PROJECT-BASED LEARNING

Project-based learning is a learning that refers to an inquiry-based learning method that involves students in knowledge construction by asking them to complete meaningful projects and develop real-world products (Guo et al., 2020). Project-based learning can also increase student motivation and problem-solving abilities (Chiang and Lee 2016). Through project-based learning, students are trained to challenge driving abilities focus on learning goals, participation in educational activities, collaboration among students, the use of scaffolding technologies, and the creation of tangible artifacts. Of all these measures, the most relevant is the development of tangible objects which can authentically solve the problem. This indicator differentiates project-based learning from other student-centered learning, for example problem-based learning (Helle, Tynjälä and Olkinuora 2006). This creation process requires students to work together to find authentic problem solutions in the process of integrating knowledge, application, and construction. Instructors and community members (clients), usually as facilitators, provide feedback and support for students to help their learning process.

Project-based learning with its indicators is a powerful teaching method that can achieve the following results: (1) motivating students, (2) preparing students for college, careers and becoming good citizens, (3) helping students meet expectations and perform well on tests that allow students to demonstrate knowledge and deep thinking skills, (4) enable teachers to teach in a more satisfying way, and (5) providing opportunities for schools and governments to find new ways to communicate and connect with parents, the community and the wider world (Larmer, Mergendoller, and Boss 2015).

For all the characteristics of each defined model or learning media, teachers are required to be able to sort, select and develop content that is integrated for pedagogical aspects to improve students' skills in the science process. Particularly in the current situation, where face-to - face learning is difficult to do, students need the psychological touch of a teacher that is represented in every learning model or media that teacher develops.

CONCLUSION

Being based on the five learning models or media outlined, the authors argue that the Virtual Science Laboratory is one of the most likely strategies to be implemented to equip science process skills in the current COVID-19 pandemic situation. It is because, in the virtual science laboratory learning, all the necessary experimental stages have been properly incorporated into the module. Then, by utilizing ICT which is very advanced and familiar to students, teachers can further develop learning programs that are in line with the current situation (contextual) and students can also be creative in exploring their environment in the search for scientific concepts like a scientist. Hopefully, everyone's creativity would be

strengthened so that it can produce something useful for all especially during the COVID-19 pandemic which no one expected or want.

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Chapter 430

POST COVID-19 COMPETENCIES OF TEACHERS

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ABSTRACT

As the COVID-19 pandemic spread around the world, most educational institutions have been temporarily closed and it affects the student learning process. A competent and skilled teacher is one of the most important inputs in the education system, but teachers are often unprepared for teaching in crisis and post-emergency settings. They are stressed since they cannot attain responsibility as their roles. It seems that some competencies in the 21st century do not efficient enough to the crisis settings. This crisis teaches a lesson to the educator to rethink the teacher efficiency competences. Research claims that a relationship and cooperation with communities for learning organization is the competency that significantly helps student learning in the crisis-affected setting. Moreover, technology literacy is advantaged to help students learning in and out the classroom. Teachers with limited qualified for technology have to be trained. To prepare the new generation student for the fast-changing world and in times of emergency, the teachers should have more efficient and competent. The competent teacher can shape the best student.

Keywords: COVID -19, 21st century competencies, teacher competencies

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INTRODUCTION

COVID -19, an emergency pandemic presents the big experience for the global citizen and all the organizations, including education. There are no schools, no exams, but teachers. The crisis is highlighting the teacher to play the roles outside the school because of the closure of schools. How could they be responsible for this challenging role, outside-school teachers? In Thailand, there are nearly 13 million students, which are out of school and 600,000 teachers are unable to teach in their classes until at least 2020; however, education has to continue as soon as possible through alternative learning pathways (Rattana Lao 2020). Online learning and distance learning program are the responses for teaching and learning within the urgent condition (Saripudin et al., 2020). This means Thailand maintains the learning and ensures that all the students retain knowledge and skills. Although that is just the action in the short term, it causes bitter stress to teachers, students, and even the parents. Not all teachers can use technology to teach. Some of them are just trained whereas the students especially those who are in the rural area are out of necessary technological tools for learning. Worst yet, some parents, who are unemployed during the crisis or have low-wage jobs, have no time to fill in the temporary teachers for their kids nor have the financial resources to afford outside support (John DaSilva 2020). Due to the big impact of the crisis to the education sector around the world, educators have to rethink what the education and teacher competencies for emergency settings in the future should be.

TEACHER COMPETENCIES AND THE STUDENT SUCCESS

Being a teacher at any level requires a significant amount of knowledge and skill. Teachers are key to success in education. The competent and skilled teachers make learning possible whether during times of crisis or not. Research confirms this common perception that all factors under the control of schools, the maximization of student success relates to the powerful influence of teacher the most (Babu and Mendro 2003). The competencies address the ability to do something successfully or efficiently. Competencies are not skills, but competencies are inherent qualities an individual possess – combining skills, knowledge, and ability. What are teacher competencies? They are a combination of skills, knowledge, behavior, and attributes that enable effective or better job performance. To fulfill student learning, teachers must have expertise and good competencies with the changing educational context where hundreds of critical decisions are required (Jakson 1990).

According to the importance of the teacher, paying attention to the competencies for teachers helps to ensure that all teachers are prepared to make school a positive experience for students and their families. The strong set of competencies that every competent teacher also needs to possess are knowledge, skills, and values. What core competencies do the modern effective teachers in the 21st need for preparing their students and equip them with the essential skills required for the future? UNESCO (2011) defines that the teacher competency in 21st Century consisted of five core competencies which are knowing and applying technology; deep understanding education policies, curricula and be updated on national, regional, and global developments, what to teach, assessment, flexibility in teaching, instructional skill for problem-solving; building the knowledge of learning process, learning

strategies, Information and Communication Technology (ICT) instruction, ICT community designing to promote the continuous learning skill; being a leader of the colleagues and community; and developing teacher profession as well as applying ICT for the professional learning community. That is the big picture of teacher competencies in the global level. Similarly, in the Southeast Asia region, the eleven Ministries of Education realize that schools today operate in a complex and constantly changing world of knowledge and information. Thus, the Teachers' Council of Thailand (TCT), in partnership with the SEAMEO Secretariat (SEAMES) and the SEAMEO Regional Center for Educational Innovation and Technology (SEAMEO INNOTECH), initiated the development of the Southeast Asia Teacher Competency Framework (SEA-TCF) in April 2017. The SEA-TCF consists of four essential competencies and twelve general competencies that high performing teachers in the region must possess. Four essential competencies are:

1. Know and understand what to teach. This is the ability of teachers to deepen and broaden their knowledge on what to teach, understand education trends, policies, and curricula and be updated on local, national, regional, and global developments.
2. Help students learn. It is the ability to know their students, use the most effective teaching and learning strategy and assess and give feedback on how students learn.
3. Engage the community. This is the ability to partner with parents and caregivers, involve the community to help students learn, and encourage respect and diversity.
4. Become a better teacher every day. This is the ability to know oneself and others, practice human goodness and then master the teaching practice. (Teacher Council of Thailand 2018).

However, the competencies listed in the framework can be interpreted based on local context and specific needs. For Thailand, the teacher competencies included five core competencies and six functional competencies. The core competencies consisted of an achievement in performance, self-development, teamwork, ethics, and teacher profession conducts, while the functional competence consisted of a curricular administration and learning management, a learner development, a classroom organization, an analysis, synthesis, and research for a learner development, a teacher leadership, a relationship and cooperation with communities for learning organization (Chatchai Wangmeechongmee 2017). It seems that the competencies defined are able to enhance the student 21st Century skills - learning skills, literacy skills, and life skills, but some are inadequate for the emergency setting.

WHAT KIND TEACHER COMPETENCY IN POST- CRISIS?

In this crisis situation, the risk-control decision of government led the students to study at home with the distance learning program or online learning. This causes a degree of inconvenience and problem. Students lack technology tools. Although they are the digital age citizen, they cannot learn. Besides, some cannot access the online system. Some teachers and parents lack of technology implementation potential and problem-solving skills. To provide technology to support the students learning opportunity and to imply technology to enhance

students' knowledge, learning is essential for the 21st Century teachers. In fact, some teachers cannot operate a computer as well. Because of the sudden COVID-19 crisis, the educators evidently perceive that teacher is incompetent in technology. The question is if the others are efficient enough for the current rapidly changing world, especially in the emergency setting.

To continue the student learning during the crisis, the educators have to emphasize on the access to learning and the quality of education as well. There is a strong evidence supported that the use of community-based education is the valuable channel to increase access to education, including accelerated learning programs, and approaches to distance learning for primary, and secondary students. For the quality of education, community-based education and community participant monitoring are needed to increase academic achievement for the primary school students related to one of the 21st century competencies (Burde et al., 2015), as well as a relationship and cooperation with communities for the learning organization. Therefore, to build a strong relationship with the community, one success key is to make strong education. Besides the community supporting, remote education in the midst crisis is the other success key.

Digital learning television, online learning, and distance learning program are the alternative nation educational pathways. Although learning through TV is user-friendly and particularly for vulnerable students, it is a one-way communication. Online learning is "the most ideal" for the current situation in Thailand because of its ability to accommodate a two-way communication and a real-time response, so digital literacy competence is also essential for the teacher in this crisis (Kertbundit 2020) UNESCO defines that knowing and applying technology is one of the 21st-century competence; nevertheless, some teachers are still inadequate in this competency. How are about students? They will be no problem for the digital age generation, but some families do not either have access to the same technology tools (internet, computer, television, smartphone) nor have the same level of knowledge and skills in using technology. It is impossible for online learning. It is crucial for the teacher to follow up and identify the specific needs of the vulnerable students to maintain their appropriate learning which reflects that learning management and learner development are also practical competencies.

The spread of COVID-19 is the great opportunity to reform the education system, including the teacher profession development (Sangsawang 2020). What should the competent teacher in post- crisis setting be? Are the teacher competencies today sufficient for tomorrow world? As the responsibility in shaping the students and community, development of the competent and skilled teachers is the most considering factor. Unfortunately, the professional teacher development in Thailand is not as successful as the expectation level. One way to develop the effective professional teacher is to develop teacher competency. Undoubtedly, there are some 21st Century teacher competencies are relevant to the research finding competence in crisis: a relationship and cooperation with communities for learning organization, learning management and technology literacy.

Right now, the educators have to learn that both pre-service teacher and in-service teachers have to be retrained some essential competencies to be more effective, especially technology literacy. Not only those competencies in 21st century are the emergency response but also some renew ones. The recently crisis teaches the educator a new lesson for preparing the better students for what the future might hold. The lessons are to educate citizens in an interconnected world, redefining the role of the educator, teaching life skill needed for the future, and unlocking technology to deliver education. Similarity, some researchers (Helen

Soulé and others (2014)) stated their researches that project based and inquiry-based learning (PBL) instructional 21st century learning practices is proven to produce positive student outcomes. They also claim that “PBL and other instructional practices that promote student engagement, real-world experiences, the acquisition of 21st-century skills, and transform the role of the teacher from lecturer to guide/facilitator have been shown to produce the desired student outcomes (Soulé, et al., 2014, <https://www.hanoverresearch.com/insights-blog/bringing-21st-century-skill-development-to-the-forefront-of-k-12-education/>, retrieved on July 1, 2020).” According to the research, the practical instructions reflect a very different role for teachers and require significant changes in behavior, pedagogy, and practice. The significant competence for the unpredicted future, emergency setting should be:

1. Pedagogy competency, including ability to design learner centered methodology, organize instructional management related to the learner requirement, the contexts, and the situations (Mulyanti et al., 2020, 271-282).
2. Flexibility and adaptability competency, including the ability to adjust profession planned work by gathering relevant information and applying critical thinking to address multiple demands and necessary priorities in a changing environment and emergency setting.
3. Social competency, including the ability to deal with social condition, get more sensitive to the problem around, access to the society well, take another’s perspective, or idea concerning a situation.
4. Critical decision competency, including the ability to critical analyze the education situations and problems, as well as to make a critical decision to solve the conflict and problem based on the information analyzed in specific context.
5. Lifelong learning competency, including the ability to gain knowledge and skills continuously to develop professional job, and to provide quality learning.

The teacher is the most important factor indicating the quality of education; therefore, they need strong and efficient professional competencies. COVID-19 is the catalyst to reform the education system and the teacher competency in managing the quality outcome, so teachers’ competencies must be reviewed and redefined depending on the fast-changing world and the unexpected crisis (Ana 2020). A relationship and cooperation with communities for learning organization the competency related to the research findings, showing that community-based education and community participant monitoring are increasing academic achievements for the primary school students related to one of the 21st-century competencies (Burde et al 2015). The competent teachers are the ones who can collaborate well with the community in order to build a learning organization. This is necessary for the crisis setting for the closure school and students have to study at home. Some parents have no time and lack of knowledge and digital skill which put them a lot of pressure. The teachers collaborate with the community to continue student learning it reflect the teacher’s proficiency in learning management. In addition, the alternative pathway in the pandemic is online learning and distance learning. Online learning is “the most ideal” for the emergency situation in Thailand, the interrupted education could be progress if the teachers and parents are potential resources.

The educators have to rethink what the other necessary competencies are required for the fast-changing global. The responses are pedagogy competency, flexibility and adaptability

competency, social competency, critical decision competency, and lifelong learning competency. As the education needs a competent teacher, the professional development (both pre-service teachers and the in-service teacher) must be a priority and carefully prepared in order to shape the best teacher that they can be. To support the success of the student, government initiatives to maintain student learning cannot be effective without the use of an invaluable educational resource.

CONCLUSION

A competent and skilled teacher is one of the most important inputs in the education system, but teachers are often unprepared for teaching in crisis and post-emergency settings. This crisis teaches a lesson to the educator to rethink the teacher efficiency competences. The relationship and cooperation with communities for learning organization is the competency that significantly helps student learning in the crisis-affected setting and technology literacy is also advantaged to help students learning in and out the classroom. Teachers with limited qualified for technology have to be trained to prepare the new generation students for the fast-changing world and in times of emergency.

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Chapter 431

PERSPECTIVES OF THAI PARENTS ON COVID-19 OUTBREAK THAT EFFECTS STUDENTS LEARNING

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ABSTRACT

The COVID-19 outbreak has caused a big problem for Thai students and parents because most of the education systems have not yet entered the world of learning. By using program for International Student Assessment digital devices, the data showed that teachers and schools are well-equipped with technology and support online teaching. In the aspect of students' access to the internet, Thailand still has students who are in unfortunate and unfavourable environment. Qualified online knowledge is essential and various fundamentals should be taken into account in order to ensure that all Thai students receive quality learning. The COVID-19 Adult Digital Technology helps students to acquire quality knowledge. However, it is a costly education learning system and paying special attention to the suitability of applications that maintain the relationships of teachers and students, including family members' relationships is needed.

Keywords: COVID-19, crisis problems, Thai parents' perspectives

INTRODUCTION

The advent of the COVID-19 crisis reveals that most education systems have not been ready to enter the world of learning using digital devices. Based on the data collected from 15-year-old students and school administrators at Program for International Student Assessment (PISA) 2018 in 79 educational systems around the world, it was found that many

opportunities and access to online learning begin with the basic necessities of online learning. Having a quiet place is the first thing that students should have in order to concentrate on learning. PISA 2018 found that only 15% of students in Organization for Economic Cooperation and Development (OECD) countries do not have a quiet place in their home to use for learning and up to 30% in Indonesia, the Philippines and Thailand (Boonsu, 2020).

In Thailand, there are students who come from schools with inferior socioeconomic status, reporting that there are no more quiet places in the house for learning than students from schools with socioeconomic status who obviously have a distinct advantage. In Thailand, important information from PISA 2018 shows that Thai students still lack important factors for online learning at home, including quiet places in the house for computer learning and internet connection. A comparison between students from disadvantaged schools and students from advantageous schools including Thailand shows the gap of having computers at home between these two groups is more than 50%, which shows the inequality of educational opportunities. Furthermore, Thailand has about 80% of students accessing the internet from home, in which the difference between students from advantageous schools and students from disadvantaged schools is approximately 30% (Institute for the Promotion of Teaching Science and Technology 2020; OECD 2020; OECD 2020b).

Thai Parents' Opinion on the Student Studying Problems

The situation of the COVID-19 outbreak affects the teaching and learning of Thai students who have to study online. However, the readiness and family status are different. Some families may be in a position to have everything, and some parents are able to access the learning media when needed, whereas other families may not be able to afford it at all and it is a huge issue that affects them. During the outbreak, students should study at home in online learning. It means the learning must be compatible with the Wi-Fi contract system including communication devices such as computers, laptops, and tablets that can be used to efficiently access the online program. Besides, the place for studying and sending the assignments to their teacher or lecturer must be a private space or a quiet room such as private bedrooms. Another problem for a university student where the student requires to follow real time online class so the student has the responsibility to a certain extent. However, in a primary or secondary school student's case, there must be a guardian to monitor them especially primary school students. They need close guardians to help them in their learning. As some comments from Thai families are as follows:

"...Since our family has two members who are students in a university and junior high school the effects found are different. In March, when the COVID-19 outbreak began in Thailand, it has impacted the exam study, which was close to the end of the semester. The government has encouraged schools to accelerate the learning and give tests faster and stop learning once the exam is completed. The regulation did not give much impact to primary and secondary schools because the school holiday is closer. However, for the student studying at the university level the student still needs lecture, therefore, the learning has changed to teaching and testing online because the student is an English language student. It is still a mid-term study and will continue to study and have exam. This may cause problems in online learning because either students or teachers have never had this type of teaching before and are not ready. The problem occurs as well as adaptation for online learning at home or on the internet via wi-fi using a laptop or tablet should also be taken. Our family is ready to promote necessary learning media equipment and support the arrangement of the health care readiness in our area, useful food discussions for encouragement..."(Taipae 2020).

"... As a parent, I wish the director of every school and the Ministry of Education help to review the teaching online learning as well. As I see the hardships of many parents and they have come to discuss to share our varied challenges and the reasons behind them. Therefore I would like to give examples below:

- 1 *In order to have online learning, it is very important for students to have a computer and internet connection. If they do not have those facilities at home, they cannot learn. Consequently, parents have to buy them in order to support the children learning but computer is quite expensive. On the other hand, at this time, parents have less work and make a living is difficult, find extra money is challenging and it is also difficult for to find money for food or buy a daily. If a family has two or three children, they have buy two or three devices because the children must study online at the same time. Some parents do not want their children to be inferior to others. As a result, parents must borrow money to buy computers so their children can learn like other students. Moreover, they must find money to pay for tuition, books, clothes, school supplies in each semester and it has already been difficult. Why should we find more money to pay for the computer?*
- 2 *Regarding online learning, if there are no adults sitting near children, do you think the children will not open other pages like YouTube, games, and other websites? Will each student study hard? And if the parents have to sit and watch over the course, when will they work to pay for the newly purchased computer?*
- 3 *For young children, such as kindergarten 1-3, is it appropriate to allow children to sit and study in front of the screen for such a long time? It affects their eyesight and also they do not have long attention span to endure sitting and listening until the class over.*
- 4 *Parents must pay tuition, but they must sit and teach all of their children. The point is why parents would pay the tuition if parents must sit and teach children. Paying tuition does not mean we will teach our children or we cannot raise children. During the online learning, the schools do not lower the tuition but still pay the same amount of tuition. And if parents have many children, the parents may not be able to take care of all the children's learning, because they study online at the same time.*
- 5 *If parents do not let the children study online for their own reasons, will children be embarrassed? When they are embarrassed, as a result children do not want to go to school the next day, suppressing various things and children will ask parents to buy a computer that every child wants. However, many students, instead of studying they play games or see the movies. Do you think most kids will do what more than each other?*

Therefore, for the aforementioned reasons, I would like to ask the director of every school and the Ministry of Education consider them as well because I think it affects parents in many ways, and these are just some examples to understand. There are still many reasons that impact how hard parents have to fight with the online education policies you have created now". (Boonsuk 2020)

Problems in online learning have also been encountered by university students since March 2020. Initially, the modifications on the learning made quite suddenly causing students and professors had not much time to prepare or adjust. It has causes problems that emerged both from teachers and students. Some teachers are old who lack information and technology skills, creating difficulties with the use of programs and instructional materials when they conduct online courses. It takes time to solve the problem or call someone to help and it takes almost an hour of study time (Mulyanti et al. 2020). Regarding the issues with the study time, as in the past, one subject took three hours but was changed to just two hours.

Other challenges include difficulties in understanding the content and learning styles, questions and also answers are not clear and distinct from the classroom. The instructors sometimes let the students study from the recorded clip. Consequently, when they do not understand the lecture, they cannot ask immediately. Additionally when doing groupwork, students encounter problems especially when they need to coordinate with peers specifically when submitting work to the teacher. The fact that students have to present their work online is also difficult (Ana 2020). Students are unable to solve problems as good as while learning in the classroom and most importantly, the problem of inter-connected signals that sometimes gets stuck or fails.



Figure 1. News in television about Thai parents and teachers concern about online study (Television Station Channel 23 2020a; Television Station Channel 23 2020b).

Furthermore, concentration span is also an issue as studying at home is different from studying at school (Sangsawang 2020). At home, other family members accidentally might disturb the student. Students commented that online learning was not as effective as studying in a classroom which was more understandable and merrier. During the online learning, some parents are willing to accommodate the learning and help solve the problem, while some families are willing to provide the tools needed for the learning. However, there are still many families who are not able to support students at all (*Figure 1*).

New semester and opening of schools and universities in Thailand arrive in July. The government announced the semester would be started, however, there is a requirement for educational institutions to manage online teaching along with studying at school by alternating days to study online. Most teachers and parents agree that for elementary and junior high school students studying online for 2-3 are plausible because this group of students still have fairly limited self-control. During school hours, parents should closely monitor the students to help them particularly on certain sections that they do not understand.

Furthermore, students may not have a lot of concentration studying outside classroom because they have never previously encountered this situation. Students may think of their peers, wonder when they could meet in school again, and think of when they start school. This condition affects the students' development. During the online study the family member who would take care of the students would then help to make the learning more efficient.

Online education requires a lot of adaptation from parents and students because each family prepares differently. Most people in Thailand are relatively in the middle level although there are still many people who are in low economic level. Thus, many families will encounter a variety of obstacles in online education. Opinions from some of the parents are:

1. Each family may have two to three children who are at the school age and does not have enough money. Each child studying at different levels, causing problems such as a place to learn at home and insufficient equipment for learning.
2. There are serious problems if a family has children in kindergarten and elementary school years. It means adults or parents should always help and closely control all the time.
3. Parents mostly have to work. Some parents have their own business while others work in public or private agencies. They may not have time to look after children and some poor families will get more problems.
4. Some families do not live with their parents and some live with grandparents or elderly people. If they have to support children education, this is very complicated because some people do not know much about education or uneducated.
5. Families will have to spend more in school supplies if they have more than one child and they will have to pay more for the monthly internet charge that allows the fast Wi-Fi signal speed that helps students to learn well.
6. Education for children is not as effective as studying in school because children may not be concentrated for a long time and lack of motivation because the learning is different from the class in the real classroom.
7. Children will become bored because it is not as fun as studying with friends in the class that has the interactive talk and have fun activities together.
8. Some students may not attend classes online at the time the teacher teaches. It can definitely happen or some students are addicted to games and the might play games instead of studying when their guardian or parents are not around.

The aforementioned are just some of the problems that many families have encountered and they are still worried. Therefore, coping with what has been happening and working on the adjustment together with the parents and students are essential. According to us, below are things that parents might need to prepare:

1. A place to study which is private and no noise, such as a children's bedroom.
2. Sufficient educational materials and equipment at least for two children in order to minimize the educational hurdles they might encounter and they can send the assignments punctually.
3. Schedule for children such as when to wake up take a shower, eat, and study online.
4. Studying time and understand the each course hour together with the children, as well as taking care of learning activities with teachers and friends while online.
5. Monitoring children homework, lesson review and others.
6. Providing children with relaxation from studying to avoid excessive tension.
7. Discussions and communication between parents and class teachers or subject teachers about various problems.
8. Allocating time to take care of the children, although parents are not sure how much they can do.

CONCLUSION

The COVID-19 outbreak has caused a big problem for Thai students and parents because the education mostly served through online classes. In the aspect of students' access to the internet, Thailand still has students who are in unfortunate and unfavourable environment. Online learning is a costly education learning system. Therefore, paying special attention to the suitability of applications (that maintain the relationships of teachers and students, including family members' relationships) is needed in order to provide continuous learning for our students and expand the home school collaboration.

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Chapter 432

CHALLENGES AND CHANCES IN LEARNING MANAGEMENT FOR THAI STUDENTS DURING THE COVID-19 OUTBREAK

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is a new deathly contagious disease that poses tremendous threats to the human race. It was announced by the World Health Organization as a global pandemic. The spread of the virus is the urgent crisis which affects the educational management in Thailand and around the world both in a direct and indirect way. This is considered a big challenge for the opportunity to develop new learning channels and blend online materials or digital technology devices with various instruction in order to broaden the teaching and learning experience on both offline and online platforms so that learners are able to learn continuously, effectively, and efficiently. In Thailand, On Site, On Air, and Online are the keys for every student, either who is able or unable to access online learning, to be able to keep up with the study during the implementation of the semi-lockdown and social distancing measures for preventing the spread of the pandemic by encouraging people, and to limit travel and refrain from participating in activities that involve a lot of people. Regarding this condition, what needed to be taken into consideration is educational inequality, resource management, readiness and cooperation of parents and family, the adaptation of teachers, and changing behaviors of learners. It is required that a strategic plan on educational management must be implemented in order to draw up short-term, medium-term, and

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long-term respond plans as well as seek cooperation from various sectors: educational, governmental, and private to support, develop, and exchange instruments or new techniques for successfully overcoming the obstacles of teaching and learning during the COVID-19 pandemic.

Keywords: COVID-19, learning management, Thai students

INTRODUCTION

In the history of Thailand's education, there have always been problems since the founding of Thailand 800 years ago. The first Thai alphabet was invented to protect the nation from losing territories to neighboring states that had already owned a written language (Office of the Education Council. Ministry of Education 2017). Until today when a large number of crises emerged due to different factors such as those relating to public health, the economy, politics, society and Thailand once again works on the crises.

The spread of the Corona Virus Disease 2019 (COVID-19) pandemic has posed a series of impacts to people involved in Thailand's educational sector, ranging from students, parents, teachers, as well as the state and future educational management. COVID-19 pandemic is a serious issue, and combating viral diseases has always been a serious challenge for many aspects, including health authorities throughout the world (Mulyanti, Purnama and Parwinanto 2020).

This COVID-19 pandemic seems to "disrupt" Thailand's instructional management since Thailand's education system has been driven mainly by schools and universities through educational intervention, interaction, and cooperation. In fact, those who are responsible for and play a role in Thailand's education have tried so hard to seek appropriate approaches to move the education system forward.

This is considered the opportunity that lies in the crisis which transforms the education system into a new form, especially the application of "technology" to the instructional system to a greater extent as identified in the Strategy for Promoting and Developing Digital Technology Systems for Education of the 12th National Education Plan (2017 – 2036), which aims at providing Thai people with the opportunity for continuous learning through information technology throughout life. This corresponds to the development in terms of access to equal and efficient services (Office of the Permanent Secretary Ministry of Education 2016). The blending of "technology" with teaching and learning enables the system to run continuously and allows both learners and teachers to access education regardless of places or locations as shown by the analysis of Jeanne Allen, the founder and CEO of The Center for Education Reform, in *Forbes* indicating that there is always opportunity lying in the midst every crisis.

OPPORTUNITY IN THE CRISIS: EDUCATIONAL TRANSFORMATION

Based on the aforementioned challenges and opportunity, information technology is considered the tool for improving and driving Thailand's education forward. The application

of “Educational Technology” to teaching and learning allows learners who are encouraged to keep learning at home during the COVID-19 pandemic be able to keep up with lessons. As for Thailand Minister of Education, Nataphol Teepsuwan, has proposed three plans for basic education teaching and learning management as follows:

1. On Site refers to the normal operations of schools based on the discretion of public health agencies.
2. On Air refers to the teaching and learning approach applied in case schools cannot return to normal operations and the social distancing measure is still implemented. This can be carried out by different means; including Distance Education which are conducted through Distance Learning Television (DLTV), Distance Learning Information Technology (DLIT).
3. Online is the teaching and learning approach applied in case schools cannot return to normal operations as mentioned in point 2 above. Therefore, the teaching and learning activities are carried out by connecting DEEP (Digital Education Excellence Platform) with other platforms such as Google Slide, Google Docs, Google Sheets, Google Jamboard, or Microsoft Teams in which many features such as Chat, Hub, and Microsoft Office are used. In regard to this, the systems proposed in point 2 and 3 above require a test before the next academic semester starts (OBEC Chanel 2020; Silpakorn University 2012).

Generally, there are two parts to online instructional management. First, to which a lot of technologies are applied on which the implementation of the channel currently known as “Live Streaming” which engages teachers and learners in real-time activities as seen in Figures 1 and 2; and synchronous learning which is based on time conditions, teaching (learning schedules), the volume of learning content, and direct transference of knowledge from teachers through technology according to the established curriculum framework. This can be conducted using Facebook Live or Zoom Meeting application.



Figure 1. Live Streaming for teaching and learning.



Figure 2. e-Books are education media on learning platform.

Second, the Asynchronous Learning Network (ALN) can also be used to enable the teaching and learning anywhere and anytime based on learners' needs with teachers to provide on-demand consultation. Through ALN (Figure 3) teachers who are accustomed to the conventional teaching approach may also take on other roles in the education system, such as mentors, counselors, and curriculum counselors. In addition, the content will be posted on media or sent to learners through various platforms, allowing learners to manage the amount of content and then be able to make choices about new knowledge information whenever they want. However, both teachers and learners need to keep up with each other through the use of blogs and social media, such as MOOC, COURSERA, OpenLearnsip (Silpakorn University 2012).

As for higher education (Higher Education, Science, Research and Innovation 2020) instructional management, a lot of precautionary measures against the COVID-19 pandemic have been implemented with the aim of reducing the spread of the virus by encouraging people to limit travel and refrain from participating in the activities that involve a large number of people. There are three practices which are related to higher education teaching and learning management introduced as follows:

1. Stop all forms of teaching and learning activities except those conducted across online platforms. It aims to complete the transition of formal education into 100 percent online learning before 1 April 2020. As for some programs that require the assignments to be completed through practices and operations, each higher educational institution can use discretion to take a careful look for appropriate approaches that encourage learners to spend as much time as possible at home as approved and considered acceptable by the president of each higher educational institution.

2. Consider canceling, postponing, or replacing all kinds of internships with more appropriate activities.
3. Adjust or replace the normal examination and assessment practices with a more efficient one that is appropriate for the online teaching and learning style created.



Figure 3. Teaching recording to provide content to students by asynchronous learning platform.

The management of education could not perform without teachers and students engaged in teaching and learning a certain subject, as its vital elements. Educational innovations can be implemented in instructional management based on the conditions of each particular process or in a mixed form that supports durations, opportunities, conditions, variables, readiness, or the ability to access learning sources primarily available in both classroom approaches or other teaching and learning methods.

Taking into account the acceptance of educational technology among stakeholders at basic education and higher education level, it is found that teachers, parents and all stakeholders in the basic education sector had to adjust slightly to optimize their application of technology due to various related factors such as parental economic disparity, school size, and technical devices. On the other hand, lecturers in the higher education sector are able to immediately apply the innovation. In conclusion, the university can manage their instruction in the new pathway in a short period. This is in line with the Innovation Decision Process Theory proposed by Roger (Rogers 1995) which stated that this process takes a certain period of time and is composed of the five steps to get through, namely knowledge, persuasion, decision, implementation, and confirmation.

This theory reflects the competence of higher education lecturers and students who may have adequate knowledge, skills, and opportunity to utilize innovations. Consequently, they have a higher level of technology acceptance than basic education teachers. However, every related sector needs to handle education inequality as the primary challenge. It is mostly

caused by economic inequality, particularly the gap between the quality of education in rural and urban areas as shown below (Bangkok Department of Education 2016);

1. In rural and urban areas, school administrators do not have adequate resources to plan facilities and technical tools to serve every student.
2. Most teachers might lack adequate knowledge and skills in technology utilization.
3. The economic inequality makes most parents unable to provide their children with access to technology in general.
4. A lot of students lack technology access opportunity due to economic inequality.

Based on the above-mentioned challenges, if the responsible sectors recognize the importance of using technology that promotes deep and wide-ranging learning, as well as equipping learners with other critical skills that technology can help, it is important to implement the following preparatory steps and instructional guidance during the COVID-19 pandemic:

1. Build an understanding and create educational readiness for school infrastructure and the development of teacher skills, use of technology to support teaching, and learning against every kind of challenges (Ana 2020).
2. Introduce guidelines as well as instructional management styles that promote the learners' development of the balance skills in all aspects and emphasize the development of practical skills and other necessary characteristics apart from those related to knowledge development.
3. Develop the required competence of teachers and the ability to connect technology with other approaches to instruction so they can design instructional management styles and provide instructional management then technology can be used as the primary, supplementary, and alternative media. In this context, the media needs to be adjusted and adapted to fit into the schools' context and readiness which take part in creating teachers' learning innovations (Maryanti et al., 2020).
4. Develop learners' competence to support the utilization of technology and promote their Media, Information, and Digital Literacy (MIDL) which is considered the necessarily desired characteristic for learners in the future and a primary factor contributing to the success in online teaching and learning.
5. Adjust and introduce a more flexible curriculum structure and learning areas that are appropriate for the COVID-19 period, and promote the development of the curriculum in which different learning areas are integrated, the loosening of the structure, and the learning approach that prevents and reduces the spread of coronavirus.
6. Use technology to yield educational measurements and assessments with the utmost efficiency. Reflect the actual competence of the learners at a degree equivalent to those measured by an ordinary method of assessment and evaluation, and in the manner suitable for online teaching and learning. This can be conducted through Assessment of Learning (AoL), Assessment for Learning (AfL), and Assessment as Learning (AaL) which cover the precise and assured assessment of all learners' competence.

7. Create a network of cooperation among public and private sectors to support technology-based teaching and learning (Hashim 2020).
8. Build an online Professional Learning Community (PLC), centered on technological usage, in which teachers gather to support each other in order to establish effective teaching and learning strategies for learners during the pandemic by sharing teaching and learning experiences, setting learner goals, evaluating and reflecting each other's personal performance along with teaching and learning consequences.

CONCLUSION

COVID-19 is challenging, however, it creates opportunities for every country to seek guidance for solving and promoting learners to keep up with their education during the pandemic under the friendly, reliable, indiscriminate, and learning-promoting environment. The blending of technology with teaching and learning to the fullest extent within a short period of time leads to new teaching and learning styles that bring about changes in the role of teachers, students, and other educational personnel or even parents. Therefore, the spread of the COVID-19 pandemic has become a valuable lesson to learn, and post-COVID-19 planning must be started so as to prepare the nation for future unexpected threats and risks.

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Chapter 433

THE ROLE OF MALAYSIAN SCHOOL ADMINISTRATORS IN FACING MOVEMENT CONTROL ORDER DURING COVID-19

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ABSTRACT

Corona Virus Disease 2019 (COVID-19) crisis may amend our world and our global outlook, it may also teach us about how education needs to change to be able to better prepare our young learners for what the future might hold. As for now, educators around the world are talking about the need to rethink how we can educate future generations. This might just a disruption that the sector needs us to rethink how we educate, and question what to be taught and what are we preparing our students for. Successful people in the coming decades need to be able to understand this interrelatedness and navigate across boundaries to leverage their differences and work in a globally collaborative way. So, as educators grapple with the new ways of communicating with students away from our classrooms, it is a good time to reflect on how this disruptive crisis can help us to define what learning should look like. What changes would need to occur in the preparation of school administrators if the focus of their training shifted to help them more consciously select the lenses that guided their school change efforts.

Keywords: COVID-19, Malaysia, pandemic, school administrator and movement control order

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) has changed how students are educated around the world. Those changes give us a glimpse at how education could change for the better and the worse in the long term (Rodriguez and Rodriguez 2015; Cosner 2014). In fact, the COVID-19 pandemic is fast-forwarding the changes in the scope of the job landscape as predicted by the World Economic Forum (WEF). WEF estimated that 65 percent of children entering primary schools today will end to keep on delivering up working in completely new job types that have yet to exist (Penton and Pettersson 2019).

In Malaysia, we still have time to start preparing ourselves in case the situation worsens and the ministry has to enforce mitigation measures (Dohlan and Ishak 2017). By all means, stock up on non-perishable items to last for about two weeks, however, we need to avoid excessive hoarding of goods, which can cause a shortage of these goods and create panic in the community. Those on regular prescription drugs for chronic diseases like diabetes, heart conditions, liver disease, kidney disease, cancer, and chronic respiratory illnesses should get additional supplies of their medication sufficient for an extra month (Bernama 2020) and stock up on face masks and hand sanitizers are top in the list as well. This is very disruptive of social life and requires the cooperation and commitment of the public (Bernama 2020; Davis 2019; Doyle 2020).

COVID-19 IN SCHOOL: NEW NORM

COVID-19 pandemic is revealing new layers of inequity that may end up setting us back even further. Education leaders are tackling the unexpected challenge of providing distance learning as the primary mode of instruction for weeks, months, and possibly the remainder of the school year (Bernama 2020; Azmy et al., 2016; Ana 2020). Rescheduling the school academic calendar and public exams as an immediate measure is reasonable but this action plan must be reviewed for the coming school session. Public exams will have to be examined thoroughly, and appropriate alternate assessment has to be the new norm in schools and institutions of higher learning (Bernama 2020; Azmy et al., 2016; Dohlan and Ishak 2017; Mulyanti et al., 2020).

The conventional written test has to go and assessments must be revamped. The Minister of Education (MOE) has announced that if schools are to reopen in the near future, each class should only accommodate 16 to 17 students at any one time (Bernama 2020). This is to ensure social distancing to prevent the possible spread of the COVID-19 virus. While it is good to hear that the ministry is making plans to bring students back to school, it must ensure that the schools, the teachers and other staff are fully prepared to operate under the new norm (Rodriguez and Rodriguez 2015; Cosner 2014). The new conditions and new norms should include the following:

1. Utmost consideration must be given to ensure that the ministry is able to ensure the safety and health of all students before sending them back to school;
2. As social distancing is going to be the practice, teachers must be better prepared to teach in a new norm environment. New ways and methods of teaching are required.

Teachers must be consulted on this and a new schooling pedagogy based on the sop may need to be rolled out;

3. In addition to social distancing in classrooms, the schools must ensure students who return to school have their body temperature retaken and be provided with hand sanitizers and face masks, shoes must be sanitized before students enter classrooms; and
4. Teachers should be able to explain to students the necessity for social distancing while emphasizing that it is not the same thing as being anti-social. They must explain why this is necessary and that it is only meant to be a temporary measure.

COVID-19 IN LEARNING: INNOVATIVE NORM

The primary challenge is to ensure adequate access and readiness of the stakeholders, students and teachers to the digital world that “real” teaming maybe missed out for the lack of learners’ “readiness” for independent self-learning as well as teachers’ wellbeing and readiness for online teaching (Mansaray 2019; Khan et al., 2014; Naseri 2019). Hence, education 4.0 strategy is perfectly befitting in the new normal, even in potential emerging pandemics in near or far future (Kilber et al., 2014; Kemp 2019). However, there are challenges (Kapur 2018). Education 4.0 strategy includes but is not limited to:

1. Encouraging more remote learning where theoretical knowledge will be disseminated through virtual communications while practical skills will be taught face to face;
2. Project based learning targeted to ensure wide set of skill roles; and
3. Personalized teaching based on students’ independence and unique approach to studying and the ability to learn.

COVID-19 pandemic has changed education dramatically as it has increased the use of personal telecommunications gadgets such as smartphones which prior to this were prohibited from school grounds, for learning and teaching purposes (Khan et al., 2014; Naseri 2019). Teachers should develop their skills in terms of online teaching and home-based learning which would be the new normal in the teaching field as e-learning is the future of education (Abu 2016; Hall and Hord 2014; Hallinger 2018). Teachers need to improve their knowledge, competency, change of attitude and be ready to embrace the new normal in education especially those which are related to online learning. This preparation will be reflected in teaching, assessment, and dissemination of knowledge (Kilber et al., 2014).

Throughout the Movement Control Order (MCO) and the Conditional Movement Control Order (CMCO), teachers continue to impart knowledge via online platforms. Teachers need to have a paradigm shift to be able to accept the new scenario in global education in order to build a generation with digital literacy which is very important to face the challenges brought forth by the Fourth Industrial Revolution (IR 4.0) (Drucker 2017; Helmi et al., 2017). This global crisis has made an impact on the conventional teaching and learning as well as on the responsibilities of educators, rendering it more challenging and they have to adapt to the new normal condition that requires the process to be conducted online (Khan et al., 2014; Naseri 2019). Online tools such as Google Meet and Zoom allowed us to keep meetings running, we

came to terms with the concept of working from home, as opposed to the cubicle layout we have grown accustomed to. Schools and higher learning education are resorting to online and virtual classes, and teachers are finding ways to teach from home while taking care of their own children (Ng et al., 2008).

ROLE OF SCHOOL ADMINISTRATION IN COVID-19: NEW NORM VS. NEW NORMAL

Over the past few months, we have experienced an unprecedented shift in our way of life due to COVID-19. One phenomenon that is certain, we know that adjusting to change can be challenging: be it planned or unplanned, gradual or sudden, change is inevitable and very much part of being human (Al-alawi et al., 2019; Drucker 2017). School administrators can play an outsized role in providing the ultimate pressure test of an organization position and purpose, as what is decided today will define the future (Haris et al., 2017). Looking into the future, some of the most important skills that employers will be looking for will be creativity, Communications, and collaboration, alongside empathy and emotional Intelligence, and being able to work across demographic lines of differences to harness the power of the collective through effective teamwork (Naseri 2019).

Throw in a pandemic, along with changes to routines and plans for the weeks and months ahead in 2020, and it is more important than ever to acknowledge the challenges and difficulties that we face in light of COVID-19. Developing an awareness and sensitivity in the school leader to these perspectives requires an attention to the process by which schools change themselves and to the interpersonal facets of school organizational life (Mansaray 2019). Professional preparation would need to focus on introducing aspiring school leaders to the different epistemologies underlying their administrative practice, to help them understand how different constructions of reality can facilitate or thwart successful change (Drucker 2007; Helmi et al., 2017; Yulk 2013). Rather than considering the relative strengths and constraints of each lens, with an eye to deciding one set of lenses is inherently superior to another (Rodriguez and Rodriguez 2015; Cosner 2014).

The COVID-19 pandemic has resulted in educational institutions across the world being compelled to suddenly harness and utilize the suite of available technological tools to create content for remote learning for students in all sectors. This pandemic and its aftermath test the stamina of organizations to preserve, to endure, and to be resilient. In this new millennium that prioritizes life-long learning, the way forward is by utilizing technology and online education (Haris et al., 2017). The current context of education demands educators to have advanced literacy on the information technology (Azmy et al., 2016). Therefore, today's leaders need a careful preparation that extends beyond the boundaries of education and civilization. In addition, leaders need to be flexible with their current and future needs in line with current world demands (Mansaray 2019). Collaboration and support from various stakeholders are essential as the leader's rise lies in the support of his environment (Naseri 2019, 35-40, Maryanti et al., 2020). Furthermore, aspects related to risk management need to be implemented effectively in order for leaders to be prepared and actionable at all levels of MOE.

CONCLUSION

In conclusion, the ideas discussed here suggest that as we seek to restructure and change schools and redefine the role of the school administrators in those efforts, there is much we can learn during COVID-19. COVID-19 pandemic has merely hastened the arrival of what experts in the human resource and management fields have predicted is going to happen in the future anyway. Undeniably, there is an overall reevaluation of the significance and nature of everyone's work especially to the role of school administrators.

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Chapter 434

NEW NORMS IN THE WORLD OF EDUCATION: THINK OUT OF THE BOX FROM MALAYSIAN SCHOOL ADMINISTRATOR'S PERSPECTIVE DURING PANDEMIC

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ABSTRACT

Online education is a hot topic that is widely concerned in various countries today. However, the education of our children and youth has to continue because staying idle is contrary to the constitutional foundation of civil societies. Online pedagogy is starting to flourish. In becoming a new normal, online, or digital teaching is a viable alternative to conventional face-to-face teaching and learning. In the era of mobile internet, countries around the world have made various effective attempts at online education, but online education is more of a supplement to school education, and large-scale normal online education lacks cases. The method of learning however largely depends on students' motivation; the motivation must come from students themselves. Beyond participating in the creation of norms, students must be given regular opportunities to interact with the norms through self-reflection, peer and class assessment, and discussion. The sudden and unpredictable nature of the COVID-19 crisis and its effect on work and enterprises call for a rethink of our way of life. Successful people in the coming decades need to be able to understand this interrelatedness and navigate across boundaries to leverage their differences and work in a globally collaborative way. Undeniably, there is an overall reevaluation of the significance and nature of everyone's work. The truth is, teaching online is not easy, but it can be done and can be rewarding. Increasing numbers of people are using their time during the Movement Control Order to build new skillsets, with an upsurge in enrolments in online learning. Therefore, the steps taken by our government

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must be supported to break the chain of transmission quickly while maintaining the competence of our students.

Keywords: Malaysian School Administrator's Perspective, new norms, pandemic, the world of education

INTRODUCTION

Coronavirus disease (COVID-19) has brought the world to a standstill but it has also helped pinpoint weaknesses in the education sector and presented opportunities for new norms and changes to kick in. None can predict the true impact of the pandemic on the global economy, but at this pivotal moment, there are clear choices to be made (Bringle et al. 2016b; Heimans and Timms 2014). To accomplish this condition, school administrators should support executive leadership and share the burden while maintaining appropriate separation from management. The way in which school administrators do their work at this time will be a critical factor in an organization's ability to emerge from the current crisis and push forward into a new era of economic recovery and opportunity for the benefit of all stakeholders (Al-Alawi et al. 2019; Cavazotte et al. 2013; Hallinger 2018).

Digital learning will continue to be a crucial part of post-Movement Control Order (MCO) education. Besides making improvements on internet accessibility and ICT facilities, the current exam-centric, the fast-paced education system needs to change (Pursel et al. 2016; Schankin et al. 2016; Zhou et al. 2020). E-learning tools provide educators and students with access to resources they could not have had otherwise, no matter their status or location (Helm et al. 2015). This has become painfully evident during the MCO. The current system's definition of success is narrow and based mainly on grades rather than outcome attainment as well as competency and character building. Economically, every additional MCO day will have a damaging impact. Making a bad situation worse, global oil prices slumped to new lows because of the COVID-19 pandemic. This makes it even more difficult for Malaysia to jump-start its economy while being mindful of fiscal prudence. Therefore, it is now more crucial than ever to think out-of-the-box to bolster the government's resources to fund its post-COVID-19 economic recovery (Husnu et al. 2016; Azmy et al. 2016).

THINK OUT OF THE BOX

COVID-19 is a pandemic that illustrates how globally interconnected we are there is no longer such a thing as isolated issues and actions. The post-COVID-19 realm requires different ways of thinking and organizing the world. Educators across the world are experiencing new possibilities to do things differently and with greater flexibility resulting in potential benefits in accessibility to education for students across the world (Bringle 2016a; Rodriguez and Rodriguez 2015).

In Malaysia, the system is there, but there are things that can be done to make it better (Dolhan and Ishak 2017). Thinking outside the box may best be summarised by the assertion 'When you think outside the box, the box goes away'. Rethink the scheduling of classes in

line with remote learning. Thinking outside the box is not easy since it involves leaving the psychological comfort zone, becoming open to new ways of seeing the world, and being willing to explore (Naseri 2019). In this ever-changing global environment, young people require resilience and adaptability skills that are proving to be essential to navigating effectively through this pandemic. So, if that is the worst outcome, what should institutions do to prevent that? Understanding how to learn involves deeper skills than mastery of study skills. Emotional intelligence, emotional health, and an understanding of the learning process are clearly related. We might conclude, therefore, that a good learner is able to think outside the box, and that since teachers are, by definition, also learners, those good teachers are out-of-the-box thinkers (Davis 2019; Stapa and Mohammad 2019).

Outside of marshaling all their resources to provide students without internet connectivity the support they need to teach and learn online, there are a few principles to follow. First, wherever possible, create active learning experiences ones in which there is synchronous communication, required class sessions, frequent opportunities for students to answer questions and defend answers, debate their peers, tackle problems, and the like (Zhou et al. 2020). Zoom might be suitable technologies for that, but schools should also investigate using an active learning platform. Second, remember that online learning is not about putting the class front and center like the MOOCs did. That means that teaching certain concepts might not be best accomplished through lecture capture technologies, but instead by showing a multimedia clip, something from Khan Academy, a brief simulation, by letting students teach each other (Khan et al. 2014).

NEW NORMS IN THE WORLD OF EDUCATION

Norms are the agreements we make with each other. They represent community goals, and as such, all classroom members should be given the opportunity to contribute to their creation. Norms exist to be used by students, thus students must be able to define and explain them (Penton and Pettersson 2019; Philips et al. 2017). Additionally, choosing a few norms promote student familiarity and ownership of the norms. The community must be empowered and parents and teachers must rally together to build a strong support system amid this crisis (Schankin et al. 2016). The parents play a role in educating children when they are at home (Maryanti et al. 2020). This includes providing a conducive environment for learning and keeping distractions at bay. Parents must get their priorities right and they must be committed. The teachers and schools need strategies to ensure that learning outcomes are achieved (Pursel et al. 2016). Children need support when using online platforms. Parents and guardians need pedagogical competencies in assisting their children with online lessons as well. However, we are optimistic that things will fall into place eventually (Naseri 2019). Schools must maintain clear and constant communication with parents. A guide for parents who have to multitask between remote work, household responsibilities, and helping their children with school work, is needed. Parents and guardians can also build their own support system via chat and social media groups to exchange ideas and experiences (Hashim et al. 2020). We need a video library with content developed according to the national syllabus and curriculum, and accessible via digital devices. Rethink the scheduling of classes in line with remote learning. Physical attendance is only for teachers and students to touch base (Schankin

et al. 2016). This method of learning however largely depends on students' motivation; the motivation must come from students themselves. Unfortunately, it will inadvertently filter those who want to learn and those who are less interested. Classrooms are made smaller to make it easier for teachers to get to know and engage with the students and parents (Bringle et al. 2016b).

These risk-control decisions have led millions of students into temporary homeschooling situations, especially in some of the most heavily impacted countries, like China, South Korea, Italy, and Iran. These changes have certainly caused a degree of inconvenience, but they have also prompted new examples of educational innovation. Although it is too early to judge how reactions to COVID-19 affect education systems around the world, there are signs suggesting that it could have a lasting impact on the trajectory of learning innovation and digitization. While school closures seem to present a logical solution to enforcing social distancing within communities, prolonged closures tend to have a disproportionately negative impact on the most vulnerable students. What we are learning from COVID-19, similar to what we have seen in previous pandemics, is that preparedness is crucial (Sangsawang 2020). While different scenarios exist, several of them assume that the COVID-19 spread will happen in waves, which means the process of addressing it should be cyclical.

EDUCATION NUDGED AND PUSHED TO CHANGE COULD LEAD TO SURPRISING INNOVATIONS

The COVID-19 pandemic has brought about a dramatic interruption in the way we do schooling across the globe. The slow pace of change in academic institutions globally is lamentable, with centuries-old, lecture-based approaches to teaching, entrenched institutional biases, and outmoded classrooms. However, COVID-19 has become a catalyst for educational institutions worldwide to search for innovative solutions in a relatively short period of time. In just the past few weeks, we have seen learning consortiums and coalitions taking shape, with diverse stakeholders including governments, publishers, education professionals, technology providers, and telecom network operators coming together to utilize digital platforms as a temporary solution to the crisis. In emerging countries where education has predominantly been provided by the government, this could become a prevalent and consequential trend to future education (Rodriguez and Rodriguez 2015).

THE DIGITAL DIVIDE COULD WIDEN

Most schools in affected areas are finding stop-gap solutions to continue teaching, but the quality of learning is heavily dependent on the level and quality of digital access. After all, only around 60% of the globe's population is online. Moreover, the less affluent and digitally savvy individual families are, the further their students are left behind. When classes transition online, these children lose out because of the cost of digital devices and data plans. Unless access costs decrease and quality of access increase in all countries, the gap in education quality, and thus socioeconomic equality will be further exacerbated (Bringle et al. 2016b).

The digital divide could become more extreme if educational access is dictated by access to the latest technologies (Firmansyah and Rahmawati 2018). Nobody thinks this is the way online education should be done. When students have expectations of face-to-face training, if the substitute for an emergency is proposed as interaction through a forum or a platform with limitations, satisfaction levels drop, because there is an apparent gap in those expectations, and students may prefer to postpone their course and wait for normal service to resume (Helms et al. 2015). If the substitution is carried out with a tool rich in interaction, this happens less often. Although e-learning from home is unavoidable in the current situation, the students are not able to focus as much as they can in a classroom. One of the ways e-learning has tried to mimic the social aspects of a classroom is with tools like message boards, Facebook groups, and yes, sometimes chatbots (Harisriani and Danuwijaya 2019). They give students the sense they are not just staring at an empty message board, but they are talking with real people about their homework (Kahn et al. 2014).

However, the pandemic is also an opportunity to remind ourselves of the skills students need in this unpredictable world such as informed decision making, creative problem solving, and perhaps above all, adaptability. The rapid spread of COVID-19 has demonstrated the importance of building resilience to face various threats, from pandemic disease to extremist violence to climate insecurity, and even, yes, rapid technological change. In our view as long as there is strict adherence to the safety guidelines and standard operating procedure (SOP), limiting the number of students to a class should not be an issue. Teaching and learning through online platforms must be strengthened as e-learning is the future of education (Ana 2020). The clear opportunity that has come out of this period is to press the "reset" button and we see areas where one can rebuild by recalibrating the mindset. The first thing that we need to do is upskill and reskill ourselves more intensively.

CONCLUSION

The COVID-19 pandemic will likely continue presenting challenges beyond those that come up in the course of routine virtual education. Even if this viral spread subsides, or a vaccination becomes readily available, the shift from online classes back to in-person learning may create disruptions of its own adjusting back to higher standards of accountability, weaning off of phone-checking habits, and transferring comments back to hard copies instead of digital notes. Hopefully, these experiences will serve as preparation for future challenges that come with the next epidemic, pandemic, and other disasters.

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Chapter 435

THE GLOBAL IMPACTS OF COVID-19: RISK AND CRISIS MANAGEMENT IN AFFECTED COMPANY

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ABSTRACT

The economic decline becomes the most severe phenomenon that hit the world besides the medical impact of the coronavirus outbreak. Southeast Asia countries as the middle-income countries require a better strategy to successfully respond to Coronavirus Disease 2019 (COVID-19) pandemic. Moreover, the highly uncertain condition makes it difficult for the affected companies' management in decision and policy-making. Therefore, this chapter aimed to develop better risk and a crisis management as the right response towards rapid and sudden change in crisis situation. In particular, it suggests ways that decision makers can adjust their company management for dealing with the extreme condition. The chapter explored risk and crisis management of some management experts using descriptive analysis, literature review, and qualitative technique. The chapter resulted in risk and crisis management strategies for reducing losses but at the same time providing protection for their employee considering people's safety is second to none. The way of how companies react will bring big impacts to control the economic downturn in the middle of a global recession that now seems inevitable.

Keywords: pandemics, risk and crisis management, companies, South East Asia

INTRODUCTION

The emergence of Coronavirus Disease 2019 (COVID-19) pandemic causes large-scale mortality and morbidity, trade and travel networks disruption, as well as stimulating civil unrest (Di Marco et al. 2020). This is not the first time when global pandemic led the world economy to devastation. The SARS outbreak in 2003, the H1N1 pandemic in 2009, and the West African Ebola outbreak from 2013 to 2016 each have caused economic damages by more than US\$ 10 billion. The current outbreak of COVID-19 once again hit the world with the huge socio-economic impact caused by international travel restriction and the quarantining of people in almost all affected countries. The considerable crisis hit almost all companies, especially in the field of tourism such as hotels, resorts, restaurants, and airlines. The disruption of supply chains also incredibly affected food, medicines, and the manufactured products industry. The economic impact is estimated to be higher than the US \$150 billion (Smith et al. 2019). On the focus as company management and from the point of view of a manager, COVID-19 that is spreading human suffering in economics has brought uncertainty conditions in all affected companies (Machmud and Minghat 2020). This extraordinary condition pushed them to provide risk analysis and risk management in order to minimize the financial and psychological loss.

Southeast Asia which is occupied by most of the middle-income countries and developing countries must prepare the appropriate strategy since the crises is predicted to be worse than the developed countries. Loayza and Pennings (2020) in their research stated that the developing countries can be more severely affected by economic crises besides mass unemployment and business closures. Its ripple effects can produce a set of other crises which are financial, sectoral, balance-of-payments, and debt crises. Furthermore, this extreme pandemic may cause a humanitarian crisis such as worsening poverty, a dire decline of basic social services in education, health, safety, and stimulating social conflict, violence, and crime (Loayza and Pennings 2020). There are 11 affected countries in South East Asia namely: Singapore, Indonesia, Philippines, Malaysia, Thailand, Vietnam, Brunei Darussalam, Cambodia, Myanmar, Laos, and Timor Leste (Sirkeci and Yucesahin 2020). The updated data on 20 April, 2020 showed that the high number of cases is suffered by Singapore, while the highest mortality number in South Asia is suffered by Indonesia (World Health Organization 2020). Even though the crisis caused by the pandemic is global, the response to anticipate the impact is local. However, different countries show different approaches in responses as well as different companies react differently toward the resulting crisis.

Extreme efforts are needed in an extreme situation. Companies need to know the risks that might occur and what risk mitigation strategies can be applied to overcome the risks. Managerial implications need to be taken from the risk analysis to make a better effect on the company (Giannakis and Papadopoulos 2016). There are several studies concerning risk analysis where the researchers predict and measure the loss caused by the COVID-19 pandemic. A research confirmed that today, Composite Stock Price Index (IHSG) significantly decreased and lost almost 50% from the initial value on December 2019 (Utari, 2015). Asian Development Bank in its research estimated a global impact of US\$77 to US\$347 billion (or 0.1% to 0.4% of global GDP) (Dayrit and Mendoza, 2020). In line with this, the Center for Economic Policy and Research stated that COVID-19 hit many factories in Asia, especially in China, Japan, the Republic of Korea, and Singapore. Collectively, the

United States, China, Japan, Germany, UK, France, and Italy account for 60% of the global economy, 65% of global manufacturing, and 41% of global manufactured exports (Maliszewska et al. 2020). The World Health Organization (WHO) researchers predicted that East Asia and Pacific (EAP) will suffer the biggest GDP losses countries due to their relatively deep integration through trade and direct impact on tourism, as an example Cambodia (3.20 %), Singapore (2.10 %), China (2.30 %), Thailand (3 %), Vietnam (2.70 %), and Malaysia (2.10 %) (Mendoza, 2020). However, the paper describing risk management from the point of view of practitioners; in this terms company management; is required to broaden insight in building better risk management. It is crucial for all companies' management to have sufficient knowledge concerning risk and crisis management including taking preventive action, predicting upcoming uncertainty, building adjustment, and developing adaptation ability to survive in the long run.

This chapter attempts to develop better risk management as the right response toward rapid and sudden change. In particular, it suggests ways that the decision-makers can adjust company management for dealing with extreme condition. The chapter used descriptive analysis, literature study, and qualitative method in order to present a well-described subject.

WHAT IS THE RISK? HOW IT CAN BE DIFFERENT FROM THE CRISIS?

In summary, the risk is anything that negatively impacts the achievement of objectives as measured by their likelihood and impact. Risk can be defined as the actual deviation from the expected yield (Gollier 2018). The definition of risk is emphasized on the negative impact of achieving goals, although the exact definition is still growing. The definition of risk is still debatable considering the fact that well-measured and well-managed risk can increase innovation and greater opportunity to achieve goals (positive impact). On the other hand, the terms of crisis refer to dangerous situations that have a huge impact on everyone which can be caused by several factors such as the plague, natural disaster, technology, bad management, terrorism, war, and scarcity (Tong and Zhang 2020), whereas crisis management can be interpreted as a process that addresses organizations with a major event that threatens to harm the organization, stakeholders, or the general public. There are three elements that are most common for defining crises: threats to the organization, elements of surprise, and short time decisions. Unlike risk management, which involves assessing potential threats and finding the best way to avoid threats, crisis management deals more with threats that have already occurred.

The crisis which is assessed through the business perspective is a situation that leads to greater intensity of the problem, disruption of daily business running, affecting the image of the company, interfering company's overall work system, affecting community social pattern. In facing the crisis, the government has the authority to intervene. In facing the risk, the company has its authority to solve the problem. The common thing from risk and crisis that is both cases may trigger companies in conducting transformation and building resilience through the hard conditions. In a good response, both conditions may become a catalyst for companies to get better and survive in the long run (Martin et al. 2017).

TYPES OF RISK VERSUS TYPES OF CRISIS

Risks can be classified differently depending on which segment of business operations they are related to. Risks are divided into two categories: internal and external risks (Salamai et al. 2019). Business risks that occur within the business activities in the companies are called internal business risks and including the following external business risks which are sources that are outside the company such as the COVID-19 pandemic. The size of risk can be predicted from the data released by WHO regarding the decline in GDP and export illustrated in Figure 1.

Figure 1 shows the decreasing of GDP that is predicted to be experienced by several countries in East Asia Pacific (EAP) released by the World Health Organization (WHO). Global GDP is expected to decrease by 2.10%, while developing and high-income countries' GDP is expected to decrease by 2.50 and 1.90%, respectively. Moreover, exports at a global level are expected to decrease by 2.50%. China is predicted to suffer a decrease in production across all sectors and goods as well as showing a reduction in exports of 3.70%. Vietnam shows a decrease in its total exports by only 1% because Vietnam fills the gap left by the decrease in Chinese exports. China is the most affected country in the East Asia and Pacific region in terms of export declines, followed by Laos (3.60%), Cambodia (3.90%), and Singapore (4.40%) (Barua 2020a).

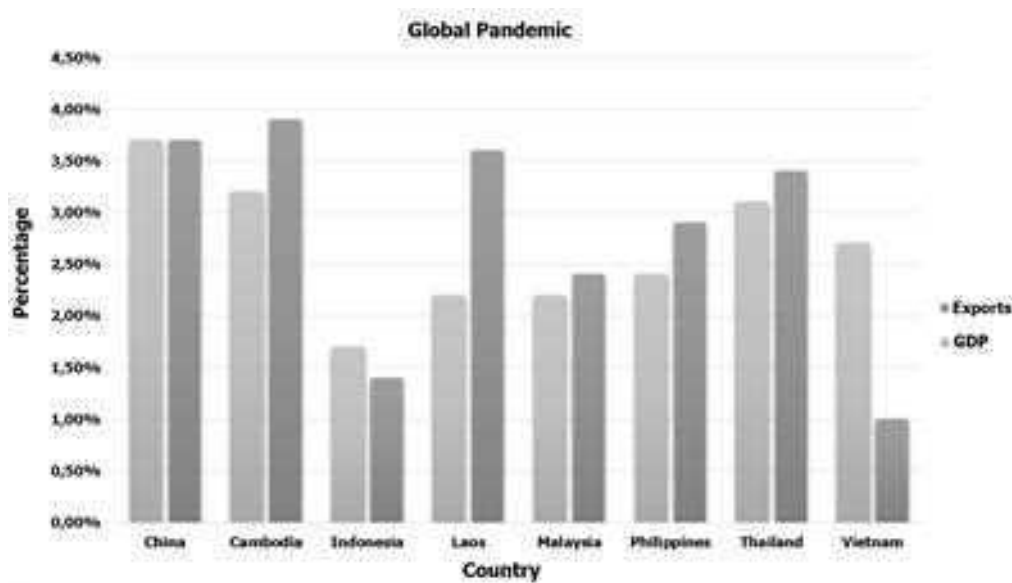


Figure 1. GDP and export implication of global pandemic scenario for EAP countries (% deviation) from the benchmark (World Health Organization 2020).

People quarantined in almost every affected area have disrupted the supply chain due to the underutilization of labor and capital. Moreover, with an increase in its trade costs, the import costs for the rest of the world turns into a decline in global exports. The decline will lead to an economic crisis. Company management needs to have good knowledge concerning the stages of the crisis, which are divided into several stages, namely prodromal or symptoms of the crisis, acute, chronic, and healing (Bundy et al. 2017).

At the stage of Prodromal or Symptoms of Crisis, all events or signals of the crisis have begun to appear but the company continues to carry out activities as usual. If the company cannot catch this signal by not implementing crisis management, it will have a big impact on the next stage. As an example, when a company hears that coronavirus had spread in various countries but Indonesia has not yet had an impact, then this is a signal for the company to prepare a strategy if the virus enters Indonesia so that at the next stage, the company can survive.

At the acute stage, the crisis is not so obvious but has begun to be felt slowly by the company. At this stage, the term “point of no return” also means the company has no chance to re-improve the situation if the signal in the prodromal process is not heeded by doing good crisis management. For example, when the government firstly found the COVID-19 cases in Indonesia, the company continued to run the company as usual and prepared scenarios for alternative work such as working from home.

At this chronic stage, government intervention has emerged and affected the entire business process as a whole because the company has had an impact on the crisis. It is at this stage that the company implements a strategic policy so that the business can continue working. As an example, when Jakarta or Indonesia is on the lockdown, it can affect overall business activities such as supply chains and also export or import activities.

The last stage of the crisis is the healing stage. The company will begin to improve and reorganize the workings and structure of human resources. However, at this time, the company also began to adapt to all conditions if the company experienced a crisis that was quite long (Barro 1991).

THREE ASSUMPTIONS ON RISK AND CRISIS MANAGEMENT PLANNING

Quick Recovery Assumption

In a quick recovery assumption, we assume that the COVID-19 pandemic will be overcome before the end of this year. Community transmissions in East Asia and Europe are brought under control. Consumer confidence also starts to return, even in the setting of sustained transmission, due to lower case fatality ratio, case-growth slowdown, and promising treatment options. Aviation, tourism, and hospitality sectors back to normal as countries lift travel bans (Maliazewaka et al. 2020). In this assumption, companies must design strategies by identifying crisis threats and opportunities. Companies must also be able to analyze the company's SWOT in facing a crisis as well as made a long-term strategy preparation. In this situation, a manager should translate theoretical planning into reality and practicing the responses with appropriate personnel and other resources. For this condition, management should involve senior members who have sufficient experience and knowledge to design risk and crisis management planning. After those who familiar with the situation conducting an analysis, companies need to implement strategic programs in dealing with crises.

Slow Down Recovery Assumption

A slowdown recovery assumption has been indicated with the transmission case in East Asia and the Middle East, while transmission in Europe is still growing (Maliazewaka et al. 2020). Consumer confidence also remains decrease. Demand recovery depends on the evolution of disease; some sectors (e.g., consumer goods) recover faster. It is too early to predict when the COVID-19 will be resolved. This also causes the vagueness of many companies about their priorities at the end of this pandemic. This is not surprising as it is difficult to predict what position the company will be in or what resources will be available in this assumption. The impact on business continuity is likely to be severe in a slow-down recovery assumption. However, in this condition, communication management and trust are very important in building resilience to a “shocking” impact. Communication management between governments, non-governmental organizations, media, and telecommunications in times of crisis should be well-maintained to make problem mapping easier.

Pessimistic (Recession) Assumption

The pessimistic assumption is indicated with the expansion of disease to other parts of the world, including confirmed transmissions in the rest of North America, Africa, and India. Consumer confidence remains low, and air-travel restrictions remain in place until late 2020 (Maliazewaka et al. 2020). During the time when we were writing this chapter, the pandemic has not reached its peak yet. The researchers predict the second phase of COVID-19. The worse assumption should be made to make companies well-prepared with this ongoing crisis.

The following are the suggested steps as risk and crisis management in all assumptions, especially in the worst condition.

Maintaining Good Communication

The COVID-19 crisis has stimulating civil unrest and labor demonstration. Communication by those who oversee the situation is often critical. Maintaining good communication also means protecting employees. This pandemic has been disturbing either mentally or economically. Therefore, good communication can stimulate resilience toward the worst assumption of the COVID-19 crisis. Since the pandemic tremendously changes the way of work and the way of life, then giving support to employees becomes more crucial. Report and socialization of new policy must be conveyed by those who have good communication skills. Leaders and top management should communicate their policy continuously to the employees.

Create a Special Team

Companies should create a special team to handle the crisis. The team is assigned to monitor the physical health and psychological condition of the employees. Companies should

provide online consultation and counseling services to reduce the stress of the employees. The team should update information related to the socio-economic conditions, report to the CEO, and inform the employees. Supply chain monitoring should also become their work priority as well as the sales number. The information must be transferred to a related division for forecasting risk and designing a good response. This team should design specific daily, weekly, and monthly targets by continuing adjustment to recent conditions. They must define priority in the effort to overcome the crisis, determine the most valuable people in the company, and make sure the liquidity of the company.

Supply Chain Management

Company management is suggested to find the second supplier. This step aims to find suppliers of raw materials with a closer location. This step has a positive side of greater long-term supply chain resilience. Safety stock and recalculate raw material inventory is also an effort that can help to maintain the supply chain. This step aims to consider the resilience of ready raw material stock for production to deal with the fluctuations in demand in times of crisis.

Customer Management

This pandemic has caused a downturn in direct sales (face-to-face method). The company management must adjust their method to maintain customer loyalty. Online sales obviously have become a new trend in the pandemic era (Dirgantari et al. 2020) Stay at home as social distancing jargon means that people are purchasing products from home. This must stimulate every company to make digital transformation and strengthen digital infrastructure.

Change the Risk into Opportunity

Several companies have changed their production to product mask, medical equipment, and many more to find opportunity in the middle of the crisis. Of course, this cannot be conducted by all companies. Creating some innovations in sales and promotions also become crucial needs for companies to survive against the crisis.

Growth is Replaced with Survival Strategies

Several business sectors are predicted to experience the worst impact of a pandemic. In these sectors, survival strategies should be well-planned to replace growth strategies. The rapid response should be managed to allocate company resources in the effort to overcome the crisis overall rather than just increasing sales targets. Below is some analysis of business continuity in the most affected sectors:

Tourism

Travel restrictions have been widely applied to minimize the spreading of COVID-19. Travel restriction is defined as government order to stay at home and prohibition to move to other jurisdictions and closure of international borders. The exception of travel restriction is made for permanent residents and essential services. Meanwhile, the closure of international border is not enforced for returning nationals and permanent residents/visa holders (Wilson et al. 2020). The tourism industry contributes around 10.3% of global gross domestic product and generates roughly one in four of the world's new jobs over the past five years. Travel restriction in such an extreme manner in almost all territories around the world would result in more than 100 million job losses this year. Asia is suffering the biggest job losses in this sector; with a total of 60 million job losses; compare to other continents (UNWTO 2020). Short- and long-term survival strategies show the organization's capacity to respond to a crisis.

The tourism product is included in the service which is intangible. It is also complex since it consists of numerous different service providers and organizations. Hotel service, transportation companies, restaurants, tourism destination management/private sector, media, local community, and government/public sector are engaged in the tourism image. These service providers should contribute to the creation of favorable images for the fast recovery of the tourism sector. However, the safety aspect is the most important for the customer to visit tourism after the pandemic. In addition, the investment in human resource management in responding and managing crises has become a major risk mitigation issue for organizations in the tourism sector. Thus, resources investment in HRM initiatives involving to change corporate culture to deal effectively with crisis situations benefit organizations in both ethical and business perspectives (Mitroff 2004; Pforr and Hosie 2008). The holistic approach should be created by involving all stakeholders. The media has a role to deliver correct and consistent information and support image rejuvenation. The government should take an action in determination of tax incentives, special import provision to stimulate foreign investment, tax relief, extended credit to businesses, increased funding. The private sector should focus on marketing and promotions and the best way to handling customers. The local community has the role to inform tourists about the situation and security advice at the destination (Martents et al. 2016).

Properties

The decrease in economic growth and purchasing power due to pandemic has a tremendous impact on the decline of demands in the properties sector. The other impact of the crisis was the fund withdrawing by the investors, and temporarily discontinuation of distributing credit from the bank to the property sector. As the survival strategy, the property companies should shift their marketing target to Suburban areas since the demand in this area may increase due to businesses relocating from areas that have been quarantined. The strategy will keep the fixed costs for businesses holding leases at the same number, even in the face of declining occupancy and declining revenue (Sikich and Gear 2018).

Utilities (Electric, Gas and Other Infrastructure Power Supplies)

The great track record as a provider of critical infrastructure in the pandemic makes the utility company to be responsive to emergency situation. The global pandemic could stimulate the permanent destabilization of the power and utility sector. The high loss of workforce has led to respond ability decreasing in the maintenance. Furthermore, the inability to meet demands resulting in the prices increasing for energy and related products. The high demand for information systems to operate facilities and pipelines creates security vulnerabilities for this industry (Sikich and Geary 2018). The information system should develop to create clean and efficient energy. Although, during the pandemic, the domestic electricity consumption increased because most people were staying at home. On the other hand, the pandemic has pursued the rapid growth of renewable energy. Hence, the focus of recovery strategy in this sector should be focused on the security of energy supply and creates innovation in renewable energy (Wang et al. 2020).

Communications Industry (Voice, Data and Other Information Systems)

Work from home becomes the most popular word during the pandemic. Through technology, people are enabled to work remotely and at the same time also enable greater information exchange. Economists predict that fixed costs remain unchanged regardless of demand in this sector (Sikich and Geary 2018). The high demand for this sector should be answered with a high investment in the skillful personnel. Human resource management should create a good system to prevent the loss of skilled workforce since it creates potential system vulnerabilities

Banking and Finance

The disruption of worldwide economy is experiencing by the banking and finance sector. However, severe outbreaks are not new for countries in Asia. The COVID-19 outbreak was often likened to the SARS epidemic in 2003, which hit mainland China, Hong Kong, and Singapore very hard, and plunged each country's economy into a recession that makes the local government better equipped to deal with a similar crisis. Major economies in Asia have learned from past crises and built strong financial balances to reduce their economies in the face of external shocks. Governments in the Asian region are also learning quickly from China's response to the outbreak. In addition, companies in Asia also have stronger cash positions. Asian and Western markets show that more Asian companies have a net cash position, which means they have the ability to reinvest in the business and potentially gain market share (Bloom et al. 2005).

Transportation

The transportation sector has become the worst devastated caused by the pandemic of COVID-19. The travel restriction, quarantine of thousand people worldwide, flight restrictions, lack of workforce, inability to ship goods to markets has made this sector experience the tremendous impact that hard to be recovered (Barua 2020). This pandemic makes people even more reluctant to switch to using public transportation because of the high concern over the transmission of COVID-19 in public spaces. We need greater efforts to get out of the crisis situation that arises in the transportation sector. The government policy to give the secure feeling to the people to use transportation is urgently needed. This effort must be supported by the discipline culture of citizens and the management of public transportation company.

CONCLUSION

This paper has presented three assumptions in risk and crisis management in the COVID-19 outbreak that might evolve. Pandemic risks may largely jeopardize the market position and financial position of affected companies in South East Asia. Even more, South East Asia which is occupied by developing countries will suffer more economic destruction compared to developed countries. Pandemic is global, but the response is local. The way of how companies react will bring big impacts to control the economic downturn in the middle of a global recession that now seems inevitable. The company management cannot merely think about the plannable or plan for the unthinkable, but they must learn to think about business continuity planning in the unplannable situation such as pandemic of COVID-19.

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Chapter 436

THE IMPACT OF COVID-19 ON THE INDONESIAN ECONOMY

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ABSTRACT

This study aimed to analyze the impact of corona virus disease 2019 (COVID-19) pandemic on the Indonesian economy. The study used a descriptive qualitative method, with the main study data taken from several articles published in several mass media and journals. The results of the study showed that the COVID-19 pandemic had a significant impact on the Indonesian economy, which in turn predicted Indonesia's economic growth in two scenarios: 2.3% (heavy) and minus 0.4% (very heavy). The implication of this finding is that the Indonesian government should prepare various post-pandemic COVID-19 policies both related to fiscal and monetary fields.

Keywords: COVID-19, economy, economic growth, pandemic

INTRODUCTION

World Health Organization (WHO) announced on 11 March 2020 regarding the change in the status of corona virus disease 2019 (COVID-19) to a pandemic. This is because of a significant increase in the number of case reports and the number of deaths from COVID-19 in whole part in the world (De Groot-Mijnes et al., 2005; Word Health Organization 2020). This pandemic has made a substantial impact on all the economic sectors. It is already widely-known that before developing into a pandemic, this virus was initially discovered in Wuhan City, Hubei Province, China in December 2019.

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COVID-19 is a type of corona virus. This virus comes from animals or we use the term zoonotic (Maryanti et al., 2020a). This virus is very dangerous because it can infect the human body and result in death. This virus enters the human body through the nose and mouth (Maryanti et al., 2020b). This virus infects organs in the human body such as the digestive organs, liver, and lungs. People with COVID-19 usually experience symptoms of shortness of breath and fever. This virus is transmitted through droplets either directly or indirectly. The very small size of the virus results in the virus being easily transmitted and infecting the human body.

The number of confirmed COVID-19 cases from 22 January to 31 March 2020 experienced a significant surge (Ana 2020; Anggraeni et al., 2020). The number of case reports worldwide was 802,639 with a total of 39,014 deaths and a total of 172,319 patients recovered (Huang et al., 2020; Zhu et al., 2020; Li et al., 2020; Machmud and Minghat 2020).

The COVID-19 pandemic caused problems in various aspects in life. The COVID-19 pandemic also has an impact on economic, social, educational and public welfare aspects. In the economic aspect, it is possible to have inflation due to price increases (Machmud and Minghat 2020). In the educational aspect, it creates new problems for teachers and parents in the learning process for children. There are several conditions for children that do not allow distance learning (Maryanti et al., 2020b; Mulyanti 2020). Economic factors, infrastructure, and student abilities are the main factors in educational problems.

This study analyzed the impact of COVID-19 on Indonesian economy. The study was motivated by a decline in the level of consumption and investment that led to the economy as a whole. The call for physical distancing, working from home (WFH), studying from home (SFH), worshipping at home, and the prohibition of activities has caused the economic wheel to be almost stagnant. This study used a qualitative descriptive method by describing the phenomena that occurred due to the impact of the COVID-19 on the Indonesian economy. The source of the study referred to several articles published in several mass media and journals.

THE IMPACT OF COVID-19 ON THE INDONESIAN ECONOMY

The impact of the COVID-19 pandemic on the economy is shown by the potential for shocks in the demand and supply of goods and services (Binder, 2020). From the supply side, the policy of physical distancing, social distancing, working from home, and staying at home caused a decline in the production activities in addition to the difficulties in the distribution of goods, while the demand side experienced a significant increase due to panic buying in meeting basic needs (Leung, Lam and Cheng 2020). This condition resulted in an increase in the prices of goods on the market (inflation). Indeed, it would ultimately reduce the purchasing power of the people, resulting in losses to producers which could result in high unemployment (Machmud and Minghat 2020; Weitzman 1982). Another economic impact is that the exchange rate of the Indonesian rupiah (IDR) against the US dollar (USD) has penetrated almost 1 USD = 17.000 IDR. This condition will have an impact on rising prices for imported goods, which incidentally still has a substantial number of goods needed by the people coming from imports. This condition is not surprising that there will lead to an economic crisis (Phelps 1968).

The Indonesian Central Statistics Agency (BPS) reported that the number of foreign tourist arrivals (tourists) recorded was 885,067 in February 2019. It decreased by 30.42% compared to the previous month and 28.85% compared to the same period in 2019. The decline in the number of foreign tourists is inseparable from the regional quarantine policy (lockdown) conducted by many countries in the world. A very significant decrease came from Chinese and Hong Kong tourists either year-on-year or month-to-month. The decline reached 94% from China and Hong Kong, down by 93.16% year on year, from February 2019 to February 2020 (Sugihamretha 2020).

Other impacts also affected the Indonesian capital market. While on the country's stock exchange, the Composite Stock Price Index (CSPI) on the trading day as of 7 April 2020 was corrected by 0.69% to 4,778.64 IDR. The transaction value on the Indonesia Stock Exchange (IDX) reached 9.6 trillion IDR with a record net sell of 527.65 billion IDR in the regular and non-regular markets. This condition shows that during the first quarter of 2020, CSPI recorded a decline of almost 28%. The most severe selling occurred in March 2020 which collapsed to value of 16.76%. Even on last 24 March 2020, the Jakarta Composite Index touched 3,911,716 IDR, the lowest level since August 2019 (Silalahi and Ginting 2020).

During the COVID-19 pandemic, the Indonesian government announced additional spending and financing for the 2020 state budget for handling COVID-19, amounting to 405.1 trillion IDR with allocations for social protection for 110 trillion IDR, health by 75 trillion IDR, tax incentives and stimulus for People's Business Credit (KUR) of 70.1 trillion IDR, as well as for financing the national economic recovery program of 150 trillion IDR, including credit restructuring and guarantees as well as SMEs and business financing to maintain economic resilience and recovery (Astuti and Mahardhika 2020).

As a further step to strengthen monetary and financial market stability together with Bank Indonesia, the Coordinating Ministry for Economic Affairs, the Ministry of Finance, the Financial Services Authority (OJK) and the Deposit Insurance Corporation (LPS) have made a policy mix in order to strengthen economic stimulus in accordance with the authority of BI in the Government Regulation in lieu of the Act Law (Perpu) No. 1 Year 2020 dated 31 March 2020 concerning State Financial Policy and Financial System Stability for Handling the COVID-19 pandemic and/or in the context of dealing with threats that endangered the national economy and/or financial system stability signed by President Jokowi, The policy mix is at least as follows:

1. Reducing BI 7-Day Reverse Repo Rate (BI7DDR) policy rates in February and March by 25 bps;
2. Increasing the intensity of triple intervention in the spot market, Domestic Non Delivery Forward (DNDF), and purchasing loan letter (SBN) in the secondary market;
3. Reducing the minimum mandatory giro (GWM) of conventional commercial bank foreign exchanges from 8 to 4%;
4. Extending the SBN repo tenor and auction every day to strengthen the easing of rupiah liquidity and increase the frequency of FX Swap auctions to every day to ensure adequate liquidity;
5. Extending the underlying DNDF transaction types so that they can hedge the ownership of ownership Rupiah in Indonesia;

6. Reducing Rupiah GWM by 50 bps for banks conducting export-import activities, financing to SMEs and/or other priority sectors;
7. Loosening the provisions of Macroprudential Intermediation Ratio (RIM); and
8. Providing hygienic money, reducing costs Payment System in Indonesia (SKNBI), the establishment of a 0% QR Code Indonesian Standard (QRIS) *Merchant Discount Rate* (MDR) for micro business merchants, and supports the distribution of non-cash funds for government programs such as the Hope Family Program (PKH) and Non-Cash Food Aid (BNPT) Social Assistance Program, the Workers Card Program, and the Smart Indonesia Card (Masudin et al., 2020).

Based on the above conditions, the overall COVID-19 pandemic has negatively influenced Indonesia's economic growth. Sri Mulyani Indrawati, Indonesia Minister of Finance, predicted two possible scenarios that occurred on Indonesia's economic growth as the impact of the COVID-19 pandemic, namely heavy and very heavy.

In a severe scenario, GDP is predicted to grow 2.3%, while this year's very scenario of economic growth could be minus 0.4%. This condition caused a significant decline in economic activities and has the potential to put pressure on financial institutions because credit cannot be paid while companies have experienced difficulties from revenues (Phan et al., 2020).

To deal with these conditions, the Indonesian government must have prepared various policies after the COVID-19 pandemic, which are both related to fiscal and monetary aspects. Quoting Ibn Khaldun's model of the father of Islamic economics, to maintain economic stability, it is possible to apply the Sharia Socio-Economic Dynamics Model (Affandi and Astuti 2013; Chapra 1999; Chapra 2008). The formulation of this model has eight important elements:

1. Government power (al-mulk) cannot be realized except by the implementation of Sharia;
2. Sharia cannot be implemented except by government (al-mulk);
3. The government cannot obtain power except from the people (ar-rijal);
4. Society cannot be supported except by wealth (al-mal);
5. Wealth cannot be obtained except from development (al-'imarah);
6. Development cannot be achieved except through justice (al-'adl);
7. Justice is a benchmark (al-mizan) that God will evaluate in His people; and
8. The government is charged with the responsibility to realize justice.

In the effort to recover Indonesia's economy, variables such as government, society, and law have important roles in bringing about the welfare of society. The economic recovery of a country will be realized depending on the strengths and weaknesses of the political authorities that they succeed in realizing.

CONCLUSION

The results of the study showed that the COVID-19 pandemic had a significant impact on the Indonesian economy, which in turn predicted Indonesia's economic growth in two

scenarios: 2.3% (heavy) and minus 0.4% (very heavy). This finding implies that the Indonesian government should prepare various post-pandemic COVID-19 policies both related to fiscal and monetary fields. This research is still in the stage of descriptive analysis related to the impact of the coronavirus on the global economy. Further other research can look at the impact of the coronavirus pandemic on society which is more focused on the conditions and behaviors that occur in society.

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Chapter 437

CONSUMER PURCHASING PATTERNS IN RESPONSE TO COVID-19 PANDEMIC IN INDONESIA

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ABSTRACT

As the coronavirus disease 2019 (COVID-19) crisis continues around the world, consumer behavior on purchasing pattern has started to change. The outbreak of the COVID-19 has a major impact not only in the health sector but also on the economy, including on economic activities relating to the process of purchasing goods or services. The condition of the COVID-19 pandemic followed by the adoption of social distancing led to consumer new behavior in determining purchasing patterns or purchasing decisions. This paper investigated whether consumers purchase decisions are changing or not during the pandemic. This study used the literature study with secondary data support. It was found that consumers are shifting to online and digital shopping decisions through online media to reduced-contact channels. The results of the study are expected to be a reference for related parties, especially for suggesting some decision in the policy makers and government.

Keywords: buying decision, purchasing patterns, pandemic

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INTRODUCTION

The world concern very well about the coronavirus 2019 (COVID-19) outbreak that occurred. The reality of this new pandemic surprised the world. Based on the Chinese National Health Commission until 12 a.m. on 4 February 2020, this pandemic has caused 20,471 people to be infected in China (including Hong Kong, Macao and 150 Taiwanese) and the Chinese National Health Commission has also confirmed that there are 23 countries outside China that have infected, including Indonesia (Wyplosz 2020; Dirgantari 2020). The positive number of COVID-19 in Indonesia has now reached five thousand cases as of 18 April 2020 with a death rate due to positive COVID-19 of 9.13%. As many as 8.68% of the number of people who are positive COVID-19 has recovered (This data was submitted by the Government Spokesperson for Handling COVID-19, Achmad Yurianto (Kompas 2020).

The increasing number of positive COVID-19 has affected many sectors such as tourism, aviation, health, mass media, government, e-commerce, social media, and entertainment media. The government has also made a policy to carry out all activities at home such as studying, working, and worshipping. So far, there have been 10 regions that have implemented Large-Scale Social Restrictions (known as PSBB) as an effort to break the spread of COVID-19. This is certainly increasingly limiting community activities outside the home, in which usually we can shop directly to markets or supermarket and nowadays people must shop Online. Indeed, this is easier and faster, and this does not have to gather with people (Kompas 2020).

During the COVID-19 pandemic, business competition was very fierce, reflected by the number of companies that sought to capture market share and new markets through a variety of ways and innovations displayed in the products or services they produced (Velavan et al., 2020). Companies must be able to determine the right marketing strategy so that the business can survive and the main objectives of the company can be achieved.

Several factors are the reason for a company to get its own place in the hearts of the community. For example, company must consider how a company sets competitive prices, conduct effective promotions, shape the image and build a good corporate reputation in the eyes of consumers, as well as good and satisfying quality of products. They also need to find ways to get their old customers back with a new mindset from the traditional mindset to the online mindset.

In most countries, customers adapt to make transactions, access Products, and services that are minimal in contact and digitally based (El Zowalaty et al., 2020). When consumers are restricted in shopping, they find and adopt newer ways to shop through technology. In countries badly affected by COVID-19, consumers begin to hoard food and other important items, and isolate themselves from the crowd. Thus, patterns in shopping change, and they adopt newer ways to shop through e-commerce (Buana 2020).

In this situation, people who were previously reluctant to shop online are now setting up online accounts on various e-commerce platforms, experiencing a completely new customer journey. Once they feel comfortable shopping online, they might never go back to their old ways. e-commerce has undermined offline retailing for a long time, but this pandemic has accelerated the trend (Bakhtiar 2020). The government also began to look at the e-commerce sector as one solution to overcome the tax deficit due to the economic slowdown. E-commerce has actually been able to attract many consumers in Indonesia before the COVID-

19 outbreak. E-commerce is also one of the main drivers of making Indonesia the country with the largest digital economic value in Southeast Asia reaching \$ 40 billion in 2019 and it is predicted to increase to \$ 130 billion by 2025. With more retail shops and consumers forced to turn to e-commerce, its growth can be increased and even further (Corbitt, Thanasankit and Yi 2013).

E-commerce or online shop, provides a variety of products needed by the community ranging from household needs, electronics, clothing, and others. They also provide various kinds of conveniences to consumers and various other promotions such as discounts, cashback, and other bonuses (Foster 2016). Various kinds of offers provided by this online shop certainly attract consumers to shop. With the closure of physical stores, brands are increasingly pivoting to a direct-to-consumer (D2C) business model. D2C brands have a simplified proposition that cuts out retailers – selling directly to consumers through mobile and digital channels. They can meet household needs easily and quickly. They still follow the rules applied without going out of the house, but the goods will arrive safely and securely with an online shop. The convenience provided in shopping is expected to help government programs to “stay at home” (Lucas et al., 2020; Dirgantari et al., 2020).

The use of various e-commerce services continues to increase, based on research conducted by similar web shows an increase of 2.05% in e-commerce in Indonesia within 28 days and will continue to increase as consumers spend more time to stay at home (SimiliarWeb 2020).

Thus, the purpose of this study was to find out how people’s buying patterns were during the COVID-19 pandemic outbreak. The results of this study are expected to provide information about businesses in selecting and determining strategies that can influence purchasing decisions with businesses able to survive in increasingly competitive competition during the COVID-19 pandemic outbreak.

METHOD

This research was a descriptive research with a literature study approach by finding references and theories, which were obtained as a research path for the study of literature serve as the basic foundation and the main tool for research practice in the middle of the field. The results of this study used to identify consumer buying patterns through changes in consumer behaviour in making purchasing decisions and strategies, so that companies could survive in increasingly fierce business competition during the COVID-19 pandemic outbreak.

RESULTS AND DISCUSSION

According to Kotler, a purchasing decision is a problem-solving process that consists of an analysis of needs and desires, information search, assessment of the source of selection for purchasing alternatives, purchasing decisions, and behaviour after purchase. In general, making a decision is the selection of actions from two or more alternative choices. Of the various factors that influence consumers in buying a product or service, consumers usually

always consider the quality, price, and products that have been previously identified (Said et al., 2020).

The purchase decision process includes five stages. These stages are

1. being aware of needs;
2. searching for information;
3. evaluating product alternatives;
4. making a purchase decision; and
5. post-purchase behaviour.

The buying process starts long before the actual purchase. Marketers need to focus on the entire buying process, instead of focusing on the purchase decision alone (Kotler and Armstrong 2018). The consumer decision-making process begins with them realizing their needs and insatiable desires. Then, the consumer will realize the difference between his actual status (as a case) and the ideal needs they want to meet through several social and psychological aspects. These needs are what motivate and stimulate them to make decisions (Mullins et al., 2011; Mullins et al., 2008). The importance of purchasing decisions appear, especially for shopping commodities. Risks that are a consequence of this decision are (Lahindah and Siahaan 2018):

1. functional risk: the product does not perform its function as expected;
2. financial risk: the product does not match (or is the same) as the price paid;
3. social risk: the product may endanger others;
4. psychological risk: products can affect (or influence) consumer from their consumers;
5. time risk: product failure can cause a loss of opportunity to be satisfied from consuming other alternative products.

To find out how and when consumers begin to show behavioural changes in making purchasing decisions, we conducted a study of shopper behaviour during the beginning of the pandemic in China and extended to other countries that were also affected. Current reports monitored a growing trend in the consumer environment when news of COVID-19 reached the public sphere and found that consumers went through six stages of knowledge based on their awareness of COVID-19 that spread in their communities (Velavan et al., 2020):

1. proactive health-minded buying: increasing interest in having a product that has a relationship in maintaining welfare or health.
2. Reactive health management: prioritizing products in an effort to prevent infection.
3. Panty preparation: increasing in product purchases that have a long-term shelf life and increase store visits.
4. Quarantined living preparation: increasing online shopping, decreased store visits and signs of supply chain irregularities.
5. Restricted living: increasing in prices due to limited availability and hinder the fulfilment of online needs.
6. Living a new normal: increasing health awareness when returning to their activities.

The literature on purchasing decisions explains that many factors influence purchasing decisions. Some factors that influence purchasing decisions include price, products and services (Basu et al., 1995). Consumers are willing to sacrifice their money to buy certain products if the product is able to meet their expectations (Parasuraman and Berry 1991). The evaluation of a product or service based on several considerations is only determined based on its external appearance, such as brand, price, or packaging, which directly or indirectly will affect the decision-making process (Zeithaml 1988). The price, promotion, and reputation of the company have a great influence on the customer in influencing the formation of a buying decision. It was explained that the more competitive the price given by the seller, the greater the purchasing decisions made by the customer. Likewise, with promotions, the more intensive and attractive promotions that are held will increase the probability of consumer decisions to buy them and a good assessment of the company is also one of the factors that can influence the formation of purchasing decisions. This is because consumers will always look for companies that provide a specification in accordance with what this is expected by consumers (Ayu 2019). Buying decisions made by potential buyers are not always direct purchasing decisions only but also pending purchase decisions. One of the reasons is that funds are not yet available for purchase (Kim et al., 2008; Anggraeni et al., 2020). When prospective buyers have an interest in a particular product and already have a trust in the seller's account in question, then they will give a 'mark' on the seller's account or product.

CONCLUSION

COVID-19 pandemic give opportunity to evaluate consumers lifestyle choices. The purchasing decisions helped to contribute to the food, electronics, clothing and other industries which were sluggish because of the closure of shopping centres and the borders of social activities. There are also negative risks that must be faced by consumers during this pandemic, namely functional risk, financial risk, social risk, psychological risk, and time risk. They are also triggered by security problems, loss of payment checks, accumulation of bills, and uncertainty the store. Thus, companies should pay more attention to prices and set a competitive price in addition to the quality of services in accordance with the wishes of consumers, update their customer personas and communication strategy, and giving maximum quality of product and good performance.

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Chapter 438

ANALYSIS OF THE APPLICATION OF THE MOBILE VENDING MACHINE AS A DISTRIBUTION TOOL FOR COVID-19 BASIC PROTECTIVE ASSISTANCE FOR THE INDONESIAN SOCIETY

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ABSTRACT

The world is currently experiencing extraordinary event after coronavirus disease 2019 (COVID-19) first appeared in Wuhan, Hubei Province, China. This event is declared as a pandemic because it spread widely throughout the world including Indonesia. Indonesia has a *Work From Home* (WFH) system that is assumed ineffective because there are still many people who are unable to stop going to their office. They have economic limitations, so they also find it difficult to get personal protective equipment to avoid being exposed by the COVID 19 viruses. This study used qualitative analysis with data obtained from online questionnaires. The data obtained states that the Vending Machine Mobile is considered effective in solving problems. The Vendible has related to the difficulties of the public to access personal protective equipment to avoid being exposed to the COVID 19.

Keywords: basic personal protective equipment, COVID-19, Indonesia, Vendible

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INTRODUCTION

Currently the world is experiencing extraordinary event after the Novel Coronavirus Disease (COVID-19) was declared as a pandemic by World Health Organization (WHO) on 30 January 2020. This virus was first discovered in Wuhan, Hubei Province, China in December 2019 and spread very quickly throughout China (Zheng et al., 2020; Putra and Abidin, 2020). In Indonesia, people infected on Nov 2019, and COVID-19 were first discovered on 2 March 2020 (CNN Indonesia, 2020a; Anggraeni et al., 2020). Based on the data obtained from Worldometers, the spread of this case takes place so quickly. On 19 April 2020, there were 6,248 cases in Indonesia, 535 of them died (CNN Indonesia, 2020b).

COVID-19 is an infectious disease caused by a newly discovered coronavirus. The COVID-19 virus spreads in the form of small droplets that are usually released by people who have been infected while sneezing or coughing (Rawan and Triwidiastuti, 2000). These droplets generally will not move but fall to the ground or a surface within a few seconds. This is the reason social distancing or physical distancing effectively prevents its spread (Sauer, 2020).

This virus spreads in the form of droplets released by the infected people (Maryanti et al., 2020). This virus will not move but fall to the surface. Social distancing or physical distancing is effective in preventing the spread of this virus. However, social distancing or physical distancing affects various aspects such as economic, social, and environmental aspects. Moreover, Indonesia is still a developing country whose economy is not as good as developed countries. In implementing the *Work From Home* (WFH) system, our society has difficulties because there are still many people who have to work to provide needs for their family.

Previous researches on COVID-19 stated that using masks or face masks during religious rituals to prevent the spread of the virus (Dong et al., 2020) are a must, and a tool or website to track COVID-19 cases in real time (Liputan 6, 2020) are needed. These two studies are different from our researches on Mobile Vending Machines (Vendbile) which can help distribute tools to prevent the spread of COVID-19 such as masks, hand sanitizers, and hand washes in areas that need these items throughout Indonesia.

This research answered some of the problem formulations including the socialization on the importance of COVID-19 prevention tools and systems to the society, how Vendbile works to the society, and how important Vendbile is for Indonesian. We conducted this research based on the apprehension we experienced because there are still many people who find it difficult to get tools such as masks and hand sanitizers to prevent COVID-19.

VENDING MACHINE MOBILE

Vendbile is one of the many ideas of transportation equipment that helps the government in distributing COVID-19 prevention tools (medicines, masks, hand wash, and hand sanitizer) using vending machines on an open truck. Illustration of a Mobile Vending Machine is presented in Figure 1.

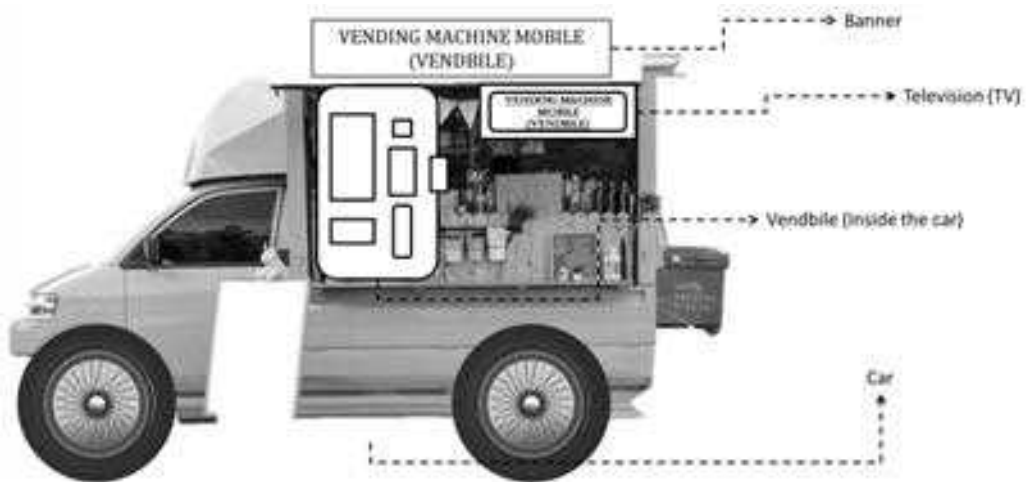


Figure 1. Illustration of the Mobile Vending Machine design as a distribution tool for COVID-19 basic protective aid.

The distribution equipment proposed is presented in Figure 2. The tool is designed in three angles view namely, the front, left and right side, and backside as shown in Figure 2a, 2b, and 2c, respectively. Figure 2d shows the media used to explain the usage procedure of this aid distribution tool.

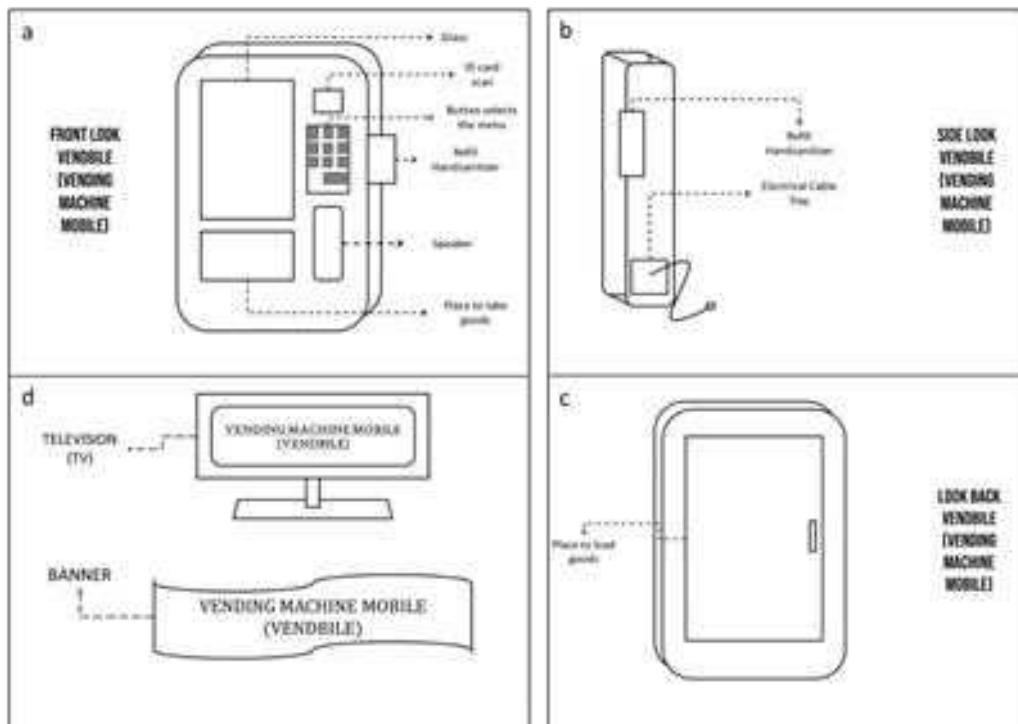


Figure 2. The visual appearance of the Mobile Vending Machine as a distribution tool for COVID-19 basic protective. Figures (a), (b), (c), and (d) respectively are the design of the device design from the front, side, back, and appearance of the media for the procedure to use the tool.

This tool is an automatic machine but it needs a driver, however, the driver still has to maintain physical distancing. Therefore, Vendbile is equipped with a guide written on the banners and small TVs in order to help people to know how to use it. People need to bring their identity cards, before using Vendbile apply hand sanitizer, scan the identity card, choose the desired items, and after getting the items, they applied hand sanitizer again.

RESEARCH METHOD

The research method used was a qualitative research method. Qualitative research methods emphasize data trends (Syandri and Akbar, 2020). This research took place during April 2020. The method in this study was a quantitative method with qualitative analysis and a questionnaire-based research method distributed online. After the information collected from a number of samples, information processed and analyzed qualitatively.

RESULTS AND DISCUSSION

This questionnaire form divided into two parts, the first part was the identity of the respondents, and the second part was related to the Vendbile. The second part consisted of 23 questions with one final question regarding suggestions and input for the further development of the Mobile Vending Machine in order to fit in with the COVID-19 prevention assistance standard (medicines, masks, and hand wash or hand sanitizer).

There were 180 respondents that answered the questionnaire which was distributed through social media.

Research showed that 75% of the respondents were female (Figure 3a). The most dominant respondents' age range is between 18-25 years (Figure 3b).

Most of the respondents' education level is a senior high school, followed by undergraduate and the rest were spread fairly evenly among the levels of junior high school education, diploma, and master degree (Figure 3.c). The majority of respondents worked as students (Figure 3d). The majority of respondents residing in West Java and many of them are from the city of Bandung, while other respondents came from various regions outside West Java, from Central Java, DKI Jakarta, and the rest were scattered in various regions in Indonesia (Figure 3e and 3f).

On the question of how the situation and condition in the environment around the respondent during the COVID-19 pandemic, the majority of people answered that it was in good situation and condition (Figure 4a).

Respondents who answered, mostly came from West Java, especially from the city of Bandung. The next question is about the respondents' understanding of the COVID-19 prevention procedure and the tools used. The majority of people understood it (Figure 4b). The result showed that the readiness and outreach based on information and messages disseminated by the government and the society have almost reached to all groups. The result of the next question is presented in Figure 4c. Respondents' opinions about the importance of standard protective equipment such as masks and gloves indicated that society has understood and considered this situation was important as well as the prevention of COVID-19. Out of

180 respondents, 138 respondents considered that the standard protective equipment was very important. Continuing from the discussion of the previous questions, it can be concluded that Indonesian people have had awareness in terms of basic prevention through the importance of using protective equipment such as mask and glove.

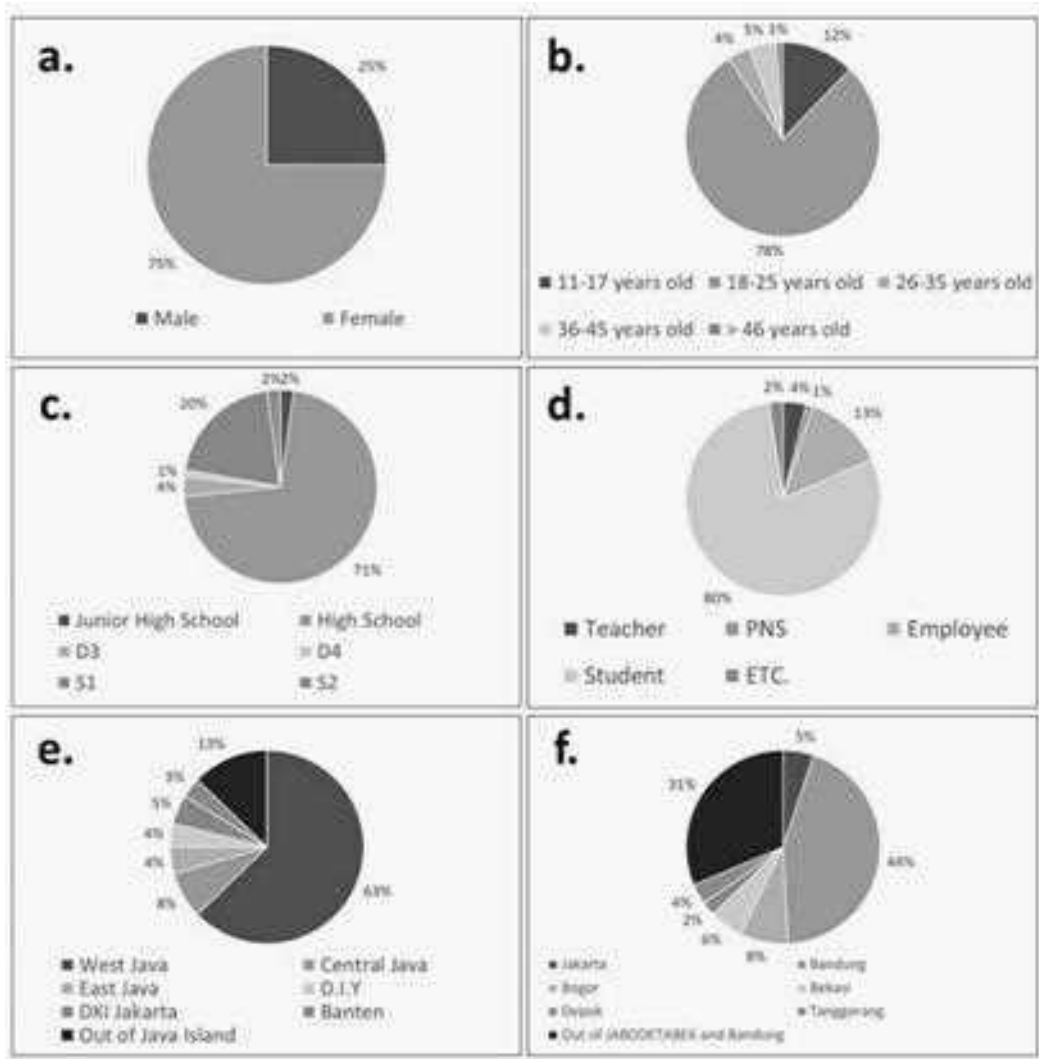


Figure 3. Identity of the 180 respondents.

Furthermore, the results in Figure 4d shows that majority of people (81%) only have masks as standard Personal Protective Equipment (PPE). This shows that the distribution of protective equipment was not evenly needed for the general public, especially those who live in West Java. Many factors could affect this, one of which is the limited access to transportation as a result the distribution only happens in certain areas.

Meanwhile, people's understanding of personal protective equipment produces data as shown in Figure 5, 176 respondents chose mask as the most important equipment. Some respondents also added other things that were also important such as disinfectant, glasses,

hazmat clothing, vitamins, herbal medicine, and jacket. Based on the response, we concluded that the society has already known items to prevent the spread of COVID-19.

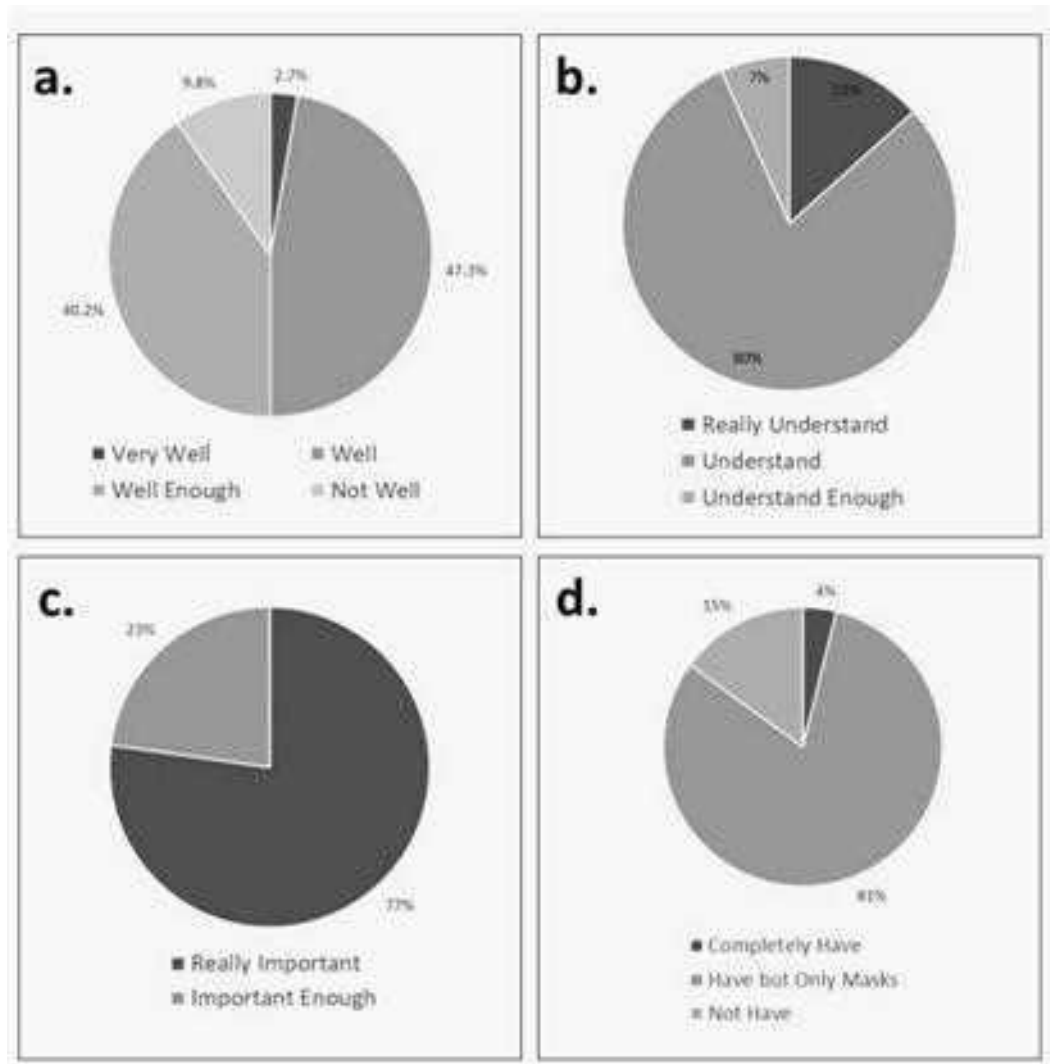


Figure 4. Public opinion about the situation and conditions in the surrounding environment (a), understanding the prevention procedures and protective equipment from COVID-19 (b), public opinion about the importance of standard protective equipment (c), and ownership of standard protective equipment that reaches all groups according to the society (d).

In Figure 6a, 88% of the respondents had difficulties in obtaining protective equipment.

In Figure 6b, the information to be taken is the availability of PPE around society. 37% of respondents lived close to a place where information about personal protective equipment to prevent COVID-19 transmission could be accessed. The status of the PPE distribution showed that respondents still felt that the distribution had the Barrier, as shown in Figure 6c. Then in Figure 6d, survey results showed that the majority of respondents, did not feel the distribution costs to the society burdensome but the rest felt the government was burdening them with the costs.

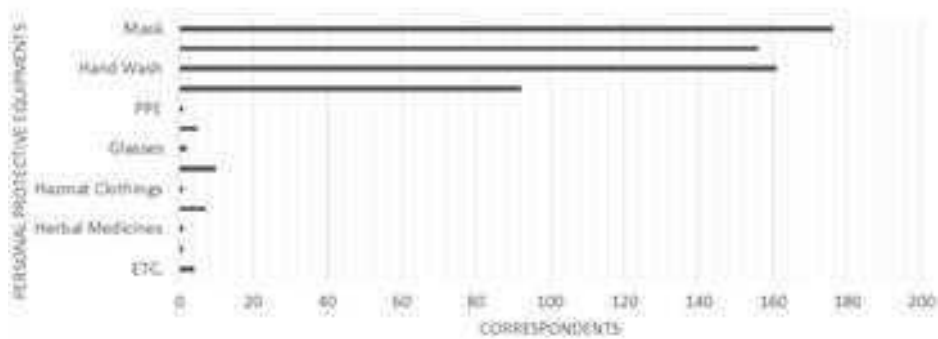


Figure 5. Graph of the most important personal protective equipment for the society.

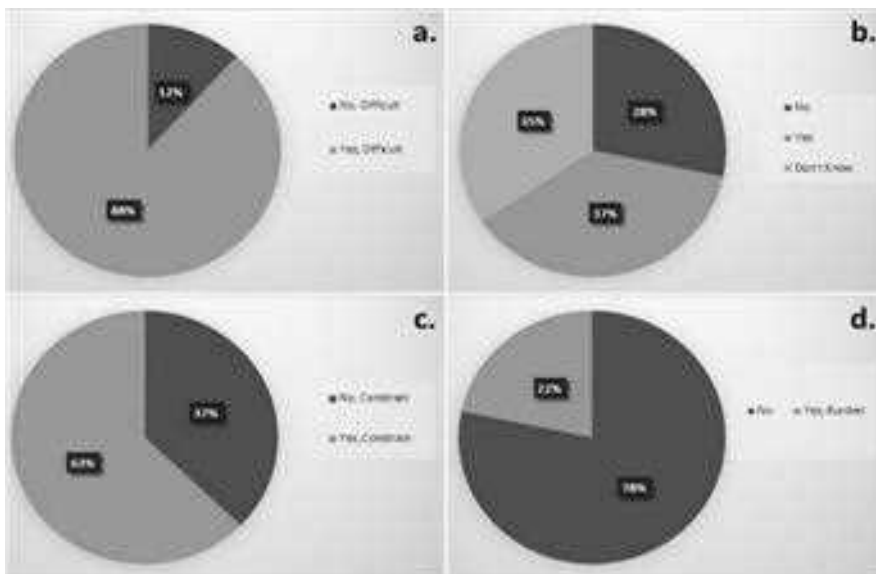


Figure 6. Difficulties of the society in obtaining personal protective equipment (a), availability of personal protective equipment in the environment around the society (b), public opinion regarding the obstacles in the distribution of aid equipment (c), and regarding the imposition of transportation costs for assistance (d).

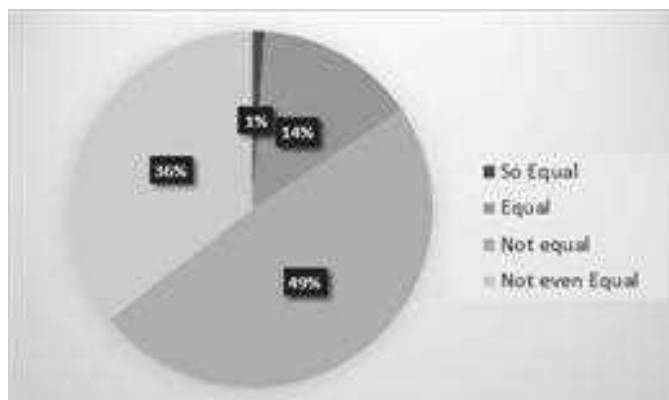


Figure 7. Equitable distribution level of personal protective aid equipment from COVID-19.

In Figure 7, 49% of the respondents stated that there was still a lack of equalization of the prevention tools. It could be concluded that the majority of respondents still felt unsatisfied with the distribution and that there was still uneven distribution.

In Figure 8a, we obtained the results of the data that the society gave full support to if an attempt was made to provide the PPE distribution tools. It could be concluded that society really needed a tool to distribute PPE so that the tool would be easily accessed by society without having to wait for a long time. In Figure 8b, the respondents would put the people who needed it first. Hospitals that received PPE assistance well were government-owned hospitals, while private hospitals still had difficulties in getting PPE assistance. In urban areas, private hospitals still found it was very difficult to get PPE and also in rural areas (World Health Organization, 2020).

In Figure 9, data collection is related to the idea of developing a Mobile Vending Machine to help distribute the personal protection and prevention tools of COVID-19.

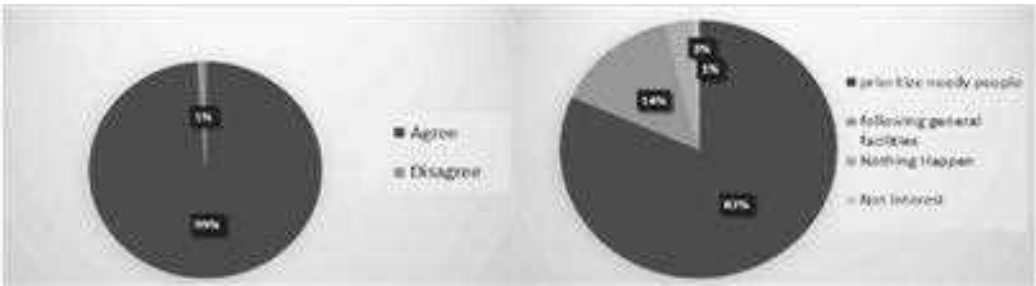


Figure 8. Respondents regarding the planned provision of aid distribution tools (Vendbile) and their impact on the distribution of distribution to the society (a) and the respondents' opinions in using Vendbile if it has been realized (b).

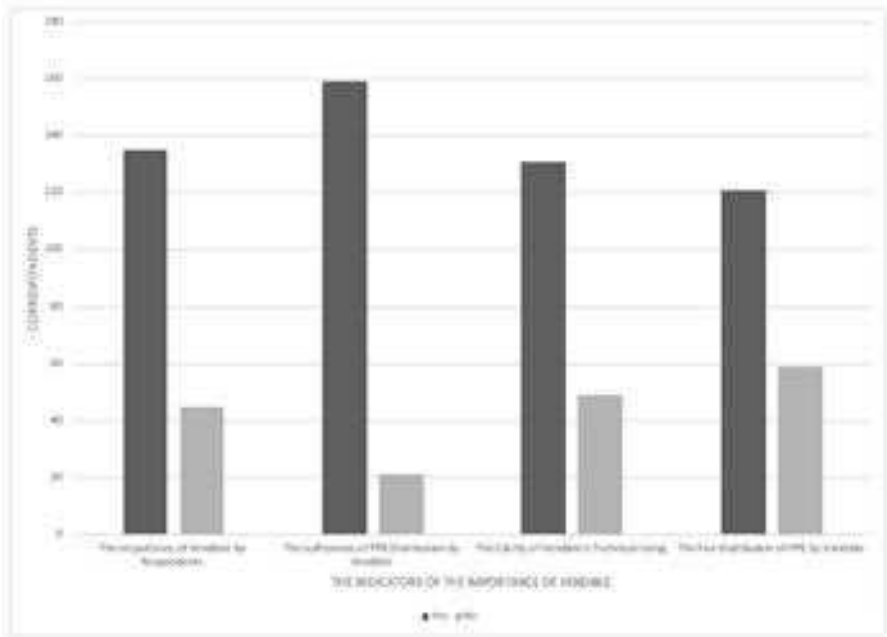


Figure 9. Graph the importance of Vendbile to the society.

Vendbible is important for respondents. According to respondents, these tools were sufficient to help the distribution evenly. The technical and procedures for using Vendbible according to respondents were quite clear. For respondents, Vendbible could be a good idea in the distribution of personal protective equipment. This shows that this idea received a positive response from society.

The next question was about Vendbible license to operate around society settlements. As a result, the majority of people responded that it should be based on the situation and conditions in the areas where it operates. Furthermore, regarding the availability of respondents to become volunteers who participated in supplying Vendbible stock, the majority of people answered that they were not willing to participate. The next question is about the availability of the society to participate in socializing Vendbible to the surrounding environment. It shows that the majority of people answered that they were willing to participate. It means that society is willing to participate in socializing Vendbible in order to help the neighborhood to get sufficient information about Vendbible.

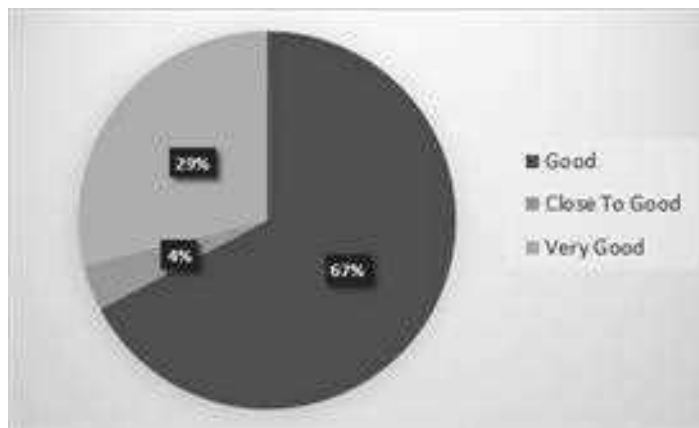


Figure 10. Vendbible breakthrough for the society.

On questions related to the existence of Vendbible in their areas regularly that can increase the number of vehicles on the road and add a little pollution in the environment, the majority answered it depended on the situation and conditions.

This shows that it would be wise if we operate Vendbible based on the situation and conditions of the areas. Furthermore, according to the respondents, the right and effective time for Vendbible to operate was in the morning. This shows that the operation of Vendbible will be more precise and effective in the morning because most people do not have many activities in the morning so, if the Vendbible would operate in the morning it can make the distribution even.

In Figure 10, the majority of people answered that Vendbible was very good. This shows that Vendbible can be useful to help the society especially on the equal distribution of COVID-19 prevention tools, especially in the red zone and in the underdeveloped, remote, and outermost regions in Indonesia. Quoted from CNN Indonesia, East Nusa Tenggara Province, for example, requires 17 million liters of disinfectant containing chlorine, while, at present, South Sumatra needs 250 million ordinary masks and DI Yogyakarta Province still lacks 3.2 million PPE (CNN Indonesia, 2020; Worldometers, 2020).

CONCLUSION

From this study, we can conclude that currently the society is experiencing difficulties in obtaining COVID-19 standard prevention tools. This problem is caused by hoarding the standard prevention tools conducted by some people. Then, based on the respondents' answers, Vendbile is a good and effective breakthrough to assist the government in distributing prevention tools in order to make it more equitable. However, the operations must be based on the current situation and conditions in society.

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Chapter 439

HEALTH TRUCK MOBILE COMMUNITY HEALTH SERVICES FOR COVID-19

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by a new type of coronavirus namely severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease has spread to 118 countries and infected 119,179 people on Feb 2020. Indonesia is currently affected by the COVID-19 outbreak. This has an impact on the economic, social, and educational systems. In these conditions, the transportation system also needs attention. The distribution of drugs and rapid test equipment to rural areas during the pandemic is a serious barrier. The number of areas that still lack of health facilities has caused lower health care for the community, including the current handling of COVID-19, such as the rapid test tool in every public health center in Indonesia. One solution that can be provided from this problem is the provision of Health Truck to help provide health services to deal with COVID-19, especially rapid tests on areas where health facilities are lacking. The rapid test tools available on this Health Truck can at least help in handling COVID-19, so that the provision of health services in remote areas can be overcome.

Keywords: COVID-19, disease, coronavirus, transportation, health, rapid test

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INTRODUCTION

The new type of coronavirus has started to become a concern of the world community after on January 20, 2020, health authorities in Wuhan City, Hubei Province, China, said three people died in Wuhan after suffering from pneumonia caused by the virus (Febrian 2020; Razon 2020). The disease is caused by a new type of coronavirus namely severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the disease is named corona virus disease 2019 (COVID-19) by world health organization (WHO) (World Health Organization 2020).

Coronavirus is a large family of viruses that cause diseases ranging from mild to severe symptoms. Common signs and symptoms of coronavirus infection include symptoms of acute respiratory disorders such as fever, coughing, and shortness of breath. In severe cases, it can cause pneumonia, acute respiratory syndrome, kidney failure, and even death (Maryanti et al., 2020). The clinical signs and symptoms reported are mostly fever, with some cases having difficulty breathing, and X-rays show extensive pneumonia infiltrates in both lungs (Kementerian Kesehatan Republik Indonesia 2017).

In March 2020, Indonesia began to be affected by this disease and after World Health Organization (WHO) declared this disease a global pandemic. At present, 18 April 2020, 5923 people have been positively identified as having COVID-19, 520 people have died, and 607 people have successfully recovered (Halim 2020). The Health Service recognizes the lack of COVID-19 treatment facilities in all regions of Indonesia to closely monitor people from exposure to the SARS-Cov-2 virus. One of them is the lack of supervision regarding public health itself (Nugraha 2020). Therefore, in the midst of the COVID-19 pandemic, Faculty of Mathematics and Science Education at the Indonesian University of Education students are developing ideas related to transportation systems that are relevant for conducting health surveillance in areas with minimal health facilities. The proposed idea is a health care transportation media that can maintain and control public health during the COVID-19 pandemic, especially for conducting rapid tests. Rapid test is an initial screening method to detect antibodies, namely IgM and IgG, which are produced by the body to fight coronavirus (Nareza 2020). These antibodies will be formed by the body when expose to coronavirus. The rapid test system used is a door to door system, so that it can prevent people from crowding in large numbers in one place simultaneously.

This idea still requires data to support it. So, we conduct research through online media. The confidentiality of personal data sent is guaranteed and processed for this research purpose only. Transportation media are provided to help the community, especially during the emergency COVID-19 pandemic, which is in an area with limited health facilities.

METHOD

The method used was a descriptive method using a questionnaire. The questionnaire was designed in such a way and then distributed randomly through online media to various regions in Indonesia. The collected data used as the source of information needed to develop ideas about the health care transportation media that can maintain and control public health during the COVID-19 pandemic. The data was processed by analyzing each question.

RESULTS AND DISCUSSION

There were 221 participants participated on the online media questionnaire about the idea of the Health Truck to maintain and control public health, specifically to carry out a rapid test. The data shows various ages for both women (71%) and men (29%), from various backgrounds such as students, civil servants, entrepreneurs, teachers, and housewives.

Table 1. The number of participants in various regions

No.	Residential area	Number of Participants
1	West Jakarta	3
2	East Jakarta	3
3	South Jakarta	0
4	North Jakarta	0
5	Central Jakarta	0
6	Bogor City	6
7	Depok City	7
8	Cimahi City	12
9	Bandung	24
10	Tangerang City	0
11	South Tangerang City	0
12	Serang City	0
13	Cilegon City	2
14	Surakarta City	0
15	Cirebon City	2
16	Bogor Regency	25
17	Bekasi Regency	2
18	Bandung Regency	17
19	Subang Regency	40
20	Karawang Regency	1
21	Purwakarta Regency	2
22	Pandeglang Regency	0
23	Tangerang Regency	3
24	Other Areas	72

Based on *Table 1*, most participants were from the areas of West Jakarta, East Jakarta, Bogor City, Depok City, Cimahi City, Bandung City, Subang Regency. Meanwhile, participants were from other regions, such as Kutai Kartanegara Regency, Garut Regency. In this context, we only choose five regions with the most participants to be discussed, which are Cimahi City, Bandung, Bogor Regency, Bandung Regency, and Subang Regency.

Most of the participants were well aware of the dangers, symptoms, and prevention of COVID-19. Some participants chose to have their health checked into various health services while others choose to stay at home or do self-isolation and then had their observation after symptoms worsen (Putra and Abidin, 2020). In accordance with the circular letter submitted by the Indonesian government, if you experience some symptoms that indicate COVID-19 and people must stay at home to isolate themselves. In addition, people who appear to be healthy or fine are still encouraged to continue to take various precautions to reduce the spread of COVID-19 (Jogloabang 2020).

Based on Figure 1, participants who need a rapid test are those live in Cimahi and Bandung cities that are red zone area, as shown in Figures 1(a) and 1(b) require a rapid test, but they do not make this much of a problem because they assume that their area has already had adequate health facilities in handling COVID-19. Meanwhile, Subang Regency, Bandung Regency, and Bogor Regency which are shown in Figures 1(c), 22.1(d), and 1(e) are areas with a high percentage of needs regarding the handling of COVID-19, especially for rapid tests. This may be due to various factors, for example, in Subang Regency has a very large number of People under monitoring, but is also limited to the procurement of rapid test equipment (Firmansyah 2020). Therefore, people really need this health facility.

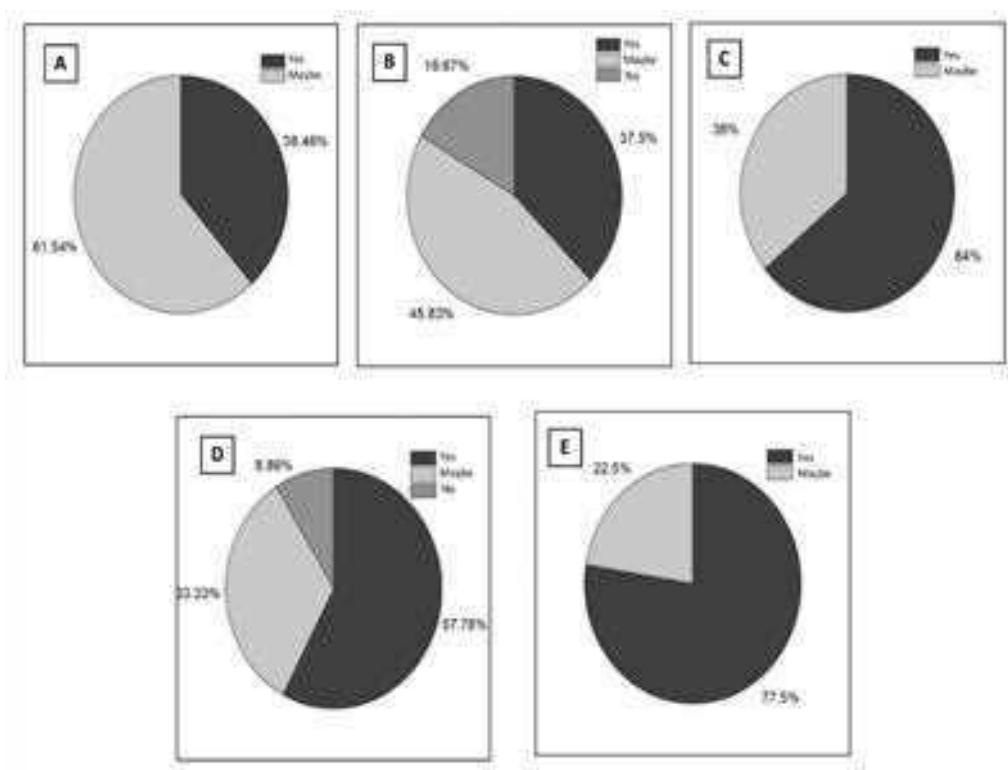


Figure 1. (a) Participants who need rapid tests in Cimahi City, (b) Participants who need rapid tests in Bandung, (c) Participants who need rapid tests in Bogor Regency, (d) Participants who need rapid tests in Bandung Regency, and (e) Participants who need a rapid test in Subang Regency.

Most of the participants (46.15%) stated that there were closest health services that could conduct COVID-19 tests, there were also participants (22.18%) who said there were no health services in their area, and the rest (31.67%) were participants who still doubted the existence of facilities in the area.

Based on the data obtained, the health services available in the participant area were mostly clinics, puskesmas, and hospitals. However, the procurement of COVID-19 tests at clinics and puskesmas was limited due to limited health facilities or a limited number of rapid test equipment. As many as 50.23% of participants stated that the community might experience difficulties in handling health, 32.58% of other participants responded that they did not experience any difficulties at all, and only 17.19% of participants stated that they

experienced difficulties in handling health. In fact, not all health services can handle problems related to COVID-19. One solution that can be provided from this problem is a health care transportation media that can maintain and control public health during the COVID-19 pandemic. Furthermore, in handling COVID-19, about 91.4% of participants needed special transportation to help with health management and control, then, only about 8.5% did not need it.

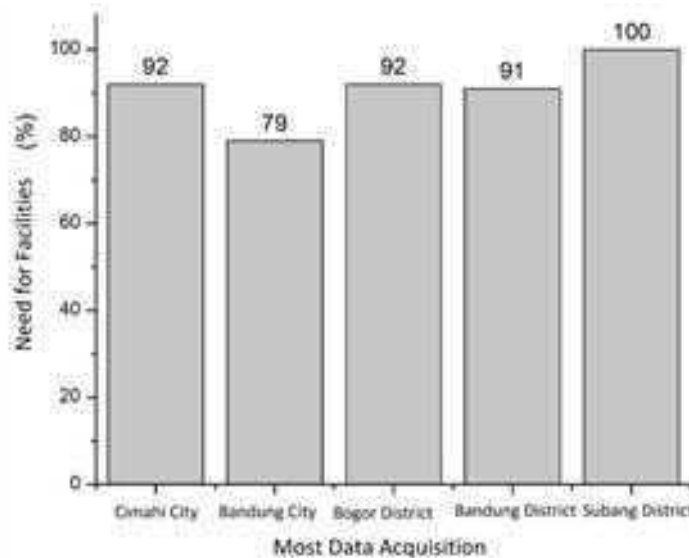


Figure 2. Distribution of needs for health facilities in various regions.

Figure 2 shows the data distribution of the needs of health facilities in various regions of Indonesia. Cimahi City, Bandung City, Bogor Regency, Bandung Regency, and Subang Regency are the regions with the highest number of participants. Based on Figure 2, Subang Regency is the area that most needs health facilities. Then, followed by Cimahi City, Bandung Regency, and Bogor Regency which are the COVID-19 red zone areas.

Therefore, to overcome the problem of limited health services, we propose ideas to participants regarding transportation media, namely Health Truck. Health Truck is a health care transportation media that can maintain and control public health during the COVID-19 pandemic. In the Health Truck, there are several health services, especially rapid tests needed by the community during a pandemic like this. In this Health Truck idea, we pay attention to various health service protocols, both for patients and medical personnel, provided by the government based on World Health Organization technical guidelines (World Health Organization 2020).

The shape of or designated Health Truck as can be seen in Figure 3, is a medium-sized car that has a futuristic look with various health facilities and personal protective equipment inside. The shape of the Health Truck is deliberately designed smaller than a truck so it can be driven on narrow roads.

Figure 4 shows the data of participants who supported our ideas. After the participants learned about the purpose and function of this Health Truck, most of the participants were very supportive of our ideas and hoped that this would be the solution to the existing health

service problems. Even after the end of the epidemic, this transportation can continuously be used, especially in remote areas that lack health facilities.

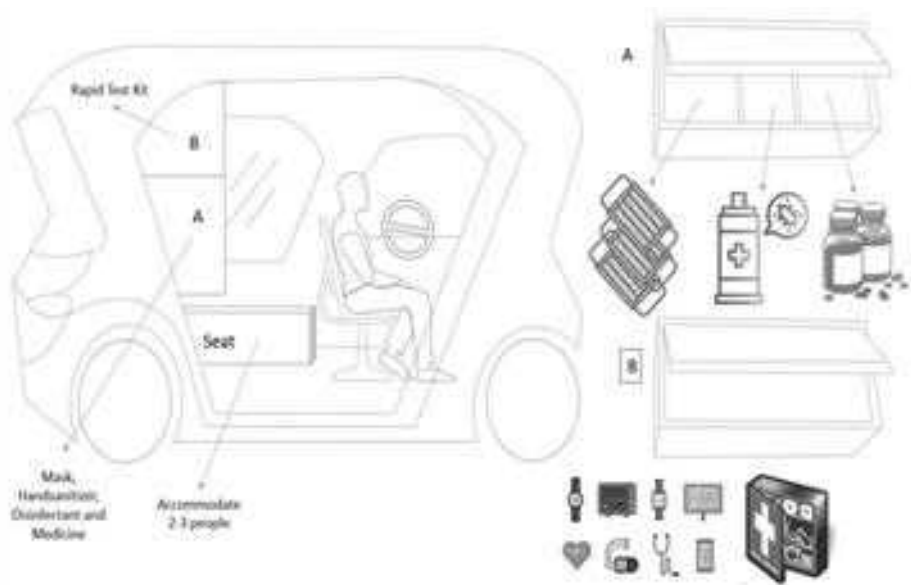


Figure 3. Health Truck design.

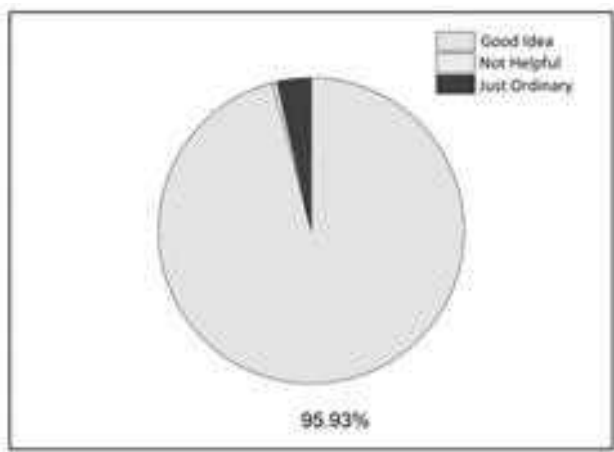


Figure 4. Participants who support the idea of Health Truck.

If this transportation media was built, most of the participants think that they would participate to take the test as long as it is free of charge. According to the participants, the Health Truck was also effective in preventing transmission of COVID-19, participants also stated that many areas or regions would need this Health Truck.

Based on the results of the questionnaire, participants revealed that there were still many needs of the community in the prevention of COVID-19 such as masks, hand sanitizers, disinfectants, Personal Protective Equipment (PPE), rapid tests and swab tests. The swab or RTPCR test results are more accurate than the rapid test. Therefore, swab test or RTPCR is important to ensure whether someone infected by the COVID-19 (Majni 2020).

CONCLUSION

Based on the method we carried out on 221 participants, it can be concluded that the majority of the community needs additional facilities to deal with the COVID-19 pandemic. Through our ideas in the form of Health Truck, it is expected that it can support the community in facing the COVID-19 pandemic.

ACKNOWLEDGMENT

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Chapter 440

AUTOMATIC SLIT FOR DELIVERING FOOD AID TO WORKERS AND MEDICAL PERSONNEL IN MOTORIZED VEHICLES

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ABSTRACT

Since the coronavirus disease 2019 (COVID-19) pandemic began to spread in Indonesia, the government has implemented several policies. Implementing physical distancing and encouraging workers to work at home and encouraging students to study at home are among those policies. Although this policy has been made, workers including medical personnel still have to work outside. COVID-19 has also impacted the workers' income and as a result, they find it difficult to meet their daily needs. Therefore, we designed an automatic box on a vehicle to distribute food aid to medical personnel and workers who do not work from home using the Drive-thru system. This drive-thru system was chosen because it is easy and supports government efforts in implementing physical distancing.

Keywords: drive-thru, automatic box, COVID-19, food transportation

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a disease that causes respiratory infections (Maryanti et al., 2020). This virus is a large family of coronavirus discovered after Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS) (World Health Organization 2020; Anggraeni et al. 2020). This outbreak started in December 2019 in Wuhan, China, until it spread throughout the world and arrived in Indonesia in early March 2020 (Azanella 2020). The existence of this outbreak affects several aspects, one of which is the distribution of logistical needs. These are in line with government policies that require a reduction in outdoor activities. Most people have to work at home, but some still have working outside as the spread of COVID-19 continues to increase. Workers are losing their incomes and having difficulty meeting their daily needs (Putra and Abidin 2020).

Coronavirus affects those who make a living as private employees, laborers, and in particular workers in the informal sector. Many companies have laid off employees without pay. Although unofficial workers continue to sell their products, their income decreases due to limited community activities (Indraini 2020). Online drivers are affected by this policy as well as they lose up to 70% of their daily income. Besides supporting the family at home, they also need to pay for other needs, one of which is lunch (Media Indonesia 2020).

Another problem that arises is a large number of medical workers who are exhausted and need food aid to meet their food needs. Medical personnel in Banten claimed that the workload was getting heavier. The shift scheduled for four turns, and medical personnel who has the third shift scheduled, from 05:00 p.m. until 1:00 a.m., do not get food (Lesmana 2020). As known, the safety of medical personnel is not only a matter of the quality and sufficiency of Personal Protective Equipment (PPE) but also of the food to sustain the stamina. The medical personnel has to give a balanced diet and sufficient vitamins to secure their immune system (SeRiau 2020).

With this idea, there is a need to evolve ideas related to the appropriate transportation network to support the government's efforts to reduce the spread of COVID-19 by adopting the concepts of physical distance, yet to accommodate the food needs of those who are unable to work from home including medical personnel. The ideas that can be executed. Our proposed idea is to build automatic cars and motorbikes transportation.

In this case, the drive-thru systems in Indonesia has conducted by the One-stop Administration Services Office. Indonesian's drive-thru system is efficient to use and has received a strong response from society (Wardani and Rumiyatun 2017). Another innovation using the drive-thru system is the rapid test in Bogor city. Besides, Bogor city, Indonesia Ministry of Communication and Information also held COVID-19 RAPID test for media workers and employees. This action is part of an attempt to break the sequence of coronavirus spread. So, there is a need to develop the ideas related to the appropriate transportation network to support the government's efforts to reduce the spread of COVID-19 referring to the effectiveness of using drive thru in the previous case. RAPID Test are carried out with the drive-thru system in order to avoid crowds and conform to the coronavirus prevention protocol on physical distancing (Kontan 2020). The drive-thru system is used to prevent greater transmission (Kosasih 2020). Many countries still continue to use the drive-thru system during the increased spread of COVID-19 one of which is Spain. Spain ranks second with the number of positive patients reaching more than 136 thousand and deaths exceeding

13,341 as per Tuesday on 7 April 2020. Facing a growing number of deaths, Spain began to apply the drive-thru system for funerals (LPPM UM 2020). It inspired us to create concepts following the drive-through system.

AUTOMATIC CAR BOX AND MOTOR

Using a drive-thru system to distribute food to people who cannot work from home starting from the middle to lower class workers and medical personnel is a breakthrough. This mode of transport supports the physical distancing efforts being implemented by the government during the COVID-19 pandemic. The designed automatic car box and motorcycle box is used to distribute free food to people who cannot work from home and to medical personnel. Workers or motorists who will distribute the food aids do not need physical contact with the recipients, because they could take the food themselves through the gap/window box.

In general, the difference between a drive-thru system using a motorcycle and a car is on the target customers. The motorbike box is used for small-scale deliveries to homes/residential areas, while car automatic box is used for larger scales such as for medical workers, or people who cannot work from home as seen in Figure 1. The automatic box can be used both for motorbikes and cars. As for motorbikes, the box is placed on the back, fitted with an inner layer that can keep food fresh and is resistant to cold and hot heat. In addition, the box is spacious in order to maintain food condition. The food is put in the package from the back of the box, as shown in Figures 1a and 1b. The rationale for using a motorcycle is to make things easier for the courier to reach densely populated areas. The courier must also follow the protocol in compliance with government guidelines, such as the use of helmets and other protective equipment. Figure 1c. shows a box in a car. The idea of a car is very much like a motorcycle case, except the scale is greater and could carry more food. The courier will press the button to open the window. People can directly take food through without having physical contact with the courier. The food is hygienic because it is placed in another room. As soon as the food is taken, the new food box will appear automatically.

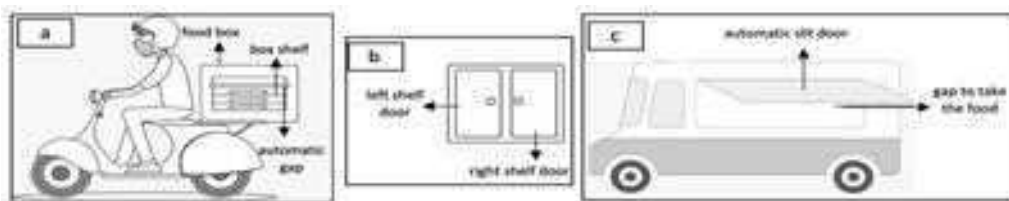


Figure 1. Automatic Drive thru box illustration. Figures (a), (b), and (c) respectively are automatic box illustration drawings on the motor from the "side" direction, from the "back", and automatic box illustration drawings on the car from the "side" direction.

Knowing that there is a large number of medical personnel who are exhausted and the declining income of people who cannot work from home, then this idea is created in order to help people who cannot work from home by distributing food aids for them. The food is free of charge. We believe that this idea requires feedback and suggestions so the concept would

be more effective and efficient. As a result, we conducted an online survey using the Google form targeted at various categories of people.

METHOD

The study was conducted online using the Google form on 17 April 2020 from 09:00 a.m. to 15.15 p.m. Forms made in questionnaires and distributed to different groups of people. The questionnaire consisted of questions relating to identity age, educational background, occupation, and the area of residence. It also had questions that matched the data needed to support this concept, as well as a comment section where the respondents could write recommendations.

RESULTS AND DISCUSSION

Questionnaire forms distributed through social media and 101 responded to it. Most respondents were in the age range of 16 - 25 years old. In the last education-related questions, more than half of the respondents were high school and undergraduate students. Knowing the respondent's education level was needed to predict their maturity in responding to the questionnaire given. Furthermore, most of the respondents were students, some of the respondents worked as civil servants, employees, and entrepreneurs. On questions related to residential areas, dominant respondents lived in West Java spreading from the city of Bandung, Cianjur regency, Bandung regency, Bekasi regency, Bogor regency, Majalengka regency, Subang regency, Cimahi city, Cirebon city, West Bandung regency, Sukabumi regency, Bekasi city, Bogor city, and Depok city. The respondents also came from outside West Java and Java.

There were 21 questions related to the data needed in developing the concept. On the final question, participants could write suggestions. On questions related to the condition and situation in their area, some respondents responded that the conditions and situation got better because the number of COVID-19 positive patients was less than in other regions. However, there were also respondents who felt that conditions and situations in their area worse because a number of COVID-19 positive patients were rising and many who lived in the Red Zone area still went working, because they had to support their families. On questions related to whether or not many communities around the area could not work from home, we found out that quite a lot of people could not work from home because they were still in the Green Zone area so they still felt safe.

We also found out that there were still quite a lot of people around the respondents who could not work from home such as online motorcycle taxi riders. Respondents' answers related to the question of whether or not the respondents knew about food aids from the government, half of the respondents had already known that the government provided food aids to the community.

On questions related to the equal distribution of food aids organized by the government, most respondents responded that food aids were not evenly distributed. That means not everyone who needed food aids was entitled to receive them.

The next question related to the need for food aids for people who cannot work from home and medical personnel, many respondents stated that food aids for them were needed because the salary that someone earns cannot be measured precisely. It means there were many who earned incomes but worried about what food to bring home for the family. Furthermore, on the question related to whether or not people who could not work from home and medical personnel found it difficult to get food aids, almost half of the respondents stated that food aids were difficult to get, but there were also people who did not know about the difficulty that medical personnel and people who cannot work from home experience in getting the food assistance.

For the question of what assistance needed by people who could not work from home and medical personnel, it was found that the majority of respondents thought they needed personal protective equipment (PPE), masks, and hand sanitizers as seen in Figure 2. We analyzed that people who cannot work from home and medical personnel needed these items because this pandemic requires everyone to be hygienic and clean to protect them from the invisible germs and viruses.

In the beginning, there was a panic buying phenomenon and some people hoarded these items. It can be concluded that this has caused difficulties for people to get PPE, masks, and hand sanitizers during this pandemic.

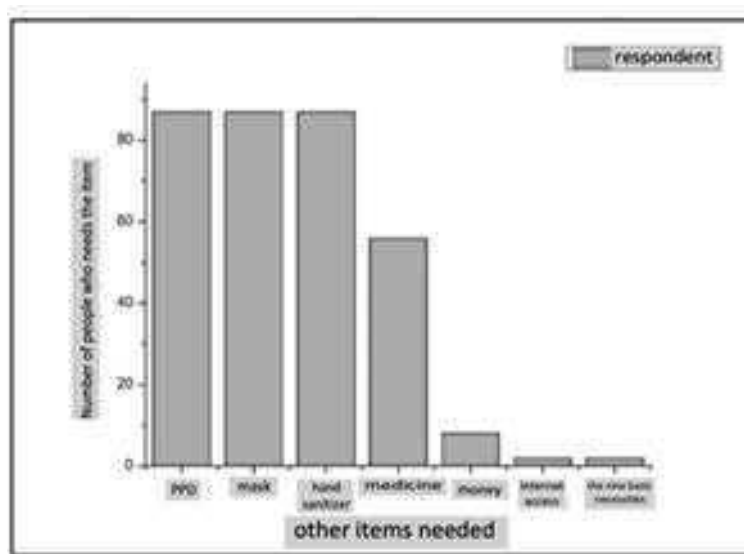


Figure 2. Data on basic needs besides food aids.

The next question related to the ideas of whether our design could be considered effective in implementing physical distancing, most of the participants answered that it was quite effective and none of them answered ineffective (Figure 3). It can be concluded that this idea could become a breakthrough in implementing physical distancing if it is executed. This idea is considered quite effective because it is quite difficult for people to maintain physical distancing due to urgent needs such as buying basic necessities.

The respondents were then asked to answer whether the government's food aids were given to the right person, and in fact, more than half the number of respondents responded that the government's assistance had not been given to the person who was entitled to receive

the aid. The next question, respondents were asked to state certain groups of people who need food aids rather than people who cannot work from homeworkers and medical personnel. Respondents gave suggestions that people who were entitled to receive food aids other than people who cannot work from homeworkers and medical workers were the poor, marginal people, people who had no income, middle-to-lower society, the elderly, traders, private employees, online motorcycle taxi riders, orphans, pedicab drivers, daily laborers, unemployed people, volunteers, workers laid off due to the COVID-19 pandemic, factory workers, farmers, homeless people, orphanages, tutors, beauty workers, homeworkers, overseas students, public transportation drivers, middle and lower workers, administrators at places of worship, and all Indonesian people who are certainly affected by the COVID-19 pandemic.

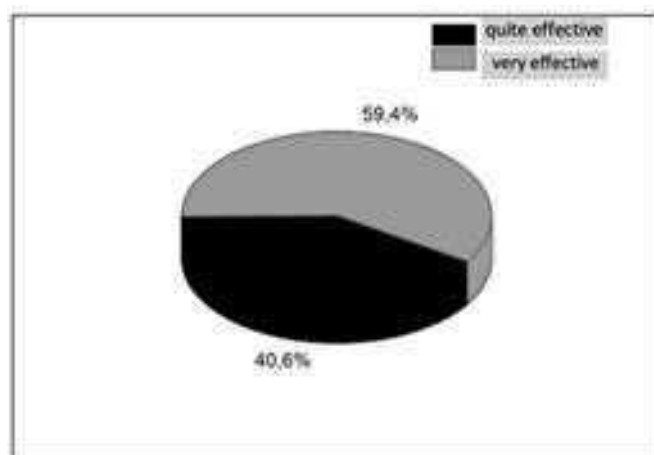


Figure 3. Data on the effectiveness of ideas to be realized by applying physical distancing.

The next question was asked to the respondent regarding whether or not the respondent knew the difficulties of people who cannot work from home workers and medical personnel in getting food, most of the respondents considered it was not difficult for them to get food. Respondents were also asked to give advice, what staple foods were needed and almost all respondents responded that the staple foods needed were rice, vegetables, side dishes, and fruits. A small number of respondents suggested that other food aids needed also include milk, vitamins, canned foods, and snacks. The next question related to the development of this idea on its effectiveness using a motorcycle, more than half of respondents answered effectively considering this idea prioritizes the principle of physical distancing to break the chain of COVID-19 spread.

Then, the next question related to the costs required whether the production would spend an excessive amount of money, some respondents stated that this idea required quite an excessive amount of money. Moreover, this idea is suspected to cause new problems because there may be a gap between recipients and non-recipients, so respondents are asked to comment on it. Most of the respondents agreed that there would be a gap between recipients and non-recipients, but some respondents believed that if this idea would be implemented in a respectful and equitable way then there would be no issue of social inequality between recipients and those who are not getting aid.

Furthermore, our design would be developed using bio solar as a fuel source. Almost all respondents thought it was possible to implement the use of bio solar, but there are also a small number of respondents who did not respond to this question. The respondents were also asked to address whether there might be hurdles to the distribution of food and to provide examples of what barriers could emerge. Respondents gave examples of obstacles that might occur, including distance, access to the area, road conditions, time, unequal distribution, corruption of food aid, food aid shortages, the goods capacity, physical contact, courier safety, and food delivery concerns exposed to COVID-19.

The last question was about the corruption of food aids which could have been found by respondents. More than half of the respondents had never seen any corruption in food aids committed by any individuals, but there were also respondents who often encountered corruption in food aids. The last data was the feedback where respondents could include ideas, feedback, and expectations that we could use to improve our design to be more effective and productive. The suggestions given by respondents include list of the eligible recipients, the impact on this idea to the community, fairness, and equity on the distribution, safety on the distribution, transparency on the distribution to prevent corruption, coordination with many parties, strict rules for couriers, and involve local community leaders.

CONCLUSION

Our idea is still possible to be implemented although it still needs to be re-examined since there are still many things that need to be considered and developed. This assistance is not only proposed for people who cannot work from homeworkers and medical personnel but is also needed for all people affected by the COVID-19 including middle-to-lower society as well as those who are unable to meet their daily needs. The community also hoped that the assistance provided would also include medical needs, financial assistance, and internet access for students and college students. The respondents also expect that this concept could be properly designed, fairly, on schedule, and uniformly implemented in order to reduce the issues or effects that might be created and would not create additional challenges for the community and would help the efforts of the government to socialize physical distancing.

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Chapter 441

MOBILE FOOD TRUCK TO ASSIST PEOPLE'S FOOD FULFILLMENT DURING THE COVID-19 PANDEMIC IN THE LARGE-SCALE SOCIAL RESTRICTIONS AREA

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ABSTRACT

The health crisis is happening in the world today because the number of infected people with coronavirus disease 2019 (COVID-19) continues to grow day by day. This happens because the virus that infects the respiratory system spreads rapidly. COVID-19 is transmitted by a droplet of an infected person. The world currently applies a social distancing to prevent the transmission of the COVID-19, including Indonesia. However, social distancing has impacted the economy, especially on the food access problem. Therefore, we carried out research aimed at developing ideas related to transportation systems for food fulfillment during the COVID-19 pandemic, which is the provision of Mobile Food Trucks. This research conducted using a quantitative method with a technique method of a survey by filling out the questionnaire online through the Google form application. The survey was responded by 259 respondents from the provinces of Banten, Jakarta, and West Java. The results of this study indicate that society indeed has difficulty in fulfilling its basic food needs in the middle of the pandemic due to the implementation of social distancing. The basic food fulfillment facilities currently available also do not fully fulfill the needs of the community. Besides, the survey results also showed that the public responded well to the idea of this Mobile Food Truck.

Keywords: COVID-19, food truck, social distancing, transportation system

INTRODUCTION

A mysterious case of pneumonia has reported in Wuhan, China, at the end of December 2019. A few days later, the virus that caused this disease has been identified and called coronavirus novel. (Anggraeni et al. 2020; Mulyanti et al. 2020). Corona virus is a type of virus that originates from animals and can infect the human body. This virus is very dangerous because it can cause death (Maryanti et al. 2020). This virus enters the human body through the nose or mouth and is transmitted through droplets. Data shows 66% of patients are related to a seafood market in Wuhan, Hubei Province of China (Huang et al. 2020). Recently, World Health Organization (WHO) has named this disease as coronavirus disease 2019 (COVID-19) (Perhimpunan Dokter Paru Indonesia 2020; Razon 2020).

Indonesia is one of the countries with a high spread of COVID-19. Quoted from the JHU Research Center website, Indonesia is among the countries with the highest spread of the COVID-19 in Southeast Asia with 5,923 infected cases as of April 17, 2020 (Johns Hopkins Coronavirus Resource Center 2020). The spread of the COVID-19 has led to many new policies made by the government. One of them is the regional quarantine policy which can help reduce the spread of the COVID-19. According to the European Centre for Disease Prevention and Control (ECDC), social distancing needs to be conducted because the COVID-19 is likely to spread through aerosols (Eurosurveillance Editorial Team 2020). Besides, social distancing is carried out to minimize the spread of the COVID-19 from infected to non-infected and aims to reduce the need for the health system. Besides, social distancing is the most effective treatment for those vulnerable to infection (Pfafftheicher et al. 2020, Maryanti et al. 2020). According to WHO in the Interim guidance issued on March 19, 2020, quarantine during the initial outbreak can slow the peak of the epidemic (World Health Organization 2020).

In Indonesia, regional quarantine has been implemented in several regions. Especially for regions with a high number of infected cases, such as Jakarta and West Java provinces, which have implemented Large-Scale Social Restrictions (LSSR) system for their residents. LSSR which is carried out as a social distancing movement does have a positive impact, that is, reducing the mobility of the community or helping to carry out social distancing to reduce the possibility of the spread of the COVID-19. However, social distancing also has significant social and economic impacts (Dalton et al. 2020). The economy can become unstable amid this pandemic situation (Center for Food Safety and Applied Nutrition 2020). These things certainly happen because of the limitation of community activities, this is what then moved us to make a breakthrough in the transportation system during the COVID-19 pandemic to facilitate access for the community. The breakthrough that we made was supported by the state of the community during the COVID-19 pandemic which required to stay at home since activities outside the home were limited.

People certainly needs to fulfill their basic needs, especially food fulfillment. The current conditions are quite impossible for people to go out routinely to fulfill their food needs because markets are usually visited by many people. Therefore, U. S. Food and Drug Administration in their article entitled Food Safety and the COVID-19 stated that we must follow four key steps for food safety which are clean, separate, cook, and chill to prevent foodborne diseases (Center for Food Safety and Applied Nutrition 2020; Machmud and Minghat 2020). Referring to the conditions mentioned earlier, we are trying to make a

breakthrough or a new idea in the transportation system that makes it easier for people to fulfill their food during the COVID-19 pandemic.

IDEA DEVELOPMENT

People need to fulfill their daily basic food needs; however, it is quite difficult to do during the COVID-19 pandemic. We developed a transportation idea during the COVID-19 pandemic named a Mobile Food Truck to assist people to provide food fulfillment during the COVID-19 pandemic in the LSSR areas in Indonesia. The idea of a Mobile Food Truck is the provision of transportation to help the implementation of social distancing where this truck will sell the needs of the basic food. This food truck will operate from house to house so that people can access food and also the foods are sold easily. This food truck operates from house to house in order to avoid direct contact with many people and minimize trading in the market. The basic foods sold are also obtained from market traders so that it can become a consideration for traders to participate in the success of LSSR. Basic foods that are sold in a food truck will not be touched directly by the buyer, the buyer only mentions items they want to buy and the seller will pick it up for the buyer. The buyer can also choose by pointing the desired items through the transparent glass on the Mobile Food Truck (Figure 1).

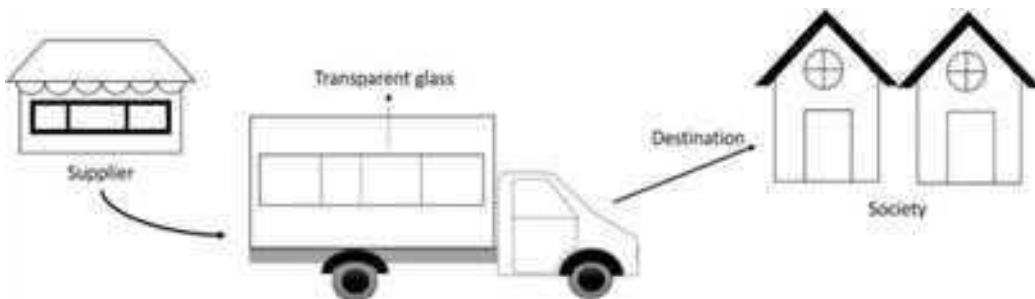


Figure 1. The illustration of food truck idea.

METHOD

We conducted a study on April 17, 2020, as a review to develop our ideas. We used quantitative data collection methods with a technique method of online surveys and questionnaire using the Google form application that contains several questions arranged according to the theme with several answer options. The data obtained then processed as a data source that could help in the development of our ideas. The questionnaire was distributed specifically in the provinces of Banten, Jakarta, and West Java in areas in the three provinces with a high COVID-19 case.

RESULT AND DISCUSSION

The total participants in this study using Google form were 259 participants, dominated by female participants. Participants who participated in filling this questionnaire were mostly in the age range of 16-20 years (see Figure 2a), and they are students. In addition, some participants were housewives and other occupations, as shown in Figure 3b.

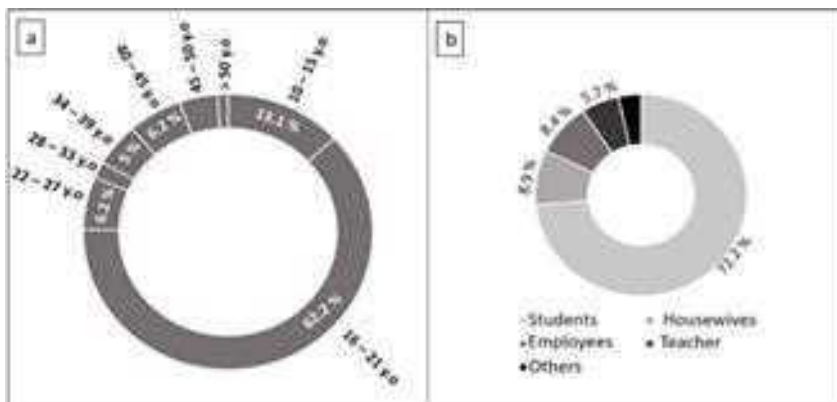


Figure 2. (a) Participants age dan (b) participants status.

Most of the participants came from regions in Banten province, followed by participants from regions in West Java Province and participants from Jakarta Province. The distribution of participants' residence is presented in Figure 3. From the personal data filled in the questionnaire distributed via Google form, it could be concluded that most participants came from among students from the regions of Banten, Jakarta, and West Java Provinces.

There were twenty questions asked to the participants relating to the COVID-19 pandemic which then led to the theme of our study. From the questions filled in by the participants, different results were obtained. Based on survey data, almost all of the participants have known and understood physical/social distancing. Survey results showed that participants were people from areas where LSSR implemented. From the data obtained it could be concluded that the average community residing in the area of the implementation of the LSSR has known and understood about physical/social distancing which is the key to the implementation of the LSSR itself.

In this survey, we presented questions related to our ideas which would later be able to support the development of our ideas. We included questions related to the fulfillment of basic food needs in participants' respective home areas during the COVID-19 pandemic. Survey data showed that most participants had no difficulty getting food during social distancing (see Figure 4a). The participants were the people who fulfilled their basic needs (mainly basic food needs) by going to markets and supermarkets. Then, although social distancing had been applied, most participants still went to the market occasionally, even some participants still routinely went to the market as shown in Figure 4b.

The types of the most needed basic food during the COVID-19 pandemic according to the survey results are presented in Figure 5. Participants could choose more than one option provided and rice was the most needed basic food according to the participants' choices, followed by vegetables, herbs, and other basic food needs.

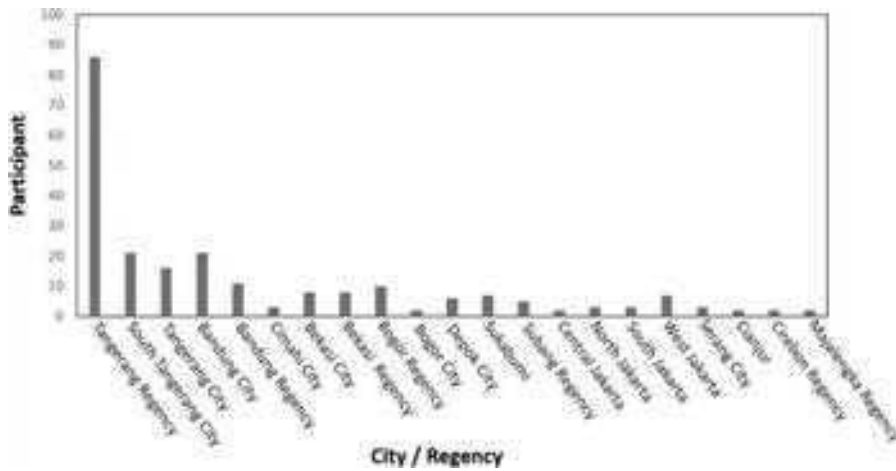


Figure 3. The Distribution of participants residence.

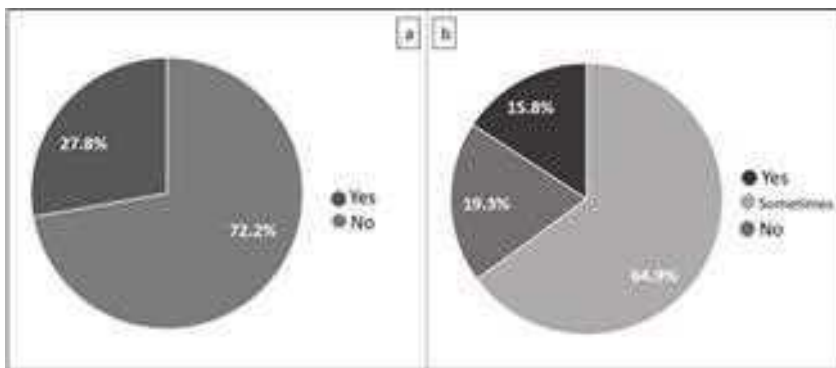


Figure 4. (a) Participants difficulties in fulfilling food and (b) intensity of participants going to the market.

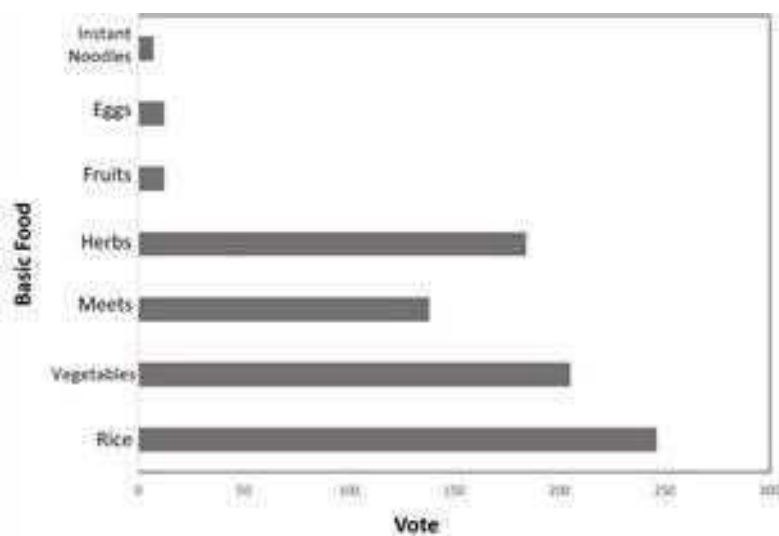


Figure 5. Participants basic food needs.

Although many participants still went to the market, most participants admitted that there was fear of going to the market during this pandemic. Most participants also admitted that it was not conducive to go to the market in the middle of this pandemic. Almost all participants were concerned about physical contact with many people when they were going to the market. Participants were also worried about food conditions that were openly displayed in the markets and had direct contact with many people (see Figure 6a). The market situation in the residence of most participants has slightly reduced visitors although it was still categorized as a crowded condition. Besides, participants responded to some difficulties in meeting basic food needs during the COVID-19 pandemic. One of the main difficulties was because some traders closed their shops, which then led to difficulties in fulfilling other basic food needs encountered by participants. Therefore, it could be stated that the implementation of social distancing, or in general the implementation of the LSSR in the residence of the participants are related to one another. Other than that, there were other difficulty factors explained by the participants, i.e., the lack of public transportation, supplies that were running out (especially in stores), and some of the participants explained because of the fear of leaving their houses as shown in Figure 6b.

Figure 7 shows the fulfillment of the basic foods of the participants if they did not go to the market. They mostly bought basic food needs at a shop near their homes. Besides, participants also chose delivery and waiting for peddlers as an option to fulfill other basic food needs. However, according to more than half of the participants, options such as food shops near houses and peddlers could not fulfill all the basic food needs of participants. Delivery options also could not fully help in fulfilling the participant's basic food needs, because according to the participant's explanation some shops did not have delivery services, making it difficult for participants to access. Some participants also explained that it was not uncommon for participants to have stored food supplies at home. However, afterward, the data was obtained that most participants felt worried that some of the stored food supplies were no longer fresh and would be stale and then wasted.

Delivery and peddlers were the options of the fulfillment of basic food needs during this pandemic that were mostly chosen by participants. The data obtained also showed that participants responded well that delivery and peddlers helped fulfill food during the COVID-19 pandemic. Some participants also responded related to peddlers, the intensity of peddlers in the participants' residence was reduced during this pandemic. Besides, from the survey data, it was found that most participants were worried about the food conditions that peddlers sold were openly displayed.

In this questionnaire, we included several questions that were directly related to the ideas we had in order to see the communities' response to our idea. The data obtained from these questions could later be used as suggestions/input. We presented our ideas related to the transportation system during this pandemic. Most of the participants responded well to our idea by assuming that this food truck idea could be a solution to reduce the difficulty of the community in accessing food during LSSR. Participants also responded that the most appropriate time for a food truck to operate in areas affected by LSSR was in the morning and operated three times a week.

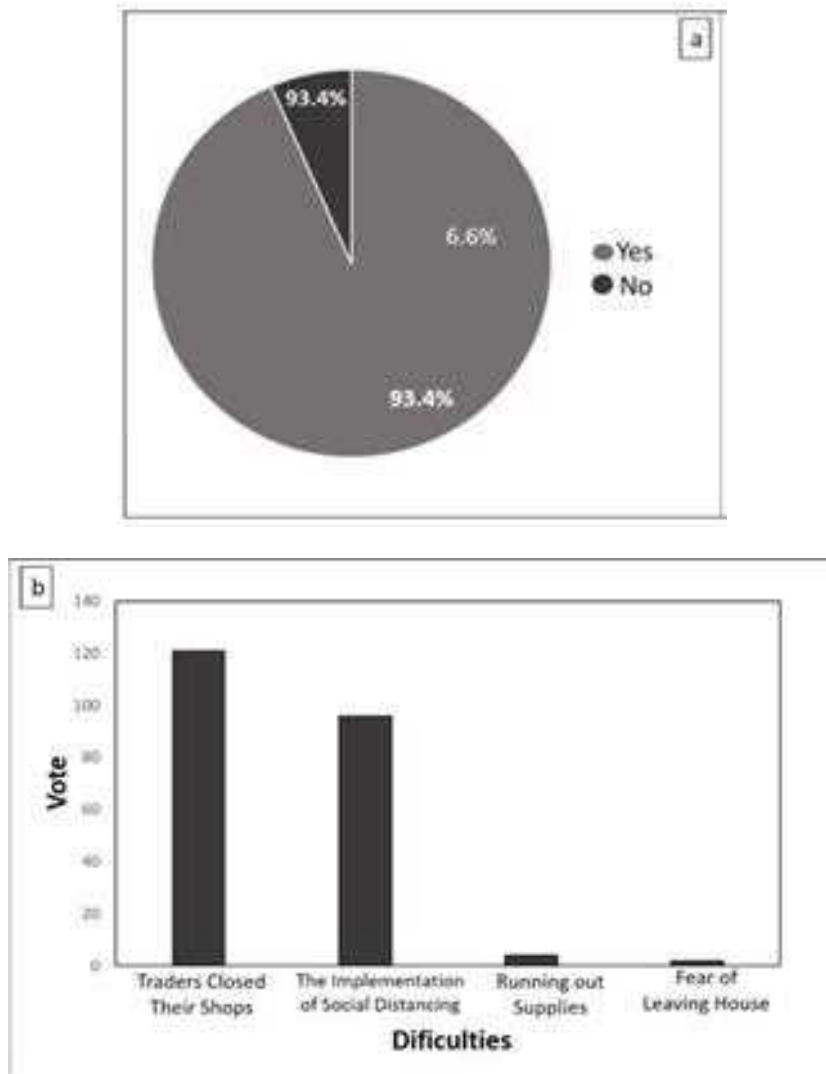


Figure 6. (a) Percentage of Participants Concerns About Physical Contact and (b) Participants Difficulties in The Fulfillment of Basic Food.

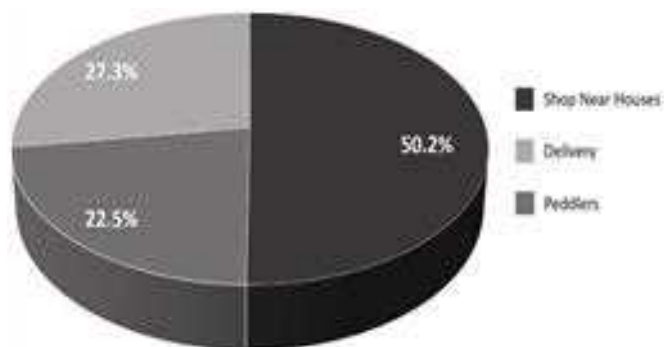


Figure 7. Sources of the food fulfillment if participants did not go to the market.

CONCLUSION

From all the survey data obtained, it could be concluded that the community indeed experienced difficulties in fulfilling basic needs during this pandemic. The problem in fulfilling food at the current pandemic is due to the limitation of citizens' activities with the implementation of LSSR in some areas. Facilities to fulfill basic food needs such as peddlers, food shops close to community houses also have shortcomings, that is, not all basic food needs could be obtained from these facilities because the citizens usually buy more complete basic foods by going to the market. The community's concern to leave the house and the condition of food that is displayed openly is also a problem. Food that is left open is feared to be contaminated by COVID-19. Then, judging from the participants' situation and response, the idea of a Mobile Food Truck that transports basic food could be a solution to the fulfillment of the needs of the basic food of the community during the COVID-19 pandemic, mainly in the area where the LSSR is implemented.

ACKNOWLEDGMENT

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Chapter 442

MINI HELICOPTER AS DISINFECTANT SPRAYER (HYPOCHLOROUS ACID)

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ABSTRACT

This research was conducted as an effort to reduce the spread of coronavirus disease 2019 (COVID-19). One of the efforts here is in the form of an idea to spray disinfectant using a mini helicopter. The background of this research is from the fact that current prevention of COVID-19 the spread conducted is still considered to be less effective. Although the government has now appealed for social distancing, there are still many people who do not understand the urgency of social distancing so that the number of COVID-19 cases continues to grow. Spraying disinfectants is also very necessary to eliminate viruses that stick to objects and viruses that are still airborne. Researchers have an alternative idea to spray hypochlorous acid periodically using a mini helicopter. This research was conducted using a survey method with the help of google form media. Based on the survey results, the research subjects argued that social distancing and spraying disinfectants became effective ways to prevent the spread of COVID-19. More than half of the research subjects stated that the idea of developing a mini helicopter for spraying disinfectants is possible to prevent the spread of COVID-19. The priority area for spraying according to research subjects is the COVID-19 the red zone area.

Keywords: disinfectant, hypochlorous acid, mini helicopter, social distancing, the spread of COVID-19

INTRODUCTION

Coronavirus is a type of virus from the corona viridae family that can infect the respiratory system both humans and animals. This virus is more commonly found in animals. The coronavirus was first identified in the 1960s. It was named Corona because of its body structure that looked like a crown (Verizarie 2020). The disease caused due to being infected with this virus is called COVID-19 (Maryanti et al. 2020). Coronavirus can cause mild disturbances to the respiratory system, severe lung infections, also death. This virus can affect anyone, both infants, children, adults, the elderly, pregnant women, and nursing mothers. This virus was first discovered in Wuhan city, China, at the end of December 2019 (Anggraeni et al. 2020). The virus is transmitted very quickly and has spread to almost all countries, including Indonesia, in just a few months (Merry 2020; Hasyim et al. 2020).

In March 2020, in Depok, Indonesia, there were two people affected by this disease. Then the spread was so fast that on 18 April 2020 there were positive cases of 19,248 people, 535 people died and 631 people were cured. The initial prevention steps set by the government to encourage people to work, worship, and study at home (BBC News 2020). It was quite effective to reduce mass gatherings. The next step is using a mask when leaving the house, washing hands with flowing water, maintaining physical endurance, and spraying disinfectants (Kevin 2005). Disinfectant in the medical view is a compound to prevent infection by destroying or dissolving pathogenic microorganisms by being imposed on non-living tissue such as operating rooms, operating instruments/medical devices, etc. In another sense, it kills germs, bacteria, and also viruses by destroying or dissolving them. This disinfectant is used in non-living tissues, such as equipment/rooms that want to be sterilized so that the disinfectant is currently used to sterilize rooms or other facilities (Vembi 2020).

Disinfection is prevention of various types of dangerous organisms, both viruses, bacteria, and fungi that can cause disease transmission. Spraying disinfectant is done to the aforementioned (Fathiyah 2020). Spraying disinfectants is often used on a person's body and WHO (World Health Organization) says disinfectants are dangerous if sprayed on the human body (Achmad 2020). Disinfectants that are sprayed on the body automatically will have accumulated harmful particles that are inhaled and enter the respiratory tract, either from detergents or alcohol (Aris 2020).

We developed ideas related to the transportation system to reduce the spread of COVID-19 in regions in Indonesia using mini helicopters. This idea still requires data from the Indonesian people, so we distributed questionnaires about our ideas for research purposes. It is hoped that this idea can be developed and be able to assist Indonesian people in preventing the spread of COVID-19. Our idea is to spray disinfectants using mini helicopters that can be used indoors or outdoors. This mini helicopter is equipped with a camera so that it can be controlled remotely. Spraying disinfectant not only by land but also through the air, this is done so that prevention of the spread of COVID-19 is more effective (Nanda 2020).

METHOD

The method used in this study was a quantitative method based on questionnaires. This questionnaire was designed in such a way and distributed to Indonesian territory through

social media so that data and information from the Indonesian people would be obtained. Questionnaires are data collection techniques that contain written questions to get responses from respondents. The data collected used as a reference in developing our ideas.

Our idea making a mini helicopter to spray disinfectant which is presented in Figure 1. This mini helicopter is small (mini), so it can be used indoors or outdoors. In the mini helicopter, there is a camera to see the surroundings, so it can be seen whether the situation is safe or not for spraying (Figure 2a). The mini helicopter is also driven by a remote control where the remote is controlled (Figure 2b). This helicopter also has a disinfectant liquid container and a tool for spraying the disinfectant. Spraying disinfectant could be easier especially at tall buildings using this mini helicopter.

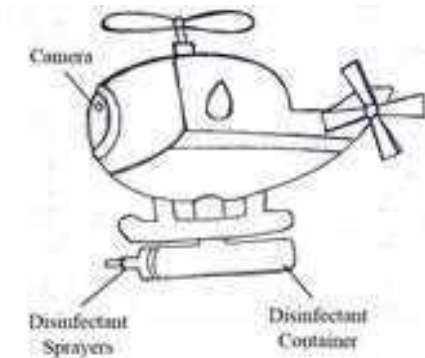


Figure 1. Mini helicopter as disinfectant sprayer.



Figure 2. The situation around the helicopter can be seen through a monitor (a), the mini helicopter is also driven by a remote control (b).

RESULTS AND DISCUSSION

Based on data from 72 respondents on the questionnaire form that distributes, this idea is possible to be implemented. However, this idea has not been completely perfect. From this idea, we still have to consider other things. Most people believed that spraying disinfectants effectively reduces COVID-19 (Figure 3a). Spraying disinfectant was considered effective to prevent the spread of this virus because according to Juan Leon, a health scientist from Emory University, coronavirus is a virus that is covered with a protective fat layer which when exposed to disinfectants, the fat layer of the virus can be torn apart and make the virus weakened. Therefore, the use of disinfectants is recommended by a lot of scientists, especially to clean the surface of objects that are often touched by humans.

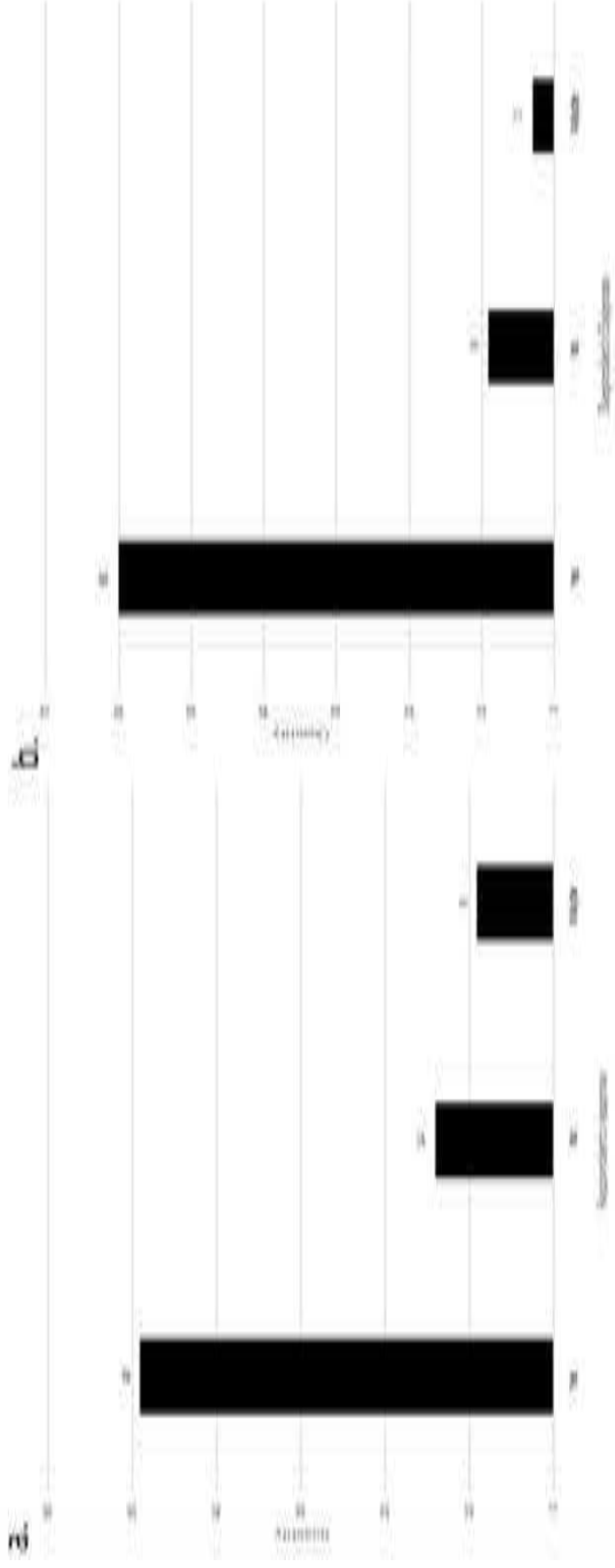


Figure 3. Spraying disinfectant is effective to prevent the spread of COVID-19 (a), it is necessary to spray in each area (b).

Spraying disinfectant in each area is needed to reduce the spread of COVID-19 (Figure 3(b)). Spraying of disinfectants is also done in places that have been visited by people with COVID-19. Spraying is conducted in an area where there is an indication that the patients exposed to COVID-19.

Meanwhile, spraying is also important in areas that have not been indicated by patients exposed to COVID-19 to reduce the spread of COVID-19.

The liquid used in spraying disinfectant is indeed safe and can reduce the spread of COVID-19 (Figure 4(a)). The disinfectant liquid is pulverizer at the right target, like at home, and the objects. It is not to be sprayed directly on a person's body because it can risk a person's health. Spraying disinfectant is done around the house (Figure 2(b)). The main priority in spraying this disinfectant is the object around the house. The part that needs to be sterilized is every surface of objects such as on door handles, toilets, and sinks. WHO does not recommend spraying disinfectants directly into the human body because it is dangerous. Alcohol or chlorine that is sprayer on the human body will not kill the virus that has entered the body but can be harmful if the alcohol and chlorine that is sprayed, are exposed to clothing or mucous membranes such as the mouth and eyes.

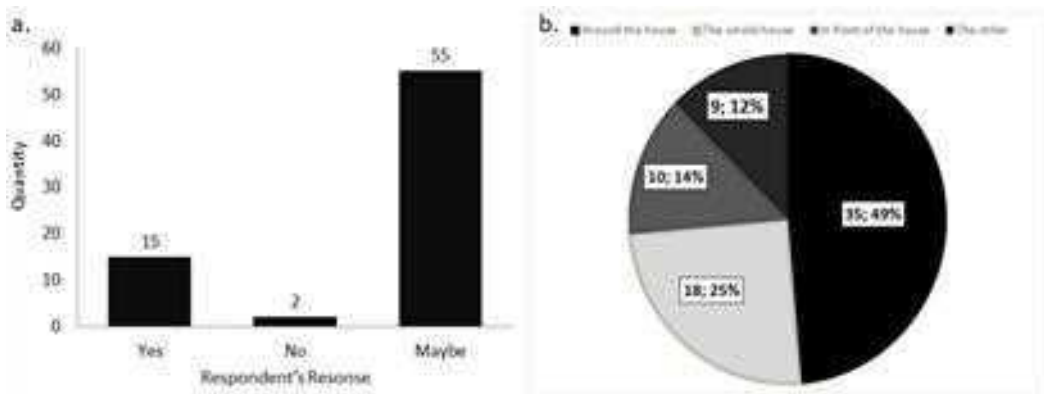


Figure 4. Disinfectant liquid is safe (a), and the part of the house that should be sprayed (b).

In the midst of this pandemic, a lot of Indonesian people have tried to anticipate the spread of COVID-19. Their efforts are like finding out or increasing knowledge about COVID-19 and ways to protect themselves from being infected by the virus. Many Indonesians already know how to make their own disinfectant liquid (Figure 5a). General knowledge about making disinfectants is certainly very useful for dealing with the current situation. Society can make their own forms of prevention without having to wait for government service. Therefore, this kind of knowledge is very important for our own good.

However, many people are still unsure about the safety of self-made disinfectants (Figure 5b). The public is also not entirely convinced that self-made disinfectants are effective in preventing the spread of COVID-19. This is because they do not know the ingredients that can be used to make disinfectants.

Regarding our idea of making a mini helicopter to help spray disinfectants in various regions, the results said that our idea could be implemented (Figure 6a). As if we implemented our idea in making this mini helicopter for spraying the disinfectant, around

56.90% of the survey results were willing to use it, while 31.90% of them still did not know whether they would use it, and the rest said they would not use it Figure 6b).

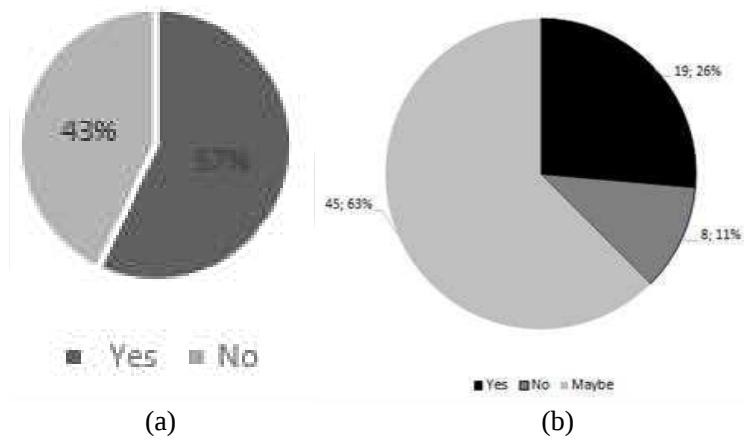


Figure 5. Lot of people can already make their own disinfectant (a), but there are still many who are not sure of the safety and effectiveness of the disinfectant that is made by themselves (b).

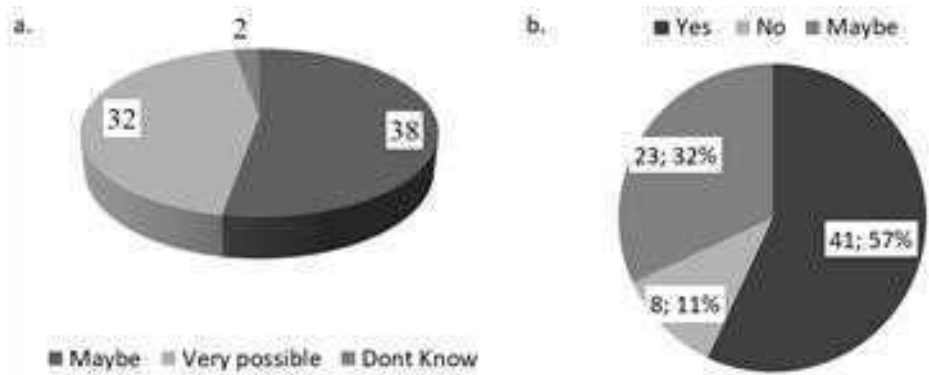


Figure 6. It is possible to develop mini helicopters for spraying disinfectants (a), and many people are willing to use mini helicopters to spray disinfectants (b).

Policies emerge due to the coronavirus outbreak can be seen with the closure of several access roads in a certain time, limitation on the amount of transportation, limitation on operating hours of transportation, which of course the policy is intended to be able to restrain the rate of society out of the house (Yunus and Rezki 2020). There are limitations to leave the house, therefore, the use of mini helicopters made unmanned to spray disinfectant on buildings and roads to reduce the spread of the COVID-19. This mini helicopter could be controlled from inside the building so that it still adheres to the government's recommendations to stay at home and reduce activities outside the home.

Based on the survey, around 42 people (58.30%) said that the fuel that should be used for this mini helicopter is solar power (Figure 7a), while others stated it would be better to use electricity. Another opinion said that we could use bioethanol or biogas fuel. It was suggested in order to maintain the environment and not adding a problem to the existing pollution. Hypochlorous acid can oxidize bacteria and other microorganisms in seconds and one of them is the coronavirus. Hypochlorous acid has anti-microbial, anti-inflammatory, and can also kill

E. coli bacteria in just 12 seconds. So, 59.70% of them said that spraying disinfectants using hypochlorous acid was an effective step in reducing the spread of COVID-19 (Figure 7b). But there are still people who do not know the benefits and functions of these fluids. There are still some people who consider that the liquid is not effective in preventing the spread of the COVID-19. In fact, by spraying the liquid, it could prevent the spread of COVID-19.

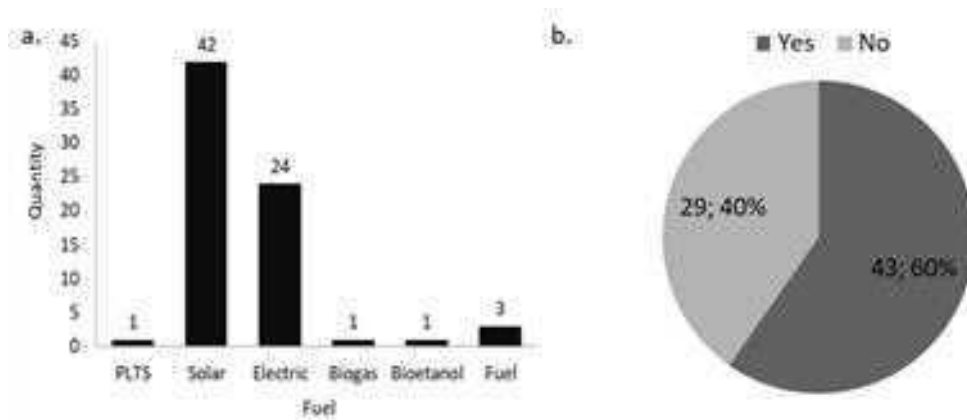


Figure 7. fuel that should be used for mini helicopters (a). effective hypochlorous acid (b).

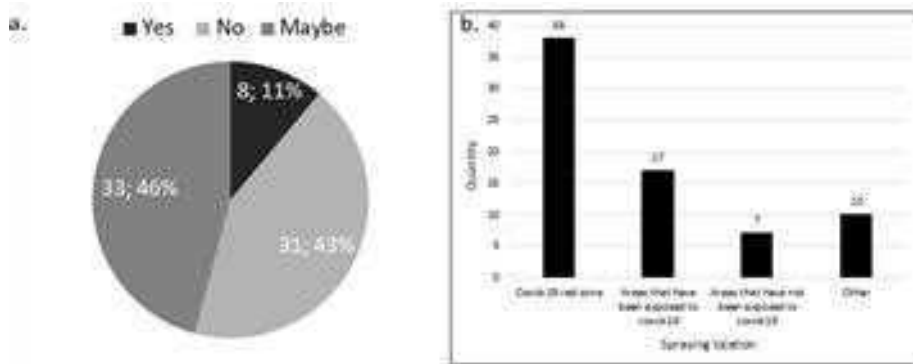


Figure 8. Effective or not spraying disinfectant through the air (a). effective parts for spraying disinfectant (b).

Most people assume that spraying disinfectant through the air is still ineffective, also they still doubt whether spraying disinfectant would be effective (Figure 8a). The reasons are misconduct during the process which can endanger public safety. Therefore, when someone is spraying disinfectant through the air, it means that person must know the procedures. Spraying disinfectants is one step in preventing the spread of COVID-19, therefore, it is necessary to spray it in all areas. Especially areas marked by the COVID-19 red zone (Figure 8b) because these areas have a significant chance of COVID-19 transmission compared with areas that have been exposed to COVID-19 and areas that have not been affected by COVID-19.

CONCLUSION

This study concluded that this idea for applying mini helicopters is still very possible to be implemented. Most people think that spraying disinfectants using mini helicopters is possible and can reduce the spread of COVID-19. In addition, hypochlorous acid that does not contain alcohol can also be used as a disinfectant that can reduce COVID-19.

ACKNOWLEDGMENT

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Chapter 443

MODIFICATION OF PUBLIC TRANSPORTATION TO PREVENT THE SPREAD OF COVID-19 IN WEST JAVA, INDONESIA

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ABSTRACT

Coronavirus disease 2019 (COVID-19) pandemic has influenced several areas, one of which is transportation, specifically public transportation. This affected captive groups or public transport users, especially public transportation cars, as city transportation. The purpose of this study is to investigate public transportation problems during the pandemic and find out community responses in West Java regarding the idea of modifying urban transport. The method used is a quantitative method based on the questionnaire. The results showed how the transportation system of urban transport was not yet effective enough to prevent COVID-19 exposure at the moment. Respondents support the idea of the modification of urban transport as a solution with affordable fees and minimal modification costs. Respondents also approved the use of electricity as a fuel for urban transport and encouraged the government to execute the idea of a modification of city transportation.

Keywords: public transportation, modification, COVID-19

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INTRODUCTION

Corona or COVID-19 virus pandemic has caused problems in various parts of the world, including Indonesia. COVID-19 is a new type of virus that attacks the respiratory system (Maryanti et al., 2020). The COVID-19 case in Indonesia has been announced since 2 March 2020 and has become increasingly epidemic. Indonesian government adopts a policy to issue health protocols implemented in all regions in Indonesia led by the Ministry of Health of the Republic of Indonesia (Kementrian Kesehatan Indonesia (Indonesia Health Ministry), 2020). Nonetheless, COVID-19 continues to expand and the number of infected people continues to increase every day. The speaker of the Indonesian House of Representatives repeatedly reminded the government to create a national team that would deal with the COVID-19 outbreak (CNN Indonesia 2020). Limited information causes the community worried and confused because they do not get safe and convincing services when they feel there are indications of exposure to COVID-19. Another problem that arises is the authority to determine public health emergencies by the central government or regional governments. The President of the Republic of Indonesia stressed that lockdowns should not be carried out, however, if the municipal leaders felt the need to carry out a lockdown in the area is allowed. The slow response of the central government and weak regulation have been seen as something obvious (Telaumbalua 2018).

The community demands that the government immediately handle the threat of COVID-19. The solution has been written in Law Number 6 Year 2018 on Health Quarantine about health quarantine and the determination of public health emergencies by the government. The rules are also laid down in the law as a follow-up to the provisions on health quarantine. Efforts are made to limit activities outside the home, stop school activities at school, encourage people to work from home and conduct religious activities at home. This has been a standard government strategy and has been optimally evaluated (Rezki and Yunus, 2020). These efforts have had an impact on various sectors in Indonesia, one of which is transport. Existing transport is not yet in a position to support the COVID-19 prevention protocol. As a result, people have difficulty traveling without worrying about being exposed to COVID-19. Therefore, we have the idea of modifying one of the public transport services in West Java, namely *minicab* by following the COVID-19 prevention protocol.

The general public group is divided into two groups, based on users of transport services, namely choice and captives. The choice group is a private vehicle user group, while the captive group is a public transport user group (Siswoyo 2008). Although some stay and work at home, the community (captive group) still needs public transport to work or purchase daily needs. As a developing country, most people in Indonesia are from the lower middle class (Siswoyo 2008). Lower middle-class people commonly use public transport. Public transport, which promotes the use of the COVID-19 prevention program, is therefore needed to facilitate the public's need for public transport.

Public transport cars, commonly referred to as *minicab* or *angkot* (in Indonesian language), are chosen by the community to travel long and short distances. The distribution is fairly even and reaches different regions at a relatively affordable cost compared to other public transport services. *Minicab* has a flexible pick-up point for passengers and can carry around 10-12 people. These advantages make *minicab* dominates West Java transportation and can be accessed by all groups (Sutandi 2015). It is also the type of public transport mode

that can be used as an alternative to public transport on the shortest, fastest and cheapest route. (Hobbs 1995; Hasyim et al., 2020). On the basis of these criteria, *minicab* is appropriate as a solution to the problems of public transport during this pandemic.

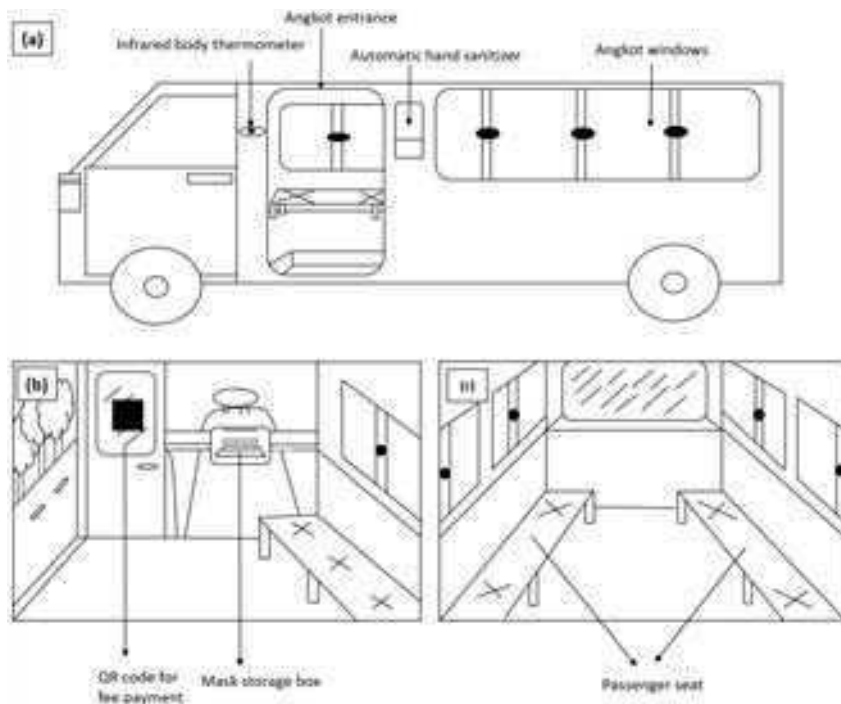


Figure 1. Illustration of exterior appearance (a), inside-front display (b), and inside-rear display on the modification of city transportation (c).

However, *minicab* modification is needed to prevent the spread of COVID-19. Illustration of changes in urban transport is shown in Figure 1. The modifications and background of the *minicab* selected are as follows.

1. Access to and from public transport is fairly simple, so that a body temperature thermometer can be installed before entering public transport (Figure 1a).
2. *Minicab* has a strategic area that can be modified to provide facilities/access to personal protective equipment. Automatic hand sanitizers can be supplied outside the *minicab* (Figure 1a) while masks are provided inside the *minicab* (Figure 1b).
3. Payment can be both digital and physical money. Money is one of the media which can spread COVID-19. *Minicab* can be equipped with digital wallet to prevent the spread of the virus through money. Payment can be made by scanning the QR code found on the *minicab* door (Figure 1b). However, *minicab* also accepts payment physical money, so that it is flexible in terms of payment.
4. The structure of the *minicab* is fairly simple compared to other four-wheeled public transportation modes. This facilitates surface sterilization of objects in public transportation (Figure 1b and 1c)
5. *Minicab* has good double-sided window air circulation (Figure 1c), to minimize the COVID-19 virus spread.

6. The distance between passengers can be easily adjusted by separating the position of the passenger seat and making it simple (Figure 1c).
7. In order to support physical-distancing efforts, the capacity of passengers is limited to 8 people by placing an X sign on the seats that cannot be occupied (Figure 1c).
8. The *minicab* pick-up points are flexible so that they can reach different regions.
9. Affordable price.
10. In addition to transporting passengers, *minicab* can carry a large quantity of food, such as sacks and boxes.
11. Modification of *minicab* requires only a small level of money and is prolonged.
12. The modification of *minicab* provides for public transport by preventing the spread of COVID-19. This solution uses active transport in West Java, so it does not cost money to create a new type of transport.

METHOD

A study was conducted in April 2020 with the implementation of the COVID-19 Distribution Prevention Protocol. The method used in this study was therefore a quantitative method based on a questionnaire. Questionnaire is a technique of collecting data through forms containing questions submitted in writing to a person or group of people to get the answers, responses, suggestions, or criticisms needed by researchers. Google form used to collect questionnaires. In addition, the literature review was also used to enhance references. Distribution of the questionnaire to all regions of West Java.

RESULTS AND DISCUSSION

The respondents were 54 people with the distribution of residential areas shown by Figure 2. The questionnaire was distributed with most of the respondents living in Cimahi, Bandung, and West Bandung Regency. The rest of the respondents lived in Depok, Cilegon, Purwakarta Regency, Sukabumi, Bogor, Garut Regency, Kuningan Regency, Sumedang Regency and Cirebon.

Each region has a different policy for public transport operations during this pandemic. Public transport was restricted as an effort to prevent the spread of COVID-19. Large numbers of public transportation have the potential to increase COVID-19 transmission (Kompas 2020a). Based on the results of the study, there were six modes of transportation chosen by the community during this pandemic, namely motorcycle taxi, taxi, train, bus, *minicab*, and pedicab (Figure 3a). The three modes of public transport most commonly used by the community are motorcycle taxi, taxi and *minicab*. All three of these transports underwent a dramatic change during this pandemic.

Motorcycle taxi still operates even though the operation is restricted by Pembatasan Sosial Berskala Besar (Large-Scale Social Restriction) rules in West Java. The Large-Scale Social Restriction (LSSR) rules state that a two-wheeled vehicle carries a maximum of two people living in the same house, as proven by their identity cards. In the meantime, both *minicab* and a car taxi could only carry 50% of their passenger capacity and are required to

limit the distance between passengers (Kompas 2020b). The use of masks is mandatory when traveling during the LSSR. This is certainly a challenge for public transport operations.

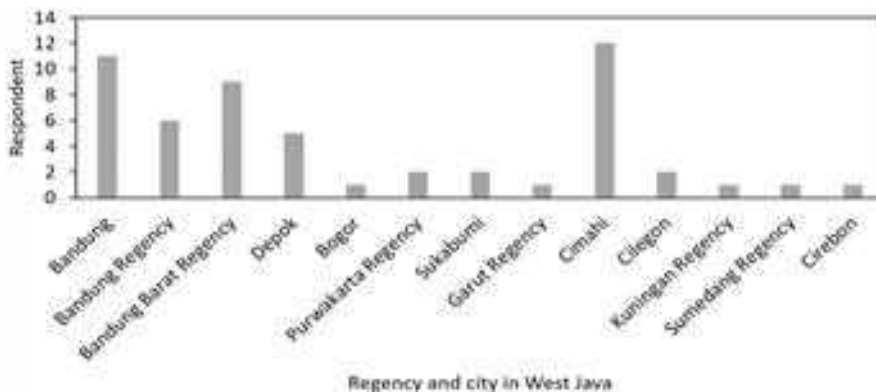


Figure 2. Distribution of respondent's residence in West Java.

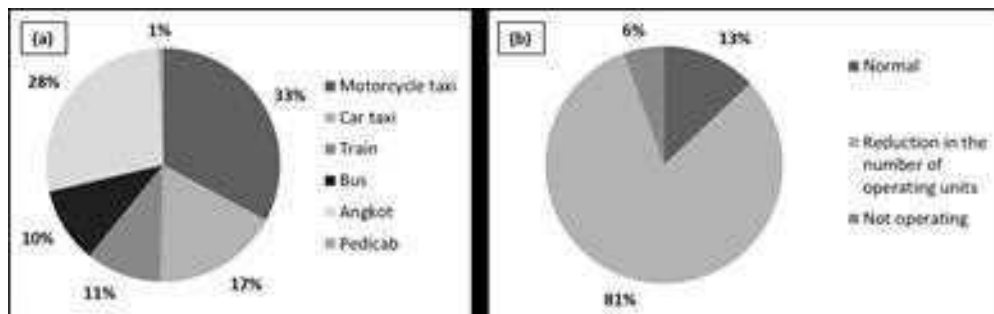


Figure 3. Public transportation in West Java, Indonesia: (a) active and (b) operation.

A balance between the quantity of supply or unit and demand is needed in public transport operations (Juanita and Pinandita 2016). The call to stay at home and work from home (WFH) has an impact on current demand, resulting in a decrease in the number of passengers (Anggraeni et al., 2020). The decrease in passenger numbers has resulted in a decrease in public transport units (Figure 3b). In addition, several regions have issued policies so that public transport does not operate.

Efforts to protect passengers from exposure to COVID-19 in public transport may be made by passengers themselves or by an authorized institution to change the transport system. Passengers can use masks and apply hand sanitizers. These things are very simple, but in fact, there are still some people who are negligent in their implementation. Such negligence can increase the chance of being exposed to COVID-19 while on public transportation. However, the possibility of the negligence of users of public transportation can be anticipated by providing access to masks and hand sanitizers on public transportation.

The Indonesian Transportation Agency has changed the transportation system to support the prevention of the COVID-19 spread. Broadly speaking, public transport policies are limiting distance between passengers (physical distances), reducing the number of passengers to support distance restrictions, periodic sterilization of public transport surfaces, and reducing operating time due to reduced passenger volume. Body temperature measurements

before entering public transport are also carried out to minimize contact with symptomatic people with COVID-19. Although these efforts have started to be socialized, not all public transport implement them. Based on the results of the questionnaire, *minicab* has not yet implemented overall preventive measures (Figure 4). This shows that *minicab* is vulnerable to COVID-19 exposure. Although such efforts have been done, respondents felt normal with the changes in the current public transportation system (Figure 5a). On a scale of 1-5, the majority of respondents are satisfied on a scale of 3. This is caused by prevention efforts that are not carried out in an optimal and thorough manner. On the other hand, the respondents assessed that efforts to prevent *minicab* from COVID-19 are still not effective in their implementation. (Figure 5b). Therefore, *minicab* modification to support efforts to prevent the spread of COVID-19 is needed to minimize the chance of COVID-19 exposure.

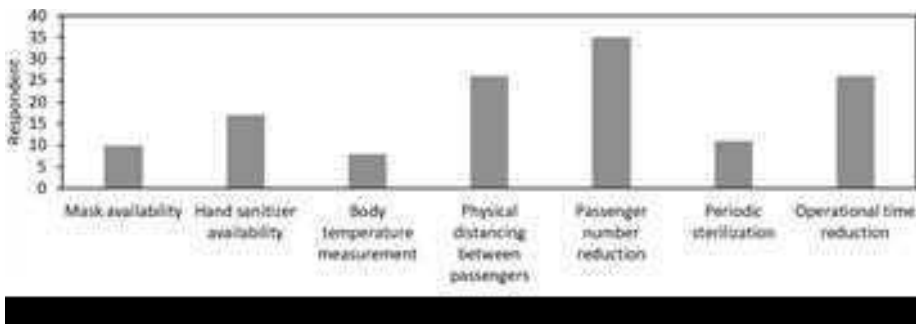


Figure 4. Changes in the city transportation system in West Java during the COVID-19 pandemic.

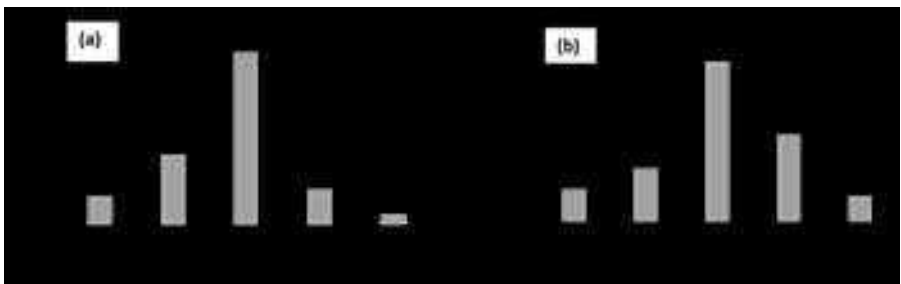


Figure 5. Satisfaction (a) and effectiveness (b) of the changes in the transportation system. Scales 1 to 5 are for dissatisfied to very satisfied, respectively.



Figure 6. The idea in modifying public transportation.

Based on Figure 6, the public welcomed the idea of modifying public transport. Respondents indicated that the modified *minicab* could reduce the spread of COVID-19. In addition, modified public transportation routes need special attention in order to be able to reach areas effectively, especially the PSBB zone and the red zone of COVID-19. The cost is expected to be affordable and modifications can be mass-produced. The community also supports the idea of using electricity as a modified public transport fuel. The idea emerged from public awareness of the impact of fuel transport on comfort, health and the environment. In addition, the use of electricity as fuel in public transport, in particular public transport, is a step towards a sustainable transport system (Sutandi 2015). The use of electrical energy will minimize air pollution caused by gasoline-fueled public transport. The community also supports this idea to be executed by the government.

CONCLUSION

Public transportation modification is needed as an effort to reduce the spread of COVID-19 in West Java, Indonesia. The modification maximizes self-protection from COVID-19 exposure by providing access to self-protective equipment and implementing physical distances, thereby reducing public concerns about travel by public transport. The community welcomes this idea with a condition that it has an affordable price and the modification is done as efficiently as possible. The public will also welcome the use of electricity as the *minicab* fuel and encourage the government to execute the idea of the *minicab* modification.

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Chapter 444

MICROFLUIDIC DEVICES IN PCR SYSTEM FOR THE APPLICATION OF COVID-19 RAPID DETECTION

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ABSTRACT

The aim of this study was to review the development of microfluidic devices in the Polymerase Chain Reaction system for the application of corona virus disease 2019 (COVID-19) rapid detection. Materials used for microfluidic devices are briefly reviewed as well. Clear descriptions for every microfluidic device, namely micropump, microvalve, and micromixer used to develop the whole Polymerase Chain Reaction system are discussed in detail, including their advantages and disadvantages. It is concluded that much progress has been achieved in the microfluidic-based on the Polymerase Chain Reaction system. The future benefits of this review are to encourage the microfluidic involvement within the Polymerase Chain Reaction system, especially for the application of COVID-19 rapid detection.

Keywords: COVID-19, microfluidic, micropump, microvalve, micromixer, PCR

INTRODUCTION

Since World Health Organization (WHO) on 11 March 11, officially stated that the corona virus disease 2019 (COVID-19) had become a global pandemic (Anjorin 2020; Anggraeni et al. 2020)), numerous countries all over the world have declared emergency state and shutdown public areas. Public areas have enormous potential for transmission of COVID-19 (Hasim et al. 2020). COVID-19 is a disease that is dangerous and can infect the human body. This disease is caused by a corona virus. This virus is transmitted through droplets

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(Maryanti et al. 2020a). The mouth or nose is a bridge for the virus to enter the human body. The very small size of the virus makes it easier for the virus to enter the human body (Maryanti et al. 2020b). Diagnostic tools can play a significant role to decrease the spreading rate of the virus. Polymerase Chain reaction (PCR) is one method that can be used as COVID-19 rapid detection. Since many microfluidic devices can be used for PCR application and rapidly identify the virus then make the microfluidic has the potential to offer an affordable point of care (POC) diagnostic.

In the recent decade, microfluidic has been particularly attractive for medical applications such as drug transportation, polymerase chain reactions (PCR), and chemical detection. Many devices in microfluidics can be integrated with one another such as on a single chip that can speed up biological analysis, reduce samples and reagents, and thus provide solutions for the medical field. PCR becomes a key process and a powerful tool in genetic investigations, clinical diagnostics, and the forensic field. Besides, currently, the PCR method is one of the techniques used for COVID-19 detection. Therefore, the role of microfluidic becomes more important and urgent because of its benefits such as rapid detection, few samples, short analysis time, good sensitivity, and disposable.

The advantages of micro-sized PCR devices have been widely studied by many researchers. Initially, the room-based PCR chip was introduced by Kopp (Kopp et al. 1998). The PCR chip model provided the basis for further development, and to date, they have been duplicated by many other researchers. The PCR chip transition from simple microfluidic components to advance integrated systems is still ongoing. Some microfluidic parts for several purposes such as sample preparation, DNA/RNA amplification, and sample detection can be integrated on a single chip (Cady et al. 2005). Micropump, microvalve, and micromixer successfully provide a higher level of integration and allow more than one sample to be run in parallel, which can reduce the analysis time.

Various progresses on the development of magnetic nanomaterials for micromixer has been reported. One of the reports presented a classification of micromixer divided into four types according to drive modes, such as external permanent magnet, electromagnet, micro stirrer, and the integrated electrode (Chen et al. 2017). Jeong et al. presented a report on micromixer based on its applications (Jeong et al. 2010). They classified the applications of micromixers into three categorized such as chemical applications, biological applications, and detection. Meanwhile, Au et al. presented a report on microvalves and micropumps for Bio-MEMS (Au et al. 2011). However, all previous reports were still too general in studying the detection process using the PCR system based on microfluidic devices.

Therefore, in this study, we reviewed the development of microfluidic devices in the PCR system for the application of COVID-19 rapid detection. Materials used for microfluidic devices are briefly explained as well. Furthermore, here explains the advantages and disadvantages of these functional components which indicate that micropump, microvalves, and micromixer technologies have played an important role in the development of integrated microfluidic chips.

MICROPUMP FOR PCR APPLICATION

Several types of micropumps have been designed and fabricated with various structures and operating mechanisms. In general, micropumps for fluid pumping in PCR chips can be divided into two categories, namely: mechanical micropumps with moving parts and non-mechanical micropumps without mechanical components (Au et al. 2011).

In 2017, one group of researchers has succeeded in developing a peristaltic pump integrated into the PCR chip (Alam et al. 2017). 3D printing using VEROTM photopolymer materials was used to fabricate the micropump. Utilization of 3D printing technology allowed for relatively short fabrication time. The minipump design is based on the concept of a planetary gear and worked in the same way as a typical benchtop peristaltic pump. The micropump was able to pump fluids between 40 mL/min and 200 mL/min and continue to work well at a back pressure of 25 kPa. Therefore, this performance showed successful interfacing between chip and device where the conceptual polymerase chain reaction (PCR) chip is fabricated well without leakage or flow disturbance in the microchannels (Alam et al. 2017).

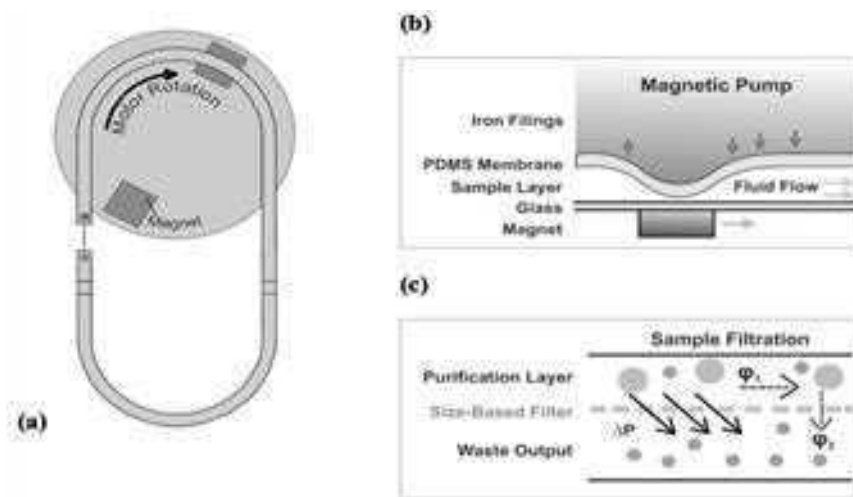


Figure 1. Magnetically-driven fluid flow. (a) As the motor rotates, (b) The cyclic magnetic pump comprises. (c) Sample filtration is driven by a pressure drop across the size-based filter (Liu et al., 2017).

In the same year, another group of researchers developed diafiltration-on-chip microfluidics integrated with magnetic peristaltic micropumps (Liu et al., 2017). The integration of magnetically driven peristaltic micropumps has the role of achieving a continuous flow of recirculation as shown in Figure 1a. This pump is operated using a three-dimensional microfluidic architecture, where magnetic material (iron filing) is joined into the layer above the flow channel which is divided from the flow channel by PDMS thin layer (Figure 1b). The filings of the iron are pulled down because the magnetic field deflecting the PDMS membrane and compressing the flow channel when a fixed magnet located below the flow channel separated from the sample by glass slide (Figure 1b). When an external magnet is moved in a plane along a flow channel, the place of this pressure in the channel moves with

the magnet and forces the fluid to move in the direction of the magnet's movement, which is similar to a peristaltic pump. The on-chip magnetic pump promotes steady flow through permeable membranes and high-resistance microfluidic pinch channels. Flux across the membrane is controlled by the relative resistance of the pinched channel and the membrane (Figure 1c).

Furthermore, Li et al. developed passive micropump which can produce and transmit microdroplets inside a microchannel with several millimeters' length in a much longer periode (Li et al. 2018). Passive micropumps can consistently carry large volume (more than 2000 μL) of fluid/oil microdroplets inside 3D spiral microchannel (4 m long and 2 cm high) in 8 hours of the period. The droplet flow rate can be easily adjusted by changing the quartz capillary parameters connected to the microchannel ends. This passive micropump was successfully applied to the home-made setup of droplet-based surfactant-free quantitative PCRs using only two syringes for droplet generation, a Teflon tube for PCR amplification and single thermostatic heater for a thermal cycle with the amplification efficiency of the virus reaching 91% of commercial PCR thermocycler (Li et al. 2018).

MICROVALVE FOR PCR APPLICATION

The completely integrated microfluidic system such as lab-on-a-chip (LOC) or a micro total analysis system (μTAS) cannot be realized without microvalve development (Vilkner et al. 2004; Dittrich et al. 2006). Therefore, microvalve becomes one of the most important components to be successfully applied to the compact integrated on-chip PCR microfluidics. In general, microvalve can be classified into two main types: active microvalve and passive microvalve depending on mechanical or non-mechanical moving parts.

Generally, the deflection of the PDMS membrane is utilized to interrupt the flow in pneumatic microvalve. This easily integrated with standard soft lithography process caused pneumatic microvalve to become one of the common valve architectures. Liao et al. developed a miniaturized RT-PCR system for the diagnosis of RNA-based viruses, in which the reagent and sample flow were controlled automatically by utilizing two micropumps and one microvalve, as shown in Figure 2. The fluid flow could be effectively interrupted when the pneumatic microvalve was closed, and the pressure of 69 kPa could cause the microvalve to close the flow of a fluid moving at $\sim 30 \mu\text{L}/\text{min}$ (Liao et al. 2005).

Manual microvalves system with 8 integrated channels for controlling up to 8 different flows of agents was developed by Lee et al. (2020). The working principle of the valve is based on flexible materials (PDMS) and mechanical structure. The plasma etching technique was used to bond 100 μm thickness of PDMS film fabricated on top microchannel. The mechanical structure for closing and opening the flow valve was integrated with two components. Firstly, the second slab of Plexiglass is fixed by a screw with 3 mm of diameter and width 0.5 mm of the thread pitch. Secondly, the screw hole is bigger than the PDMS piece (2.5 mm) make the PDMS piece move freely in this hole. The microreactor ($\sim 5 \text{ L}$ of volume) and multi-liquid mixing component is successfully connected by the valve system. The function of controlling liquid flows to the microchamber was effectively succeeded in using this valve system (Lee et al. 2020).

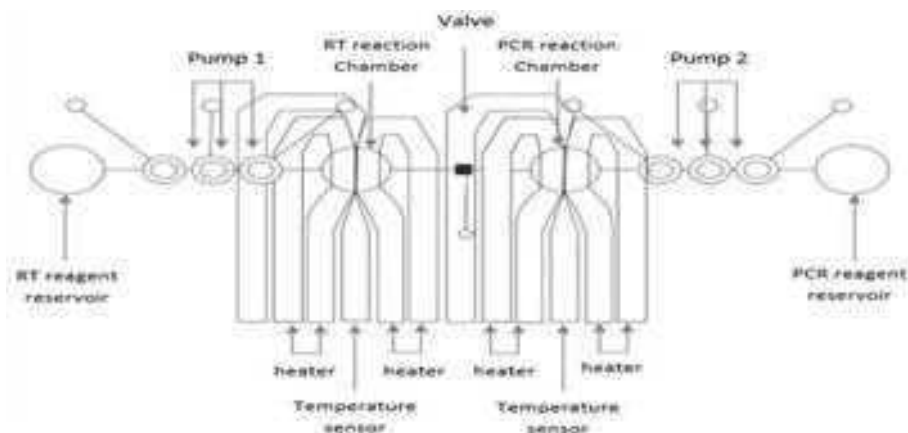


Figure 2. Schematic diagram of two-step micro RT-PCR chip integrated with two micropumps and one microvalve for controlling biosample transportation (Liao et al. 2005).

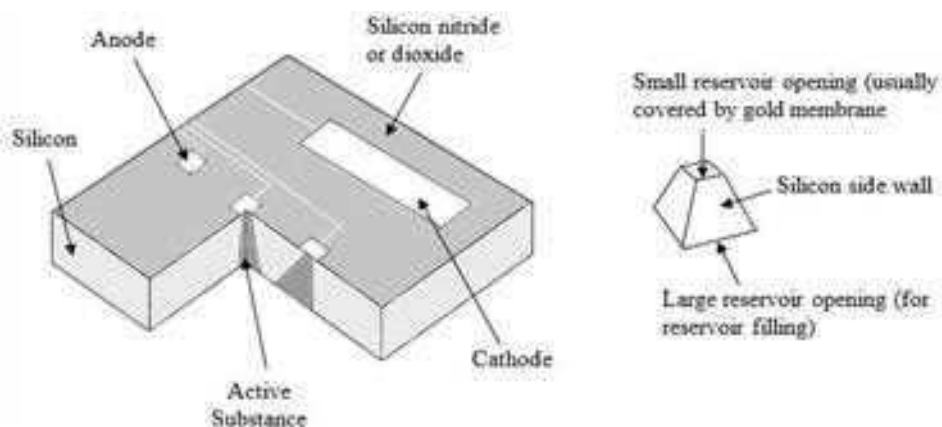


Figure 3. 3D schematics of a controlled-release microchip and a single anisotropically etched sacrificial membrane burst microvalves (Santini et al., 1999).

The other microvalve principle utilizes a sacrificial membrane. This concept introduced by Robert Langer which designs a silicone-based “drug-release” microchip containing etched cavities capped with the sacrificial” gold membrane (Figure 3) (Santini et al. 1999). The drug-containing solutions are filling the cavities prior to being sealed with the membrane. The electrical supply of 1volt was used to electrochemically dissolve the membrane. Therefore, the release of one dose (25 nL) of “drug” for every cavity is controlled by a voltage pulse. Meanwhile, Moreno et al. (2010) and Allain et al. (2010) reported the sacrificial membrane composed of silicon nitride and SU-8. When electrical current or the heat is applied to the sacrificial membrane, the microvalves are open. The debris from the disintegration of the sacrificial membrane can be released into the fluid (Moreno et al. 2010; Allain et al. 2010).

Baek and Min investigated microvalves for selectively extracting nucleic acid from bacteria and viruses by physical adsorption and beat beating (Baek and Min 2015). The principle work of microvalves in the chambers is to switch between the packed bed for the pathogen concentration and beat beater. Meanwhile, Zahra et al. presented the microfluidic system integrated with temperature actuated microvalves. The “open” and “close” position of

the valve is depending on the electrical supply to the heater. The atmospheric pressure obtained inside the chamber (microvalves) when there is no electrical supply. On the contrary, the temperature inside the chamber increases when the electrical supply is given and the generated pressure pushes up the valve membranes, which close the channel. The temperature of 92°C with an applied voltage of 4 V is given when the complete closure of the channel happened without liquid leakage. Furthermore, the time constant of the valve during the opening is 1.40 s (Zahra et al. 2015).

Tang et al. (2019) presented the multi-way microvalves with a rotor. The principle operation is based on a rotary mechanism. The five-degree rotational symmetry was obtained with a compressible rotor and a complementary stator seat valve. The Viton elastomer is used for a rotor to provide a seal and switch between outlets. The microvalves can be operated in two ways, including manually or automatically. The switching torque of below 0.03 Nm and the pressure of 370 kPa with no leakage is obtained by the microvalves (Tang et al. 2019).

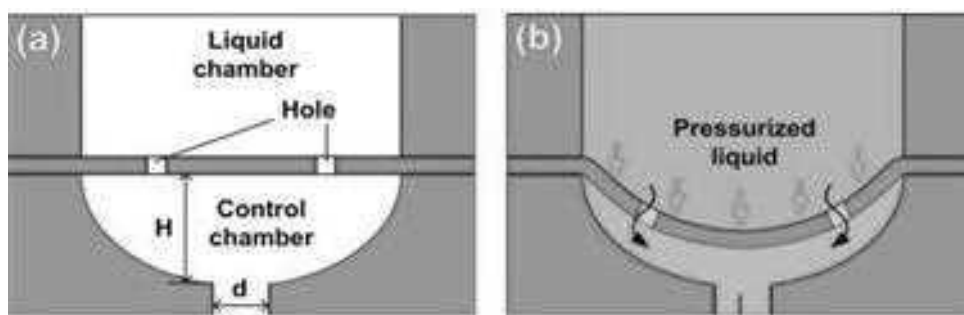


Figure 4. Working principle of the microfluidic passive valve. (a) Concept structure of the valve. (b) Schematic valve actuation under pressurized liquid (Zhang et al., 2019).

Meanwhile, a high flow rate control under an ultra-low threshold pressure was realized through microfluidic passive valve comprising of a fluid chamber, a flexible membrane, and an ellipsoidal control chamber by Zhang et al. (2019). The UV laser-cutting and 3D printing technologies were used to fabricate the microvalves. The constant flow rate of 4.03 mL/min, with a variation of $\sim 4.22\%$ under the inlet liquid pressures varied from 6 to 12 kPa was achieved by the passive microvalves. Furthermore, the microvalves could stabilize the flow rate of liquid under the time-varying sinusoidal pressures or the square wave pressures (Zhang et al. 2019).

MICROMIXER FOR PCR APPLICATION

Besides the microvalves and micropump, the micromixer is often another important and necessary component in an integrated PCR microfluidic system. In general, two basic principles are followed to generate mixing at the microscale: passive micromixing and active micromixing. Passive micromixers do not require external energy, and the mixing process relies only on diffusion or chaotic advection. For this micromixing means, the flow energy due to pumping action or hydrostatic potential is used to rebuild a flow in a way that causes faster mixing. Active micromixers use energy input from the exterior for the mixing process.

These external energy sources include electrokinetics, acoustics, magnetohydrodynamics, integrated microvalves/micropumps, and others.

The simplest micromixer structure is Y/T-type configurations that have been well applied for fluid mixing in the PCR chips (Hashimoto et al., 2006; Münchow et al. 2005). Hashimoto et al. presented Y-shaped passive micromixer to mix the continuous-flow PCR product and ligation detection reaction (LDR) cocktail for the detection of low-abundant DNA point mutations (Hashimoto et al. 2006). Meanwhile, the passive Y-type microchannel was developed to induce the reproducible metering and merging of two or more fluid volumes (0.1–10 μL) without any active valve components or external sensors in PCR chips (Münchow et al. 2005).

Chen and Zhao (2017) designed and optimized the obstacles of a three-dimensional T-type micromixer. The mixing index of above 0.9 is achieved for a wide range of Peclet numbers. The obstacles in T-type micromixers can improve the mixing performance than the conventional T-type micromixer (Chen and Zhao 2017). Another T-type micromixer with obstacles was presented also by Rasouli et al. (2018). The curve micromixer designed to create normal advection and curved microchannels to generate Dean vortices. The mixing index used in the range of 0.48–0.89 with a pressure drop of 195.6 Pa to 10,891.6 Pa for Reynolds number = 27 and mixing index range of 0.73–0.98 with a pressure drop of 1695.9 Pa to 35,543.8 Pa for Reynolds number = 81 is achieved (Rasouli et al. 2018).

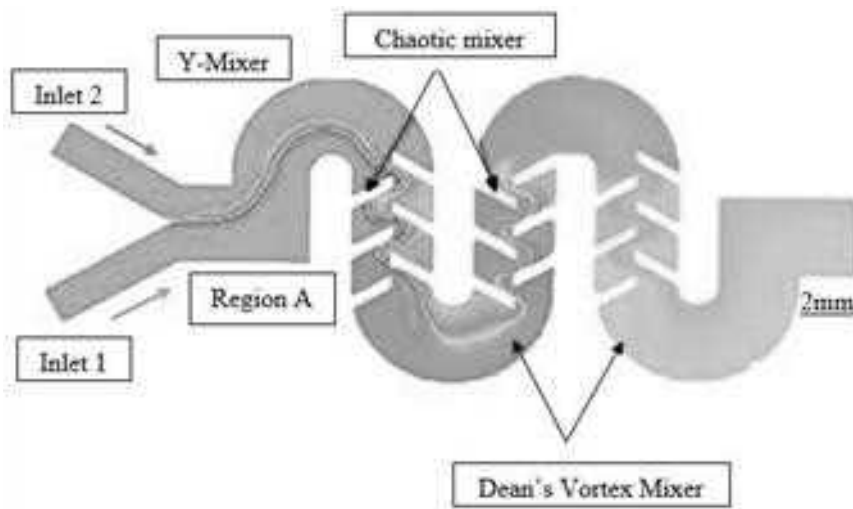


Figure 5. Schematic illustration of microfluidic mixer that simulates instant cross-contamination and sanitization scenarios (Zhang et al., 2015).

The micromixer integrated three different mixing designs including Y-junction, Dean vortex, and chaotic was presented by Zhang et al. (2015). The micromixer is used to determine precisely the reaction time and control the chlorine concentration as shown in Figure 5 (Zhang et al. 2015). Lee et al. (2009) presented an integrated microfluidic system consist of two micropumps, a pneumatic four-membrane-type micromixer, a micro coil array, and a sample purification chamber. The simultaneous detection of IgG and IgM in two different detection chambers can be done during the detection time of just 30 min. Also, the detection limit was found to be $2.1 \times 10^{-11}\text{g}$ (Lee et al. 2009).

Kastania et al., (2016) developed a passive polymeric micromixer integrated to the microfluidic chip for DNA purification. The micromixer design is zig-zag shaped PMMA microcolumn. For the DNA purification test, fluorescein (MW-332.21) which have a diffusion coefficient of $4.9 \times 10^{-10} \text{ m}^2/\text{s}$ is used. The mixing index of 0.95 is reached for 5 $\mu\text{L}/\text{min}$ per inlet and 0.88 for 10 $\mu\text{L}/\text{min}$ per inlet (Kastani et al., 2016). Kefala et al. (2015). developed a planar split and merge passive micromixer with labyrinthine microchannels. The micromixer consists of concentric rings where flow split and merges. The mixing index above 0.85 was achieved with the 11 concentric rings and a flow rate of 2.7 $\mu\text{L}/\text{min}$ (Kefala et al. 2015). Cai et al. (2019) developed a split-recombine passive micromixer integrated into the microfluidic chip for PCR application. The spit-recombine micromixer with multiple asymmetric rings has a function to mix the sample with H_2O_2 . The mixing index of 0.85 is reached at the flow rate of 0.05 mL/min with 7 asymmetric rings applied and does not improve significantly when more asymmetric rings are added (Cai et al. 2019).

To accelerate the DNA hybridization process or to expand the immunomagnetic cell capture process efficiency, Liu et al. developed micromixer based on acoustic microstreaming (Liu et al. 2004). The micromixer was integrated with pump, valve, storage for PCR application as shown in Figure 6. The PZT actuator generates the field that induced Acoustic microstreaming. The complete mixing process in the 50 μL chamber was decreased from hours to only 6s. Furthermore, acoustic microstreaming resulted in up to 5-fold hybridization reaction kinetics acceleration with significantly improved signal uniformity. Acoustic microstreaming has many advantages over most existing chamber micromixing techniques, including simple apparatus, ease of implementation, low power consumption ($\sim 2 \text{ mW}$) (Liu et al. 2004b).

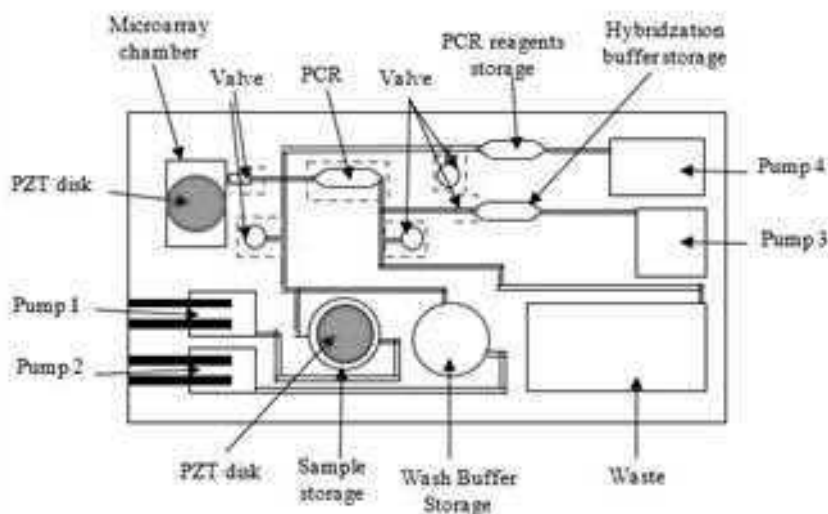


Figure 6. Schematic of the fully integrated PCR chip with a thermopneumatic air micropump and three electrochemical pumps (Liu et al., 2004b).

Another micromixer based on acoustics driven to increase antibodies-antigen binding which is forms the immunoassays such as enzyme-linked immunosorbent assay ELISA is presented by Gao et al. 2015). The external sound waves in the frequency range of 125 Hz to

150 Hz was used for micromixer. The acoustic micromixer is successfully increasing the initial binding rate of over 80% (Gao et al. 2015).

The bubble-based micromixer module fabricated with a combination of low-cost rapid prototyping techniques was presented by Conde et al. (Conde et al. 2020). The individual control of multiple micromixers embedded within the same monolithic chip can be integrated with any substrate. The static and continuous flow conditions can enhance mixing capabilities. The system is capable of performing cell-free DNA extractions from small volumes of blood plasma ($\leq 500 \mu\text{L}$) with up to a ten-fold increase. The convection mix method is used to mix the species and capillarity regulation to achieve sample transport on a single platform without the pump required is presented by Kim et al. as shown in Figure 7. The mixing rate as high as a few tens of seconds per microliter is achieved even at a low fluidic temperature of $\sim 37^\circ\text{C}$ (Kim et al. 2009).

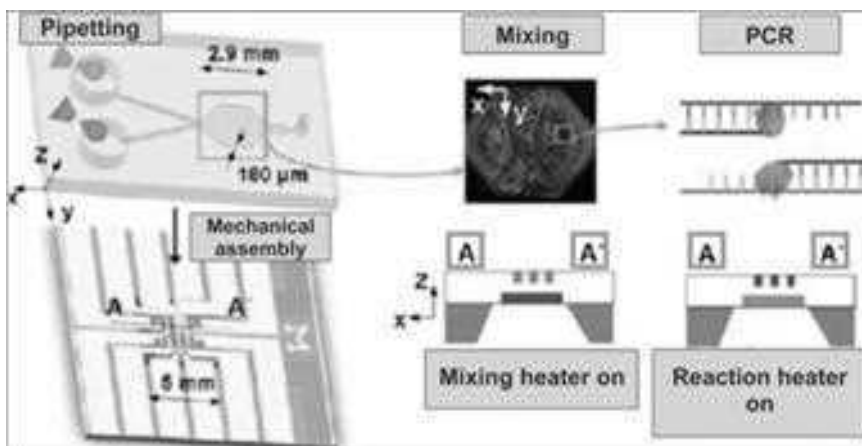


Figure 7. Schematic illustrations of single-chamber micromixing and PCR (Kim et al. 2009).

RESEARCH CHALLENGES

One of these research challenges is materials limitations. Most of the microfluidic devices are fabricated using polyurethane methacrylate which is showing elastomeric behaviors such as polydimethylsiloxane (PDMS) (Kim et al. 2009; Conde et al. 2020; Kastani et al. 2016). In the late of 1990s, the utilization of PDMS is growth to fabricate much microfluidic research because of its compatibility with the soft lithography process (Kefala et al. 2015; Cai et al. 2019). However, PDMS has many limitations and is not suitable for mass production (Chiu et al. 2017). Also, PDMS also suffers from swelling with chemicals (Lee et al. 2003). On the other hand, glass or silicon substrates are robust but require advanced fabrication processes whose cost. Interestingly, the silicon and glass are emerging as important materials for microfluidic devices with integrated electrodes, high aspect ratio channels, and able to patterned by e-beam. However, the glass materials become one of constraint when the fabrication processes required to create a deep channel in glass (Toan et al. 2016). Furthermore, the other issue is the fragility of the material.

The issues of PDMS in all microfluidic devices also should be considered. Several issues using PDMS which are as follows:

- 1) Hydrophobic small molecular absorption: Due to the PDMS has hydrophobic property from polymer network structure, the utilization of fluorescent molecules to diffuse and absorb into PDMS walls can allow some hydrophobic pharmaceutical drugs. This absorption and diffusion of small molecules can affect the accuracy and reliability of the experiments conducted in PDMS based devices (Toepke et al. 2006; Ren et al. 2010).
- 2) The leaching of uncrosslinked oligomers from PDMS: The residual uncrosslinked polymer chains by cured PDMS can freely diffuse the bulk material (Regehr et al. 2009).
- 3) The unstable surface property caused by oxygen plasma treatment: to facilitate chip bonding, oxygen plasma commonly used to convert the hydrophobic surface of PDMS to hydrophilic surfaces. Unfortunately, the hydrophobic properties return because the polymer chain can replace the hydroxyl groups by diffusing from the bulk to the surface (Eddington et al. 2006).
- 4) It works only in moderate temperatures
- 5) Surface roughness: It depends to the fabrication of the master molding process. When the roughness increase, a larger area for adsorption and air bubble production occurs.

In terms of the fabrication method, the microfluidic device is limited to quasi-3D planar formats. Several research groups have used 3D printing involving to print 3D microfluidic reactors and reagents in situ, and to print the master mold of microfluidic (Ho et al. 2015; Chan et al. 2016; Bohr et al. 2015). Both the resolution and cost of consumer-grade 3D printers have been plunging in recent years and are currently at a point where they are starting to be applied to microfluidic device fabrication. Direct printing will not only greatly accelerate device prototyping but also give scientists an easily accessible and empowering tool to express their creativity in the way that the introduction of PDMS soft lithography (Waheed et al. 2016; Zips et al. 2018; Cuarte et al. 2017).

The potential breakthroughs in the designs and development of these microfluidic elements within PCR chips are included as follows. First, inexpensive materials which are developed with the compatibility of MEMS fabrication techniques expanded should encourage the micropump, microvalves/micromixer to be integrated. Second, the concept of active “self-supplied” in the microfluidic becomes important within PCR chips where no external bulky pneumatic supply, valve connection tubing, and even power supply required. Third, the single-chip contains microvalves/micropumps/micromixers integrated will get larger to perform the high-throughput PCR amplification and subsequent analysis.

FUTURE: SMART MICROFLUIDIC PLATFORMS

The automation design of microfluidic has the potential to provide many of the above interesting issues. For example, Thakur et al. developed the programmable microfluidic platform for spatiotemporal over nanoliter droplets (Thakur et al. 2015). To control the micropump such as the number of pump cycles and rate of valve actuation, a programmable microvalves controller is used. Yu et al. presented a microfluidic chip for PCR application

that can automatically analyze the result detection within one hour (Yu et al. 2018). Meanwhile, Yehezkiel et al. designed a digital microfluidic with programmable order polymerization (Yehezkiel et al. 2015). The digital microfluidic can clone of assembled synthetic DNA by the PCR method. At present, the realization of functional digital microfluidic systems is still inception. Also, the digital microfluidic still equipped with many complex device apparatuses. However, the digital microfluidic performance will improve in a few years.

Many integrated circuit designers are rarely deal with semiconductor wafer or probe station. Therefore, the requirement for software experts that able to design and optimized the structure and then combine them with the fabrication experts and programmer experts so they can realize the smart microfluidic devices. Furthermore, the digital microfluidic will continue to have a significant potential application, especially in virus detection.

Future developments will relate also to bringing this technology into commercial devices worked on by non-specialists. Additionally, the requirement of standardization in microfluidic components is needed to be operated by unskilled end users. Commercialization of systems using microfluidic devices will become more frequent with many multinational companies investing heavily in microfluidic research. Devices for basic research will also remain very important, especially in the biological field due to researchers are trying to produce 'human-on-chips'. Future intelligent microfluidic platforms will also have a large impact on artificial intelligence and biological computations. This is ideal for applications, e.g., COVID-19 detection using the PCR method.

CONCLUSION

Much progress has been achieved in the microfluidic-based PCR system. Clear descriptions for every microfluidic device, namely micropump, microvalve, and micromixer used to develop the whole Polymerase Chain Reaction system are discussed in detail, including their advantages and disadvantages. It is concluded that much progress has been achieved in the microfluidic-based on the Polymerase Chain Reaction system. The future benefits of this review are to encourage the microfluidic involvement within the Polymerase Chain Reaction system, especially for the application of COVID-19 rapid detection.

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Chapter 445

COMMUNITY SERVICE DURING COVID-19 PANDEMIC AT UNIVERSITAS PENDIDIKAN INDONESIA

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ABSTRACT

Coronavirus 2019 (COVID-19) epidemic has become an international concern and has posed challenges to psychological resilience in all areas. As one of the three pillars of higher education system in Indonesia, students and lecturers play a role in the community through community service program. In keeping with the present situation and circumstances, the community service program conducted this year related to the COVID-19 global pandemic. Universitas Pendidikan Indonesia lecturers and students invented and developed tools used to prevent the spread of COVID-19. The invented and developed tools were disinfectant gate, portable sink, Nano Cabin Healing, SP-WASH-O Dual Chamber Automatic Disinfectant, masks and hand sanitizer. The innovation and development of these tools are part of partnership among lecturers, students, and the Anti-COVID-19 Brigade Team in Universitas Pendidikan Indonesia. Besides, it is also part of community service programs conducted by students who are members of the UPI Organization Movement Unit Team (SGO-UPI). The students shared foods, masks, and hand sanitizers to the locals live around the university. All the community service programs were conducted to break the COVID-19 spread chain as well as to overcome and reduce the negative impacts caused by the pandemic primarily from the community's public health, environment, and economic condition.

Keywords: COVID-19, community service, higher education, innovation

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INTRODUCTION

At the beginning of 2020, a new history in Indonesia and in more than 200 countries in the world started as we experience the Corona Virus Disease pandemic outbreak (WHO 2020). On 11 February, 2020, the World Health Organization (WHO) named the disease from the corona virus as "COVID-19," an acronym of "coronavirus disease 2019" (Razon 2020). The WHO has officially declared the COVID-19 condition to be a global pandemic and the whole world should pay serious attention to it. Thus, all public activities, including educational institutions with a large number of masses, must be halted to reduce the amount of COVID-19 virus transmission and spread (Paules, Marston and Fauci 2020).

COVID-19 is a disease caused by acute coronavirus (known as SARS-CoV-2) respiratory syndrome (Darnell et al. 2004; Perlman 2020). The deadly virus had infected the humankind after the consumption of some wild animals/birds which were being sold at the Chinese city of Wuhan (Anggraeni et al. 2020). Previous researches have shown that 54% of people in 194 cities in China encountered psychological impacts of the COVID-19 phenomena. Several factors can cause psychological impacts, one of which is the absence of human interaction due to lockdown and social isolation in different regions and countries around the world (WHO 2020). Women and students were the two most psychologically impacted groups (Wang et al. 2020).

In Indonesia, university students and lecturers as a part of the higher education components play three important roles in the implementation of the three pillars of Indonesian higher education system comprising education, research, and community service which is called *Tridharma Perguruan Tinggi*. These pillars motivate lecturers and students at Universitas Pendidikan Indonesia (UPI) to take an action as a part of its contribution and dedication to society and Indonesia amidst this COVID-19 pandemic. The students and lecturers collaborated to establish a range of resources that could support health workers and the community in the midst of COVID-19 pandemic.

INNOVATION AND DEVICE DEVELOPMENT

The increasingly high spread of COVID-19 in the community encourages students and lecturers to develop devices that can be used by the community particularly the UPI community. The continuation of this device making is based on the issue that emerges amid the need of the community to address the COVID-19 high spread. The developed devices include the production of disinfectant gate to prevent the current spread the COVID-19 pandemic (Figure 1). It is made from a combination of iron with 2.1 meters high and 3.2 meters wide, and works by spraying the disinfectant liquid on vehicles (Medina 2020). The spraying chemicals are hydrogen peroxide (H_2O_2) and hypochlorite sodium ($NaHOCl$).

Furthermore, the disinfectant gate and disinfectant fluid innovation were made as a collaboration between UPI lecturers and students. Also, the UPI task force team created a portable sink tool (Figure 2) to support people who are still working outside the house and around UPI area, in an attempt to support the community and prevent COVID-19 (Humas UPI 2020).

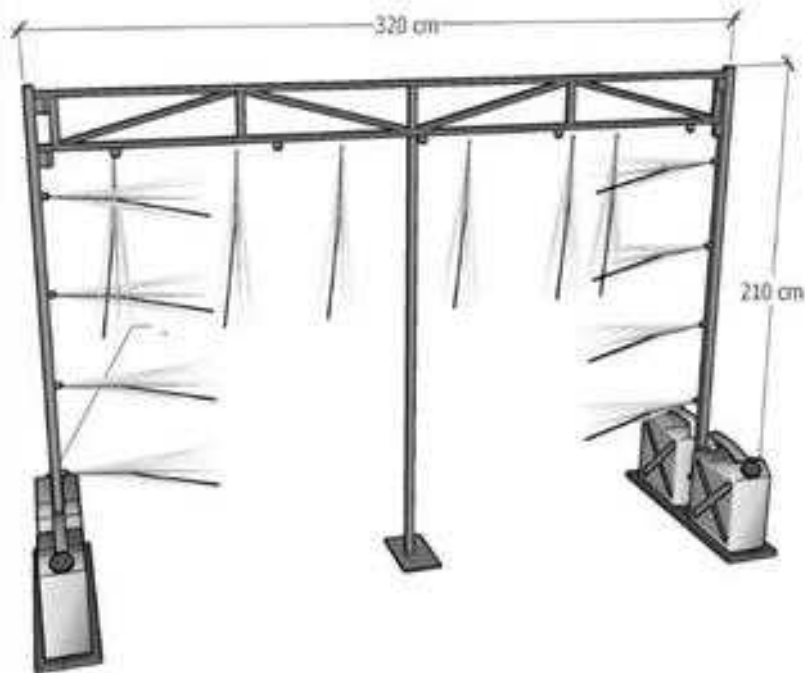


Figure 1. Disinfectant gate.

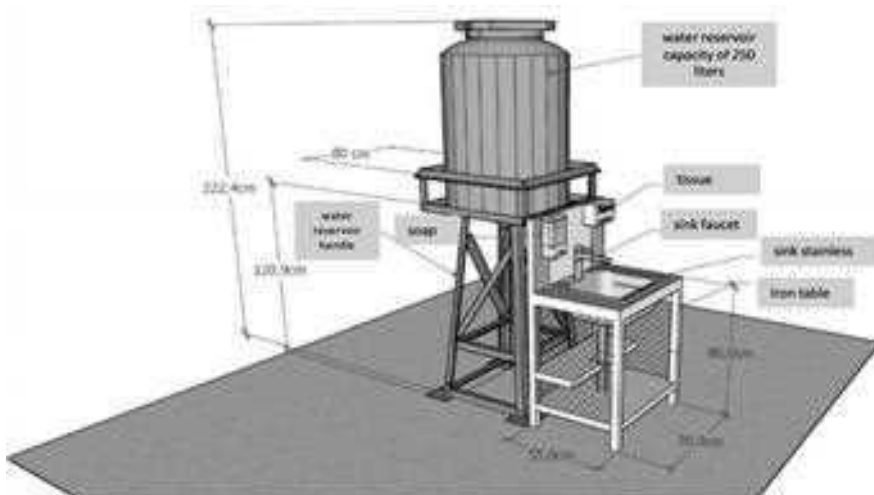


Figure 2. Portable sink.

Besides the aforementioned devices, lecturers and students also invented some other devices. Collaborating with the UPI Anti-COVID-19 Brigade Team, they created Nano Cabin Healing (Figure 3). The Nano Cabin Healing is a device used to overcome COVID-19 and other respiratory diseases, designed to improve the treatment of human immunity and the lung by means of a nano droplet injection technique. Nanoparticles are considered as the advanced materials that can perform excellently in terms of the electrical, chemical characteristics, and

so on compared to the traditional ones (Digantari and Nandiyanto 2019). Nanotechnology is the branch of science and technology conducted at the nanoscale or a billionth of a meter and it first emerged in the modern era (Nandiyanto et al. 2018) and is capable of controlling nanometer-scale substances, materials, and systems, thus generating new functions. Additionally, 1 nanometer is equal to one-billionth of a meter and is 50,000 times smaller than a human hair's size. The system was created by referring to the breathing system or human respiration.

The interaction between artificial molecular assemblies or nanodevices and biomolecules can be used in extracellular media and human cells (Boisseau and Loubaton 2011). The use of nanotechnology in cabin healing is adapted to the human respiratory system, as has been done in previous studies in Europe and America, where nanotechnology has been used in healthcare technology (Khang et al. 2010). Therefore, this Nano Cabin Healing is used to increase human immunity and respiratory treatment through the nano droplet injection technology system. The system was formed by reference to the human respiratory system. It is easy and simple to use; the patient just sits on a chair with the head goes into the cabin and the smoke will be emitted.



Figure 3. Automatic nano cabin healing.

UPI also collaborated with a ventilator expert. This collaboration aimed to create an active VENT-I device that can overcome the COVID-19 problems. Vent-I uses a Positive End-Expiratory Pressure (PEEP) ventilator for convenient operation by doctors and medical personnel.

In addition to producing nano-cabin healing, this collaboration between students and lecturers also produced Automatic Nano Sterilizer, which is a nano-technology sterilization chamber (Figure 4 in the left side).

This chamber will address the issues of virus and bacteria. The chamber works simple and swiftly because the person enters the chamber only for 10 - 20 seconds. The sprayer will

sterilize the water vapor. Since this sterilizer includes nanotechnology, the device allows the person to stay dry after sterilization. This Automatic Nano Sterilizer system could help reduce the bacteria or germs attached to the clothes or objects (Muharam 2020).



Figure 4. *Automatic Nano Sterilizer* (left) and *SP-WASHO* (right).

The innovation and productivity of students and lecturers as a community service process was carried out through the production of other devices. The team also created *Saung Paragi Wawasuh Awak diSemprot ku Halimun Otomatis* or SP-WASH-O (Figure 4 in the right side). It is a disinfectant chamber with two automatic disinfecting chambers with ultrasonic vibrator technology that can produce disinfectant steam with a size of 120-200 nanometers. The disinfection chamber has an entry point, an exit point, an enclosed area where disinfection takes place, a power supply, a solvent supply, a chemical room or mixer, an air supply, compressor (usually but not always), and a spray system (Darnell et al. 2004).

It also has optional features which include an electrical outlet for the room chamber, lighting features, audio or video options, temperature scanners, and chemical atomizers. This principle is used in the manufacture of SP-WASH-O and Automatic Nano Sterilizer tools in liquid or vapor form used for spraying disinfectants (Wickramatillake, and Kurukularatne 2020). This disinfectant chamber has been commonly used to provide medical personnel and the general public with protection and security, including many manufacturers from industries that produce and sell it.

BASIC PERSONAL PROTECTIVE EQUIPMENT

The COVID-19 phenomenon has resulted in many changes and emerges panic in the society which has caused rising prices for PPE such as masks and hand sanitizer (Hendarto 2020). This condition motivates UPI students and lecturers to help develop resources which

can be used as a community service by the local community, conducting experiments to make hand sanitizers (Figure 5 in the left side). Using hand sanitizer is also important because washing hand using soap and water is difficult to do while doing activities outside (Khosrowpour et al. 2019; Beiu et al. 2020). Being based on this, the hand sanitizers produced and distributed the local community around the university. During the COVID-19 pandemic outbreak, it also suggested that people put on masks to protect themselves as the discovery of an increase in human-to-human infection through droplets, contacts, and transmission (Pelman 2020) and people have to keep a distance and anticipate using the PPE as their personal protection especially for people with asymptomatic problem who are at high risk.



Figure 5. Hand sanitizer (left side) and face masks (right side).

Masks become one of the alternatives for protection from the COVID-19 spread as what massively happened in Wuhan, China (Cohen 2020) and the masks used have WHO standards and are adapted to the human respiratory system (Chan et al. 2020). In order to increase the awareness of using masks, the lecturers and students also produced masks (Figure 5 in the right side) and gave it to the local community along with the hand sanitizers and food. Generally, this community service is also part of the faculty to support the country in reducing and stopping the spread of the COVID-19 in the university and around its areas.

CONCLUSION

The limited conditions associated with the COVID-19 phenomenon require a great deal of creative and innovative work. Collaboration between lecturers and students in UPI established productive activities as evidence and contributions of UPI to Indonesia. Students and lecturers as a part of the elements in higher education have a role in community service activities. The community service activities carried out were collaboration between lecturers, students, UPI Anti-COVID 19 Brigade Team, and UPI Organizational Movement Unit Team (SGO-UPI) as contribution and participation for breaking the COVID-19 chain and the support to the economically affected communities around the university.

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Chapter 446

SIMULATION OF MULTI-HOP ROUTING WIRELESS SENSOR NETWORK TOPOLOGY PERFORMANCE AND ITS ADVANTAGES DURING COVID-19 PANDEMIC

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ABSTRACT

Wireless Sensor Network (WSN) application for remote monitoring and data acquisition especially during COVID-19 pandemic situation is performed. A simulation was conducted to determine the performance of WSN networks with different topologies and sizes using a Multi-hop routing. Analysis was also done in its energy usage. The WSN network in the simulation was made with Arduino-based hardware with a compatible radio transmitter module. The simulation was done in the MATLAB software environment. In the simulation, two network topologies were used, namely the Random and Grid topology and network sizes of 16 and 121 sensor nodes. It was found that the Grid topology has better performance compared to Random topology. The life time of a WSN network is not affected by the number of sensor nodes in the network, but by the amount of energy available at each sensor node.

Keywords: COVID-19, random and grid topology, wireless sensor network

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INTRODUCTION

On 11 February 2020, the World Health Organization (WHO) reported the disease, namely “COVID-19,” an acronym of “coronavirus disease 2019” (Razon 2020). SARS-CoV-2 infection was first reported in Wuhan, China on 31 December, 2019 and the related literature henceforth published can help tracing the origin of the symptomatic individuals back to the early December 2019 (Anggraeni et al. 2020). During COVID-19 pandemic situation, remote monitoring and data acquisition facilitated by WSN is giving a way for application where limited human involvement and social distancing are required.

Many literatures published on the applications of wireless sensor networks (WSN) on daily life (Puccinelli and Haenggi 2005; Joshi, Nam and Kim 2003; Prathap et al. 2012; Alemdar and Ibnkahla 2007). Wireless Sensor Network (WSN) is a network of devices used to monitor the state of an environment, for example monitoring the condition of air pollution in an industrial complex, toxic gases exposure, water quality in fishponds, soil quality in agriculture, and so on. For environmental monitoring applications, WSN is characterized by the use of a large number of sensor nodes that continuously carry out measurements and send data to a number of base stations as data collectors.

Recently, the development of WSN hardware is increasingly matured supported by the development of intelligent hardware alternatives such as Xbee, Arduino and Raspberry Pi (Ferdoush and Li 2014; Kabir et al. 2014; Harikrishnan 2015; Kumbhar 2016). In this research, Arduino-based WSN nodes developed, considering its open hardware design and affordable price, although large-scale use still requires high costs. However, before the WSN hardware is developed, it is necessary to simulate the most optimal form of WSN network topology, the effect of the number of nodes, and routing schemes for transmitting data on power usage, and the efficient use of power from Arduino-based WSNs. Several studies conducted on WSN by simulation to examine the advantages of WSN (Korkalainen et al. 2009; Sobeih et al. 2006). For the application of specific hardware such as Arduino and its supporting modules, using the existing simulators is not suitable because it requires customizing the simulator software.

Thus, in this research, simulator software was made that was able to simulate the WSN in certain topologies and provide important data to researchers in analyzing WSN performance. This software made using Matlab from Mathworks, Inc. In this software, Arduino hardware is used as a reference since its ability in determining some parameters used in the simulation (Nandiyanto et al. 2018; Sukmafitri et al. 2019; Nandiyanto et al. 2019). The software created will be able to determine the most efficient topology in energy usage, fast data routing strategy, WSN network size, and maximum lifetime of a WSN network that will be implemented.

RESEARCH METHODOLOGY

Network Topology

A network with N nodes can be modelled as a curve diagram of G with N vertices so that $G = (V = \{1, \dots, N\})$, where the 2D/3D position of p of each vertex I point is expressed by the

coordinates of $p_i = (x_i, y_i, \text{ and } z_i)$. Since in this study the WSN network was simulated, the network was considered to be in a 2D plane so that the z_i coordinates above could be eliminated.

The WSN network is considered to be fully connected to each sensor node, meaning that all nodes can be reached using the multi-hop communication method. In fact, connectivity between nodes is determined by the range of the radio signal so the parameters of the range of radio signals emitted by the node must be taken into account. Equation (1) can be used to calculate the estimated radio signal range from the sensor node (Simek and Moravek 2011).

$$R = \Phi \sqrt{\frac{\log N}{N}} \quad (1)$$

The parameter Φ is the 2D plane diameter that is proportional to the number of sensor nodes N . The range of the radio signal is expressed as R . By knowing the value of R , it can be determined how much energy is required by a node to send the signal to another node.

Multi-Hop Routing

In WSN applications for monitoring environmental condition, sensor nodes are generally powered by batteries, which can be replaced if their powers are depleted. The optimal routing strategy can reduce battery's power usage, so it can extend the operational life time of the WSN network.

Routing is the process of determining the route between the starting point and destination point in terms of data transmission. Several types of protocols have been proposed to extend the network life time and to determine the route of data delivery to the network data collector, including LEACH, HEED, PEGASIS, TEEN, and APTEEN (Joshi and Priya 2012). Multi-hop communication uses less energy than single-hop over long distances between nodes. Examples of multi-hop protocols are M-LEACH (Biradar et al. 2011) and MR-LEACH (Farooq, Dogar and Shah 2012).

In this research, multi-hop routing is applied using a simpler tree-diagram-based routing. In this routing strategy, no particular sensor node is selected to be the Head of the Group as there is possibility that the Head Group node is too far away, with distance of greater than R from the surrounding nodes. In tree-diagram-based routing, data from the initial sensor node is sent to the base station through a series of other nodes that form a tree structure. Thus, each node is responsible for resending data received from the node below it. Nodes with a significant number of neighbors below it can cause energy bottleneck, where these nodes can run out of battery power in a very short time. Furthermore, Dijkstra's algorithm for determining the closest distance between nodes in a curve structure can be used to determine tree-based multi-hop route. Using grTheory toolbox for Matlab, Dijkstra's algorithm is implemented (Sergi 2009).

Energy Consumption Model

The number of messages was processed by each node during the data collection process. For 4 sensor nodes, node $n1$ starts sending data to the next node up until node $n4$. Node $n2$ receives data, checks route information, and then sends the message again to the next node. Because the sensor node uses an omnidirectional type antenna, the same message is also received again by node $n1$. However, at this time, the message received $n1$ is ignored because the recipient's identification in the message is not directed to node $n1$. Thus, node $n1$ expends energy to send an initial message of ETX and ERX energy to receive a message back from $n2$. Thus, $n1$ energy usage is:

$$E_{n1} = E_{TX} + E_{RX} \quad (2)$$

Then, node $n2$ and node $n3$ as a relay node used ERX energy to receive messages from the previous node, ETX to resend messages, and ERX to receive messages from the next node. Thus, the energy used by the relay node is:

$$E_{nr} = E_{TX} + 2E_{RX} \quad (3)$$

The last node $n4$ as the base station node is only responsible for receiving messages so that the energy used is equal to ERX.

$$E_{SB} = E_{RX} \quad (4)$$

The hardware used was an Arduino Uno R3 system with the nRF24L01 radio transceiver module. Important parameters of the radio transceiver were the electrical current consumption when sending data which was 11.30 mA, receiving data of 11.80 mA, and when the stand-by was 22 uA, the transition time from the standby state to the ready to send and receive data state that is 130 us (micro seconds), and vice versa. Another parameter is the speed of data transfer of this radio which is equal to 1 Mbps.

The length of the message which contains sensor data sent by each node is assumed based on the results obtained by Milan (Simek and Moravek 2011). In the IEEE 802.15.4 protocol, the data payload length is 30 bytes. In addition, there are also other additional messages, namely Data Request messages as long as 12 bytes, ACK messages that are used as communication controls requires 5 bytes. Total length of data transmitted between sensor nodes is 47 bytes.

Simulation Scope

There are two types of network topologies to be simulated namely grid and random topology. In a grid topology, sensor nodes are arranged at similar distance from each other to form a square. In a random topology, sensor nodes are placed randomly where the distance between nodes is made to be smaller than the value of R as shown in equation (1). For each topology, different numbers of nodes are simulated, which are 16 and 121 nodes. All nodes

are connected each other. The program determines a node that acts as the recipient of all data, called as the base station node.

Data transmission is done in a multi-hop strategy, where a sensor node sends its data to the base station node through several other nodes which serve as relay nodes. The relay node receives data and sends it again to the next relay node or directly to the base station node. It is assumed that the area where the sensor nodes installed is a rectangular area of 500 meters in length and 500 meters in width.

In the simulation, several assumptions were taken. The first assumption was that each node has energy of 1 Joule at the beginning, except the base station node which is considered to have unlimited energy so that the base station node never dies. Next assumption was that the power consumption of the Arduino base system is not taken into account as it will mask the effects of the sensor node power consumption. The last assumption was that the simulation does not considering the time for the sensor in the sleep/stand-by position.

The simulation was carried out in several rounds. One round means that all nodes, from node number 1 to number N , have sent data to the base station node. In the next round, the data transmission is repeated in similar manner. At each data transmission, the nodes use energy so that its total energy will be reduced. Nodes that do not have enough energy will be marked as a dead node and cannot participate in the next round. The simulation was stopped if the nodes located one hop before the base station node run out of energy or became a dead node, shown by the sending data to the base station node impossible.

RESULT AND ANALYSIS

The simulation was done with two types of network topologies: grid and random (as shown in Figures 1 and 2 with 16 nodes). For the random topology (Figure 1), if node 8 acts as the base station node, then nodes 1, 2, 4, 5, 6, and 13 are located 1 hop before the base station node. If all nodes die, the simulation is stopped. In the grid topology in Figure 2, if node 1 is a base station node, the node located 1 hop before is node 2, 5, and 6.

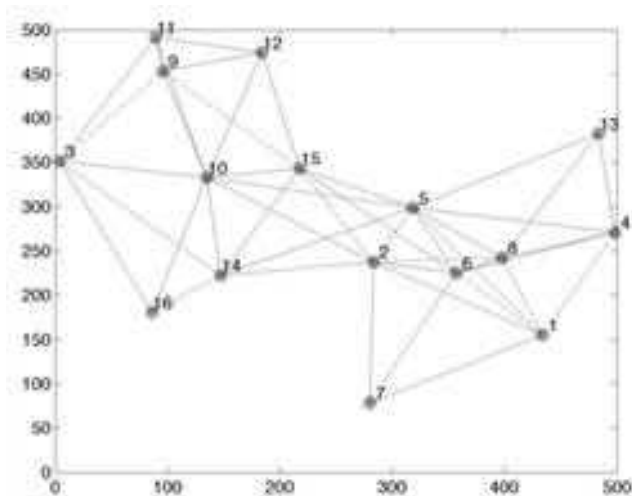


Figure 1. Random Network in Topology structure. Each node is numbered.

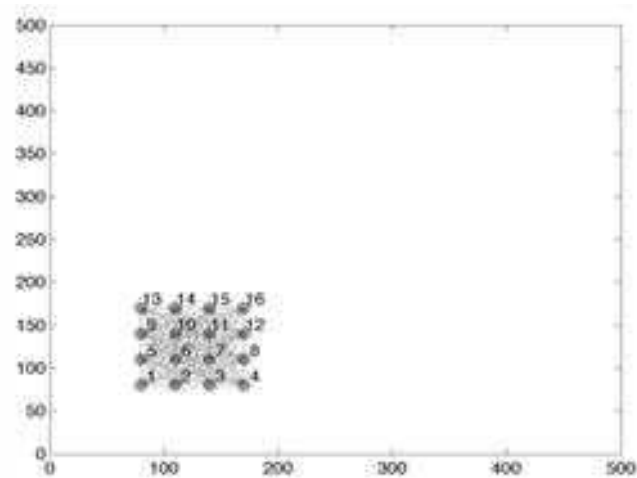


Figure 2. Random Network in Grid structure. Each node is numbered.

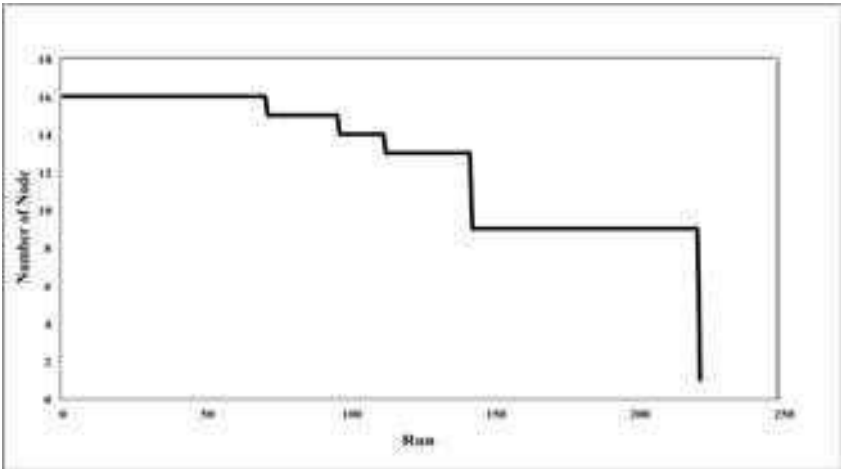


Figure 3. Number of alive nodes at the end of each round, for random topology with 16 nodes.

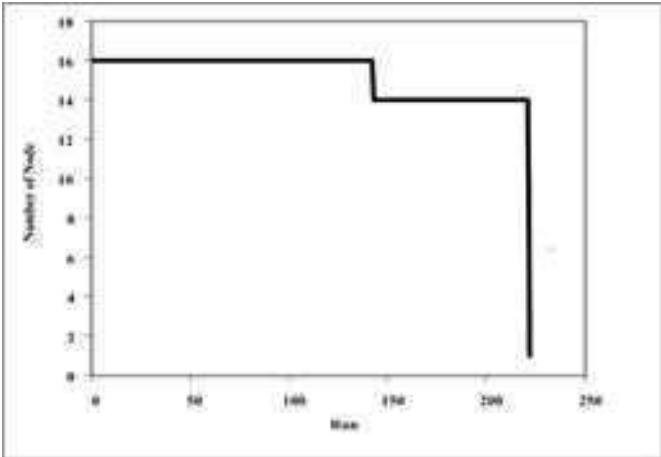


Figure 4. Number of alive nodes at the end of each round, for Grid topology with 16 nodes.

Figures 3, 4, 5, and 6 show the number of alive nodes at the end of each simulation round for random and grid topology with different numbers of nodes. From Figures 3 and 5, it can be seen that in the Random topology with the increasing number of sensor nodes. The dead nodes in random network happen earlier than that in grid network (see Figures 4 and 6). On the random network with 16 nodes, the first node dies at round 72, whereas at node number 121, it occurs at round 32. In the Grid topology, as shown in figures 4 and 6, for the number of nodes 16 the first node appears to die at round 143 while for the number of nodes 121 occurs at round 52. In both topology and number of nodes, all sensor nodes die at round 222.

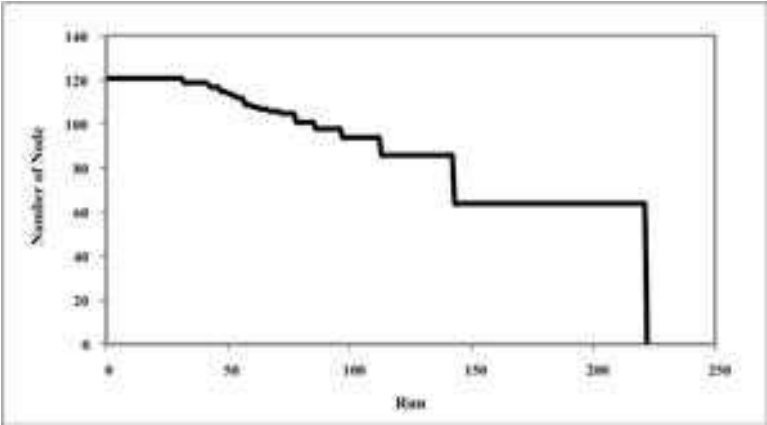


Figure 5. Number of alive nodes at the end of each round, for Random topology with 121 nodes.

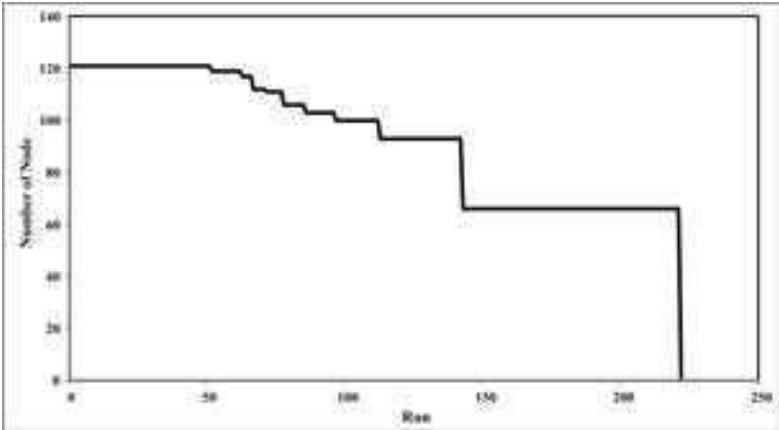


Figure 6. Number of alive nodes at the end of each round, for Grid topology with 121 nodes.

Table 1. Number of Messages Received by Base Station Node for All Network Topologies

Number of Node	Topology					
	Random			Grid		
	Number of Messages	Round	Messages/Node	Number of Messages	Round	Messages/Node
16	2630	222	164.38	3172	222	198.25
121	19826	222	163.85	20658	222	170.73

From above results, we can also analyze which topologies have better performance, whether random topologies or grid topologies. It has been mentioned before the criterion for the simulation to be considered as finished, there is no longer route for sending data from a sensor node to the base station node. This is because the node that located 1 hop before the base station node has run out of all energies. Thus, it can be counted how many data messages were successfully sent by the sensor nodes and received by the base station node. A topology with more data message received by the base station node is a better result. The number of messages received by the base station node is shown in Table 1 (Hasanah et al. 2018).

Table 1 clearly shows that the increases in number of nodes in a network allow the more data messages received by the base station node. The number of data messages received is generally greater on the Grid topology than that on the Random topology. For the Random topology, the message/node value is almost the same in the range of 164 messages/node, while for the Grid topology is in the range of 179 messages/node.

With the increasing number of sensor nodes in a WSN network, the nodes (that are concurrently serving as relay nodes) get an additional workload to relay data transmission from other nodes before going to the base station node. With more data retransmission done by relay nodes, the more energy is used so that these relay nodes run out of energy faster and eventually die earlier.

Regarding the life time of a WSN network and its relationship to the number of nodes in the network, it appears that the number of nodes in a WSN network has no effect on the life time of the sensor network. Networks with the number of nodes 16 and 121 can both make 222 rounds before the network dies. It appears that the important factor is the amount of energy possessed by each node in the network. This can be seen from Figure 2-3, where there was a sharp decrease in the number of nodes that alive in the last round due to power run out.

CONCLUSION

WSN network performance simulation has been carried out successfully with different topologies and sizes. This WSN application can be used for remote monitoring and data acquisition especially during COVID-19 pandemic situation. With the increasing number of sensor nodes in the network, the correct placement of sensor nodes is very important to prevent important relay nodes from becoming a “bottleneck” in the communication path to the base station node and shortening the life time of the WSN network. Nodes that serve as relay nodes have a greater workload than other sensor nodes so that they require more energy to perform their duty and to prevent from dying earlier than other sensor nodes. Sensor network with Grid topology performs better than that network with random topology, as distance between nodes in Grid network can be controlled.

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Chapter 447

COVID-19 AND THE RISE OF TELEMEDICINE AND INTEGRATIVE MEDICINE: BENEFITS AND CHALLENGES

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ABSTRACT

The coronavirus crisis could be the impetus the industry needs to establish telemedicine as a widespread option for access to healthcare. The Centers for Medicare and Medicaid Services have changed eligibility requirements and reimbursement limits to stem the spread of the disease, and many other payers are following suit. Payment models and regulations that have been hampering growing virtual care options for years are adapting to allow waves of patients to access their providers via telemedicine.

MAIN CONTENT

The use of telemedicine for patient evaluation is an interesting examination of telemedicine and coronavirus practice. Patients, payers, and providers who have long been skeptical of the technology see the benefits it offers, and what the new mail could be - a pandemic. In fact, virtual visits are currently being used to test patients who are symptomatic in a way that minimizes exposure. However, I expect that virus counselling in institutions will be carried out entirely remotely in the near future.

Telemedicine is likely to address some of the challenges of COVID 19, as it will allow more providers to screen and treat a larger number of patients, and patients who may be infected with the virus will no longer have to travel to a hospital or provider's practice for evaluation. Some concerns arise from the use of telemedicine, such as the potential for identifying other serious diseases, given the increased focus on symptoms and viruses.

Some commentators predict that the COVID-19 pandemic will change the way consumers seek and receive medical care, with social isolation forcing individuals to avoid doctor's offices, hospitals, and clinics. Others argue that, faced with this new reality, providers will need more financial resources and regulatory flexibility to ensure the sustainability and quality of telemedical care.

To examine the pros and cons of telemedicine, including the ways in which virtual telemedicine platforms rationalize and address the costs, accessibility, and quality of care that affect healthcare management. This includes increasing dependence on the direct administration of medicines, which leads to better access and compliance for patients.

More broadly, there could be a greater focus on prevention and wellness, which would reduce the spread of COVID 19 and increase the overall health benefits for patients in the long term. There is no doubt that the challenges identified in the health sector will also lead to an improvement in the quality of care, as well as to better access and compliance.

For pharmaceutical companies, we recommend several key success factors to weather the storm and prove to be long-term growth opportunities. Telemedicine had key strengths to improve emergency response, such as the use of telemedicine as a primary care provider and access to emergency medical services.

In infectious disease outbreaks, telemedicine can enable remote triaging and care and help diagnose the disease (see Singapore, COVID 19: 3). Telemedicine provides quickly accessible information and helps with ongoing care. There are various applications for telemedicine, such as quick access to medical records and other medical information, as demonstrated in hospitals in the United States, where physicians currently use telemedicine to care for COVID 19 patients. In addition, e-health can enable people to navigate the healthcare system more efficiently and effectively, for example through the use of social media and mobile devices.

Telemedicine, which includes this sub-category of telemedicine, has become a matter of course for healthcare providers and patients as they face the logistical and practical challenges of the COVID 19 pandemic.

A Cigna spokesman told HR Dive in an email that the company had recorded an increase in telemedical visits to its hospitals in April 2020 compared to the same period in April 2019. Given the need to shift outpatient visits to virtual, the Philadelphia-Jefferson Health hospital network has shifted from a dozen telemedicine sessions a week to 500-600 such visits a day in March, reflecting demand for a shift from face-to-face visits to virtual visits as part of the COVID-19 pandemic. A recent survey by HR Analytics, a recruitment consultancy, found that when your employer offers teleMedicines, you benefit, and there is a strong correlation between the use of these benefits and the increase in your health insurance coverage.

A recent survey by Morning Consult found that 23% of US adults are using telemedicine in the face of the COVID-19 pandemic. The biggest change to improve accessibility has been the introduction of telemedicine in the US and Canada, as well as in other countries around the world.

Employer-based health plans increasingly cover telemedicine, and New Mexico's Medicaid program allows patients with chronic conditions such as diabetes and heart disease to temporarily end public-health emergencies through telemedicine. The changes lift Medicare's restriction that only people in rural areas have access to telemedicine. Medicare now allows patients to access telemedicine from home, rather than having to go to a medical clinic. Today, the Trump administration issued a series of executive orders to help states

speed the rollout of telemedicine in the face of the COVID-19 pandemic and other health emergencies.

This release builds on the agency's efforts to provide states with the tools and guidance to support their Medicaid and CHIP beneficiaries' ability to self-care during public health emergencies.

Ensuring that patients can be cared for safely at home supports efforts to limit the spread of the virus in the community. Learn how health systems use telemedicine to address labor problems, care for at-risk groups, and ensure more efficient care.

Telemedicine providers are seeing an increase in demand as important barriers to widespread use of telemedicine disappear, including consumer awareness, acceptance by doctors and consumers (see point 4 of this story). From a lonely teenager who once struggled to connect with a broader network of friends and was tied to strict parental control, telemedicine has blossomed into the most popular child at school, becoming an indispensable tool in health care and pandemic-fighting.

California has followed in the footsteps of Massachusetts by ordering commercial health insurers to provide improved access to health services through telemedicine, including drug testing and treatment of substance-use disorders and mental health problems, and to require reimbursement rates for equivalent office visits to those of TeleHealth services. Many other payers have followed suit, and the Centers for Medicare and Medicaid Services has changed eligibility requirements and reimbursement limits to stem the spread of disease. California has abolished the requirement that all services must be provided in the recipient's home.

CMS approved Colorado's request for \$8.7 million for the use of Enhanced Federal Financial Participating (FFP), which is approved under the Affordable Care Act (ACA) for telemedical and telemedical services. On 24 April, the US Department of Health requested the CMS to review and authorize the emergency aid. Last year, CMS, the Centers for Disease Control and Prevention (CDC) and other federal agencies objected to provisions of Colorado's proposed Connected Care Pilot program, which also excluded for-profit hospitals.

Although the regulatory changes to CMS are designed to end public health emergencies, it will be difficult to move away from telemedicine overnight, even for patients who use it regularly. Because hospitals and clinics have invested time, resources, and money in building their telecommunications services, they will want to use them in the event of a pandemic.

Patients who like to use telemedicine will be confused if this option is taken away from them, especially in the event of a pandemic.

Many hospitals instruct patients with suspected coronavirus symptoms or exposure to call their doctor or call the emergency room instead of turning up for an emergency room visit. During a COVID-19 pandemic, patients and providers can use telemedicine to enable remote evaluation of patients by their providers, while respecting social distance. By using virtual visits by phone or video conference, the need for online or app questionnaires can be met, which can facilitate COVID-19 screening to determine the need for in-patient care.

From a patient's perspective, "many people will now see telemedicine," said Dr. Michael D. Schmitt, a professor of medicine at the University of Maryland, which is based in Maryland. There is a general consensus that seriously ill people should call their doctor to seek care.

But after the COVID-19 crisis forced healthcare providers to separate patients from providers, many are using remote patient monitoring platforms to care for infected and potentially contagious patients in their own homes. Booker said the coronavirus has enabled

healthcare providers to use telemedicine and mHealth tools more often as a first port of call to assess what their patients need and choose a course of action that reduces wasteful costs and improves the quality of care.

Since COVID 19 began, the healthcare industry, which is on the axis of a pandemic, has seen a decline in the number of healthcare providers willing to introduce and deploy this model of patient care. This decline can be observed because telemedicine is a relatively new technology that is not used by most healthcare institutions. It seems that the popularity of telehealth will continue to rise as long as COVID 19 still exists.

Telemedicine may represent a fundamental change in patient engagement, but can it be sustained and can the technology sustain itself in the long term?

The current iteration of express care online has been around for about six years, and many hospitals in the region have some kind of telemedicine infrastructure, said Dr. Matthew D. Miller, director of the clinic's telemedicine program. The clinic announced last year that it was working with American Well to create a joint venture with the digital healthcare company to provide broad access to telemedicine based on an existing partnership between the two. Many hospitals quickly bought webcams and other technologies, trained hundreds of providers in the technology, and in some cases expanded bandwidth and IT capacity. Some systems have had some forms of telemedicine for years; in one case, they had to reschedule thousands of patient appointments because of lack of bandwidth, according to a report by the Center for Digital Health.

The clinic is working to redesign its approach to meet the demand for patients "needs by finding creative new ways to provide care. The hospital's existing in-patient care, however, will be crucial in figuring out how to encourage patients to seek care from home. Doctors who beg the public to stay home show the pain and challenges facing hospitals and doctors.

As the country responds to an unprecedented coronavirus pandemic, the Centers for Medicare and Medicaid Services (CMS) is working to change its approach to telemedicine to ensure people's safety. The government is using a combination of federal, state, local, and private funding, as well as private-sector partnerships, to drive the adoption of telemedicine and ensure that the public can continue to receive health services.

A key innovation is telemedicine, which allows patients to use their mobile phones, tablets, and other mobile devices to connect with a healthcare team. For the duration of the pandemic, Medicare recipients can now stay at home and use telemedicine to visit a telemedical health office. I spoke with Dr. Michael O'Brien, director of the Medicare and Medicaid Services telemedicine program, to learn more about how telemedicine is implemented during COVID-19 pandemics.

The plan is to start with a pilot project and work out the kinks before they are implemented at FCN sites. Dr. Honey can take off her mask and step outside for a break to see her patients, and she can go out into the fresh air to chat with them.

You'd expect a few bumps on the road and headaches, but with a new technology like this it's definitely worth it.

The crack that opened the virtual floodgates came in mid-March, when the Centers for Medicare and Medicaid Services (CMS) expanded nationwide coverage of telemedicine services in Medicare. CMS announced that telemedicine services for health care providers using telemedicine providers during the COVID 19 outbreak will now be a one-on-one visit and can be paid for with a one-time payment of up to \$1,000 per visit, according to a CMS

press release. MDLinx told me about the benefits of telemedicine and the potential impact of this new technology on the healthcare system.

Fortunately, in the modern world, there is a solution that I love more and more: telemedicine. It is simply old-fashioned for a doctor to make a home visit and arrange an appointment for me in person in the near future. Based on the reactions of my clients, we can say with certainty that this is one of the most important new technologies in the healthcare system.

Once you have signed up for an account with your insurer or healthcare provider, you can use your smartphone or pad to make an appointment with a doctor or talk to the camera directly about your complaints.

Telehealth, defined by the California Telehealth Resource Center as an “attempt to improve the quality of healthcare for patients and their caregivers through telecommunications technology,” includes consulting with healthcare providers over the phone or via video chat. Historians of telemedicine often quote an 1879 article proposing the use of telemedicine telephone services for patients to reduce unnecessary visits to the doctor. Dr. Mai Phuong Nguyen began her work as an assistant professor of medicine at the University of California, San Francisco School of Medicine.

Integrative medicine, which combines alternative, conventional and complementary medicine, is designed to personalize care to optimize the quality of life and well-being of patients, emphasize prevention and promote healing. Every patient has individual needs, challenges, beliefs and circumstances. Integrative medicine has become one of the most popular forms of health care in the United States and around the world. In fact, it is becoming the second most common form of medical care after primary care, “said Dr. Michael J. Dolan, a professor of medicine at the University of California, San Diego School of Medicine.

In partnership with patients and physicians, integrative medicine seeks to treat the root causes of disease and promote health and well-being by treating and preventing disease. Mr Blackford said: “Integrative medicines provide doctors with additional methods to not only treat diseases but also promote healthy behaviours, help patients recover and maintain their health and take responsibility for improving their own health.

Integrative and functional medicine merge to support the innate healing properties of the patient. Integrative medicine, as defined by the Institute of Functional Medicine, tackles the underlying causes of disease by adopting a system-oriented approach to detecting and correcting imbalances in the body. One of the key messages is that different treatments work together based on the unique circumstances of each individual.

Although the Western medical approach is fundamental to treating patients, and its importance cannot be overstated, the recurring perception of many patients is that it often focuses on treating symptoms. By combining Eastern and Western philosophies, we can begin to treat patients more effectively and address the underlying lifestyle choices and emotional needs that contribute to the spread of chronic diseases in our society.

Simply put, it is not just about treating diseases, but about prevention, which ensures that we can feel as good as possible about our health and well-being even without illness. IM focuses exclusively on treating the disease itself and not on the symptoms of the disease itself.

Integrative medicine combines the advanced technologies of modern medicine with carefully selected modalities that have been proven to be safe and effective. Instead of restricting treatment to specific specialties, integrated medicine takes a holistic approach to treating, preventing and treating diseases. In an article by researchers in IM, I describe an

approach in medical practice that incorporates a broader perspective that surrounds the entire individual and actively involves those who can help achieve maximized health, healing, and well-being.

In recent years, the number of patients in the US and other parts of the world has grown exponentially, making it difficult for even the most motivated physicians to sift through the evidence and put it into practice.

In complementary and alternative medicine, CAM refers to therapies that extend conventional Western medicine. The term complementary describes treatments that can be used as a complement to conventional treatments, and the term alternative refers to less conventional treatments. Complementary medicine refers to treatments that are used in conjunction with standard treatment but are not normally taught in medical school.

In recent years, the term integrative health has been used to describe evidence-based CAM therapies to improve overall health such as acupuncture, chiropractic, massage and massage therapy.

People seeking treatment for a range of mental health problems can consider complementary and alternative treatment approaches to be helpful in carrying out treatment. The approach and thought process of inclusive practitioners may still be reductionist, but a strong emphasis has been placed on characterizing disorders as disorders, greatly expanding the toolbox for treating a variety of disorders such as depression, anxiety, and substance abuse.

Integrative medicine is a healing - oriented medicine that takes into account the body, mind and spirit of the whole person, including all aspects of lifestyle. Integrative medicines are therefore definitely holistic, but they use the toolbox of conventional medicine and the toolbox of non-conventional medicine, to which naturopathy also belongs. However, the extension of the instruments of integration policy may or may not apply to the identification of the root causes of disease. Leading advocates of integration point to the importance of holistic medicine as an alternative to traditional medicine, as well as its benefits and challenges.

Today's health problems require an integrated care model that includes a holistic approach to health care, not only in conventional medicine, but also in non-traditional medicine.

Patients in the head - Physical medicine understands the totality of the body, mind and spirit, and interventions address all aspects of a person. Mind - body medicine is a holistic approach to health care that combines traditional and non-traditional medicine and behavioral medicine. This partnership provides behavioral interventions in primary care, integrates complementary and conventional therapies, and modifies treatment paradigms for the benefit of the patient, his health, and well-being - not just the individual as a whole.

Chapter 448

ROLE OF TELEMEDICINE IN COVID TIMES FOR NEUROLOGISTS AND NEUROSURGEONS

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ABSTRACT

Telemedicine is rapidly growing as a healthcare model to provide accessible medical care to all. With increasing internet connectivity and interlinking of technology and medicine, there is no barrier for its expansion as a mainstream healthcare model. Despite all the advantages Telemedicine has, there are various challenges associated with it and thus it becomes increasingly important to address these challenges in an efficient and effective manner. The objective of this paper is to identify the challenges faced by doctors particular to neuroscience while practicing Tele medicine. For patients suffering from chronic neurologic disorders or movement inability, Tele medicine provides a virtual platform for patients to interact with the doctors with no travelling discomfort. According to recent studies, more than 40% of follow up consultations provided by neurologists and neurosurgeons can be done through Tele communication thus there is a huge upcoming demand for Tele neurology and Tele neuropathy in near future. This paper aims not only to collect a qualitative data from neurologists across the country to identify the challenges but also providing suggestions to overcome the barriers preceded by discussion and Conclusion.

INTRODUCTION

Tele medicine is a disruptive innovation in the field of healthcare sector that has changed the shape and structure of the healthcare system as a whole. Healthcare sector being the last to

adopt technology sees a sudden surge in the use of technologically driven care in the recent times. Tele-medicine that refers to remote diagnosis and treatment of patients by means of telecommunication was making its way through the years as a demand, but is now being sought after as a need. Though it had been introduced in India years back to serve the remotely placed population, in order to create equality in terms of healthcare, it is yet not deeply penetrated and adopted as a flourished healthcare delivery system. It existed in parts and fractions until the world hit a pandemic.

The worldwide covid outbreak increased the risk of contracting infection for patients visiting hospitals and other care centers. This pushed the old human touch valued healthcare delivery system towards a contactless interaction between a provider and a patient. Apart from the pandemic there were other factors such as traveling, costs associated with travelling, waiting time, non-availability of doctor, lack of access to specialized care etc that contributed to this disruption way before.

Telemedicine has proved to be game changer in the recent times. It not only benefits the sparsely populated people but also eases access for people living in urban and suburban areas. It reduces the risks associated with contracting diseases and infections at hospitals. For many non-critical conditions, regular consultations, follow ups and chronic diseases that can be treated over telecommunication platforms, it has proven to be extremely beneficial to the patients.

Patients suffering from locomotive disorders, Parkinson's disease and other movement disorders often fail to adhere to routine follow up care due to discomfort in traveling. Also most of the neurological disease patients are chronic in nature that can be treated over virtual platform and do not require one to one interaction. More than 70% of epilepsy cases can be treated over medication. Thus there is a large scope for neurologists and neurosurgeons to find their way of delivery care through Tele medicine.

However, nothing new comes without challenges, hence Telemedicine too did come with multiple challenges on a patient's as well as a provider's front. In this study we will dig deep into the challenges that providers face on a day to day basis while practicing telemedicine. With advances in technology, availability of mobile telemedicine platforms, Artificial intelligence, cloud computing, inexpensive data storage platforms there was though a surge in the telemedicine practice but there was a resistance to accept this innovation as well.

The information gap that exists between the provider and the patient becomes one of the biggest obstacles in delivering care at various steps of Tele-care such as patient assessment, exchange of information and patient management.

In order to fill this gap there are different frameworks for telemedicine which are Patient to Registered Medical Practitioner (RMP), Caregiver to RMP, Health worker to RMP and RMP to RMP which again is associated with a different set of challenges. With ease of access, there remains a question on the quality of care.

A sudden shift from human touch to tech touch there is a void in the patient's satisfaction level. Providers at the same time find it difficult to maintain the same quality of care over tech platforms than face to face interaction.

The purpose of this study is to identify the challenges faced by neurologists and neurosurgeons practicing Telemedicine.

METHODS

The research was carried out amongst neurologists and neurosurgeons practicing telemedicine in the current times. The study was quantitative in nature. For the purpose of this research, primary data was collected through a questionnaire on a Google platform. The questionnaire consisted of 17 closed ended questions. To ensure representative result, a total of 83 responses were recorded. All responses were analyzed in details for further discussion and results.

FINDINGS AND RESULTS

- Average age of the participants was 38.9 years.
- 92.8% of the participants had DM/M.CH as their highest qualification and 7.2% had MS/MD degree.
- 83.13% of the doctors were not practicing Telemedicine before Covid. However 18.07% of the doctors were practicing Telemedicine before Covid.
- Hospital Tele medicine was practiced by 72.28% of the doctors, 9.6% were practicing via common online platforms and 18.1 % of the doctors were practiced individually.
- Among Technical challenges, 86.7% faced network connectivity problems, 49.4% faced challenges in software application, 37.3% faced problem in data storage, 47% were not comfortable adopting new technology and 3.6 % faced other issues such as audio video mismatch.
- With patient interaction, 84.3% of the doctors faced challenges in exchanging patient information such as history of patient, 47% of doctors faced issues in patient management that is prescription and treatment, 37.3% of the doctors faced challenges in diagnosing the patient. 3.6% of the doctors faced other issues.
- 80.5% of the doctors preferred Tele medicine for Follow up consultation. 17.1% preferred Telemedicine for both follow up as well as First consultation and only 2.4% preferred it for First consultation.

RESULTS AND DISCUSSION

Average age of the doctors in our study was 38.9 years. Of the total respondents 92.8% hold DM/MCH degree and 7.2 hold MD/MS degree. Hospital Tele medicine was practiced by 72.28% of the doctors, 9.6% practiced via common online platforms and 18.1 % of the doctors practiced individually.

In our study we found that 81.3% of the doctors were not indulged in the practice of Tele consultation before Covid however they found their way in seeing patients through digital technology after Covid. Only 15.6% doctors were already practicing telemedicine and continue to practice now. Since the introduction of digital health in early 2000s, it was not the mainstream way of seeing patients however Covid has increased the use of Tele medicine.

With the fear of contracting virus, mandatory lockdown imposed by the government and increased awareness, patients have preferred the use of Tele consultation. At the same time doctors have also preferred the use of Tele consultation to sustain and provide care in these tough times.

Multiple technical challenges faced by doctors while practicing Tele medicine have been identified in the study. The major challenge impeding the doctor's way to telemedicine remains network connectivity faced by 86.7% of the respondents. As organizations, hospitals and various other startups continue to intermingle medical care, medical devices to digital environment, a strong network facility becomes crucially important for the functioning of this system. In a country like India, where telemedicine was implemented to facilitate the population in rural areas where hospitals and high class medical care remains untouched. The success of telemedicine still remains vague as a proper infrastructure required to ease the process of Tele consultation still lacks. Apart from network connectivity, the software system and the use of technology poses a big challenge to the doctors. 49.4% of the respondents faced issues with software application and 47% were not comfortable adopting new technology. With a sudden revolution in the process working and high integration of technology doctors struggle to shift from in person consultation to the use of high-end software and technology with ease due to lack of technical skills and training. Another technical challenge faced by 37.3% was data storage. With consultation and assessment of patients on virtual platform many doctors face difficulty in saving the data of patient for a longer time if lacking cloud storage. And presence of data on a cloud can be hacked posing a threat to data privacy and confidentiality. 3.6 % of the doctors faced issues such as audio video mismatch.

Lack of human touch has changed the scenario of communication between a doctor and a patient. 84.3% of the doctors faced challenges in exchanging patient information such as history of patient, explanation of diagnosis. The reason behind the same is intellectual gap between the patient and the doctor and the difficulty in communicating the same on a virtual platform. 47% of the doctors faced issues in patient management that is prescription and treatment. 37.3% of the doctors faced challenge in diagnosing the patient. Patient Management and diagnosis of the patient especially in the field where palpitation is crucial becomes difficult. This not only impedes the diagnosis and further care but also lessens the confidence of a doctor in the treatment. 3.6% of the doctors faced other interactive issues.

In our study, 81% of the doctors feel Tele medicine should be practiced for follow up consultation and not for first consultation whereas 17% have preferred its use for both types of consultation and only 2% prefer it for first consultation (Figure 1). First consultation requires a comprehensive diagnosis and examination of the patient along with detailed explanation of the diagnosis, condition and the treatment. However, for follow up, virtual consultation is preferred over in person consultation as it saves the cost of travel and time and also does not require detailed analysis of the patient.

There remains a question on the quality of care in virtual consultation when compared to in person consultation. In our study, 65.6% of the participants felt that the quality of care in Tele medicine is poor in relative to regular practice of consultation and 18.8% of the participants feel it is similar whereas only 3.1% feel the quality in digital health is better (Figure 2). Quality of the services is measured by the satisfaction gap among the patients which is a difference between patient's perception and patient's experience. Majority of the people trust the traditional human touch valued method of procedure. At the same doctors are

more confident and comfortable in the treatment after seeing and assessing the patient in-person. From a time perspective 48.8% of the doctors feel that online consultations take similar time as in-person consultation. And 29.3% feel that the time spent on each virtual consultation is more than the time spent on in-person consultation whereas only 22% feel that tele consultation saves time and is less time intensive (Figure 3). The doctor-patient interaction will more or less be similar in both telemedicine and in-person consultation however telemedicine reduces the overall time consumed in visiting and seeing a doctor by eliminating the travelling and waiting time.

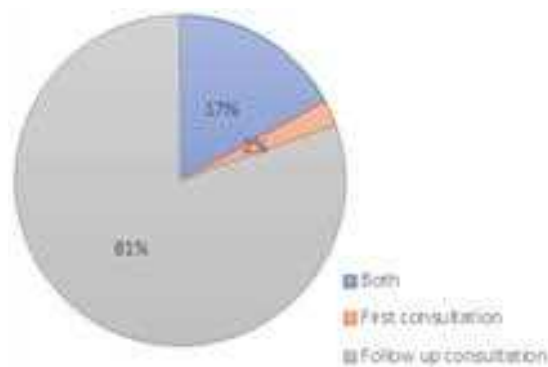


Figure 1. Preference of Telemedicine for the type of consultation.

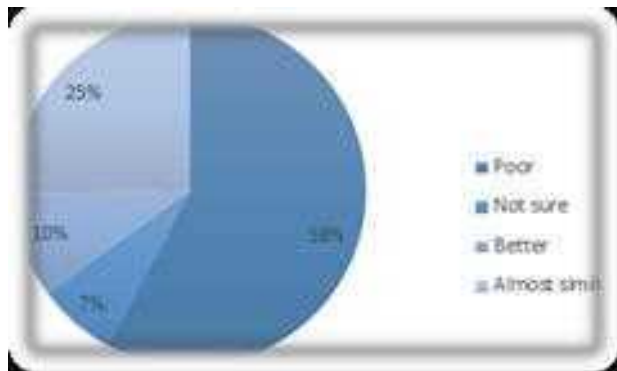


Figure 2. Quality compared to in person consultation.

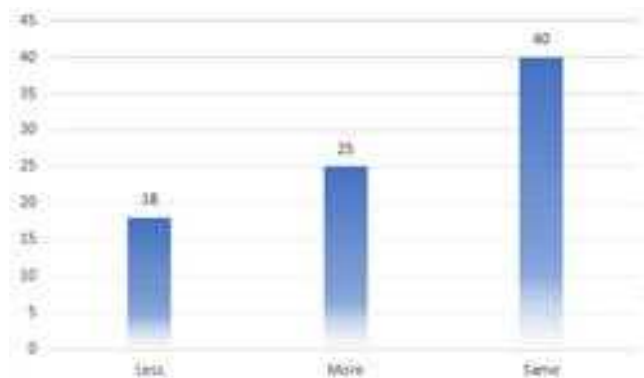


Figure 3. Time spent per each consultation relative to in person consultation.

Privacy is a major concern when it comes to telemedicine. It was measured on a scale of 1 to 5 (where 1 refers to the least privacy and 5 refer to maximum privacy). It averaged on 3.318. Sensitive information of patient, consents are storage on cloud and transmitted through virtual methods poses a threat to the confidentiality of the data.

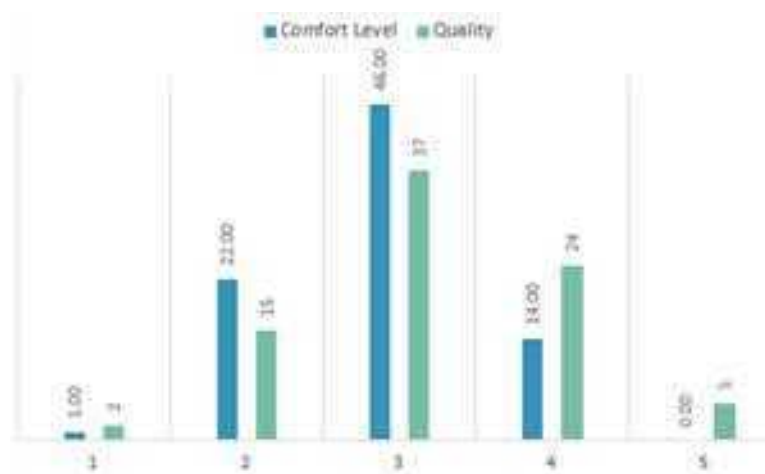


Figure 4. No of responses for comfort level and quality on a scale of 1-5.

Use of technology, sensors and presence of a third player makes the communication less secure in terms of privacy. Comfort Level while practicing Tele-medicine was measured on a similar scale of 1 - 5. The average comfort level measured on 2.87. Lack of detailed examination of the patient, lack of trust on the history provided by the patients without seeing them subsequently lack of confidence in the treatment provided makes telemedicine less comfortable for the doctors.

In the debate of whether “telemedicine is here to stay”, we found that 54.2% of the doctors in our study agree to stick to the use of online consultation even after the pandemic. 37.3% remain unsure of the use of online platform to see patients after Covid. And 8.4% of the participants refuse to the use of Tele medicine.

CONCLUSION

Despite all the advantages Telemedicine provides, there is a resistance in its acceptance especially from the provider’s perspective. The major challenge is the network connectivity on both ends of the interaction. People in rural areas yet lack a good broadband connectivity which hinders the process of Tele communication. Information asymmetry between the patient and the doctor becomes a crucial factor in explaining history, diagnosis and the treatment. With only 65.38% population of India being literate and only 2% people being well versed in English there is a huge information gap between the patient and the provider. Apart from communication challenges there are technical issues. Due to lack of technical knowledge, doctors face challenges in accepting the new software systems. The comfort level with technology is relatively low when compared to one to one interaction. Telemedicine requires a strong bandwidth connection along with heavy database infrastructure to ensure

patients and doctors experience a real time consultation. There is a lack of confidence among patients and doctors that affect the trust in Telemedicine. Majority of the participants are in the opinion that Telemedicine should be used for follow up consultation and not for first consultation. Though Telemedicine decreases the cost, saves time but there is a question on the quality of the service provided. Many doctors rate the quality of care in Tele consultation poor as compared to in person consultation.

Time spent by doctors per Tele consultation is more or similar relative to the time spent per in person consultation. With more intervention of medicine with technology and improvements in telecommunication, Telemedicine will take increased role in the healthcare system. There will be more opportunities and challenges with acceptance of technology. By addressing the various challenges effectively, technology can be exploited to a larger extent to make telemedicine stay and become more standardized as a healthcare model.

Suggestions:

- With more penetration of Tele medicine in the country, availability of high bandwidth internet connectivity becomes crucially important. However bandwidth requirement decreases with advancement in technology, for real time Tele medicine there is an extensive need of Telecom innovation. Use of Artificial Intelligence and data analytics should be enhanced to improve the service delivery.
- Technical Training should be provided to doctors before they step into practicing Tele medicine. Use of software, hardware and other technical skills should be made familiar with the providers to ease the comfort with technology.
- More User friendly Applications should be made along with provision of regional language. Agile Design thinking can be applied to make better user theories thus providing a barrier free process with higher target satisfaction.
- Incorporation of Telecommunication or Technical subjects in medicine curriculum to facilitate an effective learning process for doctors to efficient adoption of Tele medicine as a healthcare delivery model.
- Real Time Consultation should be provided than a store and forward method. This not only makes the interaction easy but a real time communication has more of a care touch that provides a higher sense of satisfaction among patients.
- Tele medicine being a technology intensive field, it demands more investments in terms of technology and innovations. There is need of support to small companies providing Tele health for more financial stability and infrastructure expansion.
- Legal and Ethical laws need to be implemented and monitored to a larger extent to ensure safety of patient's rights. Since there is a heavy database of patient and doctor, the cloud storage should be managed to ensure data privacy and confidentiality.

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Chapter 449

COVID-19 OUTBREAK REPRESENTS AN OPPORTUNITY FOR THE DEVELOPMENT OF INTERNET HEALTHCARE

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ABSTRACT

The COVID-19 epidemic has presented a severe test for the medical systems of all countries in the world. Regardless of developed or developing countries, the traditional medical service model has been dramatically affected. The traditional face-to-face treatment model has increased doctors' risk of infection. In contrast, for patients with chronic diseases, going to the hospital for treatment raises the risk of cross-infection, which seriously affects their standard medical treatment. The Internet Healthcare's non-contact treatment model, the ultra-large crowd processing capacity of computers, responsiveness that is unrestricted by time and place, multi-channel information collection, and precise diagnosis and treatment are supported by a considerable knowledge base have unleashed their full potential in the COVID-19 epidemic. Thus, these are generally considered to be reliable medical tools that can effectively perform chronic disease management amid the epidemic. COVID-19 has left us with a huge scar. Also, human society will likely face similar natural disasters in the future. So, in the face of the COVID-19 epidemic, we medical workers need to duly think about and explore medical models that align with future social development. Internet Healthcare, as an inevitable outcome of social and technological developments, needs to inherit the advantages and essence of the traditional medical model and progress on its basis. Instead of blindly relying on new technologies, it should re-examine the future of Internet Healthcare on the foundation of a traditional model. Therefore, for Internet Healthcare, this novel coronavirus pandemic is perhaps an opportunity and a challenge.

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Keywords: telemedicine, COVID-19, chronic disease management

INTRODUCTION

Internet Healthcare represents a new direction for the medical industry and has the advantages of being unrestricted by time and space. It enables communication anytime and anywhere, improves medical efficiency realizing resource-sharing among all, and offers consistent and accessible medical services, which can crack some of the hard nuts in the medical industry [1, 2]. In the context of the COVID-19 epidemic, Internet Healthcare has given full play to its positive role in preventing and controlling the epidemic, by providing the general public with online medical services without leaving home, and reducing citizens' hospital-bound medical activities. It has lowered the risk of cross-infection and protected the physical and mental health of the general public. Under these special circumstances, the number of users using Internet medical services has skyrocketed. Internet Healthcare includes various forms of healthcare service with the Internet as the carrier and technical means, such as health education, medical information inquiry, electronic health records, disease risk assessment, online disease consultation, electronic prescriptions, remote consultation, and remote treatment and rehabilitation [3]. It is conducive to resolving the contradiction between the imbalance of medical resources and people's ever-increasing demand for health care. Thus, it represents the inevitable next stage in the development of the information society and the first step in the development of an intelligent medical service model.

According to a set of data released by the Planning Department of the National Health Commission of China, during the epidemic, the number of online diagnoses and treatments in hospitals affiliated with the National Health Commission has increased by 17 times compared with the same period last year. Also, the amount of consultations on some third-party Internet service platforms has grown by more than 20 times during the same period, with prescriptions up nearly tenfold [4, 5]. After the outbreak of COVID-19, in not only China but also the United States, where the Internet medical industry originated in the early 21st century, the US government encouraged using online medical treatment instead of offline treatment. It adjusted its Internet medical care and health insurance policy accordingly [6]. The French Ministry of Health signed a decree in March 2020, allowing National Health Insurance to reimburse patients with COVID-19 symptoms and confirmed COVID-19 infection via remote video consultation and remote professional services. These remote services have had a specific effect on reducing unnecessary face-to-face medical consultations by limiting the number of people in the waiting room for triage, screening and identifying suspected patients, and enabling the follow-up of confirmed mild cases at home [7]. In Asia, South Korea, one of the first countries to develop Internet Healthcare, has been affected to a certain extent due to national medical policy restrictions. However the outbreak of the pandemic prompted it to respond to the Internet's need to provide access to healthcare services. It actively adopted various policy measures to boost Internet Healthcare as a medical solution to the pandemic [8, 9].

Internet Healthcare presents an effective solution to the current medical plight and is embracing an opportunity for its development [10, 11]. However, because of the limitations of medical policies and diverse treatment approaches among countries, the development of

intelligent Internet Healthcare has yet to explore and build advanced intelligent medical functions, such as a smart medical cloud and medical equipment informatization. During the development of intelligent Internet Healthcare, excessive attention has also been paid to hardware construction, ignoring the essence of traditional medical care, which is a typical problem in the current construction and development of intelligent medical treatment. For example, it is common to focus on hardware construction while ignoring the essence of intelligent medical care.

The COVID-19 epidemic has changed our lives, requiring more patients to experience and accept the treatment model of Internet medical services. After patients used the Internet Healthcare application during the epidemic, we found that this chronic disease management model was feasible in real life. As humans, our society is undergoing the initial steps of the fourth technological revolution, but Internet medical care remains in its infancy. So, we must take the initiative to explore the expansion potential of Internet Healthcare and work hard to solve predictable problems both currently and prospectively. Only in this way, can we effectively respond to the new challenges brought forward by Internet Healthcare.

COVID-19 OUTBREAK, AN OPPORTUNITY FOR THE DEVELOPMENT OF INTERNET HEALTHCARE

At the end of December 2019, 2019, novel coronavirus (2019-nCoV) infections and suspected pneumonia cases emerged in China, especially in Wuhan of Hubei Province, and other countries. Cities and villages in various parts of China implemented lockdown, and residents were isolated at home, as required. The sudden outbreak of the epidemic severely affected the standard diagnosis and treatment in the hospital. In the early stage of the outbreak, the treatment for the epidemic itself and the anxiety triggered by the disease has caused an influx of patients into the hospital, resulting in an insufficient supply of offline medical resources and weak response. The ensuing measures, such as the designation and renovation of fever clinics, designated hospitals, and suspension of admission, have put medical institutions into an irregular operation state. In addition, patients with chronic diseases were at high risk of infection and death during the COVID-19 epidemic. They refrained from standard medical treatment because of the social fear of cross-infection. Thus, in the context of the COVID-19 epidemic, Internet Healthcare was re-examined as a medical solution to the epidemic based on its advantages, such as non-face-to-face medical treatment, convenient consultation regardless of temporal and locational restrictions, and feasibility of traceable, and monitorable follow-ups [12-14].

Regarding the age of the clinical patients during the epidemic, most infected patients were between 40 and 60 years old, and many of them were older people with underlying diseases or obesity. Wuhan of China was the first place of the epidemic outbreak. Huang et al. also released data on the epidemiological analysis of 41 patients first diagnosed in China in *The Lancet*, among whom 32% were chronic patients with diabetes, hypertension, coronary heart disease, and others, and up to 20% were diabetics alone. In other words, diabetic patients are likely to be susceptible to this epidemic, mainly due to their chronic hyperglycemia, which itself will cause damage to blood vessels, the nervous system, and various other organs [15]. In a meta-analysis related to COVID-19, Bulut evaluated a total of

46,248 patients in eight epidemiological studies of COVID-19 and found that the most common comorbidities were hypertension, diabetes, cardiovascular disease, and respiratory diseases [16]. Another finding of this study showed that these patients with comorbidities were more likely to deteriorate into severe cases. In addition, according to Italian Weekly, the most common COVID-19 comorbidities were hypertension, diabetes, ischemic heart disease, and chronic kidney disease, each accounting for 72%, 31.5%, 27.4%, and 23.5%, respectively. It also revealed that patients without comorbidities comprised only 2.8% of deaths [18, 19]. In the face of this pandemic, patients with chronic diseases are at high risk of infection and, thus, are somewhat vulnerable. To avoid cross-infection and nosocomial infections, the number of visits by patients with chronic diseases should be reduced, and their exposure to infectious environments should be lowered. Also, it is necessary to emulate the outpatient clinic environment for them at home. Moreover, the limited distancing between people amid the COVID-19 epidemic has also triggered psychological barriers in patients with chronic diseases.

In consideration of the characteristics of the COVID-19, China's large hospitals, and Internet medical companies have rapidly rolled out online medical services [20, 21], such as (1) Online fever screening clinic: based on the existing Internet hospitals, focuses on fever, and cough clinic, emergency department, respiratory department, infection department, endocrinology department, nephrology department, cardiovascular department, geriatrics department, mental health department and general practitioners for the online screening of fever patients to provide Internet-based timely diagnosis, treatment, and consulting services. (2) Psychological intervention services: COVID-19 epidemic's prevention and control measures, such as home quarantine and social distancing between people of more than one meter, have induced psychological barriers among psychologically vulnerable groups. These have led to a surge in psychological counseling caused by the epidemic. The home-based psychological intervention service on the Internet medical platform could also provide health education and psychological intervention before medical treatment was sought. (3) Follow-up: An Internet-based medical service could collect medical information, such as vital signs, and patients' mobile device test data after outpatient visits or discharge from the hospital, so it was suitable for uninterrupted follow-up. In addition, since it also effectively reduced the risk of cross-infection because non-contact medical treatment was not restricted by time and location, it could provide comprehensive medical services for more patients to maintain their health regularly or dynamically. (4) Remote consultation service: Internet Healthcare also provided technical support for remote consultations between medical institutions. The application of 5G to back up high-definition remote consultations could keep medical images clear, seamless, and without delay so that doctors can read images freely, the technical accuracy of image reading became enhanced. High-quality expert resources could be shared with primary medical institutions, allowing for real time interaction. It has also provided technical support for the overall arrangement and command, medical treatment, and joint prevention, and control of higher-level medical institutions through the remote consultation platform between medical institutions amid the epidemic. (5) Online medical payment: Internet hospitals have connected with online medical insurance payment platforms to improve online diagnosis and treatment, follow-up examinations after chronic disease treatment, online payment, drug delivery, and other services, which effectively reduced the risk of crowd aggregation and cross-infection. (6) Application of artificial intelligence (AI): Medical assistant robots (AI) reduced the workload of nurses, cut down their contact time

with suspected and confirmed COVID-19 patients, and lowered the consumption of materials for prevention and control. Meanwhile, AI-assisted temperature measuring instruments were also used to screen the key population. The application of AI to the decision-making analysis of patient diagnosis and treatment could deliver continuous, comprehensive, individualized decisions through an overall evaluation of patients' medical information [22, 23].

The promotion of Internet medical services has not only effectively reduced the number of outpatient visits but also ensured that the demand for medical treatment is met. Through online contact between doctors and patients, the latter have gained more knowledge and methods of epidemic prevention and self-management. Also, adverse events caused by delayed treatment of chronic diseases have been avoided. Based on our research experience of Internet Healthcare, we performed it for diabetes during the COVID-19 epidemic. Our research team independently developed the u-diabetes.com system to enable doctors to make a diabetes diagnosis and prescribe treatment over the Internet, and the WeChatDiabetes mobile medicine system for patients [24-26]. With the popularity of smartphones, person-to-person communication has been separated from the Internet-based on computers, and is conducted mainly through chat tools on mobile phones. Previous studies have found that it is challenging for older patients to learn unfamiliar Apps, and they seldom use other Apps besides those to surf the Internet, communicate, and chat on smartphones, which is chiefly because most Apps are complicated to operate. However, if you allow older patients to open their commonly used chat tools, and then enter the mini-program, they will adopt a whole new attitude toward using it. This is because first, they are familiar with it, and second, they know the basic operation of the App. Although we have also developed an independent App for patients on mobile phones, we still insist on collecting information from the chat App for patient convenience. We also discovered that this was more beneficial for patients to receive information on time and not delay feedback. The reason is that if you want to know the push information on a mobile phone, you must ensure that the App is on the homepage of the phone screen. Interestingly, almost all of us will keep a chat App on the main screen of our phones. In addition, even if we accidentally erase it, we will ask others to help restore the chat App to the main screen if we cannot do it ourselves, thereby ensuring that the information is sent to the patient the first time.

During the epidemic, considering that many older patients tend to have a limited mastery of new technology, we have repeatedly conducted online video guidance and uploaded blood glucose data via blood glucose meters with a data transmission function (which can be directly connected to a smartphone via Bluetooth). Patients were required to measure blood glucose at least twice a day for 2-3 days a week. In the WeChatDiabetes mobile medicine system, subjects could check their blood sugar level, blood pressure level, and weight changes. During the epidemic, our doctors logged into the system every two weeks and adjusted drugs in time through App messages or phone calls according to the data uploaded by the subjects voluntarily, to avoid the occurrence of hyperglycemia or hypoglycemia. Meanwhile, patients were urged to adhere to blood sugar self-monitoring and strengthen diet and exercise management. Regular online medical treatment registration from patients was also accepted. Moreover, based on patients' ideal weight and nature of work, nutritionists calculated the total daily calories patients needed concerning their original living habits, determined the composition of nutrients, and formulated the recipe for three meals after converting the calories into food. Fitness trainers arranged regular aerobic and resistance

exercises for patients at least 150min a week according to different conditions such as age, sex, physical activity, and complications.

During the epidemic, we did not ask patients to go to the hospital to check glycosylated hemoglobin, but only analyzed their blood sugar control. The main purpose of patients seeking online medical treatment from February to March when the epidemic was the gravest was that patients were unable to perform online medical treatment normally because of their social fear of the sudden outbreak. They were seeking online medical treatment not to solve problems related to blood sugar control, but to consult on the novel coronavirus and how people with diabetes could prevent it. Therefore, we have produced a WeChat promotional video with the theme of “Improving Immunity and Fighting Off the epidemic.” Our Internet medical platform was based on the WeChat platform and thus had very good reach, reporting many patient clicks up to 8000. We found that patients’ top priority was to attain medical information about this serious public health emergency. So, we arranged staff to provide counseling on the platform to avoid blind and extreme behaviors of diabetics and help them enter on a normal path of self-management of diseases. In April, with the stabilized control of the epidemic in China and the gradual resumption of daily life, patients’ online medical treatment for diabetes began to increase steadily. On the contrary, the number of outpatient visits has decreased by more than 10% compared with previous years. The grim warning of diabetic patients’ susceptibility to infection and subsequent death has severely hindered their desire to seek offline, face-to-face medical treatment.

Internet Healthcare provides a safe solution during the COVID-19 outbreak and is a suitable fit for patients and the actual social situation. This epidemic also serves as a turning point in the transformation of medical service models and an opportunity for the development of Internet medical service.

THE SPACE FOR INTERNET MEDICAL DEVELOPMENT, PROFESSIONAL MEDICAL SERVICES FOR THE GENERAL PUBLIC

As a product of the times, Internet Healthcare also needs continuous improvement and expansion. The current Internet Healthcare primarily facilitates the communication of medical information between doctors and patients, and the circulation of finances and goods, which applies to all clinical departments. However, the difference in Internet Healthcare of chronic disease lies in its intelligent follow-up capabilities, such as monitoring, early warning, and clinical decision-making assistance. These advantages can be extended to many clinical departments and patients with specific diseases, and incorporate more groups, including sub-healthy groups, and the general population in need of health management.

The department of endocrinology is the primary clinical department for chronic disease management. Diabetes is currently the most suitable disease for Internet Healthcare [27]. Diabetes self-management includes medication, diet, exercise, and blood glucose monitoring. The timely sharing and analysis of blood glucose monitoring data are crucial to prevent hyperglycemia and hypoglycemia [28]. The development of glycosylated hemoglobin and diabetic complications can be predicted from the changes in a patient’s blood glucose level and routine clinical indicators, which are the most accurate reminders for patient self-management. In addition, diet, and exercise management also require monitoring data of

caloric intake and calorie used, as these two daily activities have a great impact on blood glucose. Only by combining these two influencing factors to adjust drugs can the patient's actual condition be objectively reflected [29, 30]. The prevalence of thyroid disease is increasing each year, and more than 300 million people in the world suffer from it, making it the second largest disease in the endocrine field. At present, about one in six women has hypothyroidism [31]. If the patient is pregnant, the probability of miscarriage, and fetal mortality in the third trimester significantly rises. It is very likely to lead to impaired intellectual development and growth disorders of the newborn, causing irreparable harm to the mother and child. However, it is also unrealistic for pregnant women to frequently seek medical treatment offline. Also, those with metabolic diseases need professional monitoring and treatment throughout the whole process [32]. In this aspect, Internet Healthcare has a unique advantage in the remote management of metabolic diseases during pregnancy [33]. Patients with diabetes, hypertension, and thyroid diseases are followed up through terminal monitoring equipment. In addition to the clinical nutrition department's intervention on drugs and endocrine metabolic diseases also needs to combine dietary information collection and calorie consumption monitoring with portable equipment. This combined effort could evaluate patients' daily metabolic balance and guide the nutritional follow-up of chronic diseases objectively and the diet management of metabolic diseases related to pregnancy accurately. Among patients with common kidney diseases, such as diabetic nephropathy and peritoneal dialysis, diabetic nephropathy accounts for 40% of kidney diseases. These patients key to treatment is to control their blood sugar and blood pressure. The Internet medical platform of the endocrinology department can be fully extended to the Internet-based management of nephrology patients, obtain the weight, serum potassium, and phosphorus concentration of dialysis patients, and perform accurate patient management in realtime to help improve the efficacy of dialysis [34].

In addition to the clinical departments related to endocrine diseases, coronary heart disease, hypertension, arrhythmia, and cardiovascular surgery in charge of the cardiovascular department are also suitable for Internet Healthcare [35]. Portable monitoring equipment is used in the cardiovascular field, such as a blood pressure monitor (Wireless Blood Pressure Monitor), cardiometer, and electrocardiogram [36]. The established technology has realized the portable and data transmission functions of this equipment. The monitoring data of the patient's blood pressure, heart rate, ECG, exercise volume, sleep quality, and exercise cardiac function can be automatically uploaded to the hospital server through a mobile phone in real time [37], which can provide patients with realtime and tracking monitoring services. Also, the establishment of personalized health data files based on the patient's cardiovascular signs allows doctors to understand the patient's condition and progress objectively. Respiratory diseases, including asthma, chronic obstructive pulmonary disease, sleep apnea syndrome, and other conditions, are also suitable for Internet Healthcare [38]. Portable monitoring equipment, such as a portable spirometer, can track the patient's drug use, show peak expiratory flow and lung function indicators, and use the microphone on a mobile phone to record the frequency spectrum of breath sounds. This data is then fed back to the doctor through the mobile phone. The system can interpret the data to the patient according to a comprehensive scoring method. The doctor can analyze the patient's condition and guides the patient through a standardized treatment.

Current Internet Healthcare can facilitate doctors' diagnosis and treatment activities by encouraging patients to play a more active role in assisting the clinical process in achieving

personalized, individualized diagnosis, and treatment. Outside the limitations of both time and space, Internet Healthcare can process a large amount of medical information simultaneously; it can expand its target audience from patients to sub-healthy people and healthy people who need health management [39]. Our current health management is in a passive health management model. The medical intervention is only accepted when the body is unhealthy. Medical intervention also targets a lesion by eliminating this phenomenon to relieve or cure a disease. However, active health management is a medical model that promotes the human body's adaptation by actively applying controllable stimulation to the human body. Controllable stimulation enables the enhancement of human body functions or the reversal of chronic diseases. The human body is a complex system with strong self-healing and organizing abilities. The task of medical science is to utilize controllable methods fully to activate these human body's abilities under the premise of providing the individual with the personal initiative to achieve the purpose of eliminating human diseases and enhancing the human body. This requires long-term continuous dynamic tracking, identification, and assessment of one's own state and evolutionary direction. Also, it necessitates the extensive use of various medical methods for active intervention to maintain the human body in a healthy state. Internet Healthcare meets the needs of the active health scenario. Through Internet Healthcare, the cyclical closed-loop management between hospitals, working units and families can be realized. The main scenario of active health is also in the working unit and family. Doctors are coaches for health, friends for patients, and lifestyles, such as exercise and nutrition, are tools. Internet Healthcare can take treating diseases as its purpose and can be executed based on disease prevention.

The COVID-19 epidemic is a long-term challenge that humans may encounter again in the future. This epidemic has reminded us that a healthy working style and lifestyle must be established. Everyone must change from using a passive health management model to an active health management model.

SMART HEALTHCARE IS THE CORE TECHNOLOGY FOR THE FUTURE SUCCESSFUL INTERNET HEALTHCARE

Smart healthcare is based on big clinical data, using technologies such as the Internet of Things, cloud computing, and AI as the means. It is a medical service model that is centered on patient data. The development of new information technology is profoundly changing traditional medical and health services, and big data has brought smart healthcare an unlimited development space. Smart medical solutions have potential applications in medical testing, medical image analysis, clinical decision support systems, and telemedicine [40-42].

The construction of smart healthcare, whose base is the Internet of Things technology, will be guided by intelligence with "sense, knowledge, and action" as its core. It is a smart medical platform on which medical data is more interconnected, more convenient to move, and more efficient to share. Smart healthcare solutions can continuously improve medical care accuracy through the organic operation of the data collection layer, data storage layer, business processing layer, and data application layer. "Sense" means that the family health monitoring system uses various implantable, wearable, and proximity wireless medical sensors to collect various physiological parameters of the human body. These data are

transmitted to the medical data center accurately and conveniently through network technology in real time, that is, the data collection layer [43-45]. “Knowledge” refers to using big data storage and a processing platform to model and analyze historical medical data reliably, quickly, and efficiently by applying data mining and knowledge discovery theory. It belongs to the data storage layer and business processing layer. The construction of the medical knowledge base in the data storage layer is the knowledge guarantee for smart healthcare. To achieve scientific and accurate business processing, medical experts need to make designs that simplify complex medical problems and refine simple medical problems. The data application process is the decision support for the diagnosis, treatment, and prevention of diseases, the process of fusion, screening, and analysis of multiple collected information, a design that follows the medical knowledge base and medical plan, and it should be timely and accurate in early warning and emergency response. The knowledge base includes four parts of the medical lexicon, medical term dictionary, knowledge model structure, and knowledge warehouse. The knowledge model structure forms a network structure with content related to these terms for storage and recall. The knowledge warehouse uses a powerful database as an architecture platform to assist an intelligent word processing and retrieval system. The sources of medical knowledge include medical literature (referring to archived knowledge) and the clinical experience of medical experts. For any kind of medical knowledge, the system first collects the knowledge through the acquisition engine, and then uses the knowledge model to find the corresponding solution in the knowledge base through the interpretation engine to narrow the target range gradually. Finally, the knowledge base system determines which category of medical knowledge it belongs, and stores the results in the corresponding location in the knowledge base. Auxiliary decision-making throughout the clinical process can be provided by combining simulated clinical thinking and the knowledge base. The actual process is to operate a large amount of knowledge with a neural network structure to develop medical knowledge through the following windows of “diagnosis basis,” “diagnosis of disease,” “inspection plan,” “medication plan,” “treatment plan,” “care plan,” “health plan,” and others, and generate multiple clinical decision-making channels according to the patient’s condition to provide a reference for doctors’ decision-making, so that clinical diagnosis and treatment have the nature of multi-view consultation. At the same time, it helps doctors accurately use auxiliary diagnostic methods and reduce reliance on equipment; the diagnosis, treatment, medication, and other relevant topics in the whole clinical process are included in the scope of intelligent assistance to carry out rapid, accurate, and standardized clinical diagnosis, and treatment [46, 47].

Smart healthcare can bring forward the diagnosis and treatment behavior from disease treatment to disease prevention, which can delay or prevent the occurrence and development of the disease. This advantage of smart healthcare differentiates it from traditional healthcare, and the content that needs innovation in the business processing layer. Traditional healthcare makes an accurate diagnosis through the determination of specific indicators. However, specific indicators are usually not an index for routine physical examination. The human body is an organic combination of various organs and systems. Some problems may be discovered during the routine physical examination of other organs and systems. At present, clinical examination only usually uses limited test indicator data to diagnose disease. Although many clinical test data do not significantly exceed the normal threshold of existing indicators, they may have an upward or downward trend in a certain interval. Through big data analysis and cloud computing, the logical relationship between test data and disease symptoms can be

analyzed. New disease-related markers can be revealed from these easily overlooked data. In addition, data comparison, calculation, and analysis of some conventional indicators with a variety of diseases can further discover corresponding relationships at the data level and detect new disease warning indicators through appropriate pathological verification and analysis based on big data [48, 49]. The testing of biomarkers is an important method for screening and diagnosing certain diseases. The analysis of testing big data provides new opportunities for the discovery of many disease biomarkers. Through the proteomic and metabolomic analyses of a large number of serum and urine analyses of clinical specimens of patients with chronic diseases, some abnormally expressed potential biomarkers can be found. In addition, their diagnostic efficiency is significantly higher than that of a routine examination. However, studying the change in a specific biomarker index often has only a low sensitivity or specificity. It is challenging to meet the expectations of the clinical diagnosis and prognosis of related diseases. For example, based on big data of the personalized genome, transcriptome, and proteomics, diabetes genetic marker screening adopts high-throughput, high-efficiency, and high-precision big data storage and analysis, strategies to integrate different types of data of cell phenotypes, metabolic processes, and pathogenic factors and discover significant though hidden biological markers of diabetes. Diabetes clinical index marker screening is the application of the study of existing clinical big data in the comparative analysis of diabetes risk factors, which combines traditional health data with personal data from other sources and performs a comparative analysis of health risk factors so that health-related risk factors can be selected, health monitoring and evaluation maps and diagnosis and treatment models can be made, and targeted intervention plans can be proposed [50]. Therefore, the testing of multiple markers can achieve the purpose of improving sensitivity and specificity. Integrating the biomarkers screened by various omics for data analysis will greatly improve the detection and identification of early warning signs and disease diagnoses.

“Action” is to quickly and accurately provide the analysis results of realtime data and historical data to patients through cloud services. It is necessary to form a closed-loop connection between the smart hospital system, the regional health platform, and the family health system to act effectively. The smart hospital system achieves the monitoring, tracking, chronic and infectious disease care, and the positioning and emergency deployment of medical equipment. The regional health platform can ensure a standardized diagnosis at all levels of hospitals and assist the diagnosis and treatment activities of different levels of hospitals. The family health system allows sub-healthy people to enjoy convenient, fast, and equal medical services at home through personalized health information management. The 3-sided closed-loop connection system needs to support the docking of users, such as medical institutions, collaborative consultation centers, families/individuals, enterprises, and banks through the mutual acquisition, mutual assistance, and corresponding services of cloud services and system software to realize the interaction of relevant medical information.

Based on the technological support of the data collection layer, data storage layer, business processing layer, and data application layer and the operation cases, the smart healthcare system can establish an early warning model through the storage and memorization, in-depth learning, and repeated training of massive patient clinical data, molecular data, medical images, treatment plans, and similar functions. With the aid of a large number of mathematical analysis methods, this early warning model classifies historical medical data and dynamic medical data of the patient, establishes associations and analyzes

various relationships, and extracts the characteristics and attributes of the data for comparative analysis. At the same time of making predictions, the results are fed back to the early warning model so that the model can be continuously adjusted and optimized [51].

CHALLENGES CONFRONTED BY INTERNET HEALTHCARE

Traditional healthcare strives to ensure that everyone can enjoy basic medical care and share medical resources, but it ignores the individual differences between people. With the help of new technological developments and concepts, smart healthcare can provide medical services for people according to their diseases and customize personal medical management through effective information management of medical equipment so that personalized medical management can be achieved. Also, the use of limited medical resources from disease treatment to disease prevention and healthcare can be maximized. Smart healthcare has broadened the scope of medical care and is a medical service system focusing on the full lifecycle and the whole medical process. One major feature and focus of the development of smart healthcare is the shift from disease treatment to disease prevention and healthcare. The medical process is extended to before and after the disease, focusing on health care, disease prevention, and treatment to control the disease, avoid the risk of disease, and reduce cost consumption in disease treatment and treatment costs. This approach may reduce treatment costs and relieve the patient's suffering and realize the rational use of limited medical resources.

As the online extension of the hospital's working scenario, Internet Healthcare is also a medical treatment behavior with doctors and nurses as its main body. However, the current Internet Healthcare depends too much on the design based on IT technology. Besides the hardware environment, the operation of the knowledge system and the emotional communication between people in the hospital work setting is shaped by the medical staff's study and work experience. Therefore, the design of the online working environment should be derived from the experience and designed by senior medical staff. Without sufficient medical information collection, superb logical thinking in diagnosis and treatment, and a rigorous error-correction and error-prevention system, it is impossible for doctors to achieve proper online medical behavior [52].

Sufficient medical information collection confers benefits from the data transmission capabilities of various portable devices and the development of AI recognition technology. Technologies, including the recognition and transformation of unstructured data of medical information into structured data, the recognition and digital conversion of life monitoring image information, and the integration, screening, and analysis of information from portable and home monitoring equipment, need further improvement. These improvements will enable Internet Healthcare to make full use of its own advantages to be more personalized and precise than traditional on-site diagnosis and treatment. The superb logic of diagnosis and treatment comes from the experience of senior medical workers. It cannot be replaced by clinical diagnosis and treatment manuals or diagnosis and treatment guidelines. The data and analysis processes of IBM Watson, the most representative intelligent clinical decision support system, come from guidelines, high-level literature, and experience of high-level hospitals. However, clinical practice is different from playing Go. Many factors affect the

physical condition of the human body. In addition to disease, complications, and mental conditions are contributing factors. Therefore, the diagnosis and treatment processes usually do not rely entirely on guidelines. The intelligent clinical decision support system for chronic diseases needs to be supported by sufficient personal medical information, and the integration of dynamic data. The doctor's thinking model should be strictly followed. The rigorous error-correction and error-prevention system of Internet Healthcare offers an optimal advantage. During the entire disease diagnosis and treatment process, the careful design should be established for dealing with common complicated situations, such as the identification of diagnosis and the judgment of indications and contraindications. The error-correction and error-prevention capabilities of micro-computers are a solid guarantee for the safety of Internet Healthcare.

The COVID-19 epidemic is a fight between man and nature on a global scale, which requires Internet Healthcare to expand from disease treatment to disease prevention based on its own advantages. Then, it further mandates it to maintain a healthy human body. Through the dynamic collection and comparison of health risk factors by big data technology, Internet Healthcare can select health-related risk factors and propose targeted intervention plans through an intelligent medical decision-making system to improve the comprehensive analysis capabilities of medical data and the accuracy of doctors' clinical decisions. This comprehensive medical service model of remote monitoring and intelligent diagnosis of chronic diseases is an inevitable social development trend. There is an urgent need for medical institutions to share medical diagnosis and treatment technology and patient management information on the scientific and technological service platform to realize the innovation of the chronic disease medical service model as soon as possible.

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Chapter 450

ARRHYTHMIAS IN COVID-19 PATIENTS: BENEFITS AND CHALLENGES WHEN USING TELEMEDICINE

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ABSTRACT

Patients infected with SARS-COV-2 are predisposed to rhythm problems primarily because of the treatment. Corrected QT interval should be calculated before using these drugs and if it is, already prolonged treatment options should be discussed. In addition, atrio-ventricular blocks may occur during the treatment, interfering with calcium channel blockers and beta-blockers, if they are already being administered. Lopinavir and ritonavir are also associated with prolonged PR and QT interval that may evolve in higher-grade atrioventricular blocks.

It is mandatory to assess whether arrhythmias in COVID-19 patients are preventable, treatable or permanent, or if they have long-term effects on the patient's cardiovascular status. Arrhythmias and cardiac arrest are more likely to be triggered by a severe, systemic form of COVID-19 and are not the sole consequence of the viral infection. In addition, electrolyte abnormalities such as hypokalemia, micro thrombi formation, cytokine storm, direct invasion of cardiomyocytes and hypoxemia may induce severe forms of arrhythmias in these patients.

Telemedicine is used to diagnose arrhythmias and permits left ventricular dysfunction assessment. It can evaluate the efficacy of antiarrhythmic therapy or the proarrhythmic side effects of patient's medication. An important application is pacemaker interrogation or automatic intracardiac defibrillator function assessment.

Telemedicine is a more permissive way to diagnose arrhythmias in these patients. However, automated interpretations are not sufficiently accurate without expert review,

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especially in the presence of rhythm disturbances or complex abnormalities. It is limiting the time of exposure between the doctor and the patient and offers a complete overview of the disease. It is also a competitive method for triage and has screening potential.

Telemedicine can be considered to play a major part in COVID-19 patients' management, because it provides a quick and precise diagnosis that is obtained without unnecessary exposure of the medical personnel.

Keywords: COVID-19, arrhythmias, telemedicine

INTRODUCTION

Coronavirus disease 2019, known as COVID-19, is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), resulting in a pandemic that started in the city of Wuhan late in 2019. In some cases, COVID-19 is presented with systemic manifestations that might trigger a variety of arrhythmias like atrial fibrillation, Brady arrhythmias, non-sustained ventricular tachycardia and even cardiac arrest. Critically sick patients or those admitted to intensive care units are more likely to develop these types of arrhythmias compared to other hospitalized or home based patients, primarily because of the treatment.

It is well known that drugs like hydroxychloroquine, azithromycin, lopinavir and ritonavir are involved in QT interval prolongation, so corrected QT interval (QTc) must be calculated before using these drugs and if it is already prolonged treatment options should be discussed. Atrio-ventricular blocks may also occur during the treatment making the therapy with calcium channel blockers and beta-blockers difficult, if already administered. Lopinavir and ritonavir are associated with prolonged PR interval, that may evolve into higher grade atrio-ventricular blocks.

It is mandatory to assess whether arrhythmias in COVID-19 patients are preventable, treatable or permanent, or if they have long-term effects over the patient's cardiovascular status. Arrhythmias and cardiac arrest are more likely to be triggered by a severe, systemic form of COVID-19 and are not the sole consequence of the viral infection. Electrolytes imbalance (such as hypokalemia, hypocalcemia, hypomagnesemia), microthrombi formation, cytokine storm, direct invasion of cardiomyocytes and hypoxemia may induce severe forms of arrhythmias in these patients.

Telemedicine represents a useful tool in this global context, especially when a broad range of devices like smartphones, wristwatches, patches, eye-glasses, headbands and necklaces provide a large spectrum of parameters (single or multiple-lead ECGs, heart and respiratory rate, temperature, sleep quality, blood pressure, peripheral oxygen saturation, the level of stress, apnea events, ischemia's severity and also cardio-respiratory fitness parameters).

In the case of non-COVID-19 patients with cardiovascular comorbidities who are unable to attend their scheduled appointments, telemedicine may provide complete information regarding the patient's electrophysiological status and make necessary their physical presence in our hospitals or at least limit the duration of the consult. It is an important method for triage before the patients arrive in the emergency room and facilitates a quick redistribution to other medical subspecialties.

THE SUBSTRATE OF ARRHYTHMIAS IN COVID-19 PATIENTS

In patients infected with the novel coronavirus, SARS-Cov2, the heart can be affected in many ways, the manifestation of cardiac involvement in the setting of the infection being extremely varied, as a result of direct viral damage, that is myocarditis, pericarditis or the association between them – myopericarditis, as a consequence of the homeostatic hazard caused by the respiratory infection or secondarily to the treatment given in order to manage the disorder.

In the case of primary impairment of the heart, the signs and symptoms associated with the cardiovascular system should give rise to the suspicion of SARS-Cov2 infection and, by contrast, in patients already known with COVID-19, development of the cardiac symptoms should be a warning signal, especially in those who have got already cardiovascular disease.

Arrhythmogenesis in COVID-19 Patients

Arrhythmias in patients diagnosed with COVID-19 are one of the most frequent disorders related to cardiac involvement, as studies, at this moment, indicate. In one of the very first studies addressed to COVID-19 regarding the presence of arrhythmias, in Wuhan, the epicenter of the pandemic, in a group of 168 patients, 23 had suffered arrhythmic events (16,7%), 16 of them being in intensive care unit. (Wang, et al. 2020, 1061).

Table 1. The causes of arrhythmias in COVID-19 patients

direct heart injury	dysselectrolytemia
ischemia	sympathetic nervous system over activity
hypoxia-hypoxemia	medication
systemic inflammation	previous heart damage
procoagulant status	comorbidities

The underlying arrhythmogenic process is, however, intricate. Many causes contribute to arrhythmia development but, in the end, all are related to the infection and its consequences. Table 1 sums up the main causes of arrhythmias in COVID-19 patients.

Arrhythmias Caused by Previous or De Novo Heart Injury

In this type of arrhythmias, three main causes are involved but all of them can be present at the same time (Figure 1 and Table 2).

Table 2. The mechanisms of arrhythmias in COVID-19 infection

ACUTE	CHRONIC
direct myocardial damage	proinflammatory cytokines
pericardial effusion	scars
microvascular damage	

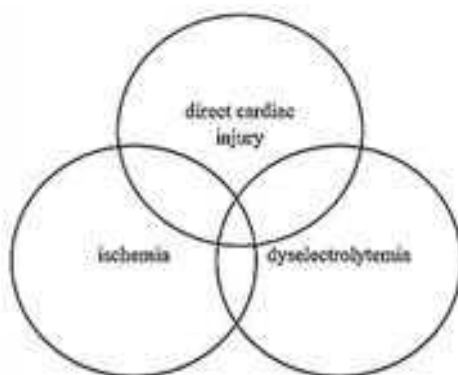


Figure 1. The three main mechanisms of arrhythmias involving heart injury.

Direct Cardiac Injury

Coronaviruses are not cardiotropic viruses like Parvovirus B19 or Coxsackie although they use type 2 angiotensin converting enzyme (ACE2) as a receptor to invade the human organism (Zisman 2005, 323). Moreover, at this point, there is not consistent evidence that SARS-Cov2 is causing myocarditis itself. In one case report, indeed, Tavazzi and all demonstrated, for the first time, based on ultrastructural examination of endomyocardial biopsy performed on a patient with severe form of COVID-19, that the virus can be present in myocardial cells (Tavazzi, et al. 2020, 911-914). The mechanism of myocarditis in COVID-19 patients is, however, more likely to be caused by the cytokine storm, as seen in previous epidemics of SARS-Cov2 and MERS.

Apparently, myopericarditis can cause arrhythmias by intricate mechanisms, from structural damage to electric activity imbalance, some of them being prevalent in the acute phase while the others occurring in the healing or chronic phase. The presumed cytopathic effect of the virus (caused by the presence of the type 2 angiotensin converting enzyme in myocyte's membrane, that being the receptor for the virus) as seen with the established cardiotropic viruses, causes de myocyte membrane to break, thus leading to electric instability among cells. Microvascular ischemia caused by the endothelial damage associated with the cytokine high levels is also predisposing to arrhythmias, frequently at ventricular level. Cytokines, especially IL-6, cause loss of intercellular adhesion followed by cardiomyocyte necrosis and replacement with fibrous and fatty tissue, an aspect similar to that in arrhythmogenic cardiomyopathy, hence the risk of arrhythmias in COVID-19, especially the severe forms. If pericardial effusion is present it may exert a compressive effect on the heart leading to arrhythmias like bradycardia. Scars consisting of fibrous tissue give rise to arrhythmias by reentry mechanisms (Siripanthong, et al. 2020, 1464-1465).

Ischemia

Ischemia is well known for causing arrhythmias in the most varied form – from premature ventricular beats to ventricular fibrillation or conduction disturbances. In COVID-19 diagnosed patients ischemia results from the corroboration between previous atherosclerotic coronary disease and consequences attributable to pulmonary infection (Figure 2). As a result of the high inflammatory condition, fever and hypoxia generated by the pulmonary affection

and, also by the microthrombi caused by the associated procoagulant status, a mismatch between supply and demand appears. Fever causes an increase in plasma catecholamines, thus resulting in overactivity of the sympathetic nervous system, all of this causing tachycardia and contributing along with the other factors (inflammation and coagulation), to plaque vulnerability and rupture. Severe forms of pneumonia cause hypoxemia and that, in the end, contributes to myocardial ischemia and arrhythmogenesis.

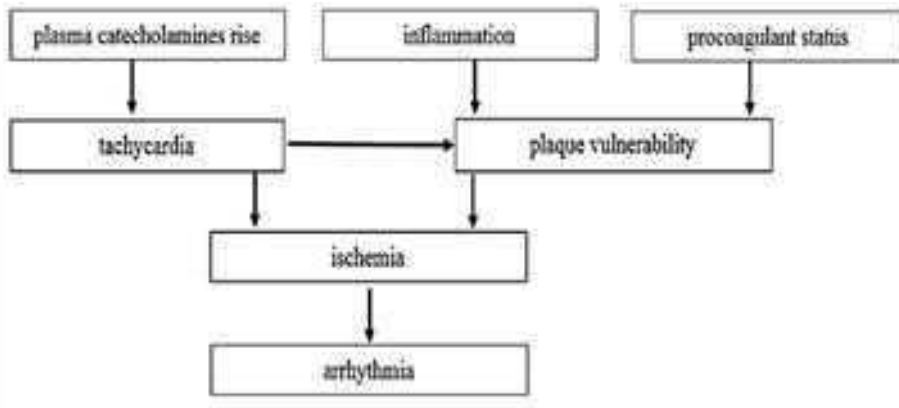


Figure 2. Mechanisms of ischemia in COVID-19.

Dyselectrolytemia

Disturbances in electrolyte balance, especially hypokalemia, cause life-threatening arrhythmias. Dyselectrolytemia occurs as a result of the consequences of viral infection: dehydration caused by fever and digestive manifestations (diarrhea, vomiting) and also by involvement of the systems that are responsible with electrolyte balance (renal, digestive, pulmonary). Special attention should be given to patients receiving thiazide, thiazide-like and loop diuretics because the hypokalemia is more pronounced in these cases.

Arrhythmias Caused by Therapy Used in COVID-19

COVID-19 treatments have known continuous dynamism since the beginning of the pandemic and most of them have cardiac side effects. Also, medication used in situations like shock or cardiac arrest caused by the disease need some attention in specific cases as we will see in this chapter. The alarm signal regarding cardiac side effects of therapeutic agents refers to the QT interval prolongation and the arrhythmias that can result from this. Using some therapeutic agents (summarized in the Table 3) that are known for prolonging the QT interval, can lead to life threatening ventricular arrhythmias of which, the most feared and with the most ominous outcome, is the polymorphic ventricular tachycardia in the form of torsade des points. Also, special attention should be given to combinations of drugs that double the risk for QT prolongation: using more drugs for treating the viral infection and, also, the concomitant use of antiarrhythmic drugs that are known for interfering with the QT interval, that is, mostly, amiodarone and sotalol, raise mortality risk especially in particular cases of congenital arrhythmias like long QT syndrome.

Table 3. Drugs implicated in QT prolongation

Drugs Known for QT Interval Prolongation	
Antibiotics	chloroquine/hydroxychloroquine quinolones macrolides
Antivirals	lopinavir/ritonavir favipiravir
Immunosuppressants	tocilizumab
Antiarrhythmics	class IA – quinidine, procainamide class III – amiodarone, sotalol

Chloroquine and hydroxychloroquine are two drugs with multiple effects, used firstly for malaria treatment, then for autoimmune disorders like rheumatoid arthritis or systemic lupus erythematosus and, since 1960s, for their antiviral effects. They prolong the QT interval and widen the QRS complex. Both chloroquine and hydroxychloroquine have cardiac side effects, the only difference between them, besides the chemical one, is that hydroxychloroquine has less ocular side effects.

Their effect on QT interval occurs as a result of the interaction with some potassium channels in the cardiomyocyte's membrane, thus lowering the transmembrane potassium currents. Emerging literature has shown that lethality is higher when giving chloroquine in high doses and for short periods of time. A study conducted on 81 patients diagnosed with severe forms of COVID-19 highlights the fact that high chloroquine doses should not be given to this kind of patients, especially in cases of combinations with other drugs that can interfere with the normal sinus rhythm. The 81 patients in the study were separated in two groups and each group has received different doses: the first group consisting of 41 patients was given high doses of chloroquine (600 mg twice a day for 10 days) while the rest received low doses of the same drug (450 mg twice a day in the first day and then only 450 mg per day for a period of 4 days). Results have shown that the first group had more cases of QT interval prolongation (defined as QT > 500 ms) compared to the rest (18.9% versus 11.1%), lethality on day 13 being higher for the first group (39% versus 15%) too (Borba, et al. 2020, 1-11).

Lopinavir/Ritonavir prolong not only the QT interval but also the PR interval leading, besides ventricular arrhythmias, to atrioventricular blocks so precautions should be taken when giving betablockers or non-dihydropyridine calcium channel blockers. These drugs also exhibit side effects on hepatic metabolism of other drugs, modifying the plasma levels of some antithrombotic agents, increasing that of ticagrelor, rivaroxaban and apixaban predisposing to bleeding, but decreasing that of clopidogrel and prasugrel, thus increasing the risk of thrombotic events. They also have effects on statins, increasing the plasma levels of atorvastatin, pitavastatin and pravastatin, yet with no effect on rosuvastatin.

Macrolides (azithromycin) increases QT interval by interfering with sodium and potassium channels, leading to myocyte overload with calcium. Apparently, azithromycin is responsible for polymorphic ventricular tachycardia in the absence of QT prolongation. Although other macrolide can increase plasma levels of some drugs that can also interfere with QT interval, azithromycin has no effect in this way.

Arrhythmias Caused by Non-Cardiac Associated Diseases and Specific Medication

Among noncardiac causes of arrhythmias, we consider that it is opportune to notice three situations: that of arrhythmias caused by endocrine disorders, postoperative atrial fibrillation and that of arrhythmias in pregnant women.

Endocrine disorders can contribute to developing arrhythmias, especially atrial fibrillation, and that happens mostly because of thyroid dysfunction although disorders like pheochromocytoma or those of adrenal cortex can also lead to changes in heart rhythm. Hyperthyroidism, defined as a hyperactive thyroid, with high levels of thyroid hormones and low levels of thyroid stimulating hormone, is one of the most frequent endocrine causes of arrhythmias, leading mainly to sinus tachycardia and atrial fibrillation. Although emerging literature does not connect the SARS-Cov2 infection with the new onset of thyroid disease, we recommend that a thorough assessment of thyroid function, including the evaluation of thyroid antibodies, should be made to raise awareness of cardiac complications associated with thyroid dysfunction.

Postoperative atrial fibrillation, named by the term “new onset atrial fibrillation” is the most common arrhythmia in the postoperative period. It is not caused by the surgical process itself but by the mixture of individual factors (hypertension, atrial dilation, fibrosis related to age) with the perioperative ones (anxiety, stress of surgery, pain, hypovolemia – all of these increasing the catecholamine levels and leading to sympathetic nervous system over activity; electrolyte imbalance – mostly hypokalemia) (Yadava, Hughey and Crawford 2016, 299-308). The reported incidence for postoperative atrial fibrillation differs for different types of noncardiac surgery, being the highest in noncardiac thoracic surgery (10-30%) and having moderate percentages for colorectal surgery (5-10%). In patients requiring surgery but diagnosed with COVID-19, we consider that the risk factors multiply because of pneumonia associated hypoxia and the metabolic disturbances occurring as the virus affects more systems.

Pregnancy is a special condition because at its center there are two lives to be taken care of, that of the mother and that of the fetus. This condition might increase the risk of COVID-19 and that of more severe forms of the disease because of the pregnant women’s intolerance to hypoxia caused by the series of anatomical and physiological changes they are facing: elevated diaphragm, increasing oxygen consumption, respiratory mucosa edema caused by hormone imbalance. Also, pregnancy can be complicated by cardiac disorders and arrhythmias are not to be excluded. The most frequent arrhythmias in pregnant women are supraventricular tachyarrhythmias while ventricular ones are rather rare, mostly seen in patients with inherited arrhythmogenic disorders and probably because pregnancy usually happens in young ages while the heart does not necessarily have structural damage. Arrhythmias in pregnant women are challenging even in normal conditions, without COVID-19, due to the teratogenic effects of therapeutic agents but the presence of the infection make it more difficult to assess and treat because COVID-19 increases the risk of dysrhythmia. Therefore, we recommend, in cases of this COVID-19-pregnancy-arrhythmia triad, that a pregnancy team consisting of cardiologist, gynecologist and infection disease doctors should evaluate the patient in order to make the best decision regarding the mother-fetus wellbeing.

Types of Arrhythmias in COVID-19 Patients

A survey study conducted by the Heart Rhythm Society from March until April 2020, addressed to electrophysiology professionals, has revealed the frequency of some arrhythmia in patients diagnosed with COVID-19. Among tachyarrhythmia, atrial fibrillation was the most common (20.79% out of 683 responders). Sinus bradycardia and complete atrioventricular block were the most common bradyarrhythmias (7.69% for each out of 663 responders). Yet, this study couldn't assert if these arrhythmias were prior to infection with SARS-Cov2 or were new. As regards life threatening arrhythmias secondary to therapeutic protocol 4.1% reported torsade des points in patients receiving the combination of chloroquine/hydroxychloroquine with azithromycin (Gopinathannair, et al. 2020, 1-8).

Supraventricular Arrhythmias

The study conducted by the Heart Rhythm Society has revealed different percentages for supraventricular arrhythmias in patients diagnosed with COVID-19 (Table 4).

Table 4. Types and incidences of arrhythmias in patients diagnosed with COVID-19

atrial fibrillation	20.79%
atrial flutter	5.42%
supraventricular paroxysmal tachycardia	5.71%
sinus bradycardia	7.69%
first degree AV block	2.71%
second degree, Mobitz I AV block	1.36%
second degree, Mobitz II AV block	1.81%
complete AV block	7.69%

Sinus tachycardia. In a study conducted on 54 patients sinus tachycardia was present in every patient in critical condition (18 patients – 100%) and in 23 patients (59%) of the 39 patients with severe form of the disease (Chen, et al. 2020, 800). There are many factors that contribute to it (fever, hypoxemia, anxiety, probably viral injury of vagal nerves) but the basis consists in sympathetic nervous system overactivity.

Atrial fibrillation. As mentioned above, most studies objected that atrial fibrillation is the most frequent arrhythmia in patients diagnosed with COVID-19. Yet, treating atrial fibrillation in these patients requires some precautions. Antiviral agents should be given with caution to patients receiving class IA and III antiarrhythmic drugs because of increased risk of ventricular arrhythmias. Also, anticoagulant therapy may require dose adjustments in patients treated with lopinavir/ritonavir.

An interesting aspect has been suggested by the Danish study of Holt et al. regarding newly diagnosed atrial fibrillation. They compared the percentage of people with new diagnosis of atrial fibrillation in the first three months of 2019 with that of the same diagnosis in the same first months of the year 2020, during national lockdown, and found out that in 2020 there was a drop of 49% regarding this matter. This is not necessarily a propitious fact because the outcome of these undiagnosed patients will, most probably, be hampered by the

complications of atrial fibrillation, that is thromboembolic events, heart failure, impaired quality of life (Holt, et al. 2020, 3074).

Both sinus tachycardia and atrial fibrillation require a full assessment of cardiac status (series electrocardiograms, echocardiography), renal and liver function, thyroid hormones, electrolyte balance (mostly serum potassium, calcium and magnesium), in order to identify possible causes that can contribute to these types of arrhythmia.

Sinus bradycardia and atrioventricular blocks. These types of disturbances can be caused by hypoxia in the excito-conductive tissue because of pneumonia and microvascular disease and by inflammation secondary to cytokine storm. Pavri et al. compared the electrocardiograms of 75 patients diagnosed with COVID-19 from before and after the diagnosis to observe the PR interval adjustment with heart rate; 38 patients (50.7%) had a normal pattern: PR interval shortening with high rates. The rest (49.3% - 37 patients) experienced either a stationary PR interval length or a paradoxical prolongation, those with this abnormal pattern having a poor outcome – 11 of them died and 16 needed endotracheal intubation. By comparison, of the 38 patients with normal PR pattern, only 3 died and 8 needed to be intubated (Pavri, et al. 2020, 1434).

Ventricular Arrhythmias

As mentioned above, a series of factors contribute to ventricular arrhythmias in patients diagnosed with COVID-19 but a central role is that of long QT leading to ventricular tachycardia. In patients with long QT previous to COVID-19 treatment (either congenital or acquired), administering more than 1 drug which can further contribute to QT prolongation, increases the risk for life threatening ventricular arrhythmia. Also, using combinations of drugs can lead to increasing plasma levels of those causing QT prolongation, hence the arrhythmia risk increasing. Torsade des points is one of the most severe and feared form of ventricular tachycardia so precautions need to be taken as follows:

- calculation of QTc by Bazett formula before giving any drug that can interfere with QT duration; remember that QTc is abnormal when is >440 ms in men and >460 ms in women; Bazett formula: $QTc = \frac{QT}{\sqrt{RR}}$
- calculation of Tisdale score (Table 5) can suggest the risk of (further) developing long(er) QT
- holding back from giving drugs that can further prolongs QT interval in patients with long QT syndrome or with QTc > 500 ms;
- withholding any QT prolonging drug when the QTc has increased >500 ms or >60 ms comparing to base value of QTc;
- comparing the electrograms before and after therapy initiation;
- assessing serum potassium levels, renal and liver function;
- electrocardiographic monitoring, including telemedicine;
- treating every factor that can contribute to QT prolongation (hypokalemia, hypomagnesemia).

Table 5. Tisdale score

Risk factors	Points
age ≥ 68 years	1
female sex	1
loop diuretic	1
serum $K^+ \leq 3,5$ mEq/L	2
admission QTc ≥ 450 ms	2
acute MI	2
≥ 2 QTc prolonging drugs	3
sepsis	3
heart failure	3
1 QTc prolonging drug	3
maximum risk score	21
Low risk	≤ 6
Moderate risk	7-10
High risk	≥ 11
K^+ = potassium, MI = myocardial infarction	

Starting from the algorithm proposed by Wu et al. for initiating, supervising and withdrawing therapy with arrhythmogenic potential in patients with COVID-19 (Wu, et al. 2020, 1459), we suggest the following approach (Figure 3).

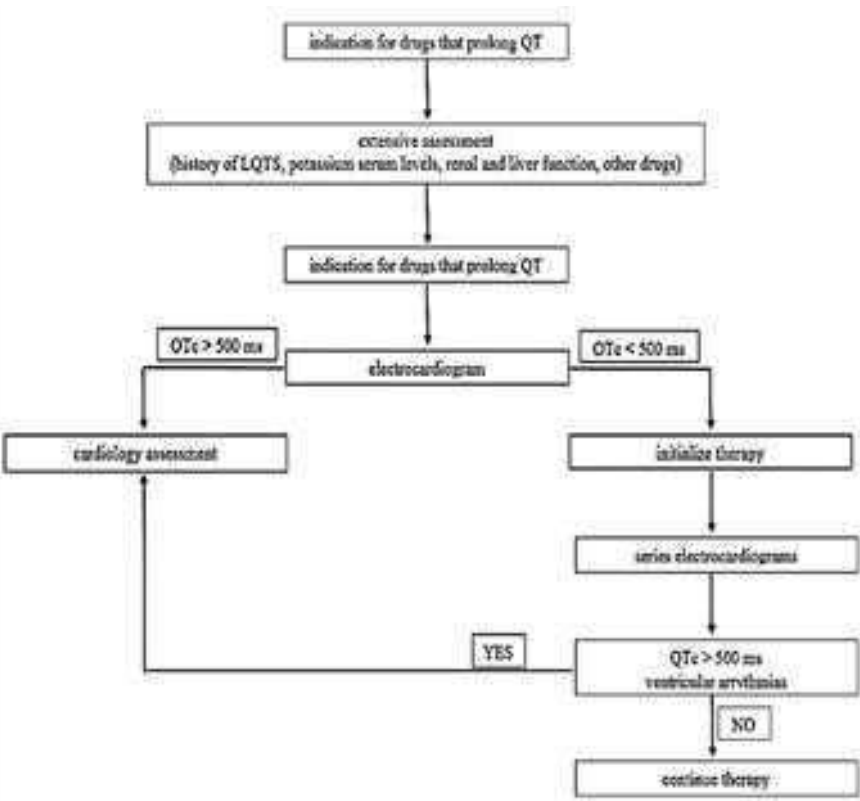


Figure 3. Algorithm proposed for follow-up of arrhythmogenic potential in patients with COVID-19.

A separate category is that of patients suffering from congenital syndromes others than long QT syndrome, which can lead to life threatening arrhythmias, those being Brugada syndrome and catecholaminergic polymorphic tachycardia.

In patients with Brugada syndrome, a congenital channelopathy, fever is known for leading to ventricular arrhythmias and sudden cardiac death and this is why it must be aggressively treated with antipyretics. Also, these patients should be placed under permanently electrocardiographic monitoring and be admitted, regardless of the form of the infective disease, in wards that have quick access to cardiac defibrillators so that medical staff could intervene promptly in cases of hemodynamically unstable arrhythmias or cardiac arrest.

As Wu et al. mention in their paper, patients with catecholaminergic polymorphic tachycardia are not at high risk if receiving the treatment for COVID-19 but they require precautions if therapy for hemodynamic support or resuscitation is needed and that because adrenaline and the other inotropic agents (noradrenaline, dopamine) cause episodes of tachycardia (Wu, et al. 2020, 1460-1461).

TELEMEDICINE IN PATIENTS WITH ARRHYTHMIAS

General Aspects of Telemedicine

Telemedicine is an umbrella term used to describe a broad variety of diagnostic, therapeutic and real-time monitoring means without involving the physical interaction between the patient and healthcare workers. Devices like smartphones or computers permit audio-video connection, while watches, wireless devices with sensors and electronic, bracelet-like devices can record and transmit physical parameters from the patients. Technology provides both advanced software and hardware components that offer qualitative recordings and artificial intelligence algorithms, to reveal only the significant information. Therefore, it is important to understand how technology works in order to see its limitations and potential sources of error (Varma N et al. 2020, 1363-1374).

A remote monitoring system is obtained when 3 major components are put together. At first, *wearable sensors* that collect specific data from the patient's skin will be placed. Then, this data will be transmitted via a *secured network* or through a special platform to a remote monitoring station where an *analytic program* based on artificial intelligence separates relevant, critical information from the redundant one and suggests possible therapeutic options. After that, physicians can let the patients know their decisions and further recommendations through a teleconferencing platform (Sana F et al. 2020, 1582-1592).

CIED's (cardiovascular implantable electronic device) interrogation offers high quality information for diagnostic and therapeutic purposes, whilst artificial intelligence is capable of sorting and organizing all the data collected from the patients and then offering diagnostic suggestions for primary care physicians or nurses. Real-time transmission is possible through secured lines and all the recorded data is sent to the patient's personal file and to the healthcare worker's computer. A new support system that facilitates clinical decisions has been implemented. CDSS (clinical decision support system) consists in a computer-based system, which processes the data received from the patients, and offers solutions to the identified issues, thus assisting the healthcare workers and optimizing the patient's

management. Early detection of life-threatening conditions, such as arrhythmias or chest pain, permits early interventions, redirecting initial diagnosis and treatment from the emergency units into primary care facilities is an option to seriously consider (Nielsen J et al. 2020, 1147–1148).

In order to understand how human sensors work, a lot of knowledge about technology and physics is required, but some basic principles are further enumerated. *Ballistocardiogram-based* technology detects repetitive movement such as heart beat or blood ejection. *Accelerometer-based* approaches are used for heartbeats and blood circulation, detecting small motions over the skin's surface, although artifacts occurrence is not a rare thing. *Photoplethysmography* signals provide information about the heart rate, but concerns about this method's accuracy have been formulated. *Phonocardiography* evaluates heart sounds, while *seismocardiography* is used for vibrations. Sensors that detect heart rate or skin's temperature can appreciate the patient's level of stress. Hospitalized patients can benefit from telemedicine through smart beds that do not need wires and limit the device-to-skin contact (Epstein AE et al. 2013, 283-352).

Telemedicine appeared as a need to reduce the burden on the medical staff and emergency care units and is not intended to replace the conventional ECG evaluation, but to give qualitative, easily accessible cardiac expertise without the disadvantage represented by distance. When telemedicine services are applied to home-based patients, they tend to be separated into two categories: those who can be monitored at home with minor therapeutic adjustments and those who must be admitted to hospital, because they demand invasive treatments or continuous surveillance. It is possible now to instantly transmit a 12-lead ECG from patient's home directly to cardiologist's computer, this system being already implemented in emergency and clinical cardiology services. One-lead ECG evaluation represents another way of monitoring the patients in places with limited resources, but an underestimation of QTc may appear when using this method. Doctors evaluate the recordings they receive and correlate them with the clinical presentation, offering a telephonic and written interpretation and possible treatment options according to the resources offered by local practices. In case of chest pain, for example, sending patients to the hospital without an ECG already performed is a stressful and time-consuming approach (Maraj I et al. 2020, 1904–1907).

In home monitored patients, it is assumed that patients alone may not place the electrodes on their chest correctly, so an initial visit to the hospital is necessary, because malposition of the electrodes is a source of errors during the recording and generates multiple artifacts. After that, the specialist's interpretation is a must, because clinical correlations and other biologic parameters may influence further therapeutic decisions. There is a chance of not being dependent on an internet connection, because the majority of devices permit an offline analysis of what they recorded.

Telemedicine, at least in a videoconference form, is highly required for emergency services, on aircraft, ships or in the case of people who live in remote locations or in isolated areas that are covered by internet connection (islands, tropical regions, mountainous region, especially during winters). Emergency services combined with telemedicine, through 4G mobile cellular systems and satellite services, permit paramedics to send the patient's data to the hospital and therefore allow doctors to analyze and prepare for the up-coming emergencies (Figure 4), especially in case of car accidents that generate multiple traumas, leading to a decrease in car accidents deaths (Sana F et al. 2020, 1582-1592).

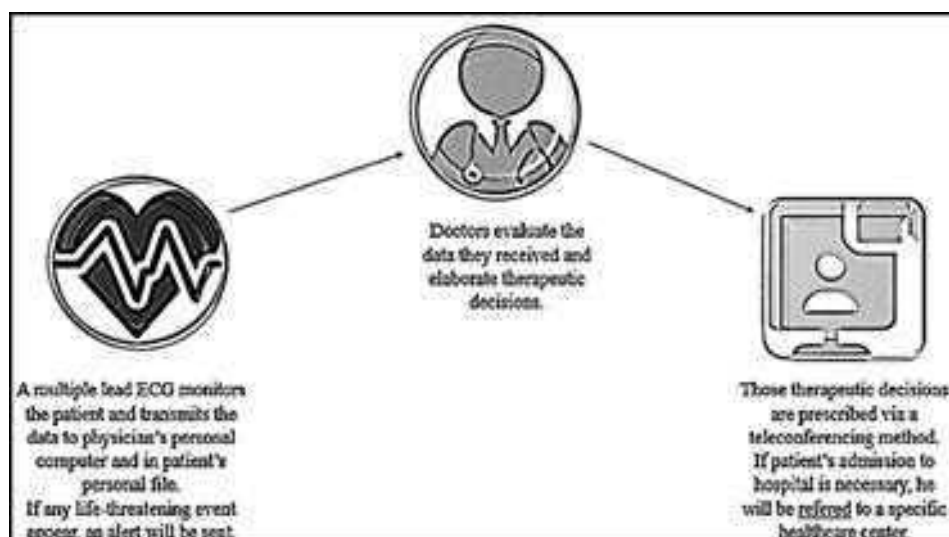


Figure 4. Schematic representation of telemedicine services.

When an ambulance arrives at the scene, health personnel can transmit essential data (real-time images and videos, physical parameters) simultaneous with providing pre-hospital life-saving care. An increase in QALY (quality-adjusted life year) achievable through prehospital diagnosis is revealed in some studies. Studies show that younger subjects are more comfortable than older patients about sending personal data to physicians through technology, but they require less medical care services.

Telemedicine is a more permissive way to diagnose arrhythmias and permits left ventricular dysfunction assessment. It is able to evaluate the efficacy of antiarrhythmic therapy or the proarrhythmic side effects of patient's medication. However, automated interpretations are not sufficiently accurate without the expert's review, especially in the presence of rhythm disturbances or complex abnormalities. It limits the time of exposure between the doctor and the patient and offers a complete overview of the disease. It is also a competitive method for triage and has screening potential (Lieberman J, 2008, 123-126). An important application is pacemaker interrogation or automatic intracardiac defibrillator function assessment, leading to an optimal device monitoring and lowering the risk of inappropriate shocks related to these devices. Information about some forms of cardiomyopathies, myocardial ischemia or congestive heart failure can also be obtained. The importance of online platforms like Patients Like Me (<https://www.patientslikeme.com/>) cannot be neglected. This system facilitates connections between patients and increases therapeutic compliance, optimism and overall patient's education about their own disease, especially in the case of rare disorders.

A major issue that healthcare workers were confronted with was the validity of digital forms of written consent. Although this new kind of medical services is extremely permissive, verbal consent offered at the beginning of the consultation may not be enough. Patients need to be assured that their data and medical history are very well kept and a list of the departments that have access to their personal information should be provided to them every time they ask. Considering this, patients will receive some pre-evaluation documents to read and then, after they sign it, an e-mail with filled documents will be directed to physician's

computer. If they agree and sign this form of consent, healthcare providers are covered from further misunderstandings.

Although technology is evolving at a fast pace, another concern comes to light. Studies show that patients are frequently worried about their privacy, security and data ownership and do not always feel confident with their parameters being continuously recorded and transmitted to physicians and healthcare insurance companies. The recent European Union's GDPR (General Data Protection Regulation) came to limit these concerns, rigorously informing the patients and clarifying what can and cannot be done with the patient's private information, so the best interest for patients is permanently sought (Nielsen J et al. 2020, 1147–1148).

Another issue is finding a fair equivalent between the physical consultation and the telemedicine one, regarding costs and material resources usage. This pandemic found our National Healthcare services in a state where pre-defined costs were very well established for every type of consultation and procedure. This was not applied for telemedicine services too, where doctors and hospitals were challenged to adapt the way they used knowledge and resources. Financial support for hospitals is now most needed and lower income due to fewer hospitalizations and maybe cheaper telemedicine services are not something desirable.

Types of Devices Used in Telemedicine

Devices like Holter ECG's and ABPM's (ambulatory blood pressure monitoring) have a long history of use, but they have some disadvantages: their size and the likelihood to miss a rare event if it doesn't appear during the recording time. Therefore, devices that permit longer evaluation and higher quality recordings were introduced as a part of healthcare services (Table 6 and 7).

The Zio patch (iRhythm Technologies®, San Francisco, California) is a waterproof, long-term monitoring, adhesive patch, frequently applied to the left pectoral region. It generates a single lead ECG recording and has higher effectiveness in diagnosing arrhythmias, especially in the case of rare events. Palpitations, dizziness or syncope represent indications for these devices. The fact that it can be used for up to 14 days straight without recharging or changing the batteries and that it offers off-line analysis, are important advantages. An event marking button can be manually pressed by the patients when symptoms appear. At the end of the 14th day, patients send back the device to the healthcare services provider for interpretation and further recommendations.

On the other hand, NUVANT Mobile Cardiac Telemetry (MCT) (Corventis®, San Jose, California) is also a wearable monitoring patch provided with an event marking option for symptoms, but it offers wireless and real-time analysis of the rhythm disturbances.

Scanadu Scout (Scanadu®, Sunnyvale, California) is a more performant device that evaluates multiple physiological parameters such as heart and respiratory rate, blood pressure, oxygen saturation and temperature and has additional capacities for displaying, storing and even analyzing recorded data.

Table 6. Health platforms (modified from Varma et al. 2020, 1363-1374)

HIPAA- or PHI-secure telehealth platform	
Short name	Online access site
AccuRx	https://www.accurx.com
AMD Global Telemedicine	https://www.amdtelemedicine.com/telemedicineproducts/Working-ClinicTelemedicine.html
Attend Anywhere	https://www.attendanywhere.com
BlueJeans for Healthcare	https://www.bluejeans.com/use-cases/healthcare
Care Connect by KRY/LIVI	https://www.kry.care
Caregility	https://caregility.com/uhe-applications
Cisco Webex	https://www.webex.com/webexremotehealth.html
ClickDoc	https://www.cgm.com/be/index.fr.jsp
Conexa Saude	https://www.conexasaude.com.br
Docobo	https://www.docobo.co.uk
Doctena	https://secure.doctena.com
Doctorlink	https://www.doctorlink.com/video-consultation
Doximity	https://www.doximity.com
Doxy.me	https://doxy.me
EMIS Health Video Consult	https://www.emishealth.com/products/videoconsultation
Exprivia	https://www.exprivia.it
FaceTalk	https://facetalk.nl
Google G Suite	https://gsuite.google.com/industries/healthcare
Helena	https://qa.helena.care
Intersysto	http://www.intersysto.eu
InTouch Health	https://intouchhealth.com/telehealth-solutions
pMD	https://www.pmd.com/secure-messaging-telemedicine
M Teams/Skype for Business E3 and E5	https://www.microsoft.com/enus/microsoft365/microsoft-teams/healthcare-solutions
Signal	https://signal.org
Spruce	https://www.sprucehealth.com
TeleMedi	https://telemеди.be
Updox	https://www.updox.com
VSee	https://vsee.com
Zoom for Healthcare	https://zoom.us/healthcare
Videoconferencing platforms (not HIPAA/PHI secure)	Non-public-facing mobile communication platforms (not HIPAA or PHI-secure)
Skype	Apple FaceTime
GoToMeeting	Google Duo, Google Hangouts
Zoom	WhatsApp

EMR = electronic medical record; HIPAA = Health Insurance Portability and Accountability Act; PHI = protected health information.

Smart-phone applications like Pulse-Smart (Pulse Smart®, University of Massachusetts Medical School, Worcester) and others can detect atrial fibrillation by trans-illuminating the right index fingertip using phone camera light. It ensures an important accuracy to discriminate between atrial fibrillation, sinus rhythm, premature atrial or ventricular contractions. A 12-lead ECG device called cvrPhone (Massachusetts General Hospital, Boston, Massachusetts) has the capacity of discriminating apnea events and can evaluate pro-arrhythmic or ischemic risk and even the risk for sudden cardiac death. Another kind of ECG-recording device based on mobile phones is AliveCor's Kardia Mobile (AliveCor®, Mountain View, California). Studies show that it is a better registering device than external loop recorders and can detect atrial fibrillation relatively fast. Wearable devices can also contribute to risk stratification in AF, but there are concerns regarding false positive results in

asymptomatic patients. (Varma et al. 2020, 1363-1374) ECG Check (Cardiac Designs®, Park City, Utah) uses also a smart-phone application and registers a single-lead ECG directly on the screen, instantly redirectioning it to the physician.

Table 7. ECG recording devices (modified from Varma 2020, 1363-1374, Sana et al., 2020, 1582-1592)

	Device	Type	Additional features	Website
Handheld devices	AliveCor	Wireless	ECG monitoring, AF detection Cleared for AF (1-lead) and for QTc (6-leads)	https://www.alivacor.com/kardi
	KardiaMobile			amobile
	Beurer ME 90	Wireless Bluetooth	1-lead ECG	https://www.beurer.com/web/gb/products/medical/ecgand-pulse-oximeter/mobileecg-device/me-90-bluetooth.php
	Cardiac Designs ECG Check	Wireless	1-lead ECG Smartphone case	https://www.cardiacdesigns.com
	Cardio Comm Solutions HeartCheck	Wireless	1-lead ECG	https://www.theheartcheck.com
	CardiBeat and ECG Pen			
	COALA	Wireless	1-lead ECG Remote lung auscultation	https://www.coalalife.com
	Eko DUO	Wireless	1-lead ECG Remote cardiac auscultation Phonocardiogram	https://www.ekohealth.com
	Omron Blood Pressure + EKG Monitor	Wireless	United States and Canada only 1-lead ECG + BP cuff	https://omronhealthcare.com
	EKGraph	Wireless	1-lead ECG	https://sonohealth.org
Mobile cardiac telemetry devices	Scanadu Scout	Handheld	HR, RR, blood pressure, temperature, O ₂ saturation	
	NUVANT MCT	Patch	ECG monitoring Arrhythmia detection	https://www.getqardio.com/qard
	BardyDx CAM	Patch	1-lead ECG Under clinical investigation for QTc monitoring in COVID-19 patients	https://www.bardydex.com
	BioTel Heart	Patch	1-lead ECG FDA cleared for QTc monitoring	https://www.myheartmonitor.com/device/mcot-patch
	iRhythm Zio patch/Zio AT	Patch	1-lead ECG monitoring Arrhythmia detection	https://www.irhythmtech.com
	InfoBionic MoMe	Wired	3-lead ECG	https://infobionic.com
	Kardia		Remote lung auscultation	

	Device	Type	Additional features	Website
Smart-watches	MediBioSense	Patch	1-lead ECG	https://www.medibiosense.com
	MBS		Monitors up to 8 vital signs	
	HealthStream, VitalPatch, MCT			
	MedilynX	Wired	3-lead ECG HRV	https://www.pocketecg.com
	PocketECG			
	RhythMedix	Wired	3-lead ECG	https://www.rhythmmedix.com
	RhythmStar			
	Pulse-Smart	Smartphone camera based app	AF PAC PVC detection	
	cyr Phone	Smartphone app	ECG monitoring Ischemia and apnea Detection	
	Masimo	Personal Health Smartphone	Arrhythmia susceptibility Connected probe HR SpO2	
Other Devices	Apple Watch	Wristwatch	1-lead ECG FDA cleared for AF detection and notification ECG monitoring, HR	https://www.apple.com/watch
	Withings Move ECG	1-lead ECG	Requires Health Mate app ECG Analysis and AF detection	https://www.withings.com/us/en/move-ecg
	Google	Glass Head mounted	HR, RR	
Other Devices	-	Smartphone connected device	HR Blood pressure	
	-	Flexible patch	Blood pressure	
	-	Patch and wristwatch	ECG Blood pressure	

AF = atrial fibrillation; AZM = azithromycin; BP = blood pressure; ECG = electrocardiogram; FDA = Food & Drug Administration; HCQ = hydroxychloroquine; HR = heart rate; HRV = heart rate variability; RR = respiratory rate.

As regards oxygen's saturation monitoring, when studies compared standard pulse-oximetry to phone apps like Pulse Oximeter (DigiDoc®, Egersund, Norway), a camera-based app, or Masimo Health (Masimo®, Irvine, California), a probe-based app, results showed the non-inferiority in the first case and the superiority of probe-based devices (Varma et al. 2020, 1363-1374).

Implantable loop recorders (ILR) are small, placed under the skin devices, used for recording heart's electrical activity. These devices are used in patients with uncertain origin, rare and recurrent syncope in the absence of high-risk criteria. Another indication is in patients with high risk criteria in whom ambulatory or previous in-hospital evaluation did not identify a cause or lead to a treatment and also do not have an indication for implantable cardiac defibrillator (ICD) or pacemaker implantation. An ILR can also be considered in patients with dizziness, palpitations, frequent premature ventricular complexes or non-sustained ventricular tachycardia and in those with suspected AF or previous AF ablation.

**Table 8. ECG recording devices - benefits, performance and limitations
(modified from Sana et al. 2020, 1582-1592)**

Device's name	Benefits	Reported performance and limitations
Zio Patch	Up to 14 days utilization without battery replacement or recharge	No real-time analysis/ transmission Higher accuracy than Holter monitors;
NUVANT MCT	Real-time analysis/ transmission	Real-time data Not available to the user
Scanadu Scout	Real-time analysis Available to the user	The device is no longer used
Masimo Personal Health	Portable method to evaluate oxygen saturation Cost-effective, Noninvasive	Higher performance than standard pulse-oximetry
-	Used to perform 6-min walk test	Detects dynamic changes in cardiopulmonary function during the test
Google Glass	Higher accuracy (gyroscope vs. accelerometers)	Low mean absolute error: 1.18 beats/min for the HR 0.94 breaths/min for the RR
-	Cuff less blood pressure measurement	Precision errors: 3.3 and 8.8 mm Hg for systolic -5.6 and 7.7 mm Hg for diastolic BP
cvrPhone	Cardio and respiratory event detection	Ischemia detection within 2 min of occlusion Apnea detection within 7.9 - 1.1 s
ECG Check	Single-lead ECG Real-time analysis and transmission	Ventricular escape beat detection: sensitivity of 93.91% and predictability of 94.12%
Kardia Mobile	AF detection in less than 30 s	100% diagnostic accuracy (72.7% with external loop recorder)
Apple Watch	Lightweight Easy to operate	Patients with silent AF Sensitivity of 87% and specificity 97%
Pulse-Smart	Uses standard smartphone camera and flashlight, real-time analysis	Irregular pulse identification PAC and PVC discrimination

A novel approach is represented by in-hospital telemetry, used for high risk-patients, which also uses smart devices and may be continued even after discharge, facilitating prolonged, intensive evaluation of heart rhythm and other individual parameters such as peripheral oxygen saturation, heart rate, blood pressure and sleep quality. In-patients are frailer and may suffer acute degradation of the cardiovascular status evolving in life-threatening conditions. In their case it is very important to reduce the interactions with healthcare workers, especially if an immunosuppressed status is associated (Sana F et al. 2020, 1582-1592).

Telemedicine in Supraventricular and Ventricular Arrhythmias

Atrial fibrillation (AF) is the most frequent supraventricular arrhythmia found in patients, with a prevalence of 2% and an incidence range between 0.21 and 0.41 per 1,000 person/year, according to guidelines. AF's simplified management was proposed to cover all the concerns this disease poses and requires three main steps:

“A” Avoid Stroke with anticoagulation;

“B” Better symptom management, with a symptom-directed and patient-centered attitude regarding both the control of rate and rhythm; and

“C” The management of Cardiovascular disease and Comorbidities. Firstly, a 24h Holter ECG is recommended and if AF remains undetected although the patient continuously declares symptoms, further investigation is recommended. (Linz D et al. 2020, 1954-1955).

In case of a cryptogenic stroke, early implantation of a loop recorder that provides continuous monitoring may be the optimal decision, especially in elderly patients with cardiovascular risk factors. An important alternative is represented by trans-telephonic ECG-monitoring, external loop recorders or cardiac event recorders. Cryptogenic stroke is defined as an ischemic stroke whose etiology is still undetermined. Although its diagnosis is made by exclusion, a major cause for cryptogenic strokes is represented by undetected paroxysmal AF. Other causes are paradoxical embolism through a patent foramen oval or atherosclerotic lesions of the aortic arch, so a trans-thoracic and a transesophageal echocardiography can clarify the diagnosis and lead to a treatment (Linz D et al. 2020, 1954-1955).

Another important project is TeleCheck-AF that monitors heart rate and rhythm of patients with atrial fibrillation and offers support without the need of their presence in the hospital. It is represented by three important parts: *a structured teleconsultation*, an *app-based on-demand heart rate and rhythm monitoring infrastructure* and *comprehensive AF management*. The on-demand monitoring infrastructure consists in a photoplethysmography-based smartphone application (www.fibricheck.com) that permits a semi-continuous heart rate and rhythm evaluation of AF patients before and during the teleconsultation. The patients download the application and are instructed to evaluate their heart rhythm and rate three times daily and note correlated symptoms. All recorded data are sent via cloud, through a secured network to the physician's database for 7 days in a row and orientate the physician in indicating a treatment. Finally, the doctor re-evaluates the patient via teleconferencing and gives his recommendations (Linz D et al. 2020, 1954-1955).

Patients with unexplained syncope or during hemodialysis represent another important indication for implantable loop-recorders, because they associate a higher risk for ventricular arrhythmias and sudden cardiac death.

Telemedicine in Patients with Inherited Arrhythmia Syndromes

Brugada syndrome (BrS), Long QT syndrome (LQTS), Short QT syndrome (SQTS) and Catecholaminergic polymorphic ventricular tachycardia (CPVT) are the main types of inherited arrhythmia syndromes. Antiarrhythmic therapy and the administration of pro-arrhythmic side effect drugs are particularly challenging in these patients, so a careful monitorization is necessary. Telemedicine finds its importance in these pathologies, facilitating better healthcare and increasing survival rate in these patients (Wu CI et al. 2020, 1456-1462).

Brugada syndrome is a familial condition included in the broad spectrum of channelopathies, characterized by the type 1 ECG pattern: coved-type ST-segment elevation, J point elevation of at least 2mm and T-wave inversion in V1 and/or V2 lead. It appears due to a genetic mutation in alpha subunit of the cardiac sodium channel (SCN5A) often causing the loss-of-function in sodium channels, although other 12 mutations can be responsible for this syndrome. The absence of structural heart disease and an increased risk for ventricular fibrillation are also characteristic. Atrial fibrillation is the most frequent supraventricular

tachycardia found in these patients and comes with an important rate of inappropriate shocks when devices are used in these patients (Wu CI et al. 2020, 1456-1462).

Young patients (<45 y.o) with a family history for sudden cardiac death, often during the night is the scenario frequently presented. Type 2 and 3 of BS cannot be diagnosed with the surface ECG (although a saddle-shaped ST segment with or without elevation can be observed) and need an Ajmaline or other sodium channel blocker diagnostic test to induce the type 1 ECG aspect. Drug induced forms of BrS may also appear. Fever, especially in children, may reveal this syndrome and generate life-threatening arrhythmic events because of the sensitivity to temperature in sodium channel function. Patients with BrS should take paracetamol immediately when fever appears, those without an implantable cardiac defibrillator being at higher risk. If the temperature is over 38.5°C, emergency care should be sought, with some exceptions.

LQTS is characterized by excessively prolonged ventricular repolarization and comes with an increased risk of malignant arrhythmias such as torsade de pointes (TdP), ventricular tachycardia (VT) that may degenerate into ventricular fibrillation (VFib) and sudden cardiac death. It is an inherited pathology that is frequently revealed during childhood, so genetic testing should be performed within families when a case is discovered. Mutations in genes encoding ion channels (more often *KCNQ1*, *KCNH2* and *SCN5A*) cause electrical instability within the myocardium and an additive effect of acquired *LQTS*'s causes (such as hypokalemia, hypothermia or fever, sepsis, myocardial ischemia and a broad range of drugs) are demonstrated. Since fever and electrolytes imbalance are capable of inducing rhythm disturbances, antipyretic treatment and metabolic homeostatic status are highly recommended (Wu CI et al. 2020, 1456-1462).

Before initiating a QTc prolonging drug and after two doses of the drug an ECG assessment is mandatory and can reveal „QTc reactors”- like the patients with normal ECG's before treatment that show an intense response in QT prolongation when exposed to particular contexts. A QTc measured in 12 leads (or at lead DII and V5) and calculated through Bazett formula that exceeds 450 ms in men and 460 ms in women is considered to be prolonged. Thus, patients that undergo a QTc prolonging treatment will be separated into two groups given the risk of developing life-threatening arrhythmias: lower risk patients vs. higher risk patients. Patients considered to have a low risk for ventricular arrhythmias under QT-prolonging medication may be monitored with wearable digital devices that transmit twice daily and are capable of alerting the physician in case of an emergency (Figure 5).

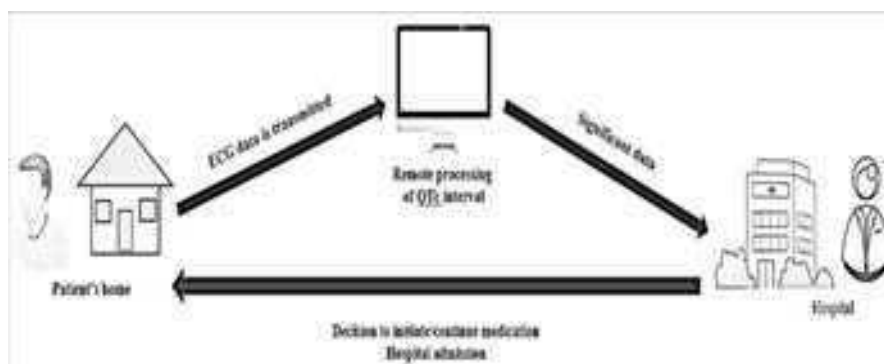


Figure 5. Schematic representation of telemedicine services.

When referring to patients that are at a high-risk for QT-prolongation, long-term monitoring through telemetry and constantly evaluation of QTc interval is necessary. QTc must be evaluated at least before and after 24h, 48h and 96h from the treatment's initiation. If an increase of QTc higher than 60ms or a QTc > 500ms is detected, an important chance for ventricular arrhythmias appears, so a careful reassessment of risks over benefits in continuing the treatment is the next step to take.

Although there is a small subset of young patients with long QT-syndrome, their screening is an important matter, so when a suspicion arises, further tests should be recommended. Reversible causes for QTc prolongation will be identified and corrected rapidly. Some studies evaluated three main groups of patients while receiving hydrochloroquine alone, hydrochloroquine combined with azithromycin and compared them with placebo. Smart devices that registered a 6-lead-ECG were offered to the patients and the QTc interval was measured several times during the day. The recordings were sent to a remote QTc monitoring site, and if an increased QTc value was detected, physicians were notified. Telemedicine via smartphones turned out to be a simple, innovative and cost-efficient method to evaluate cardiovascular patients.

SQTS is an extremely rare disease caused by mutations of different types of potassium channels or in cardiac chloride-bicarbonate exchanger gene, and comes with a risk for ventricular arrhythmias.

CPVT is an inherited, autosomal dominant disorder that is frequently revealed during effort or stress, caused by some pathogenic variants in the human ryanodine receptor type 2 on a normal structural heart. Patients are often young adults or children that declare an episode of syncope. Syncope appears due to arrhythmic events like bidirectional ventricular tachycardia, polymorphic ventricular tachycardia or ventricular fibrillation generated by emotional or physical stress. Resting ECG shows a normal aspect or sinus bradycardia, but effort testing or i.v catecholamine infusion reveal the abnormalities and are diagnosed. Intensive treatment with beta-blockers is the option of choice, followed, if necessary, by flecainide administration or left sympathetic denervation. Implantable cardiac defibrillators are not usually recommended and intense emotions, effort, stress or sympathomimetic drugs need to be avoided. If an ICD is placed, there is a high risk that missed detected AF episodes will result in inappropriate shocks and pro-arrhythmic events, even death, therefore periodic, non-invasive surveillance is recommended. Telemedicine implications and necessity in these patients are demonstrated (Epstein AE et al. 2013, 283-352).

Telemedicine in Heart Failure

Heart failure exceeds 26 million cases globally, 74% of these patients having at least one additional comorbidity. Daily evaluation of weight gain does not correlate precisely with the debut of cardiac decompensation, but it is a valuable marker and in the case of an increase, over 1 kg per day, medical assistance should be sought (Gensini GF et al. 2020, 116–121).

Although telemedicine may be a very useful tool in the case of these patients, the fact that 80% of them are older than 65, slows the implementation of these techniques. Telemedicine's tools frequently require some knowledge about smart devices and computer science. In some cases, younger family members offer permanent assistance and facilitate smart device usage.

A non-invasive multidetector external device can be used to measure and immediately transmit bio-impedance parameters, physical activity duration and intensity, heart and respiratory rate, blood pressure and SpO₂. These parameters are frequently sent alongside with a predefined questionnaire in which patients declare the presence of edema, dyspnea, fatigue, dietary changes, adherence to treatment or side effects appear during the day. The information obtained from the patients is sorted by informatized programs and, after that, by qualified nurses or primary care physicians and if suggestive elements for cardiac decompensation appear, specialist physicians receive all the recorded data (Gensini GF et al. 2020, 116–21).

AF and heart failure share many common risk factors, so screening AF through frequent interrogation or remote monitoring of stored data in patients with HF can reduce the supplementary burden that is AF in HF patients. The majority of the studies show earlier intervention, a decrease in decompensating rate and an overall reduction in symptoms control and mortality from heart failure.

Telemedicine in Inherited Cardiomyopathies

Inherited cardiomyopathies like Fabry disease require a careful monitoring for life-threatening arrhythmias and sudden cardiac death. Fabry disease represents a rare, X-linked genetic anomaly of glycosphingolipid metabolism, caused by absent or severely deficient activity in lysosomal enzyme, α -galactosidase A. This disease affects the cardiac muscle by the progressive appearance of fibrosis, with an increased risk for arrhythmias, due to the electrical instability and dispersed refractory periods in the myocardium, that are rarely observed on a 24h ECG monitoring. Although a precise correlation between the location, quantity of fibrosis and the types of arrhythmias cannot be made, it seems that mid-ventricular fibrosis is linked to more cases of ventricular tachycardia (Weideman F et al. 2016, 264-274).

Weidemann et al. pinpoint clinically relevant arrhythmias in the case of Fabry disease patients: bradycardia (HR < 40 beats/minute during daytime)- for this patients an indication for pacing therapy is made; ventricular pauses (>3 seconds during daytime), also with an indication for pacing therapy; sustained or symptomatic non-sustained ventricular tachycardia, that come with an indication for ICD implantation; and finally, episodes of atrial fibrillation longer than 3 minutes who comes with an indication for anticoagulation therapy.

Considering this, permanent monitoring in Fabry disease patients becomes necessary in their multidisciplinary care algorithm, especially when they complain of palpitations, dyspnea or angina and the 24h Holter ECG does not reveal significant aspects. The place of telemedicine in this case is clear and loop-recorder devices with daily transmission to physicians are important surveillance options and should be a part of their routine clinical care. Telemedicine is to be included in primary prophylaxis of syncope and sudden cardiac death. However, the number of cases that undergo a change in clinical management is yet to be determined (Weideman F et al. 2016, 264-274).

Telemedicine in the Case of Implantable Cardiac Defibrillators and Pacemakers

Another important role of telemedicine is represented by the evaluation of ICDs, pacemakers, implantable loop recorders and CRTs (defined as CIED-cardiac implantable electronic devices), that will always be made by a fully trained physician in device implantation and follow-up. Home monitoring of implantable cardiac defibrillators with remote data access through wireless network will reduce the number of visits during a year and the annual cost of care, especially when the patient is located at longer distances. However, telemedicine cannot entirely replace clinical visits, although the information obtained is accurate and can be formatted, analyzed, easily stored and accessible. Generally, an evaluation that is made every 6 months is sufficient and safe, but there are some situations when a shorter time between presentations is required. Also, it increases the necessity of qualified staff, due to the higher amount of information that is obtained from the patients. Each manufacturer provides guidelines for appropriate device interrogation, recommended time between evaluations and potential problems associated with the device. Interrogation systems vary with the producing company. Internet based systems or radio-frequency ones have both advantages and disadvantages. Collected data is sent to central monitoring center via a smartphone and then to physicians (Figure 6), but remote reprogramming of these devices is not yet available (Varma N et al. 2016, 1363-1374).

Risk factors of ICD shock are:

1. risk factors for appropriate ICD shocks:
 - a. male sex
 - b. atrial fibrillation
 - c. elevated NT-proBNP
 - d. non-sustained ventricular tachycardia
 - e. left atrium diameter
 - f. impaired renal function
 - g. higher NYHA class
 - h. lower left ventricular ejection function
 - i. the absence of beta-blockers therapy
2. risk factors for inappropriate ICD shocks:
 - a. lower left ventricular ejection fraction
 - b. atrial fibrillation
 - c. atrial flutter
 - d. younger age

This type of evaluation prolongs ICD's life by limiting the number of inappropriate shocks that cause early depletion of the battery, but complete guidelines for remote monitoring will further be optimized. Each ICD shock promotes an increase in the mortality rate and progressive heart failure and with a number of 12-17% of patients receiving inappropriate therapy, there is a clear need for standardization and optimization in this field (Nielsen J et al. 2020, 1147–1148).

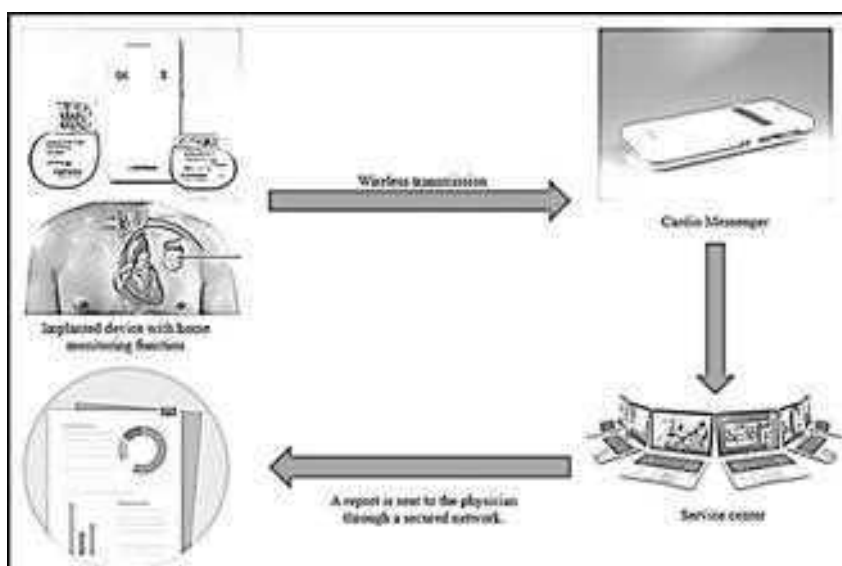


Figure 6. Schematic representation of telemedicine services through implanted devices with home monitoring function.

Acute Myocardial Infarction

A reduction of waiting time and delay in patients with acute myocardial infarction can be observed when pre-hospital telemedicine is applied and a 12 lead ECG is performed in case of a suspected acute coronary syndrome. This also generates a significant reduction in mortality because the percutaneous coronary intervention (PCI) will be performed faster, whereas emergency department is by-passed, some studies showing a decrease up to 1h or more for door to PCI time. STEMI patients who received a pre-hospital triage were associated with a lower rate of importantly depressed left ventricular ejection fraction.

CONCLUSION

In an era of continuous development of medicine knowledge and improvement of medical techniques, using telemedicine means for remote caring of patients enables health care professionals to perform a better assessment of patients' health status. Moreover, regarding the current situation generated by COVID-19, telemedicine finds its place as a helping hand for both medical personnel and patients. For cardiology matters, telemedicine occupies a leading place among diagnostic, therapeutic and monitoring means, especially in cases of arrhythmia due to all of the existing equipment and wearable devices.

Of course, like any other tool in medicine, telemedicine has its own strengths and weaknesses. We shall remember that means of telemedicine allow us to evaluate and monitor the patient whether this is happening in COVID-19 hospital wards, thus leading to limited exposure of health care professionals to the virus, or for at home patients. Because in many countries measures for limiting the patients' access to hospitals have been taken, use of

telemedicine could have improved the quality of life for those who were unable to address medical care, ensuring the patients' comfort regarding their own health and viral transmission.

Telemedicine might be a promising solution in times to come given its accessibility and it will probably lead to revolutionary changes in the health care systems.

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Chapter 451

LEGAL ETHICAL DILEMMAS RELATED TO THE CARE OF COVID-19 PATIENTS THROUGH TELEMEDICINE

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ABSTRACT

In this text, a reflection with a humanistic approach is made on Telemedicine in the context of the pandemic due to covid 19 and the Human Rights of patients. Situations such as the urgent demand for medical services, the eminent risk of the elderly population, the corruption of the health system in Colombia, the costs of therapeutic treatments, the existing dialectic between the promotion and prevention of health and the distance between the ethical and the legal in medical procedures; they challenge telemedicine and configure ethical dilemmas that question medical responsibility, the risk of error in teleconsultation diagnoses and decision-making. In all this situation, Communication for Health, which mediates between the state of opinion and the rule of law, has a special validity. This writing presents the analysis of a case of COVID 19 in an elderly patient, treated in the city of Medellín, in which a serious impact on their Human Rights is demonstrated in the expression of ethical dilemmas, which the health authorities could not resolve, leaving the patient's relatives in the midst of uncertainty and skepticism, in the face of government measures to address the pandemic.

Keywords: ethical dilemmas, human rights, COVID-19, telemedicine, communication for health

INTRODUCTION

For the purposes of developing the topics in this text, it is important to highlight the importance of the medical act and its relationship with telemedicine in the context of the covid-19 pandemic. Thus, the medical act includes all treatment, examination, or intervention of the patient by the doctor, for diagnostic, prophylactic or therapeutic purposes, in order to

regain their health (Perales Cabrera, 2001). Now, according to Law 1419 of 2010 of the Congress of the Republic of Colombia, telemedicine is defined with these terms: “It is the provision of distance health services in the components of promotion, prevention, diagnosis, treatment and rehabilitation, for Health professionals who use information and communication technologies, which allow them to exchange data with the purpose of facilitating access and opportunity in the provision of services to the population with limited supply, access to services or both in their geographic area.”

From the outset, two positions can be established: one, that the medical act is disfigured, as it is mediated by communication and information technologies, since it loses its humanistic, face-to-face, and synchronous categorization. Another, that the medical act is updated, reduces the costs of treatments and travel, making care effective and fast. Both positions on telemedicine are impacted by the presence of covid 19, which since March 15, 2020 has unfailingly marked the social life of the country.

According to the World Health Organization WHO, COVID 19 is the most recently discovered infectious disease caused by the coronavirus. Both this new virus and the disease it causes were unknown before the outbreak broke out in Wuhan, China, in December 2019. Currently, COVID 19 is a pandemic that affects many countries around the world.

At the beginning of March 2020, the Ministry of Health and Social Protection of Colombia announced the imminent arrival of the coronavirus, the first case was confirmed on March 6 and for the 15th of the same month the President of the Republic scheduled restrictions and confinements. The Communication for Health was in the hands of the state, opinion, and accusations of the government representatives. First, that the incipient biosecurity protocols were not properly applied at international airports, that the media misrepresented the information to their liking and that local governments did not know how to measure up to the gravity of what was happening. During this, citizenship in suspense, between skepticism and recklessness. After several months of prolonged quarantines, the collapse of the economy and the reinvention of management for many sectors of Colombian public life, the outlook is bleak. The number of deaths due to the pandemic, the lack of infrastructure for the management of patients and the insufficient resources for their care, configured some ethical dilemmas that this text intends to analyze: The ethical allocation of medical resources and the medical-medical relationship, patient in telemedicine as communicative competence for the medical act (Ratzan D, 1994).

ETHICAL ALLOCATION OF MEDICAL RESOURCES

In medical procedures during the COVID-19 pandemic, altruistic situations appear of those who give up their place and opportunities in resources, so that other young family members, also infected, can access treatments more quickly. This could be considered an ethical and moral problem, but the question reverses as follows: who should be served with the highest priority?

The state of opinion in Colombia was impacted since January 2020 with the informative presence of the coronavirus, capturing the attention of the country's news and information agents. Growing numbers of infected, dead, emerging economies and deterioration of social life, has achieved a worldwide impact of great repercussions and without any precedent.

Likewise, the already damaged health system collapsed with the number of infected and the Communication for Health was distorted in its commendable and philanthropic ideals, leaving in question the duty of medical practice and its deontological nature. The structure of society was disrupted.

This time of confinement and extensive quarantines has also questioned medical responsibility in relation to the covid 19 pandemic. Worthy and philanthropic institutions such as the World Health Organization WHO have been questioned for the handling of information in relation to the infection. Multiple clinical presentations of the virus and the constant threat of death for the most vulnerable have unfailingly constructed a scenario that oscillates between disbelief and citizen indiscipline (Ratzan D, 1994).

The ethical allocation of medical resources to face the covid 19 pandemic is part of the public health emergency declared by the National Government, but the named resources have not been equitably distributed among citizens. The hardest hit are the emerging sectors of the population, which are also the most incredulous and undisciplined in this crisis. However, the health infrastructure in Colombia consolidated the need to rationalize resources, equipment, and medical interventions. Therefore the incessant death of the elderly is not part of the dilemma of distribution of medical resources in the pandemic. It is naturalized and justified, insofar as they are the most vulnerable and the resources must be helping the youngest, for the productive life of society (Ratzan, Payne, & Bishop, 1996).

Medical decision-making is also part of this itinerary and indicates a course of ethical implications in this emergency, which has caused difficult episodes. The duty of medical practice has been questioned, while other sectors have cataloged it as heroic. Not without first mentioning that a rather significant number of health workers have been infected and others have died.

Difficult ethical decisions of medical and paramedical personnel, pressured in the midst of the crisis, with evident conditions of physical and emotional exhaustion, have been prevailing and mandatory, and this can compromise the deliberative process of a decision. This affects the fair allocation of resources in the customary altruistic and philanthropic vision of medical practice. However, the opportunities for access to health are questioned, which requires that the damage caused by the pandemic be minimal and that medical action be transparent and equitable.

THE DOCTOR-PATIENT RELATIONSHIP IN TELEMEDICINE AS A COMMUNICATIVE COMPETENCE FOR THE MEDICAL ACT

The practice of telemedicine has achieved over time the implementation of different computer tools, which have shown significant advances in the progress of “distance medicine,” applying expert tools in telematics, which have shown dizzying advances in consultation virtual, in the promotion and prevention of health (Vergeles Blanca, 2001).

According to the World Health Organization, telemedicine is “the provision of health care services, in which distance is a critical factor, by professionals who use information and communication technologies in order to exchange data to make diagnoses, advocate treatments and prevent diseases and accidents, as well as for the permanent training of health

care professionals and in research and evaluation activities, in order to improve the health of people and the communities in which they live" (IOM, 2007).

At present, the development of new technologies has had a great impact on all social, cultural and economic spheres of human life; One of them is medicine, since telemedicine or distance medicine has been implemented in the Colombian territory for two decades, which can bring significant advantages, however, the doctor-patient relationship can be affected as communicative competence in the act doctor.

Communicative competence in the medical act greatly strengthens the processes that forge the doctor-patient relationship, therefore, when this circle is suppressed, said relationship is directly affected. The importance of the bond that is created between the doctor and the patient lies in achieving a more comprehensive care, in which the spheres of the patient's life are positively influenced by medical care (Cuesta, Ugarte, & Menéndez, 2008).

Telemedicine provides greater agility when faced with solving problems, since technology greatly favors the reception of consultations, reading of exams and delivery of results, however, the implementation of this modality has brought deterioration as its main disadvantage of the close bond that is created between the doctor and the patient. Likewise, medical care through this means becomes something very elementary, leaving aside the other spheres in which a patient operates, making comprehensive care falter.

The medical *lex artis* can be compromised in multiple scenarios, the most common being in the precarious state of the health system, because in the absence of infrastructure and resources, the medical act and the doctor-patient communication are fragmented; Similarly, when in medical education there was not an adequate development of communication skills, it is possible that the doctor-patient relationship is dehumanized, it is not comprehensive and it is possible that there is an ineffective communication, having as a consequence the provision of a poor service in both situations.

Strengthening the doctor-patient relationship as a communicative competence for the medical act is of great importance so that comprehensive care is carried out in the best way, but on the other hand, in telemedicine that relationship can be violated, by preventing direct contact with the patient; However, this distance interaction that provides medical knowledge through cyberspace has allowed increasing accessibility to health services, breaking down geographic barriers.

Telemedicine establishes a model of care that today brings countless advantages in terms of care that requires agility and speed, due to the fact that technological advances are increasingly globalized, allowing greater coverage, however, communication skills in the medical profession must be preserved, since comprehensive care is a characteristic that the medical act should never lack.

A "CASE" IN THE CONTEXT OF HUMAN RIGHTS

The case study is theoretically referenced by Robert Stake (1999). It is very pertinent in ethical-legal studies and its object is made up of people. For this, the judgment derived from observation and interaction with various components related to the subject and the relationships that are structured in the case is very important. Among its characteristics is that it is an empathic, non-interventionist method. Here is the case for this study:

“Home care physician at the service of an EPS, attends the provision of services at home. Relatives request care of an adult patient over 88 years of age, who according to his relatives had an episode of nausea and vomiting with blood. Patient with a history of chronic obstructive pulmonary disease. HBP and hypothyroidism. Relatives deny respiratory symptoms. Therefore, the doctor attends the service, when arriving at the home to the simple inspection of the patient, the doctor shows respiratory difficulty, coughing spells, and significant deterioration of the general condition. Therefore, the doctor stops the assessment and proceeds to protect herself by wearing a suit for suspected covid given the current context of the patient and the ongoing pandemic. Additionally, he requests the support of a colleague to transfer the patient to the Intermediate Care Unit with adequate isolation conditions. The relatives get angry and lash out at the doctor for using the suits and, in her judgment, labeling the patient as covid, since they do not believe in the pandemic. The doctor had to make use of support from the community police line 123, since the family members verbally and physically attacked the doctor.”

The case in question is an open omission of information and a deterioration of the communicative relationship in the medical act. Hiding patient information during this pandemic becomes a clear violation of Human Rights. In his treatise on old age, “De senectute,” Marco Tulio Cicero says in a very brief sentence that “If we are not going to be immortal, it is desirable, at least, that man cease to exist in due time. Well, nature has a limit for life, as for all other things.” Also throughout the beautiful text on old age, which airs a strong stoic resignation, makes it clear that it is natural for man to turn off in his bed as the afternoon dies when the sun sets, because it is against nature to shorten life “before its time” as well as to extend it beyond what is “due” “by pouring oil like a nightlight” (Cicero, 2001).

The Colombian State is obliged to protect the lives of the elderly in the midst of the coronavirus pandemic, but this function is fully adhered to with respect for human dignity, personal autonomy, the free development of personality and the prohibition of cruel treatment and inhumane, about the inalienable rights of the person, protected by the Political Constitution of Colombia. The foregoing acquires a capital importance when these rights are invoked by a citizen who suffers from an irreversible state of health (Article 8 ACHR., 2002).

Lack of care for the elderly in the covid 19 pandemic discourages medical research, changes public awareness, violates historically accepted codes of medical ethics. The life of the weakest is in the hands of the strongest. With this, the sense of justice, reciprocity and trust in society is lost. A social and democratic collective cannot oversee the organized murder of citizens. Allowing the elderly to die during the pandemic endangers the lives of the vulnerable, corrupts medical practice, and puts at risk the family institution and generational commitment to maintaining human dignity and the equality of citizens (Garcia, 2017).

CONCLUSION

Police reports during the coronavirus pandemic assure that cases of domestic violence increased. The home became a place of fear and abuse, especially for the elderly. The situation worsens considerably in cases of isolation such as quarantines imposed during the pandemic.

During this humanitarian crisis, many elderly people have been abandoned and the bodies of many of them have been found without any mourners. This is unacceptable during a Social State of Law in justice and equity.

Immigrants and internally displaced persons are more exposed to the risk of covid 19, due to its restrictions on access to health care and decent housing. They are highly discriminated against. This crisis has unleashed xenophobia, hatred and exclusion.

COVID 19 patients treated by telemedicine access the consultation virtually, mediated their relationship with the doctor by a computer, connected to the internet in cyberspace. This allows you to know clinical information, manage documentation, make controls, communicate with doctors, use prescribed applications, observe protocols, among others. This reduces travel expenses and shortens geographic distances. Likewise, it offers the possibility of diagnosing experts located in different parts of the world, sending exams quickly and managing a wealth of medical information.

Telemedicine appears as a new contemporary paradigm in the medical vision, with little-studied models, in its expertise and benefit. The error in virtual medical practice is not conceived and there are no guarantees to hold the doctor responsible for an alleged harm to the patient. To a large extent, the practice of telemedicine is not supported by clinical protocols that can guarantee the medical practice of the “Lex Artis” (García & Others, 2019).

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Chapter 452

EPIDEMIOLOGY AND PATHOGENESIS OF COVID-19

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ABSTRACT

COVID-19 is a pandemic caused by the coronavirus, Severe Acute Respiratory Syndrome Coronavirus (SARS CoV-2), that affects the entire world, which can result in death, especially in the elderly and people with underlying disease (hypertension, diabetes mellitus, coroner artery disease). The number of patients and deaths continues to increase rapidly in the world. Today, the most important source of infection is sick people. Contagiousness in the asymptomatic and presymptomatic period is the most important problem in preventing the pandemic. The most important route of transmission is the droplets. Aerosols can be transmitted by aerosol- generating procedures in health-care. Fomites that spread to the immediate environment of sick people play a role in transmission through contact. There is insufficient data on other transmission routes. In the first period, COVID-19, which spread as a travel disease, spread to all societies in closed environments (home, meeting, public transportation, ceremonies, prisons, long-term care units...) where many people are together. Local outbreaks occur, especially in hospitals and health centers. There are many uncertainties in the pathophysiology of Covid-19. Studies at different stages of the disease and with different methodologies are published and this provides conflicting data. Lymphopenia, cytokine storm, ferritin elevation, and D-dimer elevation were found to be associated with poor prognosis. Acute respiratory distress syndrome (ARDS) and sepsis are the most important causes of mortality. In this section, a perspective for the future is presented by addressing the issues in the light of the available data.

Keywords: COVID-19, epidemiology, pathogenesis

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INTRODUCTION

Coronaviruses; enveloped single-stranded, positive-sense RNA viruses. The coronavirus has a large genome of approximately 30 000 bases and an RNA polymerase activity with “proofreading” activity to correct mutations. This family is found in many mammals, especially cats, dogs, pigs, and bats, and includes important human pathogens. Viruses that adapt to new hosts with genetic recombination and variations in different hosts become important pathogens for humans when they gain the ability to be transmitted and spread from person to person. These viruses, which can settle in the respiratory and digestive systems in many mammals, were first identified as the agents with upper respiratory tract infection (HCoV-NL63, HCoV229E, HCoV-OC43, HCoVHKU1). With the clinic of Severe Acute Respiratory Syndrome Coronavirus (SARS) in 2003 and Middle East Respiratory Syndrome (MERS) in 2012, it was observed that it could cause diseases and epidemics with high mortality in humans with pneumonia. SARS-CoV-2 is an agent with long spike structures (9-12 nanometers) in dimensions of 60-120 nanometers. Bats were found as the reservoir of this virus, and although pangolin as an intermediate host was identified as the most likely source, this issue has not been fully clarified. A new coronavirus was identified as the cause of a series of pneumonia cases at the end of 2019 in Wuhan, a city in China’s Hubei province. This infection, which spread rapidly, resulted in an epidemic throughout China and then spread to other countries in the world, this epidemic was declared by WHO as a Public Health Emergency of International Importance (PHEIC). In February 2020, the World Health Organization took the name Covid-19 disease, which means coronavirus disease 19, and the virus that causes COVID-19 was named SARS-CoV-2. WHO declared COVID-19 as a pandemic on March 11, 2020. On September 25, 2020, a total of 32.110.656 detected cases and 980.031 COVID-19 deaths were recorded worldwide, and the numbers continue to increase [1].

EPIDEMIOLOGY

The global epidemiology of COVID-19 in the first phase of the pandemic was evaluated as a cross-sectional analysis using web-based surveillance [2]. In the web-based surveillance study, almost two-thirds of the COVID-19 cases first reported were those with travel links to China, Italy, or Iran. In the first period of the outbreak sixty-five studies were evaluated and most of these have been reported from China. It has been stated that most of these are due to family contacts. The major types of cluster infections were families, gatherings, religious organizations, transportation, community transmission, conferences, shopping malls, respectively [3]. Although there were many household contagion clusters among the early cases, the numbers in these clusters were low (2-22 cases) clusters in occupational or community settings tended to be larger (gathering 112, shopping mall 40, religion 53 cases was found to be affected) and physical distance was a possible risk to slow the progression of SARS-CoV-2 was supportive of its role [4]. A total of 161 studies (n = 17 648) provided data for the mode of transmission. The most common mode of transmission was travel-related (58.1%, 95% CI: 51.1-64.8), followed by close contacts (43.1%, 95% CI: 37.2-49.2), and finally community spread (27.4%, 95% CI: 18.4-38.7) [5]. At present, general findings show

that test strategies, socioeconomic differences, and reporting systems of countries affect the spread in society.

In children, it is stated that the number of cases detected is less, the disease has a milder course, and asymptomatic cases are more common in this situation. In a systemic review and meta-analysis, it is stated that approximately 4% of patients with a diagnosis of COVID-19 are symptomatic, having underlying diseases play a role in this course [6].

Severe or critical illness has been reported among 2.5% to 5% of pediatric cases, and more recently, 4% of cases were reported as severe or critical, and pre-existing medical conditions have been suggested as a risk factor for severe disease and ICU admission in children and adolescents [7]. Several countries affected by the COVID-19 pandemic reported cases of children who were hospitalized in intensive care units due to a rare pediatric inflammatory multisystem syndrome (PIMS) or multisystem inflammatory syndrome in children (MIS-C) [8], characterized by a systemic disease involving persistent *fever, inflammation* and organ dysfunction following exposure to SARS-CoV-2 [9, 10].

COVID-19 course has not been shown to be worse in pregnant women. Pregnant women are often tested for SARS-CoV-2 infection at admission for hospital delivery. According to this may explain the high proportion of asymptomatic cases found among pregnant women in different countries. In addition, infants and newborns have been described as more vulnerable to severe COVID-19 than other pediatric groups [11, 12]. Although a low mortality rate (0.006%) has been reported for this group in most cases [13, 14]. Among the COVID-19 cases with serious illness and death and the rates of people with underlying health conditions are remarkable. Primary health conditions reported among COVID-19 patients and admitted to the intense care unit (ICU) include hypertension, diabetes, cardiovascular disease, chronic respiratory disease, immunocompromised status, cancer, and obesity. A high proportion of long-term care facilities and nursing homes in Europe and the world are also severely affected by COVID-19. Consequently, high morbidity and mortality and high rates of absenteeism due to SARS-CoV-2 infections have been observed in residents [15-17]. In a systematic analysis study, 6007 articles, 212 studies from 11 countries/regions involving 281 461 individuals were analyzed (the mean age 46.7 years, and female-male ratio 49.2%-51.8%). Older age, male gender, diabetes, and hypertension were also associated with higher mortality with severe COVID-19, and the mortality rate was 5.6% and severe disease rate was 22.9% [5].

Health-care workers are at high risk of covid-19. Higher rates of cases are detected in contrast to other segments of society. This risk is thought to be caused by their exposure to higher concentrations of the virus. Since healthcare workers are younger and have fewer comorbidities, a milder disease picture is generally observed. Despite that, a large number of health-care workers died due to Covid-19. Mistakes in the use of personal protective equipment, problems with compliance with hand hygiene, intensive work, deficiencies related to hospital organization are factors that increase the risk of health-care workers [7]. Health-care worker's risk of Covid-19 transmission has been associated with the misuse of personal protective equipment during contact. In one study, 2% of the health-care workers who came into contact with Covid-19, and post-contact findings appeared within an average of 3.6 (0-17 days) days. In contamination, male gender, comorbidity, high-risk contact, and auxiliary personnel were identified as factors that increase the risk [18].

In a study, in our country, inappropriate use of personnel protective equipment, staying in the same personnel break room as an HCW without a medical mask, consuming food within, and failure to keep a safe social distance from an HCW were statistically significant risk

factors for infection [19]. One of the studies concluded in our hospital, it was found that approximately half of the health-care workers with Covid-19 were infected with their colleagues in social areas (unpublished data).

The elderly in long-term care (LTC) and their caregiving staff are at elevated risk from COVID-19. Coronavirus disease (COVID19)-related deaths in LTCF residents represent 30-60% of all COVID-19 deaths in many European countries [20].

In all epidemiological studies, the reliability of the data is low due to the lack of genome data of the virus, the fact that many asymptomatic cases can be contagious, and the studies are generally conducted using cross-sectional data.

PATHOGENESIS

The high infectivity of the virus, the lack of effective antivirals and vaccines, and potentially large asymptomatic populations have made the management of COVID-19 extremely difficult. Continuous efforts to better understand the pathogenesis of this disease, in addition to rapid medical interventions, will undoubtedly shed light on the management of the growing pandemic.

SARS-CoV-2 first affects the respiratory tract cells and the first proliferation site is the nasal mucosa. Viral load reaches its highest level at the onset of symptoms, but its spread (viral shedding) begins about 2-3 days before symptoms. Clinical course viral load is determined by the complex processes of infective dose and immune system response. The virus binds to cells with the spike S-protein and its main receptor is the angiotensin-converting enzyme 2 (ACE-2) receptor [21].

In the disease course, COVID-19 of viral replication in the lower respiratory tract, and generates secondary viremia, followed by an extensive attack against target organs. SARS-CoV-2 extensive attack against target organs that express ACE2, such as heart, kidney, gastrointestinal tract [22]. When SARS-CoV-2 infects cells expressing the surface receptors angiotensin-converting enzyme 2 (ACE2). Transmembrane protease serine 2 (TMPRSS2) activates viral S protein (especially Furin-like cleavage region) and cleaves the ACE2 receptor to facilitate viral binding to the host cell membrane. This binding triggers endocytosis allowing SARS-CoV-2 to enter the cell type in the virion cell membrane. The virus enters the host cell via endocytosis releases its RNA, and uses cell machinery to replicate itself and assemble more virions. Bronchial epithelial cells, type I and type II alveolar pneumocytes, and capillary endothelial cells are infected, an inflammatory response ensues.

The active replication release of the virus causes the host cell damage and release damage-associated molecular patterns (ATP, nucleic acids, and caspase proteins). Antagonism of the interferon (IFN- α and IFN- β) response aids viral replication, resulting in increased release of pyroptosis products that can further induce aberrant inflammatory responses. These are recognized by neighboring epithelial cells, endothelial cells, and alveolar macrophages, triggering the generation of pro-inflammatory cytokines and chemokines (including IL-6, IP-10, macrophage inflammatory proteins, MCP1...). All these proteins attract monocytes, macrophages, and T cells to the site of infection, promoting further inflammation (with the addition of IFN γ). Continued inflammatory response results in

alveolar interstitial mononuclear inflammatory infiltrate and edema develops and appears as ground-glass opacities on radiological imaging. In the late stage, thickened interstitium, hyaline membrane formation, the influx of monocytes and neutrophils, increased vascular permeability compatible with early-phase acute respiratory distress syndrome (ARDS) [19, 23].

When the immune response is excessive, it causes a cytokine storm with excessive production of proinflammatory cytokines in the lungs. This response can effectively lead to multiple organ damage in other organs. In addition, non-neutralizing antibodies produced by B cells may exacerbate antibody-dependent enhancement (ADE) organ damage. This process is mainly observed as clinical worsening observed 7-14 days following the onset of the disease. These findings show that the disease symptoms are particularly related to immune response, apart from viral damage. In severe and critically ill patients with COVID-19, two distinctive features of progressive increase in inflammation have been recognized. Possible pathways contributing to hyperactivation and hyperinflammation of monocyte-derived macrophages in COVID-19. Delayed type I interferon production, leading to increased cytopathic effects and greater perception of microbial threats, promote the increased release of monocyte chemoattractants by alveolar epithelial cells, leading to the continuous accumulation of monocytes into the lungs. Monocytes differentiate into proinflammatory macrophages through Janus kinase (JAK) activation. Activated natural killer (NK) cells and T cells further promote the recruitment and activation of macrophages through the production of granulocyte - macrophage-colony-stimulating factor (GM-CSF), tumor necrosis factor (TNF), and interferon-(IFN γ). The binding of Fc receptors (FcRs) by anti-spike protein IgG immune complexes may contribute to the increased inflammatory activation of monocyte-derived macrophages. Activated monocyte-derived macrophages contribute to the COVID-19 cytokine storm by secreting large amounts of pro-inflammatory cytokines [24].

Several factors may contribute to the hypercoagulability in COVID-19 patients. Certain cytokines including IL-6 could activate the coagulation system and suppress the fibrinolytic system. In the setting of COVID-19, activation of coagulation leads to microthrombus formation. COVID-19 patients elevated levels of D-dimer and fibrinogen associated with poor prognosis.

Lymphopenia is an important feature of patients with COVID-19. Lymphopenia is more common in patients with severe COVID-19, and this is an important sign of a poor prognosis [25, 26]. Declining lymphocyte groups are especially T lymphocytes and NK cells. Showed that T-lymphocyte count was inversely proportional to TNFa, IL-6, and IL-10 levels in particular and that an increase in inflammatory cytokine levels may promote depletion of T-cell populations along with disease progression [27]. Activation of CD14+CD16+ inflammatory monocytes was associated with an increase in IL-6, one of the key cytokines in the cytokine storm [28].

The clinical course of SARS-CoV-2 infection can be divided into three stages: the viremia stage, the acute stage (Immune response stage), and the progression or recovery stage. Patients with appropriate immune functions and without obvious risk factors (old age, comorbidities, genetic factors, etc.) can generate effective and sufficient immune responses to suppress the virus in the first or second stage without an excessive immune reaction. In contrast, patients with immune dysfunction may have a more severe clinical picture, intensive care admission, and a higher risk of death. There are no proven effective antivirals. Therefore, it mainly focuses on the close monitoring of disease stages and the application of ways of

stopping or slowing the progression of the disease (IL-6 inhibition, corticosteroid, immune plasma). In contrast, in a healthy immune response, the initial inflammation draws virus-specific T cells to the site of infection and they can eliminate infected cells before the virus spreads. Neutralizing antibodies in these individuals can block viral infection and alveolar macrophages recognize neutralized viruses and apoptotic cells and clear them by phagocytosis. All of these processes result in recovery by causing the virus to be cleared and minimal lung damage [19, 28].

In a post-mortem study of 10 consecutive patients who died of COVID-19 in Germany (mean age 79, 70% male, mean time between hospitalization and mortality 7.5 days), significant ARDS findings were found in the lungs, especially in the middle and lower lobes. Organizing-stage diffuse alveolar damage with pronounced fibroblastic proliferation, partial fibrosis, pneumocyte hyperplasia leading to interstitial thickening and collapsed alveoli, and patchy lymphocyte infiltration was the predominant finding.

In a post-mortem study of 10 consecutive patients who died of COVID-19 in Germany (mean age 79, 70% male, mean time between hospitalization and mortality 7.5 days), significant ARDS findings were found in the lungs, especially in the middle and lower lobes. Neutrophil infiltration was also detected in five cases with suspected aspiration and secondary infection [29].

Grifoni et al. Found SARS-CoV-2-specific CD8 and CD4 cells between 70-100% in 20 COVID-19 patients. CD4 cell response was correlated with the magnitude of the IgG response to spike protein. Interestingly, in the study, CD4 T lymphocytes reacting with SARS-CoV-2 were detected in 40-60% of those who were not in contact with the virus. This finding suggests a cross-response. These findings may be related to some people and children having milder COVID-19 disease [30]. Virus-specific IgM and IgG are detectable in serum between 7 and 14 days after the onset of symptoms. Viral RNA is inversely correlated with neutralizing antibody titers. Higher titers have been observed in critically ill patients, but it is unknown whether antibody responses somehow contribute to pulmonary pathology. The SARS-CoV-1 humoral response is relatively short-lived, and memory B cells may disappear altogether, suggesting that immunity with SARS-CoV-2 may wane 1-2 years after primary infection [31].

Non-neutralizing virus-specific IgG facilitates the entry of virus particles into cells expressing the Fc receptor (FcR), particularly macrophages and monocytes, and can lead to inflammatory activation of these cells. This phenomenon is called antibody-dependent enhancement (ADE), it is a condition that needs attention for immunoglobulin treatments and vaccine studies [32].

CONCLUSION

The Covid-19 pandemic cannot be expected to end soon. It has been understood that personal protective measures (mask, social distance, and hand hygiene) are effective methods against pandemics. There are many uncertainties regarding pathogenesis. Studies on this subject provide important findings on treatment and vaccination. Learning to live with the virus and accessing new information about pathogenesis will be the primary goal of science.

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Chapter 453

TRANSMISSION OF SARS-COV-2 AND PREVENTION STRATEGIES

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ABSTRACT

The main transmission routes of SARS-CoV-2 are through respiratory droplets and close contact with the index case but other possible routes are also reported. Although the virus may spread during aerosol-generating procedures, the probability of airborne transmission in other circumstances is controversial. Experimental studies demonstrated that SARS-CoV-2 remained viable in aerosols and on fomite surfaces up to 72 hours. However, no reports directly demonstrated transmission from the fomites. SARS-CoV-2 RNA was isolated in various biological specimens but currently, there is no report demonstrating direct transmission of SARS-CoV-2 apart from respiratory secretions except for two cases of vertical transmission.

The type, time, and duration of exposure, application of preventive measures, and the amount of the virus are among the most important predictors of the risk of transmission. Infectiousness begins approximately 3 days before symptom onset and peaks on the day of onset. The risk of transmission remains high in case of exposure to the index case within 5 days of symptom onset and is thought to continue until to 10-20 days depending on the severity of the disease and presence of underlying immunosuppressive diseases.

Although the preventive measures may differ according to public and healthcare settings the main strategy is to accept everyone as potential COVID-19 patients. In public settings, everyone should be encouraged to wear a facemask, maintain social distance, apply hand hygiene, avoid touching mouth, nose, and eyes, keep clean high touch areas, and obey isolation rules in case of illness or contact with COVID-19 patient. Every

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healthcare center should redesign the structuring of its facility to maintain the physical distance and isolate COVID-19 patients. The administration should consider making arrangements regarding surgical and invasive procedures, outpatient and inpatient clinics in terms of COVID-19.

Patients and visitors should wear a facemask. Healthcare workers who care for patients with suspected or confirmed COVID-19 should wear personal protective equipment.

INTRODUCTION

At the end of 2019, a new virus later named as SARS-CoV-2 was thought to be transmitted firstly in a seafood market where live animals were sold, in Wuhan. Later on, person to person transmission was reported to be the main route of spread [1]. The routes of transmission and prevention strategies will be mentioned in this chapter.

ROUTES OF TRANSMISSION

Although the main transmission routes for SARS-CoV-2 are through droplets and close contact, many other ways also are reported [2-4]. Other possible routes consist of airborne, fomite, fecal-oral, bloodborne, vertical, and animal to human transmission [2].

Droplet and Contact Transmission

The primary means of transmission is via respiratory droplets ($> 5 \mu\text{m}$, not traveling more than 1-2 meters). Direct, indirect, or close contact with infected respiratory secretions or droplets may lead to transmission. Infected patients may spread the respiratory droplets including SARS-CoV-2 during coughing, sneezing, singing, or talking to people in a close range contact. The droplets may reach directly the mucous membranes (mouth, nose, or eyes) of a susceptible host [2, 4]. Indirect contact transmission may occur after contact with a contaminated object/surface and then spreading the virus to eyes, nose, or mouth by touching [3].

Airborne Transmission

Airborne transmission occurs when aerosols (droplet nuclei $< 5 \mu\text{m}$, traveling more than 2 meters) containing the microorganism suspended in air disseminate over a distance. Although SARS-CoV-2 may spread during aerosol-generating procedures; the probability of airborne transmission in other circumstances is controversial [2]. Various experimental studies evaluated this issue: some revealed that aerosols may develop during coughing or talking varying according to the modes of practices (such as loud speech, shouting), the others demonstrated that SARS-CoV-2 RNA may remain in aerosols generated via high-powered jet nebulizers for up to 3-16 hours and some investigators identified viral RNA in ventilation

systems or air of COVID-19 patients' rooms. But the presence of a viable virus in air samples is reported only in a limited number of studies [2, 5-11]. Although outbreak reports in a closed, crowded, and poorly ventilated area (such as restaurants, buses) may suggest the probability of airborne transmission, the transmission in these cases may also be associated with droplet and fomite surfaces [2, 12, 13].

Until further research clarifies the possibility of airborne transmission in SARS-CoV-2 infection in the community, it would be reasonable to accept that the virus may be transmitted via droplet nuclei during aerosol-generating procedures.

Fomite Transmission

Respiratory droplets may contaminate the surfaces and the objects around the patients and touching mouth, eyes, or mouth after contact with these surfaces may lead to indirect transmission of the virus [2]. The virus may be disseminated all over the ward including bed handrails, doorknobs, trash cans, computer mouse, floor, shoe soles, and other surfaces. However, the detection of the nucleic acid over these surfaces does not indicate that the virus is viable [14]. The environment temperature and humidity and the type of surfaces are predictors of stability of the virus over the fomites [2]. Van Doremalen et al., in their experimental studies demonstrated that SARS-CoV-2 remained viable in aerosols, on copper, cardboard, plastic, and stainless steel up to 3, 4, 24, and 72 hours respectively while the virus titer reduced with time [7]. Although many studies evaluated the survival of the virus on environmental surfaces there are no reports directly demonstrating transmission from the fomites [2].

Other Modes of Transmission

SARS-CoV-2 RNA was isolated in other biological specimens such as urine, feces, semen, or ocular secretions, but the presence of viable viruses was reported only in some studies [11, 15-18]. Although there are various hypotheses, currently there is no report demonstrating direct transmission of SARS-CoV-2 via these routes [2]. Viral RNA was also detected in blood but the role of transmission via blood and blood products is controversial [15-19].

Nasopharyngeal specimens, umbilical cord blood, and placental specimens of neonates born to infected mothers were demonstrated to include viral RNA, however evidence of intrauterine transmission is sparse [20-22].

World Health Organization (WHO) in its scientific brief reported that viral RNA fragments have been found in breast milk samples of infected mothers. But since the viable virus could not be detected, WHO recommends that mothers with suspected or confirmed COVID-19 should be encouraged to breastfeed [23].

Dogs, cats, and farmed minks have been reported to be infected by humans but the probability of transmission of COVID-19 from infected animals to humans is unclear [24-26].

Period of Infectiousness

With the first report of transmission of SARS-CoV-2 after contact with an index case during the incubation period in Germany, the variability in the probability of transmission during COVID-19 has become a matter of interest [27]. He et al., in their experimental study demonstrated that infectiousness begins 5–6 days before symptom onset and peaks on the day of onset. Upon observation that 1% of transmissions would occur 5 days and 9% of transmissions 3 days before symptom onset, they concluded that 3 days before symptom onset is critical in terms of transmission [28]. In another study performed in Taiwan, 2500 close contacts of 100 patients were analyzed and a secondary clinical attack rate was found to be higher in case of exposure to the index case within 5 days of symptom onset [29].

Although viral RNA may be detected in biological specimens after months of SARS-CoV-2 infection, Wölfel et al., demonstrated that this may not mean that the virus is infectious if the RNA level was $< 10^6$ copies/mL [30, 31]. On the other hand viable viruses although not replication-competent, may be isolated after more than 10 days in some cases depending on the severity of the disease and underlying immunosuppression [30, 32, 33]. According to the Centers for Disease Control and Prevention (CDC), patients with mild to moderate disease and with more severe disease or immunosuppression most probably are not infectious for longer than 10 days and 20 days after symptom onset, respectively [33].

PREVENTION STRATEGIES

The type, time, and duration of exposure, application of preventive measures, and the amount of the virus are among the most important predictors of the risk of transmission [3, 28, 29]. The risk of transmission is high among household contacts where the secondary attack rate ranges between 15-38% [34, 35]. Besides household contacts and gathering activities, traveling with an index case without preventive measures or indoor activities are associated with a high risk of transmission. Since the probability of neglect of wearing a facemask or social distancing may be high while eating or drinking in indoor environments, the risk for transmission remains an important concern [36, 37]. Outdoor activities carry a low risk for transmission except for close contact with an index case [3].

The best way of prevention of transmission includes testing the suspected individuals, isolating the infected cases, determining all close contacts, and self/quarantine them [3].

The prevention strategies can be classified under 2 subgroups: public and healthcare settings.

Public Settings

On individual and public health basis, these measures should be applied by everyone in the public:

- *Washing hands with soap and water for at least 20 seconds or rubbing hands with hand antiseptic containing at least 65% alcohol, after being in a public area, before*

or after touching the face, after handling the mask, after sneezing or coughing, after touching surfaces, before eating or preparing food, after going to the restroom

- *Avoiding touching eyes, nose, or mouth*
- *Avoiding close contact (maintaining a distance of 1-2 meters between people)*
- *Wearing a mask (facemask or cloth covering) covering the mouth and nose in public settings*
- *Using tissues to cover mouth and nose during coughing and sneezing and throwing them into the trash can or bent elbow when coughing or sneezing*
- *Cleaning and disinfecting touched surfaces daily [38].*
- *Individuals having close contact (< 2 meters for ≥ 15 minutes) with people having COVID-19 symptoms (laboratory-confirmed or clinically compatible) 2 days before symptom onset and until discontinuation of isolation are accepted to have a high risk for exposure. They should quarantine themselves for 14 days after the last exposure, maintain social distance between people, self-monitor for symptoms of COVID-19 [39].*

Each country can make different arrangements to re-organize environmental conditions in schools, workplaces, prisons, dormitories, nursing homes, shopping centers, fitness centers, restaurants, and other indoor areas, and ameliorates travel conditions, taking into account the number of confirmed cases, current resources, and sociocultural characteristics.

Healthcare Settings

Every healthcare center should implement its prevention strategies to the utmost to protect its workers and patients. These measures should include some major principles:

General Principles

- Telemedicine policies should be implemented if possible, to eliminate the unnecessary admission of patients to the centers and transmission of SARS-CoV-2. Besides telemedicine, general information about the facilities' strategies during the pandemic period should be mentioned on the website. If the patients have to apply to the healthcare center, they should be questioned about the signs and symptoms of COVID-19. Patients without compatible symptoms should be advised to cover their mouth and nose with a facemask or cloth covering upon admission.
- Every healthcare center should redesign the structuring of the facility to maintain the physical distance, constitute separate entrances for patients admitted with signs and symptoms of COVID-19 and separate outpatient clinics, wards, or buildings for COVID-19 patients, and display (posters and visuals) information at the entrance to direct the patients to these designated areas.
- Posters and visuals should be placed at the entrance and in common places to mention the use of facemasks and proper hand hygiene.
- Rearrangements should be made to maintain social distance in strategic places such as waiting areas, elevators, and cafeterias to prevent crowding. Regular cleaning and disinfection of these areas should be provided.

- All staff in the institution should be educated in terms of prevention measures.
- The administration should consider postponing elective procedures, outpatient admissions, and surgeries if relevant and update the decisions when convenient.
- Patients and visitors should wear facemask or cloth face-covering upon arrival to the hospital. If facemasks or cloth coverings are not worn facemasks should be provided at the entry.
- Every patient admitted to the healthcare facility for any reason should be screened for COVID-19 signs and symptoms (the body temperature should be actively measured) and questioned for exposure to COVID-19 patients within the last 14 days upon entry. In case of suspicion, the patients should be transferred to a special area dedicated to COVID-19 patients.
- Restrictions to visitors should be applied. They should also be screened for COVID-19 symptoms and questioned for exposure to COVID-19 patients within the last 14 days. Those with symptoms and with a history of exposure should not be permitted to enter the healthcare centers and directed to the COVID-19 outpatient clinic.
- Environmental and engineering controls should provide adequate ventilation, structural design, environmental cleaning. Air conditioners should not be run in areas where more than one person is present.
- Commonly used and frequently touched surfaces (push buttons, door handles, etc.) should be cleaned and disinfected regularly. Equipment such as stretchers and wheelchairs used by patients should be disinfected after each patient use.
- Disinfection of devices such as phones, computers, etc. should be provided by the handler (70% of alcohol).
- Communication and transfer with paper, cardboard files, etc. should be minimized in the whole facility and online communication should be encouraged.
- All scientific and educational meetings should be held online at the utmost.

Outpatient Clinics

- Arrangements should be made to provide 1.5-2 meters of distance between healthcare workers (HCW) and patients in outpatient clinics.
- Alcohol-based hand antiseptics and substances required for the disinfection of the surfaces should be provided.
- The patients should wear facemasks and the HCWs should wear medical masks and goggles/face shields.
- Disinfection of common equipment after each use (70% alcohol) should be provided.

Inpatient Clinics

- All wards should be rearranged to place patients in a single room, if not possible, the patients should be separated by 2 meters from each other to prevent the transmission.
- COVID-19 patients should be followed up in a well ventilated private room with the bathroom placed within and the door closed. If isolation of the patient is not possible, confirmed COVID-19 patients may be cohorted.
- Inpatients should be provided facemasks. Patients may remove their masks when in their rooms but should put on when leaving their room, or when HCWs, other staff,

or visitors enter their room. Alcohol-based hand antiseptics should be available in every patient room and common areas.

- Equipment used for patients should be patient-specific and shared equipment should be disinfected (70% alcohol) after use.
- Patient rooms should be cleaned every day and in case of contamination.

Healthcare Workers

- Besides standard precautions, contact and droplet prevention measures should be taken during the care of suspected or confirmed COVID-19 patients.
- All HCWs who care for patients with suspected or confirmed COVID-19 should wear personal protective equipment (PPE). Standard PPE includes the use of a respirator or medical mask, goggles or face shield, a gown, and gloves.
- In conventional settings HCWs caring for patients with suspected or known COVID-19, should use a medical mask (CDC recommends the use of a medical mask or N95 or equivalent or higher level respirator; in case of respirator shortages, medical mask or reprocessed respirator can be used).
- Gloves and gowns are recommended in procedures carrying the risk of exposure to body fluids. They should always be changed after each patient contact. In case of heavy exposure to body fluids waterproof gowns may be preferred.
- HCWs should wear medical masks the day in the healthcare center including breakrooms or meeting areas since they may be exposed to asymptomatic or presymptomatic people.
- HCWs should avoid touching their face to eliminate the risk of self-contamination.
- Aerosol-generating procedures may lead to airborne transmission. These procedures include the following:
 - Endotracheal intubation and extubation
 - Manual ventilation before intubation
 - Noninvasive ventilation
 - Filter changes on the ventilator
 - Bronchoscopy (including mini bronchoalveolar lavage)
 - Cardiopulmonary resuscitation
 - Sputum induction
 - Open suctioning of airways
 - Tracheotomy
 - High-flow oxygen
 - Nasal endoscopy
 - Upper endoscopy (including transesophageal echocardiogram)
 - Use of nebulizer
 - Colonoscopy
 - Autopsies
- Aerosol-generating procedures should be carried out in a negative pressure room if possible or in a single room with the door kept closed and the room should be ventilated after the procedure.
- HCWs should wear an N95 (or equivalent or higher level) respirator, goggles or face shield, gloves, and gowns during these procedures. If N95 respirators are not

available reprocessed respirators should be reused or a face shield or medical mask should be put on the respirator as a cover for extended use.

- Respirators with exhalation valves are not recommended.
- Hand hygiene should be performed before and after patient contact, after exposure to infectious material, before wearing and after removing all PPE.
- *Alcohol-based hand antiseptics containing 65-95% of alcohol should be used for hand hygiene or the hands should be washed with soap and water [40-45].*
- *Although* nasopharyngeal specimen collection is not considered as aerosol-generating procedure CDC recommends the use of respirator, face shield or goggles, gloves, and gowns [40].
- Exposure of contaminated material to HCW's eyes nose or mouth during aerosol-generating procedures is defined as high-risk exposure if the HCW has no any PPE.
- The HCW should be excluded from work for 14 days after last exposure in case of a prolonged and close contact (< 2 meters for ≥ 15 minutes) with a confirmed COVID-19 patient before 2 days of symptom onset until the end of the isolation period:
- if the HCW does not wear a medical mask or respirator or
- if the HCW does not have eye or face protection when the patient does not wear a mask or
- if the HCW does not wear all PPE during aerosol-generating procedures (any duration of the contact is accepted as prolonged and close contact)
- In the case of the staffing shortage, HCW with a history of exposure can be allowed to work as long as he/she obeys preventive measures strictly. The HCW should monitor him/herself for signs and symptoms for the next 14 days after exposure.

Surgical Procedures

- Elective surgeries should be postponed. If the surgical procedures can not be postponed patients should be screened for COVID-19 signs and symptoms and in the presence of symptoms they should be tested for COVID-19 by molecular methods. If the suspicion level for COVID-19 is high and the nasopharyngeal swab test result by polymerase chain reaction (PCR) is negative, a second test may be performed. Some centers may consider testing all patients before surgery independent of symptoms. However, delays in results and the probability of negative results during the incubation period should be taken into consideration.
- COVID-19 patients should wear a medical mask and transport staff should apply droplets and contact prevention measures during transfer to the operating room.
- All HCWs in the operation team should wear N95, FFP2, or equivalent or higher level respirators, waterproof sterile gown, sterile gloves, goggles/face shield during the operation of a suspected or confirmed COVID-19 patients.
- Even if COVID-19 is excluded at the end of the evaluation, general contact and droplet precautions should be taken in operating rooms during the pandemic period.

Environmental Cleaning and Disinfection

- Surfaces should be cleaned with water and detergent firstly. Then application of 0.1% (1000ppm) sodium hypochlorite or 70-90% ethanol is effective. In the case of contamination with blood or body fluids, a concentration of 0.5% (5000ppm) sodium hypochlorite should be used.

- For sensitive surfaces and screens, 70% of alcohol can also be used for surface disinfection.
- Cleaning staff should use PPE [40-45].

CONCLUSION

COVID-19 pandemic continues all over the world. Although investigations in the fields of vaccination and treatment continue, the pandemic is not expected to end in a short time. Except for aerosol-generating procedures, the main route of transmission is thought to be through droplets and close contact. Considering all these factors, the use of masks, social distance, and hand hygiene should be provided based on the public setting. In the healthcare settings, except for aerosol-generating procedures, HCWs should take standard, contact, and droplet precautions.

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Chapter 454

CLINICAL ASPECT OF COVID-19

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ABSTRACT

COVID-19, named by the World Health Organization in February 2020, is an infectious and fatal disease that first started in China in December 2019 by the determination of pneumonia cases secondary to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has been rapidly spreading all over the world since then. Although COVID-19 was first thought to be a disease manifested only by respiratory symptoms at the beginning of the outbreak, we learned in time that it is a disease that can develop symptoms in a wide spectrum from asymptomatic infection to cardiovascular complications. Experience in the diagnosis, clinical characteristics and treatment of COVID-19 has been accumulating in the time since it is a new disease. The severity of the disease might be variable according to the viral load received and the immune response of the individual. The frequency of asymptomatic disease is substantially high. The most commonly seen complaints in symptomatic disease are fever, cough, fatigue, and myalgia, while nausea, vomiting, and loss of taste and smell can also be seen. The longer the duration of the symptoms, the higher is the risk of developing a more severe disease necessitating hospital admission and intensive care, and invasive ventilation. Solid knowledge of clinical symptoms and diagnostic tests is important since early diagnosis may prevent the spread and intensification of the disease.

Keywords: COVID-19, SARS-CoV-2, coronavirus, clinical findings, laboratory findings

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INTRODUCTION

COVID-19 infection has caused a fatal outbreak which started in the Wuhan City of China and spread all over the world from there. COVID-19 developed secondary to SARS-CoV-2 has been officially declared to be a pandemic by the World Health Organization on March 11, 2020 [1]. The clinical picture is variable from a completely asymptomatic one to a rapidly destructive course. The clinical picture of COVID-19 including the incubation period, asymptomatic patients, symptoms, risk factors for severe disease, and complications will be reviewed in this chapter.

INCUBATION PERIOD

The incubation period of COVID-19 disease is 2-14 days in 98% of the patients with a mean duration of 4-5 days [2-5]. The symptoms were reported to begin in 11.5 days (8.2-15.6) in 97.5% of the patients in a modeling study including 181 patients with a definitive diagnosis of Covid-19, while the mean duration of incubation was determined as 5.1 days [5]. Typically, the period from the initiation of symptoms and the development of the severe disease is a week [2]. The mean duration of incubation was predicted to be 5 days (4.4-5.6 days) in an analysis performed at a center out of Wuhan including 158 definitive cases [6].

It was reported in a striking study that the duration between the exposure and initiation of contagiousness (latent period) might be shorter [7]. Another study revealed that the viral load was high 2-3 days before the symptoms with a peak value of 0.7 days before the start of symptoms [8]. Therefore, it is important to screen the contacts of patients diagnosed to have COVID-19 and to consider the period before the start of symptoms.

ASYMPTOMATIC INFECTIONS

Asymptomatic infections and infections that are not symptomatic at the time of the diagnosis (pre-symptomatic) have been documented thoroughly in several studies [9-21]. Knowledge of the frequency of asymptomatic infections is crucial to understand the spread of the virus and the dynamics of the disease. Asymptomatic infections were reported to constitute 40-45% of SARS-CoV-2 infections in a study based on the data obtained from three major cohort studies [21]. However, no longitudinal follow-up was performed in that above mentioned and other similar studies to observe the development of symptoms. The prevalence of asymptomatic infections and the diagnosis of pre-symptomatic infections has yet to be understood since asymptomatic individuals are not routinely tested. The definition of asymptomatic is variable in several studies due to the specific symptoms evaluated. For example; 328 out of 634 (51.7%) cases were found to be asymptomatic in the Diamond Princess cruise in which all passengers and crew were quarantined in the Yokohama City of Japan. Considering the incubation period varying between 5.5 and 9.5 days, the authors calculated the actual rate of asymptomatic cases as 17.9% [14]. The rate of asymptomatic cases was 26% in an observational cohort study conducted on 199 infected patients in an inpatient treatment center in South Korea [22]. The percentage of patients tested positive for

SARS-CoV-2 but without any symptoms was reported to be 44% in a screening study performed in Ireland; however, some of them might be pre-symptomatic [20]. Higher rates of asymptomatic cases have been reported in some studies. For example, 29 out of 210 pregnant women (14%) admitted to two New York hospitals for childbirth at the time of the peak of the pandemic were tested to be positive for SARS-CoV-2 using polymerase chain reaction (RT-PCR). Other than those, four women who were tested positive for SARS-CoV-2 had a fever and other symptoms. Therefore, 29 out of 33 women with a positive test for SARS-CoV-2 (88%) were asymptomatic at the time of presentation to the hospital [19]. The rate of asymptomatic patients was around 20-40% in all those studies, while this wide range might be due to the different properties of the populations analyzed.

Asymptomatic patients might present clinically objective findings [10, 23]. An example of this is a study including 24 patients with asymptomatic infection; 50% of the patients had typical CT involvement of COVID-19 and another 20% of them had atypical radiological abnormalities [10]. In another study including 55 patients with asymptomatic infection, pneumonia was detected by CT in 67% of the patients at presentation; only two patients developed hypoxia, and all patients recovered (23). Cases that were asymptomatic at the time of the diagnosis as the cases mentioned above can be classified as pre-symptomatic infections. The initiation of symptoms was seen as a mean of 4 days (3-7 days) after the first positive RT-PCR test in a study performed [24].

CLINICAL PRESENTATION

Differentiating the first symptoms of COVID-19 from other viral upper respiratory infections is almost impossible. However, with the accumulating experience, it has now been acknowledged that COVID-19 infection is not a disease of the respiratory tract alone, but it is a disease involving many organs and is manifested with different symptoms according to the organ involved and the degree of the immune response [25].

The most frequent symptoms seen in COVID-19 infection are as follows [3, 26-31]:

- Fever
- Cough
- Dyspnea or difficulty in breathing
- Fatigue, weakness
- Muscle pain (myalgia) or the ache of body parts
- Headache
- Loss of smell (anosmia) and taste (ageusia)
- Sore throat
- Nasal congestion
- Nausea or vomiting
- Diarrhea

Symptoms vary according to the severity of the disease. For example, fever, cough, and dyspnea were reported to be more common in hospitalized patients with COVID-19 compared to patients with less severe disease and thus not admitted to the hospital. Atypical

symptoms might be seen in the elderly and patients with comorbidities, and the manifestation of fever and respiratory symptoms might be delayed [32, 33]. Fever was reported to be present in 44% of 1099 patients at admission to the hospital and 89% had fever rising after admission in a study performed in China [3]. No differentiation between mild and severe cases and prediction of the clinical course can be made according to the presence or absence of fever and cough [34, 35]. Dyspnea was demonstrated in larger studies to be a powerful predictor of severe disease. Respiratory distress might be developed generally during the second week of the disease and might progress to hypoxemia [3]. A clinical picture of viral pneumonia predominates and may include fever, cough, and hypoxia. Imaging of the lungs reveals bilateral ground-glass imaging and infiltrations [36].

Fatigue, headache, and myalgia are the most commonly reported symptoms with an incidence of 15-40% among outpatients with COVID-19 [37, 38]. These symptoms, although frequently disturbing, are not indicators of a severe clinical picture. Headache is bilateral with an intermediate severity and experienced in the temporo-parietal, frontal or periorbital areas [39]. A part of the patients may present with gastrointestinal symptoms such as nausea, vomiting, or diarrhea before the development of fever and lower respiratory tract signs and symptoms [31]. Diarrhea and nausea and vomiting were observed in 24% and 19%, respectively among the first 393 patients admitted to two hospitals in New York [40]. Enteric symptoms are generally seen together with fever and respiratory tract complaints. Among the 18,605 patients presenting to the hospital in the United Kingdom, 29% had enteric symptoms, generally together with respiratory symptoms, while only 4% of all patients reported enteric symptoms alone [38]. Symptoms of the upper respiratory tract such as nasal congestion, nasal discharge, sneezing, and sore throat are quite rare in COVID-19 infection.

On the other hand, loss of taste (ageusia) and smell (anosmia) has been reported widely before the start of the symptoms in young women and young and middle-aged individuals who needed no hospitalization [41, 42]. The largest study on this subject revealed the loss of smell in 1754 (87%) and loss of taste in 1136 (56%) out of 2013 patients [43].

Although most symptoms of COVID-19 are common in other respiratory tract infections or viral diseases, anosmia seems to be a more specific sign of COVID-19 [42]. In conclusion, the presence of anosmia and ageusia demonstrate no severe disease; however, they might be important indicators of SARS-CoV-2 infection.

CLINICAL COURSE OF THE DISEASE

The severity of COVID-19 infection might be variable from mild to critical. The course is frequently mild [9, 26, 27, 28, 41, 44]. Currently, there is no definitively accepted clinical classification for COVID-19. The following classification including four categories has been used by some authors [45].

- Mild cases: symptomatic cases with no observed pneumonia with imaging.
- Ordinary cases: Fever and signs of pneumonia with imaging.
- Severe cases: Dyspnea, hypoxia ($\text{SpO}_2 \leq 93\%$), abnormal blood gas analysis $\text{PaO}_2 < 60\text{mmHg}$, $\text{PaCO}_2 > 50\text{mmHg}$).

- Critical cases: Respiratory failure necessitating mechanical ventilation, shock, other organ failure requiring admission to ICU.

A similar classification was used in the study of Chinese Disease Control Center including 44,500 confirmed infections; however, item 1 and 2 were combined, such as;

- Mild to intermediate disease (pneumonia is mild or absent), reported in 81%
- Severe disease (dyspnea, hypoxia or findings such as more than 50% lung involvement in imaging studies in 24 to 48 hours) in 14%
- Critical disease (clinical pictures such as respiratory failure, shock, or multiorgan dysfunction), reported in 5%.

No death was seen in non-critical patients in that study. The General case fatality rate was reported to be 2.3% [46]. Asymptomatic/mild-intermediate disease, respiratory failure and death were seen in 80.5%, 19.5% and 5.5%, respectively in a meta-analysis including 38 studies [47]. The rate of critical disease and death are higher in hospitalized patients [34, 35, 48, 49]. Some 665 patients (24%) died or were referred to nursing care in a study including 2741 patients hospitalized due to COVID-19 in New York [35]. The clinical course of the disease and death rates are variable according to the region. The rate of admission to the intensive care unit was 12% among all cases with COVID-19 and 16% among all patients hospitalized in Italy with an estimated case fatality rate of 7.2% in mid-March [50, 51]. In contrast, the estimated case fatality rate in mid-March in South Korea was 0.9% [52]. This might be due to the demographic variability of the infections such as the median age of the infected patients (64 years in Italy and 40 years in Korea).

CLINICAL PROGRESSION

The clinicians must be careful on clinical progression since it generally occurs a week after the initiation of the disease. Mean duration between the initiation of symptoms to development of dyspnea among patients who develop severe disease has been reported to be 5-8 days, between the start of the disease to the development of acute respiratory distress syndrome (ARDS) as 8-12 days and from the initiation of symptoms or the disease to the admission to intensive care unit (ICU) as 10-12 days in the studies performed [27, 28, 32, 41]. The rate of admission to ICU among hospitalized patients has been reported to be 26-32% [28, 41]. The mortality rate in patients admitted to the ICU, depending on the study and the properties of the population is 39-72% [27, 30, 32, 41]. The mean duration of hospital stay in surviving patients has been 10-13 days in the studies performed [3, 28, 30].

RISK FACTORS FOR SEVERE ILLNESS

Advanced age; is a powerful risk factor for severe disease, and the development of complications and mortality [3, 28, 30, 46, 53, 54, 55]. Mortality rate among more than 44,000 confirmed COVID-19 cases in China was reported as 14.8%, 8%, 3.6%, 1.3%, 0.4%

and 0.2% in patients aged 80 years and above, 70-79 years, 60-69 years, 50-59 years, 40-49 years and <40 years, respectively [56, 57]. Advanced age has been defined as a serious risk factor for severe disease and death rates in recent literature from all over the world. One example of these studies is a large one evaluating the outbreak in 20.133 patients in the United Kingdom and the mean age of 5.165 patients who died in the hospital (26%) due to COVID-19 was reported as 80 years in that study [58]. A dramatic increase was observed among the group of patients with advanced age among 5700 patients in New York and the mortality rate reached up to 61% (122/199) in males and 48% (115/242) in females with the age of more than 80 years [34].

The mortality rate was markedly higher among the elderly patients (>63 years) compared to young patients (36% and 15%) in 1.591 patients admitted in the ICU in Italy. The mortality rate in 362 patients with an age above 70 years was reported to be 41% [59].

Other risk factors: Initial studies from China revealed that diseases such as hypertension, cardiovascular disease, and diabetes were associated with severe disease and mortality [3]. Later, other studies from various regions have demonstrated that the risk of development of severe disease and mortality was higher in patients with comorbidities [32, 46, 35, 60, 61, 62, 63].

- Cardiovascular disease
- Diabetes mellitus
- Hypertension
- Chronic lung disease
- Cancer (in particular hematologic malignancies, lung cancer, and metastatic disease)
- Chronic kidney disease
- Obesity
- Smoking

Individuals with hypertension, cardiovascular disease, and chronic lung disease were reported to carry a higher risk of having a severe course in a meta-analysis evaluating 46.248 confirmed cases of COVID-19 in eight studies [64]. The mortality rate was 12-fold among patients with reported comorbidities compared to the ones with no comorbidities in a study from the United States of America including 300.000 confirmed COVID-19 cases [65].

In conclusion; advanced age and presence of comorbidity, alone or combined, are marked risk factors for severe disease and mortality.

COMPLICATIONS

Patients with a mild course are generally not hospitalized. The treatment of most patients can be managed at home. The decision for hospitalization depends on the clinical picture, necessity of supportive care, potential risk factors for severe disease, and the ability of the patient for self-isolation. Patients with risk factors should be closely followed-up especially during the second week since there is a risk of advancement to severe disease. Patients with COVID-19 with initially mild symptoms may deteriorate during the first week [66]. Dyspnea was reported to develop mean five days after the start of the symptoms and admission to

hospital was required a mean of seven days after the initiation of symptoms in a study including 138 patients admitted to the hospital with pneumonia secondary to SARS-CoV-2 in Wuhan [28].

The most significant complications of COVID-19 can be defined as:

Respiratory Failure

Acute respiratory distress syndrome (ARDS) is the most important complication in patients with COVID-19 and might be observed a short period after the initiation of dyspnea. ARDS develops on day 8-14 in 10-20% of the patients [67, 68]. Non-cardiogenic pulmonary edema develops in those patients and mechanical ventilation might be required. Hypertension, diabetes mellitus, and cardiovascular and cerebrovascular diseases have been reported to be a risk factor for ARDS [68]. Retrospective studies on patients with critical illness established that initiation of dyspnea was average 6.5 days after the start of the disease; however, the development of ARDS was seen even in a shorter period after the start of dyspnea (mean 2 days) [28, 32, 41, 55]. Some 12-24% of the hospitalized patients required mechanical ventilation according to the studies performed in the USA [34, 35].

Cardiac and Cardiovascular Complications

Arrhythmia, acute cardiac damage, and shock are reported complications [28, 55, 69]. The rate of these complications was reported to be 17%, 7%, and 9%, respectively in a study [28]. On the other hand, acute cardiac damage and heart failure was seen in 77% (72/94) and 49% (41/83), respectively in a retrospective study evaluating 113 patients who died due to COVID-19 infection [69]. The development of cardiomyopathy was reported in one-third of the patients in a series including 21 severe cases admitted to the ICU in the USA [55].

Thromboembolic Complications

Coagulation disorders that complicate the clinical management of the disease are seen in some patients with COVID-19. These patients carry a high risk for arterial and venous thrombosis of small and large vessels due to hypercoagulation [70, 71]. SARS-CoV-2 directly invades endothelial cells and causes cell damage. Endothelial damage, microvascular inflammation, endothelial exocytosis, and/or endothelitis play a central role in the pathogenesis of acute respiratory distress syndrome and organ failure according to some experts [72, 73]. Induction of endothelial cells due to infection causes excess production of thrombin and fibrinolysis is prevented. Also, patients are prone to venous and arterial thromboembolic events due to hypoxia, increased inflammation, and immobilization. Commonly observed laboratory findings among hospitalized patients with COVID-19-associated coagulopathy are mild thrombocytopenia, increased level of D-dimer, fibrin degradation products, and prothrombin time. High levels of D-dimer have been highly associated with a higher death rate [70, 74, 75, 76]. Pulmonary embolism, deep venous

thrombosis, myocardial infarct, ischemic events, or systemic arterial embolism can be frequently seen in these patients. Cases with severe COVID-10 have been generally shown in the studies performed to be complicated with coagulopathies and DIC has been demonstrated in most cases of mortality.

Inflammatory Complications

A “cytokine storm” including an increase in the levels of inflammatory cytokines such as IL-1, IL-6, IL-8, and levels of TNF- α and IFN- γ is present in the pathogenesis of COVID-19 disease [77, 78]. Persistent high fever and high levels of inflammatory markers (i.e., D-dimer and ferritin) and increased proinflammatory cytokines have proven a marked inflammatory response on a laboratory basis and these laboratory values have been associated with critical and fatal diseases [27, 79, 80]. Levels of many cytokines such as C-reactive protein (CRP), ferritin, and IL-6 were reported to increase in severe disease in a meta-analysis [32]. Decreased interleukin-6 (IL-6) levels were revealed to be closely associated with treatment efficacy, while increased levels of IL-6 demonstrated exacerbation of the disease in a retrospective observational analysis including 69 cases with severe COVID-19 [81]. The authors concluded that the dynamic changes in the IL-6 levels could be used as a marker during the follow-up of the disease in patients with severe COVID-19. Finally, cytokine storm should be considered in patients with persistent fever despite treatment, increased D-dimer, ferritin, and CRP levels, decreased lymphocyte and platelet counts, increased fibrinogen levels, and deteriorated liver function tests. Early diagnosis of this clinical picture is substantial since it is a condition that needs emergency treatment. Patients demonstrating signs of severe COVID-19 infection should be daily monitored for markers of a cytokine storm. Other inflammatory complications and auto-antibody mediated signs have been defined other than the cytokine storm [82, 83]. Myasthenia gravis is one of them [82]. Guillain-Barré syndrome can be developed 5-10 days after the initial symptoms [84]. In addition, a multi-system inflammatory syndrome with similar clinical properties with Kawasaki disease and toxic shock syndrome has been defined in children with COVID-19. This syndrome, rarely reported in adults also has been characterized with markedly increased inflammatory markers and multi-organ dysfunction (especially cardiac dysfunction) and minimal pulmonary involvement [85].

Secondary Infections

Secondary infections don't seem to be a common complication of COVID-19, although the data is limited [86, 87]. The rate of the reported bacterial or fungal infections was 8% in a publication evaluating nine studies, mostly from China and they mainly included respiratory tract infections and bacteremia [86]. Possible invasive aspergillosis has been reported among the patients with ARDS secondary to COVID-19 and no immune suppression; however, the incidence of this complication is unknown [88, 89, 90, 91].

RECOVERY AND LONG-TERM SEQUELA

According to the World Health Organization (WHO), the period of recovery seems to be almost two weeks for mild disease and three to six weeks for the severe disease [92]. Nevertheless, the period of recovery varies based on age and previously present additional diseases in addition to the severity of the disease.

A survey on 350 patients with COVID-19 in the United States of America revealed that only 39% of the patients admitted to a hospital had a full recovery 14-21 days after the diagnosis [93]. Similarly, only 13% of 143 patients admitted to the hospital (7 of them were intubated) due to COVID-19 in Italy were without symptoms after a mean of 60 days starting from the initiation of the disease [94]. The most common persistent symptoms were fatigue (53%), dyspnea (43%), joint pain (27%), and chest pain (22%); however, none of the patients had a fever or acute findings of the disease. On the other hand, persistent severe disease together with persistent fever for weeks and pneumonia associated with underlying immunosuppression has been reported in another study [95].

Symptoms may persist for a long time also in patients with COVID-19 and milder symptoms [98, 96]. In a survey with 292 participants diagnosed to have COVID-19 and were treated on an outpatient basis, 65% of the patients reported being as healthy as before they had the disease 14-21 days after the diagnosis [96]. Individuals with full recovery recovered in a mean of 7 days after the diagnosis. The symptoms that patients most possibly continued to have 14-21 days after the diagnosis were cough (43%) and fatigue (35%).

As of the established data, a potential of respiratory insufficiency and the cardiac sequel has been suggested, although the evaluation of long-term sequela of COVID-19 has not been adequately evaluated yet [97-102].

LABORATORY FINDINGS

The most common laboratory findings seen in patients hospitalized with the diagnosis of COVID-19 are lymphopenia, high levels of serum aminotransferase, lactate dehydrogenase, and inflammatory markers (i.e., ferritin, C-reactive protein, and erythrocyte sedimentation rate), and abnormalities in coagulation tests. [28, 3, 40, 27, 30].

Lymphopenia is the most common laboratory finding of COVID-19 and is present in 83% of hospitalized patients [3, 27]. High D-dimer levels and lymphopenia are associated with mortality [30, 46].

Although procalcitonin level is normal at presentation; its level is possibly increased in patients admitted to the ICU [27, 26, 28]. Cardiac troponin I levels were found to be substantially high only in patients with severe COVID-19 in addition to low level of lymphocytes, high levels of LDH, and D-dimer in a meta-analysis evaluating 341 patients [103].

CONCLUSION

COVID-19 disease is a contagious and fatal infection that has spread all over the world in a short time. We have observed up to now that the infection is mostly asymptomatic; symptomatic and severe infection develops less frequently. The incubation period is 2-14 days with an average of 4-5 days. The most commonly seen complaints are fever, cough, myalgia, fatigue, diarrhea, and loss of taste and smell. Pneumonia is the most common sign of serious infection and severe infection is developed in approximately 15% of the patients with hypoxia, dyspnea, or diffuse pulmonary involvement. ARDS is the main complication in patients with severe disease and it might be observed a short while after the start of dyspnea. Many other complications including thromboembolic events, acute cardiac damage, and inflammatory complications have been reported. The risk of developing severe disease and mortality is high in elderly individuals and individuals with comorbidities. Laboratory parameters and imaging studies will be of guidance in the course of the disease. A good understanding of the clinical and laboratory findings of the COVID-19 disease will play a major role in the early diagnosis of the disease and the control of the outbreak.

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Chapter 455

DIAGNOSIS OF COVID-19

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ABSTRACT

The pandemic that emerged at the beginning of this year spread rapidly all over the world. The most effective way to combat such a large-scale epidemic is to quickly diagnose infected individuals and take necessary isolation measures. Although rapid antigen tests used in the first stage in the diagnosis of COVID-19, they have quickly left their places to molecular-based real-time PCR tests due to sensitivity problems. Antibody response based diagnosis can be problematic because those found can become detectable as early as 2 weeks after the onset of infection, which is not a suitable acquisition for the diagnosis of acute infection. In this article, applications and methods used for the diagnosis of COVID-19, will be discussed.

Keywords: SARS-CoV-2, COVID-19, real-time PCR, diagnosis

INTRODUCTION

At the end of 2019, a new type of pneumonia caused by a novel coronavirus emerged in the city of Wuhan, China. Then this virus has spread rapidly worldwide. The World Health Organization (WHO) named the disease Coronavirus Disease 2019 (COVID-19) and the virus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 infections can cause common symptoms of viral pneumonia, like cough, fever, dyspnea, and

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myalgia. These symptoms are not specific for COVID-19. Therefore, patient history (contact with a suspicious or confirmed case, travel, etc.) constitutes the starting point for the diagnosis of COVID-19. The diagnostic algorithm of COVID-19 initially includes epidemiological history, clinical signs, CT scan, blood count, and biochemistry test results. Following these routine tests, showing the viral genome by nucleic acid amplification techniques (NAT) (like real-time PCR) may prove the diagnosis. Besides NAT, detection of IgM/IgG responses by serological tests and viral antigens by point-of-care tests (POCT) may be helpful.

COMPUTED TOMOGRAPHY AND OTHER BIOCHEMICAL PROPERTIES

Computed tomography (CT) results may give information about the severity of SARS-CoV-2 infection and be used for rapid pre-diagnosis and prognosis prediction. Abnormal CT scans with bilateral patchy shadows or ground-glass opacity, bilateral pulmonary parenchymal involvement, and consolidative pulmonary opacities in the lungs found around 86% of the patients at the time of their hospital admission. Besides these findings no radiographic or CT abnormality was found in 3% of patients with severe disease and 18% of patients with mild disease also had no radiological sign. Nevertheless, there is a limitation in these early reports in regards to severity classification because the criteria were not well defined. However, these findings cannot be differentiated from other viral pneumonia, and in some different clinical situations, they have similar images. It should not be forgotten that it can be obtained [1-4].

The most common finding in hemogram is lymphopenia. It may occur in 70-83% of patients. Detoloration and persistence of lymphopenia combination with high levels of inflammatory cytokines, correlated with disease severity and mortality. Coagulopathy and disseminated intravascular coagulation related to other biomarkers like D-dimer and fibrinogen, procalcitonin, and troponin, also strongly correlated with clinical severity and mortality [4-6].

Sample Collection

The virus begins to spread in the upper respiratory tract 1-3 days before onset of the symptoms. Virus especially has high titers in the first week of the disease. The virus load in the upper respiratory tract decreases in the second week and it is found in greater amounts in the lower respiratory tract samples. For the diagnosis of COVID-19, upper respiratory samples are the most common samples, but sputum (who can produce sputum) or lower respiratory tract samples such as broncho alveolar lavage fluid (BAL), endotracheal aspirate can also be taken in patients. In the second week of the disease, lower respiratory tract samples can be preferred. Nasopharyngeal and oropharyngeal swab samples (alone or, preferably, in a combination of them) nasopharyngeal irrigation and nasal aspiration fluids are samples of upper airways. A healthcare professional can take these samples or the patient can give these samples to himself. Similar results reported both nasopharyngeal swabs and nasal swabs that the person obtains himself. Apart from this, more reproducible results can be

obtained, especially with saliva samples originating from the pharynx posterior wall. Because of a high risk of aerosol generation, infection control measures should be taken when collecting lower respiratory tract samples such as induced sputum, BAL, or endotracheal aspirates. In the first 14 days after the onset of the disease, the most reliable example to detect SARS-CoV-2 is nasopharyngeal swab after sputum and then throat swab. In addition, the virus begins to be excreted with feces, especially from the second week and continues to be excreted with feces for a long time. Since viral excretion in upper respiratory tract samples may be low or irregular, especially in advanced stages of the disease, stool samples can be useful for diagnosis. However, since the viral load varies according to the samples and the severity/period of the disease, the negative test result obtained with samples taken from the upper respiratory tract does not exclude the disease, and in case of clinical suspicion, the test should be repeated a second time or by taking a different sample that may have higher sensitivity [6-8]. Single nasopharyngeal swab samples are becoming more preferred because they have better tolerated by the patient and safer for the sampler.

Timing and technique of sample collection have grand effect on the sensitivity of molecular tests. Yang et al. found the highest positivity rates in the first 7 days and samples taken from seriously ill patients. They obtained the highest positivity rates in BAL samples (78.6-100%) in severe patients [9]. In another study conducted in China, the positivity rates were 93% for BAL, 72% for sputum, 63% for nasal swabs, 32% for pharynx swabs, and around 29% for feces [10]. In contrast, besides more frequent usage of oropharyngeal swabs, compared to nasopharyngeal swab samples, SARS-CoV2 RNA was detected in only 32% of oropharyngeal swabs, which is significantly lower than the detection rate (63%) of nasopharyngeal swab samples [6, 9, 10]. Sampling technique (depend on the experience of health care worker), timing, quantity, so many other factors such as where the sample is taken, the transport and storage of the sample, the performance of the molecular test used, and the severity of the disease can seriously affect the test results.

Molecular and Serological Methods

The widely used technology for SARS-CoV-2 is reverse transcription followed by real-time polymerase chain reaction (RT-PCR) technology. RT-PCR is currently used in many microbiology laboratories in a very wide range from detection and quantification of the single pathogen to syndromic approaches and panels for the diagnosis of different infectious agents [1, 7]. Following the emergence and rapid spread of SARS-CoV-2 in China, many organizations have published their diagnostic protocols and then different commercial companies have released RT-PCR test kits for diagnosis, and some of these have been pre-approved or approved by different organizations such as the FDA and WHO.

The first step in RT-PCR is the synthesis of complementary DNA (cDNA) from the RNA genome. Then, the cDNA is amplified and detected using unique primer and probe systems. The development process of these tests generally involves two main steps, (i) selection of suitable gene regions means the selection of conserved regions in known sequences and performing primer/probe design (ii) Optimization and validation of the developed test. In a study by Corman et al., viral genomes associated with SARS include the RdRP gene (RNA-linked RNA polymerase gene), open reading frame ORF1ab region, E gene (envelope protein

gene), and N gene (nucleocapsid protein gene) are reported as conserved regions, and these regions are still frequently used target regions for RT-PCR [5, 6, 8, 11]. Studies on these gene regions have also reported that both RdRP and E genes have high analytical sensitivity (3.6 and 3.9 copies per reaction) and the N gene has weaker analytical sensitivity (8.3 copies per reaction). At the same time, the reaction buffers used in the tests, sample collection, and nucleic acid extraction methods, the devices used for performing RT-PCR and detection can affect the test's performance [7, 8, 12]. In the United States, CDC recommends two nucleocapsid protein targets [N1 and N2], while WHO recommends an initial screening with the E gene followed by a confirmatory test using the RdRp gene for more sensitive and specific results. Since the viral genes have equal copy numbers, the test should be well optimized as the test performance is usually determined not by the target itself but by the reagent design. At least two molecular targets should be included in the analysis to prevent false positive or negative results from potential genetic alterations of SARS-CoV-2, as well as potential cross-reactions with other endemic coronaviruses [6]. However, the WHO should include single target test formats with high specificity, especially during the epidemic period.

It is developed and evaluated in molecular methods worldwide other than RT-PCR. These include loop-mediated isothermal amplification, multiplex isothermal amplification methods, followed by microarray detection and CRISPR/Cas systems [30]. Cas13-based SHERLOCK (specific high-sensitivity enzymatic reporter unlocking) platform, that tested for detection of ZIKA and Deng viruses in patient samples. This method could detect at concentrations as low as 1 copy per microliter. Currently, Zhang et al. have adopted this technology to detect SARS-CoV-2, and the test has received FDA pre-approval [13].

According to WHO, the urgent priority for COVID-19 diagnostic research is the development of nucleic acid and protein tests and providing the opportunity to test at the bedside of patients (point of care tests, POC). The longer-term priority is to integrate these tests into multiple panels, as the leading multi-parametric respiratory pathogens panel manufacturers are adding SARS-CoV-2 to their panels. To improve surveillance efforts, serological tests using proteins are needed in addition to nucleic acid tests. These tests, unlike nucleic acid tests, have post-recovery detection advantages. This allows clinicians to monitor both sick and recovered patients, providing a better estimate of total SARSCoV-2 infections. POC tests are cost-effective devices used to diagnose patients outside of central facilities. These can be employed in areas such as community centers to reduce the burden on clinical laboratories [8].

Although RT-qPCR is specific for the diagnosis of COVID-19, false negativities cannot be ignored. The sensitivity of RT-PCR was found around 89% in a meta-analysis [14]. Since the sensitivity changes depending on the samples, their sensitivity in practice is even lower. Because of mild or asymptomatic cases with infection, the number of COVID-19 infections reported around the world so far does not reflect the actual infected people. For example, asymptomatic cases were reported to be 17.9% in the Diamond Princess ship study. All of these findings point to be considered in preventing the spread of the disease, as asymptomatic individuals constitute a serious source of transmission [8]. In this regard, the deficiencies of nucleic acid detection and CT scans for the diagnosis of COVID-19 and the fact that they are more applicable in central institutions. Considering that, there is a need for test formats that can work with samples that can be taken quickly and easily in the field. Immunologically based tests that can detect antigens or antibodies in cases where no results obtained with PCR tests may work in practice.

For the rapid detection of SARS-CoV-2 antigens or antibodies, some serological tests have been developed, and some of them have been approved by many institutions. Many different commercial companies develop serological tests for detection of SARS-CoV-2 infection in lateral flow tests, automated chemiluminescence immunoassay systems (CLIA), ELISA, and other formats. Although antibodies reach the detectable level from the seventh day of the disease during COVID-19, generally IgM responses can be detectable in the second week and IgG responses start from the 3rd week safely. Antibody responses can also be affected by several factors such as disease severity and host immune status. Although IgM responses remain positive for a shorter time, IgG positivity may persist for a long time. The level and duration of protection of antibody responses that develop after SARS-2 virus infections are not yet known. Its protection is estimated not to be very long (longer than 6 months). It is attractive that rapid antigen tests will theoretically allow low-cost and rapid detection of SARS-CoV2, but as with influenza (Flu) viruses, their sensitivity will be lower than molecular tests. The sensitivity of an antigen test approved by the FDA is 80%. Especially with the development of monoclonal antibodies, more and more sensitive antigen tests are being developed [6, 15]. Considering the variability of viral loads and sample diversity in COVID-19 patients, the problem of sensitivity of antigen tests will be better understood. Antibody tests that examine the host's response to the agent, on the other hand, maybe more useful in showing the previous infection. They can also be used as additional tests in confirming COVID-19 infection; However, in a situation where the prevalence is low, the false positivity rates of these tests will be very high despite their high specificity (for example, if the seroprevalence in the population is 1%, the probability of antibody positivity obtained with a specificity of 99% will remain around 50%). Therefore, it is recommended that they be used carefully, considering the limitations mentioned in auxiliary tests and seroepidemiological studies. The use of antibody tests for purposes such as investigating the presence of protective antibodies in individuals should be avoided. Previously, this type of serological testing has played an important role in the epidemiology of SARS and other coronavirus outbreaks. Rapid lateral flow tests that can detect both IgM and IgG antibodies will undoubtedly play an important role in COVID-19. However, there are specificity problems in IgM responses and the development of specific IgG response takes time. In this regard, serology tests do not seem likely to play a role in active case management, apart from tasks such as diagnosing/confirming late COVID-19 cases or determining individual immunity [1, 6, 8]. Serological tests can be used as an IVD test to complement existing RT-PCR tests, this can also lead to a much better diagnosis of COVID-19 and provide additional information about the immune status of suspected cases. However, the clinical accuracy of rapid tests must be rigorously evaluated before they can be authorized for mass screening of COVID19. Recent reports from many European countries suggest that most rapid tests for COVID-19 sourced from China did not show good analytical performance and did not work in more than 70% of COVID-19 cases. Besides, due to the late development of IgM and IgG responses, there is a need to include other biomarkers of the early stage of SARS-CoV-2 infection to develop practical COVID-19 rapid tests [5].

Although its use in the diagnosis of SARS-CoV-2 is limited due to its high cost, next-generation DNA sequence analysis is used especially for understanding and monitoring viral evolution and for genoepidemiological studies. At the same time, the US Food and Drug Administration granted Emergency Use Authorization (EUA) for Illumina's next-generation sequencing (NGS) test for COVID-19, in June. This is the first such authorization for an NGS

diagnostic. The testing yield was reported as 3,000 tests of nasopharyngeal or oropharyngeal samples with a 24-hour turnaround. The detection performance was reported at least 1,000 copies of the viral genome per milliliter and displays 98% sensitivity and 97% specificity by the company literature [5, 6, 8, 16, 17].

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Chapter 456

TREATMENT OPTIONS FOR COVID-19 PATIENTS

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ABSTRACT

COVID-19 disease was first defined in December 2019, and its causative agent was determined as SARS-COV-2 in January 2020.

There is no specific treatment for this infection that affects more than one organ system, especially the pulmonary system. Many medical treatments have been tried until today, and studies on their efficacy and safety have been published.

Anti-malarial drugs; anti-retrovirals, ribavirin, remdesivir, favipiravir, and other antiviral agents; corticosteroids; anti-cytokines and immunomodulatory agents; immunoglobulins are listed among the drugs evaluated. The mechanism of action, pharmacokinetic and pharmacodynamic properties, and side effects of each drug group are different. Medical treatment should be individualized considering these differences.

Keywords: COVID-19 treatment, chloroquine, ribavirin, remdesivir, favipiravir, corticosteroids

INTRODUCTION

Coronavirus-19 disease (COVID-19) was first reported in the Wuhan province of China in December 2019. Then, it was declared as a pandemic threatening the whole world by WHO on March 11, 2020. The causative agent, SARS-COV-2, belongs to the beta-coronaviridae family and has a single-stranded RNA structure. SARS-COV-2 encodes the S protein that binds human angiotensin-converting enzyme 2 (ACE2), thus membrane fusion occurs and the virus is allowed to enter the cell [1, 2]. Once inside the cell, SARS-COV-2,

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like other coronaviruses, controls the cell's synthesis mechanisms for the synthesis of viral proteins and viral replication [3].

Once the virus enters the human body, it usually induces a range of host responses such as autophagy, apoptosis, stress response, and innate immunity [4].

Some of these immune responses can be protective for patients, while others can be harmful. The protective immune response allows the patients to go through the disease with asymptomatic or mild symptoms. It has been found that approximately 80% of people infected with SARS-COV-2 developed a protective immune response. Providing interferon synthesis by stimulating the natural immune system including natural killer cells and T cells plays an important role in the formation of a protective immune response [5, 6].

In elderly, immunosuppressed patients or individuals with diabetes, hypertension, obesity, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, asthma and interstitial diseases, COVID-19 progresses with more severe respiratory symptoms and acute respiratory distress syndrome (ARDS), and may even result in death. SARS-CoV and MERS-CoV, which are members of the coronavirus family, have mechanisms that reduce or delay interferon production; this leads to increased inflammatory response and exacerbation of lung damage [7, 8]. Cytokine storm, known as overproduction of inflammatory cytokines, is associated with increased disease severity and poor prognosis [4, 9].

An increase in cytokine production, indicative of cytokine storm, has been detected in the bronchoalveolar lavage fluid and peripheral mononuclear blood cells of COVID-19 patients [10]. Besides the lungs, SARS-Cov-2 also affects other organs, especially the heart and brain. There is no specific drug or vaccine for SARS-Cov-2 yet. Therefore, the treatment of severe cases is challenging. Until specific drugs or vaccines are found, it is recommended to use other drug groups that have been shown to be effective in studies.

CURRENT DRUGS IN THE TREATMENT OF COVID-19

Since there is no specific drug for treatment; early diagnosis, isolation of patients and rapid provision of supportive treatments are life-saving. Treatment of COVID-19 patients is based on the reassessment of existing medications and, primarily, improvement of symptoms. Since ARDS and secondary bacterial infections frequently develop in patients; antibacterial, anti-inflammatory, and immunomodulatory drugs take their place in the treatment in addition to antiviral agents.

ANTIMALARIAL AGENTS

Chloroquine and hydroxychloroquine have been developed for the treatment of malaria and have proven effective in the treatment of chronic inflammatory diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). By inhibiting the glycosylation of host receptors, proteolysis and endosomal acidification prevent viruses from entering the cell. In addition, they decrease cytokine production and regulate immunomodulation by inhibiting autophagy and lysosomal activity. In a multi-center,

randomized study, it was shown that the anti-inflammatory effect of hydroxychloroquine may be beneficial in COVID-19 patients [11].

However, hydroxychloroquine added to standard therapy does not increase the virus response; it decreases inflammation and the severity of lymphopenia and accelerates the regression of symptoms. It is thought that the patient group benefitting the most from hydroxychloroquine is the patients with high CRP and lymphopenia.

A meta-analysis of 42 studies showed that hydroxychloroquine was not associated with overall mortality [11]. In the same meta-analysis, it was shown that the fever response developed more rapidly in patients using hydroxychloroquine.

For the treatment of COVID-19, the chloroquine dose is 500mg orally, once or twice a day [12]. However, there are very few data proving the safety and efficacy of these doses. The recommended dose of hydroxychloroquine is 2 x 200mg per day after a 2 x 400mg loading dose [13].

Antimalarial drugs are generally well tolerated. QT prolongation, hypoglycemia, neuropsychiatric effects, and retinopathy are rare (10%) but serious side effects of hydroxychloroquine. QT prolongation; especially in patients with advanced age, female patients, individuals with a history of heart disease, hypokalemia or kidney and liver failure, patients using diuretics, such as furosemide and thiazide, and other drugs that prolong the QT interval is more frequently observed. ECG should be taken before treatment to evaluate and follow-up on the QT prolongation. No significant side effects of chloroquine used at the indicated doses and duration for the treatment of COVID-19 have been reported. These drugs are safe during pregnancy.

In a review evaluating 12 studies, it was found that chloroquine and hydroxychloroquine used during pregnancy do not cause ocular toxicity in the newborn [14].

ANTIVIRAL AGENTS

Favipiravir

Favipiravir is used in the treatment of avian influenza or influenza that is resistant to neuraminidase inhibitors. It is a guanine analog, its antiviral activity is reduced by competition in the presence of purine nucleosides. Favipiravir is taken up into the infected cell by endocytosis and transforms into the active form by phosphoribosylation and phosphorylation. It targets the catalytic part of the RNA-dependent RNA polymerase, thus, it shows antiviral activity by disrupting the nucleotide sequence during viral RNA replication. It has been used in the treatment of RNA virus infections such as influenza, Ebola, and norovirus [15]. There are in- vitro and human studies which is used experimentally in the treatment of SARS-CoV-2. In a randomized controlled study comparing favipiravir and umifenovir, it was reported that the recovery rate was higher (71.4%) and the recovery time of fever and cough symptoms was shorter in the favipiravir group [16]. In another study, significant radiological improvement, faster reduction in viral load, and fewer side effects were observed in patients who received favipiravir compared to the control group [17].

The dose of favipiravir varies according to the viral agent detected. For example, in influenza treatment, lower doses are sufficient compared to ebola and SARS-Cov-2 treatment.

The high dose range is also considered for the treatment of COVID-19 [18]. After a loading dose of 2400-3000 mg given every 12 hours on the first day, a maintenance dose of 2 x 1200-1800 mg/day is recommended. Its side effects are mild and can be treated. An increase in liver enzymes, hyperuricemia, psychiatric symptoms, and gastrointestinal side effects are seen.

Lopinavir/Ritonavir

Lopinavir is a protease inhibitor with a high affinity for HIV-1 protease. It is used in combination with ritonavir to increase the oral bioavailability and effectiveness of lopinavir. Since SARS-CoV-2 is an RNA virus like HIV, lopinavir/ritonavir has been used in the treatment of this infection. It has also been recommended in the treatment of COVID-19 due to the existence of studies that have found that it reduces the mortality in patients infected with SARS-CoV-1 [19]. Preliminary studies are showing increased viral clearance in COVID-19 patients treated with lopinavir/ritonavir [20]. However, a meta-analysis showed that this combination did not reduce the time of hospitalization and mortality compared to the control group [21]. The dose of lopinavir/ritonavir in the treatment of COVID-19 is 400mg/100mg twice a day. The duration of treatment is 14 days. Since there are prominent drug-drug reactions and side effects, the drugs used by the patients should be reviewed before the treatment and their side effects should be closely monitored. The most common side effects are nausea, vomiting, and hepatotoxicity. Approximately 50% of patients using lopinavir/ritonavir experience side effects; the rate of quitting the drug due to these side effects is 14% [22].

Ribavirin

Ribavirin is a guanine analog that inhibits RNA-dependent RNA polymerase. Although its effectiveness against other coronaviruses is known, its in-vitro activity against SARS-CoV2 is limited and requires higher doses. It is not recommended in first-line therapy. The efficacy of ribavirin has mostly been evaluated in combination therapy. In a multicentre, prospective, open-label, randomized controlled trial, it was shown that lopinavir and ribavirin combination therapy resulted in better compliance, faster viral clearance, and shorter hospital stay compared to lopinavir/ritonavir and ribavirin combination or ribavirin monotherapy [23]. In a systematic review that included 30 studies evaluating the effectiveness of ribavirin in COVID-19, inadequate results were obtained in 26 studies; severe hematological and hepatic side effects were reported in 4 studies [24]. The recommended dose of ribavirin is 1000-1500mg per day [25]. It is administered intravenously, the maximum duration of treatment is 10 days [25]. Ribavirin commonly has haematologic and hepatic side effects. Its hematological side effects are dose-dependent. It has been reported that hemolytic anemia developed in 60% of the patients and increased transaminases in 75% of the patients who received high-dose ribavirin for the treatment of SARS [24]. Also, ribavirin is teratogenic and should not be used during pregnancy [26].

Remdesivir

Remdesivir is the first antiviral drug developed for Ebola virus treatment [27]. It is an adenosine analog and a prodrug that disrupts viral RNA synthesis. In addition to the Ebola virus, it is effective against different virus families including Filoviridae, Paramyxoviridae, Pneumoviridae, and Orthocoronavirina. In animal studies evaluating its efficacy on SARS-CoV-2, remdesivir has been observed to reduce viral load, rate of disease progression, and improve pulmonary function [28]. A randomized, double-blind, placebo-controlled trial demonstrated that the duration of clinical recovery was similar in the remdesivir and control groups [29]. A limitation of this study was that lopinavir/ritonavir, corticosteroid, and/or interferon could be used in both remdesivir and control groups. There are also studies proving the opposite. In another randomized controlled study comparing 538 patients treated with remdesivir and 521 patients treated with placebo, the mean recovery time in the remdesivir group was four days shorter than the control group [30]. Remdesivir is the first antiviral agent approved recently by the FDA for the treatment of COVID-19.

For the currently studied therapeutic dose of remdesivir; after a single loading dose of 200 mg on the first day, the maintenance dose is 100mg once a day. It is administered as an IV infusion. There are no clear data on the duration of treatment, and no significant difference was found between the two treatment durations in the Phase III study evaluating the 5 and 10-day treatment durations (NCT04292899). The most common side effects are constipation, hypokalemia, anemia, thrombocytopenia, and increased bilirubin levels. It is not recommended for use in patients with liver and kidney failure.

ANTIBACTERIAL AGENTS

Azithromycin

In vitro efficacy of azithromycin, an antibiotic from the macrolide group, against the Ebola virus has been demonstrated [31]. It is also effective in preventing severe pulmonary infections in patients with viral infections. In a study evaluating the combined regimen with hydroxychloroquine in 20 COVID-19 patients, azithromycin was shown to increase the efficacy of hydroxychloroquine [32]. However, the risk of QT prolongation should be considered in combination with hydroxychloroquine.

Teicoplanin and Other Glycopeptides

Another antibacterial agent that stands out in the treatment of coronavirus infections is teicoplanin. It has been shown in vitro that teicoplanin prevents the entry of other coronaviruses such as Ebola, MERS, and SARS into the cell [33]. However, there is no study showing its effectiveness on SARS-CoV-2.

IMMUNOMODULATOR AND IMMUNOSUPPRESSIVE AGENTS

Interleukin-6 Inhibitors

Tocilizumab is a human IL-6 receptor antagonist; it is used in the treatment of RA and cytokine release syndrome (CRS). It is observed that IL-2 receptor, IL-6, IL-8, IL-10, and TNF-alpha levels are increased in COVID-19 patients with cytokine storm. Increased cytokine release is associated with increased disease symptoms. Since IL-6 may play an important role in stimulating the excessive inflammatory response in the lungs with COVID-19 involvement, tocilizumab is thought to be effective in the treatment of this infectious disease. In a multi-center study, it was observed that 75% of the patients with severe COVID-19 disease experienced an improvement in fever and a decrease in oxygen demand [34]. In the same study, regression was found in CT findings and improvement was seen in CRP increase and lymphopenia [34]. The mortality rate was also significantly lower in the tocilizumab group compared to the control group. However, the most important disadvantage of this study is that it was not randomized and double-blind.

The dose of tocilizumab with demonstrated efficacy in the treatment of COVID-19 is a single 400mg IV infusion [35]. If fever persists within 12 hours after the first dose, a second dose may be administered. Its known side effects include increased risk of bacterial infection, gastrointestinal perforations, infusion-related reactions such as hypertension, headache, skin reactions, anaphylaxis, thrombocytopenia, increased liver enzymes, and hyperlipidemia [36]. The same side effects are seen in the treatment of COVID-19 [37]. Sarilumab is another human monoclonal IL-6 receptor blocker. The multi-center, double-blind, phase II/III study (NCT04315298) evaluating the effectiveness of this molecule, which has been developed for the treatment of RA, in COVID-19 treatment has not yet been concluded. Nevertheless, it showed that it may be more effective to reduce CRP than placebo. However, no data is showing the benefit of sarilumab in severe disease. It is not recommended for the treatment of COVID-19 for now due to insufficient efficacy and safety studies.

IL-1 Receptor Antagonists

Anakinra is a recombinant human IL-1 receptor antagonist and is used in the treatment of RA. Studies are showing that it is effective in macrophage activation syndrome (MAS) in which severe cytokine storm is observed [38]. Therefore, it is thought that anakinra may prevent symptoms of COVID-19 related cytokine release syndrome. Use of anakinra improved survival in patients with sepsis in a phase III, randomized controlled trial [39]. Currently, no randomised controlled studies are evaluating the efficacy and safety of its use in the treatment of COVID-19. In case series and cohort studies published so far, anakinra has been shown to improve clinical and laboratory markers, reduce the need for mechanical ventilation and mortality rates [40, 41].

Janus Kinase Inhibitors

It is suggested that Janus kinase (JAK) inhibitors may be effective in the treatment of CRS in severe COVID-19 disease by inhibiting the JAK-signal converting activator (JAK-STAT) pathway. Ruxolitinib is a potent and selective oral JAK1 and JAK2 protein kinase inhibitor. It is indicated for intermediate and high-risk myelofibrosis, polycythemia vera, steroid-resistant graft versus host disease. There is not yet sufficient data regarding the use of ruxolitinib and other JAK inhibitors in the treatment of COVID-19. In ongoing phase III studies (RUXOCOVID, RUXCOVID-DEVENT), the efficacy of ruxolitinib in the treatment of COVID-19 associated CRS and ARDS patients in need of mechanical ventilation is evaluated.

Anti-Tumor Necrosis Factor- α

Tumor necrosis factor- α (TNF α) plays a role in all acute inflammations induced by acute stress and inflammation. TNF α is a molecule produced mainly in macrophages, monocytes, B cells, and other tissues. With the activation of TNF α , IL-1 and IL-6 begin to be produced. Plasma and tissue TNF levels were found to be high in COVID-19 patients [42]. Anti-TNF α agents such as adalimumab and infliximab are indicated for the treatment of inflammatory and autoimmune diseases such as RA, inflammatory bowel disease, and ankylosing spondylitis. Experimental studies are showing the effectiveness of anti-TNF α in the treatment of viral pneumonia [43].

The ability of a single dose of anti-TNF α to significantly lower blood TNF α levels suggests that it may be useful in the treatment of COVID-19 [44]. However, it should be considered that anti-TNF α therapy causes an increased risk of bacterial and fungal infections [44].

Intravenous Immunoglobulin

Intravenous immunoglobulin (IVIG) includes Ig G subtypes obtained by pooling from human plasma. It was used to provide immunity in the treatment of SARS, but thromboembolic complications were reported in some cases and the expected benefit could not be obtained [45, 46]. There may be several mechanisms that are effective in the therapeutic benefit of IVIG. IVIG can inhibit the function of many innate immune cells and neutralize active complement components.

It can also affect the acquired immune response by regulating the functions of B and plasma cells, regulator T and T helper cells, and inhibiting inflammatory cytokines.

In addition, it can stimulate the anti-inflammatory response by binding to antiviral antibodies and pro-inflammatory cytokines [47]. In a retrospective study of 58 patients with severe COVID-19 pneumonia, it was observed that IVIG treatment administered within 48 hours after the appearance of clinical findings significantly reduced 28-day mortality compared to the administration of the treatment 48 hours later (23.3%; 57.1%, $p = 0.009$) [48].

In contrast, another retrospective study involving 325 patients reported that IVIG treatment given to severe COVID-19 patients had no positive effect on 28-day or 60-day mortality [49]. Since current IVIGs do not contain antibodies against SARS-CoV-2, IVIG treatment is recommended in COVID-19 treatment guidelines of the National Institute of Health and Surviving Sepsis Campaign [50, 51].

Interferons

Interferons (IFNs) are cytokines that play a key role in reducing viral replication and regulating the immune response against viral infection. The effectiveness of IFN treatment against MERS-CoV and SARS-CoV has been studied. Due to their nonspecific antiviral effects, the effectiveness of combination therapies with other agents has generally been evaluated [52]. In a multi-center, prospective, open-label, randomized, phase II study evaluating 127 patients with COVID-19 disease, it is suggested that the duration of weaning from the mechanical ventilator, hospital stay, and viral carriage time were shorter with lopinavir/ritonavir, ribavirin, and IFN β -1b combination therapy compared to monotherapies [23]. Clinical studies evaluating the effectiveness of nebular and subcutaneous forms of interferons in the treatment of COVID-19 (NCT04293887, NCT04350281) continues.

Corticosteroids

Corticosteroids have taken their place in the treatment of many diseases such as asthma and other allergic diseases, autoimmune diseases, septic shock, and cancer. On the one hand, they suppress inflammation, on the other hand, they may predispose to infections by causing immunosuppression. It is a class of drugs that have been tried in treatment since the beginning of the COVID-19 pandemic. WHO and CDC did not recommend corticosteroids in the treatment of COVID-19 if there are no comorbidities such as asthma, COPD, and sepsis since their efficacy on SARS and MERS could not be determined and their side effects could be fatal. However, many studies have shown the opposite. Treatment with steroids has been shown to reduce the risk of death in COVID-19 patients who develop ARDS. While the mortality rate is 46% in patients receiving steroid treatment, it is 61.8% in patients who do not [53]. Similarly, the randomized, controlled RECOVERY study showed that dexamethasone reduced the mortality rate in 1/5 of the patients who needed noninvasive oxygen treatment, and in 1/3 of the patients who needed mechanical ventilation [54]. In addition, dexamethasone reduced the length of hospital stay and the need for mechanical ventilation [54].

Important side effects of corticosteroids are avascular necrosis, psychosis, gastrointestinal effects, and diabetes. In the aforementioned RECOVERY study, no side effects were reported in patients given dexamethasone compared to the control group [54]. As a result of the increase in studies supporting the efficacy and safety of corticosteroids, it has been emphasized in the treatment guidelines that short-term (<8 days) and low-dose (0.5 - 1mg/kg/day methylprednisolone and its equivalent) steroid treatment can be administered [55].

OTHER PHARMACOLOGIC THERAPIES

Convalescent Plasma Therapy

Serum obtained from people who have recovered from an infectious disease, called convalescent plasma, has been used for a long time in the treatment of infectious diseases. Antibodies in plasma show their therapeutic effects by more than one mechanism. The antibodies can act by binding directly to the agent. In a second mechanism, antibodies produce their therapeutic effect by stimulating complement activation, phagocytosis, and antibody-mediated cytotoxicity. Plasma therapy has been used effectively and reliably in the SARS, MERS, and H1N1 pandemics for the last 20 years [56-58]. Since SARS-CoV-2 has similar virological and clinical properties with SARS-CoV-1 and MERS, it is thought that plasma therapy may also be effective in the treatment of this viral infection [59]. In the first studies conducted with COVID-19 patients, it was reported that ARDS symptoms regressed, the duration of mechanical ventilation was shortened, fever decreased, and viral clearance increased [60, 61].

However, these studies are small-scale and single-center studies. Plasma therapy is generally well tolerated; Common side effects are transfusion-related skin reactions, hypervolemia, and lung damage. Recently, an FDA-supported, national, multi-center, open-label EAP study was conducted in 5,000 inpatients with high-risk and very severe COVID-19 findings [62]. Less than 1% of the patients developed serious side effects such as transfusion-related hypervolemia, transfusion-associated lung injury (TRALI), and severe allergic reaction.

On the other hand, a multi-center, randomized controlled study evaluating the efficacy and safety of plasma treatment in 103 COVID-19 patients with severe or life-threatening diseases conducted in China; found recovery time, mortality rate, and length of stay to be similar to the control group [63].

In the same study, no major side effects were reported [63]. The recommended plasma dose for the treatment of COVID-19 varies depending on the neutralizing antibody level and is one or two infusions.

Renin-Angiotensin-Aldosterone System (RAAS) Inhibitors

Besides the protective effects of RAAS inhibitors on the cardiovascular system, they also have anti-inflammatory and immunomodulatory effects.

ACE2 is secreted from all epithelial cells, including lung epithelial cells. ACE2 receptors are the entry point to the host cell for SARS-CoV-2 [64]. The virus binds to ACE2 and inhibits it and the level of angiotensin 2 increases. It has been hypothesized that ACEIs and ARBs exacerbate clinical findings by increasing the number of ACE2 receptors that will allow SARS-CoV2 to bind. However, this hypothesis has not been proven by human studies.

In a large-scale, observational study, SARS-CoV-2 positivity was found in patients using ACEI/ARB at a similar rate to patients not using it [65]. In addition, disease severity was similar in both patient groups [65]. In a case-control study conducted with 6272 COVID-19 patients, it was shown that the use of ACEI/ARB was not associated with the risk of COVID-

19 infection, the severity of clinical findings, or the course of infection [66]. Based on these and similar studies, discontinuation of ACEIs/ARBs in the treatment of patients is not recommended unless there is hemodynamic impairment.

Statins

Statins play an important role in the treatment of cardiovascular diseases. They may be useful in the treatment of COVID-19 due to their anti-inflammatory effects and protective effects on the innate immune system [67].

In a multi-center retrospective study aimed at determining the prevalence of myocardial damage in COVID-19 patients, statins have been reported to increase survival in these patients [68]. In another retrospective study, it has been shown that statin use is notably associated with asymptomatic disease [69].

In the same study, the severe disease was observed in 19% of those using statins, while it was observed in 25% of those who did not; but this was not statistically significant [69]. In patients diagnosed with COVID-19, if treatment with a statin is indicated, the drug should be started or continued.

CONCLUSION

Since the beginning of the SARS-CoV2 pandemic, many different drug groups have been tried for the treatment. However, no specific agent has been developed so far. Drugs act by blocking virus entry into host cells, inhibiting viral replication, and suppressing excessive inflammation. The side effects of the drugs also differ. Treatment protocols should be individualized, taking into account factors such as the patients' clinical conditions, accompanying diseases, and other medications. Treatment protocols will change as the efficacy and safety studies of each drug group are completed.

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Chapter 457

INTENSIVE CARE MANAGEMENT OF COVID-19 PATIENTS

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ABSTRACT

COVID-19 has affected millions of patients and healthcare workers in an unprecedented way. The pandemic took clinicians and hospitals by surprise. Intensive care units should be modified to handle the patient surge. There are few remedies to decrease the burden imposed on the healthcare system. These include management of acute respiratory failure, thrombotic events, cytokine modulating therapies. Only dexamethasone and prone positioning seem to have beneficial effects on oxygenation and need for mechanical ventilation. Nevertheless, tailoring the therapy for specific needs of the patient can decrease adverse effects. In this chapter, we review the current knowledge in the management of the critically ill COVID-19 patients as of September 2020.

Keywords: COVID-19, pneumonia, ARDS, prone position, thrombosis, mechanical ventilation

INTRODUCTION

Since December 2019, a novel coronavirus, named “Severe Acute Respiratory Syndrome Coronavirus 2” (SARS-CoV-2), affected millions of lives. The illness it causes was termed Coronavirus Disease 2019 (COVID-19). It reached pandemic status by March 2020 and has been putting enormous strain on Intensive Care Units (ICUs) worldwide, both by overwhelming limited ICU capacity and lack of effective treatment options. [1] This new

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disease showed an unpredictable clinical course, especially in critically ill patients leading to high intensive care mortality exceeding 50 % [1, 2].

ICU ORGANIZATION DURING COVID-19 SURGE

In a recent retrospective cohort of 83,619 patients, mean ICU admission among hospitalized patients with COVID-19 pneumonia was 20.1% [range 4.6-32%]. 48.8% of these patients required invasive mechanical ventilation for a mean of 7.8 days or longer [3]. One of the early studies from the Lombardy region in Italy showed that the patients were generally admitted to the intensive care 10 days after the symptom onset, had a median 12 days length of stay. Main risk factors associated with mortality were advanced age, male sex, comorbidities like chronic obstructive respiratory failure and diabetes mellitus, low PaO₂/FiO₂ ratio and need for high positive end-expiratory pressure (PEEP)[1].

There are vast differences in ICU capacity not only among countries but also on the regional level. Thus, it would be impossible to assess the adequacy of all ICU beds for any given pandemic. However, measures to support the ICUs in case of overwhelmed capacity should be taken beforehand. The consequences of not doing so are possible delays in treatment, which is directly associated with mortality[4].

In contrast to a laypersons' belief, ICUs are driven by specialized physicians, skilled nurses, and other healthcare workers, not by medical devices. Insufficiently trained staff may jeopardize patient care. An intensivist-to-patient ratio lower than 1/15 was associated with increased ICU length of stay [5]. The nurse-to-patient ratio is another parameter that assures patient safety. During the peak patient surge in our ICU, we addressed this issue with former ICU nurses and anaesthesiologists to triple our capacity. It should be underlined that unskilled or too much staff may cause problems rather than benefit[6].

Lack of mechanical ventilators led to excess mortality in Northern Italy during early 2020. Strategies should be developed to overcome the shortage. High-flow nasal oxygen (HFNO) and non-invasive ventilation (NIV) can be employed to reduce the need for intubation. However, when intubated, a full-featured ventilator is necessary to manage a COVID-19 patient as opposed to basic volume control resuscitation devices or flow generators[3]. If a shortage occurs, alternative devices such as transport ventilators, anesthesia ventilators can be employed as a last resort. Concomitant use of a single ventilator on multiple patients is nowhere near logical or physiological and never advised.

Although healthcare staff and mechanical ventilators seem to bore the brunt of the surge, many supplies and resources are necessary for an intubated ICU patient. An exhaustive list can be found in [3]. To better deploy sources during a crisis, postponing all elective and medical procedures, providing refresher courses to former critical care staff and transfer of essential healthcare workers from less strained regions should be considered. However, a treatment that has been administered only in an ICU setting before the crisis (such as non-invasive ventilation), should never be transferred to another facility without sufficient experience (like wards).

COVID-19 RELATED ACUTE RESPIRATORY FAILURE

Physicians have been encountering an unprecedented number of acute hypoxemic respiratory failure and ARDS due to COVID-19 for the past 10 months. Acute Respiratory Distress Syndrome (ARDS) occurs in 20-41% of severe COVID-19 patients and they exceedingly require some form of ventilatory support. Non-invasive ventilatory support can be appropriate. However, the failure rate is high and, in some patients, invasive ventilation is inevitable [7].

ARDS is a heterogeneous syndrome that can present as in strikingly different types. Unfortunately, this fact seemed to be forgotten during the start of the pandemic, and patients were termed based on observations. “Happy hypoxemia, Type L and Type H (or high and low elastance), cytokine storm” were proposed in a desperate attempt to clarify a previously unknown disease. Although different treatments for different ARDS types were proposed, emerging evidence shows that respiratory system mechanics of patients with ARDS (with or without COVID-19) are similar [8]. Evidence-based management of “conventional” ARDS includes conservative fluid strategy, early and proper antibiotics for possible bacterial pneumonia, consideration for early invasive ventilation, lung-protective ventilation, use of prone positioning, and considering extracorporeal membrane oxygenation (ECMO) [9]. Additionally, three recent studies proved dexamethasone to be effective in severe COVID-19 patients (see below). Lung protective ventilation, even in patients with relatively conserved lung compliance, can be beneficial [10]. Also, lung-protective ventilation decreases progression to more severe ARDS and pulmonary complications [11]. Furthermore, permissive hypercapnia is mostly well tolerated. However, the acceptable level of carbon dioxide may significantly differ between patients. Thus, before advancing to more liberal tidal volume ventilation, other causes for the hypercarbia should be addressed. PEEP titration remains necessary and complicated for each patient as it possesses the risk of reducing oxygen delivery if the underlying cause leading to hypoxemia is vascular derangement (i.e., pulmonary emboli).

Prone positioning, both in non-intubated and intubated patients, improves oxygenation due to better ventilation-perfusion matching. Prone positioning the patient relieves the dorsal compression of the alveoli by the weight of mediastinum and intraabdominal organs. Subsequently, recruitment occurs and more alveoli are available for gas exchange. Also, continuous alveolar recruitment and derecruitment decrease within tidal volumes [7, 12]. It remains the mainstay of the management of ARDS patients. It can also be performed in awake patients with non-invasive forms of ventilatory support. In a prospective cohort of 56 patients, prone positioning was feasible in 84%. These patients maintained a prone position for at least 3 hours. Oxygenation improved remarkably after prone positioning. However, oxygenation could not be maintained in half of the patients when supine positioning was reinitiated. Early initiation of prone positioning after hospital admission (i.e., 2.7 days vs 4.6 days) was associated with retaining oxygenation [7].

One of the most crucial problems in the management of COVID-19 related ARDS is the timing of intubation and whether to commence invasive mechanical ventilation early. Unfortunately, anecdotal reports and expert opinions are insufficient to answer these questions. In one retrospective study, which analyzed patients from the Wuhan district in China, it was suggested that early intubation and invasive mechanical ventilation were more

effective in reducing mortality [13]. However, in this study, invasive mechanical ventilation was initiated only after failed non-invasive respiratory support, and this is hard to consider as an early intervention. Another retrospective multicenter study involving 48 ARDS patients from China had a better methodology, which compared the outcome in patients who were intubated at the time when they fulfilled the ARDS criteria versus the patients intubated after failed noninvasive support [14]. In this study, no difference in mortality was observed in early or late intubation groups. Additionally, 8 patients in the late group never received intubation. A recent survey replied by 1132 ICU physicians from 85 countries showed great heterogeneity in treatment practices regarding admission time, initial oxygenation strategies, ventilator management, etc. In this survey, only 8% of the respondents opted for early intubation in a hypoxaemic patient despite conventional oxygen treatment. Half of the respondents indicated 4 hours of observation before switching to invasive ventilation [15].

Corticosteroids, such as dexamethasone, can reduce the duration of mechanical ventilation and mortality in ARDS patients. In a multicentre randomized controlled trial on 277 patients with (non-COVID) ARDS, patients receiving dexamethasone had more ventilator-free days (12 vs 7, between group difference 4.8 days (95CI% 2,57 to 7,03). There was a slight increase in newly acquired infections and hyperglycemia [16]. The first major trial to show benefit in COVID-19 patients was the recovery trial that enrolled 6425 patients [17]. Of these, 2104 patients received 6 mg/day dexamethasone for 10 days. The mortality was significantly reduced in patients receiving respiratory support (including supplemental oxygen). However, there was no mortality difference among patients that did not receive respiratory support. Three subsequent RCTs were published in ICU settings to address the use of corticosteroids. In the REMAP-CAP trial, hydrocortisone was likely to be superior to no hydrocortisone (93% probability) [18]. CoDEX trial enrolled 299 moderate and severe ARDS patients to 20 mg/day dexamethasone for 5 days, which was tapered down to 10 mg/day for another 5 days [19]. Patients receiving dexamethasone had more ventilator free-days on day 28 (6.6 vs 4). However, the 28-day mortality was similar between groups (56.3% vs 61.5%). In the CAPE COVID trial, which enrolled 149 patients, severe ARDS patients received 200 mg/day hydrocortisone [20]. There was no significant difference between groups on day 21 in terms of death or respiratory support (42.1 vs 50.7, $p = 0.29$). All of these studies were included in a prospective meta-analysis. 28-day mortality was lower in those receiving corticosteroids (odds ratio 0.66 [95CI% 0.53-0.82]) [21]. However, questions remain regarding side effects, optimal dosing, administration trigger, or illness severity threshold [22]. Nevertheless, corticosteroids remain the only drug that is shown to be beneficial in severe ARDS patients.

Coinfections and secondary respiratory infections also increase in COVID-19 patients and they are associated with decreased survival. Usually, an elevated procalcitonin (PCT) is found in patients with septic shock. Bacterial infections trigger the synthesis of PCT via interferon- γ . On the other hand, viral infections do not stimulate the same response in the host. Thus, PCT remains mostly normal in the uncomplicated COVID-19 cases and an increased PCT may indicate co-infection in the critically ill patients. A $PCT \geq 0.5$ mg/l indicated a poor outcome in COVID-19 patients with a sensitivity of 88% and specificity of 68% [23].

COVID-19 AND THROMBOSIS

COVID-19 is a hypercoagulable state and it is associated with increased thrombotic events, including pulmonary embolism (PE) [24]. However, the pathophysiology is not fully understood. Very high d-dimer levels may reflect not only systemic inflammation but also thrombosis triggered by the virus [25]. In a retrospective study enrolling 81 COVID-19 pneumonia patients, a D-dimer cut-off value of 1.5 mcg/ml predicted venous thromboembolism (VTE) with 85% sensitivity, 88.5% specificity [26]. In another retrospective study including 127 patients, only D-dimer and CRP levels were found to be associated with VTE. When combined with a D-dimer > 15, a CRP > 280 had a predicted probability of 98% for VTE [27].

The incidence of PE in hospitalized patients is around 1.9%-8.9%. This increases to 26.6% in the critically ill, despite prophylaxis. These numbers are possibly an underestimation of the real incidence as symptoms and findings of PE is nonspecific. For instance, an autopsy of 12 patients revealed deep venous thrombosis (DVT) in 7; none were suspected of having an embolism before death [28]. Nevertheless, routine screening for VTE is currently not recommended [29].

There are several guidelines for laboratory testing in the critically ill with COVID-19. An increase in D-dimer levels (3 to 4-fold (ISTH-IG) or 6-fold (SCC-ISTH) may indicate an embolic event. Regular (not daily) monitoring of platelet count, prothrombin time, and fibrinogen are also recommended [30]. A prophylactic dose of Low Molecular Weight Heparin [LMWH] or subcutaneous unfractionated heparin should be initiated in all suspected or confirmed COVID-19 patients admitted to the hospital [31, 32]. Additionally, mechanical thromboprophylaxis should be considered whenever pharmacological treatment is contraindicated. There is insufficient evidence to suggest mechanical thromboprophylaxis in addition to pharmacological one [30]. Therapeutic anticoagulation should be considered in case of high suspicion of a thromboembolic event. Sudden onset of hypotension or hemodynamic instability should prompt bedside echocardiography. Thrombolytic therapy should be initiated if there is any evidence of right ventricular dilatation or increased pulmonary arterial tension. Other thrombolytic indications include STEMI and acute ischemic stroke [30].

OTHER THERAPIES TO MITIGATE THE EFFECTS OF COVID-19

Although the term “cytokine storm” is broadly defined, it mostly implies an extreme pro-inflammatory response. Manifestations of the cytokine storm include fever, tachycardia, tachypnoea, and vasoplegia leading to hypotension due to endothelial dysfunction and inflammation [33]. Initial reports on observations of severe COVID -19 infection suggested that cytokines, particularly IL-6, played a key role in propagating lung damage and multiorgan failure. A study found that hyperinflammatory type of COVID-19, defined as CRP greater than 150 mg/dl and ferritin greater than 1500 mcg/l, had increased mortality [34]. Subsequently, cytokine removal therapies and monoclonal antibodies targeting interleukins were administered. As of September, there are over 50 interventional studies listed in the clinical trials database for tocilizumab (an anti-IL-6 drug) alone. However, the

presence of a cytokine storm in severe COVID-19 patients is debated. In a healthy volunteer study, plasma IL-6 levels ranged from 1 to 79 pg/ml [35]. On the other hand, patients with ARDS had a median IL-6 concentration of 1618 pg/ml [33], 723 pg/ml [36], 238 pg/ml [37] or 376 pg/ml [38]. Although IL-6 was also increased in patients with COVID-19, the increase is milder compared to ARDS. IL-6 levels of 25, 26 and 64 pg/ml were reported [38]. Furthermore, a single dose of an IL-6 inhibitor can suppress CRP levels and fever for a week and secondary infections can go unnoticed.

Nevertheless, a retrospective observational study in critically ill patients revealed improved mortality among those with baseline CRP levels 15 mg/dl or higher [39]. The authors concluded that tocilizumab may exert its effects in patients progressing to an inflammatory state. It is noteworthy that, tocilizumab was administered on the principal day (a single dose of 400 mg, repeated in case of deterioration) of ICU stay in this study. However, a preprint of the RCT comparing tocilizumab to placebo revealed that tocilizumab failed to improve mortality at day 28. A considerable positive aspect of this study is tocilizumab reduced the duration of ICU stay by 5 days [40].

Extracorporeal cytokine removal therapies have been used for patients with septic shock. The rationale behind the cytokine removal in these patients is to limit the ensuing end-organ damage due to propagated inflammation. Additionally, lung-kidney crosstalk has been proposed recently in ARDS patients [41]. Although the direct mechanism is still not definite, cytokine overproduction and renal medullar hypoxia seem to be relatable [42]. Continuous Renal Replacement Therapy with high and middle cut-off membranes can selectively filter or absorb middleweight molecules, such as IL-6. Subsequently, blood purification therapies were put forward for COVID-19, also. However, only a few case reports reported the benefit of such therapies in this population, and future trials are awaited for definite evidence [43, 44].

Convalescent plasma is collected from the patients who have contracted and recovered from the disease. It has been used for previous pandemics, such as H1N1, SARS, and Ebola, and MERS. Initial case reports showed clinical benefit and reduced mortality in COVID-19 patients, also. Virus load decreased significantly and patients were soon virus negative. A subsequent RCT comparing convalescent plasma to standard treatment showed some clinical improvement in severely ill patients but not in critically ill patients. Likely, pathologic process in those receiving mechanical ventilation and in shock was probably irreversible. Given that the median time between symptom onset and randomization in this study was 30 days, earlier convalescent plasma administration may show better results in the critically ill. Additionally, the study was underpowered to detect significance between the groups. A high-titer antibody may have efficacy against SARS-CoV-2 [45, 46].

CONCLUSION

COVID -19 has caused tremendous constraints on the healthcare system and workers, as well as the patients. The first wave took the clinicians by surprise as many institutions did not have any structured plan to deal with a pandemic; we should not be surprised twice. However, we are now more prepared for patient surges in the intensive care units albeit lacking evidence-based treatment options for the critically ill COVID-19 patients [2].

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Chapter 458

ANATOMICAL BASIS OF THE COVID-19

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ABSTRACT

The system most affected by the corona virus disease (COVID-19) is the respiratory system. Typical symptoms of the disease and most of the diagnostic and treatment interventions are related to the respiratory system. In this chapter, we address the basic anatomy of the respiratory system, the anatomical background of some of the respiratory-system-related symptoms of the disease, basic clinical anatomy of some of the diagnostic interventions, and to shed some light on the rationale behind some of the clinical interventions applied during the treatment of the disease. In this chapter, readers will find basic clinical anatomy information about of the nasopharyngeal sampling, tracheostomy, pulmonary volumes and capacities, and effects of the prone position on the prognosis of the patients.

Keywords: anatomy, sampling, prone position

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) affects many systems in the body but most of the typical symptoms of its disease (COVID-19) are related to the respiratory system. The typical symptoms of COVID-19 are fever, dry cough, fatigue, sputum production, and dyspnea [1-3]. When the clinic of the COVID-19 is considered, microbiology, immunology, biochemistry, internal medicine, pharmacology, intensive care, and radiology are some of the medical areas that come into mind firstly; anatomy is not one of them in general. On the other hand, some diagnostic interventions (such as nasopharyngeal and oropharyngeal samplings, bronchoalveolar lavage), some of the clinical interventions

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(such as intubation, tracheostomy, prone positioning) necessitates firm anatomical knowledge to apply them properly or to understand the rationale behind them. This chapter aims to give basic clinical anatomy information about the clinic of the COVID-19.

BASIC ANATOMY OF THE UPPER RESPIRATORY TRACT

Coronavirus transmission occurs via respiratory droplets, and the first entry point is mainly the upper respiratory tract [1, 4]. The upper respiratory tract is the first part of the conducting portion of the respiratory system. Nose, pharynx, and larynx are the main parts of the tract [5, 6].

Nose

The nose is the first part of the airway and can be subdivided into external nose and nasal cavity. Air enters through the external nose, which is the pyramidal-shaped portion that projects from the face, via two elliptical openings called nostrils or nares. These openings are separated by the nasal septum and covered laterally by alae (wings) of the nose. Nostril dimensions vary greatly among individuals. They approximately measure 0,5-1 cm horizontally and 1,5-2 cm anteroposteriorly, with a narrowing in front. The supporting skeleton of the external nose is made up of bone and hyaline cartilage. Bony part is composed of two nasal bones, the frontal process and the anterior nasal spine of maxillae, the nasal part of the frontal bone and, the bony parts of nasal septum. Paired lateral nasal cartilage, which is continuous with septal cartilage, and two alar cartilages form the cartilaginous part [6-8].

Nasal Cavity

The nasal cavity is located between the roof of the oral cavity and the cranial base. It is divided into two halves by the nasal septum, which is formed by the perpendicular plate of ethmoid, vomer, and septal cartilage. The anterior part of the cavity, which is covered by alar cartilage, is called the nasal vestibule. Air enters the cavity via nostrils into the nasal vestibule and travels through the cavity until it reaches the choanae or the posterior nasal aperture, where the nasal cavity opens into the nasopharynx. The adult choanae usually measure 2,5 cm and 1,3 cm in height and width, respectively. Each half of the nasal cavity possesses a roof, a medial and lateral wall, and a floor. The roof can be examined in three parts. The anterior (frontonasal) part is formed by the frontal and nasal bones. This part slopes upwards and backward to form the bridge of the nose. The Central (ethmoidal) part is horizontal and is formed by the cribriform plate of the ethmoid bone which separates the anterior cranial fossa from the nasal cavity. The posterior (sphenoidal) part is a downward-sloping segment that is formed by the anterior part of the sphenoid bone. The floor extends from the anterior to the posterior aperture and has a smooth and concave surface. It slopes up from anterior to posterior. The palatine processes of maxillae and horizontal plates of palatine bones form the floor of the nasal cavity. The medial walls of both halves of the nasal cavity are formed by the nasal septum. The lateral wall is the broadest and the most complicated one among the walls

of the nasal cavity. From anterior to posterior, the maxilla, the labyrinth of the ethmoid, and the perpendicular plate of the palatine bone form the lateral wall. Besides, this wall contains three scroll-like projections of bone called superior, middle, and inferior conchae (turbinates). The superior and middle conchae are medial processes of the ethmoidal labyrinth, whereas the inferior conchae are independent bones. The space underlying each concha is named meatus. Air passes through these meatuses and becomes turbulent. Turbulence keeps air in the cavity for a longer period, so it helps the inhaled air become warmer and humidified. There are several openings which connect the nasal cavity with other structures. The sphenoidal recess, located superoposterior to the superior concha, receives the opening of the sphenoidal sinus, and the superior nasal meatus receives the openings of posterior ethmoidal sinuses. Middle ethmoidal cells form a rounded elevation at the middle nasal meatus called ethmoidal bulla, on which they open. Below the ethmoidal bulla lies a semi-circular groove called semilunar hiatus. The maxillary sinus opens into the nasal cavity via semilunar hiatus. This hiatus curves in front of the ethmoidal bulla and forms a funnel-shaped passage called the ethmoidal infundibulum, which drains the frontal sinus. The inferior nasal meatus is the longest nasal meatus and it receives the opening of the nasolacrimal duct, which drains tears from the lacrimal sac [6-9].

Paranasal Sinuses

Frontal bone, ethmoid bone, sphenoid, and maxilla house air-filled cavities, which are named after the bones they are located in, called paranasal sinuses. These sinuses, lined with respiratory epithelium, help to warm and humidify the inhaled air, add resonance to the voice, and decrease skull bone weight. Only maxillary and ethmoidal sinuses are present at birth. All sinuses enlarge and become fully developed at adolescence [5-8].

Pharynx

Pharynx is a cone-shaped muscular tube which belongs to both alimentary and respiratory systems. It lies between the cranial base and C6 vertebra, posterior to nasal cavities, oral cavity, and larynx. Pharynx has three parts; nasopharynx, oropharynx, and laryngopharynx. Choanae connects the nasal cavities to the nasopharynx, isthmus of fauces (oropharyngeal isthmus) connects the oral cavity to the oropharynx, and the laryngeal inlet connects the laryngeal cavity to laryngopharynx. The nasopharynx is found above the soft palate behind nasal cavities. Mucosa covering the inferior part of the body of the sphenoid and the basilar part of the occipital bone form the roof and the superior portion of the posterior wall of the nasopharynx. In the middle part of the junction of the roof and the posterior wall, a lymphoid tissue called the pharyngeal tonsil (adenoid) is found. The pharyngeal opening of the pharyngotympanic (Eustachian) tube occupies the lateral wall of the nasopharynx on both sides. The opening is located approximately 1 cm posterior and just below the posterior end of the inferior nasal concha. The superoposterior part of the opening has an elevation called torus tubarius. Under the mucosa covering the torus tubarius, a mass of lymphoid tissue, called tubal tonsils (Gerlach's tonsil), can be found. The salpingopharyngeal fold, which

covers the salpingopharyngeal muscle, descends posterior to the torus tubarius. A small depression, called pharyngeal recess (fossa of Rosenmüller), which extends posteriorly and laterally, is also located posterior to the torus tubarius. The oropharynx is the middle part of the pharynx and is located posterior to the oral cavity, between the soft palate and the superior border of the epiglottis. It has both digestive and respiratory functions. The anterior part of its lateral wall is bordered by two arches; palatoglossal arch and palatopharyngeal arch. Palatine tonsil is located between these two arches. The inferior part of the anterior wall of the oropharynx is made by the root of the tongue. There is a collection of lymphoid tissue under the mucosa covering the root of the tongue, called lingual tonsil. Single pharyngeal tonsil, bilateral tubal tonsils, bilateral palatine tonsils, and single lingual tonsil form a lymphoid ring at the pharynx. This ring is called the pharyngeal lymphoid ring or Waldeyer's ring. It acts as the first line of defense for infections. Laryngopharynx is the inferior part of the pharynx. It is located between hyoid bone (the level of C3 vertebra) or the upper margin of the epiglottis and the inferior border of the cricoid cartilage (the level of C6 vertebra) or the superior border of the oesophagus. Laryngeal inlet is located on the anterior wall, and has two depressions on each side, called piriform fossa (recess) [5-9].

Larynx

Larynx is a specialized organ that functions as a sphincter for air passage and responsible for voice production. It is located at the anterior part of the neck, between laryngopharynx and trachea. The supporting skeleton of the larynx is composed of hyaline cartilages, which are connected by membranes and ligaments, and moved by muscles. There are nine cartilages that forms the framework; thyroid cartilage (1), cricoid cartilage (1), epiglottis (1), arytenoid cartilage (2), corniculate cartilage (2), and cuneiform cartilage (2). Thyrohyoid membrane is a broad structure that connects the hyoid bone to the superior border of thyroid cartilage. Internal branch of the superior laryngeal nerve and the superior laryngeal vessels pass through this membrane. Cricotracheal ligament attaches the cricoid cartilage to the first ring of the trachea. Quadrangular membrane is stretched between the lateral border of the epiglottis and anterolateral face of the arytenoid cartilage on the same side. The free inferior border of this membrane thickens to form the vestibular ligament which then constitutes the vestibular fold when covered with mucosa. Cricothyroid membrane extends between thyroid cartilage and cricoid cartilage. In cases of emergency (laryngeal obstruction), it is recommended to perform a laryngotomy at the site of this membrane. Conus elasticus (cricovocal membrane) also attaches to the superior border of cricoid cartilage inferiorly but it has a free superior border which forms the vocal ligaments on each side. Vocal ligaments then form the vocal folds when covered by mucosa. The gap between the vocal folds is called rima glottidis. The muscles of larynx can be categorized as extrinsic and intrinsic muscles. Extrinsic muscles (digastric, stylohyoid, mylohyoid, geniohyoid, stylopharyngeus, salpingopharyngeus, palatopharyngeus, sternothyroid, sternohyoid, omohyoid muscles) are mainly responsible for elevation and depression of the larynx whereas the intrinsic muscles (oblique arytenoid, transverse arytenoid, thyroepiglottic, cricothyroid, thyroarytenoid (vocalis), lateral cricoarytenoid, posterior cricoarytenoid muscles) are responsible for phonation and sphincter function of the larynx [5-9].

ANATOMY OF OLFACTORY DYSFUNCTION

The lining of the nasal cavities consists mainly of respiratory epithelium, except for the nasal vestibule and the olfactory cleft where the olfactory epithelium is present [6]. The olfactory epithelium (mucosa) contains olfactory receptor nerve cells, which enter through the cribriform plate of the ethmoid bone [8]. Olfactory mucosa lines approximately 5-9 cm² of the total 150 cm² mucosal area covering the nasal cavities, including structures that are superoposteriorly located in the nasal cavity [6, 10]. The spike of SARS-CoV-2 uses the host receptor Angiotensin-Converting Enzyme 2 (ACE2), which is found abundantly in the respiratory epithelium, to enter the cells [1, 3]. The olfactory epithelium and respiratory epithelium are closely related, so it is only natural for COVID-19 to cause olfactory dysfunction due to the neurotropic properties of the virus [10, 11].

ANATOMY OF OCULAR TRANSMISSION

Lacrimal gland, which is located in the superolateral portion of the orbit, constantly produces tears [6, 7]. Some tears are absorbed by cornea and conjunctiva or evaporate [6, 12]. Remaining tears are drained by lacrimal canaliculi into the lacrimal sac. Then tears pass through a 12 mm long nasolacrimal duct to reach the upper respiratory tract via an opening located at the inferior nasal meatus [6, 12]. This transport allows pathogens like SARS-CoV-2 from conjunctival or corneal epithelium, which expresses ACE2, to be transferred to the respiratory epithelium [10, 12].

ANATOMY FOR UPPER RESPIRATORY TRACT SAMPLING

For diagnostic testing for SARS-CoV-2 in patients who meet the diagnostic criteria, that are put forward by World Health Organization (WHO), Central for Disease Control and Prevention (CDC) recommends collecting upper respiratory system specimens [1, 13]. These samples include nasopharyngeal swaps, oropharyngeal swaps, mid-turbine swap, nasal swab, and nasopharyngeal wash/aspirate or nasal wash/aspirate [1, 13, 14]. Anatomy knowledge of the respiratory system is required to collect these specimens safely and correctly [4, 15]. Nasopharyngeal and oropharyngeal swaps are frequently used [4], therefore anatomic considerations for both will be discussed below.

Nasopharyngeal Swab

Nasopharyngeal swap is recommended by WHO as a reference diagnostic method in COVID-19 [16]. Specimen is collected by inserting a flexible swab stick through the nostril [13]. Tilting the patient's head slightly posterior is recommended to make the nasal passages more accessible [4, 17]. The swap is inserted parallel to the palate along the floor of the nasal cavity until encountering a resistance that indicates contact with the nasopharynx or reaching

the estimated distance [4, 13]. The distance between nostrils to the nasopharynx is approximately 9,4 cm in females and 10 cm in males [18]. The required distance can also be estimated by measuring the distance between nostrils (or the philtrum) and tragus, which is roughly 5 cm longer than the distance between nostrils and the nasopharynx in both genders [4, 13, 18]. The swap should not be directed medially, because the nasal septum contains anastomosis of arterioles and veins that are prone to bleeding [4, 6]. The most notable one is the Kiesselbach's plexus (Little's area) which is formed at the anterior part of the nasal septum by the anterior ethmoidal artery (from the ophthalmic artery), the posterior ethmoidal artery (from the ophthalmic artery), the sphenopalatine artery (from the maxillary artery), the greater palatine artery (from the maxillary artery), and the septal branch of the superior labial artery [4, 6, 7].

Oropharyngeal Swab

Oropharyngeal swab shows a lower positive rate than nasopharyngeal swab but has a lower risk of bleeding compared to nasopharyngeal swab [2, 4]. The swab is inserted through the mouth and the specimen is collected from the posterior wall of the oropharynx and over the palatine tonsils.

BASIC ANATOMY OF THE LOWER RESPIRATORY TRACT

The airways below the larynx are collectively called tracheobronchial tree. The tracheobronchial tree is morphologically divided into trachea, bronchi, bronchioli, and alveoli.

Trachea is the first and most superior part of the tracheobronchial tree. The trachea is mobile and has a tubular form. It starts from the lower border of the cricoid cartilage of the larynx at the C6 vertebra level and ends at the tracheal bifurcation at the level of the intervertebral disc between T4 and T5 vertebrae. The tracheal bifurcation may rise about one vertebral level during expiration, and lower to T6 vertebral (or manubriosternal junction, i.e., angle of Louis) level during deep inspiration. The length of the trachea is between 10 and 15 cm [6, 9], and its cross-sectional area is about 3 cm² in adults [19]. The size of the trachea is correlated with the size of the person. The general rule is that the width of the trachea is the same as the diameter of the index finger of the same person. The external transverse diameter of the trachea is approximately 2-2,5 cm in adult males, approximately 1,5 cm in adult females, and approximately 0,5 cm in infants [6, 7, 20]. It consists of 16-20 C-shaped hyaline cartilages. These cartilages are oriented horizontally, and their convex surfaces are directed anteriorly. A fibroelastic tissue connects tracheal cartilages. Because the tracheal cartilages are C-shaped and the posterior wall, which is composed of smooth muscle (i.e., tracheal muscle), is flattened, the cross-section of the trachea is D shaped.

The cervical part of the trachea is between the lower border of the cricoid cartilage and the thoracic inlet. This part of the trachea has important relations regarding the tracheostomy. The jugular arch, sternohyoid and sternothyroid muscles, isthmus of the thyroid gland (in front of the 2.-4. tracheal cartilages), an anastomotic branch of the superior thyroid arteries,

inferior thyroid veins, thyroid ima artery (variation) are located anteriorly; in children, the brachiocephalic trunk crosses in front of the trachea at or a little above the upper border of the manubrium of the sternum. The oesophagus is posterior to the trachea. The common carotid arteries, inferior thyroid arteries, lobes of the thyroid glands are located lateral to the trachea. The recurrent laryngeal nerves ascend in the tracheoesophageal groove. The cervical part is supplied by inferior thyroid artery, and innervated by the vagal branches and sympathetic trunk [6].

The thoracic part of the trachea is located within the superior mediastinum. It bifurcates at the level of the sternal angle (manubriosternal junction, angle of Louis) into two main bronchi for each lung, passing inferolateral to enter the lungs at their hila. The right main bronchus is wider, shorter, and runs more vertically than the left one as it passes directly to the hilum of the lung. The left main bronchus passes inferolateral, inferior to the arch of the aorta and anterior to the esophagus and thoracic aorta, to reach the hilum of the lung. Because of differences in sizes and directions of the two main bronchi, inhaled foreign bodies tend to enter the right bronchus [6, 7, 20]. The cartilage at the tracheal bifurcation is the carina. If the sharp edge of the carina becomes flattened, this usually indicates enlargement of the hilar lymph nodes or gross distortion of the pulmonary anatomy by fibrosis, tumor, or other pathology [9].

Within the lungs, the bronchi branch to form the rest of the branches of the tracheobronchial tree. Each primary (main) bronchus divides into secondary (lobar) bronchi, each of which supplies a lobe of the lung. Each secondary bronchus divides into tertiary (segmental) bronchi that supply the bronchopulmonary segments. The bronchopulmonary segments are the largest subdivisions of a lobe. They have a pyramidal shape, and their apices are directed towards the root of the lung. They are supplied independently by a segmental bronchus and a tertiary branch of the pulmonary artery. There are usually 10 segments in each lung, but this number is subject to variation. Because each segment has separate bronchial, vascular, lymphatic, and nervous supply, they are surgically resectable [6, 7, 20]. After the tertiary segmental bronchi, bronchioles start. There are 20-25 generations of bronchioles that end as terminal bronchioles. Bronchioles lack cartilage in their walls. Each terminal bronchiole gives rise to several respiratory bronchioles, which have alveoli extending from their lumens. The pulmonary alveolus is the basic structural unit of gas exchange in the lung. Each respiratory bronchiole gives rise to 2-11 alveolar ducts, each of which gives rise to 5-6 alveolar sacs. Alveolar ducts are elongated airways densely lined with alveoli, leading to the alveolar sacs, into which alveoli open. The total number of the alveoli in the adult is between 300-400 million [6, 7, 20, 21], and the total surface area is approximately 140 m² [19].

ANATOMY OF THE TRACHEOSTOMY

Tracheostomy is the creation of a hole in the anterior aspect of the trachea. This intervention is applied during clinical situations such as upper airways obstructions, laryngeal and craniofacial traumas, laryngeal edema, and laryngeal cancers. The hole can serve independently, or a tube can be inserted through it. After identifying the thyroid and cricoid cartilages, the neck is extended, and a vertical incision is made from the cricothyroid membrane to the suprasternal notch. Superficial fascia and the fibers of the platysma are

dissected (anterior jugular veins should be avoided), investing fascia is incised, the pretracheal muscles are split. Depending on the decision of the physician, the second tracheal ring (which is superior to the isthmus of the thyroid gland), third to fifth tracheal rings (after dissecting the isthmus of the thyroid gland), or tracheal rings below the isthmus can be cut. The major structures around the trachea should be avoided during the procedure [6, 20].

BASIC ANATOMY OF THE LUNGS

Lungs are soft and spongy organs, which are essential for respiration. Each lung consists of lobes, which are two on the left and three on the right side. Each lung is situated in the thoracic cavity on both sides of the mediastinum in their pleural cavities. In adults, right lung weighs approximately 620-625 g, and the left 565-570 g [6, 8, 9].

Each lung has a cone shape and has apex, base, three borders, and two surfaces. The apex of the lung is the part that extends superiorly through the thoracic inlet. It rises 3-4 cm above the first costal cartilage and is in contact with the cervical pleura, which is covered by suprapleural membrane (Sibson's fascia). The tip of the apex is 2,5-4 cm above medial third of the clavicle [6, 8, 9]. Base of the lung is deeply concave and sits on the diaphragm. Because the right half of the diaphragm is higher, the base of the right lung is deeper [6]. The costal surface is smooth and relates to the thoracic wall. The posterior costal surface is vertically longer than the anterior surface [6, 9]. The mediastinal surfaces of the lungs constitute the lateral walls of the mediastinum. The left mediastinal surface is closely related to the left ventricle and auricle, the arch of aorta, the left subclavian and common carotid arteries, left brachiocephalic vein, trachea, oesophagus, the left vagus, and the thoracic duct. The right mediastinal surface is closely related to the right atrium and right ventricle, superior and inferior vena cava, the azygos vein, the trachea, the right vagus, and phrenic nerves [6, 9]. The most peculiar feature of the mediastinal surface is the hilum, which is the site of entry and exit for the principal bronchus, pulmonary artery, pulmonary veins, bronchial vessels, pulmonary autonomic plexus, and lymphatic vessels. All these structures are enveloped by a pleural sleeve and are collectively called pulmonary root.

COUGH REFLEX

Cough is one of the most important defensive mechanisms of the respiratory system, and one of the most common symptoms of COVID-19 infection [1]. It clears the secretions and particles from the airways and serves protection against foreign material (including inflammation and mediators associated with inflammation) aspiration. The trachea (especially carina) and bronchi are very sensitive to light touch, and the terminal bronchioles and the alveoli are sensitive to corrosive chemical stimuli. Afferent nerve impulses from the airways pass mainly through the vagus nerves (CN X) to the medulla of the brain. There, an automatic sequence of events causes some sequential events: 2,5 L of air is inspired rapidly, the epiglottis and glottis close, abdominal and internal intercostal muscles contract forcefully, the pressure inside the lungs rises to 100 mmHg, the epiglottis and glottis open, air inside the lungs expelled with a very high velocity (75-100 miles/hour) [6, 22].

PLEURA

Pleura is the serous membrane covering all the surfaces (except the hilum) of the lung, internal surface of the thoracic wall, and most of the superior surface of the diaphragm. Each lung has its own pleura. The pleura has two layers which are named according to their site of attachment: parietal pleura is attached to the thoracic wall and diaphragm, and the visceral pleura to the lung parenchyma [6, 9].

MUSCLES OF RESPIRATION

Respiration has two phases: inspiration and expiration. While the quiet and forced inspirations are active (accomplished by muscular activity), the expiration is passive (accomplished by elastic recoil of the tissues) in quiet respiration but active in forced expiration. The muscles of respiration can be divided into two groups: inspiratory muscles and expiratory muscles. The primary inspiratory muscles are the diaphragm and the external intercostal muscles; secondary inspiratory muscles are sternocleidomastoid, scalene (anterior, middle, and posterior) muscles, and pectoralis major and minor. Primary expiratory muscles are the internal and innermost intercostal muscles; secondary expiratory muscles are transversus thoracis, subcostals, serratus posterior inferior, rectus abdominis, external and internal obliques, transversus abdominis, latissimus dorsi, and quadratus lumborum [6, 23]. Depending on the muscles used during inspiration, breathing can be grouped in two types: abdominal (diaphragmatic) breathing uses the diaphragm as the power generator, while the thoracic breathing uses external intercostal muscles as the power generator. Infants and small babies have ribs lying horizontally and weak intercostal muscles, so the diaphragm and abdomen are the primary means of ventilation [21].

PULMONARY VOLUMES AND CAPACITIES

Pulmonary volume (also known as lung volume or respiratory volume) refers to the volume of air in the lungs at a given phase of the respiratory cycle. A combination of the pulmonary volumes is called pulmonary capacity. There are four pulmonary volumes and four pulmonary capacities. The tidal volume is the volume of air inspired or expired with quiet respiration (~0,5L). The inspiratory reserve volume is the extra volume of air that can be inspired when the person inspires with full force (~3L). The expiratory reserve volume is the maximum extra volume of air that can be expired after the end of the tidal expiration (~1,1L). The residual volume is the volume of air remaining in the lungs after the most forceful expiration (~1,2L) [22]. The inspiratory capacity is the sum of the tidal volume and the inspiratory reserve volume (~3,5L). The functional residual capacity is the sum of the expiratory reserve volume and the residual volume (~2,3L). The vital capacity is the sum of the inspiratory reserve volume, the tidal volume, and the expiratory reserve volume (~4,6L). The total lung capacity is the maximum volume to which the lungs can be expanded with the maximum effort and is the sum of the vital capacity and the residual volume (~5,8L) [22].

EFFECT OF THE PRONE POSITION ON THE VOLUMES, PERFUSION, AND VENTILATION OF THE LUNGS

During the COVID-19 pandemic, the media shared different images of hospitalized patients lying in prone position (PP) in intensive care units. PP is being used since 1970s to treat hypoxemia in patients who have acute respiratory distress syndrome (ARDS) [19, 24]. Treatment of the ARDS requires tracheal intubation and mechanical ventilation. PP was shown to be beneficial in ARDS patients; it may even postpone or avoid tracheal intubation [25]. PP improves gas exchange [19, 24, 25], provides more even tidal volume distribution in the lungs [24], improves resting lung volume in the dorsocaudal regions of the lungs [24], improves ventilation-perfusion relationship [19, 24, 25], improves peripheral oxygen saturation [25], ameliorates the severity or development of ventilator-induced lung injury [25], improves clearance of lung secretions [26], reduces neutrophil and pro-inflammatory mediator levels (IL-1 β , IL-6, and 1 IL-8) in bronchoalveolar lavage fluid [24] and improves mortality in ARDS patients [19, 24, 25]. PP is most effective in improving oxygenation when initiated during the exudative phase of the ARDS [24]. PP improves lung mechanics, which occurs via changes in anatomical relationships.

PP has effects on the transpulmonary pressure (Ptp), and ventrodorsal transpulmonary pressure difference. The Ptp is defined as the difference between the alveolar pressure (Pal) and pleural pressure (Ppl). In supine position (SP), the dorsal Ppl raises (because of the compressive effect of the lung weight on the dorsal parts of the lung) and Ptp diminishes; ventral Ppl diminishes and Ptp increases. The net result is ventral alveoli are overinflated and the dorsal alveoli are underinflated (atelectasis) [19, 25, 27, 28]. PP diminishes the difference between ventral and dorsal Ptp; when the patient is in PP, larger mass of lungs is suspended from a wider posterior chest area and Ppl diminishes at the dorsal parts of the lungs. Because of this, dorsal Ptp increases, dorsal alveoli open, ventilation in the dorsal parts of the lungs improves, difference between ventral and dorsal Ptp decreases, and more uniform ventilation is achieved [19, 24, 27, 29].

The effect of the PP on the perfusion of the lungs is slight [27] and pulmonary perfusion is preferentially distributed to the dorsal lung regions in both SP and PP [24]. Because perfusion is unaffected and ventilation is diminished in the dorsal part of the lungs, V/Q ratio diminishes (V/Q mismatch). This mismatch creates a physiological shunt in the dorsal part of the lungs [29]. In PP, dorsal alveoli are inflated, ventilation is improved, V/Q mismatch improves, intrapulmonary shunt decreases (~50%) and oxygenation improves [24, 29].

When an ARDS patient lies in SP, the heart and diaphragm compress the dorsal lung parenchyma. Because of the compression of the lungs by either structure, hypoxemia increases, and ventilator-associated lung injury worsens [19, 24, 27, 29] and this effect is exacerbated by obesity [19]. In PP, heart lies on the sternum, compression of the heart on the dorsal lung parenchyma decreases, ventilation and oxygenation improves.

PP reduces neutrophil and pro-inflammatory mediators (IL-1 β , IL-6, and IL-8) levels in bronchoalveolar lavage fluid. Of particular interest is IL-8, which is a chemo-attractant cytokine for neutrophils and secreted by the alveolar epithelium and macrophages in response to excessive stretch. The result of the neutrophil infiltration is proteolytic enzyme release that causes lung injury. PP creates more homogeneous pleural pressure gradients and more

uniform strain-stress relationships throughout the lungs, so the stretch is released, IL-8 is secreted less, neutrophil attraction and lung injury diminishes [24].

In SP, ventral parts of the lungs are overinflated and overdistended, and dorsal parts open and collapse cyclically during mechanical ventilation. These changes cause ventilatory-induced lung injury that increases IL-6 expression. Another cause for increased levels of IL-6 is hyperoxemia during mechanical ventilation. In PP, ventilation becomes uniform in the lungs, need for mechanical ventilation diminishes, and FiO₂ lowers rapidly. As a result, IL-6 levels decrease [30].

CONCLUSION

For a proper and effective treatment of a disease, firm knowledge of pathology and pathophysiology of that disease is necessary. In COVID-19, the anatomy does not seem to be related to the clinic of the disease. However, basic clinical anatomy knowledge is necessary during some diagnostic (nasopharyngeal sampling, oropharyngeal sampling) and therapeutic (tracheostomy, prone positioning) treatments. Physicians applying those treatments should be aware of the potential risks, their prevention, and treatment, as well.

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Chapter 459

GENETIC BACKGROUND OF DIFFERENCES IN THE INCIDENCE OF CORONA VIRUS INFECTION

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ABSTRACT

Variability in susceptibility and disease severity in response to viral exposure is a distinctive feature of infectious diseases. It has also been noted a wide range of inter-individual variations in the infectivity, disease severity, and progression of COVID-19. Furthermore, it has been observed that susceptibility to COVID-19 shows geographical variation. Increasing evidence suggests a major role for host genes that affect viral infectivity and pathogenicity in explaining inter-individual and ethnic differences in susceptibility to coronavirus infections. Comparison of more than half a million genetic variants in individuals with the disease and population controls shows that many genes might be involved in susceptibility to COVID-19 infection. Some hypotheses have been proposed to explain how genes play a role in determining or influencing the efficacy of infection, the immune response to infection, or the severity of COVID-19 symptoms. These hypotheses include several genomic variants in the Angiotensin-Converting Enzyme, TMPRSS2, histocompatibility complex class I, and other few genes, the ABO blood group polymorphism, epigenetic alterations regulating host response, and telomere shortening. Throughout the recently published literature, we will discuss the recently published literature on host genetic factors related to coronaviruses, focusing on human studies in the context of COVID-19 susceptibility, severity, and progression as well as in geographical variation.

Keywords: COVID-19, SARS-CoV-2, genetics, susceptibility, genetic variation, clinical variability, gender difference

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INTRODUCTION

One of the most important research questions on the ongoing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic is why some people are more susceptible than others to SARS-CoV-2? Additionally, it is now evident that susceptibility to COVID-19 shows geographical variation. There are enormous clinical variabilities between individuals infected with SARS-CoV-2. This condition is ranged from silent to fatal infections [1]; the reason for this is currently not clear. Hypotheses suggested explaining observed differences include age, biological sex, other prior existing health conditions, and genetic factors. A twin study reported that 50% of the variance of the ‘predicted covid-19’ phenotype is due to genetic factors [2]. As with many complex diseases, the reality for most individuals most likely involves a complex interaction of genetic (viral and host genetics) and non-genetic variables. As related to hosting genetic factors, multiple *in silico* and molecular prediction studies show that multiple genes can be crucially involved in infection and progression of COVID-19. The scientific community suggests that single nucleotide polymorphisms (SNPs), or commonly known gene polymorphisms in the angiotensin-converting enzyme (ACE2), the transmembrane serine protease 2 (TMPRSS2), and other few genes reported, genetic variability in major histocompatibility complex (MHC) class I genes (human leukocyte antigen [HLA] A, B, and C), the ABO blood group polymorphism, epigenetic changes that might affect viral entry and replication, and excessive immune response to the virus, and telomere shortening may influence susceptibility to SARS-CoV-2 infection and the outcome of the COVID-19 disease. The preliminary results from the COVID-19 host genetics consortium which was established to discover and study the human genetic variants that modulate the susceptibility of developing COVID-19 symptoms and severity show several suggestively associated loci. However, very little is understood about the role of gene networks in determining or influencing the efficiency of infection and progression of COVID-19. Understanding these gene networks can situate susceptible individuals/populations, inform personalized treatment, and help vaccine development.

Throughout the recently published literature, we will focus on the most studied genetic variations which play a pivotal role in determining or influencing the efficacy of infection, the immune response to infection, or the severity of COVID-19 in the context of human studies.

ASSOCIATION OF SEX CHROMOSOMES WITH COVID-19

Gender difference has always been interesting in infectious disease research according to the World Health Organization (WHO) (as of April 18th, 2020). The male to female ratio among confirmed cases is 1.03:1 with a median age of 51 (interquartile range, IQR: 36–65) years [<https://www.who.int/emergencies/diseases/novelcoronavirus2019/situation-reports>. Accessed 25 Apr 2020]. Interestingly, the International Organization for gender equality and health equity Global Health reports sex-disaggregated data as 50/50. The gender difference in response to COVID-19 infection may play a larger role in the clinical disparity. Often reported, men are more susceptible to coronavirus infection and severe prognosis of the disease. On the other hand, studies shown that Sry expression on the Y chromosome is related to the reduction of the immune response. As known, the X chromosome has about 3000

different genes and encoding for more than 800 miRNAs. Genes of importance for immune response are encoded on the X chromosome. X chromosome inactivation (XCI) provides an equivalent gene dosage for both sexes [4].

X Linked Genes and X Inactivation

During early female embryogenesis, one of the X chromosomes is inactivated to have an equal dosage in the products of X-linked genes in males and females [5, 6]. The XCI process is formed by a multistep epigenetic mechanism. However, inactivation is not uniform and one-third of X-chromosomal genes escape from inactivation. XCI is incomplete in humans with one-third of X-chromosomal genes been expressed from both active (Xa) and inactive (Xi) X chromosomes in human female cells. These genes that escape X inactivation have been called ‘escapers’. Many of these genes are located at the ends of each arm of the X chromosome in areas known as pseudoautosomal regions (PAR1 and PAR2). These regions are present on both sex chromosomes. The genes that escape from X-chromosome inactivation may transcribe as two working copies [7]. There are other genes escaping from XCI, besides the genes in the PAR regions. These genes are defined as showing >10% expression from the inactive X allele compared to the active X allele [8]. In addition, the evidence was reported that at least 23% of X-linked genes continue to be expressed by the inactive X chromosome, and this condition is leading to a female bias less than two folds in the expression levels [9]. These regions escaping from XCI are including immune-related factors. For example, toll-like receptors (TLRs) [4], and *ACE2* gene are biallelically expressed in females in keeping with their location to Xp22 within a chromosome region prone to escape XCI. The *TIMP1* (tissue inhibitor of metalloproteinase 1) gene encoding proteins involved in response to infections and septic shock, maps to Xp11, within a region enriched in dosage-sensitive genes with a low chance of escaping XCI and is characterized by a variable expression from the inactive X chromosome. However, there are regions with immune-related genes escaping silencing in female lymphocytes, such as *CXCR3* at Xq13, encoding a chemokine receptor and *CD40L* at Xq16 encoding CD40 ligand, a B cell costimulatory molecule member of the tumor necrosis factor (TNF) family, for which biallelic expression is restricted to some mature B and T cells. Because of a functional advantage, these cells become overexpressed in tissues involved in the immune response. In addition, it has been suggested that there are miRNA-223 at Xq12, a fine tuner of granulocyte production and the inflammatory response, and miRNA-424 at Xq26, regulating monocyte/macrophage differentiation [10]. Different females may have different levels of mosaicism according to the percentage of the cell population with the parental X chromosome preferentially inactivated. This process may occur randomly or by selection against the cell population with a pathogenic variant on the active X. But 10% of healthy females over 50 years have haploinsufficiency for X-linked genes in immune-related cells with reduction of variation in their expression, losing their advantage compared to males. It has been shown that females have the capability to stronger and adaptive immune response than males. Likewise, Larissa said that X-linked genes may have a role in the emergence and maintenance of different immune reactions against COVID-19 in women and men, but there is no study on this issue yet [11].

Toll-Like Receptor 7 (TLR7)

Anti-viral immunity includes both innate immune and adaptive immune responses. Innate immune receptors have two main varieties as transmembrane and cytosolic. This situation is important for innate immunity, and thus adaptive for immune responses. Toll-like receptors (TLRs) are a family of sensor proteins that help the immune system to differentiate between “self” and “non-self.” TLR 3, 7, 8, and 9 are immune receptor which play role in host survival to viral infection [12]. They can detect the complete viral particles, including viral nucleic acid and viral envelope proteins, and defective viral particles [13]. Upon recognition of a virus, TLR signaling upregulates the expression of pro-inflammatory cytokines and costimulatory molecules, by the accumulation of type I interferons (IFNs) and IFN-stimulated genes (ISGs) [14, 15].

TLR7 activating by synthetic ligands such as imidazoquinolines is an endosomally located sensor. It is also a key component of antibody-mediated immunosuppression against the reactivation of endogenous retroviruses [12]. TLR7 detect single-stranded RNA viruses. It is expressed on variable immune cells such as plasmacytoid dendritic cells, B lymphocytes and myeloid cells, and non-immune cells including hepatocytes, epithelial cells, and keratinocytes [4]. After ligand binding, TLR7 dimerizes and activates signaling pathway involving myeloid differentiation primary response gene 88 (MyD88), mitogen-activated protein kinase (MAPK) cascades, NF- κ B activation, as well as IFN regulatory factor (IRF)-7 and IRF-5 activation via IL-1 receptor-associated kinases (IRAK)-1/2/4 and TNF receptor-associated factor-3/6. As a result, pro-inflammatory cytokines (TNF- α , IL-6, IL-1 β , IL-12) and IFN- α are produced, and TLR7 may stimulate B cells to enhance antibody production [12]. It is reported that IL-6 is very important in the dysregulated host immune response of poor prognosis COVID-19 patients [16]. The lower susceptibility to viral infections in females is observed from birth to adulthood. It is accepted that females develop stronger innate and adaptive immune responses than males. The activity of the innate immune response was reported to vary between males and females. Firstly, the TLR7 expression level is increased in women. Biallelic expression of TLR7 has been found in immune cells of women (and Klinefelter syndrome males) and this results in higher TLR7 protein expression in leukocyte populations of females [12]. Secondly, higher IFN- α production in females was demonstrated by several *in vitro* studies using stimulation with synthetic TLR7 ligands. Berghöfer et al. suggested that female peripheral blood lymphocytes produced much higher IFN- α levels than males after TLR7 stimulation by a large cohort study of healthy individuals [16]. TLR7 expression is higher on the immune cells of females after puberty. Also, in XX females IFN- α production was always above than monosomy X (Turner’s syndrome) females and XY males [4]. So, males have a relatively reduced antiviral immunity, since they produce a lesser amount of IFNs and inflammatory cytokines and possess a lower number of circulating T cells [11, 13]. Although females have stronger immunity, they also develop more autoimmune diseases than males [4].

HOST GENETIC FACTORS RELATED TO SARS-CoV-2 ENTRY INTO HOST CELLS

Host genetic studies using both candidate-gene and genome-wide strategies approaches identified significant associations between SARS-CoV-1 susceptibility or outcome and genetic variations such as single nucleotide polymorphisms in the human genome. Some of these genetic variations are associated with the human genes required for SARS-CoV/CoV-2 entry. The endosomal cysteine protease cathepsin B and L, TMPRSS2, glucose-regulated protein 78 kDa (GRP78), and ACE2 are commonly exploited by SARS-CoV/CoV-2 for cellular entry. Single nucleotide polymorphism variants in the genes for these proteins have significant differences in frequencies among the population groups. Also, several polymorphisms of genes required for SARS-CoV/CoV-2 entry has linkages with diabetes, cardiovascular disease, and hypertension, which, as comorbidities, significantly increase the severity of virus infection.

ACE2 and TMPRSS2

When coronaviruses, as well as influenza viruses, invade the target cells, usually the lungs, they need two proteins in the cell membrane, ACE2 receptor, and TMPRSS2. Following the surface spike proteins on the viral capsid attach to the ACE2 receptor, the virus initiates non-endosome entry of its genome across the cell membrane with the assistance of TMPRSS2, which catalyzes the cleavage of the bound spike protein. Thus, it causes a conformational change that promotes the fusion of viral and cellular membranes and thereby allows the release of the virus into the cell.

As regards the role of host genetic factors in coronavirus susceptibility or outcome, the human ACE2 has a rich pool of rare variants and is one of the most studied genes. The SARS-CoV-1 and COV-2 genomes shared around 80% of homology and used the same ACE2 to enter the cell [17]. Comparative genetic analyses of data from different databases indicate that several ACE2 variants could reduce the association between ACE2 and S-protein in SARS-CoV [18]. Several studies also suggest that the expression level and expression pattern of human ACE2 in different tissues might be critical for the susceptibility and progression of 2019-nCoV/SARS-CoV-2. Although a study group did not identify genetically supporting the existence of coronavirus S-protein binding-resistant ACE2 mutants in different populations by using the GTEx database [19], another group demonstrated that certain variants in the gene (rs73635825 and rs143936283) result in different intermolecular interactions with SARS-CoV-2 spike protein [20]. Hussain et al. [20] by a comparative modeling and molecular super-imposition study revealed that ACE2 alleles, rs73635825, and rs143936283 have a low binding affinity for SARS-CoV-2 spike protein. Therefore, these alleles may lead to resistance against COVID-19. It has been generally accepted that the ACE2 genetic variants may influence the protein's binding to the virus and its subsequent invasion of the cell. Although the frequencies of allelic variants of the ACE2 varies from one country to another [21], the genetic basis of ACE2 expression and function in different populations is still largely unknown.

Although it has been known that increased TMPRSS2 expression is related to two SNPs (rs2070788 and rs383510) and the susceptibility to H7N9 influenza [22], it has received less attention in genetic association studies to date. An in vitro study showed that a cell line expressing TMPRSS2 is highly susceptible to SARS-CoV-2 infection [23]. Recently, it has been recognized that SARS-CoV-2 uses the cellular protease TMPRSS2 for S protein priming. Russo et al. [24] published that the lung-specific expression quantitative trait loci (eQTL) variants for TMPRSS were associated with increased expression of TMPRSS2. They suggested that the eQTL variants may confer different susceptibility or response to SARS-CoV-2 infection. However, further research is needed to determine if these genetic variants in COVID-19 susceptibility, incidence, and progression.

Interferon (IFN)-Induced Transmembrane (IFITM)

It is generally postulated that RNA virus entry into cells by endocytosis is regulated with interferon (IFN)-induced transmembrane (IFITM) proteins, which confer cellular resistance to many pathogenic viruses by preventing viral fusion with cholesterol depleted. IFITM3, the most potent antiviral IFITM, inhibits an early event after endocytosis of virion particles. Sequence variants of the IFITM3 gene exhibit ethnic differences [25]. Among these variants, the polymorphism rs12252 C allele is considered to produce an alternate spliced transcript that encodes an aberrant truncated protein of IFITM3. Zhang et al. (2013) found a significant association between the IFITM3-rs12252CC genotype and influenza severity and hypothesized that the high frequency of the C allele in Asian populations may influence the epidemiology of influenza since this genotype was the much higher in the Han Chinese population compared with Caucasians [25]. A recent Indian study by a clinical exome data of 103 individuals also identified this genotype as risk inducing for SARSCoV-2 infection [26]. In the same study, one IFITM3 polymorphism, rs34481144 is also proposed as a protective variant for COVID-19 by increased memory Cytotoxic T Lymphocytes (CTLs) survival and more efficient viral clearance from infected airways. Therefore, genetic variations in the genes coding for IFITM proteins can lead to variability in establishing SARSCoV2 infection in the host.

HOST GENETIC FACTORS RELATED TO SARS-CoV-2 REPLICATION/PROTEIN EXPRESSION FOR REGULATING CORONAVIRUS INFECTION

Glucose Regulated Protein 78 kDa (GRP78)

Glucose regulated protein 78 kDa (GRP78) or immunoglobulin heavy chain binding protein (BiP) localizes to the lumen of the endoplasmic reticulum (ER) and is involved in the folding and assembly of proteins as an ER stress sensor under reasonable conditions. GRP78 is also found on the cell surface as a signal receptor. During cellular stress, elevated expression of GRP78 increases the chance for GRP78 to escape ER retention and translocate

to the cell membrane. Cell surface GRP78 (csGRP78) triggers various downstream cell signaling pathways by interacting with its ligands. Various pro-proliferative, pro-survival ligands, and pro-apoptotic ligands have been discovered. Furthermore, there is evidence that the substrate-binding site of csGRP78 is susceptible to virus recognition and it can be mediate the virus entry into the host cell [27]. Chu et al. (2018) published that GRP78 is capable of facilitating surface attachment of MERS-CoV spike protein. An *insilico* study suggests the existence of a SARSCoV-2 spike protein-GRP78 binding site. However, it is not yet known whether the expression of GRP78 and its polymorphisms have a role in determining the susceptibility and resistance to coronaviruses.

Cyclophilins

Cyclophilins (CyPA), a subgroup of the large immunophilins protein family, are peptidyl-prolyl isomerases involved in the folding of cellular proteins and cell signaling. They play a pivotal role in the replication of several RNA viruses, including nidoviruses (arteriviruses and coronaviruses), and are necessary for proper viral propagation. Cyclophilin A (CypA) and B have been shown to interact with non-structural protein 1 (nsp1) of SARS-CoV intracellularly [29]. Therefore, cyclophilins and its overexpression are significant in the pathogenesis of viral infection. It has been reported that SNP variants causing amino acid exchanges around enzymatic peptidyl-prolyl cis/trans isomerase in CypA may directly affect the propagation of HCoV-229E [30]. Although polymorphisms in the CypA gene have also been documented to influence susceptibility to HIV-1 infection, whether these variations play a role in COVID-19 susceptibility and progression remains largely undocumented.

HOST GENETIC FACTORS IN THE IMMUNE RESPONSE TO SARS-CoV-2

HLA Loci

Classical human leukocyte antigen (HLA) molecules encoded by MHC genes are a specific group of molecules expressed on the cell surface. They are crucial for the recognition of non-self molecules by the acquired immune system. MHC molecules acting as a receptor for viral peptides present the peptides to the virus-specific cytotoxic CD8⁺ T lymphocytes. These cells recognize the conformational structure of the peptide-binding groove of the MHC class I molecules, bound to viral peptides. Variations within MHC class I genes determine both variation in the conformational structure of the peptide-binding groove and its binding to varied antigen peptides. Therefore, it is generally accepted that HLA genes are critical in the immune response against pathogens and more authors consider them as the leading candidates in conferring susceptibility to infectious diseases. MHC classical class I and class II genes exhibit many variants (alleles) and have several thousand reported polymorphisms. Several genetic variants at HLA genes have been identified that account for inter-individual differences to the immune response against common viruses. Accumulating evidence suggests that genetic variability in the HLA-A, -B, and -C genes may also affect susceptibility

to and severity of the disease caused by SARS-CoV-2 [31]. However, whether distinct HLA allele distribution in various populations provide distinct protection or vulnerability to COVID-19 is unclear.

A Genome-Wide Association Study (GWAS) demonstrated that HLA may act as a susceptibility factor for several common infectious diseases [32]. Several studies on SARS-CoV-1 reported higher risk allele frequency of HLA-B*46:01, HLA-B*07:03, HLA-C*08:01, and HLA-DRB1*12:02 and the increased protective allele frequency of HLA-DRB1*03:01, HLA-C*15:02, and HLA-DRB1*03:01. Contrary to this, some studies have been inconsistent and conflicting. On the other hand, *in silico* studies predicted that HLA-B*15:03, HLA-A*02:03 and HLA-A*31:01; and HLA-A*02:01 as effective antigen presenters for SARS-CoV-2, implying that these would provide protection, while HLA-A*03:02 and HLA-B*46:01 had fewest predicted binding peptides for the virus, implying that these would increase susceptibility to COVID-19 [31, 33, 34]. These studies also suggested that HLA-A*02:02, HLA-B*15:03, HLA-C*12:03 haplotypes exhibited the highest and HLA-A*25:01, HLA-B*46:01, HLA-C*01:02 haplotypes displayed the lowest predicted repertoire of epitopes from SARS-CoV-2. Based on bioinformatic prediction and molecular modeling studies with reporting positive findings, HLA molecules could be considered as a genetic gateway for SARS-CoV-2 infection.

Taking into account spatial variation of COVID-19 positive cases, it is becoming increasingly apparent that population-specific HLA alleles or haplotypes could act as a critical intrinsic determinant of protective immunity against SARS-CoV-2 and make population groups and some individuals resistant or susceptible to COVID-19 infection. Results from the studies investigating the geographical pattern in COVID-19, the risk of virus infection, and its clinical outcome in African and Indian populations have been comparatively less than European and other world populations. Based on their comprehensive *in silico* analyses, HLA-A*02 subtypes that are predicted to be protective exhibit higher frequency in Indian and several African populations, which are comparatively less than among populations for the risk and severity of COVID-19. HLA-C*12:03 as the susceptibility allele appears to be the most frequent in the European population. However, whether distinct HLA allele distribution in various populations confers protection or vulnerability to COVID-19 is a topic of debate and discussion.

Inflammatory Factors and IL-6

Cytokine storm and then an exacerbated inflammatory response have been proposed as the basis of the pathophysiological process of SARS-CoV-2 infection. The severity of the disease has been demonstrated to be correlated with high serum levels of IL-2 receptor (IL-2R) and IL-6 (≥ 80 pg/mL) in patients with COVID-19.

Variations in the production and activity of cytokines are associated with SNPs in various regions of cytokine genes, such as IL12RB1 and IFN- γ +874A allele, and influence the susceptibility and/or resistance to various infectious pathogens. It is now well-established that ethnicity greatly influences cytokine gene polymorphism distribution. Although there is evidence supporting the associations between several cytokine gene polymorphisms and SARS-CoV, there are no studies on the impact of cytokine gene polymorphisms on the risk of

SARS-CoV-2. But, taking into account a critical role of cytokines in influencing the severity of COVID-19 and an important role of genetic background in determining the pattern of the inflammatory response, allelic variations in cytokine genes look like to play an underlying role in COVID-19.

Some Other Possible Candidate Immune Genes to COVID-19 Susceptibility

As known, there are various upstream regulators, such as the Toll-like receptor (TLR) involved in the control of cytokine expression. Additionally, components of the innate immune system such as complement components have also close interactions for cytokine responses. Therefore, host genetic factors concerning these components may affect disease susceptibility and pathogenesis.

Few other genetic factors in the immune response to SARSCoV-2 about these components were suggested or reported. One of them is *Ticam2*, codes for an adaptor protein in the activation of the TLR signaling pathways. A mice study revealed that allelic variation in the *Ticam2* influences susceptibility to SARS-CoV infection [35]. Also, researchers demonstrated that *TRIF* which is another adaptor protein of TLR signaling pathways, required for initiating the innate immune response to severe SARS-CoV infection and it protects mice from coronavirus infection [36]. Although, there are no studies on the role of the TLR pathway in SARS-CoV-2 infection, given the genetic variation within the TLR genes or components of the TLR pathway and its distinct distribution pattern in various ethnic populations, the genes involved in TLR signaling could emerge as a major host determinant of differential susceptibility to SARS-CoV-2 infection and severity. However, this assumption needs to be tested empirically for SARS-CoV-2.

TLR pathway genes reported concerning COVID 19 susceptibility or outcome are also discussed in Section “sex chromosomes and COVID-19”.

The complement system efficiently recognizes and eliminates viral pathogens by opsonizing viruses and virus-infected cells. Some writers note that coronaviruses activate multiple complement pathways; There are *in vitro* and *in vivo* evidence indicating that complement activation plays a critical role in pathogenesis and disease progression of SARS-CoV and SARS-CoV-2. For example, a recent study demonstrated that highly pathogenic N proteins of SARS-CoV, MERS-CoV, and SARS-CoV-2 aggravated inflammatory lung injury by aberrant complement activation [37]. Considering that polymorphisms of complement genes are associated with the risk of various infectious diseases as well as various diseases, perhaps complement gene variations in ethnic populations modulate the risk and severity of SARS-CoV-2 infection.

EPIGENETIC MODIFICATIONS AND COVID 19

Epigenetic changes that regulate chromatin structure have a major impact on genome stabilization and maintenance of cellular homeostasis. They have been implicated in the pathophysiology of the virus infection. The epigenetic regulation of gene expression relies on post-translational chemical changes. These changes occur at the level of chromatin as well as

on RNA and DNA, are including primary methylation, but also acetylation, phosphorylation, ubiquitination, and sumoylation. These modifications bridge between genotype and phenotype by changing the function of the gene locus without changing the DNA sequence. DNA methylation is the inheritable epigenetic process by which methyl groups are added to the C-5 position of the cytosine ring of DNA by DNA methyltransferases (DNMTs). In addition, more than 98% of DNA methylation occurs in a CpG dinucleotide context in somatic cells, while as much as a quarter of all methylation appears in a non-CpG context in embryonic stem cells (ESCs). DNA methylation is erased during zygote formation and then reestablished in the embryo at approximately the time of implantation. Most DNA methylation is essential for cell development, and it plays a key role in several processes including the packing of DNA in the nucleus genomic imprinting, X-chromosome inactivation, and suppression of repetitive element transcription and transposition and, when dysregulated, causes to diseases like cancer. DNA methylation is regulated by a family of DNMTs. These family members have been determined as DNMT1, DNMT2, DNMT3A, DNMT3B, and DNMT3L [38]. In recent years, 110 types of RNA nucleotide modifications have been reported, spanning RNA types including messenger RNA (mRNA), transfer RNA (tRNA), ribosomal RNA (rRNA), transfer-messenger RNA (tmRNA), small nuclear RNA (snRNA), and chromosomal RNA, many of which are currently well cataloged at the RNA Modification Database (<http://mods.rna.albany.edu/mods>). RNA modifications not only mark and regulate mentioned these transcripts but also diversify and extend the protein's functionality from the annotated genes [40]. Recent work in this area showed that chemical modifications at the RNA level play a role in gene transcription, translational efficiency, and RNA stability [41]. These modifications of coding and non-coding RNA are including, adenosine methylations, cytosine modifications, isomerization of uridine, and ribose modification [42]. Mass Spec technologies have discovered a series of RNA modifications that are not only non-coding RNAs, including tRNA) and rRNA but are also commonly found within functional mRNAs. Thus, some of the mapped modifications showed dynamic patterns and tissue-specific distribution explaining to the new field of RNA-epigenetics or epitranscriptomics domains. Transcriptomic and epitranscriptomic analyses have primary importance in the study of viruses by determining their structure and function. So, it is provided important information about host infection [41]. Likewise, new data from the Centre for RNA Research and their collaborators at the Korean National Institute of Health (KNHI) within the Korea Centers for Disease Control and Prevention (KCDC) have presented a high-resolution map of SARS-CoV-2. As known, each RNA viral transcript has 5'-cap structure and a 3' poly(A) tail. Nanopore-based direct RNA sequencing was observed motif being the AAGAA present throughout the viral genome. The poly(A) tail plays an important role in RNA turnover and this internal modification may contribute to viral RNA stability and translation efficiency. When the virus enters the host cell, it replicates a genomic RNA that consists of nine open reading frames (ORFs). Thus, the genomic RNA is translated to produce proteins. There are nine subgenomic RNAs transcribed from the genomic RNA. They are encoding conserved structural proteins, namely, the spike protein (S), an envelope protein (E), membrane protein (M), and nucleocapsid protein (N) that synthesize the viral particle [41, 43]. Generally, the virus entering point at the host cell is the ACE2 type I membrane receptor. These receptors are present in arterial and venous endothelial cells, lung type II alveolar cells, enterocytes of the small intestine, and arterial smooth muscle cells in the cerebral cortex and brainstem. According to obtained the data, during SARS-CoV-2 enters

into cells, it is using the receptor-binding domain (RBD) of the spike (S1) protein that contains a core structure and a receptor-binding motif (RBM) to bind the outer surface of the receptor.

Previous studies have shown a strong association between SARS- Cov infection and ACE2 expression levels. Also, a series of comorbidities have been reported in patients who died of COVID-19 infection, including chronic diseases. As known, the *ACE2* gene is located on the X chromosome and is closely related to XCI [41]. XCI is an epigenetic regulation and explained in more detail above. Zyllicz et al. mapped the X chromosome inactivation in several human tissues. Male and female differences were investigated in the expression of X-chromosomal protein-coding and long non-coding RNA (lncRNA) genes and single-cell transcriptomes, along with genomics in Genotype Tissue Expression (GTEx) project. It was detected that although XCI is essentially uniform across human tissues, some heterogeneity can also occur between cells, tissues, and individuals. The data have shown that escaper genes were caused to result in sex biases in gene expression and so in phenotypic diversity. *ACE2* was found among one of these genes in female lung tissue, showing a more heterogeneous sex bias. Moreover, *ACE2* expression was slightly higher in males than in female tissues. This condition may be the reason for higher respiratory infection severity in male than in female patients [9, 44]. Recently research studies in the regulation of the *ACE2* gene by DNA methylation indicated that the host epigenome may represent a risk factor for COVID-19 infection [41]. Moreover, age-dependent DNA methylation was detected close to the transcription start site of the *ACE2* gene by the techniques of DNA methylation analysis in airway epithelial cells. Corley et al. using Illumina DNA methylation sequence data from samples of different biological ages, they found that a CpG near the *ACE2* transcription start site showed a decreased level of methylation during aging. Previous studies had suggested that DNA methylation levels are reduced during aging. Thus, differential methylation patterns of genes involved in inflammation, aging, and immunity response were obtained. These data could explain the higher morbidity rates of the virus infection in older individuals and patients with underlying medical conditions [45]. Additionally, the *ACE2* promoter has been found hypomethylated in endometrial carcinoma and renal papillary cell carcinoma tissues. Thus, *ACE2* expression levels increase in these patients. When these patients were affected by SARS-CoV-2, their prognosis may worsen [46].

It was reported that epigenomic alterations play a basic role in distinguishing immune cell phenotypes and regulating inflammatory responses to intrinsic or extrinsic stressors with aging. Specific epigenetic modifications such as histone acetylation/ methylation in chromatin play essential roles in response to viral infection. Epigenomic patterns of aging result in decreases in naive T cells and increases in monocytes and cytotoxic cell functions. Whereas, the size of alterations is more significant in men than in women, with an accompanied loci specific methylation decline in the B cells. Thus, it is thought that gender and age differences in epigenetic patterns of immune cells may partially explain the diversity in the severity of COVID-19. However, the epigenetic changes in CpG-sites located in subtelomeric regions which control innate immunity can mediate inflammatory responses to COVID-19 [47].

Epigenetic and Possible Treatment/Vaccine Options for SARS-CoV-2

As is known, the epigenetic regulation of multiple genes can be intervened by natural factors and named as epi-drug. Inhibition of *ACE2* and furin expression with the use of drugs such as vitamin D and quercetin for the treatment of SARS CoV-2 is recommended [48]. Other candidate epi-drugs for epigenetic silencing of *ACE2* and interferon genes are curcumin, deferasirox, 8-hydroxyquinolones (8HQ), and sulforaphane (from broccoli) [49 - 51]. It is suggested that all of these substances are natural medicines and could help to reduce disease severity and susceptibility. Ferritin values in severe SARS-CoV-2 patients increase and accordingly their clinical results worsen [48]. Curcumin is especially important as it has ferritin-lowering effects [52].

TELOMERE LENGTH AND COVID 19

Telomeres are repetitive nucleotides (TTAGGG)_n at the ends of each chromosome. They play a role in maintaining genome stability and regulate immunity in response to viral infection. Subtelomere regions contain CG-enriched genes that regulate immunity. These genes are influenced by telomere length and regulate telomere repeat-containing RNA (TERRA) transcription. Their expression can be upregulated in response to viral infection by activation of interferon-stimulated genes. Thus, telomere shortening, coupled with dysregulated innate and adaptive immune responses to viral infection, can cause severe outcomes in older adults with COVID-19 [47, 53]. Earlier studies reported that telomeres play a major role in influencing the process of cellular senescence and can be associated with maintaining lung health. In addition, telomere dysfunction was also associated with smoking and chronic obstructive pulmonary disease [54 - 56]. Some agents in smoke may activate DNA damage response by influencing telomere function and the level of CD4⁺ and CD8⁺ T cells significantly is reduced. Furthermore, viral replication activates interferon regulatory factors (IRFs) and TLR-3-induced NF- κ B pathway; which towards the increase in the production of proinflammatory cytokines and cytokine storm. There is evidence that the NK cells are significantly increased in older adults while the percentages of type T of cells decreased. In aged individuals, APCs secretion of pro-inflammatory cytokines increased while they secrete reduced levels of anti-inflammatory and immune-regulatory cytokines. One of the especially differences at the DNA level between old age persons and children is their telomere length. The immune system is extremely sensitive to the shortening of telomeres. Because the immune system depends on cell renewal and clonal expansion of T and B types of cells [57]. Lymphopenia which a decline in the number and exhaustion of T lymphocytes characterizes severe acute respiratory syndrome by betacoronaviruses. It is thought that the short leukocyte telomere length (LTL) may partially explain the lymphopenia associated with COVID-19. As known, within every person, hematopoietic cells show age-dependent telomere shortening. Lymphopoiesis is linked to telomere length and telomerase, whose activity varies in different lymphocyte lineages [58]. There is a marked variation in LTL between humans. This difference is dependent on the effects of gender, paternal age at conception, and environmental exposures. Various research showed that short LTL was associated with a high risk of hospitalization due to pneumonia and a significant risk of death

related to infections. Another study on immunity after flu vaccination documented that, individuals with long telomere length in B-lymphocytes produced a more strong antibody response when compared to individuals with short B-lymphocyte telomere length [57]. According to authors, inter-individual differences in telomere length and the concomitant propensity of T cells to undergo senescence due to aging might play a critical role in severe lymphopenia associated with COVID-19 and its often fatal outcome. Older people and those with pre-existing conditions are very much affected by COVID-19 and are more susceptible to poor clinical prognosis. The aging-related decreases in NAD⁺ with a reduction in telomeres length negatively influence the immune response and COVID-19 outcome. In addition, the use of NAD⁺ as an immunomodulator in older patients with COVID-19 could decrease the severity of immune reaction in those patients and improve their clinical condition [57, 58].

RELATIONSHIP BETWEEN ABO BLOOD GROUP DISTRIBUTION AND COVID-19

The ABO blood group consists of two antigens (A and B antigens), which are the ABO gene product and includes 4 blood types, namely, A, AB, B, and O. Blood typing are performed as ABO, Rh with standard antibody-based methods. Blood group antigens present at least 300,1 on red blood cells (RBCs), since the discovery of the ABO system [59, 60]. The human ABO blood group is located on chromosome 9 (9q34.1–34.2) [61]. Many studies have reported that the ABO blood group plays an important role in various human diseases, such as cardiovascular, oncological, and some infectious and non-infectious diseases. Human histo-blood group antigens (HBGAs) are some of the important antigens on the surface of human red blood cells. These antigens are highly expressed in a wide variety of cells and tissues, including epithelia, platelets, vascular endothelia, and neurons, and also important as receptors for immune responses. The ABO blood types have polymorphic traits within the ABO gene, and blood types have considerably different distributions across ancestry groups. Differences in blood group antigen expression can affect a different level to host susceptibility to many infections. A series of studies shown that the ABO blood group has been previously found to relate to the risk of multiple infectious diseases such as hepatitis B, malaria, rota, dengue viruses, and SARS coronavirus. Furthermore, many blood group antigens have the effect of facilitating intracellular uptake, signal transduction, or cell adhesion through the organization of membrane micro-domains. Blood group antigens can modify the innate immune response to infection [61 - 65]. In addition, an association was shown between variants within ABO and activity of ACE which modulating sensitivity to SARS-COV 2 by genome-wide association studies. The numerous association studies between blood type and COVID-19 present reasons to believe true associations may exist between blood type with morbidity and mortality due to COVID-19 [64]. In recent data, the results of studies demonstrated that there was a significant association between the A blood group and COVID-19. They reported that females with blood type A are more susceptible to COVID-19 infection [60, 63]. Similarly, Li et al., determined that the rate of patients with SARS-CoV-2-infected A blood group was significantly higher than healthy controls, while the proportion of patients with SARS-CoV-2-infected O blood group was lower. Also, they

suggested that blood group A patients were at higher risk of hospitalization than blood group O patients following SARS-CoV-2 infection [66]. As known, blood type O individual expresses the H antigen, the biosynthetic precursor to A and B antigens. In addition to red blood cells, numerous tissues and secretions such as the endothelium, intestinal mucosa, heart, kidney, and other organs express ABH antigens. This antigen is a carbohydrate antigen and expressed on glycoproteins and glycosphingolipids (GSLs). Earlier, glycan analysis of SARSCoV S protein shown that SARSCoV S protein has a broad range of structures, such as complex Nglycans with 2–4 antennae able to support ABH epitopes. This is highly probable for the virus targeted to respiratory and gastrointestinal mucosa [60]. Several different study groups, reported a possible association between blood type A and a higher risk for COVID-19 infection and mortality while blood group O was associated with a lower risk of infection and mortality. However, there is still a lack of data on the relationship between ABO blood typing and the severity of COVID-19 disease [64, 67, 68]. There are also opinions against these data. For example, Latz et al. performed a study using a large multi-institutional cohort of patients. According to this study, there was no association noted between ABO blood type and COVID-19 disease severity defined as intubation or death, but blood type O had the lowest frequency of disease positivity, similar to other groups [62]. Conversely, Ellinghaus et al. suggested that there is also a lower probability of intubation for all non-O blood types [68].

Cheng et al. suggested that patients with blood group O had decreased susceptibility to SARS-CoV infection [69]. It has been reported that anti-A antibodies found in individuals with blood group O might block the interaction between SARS-CoV and its receptor, thus protecting against SARS-CoV infection. Based on these results, it can be speculated that the susceptibility to COVID 19 decreased in individuals with blood type O, while increased in individuals with blood type A may be related to the presence of anti-A antibody in the blood. Because anti-A antibodies can block the interaction between the virus and its receptor. This condition may explain why blood group A is sensitive to the virus while blood group O is not. In addition, Wu et al. indicated that blood type might have some influence on the clinical characteristics of patients with COVID-19 in their study. They observed that the clinical features of people with different blood types after infection with COVID-19 were different. As a result, it is thought that the blood type of individuals may not be one of the risk factors for COVID-19, but may be related to the clinical characteristics of COVID-19 patients [61, 70].

There is also evidence for the relationship between Rh type and very few diseases compared to ABO. Similarly, Rh(D) phenotypes (positive and negative Rh blood types) are important for immune response. Zietz et al. found that there were greater risk differences between Rh blood than between ABO strains, and in particular Rh-negative individuals had a lower risk [62, 64].

CONCLUSION

Some human genetic variants have previously been identified that influence susceptibility or resistance to infection with various virus pathogens. Even though many questions remain unresolved, there is also a growing consensus among the scientific community that some

Table 1. Host genetic factors related to COVID-19 disease reported from previous studies as protective and permissive genes

Gene(s) or Locus	Genetic variation/alteration	Effect of genetic alteration	Association/ Possible mechanism (s) -process influenced by host genetic factor/variation	Ref (s)
ACE2	Escaping from XCI Epigenetic modifications SNPs: rs73635825 rs143936283	Two dose expressed in females Hypomethylation during aging	Excessive Immune response Susceptibility to infections Protection/ low binding affinity with SARS-CoV-2 spike protein	[4, 10, 11] [9, 41, 44, 45] [20]
TMPRSS2 IFTM3	eQTL rs34481144	Increased expression of TMPRSS2	Different susceptibility or response to SARS-CoV-2 Protection/increased memory CTLs survival and more efficient viral clearance	[24] [26]
TLRs HLA	Escaping from XCI HLA-B*15:03, HLA-A*02:03 and A*31:01; and HLA-A:02:01 <i>Haplotype</i> : HLA-A*02:02, HLA-B*15:03, HLA-C*12:03 HLA-A*03:02 and HLA-B*46:01 <i>Haplotype</i> : HLA-A*25:01, HLA-B*46:01, HLA-C*01:02	Two dose expressed in females	Protection/relatively reduced antiviral immunity Protection/ effective antigen presentation for SARS-CoV-2	[4, 11, 12] [31, 33, 34].
CG-enriched genes in sub telomere which are regulated TERRA transcription	Short telomere length		Susceptibility/ fewest predicted binding peptides for virus- increased susceptibility to COVID-19	
The ABO blood group	Blood type O		Susceptibility dysregulated innate and adaptive immune responses/Lymphopenia -T lymphocytes Protection/ blocking the interaction between the virus and its receptor	[47, 57, 58] [61, 69, 70]

genetic variants in genomes of individuals might confer differential susceptibility and influence the severity and progression of SARS-CoV-2 infection, as well as age, biological sex, and major comorbidity factors such as cardiovascular disease and metabolic disorders. Taking into account the general findings in the literature (Table 1), we discussed the expression level or mutation and variation in some host genetic factors such as ACE2, TMPRSS2, GRP78, TLR7, HLA, ABO blood group, as well as epigenetic changes regulating host response and inter-individual variation in leukocyte telomere length. Many of these host genetic factors also exhibit population-specific variation and is associated with susceptibility and/or resistance to various viral diseases.

There are multiple limitations to our summaries for each identified genetic variations concerning COVID-19 susceptibility. Firstly, the studies and information on SARS-CoV-2 infection continue to increase very rapidly since its emergence. Therefore, we can't cover them all here. Secondly, some studies that have been conducted may not have reported relevant data because of publication biases. Thirdly, most studies, including a large patient population, were conducted in China, and the study of asymptomatic carriers was limited. Lastly, the potential impact of previous exposure to other coronavirus species in influencing population discrepancy and severity of SARS-CoV-2 is also uncertain. Moreover, it should be kept in mind that the large majority of studies reporting positive findings may be affected by a strong risk of bias or confounding. More research findings with a larger dataset are needed to help to understand the role of gene networks in determining or influencing the efficiency of infection and progression of COVID-19.

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Chapter 460

THE CLINICAL COURSE OF COVID-19 IN ELDERLY PATIENTS

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ABSTRACT

COVID-19 disease, which affects the whole world and is declared as a pandemic by the world health organization, affects the elderly mostly due to both physiological changes because of aging and its comorbidities. Studies have reported that mortality and morbidity are higher in the elderly than young people. Like other infections, COVID-19 disease can manifest itself with different symptoms, as the immune response decreases with aging. Also, they have difficulties in describing and expressing the symptoms because of the decrease in their cognitive functions, which leads to a delay in hospital admissions. Although there are no findings specific to the elderly in laboratory values and radiological imaging, some findings were found to be more common in the elderly. Among the treatment options, a different treatment protocol specific to the elderly is not applied. However, since the comorbidities of geriatric patients and the number of medicine they use are high, care should be taken in terms of medicine side effects and drug-drug interactions during treatment. The COVID-19 epidemic affects the elderly not only physically, but also socially and psychologically. All these situations lead to a more severe course of COVID-19 disease by causing increased malnutrition and sarcopenia in the elderly and making them frailer. During the COVID-19 pandemic process, elderly patients should be evaluated considering all these conditions and necessary medical, psychological, and social support should be provided.

Keywords: COVID-19, clinic, elderly, SARS-CoV-2

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INTRODUCTION

The Coronavirus disease 2019 (COVID-19) outbreak, which occurred due to the new coronavirus (SARS-CoV-2) and spread rapidly all over the world, was declared as a pandemic by the World Health Organization (WHO) on March 11, 2020 [1]. The pathogen has been identified as a novel enveloped RNA beta-coronavirus called acute respiratory syndrome coronavirus 2 (SARS-Cov-2). It can cause a wide range of diseases ranging from mild illness like flu to critical illness such as sepsis, multiple organ failure, and severe respiratory failure. The disease is transmitted from person to person by droplets and by touching mouth, nose, and eye mucosa with dirty hands after touching surfaces containing viruses. Symptoms of the disease; the first symptoms appear within an average of 5-6 days (may extend from 2-14 days) after the virus enters the body [2].

The elderly population in the world is gradually increasing. While the population aged 65 and over was 6% in 1990, it increased to 9% in 2019. In 2050, it is expected to be 16% [3]. It is known that patients over the age of 65 are frailer due to comorbidities and age-related physiological changes and they are more affected by many diseases than young people [4]. It has been reported that the majority of those who were hospitalized and died among patients infected with COVID-19 consisted of elderly patients causing higher mortality rates, especially in the elderly with cardiovascular disease, chronic respiratory disease, diabetes, or another health problem such as cancer [5]. The Centers for Disease Control and Prevention (CDC) reported that 17% of the total population in the United States is over 65 years. However, 65 years and older patients were responsible for 31% of COVID-19 infections, 45% of hospitalizations, 53% of intensive care unit admissions, and 80% of deaths caused by COVID-19 [6]. Also, many studies have shown that mortality increases with an increasing age [7]. In a study with 72,314 cases, it was shown that the overall mortality rate was 2.3% but increased to 8% between the ages of 70-79 and 14.5% in patients over 80 years old [5]. Therefore, it is important to know the clinical, laboratory, and radiological characteristics and treatment options of elderly patients infected with COVID-19.

CLINICAL CHARACTERISTICS

Older individuals are more prone to infections due to multiple chronic diseases, weak immune systems and their recovery are slower than younger people. As a result of natural changes that occur in the body with aging, the symptoms and clinical course of COVID-19 may be different from young individuals.

According to the CDC, 63.1% of adults aged 60 and older have hypertension, 38% of people aged 65 and older have chronic kidney disease (CKD), and 26.8% of adults aged 65 and older have diabetes [8-10]. In a study in which 312 patients infected with COVID-19 aged 65 and older were included, 77.2% of the patients were reported to have comorbidity. Like the general population, the most common comorbidity in these patients (57.1%) was hypertension, followed by diabetes mellitus (38.8%), cardiovascular disease (29.8%), chronic lung disease (8.65%), cerebrovascular disease (6.4%) [11]. In another study, 69.5% of geriatric patients had comorbidity, and the most common comorbidities included hypertension (43.8%), diabetes (25.7%), and cardiac disease (16.2%) [12]. Older patients

with comorbidities were more likely to progress to severe disease [13]. Therefore, it is vital to know and control chronic diseases in elderly patients with COVID-19. For example, when we consider the most common comorbidities, it is very important to keep blood pressure and glucose under control.

The risk and severity of developing an infection depend on the relationship between the pathogen's virulence, its inoculum, and the host's defense system. Virulence of a pathogen is determined by the ability to attach and replicate in a host environment. With the physiological changes brought about by aging, macrophage function changes, mucocutaneous defenses are compromised, cytokine production decreases, and T cell function is insufficient. Comorbid conditions such as diabetes, congestive heart failure, kidney failure, chronic lung disease, and malnutrition deteriorate the immune system. For these reasons, infections may show an atypical course in geriatric patients. Current data show that COVID-19 infections may also start with atypical presentations in a significant portion of the elderly [14]. Geriatric patients with COVID-19 may only have fatigue, myalgia, headache, or vomiting without fever or cough. It should be kept in mind that this situation may cause patients to apply to the hospital later, to be diagnosed later, and to start treatment later, and therefore to be more fatal. For example, traditionally, fever is defined as the body temperature above 38°C, but one-third of the elderly with acute infection usually does not have a fever at these values. A previous report noted that fever may be reduced or even absent in elderly patients with bacterial or viral infections due to low basal temperature, impaired thermal homeostasis due to aging, and frequently-used medicine such as aspirin [15]. In addition, healthy elderly people tend to have lower body temperatures compared to young people. The Infectious Diseases Practice Guidelines Committee of America has defined fever in the elderly as:

1. A single oral temperature > 100°F (37.8°C)
2. Repeated oral temperatures > 99°F (37.2°C) or rectal temperatures > 99.5°F (37.5°C)
3. Temperature increase > 2°F (1.1°C) relative to baseline temperature

The most common symptoms in the general population are fever (98%), cough (76%), shortness of breath (55%), and myalgia or fatigue (up to 44%) [16]. Although these symptoms are the most common in elderly patients, their incidence is different compared to young people. In studies of elderly individuals with COVID-19 infection, the most common symptoms were reported to be shortness of breath (76%), high fever (52%), and cough (48%) [7]. In another study; 66.7% of elderly patients had a fever, 64.8% cough, and 33.3% fatigue on admission. Other symptoms include shortness of breath (29.5%), diarrhea (9.5%), anorexia (8.6%), headache (8.6%), myalgia (7.6%), and vomiting (5.7%). In the same study, the median incubation period in elderly patients was 8 days, and the time from the onset of symptoms to hospitalization was 5 days. The atypical course of the disease in the elderly and the delayed perception of the symptoms due to the decrease in the cognitive functions of the elderly cause late admissions to the hospital. This causes the late initiation of treatment and a more serious and mortal course of the disease.

Cough and shortness of breath symptoms can be misleading in older individuals. The cough reflexes in the elderly are weakened and differential diagnosis should be made well in the elderly who present with dyspnoea due to the prevalence of chronic respiratory failure and heart failure causing dyspnoea. It was observed that the complaints of cough and sputum were

similar among the elderly and young people, while the complaints of shortness of breath were more common in the elderly [17].

In a study in which 214 patients were evaluated, neurological findings were detected in 36.4% of the patients. In this study, neurological symptoms were classified into three categories. CNS symptoms or signs (headache, dizziness, impaired consciousness, ataxia, acute cerebrovascular disorder or epilepsy) were detected in 24.8% patients, neuropathy symptoms (hypogeusia, hyposmia, or neuropathic pain) were detected in 8.9% patients, skeletal muscle symptoms were detected in 10.7% patients [18].

In a review in the literature, the smell changes were reported as 60.7%, and the frequency of taste changes was reported as 56.4% [19]. Fatigue, weakness, headache, and gastrointestinal system findings in elderly patients are similar to those in young people. Along with these, elderly patients may present with confusion and impaired oral intake. In addition, it has been reported that cardiac complications such as myocarditis, pericardial effusion, and arrhythmia can be seen in cases with a severe course of the disease [20]. The pre-diagnosis of COVID-19 infection should be kept in mind in patients presenting with these complaints.

While trying to control the infection in elderly patients, we should also consider the complications we encounter frequently. Delirium is a common complication of infections, especially in older adults. In the first studies, it was shown that 20-30% of COVID-19 patients develop delirium on admission to the hospital or during the disease [21]. In all age groups, this rate has been reported to be 60-70% in those with severe disease. Although the exact cause of this relationship is unknown, it is thought that there may be multiple factors such as direct neurological invasion, cerebrovascular involvement or indirect high fever, hypoxia, dehydration, inflammation, medications, or metabolic disorders.

COVID-19 disease has been reported to increase the risk of thrombotic events, including stroke. In some studies, the incidence of ischaemic stroke in patients infected with COVID-19 is approximately 2.5%. In a study, the rate of hemorrhagic stroke was found to be 0.9%, and it was reported that 88% of these patients were using anticoagulants [22]. Although the mechanisms of cerebrovascular events in COVID-19 have not been clarified, it has been reported that coronavirus directly infects endothelial cells and causes widespread endothelial inflammation in cases with severe respiratory syndrome. This may be a mechanism leading to ischaemic stroke or hemorrhagic stroke.

LABORATORY CHARACTERISTICS

In available studies in the literature, it has been reported that lymphopenia is common in patients with SARS-CoV-2 infection. It has been observed to occur in 32.5-75.4% of COVID-19 patients in different studies [23]. Lymphopenia was also a common finding in severe acute respiratory syndrome coronavirus (SARS CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). Also, one study reported that severe cases of COVID-19 were reported to have lower lymphocyte count and higher neutrophil count than non-severe cases; therefore Neutrophil/lymphocyte ratio (NLR) tends to be higher in patients with severe infection [24].

Commonly, the studies reported that D-dimer, lactate dehydrogenase (LDH), and C-reactive protein (CRP) levels increased, and albumin level decreased among elderly patients

with COVID-19 [12]. In a study comparing elderly people with middle-aged and younger individuals, it was shown that elderly patients had lower lymphocyte counts and higher CRP levels [25]. CRP is an acute-phase protein produced by the liver that can be elevated in a variety of conditions such as inflammation, cardiovascular disease, and infection. Some studies reported that CRP height is related to COVID-19 mortality [26]. Although D-Dimer is a specific marker of fibrinolysis used to predict venous thromboembolism, it may also increase inflammation and indicate a poor prognosis. As a matter of fact, there are investigations in the literature that show that high D-dimer levels predict COVID-19 mortality [27]. The decreased albumin and increased LDH suggest that SARS-CoV-2 infection is associated with extrapulmonary organ injury, such as hepatic or myocardia injury. In addition, there is reliable evidence that increasing LDH values reflect the degree of pulmonary damage in Acute Respiratory Distress Syndrome (ARDS) patients [28]. High procalcitonin levels have been reported in moderate-to-severe cases [29]. In a meta-analysis, it was reported that troponin, CK-MB, and NT-proBNP were significantly higher in severe COVID-19 cases than in mild cases and mortality was higher in patients with acute cardiac injury [30].

Ferritin is a protein that contributes to cytokine storm with its immunosuppressive and proinflammatory effects. In some studies, it has been reported that the ferritin level correlates with the severity of the COVID-19 disease [31]. Publications are showing that it predicts mortality. Therefore, it may be important to check the ferritin level on admission to the hospital and follow-up of the disease ints, including elderly patients, to be more controlled against the disease.

Especially in elderly patients with COVID-19, it is important to monitor the course of the disease and its response to treatment with laboratory tests, as patients may have difficulty in identifying symptoms and the disease may be atypical.

RADIOLOGICAL CHARACTERISTICS

The most important involvement site of Coronavirus Disease 2019 (COVID-19) is the lung [32]. Therefore, it is very important to demonstrate lung involvement radiologically. Although the gold standard in the diagnosis of the disease is the Real-Time Polymerase Chain Reaction (RT-PCR) test, radiological imaging has started to be used extensively due to the inadequacy of the test in some places and its early false-negative results [33]. However, radiological methods are not screening tests in the diagnosis of COVID-19; It should not be forgotten that it should be used as a method to help diagnose and monitor the disease. In imaging, chest radiography, thoracic computed tomography (CT), and in some limited centers, thoracic ultrasonography (US) is used for this purpose. Chest radiography is the first-choice imaging method for demonstrating COVID-19 pneumonia. However, it should be kept in mind that the limited ground-glass opacification (GGO) in the lungs, especially in the early phase of the disease, cannot be seen on radiography. The sensitivity of chest radiography in demonstrating disease involvement has been reported to be 30-60% [34]. Typical findings on CT related to COVID-19 pneumonia are GGO, flagstone appearance, consolidation, air bronchogram, vascular enlargement, bronchial dilatation, halo sign, inverted halo sign, nodules, air-bubble sign, subpleural - parenchymal bands, and pleural changes [35]. In a study

evaluating 919 COVID-19 patients, it was found that 88% of patients had ground-glass opacification (GGO), 87.5% had bilateral involvement, 76% had peripheral distribution, and 78.8% had multilobar involvement. Isolated GGO or GGO and consolidations were found to be the most common CT findings [36]. In the studies comparing the elderly and middle-aged groups, it was observed that multilobar and widespread involvement were more common in elderly individuals [27]. In the chest imaging of older adults; bilateral reticular-nodular opacities (58%), GGOs (48%), pleural effusions (about 33%), peribronchial thickening (about 25%), and focal consolidations (20%) have been reported [37].

TREATMENT

There is currently no specific treatment for COVID-19 infection with proven efficacy. Over 100 randomized controlled trials are being conducted for effective treatment trials against COVID-19. Since there is no treatment specific to COVID-19, medicines such as hydroxychloroquine, favipiravir, remdesivir, lopinavir-ritonavir, which were licensed for the treatment of other diseases in humans before, has been recommended and used during the current pandemic in our country and other countries. Numerous studies are still going on for the effectiveness and safety of these medicines in COVID-19. There is no difference between elderly patients and younger patients in terms of treatment options.

Chloroquine (CQ) and hydroxychloroquine (HCQ) have been used for more than 70 years to treat malaria and some autoimmune diseases. These medicines have become the candidate medicines for the treatment of COVID-19 infection because of their immunomodulatory effects and the effects that prevent viruses from entering the cell. It has been reported that at the beginning of the pandemic process, the use of CQ shortens the duration of the disease and slows its progression [38]. In addition, there are studies in the literature that suggest the use of HCQ reduces viral load in COVID-19 infection [39]. There are also studies on the negative effects of CQ and HCQ treatment. Despite their conflicting results, CQ and HCQ are included in COVID-19 treatment guidelines around the world. HCQ therapy is known to prolong the QT interval. Risk factors for QT prolongation include advanced age, female gender, history of heart disease, hypokalaemia, the use of furosemide and thiazide diuretics, kidney and liver failure, and the use of other medicines that prolong the QT interval. Elderly individuals are particularly at risk for QT prolongation and Torsades de Pointes. There is a risk of QT prolongation due to the high risk of hypertension in many elderly people, history of using antihypertensive medicines combined with diuretics, concomitant heart failure, polypharmacy, and inappropriate medicine use, and care should be taken in the use of HCQ in these patients. In patients without risk, the corrected QT (QTc) should be calculated by taking a basal electrocardiogram (ECG) before starting the medicine. If basal QTc is > 500 ms, HCQ therapy should be avoided. If the QTc length is normal, treatment is started and daily ECG monitoring is recommended [40]. Care should be taken in this regard especially in elderly patients, and they should be evaluated in detail regarding drug interactions during the treatment of COVID-19 infection. In addition, the combined use of azithromycin-HCQ, which was previously included in the guideline, is no longer recommended due to the high number of side effects.

It has been shown in animal studies and in vitro studies that Lopinavir inhibits the protease activity of coronaviruses. Additionally, in SARS and MERS outbreaks, lopinavir/ritonavir treatment is effective and reduces mortality, so it has been a candidate medicine for COVID-19 treatment [41]. In a lopinavir/ritonavir versus arbidol comparative study of individuals with mild to moderate COVID-19 infection, no significant difference was found between treatments [42]. In severe cases of COVID-19, the addition of lopinavir/ritonavir therapy to standard therapy has been reported to provide no additional benefit in terms of clinical improvement but rather increase the frequency of side effects [43]. The results of other studies in the literature were similar. In summary, lopinavir/ritonavir monotherapy or combination therapy has not been shown to contribute to the standard therapy.

Remdesivir, which has a broad antiviral activity and works by targeting viral RNA-dependent RNA polymerase (RdRp), has also been shown to be effective against coronaviruses [44]. In a randomized study involving 1059 patients (538 assigned to remdesivir and 521 assigned to placebo), it was shown that the mean recovery time for those who used the placebo was 15 days while it was 11 days for those who used remdesivir. In addition, remdesivir was found to be sufficiently tolerated and safe. It was found that serious side effects were lower in those who used remdesivir compared to those using a placebo. However, adverse events such as gastrointestinal symptoms (anorexia, nausea, and vomiting), increased liver enzymes, and worsening of cardiopulmonary status were seen at a higher rate in remdesivir users than in placebo users [45]. There is no different data on the use of remdesivir in the elderly.

Favipiravir acts by inhibiting RNA-dependent RNA polymerase. Vitro studies have shown that favipiravir is effective against coronaviruses. In a study of 120 patients with mild to moderate infections, when favipiravir and arbidol therapies were compared, clinical improvement at day 7 was better in patients using favipiravir [46]. In another study, favipiravir and lopinavir/ritonavir treatments were compared; it has been shown that viral clearance is faster (4 vs 11 days) and radiological lung recovery is better (91% vs 62% in 14 days) using favipiravir [47].

In patients with severe COVID-19 pneumonia, macrophage activation syndrome (MAS) and secondary lymphocytic lymphohistiocytosis may develop due to excessive hyperstokemia (IL-1, IL-6, IFN-gamma, etc.). In the MAS table of COVID-19 patients, especially the elevation of IL-6 is remarkable. For this reason, cytokine suppression treatments have come into question in the treatment of these patients. Tocilizumab is an agent that functions as an IL-6 monoclonal antagonist. Tocilizumab has recently come to the fore as a medicine that has shown serious benefits in clinical improvement in severe COVID-19 pneumonia. Some studies have shown that administration of tocilizumab (4 mg/kg/d) given through intravenous infusion at 24-hour intervals at the beginning of the patient's SARS is effective in reducing the need for ventilator support and improving lung functions in patients with severe COVID-19 [48].

Corticosteroids have been shown to shorten the intensive care period in COVID-19 patients with severe persistent shock. In one study, it has been shown that 10-day oral or intravenous 6 mg dexamethasone treatment reduces 28-day mortality in patients who need oxygen or require ventilator support [49]. It has been reported to be beneficial only to patients with COVID-19 with respiratory failure [50]. Its effect has not been demonstrated in patients who do not need respiratory support.

Studies on convalescent plasma therapy continue, and the studies so far have shown that it is useful in the treatment of severe and life-threatening COVID-19 infection. It has been reported to be more beneficial especially when administered before intubation [51].

In addition to all these treatments, the medicines used by the elderly infected with COVID-19 should be evaluated and necessary recommendations should be made due to their comorbidities. For example; Angiotensin-converting enzyme 2 (ACE2) is a co-receptor for viral entry into SARS-CoV-2; this suggests that it has a role in the pathogenesis of COVID-19. Therefore, angiotensin-converting enzyme inhibitors (ACEIs) and Angiotensin II receptor blockers (ARBs) use are thought to increase COVID-19 mortality and morbidity. However, some studies have shown that ACEIs prescribed at the clinic do not inhibit ACE2, which acts as a carboxypeptidase [52]. As a result, no evidence was found regarding the benefit or harm of ACEI/ARB use in observational studies. Elderly patients who are currently using ACEI/ARB as antihypertensive do not need to discontinue the medicine unless they have a different indication. Although studies are reporting that the use of statins is more likely to increase liver enzymes in patients with COVID-19 infection, there are also studies suggesting that COVID-19 infection increases the risk of acute cardiac damage and therefore the use of statins should be continued. Therefore, evaluation of the use of statin on an individual basis was decided. The ESC guidelines recommended that statins be continued in patients who use them because of their immunomodulatory and cardioprotective effects [53]. Also, when using antipyretic in elderly patients; considering the renal failure, toxicity, and gastrointestinal bleeding side effects, nonsteroidal anti-inflammatory medicines (NSAIDs) should be avoided as much as possible, and paracetamol should be preferred primarily.

During the pandemic period, elderly patients without COVID-19 infection who remain at home and immobile for a long time should be evaluated in terms of sarcopenia and malnutrition, which are important geriatric syndromes, and necessary supportive treatments and recommendations should be made. Also, malnutrition and sarcopenia may increase the frailty of patients, causing them to have a more serious COVID-19 infection.

Another important point that should not be ignored during the pandemic process is that the elderly are undoubtedly affected psychologically. The curfew imposed on people aged 65 and over in many countries and their relatives' not visiting them to protect the elderly from COVID-19 infection caused social isolation and some psychological problems. Psychological problems may also cause more malnutrition and frailty in the elderly, leading to a decrease in immune responses and a more serious COVID-19 infection, and increased morbidity and mortality. For this reason, it is very important to evaluate the elderly psychologically and to provide the necessary support during the pandemic process.

CONCLUSION

It is known that the elderly are the most affected group by the COVID-19 epidemic that affects the whole world. The initial symptoms and course of the disease in the elderly may differ from other age groups. Therefore, these differences should be taken into consideration when evaluating geriatric patients. Although there is no difference in the treatment protocol, the comorbidities of the elderly and multiple medicine use should be considered, and alert should be made in terms of medicine side effects and drug-drug interactions. In addition, it

should not be forgotten that elderly patients are affected by the epidemic not only physically, but also socially and psychologically, and the necessary support should be provided in these areas.

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Chapter 461

SARS COV-2 IN PEDIATRIC PATIENTS: HEMATOLOGICAL FACE OF THE DISEASE

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ABSTRACT

The COVID-19 pandemic is the biggest health problem of our last 10 months, Pediatricians were more fortunate than internal medicine specialists due to the low number of pediatric cases with COVID 19. As the disease spread rapidly throughout the world, the experience with the diagnosis, follow-up, and treatment are collected. There is no clear-cut data for an effective drug against the SARS-CoV2 virus or an effective vaccine to prevent infection. On the other hand, epidemiological data from infected people are promising for the strategy for future. Unlike other infectious diseases, the incidence of the infection and mortality rate is significantly higher in developed countries. COVID 19 is generally mild in children, some might not show any symptoms at all. In this paper, we tried to share latest data about childhood COV-2 infection, especially focused on hematological signs and symptoms and their physiopathology.

Keywords: COVID 19 pandemic, pediatric cases, hematological signs

INTRODUCTION

Coronaviruses are a group of RNA viruses with a roughly 30 kb genome surrounded by a protein envelope belonging to the *Coronaviridae* family, *Nidovirales* order [1]. The exact origin of the virus is unknown but current studies have revealed that 2019-nCoV has a zoonotic origin, it emerged from a bat-borne virus. It can easily spread between persons through respiratory droplets [2]. It has resulted in a worldwide outbreak and is classified as a

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pandemic by the World Health Organization on March 11, 2020 [3]. By March 1, 2020, SARS-CoV-2 had led to 80 981 confirmed cases of COVID-19 in China, and 44 067 cases in 117 countries. In Korea, the ratio of patients younger than 19 years is 6.7% of total cases, and no child deaths have been reported [4].

Italy, having the second-highest number of Covid-19 infections and the greatest number of deaths after China, reported that children younger than 18 years of age who had Covid-19 composed only 1% of the total patients; and only 11% of these children were hospitalized, and none died [5]. Recent reports on pediatric cases of COVID-19 suggest that COVID 19 is less common in children and they usually have mild illnesses. However, the full spectrum of illness in children is not clearly understood because many pediatric patients might not have been subject to viral testing. Furthermore, there is limited information regarding the duration of SARS-CoV-2 RNA detection in children's respiratory tracts [4]. Thus far, all pediatric cases with laboratory-confirmed 2019-nCoV infection were mild cases, and no deaths had been reported.

TRANSMISSION

Respiratory droplets and contact are the main transmission routes in COVID 19 [6]. The incubation period is about 1 to 14 days, and that can last up to 24 days. The virulence of the virus could peak 2 to 3 days before symptom starts, and transmission during the presymptomatic stage is estimated to make up %44 of secondary infections [4]. At the beginning of the Sars COV- 2 outbreak, the infection is transmitted by adults in the community. Then the virus spread to the family and children via infected adults. The first pediatric case was identified in the familial cluster [7]. Close contact with symptomatic or asymptomatic cases with silent infection are the main transmission routes of 2019-nCoV infection in children [6]. Children tend to have no or milder symptoms, so they can easily spread infection to their household. Therefore understanding infectious burden and potential for transmissibility within the pediatric population is critical for developing both short- and long-term responses, including public health policies, to the current pandemic [8]. There is an urgent need for further investigation of the role of children who have an important role in the chain of transmission.

Perinatal transmission of COVID 19 is also not known exactly. There are several reported cases of neonatal infection suggesting a possible neonatal and vertical transmission. In a study by Chen et al., nine neonates born to COVID 19 positive mothers tested negative after cesarean delivery [7]. Breastmilk and placental pathological specimens from COVID 19 positive mothers remained negative for the viruses. Like other coronaviruses (SARS and MERS) it is thought that vertical transmission during third trimester is very rare. But the consequences of SARS COV-2 in early pregnancy like abortion, premature delivery, malformations, organ development is not well known. Also, Dong et al. emphasize that the proportion of severe and critical cases were higher in neonates when compared to the other childhood age group [9]. Breastmilk of the mother with suspected or confirmed COVID 19 is still the first choice in newborns feeding. Secretory IGA in breastmilk can be protective against COVID 19. Also, breastmilk improves the neurocognitive and immunologic development of the newborn.

CLINICAL PRESENTATION

Children infected with COVID 19 might be asymptomatic or generally presented with fever, dry cough, fatigue, and have mild upper respiratory symptoms. Gastrointestinal complaints like abdominal discomfort, nausea, vomiting, diarrhea and are rarer clinical symptoms of pediatric COVID 19 [6]. ACE2 the receptor for SARS-COV-2 in human cells is highly expressed in olfactory neuroepithelium lead to the infection in this site, resulting as a typical symptom, anosmia. The severity of COVID-19 was defined based on the clinical features, laboratory testing, and chest X-ray imaging, including asymptomatic infection, mild, moderate, severe, and critical cases. The diagnostic criteria were as follows [10]:

1. **Asymptomatic infection:** Patient has no clinical symptoms and signs and the chest imaging is normal, while the 2019-nCoV nucleic acid test is positive.
2. **Mild:** Patient is presented with acute upper respiratory tracts infection symptoms like fever, fatigue, myalgia, cough, sore throat, coryza. Some cases may have no fever, or have only digestive symptoms such as nausea, vomiting, abdominal pain, and diarrhea.
3. **Moderate:** Pneumonia occurs, frequent fever and cough, mostly dry/productive cough, some may have wheezing, but no obvious hypoxemia such as shortness of breath, and dry snoring, and/or wet snoring. Some cases may have no clinical signs and symptoms, but chest CT shows subclinical lung lesions.
4. **Severe:** The disease usually progresses and dyspnea occurs, with central cyanosis. Oxygen saturation is less than 92%, with other hypoxia manifestations.
5. **Critical:** Children can quickly progress to acute respiratory distress syndrome (ARDS) or respiratory failure, and may also have shock, encephalopathy, myocardial injury or heart failure, coagulation dysfunction, and acute kidney injury.

In Dong's study, 94.1% of all patients were confirmed as asymptomatic, mild, or moderate cases, 5.9% of them were severe. Severe cases and their proportion was 10.6%, 7.3%, 4.2%, 4.1%, and 3.0% for the age group of <1, 1-5, 6-10, 11-15, and ≥ 16 years, respectively [10]. This study revealed that children under 5 years old, especially infants with COVID-19 had more severe disease than the others.

A study suggests that children are just as likely as adults to become infected with SARS-CoV-2 but are less likely to be symptomatic or develop severe symptoms [11]. In several studies, it is reported that children and younger adults who do not have underlying conditions, such as impaired lung function or immunosuppression, have a much lower risk for severe forms of COVID-19 [12].

There are some suggested hypotheses for this viewpoint:

1. The immune system of children and adults is different from composition and responsiveness. Also immune system's function and component developed with the age of the children (infant, preschool, adolescent)
2. Presence of other simultaneous viruses in the mucosa of lungs and airways, which are common in young children, could limit the growth of SARS-CoV2 by direct

virus-to-virus interactions and competition [8]. As the amount of viral copy is diminished; the severity of COVID 19 is reduced.

3. The angiotensin-converting enzyme (ACE) 2 receptor is necessary for SARS-Cov2 binding and infection. These receptors in children are relatively less than adults. ACE2 expression did not correlate with viral load, suggesting that although increased ACE2 expression increased susceptibility for infection, once infected, children could carry high viral loads regardless of level of ACE2 expression.
4. In severe COVID-19 infection; the viral and pulmonary phases are followed by the final hyperinflammatory phase, which can lead to severe acute respiratory distress syndrome (ARDS), impaired cardiac function, and death. Children are less inclined to develop ARDS during respiratory tract infections than adults.

Although children tend to have mild clinical forms of COVID 19 or they are asymptomatic, they can have a large number of viruses and transmit to the other people easily. Also, viruses can persist in feces long after they are absent from nasopharyngeal secretions. For coping with this pandemic, we must protect the children from COVID 19 infection [12].

While acute SARS-CoV-2 infection tends to be mild or symptom-free in most pediatric cases, some children develop a multisystem inflammatory syndrome (MIS-C). Several weeks after possible SARS-CoV-2 infection or exposure, with severe cardiac complications, including hypotension, shock, and acute heart failure. MIS-C criteria, defined by Centers for Disease Control and Prevention (CDC): fever $>38^{\circ}\text{C}$ for >24 hours, laboratory evidence of inflammation, at least two organs involved, and no alternative possible diagnoses and a positive SARS-CoV-2 test by RT-PCR, serology or antigen test, or exposure to a COVID-19 positive patient within 3-4 weeks before the onset of symptoms. In Yonker's et al. study although 11-16 years of group children were mostly affected by COVID 19, the children ages 1-4 years and males are the most highly presented with MIS-C. In addition to fever, MIS-C complained more often about nausea/vomiting and rash and few symptoms of an upper respiratory tract infection. Co-morbidities like asthma, heart disease, hypertension, and diabetes do not differ between MIS-C positive/negative COVID 19 children. Children with severe MIS-C (with hypotension or cardiac abnormalities requiring therapeutic intervention such as steroids, IVIG, and/or anakinra) have more elevated IgM and IgG. Children with MIS-C do not have high levels of viral load on nasopharyngeal or oropharyngeal viral testing, nor do they have detectable viremia, however, they do have hyperactive antibody responses. Children with severe MIS-C have elevated SARS-CoV-2 IgM and IgG levels, showing T and B cell over-reactivity, or auto-antibodies that may be driving an inflammatory process causing MIS-C [8].

IMAGING

Like other types of pediatric pneumonia, chest plain film (CXR) is not indicated for most pediatric patients with known or suspected COVID-19 with mild clinical symptoms that do not require hospitalization; although CXR is usually indicated in neonates with fever and respiratory symptoms[13]. Sequential CXRs may be helpful to assess pediatric patients with

COVID-19 who demonstrate worsening clinical symptoms or to assess response to supportive therapy. However, routine daily chest radiographs for stable pediatric COVID-19 patients in the intensive care unit (ICU) are not recommended as they have not been shown to impact adverse outcomes, pediatric ICU or hospital length of stay, or duration of ventilator requirements.

Chest CT imaging is not recommended as a first imaging modality because of the increased radiation sensitivity of pediatric patients. In some clinic situation, for example, the pediatric patients presenting with acute symptoms (i.e., hypoxia, dyspnea, tachycardia), worrisome abnormal laboratory findings (such as an elevated D-dimer), or to evaluate a patient demonstrating clinical deterioration or not responding as expected to supportive treatment, chest CT can be the appropriate diagnostic method [13].

Although CXR is the first imaging study recommended for evaluation of pediatric COVID-19 disease, most of the SARS- COV2 pediatric patients were not severe, plain chest X-ray could not identify all the pulmonary lesions, so Chest CTs were obtained to provide supportive information for diagnosis and management. CXR sensitivity for detection of COVID-19 pneumonia in adult patients has been reported ranging from 69% to 89%. A single pediatric COVID-19 study reported observing patchy unilateral opacities in 40% of patients. In some suspected pediatric patients with a negative nucleic acid of COVID-19 virus, chest CT findings revealed the diagnosis, which could provide the early treatment of the children and also isolation of the source of infection [14].

CT images of pediatric COVID 19 are similar to those in adults. The typical radiologic findings are unilateral or bilateral subpleural ground-glass opacities, and consolidations with surrounding halo sign. Pleural effusion was not seen. The absorption of lesions on chest CT lagged behind clinical symptoms and nucleic acid detection. Lesions could be still visible on chest CT when two consecutive nucleic acid tests were negative.

Bacterial coinfection and other viral infections are more common in pediatric COVID, so the CT imaging of COVID-19 infection should be differentiated with other virus pneumonia. Adenovirus pneumonia lesions had a higher density, more consolidations, and fewer subpleural lesions. Respiratory syncytial virus and parainfluenza virus pneumonia lesions were mostly distributed along the bronchial tree with a thickened bronchial wall. Influenza viruses could cause grid-like changes in the lungs. In addition, it should be differentiated from bacterial pneumonia, mycoplasma pneumonia, and chlamydia pneumonia, and the density of pneumonia lesions caused by the latter pathogens is relatively higher. COVID-19 pneumonia can be superimposed with pneumonia caused by other types of pathogens, presenting more serious and complex imaging manifestations, so epidemiological and etiological examination should be combined.

Imaging findings in post-COVID 19 Multisystem Inflammatory Syndrome in Children (MIS-C), including airway inflammation, rapidly progressive pulmonary edema, coronary artery aneurysms, and extensive abdominal inflammatory change within the right iliac fossa, with lymphadenopathy and bowel wall thickening. In Hameed et al. study, central bronchial wall thickening is commonly seen in these children (34%) and with none exhibiting lower respiratory tract symptoms. These findings are more likely attributable to airway inflammation and pulmonary arteritis. Echocardiography must be done in MIS-C because it has more aggressive cardiovascular findings than that in Kawasaki disease. Abdominal USG/CT showed features of right iliac fossa mesenteric inflammation and lymphadenopathy.

The clinical findings of MIS-C overlap with Kawasaki disease and ischemic stroke as a complication of vasculitis seen in both diseases [15].

Furthermore, as no long-term data is yet available, future studies investigating post-recovery sequelae of disease including alterations of pulmonary function tests and risk for development of permanent lung injury such as pulmonary fibrosis will be important [13].

LABORATORY FINDINGS

In SARS-COV2, some of the inflammatory biomarkers are associated with poor prognosis. C-reactive protein (CRP) elevation was seen in up to 40% of patients and associated with ARDS, cardiac injury, and mortality. Elevated LDH and serum ferritin levels have also been linked in multiple retrospective analyses with a higher risk of ARDS and death. Interleukin-6 (IL-6) was elevated at admission in 52% of patients in a study by Chen et al. and linked to increased mortality [16, 17]. Blood counts and coagulation parameters are deteriorated in severe COVID 19. Lymphopenia, thrombocytopenia, and coagulopathy indicate severe illness and often progress to the disseminated intravascular coagulation (DIC). COVID-19 has also been associated with an increased risk of venous thromboembolic events (VTE).

Lymphopenia

In a retrospective analysis of patients in Hong Kong and Singapore, lymphopenia was first described with SARS-CoV in 2003. It has been associated with adverse outcomes and intensive care unit (ICU) stay. Severe lymphopenia ($< 0.6 \times 10^9/L$) can be considered as one of the indicators of early admission to ICU. Li and Wang et al. reported that there was no correlation between WBC count and severity of the disease. It was also shown that lymphopenia can develop when the leukocyte count was normal [18]. Patients with severe infection were observed to have a significantly lower lymphocyte count and the lymphocyte/WBC ratio. Guan et al. obtained clinical data and showed that on admission, 83.2% of patients had lymphopenia and 33.7% had leukopenia. Thrombocytopenia was also seen in 36.2% of cases, as discussed later. On the other hand, anemia was usually not present with hemoglobin values at normal to very mildly decreased. Hematologic abnormalities were more prominent in patients with severe disease when compared to non-severe presentations. [16]. Wu et al described similar findings with 64% of patients having lymphopenia at presentation. Decreased lymphocyte counts were associated with poor prognosis and an increased risk of ARDS [19]. Lymphopenia was again documented in 70.3% of patients in Wuhan, with lymphocyte count, $>1100/mL$ were significantly less likely to have a severe illness than those in the 0–500/ mL and 500–1100/mL ranges [20]. Tan et al. emphasized that blood lymphocyte percentage (LYM%) showed the most significant and reliable trend in predicting disease progression [21]. Days 10–12 and 17–19, patients whose lymphocyte percentage was less than 20% and 5%, had the worst clinical outcomes.

The pathophysiology of the association between lymphopenia and clinical course and prognosis is multifactorial. In the incubation period, lymphocyte count is in the normal range.

As the virus spreads and concentrates in tissues (lungs, heart, gastrointestinal tract via cell receptor for the SARS COV2 (the angiotensin-converting enzyme 2 (ACE2)), symptoms worsen and radiographic findings become more evident. At this point, both T- and B- cell lymphocyte counts decrease in conjunction with a significant rise in inflammatory markers [22]. Excessive increase in cytokines causes exaggerated inflammatory response named as a cytokine storm. That is characterized by increases in levels of IL-2, IL-6, IL-7, tumor necrosis factor (TNF)- alpha and granulocyte colony-stimulating factor, promoting lymphocyte apoptosis. The ACE receptor is also expressed on the surface of a lymphocyte that was infiltrating various organs of the oral mucosa and the lungs etc. Thus, this can be the other mechanism of the observed lymphopenia, involving direct cytotoxic effects of the virus and cell membrane lysis. Inhibitory effects of lactic acidemia on lymphocytes can be the other potential contributing factors to the development of lymphopenia [23].

Thrombocytopenia

Thrombocytopenia is one of the pathologic laboratory findings that can be seen in SARS COV2 positive patients. Contrary to these findings, some authors reported that patients with significantly higher platelets during treatment have longer average hospitalization periods, and patients with higher platelet lymphocyte ratio (PLR) during treatment prolong their average hospital stay [24]. We thought that thrombocytosis, being an acute phase reactant, might be a good marker for infection at the beginning of COVID 19 infection. It has been interpreted that the PLR of the patients could provide a new indicator in the follow-up of patients with COVID-19 and could indicate the degree of the cytokine storm. Liu et al. also looked into the association between platelet parameters and mortality from COVID-19: In a series of 383 patients, thrombocytopenia at admission was linked to a three-fold increase in mortality compared to patients with normal platelet counts. An increase of $50 \times 10^9/L$ of platelets was found to be associated with a 40% decrease in mortality [25]. During the infection period thrombocytopenia is not generally severe enough to cause bleeding complications.

Thrombocytopenia is likely multifactorial and several contributory mechanisms have been postulated. Viral epitopes circulating in the bloodstream would mimic antigens present on platelet surfaces and lead to the formation of antibodies and the platelet- antibody complexes would be destroyed through a complement independent immune-mediated response, just like ITP [26]. Furthermore; multiorgan failure, disseminated intravascular coagulation (DIC) is a common risk for thrombocytopenia. Endothelial damage triggered by a systemic inflammatory response and mechanical ventilation leads to hyperactivation of platelets and thrombosis causing disseminated platelet consumption.

Eosinopenia

Eosinophils are the type of white blood cells that are usually linked with allergic and parasitic diseases. Now they have been demonstrated to possess antiviral capacities and enhance the immune response and reduce the inflammation. It is currently not known whether

COVID-19 patients with eosinopenia are also more likely to develop into critical illness. In Zhang's study, 35.3 % of patients showed a decrease in eosinophil absolute number ($<0.02 \times 10^9$). Compared with normal eosinophil groups, eosinopenic patients showed serious vital signs on admission, with faster heart rate and relatively higher temperature and a greater proportion of eosinopenic patients were fell into severe conditions. Eosinopenic patients tended to have a lower lymphocyte count and monocyte absolute number. Following the inflammatory markers, eosinopenic patients have higher high sensitive C-reactive protein and procalcitonin. These findings revealed that eosinophils play an important role in maintaining immune regulatory system, by producing inflammatory and homeostatic mediators. Eosinophils were responsible for local immunity and tissue repair. The pathophysiology for eosinopenia in COVID-19 could be multifactorial, involving the suppressed eosinophil egress from the bone marrow, inhibition of eosinophilopoiesis, reduced eosinophil-driving cytokines, or direct interferon-induced apoptosis. IL -33 is responsible for eosinophil activation in the airways, bone marrow, and ciliated epithelial cells which are the main target of coronavirus. Also, IL -33 activates the innate lymphoid cells that produce IL-5 which is important for eosinophil cumulation in the airways. Eosinopenia was very frequent in COVID-19 and could be used in the early prediction of severity before clinical symptoms have significantly worsened, which may help clinicians in identifying potentially severe cases with COVID-19 [2].

COAGULATION DISORDERS IN COVID-19

SARS-CoV-2 infection is often associated with hypercoagulability and disseminated intravascular coagulation (DIC). This hypercoagulability is manifested as progressive lung and kidney disease, pulmonary emboli (PE), venous thrombotic events (VTE), recurrent line obstruction, and stroke in adults (SARS-CoV-2) infection.

It is thought that SARS-CoV-2 virus was diffusely present in endothelial cells and the virus uses the ACE2 receptor to directly infect the endothelium and recruit immune cells. Inflammation of the endothelium leads to microvascular dysfunction, vasoconstriction, organ ischemia, and a hypercoagulable state [27].

Although many authors recommend anticoagulation of hospitalized symptomatic adults with COVID-19, guidelines regarding the thrombotic evaluation and anticoagulation management of hospitalized children with COVID-19 remain lacking. Pediatric hematologists developed pediatric recommendations for children hospitalized due to SARS-CoV-2 infection after revision of anticoagulation recommendations for adults [28]. Fibrinogen and D-dimer are elevated and correlated with acute inflammatory markers such as C-reactive protein. Prothrombin time prolongation is often seen. Unlike classic DIC laboratory findings, a platelet count that is only mildly decreased, a partial thromboplastin time that is normal-to-mildly prolonged, and no signs of microangiopathy and bleeding in contrast to DIC. While an elevated D-dimer may also reflect underlying inflammation, immobility, or liver disease, patients with COVID-19 infection with markedly raised D-dimers are significantly at risk of mortality, and a raised level also implies increased thrombin generation [29].

In the coagulation cascade, activated factor V interacts with activated factor X to form the prothrombinase complex, which catalyzes formation of thrombin and leads to fibrin clot

formation. Dysregulation of factor V due to factor V Leiden is a well-known cause of a prothrombotic state. Concurrent elevations of factor V activity and factor VIII activity have also been linked to increased VTE risk. In Stefely's study factor V was significantly elevated in the COVID-19 cases (median 150 IU/dL) compared to both control cases on ventilators and the non-ventilated ones. These findings suggest that the elevation of factor V in severe COVID-19 cannot be simply explained by a general state of severe illness or by ventilator use. Together with the rarity of factor V elevations before the COVID-19 pandemic, these findings suggest a more specific relationship between COVID-19 and factor V elevation. High factor V levels in COVID 19 can be explained by the high amount of megakaryocytes in patient's organs which contain %20-25 of the factor V. While patients with severe COVID-19 might initially present with markedly elevated factor V activity, a subsequent decline in factor V activity could be associated with clinical decompensation. For these reasons factor V can be a candidate biomarker for future clinical trials investigating VTE and anticoagulation therapies in patients with COVID-19 [30].

As there are no clear-cut definitions for anticoagulation for pediatric hospitalized VTE patients, prophylactic anticoagulation may be considered for children with the following risk factors: (a) strong personal or family history of VTE, or (b) an indwelling central venous line and two or more additional risk factors, or (c) four or more risk factors. Prophylactic anticoagulation therapy in children must be done by considering bleeding risk. Confirmation of VTE by imaging may not be needed prior to treatment with anticoagulation if clinical suspicion is high. Therapeutic anticoagulation is considered for the children who used anticoagulation prior to admission and those who are receiving extracorporeal organ support. Catheter-directed alteplase and mechanical thrombolysis can be used for hemodynamically unstable PE or limb-threatening deep vein thrombosis. Use of systemic alteplase for progressive respiratory failure is still investigating. As the pediatric experience in COVID-19 increases, new recommendations for laboratory and imaging evaluation, assessment of thrombotic risk, and anticoagulation therapy in the pediatric patient will be improved [28].

TREATMENT

Although (COVID-19) is mild in nearly all children, a small proportion of pediatric patients develop a severe or critical illness. The four main principles for adequate therapeutic management are early identification, isolation, diagnosis, and treatment [31]. If there is a suspicion about COVID 19 the patient must be isolated in a single room to prevent the possible transmission of disease before laboratory confirmation. Mild cases should be isolated and treated with symptomatic relief medication, preferably paracetamol or dipyrone, to control fever.

The majority of children with COVID-19 experience a mild, self-limited illness, and there is a lack of evidence of efficacy for any antiviral, and due to the possible harms of these medications, the risk-to-benefit ratio must be considered for pediatric patients. Our experience in a hematology-oncology ward also supports the therapy which is tailored for each patient for beginning anticoagulation, antiviral regimens besides supportive therapy. Therefore supportive care is the mainstay of the management strategy [32].

The clinical presentation of COVID-19 in children overlaps significantly with other infections. No clinical, radiographic, or laboratory criteria are sufficiently specific to distinguish COVID-19 from these other pediatric conditions. So that antiviral drug therapy must be started after confirmation of SARS COV 2 infection. A rare exception might be made for critically ill patients with a high suspicion for COVID-19 [32].

Children with mild or moderate disease (there is no need for O₂ therapy) recover with supportive care alone. Administration of antivirals early in the disease course to prevent progression thus does not seem warranted because of the possible harms of these drugs. Most children with severe infection will recover with supportive care alone. Use of potentially active antivirals could be considered on a case-by-case basis, taking into account underlying medical conditions and health status that may confer risk for progression to more serious illness.

Antiviral Treatment

Supportive care is the suggested approach for nearly all children. Antivirals may be considered on a case-by-case basis according to underlying conditions. (Table 1)

If an antiviral is used, the panel suggests remdesivir as the preferred agent. Remdesivir is a nucleoside analog prodrug that, when activated, binds to viral RNA-dependent RNA polymerase, resulting in premature RNA chain termination. A recent case series of 53 patients with severe COVID-19 pneumonia who received remdesivir under a compassionate-use protocol reported clinical improvement in 68% after a median follow-up of 18 days, with 13% mortality and a generally acceptable toxicity profile [33]. Efficacy in pediatric patients and optimal dosing, duration of therapy is not established yet.

The Infectious Disease Society of America (IDSA) guideline panel for COVID-19 treatment, recommends hydroxychloroquine/chloroquine in the context of a clinical trial [33]. The antiviral activity is inhibition of viral entry into human cells by increasing the pH of the endosomes required for cell entry, broad anti-inflammatory and immunomodulatory effects, and inhibition of glycosylation of the ACE-2 receptor, the binding site for SARS-CoV-2 [34]. The recommended dose is 3–5 mg/kg/day (max dose 400 mg) hydroxychloroquine sulfate iv, in pediatric patients, twice daily for five days. The use of azithromycin in combination with hydroxychloroquine was associated with a more rapid resolution of virus detection than hydroxychloroquine alone [35]. But combined use of these drugs potentiate QTc prolongation.

According to Chen's review in pediatric patients, interferon- α 2b nebulization (100,000–200,000 IU/kg for mild cases, and 200,000–400,000 IU/kg for severe cases, two times/day for 5–7 days.) can be applied [36].

Favipiravir is an RNA polymerase inhibitor. It is thought to have potential antiviral action on SARS-CoV-2. In February, a clinical trial on favipiravir for the treatment of COVID-19 was initiated, and results were promising. The preliminary results from a total of 80 patients indicated that favipiravir had more potent antiviral action than lopinavir/ritonavir which were protease inhibitors approved by the FDA for treatment of pediatric HIV [33].

Immunomodulator Treatment

Pediatric COVID-19 patients with hyper inflammation whose illness progress to critical COVID-19 may be considered for immunomodulatory treatment. Small subset of pediatric patients is severely affected by COVID-19 with a presentation ARDS, hypercoagulability, hyper inflammation, and multiorgan failure [37]. There are no immunomodulators with proven efficacy for the treatment of COVID-19 in pediatric patients as of July 24, 2020. Therefore, no guidance can be provided to support the use of one immunomodulatory therapy over another. If immunomodulators are used in the treatment of COVID-19, patients should be monitored for adverse effects [38].

IL-6 and IL-1 inhibition may be considered in the care of pediatric patients with critical COVID-19 with priority given to clinical trial enrollment if available. Anakinra can be used as an IL-1 inhibitor based on its safety profile and favorable pharmacokinetics. Glucocorticoid therapy may be considered for pediatric patients with critical COVID-19 with a preference for use in the setting of clinical trials, if available. Steroid is indicated like asthma or catecholamine-refractory shock in COVID 19 pediatric patients.

Convalescent plasma in pediatric COVID-19 may be considered as part of the recently established FDA emergency investigational new drug program if in the United States or as part of a clinical trial. The efficacy of passive transfer of convalescent plasma (CP) is thought to be mediated primarily through viral neutralization, although other mechanisms such as stimulation of antibody-dependent cellular cytotoxicity and enhanced phagocytosis have also been postulated. While the passive transfer of polyclonal antibodies via convalescent plasma may be of benefit, no SARS-CoV-2-specific monoclonal antibody therapies have yet been clinically tested. It is recommended that children >40 kg be dosed with 200–500 mL and children <40 kg be dosed with 10–15 mL/kg, while being aware of volume overload, especially in children with cardiac dysfunction.

The use of IVIG for treatment of acute COVID-19 in pediatric patients is not recommended except for (ya da sadece except) specific clinical situations in which IVIG is typically used and treatment of MIS-C.

JAK inhibitors and Type I or type III IFN should not be used for pediatric COVID-19 patients outside of a clinical trial.

Severe cases with respiratory distress and/or hypoxia ($\text{SaO}_2 < 94\%$) should be admitted to the hospital. Indications for ICU admission are respiratory failure requiring mechanical ventilation, shock, or other organ dysfunction requiring treatment. The main treatment principles of ARDS are as follows [39] :

1. Early tracheal intubation – rapid sequence intubation is the best practice in this situation. Preoxygenation should be performed using a flexible nasal cannula (up to flows of 4 L/min) or a reservoir mask with a lower flux to maintain a $\text{SaO}_2 > 93\%$. Positive pressure ventilation with a bag-valve-mask or other similar apparatus should be avoided not to generate aerosols.
2. Non-invasive ventilation (NIV) should be avoided because of the high risk of aerosol dispersion and contamination among health practitioners.
3. The patient should be maintained in a prone position at least 18 hours per day

4. Protective mechanical ventilation and closed tracheal aspiration systems should be used.
5. Antibiotics should be used only in patients with secondary bacterial infections based on the culture and antibiogram results. Corticosteroids can suppress lung inflammation but also inhibit immune responses and pathogen clearance, and should be avoided except for those with a specific indication (e.g., bronchospasm or some cases of septic shock) Intravenous immunoglobulin can be used in critically ill child [40].
6. Fluid therapy or vasoactive/inotropic drugs and renal replacement therapy may be needed.
7. Anticoagulation is required in presence of high D-dimers or evidence of thromboembolism [33].

VACCINATION TRIAL

NVX-CoV2373 contains Matrix-M1 adjuvant and a recombinant SARS-CoV-2 (rSARS-CoV-2) nanoparticle vaccine, constructed from the full-length (i.e., including the transmembrane domain), wild-type SARS-CoV-2 spike glycoprotein, which mediates attachment of the virus to the human angiotensin-converting enzyme 2 (hACE2) receptor of host cells for cellular entry and serves as a key target for the development of antibodies and vaccines. The spike protein of vaccine induces high titers of antibodies that blocked hACE2 receptor binding and achieved neutralization of wild-type virus. The magnitude of response is higher than that is measured in human convalescent serum. Polyfunctional CD4+ and CD8+ T-cell responses were induced with a T helper 1 (Th1) dominant phenotype. Keech et al. initiated a randomized, placebo-controlled, phase 1–2 trial to evaluate the safety and immunogenicity of the rSARS-CoV-2 vaccine in 131 healthy adults [41]. In phase 1, vaccination comprised two intramuscular injections, 21 days apart. At 35 days, NVX-CoV2373 appeared to be safe, and it elicited immune responses that exceeded levels in Covid-19 convalescent serum. The Matrix-M1 adjuvant-induced CD4+ T-cell responses that were biased toward a Th1 phenotype. Phase 2 has commenced based on the safety results of the day 35 primary analysis, and phase 3 is in preparatory stages.

Mycobacteria is previously reported to be potent Th1 stimulants [42]. Such an antigen stimulation may increase proliferation in favor of Th1 cells, Bacillus Calmette-Guerin (BCG), a live attenuated vaccine, is being administered routinely against Mycobacterium. BCG can induce sustained nonspecific reactions to infections at the level of trained immunity and heterologous Th1/Th17 responses by prolonged production of IFN- γ , IL-17, and IL-22. In Ozdemir et al. study, the mean of cases per population ratio is statistically significantly lower in BCG-vaccinated countries than in BCG-non-vaccinated countries [42]. The mean of deaths per case ratio is also significantly lower in BCG-vaccinated countries. In the Northern Hemisphere, the mean of deaths per population ratio is also found to be significantly lower in BCG-vaccinated countries than in BCG-non-vaccinated countries. Therefore it is thought that BCG vaccination has a protective role against COVID 19 infection by its immunomodulator effect. There are also many kinds of vaccines trial (inactive, recombinant) whose phase 3 trials are ongoing.

CONCLUSION

Recent studies about pediatric COVID 19 revealed that this disease is less common and mild in children. Full-spectrum of illness in children is not clearly understood because many patients might have not been subject to viral testing. At the beginning of SARS COV-2 outbreak, the children are isolated so the virus are transmitted by adults in the community. Therefore, at the beginning of the pandemic, disease was mostly seen in adults. Although ACE receptor that increased susceptibility for infection is relatively less than adults, once the children are infected, they could carry high viral loads. As the pandemic progressed, more children infected, transmission rate of virus is increased.

For coping with this outbreak, we must protect the children from SARS COV-2 by social distancing and using facial masks. The decision to open up schools and daycare centers should be reconsidered until the severity of the pandemic subsides.

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Chapter 462

COVID-19 AND OPHTHALMOLOGY

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ABSTRACT

The emergence of coronavirus disease 2019 (COVID-19) pandemic due to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) led to a global health crisis. After the report of the first case in Wuhan, China, in December 2019, millions of people were infected with the virus in only a few months. Apart from many systemic findings such as fever, fatigue, dry cough, the disease can also involve the eyes mainly in form of conjunctivitis. Therefore, all patients with red eyes became suspicious of COVID-19 conjunctivitis. Ophthalmologists are at increased risks for COVID-19 because of their close physical proximity to the patients during the eye examination. Thus, eye care providers should use proper ways of protection including wearing an N95 mask, gloves, and protective goggles. The outpatient clinics should be disinfected regularly and social distancing should be provided for all areas. Regular visits without any emergency should be postponed or those patients should be managed via telemedicine. Urgent or visually important cases should be triaged for COVID-19 risk before the ophthalmological examination. International guidelines should be followed for determining the effective and safe treatment protocols for the patients during the pandemic.

Keywords: ophthalmology, COVID-19, social distancing, severe acute respiratory syndrome

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INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a highly contagious RNA virus, causes Coronavirus disease 2019 (COVID-19) emerged on the last days of December 2019 in Wuhan city, Hubei province, China. COVID-19 is the third and largest coronavirus outbreak in the 21st century after the severe acute respiratory syndrome (SARS) in 2002 and the Middle East respiratory syndrome (MERS) in 2012. Over 80 million people have been infected and the COVID-19 has caused more than one million deaths.

There are seven types of coronaviruses known to infect humans: 229E (alphacoronavirus), NL63 (alphacoronavirus), OC43 (betacoronavirus), HKU1 (betacoronavirus), MERS-CoV (betacoronavirus), SARS-CoV (betacoronavirus), and the most recent SARS-CoV-2 [1]. Although not proven, the source of the disease has been speculated to be from bats [2].

COVID-19 can potentially be fatal and affects mainly the lungs and airways leading to the most frequent symptoms of the disease including fever (87.9%), dry cough (67.7%), and fatigue (38.1%) [3]. However, apart from the respiratory tract, it can also affect other regions including the gastrointestinal tract and ocular tissues [4, 5]. So, the manifestations of COVID-19 in other organ systems should not be ignored as they can represent an alternative mode of transmission.

From genomic and structural analyses, it has been reported that the SARS-CoV-2 has a similar receptor-binding motif as SARS-CoV, which allows it to infect host cells via the angiotensin-converting-enzyme-2 (ACE2) [6]. ACE2 has been found in the aqueous humor [7], conjunctiva, and corneal epithelium [8].

Conjunctival congestion or conjunctivitis can be an early clinical manifestation of COVID-19. In a study with a large case series, 0.8% prevalence was seen in China [9]. Previous studies reported that SARS-CoV-2 was found in tear samples of patients with COVID-19 [10]. Apart from conjunctivitis, hyperreflective lesions were observed on the papillomacular bundle and between the retinal ganglion cell layer and inner plexiform layer without causing any visual disturbance in optical coherence tomography [11]. Ophthalmoplegia cases related to COVID-19 have also been reported [12, 13].

Ophthalmologists are at increased risks for COVID-19 because of their close physical proximity to the patients during eye examination (less than 30 cm during the slit-lamp examination, and less than 5 cm at direct ophthalmoscopy examination). Also, manipulation of eyelids in some patients required during the slit lamp examination, which increases the risk of contact with tears or other ocular discharge. Ophthalmologists should routinely wear respiratory masks and gloves if contact is required.

Dr. Li Wenliang, who alerted Chinese government officials of an incipient viral syndrome (COVID-19), was a young ophthalmologist. By his account, he believed he contracted the infection from a glaucoma patient he was evaluating for conjunctivitis; a month after exposure, he passed away due to respiratory failure. With the outbreak of COVID-19, ophthalmologists may be the first to identify patients with COVID-19 seeking treatment for acute conjunctivitis before the manifestation of respiratory symptoms. They have an important role in guiding infection control measures to prevent unnecessary exposures to other patients and medical staff.

Old age is a known risk factor for more severe clinical manifestation of COVID-19 with probable additional systemic diseases (e.g., diabetes mellitus, hypertension, etc.). Cataract, glaucoma, and macular degeneration, common ophthalmic conditions, are associated with aging. Thus, additional increased risk portended to ophthalmic practice relates to the increased age of patients in ophthalmology clinics or undergoing ophthalmic procedures.

The above-mentioned factors make the role of ophthalmologists during the pandemic very crucial.

SARS-CoV-2 IN TEARS AND OCULAR FINDINGS OF COVID-19

From the experience on SARS-CoV, it was known that coronaviruses can be found in tears [4]. However, at the beginning of the pandemic, the ocular involvement of the COVID-19 was unknown. After the report of transmission of the disease in a patient (Guangfa Wang, a member of the national expert panel) who did not wear protective goggles but wore an N95 mask, the possibility of disease transmission via the eyes started to be questioned. Then a report showed that COVID-19 can be transmitted through the mucous membranes including the conjunctiva [14]. Ophthalmologists have also been shown to be infected in several case reports.

Polymerase chain reaction (PCR) analysis of the tear films of the patients with COVID-19 with or without conjunctivitis showed that the virus can be isolated from the patients with COVID-19. The patients with positive PCR in the tear film can be in the early stage of the disease without any systemic symptoms. Therefore, protection of the eyes with goggles is very important to prevent the disease spread during the examination of the patients, and tears of the COVID-19 patients are also potential sources of disease transmission. PCR positivity of the tear of a patient with COVID-19 despite no systemic symptoms 3 weeks after the disease onset should be another warning for the clinicians to be careful with handling ocular tissues or secretions even after the disappearance of the symptoms and negative nasopharyngeal swab [15].

The studies on tear samples of patients with COVID-19 are summarized in Table 1. Ocular findings of the disease were as high as 31.6% and the PCR positivity of the tear samples was as high as 24%. However, a recent meta-analysis showed that the overall prevalence of the ocular involvement in patients with COVID-19 was 5% and 28% of ocular samples showed SARS-CoV-2 PCR positivity [16]. A study on pediatric patients with SARS-CoV-2 positivity showed that asymptomatic COVID-19 pediatric patients could also have positive tear samples [17].

Several possible reasons for tear sample positivity for SARS-CoV-2 have been speculated including direct inoculation of the virus, its migration from the respiratory tract through the nasolacrimal duct, or shedding of the virus from an infected lacrimal gland [25]. The last possible transmission way might be the affinity of SARS-CoV-2 to angiotensin-converting-enzyme-2 in the ocular tissues [8].

Table 1. List of the studies investigating the PCR positivity in tear samples of patients with COVID-19

Study	Sample size	Patients	Ocular findings	SARS-CoV-2 in Tear Samples
Wu et al., [18]	38	Clinical confirmation	31.6%	5%
Xia et al., [19]	30	Laboratory confirmation	3.3%	3%
Seah et al., [20]	17	Laboratory confirmation	5%	0%
Sun et al., [21]	72	Laboratory confirmation	2.7%	1.3%
Deng et al., [22]	114	Clinical confirmation	0%	0%
Zhou et al., [23]	67	Confirmed/suspects	1.4%	4.4%
Karimi et al., [10]	43	Clinical confirmation	2.3%	7%
Arora et al., [24]	78	Laboratory confirmation	0%	24%

SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2.

COVID-19 can lead to some ocular findings including mostly conjunctivitis with complaints of itching and red-eye. Conjunctival congestion was reported in 0.8% (9/1099) of the patients with laboratory-confirmed disease in China [9]. A recent meta-analysis on ocular findings of COVID-19 showed that ocular findings of the disease can be the first presenting sign of the disease [26] and the overall prevalence of the ocular involvement in patients with COVID-19 was 5% [16]. Furthermore, the ocular involvement of the disease has been reported to be as high as 31.6% [18].

The ocular manifestation was earlier than the systemic manifestation in around a quarter of COVID-19 patients with ocular manifestation regardless of the severity [16]. However, the association of the presence of ocular manifestation with disease severity is yet to be determined due to controversial results from different studies. Furthermore, the same meta-analysis showed that one-third of ocular samples (28%) showed SARS-CoV-2 PCR positivity [16]. Therefore, since coronaviruses could be transmitted to the nasopharynx via nasolacrimal duct and tear positivity can be observed in asymptomatic patients, eyes could potentially be the windows to the COVID-19 transmission.

Being healthcare workers, elderly patients (> 60 years), frequent touching of the eyes with hands, lacrimal duct abnormalities, immunosuppression, and swimming are among the reported possible predisposing factors for ocular manifestation of COVID-19 [16].

The ocular manifestation of the disease can be observed together with, before, or after the systemic manifestations. Ocular manifestation in form of conjunctivitis can be the only presenting symptom of the disease [26]. Therefore, all patients who were admitted to the emergency or ophthalmology departments should be investigated for COVID-19 related findings.

The ocular manifestation of the disease improved in all patients reported in the previous studies and did not get worse in time. Therefore, although red eyes in COVID-19 patients should be accepted as ocular involvement of the disease as conjunctivitis until proven otherwise, emergent referral or consultation of the patients to an ophthalmologist may not be needed.

After an autopsy study reporting SARS-CoV-2 positivity in retinal biopsy specimens of three specimens out of 14 COVID-19 patients [27], retinal involvement of the disease started to be questioned. An optic coherence tomography study showed hyper-reflective lesions at the level of ganglion cell and inner plexiform layers [11]. However, this finding became

controversial due to many consequent correspondences about this study. Rare neuro-ophthalmic presentations such as cranial nerve palsies, ophthalmoplegia, diplopia, and nystagmus have also been reported in patients with COVID-19 [12, 13].

CONTROL MEASURES FOR THE OPHTHALMOLOGICAL EXAMINATION AND SURGERIES

Since the risk of human-to-human transmission increases closer than 1.5 m distance, the waiting area for the patients should be designed to ensure social distancing between patients by blocking alternating seats (Figure 1).



Figure 1. Blocked seats to provide social distancing in the waiting area for the patients.

Because SARS-CoV-2 can live on the inanimate surfaces up to 9 days [28], efficient cleaning of all areas with possible contamination should be disinfected regularly with appropriate disinfectants. Povidone-iodine, a combination of chlorhexidine with ethanol and cetrimide, most alcohol-based solutions such as ethanol or isopropanol significantly reduces the viral titers and is recommended [29,30]. The Centers for Disease Control and Prevention (CDC) specifically recommended the use of alcohol solutions with at least 70% alcohol and diluted household bleach (five tablespoons of bleach per gallon of water) [31]. Some antiseptics-disinfectants formulated with only phenolic or quaternary ammonium compounds, or a combination of chlorhexidine with cetrimide may be ineffective against SARS-CoV-2, therefore should not be preferred for disinfection [32].

Ophthalmic lenses contacting eyes should be disinfected with 1:100 sodium hypochlorite or 3% hydrogen peroxide for 5 minutes followed by washing with water before the next use [33].

Due to the high frequency of fever in COVID-19 patients, all patients admitted to the ophthalmology department should be checked for their body temperature. Patients with an ocular emergency with fever should be examined in an isolated room, but those without any ocular emergency should be referred for COVID-19 exclusion to the relevant department and their ophthalmological examination should be postponed. Patients without fever should also be questioned about COVID-19 related symptoms or risk factors including the history of traveling abroad within the past 2 weeks or any suspicious contact with a COVID-19 patient.

The current recommendation from WHO for general ophthalmology patients would be wearing personal protective equipment according to standard precautions, which is wearing surgical masks in all areas. A complete ophthalmological examination usually takes around 30 minutes. Thus, longer exposure of the ophthalmologists to patients leads to another risk factor for the disease transmission. The distance during the slit lamp examination between

patient and examiner varies between 20 and 40 cm. Therefore, a large protective transparent plastic shield should be installed on the biomicroscopes to provide another control measure during slit-lamp examination (Figure 2).



Figure 2. The close proximity of an ophthalmologist to a patient during slit-lamp examination with appropriate personal protective equipment.

Since the tear can be SARS-CoV-2 positive even without any ocular or systemic finding of the COVID-19 and asymptomatic COVID-19 patients were reported to be 15.6% among all patients [34], ophthalmologists should accept all patients as possible infection sources. Therefore, ophthalmologists should wear protective goggles, N95 masks, and gloves during the examination of all patients to prevent disease transmission. While the American Academy of Ophthalmology recommended ophthalmologists to wear masks and eye protection when caring for patients with potential COVID-19 positivity [35], a report from Hong Kong during the SARS-CoV outbreak recommended the use of personal protective equipment (PPE) including the gloves for all patients regardless of SARS status [36]. The patients can be requested to speak less frequently during the examination.

Studies have shown that healthy individuals touch their eyes 10 times per hour [37]. The use of glasses may be protective against this frequent touching. Interestingly, extended daily use of glasses for more than 8 hours per day was shown to be associated with less susceptibility to COVID-19 emphasizing the importance of wearing protective goggles or glasses [38].

Ophthalmologists preferring not to wear gloves should wash his/her hands with disinfectants after each patient and the ones who prefer to wear gloves should change the gloves after each patient. Ophthalmologists should wear isolation gowns while examining the COVID-19 positive or suspicious patients in an isolated room.

The working shifts of all medical staff can be designed to work as small groups to prevent cross-infection between different staff members. To prevent disease spread among medical staff, all meetings should be made as online meetings. The personnel should also be careful about social distancing. Gathering in large groups of more than 10 people should be stopped.

Outpatient and inpatient ophthalmology care should be separated to curtail the risk of cross-infection. Inpatients should be examined at the bedside with portable devices or in an examination room designed only for inpatient use [39].

Recommendations for each subspecialty clinics in ophthalmology are given below under separate subtitles.

Retina

Retina clinics are usually very crowded, and the patient population usually consist of elderly patients. Therefore, some control measures should be administered to decrease the number of unnecessary visits. The physicians should check the patient records to postpone some of the appointments and the patients should be informed via text messages, phone calls, or emails. Implementation of telemedicine applications could also be helpful for virtual visits to determine the emergency status of the condition. During the fundus examination of the patients, indirect ophthalmoscopes can be preferred instead of slit lamp fundus examination.



Figure 3. Oculoplasty surgery with appropriate personal protective equipment.

Patients necessitating intravitreal injections are a major concern for retina specialists. One approach could be increasing the time interval between the injections. Another approach could be the decision of injection only according to the OCT imaging results. The last approach could be postponing any visits or injections until the patient complains about any significant visual loss.

Oculoplasty

Oculoplasty is a subspecialty of ophthalmology with particularly higher-risk for transmission of COVID-19 compared to the other ophthalmologists and other physicians due to the higher viral load in the nasal cavity than in the throat. Oculoplastic surgeons operate on the nasolacrimal area (lacrimal drainage system and sinuses) as well as the orbit and sinuses, they are at risk for aerosolization of viral particles from nasal mucosa and/or other mucosal surfaces [40, 41]. Therefore, protective face shields or goggles should be used during the oculoplastic surgeries (Figure 3).

Contact Lens

During the contact lens clinics' daily routine, ophthalmologists prescribing the contact lenses and contact lens nurses advising the contact lens use are in close contact with the patients. Therefore, special precautions must be taken to prevent any contamination of the equipment and working environment. Application of the contact lens should be accepted as an elective procedure and patient triaging including the COVID-19 risk assessment and the determination of the emergency status of the contact lens users must be done before accepting the patient appointment.

For former contact lens users, any newly developed complaint should be evaluated via telemedicine or clinic visits and control visits should be postponed. British Contact Lens Association recommended postponing the new contact lens examinations.

Since a study showed that extended daily use of glasses more than 8 hours per day was associated with less susceptibility to COVID-19 [38], contact lens users should be recommended the use of glasses during the pandemic for better protection against COVID-19.

Uveitis

Some uveitis patients are under immunomodulatory treatment possibly making them more susceptible to COVID-19. However, the uveitis patients should not be advised to stop their treatment since the treatment discontinuation may lead to more dangerous conditions. Telemedicine, especially evaluation with fundus photography, can be used for the diagnosis of uveitis. However, all active uveitis conditions should be examined by the physician, but the follow-up interval can be longer than usual.

The current recommendation for immunosuppressive treatment includes the continuation of the treatment apart from the patients with high COVID-19 risk and avoiding the use of

high-dose steroid treatment. Because steroid use of more than 10 mg/day was shown to be associated with a higher hospitalization risk for COVID-19 patients. Interferon and tocilizumab are highly recommended to be continued in the treatment of uveitis patients due to their possible positive effect on COVID-19 treatment. However, the use of anti-tumor necrosis factor treatment in uveitis patients is controversial [42–44].

Cataract

Cataracts are the second most common cause of treatable visual impairment globally. Since cataract surgeries are among the elective surgeries except for some relatively urgent conditions (phacolytic glaucoma, phacomorphic glaucoma, etc.), almost all cataract surgeries were canceled or postponed due to the COVID-19 pandemic. However, the increased cataract patient volume will be a big concern for the future practice of the ophthalmologists.

Some countries recommended the ophthalmologists to start some elective surgeries including cataract surgery. However, precautions should be taken to prevent cross-infection by wearing appropriate PPE including an N95 mask and protective goggles during the surgery (Figure 4).



Figure 4. Cataract surgery with appropriate personal protective equipment including an N95 mask, gloves, and protective goggles.

Cataract surgery training for ophthalmology residents was also impaired. Wet labs can be a useful tool for the training of the residents during the pandemic.

Cataract surgery may have the potential of aerosol formation. A recent study showed that aerosol formation can be reduced with hydroxypropyl methylcellulose (HPMC) coating of the cornea every 1 minute or when 2.2 mm phaco tip was used instead of 2.75 mm [45]. On the other hand, povidone-iodine is used for surgical antisepsis before the cataract surgery and is virucidal to SARS-CoV-2 [46]. Furthermore, phacoemulsification cataract surgery occurs in a closed system preventing the intraocular fluid to contact with the outer environment [45]. However, the safety of the cataract surgery with phacoemulsification regarding the COVID-19 transmission is still unknown.

Cornea

Foreign bodies that necessitate removal, active keratitis, corneal ulcers, corneal perforation, or melt, corneal graft rejection are among the corneal pathologies requiring a visit to the ophthalmology clinic. Elective surgeries including keratoplasties should be postponed. However, therapeutic tectonic keratoplasty can be performed in urgent conditions. The donors should also be checked for COVID-19 before the harvesting process. Theoretically, due to the presence of ACE2 in cornea epithelium, the viruses can be transmitted via corneal transplantation. However, further postmortem studies on corneal tissues should be conducted to better understanding the possibility of transmission via transplantation.

The use of cauterization during ocular surface-related surgeries possess a risk for aerosol formation. Therefore, irrigation will be important during cauterization and the use of cautery should be minimized in terms of power and duration. The smoke should also be evacuated effectively during cauterization.

Glaucoma

Glaucoma is an incipient disease causing painless peripheral vision loss due to progressive optic nerve damage. The well-known risk factor for the disease is increased intraocular pressure. Non-contact tonometer sprays a gas for measuring the intraocular pressure and possibly creates aerosol around that local area for a long time (3-8 hours) thereby creating a possible environment for the disease transmission [47]. Therefore, for safer intraocular pressure measurement, an applanation tonometer with efficient cleaning or iCare tonometer should be used instead of a non-contact tonometer.

Glaucoma patients can be followed only with OCT-RNFL imaging or visual field test to postpone clinical visits. Home-based IOP monitoring with contact lenses can be used for investigating the diurnal variation.

Pediatric Ophthalmology

Sight threatening conditions such as retinopathy of prematurity, congenital cataract, congenital glaucoma, or severe amblyopia can be followed and managed without postponing

any visit to prevent any permanent visual loss. Telemedicine can be used for the follow up with more benign conditions such as strabismus.

Surgery

Hospitalization should be approved only for the SARS-CoV-2 negative cases. However, in conditions requiring urgent intervention such as corneal rupture, the operation can be done without waiting for the PCR test result.

PCR tests should be implemented in all patients before their surgery. For the procedures possibly not causing any aerosol formation, wearing only a surgical mask for the patient can be enough. However, we recommend the use of N95 masks for all ophthalmological interventions.

COVID-19 positive patients should be operated in operating rooms with negative pressure, if possible. Hospitals should provide operating rooms with negative pressure given the possible long duration of the pandemic. The frequency of air change should be high in standard operating rooms. All patients should wear surgical masks.

COVID-19 AND TELEMEDICINE IN OPHTHALMOLOGY

Telemedicine is a way of transmitting any information to support healthcare by using communication technologies. Video examination visits can be used during the pandemic to postpone any elective case or to determine the emergency status of the patient. However, the limitations and medicolegal concerns of virtual visits should be understood by the eye care provider and explained in detail to the patients.

CONCLUSION

In conclusion, ophthalmologists are at increased risks for COVID-19 because of their close physical proximity to the patients during the eye examination. All eye care providers should take precautions against COVID-19 by wearing appropriate PPE including protective goggles, gloves, and N95 masks. Social distancing in outpatient clinics should be warranted for preventing cross-infection. Elective surgeries should be postponed, and only relatively urgent cases should be seen in the clinics. Telemedicine applications should be implemented for patient triaging or virtual visits. Conjunctivitis can be the presenting sign of COVID-19 as well as it can be observed concurrently with the other symptoms. Therefore, all patients with red eyes can be accepted as COVID-19 conjunctivitis until proven otherwise during the pandemic.

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Chapter 463

THE IMPACT OF THE COVID-19 PANDEMIC ON PATIENTS WITH DIABETES

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ABSTRACT

The purpose of the present chapter is to explain the impact of coronavirus disease 2019 (COVID-19) on diabetes and implications for treatment. The SARS-CoV-2 outbreak affected millions all around the world and the number of infected cases is still increasing. The available scientific data from clinical studies of COVID-19 show that is worse with comorbidities such as diabetes. According to statistical data, the mortality rate in diabetic patients is higher than non-diabetics. SARS-CoV-2 can cause acute diabetes using angiotensin-converting enzyme-2 (ACE-2), which is abundant in Langerhans islets. Anti-diabetic drugs during COVID-19 may be a novel strategy to reduce virus entry and replication in individuals with or without type II diabetes. Studies to date have shown that some drugs tried in the treatment of COVID-19 improve glucose profile but the others cause impairment of glucose metabolism and β -cell function. Dipeptidyl peptidase 4 (DPP-4) inhibitors may prevent the progression of the hyperinflammatory state associated with COVID-19. Therefore, since it is important to maintain glucose homeostasis in COVID-19 treatment, more studies are needed on the hyperglycemia or hypoglycemia molecular mechanisms of anti-diabetic drugs. Telemedicine or digital medicine plays a crucial role in monitoring glycemic control in diabetic patients with COVID-19.

Keywords: COVID-19, diabetes, hyperglycemia, ketoacidosis, anti-diabetic therapeutics

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INTRODUCTION: SARS-CoV-2 AND DIABETES

Diabetes, a metabolic disease, characterized by inappropriately raised blood glucose concentrations. Diabetes can be categorized as type I diabetes, type II diabetes, gestational diabetes, and specific types of diabetes due to other causes. The two major types of diabetes are type I diabetes and type II diabetes, which are caused by absolute insulin deficiency (type I diabetes) and/or insulin resistance (type II diabetes). Type I diabetes is caused by the destruction of the pancreatic β -cells and is found in children and adolescents, while type II diabetes results from an imbalance between insulin sensitivity and insulin levels and commonly present in older adults. Type II diabetes also called “adult-onset diabetes”, accounts for approximately 90-95 % of all diabetic individuals. A combination of genetic and lifestyle is involved in the development of type II diabetes. For example, middle-aged and older adults can have prolonged hyperglycemia due to poor lifestyle and an unhealthy diet [1].

According to the International Diabetes Federation (IDF), 1 in 11 people aged 20-79 years worldwide has diabetes in the global population. It has been estimated that the prevalence of diabetes will increase from 463 to 578 million by 2030. Unfortunately, the number will jump to 700 million by 2045. Furthermore, diabetes is among the top 10 causes of death [2]. Thus, the disease is a serious growing problem for global health.

Currently, a new coronavirus, rapidly spreading, remains a threat to most of the human population worldwide. The new virus, SARS-CoV-2, which induce the COVID-19 disease in humans, first appeared in China. One of the coronaviruses (CoVs), SARS-CoV-2, belongs to the large *Coronaviridae* family. It is known that these CoVs, a large family, are enveloped viruses with a single-strand, positive-sense RNA genome. Despite a long history of coronavirus research starting in the 1930s, with the first appearance of SARS-CoV in 2002, many scientists have realized the potential for this virus group to cause fatal infections in humans [3]. It is reported that seven types of CoVs can infect humans [4]. Human coronaviruses (HCoVs), respiratory pathogens, cause respiratory infections such as severe acute respiratory syndrome-CoV (SARS-CoV), and the Middle East respiratory syndrome-CoV (MERS-CoV) [5].

According to the latest data, the COVID-19 outbreak has caused over 1.839.660 deaths and 83.910.386 infected cases and these numbers are increasing [6]. Li et al., [7] reported that angiotensin-converting enzyme-2 (ACE-2) is a functional receptor for SARS-CoV and it infects humans through this receptor. After ACE-2, dipeptidyl peptidase 4 (DPP4) has been identified as a receptor for coronaviruses. One of the highly pathogenic CoV, MERS-CoV uses DPP4 as a cellular receptor [8]. To infect humans, SARS-CoV-2 is also used the ACE-2 cell receptor [9].

Recent evidence has presented that patients with underlying metabolic conditions of diabetes show higher morbidity and mortality than individuals without diabetes [10]. It has been reported that blocking the renin-angiotensin system (RAS) with ACE inhibitors or angiotensin II receptor blockers reduced the development of diabetes in adults [11]. On the other hand, these therapeutics upregulate the ACE-2 receptor on the surface of the host cell and so, the SARS-CoV-2 virus can enter the host cells [12]. This suggests that individuals with diabetes are more likely to be infected with SARS-CoV-2 compared to healthy humans. On the contrary, diabetes disease does not cause an increase in the risk of SARS-CoV-2

infection but may contribute to worsening the outcome of COVID-19 disease [13]. Another thought is that the anti-viral drugs used cause deficiency in glucose metabolism and other endocrine disorders, and even cause ketoacidosis [14, 15].

HYPERGLYCEMIA IS A RISK IN COVID-19

There is an association between hyperglycemia and elevated risk of mortality in stroke, pneumonia, acute myocardial infarction, trauma, and surgery [16]. Hyperglycemia was shown as a risk factor of morbidity and mortality in SARS and MERS [17, 18].

The fact that type II diabetes is the second most common comorbidity of COVID-19 is evidence that these two outbreaks are related. According to the study on adult patients with COVID-19, patients with diabetes disease have a higher probability of in-hospital death compared with non-diabetics [19]. In a study of 7337 COVID-19 patients, 952 of whom had diabetes, it was reported that type II diabetes significantly increases the risk of medical interventions and mortality. However, among the individuals with type II diabetes, patients with well-controlled blood glucose regulation (3.9 to 10.0 mmol/L) were found to perform better compared with patients with poorly controlled blood glucose (> 10.0 mmol/L) [20]. Deng et al., [14] suggested that the prevention of diabetes can contribute to reducing COVID-19 mortality. It is reported that high glucose not only damages cells and tissues but also activates interferon regulatory factor 5 (IRF5), thereby promoting cytokine storm (CS) caused by a virus [14, 21]. Furthermore, it is predicted that SARS-CoV-2 infection induces the CS as a systemic immune response. The CS can cause the progression of the disease and lead to multiple organ failure or even death [22]. Due to the CS caused by high blood glucose and SARS-CoV-2, it is estimated that patients with diabetes have a higher mortality rate.

COVID-19 ON THE REGULATION OF BLOOD GLUCOSE

Some non-diabetes-related diseases, such as systemic inflammation response syndrome, traumatic brain injury, and severe sepsis tend to have high blood glucose levels [23]. This condition is defined as stress hyperglycemia (glucose value > 7.8 mmol/L or 140 mg/dl). Stress hyperglycemia was frequently found in patients not diagnosed with diabetes [24]. Stress hyperglycemia may be occurred as a result of insulin deficiency, worsening of insulin resistance, and increased hepatic glucose production [25]. Similarly, it is thought that COVID-19 patients may also have stress hyperglycemia. The importance of well-controlled blood glucose in COVID-19 patients was reported in recent studies. Wang et al., [16] emphasized that fasting blood glucose at admission is a significant factor for the prognosis of COVID-19. They suggested that the rise of fasting blood glucose elevates the incidence of in-hospital complications. Therefore, since most COVID-19 patients tend to glucose metabolic disorders, glycemic control is significant for all COVID-19 patients, even without pre-existing diabetes. According to another study, in 29 of 184 patients, SARS-CoV-2 infection caused new and permanent hyperglycemia. Thus, the dysregulation of glucose metabolism in patients may be induced by the SARS-Co-2 infection and, this increases the development of severe COVID-19 in patients [26]. On the contrary, Liu et al., [27] specified that a high level

in admission fasting blood glucose was not a dependent risk factor for developing critical diseases of COVID-19 patients. They suggested that fasting blood glucose may be associated with systemic inflammatory reactions and immune status. Continuous glucose monitoring may prevent infections and complications, thereby contributing to the recovery of the patient with COVID-19. According to Li et al., [28], under the persistent hypoxia state hyperglycemia can develop in the COVID-19 patients. They also recommended that to prevent the progressive COVID-19 from getting worse, adequate oxygen intake for patients are monitored, as well as blood glucose levels.

PANCREAS FAILURE

The pancreas is an important gland in diabetic patients as well as in patients with COVID-19. Recent studies have reported that patients with COVID-19 show not only fever and respiratory disease but also an increasing number of patients with gastrointestinal symptoms such as nausea, vomiting, and abdominal pain [29]. Hadi et al., [30] reported that acute pancreatitis is a complication related to COVID-19. The researchers emphasized that if patients with COVID-19 suffer from abdominal pain, lipase and amylase should be measured. In a study on 52 patients with Covid-19, 17 % of COVID-19 cases showed pancreas injury that was defined as increased lipase [31]. Ding et al., [32] reported that SARS-CoV was found not only in the lung, liver, intestine, and kidney tissues but also in the pancreas. Thus, the pancreas may be a potential target of SARS-CoV infection. Consistent with the report of Ding et al., [32], the high damage level of SARS-CoV in the pancreas is correlated with ACE-2 expression in the pancreas. Moreover, ACE-2 expression is localized especially in the endocrine part of the pancreas. SARS-CoV may enter Langerhans islets using ACE-2, the receptor of SARS-CoV, and it may cause acute diabetes after damaging the islets [33]. According to Wang et al., [31], the pancreatic damage in COVID-19 may be induced directly by the cytopathic effect mediated by SARS-CoV-2 replication. Indirectly, the damage in the pancreas may be originated from immune-mediated and systemic inflammatory cellular responses induced by SARS-CoV-2 infection. Researchers found that the expression of ACE-2 in the pancreas of healthy individuals is slightly higher than in the lungs. Similar to SARS-CoV, SARS-CoV-2 may also bind to ACE-2 in the pancreas and enter into the tissue. Therefore, SARS-CoV-2 causes damage to the pancreas. Moreover, the expression of ACE-2 has been shown in both the exocrine and endocrine regions of the pancreas [34]. In the same study on 121 cases with COVID-19, the authors found an increase in amylase and lipase levels depending on the severity of the disease. It was emphasized that more attention should be paid to the pancreas in patients with SARS-CoV-2 infection, particularly, in severe cases. Otherwise, it has been suggested that there may be pancreatic injuries associated with the use of antipyretic drugs [31].

DIABETIC KETOACIDOSIS

Diabetic ketoacidosis (DKA), one of the most serious complications of diabetes, is characterized by the triad of hyperglycemia (blood glucose level > 13.9 mmol/L), acidosis

(arterial pH less than 7.3 and serum bicarbonate level less than 18 mEq/L) and ketosis (ketonemia or ketonuria) [35].

DKA has been noticed in COVID-19 as well as in other serious infections [36]. DKA can be triggered by SARS-CoV-2 in poorly controlled diabetic patients [10]. In a case study, researchers reported that COVID-19 could cause DKA and multiorgan failure even without lung involvement in patients with diabetes [37]. Similarly, Chee et al., [38] found that DKA may be occurred by SARS-CoV-2 in a 37-years-old male diabetic patient. In the period from January 1 to March 3, 2020, a Chinese cohort study on 658 patients was reported that COVID-19 infection may cause ketosis and ketoacidosis in non-diabetic individuals, and can induce DKA in diabetic patients [39]. According to another case study, in a 54-years-old male patient with newly diagnosed diabetes, COVID-19 infection may cause an increase in DKA [40]. When SARS-CoV-2 enters pancreatic islet cells, it damages β -cells, which may induce precipitated DKA in patients.

ANTI-DIABETIC THERAPEUTICS

According to the last International Diabetes Federation (IDF) atlas, the control of blood glucose is usually initiated with metformin as a first-line drug. In cases where treatment with a single anti-diabetic drug is not sufficient, there are combination treatment options such as sulfonylureas, DPP4 inhibitors, glucagon-like peptide 1 (GLP-1) analogs. Insulin injections may be needed if oral anti-diabetic drugs are unable to control hyperglycemia [2].

Studies have shown that some of the drugs tried in the treatment of COVID-19 improve glucose profile, but some drugs cause impaired glucose metabolism [41]. On the other hand, although ACE-2 and DPP4, two coronavirus receptor proteins, are known to be important in the regulation of glucose homeostasis and inflammation, there is insufficient clinical evidence that drugs targeting these receptors benefit human coronavirus infections [42]. One study suggested that ACE inhibitor (ACEI) and angiotensin receptor antagonist (ARB) use should be considered in diabetic patients during the COVID-19 outbreak, while another study reported that the use of ACEI and ARB in diabetic patients may increase the morbidity and mortality of COVID-19 [43, 44].

The potential benefits of anti-diabetic drugs during COVID-19 are as follows.

METFORMIN

Metformin, which has been used for decades, is the most preferred drug worldwide for every diabetic patient. Jean Sterne introduced this drug as ‘Glucophage’, which means ‘glucose eater’, in 1957 [45]. Interestingly, Sharma et al., [46] suggested that when there is no specific agent against COVID-19, metformin should be among the drugs used to fight the virus. Rena et al., [47] have mentioned that metformin affects the improvement of glucose metabolism through the AMP-activated protein kinase (AMPK) dependent mechanism. Metformin is thought to provide conformational and functional changes to the ACE-2 receptor through AMPK activation that causes phosphorylation of ACE-2. As a result, binding of SARS-CoV-2 to the receptor-binding site can be prevented, so that the virus is not

able to enter the cell [46]. By contrast with Sharma et al., [46], the researchers have suggested that metformin may promote SARS-CoV2 infection by increasing the presence of ACE-2 in the respiratory system. On the other hand, researchers still not sure whether metformin is friendly or not [48]. According to a retrospective study on 283 patients by Luo et al., [49], the fasting blood glucose level in diabetic patients infected with COVID-19 using anti-diabetic drugs other than metformin was lower than in those using metformin. However, other laboratory parameters were similar in patients taking metformin and other anti-diabetic drugs. This study also suggested that the mortality of metformin users was lower than that of non-users in diabetic patients infected with COVID-19.

DIPEPTIDYL PEPTIDASE 4 (DPP4) INHIBITORS

DPP4 inhibitors are commonly used to control glucose in patients with diabetes [42]. To facilitate virus entry, SARS-CoV-2 uses co-receptors as ACE-2 partners. DPP4, a membrane protein, has also been reported among these co-receptors [50]. It has been reported that DPP4 inhibitor anti-diabetic drugs such as gliptins (sitagliptin, vildagliptin, or linagliptin) can prevent coronavirus / DPP4 interaction and thus protect the cell from virus entry [51]. Consistent with this study, Solerte et al., [52] suggested that the inhibition of DPP4 may be a new strategy to strengthen COVID-19 therapy in diabetic patients or not. Besides, DPP4 inhibitors may also be used to prevent the progression of the hyperinflammatory condition associated with COVID-19, thanks to its inflammatory healing properties [53]. In a review article by Bassendine et al., [54], it was emphasized that DPP4 activity is higher in elderly individuals and the increase of DPP4 in plasma is an indicator of the onset of metabolic syndrome. Thus, gliptins used in DPP4 inhibition may be a treatment strategy to reduce the severity of COVID-19 disease.

GLUCAGON-LIKE PEPTIDE 1 (GLP-1) RECEPTOR AGONISTS

GLP-1 receptor agonists, which are more widely used in the treatment of diabetes in recent years, reduce cardiovascular risk [55]. Beyond their anti-diabetic effects, GLP-1 receptor agonists have anti-inflammatory effects [56]. Thus, Ceriello et al., [57] suggested that GLP-1 receptor agonists might be useful in COVID-19 patients due to their anti-inflammatory effects. Similarly, Longo et al., [58] also reported that GLP-1 receptor agonists could be used in diabetic patients with COVID-19 due to their glucose-lowering and anti-inflammatory effects. However, they suggested that data on the use of GLP-1 receptor agonists in these patients were insufficient.

SULFONYLUREAS AND THIAZOLIDINEDIONES

Sulfonylureas and thiazolidinediones provide excellent improvements in glycemic control in different mechanisms. Sulfonylureas stimulate insulin secretion and act immediately on HbA1c, whereas thiazolidinediones sensitize insulin and take longer to express their effect

[59]. According to Derosa and Maffioli [60], thiazolidinediones may provide a more adequate control in diabetic patients compared to sulfonylureas due to their cardiovascular risk lowering effect. Sulfonylureas have been reported to show no interaction with ACE-2 and its use can be safely continued [61].

It has been reported that sulfonylurea treatment affects the risk of hypoglycemia in diabetic patients with COVID-19 [62]. Thiazolidinediones treatment may reduce the development of pulmonary fibrosis (PF) in patients with COVID-19 and thus be a valuable approach to alleviating the course of the disease, especially in diabetic patients. However, due to insulin sensitivity, it is recommended that diabetic patients be followed carefully for any signs of hypoglycemia [63]. Other than these features, thiazolidinediones have anti-inflammatory properties through PPAR- γ activation and affect severe viral pneumonia [64].

INSULIN

To control glucose in hospitalized diabetic patients, insulin treatment has been used extensively for decades. Some case studies have shown that intravenous insulin administration accompanies anti-viral agents and empirical antibiotics for the treatment of both COVID-19 and DKA [10,37]. According to Nakhleh and Shehadeh [65], there is a relationship between SARS-CoV-2-induced lung injury and hyperglycemia. Researchers defend that insulin can be promising in the treatment of COVID-19 patients, thanks to its immunomodulatory effect, its ability to prevent the spread of cytokine storm and lung damage by regulating ACE-2 expression and angiotensin II levels, and its ability to reduce the risk of developing DKA or hyperglycemic hyperosmolar states. Similarly, in a study conducted on 59 patients with COVID-19, it was stated that insulin therapy could be an effective method to control glycemic targets and reduce mortality [66].

SODIUM GLUCOSE TRANSPORTER-2 (SGLT-2) INHIBITORS

Current guidelines for the management of type II diabetes recommend SGLT-2 inhibitors can use in patients with type II diabetes and heart failure to reduce heart failure, major adverse cardiovascular events, and cardiovascular disease death [67]. However, according to the study by Hamblin et al., [68], the use of SGLT-2 inhibitors has been associated with an increase in DKA. In the study, it was observed that SGLT-2 inhibitor users were more likely to develop DKA than non-SGLT-2 inhibitor users. In the same way, Orioli et al., [69] also recommend discontinuation of SGLT-2 inhibitors in patients with serious forms of COVID-19 because of the risks of ketoacidosis and lactic acidosis. On the other hand, it is predicted that the careful use of dapagliflozin, an SGLT-2 inhibitor, and insulin together avoiding dehydration in COVID-19 may be beneficial in the treatment of diabetes [70].

CONCLUSION

Diabetes plays a significant role in further deterioration of the clinical severity of COVID-19. It is a fact that blood glucose levels should be monitored regularly in COVID-19 patients. Unfortunately, the impact of anti-diabetic drugs on COVID-19 outcomes remains unclear. It is important to investigate how SARS-CoV-2 interacts with glucose metabolism to understand disease pathogenesis and improve treatments.

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Chapter 464

THE IMPACT OF COVID-19 PANDEMIC ON THE PATIENTS WITH CHRONIC RESPIRATORY DISEASES

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ABSTRACT

The process beginning with some cases of pneumonia of unknown etiology in the city of Wuhan in China at the end of 2019 has continued with the agent being defined as a new virus and announced as a pandemic by World Health Organization (WHO). It has been seen to spread by droplet route and direct contact and usually locate to and cause disease condition in the respiratory tract. It may present asymptotically or cause a clinical presentation ranging from mild upper respiratory tract infection to adult respiratory distress syndrome due to viral pneumonia. The clinical condition it causes has been named *coronavirus disease 2019 (COVID-19)*.

The first impressions on the disease have shown that the disease caused by this new type of virus presents with higher rates of mortality and morbidity in the elderly patients with several co-morbidities including cardiovascular conditions, immune suppressive diseases, metabolic, and chronic respiratory tract diseases. In the initial phase of the pandemic, it has been predicted that the presence of an underlying chronic respiratory tract disease may cause serious co-morbidity because the disease involves the respiratory tract particularly. In the forthcoming period, it has been found that cardiovascular and metabolic diseases might cause more severe co-morbidity compared to respiratory tract diseases.

Chronic respiratory tract diseases that may lead to serious co-morbidity during the pandemic include chronic obstructive and restrictive respiratory tract diseases, and respiratory sleep disorders.

The first and most important recommendation for patients with chronic respiratory tract diseases should be protection and the precautions. Concern on this point is whether the inhaler and systemic steroids used in the treatment of chronic obstructive pulmonary disease (COPD) and asthma are an extra risk factor. While research on this topic

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continues, it has been recommended that the patients should continue their treatment as always because no data exists suggesting that they increase the risk. Thus, it has been aimed to maintain stabilization of the disease, decrease hospital exposure, and reduce the risk of COVID-19 contamination. Pulmonary rehabilitation should be recommended to these patients in this process.

The similarity between the radiological findings of COVID-19 and interstitial pulmonary diseases is of importance in the differential diagnosis. Additionally, the patients with COVID-19 are a candidate to be a patient with interstitial pulmonary disease because fibrosis may occur in the recovery process of the disease.

Patients with obstructive sleep apnea syndrome (OSAS) also have several cardiovascular and metabolic disorders. Thus, OSAS is an extra high-risk factor for COVID-19. Furthermore, positive airway pressure (PAP) devices used in its treatment are additional important threats because they spread aerosols.

Keywords: COVID-19, chronic respiratory diseases, pandemic

INTRODUCTION

A virus that emerged in Wuhan city of China in December 2019 and was found to be originating from the livestock market has spread among the humans and caused a pandemic. The virus named Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) spreads by route of the droplet or direct contact.

With the emergence of the first cases, it was observed that SARS-CoV-2 was characterized by the upper and lower respiratory tract infection in particular and presented with more severe clinical courses especially in the elderly, immune-suppressive, and with co-morbid patients. It utilizes the receptors of angiotensin-converting enzyme-2 (ACE-2) for entering the cells. ACE-2 receptor is a protein present on the cell surface. It is most abundantly present in the lungs, heart, blood vessels, kidneys, liver, and gastrointestinal tract [1]. The virus binds to the ACE-2 receptor via the spike protein on its surface. The nasal mucosa, bronchi, and lung parenchyma all of which have a high degree of expression of ACE-2 receptors are more sensitive to the SARS-CoV-2 virus. Thus, the respiratory tract is frequently involved by the disease.

The primary viral replication is considered to occur primarily and frequently in the mucosal epithelium of the upper respiratory tract including the nasopharynx and then to continue in the lower respiratory tract. It may be asymptomatic or show clinical presentation ranging from mild upper respiratory tract infection to acute respiratory distress syndrome (ARDS) due to viral pneumonia. Although it primarily causes clinical disease of the respiratory tract, it may also involve other systems.

Advanced age and presence of co-morbid conditions are predisposing factors for both infection with SARS-CoV-2 and increased severity of the infection. Especially the conditions such as hypertension, ischemic heart diseases, diabetes mellitus, chronic obstructive lung disease have been reported as the most important risk factors for the severe course of the disease [2–8].

It has been thought that the presence of chronic respiratory tract diseases might be a cause of serious co-morbidity because the virus involves the respiratory tract after it begins to spread. For a virus that may involve the respiratory tract, the presence of underlying

pathology of the respiratory tract will facilitate contamination of the infection as well as it will lead to a worse clinical course. Thus, a high rate of mortality and morbidity is expected in the cases of COVID-19 with chronic lung diseases. Additionally, considering that these patients are elderly, the risk is much higher. Based on the first impressions and data, however, lung diseases have been observed to cause lower risk for COVID-19 compared to other chronic diseases. In a meta-analysis on 1.576 patients with COVID-19, the frequency of hypertension was reported as 21.1%, diabetes mellitus as 9.7%, and cardiovascular diseases as 8.4% whereas the frequency of the lung diseases was reported as 1.5% [8]. Studies are still going on because of the short time from the emergence of the disease.

COVID-19 PANDEMIC AND THE PATIENTS WITH ASTHMA

Asthma is a heterogeneous disease related to hypersensitivity of the airway to the direct or indirect stimulants and is characterized by chronic airway inflammation [9]. Genetic factors usually play role in the development of asthma. Its exacerbations, however, are usually due to environmental factors. The infections and exposure to allergens are leading causes of asthma attacks. The most common infectious causes are viral respiratory tract infections. Virus-related attacks may present with poorer clinical findings, especially in uncontrolled asthma.

During the initial phase of the pandemic, asthma was considered to be an important risk factor for COVID-19 because of its chronic nature as well as its risk of exacerbation. It was also predicted that the inhaler and systemic steroids used in the treatment of asthma might trigger this risk by predisposing to the infections. But surprisingly, the first analyses on COVID-19 revealed that the patients with asthma showed a similar presentation to the general population, and studies were published supporting that asthma was not a risk factor for being contaminated with COVID-19 and for mortality [10–13]. Consequently, a few opinions were suggested for a lower prevalence of asthma than expected in patients with COVID-19.

The first of these opinions was that patients with asthma were protected from the disease because they used medication regularly and because of their conscious behaviors. Although it was expected that long-acting inhaler steroids used in the treatment of asthma might increase this risk, it is also possible that they might decrease the risk because they suppress replication of the coronavirus and the production of cytokines [14]. The studies on budesonide and cyclosonide suggested that these agents had effects of inhibiting HCoV-229E replication and cytokine production in the human nasal and tracheal epithelial cells, that cyclosonide blocked in vitro COVID-19 RNA replication and prevented cytopathic activity of the virus [15, 16]. Data on this topic, however, are limited, and comprehensive and new studies are needed.

The second opinion is that the most common symptoms in COVID-19 are dyspnea and cough, and there was a possibility of missing out on the presence of COVID-19 in the patients with asthma because of the similarity of symptoms. Accuracy of this possibility, however, was weakened after the first impressions on the pandemic. COVID-19 shows different presentations from asthma exacerbations radiologically as well as in terms of laboratory findings. While cough and dyspnea occur in both of them, a sudden increase in dyspnea and wheezing are in the foreground in the asthma exacerbations and sore throat, high fever, anosmia and ageusia, and diarrhea are predominant findings in COVID-19. On the laboratory

findings high level of D-dimer and ferritin, presence of lymphopenia, and radiological view of dispersed viral pneumonia are supportive findings for COVID-19. However, the theory may be validated by confirmation by the studies on the patients with COVID-19 and asthma together.

Another point on the lower prevalence of COVID-19 than expected in asthma may be that prevalence of smoking is lower in patients with asthma compared to the general population. Studies have shown that smoking is an important risk factor for contamination with and poorer clinical course of COVID-19. This may be associated with a lower risk for patients with asthma than that predicted for COVID-19 [17].

Another opinion was that presence of chronic respiratory tract disease might have protected from COVID-19 through a different mechanism. It has been demonstrated that the virus utilizes the ACE-2 for entering the cells. ACE-2 expression is known to be lower or less active in asthma [18], which means protection for patients with asthma from COVID-19.

Even though it has been understood that asthma isn't a risk at the predicted level in patients with COVID-19, SARS-Cov-2 is an important risk factor for exacerbations of asthma similar to other viruses. It may cause severe clinical course in patients with asthma. Thus, the approach that patients with asthma will follow during the pandemic process is of importance. National Institute for Health and Care Excellence (NICE) and Global Initiative for Asthma (GINA) published interim reports to give recommendations on the management of asthma during the pandemic [19, 20]. The main items suggested are as follows:

- To prevent contamination risk of the infection, the patients should be educated on social isolation, keeping the distance, not contacting, hand hygiene, and using the masks correctly.
- Patients with asthma are recommended to continue their current medications during the pandemic; the dose of the inhaler steroids may be increased, if necessary, and lowering the line of medication is not recommended even though asthma is controlled during the pandemic. Discontinuing the disease-modifying drugs or lowering their dose may jeopardize controlling asthma, increase the risk of exacerbation, and consequently may cause the risk of contamination of the virus by leading to presentation to the hospital.
- During the attacks, using short-acting systemic steroids shouldn't be avoided.
- During the attacks, using nebulizers should be avoided because they may spread aerosols; metered-dose inhalers should be preferred and the spacer may be used when necessary.
- Allergic rhinitis is one of the diseases accompanying asthma and its treatment is important in controlling asthma. It is recommended that patients with asthma using nasal steroids for allergic rhinitis should continue their treatment during the pandemic in order not to impair asthma control.
- The pandemic process during which social isolation and time at home are increased has been a disadvantage for the patients with allergy, especially to house dust mites. In contrast, increasing time at home has been an advantage for the patients with allergy to the pollens. Controlling the signs of coughing and sneezing by giving the right patient symptomatic treatment at the right time is of great importance in decreasing the attacks as well as the spread of the aerosols.

- Routine examination of the patients with asthma should be delayed to protect them from exposure to the hospital environment and the virus. Interviews may be done and required recommendations may be given via telephone, internet, e-mail, etc.
- Spirometric tests should be avoided as much as possible. If they should be performed absolutely, all individual protective equipment should be worn by the technician because of asymptomatic and unknown COVID-19. The room should be well ventilated, and it should be carried out in a negative-pressure room, if possible.

Treatment with anti-IgE, anti-interleukin (IL)-5/IL-5 alpha, IL-4-alpha receptor antagonists used to control patients with severe asthma have been reported not to increase the risk for COVID-19. Although it has been recommended that the patients using biological agents should continue their treatment, it is also recommended that these patients should extend the interval between the treatments to decrease hospital exposure [21].

In conclusion, based on the information collected so far asthma is not considered as a factor increasing the risk for COVID-19 although more comprehensive studies are needed to confirm the validity of and discuss reasons for this. COVID-19, however, may be a poor prognostic and exacerbation factor for asthma. Thus, taking measures for protection from the infection as well as giving optimal treatments to control asthma during the pandemic process is considered as the most important factor in patients with asthma.

COVID-19 PANDEMIC AND THE PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

COPD is a disease characterized by irreversible and progressive airway obstruction. This condition develops as a consequence of the inflammatory process to the harmful gases and particles. Being a preventable and treatable disease, COPD presents with exacerbations of which severity and frequency increases in time. It is an important cause of morbidity and mortality in the world. The most common cause of COPD exacerbations is tracheobronchial infections. It is known that these infections are mostly viral.

COPD is considered as a co-morbidity factor for COVID-19. Its prevalence ranges between 1.1% and 2.9% [2, 8, 11]. COPD is a chronic respiratory disease condition although it has a lower prevalence for COVID-19 compared to other co-morbid diseases. Thus, question marks and research are still going on. COPD has been reported to have 5 folds higher risk for severe COVID-19 infection [22]. It may be suggested that this is due to advanced age, inhaler steroid use, structural damage, suppressed immunity, and exacerbations in the patients with COPD. Difficulties in adapting the protective measure due to advanced age in the patients with COPD is another factor increasing the risk of contamination of the infection. A short time from the beginning of the pandemic and the limited number of studies conducted on this topic so far leave controversial areas behind.

The main harmful particle leading to the development of COPD is tobacco. Nicotine, which is present in tobacco causes increased expression of the ACE-2 receptors. This is considered to facilitate entry of the virus to the cell and development of the disease for COPD patients [23, 24].

Differential diagnosis between exacerbations of COPD and COVID-19 may be difficult due to the similarity of the symptoms at the time of presentation. High fever, cough, and dyspnea are present in both of them. In the laboratory findings, a high level of D-dimer and fibrinogen is supportive of COVID-19 although they may be elevated in the patients with COPD due to several confounding factors such as co-morbidity and advanced age and these may not be helpful in the differential diagnosis. Imaging studies may be helpful in the differential diagnosis. Even though findings supportive of COVID-19 may facilitate diagnosis, alterations that may be present in the background of the lung in the COPD such as emphysema, bronchiectasis, peribronchial thickening may overlap with findings of COVID-19 and cause difficulties in diagnosis. At this point, comparative evaluations with the previous radiological examinations may be utilized.

The rate of development of severe disease with oxygen desaturation and rates of admission in the intensive care unit, intubation, and mortality in COVID-19 has been reported to be higher in the patients with COPD. This may be suggested to be related to structural parenchymal disorders of the lung and reduced respiratory function.

The measures that should be taken for patients with COPD are as follows:

- In addition to the rules of social distance and routine hygiene for being protected from the pandemic, extra measures should be taken for the patients with COPD not to encounter the virus. First of these should be delaying routine controls of the patients.
- Several studies exist indicating that the use of inhaler corticosteroids might cause an increased risk of pneumonia in COPD [25]. At the beginning of the pandemic, this was predicted to be an extra risk for COVID-19, and the opinion that using inhaler and steroid treatments will not be appropriate during the pandemic was proposed. However, the Global Initiative of COPD (GOLD) noted that the opinion that use of the inhaler and systemic steroids will not be appropriate during the pandemic of COVID-19 didn't have a scientific basis by publishing an interim report in 2020. It was reported that destabilizing COPD as a consequence of interrupting the treatment would be a higher risk for the patients. The recommendation of the patient with COPD during the pandemic would be continuing the current treatment exactly as usual. Even previously planned interruptions have been recommended to be delayed [26]. It has been recommended to wait until the efficacy of the pandemic will cease to switch the treatment. The main objective during the pandemic is to decrease hospital exposure of the patients by avoiding the exacerbations without destabilizing COPD.
- In the context of pulmonary rehabilitation with a multidisciplinary approach, the patients receive education on nutrition, psychosocial support, regulation of the daily life activities, and exercise. It is appropriate to incorporate a pulmonary rehabilitation support program to the medical treatment in the patients not receiving such supportive treatments because pulmonary rehabilitation will contribute positively to the respiratory reserve and thus, it will provide an advantage in the case of encountering COVID-19.
- Spirometric tests should be avoided in the patients presenting admitted to the hospital in the presence of attacks or symptoms. Assisting devices such as nebulizers, high-

flow oxygen, and non-invasive mechanic ventilators cause the spread of the aerosols and carry a high risk for contamination; their use should be limited as much as possible. In the case of using them for mandatory reasons, negative-pressure rooms should be preferred [27]. NICE guideline for the nebulizers states that the use of the nebulizer by the patients will not be an additional risk factor for contamination because the aerosol comes from the reservoir of the nebulizer and doesn't carry viral particles from the patient [26]. Nonetheless, it would be useful to limit their use as much as possible. Metered-dose inhalers should be preferred instead of nebulizer; spacer may be used. In the case of using nebulizer in the patients not being able to use metered-dose inhalers, the patient should be alone in the room and the room should be ventilated well after their use.

- If it is mandatory to provide non-invasive mechanical ventilator (NIMV) support in the case of problems of limited sources of intensive care bed and available invasive mechanical ventilator, it should be given with a full-face mask with Helmet mask to minimize the risk.
- The procedures should be avoided such as sputum induction and nasotracheal aspiration creating a high risk for contamination of COVID-19 because of the risk of development of aerosols in patients with COPD.

In conclusion, COPD is a risk factor for COVID-19. Risk in COPD, however, is lower compared to other chronic diseases related to other systems (i.e., diabetes mellitus, hypertension) although it is a chronic lung disease. The diagnostic process of the patients is of importance because of the similar clinical presentation of both conditions. As in other chronic diseases, the main objective in patients with COPD should be to protect the patient from the virus. For this purpose, the current treatment should be continued in the usual manner and the dose of the inhaler steroid shouldn't be reduced in order not to destabilize the treatment. Use of the nebulizers, high-flow oxygen, and NIMV should be avoided as much as possible.

COVID-19 PANDEMIC AND THE PATIENTS WITH INTERSTITIAL LUNG DISEASE

Interstitial lung diseases is a common name of diseases presenting with varying degrees of fibrosis, inflammation, and structural alterations in the lung parenchyma and affecting the lungs diffusely. The fact that immune-suppressive agents are usually used for their treatment is a facilitating factor for being contaminated with SARS-CoV-2. Additionally, destruction in the lung parenchyma and reduced respiratory reserve may also cause severe clinical presentation of COVID-19.

Both interstitial lung diseases and COVID-19 have similar clinical and radiological features. Clinically dyspnea, the non-productive cough may be present in both; the presence of fever, sore throat, anosmia and ageusia, muscle pain, and diarrhea should suggest a diagnosis of COVID-19. Radiologically, lesions of ground-glass density may be seen in both diseases. Comparing with the previous images is of importance in distinguishing the new appearing ground-glass lesions.

In COVID-19, apoptosis of the epithelial and endothelial cells occurs in the early periods along with rapid viral replication and increased pro- inflammatory/chemokine responses [28–30], followed by vascular leakage, edema, and uncontrolled inflammatory response [31–34]. In the later periods, these are followed by widespread lung damage, fibrosis in the interstitium and alveolar space, hyperplasia of the pneumocytes, and uncontrolled cellular proliferation. These alterations are accompanied by the abnormal immune response to the viral invasion and consequent imbalance in the increased production of cytokines. During this process, pulmonary epithelial cells and alveolar microvascular endothelial cells become the target organs attacked by the inflammatory mediators and lead to characteristic damage of ARDS.

Tissue injury on one hand and impaired remodeling on the other hand increase mortality. In the patients surviving ARDS develop pulmonary fibrosis. On the other hand, there is a possibility that pulmonary involvement of COVID-19 may heal with fibrotic scar tissue in the patients not developing ARDS. Thus, all patients with COVID-19 are a candidate for interstitial lung disease independent of the development of ARDS. Thus, preventing and treating pulmonary fibrosis may be one of the targets in treating COVID-19. Several options exist to resolve the cytokine storm and inflammatory factors including cytokine inhibiting agents, plasma replacement therapy, and blood/plasma filtration. The long-time effects of these medicines are not known yet.

Recommendations for patients with interstitial lung diseases are as follows [35]:

- First of all, the patients should take measures of using a mask, hygiene, and social distance for protection from the disease.
- Routine controls should be delayed during the pandemic and they should be instructed on that they shouldn't apply to the hospital if they don't have symptoms.
- Respiratory function tests should be avoided even though they are presented to the hospital with new symptoms.
- In addition to the medical treatment, the patients should be recommended pulmonary rehabilitation.
- Idiopathic pulmonary fibrosis (IPF) is an important group of interstitial lung diseases. Anti-fibrotic agents are used for their treatment. Using anti-fibrotic agents for IPF isn't an additional risk for COVID-19. Continuing to use the drugs should be recommended during the pandemic.
- In the case of making a diagnosis of COVID-19 in the patients with IPF using anti-fibrotic agents, the drugs may be discontinued for 4 to 8 weeks; in the case of discontinuation, however, the risk of exacerbation of IPF should be kept in mind and the decision should be tailored on an individual basis.
- Discontinuing medication in patients using immune suppressive therapy may exacerbate the findings of the present disease. There is no consensus on this topic.
- If a patient with interstitial lung disease is diagnosed as having COVID-19, immune suppressive therapy is discontinued during the active infection and then for 2 weeks following the recovery of the disease (or for a longer period if the patient can tolerate). Discontinuing the immune-suppressive treatment should be considered if COVID-19 is detected in patients with interstitial lung disease.

COVID-19 PANDEMIC AND THE PATIENTS WITH OBSTRUCTIVE SLEEP APNEA SYNDROME

OSAS is a condition characterized by a complete or partial obstruction of the upper airway during sleep. It manifests with apnea or hypopnea episodes followed by desaturation and subsequent arousals [36].

OSAS is usually accompanied by cardiovascular and metabolic conditions. Several factors including advanced age, male gender, obesity, hypertension, cardiovascular diseases, and diabetes mellitus make the high risk for both OSAS and COVID-19, increasing the frequency of development of COVID-19 in the patients with OSAS. COVID-19 presents mortality for the group of elderly patients with serious co-morbidities [37].

OSAS is one of the most common chronic respiratory diseases. The presence of quality sleep is of great importance to boosting immunity and for a healthy life. Treatment of patients with sleep apnea is much more important during the pandemic process because they have poor sleep unless they are treated. Thus, measures for the patients with OSAS gain extra importance during the pandemic.

OSAS and obesity have been suggested to worsen clinical course in the patients with coronavirus infection by increasing hypoxemia and cytokine storm.

The most effective therapeutic option for OSAS is PAP. Regularly and appropriately using the treatment during the pandemic is of great importance for quality sleep [38].

In contrast, another opinion exists advocating to discontinue PAP treatment during the pandemic. It suggests that treating the asymptomatic virus-carrying patients with OSAS with PAP at home may contaminate the virus to the household [39]. In this case, considering the risk-benefit ratio, it would be more appropriate to recommend the patients without diagnosis of COVID-19 to continue the treatment during the indeterminate pandemic period. If the patient having a diagnosis of COVID-19 is being followed at home, treatment may be interrupted for 2 weeks to protect the household again considering the risk-benefit ratio.

If the patient with a diagnosis of COVID-19 has been admitted to the hospital:

- It is recommended to discontinue the treatment until the attendant physician allows using PAP [38].
- If a PAP device will be used, it should be used in negative- pressure rooms, or if unavailable in the single rooms in which the health providers use full individual protective equipment [27].
- In the hospital, if the one-circuit device of the patients own will be used and the mask has an expiration valve, changing it with a mask without a valve and mounting a viral/bacterial filter will substantially reduce the risk of droplet contamination [40].

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Chapter 465

THE IMPACT OF THE COVID-19 PANDEMIC ON PATIENTS WITH CARDIOVASCULAR DISEASES

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ABSTRACT

Cardiovascular diseases are the leading cause of morbidity and mortality in the world, but with the Corona Virus Disease-2019 (COVID-19) pandemic emerging at the end of 2019, this issue has gained different importance. The presence of cardiovascular diseases leads to more severe COVID-19 infection and an increased mortality rate. On the other hand, COVID-19 itself causes myocardial damage and this contributes to morbidity and mortality. At the beginning of the pandemic, there was a concern that angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) would up-regulate the ACE2 receptor at the tissue level, increasing viral binding and facilitating the infection. With the current studies, this opinion has lost the influence and it was decided not to change the treatment of patients using ACE inhibitors or ARBs. Another important point is that patients with cardiovascular diseases are now far from the healthcare they could receive before as both pre-hospital and hospital health care is directed towards the COVID-19 pandemic. Considering that the epidemic will not disappear rapidly, a different arrangement may be planned in healthcare services.

Keywords: cardiovascular disease, COVID-19, coronavirus

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INTRODUCTION

The disease caused by “Severe Acute Respiratory Syndrome-Coronavirus-2” (SARS-CoV-2), which is accepted as a global pandemic by the World Health Organisation (WHO), has been named Corona Virus Disease-2019 (COVID-19) [1, 2]. By September 2020, COVID-19 infection affected more than thirty million people and caused nearly one million deaths. SARS-CoV-2 is a highly contagious virus and spreads mainly through droplets and direct contact. The average incubation period is 5.5 days but extension up to 14 days is known [3]. In symptomatic cases, the most common symptoms are fever, fatigue, muscle pain, sore throat, and dry cough, less frequently nausea-vomiting, and diarrhea [4]. It is important not to forget the atypical presentations including delirium, hypothermia, and abdominal pain, especially in elderly patients [5].

SARS-CoV-2 is genetically 79% similar to the SARS-CoV that caused the SARS epidemic between 2002 - 2003 and 96% similar to coronaviruses in bats. The main feature of SARS-CoV-2, thought to be formed as a result of a new mutation, is that the virus causes infection by binding to the human angiotensin converting enzyme 2 (ACE2) receptor, after activation of its spike (S) protein by the transmembrane protease serine 2 enzyme [6]. ACE2 is expressed in the lung, particularly in type 2 alveolar cells, and it appears to be the main gateway for the virus [7]. By this way, it causes lung damage. In addition to the lungs, ACE2 is also expressed in the myocardium, oesophagus and intestinal epithelium, vascular endothelium, bladder urothelial cells, and kidney proximal tubule. So, this is already shown as the reason for the course of Covid-19 infection towards multiorgan failure [8].

COVID-19 infection is much more aggressive and fatal in patients with comorbidities and the geriatric population. Studies show that advanced age is the most important determinant for mortality [9]. Epidemiological data reveal that the risk of death is significantly increased in people over 80 years of age compared to young people [10, 11]. At the same time, the frequency of cardiovascular disease (CVD) is also high in people who die due to COVID-19. In an epidemiological study involving 72.314 patients in China, 22.7% of fatal cases had a history of CVD [12]. In a study including seven hospitals in Spain and comparing 1139 COVID-19 positive patients with 11.390 healthy people, it was found that the CVD (odds ratio, OR, 1.98) and CVD risk factors (OR, 1.46) and comorbid diseases such as hypertension (HT) (OR, 1.27), chronic obstructive pulmonary disease (COPD) (OR, 1.35), diabetes mellitus (DM) (OR, 1.5) and heart failure (HF) (OR, 2.18) are more common in COVID-19 positive patients than in healthy control group [13]. Similarly, with the information we have obtained from “Severe Acute Respiratory Syndrome” (SARS) and “Middle East Respiratory Syndrome” (MERS) infections, the mortality rate is higher in patients with cardiovascular diseases. The prevalence of DM and CVD in SARS was determined to be 11% and 8% respectively, and the presence of these two comorbidities has been shown to increase the risk of death 12 times [14, 15]. In MERS, DM and HT were seen in approximately 50% of the cases, and CVD were seen in approximately 30% of the cases [5]. As a result, the most affected group and the group with the highest mortality rate are the elderly with cardiovascular diseases.

As the symptoms and signs of the disease were recognized, the importance of cardiovascular damage was understood and it attracted more attention [16]. COVID-19 affects the cardiovascular system in many ways. It increases morbidity and aggravates

myocardial damage and dysfunction in patients with accompanying cardiovascular diseases. The virus can affect the cardiovascular system and heart direct and/or indirect ways. Hemodynamic compromise, hypoxemia, inflammatory myocarditis, stress cardiomyopathy, microvascular dysfunction, or thrombosis due to hypercoagulability and systemic inflammation may impair the stabilization of coronary artery plaques [17]. In severe COVID-19 infection, the risk of type 2 myocardial infarction (MI) may increase by the need for increased cardiac output with hypoxia due to lung disease. Although the data on Covid-19 are still insufficient, studies are showing that pneumonia and influenza infection increase acute MI 6 times [18, 19].

HYPERTENSION

Considering that there are approximately 1.5 billion hypertensive patients in the world, it is not surprising that HT was the first co-morbid disease to be noted in articles on COVID-19 infection [17]. In a study conducted in the United States of America (USA), while 89.3% of 1482 patients hospitalized due to COVID-19 had at least one chronic disease, HT was the most common one with a frequency of 49.7% [20]. In the meta-analysis of four case-control studies including 1352 patients, HT was found to be the most common comorbidity and it was reported that the risk of the need for intensive care unit (OR, 2.54) increased in cases accompanied by HT [21]. In a retrospective cohort study in which acute respiratory distress syndrome (ARDS) and risk of death were analyzed in 201 COVID-19 positive patients, HT was found in 27.4% of patients who developed ARDS, while this rate was found as 13.7% in those who did not develop ARDS; however, a statistically significant difference could not be demonstrated [22]. In a multi-center study examining the impact of chronic diseases in 1590 COVID-19 positive patients in China, mortality was found higher in patients with HT (10.4%) compared to those without HT (1.7%) [23]. It has been demonstrated in many observational studies originating from China that mortality and morbidity increase in COVID-19 positive patients with HT [24, 25]. In the data from China and Italy, it has been shown that hypertensive patients constitute approximately 70% of the population, and progression to ARDS is significantly higher in patients with HT [26].

These have led to the discussions that the antihypertensive drugs that are effective through ACE, the cell entry protein of the virus, and increasing ACE2 [angiotensin 1 receptor blockade (ARB) and ACE inhibitors] may play a role in the pathogenesis of COVID-19 infection. However, these studies did not investigate the relationship between HT and mortality-morbidity in age-adjusted regression models. In addition, in these studies, HT is highly variable and mostly defined as being on antihypertensive treatment. Drug compliance and blood pressure control parameters were not mentioned.

The SARS-CoV-2 spike (S) protein uses the ACE2 receptor to enter the host cell, as in SARS and MERS [6]. The S protein binds to the catalytic domain of ACE2 with high affinity. The binding of the S protein to ACE2 triggers a conformational change in the S protein of the coronavirus and in this way, viral RNA enters the cell and infects the cell [27]. The concern that the treatment with ACE inhibitors or ARBs will increase viral binding and infection by causing tissue-level up-regulation of the ACE2 receptor in HT patients is the basis of the controversy [28]. Studies are showing increased ACE2 mRNA expression in the left ventricle

of normotensive Lewis rats and enalapril in rat heart tissue after treatment with Lisinopril and Losartan [29, 30]. Ishiyama et al. reported the increase of ACE2 mRNA levels in the coronary endothelium after the treatment with ARBs in their study with coronary artery ligation [31]. On the other hand, there are also experimental studies that have not shown a similar effect. In a study, after coronary artery ligation and treatment with ramipril, no increase in ACE2 mRNA compared to control was shown [32].

Also, Burchill et al. observed no increase in ACE2 protein in rat coronary endothelium after coronary artery ligation and treatment with valsartan, ramipril, or both [33]. The human studies showing ACE2 up-regulation with the renin-angiotensin aldosterone system (RAAS) are highly contradictory. In the study of Walters et al., no association was found in plasma ACE2 levels with the use of ACE inhibitors or ARBs [34]. Furuhashi et al. showed increased urinary ACE2 levels in patients with HT after using Olmesartan [35].

As can be seen from the current literature, the ACE2 receptor up-regulation hypothesis with RAAS blockers is based only on limited in-vitro and in-vivo animal experiments, and the studies in which this hypothesis cannot be demonstrated in humans and animals are also available in the literature.

In none of the accessible studies, there is no data on ACE2 up-regulation in respiratory epithelium and type 2 pneumocytes, the entrance gate used by SARS-CoV2 to infect the body. On the other hand, it has been shown in animal experiments that ACE2 transforms angiotensin 2 to angiotensin 1 - 7, and this vasodilatory effect occurring in this way can reduce lung damage in viral pneumonia [24]. Similarly, it has been suggested that ACE2, which is down-regulated by the SARS-CoV-2 surface spike protein, can be increased by RAAS blockade, thus antagonizing the effects of SARS-CoV-2 [36]. The guideline published by the American Heart Association and the American College of Cardiology (AHA/ACC) recommends the continuation of RAAS antagonists, which have proven useful in diseases such as heart failure, ischaemic heart disease, and HT, in COVID-19 patients [37]. In a study including seven hospitals in Spain, it was shown that there was no increase in the risk of hospitalization due to COVID-19 in patients using RAAS inhibitors, and there was no significant difference between long and short-term drugs use. One of the important findings of this study is that DM patients using RAAS inhibitors have a lower risk of hospitalization due to COVID-19 (OR 0.53, $p = 0.004$) [13].

Roffi et al. suggested that ARBs may be protective for COVID-19 depending on their mechanism of action [38]. However, since there is not enough evidence to support these hypotheses, it is not appropriate to use ACE inhibitors and ARBs as a potential treatment for COVID-19. As a result, if there is no contraindication such as hypotension or acute kidney damage, patients using ACE inhibitors or ARBs should continue their medication during COVID-19 infection.

CORONARY ARTERY DISEASE

It is known that the prevalence of coronary artery disease (CAD) among cardiovascular diseases varies depending on the society. For this reason, there are significant differences in the frequency of CAD among patients diagnosed with COVID-19. The studies about COVID-19 have also reported a wide range from 4.2 to 25% for CAD [39, 40]. These numbers are

much higher when considering patients treated in intensive care units [40]. In a large series of 72,314 people in China, the death rate was 2.3%, while the mortality rate over 80 years old was 14.8%. While 4.2% of all patients had a history of CAD, 22.7% of those who died had CAD [41].

ACE2, the cell-entry receptor of SARS-CoV-2, is also found in endothelial cells. Whether the vascular irregularities in COVID-19 infection are caused by the endothelial cell involvement of the virus or not is currently unclear but SARS-CoV-2 has been shown to infect human blood vessel organoids in-vitro [42]. Varga et al. demonstrated viral inclusion patterns in endothelial cells in an autopsy analysis of a 71-year-old male patient who died of COVID-19 and had CAD, HT, and kidney transplant, the recipient. This way, they found evidence of direct virus infection and widespread endothelial inflammation in the endothelial cell [43]. The vascular endothelium is an active paracrine, endocrine, and autocrine organ indispensable for regulating vascular tone and maintaining vascular homeostasis. Endothelial dysfunction is the main determinant of microvascular dysfunction by shifting the vascular balance to more vasoconstriction with organ ischemia, inflammation, and a pro-clotting state [44]. Thus, interest in treatments for stabilizing the endothelium has increased. Statins commonly used in the treatment of CAD are inhibitors of the inflammatory pathway MYD88 and have been shown to stabilize MYD88 at in-vitro and animal studies [43]. The instability of MYD88 has been associated with negative consequences in SARS-COV and MERS-COV infections, but this relationship has not been identified with SAR-COV-2. Statins may be useful in treating COVID-19 infection, but further studies are needed for a recommendation. It is also important for the patient to use statin therapy regularly, as COVID-19 is also a risk factor for acute cardiac damage.

Continuation of the drugs used in the routine treatment of CAD has been recommended as it is recommended in hypertensive patients. None of the medications we use in treatment such as acetylsalicylic acid, beta-blockers, statins, and nitrate have been associated with poor results in the management of COVID-19 infection.

Pulmonary involvement of COVID-19 infection can cause arterial hypoxia and acidosis, and this can result in myocardial dysfunction. Although there are no cardiac complaints due to myocardial damage and microvascular deterioration, an increase in cardiac biomarkers (troponin and natriuretic peptide) and nonspecific ECG changes can be observed [43]. Studies showing the SARS-CoV2 primarily attacking pericytes in the heart may explain the capillary endothelial cell dysfunction and an increase in cardiac damage markers [45]. COVID-19 infection may also be present with type 1 and type 2 myocardial infarction (MI) as a result of respiratory failure and exposure to hypoxia, especially in elderly patients, or COVID-19 may be tested positive in the course of MI.

It should be kept in mind that the patient considered to have the acute coronary syndrome in clinical and laboratory terms, should be questioned in terms of COVID-19 and tested for SARS-CoV2. When the intervention is to be performed, the patients are accepted as positive only if there is a suspicious contact history. Percutaneous coronary intervention may be preferred instead of coronary artery bypass graft surgery in suitable patients for revascularisation to reduce exposure. In addition, in low-risk ST-segment elevation myocardial infarction (STEMI), thrombolytic therapy can be considered instead of the invasive procedure [45]. A separate catheter laboratory for COVID-19 patients can also be beneficial for both the patient and the healthcare team.

COVID-19 can cause MI, myocarditis, or arrhythmia directly and indirectly. In addition, hydroxychloroquine and chloroquine used in the treatment of COVID-19 infection may cause prolongation of the QT distance, development of the atrioventricular block, sick sinus syndrome, and bundle branch block by making sodium/potassium/calcium channel blockade. Hydroxychloroquine and chloroquine are widely used in the world due to their antiviral activity as well as their anti-inflammatory activity, but there are some points to be careful about when using these drugs. These agents are relatively well tolerated but may cause rare and serious side effects (<10%) such as heart conduction system, hypoglycemia, neuropsychiatric effects, and retinopathy.

Monitoring the patient by electrocardiography is recommended especially in critically ill patients and in patients receiving concomitant agents that prolong the QT interval (such as macrolides, fluoroquinolones, amiodarone). Efficiency and side effects will be revealed better as the studies continue.

As the health system is overburdened due to the COVID-19 pandemic, neglecting the patients with CAD is a serious problem. In Hong Kong, Tam et al. showed that the rate of care for STEMI cases was seriously affected after COVID-19. In Hong Kong, the time for the ambulance to reach the patient after the call has increased from 80-90 minutes to 318 minutes on average [46].

In a study from Italy, they found that there was a 48.4% total decrease in STEMI and Non-ST segment elevation myocardial infarction (NSTEMI) cases taken to the catheter laboratory during the COVID-19 pandemic, a decrease of 26.5% in STEMIs and a 65% decrease in NSTEMIs compared to the same period of the previous year ($p < 0.001$). The mortality rate of STEMI increased significantly with the pandemic compared to the previous year (risk ratio (RR) = 3.3; $p < 0.001$) and there was a significant increase in complications (RR = 1.8; $p = 0.009$). This situation is a serious alarm finding for public health and should be emphasized [47]. The reasons for this situation can be caused by the patient or the healthcare system.

The most important reasons arising from the patient could be considered as disruptions in drug usage and health control, delaying hospitalization due to the fear of the virus.

Considering the reasons caused by the healthcare system, the home care system is not adequately provided, and a safe intervention system cannot be organized.

HEART FAILURE

Heart failure (HF) can be triggered by COVID-19 infection in patients with previously known or undiagnosed HF. In addition to the infection increases the workload of the heart, acute myocardial damage may develop due to events such as acute MI, stress cardiomyopathy, cytokine storm, and this way, heart failure may develop or the existing disease may be decompensated. It is not clear whether the underlying heart failure is exacerbated or a de novo HF is developing in COVID-19 positive patients [48]. In the study of Zhou et al., they retrospectively evaluated the patients presenting with COVID-19 and found that although HF was observed in 23% of the patients during the follow-up, HF ratio among people lost was 52% [49]. In a study where 799 patients in Wuhan were screened, heart failure was found in 49% of the patients who died and 3% of those who recovered [50].

In patients infected with COVID-19, the clinical picture is usually in the form of acute respiratory failure and may progress to ARDS with a ground-glass opacity in imaging. This clinical presentation is not much different from patients admitted to the hospital with acute HF [51]. Therefore, in patients presenting with acute pulmonary edema, heart-related causes alone, or mixed causes related to COVID-19 infection should also be considered. For differential diagnosis, bilateral multilobar ground-glass opacification with peripheral or posterior distribution mainly in the lower lobes is typical for COVID-19 infection in computed tomography of the chest. Atypical views such as superposed consolidated areas on ground-glass opacity can be seen in the elderly population. Findings starting from a single focus and progressing to bilateral lung involvement are in favor of infection. The use of cardiac biomarkers and, more often, echocardiography are effective in differentiating the clinical picture of infection and heart failure [52].

We do not have any conclusive evidence that will require the cessation of treatments that have proven effects on mortality such as ACE inhibitor, ARB, angiotensin receptor blocker-neprilysin inhibitor (ARNI), and mineralocorticoid receptor antagonist (MRA). In the treatment of HF, drug changes and discontinuation of drugs are not recommended, as in HT and CAD.

CONCLUSION

As a result, the group most affected by the epidemic and having the highest mortality rate are the elderly with known cardiovascular diseases. In the guideline published by the AHA/ACC, they recommended the continuation of RAAS antagonists proven to be beneficial in diseases such as heart failure, ischaemic heart disease, and hypertension in COVID-19 patients. As the health system is overburdened due to the increase in COVID-19 cases during the pandemic process, it resulted in ignoring the patients with CAD, and thus the death rate of patients with CAD during the pandemic process has increased and this is a serious problem.

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Chapter 466

THE IMPACT OF THE COVID-19 PANDEMIC ON CANCER PATIENTS

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ABSTRACT

COVID-19 infection in patients with cancer is associated with a significantly increased risk of case fatality. Strategies to reduce the likelihood of infection and improve early identification in this immunocompromised patient population is crucial. Clinicians must balance the risks of delaying cancer treatments versus the risks for SARS-CoV-2 exposure and the potential increased adverse outcomes of COVID-19 infection in cancer patients. Physical distancing rules and contact limitations should be essential components of cancer care delivery. Mortality from COVID-19 in cancer patients appears to be principally driven by age, gender, and comorbidities such as diabetes and obesity. Likelihood of severe illness from COVID-19 is higher among patients with lung cancer and hematologic malignancies. There is no identified evidence that cancer patients on cytotoxic chemotherapy or other anticancer treatment are at an increased risk of mortality from COVID-19 disease compared with those not on active treatment. Anti-CD20 monoclonal antibodies causing B cell depletion and lymphopenia may contribute to the severity of COVID-19 infection. Treatment with immune checkpoint inhibitors may have the potential to alleviate inflammation in COVID-19 infection. In retrospective cohort studies there are conflicting results but there is no clear data for increasing the severity of the infection. The management of COVID-19 infection in cancer patients is generally the same as in the general population. Mild cases and asymptomatic infections can be managed conservatively at home. Agents used specifically for COVID-19 are reserved for patients with severe disease. Clinicians delivering cancer care should have discussions with their patients about goals of care and future care planning's.

Keywords: COVID-19, cancer patient, lung cancer, cancer treatment

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INTRODUCTION

COVID-19 pandemic has a tremendous effect on daily life, economic conditions, and the health care system all over the world. This impact of the pandemic on health care of cancer patients is also very challenging because of the competitive risks of death from cancer versus death from infection, and the higher lethality of SARS-CoV-2 infection in immunocompromised hosts.

Cancer patients are more prone to infections because of their immunosuppressive state resulting from their malignancy and anti-cancer treatments. Delaying cancer treatments should be balanced with SARS-Cov-2 exposure and the increased risk of severe infection in an immunocompromised group of patients.

A survey study involving health care representatives from the international oncology community from 18 countries presented by Jerusalem et al. At the European Society for Medical Oncology (ESMO) Congress 2020, highlighted the extent to which COVID-19 has challenged the organization and delivery of cancer care. Overall, 60.9% reported that clinical activity was reduced at the peak of the pandemic, while nearly two-thirds (64.2%) cited undertreatment as a major concern, and 37% expected to see significant reductions in a clinical trial data. Cancer treatments canceled or delayed were surgery (in 44.1% of centers), chemotherapy (25.7%), and radiotherapy (13.7%). Earlier cessation of palliative care was observed in 32.1% of centers. Thirty-four percent of respondents reported that surgery was the treatment modality that was most affected by the pandemic, followed by chemotherapy (22.0%), radiotherapy (13.7%), checkpoint inhibitor therapy (9.1%), monoclonal antibodies (9.0%), and oral targeted therapy (3.7%) Increased use of granulocyte colony-stimulating factor in 34.8% and a decreased corticosteroid use in 21.9% was observed. Telemedicine, or teleconsultations were reportedly performed for 94.5% of follow-up visits. Also, approximately 82% of participants projected that they would continue with the use of telemedicine more frequently in their practices after the pandemic [1].

INCIDENCE OF COVID 19 INFECTION IN CANCER PATIENTS

Though most data suggest a higher incidence of COVID-19 infection in cancer patients when compared to the general population, there are conflicting results. Chinese reports the incidence of COVID infection to be 1% in cancer patients; a higher ratio when compared with 0.29% of infection rate in the general population [2].

A study of 1069 cancer patients in Madrid, Spain the incidence of COVID-19 infection was found to be 4.2% much higher than 0.62% incidence of the city population but an Austrian study found a similar and even lower incidence of SARS-Cov-2 infection in cancer patients compared to the general population [3, 4].

CLINICAL OUTCOMES OF COVID-19 INFECTION IN CANCER PATIENTS

The clinical presentation and outcome of COVID-19 infection in cancer patients can be heterogeneous. Some meta-analysis suggests that severe and lethal COVID-19 infection rate is higher in cancer patients particularly with hematological malignancies, lung cancer, metastatic disease, and in older patients having comorbidities including obesity. [5].

A meta-analysis including 32 international studies from Europe, Asia and the United States for a total of 46499 patients including 1776 cancer patients showed that cause mortality rates were found to be higher in cancer patients (RR, 1.66; 95% CI, 1.33 to 2.07; $P < .0001$); However, in a prespecified subgroup analysis of patients > 65 years of age, all-cause mortality was comparable between those with versus without cancer (RR, 1.06; 95% CI, 0.79 to 1.41; $P = .71$); and the intensive care unit (ICU) admission was also more likely in patients with cancer (26 studies, 15,375 patients; RR 1.56, 95% CI 1.31-1.87). The authors concluded that cancer is associated with worse clinical outcomes among patients with COVID-19. However, elderly patients with cancer may not be at increased risk of death when infected with COVID-19 [6].

In Spain, a hospital-based study showed that the fatality rate was 9.8 % in Covid-19 infected patients however, the mortality rate in cancer patients was 42.2% ($p = 0.0001$) [7].

In a study conducted in New York City Hospital, a total of 218 COVID-19-positive patients from a malignant diagnosis were identified. A total of 61 (28%) patients with cancer died from COVID-19 with a case fatality rate (CFR) of 37% (20/54) for hematologic malignancies and 25% (41/164) for solid malignancies. Six of 11 (55%) patients with lung cancer died from COVID-19 disease. Increased mortality was significantly associated with older age, multiple comorbidities, need for ICU support, and elevated levels of D-dimer, lactate dehydrogenase, and lactate in multivariate analysis. Age-adjusted CFRs in patients with cancer compared with noncancer patients reported a significant increase in case of fatality for patients with cancer. The authors suggest the need for proactive strategies to reduce the likelihood of infection and improve early identification of Covid-19 infection in vulnerable cancer patient population. It remains uncertain if cancer patients other than those with hematologic malignancies or lung cancer are at increased risk of severe outcomes from COVID-19 when the analysis is controlled for age, the mortality/morbidity associated with their cancer, and other comorbidities [8].

Lung cancer is a leading cause of cancer related mortality but also case fatality rates from COVID-19 infection are high in patients with lung cancer. One of the challenging issues in delivering cancer care for patients with lung cancer is that discrimination of clinical symptoms and radiological findings from COVID-19 infection, lung cancer involvement, and progression or other infective conditions can sometimes be very difficult. This difficulty may render the clinicians from delivering the optimal treatment. The Thoracic Cancers International COVID-19 Collaboration (TERAVOLT) registry is a multi-centre observational study composed of a cross-sectional component and a longitudinal cohort component 200 patients with COVID-19 and thoracic cancers from eight countries were identified and included in the TERAVOLT registry. 152 (76%) patients were hospitalized and 66 (33%) died. 13 (10%) of 134 patients who met the criteria for ICU admission were admitted to ICU; the remaining 121 were hospitalized, but were not admitted to ICU Univariable analyses

revealed that being older than 65 years (OR 1.88, 95%CI 1.00–3.62), being a current or former smoker (4.24, 1.70–12.95), receiving treatment with chemotherapy alone (2.54, 1.09–6.11), and the presence of any comorbidities (2.65, 1.09–7.46) were associated with increased risk of death. However, in multivariable analysis, only smoking history (OR 3.18, 95% CI 1.11–9.06) was associated with an increased risk of death [9].

THE EFFECT OF CANCER TREATMENT ON COVID-19 INFECTION

The international COVID-19 and Cancer Consortium registry including 928 cancer patients from the United States, Canada, and Spain with confirmed SARS-CoV-2 infection over one month (The most prevalent malignancies were breast (21%) and prostate cancer (16%) percent); 43 percent had active cancer and 39 percent had received chemotherapy treatment within four weeks of virus diagnosis. The use of any form of anticancer therapy (cytotoxic or noncytotoxic) within four weeks of infection was *not* associated with higher 30-day mortality rates. In multivariate analysis, independent factors associated with greater 30-day mortality included older age, male sex, former smoker, two or more comorbidities, Eastern Cooperative Oncology Group (ECOG) performance status of 2 or worse and active cancer (versus those in remission; OR 5.2, 95% CI 2.77–9.77) [10].

Cancer, patients who are receiving systemic anticancer treatments, have been postulated to be at increased risk of mortality from COVID-19 infection. In the UK Coronavirus Cancer Monitoring Project (UKCCMP), a study including 800 cancer patients with COVID-19 infection, 52 percent of patients had a mild COVID-19 disease course while 28% of patients died. After adjusting for age, gender, and comorbidities, chemotherapy and other forms of cancer treatments such as immunotherapy, hormonal and targeted therapies and radiotherapy in the past 4 weeks had no significant effect on mortality from COVID-19 disease [11].

Immunotherapy in the form of Immune Check Point Inhibitors (ICI) is being used in cancer therapy especially in metastatic lung cancer patients in recent years. The answer to the question of whether programmed death 1 (PD-1) blockade therapy which has an immunostimulating effect can alleviate the severity of disease from COVID-19 in patients with cancer is not clear. A study in New York State Memorial Sloan Kettering Cancer Center; 423 cases of symptomatic COVID-19 were diagnosed (from a total of 2,035 patients with cancer tested). Hospitalization rate was, 40% in the patient group, and 20% developed a severe respiratory illness and 12% died within 30 days. Age older than 65 years and treatment with ICIs were predictors for hospitalization and severe disease, whereas receipt of chemotherapy and major surgery was not [12].

A retrospective study of a single-center 69 patients with lung cancer who were diagnosed with COVID-19 examined the severity of the infection based on no or prior receipt of PD-1 blockade. Overall, the severity of COVID-19 in patients with lung cancer was found to be high, including the need for hospitalization in more than half of patients and death in nearly a quarter. After adjustment for smoking status, PD-1 blockade exposure was not found to be associated with an increased risk of severity of COVID-19 [13].

TESTING FOR COVID 19 IN CANCER PATIENTS

Patients with cancer *with* symptoms concerning for COVID-19 (e. g., fever, cough, dyspnea, hypoxia), *or* those with exposure to someone with COVID-19, should be offered to test. Alternative causes for their symptoms (eg, influenza, bacterial pneumonia, cancer progression, treatment-related side effects) must also be considered. For patients with cancer *without* symptoms of COVID-19, guidance regarding SARS-CoV-2 testing is evolving, and the approach among is variable. Given the risk of transmission from asymptomatic carriers, some institutions are routinely testing all cancer patients before immunosuppressive therapies, as long as testing capacity is not limited. However, this is not a widespread practice and it is not supported by guidelines from the *American Cancer Society* and *ASCO*. On the other hand, this policy is supported by updated guidelines from the *Infectious Disease Society of America*, which now recommends SARS-CoV-2 RNA testing in asymptomatic individuals before immunosuppressive procedures, regardless of known exposure to COVID-19. According to these guidelines, immunosuppressive procedures are defined as cytotoxic chemotherapy, solid organ or stem cell transplantation, long-acting biologic therapy, cellular immunotherapy, or high-dose corticosteroids [14-15].

Unnecessary testing could lead to a delay in the administration of antineoplastic therapy and additionally could increase the risk of exposure to COVID-19. SARS-CoV-2 RNA can be detected for several weeks after initial infection but does not distinguish between active and resolved infection. In patients with mild to moderate illness, replicating the virus cannot be detected after the first testing for the asymptomatic patient without a history of COVID-19. The task force recommended that only patients with hematologic malignancies should be tested for COVID-19 RNA before the initiation of outpatient antineoplastic [16].

Resuming antineoplastic treatment therapy in a patient who previously tested positive for COVID-19 or who has had presumed recent COVID-19 infection. The task force recommended that in a previously symptomatic patient with COVID-19, resumption of antineoplastic therapy be considered when COVID-related fevers have resolved for at least 7 days without the use of fever-reducing medications, there has been a substantial improvement in respiratory symptoms, and at least 14 days have elapsed since the onset of symptoms and/or initial positive COVID-19 test, whichever came earlier. Repeat COVID-19 RNA testing is not recommended. In a previously asymptomatic patient with COVID-19, resumption of antineoplastic therapy can be considered when at least 14 days have elapsed since the initial positive COVID-19 test and no symptoms have developed during this time. [16].

The task force recognized that certain patients may require additional time to recover before resumption of antineoplastic treatment. These include patients who experienced more severe symptoms due to COVID-19 (i.e., required hospitalization and/or supplemental oxygen), older patients, and patients with certain malignancies, such as lung cancer, hematologic malignancies [16].

COVID-19 testing is not recommended for most asymptomatic cancer outpatients, and antineoplastic treatment can be resumed after the resolution of fever or the passage of time in patients who have tested positive, according to an expert task force. Clinicians must weigh the benefits of initiating or resuming antineoplastic therapy against the risk of worsening outcomes related to COVID-19 [16].

SARS-CoV-2 RNA testing of asymptomatic patients without a history of COVID-19 only for those with hematologic malignancies before the initiation of outpatient antineoplastic therapy. For patients with solid tumors, including lung cancer, routine pretreatment SARS-CoV-2 RNA testing was not recommended, according to the online report in the Journal of the National Cancer Institute [16].

Previously symptomatic patients with COVID-19 can resume antineoplastic therapy when COVID-19-related fevers have resolved for at least 7 days without use of fever-reducing medications, there has been a substantial improvement in respiratory symptoms, and at least 14 days have elapsed since the onset of symptoms and/or initial positive SARS-CoV-2 test, whichever came earlier [16].

In previously asymptomatic patients who tested positive for SARS-CoV-2, resumption of antineoplastic therapy can be considered when at least 14 days have elapsed since the initial positive test if no symptoms have emerged during this time. Patients who experienced more severe symptoms due to COVID-19, older patients, and patients with certain malignancies (lung cancer and hematologic malignancies, for example) might require additional time to recover before resumption of antineoplastic treatment [16].

Other institutions leave the decision to individual clinician's judgment as to the immunosuppressive potential of the specific regimen. At some institutions, testing of asymptomatic outpatients before initiating anticancer treatment is limited to those with hematologic malignancies especially for patients with a B-cell hematologic malignancy who are receiving anti-CD20 monoclonal antibodies, which are associated with B-cell depletion, and severe lymphopenia. At many institutions, testing is offered to lung cancer patients who present for surgery, bronchoscopy, or high-risk outpatient testing (eg, pulmonary function tests), as well as to those who are symptomatic or potentially exposed to a virus carrier, but not to others [16, 17, 18].

TREATMENT OF COVID-19 INFECTION IN CANCER PATIENTS

All patients should be informed regarding the symptoms of COVID-19, trained in proper handwashing and hygiene, and advised to wear facial masks in public and minimize exposure to large crowds [14].

COVID-19 disease management is the same in cancer patients as in the general population. Many mild cases (e.g., fever, cough, and/or myalgias without dyspnea or hypoxia) and asymptomatic infections can be managed conservatively at home if individuals can be adequately isolated. However, patients with more severe disease may warrant a higher level of care. Agents used specifically for COVID-19 are reserved for patients with severe disease [19].

One area of the potential impact of specific COVID-19 treatments is in cancer patients who have been receiving anti-CD20 therapies, which induce rapid and prolonged B cell depletion. In a case report of a patient with persistent viremia from SARS-CoV-2 who had received rituximab for lymphoma, convalescent plasma resulted in rapid recovery [20].

Another issue is drug interactions between COVID-19 therapies and anticancer agents. The French Society for Oncology Pharmacy has published detailed information about these

potential interactions that may be of value in decision-making around the choice of both anti-COVID and anticancer therapy [21].

ASCO recommends that until more definitive information emerges, decisions about interrupting anticancer treatment in patients with active COVID-19 should be based on a clinical benefit: risk assessment that considers the risk of interrupting cancer treatment versus the still poorly defined risk of adverse COVID-19 outcomes in patients receiving active cancer treatment [14].

Although data are very limited, one small study and at least two case reports have suggested that the use of Bruton tyrosine kinase (BTK) inhibitors for patients with a chronic hematologic malignancy may be associated with less severe infection [22, 23].

Glucocorticoids may be beneficial for patients who are hospitalized with severe SARS-CoV-2 infection. In other situations, for patients who are receiving glucocorticoids for management of their cancer or treatment-associated toxicities, the decision as to whether to continue or discontinue in a patient diagnosed with COVID-19 must be individualized, and depends in part on the dose and indication for the glucocorticoid. As an example, decision-making for high-dose glucocorticoids in a patient with brain metastases or epidural spinal cord compression, or a serious immunotherapy-related adverse event, is more difficult and must be addressed on a case-by-case basis [24].

Some oral none immunosuppressive therapies such as hormonal therapies, including androgen deprivation therapy or drugs targeting activating mutations (epidermal growth factor receptor inhibitors or BRAF/MEK inhibitors) may be continued on a case-by-case basis [14].

According to ASCO guidelines, cancer therapy can be reinitiated if at least 24 hours have passed since the resolution of fever without the use of antipyretics, and there is an improvement in symptoms (eg, cough, shortness of breath). For asymptomatic patients, waiting at least 20 days after the initial positive test is recommended. For most patients, obtaining at least one negative SARS-CoV-2 test before reinitiating anticancer therapy is preferred [14].

Cancer patients who have a persistently positive test, despite symptom resolution should avoid treatment in the same infusion room with other uninfected cancer patients receiving chemotherapy until they convert to a negative test. ASCO guidelines suggest that specific areas and dedicated staff be designated for treatment of COVID-19-positive patients. Physical distancing rules and contact limitations remain essential components of cancer treatments amid the pandemic to protect the patient, the health care workers, and other non-COVID-19 patients being treated in the same center [14].

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Chapter 467

COVID-19 FROM GENERAL SURGERY PERSPECTIVE

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ABSTRACT

With the rapid incline of Coronavirus Disease 2019 (COVID-19) cases, healthcare staff was urged to get organized for this new period. While preserving personal protective equipment, general ward beds, and intensive care unit beds physicians face difficulties. Getting infected for surgical teams mean additional workload for the remaining staff and in some cases, loss of the senior surgeon. Only emergent surgical cases are suggested to be performed to keep the healthcare staff ready and healthy for further months. Surgical staff should be minimized and personal protective equipment should be provided for hospital staff. Basic knowledge of COVID-19, action plans, algorithms for emergency and elective surgeries are necessary for surgical teams.

Keywords: surgery, COVID-19, personal protective equipment

INTRODUCTION

In Wuhan, China, pneumonia cases with unknown cause occurred in December 2019 [1]. Then it was discovered that this pneumonia is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease spread throughout the world and on March 11, 2020, World Health Organisation declared pandemic and the disease was started to be called as Coronavirus Disease 2019 (COVID-19) [2].

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DIAGNOSIS

In patients with COVID-19 diagnosis; fever, dyspnea, fatigue, and muscle pain are the most common symptoms encountered [3]. Also nearly half of the infected patients remain asymptomatic. The diagnosis is confirmed by the real-time reverse transcription-polymerase chain reaction of viral nucleic acid [4]. In the laboratory evaluation; elevated D-Dimer, ferritin, alanine aminotransferase, aspartate aminotransferase, creatine kinase, lactate dehydrogenase, leukopenia, and lymphopenia are detected [5]. Radiologically, multiple ground-glass appearance and bilateral opacities, infiltrates are reported in chest X-rays. It should be kept in mind that patients with normal X-rays can also be diagnosed with COVID-19. In patients with suspected clinical, laboratory, and X-ray findings, chest computed tomography (CT) is the next step for diagnosis. Ground glass opacities and parenchymal consolidation are some characteristic findings in chest CT. These findings are usually seen bilaterally, in peripheral zones and lower lobes of lungs [3].

PRECAUTIONS IN THE COVID ERA

With the rapid incline of COVID-19 cases, healthcare staff was urged to get organized for this new period. To reduce the exposure and keep the healthcare staff safe, it is important to minimize the number of surgical teams and healthcare providers. In high-risk interventions producing aerosols, healthcare providers should use personal protective equipment (PPE) such as disposable head caps, gloves, long sleeve waterproof coats, long shoe covers, FFP2 (filtering facepiece) and FFP3 facial masks [6]. Disease Control Center suggested canceling all the elective procedures to keep healthcare providers safe. So, the healthcare staff have a reduced exposure risk and can provide longer healthcare service for emergency surgeries [7].

Also, face-to-face outpatient visits of non-emergent patients were postponed in many hospitals. In the pandemic, all of the hospitals in Turkey, reduced the staff in the operating theater, rounds, canceled clinical routine meetings and student lectures were held online.

WHICH CASES AND HOW SHOULD WE OPERATE?

With the high transmission rate of the disease, workload and stress are high among healthcare providers. Getting infected in surgical teams mean additional workload for the remaining staff and at some cases, loss of the senior surgeon [8]. Only emergent surgical cases such as patients with life-threatening situations, active symptoms, and malignancy diagnosis should be performed in order to keep the healthcare staff ready and healthy for further months. Surgical staff should be minimized and personal protective equipment should be provided for hospital staff [6]. Efficiency in resource usage and reduction of the contamination risk may be provided by prioritizing the emergency surgeries and postponing elective surgeries, nonurgent procedures, and outpatient visits. To provide healthcare for nonemergent patients who were diagnosed with a disease; followup and treatment of these patient groups may benefit from remote medical care. Face-to-face visits may be replaced by video conferences [9].

Turkish Surgical Society suggests that in emergency surgery, patients should be tested for COVID-19 and every patient should be treated as positive unless proven otherwise. Personal protective equipment should be used [8]. Also, if the abdominal computed tomography (CT) is performed, thorax CT should be added. In elective surgeries, risk evaluation for COVID-19 should be done and a consent form stating that surgery has a high risk for COVID-19 disease, should be taken from the patient [10]. In the safe surgery algorithm, only emergency upper gastrointestinal endoscopies should be done. The laparoscopic procedure should not be used rather open procedures should be preferred. However, during the COVID-19 period, there is not a consensus on whether to do laparoscopy or laparotomy in emergency surgeries. Morris et al. suggested that laparoscopy can be used safely since no studies show COVID-19 is transmitted through aerosolized laparoscopic gas [11]. Also, with the laparoscopic approach, a hospital stay will be shorter so that more bed capacity could be provided for infected patient care and there will be less infection risk for the operated patient.

In the operating theater, a minimum number of medical staff should be assigned and all of them should wear PPE [6]. Positive pressure ventilation is preferred in the operating theater. All patients should wear a face mask if they are not intubated during the procedure. If a patient is proven to be COVID-19, the surgical procedures should be postponed if possible [10]. If resource usage is not done in a planned fashion, it is possible that soon, there will be a shortage of healthy senior surgeons, experienced medical staff due to infection .

When dealing with COVID-19 surgical patients, it is important to have a preemptive plan to minimize the risk of contamination. There should be separate pathways for suspected patients for operating theater transit. So that medical staff shortage is prevented due to unexpected viral spread [12]. A dedicated operation room is needed for COVID-19 patients and this room should be the nearest to the theater block entrance. Transfer routes should be short and transfer through these paths should be as quick as possible with a trained medical staff who wear PPE [12]. In the operating theater for COVID-19 surgical patients, a minimal number of medical staff should work and minimal material and if possible disposable material should be used. The operating theaters usually have positive pressure air exchange [13]. Negative pressure operating rooms with a high air exchange of ≥ 25 cycles/hour is suggested to minimize the infection risk [14]. Surgical theater should be sanitized after each procedure [12].

Alcoholic solutions are suggested to be used for hand sanitation. Also, PPE should be worn during the whole procedure. Goggles is crucial for preventing conjunctiva from viral transmission [15]. There is no research on whether there is a viral load in tissue samples or body fluid of the infected patient. But still, precautions with PPE should be taken before entering the surgery. Disposable materials are preferred to be used but if reusable materials are utilized they should be sterilized carefully. Also, ventilators should be disinfected with chloroderivate solution in a concentration $\geq 0.1\%$ or 1000 parts per million [16].

Each hospital should have a detailed internal protocol for emergencies with COVID-19 patients so that a safe surgical procedure may be planned for all medical staff [12].

ONCOLOGICAL OPERATIONS DURING THE PANDEMIC

In this public health emergency period, other than emergency surgeries, how to handle oncological surgeries is crucial. Postponing elective surgeries in order to maintain capacity in

the healthcare system reduces the risk of additional exposure to infection [10]. There is an erratic dilemma in dealing with cancer patients. On one hand, there is a concern of tumor progression, a decline in survival, and increased risk of complications; on the other hand, there is an increased risk of cancer patients dying from COVID-19. A safe delay strategy is needed for this issue. Turage et al. analyzed 4 million cancer patients and found out that most cancer surgeries can safely be postponed for at least one month without having a drastic impact on tumor progression or survival rate [17].

American College of Surgeons (ACS) divided COVID-19 period into three phases: semi-urgent setting, a period where hospitals have enough intensive care units and COVID cases does not increase rapidly; an urgent setting where intensive care units and mechanical ventilators are limited, operating theater supplies are limited and there is a rapid incline of COVID patients; phase 3, where all intensive care units and mechanical ventilators are full [18].

In a semi-urgent setting, for breast malignancies and emergencies, ACS recommended operating on malignancy recurrence, triple-negative, and HER 2 positive patients. Breast abscess, hematoma drainage, ischemic mastectomy flap, and autologous tissue flap revision are suggested to be operated in an urgent setting in phase 3 [18].

For gastrointestinal tumors, early-stage rectal cancers for which adjuvant therapy is not recommended, rectal cancers after neoadjuvant chemoradiotherapy with no regression, nearly obstructing rectal cancer, cancers with the risk of local perforation are suggested to be operated in the semi-urgent setting. In an urgent setting, nearly obstructing colon cancer where the stent is not an option and cancers with local perforation, should be operated. In phase 3, only actively bleeding, perforated, and obstructed cancers are suggested for operation [18].

EMERGENCY SURGERY IN THE COVID-19 PERIOD

Although elective surgeries are postponed in the COVID-19 pandemic, emergency surgeries such as the acute abdomen, trauma surgery, and emergency endoscopies cannot be delayed [19]. To deliver surgical care safely and effectively is the main goal. Nepogodiev et al reviewed 13 articles and found out that reducing elective surgeries will reduce the risk of infection, provide more beds in general ward and intensive care units for COVID-19 patients and boost the number of doctors to take care of COVID-19 patients [20].

American College of Surgeons stated that mesenteric ischemia, perforated hollow organs, necrotizing fasciitis, incarcerated hernia, close loop obstruction and patients in septic or hemorrhagic shock should be operated without delay as emergency cases [18].

Uncomplicated appendicitis could be followed with oral antibiotherapy while appendicitis with abscess or perforation could undergo percutaneous drainage. However, if conservative management fails, surgery should be the only choice [18]. Necrotizing soft tissue infections or large soft tissue abscess and large perianal abscess should be treated in operating theater [18].

SURGICAL EDUCATION DURING THE PANDEMIC

In this unprecedented time of the COVID-19 pandemic, residents had flexible working hours and shift based schedules to take care of patients in order to minimize the exposure risk. Other than their own department, they had to work directly with COVID-19 patients so, they were more exposed to getting infected. Moreover, since they were only able to get involved in emergency surgeries, they had a quantitative loss of operation experience, clinical judgment, teaching, leadership skills, and basic patient-physician relationship [21]. In many countries, residents were engaged in virtual education and online theoretical sessions to recover the loss of education and training. Continuing surgical education is difficult in this era. However, with new ways of training the lost time will be recovered in a way [22].

TELEMEDICINE

During the pandemic, telemedicine becomes popular since many healthcare givers were able to contact their followup patients through this route. It reduced the visit time, cost, and increase patient satisfaction [23, 24]. Through video calls or teleconferences, suitable patients could be followed.

In surgeries with low postoperative complication risks or in patients who are already diagnosed with a disease and just need a close followup, telemedicine is an ideal approach to seek healthcare guidance [9]. In the COVID-19 period, teleconferences reduce face-to-face contact and also contamination risk. It also decreases the burden on outpatient clinics. However, before the application of telemedicine services, technological infrastructure and patient privacy issues should be considered with care [25].

Although many physicians are doubtful about any superiority of telemedicine to traditional outpatient clinic visits, some publications are supporting the applicability and cost-effectiveness of telemedicine [26, 9].

We believe that the first patient visit should be done face-to-face during the pandemic period since physical evaluation, the stress level of a patient is crucial for clinical decision making. After the first visit, according to the disease status and patient's compliance, telemedicine could be used.

CONCLUDING REMARKS

In the COVID-19 pandemic, it is important to keep healthcare providers safe by using personal protective equipment with great care and thus reducing the risk of contamination. All surgeons from different subspecialties should be trained to recognize COVID-19 patients. First, when physicians from other specialties such as internal medicine, infectious diseases, ear-nose-throat get infected or exhausted, they will be replaced with physicians from other specialties such as surgery. Second, in patients undergoing emergency surgery due to perforated gallbladder, bowel or mesenteric ischemia, it should be kept in mind that there can be concurrent COVID-19 [20]. Third, after an emergency or elective surgery, the patient could get infected with COVID-19 when observed in the general ward. [20].

The surgeons should think of their safety first to keep on working during this unprecedented period. Guidelines and recommendations for each hospital or country should be prepared. Strict rules on how to transport a COVID-19 patient for operation and protection measures that need to be taken before, during, and after surgery should be established. Guidelines for elective and emergency surgeries during the COVID-19 period will help the physicians to decide when and how to operate.

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Chapter 468

CYTOKINE STORM AND OXIDATIVE STRESS IN SEVERE COVID-19

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ABSTRACT

Some patients infected with the SARS-CoV-2 virus show rapid progress to acute respiratory distress syndrome, multi-organ failure, and death. Acute respiratory distress syndrome is a large concern of death in COVID-19. Current therapeutic strategies focus on the virus itself and antiviral drugs are used to manage the disease. Unfortunately, the benefits of antiviral drugs are not satisfactory in every patient. It seems that the excessive inflammatory response rather than the virus titer is more relevant to the death. A brisk immune response generally destroys the virus but can cause significant local and long-term damage in tissues. In severe COVID-19, acute respiratory distress syndrome and multi-organ failure are associated with cytokine storm. Cytokine storm triggers the production of reactive oxygen species storm in immune system cells to destroy the virus. Although a certain amount of reactive oxygen species is helpful in the regulation of immune response and killing viruses, an excessive amount of reactive oxygen species damages the cellular lipids, proteins, and DNA. Extensive damage by reactive oxygen species results in apoptosis. Apoptotic death of endothelial and epithelial cells in the lungs plays important role in the development of acute respiratory distress syndrome in COVID-19 patients. Here, we will summarize the current molecular understanding of the vicious circle between the cytokine storm and oxidative stress that is an executive factor for cells.

Keywords: COVID-19, cytokine storm, reactive oxygen species, oxidative stress

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INTRODUCTION

COVID-19 (coronavirus disease 2019) caused by the SARS-CoV-2 virus is spreading rapidly worldwide. No specific antiviral therapy and vaccine are available. Although many patients have mild or moderate symptoms, some patients show rapid progress to acute respiratory distress syndrome (ARDS), septic shock, multi-organ failure, and death [1]. In general, conditions such as advanced age, comorbidity, high body mass index are associated with severe disease. Besides, in COVID-19 survivors, life quality was observed to be low even 12 months after discharge from the hospital. Reduced lung function, reduced ability to exercise and mental health problems were seen in some survivors up to 6 months and beyond [2]. These long-term complications of COVID-19 in survivors indicate that not only acute executive conditions but also some long-term degenerative processes are triggered during the disease. Cytokine storm is a common feature in critically ill COVID-19 patients. Cytokine storm occurs due to uncontrolled activation of the immune system. It can lead to hyper inflammation, multi-organ failure, and can even die. Increased plasma levels of the cytokines including IL-2, IL-6, IL-7, IL-10, TNF- α , IFN- α , granulocyte-macrophage colony-stimulating factor (GM-CSF) were reported in severally ill COVID-19 patients [3].

CYTOKINE STORM IN COVID-19

Cytokine storm is a general term used to define abnormal cytokine release in response to infection and other stimuli. It occurs due to loss of regulatory control on proinflammatory cytokine production. The innate and adaptive immune responses activated by SARS-CoV-2 infection cause uncontrolled inflammatory responses leading to the cytokine storm [4]. Cytokines and chemokines are small peptides or glycoproteins that exert their actions by binding cell surface receptors. They act as signal molecule to activate immune system cells for chemotaxis and diapedesis and induce acute phase response. The overproduction of cytokines and chemokines increases the severity of the inflammation and a vicious cycle starts. The immune system is stimulated more than usual in patients with severe COVID-19. Especially if the patient had already got a chronic inflammation, the outcome gets worse. The cytokine storm can lead to excessive cellular damage that triggers apoptosis of epithelial and endothelial cells, vascular leakage, and finally results in acute respiratory distress syndrome (ARDS), multi-organ failure, and death [5]. The cytokine storm may be responsible for long-term complications of COVID-19 in survivors.

In viral infections, the body's first line of defense is the innate immune response. The SARS-CoV-2 virus induces a delayed elevation in the levels of proinflammatory cytokines and chemokines [6, 7]. In the early phase of SARS-CoV-2 infection, the release of cytokines and chemokines from respiratory epithelial cells, dendritic cells, and macrophages is delayed. Afterward, cells secrete low levels of antiviral factors, INF- α and INF- β , but high levels of proinflammatory cytokines such as interleukin (IL)-1 β , IL-6, and tumor necrosis factor (TNF) and chemokines such as C-C motif chemokine ligand (CCL)-2, CCL-3, and CCL-5 [8-10]. Publications indicate that interferon response is dysfunctional in critically ill patients during the pandemic COVID-19 [11]. IFN-1 α and IFN-1 β are the key molecules that trigger the innate immune response in the early stages of viral infections. IFN-1 α and IFN-1 β exert

antiviral activity by the induction of numerous interferon-stimulated genes that antagonize viral replication by various mechanisms. However, along with the activation of immune cells, SARS-CoV-2 expresses proteins that inhibit the synthesis of IFN-1 α and IFN-1 β thus weakens the immune responses and provides an optimal environment for rapid replication of the virus [12]. The low IFN-1 level at the onset of the disease delays the body's antiviral response. Afterward, the rapid increase of cytokines and chemokines attracts a large number of neutrophils, monocytes, and pathogenic inflammatory mononuclear macrophages to the infection site. Neutrophils migrate through the blood vessels and are recruited to the site of infection. Monocytes move into tissues and differentiate into macrophages. Excessive infiltration of these phagocytic cells into the lungs causes tissue damage, likely oxidative damage.

CYTOKINE STORM-INDUCED REACTIVE OXYGEN SPECIES PRODUCTION

When activated, all phagocytic cells bind and engulf pathogens to destroy. They can use oxygen-dependent and oxygen-independent mechanisms to kill pathogens. In oxygen-dependent systems, membrane-bound NADPH oxidase is activated, oxygen utilization increases (respiratory burst), and reactive oxygen species (ROS) are produced. ROS can cross the membranes of bacterial pathogens and destroy them by damaging their nucleic acids, proteins, and cell membranes. Superoxide anions produced by NADPH activity generate hydrogen peroxide (H_2O_2) via superoxide dismutase. The myeloperoxidase chlorinates H_2O_2 and produces hypochlorous acid (HClO) which is the strongest bactericidal agent. NADPH oxidase is a multi-protein complex that is made up of five components and a small GTPase protein, Rac2. Flavocytochrome b558 (cytb558) is found in the active site of the enzyme and transfers electrons from cytosolic NADPH to molecular oxygen. At resting state, cytb558 resides at the membranes of phagosomes, secretory vesicles, specific granules, and the plasma membrane. When neutrophils are activated, the regulatory cytosolic complex translocates to the membrane and interacts with cytb558 to activate NADPH oxidase. Activated GTP-bound Rac2 contributes to the assembly of the regulatory cytosolic complex [13]. Superoxide anions produced by the NADPH oxidase activity are the precursor in the generation of other ROS that all contribute to the destruction of the pathogens. In the presence of transition metal ions such as Fe^{2+} or Cu^{2+} superoxide anions can react with H_2O_2 to produce hydroxyl radical ($OH^\cdot$) that is the most active form of ROS.

Nitric oxide (NO) that is synthesized from arginine and NADPH by inducible nitric oxide synthase is the precursor of reactive nitrogen species (RNS). Superoxide anions can react with NO to produce peroxynitrite ($ONOO^-$), a strong oxidant. When the respiratory burst is triggered and superoxide anions are produced, if NO is present, peroxynitrite is generated as long as the respiratory burst lasts [14]. Superoxide anion is a short-lived ROS with limited diffusion within the cell, its cytotoxic effect occurs due to its derivatives including H_2O_2 , hydroxyl radical, and peroxynitrite. Both peroxynitrite and NO are toxic to mitochondria [15] leading to mitochondrial dysfunction which in turn increases superoxide anion production. Mitochondrial dysfunction is a general mechanism of ROS production detected in most viral infections because several viruses induce oxidative stress to facilitate their replication in the

host cell [16-18]. In viral infections, tissue damage occurs due to oxidative stress formed by cytokine storm and mitochondrial dysfunction. COVID-19 does share many similar symptoms with SARS and influenza. In an experimental study, viral replication increased rapidly and peaked on day 4, then reduced to baseline on day 8 in mice infected by the influenza virus. The lung damage index increased from day 2 and peaked from day 8 to day 10. Mice began to die from day 8 to day 14 [19]. ROS and NO in the infected mice started producing from day 5 and peaked on day 8 [20]. These results confirm the idea that cytokine storm triggers a ROS storm in COVID-19 and oxidative damage is responsible for worse outcomes in patients.

Pro-inflammatory cytokines including IL-6, TNF- α , IFN- α , IFN γ , and chemokines such as GM-CSF are up-regulated in COVID-19 patients [3]. IL-6, TNF α , GM-CSF, IFN γ can induce the production of ROS and RNS in neutrophils. IL-6 and IFN γ induce expression of NADPH oxidase. IFN γ triggers the production of superoxide anions by inducing NADPH oxidase 2 (NOX2) [21]. IL 6 induces expression of NOX2 in human aortic endothelial cells [22]. Nrf2 is a transcription factor that up-regulates the expressions of many antioxidant enzymes. It was reported that the overexpression of circulating IL-6 increases the ROS production and accumulation in the diaphragm muscle of adult NSE/IL-6 mice, by deregulating the nuclear factor erythroid 2-related factor 2-(Nrf2-) mediated antioxidant response [23]. Respiratory viral infections are associated with inhibition of NRF2-mediated pathways. These viruses have evolved to acquire the ability to suppress the Nrf2 pathway in their favor [24].

At the inflammation site, neutrophils express a large number of cell surface receptors including cytokine receptors such as tumor necrosis factor receptors (TNFRs), and toll-like receptors (TLRs). All receptors are G-protein-coupled. Ligand binding to these receptors can prime neutrophils for a more strong response if additional signals are available. Activation of these receptors induces tyrosine kinase and MAP Kinase activation. Both pathways stimulate the regulation of the NADPH oxidase components to cause activation of the enzyme. One group of the priming ligands are proinflammatory cytokines such as tumor necrosis factor TNF- α , GM-CSF, IL-1b, IL-8, and IL-18. IL-1b and IL-18 induce respiratory burst weakly but TNF- α and GM-CSF exert a strong priming effect [25]. TNF- α primes neutrophils for oxidative burst by inducing calcium flux and p38 MAPK-dependent mobilization of cytb₅₅₈ to the plasma membrane [26]. GM-CSF primes cells by inducing phosphorylation of certain residues on regulatory components which in turn promotes translocation and docking of the cytosolic complex to the membrane that is required for activation of NADPH oxidase [25, 27].

OXIDATIVE DAMAGE IN COVID-19

ROS are highly active chemical compounds that easily react with other molecules and damage them. The harmful effects of ROS occur in a few ways: (1) ROS can act as signaling messengers to stimulate inflammatory pathways, (2) ROS can impair cellular integrity and intracellular metabolism by oxidizing lipids, proteins, and nucleic acids (3) ROS can trigger apoptosis and lead to cell death, and organ failure, (4) ROS can consume antioxidant reserve and make macromolecules more vulnerable. The interaction between cytokines and ROS

constitutes a *vicious cycle* in which cytokines stimulate production ROS and then ROS form an oxidative signal that stimulates inflammatory signaling pathways. For instance, an increase in H_2O_2 level act as a signal to induce expression of the IL-2 and IL-4 and facilitate induction of the transcription factor NF- κ B which mediates induction of pro-inflammatory cytokines.

The harmful effects of ROS are counteracted by antioxidant enzymes and non-enzyme antioxidant molecules. Antioxidants inactivate ROS and prevent oxidative stress. Oxidative stress is a state in which ROS production overwhelms cellular antioxidant capacity. Cytokine storm leads to oxidative stress in COVID-19 patients by stimulating ROS production. While high ROS causes the rapid depletion of antioxidants, they also suppress the antioxidant defense mechanism by modulating Nrf-2 and/or NF- κ B pathways resulting in exacerbation of inflammation and oxidative stress [28]. According to preclinical studies, overproduction of ROS and disruption of the antioxidant system play a key role in the pathogenesis, progression, and severity of SARS-CoV infections [29-31].

ROS attack to membranes causes oxidation of membrane proteins and lipids which results in impaired membrane integrity and function. Oxidation of intra-cellular proteins leads to their denaturation and functional loss. Oxidized phospholipids were detected in human and animal lung cells infected with SARS viruses. Oxidized phospholipids can induce cytokine storm and lung injury in SARS-CoV infection [32]. On the other hand, the damaging effects of excessive ROS on the red blood cell membrane and heme group function play an important role in hypoxic respiratory failure observed in the most severe patients of COVID-19. Excess ROS can disrupt the lateral and transversal distribution and organization of red blood cell membrane lipids by oxidizing polyunsaturated fatty acids of phospholipids. This alteration affects the diffusion of oxygen and carbon dioxide and the deformability capacity of red blood cells in the capillary vessels which in turn favors thrombocytosis. Excess ROS can impair the function of hemoglobin to carry oxygen. Heme iron must be kept in the reduced state (Fe^{2+}) to bind oxygen. ROS excess can disrupt the Fe^{2+}/Fe^{3+} balance by oxidizing iron to a Fe^{3+} state. Fe^{3+} can not bind oxygen, resulting in less efficient oxygen transport despite a high oxygen supply [33].

Microvascular thrombosis is the most important aspect of severe COVID-19. COVID-19 infection appears to be hypercoagulability and vascular endothelial dysfunction [34, 35]. COVID-19 patients who present a hypercoagulability state characterized by longer prothrombin times, higher fibrinogen levels and inflammatory markers have statistically significantly worse outcomes [36]. Over-activation of neutrophils may be a potential explanation for the diffuse microvascular thrombosis and capillary leak syndrome observed in critical COVID-19 patients. Endothelial function plays a key role in the maintenance of vascular integrity and inhibition of excessive thrombosis. Oxidative stress that is induced by cytokine storm is one of the causes of endothelial dysfunction in COVID-19 [37, 38]. TNF- α can stimulate both mitochondrial and NADPH oxidase-mediated ROS and NO production in endothelial cells. TNF- α induced oxidative damage plays a critical role in endothelial dysfunction [39].

ROS interaction with nucleic acids causes oxidation of purine/pyrimidine bases and DNA strand breaks. All contribute the impaired cell metabolism and function. In the case of mild to moderate oxidative stress, DNA strand breaks, and oxidized bases are repaired by DNA repair systems. However massive oxidative DNA damage is fatal to the cells. When genomic damage exceeds the DNA repair capacity, apoptosis is triggered. Apoptosis is one form of programmed cell death. Apoptotic changes in endothelial cells were showed histologically in

COVID-19 [40]. Apoptosis of endothelial and epithelial cells damages the pulmonary microvascular and alveolar epithelial cell barriers and disrupts oxygenation by triggering coagulopathy in the alveolar vascular bed and vascular fluid leaking to the lung tissue. Therefore, apoptosis appears to be the most important pathogenic mechanism underlying ARDS. In cell culture experiments, a viral protease (SARS-CoV 3CL^{pro}) was found to trigger ROS production and apoptosis in the host cells [31, 41]. SARS-CoV 3CL^{pro} activates the NF- κ B-dependent reporter gene in HL-CZ cells. ROS-activated NF- κ B signaling induced by SARS-CoV 3CL^{pro} was suggested as a contributory factor in SARS-CoV pathophysiology [31]. All mitogen-activated protein kinases (MAPKs) are activated in the response of environmental stresses including oxidative stress and DNA damage derived from viral infections. A SARS-CoV's protease, the 3a protein, was found to be associated with the activation of apoptotic cell death through p38 MAPK activation [41]. In autopsy studies, hallmarks of apoptosis were observed in SARS-CoV-infected lung, spleen, and thyroid tissues [42].

In addition to ARDS, some patients develop various neurologic symptoms, ranging from hyposmia, headache, and dizziness to seizures and stroke. Severely affected patients are more prone to develop neurological damage than mild or moderate cases [43]. The neurological symptoms may be derived from the direct effects of the coronavirus on the nervous system and/or systemic effects of the disease. The local increased production of cytokines in the cerebral tissue can induce neuroinflammation, oxidative stress that are underlying pathogenic mechanisms of neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. Particularly in elderly individuals, neurological damage that occurs due to COVID-19 may lead to serious neurodegenerative diseases in the post-COVID-19 term.

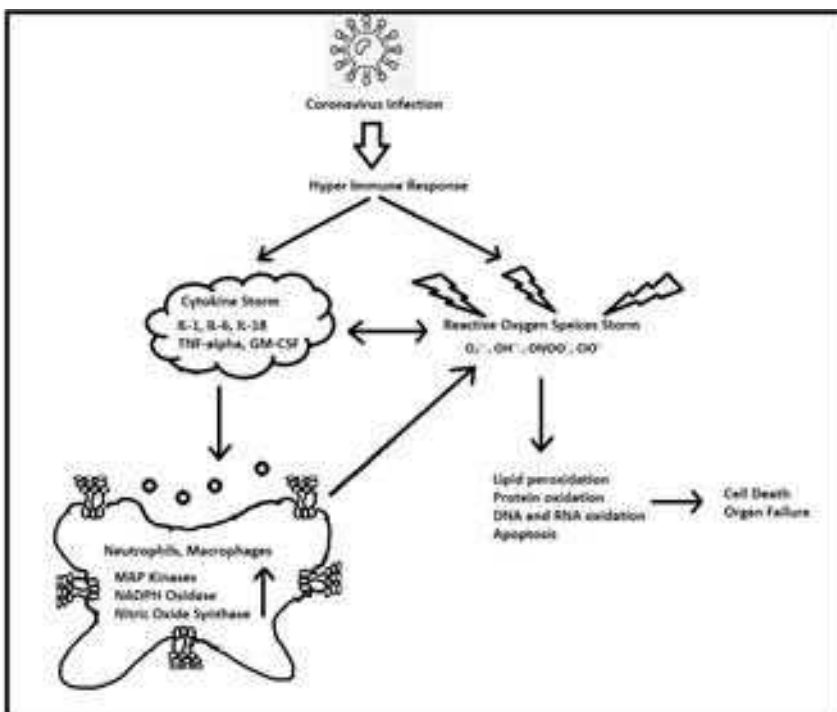


Figure 1. Cytokine storm-driven oxidative damage in severe COVID-19.

CONCLUSION

ARDS is a large concern of death in COVID-19. In severe COVID-19, the development of ARDS and multi-organ failure is associated with cytokine storm. When discussing the prevent ARDS and death in COVID-19, it is critical to understand that the closed-circuit between cytokine storm and oxidative stress is the executive factor for direct damage to cells and multiple organs. As a result of cytokine storm, the number of innate immune system cells increases in the inflammation zone and they produce an excessive amount of ROS and NRS to destroy the virus. In addition to killing viruses, ROS, and NRS damage cells by directly damaging or depleting cellular antioxidant reserves. The depletion of the antioxidant system exacerbates oxidative stress which in turn triggers apoptosis, causing cell death. Apoptotic death of endothelial and epithelial cells in the lungs is one of the most important causes of ARDS in critically ill COVID-19 patients. Elders and people suffering from diabetes, hypertension, and cardiovascular diseases have already a state of oxidative stress. SARS-CoV-2 infection will increase this stress. This may be the cause of the severity of COVID-19 in these categories of patients and elderly individuals. Astonishingly very few medical scientists mention the pivotal role of oxidative damage in patients with severe COVID-19. Current therapeutic approaches focus on the virus itself and try desperately to apply antiviral medicine. Unfortunately, the benefits of antiviral drugs are not satisfactory in every patient due to severe side effects. The suppression of the cytokine storm and oxidative stress may help to prevent tissue damage, save the patients' lives, and prevent complications after recovery. Drugs with antioxidant and anti-apoptotic properties may be helpful in the management of severe COVID-19 patients. In this context, anti-oxidative therapeutic strategy in COVID-19 was evaluated in the next chapter.

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Chapter 469

ANTIOXIDANT AGENTS IN THE TREATMENT OF COVID-19

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ABSTRACT

SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2) belongs to the beta coronavirus family and shows an important global spread that is forcing the worldwide health care capacity, economic and social public life. It was referred that this deadly infection (COVID-19) has resulted in more than 1 million deaths and a lot of multiorgan failure around the world. The virus seriously affected people of old age, chronic cardiac problems, chronic respiratory syndromes, and hypertension. But in some cases, the disease may have a moderate or asymptomatic indication. Oxidative stress occurs because of an imbalance in the organism between the formation of the oxidizing system and antioxidant mechanisms. After the production of free radicals, antioxidant enzymes such as glutathione, melatonin, quercetin, curcumin, and vitamins, play an important role in neutralizing the effects of free radicals. The imbalance of oxidative stress and accumulating free radicals may get involved in the formation of cancers, degenerative diseases, hypertension, diabetes mellitus, heart and vessel diseases, and virus infections, especially RNA viruses like HIV 1, SARS, MERS, and coronaviruses.

A common approach in COVID-19 infection is the disruption of the antioxidant balance so free radicals can be exposed and accumulate in the organism. The depletion of the glutathione content, which is the most common antioxidant molecule of the tissues, causes the organism to increase the inflammation.

In this article, we will discuss the role of free radical mechanisms in the formation of infection by COVID-19 and the treatment of the disease by different antioxidants such as GSH, melatonin, vitamins (C, D, E, A), and food additives.

Keywords: COVID-19, antioxidants, glutathione, vitamin, flavonoid

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INTRODUCTION

Free radicals are chemical products that carry an unshared electron in its outer orbit. They are formed by the release of an electron from a non-radical atom or molecule, or by the addition of an electron to an atom or molecule. Free radicals are produced in animals and plants during aerobic metabolism and reduce the effects of the antioxidant activity or amount of compounds, as to behave as antioxidants (albumin, melatonin, urea, glutathione, vitamin D), exogenous antioxidants (vitamin E, vitamin C, vitamin A, polyphenols, curcumin), and enzymes (superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione S transferase (GST), catalase (CAT)). Dietary antioxidants are beneficial in protecting against free radicals. Decreasing amounts of them cause the death of cells by lipid peroxidation, protein and DNA damage. They play an important role in preventing many diseases in humans, e.g., infection diseases, cardiovascular diseases, and cancer. Antioxidant enzymes and other non-enzyme antioxidants exhibit synergistic effects in scavenging free radicals.

Large different kinds of chemical carcinogens, viruses cause the formation of DNA and protein hazards and require activation by enzyme systems like cytochrome P450 [1]. In opposite to this situation, phase 2 xenobiotic-metabolizing enzymes and compounds such as Glutathione related enzymes (Glutathione peroxidase, glutathione s transferase, glutathione reductase), NAT (N-Acetyl Transferase), epoxides hydroxylase, sulfotransferase, GSH and NO takes place in the detoxification of chemicals, viruses, and consequently, known to be protective [2].

For a long time, the association of the environmental risk factors such as viruses was interesting for researchers. They increase oxidative stress that is triggered by various viral infections such as reactive oxygen species (ROS) production that disrupts the cell membrane integrity, and mitochondrial dysfunction [3]. Most of these viruses are RNA viruses which are, herpes viruses, respiratory viruses, HIV 1, viral hepatitis, and coronaviruses. Coronaviruses are single-stranded and encapsulated viruses which shown in 3 types: the classic coronaviruses, responsible for mild respiratory infections in general, the SARS-CoV and second one MERS-CoV (Middle Eastern respiratory syndrome) seen in epidemics of severe respiratory infections, and the third one; new coronavirus (caused by SARS-CoV-2) spread in December 2019 responsible for an infectious disease called COVID-19 which is currently accomplishing a worldwide pandemic [4].

Generally, viral infections produce an augmentation in the production of free radicals and a reduction of antioxidant capacity in the organisms in which they live [5]. This was previously shown in a study of HIV infection [6]. Oxidative stress caused by RNA virus infections can take part in the formation of several aspects of viral disease pathogenesis which are apoptosis, disruption of the immune system, viral replication, increased inflammatory response. SARS-CoV-2, MERS-CoV, and COVID-19 infections increase oxidative stress and ROS increases in the cell and disrupt the mitochondria after the cells get infected with these viruses. The release of acute-response cytokines (TNF and IL-1 β), chemotactic cytokines (IL 1, IL 6, IL-8, and MCP-1) increases (Figure 1).

Increasing these cytokines causes a shock by hyper inflammation and generates a lot of ferritin by the reaction of Fe²⁺ by hydrogen peroxide and increases OH⁻ radicals, ROS and Fe³⁺. Because of this dysfunction, interleukins increase in the organism, and the cytokine storm begins [7]. In studies, the oxidative storm also investigates that lipid peroxidation and

protein oxidation may disrupt the alveolar membranes and cause serious respiratory problems [8]. Elderly people and patients with hypertension, diabetes, obesity, and cardiovascular diseases are affected by the virus more than healthy and young people do because of the existing accumulation of oxidative stress [9].

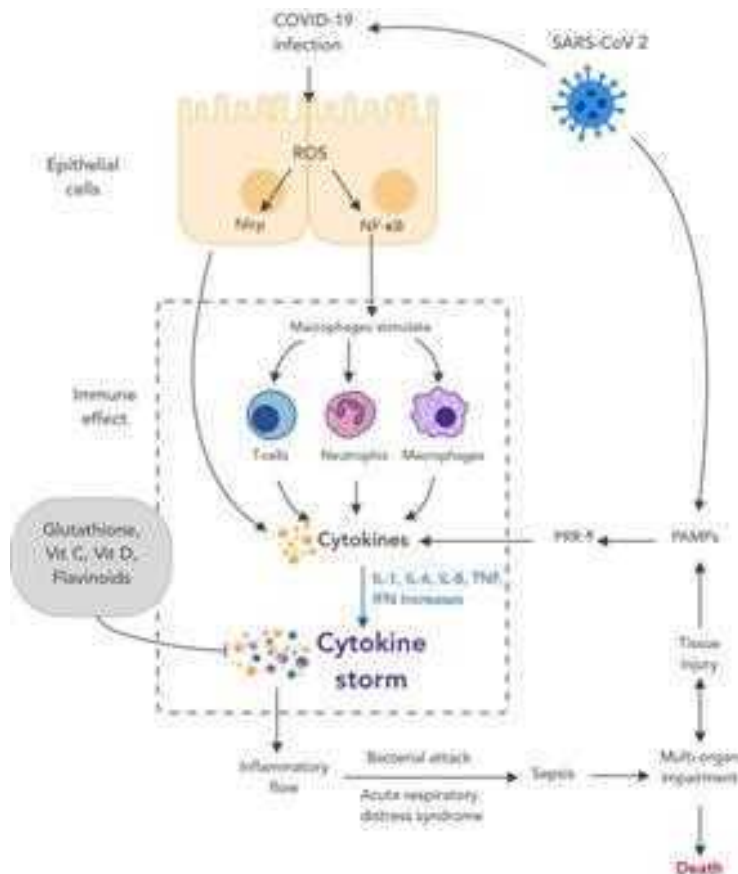


Figure 1. Mechanism of SARS-CoV-2 after entering to the organism. Pattern recognition receptors (PRR), pathogen-associated molecular patterns (PAMPs). Interleukin (IL). TNF(tumor necrosis factor).

In the people infected by COVID-19, the antioxidant therapy aims to reduce the number of oxygen radicals by reducing oxidative stress with substances such as Glutathione and its precursors like N acetylcysteine, melatonin, vitamin C, vitamin D, some substances like curcumin and quercetin.

EXAMPLES OF MEDICALLY USED ANTIOXIDANTS

Glutathione

GSH (glutathione) consists of a tripeptide (cysteine, glycine, and glutamate) and is the most abundant antioxidant in the whole body and has a master role in most of the organisms to reduce the oxidative stress caused by an increase of ROS (reactive oxygen species) [10].

As a substrate of the GSH redox cycle, it is useful in scavenging singlet oxygen with hydroxyl radicals. In addition to directly scavenging free radicals; it also acts enzymatically with GPx. GSH plays a vital role in keeping enzymes and other cellular components in the cells in a reduced state. GSH is mostly synthesized in the liver and about 40% of it is excreted in bile. It is spread % 85 in the cytosol, the lesser amount at the subcellular parts of the cell which are; mitochondria, endoplasmic reticulum, and nucleus [11]. Its amount is measured 0.1-10 mM in living cells [12]. It reduces the amounts of ROS by using the reduced GSH to form oxidized GSSG (glutathione disulfide). Another important GSH function is to support the maintenance of the intracellular redox balance and thiol levels in the cell [13, 14] In the case of inflammation diseases, intrinsic oxidative stress has been found as depletion of total free thiol levels (free sulfhydryl, free thiols, and glutathione) [14]. It is found in most cells especially in upper and lower respiratory tract epithelial cells fluids and it protects the nose throat and lungs from pro-inflammatory processes. Glutathione has increased the immune response at herpes and influenza by blocking their replication [14].

The glutathione synthesis may increase by the GCS (gamma-glutamyl synthetase), this is a rate-limiting step for the synthesis and causes a rapid increase at the amount of the GSH. The other synthesis way is the induction of GCS by Nrf2 (The nuclear factor erythroid 2-related factor 2). Nrf2 is a transcription factor that increases the expression of a group of antioxidant, anti-inflammatory, neuroprotective protein [15].

In a study, N acetylcysteine, a GSH precursor, was given to two COVID-19 infected patients and it is found that this treatment inhibited the cytokine storm by blocking NF Kappa B (Figure 1) [16]. They applied glutathione to the patients infected by COVID-19, they showed the relieving of the respiratory symptoms. The increasing amount of GSH induce the Nrf2 and this inhibits the excess cytokine production that causes cytokine storm. In this study, the authors also used potent Nrf2 activators such as curcumin and sulforaphane.

In another study from Russia, it is postulated that increased age may reduce the synthesis of glutathione and the antioxidant protection may disrupt because of this reason [17].

According to various studies, this hypothesis recommends that the SARS-CoV-2 virus shows a major risk for people with endogenous glutathione deficiency, anyhow which of the factors old age, chronic disease, comorbidity, smoking, cardiovascular diseases, and obesity were responsible for this defect [18, 19, 20]. The hypothesis shows a new explanation into the etiology and mechanisms responsible for the serious appearance of COVID-19 infection and proves the right promising statutory for powerful treatment and controlling of the illness through glutathione rescuing with N-acetylcysteine and reduced glutathione.

Onward the antiviral influence of glutathione is non-standard, there is cause to count on that glutathione is also effective against COVID-19. Therefore, increasing glutathione levels in COVID-19 patients would be an encouraging perspective for saving the health of the new coronavirus for SARS-CoV-2 infection also.

Melatonin

Melatonin (*N*-acetyl-5-Methoxytryptamine) is a natural antioxidant molecule synthesized from tryptophan in the pineal gland and all organs of the body because its synthesis occurs in the mitochondria [21]. It neutralizes antioxidant molecules ten times more than vitamins C

and E that binds only one. The antioxidant effects of melatonin are connected to the increased activity of superoxide dismutase, glutathione S transferase, reductase, peroxidase, and catalase [22, 23].

COVID-19 caused long-term stress in people resulting in anxiety and sleep defects.

Sleep defects may have negative effects on the immune system [24]. Prolonged anxiety causes a decrease in the amount of the immune cell and increases immunosuppressive mechanisms (increases T Cells). Inflammation and oxidative stress are implicated together in COVID-19 pathogenesis [25]. Oxidative stress-sensitive genes were stimulated in the peripheral blood mononuclear cells of SARS-CoV-2 infected patients [26]. Melatonin is found as a free radical scavenger and antioxidant at researches [27]. The metabolites of melatonin are cyclic-3-hydroxymelatonin (c3OHM), N1-acetyl- N2-formyl-5-methoxykynuramine (AFMK), and N1-acetyl-5-methoxykynuraminem (AMK) are produced by true scavenging free radicals. These metabolites have also been indicated to have protective properties of the melatonin [28]. Besides this, melatonin and its metabolites act as anti-excitatory agents that reduce prooxidant enzyme activity, inducing glutathione synthesis, and it elevates antioxidant enzyme synthesis. Furthermore, melatonin plays a significant action in ameliorating mitochondrial function with mention to the promotion of mitochondrial complex I and complex IV activities and inhibits of electron loss [29].

According to the studies, melatonin can not destroy the virus directly but it has an indirect antioxidant and immune system enhancer [28, 30]. In a study performed by respiratory virus models, melatonin caused a serious decrease in acute lung oxidative injury, depressed pro-inflammatory cytokine release, and inflammation in the cell [31].

Nevertheless for using this supplement the safety and side effects should be investigated. Metionin's characteristics scavenging free radicals show antioxidant property and increase in the immune system and may cause its potential decrease of COVID-19 infection.

A significant number of the long and short term of clinical studies suggest the safe use of melatonin up to 100 fold higher its physiologic concentration [32, 33]. Further, the brain is the organ where the number of drugs at the lowest level after melatonin administration, which could excuse the use of high doses for the potential treatment of SARS-CoV-2 [32].

Vitamin C

Ascorbic acid (vitamin C) is a very vital vitamin for the overall health and development of humans and other animals because it protects these organisms from serious diseases. It exists especially in vegetables and fruits [34]. It's synthesized from glucose in the liver of different mammalian species, permitting the preservation of physiological levels at the organisms. However in some species, including humans, it does not have the functional enzyme for the last step of the synthesis that's why they have to use exogenous sources of ascorbic acid [35]. It has very different effects on the rearranging the immune system of the organisms. The most important function and need for using of vitamin C is its antioxidant property to decrease the reactive oxygen radicals, which responsible for free radical hazards, biomolecular, cellular, and tissue damage related diseases, as well as cancer, atherosclerosis, and virus infections [36, 37]. Vitamin C also has been shown to increase the migration of neutrophils to the infection region, stimulating phagocytosis, and ROS generation [38].

Because of the required high need, it's recommended that the human daily intake of vitamin C (60 mg) is the highest of all vitamins [39].

The antiviral properties of ascorbic acid were known and it was searched around for a long time before [40, 41]. It has been applied to patients who were infected by influenza and herpes and found healing for these patients [42]. COVID-19 pneumonia is a serious disease with the risk of death with chronic organ disorders. This helps to provoke severe lung injury which causes Acute Respiratory Distress Syndrome (ARDS), causes a deadly injury in the lungs. This process inhibits adequate oxygen to enter into the lungs and at last cause death. Coronaviruses increase oxidative stress that promotes cellular damage and the results in organ failure. It is thought that pulmonary failure (ARDS) is the main reason for COVID-19's action on humans. This causes to increase in oxidative stress markedly because of the production of free radicals and cytokines. This action causes important cellular injury, organ damage, and death. The application of anti-oxidizing agents forward with known antioxidant property counts on to have a serious role in stopping these medical symptoms. Although evidence for the consumption of vitamin C for healing COVID-19 infections is not strong enough, there were studies from investigations of vitamin C in other respiratory diseases to begin conducting [43]. In a meta-analysis published by Ran, it is concluded that daily supplementation in vitamin C with more than daily doses decreases the time of period having a catching cold [44]. In acute lung injury and ARDS as seen in COVID-19 infections, overage neutrophil aggregation in the inflammatory region causes lung tissue damage via the release of necrotic cell ingredient [44], and vitamin C is declared to prohibit this action [45]. The antiviral characteristics of vitamin C may support depress symptoms and death seen in COVID-19 cytokine storm and could be a promising candidate for the treatment [46].

Vitamin D

Vitamin D is a steroid hormone that classically regulates bone calcium and phosphate metabolism, modulates the immune system, and its insufficiency is related to increased autoimmunity as well as enhances sensitivity to infection [47]. Its decreased amount is an important health problem seen all age range worldwide. In the last years, the relationships between low levels of vitamin D and various diseases has been shown by several studies, it increases innate and adaptive immunity, secretes antiviral peptides and augments mucosal resistance, improves membrane permeability [48, 49]. The studies have shown that the vitamin D₃ synthesized in the skin by the UVB radiation is converted to the 25(OH)D in the liver and it has changed to its active form 1,25-dihydroxy vitamin D in the kidney and other organs [49]. In human normal serum 25(OH)D levels in between 40-60 ng/mL (100-150 nmol/L) [50].

These vitamin D amounts are stable with the published studies for decreasing the risk of various types of immune system diseases, cancers, cardiovascular diseases [51, 52, 53]. Several reviewers consider that the relationship between low level of serum 25(OH)D and the effectiveness and severity of respiratory tract infection in children and adults [54, 55, 56]. At a prospective study in healthy individuals, it is found that the acute respiratory tract infection reduced at the patients which have high levels of vitamin 25 (OH) D (38 ng/mL) in their serum [56]. In another study carried out in New Zealand children aged less than 2 years,

showed the severity and hospitalization of acute respiratory infection percentage higher at the vitamin D deficiency [55]. This may explain the preventive effects of sufficient vitamin D status against respiratory viral infection. 1,25(OH)₂D shows anti-viral activities by increasing innate immunity by enhancing the antimicrobial peptides and regulates inflammatory reply to viral infection by adjusting of toll-like receptor generation and NK cells production, inhibiting excess expression of proinflammatory cytokines [54]. Besides the immune modulatory and anti-viral influences, 1,25(OH)₂D may act as to the disposition of the renin-angiotensin pathway and decreases the angiotensin-converting enzyme-2 expression, which may act as the subjects cell receptor which regulates infection of SARS-CoV-2 [56]. In a study done at African American and obese individuals, it is observed high morbidity, mortality and increased hospitalization at these subjects may be depends on their vitamin D deficiency [58].

Flavonoids

Flavonoids have a lot of secondary metabolites, that are found in vegetables, seeds, fruit, and beverages, like red wine and green tea [59]. There are very different kinds of structurally identified flavonoid molecules such as hesperidin and quercetin.

These chemicals are synthesized in plants to protect them from stressful mediums and play an important role in defending the plant cells from pathogens and insects [59].

The prophylactic characteristics of flavonoids implicate antibacterial, antioxidant, anti-inflammatory, and antiviral functions. Flavonoids work to defend the organisms from a group of DNA and RNA viruses [60].

After spreading the COVID-19 pandemic worldwide, the interest of researchers to the potential therapeutics other than antiviral drugs, the utilization of flavonoids against coronavirus infection concentrated on the SARS-CoV-2 virus [60, 61].

Hesperidin is a common flavon glucoside which used as an herbal medicine continually. It is mainly found in citrus fruit such as lemon, orange, and grapefruit [62]. It has various activities against the viruses. It's the antiviral and anti-inflammatory activity has been attributed to it an antioxidant property and reduce the pro-inflammatory cytokine production. In a study after SARS-CoV 2 pandemic, it has been shown that COVID-19 uses the ACE-2 receptor for entering the organism the serine protease TMPRSS2 for priming of S-protein. Recently in a work Camostat mesylate used which a serine protease inhibitor drug blocked virus entry and was used as a COVID-19 treatment has been shown in research [63].

Another flavonoid compound quercetin was studied for their chemical activity in searching capillary wall resistance [64]. The *in vitro* and *in vivo* investigation shows that Quercetin affects the organism as a free radical scavenger, which gives two electrons by o-quinone/quinine methide [65], studies also in agreement that quercetin as a potent antioxidant [65, 66].

An important flavonoid naringenin has the chemical name of 4' 5 7-trihydroxyflavone, is accepted as a very important flavonoid, mostly a flavanone, because of its potential biological activities such as antioxidant, anti-inflammatory, and antiviral food additive. In a recent meta-analysis, it was indicated that naringenin may show curative effects against COVID-19 via

inhibition of COVID-19 main protease, 3-chymotrypsin-like protease (3CLpro), and decreasing of angiotensin-converting enzyme receptors activity [67].

CONCLUSION

In a conclusion During the COVID-19 pandemics, as in all other health conditions, or saving health, it is recommended sustainable nutrition which affluence in antioxidant food. Glutathione, melatonin, Vitamin C, and D play an important role in regulating the immune system. But it can not evaluate these supplemental amounts of the vitamins that might give an efficacy. Some reports show the benefit of intra-venous utilization of vitamin C at the high dose in hospitalized COVID-19 patients [43, 68]. Vitamin D insufficiency has been associated with an increased probability of respiratory tract infection, therefore it is sensible, even in enough of specific data, to give vitamin D to healthy individuals and COVID-19 patients [48, 55, 57]. Flavinoids also found increased cell defense mechanisms against the COVID-19 virus [61, 62]. The diet is also important nutritional supplements, researches recommend advice for preventing and healing COVID-19, but the important size of clinical research data is required to support that suggestion.

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Chapter 470

VACCINE DEVELOPMENT STUDIES FOR COVID-19

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ABSTRACT

The ongoing coronavirus disease (COVID)-19 pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has affected people worldwide both sociologically and economically. This crisis might be controlled by a safe, tolerable, and immunogenic vaccine. Multiple vaccines are in development, and some of them are even in phase III trials but, no approved efficacious vaccine is currently available. Vaccines protect from infection, reduce symptom development, lower mortality rates, and reduce the extent of virus circulation. Therefore, hopefully in the near future, when the vaccine is roll-out, we can overcome this pandemic by informing the people correctly on vaccine safety and importance for public health and by vaccinating susceptible people in the most effective policies.

Keywords: COVID-19, SARS-CoV-2, vaccine, pandemic

INTRODUCTION

The first SARS-CoV-2 case identified in December 2019 within a month, the genetic sequence of the virus became available (MN908947.3). On 11 March 2020, the World Health Organization (WHO) declared the SARS-CoV-2 outbreak as a pandemic. Since then, the virus has infected millions of people globally [1]. Current public health interventions aimed at blocking the spread of SARS-CoV-2 have been limited to nonpharmaceutical interventions (NPIs), including travel-associated quarantines, contact tracing, mask usage, and implementation of social distancing regulations. These measures have had various degrees of

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success worldwide. While critical to slowing viral spread, some of these NPIs have resulted in widespread job loss and economic hardship. Considering the substantial political and economic costs associated with NPIs, long-term and effective solutions are needed [2, 3].

In this context, the vaccine remains the most promising solution. Thanks to devoted research efforts worldwide, vaccine development is well underway, with more than 100 vaccine candidates in clinical trials, including candidates in phase III trials. Clinical trials for SARS-CoV-2 vaccines evaluate both the safety and efficacy of vaccine candidates. Ethically, a vaccine cannot be licensed if it does not provide a direct protective benefit to the vaccine. Direct protective benefits of vaccines include protection from infection, reduced symptom development, and lower mortality rates [4].

For vaccine-preventable diseases, not all susceptible individuals can be immunized for various reasons, such as they are too young or too old to be vaccinated, they have co-morbidities and weakened immune systems or they reject the vaccination for cultural, traditional, or religious reasons. The question then is what is the minimum proportion of those we can vaccinate that we need to vaccinate so that those that we cannot vaccinate can be protected from developing severe disease or dying of the disease. The notion of herd immunity in the transmission dynamics is associated with the indirect protection against acquisition of a communicable disease, members of the community receive when a large percentage of the population has become immune to the infectious disease due to natural recovery from prior infection or vaccination. The consequence of herd immunity is that individuals who are not immune (e.g., those who cannot be vaccinated or those who have not been infected yet) receive some protection against the acquisition of the disease. The safest and fastest way to achieve herd immunity is obviously vaccination [5]. This indirect effect decreases the infection risk of both vaccinated and unvaccinated susceptible individuals by reducing the extent of virus circulation in a community. Virus circulation can decrease because vaccinated individuals are less susceptible to infection, or because vaccinated individuals have shorter durations of infection or lower viral loads that reduce their infectiousness. Vaccination campaigns can significantly reduce the number of infections and deaths in subpopulations that remain unvaccinated, even when the vaccination percentage is quite low [6]. The vast majority of the global population remains susceptible to the virus and we are likely well below the herd immunity threshold, despite the staggering rates of infection that some regions have already experienced. Therefore the indirect effects of vaccine candidates are critically important to consider when evaluating SARS-CoV-2 vaccine candidates and formulating strategies for their roll-out. Clinical trials to test vaccine effectiveness do not evaluate population-level effects. Quantifying both the direct and indirect effects of vaccines on population-level outcomes, such as disease incidence and mortality, requires evaluating data after a vaccine has been in use for some time. Therefore, mathematical models are needed to assess the potential indirect effects in advance.

With the hope of producing a vaccine in the near future comes the difficult task of deciding who to vaccinate first as vaccine shortages are inevitable. According to our knowledge on COVID-19 so far, children are less susceptible to infection than middle-aged adults (20 to 65 years old), while older adults (older than 65) were relatively more susceptible. Studies showed that a vaccine with an effectiveness $\geq 50\%$ would be enough to substantially mitigate the ongoing pandemic provided that a high percentage of the population is optimally vaccinated [7]. When minimizing deaths, for low vaccine effectiveness (VE), it is optimal to allocate vaccine to high-risk (older) age-groups first. In contrast, for higher vaccine

effectiveness, there is a switch to allocate vaccine to high-transmission (younger) age-groups first for high vaccination coverage [8]. Any vaccine with medium to high effectiveness ($VE \geq 50\%$) would be able to considerably slow the epidemic while keeping the burden on healthcare systems manageable, as long as a high proportion of the population is optimally vaccinated. Moreover, once $VE = 70\%$, the attack rate drop and full containment of the epidemic would be possible [9].

VACCINE DEVELOPMENT AND CLINICAL TRIALS

Despite many organizations have announced plans to start efficacy testing for their candidate vaccines, an approved vaccine is not expected until 2021, even with substantially compressed development timelines, smooth proceeding of clinical trials, and not accounting for possible failures [10]. Unlike typical therapeutics that are administered to sick patients, vaccines are intended for the healthy. Therefore, confirming the safety and effectiveness of a vaccine is of critical importance [11]. The two primary methods for demonstrating vaccine safety and efficacy are through either a vaccine efficacy randomized clinical trial (RTC) or a vaccine immunogenicity RTC. In the former, large numbers of recruited healthy volunteers are randomly selected to receive either the vaccine or a placebo and then monitored for some time. At the end of the surveillance period, the difference in the proportion of infections between the treatment and control arms is computed to demonstrate the ability of vaccine prevention. In a vaccine immunogenicity RCT, the primary endpoint is an immunity measurement or marker which is known to correlate with protection against infection or disease. This type of trial involves a smaller number of volunteers and requires a shorter follow-up period, and as a result, is quicker and less costly. Given that SARS-CoV-2 is a novel pathogen for which we do not yet know how to determine whether a subject is protected, vaccine efficacy must be confirmed using the longer and more costly vaccine efficacy RCT. Follow-up continues for all participants and includes a collection of serious adverse events for 6 months, and COVID-19 infection and multiple additional immunogenicity measurements through up to two years. Later phases of the study prioritize enrollment of more diverse populations, including those with chronic underlying health conditions and from racial/ethnic groups adversely affected by COVID-19 [12].

A human challenge trial (HCT), in which volunteers are randomized into either the vaccine or placebo arm and then infected deliberately with a live virus in a controlled setting, has been proposed as an alternative to accelerate the vaccine development process. Upon challenge, HCTs can quickly demonstrate the safety and efficacy of candidate vaccines in preventing infection or disease.

Depending on sample size, HCTs could also help to establish functional immune correlates of protection to inform the design of future vaccines. Since an HCT allows comparison of immune responses in vaccinated and unvaccinated individuals, precise measurements of post-vaccination viral loads, characterization of immune responses (innate, adaptive, cell-mediated) and antibody titers, and close monitoring and care of patients, it can help establish the correlates of protection and prove vaccine efficacy concurrently.

Moreover, a properly designed HCT can determine the transmission risk of the infected in a controlled setting with minimal exposure to investigators and the public.

While concerns have been raised regarding the ethics and morality of HCTs, it is generally accepted that HCTs are ethically permissible when the benefits to society outweigh acknowledged risks [13], and they have been deemed acceptable for developing vaccines for multiple infectious diseases such as influenza [14], malaria [15], typhoid [16], cholera [17], and dengue fever [18]. To the best of our knowledge, there have been no published studies of a quantitative analysis of the potential societal value of a COVID-19 HCT.

VACCINE TECHNOLOGIES AND TARGETS

RNA vaccine technology which has been preferred for vaccine candidates so far has enabled rapid vaccine development in response to this pandemic. RNA vaccines provide flexibility in the design and expression of vaccine antigens that can mimic antigen structure and expression during natural infection. RNA is required for protein synthesis, does not integrate into the genome, is transiently expressed, and is metabolized and eliminated by the body's natural mechanisms and, therefore, is considered safe. RNA vaccines for the prevention of infectious diseases and treatment of cancer have been shown in clinical trials to be safe and well-tolerated. In general, vaccination with RNA elicits a robust innate immune response. RNA directs expression of the vaccine antigen in host cells and has intrinsic adjuvant effects. A strength of the RNA vaccine manufacturing platform, irrespective of the encoded pathogen antigen, is the ability to rapidly produce large quantities of vaccine doses against a new pathogen. Most RNA vaccine candidates encode the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein, a key target of virus-neutralizing antibodies [19]. Another well-known vaccine design strategy is incompetent virus vectors, which stabilized SARS-CoV-2 Spike (S) protein. These candidates are selected based on their immunogenicity and manufacturability profile. Vector vaccines are also used for Ebola, RSV, HIV, and Zika viruses [20].

COVID-19 VACCINE EFFECTS AND ADVERSE-EFFECTS

Phase III findings from ongoing vaccine trials being published, recently. Up to these results, after administration of prime and boost doses for RTCs, IgG concentrations, and SARS-CoV-2 neutralizing titers (in neutralization assays) in sera increased, TH1 skewed T cell immune responses with specific CD8⁺ and CD4⁺ T cell expansion. Interferon (IFN) γ was produced by a high fraction of specific CD8⁺ and CD4⁺ T cells. No serious adverse events were reported. Local injection site reactions and systemic events (mostly flu-like symptoms) were dose-dependent, generally mild to moderate, and transient. Symptoms such as fever, fatigue, chills, headache, muscle pain, joint pain, injection site pain, and tenderness occurred within 7 days after each dose. Reactogenicity resolved spontaneously or could be managed with simple measures (e.g. paracetamol). Whereas no relevant change in routine clinical laboratory values occurred after vaccination, temporary reduction of blood lymphocyte counts -related redistribution of lymphocytes into lymphoid tissues- and a transient increase in C-reactive protein (CRP) were observed in a dose-dependent manner in vaccinated participants. CRP is a well-known inflammatory serum protein previously

described as a biomarker for various infectious disease vaccines and an indicator of vaccine adjuvant activity [21].

CONCLUDING REMARKS

Immunization programs are only successful when there are high rates of acceptance and coverage. To accomplish this, it is critical to understand risk perceptions about COVID-19, acceptance of a COVID-19 vaccine, and confidence in media sources, specifically those used to obtain information about the COVID-19 pandemic. We must clearly understand the hesitancy and acceptance of a COVID-19 vaccine to develop evidence-based interventions. This will allow healthcare professionals and health officials to develop messaging to best address concerns and educate all people, especially vulnerable groups [22]. Since the beginning of the COVID-19 pandemic, our government has taken precautions, plans have been made, taken into account the risk that immunization services may be interrupted and there may be an increase in other vaccine-preventable diseases. Immunization is an indispensable part of the healthcare system and is carried out in our healthcare institutions without interruption following the COVID-19 pandemic period measures. Parents should follow the vaccination programs of their children, and when the vaccination time comes, they should contact family physicians and get information about vaccination practices. Children must be vaccinated during the COVID-19 pandemic, too. It has been reported by the World Health Organization that there are currently no known medical contraindications to vaccination of people with COVID-19, either. Also, studies show that the effect of mass influenza vaccination on the spread of COVID-19 and other influenza-like pathogens co-circulating during an influenza season [23]. Therefore, increasing influenza vaccine uptake, or enhancing the public health interventions, would facilitate the management of outbreaks of SARS-CoV-2 and other respiratory pathogens circulating during the peak flu season.

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Chapter 471

MOLECULAR APPROACHES IN COVID-19 TREATMENT

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ABSTRACT

Coronaviruses are a family of enveloped RNA viruses that cause diseases in various mammals and birds. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus identified as the cause of a global infectious disease called coronavirus disease 2019 (COVID-19). To date, there are currently no specific antiviral drugs that have been shown to effectively treat COVID-19. Moreover, vaccines based on viral-encoded peptides may not be effective against COVID-19, as virus mutations could make them futile. Many therapeutic strategies can be predicted in controlling and preventing the SARS-CoV-2 infections, such as oligonucleotide-based therapy, neutralizing monoclonal antibody therapy, autophagy pathway as therapeutic targets, chimeric antigen receptor T-cell (CAR-T) therapy, and mesenchymal-derived exosome therapy. Synthetic oligonucleotide-based therapeutic options containing small interfering RNA (siRNA) and antisense oligonucleotide (ASO) target the virus itself and mediate the silencing of its genome. Neutralizing monoclonal antibodies that target the receptor-binding motif (RBM) can prevent the virus from binding to angiotensin-converting enzyme 2 (ACE2), and are therefore promising antiviral drugs. On the other hand, vaccines and drugs can be developed to target the spike (S) glycoprotein of the coronavirus.

Autophagy plays an important role in viral infection. Autophagosomes can induce apoptotic cell death of virally infected cells and disrupt the virus replication cycle. CAR-T treatment is a successful therapeutic option for patients with relapsed and/or refractory hematologic malignancies. Increased interleukin-6 (IL-6) is related to cytokine storm

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syndrome (CSS) in COVID-19 patients. CAR-T therapy is used successfully in the blocking of IL-6. Therefore, IL-6 can be a specific target for CAR-T therapy in SARS-CoV-2 infected patients. Mesenchymal-derived exosomes demonstrate anti-inflammatory and immunomodulatory effects. MSC-derived exosomes can modulate the activity of T cells. MSC-derived exosomes may inhibit pro-inflammatory cytokines and increase the levels of anti-inflammatory cytokines such as IL-10 in SARS-CoV-2 infection. MSC-derived exosomes have been considered a specific therapeutic option for COVID-19 patients. Future preclinical and clinical investigations are needed to understand the critical roles of these therapy approaches in COVID-19.

Keywords: angiotensin-converting enzyme 2, autophagosomes, CAR-T, exosomes, monoclonal antibody, antisense oligonucleotide, SARS-CoV-2

INTRODUCTION

Therapeutic drugs affect molecular compounds, cellular pathways, and cellular processes for the treatment of diseases. Small molecule targets and peptides are the basic types of medical use.

RNA molecules containing antisense oligonucleotides (ASO) and small interfering RNAs (siRNA) are promising approaches for clinical trials [1]. These options can be used to inhibit and disrupt the virus RNA genome. Moreover, several mRNAs and microRNAs (miRNAs) are assessed for vaccination [2]. Besides, ribosomal RNA (rRNA)-targeted antibiotics are designed for the control of infections [3]. If these oligonucleotides are effectively delivered into the lungs, they can stop the infection.

Another promising option is neutralizing monoclonal antibodies that can be used as therapeutics. The major target of these agents is the viral spike (S) that mediates the binding of the virus to the angiotensin-converting enzyme 2 (ACE2) membrane receptor on the host cell. S1 subunit and S2 subunit are the two subunits of the viral S protein. The S1 subunit has two primary structural domains, receptor-binding domain (RBD) and N-terminal domain (NTD). The S2 subunit acts on virus-cell membrane interaction and fusion. Neutralizing monoclonal antibodies to the S protein provide immune protection against SARS-CoV and MERS-CoV [4, 5]. It is possible to produce efficacy humanized monoclonal antibodies. The SARS-CoV-2 infection could be prevented and treated by human monoclonal antibodies [6]. ACE2 receptor would be also created as an antibody-like molecule. For this strategy, a soluble form of the ACE2 receptor would bind to the S molecule of SARS-CoV-2 and neutralize the virus [7].

Coronaviruses can target the autophagy pathway and promote viral replication [8]. Stressful conditions upregulate autophagy. Autophagy provides cellular homeostasis and involves the organization of numerous molecules. These molecules are generally called autophagy-related (ATG) proteins. Autophagosome formation is a major process for the canonical autophagy pathway. Autophagosome fuses with the lysosome and performs enzymatic degradation.

Autophagy plays a role in regulating pathogen degradation mechanisms. Thus, autophagy is a major part of the immunity against pathogens, such as viruses.

Severe COVID-19 patients have elevated serum levels of IL-6. Increased IL-6 plays a key role in cytokine storms. Chimeric antigen receptor T-cell (CAR-T) immunotherapy appears to control and prevent cytokine storms in SARS-CoV-2 infected patients [9].

Exosomes contain several molecules such as mRNAs, tRNAs, proteins, and microRNAs (miRNAs). Mesenchymal-derived exosomes exhibit immunomodulatory and anti-inflammatory responses. Molecular components of exosomes can regulate immune reactions [10]. Thus, in COVID-19, mesenchymal-derived exosomes can be used as a therapeutic option.

Many drugs are known for clinical evaluation of COVID-19. However, more attention has been paid to these treatment strategies.

OLIGONUCLEOTIDES AS THERAPEUTIC DRUGS

In recent years, it has been made promising progress in the understanding of viral genomics and target-based drugs have been designed for silencing viral gene expression as new therapeutic approaches. Oligonucleotide-based therapeutics have significant anti-viral properties [11]. Oligonucleotide-based therapies, such as ASOs and siRNAs neutralize the viral mRNA molecules.

ASOs are single-stranded DNA or RNA molecules. These oligonucleotides are approximately 15-20 nucleotides in length. ASOs bind to target mRNA and block its function or gene transcription. ASOs have been commonly used in the studies of gene functions and the development of new therapeutics [12]. ASO was first used to block HIV replication [13]. Treatment on ASO strategy requires knowledge of the DNA sequence. Therefore ASOs would be improved against the SARS-CoV-2 DNA sequence and block viral infection.

siRNA also called short interfering RNA or silencing RNA is a double-stranded non-coding RNA molecule. siRNA is approximately 20-25 base pairs in length. Gene expression can be regulated by siRNAs. siRNA-based therapeutic molecules have been designed and applied for antiviral diseases [14]. siRNA-mediated treatment can be an effective option for combating with COVID-19.

The SARS-CoV-2 viral genome is approximately 30 kb long. This genome consists of fourteen open reading frames (ORFs) and codes twenty-seven structural and nonstructural proteins [15]. Ribosome translates ORF1a and ORF1b into a single large poly-protein. The ORF1a contains two viral cysteine proteases, papain-like protease (nsp3) and 3-chymotrypsin-like protease (3CL). The sequence in which codes the nsp3 has been less conserved, however sequence which codes the protease 3CL (nsp5) has been highly conserved. In recent, the protease has been a major drug target for multiple antiviral pathogens. Thus, the nsp5 coding sequence can be treated as a potential target for siRNA-based therapeutics.

Viral RNA dependent RNA polymerase (Rd-Rp) is the other possible target. Rd-Rp is located in the ORF1b and encompasses 13-16 kbp on the viral genome. Rd-Rp site is a highly conserved genome of SARS-CoV-2. Therefore, this region can be evaluated as a potential target for siRNA.

Currently, nanoparticles based carriers and viral vectors have been used as delivery systems for siRNA. In 2003, a siRNA drug was developed targeting SARS-CoV and H5N1

influenza genome by Sirnaomics, Inc. (Maryland, USA). Furthermore, in 2017, Alnylam Pharmaceuticals (USA) and Vir Biotechnology have developed six siRNA against infectious diseases [16]. Nevertheless, more effective carriers should be identified for the targeted specific delivery of the drug.

MECHANISMS RELATED TO CELL ENTRY OF SARS-CoV-2 AS THERAPEUTIC TARGETS

The scientific community has little knowledge of the molecular pathogenesis of SARS-CoV-2. Viruses must enter host cells before they can initiate their life cycle. Therefore, one of the critical steps for the development of effective therapeutics for COVID-19 is to clearly understand the exact mechanism of how the virus enters the human body. The majority of viruses have developed strategies to invade the cell by a process called receptor-dependent endocytosis [17]. Knowledge about the receptor recognition mechanisms of coronaviruses is critical for the development of targeted antiviral treatments focused on blocking that pathway. The cell entry mechanism of SARS-CoV-2 has been extensively studied.

The crown-like appearance of coronaviruses is caused by spike proteins, which are necessary for the viruses to enter the target cell by endocytosis. Three spike proteins assemble into trimers on the virus surface to form a crown-like appearance. The SARS-CoV-2 coronavirus uses a spike protein to bind to the ACE2 receptor on the cell surfaces. Therefore, the distribution and expression of ACE2 may be critical for the target organ of the SARS-CoV-2 [18].

The spike protein is composed of two subunits; S1 and S2. The S1 subunit contains two distinctive domains, the N-terminal domain, and the C-terminal domain. These domains of the S1 subunit can function as receptor-binding domains (RBD). The S2 subunit is the most conserved region of the protein and responsible for mediating membrane fusion between the virus and the host cell membrane. After the spike protein of SARS-CoV-2 binds to ACE2 through its RBD, the S protein priming, allowing the fusion of viral and cellular membranes and viral entry into the cell is done by a protease enzyme [19]. Recent studies revealed that the transmembrane serine proteinase 2 (TMPRSS2), furin, trypsin, and elastase prime the S proteins and provided evidence that successive S protein cleavage at two sites is required for S protein priming. After cleavage, the spike protein S1 segment remains attached to ACE2, while the spike protein S2 segment anchors the viral and cellular membranes, inducing fusion, and viral entry [20].

The ACE2/SARS-CoV-2 complex undergoes endocytosis, which is typically mediated by the acidic endosomal pH, resulting in the fusion of the viral and endosomal membranes and release of the viral genome into the cytosol for productive infection. The results revealed that the cellular entry of SARS-CoV-2 is through clathrin-mediated endocytosis [17].

This discovery is important in the search for several inhibitors targeting the endocytic pathway including endosome and lysosome in the treatment of COVID-19. Several inhibitors targeting the endocytic pathway appear to have therapeutic potential including lysosomotropic agents, clathrin-mediated endocytosis inhibitors, and endosomal/lysosomal protease inhibitors [21].

Chloroquine and hydroxychloroquine, often in combination with a second-generation macrolide, are probably the most well-studied lysosomotropic agent that accumulates in the acidic organelles such as endosomes and lysosomes and neutralizes their pH. They have widely used malaria drugs that have yielded mixed results for the treatment of COVID-19.

Chlorpromazine (CPZ) inhibits membrane fusion processes on clathrin-dependent endocytosis and thereby prevents the entry of the virus into host cells [21]. Therefore, it can be used for the treatment of COVID-19. The inhibition of SARS-CoV-2 by CPZ was suggested in an in vitro study using cell lines. The first clinical study on the treatment of COVID-19 of CPZ has started in Paris. The results in this study suggest that CPZ is unlikely to have the therapeutic potential in the treatment of COVID-19 [22].

Cathepsins are endosomal and lysosomal proteases that play important roles in various cellular processes including both the endocytic pathway and autophagy. Several studies suggested that the inhibitors of cathepsin proteases such as teicoplanin acts to inhibit entry of the virus [23].

The endocytosis route of SARS-CoV-2 involves key proteins involved in endosome formation. The phosphatidylinositol 3-phosphate 5-kinase (PIKfyve) synthesizes a class of phosphoinositides that are required in the maturation process of endosomes. The activity of PIKfyve has been discovered to be essential in the SARS-CoV-2. Apilimod and Vacuolin-1, small molecule inhibitors of PIKfyve were found to significantly reduce SARS-CoV-2 entry. These results suggest the potential for targeting PIKfyve in developing new antiviral molecules against SARS-CoV-2 [24].

The other target is proton pumps that drive protons into endosomes and lysosomes, lowering the pH. Thus, the acidic environment that is required for pH-dependent protease activity is provided. Zohreh et al. hypothesized that metformin may be an effective treatment of COVID-19-related pulmonary fibrosis because it a potential regulator of Vacuolar ATPase and endosomal Na^+/H^+ exchangers, and additionally a regenerative agent for lung fibrosis [25].

Two pore segment channel 2 (TPC2) is a calcium release channel expressed in lysosomal membranes. An article by Ou et al. demonstrated that the activity of human TPC2 is a key player for SARS-CoV-2 cell entry [24]. They suggested that the blocking TPC2 activity by tetrandrine, an inhibitor for TPC2, decreased entry of SARS-CoV-2 S pseudovirions.

SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2. TMPRSS2 is a member of transmembrane protease serines, which are a family of proteins with conserved serine protease domains located on the cell membrane. TMPRSS2 is expressed by human lung cells. Therefore, it is thought that TMPRSS2 plays an important part in virus entry into respiratory system cells. Also, TMPRSS2 happens to be present near the spike-ACE2 binding interface. This cleavage must occur after spike S1 Subunit -ACE2 binding. If it occurs before, the virus is less able to infect the cell. TMPRSS2 inhibitors (Nafamostat, Bromhexine, Aprotinin, Camostat) play a key role in the treatment of COVID-19 disease. The protease inhibitor camostat mesylate is already in clinical use for the treatment of pancreatitis. It was known to inhibit TMPRSS2 and effectively protected the mice against death caused by SARS-CoV infection [26].

SARS-CoV-2 has a high binding capacity for ACE2 – between 10-20 times more than the original coronavirus. This means it is much easier for SARS-CoV-2 to get into human cells compared to the original coronavirus. The structures of SARS-CoV-2 RBD that are essential for ACE2 binding showed that it contains a core and an RBM. The RBD is the most

immunogenic region of COVID-19 spike protein and contains major neutralization epitopes, which induce most of the host immune responses [24]. Therefore, these epitopes may serve as subunit vaccines against coronavirus infections. Therefore, it presents a major challenge to both vaccination and antibody-drug. A structure-based strategy for SARS-CoV-2 RBD may help design subunit vaccines. The hot spot residues at the SARS-CoV-2 RBM are important for SARS-CoV-2 binding to ACE2 receptors.

Monteil et al. suggested that human recombinant soluble ACE2 can significantly block the early stages of SARS-CoV-2 infections in artificial human tissues [27]. Thus, an antibody-drug with a significantly higher RBD binding affinity than ACE2 can block viral attachment. On the other hand, vaccines and drugs can be developed to target the S2 subunits of the spike glycoprotein of the coronavirus. However, the success of this approach may be limited because the spike S2 subunit is less immunogenic than the SARS-CoV-2 Spike S1 protein RBD.

Another potential drug target might be the cellular enzymes that attach fatty acids to a cluster of cysteines in the cytoplasmic tail of spike protein. However, enzymes that attach acyl chains to S have not been identified.

AUTOPHAGY PATHWAY AS THERAPEUTIC TARGETS

Autophagy is conserved in all eukaryotic cells. Autophagy is a constitutive pathway, also it is activated by endoplasmic reticulum stress, starvation, and pathogen infections. Autophagy involves the formation of autophagosomes. Autophagosomes enclose cytoplasmic components, such as protein aggregates and organelles. Furthermore, autophagosomes deliver these components to lysosomes for degradation. Therefore, autophagy is one of the major degradation pathways.

The autophagy pathway is regulated by several proteins encoded by autophagy-related genes (ATGs). The autophagy process is performed through many stages. First, class III phosphatidylinositol 3-kinase (PtdIns3K) protein complex forms autophagy-specific phagophore. Second, the ULK complex expands the phagophore. Also, the Atg8 protein family matures the phagophore. Then, cytoplasmic components are recruited through autophagic receptors followed by the fusion of vesicles with endosomes. The vesicle-endosome complex is called as amphisome. Last, amphisome fuses with a lysosome and subsequently, degradation occurs.

Coronaviruses like other RNA viruses stimulate the development of double-membrane vesicles (DMVs), a hallmark of autophagy [28]. These vesicles mimic autophagosomes. The fusion of viral DMVs with lysosomes (also with late endosomes) results in viral acidification which induces viral replication or virion maturation [29]. Some coronaviruses release their genome into the cytoplasm of the host cell during the entry of the virus [30]. SARS-CoV replicates and transcribes its genome through the autophagic pathway.

The fusion of DMV-lysosome is a crucial stage in the autophagy pathway. The fusion between the autophagy pathway and DMVs may occur during the life cycles of coronaviruses [31]. Coronavirus DMVs play a role as the RNA synthesis site for coronaviruses [32].

Chloroquine, an anti-malarial drug, is a lysosomotropic agent. It neutralizes endosomes and lysosomes. Chloroquine mainly blocks the autophagic pathway by impairing

autophagosome fusion with the lysosome and inhibits the lysosomal degradation activity [33]. The acidic subcellular compartments, lysosomes, and endosomes, are neutralized by chloroquine. Besides, chloroquine can stimulate autophagy-independent dysfunctions of endosomal-lysosomal systems. Thus, chloroquine may affect on the fusion between autophagosome and lysosome [33].

It is well known that chloroquine has anti-viral effects, such as anti-CoVs, anti-HIV, and anti-influenza [34]. It has been suggested that chloroquine treatment suppressed the viral infection in SARS-CoV-infected Vero E6 cells [35]. Also, a recent study revealed that chloroquine inhibits the SARS-CoV-2 infection in Vero E6 cells [36]. In another study, chloroquine has been tested for COVID-19 treatment. The first evidence on in vitro assay showed that they could act on anti-SARS-CoV-2 [37].

The mechanisms of the chloroquine effect are not known clearly during SARS-CoV2 infection. Also, the clinical efficacy of chloroquine is unclear and needs further studies.

Autophagy regulates innate and adaptive immunity. Activation of autophagy can induce the immune system [38]. Targeting the immune system, such as autophagy that regulates immunity could be a therapeutic approach against SARS-CoV-2 infection.

A viral-infected body encounters infection through the innate immune system also the adaptive immune responses are carried out by recruiting virus-specific T lymphocytes and B lymphocytes, respectively. Cell-mediated and humoral immune responses are stimulated. These immune responses both potentiate inflammatory effects and neutralize against viral invasion.

Macrophages and dendritic cells, antigen-presenting cells (APC), present the viral antigen to T cells through human leukocyte antigen (HLA). Activated T cells are transformed into CD8 + T cells and CD4 + T cells. These cells activate both cell-mediated and humoral immune responses. CD8 + T cells disrupt virus-infected cells. CD4 + T cells play a pivotal role in priming CD8 + T cells and B cells. Th1 cells, one of the subsets of CD4+, both stimulate natural killer (NK) cells and CD8 + T cells or remain as memory T cells. However, CD4 + Th2 cells activate B cells to be converted into plasma B cells. Then, B cells produce SARS-CoV-2-specific IgM and IgG antibodies [39]. These antibodies bind and neutralize SARS-CoV-2. Many B cells form immune memory.

Some of the viruses block autophagy by inhibiting autophagy-inducing pathways, AKT1/BECN1, to stimulate viral replication [40]. A recent study has confirmed that SARS-CoV-2 infection also inhibited autophagy [41]. Also, this study suggested that autophagy stimulation revealed the potentiality against this infection [41].

Fasting activates autophagy [42], which induces immunity [43]. Therefore, fasting may control and prevent to COVID-19 [44]. However, to date, there is no experimental evidence that determined the effects of fasting against SARS-CoV-2 infection.

CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPEUTIC STRATEGY FOR COVID-19

T cells play a key role in the initiation of antiviral immune responses. Investigations in lymphocytes of COVID-19 patients are beginning to emerge [45]. Lymphopenia is one of the

major hallmarks of severe COVID-19. T cells, B cells, and natural killer (NK) cells are affected by lymphopenia [46]. It has been demonstrated that SARS-CoV-2 has an impact on T cell function [47]. Patients with severe COVID-19 are most likely to have a reduced number of lymphocytes, monocytes, eosinophils, and basophils. COVID-19 patients have decreased Th cell counts and suppressor T cell counts. These findings show the importance of the T cell-based immunotherapies for COVID-19.

Immunotherapy has promising success in cancer, autoimmune diseases, and other immune system-related diseases [48, 49]. Immunotherapy can be accepted to improve immune responses in COVID-19. It has been well known for the success of interferons in viral infections, so several studies investigate the efficacy of interferon-alpha-1b and alpha-2b for the treatment of COVID-19 [47].

Chimeric antigen receptor T-cell (CAR-T) immunotherapy, adoptive cell therapy, is extensively used for the treatment of patients with hematologic malignancies due to their immune dysregulation and long-term immune reconstitution. Current, CAR-T cell therapy has made promising progress in the treatment of refractory and/or relapsed (R/R) hematological malignancies. Targeting the CD19 CAR-T cell therapy has shown efficient remission in non-Hodgkin lymphoma (NHL) and acute lymphocytic leukemia (ALL) [50].

Importantly, antigen-specific T cells were developed against chronic viral infections. HBV-specific T cells were renewed by CAR-T cells [51]. Böhne et al. first produced CAR-T cells targeting the hepatitis B surface antigen (HBsAg). CAR-T cells were developed to recognize a determinant of HBsAg and to direct aa37-43 in the preS1 peptide. Thus, HBsAg-positive primary human hepatocytes were able to target, and specifically, HBV-infected target cells were eliminated [52]. HIV-targeted CAR-T cells have been generated for the treatment of HIV/AIDS. In recent years, anti-HIV neutralizing antibodies (bNAbs), and bNAb-based CAR-T therapy has been developed as a potential treatment strategy to control HIV infection [53].

To date, numerous immune cell-based immunotherapeutic options against SARS-CoV-2 are being significantly improved. A study demonstrated that CAR-NK cells may have the potential to treat patients with severe COVID-19 [54]. NK cells are extracted from peripheral blood and can be modified to express CAR.

NK cell therapy has a significant anti-tumor effect, which is the direct activity of NK cells on the immune system [55]. Thus, COVID-19, a viral infection associated with immune dysregulation, can be treated with regenerative medicine and its immunoregulatory actions [56].

COVID-19 patients exhibit increased serum inflammatory cytokines. Interleukin-6 (IL-6) seems to play an important role in COVID-19 associated cytokine storm syndrome (CSS). Based on the successful use of IL-6 receptor blockade for CAR-T cell therapy-related cytokine release syndrome (CAR T-cell CRS), similar strategies using tocilizumab, an anti-IL-6 receptor antibody, are being investigated in COVID-19 [9].

CAR-T immunotherapy might be considered for severe COVID-19 patients at increased risk of complications. If patients are affected by hematological diseases and are suffering from relapsed and/or refractory diseases, CAR-T might be useful to control SARS-CoV-2 infection [57].

MESENCHYMAL STEM CELLS-DERIVED EXOSOMES IN COVID-19 TREATMENT

Cell-based therapies aim to control or prevent the damage and disease by repairing and/or replacing the injured cells and tissues. Also, many cell-based therapies contribute to stopping degenerative and pathophysiologic progress [58].

Mesenchymal stem cell (MSC) treatment is one of the major therapy among stem cell-based therapies. MSCs are widely used in regenerative medicine. These cells can repair damaged tissues and organs. Also, MSCs have anti-apoptotic, anti-inflammatory, pro-inflammatory immune reactions. MSCs regulate the immune responses through the transforming growth factor b1 (TGF β 1), which can stimulate the Treg proliferation, activate IL-6, which inhibits the neutrophil proliferation, and induce the prostaglandin E2 (PGE2), which prevents the antigen presentation by dendritic cells and T-effector cell proliferation [59, 60]. MSCs play an important role in immunomodulatory activity [61]. These features have revealed that MSCs are clinically significant.

MSC treatment has been effectively applied to treat many disorders such as degenerative, inflammatory, and metabolic diseases. Furthermore, MSCs are used for cancer therapy. Moreover, Recently, it has been suggested that the transplantation of MSCs enhanced the pulmonary function of COVID-19 patients [62]. Many reports revealed that MSC treatment is associated with low mortality and morbidity rates in COVID-19 patients [63]. The MSCs could use in immunomodulatory effects and differentiation potency for the COVID-19 treatment [64]. MSC treatment of COVID-19 patients is limited.

The exosomes are released from all types of cells, including stem cells [65]. The exosomes are membrane-enclosed extracellular vesicles (EVs). The exosomes include several molecules, such as miRNAs, tRNAs, long noncoding RNAs (lncRNAs), growth factors, proteins, and lipids. Molecular structures of exosomes can affect the immune regulations and epigenetic alterations [10]. Exosomes can be used as promising therapeutic approaches.

MSC-derived exosomes can be useful for repairing damaged tissues and organs. MSC-derived exosomes provide several advantages in comparison to traditional cell-based therapies. MSC-derived exosomes are safer and more stable than cells [66]. In addition to these advantages, MSC-derived exosomes increase their therapeutic potential, exosomes could be modulated with several types of cargos, such as mRNA, miRNA, and proteins [67].

MSC-derived exosomes can modulate the function of T cells. It has been found that MSC-derived exosomes treatment both enhanced the interleukin-10 (IL-10) and TGF- β 1 expression levels, therefore the function of immunosuppressive regulatory T cells increased [68]. Moreover, MSC-derived exosomes reduced the levels of inflammatory cytokines, eosinophils, infiltrated mast cells, IgE, and CD86+ and CD206+ cells [69].

Many infected COVID-19 patients have a multiorgan injury. MSC-derived exosomes are known to reduce lung injury in asthmatic models and acute respiratory distress syndrome (ARDS) [68, 70]. Thus, Organ and tissue damage related to COVID-19 can be treated by MSC-derived exosomes.

Preclinical and clinical findings support the investigational MSC-derived exosomes application due to their anti-inflammatory and immunomodulatory abilities. MSC-derived exosomes can be a useful treatment strategy to reduce the effect of SARS-CoV-2 infection.

CONCLUSION

Currently, no therapeutic approach is approved for COVID-19. The development of diverse therapeutic strategies directing SARS-CoV-2 is needed for the treatment of patients with COVID-19. Oligonucleotide-based therapy, neutralizing monoclonal antibody therapy, autophagy pathway as therapeutic targets, chimeric antigen receptor T-cell (CAR-T) therapy, and mesenchymal-derived exosome therapy are novel therapeutic options against SARS-CoV-2 infection. The use of biomolecules associated with these novel therapeutics can provide significant results for the treatment of COVID-19 patients.

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Chapter 472

OVERVIEW OF U.S. DOMESTIC RESPONSE TO THE 2019 NOVEL CORONAVIRUS (2019-nCoV)*

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BACKGROUND

On December 31, 2019, the World Health Organization (WHO) was informed of a cluster of pneumonia cases in Wuhan City, Hubei Province of China.¹ Illnesses have since been linked to a previously unidentified strain of coronavirus, designated 2019 Novel Coronavirus, or 2019-nCoV. As of February 7, 2020, tens of thousands of people have been infected and over 500 have died, mostly in China.² The disease has spread to several other countries, including the United States.

On January 30, 2020, the Emergency Committee convened by the WHO Director-General declared the 2019-nCoV outbreak to be a Public Health Emergency of International Concern (PHEIC).³ The next day, on January 31, 2020, U.S. Department of Health and

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¹ World Health Organization (WHO), “Novel Coronavirus (2019-nCoV),” <https://www.who.int/westernpacific/emergencies/novel-coronavirus>. International Health Regulations (2005) require countries to notify the World Health Organization (WHO) of events that may constitute a public health emergency of international concern (PHEIC). See CRS In Focus IF10022, *The Global Health Security Agenda and International Health Regulations*.

² WHO, “Novel Coronavirus (2019-nCoV) Situation Report-17,” February 6, 2020, https://www.who.int/docs/defaultsource/coronaviruse/situation-reports/20200206-sitrep-17-ncov.pdf?sfvrsn=17f0dca_4.

³ WHO, “Statement on the second meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV),” January 30, 2020, [https://www.who.int/news-room/detail/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-\(2005\)-emergency-committeeregarding-the-outbreak-of-novel-coronavirus-\(2019-ncov\)](https://www.who.int/news-room/detail/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-(2005)-emergency-committeeregarding-the-outbreak-of-novel-coronavirus-(2019-ncov)). A PHEIC is defined in the IHR (2005) as “an extraordinary event which is determined, as provided in these Regulations: i) to constitute a public health risk to other States through the international spread of disease; and ii) to potentially require a coordinated international response.” This definition implies a situation that is serious, unusual or unexpected; carries implications for public health beyond the affected State’s national border; and may require immediate

Human Services (HHS) Secretary Alex Azar declared the outbreak to be a Public Health Emergency pursuant to Public Health Service Act (PHSA) Section 319, retroactively dated to January 27, 2020.⁴

As the scope of the epidemic widens in China, as of early February, U.S health officials continue to state that the immediate health risk from the new virus to the general American public is low.⁵ With the situation rapidly changing, both WHO and the U.S. Centers for Disease Control and Prevention (CDC) post frequent updates.⁶

The Response to 2019 Novel Coronavirus: Status as of February 6, 2020

International: Selected World Health Organization (WHO) Declarations

<https://www.who.int/emergencies/diseases/novel-coronavirus-2019>

- January 22, 2020: WHO Director-General convened Emergency Committee for Pneumonia due to the Novel Coronavirus 2019-nCoV, which agreed on the “urgency of the situation” but did not declare it a Public Health Emergency of International Concern (PHEIC).
- January 30, 2020: The Emergency Committee convened by the WHO Director-General declared the 2019-nCoV outbreak to be a PHEIC.

Domestic: Selected Events and United States Government Actions

<https://www.hhs.gov/about/news/index.html>; <https://www.cdc.gov/coronavirus/2019-nCoV/summary.html>;
<https://travel.state.gov/content/travel/en/traveladvisories/ea/novel-coronavirus-hubei-province—china.html>; and
<https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/novel-coronavirus-2019-ncov>.

- January 7, 2020: CDC established a 2019-nCoV Incident Management Structure.
- January 21, 2020: First travel-related case of 2019-nCoV detected in the United States.
- January 21, 2020: CDC activated its Emergency Operations Center to better provide ongoing support to the 2019-nCoV response and issued updated travel guidance for China, recommending that travelers avoid all nonessential travel to all of the country.
- January 23, 2020: U.S. Department of State ordered the departure of all nonemergency U.S. personnel and their family members from Wuhan.
- January 29, 2020: President Donald Trump announced the formation of the President’s Coronavirus Task Force, led by HHS and coordinated by the National Security Council.
- January 29, 2020: State Department allowed for the voluntary departure of nonemergency personnel and family members of U.S. government employees from China.
- January 30, 2020: First U.S. person-to-person transmission of 2019-nCoV.
- January 30, 2020: State Department updated the Travel Advisory for China from a Level 3: Reconsider Travel to Level 4: Do Not Travel due to novel coronavirus first identified in Wuhan, China.
- January 31, 2020: U.S. Department of Health and Human Services (HHS) Secretary Alex Azar declared the outbreak to be a Public Health Emergency pursuant to Public Health Service Act (PHSA) Section 319.
- January 31, 2020: President Trump issued a proclamation that suspends the entry of any foreign national who has been in China within the prior 14 days, subject to some exceptions.
- February 2, 2020: Travel restrictions and additional quarantine requirements on travelers from China went into effect.
- February 3, 2020: CDC submitted an Emergency Use Authorization (EUA) package to the U.S. Food and Drug Administration (FDA) for the 2019-nCoV diagnostic test—Real-Time RT-PCR Diagnostic Panel.
- February 4, 2020: FDA issued an EUA enabling emergency use of CDC’s Real-Time RT-PCR Diagnostic Panel, permitting CDC to share diagnostic kit with other labs.

international action. See WHO webpage on PHEIC at <https://www.who.int/ihr/procedures/pheic/en/>, accessed on January 31, 2020.

⁴ U.S. Department of Health and Human Services (HHS), “Secretary Azar Declares Public Health Emergency for United States for 2019 Novel Coronavirus,” press release, January 31, 2020, <https://www.hhs.gov/about/news/2020/01/31/secretary-azar-declares-public-health-emergency-us-2019-novel-coronavirus.html>.

⁵ Centers for Disease Control and Prevention (CDC), CDC “Media Telebriefing: Update on 2019 Novel Coronavirus (2019-nCoV),” February 3, 2020, <https://www.cdc.gov/media/releases/2020/t0203-coronavirus-update.html>.

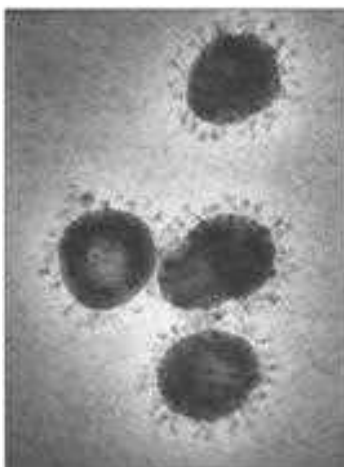
⁶ WHO, “Novel Coronavirus (2019-nCoV) Situation Reports,” <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports>; and U.S. Centers for Disease Control and Prevention (CDC), “2019 Novel Coronavirus (2019-nCoV) Situation Summary,” <https://www.cdc.gov/coronavirus/2019-ncov/summary.html>.

This report discusses selected actions taken by the federal government to quell the introduction and spread of 2019-nCoV in the United States. The HHS Secretary has taken several specific actions to address the 2019-nCoV threat. While some of these actions are based in generally applicable authorities of the Secretary, other authorities may be contingent upon the Secretary or another federal official making a determination or declaration, specific to that authority, regarding the existence of a public health emergency or threat. Each of the actions taken by the Secretary, its statutory basis, and any distinct declarations and determinations supporting the action is presented in this report.

Additional CRS products about this outbreak may be found on the “2019 Novel Coronavirus” Hot Topics tab at www.crs.gov/.

2019 NOVEL CORONAVIRUS (2019-nCoV)

Coronaviruses (see Figure 1) are common respiratory pathogens, usually causing mild illnesses such as the common cold; however, several strains that cause serious illness have emerged in recent years. 2019-nCoV is causing the third serious outbreak of novel coronavirus in modern times, following severe acute respiratory syndrome (SARS) in 2002 and Middle East Respiratory Syndrome (MERS) in 2012.⁷ The global health community is closely monitoring 2019-nCoV because of the severity of symptoms (including death) among those infected and the speed of its spread worldwide. Experts do not know the origin of 2019-nCoV, though genetic analysis and other features suggest an animal source.⁸



Source: CDC Public Health Image Library: <https://phil.cdc.gov/Details.aspx?pid=10270>.

Note: Surface projections on the viral envelope of a poultry coronavirus form the halo or “corona” that gives this virus group its name.

Figure 1. Coronaviruses, electron micrograph.

⁷ CDC, “Human Coronavirus Types,” accessed February 4, 2020, <https://www.cdc.gov/coronavirus/types.html>.

⁸ Jon Cohen, “Mining Coronavirus Genomes for Clues to the Outbreak’s Origins,” *Science*, January 31, 2020, <https://www.sciencemag.org/news/2020/01/mining-coronavirus-genomes-clues-outbreak-s-origins>; and CDC, “2019 Novel Coronavirus (2019-nCoV) Situation Summary,” updated February 3, 2020, <https://www.cdc.gov/coronavirus/2019-nCoV/summary.html>.

Health officials and researchers are still learning about 2019-nCoV. According to CDC, 2019-nCoV typically causes respiratory infections characterized by a fever, cough, and sometimes breathing difficulty—a suite of symptoms that is common during influenza season.⁹ Features that have yet to be clarified include routes of transmission (e.g., through the air, from contaminated surfaces); the incubation period (the time between infection and the onset of symptoms); and whether an infected person without symptoms can transmit infection.¹⁰ Although it was first reported that 2019-nCoV infections resulted from an animal contact, Chinese officials confirmed person-to-person transmission on January 21, 2020.¹¹ Chinese officials have also reported transmission of the virus from asymptomatic patients.¹² However, this finding has yet to be confirmed by U.S. and international health officials and other experts. While WHO and other health experts acknowledge transmission among asymptomatic individuals is possible, scientists agree that asymptomatic transmission is unlikely to be a driver of the outbreak.¹³

At this time no specific treatment or preventive vaccine exists for 2019-nCoV infections. Care for patients is supportive: maintaining hydration, preventing secondary infections, and providing respiratory support, such as use of a ventilator, if needed.¹⁴

DOMESTIC RESPONSE

In the United States, communicable disease control involves collaboration among federal agencies, state health departments, and international partners. Authority to compel isolation (for sick patients), quarantine (for healthy exposed persons), and disease reporting generally rests in state law.¹⁵ The HHS Secretary and, by delegation, CDC have broad authority to assist in the control of communicable diseases through international cooperation, federal-state cooperation, and public health emergency response activities.¹⁶ In addition, CDC (by delegation) has explicit authority to detain, examine, and release persons arriving into the United States, and traveling between states, who are suspected of having a communicable

⁹ CDC, “Symptoms—2019 Novel Coronavirus,” accessed February 4, 2020, <https://www.cdc.gov/coronavirus/2019-ncov/about/symptoms.html>.

¹⁰ CDC, “Transmission—2019 Novel Coronavirus,” accessed February 4, 2020, <https://www.cdc.gov/coronavirus/2019-ncov/about/transmission.html>.

¹¹ Matthew Walsh and Han Wei, “Wuhan Virus Update: China Confirms Human-to-Human Transmission,” *Caixin Global*, January 21, 2020, <https://www.caixinglobal.com/2020-01-21/wuhan-virus-update-china-confirms-human-to-human-transmission-101506555.html>.

¹² WHO, “Novel Coronavirus (2019-nCoV) Situation Report -12,” February 1, 2020, <https://www.who.int/docs/defaultsource/coronaviruse/situation-reports/20200201-sitrep-12-ncov.pdf>.

¹³ On January 30, details about a cluster of 2019-nCoV cases in Germany thought to have originated from an asymptomatic patient were reported in the *New England Journal of Medicine*. These findings were later questioned by observers as new information emerged about the index patient and her symptoms at the time of transmission. For further details, see “Transmission of 2019-nCoV Infection from an Asymptomatic Contact in Germany,” *New England Journal of Medicine*, January 30, 2020, and Kai Kupferschmidt, “Study Claiming New Coronavirus can be Transmitted by People Without Symptoms was Flawed,” *Science*, February 3, 2020, <https://www.sciencemag.org/news/2020/02/paper-non-symptomatic-patient-transmitting-coronavirus-wrong>.

¹⁴ CDC, “2019 Novel Coronavirus: Information for Healthcare Professionals,” <https://www.cdc.gov/coronavirus/2019-nCoV/hcp/index.html>.

¹⁵ CDC, “Legal Authorities for Isolation and Quarantine,” <https://www.cdc.gov/quarantine/aboutlawsregulations/quarantineisolation.html>.

¹⁶ CDC, “Selected Federal Legal Authorities Pertinent to Public Health Emergencies,” August 2017, <https://www.cdc.gov/phlp/docs/ph-emergencies.pdf>.

disease.¹⁷ Other authorities, such as those in the Immigration and Nationality Act of 1952 (INA, P.L. 82-414), allow for other actions relevant to communicable disease control, such as travel restrictions.¹⁸

The use of federal and state disease control authorities and other key actions taken in response to the 2019-nCoV outbreak are discussed below. These activities of federal agencies in collaboration with state and local governments include, among others (1) investigation of 2019-nCoV cases and infection control measures in the community, (2) travel restrictions and/or quarantine requirements on certain travelers who have recently visited China, (3) medical countermeasure development, and (4) health system preparedness. Federal agencies involved include several HHS agencies, such as CDC, the Assistant Secretary for Preparedness and Response (ASPR), the National Institutes of Health (NIH), and the U.S. Food and Drug Administration (FDA), in collaboration with other agencies such as the U.S. Department of State and the Department of Homeland Security (DHS).

Investigation and Control of 2019-nCoV Cases in the Community

To curb the spread of 2019-nCoV cases in the community, state, tribal, and local health departments, with support from CDC, work to identify cases, investigate the possible spread of disease, and take infection control measures.

Case identification begins with testing for 2019-nCoV. CDC urges clinicians to consider a patient's travel and/or contact history and a 14-day incubation period when deciding whether to inform health departments and obtain patient specimens (e.g., mucus, urine) for 2019-nCoV testing. Health care providers are urged to report possible cases to state, tribal, and/or local health departments, which then report to CDC.¹⁹

CDC has developed a diagnostic test for the 2019-nCoV virus and initially performed all domestic testing on suspected patients.²⁰ On February 5, 2020, CDC announced that it would begin distributing test kits to state and local laboratories, following an authorization from the FDA (see the "Medical Countermeasures" section for more details).²¹ CDC has been facilitating the collection and transport of specimens until the diagnostic test is made locally available.²²

Once a patient is reported and in the process of having specimens tested, he or she is considered a *patient under investigation* (PUI) for 2019-nCoV. CDC has developed guidelines for isolation and other precautions for PUIs (including potential PUIs) or those

¹⁷ Interstate Quarantine regulations: 42 C.F.R. Part 70, and Foreign Quarantine regulations: 42 C.F.R. Part 71.

¹⁸ 8 U.S.C. Chapter 12.

¹⁹ Anita Patel, Daniel B. Jernigan, and 2019 n-CoV CDC Response Team, "Initial Public Health Response and Interim Clinical Guidance for the 2019 Novel Coronavirus Outbreak—United States, December 31, 2019–February 4, 2020," *Morbidity and Mortality Weekly Report (MMWR)*, vol. 69 (February 5, 2020).

²⁰ CDC, "2019 Novel Coronavirus (2019-nCoV) Situation Summary," updated February 3, 2020, <https://www.cdc.gov/coronavirus/2019-nCoV/summary.html>.

²¹ CDC "Media Telebriefing: Update on 2019 Novel Coronavirus (2019-nCoV)," February 5, 2020, <https://www.cdc.gov/media/releases/2020/a0205-cdc-telebriefing-coronavirus-update.html>.

²² CDC, "Interim Guidance for Healthcare Professionals," updated February 2, 2020, <https://www.cdc.gov/coronavirus/2019-nCoV/hcp/clinical-criteria.html>.

receiving supportive care for 2019-nCoV infection in healthcare settings.²³ A key goal of the guidelines is the prevention of disease transmission to health care workers, who may be exposed through high-risk procedures, such as maintaining an ill patient on a ventilator.²⁴

Disease investigation for confirmed cases involves *contact tracing*—identifying and evaluating individuals who had contact with the patient to determine if transmission has occurred. These investigations are generally conducted by state, tribal, and local health officials, often with support and technical assistance from CDC.²⁵ As of February 3, 2020, CDC has reported two U.S. cases of person-to-person transmission of 2019-nCoV among close household contacts and has indicated that it expects to find additional cases of person-to-person transmission.²⁶

As of February 3, 2020, CDC reported that it had “deployed multidisciplinary teams to Washington, Illinois, California, and Arizona to assist health departments with clinical management, contact tracing, and communications.”²⁷ In addition, the Public Health Emergency Declaration by Secretary Azar, pursuant to PHSA Section 319, gives state, local, and tribal health departments more flexibility to reassign personnel to respond to 2019-nCoV if their salaries are funded in whole or in part by PHSA authorized programs.²⁸

Travel Restrictions and Quarantine Requirements

Restrictions and Requirements in Effect

CDC and the U.S. Department of State have issued advisories to avoid unnecessary travel to China, including a rare Level 4 advisory from the State Department to avoid all travel to China.²⁹ In addition, the Trump Administration has imposed entry restrictions and quarantine requirements in response to the entry of individuals who may pose a risk of introducing the 2019 Novel Coronavirus into the United States.

With respect to entry restrictions, President Trump issued a proclamation on January 31, 2020, that suspends the entry of any foreign national who has been in China within the prior 14 days, subject to some exceptions.³⁰ The exceptions cover lawful permanent residents

²³ CDC, “Interim Infection Prevention and Control Recommendations for Patients with Confirmed 2019 Novel Coronavirus (2019-nCoV) or Patients Under Investigation for 2019-nCoV in Healthcare Settings,” updated February 3, 2020, <https://www.cdc.gov/coronavirus/2019-ncov/hcp/infection-control.html>.

²⁴ Chaolin Huang, Yeming Wang, Xingwang Li, et al., “Clinical features of Patients Infected with 2019 Novel Coronavirus in Wuhan, China,” *The Lancet*, January 24, 2020.

²⁵ CDC, “Transcript of 2019 Novel Coronavirus (2019-nCoV) Update,” January 27, 2020, <https://www.cdc.gov/media/releases/2020/t0127-coronavirus-update.html>.

²⁶ CDC, “Transcript for CDC Telebriefing: CDC Update on Novel Coronavirus,” February 3, 2020, <https://www.cdc.gov/media/releases/2020/t0203-coronavirus-update.html>.

²⁷ CDC, “2019 Novel Coronavirus (2019-nCoV) Situation Summary,” updated February 3, 2020, <https://www.cdc.gov/coronavirus/2019-nCoV/summary.html>.

²⁸ HHS, “Secretary Azar Declares Public Health Emergency for United States for 2019 Novel Coronavirus,” press release, January 31, 2020, <https://www.hhs.gov/about/news/2020/01/31/secretary-azar-declares-public-health-emergency-us-2019-novel-coronavirus.html>.

²⁹ CDC, “Travel Health Notices: Novel Coronavirus in China,” <https://wwwnc.cdc.gov/travel/notices/warning/novelcoronavirus-china>; and U.S. Department of State, “China Travel Advisory,” February 2, 2020, <https://travel.state.gov/content/travel/en/traveladvisories/traveladvisories/china-travel-advisory.html>.

³⁰ The White House, “Proclamation on Suspension of Entry as Immigrants and Nonimmigrants of Persons Who Pose a Risk of Transmitting 2019 Novel Coronavirus,” January 31, 2020, <https://www.whitehouse.gov/presidential-actions/proclamation-suspension-entry-immigrants-nonimmigrants-persons-pose-risk-transmitting-2019-novel-coronavirus/>.

(LPRs), most immediate relatives of U.S. citizens and LPRs, and some other groups.³¹ The proclamation directs the Department of State and the Department of Homeland Security (DHS) to establish procedures for implementing and enforcing the entry restrictions, which by the terms of the proclamation took effect at 5:00 p.m. (EST) on February 2, 2020. For statutory authority, the proclamation relies principally upon Section 212(f) of the INA.³² That statute authorizes the President “to suspend the entry of all aliens or any class of aliens” whose entry he “finds ... would be detrimental to the interests of the United States.”³³ The Supreme Court has held that Section 212(f) “exudes deference to the President” and gives him mostly unfettered discretion to decide “when to suspend entry,” “whose entry to suspend,” “for how long,” and “on what conditions.”³⁴ The presidential proclamation is in effect until terminated by the President.³⁵ The proclamation also directs the HHS Secretary to “recommend that the President continue, modify, or terminate this proclamation.”³⁶ Such recommendation is required “no more than 15 days after the date of this order and every 15 days thereafter.”³⁷

Quarantine requirements also went into effect on February 2, 2020, according to a DHS announcement.³⁸ All persons, including U.S. nationals, LPRs, and their immediate families who arrive in the United States within 14 days after having been in China are to arrive and be screened at one of 11 designated arrival airports, and such persons may be subject to mandatory quarantine, pursuant to the standing quarantine authorities of the HHS Secretary under PHSA Section 361.³⁹ Persons showing symptoms of illness are to be evaluated by CDC staff to determine if they should be taken to a hospital for medical evaluation and to get care as needed.⁴⁰ Asymptomatic persons are generally to be held under federal quarantine for up to 14 days if they have traveled from China’s Hubei province. However, asymptomatic persons who have traveled from other parts of China may be allowed to self-quarantine for 14 days.⁴¹

Personnel from DHS components—namely Customs and Border Protection (CBP) and the Transportation Security Administration (TSA)—are involved in excluding foreign nationals from entry and in assisting CDC personnel with implementation of quarantines for those who are permitted entry under these requirements.⁴²

³¹ *Id.*

³² 8 U.S.C. § 1182(f).

³³ *Id.*

³⁴ *Trump v. Hawaii*, 138 S. Ct. 2392, 2408 (2018).

³⁵ *Proclamation*, *supra* note 4, §5.

³⁶ *Id.*

³⁷ *Id.*

³⁸ Department of Homeland Security (DHS), “DHS Issues Supplemental Instructions for Inbound Flights with Individuals Who Have Been in China,” press release, February 2, 2020, <https://www.dhs.gov/news/2020/02/02/dhsissues-supplemental-instructions-inbound-flights-individuals-who-have-been-china>.

³⁹ 42 U.S.C. §264. See “Domestic Quarantine and Isolation: Legal Authority and Policies,” in CRS Report R43809, *Preventing the Introduction and Spread of Ebola in the United States: Frequently Asked Questions*; and CDC, “Legal Authorities for Isolation and Quarantine,” <https://www.cdc.gov/quarantine/aboutlawsregulations/quarantineisolation.html>.

⁴⁰ CDC, “2019 Novel Coronavirus: Travelers from China Arriving in the United States,” <https://www.cdc.gov/coronavirus/2019-ncov/travelers/from-china.html>.

⁴¹ DHS, “DHS Issues Supplemental Instructions for Inbound Flights with Individuals Who Have Been in China,” press release, February 2, 2020, <https://www.dhs.gov/news/2020/02/02/dhs-issues-supplemental-instructions-inboundflights-individuals-who-have-been-china>.

⁴² *Ibid.*

Of note, in addition to announcing the United States' use of entry restrictions and quarantine authority on January 31, HHS Secretary Azar declared the 2019-nCoV outbreak to be a Public Health Emergency, pursuant to PHSA Section 319.⁴³ This declaration was not statutorily required for the abovementioned entry restrictions and quarantine requirements to go into effect. Each of these authorities is independent of the others.

Potential Effects of Travel Restrictions on the Spread of 2019-nCoV

Proposals to restrict the movement of people from affected regions or countries are part of early discussions when novel communicable diseases arise. WHO generally advises against nations imposing travel restrictions on other nations, citing limited evidence of the effectiveness of such measures in controlling outbreaks and the harmful economic effects they have on nations struggling with outbreaks.⁴⁴ Voluntary movement restrictions are urged instead (see text box below).

In sum, WHO recommends exit screening—screening for symptoms of illness at the point of departure—as preferable to entry screening (i.e., at the point of arrival) as a means to prevent spread of the disease. Other than interventions for individuals who are found to be ill at exit and/or entry screening, WHO does not recommend broader travel restrictions.

The effect of travel restrictions on the spread of communicable diseases is considered poorly understood for several reasons, including (1) limited contemporary examples for study; (2) the inherent variability in the natural progression of global disease outbreaks, even those caused by the same pathogen; (3) variation in actions taken by affected countries and restrictions imposed by other countries; and (4) difficulty in accounting for the effects of nongovernmental actions such as event cancellations and airline flight adjustments. In response to the emergence of 2019-nCoV, China imposed sweeping internal movement restrictions,⁴⁵ a measure that is likely, in later analyses, to obscure or confound any additional transmission-damping effects that the U.S. imposed travel restrictions may achieve.

Several studies have examined the potential effects of travel restrictions on disease spread, particularly looking at the global spread of influenza and at the SARS outbreak in 2002-2003. Of note, these analyses sometimes indicated delays in the speed of spread of an outbreak. However, the effect of travel restrictions on the ultimate geographic spread of the outbreak—or on the reduction of overall morbidity or mortality—is unclear, and the evidence base is limited. Some studies have found no effect of travel restrictions on overall morbidity and mortality of infectious disease.⁴⁶ Others have found that very strict travel restrictions may effectively prevent the spread of disease (i.e., complete border closure) or that travel restrictions might be more effective when combined with other infection control measures,

⁴³ HHS, “Secretary Azar Declares Public Health Emergency for United States for 2019 Novel Coronavirus,” press release, January 31, 2020.

⁴⁴ See, for example, World Health Organization (WHO), “No Rationale for Travel Restrictions,” May 1, 2009, in the context of the 2009 H1N1 influenza pandemic, https://www.who.int/csr/disease/swineflu/guidance/public_health/travel_advice/en/.

⁴⁵ Michael Levenson, “Scale of China’s Wuhan Shutdown Is Believed to Be Without Precedent,” *The New York Times*, January 22, 2020.

⁴⁶ Several such studies are discussed in Julia Belluz and Steven Hoffman, “The evidence on travel bans for diseases like coronavirus is clear: They don’t work,” *Vox*, January 23, 2020, <https://www.vox.com/2020/1/23/21078325/wuhanchina-coronavirus-travel-ban>.

such as quarantine and isolation.⁴⁷ In particular, compulsory movement restrictions may rely on public support in order to be effective, as well as to avoid discrimination and loss of public trust. Many suggest that if public support and trust are essential in any case, enlisting movement restriction through voluntary measures may be just as effective, with less societal disruption.⁴⁸

WHO Current Guidance Regarding International Travel During 2019-nCoV

“With the information currently available for the novel coronavirus, WHO advises that measures to limit the risk of exportation or importation of the disease should be implemented, without unnecessary restrictions of international traffic....

Advice for exit screening in countries or areas with ongoing transmission of the novel coronavirus 2019-nCoV (currently People’s Republic of China): Conduct exit screening at international airports and ports in the affected areas, with the [aim of] early detection of symptomatic travellers for further evaluation and treatment, and thus prevent exportation of the disease, while minimizing interference with international traffic;

Advice for entry screening in countries/areas without transmission of the novel coronavirus 2019-nCoV that choose to perform entry screening: The evidence from the past outbreaks shows that effectiveness of entry screening [to prevent disease spread] is uncertain.... Temperature screening to detect potential suspect cases at Point of Entry may miss travellers incubating the disease or travellers concealing fever during travel and may require substantial investments. A focused approach targeting direct flights from affected areas could be more effective and less resource demanding....Currently the northern hemisphere (and China) is in the midst of the winter season when Influenza and other respiratory infections are prevalent. When deciding implementation of entry screening, countries need to take into consideration that travellers with signs and symptoms suggestive of respiratory infection may result from respiratory diseases other than 2019-nCoV, and that their follow-up may impose an additional burden on the health system.... WHO advises against the application of any restrictions of international traffic based on the information currently available on this event.”

Source: WHO, “Updated WHO Advice for International Traffic in Relation to the Outbreak of the Novel Coronavirus 2019-nCoV,” January 27, 2020, https://www.who.int/ith/2019-nCoV_advice_for_international_traffic/en/.

In explaining the difference between the United States’ response to the 2019-nCoV and the 2009 h1n1 pandemic flu, CDC official Nancy Messonnier stated that in the case of 2019-nCoV, the virus was caught early, before it spread around the world, and that CDC is taking advantage of the window of opportunity to slow its spread into the United States.⁴⁹

Medical Countermeasures

Potential Products for Use in the 2019-nCoV Response

Medical countermeasures (MCMs) are medical products that may be used to treat, prevent, or diagnose conditions associated with emerging infectious diseases or chemical, biological, radiological, or nuclear (CBRN) threats. Examples of MCMs include biologics (e.g., vaccines, monoclonal antibodies), drugs (e.g., antimicrobials, antiretrovirals), and devices (e.g., diagnostic tests and personal protective equipment such as gloves,

⁴⁷ Sukhyun Ryu, Huizhi Gao, Jessica Y. Wong, et al., “Nonpharmaceutical Measures for Pandemic Influenza in Nonhealthcare Settings—International Travel-Related Measures,” *Emerging Infectious Diseases*, vol. 26, no. 5 (May 2020).

⁴⁸ Francesca Matthews Pillemer et al., “Predicting Support for Non-pharmaceutical Interventions during Infectious Outbreaks: A Four Region Analysis,” *Disasters*, vol. 39, no. 1, pp. 125-145, January, 2015, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4355939/>.

⁴⁹ CDC, “Transcript for CDC Telebriefing: CDC Update on Novel Coronavirus,” February 5, 2020, <https://www.cdc.gov/media/releases/2020/t0205-coronavirus-update.html>.

respirators/masks, and gowns).⁵⁰ FDA regulates MCMs domestically. Currently, there are no FDA-approved MCMs for 2019-nCoV, although FDA has authorized the use of an *unapproved* diagnostic test via an Emergency Use Authorization (EUA).⁵¹ Federal agencies, pharmaceutical and biotech companies, nongovernmental organizations, and global regulators have been working to expedite the development and availability of MCMs for 2019-nCoV. Examples of such efforts include the following:

- **Diagnostics.** CDC developed the 2019-nCoV Real-Time RT-PCR Diagnostic Panel.⁵² On February 4, 2020, FDA issued an EUA, which permits the distribution of the unapproved diagnostic test to and for use by state and local partners.⁵³ (EUs are described in more detail below). Several federal agencies are working with industry partners to develop rapid diagnostic point-of-care tests for 2019-nCoV, including NIH, particularly through the National Institute of Allergy and Infectious Diseases (NIAID); ASPR, through the Biomedical Advanced Research and Development Authority (BARDA); and the Department of Defense (DOD).⁵⁴

On February 5, 2020, BARDA announced an Easy Broad Agency Announcement (EZ-BAA) to solicit applications for development funding of 2019-nCoV molecular diagnostics. The submissions must have a viable plan to meet requirements for the FDA to consider EUA within 12 weeks of an award.⁵⁵

- **Therapeutics.** Research and development into several treatment strategies for 2019-nCoV are underway by federal agencies, international partners, and industry. Drawing from research on the SARS and MERS coronaviruses, NIAID is assessing potential treatment strategies such as antiviral drugs and animal models that can be used to test potential MCMs. In addition, NIAID is developing assays and other research tools to study 2019-nCoV.⁵⁶ On February 4, 2020, BARDA announced that it would expand an existing collaboration with Regeneron Pharmaceuticals Inc. to

⁵⁰ FDA, “What Are Medical Countermeasures?” accessed February 4, 2020, <https://www.fda.gov/emergency-preparedness-and-response/about-mcmi/what-are-medical-countermeasures>.

⁵¹ FDA, “Novel coronavirus (2019-nCoV),” accessed February 4, 2020, <https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/novel-coronavirus-2019-ncov>.

⁵² Reverse transcriptase-polymerase chain reaction (RT-PCR) is a very sensitive technique that, in this use, allows the detection of otherwise undetectably low amounts of biological components specific to coronavirus.

⁵³ FDA, “FDA Takes Significant Step in Coronavirus Response Efforts, Issues Emergency Use Authorization for the First 2019 Novel Coronavirus Diagnostic,” February 4, 2020, <https://www.fda.gov/news-events/press-announcements/fda-takes-significant-step-coronavirus-response-efforts-issues-emergency-use-authorization-first>.

⁵⁴ Dr. Anthony Fauci, Director of the National Institute of Allergy and Infectious Diseases (NIAID), HHS News Conference on Coronavirus, January 28, 2020, <https://plus.cq.com/doc/newsmakertranscripts-5822133>; and HHS Representative, White House Coronavirus Task Force news conference, January 31, 2020, <https://plus.cq.com/doc/newsmakertranscripts-5826415>.

⁵⁵ HHS, “HHS Seeks Abstract Submissions for 2019-nCoV Diagnostics Development,” press release, February 5, 2020, <https://www.hhs.gov/about/news/2020/02/05/hhs-seeks-abstract-submissions-for-2019-ncov-diagnostics-development.html>.

⁵⁶ Anthony Fauci, Director of the National Institute of Allergy and Infectious Diseases (NIAID), HHS News Conference on Coronavirus, January 28, 2020, <https://plus.cq.com/doc/newsmakertranscripts-5826415>; and Hilary Marston, NIAID, “2019 Novel Coronavirus Stakeholder Listening Session Transcript,” January 30, 2020, <https://www.phe.gov/Preparedness/nCoV/Documents/2019nCoV-Listening-Session-Transcript.pdf>.

develop monoclonal antibodies that could be used to treat 2019-nCoV infections.⁵⁷ This partnership would build upon an existing technology used to develop monoclonal antibody therapeutics to treat Ebola and MERS.

Scientists in China are testing drugs currently approved for treatment of HIV, influenza (flu), or malaria for potential effectiveness against 2019-nCoV.⁵⁸ For example, in China, AbbVie's HIV drug Kaletra has been recommended as treatment for patients who have tested positive for 2019-nCoV, while the drug undergoes clinical testing. Johnson & Johnson has reportedly provided its HIV drug Prezcoibx to China to test as a potential treatment as well.⁵⁹ Scientists are also testing many experimental treatments in the research pipeline.⁶⁰ For example, Gilead is working with health authorities in China to determine whether its experimental antiviral drug Remdesivir can safely and effectively treat 2019-nCoV infections.⁶¹

- **Vaccines.** At least eight different 2019-nCoV vaccine development initiatives among federal agencies, industry, research institutions, and philanthropies have been announced.⁶² Of note, the NIAID Vaccine Research Center (VRC) is collaborating with the drug company Moderna and the Coalition for Epidemic Preparedness Innovations (CEPI) to advance a vaccine candidate. Moderna expects this vaccine to enter phase 1 clinical testing in the spring of 2020.⁶³ CEPI is also supporting vaccine development by the University of Queensland (Australia) and the drug companies GlaxoSmithKline and Inovio.⁶⁴ Johnson & Johnson stated that it is mobilizing efforts to develop a possible preventive vaccine candidate against 2019-nCoV.⁶⁵

⁵⁷ HHS, "HHS, Regeneron Collaborate to Develop 2019-nCoV Treatment," February 4, 2020, <https://www.hhs.gov/about/news/2020/02/04/hhs-regeneron-collaborate-to-develop-2019-ncov-treatment.html>.

⁵⁸ Manli Wang, Ruiyuan Cao, Leike Zhang, et al., "Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro," *Cell Research*, February 4, 2020, <https://doi.org/10.1038/s41422-020-0282-0>; and Panu Wongcha-um, "Cocktail of flu, HIV drugs appears to help fight coronavirus: Thai doctors," *Reuters*, February 2, 2020.

⁵⁹ Jared Hopkins, "U.S. Drugmakers Ship Therapies to China, Seeking to Treat Coronavirus," *Wall Street Journal*, January 27, 2020.

⁶⁰ Manli Wang, Ruiyuan Cao, Leike Zhang, et al., "Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro," *Cell Research*, February 4, 2020, <https://doi.org/10.1038/s41422-020-0282-0>.

⁶¹ Gilead, "Gilead Sciences Statement on the Company's Ongoing Response to the 2019 Novel Coronavirus (2019-nCoV)," January 31, 2020, <https://www.gilead.com/news-and-press/company-statements/gilead-sciences-statement-on-the-company-ongoing-response-to-the-2019-new-coronavirus>.

⁶² Steve Usdin and Karen Tkach Tuzman, "The Race Is on to Develop Therapies and Vaccines for the Coronavirus Outbreak," *Biocentury*, January 24, 2020, <https://www.biocentury.com/article/304290/the-coronavirus-outbreak-is-creating-a-testbed-for-new-vaccine-and-therapeutic-technologies>.

⁶³ Moderna, "Moderna Announces Funding Award from CEPI to Accelerate Development of Messenger RNA (mRNA) Vaccine Against Novel Coronavirus," January 23, 2020, <https://investors.modernatx.com/news-releases/news-release-details/moderna-announces-funding-award-cepi-accelerate-development>.

⁶⁴ Coalition for Epidemic Preparedness Innovations, "CEPI and GSK announce collaboration to strengthen the global effort to develop a vaccine for the 2019-nCoV virus," February 3, 2020, https://cepi.net/news_cepi-cepi-and-gskannounce-collaboration-to-strengthen-the-global-effort-to-develop-a-vaccine-for-the-2019-ncov-virus/.

⁶⁵ Johnson & Johnson, Novel Coronavirus, accessed February 4, 2020, <https://www.jnj.com/coronavirus>.

FDA Emergency Use Authorization (EUA)

Clinical testing and the FDA review process typically take several years, so it will take time for MCMs in development to reach the commercial market. However, experimental products may become available in the United States prior to FDA approval pursuant to an EUA. FDA encourages industry and government sponsors (e.g., CDC) to engage with FDA prior to submitting a formal request for an EUA, if possible.

Under most circumstances, drugs, medical devices, and biologics may be introduced into interstate commerce only if they have been approved, cleared, or licensed by FDA. Under certain circumstances, however, FDA may permit a medical product to be provided to patients outside the standard regulatory framework, including through issuance of an EUA. In the absence of an approved MCM for 2019-nCoV, FDA may enable access to investigational MCMs by issuing an EUA, if the HHS Secretary declares that circumstances exist to justify the emergency use of an *unapproved product* or an *unapproved use of an approved medical product*.⁶⁶ The HHS Secretary's declaration must be based on one of four determinations; for example, a determination that there is an actual or significant potential for a public health emergency that affects or has significant potential to affect national security or the health and security of United States citizens living abroad.⁶⁷ Following the HHS Secretary's declaration, FDA, in consultation with ASPR, NIH, and CDC, may issue an EUA authorizing the emergency use of a specific drug, device, or biologic, provided that certain criteria are met (e.g., that there is no adequate, approved, and available alternative to the product).⁶⁸

On February 4, 2020, the HHS Secretary determined that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the 2019-nCoV.⁶⁹ This determination allowed FDA to assess and ultimately allow the emergency use of the CDC-developed diagnostic test for 2019-nCoV. This emergency determination by the HHS Secretary is distinct from the Public Health Emergency declaration made pursuant to PHS Act Section 319.

⁶⁶ 21 U.S.C. §360bbb-3. For additional information, see CRS In Focus IF10745, *Emergency Use Authorization and FDA's Related Authorities*.

⁶⁷ 21 U.S.C. §360bbb-3(b)(1). A determination by the Secretary of Homeland Security that there is an actual or significant potential for a domestic emergency involving a heightened risk of attack with one or more CBRN agents; a determination by the Secretary of Defense that there is an actual or significant potential for a military emergency involving a heightened risk of attack with either with one or more CBRN agents, or with one or more agents that may cause or are associated with an imminently life-threatening and specific risk to United States military forces; a determination by the HHS Secretary that there is an actual or significant potential for a public health emergency that affects or has significant potential to affect national security or the health and security of United States citizens living abroad, and that involves one or more CBRN agents; or the identification by Secretary Homeland Security of a material threat pursuant to Public Health Service Act §319F-2.

⁶⁸ 21 U.S.C. §360bbb-3(c).

⁶⁹ This determination, made pursuant to Section 564(b)(1)(C) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. §360bbb-3(b)(1)(C)), is noted on page 1 of the letter of authorization from FDA to CDC, advising of the authorization for emergency use of the CDC-developed diagnostic test. This letter is available at "Novel coronavirus (2019-nCoV) EUA Information" on the FDA webpage "Emergency Use Authorization," <https://www.fda.gov/emergencypreparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization>. See also footnote 53.

Health System Preparedness

There is concern that if 2019-nCoV spreads widely in the community, it will overwhelm existing health care system capacity to care for patients and prevent future infections. Given that it is currently flu season, many health care facilities are already at or near patient capacity. The ASPR is the principal advisor to the HHS Secretary on the public health and medical preparedness and response for public health emergencies.⁷⁰ While 2019-nCoV has not spread widely enough to warrant broad U.S. health system response activities, ASPR and CDC have indicated the following actions in preparation for the potential spread of 2019-nCoV:

- **Capacity assessment and monitoring.** ASPR and CDC are projecting the potential long-term impact of 2019-nCoV and assessing the capacity of the health care system to respond to a larger outbreak. A sustained response could engage the Regional Treatment Network for Ebola and Other Special Pathogens, a tiered health system response network developed with funding provided by Congress for response to the Ebola outbreak in 2015.⁷¹
- **Supply chain management.** Both ASPR and CDC have indicated that they are working with health care and industry partners to ensure an adequate supply of medical products needed to contain the outbreak, such as personal protective equipment (PPE; e.g., surgical masks). A chief concern in supply chain management is that many medical products or drugs are manufactured, at least in part, in China, the epicenter of the current outbreak.⁷²
- **Strategic National Stockpile (SNS).** The SNS, managed by ASPR, provides select medicines and medical supplies during public health emergencies when local supply chains are disrupted.⁷³ ASPR states it is working to ensure the adequacy of SNS supplies to prepare for the possible spread of 2019-nCoV.
- **Mobilization of health care surge capacity.** ASPR has indicated that it is working to ensure the availability of additional HHS health care support, such as deployment of the National Disaster Medical System (NDMS), in the event that local health care systems require augmentation to respond to the 2019-nCoV outbreak.⁷⁴

⁷⁰ HHS, “2019 Novel Coronavirus,” <https://www.phe.gov/Preparedness/nCoV/Pages/default.aspx>. See also CRS Insight IN11038, *U.S. National Health Security: Homeland Security Issues in the 116th Congress*.

⁷¹ HHS, “HPP Funds Regional Treatment Network for Ebola and Other Special Pathogens,” <https://www.phe.gov/Preparedness/planning/hpp/Pages/hpp-pathogens.aspx>.

⁷² Robert Kadlec, HHS Assistant Secretary for Preparedness and Response (ASPR), “2019 Novel Coronavirus Stakeholder Listening Session Transcript,” January 30, 2020, <https://www.phe.gov/Preparedness/nCoV/Documents/2019nCoV-Listening-Session-Transcript.pdf>; and CDC, “CDC Update on Novel Coronavirus,” February 5, 2020, <https://www.cdc.gov/media/releases/2020/t0205-coronavirus-update.html>.

⁷³ HHS, “Strategic National Stockpile,” <https://www.phe.gov/about/sns/Pages/default.aspx>.

⁷⁴ The National Disaster Medical System is described in CRS Report R43560, *Deployable Federal Assets Supporting Domestic Disaster Response Operations: Summary and Considerations for Congress*; and HHS Assistant Secretary for Preparedness and Response (ASPR), “2019 Novel Coronavirus Stakeholder Listening Session Transcript,” January 30, 2020, <https://www.phe.gov/Preparedness/nCoV/Documents/2019nCoV-Listening-Session-Transcript.pdf>.

Response Funding

CDC and other federal agencies may have the authority needed to respond to the 2019-nCoV epidemic, but their ability to act may be affected by the availability of appropriations. Annual appropriations and standing transfer authority provide the HHS Secretary with some flexibility.⁷⁵ Upon a declaration of a Public Health Emergency pursuant to PHSA Section 319—which HHS Secretary Azar made on January 31, 2020—HHS may access a Public Health Emergency Fund,⁷⁶ but the fund does not have an available balance at this time. Separately, funding has generally not been available under the Robert T. Stafford Disaster Relief and Emergency Assistance Act (the Stafford Act) for the response to infectious disease outbreaks. As a result, Congress and the President provided supplemental appropriations for the response to the recent Ebola and Zika virus outbreaks in FY2015 and FY2016.⁷⁷

In 2018, Congress established an Infectious Diseases Rapid Response Reserve Fund (IDRRRF) for CDC, providing appropriations of \$50 million for FY2019 (P.L. 115-245) and \$85 million for FY2020 (P.L. 116-94), available until expended.⁷⁸ These funds may be made available for an infectious disease emergency if the HHS Secretary either (1) declares a Public Health Emergency pursuant PHSA Section 319, or (2) determines that the infectious disease outbreak has significant potential to occur and, if it occurs, the potential to affect national security or the health and security of U.S. citizens, both domestically and abroad.

Before HHS Secretary Azar declared the 2019-nCoV outbreak to be a Public Health Emergency under PHSA Section 319, he issued a determination on January 25, 2020, allowing the allotment of \$105 million from the IDRRRF for the 2019-nCoV response.⁷⁹ Secretary Azar had previously determined that the U.S. response to the Ebola outbreak in the Democratic Republic of Congo allowed the use of up to \$30 million from the IDRRRF. If both the Ebola and 2019-nCoV amounts are fully used, all funds currently in the IDRRRF would be exhausted.⁸⁰ On February 2, 2020, HHS reportedly notified Congress of its intention to use the Secretary's standing authority to transfer up to \$136 million for 2019-nCoV response efforts, of which \$75 million would be made available to CDC, \$52 million for ASPR, and \$8 million for the HHS Office of Global Affairs.⁸¹

⁷⁵ Annual appropriations acts give the HHS Secretary limited authority to transfer funds from one budget account to another within the department. For instance, a provision in the FY2020 HHS appropriations act (P.L. 116-94, Division A, Title II, §205) generally allows the Secretary to transfer up to 1% of the funds from any given account. However, in general, a recipient account may not be increased by more than 3%. Congressional appropriators must be notified in advance of any transfer. Another FY2020 appropriations provision (P.L. 116-94, Division A, Title V, §514) addresses the Secretary's authority to reprogram funds from one program, project, or activity in a given budget account to a different program, project, or activity within the same budget account. This provision places certain limits on such actions and clarifies the circumstances in which appropriations committees must be consulted in advance. (See P.L. 115-245).

⁷⁶ See HHS, "Legal Authority with Declaration of Public Health Emergency," <https://www.phe.gov/Preparedness/support/secauthority/Pages/default.aspx#phe>.

⁷⁷ Rebecca Katz, Aurelia Attal-Juncqua, and Julie E. Fischer, "Funding Public Health Emergency Preparedness in the United States," *American Journal of Public Health*, vol. 107, suppl. 2, pp. S148-S152, September, 2017, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5594396/>.

⁷⁸ The IDRRRF authority is codified at 42 U.S.C. §247d-4a.

⁷⁹ CQ Newsmaker Transcripts, "Health and Human Services Secretary Azar Holds News Conference on Coronavirus," January 28, 2020, <https://www.phe.gov/Preparedness/support/secauthority/Pages/default.aspx#phe>.

⁸⁰ Communication with CDC, January 28, 2020.

⁸¹ Yasmeen Abutaleb and Erica Werner, "HHS Notifies Congress that it May Tap Millions of Additional Dollars for Coronavirus Response," *Washington Post*, February 3, 2020. Likely the authority described in footnote 75.

CDC has an additional source of emergency support through the CDC Foundation, a 501(c)(3) public charity established by Congress “to support and carry out activities for the prevention and control of diseases, disorders, injuries, and disabilities, and for promotion of public health.”⁸² The CDC Foundation activated its Emergency Response Fund (ERF) to support 2019-nCoV response on January 27, 2020, as requested by CDC.⁸³ Funds have been donated to the ERF for this response by the Robert Wood Johnson Foundation, among others. Although the support provided by the foundation for outbreak response has been modest compared with supplemental appropriations, the foundation has greater spending flexibility and can sometimes procure response supplies and services more quickly than CDC through federal procurement processes.⁸⁴

The trajectory of the 2019-nCoV outbreak is uncertain. If the United States experiences sustained person-to-person transmission of the novel virus in the future, the nation’s public health and health care systems could be stretched to respond, and resources mobilized from the IDRRRF, HHS transfer authority, and the CDC Foundation may potentially be insufficient. Some Members of Congress have suggested that the Trump Administration consider a request for supplemental funding.⁸⁵

ACKNOWLEDGMENTS

Edward C. Liu, Legislative Attorney, and Ben Harrington, Legislative Attorney, contributed to this report.

⁸² Public Health Service Act Section 399G, 42 U.S.C. §280e–11. See “National Foundation for the Centers for Disease Control and Prevention” in CRS Report R46109, *Agency-Related Nonprofit Research Foundations and Corporations*.

⁸³ CDC Foundation, “Responding to Coronavirus,” <https://www.cdcfoundation.org/coronavirus>.

⁸⁴ See, for example, CDC Foundation, “2018 Ebola Outbreak,” <https://www.cdcfoundation.org/2018-ebola-outbreak>.

⁸⁵ Andrew Siddons, “HHS Chases Virus Treatment as Congress Weighs Additional Funds,” CQ, February 4, 2020.

Chapter 473

ANOTHER CORONAVIRUS EMERGES: U.S. DOMESTIC RESPONSE TO 2019-nCoV*

Sarah A. Lister and Kavya Sekar

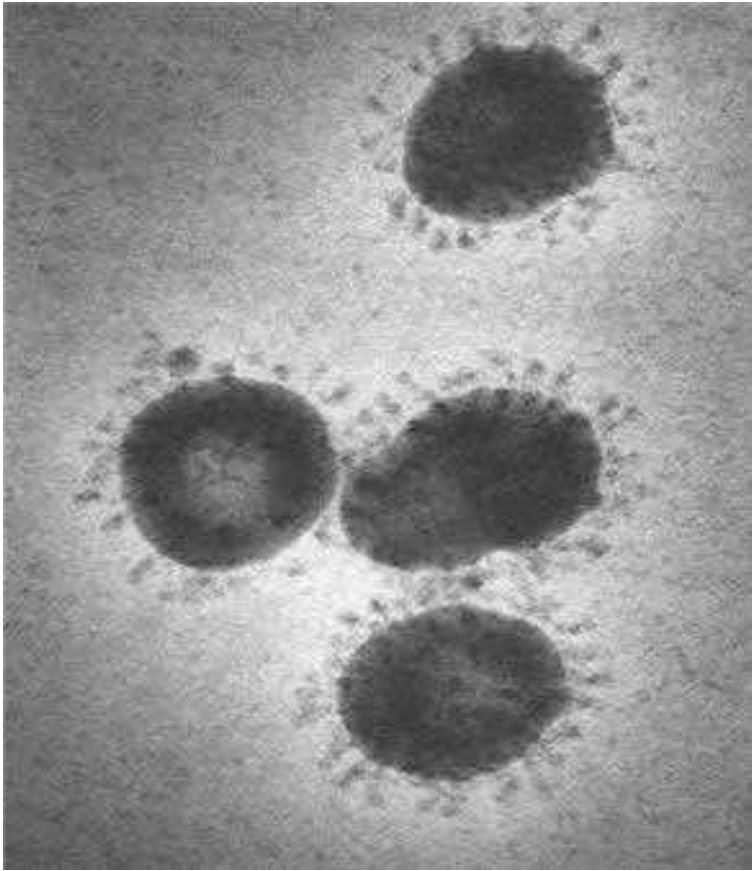
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CRS Report R46219, Overview of U.S. Domestic Response to the 2019 Novel Coronavirus (2019-nCoV)

THE EMERGENCE OF 2019-nCoV

On December 31, 2019, the World Health Organization (WHO) was informed of a cluster of pneumonia cases in Wuhan, China. Illnesses have since been linked to a previously unidentified strain of coronavirus, designated 2019 novel Coronavirus, or 2019-nCoV. To date, thousands have been infected, mostly in China, and over 100 have died. The disease has spread to several other countries, including the United States. As the scope of the epidemic widened in China, the U.S. Centers for Disease Control and Prevention (CDC) stated on January 27, 2020, that “the immediate health risk from the new virus to the general American public is low currently.” With the situation rapidly changing, both WHO and CDC post frequent updates.

* This is an edited, reformatted and augmented version of Congressional Research Service Publication No. IN11212, dated January 29, 2020.



Source: CDC Public Health Image Library: <https://phil.cdc.gov/Details.aspx?pid=10270>.

Note: Surface projections on the viral envelope of a poultry coronavirus form the halo or “corona” that gives this virus group its name.

Figure 1. Coronaviruses, electron micrograph.

Coronaviruses (see *Figure 1*) are common respiratory pathogens, usually causing mild illnesses such as the common cold. The global health community is closely monitoring 2019-nCoV because of the severity of symptoms (including death) among those infected, and the speed of its spread worldwide. 2019-nCoV is causing the third-serious novel coronavirus outbreak in modern times, following severe acute respiratory syndrome (SARS) in 2002 and Middle East Respiratory Syndrome (MERS) in 2012. Experts do not know the origin of 2019-nCoV, though genetic analysis and other features suggest an animal source.

INFECTION AND TRANSMISSION

Health officials and researchers are still learning about 2019-nCoV. According to CDC, 2019-nCoV typically causes respiratory infections characterized by a fever, cough, and sometimes breathing difficulty—a suite of symptoms that is common during influenza season. Features that have yet to be clarified include routes of transmission (e.g., through the air, from contaminated surfaces), the incubation period (the time between infection and the

onset of symptoms), and whether an infected person without symptoms can transmit infection. Although it was first thought that all 2019-nCoV infections resulted from an animal contact, Chinese officials recently reported evidence of person-to-person transmission.

The U.S. Domestic Response

In the United States, communicable disease control involves collaboration among federal agencies, state health departments, and international partners. Authority to compel isolation (for sick patients), quarantine (for healthy exposed persons), and disease reporting generally rest in state law. The Secretary of Health and Human Services (HHS) and, by delegation, CDC have broad authority to assist in the control of communicable diseases through international cooperation, federal-state cooperation, and public health emergency response activities. In addition, CDC (by delegation) has explicit authority to detain, examine, and release persons arriving into the United States, and traveling between states, who are suspected of having a communicable disease.

Case Identification and Investigation

CDC has developed a diagnostic test for the 2019-nCoV virus, but it is not widely available. At this time, all testing is being done by CDC, which has announced plans to share the test with domestic and international public health partners. Until local testing is available, CDC urges clinicians to consider a patient's travel history and a 14-day incubation period in deciding whether to obtain patient specimens (e.g., blood, urine) for testing. Health care providers are urged to report possible cases to state and local health departments, which then report to CDC. CDC is facilitating the collection and transport of specimens.

Although CDC reports that no person-to-person transmission has been confirmed in the United States, disease investigation for confirmed cases involves *contact tracing*—identifying and evaluating individuals who had contact with the patient to determine if transmission has occurred. These investigations are generally conducted by state and local health officials.

Clinical Guidance

No vaccine or specific treatment exists for 2019-nCoV infection at this time. Based on knowledge of the novel virus and other coronaviruses, CDC has developed guidance for isolation and other precautions for *patients under investigation* or receiving supportive care for 2019-nCoV infection. A key goal is the prevention of disease transmission to health care workers, who may be exposed through high-risk procedures such as maintaining an ill patient on a ventilator.

Travel Notices and Entry Screening

CDC and the State Department have issued advisories to reconsider or avoid unnecessary travel to China, including a rare Level 4 advisory from the State Department to avoid all travel to Hubei Province. In collaboration with U.S. Customs and Border Protection, CDC is screening passengers returning on flights from certain areas of China at 20 U.S. airports, looking for symptoms of illness and disseminating information. On January 29, a U.S. government-chartered flight from Wuhan, China, repatriated 201 Americans, who have been

screened for illness and advised on procedures to follow should symptoms arise in the coming weeks.

Medical Countermeasures

CDC and the National Institutes of Health (NIH) continue to study the virus to inform response efforts. NIH reports that a vaccine candidate is in development and could be available for initial clinical trials within three months.

Considerations for Congress

CDC and other federal agencies may have the authority needed to respond to the 2019-nCoV epidemic, but they may lack available funds to support their efforts. Annual appropriations and standing transfer authority provide the HHS Secretary with some flexibility. Under certain circumstances the Secretary may access a Public Health Emergency Fund, but the fund does not have an available balance at this time.

Generally, funding has not been available under the Robert T. Stafford Disaster Relief and Emergency Assistance Act (the Stafford Act) for the response to infectious disease outbreaks. As a result, Congress provided supplemental appropriations for the response to the recent Ebola and Zika virus outbreaks.

Subsequently in 2018, Congress established an Infectious Disease Rapid Response Reserve Fund (IDRRRF) for CDC, providing \$50 million for FY2019 (P.L. 115-245) and \$85 million for FY2020 (P.L. 116-94), available until expended. These funds can be made available for an infectious disease emergency if the HHS Secretary either (1) declares a Public Health Emergency or (2) determines that the infectious disease outbreak has significant potential to occur and, if it occurs, the potential to affect national security or the health and security of U.S. citizens, both domestically and abroad. HHS Secretary Alex Azar has not declared the 2019-nCoV outbreak to be a Public Health Emergency, but has issued a determination allowing the allotment of \$105 million from the IDRRRF for the 2019-nCoV response.

The trajectory of the 2019-nCoV outbreak is unknown at this time. Congress may choose to conduct oversight of federal response efforts, and monitor the expenditure of funds, as the situation progresses.

Chapter 474

THE CORONAVIRUS: U.S.-CHINA ECONOMIC CONSIDERATIONS*

Karen M. Sutter and Michael D. Sutherland

The novel coronavirus outbreak (COVID-19) is slowing economic activity in China and raising concerns about potential U.S. supply chain vulnerabilities in a range of sectors that rely directly and indirectly on China-based suppliers. These sectors include medical supplies, pharmaceuticals, auto parts, microelectronics, and strategic raw materials. Similar to the outbreak of severe acute respiratory syndrome (SARS) in China in 2002-2003, most cases so far are concentrated in China, but the current number of infections is already an order greater and every Chinese province is affected. U.S. senior officials have expressed concerns about the completeness and timeliness of the information China is reporting, complicating assessments of the scope, trajectory, and economic impact of the outbreak. The Chinese government has also imposed tight content controls on media reporting and placed Sina Weibo, Tencent, ByteDance, and other Internet firms under “special supervision” of the Cyberspace Administration of China, further limiting coverage of the outbreak.

Economic Outlook

The coronavirus is hitting China during an economic downturn as the government grapples with U.S. tariffs and China’s counter tariffs, rising consumer inflation due in part to domestic pork shortages resulting from African swine fever, and efforts to rein in local government spending and shadow lending. China’s economic growth could go negative in the first quarter of 2020 and fall below 5% for the year, with more serious effects if the outbreak continues beyond March. In a sign the slowdown could last past March, the Chinese government cancelled several spring meetings: the State Council’s China Development Forum, the National People’s Congress annual legislative session, and the Canton Trade Fair.

* This is an edited, reformatted and augmented version of Congressional Research Service Publication No. IF11434, Updated March 2, 2020.



Source: New York Times, “Coronavirus Map: Tracking the Spread of the Outbreak,” March 2, 2020.

Figure 1. COVID-19 regional case map.

A key factor affecting the economic outlook in China is the ability of businesses to resume operations after the Lunar New Year was extended from late January until February 10, 2020. Business reopening has been uneven across sectors and locations in China. Many firms are awaiting government approvals to reopen and are facing difficulties in meeting new operating requirements, such as providing masks for employees. Foxconn, a Taiwan electronics firm that produces for Apple, has applied to reopen in early March. Resumption of transportation and travel appears to be a major obstacle. Chinese media has reported on employees struggling to return to work amid transportation shutdowns and contagion concerns. The American Chamber of Commerce in Shanghai reported on February 17, 2020, that most companies surveyed do not yet have sufficient staff to run a production line and face numerous logistics constraints. Almost half of the companies surveyed report that their global operations are already affected by the outbreak. These companies expect demand to be lower over the next several months.

The Chinese government has locked down cities in China’s provinces of Hubei (e.g., Wuhan, Ezhou) and Zhejiang (e.g., Wenzhou, Hangzhou, Ningbo, and Taizhou). In total, an estimated 90 cities across China face some form of restrictions. The Chinese government has leaned on online delivery services and the military for logistics support, and is restricting consumer activity across multiple cities.

Domestic and global transportation links have been significantly curtailed with ramifications for trade. Air services face reduced capacity with the canceling of passenger travel and restrictions on pilots and flight staff on cargo flights to third countries. Cargo operations in China depend on port staffing and are reportedly operating at significantly reduced capacity. While most businesses typically plan for a shut down during the Lunar New Year, including some stockpiling, companies are now likely to experience more serious shortages. Cargo shipments from China to the United States typically take approximately three weeks; slowdowns in maritime shipping could affect a wide range of industrial and consumer goods.

The Chinese government is trying to encourage economic activity, but restrictions on business reopening, travel, and transportation are hampering its support efforts. Unlike other

types of economic slowdowns, government stimulus cannot generate real economic activity on its own if business operations remain partially or completely shut down. The Chinese government is issuing economic support measures such as tax exemptions and special-purpose bonds. City governments in Beijing, Qingdao, Shanghai, and Suzhou are offering small- and medium- sized businesses in hard-hit industries support to reduce loans and delay payments for rent and social security. With a priority on social stability, localities are also offering preferences to companies that retain workers. In early February, China's central bank pumped \$57 billion into the banking system, capped banks' interest rates on loans for major firms, and extended deadlines for banks to curb shadow lending. The central bank has been setting the reference rate for China's currency stronger than its official close rate to keep it stable.

There have been press reports of shortages of medical supplies—N95 respirator masks, medical protective equipment, antiviral drugs—and food. In response, the government has repurposed some production facilities to meet health and medical needs, including the facilities of U.S. firms such as General Motors (GM) and 3M. In early February, the Commerce Ministry directed local governments to increase imports of medical supplies, production materials, and agricultural products, potentially providing U.S. export opportunities in these sectors.

Global Economic Impact

China's economy is globally connected through trade, investment, and tourism, and any slowdown and persistent travel and transportation restrictions beyond March are likely to pressure global supply chains and potentially create worldwide economic fallout. Measures to contain the outbreak have significantly curtailed domestic and global transportation links, preventing the transport of many products and manufacturing inputs. Passenger air traffic has slowed significantly, taking offline significant air cargo capacity for microelectronics and other products that ship by air. Production has slowed across China, with sharp slowdowns in sectors concentrated in Hubei, such as auto parts, LCD panels, and pharmaceuticals. Manufacturing that recently shifted offshore to other parts of Asia still often depends on intermediate inputs from China and thus is not insulated from China's production slowdown.

Disruptions in Chinese supply chains are expected to have a limited macroeconomic effect on developed markets in the short term but developing markets and Asia's developed economies, are more vulnerable. Vietnam, Taiwan, Malaysia, South Korea, Japan, Thailand, and Singapore all have strong supply chain links with China and are reporting supply shortages. South Korea's Hyundai and Kia, for example, announced production slowdowns in response to problems in securing auto parts from China. While developed economies might be insulated in the short term, the economic risks grow the longer the outbreak continues.

At the firm level, companies in sectors such as technology and autos or that are exposed to China's tourism, retail, or other services businesses could take a significant hit.

According to the United Nations World Tourism Organization, China's outbound tourism spending in 2018 was \$277 billion, of which an estimated \$36 billion was in the United States. U.S. business will likely be affected by China's slowdown, including through shortages of inputs, the cancellation of some commercial activity, and potential increased costs related to a strengthening U.S. dollar.

China’s Commerce Ministry is helping firms obtain free *force majeure* certifications—which allow firms to opt out of contractual obligations without legal recourse because of developments beyond their control—and China National Offshore Oil Company declared *force majeure* in cancelling some LNG imports.

BROADER CONSIDERATIONS FOR CONGRESS

Phase One Trade Deal: The crisis is calling into question China’s ability to implement the U.S.-China phase one trade deal signed in January 2020. Transportation constraints and a slowdown in demand could affect China’s import levels. The agreement has a *force majeure* provision that could give China flexibility in implementing its commitments. The deal was finalized in December 2019, when Chinese officials reportedly knew about the outbreak, which raises questions about the rationale and timing of the decision to include the *force majeure* provision. As part of the phase one trade deal, China and the United States on February 14, 2020, cut by 50% the tariffs they imposed in September 2019. China also announced a tariff exemption process for 700 tariff lines that include some agriculture, medical supplies, raw materials, and industrial inputs.

Pharmaceutical Market Access and IP: Pharmaceuticals are a component of *Made in China 2025* industrial plans that aim to create competitive advantages for China in certain strategic industries. The Chinese government restricts market access for foreign pharmaceutical firms, including the disclosure of proprietary information for drug trials and sales. The Wuhan Institute of Virology and China’s military recently applied to patent an adaption of an antiviral drug developed by California-based Gilead Sciences, Remdesivir. Also, Chinese firm BrightGene Bio- Medical Technology Co. announced it can produce a generic alternative to Remdesivir, potentially complicating Gilead’s way forward in China. Gilead’s patent application in China for Remdesivir use in coronaviruses has been pending since 2016. The Chinese government is also conducting an antitrust review of AbbVie’s acquisition of Allergan, Inc. and could set terms for the use or transfer of AbbVie’s antiviral intellectual property to benefit Chinese industry. China has required technology transfer in other antitrust reviews of foreign firms in *China 2025* sectors.

Table 1. Select U.S. Imports of healthcare products from China

Product	2019 value U.S.\$	2019 % of U.S. imports
Antibiotics	\$302,866,251	35%
PPE	\$1,852,214,083	30%
Medical Devices	\$3,911,308, 981	8.6%

Source: U.S. International Trade Commission, Assessed Customs Value.

Supply Chain Vulnerabilities: China’s role as a global supplier of medical personal protective equipment (PPE), medical devices, antibiotics, and active pharmaceutical ingredients means reduced production or exports from China could lead to shortages and increased costs of critical medical supplies in the United States. The outbreak is also likely to create shortages in China-sourced raw materials, manufacturing inputs, microelectronics, and finished goods.

Chapter 475

THE WUHAN CORONAVIRUS: ASSESSING THE OUTBREAK, THE RESPONSE, AND REGIONAL IMPLICATIONS*

Jennifer B. Nuzzo

Good afternoon, Chairman Bera, Ranking Member Yoho, and Members of the Committee. Thank you for giving me the chance to appear before you today to discuss the emergence and global spread of the 2019 novel coronavirus (2019 nCoV).

I am an Associate Professor in the Departments of Environmental Health and Engineering and Epidemiology at Johns Hopkins Bloomberg School of Public Health. I am also a Senior Scholar at the Johns Hopkins Center for Health Security. *The opinions expressed herein are my own and do not necessarily reflect the views of The Johns Hopkins University.* Our Center for Health Security's mission is to protect people's health from major epidemics and disasters and build resilience. We study the organizations, systems, and tools needed to prepare and respond. At the Center, I direct the Outbreak Observatory, which conducts operational research to improve outbreak response. My testimony is also influenced by my previous experiences as a public health practitioner. I have also served as a public health epidemiologist for New York City, where I conducted surveillance for infectious diseases.

My colleagues and I at the Johns Hopkins Center for Health Security have spent close to twenty years analyzing infectious disease outbreaks, including epidemics and pandemics, in attempt to better understand the resources, practices and policies that are need to prevent, mitigate and contain them. Like many others, we've been closely following novel coronavirus outbreak since it was first announced in China at the end of December. We've been trying to analyze and understand the risk the virus poses to the United States (US) and other countries around the world and to make recommendations to policy-makers, legislators and practitioners about what should be done to respond to this epidemic.

* This is an edited, reformatted and augmented version of United States House of Representatives Committee on Foreign Affairs Subcommittee on Asia, The Pacific, and Nonproliferation Publication, dated February 5, 2020.

I have two caveats regarding my testimony today. First, I have not been involved in the on-the-ground public health response to 2019 nCoV. My knowledge and assessment of this epidemic comes from my analysis of publicly shared information and conversations I have had with individuals and organizations that are closely involved in the response. Second, as you have likely heard, this is an evolving situation. Our knowledge of the virus is growing and changing as more data become available. What I offer you today is my best interpretation and judgment given the facts known at the time this testimony was prepared.

WHAT DO WE KNOW ABOUT 2019 nCoV?

The ongoing epidemic of 2019 nCoV was first recognized in the Wuhan city, Hubei Province, China. On December 31, 2019, health officials in Wuhan announced that they were investigating an outbreak of viral pneumonia involving 27 hospitalized cases in the city. Though the finding of viral pneumonia patients in any hospital during flu season is not by itself cause for alarm, health authorities were alerted to these cases by clinicians who noted the shared a common occupational exposure to the Huanan Seafood Wholesale Market. Wuhan health officials launched epidemiologic and environmental investigations. An official statement provided by the Wuhan Municipal Health Commission noted that all patients were treated in isolation and that there was no clear evidence of person-to-person transmission. Health officials closed the Huanan seafood market on January 1. One week later, health authorities in China announced that a novel coronavirus had been isolated from the viral pneumonia patients and the viral sequence was shared publicly.

Since the identification of 2019 nCoV as the likely cause of the viral pneumonia outbreak in Wuhan, we have learned several important things about the virus. First, the virus appears to be capable of sustained human-to-human transmission. Though it was initially thought that 2019 nCoV infection was limited to individuals with a history of exposure to the Huanan seafood market, cases have been found in individuals who reported never having visited markets in Wuhan. The appearance in other countries of multiple generations of 2019 nCoV cases who have not traveled to China provides additional evidence of sustained human to human transmission.

This finding differentiates the virus from the Middle East Respiratory Syndrome coronavirus (MERS-CoV), for which only limited human-to-human transmission has been reported.

Second, though severe illness and deaths have been reported, virus appears to be capable of causing a spectrum of disease. The emergence 2019 nCoV was first recognized among patients who were hospitalized with viral pneumonia. Since then 2019 nCoV cases with milder disease presentations have since been reported. Hospitalized patients also have a varied clinical picture—ranging from relatively mild symptoms to critical illness.

There is evidence that the virus jumped from animals and may have caused human infections earlier than initially recognized. A study published in the *Lancet* has shown some evidence the initial outbreak of 2019 nCoV may have started at the beginning of December or earlier--weeks before the outbreak was first recognized. It is not known when the virus became adapted to humans and capable to being spread via person-to person transmission.

Since the first report of human 2019 nCoV cases, more than 17,000 cases and 300 deaths (as of February 3, 2020) have been recorded in 23 countries. China accounts for the vast majority of cases. Cases have spread well beyond Wuhan—every province in China has since reported cases. From public reports and limited scientific studies published to-date, it appears as though the majority of reported deaths have occurred among elderly individuals and individuals with underlying medical conditions—patient groups known to be at risk for severe illness and death from other respiratory infections.

All deaths have occurred in China, with the exception of a death in the Philippines. The WHO has said that the deceased, who tested positive for nCoV, had also been infected with influenza and pneumococcus, a bacterium that causes pneumonia, bloodstream infections and meningitis. Outside of China, reported cases have so far been described as having mild disease presentations.

WHAT IS UNKNOWN?

Size and Scope of the Epidemic

What is not yet known is the true size and geographic scope of this epidemic. Though countries are quickly ramping up surveillance for this virus, it is likely that many lack the capacity to actively search for cases. Even countries that have mobilized surveillance programs are likely missing cases. Surveillance in China seem to be heavily focused on cases that show up at hospitals or clinics. Though this makes sense given limited testing capabilities, what it means is that individuals who don't seek medical attention for their infections are likely not being captured by existing surveillance in China. Outside of China, countries have, for the most part, only been testing people who have travelled to Wuhan or, in some cases, broader China.

Countries are not, as a matter of routine, looking for local cases that may resulted from infected individuals who entered the country before travel screening began.

Another complicating factor for surveillance is the occurrence of mild cases. Though there have been a concerning number of deaths and severe illnesses reported, the continued finding of mild cases raises the possibility that many more cases have occurred than have been detected. Mild cases are difficult to spot because their non-specific symptoms make them difficult to differentiate from other common respiratory illnesses. If individuals with mild symptoms don't seek medical attention, which is likely, and aren't tested, their infections will not be detected by most surveillance systems.

Hospitalization statistics are not reliable indicators of the burden of severe illness. China and other countries have been hospitalizing infected patients regardless of the severity of their symptoms. Infected patients are also remaining in hospitals until they are free of the virus, which may be well after patients' symptoms disappear.

Current US guidelines for testing for 2019 nCoV among individuals who are not contacts of confirmed cases are contingent on patients' symptoms and to travel to China. According to current guidelines from the US Centers for Disease Control and Prevention (CDC), individuals would likely not be tested for 2019 nCoV infection unless they are a symptomatic contact of a known case; traveled to Wuhan and experience fever and lower respiratory

illness; or, traveled to broader China and are hospitalized for a lower respiratory infection. It is not clear whether and how these testing criteria will change now that all provinces in China and more than 20 countries are reporting cases.

Severity

We don't yet have a clear understanding regarding the severity of illnesses caused by 2019 nCoV. The reasons for the observed discrepancies in severe illness and deaths inside and outside of China is not yet known. Though a concerning number of severe and critically ill patients and deaths have been reported, the frequency with which infected people get critically ill and die is not yet understood. But the apparent discrepancy in between the severity of symptoms and number of deaths among cases in China versus other countries raises the possibility that outbreaks in other countries may be less severe and/or comparable to other respiratory viruses, such as influenza.

The way most countries are conducting surveillance for nCoV will not allow us to directly estimate the percentage of infected individuals that develops severe illness and die. A key reason is that we are likely missing many cases, and, in particular mild cases. An outbreak caused by a new pathogen, like 2019 nCoV, is often not recognized until an unusual cluster of severely ill patients turn up in hospitals or an increase in deaths is noted and people launch an investigation to figure out why. As we stand up surveillance for novel viruses, such as 2019 nCoV, and begin to look for cases more broadly, we may identify milder cases in individuals who either didn't seek medical attention or whose symptoms were misdiagnosed. We may be vastly underestimating the total number of infected individuals, which means it is not accurate to estimate severity from the total number of reported cases and deaths. Nonetheless, people have been attempting to determine the severity by doing crude estimates with the limited information available. These crude estimates show that the percentage of deaths among total reported cases may be falling, which, if true, would be consistent with what we've observed in previous emerging infectious disease outbreaks.

Asymptomatic Spread

There have been a few case reports that have raised the possibility that individuals who experience no symptoms (asymptomatic) or have not yet developed symptoms (presymptomatic) may be capable of transmitting their infection to others. In addition, virus has been detected in patients after their symptoms went away, which raises the possibility of post-symptomatic spread. The extent to asymptomatic or presymptomatic cases are contributing to the larger epidemic is not known and the evidence supporting this is weak. If significant level of asymptomatic or presymptomatic transmission is occurring, this will make it harder to interrupt disease spread. However, the World Health Organization has said that asymptomatic patients are not likely to be the main driver of disease spread.

INTERNATIONAL RESPONSE

On January 30, the WHO declared the epidemic to be a Public Health Emergency of International Concern (PHEIC). This is the sixth time the WHO has designated an infectious disease event a PHEIC since the 2005 International Health Regulations (IHRs) gave the organization this power. This most recent declaration means that WHO is currently involved in the response to three simultaneous PHEICs— 2019 nCoV, Ebola in the Democratic Republic of Congo, and international spread of poliovirus.

In announcing that the global spread of 2019 nCoV constituted a PHEIC, the WHO Director General Tedros Ghebreyesus made clear that countries should respond with “facts, not fear.” The WHO has said that it does not recommend that countries implement travel or trade restrictions to prevent the importation of the virus. WHO has cautioned that countries that do take these measures could accelerate the spread of the virus by hindering the ability of responders and supplies to travel to where they are needed and by diverting public health resources from local disease control efforts. Nonetheless, many countries are implementing measures that the WHO has specifically advised against. Many countries, including the United States, have announced suspension of travelers from China, and an intention to quarantine travelers returning from China for up to 14 days. The IHRs were created to define the maximum measures countries could take to prevent the importation of disease; countries that take measures that are above what the WHO recommends do so in contravention of the IHRs.

But despite these unfortunate developments, I see in countries’ initial response to this nCoV epidemic some important signs for optimism. First, I must commend the astute clinicians in Wuhan, China who first recognized this unusual event. Front-line clinicians are our first defense against infectious disease outbreaks. That they recognized that their patients shared an unusual commonality—a link to the seafood market—is possibly the only reason why this outbreak was detected when it was and not later. This points to the importance of having well-trained clinicians who can recognize and rapidly report unusual events.

Second, I am greatly encouraged by the speed with which health authorities are expanding laboratory testing for a never-before-detected virus. This includes China, which isolated, identified and published the sequence of the novel coronavirus quickly, enabling other countries to develop their own laboratory tests. This also includes other countries, who immediately began screening and testing symptomatic travelers from China for a completely new virus. It is important to point out this rapid surveillance work reflects advanced laboratory capabilities that require investment, training and sustainment.

In addition, epidemiological investigations conducted in and shared by other countries have improved our understanding of the virus and its transmission. Thailand identified a 2019 nCoV case in a traveler from Wuhan who reported not having exposure to the initially implicated seafood market. This epidemiological finding first raised the possibility of infection among those without a connection to the Huanan market. The first evidence that this virus was capable of human-to-human transmission was provided by health officials in Vietnam, who identified and investigated a 2019 nCoV case in a 27-year old man who had not visited China, but had been caring for his sick father who had recently travelled from Wuhan.

Each of the above examples illustrates why it is so essential that countries have the public health capacities to prevent, detect and respond to infectious disease emergencies. The sharing of detailed surveillance and case reports from Vietnam, Thailand, and other countries that are now reporting cases is indispensable for global efforts to control the spread of this disease. It is also how, in the face of scientific uncertainties about the virus, WHO makes a determination of the global risk posed by the virus and how countries like the US gather the information they need to make decisions about how to protect their own citizens.

We should not take for granted the response successes that have occurred to date. The astute clinicians and the capacities to screen, diagnose and isolate patients with a novel virus and identify and monitor their contacts represent important global health security capacities—laboratory-based surveillance, trained epidemiologic workforce, infection prevention and control practices—that needed to be developed and maintained so that they could function in this epidemic. The speed with which countries have gathered and shared key epidemiological data has enabled others to better gauge risks posed by this virus and enhance response plans.

Comparing the 2019 nCoV epidemic to prior novel coronavirus outbreaks illustrates some of the progress that has been made in strengthening countries' global health security. In 2003, it took months before a novel coronavirus was identified as the cause of Severe Acute Respiratory Syndrome (SARS) as compared with weeks in the current epidemic. In 2015, the Republic of Korea experienced a large outbreak of Middle East Respiratory Syndrome coronavirus (MERS- CoV), in part due to delayed recognition and nosocomial spread of the virus. However, in 2019 Korea quickly detected and isolated an imported case with mild symptoms and became the third country outside of China to report cases. Korea and other countries that have experienced infectious disease challenges have done the hard work of improving their public health capacities deserve our recognition and gratitude.

The fact that countries are able to conduct surveillance for and epidemiological investigations of 2019 nCoV cases is the result of hard work and sustained investment, both by the countries themselves and by international donors. US technical and financial support has been critical to the development of surveillance systems and trained workforce in a number of countries now reporting 2019 nCoV cases. In the case of Thailand, US support spanned decades. Thailand now has a world class epidemiologic workforce and is a leader in global health security. In Vietnam, sustained US support and assistance have enabled the development an early warning surveillance system, which includes a network of emergency operations centers and enhancement of field epidemiology workforce training. These resources were used to support Vietnam's detection and response to Zika virus and are likely a supporting the country's on-going response to 2019 nCoV.

WORRISOME TRENDS IN GLOBAL READINESS FOR EPIDEMICS AND PANDEMICS

Much of the world is not fully prepared to respond to serious infectious disease epidemics or pandemics. Though there are positive examples of countries like Thailand and Vietnam rapidly responding to infectious disease threats, there are critical gaps in worldwide capacities that can inhibit the responses of many countries to this epidemic and others.

In October, my colleagues and I at the Johns Hopkins Center for Health Security and the Nuclear Threat Initiative, together with the research power of the Economist Intelligence Unit, released the Global Health Security Index (GHS Index), a first-ever assessment of 195 countries' global health security. The first GHS Index was the result of a sustained effort to define a framework to comprehensively and reproducibly understand and compare global health security at the national level and to collect and measure the extent to which countries' show evidence of having the capacities and capabilities required to respond to an epidemic or pandemic. The GHS Index builds on peer evaluations conducted by the WHO but covers all UN members, including China, and is regularly repeatable to measure progress. What we found is that no country, including the US, is fully prepared for significant infectious disease outbreaks. There is even less evidence that countries have demonstrated the ability to exercise these capacities or use them in an actual emergency. How unprepared is the globe as a whole? Out of a possible score of 100 points, we found that the average GHS Index score across 195 countries was just 40.2. Even countries with more resources are not ready, as the majority of high- and middle-income countries do not score above 50. What these results tell us is that action is urgently needed to improve countries' readiness for high-consequence infectious disease outbreaks.

In declaring the 2019 nCoV epidemic a PHEIC, WHO Director General Tedros Ghebreyesus said that a key reason for the declaration was a concern about the weakness of health systems in much of the globe. I share his worries. Among each of the 6 categories measured in our GHS Index, countries' scores were lowest (the average score was 26.4 out of 100) in the category that examined the readiness of national health systems to treat the sick and protect health workers.

This finding tracks with observed challenges in recent epidemics, such as the on-going epidemic of Ebola in Democratic Republic of Congo (DRC), which represents one of the three on-going PHEICs to which the WHO is currently responding. Though DRC has prior experience and success in containing Ebola outbreaks, disease transmission occurring in unprepared health facilities has played an important role in exacerbating the spread of disease. Transmission in healthcare facilities also occurred during the 2003 SARS epidemic and during outbreaks of MERS in 2015.

What this tells us is that there may be critical gaps in hospitals and other health facilities that will likely be the on the front-lines of responding to the 2019 nCoV epidemic. Many countries—including well-resourced ones like the US, may experience difficulties in responding to a surge of patients infected with 2019 nCoV. If the virus produces more severe illnesses than have been seen outside of China to-date, then the challenges of safely treating these patients will be even greater. The recent report of a healthcare worker in France who became infected with nCoV is a concerning development that speaks to the challenges that even well-resourced countries are likely to face in responding to this disease.

My worries about these identified weaknesses in national capacities to respond to epidemics and pandemics is increased by the lack of resources allocated to address them. The GHS Index showed that only 5% of countries—fewer than 10 countries overall—scored above 66.7 out of 100 points for financing health security. Prioritizing health security, especially in the strengthening of foundational health systems, will be critical in helping to control this epidemic, but also in addressing future infectious disease emergencies.

RECOMMENDATIONS TO IMPROVE US READINESS FOR CONTINUED SPREAD OF 2019 nCoV

The ultimate trajectory of the 2019 nCoV epidemic is hard to predict with certainty, but there are increasing signs that it may not be possible to contain the disease. We must plan for the possibility that 2019 nCoV will result in a global pandemic. My recommended priority actions to improve preparedness for global spread of 2019 nCoV are divided between international engagement and domestic readiness.

International engagement recommendations:

1. Halt the current US policy of denying visas to travelers from China and quarantining Americans returning from China.
2. Engage in a productive, collaborative dialogue with China to in order to ensure continued access to data and critical medical supplies

Domestic response recommendations:

1. Ensure health departments have the resources they need to conduct surveillance to promote proven mitigation measures, such as case isolation outside a hospital to the extent possible.
2. Ensure hospitals and other health facilities have the resources needed to safely treat a surge of patients.
3. Facilitate the development of medical countermeasures, such as diagnostics, vaccines, therapeutics.

The current US policy to deny visas to travelers from China and to quarantine returning Americans is not the right approach to controlling the spread of 2019 nCoV and may make us less safe. These measures are unlikely to keep the virus out of our country. The virus is spreading too quickly and too quietly for us to possibly know where all cases are. We do not have a complete picture of where in the world the virus is spreading to be able to stop infected people from coming to the US. It is also possible that unrecognized infections are occurring in US. In the weeks before the US began to screen travelers and airlines began reducing flights, thousands of people traveled to the US from China each day. And just because we are only looking for cases among people with a connection to China doesn't mean that those are the only individuals who are infected. As global case counts continue to grow and as more and more countries report cases, it will raise the question as to whether we should continue to focus on travel to Wuhan or broader China as criteria for testing. It is unlikely that we would be able to maintain our current approach to quarantine returning Americans and screen travelers if we needed to include additional countries or regions of the world.

I am deeply concerned that these measures will make us less safe by diverting public health resources from higher priority disease mitigation approaches that I describe below. It is not yet clear which agencies will have the responsibility of caring for and monitoring returning travelers who have been placed into quarantine. It is possible that local health authorities would play a lead role, as they did in monitoring travelers returning from West Africa during the Ebola epidemic of 2014, which required considerable resources that had to

be diverted from other public health activities. Caring for and monitoring even small numbers of quarantined individuals would likely be a challenge for many health departments and would require a large investment of resources.

By singling out China for travel bans, we are, effectively penalizing it for openly reporting and sharing data about the epidemic. Our ability to respond to epidemics depends on having access to epidemiological information generated by other countries. Geographically-targeted measures may exacerbate the social and economic tolls of this epidemic and send a signal to countries that it may not be in their best interests to be forthcoming about disease outbreaks. This could diminish countries' willingness to be transparent about outbreaks and allow diseases to spread before outbreaks are uncovered, which would make everyone less safe. We should reward countries that report cases through offers of help and assistance.

It is in our best interest to maintain a productive and collaborative relationship with China and to help it better respond to the spread of 2019 nCoV disease. To appropriately gauge how the US should respond to this evolving health threat, it will be critical to continue to have access to data from China. Just prior to the US's announcement of travel bans, China indicated that it would allow US scientists in to participate in the epidemic response. This was an important development and may have led to an improved understanding of the current epidemic. But it is now questionable whether this offer is still viable, given the on-going travel restrictions.

It is essential that we maintain positive relationships with China to ensure the continued availability of essential goods. China is a major producer of the medical resources which the US will need to respond to this epidemic, such as surgical masks and other personal protective equipment. Our dependence on medical supplies from China is not just restricted to products needed for responding to this epidemic. For example, China is a major global producer of raw materials for commonly-used medicines, such as the blood thinner heparin. The US recently experienced shortages in its supplies of heparin, which is derived from pigs, due to China's efforts to cull pigs in order to control the spread of African Swine Fever. What this example should indicate to us that should help China respond to 2019 nCoV to ensure that the actions it takes do not interrupt the production and distribution of essential goods. There are already reports suggesting that China's massive efforts to restrict the movements of tens of millions of individuals may interrupt the production of goods. China needs our help and it is in our best interest to provide it.

We must now contemplate the possibility of pandemic spread of 2019 nCoV and must plan for how we will mitigate the impacts of the virus. In my view, it is highly likely that the United States will continue to see cases of 2019 nCoV, despite the recently implemented travel bans and quarantines. Though there are still important unknowns, this epidemic bears a number of similarities to the 2009 influenza A/H1N1 pandemic. It is essential that we plan for the possibility that the 2019 nCoV virus will follow a similar pattern to the 2009 pandemic. If the virus continues to circulate and cases keep climbing, the probability of community-wide transmission will increase. Responding to a novel virus for which no specific therapy or vaccine yet exists leaves only the possibility of mitigating the disease spread. What measures we take to find cases and mitigate disease spread will be determined by the observed severity and the availability of resources. If there continue to be concerns about the severity of the virus, our priority should be to rapidly detect and isolate of cases and identify and monitor their close contacts for signs of illness. Communities will likely consider other mitigation

strategies, such as limiting public gatherings and closing schools, but the operational feasibility of these measures must be examined, and potential adverse consequences (e.g., reduced availability of healthcare personnel due to childcare obligations) should be considered. If the disease continues to demonstrate mild tendencies in cases outside of China, we may consider focusing efforts on protecting those most likely to become ill and preventing deaths.

We must ensure that responding agencies have the resources necessary to respond to 2019 nCoV cases across the country. Each of the above scenarios requires that health departments and hospitals have the resources they need to conduct surveillance to promote proven mitigation measures, such as case isolation. Unless patients require medical attention, they should be isolated outside of a hospital to reduce the possibility that they infect healthcare workers and other patients. Hospitals and other health facilities will need resources to safely treat a surge of patients.

If the number of 2019 nCoV cases in the US continues to grow, the US Congress will likely be called to appropriate emergency funds to enable states to respond to the virus. During the 2009 pandemic, the Ebola epidemic of 2014, and the response to the Zika pandemic, the US Congress approved emergency supplemental funding that went to support state and local response efforts. The current fiscal outlook in states is such that they will be unable to fully respond without additional federal funding. Federal agencies such as HHS and CDC, which have been responding to multiple on-going disease emergencies, such as Ebola in DRC, have already indicated that they may need additional emergency response funds to support the 2019 nCoV response.

Government leadership is needed to facilitate the development of medical countermeasures, including diagnostics. Though a number of efforts to develop a vaccine have been announced, it is likely that a usable vaccine will not be available for some time. Research is also being conducted to develop therapeutic medicines, which may help those with severe illness and prevent deaths. Enhanced diagnostic tools are essential to the use of both vaccine and therapeutics, yet comparatively less attention has been given to the need to accelerate the development of new diagnostic tools. CDC is currently conducting all of the testing for 2019 nCoV in the US, but has plans to roll out testing capabilities to state public health labs. This will be important to reduce current lag times in getting test results for persons under investigation for 2019 nCoV and to meet a likely increase in the demand for testing as case counts rise. However, there is also a need for diagnostics in clinical settings. If more patients seek care at healthcare facilities, there will be an increased need for diagnostic tools to help clinicians rule out infection with nCoV, make decisions about cohorting or isolating patients, and to determine course of therapy.

CONCLUSION

The points I have raised today hopefully paint a picture of an epidemic that is in many ways complex and evolving, but for which we are increasingly gaining clarity. International collaboration will be essential for continuing to monitor and learn about the virus and the epidemic it is causing. Even amid uncertainty, we should root our response in evidence. Without evidence to guide our actions, we may inadvertently exacerbate the toll of this

epidemic. In evaluating how we should respond to this public health emergency, we must consider not only whether the measures will work, but also whether the ends justify the means. While we want to do the utmost to protect health, we don't want to pursue measures that will extract a greater toll on societies and our economy than the virus would alone. We must continually assess whether our response strategies are matched to the level of threat that the virus poses and adapt our approach as new information becomes available. With evidence mounting of continued global spread despite aggressive actions being taken by countries, it is becoming clear that a change of course may be needed. Instead of trying to implement measures that likely will not work to prevent the virus from entering our country, we should focus on efforts that we know will help to lessen its impacts, such as ensuring that federal, state and local health agencies, and hospitals and health clinics have the resources they need to diagnose, isolate and safely treat cases, and to promote feasible approaches to community mitigation that are most likely to mitigate disease spread. For this we will need government leadership and additional investments.

Chapter 476

WHAT YOU NEED TO KNOW ABOUT CORONAVIRUS DISEASE 2019 (COVID-19)*

Department of Health and Human Services

WHAT IS CORONAVIRUS DISEASE 2019 (COVID-19)?

Coronavirus disease 2019 (COVID-19) is a respiratory illness that can spread from person to person. The virus that causes COVID-19 is a novel coronavirus that was first identified during an investigation into an outbreak in Wuhan, China.

CAN PEOPLE IN THE U.S. GET COVID-19?

COVID-19 is spreading from person to person in China, and limited spread among close contacts has been detected in some countries outside China, including the United States. At this time, however, this virus is NOT currently spreading in communities in the United States. Right now, the greatest risk of infection is for people in China or people who have traveled to China. Risk of infection is dependent on exposure. Close contacts of people who are infected are at greater risk of exposure, for example health care workers and close contacts of people who are infected with the virus that causes COVID-19. CDC continues to closely monitor the situation.

HAVE THERE BEEN CASES OF COVID-19 IN THE U.S.?

Yes. The first case of COVID-19 in the United States was reported on January 21, 2020. The current count of cases of COVID-19 in the United States is available on CDC's webpage at <https://www.cdc.gov/coronavirus/2019-ncov/cases-in-us.html>.

* This is an edited, reformatted and augmented version of Department of Health and Human Services Publication, No. CS 314937-A 02, dated February 21, 2020.

HOW DOES COVID-19 SPREAD?

The virus that causes COVID-19 probably emerged from an animal source, but now it seems to be spreading from person to person. It's important to note that person-to-person spread can happen on a continuum. Some diseases are highly contagious (like measles), while other diseases are less so. At this time, it's unclear how easily or sustainably the virus that causes COVID-19 is spreading between people. Learn what is known about the spread of newly emerged coronaviruses at <https://www.cdc.gov/coronavirus/2019-ncov/about/transmission.html>.

WHAT ARE THE SYMPTOMS OF COVID-19?

Patients with COVID-19 have had mild to severe respiratory illness with symptoms of

- fever
- cough
- shortness of breath

WHAT ARE SEVERE COMPLICATIONS FROM THIS VIRUS?

Many patients have pneumonia in both lungs.

HOW CAN I HELP PROTECT MYSELF?

The best way to prevent infection is to avoid being exposed to the virus that causes COVID-19.

THERE ARE SIMPLE EVERYDAY PREVENTIVE ACTIONS TO HELP PREVENT THE SPREAD OF RESPIRATORY VIRUSES. THESE INCLUDE

- Avoid close contact with people who are sick.
- Avoid touching your eyes, nose, and mouth with unwashed hands.
- Wash your hands often with soap and water for at least 20 seconds. Use an alcohol-based hand sanitizer that contains at least 60% alcohol if soap and water are not available.

IF YOU ARE SICK, TO KEEP FROM SPREADING RESPIRATORY ILLNESS TO OTHERS, YOU SHOULD

- Stay home when you are sick.
- Cover your cough or sneeze with a tissue, then throw the tissue in the trash.
- Clean and disinfect frequently touched objects and surfaces.

WHAT SHOULD I DO IF I RECENTLY TRAVELED TO CHINA AND GOT SICK?

If you were in China within the past 14 days and feel sick with fever, cough, or difficulty breathing, you should seek medical care. Call the office of your health care provider before you go, and tell them about your travel and your symptoms. They will give you instructions on how to get care without exposing other people to your illness. While sick, avoid contact with people, don't go out and delay any travel to reduce the possibility of spreading illness to others.

IS THERE A VACCINE?

There is currently no vaccine to protect against COVID-19. The best way to prevent infection is to avoid being exposed to the virus that causes COVID-19.

IS THERE A TREATMENT?

There is no specific antiviral treatment for COVID-19. People with COVID-19 can seek medical care to help relieve symptoms.

For more information: www.cdc.gov/COVID19.

Chapter 477

CORONAVIRUS DISEASE 2019 (COVID-19) SITUATION SUMMARY*

Centers for Disease Control and Prevention

This is an emerging, rapidly evolving situation and CDC will provide updated information as it becomes available, in addition to updated guidance.

BACKGROUND

CDC is responding to an outbreak of respiratory disease caused by a novel (new) coronavirus that was first detected in China and which has now been detected in almost 70 locations internationally, including in the United States. The virus has been named “SARS-CoV-2” and the disease it causes has been named “coronavirus disease 2019” (abbreviated “COVID-19”).

On January 30, 2020, the International Health Regulations Emergency Committee of the World Health Organization declared the outbreak a “public health emergency of international concernexternal icon” (PHEIC). On January 31, 2020, Health and Human Services Secretary Alex M. Azar II declared a public health emergency (PHE) for the United States to aid the nation’s healthcare community in responding to COVID-19.

SOURCE AND SPREAD OF THE VIRUS

Coronaviruses are a large family of viruses that are common in people and many different species of animals, including camels, cattle, cats, and bats. Rarely, animal coronaviruses can infect people and then spread between people such as with MERS-CoV, SARS-CoV, and now with this new virus (named SARS-CoV-2).

* This is an edited, reformatted and augmented version of Centers for Disease Control and Prevention Publication, Updated March 3, 2020.

The SARS-CoV-2 virus is a betacoronavirus, like MERS-CoV and SARS-CoV. All three of these viruses have their origins in bats. The sequences from U.S. patients are similar to the one that China initially posted, suggesting a likely single, recent emergence of this virus from an animal reservoir.

Early on, many of the patients at the epicenter of the outbreak in Wuhan, Hubei Province, China had some link to a large seafood and live animal market, suggesting animal-to-person spread. Later, a growing number of patients reportedly did not have exposure to animal markets, indicating person-to-person spread. Person-to-person spread was subsequently reported outside Hubei and in countries outside China, including in the United States. Some international destinations now have apparent community spread with the virus that causes COVID-19, including in some parts of the United States. Community spread means some people have been infected and it is not known how or where they became exposed. Learn what is known about the spread of this newly emerged coronaviruses.



Confirmed COVID-19 Cases Global Map.

[View larger image and see a list of locations.](#)

COVID-19 CASES IN THE U.S.

Situation in U.S.

- Imported cases of COVID-19 in travelers have been detected in the U.S.
- Person-to-person spread of COVID-19 was first reported among close contacts of returned travelers from Wuhan.
- During the week of February 23, CDC reported community spread of the virus that causes COVID-19 in California (in two places), Oregon and Washington. Community spread in Washington resulted in the first death in the United States from

COVID-19, as well as the first reported case of COVID-19 in a health care worker, and the first potential outbreak in a long-term care facility.

Illness Severity

Both MERS-CoV and SARS-CoV have been known to cause severe illness in people. The complete clinical picture with regard to COVID-19 is not fully understood. Reported illnesses have ranged from mild to severe, including illness resulting in death. While information so far suggests that most COVID-19 illness is mild, a report external icon out of China suggests serious illness occurs in 16% of cases. Older people and people with certain underlying health conditions like heart disease, lung disease and diabetes, for example, seem to be at greater risk of serious illness.

Learn more about the symptoms associated with COVID-19.

There are ongoing investigations to learn more. This is a rapidly evolving situation and information will be updated as it becomes available.

RISK ASSESSMENT

Outbreaks of novel virus infections among people are always of public health concern. The risk from these outbreaks depends on characteristics of the virus, including how well it spreads between people, the severity of resulting illness, and the medical or other measures available to control the impact of the virus (for example, vaccine or treatment medications). The fact that this disease has caused illness, including illness resulting in death, and sustained person-to-person spread is concerning. These factors meet two of the criteria of a pandemic. As community spread is detected in more and more countries, the world moves closer toward meeting the third criteria, worldwide spread of the new virus.

Reported community spread of COVID-19 in parts of the United States raises the level of concern about the immediate threat for COVID-19 for those communities. The potential public health threat posed by COVID-19 is very high, to the United States and globally.

At this time, however, most people in the United States will have little immediate risk of exposure to this virus. This virus is NOT currently spreading widely in the United States. However, it is important to note that current global circumstances suggest it is likely that this virus will cause a pandemic. This is a rapidly evolving situation and the risk assessment will be updated as needed.

Current risk assessment:

- For most of the American public, who are unlikely to be exposed to this virus at this time, the immediate health risk from COVID-19 is considered low.
- People in communities where ongoing community spread with the virus that causes COVID-19 has been reported are at elevated, though still relatively low risk of exposure.
- Healthcare workers caring for patients with COVID-19 are at elevated risk of exposure.

- Close contacts of persons with COVID-19 also are at elevated risk of exposure.
- Travelers returning from affected international locations where community spread is occurring also are at elevated risk of exposure.

CDC has developed guidance to help in the risk assessment and management of people with potential exposures to COVID-19.

WHAT MAY HAPPEN

More cases of COVID-19 are likely to be identified in the coming days, including more cases in the United States. It's also likely that person-to-person spread will continue to occur, including in communities in the United States. It's likely that at some point, widespread transmission of COVID-19 in the United States will occur.

Widespread transmission of COVID-19 would translate into large numbers of people needing medical care at the same time. Schools, childcare centers, workplaces, and other places for mass gatherings may experience more absenteeism. Public health and healthcare systems may become overloaded, with elevated rates of hospitalizations and deaths. Other critical infrastructure, such as law enforcement, emergency medical services, and transportation industry may also be affected. Health care providers and hospitals may be overwhelmed. At this time, there is no vaccine to protect against COVID-19 and no medications approved to treat it. Nonpharmaceutical interventions would be the most important response strategy.

CDC RESPONSE

Global efforts at this time are focused concurrently on containing the spread and mitigating the impact of this virus. The federal government is working closely with state, local, tribal, and territorial partners, as well as public health partners, to respond to this public health threat. The public health response is multi-layered, with the goal of detecting and minimizing introductions of this virus in the United States. CDC is operationalizing all of its pandemic preparedness and response plans, working on multiple fronts to meet these goals, including specific measures to prepare communities to respond to local transmission of the virus that causes COVID-19. There is an abundance of pandemic guidance developed in anticipation of an influenza pandemic that is being repurposed and adapted for a COVID-19 pandemic.

HIGHLIGHTS OF CDC'S RESPONSE

- CDC established a COVID-19 Incident Management System on January 7, 2020. On January 21, CDC activated its Emergency Operations Center to better provide ongoing support to the COVID-19 response.

- The U.S. government has taken unprecedented steps with respect to *travel* in response to the growing public health threat posed by this new coronavirus:
 - Effective February 2, at 5pm, the U.S. government suspended entry of foreign nationals who have been in China within the past 14 days.
 - U.S. citizens, residents, and their immediate family members who have been in Hubei province and other parts of mainland China are allowed to enter the United States, but they are subject to health monitoring and possible quarantine for up to 14 days.
 - On February 29, the U.S. government announced it was suspending entry of foreign nationals who have been in Iran within the past 14 days.
 - CDC has issued the following travel guidance related to COVID-19:
 - China — Level 3, Avoid Nonessential Travel — updated February 22;
 - Hong Kong — Level 1, Practice Usual Precautions — issued February 19;
 - Iran — Level 3, Avoid Nonessential Travel — updated February 28;
 - Italy — Level 3, Avoid Nonessential Travel — updated February 28;
 - Japan — Level 2, Practice Enhanced Precautions — updated February 22;
 - South Korea — Level 3, Avoid Nonessential Travel — updated February 24.
 - CDC also recommends that all travelers reconsider cruise ship voyages into or within Asia at this time.
- CDC is issuing clinical guidance, including:
 - On January 30, CDC published guidance for healthcare professionals on the clinical care of COVID-19 patients.
 - On February 3, CDC posted guidance for assessing the potential risk for various exposures to COVID-19 and managing those people appropriately.
 - On February 27, CDC updated its criteria to guide evaluation of persons under investigation for COVID-19.
 - On February 28, CDC issued a Health Alert Network (HAN): Update and Interim Guidance on Outbreak of COVID-19.
- CDC has deployed multidisciplinary teams to support state health departments case identification, contact tracing, clinical management, and communications.
- CDC has worked with the Department of State, supporting the safe return of Americans who have been stranded as a result of the ongoing outbreaks of COVID-19 and related travel restrictions. CDC has worked to assess the health of passengers as they return to the United States and provided continued daily monitoring of people who are quarantined.

This is a picture of CDC's laboratory test kit for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). CDC is shipping the test kits to laboratories CDC has designated as qualified, including U.S. state and local public health laboratories, Department of Defense (DOD) laboratories and select international laboratories. The test kits are bolstering global laboratory capacity for detecting SARS-CoV-2.

Resize iconView Larger.



- An important part of CDC's role during a public health emergency is to develop a test for the pathogen and equip state and local public health labs with testing capacity.
 - After distribution of a CDC rRT-PCR test to diagnose COVID-19 to state and local public health labs started, performance issues were identified related to a problem in the manufacturing of one of the reagents. Laboratories were not able to verify the test performance.
 - CDC worked on two potential resolutions to this problem.
 - CDC developed a new protocol that uses two of the three components of the original CDC test kit to detect the virus that causes COVID-19 after establishing that the third component, which was the problem with the original test, can be excluded from testing without affecting accuracy. CDC is working with FDA to amend the existing Emergency Use Authorization (EUA) for the test, but in the meantime, FDA granted discretionary authority for the use of the original test kits.
 - Public health laboratories can use the original CDC test kit to test for the virus that causes COVID-19 using the new protocol.
 - Further, newly manufactured kits have been provided to the International Reagent Resource [external icon](#) for distribution.
 - Combined with other reagents that CDC has procured, there are enough testing kits to test more than 75,000 people.
 - In addition, CDC has two laboratories conducting testing for the virus that causes COVID-19. CDC can test approximately 350 specimens per day.
 - Commercial labs are working to develop their own tests that hopefully will be available soon. This will allow a greater number of tests to happen close to where potential cases are.
 - CDC has grown the COVID-19 virus in cell culture, which is necessary for further studies, including for additional genetic characterization. The cell-grown virus was sent to NIH's BEI Resources Repository [external icon](#) [external icon](#) for use by the broad scientific community.

CDC RECOMMENDS

- Everyone can do their part to help us respond to this emerging public health threat:
 - It's currently flu and respiratory disease season and CDC recommends getting a flu vaccine, taking everyday preventive actions to help stop the spread of germs, and taking flu antivirals if prescribed.
 - If you are a healthcare provider, be on the look-out for:
 - People who recently traveled from China or another affected area and who have symptoms associated with COVID-19, and
 - People who have been in close contact with someone with COVID-19 or pneumonia of unknown cause. (Consult the most recent definition for patients under investigation [PUIs].)
 - If you are a healthcare provider or a public health responder caring for a COVID-19 patient, please take care of yourself and follow recommended infection control procedures.
 - If you are a close contact of someone with COVID-19 and develop symptoms of COVID-19, call your healthcare provider and tell them about your symptoms and your exposure.
- If you are a resident in a community where person-to-person spread of COVID-19 has been detected and you develop COVID-19 symptoms, call your healthcare provider and tell them about your symptoms.
- For people who are ill with COVID-19, but are not sick enough to be hospitalized, please follow CDC guidance on how to reduce the risk of spreading your illness to others. People who are mildly ill with COVID-19 are able to isolate at home during their illness.
- If you have been in China or another affected area or have been exposed to someone sick with COVID-19 in the last 14 days, you will face some limitations on your movement and activity for up to 14 days. Please follow instructions during this time. Your cooperation is integral to the ongoing public health response to try to slow spread of this virus.

Chapter 478

SCIENCE AND TECH SPOTLIGHT: CORONAVIRUSES*

Timothy M. Persons

WHY THIS MATTERS

Coronaviruses can spread rapidly and cause outbreaks with high mortality rates. They were not considered a major risk for humans until the SARS outbreak in 2002. Since then, there have been multiple highly contagious outbreaks originating in animals and spreading to humans—most recently the outbreak in Wuhan, China of Coronavirus Disease 2019 (COVID-19).

THE SCIENCE

What is it? While the outbreak of COVID-19 in China has brought the term coronavirus into daily usage, coronaviruses can vary in severity. They can cause respiratory issues, such as pneumonia, and are believed to be one cause of the common cold. According to the Centers for Disease Control and Prevention (CDC), most people will be infected by a coronavirus at some point in their lifetimes. As of March 2020, seven coronaviruses have been identified that can cause illness in humans. Most infections result in mild to moderate symptoms, such as runny nose, headache, cough, sore throat, fever, and a run-down feeling.

Coronaviruses are most commonly transmitted by coughing, sneezing, person-to-person contact, and touching objects that have viral particles on them, according to CDC. The best prevention is washing hands with soap and avoiding contact with people who are sick or work in quarantine areas. Current treatment methods are limited, and research is being fast-tracked to develop a vaccine against existing and emerging coronaviruses.

Recent high-profile coronavirus outbreaks have raised new concern because of high mortality rates relative to the coronaviruses that cause the common cold. In addition, the

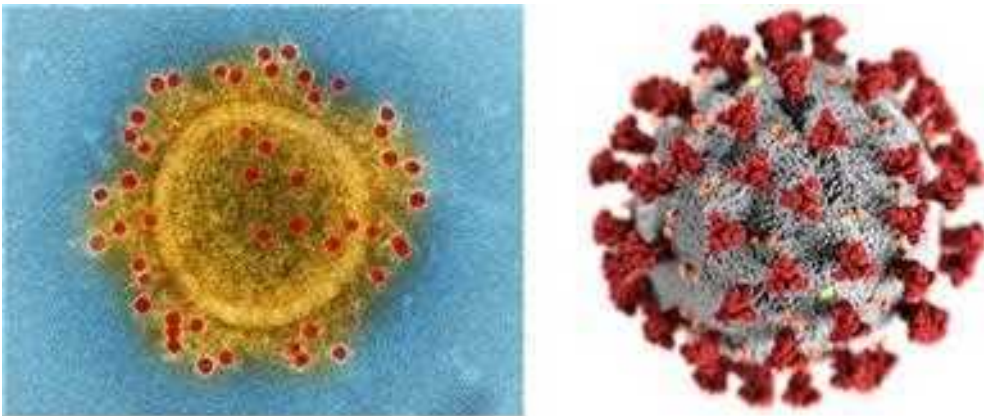
* This is an edited, reformatted and augmented version of the United States Government Accountability Office Publication, No. GAO-20-472SP Coronaviruses, dated March 2020.

severe coronaviruses can cause both upper- and lower-respiratory-tract infections, including pneumonia.

Since 2002, there have been three severe outbreaks of respiratory illness caused by coronaviruses, all three originating in animals. In 2002, an outbreak of Severe Acute Respiratory Syndrome (SARS) began in China and had a mortality rate of approximately 10 percent. In 2012, an outbreak of Middle East Respiratory Syndrome (MERS) had a mortality rate reported as high as 34 percent. Most recently, a December 2019 outbreak of a new coronavirus, SARS-CoV-2—which causes COVID-19—has seen a high infection rate, with over 70,000 infected and over 2,600 deaths—a mortality rate of approximately 3 percent as of February 24th, 2020, according to the World Health Organization (WHO). Estimates of the reproductive ratio, or R_0 , for COVID-19 have also indicated that it has the potential to spread rapidly. These estimates are tentative, however, because the R_0 is a complex epidemiologic measure that is context-specific and affected by numerous biological, behavioral, and environmental factors.

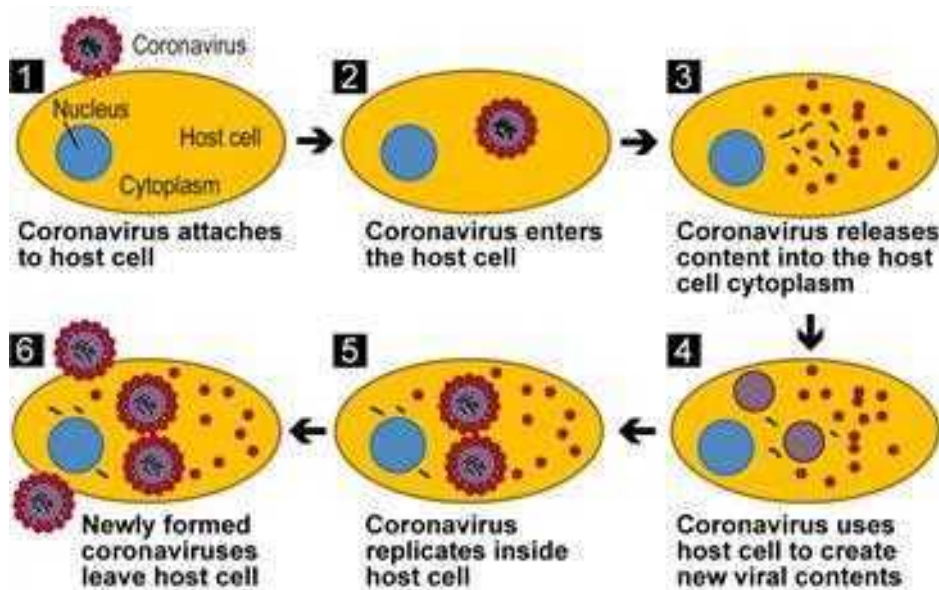
How does it work? Coronaviruses are believed to work in similar ways. Viral particles attach themselves to specific molecules, known as receptors, on the surface of a human or animal cell, allowing the virus to enter. Once inside, the virus discards its outer coating, releasing its genetic material into the host cell. This can occur in many cells at the same time. The virus can then use the cell's own mechanisms—for example, the mechanism to produce proteins based on genetic code—to replicate itself. The hijacking of the cell's functions causes the release of new viral particles and restarting the process, either in more cells of the same host or in another host that becomes infected.

Coronaviruses mutate rapidly compared to other viruses, enabling them to adapt to new environments. Coronaviruses are ribonucleic acid (RNA) viruses, which are more prone to random mutations than deoxyribonucleic acid (DNA) viruses. Because DNA viruses, like chickenpox and many others, are more stable, it is easier to create long term effective vaccines against them. In contrast, RNA viruses, like flu, may regularly require new vaccines.



Sources (left to right): National institute of Allergy and Infectious Diseases; Centers for Disease Control and Prevention, Alissa Eckert, Dan Higgins. | GAO-20-472SP.

Figure 1. Electron microscope image and schematic of coronavirus particles (Middle East Respiratory Syndrome Coronavirus and general coronavirus respectively).



Source: GAO analysis of Fenner's Veterinary Virology edited by N. James MacLachlan and Edward J. Dubovi. | GAO-20-472SP.

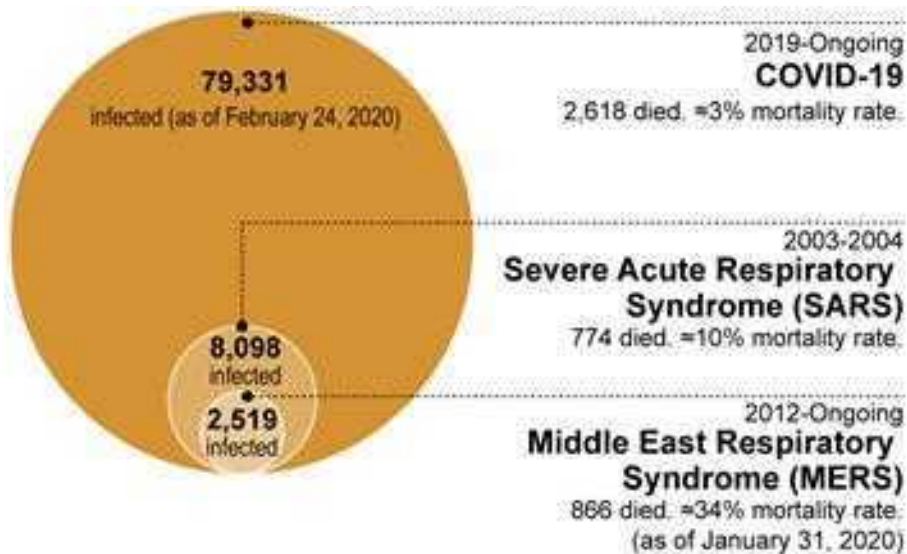
Figure 2. Schematic of how a coronavirus infects host cells. This process is similar for all RNA viruses, the large class to which coronaviruses belong.

Generally, coronaviruses originate in animals, with the most likely origin being bats, and can spread from animal to animal. In environments where humans and multiple animal species mix, such as live animal markets and farms, there is an increased likelihood that a coronavirus can mutate and spread into humans. The original animal vector for SARS-CoV-2 has not yet been determined.

How mature is it? Several procedures, including diagnostic testing, are available to address coronaviruses, and are being used in the U.S. response. However, vaccines and therapies are not yet mature.

In the wake of the COVID-19 outbreak, Chinese researchers isolated the virus, sequenced its genome, and shared the results with the scientific community. The sequencing allowed CDC to develop a diagnostic test that is now being distributed to local labs. Also, based on genetic similarities, a vaccine developed for SARS has been recommended by researchers as a possible option for SARS-CoV-2. And researchers are drawing on the SARS-CoV-2 genome to help determine which aspects of the coronavirus might be used to develop a more specific vaccine against it.

For those already infected, doctors are trying a drug originally made to treat Ebola that also works against SARS and MERS. The first U.S. patient diagnosed with COVID-19 was treated with this drug under compassionate use (a policy allowing some use of non-approved drugs), and additional antivirals are being tested.



Source: World Health Organization (WHO). | GAO-20-472SP.

Figure 3. The recent outbreaks of coronavirus-caused diseases known to infect humans (COVID-19 numbers are confirmed and as reported by China).

OPPORTUNITIES

- Identification of common targets in coronaviruses to develop
- vaccines against all coronaviruses.
- Increased coordination by industry, academia, and government could improve awareness of treatment options for future outbreaks.
- Advances in predictive infectious disease modelling to better inform decisions about interventions in future outbreaks.

Challenges

- For rapid deployment, potential treatments need to be prepared prior to an outbreak despite limited information and incentives.
- Development of vaccines for RNA viruses requires frequent evaluation and reformulation. It is complex, costly, and time consuming.
- Outbreak detection requires constant monitoring and coordination among nations, which can be impeded by more closed societies.
- Global economic consequences of such outbreaks can be serious. According to multiple economic forecasting models, SARS cost the global economy \$30-100 billion.

Policy Context and Questions

- To what extent are surveillance and clinical data, computational models, and information sharing mechanisms in place to promote agile and effective risk management during disease outbreaks?
- What policies and mechanisms are in place or needed to help maintain medical supply chains during global disease outbreaks?

Selected GAO Work

- National Biodefense Strategy: Additional Efforts Would Enhance Likelihood of Effective Implementation GAO-20-273
- Infectious Disease Threats: Funding and Performance of Key Preparedness and Capacity-Building Programs GAO-18-362

Selected References

Centers for Disease Control and Prevention
<https://www.cdc.gov/coronavirus/index.html>
World Health Organization
<https://www.who.int/health-topics/coronavirus>

Chapter 479

COVID-19: CURRENT TRAVEL RESTRICTIONS AND QUARANTINE MEASURES*

Edward C. Liu

The United States, along with many countries, is responding to an outbreak of a respiratory disease, now referred to as COVID-19, which is caused by a novel coronavirus first detected in mainland China's Hubei Province in late 2019. Cases of COVID-19 have now been detected in several countries, including the United States.

To date, the federal government has taken two key actions to deter persons with suspected COVID-19 infection from entering the country or spreading the virus to persons within the United States. First, the federal government has restricted many non-U.S. nationals (aliens) who recently travelled to mainland China or Iran from entering the United States. Second, the federal government has imposed a quarantine requirement on all persons entering the United States, regardless of citizenship status, who have recently been to mainland China. This Legal Sidebar examines the legal authorities underlying these actions, as well as possible legal challenges to their use.

ENTRY RESTRICTIONS

To deter the entry of aliens into the United States who may have been exposed to COVID-19, President Trump has invoked his authority over alien entry under Section 212(f) of the Immigration and Nationality Act (INA). That provision allows the President to "suspend the entry of all aliens, or any class of aliens" whose entry he "finds . . . would be detrimental to the interests of the United States." Under this authority, President Trump issued a Proclamation on January 31, 2020, generally suspending the entry of any foreign national who had been in mainland China at some point within the prior 14 days. But lawful permanent residents (LPRs), most immediate relatives of U.S. citizens and LPRs, and some other groups, such as some airplane and ship crew members, are exempted from this

* This is an edited, reformatted and augmented version of Congressional Research Service Publication No. LSB10415, dated March 5, 2020.

restriction, as are those with prior presence in Hong Kong or Macau. On February 29, 2020, President Trump issued a second Proclamation that similarly suspends the entry of any foreign national who has been in Iran within the prior 14 days, in addition to making minor amendments to the earlier Proclamation.

While this appears to be the first time Section 212(f) has been used to control the spread of a communicable disease, the provision has been previously invoked to restrict foreign travelers from coming into the United States. Perhaps most notably, Section 212(f) provided the legal basis for the Trump Administration's imposition of the so-called "travel ban" on certain foreign nationals from designated countries. In the context of a challenge to that invocation of Section 212(f), the Supreme Court held that the provision "exudes deference to the President in every clause" and gives him mostly unfettered discretion to decide "when to suspend entry," "whose entry to suspend," "for how long," and "on what conditions." In light of the deference afforded to the President's determinations over these matters, coupled with the amount of evidence demonstrating the communicability of COVID-19, it seems unlikely that a court would find that the Proclamations issued with respect to mainland China and Iran exceed the scope of the President's authority under Section 212(f).

QUARANTINE AND ISOLATION

The Administration's January 31, 2020, Proclamation also directed the Secretary of Homeland Security "to regulate the travel of persons and aircraft to the United States to facilitate the orderly medical screening and, where appropriate, quarantine of persons who enter the United States and who may have been exposed to the virus." To this end, on February 2, 2020, the U.S. Department of Homeland Security (DHS) imposed screening and quarantine rules for persons – including U.S. nationals, LPRs, and their immediate family members – who arrive in the United States within 14 days after having been in mainland China. Those persons travelling by air must arrive at one of 11 designated airports where they will be screened. On March 2, 2020, DHS imposed similar requirements for air travelers who were recently present in Iran. Screened persons will be taken to a medical facility for isolation and treatment if fever, cough, or difficulty breathing is detected. Asymptomatic persons are generally to be held under federal quarantine for 14 days from the time they left mainland China if they visited Hubei Province. But asymptomatic persons whose recent travel did not include Hubei Province are asked to self-quarantine for 14 days. State and local health authorities are to provide oversight of individuals who self-quarantine.

Authority for these quarantine rules comes from Section 361 of the Public Health Service Act, which authorizes the U.S. Department of Health and Human Services (HHS) to promulgate and enforce regulations "necessary to prevent the introduction, transmission, or spread of communicable diseases from foreign countries into the States or possessions, or from one State or possession into any other State or possession." Besides authorizing the apprehension and examination of "any individual reasonably believed to be infected with a communicable disease in a qualifying stage" who is "moving or about to move from a State to another State," Section 361 also authorizes the apprehension and quarantine of persons who are not engaged in interstate travel, but are reasonably believed "to be a probable source of infection to individuals who, while infected with such disease in a qualifying stage, will be

moving from a State to another State.” To facilitate these quarantine requirements, HHS promulgated an interim final rule, effective February 7, 2020, requiring airlines with flights arriving in the United States to transmit to HHS’s Centers for Disease Control and Prevention (CDC) identifying information about passengers or crew who may be at risk of exposure to communicable disease.

In addition to federal quarantine authority, states may quarantine or isolate persons as public health risks using their police powers. State mandatory quarantine laws vary, with some implemented through public health orders issued by state health departments, and others effectuated through court orders authorizing the detention of an individual upon some evidentiary showing that the person poses a public health risk.

Possible Constitutional Challenges

Because quarantine requirements involve a deprivation of a person’s liberty to move freely, they have occasionally been challenged on constitutional grounds. Specifically, the Supreme Court “repeatedly has recognized that civil commitment for any purpose constitutes a significant deprivation of liberty that requires due process protection.” Accordingly, quarantine measures may be challenged as violating the Constitution’s *substantive* or *procedural* due process protections.

Substantive due process challenges center on whether a governmental action “is so egregious, so outrageous, that it may fairly be said to shock the contemporary conscience,” without regard to “the fairness of the procedures used to implement” the action. Recent challenges to quarantine and isolation for public health reasons have borrowed from substantive due process precedents involving involuntary commitment. In that context, substantive due process challenges question whether the government has set forth an adequate justification to support the deprivation of liberty effected by a quarantine policy (a type of challenge that might also be viewed through an equal protection rather than a due process lens). In either case, a substantive due process challenge to quarantine policies affecting those suspected of COVID-19 seems unlikely to succeed given the degree of public health risk posed by the virus. Courts have recognized that expeditious actions by government officials are frequently required to protect public health or safety, and have been reluctant to find substantive due process violations even if those actions are found to be erroneous after the fact.

There might also be concerns as to whether a quarantine policy satisfies the Constitution’s *procedural due process* requirements. These requirements concern whether the *process* attending a particular deprivation by the government – in this case the restraint on liberty during the quarantine period – is fair. The degree of protection required by procedural due process is a “flexible” concept, requiring an examination of the private interests at stake; the risk of an erroneous deprivation of such interest and the probable value of additional safeguards; and the government’s interests. In the context of state action, the Supreme Court has said that the Due Process Clause typically “requires some kind of a hearing *before* the State deprives a person of liberty,” but has also held that the “necessity of quick action by the State or the impracticality of providing any predeprivation process” may mean that a *post-deprivation* remedy is constitutionally adequate. Here, the government may argue that the

contagiousness of the COVID-19 virus may make predeprivation process impractical before requiring the quarantine of a person suspected of COVID-19 infection.

In 2014, a federal district court applying this standard in the context of a Friday-to-Monday quarantine of a nurse who had recently been in contact with Ebola patients found that the lack of a predeprivation hearing was not a clear violation of due process because quarantine is “necessarily prophylactic and peremptory.” However, the court noted that the relatively short duration of the quarantine (80 hours) also factored into its conclusion. Moreover, to the extent that post-deprivation procedural due process claims may be made, government actors may still enjoy qualified immunity to civil liability if the action “does not violate clearly established statutory or constitutional rights of which a reasonable person would have known.”

OTHER LEGAL ISSUES

Federal officials have warned that as the United States begins to see “community spread” of COVID-19, actions taken to limit entry of persons into the country may be less important than domestic quarantine and isolation of persons already present in the United States. Shifts in the types of actions taken in response to the disease may also present distinct legal issues from those discussed above. For example, questions have arisen regarding the employment protections that workers may have under federal laws, such as the Family and Medical Leave Act (or perhaps under state laws), if those workers fall ill, are placed under mandatory quarantine, or choose to stay home voluntarily to avoid exposure to themselves or others or to take care of an infected family member.

The federal government may also seek to facilitate the distribution of medical countermeasures to COVID-19 as they continue to develop through the issuance of emergency use authorizations (EUA) under Section 564 of the Federal Food, Drug, and Cosmetic Act. One such EUA was issued on February 4, 2020, to enable emergency use of the CDC’s real-time COVID-19 diagnostic test. On February 29, 2020, FDA issued additional guidance stating that it would not object to the use of certain diagnostic tests prior to issuance of an EUA. In addition, the federal government has the authority to waive liability for manufacturers, distributors, and providers of such countermeasures, under the Public Readiness and Emergency Preparedness Act, which it most recently invoked with respect to Ebola countermeasures.

Chapter 480

COVID-19: FEDERAL ECONOMIC DEVELOPMENT TOOLS AND POTENTIAL RESPONSES*

Michael H. Cecire

The current coronavirus disease (COVID-19) outbreak has led to tens of thousands of cases and thousands of deaths worldwide. In addition to the disease's mortality and public health effects, it may have potentially significant economic implications, including productivity losses, supply chain disruptions, labor dislocation, and potential financial pressure on businesses and households. Relatively few federal programs are available to provide timely economic relief to affected businesses. This Insight considers the outbreak's economic development implications and policy considerations for Members of Congress who have shown interest in addressing the economic dimensions of this public health issue.

COVID-19 ECONOMIC DEVELOPMENT IMPLICATIONS

COVID-19 is a newly designated disease caused by a previously undetected coronavirus. Most cases have been reported in China, with additional cases on every inhabited continent. Clusters of illness have occurred in South Korea, Japan, Singapore, Italy, and Iran. For more information on the health and epidemiological aspects of COVID-19, see CRS products R46219 and IF11421.

The COVID-19 outbreak is foremost a public health issue. However, the epidemic itself and containment measures in China and elsewhere could have significant economic implications for the United States and globally. In the short-term, the COVID-19 outbreak is primarily a threat to businesses dependent on supply chains in China, or for exports there. However, many economists have warned that a more prolonged crisis may see broader economic disruptions if workplaces and schools are closed to contain the outbreak, and medical and food supplies dwindle due to disrupted supply and increased demand.

* This is an edited, reformatted and augmented version of Congressional Research Service Publication No. IN11228, dated February 28, 2020.

In China, mass containment measures have disrupted global supply chains and capital markets. In the near term, the outbreak's effects on the U.S. economy could be limited to localized disruptions for businesses and workers—particularly in communities dependent on technology manufacturing and tourism. In certain cases, supply chain issues may stall production, prevent companies from fulfilling orders, and potentially impact firm revenues.

In a prolonged or wider epidemic, supply chain issues may further compound. Growth could slow further, and affected companies may be forced to furlough or lay off workers, and others may slow hiring. As demonstrated in China and elsewhere, social distancing measures can effectively stop local economic activity, which may impact localized labor markets, household finances, and governmental tax revenues and service delivery. Additional considerations include potential shortages of medical supplies and foodstuffs, other ancillary health effects, and the U.S. medical and public health system's ability to cope with a significant outbreak.

CONSIDERATIONS FOR CONGRESS

Many Members of Congress have heard concerns from constituents affected by supply chain-, exports-, and tourism-related disruptions from the outbreak. Relatively few federal programs exist to provide timely relief to businesses for outbreak-related disruptions. Some programs include

- The Small Business Administration (SBA) administers disaster and non-disaster loans for small businesses and organizations, and supports an extensive network of SBA-affiliated resource partners who provide management and technical assistance to small businesses;
- The Department of the Treasury's Community Development Financial Institution Fund supports organizations that provide loans to businesses, homebuyers, community developers, and investors in distressed areas; and
- The Department of Agriculture's (USDA) Rural Development program offers limited services to support rural businesses to create or retain jobs.

In the event that disruptions continue and grow, public and non-profit organizations may consider tapping various federal economic development resources, including

- The Department of Housing and Urban Development's Community Development Block Grant (CDBG) program may be used for technical assistance, community assets, and workforce development;
- The Department of Commerce's Economic Development Administration programs may be used to diversify local economic bases;
- USDA programs can provide technical assistance and infrastructure support; and
- Federal regional commissions and authorities support economic diversification, workforce development, and technical assistance in their service areas.

Federal economic development programs are generally not equipped to provide rapid support to firms or communities affected by public health emergencies, though unemployment compensation programs have the ability to rapidly respond and provide immediate income support. In response to a COVID-19 outbreak, Congress may consider measures used in past disasters or economic crises:

- CDBG authorities for disaster recovery (CDBG-DR) could be utilized to address the outbreak's economic impact. Previous CDBG-DR uses included loans and grants to small and medium-sized enterprises (SMEs), workforce development, and community stabilization.
- Public health-related disruption eligibility for SBA's Economic Injury Disaster Loans (EIDLs) could be made explicit. EIDLs provide up to \$2 million to small businesses that suffer economic injury following disasters such as hurricanes. EIDLs may be awarded if the President issues a disaster or emergency declaration, or a disaster declaration by the SBA administrator upon request from a state governor.
- In response to the 2007-2009 recession, federal measures included direct interventions to stabilize industries and markets. A similar effort could support affected industries or supply chains, and/or federal loan guarantees to assist affected SMEs.
- In the recession, Unemployment Compensation benefits were temporarily augmented and extended, with some costs temporarily assumed by the federal government. Disaster Unemployment Assistance, which provides federally funded unemployment benefits to those unable to work as a result of a federally declared disaster and otherwise ineligible for regular benefits, could be a model for responding to public health emergencies.
- Following a federally declared disaster, the Internal Revenue Service (IRS) can provide tax relief to affected individuals. The IRS could provide such allowances to affected individuals and SMEs affected by a public health emergency.

Other federal emergency authorities could be utilized in more severe scenarios for individual and public assistance. In such cases, localities with major revenue shortfalls from federally declared disasters—such as those highly dependent on a dislocated industry, such as tourism—could utilize Community Disaster Loans, which provide up to \$5 million in liquidity and are potentially forgivable. The President may also call upon the Defense Production Act (DPA) to mobilize key segments of the economy in response to the outbreak. In major national emergencies, DPA authorities may be used to rebalance disrupted critical supply chains, and to allocate and procure emergency supplies.

Chapter 481

COVID-2019: GLOBAL IMPLICATIONS AND RESPONSES*

***Tiaji Salaam-Blyther, Susan V. Lawrence,
Sara M. Tharakan and Frank Gottron***

OVERVIEW

As of February 27, 2020, the novel coronavirus first identified in patients in Wuhan, China, in early January 2020 had spread to over 45 countries, including the United States. Daily new cases reported outside China now exceed those reported in China. The World Health Organization (WHO) has declared the outbreak a Public Health Emergency of International Concern but has resisted labeling it a “pandemic.” WHO Director-General Tedros Adhanom Ghebreyesus stated on February 26 that using the word “pandemic” could “signal that we can no longer contain the virus, which is not true.” WHO has named the new virus “severe acute respiratory syndrome coronavirus 2” (SARS-CoV-2) and the disease that it causes “coronavirus disease 2019” (COVID-19).

THE VIRUS

Coronaviruses are a large family of zoonotic viruses (viruses transmissible between animals and humans) that can cause illness ranging from the common cold to more severe diseases such as Middle-East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS). The most common symptoms among confirmed COVID-19 patients include fever, dry cough, and shortness of breath. As of February 26, 2020, WHO reported more than 80,000 confirmed COVID-19 cases globally, including more than 2,700 deaths. All but 5% of the cases and 60 of the deaths were in mainland China, and over 80% of cases in

* This is an edited, reformatted and augmented version of Congressional Research Service Publication No. IF11421, Updated February 27, 2020.

mainland China were reported in Hubei Province, whose capital is Wuhan. Of confirmed COVID-19 patients in China, about 80% experienced only mild symptoms, 13% experienced severe symptoms, and 6% became critically ill. Outside mainland China, the jurisdictions with the highest reported caseloads were South Korea, Italy, Japan, and Iran. More than 700 cases have been detected from the Diamond Princess cruise ship, docked alongside Yokohama, Japan. In addition to China, the United States and Germany have confirmed community transmission of COVID-19, indicating the global response may need to move from a containment strategy to one of mitigation.

Within days of Chinese scientists' sequencing the virus, scientists around the globe developed lab tests to diagnose COVID-19. Current diagnostic supplies are insufficient to meet global demand, however. While trying to increase supply of these tests, developers are also trying to create faster, cheaper, and more easily administered tests. No specific treatments or vaccines for COVID-19 exist. The U.S. National Institutes of Health (NIH) indicated in late January that a candidate vaccine for COVID-19 could be ready for early-stage human testing within three months, compared to the 20 months it took to begin early-state development of an investigational SARS vaccine.



Source: World Health Organization and National Health Commission of the People's Republic of China.

Figure 1. Locations with confirmed COVID-19 cases globally, as of February 27, 2020.

DEVELOPMENTS IN CHINA

China first reported cases of pneumonia of an unknown cause to the WHO on December 31, 2019. Chinese scientists isolated the virus on January 7, 2020, and shared its genetic sequence with the world on January 12. China's government did not raise the alarm to its own people until January 20, however. Before then, the government appears to have worked to suppress information about the outbreak. Observers have suggested that by withholding

information, the government may have squandered an early window of opportunity to stem the virus's spread.

After January 20, Chinese authorities began taking aggressive actions to prevent the virus from spreading further. By February 20, they had imposed *cordon sanitaires*, or restrictions on movement in and out of defined areas, on as many as 760 million people. Human rights groups and others have questioned such measures. Bruce Aylward, the Canadian co-team leader of a WHO- China Joint Mission on COVID-19, praised China, however, for a "bold approach" that "changed the course" of the epidemic and prevented "probably hundreds of thousands of cases of COVID-19 in China."

The WHO-China Joint Mission, which included representatives from the U.S. Centers for Disease Control and Prevention (CDC) and NIH, carried out an on-the- ground investigation of the outbreak in China from February 16 to 24. The mission concluded that the epidemic in China peaked and plateaued between January 23 and February 2, and has been waning since. Aylward acknowledged that the outbreak is not yet controlled in Wuhan, and he warned of the risk that the epidemic could "come back up again as people start to move again, the shops start to open, restaurants open, schools open." He said that risk was "being managed very carefully."

WHO RESPONSE

PHEIC. Following the emergence of a disease that might be deemed a Public Health Emergency of International Concern (PHEIC), WHO convenes an advisory group, the IHR Emergency Committee, to review data and make recommendations to the WHO Director-General. At its second meeting, on January 30, WHO's 15-member IHR Emergency Committee for Pneumonia due to the Novel Coronavirus COVID-19 concluded the outbreak had become a PHEIC. That day, WHO Director-General Tedros issued a PHEIC declaration, prompting countries to take specific actions, including heightening surveillance and reporting of the disease. In the case of the United States, Department of Health and Human Services (HHS) Secretary Alex Azar declared "a public health emergency for the entire United States." A PHEIC declaration can prompt countries to provide additional resources for global and domestic response and enable WHO to access certain emergency funding, such as from the United Nations Central Emergency Response Fund (CERF) and the World Bank Pandemic Emergency Financing Facility (PEF).

Pandemic Designation Debate. Some observers have questioned why WHO has not labeled the global COVID- 19 outbreak a pandemic. On February 26, WHO Director-General Tedros defended WHO's caution, arguing, "For the moment, we are not witnessing sustained and intensive community transmission of this virus, and we are not witnessing large-scale severe disease or death." He nonetheless urged countries to "prepare for a potential pandemic," stating, "Every country needs to be ready to detect cases early, to isolate patients, trace contacts, provide quality clinical care, prevent hospital outbreaks, and prevent community transmission."

WHO Funds. On February 5, WHO announced a \$675 million COVID-19 preparedness plan for February through April. It aims to provide international coordination and operational support, bolster country readiness and response capacity (particularly in low-resource

countries), and accelerate relevant research and innovation. As of February 26, six donors had pledged to provide \$30.0 million in support of the plan and WHO had received \$1.4 million.

U.S. RESPONSE

Leadership. On January 29, President Donald J. Trump announced the formation of the President's Coronavirus Task Force, led by HHS and coordinated by the National Security Council. On February 27, the President appointed Vice President Mike Pence as the Administration's COVID-19 task force leader, and the Vice President subsequently appointed President's Emergency Plan for AIDS Relief (PEPFAR) Ambassador Deborah Birx as the "White House Coronavirus Response Coordinator."

Funds for Global COVID-19 Control. On February 7, the Department of State and the U.S. Agency for International Development committed to use up to \$100 million of existing funds to assist China and other affected countries with COVID-19 responses. HHS has made available up to \$105 million from the Infectious Disease Rapid Response Reserve Fund for domestic and international COVID-19 responses. In late February, the Administration stated those funds would be exhausted by the end of the month. On February 24, the Administration asked Congress for an emergency supplemental appropriation of \$1.25 billion for COVID-19 response efforts. The Administration also asked Congress to allow repurposing of another \$1.25 billion in existing funds from across the government, including HHS funds for current Ebola response activities.

Travel Issues and Evacuations. On January 31, 2020, the President suspended the entry into the United States of any foreign national who has been in China within the prior 14 days. On February 2, the Department of Homeland Security issued instructions subjecting returning U.S. citizens with recent travel to Hubei Province to mandatory quarantine of up to 14 days. The State Department has issued a Level 4 ("Do Not Travel") advisory for China and evacuated U.S. citizens and others from Wuhan. The Department ordered the mandatory departure of nonemergency U.S. personnel and their families from the U.S. consulate in Wuhan, and the voluntary departure of nonemergency U.S. personnel and their families from other diplomatic posts in China. The U.S. government also repatriated U.S. citizens from the *Diamond Princess* cruise ship in Japan.

Chapter 482

CORONAVIRUS DISEASE 2019 (COVID-19) HOSPITAL PREPAREDNESS ASSESSMENT TOOL*

Department of Health and Human Services

All U.S. hospitals should be prepared for the possible arrival of patients with Coronavirus Disease 2019 (COVID-19). All hospitals should ensure their staff are trained, equipped and capable of practices needed to:

- Prevent the spread of respiratory diseases including COVID-19 within the facility
- Promptly identify and isolate patients with possible COVID-19 and inform the correct facility staff and public health authorities
- Care for a limited number of patients with confirmed or suspected COVID-19 as part of routine operations
- Potentially care for a larger number of patients in the context of an escalating outbreak
- Monitor and manage any healthcare personnel that might be exposed to COVID-19
- Communicate effectively within the facility and plan for appropriate external communication related to COVID-19

The following checklist does not describe mandatory requirements or standards; rather, it highlights important areas for hospitals to review in preparation for potential arrivals of COVID-19 patients.

* This is an edited, reformatted and augmented version of Department of Health and Human Services Publication.

Elements to be assessed

1. Infection prevention and control policies and training for healthcare personnel (HCP):

- Facility leadership including the Chief Medical Officer, quality officers, hospital epidemiologist, and heads of services (e.g., infection control, emergency department, environmental services, pediatrics, critical care) has reviewed the Centers for Disease Control and Prevention's COVID-19 guidance. <https://www.cdc.gov/coronavirus/2019-nCoV/guidance-hcp.html>. ☐
- Facility provides education and job-specific training to HCP regarding COVID-19 including: ☐
 - Signs and symptoms of infection
 - How to safely collect a specimen
 - Correct infection control practices and personal protective equipment (PPE) use
 - Triage procedures including patient placement
 - HCP sick leave policies and recommended actions for unprotected exposures (e.g., not using recommended PPE, an unrecognized infectious patient contact)
 - How and to whom COVID-19 cases should be reported

2. Process for rapidly identifying and isolating patients with confirmed or suspected COVID-19:

- Signs are posted at entrances with instructions to individuals with symptoms of respiratory infection to immediately put on a mask and keep it on during their assessment, cover their mouth/nose when coughing or sneezing, use and dispose of tissues, and perform hand hygiene after contact with respiratory secretions. ☐
- Facemasks are provided to coughing patients and other symptomatic individuals upon entry to the facility. ☐
- Signs are posted in triage areas (e.g., ED entrances) advising patients with fever or symptoms of respiratory infection and recent travel outside the US, specifically to China, to immediately notify triage personnel so appropriate precautions can be put in place. ☐
- Alcohol based hand sanitizer for hand hygiene is available at each entrance and in all common areas. ☐
- Facility provides tissues and no-touch receptacles for disposal of tissues in waiting rooms and in common areas. ☐
- Facility has a separate well-ventilated space that allows waiting patients to be separated by 6 or more feet, with easy access to respiratory hygiene and cough etiquette supplies. ☐
- Facility has a process to ensure patients with confirmed or suspected COVID-19 are rapidly moved to an Airborne Infection Isolation Room (AIIR). ☐
- Alternatively, for patients that cannot be immediately placed in a room for further evaluation, a system is provided that allows them to wait in a personal vehicle or outside the facility (if medically appropriate) and be notified by phone or other remote methods when it is their turn to be evaluated. ☐
- Triage personnel are trained on appropriate processes (e.g., questions to ask and actions to take) to rapidly identify and isolate suspect cases. ☐
- Facility has a process that occurs after a suspect case is identified to include immediate notification of facility leadership/infection control. ☐
- Facility has a process to notify local or state health department of a suspect case soon after arrival. ☐
- Facility has a process for receiving suspect cases arriving by ambulance. ☐

3. Patient placement:

- Confirm the number and location of Airborne Infection Isolation Rooms (AIIRs) available in the facility (ideally AIIRs will be available in the emergency department and on inpatient units). ☐
- Document that each AIIR has been tested and is effective (e.g., sufficient air exchanges, negative pressure, exhaust handling) within the last month. The AIIR should be checked for negative pressure before occupancy. ☐

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cont.

- Verify each AIR meets the following criteria:
 - Minimum of 6 air changes per hour (12 air changes per hour are recommended for new construction or renovation).
 - Air from these rooms should be exhausted directly to the outside or be filtered through a high-efficiency particulate air (HEPA) filter before recirculation.
 - Room doors should be kept closed except when entering or leaving the room, and entry and exit should be minimized.
 - When occupied by a patient, the AIR is checked daily for negative pressure.
- A protocol is established, which specifies that aerosol-generating procedures that are likely to induce coughing (e.g., sputum induction, open suctioning of airways) are to be performed in an AIR using appropriate PPE.
- Facility has plans to minimize the number of HCP who enter the room. Only essential personnel enter the AIR. Facilities should consider caring for these patients with dedicated HCP to minimize risk of transmission and exposure to other patients and HCP.
- Facility has a process (e.g., a log, electronic tracking) for documenting HCP entering and exiting the patient room.
- Facility has policies for dedicating noncritical patient care equipment to the patient.

☐☐☐☐☐**4. Transmission-Based Precautions (use Standard, Contact, Airborne Precautions plus eye protection for patients with confirmed or suspected COVID-19 cases):**

- Personal protective equipment (PPE) and other infection prevention and control supplies (e.g., hand hygiene supplies) that would be used for both healthcare personnel (HCP) protection and source control for infected patients (e.g., facemask on the patient) are located in sufficient supply including at patient arrival, triage, and assessment locations.
- Facility has a respiratory protection program. Appropriate HCP have been medically cleared, fit tested, and trained for respirator use.
- HCP receive appropriate training, including "just in time" training on selection and proper use of (including putting on and removing) PPE, with a required demonstration of competency.
- Facility has a process for auditing adherence to recommended PPE use by HCP.

☐☐☐☐**5. Movement of patients with confirmed or suspected COVID-19 within the facility:**

- Patient movement outside of the AIR will be limited to medically-essential purposes.
- A protocol is in place to ensure that, if the patient is being transported outside of the room, HCP in the receiving area are notified in advance.
- Patients transported outside of their AIR will be asked to wear a facemask and be covered with a clean sheet during transport.

☐☐☐**6. Hand hygiene (HH):**

- HH supplies, including alcohol-based hand sanitizer are readily accessible in patient care areas, including areas where HCP remove PPE.
- Facility has a process for auditing adherence to recommended hand hygiene practices by HCP.

☐☐

7. Environmental cleaning:

- Facility has a plan to ensure proper cleaning and disinfection of environmental surfaces and equipment in the patient room. ☐
- If environmental services personnel are given this responsibility, they should be appropriately trained and fit-tested. ☐
- All HCP with cleaning responsibilities understand the contact time for selected products. ☐
- Facility has a process to ensure shared or non-dedicated equipment is cleaned and disinfected after use according to manufacturer's recommendations. ☐
- Facility uses an EPA-registered hospital-grade disinfectant with EPA-approved emerging viral pathogens claims on hard non-porous surfaces. ☐
 - If there are no available EPA-registered products that have an approved emerging viral pathogen claim for COVID-19, products with label claims against human coronaviruses should be used according to label instructions.

8. Monitoring and managing HCP:

- The facility follows the local/state public health authority's policies and procedures for monitoring and managing HCP with potential for exposure to COVID-19, including ensuring that HCP have ready access, including via telephone, to medical consultation. ☐
- Facility has a process to track exposures and conduct active- and/or self-monitoring of HCP if required by public health. ☐
- Facility has a process to conduct symptom and temperature checks prior to the start of any shift of asymptomatic, exposed HCP that are not work restricted. ☐

9. Visitor access and movement within the facility:

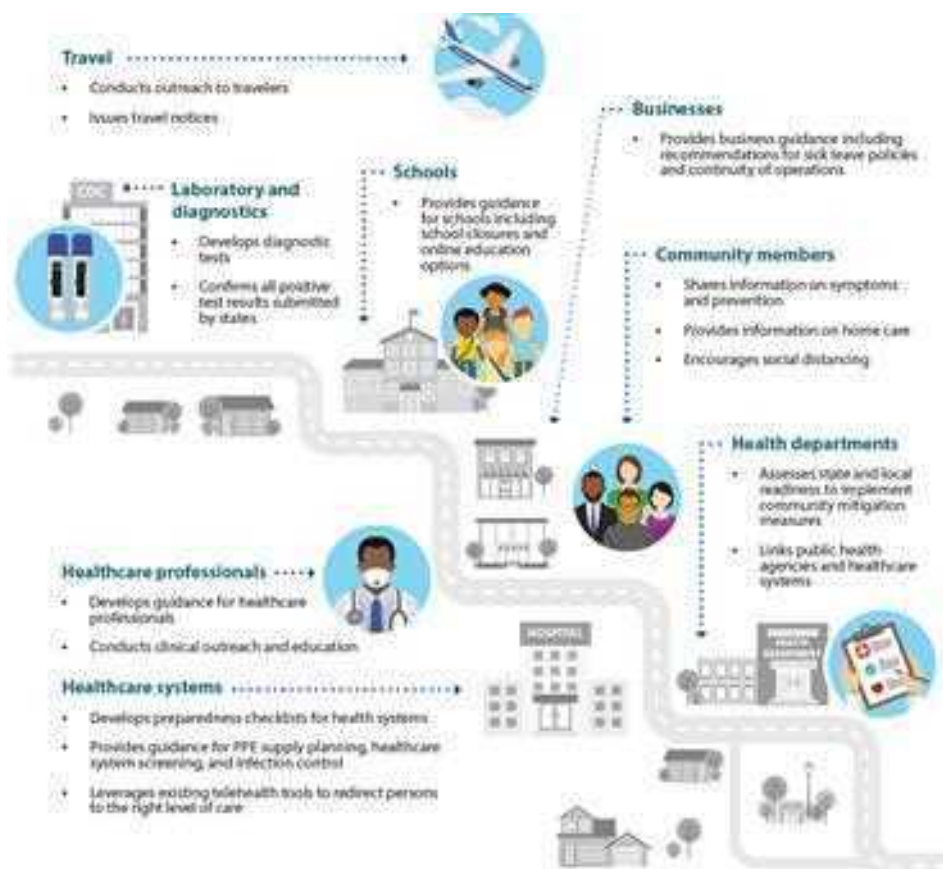
- Plans for visitor access and movement within the facility have been reviewed and updated within the last 12 months. ☐
- Visitors are screened for symptoms of acute respiratory illness before entering the hospital. ☐
- Facility has a plan to restrict visitation to rooms of patients with confirmed or suspected COVID-19. ☐
- If visitors are allowed to enter the room of a confirmed or suspected COVID-19 patient, the facility will: ☐
 - Enact a policy defining what PPE should be used by visitors.
 - Provide instruction to visitors before they enter a patient room, on hand hygiene, limiting surfaces touched, and use of PPE according to current facility policy.
 - Maintain a record (e.g., a log with contact information) of all visitors who enter and exit the room.
 - Ensure that visitors limit their movement within facility (e.g. avoid the cafeteria).

10. Facility regularly monitors the situation on CDC's coronavirus disease (COVID-19) web page, www.cdc.gov/COVID19☐

Chapter 483

COVID-2019: CDC PROTECTS AND PREPARES COMMUNITIES*

Department of Health and Human Services



* This is an edited, reformatted and augmented version of Department of Health and Human Services Publication No. CS 315454-A, dated February 25, 2020.

CDC PROTECTS AND PREPARES COMMUNITIES

CDC is aggressively responding to the global outbreak of COVID-19 and preparing for the potential of community spread in the U.S.

For more information: www.cdc.gov/COVID19.

Chapter 484

COVID-19: WHAT TO DO IF YOU ARE SICK WITH CORONAVIRUS DISEASE 2019 (COVID-19)*

Department of Health and Human Services

If you are sick with COVID-19 or suspect you are infected with the virus that causes COVID-19, follow the steps below to help prevent the disease from spreading to people in your home and community.

STAY HOME EXCEPT TO GET MEDICAL CARE

You should restrict activities outside your home, except for getting medical care. Do not go to work, school, or public areas. Avoid using public transportation, ride-sharing, or taxis.

SEPARATE YOURSELF FROM OTHER PEOPLE AND ANIMALS IN YOUR HOME

People: As much as possible, you should stay in a specific room and away from other people in your home. Also, you should use a separate bathroom, if available.

Animals: Do not handle pets or other animals while sick. See COVID-19 and Animals for more information.

CALL AHEAD BEFORE VISITING YOUR DOCTOR

If you have a medical appointment, call the healthcare provider and tell them that you have or may have COVID-19. This will help the healthcare provider's office take steps to keep other people from getting infected or exposed.

* This is an edited, reformatted and augmented version of Department of Health and Human Services, Publication No. CS 314937-D, dated February 24, 2020.

WEAR A FACEMASK

You should wear a facemask when you are around other people (e.g., sharing a room or vehicle) or pets and before you enter a healthcare provider's office. If you are not able to wear a facemask (for example, because it causes trouble breathing), then people who live with you should not stay in the same room with you, or they should wear a facemask if they enter your room.

COVER YOUR COUGHS AND SNEEZES

Cover your mouth and nose with a tissue when you cough or sneeze. Throw used tissues in a lined trash can; immediately wash your hands with soap and water for at least 20 seconds or clean your hands with an alcohol-based hand sanitizer that contains at least 60 to 95% alcohol, covering all surfaces of your hands and rubbing them together until they feel dry. Soap and water should be used preferentially if hands are visibly dirty.

AVOID SHARING PERSONAL HOUSEHOLD ITEMS

You should not share dishes, drinking glasses, cups, eating utensils, towels, or bedding with other people or pets in your home. After using these items, they should be washed thoroughly with soap and water.

CLEAN YOUR HANDS OFTEN

Wash your hands often with soap and water for at least 20 seconds. If soap and water are not available, clean your hands with an alcohol-based hand sanitizer that contains at least 60% alcohol, covering all surfaces of your hands and rubbing them together until they feel dry. Soap and water should be used preferentially if hands are visibly dirty. Avoid touching your eyes, nose, and mouth with unwashed hands.

CLEAN ALL "HIGH-TOUCH" SURFACES EVERY DAY

High touch surfaces include counters, tabletops, doorknobs, bathroom fixtures, toilets, phones, keyboards, tablets, and bedside tables. Also, clean any surfaces that may have blood, stool, or body fluids on them. Use a household cleaning spray or wipe, according to the label instructions. Labels contain instructions for safe and effective use of the cleaning product including precautions you should take when applying the product, such as wearing gloves and making sure you have good ventilation during use of the product.

MONITOR YOUR SYMPTOMS

Seek prompt medical attention if your illness is worsening (e.g., difficulty breathing). Before seeking care, call your healthcare provider and tell them that you have, or are being evaluated for, COVID-19. Put on a facemask before you enter the facility. These steps will help the healthcare provider's office to keep other people in the office or waiting room from getting infected or exposed.

Ask your healthcare provider to call the local or state health department. Persons who are placed under active monitoring or facilitated self-monitoring should follow instructions provided by their local health department or occupational health professionals, as appropriate.

If you have a medical emergency and need to call 911, notify the dispatch personnel that you have, or are being evaluated for COVID-19. If possible, put on a facemask before emergency medical services arrive.

DISCONTINUING HOME ISOLATION

Patients with confirmed COVID-19 should remain under home isolation precautions until the risk of secondary transmission to others is thought to be low. The decision to discontinue home isolation precautions should be made on a case-by-case basis, in consultation with healthcare providers and state and local health departments.

For more information: www.cdc.gov/COVID19.

Chapter 485

THE DEFENSE PRODUCTION ACT (DPA) AND COVID-19: KEY AUTHORITIES AND POLICY CONSIDERATIONS*

Michael H. Cecire and Heidi M. Peters

As the coronavirus (COVID-19) outbreak develops, the United States faces drug and medical supply scarcities due to disrupted supply chains and increased demand. In response, the President may exercise emergency authorities under the Defense Production Act of 1950 (DPA; 50 U.S.C. §§4501 et seq.) to address supply shortages and economic development impacts, and may have begun the process of doing so. This Insight considers DPA authorities that may be used to address domestic essential goods and materials shortages caused by the outbreak, and explores potential policy considerations for Congress. For more information on the health and epidemiological aspects of COVID-19, see CRS products R46219 and IF11421.

DPA PROVISIONS AND RECENT USE

The DPA confers broad presidential authorities to mobilize domestic industry in service of the *national defense*, defined in statute as various military activities and “homeland security, stockpiling, space, and any directly related activity” (50 U.S.C. §4552.) including emergency preparedness activities under the Stafford Act, which has been used for public health emergencies. Many of these authorities are delegated to executive agencies under Executive Order 13603.

Current DPA authorities include, but are not limited to:

* This is an edited, reformatted and augmented version of Congressional Research Service Publication No. IN11231, dated March 6, 2020.

- *Title I: Priorities and Allocations*, which allows the President to require persons (including businesses and corporations) to (1) prioritize and accept government contracts for materials and services, and (2) allocate or control the general distribution of materials, services, and facilities as necessary to promote the national defense. Title I prioritization authorities are regularly utilized by the Department of Defense (DOD) to acquire critical military capabilities and less frequently by the Department of Homeland Security (DHS) for disaster response and preparedness needs. The allocations authority has not been invoked since the Cold War, such as to promote energy development in 1974.
- *Title III: Expansion of Productive Capacity and Supply*, which allows the President to provide economic incentives to secure domestic industrial capabilities essential to meet national defense and homeland security requirements. DPA Title III is specifically intended to “create, maintain, protect, expand, or restore domestic industrial base capabilities” (50 U.S.C. §4533). Authorized incentives include loans, loan guarantees, direct purchases and purchase commitments, and the authority to procure and install equipment in private industrial facilities. DOD regularly utilizes Title III authorities and operates a standing DPA Title III program funded by annual congressional appropriations.
- *Title VII: General Provisions*, which includes key definitions and other distinct authorities. These provisions grant the President the authority to establish voluntary agreements with private industry; the authority to block proposed or pending foreign corporate mergers, acquisitions, or takeovers that threaten national security; and the authority to employ persons of outstanding experience and ability and to establish a volunteer pool of industry executives who could be called to government service in the interest of the national defense.

For a more in-depth discussion of DPA authorities, see CRS Report R43767.

DPA AUTHORITIES AND COVID-19

As the DPA’s definition of national defense encompasses homeland security issues, the DPA could potentially be used to respond to public health emergencies, though this has not occurred before. At the President’s discretion, DPA authorities could be employed to address concerns over medical supplies shortages due to the COVID-19 outbreak.

Case Study: Using DPA to Expand Medical Protective Gear Production

As an example of how DPA authorities could be exercised, consider the availability of personal protective equipment (PPE), such as respirator masks, amid the outbreak. Reported PPE shortages may be due to significantly increased consumer demand related to the outbreak itself, and supply chain disruptions resulting from containment measures in China and elsewhere.

Under Title I, the President could prioritize domestic production of PPE to ensure sufficient national stockpiles, and allocate them according to the needs of the emergency. Under Title III, the federal government could use authorized incentives to expand domestic capacity for PPE manufacturing to meet the needs of the emergency. Under Title VII, the President could establish voluntary agreements with private industry—which might normally be subject to anti-trust statutes—to coordinate industry PPE production.

Policy Implications for Congress

The decision whether to employ DPA authorities generally lies with the President. However, in addition to Congress's inherent oversight authority, the DPA statute outlines several specific congressional equities:

1. Title I authorities can only be used for wage and price controls if accompanied by a joint resolution of Congress (50 U.S.C. §4514). This could be applicable in this case in the production and sale of PPE, drug treatments or vaccines, or other necessary goods, and would require coordination between the Administration and Congress.
2. Budget authority for Title III direct loans and guarantees must be specifically included in an appropriations act passed by Congress (50 U.S.C. §4531).
- 3.
4. Title III projects that cumulatively cost more than \$50 million must be authorized by an act of Congress, and the President is required to notify the committees of jurisdiction (the House Committee on Financial Services and the Senate Committee on Banking, Housing, and Urban Affairs), and provide 30 days for comment (50 U.S.C. §4533). A large-scale effort to expand outbreak-related production capacity may require sums far greater than \$50 million.

However, the DPA confers broad waivers to its Title III requirements:

During a period of national emergency declared by Congress or the President; or upon determination by the President, on a nondelegable basis, that action is necessary to avert an industrial resource or critical technology item shortfall that would severely impair national defense capability. (50 U.S.C. §4531(d)(1)(B))

Another area of possible congressional interest is DPA funding, which is appropriated annually. The FY2020 appropriation to the DPA fund was \$64.4 million; the President's FY2021 budget requested \$182 million for the DPA fund (p. 276). DPA appropriations could also be made as part of a supplemental appropriations package if the DPA fund is exhausted and/or to provide resources for other DPA authorities.

Chapter 486

FROM SARS TO 2019-CORONAVIRUS (nCoV): U.S.-CHINA COLLABORATIONS ON PANDEMIC RESPONSE*

Jennifer Bouey¹ and The RAND Corporation²

Chairman Bera, Ranking Member Yoho, and members of the subcommittee, thank you for inviting me to testify about U.S.-China collaboration on pandemic response, especially in light of the recent novel coronavirus outbreak. First, I will describe the 2002–2003 outbreak of severe acute respiratory syndrome (SARS) and the global response. Next, I will discuss U.S.-China collaboration from 2003–2012, followed by developments in the years prior to the current coronavirus outbreak. Lastly, I will analyze the characteristics of 2019-nCoV and China's early responses, and offer policy recommendations.

2002–2003: SARS

Almost 17 years ago, a novel coronavirus was silently causing deadly pneumonia outbreaks—which later became known as SARS—in China. The index case of the SARS outbreak occurred in the city of Foshan in Guangdong Province, China, on November 16, 2002. Neither this case nor a few other cases in December attracted any notice from the public. A public health expert team from the province, which included a few representatives from the national Ministry of Health, went to one of the cities in Guangdong province in January 2003 to investigate. The team concluded that the atypical pneumonia diagnoses were

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¹ The opinions and conclusions expressed in this testimony are the author's alone and should not be interpreted as representing those of the RAND Corporation or any of the sponsors of its research.

² The RAND Corporation is a research organization that develops solutions to public policy challenges to help make communities throughout the world safer and more secure, healthier and more prosperous. RAND is nonprofit, nonpartisan, and committed to the public interest.

probably caused by a virus. The team then suggested in a “top-secret” report that the provincial health bureau should establish a case-reporting system. This reasonable—although rather feeble—suggestion was expressed in a news bulletin for local health care professionals but fell on deaf ears during the Chinese New Year. The world did not find out for another two months that this was severe acute respiratory syndrome (SARS), a viral pneumonia that would infect more than 8,000 people globally and lead to 774 deaths.

At that time, China lacked a national center for disease control, which would have been responsible for maintaining a robust surveillance system for detecting emerging diseases. It also lacked a national case-reporting system. In addition, according to the *Implementing Regulations of the Law of the People’s Republic of China on Guarding State Secrets* regarding the handling of public health-related information, any occurrence of infectious disease should be classified as a state secret before it is “announced by the Ministry of Health.”³ No physician or journalist can alert the public without breaking the law. With no information from government or media, the Chinese public was unaware of the outbreak until cell phone messages about a “deadly flu” started to circulate in early February 2003 in Guangzhou. A widespread panic caused residents to clear out antibiotics and flu medicines in pharmacies. Prompted by the public panic, the Guangdong health officials finally held a press conference on February 11 to announce the 305 atypical pneumonia cases in the province. China submitted the case report to the World Health Organization (WHO) as *atypical pneumonia*, probably caused by chlamydia or a virus around the same time. Afterward, information about the disease was reported on the news media, but the flow of information stopped on February 23. The news blackout from February 23 continued during the run-up to the National People’s Congress in March, and the government shared little with the public until early April.⁴

Meanwhile, a “super-spreading” chain of transmission emerged at the end of the January and lasted until March, causing international attention on the outbreak: A patient with pneumonia in Guangdong was transferred between three different hospitals, ultimately infecting 200 people, including a doctor from Zhongshan Hospital. The doctor traveled to Hong Kong and infected 12 people in a hotel, and these 12 people then carried the virus to Singapore, Vietnam, Canada, Ireland, and the United States.⁵

By mid-March 2003, SARS clusters started to appear in Vietnam, Hong Kong, Singapore, and Canada. The WHO subsequently picked up the alerts from the Global Outbreak Alert and Response Network (GOARN) and issued a global alert about a new infectious disease of unknown origin. Between March 16 and March 21, the WHO started to suspect that the more than 300 cases from February—which China had labeled “atypical pneumonia” in its report—were actually SARS cases. At China’s request, the WHO sent a team to China on March 23. On March 27, the WHO team concluded that the “atypical

³ Yanzhong Huang, “The SARS Epidemic and Its Aftermath in China: A Political Perspective,” in Stacey Knobler, Adel Mahmoud, Stanley Lemon, Alison Mack, Laura Sivitz, and Katherine Oberholtzer, eds., *Learning from SARS: Preparing for the Next Disease Outbreak: Workshop Summary*, Washington, D.C.: The National Academies Press, 2004.

⁴ Huang, 2004 *ibid*.

⁵ Institute of Medicine, “Summary and Assessment,” in Stacey Knobler, Adel Mahmoud, Stanley Lemon, Alison Mack, Laura Sivitz, and Katherine Oberholtzer, eds., *Learning from SARS: Preparing for the Next Disease Outbreak: Workshop Summary*, Washington, D.C.: The National Academies Press, 2004.

pneumonia” cases were same as SARS, and China announced 792 cases and 31 deaths.⁶ Under intense international pressure to mobilize against the pandemic threat, the Chinese government publicly acknowledged the SARS outbreak at the end of March and undertook a series of responsive actions in the following weeks, including

- establishment of new rules requiring all local health officials to report the number of cases daily, with severe penalties for noncompliance
- streamlining of interdepartmental communication and cooperation on the crisis
- creation of national and provincial interdepartmental SARS task forces
- dedication of over \$1 billion to treating the patients and controlling the epidemic.⁷

In late April 2003, China’s health minister and Beijing’s mayor were fired one day after the Chinese Premier announced severe consequences for local officials who failed to report SARS cases in a timely and accurate manner. (That same day, the number of cases in Beijing jumped from 37 to 407.) By the end of May, more than 1,000 officials were fired or penalized for their “slack” responses to SARS.⁸ The remaining officials, driven by political zeal, began to seal off villages, apartment complexes, and university campuses; quarantined tens of thousands of people; and set up checkpoints to take temperatures. A new hospital was built within 20 days in Beijing to accommodate and quarantine SARS patients. The epidemic started to subside in late May. By June 27, the WHO announced that China was “SARS-free.” On August 16, the last two SARS patients were discharged from a Beijing hospital.

SARS revealed the state of China’s unprepared public health system. It led the country to significantly rethink its approach to both domestic and global health. The government soon invested 6.8 billion renminbi (RMB) (850 million U.S. dollars [USD]) for the construction of a three-tiered network of disease control and prevention. The outbreak also spurred China to strengthen its relationships with the United States and the wider international community around issues of public health concerns. The change in China was welcomed and enthusiastically supported by governments and scientists around the world.

2003–2013: U.S.-CHINA COLLABORATIONS AND CHINA’S PUBLIC HEALTH RESTRUCTURING AND CAPACITY-BUILDING

Increased U.S.-China collaboration on global health was an important result of the SARS response. In October 2003, three months after the conclusion of the SARS pandemic, U.S. Secretary of Health and Human Services Tommy Thompson visited China and signed a multiyear partnership with the Chinese Ministry of Health to develop a more robust public

⁶ World Health Organization, “Severe Acute Respiratory Syndrome (SARS) Multi-Country Outbreak – Update 10: Disease Outbreak Reported,” news alert, March 26, 2003. As of February 3, 2020: https://www.who.int/csr/don/2003_03_26/en/.

⁷ Yanzhong Huang, “The SARS Epidemic and Its Aftermath in China: A Political Perspective,” in Stacey Knobler, Adel Mahmoud, Stanley Lemon, Alison Mack, Laura Sivitz, and Katherine Oberholtzer, eds., *Learning from SARS: Preparing for the Next Disease Outbreak: Workshop Summary*, Washington, D.C.: The National Academies Press, 2004.

⁸ Huang, 2004.

health infrastructure in China. Thompson also established an HHS health attaché at the U.S. embassy in Beijing. The following month, U.S. Secretary of State Colin Powell noted that

It is upon such concrete forms of cooperation on issues of regional and global importance that a 21st century U.S.-China relationship will be built, issue by issue, experience by experience, challenge by challenge, initiative by initiative, program by program.⁹

H5N1: 2003–2009

Not long after the SARS pandemic, China and the international community confronted another complex challenge with the H5N1 influenza virus—commonly known as “avian flu” or “bird flu” because it infects and spreads largely through birds. Cases of bird-to-human transmission were discovered in Fujian Province in 2003. In 2004, the Chinese National Influenza Center and the U.S. Centers for Disease Control and Prevention (CDC) initiated cooperative agreements to build Chinese capacity in influenza surveillance. The two agencies collaborated on 1) developing technical expertise in virology and epidemiology in China; 2) developing a comprehensive influenza surveillance system by enhancing influenza-like illness reporting; 3) strengthening analysis, utilization, and dissemination of surveillance data; and 4) improving early response to influenza viruses with pandemic potential. In 2005, both governments inaugurated the Collaborative Program on Emerging and Re-emerging Infectious Diseases, which turned into the CDC’s China Center. That same year, both countries established the U.S.-China Health Care Forum to address bilateral commercial, trade, and policy issues relating to health. Additionally, U.S. President George W. Bush announced the International Partnership on Avian and Pandemic Influenza—an ongoing framework for U.S.-China cooperation around the issue—in an address to the United Nations (UN).¹⁰ In 2006, the U.S. Department of Health and Human Services (HHS) and China’s Ministry of Health (MOH) further expanded their collaboration on biomedical research with a memorandum of understanding on research, technology, training, and personnel exchange.

H1N1: 2009

The capacity-building and infrastructure put into place to monitor the continuing threat from avian flu served China and the United States well when another novel influenza strain—H1N1, commonly known as “swine flu”—emerged in 2009. The epicenter was in the United States and Mexico, but the flu soon spread across the globe. American and Chinese health authorities shared information and technology to facilitate national monitoring of H1N1’s spread and to develop a vaccine; China subsequently became the first country to mass-produce an H1N1 vaccine. During the summer lull in the 2009 pandemic, the two countries strengthened their bilateral health communications through the U.S.-China Strategic Economic Dialogue. As then–U.S. President Barack Obama visited China in November 2009

⁹ Colin L. Powell, “Remarks at Conference on China-U.S. Relations,” College Station, Tex., November 5, 2003.

¹⁰ George W. Bush, statement delivered to the 2005 World Summit of the United Nations, High Level Plenary Meeting, New York, September 14, 2005. As of February 3, 2020: <http://www.un.org/webcast/summit2005/statements/usa050914.pdf>.

in the midst of the H1N1 outbreak, the two countries addressed global public health in a joint statement, pledging to “deepen cooperation on global public health issues, including Influenza A (H1N1) prevention, surveillance, reporting and control, and on avian influenza, HIV/AIDS, tuberculosis, and malaria.”¹¹

China’s National Influenza Center Expansion: 2010–2014

From 2010 to 2014, China expanded the Chinese National Influenza Center (CNIC) to include 408 laboratories and 554 sentinel hospitals, and it trained 2,500 public health staff. CNIC became the fifth WHO Collaborating Centre for Reference and Research on Influenza. CNIC established viral drug resistance surveillance and platforms for gene sequencing, reverse genetics, serological detection, and development of vaccine strains. CNIC also built a bioinformatics platform to strengthen data analysis, publishing weekly online influenza surveillance reports in English and Chinese. The surveillance system now collects between 200,000 and 400,000 specimens and tests more than 20,000 influenza viruses annually, which provide valuable information for WHO influenza vaccine strain recommendations. CNIC now provides training for other countries to improve global capacity for influenza control.¹²

H7N9: 2013

CNIC was fully functional when another novel strain of avian influenza, H7N9, emerged in eastern China in 2013. This form of avian influenza has a high fatality rate, of 30 percent (similar to Middle East Respiratory System [MERS]), but human-to-human transmission proved extremely rare, allowing the outbreak to remain in check with effective public health measures.

This time, China quickly reported the new viral strain to the WHO after only three cases were detected, and it also posted the full viral genome sequences of these cases in a public international database to facilitate research around the world. The outbreak plateaued in June at around 130 confirmed cases with more than 40 confirmed deaths, but, as expected, the virus reemerged the following winter, with more than 100 confirmed cases and 20 deaths in China in January 2014 alone.

China’s domestic response to the H7N9 outbreak prevented the virus from spreading beyond mainland China, save for a handful of cases in Hong Kong, Taiwan, and Malaysia. Chinese scientific cooperation with the international community also allowed other countries to prepare for further spread of the virus. Chinese scientists developed a vaccine in October 2013—the first influenza vaccine developed entirely in China—and shared their method with the world, facilitating vaccine development efforts by the U.S. CDC and private

¹¹ The White House, Office of the Press Secretary, “U.S.-China Joint Statement,” statement by U.S. President Barack Obama and Chinese President Hu Jintao, November 17, 2009. As of February 3, 2020: <https://obamawhitehouse.archives.gov/realitycheck/the-press-office/us-china-joint-statement>.

¹² Yuelong Shu, Ying Song, Dayan Wang, Carolyn M. Greene, Ann Moen, C. K. Lee, Yongkun Chen, Xiyan Xu, Jeffrey McFarland, Li Xin, Joseph Bresee, Suizan Zhou, Tao Chen, Ran Zhang, and Nancy Cox, “A Ten-Year China-US Laboratory Collaboration: Improving Response to Influenza Threats in China and the World, 2004–2014,” *BMC Public Health*, Vol. 19, No. 520, 2019.

pharmaceutical companies. The Chinese and American CDCs collaborated throughout the H7N9 outbreak by sharing epidemiological data and engaging in joint research on the virus. The Chinese efforts to manage the outbreak of H7N9 were widely praised by governments and scientists around the world.¹³ In the United States, the CDC partially activated its Emergency Operations Center to conduct epidemiological and vaccine research, provide assistance to the Chinese, and develop and distribute test kits capable of detecting the virus worldwide.¹⁴

HIV/AIDS: 2003–2014

Besides preparing for and responding to influenza epidemics, the United States also helped China in its campaign against HIV/AIDs. In 2002, the U.S. National Institutes of Health (NIH) gave the Chinese CDC a five-year, \$14.8 million grant to develop infrastructure to improve research and better monitor the spread of the disease in the country. Beijing also partnered with the U.S. CDC to establish the CDC's Global AIDS Program (GAP) in China in early 2003. GAP quickly developed and implemented a comprehensive HIV prevention and mitigation plan across 15 Chinese provinces to promote increased surveillance of high-risk populations. The CDC, in partnership with China's National Center for AIDS/STD Control and Prevention, has assisted with capacity-building, including the improvement of the quality and geographical reach of laboratory testing capabilities, the development of an epidemiological surveillance system, and the expansion of treatment options. The U.S. CDC has assisted Chinese health authorities with the establishment of three HIV/AIDS clinical training centers in rural areas, which have educated more than 300 graduates who are now providing antiretroviral therapy for 50,000 patients in 16 provinces.¹⁵

2013–2019: The Years Leading Up to the 2019 Coronavirus

Ebola

In 2014, the Chinese government launched an unprecedented response to the Ebola epidemic in West Africa in 2014.¹⁶ China's State Council dispatched one of its largest medical teams of about 1,200 clinicians, public health experts, and military medical officers after the WHO declared a Public Health Emergency of International Concern (PHEIC). The Chinese team opened a 100-bed treatment unit and established three field demonstration sites in Sierra

¹³ Carina Perkins, "OIE Meeting Congratulates China on Bird Flu Response," *Global Meat News*, June 4, 2013; Mara Hvistendahl, "A Decade After SARS, China's Flu Response Wins Cautious Praise," *Science*, Vol. 340, No. 6129, April 12, 2013, p. 130; Dobri Genchev, "H7N9 Response Discussed During World Health Assembly," news release, World Health Organization, November 9, 2018.

¹⁴ Centers for Disease Control and Prevention, "Asian Lineage Asian Influenza A(H7N9) Virus" December 7, 2018. As of February 3, 2020: <https://www.cdc.gov/flu/avianflu/h7n9-virus.htm>

¹⁵ Bulterys M. (2020) The US CDC Global AIDS Program in China. In: Wu Z., Wang Y., Detels R., Bulterys M., McGoogan J. (eds) *HIV/AIDS in China*. Springer, Singapore.

¹⁶ Yanzhong Huang, "China's Response to the 2014 Ebola Outbreak in West Africa," *Global Challenges*, Vol. 1, No. 2, February 27, 2017.

Leone while providing free treatment. Within six months, China also built a biosafety level 3 laboratory, transporting all construction materials into the laboratory in only 87 days.¹⁷

The United States took similar actions but on a larger scale, with aid exceeding \$1 billion. In some cases, U.S. and Chinese teams collaborated on the ground in Africa. On the international stage, the United States and China worked together at the UN Security Council, jointly declaring the Ebola outbreak a “threat to international peace and security,” and called on governments around the world to respond to the crisis.¹⁸ In June 2015, at the U.S.-China Symposium on Ebola, Research, and Global Health Security hosted by the NIH, both countries renewed their commitment to building systems to detect, prevent, and respond to global health threats.

Indeed, these collaborations between U.S. and Chinese public health agencies are the ones that the 2016 U.S.-China Strategic and Economic Dialogue highlighted as venues for deeper cooperation moving forward: “The United States and China are committed to strengthening cooperation to improve global health security,” both sides agreed. They pledged to further “strengthen their partnership to build capacity to prevent, detect and respond to infectious disease threats including but not limited to influenza, malaria, laboratory capacity, and antimicrobial resistance.”¹⁹

However, a big change in the U.S.-China relationship was on the way. Afraid of western influences, China enacted new legislative restrictions on foreign nongovernmental organization (NGO) activity on January 1, 2017; the law requires foreign-based researchers in China to have a government partner who will report their activities to central and local security agencies. Then, in 2018, due to a U.S.-China trade war, such diplomacy dialogues as the strategic and Economic Dialogue and bilateral diplomatic and security dialogues halted. Subsequently, the United States closed the National Science Foundation office in Beijing in 2018 (along with its offices in Tokyo and Brussels) and the GAP program. Currently NIH and the CDC both reduced their staff in the Beijing office.

In summary, in the 18 years since SARS, with help from the international community and through the commitment of the Chinese government, China has invested in a nationwide network of its own centers for disease control at the national, provincial, prefecture, and county levels; they are connected by a real-time, web-based reporting system for emerging public health events. The workforce for China’s CDCs is large, relative to the 15,000 employees at the U.S. CDC, consisting of 3,481 units and 877,000 public health professional positions at all levels of government. China also has a world-class National Influenza Center. However, the question on the minds of global health organizations around the world is, is China truly ready for the next pandemic?

A report in late 2018 from China’s CDC casts some doubts.²⁰ The challenges, as the authors highlighted, are multifaceted. First, the growing public health needs (and the voids after the departure of international funders) have stretched still-limited investments in China’s

¹⁷ Kun Tang, Zhihui Li, Wenkai Li, and Lincoln Chen, “China’s Silk Road and Global Health,” *The Lancet*, Vol. 390, No. 10112, December 2017, pp. 2595–2601.

¹⁸ “Ebola ‘Threat to World Security’-UN Security Council,” BBC News, September 19, 2014. As of February 3, 2020: <http://www.bbc.com/news/world-africa-29262968>.

¹⁹ U.S. Department of State, Office of the Spokesperson, “U.S.-China Strategic & Economic Dialogue Outcomes of the Strategic Track,” Washington, D.C.: June 7, 2016. As of February 3, 2020: <https://2009-2017.state.gov/r/pa/prs/ps/2016/06/258146.htm>.

²⁰ One hundred years of Influenza since the 1918 Pandemic -Is China prepared today? CCDC weekly; 2018:1 (4) 56-61.

public health and its preparedness and response. In the past decade, many Chinese agencies have prioritized innovation in technology, including biomedical research. They have also invested in restructuring the health system for the population of 1.4 billion. Public health, in comparison, was relatively underfunded due to these competing priorities. At the local level, local CDCs are supported by provincial governments. In places where the local government's resources are less robust or declining, local public health resources, including personnel, can also suffer from insufficient funding. Low salaries are a significant barrier to the recruitment and retention of high-quality professionals, and local Chinese CDC staffing has declined at all levels. Secondly, suboptimal multisector coordination, such as inadequate communication and inconsistent data sharing between health and veterinarian sectors, between clinicians and public health professionals, can delay early detection of emerging diseases. Insufficient health care surge capacity was also identified as a potential barrier for providing sufficient response to pandemics, as well as the lack of an official technical framework to communicate an epidemic's intensity, severity, and risks to public.

These underlying issues with the Chinese CDC—especially its dwindling funding and lack of effective communication with public and other sectors—may explain the different fate of the two main surveillance systems in China for detecting and monitoring emerging pathogens. One is China's national sentinel surveillance system for influenza-like illness (ILI), as mentioned earlier, anchored by more than 500 sentinel hospitals in 31 provinces.²¹ The other is the national pneumonia surveillance system, which was built and has been maintained by China's CDC since 2004. The latter is designed to monitor pneumonia of unknown etiology (PUE) and facilitate timely detection of novel respiratory pathogens, such as SARS or the 2019 coronavirus. The ILI system is able to use the hospital information system for case recording and outpatient monitoring since the network is hospital-based. The PUE surveillance system, on the other hand, belongs to the CDC system, and has not been used consistently. One study found that 29 percent of community-acquired pneumonia cases that met the PUE criteria were not reported to the PUE system in 2009.²² Only 1,016 PUE cases in all of China were reported during a nine-year period. A study showed that the number of cases surged when an outbreak occurred, either during the SARS outbreak or during A(H5N1) outbreaks. This surge may reflect enhanced administrative requirements from health authorities or enhanced clinician awareness of respiratory viruses.²³ This illustrated that the hospital system (a system paralleled to the CDC system) is in better fiscal condition to maintain a surveillance system compared with the CDC system, which is underused and not sensitive unless it is triggered by an established outbreak.

²¹ Dennis KM Ip, Qiaohong Liao, Peng Wu, Zhancheng Gao, Bin Cao, Luzhao Feng, Xiaoling Xu, Hui Jiang, Ming Li, Jing Bao, Jiandong Zheng, Qian Zhang, Zhaorui Chang, Yu Li, Jianxing Yu, Fengfeng Liu, Michael Y. Ni, Joseph T. Wu, Benjamin J. Cowling, Weizhong Yang, Gabriel M. Leung, and Honjie Yu, "Detection of Mild to Moderate Influenza A/H7N9 Infection by China's National Sentinel Surveillance System for Influenza-Like Illness: Case Series," *The BMJ*, Vol. 346, June 24, 2013.

²² Nijuan Xiang, Fiona Havers, Tao Chen, Ying Song, Wenxiao Tu, Leilei Li, Yang Cao, Bo Liu, Lei Zhou, Ling Meng, Zhiheng Hong, Rui Wang, Yan Niu, Jianyi Yao, Kaiju Liao, Lianmei Jin, Yanping Zhang, Qun Li, Marc- Alain Widdowson, and Zijian Feng, "Use of National Pneumonia Surveillance to Describe Influenza A(H7N9) Virus Epidemiology, China, 2004-2013," *Emerging Infectious Diseases*, Vol. 19, No. 11, 2013, pp. 1784-1790.

²³ Xiaorong Guo, Dong Yang, Ruchun Liu, Yaman Li, Qingqing Hu, Xinrui Ma, Yelan Li, Heng Zhang, Xixing Zhang, Benhua Zhao, and Tianmu Chen, "Detecting Influenza and Emerging Avian Influenza Virus by Influenza and Pneumonia Surveillance Systems in a Large City in China, 2005 to 2016," *BMC Infectious Diseases*, Vol. 19, No. 825, September 18, 2019.

But a more fundamental question is, what role will China's CDC take in an outbreak response? From what I have witnessed in SARS and 2019-nCoV, the CDC's role is mostly that of consultation rather than decisionmaking.

2019–2020: IS 2019-nCoV ANOTHER SARS?

As millions of Chinese prepared to celebrate the 2020 Chinese New Year, the country was seized by anxiety over the emergence of a rapidly evolving epidemic of pneumonia associated with a new coronavirus, 2019-nCoV. At the time of this writing, more than 17,000 confirmed cases and more than 20,000 probable cases have spread throughout China and 23 other countries, causing more than 360 deaths. After person-to-person transmission was reported in four of the 23 countries known to be experiencing cases of the virus, the WHO declared a Public Health Emergency for International Concerns (PHEIC) on January 29, signaling global consensus on deeming the 2019-nCoV outbreak as an extraordinary public health risk. Therefore, to address the question, "Is this another SARS?" I will provide my thoughts from two angles: (1) Will the 2019-nCoV epidemic be similar to that of SARS? (2) What can we learn from comparing China's current response with that of SARS 18 years ago?

Agent, Host, Environment, and Transmission

2019-nCoV is the latest member of the coronavirus family. This type of virus is commonly found in humans and other mammals, such as bats, civet cats, and camels. In humans, coronavirus has four strains that cause mild clinical symptoms, usually referred as the common cold. Two other strains are more lethal: SARS and MERS. Currently, I do not know whether the new virus will cause clinical symptoms similar to the strains that cause the common cold or to the two strains of coronavirus that caused large-scale epidemics and fatalities. We do know that it shares a high degree of genomic similarity to coronavirus in bats, and to SARS-CoV in humans.²⁴ It is as contagious as SARS, but so far, the reported statistics indicate a lower proportion of case fatalities (around 2–3 percent) compared with SARS (10–14 percent) and MERS (35 percent).²⁵ The severe symptoms and fatalities seem to be associated with individuals with medical complications. These estimates can change if the virus continues to mutate or the data are, in reality, different from what we know. For now, the moderately high infectivity, mild clinical symptoms, and wide-ranging incubation period may mean that the novel virus is less harmful to individuals but may coexist with humans and become endemic. In this sense, 2019-nCoV has the potential to cause a pandemic.

The physical and social environments of 2020 are also very different from those in 2002.

²⁴ Peng Zhou, Xing-Lou Yang, Xian-Guang Wang, Ben Hu, Lei Zhang, Wei Zhang, Hao-Rui Si, Yan Zhu, Bei Li, Chao-Lin Huang, Hui-Dong Chen, Jing Chen, Yun Luo, Hua Guo, Ren-Di Jiang, Mei-Qin Liu, Ying Chen, Zu-Rui Shen, Xi Wang, Xiao-Shuang Zheng, Kai Zhao, Quan-Jiao Chen, Fei Deng, Lin-Lin Liu, Bing Yan, Fa-Xian Zhan, Yan-Yi Wang, Gengfu Xiao, and Zheng-Li Shi, "Discovery of a Novel Coronavirus Associated with the Recent Pneumonia Outbreak in Humans and Its Potential Bat Origin," *bioRxiv*, January 23, 2020.

²⁵ Chen Wang, Peter W. Horby, Frederick G. Hayden, and George F. Gao, "A Novel Coronavirus Outbreak of Global Health Concern," *The Lancet*, January 24, 2020.

China is wealthier and more globalized today. Today, there are 739 international air travel routes originating from China—three times the number of routes (233) available in 2002. On average, 51 million people travel between China and another country per year, a number many times higher than the 3 million back in 2002. The epicenter of the outbreak, Wuhan, is a major transportation hub in central China, sometimes known as “Chicago of China.” On an average day, 30,000 people fly out of the city, and many more use the bullet trains from three railway stations in the city. The outbreak began right before the Chinese New Year, a time during which more than three billion trips typically occur under normal circumstances. January is also the time when students from overseas colleges to return to school after the winter break and students from Chinese universities start the winter break. The environmental difference between the 2019- nCoV epidemic and SARS is the scale of mobility, which makes the global spreading of the disease much easier than that for SARS.

Prevention and treatment methods are similar between SARS and 2019-nCoV. In both cases, vaccine development takes months to a year and can hardly be helpful in stopping the outbreak. Quarantines, travel bans, and case-tracing can slow down the disease transmission and buy precious time for countries to plan their responses, but they are not perfect prevention methods.²⁶ Quarantine will only be effective if it can guarantee stopping people’s mobility, which is hard to do for a city of 11 million people. Early detection is conducted using proper reverse transcription polymerase chain reaction (RT-PCR) testing kits, thanks to the Chinese scientists who have isolated the novel virus, conducted genomic sequencing, and shared the data with the world in an astonishingly short amount of time. This has helped to identify the virus and has enabled China and other countries to develop effective testing kits for early detection. The treatment of 2019- nCoV mostly focuses on supportive therapy, but a few antiviral medicines are being used experimentally.

The Chinese Government’s Response to 2019-nCoV

The Chinese government’s response to 2019-nCoV has followed a similar pattern to that of the SARS outbreak and is characterized by three common features: (1) delaying public acknowledgement of a public threat, (2) downplaying the severity of the outbreak in its early days, and (3) relying on quarantine, social control, and large-scale health care system mobilization to stop the outbreak. The current response also has a few major differences, including the use of social media, better research, and technology, which have helped mitigate some of the negative effects.

The first common feature response of SARS and 2019-nCoV is the delay in acknowledging the initial case cluster to be a public health threat. If we recognize that stability is what the Chinese political system values most, and an acute public health threat, such as an epidemic, is precisely the “black swan” that can threaten such stability, then it is not too difficult to understand the Chinese government’s reluctance toward acknowledging an epidemic. China’s law prohibits anyone from talking about a public health threat before an official government announcement. For the government to make an announcement on an epidemic, a full process of upward reporting and verifying at every political level has to be

²⁶ Jennifer B. Nuzzo, “Past Epidemics Prove Fighting Coronavirus with Travel Bans Is a Mistake,” *Washington Post*, February 2, 2020.

accomplished. Once the verified report reaches the Ministry level, a special expert group is often sent to investigate. Following such a process, a timely acknowledgement of an epidemic to the public is almost impossible. The exception has been when social stability itself is being threatened. For example, we saw Guangdong government officials breaking the silence three months after the first SARS case only when the public panicked after seeing phone messages regarding a deadly flu in February 2003. We also saw Wuhan health officials announcing the 27 cases of 2019-nCoV on December 31, 2019 after a few doctors in Wuhan sent WeChat messages warning their acquaintances about a “SARS-like” pneumonia. (The informants were later publicly reprimanded by the government.) In this case, wide use of social media, no matter how closely monitored, helped the local officials significantly shorten the waiting period that is usually required for an official announcement.

The second characteristic of the government’s response is the downplaying of the severity of the threat at the beginning of an epidemic. For SARS, the results from the first investigation did not alarm the Ministry—and therefore, there was no public announcement—in January 2003. For the next two months, the government continued downplaying the severity of SARS to the public until the Minister of Health was fired in April. In this recent response to 2019-nCoV, the first expert team went to Wuhan in January 2020 and concluded that there was no person-to-person transmission and the outbreak was well controlled after the closing of the seafood market where many cases (not all) were identified. For days, the local health officials assured the public that there were no new cases in Wuhan and no cases outside Wuhan. This inaccurate portrayal of the disease may have allowed sufficient time for the virus to be spread widely in Wuhan, to other cities in China, and to the world. It was not until the 2019-nCoV cases were confirmed in Thailand and Japan in patients who had had no exposure to the seafood market that the MOH sent a second expert group to Wuhan on January 19. This time, person-to-person transmission was immediately confirmed, and the national case reporting system was triggered on January 20. Although the downplaying of the severity of the epidemic did occur, this time it only lasted 20 days, compared with the 2.5 months during the SARS outbreak. This was due to better biomedical and research capacity of the Chinese researchers in 2019. Chinese scientists were able to quickly culture the virus and share the genomic sequencing data with international researchers by January 11. The genetic sequencing data helped many countries quickly develop testing kits for early detection of the disease. When cases showed up in Thailand and Japan, international genomic researchers were able to quickly identify the matching genomic patterns and confirm the presence of 2019-nCoV. This success helped provide the evidence for understanding the greater geographic spread of the epidemic and the role of person-to-person transmission. During the SARS epidemic, however, because of the lack of virus identification, China’s pneumonia outbreaks were not linked to those in Hong Kong and Vietnam until four months after the index case happened.

Finally, during SARS, once the government finally geared up to stop the outbreak, they swiftly initiated a quarantine policy. With 2019-nCoV, the decision on quarantine was made three days after the government accepted the fact that the outbreak was fueled by person-to-person transmission. This time, the scale of the quarantine was unprecedented. The mayor of Wuhan announced that the government would shut down all public transportation, including airports and railways, in Wuhan—a city of 11 million people—on January 23, two days before the Chinese New Year. The national government also employed social policing to

enforce self-quarantine, canceled public events, and prohibited crowd gatherings across the country.

Without a vaccine, a quarantine is one of the few effective ways to prevent disease transmission. China's decision on a city lockdown has been praised by the WHO and probably buys precious time for many other countries to activate their public health responses. However, there are debates on the effectiveness of the lockdown over such a large area. First, some would argue that by issuing a lockdown only two days before the Chinese New Year, the government missed many people who had left earlier, since new year travel usually starts a week before the new year. The lockdown also took effect a day after the announcement, and many people from Wuhan rushed to get out of Wuhan before it started. As the mayor of Wuhan mentioned in a news conference on January 27, about five million people had left Wuhan by then.²⁷ Second, the lockdown of a city of 11 million people made it harder to implement the typical door-to-door or community-by-community screening, assessment, and provision of supportive care that usually happens after a quarantine is established. Quarantine may also bring heightened fear and stigma among the affected population, accelerate the shortage of medical supplies and health care resources, and provide a false picture that the epidemic is under control. In addition, the economic impact of the quarantine can be large.

SARS cost the world 40 billion USD and China 1 percent of its GDP in 2003. China may suffer more economic loss this year due to the 2019-nCoV, given that quarantine was initiated before the Chinese new year and at a relatively early stage of the epidemic. (Quarantine may last longer than two months.) In 2003, the industries hurt most were tourism, retail, and entertainment, which was 43 percent of China's GDP. Today, these industries account for 54 percent of the GDP.²⁸ China now contributes 17 percent of world's economy, compared with 4.3 percent in 2003, when the SARS epidemic was unfolding. China's current stature in the world economy means that the impact of 2019-nCoV outbreak is likely to substantially exceed that of SARS.

Currently, the national case report system is in use, and the case numbers have surged in the last weeks. However, given that many hospitals in China are overwhelmed by the large volume of people with cold-like symptoms coming for testing and treatment because of the fear of the epidemic, patients are often being turned away, and delayed diagnosis and deaths that are not counted (when infected people die before the diagnosis or at home) are both possible. The two new 1,000-bed hospitals that China built in two weeks may help relieve the severe shortage of hospital beds and improve health care for many infected people. It may also help improve the accuracy of the epidemic's statistics.

In summary, the 2019-nCoV is the third of its type, after SARS and MERS, to cause a global outbreak. The Chinese government's response to 2019-nCoV has been similar to that of SARS; however, the initial delay and the "downplay" time were much shorter this time due to the widespread use of social media and the much-improved local research capacity. The unfolding battle against this new pandemic, meanwhile, highlights the importance of

²⁷ Gerry Shih, "Coronavirus Prompts CDC to Expand Travel Warning to All of China; Top U.S. Health Official Urges Beijing to Admit Disease Experts," *Washington Post*, January 27, 2020.

²⁸ Bloomberg News, "Coronavirus Is More Dangerous for the Global Economy than SARS," January 31, 2020. As of February 3, 2020: <https://www.bloomberg.com/news/articles/2020-01-31/the-coronavirus-is-more-dangerous-for-the-economy-than-sars>.

transparency and open collaboration among scientists globally. It is a reminder that all nations should prioritize and protect global health research, capacity building, and cooperation.

RECOMMENDATIONS

Given that my fellow panelists both have more experience on leading pandemic preparedness programs in the United States, I will focus my recommendations on the China-related issues. I have short-term, medium-term, and long-term suggestions.

Short Term

First, China is on the front line of a full-fledged battle with the new coronavirus. Health care workers are exhausted, and testing kits and personal protection, such as face masks, goggles, and gloves, are all in short supply and have been rationed.²⁹ At this time when many Chinese people are suffering from illness, anxiety, and uncertainty, it is important and opportune for U.S. public health and health care professionals to reach out to China and provide humanitarian and technical aid. Such support will boost the morale of their Chinese colleagues, serve as an international witness to the health care professionals' work at the front line of the epidemic, and help provide technical support on trials of the latest antiviral medicines. I am quite encouraged to hear that the U.S. CDC office in Beijing will be hosting a medical team in the near term.

Secondly, any efforts by the U.S. government to reduce stigma and unfriendly gestures toward people from China and Wuhan at this tense and sensitive moment will increase the soft power of the United States and bring more goodwill from Chinese people toward the United States. Conversely, stigma, prejudice, and any punitive remarks will preclude any sense of goodwill and will also more likely undermine the level of transparency the Chinese government is willing to allow now.

Finally, given that the WHO has declared 2019-nCoV a PHEIC, there are concerns regarding developing countries that do not have a health care system capable of stopping the spread of the virus. In the worst-case scenario, the epidemic may affect more people in these countries when the epidemic subsides in China and the United States. The U.S. CDC may consider working with China's CDC and the China International Development Cooperation Agency (CIDCA) to map out potential collaborations to help these countries in distress.

Medium Term

Once the epidemic is under control, studies on the country response systems and global pandemic management will begin. It might be valuable for the United States to help lead the evaluations with government officials and scholars from China and other countries. There

²⁹ Rosie Perper, "As the Wuhan Virus Spreads, Doctors in the City Say They Face a 'Flooding' of Patients and Not Enough Protective Gear," *Business Insider*, January 24, 2020. As of February 3, 2020: <https://www.businessinsider.com/wuhan-coronavirus-doctors-wuhan-patients-protective-gear-2020-1>.

will be several questions for China to contemplate: What can China do in the future to improve communication about new public health threats? What can be done to increase the transparency about the occurrences and the severity of the outbreak? To what extent are quarantines effective, and how should they be implemented? How can China make its CDC more sustainable and improve multi-sector communications? The lessons learned will benefit not only China, but also other countries that encounter similar issues.

To take such a leadership role, I hope the U.S. government can build a realistic and consistent policy about future U.S.-China collaboration on global health and seek consensus with China on what data to share and what rules to follow.

Long Term

As I mentioned earlier in my testimony, during most of the years between SARS and 2019- nCoV, the United States and China were working side by side to confront the challenges of epidemics. In doing so, both countries have benefited from capacity building for their current and future public health workforces. In our current situation, as the first phase of the trade war is resolved, this could be an opportune time to restart the U.S.-China dialogues on economy, diplomacy, and security. I hope U.S.-China collaboration on global health and pandemic preparedness will benefit from these future talks between the two countries.

Chapter 487

LESSONS FROM THE WEST AFRICAN EBOLA RESPONSE: HOW TO SAVE LIVES AND PROTECT OUR NATION DURING THE NOVEL CORONAVIRUS EPIDEMIC OF 2020*

Ronald A. Klain

Chairman Bera, Ranking Member Yoho, other members of the Subcommittee:

Thank you for inviting me to participate in this hearing today. I want to commend the Subcommittee for moving quickly to gather information and educate the public about the novel coronavirus epidemic that originated in Wuhan, China, and has now spread to countries around the world, including our own. It is a privilege to be able to present my perspective on this, and to answer your questions about the emerging US response.

Before I begin my substantive presentation, I want to make two preliminary points.

First, as frustrating as it may be, it is important to understand that what we know about this epidemic and the virus that causes it remains uncertain and preliminary. We know much less about coronavirus today than we did about Ebola in 2014. Scientists in the US and around the world are working at unprecedented speed to improve our understanding about the virus and its spread; new papers are being published every day, literally. Nonetheless, there are critical questions about the virus, how quickly it spreads, how infectious it might be, how lethal it will be – and others –for which we still do not know the answers, and that (once learned) will have huge impacts on our response. Part of this is due to a lack of full transparency and cooperation by the Chinese government, which hopefully will improve. But part of this is simply due to the fact that it takes time for science to learn key facts about a novel virus. As someone who has coordinated the policymaking and implementation of a response to an epidemic, I know that these information gaps are vexing: many decisions cannot wait, and have to be made on the best information available. But it is important that we understand this limitation, understand that policy choices will have to change as our fact

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base changes, and that we be careful not to make definitive or declarative pronouncements when the science does not justify such statements.

Simply put, at present, we do not know how serious this epidemic will become, how many people – in China, in the US, and elsewhere – will contract the virus, how many will die, and how grave the threat is to our own country. Such a lack of knowledge does not counsel a lack of action, indeed, perhaps it counsels just the opposite. But it does advise modesty in the forcefulness of our conclusions, and awareness of the need to make changes in policy choices as we gain more information.

Second, a point about partisanship and the response. I am an outspoken political partisan – that is well known. But I come here today in the same way that I approached my tenure as White House Ebola Response Coordinator: putting partisanship and politics aside. The coronavirus will not ask any person's partisan affiliation before infecting them. There is no Democratic or Republican approach to fighting infectious disease; only sound and unsound measures.

To reinforce this point: what we did during the Obama administration's Ebola response relied heavily on lessons learned and expertise acquired during the Bush administration's efforts to fight AIDS and malaria in Africa. Key players in the Ebola response were veterans of both Democratic and Republican administrations. President Obama's emergency funding package passed this House with strong, bipartisan support; our implementation of it domestically involved work with state and local officials from both parties, and the input of Members of Congress of all political and ideological camps. Saving lives, abroad and at home, turns on putting politics aside and allowing science, expertise, and sound decision making to govern our actions.

With these two preliminary points made, I want to move on to the subject of my testimony today: how the lessons we learned during the Ebola response in 2014-15 should shape how our government – in the Executive and Legislative branches – approaches the threat now posed by the novel coronavirus.

To be clear, the Ebola response was not without its own problems and mistakes. Particularly early on, the danger to Africa and the world was underestimated; early signs of progress in containing the disease in the Spring of 2014 led to a false sense of security. The fact that no Ebola outbreak prior to 2014 had ever involved more than 500 cases of the disease also led to a false confidence that a large-scale epidemic was unlikely. Early initiatives in West Africa lacked a full understanding of the complexities of implementation there and cultural and religious barriers to some aspects of the response. And confusion and a lack of preparation led to missteps when the first case of Ebola arrived in Dallas, Texas, in late September, 2014.

But ultimately, the US got the response organized; quickly adapted and improved its approach; and made adjustments to what responders were doing in Africa and here at home. President Obama mustered an all-of-government response to the challenge, authorized the first-ever deployment of US troops to combat an epidemic ("Operation United Assistance"), appointed me to lead a team of dedicated and talented professionals at the White House to coordinate this effort, implemented novel and innovative policies on travel screening and monitoring, and worked with Congress to enact a \$5.4 billion emergency package to fight the disease abroad and improve our preparedness at home and around the world for future such epidemic threats.

In the end, the epidemic in West Africa was tragic: an official death toll of over 11,000, with the real count likely higher. But the backdrop for this loss of life must be considered. In September of 2014, experts forecast that the death toll could be over 1 million people; thus, the response succeeded in helping to reduce the projected loss of life by as much as 98%. America's actions – as part of a global response, with Africans playing the largest part, deserving the greatest credit, and suffering the harshest losses to its health care workers – saved hundreds of thousands of lives. It was a great humanitarian achievement.

Here at home, after the initial missteps in Dallas, no one contracted Ebola on US soil, and Americans evacuated for medical care in the US were successfully treated and released, with only a lone fatality. Once implemented, our monitoring system successfully insured no domestic transmission of the disease, routed suspected cases to prepared medical facilities before those patients could be infectious, and enabled ample time for successful testing and response.

The ongoing legacy of this response is likewise enormous. With Congress' support, we implemented a national four-tiered network of hospitals and medical facilities that remain prepared to this day to identify and isolate cases of dangerous infectious disease, and to provide treatment to those who are infected – nothing like this existed in 2014 when the Ebola epidemic began, as many earlier investments made after the anthrax attacks in 2001 had been allowed to dissipate. The capacity to test for and promptly identify diseases like Ebola grew from three laboratories in the US in September 2014 to almost 100 by the end of that year. We developed rapid diagnostics that ended the risky practice of having patients wait days to learn if they were sick and/or infectious. Vaccines against Ebola were tested and developed, and as a result of that work, an effective vaccine now exists and is being used in the field. New therapeutics were developed that helped reduce the mortality rate of Ebola dramatically.

It is no wonder that this effort – without in any way minimizing the devastation in West Africa – is seen today as a huge success. Tom Friedman wrote last year that that West African Ebola response was:

“[President Obama's] most significant foreign policy achievement, for which he got little credit precisely because it worked — demonstrat[ing] that without America as quarterback, important things that save lives and advance freedom at reasonable costs often don't happen.”

From mid-October 2014 to mid-February 2015, I was proud to lead the team at the White House that coordinated this response. We saw the weekly new case count in West Africa drop from about 1,000 a week to fewer than five a week, at which point the President announced the end of Operation United Assistance and began the withdrawal of US troops serving in that mission.

This was a truly global response, with tremendous contributions by government officials, NGOs, and volunteers from around the world, with a particularly close partnership with our allies in the United Kingdom and France. With regard to the US part of this global effort, special thanks should go to the men and women on the frontlines. This includes members of the 101st Airborne (who constituted the bulk of Operation United Assistance), and also, civilian responders -- via US AID DART teams and CDC employees deployed to the region, and contractors who supported them. It includes the men and women of the US Public Health Service who staffed the Monrovia Medical Unit in Liberia. It includes career Ambassadors and other diplomats who served in all three effected countries with skill and played such a

large role in the response. It includes the doctors, nurses and other health care workers – many of them volunteers -- who served in Ebola treatment units, hospitals, and other facilities – treating the sick under extreme conditions. It includes the scientists of the NIH and the CDC who pioneered new diagnostics, therapeutics, and vaccines. The US response put over 10,000 people – soldiers and civilians, government workers and NGO teams, contractors and volunteers – on the ground in West Africa in 2014-2015. It was a gargantuan undertaking, and a story in which all Americans should take pride.

To make that effort effective, and to match it with preparation and protection here at home, it took talented teams in Washington, in Atlanta at the CDC, and in government agencies and private health care facilities around the country. Public servants of all ranks and all levels worked around the clock. And as I mentioned before, Congress acted swiftly and on a bipartisan basis to approve most of the Obama administration's request for \$6 billion in aid, less than five weeks after it was sent to Capitol Hill.

I would be remiss if I did not say that, of course, President Obama, too, deserves credit for this success. He weathered sharp criticism for his actions during the Ebola response, and had to ignore pressures to put aside the advice he was getting from top scientists and medical experts. He made difficult decisions about the actions we took abroad and at home. He communicated openly and directly with the American people, and chaired repeated meetings of the National Security Council as the response took shape. He used every tool at his disposal – from his bully- pulpit (to destigmatize survivors by publicly hugging Ebola patient Nina Pham in the Oval Office after her discharge from the hospital), to authorizing the massive deployment to West Africa, to personally engaging numerous world leaders to activate their resources and support for the response, to urging Congressional leaders to approve his emergency spending package, and much more: he did so much to achieve these results.

The challenge we face from the novel coronavirus that began in China late last year contains many similarities, but also, many differences from the challenge posed by the Ebola epidemic in West Africa in 2014-15. It would be a mistake to simply repeat what we did at that time, given those many differences. But likewise, it would also be a mistake to ignore the lessons that can be learned from that response, given the similarities. And hence, I am grateful for the opportunity to talk about the lessons I think are most applicable from this experience, to be applied in the current circumstance.

Among the many possible lessons that should be employed now, there are seven in particular that I would like to call out today. I will do so briefly, but I am happy to go into more depth on any of them in response to your questions or any subsequent follow-up from the Subcommittee.

First, in a complex, rapidly evolving scenario like the one we are seeing, there is no substitute for White House coordination and leadership. There should be a single official inside the National Security Council at the White House, supported by an appropriate team, working on this full-time, overseeing our response.

This does NOT mean that we need a “Coronavirus Czar” to serve the same role that I played during the Ebola epidemic. At the end of my tenure as Ebola Response Coordinator, I said, in fact, there should never be another specific “Disease Czar” at the White House. Instead, I recommended to President Obama that he create a permanent “Pandemic Preparedness and Response Directorate” inside the NSC, led by a Deputy National Security Adviser-level appointee with direct access to the President as needed, to oversee ongoing

work to prepare for future infectious disease threats, and to coordinate a response when such threats arrive.

President Obama accepted this recommendation, and set up such a unit in 2015. President Trump continued with the structure, and named Admiral Tim Ziemer – a respected long-time public servant – to fill this post. If Admiral Ziemer were still in place, I believe that America would be much better positioned to respond to the coronavirus threat today.

But unfortunately, in July of 2018, when John Bolton took over as head of the NSC, he disbanded this unit, and Admiral Ziemer was reassigned to US AID. As a result, there has been no special unit at the NSC to oversee preparedness for epidemics, or the current response. In addition, the Trump administration has dismantled the Homeland Security Advisor structure that Presidents Bush and Obama used to deal with complex transnational threats, further undermining our preparedness for events like these.

The administration's recent decision to create a "Task Force" to oversee the response, led by Secretary Alex Azar, is a valuable step, but an insufficient one. This is not a criticism of Sec. Azar, who I believe is playing a critical role in the response, and brings great experience and judgment to this effort. But a response to a challenge like this one requires action from a number of federal agencies outside of Sec. Azar's authority: Homeland Security, State, US AID, Transportation, DOD – and probably also Labor, Commerce and Justice. Given the nature of Cabinet government, the fundamentals of bureaucratic behavior, and the realities of competing demands on a Cabinet secretary's time, no single Cabinet agency head can lead such a response. There are global implications as well: in dealing with other nations as the world shapes and implements the response, a single point of coordination inside the White House both emphasizes the response's importance to the President, and facilitates high-level government-to-government cooperation.

For these reasons, and many more, an effective response to a challenge like coronavirus should be led by a full-time, high-level appointee at the White House. Ideally that decision would be made by the Executive Branch, but another avenue to achieve this structure would be for Congress to move ahead on the Global Health Security Act (HR 2166), introduced by Reps.

Connolly and Chabot, as that bill would create much of this apparatus by statute.

Second, the US must "lean forward" to fight this epidemic overseas, using all of the tools and leverage that it can commit to the effort. Unlike West Africa in 2014, China in 2020 probably does not need, and would not accept, thousands of US responders on the ground treating patients, testing new approaches, conducting research, providing infrastructure, and helping bring the disease under control. This is a huge difference.

But that should not get us off our toes, or have us sitting back and believing that our only sphere of action is the homeland. Dr. Tony Fauci of NIH has publicly urged the deployment of medical researchers and investigators to China, and key administration leaders – at State and the White House – should apply pressure to encourage the most open access possible. Nations less advanced or well-resourced than China may experience significant coronavirus outbreaks and require more direct forms of US assistance, akin to what we provided during the 2014 Ebola epidemic, albeit on a smaller scale. We should send CDC experts wherever they would be helpful, and task US AID to determine where DART teams and other assistance could be usefully deployed. Likewise, we should bolster preparedness in low-income countries now – before the disease spreads further – to avoid spread in places where local containment efforts might fail.

Our diplomats should be empowered and engaged around the globe, and our government must press WHO – with stronger leadership today under Dr. Tedros Adhanom Ghebreyesu than it had during the 2014 Ebola epidemic – to do the right thing.

This is a global challenge, and America must provide global leadership. There is no room for isolationism or withdrawal. The best way to keep Americans safe is to contain and combat the virus overseas. We should do this not only because it is generous or humanitarian – though it would be generous and humanitarian, both great American traits – but because it will make America safer and reduce the risk of a larger outbreak here.

Third, the administration must ensure that science and expertise guide our actions, not fear or politics. One of the first casualties in an epidemic is rational thinking, replaced by fear, bias and poor decision-making. We saw this in 2014 with calls for needless travel bans and baseless quarantine restrictions; President Obama was right to reject these misguided calls, and to implement travel and monitoring policies based on the scientific advice he got from the nation's leading experts.

Travel warnings and advisories make sense in the face of the coronavirus; telling people not to take trips to China right now, except in special or compelling cases, is wise. That is quite different from banning people – including, for example, Americans in China, or family members of Americans – from coming back home, or going for essential purposes. Congress should press the administration for the science behind recently announced quarantines and exclusions of non-US persons from travel to the US; also, it should inquire as to the effectiveness of the measures being implemented. Banning travel to or from China altogether would impede the flow of medical assistance, expert investigation, or other key response functions; in addition, key supplies – including supplies critical to our own health care system – come from China.

More generally, there will be many policy decisions to be made in the days and weeks ahead. Science, medicine and expertise should guide them. The American people are lucky to have the world's leading experts on infectious disease working in their government, led by men and women like Tony Fauci at NIH and Anne Schuchat at CDC. They have served Democratic and Republican administrations, and helped Presidents with a wide variety of political perspectives save lives and protect our nation. This expertise should be paramount in decision making at all levels of government.

Fourth, the administration should quickly assemble, and transmit to Congress, an emergency funding package to ensure that there are no delays in responding to the coronavirus challenge. Fighting the coronavirus overseas and at home will cost money. HHS (and its units like ASPR, BARDA, NIH and CDC), US AID, DHS, and other agencies will have costs. State and local governments will feel a pinch from monitoring contacts of those who have the virus, and tracking and monitoring individuals who have been in effected countries. Hospitals treating patients with the virus may need assistance. Research and deployment of new therapeutics and vaccines needs government support, and funding for private-public partnerships. The list of needs goes on.

While Congress responded quickly to a funding request from the Obama administration for Ebola, even that short delay had some impact on our response. The delay of months in approving funding for the Zika response was quite consequential. Most importantly, Congress is unlikely to even begin considering these funding needs until the administration makes a request.

The Trump Administration has tools that we lacked in 2014, most importantly – and to the Congress’ credit – it has a new Emergency Fund on which the Administration can (and has) drawn. But I expect that this will not be adequate, and it would be wise for the administration to begin putting together a Supplemental Funding request immediately.

Fifth, Congress must do its own work in dealing with the novel coronavirus. The burden of action does not rest entirely with the Executive Branch; Congress too must do its part.

This starts with the point I made above: once the administration makes an emergency funding request, Congress should act on it without delay. Of course, Congress should not rubberstamp the request: any proposal to use public funds should get scrutiny and review. But prompt action must drive this process, and divisions between parties or chambers should not result in delay. Indeed, Congress might want to begin now – given the expertise of many in this body – preparing for such a request even before it is made, and contemplating the likely funding needs.

But Congress’ role does not end with acting on the emergency funding question; there are a number of other elements of the response that demand Congressional attention. Hearings like today’s are important, to help ascertain how the response is going and where it needs to be improved. Congress wisely funded the Public Health Emergency Fund last year – but did so only on a limited basis. Adding to that funding, and funding an additional emergency fund specific to the development of therapeutics and vaccines via public-private partnerships, should be considered.

Additionally, as I wrote in the *Post* with Dr. Syra Madad in December – before the coronavirus hit -- Congress is overdue to renew the funding for the network of “Ebola and Special Pathogens Hospitals.” This network was created during the Ebola epidemic in 2014, and funding for it expires in May of 2020. Pending legislation would fund only the 10 most advanced such facilities, and would end federal funding for the 60 other hospitals that screen, test, and provide initial treatment for these cases. Allowing this funding to expire in May would be a huge mistake; funding for these specialized facilities should be renewed, and the network should be strengthened with greater help for frontline facilities, EMS responders, and other touch points in our medical system that are least prepared and most exposed.

Sixth, both the Executive Branch and the Congress should take this as a wake-up call to finish the work we need to do on pandemic preparedness and readiness. Recently, America marked the 100th anniversary of the single largest mortality event in our history: the Spanish Flu epidemic of 1918-19. More Americans died from this epidemic than from World War I, World War II, the Korean War, and the Vietnam War - -combined. While, on the one hand, science has made great strides since 1918, on the other hand, increased global travel, human incursion on animal habitats, and the stresses of climate change have raised the risk that we will face such a “great pandemic” once again.

At present, it seems very unlikely that the coronavirus poses such a threat to the United States – but we cannot know for certain. Moreover, even if this current epidemic is not “the big one” that is coming, it is a reminder that this danger lurks, and our preparedness for it is lacking. As Dr. Ashish Jha of the Harvard Global Health Institute often says, “Of all the things that can kill millions of Americans quickly and unexpectedly, an epidemic is probably the most likely ... and the one in which we invest the least to prevent.”

The Global Health Security Agenda, legislation such as HR 2166, Blue Ribbon Commission reports, table top exercises, proposals from members of this Subcommittee – and my own extensive writing over the past five years – have set forth detailed agendas of what

we need to do to prepared for this event. These bipartisan calls for action have largely been ignored. The current public focus on infectious disease generated by the coronavirus should spur us into action. The time to act on this agenda is now. If we wait until the catastrophic pandemic arrives, it will be too late.

Seventh, we need to be on the watch for discrimination against people in our country of Chinese origin and ancestry, and speak out strongly against any such fear-driven racism. The coronavirus strikes humans – not people of any particular ethnicity or race. Chinese-Americans or Chinese people in America are no more likely to get the disease, carry the disease, or transmit the disease, than any other group of people.

Yet we have already seen signs that such people are the targets of discriminatory fear – with some already being hassled, threatened with expulsion from schools and other mistreatment. As fears of the coronavirus accelerate, so too will these incidents. This kind of discrimination not only is wrong, but also makes it harder to combat the disease. If some members of the Chinese-American community feel that they are likely to face hostility, they are less likely to work closely with authorities, and less likely to heed advice of public health experts.

It is incumbent on every person in authority in this nation to speak out against such racism, and to ensure that this does not become part of our civic life during the coronavirus epidemic.

Americans need to pull together to fight a disease, not pull apart to fight one another.

In closing, I want to thank, again, the Subcommittee for holding this hearing, and for inviting me to participate. I stand ready to answer your questions about any of these points, or any other aspects of the response.

America has the tools, the talent, and the expertise to combat the coronavirus, both abroad and at home. The question now is whether our leaders, in the Executive Branch and the Congress, will deploy them effectively; act promptly and wisely; rely on expertise – not bias and fear; organize and implement our response appropriately; and allow science and medicine to be our touchstone. For the sake of people around the world, and for the sake of the American people, let us work to see that it is so.

Chapter 488

**THE STATE OF U.S. PUBLIC HEALTH
BIO-PREPAREDNESS: RESPONDING TO BIOLOGICAL
ATTACKS, PANDEMICS, AND EMERGING INFECTIOUS
DISEASE OUTBREAKS***

Subcommittee on Oversight and Investigations

FRIDAY, JUNE 15, 2018

HOUSE OF REPRESENTATIVES,

SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS,

COMMITTEE ON ENERGY AND COMMERCE,

Washington, DC.

The subcommittee met, pursuant to call, at 9:01 a.m., in room 2123, Rayburn House Office Building, Hon. Gregg Harper (chairman of the subcommittee) presiding.

Present: Representatives Harper, Griffith, Burgess, Brooks, Collins, Walberg, Walters, Costello, Carter, Walden (ex officio), Degette, Schakowsky, Castor, Ruiz, and Pallone (ex officio).

Also Present: Representative Eshoo.

Staff Present: Jennifer Barblan, Chief Counsel, Oversight and Investigations; Adam Fromm, Director of Outreach and Coalitions; Ali Fulling, Legislative Clerk, Oversight and Investigations, Digital Commerce and Consumer Protection; Christopher Santini, Counsel, Oversight and Investigations; Jennifer Sherman, Press Secretary; Alan Slobodin, Chief Investigative Counsel, Oversight and Investigations; Austin Stonebraker, Press Assistant; Christina Calce, Minority Counsel; Jeff Carroll, Minority Staff Director; Chris Knauer, Minority Oversight Staff Director; Miles Lichtman, Minority Policy Analyst; C.J. Young, Minority Press Secretary; and Perry Lusk, Minority GAO Detailee.

* This is an edited, reformatted and augmented version of Hearing before the Subcommittee on Oversight and Investigations, of the Committee on Energy and Commerce, House of Representatives, One Hundred Fifteenth Congress, Second Session, Serial No. 115–140, dated June 15, 2018.

**OPENING STATEMENT OF HON. GREGG HARPER, A
REPRESENTATIVE IN CONGRESS FROM THE STATE OF MISSISSIPPI**

Mr. HARPER. Good morning. Today, the subcommittee continues its longstanding oversight of the U.S. public health system's preparedness to respond to biological threats and emerging infectious diseases that endanger the public health. The purpose of today's hearing is to hear from top public health experts on the good work being done at their agencies to protect the public and to explore where improvements need to be made.

The biological threats facing the United States in today's global society are varied, ever-evolving and, in some cases, intensifying. The CDC just reported that the seasonal influenza claimed the lives of 172 children during the most recent flu season, making it the deadliest seasonal flu season for children on record.

In recent years, the U.S. has also seen an increase in the number of antibiotic-resistant bacteria. Around the world, viruses are emerging, adapting and, in some cases, reemerging. Currently, there is an Ebola outbreak in West Africa and a Nipah virus outbreak in India that has killed at least 17.

In recent years, we have also seen humans in China contract the H7N9 strain of influenza which has been confined to birds. The H7N9 influenza strain is rated by the CDC's influenza risk assessment tool as posing the greatest risk to cause a public pandemic.

The 2013 ricin mailings addressed to President Obama and Senator Roger Wicker that originated in my home State of Mississippi, as well as the 2001 anthrax mailings and foreign terrorist threats, is a reminder of the risk of intentional biological attacks.

Today's hearing is especially timely, given that the committee is considering bipartisan legislation sponsored by Mrs. Brooks and Ms. Eshoo to reauthorize the Pandemic and All Hazards Preparedness Act, PAHPA, which is set to expire at the end of September. Passage of PAHPA's reauthorization would not only provide critical certainty for public health agencies and industry partners, it would also bring about some much needed reforms. One such reform proposed in the legislation is transferring control of the Strategic National Stockpile from the CDC to HHS' Office of the Assistant Secretary for Preparedness and Response, to improve management of the stockpile.

A year ago, HHS' Office of Inspector General reported systemic issues with security and inventory management of the stockpile, risking CDC's ability to deploy the stockpile during a public health emergency. These issues need to be addressed, as does improving the training of State and local stakeholders on deployment of medical countermeasures.

Administrative reforms are also of interest. For example, are there ways to improve the timeliness of the decisionmaking process on threat assessments and appropriate countermeasures? Effective threat detection has been a subject of committee oversight. In 2016, the committee questioned the CDC about the effectiveness of its Laboratory Response Network, or LRN, which is responsible for developing assays for public health labs to test for the presence of Federal select agents.

In a May 2017 letter to the committee, the CDC reported that the LRN had only developed three assays approved by the FDA to detect specific Federal select agents. While the LRN has also had those cleared by the FDA under emergency use authorization, after nearly 20 years of this program, with about \$135 million in funding over the last decade,

could the LRN have cleared a significantly higher number of assays through the most rigorous FDA 510(k) process?

Finally, maintaining public confidence in critical Federal biopreparedness research is essential. In response to safety lapses in 2014 and to an expert panel's recommendations, the CDC and FDA each formed new offices in 2015 to centralize and elevate oversight of laboratory safety, with the directors of those offices reporting directly to the agency head.

These changes sent a strong message that lab safety was a top priority, backed by the clout of direct backing from the agency head. Unfortunately, both agencies seem to be backtracking from this good direction.

In the FDA's case, less than a year after this administration approved the direct report organization—or reorganization, the sudden change is curious and would seem to be a step in the wrong direction. So we need to hear more details about the basis for this new direction.

I would like to thank the distinguished members of our panel for being here today and for your service to our country.

I now recognize the ranking member of the subcommittee from Colorado, Ms. DeGette, for 5 minutes.

[The prepared statement of Mr. Harper follows:]

PREPARED STATEMENT OF HON. GREGG HARPER

Good morning, today the Subcommittee continues its long-standing oversight of the U.S. public health system's preparedness to respond to biological threats and emerging infectious diseases that endanger the public health. The purpose of today's hearing is to hear from top public health experts on the good work being done at their agencies to protect the public, and to explore where improvements in biopreparedness may still be needed.

The biological threats facing the United States in today's global society are varied, ever-evolving, and in some cases, intensifying. The CDC just reported that the seasonal influenza claimed the lives of 172 children during the most recent flu season, making it the deadliest seasonal flu season for children on record. In recent years the U.S. has also seen an increase in the number of antibiotic resistant bacteria.

Around the world, viruses are emerging, adapting, and in some cases, re-emerging. Currently, there is an Ebola outbreak in West Africa and a Nipah (*pronounced Knee – Pah*) virus outbreak in India, that has killed at least 17 people.

In recent years, we have also seen humans in China contract the H7N9 strain of influenza, which had been confined to birds. The H7N9 influenza strain is rated by the CDC's Influenza Risk Assessment Tool as posing the greatest risk to cause a possible pandemic.

The 2013 ricin mailings addressed to President Obama and Senator Roger Wicker that originated in my home state of Mississippi, as well as the 2001 anthrax mailings and foreign terrorist threats, is a reminder of the risk of intentional biological attacks.

Today's hearing is especially timely given that the Committee is considering bipartisan legislation, sponsored by Ms. Brooks and Ms. Eshoo, to reauthorize the Pandemic and All-Hazards Preparedness Act (PAHPA), which is set to expire at the end of September. Passage of PAHPA's (*pronounced Pah – Pah*) reauthorization would not only provide critical

certainty for public health agencies and industry partners, it would also bring about some much-needed reforms.

One such reform, proposed in the legislation, is transferring control of the Strategic National Stockpile from the CDC to HHS' Office of the Assistant Secretary for Preparedness and Response to improve management of the Stockpile. A year ago, HHS's Office of Inspector General reported systemic issues with security and inventory management of the Stockpile, risking CDC's ability to deploy the stockpile during a public health emergency. These issues need to be addressed, as does improving the training of state and local stakeholders on deployment of medical countermeasures.

Administrative reforms are also of interest. For example, are there ways to improve the timeliness of the decision-making process on threat assessments and appropriate countermeasures?

Effective threat detection has been a subject of Committee oversight. In 2016, the Committee questioned the CDC about the effectiveness of its Laboratory Response Network (LRN), or LRN, which is responsible for developing assays for public health labs to test for the presence of federal select agents. In a May 2017 letter to the Committee, the CDC reported that the LRN had only developed three assays approved by FDA to detect specific federal select agents. While the LRN has also had assays cleared by the FDA under Emergency Use Authorization, after nearly 20 years of this program with about \$135 million in funding over the last decade, could the LRN have cleared a significantly higher number of assays through the more rigorous FDA 510(k) process?

Finally, maintaining public confidence in critical federal biopreparedness research is essential. In response to safety lapses in 2014 and to an expert panel's recommendations, the CDC and FDA each formed new offices in 2015 to centralize and elevate oversight of laboratory safety, with the directors of those offices reporting directly to the agency head. These changes sent a strong message that lab safety was a top priority backed by the clout of direct backing from the agency head. Unfortunately, both agencies seem to be backtracking from this good direction, in the FDA's case less than a year after this Administration approved the direct-report reorganization. The sudden change is curious, and would seem to be a step in the wrong direction. We need to hear more details about the basis for this new direction.

I would like to thank the distinguished members of our panel for being here today and for your service to our country. I now recognize the Ranking Member of the Subcommittee from Colorado, Ms. DeGette, for five minutes.

OPENING STATEMENT OF HON. DIANA DEGETTE, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF COLORADO

Ms. DEGETTE. Thank you, Mr. Chairman.

I know we agree that preparing this country for a bioincident is of critical importance. The threat, as you said, is real and it's growing.

In April, the CDC reported that in 2017, Colorado saw 25 cases of an antibiotic-resistant bacteria known descriptively as the nightmare bacteria, because 50 percent of those infected by it die. Thankfully, those cases were isolated, but the same CDC study noted that it's

possible for these germs to “spread like wildfire.” If that happens, we need to know that we’re able to respond.

We’ve looked at this issue in this subcommittee many times over the years, as our panel well knows. It’s a regular appearance, and I want to thank you for coming again. And again and again, we’ve found that the Federal Government has to scramble to address biosafety incidents.

Those of us who were here during the fall of 2001 vividly recall the chaos that a few small envelopes of anthrax caused on Capitol Hill. Offices were closed. Buildings were fumigated. Some congressional business was suspended, and thousands of staffers and other personnel lined up for days to get tested for exposure. Far worse, some of the workers in our Postal Service were infected and died.

In 2009, we again had to scramble to produce sufficient doses of the H1N1 swine flu vaccine to protect against this new strain of the disease.

In 2014, hospitals and healthcare providers were not adequately prepared to deal with the arrival of Ebola patients in America. In one case, a hospital in Dallas failed to diagnose Ebola in a patient who had traveled to West Africa and discharged him. The virus was later transmitted from that patient to two healthcare workers. In the days and weeks that followed, important questions were raised about how this event was handled and were we adequately prepared for the larger event.

And then, of course, in 2015, the Zika outbreak underscored the need for the U.S. Government to focus on disease preparedness every day. And I know our panel here today does just that.

I’d like to know today, though, what lessons we’ve learned from these incidents, and I want to know how the agencies are using what we’ve learned to better prepare for the next crisis, because there will be one.

For example, do we have adequate medical countermeasures in place to respond quickly when an outbreak occurs or a toxin is released? Do we have the capacity to quickly deliver these counter-measures to the doctors and nurses who will actually use them? And do the healthcare workers understand how to deploy the countermeasures?

Similarly, research into emerging pathogens and existing pathogens that have mutated is key to helping us quickly respond to new and expanding outbreaks. How is this research informing our surveillance and detection methodologies? Are we prioritizing research into threats of greatest concern? And are we dedicating adequate resources to the threats?

I also want to hear more about how all of our agencies—CDC, ASPR, NIAID and FDA—coordinate their research, surveillance, and response efforts. Because while each one of these agencies today has a specific valuable role to play in ensuring preparedness, nobody can operate effectively alone.

In fact, one major finding of the Blue Ribbon Panel’s 2015 report on biodefense preparedness was these agencies must ensure they’re equipped to work together to respond to pandemics. The Blue Ribbon report also found that the Federal Government must dramatically increase the support provided to local jurisdictions to help them build and sustain their biodefense capabilities.

Local providers like hospitals and healthcare workers will be on the front lines in a public health emergency. I want to ensure that we’re adequately supporting these providers, as well as State and local Health Departments, so they are equipped to detect incidents when they happen and respond appropriately.

Mr. Chairman, I'm really hoping we'll hear today that we've made tangible, measurable progress in this area, but, again, I urge us to revisit the work of the Blue Ribbon Panel and some of its findings to determine what more we need to do to better prepare the Nation for the threats that we will be discussing today.

I just can't thank our panel today enough for the tireless work that they put in to keeping America safe. We always have a great opportunity to hear from you, and we know that you're working hard. We think by having you come up here and take the time, it really helps us represent our constituents, and it helps all of us be better prepared for the next emergency that faces us.

Thank you, and I yield back.

Mr. HARPER. The gentlewoman yields back.

The chair now recognizes the chairman of the full committee, the gentleman from Oregon, Mr. Walden, for 5 minutes.

OPENING STATEMENT OF HON. GREG WALDEN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF OREGON

Mr. WALDEN. Thank you very much, Mr. Chairman. To all our committee members, thanks for your work on this. And to our panelists, thank you, not only for your guidance on this issue, but also what we tap into you for along the way. And so we appreciate your professionalism and your assistance in our policy debates.

The topic of biopreparedness really hits home for me. I think I was the first Member of Congress to be diagnosed with H1N1 years ago. Not a distinction I was glad to get, but one apparently I had.

But more than that, 30 years ago, a religious group called the Rajneeshees moved to Oregon. You may have seen the documentary on Netflix called *Wild Country*. And if you read Judith Miller's book *Germs*, you'll find it was the largest bioterror attack in the Nation's history, but it took the Federal Government a year, I think she wrote, to admit that that's really what it was. They grew their own salmonella and then sprinkled it over salad bars in Dalles, Oregon, and sickened 751 people, many of whom I know.

Deliberate biological attacks are just one risk. With more global travel, there's, of course, increased risk of spread of infectious diseases. As we've seen with influenza, our vaccines must be constantly updated to keep up with the latest strains. Meanwhile, other pathogens can develop antibiotic resistance, and our ability to quickly recognize evolving diseases and respond to new outbreaks is reliant on the testing and treatment and capabilities in the men and women who do the work that you all oversee.

Lack of preparation is not an option. A mock pandemic exercise hosted last month by Johns Hopkins Center for Health Security with a group of current and former government officials, including our own colleague Susan Brooks, I'm told was quite eye-opening. The exercise resulted in a failure to develop a vaccine within 20 months, and that led in this exercise to 150 million deaths globally. So obviously, we've got to do more to be prepared for these types of outbreaks.

So that's where the reauthorization of the Pandemic and All Hazards Preparedness Act comes in. PAHPA originally was adopted in 2006. It's set to expire at the end of September. We intend to move forward with legislation prior to that.

Our Health Subcommittee met just last week to consider a bipartisan discussion draft to reauthorize this law and continues to fine-tune it. It's critically important Congress reauthorizes this law in time and to make sure that all levels of government are well-equipped to handle, not just current and emerging biothreats, but also chemical attacks, radiological emergencies, cybersecurity incidents, and mass casualty events.

Through letters, hearings, and investigations, the Committee has raised numerous issues regarding biological threats to the U.S. and our nation's ability to respond to infectious disease outbreaks. For example, the Committee has examined concerns about the CDC's management and the security of the Strategic National Stockpile and the capabilities of CDC Laboratory Response Network. The Trump administration is set to transfer management of the stock-pile from the CDC to the Assistant Secretary for Preparedness and Response, known as ASPR. And we look forward to hearing more details about how this transfer will work.

Another area of interest to the Committee is the improvement of our biosurveillance capabilities. Innovation in this field could bolster our public health response in the event of an attack or epidemic. So I'll be interested in learning more about that as well.

One thing we do know, the Federal Government needs to act faster to identify and determine material threats. The Department of Homeland Security in March 2018 made a material threat determination for pharmaceutical-based agents such as Fentanyl. It took 2 years for the DHS to make this designation, yet carfentanil, a highly potent form of Fentanyl, was used in a terrorist attack more than 15 years ago. So it's only after that designation is made that the Public Health Emergency Medical Countermeasures Enterprise can approve countermeasure development and acquisition. If we knew about it 15 years ago and it took 2 years to get that designation, we can do better.

Maintaining public support for critical biopreparedness research relies on Federal scientists and researchers working with these diseases and dangerous pathogens in a safe and secure manner. Following several safety lapses at CDC and FDA labs in 2014, both FDA and CDC created new offices to oversee and prioritize lab safety. These are positive steps. The recent proposals at these agencies to lower the status of their lab safety offices raises concerns with this committee.

So I thank you for being here today.

And I'd like to yield the balance of my time to Dr. Burgess and hopefully to Mrs. Brooks.

[The prepared statement of Chairman Walden follows:]

PREPARED STATEMENT OF HON. GREG WALDEN

Mr. Chairman, thank you for holding this hearing. The topic of biopreparedness hits home for me. Some of you may recall that in 2009 I was diagnosed with H1N1—the swine flu. It was reported at the time that I was the first Member of Congress to contract swine flu—a distinction I'm not particularly proud of. But that's not all. The first and single largest

bioterrorism attack in the U.S. occurred in my district. More than 30 years ago, a group of Rajneeshee cult members used salmonella to contaminate at least 10 restaurant salad bars in The Dalles, Oregon, causing at least 751 people to get ill.

Deliberate biological attacks are just one risk. With more global travel, there is increased risk of the spread of infectious diseases.

As we've seen with influenza, our vaccines must be constantly updated to keep up with the latest strain mutations. Meanwhile other pathogens can develop antibiotic resistance. Our ability to quickly recognize evolving diseases and respond to new outbreaks is reliant on our testing and treatment capabilities.

Lack of preparation is not an option. A mock pandemic exercise hosted last month by Johns Hopkins Center for Health Security with a group of current and former government officials, including our colleague Susan Brooks, was eye opening. This exercise resulted in a failure to develop a vaccine within 20 months and led to 150 million deaths globally. We must do more. We must be prepared for potential out-breaks.

That's where the reauthorization of the Pandemic and All-Hazards Preparedness Act (PAHPA) comes in. PAHPA, originally adopted in 2006, is set to expire at the end of September. Our Health Subcommittee met just last week to consider a bipartisan discussion draft to reauthorize this law and continues to fine tune it. It is critically important Congress reauthorizes this law to ensure that all levels of government are well-equipped to handle not just current and emerging biothreats, but also chemical attacks, radiological emergencies, cybersecurity incidents, and mass casualty events.

Through letters, hearings and investigations, the committee has raised numerous issues regarding biological threats to the U.S. and our nation's ability to respond to infectious disease outbreaks. For example, the committee has examined concerns about the CDC's management and security of the Strategic National Stockpile, and the capabilities of the CDC Laboratory Response Network. The Trump Administration is set to transfer management of the stockpile from the CDC to the Assistant Secretary for Preparedness and Response (ASPR), and we look forward to hearing more details about how this transfer will work.

Another area of interest to the committee is the improvement of our biosurveillance capabilities. Innovation in this field could bolster our public health response in the event of an attack or epidemic. I will be interested to learn whether more intensive research could help expedite addressing the technical challenges.

One thing we do know: The Federal Government needs to act faster to identify and determine material threats. The Department of Homeland Security (DHS) in March 2018 made a material threat determination for pharmaceutical-based agents such as fentanyl. It took 2 years for DHS to make this designation. Yet carfentanil, a highly potent form of fentanyl, was used in a terrorist attack more than 15 years ago. It's only after that designation is made that the Public Health Emergency Medical Countermeasures Enterprise can approve countermeasure development and acquisition. We must move faster.

Maintaining public support for critical biopreparedness research relies on federal scientists and researchers working with these diseases and dangerous pathogens in a safe and secure manner. Following several safety lapses at CDC and FDA labs in 2014, both CDC and FDA created new offices to oversee and prioritize lab safety. These were positive steps, but recent proposals at these agencies to lower the status of their lab safety offices raise concerns.

I'd like to thank our witnesses for being here with us today. We value the feedback and insight you provide and look forward to today's discussion.

* * *

Mr. BURGESS. Thank you, Mr. Chairman.

And this issue is one that is important and timely for this sub-committee. And last week, the Health Subcommittee had a hearing on the discussion draft of the Pandemic and All Hazards Preparedness Act authored by Representatives Brooks and Eshoo. At that hearing, we heard from witnesses with firsthand experience in combating these biological threats to our nation and received input on the draft legislation.

Certainly, our witness panel today is well-known to us and they are all experts. I look forward to hearing from our witnesses.

And I thank you, Mr. Chairman, and I will yield to Mrs. Brooks.

Mr. HARPER. Maybe with unanimous consent, due to your leadership role in this, 30 seconds.

Mrs. BROOKS. Thank you, Mr. Chairman.

And thank you to our witnesses for your work on this public health and national security issue.

Last February, our subcommittee here held a hearing examining how we best combat biological threats. And I'm pleased we're once again examining the state of our preparedness as we prepare to reauthorize PAHPA.

As everyone here knows, it is not a question of if we face a threat; it's a question of again, once again, when we face a threat. And we've been reminded by the stories that we've heard here today that these types of incidents have already happened in our country over the last decade and a half.

Created in 1999, the National Stockpile is the repository of vaccines, antibiotics, and supplies used in the event of an attack or an outbreak. But HHS OIG, in June of 2017, issued a report identifying serious systemic issues within the CDC's management of the stockpile.

I look forward to hearing from our witnesses today how we are going to ensure that our stockpile is properly managed and that we can be prepared as a country for whatever threat we are and may face.

I yield back.

Mr. HARPER. The chair now recognizes the ranking member of the full committee, the gentleman from New Jersey, Mr. Pallone, for 5 minutes.

OPENING STATEMENT OF HON. FRANK PALLONE, JR., A REPRESENTATIVE IN CONGRESS FROM THE STATE OF NEW JERSEY

Mr. PALLONE. Thank you, Mr. Chairman.

Ensuring that our nation is equipped to respond to pandemics, natural disasters, and the accidental or intentional release of toxins is a key part of protecting public health. Past work by this committee has suggested that our nation has not always been as prepared as we need

to be, so I'm glad that we're having this hearing today, and I hope to hear that we have made tangible progress towards increasing our Nation's preparedness.

In 2015, the Blue Ribbon Panel on Biodefense conducted a comprehensive review of the Federal Government's biopreparedness efforts. The panel found that, "The Nation is dangerously vulnerable to a biological event." It produced an extensive report recommending 30 action items for our public health infrastructure to address.

While the Blue Ribbon Panel was the most recent high-level commission to examine our nation's biopreparedness, it was not the first. In fact, for many years, experts have warned that our ability to respond to biologic and other emerging threats must be improved.

These recommendations remain important today, because the emerging health threats this country faces continue to grow. Just this week, officials announced that a child in Idaho had contracted bubonic plague. Last year, an outbreak of this plague killed 200 people in Madagascar.

In March, we heard at a hearing that the threat of pandemic flu is among the greatest concerns in the public health world. And antibiotic resistance also poses a major threat to public health, killing 23,000 Americans every year and making everyday procedures like surgery and chemotherapy increasingly risky. In May, a study showed that warming temperatures were associated with higher levels of antibiotic resistance in common strains of bacteria.

Extreme weather events can also lead to serious public health emergencies. The hurricanes in Puerto Rico, the Virgin Islands, Texas, and Florida last year were a stark reminder of this fact. We must be prepared to address threats from all these sources.

The Blue Ribbon Panel produced many recommendations for improving our biopreparedness, and I hope our witnesses will show that we have made real progress. For example, I hope to hear that the agencies have established a plan for who will take the lead in response to a public health threat and how the efforts will be coordinated.

Along these same lines, I hope we will learn how CDC, NIH, ASPR, and FDA are working together to identify the greatest threats and to prioritize the research, surveillance, and response capabilities needed to target these threats.

We must also focus on how these agencies collaborate with State and local health departments as well as healthcare providers, such as hospitals. These entities are likely to be the first to see patients impacted by an infectious disease outbreak or other incident. In most cases, they'll be the ones to dispense countermeasures and to treat those impacted.

In 2014, for example, we witnessed the negative consequences that ensued when our healthcare infrastructure was unprepared to diagnose and treat patients with Ebola. A hospital failed to detect the disease in the patient in Dallas, and that patient later transmitted Ebola to two healthcare workers. This incident led to a serious question about whether we would be able to handle a larger scale event or incident. And we must make sure everyone on the ground has all the resources they need to respond effectively in such a crisis.

We also want to hear more about how we are conducting surveillance so that when an outbreak happens or a toxin is released, we know as soon as possible. While we cannot anticipate every possible new or mutated pathogen, if we can quickly detect when such a pathogen has emerged, we can respond much more effectively.

And along these same lines, I understand the CDC is gathering a substantial amount of data from laboratories, public health departments, and clinicians across the country every day. So we must ensure that this agency has the resources it needs to effectively use and analyze this data as it comes in.

And finally, I want to hear more about what we're doing to prioritize development of medical countermeasures to help us respond to a biosafety incident. Countermeasures include preventative measures like vaccines as well as therapeutics like antibiotics and antivirals.

BARDA, I understand that you work closely with the private sector to develop many of these products, and I hope that we will hear today about how these partnerships have produced useful, safe, and effective products that truly address the challenges we face.

So, Mr. Chairman, I'd like to thank our panel once again for being here. Preparing for these threats is certainly not easy, but I'm confident that you're up for the task as long as we do our part and provide you with all the resources that you need.

I yield back, Mr. Chairman.

Mr. HARPER. The gentleman yields back.

I ask unanimous consent that the members' written opening statements be made part of the record. Without objection, they will be so entered into the record.

And additionally, I ask unanimous consent that Energy and Commerce members not on the Subcommittee on Oversight and Investigations be permitted to participate in today's hearing. Without objection, so ordered.

I would now like to introduce our witnesses for today's hearing. First, we have Dr. Rick Bright, Director of Biomedical Advanced Research and Development Authority and Deputy Assistant Secretary at the Office of the Assistant Secretary for Preparedness and Response. Next is Dr. Anne Schuchat, Principal Deputy Director at the Centers for Disease Control and Prevention. Then we have Dr. Anthony Fauci, Director of the National Institute of Allergy and Infectious Diseases at the National Institutes of Health. Finally, we have Rear Admiral Denise Hinton, Chief Scientist at the U.S. Food and Drug Administration.

We welcome all of you.

And you are each aware that the Committee is holding an investigative hearing and when doing so has had the practice of taking testimony under oath. Do you have any objection to testifying under oath?

Let the record reflect that all of the witnesses have reflected that they do not.

The chair then advises you that under the rules of the House and the rules of the committee, you're entitled to be accompanied by counsel. Do you desire to be accompanied by counsel during your testimony today?

Let the record reflect that each of the witnesses reflected that they do not.

In that case, if you would please rise and raise your right hand, I will swear you in.

[Witnesses sworn.]

Mr. HARPER. You are now under oath and subject to the penalties set forth in title 18, section 1001 of the United States Code. You may now give a 5-minute summary of your written statement.

And I will begin with you, Dr. Bright. Welcome back.

**TESTIMONY OF RICK A. BRIGHT, PH.D., DIRECTOR, BIOMEDICAL
ADVANCED RESEARCH AND DEVELOPMENT AUTHORITY, DEPUTY
ASSISTANT SECRETARY, OFFICE OF THE ASSISTANT SECRETARY FOR
PREPAREDNESS AND RESPONSE, U.S. DEPARTMENT OF HEALTH AND
HUMAN SERVICES; ANNE SCHUCHAT, M.D. (RADM, USPHS),
PRINCIPAL DEPUTY DIRECTOR, CENTERS FOR DISEASE CONTROL
AND PREVENTION, U.S. DEPARTMENT OF HEALTH AND HUMAN
SERVICES; ANTHONY FAUCI, M.D., DIRECTOR, NATIONAL
INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES, NATIONAL
INSTITUTES OF HEALTH; AND DENISE HINTON (RADM, USPHS),
CHIEF SCIENTIST, U.S. FOOD AND DRUG ADMINISTRATION**

Testimony of Rick A Bright, Ph.D.

Mr. BRIGHT. Thank you.

Chairman Harper, Ranking Member DeGette, and distinguished members of the subcommittee, it's a pleasure to speak today on behalf of our Assistant Secretary for Preparedness Response to discuss the state of the Nation's health security preparedness.

I'm Dr. Rick Bright, the Director of the Biomedical Advanced Research and Development Authority, BARDA, and the Deputy Assistant Secretary for Preparedness and Response.

ASPR's mission is to save lives and protect Americans from 21st century health security threats. BARDA is a component of ASPR created to ensure that we have products to protect people from numerous dire threats that we face as a nation. ASPR's staff is dedicated to preparing for and responding to these threats.

We are currently coordinating HHS' response to the Ebola outbreak in the DRC and monitoring H7N9 influenza in China. In communities affected by last year's hurricanes, we're there for the long haul, helping local health officials manage recovery and build resilience.

ASPR coordinates across the Federal Government to support State and local partners in emergencies. We enhance medical search capacity through our National Disaster Medical System and Hospital Preparedness Program, and we oversee the development and procurement of medical countermeasures. We've made great progress in public health preparedness response since Congress established ASPR and BARDA in 2006.

BARDA was created to bridge government and industry to accelerate the development of life-saving medical countermeasures that would not otherwise be available. We use flexible authorities, multiyear advanced funding, public-private partnerships, and deep technical expertise to push vaccines, drugs, and diagnostics towards FDA approval. In our 12 years, BARDA has formed over 200 public-private partnerships with industry to accomplish our mission.

I want to pause for one second to acknowledge the hard work of our partners who, together with the U.S. Government, work very hard to create a more secure nation with not only products but capabilities to respond when needed. These partnerships have led to 35 FDA approvals of products that form a protective shield for our nation against a range of the most serious CBRN and pandemic and emerging infectious disease threats.

Through Project BioShield, BARDA has supported 27 vaccines, drugs, and devices to address national security threats, including smallpox, anthrax, botulinum, rad/nuc and chemical exposure. Fourteen of these are now in the Strategic National Stockpile for use in an emergency, and seven have now achieved FDA approval. These outcomes are the spirit of PAHPA: leadership, coordination, partnerships, and capabilities, working together to protect our nation.

While this effort has created life-saving products to be procured by the SNS, it has also created challenges to acquire and sustain sufficient quantities to address the requirements needed for each threat. Critically, each product also represents a company with a response capability that must be sustained to ensure we have these products available when they're needed. Project BioShield and the SNS together represent a marketplace for these products that would otherwise never exist and the products would quickly vanish without it.

PAHPA, ASPR, BARDA, and BioShield have all played valuable roles in enhancing our preparedness. However, the threats continue to evolve, and technology to modify and create new deadly threats have become simpler. We must modernize our capabilities, emphasizing an end-to-end approach, ranging from early detection through the last mile of administering vaccines and treatments to patients.

With new technologies and innovation, the time is here to apply transformative approaches to these daunting health security problems. Last week, we announced a new initiative called DRIVE, a nationwide business-friendly approach to identify, capture, and accelerate life-saving innovation. Using authorities you enacted in the 21st Century Cures Act, DRIVE brings together innovators, government, and now the investment community to create solutions for today's threats.

As you consider reauthorization of PAHPA, important changes to BARDA's authorities would sustain and enhance our capabilities. First, advanced appropriations for Project BioShield will attract more partners to support our mission. Without this consistent and guaranteed market, the companies are reluctant to work with us. Second, an authorization of appropriation for BARDA's pandemic influenza program will sustain our domestic flu vaccine production capabilities, modernize our vaccine technologies, and bring new treatments and faster diagnostics into the homes across America.

I look forward to working with members of this panel, this subcommittee, your congressional colleagues, and I'm grateful for the opportunity to present to you today and look forward to your questions.

[The prepared statement of Mr. Bright follows:]

**WRITTEN TESTIMONY, HOUSE COMMITTEE ON ENERGY AND
COMMERCE, SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS,
THE STATE OF U.S. PUBLIC BIOPREPAREDNESS: RESPONDING TO
BIOLOGICAL ATTACKS, PANDEMICS, AND EMERGING INFECTIOUS
DISEASE OUTBREAKS**

Statement of Rick Bright, Ph.D.

Director, Biomedical Advanced Research and Development Authority

Deputy Assistant Secretary for Preparedness and Response

For Release on Delivery Expected at

9:00 am

June 15, 2018

Good morning Chairman Harper, Ranking Member DeGette, and other distinguished Members of the Subcommittee. I am Dr. Rick Bright, the Director of the Biomedical Advanced Research and Development Authority (BARDA) and the Deputy Assistant Secretary for Preparedness and Response (ASPR) at the Department of Health and Human Services (HHS). Thank you for the opportunity to testify before you today on behalf of ASPR to discuss the state of our nation's preparedness for 21st century health security threats, including biological incidents, as the Energy and Commerce Committee prepares to consider the second reauthorization of the Pandemic and All-Hazards Preparedness Act (PAHPA).

My expertise is in developing drugs, vaccines, diagnostics and other medical countermeasures (MCMs) for health security threats. In this testimony, I will cover a broader range of ASPR programs and activities, including some background on the nature of the health security threats facing the United States, the mission and duties of ASPR and BARDA, and our vision for where these areas can be strengthened.

**Readiness for 21st Century Health Security Threats:
A National Security Imperative**

One of the federal government's fundamental responsibilities is to provide for the common defense - to protect the American people, our homeland, and our way of life. The strength of our nation's public health and medical infrastructure, and the capabilities necessary to quickly mobilize a coordinated national response to emergencies and disasters, are foundational for the quality of life of our citizens and vital to our national security. The health security threats facing the United States during the 21st century are increasingly complex and dangerous. Therefore, improving national readiness and response capabilities for 21st century health security threats is a national security imperative.

Additionally, we have witnessed the impacts of naturally occurring outbreaks such as pandemic influenza, outbreaks of Ebola and SARS, and the emergence of antibiotic resistant bacteria. ASPR is currently engaged in coordinating HHS's response to the Ebola outbreak in the Democratic Republic of Congo and monitoring other potential emerging infectious

diseases that could cause a pandemic, such as the H7N9 influenza strain circulating in China. This year marks the 100-year anniversary of the 1918 influenza pandemic, which killed more people than World War I. During that pandemic, more than 25 percent of the U.S. population became sick and 675,000 Americans, many of them young, healthy adults, died from the highly virulent influenza virus. As our healthcare delivery systems become more networked, cyber-attacks like the 2017 WannaCry incident that affected approximately 150 countries remind us that technological advancements have trade-offs in the form of new vulnerabilities and risks. Finally, we face extreme weather events, such as the recent 2017 hurricane season in which Hurricanes Harvey, Irma, and Maria caused an unprecedented amount of damage and destruction, reminding us of the awesome destructive power of nature and our vulnerability.

These are threats that most people would rather not think about. However, when natural disasters, disease outbreaks, or attacks occur, the people expect our federal government to be ready to quickly respond to save lives and decrease morbidity. Since September 11, 2001, the nation has made great progress in building our response capabilities to protect America from health security threats; however, we still have much to do.

Assistant Secretary for Preparedness and Response: Mission and Duties

ASPR's mission is to save lives and protect Americans from 21st century health security threats. On behalf of the Secretary of HHS, ASPR leads public health and medical preparedness for, response to, and recovery from, disasters and public health emergencies, in accordance with the National Response Framework (NRF) (Emergency Support Function (ESF) No. 8, Public Health and Medical Services), as well as the National Disaster Recovery Framework (Health and Social Services Recovery Support Function). ASPR also supports HHS's role in the delivery of mass care and human services in emergencies (NRF ESF No. 6, Mass Care, Emergency Assistance, Temporary Housing, and Human Services).

When ASPR was established by Congress a decade ago in PAHPA, the law's objective was to create "unity of command" by consolidating Federal nonmilitary public health and medical preparedness and response functions under the ASPR. This approach was modeled on the Goldwater-Nichols Act that created the Department of Defense (DoD) combatant commands; the impetus was the disorganized and fragmented response to Hurricane Katrina in 2005.

ASPR coordinates across HHS and the Federal interagency to support state, local, territorial, and tribal health partners in preparing for, responding to, and recovering from, emergencies and disasters. In partnership with HHS agencies, ASPR works to enhance U.S. medical surge capacity by organizing, training, equipping, and deploying HHS public health and medical personnel, such as National Disaster Medical System (NDMS) teams, and providing logistical support for HHS personnel responding to public health emergencies. ASPR supports readiness at the state and local level by coordinating federal grants and cooperative agreements, such as the Hospital Preparedness Program (HPP), by programs like the Medical Reserve Corps (MRC), and carrying out drills and operational exercises. ASPR also oversees advanced research, development, and procurement of medical countermeasures (e.g., vaccines, medicines, diagnostics, and other necessary medical supplies), and

coordinates the stockpiling of such countermeasures. As such, ASPR manages BARDA, Project BioShield, and the Public Health Emergency Medical Countermeasures Enterprise.

ASPR Priorities for Improving Preparedness, Response, and Recovery

HHS and ASPR have made significant progress since PAHPA was enacted in 2006 and was reauthorized in 2013. However, we still have work to do to ensure we are ready to save lives and protect Americans. ASPR has four key priorities for building the necessary readiness and response capabilities for 21st century health security threats:

First, provide strong leadership, including clear policy direction, improved health security threat awareness, and secure adequate resources.

Second, seek the creation of a “regional disaster health response system” by better leveraging and enhancing existing programs – such as HPP and NDMS – to create a more coherent, comprehensive, and capable regional medical emergency response system integrated into daily care delivery.

Third, advocate for the sustainment of robust and reliable public health security capabilities. For ASPR to accomplish its mission, the Centers for Disease Control and Prevention (CDC) and other partners need support to quickly detect and diagnose infectious diseases and other health security threats. This is critical to rapidly and effectively dispensing medical countermeasures in an emergency.

Fourth, advance an innovative medical countermeasures enterprise by capitalizing on new authorities provided in the 21st Century Cures Act and advances in biotechnology and science. We must develop and maintain a robust supply of safe and efficacious vaccines, medicines, equipment, and other materiel to respond to 21st century health security threats, as well as the flexible response capabilities needed to handle the unexpected.

Strong Leadership

In the area of strong leadership, ASPR should continually evaluate and incorporate national health security threats by regularly coordinating with the Director of National Intelligence, the Department of Justice, and the Department of Homeland Security to assess current and future national health security threats.

Medical Countermeasures Enterprise

Congress established BARDA to speed up the availability and use of medical countermeasures (MCMs) by bridging the so-called “valley of death” in late stage development where many countermeasures for health security threats historically languished or failed. By using flexible, nimble authorities, multiyear advanced funding, strong public-private partnerships, and cutting edge expertise, BARDA has successfully pushed innovative MCMs, such as vaccines, drugs, and diagnostics, through advanced development to stockpiling and commercial availability with FDA approval or licensure.

In the last decade, BARDA’s strong partnerships with biotechnology and pharmaceutical companies, the National Institutes of Health, and other HHS components have led to 35 FDA approvals for 31 unique MCMs addressing chemical, biological, radiological, and nuclear

(CBRN) threats, pandemic influenza, and emerging and re-emerging infectious diseases. This is a staggering accomplishment in just 12 years.

BARDA has supported the development of 27 medical countermeasures against Department of Homeland Security (DHS)-identified national security threats through Project BioShield, including products for smallpox, anthrax, botulinum, radiologic/nuclear emergencies, and chemical events. Fourteen of these products have been placed in the Strategic National Stockpile and are ready to be used in an emergency and seven have achieved FDA approval. BARDA also has supported the development of 23 influenza vaccines, antiviral drugs, devices, and diagnostics to address the risk of pandemic influenza.

Because of these successes and progress, more medical countermeasures than ever before are eligible to be procured for the Strategic National Stockpile, thereby creating new challenges in terms of acquiring and maintaining sufficient quantities of medical countermeasures to address the requirements for identified health security threats.

Just last week, we announced an exciting new public-private engagement model – called DRiVE – which is designed to accelerate innovation, address some of the nation’s most pressing health security challenges, and potentially affect major healthcare markets.

At a time when synthetic biology and personalized medicine are not just conceivable but attainable, the time is right to apply an innovative approach to some of the most daunting, far-reaching health security problems, such as sepsis and early diagnosis of infectious diseases.

By implementing the authorities you provided to us in the 21st Century Cures Act, we are opening our doors to more innovators, and most importantly investors, to catalyze advances in science and technology.

ASPR has recommended important changes to BARDA’s authorization of appropriations to meet these challenges, including, most notably, additional advanced appropriations for Project BioShield, which would help incentivize private industry to dedicate resources to developing medical countermeasures to meet the government’s national security requirements. Without this “guaranteed market,” companies are reluctant to incur the costs required to focus development on MCMs for CBRN agents that would rely upon a limited government market that may not materialize when product development is complete. ASPR has also recommended adding a direct funding line for BARDA’s pandemic influenza preparedness activities. This authorization of appropriations will help sustain domestic influenza vaccine manufacturing capacity, as well as support better, faster influenza vaccine technologies and antivirals and rapid response platform technologies.

Regional Disaster Health Response System

The 2017 hurricane season highlighted the importance of regional healthcare readiness and medical surge capacity. ASPR led the public health and medical responses to Hurricanes Harvey, Irma, and Maria under the NRF Emergency Support Function No. 8 mission. ASPR worked closely with state and territory health officials in affected areas to augment care with NDMS teams, U.S. Public Health Service Commissioned Corps Officers, Department of Veterans Affairs personnel and facility support, and DoD transportation, facilities, naval vessels with medical and surgical capability, clinicians, and support personnel. Federal personnel under the supervision of HHS treated over 36,000 patients, and evacuated nearly 800 patients. HHS deployed over 4,500 personnel, awarded over 200 contracts, and provided nearly 950 tons of equipment. Today, HHS continues to support recovery efforts in impacted communities.

Despite our progress, each event teaches us that ASPR needs to improve its internal capabilities as well as enhance our support for the healthcare infrastructure across the country. As with MCM development, the nation's healthcare delivery infrastructure is mostly a private sector enterprise. We must better leverage and enhance existing federal programs – such as HPP and NDMS – to create a more coherent, comprehensive, and capable regional medical emergency response system integrated into daily care delivery. We call this the foundation of a “regional disaster health response system.”

NDMS was created during the Cold War to take care of military casualties from overseas conflicts in U.S. civilian hospitals. To modernize NDMS, strengthen capabilities, and ensure NDMS continues to provide critical support during and immediately after national public health and medical emergencies and national security special events, ASPR is implementing administrative changes and has recommended improvements to the NDMS statute to aid in ASPR's efforts to modernize this critical asset.

The Hospital Preparedness Program (HPP) was established after the September 11, 2001 terrorist attacks, with the goal of improving the capacity of local hospitals across the country to deal with disasters and a large influx of patients in an emergency. Using HPP funding, state grantees initially purchased equipment and supplies needed for emergency medical surge capacity. Over time, the program successfully evolved to support local coordinated healthcare coalitions, including hospitals, public health facilities, emergency management agencies, and emergency medical services providers. Fifteen years after it was established, HPP can be further strengthened to better utilize existing resources and enhance healthcare preparedness and response capabilities at the local level, and ASPR has recommended modifications to the HPP statute toward this end.

Conclusion

As Congress moves forward on the second reauthorization of PAHPA, we have the opportunity to build on the great progress made and further improve our national readiness and response capabilities for 21st century health security threats. On behalf of the HHS Assistant Secretary for Preparedness and Response, Dr. Bob Kadlec, I want to thank you, again, for your bipartisan commitment to this national security imperative, and we look forward to continuing to work together to enhance our nation's health security. I am happy to answer any questions you may have.

* * *

Mr. HARPER. Thank you, Dr. Bright.

The chair will now recognize Dr. Anne Schuchat for 5 minutes.

Welcome.

TESTIMONY OF ANNE SCHUCHAT, M.D.

Dr. SCHUCHAT. Thank you.

Chairman Harper, Ranking Member DeGette, and members of the subcommittee, thank you so much for the opportunity to testify before you today to describe CDC's role in preparing, detecting, and responding to biological attacks, pandemics, and emerging infectious disease outbreaks.

Today I'll highlight CDC's role in protecting the Nation against health threats. I'll describe our role in three areas: preparedness, detection, and response.

The three themes I'd like you to take away are, first, the work CDC does every day in public health lays the foundation for responding to emergencies. Second, the CDC's world-class scientific and medical expertise ensures we're ready to respond to any threat. And third, our longstanding connection to State and local health departments ensures that public health systems function effectively, both day-to-day and during emergency response.

Let me first address how we prepare for emergencies. CDC works every day with State and local health departments. In fact, we have 590 staff assigned to State and local health departments. We fund the Public Health Emergency Preparedness Cooperative Agreement Program and the Cities Readiness Initiative.

Public Health Emergency Preparedness grants go to every State, eight territories, and four cities. These funds support staff, enable exercises to test and validate capabilities, and pay for laboratory and communications equipment.

The Cities Readiness Initiative funds this nation's 72 largest cities, to develop and test plans to receive and dispense medical countermeasures from the Strategic National Stockpile.

CDC expertise helps assure protection of vulnerable populations against diverse threats. For example, CDC worked with the American Academy of Pediatrics, the FDA, and other stakeholders to address gaps in existing countermeasures for anthrax in children, taking advantage of the agency's scientific and clinical expertise and longstanding relationships with AAP.

Turning now to detecting threats. The CDC's lab and surveillance systems are able to detect and identify agents causing illness, ranging from infectious agents to chemical or radiation exposures. Every year, labs from all over the world send specimens to CDC, because they know we'll be able to identify pathogens that other laboratories cannot.

Rapid identification of disease permits intervention before a health threat becomes a crisis. CDC's Laboratory Response Network maintains an integrated, scalable, and flexible system of 125 Federal, State, and local laboratories. The development of this laboratory network established in 1999 has provided a larger capacity to test and report more quickly than was previously possible. For example, during the Zika virus outbreak response, CDC and our Laboratory Response laboratories processed over 207,000 specimens just for Zika.

Now I'll turn to response. When there's a crisis, CDC responds. We're able to rapidly deploy scientific and medical experts anywhere in the world. By the end of the 21-month Ebola response, 3,700 CDC staff had shifted from their day-to-day duties to assist with the response. 1,500 of our staff deployed to West Africa, making over 2,000 trips. Today, we're responding to a much smaller Ebola outbreak in the Democratic Republic of Congo.

During health emergencies, CDC communicates. For example, during the 2009 H1N1 response, CDC held 39 full press conferences and 21 telebriefings. During the Zika response, CDC published 51 morbidity and mortality weekly report articles to make sure the public health and healthcare professionals had the latest and best information.

Being able to prepare, detect, and respond to public health threats is a top priority for us at CDC. Our preparedness and response capabilities are built on broad and deep scientific,

medical, and program expertise. Our longstanding partnerships with State and local public health authorities ensures an integrated approach wherever that approach is needed, resulting in better responses and better public health outcomes, which translate to better protection of the people we serve.

Thank you, and I'll be happy to answer questions.

[The prepared statement of Dr. Schuchat follows:]

**WRITTEN TESTIMONY, HOUSE ENERGY AND COMMERCE
COMMITTEE, SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS:
THE STATE OF U.S. PUBLIC HEALTH BIOPREPAREDNESS:
RESPONDING TO BIOLOGICAL ATTACKS, PANDEMICS, AND
EMERGING INFECTIOUS DISEASE OUTBREAKS**

Statement of RADM Anne Schuchat, M.D.
Principal Deputy Director,
Centers for Disease Control and Prevention
Department of Health and Human Services

For Release upon Delivery
Expected at 9 a.m.
June 15, 2018

Chairman Harper, Ranking Member DeGette, and other members of the subcommittee. I am Rear Admiral Anne Schuchat, Principal Deputy Director of the Centers for Disease Control and Prevention (CDC). I appreciate the opportunity to be here today to discuss CDC's biopreparedness mission.

CDC is the eyes and ears of the biopreparedness complex, advancing the health security of the nation by helping communities prepare for, detect, and respond to, public health consequences of all hazards. These hazards include chemical, biological, radiological, and nuclear (CBRN) threats, natural disasters, and emerging (and re-emerging) infectious disease. For 72 years, this has been CDC's core mission.

CDC draws on expertise from across the agency, including world-class laboratory testing, public health surveillance (for disease detection), epidemiology, guidance to healthcare providers, incident management, logistics, emergency risk communication, disease control programs, distribution of medical countermeasures, human and animal medicine, and responder health and well-being. Our multidisciplinary workforce and integrated national and international systems broaden our capacity to detect and respond to any developing situation that could affect the health of people in the United States. This ability is enhanced by our long-standing relationships and close collaboration with federal, state, territorial, tribal, local, and global partners.

Prepare

The CDC's Public Health Emergency Preparedness Cooperative Agreement Program (PHEP) (which includes the Cities Readiness Initiative (CRI)) is central to CDC's programs to prepare communities across the nation for the next public health emergency. Additionally, CDC's role in the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) is critical to national preparedness for chemical, biological, radiological, nuclear threats, and emerging infectious diseases.

Public Health Emergency Preparedness Cooperative Agreement Program

The PHEP cooperative agreement program is the largest CDC state program and provided approximately \$600 million to state, local and territorial public health departments in FY 2017. The program supports these jurisdictions to develop plans for public health preparedness and response, and has been instrumental in integrating state and local health departments into their jurisdictions' emergency response structures. PHEP currently supports 62 awardees – the 50 states, eight territories and freely associated states, and four directly funded cities (New York City; Washington, D.C.; Chicago; and Los Angeles). Funding is awarded according to a base-plus population formula prescribed by statute, which ensures a minimum amount of funding to each awardee. These funds support preparedness and response staff, enable exercises to test and validate capabilities, provide training, and pay for laboratory and communications equipment essential to maintaining preparedness. In addition, CDC personnel support PHEP awardees by helping to identify and address gaps in preparedness capabilities, providing planning resources to ensure the needs of vulnerable populations are incorporated into response strategies, and improving response capabilities from experience gleaned during public health responses.

Cities Readiness Initiative (CRI)

CRI, funded through the PHEP cooperative agreement, enhances preparedness in the nation's 72 largest population centers, where nearly 60% of the U.S. population resides. These cities use CRI funds to develop, test, and maintain, plans to quickly receive medical countermeasures (MCMs) from the Strategic National Stockpile (SNS) and distribute them to local communities. This program, which relies on local boots on the ground, enables effective response to large-scale public health emergencies that require life-saving medications and medical supplies.

Public Health Emergency Medical Countermeasures Enterprise (PHEMCE)

Through participation in the ASPR-led Public Health Emergency Medical Countermeasures Enterprise (PHEMCE), CDC works with other HHS agencies and other federal partners to enhance preparedness for chemical, biological, radiological and nuclear threats, and emerging infectious disease. CDC brings together its scientific expertise and its experience in public health practice to inform the use of preventative measures and treatment during a public health emergency. Specifically, CDC subject matter experts from various CDC centers:

- Develop clinical guidance on the use of PHEMCE medical countermeasures – crucial to ensure health departments and clinicians know the safest, most effective way to use medical countermeasures.
- Inform operational details for SNS deployment – this includes informing which products should be deployed first based on epidemiology and laboratory data and clinical guidance.
- Provide technical expertise to state and local partners for the development and execution of deployment and dispensing plans for PHEMCE medical countermeasures.
- Conduct regular operational readiness reviews and exercises with state and local partners to prepare them and build their capacity to receive and dispense PHEMCE medical countermeasures. (In FY 2017, CDC supported 12 full-scale and tabletop exercises, and trained 3,758 Federal, state, territorial, and local emergency responders representing 13 different jurisdictions, on how to receive and distribute products from the Strategic National Stockpile).
- Provide regulatory science expertise to inform legal mechanisms (Emergency Use Authorizations, Emergency Use Instructions, and Investigational New Drug Protocols) and guidance on the use of MCM that have not received FDA approval or the use of FDA approved MCMs for – indications other than those included in FDA approval.

Protecting Vulnerable Populations during Emergencies

CDC has expertise and programs to promote effective support and care prior to, during, and after a public health emergency, for a wide variety of vulnerable populations. CDC's PHEP program requires states to develop emergency plans covering children, pregnant women, and other vulnerable populations such, as those isolated due to geography and individuals with disabilities. Subject matter experts within CDC's Children's Preparedness Unit champion the needs of children in public health emergencies and have supported 10 responses over the past 10 years. CDC also provides guidance to state and local health departments for dosage and administration of certain MCMs to certain populations. The Children's Preparedness Unit has recently completed a draft implementation plan for the pediatric use of Anthrax Vaccine Adsorbed (AVA) in the case of a large-scale event. AVA is the only FDA-licensed human anthrax vaccine in the U.S., but it is not currently approved for use in children. This implementation plan provides critical activities to ensure that programs are prepared to, and have the resources for, the efficient and safe administration of the vaccine to children.

Federal Select Agent Program

The nearly 300 entities in the U.S. that engage in laboratory research on biological select agents and toxins are regulated under the Federal Select Agent Program (FSAP), which is jointly managed by CDC and the Animal and Plant Health Inspection Service (USDA) to regulate the possession, use, and transfer of biological pathogens and toxins (e.g., anthrax, bubonic plague, smallpox, and ricin) that have the potential to pose a severe threat to human, animal, and/or plant health. The program aims to ensure that work with these dangerous

agents is conducted in as safe and secure manner as possible, and that they are stored and transported safely and securely.

Detect

World-class scientific expertise in disease progression, epidemiology, and laboratory methods ensures CDC is ready and able to detect and develop a response to a broad range of threats, including highly hazardous and infectious diseases like Ebola, smallpox, Zika, anthrax, and H7N9 influenza.

CDC uses advanced molecular detection techniques that combine next-generation genomic sequencing, high-performance computing, and epidemiology to identify pathogens faster and more accurately. Laboratories from all over the world send specimens to CDC because they know CDC will be able to identify pathogens that other laboratories cannot.

Through Advanced Molecular Detection investments, CDC is able to detect outbreaks faster, before they have become widespread. These advances are applied in dozens of areas such as foodborne disease, influenza, antimicrobial resistance, hepatitis, pneumonia, and meningitis. Moreover, CDC shares genetic sequencing capabilities with state and local health departments, and funds them to acquire these tools that help them respond more quickly and effectively at the local level, lessening the chances that disease outbreaks will spread.

CDC also maintains unique laboratory capability to rapidly detect exposure to radionuclides and more than 150 chemical threat agents. This information about human exposure helps public health officials rapidly assess health risk, determine the most effective treatment, and reduce additional exposures.

A Strong Laboratory Response Network

Rapid identification of disease is critical to addressing public health threats before they become a crisis. This requires that high quality specialized laboratory testing be available around the country. CDC's Laboratory Response Network is an integrated system of federal, state, and local laboratories that provides early detection and characterization of biological, chemical and other public health threats. The linking of laboratories and close partnership between laboratorians, epidemiologists and clinicians at CDC, state and local health departments, and healthcare facilities ensures the most rapid detection and mitigation of health threats.

For example, in response to the MERS (Middle East Respiratory Syndrome), Ebola and Zika virus outbreaks, CDC provided Laboratory Response Network laboratories across the United States with assays authorized for Emergency Use to quickly identify cases of infection during these outbreaks.

Another important laboratory network, begun in 2016, is CDC's Antibiotic Resistance Laboratory Network, which supports nationwide laboratory capacity to rapidly detect antibiotic resistance in healthcare, food, and community settings, and inform local responses to prevent the spread of antibiotic resistant bacteria, and protect people. The Antibiotic Resistance Laboratory Network includes seven regional laboratories, the National Tuberculosis Molecular Surveillance Center, and laboratories in 50 states, five cities, and Puerto Rico.

Public Health Surveillance

Public health surveillance—the collection, analysis, and use of data to target public health prevention and intervention activities—is the foundation of public health practice at CDC, and continues to represent CDC’s core work, whether as detective work in the field, or advanced analysis to understand disease transmission. CDC uses electronic data systems to monitor population health information around the clock to detect and track diseases. For example, following 9/11, CDC invested in using health-related data based on syndromic surveillance in Emergency Departments as an early warning system for a bioterrorist attack. Those investments are paying dividends, as this information technology system now allows officials to detect a wide range of health threats beyond biological attacks, from opioid overdoses to chemical exposures to disease outbreaks.

To ensure a nationwide surveillance capability, CDC supports surveillance infrastructure, including information technology systems, and practice at the state and local levels through the National Notifiable Disease Surveillance System, the National Syndromic Surveillance Program, the National Healthcare Safety Network, the Emerging Infections Program Active Bacterial Core Surveillance, and components of national influenza surveillance.

Beginning in fiscal year 2016, Congress recognized the large and growing threat of antibiotic resistance and appropriated funding for CDC to detect and respond to resistant pathogens, prevent the spread of resistant infections, and collaborate with partners to encourage innovation with respect to new prevention strategies.

CDC has multiple surveillance systems that can detect and track resistant threats across healthcare, food, and community settings.

CDC’s Global Disease Detection Operations Center monitors outbreaks 24/7, assesses their potential risk to the United States and communities around the world, and improves global public health surveillance. Since 2017, CDC has tracked more than 170 unique diseases globally and identified outbreaks in more than 190 countries. CDC works with the 17 Phase 1 and the 14 Phase 2 Global Health Security Agenda partner countries to help them build the core public health capacities necessary for identifying and containing outbreaks before they become epidemics that could affect us all. The 17 Phase 1 countries receive direct financial support and technical assistance from CDC; the 14 additional countries receive only technical assistance from CDC. Our work through the Global Health Security Agenda emphasizes four critical areas: surveillance, laboratory, workforce development, and rapid response capability. In addition, CDC medical and public health officers staff United States Quarantine Stations that are located at 20 United States ports of entry and land-border crossings where the majority of international travelers arrive. These health officers are an important defense to prevent the introduction into, and spread of infectious diseases in, the United States.

Respond

CDC’s number one priority during any public health emergency is to protect the health of the public. CDC subject matter experts respond regularly to events such as foodborne outbreaks, natural occurring anthrax and botulism cases, smallpox vaccine adverse event cases, and seasonal influenza. CDC’s readiness activities, expertise, and infrastructure

provides the foundation for all types of public health emergency responses and is scalable and can surge to respond to events such as the 2013 meningitis outbreaks. The expertise and systems used in such responses can be augmented further for larger public health emergency responses such as the 2009 H1N1 response, 2014 Ebola response, and the Zika response.

State and local public health agencies are the front lines of public health preparedness and response. CDC provides ongoing technical assistance and, where requested, on-the-ground personnel and materials to assist with response efforts. CDC's established relationships with state and local health departments ensure that day-to-day public health systems function effectively and efficiently, and that emergency response actions are appropriate to the threat. These continuous relationships, between and during emergency responses, ensure a level of trust and collaboration that cannot be overemphasized. During the stress of an emergency response, having a trusted partner you can turn to immediately can mean the difference between life and death for patients, and ensures the rapid delivery of public health services, such as vaccinations and clean water, for communities.

CDC experts lead and staff every activation of the agency's Emergency Operations Center (EOC), ensuring response activities are effective and efficient. CDC has activated its incident management system for 67 responses over the last 16 years. During a response, in coordination with and, sometimes at the direction/request of the Office of the HHS Assistant Secretary for Preparedness and Response, CDC's EOC rapidly deploys scientific experts, coordinates the delivery of supplies and equipment to the incident site, monitors response activities, provides resources to state and local public health departments, and disseminates timely and accurate information within government, to health care providers and to the public. During the agency's Ebola and Zika responses, 3,700 and 1,700 CDC staff participated in the response, respectively. During the Ebola response, CDC staff completed over 2,000 field deployments to West Africa. CDC also responds to public health events that do not require EOC support. In fiscal year 2017, CDC assisted state, local, and overseas public health authorities in 38 epidemiologic investigations of emerging infectious disease outbreaks. In addition, the Global Rapid Response Team, stood up following the 2014 Ebola outbreaks, has over 400 ready and rostered experts.

Since its inception, that team has provided nearly 9,000 person-days of support for response activities.

We are committed to continuously improving our response capability. After each activation, whether for a real event or exercise, we conduct a thorough after-action review to identify strengths to sustain and areas for improvement. Use of this information is key to improving performance for the next incident or event.

Conclusion

I want to leave the Committee with three primary points about CDC's role in biopreparedness.

- 1) Our responses are built on our longstanding partnerships with state, local, and international public health authorities;
- 2) Our detection capabilities and surveillance programs are based on our broad and deep scientific, medical, and programmatic expertise; and
- 3) Our response capacity ensures timely aid to state and local public health systems in times of crisis.

CDC has 72 years of experience in bringing top scientific expertise to health emergencies and remains a trusted partner in the United States and around the world. CDC stands ready to do its part to protect the health and well-being of the American public and save lives. We cannot necessarily predict the next disaster, but we know that being prepared protects health, saves lives, and prevents economic losses.

Thank you for the opportunity to testify.

* * *

Mr. HARPER. Thank you, Dr. Schuchat.

The chair will now recognize Dr. Fauci for 5 minutes for your opening statement.

TESTIMONY OF ANTHONY FAUCI, M.D.

Dr. FAUCI. Thank you very much, Mr. Chairman.

Chairman Harper, Ranking Minority DeGette, members of the committee, thank you very much for giving me the opportunity today to present to you the role of the National Institute of Allergy and Infectious Diseases in addressing biodefense and emerging infectious diseases.

Our role in this really dates back many years, but was really solidified following the attacks of 9/11 with the anthrax attacks, which prompted us, together with our colleagues at HHS, to develop a strategic plan and a research agenda. For our role in that, as you know, the NIH for years, with regard to any emerging infectious disease, is involved in having a number of approaches, stemming from basic and clinical research, research resources for both industry and academic communities, with the ultimate goal of developing vaccines, therapeutics, and diagnostics.

We have been in a very strong partnership with BARDA in developing the concepts for interventions, which were then handed over to them for advanced development.

This slide just shows a representative example of some key achievements directed specifically at the category A agents that were in our strategic plan. Very briefly, for example, a better smallpox vaccine, next-generation vaccines for anthrax, antitoxins for botulism, antibiotics for plague, and, interestingly, the development of an Ebola vaccine, which long antedated the outbreak that we experienced in West Africa in 2014.

Having said that, it is important to point out, as we have in the past and as shown in this interesting article from Newsday of 2001, the worst bioterrorist may actually be nature itself.

It is interesting to point out, Mr. Chairman, that I have been testifying before this committee for the last 33 years. The first time I did, I drew a map, and it's shown here. And the reason I drew the map is I wanted to point out that there would be emerging and reemerging infectious diseases. And the first time I testified before this committee, I put HIV on the map as shown there.

Today, the map is the same structurally, but this is what it looks like. And these are the emerging and reemerging infectious diseases. Many of them, many of them are curiosities and are not really of great public health impact, but others are really important and we've experienced them recently, such as Ebola, Zika, and the threat of a pandemic influenza.

Now, let's take one of these, Ebola. You mentioned in your opening statement, as others have, about the West Africa outbreak and the recent outbreak in the Democratic Republic of the Congo. It's important that the CDC, the NIH, and other agencies of the Public Health Service responded very rapidly there.

One thing that was proven that's important is that you can do good research in the context of an outbreak. And we developed, with others, a vaccine, which is called the VSV vaccine, which was first tried in a Phase I trial right in Bethesda at the NIH Clinical Center, and then went over to Africa in a Phase II trial. This is the vaccine that was used in the ring vaccination program that was actually involved in the West Africa outbreak.

If you then fast forward a couple of years to where we are today, with the outbreak in the Democratic Republic of the Congo, we have actually learned a lot and are applying what we learned to that. Let me give you an example. The experimental vaccine that was used in the ring vaccination program has now been deployed to the Democratic Republic of Congo, and even as we speak today, it is being used in a ring vaccination with 50 rings and 150 vaccinations per ring.

Interestingly, and as I mentioned before we came, that in 1995, there was an outbreak in Kikwit in the Democratic Republic of the Congo. To just show you the connection between clinical care and research, we brought one of the survivors of Kikwit to Bethesda, took their B cells, cloned it, made a monoclonal antibody. And now the Democratic Republic of the Congo has asked us to ship that to them for their discretion use as a countermeasure in the epidemic. So it came full circle that our collaboration with them came back with something that perhaps could help them.

I want to close in the last couple of seconds with influenza. I wrote this article just a few months ago, talking about the need for a universal flu vaccine. And, in fact, we have developed a strategic plan and a research agenda because of the threat, not only of getting a better seasonal flu vaccine, but also a threat of a pandemic. And we could only do that with a vaccine that essentially is able to protect us against all subtypes of influenza.

And I'll close on this last slide—this is not working very well, sorry—which is an article that I actually wrote 17 years ago, but it's very relevant today. And what it says is that emerging infections are a perpetual challenge. We've always had them, we have them now, and we always will have them. So if they are a perpetual challenge and a perpetual risk, we must meet them with perpetual readiness and, hopefully, we'll be able to do that.

Thank you.

[The prepared statement of Dr. Fauci follows:]

**DEPARTMENT OF HEALTH AND HUMAN SERVICES NATIONAL
INSTITUTES OF HEALTH, NATIONAL INSTITUTE OF ALLERGY AND
INFECTIOUS DISEASES RESEARCH ADDRESSING BIODEFENSE AND
EMERGING AND RE-EMERGING INFECTIOUS DISEASES, TESTIMONY
BEFORE THE HOUSE COMMITTEE ON ENERGY AND COMMERCE,
SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS**

Anthony S. Fauci, M.D.

Director of the National Institute of Allergy and Infectious Diseases

June 15, 2018

Mr. Chairman, Ranking Member DeGette, and members of the Subcommittee, thank you for the opportunity to discuss the research response of the National Institutes of Health (NIH) to potential attacks with chemical and radiological/nuclear agents as well as biological threats, including emerging and re-emerging infectious diseases. I direct the National Institute of Allergy and Infectious Diseases (NIAID), the lead NIH institute for biodefense research.

The NIH conducts and supports basic and clinical research to better understand the biological effects of, and to develop medical countermeasures (MCMs) for, chemical, biological, and radiological/nuclear threats. Most of this work is conducted by the NIAID at the NIH. NIAID supports basic research on microbiology and immunology as well as applied and clinical research to evaluate candidate MCMs including diagnostics, therapeutics, and vaccines. This strategic effort includes the pursuit of foundational platform approaches that could be used to develop MCMs against multiple threats or pathogens. These platforms include molecular biological technologies for vaccines, targeted antibody therapeutics, and broad-spectrum antibiotics and antivirals.

NIH coordinates its biodefense research with partners in industry, academia, and the Federal Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) to ensure that promising countermeasures for biological, chemical, and radiological public health threats can proceed to advanced development. Since fiscal year 2012, NIH has supported the early development of more than 20 candidate MCMs for high-priority threats, and ultimately transitioned support for those candidate MCMs to the Biomedical Advanced Research and Development Authority (BARDA) for advanced development, with the goal of Food and Drug Administration (FDA) approval, licensure, clearance, or authorization, and for potential inclusion in the Strategic National Stockpile. NIH funding for emerging infectious disease, including biodefense, research was approximately \$2.6 billion in FY 2017.

NIH Medical Countermeasure Development

Innovative technologies and approaches supported by NIH are enabling the development of new medical countermeasures (MCMs) at an unprecedented pace. High-throughput sequencing and platform-based technologies are facilitating the development and manufacture of MCM candidates to expedite their clinical evaluation. For example, during the Zika virus

outbreak in the Americas, NIAID scientists used Zika virus genetic sequence information to develop a vaccine candidate that moved from concept to first-in-human trial in less than four months – likely the shortest development period ever for such a vaccine. The vaccine was developed with a readily deployable DNA vaccine platform that is a form of gene-based immunization previously employed by NIAID to develop a candidate vaccine for West Nile virus. These types of genetic platforms could be used to respond similarly to multiple emerging and re-emerging infectious disease threats.

Other broad-spectrum approaches are being used to advance the development of therapeutics that could be used against multiple pathogens. For example, NIAID has supported development of broad-spectrum antiviral agents such as BCX4430 (galidesivir), which has demonstrated activity against Ebola and other RNA viruses, and broad-spectrum antibacterial products, including a compound with activity against the two different bacteria that cause tularemia and plague.

NIAID continues to explore other inventive approaches to treat or prevent bioterrorism threats. Monoclonal antibodies, which precisely bind to a single target, have been used to treat certain cancers, infectious diseases, and autoimmune diseases. Monoclonal antibodies also have the potential to treat emerging and re-emerging infectious diseases, and as a first line intervention to prevent or slow the progress of infectious disease outbreaks as vaccines are being developed. A notable example is ZMapp™, a cocktail of three monoclonal antibodies targeting Ebola virus. ZMapp™ showed promise as a treatment for Ebola virus disease in an NIAID-supported clinical trial during the 2014-2016 outbreak in West Africa. Another innovative approach specific to vaccine development is the use of adjuvants. Adjuvants are valuable tools that can boost immune responses to otherwise modestly effective vaccines, and potentially can expedite development of vaccines for emerging pandemic threats. NIAID supports programs for discovery and development of adjuvants that have led to 50 novel adjuvants and 18 vaccine clinical trials.

NIAID also has invested in critical infrastructure and research resources to encourage the development and testing of biodefense MCMs. NIAID supports research capacity at high-containment laboratories where dangerous pathogens can be studied safely. In addition, NIAID provides qualified scientists with research resources, including microorganisms, research reagents, and preclinical development services that can fill knowledge gaps. These programs lower the financial risk for potential commercial partners and expedite the development of MCMs.

These NIH-supported activities are advancing a robust pipeline of candidate MCMs needed to ensure the development of safe and effective products to protect the public health. Notable successes are outlined below.

Ebola

NIAID partnered with the government of Liberia to establish the Partnership for Research on Ebola Virus in Liberia (PREVAIL). This clinical research partnership enabled a series of clinical trials, including studies testing several Ebola virus therapeutic and vaccine candidates, among them ZMapp™ and the cAd3-EBOZ vaccine developed by the NIAID Vaccine Research Center (VRC) in partnership with industry. Several Ebola countermeasure candidates developed by NIAID have transitioned to BARDA for advanced development, including a novel vaccine approach using two candidate vaccines in a prime-boost regimen.

NIAID currently is utilizing its expertise in Ebola research to respond to the ongoing Ebola outbreak in the Democratic Republic of the Congo (DRC). NIAID is providing technical assistance to the DRC-World Health Organization (WHO) effort to plan and implement a research response to the outbreak, including vaccine, therapeutics, and diagnostic research. NIAID also has developed as a therapeutic candidate mAb114, a monoclonal antibody active against Ebola. The antibody, which has shown promise in animal testing, was originally isolated from a survivor of the 1995 Ebola outbreak in Kikwit, DRC, through a research partnership between the NIAID VRC and the DRC's Institut National de Recherche Biomédicale. At the request of the Minister of Health of the DRC, NIAID is providing courses of mAb114 for treatment of Ebola Virus Disease, with specific research protocol design to be determined.

NIAID also has deployed a team to the National Public Health Laboratory in nearby Brazzaville, Republic of the Congo, to establish additional Ebola diagnostic and sequencing capacity in case the epidemic spreads to that country.

Nipah

NIAID conducts and supports research on countermeasures for Nipah, a deadly virus with case fatality rates of 40 to 75 percent. NIAID researchers have developed a candidate Nipah vaccine that was shown to protect against infection in a monkey model. NIAID-funded researchers, in collaboration with NIH scientists, discovered a potential monoclonal antibody treatment for Nipah virus. This treatment candidate, m102.4, effectively protected ferrets and non-human primates after exposure to Nipah virus. Based on this research, NIAID is assisting with the research response to the ongoing Nipah virus outbreak in India. At the request of the WHO, NIAID researchers have been working with scientists and clinicians from India to develop a clinical trial protocol to test the experimental monoclonal antibody m102.4 against Nipah virus. NIAID researchers also have evaluated an antiviral treatment for Nipah virus in collaboration with CDC and industry. This candidate, GS-5734, has been shown to protect against Nipah virus disease in monkeys.

Smallpox

NIAID supported the early-stage development of a novel smallpox vaccine, IMVAMUNE®, and a therapeutic, TPOXX® (tecovirimat), prior to their transition to BARDA for advanced development. IMVAMUNE® was shown to produce a superior immune response compared to the currently licensed smallpox vaccine. TPOXX® currently is under consideration for FDA approval pursuant to the Animal Rule, using pivotal animal model data supported by NIAID.

Anthrax

NIAID supported the preclinical and clinical development of the anthrax countermeasure ANTHIM® (oblitoxaximab), prior to its transition to BARDA for advanced development. ANTHIM® was approved by the FDA in 2016 for the treatment and prevention of inhalational anthrax, the deadliest form of the disease. NIAID also has supported the development of AV7909, a third-generation anthrax vaccine with a dry formulation that is easy to store and has increased shelf life. AV7909 has been transitioned to BARDA for further development.

Pneumonic Plague

NIAID supported critical animal model studies of ciprofloxacin and levofloxacin for FDA approval, pursuant to the Animal Rule, as treatments for pneumonic plague. In addition, NIAID scientists conduct foundational research on the bacteria that cause plague, and the fleas that transmit them, to understand plague biology and to aid in the design of new MCMs.

Pandemic Influenza

NIAID is partnering with BARDA to support the development of vaccine candidates for influenza strains with the potential to cause a pandemic, including H7N9 avian influenza. NIAID also is working to develop broadly protective, or “universal,” influenza vaccines that could protect against multiple strains of seasonal and pandemic influenza. NIAID recently developed a Strategic Plan to guide research efforts focused on the design and development of universal influenza vaccines.

Radiological/Nuclear Threats

NIH investment in radiation/nuclear research revitalized physician training and infrastructure for studying radiation injury and developing effective medical countermeasures. Since 2005, NIAID has transitioned 29 radiation/nuclear countermeasure candidates to BARDA for advanced development. Recent successes include FDA approval of NEUPOGEN® (filgrastim) and Neulasta® (pegfilgrastim) to treat radiological or nuclear injuries. In addition, NIAID is funding animal studies of Nplate® (romiplostim) for acute radiation syndrome for consideration for FDA approval under the Animal Rule.

Chemical Threats

NIAID administers a trans-NIH chemical countermeasures program that supports research and development of therapeutics for people exposed to dangerous chemicals, including nerve agents such as Sarin and VX; metabolic poisons such as cyanide; chemicals affecting the skin, eyes, and mucous membranes such as sulfur mustard; chemicals affecting the respiratory tract such as chlorine; and toxic industrial chemicals. NIH recently transitioned several candidate therapeutics to BARDA for advanced development, including those for nerve agent poisoning (midazolam and galantamine), sulfur mustard exposure (tissue plasminogen activator), and inhalation chlorine exposure (R-107 and GSK2798745).

Conclusion

NIAID has moved strategically toward a MCM research paradigm that features broader, more flexible platform technologies. This effort is yielding significant scientific advances that help protect against multiple emerging public health threats, whether man-made or naturally occurring. Together with academia, industry, and PHEMCE partners, NIAID remains committed to meeting public health emergency needs by advancing high-priority research toward development of MCMs for radiological/nuclear, chemical, and biological threats, including emerging and re-emerging infectious diseases.

Mr. HARPER. Thank you very much.

We now have the privilege of hearing from Rear Admiral Denise Hinton.

Admiral Hinton, you are recognized for 5 minutes.

TESTIMONY OF REAR ADMIRAL DENISE HINTON

Admiral HINTON. Thank you.

Chairman Harper, Ranking Member DeGette, and members of the committee, thank you for the opportunity to appear today to discuss the state of biopreparedness.

Medical and public health preparedness and response is critically important to the health and security of our nation. And I am pleased to be here today to discuss how FDA is working towards the shared goal of making sure that we have the medical products necessary to protect our nation from a range of public health threats, whether naturally occurring, accidental, or deliberate.

The outbreak of Ebola virus disease in the Democratic Republic of the Congo serves as a reminder that biological threats can and often do emerge with little to no warning and can rapidly become global challenges. I can assure you that FDA is dedicated to helping end this outbreak as quickly as possible, as we are actively engaged in supporting international response efforts.

FDA plays a critical role in facilitating preparedness for and response to biological threats. Our role focuses largely on facilitating the development and availability of medical countermeasures, or MCMs, such as vaccines, therapeutics, and diagnostic tests to protect against and respond to these threats.

Toward that end, we work closely with our HHS partners testifying here with me today as well as other U.S. Government partners, product developers, and nongovernmental organizations to facilitate the development and availability of MCMs. FDA also works closely with the Department of Defense to facilitate the development and availability of MCMs to support the needs of our nation's military personnel.

Prior to joining FDA and the U.S. Public Health Service Commissioned Corps, I proudly served as an officer in the United States Air Force. So these efforts are near and dear to me, and we are fully committed to closely working with our colleagues at the DOD to support the unique needs of the U.S. military personnel.

At FDA, we have made it a priority to utilize our authorities to proactively work with our private sector and government partners to help facilitate the translation of discoveries in science and technology into safe and effective MCMs as part of advancing public health and strengthening our national security.

We share Congress' goal of having safe and effective MCMs available in the event that they are needed, and we have made significant progress toward this important goal. For example, since 2012, FDA has approved, licensed, or cleared more than 120 MCMs, including supplemental changes to already approved products and modifications to diagnostic devices for a diverse array of threats, including anthrax, botulinum toxin, plague, smallpox, and pandemic influenza.

We have also issued more than 60 emergency use authorizations since 2005 to enable access to products to respond to threats, including for Zika virus, Ebola virus, H7N9 influenza virus, and the Middle East Respiratory Syndrome Coronavirus.

While the close collaboration and coordination among the agencies represented here today has achieved many successes in the development of MCMs, I would emphasize that developing MCMs is highly complex and there remain regulatory science gaps that can challenge development programs, such as a lack of models and biomarkers to enable the extrapolation of data generated in animal models to humans. Without such tools, it is difficult to generate the data necessary to support regulatory decisionmaking.

Addressing these regulatory science gaps remains a high priority for the FDA, and we have established a broad and robust portfolio of cutting-edge research under our MCMs Initiative regulatory science program to develop these tools and to promote innovation in the development of MCMs.

FDA is acutely aware that biothreats can emerge from an accidental release or exposure to threat agents during the course of conducting research. As such, we are working to ensure that our laboratories and workplaces are operated in a safe and secure manner to protect employees, the surrounding communities, and the environment. As the FDA's chief scientist, I can assure you that the laboratory safety is a high priority for me and the agency.

FDA remains deeply committed to working closely with its partners and fully using the authorities Congress provides to help facilitate and accelerate the development and availability of safe and effective medical countermeasures. While we have made significant progress, we know that more work remains to be done. We look forward to partnering with Congress and stakeholders as we work together to further enhance biopreparedness.

Thank you for inviting me to testify today. I look forward to answering any questions you may have.

[The prepared statement of Admiral Hinton follows:]

**TESTIMONY OF REAR ADMIRAL DENISE HINTON CHIEF SCIENTIST,
FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND
HUMAN SERVICES, BEFORE THE COMMITTEE ON ENERGY AND
COMMERCE, SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS,
UNITED STATES HOUSE OF REPRESENTATIVES, "THE STATE OF U.S.
PUBLIC HEALTH, BIOPREPAREDNESS: RESPONDING TO BIOLOGICAL
ATTACKS, PANDEMICS, AND EMERGING INFECTIOUS
DISEASE OUTBREAKS," JUNE 15, 2018**

Introduction

Chairman Harper, Ranking Member DeGette, and members of the committee, thank you for the opportunity to appear today to discuss the Food and Drug Administration's (FDA or the Agency) efforts to prepare our Nation to respond to biological threats, such as biological

weapons and naturally-emerging infectious diseases, like pandemic influenza, Zika virus, and Ebola virus.

Biological threats—whether deliberate, naturally occurring, or accidental—can and often do emerge with little to no warning. This was the case with the anthrax attacks of 2001, the 2009 H1N1 influenza pandemic, the 2014 Ebola outbreak in West Africa, the emergence of Zika virus in 2016, and the recent Ebola outbreak in the Democratic Republic of Congo (DRC), to name just a few.

We are continually reminded that biological threats know no borders, and that biological threats can rapidly become global challenges. As such, we must remain vigilant and continue to work to optimize our preparedness and response capabilities.

FDA's Public Health Preparedness and Response Mission

FDA plays a critical role in facilitating preparedness for, and response to, biological threats (as well as chemical, radiological, and nuclear (CBRN) threats). FDA's role focuses largely on facilitating the development and availability of medical countermeasures—such as vaccines, therapeutics, and diagnostic tests—to protect against, and respond to, these threats.

FDA works closely with its HHS and other U.S. government partners through the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE), as well as with regulated industry and non-governmental organizations (NGOs), to sustain and optimize the medical countermeasure framework necessary to effectively respond to public health emergencies. FDA also works closely with the Department of Defense (DoD) to facilitate the development and availability of medical countermeasures to support the unique needs of our nation's military personnel.

FDA's operations within its medical countermeasures mission cover a broad range of activities vital to facilitating the development of, and access to, safe and effective medical countermeasures, including:

- Reviewing marketing applications for medical countermeasures and approving those that meet standards for safety and efficacy;
- Providing regulatory advice, guidance and technical assistance to sponsors developing medical countermeasures, as well as to U.S. government partners, international regulators, and international organizations such as the World Health Organization;
- Supporting efforts to establish and sustain an adequate supply of medical countermeasures, including averting supply disruptions when feasible and, in certain situations, allowing products to be used beyond their labeled expiration dates when supported by appropriate scientific evaluation;
- Enabling access to medical countermeasures that are not yet approved—when necessary— through an appropriate mechanism, including through FDA's Emergency Use Authorization (EUA) authority;
- Proactively identifying and resolving regulatory challenges associated with medical countermeasure development and ensuring that FDA regulations and policies

adequately support timely medical countermeasure development and enable preparedness and response activities and capabilities;

- Fostering the professional development of FDA scientists to ensure that FDA personnel maintain the skills and abilities to support the medical countermeasure mission; and
- Supporting regulatory science to create the tools, standards, and approaches necessary to develop and assess the safety, efficacy, quality, and performance of medical countermeasures.

Fostering Medical Countermeasure Development and Availability

FDA's Medical Countermeasures Initiative (MCMi)—established in 2010—brought enhanced resources to FDA that enabled FDA to hire additional expert staff, and to become more deeply and thoroughly engaged in medical countermeasure activities. This program continues to be key to providing certainty regarding regulatory pathways for medical countermeasures, advancing medical countermeasure regulatory science to support regulatory decision-making, and advancing important policies and mechanisms to facilitate the timely development and availability of medical countermeasures.

At FDA, we fully appreciate that the development of medical countermeasures can present complex and unique challenges. FDA's increased engagement in medical countermeasure activities has helped to resolve many challenges associated with medical countermeasures development so that programs continue to move forward. For example, since 2012, FDA has approved, licensed, or cleared more than 120 medical countermeasures (including supplemental changes to already approved applications and modifications to diagnostic devices) for a diverse array of threats including anthrax, botulinum toxin, plague, smallpox and pandemic influenza. Thirteen of these medical countermeasures have been approved under the Animal Rule, which enables animal efficacy studies to substitute for efficacy trials in humans if the results can reasonably be extrapolated to the expected human use.¹ These approvals underscore the critical role the Animal Rule and animal studies can play in advancing medical countermeasures for some of the most challenging threats. And of note, through the use of regulatory science, FDA was able to approve inhalational anthrax therapeutics and a botulism antitoxin for use in children as well as adults, despite the fact that ethical concerns precluded studying pediatric patients in clinical trials.

In the area of pandemic influenza preparedness, FDA has approved several influenza diagnostic tests, which can help facilitate an effective response to an influenza pandemic by rapidly identifying infected persons and facilitating appropriate care. In addition, FDA has approved several seasonal influenza vaccines, helping increase and sustain pandemic influenza vaccine production capacity. These approvals include the first seasonal influenza vaccine produced using modern cell culture techniques licensed in the United States, and the first seasonal influenza vaccine made through recombinant deoxyribonucleic acid (DNA)

¹ To date, a total of 13 medical countermeasures have been approved under the Animal Rule, including inhalational anthrax therapeutics, a botulism antitoxin, antibiotics for the treatment and prophylaxis of plague, and treatments for acute radiation syndrome, prophylaxis against the lethal effects of soman nerve agent poisoning, and treatment of known or suspected cyanide poisoning.

technology. Both of these vaccines offer an alternative to the egg-based process and a potential for a faster manufacturing startup in the event of a pandemic. FDA also approved the first adjuvanted influenza vaccine for use in people 18 years of age and older who are at increased risk of exposure to the avian influenza H5N1 virus subtype contained in the vaccine. This vaccine is not for commercial distribution but will be part of the national stockpile in the event it is needed. Furthermore, FDA has continued to collaborate closely with the Biomedical Advanced Research and Development Authority (BARDA), the National Institute of Allergy and Infectious Diseases (NIAID), and the Centers for Disease Control and Prevention (CDC) on developing avian influenza H7N9 virus vaccine candidates.

Additionally, FDA approved the first intravenous antiviral drug to treat acute, uncomplicated influenza infection in adults and expanded its indication to include treatment of children ages two years and older. FDA also expanded the indications for use of the influenza antiviral, oseltamivir, to treat children as young as two weeks of age.

FDA also continues to facilitate the development of products to address antimicrobial resistance, including antibacterial drugs to treat patients with antimicrobial resistant infections, vaccines that can help prevent the emergence and spread of antimicrobial resistance, and diagnostic tests that can help rapidly identify the appropriate treatment for infected individuals. For example, FDA has been implementing Title VIII (Generating Antibiotic Incentives Now (GAIN)) of the Food and Drug Administration Safety and Innovation Act (FDASIA) since it became law in July 2012. GAIN created incentives to help develop new antibacterial and antifungal drugs intended to treat serious or life-threatening infections. Those meeting requisite criteria are determined to be qualified infectious disease products (QIDPs).² FDA has granted 147 QIDP designations through the end of FY 2017—approximately 74 of which were for novel drugs. Since the enactment of GAIN, 12 QIDPs have been approved.

With respect to supporting the development of diagnostic tests for antimicrobial resistant threats, FDA and CDC have collaborated to develop the AR Isolate Bank, a centralized repository of microbial pathogens with well-characterized resistance profiles. The AR Isolate Bank, which currently contains three bacterial isolate panels of pathogens of national medical concern (representing more than 160 total pathogens), provides a valuable resource to biotech and diagnostic groups in researching, designing, validating and evaluating next generation clinical tests. These tests in turn may support earlier diagnosis and development of more effective treatment options that can slow antibiotic resistance. As of January 2018, the AR Isolate Bank shipped more than 2,000 isolate panels.

There are still regulatory science gaps that can challenge development programs, however, such as a lack of animal models to support medical countermeasure development or insufficient biomarkers to enable the extrapolation of data generated in animal models to humans. Without such tools, it is difficult to generate the data necessary to support regulatory decision making. Given the urgency inherent in our medical countermeasure work, addressing these regulatory science gaps remains a high priority for the Agency.

To that end, FDA has established a broad and robust portfolio of cutting-edge research under the MCMi Regulatory Science Program to help develop these tools and promote

² A QIDP is defined as an antibacterial or antifungal drug for human use intended to treat serious or life-threatening infections, including those caused by an antibacterial or antifungal resistant pathogen, including novel or emerging infectious pathogens.

innovation in the development of medical countermeasures. A few examples of projects include: supporting the development of “organ-on-a chip” models to assess radiation damage in lung, gut, and bone marrow, and then using these models to test candidate medical countermeasures; collaborating to establish a publicly-available genomic sequence reference database for use by developers seeking to validate candidate multiplex *in vitro* diagnostic tests that could be used to diagnose multiple pathogens simultaneously (FDA-ARGOS); developing reference materials for developers to use to validate nucleic acid-based and serological diagnostic tests for Zika virus; supporting a project to identify and correlate biomarkers of host response to Ebola virus infection in animal models and humans to support medical countermeasure development; developing methods for obtaining safety and limited efficacy data from patients who receive medical countermeasures during public health emergencies; and establishing the Animal Model Qualification Program designed to support medical countermeasure development by promoting the development of animal models for use across multiple product applications, thereby minimizing duplication of effort and resources.

FDA is acutely aware that biothreats can also emerge from accidental release or exposure to threat agents during the course of conducting research. As such, the Agency works to ensure that its laboratories and workplaces are operated in a safe and secure manner to protect employees, the surrounding communities, and the environment. This includes ensuring that FDA is in compliance with the Select Agent Regulations as well as with Federal, state, and local occupational safety and health requirements (as appropriate), and environmental regulations.

FDA also works to establish and sustain an adequate supply of medical countermeasures. For example, FDA supports the Shelf Life Extension Program (SLEP), a Federal fee-for-service program, for extending the useful shelf life of military-significant and contingency-use medical products, including medical countermeasures that are owned by components of DoD or other Federal program participants, such as the Strategic National Stockpile (SNS).³ FDA laboratory personnel test and evaluate drugs submitted for shelf-life extension to ensure stability and quality before a shelf-life extension is approved.

In addition, FDA works to ensure that the U.S. Government is as prepared as possible to rapidly deploy medical countermeasures when necessary. For example, FDA has worked with government partners to prepare for potential EUA authorization of stockpiled medical countermeasures against a diverse array of threats including smallpox, anthrax, and pandemic influenza.⁴

There are tremendous opportunities to continue to further the development of groundbreaking, innovative medical countermeasures, and the Agency intends to fully seize, and build upon, these opportunities.

³ SLEP is designed to defer drug replacement costs for date-sensitive stockpiles of drugs by extending their useful shelf life beyond the manufacturer’s original expiration date.

⁴ To facilitate the issuance of EUAs, FDA has developed a pre-EUA submission process. FDA works with product sponsors or government agencies, such as CDC and DoD, to develop pre-EUA packages that will form the basis of an EUA request and decision, when circumstances justify. Pre-EUA packages contain data and information about the safety and efficacy of the product, its intended use under an EUA, and information about the potential emergency situation that might unfold.

Responding to Threats

When threats emerge, FDA works proactively with U.S. government partners, medical product developers, and, as necessary, international partners (including the World Health Organization (WHO) and international regulatory counterparts) to respond. Key FDA response activities include accelerating the development of investigational medical countermeasures, when needed, by working with U.S. government agencies that support medical countermeasure development and medical product sponsors to clarify regulatory and data requirements. For example, FDA continues to work closely with U.S. government agencies, the international community, and product developers—providing regulatory advice, guidance, and technical assistance—to advance the development and availability of medical products, including vaccines and therapies, to address Ebola virus and Zika virus. These activities are essential not only for advancing the development of investigational medical countermeasures to respond to ongoing outbreak and epidemics, but also to improve response to future outbreaks and epidemics. For example, FDA worked closely with NIH in response to the 2014 Ebola epidemic in West Africa to design an innovative and robust common clinical trial protocol to evaluate the most promising investigational products for Ebola. The experience and information gained from those efforts have been instrumental in supporting a rapid response to the recent Ebola outbreak in the DRC.

FDA also works to protect the safety of the nation's blood supply and human cells, tissues, and cellular/tissue-based products for transplantation when threats emerge. For example, FDA worked closely with developers to make rapidly available two investigational tests for blood screening for Zika virus. One of those tests has since been approved.

Another key FDA response activity to emerging threats is to enable access to investigational medical countermeasures, when necessary, through an appropriate mechanism such as under an investigational new drug (IND) application, an Emergency Use Authorization (EUA), or under expanded access mechanisms when the clinical circumstances warrant. Enabling access to available medical countermeasures in response to emerging threats is a high priority for FDA and FDA uses its authorities to the fullest to help protect public health. For example, since 2013, FDA has issued nearly 40 EUAs to enable the emergency use of in-vitro diagnostic devices for H7N9 Influenza virus, Enterovirus D68 (EV-D68), Middle East Respiratory Syndrome Coronavirus (MERS-CoV), Ebola virus, and Zika virus.

FDA also works to protect consumers against fraudulent products claiming to prevent, treat or cure conditions associated with emerging threats.

Throughout these response activities, FDA works to establish and maintain good lines of communication with WHO and regulatory authorities in affected countries, as necessary, to enable technical and information exchange, and to make sure that the needs of the affected countries are understood and addressed.

Conclusion

At FDA, we have made it a priority to proactively work with our private sector and government partners to help facilitate the translation of discoveries in science and technology

into safe and effective medical countermeasures. FDA takes seriously its responsibility to help drive and foster innovation as part of advancing public health and strengthening our national security.

Active FDA involvement is essential to encouraging industry engagement in medical countermeasure development. Working closely with its partners and exercising the authorities Congress provides to the fullest extent, FDA remains deeply committed to protecting and promoting public health, both domestically and abroad, in response to public health threats.

FDA appreciates Congress's support in continually optimizing its authorities, and providing resources, to enable FDA to achieve its public health emergency preparedness and response mission. FDA stands ready to work with Congress and stakeholders to enable us to better achieve this critical work in our mission to protect the American people.

Thank you for inviting me to testify today. I look forward to answering any questions you may have.

* * *

Mr. HARPER. Thank you very much.

I ask unanimous consent that the contents of the document binder be introduced into the record and to authorize staff to make any appropriate redactions. Without objection, the documents will be entered into the record with any redactions that staff determines are appropriate.

It is now time for members to have the opportunity to ask you questions, and I will recognize myself for 5 minutes.

Let me begin by saying that in my 10 years of service in Congress, I don't know if I've ever been at a committee hearing with a better lineup of witnesses. And so thank you all for being here. We look forward to your responses today.

And this is a question that will go rather quickly for all of you. And for each witness, which biological threat is of greatest concern to you and why? Let's start with Dr. Bright and then go down.

Mr. BRIGHT. That's a difficult question. As Dr. Fauci has laid out, there are so many threats. They're constantly emerging. And I wish I could take some of them off the table, but they keep coming at us. And even more concerning is technology advancing so much that they can change the biological threats that we know today into something different that we may not be prepared for.

I think our greatest threat for any of those is our response capabilities and being able to respond to anything that comes our way.

Mr. HARPER. Dr. Schuchat, is there one biological threat that is at the top of your list? I know they're all important, but is there one that gives you the greatest concern?

Dr. SCHUCHAT. I think influenza needs to be at the top of my list. It can affect everyone rapidly and is constantly changing. And with pandemics, all of the population of the world can be susceptible. So the threat of a pandemic has to be at the top of the list, because it can all happen fast.

Mr. HARPER. Dr. Fauci.

Dr. FAUCI. My number one and maybe number two and number three is influenza also. I agree, for the reasons that Dr. Schuchat has mentioned.

When you have a respiratory virus that can be spread by droplets and aerosol, and then you have the situation if there's a degree of morbidity associated with that, you can have a catastrophe. We've experienced in real world those types of things. The one that we always talk about is the 1918 pandemic which killed between 50 and 100 million people.

It is likely that it would be an influenza, but if not influenza, an influenza-like respiratory virus. We had a scare with SARS. Fortunately, public health measures were able to contain it, but influenza first or something like influenza is the one that keeps me up at night.

Mr. HARPER. Admiral Hinton.

Admiral HINTON. Thank you for the question. I would say the threat that would keep me up at night would be the unknown. If we don't know what that threat may be, we have to be able to anticipate. So with the emerging spectrum of diseases, it would be the unknown that would keep me up at night.

Mr. HARPER. Thank you.

For each witness, what area of biopreparedness is of the highest priority and why? Dr. Bright.

Mr. BRIGHT. The area of biopreparedness of the highest priority would be the ability to rapidly detect something that has entered our community or has been used as a weapon. The sooner we detect something, the sooner we can turn on the machinery and call in the capabilities to begin making vaccines and drugs.

Mr. HARPER. Dr. Schuchat.

Dr. SCHUCHAT. I would say our global health security would be at the top of my list, because, as you know, a threat anywhere is a threat everywhere. And I think our greatest vulnerabilities are in the weakest countries of the world.

We saw in Ebola how rapidly West African countries were overwhelmed, and that was an issue for us as well. So I think being able to strengthen the ability of every country to be able to prevent, detect, and respond to threats is where I'd place my focus.

Mr. HARPER. Dr. Fauci.

Dr. FAUCI. I would agree with those two. But let me add an additional one that may not necessarily be my first, is in our ability to respond, for example, with a vaccine, the modern day 21st century technologies of platform technology, where you don't have to wait 6 to 7 months to get a vaccine, where you can really get it out there within a period of a couple of months, which is doable if we put our mind and our resources to it.

Mr. HARPER. Thank you.

Admiral Hinton.

Admiral HINTON. Our continued efforts in the Ebola, and then making sure that we contain it within the specific regions and not letting it cross the borders.

Mr. HARPER. Thank you.

Dr. Bright, if I could ask you, obviously, the need to rapidly respond to a biological threat is essential. Does the public health system have the capability to deliver and administer medical countermeasures rapidly and effectively in a timely manner as you sit there today?

Mr. BRIGHT. As we sit here today, we are much better and can respond much more quickly than we were in the past 10 years. We've built a national response capability and an international capability incorporating new sciences and technologies. There is a lot of room for improvement. It still takes too long to respond to respond adequately to protect everyone in our nation.

Mr. HARPER. Thank you very much.

I will now recognize the ranking member, Ms. DeGette, for 5 minutes for her questions.

Ms. DEGETTE. Thank you very much.

Well, building on the question by the chairman just now, Dr. Bright, what changes do we need to make to make the system for developing countermeasures work more effectively and efficiently? ASPR has been a good start, but, you know, where do we need to go?

Mr. BRIGHT. Well, given the 12 years' experience with ASPR and the enterprise, working across government and working with our public-private partnerships, we've learned a lot in the past 12 years. Not everything is working as effectively or efficiently——

Ms. DEGETTE. So what do we need to do?

Mr. BRIGHT. We need to improve our communications and our transparency and how we bridge our different agencies and bridge government with industry. We need to ensure there's consistency in funding and availability so the partners that we work with can better align their business models with our government models as well. And we need to improve the efficiency at which we communicate and respond to proposals and other contractual mechanisms that we use to work with our industry partners.

Ms. DEGETTE. Are efforts underway being made to do all of those things?

Mr. BRIGHT. Yes, efforts are underway.

Ms. DEGETTE. And is there something Congress can do to help you?

Mr. BRIGHT. Congress has been very generous with the authorities to date. There are things that we can do to improve our language in our other transactional authorities to be able to work more fluidly and flexibly with our industry partners, and we would be happy to submit language to assist in that.

Ms. DEGETTE. We would be delighted to have that language. That would really help.

Dr. Fauci, none of these hearings can go without me asking you about what's going on with pandemic flu. And you had said that we are getting closer to being able to develop a universal vaccine. And you've said that before, because you've been trying to do it for a long time.

What does your timeframe look like now and what are the barriers?

Dr. FAUCI. Congresswoman DeGette, the timeframe really varies about the level that you're talking about. There's not going to be one home run universal flu vaccine. There will be various iterations.

So I would say the timeframe. And I know every time when asked about a timeframe, people back off, and I don't want to get in court to be able to say something that's not going to be able to deliver. But since we spoke last, we have put into a Phase 2 trial a universal flu vaccine with a company called BiondVax, which is a multiple peptide prime followed by a killed vaccine boost.

Being in a Phase 2 trial means that you're another step closer to getting a product that you'll be able to use.

Ms. DEGETTE. Right.

Dr. FAUCI. So I would think that if you——

Ms. DEGETTE. How long is this trial going on for?

Dr. FAUCI. The trial will probably take—it's a Phase 2 trial, so that probably is going to take at least a year to determine if this induces the kind of response that you would predict would have some broad protection.

The first iteration of a universal flu vaccine is not going to be against all flu, absolutely. What we're hoping for is that the first iteration will cover, for example, all of a particular type, like all of the H3N2s. If we get that successful, then maybe all of the H1N1s.

There are two major groups of influenzas. The ultimate perfect one would be one that covers all of them. I think that's years and years and years away, but the first iteration may be 5 or so years away.

Ms. DEGETTE. And I'll ask you the same question I asked Dr. Bright. What can Congress do to help you?

Dr. FAUCI. I think Congress has been extraordinary in their positive effect on us in helping us. For example, in the 2018 omnibus, we were given an additional \$40 million to develop a universal flu vaccine, and we're getting additional money in the proposal of the House for our 2019 budget. So you've been very supportive and we really appreciate it.

Ms. DEGETTE. We think it's a high priority. I think I can speak for everybody in this room.

One more question. You're developing lots of different vaccines: smallpox, flu, anthrax, Ebola. How do you prioritize your efforts to target the pathogens and toxins that provide the greatest risk?

Dr. FAUCI. That's a very good question. We do two things, Congressman. We target specific pathogens based on the threat. If you're talking about a bioterror threat, it's the intelligence that we get. And if you're talking about the possibility of an emerging infection, it's very difficult to guess what's going to come out.

Ms. DEGETTE. Right.

Dr. FAUCI. So we know, and it was mentioned in one of the opening statements, that H7N9, for example, if you look at the CDC chart, it's way up there as a threat. So we clearly made an investment of a considerable amount of money to develop a vaccine for that.

But as I mentioned in answer to one of the other questions, it's to develop platform technologies that's applicable to any disease, as opposed to picking out all the diseases and preemptively making a vaccine. In other words, making a kind of a vaccine that you could easily apply to whatever is the outbreak.

Ms. DEGETTE. Thank you. Thank you, Mr. Chairman.

Mr. HARPER. The gentlewoman yields back.

The chair will now recognize Dr. Burgess for 5 minutes.

Mr. BURGESS. Thank you, Mr. Chairman, and thanks to our panel for being here today.

Dr. Fauci, I wasn't going to do it, but you brought it up. And you said sometimes you'll give a timeframe, and then if it doesn't work out, then people will point that out to you. A couple of years ago, I think you gave us an 18-month figure on a Zika virus vaccine. How close are we today?

Dr. FAUCI. Thank you for that question. So when you're proving that a vaccine works or not, in the classical way, you have to get what's called an efficacy signal. There has to be infections in the community to get an efficacy signal.

Right now, thankfully for the countries involved, the Zika infections have plummeted almost to very, very few. However, the Phase IIb trial that I spoke to you about some months ago is still ongoing, and it's accruing volunteers in the study. So there's an interesting possibility here.

Let's say there are not enough Zika cases to be able to get an efficacy signal. We have been in discussions, with a lot of help from the FDA, about the possibility that if we get a

considerable amount, and I say thousands of volunteers with safety data, immunogenicity data, namely inducing the kind of response that you would predict would be protective, and you bridge it to the animal studies, there's a possibility that they would at least consider that there would be an accelerated approval. You never can guarantee anything, but that's at least on the table.

So my short answer to your question, Congressman Burgess, is that we are on the road to getting a Zika vaccine, and I feel pretty confident about that.

Mr. BURGESS. And from the FDA's perspective, that expedited approval that was talked about, is that something we can look for?

Dr. FAUCI. Well, I'll let the FDA speak for themselves, but you never want to anticipate what they're going to do. You can just give them the data and the information that they ask for, but—

Mr. BURGESS. I may submit that in writing, because I do want to ask you about another—on the golly gee whiz slide that you put up with all of the things that can happen to us, enterovirus D68 was included on that list.

Dr. FAUCI. Yes.

Mr. BURGESS. And CDC has put out a paper on acute flaccid myelitis and the incidence of that. And I recognize that it's low, but it does seem to peak every other August. So as we are coming up on one of those every other Augusts, do we know any more about this illness and why it has had the effect that it has?

Dr. SCHUCHAT. Yes. The outbreak of severe respiratory disease in children from the enterovirus D68 a few years ago was of concern. It was contemporary with the outbreak of acute flaccid myelitis. Very difficult to confirm that one caused the other, but there's a good probability that they did.

The family of enteroviruses are known to be able to cause neuropathic problems. And when you have a very common set of infections, it could be that that was a real rare end of the spectrum among the common ones.

So I think we do need to be ready for that. Unfortunately, there are so many different enteroviruses that it's very difficult to pick one that you would necessarily focus on for countermeasure development. There's some work on antivirals that might be promising as having a broader protection, but that's the state of it right now.

Mr. BURGESS. As you'll recall, fairly frightening when that did occur, the concern we heard from parents.

Dr. SCHUCHAT. Exactly. It was happening the same time as Ebola in Africa. When the President visited CDC, he was briefed on Ebola and on enterovirus D68.

Mr. BURGESS. Admiral Hinton, let me ask you. When Ebola was really a much more significant problem, September of 2014, the monoclonal antibody ZMapp was in trials, and then FDA put a clinical hold on it. My understanding at the time, there was a Herxheimer-type reaction that was fairly severe and so we stopped looking at it.

Is there a way—when we've got a problem of that order of magnitude going on, I guess I want some reassurance that the regulatory side is not going to interfere with the delivery of what may be a very potent tool, because several people have mentioned ZMapp. I mean, it's now a recognized tool in the toolbox. Is that correct?

Admiral HINTON. That's correct. And Dr. Fauci can please feel free to add in, but that is correct. And the FDA is not there to be a roadblock; it's to ensure that the drugs are safe and efficacious. So the reasons behind that may not be privy to us, but we do make sure that we

have safe and effective available drugs on the market to treat these and in emergency situations as well.

Dr. Fauci.

Dr. FAUCI. So ZMapp was part of a randomized controlled trial that was run by the NIH. It was published in *The New England Journal of Medicine*. The results, because of the diminution of cases at the time, were very strongly suggestive of efficacy, but not enough to be statistically significant. So the trial is technically still on. And right now, in DRC, they could use ZMapp either on a trial or, if they want, as compassionate use. But it is available.

Mr. BURGESS. It is available. Thank you all very much. Thanks for your testimony this morning.

Mr. HARPER. The gentleman yields back, who also serves as the chair of our Health Subcommittee.

Mr. BURGESS. Mr. Chairman, I'm also going to ask unanimous consent to place into the record the report of the Independent Panel of the United States Department of Health and Human Services to the Ebola response from 2015.

Mr. HARPER. Without objection, so entered.

[The information has been retained in committee files and can be found at <https://docs.house.gov/meetings/IF/IF02/20180615/108422/HHRG-115-IF02-20180615-SD003.pdf>.]

Mr. HARPER. The chair now recognizes the gentlewoman from Illinois, Ms. Schakowsky, for 5 minutes.

Ms. SCHAKOWSKY. Thank you, Mr. Chairman. I want to agree with you, Mr. Chairman, that this is an extraordinary panel.

Dr. Fauci, 33 years before this committee, that's a long time, and we appreciate you every time we see you.

I also want Dr.—I looked this up. Dr. Schuchat, it looks like you're about 28 years. Is it more than that? How many?

Dr. SCHUCHAT. It's 30 in July.

Ms. SCHAKOWSKY. OK, 30 in July. And such experience in all of you. It's just really remarkable. I thank all of you for being here today.

I'm particularly concerned about the improper and overuse of antibiotics that's driving the growth of antibiotic resistance around the world. I noticed, Dr. Fauci, in your new map with all the lines, right at the top was antibiotic resistance on the left there.

I feel an obligation to raise this issue too for my sister and colleague, the late Louise Slaughter, who was always raising this issue. In the United States, somewhere between 20 and 50 percent of all antibiotic prescriptions in hospitals are either unnecessary or inappropriate. Evidence suggests that antibiotic stewardship programs in hospitals can improve prescribing practices and help reduce the occurrence of antibiotic resistance.

So I'm interested in hearing more from our witnesses on this program. Whoever wants to go first. Dr. Schuchat.

Dr. SCHUCHAT. Yes. The problem with antimicrobial resistance is a transformational challenge for us because it obviously threatens modern medicine. CDC has been investing in efforts to improve stewardship of antibiotics, and at this point, by our latest data, two out of three hospitals had an antibiotic stewardship program, which is a big increase from before. But we think that there's much more to be done.

In addition, we have 850 hospitals around the country are reporting on their antibiotic use data to the National Healthcare Safety Network. So we're tracking data.

What we find in the healthcare system is when you track antibiotic use and feed back to clinicians how they're doing, they can improve. A lot of clinicians are test takers, and we like to do really well on those tests. And so learning that we're not doing as well as our peers in terms of the appropriateness of our prescribing can help improve that.

We're also tracking resistance. And we've really invested, thanks to the congressional support, we've been able to invest in much better timely, accurate, quality antimicrobial resistance detection around the Nation. It's where we got those nightmare bacteria reports that we came out with recently.

So I would say that behavior change in clinicians is difficult, but we're making progress. And a stewardship program in every hospital is a good start, but it takes more than the hospital to make that happen. We need the whole plans, the outpatient prescribers as well, to be part of the system.

Ms. SCHAKOWSKY. But you're saying that we do have a tracking system now for clinicians, for hospitals?

Dr. SCHUCHAT. Right. In our National Healthcare Safety Network, I'm told that 850 hospitals are already reporting to us on their antibiotic use. It includes 80 VA hospitals and 30 military hospitals. And they're having that be part of their—it's voluntary, but it's part of their ability to monitor what's going on in their own institution and then look across institutions.

Ms. SCHAKOWSKY. What percentage of hospitals does that represent, do you know?

Dr. SCHUCHAT. I don't actually have that information, but we could get that for you.

Ms. SCHAKOWSKY. OK. Has the CDC identified any obstacles to successfully implementing stewardship programs? If so, how are you addressing those?

Dr. SCHUCHAT. I would say that incorporating the outpatient facilities in the stewardship is important. We also found that rural areas, critical areas, we're challenged in being able to do all the things that we recommend in terms of antibiotic stewardship.

Our program convened a batch of the rural or critical area hospital stewardship leads, who had figured out ways to make a difference, and we're working with them to share their best practices more broadly. So I would say that large hospitals are really on the case now, and helping the smaller facilities get up to speed is important.

Ms. SCHAKOWSKY. Thank you. In the remaining seconds, does anybody else——

Dr. FAUCI. Yes. How we address antibiotic resistance is really governmentwide, and it's a program called CARB, Combating Antibiotic-Resistant Bacteria, that was established years ago, a few years ago, that involves what Dr. Schuchat had mentioned regarding the CDC. It involves the FDA research component from the NIH to develop new drugs to understand the mechanisms of resistance to harness the immune system, but also an organization called CARB-X, which BARDA has a major role in.

So maybe, Rick, you want to just mention that briefly.

Mr. BRIGHT. Very briefly. So since 2010, BARDA has invested over a billion dollars in addressing the development of new antibiotics to address antimicrobial resistance. We have, just in the last year, had the first antibiotic drug licensed in our program. We have several more in Phase 2 and Phase 3.

We also realized that the early stage pipeline was not sufficient to have a stream of new candidates going into advanced stage development. So we did launch a public-private

partnership called CARB-X, in collaboration with NIAID, also sponsored by Wellcome Trust, now Bill and Melinda Gates Foundation in the U.K. Government. So we have now funded 34 different novel technologies to address new mechanisms of action for new antibiotics and vaccines.

Ms. SCHAKOWSKY. Thank you. My time is up, but I hope that in addition to development, that we're looking at prevention here as well.

Thank you for your courtesy, Mr. Chairman. Thank you.

Mr. HARPER. Thank you. The gentlewoman yields back.

The chair will now recognize the chair of the House Ethics Committee and a valuable member of this subcommittee, the gentlewoman from Indiana, Mrs. Brooks, for 5 minutes.

Mrs. BROOKS. Thank you, Mr. Chairman.

Dr. Schuchat, and if, Rear Admiral Hinton, if you could pass that binder, please, over to Dr. Schuchat. The last page of that binder has a chart that I would like to enter into the record and ask unanimous consent to enter into the record. It's PHEMCE's budget report for fiscal year 2016–2020.

Mr. HARPER. Without objection.

[The information appears at the conclusion of the hearing.]

Mrs. BROOKS. A large percentage of the CDC's Strategic National Stockpile budget appears to not go to procuring and updating medical countermeasures for the stockpile, but instead, goes to a category entitled nonprocurement costs. And in an effort to inform the discussion today, committee staff did ask CDC to provide a breakdown for what is in this nonprocurement, but we never got it.

Can you please share with us very briefly, and you might need to supplement with written response, what makes up the non-procurement spending for the Strategic National Stockpile?

Dr. SCHUCHAT. Thanks so much for your question. As you know, the Strategic National Stockpile has an inventory of about \$7 billion. So the annual appropriation is just a piece of that. Most of the dollars that are in the nonprocurement go for sustaining and operating. So that would be the rental space, the security for the warehouses, the staff that work, the salaries for the staff, as well as the clinical expertise that's helping with the guidance on how to use the product.

Mrs. BROOKS. Thank you. Could we get a written breakdown of what that is?

Dr. SCHUCHAT. Absolutely.

Mrs. BROOKS. Because we could not tell what that was.

Dr. SCHUCHAT. That should be on its way to you.

Mrs. BROOKS. Thank you very much.

Dr. Bright, last year, HHS OIG issued a report after conducting five site audits at the various Strategic National Stockpile locations over a 2-year period, and they talked about systemic issues, putting that \$7 billion that was just mentioned into great concern.

So, Dr. Bright, what actions does ASPR plan to take in the transfer that is anticipated October 1 to ensure the Strategic National Stockpile assets will be available in case of public health emergencies?

Mr. BRIGHT. As you probably know, we have several working groups working very closely between CDC and ASPR to evaluate various components of the stockpile transfer. So we are still——

Mrs. BROOKS. Can I interrupt one second? We just heard, in her opening testimony, Dr. Schuchat talk about all the many things CDC does relative to public health and these

emergencies. And so are you going through all of those things to make sure there is coordination? And is that what the working groups are actually doing, figuring out what part CDC is going to maintain and what part ASPR will have? Is that what the working groups are doing?

Mr. BRIGHT. Absolutely. There's five different working groups. They're meeting weekly actually, and some of them have daily communications, to understand the various components, understanding how we maintain and sustain the best science and expertise that's currently in the SNS, understanding how we're building and augmenting the relationship with States and locals to ensure that that is also maintained for a robust SNS enterprise. We're also looking at the contracting and the financing. We're looking at the non-procurement cost as well.

We assure you that we are doing everything we can to make sure that those nonprocurement costs are supporting the SNS and its mission.

Mrs. BROOKS. I have a question with respect to—I understand there have been instances where BARDA—and you mentioned it—had to use Project BioShield funds to procure FDA-approved clinical countermeasures or medical countermeasures, because, for whatever reason, CDC declined to procure those countermeasures for the stockpile.

How does that uncertainty affect BARDA's ability to partner with industry, and is that being addressed in your working groups?

Mr. BRIGHT. That uncertainty is critical. As you know, it's very difficult to make these countermeasures. It's very lengthy, very risky, and the companies put aside other very profitable and successful endeavors to work with us in these areas. That marketplace assurance is absolutely essential to them working with us.

So we realize that, as we've been more successful with our partners and making additional countermeasures, it has created an additional burden on the SNS. We are working with the SNS at the CDC and our internal staff now to make sure that we are able to address those lapses or those gaps in communication or transparency to make sure that we have a successful——

Mrs. BROOKS. Thank you. I'd also like to enter into the record a letter from the Blue Ribbon Study Panel on Biodefense that was sent to Dr. Kadlec with a very detailed seven recommendations to improve our biodefense posture.

Mr. HARPER. Without objection.

[The information appears at the conclusion of the hearing.]

Mrs. BROOKS. And among those was the need to improve the coordination with State and local partners and to address problems that have existed in the past.

Can you tell us how ASPR plans to engage with State and local partners once it assumes control of the stockpile, which is of great concern to State and local partners?

Mr. BRIGHT. I agree that it is an essential part of an effective enterprise, the end-to-end approach, from early detection down to distribution. The State and local and tribal and territorial partners are the front line. They are the ones who are distributing and administering the vaccines and treatments. So we are dedicated to working with them, making sure they have a voice in the structure, in our system, to understand how they need those medical countermeasures and how they need them to be delivered most effectively.

It doesn't do us any good to make new drugs and vaccines if they're not suitable for our frontline workers at the State and local and tribal and territories to deliver and administer those.

Mrs. BROOKS. And so they know how to deliver and administer.

Mr. BRIGHT. Absolutely.

Mrs. BROOKS. Thank you. With that, I yield back. Thank you for your time.

Mr. HARPER. The gentlewoman yields back.

The chair will now recognize the gentlewoman from Florida, Ms. Castor, for 5 minutes.

Ms. CASTOR. Thank you, Mr. Chairman.

Good morning. Last year, Florida recorded 262 known cases of Zika. They were overwhelmingly travel-related cases, but of those known cases, 136 were pregnant women, and three babies were born in Florida with congenital Zika syndrome. Thankfully, those statistics are down substantially from 2015 and 2016, but the threat to young women of childbearing years and families remains very serious.

A study was just published where researchers from the CDC and the Annenberg Public Policy Center determined that most people have let their guard down now, that they're not taking the precautions that they should when it comes to Zika.

So, Dr. Schuchat, now that you have the results of that study and the threat of congenital Zika syndrome remains very serious, what do you plan to do to help keep families informed and make sure they're taking all precautions?

Dr. SCHUCHAT. Thank you. Zika was such a devastating new problem to have. For a mosquito bite to be able to cause birth defects, not something that was on any of our radars, really.

I think you know that, in May, we issued one of our monthly high-visibility reports of vital signs on mosquito and tick-borne diseases, which have really been increasing, trying to get that word out in advance of the mosquito season so people would take these threats seriously.

We have another report that's focused on Zika that will be coming out in about 2 months, really highlighting what have we learned from the, unfortunately, thousands of pregnancies that were complicated by Zika in folks who reside in the 50 States, to show what the followups have been and what has happened to the babies as they develop.

We need to make mosquito protection much easier for individuals and we need to have better tools for countering mosquitoes, in terms of environmentally safe and acceptable tools for them. We have been appreciative of the investments in strengthening our vector control so that there's better surveillance for vector-borne disease, and also better understanding of resistance patterns so we have the right products that can be used.

Ms. CASTOR. And there must be more we can do to communicate to young women and young men, especially now that—I mean, it was very strange that Zika became transferable via sex as well. So——

Dr. SCHUCHAT. Yes. The signs are still up in the airports, but people turn them off. So I think continuing to raise concerns is a challenge when people become complacent. So it's sort of our perpetual challenge in prevention.

Ms. CASTOR. Thank you.

Responding to public health emergencies requires us to have a good understanding of what is happening on the ground in real time. And doctors and nurses and others who work directly with patients are likely to be the first to interact with individuals affected in a public health emergency.

How does CDC gather data from these clinicians to detect emerging illnesses and other threats?

Dr. SCHUCHAT. We have a variety of surveillance systems to try to identify both the known threats and then the unknown or the new unusual clusters. Most important is for there to be a close connection between the clinical community, the doctors and nurses on the front line, and their local and State public health authorities.

The first cases of West Nile virus disease in New York City were detected, there were some animal losses, but it was that link between clinicians and the local health department. So part of our day-to-day everyday public health system is vital for the unknown emerging——

Ms. CASTOR. And CDC has a Laboratory Response Network that plays a vital role in biopreparedness by ensuring that we are able to quickly diagnose public health threats using rapid testing methods known as assays, but I understand that right now, there are no assay kits or rapid tests available for many dangerous pathogens and toxins.

What is going on here, and what are the barriers to developing assays targeting a wide variety of pathogens and toxins?

Dr. SCHUCHAT. Yes. What I would say is that the Laboratory Response Network, or LRN, is a group of 125 hospitals around the— or laboratories around the country that are within a 2-hour drive of 85 percent of all of the population. They are equipped to use validated, standardized assays to detect a variety of conditions.

The CDC has the ability to detect and confirm a longer list of the select agents and dangerous pathogens, and we prioritize which of the detection methods or assays need to be deployed close to where people live, which ones can be deployed and maintained centrally, because it's quite expensive to have the standards high enough to be able to reproduce the results in all of the 125 hospitals.

So while there's 45 select agents, we have assays for nearly all of them. Many of those are managed at the CDC or at Regional Centers of Excellence, while the 125 laboratories can test for the things that we think are the most likely, including things like MERS, where we rolled out an emergency use authorization for a new diagnostic test for that, Ebola, et cetera, the H1N1 initially. So we try to deploy distally the assays for the threats that are the most important to have local ability to detect rapidly.

Mr. BRIGHT. If I can add just a second on that too. That is another area of innovation that BARDA has been focusing on with our industry partners is to drive diagnostics, not only out of centralized labs to augment that centralized laboratory network, but put the diagnostics in the hands of the physicians in the physician's office at point-of-care testing. And even go further now, to drive diagnostics into the home, so people will know earlier when they've been infected with something so they can take responsible action to either get treated sooner when drugs are more effective and also to take activities to reduce the further spread or transmission of that virus. This area is ripe for innovation to augment our national laboratory support system.

Ms. CASTOR. Thank you very much.

Mr. HARPER. The gentlewoman yields back.

The chair now recognizes the gentleman from New York, Mr. Collins, for 5 minutes.

Mr. COLLINS. Thank you, Mr. Chairman.

I want to thank our witnesses and follow up a little bit more on the Laboratory Response Network, Dr. Schuchat. I understand that's been around about 9 years or thereabouts, since I think 1999?

Dr. SCHUCHAT. Yes, since 1999.

Mr. COLLINS. Actually, I've lost 10 years. Twenty years. I deliberately lost those 10 years, by the way.

So I know you mentioned 125 labs here in the country, but this is, from what I understand also, there's international labs. We all know the key to a lot of this is early detection, whether it was Ebola or some other things, SARS, which initially people thought they had the flu, even anthrax. But early detection's the key to jumping on top of this, which means the laboratories that are located outside the country. And I know this is a collaborative effort.

Are you, let's use the word "comfortable," and how is that collaboration between the United States and other countries around the world—as you mentioned, in many cases, these could be in Africa and other places—for the ability to identify these select agents?

Dr. SCHUCHAT. The Laboratory Response Network is in other countries as well, but I would say there's other means, other laboratories that we collaborate with around the world to help have that rapid detection and response. And actually, that's really what the global health security agenda is about, making sure that there are abilities to find, stop, and prevent epidemics wherever they occur, natural or not.

And the international collaboration, I think, is strengthened by the daily links we have in partnership on other threats. As you heard, we're working on Ebola in DRC right now. The Nipah virus detection in India was based on training that CDC had given to the laboratory in India years before so that India could recognize that pathogen themselves without having to take the time to ship the specimens out of the country.

Mr. COLLINS. So, following up on that, what I would call proficiency testing that we do for all of our labs, whether it's on influenza or HIV or any of the STDs, I'm assuming there's also a proficiency testing program related to our LRNs, which is always maybe a little more complicated because the 45 select agents are not nearly as prevalent as influenza. But can you speak to the proficiency program, how often these laboratories are tested, their workers, how their grades are, so that, in fact, we're comfortable that, if there is an outbreak, they're properly identifying it?

Dr. SCHUCHAT. Yes. The proficiency testing and assuring the quality of the laboratory test is vital. That's one of the reasons that we don't have assays for every one of the select agents in each of the LRN labs, because we want to certify that lab for that test and make sure that they maintain their reagents adequately and that everyone who's working on that test is doing it the right way. So we really try to prioritize which assays will be run regularly in every lab, because we do have to make sure that year in and year out, they're getting the accurate results. Otherwise, it makes no sense to run the test.

Mr. COLLINS. Is that done yearly, more than yearly? How often is that done? And does the CDC conduct the proficiency tests themselves or do you use outside agencies like CAP or someone like that?

Dr. SCHUCHAT. Let me get the details on that for the committee in followup, because I don't have all of them myself.

Mr. COLLINS. OK. Thank you. I think that's an important piece. In the remaining time, Admiral Hinton, egg-based versus cell-based vaccines, could you comment? YIs the FDA looking at—as we're moving forward certainly through our influenza season, are you making progress on the cell-based? Are you seeing positive potential there?

Admiral HINTON. Absolutely. And we actually have both. We have the egg-based versus the cell-based vaccines available, and continue to do evaluation and work in that area. But both are available, both are promising.

Mr. COLLINS. Because, there's always been some folks—if anyone else would like to comment on potential problems with the egg-based. Are we seeing positive steps in the other or——

Admiral HINTON. We are seeing positive steps in the other direction. And then as far as the egg-based, I know we run into issues with people having allergens and the like to them and not being able to have them. So having different options there to be able to provide and treat people with is promising and is available.

Mr. HARPER. Dr. Fauci.

Dr. FAUCI. There are other problems with egg-based, which is the reason why we're really trying to get away from egg-based and get more towards more advanced platform technologies.

One of the accidental mismatches that we had in 2016–2017, particularly in Australia, was that the virus was chosen for the vaccine, was put into eggs, and as it mutated in the eggs as it was growing, it mutated so that the virus that came out of the eggs was not the virus that you put into the egg. So we had an accidental mismatch.

That doesn't happen all the time by any means, but the idea of having to grow a virus in a 6-month process is something that we really need to, as I often say, graduate into the 21st century and do it a little bit better with more advanced technologies.

Mr. COLLINS. Thank you for that. Mr. Chair, I yield back.

Mr. HARPER. The chair is going to allow Dr. Bright to finish his response that he wanted to make here quickly.

Mr. BRIGHT. Thank you very much. I'd like to add just a little bit more to that as well. It's very important to understand the need for diversified vaccine production systems for influenza. Influenza's a tricky virus. Eggs have been a reliable vaccine substrate for a number of years. We are working to find ways to not only diversify and augment our cell-based and recombinant-based influenza vaccines, but also to improve egg-based vaccines. It's important not to completely discard a reliable technology without having a modernized technology to replace that. So we are working with each of the manufacturers now to identify ways to make our flu vaccines more effective now while we wait for that universal flu vaccine candidate in the future.

Mr. HARPER. The chair will now recognize the gentleman from California, Mr. Ruiz, for 5 minutes.

Mr. RUIZ. Thank you, Mr. Chairman.

Emerging infectious diseases are a major threat to the health of American citizens and to people around the world. This includes both new diseases that emerge in populations, as well as previously known diseases that re-emerge. In just the past 2 months, for example, we have seen outbreaks of Ebola in the Congo and Nipah in Northern India.

Dr. Schuchat, what steps are we taking to monitor emerging and re-emerging infectious diseases in the developing world, and how are we partnering with international players on this?

Dr. SCHUCHAT. Yes. CDC works closely with dozens of ministries of health around the world, as well as with international partners like the World Health Organization and the World Food Organization to—or the World Animal Health Organization to be able to find, stop, and prevent epidemics.

Mr. RUIZ. Give me an example of how you do that in a very underdeveloped, poor infrastructure nation.

Dr. SCHUCHAT. Right. As you know, in Liberia, they suffered from a devastating outbreak of Ebola in 2014. We have a country office in Liberia that's working closely with them focused on four key areas: strengthening laboratory systems, strengthening surveillance, strengthening emergency operation centers and rapid response, and workforce development through the disease detective program that we call the field epidemiology training program.

That means they can shorten the time to recognition of Ebola or something else and respond capably.

Mr. RUIZ. Thank you.

And in 2014, 2016, the Ebola epidemic killed more than 11,000 people in West Africa, and we know in October 2014, a physician who traveled from West Africa to Dallas in Texas died of Ebola; two others that contracted the Ebola virus survived.

What did we learn from that experience? And what are the changes that you've made because of that?

Dr. SCHUCHAT. There are three key lessons learned. One was that we need every country to have the ability to find, stop, and prevent epidemics, and that's what we call this Global Health Security Agenda.

A second thing was that we need the world organizations, the global organizations, to be able to surge rapidly when a country's capacity is overwhelmed. And that has actually happened effectively in the Democratic Republic of Congo with this Ebola outbreak recently.

And the third thing that we've learned is that infection control is essential; that an issue that is one illness or a couple illnesses can amplify into a very large-scale problem when we don't have adequate infection control. That's important in the United States for antimicrobial resistance, it's important in developing countries for TB, and it's very important for Ebola in SARS.

Mr. RUIZ. This patient and these two other healthcare workers who contracted Ebola, obviously, were in emergency departments, went to emergency departments, were treated in emergency departments. The first line of defense against any emerging infection or outbreak in the United States is going to be the emergency departments and also the first responders.

So what are you doing in terms of the CDC to coordinate to make sure that they are well-equipped? And then I'm going to ask Dr.

Bright that same question.

Dr. SCHUCHAT. Yes. We have a family of efforts to educate and keep up-to-date clinicians that include tens of thousands of clinicians regularly getting updates from us, whether it's through phone calls——

Mr. RUIZ. It's hard for very busy clinicians who work in emergency departments, seeing 20 patients at once to——

Dr. SCHUCHAT. Right. And that's——

Mr. RUIZ. How do you integrate that into their daily practice?

Dr. SCHUCHAT. Yes. The system changes are really important. When I saw a doctor at Emory last week, before I could even talk to anyone, I was asked, Have you traveled out of the country the last 3 weeks? It's actually on their phone line before you make an appointment.

So institutions instituting systemwide checks can help make sure that you don't have problems with human error.

Mr. RUIZ. Dr. Bright?

Mr. BRIGHT. Also, I'd like to highlight that ASPR has spent a lot of time with our hospital protection program and our healthcare coalitions to establish now even a national Ebola training center and education center, so we can train the hospital and first responders.

We now have 178 Ebola assessment hospitals. We have 69 State or jurisdictions designated Ebola treatment centers. We have 10 regional Ebola and other special pathogen treatment—

Mr. RUIZ. Well, I'm an emergency physician. I have to take exams like crazy just to keep my board certifications and my licensing. So I think integrating it as part of their continuing medical education and training would be very essential.

Now, the President's budget—or the administration wants to move the strategic National Stockpile under the ASPR. I'd like to ask Dr. Schuchat what are your competitive advantages and why should I think about even considering keeping it at the CDC?

Dr. SCHUCHAT. What I could say is that there's already been an administrative decision to move the stockpile, and so currently, CDC is working diligently very closely with ASPR to make that transfer as seamless as possible and to mitigate any negative consequences that may have been unintended but that may occur.

I think the critical areas that we are going to focus on are to make sure that State and local support is seamless, and that we work with State and local health departments every day on a variety of things and know them and know where our gaps are and where we need to make progress. We need to make sure that that close relationship continues in a way that doesn't jeopardize the American public.

Second area is the deep scientific expertise that we have across the agency that has contributed to maintenance of the SNS so that when we need clinical guidance for children for anthrax counter-measures, we can get that best advice incorporated. We need to make sure that that continues, but we are well on the way to executing that seamless transition.

Mr. HARPER. The gentleman yields back.

The chair will now recognize the vice chair of the subcommittee, the gentleman from Virginia, Mr. Griffith, for 5 minutes.

Mr. GRIFFITH. Thank you, Mr. Chairman.

After a series of safety lapses in 2014 involving the mishandling of anthrax and smallpox, in response to recommendations from a lab safety expert panel, both the FDA and CDC formed new offices to provide centralized oversight of laboratory safety and science.

Rear Admiral Hinton, I have several questions for you regarding the FDA's Office of Laboratory Science and Safety.

First, how many labs does the FDA have, or oversee?

Admiral HINTON. The FDA has 56 lab facilities.

Mr. GRIFFITH. And do you oversee more than that?

Admiral HINTON. No.

Mr. GRIFFITH. And are you counting everything in a single building, or is that all your labs combined?

Admiral HINTON. Those are the facilities. Within those facilities, there might be a total of 2,800 rooms, with those rooms being described as a space, an office, a closet.

Mr. GRIFFITH. Yes, ma'am.

How many safety inspections of these labs were conducted by the OLSS over the past year?

Admiral HINTON. No inspections have been conducted by OLSS in the past year. However, their labs have been inspected by other entities.

Mr. GRIFFITH. OK. Have there been any laboratory-acquired infections at FDA labs during the past year?

Admiral HINTON. There have been two noted infections within the last year. The staff that had acquired those infections have been observed and the case is closed.

Mr. GRIFFITH. All right. And can you get us the reports on those two incidences, please?

Admiral HINTON. I'll work with my staff to get that to you. Mr. GRIFFITH. Thank you very much.

Likewise, have there been any potential exposures to threat agents at FDA labs during the past year?

Admiral HINTON. Not to my knowledge. No.

Mr. GRIFFITH. All right. At tab 5 in the document binder is a September 2016 letter to the FDA sent the committee indicating its intention to hire 13 permanent full-time employees in the Office of Laboratory Science and Safety, OLSS.

The FDA told the committee this week that OLSS is staffed by only three permanent full-time employees, and three detailees.

Why doesn't the OLSS have the 13 permanent employees that were promised in a September letter of 2016?

Admiral HINTON. Sir, we have put forth the proposal, and as soon as we have the dedicated budget for OLSS, we expect for their current staff to double.

They actually have three permanent staff and three detailed working on this space.

Mr. GRIFFITH. That still only puts you at six as opposed to the 13 that was indicated in 2016.

Admiral HINTON. I agree. And we note that, and then with the approval of the upcoming budget, we will be able to double that and they will have the 13 staff.

Mr. GRIFFITH. The FDA, in the September 2016 letter, committed to this committee, and in July of 2017, published a notice in the Federal Register evaluating the OLSS so the office would directly to the FDA commissioner instead of the chief scientist.

Earlier this week, the FDA told committee staff that the FDA has decided to reorganize again, and that under the new proposal, OLSS will no longer be a direct report to the commissioner and will report to the chief scientist again, just as they did when we had the lapses back in 2014 and contrary to the expert panel's recommendations.

I just would like to know, first, is the chief scientist reporting to you now?

Admiral HINTON. I am the chief scientist. But the Director of OLSS——

Mr. GRIFFITH. Is OLSS reporting to you?

Admiral HINTON. Yes, sir.

Mr. GRIFFITH. And then you report on up the line?

Admiral HINTON. Yes. I do.

Mr. GRIFFITH. So why did FDA reverse course in less than a year and decide to have the OLSS revert back to reporting to the chief scientist?

Admiral HINTON. Well, sir, since that was announced, we have had the chance over the past year to observe and to see where it might be best fit for the alignment within the office.

Within the office of the chief scientist, which reports into the office of the commissioner and to the commissioner, we work on cross cutting cross-scientific issues to include those within laboratory science space.

So we thought that the OLSS would be best aligned there under my direct supervision on their day-to-day activities. The commissioner will be fully apprised of those activities.

Mr. GRIFFITH. Well, and I certainly mean no disrespect to you, but that was the same setup we had when there were problems being reported and we had the expert panel come in and give us recommendations, which FDA agreed to, and now you all are back-tracking.

I understand some different personnel, but it seems to me we're just creating the same problem we had before.

I see my time is up, and I have to yield back. Thank you, Mr. Chairman.

Mr. HARPER. The gentleman yields back.

The chair will now recognize the gentlewoman from California, Ms. Walters, for 5 minutes.

Ms. WALTERS. Thank you, Mr. Chairman.

Dr. Bright and Dr. Schuchat, either through stockpile procurement or through other means, how do your agencies ensure we have sufficient diagnostic test capacity to identify cases of pandemic influenza or other infectious diseases?

Mr. BRIGHT. In terms of development, so we have worked with a number of different manufacturers through the last 10 years to develop diagnostics for influenza, not only laboratory-based diagnostics, but to standardize and update the point-of-care diagnostics for influenza to make sure those are available and in the marketplace for use for pandemic and seasonal influenza detection.

Dr. SCHUCHAT. Yes. And I would say that CDC both develops assays and helps with validation.

You know, a number of years ago, there were quite a few point-of-care tests for influenza detection, and some of them didn't perform as well in the field as we had hoped. So we did quite an effort of validation comparison, shared the data with FDA, and new labeling and improvements in the tests followed from that.

So we will develop tests against pandemic or avian flu and other high-threat concerns, develop them through to emergency use authorization when appropriate, 501(k) when possible.

The 501(k) final process is very labor intensive, very expensive, and there's a limited number of our tests that we are able to put through to that level. But we do work closely with FDA and BARDA on a number of the priority ones.

Ms. WALTERS. Thank you.

Dr. Fauci, you mentioned work by the National Institute of Allergy and Infection Diseases to support research involving diagnostic testing.

From a Homeland Security and public health perspective, multiplex point-of-care technologies are beneficial because they can be used to simultaneously test for multiple infectious disease pathogens with a single blood or urine sample.

Can you tell us about the research NIAID is doing with respect to multiplex point-of-care technologies and how these technologies enhance our ability to detect material threats and infectious diseases?

Dr. FAUCI. Thank you very much for that question.

Yes. We are very heavily involved in that, both with our grantees to get concept to develop into something that's translatable, as well as contract.

There's multiplex, as you mentioned in your statement, is a very important tool of the future now for detecting outbreaks. For example, we have multiplex assays involving a whole series of particular types of viruses. For example, the flaviviruses, which are many of them that we have, particularly in the Western Hemisphere, that we are involved right now in research for the development of a multiplex that would essentially cover all of the associated flaviviruses, and we're doing that with a number of other viruses.

So there's really a very important, I believe, and aggressive ongoing research program at the NIH, mostly through our grantees and contractors.

Ms. WALTERS. OK.

Mr. BRIGHT. If I can jump in, the challenge with the beauty of multiplex assays is that they can do a lot. And the challenge with them is they're very large instruments generally in centralized laboratories in a hospital or a public health laboratory.

The innovation that we're driving today with companies that move multiplex assays to point of care into a physician's office, and even to work with those multiplex technologies to push some of those now out into the home, one of our greatest challenges with our diagnostics for any disease is how long it takes for a patient to get to that system and into the system so they can get a sample drawn and can get a result.

Too much time elapses in that. So we're trying to also use this new technology for multiplex point of care to multiplex point of need into the home to get people earlier notification to empower patients to get treated sooner.

Ms. WALTERS. OK. Thank you.

Rear Admiral Hinton, how many multiplex point-of-care diagnostic tests has the FDA approved for use?

Admiral HINTON. Thank you for your question, ma'am.

Work in this area is progressing well at FDA. We've cleared more than 25 multiplex tests that could be suitable for point-of-care tests.

Ms. WALTERS. OK. And how many others are currently under assessment by the FDA?

Admiral HINTON. I'll have to get back to you. I don't have the exact number.

Ms. WALTERS. OK. Can you describe the range of capabilities that these tests have? You know, how many diseases can one multiplex point-of-care diagnostic test detect?

Admiral HINTON. It can detect many. We can do up to 20—and more than—at one time, which is incredibly important, especially at the point of care so that we can help to easily detect in order to find the best treatment.

Ms. WALTERS. OK. Thank you, and I yield back the balance of my time.

Mr. HARPER. The gentlewoman yields back.

The chair will now recognize the gentleman from Georgia, Mr. Carter, for 5 minutes.

Mr. CARTER. Thank you, Mr. Chairman.

And, Mr. Chairman, I want to echo your comments earlier about what an outstanding panel this is. Thank you all for the very important work that you do. It is extremely important to our country, and we appreciate it very much.

Dr. Bright, I want to start with you. Being, of course, from Georgia, I am somewhat concerned, even still, about the move of the strategic National Stockpile and the management of that from the CDC to ASPR, and I just want to be assured again from you. I've met Dr. Redfield, and I think he's doing a great job. Dr. Schuchat and I have worked together, and I

just can't say enough good things about the CDC and the outstanding work that they do for our country.

And I just want to make sure that they're still going to have the opportunity to stay involved and to be involved in the medical counter-measurement development and everything else that goes along with the SNS.

Mr. BRIGHT. Sir, you have my complete assurance. I echo your comments about the CDC and the great work they are doing. Many people don't know I got my first start in science at the CDC as an ORISE fellow coming from Emory University in Georgia.

I understand and appreciate the great scientific leadership of the CDC and their relationship with state and local and the value of that.

We plan to always include that in our assessment and our programs for the new strategic National Stockpile management.

Mr. CARTER. We talked on it earlier. One of my colleagues had mentioned about the concern particularly that the transfer is not disruptive for the state and local agencies.

What would you suggest that we do to make that as least disruptive as we can?

Mr. BRIGHT. Well, the most important thing is to recognize the value of their voice in the entire process, not just in the transition of the management of the SNS, but an entire end-to-end process of our efficient response to any emergency or public health emergency threat.

So we already have an intentional working group focusing on the state and local and tribal and territory partners and their specific needs and their specific interests to make sure those are encapsulated in our management of the SNS.

Mr. CARTER. Great.

Dr. Schuchat, would you care to comment on that as well? How can we assure that this is not disruptive to our local and state communities?

Dr. SCHUCHAT. I think that change is, by necessity, disruptive, and I think our job is to mitigate that disruption so that people aren't harmed. So I think it's on our radar. We're working really closely together. The Association of State and Territorial Health Officers Board was just at CDC yesterday talking to us about how we can make sure this all goes as well as possible.

Mr. CARTER. And let me ask you—I run the risk of being a little self-serving here—but wouldn't it make sense to look at perhaps just having ASPR colocate down to Atlanta with the CDC? I recognize you're part of HHS, but we have to get out of the mindset that not everybody's got to be in Washington, D.C. We have a big country out here. Dr. Bright, I'm looking at you.

Mr. BRIGHT. We have a big and beautiful country, sir, and I agree with you, and there is no intent to move the strategic National Stockpile from Atlanta to Washington, D.C. There might be one or two individuals who are located in our ASPR office to ensure we have smooth and efficient ongoing communication with the expert staff that is in Atlanta, Georgia.

Mr. CARTER. OK. Well, that might be a good compromise, and we appreciate that very much.

The Ebola crisis that we had, obviously we learned a lot of lessons there, but I was so proud of the public/private partnership between Emory University and the CDC, and all four patients recovered.

And I just wanted to know, will you be using that model in the future for other pandemics and other risks that we might run into? Because we're very proud of the work that was done at Emory University, and I think it's a great example of what we can do in the future.

Dr. Schuchat?

Dr. SCHUCHAT. I would say that CDC benefits tremendously from being located right next to Emory, and there's a really close working relationship. We were fortunate that they such a terrific job in the Ebola—in the care of the patients there.

There's ongoing collaboration and communication and support.

I think ASPR may have a more direct role in the hospitals and the care of such patients, and Dr. Bright might want to comment.

Mr. BRIGHT. I also want to make sure that we capitalize and not lose that expert and lessons learned from Emory University.

As you may know, we stood up a National Ebola Training and Education Center. It's based in Nebraska as collaboration with Emory University, University of Nebraska, and Bellevue. It is an example of one the finest educational centers on Ebola and other epidemic treatments in the world now.

Mr. CARTER. OK. Again, I want to thank all of you for the work that you do. Extremely important, and especially shout out to CDC and the work that they do.

Thank you, and I yield back, Mr. Chairman.

Mr. HARPER. The gentleman yields back.

The chair will now recognize the gentlewoman from California, Ms. Eshoo, for 5 minutes.

Ms. ESHOO. Thank you, Mr. Chairman, for extending the legislative courtesy to me, since I'm not a member of this subcommittee, but I have a great interest in the subject matter, since we're looking to reauthorize PAHPA and all of the listening to what's taken place in this hearing and the superb testimony from each one of you. We've made great progress since the legislation was first written in 2006.

So I'm pleased, but in America, we're never satisfied with exactly where we are. We always want to improve. And so there's been an important pathway of improvement, and I thank each one of you.

I'm very proud of the two women that are here. Rear Admiral Hinton, it's really a source of pride to me to hear you respond to the tough questions that have come your way. To Dr. Schuchat, it's always a pleasure to hear you. Dr. Bright, the partnership with BARDA has been a very important one, and I think that you're taking it to new places.

And to Dr. Fauci, I don't have any questions to ask you. I wish I could canonize you. You are such a gift to our country. You could be in the private sector probably making millions of dollars. You've devoted your entire life to the people of our country, and you make the National Institutes of—the NIH really stand for the National Institutes of Hope. You're a leader in that, and I just revere your record, your leadership, and what you've done and what you continue to do.

To Dr. Bright, how has restoring BARDA as a contracting authority led to increases in the efficiency and the certainty that surrounds the medical countermeasures at research and development? That's my first question.

And my second one is, does your agency interpret your existing authority to allow the stockpile to invest in countermeasures other than those explicitly mentioned in the current statute?

Maybe start with the second question.

Mr. BRIGHT. Thank you very much.

Ms. ESHOO. Do you need any additional authorities?

Mr. BRIGHT. To be more effective, I believe we need to modify some of the authorities that we have to allow us to work more flexibly with our industry.

Ms. ESHOO. So you don't need additional authorities?

Mr. BRIGHT. We don't need additional authorities. I believe we need to modify the authorities that we have.

Ms. ESHOO. What does that mean, modify the authorities?

Mr. BRIGHT. Our other transactional authority, for example, does have limitations on how we can interface with our industry partners and how they might qualify for that type of partnership. So we have a draft of suggested language that might allow us that greater flexibility to do so.

Ms. ESHOO. And have you gotten that to us?

Mr. BRIGHT. If it hasn't been sent to you yet, we will make sure that it is quickly.

Ms. ESHOO. Do BARDA's existing additional authorities promote work on the, and it's been brought up, not only at this subcommittee, but at others, of the antimicrobial resistance and the antibiotic development, or does your agency need additional authorities to engage in that work?

Mr. BRIGHT. We've been working with the authorities we have since 2010 to address antimicrobial resistance.

One area of authority that is lacking, we believe, would be beneficial would be a specific authority for the appropriations for pandemic influenza, because there's a lot of critical work that needs to happen in pandemic——

Ms. ESHOO. Have you gotten that to us?

Mr. BRIGHT. I do not have that authority yet.

Ms. ESHOO. Are you going to make that request of us?

Mr. BRIGHT. I believe that request has been submitted. I hope so.

Ms. ESHOO. There was some mention earlier about how important the advanced—I think you might have raised it in your opening statement, on advanced appropriations. I believe that, because the Senate has different rules on this, that we will meet the standard that needs to be met. That's probably the tidest way for me to say it.

But it is critical, because if you don't have the advanced appropriations at BARDA, then our partners in the private sector are not going to be able to continue the important work that they're doing.

Mr. BRIGHT. That's absolutely correct. They are business partners working in long-term cycles and forward-looking cycles, and the consistency and assurance of that advanced appropriations allows them to have that assurance that we will still be there doing our part so they can plan appropriately as well.

Ms. ESHOO. Thank you very much to each one of you for what you're doing for our country. You're all heroes of mine.

Thank you, Mr. Chairman. Yield back.

Mr. HARPER. The gentlewoman yields back.

The chair will now recognize Ranking Member DeGette for concluding remarks.

Ms. DEGETTE. Thank you very much, Mr. Chairman, for the moment of personal privilege.

I wanted to bring up another issue that I think is a real crisis right now in this country.

I know we have a lot of HHS agency representatives here, and, of course, ASPR is under the purview of HHS.

Yesterday, our ranking member, Frank Pallone, wrote a letter to Secretary Azar about the HHS Office of Refugee Resettlement. And these kids who are being taken from their parents at the border, and then being put under the auspices of this agency, we have real concerns about what's happening to these children. And we have real concerns about their long-term prospects, being taken from their parents.

And, Mr. Chairman, I just wanted to bring this up, because you're going to be getting a request from the minority to have a hearing about this, and we would hope that you would seriously consider this, because we are quite concerned about the human aspects of this situation.

Thank you, and I yield back.

Mr. HARPER. The gentlewoman yields back.

The chair will recognize Dr. Burgess for a concluding remark.

Mr. BURGESS. Well, Mr. Chairman, thank you for the recognition.

I would just point out that this committee, and this subcommittee in particular, has a significant history of oversight on the ORR. I do feel obligated to point out this is not the agency that makes the decision about whether or not a family unit is kept together, but they are obligated to take care of—whether a child arrives unaccompanied or is separated from their family at the DHS facility. But that is the responsibility of, in fact, the Health Subcommittee, and we do take that responsibility very seriously.

In fact, it was our work in July of 2014 that allowed them to acquire an actual physician to be in those facilities to assess those children as they were brought in.

And it was our committee that raised the question shouldn't we at least have some way of contacting the children after they have been placed with a family, at least on a voluntary basis.

So it was our committee that did that work, and that work will continue. I've been in contact with both Secretary Azar and with the gentleman that runs ORR, and I expect to have robust discussions with them going forward, and I yield back.

Ms. DEGETTE. If the gentleman will yield, thank you very much, and I look forward to working with you on this, because it's really a critical issue, and I'm on that subcommittee, too. Thank you.

Mr. HARPER. I want to thank each of you for being here. Great insights and expertise, and I thank you for participating in today's hearing.

I remind Members that they have 10 business days to submit questions for the record, and I ask that the witnesses agree to respond promptly to any such questions.

With that, the subcommittee's adjourned.

[Whereupon, at 10:58 a.m., the subcommittee was adjourned.]

[Material submitted for inclusion in the record follows:]

U.S. HOUSE OF REPRESENTATIVES COMMITTEE ON ENERGY AND COMMERCE

June 13, 2018

TO: Members, Subcommittee on Oversight and Investigations

FROM: Committee Majority Staff

RE: Hearing entitled “The State of U.S. Public Health Biopreparedness: Responding to Biological Attacks, Pandemics, and Emerging Disease Outbreaks.”

The Subcommittee on Oversight and Investigations will hold a hearing on Friday, June 15, 2018, at 9:00 a.m. in 2123 Rayburn House Office Building. The hearing is entitled “The State of U.S. Public Health Bio-preparedness: Responding to Biological Attacks, Pandemics, and Emerging Disease Outbreaks.”

The purpose of this hearing is to follow up on the past biopreparedness oversight issues examined by the Subcommittee, and to receive updates from the agencies on current assessments and strategies. This hearing will also highlight the need to reauthorize the Pandemic and All-Hazards Preparedness Act (PAHPA), which is due to expire at the end of September 2018.⁵

I. Witnesses

Rick A. Bright, Ph.D., Director, Biomedical Advanced Research and Development Authority; Deputy Assistant Secretary, Office of the Assistant Secretary for Preparedness and Response, U.S. Department of Health and Human Services;

- Anne Schuchat, M.D. (RADM, USPHS), Principal Deputy Director, Centers for Disease Control and Prevention, U.S. Department of Health and Human Services;
- Anthony Fauci, M.D., Director, National Institute of Allergy and Infectious Diseases, National Institutes of Health; and
- Denise Hinton (RADM, USPHS), Chief Scientist, U.S. Food and Drug Administration.

II. Background

This section will outline four areas of continuing oversight interest in the area of biopreparedness: biological threats; detection and diagnostics; development and stockpiling of medical countermeasures (MCMs); and science, safety and security of laboratories in the life sciences-biodefense complex.

A. Biological Threats

Biological threats fall into three main categories: natural infectious diseases, synthetic biology/engineered pathogens, and bioterrorism. Synthetic biology could cause harm either

⁵ PAHPA created and expanded programs to enhance the public health system’s capacity to monitor and respond to public health emergencies. The act expanded programs for state and local public health emergency preparedness activities and mandates the use of evidence-based benchmarks and standards to measure levels of preparedness. Ass’n of State and Territorial Health Orgs., *ASTHO Legal Preparedness Series Emergency Authority & Immunity Toolkit -Pandemic and All-Hazards Preparedness Act*, <http://www.astho.org/Programs/Preparedness/Public-Health-Emergency-Law/Emergency-Authority-and-Immunity-Toolkit/Pandemic-and-All-Hazards-Preparedness-Act-Fact-Sheet/>(last visited June 11, 2018).

intentionally (e.g., an engineered pathogen used in a bioterrorist attack) or accidentally (e.g., through the accidental release of dangerous agents from a lab conducting dual use research).⁶

In this century, the nation has witnessed the impacts of naturally occurring outbreaks such as influenza, Ebola, and SARS.⁷ Health authorities are currently monitoring other potential emerging infectious diseases that could cause a pandemic, such as the H7N9 influenza strain circulating in China.⁸ Further, as recently noted by Department of Health and Human Services (HHS) Assistant Secretary for Preparedness and Response (ASPR) Robert Kadlec, “[t]errorist organizations such as ISIS and al-Qaida remain determined to attack; further ISIS has demonstrated no compunction about using chemical and other unconventional weapons in attacks overseas. State actors have already threatened our homeland with nuclear weapons and have shown the means to employ both chemical and biological weapons.”⁹

The Subcommittee explored the growing nature of these biological threats and the need for an elevated response at a hearing held on February 12, 2016.¹⁰

An attachment to this memorandum provided by the National Institute of Allergy and Infectious Diseases (NIAID) shows examples of emerging and re-emerging infectious diseases as of June 2018.

B. Detection and Diagnostics

Laboratory Response Network

The Centers for Disease Control and Prevention (CDC) Laboratory Response Network (LRN) is a network of 134 local, state and federal laboratories that can provide the laboratory infrastructure and capacity to quickly respond to public health emergencies, and incidents of biological and chemical terrorism. The network, established in 1999 and overseen by the CDC, enables rapid detection of and response to emerging infectious diseases such as Zika, Ebola and influenza, as well as select agents and toxins. All 50 states have at least one member laboratory and 85 percent of the U.S. population lives within a two-hour drive of an LRN lab.

The ability of the LRN to respond to quickly unfolding emergencies is essential and, as such, the network was designed to deploy rapid detection technology and laboratory tests (known as assays) to quickly test suspicious materials and detect the presence of biological or chemical agents in the event of a bioterrorism attack.

In August 2016, the Committee launched a bipartisan investigation about the current capabilities of the CDC LRN, and two additional information request letters followed on

⁶ GiveWell, *A conversation with George Poste on February 12, 2014*, <https://www.openphilanthropy.org/sites/default/files/Poste%202-12-14%20%28public%29.pdf> (last visited June 11, 2018). George Poste, DVM, PhD., is Director, Complex Adaptive Systems Institute, Arizona State University and an ex officio member of the Blue Ribbon Study Panel on Biodefense.

⁷ See *Examining the Reauthorization of the Pandemic and All-Hazards Preparedness Act Before the Subcomm. on Health of the H. Comm. on Energy and Commerce*, 115th Cong. (2018) (written testimony of Hon. Robert Kadlec, M.D., Assistant Sec’y for Preparedness and Response, U.S. Dep’t of Health & Human Services).

⁸ *Id.*

⁹ *Id.*

¹⁰ See *Outbreaks, Attacks, and Accidents: Combating Biological Threats Before the Subcomm. on Oversight and Investigations of the H. Comm on Energy and Commerce*, 114th Cong. (2016) Serial No. 114-117.

October 26, 2016, and February 28, 2017.¹¹ These letters requested information regarding the LRN's lab capacity, funding levels, and laboratory test development.

In response to questions about funding for the network, the CDC provided documentation indicating that spending decreased over the last decade. The LRN's expenditures have gradually decreased from \$15 million in 2007 to \$9 million in 2016. Expenditures for the LRN totaled \$116.2 million during that 10-year period.¹² The CDC has also at times received funding from other federal agencies to help support network activities. The Department of Homeland Security's Science and Technology Directorate, Department of Defense's Defense Threat Reduction Agency and its Joint Program Executive Office, and the Department of Health and Human Services' Office of the Assistant Secretary for Preparedness and Response (ASPR) and Biomedical Research and Development Authority (BARDA) have each provided funding for LRN support over the last 10 years. Funding has varied year-to-year by agency, but the total amount the four agencies have provided to the LRN since Fiscal Year 2008 is \$21.5 million.¹³

In response to questions on lab test development, the CDC provided information about the process by which it selects and develops new assays the LRN can use to detect for biological agents, toxins and emerging infectious diseases. The CDC has indicated that the Food and Drug Administration (FDA) has approved 510(k) clearances for four assays and issued emergency use authorization for another six assays.¹⁴ Out of a total of 45 select agents affecting humans on the current select agents and toxin list,¹⁵ the CDC LRN has assays cleared by FDA under the 510(k) process for three, after nearly 20 years of the LRN program and more than \$135 million in funding during the last decade.¹⁶

Most recently, the CDC arranged for the evaluation and deployment of a Department of Defense Ebola Zaire assay by the LRN amid the 2014 Ebola epidemic in West Africa. After the 2015 Zika outbreak in Brazil, the CDC also began development of an LRN diagnostic for the Zika virus.¹⁷

¹¹ Letter from Hon. Fred Upton, Chairman, H. Comm. on Energy and Commerce, et al. to Thomas Frieden, M.D., Dir., Centers for Disease Control and Prevention (Aug. 11, 2016) *available at* <https://archives-energycommerce.house.gov/sites/republicans.energycommerce.house.gov/files/documents/114/letters/20160811CD C.pdf>; Letter from Hon. Fred Upton, Chairman, H. Comm. on Energy and Commerce and Hon. Tim Murphy, Chairman, H. Comm. on Energy and Commerce, Subcomm. on Oversight and Investigations to Thomas Frieden, M.D., Dir., Centers for Disease Control and Prevention (Oct 26, 2016) (On file with the Committee); Letter from Hon. Greg Walden, Chairman, H. Comm. on Energy and Commerce and Hon. Tim Murphy, Chairman, H. Comm. on Energy and Commerce, Subcomm. on Oversight and Investigations to Anne Schuchat, M.D., Acting Dir., Centers for Disease Control and Prevention (Feb. 28, 2017) *available at* <https://archives-energycommerce.house.gov/sites/republicans.energycommerce.house.gov/files/documents/114/letters/20170228CD C.pdf>.

¹² Letter from Anne Schuchat, M.D., Acting Dir., Centers for Disease Control and Prevention, to Hon. Greg Walden, H. Comm. on Energy and Commerce. (May 23, 2017) (On file with the Committee). In the letter to the Committee, the CDC represented that there may be additional funding sources for the LRN than those it had identified.

¹³ *Id.*

¹⁴ *Id.*

¹⁵ See Fed. Select Agent Program, *Select Agents and Toxins List*, <https://www.selectagents.gov/selectagentsandtoxinslist.html> (last visited June 11, 2018).

¹⁶ Schuchat, *supra* note 8.

¹⁷ *Id.*

Biosurveillance

Two areas of biosurveillance of interest to the Subcommittee have been BioWatch and multiplex point-of-care technologies (MPOCTs). BioWatch is an early warning system designed to detect a large-scale, covert attack that releases anthrax or other agents of bioterrorism into the air. Overseen by the Department of Homeland Security (DHS), the BioWatch program involves a system of aerosol collectors deployed in more than 30 cities, as well as laboratory facilities and personnel to analyze samples from these collectors. This program relies heavily on CDC, and the state and local public health laboratories that are members of the CDC LRN. The program aims to reduce the time required to recognize and characterize potentially catastrophic aerosolized attacks by monitoring for the presence of certain biological agents considered to pose high risk for an aerosolized attack. A committee investigation and a U.S. Government Accountability Office (GAO) report found that DHS lacked reliable information about BioWatch's technical capabilities to detect a biological attack and therefore lacks the basis for informed cost-benefit decisions about upgrades to the system.¹⁸ DHS continues to work on ways to upgrade the BioWatch system.

MPOCTs are technologies that can simultaneously test for more than one type of human infectious disease pathogen from a single patient sample (such as blood, urine, or sputum) in one run at or near the site of a patient. MPOCTs can enable rapid testing while the patient is at the doctor's office, clinic, or other testing location, including the home. From a homeland security and public health perspective, MPOCTs are of interest as an early detection tool, and can help assess the potential spread and effect of the disease in the case of dangerous pathogens. At the Committee's request, the GAO conducted a technical assessment of MPOCTs.¹⁹ The GAO found that MPOCTs have a range of performance characteristics that describe, among other things, the ability of the technology to correctly identify the presence or absence of a pathogen. Developers identified several technical challenges to developing multiplex assays that can slow MPOCT development and raise costs. GAO also identified potential benefits of MPOCTs included improved patient health care and management, more appropriate use of antibiotics, improved ability to limit the spread of disease, and health care cost savings.

C. Development and Stockpiling of Medical Countermeasures

Public Health Emergency Medical Countermeasures Enterprise

In 2006, HHS established the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) to coordinate federal efforts to prepare for, and respond to, public health emergencies from a MCM perspective.²⁰

¹⁸ See *Continuing Concerns Over BioWatch and the Surveillance of Bioterrorism Before the Subcom. on Oversight and Investigations of the H. Comm. on Energy and Commerce* 113th Cong. (2013) Serial No. 113-56; U.S. Gov't Accountability Office, *Biosurveillance: DHS Should Not Pursue BioWatch Upgrades or Enhancements Until System Capabilities Are Established*, GAO-16-99 (Oct. 2015) available at <https://www.gao.gov/assets/680/673309.pdf>.

¹⁹ U.S. Gov't Accountability Office, *Medical Devices: Capabilities and challenges of technologies to enable rapid diagnoses of infectious diseases*, GAO-17-347 (Aug. 2017) available at <https://www.gao.gov/products/GAO-17-347>.

²⁰ See 71 C.F.R. § 129 (2006) and U.S. Dep't of Health & Human Services, Assistant Sec'y for Preparedness and Response, *Public Health Emergency Medical Countermeasures Enterprise*, <https://www.phe.gov/Preparedness/mcm/phemce/Pages/default.aspx> (last visited June 11, 2018).

Pursuant to the 2013 Pandemic and All-Hazards Preparedness Reauthorization Act, the PHEMCE is led by the ASPR and is comprised of senior leadership from the CDC, the NIAID at the National Institutes of Health (NIH), the FDA, the Department of Defense (DoD), the DHS, the Department of Veteran's Affairs (VA) and the Department of Agriculture (USDA).²¹

The PHEMCE's mission components include:²²

- Requirements Setting: The PHEMCE is responsible for establishing requirements for MCMs based on factors such as threat and risk assessments, which are principally conducted by the DHS.
- Early Stage Research: The NIH is the lead federal PHEMCE agency for conducting and facilitating research into areas of public health concerns, which could ultimately lead to the development of MCMs to diagnose, treat, and prevent a wide-range of public health threats.
- Advanced Development/Manufacturing: The Biomedical Advanced Research and Development Authority (BARDA), within HHS' ASPR, develops MCMs for emerging public health threats and partners with industry to accelerate development and increase MCM manufacturing capacity. In the past decade, BARDA's efforts, supported by industry and government partnerships, have resulted in 35 FDA approvals for 31 unique MCMs for threats to the public health.²³ BARDA has also supported the development of 27 MCMs against threats that have been identified by the DHS, through Project BioShield, as being national security threats.²⁴
- Regulatory Science Management: The PHEMCE endeavors to ensure MCMs are safe and effective, which is generally the responsibility of the FDA.
- Procurement/Inventory Management/Stockpiling: The PHEMCE oversees the procurement and management of MCMs to respond to public health threats. Currently, the CDC and BARDA are the lead PHEMCE agencies for this mission component.
- Response Planning, Policy, Guidance and Communication: The PHEMCE, led by CDC and ASPR, coordinates federal medical response and communication strategies when faced with a public health emergency.
- Deployment/Distribution/Dispensing/Administration: The CDC and ASPR engage and coordinate with state and local partners to facilitate the distribution of MCMs and administration of other medical assets in times of public health emergencies.
- Monitoring/Evaluation/Assessment: The CDC and FDA are the principal PHEMCE agencies for monitoring the safety and performance of MCMs that have been deployed in response to public health emergencies response.

²¹ 42 U.S.C. § 300hh – 10.

²² U.S. Dep't of Health & Human Services, Assistant Sec'y for Preparedness and Response, *PHEMCE Mission Components*, <https://www.phe.gov/Preparedness/mcm/phemce/Pages/mission.aspx> (last updated Feb. 27, 2015).

²³ Kadlec, *supra* note 3.

²⁴ *Id.*

Concerns have been raised about the length of time it takes to classify a hazardous pathogen as a material threat and then approve the development of medical countermeasures. According to ASPR, it can take upwards of two years for the DHS to designate a pathogen as a material threat.²⁵ For example, carfentanil, a highly potent form of fentanyl, was known as a weapon of mass destruction after Russian forces used it in the Moscow theatre against Chechen terrorists in 2002,²⁶ but pharmaceutical-based agents, such as fentanyl, were only recently added as a material threat. ASPR would like to reduce the time it takes for the DHS to designate a material threat to 90-days or less.²⁷ After a pathogen is classified as a material threat, PHEMCE can approve the development of MCMs for a material threat. ASPR is currently considering other steps that could reduce the timeframe to approve countermeasure development while still maintaining an adequate level of input from all PHEMCE partners and experts, and hopes to devise a plan to reduce the MCM development timeframe by year's end.²⁸

Strategic National Stockpile

The CDC is the primary federal agency responsible for public health surveillance, epidemiologic investigations, and public health communications. The CDC is also currently responsible for managing the Strategic National Stockpile (SNS), though the President's Fiscal Year (FY) 2019 Budget Request transfers SNS management authority from the CDC to HHS' ASPR.²⁹

The SNS is a federal repository of MCMs such as vaccines, antibiotics, and other medical supplies that are to be used in public health emergencies.³⁰ For FY 2018, the SNS received a total of \$610 million, including supplemental funding included in the omnibus spending bill passed earlier this year. Since FY 1999, the federal government has appropriated more than \$9.15 billion to the SNS, with annual SNS funding levels significantly increasing in the years following the September 11, 2001, terror attacks and 2001 anthrax attacks.³¹

Through coordination with the PHEMCE, CDC's current responsibilities regarding the SNS include MCM procurement, shelf life analysis, and MCM replenishment. In addition, the CDC, through its Office of Public Health Preparedness and Response (OPHPR), is also responsible for the delivery of MCMs to areas that have been affected by public health emergencies. OPHPR also provides training to state and local medical personnel and public health officials on how to properly receive and distribute MCMs from the SNS in the case of

²⁵ Briefing by staff, U.S. Dep't of Health & Human Services, Assistant Sec'y for Preparedness and Response with staff, H. Comm. on Energy and Commerce, June 11, 2018.

²⁶ See, e.g., Erika Kinetz and Maria Danilova, *Lethal chemical now used as a drug haunts theater hostages*, Associated Press, Oct. 8, 2016, <https://apnews.com/256605b7679d4a61bde9a8eac8906ea9>.

²⁷ Assistant Sec'y for Preparedness and Response, *supra* note 21 and E-Mail from staff, Assistant Sec'y for Preparedness and Response to staff, H. Comm on Energy and Commerce (June 12, 2018 9:13am).

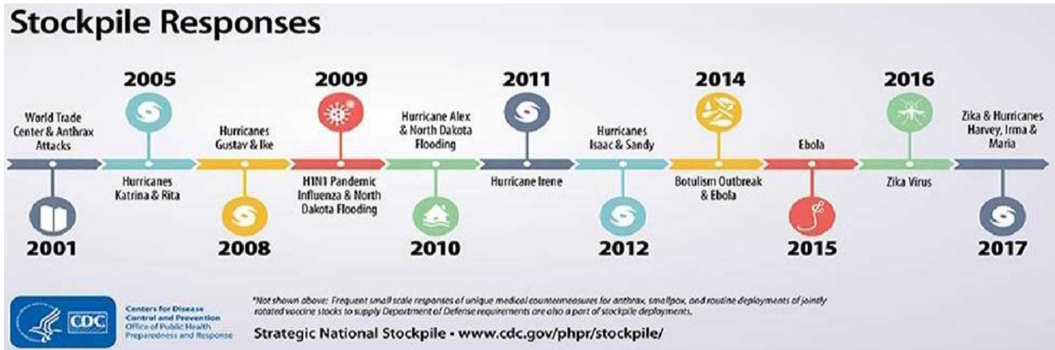
²⁸ Assistant Sec'y for Preparedness and Response, *supra* note 21.

²⁹ U.S. Dep't of Health & Human Services, Centers for Disease Control and Prevention, *Fiscal Year 2019 Justification and Estimates for Appropriation Committees*, available at <https://www.cdc.gov/budget/documents/fy2019/fy-2019-cdc-congressional-justification.pdf>.

³⁰ 42 U.S.C. § 247d-6b.

³¹ Source: Total tabulated from tables in Congressional Research Service e-mail to staff, H. Comm. on Energy and Commerce (June 1, 2018).

a public health emergency. In 2017, OPHPR provided such training to more than 3,700 state and local personnel and led a total of 12 medical emergency simulation exercises.³²



Source: Centers for Disease Control and Prevention.

Over the last few years, independent audits have raised concerns over CDC’s logistical management of the SNS. In June 2017, HHS’ Office of Inspector General (OIG) issued a report which called into question the readiness of the CDC to effectively deploy SNS resources during a public health emergency.³³ In its review, OIG identified “systemic issues [that] could put at risk approximately \$7 billion of Stockpile inventory and negatively affect Stockpile readiness during a national emergency.”³⁴ The OIG’s conclusion was based on a review of findings from each of five SNS site audits that covered FYs 2013 and 2014, and additional information related to the value of the SNS, security, and funding.

Questions have also been raised about the SNS Division of State and Local Readiness (DSLRL), which oversees expenditures of about \$8.6 million. The DSLRL initiatives are meant to ensure that local partners have the resources and training in place to distribute and properly use products from the SNS in the event they need to be deployed. ASPR, however, has identified concerns with state and local partners’ current state of readiness, specifically regarding “last mile” distribution and how quickly partners are able to distribute products on the ground after receipt from SNS.³⁵ Among the concerns highlighted by ASPR is that state and local partners currently do not know what products are in the SNS and therefore do not know how to properly deploy the products.³⁶ To improve state and local readiness, ASPR intends to bolster education and training programs so local partners and first responders have familiarity with SNS products. ASPR also intends to review assessment tools used to rank state and local partners’ readiness status and to design an array of distribution models that could be implemented by local entities to improve their response plans.³⁷

Other issues raised regarding the CDC’s management of the SNS include instances in which the CDC failed to fund the procurement of an MCM for the SNS after the MCM’s

³² Centers for Disease Control and Prevention, *Public Health Preparedness and Response 2018 National Snapshot*, available at https://www.cdc.gov/phpr/pubs-links/2018/documents/2018_Preparedness_Report.pdf.

³³ U.S. Dep’t of Health & Human Services, Office of Inspector Gen., *Readiness of CDC’s Strategic National Stockpile Could Be at Risk in Case of a Public Health Emergency* (A-04-16-03554) (June 2017) available at <https://oig.hhs.gov/oas/reports/region4/41603554RIB.pdf>.

³⁴ *Id.*

³⁵ Assistant Sec’y for Preparedness and Response, *supra* note 21.

³⁶ *Id.*

³⁷ *Id.*

development and FDA approval.³⁸ For example, there have been instances where BARDA has had to use Project BioShield funding to procure MCMs that have been FDA-approved but were not ultimately purchased by the SNS. The reason for this was due to the fact that the government has to not only ensure that the specific MCMs remain available, but also must sustain a company since they are developing MCMs that do not have a traditional commercial market. Some of the MCMs that have been produced in this manner include: anthrax vaccine adsorbed; axibacumab; and obiltoxaximab.³⁹

Recently, members of the Blue Ribbon Study Panel on Biodefense wrote to Dr. Robert Kadlec, HHS ASPR, with a number recommendations to enhance the United States' MCM infrastructure. Included among the Panel's recommendations were proposed SNS management reforms, which, according to the Panel, were precipitated by the CDC's inadequate management of the SNS.⁴⁰

Pursuant to the President's FY 2019 budget, the transfer of the SNS from the CDC to the ASPR will be effective October 1, 2018.⁴¹ According to HHS, the benefits of moving the SNS to ASPR include that: (1) a unified command for the SNS as the reorganization will vest the MCM production and stockpiling responsibilities with a single agency; (2) ASPR's mission is more targeted than that of the CDC's, enabling it to be a better advocate for the SNS; and (3) ASPR has established relationships with state/local emergency responders, who would play a critical role in a SNS deployment.⁴²

National Pre-Pandemic Influenza Stockpile

In November 2005, the White House Homeland Security Council issued the *National Strategy for Pandemic Influenza*, designating HHS as the department to lead the nation's medical response to pandemic influenza.⁴³ According to the CDC, a pandemic influenza occurs when a new influenza A virus emerges, usually originating in animals, that is able to easily spread from person to person due to lack of effective treatments and acquired immunity.⁴⁴ The *National Strategy* also emphasized the need to ensure that the nation had an adequate MCM production capacity and stockpile to respond to potentially pandemic strains of influenza.⁴⁵ The Homeland Security Council reiterated the importance of having a pre-pandemic MCM stockpile in its *National Strategy Implementation Plan*, which was released in May 2006, categorizing the pandemic threat as a national security issue.⁴⁶

³⁸ E-Mail from staff, Assistant Sec'y for Preparedness to staff, H. Comm on Energy and Commerce (June 12, 2018 4:02pm).

³⁹ *Id.*

⁴⁰ Letter from the Blue Ribbon Study Panel on Biodefense to Hon. Robert Kadlec, M.D., Assistant Sec'y for Preparedness and Response, U.S. Dep't of Health & Human Services (May 15, 2018) (on file with the Committee).

⁴¹ U.S. Dep't of Health & Human Services, *Fiscal Year 2019 Public Health and Social Services Emergency Fund Justification of Estimates for Appropriations Committee*, available at <https://www.hhs.gov/sites/default/files/fy-2019-phssec-cj.pdf>.

⁴² *Id.*

⁴³ Executive Office of the President of the United States, Homeland Security Council, *National Strategy for Pandemic Influenza*, Nov. 2005 available at <https://www.cdc.gov/flu/pandemic-resources/pdf/pandemic-influenza-strategy-2005.pdf>.

⁴⁴ Centers for Disease Control and Prevention, *Influenza (Flu) Questions and Answers*, available at <https://www.cdc.gov/flu/pandemic-resources/basics/faq.html> (last updated May 15, 2017).

⁴⁵ Executive Office of the President, *supra* note 39.

⁴⁶ Executive Office of the President of the United States, Homeland Security Council, *National Strategy for Pandemic Influenza Implementation Plan*, May 2006 available at <https://www.cdc.gov/flu/pandemic-resources/pdf/pandemic-influenza-implementation.pdf>.

BARDA, which was established by the Pandemic and All-Hazards Preparedness Act, is responsible for the procurement and management of the nation's pre-pandemic influenza stockpile as well as the development of influenza MCMs. BARDA is also tasked with accelerating the development and procurement of MCMs related to chemical, biological, radiological, and nuclear threats as well as threats related to emerging infectious diseases.⁴⁷

In June 2017, and at the Committee's urging,⁴⁸ HHS issued an update to its *Pandemic Influenza Plan*, which was initially published in 2005 and had been last updated in 2009.⁴⁹ In the 2017 update, HHS stated that the national pre-pandemic influenza stockpile "satisfies requirements for vaccine and adjuvants to address influenza viruses that are assessed to be the highest risk for human infection."⁵⁰ BARDA, in collaboration with other HHS agencies, utilizes CDC's Influenza Risk Assessment Tool (IRAT) to assess pandemic risks that are associated with emerging novel influenza viruses and make determinations regarding a potential update to the pre-pandemic stockpile or the development of new vaccine candidates.⁵¹

CARB-X

CARB-X is a non-profit public-private partnership dedicated to accelerating antibacterial research to tackle the global rising threat of drug-resistant bacteria.⁵² With more than \$500 million to invest between 2016 and 2021, CARB-X funds the research and development of new antibiotics, vaccines, rapid diagnostics and other life-saving products to tackle the global threat of drug-resistant bacteria. CARB-X was created in response to the U.S. government's 2015 Combating Antibiotic Resistant Bacteria (CARB) initiative, and the United Kingdom's government's call in 2016 for concerted global effort to address the growing drug-resistance public health crisis. Launched on July 28, 2016, CARB-X is a cooperative effort between BARDA and the NIAID. CARB-X is funded by BARDA and Wellcome Trust, the world's largest medical charity which is based in the U.K.

D. Science, Safety and Security of Laboratories in the Life Sciences-Biodefense Complex

Currently, there are about 1,200 high-containment laboratories in the U.S. conducting research on diagnostics and cures for highly dangerous pathogens. For more than a decade, the Subcommittee has held hearings and conducted investigations related to the Federal Select Agent Program, including on the safe handling of federal select agents and other dangerous pathogens.

⁴⁷ 42 U.S.C. § 247d-7e.

⁴⁸ See Letter from the Hon. Greg Walden, Chairman, H. Comm. on Energy and Commerce, et al., to Hon. Thomas Price, M.D., Sec'y, U.S. Dep't of Health & Human Services (Apr. 20, 2017), available at <https://archives-energycommerce.house.gov/sites/republicans.energycommerce.house.gov/files/documents/20170420HHS.pdf>.

⁴⁹ U.S. Dep't of Health and Human Services, *Pandemic Influenza Plan 2017 Update* (last visited June 7, 2018) available at <https://www.cdc.gov/flu/pandemic-resources/pdf/pan-flu-report-2017v2.pdf>.

⁵⁰ *Id.*

⁵¹ See Letter from Hon. Nicole Lurie, M.D., Assistant Sec'y for Preparedness and Response, U.S. Dep't of Health & Human Services to Hon. Fred Upton, Chairman, H. Comm. on Energy and Commerce (Mar. 15, 2016) available at <https://archives-energycommerce.house.gov/sites/republicans.energycommerce.house.gov/files/documents/114/letters/20160229HH%20Response.pdf>.

⁵² CARB-X, *About CARB-X*, <https://carb-x.org/about/overview/> (last visited June 11, 2018).

Federal Select Agent Program

The Federal Select Agent Program regulates the possession, use, and transfer of biological select agents and toxins to ensure laboratory research conducted on the materials is done in a safe and secure manner. Sixty-six select agents and toxins that could potentially be used in bioterrorist attacks – including anthrax, smallpox, and plague – are currently regulated through the program. Managed jointly by HHS and the USDA, the program provides oversight of more than 275 entities that have registered through the program in order to conduct research on the hazardous pathogens.⁵³

The Federal Select Agent Program was established in 1996 through the passage of the Antiterrorism and Effective Death Penalty Act. The law, passed in the aftermath of the Oklahoma City bombing, required HHS to identify a list biological agents and toxins that could threaten public health and safety and establish regulations regarding the transfer of those agents. The September 11, 2001, terrorist attacks and the 2001 anthrax mailings led to increased concern about the threat of bioterrorism attacks, and additional restrictions which banned certain individuals from transporting or receiving select agents were included in the USA Patriot Act of 2001.⁵⁴ Congress expanded the program through the passage of the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 to include regulation of the transfer and the use and possession of select agents and increased safeguards and security requirements.

Concerns raised by the mishandling of dangerous pathogens prompted the Committee to request an assessment of the select agent program by the GAO. In response to the Committee's request, the GAO reviewed oversight procedures of the select agent program and issued a report in October 2017 that highlighted deficiencies in the program's capabilities.⁵⁵ The report raised concerns about potential conflicts of interest as the select agent program is not independent from all the laboratories it oversees. The report also noted that the program has historically focused more on security and preventing thefts of select agents and toxins than on biological safety issues within the labs using the pathogens for research. The Subcommittee, which has held multiple hearings on the select agent program and safety lapses at federal labs, questioned USDA and CDC officials about the GAO report's conclusions and recommendations at a November 2, 2017, hearing.⁵⁶

Prioritizing Lab Science and Safety

Following the 2014 incidents involving anthrax mishandling at the CDC and the smallpox discovered in storage for an FDA lab on the NIH campus, federal efforts intensified to improve the management of government labs. In particular, an external scientific working group recommended improvements to the CDC and FDA for overhauling their lab safety programs.

This included the recommendation that a program director would be a single point of accountability and would have a direct reporting relationship to the head of the agency. When

⁵³ Federal Select Agent Program, *About Us*, <https://www.selectagents.gov/about.html> (last visited June 11, 2018).

⁵⁴ See USA Patriot Act of 2001, Pub. L. No. 107-56, 115 Stat. 272 (2001).

⁵⁵ U.S. Gov't Accountability Office, *Coordinated Actions Needed to Enhance the Select Agent Program's Oversight of Hazardous Pathogens*, GAO-18-145 (Oct. 2017) available at <https://www.gao.gov/assets/690/687868.pdf>.

⁵⁶ See *Concerns Over Federal Select Agent Program Oversight of Dangerous Pathogens Before the Subcom. on Oversight and Investigations of the H. Comm. on Energy and Commerce 115th Cong.* (2017) available at <https://docs.house.gov/meetings/IF/IF02/20171102/106574/HHRG-115-IF02-Transcript-20171102.pdf>.

Stephan S. Monroe, the CDC's Associate Director for Laboratory Science and Safety (ADLSS), testified before the Subcommittee in April 2016, he said the formation of the director position was "the most fundamental change implemented in the wake of the 2014 incidents."⁵⁷ Further, Dr. Monroe noted that the fact that the ADLSS reported directly to the CDC director provided "high-level oversight and coordination of critical laboratory policies and operations" across all CDC campuses.

In response to the 2014 safety lapses,⁵⁸ the FDA's Office of Laboratory Science and Safety (OLSS) was formed in order to provide oversight and to improve security and safety across all divisions of FDA. The formation of the office was announced in 2016 as a means to consolidate oversight responsibilities and standard policies for all FDA laboratories. In 2017, the FDA issued a strategic plan outlining the goals of the new office.

According to the OLSS strategic plan, the office's mission is to:

- Ensure FDA's laboratories and workplaces are operated in a safe and secure manner to protect employees, the surrounding communities, and the environment;
- Research and disseminate innovative ideas and validated methods for safe and secure laboratory practices;
- Support high-quality (i.e., accurate, reliable, and timely) FDA laboratory results; and
- Promote a culture of shared responsibility and safety.⁵⁹

Just as the ADLSS was organized to directly report to the CDC Director, the OLSS was also envisioned to directly report to the FDA Commissioner. A reorganization issued by the FDA in 2017 made the OLSS a direct report to the FDA Commissioner.⁶⁰ However, the FDA now plans to have the OLSS report to the Office of the Chief Scientist instead of directly to the Commissioner.⁶¹

In addition, the budget and staffing for the OLSS have not been consistent. In 2016, the FDA informed the Committee that the office's budget for FY 2017 was \$5.2 million and that it would support 13 full time employees.⁶² FDA officials subsequently told Committee staff that the FY 2017 budget for OLSS was \$9 million, but that funding levels would support not just OLSS operations (including staff and contractor support) but also the Employee Safety

⁵⁷ *Laboratory Safety at the Centers for Disease Control and Prevention Before the Subcomm. on Oversight and Investigations of the H. Comm on Energy and Commerce*, 114th Cong. (2016) (written testimony of Hon. Stephan S. Monroe, PhD., Assoc. Dir. for Laboratory Science and Safety, Centers for Disease Control and Prevention) available at <https://docs.house.gov/meetings/IF/IF02/20160420/104823/HHRG-114-IF02-Wstate-MonroeS-20160420.pdf>.

⁵⁸ Brady Dennis and Lena H. Sun, *FDA found more than smallpox vials in storage room*, WASH. POST, July 16, 2014, https://www.washingtonpost.com/national/health-science/fda-found-more-than-smallpox-vials-in-storage-room/2014/07/16/850d4b12-0d22-11e4-8341-b8072b1e7348_story.html.

⁵⁹ U.S. Food and Drug Admin., 2017-2022 Operating Model – *Office of Laboratory Science and Safety*, Updated Oct. 13, 2017, available at <https://www.fda.gov/downloads/AboutFDA/CentersOffices/OC/OLSS/UCM583016.pdf>.

⁶⁰ See 82 Fed. Reg. 34540 (July 25, 2017) available at <https://www.federalregister.gov/documents/2017/07/25/2017-15564/office-of-the-commissioner-statement-of-organization-functions-and-delegations-of-authority>.

⁶¹ Briefing by staff, U.S. Dep't of Health & Human Services, U.S. Food and Drug Admin. with staff, H. Comm. on Energy and Commerce, June 11, 2018.

⁶² Letter from Dayle Cristinzio, Acting Assoc. Comm'r for Legislation, U.S. Food and Drug Admin., to Hon. Fred Upton, Chairman, H. Comm. on Energy and Commerce. (Sept. 9, 2016) (On file with the Committee).

and Environmental Management staff that were transferred to OLSS.⁶³ The FDA later informed the Committee that no permanent full-time employees (FTE) were hired by OLSS in FY 2017, rather the office recruited 19 individuals through temporary detail assignments and contract support.⁶⁴ In a briefing with Committee staff, the FDA confirmed that the office's FY 2018 budget is \$5.6 million and the FY 2019 budget is \$6 million.⁶⁵ The office currently employs three FTEs and three contractors. At this time, FDA has not reported the total number of FDA laboratories to the Committee staff. FDA has not yet reported to the Committee the number of audits that OLSS has conducted.

By contrast, the CDC's ADLSS office's FY 2016 budget was \$14.5 million and supported 34 FTEs.⁶⁶ As of this month, the office had 43 FTEs with three slots vacant and oversaw audits of laboratories used by 239 teams of scientists.⁶⁷ The CDC recently reported to Committee staff that it had submitted a proposed reorganization to the Department that would eliminate the Associate Director's direct reporting relationship to the Director, and instead would report to a Deputy Director.⁶⁸

III. Issues

The following issues may be examined at the hearing:

- How timely are the PHEMCE decisions regarding biological threats being made? Can the timeliness of these decisions be improved?
- How can the number of FDA-approved assays for threat agents be increased?
- Is there adequate oversight to ensure the efficacy of MCMs in the SNS and the prepandemic vaccine stockpile?
- Are U.S. public health agencies implementing recommendations to improve laboratory science and safety?

⁶³ E-Mail from staff, U.S. Food and Drug Admin. to staff, H. Comm. on Energy and Commerce (May 17, 2017, 3:57pm) (On file with the Committee).

⁶⁴ E-mail from staff, U.S. Food and Drug Admin. to staff, H. Comm. on Energy and Commerce (Aug. 20, 2017, 12:50pm) (On file with the Committee).

⁶⁵ U.S. Food and Drug Admin., *supra* note 57.

⁶⁶ Letter from Hon. Fred Upton, Chairman, H. Comm. on Energy and Commerce and Hon. Tim Murphy, Chairman, H. Comm. on Energy and Commerce, Subcomm. on Oversight and Investigations to Hon. Robert M. Califf, M.D. Comm'r, U.S. Food and Drug Admin. (May 18, 2016) (citing E-mail from staff, Centers for Disease Control and Prevention to staff, H. Comm. on Energy and Commerce (Apr. 15, 2016)) (On file with the Committee).

⁶⁷ Briefing by staff, U.S. Dep't of Health & Human Services, Centers for Disease Control and Prevention with staff, H. Comm. on Energy and Commerce, June 8, 2018.

⁶⁸ *Id.*

Global Examples of Emerging and Re-Emerging Infectious Diseases

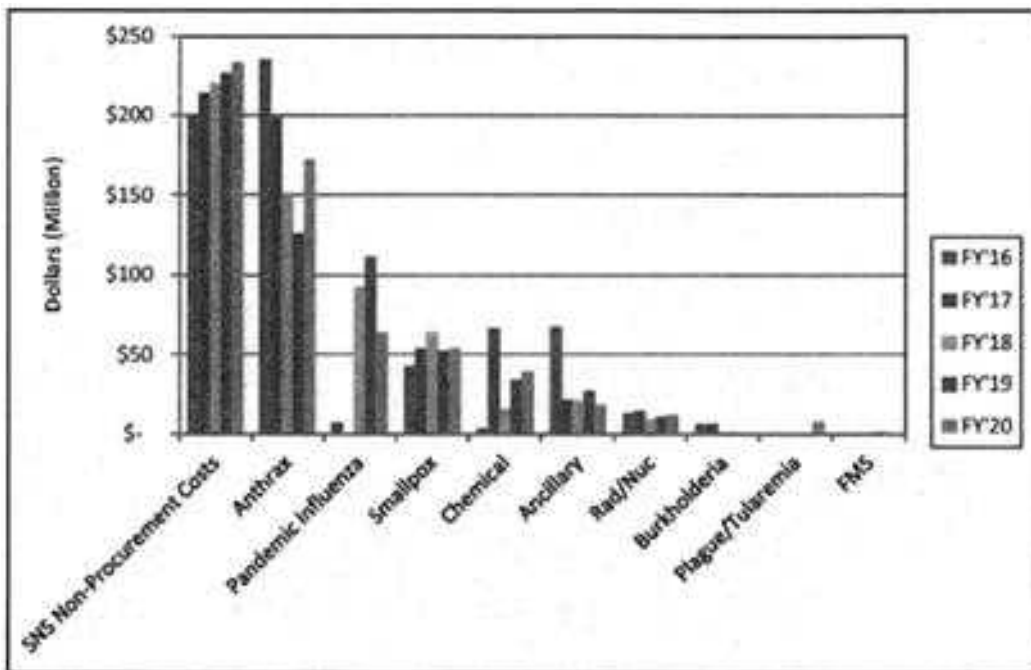
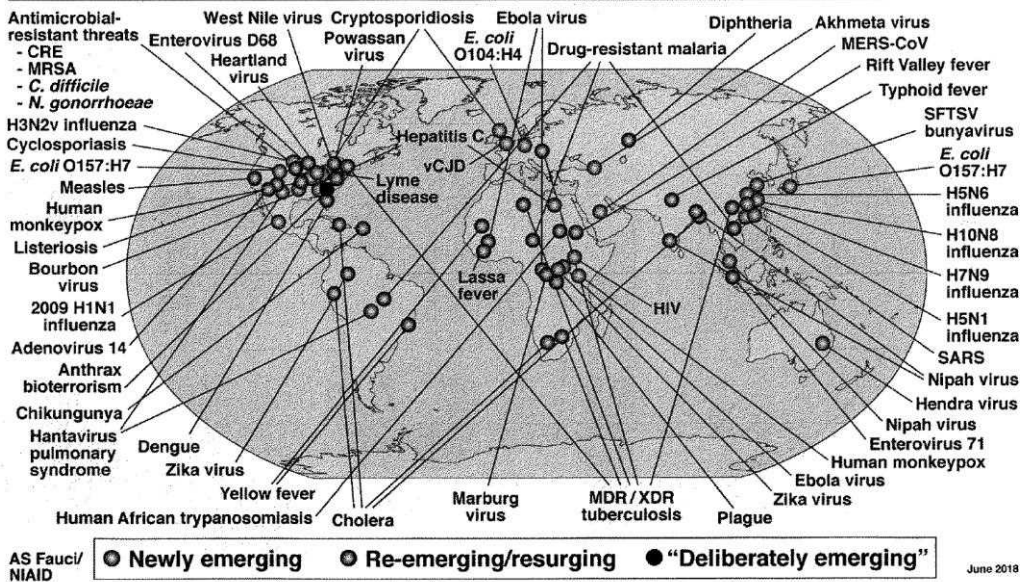


Figure 1. Estimated DSNS spending, by portfolio.

BLUE RIBBON STUDY PANEL ON BIODEFENSE

May 15, 2018

The Honorable Robert Kadlec
Assistant Secretary for Preparedness and Response
U.S. Department of Health and Human Services
200 Independence Ave., SW
Washington, DC 20201
Re: Transforming medical countermeasure technology and partnerships

Dear Dr. Robert Kadlec:

The Blue Ribbon Study Panel on Biodefense recently moderated two roundtables to identify ways to overcome some of the most vexing medical countermeasure (MCM) technology, business, and policy challenges across the biological threat domain. Private sector pharmaceutical, scientific, academic, and governmental affairs representatives attended and were joined at the second meeting by federal officials from the Department of Agriculture (USDA), Department of Defense (DOD), Department of Health and Human Services (HHS), and the White House.

The MCM assets now available to civilians and to military personnel have grown substantially in the last decade. The partnerships needed to continue to build these assets to meet persistent and advancing biological threats, however, are now at considerable risk. Real and perceived under investment, unsustained investment, process uncertainty, and strategic disparity undermine what must be a vibrant enterprise. We maintain that advancing the national MCM infrastructure needed for research, development, and procurement will reduce the risk associated with biological warfare, bioterrorism, emerging infectious diseases, and biological accidents. We urge you to demonstrate your commitment to this core national security function by advancing the following recommendations.

1. Integrate animal health into the national security approach to medical countermeasures. The gross inequality between human and animal funding levels and the segregation of research between the two sectors constitute a national security liability. Many material threats, select agents, and emerging infectious diseases are human diseases with veterinary counterparts, some of which regularly cause outbreaks elsewhere in the world in livestock and wildlife. Yet conversations about the protection of human health by controlling emerging infectious diseases in animal hosts have been extremely limited, and the authority of animal health agencies to regulate has been based on animal health, not public health.

- a) *Establish a framework for combatting emerging infectious diseases.* Most emerging infectious diseases in people originate in animals. No MCM were ready when the largest Ebola outbreak the world had ever seen -likely caused by a spillover from bats to humans-occurred. In the preceding years, the government had not sufficiently determined what to fund with its limited resources. At present, HHS prioritizes efforts to address biological threat agents via Department of Homeland Security material threat determinations (MTDs), but the U.S. government has not instituted

and budgeted for an analogous process for emerging infectious diseases. In accordance with Blue Ribbon Study Panel Recommendation 7c (*A National Blueprint for Biodefense*, 2015), HHS, in coordination with DOD and USDA, should create a similar prioritization framework for emerging infectious disease threats. This framework should address pathogens and pathogen families with the potential to cause a catastrophic public health emergency and include agents known to infect wildlife and domestic animals. It should drive funding for MCM development and other areas (e.g., biosurveillance, response planning) and engage and motivate the private sector to develop and manufacture MCM. Funders must establish a vision for an emerging infectious disease MCM enterprise, define what constitutes successful emerging infectious disease MCM, and communicate this vision along with specific product requirements to industry partners.

- b) *Make USDA part of the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE)*: BARDA was envisioned to be part of- not the entire- MCM enterprise. USDA should also participate in PHEMCE. Many diseases that could necessitate USDA MCM acquisitions are the same for DOD and HHS. USDA also has lessons to share about how it works with industry to develop effective MCM for production animals, a market in which the cost must be low and efficacy must be high. Some veterinary companies are already using platforms to develop their animal products, and the veterinary development timeline is much shorter. This means animal health pharmaceutical companies get products to market earlier. These companies also possess extensive experience in areas like animal models and manufacturability that can help inform human MCM endeavors. These experiences are relevant and should not be ignored.
- c) *Require animal disease risk assessment*. USDA should develop a risk assessment for animal diseases and work with HHS to assess the risk of diseases with zoonotic potential. USDA should assess the ability of the National Veterinary Stockpile to deploy sufficient MCM to combat high-consequence animal diseases within 24 hours of request. USDA should also use these risk assessments to prioritize the pathogens identified on the USDA *High-Consequence Foreign Animal Diseases and Pests* list. USDA should use the findings to inform its budget request; drive federal priorities for MCM innovation; and incentivize public-private partnerships to develop, transition, approve, license, and procure these products.

2. Reduce market and process uncertainty at BARDA. Variability and lack of certainty are two of the foremost hurdles to expanding industry participation in MCM advanced development and manufacturing. Indeed, these hurdles may prove so significant for some companies, even those that have successfully delivered MCM, that they may exit the market entirely. Although all biopharmaceutical ventures carry risk, larger companies can manage this risk through a balanced portfolio of projects, the most successful of which can yield a high return on investment. Pervasive market uncertainty in the far less profitable MCM enterprise makes business endeavors unattractive and unsustainable.

- a) *Create fiscal certainty*. In order to develop national security MCM, industry partners forego potential profit margins orders of magnitude higher than for commercial products. These companies need certainty in procurement to convince them and their investors that engaging in MCM development makes reasonable business sense. The annual appropriations process for advanced development and procurement, and

dependency on emergency supplemental appropriations for unanticipated threats, make doing business with companies that base their operations on multi-year outlooks and planning unsustainable. In accordance with Blue Ribbon Study Panel Recommendation 28b (*A National Blueprint for Biodefense*, 2015),

Congress must reinstate the advanced appropriation for Project BioShield for ten years at a minimum of \$7.1 billion. Additionally, in accordance with Blue Ribbon Study Panel Recommendation 28c, Congress and the HHS Assistant Secretary for Preparedness and Response (ASPR) should address prioritization and the need for guaranteed, sustained funding for pandemic influenza preparedness. The appropriation levels must be tied to rigorously established MCM requirements based on risk analysis.

- b. *Create process certainty:* In the last several years, the f IHS Biomedical Advanced Research and Development Authority (BARDA) noticeably shifted away from process and partnership toward product. Prioritizing products over partnerships has damaged partnerships and preparedness. The rules governing BARDA and DOD processes for advanced development and manufacturing should be defined with industry partners up front and with far greater clarity and commitment. Companies need to understand when and how much of their proposed product the government will procure, as the frequent moving of goalposts throughout development and procurement creates an untenable business environment. For projects in which the government is not interested, federal public health security leaders need to relay that quickly (i.e., white papers should be reviewed and comment provided within 45 days). The BARDA process at this stage of review should be more like that of the Defense Advanced Research Projects Agency (DARPA), for which program managers, not contracting officers, are the central deciding figures.

3. Accelerate platform technologies. One way to create MCM quickly, safely, and effectively for unpredictable emerging infectious diseases and outbreaks is to develop a suite of platform technologies. Generally, platform technologies rely upon a common manufacturing process backbone that uses a standard process to insert foreign genes. By relying upon a well-established manufacturing process and customization through standardized processes, platform technologies can reduce the risk associated with development. These production platforms may be based on, but not limited to, RNA expression systems; DNA cloning vectors; various virus, plant, or bacterial expression vectors; and viral-vectored vaccines. With targeted government and industry investments, these technologies could come to fruition within three to four years, especially for vaccines and diagnostics. To mature the technology, however, the government must mature the way it invests in the technology and ensure that partnership and business plans accompany technical plans for leveraging any platform capability. There is presently no business model in place that addresses how the government can work with industry to develop MCM platforms. At a minimum, elements of certification, expedited review, and the role of the HHS Centers for Innovation in Advanced Development and Manufacturing must be addressed.

- a. *Certify platforms:* The Food and Drug Administration (FDA) approves products, not platforms. FDA, in consultation with DOD, BARDA, and other PHEMCE partners, should establish an MCM platform certification process. A regulatory construct that allows for the consideration of a company's novel platform as a basis for future MCM products would serve as an industry incentive. Its establishment would

effectively reduce the risk of future product development using that platform. Determining what constitutes a platform will be difficult, but the definition should include a regularized chemistry, manufacturing, and controls (CMC) process and standardized general release criteria. The USDA Center for Veterinary Biologics policy, "Licensing Guidelines for Production Platform-Based, Non-Replicating, Nonviable Products," allows for rapid swapping of closely related immunogenic determinants, and could provide a starting point from which FDA could build a platform certification process for human products.

- b. *Priority review platforms:* The platform certification process described above is likely to be extensive and should result in a thorough FDA understanding of the platform technology (e.g., CMC, clinical experience). This advanced understanding will enable subsequent review by the FDA under the expedited Priority Review process of other products based upon that certified platform. FDA commitment to the accelerated approval times associated with Priority Review for subsequent products utilizing a certified platform would provide significant incentive for industry to utilize appropriate platform technologies.
- c. *Leverage CIADMs:* The HHS CIADMs and the DOD MCM Advanced Development and Manufacturing facility (ADM) were envisioned to make such platform-based products a reality. They could enable advanced development and manufacturing of platform technologies if aggressively integrated into the product development process. They should become places where companies want to go to advance their promising technologies. They should shrink development schedules and address significant business difficulties. At present, two major challenges prevent this: small companies are concerned about protecting their intellectual property when handed over to a privately owned ADM with its own MCM interests, and large companies are concerned about risks to their commercial business during regulatory review. The Salk Institute, a private nonprofit organization, was essentially the forerunner of what we think of as an ADM today, and BARDA should consider Salk's example as it revisits the business model for these kinds of facilities. DOD and BARDA should undertake planning for CIADM reconfiguration immediately. Planning should include industry and all federal agencies with MCM responsibility. Considerable thought must be given to contracting reform (discussed below) as the Federal Acquisition Regulation (FAR)-based, cost- reimbursable contract system in place does not work. An independent assessment (outside of DOD and HHS) of the existing CIADM model is needed to support this reconfiguration. This planning must consider the role of the USDA and its industry partners in using the CIADMs to enable mutually beneficial technologies and to keep the facilities in use.

4. Reform FDA process to develop products faster. We can get closer to on-demand MCM in just a few years and investments to improve production cycling by days or weeks are possible. These kinds of advances, however, will not provide the same near-term relief that FDA could achieved on release testing. Investment in enabling technologies must go, therefore, hand in hand with reform of regulatory process. FDA needs to be part of the advanced development process early on, describing what it wants to see in a product or an investigational new drug. Advances in the speed with which products are marketed should not compromise the FDA's high safety and efficacy standards.

- a. *Standardize and clarify regulatory process.* The FDA, in collaboration with its upstream development government partners, must address development and standardization of regulatory processes that will provide needed transparency to MCM developers. The MCM industry needs to understand all elements of the process, and the government needs to mitigate the inherent risk. Several areas of regulatory reform should be considered- for example, reducing risk associated with clinical trials, and allowing companies to focus their resources on development. Through P.L. 115-92, Congress authorized DOD to request, and FDA to provide, assistance to expedite the FDA review process for MCM for military personnel. DOD and FDA have now put a work plan in place to coordinate planning for this process. FDA and BARDA should develop a parallel plan. Expedited release testing and a plan for increased usage of emergency use authorizations (EUAs) should be addressed as part of this plan.
- b. *Expedite release testing:* Even with a vaccine platform, the response time to produce a vaccine for the foreseeable future will be 6-12 months for mass-produced product. While maintaining safety and efficacy standards, acceptable FDA release testing during an outbreak might be different from acceptable release testing at other times. FDA should consider options. For instance, FDA might release products for use on an interim basis with final release testing to follow. FDA might identify suitable surrogates in place of full toxicology panels- or at least utilize a process to pre-identify what those surrogates would be. FDA should describe what an accelerated schedule would look like in an emergency. This will be especially important for platforms that could address multiple infectious diseases. Once in place, manufacturers could then propose specific schedules for a given MCM.
- c. *Examine increased usage of Emergency Use Authorizations:* EUAs are designed for those MCM that are sufficiently well characterized to be of likely clinical benefit in an emergency. FDA essentially certifies that a given MCM fulfills EUA requirements. FDA should determine when more aggressive utilization of EUAs would be appropriate.

5. Improve contracting authorities. BARDA must be empowered to make decisions in the best interest of fulfilling its mission. This means ensuring that the contracting process is as smooth, flexible, and transparent as possible. Other Transactional Authority (OTA) is most prominent among the existing contracting authorities that would incentivize MCM partnerships, yet it is utilized very rarely and limited by the statute that provided OTA authority to BARDA.

- a. *Amend the OTA statute.* Congress modeled the OTA authority addressed in the *Pandemic All-Hazards Preparedness Act (PAHPA)* after DOD's OTA statute. In its reauthorization of *PAHPA*, Congress should customize OTA authority to fit BARDA's needs. Congress should also remove references to DOD and the need for approval by the senior executive for projects above \$20 million (as it did previously for DOD). OTA contracts should become far more common than they are now, perhaps as common if not more than FAR-based contracts.
- b. *Adopt OTA for the CIADMs:* FAR-based contracting does not work for rapid response procurements. Using OTA for the ADMs is critical to prevent abandonment of partnerships when rapidity is imperative, when the science does not go as planned, and when

intellectual property and FAR-based requirements arise. DOD has adopted this OTA-based model for its ADM.

- c. *Move contracting authority back to BARDA.* In accordance with Blue Ribbon Study Panel Recommendation 29a (*A National Blueprint for Biodefense*, 2015), and the *21st Century Cures Act* Section 3082, contracting authority should be the exclusive responsibility of BARDA, not the office of Acquisition, Management, Contracts and Grants in the Office of the ASPR. This move must be finalized.

6. Foster innovation and new capabilities. The government often bases MCM-related plans on budgets instead of basing budgets on need. A similar mindset is seen with the government's approach to industry, often issuing solicitations to assess existing capabilities, rather than fostering new capabilities to meet national security needs. At the time of its authorization in *PAHPA*, Congress envisioned BARDA to be on the leading edge of MCM innovation. Over the past decade, BARDA has focused on more, well-established, product development technologies and investments in technologies closer to full maturity. This approach certainly justified much of the development portfolio. Live viral vaccine platforms and therapeutics based on monoclonal antibodies may well provide near- to medium-term solutions. Yet BARDA needs to devote sufficient resources to novel and high-risk product development activities in parallel with their less risky investments.

- a. *Invest in novel and high-risk products.* Meeting emerging national security threats will require BARDA to employ a high-risk, high-reward model for at least a portion of its investments. Instead of issuing solicitations to assess current industry capabilities, agencies should aggressively work with the private sector to build capabilities to meet national security needs. While investment in tried-and-true technologies will remain important, aggressively pursuing technologies that fall outside BARDA's comfort zone is imperative. The *21st Century Cures Act* authorized the Director of BARDA to engage an independent, non-profit innovation partner. BARDA should leverage this opportunity to dedicate additional resources to high-risk, high-reward outputs. It should further consider the role of the animal sector in providing needed technological advancements. The animal sector has existing markets for certain pharmaceuticals (for instance, with respect to coronaviruses and influenza viruses, which happen to be the most significant viral pandemic threats to the human population) that are lacking in the human sector. A shared interagency approach to planning for, and funding in, such areas could lead to needed innovative breakthroughs. Precedence for interagency funding mechanisms can be found in the funding HHS provided to USDA in 2009 to conduct domestic biosurveillance for swine influenza virus, a pathogen with minimal health impacts on the animal carrier but large potential impacts on public health.

- b. *Invest in rapid diagnostics.* The nation needs to invest far more in patient-side, point-of-care diagnostics.

Diagnostics can guide prioritization of MCM resources, but MCM conversations often refer only to vaccines and therapeutics, omitting diagnostics altogether. Rapid diagnostics cannot continue to be an afterthought. In accordance with Blue Ribbon Study Panel Recommendation 30a (*A National Blueprint for Biodefense*, 2015), DOD and BARDA need to invest in rapid diagnostics as a core element of their MCM portfolios. This work should identify generalized biomarkers that would enable such technologies.

- c. *Drive decision-making with early warning and predictive tools.* Leadership has yet to embrace predictive science as a core capacity that can support traditional and transformative MCM development. Advances in genomics and proteomics, risk mapping, and biosurveillance data analytics should all be leveraged to create early warning that could both inform and spare the stockpile. Budget requests and corresponding appropriations should support these efforts and ensure that they are an integral part of the federal MCM development and procurement strategy by aligning MCM investments with the threats identified through early warning programs.

7. Establish end-to-end enterprise coordination. Although PHEMCE was envisioned as a coordinating body for the federal MCM enterprise, it has been too HI·IS-centric to do this effectively. Development of a far more forward-looking process -from idea to procurement to dispensing- is needed. As the Office of the ASPR reimagines the end-to-end nature of the enterprise, it has an opportunity to address some specific challenges in the current construct.

- a. *Improve interagency product transitions.* Successful research projects at the National Institutes of Health, DARPA, or other agencies, must begin competition anew for advanced development- if advanced development funding is even available or prioritized. This creates major bureaucratic hurdles to product advancement. The National Biodefense Strategy should direct the creation of more streamlined interagency transition mechanisms. A wards can be structured to assume transition from one agency to the next.
- b. *Transfer management of the Strategic National Stockpile under specific conditions.* In the President's Budget Request for FY 2019, the Administration moved management responsibility of the Strategic National Stockpile (SNS) from the Centers for Disease Control and Prevention (CDC) to the ASPR. CDC management of the SNS has been inadequate, resulting in industry confusion and losses when the agency suddenly decided to remove elements from the stockpile that it had previously approved. The Administration made this move, in part, to better enable HHS leadership to direct acquisition for, and deployment of, the SNS. The move has the potential to create a more cohesive development-to- distribution structure and apply more process certainty to procurement decisions. Concerns about how BARDA and the SNS will interact once the move is finalized, and whether investments made by BARDA will inadvertently or intentionally force the SNS to acquire those MCM it developed, must be addressed. Congress should authorize the transfer of management of the SNS to the ASPR only if it also requires the ASPR to fix SNS-related problems that the CDC and state, local, tribal, and territorial (SLTT) partners previously encountered or created, and to put controls in place to prevent automatic uptake of BARDA products by the SNS just to demonstrate BARDA success. Congress should also direct the ASPR to establish a meaningful SNS training program for SLTT partners that focuses on more than just anthrax, takes SLTT ability to distribute SNS pallets upon receipt into consideration, and does not assume distribution will occur the same as in the military.
- c. *Produce an MCM response framework.* In accordance with Blue Ribbon Study Panel Recommendation 22a (*A National Blueprint for Biodefense*, 2015), the Office of the ASPR, CDC, and the Federal Emergency Management Agency should, together with non-federal partners, identify requirements and capacities needed to achieve successful distribution and dispensing of MCM from the SNS as well as from local

caches. The framework they develop must address unresolved issues. A progressive and innovative approach should push beyond what a given agency might devise and the bureaucratic impediments associated with a federal-only distribution system. If implementation exceeds funding available through current grant allocations, additional funding must be requested.

Thank you for considering these findings and recommendations. Please contact Dr. Asha M. George, Panel Executive Director, at (202) 974-2416 or Asha.George@BiodefenseStudy.org with further questions.

Sincerely,

Joseph I. Lieberman, Chair
Donna E. Shalala
James C Greenwood
Thomas J. Ridge, Chair
Thomas A. Daschle
Kenneth L. Wainstein

CC BARDA Director Rick Bright
Jenn Alton

* * *

GREG WALDEN, OREGON
CHAIRMAN

FRANK PALLONE, JR., NEW JERSEY
RANKING MEMBER

ONE HUNDRED FIFTEENTH CONGRESS
Congress of the United States
House of Representatives
COMMITTEE ON ENERGY AND COMMERCE
2125 Rayburn House Office Building
WASHINGTON, DC 20515-6115

July 12, 2018

Dr. Rick A. Bright
Director, Biomedical Advanced Research and Development Authority
Deputy Assistant Secretary, Office of the Assistant Secretary for Preparedness and Response
U.S. Department of Health and Human Services
200 Independence Avenue, S.W.
Washington, DC 20201

Dear Dr. Bright:

Thank you for appearing before the Subcommittee on Oversight and Investigations on June 15, 2018, to testify at the hearing entitled "The State of U.S. Public Health Biopreparedness: Responding to Biological Attacks, Pandemics, and Emerging Disease Outbreaks."

Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for ten business days to permit Members to submit additional questions for the record, which are attached. To facilitate the printing of the hearing record, please respond to these questions with a transmittal letter by the close of business on Thursday, July 26, 2018. Your responses should be mailed to Ali Fulling, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, DC 20515 and e-mailed in Word format to Ali.Fulling@mail.house.gov.

Thank you again for your time and effort in preparing and delivering testimony before the Subcommittee.

Sincerely,
Gregg Harper
Chairman
Subcommittee on Oversight and Investigations

cc: The Honorable Diana DeGette, Ranking Member, Subcommittee on Oversight and Investigations
Attachment

**HOUSE ENERGY AND COMMERCE COMMITTEE, SUBCOMMITTEE ON
OVERSIGHT AND INVESTIGATIONS, "THE STATE OF U.S. PUBLIC
HEALTH BIOPREPAREDNESS: RESPONDING TO BIOLOGICAL
ATTACKS, PANDEMICS, AND EMERGING INFECTIOUS DISEASE
OUTBREAKS," DR. RICK BRIGHT, DIRECTOR OF ASPR'S
BIOMEDICAL ADVANCED RESEARCH AND DEVELOPMENT
AUTHORITY, FRIDAY, JUNE 15, 2018**

The Honorable Gregg Harper

1) In the 2017 update to HHS' Pandemic Influenza Plan, HHS provided benchmarks for manufacturing and distributing vaccines during declared influenza pandemics. HHS stated that it aims to ensure that limited vaccine distribution occurs within 12 weeks of a pandemic being declared, with distribution sufficient to meet overall public demand occurring within 16 weeks. Could you tell us why this process seemingly takes so long, and provide any recommendations for improving it? If the 12 and 16-week benchmarks are HHS's goals, what are our current capabilities?

ASPR Response:

Domestic manufacturing capacity for pandemic influenza vaccine is a critical component of pandemic preparedness to ensure vaccine is available as soon as possible after emergence of a pandemic virus. ASPR/BARDA has made significant gains in pandemic influenza vaccine preparedness over the last 10 years, including supporting the licensure of faster, more flexible cell-based, recombinant and adjuvanted influenza vaccines and modernizing and expanding domestic manufacturing capabilities. These advancements have dramatically increased the domestic influenza vaccine antigen capacity increasing from 60 million doses to 600 million doses.

Building on these successes, and to ensure vaccine is available within 12 weeks of pandemic declaration, ASPRJBARDA has a multifaceted approach in place. First ASPR/BARDA is partnering with companies to support the development of novel technologies that rely less on viral growth properties to improve the speed and robustness of vaccine production. For example, ASPRJBARDA supported the first licensed recombinant influenza vaccine (Flublok®), and ASPRJBARDA continues to fund recombinant vaccine-related efforts, moving away from the slow, inflexible production of vaccine in eggs. Second, ASPRJBARDA is supporting the sustainment of domestic production capabilities to ensure vaccines are available when necessary. Third, ASPRJBARDA is supporting further development of recombinant and cell-based vaccines through comparative efficacy clinical studies to expand use indications for a broad range of high- risk and special populations. Fourth, ASPRJBARDA is supporting the addition of currently approved adjuvanted influenza vaccines for all ages into both seasonal and pandemic vaccines, while also developing additional adjuvant options that provide safe and enhanced effectiveness to influenza vaccines that are faster to produce. Lastly, ASPRJBARDA is targeting advancements in vaccine delivery and administration to develop new approaches that would reduce reliance on needles and syringes supply chain surge capacity and allow faster and more efficient immunization with pandemic vaccine.

2) In general, what is the shelf-life for the H7N9 influenza strain vaccine that is in BARDA's pre-pandemic stockpile that will protect against the 2013 H7N9 strain? When was the last time BARDA performed a potency test on these vaccines?

ASPR Response:

The pre-pandemic vaccine made in eggs against the 2013 H7N9 avian influenza virus strain is very stable, with over 80% stability as of the last potency test conducted November, 2017. The most recent potency testing for the egg based vaccine was performed in May 2018 and we are awaiting results of this testing.

3) How serious of a pandemic threat does the BARDA view the 5th wave H7N9 influenza strain, currently circulating in China? If a pandemic were to occur, how severely would it impact public health? Is BARDA currently overseeing the manufacturing of a vaccine for storage in its pre-pandemic stockpile which will match this H7N9 influenza strain?

ASPR Response:

BARDA views the 5th wave H7N9 influenza outbreak as a serious concern, as reflected by the high Influenza Risk Assessment Tool (IRAT) score assigned by CDC. Since this assessment system, which assesses the threat of influenza viruses with pandemic potential, was initiated in 2012, the 5th wave H7N9 strain has the highest Potential Impact Risk of any influenza strain evaluated.

Given the human mortality rate seen to date, if the viruses changed to allow them to spread easily between humans, the impact on public health could be catastrophic in the absence of effective medical countermeasures such as vaccines. There is also evidence that some H7N9 influenza viruses may be resistant to most available antiviral drugs.

In response, BARDA produced bulk vaccine, currently held in storage, which matches the 5th wave H7N9 strain. Additionally, the National Institutes of Health (NIH) and BARDA are conducting clinical trials to better understand optimal vaccination approaches in the event mass vaccinations are necessary.

4) How much is BARDA currently spending on CARB-X? Does the agency anticipate maintaining this level of spending over the next five years?

ASPR Response:

BARDA established CARB-X in collaboration with the NIH's National Institute of Allergy and Infectious Diseases in 2016. CARB-X, an innovative public-private partnership that addresses the threat of antibiotic resistant bacteria, has received \$85 million in support from BARDA over two years. CARB-X is also funded by the Wellcome Trust. In 2018 the Bill & Melinda Gates Foundation and the United Kingdom Government's Department of Health and Social Care joined as funding partners. BARDA's support for new antibiotics and diagnostics is critical to address 21st century health security threats including genetically engineered bacterial pathogens, complications of bacterial infections as a result of exposure to priority threats such as nuclear and chemical agents, and to quickly identify bacterial pathogens and their susceptibility to antibiotics. BARDA anticipates continued support based on availability of funds.

5) What is the PHEMCE's role in making a material threat determination, and how can the length of time it takes for such a determination be reduced?

ASPR Response:

The Public Health and Emergency Medical Countermeasure Enterprise (PHEMCE), a Federal advisory and coordinating body led by ASPR, does have a role in advising on medical countermeasure requirements for national security material threats identified by the Department of Homeland Security (DHS). DHS's newly established Countering Weapons of Mass Destruction Office issues material threat assessments (MTAs) and the Secretary of the Department of Homeland Security (DHS) issues material threat determinations (MTDs). MTAs and MTDs are done in collaboration with other interagency departments, but the responsibility for generating these national, strategic overviews and quantification of the threat is identified by statute (section 319F-2(c)(2) of the Public Health Service Act (42 U.S.C. 247d-6b(c)(2)), added by the Project BioShield Act of 2004") as a DHS authority and responsibility. The PHEMCE benefits from these determinations and uses them to forecast

medical countermeasure requirements (type, quantity, special considerations). ASPR is currently working with other PHEMCE interagency partners to evaluate and identify opportunities to streamline and speed up these deliberative steps. We would be pleased to brief the Committee on potential process improvements after the evaluation is completed.

6) After ASPR assumes operational control of the Strategic National Stockpile on October 1, 2018, what role will CDC play in support of the stockpile's mission?

ASPR Response:

ASPR recognizes and appreciates the tremendous expertise of CDC subject matter experts including on infectious diseases, other public health threats, epidemiological and laboratory surveillance, as well as understanding of the capabilities of state and local public health departments. CDC is an active partner on the PHEMCE, which is led by ASPR and provides a venue for sharing information across HHS agencies and with interagency partners with a role in medical countermeasures requirement setting, research, development, regulatory review, procurement, stockpiling, distribution and use. CDC will remain an active participant in all PHEMCE workgroups and committees.

In order to ensure a smooth transition of the Strategic National Stockpile with no degradation of operational capability, ASPR and CDC have set up several joint transition workgroups to evaluate all aspects of the program transition. Some of the details involved in the transition have not been finalized. However, we would be pleased to provide a full briefing for Committee staff at any time before the end of the fiscal year. Subsequent to this hearing, the SNS successfully transferred from CDC to ASPR on October 1, 2018.

CDC will maintain its strong working relationships with state and local public health agencies, playing a key role in distribution and dispensing of medical countermeasures. CDC will accomplish this by continuing to provide technical guidance and funding through cooperative agreements and embedding experts in state and local health departments. Coordination with state and local agencies will be enhanced by incorporating ASPR's extensive relationships with health care organizations and emergency management agencies.

Further, to continue to increase collaboration across the Department, ASPR has invited and instituted a new senior CDC liaison who is working within the ASPR Immediate Office.

7) How prepared are the nation's hospitals to respond to biological threats or infectious diseases? What are the most pressing challenges facing non- governmental health systems and what could we do to improve their response capabilities?

ASPR Response:

Since the Hospital Preparedness Program (HPP) was established, investments have been made to enhance the overall preparedness of the nation's healthcare infrastructure. Initially, HPP supported the procurement of materials and supplies (e.g., generators, masks, etc.) that would be used should a community be impacted by a public health or medical event. In 2012, HPP shifted its focus from purchasing supplies to investing in health care coalitions (HCCs). HCCs are groups of health care and response organizations that collaborate to prepare for and respond to medical surge events. HCCs incentivize diverse and often competitive health care organizations to work together. During recent events, ranging from mass shootings (e.g., Las Vegas, Florida night club), hurricanes (e.g., Matthew, Harvey, Irma, and Maria), and the most

recent tornados in Iowa, we have witnessed the value of the HCCs in enabling communities to quickly assess healthcare capabilities to continue to support communities without requesting assistance from the federal government.

Prior to the 2014 Ebola outbreak in West Africa, the United States did not have an organized, systematic approach to preparing for, and responding to, an outbreak of a highly infectious pathogen. CDC in collaboration with ASPR developed a tiered approach to prepare U.S. health care facilities to safely and rapidly identify, isolate, evaluate, and manage, travelers or patients who have possible or confirmed Ebola. This included providing rapid technical assistance to hospitals strategically located near airports with a large number of travelers returning from Ebola-affected countries and in communities where large numbers of persons from these West African countries reside. To support this, HPP provided awardees with approximately \$214 million of Ebola emergency supplemental funding to establish a nationwide, regional treatment network for Ebola and other infectious diseases. The funding provided through HPP Ebola Preparedness and Response activities is intended to establish the foundation required for the nation's health care system to safely and successfully identify, isolate, assess, transport, and treat patients with Ebola virus disease or under investigation for Ebola (or other highly infectious diseases). Through this mechanism, ASPR awarded cooperative agreements to all 50 states, Washington D.C., all U.S. territories and freely associated states, and select metropolitan jurisdictions, over a five-year project period. Additionally, ASPR competitively awarded funding to 10 regional Ebola and other special pathogen treatment centers (i.e., one in each of the 10 HHS regions).

Additionally, to prepare for, and provide safe and successful care of patients with Ebola, HHS (in a collaboration between ASPR and CDC) awarded funding to establish a National Ebola Training and Education Center (NETEC). The NETEC provides expertise, training, technical assistance, peer review, monitoring, and recognition to state health departments, regional Ebola and other special pathogen treatment centers, state- and jurisdiction-based Ebola treatment centers, and assessment hospitals. NETEC is a consortium of three U.S. health facilities that safely and successfully treated a confirmed Ebola patient- Emory University in Atlanta, Georgia; University of Nebraska Medical Center/Nebraska Medicine (UNMC) in Omaha, Nebraska; and the New York City Health and Hospitals Corporation/HHC Bellevue Hospital Center in New York, New York.

Going forward and leveraging the best practices from investments made with the Ebola supplemental appropriations, ASPR is developing innovative tiered regional demonstration projects that can serve as a model for building a regional disaster health response system across the country. Subsequent to this hearing, ASPR awarded two grants- Nebraska Medicine in Omaha, Nebraska and Massachusetts General Hospital in Boston, Massachusetts to conduct pilot projects that show the potential effectiveness and viability of a Regional Disaster Health Response System (RDHDS).

The Honorable Michael C. Burgess

1) Dr. Bright, in 2010, BARDA established three centers to develop and manufacture medical countermeasures, such as vaccines and therapeutics, to protect our citizens during public health emergencies. Texas A&M's Center for Innovation in Advanced Development

and Manufacturing is one of these centers, and was intended to focus on surge capacity for flu vaccines. I understand that the initial contract period with the Texas facility expires at the end of this month. How does BARDA plan to utilize these centers in the future? Will BARDA maintain and grow existing partnerships that have the infrastructure to deploy capabilities in the wake of a crisis?

ASPR Response:

BARDA established the Centers for Innovation in Advanced Development and Manufacturing as public private partnerships in 2012. The program has made important investments in the domestic capacity for medical countermeasure production for public health emergencies. Each of the three centers in Texas, Maryland and North Carolina were funded to establish pandemic influenza vaccine manufacturing surge capacity, core service capabilities, and workforce development programs. Program successes include: process updates that resulted in a fourfold increase in yield for the domestically-produced cell based inactivated influenza vaccine; the development of commercially run facilities in Texas and Maryland; and a well- established workforce development program at Texas A&M in College Station, Texas. BARDA recently issued a six month extension to the base period for the Texas A&M center to facilitate additional partnering opportunities.

BARDA is currently evaluating how best to sustain and strengthen the domestic medical countermeasure manufacturing capabilities needed for the nation to be optimally prepared for 21st century health security threats.

2) How do you communicate with centers such as Texas A&M about what medical countermeasures they should develop? How involved is BARDA in helping these "centers" identify additional partners with whom they can work?

ASPR Response:

Each Center has a designated federal contracting officer representative and contracting officer. These officials monitor completion of contract requirements and subsequent task orders that the centers have to meet per the terms of the contract. BARDA also holds frequent site visits and regular status calls with each of the Centers and has encouraged potential partner discussions through those interactions. Lastly, the Centers are required to maintain other commercial business/partnerships to make use of established capacity, to offset costs, and be a shared resource.

The Honorable Frank Pallone, Jr.

1) With respect to the three types of threats we often hear about- natural, intentional, and accidental-to what extent do preparedness efforts for the different types of threats overlap?

ASPR Response:

ASPR coordinates with states and local officials before, during, and after emergencies to test existing response capabilities. While each incident, whether naturally occurring, man-made, or accidental, has its own considerations, there are common requirements that spread

across all emergencies. Common elements include supporting situational awareness and information sharing between and among all supporting officials, supporting and augmenting local healthcare entities in treating the impacted population, ensuring critical assets are available to communities in need, and supporting the recovery of the community.

Investing in technologies that have the potential to yield multiple diagnostics, vaccines or therapeutics against different pathogens ensures that capabilities are nimble and flexible to support vaccines and therapeutics for future threats. Examples of this type of investment are how BARDA is supporting development of vaccines against the Ebola Zaire virus. Currently, BARDA is supporting two candidates under Project BioShield. There is the potential that same vaccine platform used to develop the Ebola Zaire virus vaccines could be used to develop vaccines against Ebola Sudan or Marburg viruses, by replacing just one element (glycoproteins). In addition, the vaccine platform could be used to express proteins from newly identified pathogens and expedite development of a vaccine for clinical trials.

2) How can we plan long-term therapeutics and vaccines in order to respond to outbreaks that we cannot yet anticipate?

ASPR Response:

It often takes 10 or more years and over \$1 billion to develop a new drug or vaccine.

ASPR/BARDA utilizes many of the innovative authorities authorized by amendments made by the Pandemic and All-Hazards Preparedness Act to the Public Health Service Act to support development of medical countermeasures. Authorities like Other Transaction Authorities (OTA) mean ASPR/BARDA can enter into innovative agreements to support development and procurement. As an example, the first BARDA OTA was within the broad spectrum antimicrobial program. Currently three out of six BARDA OTAs are focused on development of antimicrobial products. BARDA has also utilized CARB-X- an innovative public-private partnership conducted under a cooperative agreement- to address the threat of antibiotic resistant bacteria. CARB-X involves seven partners in the U.S. and U.K. and is backed with half a billion dollars in funding. \$85 million in BARDA CARB-X investment resulted in nearly \$500 million in private equity follow on investment. The partnership has 28 different companies making novel antibacterial drugs, vaccines, and diagnostics, including eight new classes of antibiotics.

3) BARDA's CARB-X program is developing many nontraditional products at the preclinical stage. Can you briefly explain why you have supported these products, and what BARDA is doing to make sure that enough products move on to clinical trials?

ASPR Response:

Under the National Action Plan for Combating Antibiotic Resistant Bacteria (CARB), published by the White House in 2015, ASPR was directed to establish a biopharmaceutical accelerator in collaboration with NIH. BARDA established CARB-X in collaboration with the NIH's National Institute of Allergy and Infectious Diseases (NIAID), in NIH, in 2016. This was two years ahead of the three year milestone to establish the partnership. CARB-X is an international consortium of funders including BARDA, NIAID, Wellcome Trust, the Bill & Melinda Gates Foundation, and the UK Government's Department of Health and Social Care.

BARDA does not support the product portfolio alone; instead it is a collaborative effort across multiple, international organizations. BARDA funds non-traditional products because antibiotics are a solution but not the only solution for antibiotic resistant bacteria. In addition, all of the candidate products supported under CARB-X can support new treatment options for genetically engineered biothreat pathogens or the secondary bacterial infections that will result from exposures to threat agents, such as ionizing radiation from a nuclear blast or burn injuries resulting from nuclear or chemical agents.

Five products under the CARB-X portfolio have advanced to phase I clinical trials with more expected in the coming years. Candidate products may move into clinical trials when clinical trial proposals and data to support investigational new drug status are submitted to the FDA and data review does not show prohibitive adverse risk-benefit concerns. BARDA, as a funder and as a member CARB-X, works closely with the cooperative agreement awardee's program team to make sure that products are meeting the scientific milestones to advance in development.

4) Can you explain what BARDA is doing to foster public-private partnerships, and why this is important?

ASPR Response:

BARDA established and manages the Tech Watch Program (<https://www.phe.gov/about/barda/Pages/BARDA-techwatch-Mtgs.aspx>). Under Tech Watch, companies can come and discuss their technologies with BARDA to determine if the product is appropriate for BARDA to consider funding in the future. If the program does not align with BARDA priorities, we will refer them to other federal agencies that may be able to assist them with development. BARDA holds 150-200 Tech Watches per year.

BARDA also holds an annual BARDA Industry Day (BID), consistent with its authorities under the Public Health Service Act. This meeting brings together BARDA and other PHEMCE partners with industry, academic, and non-government organizations. It provides an opportunity for BARDA to highlight current and future strategic plans and priorities. BID also provides companies the opportunity to discuss their programs and how they might be able to address existing or future requirements.

Lastly, BARDA attends national and international conferences to discuss our portfolio of products, potential additional candidates, and our strategic plans. Numerous stakeholders attend these conferences allowing for another venue for BARDA to meet with potential partners.

BARDA cannot develop countermeasures alone. Public-private partnerships are critical to the continued success of BARDA and all of the ongoing medical countermeasure development initiatives.

5) ASPR has a number of programs in place, including the Hospital Preparedness Program and the Medical Reserve Corps, which are designed to help ensure readiness at the state and local level. How do these programs ensure that our front-line responders are able to respond effectively in a public health emergency situation?

ASPR Response:

ASPR's mission is to save lives and protect Americans from 21st century health security threats. On behalf of the Secretary of HHS, ASPR leads public health and medical preparedness for, response to, and recovery from disasters and public health emergencies.

All of ASPR's programs and capabilities work together to create "unity of command" by consolidating Federal nonmilitary public health and medical preparedness and response functions. ASPR coordinates across HHS and the Federal interagency to support state, local, territorial, and tribal health partners. ASPR works to enhance medical surge capacity by organizing, training, equipping, and deploying HHS public health and medical personnel, such as National Disaster Medical System (NOMS) teams, and providing logistical support for HHS personnel responding to public health emergencies. ASPR supports readiness at the state and local level by coordinating federal grants and cooperative agreements, such as the Hospital Preparedness Program (HPP), by programs like the Medical Reserve Corps (MRC), and carrying out drills and operational exercises. For example, HPP prepares the nation's health care system to save lives during emergencies and disasters. It is the only source of federal funding for health care system readiness. HPP prepares the health care system to save lives through the development of health care coalitions (HCCs). HCCs are groups of health care and response organizations that collaborate to prepare for and respond to medical surge events. HCCs incentivize diverse and often competitive health care organizations to work together, allowing them to plan together and respond jointly in emergencies.

Specific to how ASPR supports first responders, ASPR routinely partners with state and local governments, hospitals, and responders to conduct drills and exercises to test various aspects of medical response capabilities. Drills and exercises provide opportunities at all levels to examine plans, procedures, and capabilities and to work with all government partners to employ resources in response to a specific event or scenario. One recent example is ASPR's Tranquil Terminus Exercise that brought together four regions, seven states, eight cities and three federal departments to test the nation's ability to transport patients with a highly infectious disease. Communities and responders benefitted by having the opportunity to test and rehearse plans with all partners participating. They learned from each other as well as identified best practices for inclusion in their plans and procedures.

6. CDC recently concluded an operational readiness review to assess whether state and local governments and public health services will be able to effectively get medical countermeasures to the appropriate person at the appropriate time. How does BARDA work with CDC and health departments to ensure that we develop countermeasures with this "last mile" of delivery in mind?

ASPR Response:

Through its active role in PHEMCE, CDC shares information across HHS agencies, including ASPR/BARDA, who have a role in medical countermeasures requirement setting, research, development, regulatory review, procurement, stockpiling, distribution and use. Through this channel, as well as through established direct program-to-program collaborations with BARDA, CDC provides input on how countermeasure development can better meet end user needs. This includes criteria for how products developed may be stored and packaged to improve/simplify stockpiling and distribution, improved product delivery

systems, simplified dosing considerations, etc. These factors assessed by CDC, impact how products are distributed, dispensed/administrated and used.

* * *

GREG WALDEN, OREGON
CHAIRMAN

FRANK PALLONE, JR., NEW JERSEY
RANKING MEMBER

One Hundred Fifteenth Congress
Congress of the United States
House of Representatives
Committee on Energy and Commerce
2125 RAYBURN House Office Building
WASHINGTON, DC 20515-6115

July 12, 2018

Dr. Anne Schuchat
Principal Deputy Director
Centers for Disease Control and Prevention
1600 Clifton Road; Atlanta, GA 30329

Dear Dr. Schuchat:

Thank you for appearing before the Subcommittee on Oversight and Investigations on June 15, 2018, to testify at the hearing entitled "The State of U.S. Public Health Biopreparedness: Responding to Biological Attacks, Pandemics, and Emerging Disease Outbreaks."

Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for ten business days to permit Members to submit additional questions for the record, which are attached. To facilitate the printing of the hearing record, please respond to these questions with a transmittal letter by the close of business on Thursday, July 26, 2018. Your responses should be mailed to Ali Fulling, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, DC 20515 and e-mailed in Word format to Ali.Fulling@mail.house.gov.

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,

Gregg Harper
Chairman, Subcommittee on Oversight and Investigations

cc: The Honorable Diana DeGette, Ranking Member, Subcommittee on Oversight and Investigations
Attachment

ATTACHMENT-ADDITIONAL QUESTIONS FOR THE RECORD

The Honorable Gregg Harper

1. Have there been any laboratory-acquired infections or potential exposures to pathogens at CDC labs during this past year? If so, what was the nature of the exposure or infection, and were any hospitalizations required as a result?

2. How serious of a pandemic threat does the CDC view the 5th wave H7N9 influenza strain, currently circulating in China? If a pandemic were to occur, how severely would it impact public health?

3. What are the present challenges that are preventing the broader utilization of cell-based influenza vaccines, and what steps can be taken to become less reliant on egg-based vaccines? What are the advantages of utilizing cell-based influenza vaccines over egg-based ones?

4. Is there currently an approved anthrax vaccine that can be administered to children? If so, what are the dosing guidelines for pediatric administration? If not, are there any pediatric anthrax vaccines currently under development, and what is the status of this development?

5. Were any FY 2017 funds for the non-procurement costs of the Strategic National Stockpile (SNS) used for any CDC expenses outside of the SNS program? If so, please identify the type and amount of these expenses.

6. How many laboratories currently make up the Laboratory Response Network (LRN)?

7. How much funding is there for the LRN in FY 2018?

The Honorable Michael C. Burgess

1. Dr. Schuchat, in your written testimony you mentioned CDC's use of electronic data systems to monitor population health information. How does CDC use and disseminate this data such that it can coordinate a timely response? Is the data platform that CDC uses integrated or interoperable with other biosurveillance platforms?

The Honorable Frank Pallone, Jr.

1) How does CDC ensure that its laboratories are gathering data from as many sources as possible?

a. Do you need additional resources to help you analyze this data more effectively?

d) Please provide an update on CDC's concerns about the growth of antibiotic resistant bacteria?

e) In the case of an emergent biological threat, how does CDC's Emergency Operations Center coordinate the response at the front lines, such as at the state and local level?

- f) Please describe how CDC uses its Public Health Emergency Preparedness Cooperative Agreement Program to help states and local municipalities identify and address gaps in preparedness. Is there anything you need from Congress to make sure this program works as intended?
- g) What are the biggest challenges to successfully deploying countermeasures at the state and local level? How is CDC addressing these challenges?

GREG WALDEN, OREGON
CHAIRMAN
FRANK PALLONE, JR., NEW JERSEY
RANKING MEMBER

One Hundred Fifteenth Congress
Congress of the United States
House of Representatives
Committee on Energy and Commerce
2125 RAYBURN House Office Building
WASHINGTON, DC 20515-6115

July 12, 2018

Dr. Anthony S. Fauci; Director
National Institute of Allergy and Infectious Diseases
National Institutes of Health
9000 Rockville Pike; Bethesda, MD 20892

Dear Dr. Fauci:

Thank you for appearing before the Subcommittee on Oversight and Investigations on June 15, 2018, to testify at the hearing entitled "The State of U.S. Public Health Biopreparedness: Responding to Biological Attacks, Pandemics, and Emerging Disease Outbreaks."

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Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely, Gregg Harper Chairman
Subcommittee on Oversight and Investigations

cc: The Honorable Diana DeGette, Ranking Member, Subcommittee on Oversight and Investigations
Attachment

**HOUSE ENERGY AND COMMERCE COMMITTEE, SUBCOMMITTEE ON
OVERSIGHT AND INVESTIGATIONS, “THE STATE OF U.S. PUBLIC
HEALTH BIOPREPAREDNESS: RESPONDING TO BIOLOGICAL
ATTACKS, PANDEMICS, AND EMERGING INFECTIOUS DISEASE
OUTBREAKS,” FRIDAY, JUNE 15, 2018**

The Honorable Gregg Harper

1) What do we need to do as a country to be better prepared for an outbreak of pandemic influenza in the U.S.?

NIAID Response:

The National Institute of Allergy and Infectious Diseases (NIAID), the lead institute for research on influenza at the National Institutes of Health (NIH), is conducting and supporting basic, translational, and clinical research that will improve our ability to prepare for and respond to potential pandemic influenza outbreaks. A particular challenge in preparing for an outbreak of seasonal or pandemic influenza is that current influenza vaccines do not provide protection that is long-lasting or effective against a large number of influenza virus strains. To address this challenge, NIAID is prioritizing the development of universal influenza vaccine candidates that could provide long-lasting protection against multiple influenza strains including those with pandemic potential.

NIAID is galvanizing research efforts to develop universal influenza vaccine candidates and convened influenza experts from the U.S. and throughout the world at a research agenda-setting workshop in 2017. Following this meeting, NIAID outlined its universal influenza vaccine research priorities in a strategic plan that focuses on three key areas: improving knowledge of the transmission and pathogenesis of influenza infection; characterizing influenza immunity and immune factors that correlate with protection against influenza; and supporting the design of universal influenza vaccines. NIAID is actively engaging federal partners, including U.S. Department of Health and Human Services agencies and other key domestic and international stakeholders involved in influenza vaccine research, to coordinate and advance activities outlined in the strategic plan. For example, NIAID continues to collaborate with the Biomedical Advanced Research and Development Authority (BARDA) to advance the development and clinical testing of promising influenza vaccine candidates. The additional \$40 million in funding for universal influenza vaccine research provided through the Consolidated Appropriations Act, 2018 (P.L. 115-141) will support targeted research investments for the development of universal influenza vaccines that could protect vaccinated individuals against seasonal or pandemic influenza virus strains.

In addition to pursuing universal influenza vaccine strategies, NIAID is working to develop novel vaccine production strategies - such as recombinant DNA manufacturing

techniques -that may allow for a more rapid production of targeted vaccines in response to newly emerging or changing strains of influenza virus than current egg and cell-based technologies. These vaccine production techniques could help to speed the availability of vaccines that protect against new or evolving pandemic influenza virus strains.

While investing in research to improve influenza vaccines, NIAID also continues to support the development of novel diagnostics to rapidly identify influenza viruses, including potential pandemic strains, and antiviral drugs that could help to limit influenza morbidity and mortality in a pandemic. NIAID will continue to play a key leadership role in seasonal and pandemic influenza outbreak preparedness and response efforts by conducting and supporting the basic, translational, and clinical research needed to identify and develop effective medical countermeasures.

2) In your testimony, you mentioned that there will be several iterations of a 'universal' flu vaccine. How many universal vaccine candidates are currently being developed at, or supported by, NIAID and what strains will they target? Where does this research currently stand? How many iterations of a universal flu vaccine does NIAID ultimately envision?

NIAID Response:

A truly universal influenza vaccine would represent a groundbreaking advance in the fight against influenza by providing protection against a number of seasonal and pandemic influenza virus strains. NIAID currently is exploring at least 10 different strategies toward the development of universal influenza vaccine candidates. Each of these strategies may have multiple vaccine candidates in various stages of development that are being investigated by NIAID intramural researchers or NIAID-supported grantees in academia and industry. Notable highlights of NIAID universal influenza vaccine research include the development of a ferritin nanoparticle-based vaccine candidate by the NIAID Vaccine Research Center (VRC), Phase I clinical trials of a VRC-developed DNA vaccine candidate using a prime-boost strategy with a standard inactivated seasonal influenza vaccine, and the recent launch of a NIAID-sponsored Phase II clinical trial to evaluate the M-001 vaccine candidate, which contains several influenza fragments recognized by the immune system that are common among multiple influenza virus strains. Additionally, NIAID is sponsoring a Phase I clinical trial to evaluate the safety and immunogenicity of a prime-boost regimen using an intranasal vaccine candidate followed by a licensed, quadrivalent seasonal influenza vaccine.

We anticipate that progress toward the goal of a universal influenza vaccine will occur in several stages, with each intermediary stage represented by several vaccine candidates that protect against progressively greater numbers of influenza virus strains. NIAID is pursuing strategies that could protect against all strains of a single subgroup of influenza virus, such as the H3N2 strains. This could be considered a universal influenza vaccine Version 1.0. As we make progress towards more broadly protective influenza vaccines, a Version 2.0 could protect against two or more subgroups of influenza, such as all H1N1 strains and all H3N2 strains. This may lead to developing a universal influenza vaccine candidate that by itself could durably protect against all subgroups of influenza, thereby protecting against virtually any influenza strain. Each universal influenza vaccine candidate will need to be evaluated over several influenza seasons to determine the level of protection that is induced, and the durability of that protection.

Version 1.0 of a universal influenza vaccine may be available in a few years, representing an incremental improvement on currently available influenza vaccines. A universal influenza vaccine that covers all major influenza strains may be many years away, with several iterations may be likely needed to ultimately achieve a broadly protective vaccine against all or nearly all influenza strains.

3) What are the present challenges that are preventing the broader utilization of cell-based influenza vaccines, and what steps can be taken to become less reliant on egg-based vaccines?

NIAID Response:

NIAID supports the development of flexible vaccine manufacturing processes, including the use of molecular biological techniques, to help shorten manufacturing times and increase production efficiency for current and future influenza vaccines. Barriers to the broader utilization of cell-based and recombinant technologies to produce influenza vaccines include differences in manufacturing needs, development costs, and public awareness of alternatives to egg-based influenza vaccines.

NIAID is working to address these challenges through the support of basic and translational research for the development and manufacture of novel influenza vaccine strategies. NIAID scientists have devised a new method to manufacture an experimental whole virus inactivated influenza vaccine using a cell-based system. This method would provide another alternative to currently licensed egg-based and cell-based influenza vaccines. NIAID researchers also are developing and evaluating an additional cell-based system for whole virus influenza vaccine candidates to try to determine the most efficient cell-based system to produce influenza vaccines, both in terms of manufacturing time and cost. Data from these NIAID-supported studies will help improve vaccine manufacturing processes and vaccine efficacy, leading to the design of better influenza vaccines. NIAID also has supported studies of improved vaccine strain selection and optimized high-yield vaccine strains as part of the Seasonal Influenza Vaccine Improvement (SIVI) initiative, an interagency collaboration launched in 2016.

In addition to supporting the development of innovative seasonal influenza vaccines, NIAID has made a strategic shift toward a research paradigm that features broader, more flexible vaccine platform technologies such as recombinant DNA manufacturing techniques that can be rapidly mobilized when pandemic influenza viruses emerge. NIAID continues to support the early development of candidate pandemic influenza vaccine candidates that can be transitioned to BARDA for advanced development, with the goal of Food and Drug Administration (FDA) licensure and potential inclusion in the Strategic National Stockpile. NIAID also will continue to work closely with industry partners to advance promising influenza vaccine candidates, including cell-based and recombinant vaccine strategies.

The Honorable Michael C. Burgess

1) Dr. Fauci, the National Institute of Allergy and Infectious Diseases is on the front lines of vaccine development, especially in the wake of Ebola and Zika hitting the United States.

You wrote an article in the Journal of the American Medical Association in November 2017 that detailed the critical role of biomedical research in pandemic preparedness. Can you share with us some of the research approaches NIAID uses to prepare for pandemics, such as a new flu strain, that have yet to hit our shores?

NIAID Response:

As outlined in the 2017 article in the Journal of the American Medical Association, *The Critical Role of Biomedical Research in Pandemic Preparedness*, comprehensive pandemic preparedness requires a multifaceted approach. A critical component is biomedical research to support the development of vaccines, diagnostics, and therapeutics that may be quickly deployed in response to an emerging or re-emerging infectious disease of pandemic potential. NIAID supports a comprehensive portfolio of basic research on microbiology and immunology to better understand the mechanisms of pathogenesis and immune responses, as well as applied and clinical research to evaluate candidate diagnostics, therapeutics, and vaccines. This strategic effort includes the pursuit of several research approaches, including: (1) research targeting specific pathogens; (2) prototype pathogen efforts, in which fundamental research to understand the disease caused by one pathogen may inform the development of countermeasures for a closely related pathogen; and (3) development of platform-based technologies and broad-spectrum products that may be easily and quickly deployed against multiple pathogens. NIAID research complements other elements of pandemic preparedness by improving understanding of infectious disease pathogenesis and by developing candidate medical countermeasures that could be used in a pandemic.

NIAID supports a broad portfolio of pathogen-specific basic, translational, and clinical research. NIAID investments in pathogen-specific research include priority pathogens of the United States Government as designated by the Centers for Disease Control and Prevention (CDC), as well as other emerging and re-emerging diseases identified as priority pathogens by NIAID. For example, NIAID supported development of m102.4, a candidate monoclonal antibody treatment for Nipah virus infection. NIAID also is supporting the development of improved influenza vaccine candidates, including universal influenza vaccines that could provide broad protection for a range of pandemic and seasonal influenza strains. Additionally, it was an NIAID investment in basic research nearly 40 years ago that enabled the development of the novel influenza antiviral Xofluza (baloxavir marboxil), which was approved for use in Japan in early 2018 and is currently undergoing FDA priority review for use in the United States.

NIAID has built upon increased understanding of infectious disease pathogenesis to move strategically toward a medical countermeasures research paradigm that features broader, more flexible platform technologies that can be used to respond to several biological threats. High-throughput sequencing and platform-based technologies are facilitating the development and manufacture of vaccines, targeted antibody therapeutics, and broad-spectrum antibiotics and antivirals by significantly decreasing the time from identification of a public health threat of an emerging infection to clinical evaluation of candidate countermeasures. For example, in 2015-2016 when Zika virus emerged in the Americas, clusters of microcephaly and other birth defects were identified, and a Public Health Emergency of International Concern was declared by the World Health Organization. NIAID scientists rapidly used Zika virus genetic sequence information to develop a DNA-based vaccine candidate that moved from concept to a first-in-human trial in less than four months.

The experimental DNA-based Zika vaccine, which currently is in Phase II/IIB clinical testing, was developed with a readily deployable DNA vaccine platform that is a form of gene-based immunization previously used by NIAID to develop a candidate vaccine for West Nile virus. The development of a broadly applicable platform technology facilitated an accelerated response to a previously unrecognized public health threat. As mentioned in the 2017 article in the *Journal of the American Medical Association*, NIAID is supporting development of additional vaccine platform technologies, including nanoparticle, virus-like particles, and mRNA platforms. NIAID also supports development of broad-spectrum therapeutics, including antiviral and antibacterial agents that have demonstrated activity against multiple viral or bacterial pathogens.

Together with academia, industry, and Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) partners, NIAID remains committed to meeting public health emergency needs by advancing high-priority research to support development of medical countermeasures for emerging and re-emerging infectious diseases, including influenza viruses with pandemic potential. NIAID-supported research into specific pathogens, prototype pathogens, and the development of platform-based technologies will continue to play an essential role in PHEMCE pandemic preparedness and response efforts.

The Honorable Frank Pallone, Jr.

1) How can we plan long-term for therapeutics and vaccines in order to respond to outbreaks that we cannot yet anticipate?

NIAID Response:

NIAID supports a comprehensive portfolio of basic research on microbiology and immunology to better understand the mechanisms of pathogenesis and immune response, as well as applied and clinical research to evaluate candidate diagnostics, therapeutics, and vaccines. This strategic effort includes the pursuit of foundational platform approaches that could be used to develop medical countermeasures against multiple pathogens.

NIAID is pursuing the development of platform approaches including molecular biological technologies that could be rapidly mobilized to generate candidate vaccines against emerging infectious disease threats. For example, during the 2015-2016 Zika virus outbreak in the Americas, NIAID scientists developed a novel DNA-based vaccine for Zika virus using viral genetic sequence information. The candidate vaccine moved from concept to a first-in-human trial in less than four months, and currently is in a Phase II/IIB trial. In order to respond so quickly, NIAID utilized a readily deployable DNA vaccine platform that was previously used by NIAID to develop a candidate vaccine for West Nile virus. These types of genetic platforms could be used to respond similarly to multiple emerging and re-emerging infectious disease threats.

NIAID investments in basic, translational, and clinical research also are contributing to the development of novel broad-spectrum therapeutics that can target several pathogens. For example, NIAID has supported early-stage development of broad-spectrum antiviral agents such as BCX4430 (galidesivir), which has demonstrated activity against Ebola and other RNA viruses, and broad-spectrum antibacterial products, including a compound with activity

against the two different bacteria that cause tularemia and plague. Such broad-spectrum therapeutics may decrease the time necessary to identify and distribute an effective treatment during an outbreak setting.

NIH, led by the Fogarty International Center and NIAID, also supports the development of research infrastructure and partnerships in foreign countries to aid in the identification, monitoring, and response to the emergence and reemergence of infectious diseases. Long-standing international investments in disease monitoring and response made by NIH were vital in the immediate response to the 2014-2016 Ebola outbreak in West Africa and provided critical in-country expertise that helped to contain the spread of the disease. In addition, the clinical research partnership between NIAID and the government of Liberia, the Partnership for Research on Ebola Virus in Liberia (PREVAIL), demonstrated the ability to do rigorous scientific research in developing countries. The PREVAIL partnership enabled in-country clinical trials testing of several Ebola virus therapeutic and vaccine candidates, among them the ZMapp™ therapeutic, the Merck VSV vaccine, and the cAd3-EBOZ vaccine developed by the NIAID VRC in partnership with industry. NIAID, through a partnership with the French National Institute of Health and Medical Research (Inserm), the London School of Hygiene and Tropical Medicine, and the host country governments, has launched the Partnership for Research on Ebola VACcination (PREYAC), a Phase II clinical trial comparing three experimental Ebola vaccination strategies in Mali, Guinea, Sierra Leone, and Liberia. Medical countermeasures tested by the PREVAIL partnerships were recently deployed in the Democratic Republic of the Congo to help address an Ebola outbreak from May to July 2018, emphasizing the key contributions of this effort. NIAID-supported international research partnerships also contribute to the development of site infrastructure and sustainable research capacity in developing countries, enhancing global preparedness to respond to unanticipated outbreaks and to conduct clinical research to better understand the disease and to test candidate countermeasures during these outbreaks.

2) In your view, are there specific pathogens or diseases we should be most concerned with?

a. With so many dangerous pathogens, how do we prioritize research to try to target those posing the greatest threat?

NIAID Response:

NIAID prioritizes research and early-stage development of medical countermeasures against bioterror threats and emerging and re-emerging infectious diseases of public health importance. The persistent threat of pandemic influenza and other respiratory viruses that may spread quickly and cause significant morbidity and mortality, such as severe acute respiratory syndrome coronavirus (SARS-CoV) or Middle East respiratory syndrome coronavirus (MERS-CoV) remain a particular area of concern. NIAID maximizes its efforts to develop effective medical countermeasures against these, and other potential emerging and re-emerging diseases, by prioritizing research into broad-spectrum antibiotics and antiviral drugs, as well as efficient platform technologies to more rapidly develop vaccines and diagnostics for a variety of threat pathogens.

NIAID's efforts to develop a broader, more flexible research paradigm is yielding scientific advances that will facilitate public health emergency preparedness and our ability to respond to emerging public health threats. NIAID is supporting the development of

diagnostics platforms capable of distinguishing between several pathogens, as well as broad-spectrum therapeutics, including novel antiviral agents, effective against several pathogens. In addition, NIAID is prioritizing the development of several vaccine platforms that could be used to quickly develop vaccine candidates against newly identified threats. This includes the DNA-based platform used to develop a candidate vaccine against Zika virus that moved from concept to a first-in-human trial in less than four months. The development of these and other broad-spectrum therapeutics and platform technologies remains a NIAID priority.

In addition to supporting the development of platform technologies and broad-spectrum therapeutics that may decrease response time in the event of a pandemic, NIAID also supports a targeted portfolio of basic, translational, and clinical research on priority pathogens with pandemic potential, including influenza and other respiratory viruses. This includes detailed studies of immune system responses to infection, as well as research to better understand the transmission, evolution, and pathogenesis of the viruses to inform the development of vaccines, diagnostics, and therapeutics that could be deployed during a pandemic. The NIAID Vaccine and Treatment Evaluation Units currently are conducting two Phase II clinical trials of a new vaccine candidate to protect against emerging H7N9 influenza virus strains, and NIAID intramural scientists are conducting clinical studies of prime-boost vaccine regimens for swine (H1) and avian (H7) influenza viruses.

NIAID is galvanizing research efforts to support the development of universal influenza vaccine candidates. A universal influenza vaccine that is effective against both seasonal and pandemic influenza strains would be a vital tool to prepare for future pandemics, as well as to improve our ability to prevent seasonal influenza. In addition, NIAID is supporting novel antiviral therapies for influenza, including RNA polymerase inhibitors, peptide inhibitors, and next-generation neuraminidase inhibitors. NIAID support for influenza diagnostics research has led to the development of a rapid molecular *in vitro* assay recently cleared by the FDA to accurately distinguish influenza A from influenza B in nasal swab specimens.

NIAID continues to make progress against other respiratory viruses with pandemic potential. NIAID is supporting early-stage clinical trials of antibodies designed to treat people infected with MERS-CoV, as well as development of a vaccine candidate for MERS-CoV based on information from previous vaccine studies on SARS-CoV. NIAID-funded researchers also have identified a novel SARS-related virus, swine acute diarrhea syndrome coronavirus (SADS-CoV). SADS-CoV was responsible for 25,000 piglet deaths in China in 2016-17; however, no infections in humans have been identified. The identification of pathogens with zoonotic potential such as SADS-CoV that may emerge as human diseases contributes to our preparedness, as it may facilitate early identification if the pathogen becomes capable of causing disease in humans. NIAID will continue to prioritize research on pathogens with pandemic potential such as influenza and other respiratory viruses and support the development of platform-based technologies and broad-spectrum products that may be easily and quickly deployed against multiple pathogens.

3) Can you briefly explain the barriers that make it harder for scientists to discover new antibiotics?

NIAID Response:

NIAID supports a comprehensive basic research portfolio on antibiotic resistance to aid in the discovery of new antibiotics. NIAID antimicrobial resistance research includes the

elucidation of major mechanisms of pathogenesis, host-pathogen and drug-pathogen interactions, and the identification of new candidate antibiotics. NIAID has found that the major challenges in the development of new antibiotics are in the later stages of clinical development of these drugs. NIAID has identified three main barriers to the advanced development of new antibacterial therapeutics: 1) the scarcity of new antibacterial drug candidates effective against Gram-negative infections; 2) the challenge of enrolling patients in clinical trials needed to show efficacy of new therapeutics, especially in the case of Gram-negative drug-resistant infections; and 3) a lack of market incentives for pharmaceutical companies to invest in the final stages of antibiotic development and licensure. NIAID is working to address these challenges in several ways, including through the support of basic, translational, and clinical research to identify and advance promising antibacterial candidates to late-stage development. NIAID estimates that more than 25 percent of the antibacterial candidates currently in clinical development previously received some form of NIAID support.

NIAID is addressing these challenges by supporting early-stage development and clinical trials of new therapeutics to help offset the investment required to successfully test these therapeutics and bring them to market. The NIAID-supported Antibacterial Resistance Leadership Group (ARLG) has supported over 35 clinical studies investigating new therapeutics, optimized treatment regimens, diagnostic devices, and projects on antimicrobial stewardship. The ARLG places a priority on research involving Gram-negative bacteria that represent a major antimicrobial resistance threat. NIAID-supported scientists also completed two Phase I clinical trials for a new class of antibiotics (CRS3123) to treat *Clostridium difficile* infections, which are increasingly difficult to treat effectively. In addition, NIAID is supporting clinical trials to evaluate the efficacy of new therapeutic candidates, as well as new treatment regimens that utilize existing antibiotics in new combinations or regimens. NIAID also has solicited research for the development of tools to advance drug discovery of agents against Gram-negative pathogens through the "Partnerships for the Development of Tools to Advance Therapeutic Discovery for Select Antimicrobial-Resistant Gram-Negative Bacteria" program. NIAID is facilitating scientific discussions and partnerships to address key questions and challenges in the development of new antibiotics. NIAID and The Pew Charitable Trusts sponsored the 2017 scientific workshop entitled, "Challenges in the Discovery of Gram-negative Antibacterials: The Entry & Efflux Problem." The goal of the workshop was to identify next steps and opportunities for collaborations to determine factors that affect the entrance of antibiotics into, and accumulation within, Gram-negative bacteria to inform the identification and design of new types of antibiotics. Resolving these early-stage research questions will help address the growing threat of resistant Gram-negative bacteria by facilitating the later-stage development of promising new therapeutic candidates.

NIAID also addresses barriers to the advanced development of new antibacterial therapeutics by helping to de-risk antibacterial product development for researchers in industry and academia through targeted research support and services. NIAID supports the National Database of Resistant Pathogens, which contains genomic data for more than 205,000 drug-resistant microbes. This database was established by the NIH, in partnership with FDA and CDC, as a publicly available resource that scientists from all over the world can access to inform the development of novel antibacterial products. NIAID also funds the Centers of Excellence for Translational Research that have recently discovered a new class of antibiotics produced by soil-dwelling bacteria. These antibiotics, known as malacidins, have a

unique mechanism of action that may make the development of resistance less likely. NIAID also supports CARB-X, a unique public-private partnership led by BARDA. CARB-X is dedicated to accelerating the development of innovative antibacterial products from target/candidate identification and characterization through Phase I clinical trials. CARB-X is currently supporting 29 therapeutic candidates, including 11 new classes of antibiotics, as well as 6 diagnostics products. To facilitate the discovery and development of promising therapeutic candidates, NIAID provides unique no-cost preclinical and clinical services that include screening tests for antimicrobial activity and access to research reagents to assist in product testing. Additionally, NIAID supported preclinical development and first-in-human Phase I clinical testing of VNRX-5133, a novel beta-lactamase inhibitor (BLI). VNRX-5133 is the first BLI in clinical development that inhibits all known classes of beta-lactamases bacterial enzymes involved in resistance to the beta- lactam class of broad-spectrum antibiotics such as penicillin.

NIAID continues to support the development of antibacterial products in collaboration with academia, industry, and federal partners. A concerted research effort is required to combat the growing public health threat of antibiotic resistance. NIAID remains committed to facilitating the development of new antibiotics by supporting innovative research and offsetting the development costs of industry and academia.

* * *

GREG WALDEN, OREGON
CHAIRMAN

FRANK PALLONE, JR., NEW JERSEY
RANKING MEMBER
ONE HUNDRED FIFTEENTH CONGRESS
Congress of the United States
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July 12, 2018

Rear Admiral Denise Hinton
Chief Scientist
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Admiral Hinton:

Thank you for appearing before the Subcommittee on Oversight and Investigations on June 15, 2018, to testify at the hearing entitled "The State of U.S. Public Health Biopreparedness: Responding to Biological Attacks, Pandemics, and Emerging Disease Outbreaks."

Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for ten business days to permit Members to submit additional questions for the record, which are attached. To facilitate the printing of the hearing record, please respond to these questions with a transmittal letter by the close of business on Thursday, July 26, 2018. Your responses should be mailed to Ali Fulling, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, DC 20515 and e-mailed in Word format to Ali.Fulling@mail.house.gov.

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely, Gregg Harper
Chairman
Subcommittee on Oversight and Investigations

cc: The Honorable Diana DeGette, Ranking Member, Subcommittee on Oversight and Investigations
Attachment

ATTACHMENT-ADDITIONAL QUESTIONS FOR THE RECORD

The Honorable Gregg Harper

I. Medical countermeasure (MCM) development can be a costly, time-consuming venture for the private sector. It is often one of the reasons why companies are reluctant to enter the MCM product space. How could the FDA provide better guidance and get involved earlier in the development process to help reduce this burden?

The Honorable Michael C. Burgess

I. Pharmaceutical companies face economic barriers to discovering and developing urgently needed new antibiotics to address drug resistant infections. I was encouraged by Commissioner Gottlieb's announcement earlier this week that FDA is working with CMS and other agencies to develop new payment models that would incentivize antibiotic research and development and the appropriate use of new antibiotics. Can you describe how these new models may work? Does Congress need to provide additional authorities or resources?

The Honorable Frank Pallone, Jr.

1. When a crisis does occur, what can FDA do to fast-track approval of countermeasures like vaccines and therapeutics?

2. How have GAIN and ADAPT helped FDA to incentivize antibiotic development in the private sector?

Chapter 489

**FACING 21ST CENTURY PUBLIC HEALTH THREATS:
OUR NATION’S PREPAREDNESS AND RESPONSE
CAPABILITIES, PART I***

Committee on Health, Education, Labor, and Pensions

Wednesday, January 17, 2018

U.S. Senate, Committee on Health, Education, Labor, and Pensions,
Washington, DC.

The Committee met, pursuant to notice, at 10:04 a.m. in room SD–430, Dirksen Senate Office Building, Hon. Richard Burr, presiding.

Present: Senators Alexander, Burr [presiding], Isakson, Collins, Cassidy, Young, Murkowski, Murray, Casey, Bennet, Murphy, Warren, Kaine, Hassan, Smith, and Jones.

OPENING STATEMENT OF SENATOR BURR

Senator Burr [presiding]. I would like to call this hearing to order, the Senate Health, Education, Labor, and Pensions Committee.

This morning, we are holding a hearing titled, “Facing the 21st Century Public Health Threats: Our Nation’s Preparedness and Response Capabilities.” We will hear from Dr. Robert Kadlec, the Assistant Secretary for Preparedness and Response at the Department of Health and Human Services; Dr. Stephen Redd, Director of the Office of Public Health Preparedness and Response at the Centers for Disease Control and Prevention; and Dr. Scott Gottlieb, Commissioner of the Food and Drug Administration.

* This is an edited, reformatted and augmented version of Hearing of the Committee on Health, Education, Labor, and Pensions, United States Senate, One Hundred Fifteenth Congress, Second Session, Publication No. S. HRG. 115–712, dated January 17, 2018.

This is the first of two hearings we plan to have on this topic. The second will be noticed for Tuesday, January 23.

Senator Murray and I each have an opening statement, then I am going to turn to Senator Alexander and Senator Casey for any opening remarks they might have. After that, we will introduce our panel of witnesses and hear their testimonies. And then each Member will have up to 5 minutes for any remarks and questions.

First, I would like to welcome the Chairman and thank him for giving me the opportunity to hold the gavel today. This hearing discusses a topic that is critical to our national security and has seen many years of bipartisan work in this Committee and in this Congress.

Together, we have developed and strengthened the framework to ensure we are prepared for chemical, biologic, radiological, and other nuclear threats with the potential to jeopardize the health of all Americans.

The Pandemic and All-Hazards Preparedness Act of 2006 created a framework which has grown and changed as we have learned from each public health experience we have been through. We should be proud of the accomplishments under PAHPA and the progress made over the last decade.

Our work has resulted in strong partnerships with our states and local counterparts, created greater certainty and accountability to bring forward medical countermeasures, and established a clear strategy with which we can combat the full range of public health threats we face today and those we may encounter in the future. Despite this progress, we are not fully prepared and more work remains to accomplish our goals. The Blue Ribbon Study Panel on Biodefense stated in their 2015 report that there are, and I quote, “Serious gaps and inadequacies that continue to leave the Nation vulnerable to threats from nature and terrorists alike.”

As we move forward in revisiting this successful and bipartisan law, I want to make it very clear to my colleagues that this is a reauthorization of a national security bill, and I look forward to working with each of you on this important issue.

The threats we face continue to evolve and it is critical that we bring, with this discussion, the vigilance, urgency, and resolve this mission demands. We are in an unprecedented era of technological and biomedical innovation and advancement.

In November 2016, the President’s Advisory Council on Science and Technology warned that, and I quote, “While the ongoing growth of biotechnology is a great boon for society, it also holds serious potential for destructive use by both states and technically competent individuals.”

I urge the U.S. Government’s past ways of thinking and organizing to meet biological threats needs to change to reflect and address this rapidly developing landscape. For this reason, it is critical that fostering and advancing innovation, particularly in the development of medical countermeasures, is top of mind and that we work through this reauthorization process to ensure CDC, FDA, ASPR, BARDA have what they need to keep pace with these rapidly changing and evolving threats.

This Committee has worked to push the Federal Government, and HHS in particular, to meet these challenges. An HHS that fosters innovation in the development of medical countermeasures and across PAHPA’s framework provides the greatest hope to ensure the safety of the American people. The witnesses we have before us today will be able to provide insight into the urgency of this mission and the promise innovation holds if properly leveraged.

I look forward to hearing from each of you about the progress that we have made, and where we can continue to improve policies and programs to realize their full potential to save Americans' lives.

Now, I would like to turn to Senator Murray for any comments she might have.

STATEMENT OF SENATOR MURRAY

Senator MURRAY. Thank you very much.

And thank you, to all of you, for joining this hearing on our Nation's preparedness to combat public health threats as we look toward now reauthorizing the Pandemic and All-Hazards Preparedness Act later this year.

I especially want to thank Senator Casey and Senator Burr for their bipartisan work and leadership on this really important issue. Local Washington state papers show why today's discussion is so important to families across this country. We have headlines like, "Flu Deaths And Cases Increasing In Pierce County." And, "Flu Outbreak In Snohomish County Kills Five; 50 Hospitalized."

A bad flu season can be a nightmare for families and too often ends in horrible tragedy. Just as we must continue to improve our public health response across the board to prevent those tragedies on the local level, we have to also make sure we are vigilant against pandemics of a global scale.

A pandemic could affect half a billion people, more than the entire population of the United States; and that is not speculation. It happened 100 years ago. The 1918 influenza epidemic was a tragedy more deadly to the human race than World War I. And today, the threat of pandemic flu is joined by new threats.

What have we learned in the last century? Are we better prepared for the next catastrophe?

When we consider Ebola and how the Centers for Disease Control and Prevention, and so many partners, supported Nigeria as they instituted evidence-based policies and tracked the path of that disease, and contained it when the outbreak reached Lagos, the answer is clearly, yes.

When you consider our Strategic National Stockpile which can deliver 50 tons of emergency medical supplies anywhere in the U.S. in 12 hours, the answer is clearly, yes.

When you consider the FDA's approval of new medical counter- measures to combat anthrax, and flu, and radiation, and plague, the answer is clearly, yes.

However, our track record is far from perfect. We still can do better.

We can do better than the President's way too slow response in Puerto Rico and the U.S. Virgin Islands after Hurricane Maria. The storm left many Americans without access to clean water, and electricity, and healthcare for months.

We can do better than the Administration's response to the opioid epidemic. President Trump declared the crisis a public health emergency 83 days ago and has taken little meaningful action since.

So I am glad this Committee will continue its bipartisan work to address the opioid crisis in another hearing soon.

We can also do better than our slow response in approving funding to combat Zika in 2016. The World Health Organization declared Zika a global health emergency in February. Instead of a fast response with needed funding, the response got politicized around some Republicans who pushed to undermine women's healthcare and access to contraception, which was a key requirement to prevent the virus from causing devastating birth defects. As a result, that took Congress 9 months to pass emergency funding for a public health crisis that endangered mothers, and babies, and families across the world. That delay hurt people and it harmed families in ways they are going to carry for the rest of their lives. So we have to do better.

We are most successful at protecting our families against pandemic threats when we respond with quick, bipartisan action.

We need decisions based in science and expert medical opinion, not ideology, especially when it comes to women's health.

We need Federal, state, and local agencies to hire the people, and capacity, and have the funding they need to protect communities. Hiring freezes and funding cuts make us less prepared, not more. We need to plan for everyone. We cannot overlook the young or the elderly. We cannot forget pregnant women, or individuals with disabilities, or those fighting chronic diseases like diabetes.

We need innovative medical countermeasures to protect us from today's threats like a universal flu vaccine and antibiotics to combat resistant bacteria. And we must continue strong partnerships with industry that will allow us to rapidly respond to new threats. We need to stop fear and uncertainty before they create panic by getting families helpful and accurate information from sources that they trust. We cannot allow anyone to undermine the science of proven solutions like vaccines.

We need to respond to global health crises abroad before they travel here to home. Diseases are not stopped by borders, or walls, or bans. This is a place where the United States can, and should, lead.

We should continue to show our international partners that we are focused on these issues and will be their ally in preparing for, and addressing, public health threats.

Congress has a strong, bipartisan track record of addressing these challenges through the PAHPA, which strengthened our Nation's public health preparedness and created new roles, and programs, and authorities for public health emergency response.

Reauthorizing the Act in 2013, we built on that record and enhanced medical surge capacity. We modernized biosurveillance capabilities and increased our focus on at risk individuals.

I am hopeful we can continue that progress with legislation that focuses on the science and evidence based policies we know work to mitigate public health crises, that considers the needs of everyone, and puts families and women before politics, supports state and local public health officials, ensures communities do not spend months waiting for emergency resources, and enables us to respond to the next crisis with foresight rather than learn from the next tragedy with hindsight.

We do not know what the next public health threat will be. We do not know where, or when, or even how it will start. But we do know that being prepared starts now.

All of you here today have a critical role to play in keeping our communities healthy and safe. The Food and Drug Administration helps facilitate the development and review of

medical counter-measures and grants emergency use authorizations for products that are needed on the frontlines.

The Assistant Secretary of Preparedness and Response guides our Nation's preparedness planning. They help ensure our healthcare system is ready to face any emergency. And it invests

in the medical countermeasures pipeline through biomedical advanced research and development authority.

The Centers for Disease Control and Prevention is on the frontlines supporting state and local public health departments, overseeing the Strategic National Stockpile, gathering and analyzing key data, and serving as a trusted source of information to the public.

I am interested to hear from all of you today about your work to fulfill these important roles and keep our country safe.

Mr. Chairman, I do want to say I am frustrated that Director Fitzgerald is, once again, unable to join us here today. Due to conflicts of interest presented by investments, our CDC Director still has to recuse herself on some of the important health issues that we face, including issues related to data collection and information sharing, which are very relevant to the conversation that we are having today. I am concerned that she still cannot give her full attention to all the pressing health threats we face and hope that these conflicts of interest will be resolved soon.

Thank you, Dr. Redd, for joining us in her place and I look forward to hearing from you.

Thank you, Mr. Chairman.

Senator BURR. Thanks, Senator Murray. Senator Alexander.

STATEMENT OF SENATOR ALEXANDER

The CHAIRMAN. Thank you, Senator Burr.

Senator Burr, thank you for your willingness to chair this hearing.

In March 2013, President Obama signed into law the bipartisan Pandemic and All-Hazards Preparedness Reauthorization Act. Senator Burr was the author of that reauthorization and the original legislation, which became law in 2006. He worked with many Senators on this Committee, both Democratic and Republican, and I thank them all for that. Senator Murray, Senator Casey, and others, Senator Isakson was another of those. So Senator Burr is chairing the hearing and I thank him for that.

I would also like to welcome Senator Smith from Minnesota, who is joining our Committee and replacing Senator Franken, who was a valuable Member of the Committee.

Senator Jones, from Alabama, is also a new Member of the Committee. We welcome him. He replaced Senator Whitehouse, who was a very valuable Member of the Committee, and who has taken a lesser assignment on the Finance Committee for some reason.

[Laughter.]

The CHAIRMAN. But we will miss Sheldon and his work on this Committee.

Mr. Chairman, I am going to withhold my comments, although what I would like to do is call on Senator Isakson for 1 minute, just to make some comments, and then we will go to Senator Casey.

Senator BURR. Senator Isakson.

Senator ISAKSON. Thank you, Mr. Chairman.

I just wanted to, in reference to the statements made by the ranking Member, Senator Murray, whom I have talked to about Dr. Fitzgerald. I talked with Dr. Fitzgerald yesterday.

As chairman of the Ethics Committee, I have gotten her in touch with the appropriate people to deal with the issue. She is forthrightly dealing with it to the best I can determine and I am working expeditiously to see we get it done as quickly as possible, so she will not have any conflict to testify whatsoever. And that is her desire as well.

Thank you.

Senator BURR. Senator Casey.

STATEMENT OF SENATOR CASEY

Senator CASEY. Thank you very much, Senator Burr.

I am grateful for this hearing, and grateful to be working with you again on this reauthorization, and commend your work on this for many, many years.

I also want to thank, of course, the Chairman, Chairman Alexander and Ranking Member Murray for this bipartisan hearing on the Nation's preparedness and response capabilities in advance of the reauthorization of the Pandemic and All-Hazards Preparedness Act known as PAHPA.

I will give you one story, one brief story, but I think, instructive about how important preparation is. This is a good example of preparedness infrastructure that PAHPA supports, in this case, in the aftermath of a tragedy, a train derailment that occurred in Philadelphia in May 2015.

The train was carrying 238 passengers. When it derailed, eight people lost their lives. Over 200 were injured in that derailment. Fortunately, through funding from PAHPA's Hospital Preparedness Program, which we know by the acronym HPP, the Pennsylvania Department of Health and a regional healthcare coalition had long been working together to prepare local healthcare systems for emergencies that could cause a surge in patients.

When the train derailed, HPP funded systems were tracking bed availability in local hospitals and providing that information in real time to emergency responders who were at the scene, helping them to effectively triage patients, send them to hospitals that had the capacity to accept additional patients so they could begin to receive the care they needed.

Because these systems were in place before the train derailed, they were ready to protect both health and to save lives when seconds, literally seconds, counted.

Yet, health security threats are increasing in frequency and intensity due to a combination of factors including newly emerging infectious diseases, extreme weather events, and our aging infrastructure.

So now, more than ever, we must continue to build our Nation's resiliency by investing in countermeasure development, surveillance, and supporting state and local partners to reduce the impact of health events in the country.

So I would like to thank today's witnesses for their service. It is important to mention your service to the country, as well as your commitment to protecting America's public health.

We look forward to the hearing and grateful for the work that we can do today at this hearing.

Thank you, Mr. Chairman.

Senator BURR. Senator Casey, thank you.

Thank you for your continued help and work on this issue.

Let me just remind Members that this is the start of the reauthorization of PAHPA. Now, having been in Congress for 24 years, I realize that when you get involved in HHS legislation and FDA legislation, there is always a temptation to fix other things.

I want to encourage you to fight the urge. Let us keep this focused on perfecting PAHPA. It has been successful. We still have work to do, but if we become distracted and create a fight over changes within the FDA that have nothing related to this, or HHS, or somewhere else because the sheer geography that just PAHPA allows us to get into, we will lose the focus of what we are doing, and that is trying to make PAHPA even more effective in the future.

So with that, I would like to introduce our witnesses, which each have up to 5 minutes to give their testimony.

I am pleased to welcome today Dr. Robert Kadlec. Dr. Kadlec is the Assistant Secretary for Preparedness and Response at the Department of Health and Human Services. If he does not like the title, he was the one that created it.

It was with Dr. Kadlec's help that we created the ASPR position as part of PAHPA to establish a clear line of authority in the event of a public health emergency. The APSR is the person at HHS solely responsible for leading and coordinating the Federal medical and public health preparedness and response effort across all the agencies within HHS including FDA and CDC.

Dr. Bob, delighted to have you back today.

Next, we will hear from Dr. Scott Gottlieb. Dr. Gottlieb is the Commissioner of the Food and Drug Administration.

The FDA plays a critical role in our emergency preparedness and response capabilities through its review of medical countermeasures, including drugs, vaccines, diagnostic tests, and by ensuring these countermeasures are safe and effective.

Further, the 2013 reauthorization of PAHPA aimed to improve regulatory certainty and predictability for medical countermeasures under review at the FDA, while also providing the agency with the additional authorities to support rapid response to public health emergencies.

Scott, we are delighted to have you here and delighted to have you in that position at FDA.

Finally, we will hear from Dr. Stephen Redd. Dr. Redd is the Director of the Office of Public Health Preparedness and Response at the Centers for Disease Control and Prevention.

The CDC serves a number of roles under the PAHPA framework and has built strong relationships with state and local public health departments, an important aspect of preparing for, and responding to, emergency public health threats.

The CDC also works to make sure we have the information we need in advance of and during a public health emergency. As part of this effort, the CDC houses an expansive epidemiology laboratory capacity and is responsible for biosurveillance and public health data collection activities.

Again, we welcome all of you.

Let me just say at the beginning, I believe the hurdle that is in our way is not available innovation. I believe the hurdle that is in our way is government. Clearly defining what it is that our need is, and the certainty of a pathway for getting the approvals that we need for those to actually be deployed.

So I hope you will keep those in mind as you go through, not just your testimony, your questions, but more importantly in the roles that you carry out after leaving. Understand that you are on the frontlines at making this happen.

Dr. Bob, the floor is yours.

**STATEMENT OF ROBERT KADLEC, M.D., ASSISTANT SECRETARY
FOR PREPAREDNESS AND RESPONSE, DEPARTMENT OF HEALTH
AND HUMAN SERVICES, WASHINGTON, DC**

Dr. KADLEC. Well, thank you, sir. Sorry for the false start there. I was excited to be here, sir. I was ready to go.

Good morning, Mr. Chairman, both of you, sirs and Senator Murray, and distinguished Members of the Committee.

I assumed this role 5 months ago just a week before Hurricane Harvey struck Texas. It has been an interesting experience so far and I have much to share from that experience.

I appreciate the opportunity to appear before you today as you prepare to consider the second reauthorization of PAHPA. This Committee championed the bipartisan effort to draft and pass this groundbreaking legislation and I want to thank you for your continuing commitment to this endeavor.

I am proud to have played a part in the original legislative process during my tenure with this Committee, and acknowledge the vision and leadership of Senator Burr and the late Senator Ted Kennedy.

This morning, I will share with you my perspective on the national security imperative of PAHPA, the mission and duties of ASPR, and my vision for areas of improvement.

The Constitution states that one of the Federal Government's fundamental obligations is to provide for the common defense, to protect the American people, our homeland, and our way of life. The strength of our Nation's public health and medical infrastructure, as well as the capabilities to quickly mobilize a coordinated national response to pandemics, attacks, and disasters are essential to save lives and protect all Americans.

Therefore, improving national readiness and response capabilities for 21st century threats is a national security imperative, as Senator Burr outlined earlier, and is the crux of my efforts as the ASPR.

The 21st century health security environment is increasingly complex and dangerous. It demands that we react with urgency. Having recently left my job with the Senate Select Committee on Intelligence, I know these threats all too well.

Terrorist organizations remain determined to attack the United States. State actors now directly threaten our homeland with nuclear weapons and have the means to employ both chemical and biological weapons.

Further, we have witnessed the increased frequency of naturally occurring disasters as well as disease outbreaks and are currently monitoring potential emerging infectious diseases that could cause a pandemic such as the H7N9 influenza strain circulating in China.

The bottom line is whatever happens, your constituents, the American people, expect our Federal Government to be ready to respond to save lives.

When APSR was originally established by PAHPA a decade ago, the objective was to answer a simple question: who is in charge of all Federal public health and medical preparedness and response functions? The approach adopted was based on the Goldwater-Nichols Act that created the Unified Combatant Commands at the Department of Defense.

APSR's mission is to save lives and protect Americans from these threats by recruiting the entire weight of the federal, medical, and public health assets and recruit support of the public health sector to support state and local activities and responses to help Americans in distress.

As APSR, I have four key priorities.

First, provide strong leadership. Focus on coordination, planning, and preparing for events that threaten the national health security.

Second, develop the national disaster healthcare system.

Third, advocate for CDC's sustainment of a robust and reliable public health security capabilities.

Last, but certainly not least, advance an innovative medical countermeasure enterprise.

Two areas of progress and opportunity I will elaborate on are operational healthcare readiness capacity and the medical counter- measures enterprise.

The importance of the national healthcare readiness and medical surge capacity was highlighted during this hurricane season. After Hurricanes Harvey, Irma, and Maria, ASPR led federal medical and public health response and recovery activities under the national response framework. We worked closely with FEMA, and state, and territorial health officials to augment healthcare with HHS disaster medical assistance teams, as well as V.A. and DOD assets.

We learned from these disasters that ASPR needs to update its incident command and deployable medical capabilities, as well as enhance our support for the healthcare infrastructure across the country.

As with medical countermeasures, the Nation's healthcare delivery infrastructure is mostly a private sector enterprise that must be effectively engaged in improving readiness.

To address the potential catastrophic medical consequences of the 21st century threats, we need a tiered regional system that is based on existing local healthcare coalitions and trauma centers that integrates all medical response capabilities, including Federal assets, as well as emergency medical services, the frontline of our response capabilities.

We must expand specialty care expertise and trauma, behavioral healthcare and chemical, biological, radiological nuclear response. And certainly, but not least, incentivize the healthcare system to integrate measures of preparedness into daily standards of care. I call this the foundation of a national disaster healthcare system.

The second area is our medical countermeasure enterprise, and I am grateful that Dr. Rick Bright behind me—Rick, why do you not wave to the crowd—who is the Director of BARDA, is joining me today.

BARDA was established as part of PAHPA and is a component of ASPR to bridge the so-called “valley of death” in the late stage development of vaccine, drug, and diagnostic development when many products historically languished or failed.

By using flexible, nimble authorities, multiyear advanced funding, strong public-private partnerships, and cutting edge expertise BARDA has successfully pushed many innovative products from advanced development to stockpiling FDA approval. To this date, 34 products have been approved by the FDA for the purposes of responding to disasters to the credit of Dr. Bright and his predecessor, Dr. Robin Robinson and the team at BARDA.

We have opportunities to further improve this enterprise by streamlining our internal decision-making processes, finding new ways to support innovation, promoting flexible, fast response capabilities, and increasing our collaboration with Federal interagency partners.

We also must work closely with our state and local partners, as well as the private sector to enhance the capability to quickly distribute and dispense medical countermeasures in an emergency.

In times of great challenge, we have the opportunity to build on the great progress made and further improve our national readiness and response capabilities.

I look forward to working with you and your staff. And thank you, again, for your bipartisan support and commitment to national security.

I am happy to answer any questions you have. [The prepared statement of Dr. Kadlec follows:]

PREPARED STATEMENT OF ROBERT KADLEC

Good morning Mr. Chairman, Senator Murray, and other distinguished Members of the Committee. I am Dr. Bob Kadlec, the Assistant Secretary for Preparedness and Response (ASPR) at the Department of Health and Human Services (HHS). I assumed this role 5 months ago, a week before hurricane Harvey struck Texas. I appreciate the opportunity to appear before you today as you prepare to consider the second reauthorization of the Pandemic and All-Hazards Preparedness Act (PAHPA), which expires at the end of this fiscal year.

Building upon years of incremental legislative changes in the prior decade, this seminal legislation transformed the Federal Government’s medical and public health preparedness for threats to our national security. This Committee championed the bipartisan oversight and analysis that led to the drafting and passage of this groundbreaking legislation. I want to thank you for continuing that commitment here today.

I am proud to have played a part in that original legislative process, when during the 109th Congress, I was Staff Director of this Committee’s Subcommittee on Bioterrorism and Public Health Preparedness, led by Senators Burr and Kennedy. In the decades before and after PAHPA was passed, I worked in various government capacities focused on biodefense and national security. I spent more than 20 years in the United States Air Force as an officer and physician, and served as Special Advisor for Counter Proliferation Policy within the Office of the Secretary of Defense during 9/11 and the 2001 anthrax attacks. I served two tours of duty at the White House Homeland Security Council, first as the Director for Biodefense then as Special Assistant to President Bush for Biodefense Policy from 2007 to

2009. Most recently before taking my current position, I served as the Deputy Staff Director for the Senate Select Committee on Intelligence.

This morning, I will share with you my perspective on the national security imperative of PAHPA, the mission and duties of ASPR, the status of our Department and our Nation's public health and medical preparedness and response capabilities, and my vision for areas of improvement. I welcome the opportunity to engage with you and your staff in the months ahead as you continue your oversight and legislative drafting.

The National Security Imperative

The Constitution states that one of the Federal Government's fundamental responsibilities is to provide for the common defense—to protect the American people, our homeland, and our way of life. The strength of our Nation's public health and medical infrastructure, and the capabilities necessary to quickly mobilize a coordinated national response to emergencies and disasters, are foundational for the quality of life of our citizens and vital to our national security. Therefore, improving national readiness and response capabilities for 21st century health security threats is a national security imperative and is my singular focus as the ASPR.

The 21st century health security environment is increasingly complex and dangerous; it demands that we act with urgency and singular effort: to save lives and protect Americans. Terrorist organizations such as ISIS and al-Qaida remain determined to attack the United States as we experienced first-hand in 2001. ISIS has demonstrated no compunction about using chemical and other unconventional weapons in attacks overseas. State actors, such as North Korea, have already threatened our homeland with nuclear weapons, and have the means to employ both chemical and biological weapons; the Syrian regime has already used chemical weapons against its own citizens.

Furthermore, we have witnessed the impacts of naturally occurring outbreaks such as influenza, Ebola, and SARS, and we are monitoring other potential emerging infectious diseases that could cause a pandemic, such as the H7N9 influenza strain circulating in China. 2018 marks the 100 year anniversary of the 1918 influenza pandemic, which killed more people than World War I. During that pandemic, more than 25 percent of the U.S. population became sick and 675,000 Americans, many of them young, healthy adults, died from the highly virulent influenza virus. Cyber-attacks like the WannaCry incident remind us that technological advancements have tradeoffs in the form of new vulnerabilities and risks, as our health delivery systems become more networked.

Finally, we face extreme weather events, such as the recent 2017 hurricane season in which Hurricanes Harvey, Irma, and Maria caused an unprecedented amount of damage, reminding us of the awesome destructive power of nature.

These are threats that most of us would rather not think about. However, when natural disasters, disease outbreaks, or attacks occur, the people expect our government to be ready to respond to save lives and protect Americans.

The ASPR Mission and Duties

When ASPR was originally established by PAHPA a decade ago, the objective was to create “unity of command” by consolidating all Federal nonmilitary public health and medical preparedness and response functions under the ASPR. This approach was modeled on the Goldwater-Nichols Act that created the Department of Defense (DoD) combatant commands; the impetus was the disorganized and fragmented response to Hurricane Katrina in 2005.

ASPR’s mission is to save lives and protect Americans from 21st century health security threats. ASPR is, in effect, the national security mission manager for HHS. As such, on behalf of the Secretary of HHS, ASPR leads the public health and medical, preparedness, response and recovery to disasters and public health emergencies, in accordance with the National Response Framework (NRF) and Emergency Support Function No. 8 (Public Health and Medical Services). It is my responsibility to coordinate the Nation’s medical and public health capabilities to help Americans during such events, whatever their cause. ASPR also coordinates with other components of HHS with respect to HHS’s role in ESF No. 6 (Mass Care, Housing, and Human Services) and HHS’s lead role as the coordinating agency with respect to the Health and Social Services Recovery Support Function.

ASPR coordinates across HHS, the Federal interagency, and supports state, local, territorial, and tribal health partners in preparing for and responding to emergencies and disasters. ASPR, in partnership with HHS agencies, works to enhance medical surge capacity by organizing, training, equipping, and deploying Federal public health and medical personnel and providing logistical support for Federal responses to public health emergencies. ASPR supports readiness at the state and local level by coordinating Federal grants and cooperative agreements and carrying out drills and operational exercises. ASPR oversees advanced research, development, and procurement of medical countermeasures (e.g., vaccines, medicines, diagnostics, and other necessary medical supplies), and coordinates the stockpiling of such countermeasures. ASPR manages the Biomedical Advanced Research and Development Authority (BARDA), Project BioShield, and the Public Health Emergency Medical Countermeasures Enterprise.

HHS and ASPR have made significant progress since PAHPA was enacted in 2006 and was reauthorized in 2013, which I will discuss shortly. The ASPR organization is filled with very capable, committed, and mission-driven staff; I am proud to lead them. It is my goal to further improve national public health and medical readiness and response capabilities, which have been developed by my predecessors who worked long hours to establish ASPR and build the capabilities that exist today. I aim to do that through four key priority areas:

First, provide strong leadership, including clear policy direction, improved threat awareness, and secure adequate resources.

Second, seek the creation of a “national disaster healthcare system” by better leveraging and enhancing existing programs—such as the Hospital Preparedness Program (HPP) and the National Disaster Medical System (NDMS)—to create a more coherent, comprehensive, and capable regional system integrated into daily care delivery.

Third, advocate for the sustainment of robust and reliable public health security capabilities, primarily through the Centers for Disease Control and Prevention (CDC), but also through other components of HHS, including an improved ability to detect and diagnose

infectious diseases and other threats, as well as the capability to rapidly dispense medical countermeasures in an emergency.

Fourth, advance an innovative medical countermeasures enterprise by capitalizing on additional authorities provided in the 21st Century Cures Act, as well as advances in biotechnology and science, in order to develop and maintain a robust stockpile of safe and efficacious vaccines, medicines, and supplies to respond to emerging disease outbreaks, pandemics, and chemical, biological, radiological, and nuclear incidents and attacks.

The State of Public Health and Medical Preparedness and Response Capabilities

In 2006, when then Secretary of Health and Human Services Michael Leavitt testified before this Committee in advance of PAHPA's passage, he told Senators that we had the ability to "become the first generation in history to be prepared for a possible pandemic." At that time, HHS was closely watching the H5N1 influenza virus, and was concerned about the potential for another human influenza pandemic. Congress invested heavily by passing emergency supplemental appropriations bills, which were used to greatly expand our domestic vaccine manufacturing infrastructure, invest in new vaccine development, and provide funding to state and local governments to enhance medical and public health readiness.

Today, our capabilities are far greater than they were then; for example, we have sufficient domestic vaccine manufacturing capacity to produce bulk vaccine for every American within 6 months. However, we have exhausted the emergency supplemental funding balances at a time when we are now closely watching the H7N9 influenza virus circulating in China, and we are concerned with the ominous trends that we are seeing. While building domestic manufacturing capacity may be a onetime expenditure, maintaining that capacity as well as sustaining, testing, and strengthening the readiness of our medical and public health infrastructure at the state and local level requires continuous support and an enduring commitment to the Public Health Emergency Medical Countermeasures Enterprise.

Last month, a report by the public health organization Trust for America's Health found that half of states scored five or lower out of 10 on health emergency preparedness. Earlier in 2016, the National Health Security Preparedness Index from the Robert Wood Johnson Foundation found that health security metrics showed modest 1.5 percent improvement overall during 2016, reaching the highest level of out of 10 total; however, levels of readiness varied significantly across the country. So, while we have made progress in the last decade, we still have work to do. Two areas of progress and opportunities I would like to highlight are our medical countermeasures enterprise, specifically BARDA, and our healthcare readiness capacity.

Medical Countermeasures Enterprise—BARDA

PAHPA established BARDA to bridge the so-called "valley of death" in late stage development of medical countermeasures where many products historically languished or

failed. By using flexible, nimble authorities, multiyear advanced funding, strong public-private partnerships, and cutting edge expertise, BARDA has successfully pushed innovative medical countermeasures, such as vaccines, drugs, and diagnostics, through advanced development to stockpiling and FDA approval or licensing.

In the last decade, BARDA's strong partnerships with the National Institutes of Health, other HHS components, and biotechnology and pharmaceutical companies have led to 34 medical countermeasures approved or licensed by the FDA, which is a staggering accomplishment. BARDA has supported the development of 27 medical countermeasures against Department of Homeland Security (DHS) identified national security threats through Project BioShield, including products for smallpox, anthrax, botulinum, radiologic/nuclear emergencies, and chemical events. Fourteen of these products have been placed in the Strategic National Stockpile and are ready to be used in an emergency. BARDA also has supported the development of 23 influenza vaccines, antiviral drugs, devices, and diagnostics to address the risk of pandemic influenza. As a result of this progress, more medical countermeasures than ever before are eligible to be acquired for the SNS, thereby creating new challenges in terms of acquiring and maintaining sufficient quantities of medical countermeasures for identified threats.

We are supporting the development and stockpiling of many more novel medical countermeasures within the next few years, such as H7N9 influenza vaccines, next generation anthrax vaccines, enhanced smallpox vaccines, biodosimetry diagnostic devices, thermal burn radiation drug and skin replacement therapies, radiation cell therapies, new antibiotics, and new chemical antidotes.

We also have opportunities to further improve our national security medical countermeasures enterprise by streamlining our internal decision-making processes, finding new ways to support innovation, promoting flexible, fast response capabilities, and increasing our collaboration with Federal interagency partners, such as DoD and Department of Veterans Affairs (VA). We also must work closely with our state, local, territorial, and tribal partners, as well as the private sector to enhance the capability to quickly distribute and dispense medical countermeasures in an emergency—if we can't get these products to the right place, at the right time, then the enterprise has failed.

Healthcare Readiness to Respond

The 2017 hurricane season highlighted the importance of national healthcare readiness and medical surge capacity. ASPR led the public health and medical responses to Hurricanes Harvey, Irma, and Maria under the National Response Framework Emergency Support Function No. 8 mission. We worked closely with state and territory health officials in affected areas to augment care with NDMS teams, VA personnel and facility support, and DoD transportation, facilities, and clinicians. Personnel under the supervision of HHS treated over 36,000 patients, and HHS deployed over 4,500 personnel, evacuated nearly 800 patients, awarded over 200 contracts, and provided nearly 950 tons of equipment.

During the response, due to the combined efforts of ASPR and the Centers for Medicare & Medicaid Services (CMS), we utilized the innovative HHS emPOWER program to identify and treat at risk individuals requiring electricity-dependent medical and assistive equipment

(e.g., ventilators, oxygen concentrators, feeding machines, intravenous infusion pumps, suction pumps, dialysis machines, wheelchairs). In one instance, ASPR teams used this data and worked with Urban Search and Rescue teams to identify all of the dialysis patients in the U.S. Virgin Islands and evacuate those patients for treatment since the local dialysis centers were destroyed. Despite our successes, we also learned that ASPR needs to improve its internal capabilities as well as enhance our support for the healthcare infrastructure across the country. As with medical countermeasures, the Nation's healthcare delivery infrastructure is mostly a private sector enterprise. We must better leverage and enhance existing Federal programs—such as the Hospital Preparedness Program and NDMS—to create a more coherent, comprehensive, and capable regional system integrated into daily care delivery I call this the foundation of a “national disaster healthcare system.”

Conclusion

Through this second reauthorization of PAHPA, we have the opportunity to build on the great progress made and further improve our national readiness and response capabilities for 21st century health security threats. The Department looks forward to working with you in the months ahead to consider any legislative changes needed to achieve this objective. I am committing the entire ASPR team's grit, ingenuity, expertise, and perseverance to this mission. Thank you, again, for your bipartisan commitment to this national security imperative, and I look forward to continuing to work together to enhance our Nation's health security. I am happy to answer any questions you may have.

Senator BURR. Thank you, Dr. Bob. Dr. Gottlieb.

STATEMENT OF SCOTT GOTTLIEB, M.D., COMMISSIONER, U.S. FOOD AND DRUG ADMINISTRATION, SILVER SPRING, MD

Dr. GOTTLIEB. Senator Burr, Ranking Member Murray, and Members of the Committee.

Thank you for the invitation to testify today about genome editing technology.

Our Nation has faced many emerging public health challenges and unfortunately, will face additional challenges in the future. Thankfully, our preparedness and the ability to respond to such challenges has improved greatly since the original enactment of the Pandemic and All-Hazards Preparedness Act.

Each emergency is unique. Many are the result of emerging infectious threats, but the technology for manipulating science for diabolical purposes is becoming more ubiquitous and widely understood. So we face new and pervasive risks.

2017 was marked by the risks posed by several extreme natural disasters, which caused significant devastation and human suffering. These tragedies tested our Nation's capabilities to respond. Today, I am going to focus my remarks on the impact of these storms on medical products manufactured in Puerto Rico and the actions we are taking to mitigate existing and potential product shortages.

The impact of Hurricane Maria showed the importance of Puerto Rico to our medical product manufacturing base, as well as the intricate and sometimes fragile nature of that supply chain.

I want to focus on the complexities of the saline shortage because it has stressed our system and I know that many of you are deeply and rightly concerned by this situation.

Saline solution has been in and out of shortage for several years. There are only a small number of primary manufacturers. So when one manufacturer lowers production, even for routine maintenance, there is stress on the entire system.

One of the largest manufacturers of I.V. saline is Baxter, and their primary sites for small volume bags are located in Puerto Rico. These sites struggled to regain power and return to full capacity following the storm when roads to some of the manufacturing plants were disabled.

We worked closely with Baxter in partnership with the Department of Homeland Security, and Puerto Rico authorities, and Bob—so thank you for your support, as well—to ensure that they were able to get back on the power grid on a priority basis to stabilize production.

We also worked with various saline manufacturers to find other manufacturing facilities globally that could help supply the U.S. until Baxter's Puerto Rico location was back up and running and the shortage was addressed.

To mitigate that shortage, we worked with manufacturers on the importation of saline from locations in Ireland, Australia, Mexico,

Canada, Germany, and most recently, Brazil. When we import from international facilities, generally, the manufacturers adjust their distribution to send some product to the U.S., but there is no actual increase in the total global production of product.

Baxter's manufacturing facilities in Puerto Rico are now stable and on the grid, although the power situation on the island is still fragile. We expect their return to normal production will improve the situation.

Before the storms hit, and in anticipation of the crisis, FDA also prioritized the approval of saline products by two manufacturers, Fresenius Kabi laboratories, and Grifols. Both should start production soon, and having these two additional manufacturers online will help increase the overall supply of saline produced and distributed in the U.S.

But this shortage has also had ripple effects. In order to find workarounds for the filled saline bags that were in shortage, providers have put various mitigation strategies in place. One strategy has hospitals compounding product themselves and this has caused an increased demand for empty i.v. bags. There have been signals indicating that this increased demand is putting pressure on the supply of empty i.v. bags. The FDA is taking steps to address that situation and determine which manufacturers could potentially increase capacity if necessary.

I have reached out to some of these medical device manufacturers personally to inquire about their capacity to increase production as demand for I.V. containers continues to increase.

The scope of the flu outbreak across the country has also added to the strain on this tight supply chain. The shortage, and the impact of the crisis in Puerto Rico, underscores the need to continuously elevate our preparedness.

There are going to be lessons learned from this episode, and already, we have made some key observations about our ability to detect device shortages. Since we lack authority to

require notification of device shortages, we have had to depend on manufacturers and distributors reaching out to the FDA or had to seek them out proactively.

Our work in the shortage situation is an example of how the FDA has reacted in response to emergency situations. At the same time, we continue to work hard to improve our regulatory clarity and predictability for the development of medical countermeasures. That is an essential component of our national preparedness strategy.

Today, we released draft guidance on Material Threat Medical Countermeasure and Priority Review Vouchers which explains how the FDA is implementing the PRV program to incentivize the development of certain drug and biologics medical countermeasures. I look forward to working with Congress to continue to increase our readiness for emergencies, and look forward to answering your questions today.

[The prepared statement of Dr. Gottlieb follows:]

PREPARED STATEMENT OF SCOTT GOTTLIEB

Chairman Alexander, Ranking Member Murray, and Members of the Committee, thank you for the opportunity to appear today to discuss reauthorization of the Pandemic and All-Hazards Preparedness Act (PAHPA). PAHPA, which was passed in 2006 and reauthorized in 2013, is a key piece of legislation that—along with other significant legislative achievements such as the Project BioShield Act of 2004, the Public Readiness and Emergency Preparedness (PREP) Act (2005), and the 21st Century Cures Act (Cures Act) enacted in 2016—has served to significantly strengthen our country’s preparedness for, and response to, public health emergencies involving chemical, biological, radiological, and nuclear (CBRN) threats as well as emerging infectious disease threats, such as the Zika virus and pandemic influenza.

The Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 (PAHPRA), in particular, recognized the key role the Food and Drug Administration (FDA or the Agency) plays in emergency preparedness and response, and codified and built on FDA’s ongoing efforts to augment review processes and advance regulatory science to enable FDA to better respond to public health emergencies. The provisions in PAHPRA—as well as in the other key pieces of legislation I mentioned—have provided FDA with essential tools that continue to support us in our mission to protect and promote public health.

FDA’s Public Health Emergency Preparedness and Response Mission

FDA plays a critical role in facilitating preparedness for and response to CBRN and emerging infectious disease threats. These threats can and often do emerge without warning as was the case with the anthrax attacks of 2001, the 2009 H1N1 influenza pandemic, the 2014 Ebola outbreak in West Africa, as well as in the ongoing Zika virus outbreak.

FDA’s role in facilitating preparedness for, and response to, CBRN and emerging infectious disease threats focuses largely on facilitating the development and availability of medical countermeasures—such as vaccines, therapeutics, and diagnostic tests—to respond to these threats. FDA works closely with its HHS and other U.S. Government partners through the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE), as well as with regulated industry and non-governmental organizations (NGO’s), to build and sustain

the medical countermeasure programs necessary to effectively respond to public health emergencies. FDA is also committed to working closely with the Department of Defense (DoD) to facilitate the development and availability of medical counter-measures to support the unique needs of our Nation's warfighters. The Agency is already actively implementing the legislation enacted at the end of last year to further prioritize this critical work with DoD. Senior leadership at the Agency is leading these efforts, and we look forward to keeping Congress informed of our progress in these critical areas.

FDA's Medical Countermeasures Initiative (MCMi)—established in 2010—brought additional resources to FDA that enabled FDA to hire additional expert staff and to become more deeply and thoroughly engaged in medical countermeasure activities. This program continues to be key to establishing clear regulatory pathways for medical countermeasures, advancing medical countermeasure regulatory science to support regulatory decisionmaking, and advancing important policies and mechanisms to facilitate the timely development and availability of medical counter-measures. FDA's goal is to be modern and efficient in its regulation of safe and effective medical products, and that includes medical countermeasures.

FDA's operations within its medical countermeasures mission cover a broad range of activities vital to facilitating the development of, and access to, safe and effective medical countermeasures, including:

- Reviewing medical countermeasure marketing applications and approving those that meet standards for safety and efficacy;
- Providing regulatory advice, guidance and technical assistance to sponsors developing medical countermeasures, as well as to U.S. Government partners, international regulators, and international organizations such as the World Health Organization;
- Supporting efforts to establish and sustain an adequate supply of medical countermeasures, including averting supply disruptions when feasible and, in certain situations, allowing products to be used beyond their expiration dates when supported by appropriate scientific evaluation;
- Enabling access to medical countermeasures that are not yet approved for use—when necessary—through an appropriate mechanism, including through FDA's Emergency Use Authorization (EUA) authority;
- Proactively identifying and resolving regulatory challenges associated with medical countermeasure development and ensuring that FDA regulations and policies adequately support medical countermeasure development and enable preparedness and response activities;
- Fostering the professional development of FDA scientists to ensure that FDA personnel maintain the skills and abilities to support the medical counter-measure mission; and
- Supporting regulatory science to create the tools, standards, and approaches necessary to develop and assess the safety, efficacy, quality, and performance of medical countermeasures.

FDA is also a critical partner in preparing for, and responding to, natural disasters, as demonstrated by its ongoing 2017 hurricane recovery efforts, including its work in Puerto Rico following Hurricane Maria. FDA performs extensive preliminary work in advance of storms to help prepare for potential impacts. For example, FDA utilizes storm prediction data and firm registration data bases to prepare maps to identify FDA regulated firms, including those that manufacture critical products that could be impacted by the storms. Where necessary, FDA may take contingency steps to help ensure a continuous supply of critical medical product manufacturing. The most significant role that FDA plays comes after the storm, as facilities come back on line and may need remediation, and farmers seek to put crops or farmland that were damaged back into commercial use. FDA has supported the many pharmaceutical and medical device manufacturers in Puerto Rico to help address and prioritize recovery operations based on the potential for medical product shortages based on public health needs. Many of the requests FDA received were for infrastructure support, primarily getting a reliable source of power, and FDA worked with partners at the Department of Homeland Security to support getting critical manufacturing back online. Through product registrations and communications with manufacturers, FDA was able to identify the medically necessary products manufactured in Puerto Rico and determine which were the top public health priorities. FDA continues to be focused on storm-related shortage issues, including shortages of saline solution and amino acids, as well as the cascading increase in demand for other medical products, such as empty IV containers which are now being used in higher quantities for compounded products. FDA has been in direct communication with manufacturers, distributors, hospitals and other health care providers, including the Department of Veterans Affairs (VA), and we are assessing existing product supply, demand trends and manufacturer capacity to increase availability of the empty IV containers.

Fostering Innovation in Medical Countermeasure Development

At FDA, we fully appreciate that the development of medical countermeasures can present complex and unique challenges. For example, it is not ethical to conduct human studies for many of the high-priority threat agents. In these situations, the Animal Rule, which enables animal efficacy studies to substitute for efficacy trials in humans if the results can reasonably be extrapolated to the expected human use, can be used to facilitate the development and availability of medical counter-measures. PAHPRA recognized the importance of the Animal Rule; and in 2015, FDA finalized guidance for product development under the Animal Rule, incorporating the learnings of considerable product development experience and providing scientific and regulatory expectations for animal data intended to support medical countermeasure approval.

To date, 12 medical countermeasures have been approved under the Animal Rule, including inhalational anthrax therapeutics, a botulism antitoxin, antibiotics for the treatment and prophylaxis of plague, and treatments for acute radiation syndrome. These approvals underscore the critical role the Animal Rule and animal studies can play in advancing medical countermeasures for some of the most challenging threats. Of note, through the use of regulatory science, FDA was able to approve the inhalational anthrax therapeutics and the

botulism antitoxin for use in children as well as adults, despite the fact that pediatric patients were not actually studied in clinical trials, due to ethical concerns.

However, for many threats there are not yet adequate regulatory science foundation, such as animal models to support medical countermeasure development or sufficient biomarkers to enable the extrapolation of data generated in animal models to humans. Without such tools, it is difficult to generate the data necessary to support regulatory decision-making.

FDA has established a broad and robust portfolio of cutting-edge research under MCMi's Regulatory Science Program to help develop these tools and promote innovation in the development of medical countermeasures. A few examples of projects include: supporting the development of organs-on-chips models to assess radiation damage in lung, gut, and bone marrow, and then using these models to test candidate medical countermeasures; collaborating to establish a publicly available genomic sequence reference data base for use by developers seeking to validate candidate multiplex in vitro diagnostic tests that could be used to diagnose multiple pathogens simultaneously; developing reference materials for developers to use to validate nucleic acid-based and serological diagnostic tests for Zika virus; supporting a project to identify and correlate biomarkers of host response to Ebola virus infection in animal models and humans to support medical countermeasure development; developing methods for obtaining safety and limited efficacy data from patients who receive medical countermeasures during public health emergencies; and establishing the Animal Model Qualification Program designed to support medical counter-measure development by promoting the development of animal models for use across multiple product applications, thereby minimizing duplication of effort and resources.

PAHPRA also provided authorities to ensure that FDA personnel are well-trained in how to review medical countermeasure applications for approval. Under these authorities, FDA has established a professional development program, including speakers' series and academic certifications, to ensure that FDA scientists are working through the regulatory challenges posed by new areas of science and technology as they relate to medical countermeasure development. FDA also has spent considerable energy and resources establishing an efficient approach to conduct and support training within the agency.

More recently, the Cures Act included several provisions that are intended to advance innovation in medical product development more generally, but will also help to facilitate the development of medical countermeasures, including the provisions to encourage novel trial designs, and to develop new antimicrobial drug products. Through the Cures Act, Congress also provided a new priority review voucher (PRV) program to help incentivize the development of material threat medical countermeasures. Under this program, FDA will award a PRV upon approval of a material threat medical countermeasure application provided that certain criteria are met. The PRV may in turn be used by the sponsor who receives it, or sold to another sponsor, who may then use it to obtain priority review for a product application that would otherwise not receive that benefit, enabling a developer to potentially bring a product to market sooner than otherwise possible—something that may be of great value to product developers. FDA plans to issue guidance to address medical countermeasure specific considerations with the intent to implement the program consistently with the other PRV programs, such as the Neglected Tropical Disease Voucher Program.

There are tremendous opportunities to continue to further the development of groundbreaking, innovative medical countermeasures, and the Agency intends to fully seize and build upon these opportunities. Toward that goal, this past July FDA announced the

launch of a comprehensive Innovation Initiative aimed at making sure its regulatory processes are modern and efficient so that safe and effective new technologies, including medical countermeasures, can reach patients in a timely fashion.

Facilitating Access to Safe and Effective Medical Countermeasures

Enabling access to medical countermeasures when they are needed is a high priority for FDA. Amended and new authorities provided by Congress have enabled the Agency to further prepare for, and better respond to, emerging public health threats. For example, PAHPRA amended FDA's EUA authority to provide additional flexibility for issuing EUAs. These additional flexibilities have enabled FDA to better support responses to emerging health threats by issuing nearly 40 EUAs to enable the emergency use of *In Vitro* diagnostic devices for H7N9 Influenza virus, Enterovirus D68 (EV-D68), Middle East Respiratory Syndrome Coronavirus (MERS-CoV), Ebola virus, and Zika virus. FDA also issued an EUA to enable the emergency use of an autoinjector medical countermeasure to maintain preparedness for chemical threats, which has been critical for supporting both warfighter and first responder preparedness goals related to an emergency involving nerve agents. The authority for prepositioning medical countermeasures provided in PAHPRA also proved useful to allow the manufacturer to ship, and the U.S. Government stakeholders to receive, certain strengths of the unapproved autoinjectors that were not yet authorized for use under that EUA.

PAHPRA also provided FDA with several new streamlined authorities to facilitate the emergency use of approved medical countermeasures without the need for issuing an EUA. For example, PAHPRA provided FDA with the authority to issue emergency dispensing orders (including mass dispensing at a point of dispensing (POD)) for approved medical countermeasures during an actual CBRN emergency without requiring an individual prescription for each recipient of the medical countermeasure, if permitted by state law or in accordance with an emergency dispensing order issued by FDA. FDA has used this authority to issue emergency dispensing orders to permit emergency dispensing of doxycycline and ciprofloxacin for post-exposure prophylaxis of inhalational anthrax, to ensure government stakeholders can rapidly provide these therapies in the event of an anthrax attack.¹

Another new FDA authority created by PAHPRA is the explicit ability to extend expiration dating of eligible FDA-approved medical countermeasures stockpiled for use in CBRN emergencies, if the extension is supported by an appropriate scientific evaluation. This authority streamlines FDA's ability to authorize expiration dating extensions without the need to issue an EUA, which will enable faster response, and has been crucial to FDA's ability to support preparedness efforts. For example, when production stopped after quality issues were identified in the manufacturing process of autoinjectors used for the treatment of nerve agent and insecticide poisoning, FDA used this authority to help prevent shortages of auto-injector products to help ensure that the Nation's warfighters and first responders continue to have ready access to these products. FDA also used this authority to extend the expiration date of

¹ The term "stakeholder(s)" means the public agency or its delegate that has legal responsibility and authority for responding to an incident, based on political or geographical boundary lines (e.g., city, county, tribal, state, or federal), or functional (e.g., law enforcement or public health range) or sphere of authority to prescribe, administer, deliver, distribute, or dispense oral doxycycline products in an emergency situation.

certain lots of doxycycline capsules held in strategic stockpiles by the Centers for Disease Control and Prevention, state and local public health, and other response stakeholders and issued draft guidance to provide recommendations to government stakeholders on testing that can be conducted to support future extensions, in order to help sustain preparedness levels.

The Cures Act also amended the EUA and related emergency use authorities to clarify their applicability to animal drugs. FDA encourages anyone interested in utilizing these authorities to contact FDA to discuss how to proceed.

Most recently, Congress passed H.R. 4374, legislation that amends FDA's EUA authority to enable FDA to issue EUAs for medical products to reduce deaths and mitigate injuries from agents that may cause imminently life-threatening and specific risks to United States military forces. Prior to the passage of this legislation, the EUA authority was only applicable to medical products to address CBRN threats. In addition, the legislation contains provisions codifying enhanced collaboration between FDA and DoD, in order to facilitate the development of medical products and countermeasures for the warfighter. FDA is working closely with DoD to implement these new and amended authorities as quickly as possible.

Conclusion

At FDA, we have made it a priority to proactively work with our private sector and government partners to help facilitate the translation of breakthrough discoveries in science and technology into innovative, safe, and effective medical countermeasures. FDA takes its responsibility seriously to help drive and foster innovation as part of advancing public health and our national security. Active FDA involvement is essential to encouraging industry engagement in medical countermeasure development. FDA remains deeply committed to working closely with its partners and continuing to use the authorities Congress provides to the fullest extent to help facilitate the development and availability of safe and effective medical countermeasures. We believe that partnership and innovation will continue to be key drivers to success in the medical countermeasure space and are taking steps to further empower FDA's scientific and clinical experts to drive the innovation necessary to help protect the Nation from the threats we may face.

FDA appreciates Congress's support in continually delineating, clarifying, expanding, and extending its authorities—and providing resources—to enable FDA to achieve its public health emergency preparedness and response mission. FDA stands ready to work with Congress and stakeholders to enable us to better achieve this critical work.

Thank you for inviting FDA to testify today. I am happy to answer any questions you may have.

Senator BURR. Thank you, Scott. Dr. REDD.

**STATEMENT OF STEPHEN C. REDD, M.D., RADM, DIRECTOR,
OFFICE OF PUBLIC HEALTH PREPAREDNESS AND RESPONSE,
CENTERS FOR DISEASE CONTROL AND PREVENTION, ATLANTA, GA**

Dr. REDD. Senator Burr, Chairman Alexander, and Ranking Member Murray.

I am Dr. Stephen Redd, the Director of the Office of Public Health Preparedness and Response at the Centers for Disease Control. And I am pleased to be here to talk with you today about the role the CDC plays in public health preparedness and response, including those responsibilities under the Pandemic and All-Hazards Preparedness Reauthorization Act.

The CDC is the common defense of the country against health threats. Our work to prepare and respond to health emergencies require that we build on our day to day in two particular areas.

No. 1, our longstanding partnership with state and local health departments and;

No. 2, our medical, scientific, and program expertise.

I will describe the three pillars of our defense strategy: science, surveillance, and service.

First, the CDC has a unique collection of scientific expertise that exists nowhere else in the world. We have the ability to identify agents causing illness, whether that illness is caused by an infectious microbe, or a chemical, or a radiation exposure.

We are ready to respond to a broad range of threats including diseases like Ebola, small pox, and H7N9 influenza.

The CDC plays a key role in discovering new and emerging infectious diseases using advanced detection techniques to identify pathogens quickly and more accurately.

Every year, laboratories from all over the world send hundreds of thousands of specimens to the CDC for testing.

The second pillar enabling the CDC's common defense of the country is surveillance. Public health surveillance is the collection, analysis, and use of data to target public health prevention and response. It is basically making sure the best information is used to make the right decisions.

Examples of this work include what we do to track influenza, the National Syndromic Surveillance system and the Global Disease Detection Program.

Influenza is probably the greatest natural health threat we face. Influenza viruses change continuously and require vigilance to detect these changes. The CDC provides support to every state, to several major cities, and to a number of ministries of health throughout the world to conduct influenza surveillance and laboratory work.

With the National Syndromic Surveillance Program, the CDC collects deidentified health information on causes of emergency room, urgent care, and hospital visits. We, along with state and local health departments, use the data in real time to detect abnormal situations requiring public health response.

The CDC's Global Disease Detection Operation Center monitors 30 to 40 outbreaks every day across the globe, 24/7, and assesses the potential risk to the United States from these events. In addition to science and surveillance services, the final pillar is supporting the CDC's common defense of the country.

Let me focus on three particular programs, the Public Health Emergency Preparedness Program, the Strategic National Stockpile, and the Cities Readiness Initiative.

In each of these programs, the keys to success are the close collaboration between CDC and state and local public health departments, and the connection of these programs to CDC's scientific expertise.

The Public Health Emergency Preparedness grants go to every state and support staff, enable exercises to test and validate capabilities, and pay for laboratory and communications equipment.

The Strategic National Stockpile is a \$7 billion repository of pharmaceuticals, medical supplies, and medical equipment that is available for rapid delivery to support responses to health emergencies.

The CDC's Cities Readiness Initiative enhances preparedness in the Nation's 72 largest cities where nearly 60 percent of the U.S. population resides. These funds are used to develop, test, and maintain plans to receive countermeasures from the CDC's Strategic National Stockpile and rapidly dispense them.

I would like to leave the Committee with three primary points about the CDC's role in public health emergency preparedness and response.

First, the CDC is the common defense of the country against health threats.

Two, CDC's preparedness work is built on a day to day foundation of our broad and deep scientific medical and program expertise.

Three, the CDC's longstanding partnerships with state and local health authorities are essential.

Thank you for the opportunity to testify today. [The prepared statement of Dr. Redd follows:]

PREPARED STATEMENT OF STEPHEN C. REDD

Chairman Alexander, Senator Murray, and other Members of the Committee. I am Rear Admiral Stephen Redd, Director of the Office of Public Health Preparedness and Response at the Centers for Disease Control and Prevention (CDC). I appreciate the opportunity to be here today to discuss CDC's public health preparedness and response mission, and the agency's role in implementing the Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 (PAHPRA).

CDC provides for the common defense of the country against public health threats. Through our dedication to science, surveillance, and service, CDC focuses on protecting the public health of the Nation from threats such as emerging infectious diseases, natural disasters, and terrorism.

In carrying out the mission set forth under the Pandemic and All Hazards Preparedness Reauthorization Act, CDC draws on expertise from throughout the agency. CDC's expertise includes world-class laboratory testing, surveillance (for disease detection), epidemiology, guidance to healthcare providers, incident management, logistics, emergency risk communication, disease control programs, distribution of medical countermeasures, human and animal medicine, and responder health and well-being. Our multidisciplinary workforce enables an integrated national system that is nimble and prepared to detect and respond to any developing situation that could affect the health of people in the United States. In addition, CDC draws on its long-standing relationships and close collaboration with state and local

partners to protect the health of communities across the country, and collaborates closely with the Assistant Secretary for Preparedness and Response (ASPR), the Food and Drug Administration (FDA) and other Federal partners.

CDC experts lead and staff every activation of the agency's Emergency Operations Center (EOC), ensuring response activities are effective and efficient. HHS/CDC has an emergency management program accredited by the Emergency Management Accreditation Program. CDC activated its incident management system for 67 responses over the last 16 years, between September 2001 and December 2017. During a response, CDC's EOC rapidly deploys scientific experts, coordinates the delivery of supplies and equipment to the incident site, monitors response activities, provides resources to state and local public health departments, and disseminates timely and accurate information within government, to health care providers, and to the public. During the agency's Zika and Ebola responses, CDC deployed over 1,700 and 3,700 staff, respectively. CDC also responds to public health events that do not require EOC support. In fiscal year 2017, CDC assisted state, local, and overseas public health authorities in 23 epidemiologic investigations of emerging infectious disease outbreaks as well as more than 20 environmental responses.

CDC Programs under the Pandemic and All Hazards Preparedness Reauthorization Act

The Pandemic and All Hazards Preparedness Reauthorization Act of 2013 (PAHPRA) reauthorized several public health preparedness programs. The discussion immediately below focuses on two of those programs: CDC's Public Health Emergency Preparedness cooperative agreement program (which includes the Cities Readiness Initiative (CRI)) and the Strategic National Stockpile (SNS). Later in the testimony I will discuss CDC's work related to a third PAHPRA program, bio-surveillance.

Public Health Emergency Preparedness Cooperative Agreement (PHEP) Program: The PHEP cooperative agreement program is the largest CDC state program and provided approximately \$600 million to state, local, and territorial public health departments in 2017. The program developed the first playbooks for public health preparedness and response, and has been instrumental in integrating state and local health departments into their jurisdictions' emergency response structures. PHEP currently supports 62 awardees—including all 50 states, eight territories and freely associated states, and directly funded cities (New York City; Washington, DC.; Chicago; and Los Angeles). Funding is awarded according to a base plus population formula prescribed by statute, which ensures a minimum amount of funding to each awardee. These funds support preparedness and response staff, enable exercises to test and validate capabilities, provide for timely training, and pay for laboratory and communications equipment essential to maintaining preparedness. In addition, CDC personnel support PHEP awardees by helping to identify and address gaps in preparedness capabilities, providing planning resources to ensure the needs of at risk individuals are incorporated into response strategies, and improving response capabilities from experience gleaned during public health responses, most recently to Ebola and Zika.

Strategic National Stockpile (SNS): The SNS is the largest federally owned repository of vaccines, drugs, medical supplies, Federal Medical Stations, and medical equipment available

for rapid delivery to support federal, state, and local response to health security threats. The SNS was created in 1999 to ensure the Nation's readiness against public health emergencies by ensuring delivery of lifesaving medical countermeasures (MCMs) during deliberate or naturally occurring outbreaks and other events that threaten public health. Since its inception, SNS products and staff have been deployed more than 100 times for events ranging from natural disasters to infectious disease outbreaks. CDC works with the HHS Assistant Secretary for Preparedness and Response and with other Federal agencies through the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) to prioritize Federal investments in medical countermeasures based on analysis of risk, benefits to the American people and sustainability of the MCM pipeline.

Management of the SNS and deployment of its assets are complex endeavors which rely on a broad range of scientific expertise, surveillance systems, public health communications systems, and state and local partners. The SNS ensures that the right medical countermeasures and supplies are available when, where, and in the quantity needed to stop or slow a public health emergency and save lives. And, scientific experts ensure that medicine and supplies expeditiously get to our public health partners at the state and local levels, who have had the necessary training, exercises, and clinical guidance to effectively and efficiently receive those assets from the SNS and get them to those who need them.

Cities Readiness Initiative (CRI): CRI, funded through the PHEP cooperative agreement, enhances preparedness in the Nation's largest population centers, where nearly 60 percent of the population resides. The 72 cities (at least one in every state) use CRI funds to develop, test, and maintain plans to quickly receive medical countermeasures from the SNS and distribute them to local communities. This program, through reliance on local boots on the ground, enables effective response to large-scale public health emergencies needing life-saving medications and medical supplies.

Public Health Preparedness through Science, Surveillance and Service

In carrying out its public health mission CDC's subject matter experts from across the agency collaborate to detect and respond to emerging threats that could affect Americans' health.

Science

Exceptional and world-renowned scientific expertise and world-class laboratories ensure CDC is ready and able to respond to a broad range of threats, including highly hazardous and infectious diseases like Ebola, smallpox, and H7N9 influenza. For example, CDC's research on the smallpox virus helps find better drugs to treat the disease, stop the virus from spreading, make safer vaccines, and improve tests to detect the virus. Additionally, CDC's global influenza capacity-building efforts helped facilitate the rapid detection of the novel Asian lineage influenza A (H7N9) virus in 2013. Most human infections resulted from exposure to infected poultry, but CDC assesses that the virus poses the greatest pandemic risk of all influenza viruses not yet circulating among humans, and is working with global health partners to monitor that virus and detect changes in it that could trigger a pandemic. CDC has developed two candidate vaccine viruses and shared them with vaccine manufacturers, for use

in BARDA-supported vaccine production and in clinical trials by NIH's National Institute of Allergy and Infectious Disease. If the H7N9 virus develops the capacity to spread among humans, an effective vaccine would be key for preventing a pandemic.

CDC plays a critical role in discovering new and emerging infectious diseases, using advanced molecular detection techniques that combine next-generation genomic sequencing, high-performance computing, and epidemiology to identify pathogens faster and more accurately. Laboratories from all over the world send specimens to CDC, often in cases where the cause of illness is unknown. Annually, CDC receives hundreds of thousands of specimens to examine and helps diagnose hundreds of cases of unexplained illness or death. Through advanced molecular detection investments, CDC is seeing improvements in faster detection of outbreaks (catching them when they are smaller) and in faster development of diagnostics, applying these technologies in dozens of areas such as foodborne disease, influenza, antimicrobial resistance, hepatitis, pneumonia, and meningitis. CDC shares genetic sequencing technologies with state and local health departments, and funds them to acquire new technology that helps them to respond quicker and more efficiently at a local level.

CDC is critical to preparing for the next influenza pandemic. In an influenza emergency, CDC's public health and infectious disease experts use advanced molecular detection techniques to identify disease strains that could cause a pandemic, release recommendations for the prevention, diagnosis, and treatment of disease, and provide communication to the Nation about the pandemic. For example, each human case of infection with a new animal influenza virus represents the potential for a pandemic. CDC receives and studies viruses like these in its laboratories to better understand where and how they spread and the nature of illness they cause. This informs development of clinical and public health recommendations before and during emergency responses. In the event of an influenza pandemic, CDC's scientific experts use the best epidemiologic and laboratory data available to update or develop guidance to inform purchasing, distribution, and use of medical counter-measures including vaccines, antiviral drugs, respirators or masks, and ventilators. CDC also develops and evaluates solutions to lessen the impact of an influenza pandemic through non-pharmaceutical interventions or actions that people and communities can implement to help slow the spread of influenza, such as staying home when ill, coordinating school closures, and postponing mass gatherings.

CDC has longstanding collaboration with countries and institutions around the world. These strategic partnerships coupled with forward deployment of our scientists stationed in more than 60 countries enable CDC to identify new pathogens, assess risks, and devise effective control measures. Our partnerships provide the platforms for timely sharing of laboratory specimens, innovations and distribution of diagnostic materials and technologies to prevent epidemics, and promptly respond to disease outbreaks before they cross international borders.

Vector-borne diseases present another preparedness challenge, as we saw in the Zika emergency. CDC is one of the Nation's public health authorities on vector-borne diseases, like Zika, plague, and dengue. CDC scientists who specialize in vector-borne disease have deep expertise in entomology, microbiology, virology, veterinary medicine, zoology, and public health that does not exist elsewhere. These experts develop diagnostic tools and clinical guidance, as well as methods of treatment, prevention, and vector control, in order to slow the spread of these diseases. For example, CDC scientists have determined that a natural plant ingredient called nootkatone effectively repels and kills the mosquitoes and ticks that

can spread disease. Nootkatone appears to work differently than available insecticides, and it could help fight mosquitoes that are resistant to existing insecticides.

CDC's scientific experts protect people from environmental health threats like contaminated water, radiation, and chemical emergencies. To do so, CDC identifies the environmental exposures that make people sick, investigates how those exposures are transmitted in the environment, and finds ways to eliminate the threat to people's health. For example, CDC's radiation guidelines help public health officials and clinicians prepare for, and respond to, radiation emergencies and treat exposures.

The list of CDC's scientific expertise is much longer than I have detailed, including myriad chronic diseases and also includes foundational scientific expertise critical to effective public health impact such as in the areas of workforce, laboratory systems, and data sciences.

Surveillance

Public health surveillance—the collection, analysis, and use of data to target public health prevention and intervention activities—is the foundation of public health practice. CDC monitors health surveillance information around the clock to detect and track diseases and protect Americans. As one example, following 9/11, CDC made investments in enhancing syndromic surveillance—using health-related data based on patient symptoms that precede diagnosis—as an early warning system for bioterrorism. This system now allows officials to detect a much wider range of health threats—from opioid overdoses to chemical spills to disease outbreaks. Moreover, CDC collects, analyzes, and interprets human, animal, environmental, and food surveillance data, in order to identify and respond to potential health threats before they become emergencies. In aggregate, CDC's specialized surveillance systems provide prompt situational awareness and early warning for unknown or unexpected threats. CDC's surveillance activities directly support states in their primary responsibilities in protecting the public's health. Surveillance data, collected in collaboration with domestic and international partners, inform CDC's threat assessments and ensures response actions are at the right speed, scope, and scale to protect Americans.

CDC supports integrated disease surveillance activities at the state and local level through funding and provision of surveillance tools and services. The following are examples of the surveillance systems and support that CDC provides to state, local, and territorial public health departments to develop and strengthen their surveillance activities:

- *National Notifiable Diseases Surveillance System (NNDSS)*: NNDSS is a nationwide system that enables all levels of public health—local, state, territorial, Federal, and international—to collect and share data on approximately 100 diseases and conditions that are required to be reported in all 50 states, and keeps them under continuous surveillance. This system provides comprehensive, timely, and high-quality data for public health decision-making, enabling CDC programs to work with state partners to better monitor disease occurrence, identify potential outbreaks, recognize emerging trends, track the impact of public health interventions, and respond..
- *Influenza Surveillance*: Influenza viruses are constantly changing, and, thus, require continued vigilance to protect the United States and the rest of the world from both seasonal and pandemic influenza threats. Influenza surveillance, both epidemiologic

and virologic, is at the core of influenza preparedness. The surveillance platforms used year round to combat seasonal influenza threats serve as the foundation for pandemic influenza surveillance. CDC provides support to every state, and several major municipalities and territories, to conduct influenza surveillance and laboratory work. For many decades, CDC has served as an international leader in global influenza surveillance. We have partnered with more than fifty countries to establish, maintain, and expand influenza surveillance and laboratory capacity, in order to find influenza viruses where they emerge as quickly as possible to mitigate their potentially devastating impact on the United States. Domestic funding supports seasonal influenza surveillance through a network of interrelated systems that provide data on where influenza and influenza-like illnesses, hospitalizations, and deaths occur.

- *National Syndromic Surveillance Program (NSSP)*: CDC, through state and local collaborations, collects deidentified health information on emergency room, urgent care, and hospital visits, as well as pharmacy and laboratory data. This investment has revolutionized public health surveillance to include this new type of data collection on top of traditional type and methods of data collection. States and local public health departments use the syndromic data to detect and characterize abnormal situations meriting further public health investigation. This strengthens local public health capacity to detect, respond to, and manage, outbreaks and other critical public health events. CDC has negotiated access to the data to enable situational awareness at regional and national levels. The series of three recent hurricanes presents a poignant example that demonstrates the usefulness and flexibility of this asset. Before the hurricanes, CDC and ASPR had begun establishing a mechanism to share National Disaster Medical Assistance Team (DMAT) data during mass gatherings. As the hurricanes hit, CDC and ASPR established data flow mechanisms and rules, and in 2 days put in place a system to receive hourly data from DMATs, resulting in timely information that helped responders target communities at greatest need for public health interventions.
- *Vector-Borne Surveillance*: CDC operates systems that allow for national and state-based monitoring of specific vectors, such as ticks and mosquitoes, which carry diseases and pose risks for outbreaks. These systems monitor laboratory documented cases of disease, allowing for the early detection of outbreaks and helping decisionmakers determine when and how to act in the interest of the public's health. State, territorial, city, and local health departments populate CDC's surveillance systems to inform vector control and management activities.
- *Antibiotic Resistance Surveillance*: Beginning in fiscal year 2016, Congress recognized the large and growing threat of antibiotic resistance and appropriated funding to CDC to detect and respond to resistant pathogens, prevent the spread of resistant infections, and collaborate with partners to encourage innovation for new prevention strategies. CDC has multiple surveillance systems that can detect and track resistant threats across healthcare, food, and the community. One important investment begun in 2016 is CDC's Antibiotic Resistance Laboratory Network (ARLN), which supports nationwide laboratory capacity to rapidly detect antibiotic resistance in healthcare, food, and the community, and inform local responses to

prevent spread and protect people. The ARLN includes seven regional laboratories, the National Tuberculosis Molecular Surveillance Center, and laboratories in 50 states, five cities, and Puerto Rico. The ARLN is vital to detecting new and emerging resistant pathogens, including those that are untreatable, to trigger infection control response measures to prevent spread. The ARLN collects actionable data on threats including the “nightmare bacteria,” carbapenem-resistant Enterobacteriaceae (CRE), *Candida auris*, and *Neisseria gonorrhoeae*; some strains of these pathogens have become resistant to all or nearly all available antibiotics. In addition, samples from the ARLN can be made available to researchers to support innovations in antibiotic and diagnostic development.

- *Global Disease Detection*: CDC’s Global Disease Detection (GDD) Operations Center monitors outbreaks 24/7 across the globe, assesses their potential risk to the United States and communities around the world, and improves global public health surveillance. The GDD Operations Center monitors approximately 30–40 public health threats each day, including outbreaks, disasters, poisonings, and chemical, radiological, or nuclear events. Since 2007, CDC has tracked more than 170 unique diseases globally and identified outbreaks in more than 190 countries. This tracking provides the agency with critical early warning and response capabilities.
- *Global Polio Surveillance*: CDC, as part of the Global Polio Eradication Initiative, supports polio surveillance to track potential cases and circulating viruses and to effectively target polio immunization efforts. The goal of these efforts is polio elimination in every country and eventual worldwide eradication, and we are closer than we have ever been to achieving that monumental accomplishment. In 2017, the Global Polio Eradication Initiative identified just 20 wild poliovirus cases worldwide, down from 350,000 cases in 1988 when the global eradication initiative began. The global polio surveillance system, coupled with the CDC-supported Global Poliovirus Laboratory Network (comprised of 145 laboratories around the world), also detects and assists in the diagnosis of other epidemic prone diseases such as measles, rubella, and yellow fever.

Taken together, these surveillance systems provide an early warning alert, allowing CDC to protect the health of Americans through rapid, evidence-based action.

Providing Public Health Services

State and local public health agencies are the cornerstones of preparedness and response. When states are prepared to respond, communities are better protected and more resilient in the face of threats. CDC has long-established relationships with state and local officials, and coordinates with them effectively and efficiently during public health emergency responses. CDC also collaborates with foreign ministries of health to protect global health security that directly impacts United States health security. Examples of CDC’s critical support of state, local, and foreign health agencies to ensure they are ready to respond to emergencies include:

- 24/7 public health consultation and disease expertise.

- Enabling a quality public health laboratory system while maintaining critical laboratory infrastructure and specimen testing support.
- Managing and delivering medical countermeasures.
- Public health workforce development that complements preparedness-specific provision of guidance, training, and exercises to ensure jurisdictions are ready to detect and respond to an emergency.

In the event of an outbreak, bioterrorist attack, or chemical or radiological release, laboratory capacity is essential to quickly detect, diagnose, and treat those who are impacted. CDC's Laboratory Response Network (LRN) maintains an integrated network of state and local public health, Federal, and international laboratories that can respond to all types of public health threats. The linking of state and local public health laboratories, and veterinary, agriculture, and water-and food-testing laboratories is unprecedented and provides for training, rapid testing, timely notification, and secure messaging of laboratory results. With the LRN, CDC has developed and deployed tests to combat our country's most pressing infectious and non-infectious health issues, from Ebola to Zika to ricin toxin to nerve agents. CDC ensures the Nation is able to respond to influenza pandemics, vector-borne or vaccine-preventable disease outbreaks, other emerging infectious disease threats, and environmental health threats by supporting planning efforts among health departments, hospitals, and emergency responders. CDC tests its pandemic influenza response capabilities with federal, state, and local partners through virtual tabletop and functional exercises. CDC evaluates and improves its response plans based on lessons learned from previous responses and exercises. CDC supports state and local health departments directly during vector-borne and environmental health incidents by developing and evaluating novel repellents and other prevention tools; improving and deploying diagnostic tools and tests; responding to toxic health threats; and providing unique expertise and training regarding radiation.

The existing public health system, its people, networks and resources, form the basis for response to health emergencies. For example, CDC's National Center for Immunization and Respiratory Diseases funds state infrastructure awards, manages vaccine shortages, prevents disease outbreaks and responds early and rapidly should they occur, and stands ready to respond quickly and comprehensively to other urgent emergencies requiring vaccination such as a pandemic or biologic attack. CDC also funds state and local public health agencies through the Epidemiology and Laboratory Capacity for Infectious Diseases cooperative agreement (ELC). This funding allows jurisdictions to strengthen their basic epidemiologic and laboratory capacity to address infectious disease threats. Multiple CDC programs use the ELC platform to protect the public health and safety of the American people by supporting health departments to effectively detect, respond to, prevent, and control a wide range of known and emerging (or reemerging) infectious diseases. These CDC programs and others provide ongoing support to prevent, prepare for, and respond to public health emergencies.

An outbreak that starts in another country can hit our shores in a matter of hours. Strengthening global health security protects Americans' health. New diseases, like MERS and influenza H7N9, can emerge without warning and have the potential to cause widespread infection and fear. CDC works with 31 Global Health Security Agenda partner countries to help them build the core public health capacities necessary for identifying and containing outbreaks before they become epidemics that could affect us all. This work is focused on

strengthening four critical areas: surveillance, laboratory, workforce development, and rapid response capability. In addition, CDC medical and public health officers staff United States Quarantine Stations that are located at 20 ports of entry and landborder crossings where the majority of international travelers arrive. These health officers are the first line of defense to prevent the introduction and spread of infectious diseases.

Conclusion

I want to leave the Committee with three primary points about CDC's role in public health emergency preparedness and response.

- CDC is the common defense of the country against threats to public health,
- CDC's preparedness work is built on a foundation of our broad and deep scientific, medical, and programmatic expertise, and
- CDC's longstanding partnerships with state and local public health authorities are essential to the health security of our country.

Through the three interconnected pillars of science, surveillance, and service, CDC plays a critical role in working to ensure that the United States is ready to respond to public health emergencies. CDC has over 70 years of experience in bringing top scientific expertise to health emergencies and remains a trusted partner in the United States and around the world. CDC stands ready to do its part to protect the health and well-being of the American public and save lives. We cannot necessarily predict the next disaster, but we know that being prepared protects health, saves lives, and prevents economic losses.

Thank you for the opportunity to testify.

Senator BURR. D. Redd, thank you very much.

You won the award for getting the closest to the 5 minutes of all our witnesses today.

[Laughter.]

Senator BURR. The Chair would recognize himself and the Ranking Member, and then Senator Alexander, Senator Casey, and then Members in the order of attendance to today's hearing.

Dr. Bob, my first question is simple. Are we prepared for public health threats we face?

Dr. KADLEC. Sir, I would have to say equivocally for some, but not all.

I think the reality is when this concept of PAHPA first came up in 2005, we had witnessed the terrorist attacks of 9/11. We were anticipating potentially a pandemic and we had just experienced Katrina. But those are all in the rearview mirror in terms of the threats that we are prepared to deal with.

Quite frankly, if you had to look at Nation State threats that we are considering today, or multiple Nation States that are willing to use terrible weapons against, both physical as well as potentially cyber, I think we are not prepared. And quite frankly, those are the things that keep me up at night as well as a pandemic that could emerge again from Asia. As well as the risks that have come up that Dr. Gottlieb identified with synthetic biology tools now that allow nefarious people to do unimaginable things potentially.

So I think we have a long way to go. We have done very well in some areas; again, a compliment to the effort that was done by the Federal Government in support of state and local authorities. And again, for those three hurricanes nearly consecutively, I think that was a great commitment of effort by everyone.

But there is no time to rest on our laurels in that respect.

Senator BURR. The statute is very clear on BARDA's specific and targeted medical countermeasure mission to ensure that BARDA is staying focused in bringing forward the countermeasures we need to protect the American people from a range of chemical, biologic, radiologic, and nuclear threats. All of BARDA's work should be tied to this threat context.

Why is it important that BARDA's mission not be diluted by matters or mandates that would require BARDA work on areas outside of those tied to threats specifically? And how does the comment of 34 innovations out of BARDA relate to a focus on its mission?

Dr. KADLEC. Yes, sir.

Well, I think the key thing here is to remember what the mission was originally. And again, BARDA was only part of the puzzle here.

Project BioShield, which was a 10-year advanced appropriation, was another critical element of that formula of success, which was a guaranteed market to manufacturers should they get across the finish line.

But the key issue that you have raised, sir, is that we cannot boil the ocean. Quite frankly, the BARDA model works. The resources that have been given to BARDA to date have been somewhat limited. We have had, literally in some circumstances, to rob Peter to pay Paul given events that have transpired with Ebola and other events.

We do not have a sustained level of funding necessarily, a line item for pandemic influenza, for example. That would give us great confidence that we would have a sustained, uninterrupted funding stream.

So the answer is arguably, you could do more things, but the answer is you cannot do more things with limited resources. If we focus on the national security mission which, I think, is vital—again, vital to the role of BARDA—then I think we have to stick to our lane and highlight the fact that right now, to use a defense analogy, we are operating with about half an aircraft carrier of resources to basically do this mission. A national security mission to basically protect 320 million people and that is a challenge.

Senator BURR. Dr. Gottlieb, in your experience, what is working well in the agency's review of medical countermeasures? And what challenges have you seen in the medical countermeasure pipeline?

Dr. GOTTLIEB. I think we are doing a much better job now. I look at this over a 15 year period.

I came into the agency shortly after the animal rule was implemented back in 2002. Between my two tours at the agency, I think we are doing a much better job at leaning in with respect to trying to bring some of these technologies forward; trying to look at ways that we can lean forward and develop the animal models that are going to form the basis of some of the product approvals; trying to put out perspective guidance and talk to manufactures and provide more regulatory clarity.

I think there are still challenges around the incentives in this market. Frankly, I think having been on the other side of this in the private sector, the prospect of being able to commercialize something just for stockpiling purposes sometimes is not enough of an incentive to offset the enormous capital costs of some of these endeavors.

I think we are also looking at, we focused on some of the immediate dangers, some of the pathogens we knew and we are developing countermeasures on them. I think we are looking at a future where it is going to be much easier to bioengineer some of these things in ways that we cannot fully anticipate and create very new risks.

Senator BURR. Senator Murray.

Senator MURRAY. Well, thank you very much to all of you.

In the wake of Hurricane Irma, as hospitals were evacuating, the top priority was protecting vulnerable populations including people and individuals with disabilities, and children, and pregnant women.

In every public health emergency, we have to pay unique attention to people with functional needs that put them particularly at risk. That is true for preparedness planning and for emergency response, including, for example, making sure that there is adequate medical countermeasure development and dosing guidance for children and pregnant women.

PAHPA actually acknowledges that there must be specific attention paid to at risk individuals, and we want to build on that last authorization, because I think we can do better.

So I wanted to ask each of you to briefly describe your agency's efforts to meet the needs of all people. And, what more can we do to ensure that when it comes to public health preparedness, we are prepared for everyone?

Dr. Redd, let me just start with you, and if we could, just go down the panel.

Dr. REDD. Thank you for that question.

Let me just highlight a couple of things that we are doing at the CDC.

First of all, our guidance through the Public Health Emergency Preparedness Program requires that states have a plan for persons with functional needs. So that is part of the planning process.

We also work closely with the American Academy of Pediatrics and the American College of Obstetrics and Gynecology, depending on what the emergency is, but work with them to make sure that those needs are being covered.

I would also say in the stockpile that we have made progress in procuring products that are needed to treat children.

For example, there are 100,000 treatment courses of Oseltamivir in suspension form that are intended, or targeted, for children.

Senator MURRAY. What could we do better?

Dr. REDD. I think there is always more work to do.

I think that we need to make sure that these plans are exercised and that we have actually covered all the bases. That they are not just written on paper, but that we actually are able to execute the plans that we have made.

Senator MURRAY. Dr. Gottlieb.

Dr. GOTTLIEB. I would just highlight that PAHPA gave us new authority to put forward, to your point, treatment guidelines that can help guide the applications of some of these therapeutics, particularly with respect to pediatric dosing, which we have used. We have approved 12 drugs under the animal rule; 7 have been approved with pediatric dosing requirements.

I think this is something that we can continue to do better. I think one of the ways that we are going to do that is to have better development of animal models that have better natural histories associated with the pathogens in those animal models that allow us to predict what the therapeutic impact is going to be on a pediatric population.

So, this is some basic research that we need to do to develop those models that are going to, then, allow us to extrapolate into a pediatric population; and other populations, for that matter, other vulnerable populations, to your point, and allow us to have dosing guidelines for those populations.

Senator MURRAY. Is there anything we can do within PAHPA to help improve that?

Dr. GOTTLIEB. I think to Senator Burr's point as well, I think this, as a scientific basis, still needs further development. PAHPA gave the agency resources and we have developed discrete expertise in this area as a result of the legislation.

I think that is a place where we can continue to make more investment.

Senator MURRAY. Okay. Dr. Kadlec.

Dr. KADLEC. Thank you, ma'am, for the question.

I would just like to highlight during the hurricanes, we actually did some very specific things around people with functional disabilities.

I do not know if any of the Members have heard of emPOWER. It is a program that allows us to basically identify, in the CMS data base for Medicare, people who are dependent on durable medical equipment.

Based on requests from states, we can provide actually very specific information where these people live by ZIP Code and by address. In cases like Irma, Florida was able to do a reverse 9-1-1 call to those people at risk well before any evacuation orders went out to the general public to advise them that they should consider leaving before things got worse.

In the cases of Maria, we actually used that data to identify, on the islands St. Thomas and St. Croix, people who were dialysis dependent. And after the storm passed, we were able to basically link up with the urban search and rescue teams, and actually recover dialysis dependent people, and basically evacuate them to safety. So there is that part of it.

One of the limitations currently is that it is only for Medicare data. The State Medicaid data is limited. We can do that if we have access to that and provide the same information. So that is one area that we could probably benefit from working with you all to see how we can have the states work collaboratively to use that information prospectively.

To add to the points that were made by the other gentlemen, clearly BARDA has looked at specific products for pediatric patients, as well as people with immune-compromise, and there are products that are in the stockpile today that are to benefit both of those populations.

One of the areas, and I highlighted it in my testimony, is on the National Disaster healthcare System. One of the specific areas we would like to do is take the learnings or lessons learned from Ebola where we created a national Center of Excellence at Nebraska University for infectious disease and replicate that for other very important trauma-related or disaster-related areas like pediatrics.

We think that that would be a way where not only can you create the necessary, if you will, critical mass of expertise, but also teach through telemedicine and through teleconsultations to provide support during disasters.

The last area I would like to do, and a shout out to our V.A. colleagues, is the V.A. was a very significant contributor to our response to Harvey. HHS responded and took care of 36,000 patients. The V.A. provided care to 21,000 patients, many of those were V.A. beneficiaries, but some of those, many of those were families of V.A. beneficiaries. And then a larger number were actually the general public.

The V.A. has unique capabilities as it relates to geriatric populations, and that is one area that we can probably benefit from in terms of utilizing some of their expertise.

Senator MURRAY. Thank you very much. Senator BURR. Chairman Alexander.

The CHAIRMAN. Thanks, Mr. Chairman.

Dr. Kadlec, Dr. Gottlieb, let us talk about the flu. This is the 100th anniversary of the 1918 influenza pandemic that killed an estimated 50 million people worldwide; 600,000 in the United States.

According to the Centers for Disease Control, year in and year out, between 12,000 and 56,000 Americans die as a result of seasonal flu.

We heard last week in our opioids hearing that opioids kill more Americans than car accidents. And those statistics that I just read would suggest that in a severe year, so could the flu.

Dr. Collins, the head of the National Institutes of Health, has made the prediction before our Committee that if we keep up our investments in biomedical research—which Senator Blunt, and Senator Murray, and the rest of us have been doing pretty well the last 3 years—that we may have a universal flu vaccine, as well as a vaccine for Zika, within the next decade.

Dr. Fauci at NIH has said that the most effective method for protecting Americans against another pandemic influenza is to encourage and invest in the development and stockpiling of influenza vaccines that will broadly protect against the virus.

Well, in Tennessee right now, the hospitals are filling up with people with the flu. So Dr. Kadlec and Dr. Gottlieb, if researchers at NIH, or any partners with them, discover a platform technology that could speed the development of a universal flu vaccine, what would BARDA do to support the advanced research and development of that technology?

Dr. Gottlieb, what is the FDA ready to do to encourage the use of that technology for new and innovative vaccines?

I have 3 minutes.

Dr. KADLEC. Chairman, I will be very brief, then, in the sense that BARDA has an integrated portfolio with NIAID. So once a product gets through Phase 2a clinical trials, it would be transitioned over to BARDA, which would take the advanced development through to fruition. So that part of it is done.

They have the capacity to basically identify manufacturers who could produce that either in eggs, or tissue cell culture, or emerging technologies.

The CHAIRMAN. Dr. Gottlieb.

Dr. GOTTLIEB. Yes. I will just quickly add, we already have, in development, vaccines that might be universal flu vaccines that, presumably, could elicit a T-cell response and could achieve what you are outlining.

We continue to provide advice to clinical developers and manufacturers on the proper pathway for looking at trying to bring those new technologies through.

I would point to one place where the legislative suite that we have adopted to try to address some of these biological threats has been helpful in the development of manufacturing capacity. That could greatly aid in the scope of these new vaccines, particularly cell-based manufacturing, which we have made a lot of investments in, as you know, that could provide the proper platform for the development of these vaccines.

The CHAIRMAN. Dr. Gottlieb, this is a related matter.

We are all concerned about Puerto Rico and the impact of the hurricane there. I think you told me at one point that maybe one-third of the economy of Puerto Rico has to do with medical technology.

Is that right?

Dr. GOTTLIEB. That is about right. It is about 30 percent.

The CHAIRMAN. And many of those facilities, as you described, were destroyed.

Are they rebuilding in Puerto Rico, or are they rebuilding other places, or do you know yet, because that could have a major effect on Puerto Rico's future?

Dr. GOTTLIEB. Right. And we are obviously very concerned about the situation in Puerto Rico for a host of reasons, not the least of which is that the Puerto Rican economy is very dependent upon that skilled manufacturing base.

I am happy to tell you that all of the facilities that we are concerned about—that produce product that we were worried could go into shortages if the facilities continued to remain offline—are now back on the grid.

So the facilities themselves actually did not sustain a lot of damage. It was the power grid and the infrastructure in between the facilities to try to move equipment in and off the island, and that sustained a lot of the damage. The facilities actually were fairly hardened.

But the ones we were worried about are back on the grid. There are still some facilities that are not on the grid, but they have such redundant electric generation capacity that we do not really have concerns about the product supply coming out of facilities.

So the situation now looks a lot better than it did 4 months ago. The CHAIRMAN. Mr. Chairman, I think my time is about up, and

I will give the rest of it back. Senator BURR. Senator Casey.

Senator CASEY. Thank you, Mr. Chairman.

I wanted to start with the reference that I made earlier to the train derailment in Philadelphia as an example of good preparation. Part of that has its origin in the fact that it happened in an urban area where you have not just the resources, but you have hospitals and the healthcare infrastructure, which is close by way of distance, as well as by way of coordination.

I represent a state that has 48 rural counties out of a total of 67 counties. So we have a lot of small towns and rural areas where you do not have the institutional capacity necessarily. In the event of an emergency, that could be exacerbated by distance and other challenges, so you have this type of gap or potential gap, where some communities may be particularly vulnerable.

I would start with Dr. Kadlec and then go to Dr. Redd.

In terms of the Hospital Preparedness Program, the so called HPP, as well as PHEP, how do those programs attempt to close the gap in preparedness among states and regions?

Dr. KADLEC. Thank you, sir, for the question.

I think the point is that the way we are structuring it right now, we are trying to actually build healthcare or promote healthcare coalitions which are collections of hospitals, as well as other entities like emergency medical services. So you can build a regional.

That is why we would like to expand that effort to basically do it so not only would it cover specific regions within a state, but statewide and across states so that you can develop a much stronger backbone, if you will, to do this.

I think the idea of basically building out the National Academy of Sciences' study on trauma systems is worthy of reviewing because it highlights the important role that has a foundational capability for the country. Not only for day to day routine activities, but for these extraordinary events, train derailments that happen not only in Pennsylvania, but in the State of Washington, as an example, become a central piece of that.

My interest in this is seeing how we can leverage all those pieces together with some of the Federal assets the V.A. identified. Madigan Army Medical Center was a critical first responder in the train derailment in Washington State.

The thing is, how do we basically build, forge a public-private partnership for those purposes that can basically strengthen it? So not only do you have the transport mechanisms with emergency medical services, but also telemedicine and teleconsultation that would be available from this specialty services, these Level I trauma service hospitals or Level I expert hospitals like Nebraska to basically deal with a range of topical areas.

Senator CASEY. Doctor, before moving to Dr. Redd, I just want to inject another question.

This is an authorizing Committee and a reauthorization process. But I want to specifically ask, in light of the question I posed, are there additional authorities you need or additional dollars?

Dr. KADLEC. Sir, I would suggest both. We have a \$3.3 trillion healthcare system for which, right now, we invest approximately \$250 million annually for preparedness and resilience. I think it just highlights the fact that it is kind of a drop in the bucket.

I do not think it is necessarily the role of the Federal Government to pay for the whole bill, but certainly, we need to look at a variety of incentives, whether that is through CMS reimbursements, whether that is through insurance programs, or tax benefits that would incentivize hospitals to do it.

Our conversations with some of the outside partners, we held kind of a listening session with 35 stakeholders last week, including hospital associations. They are all willing and we have the hospitals volunteering to help. I think they are just looking for a means to do this in a way that is mutually beneficial.

Senator CASEY. Thank you, doctor. Dr. Redd, I only left you 45 seconds. Dr. REDD. I will be brief.

We actually met with selected state health officials last spring to ask this exact question that you asked. Are there things that we should be doing differently to support rural health departments?

The conclusion was, it was a little bit surprising to me that the capabilities needed for rural districts and urban are largely the same: detection capability, communications, incident command or the structure to run responses. But there are additional, as you mentioned, there are additional layers of challenge with transport and access to medical care.

I think that this is an issue a little bit beyond emergency response and I think the idea of telemedicine as a tool is a great idea. But it is essentially a question of, how do we make sure that those communities have access to medical care during and not during emergencies?

Senator CASEY. Thank you, Mr. Chairman. Senator BURR. Senator Isakson.

Senator ISAKSON. Thank you, Senator Burr.

Thank you for your work on pandemics and on BARDA for a long period of time. It is very valuable. The Committee has worked on it a long time.

I appreciate Chairman Alexander and Senator Murray, and the work that they have done.

Thanks, Dr. Kadlec, for calling out the V.A.

As Chairman of the Veterans Committee in the Senate, I have learned a lot of things about our delivery system and capabilities in terms of V.A. healthcare, which is the second largest employer in the United State Government. A lot of people do not realize that, but that

is how big and pervasive the V.A. is, and they provide significant healthcare to seniors by virtue of their delivery system.

Your callout for them and what they did in Houston, Houston has appreciated it.

Also, I would say that most of the research dollars that are invested by the U.S. Government in control groups are through the V.A. because you have a control group of patients where you can do a good research sample. Our veterans, and our Veterans Administration, provide a great service in terms of that, which brings me to Admiral Redd.

You have your emergency preparedness grant that you give to the local governments. When we had the incident we had happen in Hawaii last week, where we had a false alarm on a missile attack, which was rather unsettling to the people of Hawaii and, quite frankly, it was unsettling to me. That is an emergency grant challenge you want to make sure you do not ever have with a pandemic where you get the wrong information going out from a designated agency at the wrong time.

Do we concentrate a lot on that to protect ourselves from bad information getting out on pandemics or on diseases?

Dr. REDD. I think that really gets to one of the core requirements that we have, which is to be sure that the information we are providing is as valid as it can be. And if we are not certain, but we believe people need to know, we make sure that those caveats are expressed.

It really gets to some of the basic principles of risk communication to tell people what we know, what we do not know, and what we are doing to find out those things that we do not know.

Senator ISAKSON. Dr. Gottlieb, I appreciate your mention of Priority Review Vouchers.

Senator Casey and I worked on PRV's for rare diseases that affect children and successfully passed legislation. I think the first drug has been approved now and put on PRV. It was issued by the department, and we appreciate that.

Your use of that to expand the use of PRV's to encourage the development of drugs that are either very costly to develop or hard to develop is very important.

How do you intend to use that to expand the development in terms of new pharmaceuticals?

Dr. GOTTLIEB. Well, as you know, the PRV program provides an additional incentive for manufacturers to try to develop products for these purposes. And so, I think it is one of the tools that Congress contemplated to try to address some of the challenges that we have already talked about that I mentioned, which is that sometimes this is not a typical market where you have the usual market-based incentives to try to make the capital investments to develop these products.

There is work going on to look at what impact the PRV's have had. We have implemented the program. We have seen sponsors come forward and be awarded these PRV's and sell them in the secondary market as a way to try to recoup some of the cost of the investment.

Senator ISAKSON. On that same subject, I have done a lot of work on a disease called Batten's, which is an incurable disease of young people. I had a personal situation that piqued my interest in my district when I was in the House, and I have remained interested in that.

It is a very difficult disease for which there is no cure, but with the gene therapy development and the delivery system of pharmaceuticals to specific parts of the body, and the brain in particular, there is hope and promise for that.

Do you issue guidance letters to research hospitals or research facilities to give them guidance on how they can test or develop to work on a breakthrough drug for a disease like Batten's?

Dr. GOTTLIEB. Senator, I think one of the areas of the most promise right now that we are looking on when we look across our portfolio is what is going on, as I said, with biologics with respect to cell based therapies, machine based therapies where we have the ability to cure inherited disorders, devastating inherited disorders that were not treatable just a short time ago.

We are going to be putting out this starting probably this spring, maybe a little earlier, a suite of products with specific guidance on how sponsors can address certain disorders with gene therapy to try to provide as much regulatory clarity as possible.

We are going to look at some of the more common disorders first, but we are going to try to work through some of these rarer diseases to make sure that product developers have a lot of clarity around what the pathway forward would be.

Senator ISAKSON. I commend you on the leadership you have shown in that effort already and plan to support you in any way we can to help you do that in the future.

Thank you very much. Thanks to all of you for testifying. Senator BURR. Senator Smith.

Senator SMITH. Thank you very much, Senator Burr, and Chair Alexander, and Senator Murray.

I am so pleased to be able to serve on this Committee. Thank you very much.

I would like to come back to something that Senator Murray and, I think, several others have talked about, which is the importance of a connection and support to local public health organizations.

In the past year in Minnesota, we have dealt with three infectious disease outbreaks: measles, multidrug resistant tuberculosis, and also syphilis. And all of these outbreaks have required a really immediate response, as well as a sustained response, as we have gone forward.

Minnesota has traditionally, as I am sure you know, invested heavily in emergency preparedness and dealing with infectious diseases, probably because of our history in agriculture more than anything.

But in these particular situations, the financial resources that we had were not enough and so, we turned to the CDC for support. And, of course, no fault of yours, there were no resources there.

What we did is we moved forward with the state legislature to pass an emergency public health response account so that we could respond quickly because speed is of the essence when you are dealing with these kinds of outbreaks.

My question is in what ways do you think that an emergency response fund would strengthen our federal and state efforts during an outbreak or after a disaster?

Maybe if you could just talk a little bit about that, that would be helpful.

Dr. REDD. Thank you very much.

I think that resources are critical in responding to an emergency. We had lengthy delays, both in the Ebola response and in the Zika response before funding became available, and I think that hindered what we were able to accomplish.

There has been discussion both in Congress and in the Administration about how to do that, and I think that those discussions will continue. But I think something along those lines would be quite helpful.

Let me mention one thing that we have done specifically once funds are available to make sure that they are used more quickly. We had a Notice of Funding Opportunity that we opened to our grantees through the Public Health Emergency Preparedness program and allowed them to apply for funds. There were no funds in this award, but we have an approved, but unfunded, grant mechanism so that we do not get delayed at the Federal level once funding is appropriated.

Senator SMITH. Thank you.

Dr. KADLEC. Senator Smith, if I could just add.

There exits already in authorizing language for a fund for HHS that has \$57,000 in it. Obviously, it is not an authorization problem.

But I just want to highlight the fact that, yes, there is a fund that is needed. It should be a fund that necessarily is managed by the Secretary and based on a public health emergency. There can be, if you will, distribution of funds from that, and that it can be used across HHS, or to fund states and locals in a way that would be rapid.

Obviously, there is going to be a need for, it would be like the medical equivalent of the disaster relief fund, I think. But I think there would be, obviously, a requirement to notify Congress in those sorts of situations on a basis of reporting back on some occasions to make sure the funds are being spent appropriately.

Senator SMITH. Right. Thank you.

Essentially, we need to make sure we have good accountability. Dr. KADLEC. Right.

Senator SMITH. That the funds are being spent the way they are supposed to be spent—

Dr. KADLEC. Yes, ma'am.

Senator SMITH —which I would completely agree with.

I realize that this is an authorizing question and not an appropriating discussion here, but Dr. Kadlec, if such a fund were to be made available, what would you advise in terms of the level of funding that would be necessary to have this actually be workable? Dr. KADLEC. Well, ma'am, I would have to back in a firm number, but I think what you probably looked at is what happened with Ebola or the original pandemic influenza appropriations, which are on the order of \$2.5 to \$3.5 billion.

Again, what you need to hedge is the opportunity for Congress to weigh in fully, and again, on the basis of time. So obviously, there are a lot of factors to be considered in there, but there is a rich, historical record that could probably be drawn upon to identify an appropriate level that would get us through the initial crisis to the point where Congress can basically perform its fiduciary responsibilities.

Senator SMITH. Right. Thank you very much.

Senator Burr, I was struck by what you said about how we need to stick to our knitting on this Committee and not expand too much. And also how important it is to think about the processes that we have in place with this authorized legislation, to make sure that it works well.

I appreciate your comments. I think it gives us some good food for thought as we consider how we can respond as quickly as possible when there is an emergency.

Thank you.

Senator BURR. We, again, welcome you to the Committee. Senator Young.

Senator YOUNG. Well, thank you, Chairman.

The World Organization for Animal Health estimates that roughly 60 percent of known human diseases are transmitted from animals to people. They are of so called zoonotic origin.

Every year, an average of five human diseases appear such as Ebola, HIV, and new strains of influenza; three of which are zoonotic.

In my home State of Indiana, we suffered considerable losses in the widespread bird flu outbreak, one that led to the destruction of 400,000 turkeys. And this followed in 2015 and the outbreak that led to the loss of 48 million poultry.

Dr. Kadlec, what are we doing now to prevent the spread and transmission of diseases from animals to human beings?

Dr. KADLEC. Well, sir, I have to say that, quite frankly, we need to do more.

The one health concept that you are outlining is an important one. Influenza is not the only disease that is of zoonotic importance that has pandemic potential; SARS and MERS are examples of others.

But I think I need to really defer to Admiral Redd to talk about the role of the CDC here and their role of surveillance because, quite frankly, they are on the cutting edge to ensure that you can recognize those events rapidly as they have in Iowa, I think.

Senator YOUNG. Thank you. Admiral.

Dr. REDD. Thank you, Dr. Kadlec and Senator Young.

We are working very closely with USDA on this issue and particularly on influenza. We were really joined at the hip in the response to this importation of these avian influenza viruses.

Our role was to make sure that we understood the biology and that if any human infections occurred, that those were rapidly detected and treated, and to protect workers in the process of the culling that was going on.

Senator YOUNG. You, no doubt, do the best you can with the resources and authorities you have.

No. 1, how are we doing with respect to tracking and then the responding to these situations and preparing for the next one?

Then secondarily, speak to any additional authorities or resources you might need to optimize your efforts.

Dr. REDD. I think that given the strategy that we have, which is a reactive one, I think we are doing well at detecting and containing importations.

Senator YOUNG. That predicate caught my attention. Dr. REDD. Yes.

Senator YOUNG. Given that our strategy is a reactive one. Dr. REDD. Right.

I think that the ability to prevent importation of influenza viruses that could be transmitted by migratory waterfowl, for example.

Senator YOUNG. Yes, sir.

Dr. REDD. It is very challenging.

I think there is a lot being done on the animal health side. I think that it is a challenge and the basic strategy is to identify and limit, to the extent possible, to one flock or as small an area as possible. And through that process to prevent human infection should the virus have the capability to be transmitted or to be infectious to humans.

Dr. GOTTLIEB. If I may, just for 15 seconds.

I would also talk about the importance of thinking about animal drugs in our approach. And Cures, as you know, extended the EOA authority to animal drugs. We might also contemplate trying to think about how we create incentives for the development of animal drugs to target some of these threats including maybe a break through therapy designation for

animal drugs or other kinds of creative policy approaches to make sure that that is a part of our approach as well.

Senator YOUNG. Well, thank you.

I look forward to working with each of you. I will probably have some follow-up questions I will submit in writing, and hopefully we can improve our current systems for dealing with these matters.

Senator YOUNG. Dr. Gottlieb, you just once again mentioned incentives in the animal context, but I would like to pivot to our antibacterial resistance threats.

Every year, at least 2 million people in the U.S. acquire serious bacterial infections that are resistant to one or more types of antibacterial drugs.

However, as I understand it, there are very few companies that are developing new antibiotics, and those that are focused on the most serious bacterial threats are even fewer.

Is additional action needed to immediately incentivize the development of drugs to combat this growing global problem? And if so, what might new incentives look like? And what might we do as Members of Congress to provide those incentives?

Dr. GOTTLIEB. Senator, thank you for the question.

As you know, Cures created a number of new vehicles, and some incentives, for development in this space. We are encouraged by the early interest we are seeing in those pathways, things like the LPAD pathway. I think we are going to have more information soon on how well they are working.

I mean, we can always contemplate additional policy steps, and I would be happy to talk to your office and work with you on that. I think that this is an area, to your point, that we need to think about what more we can be doing.

But Congress has done, taken some steps recently that we are very encouraged by. We are seeing a lot of good, early interest in them.

Senator YOUNG. Thank you. Senator BURR. Senator Kaine.

Senator Kaine. Thank you, Mr. Chair, and thanks to the witnesses.

I have great confidence in this Committee's ability to work on this PAHPA reauthorization in a bipartisan way. I have two observations and a concern. So an observation is this and some of you have alluded to it, and Senator Isakson's questions alluded to it. One of the tasks of emergency preparedness is to prepare for attack, and you have talked about chemical and biological. Senator Isakson talked about the incident in Hawaii this weekend.

I just want to say for the record and for the public. The prospect of nuclear war is being discussed with a lot of frequency in this building to a degree that I have not seen in the time I have been in the Senate.

I am on the Armed Services and Foreign Relations Committees. We have had a series of hearings, even open, where there has been discussion about the prospect of land war on the Korean peninsula. We had an Armed Services hearing recently where a witness volunteered in public—and it was sort of a non sequitur, why he would bring it up as a Member of the Administration—about what the likely cost of reconstructing Kansas City would be after a nuclear attack.

I noticed an article in "The New York Times" a few days ago. "The C.D.C. Wants to Get People Prepared for Nuclear War." That was supposed to happen yesterday.

"On January 16, the Centers for Disease Control and Prevention will present a workshop titled 'Public Health Response to a Nuclear Detonation,' for doctors, Government officials,

emergency responders, and others whom, if they survive, would be responsible for overseeing the emergency response to a nuclear attack.”

Quote, “‘While nuclear detention is unlikely,’ the C.D.C. stated on its Website, ‘It would have devastating results and there would be limited time to take critical protection steps. Despite the fear surrounding such an event, planning and preparation can lessen deaths and illness.’

Quote, “‘Join us for this session of Grand Rounds to learn what public health programs have done on a Federal, state, and local level to prepare for a nuclear detonation. Learn how planning and preparation efforts for a nuclear detonation are similar and different from other emergency response planning efforts.’ ‘That is off the CDC Website.

The article goes on to say, “The agenda for the day includes, ‘Preparing for the Unthinkable,’ to ‘Roadmap to Radiation Preparedness,’ and, ‘Using Data and Decision Aids to Drive Response Efforts.’

I understand the CDC rescheduled that, canceled it from yesterday, and had a roundtable on the flu instead, but this is a realistic discussion about these prospects. And then add to it the “Dr. Strangelove” like incident over the weekend where a state sent out a mass e-mail telling people there was a ballistic missile incoming to Hawaii, which occasioned 38 minutes of panic.

Then on Tuesday, the Japanese state broadcaster, NHK, put out a warning that North Korea had fired a nuclear missile and urged Japanese citizens to take cover. That was retracted within a very few minutes.

There is a lot of discussion, some very intentional and some frightening, about the prospect of nuclear war that is happening, and this is in the provenance of your agencies.

I just want to put that on the record that that is sort of a normal area for discussion these days. I find it incredibly frightening and the normality of it I find incredibly frightening.

The second observation I want to make is this. This is a discussion about national security. We are involved in a budget debate right now. Right now, the spending bill ends January 19 and one of the points of argument is whether we might fund defense accounts over the budget caps of nondefense accounts.

You are about national security. You are about national defense and all of your agencies are funded through the nondefense accounts of the Federal budget.

Any suggestion that we would increase defense budgeting, but hold the line and put nondefense agencies subject to their caps, would not really fund the national security priorities that you are here about, and that is something we have got to grapple with.

Here is my question.

I am very worried about this Hawaii incident because in a time of heightened tension, we know from history that wars often start accidentally. There is a miscommunication and a misunderstanding; there is an overreaction. That is how World War I started. That is how most wars start.

I know there is going to be a hearing later in the week, I think, on the House Armed Services Committee about this. I am sure that there is an investigation at the state level. But part of the responsibility—and Dr. Kadlec, I guess this is mostly directed to you—part of the responsibility in the emergency preparedness and response side is accurate communication. As a former mayor and Governor, that depends heavily upon communication between Federal, state, and local officials.

As you approach this thought of thinking about reauthorization in this climate where things can sometimes be pretty tense, how do you look at that state, local, and Federal coordination effort, especially as it deals with the communication of accurate information, and knocking down inaccurate information?

As quickly as you can.

Dr. KADLEC. Well, sir, we take it very seriously, No. 1.

No. 2 is the experience we had with the hurricanes, particularly Hurricane Maria, I think, highlighted some of the challenges. In my testimony, I identified some of the incident command issues that we have to address, which really is not only information out, but information in.

I think the issues that we need to work with—not only with our CDC brethren, but with state and local authorities, as well with FEMA; I met with them just as of yesterday—talking about, how do we integrate our efforts closer so that we have better information exchange on these kinds of issues? Whether they are hurricanes, pandemics, or whatever it is that, quite frankly, you need to kind of think through, learn through not only experience, as we did with the hurricanes, but exercises, as we did.

Sir, just to highlight one thing, since I have been around the block on these sets of issues. Going back to 2000, it has been a routine practice in the U.S. Government, the Federal Government at least, to exercise the idea of a nuclear detonation. Most concerning then was terrorism as a matter of an improvised nuclear device.

It is not necessarily new. Obviously, the context is different.

But I think the point here, though, to your issue is it does require a closer lash up with our Federal partners on these issues to make sure that we have good cross lateral, horizontal flow of information, as well as with our state and local folks.

We are investigating with FEMA just as another example of how we can basically work together in bed both our health and disaster people in state and local state EOC's to, again, work more seamlessly with our state colleagues.

We are looking at all kinds of options right now to that effect. Senator KAINE. I appreciate it.

Mr. Chair, thank you for letting me go over.

I hope you will follow the investigation of the Hawaii incident for your own purposes because for purposes of having good information and that coordination, I suspect there will be some lessons that will come out of that that would be relevant to other circumstances as well.

Thank you, Mr. Chair.

Senator BURR. Thank you, Senator Kaine. Senator Collins.

Senator COLLINS. Thank you, Mr. Chairman.

I want to applaud you for your leadership in this area.

More than a decade ago, we established a Port Security Program that led to radiation portal monitors being installed at our major ports so that they could screen incoming and outgoing cargo, trucks, and individuals for radiological material.

I contrast that port security effort with what I perceive to be a real vulnerability in our ability to detect and effectively and quickly respond to an attack using biological or chemical agents.

Dr. Kadlec and Dr. Redd, I would like you both to address the level of preparedness that we have to respond and detect, first of all to detect, a biological or chemical attack and to respond to it. I would like specifically to know whether cities

have used some of the Federal funds that the Admiral referred to, to install sensors that would be able to detect these agents.

I would also like you both to comment on the preparedness of our hospitals to cope with the victims of a biological or a chemical attack.

I remember being in Israel many years ago and being so impressed with their preparation and their ability to convert their hospitals to respond to that kind of attack.

Dr. Kadlec, why do we not start with you and then Admiral Redd?

Dr. KADLEC. Thank you, Senator Collins. I think one of the issues, and again, I have some insights on this historically.

But currently, the biologic program run by the Department of Homeland Security provides area protection for cities. So I think there is a real desire.

I have met with the new WMD, I do not know, directorate, Assistant Secretary over at DHS about improvements we can make to our chemical and biological attack kind of detection.

Quite frankly, our capabilities are fairly still limited and primitive, quite frankly. And I think there is a sincere desire on the part of DHS and HHS between ourselves to basically do improvement to do that.

To your second issue, how well prepared we are. Certainly, we have a Strategic National Stockpile that can address many, but not all, of these threat agents. So there is work to do there in terms of some of the development and procurement we need to do on those issues.

But one of the critical areas that collectively the CDC and our office are considering is really on the last mile of distribution.

As mentioned by Senator Murray, we can move Strategic National Stockpile resources anywhere in the country within 12 hours. The question is from that point forward getting it into the hands and into the mouths of every American person who is at risk is a significant challenge that, I think, collectively, we need to work on.

But now, I will defer to Admiral Redd for his comments.

Dr. REDD. Thank you. I think this is a really important question. If we are attacked in this way, the effectiveness of our response will depend on the speed and the scale with which we respond.

I think that the way that a biological attack would manifest itself would probably be different than a chemical attack. A chemical attack would primarily require a local, a near-instantaneous local response.

The CDC's Strategic National Stockpile has deployed antidotes for nerve agents. Over 1,000 different locations have pallets of these antidotes that are available to supplement the treatment that would be available immediately.

We also have and getting ever better capability to determine exactly which toxin has been used. So there is a laboratory element that the CDC is also responsible for.

On the biological side, we have made great strides with the laboratory response network. Every state has at least one laboratory that is able to use advanced techniques to diagnose these infections. There are a total of 150 laboratories around the world, including laboratories that can test food, can test water, and environmental samples from animals.

So looking to the future, the technology of whole genome sequencing is something that we need to continue to push out that would allow very rapid——

We talked about faster and more accurate. This is actually more information than we can get from current technologies; things like resistance to antibiotics or relationships of certain organisms to other, “where did it come from?” kinds of questions.

Senator COLLINS. Thank you.

Dr. KADLEC. Ma’am, can I just add one thing? Senator COLLINS. Yes.

Dr. KADLEC. To your question about how our hospitals would do. Senator COLLINS. Yes.

Dr. KADLEC. I think it was noted by the Chairman that even a bad flu seasons, as the current one we have, is overwhelming our hospital system.

Senator COLLINS. Exactly. That is one reason that I asked the question.

Thank you.

The Chairman [presiding]. Thanks, Senator Collins.

Senator Jones, welcome. We are glad to have you a part of this Committee. I acknowledged your new membership a little earlier, but we are glad to have you here. This is a Committee that has many different points of view, but works well together. So this is another subject that we intend to have some bipartisan success on.

Senator JONES. Thank you.

The CHAIRMAN. Senator Warren.

Senator WARREN. Thank you, Mr. Chairman.

So we are here today to talk about PAHPA, the framework for our response to all sorts of emergencies: natural disasters, accidents with hazardous materials, terrorist attacks, pandemics, you name it.

I returned, just a few days ago, from a trip to Puerto Rico and I know some of my colleagues have also been to Puerto Rico recently.

During my trip, it was clear that nearly 4 months after the storm, the crisis in Puerto Rico is a daily reality for tens of thousands, hundreds of thousands of people.

Dr. Kadlec, you are the top official in charge of preparedness and response at HHS. What is the biggest thing you have learned from the situation in Puerto Rico and the U.S. Virgin Islands about how we need to strengthen our preparedness and response capabilities?

Dr. KADLEC. Well, thank you, ma’am.

I think there are a couple of levels to go here.

One is improving the resilience of our innate hospital healthcare structure. That is one area.

The other thing is really the resilience of our public health system, which is a separate piece, but a related piece.

In Puerto Rico in particular there were, in the initial stages— after that terrible devastation that literally devastated the whole island and every life was touched—it was very difficult for the local public health and medical infrastructure.

There are some incredible heroic stories of doctors, nurses, laboratorians who basically responded, public health officials, who left their families, left their houses in disarray and basically went to respond to help their neighbors and their communities. But I think that is one piece of this that needs to be addressed, what happens before the storm.

The second piece is, how quickly can we move in? We had deployed teams to Puerto Rico in advance of both Irma and Maria to be available once the storm passed, both storms passed, to basically respond quickly. But even so, with the level of devastation, that was a huge piece of it. And a huge piece of it was the lingering devastation, not only the loss of

communications and electricity, but also the damage to the ports and the airfields that limited some of the movement.

So I think one of the lessons learned was you want to go in aggressively before the storm, if you can. We literally put peoples' lives at risk from our response teams, including people from Massachusetts, Massachusetts One, that responded to all three storms.

Senator WARREN. Yes.

Dr. KADLEC. They are great people and, again, representative of your constituents from other states around the country that responded.

But also, there is a piece of this that we have to somewhat remove some of the dependencies in the responses. Seeing how we can move quicker and faster, if that is possible. A lot of it was dependent on being able to transport through air or barge, again, responding to an island is a tough one.

Senator WARREN. So I appreciate this and I am glad we are trying to think about what we need to do and what we need to do better, and to acknowledge heroic efforts, but we need a better structure here.

But to apply these lessons, we also need good data. We need to know not just what we got right or what we got wrong, but when we got it right, when we got it wrong, by how much, and what kind of difference it would make on the ground.

One of the things that struck me during my trip last week was how sketchy the data are. For example, I met with the Federal and Puerto Rican officials at FEMA's field office and they said, "No more issues with potable water." No waterborne diseases, all the water is drinkable. And I asked this specifically. Turn on the taps. You hold a glass under it. The water will be drinkable, is drinkable, everywhere on the island. It sounds great.

Not so much though.

I met with the Massachusetts State Police volunteers who told me that they had observed raw sewage in the water. At the public health center that I visited in Loiza, they said they still do not have potable water, no drinkable water for their patients. They said they serve 100,000 people and that none of them have drinkable water.

We heard the same kind of contradictions when it came to statements about how many people lacked power.

Dr. Kadlec, I get that public health emergencies are really challenging circumstances, and it is hard to get good data. But how does HHS and other agencies collect data in a way that is reliable so that you can deploy your resources effectively, hold yourselves accountable to get the job done that needs to be done?

Dr. KADLEC. Well, ma'am, we learned a lot from the experience in Puerto Rico and we are trying to rectify that.

Because of the loss of communications, cell towers, and the like, the ability to get information either from local authorities or local hospitals or clinics was practically nil.

We literally went to the point, at one time, to basically use runners from the National Guard who would have satellite phones to basically go to hospitals and clinics to report information out.

But that is a major consideration and lesson that we are still learning that we have to address because it is a major shortfall. Because if you were to add, again, a terrible event like this, a terrible earthquake or a nuclear or radiological event, you could imagine that the circumstances would be even more challenging.

But that is an area of great, intense concern, quite frankly, and work that we have to do.

Senator WARREN. I am very concerned about this and I do not have time. I am out of time now, so I cannot ask Rear Admiral Redd and Dr. Gottlieb about their work in Puerto Rico.

But Senator Cassidy and I sent a letter to Chairman Alexander signed by seven other Members of this Committee asking for a hearing on the recovery efforts in Puerto Rico and the U.S. Virgin Islands, and I hope we will be able to hold that hearing.

Puerto Rico might not be on the front pages anymore, but it is a humanitarian crisis and we have a moral, and a constitutional, responsibility to exercise oversight responsibilities here. Thank you.

Thank you, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Warren. Senator Cassidy.

Senator CASSIDY. Well, thank you.

Dr. Kadlec, I am going to put you on the payroll, man. Earlier, you were responding to Senator Smith regarding a possible bill. We have that bill.

The Public Health Emergency Fund, actually stimulated by conversations with Dr. Frieden. He said that in the Ebola crisis, “There were ten different authorizations that had to be signed off on,” before he could get somebody to travel immediately to Africa. Kind of crazy.

And, “I kept on contrasting the authorization process we were going through, which was cumbersome and slow with that before and after Katrina.” Before Katrina, FEMA had to come to get the initial dollars. After Katrina, Congress recognized that is not the best way, so there is a pot of money that can immediately be accessed. And if it goes over that, then they come back and get another authorization.

Senator Schatz and I have put together a bill that, one, waives these contracting requirements for that immediate period so you can actually deploy people.

Second, based upon—and Dr. Kadlec this is where you nailed it—the previous 14 years of public health emergencies, we take the average of that expenditure and we make those dollars available upfront to be immediately drawn down.

Still accountability; GAO is going to do a report and make sure that the CDC has not used it to go to Hawaii for a conference as opposed to Africa to fight Ebola. No offense, Dr. Redd. But still, the point being that we would have the accountability built in, but we think it is a good bill.

Now, let me move onto something different.

Dr. Redd, I was struck speaking to people after Zika hit that in retrospect—and of course, everything in retrospect, if I could do things in retrospect I would be a millionaire on the stock market—but in retrospect, you could have predicted what was going to happen because supposedly Brazil was flying in folks from the South Pacific to work on their Olympic stadiums that Zika had been breaking out in the South Pacific where these workers were coming from. Brazil is like a Petri dish for Zika, and you could have predicted it.

Now, of course, it is retrospective. But the thought occurs to me with Big Data, we can actually put in travel patterns. We can put in areas of receptivity. We can put in where there are outbreaks and make some, at least, first blush guess as to where the next epidemic is going to be.

Is that just me, “would that not be great,” sort of thing or is this something practical? And if it is practical, is the CDC doing it?

Dr. REDD. I agree with your overall statement.

I think another way of looking at this is that the pathway that Zika followed was very similar to Chikungunya just a few years before where it existed in the Pacific and then caused big outbreaks in Brazil and South America.

Another point that is the same is when we had outbreaks in the Caribbean, we knew locations of lots of travel to the U.S. and where the vector was, the *Aedes aegypti* mosquito lived. It is the same place that we have seen small dengue outbreaks in the past. Senator CASSIDY. So, can we use this predictively? Because if we could use it predictively, if we could see, “Well, Brazilians are going to be having this problem. Let us go down there and encourage them to spray for mosquitoes,” et cetera. Dr. REDD. I think it is hard to do that.

I think that the vector is very resilient and there were some questions——

Senator CASSIDY. Now, I was just giving the example of spraying the mosquitoes as a concrete action. But what I am asking about is not the vector of resilience.

Can we use Big Data just to look at travel patterns where there is an outbreak and guess where there might be a spread of such an outbreak?

Dr. REDD. I think we can. I think the challenge is what do you do with that information. And is there a way to use that, for example, to have prevented the Zika outbreak in Miami-Dade County?

I think that the things that you do——

Senator CASSIDY. So you were ahead of us. What you use the information is different than if you can actually acquire the information.

If it is practical and right, if you will, to acquire the information, are we putting such systems in place?

Dr. REDD. Well, just to take the Zika example, there was a lot of communication with Texas and Florida, Louisiana, the Gulf Coast areas that have the *Aedes aegypti* mosquito recognizing that——

Senator CASSIDY. Okay. You are still after me because that is after it hit Brazil and after we knew that there was going to be travel from Brazil up.

I am actually trying to go proactively before that in that we could see the Brazilians were bringing in lots of workers from the South Pacific and therefore, it was predictable that whatever was breaking out there was going to breakout here.

Now, that is taking the battle to the enemy, if you will. Are we doing that?

Do we have a worldwide kind of map—and I have seen such a map of hotspots of infectious diseases—overlaid with travel patterns to guess whether or not? And I understand the CDC has worldwide outposts.

So again, I am asking something closer to the point—— Dr. REDD. Sure.

Senator CASSIDY ——than whether it gets to Texas.

Dr. REDD. I think the quality of information is variable. I do not think we have——

For example, I think the information we have about influenza is much better than we have about all the vector-borne, all the mosquito-borne diseases that are out there where we know what viruses are circulating in China because of the known importance of influenza and the risk it poses for a global pandemic.

Senator CASSIDY. Now, I have seen maps—and I am overtime, and I will stop after this—but I have seen maps put out by the CDC and the World Health in which it shows, “Oh, yes. Here is this and there is that.” And it is a hotspot of a particular virus.

Can that not be, again, overlaid with travel patterns?

Dr. REDD. Well, there are parts of the world that some of the discussion earlier about the number of zoonotic diseases that are detected that cause infections in humans, there are certain parts of the world that are more prone to those emergences.

I think, again, your question is, how do we use that information? We certainly do have travel maps of where people travel to and from. We have information about where various diseases occur at variable degrees of granularity. I think those two things do go together.

I think how we would use that to take a preemptive action is really, I think that is the question that you are getting at.

Senator CASSIDY. Okay. I yield back. The CHAIRMAN. Senator Murphy.

Senator MURPHY. Thank you very much, Mr. Chairman.

This is incredibly informative. Thank you to all of the witnesses. I want to raise two concerns that I have emanating from conversations I have had with companies in Connecticut that operate in the pandemic response field.

The first is regarding response to an influenza outbreak and this is for either Dr. Kadlec, I think, or Dr. Redd.

Dr. Kadlec, in your testimony, you write that we have sufficient domestic vaccine manufacturing capacity to produce a bulk vaccine for every American within 6 months.

But I want to ask either of you about the question of vaccine delivery. This comes from conversations with a manufacturer in Connecticut, BD, which is one of the bigger syringe manufacturers.

My understanding is that if you needed to get a vaccine to everybody, you would need about 600 million drug delivery devices. Now, BD is one of the biggest manufacturers, but it would take them 6 years to do 600 million units.

What are your thoughts on preparation to make sure that we not only have the right amount of vaccine, but the right amount of vaccine delivery devices?

Dr. KADLEC. Well, thank you, sir.

That is one of the issues, and then problems, that has to be addressed, quite frankly, and I have my Director from BARDA, if he wants to make a comment. He is welcome to at this point.

But I think part of the strategy we are looking at also is, how can we innovate and either have better delivery devices? Or specifically, can we make better vaccines that only require one dose? Remember, the 600 million doses are for two per person.

The third thing is there are maybe new vaccine technologies that allow you to do it orally, or intranasally, or a variety of other means beside subcutaneously with a needle. So I think all those issues are being evaluated and pursued.

But yes, there are some very significant shortfalls and there are other disposables as well that are a matter of concern when you get into that kind of circumstance.

Rick, do you have anything? Senator MURPHY. I am sorry.

Dr. KADLEC. I just wanted to make sure if I left something out, if Dr. Bright could offer it.

Dr. REDD. I think this is a modeling problem. Particularly from the supply standpoint, making sure that we are tapping into the existing commercial market, and we are able to leverage that system in addition to stockpiling what that market cannot produce.

Senator MURPHY. Dr. Kadlec, back to you, and my second concern.

BARDA, as we have talked about, is such a wonderful model and working with industry, you have developed 34 approved medical countermeasures, 23 influenza vaccines.

Again, coming back to a company that BARDA has worked with in Connecticut, Protein Sciences, which as you may know, has come up with an innovative way to develop a vaccine; not the traditional egg-based vaccine, but a recombinant DNA technology mechanism. They raised the issue of how you make sure that having spent the money to develop these vaccines, there is a market so that they can continue to develop processes and make sure that they are available.

What is the responsibility of BARDA, or HHS or, I guess, if the CDC wants to weigh in, on how you make sure that the money being spent on research ends up on a marketable vaccine? And that you are working with companies to make sure that a bridge market exists so that they are available in the case that you need them for a pandemic.

Dr. KADLEC. Well, clearly, that is one of the factors that goes into this public-private partnership. And I would also invite Dr. Gottlieb because it has been the case with the PRV's, like with the vouchers, if you get through that you can get some benefits. But we need to look at the whole variety of incentives to not only get companies into the market, but keep them in the market and keep them viable going forward.

There is this issue of "the second valley of death," which has been raised at some point in time that once you have delivered your vaccine—and if you do not get either the opportunity to replenish or use that technology for some other commercial purpose—that the company may still be at risk, and you may still basically be confronted by the limitations that you do not have the producer. So these are issues that are still pretty thorny and, quite frankly, that is one of the areas, I think, that probably deserve a little more consideration during your reauthorization.

Senator MURPHY. I do not mean to keep Dr. Gottlieb out of this conversation.

You raised this in some of your earlier testimony, some of the market disincentives here and I would love to hear your thoughts. Dr. GOTTLIEB. Yes, I think you raise a very valid point, Senator. If you are talking about a countermeasure that does not necessarily have a dual use for another public health application, your only market is going to be in preparedness and presumably the only market is going to be for stockpiling. And if it is not something that turns over a lot, so you are not going to have to constantly replenish your stockpile.

Depending on what you are developing, the cost of capital to try to develop that product might be too high to justify the investment. I saw this when I was on the other side of this equation.

We have tried to offset some of that with the PRV's, but I will say that the value of the PRV's in the marketplace have diminished as we had more PRV's. So the value of the incentive has also gone down over time.

So I think this is something we should all contemplate. Senator MURPHY. Thank you.

Thank you, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Murphy. Senator Murkowski.

Senator MURKOWSKI. Thank you, Mr. Chairman. Appreciate the discussion here this morning.

Dr. Kadlec, you recognized, in response to Senator Warren's question, the challenge that Puerto Rico faced after the devastating hurricanes. I mean, it is difficult in an island area where you are not connected, where you are remote.

Well, that brings it close to home to me. We are not an island in Alaska, but we are not connected to the continental United States, and we are really big, and we do not have a lot of

roads. It was just about 75, 78 years ago that we had a diphtheria outbreak in Nome and we were able to deliver the serum by dogsled.

We are not doing that anymore, thankfully.

But it does speak to the reality of how to respond when you have an outbreak, and your ability to move in quickly is limited either because of weather or just access limitations.

We were reminded of this at 9/11 when all the airspace was shutdown, when you now have 80 percent of your communities that have no way to get things in and out. A major earthquake that can take out a major port that serves access or airports. And so, for us particularly in Alaska, we had to be our own little island when it comes to response.

But when you are trying to get stockpiles of vaccines or the like, that makes it very, very challenging. And I do not recall whether it was you, Dr. Kadlec or Admiral Redd, mentioned that you can get stockpiles, I believe, of vaccines anywhere in the United States within 12 hours.

Did I hear that correctly? [All nod in assent.]

Senator MURKOWSKI. Should I be worried in a small, remote, not accessible by road, shut out by weather? We cannot even get a state trooper in for 3 days into certain of our villages at certain points in time.

What can you do to assure me that we can be that responsive in our more rural areas? That is one part of the question.

The other part is when it comes to infrastructure itself.

Several years back, we had the first sizable cruise ship going through the Arctic. We had all kinds of emergency preparation drills and it was not because we were most fearful of an oil spill from a ship that might hit the ice. But an issue on a ship where you now have 500 passengers who need some level of healthcare and there is no healthcare facilities to be had in the region.

So for purposes of how we can be responsive when there is a public health crisis, whether it is an outbreak or some kind of a disaster, manmade, natural, or otherwise, what assurances can you give us from these rural states?

I will turn to Dr. Kadlec and you, Admiral. Dr. KADLEC. Well, thank you, ma'am.

That is a challenge. I think the reality is the Strategic National Stockpile can get anywhere to be delivered to the state authorities within 12 hours.

Senator MURKOWSKI. So that would get to?

Dr. KADLEC. To Anchorage, for example. And then, it is really the state's responsibility to basically get those products, or those vaccines, or drugs to the last terminal mile to those people who need them.

That is an issue, quite frankly, I think ASPR and the CDC share concern, that that is an area where concerted work has to be done because there are other places in the country that probably would have similar challenges.

Admiral Redd, do you want to?

Dr. REDD. Yes, I think this is a very challenging scenario and I think that if it were a challenge to move product to a location, there would be other challenges as well; understanding the problem of the disease in that location.

We might have telecommunication, but access to laboratories, access to epidemiologic investigation, those would also be things that would be limited.

I think this probably needs to be thought of as a broader set of capabilities that are needed to assure the protection of these populations. Not just the stockpile, but medical care and really situational awareness as to what is happening in those locations.

Senator MURKOWSKI. Well, and it is something, of course, that we clearly think about.

The last thing I am going to leave you with. The State of Alaska just conducted an Alaska Health Impact Assessment. It was a framework based on the current National Climate Assessment predictions and the impact to Alaska as a state that is seeing the impact of climate change as warming temperatures. You might not feel it here on the East Coast, but it is warmer back home.

It outlines some of the potential health effects that could be coming our way several decades out. We recognize that.

But one of the concerns, of course, is infectious diseases that are particularly associated with vector borne. Usually, we are able to freeze those nasty mosquitoes and they cannot move these levels of outbreaks.

But it is something that, as we think about public health emergencies, we are so focused on the here and the now, and the disaster of the day, but I do think it is important that we be thinking long term about the changes that might be headed our direction.

Thank you, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Murkowski. Senator Jones.

Senator JONES. Thank you, Mr. Chairman.

Once again, thank you for your kind welcome to this Committee. To kind of follow-up on, I think, Senator Casey may have highlighted it and Senator Murkowski was talking about the rural health areas.

I can understand the challenges when there is a pandemic and you need to get access, but I have a state that is also very rural, but we have roads. We have the ability to get serum in and things like that. But yet, we are in Tornado Alley. We are in Hurricane Alley. It comes through.

My concern is the preparedness for healthcare delivery on an immediate basis when you have those disasters because in Alabama, like so many other states, rural healthcare is disappearing, and that is a real challenge.

So I would like to have you address what is being thought about, what is being done to prepare for those types of emergencies for those communities that do not have the daily healthcare that they have got, so that immediate healthcare needs can be given to them. Dr. KADLEC. Sir, I would just say one of the areas I touched in my written testimony is on this idea of creating a National Disaster Healthcare System, really taking advantage of the nascent trauma system that we have in our country that clearly needs to be amalgamated or, if you will, kind of unified.

We would like to basically use the Hospital Preparedness Program as a means to do that. It certainly would need more resources to do that. But basically expand the regional coalitions to not only cover states, but regions, Mississippi, Alabama, that part of the country where you can actually share resources and basically do better coordination, mutual aid in those kinds of situations. Build the kind of relationships where you know about bed availability, work with the EMS systems in terms of transportation to basically identify the appropriate places to take people with different injuries or different kinds of casualties to the right place to ensure their survival.

There is a lot that can be done and quite frankly, we think by regionalizing this will help. Because Alabama has a few major cities, Mobile, clearly there are some great facilities there, as well as other parts of the state, as well as adjacent parts in Mississippi. If you can build that coalition on a regional basis, you can probably address some, but not all, of those issues.

Dr. REDD. This is a little bit beyond preparedness, but one of the things we had done at the CDC is to examine rural health. The way that we have done that as a first step is to actually examine the data that we have.

There are a series of publications on issues related to rural health in our in-house journal, “The Morbidity and Mortality Weekly Report,” and we would be happy to get those to you to define the problem.

Senator JONES. Okay, that would be great.

I also was going to ask a similar question about citizens with disabilities.

Do you have specific guidelines, things that you do to take care of those with disabilities, whether it is a physical disability, a mental disability, or whatever?

Dr. KADLEC. Sir, we have a program at HHS and the ASPR that basically uses CMS data, Medicare data to basically identify people in different regions or in states by ZIP Code, by home address, even by phone number to identify people who are dependent on durable medical equipment.

So in advance of a hurricane, for example, we provide the states, like in the case of Florida and, I believe, in Alabama too prior to Norm, before that hit that we identified people who would be at risk to power outages or who need probably special assistance if they needed to be evacuated. That is one piece of the problem.

Quite frankly, we do not have that data from Medicaid from individual states. So that would be another way to enhance that if we could get data on that.

But that is just one way to basically preidentify people at risk and it goes a long way to basically take care of folks.

Senator JONES. All right.

Dr. REDD. Just three quick things. Senator JONES. Sure.

Dr. REDD. We require our state grantees to include a section on vulnerable populations in their emergency response plans. So that is one thing.

The second is that we work with professional associations—predominantly, I am thinking more of the American Academy of Pediatrics, the American College of Obstetrics and Gynecology—when there is an emergency to make sure that we are addressing those populations.

Also, when we activate our operations center for an emergency response, there is a functional desk on vulnerable populations to try to deal with the kinds of issues that come up.

Senator JONES. Great, thank you. Thank you, gentlemen. Thank you for your testimony.

Thank you, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Jones.

Senator Casey, do you have any questions or concluding remarks you would like to make?

Senator CASEY. Mr. Chairman, just some concluding remarks, and I will read through them quickly.

I want to thank our witnesses, obviously, for their insights and expertise today and their ongoing as part of the Federal Government to develop and maintain the necessary public health preparedness capabilities.

I will have some questions for the record in addition to the ones I asked already.

Senator CASEY. Next week, we look forward to hearing from non- governmental stakeholders about how we can continue to strengthen our readiness for future public health emergencies and keep the American public safe.

As we heard today, preparedness is continuous and must evolve to face new and different types of threats. I remain committed to ensuring we sustain the progress we have already made in preparing for public health emergencies, while continuing to work to anticipate the next threat.

We have a strong, bipartisan history of working together on this Committee to improve our communities' ability to respond to all manner of public health threats, and I look forward to continuing that tradition in the months ahead.

Mr. Chairman, I want to thank you for your work on this, as well as Ranking Member Murray and Senator Burr, of course.

Thank you.

The CHAIRMAN. Thank you, Senator Casey.

Senator Casey is exactly right. This is one of the many areas that this Committee has effectively worked on, both in the authorization and reauthorization of legislation to prepare our country for the unexpected disaster that might occur to us.

A lot of progress has been made and I want to thank Senator Casey and Senator Burr, especially, for their leadership over the years in this area.

As he indicated, we will be having our second hearing on this topic next Tuesday, January 23 working with Senator Murray, Senator Casey, Senator Burr, and others. We hope to be able to write legislation revisiting this Act, and mark it up in Committee this spring, and present it to the Senate for bipartisan action.

I thank the witnesses for coming today. The testimony has been very helpful. The attendance has been good.

The hearing record will remain open for 10 days. Members may submit additional information within that time, if they would like. The CHAIRMAN. Our Committee will meet again tomorrow on a different topic at 10 a.m. for a hearing entitled, "Reauthorizing the Higher Education Act: Financial Aid Simplification and Transparency."

We have been working for more than 4 years on taking a new look at the Federal Government's relationship to our colleges and universities. There are 6,000 of them. Our major role is that we appropriate about \$34 or \$35 billion a year in grants for students to attend colleges. There is more than \$100 billion of new student loans each year.

In connection with all of that money, there is a lot of opportunity and a lot of need for us to take a look at accreditation, innovation, simplification, getting through the jungle of red tape, another whole set of activities.

That will be our major focus during this year and we hope also to have that bipartisan legislation to the Senate floor sometime this spring.

Thank you for being here today.

The Committee will stand adjourned.

[Whereupon, at 12:08 p.m., the hearing was adjourned.]

Chapter 490

THE DILEMMAS OF THE LOCKDOWN: A SOCIETY IN POST COVID-19 DAYS

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ABSTRACT

This preliminary chapter introduces readers to the content of the book; so to speak an editorial project oriented to discuss the durable effects of the global pandemic (COVID-19) in society. Although a whole portion of studies, books and publications aimed at exploring the economic consequences of the virus, less attention was given to the social maladies – i.e. racist and separatist discourses, violence and phobias- the COVID-19 certainly generates. The COVID-19 potentiates the fear of stranger closing the West in a philosophical dilemma. All restrictions and travel bans that nation-states dispose for stopping the contagion inscribe into a process that political scientists know as the “securitization process”. The present chapter holds the thesis that COVID-19 affirms a tendency originated in 9/11 which accelerates the death of hospitality. In the new normality, the “Other” has become an *undesired guest*.

Keywords: death of hospitality, west, COVID-19, terror, society

INTRODUCTION

The COVID19 left incalculable financial losses, as well as human deceases, changing not only the geopolitics but gridding the global trade into an unparalleled halt (Sheridan et al. 2020). The global pandemic shocks directly the world while evincing the material asymmetries and inequalities culturally enrooted in the postmodern capitalism (Ali, Asaria and Stranges 2020; Matthewman and Huppertz, 2020; Black 2020). Sociology of COVID19 remains in its infancy. Some voices alert on the end of capitalism, at least as we know it

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(Zizek 2020). To date, it is very hard to precise the evolution of the pandemic. At the end of December of 2019, the Western audience captivated by the news coming from China revolving around a new virus outbreak originated in Wuhan city. Doubtless, this new virus, which is known as SARS-CoV2, gradually becomes in a global pandemic infecting more than 93 million peoples and causing more than two millions of deaths (numbers updated at 15 January of 2021).

Although governments suddenly disposed of radical measures such as the closure of borders, airspace without mentioning the imposition of strict lockdowns the virus showed higher transmissibility. Over the recent decades, the West faced similar crises associated with SARS, Ebola and Swine Flu, but nothing like COVID19 (Richardson et al. 2017). The virus disseminates rapidly because of the mobile infrastructure of the Western Hemisphere which connects far-away cities in hours, as well as the overcrowding that characterizes the urban areas (Adey et al. 2014; Lapointe 2020). To enumerate some mediate consequences of the pandemic we come across with discourses of racism or chauvinism directed against Asian tourists (Mostafanezhad and Cheer 2020), geopolitical tensions (Lee and Haupt 2020), without mentioning political crisis and turmoil derived from the economic crisis (Rogerson and Baum 2020).

The mass transport means, as well as the tourist travels, were the key factors that allowed a rapid propagation of the virus worldwide. Although sociologists and colleagues of different pundits have captivated by the advance of COVID19, less was known about its aftermaths. Sociologists are often educated to study social phenomena in normal conditions, but few voices are experts in *disaster studies*. As Enrico Quarantelli puts it, a disaster denotes the idea that the normal conditions of existence that make the life possible in society are temporal suspended or simply disappeared. Any state of disaster speaks of the incapacity of society to give a valid response to external or internal danger, in which case the social order is in jeopardy. The question of whether of disaster interrogates furtherly our vulnerability as well as the existent deficiencies to deal with urgent matters. In fact, post-disaster manuals never apply at the best as they were written when the disaster takes hit (Quarantelli 1988; 1997; 1998). Of course, this is the case of COVID19. The invitation of a leading worldly publisher as Nova Science Publisher to edit a book with a focus on COVID19 was a brilliant idea we – jointly to Argentinean philosopher Adrian Scribano- will not waste. Also, we started to work in the selection of authors who come from different latitudes and cultures. To avoid the Anglo-centrism which marks the pace in social science, we invited scholars who are not native English speaker. This seems to have some limitations because of the grammar barriers, but we bet it worth our times. The present (short) chapter discusses the long-durable effects of COVID19 in society while discussing the different chapters that form the present book while lays the foundations towards new paradigms to understand the effects of the pandemic in postmodern society.

COVID19, SOCIETY AND POLITICS

In a seminal paper, which entitles *sociology of COVID19*, Steve Matthewman and Kate Huppatz (2020) locates the COVID19 in the epicenter of the most serious health and economic crisis of human history. Global citizens who were accustomed to travel across the

globe were suddenly immersed in a new social experiment where their basic rights to circulate freely were radically altered by the governments. The pandemic is changing human relationships, reciprocities and emotions and of course the ways of making sociology; so to speak, different social maladies already existent in the late capitalism – far from being resolved- become more acute in the post COVID19 context. Sociologists should re-imagine the infrastructure of a new social world based on social distancing, lockdowns and indifference by the “Other”. In this vein, Korstanje and George (2020) called the attention to the shifts in the travel behavior as well as in the ways the alterity is imagined in Western civilization. The scientific expedition that inspired the rise of sociology and anthropology started from the needs of “being there” to study the natives. The “Other”, for better or worse, was an object of curiosity which should be subordinated to the scientific gaze. In the days after 9/11, the “Other” is seen as an undesired guest, a potential enemy who looms to attack anytime and anywhere. In the post 9/11 days, anyone could be a potential terrorist while just after COVID19 all us are potential (terrorists) carriers of a lethal disease. Without any doubt, the world is experiencing a feudalization process where the national borders are in constant tension and negotiation but far from being a foundational event, COVID19 closes a process initiated after 9/11. In that process, the *Non-Western “Other”* is suspected to be a future enemy, neglected and exiled through the scrutiny of modern surveillance. In a nutshell, authors hold the polemic thesis that Western hospitality is dying by the introduction of a fear culture to govern the workforce (Korstanje and George 2020). In consonance with this, Geoffrey Pleyers (2020) acknowledges that the pandemic affirms the authority emanating from the classic nation-states in detriment of the global forces. Having said this, political scientists deal with the risks the world witnesses the emergence of populist leaders who foster nationalist discourse. As he eloquently notes, while the nations closed their borders, citizens looked inside their countries in quest of security and protection. As a result of this, international institutions titter in the brink of collapse. The consequences of COVID19 entail various geopolitical disputes accompanied by authoritarian guidelines for protection. Everything is allowed in the state of exception. Last but not least, social psychologists Lee Monaghan (2020) continues the discussion left by Scambler who coins the term *fractured society* to explain the inter-class (group) social conflict or tensions -in this case- generated because of COVID19. Departing from Klein’s concept *disaster capitalism*, Monaghan argues convincingly that COVID19 finally corroded the basis of human solidarity that was previously affected by the neoliberal agenda, in so doing, some social maladies that characterized liberal society abruptly surfaced.

This book, as stated, combines different theories, and conceptual frameworks giving fresh insights into the effects of COVID19 in modern society. If this represents the end or a re-start of capitalism only God knows, but what is insure is that the pandemic fractures human relations as never before paving the ways for the emergence of a new society based on the Spectacle of death. The “Other’s death” becomes mainly a factor of cultural entertainment for the global audience worldwide (Tumarkin 2005; Howie 2012; Korstanje 2016; 2018).

HOW TO READ THIS BOOK

Chapters organized in the present editorial collection can be read separately but they are integrated into a common-thread argument: the consequences of the pandemic in the different micro-sociological spheres of daily life. As remarked, the invited authors who are experts in their fields have no English as their native tongue. The main goal of this book aims to describe how COVID19 confronts with the Anglo-Saxon cosmology of the world. In so doing, the lens of authors plays a leading role to reconstruct the foundations to new critical sociology in ever-changing capitalism.

As the previous backdrop, the foreword elegantly, which is written by Freddy Timmermann-Lopez, interrogates furtherly the role played by *anger* in the constitution of the neoliberal agenda. Per his viewpoint, neoliberalism started with Allende's coup and the access of Augusto Pinochet to the presidency of Chile in 1975. Politically speaking, the climate of fear imposed by Pinochet not only paved the ways for the political disinterest but also facilitated the worker union dismantling. The recent protest and social discontent that destabilizes Piñera's administration comes from a belated retaliation resulted from decades of oppression. The private property which was the quintessential feature of the neoliberal order is now under attack. The recent virus outbreak (COVID19) activates old-fashioned (authoritarian) practices and dispositions such as the curfew or, army-force patrolling originally characteristic of Pinochet's Regime.

In the second chapter, Adrian Scribano discusses the interplay of hunger and the sociology of bodies (emotions) in the context of COVID19. He focuses his analysis on the pre-pandemic situation in Argentina which associates to a much deeper market stagnation, unemployment and perpetual economic crisis. Scribano holds the thesis that – far from being part of the solution, NGOs, the state and the market are allies who have disposed of the citizens' bodies to manage a climate of scarcity and exploitation. The struggle for containing the virus propagation alludes to a *bellicose metaphor*, the war against a virus!

Primavera Fisogni, in the third chapter, brings some reflections on the doctrine of living with the enemy in, which was originally forged by counter-terrorism experts. His chapter dissects the problem of West to understand the "Alterity", as a potential enemy – like the virus- living within. Her reasoning comes from the model friend-enemy in Carl Schmitt who has molded modern politics. As she puts it, the immunization makes the enemy (the virus) and the host adversaries. In this respect, any process of immunization disciplines the virus keeping it under the human control.

In this vein, Pedro Lisdero and Marion Fonrouge alert on the durable effects of the pandemic in society. To the problem of the internal enemy debated in an earlier chapter, this fourth one adds a more than innovating insight, the big data models and the digital platforms oriented to scrutinize daily social interaction.

These researchers find that the same technology used to follow up the traceability of messages, discussions revolving around COVID19 paradoxically commoditizes its users.

In the fifth chapter, Irina Burak and Tatiana Razumova expose the study case of the Russian Federation. From different angles, they review the negative effects of COVID19 in the Russian Federation. The COVID19 teaches us three sad realities, some people simply die (when their conditions aggravate), some lose their jobs and others may panic. The government adopted not only restrictive measures but also launched to bail out citizens and

private companies. The digital technology allowed social distancing as well as the home office in the entire federation. Resiliency will occupy a central position in the economic recovery of the Russian Federation.

In the sixth chapter, Fabio la Rocca explores the archetype of the urban landscapes (the city) in the context of social distancing. As he eloquently notes, the face of the city has been radically transformed by the restrictive measures adopted by Western states. The city, which historically was a site of connection, now becomes in a space of eradication. He coins the term *the desert city* to symbolize the days of lockdown in different in Europe. It is safe to say that the extension of the interior in our apartments was exteriorized beyond the window to recreate a social manifestation of tribal reciprocity during the COVID19. While forcefully constrained to stay safer at home, lay-citizens get out balconies to interact with “the Other”.

Angelica de Sena, in the seventh chapter, shows the grim future of La Matanza, one of the poorest and largest regions of Buenos Aires Metropolitan area. When President Alberto Fernandez decided to impose the lockdown it generated devastating effects for citizens who witnessed how the economy plummeted. She conducts some online surveys to describe the emotions of La Matanza’s dwellers. The obtained outcomes reveal that fear, and anxiety followed by boredom and worry are the main axes of what consulted people normally feel as long as the COVID19.

In the eighth chapter, Aldana Boragnio proffers a more than interesting diagnosis about COVID19 and the needs to be safe at home. For those who are forced to stay at home, the act of eating becomes a practice of the private domain. As she remarks, eating seems to be a social practice that reproduces the body while framing habits and customs as well as countless social sensibilities. The global pandemic not only alters diets but food practices in different ways. The chapter aims at describing the sensibilities of eating in the post-pandemic days while laying the foundations towards a new understanding of commensality, and the rite of the banquet.

The last chapter -on the ink of Adrian Scribano and Jorge Duperre- draws a comparison between COVID-19 and the Spanish Flu, a virus that whipped humanity in the former century. Authors use the term *present, mediated and cherished death* to explain the disposition of audiences to the spectacle of death, packaged and sold by the mass media. The pandemic suspended and radically changed all funerary rites, stripping out the veil of death from its sainthood. The act of dying accompanied or alone -exiled like Oedipus-, which is the core of the tragedy, seems to be one of the controversial themes this chapter deals with.

CONCLUSION

One of the problems of COVID19 remains with the fact that we know nothing respecting how this game ends. The chapters lumped together in this volume study the durable effects of COVID19 in different fields of private or public life. Basically, far from being a turning point, this pandemic seems to affirm the material inequalities and social maladies proper of capitalism which ranges from digital exploitation, to labor precarization or the introduction of a fear culture as a form of cultural entertainment. What is equally important, our travel behavior and customs changed in the same way how the foreign tourists are treated. Asian tourists not only are feared but discriminated as potential carriers of COVID19. The national

or inter-estate borders have been re-drawn in view of a new politics where the “Other” is the enemy – if not the terrorist- (Korstanje 2017). Whatever the case may be, the social distancing as well as the lockdown, recreates the conditions to the rise of new geopolitical disputes, chauvinist discourses, or long-dormant sentiment of separatism. Probably the global economy sets the pace to a more feudalized world where “the Other” becomes in an *undesired guest*. This process does not begin with the pandemic, but with 9/11 and the War on Terror. The virus, so to speak, closes the doors of an epoch I has dubbed as the *End of hospitality*, at least as we know it.

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Chapter 491

THE HUNGER GAMES: A LOOK AT FOOD INTERVENTIONS IN THE CONTEXT OF COVID-19

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ABSTRACT

Since government actions at all levels began in relation to the COVID-19 pandemic in Argentina, the State, the market and NGOs have been targeted at the poorest and most impoverished sectors of the country. Based on the analysis and interpretation of various records of the mass media and official documents, this article systematizes various difficulties around hunger, with the aim of opening a critical discussion on them from the perspective of sociologies of bodies/emotions. The expository strategy will be as follows: a) the theoretical starting point of the connection between hunger, the body and emotions is synthesized, b) the situation of poverty and pre-pandemic hunger in Argentina is outlined, c) some of the multiple emotions of the intervention are characterized and d) some interpretations of the interventions characterized are presented.

Keywords: hunger, social interventions, body, emotions

INTRODUCTION

Natural cataclysms, environmental catastrophes, wars, epidemics and pandemics have a common social phenomenon: hunger. Every society, by establishing food production procedures, satiety criteria and the practices of feeling associated with them, somehow establishes a politics of hunger. The political economy associated with capitalism, at least in

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the last 400 years, set out to be a scientific regulation of scarcity as a “natural phenomenon”, generating a system of resource allocation based on unilateral accumulation and a social dispute of systemic adaptation. The state, the market and NGOs are part of the aforementioned processes of managing the scarcity associated with food and hunger. The declaration of social emergency and compulsory isolation immediately impacted the productive structure, labour management and consumption, causing the informality, precariousness and organizational disorganization existing in the country to emerge. Thus, since government actions at all levels began about the COVID-19 pandemic in Argentina, the State, the market and NGOs have made interventions aimed at the poorest and most impoverished sectors of the country. In this context, the present article tries to systematize various interventions around hunger, so as to open a critical discussion about them from the perspective of the sociology of bodies/emotions.

The research strategy and the material that serves as the basis for the analysis and interpretation come from three types of sources: a) records of the mass media and social networks, b) official documents and c) secondary data of other investigations that are being carried out in the Research Centre to which the authors of the article belong. The expository strategy that we have chosen is the following: a) the theoretical starting point of the connection between hunger, the body and emotions are synthesized, b) the situation of poverty and pre-pandemic hunger in the country is outlined, c) some of the emotions that characterize the multiple practices of intervention are outlined, and d) some interpretations are offered about the interventions characterized. The article tries to elaborate a critique of some practices, beyond their legitimacy, of being the product of existing needs, of enjoying political consensus, and of having the character of unavoidable actions to lessen the impact of the crisis. The militarization of the poorest sectors, the persistence of charitable models and the spectacularization of aid, today exacerbated pornographically, must be understood as the reproduction of a social structure configured several decades ago. We end up remembering the immense possibility that the emergency offers as a springboard for non-dependent social practices.

HUNGER, BODY AND EMOTION

Hunger is a social phenomenon that impacts the body. People need to feed to maintain the minimum state of reproduction of the organic processes that constitute what is called the body. The human person seen from a biological perspective is a complex interrelation between the volume of nutrients ingested, the energy expended to obtain them, and the quantum social energies available to manage these two components.

Hunger is a phenomenon of great variability that has various nuances: there is no single modality of hunger. Among the main types of hunger that can be identified in a diet, we find the following three: a) acute hunger, which is an intermittent phenomenon, with periodic but not continuous exacerbations and restitution; b) chronic hunger, of persistent and prolonged action, at the same time, that it can be qualitative or quantitative hunger - or both - depending on whether it refers to a diet with insufficient protein and vitamins or with insufficient calories; and finally, c) hidden hunger, which refers to malnutrition based on the lack of essential micronutrients for the biological, psychological and social development of people

(De Castro, 1962). The three types of hunger coexist worldwide, locating themselves to a greater or lesser extent in some countries and spreading differentially across the social strata. Today, hidden hunger is found in both industrialized and poorer countries; in the former due to excess consumption, and in the latter due to the decrease or absence of certain foods, to which chronic hunger and acute hunger are added as part of the global reality. This points to hunger as a primarily social fact since “hidden hunger today constitutes the most typical form of human-made hunger” (De Castro, 1962, p.54). But what is relevant about hidden hunger or malnutrition is not only the lack of nutrients but its extension over time and the consequences it generates, since hunger will not only have consequences on the bodies of people who experience it. It will also impact their offspring and thus the entire process of social structuring. Taking this characterization elaborated by De Castro and placing it in the context of the body, we find a conceptualization proposal around hunger from a vision of the sociology of bodies/emotions that emphasizes their relational character. So, individual hunger refers to the “lack of nutrients” experienced by the individual body at the biological level (socially understood). It refers to the absence of nutrients (in a broad sense) for the reproduction of that body. It is enacted at the level of the relations between individuals, social organizations, and the environment. Subjective hunger affects the “auto-reflexivity of the self”, i.e., it links the consequences of “identity” order, in the cognitive sphere which are related to hunger. It is enacted in the field of the relations of the human being with himself and its consequences in the embodied self-image of the subjects. Social hunger has an impact on the social presentation of the subject” (Scribano and Eynard, 2011, p.67).

Thus, we understand that individual hunger refers to the relationship between the human being and the environment, and subjective hunger refers to the relationship of the human being, while social hunger articulates the other two planes in connection with a life lived in a society. At the same time, these distinctions of hunger are connected with the distinctions of the body; therefore, hunger will affect the bodies on their individual, subjective and social¹ planes due to the unequal distribution of energy and nutrients, jeopardizing the corporeal existence as well as the possibility and power of action (Boragnio, 2018).

Bodies exist in connection with the environment from the processes that occur in the interaction between the brain, the central nervous system, nutrients and energies. Specifically, the concept ‘body energy’ refers to the direct relationship between the body and nutrients as a result of the exchange of physiological systems and biological processes that allow the durability of systemic functioning. This brings us closer to understanding the direct relationship that occurs between nutrients and the possibilities of action since social energy arises from this relationship, which “is based on body energy and refers to its distribution processes as a substrate of the conditions of movement and action. The power to plan, execute and resolve the consequences of the agents’ actions constitutes the social energy that they have” (Scribano and De Sena, 2016, p.116).

While body energy is directly linked to nutrients, without nutrients there will be nobody energy, so the greater the nutritional deficiency, the less the possibility of action. At the same time, “social energies are closely related to bodily energies, since the greater the nutritional deficiency, the greater the probability of structuring a set of weak human relationships”

¹ The individual body refers to phylogenetic logic, to the articulation between the organic and the environment; the subjective body is configured by self-reflection, in the sense of “I” as a centre of gravity through which multiple subjectivities are woven and passed, and the social body that is (in principle) the social made body. See Scribano, 2007; Scribano, 2005.

(Scribano and De Sena, 2016, p.116). Therefore, the possibility and power to plan and execute the action will be conditioned by the availability of energy and, thus, by the possibility of access to food. For this reason, it must be taken into account that the availability of food resources alters the quantities and the energy qualities that each individual has at their disposal, allowing these bodies to reproduce and be socially available. Thus, hunger will configure in the bodies small potentialities of the possible states of life of the subjects as social agents. Meanwhile, unequal distribution and appropriation of energy and nutrition affect the corporal energies and, therefore, the social energies. This defines hunger as a central experience of life, as it is structuring of emotions and sensibilities. Hunger highlights the intersections and networks between bodies/emotions due to their socially constructed character, while the direct relationship between energies and nutrients establishes limits and socio-biological spaces from which it is possible to observe how the individual body is the result of policies of bodies and policies of emotions, and its consequences that organize the reproduction of bodies and their availability.

POVERTY AND HUNGER IN PRE-PANDEMIC ARGENTINA

Hunger is always there. In Argentina, since the 1970s, poverty has continued to manifest itself as a problem of great magnitude and associated with it is the reproduction of forms of hunger. In the last quarter of the 20th century, there were global transformations that gave shape to what is known as the “new social question”, the sociabilities and experiences of poverty and hunger being a fundamental part of the politics of sensibilities across the century. In Latin America and the Caribbean, the problems related to the resources necessary for the reproduction of life implied an approach and strategies for the regulation of conflict and social consensus. For the first decades of the 21st century, new poverty assistance interventions were required that would reach levels of great massiveness. For the year 2017, the number of people living in poverty reached 184 million, approximately 30.2% of the region’s population, of which 62 million were in extreme poverty –10.2% of the population–, the highest percentage since 2008 (CEPAL, 2019).

In Argentina, poverty did not develop in a very different way. Poverty levels have skyrocketed since the early 1980s, with increases marked by economic crises, and it impacted between 20% and 35% of the population according to the period measured. At the same time, except for the 2001 political-economic crisis, poverty levels always found a new ceiling, higher than the previous measurement (De Sena, 2020). The latest data from the National Institute of Statistics and Censuses (INDEC) referring to 31 urban agglomerates, involving a population of 28,022,735 people,² indicate that, for the second half of 2019, the percentage of households below the poverty line (LP) reached 25.9%, which represents 35.5% of the population. Within this set, 8% of people (5.7% of households) can be distinguished below the indigence line (LI)³ (INDEC, 2020).

² The total population of Argentina estimated for 2020 is 45,376,763 people.

³ This refers to the fact that below the poverty line is 2,423,562 households, that is, 9,936,711 people, of which 2,236,739 people are indigent. These data are constructed from the Permanent Household Survey, referring to 31 urban agglomerates. https://www.indec.gob.ar/uploads/informesdeprensa/eph_pobreza_02_19SEFE752E31.pdf

Along with the historical journey that can be made through poverty data, data on social food policies must be added as ways of responding, regulating, normative, normalizing and mitigating conflict (Grassi, 2003; De Sena, 2011). Since the 1970s, the availability of food worldwide has been increasing. And since 1985 full availability of food was reached worldwide. This means that, statistically, with the current world food production, all the inhabitants of the world could obtain 2,700 Kilocalories (Kcal) daily⁴ (Aguirre, 2010). However, for that year, the Food and Agriculture Organization of the United Nations (FAO) registered 875 million people as malnourished (Aguirre, 2015). Currently, the figure rises to 820 million people who suffer from chronic hunger and reaches almost 2 billion if we talk about those who suffer from hidden hunger and malnutrition (FAO, 2019). In this way, it is exposed that hunger is not a problem of availability or production, but rather a problem of access to food. In Argentina, in mid-1984, during the government of Raúl Alfonsín, the National Food Program (PAN)⁵ was launched, which consisted of delivering food bags to families that presented some nutritional risk, popularly known as “box PAN”. This was conceived as a two-year emergency program, but President Alfonsín kept it running until the end of his term. In the beginning, the PAN was estined for 907,360 families; in 1985, it was extended to 1,487,118, but three years later, boxes were being distributed to 1,506,470 families⁶ (Sordini, 2018).

Subsequent governments, to date, have continued with food policy, but PAN was the first strictly food-related government program⁷ and is considered the tracer thread of Argentine food programs, due to its scope, coverage and mode of implementation (Sordini, 2018). In this context, the “social question” was present, taking the form of hunger experienced by those social sectors that remained stuck in the place of the structural failure of the current accumulation regime. As De Sena maintains, “the processes of inequality and expulsion generated in the structuring of a society based on the commodification of life cause conflictive breaks that must be systematically remedied” (2014, p.155), and the taking of food is one of the main breaks that were configured from the 1980s.

Beginning in the 1990s, the Conditional Cash Transfer Programs (CCTP) began to be implemented as a modality of attention to poverty. These programs underwent rapid expansion and attained a massive reach, but at the same time that they were incorporated, those referring to food were not neglected, therefore the beginning of the overlap of programs can be observed. From 1990 to date, a variety of national food programs have been established. Among those that are still in force are the ProOrchards program, which has been operating since 1990, the Program for the Promotion of the Welfare of the Elderly (PPB), since 1992, and the National Plan for Food Security (PNSA), which was reconverted in 2003. To these, we can add the National Care Prices Program, which began in 2014.⁸

⁴ The amount of Kcal changed over time.

⁵ ‘PAN’ is the acronym in Spanish.

⁶ A separate issue is the number of boxes that were delivered, since although the number of families that were part of the PAN increased, the boxes did not always increase in the same proportion. Thus, we found that, if in 1987 16,488,304 boxes were delivered to 1,341,078 families, in 1988, 14,950,678 boxes were delivered for a little more than 165,000 extra families (Aguirre, 1990).

⁷ In 1936, Law 12,341, “Palacios Law”, was enacted, which was regulated in 1938. It attempted a “response from the State to the health, food and nutrition problems of the maternal and child population of Argentina, in a situation of poverty” (Abeya, 2016, p.591), but it was only put into national operation in 1952 delivering milk under the name of Maternal and Child Plan, which continues to this day.

⁸ To this, it is necessary to add the Universal Assignment per Child (UAC) that was implemented in 2003 and the Pregnancy Allowance for Social Protection, since 2011. Both programs enter the conceptualization of PTCI

At present, the current food policy at the national level is called Plan Argentina contra el Hambre and “it is supported by the strengthening of the actions carried out by the National Program for Food and Nutrition Security. It implies the promotion and strengthening of Access to the Basic Market Basket.” (Argentina, n/d-b). Within this program, there is the Alimentar Card, which is a pre-loaded card that allows you to buy food –except for alcoholic beverages– and is intended for mothers or fathers with sons and daughters up to 6 years of age who receive the UAC, for pregnant women who from 3 months after pregnancy receive the Pregnancy Allowance, and people with disabilities who receive the Universal Assignment per Child. This program is “a comprehensive food supplement policy” (Anses.gob, n/d). As of March 11, 2020, 1,100,000 cards were delivered and “it is anticipated to deliver more than 1,500,000 cards, which will reach more than 2,800,000 recipients” (Argentina.gob.ar, 2020, March 16).

Hunger as a topic was of concern to various governments as well as serving as a political flag –and it is again today. This brief overview shows that, since the implementation of the PAN, the target population did not overcome the need for help to respond to their food needs. Thus, the applied programs, far from solving the food problem, denote a plot that sustained over time not only the dependence of the recipients on them and the reproduction of inequalities but also an increase in the number of people who are in need of state interventions. In this way, we can observe that, in Argentina, for a long time, there have been food policies that attest with their mere presence that hunger is always in any of the aforementioned modalities, thus configuring the pre-pandemic context of a structural problem: the uneven distribution of nutrients. In what follows we will describe the special association between militarization, policing, spectacularization and the commodification of aid that actions against hunger imply in the days of the COVID-19 Pandemic.

HUNGER INTERVENTIONS AND POLICIES

In the context of the generalized crisis produced by the planetary extension of the COVID-19 pandemic, the Argentine National State designed a battery of state actions to avoid its untimely and deadly eruption. Since the beginning of the Preventive and Compulsory Isolation decreed by the National Government on March 20, a reinforcement of state assistance to the poorest families in the Metropolitan Area of Buenos Aires and the country in general began. The Army and the Churches are involved in a variety of them, at the same time as solidarity actions by companies were added, which had as a point of maximum visibility the holding of a televised event to raise funds for aid to the Red Cross.

Army, Food and Conflict

A basic feature of state interventions in this time of pandemic is the use of the war metaphor to describe the set of actions configured to lessen their impact. The President of the Nation in his speech announcing the Isolation maintained:

since they grant money through transfer in exchange for some conditionalities. For more detail, see De Sena, 2011; Dettano, 2019.

"I thank you too, you are part of those who are exempt from the rule of staying at home, those who work in the media, journalists, I thank you very much for being here, I please ask that you help me to inform well, because as I told you last time, *one is fighting against an invisible enemy, who gets into our room, and one cannot detect it, but one has two fights: they are the fight against the pandemic and the fight that is constantly going on against psychosis*, those feeling that everything is very serious, that everything is irreparable and that nothing can be done." (Words from the President, 2020, March 20)

In this generalized and normalized context of the war metaphor, the participation of the Armed Forces is something very foreseeable as a material "reinforcement" of this war due to the politics of sensibilities launched by an invisible external enemy: biologically and psychologically invisible. In Argentina, the Army in the streets implies updating phantoms of the set of policies of the sensibilities associated with dictatorships. Although the presence and reconversion of the Gendarmerie to policing tasks has indeed become daily since at least 2004, the decision to "use" the army is a practice that fortunately has not been naturalized. The Argentine Army is currently forming part of the emergency plan about the pandemic. On its website it specifies:

"In compliance with the directives issued by the national executive power, the Argentine Army enlists and prepares for the maintenance of the necessary means so that the Operational Command of the Joint Chiefs of Staff of the Armed Forces uses the necessary military resources (mainly health and logistics) to support the community in this Emergency caused by the COVID 19 Pandemic." (Argentina.gob.ar, 2020, March 27)

At the beginning of this fulfilment of tasks, they were involved with the logistical service of food distribution and food assistance. For example, in La Matanza,⁹ Army personnel are deployed to carry out food distribution tasks –rice stew, noodle stew or lentil stew– in three-hour shifts per day, in which 24,000 food rations are distributed daily (Ayerdi, April 5, 2020). The explanation for the need to call upon the army to carry out this task focuses on the fact that "a food delivery operation of this magnitude is unprecedented" (Fuego Simondet, April 5, 2020) and that the army has the necessary resources such as kitchen equipment, industrial-size cooktops and the logistics necessary for the distribution.

These tasks gain greater visibility based on observing the geographical location map of military personnel, whose activities are detailed and range from assembling tents and beds for patient isolation, water supply, food processing and distribution, to satellite telecommunications support, air patrol and reconnaissance flights; these activities are concentrated in the east, northeast, west, northwest and the Metropolitan Area of Buenos Aires (Argentina.gob.ar, n/d-a).

But, the participation of the Army in the social tasks of the pandemic must be related to the diversity of "anti-looting" plans that are carried out mainly in the Metropolitan Area of Buenos Aires by the Security Forces. In this sense, an Emergency Operations Centre was created, made up of the areas of Security, Social Development and Health (Ayerdi, April 5, 2020) to work together on an emergency plan linked to avoiding social conflict. This further complicates the Army's presence with the phantom structure of the looting associated with the 2001 crisis and the set of social responses to various food, poverty and work crises. In the recent history of Argentina, it is possible to verify, in the last four decades, the repetition of the crisis, looting and repression connection.

⁹ It is the largest and most populous party in the Metropolitan area of Buenos Aires and in the province of Buenos Aires. It has a population of 1,775,816 inhabitants according to the 2010 census.

"In this sense, the records of 'Nueva Mayoría' (2013) indicate that, for the period 1989 and 2013, 3,356 cases of looting have taken place, place in the context of the "outbreak of hyperinflation" (1989) some 676 cases; in the "outbreak of convertibility" (2001) 875 cases, 10 to which 151 lootings occurred in the first weeks of 2002 are added. In the subsequent period, looting has a low frequency (2003: 14 cases; 2008: 9 cases; 2009: 5 cases; 2010: 26 cases; 2011: 11 cases) until December 2012. That month, the looting began in Bariloche, spreading to several provinces, reaching a relative peak of 228 cases. In 2013, the phenomenon acquired a greater magnitude, accounting for a total of 1,266 cases (surpassing previous peaks)." (Scribano and Lisdero 2017, p. 338)

On April 15, the President of the Nation, Alberto Fernández, gave a speech at the Gendarmería School where he not only referred to the health/economy dichotomy but also announced the tripling of the Gendarmería's participation as a force that will control "compliance with quarantine" in La Matanza (Coronavirus en Argentina..., April 15, 2020). As of that day, the Gendarmerie is in charge of carrying out security care and quarantine control tasks in the largest municipality in the country (Fernando..., April 15, 2020). Given this, the communal chief ended the event saying that:

"Today is a happy day for La Matanza. The President came to fulfil our request for more than four years: that the National Gendarmerie patrol the streets of La Matanza again. Today we are responding to a complaint from all our neighbours. That an institution so loved by our citizens returns to our streets generates a lot of tranquillity, because the Gendarmerie came to take care of the best capital we have, our people. (...) That the National Gendarmerie returns in these difficult times that we are living in Argentina and the world with the coronavirus pandemic, it also gives great peace to all the neighbours." (Fernando ..., April 15, 2020)

To this must be added that at the beginning of the period of Preventive and Compulsory Isolation there was an intense wave of control and "discipline" for those who broke the isolation, since "between March 21 and 31, only the national security forces had 644,009 people notified and/or controlled on public roads, of whom 19,939 were declared infringers" (Colectivo Editorial Crisis, April 1, 2020).

At the same time, in the future, there is already talk of a joint action initiative between state entities, social organizations, universities and the Army for the reconstruction of areas affected by the pandemic (Acción Social..., April 16, 2020).

To the deployment of the army in relation to food assistance has been added the aid of the national government. According to the journalistic note published on April 5 in the newspaper Perfil, the national government went from assisting eight million people to assisting 11 million. At the same time, "more than 300 million pesos was allocated to the municipalities for the purchase of food and there was an increase of 50% in the amount of aid to 3,000 soup kitchens that the ministry assists" (Ayerdi, April 5 2020). For their part, the municipal mayors signed agreements with supermarket chains, some of whom collaborate with the preparation of the food bags that the municipality distributes.

The National Administration indicates that the need for assistance increased as workers in the informal economy, who until now had no link with the ministry of social development, joined the demand for food. Additionally, there is an increase in attendance at soup kitchens, which look for a way to continue operating at a time when the demand from neighbours increases day by day. For this, they mainly make pot meals that allow the portions to be "stretched" to increase the quantity. Later, some soup kitchens organized a "delivery picketers" to bring food to the elderly in the neighbourhood. Likewise, the news highlights that, despite the changes and the efforts at organization, there was a lack of food (Colectivo Editorial Crisis, April 1, 2020) and that individual actions add to the attempts to feed

neighbours and people in the neighbourhood (Cassini, April 18, 2020). This scene prepares us for the next section where it is possible to capture the unfolding of the commitment of all the Churches to addressing hunger in the context of COVID-19.

Churches and Charities

The history of the so-called “social question” has involved from its inception various forms of charity and philanthropy; the consequences of the pandemic bring with it new scenes of an elaborate narrative between good intentions, guilt, and manipulation.¹⁰ For their part, the Churches organized an initiative called “#SeamosUno”, in which various religious, Catholic, Christian and Jewish associations participate. They, in turn, solicited participation in the form of donations from associations and chambers of commerce. On its website, where “who we are” is defined, we see the slogan:

“Together with CIAS-Compañía de Jesús, CARITAS, Banco de Alimentos, the Council of Evangelical Pastors of CABA, AMIA, ACIERA-Alianza Cristiana de Iglesias Evangelistas de la República Argentina and other business and social organizations, we have decided to launch the project #SeamosUno with to raise funds to be used to buy food and cleaning units, which will be distributed to those who need it most. The initiative implies an exhaustive control in the processes of collection, acquisition of products, assembly and control of boxes, delivery of the same. The project is being jointly audited by Deloitte, EY, KPMG and PWC to ensure the transparency of the process.” (Seamosuno, 2020)

It seeks to raise funds and donations in kind that allow the elaboration and distribution of food boxes (Ini, April 4, 2020). By April 17, 100,000 boxes with 15 kg of non-perishable food each had been distributed,¹¹ and funds are being raised to complete 400,000 more boxes, but the objective of the action is to deliver one million boxes of food to four million people, “especially to the informal sectors that do not have the habitual assistance of the State” (Naishtat, April 19, 2020).

In the conformation of these boxes, you can find donations from large national and some international companies, which provide products, boxes and logistics. The goal is to deliver 1,000,000 boxes. As we can see, the one million became a social fantasy: represented with the imaginary of multiplicity, of the exaggerated and the uncountable quantity of opulence.

The Jesuit priest Rodrigo Zarazaga, the main promoter of this practice, stated in an interview: “The people of the villages do not want chaos, but hunger leads to despair and their persistence can end in situations that we do not want; for this reason, this campaign seeks above all that no one goes hungry and that we stop in the face of the abyss” (Rubin, April 7, 2020). It is clear, once again, that the objective of conflict management and suppression of inequality lies in the conditions that preceded and pre-existed the pandemic. The other side of these commitments is the presence of the Army and its relationship with the Churches present

¹⁰ We want to make clear, once again, that our criticism of being structural and sociological implies not making the mistake of adopting the ecological fallacy, that is attributing to each individual what in fact refers to the level of the collective and systemic.

¹¹ The seamosuno page states: “Each box contains different food and hygiene products to cover the essential needs of a family for a week. Food products cover up to 56 food servings. Next, we give you the details of the products included: Rice/dry noodles - 4 kilos, Flour - 2 kilos, Tomato puree - 2 units, Tin cans - 2 units, Dried lentils or beans - 1 kg, Long-life milk - 3 litres, Mince can - 4 units, Canned fruits - 2 units, Toilet soap - 2 units, Detergent - 1 unit (300 cm3)” (Seamosuno, 2020).

in the poorest areas of the Metropolitan Area of Buenos Aires. In the GPS television program hosted by the journalist Rolando Graña, on A24,¹² on April 24, 2020, a segment titled: “Soup kitchens in the Metropolitan Area of Buenos Aires are seen. If there is no mass, there is a table”. In this segment, the host of the program visits one of the Chapels of Padre Pepe¹³ in the Barrio Independencia of the Partido de San Martín,¹⁴ showing how, due to the prohibition of religious ceremonies and the food emergency, the chapel has become a community feeding centre. In the scene, lasting 1.36:33 minutes, you can see the host of the program showing how to eat where mass is commonly celebrated and showing the place to viewers, while saying: “[we can see that] the care of the Parish, the order... is in charge of army personnel...”,¹⁵ while at the same moment, the camera takes a shot of two uniformed men and women, standing in a military posture. The synthesis is more than clear, the two institutions that guarantee social and moral order together in an intervention against hunger, the questions that arise are more than obvious: How will the situation of citizen security be if the Army has to guarantee order? What will be the level of poverty if it is the Church that must complement/replace the functions of the municipal state? The first answer, also obvious, is that this is Argentina before, during and after the Pandemic. One more band in Moebius’s to which our investigation takes us here is the connection between dealing with hunger and the show.

Spectacle and Pandemic Sensibilities

The COVID-19 pandemic involves a contradictory set of modifications in sensitization policies on a planetary scale, and one of the most evident aspects is the acceleration of the spectacularization through the mass media and social networks. In Latin America, at least, every earthquake, volcano eruption, hurricane, torrential rain leaves bare what society only hides behind a pornographic acceptance: the existence of some structural absence.

With the “Teleton”,¹⁶ at the regional level, and with “A sun for children”¹⁷ in Argentina, as paradigmatic television programs of the spectacularization of humanism diminished in its form of “anonymous donation”, it constitutes one of the pillars of the systematic acceptance of the object of the collection: inequality about televised absence.

The centrality of the show is one of the fundamental components of global awareness policies:

“...the processes of crisis and metamorphosis of capitalism have been associated with staging and spectularity. From the Paris Fair of 1910, through the Hitlerian concentration camps, to NASA’s launches, capitalism has always shown its power through public spectacles. Today, in the Internet era and live broadcasts for billions of subjects, the spectacularization takes (and re-takes) other features to gain importance and centrality. All that is lived must be represented in public, massively transmitted and recognized/approved by “many”. Every day of spectacle implies the appearance of a “reality show”-spirituality... .” (Scribano 2017, p. ...)

¹² A news channel that can be seen throughout the country.

¹³ Argentine priest dedicated to helping in the villas of the Metropolitan Area of Buenos Aires.

¹⁴ The Metropolitan Area of Buenos Aires

¹⁵ https://www.youtube.com/watch?v=_CsFzAfOEu0

¹⁶ <https://teleton.org/>.

¹⁷ https://es.wikipedia.org/wiki/Un_sol_para_los_chicos.

On April 5, the programme “United by Argentina” was broadcast, a television program organized at the request of the wife of President Alberto Fernández to the Argentine Red Cross to channel donations to acquire basic supplies for the pandemic: mouth cap, gel, respirators, etc. The program - which was broadcast in unison on all the broadcast channels and in which the collection of 88 million pesos was reached between donations and advertising guidelines (Trzenko and Fernández Cruz, April 5, 2020) - sought to “provide the opportunity Argentines to come together in the same voice of solidarity” (Unidos por Argentina [United for Argentina], n/d).

When closing the program (in a pre-recorded video of 3:56 minutes) Fabiola Yañez - first lady of the country - said “...*Thank you for being there ... I love you, love us, we love each other.*”

The television special lasted almost 6 hours, in which recognized figures from the show and local television made their appearance, taught viewers recipes to cook at home, showed activities that could be shared with the family at home, and doctors known to the public advised about how to prevent and control coronavirus. At the same time, tributes were offered to the security forces, accompanied by speeches and the language of war. Thus, there was talk of “an invisible enemy”, of a “silent war” and allusions were made to the Falklands War.¹⁸

Along with this special moment and demonstration of donation, it is also possible to find other initiatives by businessmen, unionists and officials around food and its distribution that are “made known” or that are directly part of the marketing of companies. An example is Orange Card, which targets its advertisements with the motivation “we can all do it together” and aims to donate 20,000,000 pesos.¹⁹ As another example, in Chubut a fishing vessel that had to make a transfer trip caught 40 tons of hake (with fishermen who carried out the work as solidarity cooperation, not charging wages) to “distribute it among the poorest sectors of three cities in the province of Chubut “ at Easter (Carpena, April 9, 2020).

All this has been complemented by numerous proposals for donations and contributions from a “solidarity of companies” of various kinds, amongst which stands out that of the “Group One Led”, the leading firm in advertising business on Led screens:

“With the focus on awareness, Miranda and his company decided to donate advertising space on their screens to help protect against the pandemic. How does it work? As he explained, it is a campaign that is projected free of charge on more than 60 screens located on public roads throughout the country where they transmit dynamic content in real-time that promote care and protection against COVID19 and that are part of the “Stay Home” campaign.” (Zanotti, April 8, 2020)

The need is to make the population and the newly connected advertising media known in a society where if you don’t see you don’t feel. Thus, shows, celebrities, companies, and advertising reconnect “as they know how to do it”: the best way to generate an impact is by creating sensibilities. Where there are no state resources, the spectacular sensibilities raised to serve as an appeal to dissolve institutional responsibility. Once again, Argentina’s everyday reality appears in exceptional times.

¹⁸ During those days, in various places on social networks, allusions were made to a historic and well-remembered program called “The 24 hours of the Falklands” which “... was a program broadcast in 1982 for 24 hours to raise funds for the men who were to fight the Falklands War. However, although the fate of the proceeds cannot be established, it is clear from the statements of its protagonists that it never reached its destination.” https://es.wikipedia.org/wiki/Las_24_horas_de_las_Malvinas.

¹⁹ <https://www.naranja.com/donaciones>.

HUNGER GAMES IN THE CONTEXT OF A PANDEMIC

In the movie “The Hunger Games”,²⁰ games with the same name are developed, which are a televised competition for the hungry to survive.

“The nation of Panem emerged from the ruins of what was once known as North America. 74 years ago, the 12 poverty-stricken districts in Panem revolted against the wealth that the Capitol controls. After its overwhelming victory, the Capitol devised “The Hunger Games.” Each year, each district must hold a raffle (known as the harvest) to choose a man and a woman (ages 12-18) to participate in “The Hunger Games,” a competition in the that each of the 24 participants (known as tributes) will fight to the death in a televised arena until only one is alive. However, this is simply an annual reminder to the twelve districts of their authority and as punishment for the rebellion made 74 years ago.”²¹

As in this film, the Argentine National State, in coordination with that of the Province of Buenos Aires, inaugurated an intervention based on the militarization of the struggle for survival. The “presence of the army” in the Metropolitan Area of Buenos Aires (and later throughout the country) and the results of containment are obvious: given the impossibility of quarantine by millions of people, the risk of social conflict increases and this leads to the pursuit of three goals: a) organize the population “on-the-street” (queues, clubs, neighbourhood centres, schools, etc.), b) reduce the risk of looting and c) control crime in the “assisted” areas.

These practices, beyond the obvious consequences for the risk of contagion, imply legitimization of the police and of the armed forces, the consolidation of the food dependency and the acceptance of the almost non-existent capacity of the Social Organizations which today occupy positions in the Ministry of Social Development among other state agencies.

The religions, with obvious and indisputable goodwill, reproduce a mechanism of direct assistance with the support of the technology of the 21st century - traceability of what is delivered - but with the charitable scheme of the 19th century where the other continues to be a passive agent and receiver. The articulation of different religious expressions, especially between the Christian and Catholic churches, guarantees the initiative a reticular procedure that efficiently links need and satisfaction, but with the limitation of the duration and contingency of such assistance.

The companies have initiated a set of interventions as we have narrated, but the “public-private television festival” is the one with the most massive consequences. Three elements should be highlighted: a) the open and massive television channels are the vehicles of the initiative, reproducing the political economy of current morality, conflating the logic of the show, donation and enjoyment; b) the reproduction of diminished humanism and the trivialization of the good; and c) the consecration of state failures in the acquisition of supplies necessary to face the health crisis.

To close the interpretation that we have been making, we want to point towards the recognition of two intervention devices on the survival of the poorest and hungry.

The s+c+c device (state+churches+companies) that was undoubtedly designed to “alleviate” the crisis, has an unintended consequence of its action and performative

²⁰ The Hunger Games is a science fiction, action and drama movie. Directed by Gary Ross and based on the best-selling novel of the same name by Suzanne Collins. It stars Jennifer Lawrence, Josh Hutcherson, Elizabeth Banks, Liam Hemsworth, and Woody Harrelson.

²¹ [https://es.wikipedia.org/wiki/Los_juegos_del_hambre_\(pel%C3%ADcula\)#Recepci%C3%B3n](https://es.wikipedia.org/wiki/Los_juegos_del_hambre_(pel%C3%ADcula)#Recepci%C3%B3n)

effectiveness: it clearly shows that Argentina was already in crisis. It shows that the depth of the crisis is such that there is nothing more appropriate than the word Emergency to describe it: the weak institutional fabric emerges. And the S+I+E (State + Intervention + Emotions) device, understood as an active equation in interventions on hunger, functions in terms of the policies of sensibilities that the construction of specific emotions provides in the context of the pandemic and food.

The diminished humanism that characterizes the aforementioned spectacularization is constituted by “a set of practices that operate as a mechanism for suturing differences and inequalities between classes. These practices are characterized, among other features, by inverting the place of the collective and the individual, erasing their differences; dilute social cooperation regimes, replaced by blaming fictions; leave the receiving subjects in an iterative situation as a grantee; replace state presence with private action; and re-inaugurate philanthropy and private charity as mechanisms for attention to deficiencies” (Scribano 2014, p. 81).

Beyond the analysis provided here, and further, on what emerges when the crisis deepens, beyond the politics of perversion (Scribano, 2015) and further than meanness and selfishness, it is possible to perceive hundreds of thousands of interstitial practices that speak of a different way of understanding what is happening. Precisely, the fact that millions of people around the world and in Argentina have grasped the “logic of what emerges” implies that there are other opportunities not to repeat the spectacular militarization of a diminished humanism that always leaves us in a state of dependency.

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Chapter 492

THE ENEMY INSIDE

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ABSTRACT

The global world has recently been under attack from a new enemy, whose microscopic shape shuttered every aspect of human life: health, relations, social and economic frames. The COVID-19 outbreak can be compared to a war, with relation to the number of victims made worldwide. Still unknown in its several biological aspects, Coronavirus is currently going to update the concept of enemy. As I intend to argue, the pandemic brought to the forefront the idea of *enemy as an insider which constantly interacts with the host*. The enemy can be attacked only assuming it, making it part of both the individual body and the social body. According to this perspective immunization cannot be seen in terms of an exemption but properly as an inclusion. My reasoning starts from a short account of the classic paradigm of friend/enemy sketched by Schmitt (1932) and developed by Vitale (1992) in order to show the novelty of the ‘enemy inside.’ Then I’ll take in consideration the processes that give rise to immunization, through the lens of General System Thinking (Urbani Ulivi, 2019) that better fit the purpose to explore such a complex topic. I’ll reach the conclusion that immunization makes the enemy (virus) and the host (the biological substratum) adversaries: this dynamic, by reducing the dangerous potential of enemy, puts it under control. Thus, any process of immunization can be interpreted as the making of a community, differently from Esposito’s theory (1998; 2001) of a sharp distinction between *immunitas* and *communitas* (immunity/community).

Keywords: coronavirus, enemy, conflict, immunization, immunity, community

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UNDER ATTACK OF A VIRAL ENEMY¹

An epidemic plague initially focused on China, affected the world as never before in the last century. A short account of it is necessary before investigating the topic of the present paper. The Coronavirus Disease 19 (COVID-19) outbreak has brought about a radical turn of the social, economic, and cultural scenario since January 2020. The speed of the contagion has spread faster than the SARS epidemic rush in 2009 so that the Chinese Government decided to lock down Wuhan, the main town of the Hubei region. Although the report from China profiled a red alert from the very beginning of the epidemic emergency, it took time before the WHO (World Health Organization) declared that the epidemic outbreak was turning into a global pandemic. Face masks, gloves, special protection and careful attention to cleaning have become new social practices for everybody. After struggling against the viral attack, the world is aware that the war is far from over and a new enemy is taking the scene. The micro-organism that affects all social levels in a macroscopic way is a case study also for philosophy and political sciences because it updates, with the power of an earthquake, models and frames that, after the pandemic, seem worn and inadequate.

The Virus as an Enemy: Limits of the Discourse

Since the very beginning, the Coronavirus pandemic has been equated by the media to a “public enemy number one” (Boseley, 2020), whose potential could be easily compared with that of terrorism, as the director-general of the World Health Organization Tedros Adhanom Ghebreyesus warned (“Viruses can have more powerful consequences than any terrorist action”). The media coverage focused on military metaphors for sketching its profile, so that COVID-19 was said to be the “biggest challenge since Second World War” (Angela Merkel, *The Telegraph*, 2020), “the invisible enemy” (James McAvoy, *Daily Mail*, 2020) who “moves among us unseen” (*The Conversation*, 2020) in the “frontline” (*The Guardian*).

The microscopic bio-organism is a veritable enemy for life because it moves inside blood circulation and the respiratory system. Differently from a parasite, which can be taken together as a companion, the virus immediately shows its hostile intentions to the guest, through a huge attack to the very heart of the life in itself. What makes the situation more complicated for COVID-19 is that, in the majority of the cases, the virus does not show itself with the unfriendly consequences of its deadly potential. As always happens for the phenomena described through metaphors, the war against COVID-19 highlights the limits of any discourse and the urgent need to know what sort of enemy coronavirus is. The conceptual difficulty that coronavirus designates does not only depend on the still unknown biological dynamics of the virus; as I intend to argue in my paper, the pandemic updated the notion of the enemy by introducing a substantial novelty within the traditional debate about this topic. More precisely, the pandemic provides us with a better understanding of how the concept of enemy works within the frame of the immunization processes, as will be explained in the following paragraphs.

Deeply interwoven with interdisciplinary implications, the term enemy is generally referred to an individual of whom to beware because of its dangerous potential. The notion of

¹ This investigation is dedicated to Mario Antonio Clerici, with whom I discussed the main argumentations of the present work.

the enemy makes primarily refers to the opposite of friend, as someone we can trust and deal with. On the psychological ground, an enemy is a subject who gives rise to a cluster of bad feelings – fear, anxiety, anguish, terror – which are expected to destabilize a single individual (Gosio, 2020) or a community (Ceri and Lorini, 2019; Schlee, 2010). In his pioneering investigation on the concept of the enemy, the *Der Begriff des Politischen* (1932), Schmitt assumes that it is the intensity of the degree of association/dissociation to decide who is ‘friend’ (*Freund*) or ‘enemy’ (*Feind*) in political terms.

A very complex word, the enemy is rooted in the Latin word *inimicus*, formed by the negative element *in-*; hence, an enemy is “what a friend is not.” In Slavic languages, where the enemy is *neprijatelj*, this conceptual framework is still relevant, different from the Latin and German languages, as noted by Vitale (1992). Schmitt shed light on the ‘private enemy,’ a concept that differs from the ‘public enemy’ (*Feind*) and the ‘other/stranger’ (*Fremde*). The best reference for framing a ‘private enemy’ can be found in the Latin word *hostis* [*host*], an ambiguous term where two semantic areas are deeply intertwined: the one belonging to the guest as someone who is accepted, included, recognized and another one dealing with the enemy, who gives rise to hostile behaviors against the community (Plumper and Neumayer, 2010).

What makes an enemy a ‘private foe’? The conceptual field of *hostis* embraces the main idea, among others, which deals with the domestic frame in which both the guest and the host are dwelling. It may be concluded that the ambiguity that entails the term is strictly related to the kind of relationship existing between two subjects, both within a commonplace. Despite the rough description, this passage is highly relevant in the perspective of this current investigation, because it could be applied to the immunization process, in order to prove that COVID-19 brought in to act a private enemy, a contemporary *hostis* who currently inhabits the global fears.

What Kind of Enemy? The Identification of the Foe

Only the identification of the enemy makes the hostile individual a target against whom to act, with good chances of stopping it. As Aho underlines, groups socially construct enemies according to five steps, moving from the naming of the foe, the most crucial rank of the operation followed by legitimation, mythmaking, sedimentation and ritual (Aho, 2010). Profiling the enemy in the process, often questioned (Lyon, 2003, 2007), through which the ‘public enemy’ is set up. It is proper at this point of the process that the traditional distinction between 1) enemy and 2) friend makes sense. When the foe is detachable, community glues together against it and empowers itself (Schlee, 2010). This dynamic, on which the classical idea of war is based, has been completely surpassed in the last two decades by global conflicts and especially by the war on terrorism, where the difficulty to focus on a visible enemy gave rise to the new categories of the ‘terrorists from next door’ and the ‘lone wolves’ (Fisogni, 2014, 2019).

In the struggle against a pandemic, as in any conflict, the need to focus on the public foe is necessary to delete it. When scientific investigations proved unable to forge biochemical weapons to flatten it, superstition and rage easily took their place. During the bubonic plague that struck Milan, in Italy, in 1630, the plague spreaders (the *untori*) were hunted and executed. These persons, as Italian leading novelist Alessandro Manzoni reported in the *Infamous Column* (*La storia della Colonna infame*, 1843), were innocent but reputed guilty by

the crowd. The necessity of identifying them as ‘public enemies’ by the social community and the execution that occurred on the public square, was endorsed by the Milanese judges although it was illegal (Ciacca, 1985). As this episode witnesses, the wish to shape the enemy goes along with the necessity to bring a scapegoat onto the stage.

According to the victimization hypothesis theorized by Girard (1982), even if an innocent is going to be executed, the act is expected to solve a social crisis through exceptional measures that surpass any prescribed laws.

The COVID-19 pandemic updated this frame more softly. The single scapegoat, which is identified and then destroyed by the enemy, has been replaced by the collective ritual of wearing a face mask. Behind a behaviour due to the collective wealth, a powerful metaphorical operation for targeting the enemy can be noticed. In a pandemic, everyone can be seen as a potential enemy and a virus spreader. At the same time, anybody may be a victim of the virus itself. The two grounds of the phenomenon interfere, interact and are faced up together. As it happens with someone guilty for having committed a crime, in the lockdown as well as in the quarantine people have been imprisoned at home for weeks and have to abdicate several freedoms guaranteed by civil laws (Campi, 2020). We all were protected, we all had to guard against the enemy from the next door.

In the bubonic plague of 1630 ordinary justice was left outside tribunals, as Manzoni underlined, for allowing the public rage to compensate the frustration of coping with an epidemic that took nearly 50% of Milan’s population. Although the constitutional laws of democratic countries consider several freedoms as unquestionable, social or pandemic emergencies, as happened within the Coronavirus outbreak, it nevertheless tends to inhibit several personal rights for the sake of public health. The lockdown experienced worldwide made it visible on a global scale. We are now in the condition to move into a further stage that will allow us to highlight the main novelty of the concept of enemy provided by the COVID-19. As I intend to argue, the pandemic brought on the scene the idea of the enemy as an insider. The enemy can be attacked by only assuming it, making it part of both the individual body and the social body. Hence, the topic of immunization becomes very key to reshaping this issue.

Immunization as the Integration between Host and Enemy

Immunization is a recurrent topic within the Coronavirus pandemic. In the biomedical language, it is the process that brings immunity or protection to the living organism. This kind of response, which is the specific reaction of the immune system to a pathogen, allows the system to generate an immunological memory that keeps the individual safe from the risk of getting infected by the same virus or bacteria. The second relevant process related to the immune system is its innate response to pathogenic attacks, by the immediate mobilization of cells against infection.

The origin of immunology as a science dates the inoculation of cowpox introduced by Jenner against smallpox in 1796; however, it should be ascribed to Pasteur the idea of inducing immunity throughout attenuated microorganism (vaccination) in 1880.

Mainly regarded as “a complex mechanism of integration of microbes into the cell community of the host” (Igea, 2015: 55), the term immunity is frequently applied to several different fields. During the last two decades, the concept expanded from the biological domain into political philosophy giving rise to a new field of investigations, especially in

Italy where Esposito theorized (1998, 2001) immunity as the paradigm for globalization. In his analysis, immunity and community share the idea of an obligation, a *munus* in Latin, on which a couple of terms is semantically rooted. The immune person is someone who got free from the obligation and, for it, has temporary or placed himself outside the community. Although immunity is expected to safeguard the individual/social body, Esposito argues that it is at the same time something that inhibits the development of a community and, over a certain degree, it can destroy social cohesion.

As Igea argued from the biological perspective, there is a gap between “what ‘immunity’ etymologically means and what the term implies today” (2015: 55), however, the conceptual core of the word maintained certain stability throughout its semantic changes: it refers to an exemption/freedom of duties for some individuals with which other subjects have to comply. It is in fact in virtue of this particular condition, within the social/political discourse, that the social *community often looks at the immune as an outsider*, someone about whom to be cautious for his being out, free from a collective *munus*. Within the frame of the COVID-19 pandemic, an immune individual is someone free from the infectious disease, nevertheless, he remains involved at large with the hostile agent for having hosted it. The infection has changed his biological structure and made of him the ‘other,’ that’s to say a subject that stands apart from the community and can be included only with a watchful approach.

At this point in the paper, a question arises. *Why does a community tend to isolate immune subjects?* They felt as potentially hostile as if they were still in relation with the pathogenic agent. I call this condition ‘the enemy inside.’ In the next paragraph, I’ll seek to get deeper into this insight through the lens of General System Thinking.

Processes of Immunization: from Exemption to Integration

In this section, I aim to clarify the concept of the ‘enemy inside,’ as a result of the immunization process. This conceptual frame cannot be understood according to linear thinking because, as already seen in Esposito’s theory, immunity and community stand apart as separate poles. Therefore, I suggest changing the interpretative paradigm, by investigating this topic through the lens of General System Thinking (Urbani Ulivi, 2019; Minati and Pessa, 2019).

According to GST, living phenomena are considered in term of open systems; it means that they are not mere aggregations or sums of parts, but primarily dynamic units, to which belong qualities that depend upon many interactions and processes, internal or external to the system, the continuous exchange with the environment that gives rise to systemic properties or II type systemic properties. According to this philosophical perspective, immunization cannot be considered first and foremost an isolated phenomenon which stands outside a community. Living systems, as human individuals or societies, are coherent structures engaged in “a continual (extended) critical transition” (Minati, 2019: 16). This instability is due to the degree of organization that is “maintained by the integration/regulation activities of the organism that is by its global coherent structure.”

It follows that immunization is a twofold shaped phenomenon: it is a dynamic system involved in a permanent critical transition. If we come back to Esposito’s dualistic frame (1998, 2001), it becomes clearer why the immune subject cannot be fully integrated by the community. An immune is someone who experienced a radical change in the very intimate texture of the system. Thus, he can change his mind, he can assume behaviors and beliefs that

are different from the ones shared by the social group and, for it, they may destabilize society in reason of his ‘permanent critical transition.’ *Communitas* of non-immune people, on the contrary, maintains its properties stable over time, “including evolutionary patterns” (Minati, 2019: 16). A community tends to glue together its components, leaving outside whatever can destabilize it, within an incessant demand of self-protection. However, being involved in several processes, a community needs preventive immunization from any thrust that might undermine its coherence.

The contradiction that *immunitas/communitas* paradigm brings to surface can be easily solved, within the frame of General System Thinking, by taking in account the conflict between 1) transition and 2) coherence of change and stability, two aspects that are deeply intertwined in open systems that pertain to life’s domain.

At this point in the discussion, we can take another step into the discussion.

Immune people and non-immune individuals can be equated to systems with different dynamics, which constantly interact. They show different degrees of reactivity to the thrust of the environment. Immunization belongs to the domain of dissipative structures, referring to the coexistence of change and stability (Prigogine, 1967, 1981, 1999). As Minati notes, non-equilibrium conditions allow the emergence of ordered structure. Furthermore, the stability of dissipative structures “is due to their ability to transfer a large amount of entropy to their environment” (Minati, 2019: 33). Concerning a community system, where stability is provided primarily by coherence, an immunization system constantly transfers energy outside itself, it is more dynamic and for it, less predictable. At this point, we can better grasp why immune subjects are perceived as destabilizing although immunity is a necessary step for protecting a social group: their access to the community brings into it the sphere of what is *out* and can be hostile *in* a community because it is not known.

In the next paragraph, we’ll focus on these two poles.

In and Out, Two Conflicting Poles?

The terms *in* and *out*, which take a relevant part in the friend/enemy discourse also belongs to the immunization process and, at large, to the dissipative systems, to which also immunization belongs. This consideration is highly relevant in order to move from the biological frame into the political environment. Before discussing this passage, I briefly recall that a *community* is the typical in-group society, where the individual share common values, laws, habits, cultures and way of life. The notion of humanity itself “can be understood as a set of concepts related by family resemblances” (M. Bilewicz, A. Bilewicz, 2012: 341). If commonalities are expected to paste together a society, they need to be constantly reinforced by differences which belong to the ‘out’ environment. The out-group is perceived as stranger, different, hostile. Qualities that properly belong to the semantic field of ‘enemy,’ as also Schmitt underlined in *Der Begriff des Politischen*, by assuming that *Fremde*” was primarily the other, the stranger” (Vitale, 1992: 92, translation is mine). The divide between the two poles is sharp in social dynamics, however in terms of open system processes, the two poles are closely involved in relation, in a continually in-out-in-out interaction.

In the dissipative systems – where change and stability coexist as seen before – the environment is a perfect copy of the system because of the interacting fluxes that move from both. It is the case, for example, of human brain dynamics, where environment is generally called ‘the double’ of the brain (Vitiello, 2010: 115). The entrance/exit streams have to

balance to allow the stability of their interrelation. If the problem of enemy is considered from this perspective through the lens of General System Thinking, the terms *in/out* can hardly be separated. They are activities whose interaction is needed for allowing coherence. What makes it difficult for the community to include immunity and the related phenomena within its borders is the possibility to cope with processes that may bring about changes in the social environment. From the GST perspective, this is the particular kind of interactions that belong to any dissipative system. A community tends to prefer compatibility to irregularity or unpredictability. When the interaction is provided by dissipative systems like immunization, where the poles *in/out* are in constant relation, the possibilities that new emergences emerge is highly predictable. In terms of social dynamics, deep changes are expected to affect the community. Immunization, being an emergence as “a continuous, irregular, and unpredictable process of acquisition of non-equivalent (...) properties” gives rise to II type systemic properties.

This passage focuses on the possibility that immunization can eventually allow the community to become steadier through internal changes. What the dynamics previously explored highlight a profile which seems suspended between safety and danger, the conflict between friend and enemy.

Let's turn to our topic: are *in/out* conflicting poles?

An immune individual cannot be considered an enemy anymore but it is not fully a friend, it is a non-friend. It is a concept that is attested in the Slavic languages, as Vitale underlined (1992) and Schmitt intuitively grasped in *Der Begriff des Politischen*. As the semantic roots from Indo-European domain highlight, an enemy originally refers to someone who stands outside the peaceful community, which is ruled by divine laws. Differently from the enemy, who is permanently in conflict with the State, a non-enemy plays a constructive role for the community because, as Vitale assumes, political friendship can be built only in presence of him (Vitale, 1992: 90). While the enemy questions the existence of the community, the non-friend presents a variety of shades, within a psychological frame that enhances the processes of dialogue/understanding. As Vitale notes, the “non-friend should be seen as an eminently psychological relation” (1992: 93). Nevertheless, Schmitt had already grasped in his seminal work – as Portinaro argues (1992) – that legacy rooted on a common offspring were too feeble for grounding a valuable theory of political friendship.

I'm now able to formulate my argument and to set my argumentation on more secure ground. At this point in the paper, we should move forward, into the very heart of the immunization process, which will surprisingly reveal a community-like environment more than an exemption place. This premise will bring about a change in the notion of an enemy.

Immunization: a Process of Integration. How the Enemy Builds Up Friend

As Vitale assumes, “the category of friend derives from a psychological process of auto-ascription that is possible only in virtue of the counter opposition” to the enemy (1992: 105, translation is mine). It follows that “it is impossible to elaborate a theory of the political friend (...) that prescind from the opposition to the enemy.” Thus, a conflict always goes along with the need of sharing a common environment, at least from a psychological perspective. I argue that immunization is very key for highlighting this interconnection. By bringing inside the enemy, immunization clarifies the process that turns hostility into peaceful coexistence, or a permanent transition from conflict to regulation from the systemic outlook.

This dynamic maintains a coherent level of organization because of its systemic novelty: it is an emergence, or a II type systemic property, which does not belong to the enemy (out), nor to the community of friends (in) but always need to be fed by both systems. We are at the very heart of the problem investigated in this paper.

It can be expressed by the question: *how does the category of 'friend' be built by 'the enemy inside'?*

The first step is to highlight on *coherence*, which is the process that supports any emergence. In the biological frame of living entities, for instance, health is the state of maximum coherence; on the contrary, any disease gives rise to the isolation of a part, or function, or property of the whole system from the systemic unitary and general coherence. The virus, as a pathogenic agent, by infiltrating within the bodily system as an enemy, disconnects the previous harmonic balance of the bodily system. The loss of coherence clarifies why a process of emergence may be extinguished as the consequence of an inconsistent organization. At the same time, coherence also supports the unitary and integrated response of the system to disturbances/perturbations, avoiding isolation or the independent organization of some parts or functions. Both the innate and the adaptive response of the immune system work as such against the infection.

If the individual 1) is strong enough to react to the virus or 2) a vaccine has been injected into his body, the biological response against the pathogenic agent will not simply destroy it; it will give rise to a reaction that reconnects – in a completely new and different way – functions and properties previously being offended. This leading reaction, within a frame where structural incompleteness is a condition of the process, makes an emergence to be possible. Thus, the enemy, as a process of dissipation and rupture, is expected to provide a stronger coherence in the system.

An enemy could be regarded as a change enabler, an activator of emergence.

We can refer once again to biology, focusing on the parasite/host interaction. The host is commonly perceived as an organism that harbors another living entity inside its specific environment. Worth noting that the Latin word *hostis* resonates in the word *host* with its inner ambiguity of either 1) a guest and 2) a hostile attacker. This set of considerations provides a valuable premise to assume that the process of immunization, where a “friend” of the organism (the host) is targeted by an “enemy” (the pathogen, the virus) is a peculiar battlefield where each attack becomes an integration, in an incessant dynamic that keeps the organism safe or the reverse. From this point of view, immunity cannot be the opposite of a community because integration is a process that lies at the very heart of both. The notion of ‘enemy inside’ inhabits this environment.

At this point in the discussion, it would be easier to understand why this integration/connection between an *enemy* and a *friend* (of the community) might be highly relevant for understanding how an enemy is expected to lose its destructive potential, turning into a non-friend. As Vitale noted, political friendship can be built through the enemy and only in virtue of this immunization process. If we look at the two poles (enemy/friend) as separate entities that never match or interact, we’ll never be able to solve the contradiction. On the contrary, as argued before, they are regarded in terms of open systems that interact. The immune system proves that pathogen/host interactions do not only exist but are part of the process. Criticism can be made, through a question: *how to move from the biology to the classic conflict dynamics?* I’ll reply by providing an argument that has been already briefly sketched by philosopher Derrida (1995) and now seems highly valuable to strengthen the idea

of the ‘enemy inside’ as a *trait d’union* between enemy and friend. It recalls, on the political discourse, what has been previously understood in the biological and systemic fields.

In his analysis of Schmitt’s *Der Begriff des Politischen*, Derrida assumed that the enemy is an individual who is entirely shaped by the conflict, according to what also Vitale underlined (1992). It is right there in the battlefield, within the crucial space of the frontline, that the foe becomes fully identifiable; however, while the *polemos* builds up the enemy’s identity, it also seems to do the reverse, forging a sort of commonality between the two parts in the battlefield. In Derrida’s view, this face-to-face condition is expected to delete any difference between enemy and friend. The making of *adversaries* is really what happens in virtue of the *polemos*, which brings together, as Derrida states “those two are opposed and it provides a historic figure for this *polemos* that brings enemies together as though they were conjoined in the extreme proximity of face-to-face” (p. 37). In the conflict, in other words, ‘enemy’ is no more a term that stands in opposition to ‘friend’; it turns into an adversary who *participates* in strengthening its identity as well as the one of the other adversaries who are now sharing the conflict experience. On the other hand, this frame highlights on how crucial it is “to construct a distance between soldiers and their enemies” in order “to be able to kill adversaries” (Grossman, 1995).

If we come back to immunization as a conflict that takes place within of the biological system of the individual against the virus, we understand that the enemy (the virus) is defeated when the body assumes some properties of the *enemy* itself, turning into the *adversary* of the virus. Hence, in the immunization battle, the enemy, which is “existentially something different and alien” (Schmitt, 1996: 27) makes its double: the adversary.

CONCLUSION

This paper was intended to focus on the novelty that COVID-19 brought into the discourse about the concept of enemy. As we noticed at the beginning, the metaphors of war are deeply related to the pandemic: what I sought to do, in my investigation, is to turn the limits in understanding the phenomenon into a fruitful resource to understand its opaque ground. I noticed that the concept of the enemy cannot be easily separated from the one of a friend, since the classic Schmitt’s theory (1932) to Vitale’s investigations on the non-friend, which introduced a more complex understanding of Schmitt traditional divide between (public) enemy, friend and private enemy.

Secondarily, I argued that the very idea of enemy, in the COVID-19 pandemic, should be about the immunization process, that’s to say with the battlefield where the conflict against the pathogen coronavirus is performed. Immunity, the condition provided by immunization, is a term that turned from biology into politics and philosophy, in opposition to community. As for the couple enemy/friend, the distinction between these two poles gives rise to a contradiction (Esposito, 1998; 2001). However, if we look at the COVID-19 outbreak scenario, we realize that – at least on the biological ground - immunity is not in conflict with the community. Thus, the idea of an ‘enemy inside’ which could be a relevant part of the process of immunization, kept on being shaped by the discussion.

A change of paradigm was due, to reach some valuable results. Far from being a universal key for grasping complexity, the systemic perspective might be seen as a toolkit to

solve some – not all – traditional philosophical problems, as the enemy/friend dual pole. According to the GST I could argue that immunization, which is a II type systemic property could be regarded as an integration more than an exemption. This idea, gained from the dynamics of dissipative systems can be found also in the biological dynamics of the pathogen/host interactions.

One of the most relevant insights that come from this passage is about the in/out poles, whose interaction is as relevant as their opposition. A further step was to assume that immunization, too, is a process of integration which may be highly relevant to clarify how the enemy builds up the friend, as Schmitt had already shown in his seminal essay (1932) but never developed, and Vitale (1992) integrated with an enlarged perspective on political psychology.

Finally, I noted that conflict is necessary to transform an enemy into an adversary: this is the very basis for making political friendship possible. Pacts can be done between adversaries, because they are a peer in the *polemos*, in virtue of being face-to-face on the frontline. Immunization is not simply the destruction of the foe; it is a more complex process that turns two parts in conflict into adversaries: thus, the enemy does not disappear completely; it turns into an adversary who can be controlled and can enhance the capacity of the reaction of the immune subject. Immunization is the phase in which the enemy is defeated according to a pact with him. Since the virus is an enemy outside the biological body the war cannot be won. What does this phenomenon say to the traditional debate about the concept of the enemy? It highlights the impossibility of making a sharp separation between enemy and friend, as if they were two separated poles, without any communication or any mutual exchange. Through the lens of the General System Thinking, friend and enemy are open systems that interact, especially in the immunization process, a veritable conflict where the two subjects/systems become adversaries. The adversary emerges as a II type systemic property that does not belong to any previous system but cannot be shaped without their mutual interactions.

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Chapter 493

PANDEMIC, INTERNET AND EMOTIONS: POLITICS OF SENSIBILITIES AND COMMODIFICATION OF AUDIENCES

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ABSTRACT

On March 11, 2019, the World Health Organization declared the status of a pandemic for the rapid expansion of COVID-19. In a short period of time, the daily lives of billions of people around the world would never be the same: the successive strategies that were adopted in different countries implied significant changes in most of the subjects' daily experiences, from the way of working to the family relationship itself. Most of the situations of interactions in the context of the pandemic are carried out in virtual contexts, and specifically through social networks. Thus, COVID-19 is imposed as a recurring "topic of discussion": WhatsApp groups, Facebook, etc. are filled with messages and discussions about it. Thinking in terms of social research, it is possible to imagine a Big Data strategy to analyze the traceability of messages, and to map the density of the circulation of information. However, it is also possible to ask ourselves some questions that seek the qualitative meanings of the practice of receiving and re-sending messages related to the subject, while taking into account its relationship with their form. In this direction, the objective of this chapter is to analyze the emotions linked to the interactions in social networks associated with COVID-19. To do this, we applied a self-administered survey to 307 respondents in 17 European countries, selected using the snowball sampling technique between March 17th and April 18th, where we inquired about how people feel when they receive/send information related to the pandemic. Given the multiple possible interpretations, we are interested in linking some discussions around digital labor, that is, the ability of social networks to market to an audience. This means emphasizing one of the ways these media have, in the framework of the renewed

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and massive situations of digital interaction, of capturing people's energies and transforming them into merchandise (Fuchs, 2014). The analysis focuses on the fact that what is commercialized is the willingness to be part of a group that receives messages, so it is not enough to just know the quantifiable dimension of the action of forwarding, but also what is at stake is the relationship between the objective field and the willingness of the subjects to be part of these audiences. Therefore, beyond the re-production of the practice (whether it is re-sent or not re-sent), we are interested here in exploring how the qualitative sense that agents give to it could be associated with policies of digital sensibilities (Scribano and Lisdero, 2019). That is, perceptions framed in specific regimes of sensibilities that allow connecting bodily geometries with grammars of action (Scribano, 2017) that have a specific support and content in the digital field. This allows us to advance in the description of "platform sensibilities" as a sign of the ongoing social structuration processes.

INTRODUCTION

On March 11th, 2019, the World Health Organization declared the status of a pandemic for the rapid expansion of COVID-19. In a short period of time, the daily lives of billions of people around the world would never be the same: the successive strategies that were adopted in different countries implied significant changes in most of the subjects' daily experiences, from the way of working to the family relationship itself.

Most of the situations of interactions in the context of the pandemic are carried out in virtual contexts, and specifically through social networks. Thus, COVID-19 is imposed as a recurring "topic of discussion": WhatsApp groups, Facebook, etc. they filled with messages and discussions about it. Thinking in terms of social research, it is possible to imagine a Big Data strategy to analyze the traceability of messages, and to map the density of the circulation of information. However, it is also possible to ask ourselves some questions that seek the qualitative meanings of the practice of receiving and re-sending messages related to the subject, while taking into account its relationship with their form. In this direction, the objective of this chapter is to analyze the emotions linked to the interactions in social networks associated with COVID-19. To do this, we applied a self-administered survey to 307 respondents in 17 European countries, selected using the snowball sampling technique between March 17th and April 18th, where we asked about how people feel when they receive/send information related to the pandemic. Given the multiple possible interpretations, we are interested in linking some discussions around digital labor, that is, the ability of social networks to commodify an audience (Fuchs, 2014). This means emphasizing one of the ways these media have, in the framework of the renewed and massive situations of digital interaction, of capturing people's energies and transforming them into a commodity. The analysis focuses on the fact that what is commercialized is the willingness to be part of a group that receives messages, so it is not enough to just know the quantifiable dimension of the action of forwarding, but also what is at stake is the relationship between the objective field and the willingness of the subjects to be part of these audiences. Therefore, beyond the re-production of the practice (whether it is re-sent or not re-sent), we are interested here in exploring how the qualitative sense that agents give to it could be associated with policies of digital sensibilities (Scribano and Lisdero, 2019). That is, perceptions framed in specific regimes of sensibilities that allow connecting bodily geometries with grammars of action

(Scribano, 2017) that have a specific support and content in the digital field. This allows us to advance in the description of “platform sensibilities” as a sign of the ongoing social structuration processes.

THE EMOTIONAL COMMODIFICATION OF THE AUDIENCE

Given the breadth of the problem linked to the relationship between emotions and pandemic, we have focused on the specificity of digital labor, and its links with the processes of commodification enabled in digital media. To do so, we will rely on the analysis of empirical data built from the "Covid and Emotions" Survey (CIES). This study was undertaken using a non-probabilistic, exploratory design, where the snowball technique was used for the construction of the sample. A self-administered form was applied, elaborated from the "google form" tool, which contains a series of closed and open questions related to the relationship between emotions and COVID-19 (in addition to other general information). Thus, a total of 307 responses were collected between March 17th and April 18th. Most of the responses are concentrated in Italy (152 cases, or 49.5%), Spain (62 cases, or 20.2%), France (33 cases, or 10.6%), United Kingdom (11 cases, 3.5%), Portugal (11 cases, 3.5%), and Russia (10 cases, 3.2%). Other countries from which responses were received are Belgium, Austria, Germany, Greece, Ireland, Sweden, Hungary, Finland, Luxembourg, Czech Republic and the Netherlands. The age of the respondents ranges from 17 to 73 years, grouped as follows: 23.1% are between 17 and 25 years; 32.2% are between 26 and 35 years; 24.8% are between 36 and 45 years; 13% are between 46 and 55 years; 4.2% are between 56 and 65 years, and 2.6% are 66 years of age or older (about 57% of the sample is between 26 and 46 years). Sixty-four percent (64%) of the respondents are women, while 33.2% are men (1.9% responded "Prefer not to say"). With respect to educational level, 89% of the sample has completed university studies. The main occupations recorded are: "Professional, technical and related worker" (28.3%), "Student" (27.7%), "Government/public sector" (14%), "Administrative, managerial" (9.4%), "Unemployed/looking for work" (4.6%), "Other service worker" (3.6%), "Sales" (3.3%), "Home-based worker/subcontractor" (2.6%), and "Housework" (1.6%).

In this chapter we will focus on two questions: "Have you re-sent information related to COVID-19 through WhatsApp, We-Chat, Facebook, Twitter, Instagram or other social networks?"; and "Why?." Next, we advance making explicit an analytical proposal, and presenting some preliminary results that make it possible to draw some interpretative lines regarding the proposed objectives.

Digital Labor, Audience Commodification, and Emotional Work: Contributions from Sociology of Sensibilities

Many of the interaction situations in the context of the pandemic are carried out through digital media, and specifically through social networks. Within this framework, COVID-19, as well as all the "news" that were installed about it, was imposed as a "topic of discussion":

WhatsApp groups, Facebook, Twitter, Instagram, TikTok, and in general the most popular social networks were invaded by messages and discussions about it.

A first interesting question could be "what does these media, which we summarize here as Social Networks (WhatsApp, Facebook, Twitter, etc.) have in common?" In what sense does the capacity of digital media to "commodify an audience" expand from the practices involved in the use of these social networks? Recovering the analysis of Dallas Smythes (1977) on the notion of audience commodity, Fuchs (2014) observes:

"(...) the rise of user-generated content, free access social networking platforms and other free access platforms that yield profit by online advertisement—a development subsumed under categories such as Web 2.0, social software and social networking sites—the web seems to come close to accumulation strategies employed by capital on traditional mass media like TV or radio. Users who upload photos and other images, write wall postings and comments, send mail to their contacts, accumulate friends or browse other profiles on Facebook constitute an audience commodity that is sold to advertisers. The difference between the audience commodity on traditional mass media and on the Internet is that in the latter case the users are also content producers, there is user-generated content and the users engage in permanent creative activity, communication, community building and content production. That the users are more active on the Internet than in the reception of TV or radio content is due to the decentralized structure of the Internet that allows many-to-many communication. Because of the permanent activity of the recipients and their status as prosumers, we can say that in the case of corporate social media the audience commodity is an Internet prosumer commodity. (Fuchs 2010b)" (100)

Within the framework of a sociology of sensibilities¹, the discussion raised at the crossroads between digital labor² and the commodification of audiences opens up the possibility of asking ourselves about the bodily energies that support these renewed processes of capitalist accumulation. For this we need to incorporate the notion of emotional work:

¹ Schematically, we could say that the aforementioned Sociology of Sensibilities is inscribed in a particular perspective (Scribano, 2017; Scribano and Lisdero, 2019) that recovers the centrality of the body/emotions in social theory in order to understand the current processes of social structuration. The idea of body seeks to stress an individual body (bio-physical substrate), a subjective body and a social body. Emotions can be seen as the puzzle that comes as an action and effect of feeling or sensation: these situate in the states of feeling the world that allow the organization of perceptions associated with socially constructed forms of sensations. From this we understand "bodily energy" as the result of the exchange of physiological systems and biological processes associated with the durability of the individual body, but also as the (insubstantial) substratum of the processes of value creation in societies. The work in Western capitalist history can be historicized in an important dimension of its expression, starting from the constant re-inventions of the corporal energies, in consonance with the metabolic mechanisms linked to the accumulation regimes. Within this framework of general understanding, we think that the consequences and central effects of the relationships between Society 4.0, digital labor and the social structuration process are the changes in the politics of sensibilities, understood as the set of cognitive-affective social practices tending to the production, management and reproduction of horizons of action, disposition and cognition. (Scribano, 2017, Scribano and Lisdero, 2019).

² Three analytical nodes are differentiated in the available research on the notion of digital labour: (a) the discussion about the objects of expropriation in digital processes, highlighting the differential place occupied by the body and knowledge within the framework of a renewed discussion about the theory of value (Fuchs 2014; Fumagalli, 2015; Dyer-Witheford 2015; Morini and Fumagalli 2010; Huws 2016; Andrejevic 2012; Fisher 2012; Fisher and Fuchs 2015; Heam 2010; Vercellone 2006); (b) discussions about work processes and their material supports (time/space coordination of productive interactions), in the framework of which the notions of "Prosumption" (Ritzer and Jurgenson 2010), or "Playbour/Gamebour" (Arwid 2015), "free labour" (Newfoundland 2013; Kosnik 2013) "unpaid labour" (Fuchs, 2014), and cooperative/collaborative work (Meil and Kirov, 2017) are discussed. The idea of a "platform capitalism" (Cingolani, 2016) characterized by the growing place of the so-called "sharing economy" (Irani 2015; Cingolani 2016) emerges here. (c) Finally, a third group of researches deals with the constitution of the subjects that work, highlighting intensification, dependence (global), feminization and neo-taylorization (Huws, 2016), precariousness (Dyer-Witheford, 2015) and heterogeneity (types of organization, environments, contractual relations) (Fuchs and Sandoval, 2015). The perspective proposed here starting from the discussion about the body/emotions linked to digital labour, and seeks to establish the mediations between the vitality of bodies and emotions as an object of exploitation.

early on, A. Hirschfeld (1983) analyzed flight attendants and insurance salesmen by taking as a focus of reflection the connections between the emotions produced in work and the processes of value production. The author proposes that there is an institutionalization of the emotional order of the work environment on the intimate sphere, where the management of affects in the labor world begins to possess a certain predetermined and coercive character. Emotions are no longer elaborated from a discreet and personal management, and become instead a work that is marketed to the public. Precisely his study shows that many workers now do not simply sell their physical strength, nor their knowledge or rational capacity, but they also place their emotions on the market. Taking up Hirschfeld's idea, we are interested here in asking about the expansion and mutation of this trend, specifically in the context of the expansion of digital labor.

It would be impossible in this space to expand on the various responses that have been offered regarding this relationship (digital labor - emotional work): we ourselves have provided some analytical keys in order to make explicit the possible contributions of a sociology of sensibilities in the complexities of the notion of digital labor (Scribano and Lisdero, 2019). In this direction, the centrality of emotional work in our societies could be connected to the observations that Fuchs makes about the processes of value creation in digital labor assumed in social networks. In this regard, Fuchs notes:

“Whereas wage labour is coerced by the threat of physical violence (the threat is death because of the lack of being able to purchase and consume goods), audience labour is coerced by ideological violence (the threat is to have fewer social contacts because of missing information from the media and missing communication capacities that are needed for sustaining social relations). (...) If for example people stop using Facebook and social networking sites, they may miss certain social contact opportunities. They can refuse to become a Facebook worker, just like an employee can refuse to work for a wage, but they may as a consequence suffer social disadvantages in society. Commercial media coerce individuals to use them.” (2014: 90-91)

“(...) Marx argues that for being considered a productive worker, “it is no longer necessary for the individual himself to put his hand to the object; it is sufficient for him to be an organ of the collective labourer, and to perform any one of its subordinate functions” (ibid., 643–644). This means that productive labour understood this way implies that a worker who contributes to a “social product” that is controlled by a capitalist and is the “joint product of a collective labourer” (ibid., 643) is an exploited worker, no matter if s/he receives a wage for it or not. S/he is part of a collective or social worker. (...) “(2014: 109)

“Social media users are double objects of commodification: they are commodities themselves and through this commodification their consciousness becomes, while online, permanently exposed to commodity logic in the form of advertisements. Most online time is advertising time “(2014: 101)

In the quoted fragments, we highlight three elements: 1. the extortion associated with the “ideological violence” to which the “digital workers” are subjected is experienced from the “fewer social contacts” and “the suffering social disadvantages,” which puts the “body” at the center of the scene as the origin of social relations, and as the privileged “platform” where the social processes of production begin and end; 2. the productivity of connection, as well as the exploitation associated with the mutations of the value chain, needs to be explained from a collective body - a “living organ” that as the engine of life is captured in its productivity from a sociability that requires a particular “way of being”; and 3. precisely this is what we could read behind the idea of “commodification of consciousness,” a subsidiary of the digital moment of the “consciousness Industry” (Hans Magnus Enzensberger, in Fuchs 2014). Accommodating the collective body of digital workers to the demands of the 4.0 “consciousness industry” implies a self-production that we could associate with “emotional work.” The key to this association is to think about embodied consciousnesses: emotions

connect the sensitive and biographical expression of bodies with the social trends from which these bodies are marked. Contrary to the notions that consecrate the body-mind division, our proposal lies in connecting digital labor with emotional work to emphasize that affects are re-invented as "productive muscle." This has a differential characteristic in a world where social networks have colonized the internal planet: this "emotional muscle" cannot be thought of without the digital context. Thus, thinking about emotions in the context of social networks allows us to take a relational look at the "collective body" of digital workers as the (insubstantial) substratum of the processes of value creation and valorization from the affects that are commodified in/by social networks. We propose here to think about the commodification of affects as a necessary element to understand the "commodification of audience."

In order to operationalize this discussion, and advance in an analytical approach that allows us to put it in the context of some emerging empirical evidence, we will recover the two questions referred to in the survey on "Emotions and Covid-19." In this direction, we could think that the first question (Have you re-sent information related to "COVID-19" on social networks?) is an indicator of the processes of "commodification of audiences" in a double sense: in the first place it is an objective indicator of the potential of future communications, as a multiplier possibility to demarcate and build the audience (by amplifying interactions). Secondly, even when the subjects do not re-send the message, they are still not exempt from reproducing audience commodification, as long as they remain interacting in the digital medium, and therefore, building (possibly) data that are captured, processed and sold as commodities by the corporations that control the digital interactions. We will call this second dimension "limited re-production" of the audience, to differentiate it from the alluded to "extended re-production," although we must also clarify that the range of possibilities of digital relations should also include the possibility that the subjects can remove this logic from the commodity. However, we will not analyze this dimension here, since our objective is to explore the "emotional environment" that can be linked to the commodification of the audience.

It is not enough just to know whether or not the subjects re-sent messages: one may not have re-sent but even receiving it is part of a chain whose objective conditions of reproduction far exceed the calculation of individual behaviors. In other words, what is at stake is the relationship between the objective field and the willingness of the subjects to be part of those audiences. Therefore, beyond the re-production of the practice (whether or not to re-send), exploring the meaning that the agents imprint on it is more interesting from our perspective, inasmuch as in this set of dispositions they express the objective conditions of this chain of value production.

Thus, the information contained in the second question is important: "why did you decide to send/not send?." Since this is an open question, we chose to recategorize the answers received by registering them as an indicator of the "policies of sensibilities," that is, by differentiating in them (only for analytical purposes) the cognitive content from the affective one. The first dimension grouped the responses according to four emerging logics: 1. "Logic of Communication" - the meaning of the action is related to different motives aimed at facilitating communication, clarifying information, denouncing fake news, avoiding "noise" in communication, and so on e.g., "to inform people about fake news"; 2. "Logic of knowledge" - the sense of action is related to the search for intervention in the processes from which to approach the "truth" (about what is happening) e.g., "share knowledge"; 3. "Logic of

responsibility" - the sense of action emphasizes the consequences of individual actions aimed at the achievement of the "common good" e.g., "because I don't want to help spread fear"; and 4. "Logic of imitation" - the reason for action is to ensure a minimum degree of interaction without reflecting on the meaning of the action, imitation, or entertainment e.g., "to have a conversation."

The second dimension mentioned (affective) was reconstructed by identifying six groups of "feelings practices": 1. "Knowledge/awareness" - this includes feelings practices associated with the need to "become aware" (e.g., "because it's important for people who don't know what the problems are"); 2. "Trust" - sensations linked to trust/distrust with respect to people, institutions, etc. (e.g., "I'm not sure of its truth"); 3. Feeling useful/Care/Interest/Solidarity-Hope" - a set of feeling practices that, although they have certain peculiarities, all highlight the personal affective involvement in the consideration and possibility of action oriented towards an "other" (e.g., "I feel like adding some help for the society"); 4. "Love/friendship" - sensations where what is emphasized is the bond of love or friendship (e.g., "to inform my friend about some topic"); 5. "Fear/Anxiety" (e.g., "I'm against panic"); 6. "Entertainment": practices of feeling associated with the sensation of entertainment (e.g., "For sharing ... coronavirus jokes").

We would like to offer some clarifications here: the construction of categories for the dimensions mentioned was undertaken aiming at the greatest capacity for grouping them, fulfilling each one of the options the necessary characteristics of exhaustiveness and mutual exclusion. In this sense, the imputation of meaning in the re-coding process emphasized the identification of the cognitive logics and "feeling practices" predominant in the expressions made by the subjects in the form. The proposed categories constitute an analytical effort to reduce the complexity of meaning that these expressions embody.

Finally, before presenting some preliminary results from the analytical proposal presented, it would be relevant to say something more about our point of arrival, an issue that we could discuss based on the relationship between policies of sensibilities – the geometry of bodies and grammars of digital actions³. In other words, we would like to ask ourselves here in what sense the constructed information informs us about the perceptions that the subjects have about their practice (condensing and paradigmatic linked to networks and coronaviruses), and how those perceptions are framed in specific regimes of sensibilities that allow connecting geometries with possible digital grammars.

As a summary, the analytical proposal presented here could be summarized as follows (Figure 1):

Presentation of Data and Preliminary Readings

The study shows that a significant majority of people (71% of the respondents) resent messages linked to "COVID-19" through their social networks (Figure 2). If we take the reasons for these actions as a group between those who forwarded and those who did not forward, we find that:

³ The notion of the geometry of bodies refers us to the dispositions that "shape" society from particular coordinates of the social positioning of bodies. For its part, the idea of the "grammar of actions" allows us to access the common ways of giving meaning to social practices in-and-by-the bodies referred to (Scribano, 2004b).

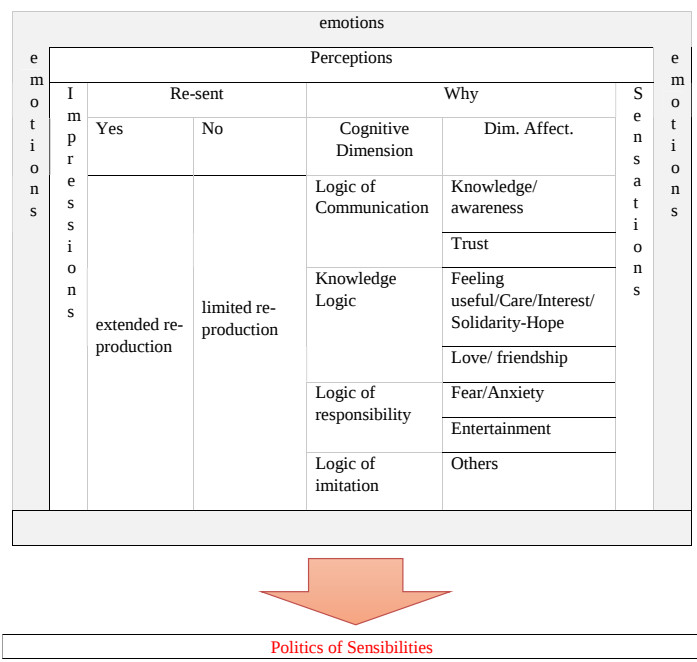
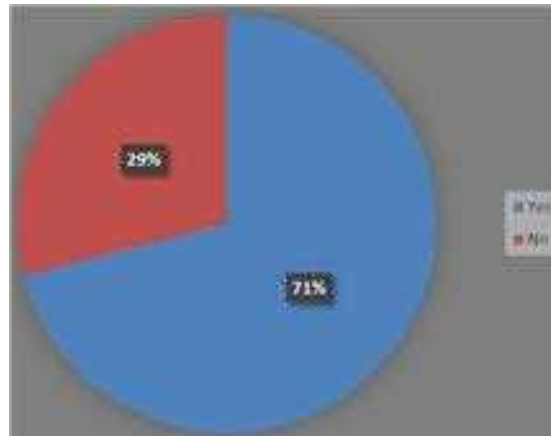


Figure 1. Analytical proposal.

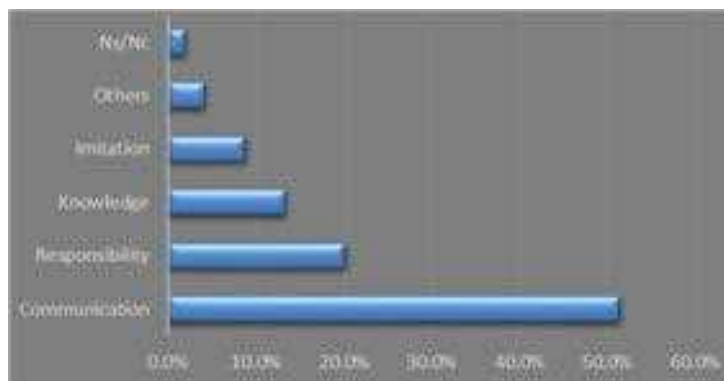
- Regarding the "Cognitive Dimension" (Figure 3) of the practice, the "Logic of Communication" stands out, gathering 51.5% of the cases (158 answers), followed by the "Logic of Responsibility," with 20.2% of the cases (62 answers), while the "Logic of Knowledge" and "Logic of Imitation" account for 13.4% (41 answers) and 8.8% (27 answers) of the cases.
- The "Affective Dimension" (Figure 4) shows that most of the responses concentrated on the sensations of "Knowledge/Awareness" (31.6%, 97 answers), "Trust" (20.2%, 62 answers), "Love/Friendship" (16%, 49 answers) and "Feel useful/Caring/Interest/Solidarity-hope" (12.4%, 38 answers). All these emotions grouped together concentrate then more than 80% of the answers. Finally, less frequently the respondents mention "Fear/Anxiety" (6.8%, 21 answers) and "Entertainment" (5.5%, 17 answers).

An interesting appreciation arises from the comparison of responses between those who re-send and those who do not. If we look at the cognitive content (Figure 5) of the practice associated with re-sending, we find that most of the responses are distributed uniformly across all categories, from which we could say that the "cognitive dimension" is not a significant factor in this action. This is not the case with what we call here the "Logic of Imitation," where we assume that a smaller set in the sample (13.4% of the total), which brings together motives linked to "keeping in touch," or deliberately seeking to "have some conversation" or "entertain/be entertained," predominantly brings into play this "cognitive dimension" of the action when re-sending messages.



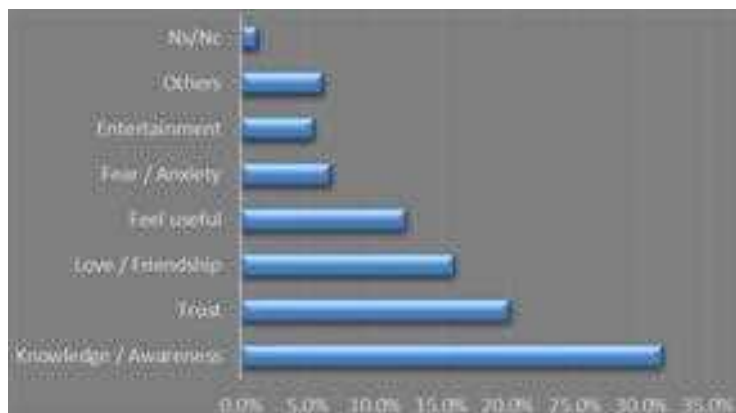
Source: Own elaboration. Survey "Emotions and COVID" (CIES).

Figure 2. Have you re-sent information related to "COVID-19" through social networks?



Source: Own elaboration. Survey "Emotions and COVID" (CIES).

Figure 3. Cognitive dimension.



Source: Own elaboration. Survey "Emotions and COVID" (CIES).

Figure 4. Affective dimension.

If we pay attention to the affective content (Figure 6) of the practice, we find that the re-sending variable constitutes a factor that brings together two well-differentiated groups of "feeling practices": the action of re-sending is significantly associated with "Knowledge/Awareness," "Feel useful/Caring/Interest/Solidarity-hope," "Love/Friendship," and "Entertainment"; while "non-re-sending" seems to be associated with "Trust" and "Fear/Anxiety."

	Communication	Knowledge	Responsibility	Imitation / Entertainment	Others	Ns/Nc	
Yes	53.7%	12.4%	19.7%	11.5%	1.4%	1.4%	100%
No	46.1%	15.7%	21.3%	2.2%	11.2%	3.4%	100%

Source: Own elaboration. Survey "Emotions and COVID" (CIES).

Figure 5. Re-sent/cognitive dimension.

	Knowledge / Awareness	Trust	Feel useful	Love / Friendship	Fear / Anxiety	Entertainment	Other	Ns/Nc	
Yes	38.5%	12.4%	15.1%	22.0%	1.8%	7.3%	2.3%	0.5%	100%
No	14.6%	39.3%	5.6%	1.1%	19.1%	1.1%	15.7%	3.4%	100%

Source: Own elaboration. Survey "Emotions and COVID" (CIES).

Figure 6. Re-sent/affective dimension.

It is important to emphasize at this point that the "affective dimension" seems to have a certain preeminence in explaining the action of forwarding/non-forwarding. If we observe the links between the cognitive and affective dimensions (Figure 7 and Figure 8) we can see some associations that qualify the alluded preeminence:

- The category that brings together a series of practices of feeling associated with fun and entertainment are linked, from the action of forwarding, with the "Logic of Imitation." That is to say, there is here a two-way connection between the cognitive and affective dimensions that is condensed in the action of re-sending. This speaks to us of the power, embodied in the expanded reproduction of audiences as the balance of the action, of the vertigo produced by the extortion of staying outside the digital-emotional world as a univocal feature of the politics of sensibilities.
- The practices of feeling linked to "awareness" and "love/friendship" seem to be the most frequent among those who forwarded messages as a way of intervening in the communicational process. On the other hand, feeling useful, supportive, hopeful, etc., explains a great part of the sensations of those who re-sent messages looking for some sense linked to the "common good." Both groups of sensations, as a whole, inform us about the horizon of the action embodied in the subjects, which is structured as the emotional basis of "the possible" in this digital world. In the face of the ominous nature of communicational processes, the need to become aware of and "care for" those close to us, to initiate solidarity actions, etc., emerges as sensations that paradoxically are articulated with the deliberate intention of intervening in communicational processes by amplifying them, or looking for the "common good"

by reproducing the practices of differential appropriation of information (not only as a common good but also as a strategic one).

- Finally, the feeling of trust (or lack of trust) describes the emotional state of those who decided not to forward messages, orienting the effects of their practices both in the communicational logic, and in the processes from which it approaches the "truth" ("Logic of Knowledge"). Fear and anxiety characterize the sentimental practices of those who did not send messages, looking to influence both the communicative process and participate in the construction of the "common good." In general, this group of sensations seems to structure two opposite poles (on the one hand confidence and on the other fear/anxiety) that give us insights about uncertainty as a central component of emotionality. This emotionality could be associated with "paralysis," "immobility" as a balance of personal experiences. Not to forward, "not to do" is not synonymous with destitution of the value chain of the audience as a commodity, in such a way that those who pretend "a certain quietness" as a way of "resistance to the "communicational logic," or those who due to fear or anxiety did not dare to forward the messages, are also a "transmission pulley" of the limited re-production of the audiences.

Gathering the tendencies that are described, we can advance in some statements of sense anticipation that allow us to understand how this particular association of cognitive and affective elements can be read as a particular configuration of the politics of sensibilities that underlies the digital practice. These policies constitute an interesting reading key regarding the predispositions with which subjects intervene in the interactions mediated by social networks.

	Entertainment		Love /Friendship		Feel useful		Knowledge/ Awareness		Trust		Fear/ Anxiety	
	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N
Imitation	16	1	7				2	10				1
Communication			29			9	55	3	42			8
Knowledge				1	3		11		6	11	1	
Responsibility			5	6	22	3	16			3		11
Total	17		48		37		97		62		21	
	Re-sent								Not- re-sent			

Source: Own elaboration. Survey "Emotions and COVID" (CIES).

Figure 7. Re-sent/affective dimension/cognitive dimension.

Reproduction Amplified		Re-production limited	
Knowledge/Awareness	Communication	Trust Fear/Anxiety	Communication/Knowledge
Love/Friendship	Communication		
Feel Useful	Responsibility		Responsibility
Entertainment	Imitation		

Source: Own elaboration. Survey "Emotions and COVID" (CIES).

Figure 8. Politics of sensibilities.

The first consideration arises from the question of what is the bodily disposition to participate in these kinds of digital interactions? How do these interactions occur? The data presented lead us to think that, beyond rational calculation, and framed in a series of specific cognitive logics, the digital practice in/by social networks involves a way of being for others. In other words, "being" in the expanding digital world increasingly implies "being" in social networks, and this presupposes, in addition to many other "skills," being able to "get emotional." Thus, a first point to note is that the affective dimension of the practice which refers to the interplay between the individual's sensations and social emotions seems to invade the cognitive contents with different senses, constituting a kind of "compass" that allows the individual to "navigate" the digital world.

Thus, the "logic of communication," as the predominant cognitive component (both in forwarding actions and in non-forwarding actions) appears to be traversed by various practices of feeling that underlie the communicational field. We can think in this respect that by sharing information an affective content is generated with multiple senses, all of which contribute to elaborate the "viral" dimension of the pandemic as an effect of "ideological violence" (Fuchs, 2014). That is to say, the pandemic constitutes (among other dimensions) first of all an "emotional product" that threatens and extorts those who cannot live it affectively in the networks. The irreversible balance of this practice is a world where the production, circulation and consumption of information-emotion turned into commodity is expanded and consecrated.

This refers directly to the notion of "audience commodification," but from the observation of a specific feature that emphasizes the place occupied by emotions: the data presented announce that the practices of feeling seem to organize the perceptions linked to the cognitive associated with them, constituting in themselves a condition and at the same time a specific content of the relationships in/by social networks. The substratum of value takes the form of the body's affective expression as a reservoir of motives for being in the network. Thus, the idea of production, circulation and "consumption" of information opens the way not only to the image of the "prosumer," but centrally to an "emotional prosumer." The notion of an "affective community" (Ahmed, 2019), as a concept that analyzes the function that emotions have in the construction of collective practices, leads us to think that digital affective exchanges build an "emotional platform" that works by organizing the metabolized energy flows in the processes of audience commodification.

The commoditization of emotions (as a process of delimitation and management of the practices of feeling) associated with the commoditization of audiences, provides the quality of "ambivalence" as a characteristic feature that ensures the effectiveness of these processes in digital contexts. As we observe, there is no difference in the cognitive logics that explain the passage from forwarding to not forwarding: however, the prevalence of certain sensations over the same logics builds a "plus" that allows agents to place themselves in the social world, and the process of audience commodification to expand with different values. Ahmed (2019) suggests that emotions are public, since they are constructed and signified through a collective imaginary. Based on this idea, she makes an analogy with Marx's vision of the movement of money and material goods, to develop the concept of "affective economies," which refers to the way emotions "circulate" and are distributed both in the psyche and in society. Re-appropriating this idea, and putting it in relation to what has been discussed about the commodification of audiences as well as the possibility of thinking from a sociology of

sensibilities, social emotions appear as that "plus" associated with sensations, which draw the conditions of operation of the "digital affective communities."

In this direction, the cognitive dimension of the practice informs us about a specific content of the regime of sensibilities as a condition of possibility of these "communities." A transversal look at the cognitive logics presented allows us to observe that what we here call "logic of communication," "of responsibility," and "of knowledge" are configured in the answers of the agents as a way of finding understanding about certainties, and the ways in which these are constructed and distributed. The fact that this cognitive framework is completed with the "logic of imitation" helps us to think that what is at stake is a profound process of reconfiguration of sociabilities, since this whole set of senses puts the "connection," already stripped of its technological garb, at the center of the scene as a condition of the collective body.

However, as we have been observing, if part of the expressed experiences refer us to a mutation of the sociabilities, another part of them refers us to the sensibilities as a central component for understanding this metamorphosis. In this direction, the preeminence of the affective dimension does not respond to an ontological consideration, but rather to an analytical one. It seems to be these explored sensations that orient the "connection" in a double sense: as a way of meaning for the cognitive dimension of the practice, as well as a "plus" that allows an interpretation of the content that constitutes the social emotions as a central component of the regime of sensitivities in course.

CONCLUSION

As an opening we would like to take up again the idea of "platform sensibilities" (Scribano and Lisdero, 2019) to refer to the cognitive-affective state linked - at least - to the following characteristics. In the first place, we should think of this particular state of the "politics of sensibilities" as processes extended in the "here and now" of labor times/spaces, but which operate in an expansive way from the mediations that enable relationships in/through the internet. Thus, as a regime, it stands out for the "intimacy" of the mechanisms that work as a necessary gear for the fluid deployment of the "digital production chain" ("audience commodification").

In this sense, sensibilities of platform imply a particular body policy, where sensitive terminals are processed by the phenomenal capacity of digital sensors to capture the creative forces of the bodies. This requires us to think beyond the processes of "consciousness" centered in the "brain," opening up questions about the complexity of the vital energies that are re-invented in a social body as a surface for the exploitation of digital processes. At the same time, these sensibilities also imply a "politics of emotions" that, as an accepted form of "feeling" oneself with respect to a range of expected practices, is related to a particular potential capacity to act on "others." These social emotions, connected to the sensations experienced by the agents (as we develop), constitute the conditions of digital labor. That is, they come as the mechanisms that occlude the corporal trace of digital energies from the affective tension that orient the perceptions in a "beyond" of the digital processes.

In this work, then, we have tried to move away from dichotomous models in the understanding of emotions, organizing the data from certain continuities of the process of

commodification, and following a certain analogy in the tensions between technology and the body. We resynchronize the notion of the body in the context of digital interactions from the basic certainty that if the "instruments" we use change, so do bodily sensations. The individual "supports" (in the Weberian sense) new forms of relationship, becoming the embodiment of digital technology. There are different ways of taking over the world, and technology is a new "logic of proximity." The body becomes an instrument, and in a way, it is a technology of communication with the other: the acts of bodily speech are modified according to the instruments, rewriting the body as the territory of life (and therefore of the productive processes in which it is inscribed). The problem of capitalism in societies 4.0 (Scribano and Lisdero, 2019) is the colonization of human and non-human nature, and "the digital" is no different from life. However, in the amplification of its re-productive processes, the logic of the commodity in-corporates the expressive forms of "being" in the digital world as a privileged component: being productive today is not only about "adapting" to the use of digital technologies, but above all about being willing to get emotional (not in any way).

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Chapter 494

ECONOMIC, SOCIAL AND PSYCHOLOGICAL ISSUES OF SURVIVAL IN THE PANDEMIC: THE CASE OF RUSSIAN FEDERATION

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ABSTRACT

This chapter contains the broad economic and social review of the COVID-19 consequences which Russian Federation faces today. COVID-19 epidemic update had a great impact on all spheres, people's lives had changed dramatically: many people have contracted the illness, others lost their jobs and incomes, almost all were overcome with panic. So, the main objective of the Russian Government was to rapidly develop a program of urgent response in the sphere of healthcare as well as in preventing deep negative consequences in decrease of peoples' incomes and welfare. The special measures of economic and social support were undertaken by the government towards SMEs and people under great risks of poverty. Volunteers' activities aimed at care of elderly people under the isolation restrictions became widely developed. To prevent the risk of contamination lots of people in different spheres were urged to work distantly, this process was supported by wide access to informational technologies and equipment and well-developed skills of specialists. Still, for many companies it was a severe challenge which required training of personnel and new management tools. During the isolation period distant professional learning was of great importance and popularity: it helped to prepare people to overcome the crisis with marketable knowledge and skills.

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INTRODUCTION

The Russian Federation, together with other countries, faces serious challenges due to the pandemic. From February 2020 till April 2020 there were slowly increasing rates of infection in Russia, but then the situation became worse, so the Russian government enforced quarantine from the 30th of March. Since March 30th, restrictions were imposed on movement across the Russian border. They concerned automobile, railway, pedestrian, and river traffic, and mixed checkpoints at the border, as well as the land section of the Russian-Belarusian state border. Moreover, there were serious restrictions inside the country: on transitions between Russian regions and even between districts in big cities. A lot of attention has been paid to maintaining immediate medical services for everybody who needed them. All these efforts were implemented efficiently and successfully, and rates of contamination began to fall. But when the restrictions were lifted and people began to live their usual lives, we all faced the second wave of the Coronavirus pandemic. As of the 25th November, there are 2,162,503 Coronavirus cases in Russia, among them 1,660,419 recovery cases and 37,538 fatal outcomes. Of course, Moscow, Saint Petersburg and other big cities are the most affected (Russian Government, 2020). In such a difficult, worsening epidemiological situation, the government needs to respond quickly to new challenges and take the most effective measures to mitigate the situation and its consequences; organizations need to ensure the safest working conditions for their employees with the maximum preservation of productivity, and it is very important for citizens not to give in to panic and to observe the prescribed precautions as much as possible. That's the background we're seeing today.

SOCIO-ECONOMIC ISSUES

The first wave of the Coronavirus pandemic lasted from the second half of March 2020 till August 2020. The second wave of the pandemic, started approximately at the beginning of September 2020, slowing down the recovery of the labor market in Russia, but the number of vacancies did not decrease, as Head Hunter's research showed. According to that data, the level of competition for jobs in mid-autumn dropped slightly compared to the "before pandemic" period. On average there are six active resumes per vacancy against seven in February-March. In the second half of October the labor market experienced the second wave of the epidemic, the number of vacancies in the labor market did not fall, but the recovery trend observed since June slowed down. Thus, in October the number of vacancies published at hh.ru exceeded the figure for September by only 1%, while the annual growth is more tangible - 18%. In early November in most regions, there was a slight decrease in demand. The number of active vacancies increased only in the North-Caucasian Federal District. In early November the demand for specialists in consulting, transport and logistics, as well as in civil service, increased. The maximum decrease of demand is observed in-home staff, in tourism and hotel and restaurant businesses, as well as in the sports and beauty industries (Business Journal, 2020).

The economic situation of the Russian population during the period of self-isolation has deteriorated. According to the United Credit Bureau, in the second quarter of 2020 (April-June), working Russians lost 841 billion rubles of income. This is the equivalent of 16 million

average wages. The main reason for the losses is part-time work or a reduced working week. Such measures were used by businesses to optimize costs. During the pandemic, the government financially supported certain groups, such as families with children, and subsidized entrepreneurs who did not fire employees because of the crisis. Therefore, large-scale cuts were avoided. However, after self-isolation, the number of announcements about the sale of businesses in cities with a population of millions increased by 28% - this is indirect evidence that entrepreneurs were on the verge of bankruptcy. It can be supposed that as soon as the pandemic goes down and the government stops subsidizing businesses, small companies will start closing down and unemployment will increase (Brusentseva, Vtoraja volna koronavirusa i obshhie sny: dajdzhest trendov obshhestva № 20, 2020).

During the Coronavirus lockdown in Russia, unemployment rose by 30% on average in the regions. Many companies reduced their employees during quarantine or ceased to exist at all. Moscow, St. Petersburg and the Moscow region were the most affected by layoffs, while 3.5 million employees have been laid off since the beginning of the pandemic. According to the Russian Federal State Statistics Service (Rosstat), the total number of unemployed in the country exceeded 4.5 million in May 2020, and the unemployment rate reached a record 6.1%. In July, registered unemployment growth slowed by a third, and the market began to slowly recover after restrictive measures were lifted (Sycheva, 2020).

The social network "Odnoklassniki" and the research center "ResearchMe" conducted an online survey on women's income during the Coronavirus pandemic. The study involved 1,603 women over the age of 18. One in five women claimed they had lost their jobs during the pandemic. Most affected were the respondents between 18 and 24 years of age (30%). Among those who lost their jobs during the pandemic, about 36% have not yet found new employment. Women aged 25-34 noted that employment was hindered by the presence of a child (22%), while in the group of respondents over 45 years old the cause of difficulties in employment most mentioned was that of age (49%). According to the survey results, 61% of female respondents who worked during the pandemic experienced a decrease in their monthly income (Telegraph Agency of the Soviet Union (TASS), 2020).

The pandemic and general quarantine have confused all previous plans of employers. Some companies have started to send employees on vacation for an indefinite period and reduce their salaries, and most employers are waiting for the situation to develop and have suspended recruitment, while some continue to hire staff. According to the recruitment company Antal Russia, 12% of employers stopped recruiting employees in February and 40% in March. The share of those who planned to fill vacancies decreased from 47% to 21% during the month. 75% of companies have already reduced their staff costs due to coronavirus. 54% cancelled team retreats and teambuilding, 47% saved on travel expenses (business trips were cancelled), and 43% reduced the cost of education and training. Furthermore, 26% of respondents said they are looking for ways to avoid salary cuts and the cancellation of bonuses (Podtserob, 2020).

According to the KPMG survey "HR Actions in the Situation of the Pandemic," 49% of respondents - large companies - have already translated face-to-face interviews fully online, and 22% - partially. In the next year, 59% of companies will optimize personnel costs, 44% will switch to a new management model (flexible schedule, remote work, online recruitment), and 41% will automate personnel management processes. The study also says that after the end of the crisis, regular management practices will include the tools that had to be switched to during the epidemic: remote work (36% of respondents), online recruitment (46%) and

online training (41%) (Podtserob, 2020). In this respect, Coronavirus has given a powerful impetus to cloud technologies. In the first half of the year alone the demand for them grew by 30%. Thanks to the migration to the cloud, companies working mainly in the delivery of food, FMCG goods and electronics, managed to survive organizational “overloads” associated with the transition to the “remote.” While the sites of those companies, which in the old days relied on their own data centers, regularly lost profits. Quarantine and fear of infection led to strong growth in e-commerce and e-retail. Thus, according to the research center “NAFI,” 67% of Russians during self-isolation ordered food and non-food products in online stores. The share of online purchases in the FMCG market almost doubled compared to 2019: from 1.9% in 2019 to 3.2% in March 2020. It is expected to grow to 4% by the end of 2020. Moreover, isolation has led to accelerated modernization of remote communication technologies in several areas at once. On the one hand, many companies have started to establish new technology solutions, which were previously considered “non-priority” to ensure synchronization of all processes outside the office, as well as to integrate chat bots and applications for the analysis of big data (Sysoev, 2020).

On the other hand, for the first time, telemedicine became a truly global trend. For example, in the first half of 2020, remote medical consultations through mobile applications and online services increased by 177% compared to the corresponding period in 2019. In response, both the development of algorithms for medical artificial intelligence (AI) and the development of AI services for the decoding of medical images have intensified (Sysoev, 2020).

The market situation has formed a “window of opportunity” for all digital segments of the economy. E-commerce, companies offering digitization business services, online video, online games and many other digital services are now growing. The field of online education is one of them. Schools, universities and kindergartens forced to switch to remote operation in an accelerated mode were generally not ready for this “new normality.” Not all teachers have been able to quickly restructure the learning process “from a distance,” arrange lessons and lectures in such a way as to retain students’ attention and move to an individual, more flexible teaching process. Besides, not all teachers have been able to quickly adapt to new learning technologies on online platforms. Parents were also not ready for a remote format, mainly for combining work and supervising their child’s learning (Sysoev, 2020). The Russian school education system was not ready for online education. The technical equipment of schools, teachers and pupils still leaves much to be desired. At the moment of urgent changes teachers did not know how to teach effectively online and could not get fast methodological and administrative support from above. It was a systemic failure which, although not officially recognized, was understood by all participants. At the same time, the Ministry of Education tried to face the truth and take quick steps to correct various processes, including involving commercial companies and platforms (Mjagkov, 2020).

Recently, together with the research group EdMarket and TalentTech, one of the largest EdTech companies in Russia “Netology-groups” has conducted a study of the online education market: in 2019 its volume amounted to 38.5 billion rubles. With “pre-quarantine” growth rates by 2023, this figure would reach 60 billion rubles. It’s worth noting that Edtech grew significantly before Coronavirus and the pandemic has only sped it up. For example, in “Foxford” - a project focused on schoolchildren - more than a million new users registered during the first week of quarantine (Spiridonov, 2020).

The free access to courses opened by many online platforms is an opportunity for mass users to at least try distance learning in its various forms. But it may take time for everyone to get used to the online format and start learning fully. The trend for digitalization of business, which has been going on for several years, but during the pandemic is more relevant than ever, affects business education as well. On the one hand, it may seem that the crisis is hitting hard on the sector of business education, making it less popular due to the worsening economic situation. But this is not true; traditionally all segments of business education, including MBA programs, are in great demand during the crisis in the market. Managers and top managers today are most eager to learn how to run a digital business: business strategy development, teamwork, management and administration, sales and marketing with a focus on digitalization. And the interest is observed in representatives of companies from all market segments, even such conservative ones as medicine and construction. And business education is ready to take into account the needs of the business, to adapt to them and offer relevant and current knowledge. Changes in the employer's requirements for employees are based on changes in the set of competencies for certain positions. For example, to perform the functions of the head of the planning and financial department, a leading economist does not need to obtain a second higher education; in addition to the available knowledge in the field of economics and finance, it is enough for him or her to master managerial competencies. Through further professional education, the employee can fill in gaps in the required skills in a short period. In times of economic instability, employees may face the challenge of retaining them in the workplace, which is also possible through further professional education programs that will strengthen the employee's competitive position in the labor market (Razumova & Burak, 2019).

The initial increase in productivity shown by workers transferred from home to work was quickly replaced by an increase in fatigue. There were several contributing factors at once: lack of workspace, specific 'home factors' such as children, relatives or neighbors that constantly distract attention, lack of communication in the team, and excessive or minimal control by the employer. All this has become an obstacle to normal work, which for many has resulted in a loss of motivation to work. The uncertainty factor associated with the unstable economic situation and layoffs, which affected many industries, was also imposed on this. So, the spring prophecies about the "convenience" and "efficiency" of remote work were false for many people. On the contrary, we can say that today a new privilege has been formed - to work in an office at least for a few days a week. In fact, as JLL's global research shows, post-pandemic demand for office space may not be so different from recent trends. Instead, the way space is used will change. Lower occupancy levels will be compensated for by allocating more space to each workplace. Employers will pay more attention to supporting direct communications, learning and development, creativity and collaboration - the real reasons why people want to work together (Sysoev, 2020).

Sharing services are gaining popularity on the labor market, and at all levels - from simple tasks to expensive consultations. For many of those who have lost their job, but have the right skills, it becomes a way to stay afloat, and for companies a means to save money. Uberisation is not just a cab service: business in Russia uses sharing to get the expertise of highly competent specialists. Another common type of request on the sharing platform is an independent opinion. Companies focused on rapid growth are not always ready to spend time on long study and long decision-making when the issue can be resolved with independent analysis from an external expert within an hour (Bindjuk, 2020).

Because of the Coronavirus pandemic, it became more difficult for a migrant worker to come to Russia to work. According to the Ministry of Internal Affairs, in August 2020, 33.9 thousand people received work permits; a year earlier there were 82.4 thousand. According to a study by the Center for Strategic Research (CSR), 40% of companies are now experiencing labor shortages. The deficit of couriers and cab drivers is especially acute. The business is again moving employees to remote locations and the number of orders in online stores is growing. However, due to the outflow of migrants, there is no one to deliver additional orders. Many residents of the regions, who lost their jobs in the capital during the pandemic, have returned home (Brusentseva, 2020). For regional companies, who have vacancies, this is a chance to hire good specialists and implement new projects.

PSYCHOLOGICAL ISSUES

Sudden changes have now occurred in everyone's lives. They happened faster than the human mind can adapt. The overall level of fear and anxiety, which has increased significantly due to the pandemic and the global economic crisis, may lead to unwanted long-term psychological consequences, experts believe. On the one hand, the fear of a future filled with uncertainty may not only increase the already high level of anxiety but also lead to a deep depression, especially among the poor. On the other hand - for people with a genetic predisposition to some forms of obsessive-compulsive disorder (OCD) - i.e. various obsessions leading to compulsive actions - COVID-19 stress can only exacerbate OCD.

Compared to other generations, during the period of self-isolation, "zoomers" (youth aged about 11-25 years) felt the worst. Mainly, they complained about a feeling of boredom (51%), less physical activity (47%) and an increased sense of loneliness (41%). They also expressed concern about the negative impact on health due to increased screen time: 31% vs. 25% of millennials and 14% of Gen X. The younger generation was also more likely to experience increased anxiety and stress compared to the older generation: for example, almost half of the "zoomers" said they were worried about COVID-19 (Sysoev, 2020).

Brand Analytics decided to analyze how the COVID was discussed during the year in Russia, Ukraine, Kazakhstan, Belarus, Armenia and Moldova. Where the COVID-anxiety was higher, what are the dynamics and platforms for discussion, and whether there is a correlation between the dynamics of references and the dynamics of morbidity. To understand how much the topic of Coronavirus excited people in different countries from the full flow of messages in the social media of each country, publications with mentions of COVID-19 was highlighted. Taking into account the population size, the index of "COVID-anxiety" equal to the number of mentions of the virus subject for a day for every 10 thousand of the country's population was calculated. The peak of anxiety everywhere occurred at the end of March. The greatest degree of anxiety was demonstrated by Russians and Moldovans. Inhabitants of Ukraine and Belorussia were less worried; the latter joined the discussion of COVID later than others. In Kazakhstan and Armenia, users were less actively discussing coronavirus publicly. In the central regions of Russia, residents met the second wave more calmly. The anxiety increases with the distance from the center (Cherniy, 2020).

The top 5 the most "alarming" regions look like this:

1. Magadan Region - 132 (COVID-anxiety index)
2. Chukotka Autonomous Okrug - 127
3. Republic of Crimea - 123
4. Kurgan region - 107
5. Jewish Autonomous Region - 97

The top 5 “quietest” regions were:

1. Chuvash Republic - 35
2. Kabardino-Balkarian Republic - 35
3. Pskov region - 35
4. Sakhalin Oblast – 35
5. Republic of Dagestan – 34 (Cherniy, 2020).

According to the All-Russian Public Opinion Research Center (VTsIOM) survey, 15% of Russians believed that Russia was going through the worst period of the pandemic in September 2020. Another 16% answered that all difficulties are over. But the majority (60%) is sure that hard times await them in the future. In particular, the difficulties will be related to the economic crisis. But this is not the only concern of Russians (VTsIOM, 2020).

The Public Relations Development Company (PRDC) has published a new “National Index of Concerns,” a survey that shows what fears are prevalent in society. PRDC experts assess phobias by analyzing media materials and discussions on social networks. To make the rating, they use the media young index (MJng). It is calculated as a ratio of three variables: the frequency of appearance of a worrying topic in the media, its popularity in social networks and the duration of discussion of the topic. In the course of the study, PRDC analyzed 130,000 media publications and 1 million posts in social networks from June to the end of September 2020 (Brusentseva, 2020).

These are the four reasons why Russians are most worried:

- The second wave of Coronavirus (total index 353.27);
- Russia’s participation in the political crisis in Belorussia (129.99);
- Dismissals and unemployment (122.06);
- Environmental pollution (63.06).

Interestingly, the first three problems are most frequently mentioned in media reports, while the climate agenda is discussed in social networks and media with equal frequency (ratio 1.09). This indicates the relevance of the topic for society and the involvement of Russians in the discussion (Brusentseva, 2020).

Due to social isolation, time spent with the family has naturally increased, and this can play an important role in the next generation of children. The fact that parents accustomed to business trips and office work have settled at home and become more flexible in structuring time can lead to a change in priorities within the family through a more balanced distribution of work and personal time. A truly comfortable family environment will result in parents being able to work more efficiently. By the way, transformations can also happen to children: although COVID-19 has further strengthened the role of technology in the life of the “Alpha

generation,” the virus has emphasized the value of personal communication for them (Sysoev, 2020).

According to a survey of the research company Ipsos, after the abolition of self-isolation, the level of happiness in Russia increased by 11%. This is a record figure among 27 countries in which the study was conducted. The same high value was recorded in China. Despite the sharp increase, Russia took only 18th place in the ranking of countries in terms of happiness. In first place was China, as 94% of the Chinese consider themselves happy (Ipsos, 2020).

Table 1. Level of happiness

	Dec-11	May-13	Mar-17	Feb-18	Jun-19	Aug-20	Change since December 2011	Change since June 2019
Global Average	77%	77%	61%	70%	64%	63%	-14%	-1%
China	78%	79%	84%	85%	82%	93%	15%	11%
Netherlands						87%		
Saudi Arabia	83%	74%	75%	76%	78%	80%	-3%	2%
Canada	85%	83%	81%	81%	86%	78%	-7%	-8%
France	84%	81%	68%	77%	80%	78%	-6%	-2%
Australia	86%	84%	72%	82%	86%	77%	-9%	-9%
Great Britain	79%	81%	71%	78%	82%	76%	-3%	-6%
Sweden	80%	87%	74%	81%	75%	74%	-6%	-1%
Germany	76%	77%	71%	68%	78%	73%	-3%	-5%
Belgium	80%	80%	71%	80%	73%	71%	-9%	-2%
United States	85%	83%	80%	82%	79%	70%	-15%	-9%
Poland	75%	72%	66%	71%	71%	68%	-7%	-3%
India	89%	87%	78%	83%	77%	66%	-23%	-13%
Brazil	77%	81%	56%	73%	61%	63%	-14%	2%
Italy	73%	68%	53%	60%	57%	62%	-11%	5%
Malaysia				69%	52%	62%		10%
Turkey	89%	83%	58%	60%	53%	59%	-30%	6%
Russia	61%	62%	56%	62%	47%	58%	-3%	11%
Japan	70%	69%	62%	60%	52%	55%	-15%	3%
South Korea	71%	62%	48%	57%	54%	54%	-17%	0%
South Africa	79%	83%	59%	72%	59%	52%	-27%	-7%
Mexico	78%	80%	43%	67%	59%	46%	-32%	-13%
Hungary	43%	52%	48%	48%	50%	45%	2%	-5%
Argentina	68%	67%	48%	56%	34%	43%	-25%	9%
Spain	63%	57%	43%	53%	46%	38%	-25%	-8%
Chile			41%	71%	50%	35%		-15%
Peru			36%	54%	58%	32%		-26%

The increase in the level of happiness in Russia in the short term after the period of self-isolation can be explained by the removal of restrictions on such important universal things as meetings, personal communication, and free movement. During the period of self-isolation people have never felt their importance and value, and after the removal of restrictions a return of the lost and the feeling that the pandemic has retreated, allowed many to feel the tide of happiness in life (Ipsos, 2020).

The things that bring Russians happiness are children (59%) and relationships with a partner (56%). The feeling that their life is full of meaning was mentioned by 49% of respondents, another 45% of respondents chose good living conditions and financial well-being, and a little less - 44% - health (Ipsos, 2020).

Compared to 2019, the prevalence of happiness globally has remained nearly unchanged. It has increased by at least 5 points or more in six countries, most of all China, Russia, Malaysia, and Argentina. It has decreased by 5 points or more in 12 countries, most of all Peru, Chile, Mexico, and India (Ipsos, 2020).

POLICY ISSUES

Measures to support the economy and population have been taken in different countries of the world. The introduction of quarantine measures has a serious impact on the economies of all countries. Many kinds of activities stop at once. The production scale of many enterprises is limited. That is why the support measures are very important. Several support packages have also been approved in Russia: these are point measures to support the population and several business sectors, which we will consider in detail below.

The Government of the Russian Federation is constantly developing and taking new measures to counter the spread of new Coronavirus infection. They can be divided into two groups: social and business support measures. The first group includes:

1. Benefits for families with children. All families with children under the age of 16 received financial support, and families whose average per capita income does not exceed the minimum per capita subsistence level established in the constituent entity of the Russian Federation are entitled to monthly payments.
2. Sick leave for workers over 65 years of age. Working citizens of 65 years of age or older, observing the regime of self-isolation due to Coronavirus, who have not switched to remote work and are not on vacation, can remotely issue an electronic sick leave.
3. Support for the unemployed. Citizens who have lost their jobs will be able to apply through the portal "Work in Russia" for help in finding a job, as well as to apply for registration as unemployed and apply for unemployment benefits online. Additional payments are also granted to citizens who are dismissed and recognized as unemployed and have children.
4. Helping people with disabilities. Almost all interactions to formalize a disability and receive the corresponding allowance have been transferred online. Individual rehabilitation programs are automatically implemented without additional applications.
5. Support for employees of social institutions. Additional payments apply to those institutions that have entered quarantine - that is, where employees worked for at least 14 days inside the institution to minimize the risk of infection of citizens living there.
6. Support of employees and volunteers. Special payments are made to employees of state and non-state organizations and volunteers who have accepted accompanying and temporary accommodation, including temporary care, disabled persons, older citizens, orphans and children without parental care, social service organizations and orphanages.
7. Assistance to tourists. Citizens who have planned a trip from the beginning of the restrictive measures until June 1, 2020 will be able to receive a refund for a disrupted trip. In case of cancellation of a flight abroad, which should take place during the period of prohibition of international air travel, the passenger will be refunded the full amount for the ticket. Besides, there is an organized return of Russian citizens from abroad. For all who find themselves abroad and are unable to return to Russia

due to the spread of new Coronavirus infection, the necessary social support is provided.

8. Extension of documents. Passports and driver's licenses that have expired or expire between February 1 and July 15, 2020, inclusive, are considered valid.
9. Credit vacation. This is a grace period for possible reduction or suspension of regular payments on the loan for up to 6 months. They are granted to citizens who have difficulties with payments on loans or credits, if their income for the month preceding the date of application, decreased by at least 30% compared with the average monthly income in 2019.
10. Moratorium on payment of penalties for housing and communal services. It is forbidden to levy penalties for late or incomplete payment for housing, utilities and repairs. It is also prohibited to limit the provision of utilities in case of their late payment by citizens.
11. Monitoring of essential goods. In order to prevent the spread of new coronavirus infection in Russia, a list of non-food items of prime necessity and rapid monitoring of their availability in trade organizations was compiled so that there would not be a shortage of these items. The list of essential goods includes disinfectants and personal protective equipment, hygiene supplies and detergents, baby products, pet food, various fuels, candles, and matches. State authorities of the subjects of the Russian Federation have the right to make changes in the list of non-food items of prime necessity at the regional level based on the sanitary and epidemiological situation in the region.
12. Sale of medicines online. Medicines released without prescription can be purchased through the Internet with home delivery. It is not possible to buy prescription drugs, as well as over-the-counter drugs, narcotic and psychotropic drugs, alcohol-containing drugs with a volume fraction of ethyl alcohol exceeding 25% via the Internet (Russian Government, 2020).

The second group contains:

1. Bankruptcy moratorium. Acceptance of creditor bankruptcy applications from creditors is suspended. The courts also suspend proceedings in accepted cases where bankruptcy proceedings have not yet commenced. The debtor is relieved of the obligation to go to court if there are signs of bankruptcy, but the right to do so remains.
2. A moratorium on business audits. Suspends field audits of small and medium-sized businesses. All licenses and permits are automatically renewed for six months. Only unscheduled inspections are preserved, the basis for which is harm to life and health of citizens, the emergence of emergencies of a natural and man-made character.
3. Credit vacation for business. Entrepreneurs can get a grace period on the loan for 6 months, as well as count on reducing the amount of deferred debt due to federal subsidies for banks, if the credit organization participates in the program of the Ministry of Economic Development. This measure applies to SMEs working in the most affected areas: air and road transport, tourism, the hotel business, catering, culture, entertainment and leisure (including cinemas, museums and zoos), physical

education and sports, conferences and exhibitions, consumer services to the public, dental practice, additional education, and retail trade in non-food products.

4. Interest-free loans for salaries. Large, medium and small businesses, as well as individual entrepreneurs from the most affected industries, can take an interest-free loan from the bank for six months to pay salaries to employees. Credits for small and micro businesses will be provided by the bank, taking into account the main and additional OKVED. For large and medium-sized companies - only the main.
5. Decrease in insurance premiums. For organizations and private entrepreneurs included in the Single Register of SMEs, the total amount of insurance premiums is reduced from 30% to 15%. The rate of contributions to the Pension Fund of Russia will be 10%, to the Federal Compulsory Medical Insurance Fund - 5%. Contributions to the Social Insurance Fund (for disability and maternity) are not paid.
6. Tax vacations. This means that almost all taxes are deferred for companies in the ten industries most affected by the epidemic and part of the taxes for all other entrepreneurs.
7. Postponement of rent payments. Delayed payment of rents applies to state, municipal and private property.
8. Assistance to exporters. The Russian Export Center provides businesspeople with targeted consultations taking into account the situation in the industry and the specifics of the enterprise. The operational headquarters of the Russian Export Center helps solve logistics problems and obtain financial support in connection with emerging cash gaps, assists in concluding new export deals and advises on a wide range of issues in the sphere of certification, subsidies, cooperation with customs authorities, etc.
9. Non-refundable subsidies. Small and medium enterprises from 11 affected industries can benefit from direct financial support from the state. Entrepreneurs can receive an amount equal to the established minimum wage per employee.
10. Extension of licenses. If a company is engaged in licensed activities, there is no need to renew licenses in 2020 - many licenses are automatically renewed for one year.
11. Support for systemically important enterprises. System forming enterprises are companies that have a significant impact on the development of the country's economy, provide the greatest employment in their industries and are the largest taxpayers. The government has developed several special measures for system-forming enterprises: preferential credits for replenishment of working capital and maintenance of employment, special conditions for obtaining deferral or installment payments for some tax payments with payment deadlines in 2020, credits at a preferential rate can be obtained by subsidiaries of system-forming enterprises, as well as their parent companies. Besides, systemically important companies that are at special risk can also apply for subsidies to reimburse production, work and service costs and government guarantees necessary to restructure existing loans or issue new loans and bond issues.
12. Non-performing loans. Such loans may be claimed by enterprises from affected industries, as well as socially oriented non-profit organizations. For enterprises that retain at least 90% of their employees, the loan will be written off along with interest - the state will pay the entire amount. If at least 80% of employees remain on the

staff, the entrepreneur will have to repay only half of the loan and the interest on it (Russian Government, 2020).

Thus, we see that we are talking about supporting the population and business through a softer monetary policy, accompanied by extensive budget guarantees, which reduce the risks of bank lending. It should be noted that the measures taken by the Russian government have helped the population and business to survive difficult times, as well as kept the country's economy from collapse, preventing a sharp downturn.

VOLUNTEER ISSUES

Within the framework of the All-Russian action of mutual assistance during the Coronavirus Pandemic "My Vmeste," volunteers help elderly people in the delivery of products, medicines and necessities, they also perform such functions as psychological and legal advice, online assistance, and volunteers with specialized education help in medical organizations. The target audience for assistance comprises elderly people and citizens with low mobility (My Vmeste, 2020). Appeals are accepted twenty-four hours a day on a "hot line." There are four main volunteer focus areas:

1. Buying and delivering products, medicines and essential commodities. People who are now at home in self-isolation due to Coronavirus need assistance in buying and delivering products, medicines and household goods. Volunteers purchase everything they need and bring it to beneficiaries observing all safety precautions.
2. Assistance with medical organizations. Due to the high load on medical staff, assistance in patient care, manipulation, document management and patient routing is required. Volunteers are distributed according to their specialization. Non-medical assistance in this area can also be joined by those who do not have a medical education.
3. Providing psychological assistance. Due to the wide spread of various information about Coronavirus infection, people are not always able to perceive it adequately, and there are stressful reactions. Volunteers with appropriate training provide psychological support to people by telephone and text consultation. To become a volunteer in this area, individuals need an education in psychology.
4. Help in call centers. Patients with a mild course of the new coronavirus infection are given outpatient treatment. Volunteers make calls to these patients using prepared scripts to monitor the dynamics of their condition and refer them to the doctor's surgery if necessary. Volunteers also respond to citizens' questions about the coronavirus, talk about its prevention and diagnosis, report the results of tests, and pass on necessary information. General volunteers and volunteers with medical education can work in this area (My Vmeste, 2020).

Each volunteer must take a distance learning course on the following topics:

- Hygienic norms for volunteers;
- Mechanism of providing volunteer assistance to elderly people;
- The specifics of interaction with elderly people;
- The actions of volunteers in emergency and non-standard situations (My Vmeste, 2020).

After that, they will receive a face-to-face briefing on safety at the headquarters in groups (up to 20 people) or individually. Then they receive an accreditation badge and admission to work, after which they undergo a check-in procedure before starting work: temperature measurement, safety briefing and receiving individual safety kits (My Vmeste, 2020).

To avoid cases of fraud, applicants are informed about the identity of the real volunteers:

- Volunteers wear a special badge and a passport.
- Volunteers are provided with personal protective equipment: a disposable medical mask, gloves and antiseptics.
- Volunteers do not enter the apartment/house.
- The volunteer knows the beneficiary's application number and must inform him/her at the beginning of communication.
- You can check the identity of each volunteer by contacting the regional volunteer organization (My Vmeste, 2020).

This is the largest, but not the only, action of mutual aid in Russia that appeared during the epidemic. Obviously, in such a difficult period, the main pressure falls on medical personnel, who also need support, including of a moral kind. For example, in Blagoveshchensk there is an action "Doctors are our heroes," where the city entrepreneurs collect gifts for medical workers to support them during the pandemic. They buy medical hand creams, moisturizing facial masks, honey and other sweets, which they put into gift sets and give to doctors who work with patients with COVID-19. Gifts are bought at the expense of entrepreneurs and citizens who care about them. Businesspeople also donated fruit and fresh baked goods to the staff of the emergency station and Blagoveshchensk city hospital. The initiative group plans to form gifts for medical workers from hospitals in the region. The coaches and sportsmen of "Mashina" club in Blagoveshchensk help doctors unload medicines and furniture, which were transported from one medical institution to another to equip infectious diseases hospitals (My Vmeste, 2020).

CONCLUSION

Nowadays it is obvious that such a great pandemic will have a long-lasting and even controversial effect on all spheres of people's lives. And its consequences are highly dependent on the expediency and efficiency of specific measures undertaken by the government and peoples' economic and social behavior. Of course, the Coronavirus pandemic has such a huge scale that preventing and defeating it cannot be an objective of each country in particular. There must be a strong collaboration between countries, at least between those who have common frontiers.

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Chapter 495

LONG LIVE TO THE URBAN FLESH

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Panic on the streets of London
Panic on the streets of Birmingham
I wonder to myself
Could life ever be sane again?
The leeds side-streets that you slip down
I wonder to myself
Hopes may rise on the Grasmere
But honey pie, you're not safe here
So you run down
To the safety of the town
The Smiths – Panic (1987).

ABSTRACT

In the present chapter we bring some reflection about changes of the current reconfigured urban space and the orientation of a revaluated vision of ecosophy with some specific elements of the ambiance that we can observe in the daily experience. With this structure, we build in our way a kind of sensible thought to elucidate a vision of some forms of urban social dimension. Our intention in this hot-debate aims to show some fragments constructing a particular vision of the spirit of the time in order to analyze the actual socio-urban dimension. In this perspective, will bring together some goals as the illustration of the actual city, the experience in the post COVID19 situation, the idea of proximity, the new vision of ecological sensibility, where each of them encloses other peculiars aspects of our experience of the social urban world.

Keywords: urbanity, emotions, pandemic, COVID19, ecosophy

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INTRODUCTION

How to think the city and its spaces in the actual social situation? We assist in a renewal of the approach of the way to live in urban space and the changes in the lifestyle. Is the city in crisis? It is dead? What is its future?

The explosion of the epidemic situation has generated a particular condition in the whole world where the imposition of ‘social distancing’ and the political interventions about the virus Covid 19 have transformed the face of the city. One of the first impressions is that we witness a materialisation of post-apocalyptic imaginary, the catastrophic dimension of urban space where the persons disappear and the city becomes empty of social life. This is a sort of imaginary to live on new ruins of an actual social world where all the images that circulate on social media, on tv, web or journals, exhibit the empty cities as we lived in a kind of science-fiction dimension: Into the void.

Despite all, the first global lockdown shows us a ‘particular beauty’ of the cities: it’s a paradox maybe, but strangely all the images that we have consumed can be considered as ‘the unsettling beauty’ or a ‘sadness beauty’ of global cities. The images of empty cities that we observed, like Time Square in New York that is usually a pulsing heart, or California Street in San Francisco without the full dimension of tram and cars, the alleys of Venice, Plaza Mayor in Madrid, Ponte Vecchio in Florence, Champs Élysées in Paris, habitually places of the crowd and animated temporalities like many other examples. This gives us the feeling that the city without the human is more romantic, attractive, scenic! Everyone in front of these images can have the impression of this ‘strange beauty.’

Our intention in this reflection, is to show some aspects or better some fragments constructing a particular vision of the spirit of the time in order to analyze the actual socio-urban dimension. The fragments are like images of thinking, as the work of Walter Benjamin teaches us, to illustrate the signs of our present and re-think our time. In this perspective, will bring together some goals as the illustration of the actual city, the experience in the Covid situation, the idea of proximity, the new vision of ecological sensibility, where each of them encloses other peculiar aspects of our experience of the social urban world. In the first step, we clarify the image of the city through the effect of the pandemic situation and after concentrate the reflection about how the Covid affects our life in the urban and the interior dimension with the particular effect of digital experience. After that, the discussion will be oriented towards the notion of proximity and the semiotic changes of the current reconfigured urban space and the orientation of a revaluated vision of ecosophy with some specific elements of the ambiance that we can observe in the daily experience. With this structure, we build in our way a kind of sensible thought to elucidate a vision of some forms of urban social dimension.

SHORT DEBATE: THE CITY

The desert city, the phantom city, or the silent city where one can just listen to the sound of nature. These are the impressions of a fascinating atmosphere where the calm dominates transforming the city into a unique historical moment. We can witness this show during a digital promenade on Instagram where is possible to rediscover the splendor of the city. This

illustrates a kind of impossible dream of seeing the beauty of the landscape without traffic, pollution, noises... The pandemic is affecting the emotional aspect of the images that circulate as conversational moments of daily life shared by the internauts (or netizen). They create a mosaic of this kind of landmark proving the world as a post-apocalyptic appearance. During this period, we have been spectators of external life from the interior. Our windows represent a porosity instrument, a medium to look at this spectacular desert. At the same time all the web's windows permitting us to circumnavigate all over the city of the globe to assist at this world in ruins. In this perspective, we can think, in reference to the theory of Walter Benjamin, at a compenetrating of spaces. That would be a duality where the urban space has a texture of an image like a new kind of phantasmagoria. It would allow us to dream, from the windows, the external urban life. This particular porosity represents an allegoric form of presence with an emphasis on emotions and feelings. Emotions must be understood as a social language, a collective expression, in the perspective of Marcel Mauss (1921). In our reflection, we can see how the extension of the interior of our apartments during the lockdown was exteriorized from the window to create a social manifestation of an emotional tribality (Maffesoli, 1988). It's an emotional resonance that the people create with this kind of 'sociology of balconies.' It became an expression to this extension from inside to outside, the intimacy became extremity (*extimité*) according to the analysis of the French psychiatrist Serge Tisseron. Our balconies and windows, from Paris to Naples, from New York to Barcelona, etc., testified this desire to make visible the aspects of our social existence without the possibility to be on the street. It gave the possibility to live the street through the lockdown. We can conceive them as an 'opening on the world' (Teyssot, 2009) or also as an instrument of political act. Show drawing of children, clapping, sing together as a kind of flash mob, the music on high volume are some actions that people organize from this particular space, the balcony, became for a special period the 'new street.'

This special emotional moment describes an imaginary of 'cultural apocalypse,' using here a terminology of the Italian anthropologist Ernesto Di Martino (1977), that indicates a relevant change transforming the entire community of people. The apocalypse means the end of a paradigm and its cultural organization that generate the production of a new kind of behavior, thought and interests. Each epoch can have its 'end of a world' that signifies a deeper social change and, in our reflection, an actual reconfiguration of urban life. The question, following Di Martino, is about the 'how.' In our consideration how is or must be the human in the city and this 'how' represents an ontological question of the presence and the way to be in the world and renovate it through different forms. How is the way to be in the social world and in the urban dimension in this particular *zeitgeist*? The approach of Georg Simmel concerning the idea of sociology as *nova scienza* (a notion used by Gianbattista Vico) is relevant in this consideration. Reality isn't static but always in movement and the same goes for the city and its urban atmospheres. So, we must observe this reality in movement and try to put in evidence some forms, some essential characters. In this direction the modalities we inhabit the world are in relation to the urban sphere. In this case, the balcony assumes a significant dimension of social interrelation fusing with the digital space to create a fortification of the social connection.

THE COVID19 AND THE EXPERIENCE

COVID19 instils emotional affectivity of the human action also developed via the web life's experience creating. Therefore, it becomes an expressive space, or a 'grammar of experience' (Goffman, 1991) made possible through the urban photos shared by the citizens to show the reality of the present city. It shows a city of ghosts lived by images that remind us of an imaginary post-apocalyptic. This is carried by science fiction or from the narration by tv-series and cinema that absorb reality in a kind of melancholic feeling. This can be the logic that constructs a type of presentation of the vestiges of our social dimension. They are almost like a romantic scene suggesting, additionally, a scenario of quietness where the city became a postcard. But at the same time, this sad beauty is the sign of the time dominated by the 'a-social' dimension of the pandemic. The city struggles with the effect of reciprocity interaction and its fundamental quality: the instrument to be present, to inhabit the world. In fact, the relation of individual/urban space is one of the primary meanings of the way to inhabit the world. The destruction of social relations with the spacing means, at the same time, the ruination of the urban social dimension with the lockdown factor that isolates people inside, thus developing an electronic social construction of reality.

The electronic space, lived in the sharing life of emotions, show us the potentiality of the digital windows creating a conceivable manner to stay together and animate the world. The outside without human beings seems something different. Many opinions put the accent on the possibility to appreciate the beauty of the urban landscape, the soundscape of the urban structure with the absence of noises, the flowering of nature. This makes us think about the place of humans. Today, many discourses arguments about 'how' to think the city of tomorrow with the resilience, the co-construction with nature or simply a more ecological city. But at the same time, we can perceive the intensity of technological control with drones, cameras, new apps and militarization generating contemporary anxiety by surveillance.

So, how to think the actual transformation and of social life through the urban space? (Re) think the urban space pay attention to dissimilar elements but, succinctly, suggest that the urban body is a part of us, an extension of the human body. The new settlement and frequent of the street are synonymous of an intensity to be together. The street is a magma, a social glue indicating societal energy that must never die. The importance of the street for the construction of social reality means to revoke the duality individual/urban space as an evident element of vitalism. Life is also synonymous of the street and urban sections where the Being is externalized as an ontological dimension. The open windows with the sound of music from inside that invade the street, for example, was one of the modalities or better a tactic, following the idea of the 'invention of daily life' in Michel de Certeau (1981). It marks a presence, to animate the outside and construct an emotional atmosphere shared with the others.

We know how emotions are important to the structure of daily life. Urbanity is also designed from this point because emotions participate in the creation of urban ambience as a sensorial impact on the human and urban spaces. The emotions can be considerate, through the senses of course, as an interface between the urbanity and the individuals configuring our environment and the way to be in this environment. Urbanity must be considered not only for the simple functions or materiality but it is necessary to put attention on the 'immateriality' i.e., the way we feel the urbanity. We can also talk about sensations, sentiments that allow a

perception of the city. It would compose an imaginary of emotional spaces shared by the individuals and, in this direction, we assist to particular manners to do, to be in the space considering also the porosity inside/outside.

The spatial dimension acquires new sensorial forms as consequences to the reconfiguration of the space to manage the pandemic situation. We can perceive in the urban panorama new signs and symbols that the individuals must recognize in its visual sensitivity as a kind of new alphabetization of spatial semiotic. The predominating of visibility is one of the keys of lectures to approach the urbanity and because it's one of the most stimulated senses and our eyes must decrypt many stimuli to read the city as a text. The various signs and symbols became a language for us and all the transformations change the inter-sensorial mode to be in the space developing as well the social reality in the urban configuration. In this phase, we can assist in a reorganisation of space through new codes to decipher and interpret. In this layout, we can say that there is a new alphabetisation because we must reorganize our visual perception. It is possible to apprehend a new symbolic language that redefines our urban social life in the optic to observe the relations between social comportment and urban forms. One can talk about altered architectonic affecting new categories of open and enclosed spaces where generate different settlements of distance.

THE NOTION OF PROXIMITY

Proximity is within a re-arrangement of presence where demarcations, limits, restrictions transform our spaces of 'contacts,' often generating a crisis of presence. In fact, one of the first appearances was to desert urban life with many places closed. It is impossible to be lived because the settlement was the non-contact and the inside private space was the 'safe' universe. The non-contact or more common the 'social distance,' influences and re-defined the practice of the social urban space. New sensorial orientations are also the significance of the practice that the individual must interiorise concerning the multiple marks on the ground. These marks proliferate actually in our cities on the sidewalk or inside the malls, schools, markets, shops, etc. The sensorial attitude is characterized by the signals directing our glance, signs and symbols of new social parameters to be in the space. They remind to manners to apply with the calculation of distance, use of masks, put the gel, wash your hands, etc. This is the visual symbolic panorama of the actual urban situation. Individuals are confronted to recognize some signs incarnate in the new dimension of architecture and urbanism. This also means a new perspective of the significance of something that changes our mental, corporal and emotional feeling within the city. An epochal question that arises in a complex dimension with a phenomenological topic where the city must answer with a proposition of mutations in conformity with the distinctive situation. In this condition, the urban and architectural factors are considered as an illustration of inhabited spaces. It has a direct impact on forms of perception of external and interior lived spaces because are a prolongation of the individual and the evident manifestation of social behaviours with a determinate influence on lived experience.

There is a relation between the natural space and the anthropized space that configures the social landscape. It's a typology of the aesthetical process of architecture and spatial dimensions as a predisposition to lived experience. It must assume a disposition to the

strategy of ‘transformability’ of the city and, consequently, human nature. Many questions and interrogations of possible changes and directions are stipulated where the urban and social dimensions must answer for a ‘better’ future! The problem is that we put many attentions on the future and we forget the present, the lived experience in the *hic et nunc* of our situation. The impression is that people need urban places to be present in the world. This is because there is a concatenation, a vitality of forms between human being and urban spaces. We see that the reaction of people after the confinement was the invasions of the street, the pleasure to be on terraces of bars, restaurants, coffees that means, simply, a manifestation of social life presence. The pandemic situation creates a kind of annihilation of urban atmosphere generating mutations of sensations. This does not mean that social vitalism is gone! But just a kind of an ‘adaptation to the situation,’ a famous theorem of William Isaac Thomas, where people ‘do with’ (as a strategy of daily life in Michel de Certeau theory and Michel Maffesoli idea of real). This ‘do with’ is also accommodation, adjustment, where people readapt its manners to respond to a social situation.

THE ECOLOGY RE-IMAGINED

The key can be to reinvent new codes where the space is hybrid with contamination and not just a simple function. It is similar to ‘open urbanism’ proposed by the reflection of Richard Sennet, in some recent interviews, with a flexible environment and the proposition of porosity to redefine the structure and manners. The problem is to think of a way to inhabit, the way we use the physical environment and how the behaviour can be adequate. One of the most recurrent opportunities to adapt the social life is the pregnancy of a green attitude. In our reflection, it would be better for the emphasis on the eco-sophical perspective to understand the pregnancy on the sensible and the collective way to inhabit. The ecosophy for the French philosopher Félix Guattari (2013) is an articulation between nature or environment, social relations and subjectivity. In our opinion, this synergy influences urbanity and the architecture and the way to live in the urban and social geography and represents a specific relation of an ontology of actual dimensions. Ontologically the need for ‘nature,’ also illustrated by the important contribution of the theory of Augustin Berque, is integrated into the connection that the human being has with its environment and *milieu*. It is an ‘onto-geographical’ relation (Berque, 2000) that redefines the attention of nature as the interaction between the individuals and space. The way we are interconnected to the urban social environment is also characterized by the way to feel through the sensible perception that generates a particular ambience. This produces a spatial experience and way to inhabit. The discussion about ‘green’ today is very common. Nevertheless, our intention isn’t an ideological reflection but a consideration of a relation with the contest where we live to re-build the social reality. The city, in this direction, represents a significant element to think about the aesthetic of ecosophical paradigm from the recreative forms to inhabit. This signifies a new creation of the sense of urbanology that put the attention on the knowledge of the city and its lived spaces. The ecosophy must be thanked, following the proposition of Maffesoli (2010) as a way to be in the world.

The idea of Guattari was also to think the hypothesis of ecology as a mode to re-invent new manners to be in the world and new forms of sociality. The ecosophical sensibility can

be a societal transformation with a particular highlighting on the relational ethic. This can be in consonance with the proposition of Arne Næss (2008) about a relational ontology where all the forms of life are interdependent. This interdependence can be based on some attention about architectural forms and the transformation of the inhabited landscape, where the technology has a big impact on the contribution of the mutations. The rhythm of actual urbanology is structured by the immersion in a relation between technique, culture and technology. Often the perception, when we think to the association urbanity and technology, is something similar to a dystopic sensation (i.e., a type of *black mirror* scenario¹). Technology is control of urban space and during the pandemic period, we have assisted to a 'dronization' of the territory. This fed the idea of an immersive control also structured by some apps of our smartphone and QR codes to verify the displacement of people in the epoch where we transform ourselves into simple data... Examples, among others, confirming a political strategy of control, an increase of surveillance as the progress of a new *Big Brother watching us!*

We don't have the intention to enter here in this argument that also generates many reactions about neo-liberalism and the asphyxia of terror provoked by the pandemic that struggles our social reality through the social distance and all the gestures we must apply. But we know that the human being needs contacts and, in this situation, new technology is also used to create forms of socialization (and in our opinion isn't a novelty), forming a digital society where the union between the Net and the lived spaces are a common fact. The city is more eco-systemic where the informatics architecture transforms the relation creating a rhizomatic experienced established on the connectivity. This generates hybridism of experiences and vital flux. In the optic of thought proposed by Massimo Di Felice (2010; 2012), we are in a biosphere defined like an 'info-material' where the individual is in interaction with nature through media prothesis creating an 'atopic connection.' For Di Felice, the informatics architecture based on the Net and with interactive and connective ecology produces another vision of the ecology that isn't a simple idea of the environment. On the contrary, it is a complex union of networks composing a new form to inhabit the world that we can call cohabitation. This generates at the same time a new version of a 'poetics of the space.' Poetic that the famous French philosopher Gaston Bachelard (1957) explained like a sensible phenomenology of the space and the instantaneity of lived experience. Urban spatiality is a coincidence with the existential spatiality.

In this direction, we must think that the interconnection of the physical environment with the social atmosphere and the human actions and the environment represent our surroundings. Well, it is obvious that one of the questions of our times is the requalification of the urbanity with special attention of the ecosophy and not simple ecology. A requalification that also concerns the life-style and the production of new spatiality where is possible to re-enchant the urban ecosystem. In this illustration, the biophilia seems to be a tendency of contemporary life. It represents a connection with nature and also a kind of well-being generating some specific configurations in an urban atmosphere. Our relation to nature products this 'biophilic city' where the cohabitation and the nature can be factors of social cohesion. In the optic of urban planning and metropolitan design, the empathy with nature is a topic that recreates the social urban space. The design conception of urban spaces, in fact, put the focus on biodiversity through the conception of spaces that sensitize the ecosophical values producing,

¹ The reference, of course, is to the British dystopian series *Black Mirror* created by Charlie Brooker.

in this way, a reciprocal relationship between human, nature and urbanity. We can also understand the vegetal design trying to engender well-being in urban dimensions as a strategy of social reconstruction of reality.

The vegetal design transforms our imaginary of nature creating a valorization of this effect and an urban emotionality linked to the ‘vegetalization’ of daily life experience. The idea of biophilia is one of the tendencies to regenerate our urban body. This can produce a straighten of social ties where space plays a vital role. The presence of nature, a strategy more and more current in the discussion of the city ‘post-covid,’ must be read like the creation of sensible ambience that influences the sensorial perception of the citizen and creates a kind of pleasantness. We can feel more and more in all the cities and for the human body, this necessity of green. In fact, one of the consequences of the lockdown was the escape from the metropolis and the refuge in green spaces outside from urbanity (that means in our opinion the danger to destruction the countryside). For this reason, some actual project – that we can also define as a projection of a sci-fi imaginary –, concentrates the attention on the ‘post-covid city’ as the eco-district thanked in the perspective of a self-sufficient city.

For instance, we can refer to the project in China by the Spanish architect Vicente Guallart. Its proposition of ‘self-sufficient city’ is a response to the climate catastrophe and to the covid crisis. It can generate new forms of architecture and lifestyle with the integration of porosity. This is also the idea of the theorization of the concept ‘the 15-minute city’ idealized by Carlos Moreno, one of the pioneers of the ‘Smart City,’ as an urban design approach to ameliorate the quality of life. This is done by creating cities where all the residents can reach everything they need within 15 minutes by bike, public transports, walk. A ‘no-car city’ we could say, following the dream of the current Paris Mayor Anne Hidalgo that is one of the most enthusiastic supporters of this kind of city in her proposition to transform the *City of Light*. For Moreno (2020), the object is the city of proximity with a massive network of places redefining the lifetime, a redefinition of the idea of city form that must overlook the ‘world-city.’ We must understand the mutations and risks of climatic change, new pandemic and the extreme forms of neo-liberalism and savage capitalism that smashed the social reality.

The project of Guallart and the idea of Moreno are conceptions of the mutation provoked by the actual crisis. They offer a proposition of a lifetime harmony where, again, the porosity as an extension is one of the keys. There are also many other suggestions where the individual has a central place and can contribute. We think to the ‘makers’ for example, to the reconfiguration of urban social life. For us, the mutation is also an occasion to humanize spaces through nature, reintegrate green strategies. The mutation is not just some interesting ideas and actualization of interventions (green architecture, shared gardens, vegetal wall...) but rather ontological and paradigmatic. This means rethinking the urbanity from ‘natural green’ creation as integration in the life-style. This also adds a poetic and sensible dimension as the complement of the re-signification of urban social life as a possibility to think all this arrangement as facilitation of eco-systems in an organic city to think like a body with its flesh, skin, organs. This is, at the same time, a mode to actualize the transformation of urbanity and the renewal of the urban panorama where the vegetation of lived spaces became a style that proliferates.

This must be imagined as an answer to the nervous intensification of life that showed Georg Simmel (1903) as the effect on the metropolitan cities. The ecosophy of the urban space, following the thought of Simmel, can be a way to forge the psychology of the urban and the way to think. For this reason, all the ‘natural’ conception are emblems of an eco-

societal stabilisation of actual metropolis with the scope to transmute the manners to live-together.

We can propose the idea of an ‘organi-city’ like an inclination to the modes to edify the human and urban habitat by the sensible mutation of the ambience. It offers a social harmony between human and environment where, for the ecosophical perspective, the man and the world are aspects of the same reality. And in this reality often we listen to discussions about the concept very common and popular like the resilience with the proposition of a ‘resilient city’ as a strategy of urban regeneration. This that signifies adequacy to the spirit of the time to develop the community capacity of a way to inhabit-together as a mode to be in the world; adaptation of a new form of urban life with an emergency of socio-aesthetical solidarity. But the ‘resilient city’ is often thanked as models of planning of risks and vulnerability of society. This is more ‘collapsological’ (another popular concept that invades our daily life with the proliferation of opinions and catastrophic analysis).

In our intention, associating to resilience the *reliance* (a way to be linked), we try to think to a process where the *homo urbanus* is connected to the *milieu* in its organic experience where the actions are a synergy of eco-social-urban well-being. In this sensibility, we can feel the tonality with spaces through sensible experience where the individuals adapt the way to be with the environment. Being in tonality in a sensible and effective way is a reflection about the importance of ambience. It also reflects the *Stimmung* that in Heidegger *Sein und Zeit* is a way to have access to being there, a manifestation of being revealing a *das Gestimmte* that means ‘to be-intoned.’ The intonation is a harmonic disposition that, in a reflection about the actual reality of the city, can be in relation to nature, to the ecosophical essence.

CONCLUSION

After further discussion, the present chapter holds that we are affected by the space and this is usually to the entire situation even in the pandemic period where people must have a new attitude that with time became incorporate in our sensorial modus. And the effect to be ‘affected by’ is essential to understand the way we react to singular situations. It also allows proving that the relationship that we have with the surrounding environment is effectual in a typology of ‘fleshly space’ that in the logic of ambience theory we can perceive from the sensible point of view that unites us to the urbanity. The urban space isn’t conceived as an anthropocentric dimension but, instead, through the re-valorization of daily life in congruence with the living space. We can also talk about the effect of topophilia that the geographer Yi-Fu Tuan (1974) illustrated as the perception of the environment that concerns the place with which the individuals have an affection relation and feel to be linked. To be attached is one of the keys to understanding the potentiality of the urbanity because the human being needs an intimate relationship with the city and environment that create, at the same time, the condition to be related with the others.

Also, within the effects of the pandemic situation, where many discourses are centred on a catastrophic point of view that announces (again) the ‘death of the city’ and social relation, the city endures being the sensible container of the lived experience of which the Being needs just to be in the world. The Being adapts itself to all kinds of situations and the street, the places, the spaces are a prothesis of ourselves; the condition of reality shows us that the

sociality is the way to support the world. Then, sociality is the hope to redefine the construction of reality also with the consideration of the importance of digital dimensions. The interconnection with a new arrangement of the interior spaces that are more than more windows open on the world. In substance, the city must be perceived as a body. This requires a change of paradigm that finished with the obsessive vision of functionalist planning and achieve the perception of the organic city with all its pores that exude the vitality and made manifest the urban epidermis. 'This is the way, step inside'²....

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² This is a verse of the song *Atrocity Exhibition* by Joy Division (1980).

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Chapter 496

PANDEMIC, SOCIAL POLICIES AND EMOTIONS IN THE METROPOLITAN AREA OF BUENOS AIRES

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... as is often the case, observing current events illustrates the understanding of the past and delving into what has happened clarifies what is happening: many of the Interdependence mechanisms of our days continue the changes of the past ... (Elias, 1993).

ABSTRACT

The Metropolitan Area of Buenos Aires is one of the poorest areas of Argentina. In this area is located La Matanza, the largest geographic municipality with the largest population and greatest vulnerability, as indicated by data from a pre-pandemic investigation. In March 2020, in Argentina the “social, preventive and mandatory isolation” was declared in the face of the Covid-19 pandemic, which meant an increase in poverty and social assistance. In this context, an online survey study was carried out (in four waves: April, May, June and September/October) in order to ascertain the changes in the poverty situation of the population of La Matanza among the people receiving a social benefit, and related emotions around the pandemic and their own situation of vulnerability. For this, the exposition of the article will be: a) a review of the social and economic situation of the territory in question pre-pandemic; b) development of the theoretical perspective regarding social policies to address poverty in connection with emotions, considering social interventions that construct meanings, elaborate perceptions, and are located in the performativity of the aforementioned policies; c) development of the methodological aspects of research and analysis of quantitative information, taking into account the population that receives a social program and the emotions that emerge in relation to the pandemic. In this way, this chapter aims to make a substantial contribution to understanding the impact on the sensitivities of the recipients of the social interventions implemented in the context of a pandemic.

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Keywords: pandemic, social politics, emotions, La Matanza, poverty

REVIEW OF THE PRE-PANDEMIC SOCIAL QUESTION IN THE TERRITORY OF LA MATANZA

Greater Buenos Aires is an area that surrounds the City of Buenos Aires, made up of 24 districts¹; which as a whole form an “urban area,” since they make up the largest urban complex in the country. According to the last census of 2010 (INDEC), the city concentrates almost 25% of the country’s inhabitants. This region not only represents the largest single segment of the population, but is also where the highest levels of poverty and indigence are concentrated. In 2019, poverty affected 39.84% of the people who live in this area, and in the first quarter of 2020, with the start of quarantine due to the COVID-19 pandemic, it reached 47.5% (INDEC). The municipality of La Matanza, located in this region, is characterized not only by being the most populated - in 2010 it reached 1,772,130 people in a total of 483,397 homes (INDEC)- and extensive with 325.71 kilometers squares, but because it has a deep spatial segmentation that, in principle, can be subdivided into three large areas that are very different in terms of their socio-housing, economic and cultural characteristics. The first of these areas is that bordering the Autonomous City of Buenos Aires, where the inhabitants have more possibility of accessing drinking water and sewer services, it has most of the paved streets. The presence of villages and settlements is focused on relatively small sectors since they present to a lesser extent in comparison to the following areas. It is the area with the highest tax collection and the lowest rates of poverty and indigence due to the fact that it is the area that has achieved the greatest development over the years. The second zone has an intermediate population density. Only in recent years was the coverage of drinking water and sewers expanded, only half of the streets are paved and tax collection is irregular and/or poor. The third area is the one with the greatest vulnerability, where there are the greatest infrastructural and social deficits, the possibility of accessibility to services, educational and health centers decrease compared to the other areas, with the highest poverty index and the one furthest from the City Buenos Aires. Precarious employment and housing conditions deepened in the 1990s and have spread, with alterations, to date, generating new configurations in existing social networks. The district stands out for the development of grassroots organizations and social movements that emerge as a strategy to achieve occupation processes and popular settlements (Manzano, 2007; Barna, 2014).

In order to establish a map of the situation of social and economic vulnerability of the district, a description of the habitation conditions will be presented, considering the overcrowding conditions, access to services, working conditions and reception of social programs, ending with the elaboration of an index regarding the basic living conditions of the homes of La Matanza.

¹ It is necessary to consider that the National Institute of Statistics and Censuses (INDEC) mentions 24 districts in the official website of the Autonomous City of Buenos Aires (<https://www.buenosaires.gob.ar/gobierno/unidades%20de%20proyectos%20especiales%20y%20puerto/que-es-amba>) are indicated 40 and, the CIPPEC 31. These distinctions run the limit towards municipalities traditionally considered of rural type, called “inland.”

Following the results of our investigations² prior to the pandemic, we have identified that the district presents a deep segmentation and spatial segregation among the three aforementioned zones (PELM, 2005, De Sena et al. 2020). Regarding the issue of habitation, 122 informal settlements were identified (TECHO, 2016)³, mostly in the second and third zones. It is in this sense that we have found that the population in the worst socio-economic situation, the one located in zones two and three, is the one that must buy water for cooking, and the one that has least access to sewers, with only 3.1% of homes in zone three having such access. In this framework, it is noted that 8% of the homes are in critical overcrowding conditions.⁴

La Matanza is a district of humid areas, bathed by a large number of streams and the Matanza-Riachuelo river. These streams and waterways cross large areas, which generate floods and contamination⁵, so living nearby can mean damage to homes and human health. We have observed that in a third of La Matanza the neighborhoods have a stream nearby. This is more serious in the second and third zones where almost half of the neighborhoods have a nearby stream. In this sense, the news regarding floods are frequent. We have detected that 43.6% of the lands are flooded. This information is completed with two more elements: the existence of storm drains in the neighborhood and the type of streets (paved or dirt). The storm drains serve to collect the water derived from the rains and prevent floods from occurring. In this municipality, a third of the neighborhoods do not have storm drains, a situation that worsens in the second zone - 58.3% do not have it - and in the third, 57.1% do not have it. This set of factors begins to explain the floods, but the public health problems they cause also deserve attention (De Sena et al. 2020). Along with this, the industrial discharge without previous treatment, and the clandestine dumping of garbage, is not only a constant factor of contamination of the Matanza river, but also of the water courses of the tributary streams in the district, especially Arroyo Morales, the longest within the district's territory (PELM 2005).

Regarding the employment situation, it was identified that 52% of the working population does so in informal conditions and most of the occupations refer to semi-skilled and unskilled activities. It is possible to observe some differences by gender. For example, a third of women perform cleaning tasks, and 14.1% of men are street vendors or laborers. And the situation is always more unfavorable for the second and third zones (De Sena, 2019).

Regarding the means of income that the household has, we have observed that 16% lack a regular monthly income, and that they subsist on exceptional income or due to debt, evidencing the precarious situation in which life develops.

Regarding the socio-economic level⁶, where ABC1 refers to the high level, with better economic and social position, the medium-high and medium-low level C2 and C3

² We refer to the quantitative and qualitative project: "Main features of the" social question "at the beginning of the XXI century. La Matanza 2017-2019." (PROINCE) PIDC code 55 B 206. National University of La Matanza. 2017-2018; under the direction of Angélica De Sena. The data presented here respond to a household survey witnessed, with a probabilistic sample of 829 households throughout the municipality of La Matanza.

³ <http://relevamiento.techo.org.ar/index.html>.

⁴ Critical overcrowding: corresponds to households with more than three people per room. For the calculation here, three or more people were taken to determine overcrowding.

⁵ <http://www.acumar.gob.ar/caracteristicas-cuenca-matanza-riachuelo/>.

⁶ This was taken as a base model NSE simplified (Socio-economic Level) questionnaire, corresponding to the year 2015 (latest version), of the Argentine Society of Marketing and Opinion Researchers (SAIMO). For this, the following variables were considered: income (considering the values of the total basic basket according to INDEC); medical coverage; level of studies achieved; working condition; and type of work activity.

respectively, and the low level divided into D and E refers to the low-high and low-low respectively. In La Matanza, the results indicate that 69.6% of the homes are of low socioeconomic level, and only 1.2% reach the high level and 23.7% the medium level. When reviewing the socio-economic level according to the area where the home is located, it is observed that the small percentage that achieves the ABC1 level is essentially located in the first area. While it is relevant to note that level E, in the first zone reaches 25.1%, in the second 39.4%, reaching 48.2% in the third. In other words, although the population in general is of a low socio-economic level (almost 70%), almost half belongs to the third zone.

Finally, and with the aim of broadening the view, we elaborated an index that would allow us to determine living conditions in a multidimensional way. Understanding by “basic living conditions” of a person the ways in which they develop their individual and social existence, linked to economic, health, education, employment and habitat aspects. Based on this, the following dimensions were designed: a) employment, whose indicators refer to the condition of activity and quality of employment; b) economic sustainability, in this case the indicators are related to the origin of the household income (work, social programs) and the receipt of different products (food, medicines, etc.); c) access to health, which refers to having some type of medical coverage and accessibility as distance from the health center or hospital⁷; d) education, taking into account the educational level of the respondent and the schooling of boys and girls in the home; e) housing, the level of overcrowding and access to health services were considered as indicators; and f) the environment of the home, in this case the indicators are related to the neighborhood conditions (garbage collection, flooding streets, storm drains, and nearby public transportation, among others). Based on this, the results obtained indicate that only 58% of households have basic living conditions; of the remainder, 3.1% do not possess these, and 39% only partially have them. This situation worsens in the second and third zones, where only 47.8% and 44.1% respectively have basic living conditions.

It is in this context that we identify that in 26.2% of the households at least one person receives a social program to address poverty, and in these households the index showed lower results. Among households where there is a social program, only 22.9% have basic living conditions, while where there are none, almost 70% have such conditions.

The data presented so far show that the entire municipality of La Matanza prior to the Covid-19 pandemic was clearly exposed to deficient social and economic conditions. This situation is even more serious among people who receive a social program to address poverty⁸. In this context of high vulnerability, with a high percentage of people living from informal jobs⁹ and with social programs, that is why we wonder about the impact of the Covid-19 quarantine and the emotions associated with it in this population.

⁷ This is a relevant indicator considering the geographical distances of the municipality and the inequalities between the first, second and third zones.

⁸ 76% receive a cash transfer and they are women (Dettano, 2020).

⁹ The informal workers mentioned must be added to the recipients of social programs who, in order to improve their income (given that according to our inquiries the subsidy only occupies the place of a “help”) perform roles such as domestic workers, street vendors or other unskilled activities (Dettano, 2020).

Table 1. Basic living conditions according to whether or not they have received programs to alleviate poverty, from the Matanza district, in percentages

Basic living conditions	General population	Households with at least one person receiving a SP	Households without receiving a SP
Has	54.9 %	22.9%	69.4%
Partially has	39%	65.6%	30.2%
Does not have	3.1%	11.5%	0.4%
Total	100 (829)	100 (216)	100 (613)

Source: Own elaboration.

In the next section, a review of the theoretical perspective regarding social policies to address poverty in connection with emotions will be carried out, considering social interventions that build meanings, elaborate perceptions, considering the performativity of the aforementioned policies.

EMOTIONS, SOCIAL POLICIES AND POVERTY

The social question approached as an aporia between formal equality and inequality of the Modern State (Castel, 1997) or as the contradictions of the Welfare State in capitalism (Offe, 1990), is associated with the social policies as interventions from the State towards the population in order to tend towards the *welfare* of the population and/or to suture market failures.

The question regarding what social policies are has been widely problematized from different disciplinary spaces - essentially the economic and social - and linked to the Welfare State, considering the strong presence of the State in people's daily lives since it is the one who assigns and redistributes the resources. Therefore, social policies will affect the production and reproduction of life and therefore in the construction of our daily lives, whether they aim to ensure certain minimum levels and certain opportunities to all members of the community (Hegenbuch, 1958 , in Titmuss, 1981), or as an attempt to direct the life of society along a path that it would not follow if it were allowed to run its course (Lafitte 1962, in Titmuss, 1981), or as state actions that contribute to the reduction of social conflicts ensuring the temporary persistence of the capitalist accumulation regime (Fleury Teixeira, 1997; Faleiros, 2004; De Sena and Cena, 2014). In other words, beyond the definition of what we call social policies, these always refer to State interventions for specific purposes, which respond to the ideological conceptions of a given government, which intervene in the life of the community. Therefore, both the actions and the omissions of each social policy construct meanings and shape individual and social subjects, from which a social fabric is built and socialities are consolidated. In this way, if they are interventions that shape the conditions of production and reproduction of the life of the different sectors and social groups, then they condense the possibilities of naming meaning and doing (De Sena, 2016). We have already mentioned in other places that social policies have a normative character, that they also establish meanings, ways of seeing and feeling the world that perform the social question and structure emotions in the bodies of millions of subjects, as recipients, designers, and

implementers of social policies (De Sena, 2016, De Sena and Scribano, 2020, Cena 2015, Dettano, 2017, Cena & Chahbenderian, 2012, Sordini, 2020, among others). For this reason, the sociological analysis of social policies from the perspective of bodies/emotions contributes to the study and understanding of the structuring mechanisms in contemporary capitalism. This is based on trying to combine a vision of these policies and how they build and consolidate ways of being, doing, thinking, and feeling, that structure the bodies and emotions in the subjects. There are intersections and articulations between the redefinitions of the “social question,” the elaboration of social policies within the framework of the processes of state regulation of the conflicts between capital and labor, the necessary and desired sensitivities for this to happen, and the interventions of the agencies that are involved.

This means that social policies have a central place in defining the characteristics that the process of social production and reproduction will have in a given historical context, generating the conditions for it and for developing sociability. Therefore, these policies also operate in the symbolic aspects of life and in those associated with the cognitive-affective. In doing so, they institute and reproduce (causing, imposing, canceling and/or repressing) certain images, models and stereotypes of society, the subject, women, work, family, motherhood, among others, and emotions: anger, happiness, love, anger, fear. This configures the structure of sensitivities (De Sena, 2014, Scribano and De Sena, 2013) that affect the daily ways of living and the vicissitudes of the intervened subjects (Scribano, 2010).

The feelings and emotions experienced by the agents, as cognitive-affective practices, have an intertextuality linked to a specific historical and social context that corresponds to specific social situations (Luna Zamora, 2007, Scribano, 2007). “There is a necessary link between affective subjectivity and objective social situation” (Bericat Alastuey, 2000: 152) from where a set of emotions are induced in the actors, but also where controls that affect their feelings are incorporated. These norms are barely perceptible when *we feel what we should feel*, and we learn to manage the emotions corresponding to each moment, towards better social regulation (Scribano, 2007, 2012).

Therefore, the approach to the social question materialized in social policies It not only promotes or restricts certain emotions, but also the social implications of such affectation, that is, how to build the daily life from conditions of deficiencies, what will be the ideal “emotional competencies” to reverse them, to print them or to get used to them (Luna Zamora, 2007; Hochschild 2011). Therefore, reviewing the emotions in the populations intervened through social programs leads us to understand the modes of social structuring. From these positions, in the following section, four surveys carried out during the quarantine by Covid-19 in the population receiving poverty care programs will be analyzed in order to uncover their emotions, as indicators that will allow us to later understand their practices.

EMOTIONS, SOCIAL PROGRAMS, QUARANTINE AND COVID-19

In this section we will analyze a series of results obtained from an investigation¹⁰ that was carried out at the UNLaM in order to make visible some behaviors of the population of

¹⁰ Project “The social question in the party of La Matanza in the context of a pandemic.” Vincular 2020 Program. UNLaM Rectoral Resolution No. 218/20. Secretariat of Science and Technology. National University of La Matanza. Director Angélica De Sena.

La Matanza against the restrictions established by the quarantine established in response to Covid-19. It was carried out through an online survey across four moments, the first from April 4 to 11, the second in May, the third in June, and the last at the end of September and the first days of October, from a non-probabilistic sample, based on a self-administered questionnaire with 3,291 respondents. The distribution ranged from the “snowball” technique to people over 18 years of age residing in the La Matanza district as part of the Greater Buenos Aires region. In this discussion, we will take as the focus of analysis the surveys completed by the people who receive a social program aimed at the alleviation of poverty (a total of 504 cases).

The year 2020 will be marked by Covid-19, with the first confirmed case in Argentina appearing on March 5, after which the number of infections increased rapidly, and on March 11 the World Health Organization declared the coronavirus outbreak to be a pandemic. In this context, and for the purpose of preventing the health system from collapse, on March 20 the Argentine national authorities established Social, Preventive and Mandatory Isolation (ASPO) in decree 297/2020¹¹, known as “quarantine.” The isolation was maintained -with some openings- until November 7, 2020,¹² the date on which the start of the stage of the “Social, Preventive and Obligatory Distancing” (DISPO) was announced¹³ in the Autonomous City of Buenos Aires and Greater Buenos Aires Ulna (GBA), the area where the greatest number of cases and the longest period of isolation were concentrated. The ASPO decree limited the possibilities of mobility and travel along routes, roads and public spaces, and only tasks considered as *essential* could be carried out. So the cities were “closed,” the streets were emptied, and we all had to “stay at home” in the face of ignorance of the behavior of the virus. One certain reality was the high level of contagion, and the only known means of prevention was a strategy of “isolation,” a method that is not new and has been used in other pandemics over the years, such as the ‘Spanish flu’ of 1918.

This meant the closure of all face-to-face activities and only those related to food, hygiene and health were enabled. The rest compulsively entered virtuality. The advice that had to be followed were: “stay home,” “wash your hands,” “disinfect surfaces,” and “keep distance between people.” These councils were operationalized in a different way in the population, in relation to their social, labor, and accessibility conditions prior to the pandemic.

In the previous point we made mention of emotions as the result of the structuring and organization of life processes, tied to the different and multiple modes of State intervention, and particularly towards this population that receives interventions from a social program given their situation of poverty.

Elias (1993) refers to the relationship between the control of the subject in relation to emotional structures and how these are different according to social classes. Said control is made effective through the regulation of individual emotions by means of internal or external coercion and - in some way - the structures of human manifestations. In this way, external coercion becomes internal and the different emotions (shame, fear, etc.) are structured as a certain continuous *self-control*, as unplanned configurations but in a specific order. Scribano (2009, Scribano and Vergara, 2009) refers to the mechanisms of social supportability and the

¹¹ See <https://www.boletinoficial.gob.ar/detalleAviso/primera/227042/20200320>.

¹² Therefore, the surveys were carried out in different months.

¹³ According to Decree 875/2020, DECNU-2020-875-APN-PTE. Official Gazette <https://www.boletinoficial.gob.ar/detalleAviso/primera/237062/20201107>.

devices for regulating sensations as a way of living life for those who are part of the world of No (no health, no education, no housing, etc.), but that in Argentina for some decades these have *not* been replaced with a massive array of social programs (De Sena, 2011).

Elías (1993) argued that emotions are made up of three major components, namely the somatic, behavior and feeling. For this reason, subjects faced with situations of uncertainty or danger prepare to face them by fighting or fleeing; it is in this sense that Scribano (2012) affirms that body/emotion are inseparable elements. In this way, it stresses those biologicistic positions, constructionists or naturalists, with an approach that understands them as a result of social structuring processes. Hence, for Luna Zamora, emotions can be conceptualized as “learned schemes, reinterpreted, negotiated and functionalized or refunctionalized to structured and structuring sociocultural contexts (...) attention must be paid to the preconditions and structures that determine the experiences of certain emotions or other individuals who interact under these premises, defining and getting involved based on them” (Luna Zamora, 2005: 29). For this reason, although experienced individually, they are recognized by others in daily life and the State, based on the diverse and profuse modes of intervention, and this is constituted in the elaborator of a cognitive-affective text, in which social policies become the organizers of everyday life.

The ways in which modern states work, the configuration of societies, and the different institutions, all impact the moods of populations. The State configures a mode of sociability, which accentuates aspects such as joy, vivacity, happiness, cordiality, and kindness; inscribed in each historical context that grants a type of life experience, it elaborates a mode of interaction and exchanges (Simmel, 1939).

For this reason, we question ourselves about the behavior of the population that, as shown in point 1, find themselves in a situation of social vulnerability. The pre-pandemic economy was complex, with respect to the emotions associated with Covid-19.

In the pre-pandemic investigation, we investigated the people who receive a social program, and there are two indicators that we present here. The first question regards how it feels to receive a social program, and the highest percentage responses are: 22.6% that it is a “help”¹⁴, 13.9% that it is a “relief,” 8.7% “joy” and 7.8% “Anger, anger.” In other words, in one way or another, the different ways of accounting for the emotions around the program refer to a further contribution to the family economy.¹⁵ The next question refers to how they feel each day, to which the most frequent responses were: 20.7% mentioned feeling “joy,” while 15.6% felt “sadness, pain or suffering.” These are followed by 10.8% with “anger,” 7.4% feel “good,” 6.6% “tired” and 4.9% “happiness.” In this way, we can observe that in everyday life in limited conditions, both contextual and individual, only a quarter (joy + happy) of the population mentions emotions related to *well-being*.

In this context, the quarantine restricts people’s possibilities for carrying out their work activities, especially considering that they were informal, further limiting their meager income. This is so much so that 62.8% respond that their economic situation is worse after quarantine since their income is lower. This situation is more serious according to the area of

¹⁴ In this regard, see Scribano Adrian and Angélica De Sena (2018) “Aid as the central axis of policies for the sensitivity of conditional income transfers,” in De Sena, A. (editor). *Social intervention at the beginning of the XXI century: conditional transfers in the global order*. ESEditor. Buenos Aires. Pp 253-284. Available in <http://estudiossociologicos.org/portal/la-intervencion-social-en-el-inicio-del-siglo-xxi-transferencia-condicionadas-en-el-orden-global/>.

¹⁵ It is necessary to consider that most of the programs refer to a Cash transfer.

residence. That is to say, although the situation is always bad - in line with what was mentioned in point 1- in the first zone for 56.5% their income decreased, in the second zone this was the case for 62.7%, and in the third for 69.2%. The economic situation worsened from the age of 40, among the ages of greatest work activity between 25 and 64 years, and among women. The income of this population was decreasing with the quarantine and associated with it the impossibility of carrying out the work activities in which they were previously engaged; but the high level of inflation in the Argentine economy must also be added.¹⁶ It is in this context that it should be analyzed that only 37.5% of the population mentioned that “they do not leave their home,” making it clear that the rest do, and possibly for some task related to improving their day-to-day life. This behavior was modified with the months of quarantine and the worsening of the economic situation for people who receive social programs.

	April	May	June	September	October
<i>Your income is lower than before the quarantine</i>	52.4%	83.3%	72%	71.4%	73.3%
<i>Today your economic situation is worse than before the quarantine</i>	57.7%	58.3%	66.7%	67.1%	76.7%

When asked why sustaining household expenses from quarantine only 5.9% can sustain all household expenses, while 54.5% can only sustain basic household expenses and 39.6% cannot even sustain expenses basic.

It is in this context that we will try to review the emotions of this population in relation to the first three months of quarantine (April, May and June) and then those of September/October, given that at that time, although the decree of isolation was still in force, according to our notes¹⁷ field, the isolation was no longer fulfilled and the streets were already populated with people circulating.

We will first analyze the initial moment of the quarantine (surveys of April, May, June¹⁸). At this time, among the recipients of poverty care programs, the emotion that arises in the first months of quarantine is fear with 48.8%, followed by anxiety with 26.5% and concern with a residual percentage of 1.2%¹⁹.

But these emotions change as the days pass and the quarantine continues: fear decreases since the month of April when it reached 53.3%, and in the month of May it drops to 45.7%, and in June it falls further to 37.3%. Conversely with anxiety: in April it is 23.6%, in May it is 30% and in June it rises to 32.2%. A quick explanation is that people are getting used to living with the virus, but also have to carry the anxiety that living with it means.

In order to better understand these two emotions, we will review them with two indicators that bring us quite close to the living conditions of this population: one refers to the area of residence (first, second and third) and the other to the level of education achieved.

¹⁶ Inflation in Argentina is a long-standing problem, in 2019 it reached 53%. For 2020, inflation in April and May was 1.5% respectively, in June 2.2%, September 2.8%, and October 3.8%. The largest price increases are in food products (INDEC, 2020).

¹⁷ Information emerged from the research team that resides in La Matanza.

¹⁸ We refer to 329 cases.

¹⁹ Although in this writing we refer only to the recipients of programs of attention to poverty in the face of Covid-19, we highlight that this relationship is inverse among non-recipients, with 35.5% feeling anxiety and 28.9% feeling fear.

Regarding the area of residence, in the first area (the most affluent) fear reaches 35.6%, in the second area 51.7% and in the third 53%, that is to say, when conditions are worse fear increases. Regarding anxiety in the first zone it reaches 35.6%, in the second to 20.2% and in the third to 25.9%; then this emotion is felt mostly in more favored socioeconomic areas.

Zone of residence	First Zone	Second Zone	Third Zone
Fear	35.6%	51.7%	53%
Anxiety	35.6%	20.2%	25.9%

Regarding the level of educational achievement in relation to fear of Covid-19: 57% had a low level of educational attainment²⁰, 43.1% had completed intermediary studies, and 35% had a high level of education. On the other hand, anxiety appears for 21.1% of those who had only reached a low level of education, it increases to 29.7% for those with intermediate levels of attainment, and 40% for those who have completed higher education. In this way, it is observed that lower levels of formal education increase fear, and vice versa with respect to anxiety.

Studies achieved	Low	Medium	High
Fear	57%	43.1%	35%
Anxiety	21.1%	29.7%	40%

What has been said so far allows us to hypothesize that fear increases as living conditions are worse and anxiety is less.

To continue with our analysis, we will consider the emotions that arise in this population after completing the 6 months of isolation decreed by the national government. Although according to our studies of the population, compliance with isolation was in fact limited. In this period emotions not mentioned above arise. Thus, the emotions most mentioned in the face of Covid-19 by people²¹ who receive a poverty care program are: fear amongst 25.1%, boredom amongst 18.3%, anxiety amongst 17.1% and worry amongst 15.4%. Concern previously was at only 1.25%, and with the continuity of the increase in cases and the permanence of the ASPO it increases. And, an emotion not mentioned above also appears such as boredom.

When analyzing according to the area of residence of the respondents, the same relationship is maintained as in previous months: in the first area, a lower percentage than in the third and the same as in the second. Concern tends to be less in more disadvantaged areas since in the first it reaches 20%, 11.5% in the second and 14.3% in the third.

	First Zone	Second Zone	Third Zone
Fear	23.1%	23%	30.6%
Boredom	15.4%	24.6%	14.3%
Anxiety	16.9%	16.4%	18.4%
Concern	20%	11.5%	14.3%

²⁰ Low refers to those who reached primary schooling, medium those who managed to finish middle school, and high those with university studies.

²¹ In this case we refer to 175 cases.

Continuing with the same criteria, educational attainment was also considered. This indicator seems to have a behavior similar to that of previous months. Fear continues to be greater as the education achieved decreases (36.34% for low studies, 26.7% medium and 12.1% high). Anxiety is greater for those who have completed higher level studies (9.1% low studies, 16.7% medium, and 24.2% high). Concern also increased with education, reaching 21.2% in those with higher education and 13.6% for those with a low level of education. Meanwhile, boredom goes down with educational attainment, given that 27.3% of those reporting this emotion have low levels of education, 18.3% medium and 12.1% high.

Studies achieved	Low	Medium	High
Fear	36.4%	26.7%	12.1%
Boredom	27.3%	18.3%	12.1%
Anxiety	9.1%	16.7%	24.2%
Concern	13.6%	14.2%	21.2%

One more element to take into account is that 67% of the population who mention feeling afraid are aged between 25 and 44 years old. It is women (35.6%) who feel fear more than men (20.4%), while anxiety is almost the same between genders.

And finally, regarding the economic issue, among those who evaluate their economic situation worse than before the quarantine, 31.4% feel fear and 32.6% anxiety. Among the beneficiaries of programs who consider that their situation is better than before quarantine, 16.7% feel fear and 22.4% feel anxiety.

Economic situation	Worse than before quarantine	Same as before quarantine	Better than before quarantine
Fear	31.4%	34.9%	16.7%
Anxiety	32.6%	25.7%	22.4%

Fear is an emotion that has been identified prior to the appearance of Covid-19, in the narratives of this population associated with the social program as a triple structuring linked to chance, the government, and the instability of both access and continuity to these policies of attention to the situation of poverty (Cena, 2019).

Feeling fear constitutes an emotion intimately linked to everyday life. In terms of Koury's study (2017) of fears in the city, this emotion impacts the organization of daily life, directly or indirectly affecting the practices of populations. Complementarily, Luna Zamora (2005) maintains that fear is constituted in and from an emotional experience, the product of the interaction between individual agency, biology, biography and society.

Continuing with Elias (1993), violence and fear are two strong elements in the processes of historical changes and, as a counterpart, trust and tolerance, the latter two were not mentioned even once by the respondents. The quarantine established through a decree told us what it is allowed to do and what is not allowed, leaving room for the configuration of behaviors and their regulation; a new organization of fears.

... "the structure of fears is nothing more than a psychic response to the constraints that men exert on others within social interdependence. Fears constitute one of the ways of union -and the most important- through which the structure of society flows over individual psychic functions. The engine of this civilizational transformation of the behavior of the social constraints that operate on the individual, such as fears, is constituted by a complete modification of the social constraints that operate on the individual, by a specific

change of the entire relational network, and above all, a change in the organization of violence” (Elias, 1993: 527-528).

The author refers to fear as a powerful element in the process of civilization towards the achievement of social prohibitions. These prohibitions rest on a “natural and historical” fear, but it is never natural but responds to history and the structure of social relations. Fear, then, serves as a mechanism of *social support* based on self-control and as a barrier to any conflict.

On the other hand, fear for some authors has a common thread with anxiety, although others try to separate it (Sierra, Ortega & Zubeidat, 2003). Anxiety appears linked to a forward action, this agitation or anxiety also leads to a state that does not allow calm. Anxiety appears on the one hand as an adaptive response, and on the other with a certain link to fear, although Marks (1986) differentiates it by linking it with some anticipation of future or unpredictable dangers, and as a consequence of capitalist structures of pessimism towards the future (Woods and Grant, 2006).

In this way we can continue to hypothesize that fear and anxiety are in relation to the material conditions of life, so that when these conditions are worse fear and anxiety are also. In other words, the strong interdependence between what Elias (1993) calls the “inner world” and the “outer world,” forming interdependence networks, giving way to what the author calls the self-control apparatus.

According to Sauri (1984), fear is a ritual and symbolic process (not basic) whose purpose is to reduce anxiety in the face of uncertainty, as regulatory mechanisms, in some cases it can be lurking until it leads to an extreme degree of terror or panic. When this happens, the subject abandons direct confrontation and starts to flee or becomes paralyzed (Saurí, 1984). Meanwhile, for Bauman (2008), “fear” deepens when it is dispersed, unclear and cannot be identified with a specific object or place and considers it responsible for the continuous state of fear of (liquid modernity). Finally, Geoffrey R. Skoll (2010) points out fear as functional to the interests of an elite that intends to extend its hegemony and for this, “global fear” is fundamental. From discourses of fear as a restrictive, but at the same time stimulating, political being, as a result of a capitalist state where many have little and most of the wealth produced is little distributed. In this state of constant conflict, fear works as a deterrent mechanism so that citizen demands are dispersed or at least cannot be organized as a coherent whole.

CONCLUSION

A few brief lines to reflect on Covid-19 and the modes of social regulation. The 21st century was embedded in a resounding way in our lives, illuminating to the point of being dazzling the precarious situations in which populations lived accustomed to lack. In this case in La Matanza as a sample of a Greater Buenos Aires, once a symbol of industrialization and now as a constant unease, vulnerabilities and precariousness: in education, in the type of work activity, socioeconomic level, access to housing, access to infrastructure and conditions of habitation (sewer, gas, storm drains, flood streets). This lack of access to services increases household living costs (purchase of water cans, gas from a carafe) and worsens sanitary conditions (floods, streams, lack of sewers). The situation of spatial segregation is combined with a certain favelization. And, poverty is presented as structural against which *the battle*

was lost²², where social programs “served as a cushion to moderate the increase in the number of poor”²³

In this context, fear and anxiety, along with boredom and worry, constitute the threads that bind behaviors such as Weber’s iron cage towards this population, where the quarantine in response to Covid-19 crystallizes the non-thematization of entering/leaving.

Fear conditions life, from here it is necessary to consider that it is the emotion most pronounced by the recipients of a social program, from the emergence of Covid-19 and the various modes of isolation in the global order. Fear as a coagulation mechanism of action (Scribano, 2007), in terms of Elias (1993) is established as a coercion that operates on individuals in the configuration of violence.

In this way, the 21st century, paraphrasing Elias in this “new civilization,” opens the doors for a new emotional constraint, which encompasses the inner world; that is, not only the social construction of emotions but also the social construction of the world’s perceptual apparatus, and with it the construction of sensation (Scribano, 2020).

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²² The Minister of Social Development of the Nation when announcing the increase in poverty due to the quarantine, indicated that “three generations of structural poverty, that is, intergenerational poverty in the same family” (<https://dib.com.ar/2020/09/daniel-arroyo-it-is-evident-that-we-have-had-an-increase-in-poverty-in-pandemic/>).

²³ Statements of the Minister of Social Development of the Nation, <https://www.lanacion.com.ar/economy/daniel-arroyo-poverty-nid2465769>.

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Chapter 497

SENSIBILITIES OF EATING INSIDE: EMOTIONS AND FOOD PRACTICES IN A TIME OF A PANDEMIC

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ABSTRACT

In the pandemic situation, where social distancing and confinement were presented as the main tools for its prevention, eating became confined to the inside of the home. For those who have a home to stay in, eating has been reinstated as a practice in the private sphere and as a need to be met while remaining indoors. Eating is a daily practice that produces and reproduces the body, and it is shaped from habits, norms and customs that are expressed in social sensibilities. At the same time, it is directly linked to the configuration of emotions as the body/food/hunger/emotions relationship unfolds in an unbreakable continuum. While the diet is configured as a set of practices that are practices of the politics of sensibilities, food and commensality practices imply and express sociabilities and experiences. In this case, by knowing about diet, food practices and commensality, we will know how people put into practice specific knowledge about food to organize and regulate the planning, preparation and consumption of their daily meals in the context of isolation and of a new organization of time. Thus, knowing about diet and its practices will allow us to know the sensibilities and experiences in the context of a pandemic, where food practices take on a greater importance, since it highlights not only the possibilities of access, variation, diversification and consumption, but specific sensibilities around cooking, eating and the home. The objective of this chapter is to expose the sensibilities of eating in a time of pandemic in Argentina and Spain, based on a comparative study between the two countries. To do this, we conducted an online survey, self-administered during the first five weeks of isolation and confinement, and in-depth interviews with young people from the tenth week, seeking to discover the eating practices of isolation in articulation with the time/space relationship, which are configured from a politics of sensibilities as cognitive-affective practices of feeling in the pandemic world.

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INTRODUCTION

The COVID-19 pandemic came as a surprise to many and was suddenly imposed, shifting from the news to mandatory confinement and isolation measures that not only immediately and strongly impacted the productive structure, but also immediately modified daily life in a way not previously known to many.

In Spain, the period of physical confinement and total social isolation due to COVID-19 –called the State of Alarm and Confinement (EAC, for its acronym in Spanish)– was established by Royal Decree 463/2020 on March 14, 2020. A few days later, on March 20, 2020, in Argentina, the Social, Preventive and Mandatory Isolation (ASPO, for its acronym in Spanish) came into effect. This new reality forced the subjects to not only modify their daily life, but also involved returning the home to the centre of all activities. Work, education, entertainment, training, and consumption were modified to be held indoors and in several cases, transformed to be able to be realized.

From the confinement and isolation policies due to the COVID-19 pandemic, food took on a new centrality in this context. First, it exposed the possibility of the lack of food amongst people who were born in the era of overabundance, while the fragility of the food system was exposed, reconfiguring this as an essential activity. During this period, eating was again configured as a practice inside the home, where, in many cases, it brought the subjects together again socially in the shared act. Thus, the reinstatement of eating as a practice in the private sphere and as a need to be answered on a daily basis within the home led to a readjustment of food practices and commensality.

The objective of this chapter is to expose the sensibilities of eating in a time of pandemic in Argentina and Spain, seeking to uncover the food practices and commensality practices in conjunction with the temporal/spatial relationship of confinement, which is configured from a policy of sensibilities as cognitive-affective practices of sentiment in the world of the pandemic.

The data presented comes from an online survey, self-administered, in which the food practices related to the purchase, cooking and consumption of food in households were investigated. The survey was carried out during the first five weeks after the implementation of the ASPO in Argentina and the EAC in Spain, obtaining 472 responses for the case of Argentina and 290 for Spain.

Secondly, from the tenth week of ASPO and EAC, in-depth interviews were conducted with young people from Spain and Argentina between 20 and 29 years old, since this age group was the one that offered the most responses to the survey. The main objective of the interviews was to collect information on the eating practices in isolation in conjunction with the temporal and spatial relationship of the period of exit from the prohibitions. Informed consent was requested to carry out the interviews and the anonymity of the participants was preserved. These were recorded and fully transcribed to be subjected to data analysis, classifying their content defined according to emerging themes.

The argumentative strategy will be as follows: a) a brief overview is offered of the relationship between body/emotions/eating from the standpoint of a sociology of bodies/emotions; b) the specificities of the concepts of food practices and commensality are explicated; c) the data from the surveys and interviews are presented, detailing the emotions

around eating and the changes produced by confinement; and d) some final lines are presented by way of conclusion and identifying future openings for inquiry.

EATING BODIES/EMOTIONS

When we talk about bodies and food we talk about bodies that eat. We refer to biological bodies that need to ingest food and nutrients for their reproduction, but also to the emotions that are configured from the availability and appropriation of daily energies. This occurs without ceasing to relate the social relationships necessary for this to happen. Thus, eating is not only central to the reproduction and social availability of bodies, but the organic/cognitive/affective is intertwined in the production and reproduction of bodies/emotions.¹

From the sociology of bodies/emotions, we understand that

“The bodies are such, given their connection with the environment/environment (material conditions of existence) through (and by) the complex processes that are generated in the interaction between (with and from) the brain/central nervous system/nutrients/energies. b) The brain “houses” (in a complex and indeterminate way) the processes of the social construction of bodies and emotions mediated by a set of interactive modularities between the chemical and electrical “causes” of the life systems that articulate the capacities that have nutrients/energies to enable/block, produce/reproduce and/or balance/unbalance the existence of those bodies/emotions. c) The unequal distribution and appropriation of nutrients/energies model the potentialities that the neurophysiological system has to “maintain” the possible states of life of the subjects as social agents. d) The processes of social structuring by “modelling” the possible connections between impressions/perceptions/ sensations/emotions and the brain/energies/environment are variables that co-embody the possible forms of bodies/emotions” (Scribano 2012: 97).

From this conceptualization, it is possible to observe the limits of a society that becomes a body, while bodies will be produced and reproduced within the limits of the material conditions of existence that society distributes unequally among subjects. In this sense, the relationship between bodies/environment/nutrients is essential for the conformation of bodies, at the same time that it will enhance/block the perceptual, emotional and cognitive capacities of those bodies as they grow.

Emotions will allow the subject to feel (himself), which gives him the capacity for action, understanding it as “action tendencies instead of specific actions” (Von Scheve & Slaby 2019: 10). But, emotions are not the result of a single cause/motivation but rather “are the result of the co-bordering² of a constellation of previous interactions between multiple factors” (Scribano 2018: 7) and, in their indeterminacy and complexity, they emerge from the processes of adjudication and correspondence between perception/sensation/emotion.

¹ The bar (/) implies the possibility of writing and inscribing the connections/disconnections that involve bodies and emotions and allows us to grasp/understand that seeing, tasting, smelling, hearing, feeling, perceiving, thinking, wanting, acting are complex, indeterminate moments and nodes through which the multiple subject/society relationships are woven (Scribano, 2012).

² “Cobordism is basically an equivalence relation between compact varieties. Two varieties are said to be cobordant if their alien union is the border of a third compact variety. As we will see, the border of a variety of dimension $n + 1$ is a variety of dimension n , and the border of a variety with the border is a variety without border” (Pérez and Ávila, 2011: 3). The main problem with cobordism is “knowing when two varieties can be deformed into each other without encountering a singularity in the resulting space, at any moment in this deformation” (Thom, in Wiley & Sons Aubin 2004: 103).

At this point it is important to note that the sensations are distributed according to the specific forms of bodily capital that are the conditions of existence housed in the body, understanding it from three registers: a) an individual body, which refers to the body as a biological organism, as an organism that has organs, functions and processes that are genetically constituted; b) a subjective body, which is found in the field of the “I” that constructs a narrative of its existence as a biography - in this plane, interactions and relationships with others take place; and c) the social body, which is the incorporation of learning, practices and habits that shape the body and that constitutes subjectivity from socialization (Scribano 2007).

This way of understanding the body with analytical distinctions that occur in an inter-crossed and superimposed way makes it possible to think of the connections between sensations and the body as a given state of affairs. In this way, the subject and her material conditions of existence are interconnected in dialectical tension with the result of feeling-in-a-body. For its part, talking about bodies implies talking about a politics of bodies, understood as “the strategies that a society accepts to respond to the social availability of individuals” (Scribano 2015: 35). In this case, the politics of bodies will organize socially accepted practices and strategies to respond to the daily need to eat in their relationship between bodies/environment/ nutrients.

On the other hand, all politics of the bodies implies a politics of sensibilities, which regulates how the actors experience the states of feeling and feeling the world. In this sense, the politics of sensibilities is linked to a

set of cognitive-affective social practices aimed at the production, management and reproduction of horizons of action, disposition and cognition. These horizons refer: 1) to the organization of daily life (day-to-day, wakefulness/sleep, food/withdrawal, etc.); 2) to information used to order preferences and values (adequate/inappropriate, acceptable/ unacceptable, bearable/unbearable) and 3) to the parameters for time/ space management (displacement/location, walls/bridges; infrastructure for the valorization of enjoyment) (Scribano 2018: 10).

This interconnection allows us to understand that the body/food/ emotions relationship is a central node in the structuring of sensibilities since eating elaborates, inscribes and reproduces the possibilities of living and narrating the world based on the potentialities and obturation that are nested in the distribution of nutrients and energies, constituting the possibilities of feeling-in-the-world from a-body.

EATING PRACTICES: FOOD PRACTICES, COMMENSALITY AND SENSIBILITIES

Now, if we talk about eating, we refer to a practice that subjects carry out throughout their lives and that, under ideal conditions, they should repeat a couple of times a day. At the same time, it must be taken into account that this practice can be carried out from a complex system of relationships that ranges from the production of food to the intake itself.

Eating practices encompass elements of a cultural, economic, social and individual nature, which intersect with the actions necessary to reach the act of eating. On the one hand, we find food practices, which as “the actions of obtaining, accumulating, preparing,

conserving food, together with the knowledge in this regard, held by a specific group in a specific historical context” (Boragnio and Sordini 2019: 74). And, on the other, commensality, which is organized based on habits, norms and customs.

Commensality is the way of eating typical of human beings. From omnivorism, and with the difficulties involved in obtaining the necessary food in solitude, sharing food became essential for the reproduction of the species, generating specific norms that constituted the moment of eating at the same time as a community of diners (Fernández-Armesto 2009; García 2013). Therefore, ‘eating’ is organized by cultural guidelines before the specific moment in which the food will be eaten. These guidelines will vary in each culture and will be modified according to gender, age, the social position of who eats along with the specific context of space/time where the act of eating will take place.

If commensality is the form acquired by sharing food among human beings, and if these forms are constituted by the set of social relations, the rules of commensality will focus on legitimate ways to carry out sharing. Thus, commensality has four main axes: rules/norms, time, space, types of interaction, the latter being the various ways of carrying out the rules/norms—every day, extra-daily, festive, in physical presence, alone—.

In western societies, from the twentieth century, the process of change called “food modernity” or “late modernity” began, in which commensality enters into crisis and the shared rules fall, producing a destructuring of eating behaviors (Fischler 1995, 2010; Contreras Hernández 2005). The entry of women into the labour market, the extension of school hours and working distances, the development of the food industry on a massive scale and the production of ultra-processed products, as well as the creation of a market segmented by income, they modified daily life, which led to changes in food practices.

The first modifications that were made focus on “de-structuring, de-socialization, de-implantation of hours and de-ritualization” (Poulain 2002). These “de-” tendencies are observed in three concrete practices of daily life: a) the simplification of the structure of food, making the dishes increasingly simple; b) the increase in consumption outside the home, making public a daily practice linked to the private; and, c) the increase in the number of ingestions, which separate the act of eating from a specific time, which amplifies both the hourly and spatial possibilities.

Within the framework of these changes, daily food tends to be linked to an extra load to the working day, which is quickly solved in the domestic environment, with ultra-processed industrial products. In this sense, food is no longer organized by family life, but rather, the strategies to provide a solution to the daily diet focus on individualism and the destructuring of intakes. In this way, “snacking”³ appears as the form that the subjects give to the current diet (Mintz 1996; Poulain 2002).

Although current commensality is not strictly unstructured and guided by “snacking”, the modernization of daily life, the value of time and the objectification of the body, have been continuously and deeply transforming the ways of eating, thinking and sharing the food. Thus, among the main changes in the rules of commensality is the shift of the choice of food to the individual scope, the loss of regulated times of eating, the increase in the number of times and the amount of intake, the monotony of food, the loss of culinary know-how and the ritualization of food as a consumer experience (Boragnio 2020; Aguirre et al. 2015).

³ Small portions of food or meals that are eaten at varied times, between main meals, but are not considered as a proper meal. Nutritionally the concept of snack is about what is called “junk food”.

The richness of commensality as a concept does not reside only in the specificity of the act of sharing food and the rules that are involved in that act, but also in the plurality of meanings and modes that it possesses. So, as we can see, the experience of eating will be traversed by the politics of bodies and commensality. In this way, from before birth and reinforcing themselves in the daily act of eating, people are articulated with the social structure based on habits, norms and customs that are expressed in social sensibilities.

As we can see, eating practices have a dynamic character, so they are able to readjust depending on the context, but always within the sociocultural system that gives meaning to commensality. Next, we present the main characteristics of eating in Argentine homes, then the details and pictures of eating in Spanish homes will be outlined, and then we will focus on sharing the emotions and sensibilities linked to both countries.

EMOTIONS OF EATING AT HOME

Eating in Argentine Homes

When asking respondents what place food occupies in their lives, 76.4% of Argentines gave scores of 7 upwards, the mode is 8.

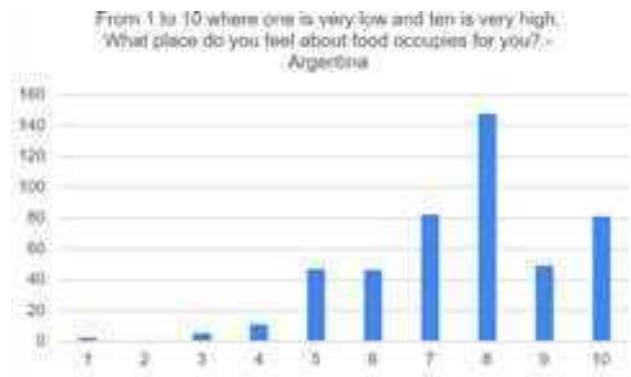


Figure 1. Place of food in life, Argentina.

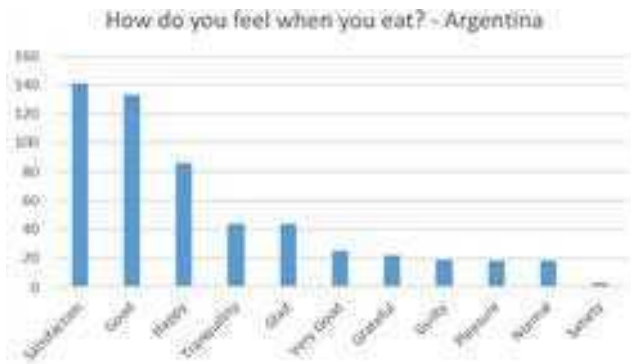


Figure 2. Emotions when eating in Argentina.



Figure 3. Word cloud of the responses of young people aged 19 to 29 in Argentina.

For young people from 19 to 29 years old, the mode about the level of importance of food is also 8, but the responses that indicated a value of 7 or more are 86%.

When the respondents were asked to indicate with three words what they felt when eating, the predominant responses, in order of frequency, were: satisfaction, good, happiness, tranquility, glad, very good, grateful, guilty, pleasure and normal. If we add the answers obtained for “good” and “very good” we can produce a category of “well-being” that would have the first place.

For their part, respondents aged 19 to 29 indicated that their feelings were mainly focused on satisfaction, happiness, good and glad. But we also find repeated responses such as enjoyment, calm, full, anxiety, energetic and healthy.

Eating in Spanish Homes

When asking Spaniards what place food occupies in their lives, 84.55% gave scores higher than 8, this being the mode.

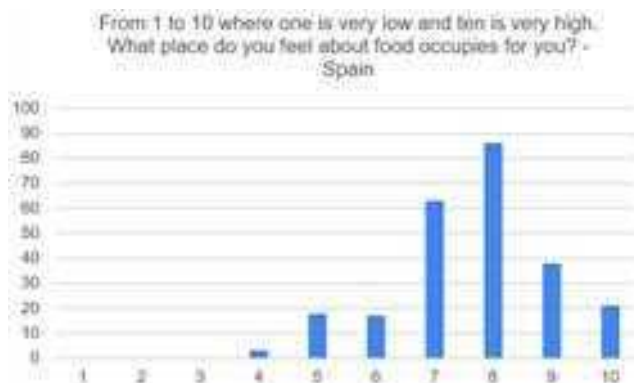


Figure 4. Place of food in life, Spain.

On the other hand, in a population of 19 to 29 years of age in both countries, responses are the same. In Argentina, the three most repeated emotions are satisfaction, good and happy, while in Spain they are also good, happy and satisfaction. As for differences, we find that young people from Argentina also indicate feeling glad, enjoyment, anxiety, full, healthy and grateful; while young Spanish people feel comfortable, grateful, satiety, full, guilty and healthy.

EATING IN TIMES OF CONFINEMENT

When analyzing the data from the surveys and interviews together, new axes appear to take into account when thinking about the eating practices at home in times of pandemic. Among the main changes shown by the data are not only changes in what is eaten, but also in food and commensality practices.

The first modification that appears as a positive change and, at the same time, as a negative change for the research participants, is the routine of schedules. The changes in the schedules are expressed mainly in the fact of skipping a meal as in the incorporation of breakfast daily.

"I consume less purchased food, more snacks and breakfasts, also simpler meals" (26-year-old female, Argentina)

"I have disorganized schedules, I eat junk food in excess as a snack" (29-year-old female, Spain)

Thus, the change in schedules allowed the subjects to organize the day, but as we can see, it also disorganized it.

On the other hand, schedule changes are directly related to changes in the menu. First appears the need to plan different menus since having to eat every day at home, taking charge of the entire purchase/planning/cooking process, and the need to innovate are imposed so as not to fall into monotony. As the interviewees tell us:

"I cook more, I got out of the dynamic of always eating the same thing." (28-year-old female, Argentina)

"I believe that at some point during this quarantine we have all made, even if it is an attempt to cook, that, although you are not always cooking throughout these days, you have tried. (...) The week has 7 days, you have to be cooking the same thing so to speak, but in 7 different versions." (25-year-old female, Spain)

These variations in the dishes were not only introduced by the need to eat other things, but could be achieved by the time available, which offered the possibility of cooking new things, of being able to dedicate time to the kitchen and more complex preparations.

"I like to vary from what I always eat because I have more time to look at recipes and cook them." (23-year-old female, Argentina)

"Take advantage of the time to make healthier and more elaborate meals." (24-year-old female, Spain)

Based on this, surveys show that the new preparations made in Argentina and Spain focus on the mains, sweets, followed by dishes that were frequently consumed, but made in a homemade way. With this, the interviewees indicate that they began to cook as a new quarantine practice, and those who already cooked before took advantage of the time to make more elaborate and complex dishes.

"Instead of buying, it was replaced by making it at home." (24-year-old female, Argentina)

In this case, it is striking that in surveys in Spain pride appears as an emotion linked to eating in a pandemic, since respondents were able to realize that they can cook and do it well.

"I am proud of the menus that I am making, but stressed by the amount of flour." (21-year-old female, Spain)

Along with the kitchen, there is the stress of flour consumption and the multiple strategies to limit its consumption and implement and sustain the consumption of healthy foods. About this, in the surveys, it can be observed that the search for a healthy diet is one of the main axes, either to stay healthy at this stage, to avoid getting sick, and not to gain weight. For this, respondents and interviewees tell us they choose light, healthy foods.

"I vary foods to maintain a balanced diet weekly." (20-year-old female, Argentina)

"I try to maintain a balanced diet (salad, baked vegetables)." (24-year-old female, Spain)

At the same time, although most of the answers about the diet in the days of isolation focused on being happy and satisfied with it, it was also clearly emphasized that there was something wrong and it was marked as something to be modified.

"Although I did eat and we eat super healthy, I know that we ate unnecessary sweet things." (23-year-old female, Argentine)

"Are you satisfied with your diet these days?"

No, I would like to eat healthier." (23-year-old female, Spain)

In this sense, several respondents said they were on a diet and/or going to a nutritionist. Among those who said they consulted a nutritionist, almost all went before the isolation period and tried to maintain the diet.

"It depends on what you are eating. When I eat every day I feel good, and I like to eat balanced and think about combining different foods. When I eat something out of the ordinary (something more "fattening") I enjoy it a lot at the moment and eat everything I think I want but knowing that later I will be blamed or I will feel very full." (woman, 24 years old, Argentina)

"It depends on what you eat. If I eat healthily I feel good. If I go off my diet I feel guilty, bad." (28-year-old female, Spain)

We understand the need to go to the doctor to learn how to eat as the loss of knowledge concerning eating practices occurs from multiple factors within food modernity. On the one hand, due to the separation between the social norms of eating, the separation of food production, the reorganization of the times where it is no longer clear what is eaten at what time and the deregulation that occurs from individualism to eat alone. Then, the cacophony (Fischler 1995) generates an excess of discourses that have as consequences the uncertainty about which one to follow, since all are expressed under the label of "the truth". This, added to the medicalization of food that led to the de-hierarchization of women in eating issues (Boragnio 2020b), which place them as the unauthorized voices and, therefore, in the space of non-knowledge. But, at the same time, we observe that this time of change in the period of the ASPO and the EAC, provided the possibility for the youngest to approach the kitchen as a way of doing, of transforming daily life, not only not to be "eating the same" but to try to "feel good."

BY WAY OF CONCLUSION: SENSIBILITIES OF EATING INSIDE

The confinement and isolation decreed by the spread of COVID-19 led to a rethinking of food practices and commensality, configuring eating practices as a central node of daily life during the pandemic. In this case, eating as a daily act that had been turned into the public sphere –from the implementation of multiple modifications in domestic, school and work-life– was redirected to the interior of the home, once again becoming a domestic and family activity. From this change, new rules of commensality were generated. On the one hand, this centered around the types of interaction that became entirely domestic and every day. And, on the other, they were configured in relation to the time and space that allowed subjects, in some cases, to re-order the daily diet.

The period of confinement and isolation brought young people closer to the practice of cooking, generating emotions of satisfaction and pride. As the body/food/emotion relationship develops, we can observe that the action of cooking seeks well-being, satisfaction and containment. But at the same time, the introduction of the multiple discourses, of a politics of sensibilities around “nutrition”, reproduces the idea of not knowing how to eat. At the same time, the practice of eating is configured as an individual learning activity. In this way, the experience of eating is articulated in young people between guilt, anxiety and enjoyment.

Nutritional sensibilities organize and classify preferences and values where health is put first when choosing what to eat. Eating is no longer organized based on calendar dates or family knowledge, but eating practices are structured by a mediated medicalization based on nutritionism configured as a sensibility to eating. Thus, the diet is configured as a set of practices that are practices of the politics of sensibilities, while the food practices and commensality imply and express different sociabilities and experiences.

From the emotions linked to eating, we can observe the connection of this as a cognitive-affective social practice, which not only tends to the production and reproduction of the body in its materiality, but also to the production and reproduction of the individual and social energies that will constitute the possible horizons of action, disposition and cognition. Eating organizes daily life. In isolation, the day is spent thinking about what to eat, when to eat, what to do to eat. But, at the same time, eating orders the day, orders the hours, what is eaten during the day, at night, based on the rules and norms of commensality.

Finally, it is important to point out that, as we can see, eating is organized based on parameters for other time/space management. In this sense, in the period of isolation and confinement, when public time/space was unable to inhabit for many –while many others inhabited it without the possibility of autonomy or decision– domestic time/space was reconfigured and multiplied. At this time, cooking was once again the main axis of daily life at home. And although industrialized foods, service foods and ultra-processed foods continue to be the edibles that reproduce eating at home, the new time allowed other possible ways of eating to be explored. Whether they are reproducing what was consumed outside at other times or producing something new, the traditional, the common shared at home, the commensality that builds edibles into food.

In this way, from the eating conditions of life and its reproduction are molded –as nutrients configure the bodies and emotions– at the same time that the ways of experiencing eating and experiencing the body are defined by possible foods and their taste, diners are

configured and social relationships are hatched. In this sense, the consequences of eating become evident in the structuring of sensibilities, based on regimes that constitute particular ways of regulating, ordering and incorporating social practices in specific socio-historical contexts.

Eating is a key determinant of people's health, but also of their daily emotional experience. This pandemic reality not only affects food practices and commensality, but also affects and configures the emotions. A long way ahead is the analysis of the eating practices of young people, to learn more about the diet that they put into practice, their knowledge and specific strategies for planning, preparing and consuming their daily meals, to know the relationships between body/food/emotions in the post-pandemic 21st century; with the final interest of being able to approach the transformations of the set of cognitive-affective social practices aimed at the production, management and reproduction of horizons of action, disposition and cognition. In other words, being able to know the policies of the sensibilities that are currently being formed.

The lines of inquiry presented in these pages allow us to continue deepening the interconnection in the relationship between body/food/ emotions as the central node in the structuring of sensibilities, since eating elaborates, inscribes and reproduces the possibilities of living and narrating the world from the potentialities and obturation that are nested in the distribution of nutrients and energies, by constituting the possibilities of feeling-in-the-world from a-body. And that, in confinement, allowed people to reconnect with others, with co-living, reproducing the social bond that modifies nature to make it a body and that builds commensality as the only human way of eating.

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Chapter 498

DIE ALONE IN ARGENTINA: A VIEW FROM SENSIBILITIES IN TIMES OF THE PANDEMIC

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ABSTRACT

The objective of this work is to reflect on the sensibilities related to dying and death, in the context of the current coronavirus pandemic. The presentational strategy that we have envisaged in this regard begins by defining and establishing the theoretical perspective in which our proposal is framed: the sociology of bodies/emotions. Then we go back to another global crisis that occurred a century ago, known as the Spanish Flu. The reason for this is to recover some antecedents that allow us to enrich our approach to this phenomenon that is still ongoing; not in comparable terms (since both episodes are not), but rather illustrative. Finally, we will deal with the three traits that, in our opinion, characterize the collective bond with the dying and corpses at the present moment: mediated death, regulated death, and cherished death.

INTRODUCTION

The pandemic (and its management) implies a politics of sensibilities that has at least three relevant characteristics for what we want to illustrate here: a) a geometry of bodies where the proximity and distance between human beings is re-structured around the medical gaze on the healthy/sick, b) a grammar of action where the definition of who the other is operates from the denial of physical contact and c) the redefinition of the ghosts and fantasies associated with the threat of death (Scribano 2020, Scribano and De Sena 2020). Having pointed out the above, we must recognize that we are witnessing a time when all horizons of

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comprehensibility and expectations become strange, opaque. Policies of distancing and preventive control alter the dynamics of social interaction, public space appears alien and threatening, and public and private institutions try, in their own way, to adapt to the challenges presented by this uncertain situation¹. Meanwhile, in the academic sphere, numerous experts are quick to characterize the current crisis as a *total social fact*, thus dusting off the analytical category that Marcel Mauss coined almost a century ago - such is the magnitude and severity of the pandemic disease, caused by the COVID-19 coronavirus. As it could not be otherwise, the catastrophe was able to acquire public notoriety as the number of deaths increased throughout the world. Just to name a few cases: on the occasion of approaching 100,000 US fatalities from the pandemic, the prestigious American newspaper *The New York Times* published, on its cover on Sunday, May 24, a list with the names of a thousand of them, accompanied by the following reflection: “They weren’t just names on a list, they were us”². Exactly two weeks earlier, the similarly prestigious Brazilian morning newspaper *O’Globo* had done something very similar, as a way of paying tribute to the 10,000 lives that COVID-19 had claimed so far in the country³. And the newspaper *ABC de España* denounced, on September 13, that the real death figures were double the official figures (53,000 compared to the 26,000 reported). The design chosen for this cover highlights the difference between the two figures, which are framed by drawings of hundreds of identical tombstones⁴. The funeral notices, for their part, witnessed how the death rate soared in the most affected cities. Such is the case of the newspaper *L’Eco di Bérgamo* (an Italian city in the Lombardy region), which, at the beginning of February, allocated only a page and a half to the obituaries, and a month later that section had reached 10 pages⁵, or *The Boston Globe*, which went from a Sunday average of seven pages to 21 on April 26⁶.

No one can foresee what political and social order will ensue. The truth is that life will not pass in the same way; neither will death and dying. Aware of how problematic it is to analyze a phenomenon still in the making –whose human and material losses are impossible to foresee in the long term– we have resorted to a precedent that, although not comparable to the present situation, gives us some keys to understand the social implications of the management of death and the dead in the context of a pandemic. We refer to that episode baptized by history as the Spanish Flu, which would claim around 50 million lives across the planet in a short period of time (1918-1920).

¹ Even the language itself has been affected by this unique situation. And it is that, for some time now, countless neologisms related to the disease have populated everyday speech. To cite just a few cases: the “zoompleaño” is a form of celebration mediated by technological devices, which has become popular during confinement; “Infodemic” is the term with which the World Health Organization (WHO) designates the massification of false or imprecise news that circulates through the media and social networks; the verb “quarantine” has to do with the voluntary action of remaining isolated; “Coronials” refers to the generation that will be born from now on. For more information on this, visit the following website: https://www.clarin.com/cultura/covidiotazoompleanos-coronials-nuevas-palabras-trae-coronavirus_0_f3apTIQIP.html

² To read more about this, go to: <https://www.nytimes.com/es/2020/05/23/espanol/portada-NYT-coronavirus-victimas.html>

³ The title of the note is “The stories behind the Covid-19 numbers”, and it is available at: <https://oglobo.globo.com/sociedade/coronavirus/as-historias-por-tras-dos-numeros-da-covid-19-24419061>

⁴ To read more about it, go to: <https://www.infobae.com/america/mundo/2020/09/13/el-diario-abc-denuncio-que-son-53000-los-muertos-por-coronavirus-en-espana-24000-mas-que-los-informados-oficial/>

⁵ To read more about it, go to: https://www.clarin.com/viste/coronavirus-italia-avisos-funebres-multiplican-miles_0_nNDh9hNWh.html

⁶ To read more about it, go to: <https://www.bostonglobe.com/2020/04/26/nation/sundays-boston-globe-runs-21-pages-death-notice-coronavirus-continues-claim-lives/>

But before entering into the problematic that summons us, we consider it necessary to make explicit the theoretical perspective from which we make our approach, namely: a sociology focused on *sensibilities*. By virtue of this, we will briefly review the theoretical-methodological and epistemological postulates on which it is based, and the centrality that the corporal/affective dimension acquires in this framework, as a fundamental indicator for the study of social structuring processes.

Once these guidelines are provided, we begin to analyze the three contingent traits that, in our opinion, make the transformations of behavior in the face of current dismissal and separation disruptive. Let us review each of them: a) a relative accentuation of that confining tendency (*ethos* of “*homo clausus* Hospitable”) and desacralizing (*ethos* of the “*homo luctuosus* Secular”), noted by Norbert Elias (2009), regarding the way in which, on the one hand, the dying person is compelled to spend their last hours, and, on the other, is cremated when dead. This is a tendency that finds, in the interaction mediated by technological devices, certain mitigating factors; b) the abrupt alteration of the standardized practices of treatment and disposition of the corpse, as a result of the appearance of new mortuary dispositions, which directly affect the health system and the funeral market; and c) the debate on “bad death” and “good death”, which puts the accent on the dignity of the suffering or deceased and, simultaneously, certain prevention campaigns whose “insolent” narratives update rhetoric typical of the grotesque, which come to question certain values traditionally associated with farewell rites.

We consider that these three traits - “mediated death”, “regulated death” and “reverent/irreverent death” - suggest possible plots about bodily distancing (the dying person, and then his remains, as an agent of contagion) and emotional expressiveness (the socialization of pain forbidden), which are symptomatic of the present moment; these are plots that - and this is where our working hypothesis lies - would show how sensibilities around human death are reconfigured in this context of humanitarian crisis.

OUR THEORETICAL PERSPECTIVE

In a broad sense it is necessary here to make some clarifications aimed at explaining some starting points about a sociology of sensibilities (Scribano 2017, Scribano 2018). We consider that humans know, build and rebuild the world in and through our bodies and emotions. The most elemental form of alluded contact is the social construction of the connections between perceptions, sensations, and emotions: this builds a tripod that allows us to understand where sensibilities are founded. Thus, a set of impressions impact in the ways that subjects “exchange” with the socio-environmental context. Such impressions of objects, phenomenon, processes and other agents structure the perceptions that subjects accumulate and reproduce. Perception, from this perspective, constitutes a naturalized way of organizing the set of impressions that are given in an agent.

This weaving of impressions configures the sensations that “produce” what can be called the internal and external world: social, subjective and “natural” worlds. Such configurations are formed in a dialectic tension between impressions, perceptions and their results, that give sensations the “meaning” of a surplus or excess. Therefore, it puts them closer and beyond such dialectic. Sensations, as a result and as antecedent of perceptions, locate emotions as an

effect of the processes of adjudication and correspondence between perceptions and sensations. Emotions, understood as the consequences of sensations, can be seen as a puzzle that becomes action and effect of feeling something or feeling oneself. Emotions are rooted in the “state of feeling” the world that allows the sustaining of perceptions. These are associated with socially constructed forms of sensations.

At the same time, organic and social senses also enable what seems unique and unrepeatable, as are individual sensations, and elaborate the “un-perceived work” of incorporating social elements turned into emotions. Sensations, as a result and antecedent of perceptions, give way to emotions which can be seen as the manifestation of the action and effect of feelings. They are rooted in the states of feeling the world that build perceptions associated with socially constructed forms of sensations.

Consequently, the politics of bodies (i.e., the strategies that a society accepts in order to offer a response to the social availability of individuals) is a chapter –and not the least important chapter– in the instruction manual of power. These strategies are tied and ‘strengthened’ by the politics of emotions that tend to regulate the construction of social sensibility.

Politics of emotions require regulating and making bearable the conditions under which social order is produced and reproduced. In this context, we understand that social bearability mechanisms are structured around a set of practices that have become embodied and that are oriented towards a systematic avoidance of social conflict.

The forms of sociability and experience are strained and twisted as if contained in a Möbius strip along with the sensibilities that arise from regulatory devices and the aforementioned mechanisms. The need to distinguish and link the possible relations between sociability, experience and social sensibilities becomes crucial at this point. Sociability is a way of expressing the means by which agents live and coexist interactively. Experience is a way of expressing the meaning gained while being in physical proximity with others, as a result of experiencing the dialogue between the individual body, the social body, and the subjective body, on the one hand; and the natural appropriation of bodily and social energies on the other. For the body to be able to reproduce experience and sociability, it is necessary that bodily energy is an object of production and consumption. Such energy can be understood as the necessary force to preserve the state of ‘natural’ affairs in a systemic functioning. At the same time, the social energy shown through the social body is based on bodily energy, and refers to the allocation processes of such energy as the basis of the conditions of movement and action. Thus, sensations are distributed according to the specific forms of bodily capital; and the body’s impact on sociability and experience shows a distinction between the body of appearance, body of flesh, and body of movement.

Social sensibilities are continually updating the emotional schemes that arise from the accepted and acceptable norms of sensations. They are just a little long or short of the interrelationships between sociability and experience. Sensibilities are shaped and reshaped by contingent and structural overlaps of diverse forms of connection/disconnection among various ways of producing and reproducing the policies of the body and the emotions.

The politics of sensibilities are understood as the set of cognitive-affective social practices tending to the production, management and reproduction of horizons of action, disposition and cognition. These horizons refer to: 1) the organization of daily life (day-to-day, vigil/sleep, food/abstinence, etc.); 2) information to sort preferences and values

(adequate/inadequate, acceptable/unacceptable, bearable/unbearable); and 3) parameters for time/space management (displacement/location, walls/bridges; enjoyment).

In this context the pandemic is itself an alteration to the policies of sensibilities and in this context of how we live death; on this we offer some considerations in the following sections.

THE SPANISH FLU AS AN ANTECEDENT

All pandemics have a high social component in their genesis, reproduction and management, as Henao-Kaffur and Hernández-Álvarez (2017) say in the case of the “Spanish flu”, a feature that impacts is the suddenness of deaths and the volume of them.

A feature that “death management” shares with “epidemic management” for both the Spanish Flu and COVID-19 is the isolation they produce, as summarized by Mejías Estévez, Domínguez Álvarez and Blanco Reina (2018), regarding that catastrophe at the beginning of the 20th century:

The tragedy of this pandemic went beyond direct deaths. Fear seized the population, causing dramatic situations such as social isolation and the stigmatization of the disease. People were absent from their jobs (they did not dare to leave home), producing a direct and disastrous effect on the economy. In some places the authorities declared a quarantine, prohibited the right of assembly to avoid crowds, schools, theaters, centers of worship were closed ... to the point that numerous deaths of children were due to hunger (they were isolated to the point prohibiting bringing them food). (p. 665)

In this section we want to refer to how the disposition of the dead was treated in the aforementioned pandemic, as a precedent of what has happened in the case of COVID-19. It is obvious that we only undertake this in an attempt to make evident some axes of possible inquiry, but also to suggest that it is feasible to analyze similar phenomena in other times.

The British military doctor Roy Grist, who was attending Devens Camp, northwest of Boston (USA), offers the following description:

... we have lost many doctors and nurses ... special trains are needed to transport the dead. For several days there were not enough coffins and it was necessary to pile up the dead. A large barrack has been vacated to adapt it as a morgue ... where the corpses rest in double file ... (Roy Grist, in Murrillo Godines 2011: 463)

A central problem is the space to deposit, bury and incinerate the corpses, their transfer, and their isolation. In special areas, cities and regions in a pandemic situation must manage lifeless bodies and thereby inaugurate differential and unequal body geometries. For the same spatio-temporal context, González Bombardiere (2007) states that:

When mortality rose to 500, 600 and 800 deaths per day, the corpses began to accumulate, there were not enough funeral homes or gravediggers, and fewer coffins. People refused to bury the dead from influenza for fear of contagion. (p. 42)

The dead and fear as a sign of the pandemic and its effects are associated with a grammar of the action of burial as a specific undertaking. All cultures have developed specific roles for those in charge of conditioning, transporting and burying their dead, practices that are

modified in a pandemic: since they are not enough, given the large number of deaths. Without coffins and without sufficient gravediggers, the structure of roles and positions is modified.

Regarding the Argentine case, Adrian Carbonetti (2010) has written:

The measures taken by the State tended to harden in November of the same year: congregations and assistance to cemeteries were suspended on the day of the dead (...) The provisions they were different in each district; thus, in the case of the province of La Rioja, these reached extremes such as the prohibition of attending wakes, except for the bereaved (p. 172)

Another modification that occurs in the Spanish Flu is that of ritual practices, which in turn, impact on the politics of the sensibilities associated with grief. The prohibition on attending cemeteries and wakes (except for the bereaved) is a clear sign of the objective difficulty of producing the practices of feeling associated with mourning and the public expression of pain. These factors end up having an impact on the social, in terms of emotional disorientation, given the key place for social affective reproduction that these practices have for society as a whole.

When Márquez Morfín and Molina del Villar (2010) analyze what happened in Mexico City, they maintain that:

In the General Hospital, 43 had already died out of an admission of 200 patients. Due to the large number of deaths, a ditch was being opened near the Pantheon from Santa Paula, where bodies had been buried during a cholera epidemic in the mid-19th century. (p. 142)

Another basic component of burial, at least in the emotional geocultures mentioned here, is the double loss that common graves produce: the loss of a loved one and the loss of their identity among many. Again, the mechanism of grief is altered, to which is added that of memory and the personal memory of those who have been lost. In her doctoral thesis María Isabel Porras Gallo (1994) entitled “A City in Crisis: the 1918-19 flu epidemic in Madrid”, makes the following components of the Spanish fever visible in the Spanish capital:

But the difficulties for citizens did not end when they died after being struck by the flu. The problems then arose at other levels: there was a shortage of vehicles to transport the corpses to the cemeteries; coffins were sometimes missing; new cemeteries had to be set up; and it was necessary to suspend religious ceremonies and any sign proper to burials. (pp. 89-90)

And later she adds that:

It is important to highlight that, although part of the Madrid population had health care through the medicine, burial and pharmacy societies, a very large population of Madrid had to go to the Private or public charity to receive medical assistance. (p. 164)

The situation in Madrid corroborates what has been described for Argentina and Mexico, emphatically pointing out the connection between the pandemic, the health system, the state and social position. The pandemic is a matter of state that puts the magnifying glass on the constitutive inequality of a system that denies itself as enclosed. In the same way as yesterday or today, the question arises: in what type of social structure did the pandemic appear? It is

relevant for the structuring of resignation as a basic citizen emotion that will continue to this day in its “subsiadiano”⁷ form (Scribano, 2019).

Finally, it is very interesting to notice the news about the flu published in the *Rif Telegram* on June 11 of 1919, that Daniel Castrillejo Pérez (2019) reproduces in his article “The ‘Spanish’ flu pandemic of 1918-1920. Analysis of mortality in Melilla”:

THE FLU SPREADS

HEALTHY MEASURES BY THE AUTHORITIES

The flu epidemic has made its appearance again in Melilla and its territory with the same intensity as last winter.

Many cases are recorded daily, some with dire consequences.

In hospitals, nursing has increased in a disturbing way in the last week.

The Deputy Inspector of Health has brought what is happening to the knowledge of the Commander General, and in anticipation of greater evils, he has ordered the hygiene measures adopted last year to be put into effect again, relative to the permanence of the corpses in the houses, persons who must attend the funerals and careers that they must follow.

Disinfection of the closed premises, of great attendance, will be carried out, and the provisions regarding the collection of garbage from homes will be taken into account.

As can be seen, the authorities are not careless in the performance of their duty. Now it requires that the neighborhood not stop lending its assistance to the health work that circumstances advise.

We will very much celebrate that the causes that motivate these measures disappear as soon as possible. (As cited in Castrillejo Pérez, D., 2019: 135)

The persistence of death management policies in African Spain clearly indicates that the “overflow” of societal mechanisms to administer, prepare, transport and dispose of dead bodies is a feature of the Spanish Flu that helps us to understand what happened 100 years later with COVID-19.

DEATH AND DYING IN ABSENTIA

Let us now turn to the first of the traits that characterize today’s dying and death: the experience experienced in a mediated way. To chart the terms in which we think about this phenomenon, we can refer to an event that took place in Milan (Italy), in mid-March. At that time, this and other cities in the country were going through one of the most pressing periods of the health emergency: massive contagion, collapsed hospitals and cemeteries. It was then that a councilor from the Democratic Party, along with other members of that group, promoted a suggestive project consisting of the donation of *tablets* to terminally ill patients, in order to alleviate the anguish caused by spending their last days in absolute solitude⁸. Under the slogan “the right to say goodbye”, the group headed by Lorenzo Musotto made it possible for patients who had been admitted to an intensive care unit (IDU) to communicate

⁷ The expression in Spanish that refers to the union of subsidized and citizen as a new modulation of the relationship of people with the state is maintained here.

⁸ To read more about it, go to: <https://www.infobae.com/america/mundo/2020/03/18/el-derecho-a-decir-adios-la-donacion-que-conmueve-a-italia/>

for the last time with their families, through video calls. In his Facebook account, the councilor stated that: “The idea of not being able to say goodbye hurts me more than death itself [...] I know of the importance of masks, gloves and medical instruments, but the right to say goodbye, for the who leave and for those who stay, it should not be less “. It is noted here that the affective bond is of the same importance as health care. At this point, a characteristic feature of the COVID-19 pandemic can be observed: the transformations in the goodbyes, in the last goodbyes, point in the direction of an awareness of a reflective act on the meeting, on the co-presence (*sensu* Giddens). Consumer capitalism, societies normalized in acts of immediate enjoyment, the vertigo of a society thrown into the accumulation and depredation of the planet put aside, put in parentheses, did not give importance to the fact that all these activities were given by the encounter, for the accompaniment. The pandemic interrupts noise, speed and demands a new redefinition of the encounter with others, and very radically so about the last encounter; death challenges us to think of life as always. In this direction, it can be argued that, by investigating how societies deal with death, there are clues to the way in which these societies define encounters. Death in the context of COVID-19 becomes a demand due to the urgency of redefining what is everyday unthought in co-presence.

With regard strictly to mortuary rites, in our country there have been services for a few years that allow non-participation *in-praesentia* in the farewell of the deceased; an alternative that, in these circumstances, is worthwhile. Among them, we highlight the one provided by two companies: a) Almavis⁹ (a compound word that combines the terms “soul” and “notice”) from the Province of Córdoba. According to what it announces on its website, it deals with providing “technological solutions” to the local and national funeral sector, specifically in everything that has to do with “multimedia condolences.” Among the tools they sell are: the “Virtual Cemetery” (a place relatives can access to view the profile of the deceased, upload content in different formats, leave greetings, etc.), the “Smart Module” (a screen with a Wi-Fi connection that plays the messages sent by the bereaved while the wake is being held), a “mobile app” (through which funeral notices from the town specified by the user are received) and the “Plaque with code” (a device that is placed on the tombstones in order for visitors to share a message, condolences or words to relatives in the profile of the deceased; b) Grupo Pieve¹⁰, from the Province of Salta, offers the option of “Wake online”, that is: “follow the wake of your loved one if he is outside the province or the country through the cameras that are located in our Wake-Up rooms and we also have a PC so that you can communicate through a video conference with the person you want to accompany.”

Similar services are provided by other companies such as the Previnca Group of the Province of Santa Fe or Previsora del Paraná, which has branches in numerous cities in Corrientes, Chaco, Misiones and Formosa. One aspect that appears frequently in all its advertisements in this regard is the importance of the human bond (although not *in absentia*), to face the anguish generated by the death of a “loved one”.

Virtual obituaries (inheritors of the traditional funeral notices that even today have a specific section in the written press), are nothing new in the mortuary category, but today they acquire greater visibility with the sophistication of ICT and the expansion of social networks. In such a way, nowadays, the relatives have countless interactive tools for the

⁹ The mission of the firm is: “to revalue the services provided at the moment the mourning process begins”. Website: <http://almavis.com.ar/nosotros>

¹⁰ In the “Grief” “tab”, the client finds several “useful tips” to better cope with a “loss”. Website: <http://www.grupopieve.com/sepelios.html>

commemoration of their loved one (greetings, reminders, events, etc.). To cite just one example, some firms promote candles and virtual flower arrangements, which clients can light and/or give away (symbolically), as an additional way of honoring the deceased. In the specific case of social networks, Facebook, for example, allows people close to a deceased user to manage their account to receive condolences, reminders, thanks and other communications.

Circumstantially (or not), the “Social, Preventive and Compulsory Isolation” –decreed by the Argentine government in March, and still in force in much of the national territory–, has radically changed the way we conduct ourselves before the dying and deceased. By virtue of this, legal, business and hygienic discourses –which knew how to permeate moral and affective imperatives at death and after, or preventive/palliative logics– seem more ancient than ever. In this framework, technological devices would contribute, to some extent, to suture the disunity resulting from this new “body geometry” (Scribano, 2007), and thereby attenuate the emotions generated by not being with (or feeling) who “is just gone” or will soon be.

In this context, one of the most interesting and important “concerns” of preventive isolation is generated, referring to the impossibility of witnessing death and therefore the impossibility of living it, since we live death through the death of the others. Beyond the sadness, pain or indignation that the death of a loved one can cause, not being able to live it makes it impossible to go through grief in the way that our society has long designed and designated this process. In this case, two moments of the same process converge related to not being able to be next to each other, and not being able to live death through the other. On the one hand, it appears to us as an impossibility of accompaniment and, on the other, as an impossibility of saying farewell. Accompaniment and farewell constitute the central axes of our relationship with death; a measure of health policy turned into a thanato-political strategy that involves the anguish and anxieties associated with the experience of death.

THE DANGEROUSNESS OF THE CORPSE: HOW TO PROCEED

In line with the previous point, we have been able to survey a set of provisions that Argentine national, provincial and municipal authorities have recently promulgated on preventive matters. Among them, we distinguish, due to the nature of their prescriptions, two regulations published on last April 23rd: a) “COVID 19. Recommendations for the Management of Corpses”, of the Ministry of Health of the Nation (MSN); and b) the “Procedure for the Management of Corpses of COVID-19 Cases”¹¹, from the homonymous portfolio of the Government of the Autonomous City of Buenos Aires (MSGCABA). Let’s review some points that are of particular importance for our analysis:

As anticipated in their titles, documents do not have the status of a mandatory compliance standard; they are, rather, recommendations or suggestions regarding how to proceed in the face of an inanimate body suspected of infection. The reason for this is the lack of

¹¹ The Buenos Aires government clarifies that the prescriptions included in this document complement the “Protocol for the treatment of corpses, stillbirths, segments and anatomical parts in GCBA hospitals”, approved in 2014, and in force to date. This material is available at: <https://www.buenosaires.gob.ar/sites/gcaba/files/protocolo.pdf>.

information on, for example, the risk of contagion from the corpse and how long this risk may last. This is how the texts express it, in their introductory parts:

There is currently no specific guide for the management of corpses of people who have died from COVID-19, but the provisions of the published World Health Organization Guidelines may apply. in 2014 on Prevention and control of acute respiratory infections with epidemic and pandemic tendencies during health care ... (MSN: 1)

Notwithstanding that, to date, the existence of a risk of infection from corpses has not been solidly evidenced of people killed by COVID-19, in accordance with the precautionary principle and what is observed for other viruses that affect the respiratory tract, it is considered that the corpses could pose a risk of infection for people who come into direct contact with them (MSGCABA: 4)

As a result of these conjectures, the authorities suggest that health and funeral personnel reduce the tasks related to the treatment, transfer and disposal of the eventually infected corpse to the minimum (respecting, they add, the “human dignity” attributed to the deceased person, and the diversity of rites and creeds professed by the deceased¹²). In addition to autopsies, it is recommended to avoid “cleaning actions” and conservation (thanatopraxy) and cosmetic (thanatoesthetic) practices. Thus, a central axis of the relationship between the pandemic and death is revealed: the body as a witness to the potency of the virus, the threat of the virus, and the brand of the virus for the future. It can be clearly seen how the connection between aesthetics and politics takes a dramatic turn: presenting the body is already a risk and death is once again killed, since, if death separates the living from the dead, this is a form of death that separates the dead.

The custom of holding a wake is also discouraged, in order to prevent the crowding of people in closed spaces and the exposure of the deceased to an “open box”. What is contemplated is the following:

Prior to the transfer of the body, with a probable or confirmed cause of death by COVID.19, the personnel in charge and with medical criteria, may only authorize a direct relative and/or legal representative with authorization judicial (spouse, partner, children, parents), access to the isolation room in the hospital environment [...] All physical contact with the body and/or material surfaces that were around them is prohibited “. (MSGCABA: 6)

It is necessary to clarify that, before these recommendations were made public, most of the country’s funeral companies had already implemented some prevention measures, which included precisely the limitation of the assistance offered to relatives in relation to funerals and other honors.¹³ We were able to verify this from a partial survey of the institutional portals that these companies have on the Internet. In order to conduct the search and make the

¹² In relation to the religious precepts on the fate of human remains, the controversy generated by the cremation, by prescription of the health authorities of the Province of Chaco, of a member of the Jewish community, in the framework of the pandemic of coronavirus disease. For more details, consult the article “Creation controversy unleashes the first Jewish deceased by COVID-19 in Argentina” (Jewish Link, 03/29/20). Available at: <https://www.enlacejudio.com/2020/03/29/desata-controversia-cremacion-del-primer-judio-fallecido-por-covid-19-en-argentina/>.

¹³ The reason for the early adoption of these internal provisions had to do, among other things, with the contagion registered in a burial house in the San Martín district (Greater Buenos Aires). The incident occurred at the beginning of April, when the funeral home received the body of a woman from a health center. Those responsible for it allegedly omitted the true causes of death (which led to a criminal case for negligence). As a result, two funeral agents were infected, as well as relatives of the deceased and clinic staff. For more information, visit the following portal web: www.filo.news/actualidad/Duenos-de-una-cocheria-se-contagiaron-de-coronavirus-de-un-cuerpo-infectado-20200417-0003.html

systematization of the information more operational, we decided to limit the survey to those firms that are part of the “Argentine Federation of Funeral and Related Services Entities” (Fadedsfya)¹⁴. Of the total number of web pages (56), we found a dozen burial houses that inform the public about the preventive measures they have taken as a result of the pandemic. Let’s look at some examples:

The Parque San Agustín company, which has branches in various towns in Tucumán, accompanies the notice of closure of its offices with the slogan “In the distance closer than ever”¹⁵. For its part, the San Bernardo Sepelios company¹⁶, located in the same province, shares a series of recommendations on how to deal with grief in isolation. To mention only one of them:

Recommendations for the care of the bereavement of the quarantined child [...] since in that case the children will not have the opportunity to visit [their grandfather or grandmother], or to show them affection such as kisses or hugs [...] it is recommended that parents suggest that their children write a letter, send a message or make video calls by phone to a loved one who is ill, to alleviate to a certain extent the impossibility of offering them signs of affection in person [...] given the impossibility of celebrating funeral rites due to confinement measures [parents are recommended] to propose to the child to carry out some symbolic activity [...] such as drawing a picture, writing a letter or choosing a photograph of themselves ...

At the regional level, the impact of the health crisis has intensified. The scenes of bodies scattered through the streets of Guayaquil, of mass burials in the Vila Formosa de San Pablo cemetery (the largest in Latin America), or of the “humanitarian command for the removal of corpses” that daily travel the streets of Lima, corroborate the diagnosis made by the World Health Organization in May, regarding that “South America has become a new epicenter of the coronavirus”¹⁷. Therefore, it is not surprising that most countries are limiting all types of public acts, and funerals are no exception. The measures have been so rigorous - and their emotional consequences so damaging - that the Inter-American Commission on Human Rights (IACHR) released a statement the same month urging OAS member states to “respect and guarantee the rights of relatives of those who died in the framework of the COVID-19 pandemic, allow mortuary rites in a manner appropriate to the circumstances and, with this, contribute to the preservation of their memory and tribute.”¹⁸

A DIGNIFIED AND IRREVERENT DEATH

In Argentina, the norms of hospital confinement and the restriction of funerals soon caused discomfort among the families of the infected, health and funeral agents and other actors involved. Consequently, a series of protocols began to be implemented to guarantee the final accompaniment and farewell. For example, we can cite the initiative that the Rodolfo Rossi Hospital of the City of La Plata (Buenos Aires) carried out in June, called “Die

¹⁴ The other organization that completes the national picture is the “Argentine Federation of Funeral Associations” (Fadaf). Website: www.fadaf.org.ar.

¹⁵ Website: <https://www.parquesanagustin.com.ar/noticia/66/informacion-importante-oficina>.

¹⁶ Website: <http://www.sanbernardosepelios.com.ar/>.

¹⁷ To read more about this, go to: <https://www.bbc.com/mundo/noticias-america-latina-52776325>

¹⁸ Press Release 097/20 of the Inter-American Commission on Human Rights (IACHR) “Respect for the mourning of the families of the people who died in the COVID19 Pandemic.”

Available at: <http://www.oas.es/cidh/prensa/comunicados/2020/097.asp>

accompanied”¹⁹. It guarantees that a family member accompanies a terminal patient with coronavirus. The interesting thing is that, in its foundations, this program affirms that “dying in company can be in itself a palliative act”.

In a similar direction, at the end of August the Legislature of the City of Buenos Aires approved a law that contemplates “the right to the last goodbye”, being the first jurisdiction in the country to sanction a measure with these characteristics. Among other concessions, it enables a person “from the affective environment of the patient to go to the hospital and facilitate, with a mobile device, communication with the rest of the family or relatives of the patient.” Days later, the Ministry of Health published the corresponding protocol for the implementation of the law. Among its provisions, it specifies that “the companion may carry objects” of emotional value to the patient, such as photos or letters.

At the national level, the health authorities released, also in August, a set of “recommendations” not only to allow the affective bond in these critical circumstances, but also the “interdisciplinary” containment of the patient’s family ²⁰. And they are recommendations because they address the particularities that a dismissal situation entails, in accordance with the availability of medical and psychological staff, beds, supplies, etc., but also deal with the specific emotional needs of each family; these are aspects that protocols tend to omit, argue the authors of the regulation.

In these examples becomes evident, once again, the centrality that the problem of what we call death acquires *in absentia* and how technological devices are considered as a valid alternative to manage the affective damages of separation. Even so, co-presence is an essential requirement to go through these final instances in the least traumatic way possible, as suggested by the aforementioned regulations, regarding containment between the bereaved, relatives and palliativists. Now, what has come to update the confinement of the dying and the estrangement from the deceased - whose bodies have now become vectors of contagion - is the discussion about the “good death” and the “bad death”. In line with what was stated by Laura Marina Panizo and Valérie Robin Azevedo (2020), we consider that the difference between both dimensions is determined not only by the causes of death, but also by the treatment given to those bodies. And the decisions made in this regard will result in a lesser or greater “pathologization” of the grief, depending on the case. Hence, those who call for the relaxation of sanitary restrictions, appeal with recurrence to the dignity of the victims of contagion and their right to be cremated in the most “humane” way possible. In this context, dignified death appears to be associated less with the claim of orthothanasia, than with the recognition of the right to jointly experience such a disturbing outcome.

At the same time that these demands acquired public status, social networks continued to be populated with countless content referring to the social emergency and its multiple effects. From testimonies of those who were directly or indirectly affected by the disease and the consequent preventive measures, to events of global impact from the four cardinal points, passing through the increasingly sophisticated *fake news*; all this production and circulation of

¹⁹ To read more about this, go to: <https://www.infobae.com/sociedad/2020/07/23/morir-acompanado-el-protocolo-que-implemento-un-hospital-para-que-las-muertes-By-coronavirus-don't-be-lonely/>

²⁰ More about these regulations at: <https://www.lanacion.com.ar/sociedad/coronavirus-argentina-buscan-habilitar-ley-ciudad-acompanamiento-nid2429492> - <https://www.baenegocios.com/sociedad/Como-is-the-CABA-protocol-to-visit-relatives-in-critical-state-20200826-0035.html> - <https://www.pagina12.com.ar/288018-corona-virus-las-recomendaciones-of-the-ministry-of-health-for>.

information has also caused the sensations, perceptions and emotions related to dying and death to be challenged with unusual assiduity.

If we conceive, as Scribano and Lisdero (2018) do, that looking/showing/feeling and receiving/sharing in and through networks suppose specific ways of elaborating perceptions - and that the latter are related to affective regimes and management of sensations mediated by ICTs-, then we can recognize the importance of the question of the way in which sensibilities are structured in virtual environments. And exchanges on fatality in times of pandemic are a good starting point.

Among the profuse material in this regard, perhaps the most viralized content (worth the term) so far is the one that has as its central theme the ballad of the Ghanaian *pallbearers*: a charismatic group of funeral directors, whose jovial choreography (edited together with a catchy identifying melody) would have sufficient ductility to adapt to any risky situation –real or apparent– that arose; including, of course, the contagion of viral disease. Such has been the popularity of this meme, that it was even used for different prevention campaigns in various countries. To mention a few cases: the Republican National Guard of Portugal shared on its official account *Facebook* a photomontage in which a poster with the African protagonists appears, accompanied by the following warning: “Stay home or dance with them! What do you prefer?”²¹. Just published, the post was shared more than 2,000 times and received hundreds of comments.

The Colombian National Police, for its part, recorded a video in which they emulate that choreography, to raise awareness of the importance of confinement to the inhabitants of Quibdó (Department of Chocó)²².

The curious thing about this phenomenon is the carefree and cheerful character with which the current crisis is approached, perhaps as a way of warding off the misery, fear and anguish caused by the daily verification of the mortality and lethality rates of COVID- 19. From our perspective, this palliative vocation would correspond to a type of affective regime with a certain preponderance in the present mediated interactions. Likewise, we suppose that the “irreverent” way of behaving in the face of dying and death in the context of a pandemic is stressed by other logics of feeling/wanting: those associated with the claim for the right to dignified treatment, dismissal and separation, which develop above.

CONCLUSION

Throughout these pages we try to reflect on the specificities, in our opinion the most relevant, that suffering/perishing acquires in the context of the current health crisis. In this sense, we base our approach on the perspective of a sociology of bodies/emotions, with the emphasis placed on the structuring of present sensibilities. The impossibility of referring to conclusive information on a phenomenon still in progress - and which, due to its magnitude and nature, does not have any contemporary referentiality either - made us go back to the Spanish Flu (1918-1920) and the corresponding hygienic measures adopted. Specifically, we

²¹ To read more about it, go to: <https://www.farodevigo.es/mundo/2020/04/17/africanos-ataud-secreto-mejor-guardado/2277242.html>.

²² To read more about this, go to: <https://actualidad.rt.com/actualidad/350268-policia-colombia-baila-ataud-calle-meme-africano-coronavirus>.

considered how the management of corpses at that time configured an unprecedented “body geometry”, heralding a practice of distancing that today acquires the status of what we have called “death in *absentia*”.

And it is precisely this reconfiguration of the links between the bereaved/deceased and the social environment that has influenced the tensions between different “affective regimes”, which gain visibility on at least two levels: a) the regulations relating to hospital and funeral procedures, and b) the “management of sensations” in and through the networks, around the treatment of death in the times of coronavirus.

Ultimately, what it is about is a tragic event that has come to question, perhaps as never before, that politics of bodies and emotions that made the disturbing “tangibility” of the perishable more bearable.

The pandemic causes human beings to die alone; poor, rich, of all and various genders, of all ethnic groups, as in all dimensions of social structuring, the pandemic operates as a magnifying glass on the contemporary global structure: it isolates. It is precisely in the gale of volatility that death installs where the world has had to cling to love beyond all the discredit that colonial/patriarchal reason throws on that energy that breaks isolation and is therefore dangerous.

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Chapter 499

CHILDREN, YOUTH, VIOLENCE, PUBLIC HEALTH AND MEXICO

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ABSTRACT

Violence is a public health concern that since 1996 has also concerned the World Health Organization. The study of violence from a public health perspective complements existing approaches (mainly from the criminal justice areas) by focusing on prevention through the identification of risk factors. The objective of this study is to address the rising levels of adolescent homicides in Mexico for the past 13 years (2000-2012) employing a socio-ecological framework, while attempting to identify patterns, temporal trends and corresponding risk factors. We confirmed that the rates of homicides among males aged 15 to 24 years old doubled between 2008 and 2010. Available evidence clearly indicates that the rise of the violent deaths curve, however, starts in younger groups. Our data also suggest that young males are much more likely to be homicide victims than females. Public health practitioners, teachers and advocates need to be more actively engaged in violence prevention activities. At the community level, potential interventions include slum upgrading, schools renewal programs and pacification projects, support for social cohesion and neighborhood policing in at risk or hot spots neighborhoods. We may face an ethical dilemma, and raise awareness to break the cycle or remain silent on these challenges.

INTRODUCTION

Violence results in more than 1.6 million people being killed each year globally with interpersonal violence as a major factor (1). Many more people suffer from sequelae of non-fatal intentional injuries, including disability, mental disease and chronic ill health (2). In

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South Africa interpersonal violence is estimated to cause around 1.0 million (6.5% of all) disability adjusted life years (DALYs) (3).

The World Health Assembly first declared violence a major public health problem in 1996. The study of violence from a public health perspective complements existing approaches (mainly from the criminal justice areas) by focusing on prevention through the identification of risk factors (4, 5). This approach has gained considerable traction since the release of the first World Report on Violence and Health by the World Health Organization in 2002, which indicated that at least 85% of homicides were recorded in developing countries. The same report estimated between 73,000 and 90,000 firearms deaths annually in Latin America, three times the world average (6); most of these homicides occurred in Honduras, Guatemala, Salvador, Brazil, Venezuela, Colombia, Mexico, as well as Puerto Rico, Haiti and the Dominican Republic, from the Caribbean. Regional proximity to the highly profitable drug market in the United States has contributed to the existence of criminal organizations (7), which have thrived in recent years aided by high levels of political corruption, impunity, growing social inequalities and a steady flow of illegal guns smuggled from the United States to the South (8).

The epidemic of violence In Mexico has attracted attention in recent years. The government strategy implemented since 2006, namely the war on drugs and Merida initiative, was to mobilize the federal security forces in a declared military operation against the drug cartels and criminal organizations (9). Despite the deployment, the homicide rate in this country increased from 8.2 to 23.4 per 100 000 population between the years 2007 and 2012. By 2010 interpersonal violence was the number one cause of death among Mexican youth aged 15 to 24 years, and number three among those aged 10 to 14 years (10).

Children and adolescents, in particular, are now growing up in an environment characterized by threat of becoming a witness or a victim to a violent act, which can be detrimental to their physical and mental health. Available evidence suggests a relationship between early exposure to violence and an increased likelihood of aggressive and violent behavior later in life (11). For some scholars, the probability of adolescents becoming perpetrators of violent or unlawful acts and therefore the increased likelihood of being murdered can be further explained by using a socio-ecological framework (12) (see Figure 1). This framework covers four different levels of an adolescent's life: individual, family/relational, school/community and societal context, all of which may be critical in identifying potential risk and protective factors for the development of evidence-based violence prevention strategies and the use of public health tools. Health policy requires not only a clear understanding of different expressions of violence (e.g., domestic, gangs, armed conflict), and the complex driving forces of this epidemic's local determinants, but also the translation of knowledge from many disciplines into human rights protection and a stronger public health framework.

The socio-ecological framework (see Figure 1) has the following components:

- Individual level (e.g., biological factors, demographic characteristics', social and racial background; substance use)
- Interpersonal level (relationship to family and friends, social capital, gang involvement)
- Community level (Neighborhood); crime rates and safety issues,

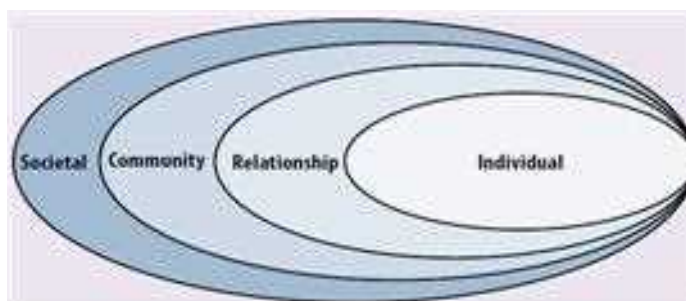


Figure 1. Ecological model of risk factors (12).

- Society level (e.g., acceptability of violence and cultural values e.g., machismo, concerning availability of guns, gangs, police corruption and weak legal framework.

The objective of this study is to address the rising levels of adolescent homicides in Mexico for the past 13 years (2000-2012) employing a socio-ecological framework, while attempting to identify patterns, temporal trends and corresponding risk factors. We will also address the potential implications of our findings for the development of a stronger public health framework aimed at violence prevention. Our research questions were:

- Which factors contribute to the increased likelihood of adolescents becoming homicide victims?
- Which factors contribute to regional variability of homicides across the country?
- How do we translate knowledge into evidence-based prevention?
- Why do we need evidence-based prevention policy?

LITERATURE SEARCH

We conducted extensive literature searches using MEDLINE, JSTOR and HOLLIS. The purpose was also to outline potential research gaps and add them to our discussion. Search terms included interpersonal violence (intentional homicide, intentional injury, violent crime, aggression, violent behavior, child maltreatment, youth, abuse; injury surveillance, distribution of fatal violence, non-fatal violence, conflict; risk factors, epidemiology, ecologic framework, social inequality, child, youth, poverty, gun control, income inequality, early childhood exposure. Then we focused on Latin America, particularly Colombia, Brazil, Venezuela, Honduras, El Salvador; and Mexico, particularly US border (e.g., Ciudad Juarez in Chihuahua and Northwest); violence outcome, such as physical injury, mortality, mental health, aggression, PTSD, depression, stress, victimization/, violence prevention, such as prevention, school programs, crime prevention, urban development, public-health approach.

Research papers were organized according to relevancy and methodology employed.

We employed a socio-ecological framework aimed at organizing the multiple risk factors associated with the occurrence of violence (see Figure 1), while assessing regional and temporal trends in homicide rates in Mexico. We selected a time frame of 10 years (2002-2012), which includes four years prior the all out ‘war on drugs’.

We collected data from the public database of the National Institute of Statistics (INEGI) (13) and the National Council of Population Demographics (CONAPO) (14) to calculate the incidence of death rates due to intentional homicide across the country. Homicide rates were calculated for each gender and two different age groups. The homicide rate was calculated as follows:

$$\text{Homicide rate} = x_{(i, j)} / 100\,000 (\text{pop})_{(k, j)}$$

with the following components as i: Number of homicides in the state, j: age group and k: Population in the state. Homicide rates were calculated for each gender and two different age groups: 0 to 14 years old and 15 to 24 years old.

Eight geographical regions in Mexico were defined (see Table 1). Maps were created to better represent the regional differences, for which we further employed a geographical categorization for subsequent analysis.

To test the association between homicide and income inequality we used the GINI coefficient which is a measure of statistical dispersion intended to represent the income distribution of a nation's residents and is the most commonly used measure of inequality. The GINI coefficient for each federal state ($n = 32$) was collected from the public database of the National Council of Policy Evaluation and Social Development (CONEVAL) (15). We proceeded to use multiple regression methods to assess associations between homicide indicator and socio-economic indicators, which included the following:

- The average median income (median of the income distribution of heads of household)
- Population density (The logarithm was used as a variance-controlling transformation)
- Illiteracy rate (% of the population over 15, who cannot read or write)
- Percentage of the population aged 19 to 25 that does not work or study (NINI)

Table 1. Geographical sub-regions of Mexico

Sub-region	States
Northwest	Baja California, Baja California Sur, Chihuahua, Durango, Sinaloa, Sonora
Northeast	Coahuila, Nuevo León, Tamaulipas
West	Colima, Nayarit, Michoacán, Jalisco
North-central	Aguascalientes, Querétaro, San Luis Potosí, Zacatecas
South-central	Mexico city, Mexico, Morelos
East	Hidalgo, Tlaxcala, Puebla, Veracruz
Southwest	Guerrero, Oaxaca, Chiapas
Southeast	Campeche, Quintana Roo, Tabasco, Yucatán

The average median income-indicator was collected from the INEGI database (13), all other indicators were extracted from the CONEVAL database (14).

Statistical analysis, models, graphs and maps were done using statistical software (SAS 9.3. and JMP), using the SAS license provided by the LMU and the JMP license for students of the Harvard School of Public Health.

FINDINGS

Homicide rates in Mexico for adults showed a downward trend between 2002 and 2006. This trend, however, changed after 2006, when homicide rates started to increase and our data suggests that the younger age groups were affected as well (see Figure 2). There were a total of 24,272 homicides victims aged 0 to 24 years old between 2002 and 2012.

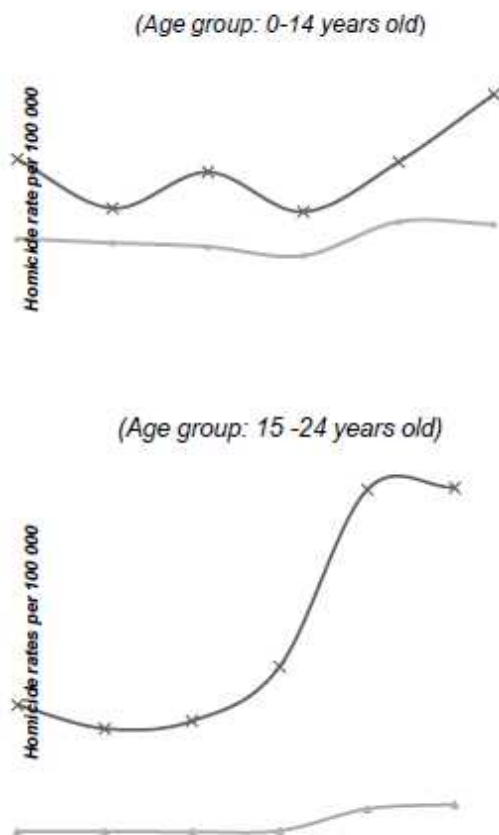


Figure 2. Average national homicide rates from 2002 to 2012 for age groups a) 0 to 14 and b) 15 to 24.

Homicide rates were calculated for the 32 federal states. The results showed great regional variability. Between 2002 and 2008, violence was mostly concentrated in the Northwest (NW) region of the country including Chihuahua, Durango, Sinaloa, Sonora and Baja California; violent deaths rates in the West (W) Central-north (CN) and Central-south (CS) regions had been declining during that period. Since 2008, however, homicides took a drastic turn and have since continuously increased. Regions the northeastern (NE) states of Tamaulipas, Coahuila and Nuevo Leon have experienced a drastic increase in homicides. The Southwest (SW) state of Guerrero also has extremely high levels of violence,

Yet it is important to note that two regions have not been as affected by high levels of interpersonal violence. The East (E) and Southeast (SE) regions remained the least violent throughout the analyzed time frame. Chiapas and Oaxaca, for example, do not have similarly high homicide rates.

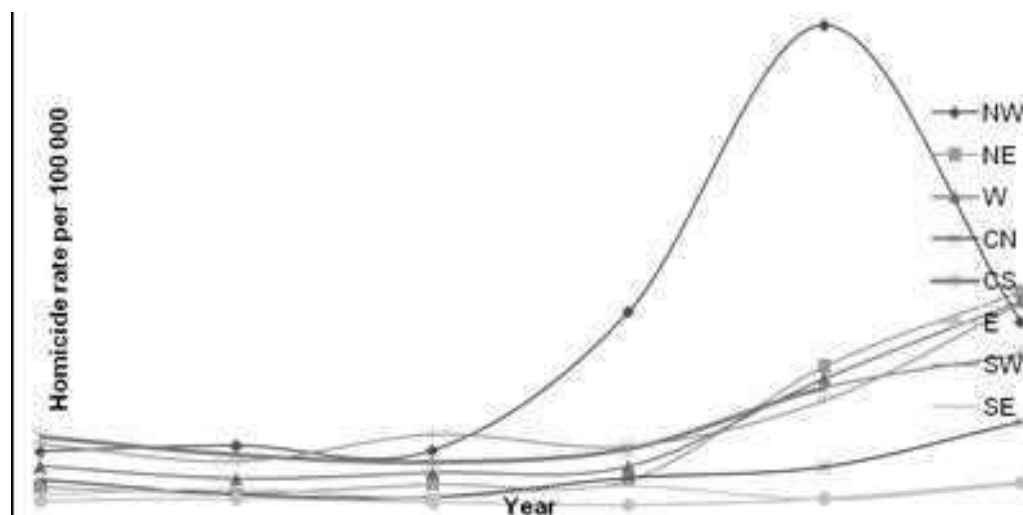


Figure 3. Average homicide rates from male and females aged 15 to 24 years old for each geographical sub-region.

The male homicide rate for 15 to 24 year old increased significantly from 24,6 in 2006 and to 170,17 in 2010 (nearly 7 x higher). The rates of homicides for males from this age group doubled between 2008 and 2010 (from 26.6 per 100,000 to 52.06 in 100,000). The female homicide rate also grew 2.05 times in the same period.

The male homicide rate was consistently higher than the female rate in both age groups. Gender differences are more apparent in the older age group where male rates were between 6.17 and 8.96 times higher than female rates (see Table 2).

Table 2. National male to female ratio of homicide rates per 100 000 population for two age groups, 0 to 14 years old and 15 to 24 years old

Year	Ratio of male to female homicide rates 0-14 years old	Ratio of male to female homicide rates 15-24 years old
2002	1.53: 1	7.41: 1
2004	1.5: 1	6.17: 1
2006	1.54: 1	6.61: 1
2008	1.35: 1	8.96: 1
2010	1.4: 1	8.58: 1
2012	1.89: 1	7.76: 1

The Pearson correlation coefficient was employed to test the relation between homicide indicator and income inequality as measured by the GINI index (see Table 3). There appears to be an inverse correlation between the two variables, but the results were not statistically significant. Income inequality, as measured by the GINI coefficient does not appear to correlate with the homicide indicator on this geographical level.

The analysis between homicide rates and multiple socio-economic indicators was carried out using multiple linear regressions and the stepwise backward process. No significant correlation ($p < 0.05$) could be observed when other socio-economic indicators were

included, e.g., average median income, population density, % of the population aged 19 to 25 years that does not work or study and literacy rate.

We also constructed a second model, with each geographical region categorized by a dummy-variable, related to its location (see Table 4) e.g., proximity to the border with the USA (i.e., strong cartel presence and history of conflict), it receives the numeric variable 3.5; by contrast, the Southeast receives 0.5 (continuously the least violent region in the country).

Table 3. Correlation between the homicide indicator and the GINI coefficient

Variable by Variable	Correlation	Significance Probability
Homicide rate by GINI	-01152	0.53 ($p > 0.05$)

Table 4. Geographical sub-regions of Mexico and regional categorization (dummy variable)

Sub-region	Dummy-Variable	States
Northwest	3.5	Baja California, Baja California Sur, Chihuahua, Durango, Sinaloa, Sonora
Northeast	3	Coahuila, Nuevo León, Tamaulipas
West	2.5	Colima, Nayarit, Michoacán, Jalisco
North-central	2	Aguascalientes, Querétaro, San Luis Potosí, Zacatecas
South-central	2	Mexico city, Mexico, Morelos
East	1.5	Hidalgo, Tlaxcala, Puebla, Veracruz
Southwest	1	Guerrero, Oaxaca, Chiapas
Southeast	0.5	Campeche, Quintana Roo, Tabasco, Yucatán

Table 5. Regression results for regional categorization of 8 sub-regions and homicide indicator

Parameter	Estimate	Std. Error	Significance
Intercept	-43.13	31.56	0.18
Regional category	48.29	13.75	0.0014 *
R ² adjusted	0.267		

Table 5 shows our results, which suggest that this categorization could be used as predictor for homicides across the country, accounting for 26.7% of the total variance in the homicide indicator. It could prove useful for the development of interventions strategies and allocation of resources and funds in priority regions, i.e., where young people may be at risk.

DISCUSSION

This study was aimed at producing preliminary data describing links between violence, particularly interpersonal violence, and some factors contributing to the increased likelihood of young individuals, including adolescents and children, becoming homicide victims or perpetrators. Further questions concerning social, economical, geographic and temporal variability of violent deaths across the country were also addressed in this investigation. The

magnitude of the epidemics, as our data show, reflects an urgent need to break the cycle of violence with prevention measures and public health interventions targeting the youngest groups of the population.

We confirmed that the rates of homicides among males aged 15 to 24 years old doubled between 2008 and 2010. Available evidence clearly indicates that the rise of the violent deaths curve, however, starts in younger groups. Our data also suggest that young males are much more likely to be homicide victims than females. We observed, however, that women are increasingly involved in violence related episodes. Similar trends were reported by Krug et al. (1).

Our approach allowed us to observe temporal and geographical patterns of violence outbreaks. We simply used the “ecological model” to assess the risk of violent deaths at different levels of analysis, i.e., from the individual to the region.

Data clearly indicates that homicide rates increased seven times between the years 2006-2010, reflecting deadly conflict among organized crime groups fighting for territories and control over routes for smuggling illegal drugs, firearms, humans and enormous criminal profits. This was particularly the case near the Mexico-US border. To our knowledge, this investigation provides original evidence of the effects of violence on the youngest groups in Mexico during the full blown of the war on drugs.

We failed to observe statistical associations between the rates of homicides and income inequality, as measured by the GINI coefficient, and the homicide indicator did not appear to correlate with other socioeconomic indicators used in this investigation. This is, indeed, a clear reflection of the limitations of the ecological method. It is necessary to point out that this investigation, however, does not pretend to show causal associations, but to contribute to the debate on the lessons from recent failures (e.g., the consequences of the war on drugs), while sharing experiences concerning what works and does not with other countries suffering similar outbreaks of violence.

The epidemics of violence in Mexico represent a complex and deeply rooted social and political disorder, for which there are no simple solutions. It may be suggested, however, that major risk factors contributing to the increased likelihood of adolescents becoming homicide victims and perpetrators need to be targeted and prevented. Children and youth, in particular, need to be protected from violent events and becoming witnesses or victims of violent acts. Available evidence suggests a relationship between early exposure to violence and an increased likelihood of aggressive and violent behavior later in life (11).

From a macro-level perspective, governance instruments need to be upgraded to reduce substantially illegal profits from the drug market, impunity and political corruption, as well as the steady flow of deadly guns smuggled from the United States to the South, all of which has contributed to the existence of criminal international organizations (7, 8). These organizations recruit youth for their illegal operations; lack of better options (e.g., jobs, higher education) may push young individuals into violence and homicide.

Furthermore, corruption at all levels has significantly impacted education (16, 17) and without an educated population, it becomes difficult to offer or create jobs resulting in high unemployment or underemployment thus resulting in the temptation to engage in activities that offer money with action, regardless of the price that has to be paid in the loss of lives – one’s own or another’s’. This chronic state of poor education resulting in unemployment has also resulted in the large migration of people to the north, to the US and its promises of

success – financial and educational; thus choosing a better life for themselves and their children (18).

Public health practitioners, teachers and advocates need to be more actively engaged in violence prevention activities. At the community level, potential interventions include slum upgrading, schools renewal programs and pacification projects, support for social cohesion and neighborhood policing in at risk or hot spots neighborhoods. We may face an ethical dilemma, and raise awareness to break the cycle or remain silent on these challenges.

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Chapter 500

LAW ENFORCEMENT AND PUBLIC HEALTH: HOW NORTH CAROLINA BECAME A LEADER IN HARM REDUCTION POLICY CHANGE

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ABSTRACT

Fatalities from accidental drug overdose are endemic across the country and have risen to epidemic levels. To curb this epidemic, several states including North Carolina have recently adopted new laws or practices to help reduce the rates of accidental overdose. This chapter focuses on the development and implementation of two harm reduction laws that passed in the 2013 legislative session in North Carolina, a Southern state with a political and social climate traditionally resistant to harm reduction pragmatism. Analysis is offered as to how these laws were successfully championed by harm reduction advocates, Republican sponsors, and with the support of law enforcement associations. Additionally, preliminary data on a study to train law enforcement officers on these new policies is presented. North Carolina's ability to pass and promote these two laws serves as a guide for how other jurisdictions can be successful in promoting pragmatic policies despite steep opposition to traditional harm reduction principles.

Keywords: policy change, Good Samaritan laws, overdose prevention, decriminalization, law enforcement

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INTRODUCTION

Fatalities from accidental drug overdose are endemic across the country and have risen to epidemic levels. The burden of drug-related overdose deaths has been well documented (Warner, Chen, Makuc, Anderson, & Minino, 2011) and some studies have shown that more than 90% of unintentional poisoning deaths in the United States involve drugs (Paulozzi, Budnitz, & Xi, 2006). Nationwide, overdose has surpassed auto vehicle fatalities as the leading cause of accidental death (Centers for Disease Control [CDC], 2013). In North Carolina, overdose rates have tripled since 2000 (CDC, 2013). The number of fatal poisonings in 2011 claimed 1,368 lives, with 91% of these deaths classified as drug overdoses, primarily due to opioid analgesics (Harmon, Proescholdbell, Marshall, & Waller, 2014; North Carolina Injury and Violence Prevention Branch, 2013).

To curb this epidemic, several states have adopted new laws or practices to help reduce rates of accidental overdose. For example, most states have passed so-called “Good Samaritan” laws intended to encourage victims or witnesses of drug overdoses to seek medical assistance by providing varying levels of immunity from drug-related criminal charges (Davis, Webb, & Burris, 2013). In addition, nearly 40 states have modified laws to increase access to naloxone (commonly known by its trade name, Narcan), a prescription medication that blocks the effects of opiates and reverses an opioid overdose (Beletsky et al., 2007; Coffin & Sullivan, 2013). While naloxone does require a prescription, it can also be what is called “a third party prescription” or standing order given to others by a health professional who has prescribing privileges (Davis, 2015).

Naloxone access has been described as “one of the most promising interventions to date” (Dasgupta, Sanford, Albert, & Brason, 2010, p. 4). The combination of improved access to naloxone, coupled with educating family and friends on how to recognize and respond to the symptoms of overdose, has been credited with preventing overdose deaths for thousands of individuals in the United States (Dasgupta et al., 2010). Despite increased efforts to improve access to naloxone and other evidence-based interventions (Coffin & Sullivan, 2013; Green, Heimer, & Grau, 2008), opiate overdose remains a major public health concern across the United States, and particularly in North Carolina (CDC, 2013; Davis & The Network for Public Health Law, 2015).

This chapter is guided by a three-fold purpose. First, the chapter outlines the political and social context of laws passed in North Carolina during 2013 to promote public health, specifically the health of those who use drugs, those at risk for overdose, and the people with whom active drug users interact. Second, this chapter describes a campaign to create public health laws that incorporate a harm reduction approach to overdose and the prevention of blood-borne diseases, despite resistance to this approach in a conservative Southern state. The specific legislation discussed includes a needlestick prevention law (HB850: Possession of Needles/Tell Law Officer) and the Good Samaritan/Naloxone Access (SB20) law. Third, this chapter presents data from a 2013-2014 law enforcement officer training designed to educate officers on these two laws. Overall, this chapter focuses on the implementation of these two harm reduction laws and offers an analysis of how these laws were passed in North Carolina, a Southern state with a political and social climate traditionally resistant to harm reduction pragmatism.

Harm Reduction: Policy and Methodological Challenges

Harm reduction policy, as defined by Marlatt and Witkiewitz (2010, p. 595), “seeks to meet individuals where they are and provide assistance with helping individuals and communities reduce the harms associated with drug use and other risky behaviors.” As previously described in this book, programs and policies based on a harm reduction approach are often met with opposition for a variety of reasons. Some of the most commonly cited objections to harm reduction approaches include opponents’ belief that this approach gives individuals permission to continue engaging in harmful and illegal behaviours, that harm reduction enables users, and that a harm reduction approach sends a mixed message to youth about substance use being condoned (Marlatt & Witkiewitz, 2010).

Inherently, the social and health problems that public policies attempt to alleviate are complex, difficult to understand, discuss, and reconcile. First, methodologically, policies related to harm reduction touch on core societal conundrums (e.g., equality, fairness, personal responsibility, and role of government) with little agreement as to the best solution. These types of problems are “thorny” in nature (Bogenschneider & Corbett, 2010, p. 8), and have been described as “wicked problems” (Rittel & Melvin, 1973) because they involve emotional, complex, and debatable components that can seldom be analyzed in isolation. Drug policies and their related social and health consequences are complicated and perplexing. Put simply, wicked problems such as drug use are often symptoms of other problems, which are never fully solved, and policies related to these wicked problems have no immediate test of effectiveness. Even when evidence is available to guide policy decisions, such as with syringe access programs, policy in this arena is often based on morality, authority, and ideology (Zerden, O’Quinn, & Davis, 2015). This dismissal of evidence is particularly true regarding programs designed for vulnerable population groups such as those with substance use disorders and those at risk for HIV/AIDS and other blood-borne pathogens (Zerden et al., 2015).

Why Policy Is Needed to Reduce Overdose Fatalities

Numerous social, economic, and emotional costs are associated with drug overdose. The most salient factor is that expanded access to opioid overdose prevention saves lives. High doses of opiates (or opiates in conjunction with other substances) depress the central nervous system, and can lead to respiratory failure and death. However, most opioid overdoses are reversible if naloxone is given before the person stops breathing and suffers irreparable harm from the lack of oxygen (Davidson, Ochoa, Hahn, Evans, & Moss, 2002; Green et al., 2008). Several studies have shown that more than half of drug overdoses occur in the presence of at least one other person, but witnesses often do not seek emergency help for the victim out of fear of criminal consequences for themselves or the victim (Tracy et al., 2005). Despite the effectiveness and safety of naloxone in reversing overdose (Coffin & Sullivan, 2013; Kim, Irwin, & Khoshnood, 2009; Walley et al., 2013), the number of fatal opiate overdoses has continued to rise in North Carolina. Further, the public is largely unaware of the use and effectiveness of naloxone to help prevent overdose fatalities.

North Carolina: Political Context

The North Carolina Legislature enacted two laws (HB850 and SB20) in 2013 as part of a statewide effort to reduce opiate overdose fatalities and to limit the penal consequences of drug use in cases of overdose (North Carolina General Assembly, 2013). The passage of these laws was remarkable because the bills were approved during a legislative session marred by a hostile social and political climate that was inhospitable to progressive policy priorities (Van der Horst, 2014). Harm reduction policy typically falls into the category of progressive policy, and therefore, proposals for harm reduction policies are most often met with a focus on abstinence and morality (Zerden et al., 2015). The political unrest and struggle for social justice around several issues in North Carolina garnered national attention due to strong partisan divisions and statewide protests, which became nationally known as “Moral Monday” protests. The Moral Monday protests were:

... carefully planned by a broad coalition of North Carolinians, including environmentalists, voting-rights advocates, leaders in reproductive health, educators, workers, and immigrants, all led by the North Carolina NAACP. The protest[s] were organized in the tradition of civil disobedience, whose history reaches back through Martin Luther King, Jr. and Mahatma Gandhi to Henry David Thoreau (Van der Horst, 2014, p. 1959).

Through unique partnerships with law enforcement and a statewide grassroots harm reduction coalition, these two laws were passed with near unanimous support in both the Senate and House of the North Carolina General Assembly. Despite the political tone of the 2013 legislative session, North Carolina became the first Republican-controlled state in the nation to pass a partial syringe decriminalization law (i.e., HB850: Needle Possession/Tell Law Officer) and a Good Samaritan/Naloxone Access law (SB20). As explained later in this chapter, North Carolina’s ability to pass and promote these two laws serves as a guide for how other jurisdictions can be successful in promoting pragmatic policies despite steep opposition to traditional harm reduction principles (Davis, Walley, & Bridger, 2015).

Legislative Advocacy: A Response to Overdose Fatalities in North Carolina

In the early 2000s, key stakeholders in North Carolina began focusing on the prevalence of the common causes of fatal injuries related to prescription drugs. These stakeholders included leading epidemiologists; public health practitioners and researchers from all sectors, including North Carolina’s Injury and Violence Prevention Branch; the Department of Health and Human Services; local health departments; overdose prevention groups, such as Project Lazarus; and grassroots advocacy organizations, including the North Carolina Harm Reduction Coalition (NCHRC). Advocacy by NCHRC, the State’s only comprehensive harm reduction organization, has been ongoing since the mid-2000s. The advocacy work of NCHRC is notable because the organization is small, with only three full-time employees. Nevertheless, during the 2012 North Carolina General Assembly legislative session, NCHRC staffers strategized with their board of directors on working toward legislative reforms related to overdose prevention while continuing the organization’s longstanding support for greater access to sterile syringes to reduce the spread of blood-borne disease.

As a result of these combined efforts, SB20 or the Good Samaritan/Naloxone Access bill, was first filed in the Senate on January 30, 2013. This bill was sponsored by two Republican State Senators and garnered bipartisan support. NCHRC first approached the Senators

through a presentation to the Child Fatality Task Force, a legislative committee designed to address child mortality and to make recommendations to reduce deaths. This Task Force recognized the rise of drug-related overdoses in the State. NCHRC attended the meeting accompanied by allied constituents who were directly impacted: North Carolinians who lost children or siblings to drug overdose. The personal testimonies of family members was pivotal in reaching the Senators and one commented in personal communication that “hearing the family speak of their loss was the most moving moment of [his] substantial legislative career.” These two State Senators together, with their many years in office, and with respect and support among their peers, were instrumental in obtaining bipartisan support for the bill and engaging law enforcement. Choosing the right sponsor is key to getting legislation passed. As one NCHRC staff member and a registered lobbyist explained, when meeting with legislators to advocate, knowing who sponsored the bill is often more important than the content being presented.

SB20 provides limited immunity for certain drug-related offenses for (a) individuals who seek medical assistance for a victim of an overdose, and (b) the victim of the overdose. In addition, the law provides immunity for practitioners who prescribe an opioid antagonist (e.g., naloxone) to a third party (e.g., a person who has close contact with someone at risk for drug overdose) and immunity for individuals who administer an opioid antagonist to a person experiencing an overdose. The goal of the law is to encourage people who might witness an overdose to summon emergency aid without fear that doing so will result in criminal justice repercussions (Center for Public Health Law, 2014) and to reduce drug-related fatalities by providing greater access to opioid antagonists.

Whereas SB20 focused on protections for those involved in an overdose situation, the second harm reduction law (HB850) focused on protecting law enforcement personnel. Under the provisions of HB850, if a person declares a needle or other sharp object to an officer prior to a search, that person cannot be charged or prosecuted for possession of drug paraphernalia. All primary sponsors were Republicans and the bill had 17 co-sponsors, including bipartisan support. NCHRC achieved this by approaching a Republican Representative who had previously served as Chief of Police for a community in High Point, North Carolina. As a former law enforcement officer, this Representative was sympathetic to the idea of helping officers avoid needle-stick injury from people carrying drug paraphernalia. This bill became a law enforcement safety issue and less focused on drug use - a reframe that helped make the issue more palatable. Representative also had connections with the Sheriffs Association and the North Carolina Association of Chiefs of Police. These groups worked with NCHRC directly to craft a bill that all parties could support. The final version of HB850 was substantially different from what NCHRC had initially proposed (e.g., full syringe decriminalization). However, as a harm reduction organization, NCHRC felt this was still considerable progress towards harm reduction policy that did not previously exist.

The lessons learned were once again, the importance of finding the right bill sponsors as well as reframing the issue to appeal to stakeholders on all sides. Often times, this means a person who is respected within the legislature, a member of the party in power, and someone who has positive relationships with powerful civic and community groups such as law enforcement associations. Additionally, NCHRC also demonstrated compromise by accepting a watered-down version of their original bill in order to move their organization’s policy agenda forward. This cooperative relationship has become an important feature of NCHRC’s

advocacy work in the State as they continue to pass follow-up legislation with these same sponsors.

Law Enforcement Officer Training and Harm Reduction Pragmatism

Once harm reduction policies are in place, the next step is to ensure that all stakeholders are informed of new laws and regulations. In this case, the next necessary step was to make sure law enforcement officers were aware of the provisions of the new laws recently passed. Implementing educational training to inform practitioners and law enforcement of practice and policy changes to increase awareness of opioid overdose and to prevent unintended death is supported within the literature (Compton, Volkow, Throckmorton, & Lurie, 2013). Moreover, the Office of National Drug Control Policy (2011) has included educational training on opioid overdose as part of their four-pronged strategy to reduce overdose fatalities. In the following section, we describe a law enforcement training project that was implemented in North Carolina to educate officers on the purpose and provisions of these two laws. This training is one example of an innovative and effective method of assessing officers' attitudes and knowledge regarding syringe decriminalization, overdose prevention, and HIV/AIDS or other blood-borne risk as an occupational hazard. In addition, the training provided officers with information regarding how the new state-level policies would directly affect vulnerable groups and individuals who interact with officers. This is particularly important in situations that are likely to be adversarial - such as arrests for drug violations.

Due to current U.S. laws, law enforcement plays a role in how social and health policies are implemented given their involvement with people using/involved in illicit drug use and other risky behaviours (e. g., sex-work, sharing needles) (Beletsky, Macalino, & Burris, 2005; Davis & Beletsky, 2009). Law enforcement officers themselves can be exposed to blood-borne pathogens through occupational risks, including the potential for needlesticks during routine pat-downs, or contact with bodily fluids while providing CPR or taking suspects into custody (Schwerha, 2004). However, the limited available research on the intersection of law enforcement and HIV/AIDS risk has demonstrated that misconceptions and myths exist, as Davis and Beletsky (2009, p. 2) noted:

Officers express significant anxiety about these risks, [but] typically have limited access to training and resources that can equip them to effectively reduce the risks and to navigate the complex set of mental health, addiction and other issues pervasive among injection drug users and other marginalized populations.

The combination of anxiety and lack of training can lead to miscommunication and apprehension between officers and those they encounter on the streets. This same dynamic can exist for officers in overdose cases, especially because officers are often the first at the scene. Equipping these professionals with naloxone could improve overdose outcomes by reducing the response time to treatment and can possibly save lives (Davis, Ruiz, Glynn, Picariello, & Walley, 2014). Yet like attitudes about occupational hazards, little is known about officers' attitudes regarding naloxone access or officers' attitudes about administering naloxone to overdose victims. Prior to the authors' previous study on North Carolina law enforcement officers, no studies had examined officers' knowledge and attitudes around HIV/AIDS risk and overdose prevention in the Southeast United States. Research to better

understand these attitudes was a necessary step to guide efforts toward overcoming resistance and misunderstanding related to harm reduction programs and policies.

The following overview highlights Davis and colleagues' (2014) study that assessed the pre- and post-training attitudes of a cohort of 349 North Carolina law enforcement officers regarding syringe decriminalization, blood-borne risk perception, and recent policy changes around SB20 and HB50. In addition, the overview highlights the work of the NCHRC in partnership with statewide law enforcement groups that coordinate trainings for Crisis Intervention Teams (CIT), a specialized law enforcement certification. CITs use evidence-based approaches to interact with people who are experiencing acute mental health crises, with the aim of helping law enforcement officers deescalate the intensity of situations they encounter.

METHOD

Through connections made with a coordinator for the state-run CIT trainings, NCHRC was invited to provide a one hour-long training for officers working to become CIT certified. The CIT model is designed to improve the response of law enforcement and the community to people who are experiencing mental health crises (National Alliance on Mental Illness, 2013; Watson & Fulambarker, 2012). The training session was required for all officers seeking the CIT certification and included an overview of HIV transmission and other blood-borne diseases and instruction in ways officers could reduce their risk of on-the-job disease transmission. In addition, the training addressed the policy changes intended to reduce officers' risk of needlestick through syringe decriminalization. The NCHRC staff collected data on trainings provided in 2012 and 2013 to 349 officers from 20 law enforcement agencies throughout North Carolina (for a full description see Davis et al., 2014).

Data Collection

Data were collected via a voluntary, anonymous survey that participants completed before and after the training session. The survey instrument collected brief demographic data and queried participants regarding perceptions of their HIV risk and attitudes toward syringe decriminalization. All items used the same 4-point Likert-type response scale, with options of *strongly agree*, *agree*, *disagree*, and *strongly disagree*. Responses were then dichotomized into *agree* and *disagree* responses. Table 1 offers a brief description of the sample of officer participants. Descriptive statistics were compiled for each question and assessed by race (Black vs. non-Black), by gender (men vs. women), and age because the research team hypothesized that attitudinal differences may exist based on these demographic characteristics.

Table 1. Sample demographic characteristics of law enforcement officers (N = 349)

Characteristics	%
Gender	
Men	79.3
Women	20.7
Race/Ethnicity	
White	65.0
Black	25.5
Hispanic	4.6
Other	4.0
Asian	.9
Age (in years)	
20-29	26.4
30-39	32.2
40-49	31.3
50-59	9.0
60-69	1.2
Years in law enforcement	
< 7	
7-13	43.3
14-20	24.7
21-27	20.6
28 +	11.3

RESULTS

Although law enforcement respondents overwhelmingly reported that they feared contracting HIV on the job, only 3.8% (about 13 of 349 officers) of the sample reported ever receiving a job-related needlestick injury (Davis et al., 2014). About 42% of respondents agreed that statewide decriminalization would promote drug use, 59% said that their impression of syringe decriminalization was generally positive, with nearly 60% agreeing that decriminalization would reduce HIV transmission, be “good for the community” and “good for law enforcement.” Interestingly, both Black and women law enforcement officers were statistically significantly less likely to report that they feared contracting HIV on the job, and more likely to agree that decriminalization would be “good for the community” and “good for law enforcement.” Although the results of the study are discussed in greater detail in our earlier work, this chapter discusses the gender and racial/ethnic differences within the sample.

First, as compared with white male officers, Black and female officers held more realistic views of their risk of receiving an on-the-job needlestick injury, and held much more positive views of syringe decriminalization. This finding is especially important because white male officers comprised the majority of the sample and, although specific public data is not available, white male officers comprise the majority of law enforcement within North Carolina. Interestingly, the finding of racial and gender differences would not be predicted based on the available literature. A recent survey of law enforcement officers receiving drug interdiction training (i.e., covers all aspects of drug enforcement), reported few differences by

race or gender in trainees' attitudes toward drugs and drug enforcement (Poteyeva & Sun, 2009).

It is important to note that whereas Black respondents comprise only 22% of North Carolina's population, nearly 67% of the cumulative AIDS cases reported in North Carolina have been among Black residents (CDC, 2012; U.S. Census Bureau, 2012). Possibly, as a result of this disparity and frequency in which HIV/AIDS impacts the Black community in North Carolina, there was more awareness regarding these risks. Possibly, this disparity in HIV/AIDS prevalence may account for some of the variation in attitudes among Black and non-Black officers regarding decriminalization and fear of on-the-job infection.

In summary, the law enforcement officer training serves as an innovative community initiative to address the growing overdose epidemic by providing educational trainings, establishing key community relationships, and organizing ongoing educational opportunities at the state level.

CONCLUSION

According to the Drug Policy Alliance (2015):

The chance of surviving an overdose, like that of surviving a heart attack, depends greatly on how fast one receives medical assistance. Witnesses to heart attacks rarely think twice about calling 911, but witnesses to an overdose often hesitate to call for help or, in many cases, simply don't make the call.

NCHRC has recently encouraging law enforcement departments to carry and know how to administer naloxone as part of their role as first responders to emergency situations. To date, five police departments and one county Sheriff's Department in North Carolina have been trained in overdose prevention and carry naloxone for possible administration on the job. In addition, NCHRC has distributed more than 10,000 naloxone kits to those at risk for overdose and has recorded more than 1,000 rescues between 2013 and 2015.

The next step in assessing the effectiveness of these two harm reduction laws requires collecting and analyzing additional data. Analysis of hospital data are underway to review emergency room utilization for overdoses, as well as calls to emergency personnel (emergency medical technicians, firefighters, and police officers) in response to overdose, whether naloxone was available and used. Determining whether the two laws enacted in North Carolina have had an impact on public health to reduce the number of overdose fatalities is an important marker of lasting-impact and positive change. The answers to this remain unknown given that policy implementation is still relatively recent, yet harm reduction policy change was possible. This achievement seems noteworthy not only because of the social and political context of our Southern State, but also due to creative partnerships working together to curb the overdose epidemic in North Carolina.

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Chapter 501

EXPANDING THE MISSION OF HARM REDUCTION: A PUBLIC HEALTH POPULATION AND ITS MEMBERS’ PERSPECTIVES TOWARDS HEALTH

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ABSTRACT

Introduction: People who inject drugs became a bounded group in the United States when the Centers for Disease Control named them as a “high risk group” for AIDS in 1981. Since then, both grassroots activists and public health officials have worked to manage and regulate this group through discourses and practices affiliated with the term “harm reduction.” Using public health research literature and social scientific renderings of the history of the HIV/AIDS epidemic, this chapter begins by historically tracing the governing of the “injection drug user” risk categorization under the rubrics of public health noting how acts of subjectification placed the drug user in certain relationships to his or her health.

Methodology: Narratives of health within forty qualitative interviews with low-income people who inject drugs in New York City are examined noting convergences and divergences from conceptions of health mobilized by public health governmentality.

Results: Through public health research and practice in the 1980s, the health of people who inject drugs was intimately tied to HIV. This sustained a trajectory of research that constructed the “injection drug user” in ways that produced surfaces for the play of normalizing power. However, in qualitative interviews people who inject drugs did not often identify health concerns related to risk for HIV. Instead, this group was largely concerned with chronic health conditions caused and made worse by living in extreme poverty. In order to address this divergence, the harm reduction movement must expand its mission.

Keywords: stigma, governmentality, harm reduction, health, access to health care, qualitative interviews, phenomenology

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INTRODUCTION

Previously considered a risk group for hepatitis B, “intravenous drug abusers”¹ began to receive increasing interest from public health researchers in the early 1980s when they were identified as an AIDS risk group. The “intravenous drug abuser” was subsequently produced and managed through scientific discourse and behavioural interventions. Grassroots activists responding to a crisis of illness among their family members and friends, began organizing underground efforts to provide syringes to enable and enjoin individuals to address their own risk for disease, as well as the risk of transmitting disease. These humanitarian efforts to produce knowledge and provide care were powerful operations that produced the subject of injection drug use. Following Deverteuil and Wilton (2009), acts of caring for individuals can be understood as forms of governance, whereby power works through enactments of care and protection and the promise of well-being. In organizing and containing the disorder, researchers and activists created an enduring categorization that would place people who use drugs by injection in particular relationships with their health and their bodies.

This chapter offers a rendering of this history of care and categorization as a way to understand the historical roots of an identity category mobilized by researchers and activists alike. Through research and activism affiliated with harm reduction, people who inject drugs were provided with education and material resources to address their risk(s) for HIV. Understanding the practices and politics of public health and harm reduction as productive of subjects who speak about their health in terms of risk (Campbell & Shaw, 2008; McLean, 2011; O’Malley, 1999), this chapter presents the self-described health concerns of a group of low-income people who inject drugs in New York City. Qualitative interviews were conducted with these individuals in 2012 and 2013 to learn if and how their articulations of health resonate with the set of health concerns mobilized by harm reduction policy (i.e., HIV, hepatitis C, and overdose). These narratives of health highlight convergences and divergences from the aims of public health governmentality.

BACKGROUND

Genealogy of a Risk Category

“... the ways in which these categorizations are made, and which categories come to have effects in the world, are never neutral.”

David Valentine (2007, p. 5)

Re-visioning the “injection drug user” as a socially constructed category beginning in the 1980s offers a penetrating reflection, in the mode of a Foucauldian (1997) genealogy, on the

¹ A note about language: There have been several terms used in the scientific literature to label people who inject drugs. The initial term that predominated was “intravenous drug abuser,” which was then changed in the late 1980s to “intravenous drug user” and very soon after to “injection drug user.” None of these changes were across the board; for example, some still use “intravenous drug user.” Recently, there has been a push among people who conduct research on injection drug use to use the term “people who inject drugs” because it represents people-centered language. In agreement with this change, I have attempted to use this language. However, when writing about older research, I use the terms employed by the authors and put them in quotes. Any inconsistency is a result of my own reticence to use this more stigmatizing language.

constructive acts of power, as it literally brings certain subjects into being on both a discursive and material level. This risk category was created as an act of governmentality by a diffuse set of actors labouring under a concern for managing a population and the individuals it contains. The Foucauldian concept of governmentality aids in understanding how power is exercised at both the level of the population and the level of the individual (Foucault, 2007). In governmentality, the sphere of the social is constituted by two types of power—policing at the population level and pastoral care at the level of the individual. These form the, “... double itinerary of a power that moves *between* managing social relations and governing individual conduct” (Orr, 2010, p. 549). The production of the drug-injecting subject through research activities involves an intersection of these two types of power, as efforts are made to regulate the population and individuals are activated to participate in self-care.

Using its risk group schematic, the Centers for Disease Control² (CDC) reported the first cases of AIDS among people who inject drugs in late 1981. The risk group organizational principle introduced more fully by the CDC in 1983 (Oppenheimer, 1988) served to make order out of the disorder generated by this new disease. By creating such a schematic the CDC contributed to an understanding of the disease that placed the onus of infection and transmission onto certain groups of people (e.g., homosexual men, drug injectors, Haitians, among others) regardless of whether they participated in practices that could lead to infection (Glick Schiller, Crystal, & Lewellen, 1994; Oppenheimer, 1988). Although the language of the risk group label has shifted over the last three decades, the categorization of people based on drug injection has persisted. This reveals that when supported by hegemonic systems of rationalization, which themselves are often undergirded by “stories,” there can be a “hardening of the categories” (Verran, 1998, p. 241).

When the CDC released its first report on AIDS, drug use researchers had been suspecting for several years that some type of ailment was impacting people who inject drugs as they were seeing a rising number of pneumonia-related deaths (Campbell & Spillane, 2009). Prior to AIDS, it was clear to public health workers and injectors alike that hepatitis B was spread through the sharing of needles. This knowledge was applied to the new condition, referred to as “walking pneumonia,” and injectors began to adjust their drug use practices (Campbell & Spillane, 2009; Des Jarlais, Friedman, & Hopkins, 1985). Beyond their association with hepatitis B, people who used drugs by injection had not received much attention as a coherent group by researchers. Most of the prominent social science literature on drug use before HIV/AIDS focused on the type of drug used or simply on “addicts” (e.g., Agar, 1973; Becker, 1963; Feldman, 1976; Preble & Casey, 1976). Beginning in 1984, “intravenous drug abusers” began to have a salient presence in public health research literature. Examining popular research articles reveals a process of construction and governance, as the person who injects drugs is surveilled, described, and subjected to behavioural interventions.³ The historical timeline offered here is broken into the following three, non-mutually exclusive eras of governance and construction: suspicions and concerns (1984-1985), surveillance and differentiation (1986), and behaviour change and self-advocacy (1987-1988).

² It was not until 1992 that this federal agency’s name became the Centers for Disease Control *and Prevention*.

³ This process was observed through the review of research publications similar to a typical literature review, except that older publications with relatively high citation numbers (as reported by Google Scholar) were specifically sought.

Suspensions and Concerns (1984-1985)

Articles published in 1984 and 1985 expressed conjectures about routes of transmission and concerns about containment of the virus. There was a common concern that AIDS could be spread from “IV drug abusers” through sex and perinatal transmission (Ginzburg, 1984; Marmor, Des Jarlais, Friedman, Lyden, & El-Sadr, 1984). This claim constructs the person who injects drugs as a vector in the spread of AIDS and also points to the necessity of containing the virus within this group. Intravenous drug users were identified as a “bridge” for the transmission of AIDS⁴ to other groups, most notably children and heterosexual partners (Des Jarlais et al., 1985, p. 98). This discursively constructs a boundary around this group placing them in opposition to two socially-sanctioned groups—non-injectors and children. In these early articles, researchers hesitantly proposed that AIDS was spread between injectors through the sharing of needles and other injection related materials (Ginzburg, 1984; Marmor et al., 1984). To further efforts aimed at managing the disease among people who inject, a call for a clearer definition of this community was made by a director at the National Institute of Drug Abuse (NIDA) in a 1984 publication (Ginzburg, 1984). These nascent ideas present pathways of intervention that demonstrate the early stirrings of governmentality by identifying a bounded group, highlighting individual-level, malleable behaviours such as the sharing of needles, and calling for the collection of more information about the group.

Surveillance and Differentiation (1986)

In 1986, literature based on ethnographic research began to appear that outlined the cultural traits of the “subculture” of people who inject drugs. As Campbell and Shaw (2008) write: “Ethnographic drug research has been a central discourse through which the construction of identity categories has metamorphosed into the IDU subject position” (p. 707). An air of hopelessness was present as researchers described the social bonding that needle sharing enabled among injectors (Des Jarlais, Friedman, & Strug, 1986; Friedman, Des Jarlais, & Sotharan, 1986). The sharing of works was described as a ritualistic part of the initiation into drug injection, a necessity and a way of demonstrating trust between sexual partners or friends (i.e., running partners), and an economic and utilitarian exchange in shooting galleries (Des Jarlais et al., 1986). These cultural practices, though deemed non-pathological by the researchers, are practices that are widely stigmatized (Stoller, 1998). Further, by showing the culture of people who inject drugs as generative of risk, external social and economic factors that shape risky behaviour were elided (Clatts, 1994; Glick Schiller et al., 1994). The act of describing these cultural traits functioned as a way to further delineate this group, and thus allow for more relevant governing. In fact, simply focusing on injection drug using culture and lifestyle opened a surface upon which interventions could spread.

Behaviour Change and Self-Advocacy (1987-1988)

The literature that followed in 1987 and 1988 focused more precisely on behaviour change initiated by both public health workers and by people who inject drugs (e.g., Becker &

⁴ The term “bridge” was used in the article published by Des Jarlais et al. (1985). Furthermore, AIDS was the infection of interest rather than HIV, because it is likely that at the time Des Jarlais et al. (1985) composed their manuscript the discovery of HIV had not been officially announced.

Joseph, 1988; Des Jarlais & Friedman, 1988; Friedman et al., 1987). People who inject drugs were now thought to be fully malleable, and thus were subjected to behavioural interventions aimed at preventing the transmission of HIV. In one proposed behavioural change framework, an aim was to attach new cognitive and emotional meanings to sharing needles (Des Jarlais & Friedman, 1988), thus behaviour change went below the surface of the body to modify people's thoughts and emotions. Behavioural interventions were also becoming more widespread as the federal government provided wide scale funding to support a research endeavour, the National AIDS Demonstration Research project, which assigned drug-injecting research participants to risk reduction interventions. The findings of this research were mixed, with some support for the enhanced risk reduction intervention (Page & Singer, 2010).

Around this time, people who inject drugs were beginning to advocate for themselves and push to legalize syringe exchange. There was a shift in popular discourse that revealed support for the efforts of people who use drugs to protect themselves from infection (Stoller, 1998). Though public health researchers had supported and in some instances worked to initiate these efforts (e.g., Friedman et al., 1987), people who inject drugs were now fashioning themselves as self-advocating and self-governing subjects. Linking their efforts to civic responsibility, these activist injectors exemplify a neoliberal cultural rationality that connects personal goals to the public good (Petersen, 1997). By supporting and collaborating with current and former drug users, researchers realized they could spur self-governance among this group. The loosening in some localities of restrictions on syringe possession meant that injectors were offered more autonomy, though this was buttressed with expectations of self-regulation. Through the interplay of research activities and grassroots actions, the image of the person who injects drugs as an activist began to form.

In 1988, the first legal syringe exchange programs (SEPs) in the United States began to open (Lane et al., 1993). These exchanges were formed and organized through the voluntary efforts of people who currently and formerly injected drugs, activists, researchers, and other advocates. In representations of the figure of the "injection drug user" in research publications, as well as in reports and news coverage of the newly opened syringe exchanges, the emerging discourse of the "injection drug user" as an active participant in self-care and advocacy appeared (Stoller, 1998). Early advocates and practitioners of needle exchange cited an ethics of pragmatism and social justice. For them needle exchange signified a protest against the exclusion and abandonment of people who use drugs (McLean, 2011). People who inject drugs were forming legally sanctioned organizations to protect themselves. In this mode of activity, they were not docile bodies being molded through outside disciplinary forces, but rather a group organized around social justice for drug users that sought to install the means for their own behavioural change.

Harm Reduction

The first stirrings of harm reduction in the United States occurred alongside the emergence of the "intravenous drug abuser" in public health research literature. John Stuenkel Parker began the first, albeit illegal, syringe exchange in the United States in 1983 in New Haven, Connecticut (McLean, 2013). However, harm reduction's roots can be traced to the

1970s formation of the *Junkiebond*, or Junkie League, of Rotterdam, which functioned as a type of trade union with a broad orientation toward drug user rights (Marlatt, 1996). Though input from the *Junkiebond* stimulated the Dutch movement toward a “pragmatic” and “humane” approach to stemming the AIDS epidemic among injectors, the initial goals of the *Junkiebond* were much broader (Marlatt, 1996, p. 784). The focus was on the “general situation of the addict,” which translated to work that involved consultations with government officials over such things as the distribution of methadone, police policy, and housing problems (Marlatt, 1996, p. 784; citing Wijngaart, 1991). This set of concerns, as well as the mission of the *Junkiebond*, are instructive for understanding the roots of harm reduction and how the movement differs in its purpose in the United States. The initial approach of the *Junkiebond* was political and service oriented, interested in drug user rights and basic needs.

The term “harm reduction” was subsequently coined in Liverpool, Merseyside, England in the early 1980s as health officials responded to a moral panic over heroin use and HIV/AIDS. In this setting and as applied by health authorities, harm reduction became more institutionalized and public health-oriented. McLean (2013) explains: “Where the Rotterdam union framed its mandate in terms of users’ rights, Merseyside health officials emphasized the public health and public order benefits of harm reduction...” (p. 22). Positioning harm reduction securely under the auspices of public health authorities has shaped its practices and politics ever since, and further cemented a disconnection from the movement’s anarchist roots (Smith, 2012; Stoller, 1998). The institutionalization of particular components of the harm reduction approach, mainly those having to do with interventions into the techniques of drug injection, steered the movement away from its earlier mission of mutual aid and an expansive approach to bettering the general situation of the drug user.

In New York, the powerful presence of the AIDS Coalition To Unleash Power (ACT-UP) aided drug user activists in their attempts to establish legitimate syringe exchanges through public and controversial direct action techniques (Lune, 2007). This connection to ACT-UP is perhaps partially responsible for the harm reduction movement’s emphasis on HIV/AIDS prevention to the detriment of the earlier mission to improve the general circumstances of drug users. As Heller and Paone (2011) note, “... ‘winning’ arguments for the expansion of syringe access have been rooted in the crisis of HIV/AIDS, rather than the need for a continuum of care and treatment services addressing problems of drug use” (p. 140). Preventing the spread of HIV was and continues to be the catalyzing force behind harm reduction activities in the United States, which limits the possibilities for this movement to address other causes of ill health among drug users, such as structured inequalities. In part, SEP administrators hesitate to pursue more progressive approaches to improving the general situation of the drug user because syringe exchange is politically unfavourable and administrators fear losing the minimal resources they do have, if they were to push the envelope (Lune, 2007).

The continued framing of harm reduction as a public health approach has disconnected it from its more radical roots. Smith (2012) writes “...the resultant disconnect between contemporary public health policy and the oppositional roots of harm reduction practice has sanitized the latter, actively drawing attention away from the role of structural factors underpinning the phenomena of drug dependence” (p. 209-210). Describing the founding philosophy of harm reduction as reflecting anarchist values and practice, Smith (2012) states, “... harm reduction discourse might therefore be seen as a disguised language developed to describe an emergent anarchist model of care for capitalism’s most oppressed, yet

symptomatic victims” (p. 213). Smith’s (2012) commentary and analysis of the current state of harm reduction in North America exhorts us to look back to the roots of harm reduction for guidance in re-shaping the movement into one that addresses the holistic concerns of drug users and the structural roots of their oppression.

Through its efforts to improve and recast the health of drug users, harm reduction is a manifestation of governmentality that regulates and normalizes bodies and creates subjectivities by implicating people who inject drugs in technologies of the self. Through harm reduction health promotion campaigns, people who inject drugs are instructed to take care of themselves by following sterile techniques of injection and in so doing an ethical subjectivity is produced (Fraser, 2004). In many ways, those labouring under the banner of harm reduction, researchers and activists alike, helped to produce the “injection drug user” subject who enacts an ethical identity in relation to peers and community through self-governance.

The governance of drug users through harm reduction policies and practices works in part through a reformulation of the discourse around drug use. Drug use is recast as a normal activity, but with a preferred range of behaviours and actions (O’Malley, 1999). Through this normalization, illicit drug users are enjoined to self-govern so that their drug using practices fall within the range of acceptability. In this way, the will of each individual drug user is aligned to the project of harm reduction (McLean, 2011; O’Malley, 1999). Much of the knowledge produced through harm reduction research efforts relies on risk calculations, which entice drug users to accept harm reduction educational interventions through their appeal to truth by way of probabilistic statistics (O’Malley, 1999). This production of statistics betrays an interest in population-level governance that surveils and normalizes such things as health and vitality. Thus, harm reduction as a mode of governmentality works to regularize bodies at both the individual and population level through a collection of statistics, which inform educational practices that inculcate people who inject drugs in a regime of self-care. Both the history of public health research publications and that of the formation of harm reduction show how the figure of the person who injects was produced through an intimate link to risk for infectious disease. This link will be explored in the next section through an analysis of qualitative interviews conducted with a sample of people who inject drugs in New York City.

METHODS

Qualitative in-depth interviews were conducted by the author with 40 economically marginalized⁵ people who inject drugs in New York City from February 2012 to May 2013. Interviewees were recruited through the use of a flier hung at two harm reduction centres and one public health research field office, all in Manhattan. With the exception of two interviews at a donut shop, the interviews took place in private rooms at the harm reduction centres and at the research study field site. In the interviews questions were asked to elucidate how the interviewees felt about their health. Much of the findings presented here were taken from a

⁵ Only participants who earn less than \$1,009.50 per month—a poverty threshold level set by New York City government—were interviewed for this research. Prior to participating in an interview potential interviewees were asked to confidentially report their estimated monthly income.

question that asked interviewees to identify their primary health concerns. The following questions were also asked during the interviews: How do you feel today? Do you feel healthy today? Can you describe a time in your life when you felt healthy? A time when you were unhealthy? What are some things you can do to make yourself feel healthy? The interviews lasted about 45 minutes each and the interviewees were compensated \$20 for their time and for their contribution to social science research. About a third of the interviews were transcribed verbatim by the author and the rest were transcribed by a professional transcription service. Data analysis was guided by an interest to understand the meaning of health for respondents and thus, the theoretical stance of the data analysis was grounded in phenomenology. The author read through the interviews multiple times and coded them according to emergent themes. This research was approved by the Institutional Review Board of Syracuse University.

In terms of race and ethnicity, age, and gender, the sample of individuals that were interviewed reflect the demographics of people who inject in New York City as collected by the city's department of health (New York City Department of Health, 2010). The age ranged in the sample from 21 to 59. Thirty of the interviewees identified as male and ten identified as female. When asked to identify race or ethnicity, 18 identified as white, 14 identified as Latino, 5 identified as African-American, 1 identified as Muslim, and 1 refused to identify a race or ethnicity.

RESULTS

In this section narratives of risk, which were inflected with harm reduction discourse, and narratives of illness, which focused on chronic health concerns, will be presented. It is important to recognize that harm reduction may have shaped the ways *some* drug users talk about their health and their selves though these instances were limited in scope and number. Narratives of illness heard during the interviews revealed the non-drug use related health concerns of low-income people who inject drugs and offered a way to understand the link between health and structural inequalities. These are representative of the majority of health concerns heard from the participants interviewed. They present health concerns that fell outside of the parameters of health put in place through public health and harm reduction governmentality.

Narratives of Risk

In limited ways the discourse disseminated by harm reduction is visible within interviewees' understandings of their health and ultimately their selves. In this section, all references to "harm reduction" are to its existence as a public health intervention rather than its historical configuration as a broader social justice movement. The behavioural practices advocated by harm reduction allow drug users to reduce the riskiness of their drug use, and thus promote a healthier way to use drugs. This claim toward healthiness has reshaped the conceptual contours of bodily health in some limited ways for the targets of these interventions—people who inject drugs. Since all but two of the interviews were conducted in

settings where harm reduction was promoted, it is perhaps unsurprising that this type of discourse emerged in the interviews. At the harm reduction centres, as well as at the research field site where interviews were conducted, participants received structured and unstructured education on harm reduction matters through interactions with staff and available educational literature.

Infectious disease and overdose were mentioned as health concerns for several interviewees, above and beyond other health problems, reflecting two of the main goals of harm reduction—to reduce the spread of blood-borne pathogens like HIV and hepatitis C and to prevent opiate overdose. For example, the immediate response of Dorian, a 40-year-old white bike messenger, to a question about his main health concerns reveals the mental proximity of harm reduction discourse. Dorian answered this inquiry right away with a concern about risk, although he may not have completely understood the question.

Kelly: These days what are your main health concerns?

Dorian: These days my health concern is not to contract HIV. I have... say that again?

Kelly: (repeats the question)

Dorian: I had hepatitis C since I have been 18 years old. I've been diagnosed with it. I am an exposure victim, not a carrier.

Dorian defined his health concerns through and with two of the key drug user health problems addressed by harm reduction interventions—HIV and hepatitis C.

Another focus of harm reduction interventions among drug users is the prevention of overdose. While overdose was mentioned by several people during their interviews, only one, Ashley, a 22-year-old biracial woman who is homeless, mentioned it as her primary health concern. When asked what her health concerns are, she responded:

Just like dying. Overdosing. Everybody I know is dying—three people in the last month. They just can't get right out of some place after a year and go back to doing a whole bundle. People go to sleep and they don't wake up. I'm just scared. I don't really sleep. I'm scared.

When Ashley referred to people getting out of “some place,” she meant a drug treatment program. This is a dangerous time for people who frequently use opiates because they have been abstinent for days or months causing their tolerance for opiates to decrease.

The interview with Dwight, a 53-year-old African-American man, was one of two interviews that took place in a setting unrelated to harm reduction—a donut shop. When he was asked questions pertaining to health, he proclaimed his HIV status. The exchange went like this:

Kelly: Okay let's talk about your health. This is a study about health so how do you feel these days? How's your health?

Dwight: It's fair. I have no AIDS. No AIDS.

Kelly: No HIV or?

Dwight: No HIV. Let me show you something. [retrieves a folded document from his wallet] I took an AIDS test over here... No hepatitis, no anything.

Kelly: That's great.

Dwight: Male, African male... I took it ten, twelve, two thousand eleven and it's been dated by these people. Okay, non-reactive and anything else non-reactive.

Dwight revealed his HIV negative status and produced documentation to, perhaps, prove that he was actually HIV negative. For him in the context of this interview, his health was intimately tied to HIV.

Across these three interviewees—Dorian, Ashley, and Dwight—infectious disease and overdose are prime concerns rising above other ailments they were concerned about or experiencing. Harm reduction educational interventions and practices address the foremost health concerns they mentioned in their interviews. Deciphering whether these risk narratives are the power-effects of governmentality may be a useless pursuit. However, when placed next to research, which has convincingly shown that these types of narratives can be linked to the governing practices and discourses of harm reduction (Bourgois & Schonberg, 2009; Campbell & Shaw, 2008; Fraser, 2004), it becomes a possibility that Dorian, Ashley, and Dwight are speaking the discourse expected from drug-injecting subjects.

Narratives of Illness

Most of the health concerns expressed by interviewees were not articulated in terms of risk but rather had to do with chronic illnesses. While telling the stories of their illnesses, interviewees did not often make mention of their drug use, and the chronic conditions they dealt with did not appear linked to drug use. Through telling these stories, the interviewees showed the efforts they made to address their conditions or in some instances expressed worry over their inability to address their conditions.

In terms of evidence-based, risk-reduction techniques, harm reduction has shown much success as a public health intervention in stemming the spread of HIV, but if these interviews are any example, health is still poor among low-income drug injectors. Besides health problems, many of the interviewees also experienced housing instability, which in some instances created or worsened health problems. This section will examine two illness narratives that vividly reveal the link between poverty and health. Offering these illness narratives and making clear their intersection with socially structured disadvantage reveals that individual-level interventions may be inadequate to address the health concerns of socially marginal populations.

Dan, a 22-year-old white man, presented an account of homelessness together with a narrative of illness that reveals the negative health impacts of poverty and how the health care system in the United States can exacerbate illness. In explaining how he came to reside in New York City—he is originally from Long Island—Dan also described how he became homeless:

Well, I was living with my girlfriend, and I had three jobs. I had custody of my brother. She had a kid too, and we ended up breaking up, and everything was in her name. So I was living out of my truck for a little while. I was working. I was doing fine. I was taking care of my brother. Somebody stole my truck. Yeah, so I lost all my jobs and just became homeless, and it was just pretty much downhill from there. Yeah, I lost custody of my brother. I mean my aunt has him. He's okay, but I just kind of ended up out here [in New York City]. It's actually a lot easier to hustle out here. It's a lot easier to be homeless out here than it is on Long Island.

At the time of this interview Dan had been living in a shelter in Brooklyn for about a month. Prior to that, he was living on the street.

It is important to point out that the harm reduction centre where this interview took place played something of a role in Dan's life. He explained:

I thought it was a place for homeless people because everybody that I knew came here, and I'm like, 'Oh, why is everybody coming here?' And I started volunteering, and I've used needles, so it worked out... It's like a hangout.

The syringe exchange services of this harm reduction centre occupy a minor position in Dan's characterization of his introduction to this so-called hang-out. It "worked out" for him to become a participant and volunteer because he injects drugs. However, Dan didn't identify the harm reduction centre as a place that addresses his injection drug use but rather, as a place for homeless people like him to hang out. Dan's prioritized needs have more to do with his homelessness than his injection drug use. However, it is his injection drug use that allowed him to gain entrance to the harm reduction centre, which he describes using for purposes of hanging out with his social network and to pass time volunteering.

When asked what his main health concerns were, Dan said: "My main health concerns? Pretty much just my diabetes." During the interview, it was clear that diabetes shaped Dan's life, as well as how he understood his health. He had previously found employment in the food service industry and described this work environment as helpful for addressing his diabetes. Notably, he did not mention the health risks associated with injection drug use though going through his drug use history revealed weekly injection of heroin, as well as the use of crack and prescription painkillers. When asked how he managed his diabetes while living on the street a story of desperation and frustration with Medicaid sanctions and hospital bureaucratic rules emerged. He described it:

Well, it was difficult in the beginning because I didn't have as much hustles and able to make as much money. So I wasn't doing so good in the beginning, and my Medicaid got cut off because I accidentally set up a case out here [in NYC] while I had a case in Long Island. They cut it off for six months. I almost died like four or five times. I was in the hospital every week because I didn't have my insulin. I can't go three days without my Lantus.⁶ I take two different types, and I can't. I just – I get sick beyond all means. I got no energy because what the insulin does is it literally makes energy in your body, so if you don't have insulin, you don't have energy. So I couldn't even make money if I tried. I was a wreck.

Kelly: Because you didn't have Medicaid, they wouldn't give you insulin?

Dan: So I would have to go into the hospital in DKA, diabetic ketoacidosis. That's when my sugar goes completely too high. I black out. I can just die, and that's pretty much the only way they would take me is if I was in DKA. And I'd have to do three days, and I'd be out for four days, three days.

Poverty, Medicaid sanctions, and hospital policy worked against Dan in acquiring the medication he needed to treat his diabetes. To receive his medication, Dan was compelled to push his diabetes to acute levels and seek treatment in the emergency room where he was not allowed to take medication with him. Faced with this dire situation, Dan's primary focus is placed on his diabetes though he did show some minor concern for contracting HIV. When asked his usual reasons for visiting the doctor, which he does about two times a month now that he has health insurance, he replied: "My sugar." Then, he continued: "To make sure everything is in check, to make sure my A1C's⁷ good. Just general... I take HIV tests like every three months, other tests..." Though Dan was concerned about contracting HIV and has

⁶ Lantus is a long-acting insulin that is taken once a day as a form of diabetes treatment. It comes in the form of a pen that uses a small, thin needle to inject the medication.

⁷ The A1C test measures average blood glucose control for the past two to three months.

himself tested while at the doctor, his diabetes is the motivating force for making the doctor's visit. Visiting the doctor for his diabetes offers access to HIV testing rather than the other way around.

John, a 56-year-old Puerto Rican man, presented a narrative of illness that also links health to poverty and housing instability. Though residing in transitional housing at the time of the interview, John was homeless and living on the street the year prior. After losing his job of 12 years in the maintenance department of an apartment complex, John began living on the streets. He attributed the year he lived on the streets directly to the loss of his job. Now that he is off the streets and working part-time as a peer educator at the harm reduction centre where the interview took place, he's been able to focus on his health. When asked what his main health concerns are these days, he replied: "My health is my main concern right now. I do have health issues... You know, I was homeless. I didn't have no insurance. I had nothing." John listed his health concerns as "an aneurysm, kidney stones, COPD [chronic obstructive pulmonary disease], and asthma and hypertension." At various points while discussing his health, John showed concern for the effects of being homeless and having no insurance on the health conditions he knew he had. He explained:

I had hypertension for a very long time. That I knew. So you know when I was homeless I knew that I had hypertension. The thing was that all the time I was walking around I didn't have insurance. I used to say, 'How am I going to get medication' and I knew my blood pressure was high because I could feel it.

Eventually, John was able to see a doctor through a homeless outreach program run by a local hospital, and he expressed deep gratitude for this connection to health care. As John explained, he is now dealing with the health consequences of a couple of years spent without insurance and therefore, without medication. John said:

... all the time I knew that I had high blood pressure but I had no way to take care of it and the fact that now, you know, when I found Dr. Marquez and I'm getting meds now it's almost like, you know, I'm getting the meds but because of the waiting time of going a couple of years without meds caused the aneurysm to happen. You know, so then I used to worry about it a lot. 'Oh my god, what am I going to do? I can't get meds. I can't do this.' I didn't know that I had the aneurysm. All I knew was I had high blood pressure. I didn't know I had COPD and I knew I had a slight case of asthma because everybody used to tell me, 'you breathe really heavy,' but now I don't, I don't feel like... I mean, I know I'm not real healthy. Like I said the things that I need to be taking care of right now are being taken in. I'm seeing the doctor that I need to see.

John's injection drug use did not figure into his explanation of his health. It seems that he has other overwhelming concerns. John was hit particularly hard by his loss of employment, which left him living on the streets. Unable to plug in to any social safety nets, John's health conditions worsened and he was left permanently affected by ailments that could have been ameliorated if he had access to health care and stable housing.

Through discussions of health with economically marginalized people who inject drugs, it was clear that despite their status as risky subjects, these individuals did not often prioritize the concerns focused upon by harm reduction interventions—HIV/AIDS, hepatitis C, and overdose. Rather, people talked about common chronic ailments such as diabetes, asthma, and hypertension. The structural roots of the circumstances that led to their illnesses are related to inequality, and the inadequacies of the social welfare and health care systems in the U.S. Often conditions of poverty and homelessness made access to health care services and specifically attaining health care insurance difficult if not impossible.

LIMITATIONS

Several omissions with regard to methodology and reporting of data affect the findings presented here. That none of the interviewees identified as indigenous or transgender means that the overall picture of health presented in the results is incomplete. Furthermore, no illness narratives from women were included in the results section. However, their accounts of health and illness figured into the conclusions made below and throughout the chapter. Finally, no community members were consulted during the analysis of data or the formation of conclusions. This limitation breaks with the harm reduction ethos, which insists on the prominence of community member voices and concerns. Informal consultation did occur when these findings were presented at the 10th National Harm Reduction Conference in October 2014. The presentation was not met with critique, though it is possible that criticism was withheld. Rather, it ignited a hearty conversation about the difficulties people who use drugs face when seeking health care.

CONCLUSION

The drug-injecting subject was created in the early 1980s as part of a risk-group organizational schematic that placed the onus for HIV infection on the individual person, rather than placing it on behavioural practices or simply, the virus itself. Though early investigators of AIDS among gay men shifted from a lifestyle model of analysis to a model that focused on the virus (Oppenheimer, 1988), among people who inject there remained a focus on lifestyle as evidenced by the ethnographic study of the culture of injection (e.g., Des Jarlais et al., 1986; Friedman et al., 1986). Research in the mid-1980s that described the cultural traits of communities of people who inject drugs served to refine and differentiate the figure of the injection drug user. Through behavioural interventions and educational campaigns people who inject drugs were governed as a population and as individuals instilled with the will to take care of themselves.

By interviewing these subjects of risk it became clear that concerns over chronic conditions that led to acute episodes of ill-health were of greater importance. The interviewees did not often prioritize the illness that formed their epidemiologic identity—HIV—nor did they often discuss the concerns that form the foci of harm reduction interventions—HIV, hepatitis C, and overdose. Since the forty individuals interviewed were all actively injecting drugs, they could fall under the care of the harm reduction movement and most of them did, though this movement mainly addresses health in terms of its relation to unsafe drug use practices. Presently, the narrow public health mandate of harm reduction externalizes non-drug-use-related health issues to other service providers, and to the individual drug user. This means that individuals living in positions of extreme vulnerability must self-manage.

Looking back upon the roots of the harm reduction movement to the *Junkiebond*, reveals that a broader sensibility with regard to the concerns of drug users is possible. This is not to say that harm reduction in the mode of health promotion should expand its intervention into the lives of drug users, intervening in new places and on new levels of intensity. Rather, harm reduction as a social movement must focus on a more structural level to reduce the harms

experienced by low-income people who inject drugs. The harm reduction movement can expand its mission through an inclusive re-formulation of what is meant by harm. This could translate into support for self-directed efforts among people who inject drugs to define their primary health concerns, and to the provision of resources to address them. By addressing the self-described health concerns of people who inject drugs, harm reduction could subvert the types of governing power that regulate populations in relation to a singular concern (e.g., infectious disease) and instill practices of self-care (due to a lack of available resources).

The findings of this chapter point to the need for a movement that is supportive of care, broadly construed and easily accessible, to those most negatively affected by inequalities and the neoliberal emphasis on personal blame, rather than narrowly-focused movements that parcel out only certain types of care. Social marginalization manifested through poverty, homelessness or housing instability, and the stigmatization of drug use detaches people from necessary resources and support, exacerbating health problems, as evidenced by the experiences of Dan and John. The harm reduction movement should expand its mission by working to combat social policies and informal social practices that make people who use drugs especially vulnerable to impoverishment and disconnection from community networks of care.

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Chapter 502

HARM REDUCTION HIPSTERS: SOCIO-SPATIAL-POLITICAL DISPLACEMENT AND THE GENTRIFICATION OF PUBLIC HEALTH

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ABSTRACT

Background: The hipster has re-emerged as the reigning subcultural identity of the early twenty-first century, spawning an emergent body of critical commentary. Tracing the relationship between hipsters, the philosophy and practice of harm reduction, and the depoliticization of institutional public health policy, this paper critically interrogates 'harm reduction hipsters' and how members of this increasingly ubiquitous global subculture are actively implicated in various forms of social, spatial, and political displacement, resulting in the consequent 'gentrification of public health.' **Methods:** Drawing from the author's cumulative ethnographic experience, this article employs critical theories concerning subcultures and social movements, radical direct action politics, and contemporary patterns of gentrification and urban redevelopment/ 'revitalization,' thus contributing to central debates in critical drug studies regarding the role and importance of equitably incorporating active drug users and/or people with lived experience of substance use in harm reduction programs and interventions through relationships based on the notion of 'collaborative autonomy.' **Results:** Arguing that the contemporary subcultural figure of the hipster is actively implicated in three interrelated forms of social, spatial, and political displacement, the paper concludes by excavating the inherently political origins of harm reduction philosophy and practice and asserting the fundamental importance of resituating people who use drugs as the central driving force behind the movement.

Keywords: harm reduction, hipster, subculture, service user involvement, pathology paradigm, drug user organizations, gentrification, public health

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INTRODUCTION: THE HIPSTER-IZATION OF HARM REDUCTION

Attempting to accommodate active injection drug users (IDU), the conference organizers established a ‘safe room’ equipped with a stockpile of injection supplies and a considerable amount of the narcotic antagonist naloxone. Given my sociological curiosity regarding in/formal drug consumption sites, I visited the safe room repeatedly throughout the three-day event, and during each visit the space was almost completely devoid of users, its only inhabitants volunteer staff and a rotating cast of what I then termed ‘harm reduction hipsters:’ mostly young, educated, white, middle class, ex-suburbanite kids with relative socio-economic privilege who worked in various harm reduction capacities and dressed in accordance with normative late-capitalist hipster style: skinny jeans, plaid shirts, black horn-rimmed glasses, thrift shop t-shirts bearing working class signifiers, and among men, ironic facial hair (i.e., handle-bar moustaches etc.).¹ Further demonstrative of this odd imbalance², by any measurement there was orders of magnitude more naloxone present during the conference than any form of opiates, illicit or otherwise. Each time I visited the ‘safe room’, in other words, instead of active injection drug users I was greeted by a group of leather-jacket clad, tattooed hipsters sitting around trading gossip and ‘war stories’ from the ‘front lines’ of harm reduction outreach (excerpted from the author’s field notes from an unnamed American harm reduction conference, Fall 2010).

Contemporaneous to the widespread adoption of harm reduction as institutionalized public health policy throughout the later 20th and early 21st centuries, a new—or, rather, old—subculture (re-)emerged to become a ubiquitous global fixture: the “hipster.” Given that the rebirth of hipster (sub) culture so closely coincided with the rise of harm reduction as institutionalized public health policy, it is perhaps unsurprising that hipsters have assumed a prominent position within the harm reduction movement in recent years, becoming leading proponents of institutionalized public health policy and practice. In the arguments that follow, however, this chapter asserts that hipsters have not served to strengthen or enhance the political trajectory of the harm reduction movement. Instead, by illustrating the various forms of social, spatial, and political displacement in which they are implicated, the chapter works to suggest that ‘harm reduction hipsters’ are actively complicit in what this paper terms the ‘gentrification of public health,’ a concept that is explicated in detail in later sections of the chapter.

The primary argument of this chapter, therefore, is that the “hipster-ization” of harm reduction has been directly responsible for three closely related and intersecting forms of social, spatial, and political displacement, thus directly leading to the corresponding gentrification of public health. Moreover, these three inter-related displacements un/consciously function to privilege and empower the prevailing pathology paradigm or biomedical ‘brain disease’ model of addiction research and treatment, a paradigm that is inseparable from the apolitical agenda of institutionalized public health policy and the depoliticization of harm reduction practice more generally (Hathaway, 2001; Keane, 2003; Miller, 2001; Reinerman, 2005; Roe, 2005; Smith, 2012b). As this paper asserts, hipsters are

¹ For more on contemporary hipster style, see: Greif (2010a), Haddow (2008), and Lanham (2002).

² Anticipating a low number of drug/service users or ‘peers’ in attendance at the conference, I wrote a provocative refrain into my talk, repeated in different iterations on at least three separate occasions: “how many institutional harm reduction agencies funded a service user or ‘peer’ to attend this conference?”

therefore complicit in the institutional co-optation and recuperation of harm reduction³, in the form of politically sanitized, ‘disease model’-driven public health policy.

Beginning with a background discussion concerning the emergence of contemporary hipster subculture, the chapter details the radical political origins of harm reduction practice in tandem with the depoliticization of institutionalized public health policy.

After tracing the origin and development of contemporary hipsterdom and its relationship to institutionalized harm reduction practice, the chapter then turns to address the complicity of harm reduction hipsters in social, spatial, and political forms of displacement within the harm reduction movement, before turning to a concluding critique of the ‘mainstreaming’ of harm reduction and the *political imperative*⁴ of situating people who use drugs (PUD) as the central driving force behind the movement.

METHODOLOGY: ETHNOGRAPHIC APPROACHES TO ADDICTION, CONTEMPORARY HIPSTERDOM, AND THE DEPOLITICIZATION OF INSTITUTIONALIZED PUBLIC HEALTH POLICY

In order to place hipster subculture in historical and contemporary context, it is first necessary to situate my own research positioning and identity as a politically engaged academic, activist, and advocate for people who use illicit drugs. Providing background to the emergence of what might be termed ‘second wave’ hipsterdom in the 1990s, this section therefore seeks to self-reflexively identify my personal research positioning vis-à-vis harm reduction and hipster subculture, as well as detail the theoretical framework underpinning the social, spatial, and political displacements that form the central argumentative structure of this work. Prior to interrogating the emergence of contemporary hipsterdom, however, it is important to briefly discuss the ‘place’ of qualitative—particularly ethnographic—methods in what Keane (2009) termed ‘critical drug studies.’

The vast majority of traditional research regarding drug use/users, and ‘addiction’ is overwhelmingly characterized by quantitative, epidemiologically-focused approaches absent of social considerations (Bourgois, 2002; Martin & Stenner, 2004), where the predominance of quantitative methods is evidenced in “funding priorities, research turf battles and hierarchical publication prestige” (Ciccarone, 2003, p. 115). The field of addiction research has thus been staked out as the primary disciplinary domain of quantitative public health scientists, where, as Bourgois (2002, p. 260) succinctly suggests, “epidemiologists are still convinced that it is possible to obtain accurate numbers that are useful for solving urgent social problems.” Recent debates in the field of addiction research have suggested the need for increased ‘cross-methodological’ dialogue and debate (Bourgois, 2002), proposing qualitative research as “either the ‘antidote’ or the necessary complement” to quantitative

³ A term coined by the mid-20th Century European avant-garde movement the *Situationist International*, Sadie Plant (1992, p. 75) defines the *recuperation* of dissenting forces as a term “intended to convey the subtlety and effectiveness by which criticism of the spectacle is enlisted in its support.”

⁴ By consciously framing user-driven forms of harm reduction as a *political imperative*, I am both borrowing from and critically flagging the central, privileged focus on public health—and consequent deprioritization of human rights—in the Canadian HIV/AIDS Legal Networks’s (2005) “*Nothing About Us Without Us*”- *Greater, Meaningful Involvement of People Who Use Illegal Drugs: A Public Health, Ethical, and Human Rights Imperative*.

methods (Martin & Stenner, 2004, p. 395). Demonstrating this acute imbalance, several recent issues of prominent addiction journals have been devoted to qualitative—and particularly ethnographic—methods in drug research⁵. The overt focus on ethnography in these publications (Bourgois, 2002; Maher, 2002; Moore, 2002; Power, 2002; Sifaneck & Neaigus, 2001), as Ciccarone (2003, p. 116) notes, “illustrate how epidemiology and ethnography are differently valued within the bio-medical establishment,” where the “hegemony of ‘publish or perish’” serves to privilege “reductionist science over time intensive field research.”

Composed of a series of ethnographic vignettes drawn from cumulative participant-observation fieldwork at harm reduction and addiction treatment sites in Canada (namely Toronto) and the US (namely New York and Philadelphia), observations were collected throughout the author’s doctoral and postdoctoral research, where ethical approval was granted by York University (Toronto, Canada) and the University of Pennsylvania (Philadelphia, US) respectively. In discussing the limitations of “traditional epidemiological methods for explaining patterns of infections among hidden populations engaged in illegal or taboo activities,” Bourgois and Bruneau (2000, p. 328) insist that ethnographic participant-observation methods “urgently need to be integrated into substance abuse and HIV prevention studies if we are to understand fully the implications of the numbers we collect and, also, if we are to prevent complex statistical data from being misinterpreted and manipulated politically.” In this article and elsewhere, Bourgois (1998, 2002) employs ethnographic vignettes as a useful tool for critically illustrating the social and structural dimensions of addiction, harm reduction and treatment policy. Following Bourgois, the self-reflexive ethnographic vignettes that serve to structure this investigation can be seen as a counter-balance or complement to the quantitative, epidemiologically-focused orientation of traditional ‘addiction research’, providing a grounded, politically informed, and socially engaged analysis of contemporary trends within the harm reduction movement in North America, as well as the broader global context of the movement. Prior to introducing the ethnographic elements of this work, however, it is necessary to provide further context concerning the origin and development of hipster subculture and its relationship to the explicitly political origins of harm reduction theory and practice, as well as its depoliticized manifestation in the form of present day institutional public health policy (Smith, 2012b).

Contemporary hipsterdom emerged around the turn of the twenty-first century, undergoing a succession of subtle social and aesthetic permutations over the last decade (Greif, 2010c). In critically considering its present day manifestation, however, it is important to bear in mind that the first use of the term hipster corresponded with new styles of jazz music in the US during the 1950s “Beat”-era (Mailer, 1957).

The American off-spring of French existentialism, mid-twentieth century hipsters borrowed heavily from the aesthetic, vernacular, and musical culture of African Americans, seeking to “exist without roots,” and “journey into the rebellious imperatives of the self,” thus creating a subculture of “urban adventurers who drifted out at night looking for action with a black man’s code to fit their facts” in neighbourhoods such as New York’s Greenwich Village (Mailer, 1957, p. 3-4).

As opposed to the original 50s-era hipster, however, over and above a series of depoliticized, pastiche aesthetic signifiers (Greif 2010a, 2010c, 2010d; Haddow, 2008),

⁵ For example, see: Rhodes & Moore (2001), Moore & Maher (2002), and Moore & Rhodes (2004).

contemporary hipsterdom constitutes a ubiquitous post-globalization subculture inextricably implicated in broader social, political, and economic forces (Clayton, 2010). Borrowing from Lanham's (2002, p. 2-3) *11 Clues You Are a Hipster*, twenty-first century hipsterdom can be defined by its relationship to socio-economic privilege, the adoption of de-contextualized working class signifiers, and superficial political orientation. The first of Lanham's (2002, p. 2) clues suggests that many hipsters "graduated from [...] liberal arts school[s]." Second, Lanham asserts that contemporary hipsters "frequently use the term 'post-modern' (or its commonly used variation 'PoMo') as an adjective, noun, and verb." Perhaps most relevant to the analysis contained within this essay, featuring at number nine on the list of clues, Lanham (2002, p. 3) suggests that second wave hipsters "enjoy complaining about gentrification even though [they] are responsible for it" themselves. Albeit in some cases unconsciously, hipsters therefore constitute active agents of gentrification, a process intimately related to notions of class displacement (Glass, 1964). An additional defining characteristic of modern-day hipster subculture is, as many contemporary cultural critics have argued, a vehement rejection of any form of hipster self-identification. Here, as Greif (2010d) describes, "[n]o one, it seemed, thought of himself as a hipster, and when someone called you a hipster, the term was an insult. Paradoxically, those who used the insult were themselves often said to resemble hipsters." Resisting any form of hipster self-identification is, in other words, perhaps one of the most central tenets of the subculture (Greif, 2010a, 2010d; Haddow; 2008).

As Haddow (2008) argues, the contemporary hipster aesthetic is constituted from an appropriated mishmash of decontextualized—and thus *depoliticized*—working class and/or revolutionary cultural symbols⁶. Hipsterdom, in other words, is a global sub-cultural movement driven by an ostensible affinity with marginal, lower-class urban populations (including people who use drugs), based on the apolitical bricolage of implicitly political signifiers (Hebdige, 1979), utterly divorced and abstracted from their original meaning and context. As an "artificial appropriation of different styles from different eras," Haddow (2008) further asserts that it is "this ironic lack of authenticity that has allowed hipsterdom to grow into a global phenomenon," representing the "end product of all previous counter-cultures ... stripped of [...] subversion and originality;" as the following arguments suggests, this statement might equally apply to the contemporary state of harm reduction and its global infection by the pathology paradigm for addiction research and treatment (Courtwright, 2010; Reinerman, 2005).

In order to adequately contextualize the three forms of social, spatial, and political displacement that are perpetuated by harm reduction hipsters—all of which effectively culminate in the gentrification of public health—it is therefore also important to detail both (1) contemporary theories of gentrification, and (2) the radical political origins of harm reduction philosophy, theory, and practice. Closely corresponding to the global rise of the pathology paradigm following the AIDS epidemic, Smith (1996) argues that the 1980s witnessed a profound shift in the nature of gentrification. Characterized by "*revanchism*"—an ideology rooted in notions of revenge that is deeply inscribed by race and social class—Smith (1996, p. xviii) suggested this emergent pattern of gentrification constituted "a revengeful and reactionary viciousness against various populations accused of 'stealing' the city from the

⁶ Emblematic working-class symbols employed by second-wave North American hipsters include *Pabst Blue Ribbon* and *Labatt 50* beer in the US and Canada respectively (Greif, 2010a, 2010c). One need only think of t-shirts emblazoned with the image of Che Guevara to understand how revolutionary signifiers are recuperated and decontextualized by contemporary hipster subculture.

white upper classes.” The *revanchist city*, Smith (1996, p. 227) insisted, was thus a “divided city, where the victors [were] increasingly defensive of their privilege ... and increasingly vicious defending it.” Based in part on case studies of Vancouver, Smith (2002) and Smith and Derkson (2002, p. 64-67) more recently suggested that this increasingly vengeful pattern of gentrification has proliferated to become a “global urban strategy,” entailing a “generalization of gentrification in the urban landscape.”

Representing a “consummate expression of neo-liberal urbanism” (p. 88), Smith and Derkson (2002, p. 67) argue that “gentrification as global urban strategy” rests on five core characteristics, each of which directly maps on to what this chapter terms the *gentrification of public health*, namely: “the transformed role of the state, penetration by global finance, changing levels of political opposition, geographical dispersal, and the sectoral generalization of gentrification.”

Drawing from the work of contemporary gentrification theorists, I therefore understand the gentrification of public health as an expression of the global proliferation of the addiction-as-disease model and its ubiquitous stranglehold on international public health policy. Extending this framework, the gentrification of public health is therefore informed by both the increasing interdependency between nation-states and “footloose,” “hypermobile” global capital (Harvey, 1990; Lees, Slater, & Wyly, 2008; Sassen, 1998; Smith, 2002; Smith & Derkson, 2002), and increasingly organized, increasingly globalized emergent forms of user-driven direct action-based activism, organizing and opposition (VANDU, 2010). Having assumed a position of global dominance in public policy, the globalized gentrification of public health therefore maintains vested interests in perpetuating the disease model of addiction—what Granfield (2004) has aptly termed “*addiction fetishism*”—at the same time as oppositional factions, from radical academics to autonomous user groups, simultaneously develop new modes of resistance and critique (Alexander, 2000, 2008; Canadian Harm Reduction Network, 2008; Cheng & Smith, 2009; Granfield, 2004; Jurgens, 2008; Kerr, Douglas, Peeace, Pierce, & Wood, 2001; Kerr et al., 2006; Reinerman, 2005; Roe, 2005; Smith, 2012b; VANDU, 2004, 2010).

Demonstrating how the North American harm reduction movement began as a clandestine, grassroots social movement (Reinerman, 2005; Roe, 2005; Smith, 2011a; Stoller, 1998), Smith (2012b) has suggested that the founding theory, philosophy, and practice of harm reduction was therefore in/directly premised on anarchist principles of mutual aid, distrust of hierarchy, and anti-authoritarianism (Bey, 1985; Crimethinc, 2002; Day, 2004; Graeber, 2002).

Through tactical affinity-based alliances with similarly marginalized and stigmatized urban populations—namely the queer community, people living with HIV, and the radical direct action tactics of activist and advocacy groups such as the *AIDS Coalition to Unleash Power* (ACT-UP)—the dawn of the HIV/AIDS epidemic during the mid-1980s was widely seen as the catalyst for a diverse range of “underground,” grassroots harm reduction interventions across North America, which in turn eventually became adopted as depoliticized public health policy, marketed by the cost/benefit, “bottom line” analysis of harm reduction and explicitly framed by the disease model of addiction (Maskovsky, 2001; Reinerman, 2005; Roe, 2005; Stoller, 1998).

Attributable to the global adoption of the pathology paradigm, the institutionalization of harm reduction therefore directly resulted in the erasure or displacement of the movement’s explicitly radical, oppositional political origins, becoming obscured by the ostensibly

“objective”—yet fundamentally ideological—discourse of biomedicine and public health science, particularly epidemiology (Bourgois, 2002; Hathaway, 2001; Hwang, 2007; Keane, 2003; Miller, 2001; Reinerman, 2005; Smith, 2012b). Effectively functioning to divorce and abstract the notion of addiction from the underlying structural forces responsible for its production, the rise of the biomedical model soon led to a dramatic shift in harm reduction discourse away from critiques of the social forces that served to produce and perpetuate harm by resituating addiction as a function of the addicted subject’s innately faulty neuro-chemical circuitry (Alexander, 2000, 2008; Granfield, 2004; Mate, 2008; Roe, 2005; Smith, 2012b).

Throughout the following sections, this essay argues that harm reduction hipsters have been actively complicit in three interrelated forms of social, spatial, and political displacement, effectively resulting in the broader gentrification of public health. As this chapter subsequently suggests, however un/conscious or in/direct, irrespective of their varying degrees of involvement, the role of harm reduction hipsters in this process has been irrefutable. Owing to the fact that there exists little or no literature (scholarly or otherwise) concerning the demographic composition of the harm reduction workforce in any given local or national context, assumptions regarding social class contained in this analysis are, therefore, a significant limitation to the research.

Based on the author’s personal experience, as well as anecdotal research observations from colleagues in the fields of critical drug studies, public health, and harm reduction, however, the socio-economic characteristics of the harm reduction workforce—from medical staff (i.e. physicians, psychiatrists, psychologists, and street nurses, etc.), to administrators (i.e., Executive Directors, board members, grant writers, front desk personnel) to ‘front line’ workers (i.e., outreach workers, ‘client’ support workers, addiction counsellors)—exhibits considerable variation, depending on a host of different factors. Chief among such factors are sources of public and private funding, organizational structure, management, differences in regional and/or state/ provincial/territorial policy, models of local and national governance, the drug use patterns that serve to characterize a given city or region, the socio-spatial character of drug/service user communities⁷, and prevailing public and professional attitudes concerning harm reduction, (public) drug use, and addiction treatment models in any given socio-spatial-political context. As this chapter works to assert, however, in spite of the sometimes stark differences in its various regional manifestations, the phenomena of ‘harm reduction hipsterdom’ is indeed global in scope, and as the following sections describe, the global ‘gentrification of public health’ is already at an advanced stage. Even in the absence of peer-reviewed literature relevant to the demographic composition of the ‘front-line’ harm reduction workforce, however, the ethnographic vignettes that follow clearly demonstrate that the various forms and dimensions of displacement brought on and perpetuated by harm reduction hipsters have become glaringly apparent.

⁷ Circumnavigating the explicitly capitalist-inscribed terms “client” or “consumer” employed by public health authorities to describe the subjects of harm reduction or addiction treatment services, Smith (2012b, p. 211) posits the term *drug/service user* as having “a potentially productive, fluid interchangeability” by encompassing both active illicit drug users’ utilization of harm reduction services such as needles exchange programs (NEPs) and/or subjects of addiction treatment programs such as MMT.

DISPLACEMENT #1: SOCIAL CLASS, USER SPACE, AND HIPSTER GENTRIFICATION

Centred on the notion of gentrification, the paper now turns to interrogate the first *spatial* form of displacement perpetuated by harm reduction hipsters. As a satirical pop cultural point of departure, the entry for “gentrification” on the popular website-turned-book entitled *Stuff White People Like* (Lander, 2008) reads:

Perhaps the safest bet a white person can make is to buy a house in an up-and-coming neighborhood. White people like to live in these neighborhoods because they get credibility and respect from other white people for living in a more ‘authentic’ neighborhood where they are exposed to ‘true culture’ every day.

The largely white sub-cultural shades that together compose modern hipsterdom are often overtly associated with processes of gentrification (Clayton, 2010; Greif, 2010a). As “neighbourhood pioneers,” therefore, hipsters often inhabit—and moreover demarcate—what Neil Smith (1996, p. 190) termed the “redevelopment frontier,” a shifting, socio-spatially contested boundary or border delineating spaces of *disinvestment* from those of *reinvestment* in both urban planning and urban redevelopment discourse, as well as the wider public imagination. Before addressing the centrally important role of hipsters, however, it is useful to revisit Ruth Glass’s founding definition of what is today referred to as “classic gentrification” in urban studies scholarship concerning gentrification and urban redevelopment or “revitalization” initiatives (Lees et al., 2008):

One by one, many of the working class quarters of London have been invaded by the middle classes ... Shabby, modest mews and cottages [...] have been taken over, when their leases have expired, and have become elegant, expensive residences... Once this process of ‘gentrification’ starts in a district it goes on rapidly until all or most of the original working class occupiers are displaced and the social character of the district is changed (Glass, 1964, p. xvii-xix).

As Glass asserts, the notion of class displacement is thus of fundamental importance to the founding definition of gentrification. Invocations of hipsterdom, as Clayton (2010, p. 29) further argues, often represent a cipher for discussions of “gentrification and neighbourhood change,” where class displacement is understood as a central element in both historical and contemporary patterns of urban “regeneration” or “revitalization” (Glass, 1965; Lees et al., 2008; Slater, 2004; Smith, 1996). Not unlike the arts community that they are so commonly associated, aligned, and involved with, therefore, hipsters can thus be seen as representing a particular sub-type of gentrification “shock troops”⁸, a group that often boasts of its tolerance for (and, moreover, embrace of) ethnic, cultural, gender, and/or class-based forms of “difference” (Blackwell, 2006; Caulfield, 1989, 1994; Clayton, 2010; Slater, 2004). In much the same manner as hipster style is constituted from a bit-piece pastiche-like assemblage of decontextualized—and thereby *depoliticized*—marginal, lower/working/under-class signifiers, Greif (2010a, p. 10) argues that “the ‘white hipster’ fetishize[s] the violence, instinctiveness, and rebelliousness of lower-middle-class [neighbourhoods]” yet with “the

⁸ This statement is drawn from the old adage that “*artists are the shock troops of gentrification*.” A military-based metaphor, such invocations fit neatly with invocations of gentrification as a “battleground” or “war zone” (Smith, 2014).

ethnicities scrubbed off,” thus effectively serving to “recolonize[e] urban neighbourhoods with a new aesthetic.”

Gentrification is a process that is always already seduced by the “sketchy” or “dodgy” nature and character of disordered, post-industrial, immigrant working class urban landscapes (Smith, 2010, 2011). In this sense, Neil Smith’s (1996) notion of the *new urban frontier* represents a transitional space where hipsters and junkies, artists and winos, yuppie “DINKs” and sex trade workers intermingle, and—at least for a time—co-exist⁹. Starting with the social construction or invention of the addict as a typology of moral-criminological deviance at the dawn of the 20th century, throughout the course of our “narcotic modernity,” furthermore, such marginal urban areas have often been associated with the “disorder of drugs” (Brodie & Redfield, 2002; Derrida, 1993; Fraser & Moore, 2008; Smith, 2010, 2011, 2012a), becoming the space of brothels and “crack houses” or “shooting galleries”¹⁰, “alkie” dive bars and “junky” parks. From this vantage point, it is therefore perhaps unsurprising that our global cities’ most notorious “ghetto” neighbourhoods — East London’s *Docklands* and *Canary Wharf*, New York’s *Harlem*, Toronto’s *Corktown* and Vancouver’s *Downtown Eastside*, to cite only a few of the most infamous examples—now arguably exist at varying stages of (post-) gentrification, retaining only faint traces of the “gritty-ness” that once gave them their heterogeneous “character” (Caulfield, 1989).

Beginning in 2006 following a series of media-fuelled moral panics concerning methadone maintenance treatment (MMT) largely focussed on accusations of fraudulent billing practices on the part of a large chain of MMT clinics throughout Ontario, the community conflict surrounding the relocation of an MMT clinic into the rapidly gentrifying neighbourhood of Corktown on the periphery of downtown Toronto—formerly home to Toronto’s industrial immigrant working class—provides a telling example of the role of hipsters in gentrification and (socio-)spatial displacement. In discussing the dramatic demographic shift the neighbourhood was witnessing, one local resident detailed the working class origins of the area, describing its “radically changing” and “upwardly mobile” socio-economic characteristics with reference to “BMW’s, lawyers and professors” (Smith, 2010, 2014).

Framed as a product of ‘creative class’ urban planning strategies (Florida, 2002), other community opponents focused explicitly on the impact of arts-oriented organizations and artists in the redevelopment of the neighbourhood, attributed in large part to an adjacent industrial complex that was transformed into a “hub of creative class culture,” complete with allocated spaces for artist studios, theatre groups, a local micro-brewery pub, an upscale independent coffee shop and other “creative class” amenities (Smith, 2010, 2011, 2014).

Noting the arrival of “trendy, cool” businesses in the immediate area, other local business owners predicted that the methadone clinic and its service user population would eventually be displaced by the growing concentration of up-scale businesses, citing Starbucks as being emblematic of this trend¹¹.

In the first instance, therefore, hipsters are implicated in the displacement of urban spaces that were once the neglected, stigmatized domain of people who use illicit drugs. Because it

⁹ Both demographic acronyms, *yuppie* is an adapted abbreviation of “young urban/upwardly-mobile professional,” while DINK stands for “dual-income no kids.”

¹⁰ For an ethnographic account of “shooting galleries” in New York City—and a corresponding feminist critique—see Bourgois (1998) and Vitellone (2010).

¹¹ Here, see: Smith, 2010, 2011, 2014.

has become a pejorative term that is seldom (if ever) deployed as a tool of *self*-identification (Greif, 2010; Haddow, 2008), however, the hipster is often invoked to absolve oneself from processes and phenomena associated with gentrification. Drawing from Bourdieu (1984), Greif (2010d, p. 3) summarizes hipster sub-types according to their relative social class positioning, social mobility, and role in gentrification, revealing a diverse demographic range that may, by extension, mirror and reflect that of the harm reduction workforce. Here, while upper-middle class hipsters largely represent active agents of gentrification, financially precarious lower-middle class hipsters (not unlike their artist “shock troop” counterparts) are often simultaneously positioned as both catalyst *and* victim of gentrification, who are themselves displaced once the process is complete (Greif, 2010d; Ley, 2003). The inherently appropriating sub-cultural force of hipsterdom—and its recuperation by real estate speculators hot on their heels—however, is inextricably implicated in the displacement of (street-based) users, user neighbourhoods, and drug/service user-oriented space more generally.

Elucidating the seemingly anomalous relationship between artists, gentrification, and “hipness” in Vancouver’s Downtown Eastside (DTES), Rob Shier (2002, p. 15) writes:

The image of artists fleeing this dilapidated urban area like rats from a ship is ironic given their reputation as the shock troops of gentrification. Typically, artists form the vanguard of urban colonization. Cheap studio and gallery spaces in a city’s ‘problem’ area brings occupancy, and raises the perception of safety and hipness. In a few years, so the story goes, an influx of tertiary shops, boutiques, restaurants, renters and loft owners follow. An area’s vices, its drug dealing and petty crime, are [therefore] bullied out by an influx of capital.

Despite every effort by municipal planners, private sectors developers, and real estate speculators, Vancouver’s DTES has not followed this model, and as Shier (2002, p. 15) concludes, it in fact “appears to work in reverse.”

Citing organized opposition by a significant population of low-income residents¹², and aggressive expansion of the hyper-capitalist “black market” drug economy as the primary deterrents to redevelopment, contrary to Shier’s (2002, p. 16) projections, the DTES has more recently begun to show increasing signs of encroaching gentrification from all sides.

Here, in spite of arguments suggesting impediments to inner-city gentrification in Vancouver (Ley & Dobson, 2008), anecdotal evidence suggests that a plethora of galleries (re-)opened in the DTES between 2010 and 2012 (Ann Livingston, *Vancouver Area Network of Drug Users* [VANDU] co-founder, personal communication).

DISPLACEMENT #2: THE DISPLACEMENT OF DIRECT USER INVOLVEMENT IN HARM REDUCTION PRACTICE

A symptomatic expression of what I have termed the “*gentrification of public health*,” the second form of displacement perpetuated by harm reduction hipsters concerns the relative positioning of drug/service users, ‘peers’ or *people with lived experience* of substance use in

¹² (many of whom are also part of the area’s large illicit drug using community, and/or members of the *Vancouver Area Network of Drug Users* [VANDU], a group that is discussed in more depth in later section of this chapter; for further information regarding VANDU’s organizational structure, mandates, and achievements, see: Kerr et al., 2001, 2006 and VANDU, 2004, 2010).

all aspects and dimensions of harm reduction, including policy development, program implementation, service delivery, and evaluation (Cheng & Smith, 2009).

Here, a plethora of recent research suggests that drug/service users can and do play a critical role in the development and delivery of a diverse range of harm reduction interventions (Allman et al., 2006; Canadian HIV/AIDS Legal Network, 2005; Canadian Harm Reduction Network, 2008; Cheng & Smith, 2009; City of Toronto, 2005; Coyle, Needle & Normand, 1998; Friedman et al., 2004, 2007; Kerr et al., 2001, 2006; Latkin, 1998; Mason, 2006; Orme & Starkey, 1999; Ruefli & Rogers, 2004; Toronto Harm Reduction Task Force, 2003; VANDU, 2004, 2010). “At this point in history,” proclaims a 2010 manifesto produced by the *Vancouver Area Network of Drug Users* (VANDU, 2010, p. 1), “the question of how drug users are organized and represented [...] is decisive.”

Masking their relative positions of socio-economic mobility and privilege, many hipsters’ ostensible affinity with marginalized, socially vulnerable populations such as people who use drugs merely constitutes a superficial alliance. Conveyed through the deception of aesthetics, this supposed affinity constitutes little more than new source material for a pastiche of unmoored signifiers of socio-economic marginality divorced from their original political context. Here, as Haddon (2008) writes, hipster style is largely composed of “symbols and icons of working or revolutionary classes” that have been “appropriated by hipsterdom and drained of meaning.”

The recent cachet of harm reduction among hipsters and the corresponding deluge of hipster involvement in institutionalized public health, in other words, in/directly functions to displace users and peers as the central engine of harm reduction policy development, service delivery, research, and program evaluation, relegating people who use drugs to passive research subjects and other stigmatizing, tokenistic positions (Canadian HIV/AIDS Legal Network, 2005; VANDU, 2010).

Clearly demonstrating the persistent systemic stigma concerning people with lived experience of substance use among biomedical and public health authorities, an ethnographic anecdote from Vancouver’s DTES provides a telling case in point regarding the under-representation—and, in many cases, complete displacement and consequent absence—of drug/service users from institutionalized harm reduction policy and practice.

During a break in a conference I attended in Vancouver hosted by the University of British Columbia (UBC) in 2011, while walking down East Hastings Street, I serendipitously arrived in front of Insite, the first and only legally sanctioned supervised injection facility (SIF) in North America. Established as a scientific trial in 2003, the fate of Insite was contested by the federal Conservative government, who, following the completion of Insite’s “trial” stage, challenged the legal status of the facility in the Supreme Court of Canada. After weeks of legal arguments and expert testimony, however, in 2011 the Canadian Supreme court ruled against the federal Conservatives, in favour of institutionalizing the facility.

Having served as co-investigator for an SIF needs assessment study that was undertaken elsewhere in Canada, and conducting a thorough, evidence-based review of the scholarly, scientific literature concerning such services and facilities throughout the world, I spontaneously decided to conduct a self-guided tour of Insite¹³.

¹³ My tour of Insite took place while the facility’s fate was still being decided by the federal Supreme Court of Canada, immediately preceding the Insite benefit event described in the following section.

Glancing around the interior space of the facility while awaiting the registration necessary to enter the supervised injection area, I noticed that the injection stalls—composed exclusively of mirror and stainless-steel—were positioned in a perfect horse-shoe arrangement surrounding an elevated monitoring post that Fischer, Turnbull, Poland and Hayden (2004, p. 361) have referred to as the “*injec-ticon*.” In their investigation of SIFs as “governmentality” (Foucault, 1991), Fischer et al.’s (2004) reference to the “inject-icon” explicitly points back to Foucault’s (1977, 1980) writings on the *panopticon*, drawn from Jeremy Bentham’s theoretical model of prison architecture. Here, according to Foucault (1977, 1980) the ever-present threat of surveillance by prison authorities resulted in behavioural self-regulation and self-disciplining among the inmates.

Entering the central area of the facility, I noticed that behind the *inject-icon* sat two young Insite employees, one engrossed in checking her Facebook account on her desktop computer terminal, while the other leaned against the wall, unconsciously stroking his waxed handle-bar moustache while casually fiddling with his iPhone. *Why wasn’t there a paid user or “peer” on site?*, I silently wondered. Standing there drinking in the scene for another few moments, the answer to my absent-minded, rhetorical query became immediately, sickeningly apparent: hipsters have come to occupy most of the central positions of power within harm reduction, effectively displacing the direct involvement of people who use drugs, and at best engaging in superficial, tokenistic—and in some cases outright exploitive—forms of sub-contracted user consultation (Canadian HIV/AIDS Legal Network, 2005; Cheng & Smith, 2009; VANDU, 2010). Arriving at this revelation, I caught myself quietly muttering the words “*harm reduction hipsters*” under my breath. Looking up from her Facebook page, the young woman at the computer terminal behind the elevated “inject-icon” immediately stopped typing, turned to face me, and vehemently responded: “I am not a hipster.” Not unlike how running from the police is read or interpreted as a sign of guilt, however, proclamations such as this that served to deny one’s hipster status essentially connoted complicity (Greif, 2010d).

Given the rapidly increasing impetus for what is generally termed “(service) user involvement” in mental health and HIV policy discourse, this problematic directly calls back to the Canadian HIV/AIDS Legal Network (2005) position-paper-turned-global-drug-user-activist-mantra, entitled “*Nothing About Us Without Us*.” Even in the DTES, arguably Canada’s most infamous open drug scene and home to VANDU, undoubtedly the most accomplished and militant (quasi-?) autonomous user-driven organization in North America, however (Kerr et al., 2001, 2006; VANDU, 2004, 2010), users have been—and continue to be—displaced from positions of power by hipsters who espouse a social, spatial, and ideological affinity with all things “marginal,” while also actively propagating the institutionalized public health model of harm reduction as a “rational,” “pragmatic,” “amoral” response to the depoliticized biomedical vision of addiction-as-“disease,” a model or paradigm that actively serves to obscure, neglect, and moreover negate the very possibility for any form of socio-structural analysis, political interrogation, or cultural critique, as the notion of “addiction” is so neatly summed and sutured up inside the faulty neuro/chemical circuitry of the addicted subject (Courtwright, 2010; Keane, 2003; Miller, 2001; Reinerman, 2005; Roe, 2005; Smith, 2012b).

DISPLACEMENT #3: THE GENTRIFICATION OF PUBLIC HEALTH

Produced by the cumulative impact of the preceding hipster-driven forms of (socio-spatial) displacement, we therefore arrive at what has been alluded to throughout this chapter as the *gentrification of public health*, entailing the displacement and subsequent erasure of radical and/or oppositional politics from harm reduction discourse, policy, and practice, a symptomatic expression resulting from the global pandemic infection of the pathology paradigm for addiction research and treatment. As a culmination of drug/service users' successive *socio-spatial* displacements, the gentrification of public health is thus catalysed, enabled, and/or facilitated by hipsters' un/conscious role in promoting a sanitized, depoliticized form of harm reduction policy and practice far removed from its philosophical, praxis-driven origins as a radical, direct action oriented social movement (Roe, 2005; Smith, 2012b; Stoller, 1998). In order to adequately unpack this final—and arguably most significant—form of hipster-implicated displacement, I therefore make reference to one final ethnographic vignette.

While attending a conference in Vancouver in May 2011, I attended an event entitled *Health, Harm Reduction and the Law*. A benefit for the Insite Supreme Court challenge, the event was held at the recently completed Woodward's redevelopment, the symbolic heart of gentrification on the border of Vancouver's DTES (Sommers, 1998; Sommers & Blomley, 2002).

Arguably one of the most contested redevelopment projects in Vancouver's history, the former Woodward's department store was built in 1903, serving as both a preeminent downtown shopping destination and the focus of several large-scale labour riots during the early twentieth century (Sommers, 1998)¹⁴.

Site of one of the most militant housing squats in Canadian history in 2002 ("*Woodsquat*"), the recently completed redevelopment of the site was based on mixed-use and mixed-income planning principles, incorporating social housing, market rent condominiums, and academic facilities for Simon Fraser University (SFU) and the University of British Columbia (UBC).

Sitting in the Woodward's courtyard as the crowd gathered for the event, I glanced up at the ornate glass and steel structure and was immediately struck by a large public art piece adorning the interior wall of the courtyard, depicting what appeared to be a riot.

An unlikely site for a public symbol of the political violence that has intermittently erupted in the DTES over the course of the last century, I later learned that the photographic mural was completed by internationally renowned Vancouver-based artist Stan Douglas, representing a curious concession to the SFU School for Contemporary Arts. Depicting the Gastown riots of 1971, Douglas's (2008) *Abbott and Cordova, 7 August 1971* is, however, not the only project to take up the shifting and highly contested political geography of the DTES.

A photograph literally depicting *Every building on 100 West Hastings* street, the title of Douglas's 2001 photographic work is not only self-descriptive, but also evocative of both the gentrifying forces encroaching on all sides of the DTES, and the relentless creative-destructive redevelopment of the 'addicted city' of our 'narcotic modernity' more generally (Berman, 1982; Derrida, 1993; Smith & Derkson, 2002; Wild, 2002).

¹⁴ For a more detailed history of the symbolic significance of Woodward's as a central site of organized protest and resistance in Vancouver throughout the twentieth century see Sommers (1998).

Detailing the place of the DTES in the increasingly acute socio-spatial polarization of Vancouver, Shier (2002, p. 10) writes that “[w]ithin this enfolding sphere of civic entitlement and reimagination, the 100 block stands out in stunning relief,” demarcating a “shifting border” between “ruin and renovation” that “waxes and wanes across a number of social boundaries.”

Deriving similar inspiration from Douglas’s (2001) work, and grounded in the social impact of political-economic forces, in slightly more stark terms Sommers and Blomley (2002, p. 19-20) suggest:

The evident changes in the 100 block of West Hastings are inseparable from the deindustrialization of the downtown waterfront and the reorientation of the downtown economy toward tourism, information, and producer and consumer services. Nor can they be understood without taking into account the widespread gentrification and redevelopment of the old working-class residential neighbourhoods in and around the urban core, which, in turn, is bound up with new forms of inequality that come with the post-industrial economy.

The first public event held at Woodward’s since the site’s multi-purpose redevelopment was completed, *Health, Harm Reduction and the Law* drew a larger than expected crowd, and with a suggested \$10 (CDN) suggested donation, the auditorium quickly filled to capacity, forcing organizers to turn away the remaining line-up of mostly young, “progressive” looking, “hip” individuals stretching out the door. Settling into my seat as the stage was prepared I scanned the crowd, noting an unusually high prevalence of leather jackets, “sleeve” tattoos, skinny jeans, ironic facial hair, horn-rimmed glasses and vintage screen-printed t-shirts among the attendees.

As the evening’s speakers were introduced, a leaflet was distributed through the crowd by members of VANDU. Bearing the title *Manifesto for a Drug User Liberation Movement* (VANDU, 2010, p. 1), the opening paragraph read: “Our liberation will come when we have real power in decisions that affect us starting with, but not limited to, laws and policies having to do with drugs and drug use.”

Detailing VANDU’s major principles and aims, the document further asserted that the key to overcoming the “oppressive drug regime and realiz[ing] liberation for drug users” was fundamentally contingent upon the formation of local, national, and international “organizations of people who use drugs that are grassroots, democratic, relevant and effective”; in order to “ensure real self-representation,” the manifesto continued, such groups must clearly insist “that people who use drugs are the one’s to define the participation of people who do not” within the organization (VANDU, 2010, p. 2). As the presentation got underway, my adjacent colleague, a middle-aged British woman, leaned over with a genuinely perplexed look on her face and whispered, “*Who are all these people in the crowd?*” “*Harm reduction hipsters,*” I quietly replied before the curtains rose and the auditorium fell to a hush, yet my cryptic response only seemed to add to her confusion.

Discussing my initial ideas for this essay with several major international harm reduction advocates, from activists to academics, drug users to policy actors, a number of individuals presented the counter-argument that the “mainstreaming” of harm reduction, irrespective of the specific demographics that were mobilized and involved, could only be seen in positive terms. In other words, if harm reduction was becoming “hip,” cool, or culturally cachet, several colleagues insisted, it mattered little *who* composed the critical mass behind it’s growing momentum. The mainstream acceptance of harm reduction, I responded, was taking place at the expense of a series of mutually constituting social, spatial, and political

displacements that were not only fundamentally antithetical to—but also responsible for—the systematic displacement and erasure of the explicitly radical, direct action oriented, oppositional political origins, and founding anarchist spirit of hard reduction as first and foremost, a compassionate, human rights based, grassroots, bottom-up social movement. If hipsterdom had become the reigning (albeit recycled) sub/cultural identity of the early twenty-first century, I argued, the colonization of the harm reduction by the apolitical and depoliticizing phenomena of contemporary hipsterdom signalled the end of the movement as an overtly critical, structurally-focused political force. Implicated in not only the spatial displacement of users through processes of gentrification and the social exclusion of people with lived experience of substance use, dependence, and treatment from the policies, research, treatment, and harm reduction interventions ostensibly conducted in their interests (Cheng & Smith, 2009), hipsters and hipster culture are moreover actively complicit in the erosion of harm reduction's historical import as an explicitly political, user-driven force (Hunt & Stevens, 2004; Roe, 2005; Smith, 2012b; Stoller, 1998).

CONCLUSION: QUESTIONING RESEARCH MOTIVES/ALLIANCES AND (RE)MAPPING UNEQUAL DISTRIBUTIONS OF POWER IN A FLUID LANDSCAPE OF CONTROL

“This is a challenge to academics, policy experts and service providers,” proclaimed the *VANDU Manifesto for a Drug User Liberation Movement* (2010, p. 2):

... we do not want to be used as cheap labour, we do not want to be studied while we die, or be turned into clients while resources are given to ‘service’ agencies. We will not tolerate actions that exploit the labour, activist work, or experiences of people who use drugs.

As we simultaneously witness (1) the disappearance of physical urban spaces for drug/service users to congregate, inhabit, and socialize; (2) the displacement of direct, active, meaningful forms of drug/service user involvement and engagement in harm reduction policy development, service delivery, research, and program evaluation; and (3) the consequent depoliticization of the movement's explicitly radical, structurally-focused founding political philosophy, this chapter urges all researchers, policy actors, and front-line workers to heed these words. “Finally,” the *VANDU Manifesto for a Drug User Liberation Movement* (2010, p. 2) concludes with a tone of militancy that arguably represents the antithesis of hipster irony: “we expect responsible researchers, experts and academics to support us.” Borrowing from the explicitly radical, critical tone of VANDU's *Manifesto*, the question of how to meaningfully engage, support, and ally one's self with such a liberation movement without displacing, dissolving, diluting, or destroying the very people, places, and politics at its core, is the challenge that this essay has provocatively posed.

As the cumulative ethnographic anecdotes scattered throughout the chapter reveal, the only thing that is clear in terms of undertaking any such endeavour is that harm reduction's stated ‘user-centred’ mandate or orientation must no longer take the form of superficial, tokenistic—and in many cases outright exploitive—initiatives in self-congratulatory, surface-level ‘consumer involvement.’ Moving forward, in other words, instead entails relationships

firmly rooted in the notions of ‘collaborative autonomy’ and ‘indigenous inclusivity,’ both through mandating direct consultation and engagement with independent drug user organizations regarding the policies and programs that are ostensibly developed and implemented in their interest, and by allowing organizations run by and for people with lived experience to maintain their autonomy and independence, and thus clearly (re-)situating the fundamentally crucial importance of drug/service users’ lived, experiential knowledge in all aspects of harm reduction policy and practice (Cheng & Smith, 2009).

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Chapter 503

ADDRESSING THE BOOTSTRAP MYTH: A PUBLIC HEALTH RESPONSE TO CHILDHOOD ADVERSITY

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ABSTRACT

A need exists to address childhood trauma and traumatic stress as a public health issue. The prevalence and impact of childhood adversity in our culture cannot be overstated. It is one of the primary roots of many of our more pervasive societal challenges including persistent poverty, health-risk behaviors, substance abuse, child abuse, and domestic violence, to name a few. Similar to other public health issues, efforts need to be placed on increasing public awareness, as well as effective prevention and treatment strategies. Efforts to increase awareness need to address societal attitudes, perceptions, and responses to childhood trauma throughout the lifespan. Specifically, the common belief that those impacted by trauma largely overcome adversity and persevere through the strength of their own character needs to be challenged based on what we know about trauma and recovery. Efforts must focus on public health messaging about the impact of trauma and building trauma-informed and trauma-responsive public and private sector systems whose policies and services recognize and respond to the impact of traumatic stress.

INTRODUCTION

The prevalence and subsequent impact of childhood trauma requires a public health response not unlike responses to other major health issues. Similar to other public health issues, efforts need to be placed on increasing public awareness, as well as effective prevention and treatment strategies. This chapter will review the prevalence and impact of

childhood trauma, address the need to change societal perceptions and attitudes about those impacted by trauma, and define ways to approach the issue from a public health perspective.

ADVERSE CHILDHOOD EXPERIENCES (ACEs)

The Adverse Childhood Experience (ACE) Study, a well-documented and independently replicated study originating from a collaboration between the Centers for Disease Control and Prevention (CDC) and Kaiser Permanente's San Diego Medical Center, demonstrates that certain experiences during childhood such as child maltreatment are major risk factors for the leading causes of illness and death as well as poor quality of life in the United States (U.S. Centers for Disease Control and Prevention, 2015). The researchers found a strong relationship between the breadth of exposure to abuse or household dysfunction during childhood and multiple risk factors for several leading causes of death in adults (Felitti et al., 1998). It is critical to understand how some of the worst health and social problems in our nation can arise as a consequence of adverse childhood experiences. Realizing these connections is likely to improve efforts towards prevention and recovery.

The ACE Pyramid (Figure 1) represents the conceptual framework for the study. The study was designed to provide data that would help answer the question: "If risk factors for disease, disability, and early mortality tend to cluster, that is, persons who had one risk factor tended to have one or more other risk factors too, what influences precede the adoption or development of them?" By addressing this question, the researchers provide scientific information that is useful for developing new and more effective prevention programs.



From the U.S. Centers for Disease Control and Prevention, 2014.

Figure 1. ACE pyramid.

The ACE Study uses the ACE Score, which is a total count of the number of adverse childhood experiences reported by participants. The ACE Score is used to assess the total amount of stress during childhood and has demonstrated that as the number of ACEs increase, the risk for the following health problems increases in a strong and graded fashion:

Alcoholism and alcohol abuse	Chronic obstructive pulmonary disease (COPD)
Depression	Lower health-related quality of life
Illicit drug use	Ischemic heart disease (IHD)
Liver disease	Adolescent pregnancy
Intimate partner violence	Multiple sexual partners
Sexually transmitted diseases (STDs)	Smoking
Suicide attempts	Unintended pregnancies
Early initiation of smoking	Early initiation of sexual activity

Stated most clearly, the ACE Study identified the “scientific gaps” linking ACEs to risk factors and the risk factors to short-term and long-term health and social consequences.

More recent studies confirm and expand on the findings of the original study. For example, the Philadelphia ACE Task Force was formed in 2012 with an interest in examining the prevalence and impact of ACEs in Philadelphia, a city with a socially and racially diverse population. The Philadelphia Urban ACE Study (2015), which was funded by the Robert Wood Johnson Foundation and conducted by the Public Health Management Corporation (PHMC) for the Institute for Safe Families and the ACE Task Force, collected data from Philadelphians regarding adversity that they faced. The questions developed for this survey expanded on the original questions from the ACE Study to include experiencing or witnessing community violence. These new questions were the first extensive survey of this kind specifically for an urban setting. The survey found a higher prevalence of original ACEs than found in previous studies. Furthermore, the study found that 40.5% of Philadelphia adults, while growing up, witnessed violence, which includes seeing or hearing someone being beaten, stabbed, or shot. In all, over 37% of Philadelphia respondents reported four or more ACEs. The findings from this study suggest the need for services that address the unique environmental stressors experienced in urban neighborhoods in order to mitigate their impact on individuals and prevent ACEs. The ACE Task Force, which is currently housed at the Health Federation of Philadelphia, continues to actively work to develop a response to these issues.

RISK AND PROTECTIVE FACTORS

The percentage of people in our society impacted by the connection between ACEs and poor health outcomes necessitates an examination of both risk and protective factors. Risk factors refer to the stressful conditions, events, or circumstances that increase an individual’s, family’s, and/or community’s chances for poor outcomes. Protective factors are conditions of individuals, families, and communities that mitigate risk, promote well-being, and reduce the risk for negative outcomes (Child Welfare Information Gateway, 2014).

Parental risk factors include but are not limited to a caregiver’s lack of parenting knowledge and skill in specific areas such as child development; a caregiver’s own adverse childhood experiences; and characteristics such as young age, low education attainment, and low income. Family risk factors include social isolation, domestic violence, parental stress, and poor parent-child relationships. Community risk factors include community violence,

concentrated neighborhood disadvantage such as high poverty and unemployment rates, and poor social connections.

Although critical to our understanding of effective prevention and intervention strategies, protective factors have not been studied as rigorously as risk factors. However, the Centers for Disease Control and Prevention (CDC, 2015) reports scientific evidence for supportive family environments and social networks. Other potential protective factors include nurturing parenting skills, stable family relationships, access to health care and social services, and caring adults outside the family who can serve as role models and mentors.

RESILIENCY

As more attention is being paid to ACEs and means to reduce risk and enhance protective factors, the concept of resiliency has more strongly emerged in the literature. Resilience is the process of adapting well in the face of adversity, trauma, and tragedy; it means “bouncing back” from difficult experiences (American Psychological Association, 2014). Resiliency in children is said to be the ability to master normative developmental tasks despite experiences of significant adversity (Luther, Cicchetti, & Becker, 2000). By definition, resiliency should be promoted and admired in those who exemplify it. However, this chapter will focus on the misuse of the term as it applies to individuals who experience significant adversity during childhood.

“Pulling yourself up by your own bootstraps” refers to the imagined feat of lifting oneself off the ground by pulling on your own bootstraps. This impossible task exemplifies the achievement of getting out of a difficult situation only by one's own efforts. It is the belief that rugged individualism, individual grit, extraordinary self-reliance, or some inborn, heroic strength of character can triumph over trauma. This myth is perpetuated and even exploited in modern culture through mass-marketed movies and television where the underdog is cheered for his/her innate strengths in the face of adversity.

One of the many dangers of this ideology, the ideology that overcoming the odds is simply a matter of individual motivation or grit, is that the failure to excel is perceived as the fault of the individual, and “blaming the victim” becomes part of the narrative (Center on the Developing Child at Harvard University, 2015). This, in turn, not only allows us to abdicate responsibility for those who have fallen but also releases us from the responsibility of creating opportunities for people to overcome adversity.

Success stories of people overcoming adversity are ubiquitous the world over. Through these stories, we learn about the complexity of trauma and recovery. Examples include Malala Yousafzai, the Pakistani activist, Nobel peace prize recipient, and author of *My Name is Malala* (Yousafzai & Lamb, 2013), who faced insurmountable barriers and trauma during her childhood; Louis Zamperini, subject of the book “Unbroken” (Hillenbrand, 2010) and a World War II veteran who endured years of torture and humiliation after being captured; and Charles Blow, author of “Fire Shut Up in My Bones: A Memoir” (2014) who suffered sexual abuse, extreme poverty, and other adversities as a child and went on to become a respected journalist. Recognizing the strengths and resiliencies in others is indeed important, and individual strengths are necessary to overcome trauma. However, a need exists to develop a

public health response to trauma, a response built on the understanding that it takes more than true grit to overcome adversity.

The narrative needs to change. Science debunks the bootstrap theory. Science tells us that the reliable presence of at least one supportive relationship and multiple opportunities to develop effective coping skills are the essential building blocks for the capacity to do well in the face of significant adversity (Center for the Study of Social Policy, 2015). These relationships begin in the family but also include neighbors, providers of early care and education, teachers, social workers, doctors, and coaches, among others. A deeper examination of the lives of each individual able to persevere in the face of adversity, including those in the previous paragraph, reveals the existence of individual, family, and community protective factors. What is critical to this discussion is the process by which one develops resiliency, as opposed to whether or not a person is resilient. For example, research shows us that children's individual strengths help them adapt only under conditions of low stress, not high levels of toxic stress (Jaffee, Caspi, Moffitt, Polo-Tomas, & Taylor, 2007). The protective effects of children's individual strengths must be understood within the context of their life circumstances. Furthermore, data suggest that efforts must also focus on parents' well-being and the conditions of the neighborhoods in which they live in an effort to understand needs and intervene successfully (Jaffee et al., 2007).

Resilience is best understood as a social construct rather than an individual trait. Resilience is the result of multiple interactions among protective factors in the social system. Protective factors constitute the foundations of resilience and evidence suggests they are cumulative in nature. Understanding resilience as a social construct makes explicit that it is more likely to occur when we provide access to needed services, supports, and resources (Fox, 2015).

The Center on the Developing Child at Harvard University (2015) illustrates resilience through the concept of a balance scale or, in a child's world, a seesaw (Figure 2). Experiences that can result in toxic stress, such as repeated or chronic exposure to violence, poverty, or maltreatment, pile on the negative side of the scale. Positive influences that can help make significant stress tolerable, such as supportive relationships, skill-building opportunities to develop coping skills, and practice dealing with manageable challenges, tip the scale the other way. Resilience is evident when positive experiences tip a person's "scale" toward positive outcomes despite the weight of negative experiences. Understanding all the influences that might tip the scale in the positive direction is critical to devising more effective strategies for promoting healthy development in the face of significant adversity. Continuing with the concept of the balance scale or seesaw, the fulcrum can represent a child's individual predispositions (Center on the Developing Child at Harvard University, 2015). Advances in science are now showing us that the position of the fulcrum is not fixed. The continuing accumulation of positive and negative experiences over time actually influences the child's mental and physical constitution and consequently has the power to slide the fulcrum in either direction. Furthermore, developmental trajectories begin in infancy but do not fully mature until age 25 to 30 years. Just as protective factors serve children well, opportunities to learn and develop skills are critically important capabilities for the adults who care for them, and can be strengthened through coaching and practice. Identifying and making available those protective factors that are shown to help children overcome adversity need to be the focus of our attention, our policies, and our resources.



From the Center on the Developing Child at Harvard University: [http:// developingchild.harvard.edu](http://developingchild.harvard.edu).
Used with permission.

Figure 2. Resilience is evident when positive experiences counterbalance negative ones to tip a person's "scale" toward positive outcomes.

The Center for the Study of Social Policy's Strengthening Families: A Protective Factors Framework (2015) is a research-informed approach to increase family strengths, enhance child development, and reduce child abuse and neglect. Its focus is on engaging families, programs, and communities in building five protective factors:

- Parental resilience
- Social connections
- Knowledge of parenting and child development
- Concrete support in times of need
- Social and emotional competence of children

A literature review and expert consultation project commissioned by the Administration on Children, Youth and Families (Child Welfare Information Gateway, 2014) found that at the individual level the protective factors with the most evidence to help children overcome adversity include opportunities to build self-regulation skills, relationships skills, and problem-solving skills. At the relationship level, protective factors with the most evidence include opportunities to build parenting capacities, positive peer interactions, and multiple interactions with caring adults. At the community level, protective factors with the most evidence include opportunities to build responsive community environments, positive school environments, and economic opportunities.

The interplay between child and environment is bidirectional. The sooner we intervene on this bidirectional chain, the better our chances of fostering positive adaptation across domains. We need to support efforts of multisystem interventions that target multiple levels of the child's world including parent well-being and neighborhood factors. Stated most directly, the combination of adaptive skill-building, supportive relationships, and positive community experiences constitutes the foundations of resilience (Center on the Developing Child at Harvard University, 2015). These foundations are built through the creation of trauma-responsive environments.

A MENTAL HEALTH RESPONSE

This chapter thus far has laid out an argument for creating opportunities for those impacted by trauma to develop resilience. It is by creating the context for recovery that those impacted by trauma may gain an understanding and learn skills necessary to thrive. Pockets exist throughout the country that focus on creating these contexts for recovery or trauma-informed systems. A trauma-informed system, organization, or program realizes the widespread impact of trauma and understands potential paths for recovery; recognizes the signs and symptoms of trauma in others; responds by fully integrating knowledge about trauma into policies, procedures, and practices; and seeks to actively resist re-traumatization (SAMHSA, 2015).

In order to exemplify some of this work, the city of Philadelphia, Pennsylvania, and more specifically a children's mental health agency in Philadelphia, Children's Crisis Treatment Center (CCTC), will be illustrated. CCTC is a private, nonprofit agency that specializes in providing mental/behavioral health services to children and their families. For over 40 years, CCTC has developed and implemented innovative ways of helping children as young as 18 months old and their families cope with obstacles that interfere with their emotional, social, and cognitive growth. Services and programs are provided at the center as well as in the home, community, and schools.

CCTC is dedicated to addressing the impact of childhood abuse/neglect and traumatic events that can affect childhood development. Our approach to providing behavioral health services to children and their families revolves around an understanding of the impact of adverse life experiences. Despite tremendous challenges, children heal from psychological injuries. Through partnerships with families, schools, and communities, CCTC creates the contexts in which this healing may occur.

With a staff of more than 450, CCTC serves over 3000 children and families annually. CCTC is recognized for its expertise in the areas of child/family mental health, trauma, and school-based services. Such acknowledgements reflect CCTC's leadership role in the children's behavioral health services community.

CCTC has a strong history of bringing focus to the impact of trauma. In the late 1980s CCTC developed one of the first programs in Philadelphia offering trauma-focused treatment for children and their families impacted by abuse, neglect, and other adverse childhood experiences. This expertise primed the organization to further educate leadership, staff, and other stakeholders on the impact of trauma.

In 2006, CCTC formalized its commitment to trauma-informed care and began implementing the Sanctuary Model. Sanctuary is an organizational change model that integrates trauma theory with the creation of therapeutic communities which provide safety for both those served and the staff who serve them (Bloom, 1997). The model organizes how we talk about treatment, fosters a shared language, promotes consistent contact with team members, children, and families, and keeps a focus on the impact of recurrent stress as well as growth and change (Sanctuary Institute). The Sanctuary Model promotes a perspective that asks: "What's happened to you?" rather than "What's wrong with you?" when organizing goals and assessing strengths and challenges. CCTC embraces the Sanctuary Model and is dedicated to creating a trauma-informed culture of open communication, nonviolence,

emotional intelligence, social learning, shared governance, social responsibility, and growth and change which encompass the values of the Sanctuary Model.

CCTC integrates trauma-informed care into its treatment approach. Examples are: including trauma histories in all biopsychosocial evaluations, viewing child and family challenges through a trauma lens, understanding that many of the negative behaviors that children exhibit are attempts to cope with their traumatic experiences and intervening accordingly, educating children and families on the impact of trauma, and ensuring that children receive trauma-focused treatment when indicated. Children and families participating in services develop Safety Plans to support their use of coping strategies during times of stress/crisis. Treatment plans, progress notes, and all other service documentation are embedded with trauma-informed language to ensure that the focus of services is not only on trauma but also on recovery and resiliency. CCTC's day treatment programs facilitate Sanctuary Psychoeducational groups, which educate children on the impact of trauma in a developmentally tailored way and teach them coping strategies. Caregiver services are infused with trauma-informed principles and techniques. For example, members of CCTC's family advisory group are ambassadors of the Sanctuary Model during their interactions with peers at CCTC and in their communities.

All programs at CCTC support the trauma-informed care approach and a resiliency framework. One such program is the Filial Parenting Program, a group-based therapeutic approach that CCTC has offered for over 10 years. The program is based on the Filial Therapy model (Van Fleet & Guerney, 2003) and infused with the Sanctuary (Bloom, 1997) and Incredible Years (Webster-Stratton, 1998) models. Each 14-week group cycle is led by two master's level clinicians and consists of a structured curriculum that includes the teaching and modeling of specific parenting skills, the practicing of these skills by caregivers, and the creation of a therapeutic community that encourages peer support through discussion and feedback.

Filial Therapy is a research-supported model that emphasizes the parent-child relationship as a means of alleviating child and/or family difficulties. Parents/caregivers learn to conduct a special type of play session with their children. Play is the natural language of children and is therefore an excellent medium for parents/caregivers to engage their children in order to enhance their relationship with them. Parents/caregivers learn to be more aware of their children developmentally, emotionally, and relationally. The Incredible Years parent training is a series of evidence-based interventions focused on strengthening parenting competencies in order to promote children's social and emotional competencies and reduce conduct problems. The foundation of CCTC's Filial Parenting Group is grounded in the application of four Filial Therapy skills and further supported by Incredible Years techniques that are introduced, discussed, modeled, and practiced throughout the 14-week cycle.

During the weekly group sessions, facilitators work with each parent/caregiver individually and in groups so that they can begin learning and practicing the skills and techniques. Initially sessions are held without the child present as parents learn the skills. Structured childcare is provided to the identified child as well as siblings in order to alleviate barriers to treatment participation. Once skills are learned, parents/caregivers then have practice sessions with their child with guidance from the facilitators. They are given supportive feedback and enhanced practice in order to gain mastery. Finally, parents/caregivers are given a complete kit of toys that they will use at home for individual "special playtime," initially with the child enrolled in the program but eventually with all of

their children. During the group experience, parents/caregivers are asked to practice the special playtime sessions at home and then return to the group to discuss the experience with the facilitators and their peers in order to further refine their skills. Also included in these sessions are discussions on how to generalize the principles to everyday life. The Sanctuary Model is embedded in the group throughout each weekly session and includes the use of the Sanctuary Community Meeting, which supports the development of a therapeutic community, and Safety Plan development, which supports the learning and practice of emotion management and coping skills.

Outcome measurement is an integral part of the Filial Parenting Program. Pre- and post-test surveys using the Adult-Adolescent Parenting Inventory and Parent Relationship Questionnaire are completed by caregivers. Data analysis demonstrates improvements in most parenting areas assessed, with significant improvement in parent/child attachment, parental involvement, parent expectations, parenting confidence, relational frustration, and attitudes on corporal punishment.

The Filial Parenting Program is an excellent example of creating a trauma-informed context in which healing may occur. Caregivers who participate in the program often present with multigenerational histories significant for adversity including child abuse, domestic violence, poverty, and homelessness, which continue to manifest in their daily lives. Despite these challenges and as the data supports, participants respond to a strengths-based approach that focuses on building protective factors including nurturing parenting skills, a stronger parent/child relationship, and peer support.

CONCLUSION

A public health response to trauma is not only necessary but critical to address the prevalence and impact of trauma. Healing does not only occur in treatment settings. The process of creating trauma-informed organizations is not exclusive to mental/behavioral health agencies but may include any type of organization, such as government-funded and -administered entities where many of the decisions that impact those affected by trauma are made. Examples include public utilities, courts, and schools.

The challenge before us is how to create trauma-informed systems and communities that work together to mitigate risk and strengthen protective factors. The Center on the Developing Child at Harvard University (2015) recommends the development of frameworks that integrate policies and practices across economic, education, health, and social sectors that can collectively reduce adversity and build our capacity to address adversity when it happens. An approach using a unified, trauma-informed, science-based framework could identify the best strategies for coordinated public-private partnerships to implement together. Strategies that build child and caregiver capacities work best when they are integrated within complementary policies across sectors that collectively lower the burden of stress on families due to the often interrelated threats of poverty, crime, mental illness, substance abuse, discrimination, and community violence.

Examples include but are not limited to the following:

- Public and private-sector entities can become trauma-informed, including but not limited to mental/behavioral health systems/providers, school districts, child welfare, juvenile justice, and court systems. The understanding that many of the struggles people internalize and externalize are rooted in trauma can dramatically transform the way services are delivered and their impact.
- Enhance efforts to hasten the research-to-practice pipeline. For example, interventions based on advances in brain research can have an immediate benefit on the resiliency of those impacted by trauma.
- When poverty-reduction policies require parents to work, we need to also assure parents' access to affordable, high-quality child care in order to promote both adult economic self-sufficiency and developmentally supportive experiences for their children (Center on the Developing Child at Harvard University, 2015).
- School settings can provide a range of opportunities for the development of knowledge, cognitive skills, and self-regulation abilities, all which enhance children's capacity to deal with adversity (Center on the Developing Child at Harvard University, 2015). School systems can address emotional development alongside cognitive development, given the fact that learning and self-regulation skills are inextricably linked. Behavioral health services can be integrated within schools to increase children's access to needed prevention and treatment services.
- Equip early-childhood programs with the high-quality tools and resources to address the impact of adversity. Young children are often asked to leave early-childhood programs for manifesting behaviors that represent the very reasons they need the program.
- Child welfare and mental health professionals can collaborate to focus on opportunities to restore family relationships and build the capacities that underlie resilience.
- Children's physical and behavioral health care can be integrated to increase families' access to and engagement in needed treatment.
- Parenting centers that offer evidence-supported, trauma-informed services can be integrated into existing community-based organizations, making parenting support universally available.
- The Strengthening Families Framework (Center for the Study of Social Policy, 2015) can be implemented throughout child- and family-serving systems to unify efforts to lessen adversity and build resilience.

Efforts must begin at building trauma-informed systems in which all parties involved recognize and respond to the impact of traumatic stress on those who have contact with the system including children, caregivers, and service providers. Agencies, programs and services within such a system infuse and sustain trauma awareness, knowledge, and skills into their organizational cultures, policies, and practices.. This process begins with leadership who promote and model an organization culture that recognizes the value of a trauma-informed framework on not only those who the organization serves but those who serve them.

We are who we are because we drink from wells that others dug and warm ourselves on fires that others struck.

- Ancient Celtic quote

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Chapter 504

SURVEY OF HEAVY METAL POLLUTION, HUMAN EXPOSURE AND PUBLIC HEALTH IMPLICATION IN NIGERIA: A REVIEW

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ABSTRACT

Nigeria is a big, important and diverse country with many potentials and problems. It is a major oil and gas producer with unique vulnerabilities. It has the potential for rapid and robust economic development given its oil and other resources and its diversity of ecosystems. A major threat to the future of Nigeria is environmental damage. The ubiquitous nature of heavy metals, in Nigeria is very worrisome; it can be encountered in every sphere of life and environment. They occur naturally in the soil, solid minerals, food, also from industrial process and consumer products (locally and imported), electrical/electronic/automobile, pharmaceuticals, cosmetics, paints, etc. They are found at hazardous and domestic dump sites, in crude oils, agro-allied chemicals. It is distributed by water, air and fugitive dust, bio-accumulated by man, animals, plants, fish and other aquatic animals and plants. Heavy metals may enter the human body through food, water, air, absorption through skin and gut. Serious health problems such as headache, malignant cancer, severe abdominal pain, vomiting, diarrhea, fever, fatigue, loss of appetite, birth defect, mental retardation, hyperactivity, liver and kidney damage etc., are associated with heavy metal toxicity, all these and many more health challenges

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that may be associated with heavy metal toxicity are increasing in Nigeria. In all these children may likely be more vulnerable.

Keywords: heavy metals, varied sources, ubiquitous distribution, environmental pollution, increasing health challenge, public health risks

INTRODUCTION

Nigeria is situated on coordinates 9.0820°N and 8.6753°E, the main latitude and longitude is 10°N and 8°E, with a total land area of 923,768sq km and an estimated population of 150m people. It is located in West Africa and shares land borders with the Republic of Benin in the west, Niger and Chad in the north, Cameroon and its southern coast lies on the Gulf of Guinea on the Atlantic Ocean. It is a big, important, diverse country with many potentials and problems. It is a major player in world's oil and gas activities, with huge proven reserves of solid mineral and agricultural resources. The exploitation of these resources has brought about environmental damage and uneven distribution of pollutants such as heavy metals amongst major environmental components (air, water and soil).

"Heavy metals" have been variously defined differently by several authors in different scientific literatures, it has been defined in terms of density (specific gravity); in terms of atomic weight (relative atomic mass); in terms of atomic number; defined based on other chemical properties such as dense alloys, intermetallic compound, metallic elements of relative high molecular weight; defined based on toxicity and non-chemical definitions used before 1936 such as guns or shot of large size (Ogilvie, 1884) and great ability (Williams, 1930). There are also several sub-definitions, with references summarized by Duffus (2002). Although, it has been established that the term "heavy metal" has not been defined by any authoritative body such as IUPAC, over the years, till date, it has been conveniently used in scientific literature, sometimes it has been used interchangeably with metals or trace elements (Zhang and Hqo, 2009; Ferreira-Baptista and De-Miguel, 2005) and it will be adopted in this study. Therefore, "heavy metals" are chemical elements with a specific gravity (density) that is at least 5 times (5x) the specific gravity of water. The specific gravity of water at 4°C is 1. Simplified definition states that specific gravity is a measure of density of a given amount of a solid substance when it is compared to an equal amount of water. Well known toxic metallic elements with a specific gravity that is five (5) or more times heavier than that of water are arsenic (5.7,) cadmium (8.65), iron (7.90), lead (11.34), Mn (7.42), Co (8.90), Ni (8.90), Cu (8.94), Ag (10.50), Au (19.30), Zn (7.10), Hg (13.60), V (6.11), Cr (7.19), etc., (Liptrot, 1983). There are 35 metals that are important because of occupational or residential exposure; 23 of these are the heavy elements or "heavy metals": antimony, arsenic, bismuth, cadmium, cerium, chromium, cobalt, copper, gallium, gold, iron, lead, manganese, mercury, nickel, platinum, silver, tellurium, thallium, tin, uranium, vanadium, and zinc (Glanze, 1996). In small quantities; certain heavy metals are essential for a healthy life. Some, such as (iron, copper, zinc, manganese) are referred to as the trace elements. These elements, or some form of them, are commonly found naturally in food stuffs, fruits and vegetables, and in commercially available multivitamin products. If heavy metals are not metabolized by the body, they accumulate in the soft tissues and become toxic. They may enter the human body through food, water, air or absorption through the skin when they come in contact with

human body through agricultural practices, manufacturing, pharmaceuticals, industrials, or residential settings. Adult exposure to metal toxicity is mainly through industrial activities while ingestion is the most common route of exposure in children. Most children may develop toxic levels from the normal hand-to-mouth activity of small children who may come in contact with contaminated soil or by actually eating objects that are not food (Dupler, 2001). A compilation has been made of 120 occupations e.g., auto mechanics, painting, printing, welding etc. that involves exposure to heavy metals (Wallace and Cooper, 1986). Other economic or occupational activities that may lead to metal exposures in adults include industrial activities like oil and gas activities, mining, smelting, refining and manufacturing processes and earth works such as road construction. Consumable products such as food drinks (Onianwa et al., 1999), pediatric syrups (Nduka and Orisakwe, 2009; Orisakwe and Nduka, 2009), canned and non-canned beverages (Maduabuchi et al., 2006), packaged water (Orisakwe et al., 2006), herbal remedies (Obi et al., 2006) and cosmetic products (Nduka et al., 2015) are veritable sources of heavy metal, non-consumable goods also contain appreciable high amount of metal element. Inhalation of fugitive dust or ingestion of road side soil/dust can predispose an individual to metal poisoning (Nduka and Orisakwe, 2010; Kakulu, 2003).

Other common routes of exposure are during a radiological procedure, from inappropriate dosing or monitoring during intravenous (parenteral) nutrition and from a broken thermometer. Geophagia-soil eating habit among children and pregnant women reported at Nnewi, South-eastern Nigeria can be a veritable means of exposure to heavy metal in Nigeria (Orisakwe et al., 2004). Acute poisoning is more likely to result from inhalation or skin contact of dust, fumes or vapours, or materials in workplace. However, lesser levels of contamination may occur in residential homes, especially in older homes with lead paint or old plumbing (IOSHIC, 1999). Heavy metals are dangerous because they tend to bio-accumulate in a biological organism over time compared to the chemical concentration in the environment. Metallic compounds accumulate in living things anytime they are taken up and stored faster than they are broken down (metabolized) or excreted and these leads to health impairment. Toxicity of heavy metal can result in significant illness and reduced quality of life (Ferner, 2001). This work is to remind policy makers in Nigeria that our country is under serious heavy metal pollution and that it is a threat to the health of future generations.

SOURCES OF HEAVY METALS IN NIGERIA

Solid Minerals

Though Nigeria is well known for its crude oil and gas reserves, little is known of its huge solid mineral deposits. That Nigeria is endowed with abundant mineral resources is stating the obvious, the minerals include (1) Limestone deposit which exist throughout the country. It is on record that Nigeria has over 8000 million tonnes of proven reserve of limestone deposits and these deposits far exceed requirements of the cement industry (Olaniyan, 1994). (2) Tin and columbite these are the principal metalliferous mineral exported from Nigeria. The country began refining its own tin in 1961 and exports refined tin mineral metal of 99.9 percent grade. (3) Iron ore-about 400 million tones of good quality iron

ore deposits have been discovered at Itakpe, near Okene in Kogi State, other deposits of iron ore with an average iron content of 40 to 50 percent are also found near Niger, Benue and Enugu States. (4) Lead-zinc-the Nigerian lead-zinc deposits extend continually for about 560 km in a narrow belt in Ishiagu, Abakalike in Ebonyi State and Bende area of Abia. (5) Gold-Gold is also available in Nigeria. The bulk of it is found in Sokoto, Niger, Kogi and Osun States. (6) Marble-this is found mainly in Kogi, Oyo and Niger State. (7) Stone is found in most parts of the country and it is extensively quarried and used for building purposes, roads, rail ballast, dam foundations and harbour works, (8) Zircon-quantities of this mineral are found in some rivers and streams in Nigeria and it is extracted as a by product of tin-columbite mining in Plateau state (9) Coal- is of note that Nigeria is the only West African country that produces coal. Its major coal mines are located in Enugu and Kogi States (<http://www.nigerianembassy-chile.org/nigeria/xgeography.shtml>) (10) other major minerals abundant in Nigeria include Tantalite, shale, non-ferrous metals, such as copper, aluminum, ferro-alloy metals include manganese, chromium, nickel, tungsten, cobalt, vanadium and molybdenum, gold, silver, platinum, antimony and cadmium (Obienusi, 2004). Since heavy metals are natural components of the Earth's crust, a single metallic or non-metallic ore can contain few or several of these metals in association (Oyinloye, 2004; Aneke, 1992), activities such as quarrying, mining and construction releases these metals into the atmosphere and it is inhaled by man, others settle on surface water, farmlands, and buildings and on our skin. Ako et al., (2014), reported that soil samples from and around Luku artisanal gold mining Minna, Niger State were enriched with Pb, Cd, Hg and Ag. Mining can only take place where minerals are present and economically viable. The general importance of the mining sector has been documented to include foreign exchange, employment and economic development (Nwajiuba, 2000; Obaje and Abaa, 1996). In Nigeria, minerals are extracted by unskilled and illiterate artisans in addition to simple and crude implement and these sometimes regarded as informal sector and therefore outside the legal and regulatory frame work (Azubike, 2011). Toxic heavy metals are released into the environment, posing serious health risks to the miners, family members and to the general populace. Acidic rains can also breakdown soils and soil/clay matrix and release heavy metals into streams lakes, rivers, and groundwater.

Crude Oil

Crude Oil consists of hydrocarbons with carbon and hydrogen in proximate ratio of 1:6 by weight (O' Donell, 1975) and other related inorganic metals. Amongst these constituents are sulphur, nitrogen and oxygen and trace metals. Nigeria's crude oil is known to contain varying proportions of heavy metals (Achi and Shide, 2004; Nwadinigwe, 1984; Nwadinigwe and Nworgu, 1999). Over sixty metals have been identified in crude oils with vanadium (V) and nickel (Ni) as the most abundant (Tiratsoo, 1973), Metallic components in crude oils occurs as metalloporphyrin chelates, transition metal complexes, organometallic compounds, carbonyl acid salts of polar functional groups and colloidal minerals (William and Roberts 1967, Lewis and Sani 1981). The abundance of certain trace metals, especially Ni and V in crude oils, is geo-chemically significance and provides information on the origin and maturation problems. Petroleum has been classified on the basis of wax and asphalt contents (Lewis and Sani, 1981), or on the basis of concentrations of trace metals content, others on

the basis of vanadium-nickel ratio (Punanova et al., 1994). Most trace metals are indigenously associated with the oil during formation whereas some trace elements are introduced into the oils during transportation, from oil wells to processing sites, storage tanks or processing equipment (Achi and Shide 2004).

Refuse Dumps

Most Nigerian cities are littered with refuse dumps with many domestic and sundry wastes. A typical refuse dump in Nigeria comprises wastes like clothing materials, beverages and food can, glass wares, worn-out tires, foods and waste papers, pharmaceutical and chemical containers, tobacco and match sticks and packets, cow dungs and poultry litter, wood and furniture wastes, metal scraps and aluminum foils, vegetable and food residue, batteries, exhaust pipe, water pipes, polymeric materials and agro-chemical containers. (Nduka et al., 2006); it is a known fact that organic compounds are associated with heavy metals, HEME a coloured pigment of haemoglobin called ferroprotoporphyrin contains iron as its central element (Hayid, 1991), haemocyanins found in molluscs and arthropods contains copper, both alcohol dehydrogenase found in horse liver and carboxypeptides present in pancreatic juice of man contains zinc, haemovanadins- an oxygen carrier in sea squirt contains vanadium. Vitamin B₁₂ also called cobalmine because of its tightly bound cobalt. Organotin compounds widely used as insecticide and fungicides while copper arsenate used as wood preservative gives rise to tin and arsenic respectively (Wentz, 1989). Since these organic or inorganic compounds that contain heavy metals are common at refuse dump sites in Nigeria, following favorable weather condition, they degrade and decompose releasing these toxic metals into the environment. We have previously reported high concentration of heavy metal in soils at refuse dump sites (Nduka et al., 2006).

Electronic and electrical wastes are veritable sources of heavy metals in Nigeria, because of unhealthy importation, an estimated 500 shipping containers loaded with second hand electronic equipment are brought into Nigeria through Lagos port every month, each container can be packed, on average with a load equal in volume to 800 computer monitors or central processing units (CPUs) or 350 large TV sets. Experts estimate that between 25% to 75%, of these materials are useless or irreparable junks. This is a problem, because “e-waste” can be toxic, much of it is loaded with potentially toxic metals including lead, copper, cadmium and mercury. This is bad for a country with economy almost tending to depend on leftovers (Schmidt, 2006): Iloh (2007) established that soils sampled close to old transformers have elevated levels of mercury. The values keep increasing as one move further close the transformers.

Industrial Processes and Products

Most heavy metals or their compounds find useful application in manufacture of industrial and home goods and in sundry economic sector. Arsenic is released into the environment by the smelting process of copper, zinc and lead as well as by the manufacturing of chemical and glasses. Lead is used for manufacturing batteries, cable covering, plumbing,

ammunition, fuel additives, PVC, plastics, x-ray shielding, crystal glass production, pencils and fuel additives. Like arsenic, cadmium is a by product of the mining and smelting of lead and zinc, it is used in nickel-cadmium batteries, PVC plastics, cigarettes also contain cadmium. Mercury is generated naturally in the environment from degassing of the earth's crust, from volcanic emissions. It exists in three forms: elemental mercury, organic and inorganic mercury. Mining operations, chloralkali plants and paper industries are significant producers of mercury (Goyer, 1996). It is also used in thermometers, thermostats and dental amalgam. Chromium is used in metal alloys and pigments for paints, cement, paper rubber and other materials. Copper normally occurs in drinking water from copper pipes, as well as from additives designed to control algal growth (file://C:\Documents and settings\Ebere\Desktop\ada\heavy-metals.htm). Agricultural and allied chemicals such as pesticides, fungicides, insecticides, commercial fertilizers and wood preservatives contain metals such as arsenic, manganese, lead and cadmium. Relevant occupational fields common in Nigeria such as steel making, foundry work, thermal cutting, welding, glass, ceramic production etc., and combustion of petrol with the additive methycyclopentadienyl manganese tricarbonyl (MMT), (an anti-knock agent in lead-free petrol) can release appreciable concentrations of manganese into the environment (Spiegel-ciobanu, 2006). In our recent study of heavy metals other than lead in flaked paints from one hundred and fifty buildings each of four major cities-Enugu, Onitsha, Aba and Port Harcourt in Eastern Nigeria, cadmium ranged from 9.032 ± 0.00 to 10.575 ± 0.000 and 6.845 ± 0.000 to 10.028 ± 0.002 (mg/kg) in Enugu and Onitsha, respectively. In Aba and Port Harcourt, the levels of cadmium ranged from 7.464 ± 0.002 – 9.343 ± 0.002 and 7.293 ± 0.002 – 9.395 ± 0.000 (mg/kg), respectively. Chromium levels in Enugu (0.940 ± 0.000 – 12.793 ± 0.002), Onitsha (1.613 ± 0.002 – 15.140 ± 0.000 mg/kg), Aba (15.206 ± 0.000 – 39.215 ± 0.000 mg/kg), Port Harcourt (33.118 ± 0.002 – 55.418 ± 0.002 mg/kg). Iron copper and zinc were significantly higher (Nduka et al., 2008), also of 168 building paint flakes from the four cities, 80% of them were found to have lead level higher than the US,EPA permissible level of 5mg/kg (Nduka et al., 2008). In their work, Maduabuchi and co-worker's (2006), established that 86% and 84% of the 50 beverages (canned and non-canned) in Nigerian markets failed to meet the US, EPA criteria for acceptable lead and cadmium levels in consumer products. 95.2% of the canned beverages and 75.8% of the non-canned beverages had iron levels exceeding the MCL.42% of the canned beverages and 82.7% of the non-canned beverages had manganese level above the MCL while 80.9% of the canned and 72.4% of the non-canned had nickel exceeding the MCL (Agbo, 2006). Cosmetics, lips and finger nail paint and other beauty care products sold in the Nigerian markets are known to contain heavy metals such as mercury (Okei, 2007). Soil samples, underground and surface water samples and food (agricultural product) samples collected in and around car battery manufacturing plants, cable manufacturing plant, petroleum products and vegetable oil manufacturing plant in Nnewi, south eastern Nigeria, were found to have very significant and trace concentrations of arsenic, lead cadmium, nickel, copper, iron, manganese, zinc and mercury (Orisakwe et al., 1999, 2004; Asomugha et al., 2005). Analysis of tannery wastewaters from six tanneries in three notable industrial estates of Kano State, Nigeria showed significant level of chromium, the concentration of chromium decreases with increase in distance from the point source (Hat et al., 2005). The chromium is discharged as waste from chrome, applied in the form of Basic Chromium Sulphate (BCS) to the hides and skins during processing (Awan et al., 2003). Some locally produced and imported infant formulae (both milk-based and soy-based types) sold in Nigerian markets

were found to contain copper, manganese, lead and zinc, although most of the metals are within tolerable limits (Olu-owolabi et al., 2005). Due to high cost of orthodox medicine and its non availability in some rural areas as well as doubts over its efficacy because of faking and adulteration, many Nigerians including the middle class has resorted to local herbal preparation for medication; this has been established as a source of heavy metal poisoning (Obi et al., 2006).

Waste Water/Sewage Irrigation

There is a gradual decline in fresh water availability for irrigation in most countries of the world especially the very industrialized countries. The resultant effect is the use of sewage and other industrial effluents for irrigating agricultural lands. Waste water irrigation, solid waste disposal, sludge application, vehicular exhaust, industrial activities, mining and processing of metal ore are significant source of heavy metals in agricultural fields. Although the concentration of heavy metals in sewage effluents are low, long-term use of these waste waters on agricultural lands often results in the building of the elevated levels of these metals in soils (Rattan et al., 2002). These have been documented in countries such as India and China (Rattan et al., 2009; Khan et al., 2008), such has not been documented in Nigeria but ample examples exist. In Nigeria local farmers use of poultry droppings and cow dung as rich source of organic manure and there is possible increase in phyto availability of biosolids – applied trace metals to plants have been raised on the assumption that decomposition of applied organic matter would increase phyto availability (Sukkariyah et al., 2005). In our previous study, we showed that refuse dumps can substantially increase the environmental heavy metal burden in Awka municipality, Nigeria. This is because organic and inorganic compounds that contain heavy metals are common at refuse dump sites in Awka, they degrade and decompose following favorable weather conditions thereby releasing various pollutants into soil and ground water (Nduka et al., 2006) and food crop planted in and around the dumpsites take up these metals (Nduka et al., 2008). In our evaluation and health risk assessment of vegetables and food crops on the bank of Agulu lake Nigeria, where peasant farmers irrigate their farmland with crude method, the results showed that soil and agricultural produce contained appreciable concentration of heavy metals that can compromise the health of consumers (yet to be published data). It is a known fact that short term crops such as vegetables are grown during dry season with waste water in Nigeria. Residential wastewater is a combination of excrete, flush water and all types of wastewater generated from household, also industrial wastewater such as textile and pharmaceutical effluents contains heavy metal (Nduka, 2012; Olaitan et al., 2013). Increasing and extensive use of pesticides, herbicides and fungicides releases heavy metal into the environment. Crops raised on the metal contaminated soils accumulate metals in quantities excessive enough to cause clinical problems both to animals and human beings from the heavy metal rich crops (Tiller, 1986). It could be concluded that long term wastewater irrigation has led to contamination of soils and food crops in within irrigated areas and heavy metals were shown a substantial buildup with a significant increase over reference soils.

DISTRIBUTION CHANNELS

Air

The harmathan dust of the N-E wind which carries various contaminants including heavy metals settles on building, trees, surface soils and other objects while some may be inhaled. Nriagu (1992a) reported high dust lead levels in Lagos metropolis. He further estimated that about 10 to 30% of the children in Africa might be suffering from lead poisoning. The rain from moisture laden S-W wind (Iloeje, 1981), dissolves and carries these metals into the soil and underground water by infiltration while others into surface water. Solid particles that accumulate on outdoor, impervious materials in urban environment are collectively referred to as “street dust.” The two main sources of street dust, with its trace element constituents are deposition of previously suspended particles (atmospheric aerosol) and displaced urban soil (Ferreira-Baptista and De-Miguel, 2005). Other sources include building deterioration, construction and renovation, corrosion of galvanized metal structures etc., contribute directly to the street – dust load within their proximity (Schwar et al., 1988; Hopke et al., 1980). Street dusts laden with metals are not deposited permanently; they are easily resuspended back into the atmospheric aerosol to which it contributes reasonable amount of trace element (Maxwell and Nelson, 1978).

Metals can be accumulated in topsoil from atmospheric deposition by sedimentation, impaction and interception implying that atmospheric pollution is one of the major sources of heavy metal contamination especially in urban area (Mingkui and Hao, 2009). Vehicular emission and street dust metal pollution within the urban centres emanates from varied sources via water transported material from surrounding soils, dry and wet atmospheric deposition, biological inputs, road surface wear, road paint degradation, particulate emissions and vehicular wear (Pruvot et al., 2006; Zhang et al., 2008; Duzgoren-Aydin, 2007; Abdul-Wahabi, 2004; Zhou et al., 2007).

Therefore monitoring of the metal content of dust samples is an efficient way to evaluate the environmental status of large area (Park et al., 2008; Wang et al., 2006). Open burning of built up refuse dumpsite and open-air incineration create hazards associated with environmental pollution including air particulates laden with metals. Nigeria as a developing country is faced with several construction activities such as roads, stadia, airports, bridges, buildings (hospitals, schools, offices and residential areas), all these contribute large tones of heavy metal laden dusts into the air. Mineral quarrying and mining also contribute large volumes of dust with metals into the air (Ivan and Mwatia, 2012). Industrial emission released from petrochemical plant and refinery, gas flares, bush burning can release smoke and ash with metal into the atmosphere.

Water

Street dust laden heavy metals deposited on surfaces are washed away by precipitation and it becomes an important component of the suspended and dissolved solid in street run-off and in receiving water bodies (Vermette et al., 1991). Metals accumulated in the environment can influence the ecosystem (Ahmed and Ishiga, 2006; Steiner et al., 2007; Lough et al.,

2005). The presence of heavy metals in road deposited sediments plays an important role in establishing storm water quality (Liu and Zhao, 2007; Gans et al., 2008; Murakami et al., 2008). When rain falls, heavy metals from both natural and anthropogenic sources are transported into receiving waters where they affect storm water runoff quality evidently. In several studies carried out on surface water, shallow well and bore-hole water samples in a bid to establish potable water quality of Niger Delta. It was established that most water samples were laden with heavy metals in concentrations for above international regulatory agency's permissible limit (Nduka and Orisakwe, 2007; Nduka and Orisakwe, 2009; Nduka and Orisakwe, 2011).



Figure 1. Map of Nigeria showing the two major rivers that empties into the Atlantic Ocean.

Surface and underground water and the atmosphere (air) are the major routes through which heavy metals are distributed in Nigeria. The country seems naturally structured for that (Figure 1). The River Niger rises from the Futa Jallon Mountain to the North-east of Sierra Leone, flows through other countries, and enters Nigeria from the west and runs South easterly to Lokoja where it forms a confluence with its main tributary –River Benue. Other main tributaries of the River Niger are the Sokoto, Kaduna and Anambra Rivers. The River Benue which has its source in the Cameroon Republic receives in its course the waters of rivers kastina-Ala and Gongola. All these with so many other rivers culminate into interwoven network of rivers, streams, lake, ditches and creeks of the Niger-Delta before emptying into the Atlantic Ocean. Underground water occurs in a discontinuous manner, though major sedimentary rock areas are more significant for ground water potential. The coastal areas, the Niger-Benue valleys, the Southeastern lowland, the Sokoto-Rima basin and the chad basin are remarkable for continuous aquifers. Borehole yield in the coastal plains is of the order of 40,914 liters/hour and in the alluvium, deposits of the Niger-Delta, is 55.006litres/hour (<http://www.nigerianembassy-chile.org/Nigerian/xgeography.shtml>). Acidic precipitation which has been reported in Nigeria (Nduka et al., 2008), can demobilize heavy

metals from the soil into the aquatic ecosystem where they bio-concentrate in lugworms, barnacles, algae, other planktonic and benthic organisms enroute to food webs. Since rivers are wide open to flooding which carry various contaminants including heavy metals, ecotoxicological study of the Niger-delta area of the River Niger starting from Onitsha (source), Ishukwa in Ndokwa-East Local Government Area of Delta State (Middle point) and Adai in Ndoni Local Government of River State (Tail point) showed that of all the metals – lead, cadmium, zinc and calcium analysed, for all the sampling sites were above USA, EPA Maximum Contaminant Level (MCL) (Orisakwe et al., 2001). For the fact that open and underground water bodies are regarded as final recipients of most environmental pollutants, in a study of pollution profiles of portable water supply in Warri Nigeria, surface and underground (shallow well and deep borehole) water had cadmium, chromium and lead in concentrations that are above USA EPA MCL (Nduka and Orisakwe, 2007). A study of quality integrity of dugwell and borehole water samples in Maiduguri, Borno State of Nigeria showed that more than 75% of all the water samples had lead, zinc, selenium, copper and iron above USA EPA MCL (Kolo and Bukar, 2005). The inter-connection of soil water, rain water, flood water, underground (shallow well and Borehole) water and surface water (the entire water cycle) help to re-distribute these heavy metals in the environment.

Man/Animal/Food Chain

Several domestic animals such as goat, sheep, cow etc., are reared in Nigeria by open grazing. Most dusts laden with metals settle on plant leaves in addition to the quantity taken up by plant root from soil. Grazing animals are directly affected by the consumption of forage and feed contaminated by airborne metal and somewhat indirectly by the up-take of metals through the roots (Udiba et al., 2013). Metal intoxication is one of the most frequent diseases in farm animals, particularly in those grazed on pasture. A number of reports have confirmed the transference of trace metals from contaminated soil to plants and from plants to livestock (Ali, 2010; Orisakwe et al., 1992).

The risk of metal poisoning through food chain increases as the soil metal level rises above the permissible concentration for a given metal (Udibe et al., 2013). This implies that grazing animals are more at risk as forage grasses are consumed directly without washing (which is the case in Nigeria). In the evaluation of metal accumulation in cattle raised in a serpentine- soil area, it was observed that tissue accumulation in animals showed resemblance to concentrations of some heavy metals in soils and forage- concentration of some heavy metals in animal tissues correlated positively with the heavy metal content in the soil (Nwude et al., 2010). Heavy metal transfer from soil to plant is dependent on many factors like soil properties, plant species and metal bio- availability for uptake in the soil- plant system (Makridis et al., 2012). Evidence exists that plant foliage may take up metals such as lead and these can be moved to other parts of plants. Some species of plants have the capacity to accumulate high concentrations of metals. The mobility and phyto availability of metals depend on their chemical nature. Most of the metals absorbed by plants on lands are retained in their roots (Udiba et al., 2013; Orisakwe and Co-workers, 2012) has reported high concentration of the metals in rice and cassava based meals in Nigeria. Another study performed in Nnewi, Nigeria found that the lead content in food and soil samples were also

found to be very high, that is 19mg/kg in fruits, 21mg/kg in cassava, and as high as 12, 102mg/kg in certain soil samples (Orisakwe et al., 2012; Orisakwe et al., 2004).

In a study to investigate the environmental impact of the refuse dump sites with a capture of the heavy metal levels in potable water and agricultural produce in Awka, Nigeria. It was established that a correlation exists between heavy metal levels of soil refuse dumpsites, agricultural produce, surface (stream) water and underground water (Nduka et al., 2008). In a study of heavy metal content of fish muscles of different fish species from Aladfa River, Warri Nigeria. It was established that the levels were above any internationally accepted standard (Nduka et al., 2010). Whereas in comparative study of different metal accumulating capacity of different fish organs (brain, gills, flesh and intestines) of different fish species, the result revealed that brain, gills and intestines accumulated more heavy metals than the muscles with minor variations (Nduka et al., 2007). Heavy metals can be transported, dispersed to and accumulated in plants and animals and can be passed across the food chains to humans (Hongyu et al., 2005; Ali, 2010).

Inhalation, accidental ingestion of contaminated soil, ingestion of contaminated water and absorption through the skin were also identified as the exposure route of these contaminants (Udiba et al., 2013). The fact that metal biomagnifying from one tropic level to another, animal higher in the food chain may accumulate more toxins than their food contains (Monteiro et al., 1996). This is the bane of man, the different route through which man accumulates heavy metals includes:

- Water – human
- Soil – human
- Air – human
- Plant – human
- Animal – human
- Air – animal – human
- Soil – plant – human
- Water – animal – human
- Soil – plant – animal – human
- Water – plant – animal – human

BIO-INDICATORS

Soil, water and biological species act as indicators of presence of heavy metals. Plant through tap root absorb metals dissolved in soil water, it is then eaten by animals or man. Some residual soil metals infiltrate into the underground water while others are leached into surface waters where they bio-concentrate in planktons, lugworms, barnacles, freshwater shrimps and other planktonic and benthic organisms enroute food webs. Simple and complex food web help to recycle these metals, therefore nutrition is an important exposure pathway to heavy metal toxicity. Various food items such as rice, potato, cassava, yams, okro, baobab leaves, melon seeds, spinach and locust beans sampled from markets in Kaduna, Kano, Niger and Abuja were analysed and found to contain appreciable concentrations of chromium, iron, cobalt and zinc, with little and limited amount of arsenic, cadmium, lead and mercury (Umar,

2004). Determination of trace elements in water lily and lettuce harvested from farmland along the banks of Angwan Rogo stream in Jos, Nigeria, showed an alarming concentrations of metals in the range (mg/kg): Fe (51.12 ± 0.35 - 59.01 ± 0.10), Cu (24.21 ± 0.71 - 28.12 ± 0.02), Zn (208.78 ± 0.01 - 252.00 ± 0.91), Pb (53.99 ± 0.86 - 68.06 ± 0.03) and Cd (8.31 ± 0.97 - 9.21 ± 0.01) for water lily while lettuce had the metals in the range of: Fe (57.78 ± 0.61 - 65.35 ± 1.3), Cu (18.21 ± 0.52 - 23.16 ± 0.86) Zn (301.70 ± 2.16 - 340.13 ± 0.04), Pb (62.13 ± 0.17 - 81.15 ± 1.08) and Cd (11.83 ± 1.12 - 12.71 ± 2.15), all the results in (mg/100g) (Salami and Non, 2002). Marine crabs, crustacean specimen, collected from different marine locations at Epe (Lagos State) and Warri (Delta State) had metals such as lead, zinc, copper, nickel, arsenic, mercury and cadmium in an amount above USA EPA MCL that may be detrimental to life (Okoye et al., 2002). Methyl mercury poisoning has been reported among people that depend on fish for their protein (Jemelov and Ramel, 1994). Metal bio-accumulation studies of *synodontis membranaceus* (catfish) and *Tilapia zili* (tilapia) from Anamabra River shows that the prevailing levels for the metals were Pb (61.32mg/kg), Fe (201.50mg/kg), Cu (5.13mg/kg), *synodontis membranaceus* showed high bio-accumulation factors of 350 and 219 for Mn and Pb respectively while tilapia showed 210 and 224 for Mn and Pb (Obodo, 2004). We have reported that fish parts such as gills, brain, liver, muscles and intestine of fish species from crude oil polluted water bio-accumulated Ni, Cr, Fe, Pb, Cd etc., differently (Nduka et al., 2006). Several studies have shown that plants have the ability to concentrate lead, leaf and root contain more lead than stem, and the contents of lead in different plant organs were positively correlated to the lead content in soil (Sridhar, 1988). Urine samples of occupational exposed artisans in Awka, Nigeria such as auto-mechanics, automobile riders and filling station fuel attendant had lead level in the range of 0.02-0.09 mg/l, urine been an excretory product, is an indication of high blood lead level among the subjects. (Nduka et al., 2008). Asogwa (1979) reported high blood lead levels among battery workers in Nigeria. Lead, cadmium, nickel and other industrial metals used as part of paint varnishes have been reported in liver and kidney amongst paint factory workers in Nigeria. An evaluation study on some toxicological effects of occupational exposure to paint, among 25 occupational exposed artisans and 25 students (control) was carried out in Nigeria, the results showed that, occupational exposure to cadmium, lead or nickel among paint factory workers, may compromise the liver and renal functions in man (Orisakwe et al., 2007).

PUBLIC HEALTH IMPLICATIONS OF HEAVY METAL POLLUTION IN NIGERIA

Chronic toxicity of heavy metals results from repeated or continuous exposures, leading to an accumulation in the body. Exposures may result from contaminated food, air, water or dust, living near hazardous waste site, and maternal transfer in the womb: Chronic exposure may occur in either the home or workplace. Symptoms of chronic toxicity may be similar to many common conditions and may not be readily recognized (Anon, 1993; Ferner, 2001). Exposure to arsenic occurs mostly in the workplace, near hazardous waste sites, or in areas with high natural levels. Symptoms of acute arsenic poisoning are sore throat from breathing, red skin at contact point or severe abdominal pain, vomiting and diarrhea. Cardiovascular changes in early stage, neuropathy (Inflammation and wasting of the nerves) occurs over

several years. Excessive darkening of the skin (hyperclose pigmentation) in areas not exposed to sunlight, excessive formation of skin on the palms and soles (hyperkeratosis), or white bands of arsenic deposits across beds of the fingernails as well as birth defects, liver injury and malignancy. Ayoola (1979) reported on ten (10) cases of lead (Pb) poisoning. He drew attention to the difficulty of the diagnosis of Pb toxicity and cautioned that with the rapid industrialization of Nigeria, doctors and other health workers should be aware of the possible increase in the incidence of plumbism. Ayoola (1979) also noted the long term consequences of Pb even after quitting a Pb-based occupation. The levels of black carbon and tetraethyl lead (TEL) were measured in the tear film of 100 children selected by a simple random technique from each industrial location-children attending eye clinics in Delta State government hospital located at Warri, Ekpan and Aladja, were used, persistent itching, foreign sensation and specified areas of conjunctival/limbal discoloration were used as markers for pollution keratoconjunctivitis (PKC). Biochemical assays showed that tears samples contained some levels of TEL among the sample population. This is ascribed to rapid urbanization and industrialization occasioned by pollutants from drilling, production and refining of crude oil and production of petrochemicals (Asonye and Bello, 2004). Lead exposures acts synergistically with iron deficiency and sickle cell traits as low dose inocula which can attenuate plasmodia blood-stage infections. This leads to the suggestion that a reduction in the level of some environmental exposures may interfere with the natural acquisition of immunity to malaria. Lead poisoning is the 6th most important contributor to the global burden of diseases measured in disability adjusted life years (DALYs), with sub-saharan African countries being predominantly responsible for the global DALYs (Pruss-Ustun and Corvalan, 2006). Recent studies confirm that lead protect against parasitemia in individuals (Nriagu et al., 2007) as well as in plasmodium-infected mice (Kempe et al., 2005; Koka et al., 2007). High intra-erythrocyte concentration of lead can also affect several essential cellular processes adversely, such as inhibition of protein synthesis (Graziano et al., 1991). It has high affinity for the side chains of many proteins such as tranferrin (Qian et al., 1997), Mucin (Conrad et al., 1991), mobilferrin-divalent metal; ion tranporter, DMTI (Gunshin et al., 1997), hemoglobin (Bartrop and smith, 1972) and enzymes of heme synthesis (Goldberg, 1972). The ability of Pb^{2+} to undergo metathesis reaction with Zn^{2+} and Ca^{2+} metalloproteins resulting in loss of metabolic function continues to be a primary hypothesis underlying the detrimental effects of lead exposure (Lewis and Cohen, 2004). Several studies have shown that lead can cause adverse effects on various organ and systems in all species under experimental conditions, including the blood, reproductive, immune system and kidneys (WHO, 1995). Lead is a highly neurotoxic agent that particularly affects the developing CNS and also interferes with excitatory neurotransmission by glutamate, which is the transmitter at more than half the synapses in the brain and is critical for learning (Cory-Slechta, 1995). Manganese is best characterized as neurotoxin, occupational exposures are associated with characteristic syndrome called manganism which involves both psychiatric symptoms and parkinsonism features (Dobson et al., 2004). Exposures through drinking water has been associated with sub clinical neurologic effects in Greek adults (Kondakis et al., 1989). Toxicological studies have suggested that copper, manganese and lead can reduce testosterone production in, in vitro and in vivo (Zeng et al., 2013). Although copper and manganese are essential for good health (Meeker et al., 2008; Kendall et al., 2000), relatively high levels of exposure to these essential metals may result in adverse male reproductive health for example, exposure to manganese at high doses has been found to decrease

testicular weight and semen quality in rat and mice (Laskey et al., 1982). Excessive human exposure to copper and manganese in blood has also been associated with decreased semen quality (Meeker et al., 2008). Manganese is a potent toxin with a myriad of neural deficit ranging from learning disabilities (Henn et al., 2011), manganism and manganese-induced Parkinsonism (Aschner et al., 2009; Sahnib et al., 2007), compulsive behaviors, emotional lability, hallucinations and attention disorders (Solis-Vivanco et al., 2009). High maternal manganese levels are associated with low fetal birth weight (Zotal et al., 2009) and increased infant mortality (Spangler and Spangler, 2009). Copper is also an essential trace element, its absorption occurs through the lungs, skin and gastro-intestinal tract (US EPA, 1985). Individuals with copper toxicity shows an abnormally high levels of copper in the liver, kidneys, brain, eyes and bones (ATSDR, 1990). Copper has been implicated in early childhood liver cirrhosis (ECLC) regarded as non-indian childhood cirrhosis (NICC). High copper levels in the body may pose a risk in reduction of total homo-cysteine and folate which are essential to body metabolism (Tamura and Turnlund, 2004). Though, iron is regarded as non toxic since it is contained in most blood supplement and food, hence a blood builder. Biologically, iron is the most important transition element. The human body contains about 4g of iron out which about 70% is found in hemoglobin, the red pigment in erythrocytes. Most of the iron is stored in the body as ferretin (Lee, 1996). Although iron performs a number of bio-inorganic functions in living things, such as oxygen storage in muscles tissue (myoglobin), electron transfer in plant and bacteria (ferredoxins) and electron carrier in plants, animals and bacteria (cytochrome), etc. (Lee, 1996). Excessive intake of iron can cause a disorder which leads to serious health problems or premature death (Oliver and Brittenham, 1997). Iron toxicity may damage the liver, heart and endocrine glands, leading to debilitating and life threatening problems such as diabetes, heart failure and poor growth (Andrews, 1999; Porter, 2001). Cadmium concentrates along the food chain and ultimately accumulates in the body of people eating contaminated food. It is present in tobacco smoke and further contributing to human exposure. Cadmium is highly toxic, accumulating in the body and eventually causing effects as tubular dysfunction, disturbances in calcium homeostatis and metabolism (WHO, 1992). It is capable of inducing renal, hepatic and testicular injury (Suzuki et al., 1989). Although cases of over cadmium nephropathy was described in the context of high occupational or environmental exposures, some studies has suggested that cadmium at low environmental exposures and as currently found in industrialized countries can cause subtle renal effects leading to modest increase in the urinary excretion of micropoteins (Buchet et al., 1990; Jarup et al., 2000; Barbure et al., 2006; Akesson et al., 2005). Cadmium and several cadmium containing compounds are carcinogens and can induce many types of cancer. It is estimated that about 10% of the cadmium content of a cigarette is inhaled through smoking, therefore absorption of cadmium from the lungs is much more effective than that from the gut and as much as 50% of the cadmium inhaled via cigarette smoke may be absorbed (Friberg, 1983). Previously, the International Agency on Cancer Research (IARC) has classified cadmium as a human carcinogen (group 1) on the basis of sufficient evidence in both humans and experimental animals (IARC, 1993). Cadmium (Cd^{2+}) because of its size and charge similarity can substitute for calcium (Ca^{2+}) and included in bones with its attendant toxic effect on the bones.

Occupational exposure to chromium mainly occurs by inhalation, but it may involve the gastro intestinal tract and skin (De flora, 2000), this means that the respiratory tract is the

primary target organ for Cr (VI) compounds. Improved work ethics, procedures and hygiene measures have reduced occupational exposure to Cr (VI) compounds but long-term Cr (VI) exposure may still cause human health problems.

Long term exposure to chromium can cause kidney, liver and nerve tissue damage. Chronic exposure leads to ulcerations and perforations of the nasal septum, chronic bronchitis, decreased pulmonary function, pneumonia and other respiratory effects (Bradshaw et al., 1998). Acute exposure may cause shortness of breath, coughing and wheezing (Sobaszek et al., 2000).

Most chromium compounds are carcinogenic, long exposure may cause kidney, liver and nerve tissue damage (Praydot, 1999). Although the mechanism of Cr(VI) cytotoxicity is not completely understood, several studies have shown that its compounds induce oxidative stress, DNA damage, apoptotic cell death and altered gene expression (Bagchi et al., 2002; Zhitkovich, 2005). Unstable intermediates such as Cr(IV) or Cr(V) can be formed by redox-active enzymes and small molecules which mediate the formation of free hydroxyl, thiyl, ascorbate and carbon-based radicals (Ding and Shi, 2002; Levina and Lay, 2005), these are capable of damaging macromolecular targets such as DNA (Stohs et al., 2001).

The carcinogenic properties of chromium (VI) have been known for a long time (Barceloux, 1999). The acute toxicity of chromium (VI) is due to its strong oxidational properties, when it reaches the blood stream; it damages the kidneys, liver and blood cells through oxidation reactions. Hemolysis, renal and liver failure are the results of these damages (Dayan and Paine, 2001). Human exposure to nickel causes a variety of pathologic effects but adverse health effects depend on the route of exposure (inhalation, oral or dermal) and can be classified according to systemic, immunologic, neurologic, reproductive, developmental, or carcinogenic effects following acute (01 day), subchronic (10 – 100days), and chronic (100days or more) exposure periods (Das et al., 2008).

Pharmacokinetic studies in humans indicate that nickel is absorbed through the lungs (Bernnett, 1984; Sunderman and Oskarsson, 1991), gastrointestinal tract (Patriarca et al., 1997; Sunderman Jr, 1989) and Skin (Fullerton et al., 1986), following absorption from the lungs and the gastrointestinal tract, nickel is excreted in the urine (Bernacki et al., 1978, Angerer and Lehnert, 1990). Major accumulation of nickel in the body occurs in the kidney and inflammation in the bronchioles, alveolar congestion, alveolar cell hyperplasia and congestion in the lumen do occur (Gupta et al., 2006). Some major clinical effects of mercury and arsenic include tremor, gingivostomatitis, peripheral neuropathy, acrodynia, acute tubular necrosis, gastroenteritis, CNS effects and birth effects (Das et al., 2011). Despite the awareness of health hazards associated with organic and inorganic chemical compounds as well as heavy metal exposures, medical diagnosis of patients who may be suffering from heavy metal poisoning are highly reported in Nigeria hospitals. Although serious evidence that non communicable diseases (NCDs) such as cardiovascular diseases, diabetes mellitus, cancer and respiratory diseases which may be associated with heavy metal exposures and which were, before now, the major causes of morbidity and mortality in the developed world are now emerging as an important component of the disease burden in developing countries like Nigeria (Gill, 1999). In their work, Unachukwu et al., (2008), showed that out of 3294 total medical admissions at the University of Port-Harcourt Teaching Hospital (UPTH) Nigeria, from June, 2000 to June, 2004, 56.2% (1853) were cases of various non-communicable diseases. The breakdown showed that diseases of the cardiovascular, endocrine and renal systems occurred most accounting for 35.7% (662), 18.5% (342), and

18.6% (311) respectively. Others were neurological 14.5% (269), gastrointestinal 5.0% (93), haematological 4.9% (911), respiratory problems 2.4% (44), musculoskeletal 1.82% (33) while dermatological diseases accounted for 0.4% (7) of non-communicable admissions (Unachukwu et al., 2008), hypertension, diabetes mellitus and chronic renal failure were the most common cardiovascular, endocrine and renal disorders respectively but most Nigerian medical personnel, during diagnosis do not look on the direction of heavy metals as possible causes of these non communicable diseases .Various heavy metals have been implicated in most of these non-communicable diseases. Some major clinical effects of mercury and arsenic include tremor, gingivostomatitis, peripheral neuropathy, acrodynia, acute tubular necrosis, gastroenteritis, CNS effects and birth effects (Das et al., 2011). Various heavy metals have been implicated in most of these non-communicable diseases. Several studies suggest that the presence of lead and cadmium in the reproductive tract of the men attending infertility clinics may be related to a moderate alteration of their seminal parameters (Mendiola et al., 2011). In his well reported work, Giwa-Osagie (2003) revealed that Nigeria has 12 million infertile persons, which was originally believed to be caused by infection (Cates et al., 1985) but majority of the cases remained after treating infection. Amongst African adult couples, it is estimated that 10-25% are subfertile and of the subfertile couples, female factors accounted for about 55% and male factors about 30-40% while 5-15% are unexplained causes (Giwa-Osagie, 2011). A study carried out in Port Harcourt south-south Nigeria on the prevalence hypertension by Onwuchekwa and Asekomeh (2009) correlated with that of Adedoyin and Adesoye (2005), Onwuchekwa and Asekomeh (2009) work showed that congestive cardiac failure implicated hypertension (56.3%) as the major cause while other cardiomyopathy, chronic renal failure, rheumatic heart disease and ischemic heart disease accounted for 12.3%, 7.8%, 4.3% and 0.2%, that of Adedoyin and Adesoye (2005), showed hypertension (32%), stroke (17.4%), cardiomyopathies (7.6%) while other cardiovascular diseases accounted for (5.6%). Clinical profile of hypertension in Port Harcourt reviewed by Onwuchekwa and Chinenye (2010) showed that 28.2% of all the medical admissions were due to hypertension with its attendant complications such as stroke (39.9%), heart failure (22%), and renal failure (9.4%). Mortality rate caused by stroke (51.5%), heart failure (14.1%) and renal failure (12.1%) follows the same sequence. Most Nigerian adults (about 20-25%) are regarded as being hypertensive (Ogah, 2006). In study carried out in Abeokuta, south western Nigeria, hypertension (56.7%) was the major cause of cardiovascular ailment, rheumatic heart disease (3.7%) and cardiomyopathy (3.0%) while other CVDs accounted for 4.4% (Ogah et al., 2008), These studies correlating that of Unachukwu et al., (2008), shows that non communicable diseases are a major cause of death in Nigeria. Previously the battle with communicable diseases, hygiene and other third world health challenges ignored health hazards posed by environmental heavy metals. Environmental contamination and exposure to heavy metals is on the rise in Nigeria and their excessive dietary intake are linked with cancers of stomach, small intestine, large intestine, ovary, kidney, lungs, myeloma, all leukemia and all lymphomas (Reddy et al., 2004). These fact are complicated the very facts that human biological half-lives for heavy metals are variably long, example the half-life for cadmium in the kidney is decades, other heavy metals can readily pass across the placenta, found in the breast milk and exert very detrimental effect on the behavior, intellect and developing nervous system in children (Sanders et al., 2009) In all most heavy metal accumulation have been associated with shortening of life expectancy, progressively steady decline in energy, productivity quality of life to accelerated CVDs,

premature, dementia and total debilitation (Orisakwe, 2014) and a total increase in family health problems, reduced joy and happiness and medical expenses. In the aftermath of Lead poisoning in Zamfara State, Nigeria, particularly in Anka and Bukkuyum Local Government Area of the State, Subsequent investigations by the centers for Disease Control, the World Health Organization (WHO) and Zamfara State Ministry of Health confirmed that hundreds of children below five years were at risk of death or serious acute and chronic health effects due to high levels of lead and mercury (WHO, 2011).

CONCLUSION

We conclude that greater Nigerian environment is increasingly contaminated with heavy metals, and that the populace including children, and occupationally exposed artisans is environmentally exposed to these heavy metal contaminations through various means such as air, water and food and that human health problems associated with heavy metal exposure other than communicable diseases are on the increase and should be declared public health emergency by Nigerian policy makers.

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Chapter 505

**TESTIMONY OF DR. KATHRYN M. WELLS, MEDICAL
DIRECTOR, DENVER HEALTH CLINIC AT THE FAMILY
CRISIS CENTER. HEARING ON “IS THE DEPARTMENT
OF JUSTICE ADEQUATELY PROTECTING THE PUBLIC
FROM THE IMPACT OF STATE RECREATIONAL
MARIJUANA LEGALIZATION?”***

Chairman Grassley, Co-Chairman Feinstein, distinguished members of the Caucus and guests: Thank you for providing me with the opportunity to appear before you today to discuss my perspective of the impact legalization of recreational marijuana has had on Colorado’s children and the child welfare system. As a Child Abuse Pediatrician and someone who has observed and studied the impact of substance abuse on children and child maltreatment for almost 20 years, I am hoping that my experiences related to marijuana legalization in Colorado might help inform your decisions regarding the role of the Department of Justice in assisting states in measuring, understanding and mitigating its impact on children. In Colorado, we have come to understand that these are extremely complex issues that seem to generate many more questions than answers. In the next few minutes, I will speak to the impact such policies have on children as informed by my experience in Colorado.

Most of my comments can be viewed through the Department of Justice’s marijuana enforcement priority of preventing the distribution of marijuana to minors. Regardless of one’s overall position on marijuana legalization, I trust most would accept this priority. However, child health and welfare in Colorado has been endangered for many reasons but largely because of the skyrocketing access to and subsequent use of marijuana edible products. Although there are many complex issues, I will use my time this morning to share my experiences and observations on three issues:

* This is an edited, reformatted and augmented version of testimony presented April 5, 2016 before the Senate Caucus on International Narcotics Control.

- Marijuana edibles;
- Additional issues related to child safety and welfare, and
- The impacts of the use of marijuana during pregnancy and breastfeeding.

MARIJUANA EDIBLES

Marijuana infused products such as candy, brownies and cookies are all inherently appealing to children. Because of this appeal, better regulations around edibles is essential to prevent child ingestion. A systematic literature review of unintentional marijuana exposures in children undertaken by Colorado's Retail Marijuana Public Health Advisory Committee found substantial evidence that more unintentional marijuana exposures of children occur in states with increased legal access to marijuana, and that such exposures can lead to significant clinical effects requiring medical attention.^{1, 2,3} Additionally, they found moderate evidence that the use of child-resistant packaging reduces unintentional pediatric poisonings in general, while there is little data specifically related to marijuana.^{4,5,6}

Indeed, review of Colorado data over the past decade has revealed a very concerning trend. According to data compiled by the Rocky Mountain Poison and Drug Center, the number of marijuana-related exposures in children ages 0 to 5 increased from an average of 4 per year during the pre-commercialization years of 2006-2008, to 13 per year during post-commercialization from 2009-2012, a 225% increase, to an average of 31 per year following legalization in 2013 and 2014, a subsequent 138% increase. In this same time period (2013-2014), the average percentage of all marijuana-related exposures occurring in children ages 0 to 5 in Colorado was 17.71%, far exceeding the national average of 5.95%.

Because of the increased potency of these exposures, children are often requiring more medical interventions when they present after an ingestion. According to Colorado Hospital Association data demonstrated that the rates of hospitalizations and emergency department visits in children up to 9 years of age due to possible marijuana exposures increased more than five-fold between the period from 2001- 2009 to 2010-2013. In addition to the clear health concerns, child ingestions prompt reports to child welfare and sometimes law enforcement posing additional challenges to systems that then attempt to determine the source and nature of the exposure, whether it was intentional or accidental, and the potential for future risk.

While Colorado has worked hard to address this issue with regulations that will be implemented October 2016 determining packaging guidelines for both recreational and medicinal marijuana and serving/dosage size related to recreational marijuana, it is important to note that the best packaging only protects children up to the age of 5 years.

ADDITIONAL ISSUES RELATED TO CHILD SAFETY AND CHILD WELFARE

Beyond access to edibles, Colorado has experienced several other challenges related to the impact of the legalization of marijuana on children that we are trying to understand more

completely but are hindered by the lack of data. For example, home cultivation of marijuana including home grows and processing of edibles has raised questions as to the risk to children. While we have now restricted the ability to legally extract THC utilizing butane due to the risk of explosions, other risks and mandates to report to child welfare are less clear. In general, concerns of child neglect arise when cultivation does not meet current Colorado legal standards. Electrical hazards, improper ventilation or access to pesticides or unrestricted access to marijuana itself due to improper storage are all valid concerns.

Another issue we have seen is an impact on our schools. The *Denver Post* examined marijuana store locations and found 25 marijuana stores closer than 1,000 feet to at least one nearby school.⁷ And using data compiled by PBS in Colorado, there are signs that more students are using marijuana and that this is an increasing problem for teachers, counselors, and other school personnel.⁸

Another challenge is the ability to determine if someone is impaired while operating a vehicle or parenting, whether the use is recreational or medicinal. Impairment is an important issue in determining if a caregiver is safe to care for a child, a decision that challenges child welfare workers daily. Generally, impaired parenting is defined as the inability of a caregiver to create, maintain, or regain an environment that promotes optimum growth and development of a child, a standard that is often challenging to determine in issues related to the use of marijuana. Due to the lipophilic (or fat-loving) nature of the drug and its storage in the human body in fats, standard testing levels of intoxication and impairment are much more difficult to determine than with other substances of abuse such as alcohol, prescription or illicit drugs.

Finally, another unanticipated area of concern is the issue of parental administration of cannabinoids for medicinal purposes in children without proper authorization. As you are aware, many families with children who are suffering life threatening disease processes such as intractable seizures have flocked to Colorado for the promise of the potential therapeutic benefit of cannabinoids such as cannabidiol (CBD) oil. In order to legally administer this drug to a child, parents are required to obtain special permission, a process requiring a recommendation of two physicians licensed to practice medicine in Colorado. This process takes time and while awaiting this, many parents obtain and administer the product without a recommendation, placing healthcare providers in a difficult dilemma, ignore potentially vital information related to current therapeutic interventions that may negatively interact or compromise their proposed medical management or risk family trust by following their legal mandate by reporting such information to child welfare.

PREGNANCY AND BREASTFEEDING

Another topic I wish to touch on briefly is the use of marijuana use during pregnancy and breastfeeding. The legalization of recreational marijuana has underscored the need to better understand the impact of exposure on the unborn fetus as well as the breastfeeding infant to the different forms of marijuana. The potential for adverse outcomes in exposed offspring of marijuana-using mothers prompted Colorado's Retail Marijuana Public Health Advisory Committee to review the available literature on physical, developmental and mental health outcomes of marijuana exposure during pregnancy and breastfeeding. While it is important to

note that this literature is based on smoked marijuana alone as well as much lower potency THC than is being used currently, the Committee found moderate evidence that maternal use of marijuana during pregnancy is associated with negative effects on exposed offspring, including cognitive function, IQ and attention.^{9,10,11,12 13,14,15,16} Importantly, these effects may not appear until adolescence.

Additionally, the Committee reviewed the very limited research related to breastfeeding and marijuana and found that biological evidence shows that THC is present in the breast milk of women who use marijuana and that infants who drink breast milk containing THC absorb and metabolize the THC.¹⁷ However, only mixed evidence was found for whether or not an association exists between maternal use of marijuana while breastfeeding and motor development in exposed infants.^{18,19}

The issue of prenatal exposure to marijuana has been especially challenging because in Colorado, an infant born positive for a Schedule I drug or a Schedule II drug not being used by the mother as prescribed is defined as a case of child abuse. Therefore, if an infant is born positive for THC in Colorado, under current law, this meets the healthcare provider's mandate to report the case to child welfare and can be used as evidence of child abuse in civil court. Many healthcare providers have found this new reality ethically challenging. Women who deliver an infant positive for THC, not realizing it was grounds for a child welfare action, may now be faced with child welfare involvement that may include removal of their infant and/or ongoing monitoring. Additionally, healthcare professionals, child welfare workers, and judges are often met with the challenging task of determining when and if a mother can safely breastfeed her child.

Due to these many challenges, the Committee identified many areas in need of research that may impact public health policies and prevention strategies such as the adverse health effects and marijuana use and breastfeeding including the effects of cannabidiol (CBD) and other cannabinoid use, the consumption of edibles or by vaping and the impact of potency of THC consumed. Further, research is needed to determine the length of time THC remains in breast milk, the comparison of amount of THC in breast milk to maternal blood or urine THC levels.

CONCLUSION

Due to the many challenges faced by Colorado's child-serving professionals, the Colorado School of Public Health has undertaken a Health Impact Assessment as a systematic process in which evidence based/informed recommendations are developed to be responsive to community and stakeholder input in a local policy context. This effort was largely initiated due to perceived inconsistencies in how marijuana use and exposures were operationalized in child welfare in an effort to define greater consistency and develop evidence based/informed recommendations. This challenging work continues specifically related to issues related to mandatory reporting, child welfare screening and assessment and the management of open child welfare cases where marijuana is a factor. This process has also combined with ongoing efforts to better define situations related to substance use and children, including child welfare, in the Colorado Children's Code where House Bill 16-1386 was just introduced and set for hearing next week.

I urge the Federal government and other states contemplating similar legal changes involving the legalization of recreational marijuana to take the time to consider the impact of such policy on the health and wellbeing of our youngest citizens. We desperately need funding support and laws that allow research needed to inform these critical policies and regulations that impact the health, welfare and safety of our most vulnerable but critical resource, our children.

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Chapter 506

PUBLIC HEALTH SERVICE AGENCIES: OVERVIEW AND FUNDING (FY2015-FY2017)*

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SUMMARY

Within the Department of Health and Human Services (HHS), eight agencies are designated components of the U.S. Public Health Service (PHS). The PHS agencies are funded primarily with annual discretionary appropriations. They also receive significant amounts of funding from other sources including mandatory funds from the Affordable Care Act (ACA), user fees, and third-party reimbursements (collections).

- The *Agency for Healthcare Research and Quality (AHRQ)* funds research on improving the quality and delivery of health care. For several years prior to FY2015, AHRQ did not receive its own annual appropriation. Instead, it relied on redistributed (“set-aside”) discretionary funds from other PHS agencies for most of its funding, with supplemental amounts from the ACA’s mandatory Patient-Centered Outcomes Research Trust Fund (PCORTF). In FY2015 and FY2016, AHRQ received its own discretionary appropriation in lieu of set-aside funds, with the FY2016 level of \$428 million below the FY2015 level of \$443 million.
- The *Centers for Disease Control and Prevention (CDC)* is the federal government’s lead public health agency. CDC obtains its funding from multiple sources besides discretionary appropriations. The agency’s funding level has fluctuated in the past few years, with the FY2016 level of \$11.8 billion above the FY2015 level of \$11.2 billion. The *Agency for Toxic Substances and Disease Registry (ATSDR)* investigates

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the public health impact of exposure to hazardous substances. ATSDR is headed by the CDC director and included in the discussion of CDC in this report.

- The *Food and Drug Administration (FDA)* regulates drugs, medical devices, food, and tobacco products, among other consumer products. The agency is funded with annual discretionary appropriations and industry user fees. The FDA's funding level in FY2016 was \$4.7 billion—above the FY2015 level of \$4.5 billion—with user fees accounting for about 43% of FDA's total funding.
- The *Health Resources and Services Administration (HRSA)* funds programs and systems that provide health care services to the uninsured and medically underserved. HRSA, like CDC, relies on funding from several different sources. The agency's funding increased from \$10.6 billion in FY2015 to \$10.8 billion in FY2016.
- The *Indian Health Service (IHS)* supports a health care delivery system for Native Americans. IHS's funding, which includes discretionary appropriations and collections from third-party payers of health care, increased between FY2015 and FY2016 from \$5.9 billion to \$6.2 billion. Appropriations and collections both increased during that period.
- The *National Institutes of Health (NIH)* funds basic, clinical, and translational biomedical and behavioral research. NIH gets more than 99% of its funding from discretionary appropriations. Recent increases in NIH's annual appropriations have boosted its funding level to a new high of \$32.3 billion in FY2016, compared to \$30.3 billion in FY2015.
- The *Substance Abuse and Mental Health Services Administration (SAMHSA)* funds mental health and substance abuse prevention and treatment services. SAMHSA's funding, about 95% of which comes from discretionary appropriations, was approximately \$3.6 billion in FY2015 and \$3.7 billion in FY2016.

INTRODUCTION TO THE PHS AGENCIES

The Department of Health and Human Services (HHS) has designated eight of its 11 operating divisions (agencies) as components of the U.S. Public Health Service (PHS). The PHS agencies are: (1) the Agency for Healthcare Research and Quality (AHRQ), (2) the Agency for Toxic Substances and Disease Registry (ATSDR), (3) the Centers for Disease Control and Prevention (CDC), (4) the Food and Drug Administration (FDA), (5) the Health Resources and Services Administration (HRSA), (6) the Indian Health Service (IHS), (7) the National Institutes of Health (NIH), and (8) the Substance Abuse and Mental Health Services Administration (SAMHSA).¹

While the PHS agencies all provide and support essential public health services, their specific missions vary. With the exception of FDA, the agencies have limited regulatory responsibilities. Two of them—NIH and AHRQ—are primarily research agencies. NIH conducts and supports basic, clinical, and translational medical research. AHRQ conducts and supports research on the quality and effectiveness of health care services and systems.

Three of the agencies—IHS, HRSA, and SAMHSA—provide health care services or help support systems that deliver such services. IHS supports a health care delivery system for American Indians and Alaska Natives. Health services are provided directly by the IHS, as

well as through tribally contracted and operated health programs, and through services purchased from private providers. HRSA funds programs and systems to improve access to health care among low-income populations, pregnant women and children, persons living with HIV/AIDS, rural and frontier populations, and others who are medically underserved. SAMHSA funds community-based mental health and substance abuse prevention and treatment services.

CDC is a public health agency that develops and supports community-based and population-wide programs and systems to promote quality of life and prevent the leading causes of disease, injury, disability, and death. ATSDR, which is headed by the CDC director and included in the discussion of CDC in this report, is tasked with identifying potential public health effects from exposure to hazardous substances. Finally, FDA is primarily a regulatory agency, whose mission is to ensure the safety of foods, dietary supplements, and cosmetics, and the safety and effectiveness of drugs, vaccines, medical devices, and other health products. In 2009, Congress gave FDA the authority to regulate the manufacture, marketing, and distribution of tobacco products in order to protect public health.

The programs and activities of five of the PHS agencies—AHRQ, CDC, HRSA, NIH, and SAMHSA—are mostly authorized under the Public Health Service Act (PHSA).² While some of FDA's regulatory activities are also authorized under the PHSA, the agency and its programs derive most of their statutory authority from the Federal Food, Drug, and Cosmetic Act (FFDCA).³ HRSA's maternal and child health programs are authorized by the Social Security Act (SSA),⁴ and many of the IHS programs and services are authorized by the Indian Health Care Improvement Act.⁵ ATSDR was created by the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA, the "Superfund" law).⁶

SOURCES OF PHS AGENCY FUNDING

The primary source of funding for each PHS agency is the discretionary budget authority it receives through the annual appropriations process.⁷ AHRQ, CDC, HRSA, NIH, and SAMHSA are funded by the Departments of Labor, Health and Human Services, and Education, and Related Agencies (LHHS) appropriations act. Funding for ATSDR and IHS is provided by the Department of the Interior, Environment, and Related Agencies (Interior/Environment) appropriations act. FDA gets its funding through the Agriculture, Rural Development, Food and Drug Administration, and Related Agencies (Agriculture) appropriations act.⁸

Secretary's Transfer Authority

The annual LHHS appropriations act gives the HHS Secretary limited authority to transfer funds from one budget account to another within the department. The Secretary may transfer up to 1% of the funds in any given account. However, a recipient account may not be increased by more than 3%. Congressional appropriators must be notified in advance of any transfer.⁹

The HHS Secretary used this transfer authority in FY2013 and again in FY2014 as part of a broader effort to provide the Centers for Medicare & Medicaid Services (CMS) with additional funding to implement the Affordable Care Act (ACA).¹⁰ In FY2013, for example, NIH was the primary source of transfers both to CMS for ACA implementation and to CDC and SAMHSA to help offset a loss of funding for those two agencies from the ACA's Prevention and Public Health Fund (PPHF, discussed below). A significant portion of the FY2013 PPHF funds that were originally allocated to CDC and SAMHSA were reallocated to CMS, also for ACA implementation. In FY2014, NIH was again the primary source of transfers to CMS to support ACA implementation.¹¹

PHS Evaluation Set-Aside

In addition to the transfer authority provided in the annual LHHS appropriations act, Section 241 of the PHSA authorizes the HHS Secretary, with the approval of congressional appropriators, to use a portion of the funds appropriated for programs authorized by the PHSA to evaluate their implementation and effectiveness.¹² This longstanding budgeting authority is known as the Public Health Service Evaluation Set-Aside (set-aside), or PHS budget "tap."

Under this authority the appropriations of numerous HHS programs are subject to an assessment. Although the PHSA limits the set-aside to no more than 1% of program appropriations, in recent years the annual LHHS appropriations act has specified a higher amount. The FY2016 LHHS appropriations act capped the set-aside at 2.5%, the same percentage that has been in place since FY2010.¹³

Following passage of the annual LHHS appropriations act, the HHS Budget Office calculates the assessment on each of the donor agencies and offices. These funds are then transferred to various recipient agencies and offices within the department for evaluation and other specified purposes, based on the amounts specified in the appropriations act.¹⁴

Table 1 shows the total assessments and transfers for FY2013, by HHS agency and office, and indicates whether the entity was a net donor or recipient of set-aside funds that year. These figures are broadly representative of the distribution of set-aside funds that occurred each fiscal year over a period of several years prior to FY2015, when the appropriators decided to make major changes to the allocation of such funds.

NIH, whose annual discretionary appropriation exceeds that of all the other PHS agencies combined, is subject to the largest assessment of set-aside funds. NIH contributed almost \$710 million (69%) of the \$1.026 billion in set-aside funds in FY2013. However, the agency received \$8 million in set-aside funding, making it a significant net donor of set-aside funds. Similarly, HRSA contributed more set-aside funds than it received in FY2013. On the other hand, AHRQ, CDC, and SAMHSA were net recipients of set-aside funding in FY2013. The Administration for Children and Families (ACF) and various offices within the Office of the Secretary (OS) also received set-aside funds.

Table 1. PHS evaluation set-aside fund assessments and transfers
dollars in thousands

	FY2013			FY2016		
Agency/ Office	Total Assessments	Total Transfers	Net Gain (Loss)	Total Assessments	Total Transfers	Net Gain (Loss)
NIH	709,536	8,200	(701,336)	733,198	780,000	46,802
HRSA	126,340	25,000	(101,340)	209,399	—	(209,399)
CDC	116,170	375,048	258,878	156,003	—	(156,003)
SAMHSA	53,867	129,667	75,800	29,661	133,667	104,006
AHRQ	78	365,362	365,284	6,555	—	(6,555)
CMS	—	—	—	—	184,000	184,000
ACF	—	5,762	5762	—	—	—
ACL	158	—	(158)	898	—	(898)
OS	19,412	116,522	97,110	29,281	67,328	38,047
Total	1,025,561	1,025,561		1,164,995	1,164,995	

Sources: Department of Health and Human Services, “Use of Public Health Service Set-Aside Authority for Fiscal Year 2013,” Report to Congress; and Department of Health and Human Services, “Use of Public Health Services Set-Aside Authority for Fiscal Year 2016,” Report to Congress.

Notes: NIH=National Institutes of Health; HRSA= Health Resources and Services Administration; CDC= Centers for Disease Control and Prevention; SAMHSA= Substance Abuse and Mental Health Services Administration; AHRQ= Agency for Healthcare Research and Quality; CMS= Centers for Medicare and Medicaid Services; ACF= Administration for Children and Families; ACL= Administration for Community Living; OS= Office of the Secretary.

Table 1 also shows the set-aside assessments and transfers for the current fiscal year (i.e., FY2016). These figures reflect the significant changes that the appropriators first made in FY2015 by returning most of the set-aside funding to NIH and eliminating any transfers to AHRQ, CDC, and HRSA. As a result, NIH has gone from being by far the largest net donor of set-aside funds to a net recipient of such funding. Meanwhile, AHRQ and CDC have experienced a significant loss of set-aside funding and are now both net donors of these funds.

The situation with AHRQ is of particular interest to many. From FY2003 through FY2014, AHRQ did not receive an annual discretionary appropriation. The agency was supported by set-aside funds and, in recent years, by amounts from other sources. In FY2015, however, AHRQ received a discretionary appropriation for the first time in more than a decade in lieu of receiving any set-aside funding. That continues to be the case in FY2016.¹⁵

Mandatory Funding, User Fees, and Collections

Although the bulk of PHS agency funding is provided through annual discretionary appropriations, agencies also receive mandatory funding, user fees, and third-party collections. As discussed below, these additional sources of funding are a substantial component of the budget of several PHS agencies.

Mandatory Appropriations

The ACA included numerous appropriations that together provided billions of dollars in mandatory spending¹⁶ to support specified grant programs and activities within HHS.¹⁷ A few

PHS agencies continue to receive these funds, which are itemized in the funding tables in this report.

The ACA also established and funded three multibillion dollar trust funds to help support PHS agency programs and activities. First, the ACA provided a total of \$11 billion in annual appropriations over the five-year period FY2011-FY2015 to the *Community Health Center Fund (CHCF)*.¹⁸ These funds help support the federal health centers program and the National Health Service Corps (NHSC), both of which are administered by HRSA. The Medicare Access and CHIP Reauthorization Act of 2015 (MACRA)¹⁹ appropriated two more years of funding for the CHCF; a total of \$3.910 billion for each of FY2016 and FY2017. A table summarizing each fiscal year's CHCF appropriation and the allocation of funds appears in Appendix A.

Second, the *Prevention and Public Health Fund (PPHF)*, for which the ACA provided a permanent annual appropriation, is intended to support prevention, wellness, and other public health programs and activities.²⁰ To date, CDC has received the majority of PPHF funds, while AHRQ, HRSA, and SAMHSA have received smaller amounts. The HHS Secretary transferred almost half of the FY2013 PPHF funds to CMS to support ACA implementation. A table showing the allocation of annual PPHF funding by agency since FY2010 is provided in Appendix B.

Finally, the *Patient-Centered Outcomes Research Trust Fund (PCORTF)* is supporting comparative effectiveness research over a 10-year period (FY2010-FY2019) with a mix of appropriations—some of which are offset by revenue from a fee imposed on health insurance policies and self-insured health plans—and transfers from the Medicare Part A and Part B trust funds.²¹ A portion of the PCORTF is allocated for AHRQ. More information on the PCORTF, including the appropriation and transfer formulas, is provided in Appendix C.

In addition to the ACA funding, HRSA, CDC, and IHS each receive mandatory funds from other sources. HRSA's Family-to-Family Health Information Centers Program has been funded by a series of mandatory appropriations since FY2007; CDC receives Medicaid funding to support the Vaccines for Children program; and both IHS and NIH receive mandatory funds for diabetes programs. These and other mandatory appropriations are itemized in the agency funding tables in this report.

User Fees

Several PHS agencies assess user fees on third parties to help fund their programs and activities. User fees collected by CDC, HRSA, and SAMHSA represent a very small portion of each agency's overall budget.²² In comparison, the industry user fees that FDA collects help finance a broad range of the agency's regulatory activities and account for a substantial and growing share of the agency's budget.

In 1992, the Prescription Drug User Fee Act (PDUFA)²³ established the first user fee program at FDA. Since PDUFA's enactment, Congress has created several other FDA user fee programs. These programs provide FDA with additional resources that allow it to hire more personnel and expedite the process of reviewing new product applications. Some user fees also pay for information technology infrastructure and postmarket surveillance of FDA-approved products. FDA's user fee programs now support the agency's regulation of prescription drugs, animal drugs, medical devices, tobacco products, and some foods, among other activities. The amount of user fees that FDA collects under these programs has increased steadily since PDUFA was enacted, both in absolute terms and as a share of FDA's

overall budget. In FY2016, user fees account for 43% of the agency's funding. More discussion of user fees is provided in the FDA section of this report and in Appendix D.

Collections

IHS supplements its annual discretionary appropriation with third-party collections from public and private payers. Most of these funds come from Medicare and Medicaid, which reimburse IHS for services provided to American Indians and Alaska Natives enrolled in these programs at facilities operated by IHS and the tribes. IHS also collects reimbursements from private health insurers. IHS collections (and reimbursements) are reflected in Table 8 of this report.

RECENT TRENDS IN PHS AGENCY FUNDING

Congress has taken a number of recent steps through both the annual appropriations process and the enactment of deficit-reduction legislation to reduce the growth in federal spending. These actions, which are briefly discussed below, have had an impact on the level of discretionary funding for several PHS agencies since FY2010.

Among the five PHS agencies that are funded through the LHHS appropriations act, AHRQ has witnessed a reduction in discretionary funding over the past six years. However, that reduction has been offset by the receipt of increasing amounts of mandatory funding. Discretionary funding for the other four agencies—CDC, HRSA, NIH, and SAMHSA—has fluctuated in recent years, dipping in FY2013 as a result of the sequestration of discretionary appropriations that fiscal year (see below). Both CDC and HRSA also have received increasing amounts of mandatory funding since FY2010, which has raised each agency's overall funding level.

FDA and IHS, which receive their discretionary funding through the Agriculture and the Interior/Environment appropriations acts, respectively, have seen their appropriations increase since FY2010. Both agencies also have witnessed a steady increase in funding from other sources; user fees at FDA, and third-party collections at IHS.

Impact of Budget Caps and Sequestration

In April 2011, lawmakers agreed to cuts in discretionary spending for a broad range of agencies and programs as part of negotiations to complete the FY2011 appropriations process and avert a government shutdown. Four months later, as part of negotiations to raise the debt ceiling,

Congress and the President then enacted the Budget Control Act of 2011 (BCA).²⁴ The BCA established enforceable discretionary spending limits, or caps, for defense and nondefense spending for each of FY2012 through FY2021, and provided for further annual spending reductions equally divided between the categories of defense and nondefense spending beginning in FY2013. Within each spending category, those further reductions are allocated proportionately to discretionary spending and mandatory spending, subject to

certain exemptions and special rules. All the spending summarized in this report falls within the nondefense category.

Under the BCA, the spending reductions are achieved through two different methods: (1) sequestration (i.e., an across-the-board cancellation of budgetary resources), and (2) lowering the BCA-imposed discretionary spending caps. The Office of Management and Budget (OMB) is responsible for calculating the percentages and amounts by which mandatory and discretionary spending are required to be reduced each year, and for applying the relevant exemptions and special rules.

Mandatory Spending

The BCA requires the mandatory spending reductions to be executed each year through a sequestration of all nonexempt accounts. Generally, the ACA and other mandatory funding discussed in this report is fully sequestrable at the applicable percentage rate for nonexempt nondefense mandatory spending (see Table 2), with the following key exceptions. First, the funds for the CDC-administered Vaccines for Children program come from Medicaid, which is exempt from sequestration. Second, CDC funding for the Energy Employees Occupational Illness Compensation Program Act (EEOICPA) and the World Trade Center Health Program also are exempt from sequestration. Third, under the sequestration special rules, cuts in CHCF funding for community health centers and migrant health centers and the cuts in mandatory diabetes funding for IHS are capped at 2% (see Table 2).

**Table 2. Sequestration of funding for PHS agency programs
FY2013-FY2017**

Mandatory Spending					
Nonexempt programs	5.1% ^a	7.2%	7.3%	6.8%	6.9%
Community & migrant health centers, IHS	2.0%	2.0%	2.0%	2.0%	2.0%
Discretionary Spending Nonexempt programs	5.0% ^a	NA ^b	NA ^b	NA ^b	NA ^b

Sources: OMB Report to the Congress on the Joint Committee Sequestration for Fiscal Year 2013, March 1, 2013; OMB Report to the Congress on the Joint Committee Reductions for Fiscal Year 2014, May 20, 2013; OMB Report to the Congress on the Joint Committee Reductions for Fiscal Year 2015, March 10, 2014; OMB Report to the Congress on the Joint Committee Reductions for Fiscal Year 2016, February 2, 2015; and OMB Report to the Congress on the Joint Committee Reductions for Fiscal Year 2017, February 9, 2016.

^a These percentages reflect adjustments made by the American Taxpayer Relief Act of 2012 (ATRA; P.L. 112-240), which amended the BCA by reducing the overall dollar amount that needed to be cut from FY2013 spending.

^b NA = not applicable.

While all the nonexempt PHS programs with mandatory funding were sequestered in FY2013 and FY2014, several of them avoided sequestration in FY2015 and/or FY2016 because they had no budgetary resources in place at the time the sequester was ordered by the President. The Maternal, Infant, and Early Childhood Home Visiting program, administered by HRSA, is one example of a program for which this occurred. The ACA authorized the home visiting program and funded it through FY2014 (see Table 7). Pursuant to the BCA, the President ordered the FY2015 sequestration on March 10, 2014. Because Congress and the President had yet to enact legislation extending funding for the home visiting program, there were no FY2015 budgetary resources to sequester.²⁵

Discretionary Spending

Under the BCA, FY2013 discretionary spending was also reduced through sequestration. However, for each of the remaining fiscal years (i.e., FY2014 through FY2021), the annual reductions in discretionary spending required under the BCA are to be achieved by lowering the discretionary spending caps by the total dollar amount of the required reduction. This means that the cuts within the lowered spending cap may be apportioned through the annual appropriations decisionmaking, rather than via an across-the-board reduction through sequestration.

FY2013 Sequestration

In general, PHS agency discretionary appropriations in FY2013 were fully sequestrable at the applicable percentage rate for nonexempt nondefense discretionary spending (see Table 2). As a result, each agency saw a dip in its discretionary funding for FY2013. OMB determined that FDA user fees for FY2013 were fully sequestrable, but concluded that IHS's third-party collections in FY2013 were exempt from sequestration.

FY2014-FY2017 Discretionary Spending Caps

Table 3 shows the original nondefense discretionary (NDD) spending caps for FY2014-FY2017 established by the BCA. For each of those four fiscal years, the BCA required the caps to be lowered by approximately \$37 billion to achieve the necessary reduction in NDD spending.

However, the Bipartisan Budget Act of 2013 (BBA13)²⁶ amended the BCA by establishing new levels for the FY2014 and FY2015 NDD spending caps, and eliminating the requirement for those caps to be reduced. While the BBA13 caps were set at a level that was lower than the original BCA caps (see Table 3), they were higher than the BCA-lowered caps that they replaced.

The Bipartisan Budget Act of 2015 (BBA15)²⁷ further amended the BCA by establishing new levels for the FY2014 and FY2015 NDD spending caps, and eliminating the requirement for those caps to be lowered. Once again, the BBA15 caps were set at a level that is below the original BCA caps for those two fiscal years (see Table 3), but is higher than the BCA-lowered caps that they replace.

The revised NDD caps allowed an additional \$26 billion for nondefense programs in FY2016 compared to the previous fiscal year. However, there is virtually no increase in NDD appropriations allowed by the FY2017 revised cap level. (The revised cap for FY2017 is only \$40 million above the revised cap for FY2016.)

Table 3. Nondefense discretionary spending limits billions of dollars

	FY2014	FY2015	FY2016	FY2017
Original caps under BCA	510.000	520.000	530.000	541.000
Revised caps under BBA13 and BBA15	491.773	492.356	518.491	518.531

Source: Budget Control Act of 2011 (P.L. 112-25); Bipartisan Budget Act of 2013 (P.L. 113-67, Division A); Bipartisan Budget Act of 2015 (P.L. 114-74).

Mandatory Funding Proposals for FY2017

The President's FY2017 budget includes a total of \$2.940 billion in proposed new mandatory funding for the PHS agencies: \$1.825 billion for NIH; \$590 million for SAMHSA; \$495 million for HRSA; and \$30 million for CDC. These amounts, which are discussed later in this report, would be used to supplement—and in one case replace—discretionary funding for existing programs, or provide funding for new initiatives. It will be up to Congress to decide whether to pass legislation to provide these funds.

The use of mandatory funding, including amounts provided by the ACA, has become an important component of PHS agency budgeting in recent years. Mandatory funds are not controlled by the annual appropriations process and do not count towards the discretionary spending caps.

REPORT ROADMAP

The remainder of this report consists of seven sections, one for each PHS agency beginning with AHRQ.²⁸ Each section includes an overview of the agency's statutory authority and principal activities, and a brief summary of recent trends in the agency's funding. This material is accompanied by a detailed funding table showing the agency's FY2015 and FY2016 funding levels and the FY2017 budget request. The amounts in the funding tables in this report are taken from the departmental and agency budget documents submitted to the appropriations committees, as well as agency operating plans.²⁹

The funding tables show the post-sequestration amounts for the accounts that were subject to sequestration in FY2015 and FY2016. The amounts shown for the FY2017 request do not reflect sequestration.

The funding tables are formatted in a similar, though not identical, manner. The formatting generally matches the way in which each agency's funding is presented in the congressional budget documents. Each table shows the funding for all the agency's budget accounts and, typically, for selected programs and activities within those accounts. These amounts are summed to give the agency's total, or *program level*, funding. At the bottom of the table any user fees, set-aside funds, ACA funds, and other nondiscretionary amounts are subtracted from the program level to give the agency's *discretionary budget authority* (i.e., annual discretionary appropriations).

The tables for AHRQ, CDC, HRSA, and SAMHSA include non-add entries—italicized and in parentheses—to indicate the contribution of funding to specific accounts from sources other than the agency's discretionary appropriations. Almost all of the CDC accounts, for example, are funded with discretionary appropriations plus amounts from other sources (see Table 5).

The use of a dash in the funding tables generally means “not applicable.” Either the activity or program was not authorized or there was no mandatory funding provided for that fiscal year. In contrast, a zero usually indicates that congressional appropriators had chosen not to appropriate any discretionary funds that year or, in the case of the FY2017 budget request, that no discretionary funding was requested.

It is important to keep in mind that the PHS agency funding tables that appear in budget documents and appropriations committee reports, as well as the tables in this report, show only the amount of evaluation set-aside funds received. They do not reflect the amount of funding assessed on agency accounts. As a result, the funding tables for the PHS agencies subject to an assessment give a somewhat distorted view of their available budgetary resources. This effect is particularly significant in the case of the three agencies—CDC, HRSA, and NIH—that are subject to a significant assessment under the evaluation set-aside authority (see Table 1). NIH, for example, is assessed approximately \$700 million annually. While the funding table for NIH shows the transfer (i.e., receipt) of set-aside funds, which count towards the agency’s overall program level funding, the amounts shown for each agency account have not been reduced to reflect the assessment. Thus, NIH appears to have about \$700 million more than is in fact the case.

AGENCY FOR HEALTHCARE RESEARCH AND QUALITY (AHRQ)³⁰

Agency Overview

AHRQ supports research designed to improve the quality of health care, increase the efficiency of its delivery, and broaden access to health services.³¹ Specific research efforts are aimed at reducing the costs of care, promoting patient safety, measuring the quality of health care, and improving health care services, organization, and financing. AHRQ is required to disseminate its research findings to health care providers, payers, and consumers, among others. In addition, the agency collects data on health care expenditures and utilization through the Medical Expenditure Panel Survey (MEPS) and the Healthcare Cost and Utilization Project (HCUP).

Health Costs, Quality and Outcomes (HCQO) Research Areas

Health Information Technology (HIT) Research. Research evaluating HIT and its impact on the quality and efficiency of health care.

Patient Safety. Research on reducing and preventing medical errors, with a focus on health care-associated infections (HAIs).

Health Services Research, Data, and Dissemination. Research on quality of health care that spans multiple priority areas including, for example, the annual National Healthcare Quality and National Healthcare Disparities Reports.

U.S. Preventive Services Task Force (USPSTF). AHRQ provides the USPSTF with scientific, administrative, and other types of support, although the Task Force is an independent panel of national experts.

Source: CRS Analysis and the FY2017 HHS Budget in Brief. <http://www.hhs.gov/about/budget/fy2017/budget-in-brief/ahrq/index.html>.

AHRQ has evolved from a succession of agencies concerned with fostering health services research and health care technology assessment. The Omnibus Budget Reconciliation Act of 1989 (P.L. 101-239) added a new PHSA Title IX and established the Agency for Health Care Policy and Research (AHCPR), a successor agency to the former National Center for Health Services Research and Health Care Technology Assessment (NCHSR). AHCPR

was reauthorized in 1992 (P.L. 102 410). On December 6, 1999, President Clinton signed the Healthcare Research and Quality Act of 1999 (P.L. 106-129), which renamed AHCPR as the Agency for Healthcare Research and Quality (AHRQ) and reauthorized appropriations for its programs and activities through FY2005. Congress has yet to reauthorize the agency's funding. Despite the expired authorization of appropriations, AHRQ continues to get annual funding.

The AHRQ budget is organized according to three program areas: (1) Healthcare Costs, Quality and Outcomes (HCQO) Research; (2) MEPS; and (3) program support. HCQO research currently focuses on four priority areas, summarized in the text box below.

From FY2003 through FY2014, AHRQ did not receive its own annual discretionary appropriation. Instead, the agency largely relied on the PHS evaluation set-aside to fund its activities and programs. In recent years AHRQ also has received mandatory funds from the PPHF and the PCORTF (see Appendix B and Appendix C). In FY2015, AHRQ received its own discretionary appropriation for the first time in more than a decade in lieu of any set-aside funding.³² This trend continued in FY2016 with the agency receiving its own discretionary appropriation and no set-aside funds.

Table 4. Agency for Healthcare Research and Quality (AHRQ)
(millions of dollars, by fiscal year)

Program or Activity	2015	2016	2017 Request
HCQO Research	229	197	224
Health Information Technology Research	28	22	23
Patient Safety	77	74	76
Health Services Research, Data, and Dissemination ^a	112	89	113
<i>PHS Evaluation Set-Aside (non-add)</i>	<i>(0)</i>	<i>(0)</i>	<i>(83)</i>
Prevention/Care Management (USPSTF)	12	12	12
MEPS	65	66	69
Program Support	70	71	71
PCORTF (Patient-Centered Health Research)^b	79	94	106
Total, Program Level	443	428	470
Less Funds From Other Sources			
PHS Evaluation Set-Aside	0	0	83
PCORTF Transfers	79	94	106
Total, Discretionary Budget Authority	364	334	280

Sources: Prepared by CRS based on AHRQ's congressional budget justification documents and the HHS *Budget in Brief* documents, available at <http://www.hhs.gov/budget/>.

Notes: Individual amounts may not add to subtotals or totals due to rounding.

^a Formerly "Crosscutting Activities;" also formerly "Research Innovations."

^b AHRQ receives funds transferred from the PCORTF to carry out PHSA Section 937, which requires the dissemination of the results of patient-centered outcomes research carried out by the Patient Centered Outcomes Research Institute (PCORI) and other "government-funded research relevant to comparative clinical effectiveness research." For FY2011-FY2013, the PCORTF transfer supplemented the agency's set-aside funding for its patient-centered health research program. Since FY2014, however, AHRQ's patient-centered health research program has been entirely funded by the PCORTF transfer, which is now shown as its own separate budget line. AHRQ's budget documents no longer list patient-centered health research as a separate program area.

Recent Trends in Agency Funding

Since FY2010, AHRQ's budget has increased from \$403 million to \$428 million (+\$25 million), with transfers from PCORTF growing from \$8 million in FY2011 to \$94 million in

FY2016. Discretionary sources of funding shifted from set-aside transfers to the agency's own discretionary appropriation in both FY2015 and FY2016, and ACA mandatory funds have been a prominent and increasing source of funding for the agency since FY2010. AHRQ's program level had been increasing steadily between FY2011 and FY2015, with decreases in discretionary funding being more than offset by transfers of PCORTF funds. However, in FY2016, the total program level for the agency decreased for the first time since FY2011, despite an increasing PCORTF transfer (see Table 4).

CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)³³

Agency Overview

CDC's mission is "to protect America from health, safety and security threats, both foreign and in the [United States]." CDC is organized into a number of centers, institutes, and offices, some focused on specific public health challenges (e.g., chronic disease prevention, injury prevention), and others focused on general public health capabilities (e.g., surveillance and laboratory services).³⁵ In addition, the Agency for Toxic Substances and Disease Registry (ATSDR) is headed by the CDC Director and is discussed in this section.

Many CDC activities are not specifically authorized but are based in broad, permanent authorities in the PHSA.³⁶ Four CDC operating divisions are explicitly authorized. The National Institute for Occupational Safety and Health (NIOSH) was permanently authorized by the Occupational Safety and Health Act of 1970.³⁷ The National Center on Birth Defects and Developmental Disabilities (NCBDDD) was established in PHSA Section 317C by the Children's Health Act of 2000.³⁸ The National Center for Health Statistics (NCHS) was established in PHSA Section 306 by the Health Services Research, Health Statistics, and Medical Libraries Act of 1974.³⁹ ATSDR was established by the Comprehensive Environmental Response, Compensation and Liability Act of 1980 (CERCLA, the "Superfund" law).⁴⁰ Authorizations of appropriations for NCBDDD, NCHS, and ATSDR have expired, but the programs continue to receive annual appropriations.

CDC provides about \$5 billion per year in grants to state, local, municipal, tribal, and foreign governments, and to academic and non-profit entities.⁴¹ It has few regulatory responsibilities.

Recent Trends in Agency Funding

Between FY2010 and FY2016, the total program level for CDC/ATSDR increased from \$10.88 billion to \$11.78 billion. During that time period, CDC/ATSDR budget authority decreased by 3% from \$6.5 billion in FY2010 to \$6.3 billion in FY2016. Table 5 presents funding levels for CDC programs for FY2015 through the FY2017 request. In addition to annual discretionary appropriations, program level amounts for recent years include funds from the following four mandatory appropriations: (1) the Vaccines for Children (VFC) program;⁴² (2) NIOSH activities to support the Energy Employees Occupational Illness Compensation Program Act (EEOICPA);⁴³ (3) the World Trade Center Health Program

(WTCHP);⁴⁴ and (4) appropriations provided under ACA, principally through the PPHF.⁴⁵ CDC receives a small amount of funds from authorized user fees, and may also receive funds through the PHS set-aside, supplemental appropriations, and other transfers.

When considering funding trends for CDC/ATSDR, it is useful to consider mandatory and discretionary funds separately. For example, for FY2016, the CDC/ATSDR total operating budget, or program level, is \$11.78 billion. Of this amount,

- \$6.27 billion (53%) is composed of discretionary funds (i.e., budget authority) for CDC provided in the LHHS appropriations act;
- \$5.42 billion (46%) is composed of mandatory funds for CDC and ATSDR programs, namely the VCF, EEOICPA, and WTCHP, and from the ACA (principally from the PPHF);
- \$75 million (<1%) is discretionary funds for ATSDR provided in the Interior/Environment appropriations act; and
- \$17 million (<1%) is from authorized user fees and other transfers.

Many of CDC's PPHF-funded activities also receive discretionary appropriations. Exceptions include the Preventive Health and Health Services Block Grant, and the Lead Poisoning Prevention Program, which were funded solely through PPHF distributions for FY2016.⁴⁶ For more discussion on the allocation of annual PPHF funding, see Appendix B.

Table 5. Centers for Disease Control and Prevention (CDC) and Agency for Toxic Substances and Disease Registry (ATSDR)
(millions of dollars, by fiscal year)

Program or Activity	2015	2016	2017 Request
Immunization and Respiratory Diseases	798	798	748
<i>PPHF Transfer (non-add)</i>	<i>(210)</i>	<i>(324)</i>	<i>(336)</i>
<i>PHSSEF Influenza Transfers (non-add)</i>	<i>(15)</i>	<i>(15)</i>	<i>0</i>
Vaccines for Children ^a	3,851	4,161	4,387
HIV/AIDS, Viral Hepatitis, STI and TB	1,118	1,122	1,127
Emerging & Zoonotic Infectious Diseases	405	580	629
<i>PPHF Transfer (non-add)</i>	<i>(52)</i>	<i>(52)</i>	<i>(52)</i>
Chronic Disease Prevention and Health Promotion	1,199	1,177	1,117
<i>PPHF Transfer (non-add)</i>	<i>(452)</i>	<i>(339)</i>	<i>(437)</i>
ACA Childhood Obesity Demonstration ^b	—	10	—
Birth Defects, Developmental Disabilities, Disability and Health	132	136	136
<i>PPHF Transfer (non-add)</i>	<i>(0)</i>	<i>(0)</i>	<i>(68)</i>
Environmental Health	179	182	182
<i>PPHF Transfer (non-add)</i>	<i>(13)</i>	<i>(17)</i>	<i>(14)</i>
Injury Prevention and Control	170	236	299
<i>Mental Health (New mandatory proposal, non-add)^c</i>	—	—	<i>(30)^c</i>
Public Health Scientific Services	481	492	501
<i>PPHF Transfer (non-add)</i>	<i>(0)</i>	<i>(0)</i>	<i>(36)</i>
Occupational Safety and Health	335	339	286
<i>PHS Evaluation Set-Aside (non-add)</i>	<i>(0)</i>	<i>(0)</i>	<i>(72)</i>
Global Health	447	427	442

Program or Activity	2015	2016	2017 Request
<i>Supplemental Appropriations for Ebola response (non-add)</i> ^d	(30) ^d	—	—
Public Health Preparedness and Response	1,353	1,405	1,402
Crosscutting Activities and Program Support	274	274	114
<i>PPHF Transfer (non-add)</i> ^e	(160)	(160)	(0)
<i>Prevention Block Grant (non-add)</i> ^e	(160)	(160)	(0)
Buildings and Facilities	10	10	31
User Fees	2	2	2
Energy Employees Occupational Illness Compensation Program Act (EEOICPA)	50	55	55
World Trade Center Health Program ^f	261	300	335
Agency for Toxic Substances and Disease Registry (ATSDR)	75	75	75
ACA Medical Monitoring (ATSDR) ^g	19	—	—
Total, CDC/ATSDR Program Level	11,158	11,781	11,868
Less Funds From Other Sources			
Vaccines for Children ^a	3,851	4,161	4,387
EEOICPA	50	55	55
PHSSEF Transfers	15	15	0
PHS Evaluation Set-Aside	0	0	72
ACA Mandatory Funds: PPHF Transfers	887	892	944
Other Mandatory Funds	19	10	—
World Trade Center Health Program	261	300	335
User Fees	2	2	2
Proposed New Mandatory Funds	—	—	30
Total, CDC/ATSDR Discretionary BA	6,073	6,346	6,043
Less ATSDR Discretionary BA	75	75	75
Total, CDC Discretionary BA	5,998	6,271	5,967

Sources: CDC and ATSDR congressional budget justifications and related documents for FY2016 and FY2017, <http://www.cdc.gov/fmo>.

Notes: Individual amounts may not add to subtotals or totals due to rounding.

Amounts in this table do not include emergency supplemental Ebola response funding for FY2015-FY2019 provided in P.L. 113-235. These funds are discussed in CRS Report R44460, *Zika Response Funding: In Brief*; and at CDC, “FY 2015–2019 Ebola Response Funding,” <http://www.cdc.gov/budget/ebola/index.html>.

PHSSEF is Public Health and Social Services Emergency Fund, a fund used by appropriators to provide the Secretary with ongoing or one-time emergency funding, such as for the response to influenza epidemics. STI is sexually transmitted infection.

^a The Vaccines for Children (VFC) program provides free pediatric vaccines to doctors who serve eligible (generally low-income) children. VFC is funded entirely as an entitlement through federal Medicaid appropriations and is exempt from sequestration. Amounts for FY2015 through the FY2017 request are estimates.

^b ACA Section 4306 appropriated \$25 million for a childhood obesity demonstration project, <http://www.cdc.gov/obesity/childhood/researchproject.html>. The Medicare Access and CHIP Reauthorization Act of 2015 (MACRA, P.L. 114-10) appropriated additional funding for the project; \$10 million for the two-year period FY2016–FY2017.

^c New mandatory funding for FY2017 is proposed for CDC to assist state health departments in implementing comprehensive suicide prevention programs.

^d Emergency supplemental appropriations for FY2015 for the response to the 2014 Ebola outbreak in West Africa, provided in P.L. 113-164. See note above re: subsequent emergency appropriations for the Ebola response.

^e For several years the budget request has called for elimination of the Preventive Health and Health Services Block Grant (also called the “Prevention Block Grant”). For each of FY2015 and FY2016, Congress provided it with \$160 million from the PPHF.

^f Amounts are estimated federal obligations.

^g ACA Section 10323(b) appropriated \$23 million for the period FY2010-FY2014, and \$20 million for each five-year period thereafter, in no-year funding for the early detection of certain medical conditions related to environmental health hazards in Libby, Montana. The amount presented (i.e., \$19 million for FY2015 through FY2019) reflects sequestration as required for non-defense mandatory spending; see Table 2.

In December 2014 Congress provided \$1.771 billion in FY2015 emergency supplemental appropriations to CDC for response to the Ebola outbreak. The funds, which are available through FY2019, are to be used for both domestic and international activities. CDC has not presented these funds within its general budget, and they are not presented in Table 5.⁴⁷ However, the table does include \$30 million provided to CDC's Global Health Program from an earlier Ebola supplemental.

FOOD AND DRUG ADMINISTRATION (FDA)⁴⁸

Agency Overview

FDA regulates the safety of human foods, dietary supplements, cosmetics, and animal foods; and the safety and effectiveness of human drugs, biological products (e.g., vaccines), medical devices, and animal drugs. It also regulates the manufacture of radiation-emitting products to protect the public from hazardous levels of radiation. In 2009, Congress gave FDA the authority to regulate the manufacture, marketing, and distribution of tobacco products in order to protect public health.

Seven centers within FDA represent the broad program areas for which the agency has responsibility: the Center for Biologics Evaluation and Research (CBER), the Center for Devices and Radiological Health (CDRH), the Center for Drug Evaluation and Research (CDER), the Center for Food Safety and Applied Nutrition (CFSAN), the Center for Veterinary Medicine (CVM), the National Center for Toxicological Research (NCTR), and the Center for Tobacco Products (CTP). Several other offices have agency-wide responsibilities.

The Federal Food, Drug, and Cosmetic Act (FFDCA) is the principal source of FDA's statutory authority.⁴⁹ FDA is also responsible for administering certain provisions in other laws, most notably the PHSA.⁵⁰ Although the FDA's authorizing committees in Congress are the committees with jurisdiction over public health issues—the Senate Committee on Health, Education, Labor, and Pensions, and the House Committee on Energy and Commerce—FDA's assignment within the appropriations committees reflects its origin as part of the Department of Agriculture. The Senate and House appropriations subcommittees on Agriculture, Rural Development, FDA, and Related Agencies have jurisdiction over FDA's budget, even though the agency has been part of various federal health agencies (HHS and its predecessors) since 1940.

FDA's budget has two funding streams: annual appropriations (i.e., discretionary budget authority, or BA) and industry user fees. In FDA's annual appropriation, Congress sets both the total amount of appropriated funds and the amount of user fees that the agency is authorized to collect and obligate for that fiscal year. Appropriated funds are largely for the Salaries and Expenses account, with a smaller amount for the Buildings and Facilities account. The several different user fees, which account for 43% of FDA's total FY2016 program level, contribute only to the Salaries and Expenses account.

The largest and oldest FDA user fee that is linked to a specific program was first authorized by the Prescription Drug User Fee Act (PDUFA, P.L. 102-571) in 1992. Appendix D presents the authorizing legislation for current FDA user fees, sorted by the dollar amount

they contribute to the agency's FY2016 budget. After PDUFA, Congress added user fee authorities regarding medical devices, animal drugs, animal generic drugs, tobacco products, priority review, food reinspection, food recall, voluntary qualified food importer, generic drugs, biosimilars, and, most recently, outsourcing facilities (related to drug compounding) and some wholesale distributors and third-party logistics providers (related to pharmaceutical supply chain security).⁵¹ Each of the medical product fee authorities requires reauthorization every five years. Several indefinite authorities apply to fees for mammography inspection, color additive certification, export certification, and priority review vouchers.⁵²

Recent Trends in Agency Funding

Between FY2010 and FY2016, FDA's funding increased from \$3.1 billion to \$4.7 billion. Although discretionary appropriations increased by 16% over that time period, user fee revenue more than doubled. In FY2016, user fees account for 43% of FDA's total funding compared with 24% in FY2010.

Table 6. Food and Drug Administration (FDA)
(millions of dollars, by fiscal year)

Program area	2015 ^a	2016	2017 request
Foods	903	999	1,024
Budget Authority	903	987	1,013
User Fees	0	12	12
Human drugs	1,370	1,395	1,408
Budget Authority	482	492	492
User Fees	888	903	917
Biologics	326	355	360
Budget Authority	211	215	215
User Fees	115	139	145
Animal drugs and feeds	175	189	193
Budget Authority	148	159	162
User Fees	27	30	31
Devices and radiological health	443	450	460
Budget Authority	321	323	326
User Fees	122	127	134
Tobacco products	554	564	596
Budget Authority	—	—	—
User Fees	554	564	596
Toxicological research	63	63	60
Budget Authority	63	63	60
User Fees	—	—	—
Headquarters/Commissioner's Office	261	290	286
Budget Authority	173	182	178
User Fees	88	108	108
GSA rent	220	239	236
Budget Authority	169	177	170
User Fees	51	62	66
Other rent and rent-related activities	162	172	169
Budget Authority	116	122	115

Table 6. (Continued)

Program area	2015 ^a	2016	2017 request
User Fees	46	50	54
Export and color certification funds	11	13	15
Budget Authority	—	—	—
User Fees	11	13	15
Food and drug safety	12	0	0
Budget Authority	12	0	0
User Fees	0	0	0
Priority review vouchers	0	8	8
Budget Authority	—	—	—
User Fees	0	8	8
Buildings & Facilities	9	9	12
Budget Authority	9	9	12
User Fees	—	—	—
Total, Program Level	4,511 ^b	4,745	4,826 ^c
Less Funds From Other Sources			
User Fees	1,903 ^d	2,017 ^e	2,084 ^f
Total, Discretionary Budget Authority	2,608 ^b	2,728	2,743

Sources: Prepared by CRS based on congressional budget justification documents and the HHS *Budget in Brief*, available at <http://www.hhs.gov/budget/>.

Notes: Individual amounts may not add to subtotals or totals due to rounding.

Consistent with the Administration and congressional committee formats, each program area includes funding designated for the responsible FDA center (e.g., the Center for Drug Evaluation and Research or the Center for Food Safety and Applied Nutrition) and the portion of effort budgeted for the agency-wide Office of Regulatory Affairs to commit to that area. It also apportions user fee revenue across the program areas as indicated in the Administration's request (e.g., 90% of the animal drug user fee revenue is designated for the animal drugs and feeds program, with the rest going to headquarters and Office of the Commissioner, GSA rent, and other rent and rent-related activities categories).

^a This column shows the FY2015 actual amounts. A "0" in this column does not reflect a lack of authorization for that program. For example, user fees for food are listed as "0," meaning that no fees were collected in FY2015 for the food program, but user fees for food were authorized in the FY2015 enacted bill.

^b The FY2015 Agriculture appropriations act provided an additional \$25 million to FDA for Ebola response and preparedness activities. Adding this amount to the FDA appropriations brought BA to \$2,633 million and the total program level to \$4,536 million for FY2015.

^c This total does not include the \$75 million in proposed new mandatory funding for the Vice President's Cancer Moonshot Initiative.

^d The FY2015 enacted bill included \$1 million for fees related to pharmacy compounding that the President's request had not included in the FY2015 request submission.

^e The FY2016 enacted bill included \$1 million for fees related to pharmacy compounding (Congressional Budget Office estimate) that the President's request had not included in the FY2016 request submission.

^f For user fees in the Administration's FY2017 request, this column shows only those that have been authorized. Including the \$202 million in proposed user fees, the President's total user fee request is \$2.286 billion, yielding a total program level request of \$5.029 billion.

The President's FY2017 budget request was for a *total program level* of \$4.826 billion, an increase of \$81 million (+2%) from the FY2016 total program level of \$4.745 billion (see Table 6). The FY2017 budget request includes \$2.743 billion for budget authority, an increase of \$15 million (+0.5%) compared to the FY2016 enacted level of \$2.728 billion, and \$2.084 billion for user fees, an increase of \$66 million (+3%) compared to the FY2016 enacted level of \$2.017 billion. In addition to the \$2.084 billion in user fees from currently authorized programs, the President requested \$202 million in as yet unauthorized fees to support export certification, food facility registration and inspection, food import, international courier,

cosmetics, and food contact substance notification activities. With those proposed fees, the President's total user fee request was \$2.286 billion, bringing the total program level request to \$5.029 billion. The FY2017 request also included \$75 million in new mandatory resources to support the Cancer Moonshot Initiative.⁵³

HEALTH RESOURCES AND SERVICES ADMINISTRATION (HRSA)⁵⁴

Agency Overview

HRSA is the federal agency charged with improving access to health care for those who are uninsured, isolated, or medically vulnerable. The agency currently awards funding to more than 3,000 grantees, including community-based organizations; colleges and universities; hospitals; state, local, and tribal governments; and private entities to support health services projects, such as training health care workers or providing specific health services.⁵⁵ HRSA also administers the health centers program, which provides grants to non-profit entities that provide primary care services to people who experience financial, geographic, cultural, or other barriers to health care.⁵⁶

HRSA Bureaus

The *Bureau of Primary Health Care* administers the Health Centers program, authorized under Title III of the PHSA. Community and other health centers provide access to primary care for individuals who are low-income, uninsured, or living where health care is scarce.

The *Bureau of Health Workforce* administers scholarship, loan and loan repayment programs that help underserved communities recruit and retain health professionals. These programs include the National Health Service Corps, NURSE Corps, and the Faculty Loan Repayment Program. The bureau also administers a number of programs for health professions training and development of diversity and cultural competence in the health workforce. These programs include the Oral Health Training Program, the Nursing Workforce Diversity Program, the Children's Hospitals Graduate Medical Education Program, the Teaching Health Center Graduate Medical Education program funded under ACA, and the Scholarships for Disadvantaged Students Program. The Bureau of Health Professions also administers the National Practitioner and Healthcare Integrity Protection Data Banks and the National Center for Health Workforce Analysis. Titles III, VII, and VIII of the PHSA authorize programs in this bureau.

The *Maternal and Child Health Bureau* administers the Maternal and Child Health Block Grant and other programs that support the infrastructure for maternal and child health services, including the Maternal, Infant, and Early Childhood Home Visiting Program that was authorized and funded by ACA. These programs are authorized in Title V of the Social Security Act (SSA). This bureau also administers Healthy Start, newborn hearing screening, autism, and other programs authorized under Titles III, XI, XII, and XIX of the PHSA.

The *HIV/AIDS Bureau* administers the Ryan White HIV/AIDS program, which is the largest discretionary grant program within HRSA and is focused on HIV/AIDS care. The Ryan White HIV/AIDS program administers grant programs that provide early intervention, minority, and family services. It also administers the AIDS Drug Assistance Program (ADAP). Title XXVI of the PHSA authorizes the Ryan White HIV/AIDS programs.

The *Healthcare Systems Bureau* provides national leadership and direction in targeted areas, such as organ and bone marrow transplantation, poison control centers, and others. It also administers the 340B drug pricing program. Titles III and XII of the PHSA authorize programs in this bureau.

Source: HRSA website, <http://www.hrsa.gov/about/organization/bureaus/index.html>.

HRSA is organized into five bureaus (see text box below) and ten offices. Some offices focus on specific populations or health care issues (e.g., Office of Women’s Health, Office of Rural Health Policy), while others provide agency-wide support or technical assistance to HRSA’s regional offices (e.g., Office of Planning, Analysis and Evaluation; Office of Regional Operations).⁵⁷

As noted in the text box, the majority of HRSA’s programs are authorized by the PHSA;⁵⁸ others are authorized by the SSA. Additionally, Section 427(e) of the Federal Mine Safety and Health Amendments Act (P.L. 95-164) authorizes the Black Lung Program, which supports clinics that provide services to retired coal miners and others.

Recent Trends in Agency Funding

HRSA funding increased from \$8.1 billion in FY2010 to \$10.8 billion in FY2016 despite a reduction in its discretionary appropriation during that time (see **Table 7**). Specifically, discretionary appropriations declined by about 17%; falling from \$7.5 billion to \$6.2 billion. Much of the decline in discretionary appropriations occurred because of the loss of discretionary appropriations for the National Health Service Corps (NHSC) and the elimination of the congressional earmark program that supported health care facility construction and renovation.

The overall growth in HRSA’s funding was primarily driven by increasing amounts from the CHCF, which more than offset the decline in discretionary funding. CHCF funding has partially supplanted (i.e., replaced) discretionary health center funding and has become the sole source of funding for the NHSC program, which has not received an annual discretionary appropriation since FY2011.

Table 7. Health Resources and Services Administration (HRSA)
(millions of dollars, by fiscal year)

Bureau or Activity	2015	2016 ^a	2017 Request
Primary Care	5,001	5,092	5,092
Health Centers	4,901	4,992	4,992
<i>Discretionary BA (non-add)</i>	<i>(1,392)</i>	<i>(1,392)</i>	<i>(1,242)</i>
<i>CHCF Transfer (non-add)</i>	<i>(3,509)</i>	<i>(3,600)</i>	<i>(3,600)</i>
<i>New mandatory proposal (non-add)</i>	—	—	<i>(150)</i>
Health Centers Tort Claims	100	100	100
Health Workforce	1,058	1,228	1,273
National Health Service Corps (NHSC)	287	310	380
<i>Discretionary BA (non-add)</i>	<i>(0)</i>	<i>(0)</i>	<i>(20)</i>
<i>CHCF Transfer (non-add)</i>	<i>(287)</i>	<i>(310)</i>	<i>(310)</i>
<i>New mandatory proposal (non-add)</i>	—	—	<i>(50)</i>
Faculty Loan Repayment Program	1	1	1
Training for Diversity ^b	82	82	85
Primary Care Training and Enhancement	39	39	39
Interdisciplinary, Community-Based Linkages ^c	73	129	105
Public Health Workforce Development	21	21	17
Nursing Workforce Development ^d	232	229	229
Children’s Hospitals GME Payments	265	295	295

Bureau or Activity	2015	2016 ^a	2017 Request
GME Targeted Support (New mandatory proposal)	—	—	(295)
Teaching Health Center GME Payments (ACA Sec.5508(c))	—	60	60
Other Health Workforce Programs ^e	39	41	41
National Practitioner Data Bank (User Fees)	19	21	21
Maternal and Child Health	1,254	1,250	1,250
Maternal and Child Health Block Grant	637	638	638
Healthy Start	102	104	104
Maternal, Infant Home Visiting (ACA Sec. 2951)	400	400	400
Family-to-Family Health Centers (ACA Sec. 5507) ^f	5	5	5
Other Maternal and Child Health Programs ^g	112	103	103
Ryan White HIV/AIDS	2,319	2,323	2,332
<i>PHS Evaluation Fund (non-add)</i>	—	—	(34)
Health Care Systems	103	103	119
Health Care Systems Programs ^h	76	76	76
Hansen's Disease Programs	17	17	17
340B Drug Pricing Programs	10	10	26
<i>User fees (non-add)</i>	—	—	(9)
Rural Health	147	150	144
Other Activities	683	685	706
Family Planning	286	286	300
Program Management	154	154	157
Vaccine Injury Compensation Program (VICP) Operations	8	8	9
VICP Trust Fund	235	237	240
Total, Program Level	10,565	10,831	10,916
Less Funds From Other Sources			
PHS Evaluation Set-Aside	—	—	34
User Fees	19	19	30
VICP Trust Fund (Mandatory)	235	237	240
ACA Mandatory Funds: CHCF Transfers	3,796	3,910	3,910
ACA Mandatory Funds: Other	5	65	65
Maternal, Infant Home Visiting	400	400	400
Proposed New Mandatory Funds	—	—	495
Total, Discretionary Budget Authority	6,112	6,197	5,743

Source: Prepared by CRS based on congressional budget justification documents and the HHS *Budget in Brief*, available at <http://www.hhs.gov/budget/>; and from P.L. 114-10.

Notes: Individual amounts may not add to subtotals or totals due to rounding.

^a Includes funds appropriated in MACRA (P.L. 114-10).

^b Training for Diversity includes the following programs: Centers for Excellence, Scholarships for Disadvantaged Students, and the Health Careers Opportunity Program.

^c Interdisciplinary, Community-based Linkages includes the following programs: Area Health Education Centers (AHEC), Geriatric Programs, and Mental and Behavioral Health Education and Training. In FY2017, the President's Budget does not request funding for the Area Health Education Center program.

^d Nursing Workforce Development includes the following programs: NURSE Corps (formerly the Nursing Education Loan Repayment and Scholarship Program); Advanced Nursing Education; Nursing Workforce Diversity; Nurse Education, Practice, Quality and Retention; Nurse Faculty Loan Program; and Comprehensive Geriatric Education.

^e Other Health Workforce Programs include Health Care Workforce Assessment, and Oral Health Training.

^f P.L. 113-93 provided \$2.5 million for this program for FY2015, which was repealed when P.L. 114-10 provided a full year of funding (\$5 million) for this program for FY2015.

^g Other Maternal and Child Health Programs include Autism and Other Developmental Disorders, Traumatic Brain Injury, Sickle Cell Services Demonstration, Universal Newborn Hearing Screening, Emergency Medical Services for Children, and Heritable Disorders.

^h Health Care Systems Programs include Organ Transplantation, National Cord Blood Inventory, C.W. Bill Young Cell Transplantation Program, and Poison Control Centers.

With CHCF funding set to expire at the end of FY2015, Congress included two more years of CHCF funding in the Medicare Access and CHIP Reauthorization Act of 2015 (MACRA);⁵⁹ see Table 7 and Appendix A. MACRA also extended funding for other HRSA programs that were established and initially funded by the ACA; notably, the Maternal, Infant, and Early Childhood Home Visiting Program and the Teaching Health Center Program.

INDIAN HEALTH SERVICE (IHS)⁶⁰

Agency Overview

IHS provides health care for approximately 2.2 million eligible American Indians/Alaska Natives through a system of programs and facilities located on or near Indian reservations, and through contractors in certain urban areas. IHS provides services to members of 566 federally recognized tribes either directly or through facilities and programs operated by Indian Tribes or Tribal Organizations through self-determination contracts and self-governance compacts authorized in the Indian Self-Determination and Education Assistance Act (ISDEAA).⁶¹

The Snyder Act of 1921 provides general statutory authority for IHS.⁶² In addition, specific IHS programs are authorized by two acts: the Indian Sanitation Facilities Act of 1959⁶³ and the Indian Health Care Improvement Act (IHCIA).⁶⁴ The Indian Sanitation Facilities Act authorizes the IHS to construct sanitation facilities for Indian communities and homes; and IHCIA authorizes programs such as urban health, health professions recruitment, and substance abuse and mental health treatment, and permits IHS to receive reimbursements from Medicare, Medicaid, the State Children's Health Insurance Program (CHIP), the Department of Veterans Affairs (VA), and third-party insurers.

As discussed earlier, IHS receives its appropriations through the Interior/Environment appropriations act. IHS funding is not subject to the PHS set-aside.

Recent Trends in Agency Funding

IHS's funding, which includes discretionary appropriations and collections from third-party payers of health care, increased between FY2010 and FY2016 from \$5.1 billion to \$6.2 billion (see Table 8). This increase was driven both by increased discretionary appropriations, which rose from \$4.1 billion to \$4.8 billion, and by increased collections, which rose from \$891 million to \$1.1 billion. Much of the funding increase was used to support clinical services. Discretionary appropriations, in particular, have increased funding for purchased/referred care, a subset of the clinical services budget line that applies to funds used to refer patients to an outside provider when the IHS cannot provide a service within its system. Funding allocated for contract support costs has also increased since FY2014.

**Table 8. Indian Health Service (IHS)
(millions of dollars, by fiscal year)**

Program or Activity	2015	2016	2017 Request
Clinical and Preventive Services	4,652	4,737	4,998
Clinical Services	4,348 ^a	4,431 ^b	4,682 ^b
<i>Purchased/Referred Care (non-add)^c</i>	<i>(914)</i>	<i>(914)</i>	<i>(962)</i>
Preventive Health	154	156	166
Special Diabetes Program for Indians ^d	150	150	150
Other Health Services	831	891	985
Urban Health Projects	44	45	48
Indian Health Professions	48	48	59
<i>Indian Health Professions Expansion (non-add)</i>	<i>—</i>	<i>—</i>	<i>(10)</i>
Tribal Management/Self-Governance	8	8	8
Direct Operations	68	72	70
Contract Support Costs ^e	663	718	800
Health Facilities	468	532	578
Maintenance and Improvement	62 ^f	83 ^g	85 ^g
Sanitation Facilities Construction	79	99	103
Health Care Facilities Construction	85	105	132
Facilities/Environmental Health Support	220	223	234
Medical Equipment	23	23	24
Total, Program Level	5,951	6,160	6,562
Less Funds from Other Sources			
Collections	1,151	1,194	1,194
Rental of Staff Quarters	8	9	9
Special Diabetes Program for Indians ^d	150	150	150
Tribal Crisis Response Fund	—	—	15 ^h
Indian Health Professions Expansion	—	—	10
Total, Discretionary Budget Authority	4,642	4,808	5,185

Sources: Prepared by CRS based on congressional budget justification documents and the HHS *Budget in Brief*, available at <http://www.hhs.gov/budget/>.

Notes: Individual amounts may not add to subtotals or totals due to rounding.

^a Includes \$1,151 million in collections from Medicare, Medicaid, CHIP, the Department of Veterans Affairs, private insurance, and other programs.

^b Includes an estimated \$1,194 million in collections from Medicare, Medicaid, CHIP, the Department of Veterans Affairs, private insurance, and other programs.

^c This was previously referred to as “Contract Health Services.”

^d PHSA Sec. 330C provides an annual appropriation of \$150 million through FY2017 for this program. As discussed earlier in this report, these mandatory funds were subject to a 2% sequestration in FY2013 and FY2014.

^e Beginning in FY2016, Contract Support Costs were funded as an indefinite discretionary appropriation. For FY2018 and beyond, the President’s Budget includes a proposal to reclassify Contract Support Costs as a mandatory three-year appropriation.

^f Includes \$8 million that IHS received from rental of staff quarters.

^g Includes \$9 million that IHS expects to receive from rental of staff quarters.

^h These funds would be available as part of a new Administration initiative to improve Tribal Behavioral Health. The initiative would include crisis response funds for Indian Tribes experiencing behavioral health crises and would increase funding for IHS scholarship and loan repayment for behavioral health providers.

Contract support costs are funds that Indian Tribes and Tribal Organizations receive, in addition to operating funds, when they operate a facility or program under an ISDEAA contract or compact. According to the U.S. Supreme Court, these costs must be fully funded even if Congress does not appropriate sufficient funds to cover all tribes’ contract support

costs. According to IHS, beginning in FY2016, the amount allocated for contract support costs is sufficient for the contracts and compacts that IHS enters into. Given the ruling that stated that these are required costs, the President's Budget includes a proposal to reclassify contract support costs as a mandatory three-year appropriation.⁶⁵

NATIONAL INSTITUTES OF HEALTH (NIH)⁶⁶

Agency Overview

NIH is the primary agency of the federal government charged with performing and supporting biomedical and behavioral research. Its activities cover a wide range of basic, clinical, and translational research, as well as research training and health information collection and dissemination. The agency is organized into 27 research institutes and centers, headed by the NIH Director. The Office of the Director (OD) sets overall policy for NIH and coordinates the programs and activities of all NIH components, particularly in areas of research that involve multiple institutes. The institutes and centers (collectively called ICs) focus on particular diseases, areas of human health and development, or aspects of research support. Each IC plans and manages its own research programs in coordination with the Office of the Director.

The bulk of NIH's budget, about 81%, goes out to the extramural research community through grants, contracts, and other awards. The funding supports research performed by more than 30,000 individuals who work at more than 2,500 universities, hospitals, medical schools, and other research institutions around the country and abroad.⁶⁷ A smaller proportion of the budget, about 11%, supports the intramural research programs of the ICs, funding research performed by NIH scientists and non-employee trainees in the NIH laboratories and Clinical Center. The remaining 6% funds various research management, support, and facilities' needs.

NIH derives its statutory authority from the PHSA. Title III, Section 301 of the PHSA grants the HHS Secretary broad permanent authority to conduct and sponsor research. In addition, Title IV, "National Research Institutes," authorizes in greater detail various activities, functions, and responsibilities of the NIH Director and the institutes and centers. All of the ICs are covered by specific provisions in the PHSA, but they vary considerably in the amount of detail included in the statutory language. There are few time-and-dollar authorization levels specified for individual activities. Congress mandated a significant reorganization of IC responsibilities in the FY2012 Consolidated Appropriations Act (P.L. 112-74, Division F) by creating a new National Center for Advancing Translational Sciences (NCATS) and eliminating the National Center for Research Resources (NCRR). Activities relating to translational sciences from NCRR and many other ICs were consolidated in NCATS, and NCRR's other programs were moved to several other ICs and the OD.

NIH gets almost its entire funding (99.5%) from annual discretionary appropriations. As shown in Table 9, the annual LHHs appropriations act provides separate appropriations to 24 of the ICs, the OD, and the Buildings and Facilities account. One of the ICs (Environmental Health Sciences) also receives funding from the Interior/Environment appropriations act. In

addition, NIH receives a mandatory annual appropriation (\$150 million) for type 1 diabetes research.

Table 9. National Institutes of Health (NIH)
(millions of dollars, by fiscal year)

Institutes and Centers (ICs)	2015	2016	2017 Request
Cancer (NCI)	4,953	5,214	5,894
Heart/Lung/Blood (NHLBI)	2,996	3,114	3,114
Dental/Craniofacial Research (NIDCR)	398	413	413
Diabetes/Digestive/Kidney (NIDDK) ^a	1,899	1,966	1,966
Neurological Disorders/Stroke (NINDS)	1,605	1,695	1,695
Allergy/Infectious Diseases (NIAID)	4,418	4,716	4,716
General Medical Sciences (NIGMS) ^b	2,372	2,512	2,512
Child Health/Human Development (NICHD)	1,287	1,338	1,338
Eye (NEI)	677	708	708
Environmental Health Sciences (NIEHS)	667	694	694
NIEHS, Interior/Environment appropriation	77	77	77
Aging (NIA)	1,198	1,598	1,598
Arthritis/Musculoskeletal/Skin (NIAMS)	522	542	542
Deafness/Communication Disorders (NIDCD)	405	423	423
Mental Health (NIMH)	1,434	1,519	1,519
Drug Abuse (NIDA)	1,016	1,051	1,051
Alcohol Abuse/Alcoholism (NIAAA)	447	467	467
Nursing Research (NINR)	141	146	146
Human Genome Research (NHGRI)	499	513	513
Biomedical Imaging/Bioengineering (NIBIB)	327	344	344
Minority Health/Health Disparities (NIMHD)	271	281	281
Complementary/Integrative Health (NCCIH) ^c	124	130	130
Advancing Translational Sciences (NCATS)	633	685	685
Fogarty International Center (FIC)	68	70	70
National Library of Medicine (NLM)	337	396	396
Office of Director (OD)	1,414	1,571	1,716
Buildings & Facilities (B&F)	129	129	129
Total, Program Level	30,311	32,311	33,136
Less Funds From Other Sources			
PHS Evaluation Set-Asideb	715	780	847
Type 1 Diabetes Research (NIDDK) ^d	150	150	150
Proposed New Mandatory Funds	—	—	1,825
Total, Discretionary Budget Authority	29,446	31,381	30,314

Sources: Funding amounts for FY2015 and FY2016 are taken from the FY2016 Justification of Estimates for Appropriation Committees, Vol. 1, Overview, table on “Budget Request for Institute and Center,” p.85 at <http://officeofbudget.od.nih.gov/br.html>.

Notes: Totals may differ from the sum of the components due to rounding.

^a Amounts for the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) include \$150 million in mandatory funding for type 1 diabetes research (see note e).

^b Amounts for National Institute of General Medical Sciences (NIGMS) include the PHS set-aside funds.

^c Reflects name change from National Center for Complementary and Alternative Medicine to National Center for Complementary and Integrative Health; provision included in P.L. 113-235.

^d Mandatory funds available to NIDDK for type 1 diabetes research under PHS §330B (provided by P.L. 114-10 for FY2016 and FY2017).

Recent Trends in Agency Funding

Between FY1994 and FY1998, funding for NIH grew from \$11.0 billion to \$13.7 billion in nominal terms. Over the next five years, Congress doubled the NIH budget to \$27.2 billion in FY2003. In each of these years, the agency received annual funding increases of 14% to 16%. Since FY2003, however, NIH funding has increased more gradually in nominal dollars. Funding peaked in FY2010 before declining in FY2011 through FY2013 with small increases in subsequent years. The NIH program level in FY2016 is \$32.311 billion.

For FY2017, the Obama Administration requests an NIH program level total of \$33.136 billion, an increase of \$825 million (2.6%) over FY2016. The FY2017 program level request includes \$847 million in PHS set-aside funds and \$1.825 billion in proposed new mandatory funding. The FY2017 request includes \$755 million for the Vice President's Cancer Moonshot, of which \$680 million is allocated for the National Cancer Institute, and \$75 million would be transferred from NIH to FDA.

SUBSTANCE ABUSE AND MENTAL HEALTH SERVICES ADMINISTRATION (SAMHSA)⁶⁸

Agency Overview

SAMHSA is the lead federal agency for increasing access to behavioral health services. It supports community-based mental health and substance abuse treatment and prevention services through formula grants to the states and U.S. territories and through competitive grant programs that fund states, territories, tribal organizations, local communities, and private entities. SAMHSA also engages in a range of other activities, such as technical assistance, data collection, and workforce development.

SAMHSA and most of its programs and activities are authorized under Title V of the PHSA, which organizes SAMHSA in three centers:

- Center for Substance Abuse Treatment (CSAT)⁶⁹
- Center for Substance Abuse Prevention (CSAP)⁷⁰
- Center for Mental Health Services (CMHS)⁷¹

Each center has general statutory authority, called Programs of Regional and National Significance (PRNS), under which it has established grant programs for states and communities to address their important substance abuse and mental health needs. PHSA Title V also authorizes a number of specific grant programs, referred to as categorical grants.

SAMHSA's two largest grant programs are separately authorized under PHSA Title XIX, Part B. The Community Mental Health Services block grant falls within CMHS.⁷² The full amount of the Substance Abuse Prevention and Treatment block grant falls within CSAT, although no less than 20% of each state's block grant must be used for prevention.⁷³

In addition to the three statutorily defined centers, SAMHSA's budget reflects a fourth category, "health surveillance and program support," for other activities such as collecting data, providing statistical and analytic support, raising public awareness, developing the

behavioral health workforce, and maintaining the National Registry of Evidence-based Programs and Practices.⁷⁴

The last comprehensive reauthorization of SAMHSA and its programs occurred in 2000 as part of the Children’s Health Act,⁷⁵ which also added “charitable choice” provisions allowing religious organizations to receive funding for substance abuse prevention and treatment services without altering their religious character.⁷⁶ Since 2000, Congress has expanded some of SAMHSA’s programs and activities without taking up comprehensive reauthorization. Although authorizations of appropriations for most of SAMHSA’s grant programs expired at the end of FY2003, many of these programs continue to receive annual discretionary appropriations.

Recent Trends in Agency Funding

Over the past 10 years (FY2007–FY2016), SAMHSA’s program-level funding has increased by 12%, from \$3.3 billion to \$3.7 billion. It has not, however, increased every year. For example, it decreased from FY2012 (\$3.6 billion) to FY2013 (\$3.4 billion) due to sequestration, then rebounded in FY2014 (\$3.6 billion).

Relative to FY2016, SAMHSA’s FY2017 request would increase program-level funding by 16% (to \$4.3 billion) while decreasing discretionary budget authority by 3% (to \$3.5 billion); see Table 10. It would make up the difference with increased PHS set-aside funds, increased PPHF transfers, and new mandatory funding proposed for FY2017 and FY2018. The proposed new mandatory funding would support three programs: (1) State Targeted Response Cooperative Agreements, which would aim to increase access to opioid addiction treatment by addressing the most commonly identified barriers to treatment; (2) Evidence-based Early Interventions, which would provide formula grants to states to support early interventions for individuals with serious mental illness; and (3) Cohort Monitoring and Evaluation of Medication-Assisted Treatment, which would evaluate addiction treatment outcomes with the goal of increasing effectiveness.

Table 10. Substance Abuse and Mental Health Services Administration (SAMHSA)
(millions of dollars, by fiscal year)

Program or Activity	2015	2016 ^a	2017 Request
Center for Mental Health Services (CMHS)	1,071	1,159	1,274
Mental Health Block Grant	483	533	533
<i>PHS Evaluation Set-Aside (non-add)</i>	<i>(21)</i>	<i>(21)</i>	<i>(21)</i>
Programs of Regional & National Significance	371	407	406
<i>PHS Evaluation Set-Aside (non-add)</i>	—	—	<i>(10)</i>
<i>PPHF Transfer (non-add)</i>	<i>(12)</i>	<i>(12)</i>	<i>(10)</i>
Children’s Mental Health Services	117	119	119
PATH Homeless Formula Grant	65	65	65
Protection & Advocacy Formula Grant	36	36	36
Evidence-Based Early Interventions (New mandatory proposal)	—	—	115
Center for Substance Abuse Treatment (CSAT)	2,181	2,192	2,661
Substance Abuse Block Grant	1,820	1,858	1,858

Table 10. (Continued)
(millions of dollars, by fiscal year)

Program or Activity	2015	2016 ^a	2017 Request
<i>PHS Evaluation Set-Aside (non-add)</i>	(79)	(79)	(79)
Programs of Regional & National Significance	361	334	343
<i>PHS Evaluation Set-Aside (non-add)</i>	(2)	(2)	(30)
<i>Monitoring & Evaluation of MAT Outcomes (New mandatory proposal, non-add)</i>	—	—	
<i>State Targeted Response Cooperative Agreements (New mandatory proposal)</i>	—	—	460
<i>Center for Substance Abuse Prevention (CSAP)</i>	175	211	211
<i>Programs of Regional & National Significance</i>	175	211	211
<i>PHS Evaluation Set-Aside (non-add)</i>	—	—	
<i>Health Surveillance and Program Support</i>	159	169	175
<i>Health Surveillance and Program Support^b</i>	119	127	125
<i>PHS Evaluation Set-Aside (non-add)</i>	(30)	(30)	(29)
<i>PPHF Transfer (non-add)</i>	—	—	(18)
<i>Public Awareness and Support</i>	13	16	13
<i>PHS Evaluation Set-Aside (non-add)</i>	—	—	(13)
<i>Performance & Quality Information Systems</i>	13	13	13
<i>PHS Evaluation Funds (non-add)</i>	—	—	(13)
<i>Agency-Wide Initiatives</i>	12	13	23
<i>PHS Evaluation Set-Aside (non-add)</i>	(1)	(1)	(1)
<i>Data Request and Publications User Fees</i>	2	2	2
<i>Total, Program Level</i>	3,586	3,731	4,322
<i>Less Funds From Other Sources</i>	—	—	—
<i>PHS Evaluation Set-Aside</i>	134	134	214
<i>PPHF Transfers</i>	12	12	28
<i>Data Request and Publications User Fees</i>	2	2	2
<i>Proposed New Mandatory Funds</i>	—	—	590
<i>Total, Discretionary Budget Authority</i>	3,439	3,584	3,489

Sources: Prepared by CRS based on congressional budget justification documents and the HHS *Budget in Brief*, available at <http://www.hhs.gov/budget/>.

Notes: Individual amounts may not add to subtotals or totals due to rounding.

^a Amounts may change during the year due to transfers, reprogramming, or other adjustments.

^b For the FY2015, FY2016, and FY2017 request amounts, SAMHSA's FY2017 budget request indicates that the figures have been comparably adjusted to reflect (1) the proposed transfer of one program (the Behavioral Health Workforce Education and Training Program) from SAMHSA to HRSA in FY2017, and (2) a proposed single appropriation for a program (the Minority Fellowship Program) that is currently funded through multiple SAMHSA centers.

APPENDIX A. COMMUNITY HEALTH CENTER FUND

ACA Section 10503 established a Community Health Center Fund (CHCF) to provide supplemental funding for community and other health centers and the National Health Service Corps (NHSC). The law provided annual appropriations to the CHCF totaling \$11 billion over the five-year period FY2011 through FY2015. Of that total, \$9.5 billion was for health center operations and the remaining \$1.5 billion was for the NHSC.

The Medicare Access and CHIP Reauthorization Act of 2015 (MACRA)⁷⁷ appropriated two more years of funding to the CHCF. For both FY2016 and FY2017, MACRA provided \$3.6 billion for health center operations and \$310 million for the NHSC.

CHCF funding has partially supplanted discretionary funding for the health center program and entirely replaced discretionary funding for the NHSC (see Table 7).

Table A-1 shows the amounts appropriated to the CHCF for each fiscal year as well as the post-sequestration levels for FY2013-FY2015. As discussed earlier in this report, the FY2016 CHCF funding was not subject to sequestration. CHCF funds are awarded to the various types of health centers that are supported by the federal health center program. Those include community health centers and migrant health centers, as well as facilities that serve the homeless and residents of public housing. Sequestration of CHCF funding for community health centers and migrant health centers is capped at 2%, whereas CHCF funding for the other types of facilities (i.e., health centers for the homeless and for public housing residents) and for the NHSC is fully sequestrable at the applicable rate for nonexempt nondefense mandatory spending (see Table 2).

Table A-1. Community Health Center Fund, FY2011-FY2017
(millions of dollars, by fiscal year)

Program	2011	2012	2013	2014	2015	2016	2017	Total
Health Center Program	1,000	1,200	1,500	2,200	3,600	3,600	3,600	16,700
<i>Post-sequestration (non-add)</i>	—	—	(1,465)	(2,145)	(3,509)	—	(3,510)	
National Health Service Corps	290	295	300	305	310	310	310	2,120
<i>Post-sequestration (non-add)</i>	—	—	(285)	(283)	(287)	—	(289)	
Total	1,290	1,495	1,800	2,505	3,910	3,910	3,910	18,820

Sources: Prepared by CRS based on ACA Section 10503, MACRA Section 221, and the HHS *Budget in Brief* (FY2015-FY2017), available at <http://www.hhs.gov/budget/>.

Notes: The ACA also included a one-time appropriation of \$1.5 billion for health center construction and renovation. Those funds are separate from the CHCF and are not included in this table.

APPENDIX B. PREVENTION AND PUBLIC HEALTH FUND (PPHF)

ACA Section 4002 established the Prevention and Public Health Fund (PPHF), to be administered by the HHS Secretary, and provided it with a *permanent annual appropriation*. Under the ACA as originally enacted, PPHF's annual appropriation would increase from \$500 million for FY2010 to \$2 billion for FY2015 and each subsequent fiscal year. However, the Middle Class Tax Relief and Job Creation Act of 2012 amended the ACA by reducing the PPHF appropriation from FY2013 through FY2021 as part of a package of offsets to help cover the costs of the law.⁷⁸ The PPHF annual appropriation is now \$1 billion through FY2017, and thereafter will increase in increments to \$2 billion for FY2022 and each subsequent fiscal year.

The HHS Secretary is instructed to transfer amounts from the PPHF to agencies for prevention, wellness, and public health activities. The funds are available to the Secretary at the beginning of each fiscal year. The Administration's annual budget sets out the intended distribution and use of PPHF funds for that fiscal year. The Secretary determined the

distribution of PPHF funds for FY2010 through FY2013. For FY2014 through FY2016, provisions in appropriations acts explicitly directed the distribution of PPHF funds, prohibiting the Secretary from making further transfers.⁷⁹

As discussed earlier in the report, the PPHF appropriation is fully sequestrable at the applicable percentage rate for nonexempt nondefense mandatory spending (see Table 2). Sequestration is applied to the entire appropriation by the Secretary before funds are transferred to the agencies.

**Table B-1. PPHF transfers to HHS agencies
(millions of dollars, by fiscal year)**

Agency	2010	2011	2012	2013	2014	2015	2016	2017 Proposal ^a
ACL	0	0	20	9	28	28	28	28
AHRQ	6	12	12	6	7	0	0	0
CDC	192	611	809	463	831	886	892	944
CMS	0	0	0	454 ^b	0	0	0	0
HRSA	271	20	37	2	0	0	0	0
OS	12	19	30	0	0	0	0	0
SAMHSA	20	88	92	15	62	12	12	28
Sequester	—	—	—	51	72	73	68	—
Total	500	750	1,000	1,000	1,000	1,000	1,000	1,000

Sources: Prepared by CRS from HHS agency congressional budget justifications, <http://www.hhs.gov/budget/>; HHS, “Prevention and Public Health Fund,” funding distribution tables, <http://www.hhs.gov/open/recordsandreports/prevention/index.html>; and Prevention and Public Health Fund transfer tables in explanatory statements accompanying appropriations for FY2014 through FY2016.

Notes: Individual amounts may not add to totals due to rounding. ACL is the Administration for Community Living; OS is the Office of the HHS Secretary.

^a Distribution proposed by the Administration. This is not a budget request, as PPHF funds have already been appropriated. Amounts do not reflect the 6.9% sequestration (i.e., \$69 million) for FY2017 required under current law; see Table 2.

^b Funds were used for implementation of insurance exchanges under the ACA. CMS, *Justification of Estimates for Appropriations Committees, Fiscal Year 2015*, p. 349, <http://www.hhs.gov/budget/>.

The distribution of PPHF funds to HHS agencies for FY2010 through the FY2017 President’s budget proposal is presented in Table B-1. Further details regarding PPHF distributions to CDC and SAMHSA are provided in the respective agency budget tables in the body of this report.

For FY2013, the Secretary transferred almost half of available PPHF funds to CMS for ACA implementation, as shown in Table B-1. This transfer reduced the PPHF funds that had been initially allocated to CDC and other PHS agencies. Along with the sequestration of discretionary⁸⁰ funding in FY2013, the loss of PPHF funds that year had a significant effect on CDC’s budget.

In determining the transfer of PPHF funds for FY2010 through FY2013, the Secretary funded a mix of pre-existing programs and activities, and programs and activities newly authorized under the ACA. In directing the distribution of FY2014, FY2015, and FY2016 PPHF funds, annual appropriations acts (and accompanying report language) in most cases funded pre-existing programs and activities. In some cases the PPHF contribution for FY2016 made up more than 50% of a program’s total funding. Examples include CDC immunization grants to states (54%) and tobacco prevention activities (60%). The CDC Preventive Health

and Health Services Block Grant and the lead poisoning prevention program received 100% of their FY2016 funding from the PPHF.

APPENDIX C. PATIENT-CENTERED OUTCOMES RESEARCH TRUST FUND

ACA Section 6301(e) established the Patient-Centered Outcomes Research Trust Fund (PCORTF) to support comparative clinical effectiveness research at both HHS and the Patient-Centered Outcomes Research Institute (PCORI).⁸¹ The law provided annual funding to the PCORTF over the period FY2010-FY2019 from the following three sources: (1) annual appropriations; (2) fees on health insurance and self-insured plans; and (3) transfers from the Medicare Part A and Part B trust funds.

Specifically, the ACA appropriated the following amounts to the PCORTF: (1) \$10 million for FY2010; (2) \$50 million for FY2011; and (3) \$150 million for each of FY2012 through FY2019. In addition, for each of FY2013 through FY2019, the ACA appropriated an amount equivalent to the net revenues from a new fee that the law imposes on health insurance policies and self-insured plans. For policy/plan years ending during FY2013, the fee equals \$1 multiplied by the number of covered lives. For policy/plan years ending during each subsequent fiscal year through FY2019, the fee equals \$2 multiplied by the number of covered lives. Finally, transfers to PCORTF from the Medicare Part A and Part B trust funds are calculated by multiplying the average number of individuals entitled to benefits under Medicare Part A, or enrolled in Medicare Part B, by \$1 (for FY2013) or by \$2 (for each of FY2014 through FY2019).

For each of FY2011 through FY2019, the ACA requires 80% of the PCORTF funds to be made available to PCORI, and the remaining 20% of funds to be transferred to the HHS Secretary for carrying out PHSA Section 937.⁸² Of the total amount transferred to HHS, 80% is to be distributed to AHRQ. Table C-1 shows the allocation of PCORTF funds through FY2017.

**Table C-1. Distribution of PCORTF funding
(millions of dollars, by fiscal year)**

Funding Recipient	2011	2012	2013	2014	2015	2016 Est.	2017 Est.
PCORI	40	120	289	376	396	472	530
HHS	10	30	72	94	99	118	132
AHRQ (non-add)	(8)	(24)	(58)	(75)	(80)	(94)	(106)
Office of the Secretary (non-add)	(2)	(6)	(14)	(19)	(19)	(24)	(26)
Total	50	150	361	470	495	590	662

Source: CRS calculations using data provided in Office of Management and Budget, *Budget of the U.S. Government*, Appendix (FY2013-FY2017).

APPENDIX D. FDA USER FEE AUTHORIZATIONS

**Table D-1. FDA user fee authorizations and revenue
(millions of dollars, in order of fy2016 anticipated revenue)**

User Fee	Initial Authorizing Legislation and Year	FY2016 Revenue
Prescription drug	Prescription Drug User Fee Act (PDUFA), 1992(P.L. 102-300)	851
Tobacco product	Family Smoking Prevention and Tobacco Control Act, 2009 (P.L. 111-31)	599
Generic drug	Food and Drug Administration Safety and Innovation Act (FDASIA), 2012(P.L. 112-144)	318
Medical device	Medical Device User Fee and Modernization Act (MDUFMA), 2002(P.L. 107-250)	138
Animal drug	Animal Drug User Fee Act (ADUFA), 2003(P.L. 108-130)	23
Biosimilars	Food and Drug Administration Safety and Innovation Act (FDASIA), 2012 (P.L. 112-144)	22
Mammography	Mammography Quality Standards Act (MQSA), 1992(P.L. 102-539)	20
Animal generic drug	Animal Generic Drug User Fee Act (AGDUFA), 2008 (P.L. 110-316)	10
Color certification	Color Additive Amendments of 1960(P.L. 86-618)	9
Rare pediatric disease priority review voucher	Prescription Drug User Fee Amendments of 2012(P.L. 112-144)	8
Food reinspection	Food Safety Modernization Act (FSMA), 2011 (P.L. 111-353)	6
Voluntary qualified importer (VQIP)	Food Safety Modernization Act (FSMA), 2011(P.L. 111-353)	5
Export certification	FDA Export Reform and Enhancement Act of 1996 [for medical products](P.L. 104-134); Food Safety Modernization Act (FSMA), 2011 [for foods](P.L. 111-353)	5
Food recall	Food Safety Modernization Act (FSMA), 2011 (P.L. 111-353)	1
Outsourcing facility	Drug Quality and Security Act (DQSA), 2013(P.L. 113-54)	1
Third party auditor program	Medical Device User Fee and Modernization Act (MDUFMA), 2002 (P.L. 107-250)	1
Tropical disease priority review voucher	Food and Drug Administration Amendments Act (FDAAA), 2007(P.L. 110-85)	0
Total		2,017

Source: FY 2017 FDA Justification of Estimates for Appropriations Committees, All Purpose Table, <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/BudgetReports/UCM485237.pdf>.

END NOTES

¹ HHS also includes three human services agencies that are not part of the Public Health Service: (1) the Administration for Children and Families (ACF); (2) the Administration for Community Living (ACL), which was created in April 2012 by consolidating the Administration on Aging (AoA), the HHS Office on Disability, and ACF's Administration on Developmental Disability; and (3) the Centers for Medicare & Medicaid Services (CMS). Departmental leadership is provided by the Office of the Secretary (OS), which is comprised of various staff divisions including the Assistant Secretary for Preparedness and Response (ASPR), the Assistant Secretary for Health (ASH), the Office of the Surgeon General, the Office for Civil Rights (OCR), the Office of Inspector General (OIG), and the Office of the National Coordinator for Health Information Technology (ONC). For more information on HHS and links to the PHS agency websites, see <http://www.hhs.gov/>.

² 42 U.S.C. §§201 et seq.

³ 21 U.S.C. §§301 et seq.

⁴ SSA Title V, 42 U.S.C. §§701 et seq.

⁵ 25 U.S.C. §§1601 et seq.

⁶ 42 U.S.C. §9604(i).

⁷ Budget authority is the authority provided in federal law to incur financial obligations that will result in expenditures, or outlays, of federal funds. Such obligations include contracts for the purchase of supplies and services, liabilities for salaries and wages, and grant awards. Appropriations are the most common form of budget authority. Discretionary budget authority represents funding that is provided in and controlled by the annual appropriations acts.

⁸ For an overview of each of these three appropriations acts, see CRS Report R44287, Labor, Health and Human Services, and Education: FY2016 Appropriations; CRS Report R44061, Interior, Environment, and Related Agencies: FY2016 Appropriations; and CRS Report R44240, Agriculture and Related Agencies: FY2016 Appropriations.

⁹ The HHS Secretary's FY2016 transfer authority was provided in Section 205 of the FY2016 LHHS appropriations act (P.L. 114-113, Division H).

¹⁰ The ACA was signed into law on March 23, 2010 (P.L. 111-148, 124 Stat. 119). On March 30, 2010, the President signed the Health Care and Education Reconciliation Act (HCERA; P.L. 111-152, 124 Stat. 1029), which included several new health reform provisions and amended numerous provisions in the ACA. Several subsequently enacted bills made additional changes to selected ACA provisions. All references to the ACA in this report refer collectively to the law and to the changes made by HCERA and subsequent legislation.

¹¹ For more discussion of ACA implementation funding, see CRS Report R43066, Federal Funding for Health Insurance Exchanges.

¹² Since FY2014, annual appropriations acts have included a provision instructing the HHS Secretary to use the PHS set-aside funds for the "evaluation ... and the implementation and effectiveness" of programs funded in the HHS title of the LHHS appropriations act. Previously such provisions had restricted tap funds to the "evaluation ... of the implementation and effectiveness" of programs authorized under the PHSA [emphasis added]. The current provision can be found in P.L. 114-113, Division H, Section 205.

¹³ P.L. 114-113, Division H, Section 204.

¹⁴ Only funds appropriated for activities and programs authorized by the PHSA are subject to an assessment. Thus, most of the funds appropriated for CDC, HRSA, NIH, and SAMHSA are assessed. The annual LHHS appropriations act excludes some funding from the set-aside; still other funding is excluded by convention. For example, funds appropriated for HHS block grants targeting prevention, substance abuse, and mental health as well as funds for program management activities and for buildings and facilities are typically excluded from the set-aside. Funding for agencies (e.g., ATSDR, FDA, IHS) and programs (e.g., HRSA's maternal and child health block grant) that are not authorized by the PHSA are also excluded.

¹⁵ For more information see CRS Report R44136, The Agency for Healthcare Research and Quality (AHRQ) Budget: Fact Sheet.

¹⁶ Mandatory spending, also known as direct spending, refers to outlays from budget authority that is provided in laws other than annual appropriations acts. Mandatory spending includes spending on entitlement programs.

¹⁷ For a complete list and discussion of all the appropriations in the ACA, including details of the obligation of these funds, see CRS Report R41301, Appropriations and Fund Transfers in the Affordable Care Act (ACA).

¹⁸ ACA Section 10503(a)-(b).

¹⁹ P.L. 114-10, 129 Stat. 87.

²⁰ ACA Section 4002, as amended; 42 U.S.C. §300u-11.

²¹ ACA Section 6301(d)-(e).

²² These user fees are listed in the agency-specific tables in this report.

²³ P.L. 102-571, 106 Stat. 4491.

²⁴ P.L. 112-25, 125 Stat. 240. The BCA amended the Balance Budget and Emergency Deficit Control Act of 1985 (BBEDCA; P.L. 99-177; Title II, 99 Stat. 1038). For more information, see CRS Report R41965, The Budget Control Act of 2011.

²⁵ While a full accounting of this anomaly is beyond the scope of this report, the following programs listed in the tables in the report were not sequestered in the years indicated in parentheses because there were no mandatory budgetary resources at the time the sequestration was ordered: (1) CHCF – health centers, NHSC (FY2016); (2) Maternal, Infant, and Early Childhood Home Visiting program (FY2015, FY2016); (3) Family-to-Family Information Centers (FY2014, FY2015, FY2016); and (4) IHS and NIH mandatory diabetes funding (FY2015, FY2016).

²⁶ P.L. 113-67, Division A; 127 Stat. 1165.

²⁷ P.L. 114-74, 129 Stat. 584.

²⁸ ATSDR and its budget are included in the discussion of CDC.

²⁹ All the budget documents and operating plans are available at <http://www.hhs.gov/budget/>.

³⁰ This section was written by Amanda K. Sarata, Specialist in Health Policy.

³¹ See the AHRQ website at <http://www.ahrq.gov>.

³² FY2009 was the one exception. AHRQ received a supplemental discretionary appropriation that year from the American Recovery and Reinvestment Act of 2009 (P.L. 111-5).

³³ This section was written by Sarah A. Lister, Specialist in Public Health and Epidemiology.

³⁴ See the CDC website at <http://www.cdc.gov/about/organization/mission.htm>.

³⁵ Information about CDC's organization is available at <http://www.cdc.gov/about/organization/cio.htm>.

³⁶ For example, PHSA Section 301 authorizes the Secretary of HHS to conduct research and investigations as necessary to control disease, and Section 317 authorizes the Secretary to award grants to states for preventive health programs.

³⁷ 29 U.S.C. §671.

³⁸ 42 U.S.C. §247b-4.

³⁹ 42 U.S.C. §242k.

⁴⁰ 42 U.S.C. §9604(i).

⁴¹ See CDC, Procurements and Grants, <http://www.cdc.gov/about/business/funding.htm>.

⁴² See CDC, Vaccines for Children Program, <http://www.cdc.gov/vaccines/programs/vfc/index.html>.

⁴³ See CDC, EEOICPA, "Frequently Asked Questions," <http://www.cdc.gov/niosh/ocas/faqsact.html>.

⁴⁴ See CDC, World Trade Center Health Program, <http://www.cdc.gov/wtc/index.html>.

⁴⁵ CRS Report R41301, Appropriations and Fund Transfers in the Affordable Care Act (ACA). See more information about the PPHF in Appendix B of this report.

⁴⁶ Budget details are available in CDC, "FY 2017 CDC Budget Overview," table on pp. 10-12, February, 2016, <http://www.cdc.gov/budget/fy2017/congressional-justification.html>.

⁴⁷ CDC, "FY 2015–2019 Ebola Response Funding," <http://www.cdc.gov/budget/ebola/index.html>. See also CRS Report R44460, Zika Response Funding: In Brief.

⁴⁸ This section was written by Agata Dabrowska, Analyst in Health Policy.

⁴⁹ 21 U.S.C. §§301 et seq.

⁵⁰ PHSA Section 351 (21 U.S.C. §262) authorizes the regulation of biological products and states that FFDCA requirements apply to biological products licensed under the PHSA. A listing of other laws containing provisions for which FDA is responsible is at <http://www.fda.gov/RegulatoryInformation/Legislation/default.htm>.

⁵¹ CRS Report R42366, Prescription Drug User Fee Act (PDUFA): 2012 Reauthorization as PDUFA V; CRS Report R42508, The FDA Medical Device User Fee Program; CRS Report R40443, The FDA Food Safety Modernization Act (P.L. 111-353); CRS Report R42680, The Food and Drug Administration Safety and Innovation Act (FDASIA, P.L. 112-144).

⁵² User fees provide varying proportions of funding for several FDA programs (see Table D-1). For example, the agency's tobacco regulatory activities are entirely supported through user fees paid by tobacco product manufacturers and importers, and the toxicology program receives no user fee funds. In FY2016, fees account for 65% of the human drugs program budget, 40% of the biologics budget, 28% of the devices and radiological health budget, 16% of the animal drugs and feeds budget, and 1% of the foods budget. Appendix D of this report presents additional detail.

⁵³ For additional information about the Vice President's Cancer Moonshot, see page 12 of the FDA FY2017 Justification of Estimates for Appropriations Committees, <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/BudgetReports/UCM485237.pdf>.

⁵⁴ This section was written by Elayne J. Heisler, Specialist in Health Services.

⁵⁵ See HRSA's website at <http://www.hrsa.gov>.

⁵⁶ 42 U.S.C. §§254b.

⁵⁷ See HRSA's website at <http://www.hrsa.gov>.

⁵⁸ 42 U.S.C. §§201 et seq.

⁵⁹ P.L. 114-10, 129 Stat. 87.

⁶⁰ This section was written by Elayne J. Heisler, Specialist in Health Services.

⁶¹ P.L. 93-638; 25 U.S.C. §§450 et seq.

- ⁶² P.L. 67-85, as amended; 25 U.S.C. §13. The Snyder Act established this authority as part of the Bureau of Indian Affairs within the Department of the Interior. The Transfer Act of 1954 (P.L. 83-568) transferred this authority to the U.S. Surgeon General within the Department of Health, Education, and Welfare (now HHS).
- ⁶³ P.L. 86-121; 42 U.S.C. §2004a.
- ⁶⁴ P.L. 94-437, as amended; 25 U.S.C. §§1601 et seq., and 42 U.S.C. §§1395qq and 1396j (and amending other sections). This act was permanently reauthorized by the ACA. See CRS Report R41630, *The Indian Health Care Improvement Act Reauthorization and Extension as Enacted by the ACA: Detailed Summary and Timeline*.
- ⁶⁵ CRS Legal Sidebar WSLG119, *Supreme Court Holds the Government Liable for Contract Support Costs in Indian Self-Determination Contracts Even When Congress Fails to Appropriate Adequate Funds*.
- ⁶⁶ This section was written by Judith A. Johnson, Specialist in Biomedical Policy.
- ⁶⁷ HHS, FY2017 Budget in Brief, p. 47, <http://www.hhs.gov/sites/default/files/fy2017-budget-in-brief.pdf>.
- ⁶⁸ This section was written by Erin Bagalman, Analyst in Health Policy.
- ⁶⁹ PHSA Title V, Part B, Subpart 1; 42 U.S.C. §§290bb et seq.
- ⁷⁰ PHSA Title V, Part B, Subpart 2; 42 U.S.C. §§290bb-21 et seq.
- ⁷¹ PHSA Title V, Part B, Subpart 3; 42 U.S.C. §§290bb-31 et seq.
- ⁷² PHSA Title XIX, Part B, Subpart I; 42 U.S.C. §§300x et seq.
- ⁷³ PHSA Title XIX, Part B, Subpart II; 42 U.S.C. §§300x-21 et seq.
- ⁷⁴ In the Consolidated Appropriations Act, 2012 (P.L. 112-74, Division F, Title II; 125 Stat. 1073) and the accompanying conference report (H.Rept. 112-331, pp. 1139-1142), Congress rejected proposed changes to SAMHSA's budget structure in the FY2012 budget request. Congress directed that future budget requests reflect the structure of the three centers (i.e., CMHS, CSAT, and CSAP) and the Health Surveillance and Program Support account. SAMHSA's subsequent budget requests have reflected this structure.
- ⁷⁵ P.L. 106-310, Titles XXXI-XXXIV.
- ⁷⁶ PHSA §1955, 42 U.S.C. §300x-65; PHSA §§581 et seq., 42 U.S.C. §§290kk et seq.
- ⁷⁷ P.L. 114-10, 129 Stat. 87.
- ⁷⁸ P.L. 112-96, Section 3205; 126 Stat. 194. Amounts in current law are codified at 42 U.S.C. §300u-11.
- ⁷⁹ See for example, for FY2015, P.L. 113-235, Consolidated and Further Continuing Appropriations Act, 2015, Sec. 219 of general provisions for Labor, Health and Human Services, and Education, 128 Stat. 2489.
- ⁸⁰ See CDC, "FY2013 Operating Plan" and "FY2013 Sequester Impacts," <http://www.cdc.gov/budget/fy2013/operating-plans.html>.
- ⁸¹ PCORI (established by ACA Section 6301(a), adding new SSA Section 1181) is a non-governmental body authorized by Congress to evaluate existing research and to conduct original research examining the relative health outcomes, clinical effectiveness, and appropriateness of different medical treatments. See <http://www.pcori.org>.
- ⁸² ACA Section 6301(b) added a new PHSA Section 937 requiring the broad dissemination of research findings published by PCORI. See Table 4.

Chapter 507

ARE CURRENT WASTEWATER TREATMENTS ENOUGH TO AVOID PUBLIC HEALTH PROBLEMS IN TUNISIA

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ABSTRACT

The reuse of treated wastewater in irrigation and to refill the aquifer became a common strategy in Tunisia to palliate the lack of water resources. However, sewage treatment processes currently used are only partially effective to remove viruses and consequently discharge of contaminated treated wastewater is a potential source of viral infections. Hepatitis A virus (HAV), hepatitis E virus (HEV), norovirus (NoV), rotavirus (RV), enterovirus (EV), astrovirus (AsV), sapovirus (SaV), adenovirus (AdV) and aichi virus (AiV) are, among enteric viruses, the major waterborne pathogens, predominantly transmitted via the faecal-oral route, and important agents implicated in gastroenteritis or hepatitis outbreaks. They are released in large quantities in raw wastewater and can survive for long periods in several environments which present an important public health hazards. Due to their persistence and low infectious dose, enteric viruses can easily infect people via water or food. Although Tunisia is considered as an endemic country for enteric viruses, routine surveillance of viral wastewater quality is not performed and data on viral epidemiology are limited. In this review we provide an overview on the prevalence of the most common enteric viruses in wastewater from different regions of Tunisia including socioeconomic data and seasonal distribution when available. Indeed, efficiency of different wastewater treatment processes for viral reduction is discussed in order to evaluate the risk associated to the wastewater in the country. Data show that RV, HAV, EV and NoV are constantly present in both raw and treated wastewater with high

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prevalence. Differences in the incidence of these viruses in wastewater within the country are linked to variations in socioeconomic and sanitary conditions, geographic area and climate. We describe also the genetic diversity of multiple pathogenic enteric viruses in sewage. Different viral reduction rates are observed demonstrating the difficulty of the present biological treatments to provide virus-free wastewater effluents. This review contributes to the understanding of the epidemiology of enteric viruses in Tunisia and underlines the need of an environmental surveillance program and official viral controls for treated wastewater. Therefore, efforts should focus on the enhancing of sewage treatment technologies to avoid a social and public health hazard.

Keywords: wastewater, enteric viruses, treatment, prevalence, STP

INTRODUCTION

Because of their arid and semi-arid climate, the Middle East and North Africa (MENA) region has only 1% of global freshwater resources (Qadir et al., 2007). The countries of the MENA depend mainly on seasonal rainfall, have very few rivers and often rely on aquifers, which some of them are non-renewable (Qadir et al., 2010). Consequently, their economies are much more sensitive to the way that water is extracted, transported and consumed than are the economies of other regions (Jagannathan et al., 2009). In addition, with the constant increasing demand of water in different sectors including agriculture, which is the main consumer of water, some of these countries are suffering from hydraulic stress and are threatened by water scarcity (Allan, 2001). Hence, most of MENA countries had established processes of integrated water resource management, which advocated new approaches for the assessment, management, and development of freshwater resources. Among these strategies, the increase of treated wastewater reuse rates, in both agriculture and industry, has been proposed as the best alternative to preserve as long as possible natural water resources in the driest part of the world (Bahri, 2008).

Tunisia is a country of MENA region, located in the extreme north of Africa, and influenced by three types of climate: Mediterranean climate in the north, semi-arid climate in the central part and desertic climate in the south. Thus, the annual rainfall is on average of 594 mm in the North, 289 mm in the Centre and only 156 mm in the extreme South (Neubert and Benabdallah, 2003). This situation made Tunisia a country with relatively limited renewable water resources, having unequalled geographical distribution. Faced to the continuous increase in water demand, due to the rapid population growth coupled with industrialization, urbanization and agricultural intensification, the country recognizes a constant drop in the availability of water resources.

As economy of Tunisia is mainly based on agriculture, irrigation consumes about 83% of the total volume of distributed water. Therefore, according to the National Sanitation Office (ONAS), a treated wastewater reuse program in agriculture, irrigation of green spaces and aquifer recharge, has been launched from the early 1980s in order to preserve water resources. However, irrigation with treated wastewater back to the year 1965 with the first perimeter of the Soukra irrigated with treated wastewater from the treatment plant of Chargaia. Thanks to initiatives taken by the State, since 1989, to encourage the use of this source and to minimize its release in the aquatic environment (Bahri and Brissaud, 1996), the policy of treated

wastewater reuse was enhanced and irrigated areas have undergone significant evolution.). The increase in wastewater production, mainly due to the urban population growth as well as the increase of public sewer connection rate, raised subsequently the annual productive reuse of treated wastewater in agriculture, reaching 120 million m³ in 1996 and 210 million m³ in 2010 (Ministère de l'Agriculture de Tunisie, 1998). From 2015, 28% of these waters (60 million m³) are reused for irrigation of 8150 hectares of agricultural areas, including citrus fruits, olives, peaches, pears, apples, pomegranates, grain and industrial crops, 1040 hectares of golf courses and 450 hectares of green spaces.

However, regulations regarding the discharge and reuse of wastewater were implemented by the Tunisian Republic (Journal Officiel de la République Tunisienne, 2010):

- Decree n° 85-86 (02-01-1985) regulates wastewater discharges in the receiving environment by setting the terms for their release from wastewater treatment plants (STPs). This decree stipulates that treated wastewater must meet the criteria established by the standard NT 106.02, approved in July 20, 1989 (INNORPI, 1989a), which regulates the discharge conditions and defines the quality of effluents according to the receiving environment (sea, lakes, rivers...). In fact, reduction values required for wastewater discharges are evaluated according to physicochemical parameters, including biochemical oxygen demand (BOD), chemical oxygen demand (COD), total suspended solids (TSS) and total phosphorus and nitrogen, bacteriological parameters, several heavy metals and some organic micro-pollutants.
- Decree n° 93-2447 (13-12-1993) specifies modalities of treated wastewater reuse in agriculture by limiting the use for only crops irrigation except vegetables, whether eaten raw or cooked (Bahri and Brissaud, 1996). It sets also the frequency of analysis for physicochemical parameters (once a month), trace elements (once every six months), and bacteriological analysis for the research of helminth eggs (once every two weeks). To be reused, treated wastewater quality must follow the standard NT106.03, approved in June 1989 (INNORPI, 1989b), which supervises the reuse of treated wastewater in agriculture in order to avoid a negative impact on public health.

Despite all the efforts made by the State to improve the quality of treated wastewater, there is neither regulation or survey program for viruses. In addition, reduced values of various parameters do not address indication of behaviour of highly stable pathogens (like viruses), and current methods of wastewater treatment are not very effective against them, which subsequently cause viral contamination of the environment. The lack of virological analysis and the inability to provide virus-free treated wastewater constitute a potential hazard to public health since the government is investigating, through pilot projects, the reuse of treated wastewater for aquifers recharge, irrigation of forests and highways, as well as for industrial use.

STPs represent the main reservoir and a spreading mechanism of all kinds of pollutants and a large variety of enteric viruses transported by urban wastewater, especially in cases of sewage system dysfunction. Tunisia was the first among Mediterranean countries to use STPs, implemented initially in big cities in order to protect citizens' health and promote their living, then on coastal areas, wetlands, small and medium communities and industrial areas. Actually, most STPs are located along the coast to protect water resources and fragile

ecosystems and to improve the quality of bathing water of coastal resorts (Bahri and Brissaud, 1996).

Many wastewater treatment processes were therefore developed and employed prior to discharge wastewater into the natural environment. The process starts with primary elimination of the bulky waste by screening, followed by secondary biological or physicochemical treatment and completed with tertiary treatment to refine the final quality of treated wastewater. Actually, Tunisia utilises both primary and biological secondary treatment processes in almost all STPs (Qadir et al., 2010). A range of biological wastewater treatment options is used, including activated sludge and lagoon processes, but treatment level varies between urban and rural areas (Qadir et al., 2010). However, with the increase in urban population, some STPs do not have the capacity to process such large volumes and consequently, retention times for wastewater become too short to be effective. Therefore, the government efforts are currently focused on the upgrade to tertiary level treatment (Melhem et al., 2014).

Human sewage can contain a wide variety of different viruses, routinely introduced in the environment through the discharge of raw and treated wastewater. The most important human pathogenic viruses are enterically transmitted and able to cause a wide spectrum of illnesses. They are transmitted primarily via faecal-oral route, either by direct contact from person to person or indirectly through consumption of contaminated water or food, being the origin of many epidemics in developing countries. However, other modes of transmission, such as sexual, parenteral and zoonosis, can be also considered. Enteric viruses are very small microorganisms, about 25 to 220 nm, non enveloped and thus very stable in the environment (Bosch et al., 2008). As obligate intracellular parasites, these viruses are unable to multiply outside the cell host and remain inert for a long period until they are ingested by accident. Once replicated, they are shed in very high numbers in the faeces of infected persons, up to 10^{11} viral particles per gram of stool, reaching then wastewater treatment plants before to be released in the environment. In water, they are preferentially adsorbed to settleable suspended solids (clay, sand, sediment) that protect them against environmental stressors, allowing their concentration in sediments and preserving their infectivity. Due to their great resistance to physical and chemical agents, their low infectious dose, their high concentrations in faeces (Patel et al., 2009), enteric viruses can, through the discharge of wastewater, easily contaminate soil, water and food.

Enteric viruses are classified into three main groups according to pathologies they produce in humans. The first group includes mainly norovirus (NoV), rotavirus (RV), sapovirus (SV), adenovirus (AdV), astroviruses (AsV) and aichi virus (AiV), causing acute gastroenteritis. The second group includes hepatitis A virus (HAV) and hepatitis E virus (HEV) that are responsible of acute enterically transmitted hepatitis. Enteroviruses (EV), members of the third group, can migrate to other organs after replication in the intestinal tract, causing lesions of the central nervous system, gastrointestinal tract infections, respiratory infections, mucocutaneous infections and conjunctivitis (Koopmans and Duizer, 2004).

In Tunisia, little is known about prevalence of these viruses in wastewater and only major pathogenic agents, such as HAV, HEV, NoV, RV, EV and AiV were studied.

HEPATITIS A VIRUS

Hepatitis A virus (HAV) is the only representative of the genus *Hepatovirus* in the family *Picornaviridae* and the etiological agent of acute hepatitis A (Bosch et al., 2008; Lu et al., 2004). It is a linear single-stranded ribonucleic acid virus (RNA), non-enveloped with approximately 7.5 kb genome, protected within an icosahedral capsid (Pintó et al., 2012). HAV has been classified into six genotypes (I to VI) (Costa-Mattioli et al., 2002; Lu et al., 2004; Cristina and Costa-Mattioli, 2007) and a single serotype (Sanchez et al., 2002; Hollinger and Emerson, 2007; Perez-Sautu et al., 2011). The first three genotypes (I, II and III), subdivided into two subtypes A and B (Byun et al., 2001), were isolated from humans while the other three (IV, V and VI) were isolated only from simian species who developed a hepatitis A-like disease (Nainan et al., 1991; Tsarev et al., 1991).

HAV is more resistant in the water environment than other picornavirus: It is found in tap water after 60 days (Enriquez et al., 1995) and in the sterile mineral water after 89 days (Debord and Buisson, 1998). It can also survive for up to 8 weeks in groundwater (Sobsey et al., 1989), over 6 weeks in the river waters (Springthorpe et al., 1993), and up to 30 weeks in sea water (Crance et al., 1998).

Waterborne transmission of HAV may occur in different ways, either by consumption of contaminated water (Kukkula et al., 1997) or during recreational activities (Fleisher et al., 1996). Since HAV is excreted in faeces in a large number of copies (up to 10^{11} copies/g of faeces) (Costafreda et al., 2006; Pinto et al., 2012), transmission is facilitated by poor sanitation (Jacobsen and Koopman, 2005). Furthermore, the use of contaminated wastewater in irrigation of green areas or in agriculture may also be the origin of several cases of hepatitis A (Koopmans and Duizer, 2004; Bosch et al., 2008). In addition, their release in seawater presents a potential risk to public health, given that the virus is concentrated by filter-feeder organisms such as mussels and oysters and their consumption, either raw or undercooked, is associated sometimes in the appearance of large scale epidemics (Costafreda et al., 2006; Pintó et al., 2009; Rodríguez-Lázaro et al., 2012). Secondly, food washed with contaminated water and eaten raw may constitute a source of infection.

In Tunisia, hepatitis A remains endemic, with high/intermediate ranking (Letaief et al., 2005; Rezig et al., 2008; Gharbi-Khelifi et al., 2007; Melhem et al., 2014; Ouardani et al., 2015), occurring primarily in young children at high rates. HAV serologic studies conducted in the 2000s in different regions, depending on age, have shown high prevalence, in young children aged under 10 years (44% - 84%) as well as children aged from 10 to 15 years (59% - 91%) and teens aged from 16 to 25 years (83% - 92%). The prevalence of infection varies between urban and rural areas, according to the development of regions, hygienic conditions and sewage facilities (Letaief et al., 2005; Rezig et al., 2008). However, in many urban areas, hepatitis incidence has not been reduced although the improvement of hygiene conditions in those areas. As hepatitis A disease may be symptomatic or not, detectable HAV in wastewater would provide an important overview of its spread in the general population (Ouardani et al., 2015). Several reports, conducted in the country on raw and treated wastewater samples, showed high HAV rates ranging between 46% and 68.3% and high HAV loads up to 1.68×10^9 genome copies(GC)/L, suggesting the important role of this source of viruses in the transmission of the disease (Gharbi-Khelifi et al., 2007; Béji-Hamza et al., 2014; Ouardani et al., 2015, 2016).

Despite of the potential public health hazard linked to the lack of good sanitation and the use of contaminated treated sewage, few studies have been carried out in Tunisia on the seasonal and geographical distribution of HAV in the environment. In these reports, analysis of the epidemiological pattern of HAV infection, taking into account the socio-economic and sanitary conditions, geographic localisation and climate, showed that viral rate detected in West-central Tunisia is slightly higher (62.96% to 69.2%) than in East-central (50.62% to 65.7%) (Ouardani et al., 2015, 2016). Analysis of the seasonal distribution of HAV in wastewater, conducted in different parts of Tunisia, have shown that HAV circulates throughout the year with certain seasonal variation. In these studies, highest viral rates were found during summer (67.07%) in coastal areas and during winter (85.4%) and autumn (80%) in West-central regions (Ouardani et al., 2015, 2016), suggesting that geographic localisation and climate may play an important role on the seasonal variation of HAV circulation. These differences would certainly be related to the proximity of these areas to the coast and the consequent condensation of tourism population, mainly from neighbouring countries such as Algeria and Libya, but also from European Union. Quantitative data showed high HAV rates during summer (10^9 GC/L) which might suggest the occurrence of outbreaks in this period (Ouardani et al., 2015, 2016).

Phylogenetic studies of HAV conducted in Tunisia from wastewater samples showed the predominance of the sub-genotype IA over several years with the presence of some strains closely related to European strains demonstrating the circulation of this sub-genotype variant in the Mediterranean region (Chironna et al., 2003). However, the sub-genotype IB remains infrequent in the country (Gharbi-Khelifi et al., 2006; Béji-Hamza et al., 2014; Ouardani et al., 2015, 2016) and was described in the coastal regions, especially in touristic areas, with high number detected during spring and summer (Ouardani et al., 2016). These facts suggest that this sub-genotype, circulating in Europe, may be imported by travellers during Easter or summer holidays vacation.

HEPATITIS E VIRUS

Hepatitis E virus (HEV) is the etiologic agent of enterically transmitted non-A, non-B hepatitis in humans worldwide (Emerson and Purcell, 2003) classified as a member of the genus *Orthohepevirus*, species *Orthohepevirus A*, within the family *Hepeviridae* (Khuroo and Khuroo, 2016; Smith et al., 2016). As for HAV only one serotype has been described for HEV but four major genotypes have been identified based on nucleotide sequencing. Genotypes 1 and 2, restricted to humans, have been found in Asia, Africa and North America, while genotypes 3 and 4 are zoonotic and can infect both humans and animals such as domestic pigs, wild boars, and other mammals (Li et al., 2005; Feagins et al., 2008). The genotype 3 is frequently found in the world whereas the genotype 4 has been found only in Asia. HEV is a positive single-stranded RNA nonenveloped virus. The genome is approximately 7.2 kb in length containing short 5' and 3' noncoding regions (UTR) and three open reading frames (ORFs 1, 2 and 3) (Wang et al., 2000; Huang et al., 2007). The virus is resistant to high temperatures at 56°C for 1 h but it is sensible to boiling, frying and chlorination (Emerson et al., 2005; Khuroo and Khuroo, 2016). HEV is primarily transmitted by the fecal-oral route (Emerson and Purcell, 2003; Phan et al., 2005) and epidemics are

usually linked to contaminated water, occurring only in developing countries of Asia, Africa and in Mexico (Meng, 2010). In these countries, outbreaks of HEV infections are closely linked to poor hygienic conditions and consumption of uncontrolled water (Masclaux et al., 2013; Garcia et al., 2014).

In Tunisia, very few studies were conducted on HEV in wastewater and its prevalence remains not well known. Unlike high prevalence reported in other North African countries (Kamal et al., 2010) as well as some developing areas, where levels in wastewater reached 40.7% in Pakistan (Ahmad et al., 2010) and 55.6% in India (Vivek et al., 2013), HEV seems to be infrequent in our country with viral contamination of 2% in wastewater (Béji-Hamza et al., 2015). This result is in line with seroprevalence studies that showed low rates (4.3% - 6.8%) of HEV in Tunisian population (healthy invidious and blood donors) (Rezig et al., 2008; Houcine et al., 2012; Ben-Ayed et al., 2015). Phylogenetic analysis, conducted by Béji-Hamza and co-workers, showed the presence of genotypes 1 and 3 in environmental samples, suggesting the circulation of these two genotypes in the Tunisian population (Béji-Hamza et al., 2015).

NOROVIRUS

Norovirus (NoV) represents the most important cause of infectious human gastroenteritis (Patel et al., 2009) and food-borne outbreaks of acute gastroenteritis worldwide (Green, 2007; Patel et al., 2008, 2009). It is a non-enveloped icosahedral virus with positive single-stranded RNA of 7.5-7.7 kb. NoVs are classified within the family *Caliciviridae*, and subdivided into five genogroups (GI–GV) (Karst et al., 2003; Zheng et al., 2006) and several serotypes. Genogroups I, II and rarely IV are known to infect humans (Green et al., 1994; Wang et al., 1994; Ando et al., 2000; Zheng et al., 2006; Patel et al., 2009) whereas GIII affects swine. Based on VP1 coding sequence analysis, more than 33 different genotypes were described within NoVs genogroups (Zheng et al., 2006; Zheng et al., 2010), with genotype II.4 being the most common cause of gastroenteritis outbreaks (Siebenga et al., 2009; Zheng et al., 2010).

Little is known about NoV occurrence in wastewater in Tunisia, and the only two studies found in the literature were carried out in the coastal region of Monastir using small samples number. Data showed a variation on the prevalence of this virus from 4.4% to 67.6% (Hassine et al., 2010; Sdiri-Loulizi et al., 2010; Hassine-Zaafrane et al., 2014), being detected during winter and spring with high rates in the months of February and May (Hassine et al., 2010). These results are one line with other reports described by Melnick (1991) and Lopman et al. (2004), demonstrating a seasonal pattern of NoV during the cold season with occasional appearance of epidemics observed especially during spring. Phylogenetic studies showed high frequency of GI NoV in the environment (Hassine-Zaafrane et al., 2014; Hmaied et al., 2015) contrary to clinical samples where GII were predominant (Hassine-Zaafrane et al. 2013). No clear explanation for this discrepancy was found but authors suggested the possibility of infection by various genotypes of NoV with GI strains might be more resistant in wastewater and less severe or lead to asymptomatic infections compared to GII (Duizer et al., 2004; Rzeżutka and Cook, 2004; da Silva et al., 2007).

ROTAVIRUS

Rotavirus (RV) is the principal cause of severe diarrhea in children below 5 years of age, with approximatively 140 million cases and 453,000 deaths described in developing countries each year (Steele et al., 2003; Tate et al., 2012). Group A rotavirus (RV-A) is associated with a large majority of severe gastroenteritis, in both humans and animals, occurring in developed and developing countries and represents the major cause of child mortality (Parashar et al., 2006; Sanchez-Padilla et al., 2009). RV-A is a nonenveloped icosahedral virus of 70 nm in diameter, containing 11 segments of a double-stranded RNA genome of approximately 18.5 kb (Okoh et al., 2010; Rodríguez-Lázaro et al., 2012). It is classified within *Reoviridae* family, genus *Rotavirus*, and divided into G and P genotypes. At least 27 G types and 37 P types of RV-A have been identified to date (Matthijssens et al., 2011; Trojnar et al., 2013), of which G1-G4, G9, G12, P4 and P8 are most commonly found infecting humans (Gentsch et al., 1996; Martella et al., 2010).

Like the other enteric viruses, RV persist in the water environment (Hurst and Gerba, 1980) and its inactivation in different types of water was correlated with higher temperatures (John and Rose, 2005). Prevalence of RV-A in wastewater were determined in only some region of the East-Central Tunisia, being detected in 72.4% of wastewater samples with viral rates of 76.1% and 68.7% in raw and treated wastewater, respectively. However, variation on RV-A prevalence between STPs (from 70.8% to 81.4%) was associated to the origin of influents where domestic wastewater may contain greater quantities of virus than industrial water (Hassine-Zaafrane et al., 2015). Seasonality of RV-A was also studied and showed high prevalence during winter (28.5%) and spring (32.8%). In addition, high viral loads were observed in December, March and July which corresponded to school holidays when high influx of invidious from other regions were noted (Hellmér et al. 2014; Hassine-Zaafrane et al., 2015).

Molecular genotyping of RV-A wastewater samples in Tunisia showed a great diversity of genotypes with the presence of 10 G types and 8 P types (Hassine-Zaafrane et al., 2015). Most of them belonged to G1-G4, G9, P[4], P[6], P[8] and P[9] and described as being epidemiologically relevant for humans, while some detected genotypes as G6, G8, G10, P[1], P[5], P[11] and G5, G11, P[7] have been commonly found in bovine and swine, respectively (Papp et al. 2013; Hassine-Zaafrane et al., 2015).

ENTEROVIRUSES

Enteroviruses (Evs) are the viruses most commonly encountered in humans and infections by these viruses have been estimated at 1 billion worldwide (Palacios and Oberste, 2005). EV consists of spherical nonenveloped virus, with a positive single stranded RNA genome of 7.2–8.5 kb, belonged to the genus *Enterovirus* within the family *Picornaviridae* (Stanway et al., 2005). Actually, more than 100 serotypes of enteroviruses, ratified by the Executive Committee of the International Committee on Taxonomy of Viruses (ICTV) (Lauber and Gorbalenya, 2012; Adams et al., 2013), are distributed in four species in humans (A, B, C and D): EV-A contains some coxsackievirus A strains; EV-B includes coxsackievirus A9, coxsackievirus B1-6 and most of the echoviruses; EV-C comprises

polioviruses 1–3 and some coxsackievirus A strains (Stanway et al., 2005). EV68 and EV70 are the two serotypes found in the EV-D species (Smura et al., 2007). EVs can replicate in the respiratory tract and the gut and are transmitted by respiratory or faecal–oral route (Rodríguez-Lázaro et al., 2012). Although most of infections are asymptomatic, EVs can be responsible for a wide spectrum of diseases in humans, including acute paralytic poliomyelitis, aseptic meningitis, encephalitis, myocarditis, pericarditis and conjunctivitis. They are also involved in respiratory system infections and gastroenteritis as well as insulin-dependent diabetes (Wagenknecht et al., 1991; Kocwa-Haluch, 2001; Griffin et al., 2003).

EVs are highly resistant in several environments and able to preserve their infectivity for months (Wetz et al., 2004; Fong and Lipp, 2005; Rajtar et al., 2008), which reflects their widespread occurrence in populations (Sellwood et al., 1981; Hovi et al., 1996; Sedmark et al., 2003). As other enteric viruses, they can contaminate soil, food crops and natural watercourses through the discharge of contaminated wastewater. In Tunisia, the presence of EV in wastewater was also documented and most studies showed high prevalence from 30.2% to 50% (Sdiri et al., 2006; Hassine et al., 2010; Ibrahim et al., 2014). Hassine and co-workers (2010) showed, through monitoring of EVs seasonality in wastewater, a regular circulation of these viruses throughout the year (except in the months of November, February and March) with predominance during summer and autumn. It has been described that in the Mediterranean climate, EVs are endemic with possibility of outbreaks appearance during summer-autumn (Nairn and Clements, 1999; Belghuith et al., 2004). Furthermore, molecular characterization of EVs from wastewater samples has shown the circulation of the three species A, B and C in the country (Ibrahim et al., 2014).

AICHIVIRUS

Aichi virus (AiV) is a causative agent of gastroenteritis in humans, transmitted like all enteric viruses by faecal-oral route (Ambert-Balay et al., 2008). It is classified as a member of the Aichivirus species, genus *Kobuvirus* within the family *Picornaviridae* (Knowles et al., 2012). The virus is nonenveloped with an icosahedral nucleocapsid of 30 nm in diameter which protects a positive single-stranded RNA of approximately 8.3 kb in length coding for a single open reading frame (ORF) (Burutarán et al., 2016). Based on their nucleotide sequences similarity (Yamashita et al., 2000; Yamashita and Sakae, 2003; Ambert-Balay et al., 2008), AiV was divided into three genetically distinct genotypes, where genotypes A and B are more frequent than the genotype C (Ambert-Balay et al., 2008; Kaikkonen et al., 2010; Jonsson et al., 2012). Since its first identification in 1989 in Japan (Yamashita et al., 1991), AiV was isolated in several countries of Asia (Pham et al., 2007), Europe (Oh et al., 2006; Ambert-Balay et al., 2008), South America (Oh et al., 2006), at low prevalence from children suffering from gastroenteritis. To date, there are only two reports that described the occurrence of AiV in Tunisia, and showed higher viral rate of 4.1% in stool samples isolated from children (Sdiri-Loulizi et al., 2009), compared to other countries such as France (0.9%), and 6% in wastewater samples collected from several STPs located in the East-Central of the country. These results confirm that AiV present in wastewater may reflect virus circulation in the community and suggest that it is an emergent virus implicated in gastroenteritis. Moreover, it has been reported that genotype A of AiV was predominant in Tunisia, in both

clinical and environmental samples, as well as in Europe and Asia (Oh et al., 2006; Ambert-Balay et al., 2008, Yamashita et al., 2000). Indeed, phylogenetic analysis showed that nucleotide sequences of the environmental strains were closely related to those found in clinical samples, suggesting a parallel evolution of the environmental and clinical strains over time.

EVALUATION OF BIOLOGICAL WASTEWATER TREATMENT PROCESSES USED IN TUNISIAN STPs

Waterborne transmission represents one of principal modes of indirect transmission of enteric viruses to humans and is the origin of many epidemics in developing countries (Ali et al., 2004; Bosch et al., 2005). Thus, great resistance of these viruses in water environment, inadequate wastewater treatment processes and reuse constitute a potential risk on public health since they are shed in high quantities in the faeces and subsequently can contaminate fresh products such as vegetables, salads, fruits and filter-feeding molluscs (Okoh et al., 2010; Bosch et al., 2009). These latter are able to concentrate viruses by filtration, through their gills, of large quantities of sea water (100 to 650 liters/ hour/kg of mussels) and their consumption, even raw or lightly cooked, presents a high risk of enteric virus carriage (Croci et al. 2007; Gabrieli et al. 2007).

Therefore, since wastewater represents the main source of enteric viruses (Rodríguez-Lázaro et al., 2012), the effectiveness of processes used to the treatment for viral removal should be assessed before wastewater reuse in irrigation and other sectors or release in the nature (Hmaied et al., 2015). There has been increasing concern about the evaluation of wastewater treatment processes efficiency to avoid viral environmental contamination and to develop new strategies to remove viruses. However, several studies were conducted in this field and showed an inefficiency of most of the current wastewater treatment processes to remove viruses with reduction rates vary from 20 to 80% (Payment et al., 1986; La Rosa et al., 2010; Prado et al., 2011; Ouardani et al., 2015). Therefore, as released viruses are able to preserve their infectivity for a long period, they can easily contaminate diverse food items (Masclaux et al., 2013) and environmental waters such as lakes, rivers, sea, and drinking water resources.

As described previously, Tunisia is one of many developing countries that developed its secondary sewage treatment plants (Melhem et al., 2014) in order to reuse treated wastewater in several sectors, mainly in agriculture, to palliate the lack of water resources (Jebri et al., 2012). It has been reported that the government is investigating the reuse of these waters to refill the aquifers, forests irrigation and in industry through pilot projects. However, quality of treated wastewater remains poor (El Ayni et al., 2013) and the lack of specific surveillance program for enteric viruses in wastewaters (Sdiri-Loulizi et al., 2010) could, among many risk factors (Jacobsen and Koopman, 2005; Rodríguez-Lázaro et al., 2012; Melhem et al., 2014; La Rosa et al., 2014), increase public health risk related to the viral contamination in wastewater. Indeed, given that Tunisia is ranked between countries highly endemic for almost enteric viruses causing hepatitis and gastroenteritis, transmission of infections may be facilitated with poor hygiene conditions and inappropriate wastewater reuse.

Little is known about the efficiency of wastewater treatment processes currently used in Tunisia to remove enteric viruses. Therefore, in several studies viruses have been detected in treated wastewater and it has been confirmed that whatever the method used by STP, it is impossible to provide virus-free wastewater (Hassine-Zaafraane et al., 2014; Hmaied et al., 2015; Ouadani et al., 2015, 2016). Tunisian urban wastewater is a mixture of human sewage, suspended solids, debris and a variety of chemical substances that originate from residential, commercial and industrial activities (Okoh et al., 2010). To ensure the depuration of these waters, STPs are using both primary and secondary treatment processes where a range of wastewater treatment options is used and treatment level varies between urban and rural areas (Qadir et al., 2010). Unfortunately, due to the rapid increase in urban population and high use of water during summer, some STPs do not have the capacity to process large volumes of wastewater and consequently retention times for wastewater treatment become too short to be effective.

Based on data provided by ONAS, the majority of Tunisian STPs are using to the depuration of urban wastewater biological secondary treatments, of which activated sludge and lagoon are the most widespread in the country (Qadir et al., 2010; Melhem et al., 2014; Ouadani et al., 2015). Within activated sludge process, we distinguish three methods as follow: conventional activated sludge (medium charge) used for large community, extended aeration activated sludge (low charge) and extended aeration oxidation ditch activated sludge (low charge) used for medium to small community. However, two varieties of lagoon processes exist, natural/ facultative lagoon and aerated lagoon, and they are used only for the treatment of small volume of wastewater. Currently, Tunisian efforts are focused on the upgrade to tertiary level treatment (Melhem et al., 2014). All these processes lead to remove pollutants, both chemical and biological, from wastewater before discharge to the environment and although they are not intended to eliminate viruses, the effectiveness of viral reduction would probably be improved (DeBusk, 1999; Okoh et al., 2010).

Data on the prevalence of enteric viruses in treated wastewater in Tunisia were provided in several reports and showed low viral reduction. For HAV, regardless the wastewater treatment process, removal rate reached 39.1% (Ouadani et al., 2016) which corresponded to viral reduction found in other reports (20-80%) (Payment et al., 1986; La Rosa et al., 2010; Prado et al., 2011; Ouadani et al., 2015). indeed, values in outflows (22.7%-40.7%) were slightly lower than in inflows (56.8%-66.9%). High viral concentration were also noted in treated wastewater samples collected from many STPs and ranged from 3.9×10^3 to 1.4×10^8 GC/L (Ouadani et al., 2015, 2016). Activated sludge process is widely used by cities and communities where large volumes of sewage should be treated in a cost-saving manner. The comparison of the three activated sludge processes showed a complete failure of conventional activated sludge (medium charge) with 63.6% of positive samples being detected in treated wastewater samples and viral reduction rate of 7.9% (Ouadani et al., 2016). Extended aeration and oxidation ditch activated sludge processes (low charge), used to overcome some of limitations associated with the conventional activated sludge (Benjes, 1976), had high/moderate efficiency against HAV varying from 32.4% to 91.47% (Ouadani et al., 2015, 2016). However, lagoon process seems to be better to remove HAV since Ouadani and co-workers showed a removal rates of 71.8% to 100% and viral load reduction was more than 1 log unit (Ouadani et al., 2015).

Other studies focused on molecular detection of NoV in effluents, treated by conventional activated sludge process, showing viral rates of 47.9% (Hassine-Zaafraane et al.,

2014). NoV GI (83.3%-96.4%) was more prevalent than NoV GII (2%-66.6%) with viral concentrations ranged from 2.72×10^2 to 2.6×10^3 GC/L for GI and from 33 to 175 GC/L for GII (Hassine-Zafrane et al., 2014; Hmaied et al., 2015). Furthermore, RV was detected in 68.7% (Hassine-Zafrane et al., 2015) of treated wastewater samples with high concentrations ranged from 5.2×10^5 to 1.3×10^7 GC/L (Hassine-Zafrane et al., 2015; Hmaied et al., 2015).

These findings demonstrate the high resistance of these viruses to all kind of wastewater treatments and point to a potential health risk if final effluents are discharged into fresh or marine water systems or reused in irrigation. This low efficiency to eliminate viruses depends generally on origin of influents, viral type, wastewater pH, the nature of the suspended solid (Arraj et al., 2005), environmental conditions and wastewater treatment level (Hmaied et al., 2015). Otherwise, it has been reported that several factors may affect the efficiency and the reliability of the treatment process, such as hydraulic and organic overloads of the STP, equipment and structures very old and deteriorated, lack of operating staff and the entering of industrial wastewaters (Ouardani et al., 2016). According to a study, conducted in a variety of STPs and introducing the latter parameter on the evaluation of treatment efficiency, has shown lowest virus removal rate in STPs collecting large volume of industrial wastewaters with higher viral loads in treated wastewater than those found in raw sewage. These findings were partially explained by the fact that industrial raw wastewater contains high loads of both organic and chemical pollutants as well as heavy metals that may inhibit the PCR (Sobsey and Hickey, 1985; Tsai and Olson, 1992).

CONCLUSION

The study and assessment of enteric viruses in Tunisian wastewaters may provide an insight on viral circulation in general population, their resistance to wastewater treatment processes and to estimate the public health risks associated with these viruses. Moreover, evaluation of secondary biological wastewater treatment processes commonly used in Tunisia has important implications on the development of official controls and the establishment of viral indicators, in order to improve the microbiological control of treated wastewater, especially that this renewable source is reused for many activities, mainly in agriculture. As an example, investigations performed up to now indicate that the replacement of conventional activated sludge treatments and the establishment of tertiary treatments seems to be necessary to reduce as much as possible viral contamination of the environment.

These measures together with an improvement of hygienic practices through educational programs would be of great help to reduce and/or avoid public health problems related with enteric viruses in Tunisia.

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Chapter 508

MICROBIOLOGICAL AND PHYSICOCHEMICAL CHARACTERIZATION OF GROUND AND SPRING WATERS: IMMINENT PUBLIC HEALTH ISSUE

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ABSTRACT

Water is an essential resource to all living beings. Ensuring good quality of drinking water is a basic factor in guaranteeing public health, the protection of the environment and sustainable development. Several studies have revealed that the chemical and microbiological qualities of ground and spring waters are in violation of acceptable standards, and may not conform to National Standards as expected by the consumers. Water can become contaminated by a number of ways, such as naturally occurring chemicals and minerals, the lack of or malfunctioning sanitary infrastructures, or land practices. The major microbiological risk associated with water is its fecal contamination, which can be a source of pathogenic bacteria, viruses or parasites; its most common indicators are the presence of coliforms such as *Escherichia coli*, intestinal enterococci or *Clostridium perfringens*. These microorganisms have been implicated as the source of several intestinal diseases, urinary tract infections, neonatal meningitis, gastroenteritis, typhoid fever and cholera. Chemical pollution, the other type of water contamination, can be organic or inorganic. Organic chemicals include leachate [e.g., from solid waste], synthetic organic compounds, and chlorinated compounds like trihalomethanes [THM], which are associated with poisoning, cancer, liver, kidney and central nervous system problems. Inorganic compounds, on the other hand, consist of substances resulting from water treatment and pesticides or pollution resulting from industry [e.g., Cd, Ba, Hg, Mo and B]. Many diseases are associated with these elements including poisoning, cancer,

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hypertension and infantile cyanosis. Thus, it is essential to control water quality regularly, focusing primarily on physicochemical and microbiological aspects. The aim of this chapter will be to perform a microbiological and physicochemical characterization of ground and spring waters associated with public health issues.

Keywords: ground water, spring water, microbiological analysis, physicochemical composition, public health

INTRODUCTION

Water is an essential resource to all living beings [1]. Therefore, it is of major importance not only to have an adequate and accessible supply, but also to have quality water that is considered safe to human consumption [1, 2]. This is crucial to assure public health, but it is also essential to environmental protection and sustainable development assurance [3].

Potable water can be divided into three groups: groundwater, springwater and the remaining forms of water suitable for human consumption. Both ground and spring waters are originated from underground, but the former is mainly characterized by its stable physicochemical characteristics, and its high content on mineral salts and oligoelements which result from its interaction with the existing underground rocks. These characteristics can bring several human health benefits [4, 5].

Water can become contaminated by a number of ways, such as naturally occurring chemicals and minerals [6], the lack of or malfunctioning sanitary infrastructures, or land practices [6, 7]. The major microbiological risk associated with water is its fecal contamination, which can be a source of pathogenic bacteria, viruses or parasites; its most common indicators are the presence of coliforms such as *Escherichia coli* [EC], intestinal enterococci [IE] or *Clostridium perfringens* [CP] [1, 8, 9].

In terms of physicochemical aspects, as water is an excellent solvent, it might contain several chemical substances that can be a hazard to human health over prolonged consumption [1, 9]. These parameters are easily changeable, especially in underground water, due to climatic and hydrogeological conditions, water flow velocity, composition of the formations, among others [2]. Chemical substances can be organic or inorganic [8]. Inorganic substances constitute by far the greatest proportion of chemical contaminants in drinking water. They can appear as a consequence of natural processes but mostly they appear from contaminants as a result of Man's activities. Inorganic contaminants are also the most important for water consumer's acceptability, affecting water's taste and color, and causing scale deposition on pipes and fittings. They have an important impact on health as well, having both beneficial and adverse effects which have been shown in human populations. Several health problems, such as poisoning, cancer, hypertension, liver, kidney and central nervous system diseases, and infantile cyanosis can be attributed to these contaminants [8, 10].

Thus, it is essential to regularly control water quality, focusing primarily on physicochemical and microbiological aspects.

In this chapter we will describe some of the most important physicochemical and microbiological parameters to be determined in drinking-waters.

PHYSICOCHEMICAL CHARACTERISTICS

Physicochemical properties are important for the water's organoleptic characteristics and their modification can cause health problems for consumers.

pH

The water pH is the negative logarithm of the molar hydrogen activity: $\text{pH} = -\log[\text{H}^+]$. It is a measure of the acid-base equilibrium and is controlled by the carbon dioxide-bicarbonate-carbonate equilibrium system in most cases [10]. The European legislation applied to consumption water has stated its legal limits (6.5-9.5) [11]. Slightly lower levels than the limits generally don't compromise groundwater quality in terms of human consumption, as they only reflect the geological composition of the grounds [4, 7].

Generally, the pH doesn't affect consumers directly, as there is no health-base guideline value proposed for this parameter, although extreme values of pH may result in irritation of the eyes, mucous membranes and skin [10]. Nonetheless, it is still a crucial parameter in water quality: for instance, pH of waters in distribution networks should be especially monitored, as low levels of pH may lead to corrosion of the metal pipes used, and to a subsequent chemical contamination. In addition, water pH is also important to the efficiency of treatment processes, as levels of pH below 8 may reduce chlorination's effects [10].

Electrical Conductivity and Total Dissolved Solids

Total Dissolved Solids (TDS) represents the amount of inorganic salts [calcium, magnesium, sodium, potassium, carbonate, chloride, sulfate, nitrate, among others] and organic matter present in the water [1].

TDS affects water's organoleptic properties, mainly its palatability, and therefore can even affect its acceptability for consumption. Taste panels have rated the palatability of water and classified it into five categories, presented in Table 1. However, water with very low mineral content can also be considered insipid and flat [10].

There are no health-base guideline values for TDS as the levels found in drinking-water are not of health concern [1].

Table 1. Influence of TDS in water palatability [10]

Category	TDS level (mg/L)
Excellent	<300
Good	300-600
Fair	600-900
Poor	900-1,200
Unusable	>1,200

In summary, this relevance of this parameter is mainly associated with organoleptic properties and it is as well a very broad indicator of chemical contaminants.

TDS is determined most commonly through the measurement of Electrical Conductivity (EC), although it can also be determined gravimetrically, and through the individual measurement of ions [4].

EC is the numeric expression of the capability of a solution to carry an electric current, and it is dependent on the concentration, mobility and valence of the present ions. Therefore, it is dependent on several factors such as the mineral composition of the grounds [11, 12]: granite grounds, as they are mainly composed of particles that don't ionize when in contact with water, are not good electrical conductors, as opposed for example of limestone grounds because of the dissolution of its carbonate minerals [12]. Also, EC has proven to be useful in determining the extent of the influence of run-off and effluent discharges in aquatic systems [13]: discharges of wastewater from a damaged sewage system should raise EC, as a result of its chloride, phosphate and nitrate composition, in contrast to oil discharges [12]. On the other hand, organic compounds don't have much influence on EC as they are not very good electrical conductors [12].

Turbidity

Turbidity is a major physical characteristic of water and therefore it belongs to the National Primary Drinking Water Regulations (NPDWR) of EPA [14]. The NPDWR are legally enforceable standards to public water systems, which are meant to protect the public against consumption of health threatening contaminants [14].

This characteristic is a measure of the cloudiness of water and it is caused by the presence of suspended or colloidal matter, which can be either organic, inorganic or both, that favors the scattering and absorption of light by particles and molecules, rather than its transmission [1, 11]. This parameter, expressed in Nephelometric Units (NTU), is determined using instruments that detect the amount of light scattered by a sample at a specific angle. This nephelometric method is calibrated using suspended formazin standards [15, 16].

In drinking water the most common sources of turbidity are: water discharges, algae, organic compounds resulting from decay of plants or decomposing animals, silt, clay, high levels of iron, and particles from water treatment [16, 17].

High levels of turbidity are not only aesthetically unappealing but they also may indicate possible microbial contamination, as the present matter can provide attachment and shelter to microorganisms (preventing proper water disinfection and increasing the risk of gastroenteritis), heavy metals, pesticides or toxic organic compounds [16].

The levels of turbidity should be 1 NTU and preferably much lower, although higher levels (up to 5 NTU) could be acceptable in groundwater if the turbidity is not of health concern (in the absence of bacteria, levels of nitrate-nitrogen inferior than 1 mg/L, construction of well is acceptable, and no evidence of other kind of contamination is present) [16].

It is highly recommended that waters with high turbidity are subjected to coagulation, sedimentation and filtration (prior to disinfection) in order to be considered microbiologically safe to drink [1].

Hardness

Total Hardness (TH) represents the water dissolved calcium and magnesium salts due to water contact with ground rocks [11] and is a measure of the capacity of water to react with soap [1].

It is composed by both temporary hardness (carbonate and bicarbonate, which might be eliminated by water boiling) and permanent hardness (noncarbonate, such as chloride, nitrate and sulphate, which are not susceptible to water boiling) [1, 11].

Table 2. Classification of waters according to TH [1]

Water Category	Quality	Hardness (mg/L)
Very soft	Good	0-60
Soft		60-150
Moderately hard	Medium	150-300
Hard	Acceptable	300-600
	Hard to soften	>600

Water is classified as “hard” when it has very high levels of these salts and is classified as “soft” when it has low levels. Table 2 show the classification and quality of water according to its hardness. Water from limestone areas is harder than water from granite areas [1].

In terms of health-based limits, there are none established as this parameter is not considered of health concern [1, 18, 19]. However, hardness levels also affect the consumer as water with hardness values lower than 100 mg/L might have low buffering properties and lead to the possibility of pipes’ corrosion and, on the other hand, hardness higher than 200 mg/L can also lead to an excessive need of soap to produce foam [1, 11], precipitation of soap scum and accumulation on tubs and showers, presence of white deposits more noticeable on glassware, and also a reduction of efficiency of water heating devices [1, 20].

Trihalomethanes

Trihalomethanes (THMs) are a group of four chlorinated chemicals [chloroform, bromoform, bromodichloromethane, dibromochloromethane] first identified in the 1970s that form in drinking-water as a result of the chlorination of the organic matter (such as algae and decaying leaves) present in water [1, 21]. Chloroform is generally the most commonly detected THM.

Although these chemicals are tasteless and odorless, they are harmful and potentially toxic, and are therefore Total THMs (TTHMs) are one of the parameters included in the NPDWR of EPA [21].

The chemical formulas and guideline values of the THMs are present in Table 3.

As THMs are volatile chemicals they are transferred to the air. Therefore, there are four main routes of exposure: ingestion of drinking-water, inhalation of indoor air, inhalation and dermal exposure during showering, bathing or ingestion of food [21].

Table 3. Chemical formulas and guideline values of THMs [1, 21]

Trihalomethane	Chemical formula	Guideline values (mg/L)
Trichloromethane [chloroform]	CHCl_3	0.3
Tribromomethane [bromoform]	CHBr_3	0.1
Dibromochloromethane	CHClBr_2	0.1
Bromodichloromethane	CHCl_2Br	0.06
Total Trihalomethanes	-	0.08

The exposure to THMs is not generally associated with acute effects, but to chronic effects, such as increased risk of cancer and liver, kidney and central nervous system problems. In terms of cancer, chloroform and bromodichloromethane are classified as possibly carcinogenic to humans (group 2B) as they were found to be carcinogenic in animal studies; bromoform and chlorodibromomethane are not classified concerning their carcinogenicity [21].

THMs can be reduced by reducing the organic material before chlorination of the water, optimization of chlorine usage, changing the point of chlorine addition in the treatment series and use alternative disinfection methods [22].

Metals

Drinking water can be a good source of essential (such as Ca, Mg, Fe and Zn) but also of nonessential heavy metals or metalloids (As, Pb, Tl, U, B) which are considered toxic to the human health [23].

Heavy metals are naturally occurring elements but they might also be present in water due anthropogenic activities, such as mining, smelting operations and industrial production. Water contamination with these metals might also result from metal corrosion, atmospheric deposition, among others [24].

Ingestion of these metals might lead to their accumulation causing several health problems, mainly in the central nervous system [specially in children], and in the reproductive system [23].

Among drinking waters, the metals with relatively high concentrations and therefore of special concern are As, Cd, Pb, Cr, Cu, and Hg [25]. Inorganic As is classified as a human carcinogen and is associated with skin damage and circulatory problems. It may be present in waters due to erosion of natural deposits and runoff from wastes [14, 25, 26]. Cd is also classified as a human carcinogen and is related with kidney damage. Its presence may be due to corrosion of pipes, discharge from metal refineries and also runoff from waste batteries and paints [14, 25]. Inorganic Hg is also associated with liver and kidney damage [14, 25]. Pb is related with the development of anemia, learning deficits, kidney damage and high blood pressure [14, 25]. Cr might be present in drinking water due to discharges from mills as well as erosion of natural deposits, and its presence is related to allergic dermatitis [14, 25]. Cu is associated with gastrointestinal symptoms and the development of Wilson's disease [14, 25].

MICROBIOLOGICAL ANALYSIS

One of the major problems in water potability is the microbiological contamination [1], mostly associated with fecal contamination from wastewater or landfills [8].

This problem is predominantly present in developing countries, such as African countries, where the mortality associated with waterborne diseases is superior to 5 million people per year, and half of these are intestinal infections [27, 28]. Also, water has the potential to disseminate microbial agents to a large number of individuals, and, in the presence of pathogens, to cause illnesses [27].

Contaminated water can lead to several health problems, from mild gastritis, to dysentery or typhoid fever, and can also be the source of disease outbreaks [1]. Diarrheal diseases account for 80% of all water related diseases and are responsible for 1.5 million deaths every year, mostly in children under five in African and Asian countries [29, 30]. In Europe, an average of 330.000 cases of water related diseases are reported every year, including typhoid fever, enterohemorrhagic EC infection, viral hepatitis A, giardiasis, or cholera [30]. Also, in the United States of America these diseases are reported to cause 12.000 death per year [30]. Hence, microbiological evaluation is essential to guarantee safe water, and it should be systematic.

Total Microorganisms

Total microorganisms count represents the water's general bacterial content [31], having little sanitary importance [1], and can be useful in monitoring treatment and disinfection processes and evaluate the cleanliness and integrity of distribution systems [31, 32]. For this reason, further studies need to be performed to evaluate the presence of fecal contamination indicators.

Total Coliforms and *Escherichia coli*

Total Coliforms is a bacteria group that belongs to the family Enterobacteriaceae and is composed of a great variety of Gram negative bacilli that grow in the presence of high concentrations of bile salts and ferment lactose [1]. Some of the most commonly genera found in water are *Escherichia*, *Citrobacter*, *Enterobacter*, *Klebsiella*, *Serratia* and *Yersinia* [33]. This group includes both fecal and environmental species [34]; therefore is also not a good indicator of fecal contamination, but its presence is a sign of inadequate treatment and disinfection [1].

If a water sample is positive for coliform bacteria is useful to determine the species of coliform to determine the significance of the contamination and potential source [34].

EC is the most adequate indicator of fecal pollution, occurring in human and animal feces, sewage and recently contaminated water and soil [1]. Hence, it can also be used as an indicator of water treatment effectiveness [31].

This species is part of the normal bacterial intestinal flora, and most strains are nonpathogenic. There are, however, certain pathogenic strains.

EC isolated from intestinal illnesses has been divided into six groups: enteropathogenic *E. coli* (EPEC), enterohemorrhagic *E. coli* (EHEC), enterotoxigenic *E. coli* (ETEC), enteroinvasive *E. coli* (EIEC), enteroaggregative *E. coli* (EAEC) and diffusely adherent *E. coli* (DAEC) [35, 36]. We will give special relevance to the ETEC, EHEC and EIEC groups.

ETEC infections are associated with infantile gastroenteritis in developing countries, and are also the most common cause of traveler's diarrhea [35, 36]. These microorganisms lead to the illness through two enterotoxins (one thermo-resistant and the other thermo-labile) that ultimately affect electrolyte transport leading to fluid loss [36, 37]. The infectious dose of microorganisms is 10^6 which leads to profuse diarrhea for several days [27].

EHEC produce Shiga-like toxins (toxins similar to those produced by *Shigella dysenteriae*) and are mostly associated with the consumption of raw or undercooked food [35, 37]. The infection has an incubation period of 3-8 days (4 days on average) and the illness has a duration of 1-12 days (4 days on average) [37]. An infection with <100 organisms of the most prevalent serotype O157:H7 causes abdominal pain and watery and bloody diarrhea. In more severe cases, the infection may also lead to Hemolytic Uremic Syndrome (HUS). In the more recent years, other serotype, O104:H4, was implicated in a great outbreak in German, with 3842 cases of gastroenteritis and 855 of HUS, with a total of 53 deaths [38].

The EIEC group contains bacteria capable of invading the intestinal epithelial cells, leading to abdominal cramps, diarrhea, among other symptoms [27, 35, 36]. The infectious dose of these microorganisms is 10^6 - 10^{10} and the illness is similar to *Shigella* dysentery.

Besides intestinal infections, *E. coli* is one of the most frequent agent of urinary tract infections [36], and an increasingly common cause of meningitis and sepsis [35].

Intestinal Enterococci

IE are Gram-positive cocci, catalase negative, oxidase negative and antigen Lancefield's group D [33]. These microorganisms are also specific for fecal pollution, although these have some differences in comparison to EC, such as being more resistant to chlorination and the capability to live longer in water [1]. Some of the most common IE to be present in water are *Enterococcus faecalis*, *E. faecium* and *E. durans* [39].

Fecal bacteria can have a negative effect in Human health, as they can lead to gastrointestinal illnesses, generally mild, but of major concern in immunocompromised individuals [39].

In case of IE positivity, it is necessary to investigate the possible sources/causes of contamination, such as inadequate water treatment, location near to a source of contamination, or lack of treatment, among others [1].

Clostridium perfringens

Clostridium are Gram-positive anaerobic rod-shaped bacteria. CP, a sulphite-reducing clostridia, is an accurate indicator of fecal contamination as well. This species produces resistant spores that are very resistant to a number of unfavorable environmental conditions and water treatments (such as ultra-violet irradiation and chlorine disinfection) [31], and,

therefore, it is used to indicate contamination that took place previously, rather than recent contamination (such as the TC, EC, or IE) [1]. CP is removed by coagulation and flocculation and, as its spores are very small, its presence can be an indicator of problems in the filtration processes [1, 31].

The consumption of CP contaminated water can lead to one of two forms of illnesses. The most common is the gastroenteritis form, a mild form, characterized by cramps and watery diarrhea, which, in most cases, goes away by itself the day after (except in immunocompromised, or in the case of a violent strain). The other, but very rare disease is called “pig-bel disease,” a type of necrotizing enteritis, which is often fatal. Nevertheless, these diseases only occur when large numbers of CP are present in the water [40].

Salmonella

Salmonella are motile Gram-negative bacilli, non-spore forming, that belong to the Enterobacteriaceae family, and are characterized by their O, H, and Vi antigens. This genus is composed only of two species: *S. enterica* and *S. bongori* [37]. *S. enterica* is subdivided in six subspecies: enterica [the one that is most associated with human infections, including the typhoid and paratyphoid bacilli], salamae, arizonae, diarizonae, indica and houtenae [41]. Furthermore, *Salmonella* is also divided in two serovars according to the caused clinical syndromes: the typhoidal and non-typhoidal serovars [41].

The clinical syndromes caused by infection with *Salmonella* are divided into three groups: gastroenteritis, enteric fever and septicemia [41]. Gastroenteritis is self-limiting and occurs up to two days after ingestion, depending on the dose of bacteria ingested. It is characterized by nausea, vomiting, diarrhea, fever and abdominal pain, and usually resolves after a few days [37]. Enteric fever is a multisystemic potentially fatal disease caused mainly by *S. typhi* and *paratyphi*. The *S. typhi* caused syndrome has an incubation period of 10 to 14 days, and symptoms are non-specific, including fever, diarrhea, abdominal pain, myalgias. Antibiotics should be promptly administrated, otherwise the infection may be fatal [37]. Lastly, *Salmonella* septicemia might be an intermediate stage without intestinal symptoms when the bacteria is not isolated in fecal samples [37].

CONCLUSION

Water is essential to the survival of all beings, and therefore it is crucial to assure its quality. The parameters to be evaluated are divided into physicochemical and microbiological. The physicochemical parameters include the pH, total dissolved solids, electrical conductivity, turbidity and hardness; the microbiological parameters include the total microorganism count, and the evaluation of the presence and count of total coliforms, *E. coli*, intestinal enterococci, and *C. perfringens*. As the alterations in these parameters might indicate water alterations or contamination and may turn it unsuitable for drinking, it is fundamental to determine these parameters in drinking waters.

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Chapter 509

NEIGHBORHOODS AND PUBLIC HEALTH ISSUES

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INTRODUCTION

Physical activity is important for a healthy lifestyle and for example parks can provide opportunities for physical activity for both children and adults in their neighborhood [1]. A study in 20 neighborhood parks in Durham, North Carolina with 2,712 children and adolescents showed that the type of activity area and presence of other active children were positively associated with physical activity, while the presence of a parent was negatively associated [1]. Results showed that physical activity of girls was more strongly affected by social effects (like other active children) whereas physical activity of boys was more strongly influenced by the availability of park facilities [1].

A study from Finland of 37,699 adults looked at childhood adverse psychosocial factors and adult neighborhood disadvantage to understand if there was a link to increased cardiovascular disease [2]. They found that combined exposure to high childhood adversity and high adult disadvantage was associated with cardiovascular disease risk factors (hypertension, dyslipidaemia, diabetes, obesity, smoking, heavy alcohol use and physical inactivity), while exposure to high childhood adversity or high adult neighborhood disadvantage alone was not significantly associated with cardiovascular disease [2].

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Another study with 1,842 adults from Brazil looked at the local retail food environment and consumption of fruits and vegetables and sugar-sweetened beverages [3]. They found that availability in neighbourhoods was associated with regular fruits and vegetables consumption, but regular fruits and vegetables consumption prevalence was significantly lower among lower-income individuals living in neighbourhoods with fewer supermarkets and fresh produce markets. A greater variety of sugar-sweetened beverages was associated with a 15% increase in regular SSB consumption.

A recent [4] study used data from the Multi-Ethnic Study of Atherosclerosis (MESA), which involve more than 6,000 men and women from six communities in the United States (New York, Baltimore, Chicago, Los Angeles, Twin Cities and Winston Salem) to look at how neighborhood environments may influence the risk for developing type 2 diabetes mellitus (T2DM). They wanted to investigate long-term exposures to neighborhood physical and social environments, availability of healthy food and physical activity resources and levels of social cohesion and safety in relationship to T2DM. During a follow-up period of about ten years of adults aged 45-84 years at baseline 616 out of 5,124 participants (12.0%) developed T2DM and the study found a lower risk for developing T2DM associated with greater cumulative exposure to indicators of neighborhood healthy food and physical activity resources [4].

The studies above are just examples of recent research interest into the interrelation between neighborhood and the effects on health [5]. This relationship is complex and also very hard to research, since it is multidisciplinary and multi agency with different community development policies, urban planning, zoning and transportation policies involved.

In order to better understand the role of these environments and identify the most effective interventions in order to improve health will require partnerships between researchers, the neighborhood communities and policy makers.

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Chapter 510

PUBLIC HEALTH ASPECTS OF SUICIDE IN CHILDREN AND ADOLESCENTS

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ABSTRACT

Suicide in children and adolescents is a complex and devastating problem for families and society both nationally and internationally. This review considers various aspects of this phenomenon including its epidemiology, risk factors, protective factors, issues of prevention, and management. Risk factors for suicide have been reviewed including personal characteristics, psychopathology of those committing suicide, history of previous suicide attempts, sexual orientation, familial factors, and access to lethal means of suicide. Protective factors include social support and religion. Principles of prevention have been considered including school-based programs, screening tools, skills training, Gatekeeper training, community-based programs, and health-care programs. Management includes principles involved in management before and after self-harm. Also considered are family therapies and therapies aimed at specific problems such as depression, bullying, substance abuse, and others. Clinicians should be actively involved with their communities to seek prevention of suicide in children and adolescents.

Keywords: childhood, adolescence, suicide, public health

INTRODUCTION

Child and adolescent suicide is a complex global public health problem that has intrigued researchers, academicians and policy makers for decades. Suicide is one of the leading causes of death; an estimated 30,000 people in the United States and 1 million people worldwide die

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of suicide. Global suicide rates have increased drastically, and lost U.S. productivity due to suicide is now estimated at \$12 billion per year. The World Health Organization and United States (US) government have taken numerous steps toward establishing policies and prevention strategies, including calls for expanded collection of suicide data. Suicide also is one of the major causes of death in the adolescent population.

Despite the fact that progress has been made in our understanding of risk factors for suicide, it remains a major global medical burden. Among the 4 million suicide attempts yearly, about 90,000 adolescents succeed, averaging one successful attempt every 5 minutes; the cumulative result is that suicide is the 5th leading cause of adolescent death worldwide. In the following review, we will examine the current research on prevalence, risk factors and prevention strategies.

EPIDEMIOLOGY

The U.S. adolescent suicide rate gradually increased during the 20th century, becoming more marked during the 1960s and reaching an overall peak in the 1990s, although there have been other significant peaks and troughs. Although adolescent suicide rates stabilized during the late 1990s, they had increased by 250% between 1960 and 1980 and doubled between 1960 and 2001. Since the late 1990s, the suicide rate has declined, reaching a 30-year low in 2003 [1]. Numerous explanations for this reduction have been put forth, including earlier identification of at-risk teens, better and more focused delivery of mental health services to families in need and increased use of antidepressants. Unfortunately, this overall epidemiological trend shifted between 2000 and 2005, with a 14% increase in youth suicide during these years. This shift may have been due to reduced antidepressant prescribing amid the public health outcry and “black box” warnings regarding the association of antidepressant use with emergence of suicidal ideation.

The US Centers for Disease Control (CDC) recently published the National Suicide Statistics, with data updated to cover 2009, the latest year for which these numbers are available. According to the CDC, suicide rates declined in both sexes for the 1991-2000-time period but were consistently higher for 2001-2009. The CDC data also identifies numerous disturbing trends, including a 233% increase in suffocation suicide rates among females 10-24 years old. On the other hand, firearm suicide rates in females aged 10 to 24 years decreased from 1993 through 2007, while poisoning remained relatively constant at 0.48 suicides per 100,000 from 2002 to 2009. During 2005-2009, use of a firearm (29.7%) was the preferred mode of suicide among 10-24 year-old males, but suffocation (48.5%) was more common among the equivalent female cohort. For the same group, firearms and suffocations caused the largest number of fatal self-injuries, while poisoning and cutting caused the fewest.

Demographically, group differences between males and females do not exist until mid-to-late adolescence (15-19 years), at which time the rate of suicide among males increases dramatically. During 2005-2009, the highest suicide rates were among American Indian/Alaskan Natives and Non-Hispanic Whites. Suffocation was the preferred method of suicide among American Indian/Alaskan Natives while Non-Hispanic Whites preferred firearms. Asian/Pacific Islanders had the lowest suicide rates among males, while Non-

Hispanic Blacks had the lowest rates among females. In 2009, more female high school students planned (13% vs 8%) and attempted (8% vs 4%) suicide, as compared to their male peers [2].

Global Suicide Rates

Nationally recorded data on child and adolescent suicide must be interpreted with caution, as there are differences in data reporting among different nations. In many cultures, suicide in adolescents is usually under-reported, due to the desire to protect families from the stigma of suicide and to avoid any future social repercussions. Another reason to be cautious in comparing data is that different studies use different questionnaires to assess suicidality; the resultant variability in results may be due to measurement bias. A few recent studies, including the WHO/EURO Multicenter Study on Parasuicide and the WHO Multisite Intervention Study, have used standardized measures to overcome this bias.

Because of the above-mentioned inconsistencies, global figures for teen suicide vary, but it continues to be the 2nd leading cause of death, after motor vehicle accidents (MVA). Worldwide, suicide is the 3rd leading cause of death among adolescent males, after violence and MVA; it is the leading cause of death among adolescent females. Rates are highest in Eastern Europe and the Russian Federation and lowest in Central and South America. The male-to-female ratio continues to range from 3:1 to 7:1, except in India and China, where no differences are found between genders.

Suicide in Young Children

Suicide in children younger than 10 years of age is considered to be a rare phenomenon. Scientific literature has reported suicidal ideation in children as young as 5 years of age; however, this is controversial. Researchers have suggested that depression and substance abuse problems, two major risk factors for suicide in adolescents, are either rare or simply not present in very young children. Others have argued that because young children engage in concrete operational thinking and have limited problem solving abilities, they are not capable of understanding the finality of death and therefore cannot plan for a suicide attempt.

On the other hand, developmental theorists agree that the common denominator in a suicide attempt is *intent* to self-harm, regardless of the child's understanding of causality, finality and lethality of attempt. Parental absence and a family history of suicidal behavior are two factors that are associated with earlier onset of suicidal ideation in children. So far, the most consistent pattern that has emerged from the literature is that the risk of suicide increases significantly at 12 years of age and peaks at 16 years of age. In the U.S., suicide mortality rates were 1.5/100,000 for 10-14 year-olds and 8.2% for 15-19 year-olds [3].

RISK FACTORS

More than 30% of youth who commit suicide have some personality traits in common. In one study, children in the 12-14 year age range who had attempted suicide were frequently described as intelligent, socially isolated, aggressive and vulnerable to criticism. A history of impulsive aggressiveness has consistently been shown to predispose to suicidal behavior. Impulsivity by itself may lead to suicide attempts, as evidenced by the fact that many adolescents with ADHD show little planning before their attempts. Low self-esteem and hopelessness also have been associated with current and future suicidal ideation and attempts. Recent loss, interpersonal conflicts and legal issues are common precipitants for suicide in conduct-disordered youth [4].

Psychopathology

Youth with psychiatric disorders carry a 9-fold increase in suicide risk as compared to their peers. More than 90% of young suicide attempters have at least one diagnosed psychiatric disorder, and increased severity and chronicity of the disorder is strongly correlated with increased suicide risk.

Mood disorders are the most prevalent psychiatric disorders among adolescent suicide victims of both genders. The odds ratio of increased suicide risk ranges between 11 and 27 among those with a mood disorder. Among the mood disorders, depression continues to be a major precipitant for suicide and disability in adolescents. In one study, more than 60% of adolescents with depression had had a history of suicidal ideation, and more than 30% of them had attempted suicide. In 2004, the US Food and Drug Administration (FDA) issued a “black box warning” for antidepressants; a decrease in the use of these medications to treat depression and a subsequent increase in completed suicides followed. Recent meta-analysis suggests that the benefits of treating depression outweigh the risks associated with these medications. Data regarding bipolar disorder and suicide is discrepant, as some studies have indicated that having bipolar disorder is a risk factor for suicide whereas others have not associated it with increased risk [5].

Substance use disorders are highly comorbid with mood disorders and are a major risk factor for suicide in older youth. It also has been noted that the diagnostic profiles of youth with suicide attempt and youth with suicidal ideation are somewhat different and that substance abuse is more closely associated with suicide attempt than with ideation. Other psychiatric disorders, including anxiety, posttraumatic stress disorder (PTSD) and conduct disorder also have been reported to be associated with increased risk of suicide.

Previous Suicide Behaviors

A history of previous suicide attempt is the single most important predictor of subsequent suicidal behavior, while suicidal ideation in the absence of a plan is associated with a decreased risk of suicide attempt in the future. Regarding the course of suicidal ideation, it is

noted that 34% of individuals with suicidal ideation will make a suicide plan and 72% of those with a plan will make a suicide attempt.

The risk of a repeated suicide attempt is highest during the first 3-6 months following the initial attempt, with greater increased risk for male adolescents (30-fold) than for females (3-fold). In comparison to the general population, this risk remains elevated for the next 2 years. Ongoing suicidal intent and the potential lethality of the method used in the previous suicide attempt are other variables that impact the future course of suicidal risk. Youth who make highly lethal attempts and have serious suicidal intent are at extremely high risk for repeated attempts. Serious suicide intent is characterized by: 1) having certain beliefs about the suicide, 2) planning for a successful attempt, 3) taking measures to avoid detection and 4) expressing a wish to die.

Sexual Orientation

Recent research has found a 2-6-fold increase in non-lethal suicidal behaviors among homosexual youth. This risk is aggravated by comorbid depressive symptoms, substance use and a sense of victimization.

Familial Factors

A family history of suicide behaviors is one of the strongest predictors of suicide in youth. There is evidence that suicidal behavior is familial and transmitted irrespective of risk for other psychiatric disorders. Youth suicide is about 5 times more likely among children whose mothers have completed suicide, while first-degree relatives of suicide attempters have a 2-6-fold increased risk of suicidal behavior, compared to the general population.

Parental psychopathology, particularly depression and substance use disorder, has been associated with completed suicide and suicide attempts in youth; however, other studies have failed to find this association after controlling for the youth's psychopathology and psychosocial stressors. Loss of a parent to death or divorce before 12 years of age is a significant risk factor for completed suicide. There is also a consistent body of research linking youth suicide with family discord. Physical and sexual abuse and poor communication with the father are other risk factors for youth suicide attempts.

Access to Lethal Means

There is a consistent body of literature linking the presence of firearms at home with completed suicides. The availability of a gun at home makes it more likely that a gun will be used as a method of suicide. Absence of guns from the home makes it less likely that one will be used for a suicide attempt and may result in the use of less lethal means. There is also an association between stricter gun control laws and lower suicide rates.

PROTECTIVE FACTORS

Protective factors are those that decrease the likelihood of a suicide attempt, despite the presence of psychopathology.

Social Support

Social support, including the perception of family cohesion, is noted to be a protective factor for suicidal behavior. Adolescents who describe family life as emotionally supportive are 3-5 times less likely to engage in suicidal behavior than peers with the same levels of mood psychopathology and life stress. Presence of young children at home is associated with *increased* risk of a *first* onset of suicidal ideation, but in the long-term this factor is protective against suicide.

Religion

Empirical research on the effects of spiritual beliefs and religious practices is in its infancy; however, the protective role of religion against suicidal behavior in African Americans is noteworthy. It has been posited that some of this beneficial effect may be mediated by meeting with like-minded people in religious services, people who can provide support during times of stress.

PREVENTION

Youth suicide prevention strategies are aimed at identifying young people who are at risk of self-harm. Traditionally these measures are implemented in school, community and health-care systems [6].

School-Based Programs

Suicide awareness programs were implemented on the premise that adolescents are more likely to confide in and seek support from their peers than from adults. The objective of these programs was to provide knowledge and to improve help-seeking behaviors in students. During the last two decades, several studies have evaluated these programs but so far have failed to find a positive effect. There is in fact evidence to the contrary, that these curriculum-based suicide awareness programs can cause at-risk students to become more distressed and less likely to seek care. Because of these results, emphasis has shifted from promoting “suicide awareness” to alternative strategies described below.

Screening

One strategy that has received attention is direct case finding via systematic screening. School-wide screening programs use self-report questionnaires and individual interviews and have focused on identifying youth with depression, recent or past suicidal ideation and attempts, and substance use problems. This systematic screening is sensitive (83%-100%) in finding youth at risk, but is less specific (51%-76%). In order to minimize false positive screening results, direct case finding using standardized interviews such as the Diagnostic Interview Schedule for Children (DISC) are employed.

Skills Training

Skills training programs are aimed at strengthening cognitive and behavioral skills, with an emphasis on problem solving and coping skills, to both reduce the impact of suicide risk factors and enhance the effects of protective factors.

School Personnel Training (Gatekeeper Training)

Only one-tenth of high school teachers and one-third of school counselors believe that they can identify a student at risk of suicide. The purpose of this training is to increase knowledge and improve skill among school personnel with regard to identifying students at risk and making referrals when needed. These programs have shown improvement in intervention and referral skills among school personnel and are well accepted by school principals.

Community-Based Programs

Crisis centers and hotlines provide immediate support to youth in crisis. There is limited information about the efficacy of hotlines in the prevention of youth suicide, but about 15% of suicidal teens report having used these hotlines.

Firearms are one of the most common methods of committing suicide. Imposing restrictions on firearms as a means of preventing youth suicide is a key strategy but has shown conflicting results. Some studies have noted reduction in overall suicide rates while others have not found such an effect. While “mean-restricting measures” are a politically volatile topic in the US, providing education to parents of high-risk youth about limiting their access to firearms is less controversial and has been found to be marginally effective.

Healthcare-Based Programs

There is a dire need for pediatricians and primary care physicians to be trained to screen for suicide and mood disorders. In one study, 72% of primary care physician stated that they

have prescribed antidepressants to adolescents, but only 8% stated that they had formal training in the treatment of adolescent depression. Educational programs for health care professionals have shown promise in reducing suicide rates, but ongoing efforts toward enhanced education are warranted.

MANAGEMENT

Despite significant public interest and public health agency concern regarding youth suicide, there is limited data available to support recommending one intervention over another. Unfortunately, it is difficult to predict suicide, but management can be broadly categorized into ‘before self-harm’ and ‘after self-harm’ groups [7].

Management before Self-Harm

In this phase of treatment, identification of at risk youth by screening and adequate treatment or referral is important. Physicians should use routine health care visits to screen for mental illness and suicidal thoughts. Risk factors need to be identified, but caution is advised in interpreting these risk factors, as many commonly occur and do not lead to a suicide attempt in the majority of cases. Common identifiable risk factors are noted in table 1.

Primary care physicians should feel comfortable interviewing depressed teens and estimating their level of distress and the extent of their dangerousness to self and others. Table 2 lists common warning signs for adolescent suicide that should be considered during the evaluation.

The recommended method for assessment of suicidal thoughts is a direct interview of the at-risk youth. It is recommended that confidentiality be discussed, with an explanation that the physician must act in the best interest of the youth if there is a danger to self or others. The adolescent and the parents should be interviewed separately, as important information is likely to be withheld in the parents’ presence. The events preceding the suicidal intent and any self-mutilation behaviors should be assessed in detail. Self-mutilating behaviors are associated with significant psychopathology and should not be dismissed as being attention-seeking or manipulative; this behavior confers a 3-10% lifetime risk of eventual suicide.

Table 1. Common youth suicide risk factors

• Family: Separation, familial discord, impaired parent-child relationship, parental divorce, loss of a parent • Parents: Parental mental health problems • Psychopathology: Mood, psychosis, and sub-stance use disorders, panic disorder, history of aggression and impulsivity • Trauma: History of past physical or sexual abuse • History of previous suicide attempts • Difficulty adjusting to gender identity • Social: Difficulties in school, limited friends, bullying, not attending school, break-up with girlfriend/boyfriend, awareness of a friend’s self-harm
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Table 2. Warning signs of youth suicide

• Sudden negative change from baseline behavior • Agitation • Intoxication • Recent stressful event • Unprovoked episodes of crying • Indications of youth being in an abusive relationship • Recent onset of apathy and withdrawal • Hopelessness, guilt and feelings of worthlessness • Preoccupation with death • Giving away prized possessions • Worsening signs of depression

Physicians should ask questions to assess known risk factors as well as level of intent. Self-harming behaviors may or may not be associated with a true intent to commit suicide and should be assessed in the context of other risk factors, in order to avoid having a false sense of security. Physicians also should assess protective factors, as listed in Table 3, including the youth’s reasons for living. Individuals who believe that it is acceptable to end one’s life have a 14-fold increase in risk of making a suicide plan. The youth’s access to lethal means, including medications and guns, should be assessed, and parents should be counseled regarding reducing access to such items.

Table 3. Protective factors

• Family cohesiveness • Supportive family environment • Engagement in school activities, including sports • Good academic achievement • Religiosity

If there is any reason to believe that an adolescent is at risk of suicide, the physician or support staff must stay with the individual until a plan is established for providing an appropriate level of care. Although data is lacking, the safest course of action in these situations is to arrange for hospitalization, which provides a safe and supportive environment for the adolescent.

Management after Self-Harm

In the majority of cases, and adolescent who has attempted suicide presents to an emergency room, where a psychiatrist, psychologist or psychiatric nurse assesses them. A thorough psychosocial evaluation, including assessment of protective factors, should be conducted [8]. Collateral information should be taken from parents; however, in more than

80% of cases, the parents are unaware of a suicide attempt. The physician should explore the adolescent’s “concept of death” by asking: “What would you expect to happen?” or “Had you thought you would still be around to see the consequences of an attempt?” Lethality of attempt also should be considered, although it is not a good indicator of suicide intent, as children may not have the cognitive skills necessary to estimate the level of lethality of their attempt. Table 4 lists the characteristics of suicide attempt that suggest high self-harm intent.

Table 4. Characteristics that indicate high suicide intent

• Planned and prepared in advance • Told others beforehand about suicidal thoughts • Timed to avoid discovery by parents • Suicide note or a message left • Others were not informed after the act
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As noted above, inpatient hospitalization is usually the safest course of action following a teen suicide attempt; however, this decision must be made in conjunction with the available data about the presence or absence of factors that may indicate risk for repeated self-harm.

Table 5. Characteristics that indicate risk for repeated self-harm

• Lack of remorse and constant hopelessness after the failed attempt • History of previous suicide attempts • Family history of completed suicide attempt • Social isolation • Ongoing substance use problems • Psychosis

If the decision is made to discharge the patient from the emergency room, it is advisable to make a referral to a child and adolescent psychiatrist for ongoing care and treatment. Among those adolescents who make a suicide attempt, there is significant heterogeneity in the clinical presentation, and treatments should be tailored according to the youth’s developmental level. Goals of outpatient treatment are stress reduction and prevention of any future suicide attempts.

Problem Solving

These therapies help adolescents to identify triggers of suicidal thoughts and to develop behavioral alternatives to suicide so that they can cope with such situations if they arise in the future. As learning is often context dependent, exposure tasks are usually included within cognitive therapy approaches. During exposure tasks, the adolescent is asked to reimagine the

situation that led to the suicide attempt and then to imagine an alternative way of confronting such situations differently in the future in order to avoid making another attempt.

Family Therapies

Therapy approaches can also be extended to the whole family. Family therapies are structured and aim to provide education and promote understanding of suicidal behaviors. Issues of validation (“no one understands me”) can also be addressed within the family framework.

Other Therapies

Depending upon the presenting problem (e.g., substance use issues, depression, bullying, etc.), additional approaches may be suggested by the outpatient provider.

CONCLUSION

Suicide in children and adolescents is a complex and emotional problem for families and societies nationally and internationally [9]. Risk factors for suicide have been reviewed including personal characteristics, psychopathology of those committing suicide, history of previous suicide attempts, sexual orientation, familial factors, and access to lethal means of suicide. Protective factors include social support and religion. Principles of prevention have been considered including school-based programs, screening tools, skills training, Gatekeeper training, community-based programs, and health-care programs. Management includes principles involved in management before and after self-harm. Also considered are family therapies and therapies aimed at specific problems such as depression, bullying, substance abuse, and others [10]. Clinicians should be actively involved with their communities to seek prevention of suicide in children and adolescents.

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Chapter 511

PUBLIC HEALTH ASPECTS OF SUBSTANCE USE AND ABUSE IN ADOLESCENCE

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ABSTRACT

Substance use and abuse remains a major public health issue of adolescents throughout the world, including the United States. Encouragement by the media, peers, and many adults along with easy access to drugs of all types continues to lure countless millions of youth into use and abuse of many drugs. Results of the 2013 US Centers for Disease Control and Prevention Youth Risk Behavior Surveillance notes that there is significant abuse of drugs including illicit drugs but also prescription medications including stimulants, synthetic narcotics, and “recreational” cough syrups. This review considers various drugs, including tobacco, alcohol, marijuana, cocaine, heroin, hallucinogens, inhalants, and designer drugs.

Keywords: adolescence, health, substance abuse, public health, behavior

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INTRODUCTION

The United States SAMHSA (Substance Abuse and Mental Health Services Administration) directs a survey every year of the US population (non-military, non-institutionalized) who are 12 years of age and older [1]. The publication is called NSDUH (National Survey of Drug Use and Health) and its 2013 report noted that 24.6 million Americans 12 years of age and older used illicit drugs in that they had used an illicit drug during the month prior to the survey [1]. Racial disparities in illicit drug use are being identified by various studies [2, 3].

It is important that clinicians who are caring for adolescents be directly involved in teaching their patients how to prevent the use and abuse of drugs (Table 1); clinicians can also remain active in the management of substance abuse disorders, if it develops in their patient [4-11]. Adolescent exposure to illicit drugs can lead to a lifetime of medical and psychiatric effects [7]. The impact of illicit drugs, when taken during pregnancy, can be devastating to the fetus and the child [12]. Drug addiction involves mesocorticolimbic circuitry dysfunction and can be a lifelong problem, especially from cannabis, cocaine, nicotine, alcohol, and ecstasy [13]. A number of factors are involved in drug addiction, including the role of serotonin, ghrelin, and other factors that are under study [14, 15]. Death from the use of illicit drugs continues, as is seen with the use of heroin, amphetamines, inhalants, and others [16].

Table 1. Drugs of abuse

– Tobacco
– Marijuana
– Alcohol
– Cocaine
– Heroin
– Amphetamine
– Methamphetamine
– MDMA [<i>Ecstasy</i>]
– Flunitrazepam [<i>Rohypnol</i>]
– Gamma-hydroxybutyrate [<i>GHB</i>]
– Ketamine [<i>Ketalar</i>]
– LSD { <i>lysergic acid diethylamide</i> }
– PCP { <i>phencyclidine</i> }
– Tryptamines
– Barbiturates
– Designer drugs
– <i>Sports Doping and Performance Enhancing Drugs</i>

Screening for substance abuse [17] is critical because the neuro-psychiatric changes caused by some drugs (i.e., Ecstasy) may be irreversible and there have been reports of acute psychosis following marijuana and phencyclidine (PCP). One should also consider the likelihood of co-morbid conditions (see Table 2) in any adolescent or young adult with a history of continuing or repeated substance abuse; these conditions include ADHD, especially when associated with or secondary to a learning disorder where treatment is protective. Risk factors for drug abuse are reviewed in Table 3, while Table 4 considers non-specific

indicators of drug abuse and Table 5 outlines protective factors for drug abuse. Screening tests may be helpful, such as the CRAFFT questions for alcohol use. The role of prescription medication dependence must be considered also by clinicians [18].

A major contribution that the primary care clinician can provide is to establish a medical home for all youth including those with substance use [19]. The success of management is partially based on the underlying genetics of addiction for a person, especially with opioid, alcohol, and cocaine dependence [20]. Straightforward talk with teens about drug use is important in the screening process, though the teenager's estimates are often lower than the actual use. The clinician can work with the community in supporting community-based drug abuse prevention programs. Models of treatment are available ranging from brief to intensive management [21]. Attention to improving sleep dysfunction in those with substance dependence and depression is an important goal in overall management of these person [22].

Table 2. Co-morbid disorders of substance abuse disorder

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|--|
| <ul style="list-style-type: none">– ADHD– Oppositional Defiant Disorder– Conduct Disorder– Personality Disorders (antisocial, borderline, narcissistic)– Mood Disorders– Anxiety Disorders– Evolving Psychosis– Post-traumatic Stress Disorder– Eating disorders |
|--|

Adolescents generally progress from initial drug use to more serious drug use behavior in a pattern that is recognizable (see Table 6). At first, there is curiosity about drugs, though no drug use may be occurring. A need for acceptance by some peer group along with a low self-esteem may lead to experimentation with some drugs—often the “gateway” drugs— tobacco, alcohol and/or marijuana.

At some point the euphoria some drugs deliver is felt by the adolescent, typically at weekend parties or when combined with other substances. In some youth, there develops a state of actively seeking out the euphoria of drug use with widening of the types of drugs used (i.e., cocaine, Ecstasy, heroin, others), using personal drug paraphernalia, buying and/or stealing drugs on a regular basis, and becoming more dependent on one or more drugs. There is often a drop in grades, change of clothes, switching of peer group, and a strong denial of using/abusing any drugs. Seeking the euphoric state becomes the center piece of the individual's life which becomes out of control as the menu of drugs tried increases in scope. There may also be evidence of depression, worsening mood swings, acting out behaviors, suicide, violence, malaise, and lethargy. At this stage, the abuser seeks the euphoric state to feel “normal.” This progression from experimenting with drugs to abuse and burnout can be seen over months to years.

Table 3. Risk factors for substance abuse in adolescents*

Genetics	Alcoholism among 1st or 2nd degree relatives Male gender
Self/Individual/Personal	Abuse Early onset of drug use Early sexual activity / homosexuality Attention deficit disorders Antisocial behavior Aggressive temperament Depression Poor self-image Learning disorders Parental rejection Lack of self-control Low self-esteem Euphoric/mood altering effects of drugs Body modification (as cutting)
Family	Dysfunctional family dynamics Permissiveness Authoritarianism Parental conflict, divorce, separation Poor supervision, lack of supervision Poor parental role modeling
Community/Environmental/ Societal	Easy availability of drugs and alcohol Acceptance of drug use behavior Poor general quality of life in the neighborhood Media influence Criminal activities in neighborhood Cultural and religious sanction Low religiosity Employment Increased use of drugs and alcohol in certain ethnic groups
Peer Group Influence	Substance using peers Rebellion Rites of passage of puberty Risk-taking behavior Curiosity Desire to belong Independence Early tobacco use
School/Academic	Poor school performance Poor school environment Truancy

*Modified with permission: Patel DR and Greydanus DE: Substance abuse: a pediatric concern. *Indian J. Pediatrics* 66:557-567, 1999.

Table 4. Non-specific indicators of substance abuse*

Physical indicators	Academic indicators	Behavioral and psychological indicators
Unexplained weight loss Hypertension Red eyes Nasal irritation	Deterioration of short-term memory Poor judgment Falling grades	Risk taking behavior Mood swings Depression, withdrawal Panic reaction
Frequent “colds” or “allergies” Hoarseness Chronic cough Hemoptysis Chest pain Wheezing Frequent unexplained injuries Needle tracks Blank stares into space Scratch marks Tattoos Excessive acne Testicular atrophy Malaise	Frequent absences Truancy Conflicts with teachers Suspensions Expulsion	Acute psychosis Paranoia Lying Stealing Promiscuity Conflict with authorities and family members Runaway behavior Altered sleep pattern Altered appetite Poor hygiene Loss of interest in extracurricular activities Drug using peers Preferences for dress, music, movies, identifying with drug using culture Drug paraphernalia

*Used with permission: Patel DR and Greydanus DE: Substance abuse: a pediatric concern. *Indian J Pediatrics* 66:557-567, 1999.

Table 5. Factors protective of substance abuse in adolescents*

– Nurturing home environment – Good communication within family – Supportive parents, intact family, appropriate adult supervision – Positive self-esteem – Assertiveness – Social competence – Academic success – Good schools – Good general health – High intelligence – Positive adult role models – Peer group with positive personal attributes – Religious involvement – A personal sense of morality

*Used with permission: Patel DR and Greydanus DE: Substance abuse: a pediatric concern. *Indian J Pediatrics* 66: 557-567, 1999.

Table 6. MacDonald's stages of substance abuse*

Stage	1. Learning the mood swing	2. Seeking the mood swing	3. Preoccupation with the mood swing	4. Using drugs to feel normal
Mood Alteration	Euphoria Normal	Euphoria Normal Some pain	Euphoria Normal Definite pain	Euphoria Normal Marked pain
Feelings	Feels good; few consequences	Excitement; early guilt	Euphoric highs; doubts, including severe shame and guilt; depression, suicidal thoughts	Chronic guilt; shame, remorse, depression
Drugs	Tobacco Marijuana Alcohol	All of the above plus inhalants, hashish, depressants, methamphetamine, prescription drugs	All listed plus psilocybin, PCP, LSD, cocaine	Whatever is available
Sources	Peers	Buying	Selling	Any way possible
Behavior	Little detectable change; moderate after-the-fact lying	Dropping extracurricular activities and hobbies; mixed friends (straight and drug users); dress changing; erratic school performance and truancy; unpredictable mood and attitude swings; manipulative behavior	"Cool" appearance; straight friends dropped; family fights (verbal or physical); stealing (police incidents); pathological lying; school failure; truancy, expulsion, jobs lost	Physical deterioration (weight loss, chronic cough); severe mental deterioration (memory loss and flashbacks); paranoia, volcanic anger; school dropout; frequent overdosing
Frequency	Progress to weekend use	Weekend use progressing to four to five times per week; some solo use	Daily; frequent solo use	All day every day

PCP = phencyclidine; LSD = lysergic acid diethylamide.

*Used with permission: Patel DR and Greydanus DE: Substance abuse: a pediatric concern. *Indian J Pediatrics* 66:557-567, 1999.

DSM-5

The American Psychiatric Association published its 5th edition of the "Diagnostic and statistical manual of mental disorders" (DSM-5) in 2013 [23]. Some changes were seen in this 5th edition in contrast to the 4th edition [24] (see the preface). The DSM-5 provided changes in the diagnostic criteria of substance related disorders (SRD). In the previous edition (DSM-IV-TR, 2000), SRDs were classified as substance use disorders (SUD) and substance induced disorders (SID). SUD was also identified as "abuse" and "dependence" disorders according to specific substances (i.e., opioid abuse and dependence, alcohol abuse and dependence, and so forth). SID included such classifications as intoxication, withdrawal, delirium, anxiety and others as induced by specific substances (i.e., opioids, alcohol, others) [25]. The diagnoses of "abuse" and "dependence" categories needed their own specific criteria. Abuse could be

diagnosed by meeting only one of those criteria while dependence needed at least three of those criteria.

In the DSM-5 SUD and SID terms remain but in SUD the previous diagnostic distinction between abuse and dependence was removed and a single category was developed called “substance use disorder” that ranged from mild to severe. A mild disorder is defined as meeting 2-3 of the SUD criteria versus 4-5 for moderate and 6 or more for a severe disorder (American Psychiatric Association, DSM-5, 2013).

In the DSM-5 there was an increase in the diagnostic threshold in that at least 2 criteria (versus 1) are required for an SUD. “Craving” is added as a new criterion and refers to an intense desire or urge for a drug. Also, the criteria, “problems with law enforcement” was removed since laws vary from country to country and over time.

A variety of illicit drugs are reviewed in this chapter with prevalence mainly based on the US Centers for Disease and Prevention (CDC) 2013 Youth Risk Behavioral Surveillance (YRBS) [2]. The reader is encouraged to review this document. A number of other drug issues are considered in this report including taking steroids without a doctor’s prescription, taking prescription drugs without a doctor’s prescription, and ever injecting any illegal drugs. This survey reveals that 3.2% of US high school students had taken steroid pills or shots without a doctor’s prescription; this increased from 2.7% in 1991 to 3.2% in 2013 [2].

The report also notes that 17.8% of students had taken prescription drugs without a doctor’s prescription one or more times during their life; these drugs included Oxycontin, Percocet, Vicodin, codeine, Adderall, Ritalin, or Xanax. The prevalence was 20.7% in 2011. Also, 1.7% of students had used a needle to inject any illegal drug into their body one or more times during their life; this prevalence was 2.3% in 2011 [2]. The survey also noted that 22.1% of students had been offered, sold, or given an illegal drug by someone on school property during the 12 months prior to the survey; this prevalence was 24.0% in 1993.

ENERGY DRINKS

The negative effects of energy drinks often containing large amounts of caffeine is becoming an increasing problem in adolescents and young adults; cardiovascular and neurological adverse effects are particularly seen [26]. The DSM-5 lists four caffeine-related disorders: caffeine intoxication, caffeine withdrawal, other caffeine-induced disorders, and unspecified caffeine-related disorders [23].

DESIGNER DRUGS

Clandestine chemists and surreptitious laboratories are developing a wide variety of designer drugs or “legal highs” which are analogs of such drugs as opioids, cannabinoids, phencyclidine, amphetamine, and others [27-32]. Their development can be traced to the 1960s but their production has escalated since 2008. They are used to mimic the effects of these drugs such as synthetic cannabinoids which mimic the psychoactive effects of cannabis and have been called spice drugs or K2 drugs. Cathinone is a natural occurring amphetamine analogue that is found in the *Catha edulis* plant leaves and synthetic cathinones (such as

mephedrone or 3,4-methylenedioxypyro-valerone[MDPV]) are derivatives of phenylalkylamines which as amphetamine-like effects. Some are piperazine derivatives. Designer psychostimulants have been developed to mimic the effects of amphetamines, cocaine, or ecstasy. Methoxydine and methoxetamine are designer drugs with phencyclidine effects.

They may be sold on the internet or elsewhere as “bath salts” or “plant foods” and marked as “not for human consumption” in order to escape legal prosecution. Many adverse side effects may result depending on the exact product, its doses, what impurities it contains and other factors. Their use can lead to negative effects that are cardiovascular, neurological, renal, psychotic and others including death. Management of adverse reactions can be difficult and complicated by lack of knowledge of the patient and clinician what was taken. Negative reactions to synthetic cathinones (“bath salts”) for example, focus on lowering the agitation and psychosis that are seen along with supporting renal perfusion; benzodiazepines and antipsychotics are used [33]. Persons seeking euphoric experiences, including adolescents and young adults, should be educated about these designer drugs that are increasingly becoming available outside local laws.

TOBACCO

Tobacco remains a widely used and abused drug that enjoys a high level of acceptance by society, including governments that allow it to be grown for profit. In a 1999 national survey conducted by the Centers for Disease Control, one in every eight middle-school students reported using some form of tobacco (cigarettes, cigars, bidis, or kreteks) in the past month. Bidis (or beedies) are brown, hand-rolled, flavored tobacco while Kreteks (clove cigarettes) contain a mixture of tobacco and cloves; both are imported from Indonesia. Electronic cigarettes (E-cigarette) are now available on the market place which also can pose a threat to adolescents, though more research is needed [34, 35]. The role of nicotine as a gateway drug has been shown by research [36, 37]. The DSM-5 lists a number of tobacco-related disorders: tobacco use disorder (mild, moderate, severe), tobacco withdrawal, other tobacco-induced disorders, and unspecified tobacco related disorders [23].

The 2013 Youth Risk Behavioral Surveillance (YRBS) reports that 41.1% of high school students had ever tried cigarette smoking with a prevalence of 42.5% in males and 39.6% in females [2]. The prevalence was higher among white and Hispanic students than black students. The prevalence of ever smoked cigarettes from 70.1% in 1991 to 41.1% in 2013. This survey also revealed that 9.3% had smoked a whole cigarette for the first time before age 13 years and this dropped from 23.8% in 1991 to 9.3% in 2013. Also, 15.7% of students had smoked cigarettes on at least one day during the 30 days prior to the survey and this had dropped from 27.5% in 1991 to 15.7% in 2013. It also noted that 5.6% of students had smoked cigarettes 20 or more days during the 30 days before the survey and this dropped from 12.7% in 1991 to 5.6% in 2013. Among the 15.7% who currently smoke cigarettes, 8.6% had smoked more than 10 cigarettes per day on the days they smoked during the 30 days before the survey; this dropped from 18.0% in 1991 to 8.6% in 2013 (Kann, 2013).

Among the 15.7% who currently smoked cigarettes, 48.0% had tried to quit smoking cigarettes during the 12 months before the survey; this prevalence dropped from 57.4% in 2001 to 48.0% in 2013. Also, 8.8% of students had ever smoked at least one cigarette daily

for 30 days and this dropped from 20.0% in 2001 to 8.8% in 2013. The 2013 survey reported that 4.0% of students had smoked cigarettes on all 30 days during the 30 days before the survey; this prevalence dropped from 9.8% in 1991 to 4.0% in 2013. Also, 3.8% had smoked cigarettes on school property on at least one day during the 30 days before the survey; this prevalence dropped from 13.2% in 1993 to 3.8% in 2013.

The 2013 report reveals that 8.8% of students had used smokeless tobacco on at least 1 day during the 30 days before the survey; this dropped from 11.4% in 1995 to 8.8% in 2013. It also notes that 12.6% of students had smoked cigars, cigarillos, or little cigars on at least one day during the 30 days before the survey; this decreased from 22.0% in 1997 to 12.6% in 2013. It also noted that 22.4% of students had reported current cigarette use, current smokeless tobacco use, or current cigar use; this prevalence had decreased from 43.4% in 1997 to 22.4% in 2013 [2].

General

The smoke of cigars is more alkaline than that of cigarettes, dissolves more easily in saliva, and achieves the desired dose of nicotine without the need to inhale smoke into the lungs. Cigars are capable of providing high levels of nicotine at a rate fast enough to produce clear dependence, even if the smoke is not inhaled. The risk of lung cancer for cigar aficionados (well-known to cigarette smokers), is much higher than once thought. This rate increases more for cigar smokers if they were previous cigarette smokers. A class of carcinogenic compounds known as tobacco-specific, N-nitrosamines (TSNA) is present in cigar smoke at significantly higher levels than in cigarette smoke. Examination on a “per gram of tobacco smoke” basis reveals that tar, carbon monoxide, and ammonia are produced at greater quantities by cigars. When equal doses are applied, the tar produced by cigars exerts a greater tumor-producing activity in mice because of higher concentrations of carcinogenic polycyclic aromatic hydrocarbons.

Nicotine, an important component in tobacco, is highly addictive and a number of genes are involved such as the nicotinic receptor gene cluster on chromosome 15q25 [38]. Current research shows that adolescents experience symptoms of nicotine dependence long before they become everyday smokers. Early and continued intervention, including the clinical use of such instruments as the HONC (hooked on nicotine checklist), is required because initiation of smoking during adolescence is related to drunkenness-oriented alcohol use and an increased risk for future substance abuse. The most powerful predictor of drunk driving in this research is regular smoking at age 14.

Nicotine is absorbed over various sites: lungs, buccal mucosa, skin, and gastrointestinal tract. Approximately 10 mg of nicotine is found in one cigarette; when smoked, 1.0 to 3.0 mg of nicotine is absorbed by the user. Nicotine is rapidly taken up by the brain’s nicotinic acetylcholine receptors that are found in numerous non-cholinergic presynaptic and postsynaptic areas. The tobacco addict has chronic exposure to many dangerous chemicals, including nicotine, tar, carbon monoxide, arsenous oxide, radioactive polonium, benzopyrene, others. The addicted cigarette abuser becomes an adult with significant risks for the many well-known complications of this drug—lung cancer, emphysema, laryngeal carcinoma, other

cancers, heart disease, and many other disorders. Lung cancer in female adult smokers is now more common than breast cancer.

A common condition noted in smokers and reverse smokers is keratosis of the mucosal palate posterior to the rugae. This was originally described in 1926 and is caused by the concentrated hot steam of smoke and chemicals producing a nicotine or “smoker’s patch.” Reverse smoking has been associated with dysplastic and malignant changes over time. Recent research also notes negative effects which occur from smoking during pregnancy, including lower birth weight and attention deficit hyperactivity disorder. Nicotine staining of the teeth, crow’s feet from the occlusion of micro-arterioles near the eyes, bad breath, cough, and dyspnea are also well-recognized and widespread stigmata of smoking. Passive smoking is also known to be dangerous to those exposed to the smoking of others. Oral cancer is a serious consequence of using chewing tobacco.

It is important for clinicians caring for adolescents to join the struggle to limit the use of tobacco by adolescents. For example, advertising to youth must be prevented, and efforts to reduce the acceptance of tobacco by society strengthened. The prevention and reduction of adolescent tobacco use and abuse must be encouraged on a national and statewide level. On a local level, a broad range program is recommended that targets the family, community, and schools.

Pharmacologic Management

Table 7 reviews current pharmacologic management options for tobacco addicts who are motivated to quit using tobacco products [39]. Clinicians should take every opportunity to remind tobacco-addicted teens that their habit is very dangerous and help is available when they are ready to stop. Psychosocial issues in the lives of teen smokers and underlying cues to smoking should be reviewed with the adolescent. Special situations may arise, such as the pregnant adolescent who also smokes. A variety of nicotine replacement (NT) products are produced, as reviewed in Tables 7 and 8; the rate of quitting smoking is doubled by use of these products for the motivated smoker (i.e., 30%), in contrast to those seeking to stop smoking without pharmacologic agents (i.e., 15%). The choice of NT product is patient-driven; teens should not smoke while on NT products, though no overt negative sequelae have been reported in such cases.

The NT patch is prescribed for two months (changed each morning), using a high strength patch for one month, and then the lower dose for one more month (see Table 8). The patch is not placed over a site with hair. Up to half will develop local dermatitis, usually improved with local hydrocortisone application. The patch is applied only while awake if patch-induced secondary vivid dreams or insomnia develop. The NT gum (nicotine polacrilex) has a bitter taste that many teens do not like; some youth feel embarrassed while choosing the nicotine gum. If the tobacco addict smokes over 25 cigarettes a day, prescribe the 4 mg gum; eventually lower the patient to the 2 mg gum. Since acidic liquids reduce nicotine absorption, they should not be used for 15 minutes before gum use and while chewing. Instructions to give patients who chew this gum are provided in Table 9. Adverse effects of this gum, though temporary, include dyspepsia, mouth soreness, jaw ache and hiccups.

Table 7. Pharmacologic products available in the USA to treat tobacco addiction*

Nicotine Medications	
Nicotine gum	– Nicorette OTC – Nicorette DS OTC
Nicotine patch	– Nicoderm CQ(SmithKline Beecham) OTC – Nicotrol Patch (McNeil) OTC
Nicotine inhaler	– Habitrol (Novartis)
Nasal spray	– Prostep (Lederle) – Nicotrol Inhaler (McNeil) – Nicotrol Nasal Spray (McNeil)
Non-Nicotine Medications Bupropion	- Zyban SR (Glaxo Wellcome) - Sustained-release tablets

*Reprinted with permission from: Patel DR and Greydanus DE: Office interventions for adolescent smokers. State of the Art Reviews: *Adolescent Medicine* 11 (3): 1-11, 2000.

Table 8. Nicotine patch regimens*

Brand	Duration	Dosage
Nicoderm CQ and Habitrol	4 weeks then 2 weeks then 2 weeks	21 mg/24 hours 14 mg/24 hours 7 mg/24 hours
Prostep	4 weeks then 4 weeks	22 mg/24 hours 11 mg/24 hours
Nicotrol	8 weeks	15 mg/24 hours

*Reprinted with Permission from: Patel DR and Greydanus DE: Office interventions for adolescent smokers. State of the Art Reviews: *Adolescent Medicine* 11 (3): 1-11, 2000.

Table 9. Recommendations for use of nicotine gum

Chew a piece each hour for 6 weeks. Then, chew a piece every 2 hours for 3 weeks. Finally, chew a piece every 4 hours for 3 weeks. Maximum limit is 30 pieces per day for the 2 mg gum and 20 pieces per day for the 4 mg gum. Chewing instructions: – Chew slowly until a peppery taste appears (often after 15 chews) – Then put the gum between the cheek and buccal mucosa until the peppery taste has disappeared (often one minute) – Start chewing again and repeat the above cycle – Get rid of the gum when the peppery taste is gone (often 30 minutes).
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The nicotine inhaler is designed to mimic the hand-to-mouth movement of the smoker; 4 mg of nicotine are delivered from the cartridge which contains about 10 mg overall (see Table 7). Low nicotine levels are produced and the user inhales 6-16 cartridges daily. Adequate nicotine absorption is accomplished with 80 inhalations over 20 minutes; absorption is through the oral mucosa. It is prescribed for 3 months and then slowly tapered off over 3 months. Adverse effects that often improve over time include coughing, dyspepsia, irritation of the mouth and throat, and nasal irritation.

The nicotine nasal spray is provided as one to two doses (1 to 2 mg of nicotine) per hour over 3 months; there is a rapid rise in nicotine serum levels (see Table 7). It is prescribed as a minimum of 8 doses per day, not over 40 per day or over 5 inhalations per hour. Bronchospasm may occur and the nasal spray is not used for nicotine addicts with asthma. Other adverse effects include cough, rhinitis, nasal irritation, sneezing, and water eyes. The use of electronic cigarette for the cessation or reduction of smoking in adults remains under active research [40].

Non-Nicotine Therapy

The use of bupropion (see Table 7) in the nicotine addict who is motivated to quit smoking is helpful in up to 40% of cases; its relative success is attributed to the drug's ability to lower the classic nicotine craving while improving the nicotine-withdrawal problems of weight gain and depression. It was found to be twice as effective as placebo. It is prescribed as Zyban in a sustained-release form that is provided as 150 mg a day for three days; if tolerated, it is increased to 150 mg twice daily. The dose should not exceed 300 mg a day. Additionally, the second dose should not be given less than 8 hours after the first to reduce the incidence of a seizure. Though NT replacement therapies should not officially be started while the adolescent is still smoking, it is acceptable to start the teen smoker on bupropion while still using nicotine; a date of stopping the tobacco should still be negotiated while providing the bupropion. Bupropion is contraindicated in adolescents who have overt seizures and those with factors that increase the risk for seizures; the latter includes those with a history of epilepsy, an eating disorder, central nervous system tumor, and any medications that may lower the seizure threshold. Bupropion is contraindicated in those on MAO inhibitors. Bupropion adverse effects include insomnia, skin reactions, tremors, headaches, and dry mouth.

Clonidine and nortriptyline may be useful to some late adolescents and adult smokers to help them quit using tobacco. Various medications have been studied but not shown to help improve the craving for nicotine; these include buspirone, mecamlamine, naltrexone, doxepin, and oral dextrose. Another smoking cessation product is varenicline tartrate (Chantix®), an alpha-4 beta-2- nicotinic acetylcholine receptor partial agonist that binds to central nervous system receptors with a greater affinity than nicotine. It is FDA approved for adults with nicotine addiction and may be more effective than bupropion. Abstinence rates are 22% versus 16% for bupropion and 8% for placebo. In the short term, 44% of study patients quit smoking v. 30% using Zyban. Starting dose is 0.5 mg per day for three days, twice a day for 4-7 days, then 1 mg twice daily. Chantix® decreases the pleasure of nicotine use and lessens the withdrawal craving. The major side effect is nausea, but weight gain is not a problem. There are reports of suicidality, agitation, hostility, and agitation [7]. The use of cytisine, a partial agonist that binds the nicotinic acetylcholine receptor, is under study [41]. The use of a nicotine vaccine is also under active research [42, 43].

MARIJUANA

Marijuana (cannabis) remains a popular euphoric and hallucinogenic drug for millions of youth and adults; it has many names, including “pot,” “hash,” “weed,” “doobs,” “BC Bud,” “Ganja,” “grass,” “smoke,” and others. It is the most widely used illicit drug in the United States, accounting for up to 85% of the illicit drug trade. The 2013 YRBS reported that 40.7% of high school students had used pot one or more times during their life [2]. Previous CDC surveys noted that the category of “ever used marijuana” had increased from 1991-1997 (31.3% to 47.1%); it did then decrease from 1997 to 2013 (47.1% to 40.7%) [2]. The survey noted that 8.6% of students had tried pot for the first time before age 13 years and 23.4% of students had used pot one or more times during the 30 days prior to the survey. The prevalence of having ever used pot was higher among males versus females and higher among black and Hispanic youth versus white youth. In the 2013 National Survey on Drug Use and Health marijuana was the most commonly illicit consumed drug with 19.8 million users 12 years of age and older over the past month of the survey [1]. From 2006 to 2013 the number of persons using daily cannabis almost doubled in this survey.

This controversial drug is derived from *Cannabis sativa* or *C indica* (hemp plant) and the active euphoric chemical is delta-9-tetrahydrocannabinol or THC. It is present in the dried leaves, stems, seeds, flowers (sensimilla) and oil. This major lipophilic drug works on the cannabinoid receptors (ECS) in the mesocortical and limbic systems. The marijuana of the 1960s and 1970s’ hippie generation contained only 2% THC, while the Hawaiian sensimilla product was about 3% THC. Today’s street pot can vary from 3 to 7%+ THC content, while cultivated sensimilla can contain 7 to 13%+. A popular brand of pot is BC Bud, a product imported by the ton from Canada at \$3000- 8,000 dollars per pound; it is grown in British Columbia and may contain up to 24% active ingredients. Many growers, commercial exporter consortiums (Canada), a significant fraction of the public and their elected officials, as well as active pot users are actively advocating for the legalization of marijuana.

Cannabis contains over 60 phytocannabinoids including cannabitol (or CBN--metabolite of THC), cannabidiol (or CBD--isomer of THC), cannabigerol (or CBG-- alpha-2-adrenergic receptor agonist), tetra-hydrocannabivarin (or THCV;THV--TCH homolog), and cannabichromene (or CBC) [8, 11]. Many other chemicals are found in this complex plant, including terpenoids, and endocannabinoids (such as 2-AG [2-arachidonoyl glycerol] and anandamide [arachidonoyl ethanolamide]). The role of pot smoking as a gateway drug is well-known and many smokers also use tobacco, alcohol, and other drugs.

Commercial preparations of synthetic cannabinoids include nabilone (schedule II drug), dronabinol (synthetic THC in sesame oil; schedule III drug), and nabiximols (phytocannabinoid marketed in Canada). Dronabinol capsules were approved on May 31, 1985 by the US Food and Drug Administration (FDA) for nausea and emesis management due to cancer chemotherapy; the US FDA also approved dronabinol on December 22, 1992 for persons with AIDS who have anorexia associated with weight loss. Oral nabilone was approved by the US FDA on December 26, 1985 for nausea and vomiting due to cancer chemotherapy. Though these and other cannabis products are suggested for various other medical disorders, they are not approved by the FDA. Smoking marijuana is not approved by the FDA nor leading medical organizations because there is no research to support smoking pot and because of the many potential adverse side effects from cannabis smoking

(Greydanus, 2014, 2015). In Canada the oromucosal spray, nabiximols, is indicated for management of cancer pain in addition to neuropathic pain and spasticity seen in persons with multiple sclerosis.

Though usually smoked, marijuana can also be eaten in such homemade concoctions as cookies, brownies, and spaghetti. The typical cannabis cigarette (joint) usually contains approximately 20 mg of THC obtained from about a gram of leaves and buds; however, much variation can be noted. The “blunt” is another popular way to smoke pot and consists of a cigarette with marijuana added to a hollowed cigarette. “Pot” is often combined with other drugs, such as phencyclidine, though glutethimide and methaqualone were also popular in the past as additives. PCP (phencyclidine) is frequently dissolved in an organic solvent, such as formaldehyde, in which a joint or hand-rolled cigarette is first dipped, dried, and then smoked. This preparation is variously referred to as “wet” “water,” or “Sherms”; the latter term refers to the well-known tobaccoist Nat Sherman. This is a good reason for doing a urine drug test with informed consent and assent of a using teenager.

Marijuana use results in a potent sensation of euphoria (“buzz”) that is noted within minutes of its use, and which can last for hours. Both THC and its metabolites are highly lipid soluble and are stored in fatty tissue. Serum half-life is 19 hours. Marijuana can be found on urine drug screen and stool for as long as one month following regular use, and ten days after a single use. The behavioral effects are mediated by cannabinoid receptors and results in the release of dopamine in the nucleus accumbens. The effects of THC also include relaxation, time and perceptual distortions, and heightened sensory experiences such as listening to music, watching television, or eating (“getting the munchies”). Some drugs (alcohol or diazepam) may potentiate the sedative effects of marijuana, while other drugs (cocaine or amphetamines) worsen the stimulatory effects of marijuana.

A large number of potential adverse effects are seen with smoking cannabis, including cardio-vascular, pulmonary, gastrointestinal (cannabis hyperemesis syndrome), dental, and central nervous system effects [8, 11]. Cardiovascular adverse effects can include arteritis, cardiomyopathy, myocardial infarction, sudden cardiac death, transient ischemic accident (TIA), cardiovascular accident (CVA), and cardiac arrhythmias. Pulmonary side effects can include chronic cough, allergic hypersensitivity, bronchitis, bullous emphysema (COPD: chronic obstructive pulmonary disease), pneumothorax/pneumomediastinum, pulmonary dysplasia, pulmonary tuberculosis, other respiratory infections, and even dust disease (talcosis) in hemp workers.

Potential adverse dental effects can include dental caries, dental dysplasia, gingival enlargement, gingivitis, leukoedema, nicotinic stomatitis, oral infections, periodontal disease, poor dental health, uvulitis, and xerostomia. Potential adverse effects on the offspring of females smoking cannabis while pregnant include low birth weight, preterm labor, small for gestational age, treatment in a neonatal intensive care unit, and various childhood effects such as inattention problems, problem-solving problems, aggression, executive function dysfunction, problems with memory and processing information, and depressive symptoms.

Cannabis poisoning can arise from consuming oral cannabis products and this is increasing being seen in young children whose parents are pot smokers. Cannabis smoking (including Spice drugs) increases risks for MVAs (double or more) and this can be worsened when combined with other drugs (i.e., alcohol, others). If one has smoked cannabis, 8 or more hours should pass before driving a motor vehicle. Pot smoking also increase road rage.

The central nervous system of young adolescents is very sensitive to cannabis and adverse effects may include decline in IQ, decreased coordination, distorted visuospatial perception, impaired executive function, impaired novel learning, impulsivity, inattention, memory loss, neuropsychiatric disorders (i.e., psychosis), and cannabis dependence. The DSM-5 has listed a number of cannabis-related disorders including cannabis use disorder (mild, moderate severe), cannabis intoxication (with or without perceptual disturbances), cannabis withdrawal, other cannabis-induced disorders, and unspecified cannabis-related disorders [23].

Management of cannabis use disorder is very difficult and there is no pharmaceutical agent approved for its management. Research continues to find medications that may be of help to those with cannabis use disorders and these include alpha 2 adrenergic agonists, antipsychotics (atypical), benzodiazepines, cannabidiol, dronabinol, gabapentin, lithium, lofexidine, nabilone, nabiximols, N-acetylcysteine (NAC), N-arachidonylethanolamine (anandamide), nefazodone, 2-arachidonoyl glycerol (2-AG), and others [11].

Therapy is typically prescribed and its efficacy may be low because of lack of motivation for the person with cannabis dependence to stop their drug of choice. Approximately 25% of the 19.8 million cannabis users in the United States meet the DSM-5 criteria for cannabis use disorders. Many fail to seek treatment and this tends to be due to failure to recognize the severity of their disorder and this denial may reflect their own brain dysfunction. Of the 7.6 million persons aged 12 or older who need treatment for an illicit drug use problem in 2013, only 1.5 million (19.5%) received management in a specialty program [11]. Of the 6.1 million persons who needed but did not receive management, only 395,000 (6.4%) reported they were aware of a need for treatment.

ALCOHOL

Alcohol continues to be among the most used and abused “licit” substances (#1 choice of 29% youth) that enjoys a wide range of societal acceptance [44]. Alcohol is the leading cause of substance use morbidity and mortality contributing to 8,000 deaths each year. Surveys have revealed that US high school seniors have a lifetime prevalence of over 80%, with over 50% noting alcohol use during the previous survey month, and 4% admitting to daily use. The average age that alcohol is first misused is age 12. The prevalence of alcohol use is higher among white and Hispanic youth than among black youth. It is important to ask youth if they drink and if so, what their drinking pattern is; repeated use of alcohol or other substances is not part of normal adolescent defiant behavior. The CRAFFT screening test for adolescent substance abuse is an easy to use instrument for screening drug use [17, 45].

About half of adolescents who are victims of a motor vehicle accident or suicide were drinking before their death. The most common pattern of alcoholic consumption is binge drinking, as defined by 5 drinks in a row in males, and four in females. Blacking out spells are frequently a result of binge drinking behavior. Binge drinking is directly related to drunk driving, increased sexual activity (and teen pregnancy), smoking, dating violence, attempted suicide, and other substance abuse.

The 2013 Youth Risk Behavioral Surveillance (YRBS) revealed that 66.2% of high school students had had at least one drink of alcohol on at least one day during their life [2].

This 2013 survey also revealed that 18.6% of students who had drunk alcohol (apart from a few sips) for the first time before age 13 years of age, 34.9% of students had at least one drink of alcohol on at least 1 day during the 30 days before the survey, and among the 34.9% of students who currently drank alcohol - 41.8% had usually obtained the alcohol they drank from someone who gave it to them during the 30 days before the survey. The prevalence of having ever drunk alcohol was higher in females versus males and higher in Hispanic youth than white or black youth.

The survey noted that 20.8% of students had had five or more drinks of alcohol in a row on at least 1 day during the 30 days prior to the survey. Also, 6.1% of students noted the largest number of drinks they had in a row during the 30 days before the survey was 10 or more. In the 2013 YRBS 21.9% of high school students rode in a car at least once with someone who had been consuming alcohol [2]. Of the 64.3% of high school students who drove a car or other vehicle during the 30 days before the survey, 10.0% had driven after drinking alcohol during the 30 days prior to the survey.

Alcohol Effects

Alcohol is a central nervous system depressant that also induces euphoria in the user; tolerance and psychological dependence may develop, in addition to physiologic dependence in alcoholics. Alcohol drinks vary in their amount of this drug, ranging from 3% to 6% in beer, 12% in wine, and 50% in various liquors. Legal intoxication is usually 0.08 to 0.10 g/dl, though judgment may be impaired at a blood alcohol concentration (BAC) of 0.01 g/dl or lower. Central effects occur at 20-30 ng/dl. Acute intoxication may lead to respiratory depression, coma, and death. Adolescents should be carefully educated about the dangers of alcohol consumption, including the deadly mixture of driving and drinking that kills “innocent” as well as alcohol-consuming victims.

Alcohol dependence is a serious psychiatric disorder in adults, and youth may be involved in this disorder as well. The genetics of alcohol dependence has been studied for decades and its molecular biologic basis is being revealed [46, 47]. The abuse of alcohol depletes a number of so-called “comfort” hormones (opioid peptides, serotonin, gamma aminobutyric acid, dopamine) in addition to inducing stress hormone release (i.e., corticotropin releasing factor). Many adolescents do not stop at the social drinking or experimental stage and rapid progression can develop through the later stages of drug abuse. Youth who abuse alcohol tend to come from families where problem drinking occurs as well as families where problem drinking is absent. The DSM-5 lists a number of alcohol-related disorders: alcohol use disorder (mild, moderate, severe), alcohol intoxication, alcohol withdrawal, other alcohol-induced disorders, and unspecified alcohol related disorders [23].

Medical complications of problem drinking include intoxication, pancreatitis, gastritis, worsening of co-morbid medical disorders (i.e., diabetes mellitus, epilepsy), and toxic psychosis. The alcohol withdrawal syndrome presents with such symptoms as tremors, seizures, hallucinations, and even overt delirium tremens. Youth who abuse alcohol may develop anemia, macrocytosis, and elevation in alkaline phosphatase, bilirubin, uric acid, glutamic-oxaloacetic, gamma glutamyl transpeptidase, or pyruvic transaminases. The diagnosis of alcohol abuse disorder is made mainly by a history of excessive alcohol use, and

not on the basis of a positive serum or drug screening test. The fetal alcohol syndrome and the effect of alcohol on neuronal migration and pruning (apoptosis) in the unborn fetus exposed to intrauterine alcohol are well recognized consequences of alcohol consumption during pregnancy. The mortality risk to the fetus is 5%, while the accidental risk of harm to family members of alcohol users is increased considerably.

Management of Alcohol Abuse

Acute alcohol ingestion is treated with gastric emptying, intravenous fluids, glucose, respiratory support, and sometimes, dialysis. The possibility of additional drug use is suggested by respiratory depression greater than that suggested by the available BAC; head injury may also have occurred in this situation. Medications used in the management of alcohol withdrawal syndrome include clorazepate, lorazepam, chlordiazepoxide, diazepam, and various antipsychotics. Medications approved for the management of adults with alcohol dependence include acamprosate, calcium carbimide, naltrexone, tiapride, and disulfiram. Various medications have been used, but have not been approved for use in adults with alcohol dependence; these include buspirone, carbamazepine, nalmefene, selective serotonin reuptake inhibitors, and tricyclic antidepressants [7]. Mothers Against Drunk Drivers (MADD) and self-help groups (Alcohol Anonymous [AA] and Alateen) are important programs found in many communities that help with the wide-spread problem of alcohol use and abuse in adolescents and adults. Attention to the sleep disruption seen in those abusing alcohol (and other drugs) is important in an overall management strategy [48].

AMPHETAMINES

Amphetamines (Dexedrine, Benzedrine, Desoxyn, chalk, meth, speed, Mollies, black beauties) are classic central nervous system stimulants which lead to a variety of complications, as listed in Table 10.

The DSM-5 lists a number of stimulant-related disorders with regard to amphetamine-type substance: stimulant use disorder- amphetamine-type substance (mild, moderate, severe), stimulant intoxication- amphetamine-type substance, stimulant withdrawal— amphetamine-type substance, other stimulant-induced disorders- amphetamine-type substance, and unspecified stimulant related disorder- amphetamine-type substance [23].

Amphetamines can be taken to develop euphoria, lessen fatigue, improve attention, lose weight, and/or allow continued sports performance. In 2003, high school seniors reported a lifetime use of 14.4%, 9.9% over the past year, and 5.0% over the past 30 days of the survey. In the 2008 MTF, Johnson reported a decline in stimulant use with a prevalence of 4.5% in 8th graders and 6.8% in 12th graders [49]. The use of amphetamines has significantly decreased but is next in frequency of abuse to marijuana. Amphetamine can be abused in various forms—oral, subcutaneous, or intravenous. Amphetamine “look alikes” have become more available through mail order sites or from garage production using simple compounds such as phenylpropanolamine, pseudoephedrine, and ephedrine—including the herbal ma huang.

Table 10. Amphetamine adverse reactions

–	Anorexia
–	Anxiety
–	Exhaustion
–	Hyperactivity
–	Hyperhidrosis
–	Hypertension
–	Insomnia
–	Mydriasis
–	Personality changes
–	Psychotic experiences
–	Tachycardia
–	Tolerance
–	Weight loss
–	Withdrawal syndrome

Table 11. Management of amphetamine overdose

Activated charcoal/magnesium citrate for oral intoxication
Cooling blanket for hyperthermia
Medical control of hypertension and arrhythmias
Haloperidol or droperidol for agitation or delusions
Lorazepam (Ativan®) or diazepam (Valium®) for seizures
Urine acidification with ascorbic acid

While the mechanism of action is not entirely known, amphetamines may act by inhibiting catecholamine re-uptake or facilitating the release of norepinephrine in the presynaptic cleft. Alternatively, they may act as monooxidase inhibitors. They are absorbed through the gastrointestinal tract within 30 minutes and within 5 minutes when used subcutaneously. An initial rush is followed by a prolonged euphoria, alertness, confidence, and excitation. Flushing, sweating, temperature elevation, tachycardia, significant rise in blood pressure, and mydriasis occur. Tolerance is rapid and confusion, irritability, headache, insomnia, seizures, and weight loss may follow. Cerebral hemorrhage and cardiac arrhythmias have been reported. A drug induced psychosis is well known in long time users, but has occurred following a single use. Acute overdose can be life threatening and diagnosis and prompt treatment is necessary (see Table 11).

An infected needle may lead to HIV/AIDS, endocarditis, hepatitis, and other infections [50]. An abstinence or withdrawal syndrome is described in amphetamine abusers, with the development of severe apathy, depression, and hypersomnia. Amphetamine abusers develop tolerance and an overdose can lead to hyperthermia, hypertension, cardiac arrhythmias, seizures, and death. Table 11 outlines basic medical support for an amphetamine overdose; avoid the use of phenothiazines, since rapid decrease in blood pressure and increased seizures activity may result.

Clinicians using stimulant medications to manage adolescents with attention deficit hyperactivity disorder (ADHD) should appreciate the potential for abuse of short acting Adderall® (mixed amphetamine salts) and Ritalin® (methylphenidate) [51]. Ritalin is also called “the smart drug” and “vitamin R” by abusers, who crush the methylphenidate tablets and snort this chemical to obtain an intense euphoria; large doses can lead to seizure activity,

stroke, and psychosis. Published guidelines should be followed carefully when providing stimulant medications to adolescents. This should include the use of the long-acting preparations, such as Concerta®, which have formulations that reduce the risk for dispersion and the quick “buzz.” Another stimulant addition with diminished abuse potential is lisdexamfetamine (Vyvanse®) a prodrug formulation. The long-acting preparations used for the treatment of ADHD do not produce tachyphylaxis, nor have they lead to addiction.

METHAMPHETAMINE

This illicit drug (meth, ice, crystal, fire, glass, chalk, crank) is an N-methyl homolog of amphetamine and has become the stimulant favored by most adolescents, due to its potent stimulant effect on the central nervous system [52]. It is a highly addictive drug prepared by illicit drug laboratories using relatively inexpensive chemicals and sold on the streets and using drug networks. The term “ice” or “crystal” comes from its production as clear, chunky crystals that look like ice; it can also be bought as an odorless, bitter-tasting, white powder that easily dissolves in liquids.

The lifetime use in the 2007 YRBS ranged from 3.7 to 5.3% while the 2013 YRBS noted that 3.2% of students had used this drug one or more times in their lifetime revealing a decreased prevalence of 9.1% in 1999 to 3.2% in 2013 [2]. Methamphetamine is now responsible for one-quarter of illicit stimulant use.

This drug can be taken as a pill or its powder can be snorted, leading to a “high” or euphoria; when inhaled via smoking or taken intravenously, methamphetamine hydrochloride induces an immediate, potent euphoria that is described as a “flash” or “rush” lasting a few minutes. It is this intense feeling that abusers seek leading to rapid addiction with increased dosage and frequency of use. This is not the case with the long acting mixed amphetamine salts preparation (Adderall XR®) that is used to manage patients with ADHD.

Users of this drug note that there is increased wakefulness, less need for sleep, and increased physical activity; sometimes extreme anorexia may develop along with weight loss. The temperature, respirations, pulse, and blood pressure are increased; there may be excited speech. Methamphetamine releases high levels of dopamine and thus can affect body movements and mood in these addicts. Central nervous system cells that contain dopamine and serotonin are damaged, eventually leading to low levels of dopamine, thought dysfunction, and a depressed mood (“blue Tuesdays”). Motor impairment or a Parkinsonian-like movement disorder can develop. Adverse reactions are many and some are listed in Table 12. As with other illicit drugs that are taken intravenously, this drug can lead to various infectious diseases, including sexually transmitted diseases, such as hepatitis B and HIV/AIDS. Urine drug testing remains positive 48 hours and may reflect look alike designer drugs or prescription psycho-stimulants.

The treatment of acute toxicity includes the support of cardiac and respiratory function. Orogastric lavage and activated charcoal may be indicated if oral ingestion of other substances is suspected. Droperidol or haloperidol are more effective than the benzodiazepines in blocking the behavioral effects of amphetamines and produce fairly rapid sedation. However, benzodiazepines are indicated for seizure management and thorazine is contraindicated. Blood pressure is best managed with labetalol or esmolol. Management of

this severe drug addiction is difficult and current research is seeking a medication to block the euphoric effects of methamphetamine to allow the addict to get off the drug, if there is motivation. This antibody-type medication research is part of other addiction research studies seeking to neutralize the euphoric effects of drugs, such as cocaine, heroin, and others. Management of methamphetamine psychosis is difficult but important as is treatment of depression or anxiety related to the use of this drug in order to reduce risks for methamphetamine relapse [53].

Table 12. Adverse effects of methamphetamine

–	Irritability
–	Anxiety
–	Confusion
–	Memory loss
–	Insomnia
–	Tremors
–	Convulsions
–	Coma
–	Hypertension
–	Cardiac damage
–	Rhabdomyolysis
–	Paranoia and psychotic behavior
–	Increased aggressiveness with violent behavior
–	Cardiovascular collapse and death

COCAINE

This central nervous system stimulant is an alkaloid made from leaves of the South American plant, *Erythroxylon coca*. There are a number of ways to take this drug: intranasal, intravenous, inhalation, smoking, chewed (coca leaves), or swallowed. Previously, this drug was produced as a crystalline powder that is water soluble and developed from an alkaloidal paste of the plant’s leaves. “Free base” and “crack” (“rock”) are popular cocaine products used for smoking. Free-base cocaine is vaporized in a water piper (bong) or even a soda can with a hole in it. “Crack” is the street name for cocaine bicarbonate pellets that are pea-sized and produced using ammonia or sodium bicarbonate (baking soda); heating this concoction to remove its hydrochloride component produces a “crackling” sound. Crack may be crushed, tobacco added, and then this “cigarette” is smoked; other chemicals often added include mannitol, quinine, or marijuana. Over half of the cocaine used on the streets is now crack cocaine because cocaine powder is decomposed when ignited to smoke. Crack cocaine has become relatively inexpensive and very popular with adolescents.

The 2013 YRBS noted that 5.5% of students had used any form of cocaine one or more times during their life [2]. The CDC surveys noted that the prevalence of ever used cocaine increased from 1991 to 1999 (5.9% to 9.5%) and decreased from 1999 to 2013 (9.5% to 5.5%) [2]. The prevalence of ever-used cocaine was higher among male youth versus female youth. Approximately 23% of Americans report they have experience with cocaine before age

30. The DSM-5 lists a number of stimulant-related disorders with regard to cocaine: stimulant use disorder-cocaine (mild, moderate, severe), stimulant intoxication-cocaine, stimulant withdrawal—cocaine, other stimulant-induced disorders-cocaine, and unspecified stimulant related disorder-cocaine [23].

Cocaine is a topical anesthetic, a peripheral sympathomimetic, and a central nervous system stimulant. The drug interferes with neuronal catecholamine reuptake and dopamine reabsorption. The popularity of cocaine is based on its ready availability and the potent euphoric feeling it produces; this high lasts 5 to 10 minutes if cocaine is smoked, in contrast to 10 to 30 minutes if taken intravenously. Because the high is short lived, the usual pattern of use is escalated and dependence is promoted. Urine and blood testing remains positive for 48-72 hours following its use. Once the euphoria is gone, irritability and fatigue set in. Users of this powerful drug develop severe psychological and physiological addiction along with tolerance. Serious physiological complications are infrequent and the death rate is low even in heavy long-term users; but, when they occur, they can be disastrous. A partial list of the serious side effects of cocaine is listed in Table 13.

Table 13. Adverse effects of cocaine

- | |
|--|
| – Anxiety |
| – Irritability and restlessness |
| – Confusion |
| – Peripheral blood vessel constriction |
| – Pupillary dilation |
| – Hyperpyrexia, tachycardia, and hypertension |
| – Cardiac complications |
| – Angina pectoris |
| – Myocardial infarction |
| – Ventricular arrhythmia |
| – Sudden death |
| – Seizures |
| – Nasal septum infection and perforation |
| – Frontal lobe infarction |
| – Intravenous needle complications (including hepatitis B, HIV/AIDS, endocarditis) |
| – Increased premature delivery |
| – Abruptio (bleeding between placenta and uterine wall) |
| – Adverse neurodevelopmental sequelae in infants |
| – Vascular spasm-induced limb reduction anomalies and strokes |

As with other drugs, addicts look to mix various drugs together to intensify the pleasant or euphoric feeling of their drug of choice. When alcohol is mixed with cocaine, cocaethylene is produced in the liver; this chemical heightens the cocaine euphoria (i.e., more potent and lasts longer), blunts some of the stimulant adverse cocaine effects, and increases the risk of sudden cardiac death 25 fold. The term, speedballing, refers to the mixture of cocaine and heroin (or morphine) and this combination also increases the risk for sudden death.

The method of using cocaine leads to various complications, as nasal perforation/infection with snorting and the infectious sequelae from intravenous use. The high abuse rate of cocaine is associated with increased risk of sexually transmitted diseases among adolescents and young adults; this includes HIV/AIDS, lymphogranuloma venereum, and

chancroid. Smoking crack may lead to the development of a very aggressive paranoia. Sudden death occurs and is a constant risk, whether it is the first time or the user is very experienced with this drug; such death is probably due to a terminal ventricular arrhythmia. Use of cocaine during pregnancy can lead to a variety of adverse effects on the fetus including preterm-labor, placenta infarction, placental abruption, pre-eclampsia, impaired fetal growth, and neurodevelopmental defects [54].

Management of Cocaine Addiction

While acute intoxication is usually not severe, it may be complicated by the use of opioids, alcohol, marijuana, and other drugs. Emergency management includes the maintenance of an airway and naloxone if opiate use is suspected. Treatment of arrhythmias may require lidocaine, phenytoin, or cardioversion. Lorazepam or diazepam can be used for severe agitation or seizures. Nitroprusside or labetalol can be used for hypertension. A cooling blanket and intravenous fluids may be used for hyperthermia. Phenothiazines are contraindicated.

Cocaine addiction is a difficult central nervous system disorder to manage. If tachycardia and hypertension develop while on cocaine, short acting beta-blockers and short-acting direct vasodilators (as esmolol) may be helpful; clinicians should avoid long-acting vasodilators, since cocaine intoxication is typically a short, self-limited phenomenon and use of these other drugs (as morphine, propranolol, thorazine) may lead to severe hypotension. Though naloxone is helpful for opioid addiction, it does not help with cocaine addiction.

Cocaine addicts with ADHD may observe that methylphenidate calms them down along with improving their concentration abilities; a reduction in cocaine use has been observed in some cocaine addicts who have ADHD and use methylphenidate.

Current addiction research seeks to find a way to stop the potent euphoric effects of cocaine and enable the motivated abuser to stop this drug. Dependence on cocaine involves various pathways (i.e., noradrenergic and dopaminergic) in the primitive midbrain reward center. Multiple CNS sites are involved with the addiction and thus any drug used to help the addict must work over many CNS areas. Table 14 lists proposed drug mechanisms that are being researched to potentially manage cocaine addiction by blocking this drug’s many effects, including the use of vaccine technology [55].

Table 14. Potential mechanism to manage cocaine addiction

– Bind to cocaine molecules and prevent movement into the CNS via the blood-brain barrier – Change cocaine molecules into harmless (inactive) particles – Remove the cocaine molecule as a vaccine using an antibody-type response – “Catalytic” antibodies changing cocaine into inactive fragments
--

For example, research is looking at drugs called “peripheral blockers,” such as Dopamine D3 Receptor Agonists (D3 agonists), to prevent cocaine-induced CNS stimulation by neutralizing this drug in the blood; such drugs may help with addiction as well as with overdose and cocaine-induced seizures. Oxytocin may be helpful via effects on the glutamate

receptor systems [56]. N-acetylcysteine is also under active research for the management of cocaine dependence.

If the addict uses other drugs, treatment of dependence on those other drugs may help. For example, naltrexone or disulfiram may help with alcohol abuse and be of benefit to the addict who uses both cocaine and alcohol.

OPIOIDS

A number of opiate narcotics are abused by adolescents and adults, as reviewed in Table 15. The DSM-5 lists a number of opioid-related disorders: opioid use disorder (mild, moderate, severe), opioid intoxication, opioid withdrawal, other opioid-induced disorders, and unspecified opioid-related disorders [23].

Prescribed narcotics have been popular for many years, and are available in many ways, as stealing them from home medicine supplies, obtained from emergency room or office clinicians by faking (exaggerating) injuries or illnesses (i.e., migraine headaches, dysmenorrhea), or simply buying the opiate of choice on the street. Most are obtained free from friends or bought from school mates. The 2008 MTF reports use by 10% of 12th graders with Vicodin being the choice of 9.7% [49]. Oxycontin use was reported by 2.1 and 4.7% of 8th and 12th graders respectively. Seven of the top 11 abused prescription medications are opiates.

Table 15. Narcotic opiates

- | |
|---|
| <ul style="list-style-type: none">– Codeine– Fentanyl– Heroin– Meperidine– Methadone– Morphine– Oxycodone– Pentazocine– Propoxyphene– Others |
|---|

Clinicians may forget or not be aware of the addictive potential of such classic analgesics as Darvocet®, Dilaudid®, Percocet®, Stadol®, Vicodin®, or Ultram®. News media have covered the recent increased popularity of Oxycodone (OxyContin®), a narcotic that is abused by some in place of heroin; a variety of ways of abuse are noted, including chewing an oxycodone tablet, crushing the pill and either snorting the contents or intravenous use after boiling the powder. Its acceptance by addicts is reflected in the many street names it has acquired, including OXY, OC, oxycotto, and killers. Fentanyl is a prescribed narcotic that is ten times more potent than heroin and there are a number of reported overdoses from this drug.

HEROIN

Inexpensive and potent heroin (diacetyl morphine hydrochloride) is available and comes from Mexico, Columbia, Afghanistan, and Pakistan. Heroin (junk, smack, Mexican brown, China white) can be abused in a snuff form, intravenously, or subcutaneously (skin-popping). China White is 2000 times more potent than morphine and responsible for some 28 documented fatalities. Speedballing, as noted above, refers to the combination of heroin or morphine with cocaine in an effort to block the sedative effect of heroin. Use of both heroin and morphine is called “New Jack swing.” “Cheese” which blends black tar heroin and Tylenol PM® has been associated with 12 deaths in the United States.

The mean age of heroin use dropped from 27 years of age in 1988 to 19 years of age in 1995. There was a doubling of high school seniors who used this drug from 1990 to 1996 at a time when the price of heroin was dropping along with a 40% increase in drug purity. The purity of available heroin has increased from 5% in the 1990s to over 80% presently. The 1999 YRBS noted that 2.4% of high school students had tried heroin on at least one occasion; this was broken down to 3.5% males and 1.3% females. The 2003 Monitor the Future (MTF) Study recorded that 1.5% of high school seniors had a lifetime use of heroin, 0.8% over the past year and 0.4% over the past survey month [49]. The lifetime heroin use for these seniors was 1.5% in the 2007 YRBS, and < 1% in the 2008 MTF Study. The 2013 YRBS reported that 2.2% of students had used heroin one or more times during their life and this decreased from 2.9% in 2011 to 2.2% in 2013 [2].

Unfortunately, this use increases as these seniors leave school and also increases in those who drop out of school before graduation of their peers who stay in school. The typical situation is an adolescent who begins to snort this drug, then develops an intense craving for the resultant euphoria, and progresses to smoking or intravenous use (mainlining). An all-consuming addiction with tolerance develops, as noted by the saying: “once is too much, 1000 times not enough;” also classic, is the development of physical addiction, psychological dependence, and a narcotic withdrawal syndrome. This may follow initiation of abuse by as little as several weeks. Approximately 30% of adolescents who smoke heroin become mainlining adults. Those who smoke or snort this drug often mistakenly feel they are bypassing the dangerous effects of heroin by smoking. However, this is not true, and the younger the addiction starts, the greater is the risk for post-cessation relapse.

Opiate overdose presents with the triad of respiratory and CNS depression associated with miotic constriction of the pupils. Mydriasis is seen with withdrawal which presents with flu-like symptoms, lacrimation, irritability, abdominal cramps and diarrhea. Cardiopulmonary failure with bradycardia, hypotension, and pulmonary edema can occur. A rapid response to the opiate antagonist naloxone is diagnostic of opiate overdose. Support of both respiratory and circulatory systems with airway maintenance is imperative. Correction of hypotension is necessary while monitoring for hypoglycemia, pulmonary edema, and arrhythmias. Thin-layer chromatography immunoassay will detect opiate metabolites for 2-3 days.

Table 16 lists some of the medical complications of heroin abuse, including an overdose that leads to death from respiratory depression and pulmonary edema. For example, an increase in heroin overdose deaths in 28 states was reported by the CDC for the period 2010 to 2012 [57]. Clinicians should observe for the use of tattoos to obscure puncture wounds or needle-tract marks made by the heroin intravenous abuse; such mainlining and tattooing

phenomena increase the infectious complications of needle use. A newborn withdrawal syndrome is described in newborns whose mothers abuse narcotics; heroin withdrawal in utero can lead to meconium aspiration, bile pneumonitis, and severe respiratory distress.

Table 16. Medical complications of heroin abuse

–	Amenorrhea
–	Endocarditis (from <i>Staphylococcus aureus</i>)
–	False-positive VDRL
–	Fat necrosis
–	HIV/AIDS
–	Hepatitis (B and C)
–	Lipodystrophy
–	Osteomyelitis
–	Peptic ulcer disease
–	Pulmonary edema and pneumonia
–	Respiratory arrest
–	Skin infections
–	Tetanus
–	Others

Management of Opioid Addiction

Addiction research of the last part of the 20th century led to the conclusion that opioid dependence is a neurobiological central nervous system disorder that involves brain receptors. This science looks at reward circuits controlling such processes as hunger, thirst, reproduction, and even drug addiction. Drug-induced alterations in CNS opiate receptors lead to drug dependence and tolerance phenomena. Opiate addiction induces significant social dysfunction with complex biological and psychological components that are not corrected by incarceration. Unfortunately, the majority of such addicts are not in treatment designed to manage their brain disorder. These patients often need acute detoxification measures followed by residential and/or outpatient management of sufficient nature to blunt their often overwhelming need to find the narcotic euphoria. Community programs as the 12-Step groups (i.e., Narcotics Anonymous) can be very helpful to these individuals to stay off the drug(s).

The opioid addict may benefit from the judicious use of various medications that are available as part of the overall management program (see Table 17) [7]. Naltrexone (ReVia[®], Depade[®]) is an opiate antagonist that can help many with opiate addiction, including addicts with additional alcohol dependence. Methadone may block classic narcotic effects without giving the user the classic opiate euphoria; it can also remove withdrawal symptomatology and help with on-going desires for additional drugs. Clinicians have used this drug as a substitute agonist for opiate dependence since the 1960s. Pharmacokinetics allow once a day dosing and the patient officially must be at least 18 years of age or older. Daily doses may range from 40 mg to 400 mg and successful patients, while on methadone, are then able to maintain a more normal life, in contrast to the addict's chaotic life of only seeking money for another high.

In search of longer-acting alternatives to methadone, addiction specialists have turned to levomethadyl acetate and buprenorphine, both of which are medications that are effective with narcotic addicts. Clinicians can also use the sublingual combination of buprenorphine/naloxone (Suboxone®) that provides benefit at least equal to that of methadone and seems more efficacious than detoxification/counseling. The naloxone part of this dual treatment is used to stop diversion of the buprenorphine to intravenous administration. There have been some reports of ventricular tachycardia with prolonged QT intervals (Torsade de pointes) after taking LAAM and more research is needed to see if this drug is safe enough to be used.

Table 17. Medications available for opioid addiction

–	Naltrexone
–	Methadone hydrochloride
–	LAAM (levo-alpha-acetyl methadol or levomethadyl acetate)
–	Buprenorphine
–	Anti-depressant drugs (as selective serotonin reuptake inhibitors)
–	Anti-stress medications (as buspirone)

HALLUCINOGENIC DRUGS

Both the hallucinogens and dissociative drugs may alter a youth’s state of mind and mood. Hallucinogens include Psilocybin, Psilocyn (Shrooms, mushrooms), LSD, and mescaline (peyote); these drugs can cause auditory, visual, and tactile hallucinations. Dissociative drugs, such as Ketamine or PCP, alter a persons’ state of mind and mood, causing a “feeling of detachment” or “dissociate reaction,” but do not cause hallucinations. The 2013 YRBS noted that 7.1% of surveyed students report having used a hallucinogenic drug one or more times during their lifetime [2]. From 2001 to 2013 the prevalence dropped from 13.3% in 2001 to 7.1% in 2013.

The DSM-5 lists a number of hallucinogen-related disorders: phencyclidine use disorder (mild, moderate, severe), other hallucinogen use disorder (mild, moderate, severe), phencyclidine intoxication, other hallucinogen intoxication, hallucinogen persisting perception disorder, other phencyclidine-induced disorders, other hallucinogen-induced disorders, unspecified phencyclidine-related disorder, and unspecified hallucinogen-related disorder [23].

PCP (phencyclidine) and LSD (lysergic acid diethylamide) are taken as pills to induce a potent reality distortion with synesthesias or alterations of sensory perception (involving sight and sound) and emotions (involving euphoria and intense fears), in addition to time and place. Tolerance is described in these individuals as are cases of psychosis and the well-known flashback that can be induced by antihistamines or marijuana. Overdosing can induce respiratory depression with coma and death. A recent addition to the “trip” scene is *Salvia divinorum* (Virgin Mary’s Herb, Mary’s leaf). This is a hallucinogenic ethnobiological plant grown in the southwest U.S. which may be smoked, squeezed into water, or steeped into a tea. It is absorbed through the mucus membranes and produces a “euphoric experience with God.” It cannot be detected by current urinary drug screens.

PHENCYCLIDINE (PCP)

This drug has many street names, including peace, pill, sternly, peace pill, angel dust, hog, and sheets. PCP is an arylcyclohexylamine that can be made in illicit laboratories; it causes adrenergic potentiation by inhibition of neuronal catecholamines. PCP can be taken as tablets, liquid, or in a powder form, sometimes sprinkled on marijuana or cigarettes (joints) to augment pot's potency. It is a dissociative anesthetic with hallucinogenic, stimulant, and depressive properties. Since it is lipophilic it has a 72 hour half-life. PCP is the active ingredient and can be detected for up to eight days after ingestion. Clinical expression may include frank psychosis, mania, delirium, and late manifestations of depression. Agitation associated with vertical and horizontal nystagmus, miotic but reactive pupils, elevated blood pressure, gait ataxia, and delusions should suggest PCP intoxication.

Diagnosis can be confirmed with gas chromatography/mass spectrometry using blood levels with or without urine testing. Excretion is pH dependent (increased in acid pH) High doses of dextromethorphan, especially when mixed with benzodiazepines, have been associated with a similar toxicity to phencyclidine.

Management of a PCP-induced "trip" (bad reaction) involves keeping the patient in a dark, padded room with the provision of diazepam (10-20 mg orally, or 10 mg intramuscularly every four hours). Lorazepam (1-2 mg) may be used IM/IV for seizures. Haloperidol may be reserved for severe agitation. Death may be caused by PCP because of the development of hypothermia, seizures, trauma, severe hypertension or hypotension, and/or psychotic delirium/coma. However, most deaths are caused by accidental injury occurring during intoxication. Psychosis may be helped with D3 agonists and research seeks chemicals to act as "antibodies" to neutralize PCP molecules.

LYSERGIC ACID DIETHYLAMINE (LSD)

LSD is the most powerful hallucinogen and has earned many street names, including acid, "L," sugar, dots, cubes, big "D," and blotters. LSD is found in morning glory seeds and rye fungus (Ergot). It is easy to produce by amateur chemists and easy to hide since it is odorless, tasteless, and colorless; because of this, it has become popular at marathon dances ("raves") where it can be given to unsuspecting victims. A dose as low as 20 mcg (placed on small objects as a sugar cube, paper blotter, or postage stamps) can lead to its classic euphoric or hallucinogen effects by increasing serotonin; sympathetic activity is potentiated with resultant tachycardia, fever, conjunctival injection, mydriasis, lacrimation, flushing, dry mouth, blurred vision, tremors, incoordination, and elevated blood pressure. Onset of symptoms following an oral dose is 30-45 minutes. The half-life is 3 hours, but routine urine drug screens do not detect LSD. Most youth with a bad trip or unpleasant flashback respond to a reassurance and calm interaction with the clinician; if necessary, haloperidol has been given for major reactions, including prolonged seizure activity.

TRYPTAMINES

Tryptamines include a number of naturally occurring Schedule I hallucinogenic substances obtained from “magic mushrooms” indigenous to South America, Mexico, and the United States. They can be synthetically produced and include Psilocybin (0-phosphoryl-4-hydroxy-N, N-dimethyltryptamine) and Psilocyn (4-hydroxy-n, n-dimethyltryptamine). These chemicals produce muscle relaxation, mydriasis, vivid auditory and visual distortions, as well as emotional lability. These drug effects are not well predictable and vary by the specific mushrooms used as well as the manner in which they are dried, brewed, and consumed. Users of tryptamines often experience a multitude of effects that include hallucinations, euphoria, dilated pupils, empathy, emotional distress, “feelings of love,” and visual-auditory disturbances or distortions. Some experience gastrointestinal effects, as nausea, emesis, and diarrhea.

Dimethyltryptamine (DMT) occurs naturally in a variety of wild plants and seeds. It is usually smoked, sniffed, or injected. DMT is inactivated orally and rapidly metabolized. The drug experience is called a “businessman’s trip” because its effects are for only one hour. Diethyltryptamine (DET) is an analogue of DMT and produces the same pharmacologic effects, but is less potent than DMT. Alpha-ethyltryptamine (AET) is another tryptamine class hallucinogen added to the list of Schedule I hallucinogens in 1994.

N,N-Diisopropyl-5-methoxytryptamine (referred as “Foxy-Methoxy”) is an orally active tryptamine recently encountered in the United States. Alpha-methyltryptamine (AMT), known as “spirals,” was designated a Schedule I drug in 2003. Tryptamines, like “Foxy” and AMT, are very dose dependent, which means that the doubling of a moderate dose could result in effects similar to LSD. The duration of effects from 20 mg of AMT usually last between 12 and 24 hours, while the effects from 6 to 10 mg of Foxy reportedly last from 3 to 6 hours. 5-methoxy-alpha-methyltryptamine (5-MeO-AMT) is also a tryptamine. Other common names for 5-MeO-AMT are “alpha-O,” “alpha” and “O-DMS.”

Bufotenine (bufagin, bufotenin, 5-hydroxy-N-N-dimethyltryptamine) is a Schedule I substance found in certain mushrooms, seeds, and most notably, the skin glands of the green and red Cane Toad (*Bufo marinus*). In the 1960s-70s, the “toads milks” in northern Florida were obtained by daring to lick (“suck the toad”) which lead to accidental handling of the toads. Historically, these toads were killed and their skin boiled to produce a bitter tasting broth. In Australia, the milk is dried into a powder and smoked. In South America, this substance is used as snuff. A mild, though frightening “trip” occurs as this 3-indoleamine works on serotonergic sites in the amygdale and ventral lateral geniculate. The toad can continuously replace the supply and, in general, most bufotenine preparations from natural sources can be extremely toxic.

MDMA (ECSTASY)

Phenethylamines are a family of over 100 chemicals that are hallucinogenic. MDMA (3,4 methylene dioxymethamphetamine) is a phenethylamine that resembles both a stimulant (methamphetamine) and a hallucinogen (mescaline). The U.S. Food and Drug Administration classified MDMA as a Schedule I drug in 1985. MDEA (3,4-methylenedioxy-N-ethyl-

amphetamine) or Eve is a close congener of MDMA. There is also a designer version of the banned decongestant and “diet” drug, phenylpropanolamine; it is referred to as U4ia and is similar in action to MDMA with both stimulant and hallucinogenic effects.

MDMA was developed in 1912 by German scientists and synthesized as an appetite suppressant; it was utilized in the 1970s and 1980s in an attempt to improve psychotherapy. Concern over this drug developed as its severe side effects became evident.

The 2013 YRBS reported that 6.6% of students had used ecstasy (MDMA) one or more times during their lifetime and this dropped from 11.1% in 2001 to 6.6% in 2013 [2].

MDMA produces an intense euphoria and energizing effect in users and thus is popular at dance or club halls (called “raves, trances, or dance parties that last all night”); it is also popular with college students. It is a designer drug that abusers feel is safe at 1-2 mg/kg and produces prolonged effects; because of this, its availability and use is more common than cocaine at teenage raves. Its effect is normally 3 to 6 hours, though it may be several days. Its purest form is as a white crystalline powder and if red or brown MDMA is found, this suggests impurities are present. MDMA has many street names, such as ecstasy, XTC, X, hug drug, lover’s speed, diamonds, clarity, dex, essence, roll, bean, M, E, and Adam.

MDMA has mescaline like effects, probably due to interaction with and destruction of serotonergic neurons in the central nervous system that are involved with thought and memory. This may result from the formation of quinones which can combine with glutathione and other thiols. MDMA produces an anxious state of “well-being,” changes in perception, moderate derealization and depersonalization without producing psychomotor agitation. MDMA abuse may lead to cognitive dysfunction, memory impairment, and behavioral problems. If taken during pregnancy, the risk for congenital anomalies is increased. Users take MDMA to enhance sensual awareness and augmented psychic or emotional energy. A number of side effects are noted, as listed in Table 18.

Table 18. Side effects of MDMA

- | |
|---|
| <ul style="list-style-type: none">– Hypertension and increased pulse– Dehydration and possible heat stroke– Fatigue– Sleep dysfunction– Muscle spasms– Sweating– Organ dysfunction: renal, liver, CNS, muscular– Intracerebral hemorrhage– Irreversible CNS damage with memory loss in chronic abuse– Confusion and paranoia– Psychosis– Depression– Anxiety, including panic attacks |
|---|

MDMA can hide thirst and eventual death that may be due to dehydration (which is not uncommon and hence its association with water bottles at raves), hyperthermia, hyponatremia, or cerebral edema. High doses can lead to muscle breakdown, breakdown of muscles, malignant hyperthermia, renal failure, and cardiovascular failure at the raves. MDMA and some of the other “designer” drugs have been associated with intracerebral

hemorrhage in adolescents and young adults who have undiagnosed vascular malformations. Also, anxiety (including paranoia and panic attacks) may last for weeks after drug cessation. MDMA is a popular date-rape drug (see below). Acute management requires diagnosis, rehydration, cardiovascular support, and the use of benzo-diazapines for sympathomimetic effects.

MDMA users may mix this drug with alcohol, marijuana, LSD, dextromethorphan, and other drugs. Preparations with camphor, menthol, and ephedrine are applied to the nasal mucosa or chest to enhance the desired MDMA effects. MDMA can also be taken in increasing doses in a “stacked” schedule similar to that used with anabolic steroids. The drug user may also take chemicals that are ecstasy-like in appearance, such as ketamine (“special K”), alpha-methyl fentanyl (“synthetic heroin,” “china white”) and ephedrine tablets (“herbal ecstasy,” “Chinese ephedra,” “Ma Huang”); large amounts of these chemicals may lead to hypertension, cardiac arrhythmias, myocardial infarction, cerebrovascular accidents, and death. The ephedrine found in Herbal ecstasy products as found in “health” food stores has only recently been banned.

“DATE RAPE” DRUGS

Novel and more creative uses for previously legitimate pharmaceuticals and “nutriceuticals” continue to emerge “on the street,” including familiar drugs as marijuana (i.e., increased THC content), phencyclidine (PCP), crack cocaine (or opium) with Viagra, variations on MDMA described previously, short acting benzodiazepines (“benzos”), and those compounds readily made using recipes available on the internet and concocted by amateur chemists.

Table 19. Club drugs

- | |
|--|
| <ul style="list-style-type: none"> – Methylenedioxymethamphetamine (<i>Ecstasy</i>, MDMA) – Rohypnol (Flunitrazepam; <i>Roofies</i>, <i>The Date Rape Drug</i>, <i>Roches</i>, <i>Rope</i>) – Gamma-hydroxybutyrate (<i>GHB</i>, <i>Liquid Ecstasy</i>) – Gamma-butyrolactone (<i>GBL</i>, <i>Blue nitro</i>, <i>Renewtrient</i>) – Butanediol (<i>BD</i>, <i>soap</i>, <i>Revitalize plus</i>) – Methamphetamine (<i>meth</i>, <i>ice</i>, <i>crystal</i>, <i>fire</i>, <i>glass</i>, <i>chalk</i>, <i>crank</i>) – LSD (<i>acid</i>, “<i>L</i>”, <i>sugar</i>, <i>dots</i>, <i>cubes</i>, <i>big “D”</i>, and <i>blotters</i>) – Ketamine (<i>Ketalar</i>; <i>Special K</i>, <i>Cat Valiums</i>) |
|--|

A variety of chemicals have been used to lower external and internal inhibitions and/or consciousness, helping to facilitate sexual assault. These so-called “date rape” drugs are named for their strong sedative and hypnotic effects that are enhanced with alcohol. They continue to be popular at all night dance parties or “raves,” and thus, have also been called Club Drugs or Party Drugs. Some are sold in “nutrition” stores or via magazine ads as sleep aids, muscle builders, and even as “party drugs.” A variety of drugs have been used, as

partially listed in Table 19; this list includes MDMA-methylenedioxy-meth-amphetamine (Ecstasy) previously discussed.

FLUNITRAZEPAM (ROHYPNOL®)

This is a potent benzodiazepine with sedative, anxiolytic, and anticonvulsant effects. It belongs to the same group as Halcion, Ambien, Xanax (Z Bars), Klonopin, Sonata, Versed, and Valium. Flunitrazepam is a central nervous system depressant produced commercially in Switzerland that reduces inhibition and results in memory loss (blackouts) with short term anterograde amnesia for activity that takes place while under the influence of the drug.

It can also lead to such adverse effects as urinary retention, drowsiness, confusion, dizziness, gastrointestinal dysfunction, visual disturbances, hypotension and others. It is available by prescription in Europe (not the United States) and used as a sedative for management of insomnia and also as a pre-surgery anesthetic.

Flunitrazepam is a tasteless, odorless, and colorless chemical that can be taken as a pill or dissolved in a beverage; anecdotal reports of snorting are noted as well. One milligram can be secretly placed in a liquid to sedate a victim for 8 to 12 hours with unfortunate amnesia for the sexual assault that may follow the ingestion. The victim is seen voluntarily leaving with the rapist, recalls little if anything of the events, and is unable to testify in any later prosecution. It has become a popular and classic date rape drug used by gang members and even high school or college students operating at local parties. Its many street names include forget-me pills, Rope, Roche, Mexican valium, and roofies. It is also an addictive drug used voluntarily by youth as an alternative or adjunctive drug to marijuana or LSD, as well as the self-treatment of anxiety. Its effects are enhanced with alcohol. If used on a regular basis, increasingly higher doses are needed for the desired euphoric effect. Its use has increased 50% over the past several years. In South Texas, along the United-States-Mexico border, it is frequently replaced by the more readily available Klonopin or Xanax, both of which are associated with blacking-out spells and “withdrawal seizures,” especially when abused with alcohol and marijuana.

GAMMA-HYDROXYBUTYRATE (GHB)

This is a CNS depressant that induces euphoria and lowered inhibition. It has many street names, including: Liquid X, Liquid E, Liquid XTC, Liquid Ecstasy, Natural Sleep-500, Organic Quaalude, G Caps, Gamma Hydrate, Georgia Home Boy, Growth Hormone Booster, Cherry Meth, Sodium oxybutyrate, Somatomax PM, Grievous Bodily Harm, G-Riffick, Oxy-Sleep, Scoop, Fantasy, Easy Lay, Soap, Salty Water, Vita G, Gamma OH, Somsanit, GHB; Liquid Ecstasy; G; Georgia home boy, caps, organic qualude, and goop.

Like Rohypnol, GHB and its analogs are used as “date rape” drugs. It has a soapy or salty taste, and hence the name salt is used until it is mixed with any liquid, including water. Because it is colorless, tasteless, and odorless, it is easily and quietly slipped into an unattended party drink to induce sedation and amnesia. Effects develop in 10-20 minutes, peak in 1 to 2 hours, and last for 4 hours. GHB is rapidly cleared from the body and is

undetected in subsequent rape investigations. The clinician providing care in an emergency situation must request that the laboratory specifically look for GHB. Adolescent females need to be warned about the danger of leaving drinks unattended.

It is used by bodybuilders and athletes because of beliefs that GHB will augment endogenous human growth hormone (HGH) release while sleeping. GHB is available in single doses that augment or mimic effects of alcohol; increasingly higher doses are needed for desired effects. The risk of seizures and death caused by GHB-induced respiratory depression is raised when mixing GHB with other drugs, such as alcohol, heroin, LSD, and psilocybin. The CNS depression occurs because of increasing CNS dopamine and GABA (gamma-amino-butyric acid); the endogenous opioid system is also activated. It became a Schedule I substance in March of 2000 and in July, 2002, GHB was approved by an FDA advisory committee for study in the treatment of cataplexy. Most of the GHB used in the United States is illegally manufactured in the US. Law enforcement in every region of the United States reports that GHB has surpassed Rohypnol as the most common substance used in drug-facilitated sexual assaults.

GAMMA-BUTYRO-LACTONE (GBL)

Because the DEA is cracking down on GHB use, some are using GHB precursors, such as GBL as well as BD (1-4 butanediol), an industrial solvent; both are promoted to enhance sexual ability and pleasure. Street names for GHL are many, including Renewtrient, Revivarent, Reivivarent G, Blue Nitro, Blue Nitro Vitality, GH Revitalizer, Gamma G, Remforce, and Soap; it is found in paint thinners and floor stripper products. BD leads to bradypnea and can induce emesis, aspiration, and coma. GBL and BD are both easily changed to GHB in vivo, and in vitro by adding water. Some producers are substituting BD for GHB, even though the FDA has identified BD as a potentially life-threatening drug. It is sold as a dietary supplement in a number of sleep aid and muscle enhancing products; names include SomatoPro, NR63, Thunder Nectar, Enliven, GHRE, Weight Belt Cleaner, Revitalize Plus, and Serenity. The FDA asked that products with GBL be recalled in January, 1999; some states, such as California, have told manufactures that it is illegal to sell these products or market them as a supplement or nutritional substance. GBL-related products have been associated with reports of at least 55 adverse health effects, including one death. In 19 of these cases, the consumers became unconscious or comatose, several requiring intubation for assisted breathing.

KETAMINE

This drug has been approved since 1970 in the role of an injectable airway-preserving veterinary anesthetic; it is taken orally to induce dissociative states, described as dream-like and hallucinatory. Street names include K, Cat Valium, Special K, and Vitamin K. It can be obtained as a white powder that can be added to tobacco or marijuana or the powder can be snorted; intramuscular abuse is also described. The effects of ketamine last one half to two hours producing an “out of body” distortion of time and space. Ketamine in low doses can

lead to dysfunction of learning ability, memory, and attention span; in high doses, it can lead to myalgia, paranoia, elevated blood pressure, delirium, motor function impairment, amnesia, long term flashbacks, and respiratory depression-induced death. There is no urine metabolite.

INHALANTS

Inhalant drugs (see Table 20) are central nervous system depressants typically abused by young (ages 6-8, peaks at 14), often male, and homeless adolescents to induce temporary euphoria and excitement [58, 59]. These inhaled chemical vapors are viewed as easily available and as inexpensive substitutes or precursors to other drugs, such as alcohol or marijuana. Delivery is by “sniffing, huffing, or bagging.”

In 1995 the lifetime use was 21.6% for 8th graders versus 19.7% in 1999 and 17.3% in 2004 [60]. Approximately 5% of adolescent girls (age 12-17) used inhalants that included nitrous oxide vials (19.3%), glue sniffing (34.9%), correction fluid (23.4%), hair spray (23%), and inhalation of paints or sprays (6-16%) [49]. The 2013 YRBS reported that 8.9% of students had sniffed glue, breathed the contents of aerosol spray cans, or inhaled any paints or sprays to get high one or more times during their life [2]. The prevalence dropped from 20.3% in 1995 to 8.9% in 2013.

The main ingredient in airplane glue and some rubber cements is toluene. Another popular inhalant is gasoline, noted especially in rural areas of the United States and with Native American adolescents. Amyl nitrite, butyl nitrite, and other volatile nitrates are found in room deodorizers and are used by older adolescents to induce “aphrodisiac” effects.

Table 20. Types of inhalant drugs*

Solvents	Gases	Nitrites (Aliphatic nitrites)
Industrial or household solvents or solvent-containing products	Gases used in household or commercial products	Cyclohexyl nitrite (available to general public)
Paint thinners or solvents	Butane lighters	Amyl nitrite (available only with prescription)
Degreasers (dry-cleaning fluids)	Propane tanks	Butyl nitrite (Illegal substance)
Gasoline	Whipping cream aerosols or dispensers (whippets)	
Glues	Refrigerant gases	
Art or office supply solvents	Household aerosol propellant and associated solvents	
Correction fluids	Found in spray paints	
Felt-tip-maker fluid	Found in hair or deodorant sprays	
Electronic contact cleaners	Found in fabric protector sprays	
	Medical anesthetic gases	
	Ether	
	Chloroform	
	Halothane	
	Nitrous oxide	

* Greydanus DE, Patel DR: Substance abuse in adolescents: A complex conundrum for the clinician. *Pediatric Clin No Amer* 59(5): 1179-1223, 2003. (with permission).

Table 21. Effects of inhalants*

Hearing loss
Toluene (paint sprays, glues, dewaxers)
Trichloroethylene (cleaning fluids, correction fluids)
Peripheral neuropathies or Limb spasms
Hexane (glues, gasoline)
Nitrous oxide (whipping cream, gas cylinders)
CNS or Brain Damage: toluene
Bone Marrow Damage: benzene (gasoline)
Liver and Kidney Damage
Toluene-containing substances
Chlorinated hydrocarbons
Correction fluids
Dry-cleaning fluids
Blood Oxygen Depletion/ Methemoglobinemia
Organic nitrites (“poppers,” “amyl,” “bold” and “rush”)
Methylene chloride
Varnish removers
Paint thinners
Loss of the sense of smell (nitrites)
Thermal burn injury with nebulized alcohol/Robitussin® (“RoboFires”)
Death
Kaposi’s sarcoma

*adapted from Greydanus DE, Patel DR: Substance abuse in adolescents: A complex conundrum for the clinician. *Pediatric Clin North Amer* 59(5): 1179-1223, 2003. (with permission).

Inhalant use is usually experimental and may occur as a group activity. Inhalation occurs after these substances are placed in a plastic bag (“bagging”), wrap, or inhaled from a soaked rag (“huffing”) to induce the intoxicating (psychoactive) effects. Absorption is rapid and the altered mental state lasts for 5-15 minutes. After a mild stimulatory effect, an inhibition reduction occurs, followed by unconsciousness. Death may occur from cardiac arrhythmias. Tolerance develops after long term use, though withdrawal is rare; dependence may develop [61].

Table 21 lists various complications known to occur with various inhalants. The DSM-5 lists a number of inhalant-related disorders: inhalant use disorder (mild, moderate, severe), inhalant intoxication, other inhalant-induced disorders, and unspecified inhalant related disorders [23].

Most abusers of inhalants discontinue these drugs by stopping substance abuse in general or moving on to other drugs. Management of those who become chronic inhalant abusers is difficult, often being hindered by their many, varied behavioral and social problems. Research on management is focusing on inhalant effects on dopaminergic, glutamatergic and GABAergic systems [61]. Unfortunately death from volatile substance misuse may occur as seen, for example, with difluoroethane can occur.

BARBITURATES

These are CNS depressants that are classified as sedative-hypnotic drugs. They act on the CNS by enhancing the neuroinhibitory action of gamma-aminobutyric acid (GABA) and

producing relief from anxiety and sedation. They are classified as ultra-short acting (thiopental), short acting (pentobarbital [yellow jackets], secobarbital [reds]), and long acting (phenobarbital). The short acting barbiturates have a higher potential for abuse and are more lipid soluble than the long acting formulations.

They can become addicting in 1 to 2 months and are deadly in high doses or when combined with opioids or alcohol. Abuse of these drugs leads to physical addiction, abstinence, and discontinuation syndrome, similar to that noted with alcohol abuse. The DSM-5 lists a number of “sedative, hypnotic, or anxiolytic”-related disorders: sedative, hypnotic, or anxiolytic use disorder (mild, moderate, severe); sedative, hypnotic, or anxiolytic intoxication; sedative, hypnotic, or anxiolytic withdrawal; other sedative, hypnotic, or anxiolytic -induced disorders; and unspecified sedative, hypnotic, or anxiolytic related disorders [23].

Barbiturates are detoxified in the liver and/or excreted unchanged in the urine. Symptoms of acute use and overdose are similar to those of alcohol and include euphoria, slurred speech, lethargy, miosis, and ataxia. Overdosing leads to low blood pressure, bullous dermatological lesions, respiratory depression, coma, and death. It is not commonly abused at current times and involves less than 3% of high school students. This reduced abuse probably reflects infrequent clinician prescription of these drugs, reduced availability on the streets, and the availability of many other illicit drugs. Barbiturates should usually not be prescribed to adolescents and then, only with extreme caution.

CONCLUSION

Substance abuse continues to be a widespread and very serious phenomenon for our adolescents and young adults in the United States and around the globe. Many factors draw our youth into these deadly drugs, leading to many acute and chronic sequelae, ranging from addiction to death. Youth must be clearly and carefully taught that drug use and abuse comes with considerable complications for their current and future life. They also must be taught that there is no scientific evidence that smoking cannabis is safe nor is medically beneficial. They must also become aware of the dangers of the designer drugs that are being produced in greater amounts.

Clinicians must join with other members of society to educate our patients to the many deadly and dangerous drugs of abuse that are available and work with society (including governments) to reduce the availability of drugs [62-78]. The human instinct for pleasure at any cost must be tempered with education and direction from clinicians. Management of those addicted to drugs is a complex, often discouraging process. Psychosocial and behavioral therapies are important that involve a variety of health specialists. Group, family, and individual therapy all have a place in management and many need intensive treatment in drug abuse programs.

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Chapter 512

FROM THE BATTERED CHILD SYNDROME TO ABUSE AND MALTREATMENT: A PUBLIC HEALTH VIEW

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ABSTRACT

This review serves as a primer for professionals who, regardless of their individual interests and fields of expertise, can improve the growth and development of children by understanding, responding to, and preventing abuse and maltreatment in the child and adolescent. It provides an overview of the types, medical assessment, and treatment of children with potential abuse and maltreatment, and the preventive community services that can be provided to help their families. It outlines areas of current research and highlights issues that still need to be addressed. The experience of the past fifty years has established a solid foundation in preparation for the work that child health clinicians still need to do in the field of child abuse medicine.

Keywords: childhood, adolescence, abuse, neglect, maltreatment, public health

INTRODUCTION

In the fifty years since the publication of C Henry Kempe's (1922-1984) landmark article, "The battered child syndrome" [1], the subject of child maltreatment has become a universal topic, not restricted to one community or to one type of provider. As the field has grown, professionals have had to broaden their intellectual and personal perspectives to not only identify maltreatment but also to provide interventions to prevent further abuse. The current goal of professionals dedicated to this field is primary prevention, to insure that child abuse, like many infectious diseases of the past century, will be eradicated in the near future.

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While each state in the United States (US) defines child maltreatment in its child welfare and criminal statutes, broad definitions have been developed for the Child Abuse Prevention and Treatment Act [2] and by the World Health Organization (see Table 1).

While child abuse overall pertains to the variety of acts committed or omitted by parents or caretakers for children, the quality of the parent-child relationship and nurturing is often left out of state laws. In the broader sense, the WHO [3] adds qualitative definition and context to this relationship and the more broad nature of caring for children.

Table 1. World Health Organization definitions*

Child Abuse - Child abuse or maltreatment constitutes all forms of physical and/or emotional ill-treatment, sexual abuse, neglect or negligent treatment or commercial or other exploitation, resulting in actual or potential harm to the child's health, survival, development, or dignity in the context of a relationship of responsibility, trust or power.
<i>Physical Abuse</i> - Physical Abuse of a child is that which results in actual or potential physical harm from an interaction or lack of an interaction, which is reasonably within the control of a parent or person in a position of responsibility, power or trust. There may be a single or repeated incidents.
Emotional Abuse - Emotional abuse includes the failure to provide a developmentally appropriate, supportive environment, including the availability of a primary attachment figure, so that the child can establish a stable and full range of emotional and social competencies commensurate with her or his personal potentials and in the context of the society in which the child dwells. There may also be acts towards the child that cause or have a high probability of causing harm to the child's health or physical, mental, spiritual, moral or social development. These acts must be reasonably within the control of a parent or person in a position of responsibility, power or trust. Acts include restriction of movement, patterns of belittling, denigrating, scapegoating, threatening, scaring, discriminating, ridiculing or other non-physical forms of hostile or rejecting treatment.
Neglect and negligent treatment - Neglect is the failure to provide for the development of the child in all spheres: health, education, emotional development, nutrition, shelter and safe living conditions, in the context of resources reasonably available to the family or caretakers and causes or has a high probability of causing harm to the child's health or physical, mental, spiritual, moral or social development. This includes the failure to properly supervise and protect children from harm as much as is feasible.
Sexual abuse - Child sexual abuse is the involvement of a child in sexual activity that he or she does not fully comprehend or is unable to give informed consent to, or that violates the laws or social taboos of society. Child sexual abuse is evidenced by this activity between a child and an adult or another child who by age or development is in a relationship of responsibility, trust or power, the activity being intended to gratify or satisfy the needs of the other person. This may include but is not limited to: The inducement or coercion of a child to engage in any unlawful activity The exploitative use of a child in prostitution or other unlawful sexual practices The exploitative use of children in pornographic performances and materials
Exploitation - Commercial or other exploitation of a child refers to the use of the child in work or other activities for the benefit of others. This includes, but is not limited to, child labour and child prostitution. These activities are to the detriment of the child's physical or mental health, education, or spiritual, moral or social-emotional development.

*World Health Organization (WHO). (1999). *Report of the consultation on child abuse prevention*. Geneva, Switzerland: Author.

In the effort to allow diagnostic coding for physicians in medical systems and for medical examiners and coroners for state public health statutes, the International Classification of Disease Codes have been developed applicable to child abuse and neglect. ICD-9 lists individual types as well as external modifiers related to perpetrator relationship ("E codes"). A revised set of codes (ICD-10) is increasingly being used [4], and comparisons of the two systems are listed in Table 2.

Table 2. International classification of disease codes applicable to child abuse (ICD-9)

<i>ICD-9</i>	<i>ICD-10</i>
995.50 Child abuse, unspecified	T74.92 Unspecified child maltreatment
995.51 Child emotional/psychological abuse	T74.32 Child psychological abuse
995.52 Child neglect (nutritional) Use additional code to identify intent of neglect (E904.0,E968.4)	T74.02 Child neglect or abandonment
995.53 Child sexual abuse	T74.22 Child sexual abuse
995.54 Child physical abuse Battered baby or child syndrome <i>Excludes: Shaken infant syndrome (995.55)</i>	T74.12 Child physical abuse
995.55 Shaken infant syndrome Use additional code(s) to identify any associated injuries	T74.4 Shaken infant syndrome
E967 Perpetrator of child and adult abuse	
E967.0 By father, stepfather, or boyfriend Male partner of child's parent or guardian	
E967.2 By mother, stepmother, or girlfriend Female partner of child's parent or guardian	
E967.3 By spouse or partner Abuse of spouse or partner by ex-spouse or ex-partner	
E967.4 By child	
E967.5 By sibling	
E967.6 By grandparent	
E967.7 By other relative	
E967.8 By non-related caregiver	
E967.9 By unspecified person	

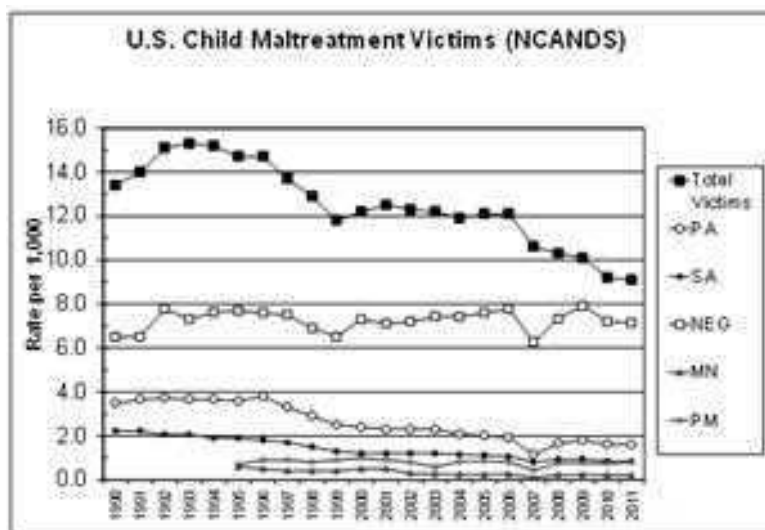
EPIDEMIOLOGY

The victimization of children through abuse and neglect remains an all too common occurrence. In the United States, 1-2 per 1,000 children are victimized by physical abuse each year, and young children and infants have the highest rates. Maltreated children suffer from a variety of behavior problems and mental disorders in addition to physical injuries [5, 6]. The Adverse Childhood Experiences study has noted the powerful relationship between adverse childhood experiences and several conditions of adulthood, including risk of suicide, alcoholism, depression, illicit drug use, and other lifestyle changes [7-9]. While the exact pathways are still being explored, childhood abuse is thought to affect adult health by putting people at risk for depression and post-traumatic stress disorders, difficulties in relationships, and negative beliefs and attitudes towards others through mechanisms of toxic stress [10-11].

Two large administrative sources provide information about the U.S. annual incidence of child maltreatment, the National Child Abuse and Neglect Data System (NCANDS) and the National Incidence Studies of child abuse and neglect (NIS). NCANDS contains aggregate and case-level data on child abuse reports received by state Child Protective Service (CPS) agencies, and almost all US states and territories provide information annually about the outcomes of child abuse reports, types of maltreatment, child and family factors and services

being provided [12]. National estimates of the overall numbers of victims (substantiated or indicated CPS reports) as well as victims identified with physical and sexual abuse show decline over the 20+ years of nationally collected data in NCANDS (see Figure 1), following similar trends in other national crime statistics [12].

In contrast, NIS samples sentinel counties to identify maltreatment under two standards: the harm standard (relatively stringent in that it generally requires that an act or omission result in demonstrable harm in order to be classified as abuse or neglect) and the endangerment standard (which allows children who were not yet harmed by maltreatment to be counted if the CM was confirmed by CPS or identified as endangerment by professionals outside CPS, either by their parents or other adults) [13]. The Fourth National Incidence Study of Child Abuse and Neglect (NIS-4) also shows an overall decrease in the incidence of maltreatment since the NIS-3, as well as decreases in some specific maltreatment categories and increases in others. Using the stringent Harm Standard definition, more than 1.25 million children (an estimated 1,256,600 children) experienced maltreatment during the NIS-4 study year (2005–2006). A large percentage (44%) or an estimated total of 553,300 were abused, and most of these abused children experienced physical abuse (58%).



MN = Medical Neglect; NEG = Neglect; PA = Physical Abuse; PM = Psychological Maltreatment; SA = Sexual Abuse [6].

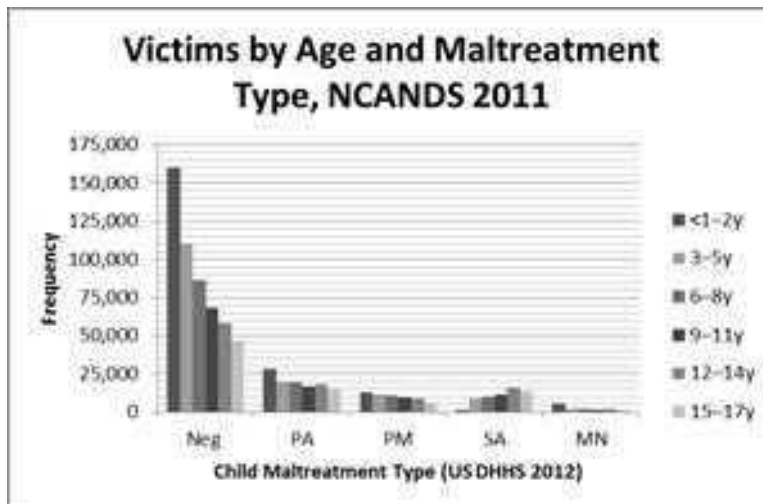
Figure 1. United States child maltreatment victims (NCANDS), 1990-2011.

Smaller independent samples offer additional information. In the Carolinas, the incidence of harsh physical discipline was found to be 4.3% of respondents (with 2.4% shaking infants), and a retrospective prevalence survey, reported 24% of adolescents being physically assaulted [14, 15]. The range of incidence rates of abusive head trauma (AHT) has been found to be 27.5-32.2 per 100,000 in a large U.S. inpatient database, with an estimates rising during 1997 to 2009 [16]. Lane et al. [17] noted hospital discharge rates of 1.8 per 100k, with 25% of head trauma in infants being abusive.

Unlike the reported incidence of sexual abuse, in which it has been suggested that at least some of the decrease is real, it is not clear if or why physical abuse rates have actually declined [18, 19]. While economic indicators improved in the 1990's during the decline, the number of cases continued to fall in NCANDS in 2008-2011 during an economic recession [20]. This may indicate that states are changing how they count child maltreatment fatalities or how they are delivering that information to NCANDS as could occur with differential response systems [12]. Further studies are needed to ascertain whether the number of physical abuse cases is continuing to decline and the causes why this is occurring. A number of smaller samples have suggested a rise in more serious child physical abuse associated with the U.S. economic recession.

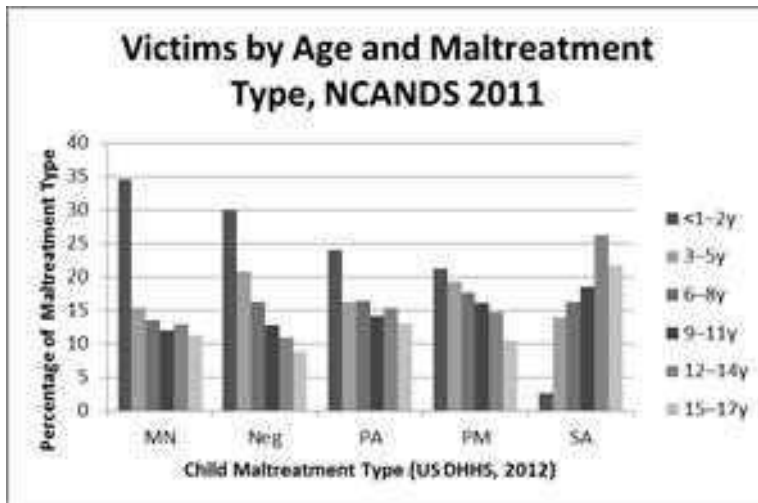
It has been noted that the abusive head trauma rate increased from 8.9 to 14.7 per 100,000 and a doubling from 0.7 to 1.4 per month during the recession [20]. Wood et al. [21] noted increasing rates of children admitted to hospitals for physical abuse over 10 years 2000-2009, rising from 0.8 to 3% annually. Rates of physical abuse reportedly also fell in the UK during 1974 to 2008 [22]. Neglect continues to affect more than 50% of those children reported to child protective services, and the parents of young neglected children were less likely to have completed high school, had more preschool children and had less parenting skills and social support [23]. Disabled children also have increased risk [24]. When broken down by age and type of child maltreatment, it is apparent that most CM occurs in very young children and most CM is neglect (see Figure 2). This pattern continues with older children, but the number falls dramatically. For sexual abuse, older children are more affected. Medical neglect, in contrast, affects mostly infants.

Similar relationships hold as a proportion of the total number of victims identified in NCANDS. Younger children are the highest proportion for all CM types, except sexual abuse (see Figure 3).



MN = Medical Neglect; NEG = Neglect; PA = Physical Abuse; PM = Psychological Maltreatment; SA = Sexual Abuse [6].

Figure 2. Victims by age and maltreatment type, NCANDS 2011 [12].



MN = Medical Neglect; NEG = Neglect; PA = Physical Abuse; PM = Psychological Maltreatment; SA = Sexual Abuse [6].

Figure 3. Victims by age as a percentage of child maltreatment types, NCANDS 2011 [20].

Although the focus of concern about maltreatment is usually the younger child, statistics show that 30 to 50% of all reported cases involve adolescents [12]. In New York State in 1985, for example, there were 84,119 child maltreatment reports with substantiation rate of 35%. Within the adolescent reports, 19% were for physical abuse, 42.4% for sexual abuse, and the remainder for neglect [25]. In 2002, there were 153,603 reports of child maltreatment in New York with a substantiation rate of 31.1%. Of those, children from ages 10-17 years accounted for 47.9% (21,727 children) of the cases. Almost half (47%) of children entering foster care were over 10 years of age, and approximately 75% remained in care for longer than one year. In the same year in New York City, there were 10,922 children ages 10 to 17 years placed in foster care. Alarming, 15% of those in foster care were adolescents who had been in the system more than one year. These child maltreatment cases can only reflect those that come to the attention of the child protection system. Based on other sources of information regarding adolescent behaviors, maltreatment is given as a comorbid factor in a spectrum of adolescent problems, such as substance abuse, truancy, runaways and psychiatric disorders [26-28].

While there are varying schools of thought on the origins of maltreatment, most theories of child maltreatment recognize that the root causes can be divided into four principal systems: (1) the child, (2) the family, (3) the community, and (4) society. While children are certainly not responsible for the abuse inflicted upon them, there are certain characteristics that have been found to increase the risk for maltreatment. Children with disabilities or mental retardation, for example, are significantly more likely to be abused [24]. Evidence also suggests that age and gender are predictive of maltreatment risk. Younger children are more likely to be neglected, while the risk for sexual abuse increases with age. Female children and adolescents are significantly more likely than males to suffer sexual abuse.

Several factors have been associated with physical abuse. Unlike previous NIS cycles, NIS-4 found strong and pervasive race differences in the incidence of maltreatment with rates of maltreatment for Black children significantly higher than those for White and Hispanic

children. Under the Harm Standard, children with confirmed disabilities had significantly lower rates of physical abuse and of moderate harm from maltreatment, but they had significantly higher rates of emotional neglect and of serious injury or harm [13]. NIS-4 also confirmed findings from other studies which associated increased physical abuse in poor, larger, unemployed families, and one parent and an unrelated caregiver present. Zhou, Hallisey, & Freymann [29] found that infant maltreatment can best be predicted when there are young mothers less than 20 years, who are unmarried, with inadequate prenatal care, are poor, who smoke during the pregnancy, or when there are three or more siblings. In an NCANDS sample, parent emotional problems, alcohol abuse and other family violence were found to be associated with the recurrence of physical abuse before age three years [30].

Community and social factors also play a role in child maltreatment. Poverty, for example, has been linked with maltreatment, particularly neglect, in each of the national incidence studies [13], and has been associated with child neglect, a strong predictor of substantiated child maltreatment [31]. The following factors have been linked to child maltreatment: fewer friends in their social support networks, less contact with friends, and lower ratings of quality support received from friends [32]. Violence and unemployment are other community-level variables that have been found to be associated with child maltreatment.

Perhaps the least understood and studied level of child maltreatment is that of society. Ecological theories postulate that factors such as the narrow legal definitions of child maltreatment, the social acceptance of violence (as evidenced by video games, television and films, and music lyrics), and political or religious views that value noninterference in families above all may be associated with child maltreatment [6].

Clinical Features

Several health effects of child maltreatment have been identified. While there is considerable overlap, specific health effects and injuries are often related to a major subtype of child abuse, and the medical diagnostic evaluation varies with the type of child maltreatment and the injuries of concern (see Table 3).

Physical Abuse

The most common injury from physical abuse affects the skin by bruising or burning. Recognition and documentation of bruises, burns and other skin lesions requires complete undressing of the child and comprehensive physical examination. Skin lesions should describe location, size, color, depth, and integrity of the epidermis and may be documented using notes, hand-drawn diagrams or photographs; law enforcement and child protection workers often have resources to assure high quality photo documentation. Even if photographs are taken, the pediatrician should also contemporaneously document skin injuries identified [33]. Additionally, specific statements by the family and child should also be copied verbatim in the medical chart for potential use later in the legal system.

Table 3. Medical diagnostic evaluation in child victimization emphasizing identification of cause and sequelae of physical injury

<i>History- Questions asked by healthcare professionals of the child and caretakers during medical encounter</i>
Chief Complaint (Why are you here today?)
History of Present Illness Circumstances surrounding injury Physical symptoms such as pain, bleeding, sensory problems, etc. Events leading to seeking medical care Timing
Prior medical treatments, surgery, medications, hospitalizations, mental health services
Prior evaluations for victimization
Chronic medical conditions, particularly bleeding, neurologic, metabolic, growth disorders
Immunizations received
Known allergies
Psychosocial history (caretakers, school attendance, housing, income, family structure)
<i>Physical Examination- done by the physician, nurse, or other practitioner based on history</i> Vital signs (pulse, respiration rate, height, weight, head circumference, Glasgow Coma Scale, pain scale) Skin (bruising, burns, pattern marks, contusions, tenderness) Head (presence of skin swelling, bruising, skull deformity, fontanelles) Eyes (pupillary response, sclera, retina, periorbital tissues) Ears (earlobes, canals, tympanic membranes) Nose (bleeding, nares, deformity) Mouth, throat (condition of teeth, tonsils, pharynx, frenula) Neck (flexibility, lymph glands, thyroid) Chest (rib deformities, air movement and congestion, tenderness) Heart (heart sounds, rhythm) Abdomen (tenderness, organ swelling, bowel sounds) Genitals (penis, scrotum, testes, urethra in males; labia, hymen, urethra, vagina in females) Anorectal (perineum, internal and external anal sphincters, rugal folds, tone) Extremities (movement, tenderness, swelling, joint involvement, pulses, ambulation) Neurological (alertness, reflexes, muscular strength and tone, cranial nerves, sensation)
<i>Laboratory – Tests performed as indicated by history and physical findings</i> Complete blood count (white and red blood cells, hematocrit, platelet counts) Coagulation studies (prothrombin, partial thromboplastin times, fibrinogen, platelet function) Blood chemistries, liver function tests X-rays of affected areas or skeletal survey of all bones for children less than three years Computer-assisted tomography (CT) scan of brain or other affected part Magnetic Resonance Imaging (MRI) of head or other affected part Specialized metabolic tests (collagen, organic and amino acids, others) Microbiologic cultures and tests for sexually transmitted infections Collection of forensic trace specimens (less than 72 hours after contact) Pregnancy testing (depending on sexual development and potential contact)
Diagnosis and Treatment- Identification of disease or sequelae of trauma Hospitalization for further diagnostic assessment or treatment (based on severity of illness/injury and/or need for surgical or supportive care) Reassurance and emotional support Referral for ongoing medical and mental health treatment CPS reporting and provision for immediate safety needs and protection

In the case of bruising, standard coagulation tests should be ordered to objectively assess platelet count and function as well as coagulation factors. Any skin lesion beyond temporary reddening should be considered as potential physical abuse when (1) the injury is inflicted and non-accidental, (2) the pattern of injury fits biomechanical models of abusive trauma, (3) the pattern corresponds to infliction with an instrument that would not occur through play or in the environment, (4) the history provided is not in keeping with the child's development, or (5) the history does not explain the injury [33].

The aging of bruises in children has received considerable attention and current guidelines are severely limited in their ability to precisely time when an injury occurred. Pattern, depth (degree), and healing of burns helps in determining their specificity for maltreatment. Developmental and other considerations need to be entertained as there are a host of potential confounders or 'mimics' which need to be reviewed when coming to a diagnosis. Some children as young as 10 months of age, for example, have been shown to have the developmental capability to climb into the bath, suggesting that nonspecific burn patterns could be attributed to actions by the child rather than the parent in some cases [34].

The distribution of lesions can be a critical factor in determining if a child has been abused. Certain sites are highly correlated with abuse, such as buttocks, the lower back, the posterior aspects of the extremities and the ears [35]. Bruising at other sites, such as the bony prominences of the forehead, the elbows and lower legs, are consistent with the normal childhood trauma seen in mobile children. Sugar et al. [36] noted "those who don't bruise rarely bruise," signaling we should be concerned when non-walking infants or motor delayed children have bruising. Inflicted bruising may have clear patterns or may be non-specific.

When an object is used, the pattern of the injury may clearly show the outline of the object. Another form of patterned bruising comes from biting. A careful inspection and measurement of the lesion can determine if a bite is human or animal, adult or child, or self-inflicted. Since the most common skin manifestation of physical abuse is multiple bruises in different stages of healing, it is imperative to use a diagram and appropriate imaging to document the color, distribution and pattern of these injuries. A burn is the destruction of skin and underlying tissue caused by the application of a physical agent. These agents may be chemicals, heat, cold, or electrical in nature. Since the spectrum of burns can range from a simple isolated injury to the involvement of major portions of the child's body, the clinician should assess the type of agent, the distribution and extent of the burn, and the history given of how the burn occurred [37]. Many burns in childhood are accidental but are also the result of poor judgment or the failure of the caretaker to provide adequate supervision. Here, as in other forms of abuse, the developmental age and the size of the child are very important. Inflicted burns often have very specific patterns such as those seen with immersion or dunking. Burns may result from splash, immersion, or contact with a heated instrument or utensil, a flame, a chemical/caustic agent or an electrical source.

Accidental burns/scalds commonly involve hot liquids in contact with a child's face, neck, and upper chest [38]. If a child pulls down a cup of hot water, this will produce a different pattern than if he had pulled a cup of thick liquid. The action may be modified by the height from which the hot liquid fell, the vehicle that contained the hot substance, and the child's size. Immersion burns present with distinctive patterns that result from placing the child in hot water. The patterns include stocking/glove burns that are symmetrical burns of the extremities. Forced immersion of the child in a tub can produce a burn pattern with well-demarcated lesions and little or no evidence of splash.

Contact burns can present with identifiable object patterns such as an iron or a cigarette lighter. A child can easily have contact with the iron left on the floor or by pulling the cord. Other sources of contact burns are room heaters, hair curling irons, electric cooking utensils, and radiators which can each produce distinctive lesions. Lit cigarettes can produce lesions that can be difficult to distinguish from chicken pox or impetigo given the similarity of the size and shape.

A variety of diagnostic issues await further study. As the Institute of Medicine [6] pointed out, there is a great deal of additional data needed by clinicians on the frontlines to assist in determining which children need evaluation for abuse, when subspecialists should be called, and what tests should be done. There are still issues on how to fund training for physicians to recognize and report abusive bruises and how to best train case workers, social workers and other investigators about medical issues. More research is needed to study innovative systems-level changes that may address challenges associated with decision making on medical issues by frontline workers.

Acute fractures may be clinically apparent as soft tissue swelling over a fracture site, a deformity of the involved limb, or as a decrease in movement with or without external bruising. Infants may present with irritability and/or not using an affected limb. Healing fractures may sometimes be identified as palpable lesions consistent with callus formation, especially over the ribs [39]. The absence of swelling or bruises near a fracture site is not uncommon in fractures of the extremities and ribs. A case series of 703 consecutive skeletal series reported 11% fractures, with higher rates in infants less than 6 months old, apparent life threatening events, seizures and abusive head trauma. 79% had healing fractures seen [40]. One study reported that when skeletal surveys were done, 23% identified additional fractures, 10% in the hands, feet or spine and follow-up x-rays in 1-2 weeks have been found to identify additional fractures in 8.5% of children [41].

There is no fracture type that is pathognomonic for abuse, and all fracture types can potentially result from inflicted injury. The diagnosis of inflicted fracture must be made through careful correlation of the history provided by the caregiver with the child's developmental level and physical and radiographic findings. Classic metaphyseal lesions, rib fractures (particularly posteriorly), scapular fractures, vertebral spinous process fractures, and sternal fractures all have a high specificity for abuse [42]. Common, nonspecific injuries include subperiosteal new bone formation, clavicular fractures, diaphyseal fractures of long bones, and linear skull fractures. There are some fracture types and findings of intermediate specificity that are concerning but may be accidental if a clearly plausible mechanism is provided. This group includes multiple fractures (particularly when bilateral), fractures of different ages, epiphyseal separation, digital fractures, vertebral body fractures and subluxations, and complex skull fractures.

The age of fractures can be helpful in assessing the plausibility of the history, and multiple fractures of different ages raise the suspicion of abuse. Fracture healing manifests as periosteal reaction, also called callus, which is radiographically apparent after 10–14 days, and can be seen earlier in infants [43, 44]. Subperiosteal new bone formation can be a normal finding in infants under 6 months of age when it is found along the shafts of long bones and is symmetrical on both sides of the body. Skull fractures cannot be dated with accuracy, however, when non-accidental trauma is suspected, appropriate skeletal studies should be done as outlined by the American College of Radiology [45] and the American Academy of Pediatrics Section on Radiology [46].

Skeletal survey is the standard diagnostic investigation when there is concern for physical abuse of infants and toddlers under two years old [46]. It includes antero-posterior (AP) views of the extremities including feet, with the exception of the hands which are imaged in the posterior-anterior view; AP and lateral skull; AP and lateral views of the thorax and oblique ribs; AP pelvis; and lateral views of the spine. Radiologic evaluation is necessary to assess both the fracture itself and overall status of the bony skeleton to identify any metabolic/genetic process that might produce bone fragility. A discussion of the various metabolic bone diseases associated with fractures is beyond the scope of this chapter, and a pediatric radiologist should be utilized since familiarity with the presentation of growth variables in the pediatric patient is very important in determining if the findings are consistent with non-accidental trauma or other explanations.

Several areas of continuing medical research include the delineation of the diagnosis, pathophysiology and injury mechanics of fractures, head trauma and other abuse injuries. Further research is indicated, and physicians should appropriately search and test for alternate explanations while appropriately weighting the strong available evidence to ensure that a child remains protected from harm. CT, for example has been suggested to be a more sensitive test for rib fractures, yet the increased radiation exposure may not warrant it for screening [47]. While it has been noted that vitamin D deficiency does not predispose to fracture in the absence of clinical rickets [48, 49], additional studies regarding the quantitative effects of such deficiencies could be helpful.

The leading cause of abusive mortality and morbidity is inflicted traumatic brain injury [50]. With mortality rates of 10–50% and more than 90% of survivors having significant developmental sequelae, physical abuse to the head has been noted to have patterns of injuries that are distinct from accidental or medical causes. At least 1,400 cases of fatal abusive head trauma occur annually in the United States, and there is growing sophistication in our ability to differentiate these fatalities from those from non-abusive causes. Prior to 1974, the presence of subdural hematomas in infants who had no apparent history or evidence of trauma was given the diagnosis of “idiopathic subdural hematoma of infancy”. With the publication of the article by Caffey in 1974 based on interviews of caretakers, this entity became known as the “Shaken Baby Syndrome” and later the “Shaken Baby/Impact Syndrome” as the awareness of this clinical entity grew and applied to related clinical situations [51]. New diagnostic technologies developed in the last century, from radiographs to sophisticated computer-assisted imaging techniques, have proved invaluable in visualizing internal bleeding and injury.

The mechanism for the injury has been described as the violent shaking of an infant resulting in the movement of the brain within the skull and related hemorrhage within the eye and optic nerve. Subdural bleeding is thought to be caused by the disruption of the bridging veins within the subdural space. Rib fractures are attributed to the compression of the chest by the caretaker as the infant was shaken. This mechanism of injury is consistent with the histories given by providers over the years in which the caretaker sought to silence the crying infant by grabbing the child around the thorax and shaking the child until the child stopped crying. Alternative terms for this clinical entity are now being used, including Abusive Head Trauma or Non-Accidental Head Injury, to indicate head trauma without reference to the mode of injury. Infants and children under 3 years with interhemispheric subdural hemorrhage were found to have a greater than 99% probability of intentional trauma, and predictive values of a variety of injuries have been calculated [52]. However, a pattern of

head crush injuries increasingly seen after TV falls reminds us that these findings are not always pathognomonic for abusive head trauma [53]. Whether external hydrocephalus or “benign extra-axial fluid of infancy” predisposes to subdural bleeding is still not clear. The potential contribution of birth and other factors such as maternal anti-Ro antibodies is also provocative [54]. Newer imaging modalities, such as diffusion tensor imaging, offer valuable ways to detect the effects of AHT, but further studies are needed to help us integrate them into clinical practice [55-57].

Approximately 4%-6% of abused children have ocular findings. Any ocular injury can be the result of abuse, and all forms of abuse may have ophthalmic manifestations [58]. The incidence of retinal hemorrhages (RH) in shaken-baby syndrome (SBS) is 85%, but higher in children who have died versus unimpaired survivors. There is an association between severity of brain injury and RH severity, and RH can rarely occur without intracranial hemorrhage or cerebral edema [59]. Approximately two-thirds of victims have RHs that are too numerous to count and are multilayered. These RHs extend out to the retinal periphery, with no particular anatomic pattern, and cover the majority of the retinal surface. Macular retinoschisis also indicates trauma. RH cannot be dated with precision. Massive numbers of superficial or small-dot hemorrhages can resolve within 24 hours.

There is some evidence that mild increases of RH, or the appearance of RH not previously present, can occur early during hospitalization in very ill children, which underscores the need for prompt ophthalmology consultation and retinal evaluation [60]. A small number of infants have been noted to have RH after birth that resolve within two weeks. It is also known that RHs in the posterior pole are associated with non-abusive causes. The overwhelming body of literature supports a conclusion that severe hemorrhagic retinopathy in otherwise previously well children without obvious history to the contrary (e.g., head crush or high velocity impact) suggests that the child has been submitted to repetitive acceleration-deceleration trauma with or without head impact [58].

There is a growing body of knowledge about abusive abdominal and chest trauma which are often ‘silent’ injuries with potentially devastating consequences. Abdominal injuries are the second leading cause of death after abusive head trauma but are difficult to assess given their occult nature, relative lack of bruising, and potential for significant delay in symptoms. Even with a history of a severe blow to the abdomen, bruising of the skin is often not seen. Examination may reveal guarding and change/loss of bowel sounds. Lab studies must address injuries to all the abdominal organs including the kidneys. CT scans of the abdomen are very useful in determining the extent of these injuries when the physical findings are diffuse and non-specific. Direct blows to the abdomen such as a punch, kick or use of an object can injure both solid and hollow organs which are both impacted and compressed against the vertebral column [61].

One study demonstrated that solid organ injuries were most common in both accidental and inflicted trauma. Hollow viscus injuries, alone or in combination with solid organ damage, were more common in cases of inflicted injuries [62]. Recent studies suggest that abdominal CT imaging and liver function and pancreatic testing should be carried out in all abusive head trauma victims to identify occult abdominal trauma given that 25% or more of even fatal abdominal trauma cases can have few or no visible external bruises [61]. Inflicted chest injuries in children are uncommon as a single episode of trauma but are often seen in conjunction with other non-accidental injuries such as inflicted head trauma with compression fractures of the ribs. Direct blows to the chest wall rarely present with damage to the heart or

the thoracic duct [63]. Many of these injuries are fatal and only identified at post mortem exam. Cardiac troponins have been found to be increased after abusive chest trauma, and the time course and screening evaluation of serologic markers for abusive abdominal trauma need further study [64].

Sexual Abuse

Sexual abuse has been defined as sexual contacts or exploitation of children by adults, which cannot be consented to, and which violate social laws or taboos. Sexual assault is a comprehensive term encompassing several types of forced sexual activity, while the term molestation means non-coital sexual activity between a child and an adolescent or adult. Rape is defined as forced sexual intercourse with vaginal, oral or anal penetration by the offender. Acquaintance or “date rape” apply when the assailant and victim know each other. Statutory rape involves sexual penetration of a minor by an adult as defined in varying state laws, regardless of assent [65].

A prime injury of sexual abuse is emotional. While most young children with proven sexual abuse have few physical injuries, patterns of anogenital injury and sexually transmitted diseases have been identified [66]. Several large case series have been published highlighting the normalcy of most examinations [66-68]. Assessing sexual abuse requires detailed knowledge of anogenital anatomy and sexually transmitted infections (STIs) in children, both of which have important differences from adults, and specialized skills and examination techniques have had to be developed [69, 70]. It has become apparent that most physicians have little knowledge about prepubertal genital anatomy and cannot identify key landmarks. This is compounded by the paucity of studies clearly documenting the differences between abusive and non-abusive injury and the changing interpretation over time. When confronted with concerns of potential sexual abuse, the pediatrician should obtain key elements of the history such as type, frequency and timing of contact and physically assess the child for gross injuries and infection [65]. Definitive assessment and treatment is increasingly handled by referral to pediatricians with specialized experience in testing, interpretation, and documentation of anogenital findings [71].

The issues surrounding sexual abuse are compounded during adolescence [25]. In surveys of high school students, over 25% reported that they have experienced unwanted sexual contact; in clinical populations, the rates are even higher [72]. A recent prospective study demonstrated that child maltreatment is an independent predictor of later adolescent pregnancies, with birth rates highest for sexually abused and neglected females when compared to a matched cohort [73]. Repeated sexual contact and pregnancy places teenagers at increased risk for several health harms. Repeated sexual contact has been associated with younger ages of sexual initiation, higher rates of depression, anxiety, substance abuse and delinquency.

Most adolescent rape and sexual assault is perpetrated by an acquaintance or relative of the adolescent, with younger adolescents having assailants more likely from the extended family. Increased rates of sexual assault are seen in adolescents with disabilities, alcohol use and other family dysfunction [74]. Males are less likely to report sexual assault, less likely to

receive treatment, and more likely to become perpetrators themselves after being victimized than are female adolescents [75].

Clinicians caring for sexual abuse victims should be trained in the procedures required for documentation and collection of evidence and the steps to minimize the child from further victimization [65, 76-78]. They should inquire about psychological traits and behaviors; also, there should be specific inquiry about the types and timing of reported sexual contact [72]. The examination begins with a comprehensive general examination followed by detailed visualization of the genitals, anus and oral cavity.

Procedures such as colposcopy and video-colposcopy offer ways to document and record trauma, to allow the child to be more relaxed and cooperative during examination, and to begin the process of emotional healing [79]. While it is beyond the scope of this chapter to detail all of the findings associated with sexual abuse, recent research suggests that only limited findings have high specificity, such as lacerations and transections of the hymen and bruising or other injury to the anus and genitals. Several findings which were once thought to indicate trauma are now considered non-specific, accidentally acquired, or congenital variations [66]. Follow-up exams can be vital for evaluating certain lesions, determining the course of healing, and treatment efficacy [80].

While all STIs should raise the suspicion of possible sexual contact, infections with *Neisseria gonorrhea* and *Treponema pallidum* are most specific for mucosal sexual contact and must generally be reported [65, 69]. The presence of STIs needs to be evaluated on a case-by-case basis, and the possibility of non-sexual or vertical transmission considered. Other infections to be considered include *chlamydia trachomatis*, *Trichomonas* species, human immunodeficiency virus and hepatitis B and C viruses. The clinician should be knowledgeable about the potential sources of infection, body sites, types of contact and testing strategies before treatment eradicates microbiologic evidence. There are several new methods being used to detect STIs, not all of which have acceptance in legal proceedings [81-84]. The clinician needs to carefully consider the types and timing of any prophylaxis for STI or pregnancy based on the age and development of the child, the type and timing of contact, and the risk factors for disease in the alleged perpetrator [69].

Psychological Maltreatment

Psychological maltreatment (PM) is commonly associated with other forms of abuse but may also occur in isolation in a small number of cases. By definition, PM is a repeated pattern of interaction between a parent and child that harms the child's emotional well-being. Spurning, belittling, degrading, ridiculing, or shaming a child is considered harming a child's self-worth. Terrorizing and otherwise exploiting the child increases the harm further. The sheer denial of emotional closeness leads to physical and developmental delays in young children and failure to thrive in infants. Rejection, isolation, and inconsistent parenting styles lead children to feel insecure in their home and relationships. An emerging form of PM occurs when a child witnesses violence in the home, including spousal violence, community violence, or even violence on television or movies [84]. PM is seldom the focus of CPS investigation and has increasingly been coupled with other forms of CM in CPS reports [85, 86].

PM is associated with a variety of negative and lasting effects. Shaffer et al. suggested that the effects of emotional maltreatment are disabling and enduring, with adjustment outcomes varying according to the type of psychological maltreatment (i.e., emotional abuse, emotional neglect), gender, and other factors [87]. PM is strongly linked to depression and problems with relationships and attachment, and it predicts more rapid onset of major and minor mental illness in a dose-dependent manner [88-92]. PM and recurrent PM in childhood and adolescence represent important risk factors for increased victimization, and children with high levels of co-occurring internalizing and externalizing symptoms are particularly likely to experience increased exposure to peer victimization, maltreatment, and sexual victimization, thereby escalating physical and mental harm [93].

Psychological neglect and failure to thrive have been significantly associated with behavior problems and poor cognitive development, even while controlling for poverty [94, 95] and services put in place [96, 97]. The psychological effects of maltreatment may be very difficult to recognize in the medical office. Sometimes the poor parent-child relationship is seen and the verbal stigmata of PM exposed, but often there are little or no physical findings demonstrating the emotional harm, other than weight loss or excessive weight gain. The quiet, depressed child is not often identified as a victim of neglect as readily as is the hyperactive, aggressive child [98]. The pediatrician needs to evaluate the harm or potential harm to the child's mental health, while realizing that it may take several years for such harm to become apparent and the effects are often confounded with exposure to other violence [85].

Documentation must be objective, with appropriate use of psychological tests and mental health referrals in the evaluation. Behavioral changes in the child are early but non-specific events, and assessment should include multiple domains, including function at home, school and at play. The psychological effects of malnutrition are further modified by the intensity, type, frequency, and severity of exposure as well as the developmental stage and resiliency of the child [84, 96]. A recent study noted that fewer than 25% of families received counseling, mental health or other services after PM, and service referrals varied significantly based on family race, ethnicity, poverty and co-occurring child maltreatment. When offered, counseling was associated with a 54% reduction in PM recurrence, and other services were not associated with significant reductions [99].

Neglect

Child neglect is the most common form of child maltreatment, affecting 50% or more of children reported annually to Child Protective Services [12]. Dr. Ray Helfer reminded pediatricians about the significant harms caused by the 'litany of smoldering neglect' and the de-emphasis of neglect that has caused mandated reporters to have second thoughts about reporting neglect because little, if anything, could supposedly be done by overwhelmed, understaffed child protective services agencies [100]. Neglect is the omission or lack of a minimal level of care by the parents or caretakers that results in actual or potential harm to the child. Neglect is often associated with poverty, but poor families are not necessarily neglectful [13].

Many subtypes of neglect often occur concurrently, but our understanding of its outcome is often aided by identifying subtypes that can direct potential interventions. Physical neglect

is the lack of food, clothing or shelter; emotional neglect is a form of psychological maltreatment, and educational neglect refers to the lack of proper educational resources. Pediatricians are most likely to identify and treat medical care neglect and failure to thrive resulting in illness [101-103].

The morbidity and mortality associated with neglect are substantial. Although poorly identified on death certificates, child death review teams consistently identify supervisory and other forms of neglect as causing as many or more deaths as physical abuse [104]. Physical conditions caused by neglect include injuries, ingestions, inadequately treated illnesses, dental problems, malnutrition, and neurological and developmental deficits. Manifestations in neglectful families include noncompliance or non-adherence to medical recommendations, delay or failure in seeking appropriate health care, hunger, failure to thrive and unmanaged morbid obesity, poor hygiene and physical and medical conditions contributing to poor cognitive and educational achievement [101].

Poor supervision is less defined but has been broken down into broad categories, consisting of not watching the child closely enough, inadequate substitute child care, failure to protect from third parties, knowingly allowing the child to participate in harmful activities, and driving recklessly or while intoxicated [105]. A comprehensive response requires that the pediatrician address the actual or potential harms that have occurred to the child and to make appropriate referrals to a myriad of community services to address a variety of social and economic issues in the family, including reporting [102, 106].

Management of neglect first centers on properly identifying the sources contributing to neglect. For example, while malnutrition is medically addressed through proper provision of fluids, calories, and protein as dictated by commonly accepted parameters, the pediatrician must also assess the lack of appropriate food, the provision of that food to the child, and the explanation, if any, as to why it was not provided. Important screening questions that can elicit further avenues of intervention include inquiring about the family's access to food, their access to appropriate medical and dental services and medicines, substance abuse during and after pregnancy, homelessness, housing and environmental safety, depression, domestic violence, and degree of supervision [101].

Failure to thrive, otherwise coded as the lack of normal physiological development, is associated with malnutrition in infancy, and has historically been grouped into organic, non-organic (NOFTT), and mixed varieties. NOFTT is more realistically called malnutrition due to neglect. To the extent that many cases fall into the mixed category, it is important to sort out the contribution of neglect in a particular case [96, 103]. While a full discussion of the evaluation of NOFTT is beyond the scope of this chapter, it is important to emphasize that the findings on a comprehensive history and physical examination should guide management and initial laboratory testing. In the face of normal basic metabolic measurements, a careful observation of parental feeding practices and the child's intake and output is often illuminating. Height and weight need to be precisely measured over multiple visits and compared to currently accepted norms, some of which are modified by race, prematurity or other medical conditions. With acceptable weight gain under direct observation and lack of significant medical cause for malnutrition, a presumptive diagnosis of NOFTT can be made and community resources activated.

Challenges for research on child neglect remain, including the changing demographics of the nation and health disparities. Evidenced-based early interventions and treatments may be an opportunity for prevention of child neglect and improving child welfare services,

particularly in an era of health care reform. Developmental researchers across the translational pipeline are encouraged to integrate child neglect research into future studies to inform prevention, treatment and policy efforts for the improved health and well-being of children, families and communities [101].

Special Issues for Adolescents

Pediatricians should be knowledgeable about legal definitions and reporting requirements; they also should provide preventive counseling and screen adolescents for a history of assault and potential emotional effects. They should be knowledgeable about the physical findings associated with sexual assault and testing for STIs and pregnancy and be able to provide these services or refer the adolescent to other providers in the community. There has been considerable growth in treatments available for victims of child abuse and neglect, but adolescents face the additional burdens of developing risk-taking behaviors, paraphilias, and becoming perpetrators as the result of their victimization if not appropriately treated [72, 75]. Sexual abuse, in particular, appears to be a strong risk factor for subsequent perpetration, influencing adolescents and young adults to develop an orientation that is abusive to other children [107]. An adolescent's exposure to a pervasive atmosphere of violence in the home is a key risk factor of future perpetration and suggests the need to address the specific behaviors and risks in the child as well as the overall environment.

There is a proper focus on the need to confront offending behavior while taking into account the developing cognitive and social abilities of the adolescent. Sex offenders report more histories of maltreatment, both physical and sexual, compared to conduct-disordered young people in general. Thus, any treatments must take into account the adolescent's victimization as well as their developing patterns of perpetration and their environment. When young people are identified as being responsible for committing abusive acts against others, it is essential to assess and intervene in their own victimization experiences to prevent post-traumatic stress and other emotional effects. Pediatricians need to be sensitive to the psychological needs of the adolescent and provide initial psychological support after sexual assault while making referrals to appropriate mental health professionals and community resources for longer-term assessment and counseling [74].

Diagnosis

At a minimum, the clinician caring for children should be able to recognize and report potential child maltreatment, using standard methods for obtaining history, physical examination and selected laboratory and imaging tests. This clinician must also be cognizant that multiple forms of maltreatment may co-exist, understand the importance of certain risk factors, assist in choosing the appropriate location and timing of evaluation, and appropriately refer children and families to specialized medical and social services. In health care, a clinical assessment of child victimization begins with a medical encounter that usually follows information-gathering, physical assessment, testing, and clinical diagnosis followed by treatment and referral (see Table 3).

Medical diagnosis of child abuse and neglect follows commonly-accepted practices for other medical diagnosis. Pediatricians should consult current Clinical Procedural Terminology for coding for encounters and International Classification of Disease codes for diagnosis (see Table 2). While the use of such coding does not guarantee reimbursement, it highlights the standard approach to maltreatment as a concern of the health care system and allows collection of population data from hospital discharge and emergency department databases [4].

Medical history, a cornerstone of medical diagnosis, plays the most important part in the diagnosis of child abuse and neglect. It is the history, taken with the physical examination findings and imaging studies, that offers a sound basis for diagnosis and treatment recommendations for the child and family. Inquiring and recording the specific complaints and disclosures of maltreatment by the child and parent, if any, in their own words is vitally important to the ultimate protection of the child. Behavioral and emotional issues are important in this assessment. Certain non-specific behaviors, developmental delays, and history of abuse should be recorded as part of the medical history; this history aids in assessing harm and planning for appropriate treatment [66]. A simple set of screening questions for use during the general pediatric encounter has been developed but has yet to be widely implemented [108]. In cases of child victimization, the content and methods used to obtain the patient's history and the techniques used for physical examination are further specialized to concentrate on areas of increased risk and the types of suspected maltreatment [109].

The practitioner then arrives at an assessment or diagnosis, usually utilizing schema of diagnostic categories, such as the International Classification of Disease [4] or a specialized diagnostic scheme for certain types of abuse [66]. Unique to child maltreatment diagnosis is a determination of certainty. A low level of certainty is required to meet general standards of a 'reasonable cause to suspect' that maltreatment has occurred for mandated reporting.

This presumptive diagnosis leads the practitioner to request diagnostic tests for the child, such as x-rays, blood work, or microbiologic cultures, if such tests are indicated. The presumptive diagnosis also leads the practitioner at the time of the encounter to begin treatment of any acute injury, ensure protection of the child from further harm, and arrange referrals to appropriate physical or mental health specialists for further evaluation and treatment [110].

Treatment, Reporting, and Court Appearance

Pediatricians have historically had an important role in the assessment and reporting of suspected child abuse and neglect, and now have an increasingly important role with mental health professionals, community, and government services in treatment and prevention activities [111]. Medical professionals have had a long history of evaluating children and participating as team members in the interdisciplinary assessment of child maltreatment [112]. Abraham Jacobi, a forefather of modern pediatric medicine, joined the New York Society for the Prevention of Cruelty to Children in New York City in 1881 [113], and multidisciplinary hospital committees were created to address this multidimensional problem

[114]. These “child protection teams” consist of social workers, physicians, nurses, and other child advocates.

A key element is the pediatrician’s understanding of child development, how injuries occur accidentally and non-accidentally, basic concepts of good parenting, and other family violence, such as intimate partner violence and elder abuse. In a recent survey, two-thirds of pediatricians reported treating injuries from child abuse, two-thirds had treated injuries from other community violence, and one-half had treated injuries related to domestic violence [115]. Pediatricians assist the community response by collaborating with community agencies (such as child advocacy centers and social services agencies) and governmental entities (such as police and child protective services) that have the resources, responsibility, and authority to protect and improve the lives of child victims.

Nurses have been increasingly called upon to perform more than routine nursing services in the evaluation of suspected abuse. For example, “Sexual Assault Nurse Examiners” or “SANE” nurses have provided medical examinations for the collection of forensic evidence of suspected sexual and physical assault [116]. In addition, some nurses also visit homes of new parents to help reduce the risk of child maltreatment [117, 118].

Physicians have legal responsibilities to report their concerns of child abuse and neglect to appropriate state agencies in all fifty states in the US [12, 119]. Although the forms of the legislation vary from state to state, these “child protection laws” stipulate that certain professionals must report their concerns of child abuse and neglect to appropriate governmental agencies. The reporting requirements of these laws supersede the confidentiality of medical records and the patient-provider relationship. The “mandated reporters” generally include physicians, nurses, and other professionals working in hospitals, in addition to a variety of other licensed professionals who include teachers, counselors, law enforcement officers, and mental health professionals.

Specific protections are usually given for reports made “in good faith,” and certain penalties are listed for the failure to report when child maltreatment would “reasonably” have been suspected. It is important to note that child abuse reporting is one of the few instances in which health care professionals are required to contact a governmental agency in the routine course of their practice. While disease reporting has traditionally existed within public health (particularly when a contagious infection may pose a hazard to the community’s health), reporting actions that are deemed to be “crimes” have historically been less accepted by the medical community. Less clear statutory requirements have been enacted in the United States for the reporting of victimization of elderly, vulnerable adults, and domestic violence.

Physicians have historically underreported suspected maltreatment [120, 121]. Several reasons have been identified for this failure, such as fear of losing patients, distaste for the legal system and liability concerns [115, 122]. Penalties for not reporting range from fines in some states to criminal charges in others, but also include civil penalties so that the child and/or the child’s family may litigate to redress financial losses sustained because maltreatment was not reported. Recent federal legislation in the United States specifically allows child abuse reporting and exempts such state reporting laws from HIPAA requirements.

Reporting child victimization to governmental agencies begins an investigation to identify the presence or absence of “evidence” to support or “substantiate” the suspicions. Requirements vary from state to state, and no national criteria exist for determining whether to report suspected abuse or neglect. General guidelines have been suggested that include the

patient meeting the definition of being a child, the act or omission having been committed by the parent or caretaker, the acts or omissions lead to harm or the risk of harm, or the features of an episode fulfill other criteria for abuse or neglect in the medical record [123].

Multiple missed medical appointments, unreasonable delay in seeking medical treatment, abandonment, illnesses that could be prevented by routine medical care and inadequate care have been identified as potential minimal criteria for a neglect report [106]. Fractures, soft tissue injuries of normally protected body parts, inflicted traumatic brain injury and witnessed physical injury caused by the caretaker indicate cause to suspect physical abuse. Statements made by the child or parent disclosing potential sexual contact with a caretaker or contrary to state law, certain anogenital injuries, and sexually-transmitted infection are generally a basis for diagnosing suspected sexual abuse.

The ultimate and perhaps most important action to protect a child from further victimization may involve going to court. Physicians and other health care providers are routinely called to provide information regarding their medical evaluation of children, particularly with regard to statements made by the child, the medical history obtained, and any findings of physical examination. While giving testimony in court, physicians and other health care professionals are often asked their opinion, “within a reasonable degree of medical certainty,” concerning the diagnosis of child abuse and neglect or victimization. Significant differences exist between standards for medical diagnosis and those for civil or criminal adjudication. Medical diagnosis is defined as “the act of distinguishing one disease from another” or “the determination of the nature of a case of disease” [124].

A constellation of the patient's history, physical examination, and laboratory findings may result in multiple diagnoses, which may lead the practitioner to a treatment plan without 100 percent or even probable certainty after diagnosis. These criteria differ significantly from legal standards, by which a level of certainty must be carefully crafted to include “credible” evidence, a “preponderance” of evidence, “clear and convincing” evidence, or evidence “beyond a reasonable doubt.” Differences in interpretation of certainty lead to difficulty in communication between legal and medical practitioners.

Court appearance and testimony, while often inconvenient, is vital to provide the evidence and opinion for the state to take action to protect children. Recently, testimony provided by physicians has been considered part of medical practice, and providing “irresponsible testimony” may have negative repercussions for a physician's practice [125]. Despite the legal system's need for health care professionals to provide evidence in maltreatment cases, it is relatively uncommon for health care professionals to be required to attend court hearings, even if they specialize in caring for maltreated children [126].

Training and Prevention

Health care professionals have a unique role in the training of child welfare professionals, law enforcement, child protection services workers, and all professionals who manage the day-to-day care of children. To fulfill their mandatory roles in reporting child abuse and neglect, teachers, child development specialists, mental health workers and others who provide daycare, education, and counseling services need to understand the medical manifestations of child victimization. They also need to identify the physical as well as

emotional signs of abuse and neglect so that they can provide the optimal treatment for children in their care. Professionals from a variety of health care disciplines provide specialized training at a national level for medical and nonmedical providers through multidisciplinary organizations such as the American Professional Society on the Abuse of Children (www.APSAC.org) or medical organizations such as the American Academy of Pediatrics (www.AAP.org). Additionally, various child protective service agencies and university programs render services to nonmedical providers and offer information about medical issues related to child victimization.

The prevention of child abuse and neglect ultimately rests with the family, but pediatricians and the community can still play important roles preventing abuse from occurring [127]. The economic burden, estimated at over \$80 billion annually, calls for prevention [128]. Local county councils for the prevention of child abuse and neglect sponsor programs, social service agencies provide childcare or foster care, and state departments of social services have the legal authority to investigate suspected child maltreatment. Community approaches, such as home visitation, parenting classes, certain cognitive behavioral therapies for children, and parent-child interaction therapy, have been shown to be effective in changing parents' behavior, and reducing social isolation and stress, particularly in families at risk for maltreatment [129, 130].

Preventing child abuse and neglect spares children physical and psychological pain and improves their long-term health. Dubowitz [131] noted that prevention "is intuitively and morally preferable to intervening after the fact." There is increasing evidence supporting the effectiveness of several universal and selective prevention interventions the effectiveness of most programs is still not known [132, 133]. Robert Caldwell [134] estimated that the costs of a home visitor program in Michigan would be 3.5% of the \$823 million estimated cost of child abuse, and small reductions in the rate of child maltreatment were thought to make prevention cost effective. However, home-visiting programs are not uniformly effective, parenting programs appear to improve parenting but not necessarily reduce child maltreatment, and some family programs are successful in reducing physical abuse but not neglect.

Ray Helfer [135] noted the "window of opportunity" that is present in the perinatal period to enhance parent-child interactions and prevent physical abuse. Several program models have shown promise based upon key periods, including pre-pregnancy planning, early conception, late pregnancy, pre-labor and labor, immediately following delivery, and at home with the child. Opportunities for prevention include teaching parents and caregivers to cope with infant crying and how to provide a safe sleep environment for their infant. A meta-analysis of several early childhood interventions concluded that the evidence for their preventing child maltreatment is weak, but longer-term studies may show reductions in child maltreatment similar to other programs such as home visiting, when longer follow-up can be achieved [136].

Several parent education programs have been evaluated for their association with decreases in physical abuse and neglect. Family Connections, a multifaceted, home visiting community-based child neglect prevention program, showed "cost effective" improvements in risk and protective factors and behavioral outcomes [137]. To address a specific form of physical abuse, Mark Dias and colleagues devised a hospital-based parent education program implemented immediately after birth that has been shown to decrease the incidence of shaken baby syndrome [138, 139]. Barr and colleagues [140] have devised a program of parent

education in late pregnancy, delivery, and early infancy to change maternal knowledge and behaviors relevant to infant shaking. Using a randomized controlled trial, they were able to demonstrate how “The Period of Purple Crying” was able to increase maternal knowledge scores, knowledge about the dangers of shaking, and sharing that information with other caretakers.

A randomized trial of the “SEEK” program in an inner-city clinic with high-risk families was able to show lower rates of maltreatment, CPS reports, harsh punishment, and improved health services after an intervention of pediatric resident education [141]. Several barriers (time, training, culture, sensitive issues) to widespread implementation could be addressed by identifying potential strategies, such as the use of handouts and local news stories, to begin a dialogue during routine pediatric visits [142].

With the generosity of the Doris Duke Charitable Foundation, the American Academy of Pediatrics launched a program called Practicing Safety: Connected Kids aimed at decreasing child abuse and neglect by enhancing anticipatory guidance and increasing screening provided by pediatric practices to children ages 0-3y, focusing on helping parents and families to raise resilient children [143]. Anticipatory guidance has significant potential for decreasing violence, and each counseling topic discusses the child’s development, the parent’s feelings and reactions in response to the child’s development and behavior, and specific practical suggestions on how to encourage healthy social, emotional, and physical growth in an environment of support and open communication. Practices screened for maternal depression and improved their discussion of coping with crying, maternal bonding, toilet training and discipline [143].

Sexual assault and rape prevention strategies begin with the child and family being able to identify and avoid high-risk situations and immediately reporting potential sexual contact. Pediatricians and others can provide screening for victims of domestic violence during routine medical care and can provide guidance and strategies to prevent or minimize abuse (such as avoiding late night use of alcohol or drugs or seeking immediate medical care after assault). Finkelhor (2007) has concluded that the available evidence supports providing high quality child-focused prevention education programs because children are able to acquire the concepts, the programs promote disclosure, there are lower rates of victimization, and children have less self-blame. Parent education and media campaigns have also demonstrated some positive effects [144].

A review confirmed the effectiveness of school-based sexual abuse prevention [145]. Pediatricians have the ability to explain child development and the special health needs of children, particularly those with chronic medical conditions, to the community and to provide the scientific background and structure for the implementation and evaluation of community programs. Prenatal clinics and other services for high-risk adolescents need to provide primary care interventions to prevent future maltreatment.

CONCLUSION

Pediatricians and other clinicians play a vital role in the assessment, identification, care, and treatment of victims of child abuse and neglect. Physicians, nurses, and other health professionals have developed increasingly sophisticated techniques for diagnosing and

documenting physical abuse, head trauma, fractures, anogenital trauma, and sexually transmitted infections. They have integrated such diagnostic findings with referral to specialized services. They are important members of the crew of the 'lifeboat' needed to save children in the sometimes turbulent 'ocean of life' [146].

While C. Henry Kempe first taught us about the battered child in 1962 and Ray E. Helfer showed the importance of understanding a child's perspective in 1984, we still have a long way to go in solving the problems of child neglect and victimization in our communities. Many segments of our population do not understand the impact of higher rates of poverty, unique health concerns, and other special circumstances of children. Our response to the needs of abused and neglected children requires earnest dedication by all medical professionals in clinical care, training, research, and advocacy to identify, treat, and prevent the devastating physical and emotional consequences of child abuse and maltreatment.

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Chapter 513

PUBLIC HEALTH ASPECTS OF YOUTH SEXUAL OFFENDERS

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ABSTRACT

Children and adolescents under the age of 18 years account for one-fifth of arrests for all sexual offenses (excluding prostitution). These young perpetrators can be found among all socio-economic groups and live in all regions of the United States. They often come to the attention of primary care clinicians when their parents bring them to the office for protection from the authorities and help with addressing their maladaptive behavior. Clinician-collected information may get used as a part of criminal investigations or to facilitate initial evaluation and coordination of services. Frequently, parents will bring their child or adolescent in for an office visit once the parents have caught them engaging in some form of sexual activity. The parent's concern is typically whether or not this is normal or abnormal behavior. Physicians who are aware of adolescent sexual offending can increase their ability to detect adolescents who have aberrant or deviant sexual behavior patterns allowing for *early* referral and comprehensive intervention.

Keywords: childhood, adolescence, behavior, crime, sexual offense, sexual offenders

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INTRODUCTION

Most of the sexual abuse literature focuses on adult perpetrators or child/teen victims. In the past five years, only a few new articles have been published discussing adolescent sexual offenders [1-4]. Most of those articles consisted of meta-analyses of previous studies. The office of Juvenile Justice Delinquency and Prevention, National Center on Sexual Behavior of Youth (NCSBY) has published statistics (2009-2011) on youth sexual offenders [1-4]. Otherwise there has not more current data since the original article by the authors of this chapter who have published on adolescent sexual offending [5-7]. There is still a paucity of data available in the literature on adolescent sexual offenders who are involved in sexual abuse of younger children. Primary care clinicians must be prepared to act in a manner that does not contaminate forensic evidence nor alter the testimony of either the perpetrator or victims in a legal trial. Clinicians may encounter these youth in their practices under several circumstances: adolescent revelation, parental report, or at the request of legal representatives.

What we know about sexual offenders, in general, is based only on those individuals who are caught or prosecuted. Even youth who are caught, arrested, and convicted frequently receive minimal punishments (i.e., probation, community service). The costs to society for the crimes of juvenile sex offenders are considerable, not only for those inflicted on crime victims and society as a whole, but also for those imposed on offenders and their families. The rehabilitation focus of interventions for those youth referred to treatment programs is considered to be controversial because the interventions are not evidenced-based for the adolescent sexual offender population. Most adjudicated adolescents live and are treated in community settings and often reoffend. Unfortunately, there remains little empirical evidence of the long-term effects of different interventions with adolescent sexual offenders [5-7].

DEFINITION

Adolescent sex offenders are defined as youth between the ages of 13 and 17 years who commit illegal sexual behavior as defined by the sex crimes statutes of the legal jurisdictions in which they reside. Legal meanings of sexual offenses vary from state to state [10]. However, statutes typically define sexual offenses in terms of: a) penetration offenses, which include penetration of virtually any body orifice for a sexual purpose, and are felonies; and b) crimes not involving physical contact (e.g., voyeurism, exhibitionism, obscene phone calls). Such offenses progress from privacy issues at the misdemeanor level to the felony level, depending on the specific circumstances of each case. The addition of physical force or coercion will almost always result in a felony life offense. Most adolescents are not sexual predators, nor do they meet the accepted criteria for pedophilia [9].

EPIDEMIOLOGY

The incidence of sexual victimization of children by adolescents has become a serious problem in our society. Juveniles account for more than one-third (35.6 percent) of those

known; less than 1 percent of all arrests of youth 17 years of age and younger were for sex offenses [3]. Each year, there are approximately 2,200 arrests of juveniles for forcible rape and this includes an additional estimated 9,200 arrests of juveniles for other types of sex offenses. The percentages of adolescents arrested for sexual offending in 2010 were for youth in the following age groups: younger than 9 years (5%); younger than 12 years (16%); between ages 12 and 14 (~13%), and between ages 15 and 17 (46%) [10-12]. The vast majority (93 percent) were male. The number of arrests of juveniles in 2010 was 21% fewer than the number of arrests in 2001.

CLINICAL FEATURES

Adolescents do not typically commit sex offenses against adults, although the risk of offending against adults increases slightly after an adolescent reaches age 16. Sexual offenses against other children are more likely to offend in groups, at school, have more male victims, and have younger victims. Sexual offenses against young children are typically committed by boys between the ages of 12 to 15 years of age. In 2011, 53% youth arrested for sexual offences involved youth younger than 16 and 28% involved females [14-16]. Most females adolescents sex offenders were mainly younger than their male peers, had more multiple-victim and multiple-perpetrator episodes, and their victims were primarily family members or males.

Researchers generally agree that there are *multiple* factors (psychological, biological and sociological) that interact in complex and poorly understood ways; these factors include the adolescent's temperament, cognitive abilities, impulse control, family variables, and socioeconomic factors as well as access to potential victims and opportunities to offend. A number of factors have been found to be associated with a higher prevalence of adolescent sexual offending and these include a history of prior physical or sexual abuse, impaired family functioning, alcohol and substance abuse, exposure to erotica, neurobiological factors, and psychiatric co-morbidity.

However, we do not know specific and direct causation. Adolescent sex offenders are considered to be more responsive to treatment than adult sex offenders and do not appear to continue re-offending into adulthood, especially when provided with appropriate treatment. Across a number of treatment research studies, the overall sexual recidivism rate for adolescent sex offenders who receive treatment is low in most US settings as compared to adults. Adolescents who offend against young children tend to have slightly lower sexual recidivism rates than adolescents who sexually offend against other adolescents. Adolescent sex offenders' rates for sexual re-offenses (5-14%) are substantially less than their rates of recidivism for other delinquent behavior (8-58%) [12].

Presentation in the Office

The serious psychosocial and legal implications for the offender and his or her family often prevent parents from seeking help. More often the offender will be brought to the physician by an appropriate agency in the course of a child abuse investigation for

a) assistance with medical and psychological evaluation, b) to facilitate further expert evaluation, c) specialized referral, or d) to co-ordinate on-going care.

Sometimes parents may bring their teen in with concerns about his or her social development and provide indirect or non-specific indicators of an adolescent being involved in the sexual abuse of younger children. The parent may express concern about their teen's sexual activities with a younger child (i.e., sibling, other relative, or acquaintance); they may also ask if such activities are "normal." Also, the parents of victims may report fear of the offender or incidences of sex play between their young child with an older teen to the offender's parents; then the offender's parents presents that information to the physician. The goal of the parent is for the physician to tell them how to help their offending adolescent.

Most offenses are committed by a small number of adolescents who repeatedly reoffend and account for the molestation and sexual abuse of half of the male victims and one quarter of the female victims. Juveniles who have committed sex offenses are males who represent a heterogeneous mix, commit multiple offenses, usually have more than one victim, and usually offend against females; if they violate very young children, then their victims are usually male. Unfortunately, they may have several types of victims. The juvenile offenders differ according to victim and offense characteristics and a wide range of other variables, including types of offending behaviors, histories of child maltreatment, sexual knowledge and experiences, academic and cognitive functioning, and mental health issues. They usually have not been victims of childhood sexual abuse. Also, very little data are available on female sexual offenders [10-16].

Adolescent sex offenders rarely have previous convictions for sexual assault, but are likely to have committed nonsexual offenses. Those who have been physically abused were 7.6 times more likely to rape or sodomize other children when compared to adolescents who were sexually abused or neglected [5-7]. One in two adult sex offenders began their sexually abusive behavior as a juvenile. Adolescents who commit incest offenses do so in the victim's home and often when providing child care services. Adolescent rapists, on the other hand, tend to victimize strangers. As the age of the victim increases, sexual intercourse becomes a part of the offense.

The families of adolescent sexual offenders tend to be two parent families, have at least one sibling living with them, and more closely resemble those of youth with severe emotional or behavioral problems. Their parents often deny sexual tensions and exhibit a paucity of sexual knowledge or education; also, one quarter of their parents have known sexual pathology. Adolescent sexual offenders who had committed sexual homicides experienced exaggerated personal and family dysfunction [5-7].

DIAGNOSIS

A significant percentage of reported criminal sexual acts against children are various types of paraphilias. The *paraphilias* represent a diagnostic category in the 2013 *Diagnostic and statistical manual of mental disorders, Fifth edition (DSM-V)* and consists of the following subcategories: exhibitionism, fetishism, frotteurism, sexual masochism, sexual sadism, transvestic fetishism, voyeurism, and pedophilia [8]. The victimization is by perpetrators who have intense sexually arousing urges, fantasies, or behaviors; also, a number

of other issues are involved in adult perpetrators, though this discussion involves children and adolescents. The reader is referred to the *DSM-V* for further details in this regard. A psychiatric diagnosis is made if the behaviors have occurred for at least six months and caused distress or impairment that impedes social, occupational, or other important areas of functioning [8]. Pedophilia is the diagnosis of our focus and involves sexual activity with a prepubescent child or children (generally ages 13 years or younger). Perpetrators should be age 18 years or older and be at least 5 years older than their victims.

Sexual Exploitation Versus Normal Sexual Play

When a parent presents with a teen who was accused or caught engaging in sexual play with a younger child or a developmentally younger child, the physician may be asked to tell the parent if this is normal or not. The physician who understands the differences between sexual *exploration* and *exploitation* will be better prepared to make that distinction when faced with a report of adolescent sexual behavior. “Normal” or *developmentally sexual curiosity* and exploration are a normal part of the developmental play and should meet the criteria listed [5-7, 16]:

- 1) The two involved individuals who are age and developmental peers.
- 2) Children and pre-pubertal adolescents may engage in exploratory behaviors.
 - The play or exploration usually involves only mutual genital display, touching, and fondling.
 - Curiosity about the differences and similarities in anatomy is normal.
 - Exploratory sexual play is not coercive.
 - Mutual consent is typical of exploratory behaviors.
 - Does not include multiple participants.
 - Observers or additional participants are not acceptable.
 - Manifestations of anger, fear, sadness, or other strongly negative responses are not present.

Exploitation involves the absence of the factors listed above and the inclusion of the following:

- If one of the individuals is cognitively impaired, then a peer relationship does not exist.
- Attempted intercourse is atypical among preschoolers and is rare in the young school-aged child (6-9 years).
- Abusive behavior often involves elements of pressure, misrepresentation, force, threat, secrecy, or other forms of coercion. Although some of the threat or coercion is obvious and violent, the evaluator must take care to recognize subtle emotional pressure or the use of implied authority by an older child or adolescent in some cases.
- If the sexual contact has been arranged for the pleasure of another older individual, it is exploitative. One of the participants manifests feelings anger, fear, sadness, or other strongly negative responses.

- The victim views the experience in negative terms; however, some abused children will appear to have a neutral or positive emotional response to this abuse.

Regardless of whether or not the sexual play is normal or abnormal, parents and adult caregivers need to be vigilant and give children other healthy outlets. Parents should be encouraged to always keep young children under surveillance, especially when older individuals are around.

If the “sex play” is determined to be experimental or exploratory, the physician should discuss normal childhood and adolescent sexual behavior with parents and outline measures to minimize inappropriate sexual stimulation in the home. Parents should be advised to provide closer supervision of the adolescent. Older adolescents can be instructed to stay away from compromising situations with younger children [16].

Co-Morbid Disorders

Adolescent sexual offender can have concurrent diagnoses of psychopathology. They rarely exhibit behavior problems; they are more likely to be shy, and more comfortable with younger children. The most common psychiatric diagnoses, respectively, are conduct disorder, substance abuse disorders, adjustment disorders, attention-deficit/hyperactivity disorder, specific phobia, and mood disorder. They frequently engage in distorted thinking to make their offenses more socially acceptable to themselves and others; much like other delinquents, their distorted thinking allows them to excuse their offenses. Male offenders are more often diagnosed with paraphilias and antisocial behavior. Female offenders are more likely to be diagnosed with mood disorders and engage in self-mutilation [8, 11, 13, 14].

INTERVENTION

In most states adolescent sexual offenders can be adjudicated for criminal behavior as young as 6 years old. However, most states set 10 years as the lowest age of criminal responsibility. Victim consent is not always considered important. Once there is sufficient evidence to identify an offender, a decision regarding prosecution is often made at the juvenile court level. If the child or adolescent goes to trial, the setting in the juvenile justice system is usually less formal and hearings are often conducted in private without the use of a jury. Juveniles in this system are more likely to receive efforts at rehabilitation and less likely to be held fully accountable for their actions, than if they were adjudicated in the adult courts. However, in the case of rape, sodomy or sexual homicide, most states have moved to address adolescent offending in the adult criminal justice system, which can impose harsher punishments.

Local statutes usually govern physician-patient privileges (i.e., the right to respect the confidentiality of all communications). Thus, the development of such privileges in each state is subject to *local* interpretation and state-by-state case law developments. Physicians should explain, at the outset, to all adolescents and their families the limits of confidentiality. If the

adolescent's behavior must be reported to the authorities or potential victims warned, the physician should inform the patient and the family.

Professionals, who deal with children, have an *enforceable* mandate to report *suspected* child abuse. All fifty states have "mandated reporting" laws which require professionals to report "reasonable suspicions" that abuse or neglect has occurred. Professional obligations pertaining to confidentiality may be seriously challenged by the requirements of the law and the local community, particularly when it involves sexual conduct. It is helpful to explain to the parents and the patient that reporting any crime changes the status of the act from private to criminal; however, this is required as part of mandatory reporting laws.

No clinician should consider serving as a witness or expert witness in sexual abuse cases involving adolescent offenders without *specific* training in this area. A more definitive treatment may not be within the purview of all clinicians and generally, the adolescent offender will be referred to professionals and programs specializing in such treatment [3, 14, 18].

RECIDIVISM

The most beneficial treatment program identified in the treatment literature is multi-systemic therapy (MST) [19]. Outcome studies contend that MST has its best effects on youth who engage in antisocial and deviant sexual behaviors. This treatment showed that interventions increased caregiver follow-through on discipline practices as well as decreased caregiver disapproval of their child's behavior. When compared to recidivism rates between adults and juvenile sex offenders, the juvenile sex offenders appeared to have lower recidivism rates and perform better in treatment than (5-14%). Those adolescents who offend against young children tend to have slightly lower sexual recidivism rates than adolescents who sexually offend against other teens. Adolescent sex offenders' rates for sexual re-offenses are substantially less than their rates of recidivism for other delinquent behavior (8-58%). Research has shown that a young person who commits a sex offense is unlikely to commit another one [1-4, 11, 14].

In the event that the physician determines that sexual abuse has occurred, he or she should follow the guidelines from the governing child protective services organizations and medical oversight organizations; also, medical examination and documentation should be performed as required by state child abuse laws. The family should be referred to the appropriate agency for further evaluation. If the adolescent has access to other children, especially very young ones, the physician should assess the level of risk posed to those children.

When it is determined that the child or adolescent is at high risk of sexually offending, then the physician should inform the family and the appropriate persons. Furthermore, the family should be advised to:

- **STOP** all baby-sitting and childcare activities under all circumstances!
- Parents must provide enhanced/additional supervision of their offender.

- The youth offender should not have access to young children or potential victims without direct supervision by a responsible adult who is aware of the problem---especially in school, churches or other related activities.
- The child or adolescent offender should not have access to, possession of or use of sexually explicit, "x-rated," media or pornographic materials.

The physician can encourage parents/care-providers to allow their youth sexual offenders to engage in most ordinary daily activities, such as going to school, church, stores, or restaurants with family, or involvement in age-appropriate and appropriately supervised peer activities. However, caution that one of the parents'/care-givers' major responsibilities is to limit the child/adolescent offender's opportunity to re-offend.

CONCLUSION

Children and adolescents under the age of 18 years account for one-fifth of arrests for all sexual offenses (excluding prostitution). They commit multiple offenses, usually have more than one victim, and may not limit their offenses to one type of victim. These young perpetrators can be found among all socio-economic groups and live in all regions of the United States. They often come to the attention of primary care clinicians when their parents bring them to the office for protection from the authorities and help with addressing their maladaptive behavior. Because most offenders are not detected, and those who are discovered are not often adjudicated, the physician can help to prevent and minimize the occurrence of sexual offending by educating parents about the importance of close supervision and seeking appropriate professional help for deviant sexual behavior in children and adolescents.

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Chapter 514

INTESTINAL/LUNG/LIVER FLUKES: A PUBLIC HEALTH CONCERN

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ABSTRACT

Current estimates indicate that 50 million people are infected with food-borne trematodes. This is a significant public health problem, but still a neglected tropical disease, because the burden of disease is in rural areas, where health care is limited. Traditional ingestion of raw or poorly cooked food contaminated by unrestrained defecation maintains the cycle of disease, and school-age children bear the predominant burden. Clinical patterns of infection, current means of diagnosis, treatment and treatment failure are reviewed in sections on intestinal flukes, liver flukes and lung flukes. New therapeutic approaches are emphasized.

Keywords: public health, tropics, flukes, food-born trematodes

INTRODUCTION

Of the 50 million people infected, most are in China, Japan, Korea and parts of Southeast Asia including Indonesia, Vietnam, Thailand, Laos and Myanmar [1]. Paramphistomatidae occurs in Africa, Echinostomatidae is endemic in India, and Hereophyidae has been reported in Brazil. International travel has made this a world-wide problem. People contract these infections by eating raw or undercooked fresh-water fish or water plants such as watercress with encysted metacercaria. Infestation of human trematodes is related to their migration.

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Intestinal, pulmonary and liver flukes present distinct clinical and diagnostic problems to physicians and health care workers who care for patients with neglected tropical diseases.

SECTION 1: INTESTINAL FLUKES

More than 70 species of intestinal flukes have been reported in humans [1, 2]. The most common are *Fasciolopsis*, *Echinostoma*, *Gymnophallidae* and *Heterophye* species. The cysts of *Fasciolopsis* are ingested when eating aquatic plants such as water hyacinth, water chestnuts, water bamboo and water lotuses, many of which are preferred raw. *Echinostoma* is encysted in fish, mollusks and amphibians which are eaten raw or incompletely cooked. Freshwater fish, carp and mullet, contain *Heterophye* cysts. *Gymnophallidae* contaminate both mollusks and vegetation. The ingested cysts, released in the duodenum, attach to the mucosa and mature into adult worms over a period of 3 months.

Epidemiology

Fasciolopsiasis is endemic to Southeast Asia and the Orient. The disease has the highest prevalence in school-age children [3]. Reported prevalence is 57% in mainland China, 25% in Taiwan, 50% in Bangladesh, 60% in India and 10% in Thailand. Control programs with effective medications have not achieved success due to continued traditions of eating raw aquatic plants and contact with domestic pigs. Change in traditional practices is slow. Although simply drying plant products kills the parasite, this practice is not acceptable in many local customs, and cooking is thought to destroy the flavor.

Recognition of the disease in Africa and reports of the disease in Brazil, Russia, Spain, Turkey and the Philippines have raised awareness of this neglected disease. The economic impact of the disease is difficult to assess but clearly affects rural communities depending on subsistence agriculture.

Clinical

Food-borne trematodes predominantly infect children in endemic areas. Many are asymptomatic but heavy infections produce severe diarrhea, abdominal pain, low-grade fever and fatigue. High inoculums cause malabsorption due to villous edema and atrophy. When cysts attach to the mucosa in duodenum and jejunum they cause inflammation, ulceration and micro-abscesses. Eosinophilia occurs as an immunologic response to trematode protein and toxins and is directly related to worm load [4]. Children tend to become re-infected after treatment, amplifying the clinical problems and confusing the understanding of which treatments are effective, and when and if eradication occurs with treatment. Flukes mature in 3 months and have an average life span of 1 year in humans [2].

Although a few flukes are asymptomatic, heavy worm burdens, considered > 500 worms cause intermittent diarrhea, constipation, anorexia, nausea and vomiting [5]. Diagnosis depends on the detection of *Fasciolopsis* eggs in stool samples. Morbidity in endemic areas is

related to anemia from chronic blood loss, malnutrition due to malabsorption from villous damage and toxic worm metabolites which are thought to cause a variety of symptoms and immunologic reactions that result in facial and generalized edema [6]. Mortality is related to malnutrition, intestinal obstruction and electrolyte abnormalities.

The *Heterophyids* infect humans eating fish or shrimp infected with viable metacercariae. Infected fish-eating mammals and birds contain the egg-producing *heterophyids*. Feces from these creatures contaminate the water and release eggs. Ingested by snails cercariae are released from the snails and then penetrate fish and shrimp in which they encyst. An Egyptian study showed fish to have the greatest intensity of infestation during the summer months [7].

Human prevalence studies in Korea showed the highest prevalence in young and middle aged adults [4]. A national survey to determine the prevalence among primary school children in Laos was unable to differentiate *Opisthorchis viverrini* (a liver fluke) from intestinal flukes [29], so most studies just report stool collection samples as ‘*Opisthorchis*-like’ eggs. Verification of disease burden by purging and stool analysis is therefore complicated by infection with multiple species that cannot be differentiated. A study of cysts in fish dishes in Vietnam restaurants showed a greater prevalence in freshwater than in brackish water fish [8]. Prevalence in Vietnam is as high as 70% depending on the region [7]. *H. tauchi* infection, though rare, is different from other flukes because it enters the mesenteric lymphatics and migrates to the heart causing myocarditis, chronic congestive heart failure, and death.

Gymnophalloides seoi contaminates raw oysters. Infestation tends to be restricted to focal geographic areas. One village in Korea had a 70% infestation rate [9], dramatically higher than the neighboring populations. The usual symptoms are indigestion, constipation and diarrhea. Microscopic examination of gastric mucosa in animal models demonstrates stimulated goblet cell production. In humans, infestation has been associated with diabetes mellitus because it causes acute pancreatitis. One study noted subsequent insulin deficiency in 46% of 37 infected patients. A case study described patients with polyuria and polydipsia but without increased blood glucose or glucosuria [10], but the cause was not elucidated. Infections with *Gymnophalloides seoi* are associated with polyuria and polydipsia and are probably toxin related [11].

Diagnostics

There are three approaches to diagnosing fishborne zoonotic trematodes: detection of parasite eggs in stool, immunodiagnosics (indirect diagnosis) and molecular biologic testing.

Detection of eggs is the most common approach, especially in epidemiological surveys. Methods include fecal flotation in salt and sugar solutions, the Kato-Katz technique and the formalin-ethyl-acetate technique [1]. Trematode species identification based on egg morphology is challenging because *F. buski*, *F. hepatica* and echinostomes all appear similar. *Heterophyids* egg-laying capacity is low, 2-28 eggs per worm (*Ascaris* by contrast produce hundreds of thousands of eggs per day) and the eggs resemble *Clonorchis* spp. A definite diagnosis can be obtained by examination of adult worms after chemotherapy expulsion.

Several tests to detect specific antibodies are available but many have low specificity and cross-reactivity. Enzyme-linked immune-absorbent assays have been developed, but consensus on their use has not been established. Recently, polymerase chain reaction [PCR]

methods have been developed to identify trematode eggs [12]. They will likely prove to be an effective research tools, but use in endemic areas is likely to be impractical in the near future. While metabolic profiling is a new approach to research, its application with intestinal trematodes is presently limited.

Treatment

A single 15mg/kg dose of Praziquantel is generally adequate for children, but adults should receive 25 mg/kg [3]. Various authors have reported that a single dose ranging from 10–40 mg/kg is curative and safe. Praziquantel is not approved for children under the age of four, but its use may be therapeutically necessary. Ivermectin is an alternative choice for children under 4 who weigh greater than 15 kg.

It has been the standard to delay treatment of pregnant women with Praziquantel until after delivery and to avoid breast feeding for 72 hours after administration of Praziquantel. The exception has been if treatment is required for saving the pregnant woman's life. However there are now more than a dozen studies such as Webb et al. in which Praziquantel has been given to pregnant and breast-feeding women [13]. There are no studies that show harm to the mother or fetus, nor are there any animal studies which show fetal harm. In fact, WHO published a bulletin 2002 which reviewed the clinical and veterinarian studies and concluded that the drug was safe despite the manufacturer's cautious recommendations [14].

Prevention

The key to prevention is education and avoidance of raw, water-derived food (for preventing *F. Buski*), raw fish (for preventing intestinal trematodes) and raw oysters from endemic contaminated locations. This has been difficult because of culinary traditions in endemic areas. Other prevention methods include treatment of infected people and livestock and increased sanitation methods to prevent infected humans and pigs from defecating near water sources. Ironically, industrialization has polluted streams and rivers, destroying the environment for aquatic animals and breaking the ecosystem life cycle which reduced the incidence and prevalence of disease in previously endemic areas [15].

Public programs address the role of animal carriers including dogs, cats, pigs and wildlife. In Vietnam, studies of fish-borne trematodes showed prevalence in cats, dogs and pigs of 48.6%, 70.2%, 35-56.9% and 7.7-14.4% respectively [16]. While pigs are generally confined and their prevalence rates are lower, their total fecal contribution is huge which makes pigs significant contributors to endemic regions. Education is important to avoid feeding domestic animals contaminated feed such as raw fish and oysters. However this is impractical for free-roaming animal reservoirs such as cats and dogs. In the commercial fish farms, practices that prevent introduction of infection and quality control are of the utmost importance.

SECTION 2: LIVER FLUKES

Opisthorciasis and clonorchiasis are primarily diseases of Southeast Asia, ranging from China to Indonesia and from Thailand to the Philippines. *Clonorchins sinensis* eggs have been found in a corpse buried in the 4th century BCE [17]. These trematodes, of which 18 varieties are known, penetrate the skin and encyst fresh water fish. Consumption of raw or undercooked fish release the harbored metacercariae to migrate in the human host.

Clinical

Liver flukes migrate through the ampulla of Vater into the common bile duct and from there infest the intrahepatic bile ducts where they cause hepatomegaly, cholangitis and periportal fibrosis. This infestation precipitates gallstones and causes cholecystitis. Ultrasonography often demonstrates gallbladder sludge and poor contractile function. In one study, intrahepatic duct dilation was noted in 68% of egg positive patients with sludge reported in 20.8%. Higher grade dilation was found to correlate with higher egg counts. Periductal fibrosis was also a common finding [18]. Treatment with Praziquantel improves biliary function and decreases intrahepatic duct dilation.

More important than the acute manifestations is the predisposition these parasites cause to bile duct cancer and cholangiocarcinoma. Thailand has the highest incidence of liver cancer in the world. Recent research has noted an exacerbation of hepatic carcinoma by N-nitrosamine. Noteworthy is the fact that N-nitrosamine levels are highest in tobacco, but it is also found in beer, fish and pickles. Tobacco product marketing in Southeast Asia historically correlates with a dramatic increase in hepatic carcinoma. Although this may be due to better case identification, cigarette smoking may be exacerbating the parasitic predisposition to hepatic cancer.

Treatment

A single 40mg/kg oral dose of Praziquantel is effective, but some authors note three divided doses of 25mg/kg as a more effective dose for treating clonorchiasis. This higher dose is associated with dizziness, vomiting and abdominal pain, but these side-effects tend to be transient. Other treatment options have been investigated and tribendimidine seems to be as effective as Praziquantel for *Opisthorchis* [19].

Prevention

If culture continues to mandate eating raw fish, then improved sanitation is the only prevention and control measure available. Molluscicides are not proven effective, are expensive and associated with an increase incidence in community disease when the snails inevitably return. Prevention should be focused on community education, especially school-aged children, for long-term control.

SECTION 3: LUNG FLUKES

Paragonimus species, lung flukes, are contracted from eating raw freshwater crabs and other crustaceans [17]. Although known to be a problem in Southeast Asia recent literature has demonstrated significant prevalence in South America [20, 21] and Africa [22]. There are about 15 species known to infect humans world-wide.

Clinical

Infection occurs when the parasite migrates into the human body and releases toxins and other proteins during migration. Pulmonary infection with cough is often non-productive, but when it is productive, gelatinous, brown sputum from pulmonary hemorrhage is characteristic. Hemorrhage is associated with leukocyte infiltrate and necrosis of the lung parenchyma. The tissue reaction leads to fibrotic encapsulation, but opening in the capsule releases fluke eggs. Hemoptysis with exertion is often reported.

The prominent bronchospasm is often misinterpreted as asthma. Prominent eosinophilia, 20-25%, is common. Persistent pleural effusions, unresponsive to parasitic treatment are related to chronic granuloma reaction. It is not uncommon that lung fluke infestation is diagnosed as tuberculosis, especially in communities where both diseases are endemic. Pneumothorax related to the inflammatory reaction and secondary bacterial infection in the infarcted lung has been reported. The immune response eventually modulates and calcification surrounds the cysts.

Extra-Pulmonary Syndromes

Cerebral migration causes eosinophilic meningitis with headache and seizures. This extra-pulmonary syndrome seems to have a predilection for male children who are under ten years of age. Spinal cord migration causes spastic paraplegia. The neurologic manifestations are usually accompanied by pulmonary symptoms. Neurologic complications such as mass effect and intracranial hemorrhage have required surgical intervention [23].

Diagnosis

The differential diagnosis of lung flukes includes tuberculosis as well as common causes of pneumonia. Clinicians need to be aware of the diagnosis in endemic areas, especially when there is eosinophilia. A careful history of exposure in travelers or patients who have migrated from endemic areas is essential since the parasite can persist for decades. Smear examination of expectorated sputum, gastric washings, pleural fluid, feces reveal eggs in infected individuals, but tissue biopsy is sometimes required. Immunodiagnostic tests are highly sensitive [24]. Complement fixation and enzyme-linked immune-osorbent assay [ELISA] tests are able to diagnose chronic infection and can monitor treatment since they decline with cure.

Treatment

Praziquantel appears to be the treatment of choice, but treatment with bithionol is still reported to be effective [25]. Treatment causes an inflammatory response, so skin lesions can flair, cerebral edema can result from neurologic infestation and pulmonary symptoms may worsen.

Prevention

Discouraging consumption of raw crustaceans is still the best prevention, but dietary custom and culture often mitigate this solution. Local customs of soaking raw crustaceans in brine or alcohol [26] to kill parasites does not appear to be effective. Community awareness and environmental sanitation can be successful. Cobalt-60 irradiation of crustaceans can prevent parasite infectivity but this requires significant economic and public health commitment.

CONCLUSION

Approximately 50 million people around the world are infected with food-borne trematodes which causes an enormous global public health burden. Much of this neglected tropical disease is round in rural parts that typically have limited health care for these infected persons. This discussion reviews epidemiology, clinical features, diagnostic measures, and treatment options for these infections from intestinal, liver, and lung flukes. New diagnostic treatment options have been developed and research will continue to provide improved treatment and renewed hope for those infected [27-30].

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Chapter 515

LEISHMANIASIS: A PUBLIC HEALTH ISSUE

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ABSTRACT

Leishmaniasis is a serious public health problem endemic in more than 88 countries worldwide. It mainly affects large areas of the tropics, sub tropics, and the Mediterranean basin. More than 350 million people are considered at risk of acquiring the disease and approximately two million new cases occur annually. The disease is caused by Leishmania, a protozoan parasite, and is transmitted by a sandfly vector. Leishmaniasis exists in three clinical forms (cutaneous, mucocutaneous, and visceral). It exhibits variable clinical manifestations and is associated with extensive morbidity and even mortality. Proper diagnosis and identification of the parasite is critical in determining prognosis and appropriate treatment. Newer non-invasive methods of diagnosis with high sensitivity and specificity have been developed. Treatment of leishmaniasis is challenging, as the drugs used for treatment are toxic and poorly tolerated. Additionally drug resistance has been reported in many areas as well. Co-infection with HIV poses a major problem and increases risk of leishmaniasis associated mortality. Currently, leishmaniasis is not a vaccine preventable disease.

Keywords: public health, tropics, leishmaniasis

INTRODUCTION

Leishmaniasis is a disease complex caused by a heterogeneous group of protozoan parasites of the genus Leishmania. There are more than 20 Leishmania species and 30

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phlebotomine sandfly species, which transmit the disease to humans [1]. Dogs, foxes, rodents, and a variety of other animals serve as reservoirs for the parasite. The parasite can also be transmitted between humans through blood transfusions and shared needles [2]. Leishmaniasis presents as three clinical syndromes: cutaneous leishmaniasis, mucocutaneous leishmaniasis, and visceral leishmaniasis. The disease is known to be associated with poverty, malnutrition, famine, population displacement, urbanization, deforestation, agriculture, poor housing, poor education, and lack of resources [3-6].

The disease not only affects the health of the patients, it hinders the socio-economic development of the area. The severity of the disease is increased in people co-infected with HIV often resulting in relapses and a higher mortality rate [7]. Clinical management of leishmaniasis depends on the species involved and severity of infection [8]. There are only a limited number of drugs available to treat leishmaniasis and these are too expensive and are associated with adverse reactions. The emergence of drugs resistance has further complicated the control of leishmaniasis [9, 10].

Epidemiology

According to the World Health Organization (WHO), more than 12 million people living in 88 countries are at risk of being infected with different species of *Leishmania*. Approximately, 1.3 million new cases and 20,000 to 30,000 deaths occur each year [1]. The true incidence and prevalence is probably much higher due to widespread under-reporting of the disease [11, 12]. Case reporting has increased due to the availability of improved diagnostic tests. The geographical distribution of leishmaniasis is limited to areas of natural distribution of the sandfly vector. The incidence of leishmaniasis is higher in Asia, Africa, and the Mediterranean basin (Old World leishmaniasis) than in Mexico, Central America, and South America (New World leishmaniasis) [1]. Women have higher risk of infection due to their greater exposure to places of sandfly habitat [1].

Cutaneous leishmaniasis (CL) is the most common form of the disease with 1 to 1.5 million new cases per year representing 50 to 75% of all new cases. About 95% of cutaneous leishmaniasis cases occur in the Americas, the Mediterranean basin, Middle East, and Central Asia [1]. Over two-third of new cases of CL occur in six countries: Afghanistan, Algeria, Brazil, Colombia, Iran, and Syria. Mucocutaneous leishmaniasis is most common in South America, especially in Brazil, Paraguay, Ecuador, Bolivia, Peru, Colombia, and Venezuela. Ninety percent of the cases occur in Brazil, Bolivia, and Peru.

Visceral leishmaniasis (VL) is highly endemic in the Indian subcontinent and East Africa.

An estimated 200,000 to 400,000 new cases of VL occur worldwide each year. Over 90% of new cases of VL occur in six countries: Bangladesh, Brazil, Ethiopia, India, South Sudan, and Sudan. VL is common in farming villages where houses are made of mud walls and earthen floors and cattle and human live in close proximity. Post kala-azar dermal leishmaniasis (PKDL), a sequel of visceral leishmaniasis occurs mainly in East Africa and the Indian subcontinent [13]. The geographical distribution of different forms of leishmaniasis is presented in Figures 1-4.

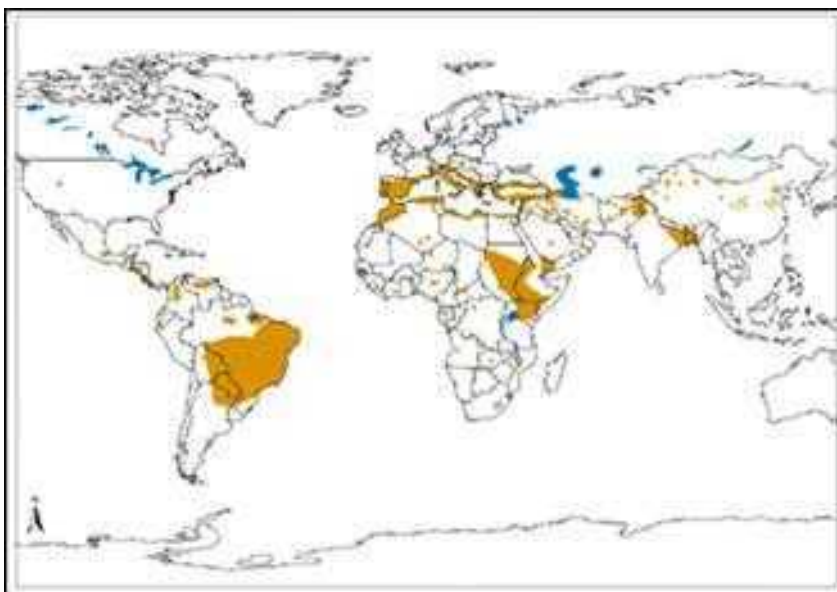


Figure 1. Geographical distribution of visceral leishmaniasis in the Old and New world (Adapted from 1 with permission from WHO).



Figure 2. Geographical distribution of cutaneous and mucocutaneous leishmaniasis in the New World (Adapted from 1 with permission from WHO).

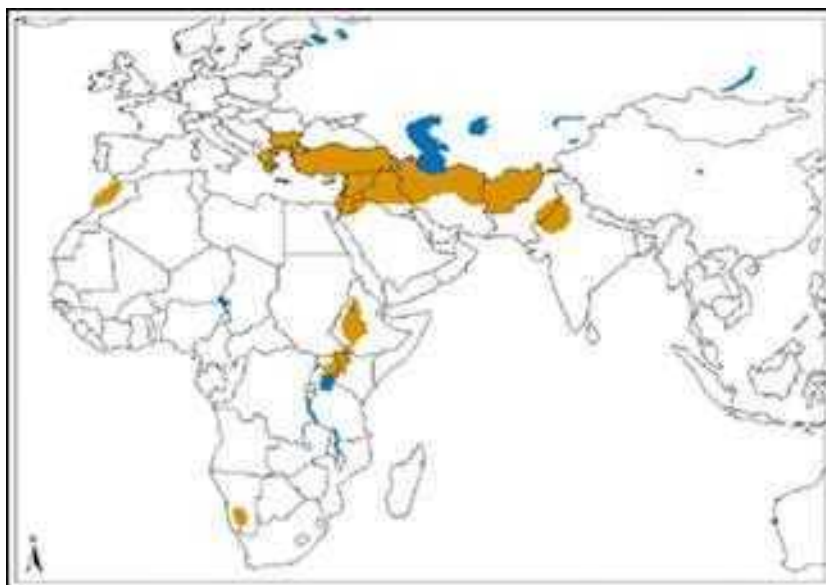


Figure 3. Geographical distribution of Old World cutaneous leishmaniasis due to *L. tropica* and related species and *L. aethiopica*. (Adapted from 1 with permission from WHO).

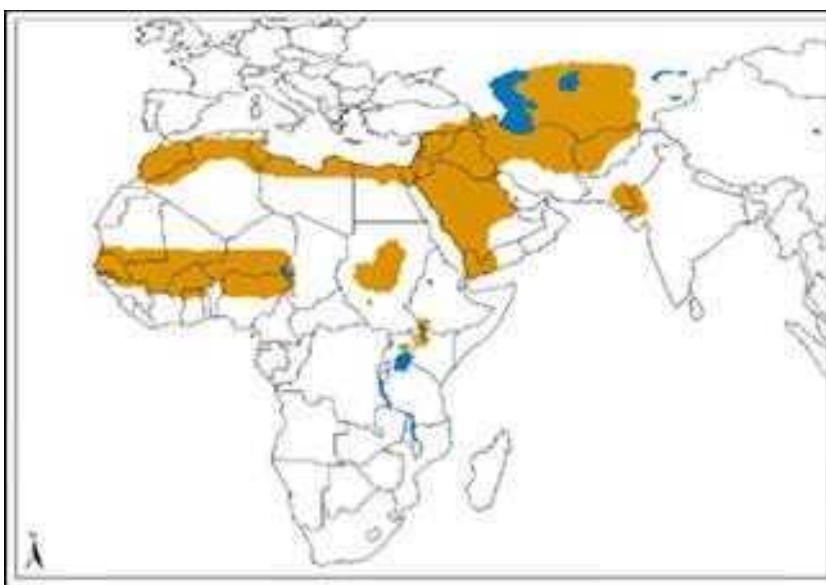


Figure 4. Geographical distribution of Old World cutaneous leishmaniasis due to *L. major*. (Adapted from 1 with permission from WHO).

PARASITE

The leishmaniasis are caused by about 20 species pathogenic for humans belonging to the genus *Leishmania*. The parasite has two distinct stages in its life cycle, amastigote and promastigote. The amastigote stage, also known as Leishman-Donovan body, is found in the

reticuloendothelial cells of the mammalian host. These are small, round, or oval, measure 3-5 μm , and contain a large nucleus and a small kinetoplast. The promastigote stage is found in the insect vector and measures 15-30 μm in body length, and 1.5-3.5 μm in width, and contains a large centrally placed nucleus and a kinetoplast located near the base of the flagella.

VECTOR

Leishmania is transmitted by the bite of a small 2-3 mm long, hairy, sand-colored insect vector, the phlebotomine sandfly. Some 30 of the 500 known phlebotomine species have been identified as vectors of the disease [1]. The phlebotomine sandfly is found throughout tropical and temperate regions of the world. Only the female sandfly transmits the parasite. The sandfly gets infected with *Leishmania* parasite when it sucks blood from an infected human or suitable mammalian host. Inside the sandfly, the parasite transforms to the promastigote stage in about 4-21 days. The sandflies live in shaded microhabitats, are most active from dusk to dawn, and have a short flight range [14].

RESERVOIR

Leishmaniasis can be broadly grouped into two broad categories according to the source of human infection. In the zoonotic form, wild animals or domestic animals serve as reservoirs, while humans serve as reservoir hosts in anthroponotic leishmaniasis. Common reservoir hosts include dog, fox, sloth, cat, opossum and many others [15]. Human beings are directly involved as a principal reservoir host in VL caused by *L. donovani* and CL caused by *L. tropica* [1].

LIFE CYCLE

The infected sandfly during its blood meal regurgitates the promastigotes into the subcutaneous tissue of the human host [16]. These promastigotes are rapidly taken up by the mononuclear blood cells at the site of the bite where they begin to multiply and infect other cells and tissues. Once inside the macrophages, the promastigotes transform to the amastigote stages. The amastigotes multiply by binary division inside the macrophages, which eventually rupture releasing the amastigotes into the reticuloendothelial system of the host. These parasites are picked up by another sandfly during its blood meal to continue the life cycle. The amastigotes transform to metacyclic promastigotes in the midgut of the sandfly in 4-21 days, and are inoculated into the human host by the sandfly during the next blood meal. The life cycle is similar for different forms of leishmaniasis [17-19].

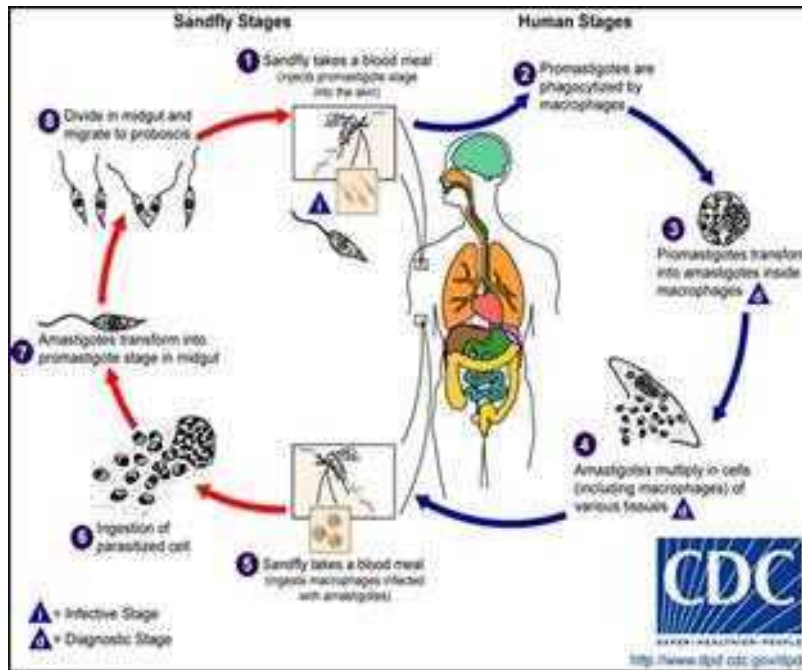


Figure 5. Life cycle of leishmania (Credit: CDC/DPDx).

TYPES OF LEISHMANIASIS

Leishmania is known to cause three forms of disease in humans: cutaneous leishmaniasis, which is the most common form, mucocutaneous leishmaniasis, and visceral leishmaniasis, which causes disseminated disease. The form of disease depends on the species of *Leishmania* involved. Deviations from these main manifestations often exist which complicates or delays proper diagnosis.

CUTANEOUS LEISHMANIASIS

Cutaneous leishmaniasis (CL), also known as '*oriental sore*', is the most common form of this disease. The clinical features as well as the causative agents of CL vary by location. *L. tropica*, *L. major*, *L. aethiopica*, *L. infantum*, and *L. donovani* are the main species in the Eastern Hemisphere, while *L. mexicana* complex (*L. mexicana*, *L. amazonensis*, *L. venezuelensis*) and *L. viannia brasiliensis* complex are common in the western hemisphere [1]. CL causes a lesion in the form of a papule or nodule at the site of sand fly bite, usually on the exposed parts of the body [20]. These lesions appear within several weeks of exposure and may persist for several months or years.

Skin lesions are usually painless unless there is secondary bacterial infection. The skin lesions take on a variety of appearances and may resemble acne, warts, or psoriasis. The lesions of CL usually self-resolve within 6-18 month, leaving scarred tissues, which often becomes a cause of social stigma for the patients [21]. In patients with poor immune

response, the primary lesion may spread to form ulcers, plaques, and nodules over the entire body resulting in diffuse cutaneous leishmaniasis [22]. These nodular skin lesions often resemble those of lepromatous leprosy (Hansen's disease) and are difficult to treat. Unlike lepromatous leprosy, diffuse CL does show any nerve involvement.

MUCOCUTANEOUS LEISHMANIASIS

Mucocutaneous leishmaniasis (ML), also called '*espundia*', occurs most frequently in the New World. In ML, the parasite disseminates from the skin to the naso-oropharyngeal region leading to mucosal destruction. The development of ML is similar to CL and the two infections can occur simultaneously. ML is commonly caused by *L. brasiliensis*, *L. panamensis*, *L. major*, *L. tropica*, *L. infantum*, and *L. guyanensis* [1]. ML usually manifests several years after sub-optimally treated original cutaneous lesions. The initial manifestations of ML include persistent nasal stuffiness or bleeding, which may progress to ulcerative destruction of the naso-oropharyngeal mucosa [23]. ML caused by *L. brasiliensis* can often lead to disfiguring and is life-threatening. Often times, this disabling form of leishmaniasis can lead to the patient being rejected by the community. ML and CL can occur at the same time [24].

VISCERAL LEISHMANIASIS

Visceral leishmaniasis (VL) is the most complex form of the disease. It exhibits a broad spectrum of severity and disease manifestations. VL is usually caused by *L. donovani*-*L. infantum* complex. The incubation period of VL generally ranges from weeks to months. The infection may remain asymptomatic for prolonged periods and may become symptomatic in patients who become immune-compromised. The onset of the disease is usually gradual. VL in India is also referred to as 'kala-azar', which means 'black fever' or 'deadly fever' in Hindi, referring to darkening of the skin of the face, hands, feet, and abdomen. VL affects internal organs particularly the spleen, liver, and bone marrow. HIV co-infected patients may exhibit atypical manifestations such as, involvement of gastrointestinal tract and other organ systems [1].

VL is associated with fever, malaise, weight loss, anorexia, and discomfort in the left hypochondrium.

Non-tender splenomegaly with or without hepatomegaly, anemia, pancytopenia, high protein level, and low albumin level with hyper-gammaglobulinemia are usually seen. About 10% of VL cases develop lesions, which are initially present on the face, but may later spread to other parts of the body. These skin lesions may be macular, papular, and/or nodular in nature. This condition is known as post kala-azar dermal leishmaniasis (PKDL). It may also affect the conjunctival, nasal, oral, and genital mucosa. PKDL occurs almost exclusively in patients with visceral leishmaniasis caused by *L. donovani*; it is rare in cases caused by *L. infantum* [25]. PKDL patients do not have fever and the physical examination is usually normal [26, 27].

DIAGNOSIS

Clinical history plays an important role in the presumptive diagnosis of leishmaniasis in patients who live in or have visited areas endemic for the disease. However, signs and symptoms alone may not be enough to differentiate the condition, especially in areas where several other infectious diseases are prevalent. Clinical symptoms of CL may mimic other skin conditions such as, mycobacterial ulcer, leprosy, and skin cancers. Similarly VL may resemble malaria, schistosomiasis, or other systemic infections [8, 20]. Definitive diagnosis is essential to initiate treatment, which varies with the species of *Leishmania* involved. Visualization of amastigotes in the form of Leishman-Donovan bodies in Giemsa stained biopsy smear or aspirates by light microscopy is the classical confirmatory test [8, 28].

Specimens of choice in the case of CL include scrapings, fine needle aspiration, or biopsy of lesions. Parasites are scarce in ML due to strong local reactions; therefore, parasites are not commonly detected in dental scrapings or mucosal granuloma biopsy. In the case of VL, microscopic detection of parasites splenic aspirates is still considered the reference standard with sensitivity exceeding 95% [1]. However, bone marrow aspirate, liver, lymph node, and whole blood or buffy coats are preferred specimens as splenic aspiration can be associated with life threatening hemorrhage [1]. The sensitivity of bone marrow smear is about 60 to 85% [1]. Diagnosis of PKDL can be made by examination of slit-skin smears or samples obtained from nodular lesions. Culture of parasite can improve the sensitivity of detection of parasite, but leishmania culture is rarely needed in routine clinical practice [29].

Serological tests have been employed for the diagnosis of leishmaniasis [30]. A direct agglutination test (DAT) and rK39 dipstick test have shown promise under field conditions but exhibit variable sensitivities in different areas of the world [30, 31]. Antibody detection tests have inherent limitation of not being able to differentiate between current infections from past exposure to the disease. Further, these tests have limited value in case of CL and ML due to inadequate antibody response in these patients. A latex agglutination test (KAtex), which can detect polypeptide fractions of 72-75 kDa and 123 kDa in the urine of kala-azar patients, has shown high sensitivity and specificity [32-35].

Isoenzyme analysis has been employed to characterize the parasite to the complex and sometimes to the species level. However, the technique is cumbersome, time consuming, need technical expertise. There is also a lack of standardization among laboratories and incomplete correlation with the results [1, 36].

Molecular methods namely PCR and DNA sequencing have been employed for detection of parasites directly in biopsy samples overcoming the need of culture organism [28, 37-40]. PCR based methods can be used to monitor the response of anti-leishmanial treatment or to rule out latent infection when the parasite load is very low [41]. The widespread use of molecular diagnostics is still hampered by the requirements of substantial laboratory infrastructure, technical expertise, and cost [42-45]. Recently, a SMART Leish PCR has become available for the rapid diagnosis of cutaneous leishmaniasis even when the parasites in the skin are so low that microscopy and culture results will be negative at day 30 [46]. This test was developed in partnership amongst the Walter Reed Army Institute of Research (WRAIR, USA), the Army Medical Research and Materiel Command (USA), and Cepheid USA [47].

TREATMENT

Leishmaniasis is a treatable and curable disease. However, any chemotherapeutic intervention warrants proper species identification and ascertainment of any concomitant infections [48, 49].

Treatment needs to be individualized and may vary with the type of *Leishmania* species, severity of the disease, and other host factors namely age, sex, and immune status [50-52].

CL lesions usually resolve without any pharmaceutical intervention. However, treatment can speed healing, reduce scarring, and decrease the risk of mucosal dissemination and relapse of skin lesions. Relapse has been noted in patients clinically cured of leishmaniasis. Thus follow-up smears and cultures are recommended 1 to 2 weeks post therapy. Non-drug options include cryotherapy (with liquid nitrogen), thermotherapy (use of localized current field radiofrequency heat), and surgical excision of lesions. ML does not resolve spontaneously and it is very difficult to treat [52]. Treatment is usually unsuccessful unless started very early when the disease is mild. Full-blown cases may need plastic surgery to repair skin damage.

VL represents a severe form of disease and requires the use of effective systemic therapy. The prognosis of untreated VL cases is poor with mortality rate as high as 75% to 95%. Adequate nutrition to enhance the immune status in VL patients is important to reduce adverse reactions. There is limited evidence for the efficacy of PKDL treatment. The prognosis may depend on the severity of the condition and the duration of symptoms prior to initiation of treatment [53].

ANTILEISHMANIAL DRUGS

Pentavalent Antimonials

Sodium stibogluconate and meglumine antimoniate have been standard first-line medicines in most parts of the world (>90% overall cure rate) [1, 54]. However, drug resistance is becoming a major concern in India and Nepal [9]. Initial treatment of VL includes a daily injection of 20 mg/kg body weight of Sb(V) for 10-20 days [1]. These compounds may be administered intravenously, intramuscularly, or may be injected directly into the lesions. Common adverse effects include anorexia, vomiting, nausea, abdominal pain, malaise, myalgia, headache, and cardiac conduction defects. Given that substandard medicines can cause severe toxicity and death, the quality of pentavalent compounds should be assured.

Miltefosine

Hexadecylphosphocholine (Miltefosine), an oral alkylphosphocholine analog, is the first effective and safe oral agent for treatment of all forms of leishmaniasis. It also shows efficacy in refractory disease and in HIV patients suffering from CL and VL. Miltefosine is teratogenic and contraindicated in pregnant women. Nursing mothers should be advised not to

breastfeed during the course of treatment or for 5 months thereafter. Adverse effects with miltefosine include anorexia, vomiting and diarrhea, skin allergy, and renal insufficiency [55-57].

Amphotericin B Deoxycholate

Amphotericin B is a polyene antibiotic. A test dose of 1 mg, given by infusion, is recommended, followed by a full dose 4-6 hours later. Amphotericin B deoxycholate given daily or on alternate days by IV infusion in 5% dextrose for 4 hours at a dose of 0.75-1.0 mg/kg per day for 15-20 doses was 99% effective in India [1]. Infusion reactions include fever, rigor, chills, nephrotoxicity, hypokalemia, and myocarditis. Treatment should be given in hospital to allow continuous monitoring of patients. Lipoid formulations of Amphotericin B (liposomal amphotericin B, amphotericin B lipid complex and amphotericin B colloidal) are less toxic and require only 5 to 10 days of treatment or even as a one stat dose [58-62]. Mild infusion reactions (fever, chills, and rigor), transient nephrotoxicity, or thrombocytopenia are occasionally seen [1].

Paromomycin

Paromomycin, an aminoglycoside antibiotic, is usually administered intramuscularly and has been used for VL and CL. A dose of 15 mg/kg paromomycin sulfate (11 mg base) for 21 days gave a cure rate of 93-95% in VL in India [1] The efficacy was 85% in East Africa at an increased dose of 20 mg/kg (15 mg/kg of base) per day for 21 days. Topical paromomycin with methylbenzethonium appears to be more effective for treatment of ulcerative lesions due to *L. major* or non-ML associated Central American species [63].

Azoles

Oral ketoconazole, fluconazole, itraconazole have variable efficacy in treatment of leishmaniasis. Their use is limited to specific circumstances depending on geography and parasite species involved [64].

Pentamidine

Pentamidine isethionate is an alternative parenteral treatment for cutaneous leishmaniasis. Severe adverse effects including drug-induced pancreatitis leading to diabetes mellitus, dysglycemia, hypotension, hyperkalemia, myocarditis, and renal toxicity have restricted the use of this drug for treatment of *L. guyanensis* infections acquired in the Guyanas [65-67].

The treatment regimen should follow national and regional guidelines, if applicable, and treatment should be given under the supervision of trained medical personnel. Detailed information on the treatment of the various forms of the disease by geographic location is

available in the WHO technical report series 949 on the control of leishmaniasis [1]. Resistance to pentavalent and other antileishmanial drugs has been reported in various geographical regions [68-71].

PREVENTION AND CONTROL

Vaccine will be the ultimate tool for eliminating leishmaniasis. The development of a safe, effective, and affordable antileishmania vaccine has become a critical global public-health priority. Insufficient knowledge of parasite pathogenesis and the complexity of immune response have made it difficult to develop an effective vaccine for leishmaniasis. Both live attenuated as well as recombinant vaccines approaches have failed to generate protective response [72-74]. Vector and reservoir control can help block the transmission of the parasite [75]. Thus, no single method of intervention is likely to be successful in the control of the disease. The most common preventive measure is to avoid the bite of the sand fly [76, 77]. Simple precaution measures include the use of protective clothing (long sleeves, long pants, socks) and use of insect repellants containing N,N-diethyl-m-toluamide (DEET).

Residual insecticide spraying of houses and animal shelters and use of fine-mesh bed nettings impregnated with insecticides such as permethrin or deltamethrin have been tested with success in endemic areas [78]. Reservoir control is very difficult. Pyrethroid-impregnated collars have been used to prevent infections in canines [1]. These measures when implemented collectively can help to manage this complex and neglected disease [79]. Preventive health education in endemic areas can play a major role in the prevention and control of this leishmaniasis. New diagnostic tools and treatment strategies need to be made available in regions where the disease is prevalent. Remote sensing and geographical information systems can be used to investigate the large-scale distribution and risk factors of the disease.

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Chapter 516

THE MIGRANT CHALLENGE TO PUBLIC HEALTH: OVERCOMING DISPARITIES IN HEALTHCARE OFFERED TO MIGRANTS

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ABSTRACT

As the world witnesses massive ongoing migration waves, numerous health and health care challenges arise as migrants venture out to new areas of residence. Among other concerns is migrants' access to health-care services which could be hindered because they fear authorities, encounter bewildering cultural and linguistic factors, have poor knowledge of the local health system, or simply are denied access to healthcare. Mostly, migrants face issues of mental health, chronic illnesses and infectious diseases. The response of healthcare agencies, NGOs and individual healthcare providers reveals a widespread inability to respond effectively and a lack of standard guidelines to address the issue. This chapter seeks to review the interplay between the phenomenon of migration and corresponding response from health care establishments, and to critically analyze the challenges posed by migrant crises and its implications for the future of public healthcare. Finally, a strong emphasis has been put on recommendations and appropriate responses have been suggested to tackle the problems associated with migrants to foster better healthcare for common welfare.

Keywords: migrants, migrant crisis, public health

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INTRODUCTION

As has been observed in many studies, health related inequalities can be better understood and explained in relation to socio-economic status. Although the decision to migrate is sometimes a personal one and based on an individual's motivations, there are structural causes that need to be considered that are beyond an individual's or even entire population's control; environmental, economic, political, social and even religious circumstances such as wars, deprivation, persecution and social unrest can lead to voluntary or forced migration [1].

The term "refugee" carries substantial connotations that vary from very positive to absolutely negative. In this work, all who move from one country to another will be labelled migrants regardless of the reason they emigrated. A proposed classification of migrants by researchers [2] suggests that migrants should be classified into two distinct types: one which is based on free choices and individual opportunities, and a second that includes forced migration as part of large population movements resulting from marked economic, political or social inequalities. As observed in the previously mentioned study [1], the scope of the problem is difficult to assess accurately since by definition, many so-called "undocumented" migrants attempt to hide from the authorities or even from agencies that are designed to help them specifically since they fear deportation or incarceration. Even if migrants do register in one country, they may simply be en route to a third country where they do not register. Although the poor, displaced migrants are most often the subject of daily reports on the "problem," there are also well-educated, talented migrants who create a brain drain in their homeland as they move from poorer nations to richer nations that have more opportunities. These "highly skilled" migrants bring their own issues with them for public health [1].

Several studies done on Hispanic immigrants [2] in the United States found that they often are in better health than the native population of the destination country; this health advantage is known as "healthy immigrant effect," which is a protective effect of migrants' healthier lifestyle, diet and strong social bonds. Unfortunately, this health advantage is lost with time and in spite of socio-economic improvements due to the process of "acculturation," the assimilation of the dominant culture. Also, it can be noted that there might be a self-selection factor since normally only younger, healthier people might emigrate, who have a better level of health than the general population in their home country at first.

This decline in health can also be partially understood in the context of the living conditions of those immigrants. Despite socio-economic improvements in the destination country, accumulated less privileged socio-economic conditions both in the country of origin and the place of destination attribute to the lower health outcomes for those individuals from poor countries, as well as continuous exposure to hardships and discrimination which all are considered as mechanism of inequality. Adaptation to a new life, legal constraints, geographical distance to the country of origin, economic hardships, as well as loss of social status, separation from friends and relatives, often effects of a forced migration, are all considered barriers for migrants leading to health-related problems and inequalities [2].

HEALTH-CARE CHALLENGES FACED AS MIGRANTS ENTER NEW BORDERS

Migration occurs in waves, and because of the current large number of migrants attempting to reach Western Europe and the United States, political involvement has grown considerably [3]. Whenever war erupts, natural disasters emerge, or persecutions take place, natives are forced to flee their homelands to a safer country as they attempt to pursue opportunity elsewhere [4]. Between the 1880's and the 1980's, there has been a mix of migration waves within the United States alone, involving many Arab immigrants from 22 countries. The migration of immigrants progressed and continued throughout the years in three consecutive waves post World War II and after the passing of the Immigration Acts. Despite their goal to come to America for a better life, there was a high rise in cultural and ethnic tension owing to interactions with the white majority, just as had happened earlier with Polish, Irish and Italian immigrants in the USA [3]. Since World War II, Arabs have been deserting their motherlands for reasons such war, terror, and the pursuit of happiness [5].

This was just the early start of recognition of the health disparities presented for Arab Americans that continued to develop as a result of social, economic, political, and even legal factors [3]. According to the International Organization for Migration (IOM), about 800,000 migrants crossed the European border in 2015 alone [5]. In one year, hundreds of thousands of people have fled their homelands and migrated to Europe. These migrants have usually come from countries and areas such as Libya, Eritrea, Iraq, Africa, Middle East, Syria, and South Asia, migrating in order to pursue a promising and peaceful life for themselves, their families and descendants [5]. This massive influx has created a complex situation, especially in the European Union, as the Europeans attempt to deal with this immigration crisis [5].

According to the Global Commission on International Migration (GCIM), there are approximately 200 million international migrants in existence, the majority of whom (60%) have fled to developed countries [6]. International migration is one of the most politically-highlighted issues of recent times. Global policy-makers often raise this concern since it leads to cultural, social, and economic burden on the migrants and host countries. Both the host countries and the countries of origin are impacted economically [6]. The countries of origin experience a serious "brain-drain" as they lose their most valuable of people, who are highly educated and skilled professionals, which influences the supply and the quality of fundamental services in the homeland. The IOM states that 300,000 professionals from Africa are currently working and living in Europe and the United States [6]. The host countries are thought to believe that immigration leads to fewer jobs for their own citizens, lower wages, and conflicts among ethnic groups, ideal institutions, and distortion of the local community's identity. However, there are also benefits in gaining experienced professionals and educators, such as cultural enrichment and different ways of approaching problems [6].

The current migration crisis is a major issue spreading across several countries. Due to acts of violence in their homelands, over 4 million Syrians have fled the country. Additionally, over 4 million Iraqis have been displaced, either internally or as international migrants [7]. Many challenges arise when migrants venture out and are introduced to a new area of residence. Some major concerns are mental health, and chronic and infectious diseases introduced by refugees unfamiliar in the host country. The notion that migrants indeed disrupt the health system of a country is not astounding. Unfortunately, not much has been done to

highlight the importance or scope of this issue. On the other hand and despite the general perception, there have been reports from the WHO stating that there is no systematic association between infectious diseases and migration, and the risk of transmitting infectious diseases is extremely low [8].

Another main concern is simple access to healthcare. Many of the refugees are unable to effectively access health care because they fear the authorities, face substantial cultural and linguistic barriers, have poor knowledge of the country's health system, or are simply being denied access. Of course, there are differences among different groups of migrants based on cultural and life-style practices. Disparities exist among migrants due to high prevalence of risk factors such as sedentary lifestyles, bad habits of social smoking, hypertension and other illnesses, and mental stress from the effects of racism and discrimination [9].

According to the WHO, Europe is currently tending to a wide range of health problems of newly arrived refugees including accidental injuries, burns, hypothermia, cardiovascular problems, gastrointestinal illnesses, pregnancy/delivery complications, hypertension, and diabetes. Women further are faced with problems such as violence, sexual and reproductive health, maternal health, and child health. Migration adds to the burden of illnesses and health-harming habits of people these European countries are faced with such as; reproductive health problems, psychological disorders, nutrition disorders, newborn mortalities, drug abuse, alcoholism, and violence [8]. A high number of children are vulnerable to respiratory infections and gastrointestinal manifestations, due to their crowded unsanitary living environments [8].

Along with the increasing levels of illnesses, a high number of accidental deaths have occurred during these migrations. This number has been estimated to be as high as 3,100 in less than one year in 2015 among migrants crossing the Mediterranean Sea, who are believed to have either died or gone missing at sea, according to the United Nations High Commissioner for Refugees (UNHCR) [8].

With regards to infectious diseases, a number of factors influence the dispersions of microorganisms. These include population movements, commercial globalization, and environmental changes [10]. However, as previously stated, infectious diseases and migration have no link. For example, leishmaniasis, not normally found in Europe, cannot be transferred among individuals and is highly treatable. Furthermore, the chances of the host population of acquiring infections from the migrants' native lands such as Ebola, Middle East Respiratory Syndrome (MERS), or the Marburg and Lassa viruses; are tremendously low. Other infectious diseases similar to tuberculosis (TB) are not easily transmissible, unless there is an active infection. In fact, the estimated rates of TB transmissions are only 39 per 100,000 individuals in Europe alone [8].

Whether it is a security or an economic concern, migration has put Europe in a situation necessitating changes in their migrant policies for better strategies [5]. These strategies include: steps for ensuring ordered and effective migration policies in order to prevent people from being exploited by recruiters, traffickers and agents, realization of the fundamental human rights of migrants, and avoidance of cultural and social conflicts [5].

PROTECTED BY GLOBAL LAWS, THREATENED BY LOCAL POLITICS

The Constitution of the World Health Organization (WHO) of 1946 was the first to establish health as a human right at an international level. Just like all other human rights protected by international instruments and national constitutions and legislations, health is a human right whose protection and fulfilment is assumed by states. They ought to protect individuals and groups from undue interference with the enjoyment of this right, and take positive steps to ensure the realization of the right to health.

The International Covenant on Economic, Social and Cultural Rights (ICESCR) also establishes the “right of everyone to the enjoyment of the highest attainable standard of physical and mental health” in its Article 12. It also makes it clear that states are to exercise all rights including the right to health “without discrimination of any kind as to race, color, sex, language, religion, political or other opinion, national or social origin, property, birth or other status.” in Article 2.2.

Governments are required by international law to protect and promote the health of every individual within its territory regardless of their socio-economic, political, cultural, legal background or other status. Therefore, migrants are protected by international human rights law. In reality however, provision of health to migrants is a challenging task. Countries witnessing the inflow of migrants are usually torn between the willingness to help migrants and concerns for health safety of the native population. Public health policies involve prioritizing tasks and problems that require more attention. This may open the door for discrimination towards a few, thus violating the non-discriminatory nature of the laws protecting health rights. Public health policies may sometimes allow countries to limit health rights of certain individuals and groups in the name of protecting the health of the larger public.

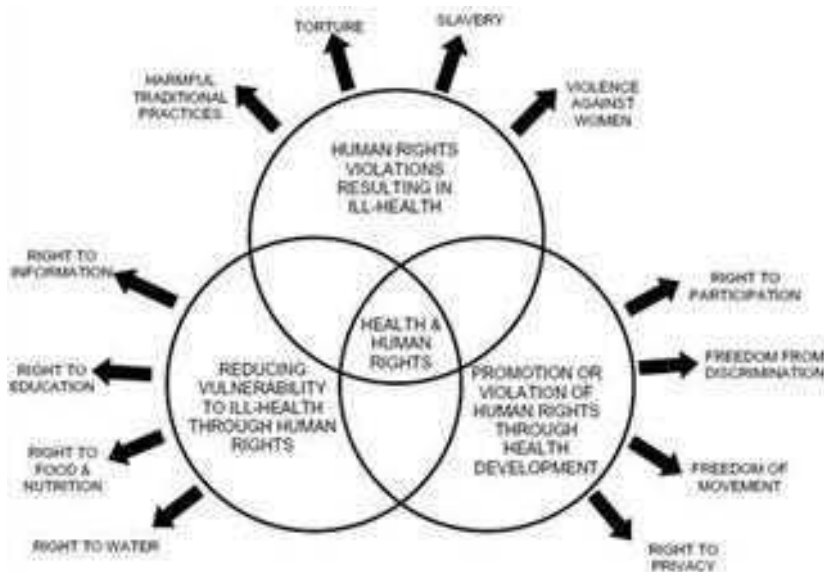


Figure 1. Examples of the linkages between health and human rights (from the World Health Organization) (www.who.int/hhr/HHR%20linkages.pdf) (email approval for usage acquired from WHO).

Migrants, due to their fragile state of affairs, are often pushed into extreme situations that threaten their basic needs and rights. Through their migratory process, they may witness violations of several rights including rights to social security, adequate housing, clean food and water, work and the right to seek and receive information. An interdependence has been demonstrated between the right to health and other human rights (Figure 1). Several rights cannot be preserved without realizing the right to health. Similarly, with the violation of other rights, the fulfilment of the right to health becomes tricky. For instance, migrants are usually forced to live in unhygienic and unsafe conditions, with limited access to clean food and water. These factors pose a serious threat to their health, and to the ultimate realization of their right to health.

TAKING ACTION: THE RECOMMENDATIONS

Introduction

Migrant health is a major issue now unfolding as a crisis, posing serious challenges to public health. Increasing concerns related to the management of incoming migrants are based on the priorities of the governments in question not the migrants themselves. Thus, processes like registration, integration into the job market, geographical allocation, etc. tend to overshadow the basic needs of the migrants, healthcare being an essential one.

It needs to be realized that migrants being a diverse group might be migrating for varied reasons like better pay or a better life for their children or more pressing concerns like loss of life when forced out of their homes by wars and political instability. As a result, migrants often arrive with few resources. For many migrants, health is the only asset they possess. Unfortunately, their health status can be severely compromised by a wide range of health-determining factors at home, in the host countries, and during travel. It gets only worse for those entering a country illegally as they are forced to avoid the public spotlight. This scenario directly hampers the migrant's willingness or ability to seek medical care thus creating a huge crisis.

Further, there is a wide variability in how each country handles migrants with regards to the health care services different migrant groups are entitled to. Undocumented migrants are often forced to stay out of the public spotlight and avoid seeking medical attention even for serious debilitating ailments from fear of being arrested, prosecuted and deported. Also, the unpredictable distribution of work amongst NGOs and governments adds to the chaos and the complexity of the situation.

Naturally, language and social barriers can strongly hinder migrants' access to healthcare. On one hand, the attitude of the local population causes problems for migrants who have reported to face discrimination and harassment at clinics and hospitals. This problem is further compounded by the public's anti-migrant sentiments and lack of empathy and consideration towards migrants, holding the belief that the migrants are living on "the taxpayers' money." On the other hand, migrants' attitudes can also contribute to the crisis as those coming from poor underdeveloped countries tend to have a weak understanding of the healthcare system (especially primary) and fail to efficiently utilize the healthcare services

they're offered. This can also be contributed to by their pre-existing social, cultural and religious notions they may have regarding health and wellbeing.

While there may be several lines of action that can be taken to tackle the issue of migrant health, progress is hampered since so far no one has been able to statistically explain the implications of rising migration rates for public health and to determine a "common minimum" of healthcare services that must be provided to all migrants regardless of their social, cultural, demographical and legal background. Without providing access to clean and safe food, water and housing, we run a risk of having our efforts to promote health and provide healthcare services negated by other factors that greatly impact health.

Particularly with regards to the development of personalized medicine in healthcare, migrant health should be a pressing concern. Given that migrants are a diverse group, from varied cultural and socio-economic backgrounds, as well as having different health goals and challenges, their wellbeing is crucial to ushering in an era of personalized medicine. What is currently being done is, instead of assessing the underlying factors impacting migrant health and focusing on the unique health needs of the subgroups within the migrant population, emphasis is being put on making healthcare as widely accessible as possible. Thus, our focus needs to be shifted from quantity to quality with how we treat migrant populations at healthcare centers being our main concern and not how many of them we treat.

Therefore, the provision of efficient primary health care should form the foundation of migrant health policies and programs. Early detection, treatment, education, and relevant preventative measures can go a long way in improving migrant health conditions and standards, thereby reducing their vulnerability towards more complex diseases. This approach is also cost-effective in the long run, as it reduces incidence of more complicated diseases and thus reducing the burden on emergency care, which is substantially costlier than primary health care. There is also a need for a multi-faceted approach, with attention to other health-determining factors like food, water and living conditions. On a political level, closer coordination between NGOs and governments is needed.

In this section, we will discuss major recommendations and steps that should be taken to streamline the management of migrants to ensure the delivery of good quality healthcare to them, while addressing underlying factors contributing to the common problems and challenges migrants face regarding their health and their access to healthcare.

Screening and Its Importance for Migrant Health

The ECDC (European Centre for Disease Prevention and Control) defines screening as 'the systematic practice of medical examination, involving laboratory or other diagnostic testing, to search for and identify cases of a specific infectious disease in a target population'. Many types of migrants go through mandatory health screening in countries of origin in order to receive a visa and recommended screening upon arrival in the host countries. They are screened for a wide range of ailments like infectious, parasitic and sexually transmitted diseases and chronic illnesses, with tuberculosis being the disease most commonly tested for. Experts state that screening can help identify new and asymptomatic cases of infectious diseases, and help in prevention and early detection of certain diseases, thus reducing long-term burden on public health.

At a time where anti-migrant sentiments are on the rise, where migrants are being blamed for causing diseases, with newspaper headlines demanding migrants be sent back home, it becomes inevitable to ask the question- How much of a threat do migrants really pose to public safety? There is no factual evidence supporting a possible increase in risk of infectious diseases within the local population caused by migrants. A study on tuberculosis in migrants moving from high-incidence countries to the UK found that migrants posed a negligible risk of onward transmission, but were at risk of developing active tuberculosis after arrival, with incidence peaking in the fourth year after arrival [11]. With a pre-entry screening program along with timely treatment of the latent infection, the incidence could be significantly reduced.

How effective or cost-effective is screening in newly arrived migrants? The issue remains contentious. Studies report that screening for infections like tuberculosis and Hepatitis-B can be implemented cost-effectively, thereby helping identify migrants with latent infections and potentially reducing related morbidity and mortality [12, 13, 14]. The implementation and practices related to screening programs vary among countries, as there is no “one-size-fits-all” approach. It is important to determine where, when and for whom screening programs can be most useful and effective.

The WHO recommends against obligatory screening of migrants (including refugees), due to the lack of clear evidence of benefits. Moreover, WHO states that it has the potential to cause fear and anxiety within migrants and the local population. Nonetheless, WHO does recommend that health checks and good-quality healthcare be provided to migrants. Human rights and the dignity of migrants must be highly respected, and screening results should not be used to justify the ejection of migrants from the country.

Nevertheless, screening results serve as valuable information for public health authorities in structuring health programs and policies to better meet migrants’ needs. It is encouraging to see that a variety of actions are being taken by countries on the basis of screening results, including provision of treatment upon disease detection [12]. Unfortunately, with poor follow-up care and low treatment completion rates, screening programs can potentially be rendered ineffective. Therefore, along with improving screening programs, it is crucial to devise strategies to facilitate migrant access to a full range of healthcare services, as well as development of treatment, vaccination and health awareness programs.

Unhygienic living conditions, contaminated water and food and poor sanitation are conditions that favor the spread of communicable diseases. Therefore, alongside the provision of healthcare services for treatment of illnesses, steps should be taken on a preventative-level by ensuring the quality of other health-determining factors such as food, water and living conditions. Nutritious food and clean water must be made widely and easily available.

Orienting Migrants to the Country’s Healthcare System: Identifying Barriers, Needs and Requirements

As mentioned earlier, migrants come from diverse cultural and socio-economic backgrounds. Migrants coming from underdeveloped countries may have a poor understanding of the host country’s healthcare system. Pre-existing social and cultural notions can also influence how migrants perceive healthcare services. Along with this, language

barriers can immensely impact the quality of health care migrants receive. These challenges are also taxing for healthcare providers, who feel incapable of addressing the migrants' illnesses in a holistic fashion, and may eventually mold their approach to make their interaction with migrants simpler and shallower, to avoid dealing with more complex and "hidden" illnesses like mental disorders.

To ensure delivery of efficient and suitable health care to migrants, it is important to assess knowledge, cultural and language barriers towards healthcare in migrants, and identify other potential challenges as early as possible. On-arrival screening programs serve as an opportunity to assess migrant attitudes and perceptions regarding the healthcare system, and identify individuals who may need immediate care and attention. Vaccination status of migrations should also be assessed. It is preferable that migrants be adjusted into the primary health care system with minimal delay.

Also, there is a need to make healthcare services more culturally-sensitive for migrants. This can be done by setting up "migrant-friendly clinics," and recruitment of a culturally-diverse staff for medical centers that regularly deal with a large number of migrants. Language interpreters should be assigned to migrant groups, who would also be in close contact with healthcare authorities with the assistance of social workers. Due to previously reported poor quality and implementation of interpreting services [15, 16], there is a need to improve integration of interpreters into the communication chain between migrants and healthcare providers. However, it is also important to train the interpreters in health care language so that they can be effective in communicating often complex and culturally specific health information from migrant to the health care worker and vice versa. Also, another step in sensitizing medical staff towards migrants is to train them to work in a culturally sensitive way with patients with traumatic experiences, including women and girls who may have been victims of sexual violence.

Another innovative approach is to train a few people from within the migrant community on topics of health issues, healthcare services the migrants are eligible for, what to do when feeling sick and equip them with basic medical and clinical skills like first aid, basic life support and administering injections. This will positively influence the migrants' outlook on health and healthcare, as they see their fellow migrants putting in efforts for the betterment of health of the community. Orienting migrants to the host country's healthcare system and educating them about important health problems through seminars, workshops and other didactic methods is crucial in making sure migrants utilize the available health services efficiently and effectively.

Clearly, there is an urgent need to include migrants in more and more health impact assessments. A review found that only 14% of health impact assessments mentioned migrants in the evaluation, with only 2% mentioning them in the recommendations [17]. Health impact assessments help us improve fairness and justice in healthcare delivery by looking into unintended harms and allowing the maximization of benefits. This in turn assists decision-makers to develop efficient and effective health policies and programs. Relevant steps must be taken to facilitate the process of data collection, so that the migrants can be represented fairly during decision-making. Underlying challenges must be addressed, like social, cultural and language barriers, and apprehension of undocumented migrants towards data collection authority and procedures. Instead of mere descriptions of the situation, there is a need for more analytical studies and explanatory models to deal with the underlying causes and wide array of challenges faced by the heavily heterogeneous migrant population.

Mental Health: A Major Concern for Migrant Health

The issue of mental illnesses among migrant populations should be a pressing concern. There is sufficient evidence to suggest that some migrant groups are at a higher risk of developing mental illnesses than others. Migrants, especially refugees, experience several distressing events prior to, during and after their migration which have an immensely debilitating impact on their mental well-being. Underlying mental illnesses can influence presentation of physical health conditions, and can even reduce effectiveness of treatment. This translates into higher migrant health costs, and potentially social exclusion by hindering integration, educational success, and employment. This in turn gives rise to the perfect breeding ground for radicalization and organized crime.

The Committee on Migration and Health Challenges of the European Health Parliament in a paper [19] called for a focus on mental health when providing primary health care to migrants. They recommend the development of community-level programs, which would increase the number of healthcare recipients, and help lower healthcare costs usually incurred by psychiatric-healthcare models, involving individual consultations. Particular attention should also be paid to the more vulnerable group of minors, through the development of school-based programs. This will help address several challenges simultaneously: language and social barriers, integration difficulties, and mental health issues. They also recommend that mental health be given increased attention under the EQUI-HEALTH initiative launched by the European Commission and the International Organization of Migration, which currently focuses more on physical health. The EQUI-HEALTH initiative aims to facilitate exchange of best practices between member states and non-governmental organizations regarding migrant health. Besides this, the Committee also proposed a transparent cost-sharing mechanism amongst the EU Member States for the provision of free primary care to migrants. Sharing costs according to State size and wealth will help ease financial burdens and will allow for a more even distribution of migrants across the EU.

On the other hand, raising awareness about mental illnesses amongst migrants is equally important and they should be encouraged to consult a physician/therapist/social worker if they experience any psychological disturbance owing to trauma and stress. Therefore, a deep understanding of the individual's social, cultural and religious backgrounds and their influence on health is essential. A migrant population's cultural influences on their perceptions of health and disease must be explored as culture can profoundly affect how people perceive illness and how they interpret and react to symptoms. More importantly, people, especially from underdeveloped and developing nations often have culturally-oriented methods of dealing with mentally ill people. Some may first suspect a "demonic possession" or "witchcraft" in a person clearly showing signs of a mental disorder. Therefore, it is crucial that the aspect of cultural perception of illness is taken into consideration when treating migrants for mental illnesses. Inquiries must be made regarding the patient's adherence to prescribed treatment and usage of any alternative medical treatment like herbs, as they may cause drug interactions and side effects. Similarly, for other psychological treatments like psychotherapy to be effective, the underlying philosophical basis must be acceptable to the patient.

Yet another crucial aspect is that of communication. Effective patient-doctor communication is an essential aspect of treating mental disorders in migrants. Patients should be encouraged to use interpreters if they have a limited proficiency in the language(s) the physician knows. Although patients may seek help from family members and friends on this matter, studies have shown that professional interpreters can improve communication and increase the likelihood of asylum seekers disclosing psychological symptoms [20-23].

Further, social support is extremely crucial to facilitate the processes of integration and acculturation among migrants, and to help them manage stress. Feelings of isolation and alienation can be reduced by developing a social support system that allows migrants to network with individuals from the same ethnic and cultural backgrounds with a significant amount of experience living in the country. Ethnocultural community and religious institutions can play a major role in the migrants' adaptation to their new lives and integration into their new society, assisting them in dealing with personal, social, financial, educational and legal challenges. Presence of and networking with role models from the same background and a strong sense of ethnic pride can help migrants tackle issues of discrimination and racism [24].

Women's Health among Migrant Populations

As in any other humanitarian crisis, women form a particularly disadvantaged group among migrants. Especially for women from highly patriarchal communities, their inferior social status along with limited educational and occupational experience makes them susceptible to poverty, sexual violence and further forms of marginalization. Particularly, the sexual and reproductive health of women in migrant communities is considered a public health crisis. There is a dire lack of research data on the sexual and reproductive health challenges faced by migrant women and girls.

The need to make healthcare more culturally-competent for migrants also applies to women's health, making it important to understand the socio-cultural influences on the topics of sexuality, body and health, as well as addressing cultural and language barriers. It is important that migrant women and girls be provided with suitable maternal health care, contraceptive counseling and safe abortion services where possible, since many host countries impose their own restrictions restricting access to contraceptives and even outlawing abortion even for rape. HIV testing, treatment and counseling should also be offered. Information related to sexual and reproductive health should be made available and easily accessible.

Since education and counseling is a vital aspect of public health, raising awareness about common sexual and reproductive health problems, how to seek healthcare services and available financial assistance through circulation of information packages can increase effectiveness of current health policies. Programs should be developed to support improvements in the socio-economic conditions of migrant women and girls. This can be done by providing them with educational opportunities, vocational training and taking steps to eventually integrate them into the workforce.

The Plight of Undocumented Migrants (UMs)

Indeed, one of the biggest challenges of the migrant crisis has its roots in the complex heterogeneity that arises from factors such as age, gender, socio-economic background and legal status. Particularly evident is the disparity in the healthcare offered to migrants based on their legal status. Where refugees may be entitled for certain free health services in a country, asylum seekers may not. UMs (Undocumented migrants) are a group of migrants who often have had a restricted access to healthcare, and whose rights are often overlooked. Data on UMs and their health challenges is scarce, as most studies are directed towards care-seeking migrants. UMs face both formal and informal barriers to health, like social and language barriers, poor understanding of the healthcare system, fear of getting reported to the police and downrightly being refused treatment at healthcare institutions.

However, the ethical argument for providing healthcare to UMs is rooted into the humanitarian notion of “right to healthcare” regardless of one’s social, economic, religious, legal or political background. One of the biggest challenges for any country is reaching out to its UMs. Only 50% of the UMs in a study from Netherlands were found to know how to get access to medical care if in need [18]. With continuously harshening immigration policies, UMs feel threatened and do their best to avoid any contact with official authorities, including healthcare providers. UMs must be educated about the country’s healthcare system, what services are available to them, how and when to access them.

Although, no country wishes to be portrayed as an attractive goal for illegal migration, steps must be taken to ensure proper access to healthcare services for UMs. Looking at the variation in the implementation of healthcare rights of UMs, there is a need for standardization of guidelines and protocols. Otherwise, migrants’ access to healthcare will continue depending on the healthcare staff’s personal persuasions and personal interpretations of the ethical code. It has also been suggested that, with reference to the international healthcare law, access to healthcare should not be intertwined with an individual’s immigration status. Therefore, as WHO recommends, all refugees and migrants must have “full, uninterrupted access to a hospitable environment and, when needed, to high-quality health care, without discrimination on the basis of gender, age, religion, nationality or race.”

Migrant Crises: Political and Institutional Contributions and Responsibility

While some countries like Canada have opened their doors to migrants of all types, others have become more restrictive by limiting the inflow of migrants, increasing deportations and going even further by blocking relief efforts of other entities, including NGOs. The United States’ recent suspension of its refugee program at the start of the Trump presidency augurs ill for the health and wellbeing of disadvantaged migrants seeking a safe haven in the United States for at least the next four years.

It is high time global leaders work together in tackling the issue of migrant health, which is of worldwide interest. There is a dire need for global cooperation, now more than ever, to deal with the financial, social, legal and political implications of migration and challenges of migrant health. With the development of cost-sharing mechanisms, financial burdens can be evenly distributed amongst countries. Steps should be taken to rectify uncertainty revolving

around the legal status of migrants in several countries, and what healthcare services they are entitled to. It is also necessary that global leaders voice the urgent need for local societies to support migrants in all possible ways, reiterating the importance of the contributions migrants have made to their societies. Prominent social figures, like politicians, sportspeople and athletes, and figures from the music and movie industries should speak up about the issue of migration, migrant health and the rights of migrants. These actions can help deal with the current fear and anti-migrant sentiments prevalent in the general public.

In addition, coordinated collaborations between governments and international as well as domestic NGOs in the countries of origin and host countries are essential. This will facilitate the development of an integrated approach towards migrant health where the concerns of all parties involved are taken into consideration. The development of innovative healthcare that better accommodates the needs and goals of migrants can be facilitated through an extensive and coordinated collection of data on the most prevalent health challenges, current health status of the migrant population as well as other health determinants related to legal and socioeconomic factors. With a better understanding of migrant health challenges, healthcare providers can be trained through international partnership agreements to achieve desired healthcare outcomes efficiently and effectively.

The Role of Technology in Improving Healthcare Access and Delivery

Advancements in technology are driving a massive reform in the operational structure and organization of the healthcare industry. Technology can be the determining factor for migrant health and creating greater equity in the near future. As human lives are becoming more “electronic” and “internet-based,” hospitals and other healthcare-providing institutions have kept up by providing “e-services” to their customers. From checking prescribed medications to viewing MRI and X-ray results, those services can be accessed over the internet through web browsers and mobile phone applications.

Undoubtedly, telehealth is an area that should be actively integrated into the migrant healthcare system. It can help address cultural, social and geographical barriers that migrants face. Development of an electronic network for migrants would facilitate their access to healthcare services. Health and healthcare-related information in the form of guidelines, recommendations, reminders and protocols could be electronically delivered to migrants, cutting down the costs of printing brochures, pamphlets and booklets, and the workforce needed to distribute them.

It is worth mentioning that iamsick.ca has set an example in developing more intelligent telehealth. It is an innovative project that aims to develop health technology platforms that helps patients’ accessibility to find the healthcare services they are looking for. Users can search for doctors and other services like pharmacies and diagnostic labs near them. What is unique about iamsick.ca is that users can search for doctors who speak their language. This feature is especially valuable for those who don’t speak the local language and are facing social and cultural barriers in accessing healthcare. Migrants very often find themselves in similar situations, and technologies like iamsick.ca can immensely help them with their healthcare needs. Similar platforms could also assist healthcare providers with dealing with migrants and providing the best possible care.

Furthermore, many electronic applications and platforms have been designed to improve doctor-patient interaction, without the need of the physical presence of the doctor with the patient, by providing a safe channel of communication that allows sharing voice, picture, video and text notes to describe the medical problem to the physician allowing him/her to reply with proper medical management. These kinds of apps can be further utilized to overcome the lack of highly specialized doctors in complex situations.

Moreover, a sensible solution for the huge language barrier between migrants and healthcare providers is applications that help in the translation of health complaints and questions such as “AOK HealthNavigator” and “refugeespeaker.” Apps like these can provide efficient language assistance to patients in the absence of professional translators.

Medical record tracking apps such as Microsoft HealthVault, are electronic services that allow users to keep their medical records safe and up-to-date, and share them securely with healthcare professionals and people they trust. Having been around for a few years, these electronic services have a dedicated following, including people with chronic conditions who need to track daily health metrics, such as blood pressure, glucose, and oxygen saturation.

Electronic apps also can help in screening for medical problems, either through self-screening tests such as the ones for depression, or through scheduling screening, or even for screening conducted by authorities to detect serious illnesses requiring urgent intervention.

Disclaimer: The authors are not affiliated with any of the mentioned applications above in any way, nor are they being compensated by any of them)

CONCLUSION

With the international growth of the phenomenon of migration, migrant health challenges are gaining global significance in public health. Given that migrants are a diverse group from varied cultural and socio-economic backgrounds, as well as having different legal status, it has been observed that migrants’ health situations can be severely compromised by a wide range of health-determining factors at the country of origin, in the host countries, and during travel. These compromises range from accidental injuries, infections, to serious chronic medical conditions.

Alongside early detection, treatment, and relevant preventative measures, we recommend ensuring the quality of other health-determining factors such as food, water and living conditions, thereby reducing migrants’ vulnerability towards more complex diseases. This approach is also cost-effective in the long run, as it reduces incidence of more complicated diseases and thus reducing the burden on emergency care, which is substantially costlier than primary health care.

The current emphasis of health care provided to migrants is being put on making healthcare as widely accessible as possible. However, this should not deviate the attention from devising health policies and programs that provide an efficient access to primary health care of an acceptable quality to all migrants in the host countries. In order to do that, all challenges for health care access should be dealt with effectively.

We recommend studying the current screening programs in addition to possible strategies that facilitate migrant access to a full range of healthcare services, as well as development of

treatment and vaccination programs. Moreover, we recommend a special focus on health education and awareness programs as well as orienting migrants to the host country's healthcare system, while providing them with all that they need to overcome the potential barriers for health care accessibility. Also we highlight the significance of health impact assessments for migrants globally in order to improve fairness and justice in healthcare delivery.

Furthermore, major concerns for migrant health such as mental health, should be dealt with carefully as there is an increased susceptibility of all migrants to have psychological problems, due to the unfortunate situations and stress they accumulate throughout their journey and residence in the host countries. Along with the typical solutions we highlight the role of the ethno-cultural community and religious institutions in the migrants' adaptation to their new lives and integration into their new society, by assisting them in dealing with personal, social, financial, educational and legal challenges.

Special care should also be given to a potentially vulnerable group in most migrant communities - women. This should be mainly through education, counseling and psychological support, keeping in mind that they are susceptible to poverty, sexual violence and further forms of marginalization. We believe that the utilization of innovative and creative solutions such as telehealth should be actively integrated into the migrant healthcare system, which would allow us to improve accessibility, outreach, and communication between migrants and health care providers. On a political level, closer coordination between NGOs and governments is needed.

In conclusion, it is clear that the lack of a personalized equitable system of healthcare has been responsible for compounding the health crisis among migrant populations. It is only through education, counselling and outreach efforts that these disadvantaged people can be helped. The key lies in setting up uniform medical guidelines and determining what basic medical facilities should be available to migrants irrespective of their status and to simultaneously train medical professionals to effectively respond to migrant health problems. Undoubtedly governments, humanitarian organizations and medical professionals will have to work together and develop methods for collecting data on the challenges faced by these migrants in order to facilitate the development of effective healthcare policies and systems addressing their health problems.

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Chapter 517

NONVERBAL COMMUNICATION BETWEEN FINNISH AUTHORITIES IN ANIMAL DISEASE EMERGENCY EXERCISE AND IN PUBLIC HEALTH BORDER CONTROL MEASURES

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ABSTRACT

In Finland, contingency planning has been implemented among veterinary and public health authorities. Contingency plans have been developed for foot-and-mouth-disease, classical swine fever, Newcastle disease and zoonotic (transmissible between humans and animals) avian influenza as well as for other easily spreading animal diseases (African swine fever, Bluetongue, epizootic haematopoietic necrosis, infectious salmon anemia, viral haemorrhagic septicaemic, infectious haematopoietic necrosis). Detailed manuals of operations have been established by the Finnish Food Safety Authority Evira and the Regional State Administrative Agencies and emergency exercises have been organized for a real emergency situation. Alongside with continuous disease control, authorities have together organized additional random controls at the borders of Finland because Finland is free of dangerous animal diseases such as zoonotic rabies and echinococcosis (*Echinococcus multilocularis*), which are found in Finland's neighboring countries.

Those animal diseases, which must be reported immediately to the veterinary authorities have been listed in the animal disease legislation. Act on animal diseases 441/2013 stipulates that if the owner or keeper of an animal, butcher or anyone with contact on animals or a veterinarian other than the municipal veterinarian, suspects an outbreak of an animal disease that is notifiable according to animal disease legislation, he or she must report this to the municipal veterinarian or, failing this, to the regional veterinary officer. The municipal veterinary officer must report further to the regional veterinary officer, who reports the suspected outbreak to the Finnish Food Safety

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Authority Evira. In case of real disease outbreak, Evira as the central competent authority can request further resources from other services (police, rescue teams, fire brigade and veterinary students). These procedures are, however, strategic procedures written in legislative level far from the level of operations and real activity. For example, the flow of information between authorities can be better organized. Thus, in the context of communication studies, the aim of the current study is to clarify the nature of interaction between different authorities.

The main question of this study was what kind of nonverbal interaction can be revealed from interaction situations between a) veterinary authorities in emergency exercise, b) veterinary authorities in additional random controls at the borders. As a research material, media pictures from Google search engine were used and these pictures were analyzed by using nonverbal communication research method. Following the Google search with well-known three controls at the borders in 2016 and African swine fever emergency exercise in 2014 four pictures about communication situations were collected. Common background context and discourses of responsibility, control and fear were constructed. Between authorities, working in a focused manner with minimal facial expressions and gestures was mainly seen. The authorities looked at important documents rather than to each other. They were seriously involved. Cultural differences in organizations must be, however, included in a final conclusion. Different contexts in multi-organizational interaction should be respected and utilization of nonverbal communication studies should be expanded over the veterinary context.

Keywords: authorities, contingency planning, disease control, emergency exercise, public health, zoonotic

INTRODUCTION

In Finland, several authorities have prepared for outbreaks of animal diseases. Both the Finnish central authority, the Finnish Food Safety Authority Evira and the Regional State Administrative Agencies have their own contingency plans, which, along with other public health contingency plans, are part of strategic public health documents. Their goal is to protect the population against diseases, which can be zoonotic (transmissible between humans and animals) or which may result losses to domestic livestock production. In Europe, authorities are well prepared for outbreaks of avian influenza (Pittman & Laddomada, 2008). Intergovernmental organization World Organization of Animal Health (OIE) organizes international emergency exercises against avian influenza but also against most important animal diseases. In Finland, contingency plans against foot-and-mouth-disease, classical swine fever, African swine fever, Newcastle disease, avian influenza, Bluetongue and some fish diseases (epizootic haematopoietic necrosis, infectious salmon anemia, viral haemorrhagic septicaemia, infectious haematopoietic necrosis) are established. All of those diseases are combated by nature in the Finnish law on animal diseases.

As a part of their normal control and monitoring of animal diseases the Finnish Food Safety Authority Evira and the Regional State Administrative Agencies organizes national emergency exercises, in which veterinary authorities can participate in a simulation of a real disease outbreak and exercise the interaction between authorities. During the simulation, they can experience a legal definition of flow of information, which must immediately flow from a municipal veterinarian to a regional veterinary officer or to the Finnish Food Safety

Authority, or from the regional veterinary officer to the Finnish Food Safety Authority. In regional level, in addition to regular exercises in the Regional State Administrative Agencies between veterinary authorities, some random controls at the borders of Finland are organized. They are organized between veterinary and other authorities (customs) and these controls' goal is to prevent the spreading of foreign diseases (rabies and *Echinococcus multilocularis*) from neighboring countries Estonia and Sweden to Finland.

Strategic procedures written in legislation or contingency or preparedness plan are not same as the real operations in the field. Although preparation in European Union countries is at a good level in some parts of preparedness plans such as surveillance, planning, coordination and communication, maintenance of essential services, putting plans into action and public health interventions are inadequate (Mounier-Jack & Coker, 2006). It has been shown in some international health crisis - origin of animal diseases - that authorities are slow to respond or have no response at all, maybe, because of inadequate information flow between authorities (Uhlenhopp et al., 2004). The authorities may comply with different laws and orders (Amarasekara, 2007; Koskinen, 2012) and thus, work in different contexts. In emergency, different authorities work in the same field and they should play a same game. They should improve and know their roles and responsibilities (Bar-Yaacov, 2008) and their chain of command from authority to authority within and over the administrative borders (Jebara, 2004). In Bourdieu's words (1971, p. 161), they should be agents in objective social relations like players in the field.

Authorities are located in subfields defined by their different administrative levels. In these subfields, players have different forms of material and symbolic power (Bourdieu 1971, 1988). One critical point is competitiveness between sectors, services, professions and persons as well as different administrative locations (Busani et al., 2006). Different subfields create different contexts and different functionalist language use, discourses, which means that subfields have unequal (linguistic) power. It is, then, the network of objective relations between (linguistic, symbolic) positions - the field itself - that subtends and orients the strategies of authorities in a practical level (Bourdieu & Wacquant, 1992, p. 16). Meaning of action arises from interaction. It is interaction between "me" and "those other people" and it is transmitted by symbols (Mead, 1932, 1967). It can be linguistic interaction with symbolic characters of language or nonverbal communication with cultural gestures and facial expressions full of symbolic meaning (Mead, 1932). Interaction can also be participation in social environment, which is full of roles, norms and models of appropriate behavior (Bandura, 1986, p. 47, 49-50).

The study of discourse is usually confined to speech and writing (Parker, 1999, p. 1). However, some researchers go beyond of that kind of discourse analysis towards wider range of texts (Allbutt, Gray, & Schofield 1999; Durmaz, 1999; Russell, 1999). In these analyses, symbolic systems (visual media with visual text and physical settings) that are not usually thought of as textual are involved (Parker, 1999, p. 1). Nonverbal gestures, facial expressions, body positions, gazes, tone of voice, dressing and physical space are all involved because the word "text" can be any interaction unit full of meaning (Kress, 1995; Parker, 1999, pp. 3-4). Nonverbal behavior means dynamic and context-specific body information with high communicative potential (Burgoon et al., 2000; Guerrero & Floyd, 2006). Nonverbal cues may be important part of the verbal accounting process (Birdwhistell, 1970) and they are usually categorized by linguistic-like structural organization. Such a categorization, like well-known Bales' Interaction Process Analysis (1951) with its categorization of both verbal and

nonverbal acts, however, is questionable for the study of nonverbal discourse because of its pre-specified, ill-defined and discrete verbal categories (West & Zimmerman, 1982).

Regardless of the nature of communication - verbal or nonverbal - it is an activity and action of people. Theoretically, activity, action and operation can be defined at various levels (Elliot, 2007, p. 37). Activity describes the ability or capacity of an individual whereas action means concrete, practical doing. Operation is a larger and upper level of communication, which includes different forms of communication and interaction between actors. It is usually this operational level with which researchers are dealing when real action have been studied. Some previous examples from verbal and nonverbal studies at this operational level come from higher education field (Fahy, 2005; Hancock, 2004; Koskinen, 2010, 2011; Koskinen & Snellman, 2011). One study has been concentrated on nonverbal style in public and civic settings in Finland (Wilkins, 2005). In current study, the aim was to describe how social reality of Finnish authorities was constructed at operational level. It was realized that social phenomena are not the same across different situations with different times and thus, it was investigated what kind of nonverbal interaction was revealed in different co-operative situations. The aim was to describe the manner in which these situations were similar to each other and, respectively, how they differ from each other.

METHODOLOGY

In the context of Finnish circumstances and interaction between Finnish authorities, qualitative case study design was utilized. Four well-known cases were included: one was a veterinary emergency exercise (African swine fever 2014) and three were random border controls in 2016 in Finland (cities of Turku, Helsinki and Tornio). Rigorous qualitative case studies give researchers opportunities to investigate or describe phenomenon in context using a variety of data sources (Baxter & Jack, 2008). In this study, visual texts, media pictures, were used as research material. These four pictures were searched from internet by Google search engine by using Finnish words (with their English translations in parenthesis) 1) "aluehallintovirasto (Regional State Administrative Agency) tullit (Customs), Elintarviketurvallisuusvirasto Evira (the Finnish Food Safety Authority Evira)," 2) "Länsisatama (West Harbour) tehovalvonta (power control) aluehallintovirasto (Regional State Administrative Agency)," 3) "Länsiraja (West border)," 4) "eläintauti (animal disease) leviäminen (distribution) estäminen (inhibition)." Final data sources consisted of internet-based media pictures from rural newspaper *Future of the countryside* (Maaseudun Tulevaisuus in Finnish), *Evening Journal* (Iltalehti in Finnish), a national daily newspaper, *Helsingin Sanomat*, and news channel Yle (Finnish news channel of public areas). In addition to different media sources, also different authorities in different media texts were introduced.

In case study design, interpretative paradigm can be preferred over traditional (normative) organizational research paradigm (Fitzgerald & Dopson, 2009). This framework was taken seriously when the media pictures from the life of organization and authorities were analyzed. Instead of measurement of frequencies of events and their consequences, the storytelling perspective was assumed. These pictures can tell a story, which means that they are texts full of meaning. They have discourses of their own. The reality is constructed in social networks in social interactions of everyday life (Berger & Luckman, 1966). In this

study design, it signified a relationship between a photographer and a reader. In the framework of social constructionism, a researcher can interpret these stories and discourses, and construct of reality behind a frame.

For the nonverbal communication analysis of pictures of cases in every case-based context, one nonverbal communication research method was adopted. It was adopted because the author was familiar with this method due to one previous study. The method was based on the action-coding sheet of Burgoon (2005) and Guerrero (2005), which is illustrated in Table 1.

Table 1. Coding sheet of nonverbal behavior (Burgoon, 2005; Guerrero, 2005)

The target		
never look at the partner	1 2 3 4 5 6 7	always look at the partner
exhibited unsteady gaze	1 2 3 4 5 6 7	exhibited steady gaze
gave no eye contact	1 2 3 4 5 6 7	gave constant eye contact
Based on your observation of the target's face, the target		
never smiled	1 2 3 4 5 6 7	always smiled
was facially pleasant	1 2 3 4 5 6 7	was facially unpleasant
smiled a little	1 2 3 4 5 6 7	smiled a lot
conveyed negative affect	1 2 3 4 5 6 7	conveyed positive affect
leaned away from the partner	1 2 3 4 5 6 7	leaned toward to the partner
faced away from the partner	1 2 3 4 5 6 7	faced toward to the partner
sat in a side-by-side position	1 2 3 4 5 6 7	sat in a face-to-face position
leaned back a lot	1 2 3 4 5 6 7	leaned foreword a lot
The distance between bodies was far	1 2 3 4 5 6 7	The distance between bodies was close
The distance between faces was far	1 2 3 4 5 6 7	The distance between faces was close
The target showed		
very little facial expression	1 2 3 4 5 6 7	a lot of facial expression
lots of nervous movement	1 2 3 4 5 6 7	very little nervous movement
frequent rocking or twisting	1 2 3 4 5 6 7	infrequent rocking or twisting
little gesturing	1 2 3 4 5 6 7	a lot of gesturing
little kinesic expression	1 2 3 4 5 6 7	a lot of kinesic expression
a lot of trunk/limb movement	1 2 3 4 5 6 7	very little trunk/limb movement
Based on his/her nonverbal behavior, the target seemed		
anxious	1 2 3 4 5 6 7	calm
inattentive	1 2 3 4 5 6 7	attentive
distracted	1 2 3 4 5 6 7	focused
unalert	1 2 3 4 5 6 7	alert
restless	1 2 3 4 5 6 7	still
flustered	1 2 3 4 5 6 7	composed
bored	1 2 3 4 5 6 7	interested
detached	1 2 3 4 5 6 7	involved
Overall, the target's body position was		
tense	1 2 3 4 5 6 7	relaxed
closed	1 2 3 4 5 6 7	open
rigid	1 2 3 4 5 6 7	loose

Contrast to the original coding sheet and because of the nature of research material, the evaluation of target's voice and speech were neglected and the characterization of conversation was excluded. Action was evaluated by coding sheet numbers (1-7) in such a way that neutral action was coded by numbers 3-5. If, for example, participant always looked at the partner, it was coded by number 7, but if he or she looked at the partner sometimes, it was coded by numbers which were closer to the other end of the scale. By the list of these

nonverbal actions four behavior patterns were reached: 1) physical closeness with the actual distance between people, 2) lean; the degree to which a person's upper trunk is tilted toward or away from the other person, 3) gaze and facing, and 4) body orientation.

Repeatability and reliability of the coding was ensured by double coding technique. During the analyzing process, all pictures were analyzed twice. Both analyses was a responsibility of the author and it was carried out so that there were break of two weeks between coding times. All findings from 30 domains of coding sheet (never look at the partner - always look at the partner, exhibited unsteady gaze - exhibited steady gaze, etc.) were compared in the framework of agreement or disagreement and the percentages of agreement in different coding times were calculated. Thus, repeatability between different coding times can be compared and reliability of the one-coder analysis can be seriously evaluated.

FINDINGS

Over the three border control situations, the authorities had focused on their role and task rather than a media representative who had illustrated them. They had really involved in the inspection and leaned toward to their target (a dog), except when the target was not in the picture. They stood close together when the target was missing and when they compared their notes, but then they looked at each others' papers, not each others' eyes. When the target was in the picture, the distance between authorities was greater and the authorities gave no eye contact with each other. In general, they never smiled and had a little kinesic expression or trunk or limb movement. The authorities appeared calm, attentive and interested. Facially they had neutral expression.

Differences between the contexts were seen when the number of participants increased. There were no smile between two or three persons, but not between four persons either. On the other hand, the participants seemed a little tense and rigid when they all (four persons) stood side by side and had a steady gaze towards the papers that one of them introduced. They stood in a face-to-face position. The situation looked like that only one of the persons spoke and the others listened. They were not anxious, but calm. However, they had focused on their future role and some of them were alert a little.

The authorities had focused on their task during the emergency exercise. In selected picture, two persons were involved and suitably equipped. These persons stood on both sides of a pig, not side by side and they gave no eye contact between each other. Instead, main actor of them looked towards a camera rather than a partner or an animal, which was interpreted as a little lack of interest and concentration on the task. None of the participants had trunk or limb movement towards each other, but the main actor showed limb movements towards an animal. The face and gaze of another person were missing, but the face of the main actor was seen. Based on the observation of this person's face, the person never smiled, was facially unpleasant and conveyed negative affect on the situation.

The person (main actor) showed facial expression only a little and had no nervous movements, but he expressed some signs of anxious and tense attitude on his face. He was inattentive rather than attentive towards the pig, although he tried to concentrate on his role as a person, who had a responsibility of ongoing and unfinished operation. The role of the other

person was the role of an assistant (keep the pig's trunk without movements) and he or she stood in a neutral position close to the pig and the main actor. He or she stood straight, with no lean backward or foreword and without rocking and twisting.

From the perspective of reliability, agreement between two different coding times in border control pictures varied from 73% to 80% according to the picture. Meanwhile, among authorities, repeated references of same nonverbal features in different border control pictures were realized. All pictures were parts of the larger picture of nonverbal behavior of the authorities in Finnish border control context. In this working context, placing the pictures side by side, it seemed that authorities, who stood side by side and listened to each other in one picture, could be calm and focused on the task in the second picture. On the other hand, when the authorities were attentive, involved and interested in their task in one picture, they could also be attentive and focused in the following picture in which common discussion between authorities was established. When the time passed, continuum between the pictures developed and the story about interaction between authorities was completed. The pictures had intertextual relationship with their reflection of deep concentration of greater goal, which was outside the pictures.

The agreement range from 70% to 80% was revealed when all four pictures were involved. In particular, differences in the evaluation of alert or unalert behavior was found in three pictures from border control situations. Moreover, the direction and the firmness of a gaze was difficult to determine in the same uniform way across all the pictures. Nevertheless, authorities in all pictures worked under visible and invisible expectations of responsibility. They had to work under the discourse of responsibility with tight focus on the task, not other people. This was actually seen by the lack of eye contact, by neutral or even unpleasant facially expressions and by little rigid and tense standing positions. The authorities took their duties and responsibilities seriously without smile and closer relationships. This was close to second discourse, which was constructed, discourse of control. The authorities were calm and showed no nervous movements, and thus, gave a message with full control of situation. Because in some situations, however, they behaved oppositely a little, the third discourse, the discourse of fear should not have been ignored. This fear came from the background context, the professional knowledge of animal diseases (rabies and echinococcosis) and their consequences for human life.

CONCLUSION

Through the analysis of all pictures, these authorities took their role seriously. They had shared roles in emergency exercise and in border control situations. They knew the important role of the exercise and border controls and thus, were focused on the task. They were, however, veterinary authorities, who should know their role in these situations. In contrast to previous reports (Amarasekara, 2007; Koskinen, 2012), they comply with same laws and orders. It is not said that the agreement between authorities would have been the same if authorities from different organizations (police, rescue teams, etc.) involved. Each organization has its own culture and own perspectives in its own context. Thus, the description of nonverbal communication between authorities should be cautiously extrapolated to other situations with other authorities or multi-organizational situations.

The analysis revealed a continuum between the pictures when they were placed side by side despite the fact that there were different authorities in different pictures. The pictures could look like a continuum because they had a common background, which provides an important relationship between pictures. This relationship rises from common animal disease context and for example, upon this context the discourse of fear was constructed. Authorities in this study worked in same animal disease context and in further analysis, this context should be deeply involved. In case study designs, in general, also a meaning of context is respected (Baxter & Jack, 2008; Fritzgerald & Dopson, 2009). Conditions outside the pictures can mean strategic goals with fight against animal diseases and in the future, the pictures can be analyzed towards these goals.

Qualitative case study becomes a valuable method for health science research to develop theory, evaluate programs, develop interventions and study complex phenomena within their contexts (Baxter & Jack, 2008). This study gave a preliminary theory framework from veterinary perspective and provided an opportunity for an evaluation of the coding sheet of nonverbal behavior. Because of special nonverbal style (matter of fact, concentrated attitude and face with straight state) in public and civic settings in Finland emphasized by Wilkins (2005), and special nonverbal features of communication focused by coding sheet (smiling, rocking or twisting, kinesic expression) not typical for Finnish authoritative agents, some cultural differences between the sheet and the target were found. It is a question of the validity of this coding sheet. Based on the previous nonverbal analysis among university students and their teachers (Koskinen, 2011), more positive and diverse nonverbal communication would have been expected. Around cases of communication between authorities, one context was represented and this context was not overlapped with educational context. On the other hand, analysis of nonverbal communication of authorities in emergency exercise and in border control situations reflected the previous description of Finnish nonverbal style in public and civic settings in general, and thus, increases the reliability of current findings.

In this study, well-known risk of qualitative research design, subjectivity, could not be totally avoided. Based on these relative low percentages of different coding times there is no guarantee of good repeatability among different coders. On the other hand, facial expressions and some gestures are universal and globally understood. They are texts with full of meaning and they can explored by general categorized standards. Nonverbal behavior is dynamic and context-specific body information with high communicative potential (Burgoon et al., 2000; Guerrero & Floyd, 2006) all over the world. Its (symbolic) meaning among organization researchers is underestimated. The efficiency of information flow, for example, may be improved by paying attention to the ways through which this information is shared. In some situations, nonverbal communication is useful. Then it would be interesting to know when nonverbal communication can enhance co-operation and collaboration between authorities. Accordingly, it would be essential to know, when it will prevent co-operation intentions.

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Chapter 518

AN EXAMPLE OF INTEGRATION OF PALLIATIVE CARE SERVICE IN AFRICA'S HEALTHCARE SYSTEM: STRENGTHENING INTERVENTION AT KIBAGABAGA HOSPITAL IN RWANDA'S PUBLIC HEALTH SYSTEM

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ABSTRACT

Palliative care and end-of-life management is rarely integrated into the public health system in developing countries. 22 years after the genocide, Rwanda has rebuilt its society, including the health sector, devastated during this dark history. In April 2011, the Rwanda Ministry of Health launched its National Palliative Care Policy committing the country to providing high-quality, affordable palliative care services for all people with incurable illness by 2020.

Rwanda became the first country in Africa to adopt a stand-alone policy, strategic plan, and implementation process. Kibagabaga District Hospital began palliative care services for children and adults in 2009 and 2010, respectively. The district integrated the

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program across the continuum of care, from the hospital to the community, and set up a Rwandan model of palliative care.

Keywords: Kibagabaga Hospital, Rwanda genocide, palliative care in Africa, public health, morphine

INTRODUCTION

In Rwanda, with 3% HIV prevalence in the general population, 200,000 persons were estimated to live with HIV in 2010 [1]. According to the Treat the Pain, an international program of the American Cancer Society, of the 10,681 Rwandans who died of HIV/AIDS or cancer between 2012-2013, 7,195 (67%) died with moderate or severe pain; reasons included a lack of education/training in palliative care and pain management, limited opioid availability, and burdensome regulation that restricted opioid access [2]. It is clear why palliative care services are necessary. Current palliative care availability in Sub-Saharan Africa is limited and the quality is uneven [3, 4].

This chapter will share the experience at Kibagabaga Hospital, a Rwanda District Hospital, in pioneering palliative care services, as well as the complexity of providing palliative care in a post-genocide society.

PALLIATIVE CARE IN RWANDA

Rwanda is a small landlocked country in Central East Africa with a population of almost twelve million. With a beautiful green landscape, called “the country of a thousand hills” (*Pays des Mille Collines*), it is bordered by the Democratic Republic of Congo to the West, Uganda to the North, Tanzania to the East, and Burundi to the South. Rwanda rose from the ashes of the 1994 genocide to articulate a program of equity-oriented national policies. The launch of *Vision 2020*, a national development plan, set an ambitious health agenda. This was especially resonant as the genocide had “robbed [the nation] of a generation of trained teachers, doctors, public servants, and private entrepreneurs” [5] and had destroyed the health infrastructure. The genocide legacy also included crippling disabilities, war crime rape-transmitted HIV infection, chronic illnesses, and a high prevalence of post-traumatic stress disorder [6].

The Rwandan constitution of 2003 codified health as a right and charged the State with its promotion and implementation [7]. Rebuilding the public health sector centered on strengthening primary care and expanding health services with a variety of development partners, emphasizing access and accountability [8]. A community-based health insurance, *Mutuelle de Santé*, was scaled up nationally in 2005. With a high burden of HIV/AIDS, there was great need for diagnosis and antiretroviral treatment as well palliative care, which was characterized as an “urgent public health problem” [9]. In 2004, the Minister of Health sent a team to Uganda, the first African country to make palliative care a priority [10], to study its palliative care program.

In 2005 the Rwanda Ministry of Health presented a three-day workshop in palliative care in collaboration with partners: the Society of Women Against AIDS, Help the Hospices UK, the African Palliative Care Association, the Rwanda Palliative Care Association, the United States President's Emergency Plan for AIDS Relief (PEPFAR), Partners in Health, IntraHealth International, and Mildmay International. In 2008 the Rwandan Ministry of Health, with IntraHealth and Mildmay, introduced the first "train the trainers" curriculum in four district hospitals (Kibagabaga, Byumba, Rutongo and Nyagatare) to incorporate palliative care principles into the treatment of patients with HIV/AIDS and cancer. Evaluation of this pilot project demonstrated that Kibagabaga Hospital had successfully integrated palliative care as an administrative and clinical priority, opening a palliative care ward for children in 2009 and for adults in 2010. It was thus chosen as a model for duplication in other district hospitals.

In January, 2011, the Rwanda Ministry of Health officially launched its National Palliative Care Policy, committing the country to the provision of high-quality, affordable palliative care services to all people living with incurable illness by 2020 [11]. In 2012, a new Rwanda narcotic control law was enacted, allowing morphine and other opioids to be prescribed as indicated for pain management across all health facilities and in home-based care [12].

Implementation steps continued in collaboration with a number of development and educational partners:

- 2011: The medical director of Kibagabaga Hospital was sponsored to attend the Harvard Medical School Palliative Care Education and Practice program and advise on the implementation of palliative care on a national level
- 2012: The United Kingdom Department for International Development began a three-year project through the Tropical Health Education Trust's (THET) Health Partnerships Multi-country Partnership Scheme to support palliative care integration into national health systems in four African countries (Kenya, Rwanda, Uganda and Zambia)
- An additional physician and two nurses from Kibagabaga Hospital were sponsored to attend a diploma course in palliative care at Hospice Uganda
- The Rwanda Ministry of Health sponsored a national ten-day "train the trainers" palliative care course for multidisciplinary teams (physician, nurse, social worker, psychologist) from all district, teaching, and referral hospitals
- The Butaro Cancer Center of Excellence opened in the Burera district of Northern Province, the first such facility in rural East Africa. Key partners, brought together by the Clinton Global Initiative, included the Rwanda Ministry of Health, Partners in Health, Dana-Farber Cancer Institute, Brigham and Women's Hospital, Boston Children's Hospital, and the Jeff Gordon Children's Foundation
- 2014: The Kibagabaga Hospital medical director, in an exchange experience between low/middle income and high income countries, was sponsored during educational leave as a visiting fellow at St. Christopher's Hospice in London and Mary Stevens Hospice in Birmingham, England. This afforded the opportunity to observe best practices in established systems (procedures, protocols, guidelines), learn from

visiting international colleagues (public policy, advocacy, challenges), and join in a reciprocal exchange of culture and experience

- 2014-2015: The Kibagabaga Hospital medical director, on educational leave, and the director of the pharmaceutical supply chain of the Rwanda Biomedical Center (the implementation arm of the Ministry of Health) participated in the African Pain Policy Fellowship of the Pain Policy Study Group at University of Wisconsin. They reviewed Rwanda's regulation of opioids and made recommendations to the Ministry of Health and Rwanda Biomedical Center to increase availability and accessibility of morphine at the national level. This fellowship also gave experience in framing pain management as a public health issue. As a result, the Ministry of Health increased the availability and formulations of morphine, including developing a national production facility to reconstitute morphine powder into 5mg/5ml solution.

POST-GENOCIDE CONSIDERATIONS

Despite remarkable steps toward recovery, Rwanda remains deeply affected by the 1994 genocide which took the lives of more than one million people in one hundred days and created millions of refugees. Providing palliative care in a post-genocide society requires a strong commitment to humanity in addition to clinical knowledge and skills. The context of this dark and complex humanitarian crisis is complicated to define. It has been important to consider the impact of genocide on both patients and health care providers to develop an approach that will benefit all parties. We regularly learn more from our patients and their families than we teach them, and we must care for them beyond treatments, procedures, and protocols.

The Rwandan culture values stoicism; the expression of feelings and emotions may be seen as weakness. Pain may be seen as an important sign of vitality, of manliness in particular. In addition, physical pain may be deemed trivial or banal compared to the genocide losses suffered by the patient and family. The Kibagabaga Hospital wards are filled with survivors' stories which minimize present pain in comparison to the genocide. Conversely, for some persons a new illness or pain may resurrect genocide loss and amplify suffering.

The Kibagabaga Hospital palliative care team learned that there is an important difference between genocide survivors with a life-limiting illness compared with patients who did not go through that traumatic crisis. We have observed that the survivor always sees the genocide experience as a contributing factor to the current illness. The treatment team must understand that dealing with that history matters as much or sometimes more than standard medical treatment. The psychological context of illness is complicated by survivorship, as the genocide experience adds to the existential distress of a serious or terminal diagnosis. A patient will ask, "Why did I survive the genocide to die from cancer?"

The annual genocide commemoration period provides an example of the complexity of providing palliative care to genocide survivors. Every year, from April to June, the people of Rwanda, from villagers to top officials, commemorate the genocide. This is a period to remember and honor loved ones, to promote unity and reconciliation, to educate to prevent genocide ideology, and to celebrate Rwandan resilience and courage in rebuilding the country since 1994. For most of the population it is still difficult to cope.

Our team has observed that a patient's previously managed pain may become uncontrolled during commemoration. An increase in medication would often be ineffective and could risk dangerous sedation. It has been imperative to develop a strong counseling program to anticipate and address this surge in "total pain," the foundational concept articulated by Cicely Saunders, because of the psychological, social, and spiritual suffering evoked by the commemoration experience.

CASE STUDY OF INTEGRATION OF PALLIATIVE CARE AT KIBAGABAGA HOSPITAL

Introduction

Rwanda is divided into five provinces, which are divided into districts. Districts are responsible for coordinating public service delivery. There are five national referral hospitals, 48 district hospitals, and roughly 440 health centers [14].

In each of Rwanda's 14,837 villages, community health workers are elected by their neighbors and trained and equipped by the Ministry of Health to deliver care and link patients to the health care system [8].

Kibagabaga Hospital is a district hospital located in Gasabo, the largest of the three districts of Kigali City, the capital of Rwanda, with 60% of the 1.2 million population. In 2008 Kibagabaga was one of four district hospitals to integrate palliative care principles into the care of patients with HIV/AIDS and cancer, with training supported by the Ministry of Health, IntraHealth International and Mildmay. Adding a palliative care approach aimed to reduce the psychosocial burdens of patients and families during antiretroviral and chemotherapy treatment.

In 2009, Kibagabaga Hospital, supported by Intrahealth/Mildmay, opened the first pediatric palliative care center for children, and in 2010 palliative care was integrated for adult patients. Each program had separate funding sources. At that time, most district hospitals struggled to cope with the needs of patients who had been transferred from the teaching hospital level to district hospitals. Many patients refused to be discharged home because of a lack of services at the health center and community level. Thus some patients spent months or even years in the hospital. In a Kibagabaga Hospital survey, 95% of patients/families cited "pain" and "lack of information" at the community level as the reason they refused discharge.

Challenges

When international development partners concluded funding for palliative care implementation in 2010, the Kibagabaga administration continued to develop the program in the hospital, but with minimal financial support compared to funding for tuberculosis, malaria, and HIV/AIDS treatment.

Our multidisciplinary team committed to three central concepts for our palliative care program:

- Holistic care: give attention to effective pain management, including making morphine available to treat physical pain. Assess “total pain,” addressing psychological, social, and spiritual aspects – a new concept for our setting – as part of daily management of patients and their families.
- Financial discipline: reduce cost by extending palliative care service to the community, eliminating the need for patients to travel to the hospital for prescriptions. Create home-based care services and a community volunteer program.
- Cultural value: learn from our patients; honor patient and family dignity; contribute to restoring the humanity lost during the genocide by incorporating “*Ubuntu*” philosophy, an African concept of interdependence detailed below.

It was also important to identify challenges within the system, such as

- Inadequate pain management knowledge and skill.
- Restricted opioid availability and use: by hospital protocol, morphine was used only for cesarean section postoperative care, was limited to a single 3 or 4 mg dose, and could be ordered only by an anesthesiologist. Prescribing a dose of morphine required multiple signatures (the prescriber, the pharmacy, the anesthesia department, and sometimes the medical director of the hospital) in red ink.
- Limited inpatient capacity: the hospital bed occupancy rate was 120% and average length of stay was six days. Patients with chronic illness were referred from teaching hospitals to the district hospital, where they subsequently refused discharge.
- Lack of outpatient care: there were few discharge resources and communication between the hospital and the community was poor.

Palliative Care through “Ubuntu Philosophy”

Education in palliative care was a cornerstone of change at Kibagabaga Hospital, with internal training of doctors, nurses, social workers, psychologists, and physiotherapists. To sustain our mission in the face of challenges, it was essential to ground our new knowledge and skills in African culture rather than duplicate a Western model. We found inspiration in the *Ubuntu* philosophy expressed in Xhosa, one of South Africa’s eleven official languages, as “*Umntu ngumntu ngabanye abantu*,” “I am what I am because of you” or “a person is a person through other people.”

We recognized that a patient must be understood as a member of society, not as a disease or data point. *Ubuntu* is the “*raison d’être*” of the African context, going beyond an individualistic perspective based on self-interest to a mutual participation grounded in interdependence and humility. It is about “we” not “me.” Through the *Ubuntu* ideal, we embraced our African communal responsibility to support patients and their families with humane dignity.

Another expression of *Ubuntu* says: “Your pain is my pain, my wealth is your wealth, your salvation is my salvation”.

Connecting the clinical concepts of palliative care to this traditional African philosophy supported the program’s acceptance and integration. It also framed our commitment to

palliative care as transforming not just the hospital but our country, restoring the sense of humanity lost during the genocide.

Palliative Care beyond the Hospital Ward

A survey of patients and families revealed that they experienced anxiety, frustration, and stress when they visited the hospital for palliative care consultation. Many claimed this distress was worse than the disease itself. The main cause was difficulty finding our location on the hospital campus, which came from a lack of knowledge about our program among the non-clinical staff. Thus, we organized a three-day “sensitization” workshop that included housekeepers, drivers, cashiers, transporters, gardeners, and security guards, as well as human resources, public relations, and data management personnel. As a result, all hospital employees learned about palliative care, gained a better understanding of the burdens of patients and families, and participated in creating a helpful visitor experience. This resulted in reduced patient/family stress and increased satisfaction for all parties.

In clinical management, the hospital revised its opioid protocol so that morphine could be ordered for moderate to severe pain via a simple prescription by a physician trained in pain management. Morphine use, ordered in only 4% of patients in 2010, increased to 25% of patients in 2012.

To extend our program, we set up a palliative care district network (PCDN) from the hospital to the community. We trained two nurses from each health center in our catchment area in pain assessment, management, triage and supportive care. We also created a curriculum for community health workers to be our eyes and ears in the community, training 481 (one per village) in a one-month period. They were educated to identify the most common symptoms in palliative care (pain, dyspnea, nausea, vomiting, constipation) and report to the health center nurses. The PCDN helped to reduce the flow of patients from the community to the hospital, decreased the burdens of transportation and living at the hospital for family caregivers, transferred competencies to the health center and community level, and involved the community in caring for its members. The Ministry of Health is evaluating the PCDN concept for replication at a national scale.

CONCLUSION

In 2014, the first ever-global resolution on palliative care, World Health Assembly 67.19, called upon the World Health Organization (WHO) member states to improve access to palliative care as a core component of health systems, especially in primary and community-based care [14].

In the past 22 years Rwanda has made remarkable steps towards recovery. The country has rebuilt the national sense of security and stability and invigorated the economy, including the health sector. However, there are still many issues which threaten the development of countries like Rwanda, such as inadequate health infrastructure, lack of access to education, high population growth, a large number of orphans, and the increasing burden of non-communicable diseases.

Even as ambitious plans are implemented, resources remain limited. Patients often have advanced disease at the time of diagnosis, limiting curative options. But care can be given, suffering can be addressed, and all patients with serious illness can benefit from incorporating palliative care into treatment.

The experience of Kibagabaga Hospital demonstrates that it is feasible for hospitals in low and middle-income countries to develop and integrate palliative care services for the benefits of patients, families, and health care providers with a minimal budget. Kibagabaga Hospital has become a center of excellence for palliative care services in Rwanda and as well as an exemplary setting for health care providers and health professions students to learn this comprehensive approach.

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BIOGRAPHICAL SKETCH

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Through his program, more than 1500 health care providers and community health workers have learned the principles of cancer & palliative care leading to a five-fold increase in prescription of morphine, an essential pain medication. Dr. Ntirimira has published on the subjects of palliative care and health systems in notable academic journals, including the

Lancet, the online palliative care resource for health professionals, www.ehospice.com, and in Rwanda's top English daily newspaper, The New Times. Dr. Ntizimira serves on the Rwandan Ministry of Health Non-Communicable Diseases Synergies Group and the National Palliative Care Policy Group. He was a 2013-2015 Palliative Medicine Fellow at the McConnell Heart Health Center Homereach Hospice in Columbus, Ohio, and 2014-2015 African Pain Policy Fellow at the University of Wisconsin-Madison Pain & Policy Studies Group/World Health Organization Collaborating Center on Pain Policy in Palliative Care. Dr. Ntizimira is a Researcher collaborator at Harvard Global Equity Initiative - Lancet Commission on Global Access to Pain Control and Palliative Care (GAPPCP). He is a 2015-2017 African Cancer Leaders Institute Fellow and member of the African Organisation for Research & Training in Cancer (AORTIC). Dr. Ntizimira holds a Doctor of Medicine degree from the National University of Rwanda and received his palliative medicine training at Harvard Medical School.

Chapter 519

RECOGNITION OF INFORMAL LEARNING IN VIRTUAL COMMUNITIES OF PRACTICE: A CASE STUDY OF PUBLIC HEALTH WORKERS

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ABSTRACT

Having identified the lack of a theoretical substrate and research on praxis in informal learning in the Spanish—specifically Catalanian—context as her core research problem, this chapter focuses its attention on a research study conducted in 2012-2014 in order to, among other objectives, propose a system for certifying informal learning in the field of Public Administration.

Five virtual communities of practice (vCoP) from the Public Health Agency of Catalonia were studied. Research was conducted by means of a self-applied online questionnaire with three dimensions represented by seven factors and 61 items, 30 in-depth interviews with 17 questions, and document analysis. Quantitative data was analyzed using SPSS v17 Inc. performing descriptive and inferential tests, whereas qualitative data was analyzed using MAXQDA 11.

Results indicate that is the moment to make progresses in vCoP by establishing a system that certifies informal learning acquired after participating in vCoP. Although it is difficult in delimitation, Public Health workers established a series of criteria essential for evaluating participation: (a) improvement made in workplace; (b) transfer of the learning process and knowledge/skills gained to the workplace; (c) integration of final products into the workplace; and (d) assessment of the quality and quantity of hours invested outside the workday. In this sense, we highlight the discussion concerning the development (or not) of methodologies that measure learning done. We can confirm that it is still necessary to make progress in the establishment of evaluation procedures that have the same validity and reliability of those used in formal systems.

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Keywords: virtual community of practice, informal learning, workplace learning

INTRODUCTION

We live in a time where challenges are different from those in past years, and consequently the answers to those problems are evolving—a fact that highlights the necessity of constant adaptation that can only be carried out through learning—formal, informal, and training.

Considering context and adaptation as elements that differentiate one organization from another—organizations are immersed in finding models and strategies that allow their members to share their knowledge and work collaboratively, in order to get effective results at the individual, group, and organizational level. In fact, individual and organizational developments are closely related. As Siemens (2014) pointed out, organizations and persons are learning organisms. Individual learning does not guarantee organizational learning, but it would seem impossible that organizational learning occurs without individuals learning (Argyris, 2001; García del Junco & Dutschke, 2007; Senge, 1992). In fact, an important percentage of the individual learning required for organizational learning is developed through mechanisms of informal learning in the workplace (Cross, 2007; Fernández-de-Álava, 2014; Marsick & Watkins, 1990).

In the recent years the number of studies concerning informal learning and communities of practice (CoP) are increasing (Bate & Robert, 2002; Dixon, Allen, Burgess, Kilner, & Schweitzer, 2005; Gairín et al., 2011); nevertheless, there are very few such studies in the field of Public Administration. Furthermore, there is even little recognition of, and information about the informal learning that is generated as a consequence of this collaborative work. So, having identified the lack of a theoretical substrate and research on praxis in informal learning in the Spanish (specifically Catalanian) context as the core research problem, this chapter focuses its attention on a research study conducted in 2012-2014 in order to, among other objectives, establish a series of considerations for evaluating participation in virtual communities of practice (vCoP), and informal learning acquired through this participation.

BACKGROUND

Informal Learning in Virtual Communities of Practice

Many scholars have tried to understand and explain informal learning (i.e., Boud & Middleton, 2003; Eraut 2004; Fernández-de-Álava, 2014; Livingstone, 1999; Marsick, 2009; Schugurensky, 2000; Straka, 2004). In 1990, Marsick and Watkins defined informal in contrast to formal learning by affirming that “[...] it is not typically classroom-based or highly structured, and control of learning rests primarily in the hands of the learner [...]” (Marsick and Watkins, 1990, 12); but other authors (e.g., Billett, 2002, 8) avoid this dichotomy pointing out that “it is probably neither helpful nor precise to describe learning outcomes solely on the basis of the structuring of learning experiences.” Even though we

cannot leave out some differences between formal and informal learning, such as design, focus or certification, we agree with Billett (2002) that both learning are two ends of a continuum with considerable overlap.

For Billett (2002), the description of workplaces as informal learning environments is unhelpful due to the use of terms such “informal” or “unstructured” probably because “informal learning can be deliberately encouraged by an organization or it can take place despite an environment not highly conducive to learning” (Marsick & Watkins, 1990, 12). So, the definition of “informal learning” used in this chapter is the one whereby informal learning is acquired through professional practice and that is propelled by challenges that appear in daily activities. Although it is not necessarily a collaborative learning experience, collaboration can be encouraged, deliberately, by the organization (Fernández-de-Álava, 2014; Marsick & Watkins, 1990; Marsick, Fernández-de-Álava, & Watkins, 2015).

Among those mechanisms of informal learning are communities of practice (CoP); a term coined by Lave & Wenger (1991). In CoP the organizational area is nothing other than a means of giving form to the different communities to which we belong in our day to day lives: family, friends, hobbies, etc. (Wenger, 1998). Through the establishment of a network structure (Castells, 1997), dialogue lends meaning to the learning, given that knowledge is constructed through feedback. However, and frequently, it is hard to define the boundaries between this type of network, CoP, and other structures in organizations, such as formal working groups, interest groups or project teams (see Table 1).

Table 1. Kinds of structures similar to CoP

Form of organisation	Purpose	Affiliation	Cohesion	Length
CoP	To develop its members' capacities. To build and exchange knowledge	Self-selection	Passion, commitment, and identification with the group's expert knowledge	Until the interest in maintaining the CoP disappears
Formal network	To perform specific jobs within a given domain of knowledge	Formal assignment (by a senior manager)	Workplace requirements and shared objectives	Until the next reorganisation or until the job is finished
Formal working group	To provide a product or service	Formal affiliation	Workplace requirements, and shared objectives	Until the next reorganisation
Informal network	To exchange knowledge within a given domain of knowledge	Voluntary involvement (colleagues, friends, acquaintance, etc.)	Mutual needs, and individual interest	Until the members lose interest in being connected
Interest group	To share knowledge, learn, and to create knowledge	Voluntary, and open involvement	Commitment to and identification with the target of interest	Until the interest disappears
Project team or target community	To perform specific jobs	Formal assignment (by a senior manager)	Project milestones, and objectives	Until the project is completed

Source: (Al-Hawamdeh, 2003; Collison & Parcell, 2003; Hislop, 2005; Müller-Prothmann, 2006; Wenger & Snyder, 2000).

Fernández-de-Álava (2014) studied CoP, but with an intensive use of technology: virtual communities of practice (vCoP). According to Kimble & Hildreth (2005) and Wenger (1998), apart from facilitating informal learning, vCoP encourage knowledge creation and management (KCM) and personal and professional development. In this respect, information and communication technologies (ICT) have come to play a fundamental role in the embedding of new forms of learning and collaborative cultures (Cobo & Moraver, 2011). So, the form used in this chapter of “vCoP” are those groups of people who share a common interest, problem or professional challenge; share their knowledge, skills and experiences (Lave & Wenger, 1991; Wenger, 1998); and learn together due to this exchange, but with an intensive use of technology (Fernández-de-Álava, 2014).

Recognition of Informal Learning

Marsick, Fernández-de-Álava, & Watkins (2015) pointed out different ways for recognizing informal learning, such as the Learning Practices Audit (Watkins & Wiswell, 1987), or the Dimensions of the Learning Organization Questionnaire (Watkins & Marsick, 1997). In 1987, Watkins and Wiswell developed a Learning Practices Audit, in order to self-assess the amount of hours per month spent participating in formal, informal or incidental learning activities. Some years later, in 2000, Watkins and Cervero went back to this Learning Practices Audit and modified it, when asked to assess informal learning for expert testimony about learning practices in the accounting context. Another example is Lohman (2006, 2009) who assessed the availability of resources that support informal learning, or Skule (2004) who studied learning conditions at work for understanding and assessing informal learning in the workplace. According to this framework, factors that made jobs more learning intensive, favoring informal learning, were (Skule 2004, 14): (i) “high degree of exposure to changes,” (ii) “high degree of exposure to demands,” (iii) “managerial responsibilities,” (iv) “extensive professional contacts,” (v) “superior feedback,” (vi) “management support for learning,” and (vii) “rewarding of proficiency.” Finally, we cannot let the Dimensions of the Learning Organization Questionnaire (DLOQ) (Marsick, 2013; Marsick & Watkins, 2003; Watkins, & Marsick, 1997) pass. This questionnaire was designed to assess organizational learning culture. Specifically, it measures how organization’s climate, culture, systems, and structures impact on workers learning “To support such learning, one needs to build a learning climate and culture. Climate and culture built by leaders and other key people who learn from their experience, influence the learning of others, and create an environment of expectations that shapes and supports desired results that in turn get measured and rewarded” (Marsick & Watkins, 2003, 134). So, when learning culture is strong, it nurtures [informal] workplace learning.

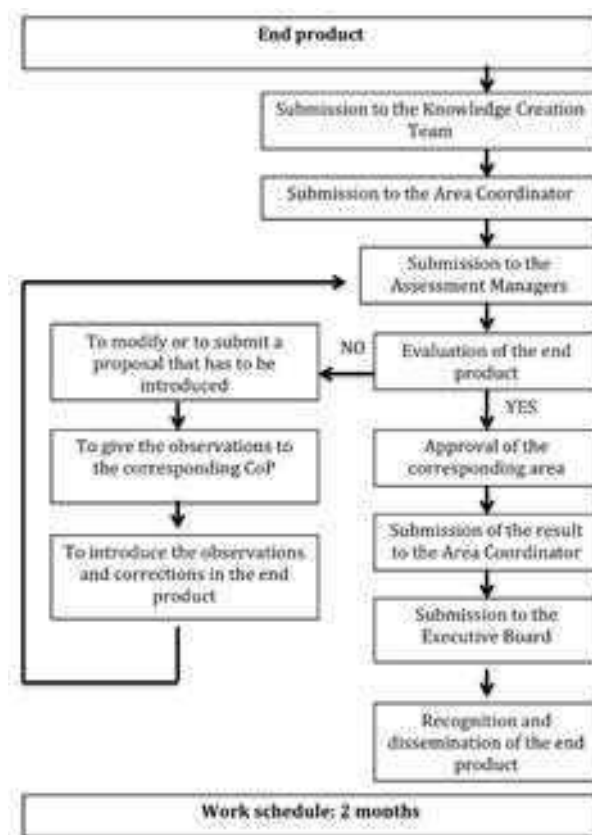
THE ORIGIN OF vCoP IN THE PUBLIC ADMINISTRATION OF CATALONIA

In 2004, the Directorate General for Citizen Attention (DGAC, is the Spanish/Catalan acronym) embarked upon a process of change in order to abandon its traditional structure—

deemed too hierarchical and rigid for optimal learning—for one more substantially more horizontal that would be based on knowledge sharing through vCoP. In order to achieve this goal, the DGAC established an online collaborative working environment, e-Catalunya (<http://ecatalunya.gencat.cat>), for all the staff of the Catalan Public Administration. The DGAC vCoP model is characterized by the following (Barrera-Corominas, Fernández de Álava & Gairín, 2014):

- **An intensive use of technologies.** e-Catalunya is the main communication channel because it is the online institutional platform. Nevertheless, there are two in-person meetings: one at the beginning of the vCoP and another one at the end. The first of these is useful for participants to get to know each other, to select the moderator, to define objectives and to schedule the latter at a time permitting development of an end product. This end product is distributed to participants in the vCoP, to participants from the other vCoP's, as well as to other internal or external professionals.
- **Participants.** Participants are, of course the core of any vCoP. Of these, there are usually three types: (i) active, those who participate consistently, promoting an enriching dialogue through the exchange of information; (ii) sporadic, those who read contributions and, from time to time, write in their own experiences, opinions, etc.; and (iii) passive or lurker, those who are in the periphery, that is, not participating in the active dialogue but reading the contributions (Rodríguez-Gómez, 2011).
- **Moderator.** He/she is the person who drives the vCoP dynamic, and he/she is responsible for guiding the process in order to achieve the objectives defined in the first face-to-face meeting and to produce an end product. The Moderator has to create a pleasant climate; to motivate participants and to encourage their taking part, to structure their work and finally, to close the debate with some consensus (Sanz, 2012).
- **A debate.** Developed through tools such as the forum or the wiki, and complemented by photos, documents and bibliography/references.
- **An end product.** Every vCoP must produce some kind of material (manual, three-page leaflet, programme, protocol, etc.) that is useful on three levels: individual, group and organizational. Once validated by the Executive Board (see Figure 1), this end product is the innovation the vCoP diffuses to others.
- **A certificate.** Participants and moderators of those vCoP that create an end product, receive a certificate of these 40 hours of training that are required. Due to the different roles of vCoP, participants' diploma certificates the training received and moderators' diploma certificates the training delivered.

It is important to point out that, by collective agreement, the staff of the Catalan Public Administration have to do 40 hours of training within their work schedule. To fulfil this obligation, they go to formal training activities (classroom and online) that the Public Administration designs and offers to them. At the end of the course(s), the course deliverer awards a diploma to the staff who have attended all the hours, which enables them to apply for promotion when the competitive exams/ civil service examination are announced.



Source: Internal documents of the Public Health Agency of Catalonia.

Figure 1. Procedure to recognise vCoP's end products.

However, at the same time, there is a second and informal way to be trained: the abovementioned participation in a vCoP - although with this approach there are no specified numbers of hours. Nevertheless, for the competitive exams/civil service examination only diplomas issued by the Public Administration are considered valid.

The Public Health Agency of Catalonia (ASPCAT, by Its Spanish/Catalan Acronym)

Law 7/2003, of 15 April, (DOGC number 3879, of 8 May, 2003), represented the beginning of a reform of public health services, based on the organization of the supply of health protection services, through the creation of the ASPCAT. Consisted of multidisciplinary teams formed by health professionals such as biologists, chemists, doctors, veterinarians, and other non-health professionals (caretakers, secretaries...), the ASPCAT is established with the aim of promoting and protecting health, and of preventing and managing epidemiological and food alerts.

Regarding the implementation of vCoP, it organized a journey whose aim was to define its training model based on work teams, informal learning, and vCoP. Basically, the ASPCAT

tried to replace individual work and isolated routines for teamwork and collaborative environments, to provide new employees with necessary skills, to improve basic skills of former employees, to stimulate internal promotion, to promote ways of informal learning and communities of practice and to strengthen transversal training within public health workers.

In 2008, ASPCAT started a pilot project of knowledge creation and management through vCoP in order to prove the interest of health workers in sharing their knowledge among other colleagues. ASPCAT developed 6 vCoP involving 76 staff-members. Their success led to form, a knowledge management team in 2009, and to approve a Plan aimed at creating a knowledge sharing culture. Also to create horizontal networks to encourage informal learning, to encourage professional development and to meet organizational requirements.

ASPCAT repeated the experience year after year and since 2014, it brought together 533 employees who have worked on different topics such as chemical dangers related to sunflower oil: description and preventive measures; water not suitable for human consumption and health education in schools: food hygiene.

METHODOLOGY

This chapter establishes a series of considerations for evaluating participation in vCoP and informal learning acquired through this participation. It draws on quantitative and qualitative data from research conducted in 2012-2014.

Sample

The scope of this study comprises all professionals that participate in vCoP, or moderate vCoP in the ASPCAT. Five successful [i.e., their collaborative work has resulted in a useful end product for the participants of the vCoP, the group and the organization] vCoP were studied. The data-producing sample consists of 33 professionals. It should be pointed out that two of the five successful vCoP were selected intentionally, based on the interviews done within research (Gairín et al., 2011), whose aim was to outline factors for success in vCoP in the two aforementioned Departments:

- Time/temperature binomial in the food industry – This vCoP was born due to the difficulties that inspectors found when they have to do inspections or audits when it comes time to evaluate the parameters of time/temperature. “The topic time/temperature binomial has a lot of controversies. So, all professionals who are in this vCoP is because we are interested in the topic and because we want to give our colleagues some work tools,” said one of the participants. The end product was a useful tool guide to them because participants describe all the necessary steps to evaluate the parameters of time/temperature in order to guarantee food safety.
- Manual on post mortem examination and dictum of fresh meat – All the participants of this vCoP work in slaughterhouses, and in isolated environments (that is, they work alone, at night and they have no interaction with other colleagues). For that reason, the opportunity of working in vCoP attracted them, because it can be a social

network where they can talk with other colleagues and solve challenging problems. An ASPCAT member noted, for example: “Slaughterhouses are isolated areas within the ASPCAT. Veterinarians work alone, in particular hours, in a group that does not interact with the rest of the organization, and they have the necessity to open their mind.” The end product of this vCoP is very useful because it contains a lot of photography and they describe the different lesions and diseases that animals can have and why they are suitable (or not) for consumption. In fact, it has been disseminated outside the Catalan slaughterhouses. This usefulness has been noted by an ASPCAT member: “I think that vCoP from slaughterhouses have been very successful because their end products have being very useful for this group.”

Instruments and Variables

The instruments used were a digital format self-applied questionnaire via LimeSurvey to facilitate response due to the geographic dispersion of the participants in and moderators of the vCoP. The items proposed were of two types: (1) 5-point Likert evaluation scale, from 1 - strongly disagree to 5 - strongly agree, for all items apart from those corresponding to mechanisms of informal learning and (2) multiple choice question for the latter. None of the items was constructed in a negative sense. The variables considered in this chapter are the ones related evaluation and certification of informal learning derived from vCoP.

After the results had been obtained from the questionnaire, interviews were conducted with the vCoPs’ managers, participants and moderators, in order to compare and contrast the same. The questions, which were asked openly, covered all of the items of the survey, apart from those of identification. Additionally, document analysis was the other data collection method.

Data Analysis

Quantitative data was analyzed using SPSS v17 Inc. performing descriptive and inferential tests, whereas qualitative data was analyzed using MAXQDA 11.

RESULTS

The outcomes presented refer only and exclusively to those data of considerations for evaluating participation in vCoP and informal learning acquired through this participation. Table 2 indicates descriptive statistics –the median and standard deviation– of each items included in ‘considerations for evaluating participation in vCoP and informal learning acquired through this participation’. Specifically, median score varies according to agree and neutral (2.80), and disagree and strongly agree (4.20). The median total score of the items and participants is 3.90; serving as a central tendency index in the analysis. Standard deviation varies between 0.79 and 1.30, the global average being 0.97.

Table 2. Descriptive statistics for items included in “considerations for evaluating participation in vCoP and informal learning acquired through this participation.”*** denotes significance**

Considerations for evaluating participation in vCoP and informal learning acquired through this participation	Median	Standard Deviation
Participation in vCoP outside working hours	2.80	1.30
Development of an end product	4.20	0.94
Usefulness of new competences acquired through the participation in vCoP for the professional practice	4.26	0.79
Improvement in professional practice due to the participation in vCoP	4.23	0.87
Transfer of knowledge/skills acquired through the participation in vCoP to other contexts	4.00	0.96

In general, those indices show a closer state of notable agreement. Nevertheless, we should specify that the effect produced by item ‘Participation in vCoP outside working hours’ because its result is quite lower than the other items, lowers the global results. Standard deviations, show moderate scores being 0.97 the global average (24.87% of the median), with the exception of the abovementioned item. From this outcome, we deduce some dispersion in responses.

In order to go into detail about results shown in Table 2, we applied t-test against the global mean. Statistical significant differences were found in four of five items that make up the dimension “considerations for evaluating participation in vCoP and informal learning acquired through this participation” (see Table 3). Specifically, statistically significant differences exist within four issues that could be considered when assessing participation in vCoP and informal learning acquired through this participation: (i) participation in vCoP outside working hours ($p = 0.028$); (ii) development of an end product ($p = 0.011$); (iii) improvement in professional practice due to the participation in vCoP ($p = 0.031$); and (iv) transfer of knowledge/skills acquired through the participation in vCoP to other contexts ($p = 0.018$).

Table 3. T-test results of items included in “considerations for evaluating participation in vCoP and informal learning acquired through this participation”

Considerations for evaluating participation in vCoP and informal learning acquired through this participation	M	St Error	t	p
Participation in vCoP outside working hours	3.18	0.22	-2.23	.028*
Development of an end product	4.52	0.14	-2.61	.011*
Usefulness of new competences acquired through the participation in vCoP for the professional practice	4.33	0.16	-.700	.486
Improvement in professional practice due to the participation in vCoP	4.48	0.15	-2.20	.031*
Transfer of knowledge/skills acquired through the participation in vCoP to other contexts	4.30	0.15	-2.42	.018*

The results derived from the self-applied online questionnaire were, afterwards, extended through interviews and document analysis. So, even though some interviewees were against assessing participation in vCoP because certification could distort vCoP (becoming another training process) “I do not agree with getting compensations. It can be dangerous.” “If you participate in vCoP, you will receive a t-shirt. It is not appropriate for vCoP and learning” or

“with or without recognition, vCoP should run because those who want to participate for training hours they can assist to formal training courses [...] it has no sense,” the vast majority thought that recognition is a way to appreciate the end product, the hours spent, the knowledge/skills acquired, and the value of learning. Likewise, it is a way for legalizing the process. “Managers should find a way to recognize vCoP and informal learning. It is not just a verbal gratitude”; “I spent around 100 hours participating in vCoP [...] it has been years since the ASPCAT offered training courses... so, at the very least the ASPCAT should recognize our work”; and “there should be any way to recognize informal learning. Participation in vCoP enriches participants and moderators, but end product enriches the organization, because those who have not participate also use them and learn.”

Regarding “participation in vCoP outside working hours,” interviewees pointed out that the inclusion of participation in vCoP in the workday represents a reduction of work at home. The majority of participants and moderators participated in vCoP outside working hours that is, in the afternoon and weekends: “I did a lot of work at home. At the slaughterhouse is very difficult to work because we have a huge work volume”; which means that they gave different days a week to participate in vCoP and not to leisure. “According to the e-Catalunya, people participate more during afternoons or weekends, and not during working hours.” So, “the recognition of hours spent will be symbolic because I remember myself uploading documents or calling colleagues during Sundays, and this work done is not recorded, and this is far from being recognized.”

Concerning the “development of an end product,” interviewees pointed out that end products improve professional practice, increase quality of work, and help to personal and professional development. As previously mentioned, at the end of the vCoP participants and moderators should submit an end product as a result of the collaborative work. The end products should improve professional practice but there should be no pressures within the vCoP. As the Plan approved in 2009 states: the delivery of the end product should not have more weight than the learning itself. As a moderator pointed out: “The development of an end product involves different efforts: to motivate, to manage, to set and keep the pace, to format, to homogenize the style (because every participant writes and communicates differently) [...].”

“The main aim of vCoP is that they are useful to public health inspectors.” We have to remember that participants and moderators share knowledge and skills in order to learn and improve their professional practice. “We, as professionals of the ASPCAT, have different backgrounds, knowledge, skills... so let’s share them and create documents that are useful to all professionals because perhaps I am not an expert in milk because I am in vegetable disinfection. So, my end product could make easier your work, and your end product, my work. That is great.” In other words, optimum conditions for vCoP should increase the quality of public services, their effectiveness and organizational outcomes. “The participation in vCoP enriches your background and improves the quality of your work.” Therefore, participants and moderators transfer the knowledge/skills acquired through the participation in vCoP to other contexts.

In short, and in addition to these considerations, interviewees highlighted other considerations such as: (i) the integration of final products into the workplace; (ii) the integration of participation in vCoP into schedule; (iii) the value that ASPCAT places on vCoP and hours spent; and (iv) the role of moderator. “If the ASPCAT integrates participation in vCoP into the schedule, all participants and moderators would make the most

of them. I trust them and I have complete faith in the end products. Their end products are good for my work.”

DISCUSSION AND CONCLUSION

Although there are great progresses in the validation of competences acquired non-formally or through professional experience, we must take into account that the aim of evaluation, in comparison to formal system, is complex having, therefore, bigger difficulties to guarantee its reliability and validity (European Commission, 2012). Nevertheless, as UNESCO (2012) pointed out, we must provide (to all of the population) the opportunity to access and participate in any learning situation and to value its results. For that reason, if ASPCAT, in 2007, thought about the different ways of learning, creating vCoP as a result, now is the moment to make progresses in those programs – establishing a system that certifies informal learning acquired after participating in vCoP.

Despite practically complete lack of European and national tools and instruments for validating and accrediting informal learning, ASPCAT can take as a reference Law 5/2002, of 19 June; Royal Decree 1506/2003, of 28 November; and Royal Decree 1224/2009, of 17 July. This would involve the evaluation of professional competences acquired through vCoP, with reference to the CNCP basis (see Chapter 6, section 6.2.).

If competences previously acquired informally are to be evaluated and recognized, we must carefully consider which knowledge and/or skills must be taken into account— or otherwise omitted them because of their unique contextual nature. Although it is difficult in delimitation, participants and moderators establish a series of criteria essential for evaluating participation in online communities of practice and informal learning acquired through it. The considerations that would be necessary for doing so are: (a) improvement made in workplace; (b) transfer of the learning process and knowledge/skills gained to the workplace; (c) integration of final products into the workplace; and (d) assessment of the quality and quantity of hours invested outside the workday.

It is important (and surprising) to recognize that few participants and moderators think that hours invested outside a workday must be considered in this evaluation of participation in vCoP and in informal learning acquired through this activity. Digging deeper into this issue in the interviews, we discovered that what they consider important is not a matter of counting hours but rather, of integrating final products into the workplace. By doing so, competences acquired can be corroborated and the acquired learning transferred, via publication of the learning of participants and moderators, to the workplace. Thus, through the establishment of a system that certifies informal learning acquired through vCoP in Public Administration, we provide the opportunity to recognize competences. Nevertheless, each person has the right to access (or not) this accreditation.

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Chapter 520

MENSTRUATION AND DEPRESSIVE DISORDERS: A RECIPROCAL RELATIONSHIP THAT CALLS FOR PUBLIC HEALTH AND CLINICAL CONCERN

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INTRODUCTION

Depression is the most common psychiatric illness experienced by women, and the second greatest cause of medical burden in this population [1]. Before puberty, rates of mental illness, and particularly depression, are highly comparable across all genders. However, by age 15, girls are twice as likely to have experienced Major Depressive Disorder (MDD) than boys [1]. Coincidentally, this is around the time that a girl is likely to have her first menses, as the median age of menarche is 12.43 years in the US, and is estimated to be about 13 years worldwide [2, 3].

The menstrual cycle is intricately linked with many aspects of a menstruator's mental health. Premenstrual Syndrome (PMS) is a diagnosis in women of reproductive age that involves the manifestation of both physical and affective (i.e., emotional) symptoms during the luteal, or premenstrual, phase of the menstrual cycle. The worldwide prevalence of PMS is difficult to estimate, as studies vary considerably in their definitions of PMS and their assessment tools. Studies conducted in the US using criteria established by the American Congress of Obstetricians and Gynecologists estimate that 15-20 percent of menstruators experience clinically significant PMS [4]. The most severe symptoms of PMS tend to appear in a menstruator's late twenties and worsen during the thirties [1]. Importantly, multiple studies have found that women with PMS are more

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likely to suffer from MDD or develop an affective disorder than those who do not have PMS [5].

Many other factors related to menstruation, apart from PMS, also may have implications for mental health. Early puberty, and early menarche are associated with increased rates of psychopathology [6]. Throughout the menstrual cycle, women tend to experience varying levels of stress during the different phases, both in terms of subjective stress response and in neuroendocrine fluctuations [7]. During the premenstrual phase in particular, women have reported the worsening of symptoms of depression, social anxiety, obsessive compulsive disorder, and psychosis [8]. These patterns of poor mental health are even more pronounced among the most severe cases of psychiatric illness as 37 percent of women who are hospitalized for such illnesses had their last menses within five days of being admitted [9].

These observed associations between menstruation and mental health, particularly with depressive disorders, pose significant health risks for women. Depressive disorders including MDD, dysthymic disorder, and seasonal affective disorder can be exacerbated during the luteal phase of the menstrual cycle [10]. For MDD in particular, the risk of recurrent episodes of this disorder increases with each subsequent episode [1]. Thus, evidence suggests that the menstrual cycle has the capacity to increase the severity of future MDD symptoms and episode length by intensifying a menstruator's current episode. This risk is especially concerning since MDD is responsible for up to 35 percent of all completed suicides [1].

In order to promote the mental health and well-being of menstruators, it is critical that the relationship between menstruation and depression be better understood. Strategies to improve can then be developed to aid in the clinical care of those who menstruate and have a depressive disorder. This chapter discusses these associations and their implications in detail.

MENSTRUATION AND DEPRESSIVE SYMPTOMS: A REVIEW OF THE LITERATURE

Depression Affects Menstrual Symptoms

The association between depression and menstruation is evident in menstruators of all ages. In one cohort of 154 girls of ages 11, 13, 15, and 17, a significant correlation between menstrual and depressive symptoms was established [11]. Two questionnaires were administered to quantify symptom experience and severity - a Menstrual Symptom Questionnaire (MSQ) and the Children's Depression Inventory (CDI). The CDI is a self-reported survey of 27 symptoms of depression that has been demonstrated to have high reliability since its introduction in 1992 [12]. The MSQ grouped symptoms reported by the subjects into five factors of dysmenorrhea. The most-reported symptoms by the cohort, in decreasing order, were menstrual pain, premenstrual pain, premenstrual bloating, premenstrual negative affect, and menstrual back pain [11]. In both surveys,

higher survey scores corresponded to higher symptom severity, and instruments were assessed for internal consistency and reliability.

The results depicted a clear trend of increasing number and severity of menstrual symptoms in girls who had greater depression. Each of the five menstrual factors were significantly and positively correlated with CDI scores. Premenstrual negative affect had the greatest correlation of 0.44 ($p \leq 0.001$) [11]. The correlation between premenstrual pain and symptoms of depression were also highly significant ($p\text{-value} \leq 0.001$), though was slightly weaker in magnitude at 0.34. The three remaining factors were significant ($p \leq 0.01$), and the correlations ranged from 0.27-0.30 [11]. Despite the fact that menstrual pain was the most reported of the symptoms, it did not have the greatest correlation with depressive symptom scores. These results suggest that depression affects premenstrual symptoms more than those experienced after the onset of menses. Additionally, the especially strong positive correlation between depressive symptoms and premenstrual negative affect implies an intricate relationship between depression and the behavioral symptoms that women experience during the luteal phase of the menstrual cycle.

Significant Alterations in Symptoms Occur during the Premenstrual Phase

Many public health concerns related to depression increase in prevalence during the premenstrual phase of the menstrual cycle. Studies have shown that of the rate of hospital admissions, suicide attempts, completed suicides, and calls to suicide prevention hotlines is higher in women during the premenstrual phase than during other phases of the menstrual cycle [13]. Furthermore, up to 50 percent of premenopausal women who are admitted for psychiatric care are in the premenstrual or menstrual phase [14]. These data identify the premenstrual phase of a menstruator's cycle as a critical window for mental health crises intervention.

It is plausible that not only are rates of suicide and other extreme events exacerbated during the premenstrual phase, but also depressive disorders at large may be intensified as well. In fact, rates of premenstrual mood-related symptoms in menstruators with depressive disorders are higher than in those who do not suffer from a mental illness. In an extensive cohort study, 68.5 percent of over 1700 women who had been diagnosed with MDD reported premenstrual mood-related symptoms [15]. Furthermore, the presence of premenstrual mood-related symptoms significantly predicted the incidence of both postpartum and perimenopausal symptoms in women with MDD [15]. It appears that depression manifesting as premenstrual symptoms earlier in life is associated with higher risk of depressive symptoms after childbirth and during perimenopause, menopause, and after menopause.

Age at Menarche Influences Depressive Disorders

Harlow et al. detailed the significant association between age at menarche and depression [16]. Participants were recruited for the Harvard Study of Moods and Cycles,

and 332 women ages 36 to 45 years from the Metro-Boston area met the criteria for diagnosis of MDD [16]. Age at menarche was inversely related to risk of depression ($P < 0.001$). Compared to women reporting menarche at age 12, women who had their first menses at age 10 or earlier were 2.4 times more likely to be diagnosed with MDD. In contrast, women with menarche at age 15 or later had a marginally significant 40 percent lower risk of MDD.

Similar findings have been reported in studies outside of the United States. A retrospective cohort study of 4,391 women aged 30 and older used data from the Finland Health 2000 survey to examine the role early age at menarche plays in mental health [6]. Symptoms and incidence of depression and general health were assessed using the Beck Depression Inventory (BDI-21) and General Health Questionnaire (GHQ-12). The participants were also asked to recall when they had their first menses and to assess the regularity of their current menstrual cycle. A younger age at menarche was associated with higher risk of MDD and with higher (i.e., worse) scores on the BDI-21 and GHQ-12 ($p < 0.01$). Younger age at menarche had significant negative correlations with feelings of past failure ($p < 0.001$), sadness, dissatisfaction, punishment, lost interest in other people, and looking ugly ($p < 0.01$). Negative correlations were also found with some indicators of general health; as age at menarche decreased, feelings of strain, depression, and unhappiness increased ($p < 0.01$).

Menstrual Irregularity Affects Depression

Other menstrual characteristics, aside from age at menarche, have also been assessed for their role in the risk of depression later in life. For example, Harlow et al. assessed menstrual symptoms that occurred during the first five years after menarche in order to discover any potential relationships between early menstrual characteristics and their effects on MDD development [16]. Of the menstrual symptoms considered, cycle irregularity (OR = 1.5) and moderate to heavy flow (OR = 1.6) were moderately associated with risk of later depression. A different study found that in women aged 30 to 55 years old who were not using hormonal contraception, irregular or absent menstrual cycles was associated with higher experience of symptoms of depression ($p < 0.001$) [6].

Premenstrual Exacerbation of Symptoms of Depression

In addition to age at menarche and irregular cycles, premenstrual exacerbation of depressive symptoms in menstruators is a well-documented phenomenon. Premenstrual exacerbation (PME) is defined as the worsening of an existing psychiatric condition, in this case depression, during the window of five to ten days prior to onset of menses [14]. PME is highly prevalent in women with MDD and has significant effects on symptoms of depression [14, 17]. In a study seeking to determine the rates of PME in different psychiatric disorders, 52 percent of women with depression who reported premenstrual symptoms specifically experienced PME of their depressive symptoms ($p < 0.005$) [14].

In one study, 58 women with depressive disorders were followed prospectively over two menstrual cycles for menstrual symptom exacerbation [13]. Insomnia/hypersomnia, appetite loss/overeating, fatigue, and feelings of worthlessness were each significantly exacerbated during the premenstrual phase. In addition, 58 percent of the women experienced a worsening of one or more of their depressive symptoms during the premenstrual phase, with a mean of 1.34 symptoms worsened [13].

Clinical features and avenues of treatment for MDD have been explored in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, introduced in 2003 and supported by the National Institute of Mental Health [18]. Patients enrolled in this study were recruited from 55 clinical sites and were all seeking treatment for depression, creating an avenue for inquiry regarding the role of these patients' menstrual cycles in their illness [17]. Participants included 433 premenopausal women with diagnosed MDD not taking oral contraceptives.

Of the 433 participants, 64 percent reported premenstrual exacerbation of their depressive symptoms in the five to ten days prior to their menses [17]. This finding is consistent with other reports of PME prevalence in the majority of worsened symptoms in this cohort were somatic. The most reported PME-associated symptom was somatic pain ($n = 227$, $p < 0.0003$), followed by mood reactivity ($n = 188$, $p < 0.045$) and psychomotor slowing ($n = 180$, $p < 0.009$), which is described as the retardation of both thought processes and physical movement [17]. Both gastrointestinal symptoms ($n = 133$, $p < 0.006$) and leaden paralysis, or the sensation of weighed down limbs ($n = 132$, $p < 0.001$), were also significant. Furthermore, the length of the current depressive episode in those who reported PME was significantly longer— a mean of 30.6 months versus 13.2 months in women without PME ($p < 0.001$) [17]. Thus, not only were the symptoms of depression worsened in this population, but women experienced MDD for a longer period of time. These results demonstrate that women may experience substantial physical symptom burden, as well as emotional symptom exacerbation, as a result of the comorbidity of depression and menstrual symptoms.

A second study by the STAR*D investigators attempted to replicate these initial findings. The second cohort consisted of 821 women who were receiving outpatient treatment for MDD and not taking oral contraceptives [19]. Of this cohort, 66.3 percent of women reported PME, again demonstrating the broad prevalence of this phenomenon. Severity scores on the Cumulative Illness Rating Scale (CIRS) were significantly higher in women with PME ($p < 0.001$), suggesting that PME is associated with a greater medical burden overall, beyond depressive disorders alone.

Results from the STAR*D study also suggested that there was a slight but significant difference in the ages of women who reported PME, with those who reported PME on average older than those who did not report PME [19]. Other studies have found similar associations of age and PME. In a community-based cohort of women and girls in the United States, women aged 34 to 53 were more likely to experience PME than those aged 13 to 33 [13]. The study determined that women aged 34 to 53 were about 2.6 times more likely ($OR = 2.59$) to have at least one symptom of depression exacerbated during the premenstrual phase of her cycle than younger women. In fact, this study found that age was the single best variable to use to predict the number of symptoms exacerbated ($\chi^2 = 10.93$, $p < 0.001$).

DISCUSSION

From these data, several key conclusions can be drawn. First, there is a significant public health burden resulting from the comorbidity of menstrual symptoms and depressive disorders. Numerous studies have shown that the premenstrual phase of a person's menstrual cycle may be a vulnerable time for mental health, including exacerbation of depressive symptoms, hospitalization, and suicidal behaviors.

It is evident that depression is a more dangerous diagnosis for those who menstruate not only because of menstruation's exacerbating effect on depressive symptoms, but also because of the higher prevalence of comorbidity. In a sample of the United States population, a cohort of 11,648 menstruating women ages 18 to 55 was studied to identify menstrual problems related to mental health [5]. Almost 19 percent of the cohort reported premenstrual symptoms or symptoms during menses. Women reporting premenstrual symptoms were 2.5 times more likely to have experienced depression in the past 12 months and 2.5 times more likely to have recurrent pain. From this representative sample of menstruators combined with the numerous other reports from communities across the United States and around the world, it is obvious that the incidence and experiences of depression in menstruators translate into a substantial public health concern.

Targeted approaches for improved clinical care are urgently needed for those people experiencing comorbid depression and menstrual symptoms. This population, already under increased health risk, has also been shown to carry a greater medical burden in general. Studies that incorporated measures of general health status found that menstruators with depressive disorders have worsened overall health and a greater incidence of general illness [6, 19]. These findings highlight a group with increased medical need. To better treat this population, healthcare professionals should be aware of the increased health risks that are associated with depression in someone who menstruates.

Another concern to be addressed is the timing of illness in this population, paying particular attention to the phases of the menstrual cycle. Since it is known that mental health issues are most prevalent during the premenstrual phase, individual care should be tailored to the phase of the menstrual cycle as well. Pharmacological intervention for depression may not address the cyclical exacerbation that occurs during the premenstrual phase; rather, medical treatment has historically been administered continuously throughout the cycle. Improved knowledge of the risks presented in the premenstrual phase may help public health and medical professionals improve future medical care and dynamic treatment regimens.

Finally, age seems to be a critical indicator for targeted treatment and monitoring in this population. Evidence suggests that in younger women, depression may increase premenstrual symptom severity. In contrast, in older women, premenstrual exacerbation of existing emotional and physical symptoms is of greater concern. Menstruation and depressive disorders are intricately intertwined. This relationship is evident across ages, countries, and personal histories. However, despite the high prevalence of these conditions and impact on women's lives, the menstruation-depression connection has not

yet been adequately addressed from either the public health or clinical standpoint. Incorporating the consideration of the menstrual cycle, in phase, severity, and symptoms, into the care of depression and other mental illnesses will increase the quality of life of patients experiencing both menstruation and depression, and will also ultimately benefit the health of all menstruators through an overall improvement in competent care.

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Chapter 521

ADVANCEMENT OF BIOCHEMISTRY AND MOLECULAR BIOLOGY IN RELATION TO PUBLIC HEALTH

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ABSTRACT

Biochemistry and Molecular Biology has been developed as disciplines in this century. Both the Biochemistry and molecular biology together are making a significant contribution to the aspect of population health. In last decade, the health care and delivery system all over the world became systematic and technologically more advanced. The doorway of the new century is a promising time to review the public health advances over the past 100 years. In the twentieth century, there was a significant improvement in public health methods, practice, and health of the general population. For the assessment and promotion of health and ultimately for the reduction of the burden of morbidity and mortality, there is an emergence of invention of new tools. Some of the contributions of Biochemistry and Bimolecular science are prominently notable for their impact on reduction of mortality and prolonging longevity. Many new and ongoing evolutions which are ultimately giving the guidance to develop a comprehensive health care system in the frame of reference of public health. Both molecular biology and biochemistry have the potentiality to achieve extensive environmental, economic and health benefits. There is a contrast between personal health and public health. The personal health attended as separate from public health. Globally the upcoming challenge is to convince the policy makers that personal health care is not the only option to improve health care and delivery system. Furthermore, allocation of funds, either in research, program operation, monitoring and evaluation, are the prime important to be started urgently and immediately with the novel goal to improve health for the entire population of the world. So public health incorporation with laboratory techniques will be more effective approach to combate future health challenges.

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Keywords: biochemistry, molecular biology, public health, advancement

INTRODUCTION

Biochemistry and Molecular Biology has been developed as disciplines in this century. Both the Biochemistry and molecular biology are making a significant contribution to the aspect of population health (Campbell P 1992). In last decade, the health care and delivery system all over the world became systematic and technologically more advanced. The doorway of new century is a promising time to review the public health advances over the past 100 years. In the twentieth century, there was a significant improvement in the method and practices of public health and also the health of the general population. There is also facilitation for effective understanding of the disease process to find out more scopes of prevention through advancement of different methodological approaches. There are stepwise advancement of epidemiological methods, lacking behind the study of the determinants of health. As a result, there is a simplistic formulation of correlating risk factors associated or contributing to different types of diseases, injuries and wellbeing of mankind at the community level, national level and globally (National Academies Press US 2002).

For the assessment and promotion of health and ultimately for the reduction of the burden of morbidity and mortality, there is an emergence of invention of new tools (Sanjiv Kumar 2012). In turns, it will ensure the effective interventions and estimations of the economic effects of different types of investments which will provide the greater efficiency and will be able to provide a comprehensive effective public health programs. To confront unprecedented challenges in public health, including rapidly growing global population, increased number of aged population, and some unprecedented changes in key environmental health indicators, there is an unavoidable need for fragmentation of infrastructure of the public health (Fielding JE 1999).

Some of the contributions from Biochemistry and Molecular Biology sciences are remarkably notable for their impact on reduction of mortality and prolonging longevity. Those are, invention of new vaccines, complete eradication of smallpox, remarkable reductions of communicable disease epidemics, and controlling over several chronic diseases. So many advancement enabled the understanding of basic disease mechanisms and provided tools to measure health in better ways and finding out appropriate intervention (Robert J. A 2010). Progressive advances of invention in public health arena are many, however few of those can be described in brief.

ADVANCES IN METHODS

In last decade, positive progresses in advancing public health has been achieved. Through the remarkable advances of the last few decades in the field of biomedical sciences, it gradually entered from basic biological science through clinical research to comprehensive public health services. These developments have gone through the transformation of both large and small-scale biological and biomedical researches in a dramatic way (National Academies Press, US; 2003). Laboratory and clinical investigations are most essential

components of health sector. There are several scientific breakthroughs which have important contributions in public health perspective in a way of how research is conducted. After gaining knowledge from population-based epidemiological studies and clinical trials, integration and correlation of knowledge regarding molecular research is important for the public health researchers. From where they are guided to learn what works and what does not work, what is safe and what is not safe. Now a days, there is an increasing demand for focusing on multidisciplinary research including genetic variation, cell dynamics, and metabolic, nutritional, environmental, and pharmaceutical variables. Also greater emphasis must be given on behavioral social sciences and health services research for more effective treatment of diseases and improvement of quality of life (Nass SJ 2009). New and ongoing evolutions which are ultimately giving the guidance to develop a comprehensive health care system in the frame of reference of public health are:

CRISPR Genome Editing Has Foreseeable Implications for Plastic and Reconstructive Surgery

The CRISPR (a family of DNA sequence) genome editing technique is affectively used in almost every branch of medicine now a day. It is the new era of “transformative leap” in genetic engineering and treatment (<http://home.lww.com/news.entry.html/2018/10/30>).

Scientists Investigate How Broad-Spectrum Antibiotic Therapy Affects Interaction of Gut Bacteria

Billions of beneficial/symbiotic bacteria habitats in human gut. They play active roles in digestion of foods, activating the immune system and helping in production of vitamins. But antibiotic therapies usually destroy these gut bacteria. Side by side, their presence facilitates the spread of pathogens which is called opportunistic infection. These intestinal micro biome, is prone to disruptions. When the gut bacteria is out of balance, then the risk of infection increases and the diabetes become more prevalent, as well as inflammatory and neurological diseases (<https://www.news-medical.net/news/20181107>).

Scientists Discover Cell Adhesion Mechanism Used by *Mycoplasma genitalium*

Globally, *Chlamydia trachomatis* bacterial infection is one of the most common causes of sexually transmitted infections (STI). It infects the human cells; by the mechanism of hijacking some parts of the host cell to create defensive layers around the *Chlamydia trachomatis* (<https://www.news-medical.net/news/20181029>).

Genetic Defect Linked to ALS Causes Sugar-Starved Cells to Overproduce Lipids

A variety of diseases like neurodegenerative and mental illness can changes in the pathways of lipid metabolism in the sugar deprived cells. A new study led by a group of researchers from the Bloomberg School of Public Health, Johns Hopkins University shows the findings could lead to new targets to treat these diseases, currently those have no cure or effective treatments (<https://www.jhsph.edu/news/news-releases/2018>).

Cryo-Electron Microscopy Helps Study Proteins Responsible for Amyloid-Based Diseases

In the past century, the aim was to understand the contribution of protein with amyloid-based diseases such as, Huntingdon's, Alzheimer's and Parkinson's diseases. Lots of initiative and steps have been taken in the last one year. There is a great revolution by the scientists to use a powerful microscopy technique (<https://www.news-medical.net/news/20181030>).

Insights into Tumor Initiation Pave Way for New Skin Cancer Treatments

In case of melanoma; the salient vulnerability is discovered by the researchers. It was found that the melanoma-specific long non-coding RNA SAMMSON in tumor initiation was responsible for melanoma. According to the researchers, it stimulates the protein synthesis in different cellular compartments. This threat begins when there is modification of protein synthesis from normal cells (<https://www.news-medical.net/news/20181029>).

Insulin Discovery Could Improve Treatment for Diabetes

Now a days, a group of researchers discovered the therapeutic Insulin through an international collaboration at the Walter and Eliza Hall. This therapeutic insulins are more effective. It is better as resembling the way actually insulin works in human body (Charilaos S 2009).

Salk Researchers Advance Sonogenetics Technology for Treating Neurological Conditions

Recently the technology of sonogenetics has been emerged. In this technique, cells are controlled by sound. It will open a new era where incase of epilepsy, PTSD (post-traumatic stress disorder), Parkinson disease, the pharmaceutical drugs or invasive surgical treatments can be replaced by sonogenetic technology (Stuart I 2015).

Understanding of Metal-Free Enzymes Used by Bacteria Could Lead to New Effective Antibiotics

In case of some bacterial pathogens, it is observed that, *Streptococcus pneumonia* has the ability to generate the components mandatory to replicate their DNA without the presence of any required metal ions (Jose M 2016).

Stem Cell Treatments for Chronic Disease and Anti-Aging

“Alarm signals”: The term indicates the process of self-repair. The living organisms have stem cells both centrally and peripherally. These stem cells can be mesmerized to sites of injured tissues. In this manner, these cells ultimately go through the proliferation, migration, and accumulation process at injured or damaged sites gradually. With the sustention of this condition of “alarm,” the stem cells become exhausted permanently. That ultimately leads to irreversible disease transformed from their original locations. Basically, it depends upon the quantity of stem cell and during active regeneration, on its effective availability until a certain time period. The function of these adult stem cells therapy is the re-population of the stem cell pool. Ultimately, this improves the immune system. The presumed consequences of this fact could be the insufficiency of an adequate amount of stem cells for the tissue replacement and regeneration. Which in turn responsible for development of diseases and ageing. An irreversible and premature stem cell exhaustion could be promoted by this process. So, in turn, make the self-repair and survival process of organism impossible. As we grow older, our circulating stem cells become diminished. So the existing cells to our body’s circulation can improve health and repopulate our stem cell pool by introducing new stem (Anastasia Y. E 2015).

Researchers Closer to Gonorrhea Vaccine after Exhaustive Analysis of Proteins

In a study of proteins, November 8, 2018 Oregon State University researchers have reached closer to an invasion of vaccine for gonorrhea. Also proceed towards interpreting why the bacteria that cause the disease are so good at shielding off antimicrobial drugs (<https://www.sciencedaily.com/releases/2018/11/181108105945>).

The Food Biochemistry

Focuses on different ideas and schemes to intensify the knowledges and understanding of composition of foods, and particularly give emphasis on food components that have beneficial effects on health. The Food Biochemistry encompasses the implementation of different method including both chemical and biochemical analytical methods of food components [20]. It also focuses on their reactions, model systems, and various statistical

tools for data analysis efficiently to find out the maximum informative value. And finally apply those knowledges on public health sector.

Recent scientific era has witnessed that there is progressive development in the fields of biotechnology and biochemistry which leads to a tremendous success in the field of medical and public health science. The achievement and advancement created in the domain of biotechnology has resulted in evolution of newer classes of potential drugs. Lots of newly designed subunit vaccines are developed from the contribution of expression of various prophylactically important proteins, polypeptides and cloning. New techniques are constantly being introduced leading to production of phenomenal and curative molecules which help in diagnosis of different diseases, invention of preventive measures and eventually unveiling the ways to cure the diseases (<https://www.encyclopedia.com/food/encyclopedias-almanacs-transcripts-and-maps/nutritional-biochemistry>).

Vaccination

Recently DNA vaccines have been introduced in the arena of vaccinology, as a new prophylactic strategy enriching the public health sector. The genetic material expresses an antigen which is originated from pathogen. It plays a role to activate host immune system. Plasmid administration, is the main involving strategy (Kishwar H 2013). This plasmid usually conform of a strong viral promoter which drive the transcription and translation of the gene in vivo. The superior one is multicistronic vectors that have the potentiality of expression of more than one immunogen. Sometimes it expresses an immunogen and also an immunostimulatory protein. Definitely this multicistronic vectors are better than those that can express only one protein.

Treatment of Genetic Disorder

During the past decade, there has been a breakthrough in the field of genome editing and genome regulation. It made a remarkable easier way of involving various technologies. Among them, the CRISPR 9 bacterial system, one of the recently adopted technologies, which has evolved as a simple, RNA-guided phenomenon (Gupta R. M 2014). This is used for an efficient and specific genome editing and regulation in case of both bacteria as well as higher eukaryotes. The technology is emanated as a revolutionary tool in biomedical research and field. It has opened a new glimpse for treatment of genetic disorders. The process involves getting the guidance from RNA. The target sequence is opened by the breaking down of the host genome endonuclease. The defective repair mechanism of the generated double strand breakdown process emanates in insertion or deletion mutations. CRISPR mediated engineering usually expedite the initiation of specific point mutations or insertions in the target DNA. By using Cas9 Multiple genomic loci can be efficiently altered at a time through the introduction of several sgRNAs concurrently. For large-scale chromosomal rearrangements, this approach can be used. This technology is also used to achieve the disease models for genetic disorders. Besides other diseases such as carcinoma, which help us for easy understanding of pathological processes in the aspect of molecular basis (Nejat M 2013).

Treatment of Cancer

Recently, there is a new era of treatment of various types of cancer by the immune-based therapeutics, which is becoming the leading asset in the treatment of cancer. Antibody mediated checkpoint blockades in cell cycle can be used effectively for the management of carcinoma now a days (<https://www.cancer.gov/about-cancer/treatment/types/immunotherapy>). Expression of the programmed death-1 (PD-1) receptor is stimulated by cancer cells, used as an approach to downplay adaptive immune response of the host. Antibody mediated blocking of PD-1 can aid in revitalizing the adaptive immune response against cancer (Han Y 2014).

Antibiotic Resistant

There is imminent upswing of pathogens which are antibiotic-resistant. Side by side, development of new antibiotics has become sluggish even though there is elevated demand for substitute therapeutics (Richard J. F_2014). Now a day's probiotics are providing a promising approach. It provides their efficacy is enhanced by introducing new genetic circuits to deliver drug biomolecules to the specific sites. The term 'designer probiotics' are basically recombinant probiotics, which has the capability to reduce the gap between increasing antibiotic resistance and the inadequacy of new antibiotics. Probiotics are emanating living therapeutic agent. The prototype of probiotics can be used for disease diagnosis and prevention. The best documented effects including intestinal disorders, infectious diarrhoea and diarrhoea associated with antibiotic use, allergic conditions (Maria K 2013).

Zika Virus

Zika virus (ZIKV) belongs to Flaviviridae family. Nowadays, the emerging pattern of Zika virus is considered as a major public health concern. Globally, the researchers gave emphasis on ZIKV pathogenesis. To inhibit Zika virus, DNA therapy may result in an emerging therapeutic or prophylactic intervention. This knowledge will help to identify fixed targets for drug design. In different animal models, lots of studies have highlighted the role of DNA vaccine, inactivated vaccine, and viral-vector vaccine (John J. S 2017). These are capable of producing adequate antibody responses for the protection against ZIKV challenge.

Therapeutic Recombinant Proteins

Very recently, the most example of therapeutic usage of recombinant technology is recombinant proteins. Normally, if there are excess accumulation of protein, it results in their misfolding that ultimately causes the development of inclusion bodies. There are several ways by which one can regulate higher recovery of bioactive protein from inclusion bodies.

Use of Nanotechnology

There is a very important role of nanotechnology in different sectors of medical science. Now a days, some techniques are actually being used in some cases, while some are at different stages of experimentation and some of them are still hypothetical only. There is a revolution of medical science based on the use of nanotechnology. Nanotechnology is a very prospective way for diagnosis and treatment of different diseases of human body. Interesting thing is that, various techniques are assumed in few years back but very recently it is making striking progress towards becoming existence.

Nanocrystalline Silver

A Nano sized metal based formulation is Nano crystalline silver. This product is already marketed in United States and many other region. It exploits powerful antibacterial effect. The ionic silver has a potent antibacterial activity, especially against Methicillin Resistant Staphylococcus Aureus (MRSA) that may contaminate wound dressing. There is a rapid and early growth of Nano medicine marketing (Valentina M 2012). Whereas some are at the stage of clinical trial, while Nano-enhanced drug delivery products are commercially produced in the meantime, moreover there is a progressive development of advanced nanotech-based medical devices in current year. At present, Nano medicine has a large therapeutic areas in the field of treatment of carcinoma. In this aspect, Nano medicine has made lots of contributions. Worldwide Abraxane, Depocyt, Oncospar, Doxil, and Neulasta are used for the purpose of treatment of carcinoma. Nano-enabled medical products are potentially blotting out other forms of medicines and drug formulations. Starting from control of infection to treatment of CNS diseases, cardiovascular disease, even carcinoma as well, Nano-medical products are widely used. According to public health researchers, social and political scientists, hindrance of new molecular biological approaches can be refined by assessing the community health. This is a dreadful but fundamental challenges to analyze a complete dimension of determinants of health of population.

Both Biomolecular and biochemistry have the potentiality to achieve extensive environmental, economic and health benefits. There is a contrast between personal health and public health. The personal health attended as separate from public health. Besides range, drug treatment or establishing a national home visiting program for new families, it is also essential to expand opportunities for awareness, physical activity, reducing illiteracy, school dropout rates and female empowerment. Globally the upcoming challenge is to convincing the policy makers that personal health care is not the only determinant of health. Further allocation in research, program, or evaluation are the prime important to be started urgently and immediately with the novel goal to improve health for the entire population all over the world.

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Chapter 522

PROMOTING EFFECTIVE TREATMENT AND PUBLIC HEALTH EFFORTS TO COMBAT USE OF SMOKELESS TOBACCO PRODUCTS AMONG APPALACHIAN MALE ADULTS AND YOUTH

Amber K. Hord-Helme and Donald W. Helme, Jr.

Tobacco use is the leading cause of preventable disease, disability and death in the United States (NIDA, 2014). For every person who dies from smoking, many more suffer from at least one serious tobacco-related illness (ACS, 2013b). Like cigarettes, smokeless tobacco (ST), such as chewing tobacco or snuff, contains nicotine and other chemicals and ST users' exhibit characteristics of nicotine addiction similar to that of cigarette smokers. They also suffer from the same health issues, including cancer, heart disease, stroke and type 2 diabetes (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, International Agency for Research on Cancer, & World Health Organization, 2007; Piano et al., 2010; USDHHS, 1986; 2002). ST is used primarily among males that live in rural settings (12.8% of rural males v. 5.8% of urban males) (ACS, 2013a; NIDA, 2014). This rate is accelerated compared with rates of tobacco use in general with 27% of rural males versus 19% in large urban areas (ACS, 2013a; NIDA, 2014).

Use of ST products has also shown to increase over time among adolescents; from 11.2% in high school freshmen to a 16.6% increase by seniors (CDC, 2018; Chaffee, Couch, & Walsh, 2015). ST use is also correlated and considered in some cases to be inextricably tied with increased demonstration and practice of high-risk behaviors and use of other substances such as other types of tobacco products, alcohol and more illicit drugs. (Levant, Wimer, Williams, Smalley, & Noronha, 2009; Meyer, Toborg, Denham, & Mande, 2008). It is imperative to address ST use in Appalachian populations in order to prevent tobacco use and other high-risk health behaviors.

Why do young males, especially Appalachian males, initiate ST use? Helme et al. (2012) and Nemeth et al. (2012) identified male gender norms and identification as primary paths to initiation of ST use. ST use has overwhelmingly been shown to be a white male phenomenon

that often occurs in the presence of other males, especially in rural areas and/or contexts that are considered male-focused - including traditionally male sports, recreational activities and occupations that are commonly valued as masculine in Appalachian culture (Chaffee et al., 2015; Nemeth et al., 2012). To further complicate the situation for adolescents, the tobacco industry has begun developing dissolvable tobacco chew products that do not have to be spit, and put them into convenient packages that are considered more discrete (Liu et al., 2014). This has enabled students to utilize ST products in schools without being detected.

It is imperative for research and prevention and treatment strategies to incorporate culturally sensitive and culturally informed methods to specifically target Appalachian males. With this population, traditional tactics to increase awareness, prevent initiation and promote cessation are not necessarily effective and, in some cases, would be considered contraindicated (Levant et al., 2009). Campaigns and treatment efforts must include appreciation aspects of traditional Appalachian male identity, family structures, and history in developing effective prevention of initiation and use of smokeless tobacco products.

INCREASED RISK FOR MALES

When considering men in health research, it seems illogical to diminish the role of gender-culture in men's health-related behaviors. Men are much more likely to begin using ST when they are with other men than when they are with women (Chaffee et al., 2015; Cohen-Smith & Severson, 1999; Couch, Darius, Walsh, & Chaffee, 2017; Helme et al., 2012; Nemeth et al., 2012; Ng, Weinehall, & Ohman, 2007; Norberg, Malmberg, Ng, & Broström, 2015). They are also more likely than women to believe that they are not at risk for problems related to ST (Courtenay, 2000). It is also important to note that men cited male peers as being most influential in their decision to initiate use of ST (Helme et al., 2012).

Historically most tobacco control efforts have been focused on educating the public (men and women) about the dangers of cigarette use and persuading them to cease tobacco use. There has been less focus on educating men specifically and persuading them to quit use of smokeless tobacco or e-cigarettes (Helme et al., 2012). Researchers have frequently employed the health belief model, the Transtheoretical model and the theory of reasoned action to predict what makes people more likely to engage in health-promoting or threatening behaviors. Critics note that certain variables used to model men's tobacco use, including age, race, and socioeconomic background are distal and possibly inconsequential to men's decision-making and health behaviors (Levant et al., 2009; "PsycNET," n.d.). This emphasizes the need for inclusion of male-specific foci in tobacco prevention efforts. Research suggests that masculinity is a critical, but largely unexplored factor for why men use ST.

The combination of the Masculinity Theory (MT) (Connell & Messerschmidt, 2005; Courtenay, 2000, 2003) and the Theory of Reasoned Action (TRA) (Fishbein & Ajzen, 1975) clarifies ST use among adolescent and adult males. MT as a theoretical approach frames masculinity as a social product that men institute through interaction rather than as an inherent characteristic of individuals (West & Zimmerman, 1987). From this perspective masculinity is not a given. Instead, men must work actively and collaboratively to assert and "prove" their manhood. Scholarship in this area suggests that proving masculinity typically

involves competition for dominance, risk-taking, emotional regulation (and sometimes suppression), displays of toughness, and (hetero) sexual prowess (Connell & Messerschmidt, 2005).

Competition and posturing among men-adolescent males in particular-establishes a hierarchy of masculinity. Within this hierarchy, those closest to the most dominant “hegemonic” ideal extract the most symbolic and material rewards (Pascoe, 2005). The exact features of this hegemonic ideal and the resources available to obtain it may vary according to time and place. Research on men and masculinity confirms that men actively police the masculinity of other men, holding others “accountable” for non-normative behavior and sometimes encouraging hyper-masculine displays (Kimmel, 2012). This competitive accountability can produce harmful collective behavior such as heavy drinking, sexual assault, bullying, substance use and other high risk behavior to demonstrate manliness to peers (Courtenay, 2000; Schrock & Schwalbe, 2009).

The Theory of Reasoned Action (TRA) (Al-Suqri & Al-Kharusi, n.d.; Fishbein, Ajzen, Albarracín, & Hornik, 2007) has a long history of utility in tobacco prevention and cessation research. TRA essentially formulates how the combination of attitudes, norms and motivation comply with behavior change to predict behavioral intentions. These intentions predict one’s future behavior change. MT and TRA together may better identify, explain, and provide solutions for male (particularly rural Appalachian male) attitudes about tobacco use. Appalachian men’s perception of the beliefs, opinions and attitudes of important others (particularly peers and older male family members) admired or emulated males and attitudes of important females, such as girlfriends, mothers, grandmothers, etc. are factors that contribute to or predict initiation and continued use of ST, and possibly assist in informing interventions to encourage cessation.

INCREASED RISK FOR APPALACHIAN MALES

Why are there excessively high numbers of youth and adult males using ST in Appalachian rural regions? What makes this male population particularly susceptible to initiation and continued use of ST? There is a confluence of factors with regard to cultural/community influences including targeted advertising, excessive exposure and access, and other risk-factor correlations that effectively promote the use of ST in larger numbers of Appalachian men when compared to the general population.

According to Nemeth et al. (2012) and Helme et al., (2012), the use of tobacco products appears to be a “rite of passage” in the development of masculine identity among Appalachian youth. Boys that begin using ST are generally following the influence of older male family members or are encouraged to do so by peer groups. Both studies found that in two different regions (rural Ohio and Kentucky) boys emulated current ST users or were actively encouraged to use ST through male family or peer networks which points to an underlying cultural value. “Enumerating cultural beliefs thus becomes a critical step in the process of understanding initiation into tobacco use behavior and developing effective interventions” (Nemeth et al., 2012).

Male-Dominated Occupations and Masculine Recreational Pursuits

The first and perhaps most crucial cultural factor that promotes the development of Appalachian identity incorporates the use of ST in traditional occupations for men in the region. Most male-dominated Appalachian occupations are associated with promoting tobacco use, particularly ST. Meyer et al. (2008) states that “tobacco growing represents an economic mainstay in many communities, a fact that contributes to the acceptance of its use.” According to Obermiller and Oldenick (1994), “The use of tobacco products not only is socially acceptable among mountain men and women but also widely perceived as critical for economic survival.”

Participants in the Nemeth et al. (2012) study observed that “farm boys” would use ST as a replacement for lighting up a cigarette or other smoking products so as to not risk fire around the barns. Another occupation where fire risk becomes a problem, hence promoting the use of ST, is in the coal mines (Meyer et al., 2008). It is noted that the prevalence of ST among coal miners contributes to its acceptability in families and boys will model their fathers’ behavior. Therefore “attacks on the tobacco industry may be effective in certain communities in the nation, but they are likely to be counterproductive in families and communities deeply tied to tobacco cultivation...Many Appalachian communities continue to depend economically on coal...Messages to prevent ST use and treat it in coal mining communities might develop messages that acknowledge and form strategies to cope with workplace influence” (Meyer et al., 2008). Factories are another place of employment where lit smoking products are not allowed, but ST products are not a problem (Nemeth et al., 2012). These industries have largely defined the Appalachian region and given opportunity to men where there otherwise was very little.

Participants in the Nemeth (2012) study commented often about using ST when participating in traditionally male, outdoor recreational activities that bolster their masculine identity. Sports such as hunting, fishing, four-wheeling, and other primarily male sports and recreation pursuits present opportunities for access and exposure which has been shown to increase likelihood of use (Levant et al., 2009).

Rural Masculine Identity Development

From a cultural standpoint, gender roles in locations that emphasize traditional masculine ideology create circumscribed expectations of men that promote risky health behaviors (Levant et al., 2009). The push toward restrictive emotionality, gender role stress and conflict, conformity to masculine social norms, and cultural beliefs/values about risk-taking in masculine identity research has been well-documented (Helme et al., 2012; Levant et al., 2009; Liu et al., 2014; Nemeth et al., 2012). Rural male identity is perhaps particularly susceptible since interpersonal factors are shown within the culture to be the single most influential element in promoting initiation among rural youth and continued use among rural adult males (Helme et al., 2012; Nemeth et al., 2012). These studies advocate the idea that use of ST is primarily promoted through male social networks in these regions. According to Sorenson (2004), cultural understanding of tobacco use is defined by “learned or shared knowledge, beliefs and rules that people use to interpret experience and to generate social

behavior.” An example of this is observed in rural college-age men whose initiation and continued use of ST began during adolescence in the company of other males and was a result of the desire to fit in with and earn the admiration or acceptance of male peers and role models (Helme et al., 2012). To use tobacco and participate in other traditional Appalachian male activities defines what it is to be a man in these communities. Therefore intervention efforts should focus on shifting the perceptions of cultural norms and address male social networks as a vehicle in ST initiation.

In addition, many of the men in the Helme et al. (2012) study also reported progressing from initial use of ST-only to use of other tobacco products, initiating poly-tobacco use. This is a finding that is observed in other studies of male smokeless tobacco use patterns and prevalence (Agaku, Ayo-Yusuf, Vardavas, Alpert, & Connolly, 2013; Arrazola et al., 2015; Cortese & Ling, 2011; Haddock et al., 2001; Liu et al., 2014; Tomar, Alpert, & Connolly, 2010; Wetter et al., 2002)

Targeted Advertising to Appalachian Males

The tobacco industry has put billions of dollars into researching effective ways to target likely users of ST products. Meyer et al. (2008) reports that an estimated \$239 million was spent by the tobacco industry to research how to market ST products effectively. Many participants in the Liu (2014) study commented on the use of images such as cowboys, lumberjacks, mountain men, timber wolves and similar “manly” motifs to appeal to the masculine ideology. In addition the images on the new dissolvable products are more animated and colorful in order to promote use by younger potential users (Liu et al., 2014). The tobacco industry recognizes that the contribution of traditional masculine ideologies, cultural factors, and male social networking promotes the use of their products. Therefore, prevention and treatment efforts must do the same.

IMPORTANCE OF MALE SOCIAL CONNECTION AND NETWORKS IN APPALACHIA

As discussed earlier, the single most important factor influencing prevalence of initiation and continued use of ST products in Appalachia is the influence of male social networks with peers and family. Helme et al. (2012) highlights the number of participants who spoke about their first and subsequent experiences with use of ST products as being in the context of older admired male family members and peers. Many participants spoke of their first experience of use as adolescents (or even younger) when an older male family member would offer ST as an honor; an acknowledgement of their developing status as a man amidst other men in the community. Despite many of them saying that their first use was distasteful or made them ill, many acknowledged the importance of using ST as a means of continued social acceptance and maintenance/improvement of status among the men (Nemeth et al., 2012).

Most authors acknowledge the importance of family in Appalachian culture. According to Meyer (2008), “kinship influence differentiated it (Appalachia) from the nation.” Since men are often in laborious and dangerous professions that frequently lead to injury, health

problems and disabilities, risk-taking commonly becomes part of the acculturation of young men. When injury, health problems, or disabilities do occur, the importance of family connection and family support in caring for incapacitated loved ones becomes essential (Meyer et al., 2008). The male bonding rituals appear to help foster the cultural values that have allowed families to survive in difficult circumstances.

Common practices in Appalachian homes extend to practiced social behavior within peer networks in communities outside of the home. If ST renders social status among family, then surely social status and connection can be fostered with peers in the same manner. Participants in many studies reported that the prevalence of evidence of ST use in schools and through sports activities are rampant. One participant in Nemeth's (2012) study commented that the "best advertisement is just the people around here...I used it to relax me after varsity football...It's just part of being a young guy around here." A female participant commented about the prevalence of ST spit in the school bathrooms and hallways (Nemeth et al., 2012).

PREVENTION AND CESSATION CAMPAIGNS

The predominate cultural perception is that "everybody does it" (Helme et al., 2012; Nemeth et al., 2012), when in fact only about 12-13% of the male population use ST (ACS, 2013b; NIDA, 2014). Campaigns to prevent use of college students from smoking and drinking have focused on publicizing the actual prevalence of use, which is almost always perceived to be much higher among populations than actually exists (University of Missouri, 2018).

The message that tobacco use is harmful to health is a message that the Appalachian community is already well aware of due to experience with family members suffering from those consequences (Levant et al., 2009). Within families, conflict is often initiated amidst those that are users versus those that are not because of the knowledge of its harmful effects (Meyer et al., 2008) and the greatest influence on ST cessation is due to the power Appalachian women exert on the patterns of use in men. Men often stop because of the wishes of important female figures in their lives such as girlfriends, wives, mothers, grandmothers, etc. Appalachian women are often the spokespersons and guardians of health in their families (Meyer et al., 2008). One participant in the Nemeth (2012) study commented, "The only one I have to hide it from is Mom." A strong influence in promoting cessation is also observed when men become fathers (Meyer et al., 2008).

Rather than bemoaning the harmful health effects of ST, it is more prudent to help families talk about their experiences of the ill effects of ST use. Additionally it is important to target the cultural perception that ST use is a requirement for being a man through the utilization of regular social networks, family and peers. Empowering men who do not use ST to speak up to those who do, or are thinking about initiating use of ST products, is imperative. The connection with family and peers is of utmost importance in the Appalachian community. It is essential that prevention and treatment efforts aim at changing cultural perceptions within existing social networks. This is much more likely to be effective than "professional" outsiders interfering in cultural practices.

Essentially it is the family system and not the individual that will need to be addressed for prevention and treatment efforts to be effective (Meyer et al., 2008). Enlisting women as

health managers of their families (Meyer et al., 2008), accepting the influence of older admired males in the lives of young men (Helme et al., 2012; Nemeth et al., 2012), and addressing the stress involved in the survival of the Appalachian family will likely be the most effective route to preventing this and other health-risk behaviors (Levant et al., 2009) that are common among Appalachian men.

IMPLICATIONS FOR COUNSELING AND PSYCHOTHERAPY

It is very uncommon for Appalachian males to seek professional help in addressing problems associated with smokeless tobacco use. However, it is common for individuals to seek out help for grief and loss issues, coping with chronic health issues, and problems with social isolation. Therefore it is imperative for counselors to recognize that ST use may be a contributing factor to these issues and must be addressed in treatment protocols. Helping clients see the connection between ST use and other health-risk behaviors as a problem so that they can then be empowered to deal with these issues within their communities could have a significant impact on health in the region.

It is also extremely important to take into consideration the cultural factors that influence ST so as not to fall into the trap of using ineffective and contraindicated methods. The family system exerts a strong influence on the behavior of its members and must be utilized in positive ways to be effective in promoting non-initiation and cessation of ST use. Capitalizing on existing knowledge within families about the risks of ST use and its impact on other family members is key. Educating the family system and involving family members in accountability efforts is very effective in decreasing the access and exposure of ST.

CONCLUSION

The impact of socio-cultural norms, traditional masculine ideology, excessive exposure and access, as well as advertising practices are significant in the explanation of increased initiation and use of ST products among Appalachian males in increasingly high numbers. Family systems, approaches to treatment and public health messages targeting ST use may also multiply the impact of the use of other tobacco products, such as cigarettes, cigars, etc. as well as alcohol use and the use of other substances in the region. Cultural perception, values and practices are the key to developing strategic public health and community treatment campaigns designed to decrease the use of ST products.

Despite the entrenched nature of ST use in Appalachia, there is hope for effective intervention strategies. The prevention, cessation campaigns and treatment in the region must be culturally aware and sensitive to the realities of ST use in Appalachian culture. Connection to family and male social networks and norms can be used as advantages in changing cultural perception of ST use. According to Meyer (2008), "Culture deeply influences the perceptions, actions and relationships among individuals who live in a community and profoundly shapes matters of personal and public health. To be effective, the message and its vehicle ultimately need to appeal to the perceptions and realities of the targeted population, and this fact requires consideration of the cultural milieu of that population." Additional research is of utmost

importance in discovering and determining the effectiveness of new treatment and cessation programs and most importantly in identifying and deploying determinants in the initiation of ST use.

It is imperative to become involved in efforts to combat the influence of the tobacco industry in their advertising. Advocating for control of advertising images, convenient packaging that allows for clandestine use, especially by youth, and advertising methods targeted at susceptible populations such as Appalachian male adults and youth is important to protecting an already vulnerable and disenfranchised group that is suffering.

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Chapter 523

MICROBIOLOGY OF FISH AND FISH PRODUCTS AND ITS IMPLICATIONS ON PUBLIC HEALTH

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ABSTRACT

This chapter reviews bacteria that deteriorate fish; those that may harm the consumer; fish contaminant bacteria; the risk ranking for consumers; limited bacteria in some legislations and worldwide recommendations; methods and techniques to detect spoilage and pathogens in fish.

Keywords: seafood, bacteria, legislations, human pathogens

INTRODUCTION

The world production of fish and fishery products in 2013 was approximately 160 million tons, and its consumption is estimated at 20 kg per inhabitant per year [1]. Although fish is one of the most sought sources of muscle meat, with high market value, its consumption in Brazil is considerably below the world average. Nevertheless, in the past years an increase of around 14.5% in demand has been observed [2]. Cultural globalization, price reduction,

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diversity of marketed products, and an ever-growing desire for a healthier diet contributed to a worldwide increase in fish consumption [3].

Due to its high amount of water and the “richness” of its chemical constituents, fish provides an excellent culture medium for bacteria, which make hygiene and temperature parts of the binomial important for its conservation and acceptance. In addition, time (i.e., fast and accurate decision-making) is another factor that, added up to the binomial in our equation, strengthens it, and tends to keep the product from spoilage and decay.

The deterioration process is caused, mainly, by psychrophilic and psychrotrophic bacteria but, above all, the quality of fishery products is measured by the risk of diseases a customer is under by consuming it. Thus, many countries adopt laws and other legislation in order to control fish quality and its products, aiming to protect consumers from any harm they may cause.

BACTERIAL DECOMPOSITION IN FISH

It is possible to describe deterioration as the set of simultaneous autolytic and microbial reactions in an animal right after its death, which originates undesirable compounds/by-products with unpleasant smells and tastes.

Fish might be contaminated with the broadest and most diverse group of microorganisms, through contaminated or polluted waters from estuaries and fishing grounds. The living animal presents bacterial contamination mainly in the skin, gills and scales; and it may spread through other tissues after its death. Therefore, an improper handling and the non-compliance with proper hygienic measures during transportation, handling and storage processes may promote the development of pathogens present in the fish itself or in the environment [4]. Given the difficulty in identifying the source of unpleasant taste and odor in decayed fish, it is interesting to establish standards for fish freshness so that, by making use of a table of attributes, trained panelists are able to analyze products through sensory signals and features. In a parallel analysis, there should be physicochemical tests and bacteriological counts at different temperatures. After these tests, a proper identification of the bacteria responsible for the deterioration should be less arduous. In crustaceans, for example, Vieira et al. [5] described a typical sequence of decomposition while studying lobsters of the genus *Panulirus* White, 1847, in Fortaleza, Ceará State, Brazil. During the first six days of the samples in ice storage, no changes in color, odor and texture of meat were observed. Bacterial counts (log CFU/g) in the muscle at 5 and 25°C did not change considerably. However, on the 13th day of the experiment, some changes were already noticeable. From that day on, meat turned flacid and for the content of total volatile bases exceeded 25 g/100g; trimethylamine reached values above 2.28 mg/100g and panelists rejected the crustaceans. On that day, the Standard Plate Count (SPC) at 5 and 25°C reached 4×10^8 and 8×10^8 CFU/g, respectively, confirming the deterioration by psychrophilic and psychrotrophic bacteria.

Generally speaking, specific spoilage microorganisms (SSO) [6, 7] produce metabolites related to certain smell and tastes of this process. In species from temperate waters, *Shewanella putrefaciens* is a typical dominant microorganism in this particular stage. Bacteria from the Vibrionaceae and Enterobacteriaceae families are also related to spoilage. In tropical waters, *Pseudomonas* have been described as dominant [8]. According to Simmonds &

Lamprecht [9], freshness of ice-stored fish correlates well with sensory analysis, when the counting occurs at 20°C. At this temperature, *Pseudomonas*, *Acinetobacter* and *Moraxella* predominate.

BACTERIA THAT MAY CAUSE HARM TO THE CONSUMER

Seafood is colonized by natural and/or pathogenic microbiota, mostly depending on where it is captured. Some factors that may contribute to an infection by pathogenic bacteria are the presence of sewage and storm water runoffs in the aquatic environment. Diseases related to seafood consumption can be caused by biological, chemical or physical agents. Biological pathogens are represented by a vast amount of bacteria, viruses and parasites [10]. According to Huss et al. [11], pathogenic bacteria detected in seafood and its related products can be divided into three groups: 1) those normally present in the habitat of the species: belonging to the *Vibrio* genus (*V. parahaemolyticus*, *V. cholerae*, *V. vulnificus*), *Clostridium botulinum* Non-proteolytic serotype E, *Plesiomonas shigelloides* and *Aeromonas* spp.; 2) those generally present in the environment: *Listeria monocytogenes*, *Clostridium botulinum* proteolytic type A and B, *Clostridium perfringens* and *Bacillus* spp.; 3) those that usually have man and other warm-blooded, terrestrial animals as their natural habitat (*Salmonella* spp, *Shigella* spp, *Escherichia coli*, *Campylobacter jejuni* and *Staphylococcus aureus*). In order to control these bacteria and prevent them from contaminating products derived from fish, it is of utmost importance to know their origin, biology, physiology and ecology; as well as their survival and growth within the products related to the diseases with which they are associated [10].

In the following sections are described relevant microorganisms; types of fishery products, where they have been most frequently observed/found are pointed out; and incidents in Brazil and/or Latin America are detailed.

Group 1: Bacteria Normally Present in Fish Habitats

Vibrio parahaemolyticus is part of the Vibrionaceae family. They live only in brackish or seawater and are known to cause gastrointestinal illness in humans. *V. parahaemolyticus* is a natural inhabitant of coastal warm waters; in countries with colder weather they are present in higher concentrations during summer; it is a halophilic organism (i.e., organisms that thrive in environments with very high concentrations of salt). Moreover, as a mesophilic organism it is eliminated from seafood by exposing it to heat. When seafood is served raw (e.g., oysters, mussels, sushi, sashimi and/or Carpaccio), its consumers are under risk of infection [8]. The illness' symptoms usually start within 24 hours of ingestion. Illness is commonly self-limited and known to last for up to 3 days. Severe disease is rare, occurring with higher frequency in people with weakened immune systems. *V. parahaemolyticus* may cause infection on the skin when an open wound is exposed to warm, contaminated seawater [12]. According to Boutin et al. [13] *V. parahaemolyticus* intrudes and invades with considerable impact and may spread throughout the body via the circulatory or lymphatic system, causing septicemia. Mahmud et al. [14] stated that the consumption of seafood products may pose risks to public health, since

toxigenic strains of *V. parahaemolyticus* (O3:K6) have been isolated from those sources, demonstrating pandemic potential. In Fortaleza, Ceará State, 26 individuals were involved with an outbreak of gastroenteritis after eating raw crab claws in a restaurant of a hotel where they were hosted. *V. parahaemolyticus* O3:K6 (Kanagawa positive) was confirmed in six samples among nine sent to The Oswaldo Cruz Foundation (Rio de Janeiro) [15]. Despite the low number of reported cases involving *V. parahaemolyticus*, detection of pandemic clones with high potential for virulence in northeastern Brazil and the high temperatures of the region are factors that favor the spread of these bacteria [16]. *V. parahaemolyticus* produces an enterotoxin similar to the one produced by *V. cholerae*, which is able to inflame the epithelial lining of the small intestine. In almost 1/3 of the cases, the diarrhea has bloody form [17]. Vieira et al. [18] while working with oysters purchased at a local restaurant in Fortaleza, Brazil, identified urease-positive and also *tdh* and *trh* positive *V. parahaemolyticus*, concluding that oysters served at restaurants in State of Ceará may cause gastroenteritis to the costumers. In Brazil, *V. parahaemolyticus* was recorded as etiologic agent in several cases of intestinal infection associated with the consumption of, crustaceans and shellfish [10, 19]. The first reference to the isolation of *V. parahaemolyticus* (O5:K17 sorotype; Kanagawa-positive) in Brazil was made by Hofer [20] in diarrheal stools from a six-year old child in Cascavel (State of Ceará).

Vibrio cholerae and *V. vulnificus*, as *V. parahaemolyticus*, also belong to the group of species that cause vibriosis naturally lives in brackish or marine waters but there is no mention to them in the legislation, neither in Brazil nor the European Union. They may infect fish and if product is consumed raw or not properly cooked, may also be transmitted to the consumer. In fact, if the *Vibrio cholerae* belongs to the serotype groups O1 and O39 it might transmit cholera, an epidemic disease characterized by abundant diarrhea.

Vibrio vulnificus is homologous to *V. parahaemolyticus*, differing only on the ability to ferment lactose. It may cause septicemia and eventually death, via ingestion or the bloodstream - reaching through the intestinal tract or open wounds exposed to contaminated marine environment [21].

C. botulinum is widely distributed in the soil and aquatic environments worldwide. It has the ability to produce the most lethal toxin, known as botulinum toxin (BoNT). Seven types of this toxin, from A to G, are known [22]; toxin E is usually associated with the consumption of marine fish and fish/seafood products [23] because its spores tend to be more confined to water, especially seawater [24]. Spores of *C. botulinum* -non-proteolytic type E can germinate at temperatures below 3°C and are often found in association with stocked marine fish [25]. The first botulism outbreak on record in Brazil was in 1958 in the State of Rio Grande do Sul: nine people died after having ingested fish using homemade preservation techniques [26]. In 2007, an isolated case of botulism - again for the same reason - occurred in city of São Paulo [27].

Clostridium botulinum serotypes E, A and B, proteolytic and non-proteolytic, are not contemplated by current guidelines (or regulations or legislation) in Brazil, only sulphite-reducing clostridia (Resolution 12 by the Brazilian Health Surveillance Agency, Ministry of Health [28]). The authors decided to include them all in one item only (Tabela 1). *Clostridium botulinum* is cited, but not limited, by FDA and CODEX.

Proteolytic types A and B of *C. botulinum* were found in samples from areas above Chesapeake Bay (USA) and in samples of fresh blue crab meat (also in the USA) [29]. During 2007, in Brazil, a case of botulism linked to the consumption of homemade canned

fish was reported in São Paulo State. The case was confirmed and related by the Center of Epidemiological Surveillance of São Paulo [30]. Zadeh et al. [31] reported a case of a 12-year old that developed symptoms of weakness and diplopia six hours after the ingestion of barbecued caviar, a fish roe product. Immediately, serum, gastric and stool samples were sent to the Pasteur Reference Laboratory (France) for botulinum toxin detection. Based on the clinical report, the patient received three monovalent antitoxins: A, B and E; and progressively evolved to better health state within 10 days. In Argentina, 21% of the cases of botulism recorded between 1980 and 1989 were related to the consumption of fish and fish products [32].

Plesiomonas shigelloides belongs to the Enterobacteriaceae family, with its primary habitat being warm water environments and fish from both freshwater and seawater. *P. shigelloides* is a Gram-negative bacillus with a positive oxidase test [33]. Ingestion of *P. shigelloides* may not always be a cause of diseases to its host, but the microorganism may remain as a non-infectious, transitory member of the intestinal microbiota. The disease caused by *P. shigelloides* is gastroenteritis, which is usually self-limiting, and yields fever, chills, abdominal pain, nausea, diarrhea or vomiting. The bacteria may be invasive and produce toxins [34]. They are not considered in any global regulation. This bacterium has been isolated from the tissue of fresh and pre-cooked mussels from a farm in Niteroi, Brazil [35]. Infections have been associated with travel to or residence in tropical and subtropical countries, with the consumption of raw seafood or with exposure to amphibians or reptiles [36, 37].

Aeromonas spp. are Gram-negative microorganisms, rod in shape but with a slight resemblance to cocci – straight but with rounded ends. They are catalase and oxidase positive, reduce nitrate to nitrite and ferment D-glucose with acid/acid and gas production. In addition, they are mesophilic and resistant to the vibriostatic agent 2,4-diamino-6,7-diisopropyl-pteridine O/129. They are found in aquatic environment, both clean and/or contaminated with waste and disposal from sewer systems. After ingestion, they may cause intra and extracellular infection. In Brazil, a case of mild diarrhea was reported after the consumption of a shrimp cocktail, and *A. hydrophila* was isolated from both the incriminated food and the patient's stool samples. Both isolates had identical ribotypes [38]. *Aeromonas* are frequently isolated from fish [39] and mollusks [40]. They usually contaminate fish due to their ubiquity in aquatic environments, with several genospecies described as pathogens of fish and humans [41].

Group 2: Bacteria Generally Present in the Environment

Listeria monocytogenes is a mobile, Gram-positive bacterium which grows at 37°C but at the same time is both psychro and halotolerant [42]. *L. monocytogenes* has been isolated from processed marine products (cooked and frozen), marinated fish, surimi, sushi and smoked fish and it is able to rapidly grow in brined shrimp and cold smoked fish. The bacterium is of little importance in semi-preserved fish products when using 2.5% acetic acid. The freezing process eliminates these bacteria, and certain levels of acid and NaCl prevent its growth [43]. However, Hofer & Ribeiro [44] studied and found *Listeria* in samples of frozen *Penaeus subtilis* and *Xiphopenaeus kroyeri* shrimps in Brazil. From a total of 45 frozen shrimps, *L.*

innocua serotype 6a was found in three samples and *L. monocytogenes* in four; 1/2a in three samples and 4b in one. Furthermore, Laciari et al. [45] reported the presence in 50 samples of fish, 22 samples of squids and shellfishes, the isolation of *L. monocytogenes* in a sample of squid and *L. innocua* in a sample of mollusk. No fish sample showed the presence of *Listeria* spp.

Clostridium perfringens is an anaerobic, Gram positive, mesophilic, spore-forming bacterium distributed in the environment; in soil, it is found at levels of 10^2 - 10^4 /g. If high levels of vegetative cells are ingested, they are likely to reach the intestine and sporulate, producing an enterotoxin which may result in abdominal pain, nausea, diarrhea and vomiting in about 8 to 24 hours after ingestion. In the USA, approximately 7 out of 200 reported cases of infection per year are related to consumption of marine fish [46]. Virulent and toxigenic strains of *C. perfringens* were also isolated in unprocessed fishes from freshwater randomly obtained from local sources in Tamil Nadu, India [47]. Poisoning outbreaks caused by *C. perfringens* are especially common in institutions where food is prepared in advance before serving, and preparation conditions favor bacterial multiplication. It is possible to detect *C. perfringens* in foods of animal origin, such as meat and meat products, meat dishes, stews, soups, gravies, and milk. Occasionally, poultry products, pork, lamb, fish, shrimp, crab, legumes (beans), potato salad, and macaroni and cheese may contain *C. perfringens*. These foods at improper storage temperatures provide risk of infection and disease from *C. perfringens* [48]. Since there is no law on mandatory reports of infections by *C. perfringens* in Brazil, there are no cases on record involving fish consumption.

The *Bacillus* species typically responsible for infections, including symptoms of diarrhea and vomiting, is *B. cereus*. Fish, meat, and vegetables are commonly associated with this type of disease transmitted by food. In industrial fish farms in Germany, *B. cereus* was identified in fish from *Clupea* genus after the addition of contaminated seasoning ingredients. The bacilli sporulated after incorrect freezing, a subsequent process that follows pasteurization procedures [46]. In Netherlands, a higher prevalence of psychrophilic strains of *B. cereus* have been reported in meat and meat products (20.8%, n = 24) and in fish and fish products (40%, n = 40) [49]. In Brazil and other Latin American countries, the habit of consuming dishes based on raw fish, with its handling and preparation based on techniques brought from Eastern cultures (e.g., sushi and sashimi) has caused frequent events of intoxication. Rice is an ingredient of sushi, which without proper acidification control introduces the risk of toxin formation by *B. cereus* [50].

Group 3: Bacteria That Usually Have Man and Other Warm-Blooded, Terrestrial Animals as Their Natural Habitat

Salmonella, *Shigella* and *Escherichia* species are fecal bacteria. They belong to the Enterobacteriaceae, having humans and terrestrial, warm-blooded animals as hosts. These microorganisms can contaminate the living animal (incl. fish), depending on the capture site. Further contamination may occur during processing. They may cause serious harm depending on contamination levels but proper cooking eliminates harm. A special attention must be directed to cross-contamination, as well as contamination in work areas (production lines in

industrial facilities for seafood processing, kitchens), and the transfer of microbial pathogens into products that are to be consumed raw [51].

Standards set by Brazilian legislation for *Salmonella* in food is that the organism should be absent in 25 g [28], due to its pathogenicity. However, outbreaks of salmonellosis are not of mandatory notification (except if the case involves typhoid fever), a factor that compromises proper monitoring and investigation of this pathogen. In a study that analyzed the occurrence of *Salmonella* in fish in northeastern Brazil, this enterobacteria was detected in 4% of the samples of fish and shellfish (shrimp and lobster) assessed in the experiment [52].

Campylobacter jejuni are Gram-negative rod-shaped, S-shaped (or of curved morphology) non-spore-forming bacteria that might present a spherical or coccoid form in old cultures. They move by a single polar flagellum at one or both ends [53]. *C. jejuni* and *C. coli* are the most common species of *Campylobacter*, and are usually associated with diarrhea [54]. Although less frequently found when comparing fish to other types of meat, the low infectious dose (500 cells), makes campylobacteriosis one of the most typical zoonotic diseases in human beings [55].

Staphylococcus aureus belongs to the Micrococcaceae. They are Gram-positive round cells, which are found grouped in the shape of grape clusters. They cause food intoxication and are transmitted due to low hygiene standards, during its use and handling. Albuquerque et al. [56] while investigating *S. aureus* in ice, water, benches and in the body parts of sellers and fishmongers (nose, mouth and hands) at a fish fair in Fortaleza, Brazil, identified the bacteria in all surveyed sites, including 100% of the fair shrimp vendors. It was then suggested that there should be more information on adequate hygiene standards and proper handling of the ice for fish refrigeration.

OTHER CONTAMINANT BACTERIA IN FISH AND FISHERY PRODUCTS

In addition to the previously mentioned bacteria, Gelli [57] lists microorganisms able to release histamine (a decarboxylation of histidine), a characteristic that involves mainly fish from the Scombridae family (tuna and bonito). Some histamine-producing bacteria are members of the *Enterobacteriaceae*, along with *Vibrio* sp., *Clostridium* and *Lactobacillus* spp. The strongest histamine producers are *Morganella morganii*, *Klebsiella pneumoniae* and *Hafnia alvei* [58]. In general, biogenic amine-producing bacteria are not part of the marine fish microbiota, their origin is due to contamination by inadequate hygiene habits during capture or associated with a contaminated aquatic environment [59]. Thus, it is possible to affirm that the presence of histamine is also an indicator of bad bacteriological quality [60].

In reference to fermented fish-based products, *Staphylococcus* spp. and *Tetragenococcus* spp. were listed as histamine-producing [61]. Oliveira et al. [59] investigated the presence of histamine in samples of canned tuna and sardines purchased in retail stores in Fortaleza, Brazil, which were analyzed by high performance liquid chromatography (HPLC) in reverse phase. All samples showed the presence of histamine. Levels above 100 mg histamine/kg were detected in 55% of the tuna samples and 13.33% in sardines. The authors concluded that it is necessary to improve the quality of the raw material, and the amounts found in the samples would be able to cause symptoms of poisoning in consumers of fish.

RISK CLASSIFICATION IN A DIETARY FISH CONSUMPTION

Considering aspects of seafood microbiology (afore-mentioned), Huss et al. [62] classified the fish by the risks they might present to its consumers. Accordingly, the highest ranked products in terms of health risks would be the mollusks (fresh and frozen mussels, oysters and sururu i.e., Charru mussel *Mytella charruana*) and raw fish (e.g., sushi, sashimi) or if ingested with no proper cooking, followed by crustaceans and fish, fresh or frozen, which should be properly prepared. Finally, the fish and fish products presenting the lowest risk levels include lightly preserved (salted, marinated, smoked or fermented), semi-preserved (caviar), with proper addition of food preservatives, such as sorbate, benzoate and nitrite, and heat-processed fish, that need to be sterilized and properly disposed into strongly sealed cans.

BACTERIA WITH SPECIFIC RESTRICTIONS AND RECOMMENDATIONS WORLDWIDE

Table 1 presents a comparison of the bacteria used as a standard to assess the microbiological quality in fresh fish and fish products under national and international codes of best practice and legislation. It allows us to compare and analyze the similarities in laws from different countries and their views on bacteria that may pose health risk to the consumer.

Table 1. Bacteria listed in different laws and guidelines concerning the microbiological quality of fish and its by-products

Bacteria listed in laws and guidelines	Source			
	Brazil ¹	FDA ²	EU ³	Codex Alimentarius ⁴
Fecal coliform		X	X	
<i>Escherichia coli</i>		X	X	X ^a
Thermotolerant coliform			X	
Coliforms at 45°C	X			
<i>Staphylococcus aureus</i>		X	X	X ^b
Coagulase positive staphylococci	X		X	
<i>Salmonella</i> spp.	X	X	X	X ^a
<i>Bacillus cereus</i>	X			
Sulphite-reducing <i>Clostridium</i>	X			
<i>Clostridium botulinum</i>		X		X ^b
<i>Vibrio parahaemolyticus</i>	X	X		X ^a
<i>V. cholerae</i>		X ^c		X ^a
<i>V. vulnificus</i>		X		X ^a
<i>Listeria monocytogenes</i>		X		X ^b
<i>Shigella</i>				X ^a
Aerobic mesophilic bacteria			X	

¹ [28]; ² [63]; ³ [64]; ⁴ [65]; ^a pre-harvest and harvest hazards in incoming fish and shellfish; ^b the post-harvest and further processing of fish and shellfish; ^c food for raw consumption.

In general, laws and codes use information related to different stages and conditions in the production, processing and marketing phases: bacteria with pathogenic potential, how they relate to their environmental origins and the quality of the water; bacteria directly related to poor hygienic conditions and their involvement in degradation and loss of food quality. Overall, *Salmonella* is a consensus in the regulations due to the severity of the diseases to which it is related.

DETECTION METHODS FOR PATHOGENS AND SPOILAGE AGENTS IN FISH

In the international market of fish products, quality is focused on two primary aspects: food safety and sensory quality; both, closely related to microbiological parameters. Several methods are used in order to determine and set the standards of freshness and/or quality. Those can be categorized in sensory and instrumental. The latter group encompasses physical, chemical and microbiological methods [66].

Unlike other characteristics, the microbiological parameters do not provide information as to the freshness or palatability of the fish. The purpose of these analyses is to provide a clearer image of the hygienic quality of the product, the hygiene standards during processing and preparation, and the possible presence of bacteria or other microorganisms of importance to public health [67]. Spoilage and deterioration by microorganisms are important sources of disease outbreaks and economic losses. Every year, about one-third of the world's food production is lost as a result of microbial deterioration [68].

In the next sections, culture-dependent and rapid methods are briefly described for further reference on methodologies to assess microbiological contamination in seafood products

Culture-Dependent Methods

Microbiological methods can be divided into detection and enumeration techniques based on classic microbiology procedures, involving selective culture media and incubation periods. Among those classic techniques, it is possible to cite direct counts of culturable bacteria (Standard Plate Count), estimation of bacterial populations (Most Probable Number), counting and detection of bacterial groups and species involved in deterioration processes of fishery products, such as psychrophilic bacteria (e.g., Mol et al. [69]) and histamine-forming bacteria (e.g., Bjornsdottir et al. [70]). Despite (or because of) being classical, these techniques constitute national and/or international standards. As a result, they are still often used in quality control (QC), research and development (R&D). For instance, Lin et al. [71] used culture-dependent methods to isolate and quantify histamine-forming strains of salted fish samples. Moreover, Dalgaard [72] employed quantitative and qualitative tests using culture media to characterize the degrading activity of the microbiota of fish products.

In the case of bacterial pathogens, monitoring may be done by a series of different detection methods. Some are only capable of a qualitative presence/absence confirmation of the pathogen, while others allow the quantification of the bacterial load [73]. For pathogens with zero tolerance criteria in food, there is no purpose in quantifying the bacterial load, but

in case of pathogens that are tolerated below an established limit; the later approach is extremely useful. In this case, conventional plating techniques and cultivation of pathogenic bacteria are still the primary choice to assess the degree and extent of contamination in food products, including fish [74].

There are well-established protocols for enumeration and detection of human pathogens related to fish, such as *Salmonella* spp., *Vibrio* spp., *Staphylococcus aureus* and *Clostridium* spp. In general, the protocol includes a nonselective pre-enrichment step, followed by enrichment in selective medium and a subsequent plating on selective agar plates. Detection of suspicious strains requires further isolation and confirmation by biochemical and serological tests [75].

Quantitative microbial techniques also have the advantage of being adaptable to meet the specific needs of each sample, as well as requirements of target microorganisms [76]. As an example, the use of culture media of different composition and the incubation at various temperatures was the strategy used by Uddin et al. [77] in order to assess the bacterial microbiota of frozen fish imported from Denmark.

However, in spite of the sensitivity of these cultivation methods and their well-established, standardized protocols, they are time consuming and often expensive, requiring specific technical skills to be run. These characteristics make them unsuitable for quick inspections in the case of fish and fish products [78, 79]. Another disadvantage is the difficulty that stressed, i.e., “viable but non-culturable” bacteria have to grow in the conditions created during the tests.

Rapid Methods

Rapid detection of pathogens and analysis of the deterioration processes in food samples is essential to ensure fish and fish-products safety and quality. Rapid microbiological methods have been developed to meet this specific demand from the global food market. In the case of fish and fish-based products, the high perishable nature of these products should be taken into consideration as a determining factor in choosing techniques that offer faster and accurate responses.

The two main groups of rapid methods to detect microorganisms are based on immunological reactions (Enzyme-Linked Immunosorbent Assay-ELISA, monoclonal antibodies) and genetic engineering techniques (Polymerase Chain Reaction-PCR, DNA probes, etc.) [80]. The first group provides faster response while the second group has a higher specificity to detect microorganisms in fish and fish products [81]. Thus, genetic techniques are used more often.

Molecular-based methods, especially those based on polymerase chain reaction (PCR) or microarray have proven accuracy both in quantification and detection of pathogens in fish-based food [82-87]. Research has proven the efficacy of these techniques in detecting pathogens in fish and in tracking sources of contaminants bacteria. Already in 1996, Destro et al. [88] used molecular-typing methods, namely random amplified polymorphic DNA analysis (RAPD) and pulsed-field gel electrophoresis (PFGE), to track the dissemination of *Listeria monocytogenes* in shrimp processing plants. Rørvik et al. [89] characterized *Listeria* isolates using multi-locus enzyme electrophoresis and restriction enzyme analysis of total

DNA to establish the environmental sources of this pathogen in marine fish and industry. Similarly, Mauffret et al. [90] tested real-time PCR to track microbial sources in samples of bivalve mollusks. Shimizu et al. [91] used the Fluorescence *In Situ* Hybridization (FISH) method to rapidly quantify *Salmonella enterica* in food samples, including fish.

These rapid techniques may also assist in monitoring and quantifying bacteria that produce metabolites responsible for off-flavors and cause sensory rejection of fish and fish-based products. Off-flavours are the main indicators used by consumers to evaluate fish freshness [92]. Compounds that produce such characteristic odors, for example trimethylamine (TMA), various nitrogen and sulfur compounds, aldehydes, ketones and esters are produced by a variety of microorganisms during the process of deterioration of fish [93, 94].

CONCLUSION

To conclude, there is a major need from all the stakeholders involved in the process of producing, processing and exporting fish and fishery products to focus on the quality of the products, for only awareness and education will make the food that gets to the consumer a harmless one.

Progress in rapid detection methods for foodborne pathogens, advancements in the fishing gear, dynamic forms on which we are able to communicate and share information in the present days - all these elements foster a standardization and a much more balanced comparison of the different regulations at a worldwide level.

There are, however, two major needs in order to improve the quality and safety of the currently marketed fish and fish products: discipline to comply with the regulations, and a huge effort from governmental agencies. This is particularly true in countries where the level of industrialization of the fishing and processing of fish or the subsequent regulations are newer and/or less consumer-oriented, or little worried about environment issues and sustainability.

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Chapter 524

THE PRECISION MEDICINE AND PRECISION PUBLIC HEALTH APPROACHES TO CANCER TREATMENT AND PREVENTION: A CROSS-COMPARISON

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ABSTRACT

Like other forms of diagnostics, genetic testing comes with a retinue of costs and benefits. Significant benefits in terms of morbidity and mortality have accrued to individuals tested for more prevalent genetic conditions like cystic fibrosis and sickle cell disease, including persons seen in the emergency room or identified through public health surveillance. These benefits do not mitigate the drawbacks of genetic testing, false and missed diagnoses and sheer cost among them.

Both medicine and public health have aimed at means of maximizing genetic test benefits in the interventions that they apply. The President's Precision Medicine Initiative (PMI) holds promise in that its results could be used to tailor medical treatments to the individual characteristics of patients, "precision" implying a more accurate and precise regimen overall. The National Cancer Institute (NCI) has already launched the NCI-MATCH precision medicine trial, which assigns targeted treatments based on the genetic abnormalities in a tumor, regardless of cancer type. Other trials, such as the NCI Pediatric MATCH trial, are yet to happen. The efficacy of cancer treatments also intersects public health concerns. The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group has evaluated the use of *UGT1A1* genotyping to determine the best dose of irinotecan to prevent side effects when treating patients for metastatic colorectal cancer. Analytic validity does not always equate with improved patient

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outcomes, however, thus the public health emphasis on development of a suitable evidence base for precision medical and public health efforts.

The public health approach to precision medicine, or “precision public health”, differs from the medical approach in several important ways: (1) population-based with attention to at-risk populations, as opposed to being strictly individualized; (2) focus on primary and secondary prevention, rather than frank disease (tertiary prevention); and (3) prioritizing interventions that have already demonstrated readiness for large-scale implementation, in contrast to the undertaking of novel clinical trials. Precision public health is exemplified in the Centers for Disease Control and Prevention’s emphasis on the implementation of Tier 1 genetic tests that have passed systematic review for analytic and clinical validity and utility – the use of family history for referral for hereditary breast and ovarian cancer genetic testing (*BRCA1/2* mutations), and hereditary nonpolyposis colorectal cancer cascade screening (Lynch syndrome *MLH1*, *MSH2*, *MSH6* mutations).

This paper will cross-compare the precision medical approach to cancer based on pharmacogenomic regimens using companion diagnostics, and the public health approach to precision management of hereditary cancer for 3 cancer types – lung, breast, and colorectal. It will describe methods of early detection and consider how lives can be saved through precise management – from predictive testing and cancer monitoring of the at-risk population, to tailored chemoprevention that fits the needs of the individual. In the population context, a cascade screening “multiplier effect” exists in that relatives can also be assessed and followed for mutations identified in the proband. Cost-benefit analyses (T4 translational research) of medical and public health approaches will be closely examined and compared. Points of commonality between the two approaches will also be discussed, since primary/secondary and tertiary disease prevention represent a continuum. These analyses point to the value of allocating resources towards the health of at-risk populations. Questions remain if particular forms of genetic testing are to become “universalized”, and if the needs of all at-risk groups, including racial-ethnic, are to be addressed.

Keywords: lung cancer, breast cancer, colorectal cancer, Lynch syndrome, genetic testing, cascade screening, universal screening, cost-effectiveness, precision medicine, pharmacogenomics, public health, race, ethnicity

FROM THE HUMAN GENOME PROJECT TO THE PRECISION MEDICINE INITIATIVE

If the twentieth century is known for its success in mapping the human genome, the twenty-first century is becoming equally well known for scientists’ attempts at making genetic interventions “precise” – appropriately chosen, and delivered to the right person and physical target within the human body. The Precision Medicine Initiative (PMI), launched by the Obama administration in January 2015 with a \$215 million outlay in the President’s 2016 Budget and continuing onward in the current administration, brought medicine closer than ever to the ability to tailor medical regimens to the needs of the individual patient [1]. An article by Francis Collins, Director of the U.S. National Institutes of Health (NIH), and Harold Varmus, former Director of the U.S. National Cancer Institute (NCI), which appeared shortly after the announcement, broke the Initiative into two stages: a near-term focus on cancers, and a longer-term aim to yield new knowledge applicable to the broader range of health and disease [2]. Muin Khoury, Director of the Office of Public Health Genomics at the

U.S. Centers for Disease Control and Prevention (CDC-OPHG), and Sandro Galea, Dean of Boston University School of Public Health, followed-up with the affirmation that the PMI could, in time, be used to develop, evaluate, and deliver health interventions with greater “precision” for both individuals and populations [3].

The distance between a strictly individualized approach to precision medicine and one that is population-oriented, fitting the right intervention to the right population, is transcended by a common denominator shared by medicine and public health – cost-effectiveness. Translational research spans several distinct territories, from basic genome-based discovery as it yields candidate health applications (e.g., new genetic tests and therapeutic interventions) - T1 translational research, to evaluation of real-world outcomes (e.g., morbidity and mortality, cost-effectiveness, and quality-of-life indicators) - T4 translational research [4]. In this piece we take the position that whatever the molecular genetic or behavioral approach used, it must make sense dollar-wise such that the interventions are being mustered in an effective and economical way. Our analysis will show that the criterion of cost-effectiveness naturally shifts the prospect of a national precision medicine effort in the population-oriented direction. Though the two may seem like strange bedfellows, both the pharmacogenomics industry and public health community are in agreement that the PMI must be a sustainable effort, so that the real question becomes, “What direction(s) can the PMI effectively take?”.

DEFINITIONS OF PRECISION MEDICINE AND PRECISION PUBLIC HEALTH

The definition of a particular medical intervention illustrates both the basic actions to be taken and its scope. Jameson and Longo define “precision medicine” as “treatments targeted to the needs of individual patients on the basis of genetic, biomarker, phenotypic, or psychosocial characteristics that distinguish a given patient from other patients with similar clinical presentations” [5]. Implicit in this definition is the goal of improving clinical outcomes for individual patients, while avoiding unnecessary side-effects that could be incurred by ignoring patients’ individual characteristics. The authors admit that medicine to date has more or less employed such an approach. Hemophilia requires the administration of an appropriate clotting factor, be it factor VIII or factor IX (these days in recombinant form), to stop the bleeding. Clinicians need to undertake a thorough work-up in order to arrive at a precise diagnosis of the hemophilia, which will enable the appropriate therapy to be administered. Choice of antibiotic is another example. For the antibiotic to take hold, the right type of antibiotic must be given for the particular bacterial infection. The latter example suggests that targeted approaches, aimed at particular persons for specific conditions, could actually have population-level applicability, since antibiotics and vaccinations are given on a widespread basis. They are the very opposite of “orphan drugs”, designed to cater to the needs of very rare cases.

Shen and Hwang point out that despite the commonality with past precedent, a substantive shift in methodology between the old medicine and the new medicine is occurring [6]. The practice of medicine has so far remained largely “empirical”. Physicians typically rely on a combination of patient and occasionally family medical history, physical examination, and laboratory data to secure a diagnosis and choose a drug. Treatments are

based on a provider's experience with similar patients. Drugs administered are most often "blockbuster" drugs designed to accommodate the "typical" patient. If the wrong analgesic, antibiotic, or antiarrhythmic is given, the patient will be weaned off the current drug, and a new one tested until the right drug and dosage are chosen. The idea behind precision medicine is to rely on new biomarkers and genomic tests to "deliver the right treatment to the right patient at the right time" [6]. It is a personally tailored, as opposed to "one size fits all" approach. The fit is "precise" – one person; one drug.

Classic pharmacogenomic examples readily demonstrate this novel approach. Warfarin (brand name Coumadin) dosing allows the frequently used anticoagulant to be titrated to the needs of the patient susceptible to clotting events associated with atrial fibrillation and deep vein thrombosis [7]. Two genes are known to be involved in warfarin therapeutic outcomes – *CYP2C9*, which codes for an enzyme primarily responsible for warfarin metabolism, and *VKORC1*, which codes for the warfarin drug target. Genotyping can yield information useful to guide a person's initial warfarin dose and allow the clinician to readily stabilize his or her prothrombin measures, a process which usually takes several weeks. Cost-effectiveness studies of genotype-guided dosing have concluded that considerable potential exists for cost savings, but that it cannot be realized until test costs decrease and the uncertainty concerning effectiveness is reduced. The U.S. Centers for Medicare and Medicaid Services (CMS) has consequently adopted a provisional "coverage with evidence development" approach [7]. A physiologic measure, the ratio of the patient's prothrombin time to a control or "normal" sample, continues to be the professional standard for warfarin dosing. Since the patient is followed with this measure, its use may be considered a tool in "personalized" or individually-tailored medicine.

Imatinib (Gleevec) for chronic myelogenous leukemia (CML) and gastrointestinal stromal tumors is another prime example of the tailoring in drug regimens that may take place. Medical researchers developed this drug over a multi-decade period to inhibit the function of a translocation-related "fusion" gene, *BCR-Abl*, which produces an abnormal tyrosine kinase that is not properly regulated [8]. In initial trials, all of 31 research participants experienced complete remission. The five year survival rate for CML has increased from 31% (1993) to 59% (2003 – 2009) [9]. The drug is administered to patients who are Ph⁺ (Philadelphia chromosome positive), with effectiveness monitored by white blood cell and platelet counts. Like warfarin, Gleevec targets a particular type of patient and has a very specific chemical target – the ATP-binding site on a particular kinase – and is a drug that can be closely monitored. Gleevec's cost is about \$3,500 per month, which may evade some patients' pocketbooks. However, it is covered by Medicare Part D and Medicare Advantage Plans. Both of the above examples describe "personalized medicine" – separating patients into different groups then individually tailoring the treatment to the patient.

Though many authors use the two terms interchangeably, Khoury distinguishes "personalized medicine" from "precision medicine" in that the latter inculcates multiple determinants of health, genetics being one rung, thus can absorb the notion of social determinants as easily as it can molecular determinants. The President's PMI plan is data intensive in a way that would allow the recording of multiple determinants for large numbers of people, ostensibly through a planned million-person cohort:

Participants will be involved in the design of the Initiative and will have the opportunity to contribute diverse sources of data – including medical records; profiles of the patient’s genes, metabolites (chemical makeup), and microorganisms in and on the body; environmental and lifestyle data; patient generated information; and personal device and sensor data. [1]

Collins and Varmus write that the numerous clinical trials stemming from the PMI and its large-scale cohort will require the building of a “cancer knowledge network” to store all the resulting molecular and medical data in digital form and make it readily deliverable to providers and patients [2]. Simonds and Khoury illustrate this idea with the example of a cancer clinical trials and effectiveness research infrastructure developed by the H. Lee Moffitt Cancer Center. The system is part of its personalized cancer care initiative started in 2006 – Total Cancer Care. The program: (1) integrates data from multiple sources (electronic medical records, biospecimen databases, and molecular data); (2) makes resultant information available to patients by providing active feedback about their health and upcoming appointments and expanded electronic health record; and (3) affords data interfaces for researchers and clinicians [10].

It is to be hoped that the streamlining of cancer clinical trials and centralization of incoming data will reduce costs and increase efficiency over standard medical practices. According to Cancer Research U.K., between 2003 and 2007 cancer trials were accompanied by a 75% increase in administrative costs, a figure in need of remedy [11]. Cost-effectiveness and clinical utility will enter into assessments of the PMI. Public health efforts in the U.S. have to date assumed a twin duty – assessment of the cost-effectiveness of clinical programs, at the same time that a vision of precision medicine’s meaning in terms of population health is being formulated. This vision departs from the medical model of precision health in a number of important respects: (1) it is population-based, with attention to at-risk populations, as opposed to being strictly individualized; (2) the focus is on primary and secondary prevention, rather than frank disease (tertiary prevention); and (3) the emphasis is on interventions that have already demonstrated readiness for large-scale implementation, in contrast to the undertaking of novel clinical trials [12]. To glimpse the future, it is helpful to visit recent experience with precision medicine in the cancer arena. This inspection will take our trek from the individually-focused domain of clinical medicine to the population-oriented territory of public health. The next section will focus on three major cancer categories of mutual interest to clinical medicine and public health – lung, breast, and colorectal cancer – from the medical pharmacogenomics point of view.

PHARMACOGENOMIC INTERVENTIONS AND COST-EFFECTIVENESS

The Precision Medicine Approach to Lung Cancer

Lung cancer is the second most common cancer in both men and women, and is the leading cause of cancer-related death in both genders [13, 14]. Of note, the lung cancer incidence rate for black women is roughly equal to that of white women, despite the fact that they smoke fewer cigarettes [13]. The two major forms of lung cancer are non-small cell lung cancer (NSCLC), and small cell lung cancer (SCLC). NSCLC comprises ~85% of all lung

cancers; SCLC ~10-15% [15]. The 5-year survival rate for NSCLC is 21%, suggesting progress that has been and that is yet to be made [16].

Targeted therapies aimed at cancers harboring very specific genetic alterations are becoming more and more common in oncogenomics. A 2012 review of the role of pharmacogenomics in moving genetic association studies from bench to bedside describes the use of EGFR tyrosine kinase inhibitors (TKI) in the treatment of lung cancer and *HER2* (tyrosine kinase ERBB2)-directed therapies in the treatment of *HER2* (human epidermal growth factor 2)-positive early-stage breast cancer as prime examples of success in the area of cancer pharmacogenomics [17]. A 2016 review of precision medicine approaches in oncology cites ALK (anaplastic lymphoma kinase) fusion oncogene and EGFR (epidermal growth factor receptor (EGFR)) mutations as the main molecular predictive biomarkers supporting NSCLC treatment [15]. Molecular testing for ALK fusion genes has proven valuable. Abbott Molecular already offers a multiplexed assay, the Vysis ALK Break Apart FISH Probe Kit, endorsed by the 2016 National Comprehensive Cancer Network (NCCN) NSCLC practice guidelines [15]. Though ALK fusion gene rearrangements are relatively rare (< 5% of NSCLC cases), clinical responses to targeted inhibitors (e.g., crizotinib) can be quite dramatic [5]. In favor of the precision medicine approach, excluding patients without these mutations can also minimize the exposure of patients to costly and potentially toxic therapies unlikely to benefit them.

EML4-ALK is the specific biomarker used in determining patient efficacy for the choice of a TKI agent such as crizotinib in the tertiary or after-the-cancer-has-arisen management of NSCLC [5]. A 2014 cost-effectiveness study on the use of *EML4-ALK* fusion oncogene testing in first-line crizotinib treatment for patients with advanced NSCLC reveals the complexity inherent in this precision medicine approach [18, 19]. The investigative team found that *EML4-ALK* testing to govern therapeutic decisions improved patient outcomes by an average of 0.011 quality-adjusted life-years (QALYs) while adding extra costs of \$2,725 per patient, of which only \$60 was attributable to the molecular assay itself. The overall interpretation of the cost-benefit calculus changes dramatically, however, when the cost of the companion drug (crizotinib) is considered. The incremental cost-effectiveness ratio is defined as the difference in cost between two alternative interventions, divided by the difference in their effect or impact. The incremental cost effectiveness ratio for administration of the drug itself was \$250,632 per QALY gained. The investigators concluded that the regimen is “likely not considered cost-effective in the current setting” [19]. This assessment was unaltered when the model was subjected to a sensitivity analysis of alternative costs for the molecular testing. States one reviewer, “Where companion diagnostic precision medicine is considered, these assays are by nature tightly coupled to the cost of the specific associated drug” [18].

Assays for EGFR inhibition may be used when other TKI inhibitors, such as gefitinib and osimertinib, are being considered for NSCLC therapy [15]. The U.S. Food and Drug Administration (FDA) has approved two multiplex assay kits, also NCCN endorsed, for this purpose – the *therascreen* EGFR RGQ PCR Kit (for use with gefitinib), and the cobas EGFR Mutation Test (for use with osimertinib). A cost-effectiveness analysis performed by an Australian team compared the use of combined multiplex testing and targeted therapy with NSCLC chemotherapy without testing, and thirdly with best supportive care without testing [20]. The combined strategy resulted in an additional 0.009 life-years (LYs) gained, compared to 1.458 LYs gained in the case of each of the other two strategies. The combined strategy resulted in an incremental cost-effectiveness ratio of \$485,199 (Australian)/QALY

comparing combined and best supportive care strategies, and \$489,338 (Australian)/QALY comparing combined and chemotherapy only strategies. Decreasing test and test interpretation costs by half reduced the ratios, but they still remained greater than \$200,000 (Australian)/QALY. The authors concluded that multiplex testing and targeted therapy is not cost-effective as a fourth-line treatment in metastatic lung cancer when first-line treatments such as chemotherapy without pharmacogenomics testing can be employed.

Other predictive biomarkers for NSCLC treatment are on the horizon. For example, *KRAS* mutations can suggest lack of therapeutic efficacy to EGFR targeted therapies. The FDA has cleared *KRAS* mutation detection assays for use in colorectal cancer, but such assays have not yet been approved for use in NSCLC [15].

The Precision Medicine Approach to Breast Cancer

Breast cancer is the most common cancer among American women. It is the second leading cause of cancer death in women, exceeded only by lung cancer [21]. About 85% of breast cancer cases occur in women with no family history of breast cancer. These cases are due to somatic cell mutations which occur as a result of aging, various exposures (such as pre- and postmenopausal hormone therapy), and other life events.

Precision medicine efforts for breast cancer due to somatic mutations fall into at least four categories, two of them – endocrine therapy and *HER2* therapy – being mainstay treatment categories. *HER2*-directed therapies, for which trastuzumab (Herceptin) is often used, are one of the two major pharmacogenomics successes in the cancer area cited by Ritchie [17]. Tamoxifen is a major drug of choice in the category of endocrine therapies, itself being a selective estrogen receptor modulator [15].

Herceptin has proven utility in reducing risk for cancer recurrence after surgery for early-stage *HER2*-positive (*HER2*+) breast cancer, and improving survival in late-stage (metastatic) *HER2*+ breast cancer, but it also poses serious side-effects such as heart damage. Herceptin therapy can also cost a sizable amount, up to \$50,000 per year [22]. Overexpression of the *HER2* gene (*HER2*+ status) is associated with rapid tumor growth and negative diagnostic and prognostic indicators. A systematic review and meta-analysis performed in Canada compared seven different strategies employing immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) to determine *HER2* status, thus appropriateness of using Herceptin [22]. Each strategy utilized an IHC score (0, 1+, 2+, 3+) alone or coupled with FISH confirmation to form this inference. The incremental cost-effectiveness ratio was lowest when cases with an IHC score of 2+ or 3+ (as opposed to 0 or 1+) were confirmed by FISH, which yielded a ratio of \$3,351 (Canadian)(minimum) to \$12,230 (Canadian) (maximum) per accurately determined case. The cost-effectiveness analysis is favorable given that accurate assessment of *HER2* status is capable of reducing the cost of Herceptin therapy by \$0.6 million per year, and saving \$12 million per year in women who are *HER2*-, thus can be kept off Herceptin [22].

Estrogen-focused therapies have been a part of standard care for more than thirty years, and have displayed an evolution in policy analysts' thoughts about the gold standard for precision management [15]. The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group was launched by the CDC Office of Public Health

Genomics in 2004 to conduct systematic, evidence-based reviews of burgeoning genetic tests and other applications of genetic technologies in transition from research to clinical and public health practice. EGAPP has produced two systematic reviews of the use of gene expression profiling to improve therapeutic outcomes in women with breast cancer. EGAPP's 2009 review examined the validity and utility of three tests – Oncotype DX, MammaPrint, and the H:I (normalized gene expression) ratio [23]. These tests have been designed to go beyond the standard estrogen/progesterone receptor status indicator to predict tumor recurrence risk for women on tamoxifen, for whom alternative therapies might be considered. The EGAPP Working Group found adequate evidence from the NSABP B-14 randomized controlled trial to support the association between Oncotype DX recurrence scores and 10-year distant metastases in estrogen receptor positive (ER+) patients, and adequate evidence to support the association between RS score and overall chemotherapy benefit, particularly for patients in the high risk category [23]. Recent publication of interim results for the TAILORx study has shown a further association between recurrence score and 5-year disease-free survival and distant recurrence in patients at low risk [24].

A follow-up systematic review by the EGAPP Working Group published in 2016 confirmed its previous findings but also noted the lack of direct evidence that the use of Oncotype DX improves clinical outcomes [25]. It also highlighted contradictory cost-effectiveness results in studies performed in the U.S. (for which \$2,000 in cost savings per patient were due to a decrease in post-testing chemotherapy use) and the U.K. (for which an incremental cost-effectiveness ratio of 26,940 £/QALY gained were due to an increase in chemotherapy use) [25]. The U.K. National Institute for Health and Care Excellence (NICE) Diagnostics Advisory Committee concluded that, under the assumption of equal chemotherapy benefit for all Oncotype DX risk categories, the test is not cost-effective at its current pricing level. In the first EGAPP review, data were adequate to support an association between the MammaPrint Index and 5- to 10-year metastasis rates, but the efficacy relative to classical clinical factors was unclear. More conclusive results await the completion of the MINDACT trial. For the H:I ratio test, populations studied were quite heterogeneous, and the test's commercial offering was based on a single study in women with primary, untreated breast cancer.

The Precision Medicine Approach to Colorectal Cancer

Colorectal cancer (CRC) is the third most common cancer in both men and women in the U.S. [26]. It is the third leading cause of cancer deaths when men and women are considered separately, and the second leading cause in both sexes combined.

Considerable effort has been placed into targeted therapies and companion diagnostics for CRC. About 70-80% of patients present with resectable localized disease, treated by surgery and often followed by adjuvant therapy [27]. CRC patients with advanced disease may receive first-line chemotherapy, or chemotherapy and radiation before surgery is considered. The EGAPP Working Group published in 2009 a systematic review of one first-line chemotherapeutic agent, irinotecan, which may be accompanied by *UGT1A1* genotyping to check for ability to adequately clear the drug [27]. Such genotyping aids decisions to either increase drug dose for more aggressive therapy, or switch to common alternate drugs,

bevacizumab or cetuximab, for instance, in individuals with reduced clearance at risk for adverse events. EGAPP had two major findings: (1) unless patients receive a certain threshold dose of irinotecan, the increase in risk for toxicity is not significant, thus testing may not be warranted; and (2) reducing the dose of irinotecan (personalized dosing) to avoid adverse events may lead to more cases of unresponsive tumors than instances of adverse events avoided. It is inconclusive that benefits outweigh harms in the application of a precision approach here.

The alternate drugs mentioned above are positioned among the three main classes of targeted therapies approved for metastatic CRC: (1) multikinase inhibitors; (2) angiogenic inhibitors; and (3) anti-EGFR antibodies [15]. Up to 50% of CRC patients respond to anti-EGFR therapy, which includes cetuximab [28]. *KRAS* wild-type status is considered an important factor in achieving a clinical response from this category of therapy [29]. However, 40-60% of patients with wild-type status do not respond to such therapy. Data suggest that *BRAF* gene status also plays a role in anti-EGFR response, and that the *BRAF* V600E mutation, present in 5-10% of CRC tumors, can lead to a positive response. To date the FDA has cleared two genetic testing kits, the *therascreen* *KRAS* kit from Qiagen, and the cobas *KRAS* Mutation Test from Roche [15]. The American Society for Clinical Oncology (ASCO) and three other professional organizations released new consensus guidelines in 2015 strongly recommending *KRAS* mutational testing for patients being considered for anti-EGFR therapy, and that *BRAF* V600 testing also be considered.

Table 1. Pharmacogenomic/companion diagnostic approach – 3 cancers

Condition	Therapy	Biomarkers	Cost-Effectiveness	References
Non-small cell lung cancer (NSCLC)	Tyrosine kinase inhibitors	<i>EML4-ALK</i>	\$255,970/QALY gained	Djalalov et al. [19]
		EGFR	\$489,338 (Austr.)/QALY gained	Doble et al. [20]
HER2+ Breast cancer	Herceptin	IHC, FISH	\$3,351 – 12,230 (Can.) saved per case	Dendukuri et al. [22]
ER+ Breast cancer	Endocrine	21-gene assay	26,940 £ (Brit.) cost/QALY gained	EGAPP [25]; Ward et al. [33]
Metastatic colorectal cancer	Topoisomerase 1 inhibitor (TOP1) – irinotecan Anti-EGFR	<i>UGT1A1</i> genotyping	ambivalent results – reducing toxicity vs. reducing tumor burden	EGAPP [27]
		<i>KRAS</i>	\$7,500 – 12,400 saved per case \$180,000/QALY gained	EGAPP [30]; Vijayaraghavan et al. [31] EGAPP [30]; Shirowa et al. [32]

The EGAPP Working Group conducted a systematic review of companion diagnostic use of *KRAS* and *BRAF* mutation testing in anti-EGFR therapy in 2013 [30]. The systematic review looked at multiple pooled assessments, each consisting of up to seven studies, which together indicated statistically significant increased response rates to cetuximab and other anti-EGFR drugs, reduced risk of disease progression, and enhanced overall survival with *KRAS* wild-type status. EGAPP cited a cost-effectiveness study of *KRAS* testing in metastatic CRC patients in the U.S. and Germany [30, 31]. For the U.S. patients, use of *KRAS* testing to

select patients for EGFR inhibitor therapy saved \$7,500 to \$12,400 per case. A second cited study from Japan displayed an incremental cost-effectiveness ratio for cetuximab with *KRAS* testing to be \$180,000 per QALY gained compared to therapy without testing [32]. Due to this cost, the investigators concluded that the protocol was not cost-effective, even when treatment was limited to patients with wild-type *KRAS*. Two of three studies looking at *BRAF* testing found associations similar to the *KRAS* studies in terms of progression-free and overall survival, but these findings, however, were not contingent on whether or not cetuximab was included in the combination therapy. Thus, while the review supported recommendations for a precision approach using *KRAS* mutation testing, it found insufficient evidence to link *BRAF* V600E mutation testing with treatment response independent of prognostic association.

Table 1 summarizes the cost-effectiveness and descriptive findings for the pharmacogenomics or companion diagnostic precision medicine approach to the three cancers.

TAKING PRECISION MEDICINE BEYOND THE PERSONALIZED LEVEL

One argument against the informativeness of the above studies is that they represent a personalized medicine approach, but not a precision medicine approach in its full capacity [3]. The electronic storage of information, which can be multifactorial, including relevant lifestyle, would seem to be crucial to maximizing benefits and minimizing cost. The investigative team looking at the infrastructure characteristics of the Lee Moffit Cancer Center “Total Cancer Care” program also examined six other major healthcare programs engaged in cancer care comparative effectiveness research in genomic and precision medicine [10]. Four of the researched programs – at Duke University, Kaiser Permanente, University of Pennsylvania, and the Fred Hutchinson Cancer Center – had established a complex infrastructure (with data and biospecimen registries and multidisciplinary research teams), were engaged in “knowledge generation” (via randomized controlled trials and observational studies), and had reached the stage of “knowledge synthesis” (horizon scanning, evidence synthesis, and decision modeling). These programs display a depth of information and range of multidisciplinary expertise that is reflective of the type of knowledge synthesis of which the PMI’s million person cohort will be capable.

The Duke University and Kaiser Permanente teams noted a number of strategic challenges to the amassing of cancer study data – limited data quality, large variation in genomic methodology used, and poor demonstration of clinical utility for the genomic tests supplying the data [10]. These observations point out challenges that could foreseeably face PMI investigators attempting to collate information from the expansive precision medicine cohort. The Kaiser Permanente group was able to show that in screening for Lynch syndrome, a hereditary form of CRC, microsatellite instability testing (MSI) was preferable compared to immunohistochemical staining (IHC). In the treatment phase, the investigators found that screening for *KRAS* and *BRAF* mutations improved the cost-effectiveness of anti-EGFR therapy, but that the cost of the therapy surpassed generally accepted cost-effectiveness thresholds of \$100,000/quality-adjusted life-year. These findings allude to the capability of the PMI to develop new data on useful oncogenomic screening, mutational testing, and therapeutic procedures, and to the correspondingly likely possibility that many of the

discoveries, while being individually beneficial, could elude effectiveness for the clinical population as a whole.

The PMI will no doubt be carried in new directions that have not yet been quantified, however. NCI is engaged a new type of clinical trial called “NCI-MATCH” [34]. In this innovative program, adult cancer patients are assigned to targeted treatments based on the genetic abnormalities in their tumors, regardless of the type of cancer they have. This concept represents the therapeutic end of what has been happening with diagnostics. *KRAS* and *EGFR* mutation testing is now occurring for multiple cancer types. Why should cancer therapies be restricted to just one cancer type? New management models may also evolve. The data infrastructure supporting precision medicine can and is being used to develop procedural algorithms that combine genetic testing with genetically targeted therapies. These algorithms, if tailored to the lay person, can then be used by both medical providers and patients in collaboration, improving the effectiveness of the prescribed regimen. Shen and Hwang use *CYP2C9* (they cite *CYP450*) testing for warfarin dose performed at home first by nurses then by patients as an example [6]. This linkage of “big” or “rich” data and the development of new, useful algorithms is cited by multiple authors [2, 5, 35]. The issue is whether providers of various types, and consumers, can understand the test results and appreciate the connection to one-size-does-not-fit-all therapeutic management [36].

Authors discussing the translation of big data into usable guidelines and algorithms are not just limiting the payoff to individualized treatment, however. Jameson and Longo, for instance, speak of not just a pharmacogenomic future, but one in which “guideline-based screening”, e.g., colonoscopy, can be targeted on the basis of age and family history [5]. Family health history is one of several tools, including individualized genetic testing and family cascade testing, fueling the public health drive towards precision interventions [37, 38].

The public health approach to precision medicine, or “precision public health”, is highly evidence-based. Precision public health is exemplified in the Centers for Disease Control and Prevention’s emphasis on the implementation of Tier 1 genetic tests that have passed systematic review for analytic and clinical validity and utility – family history-based hereditary breast and ovarian cancer (HBOC) genetic testing (*BRCA1/2* mutations in relatives), and hereditary nonpolyposis colorectal cancer genetic testing (Lynch syndrome *MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM* mutations) [39]. Indeed, genetic counseling and testing for HBOC are already incorporated into healthcare reform as services not requiring co-pay for individuals deemed at risk by their providers [40]. The PMI promises much more, however, and part of the vision of public health is that precision techniques can be used to direct genetic preventive strategies to those subsets of the population that will derive maximal benefit [41].

PUBLIC HEALTH INTERVENTIONS AND COST-EFFECTIVENESS

The Precision Public Health Approach to Lung Cancer

It has been remarked that “although personalized treatments can help save the lives of sick people, prevention applies to all” [3]. This comment applies especially to lung cancer,

which can be tackled as we have seen individually and after it has manifested, or by using a preventive, population-based approach. Initial genome-wide association studies (GWAS) published by several investigative teams in 2008 were suggestive of lung cancer susceptibility genes being situated on the long arm of chromosome 15 [42]. The studies were all large (3,500 to 14,000 participants) and replicated, yielding strong evidence for an association between SNP variations at 15q24/15q25.1 and lung cancer. Thorgeirsson et al. found a highly significant association ($P = 1.5 \times 10^{-8}$) between a common variant in the nicotinic acetylcholine receptor gene cluster on chromosome 15q24 and smoking frequency, with an odds ratio of 1.31 (1.19 – 1.44, 95% C.I.) between nicotine dependent cases and low quantity smokers plus population controls [43]. Studies by Hung et al. [44] and Amos et al. [45] found odds ratios between 1.21 and 1.77 for associations between the nicotinic acetylcholine receptor regions 15q25 and 15q25.1 and lung cancer in ever smokers, the former accounting for 14% (attributable risk) of the lung cancer cases in the first study. The second study examined 2,724 NSCLC cases, the same type of cancer being treated in later stages by pharmacogenomics regimens.

More recent GWAS in never-smoking Asian females have pointed out genetic associations independent of smoking status. Case-control studies of never-smoking Asian females funded through the National Institutes of Health [46] and the Mayo Foundation [47] have identified genetic variants in the 3q28 and 13q31.3 regions associated with risk for lung cancer ($N = 754$ to 7,254 participants). These associations show both statistical significance ($P = 10^{-6}$ to 10^{-8}) in terms of odds ratios and allelic risk, and biological plausibility (association with the regulation of cell proliferation and division). These two lines of discovery – lung cancer in connection with nicotine dependence and independent of it – could beneficially lead to both personalized smoking-cessation interventions, and to increased screening of people at risk for lung cancer [41]. The difficulty is that the association studies are at the primary research (T1) stage and do not yet imply clinical validity.

Precision medicine in public health terms involves targeting groups at risk. Various professional societies have developed guidelines for lung cancer screening, generally beginning at age 55 [48]. The NCCN lung cancer screening guidelines recommend screening individuals age 50-55 years, those who have between 20 and 30 pack-years of exposure, and who exhibit one additional risk factor, such as family history. The relative risk of developing lung cancer is 1.8 if the individual has at least one first-degree relative with lung cancer, and 3.0 given two first-degree relatives with the condition [49]. The positive and negative predictive values for lung cancer appearing in a proband's first-degree relatives are 89.9% and 99.1%, respectively [50]. In the Utah Family High Risk Program, the cost of taking a family health history varied between \$10 and \$25 depending upon receipt of follow-up educational interventions [51]. These figures indicate cost-effectiveness for the use of family history in risk assessment for lung cancer.

Public health programs are especially concerned with the rights and welfare of underserved groups, an aim that is built into public health codes of ethics [52]. Surprisingly, of the 58,160 lung disease studies published between 1993 and 2013, less than 5% reported the inclusion of minority participants [53]. NIH is presently consulting researchers adept at recruiting under-represented groups into studies as part of PMI Research Cohort formation. An admixture study of 1812 African Americans performed by the Karmanos Cancer Institute in Detroit, MI demonstrates what can come out of the use of the PMI Cohort. Excess African

ancestry was observed on chromosome 3q among ever smokers with NSCLC, a chromosomal region identified by previous studies with mostly persons of European ancestry [54].

The Precision Public Health Approach to Breast Cancer

About 10 to 15% of women diagnosed with breast cancer have germline mutations in the *BRCA1* or *2* genes. Between 10 and 30% of women under age 60 diagnosed with triple-negative breast cancer (cancer which does not have receptors for estrogen, progesterone, or *HER2/neu*) display a *BRCA1/2* mutation [55]. Ashkenazi Jewish ancestry confers an increased risk, though such mutations are by no means relegated to just one group. Like lung cancer, the public health approach to hereditary breast and ovarian cancer (HBOC) focuses on primary prevention before disease has appeared. Primary prevention can be conducted through a variety of means, several of which fit under a public health precision model. A study out of the Cleveland Clinic Genomic Medicine Institute compared two methods for cancer risk assessment – “family history-based risk assessment” and “DTC [Direct-to-Consumer] personal genomic screening,” the latter using a variety of risk alleles [56]. Of 22 high risk females appearing in clinic, family history classified eight individuals as being at risk for breast cancer, but only one of the eight was classified as high-risk through personal genomic screening method.

Family history is a quick way of identifying risk, and has value in this instance as it does with lung cancer. Valdez et al. note that the relative risk of developing breast cancer is 1.8 and ovarian cancer 2.9 if the individual has at least one first-degree relative with these conditions [49]. It is 3.0 and 14.7 given two affected first-degree relatives. The positive and negative predictive values for these cancers appearing in a proband’s first-degree relatives are 89.1% and 98.9% for breast cancer, and 76.1% and 99.3% for ovarian cancer [50]. The U.S. Preventive Services Task Force (USPSTF) has conducted evidence reviews of genetic testing for the key mutations involved in HBOC, *BRCA1* and *2*. It recommends:

Primary care providers screen women who have family members with breast, ovarian, tubal, or peritoneal cancer with 1 of several screening tools designed to identify a family history that may be associated with an increased risk for potentially harmful mutations in breast cancer susceptibility genes (*BRCA1* or *BRCA2*). Women with positive screening results should receive genetic counseling and, if indicated after counseling, *BRCA* testing. [57]

The CDC-OPHG classifies the use of family history of known breast/ovarian cancer with deleterious *BRCA* mutations as Tier 1 [39]. CDC defines Tier 1 genetic interventions as those supported by clinical practice guidelines based on thorough systematic review. These modalities are ready for implementation not just on the individual but on the level of the at-risk population as well [38].

Family history, however, is part of a train of diagnostic interventions, including genetic counseling and genetic testing. The latter can lead to annual screening via MRI or to surgery. A 2012 cost-effectiveness analysis of *BRCA1/2* testing of women ≥ 35 years at elevated risk of carrying a mutation, considering the eventual use of these MRI and surgery, determined genetic testing to be cost-effective if testing cost were $\leq \$8,948$ [58]. Currently targeted *BRCA1/2* mutation testing ranges from \$4,500 to \$650 [58, 59].

Economies of scale operate when identifying persons at risk for cancer. Identifying single individuals can be expected to be less efficient than pinpointing families at risk, just as using information reflecting population risk data can be expected to be more efficient than utilizing separate family histories. Cascade screening is the testing of successive test positive family members starting with a positive index case. Two studies delineate that the success of *BRCA1/2* cascade screening in affected families, as measured by actual uptake of genetic testing, is a function of ability of family members to communicate with one another, and to attend a clinical session [60, 61]. Uptake rates of 54% (Utah study) and 73% (Manchester portion of U.K. study) were achieved when these conditions were satisfied. The London portion of the U.K. study, which covered a more dispersed population, achieved 62% for those clinically seen. George et al. indicate that the cost of *BRCA* testing in 30 at-risk relatives can be brought down from a minimum of \$66,000 to \$12,000 once the responsible mutation has been identified in a family member [62].

On a population level, it is possible to gather information on early-stage breast and ovarian cancer, and to report aggregate information back to participating institutions. A breast cancer incidence study utilizing the Connecticut Tumor Registry found that the ability to detect cases depends on the relative population size of the groups being assessed (here white versus nonwhite) [63]. Population-based risk assessment has the advantage of detecting *BRCA1/2* carriers with a negative family history. Clinical validity goes up with the prevalence of a disorder in a given population. Rubinstein et al. performed a decision analysis of *BRCA1/2* testing in American Ashkenazi Jewish women aged 35-55 years [64]. At a cost of \$460 for founder mutation testing, the investigators concluded that such a program is cost-effective, amounting to \$8,300/QALY gained.

The PMI, like state cancer registries, is especially geared towards targeting at-risk individuals and populations. The CDC notes that state health departments have engaged in bidirectional reporting, i.e., identification of cases from the state tumor registry, and reporting back of information to participating facilities. The Michigan Department of Health and Human Services and Connecticut Department of Health have both identified thousands of cases of breast and ovarian cancer suggesting risk for HBOC, and returned back facility-specific data [65]. In the case of Connecticut, facility-specific reports on numbers of breast and ovarian cancers, compiled from 3,792 cases in the state cancer registry, were reported back to providers to alert them that patients might be at an increased risk for HBOC. Staff at 70% of the 32 involved hospitals also requested and received an HBOC training session.

In the age of electronic health records (EHRs), systems can be designed to provide physicians with decision support tools that alert them to the need for genetic testing, and assist with interpretation of results and potential impact on patients and their families [11]. It is also possible with EHR systems to flag patients who are members of high-risk families to make them aware of their risk status and available options [66, 67].

The Precision Public Health Approach to Colorectal Cancer

The hereditary form of CRC that has received the most public health and medical attention is hereditary nonpolyposis colorectal cancer (HNPCC) or Lynch syndrome (LS), which produces only a small number of polyps or none at all. LS is the most common

heritable cause of CRC, representing 1 in 35 cases [66]. Whereas the lifetime risk for developing CRC is 2 to 5% in the general population, it is 80% in those with LS.

Family history as an instrument for performing cancer risk assessment in first- and second-degree relatives is even more accurate for CRC than for the other two families of cancers. Valdez et al. report that the relative risk for CRC is 2.2 given a first-degree relative with the condition, and 4.0 given at least two first-degree relatives with CRC [49]. Lynch syndrome is notoriously underdiagnosed, however. The vast majority of families with a history of CRC do not know they may have LS, or even that a genetic test is available [66]. Nevertheless, the EGAPP Working Group, using a chain of evidence methodology comparing four preliminary testing (MSI, IHC, and *BRAF*) and mismatch repair (MMR) gene strategies leading to medical and surgical management, found that adequate evidence exists that an appropriate testing strategy can improve clinical outcomes for patients and their families [68].

A precision public health approach to Lynch syndrome entails spotting cases before the management is made more complex by disease advancement, coupled with identifying at-risk relatives free of disease. A 2014 consensus statement by the U.S. Multi-Society Task Force on Colorectal Cancer looked at initial approaches for index case identification. Use of clinical criteria (e.g., the Revised Bethesda Guidelines) and a CRC risk assessment tool using family history – “selective approaches” used to identify a range of patients – both showed adequate sensitivity in identifying individuals with germline mutations, but up to 28% of LS patients can be missed with a liberal interpretation of the revised guidelines [69]. A more “universal approach” assessing LS risk based on IHC testing of all incoming cases of CRC was found to have greater sensitivity than selective strategies including the use of the Bethesda guidelines. Such an approach is still shy of being considered population-wide risk assessment in that testing begins with confirmed colorectal cancer cases. Multiple studies have shown that: (1) the systematic application of testing among patients with newly diagnosed CRC could provide substantial clinical benefits at acceptable costs; and (2) adopting a “universal” approach towards CRC genetic testing is cost-effective [69]. Palomaki et al., for example, found that a strategy employing IHC and *BRAF* preliminary testing followed by MMR mutation testing in *BRAF* negative cases would cost an average of \$18,863 per LS case detected [70].

Having identified an index case, the public health approach is then to move on to relatives to identify those at risk for LS, and those who are not. The EGAPP Working Group cites seven studies showing how uptake of colonoscopy by relatives with LS ranged from 53 to 100% [68]. Sharaf et al., in a sub-analysis of four select articles from a broader LS studies review, concluded that 52% or less of the first-degree relatives received LS genetic testing [71]. This number was critiqued by Jasperson, who noted that the Sharaf analysis excluded a large study containing 466 family members composed almost exclusively of first-degree relatives at high-risk of developing LS [72]. The latter study found 75% of the members to have been tested for LS mutations.

The cost of cascade testing is also a consideration. The per mutation cost of MMR gene testing for LS can decrease from \$1,000 to \$350 once a specific familial mutation has been identified in the proband [59]. The consequence is that the cost per LS index case can decrease from \$18,863 to \$13,000 [68]. In the most comprehensive cost-effectiveness assessment of universal and “near-universal” genetic screening to date, covering seven LS studies that also looked at medical/surgical follow-up and testing of relatives, Grosse found

that all except one reported incremental cost-effectiveness ratios less than the threshold \$100,000 per life-year or quality-adjusted life-year gained [73].

Table 2. Public health precision approach – 3 cancers

Condition	Genetic test	Cost-effectiveness	References
Familial lung cancer	Family history (FH)	*FP rate: 1.9 (female) – 6.1 (male) FN rate: 29.1 (female) – 37.5 (male) **PPV: 81.0 (68.6 – 90.1)*** NPV: 97.1 (96.0 – 98.0) Cost \$10 – 25/FH taken	Ziogas and Anton-Culver [50] Johnson et al. [51]
	GWAS – remains investigational		
Hereditary breast and ovarian cancer (HBOC)	<i>BRCA1/2</i>	Cost-effectiveness threshold \$8,948 (current testing \$650 – 4,500) \$8,300/QALY gained (U.S. Ashkenazi population)	Goodman [58] Rubinstein et al. [64]
Hereditary nonpolyposis colorectal cancer (Lynch syndrome – LS)	Multi-gene testing (<i>MLH1</i> , <i>MSH2</i> , <i>MSH6</i> , <i>PMS2</i> , <i>EPCAM</i>)	\$18,863 cost/index case \$13,000 cost/relative \$29,600 – 63,900/QALY gained (“universal” testing)	EGAPP [68]; Palomaki et al. [70] Grosse [73]

* False positive (FP) and false negative (FN) rates.

** Positive predictive value (PPV) and negative predictive value (NPV).

*** 95% Confidence interval.

As with HBOC, collection and reporting of LS data has occurred at the state level. Michigan identified 10,000 CRC cases from its cancer registry, and returned facility-specific data and educational materials to 145 reporting institutions [74]. Connecticut reported back information on 3,517 CRC cases in its cancer registry to targeted practitioners at acute care hospitals. These bidirectional reporting efforts show that health-related information may be stored *en masse* for both practical and research purposes (as in the PMI Cohort), and can be reissued for clinical and public health purposes.

The Colorado Department of Public Health and Environment also targeted educational outreach relating to hereditary CRC to 430 medical providers and 200 at-risk cases [74]. A survey was conducted which showed that 98% of provider and patient respondents thought that the information was clear and useful, many patients having indicated they engaged in further dialogue with their physician, a genetic counselor, or a family member. About 1/3 of the patient respondents communicated that they planned to have a risk assessment as a result of receiving the materials. The Colorado educational efforts were conducted by mail. An extensive, 33-study article review by Naylor et al. found that further patient education involving phone or in-person contact combined with patient navigation of resources can lead to improvements on the order of 15% in colorectal screening rates in minority populations [75].

Table 2 outlines the array of precision public health efforts, which involves targeting of screening, genetic testing, and education for the three cancer conditions.

CONCLUSION: CONTINUITY AND EMERGENCE IN PRECISION HEALTH APPROACHES

A major point brought out by the two tables is that pharmacogenomic regimens cost considerably more than primary prevention approaches to cancer management. From the articles reviewed herein, the former often exceed cost-effectiveness thresholds, though this conclusion need not necessarily be true for the regimens that are being offered. The cancer drug being prescribed is typically the main contributor to the cost, as opposed to the companion diagnostic, which can actually bring the price down. One can then view this conclusion in three ways: (1) optimistically, economies of scale or institutional policy changes might ultimately bring the cost of the pharmacogenomic regimen down; (2) the value of a person's life is to be held paramount, thus the costs incurred, from a private perspective, are worth it; or (3) the value of the primary prevention approach, due to its cost-effectiveness, is to be emphasized.

The medical and public health approaches are not to be viewed as mutually exclusive. Their territories are more like the circles of a Venn diagram which intersect with plenty of shared space in the middle. Both the CDC and its EGAPP program have devoted considerable attention to companion diagnostics and the attempt to prove that they have overall utility, including cost-effectiveness. Public health has an evaluative role that dips into hospital-based interventions. The national view is more one of mergence [3]. The fact that *BRCA1/2* genetic testing takes off where chemotherapeutic approaches to breast cancer leave off, in terms of the host cancer's hormone receptor status, indicates that the domains of the primary/secondary and tertiary prevention camps are complementary. It would be idealistic to assume that predictive genetic testing plus monitoring could eliminate all tumors before they spread. Both ends of the prevention continuum are needed, and the more targeted they are, the better. It is also important to recognize that the medical and public health approaches both defy stereotyping. The use of *KRAS* testing in anti-EGFR therapy of metastatic colorectal cancer can be cost-saving. The value of a public health approach genetic to lung cancer is limited by the current state of GWAS findings and the heavy influence of gene-environment interactions in the genesis of lung cancer. Indeed, some would argue that federal and state policy approaches towards smoking and lung cancer should take center stage.

Policymakers have a role in deciding allocation of healthcare dollars. In providing arguments for and against utility in this paper, we are not advocating a withdrawal of dollars from either medical or public health oncogenomic approaches. The case has been made for a more detailed consideration of the proportion of dollars that go towards prevention, however. The paper has not dealt just with chemotherapy, or just with Tier 1 genetic testing, however – emphasis has been placed on a precision approach for both. In public health, this nuance translates into tailoring the intervention towards communities at-risk or in-need. It will be more cost-effective thereby, and will achieve the ethical standard of addressing the health of all by attending to those most in need.

A final point should be made about the medical and public health precision approaches that are emerging. The medical approach is showing healthy signs of growth. The PMI Research Cohort will grant it the ability to host more clinical trials with suitable cohorts of participants, and to speed up the process of conducting clinical trials. As NCI plans, some of these trials will cross typological borders and target treatments based on somatic abnormalities in the tumors regardless of cancer type [34]. Public health research will also benefit from the PMI Cohort, especially in instances where major germline mutations have not turned up and GWAS are actively identifying lower risk alleles having a cumulative effect. Given the thought being given to participating groups, the discovery of new risk alleles will most certainly benefit diverse communities. The promise of tapping into lifestyle and environmental factors as data on the cohort participants builds will strengthen prevention approaches even further. The word “precision” also applies to the educational component of health programs. Educational efforts can become more tailored to the needs of at-risk groups as the data accumulates. Precision public health does not end with the target molecule, but with the whole person and the community to which he or she belongs.

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Chapter 525

YOUTH GUN VIOLENCE: A GROWING PUBLIC HEALTH CONCERN

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ABSTRACT

Youth gun violence is a significant public health concern around the world. There have not been any certain methods or programs implemented that have been shown to significantly decrease this issue. There are some thoughts as to what would be effective interventions, but lack of research prevents evidence-based interventions from being implemented. Without addressing gun violence in the adolescent population, there will continue to be a disproportionate level of morbidity and mortality in our youth.

INTRODUCTION

Gun violence is a pervasive problem in today's society. It is difficult to watch the news without hearing of serious acts of harm toward individuals, with guns most commonly being the weapon of choice. The United States has a disproportionately high problem compared to most other developed countries, but there are growing issues around the globe. This form of violence is very frustrating for all sides involved due to the complexity of the problem. There seem to be many opinions on how to address this significant concern, but no effective solutions have been identified.

The thought as to why gun violence is more prevalent in the United States is largely due to social attitudes surrounding firearms and the ease of access. Guns are entrenched in the

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American culture [1]. There is an extremely strong gun lobby in the United States and firearm laws are more lenient than most other countries in the world. It is currently estimated that there are over 300 million guns in circulation in the United States, which is over three times as many as the 79 million throughout the European Union [2].

Overall, gun violence rates are down significantly since the peak in the 1990s [3]. Even with the decline in overall violence rates, youth gun violence prevalence remains somewhat alarming at this time. Worldwide, an average of 200,000 adolescents die from gun violence each year [4]. Unintentional injury remains the leading cause of death in adolescents in the United States, followed by suicide and homicide [5]. Homicide is the leading cause of death in African American males ages 10 to 24 years [6]. There are roughly three times the number of non-fatal injuries due to gun violence each year, which lead to significant physical, psychological, social, and financial burden to the individuals and families involved [4]. Youth homicides and assault-related injuries cost the United States alone about \$18 billion annually [6].

Not all gun violence is the same. There are two very distinct classifications of youth gun violence, which are mass shootings and street violence [7]. The characteristics of the perpetrator and their overall intent are generally very different between these groups. School shooters are statistically Caucasian males, little or no history of behavior problems, and have average to above average intelligence [7]. Many times the reason for mass/school shootings remains unknown. Street violence offenders, on the other hand, are statistically minorities from urban areas high in poverty and crime [7]. These shootings typically involve drugs, gang affiliation, neighborhood “turf” battles, and personal conflict [7]. Mass shooters will often commit suicide at the end of their rampage, but street shooters rarely do [8].

In most countries, there are laws prohibiting the legal purchase of firearms by a minor. This does not seem to stop adolescents from obtaining, carrying, and using guns. Many wonder about the ease of access and the availability of guns to this population. Mass shooters often purchase a gun legally, if over the legal age, or will obtain guns from within their homes [7]. It is estimated that 44% of homes in the United States have at least one gun [5]. Street shooters typically obtain guns from purchasing illegally on the street, taking guns from their homes, or stealing the firearms [7]. These individuals often feel the need to protect themselves and will carry guns on a regular basis [1].

It is important to be able to identify those youth that are at risk for gun violence. Statistically, males are the large majority of perpetrators of gun violence [9]. It is a common misconception that those with mental illness are at higher risk for gun violence, but actually only 4% of violent acts are committed by those with diagnosed severe mental illness [10]. Victims of bullying have been found to be at an increased risk of weapon carrying [11]. Exposure to violence in the home seems to be a large predictor of becoming a perpetrator of violence due to the physical and emotional trauma that children face [1]. One of the best predictors of violence in an individual is a history of past violent behavior [7].

PREVENTION AND INTERVENTION

One of the most difficult problems with regards to youth gun violence is prevention and intervention. There are many programs and efforts that have been initiated with varying levels

of success. The majority of these initiatives have been tailored to a certain population or geographic area to meet specific needs. There does not seem to be one strategy that is most effective and can be applied broadly. There are things that can be done by parents, school officials, the community, and medical providers that can help decrease the rates of violence in today's youth.

Parents have a large responsibility in gun violence prevention and intervention with their kids. It is essential that parents lock all guns that are inside the home to prevent easy access [9]. Parents should monitor their children closely and should know the social circles in which they belong, the places that they are going, and their exposure to violent media [1]. It is beneficial if parents are involved, supportive, and nurturing from a very early age and if they respond quickly and proactively to any signs of aggression that their child exhibits [7]. Dealing with stress and conflict in a positive way needs to be modeled by parents in the home in order to teach children the best way to react in these situations [1].

School officials have a large responsibility to monitor kids closely in the school setting in order to help identify those kids at risk for violence, but also to provide resources to parents and students about violence and potential interventions. Bullying must be monitored and handled appropriately in order to prevent those victims from acting on their frustrations [11]. School officials should foster a sense of safety for all children attending their school [1]. Any individuals that present with threatening behavior should be addressed immediately by school officials, school law enforcement, and mental health providers in order to assess the situation appropriately and identify the resources that can be used to resolve the concern. In-school violence prevention programs need to be initiated and strongly supported in order for a positive difference to be made [9].

The community has a strong influence on the actions of the individuals living there, especially the youth. There are areas, especially urban areas of high poverty, where violence is accepted as the norm and the community tolerates this behavior. It is up to community leaders and residents to change that way of thinking and the beliefs of their area, which is extremely difficult to do in most cases, in order for positive change to occur [12]. Community policing, which is where police are embedded in communities in order to form relationships and know the routines of an area, has been shown to be a positive influence on the individual satisfaction of residents and the community's trust in police. However, studies regarding community policing show no great decrease in overall crime rates due to these programs [13]. A community deterrence strategy, called pulling levers, has been shown to be successful in crime reduction. These pulling levers campaigns target individuals or areas in need and increase the social services and community resources, police activity, and frequency of communication with known violent offenders in efforts to help reduce crime rates [14]. Even though these interventions sound promising and show positive results, there is rarely sustainable funding to make these interventions a long-term solution.

Health care providers play a unique role in gun violence prevention. Since 1999, the American Academy of Pediatrics has endorsed routine screening of violence and gun safety in the child and adolescent population, but the actual number of providers performing these routine screens remains low [15]. Literature reviews show that performing routine screenings in the primary care setting can help lower overall violence rates. There are many screening tools available for various patient settings. By identifying those at risk through routine screenings, social and mental health resources can be made available to the patient in order to help prevent future violence or victimization. It is essential to provide therapy to those kids

exposed to gun violence, whether in the home or in the social setting [1]. Mental health treatment may be one of the best interventions that we have to offer in the outpatient setting at this time [9]. There have been numerous inpatient programs developed for identification and intervention on the inpatient side of care. Typically, patients are entered into these programs after being admitted to the hospital as a victim of gun violence. These programs provide different interventions while a victim is inpatient and some also have outpatient follow up. Inpatient violence prevention programs typically do show some benefit, but the programs need to be long-term in nature in order to significantly lower violent crime [16].

Due to the complexities of the gun violence problem at this time, more research is needed to explore various factors surrounding the issue in order to create better strategies for violence reduction. In the US, gun violence research has been controversial over the past two decades. In 1996, researchers at the Centers for Disease Control and Prevention (CDC) were banned from performing gun related research, which was thought to be due to the power of the American gun lobby and their influence on lawmakers [17]. By looking into certain aspects of gun violence, such as gun laws, media violence, and family and school influences, the problem could be understood better and there could be research focused interventions to help reduce youth gun violence [7].

CONCLUSION

In conclusion, youth gun violence is a serious public health concern in today's society. This issue is affecting all parts of the globe and little is being done to help resolve the problem. To decrease the rates of gun violence among youth, it will take a collaborative effort from parents, school officials, community members, and health care providers. With better research performed on the topic, these key players would be better equipped to develop effective prevention and intervention programs. It is hoped that there will be new understanding in the near future and the rates of youth gun violence will begin to decline.

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Chapter 526

HOW COMPUTER MODELS CAN DISTORT BAYESIAN UNCERTAINTY ABOUT PUBLIC-HEALTH HARM: SCIENTIFIC AND ETHICAL PROBLEMS

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Mathematics is, I believe, the chief source of the belief in eternal and exact truth as well as a sensible intelligent world.

Bertrand Russell

ABSTRACT

One of the major ways that scientists err in information-technology fields is by misusing quantitative risk assessments (QRAs) that employ flawed computer models. These computer models err because they characterize Bayesian situations of deep *uncertainty* (for which no reliable probabilities or frequency data are available) instead as situation of reliable, confirmed *risk* (for which reliable probabilities and frequency data are available). Mischaracterizing uncertainty as risk, scientists often claim low risks for breaching million-year nuclear-waste repositories, for the groundwater transmission of hazardous wastes, or for the thousand-year vulnerability of chemical facilities to terrorist attack. This chapter (1) outlines several scientific and ethical problems associated with using QRA computer models to mischaracterize potentially harmful, million-year situations of deep *uncertainty* instead as situations of *risk*. It shows that these public-health-related computer models typically (1.1) fail to do uncertainty analysis and (1.2) misrepresent the scientific nature of both prediction and uncertainty analysis. To show (1.1-1.2), the chapter (2) gives several prominent, current, scientific examples of these mischaracterizations that also threaten human welfare, namely, MIT's 1975 Reactor Safety Study; TRW's year-2000 Yucca Mountain environmental impact assessment; and the US Department of Energy's 2010 West Valley, NY environmental impact assessment. Finally, the chapter (3) reveals several practical ways to avoid such flawed computer modeling that also threatens public health and safety.

Keywords: MIT, nuclear reactor, prediction, quantitative risk assessment, subjective probability, uncertainty analysis, waste repository, West Valley, Yucca Mountain

INTRODUCTION

Henry Ford, the founder of the auto company and the developer of the assembly line, said that “Whether you think you can do it or not, you’re usually right.” Confidence alone may not generate success, but it’s usually necessary. Yet, from driving a car, to solving math problems, most people – including scientists – are more certain of their abilities and estimates than they deserve to be. Moreover, men are more over-confident than women are. When different scientists have equal ability and perform equally well on the same scientific questions, virtually all are overconfident, but women are 22 percent less so than men are (Kay and Shipman 2014).

Despite the value of confidence, overconfidence in science and engineering can lead to both error and catastrophe. This chapter shows that even prominent computer modelers have often been overconfident about their health-and-safety-related results, particularly in situations in which they either have no empirical data, or fail to use these data, to check their predictions.

OVERVIEW

The chapter reveals that a major source of scientific error in information-technology fields involves misuse of quantitative risk assessments (QRAs) that employ flawed computer models. These computer models err because they characterize Bayesian situations of deep *uncertainty* (for which no reliable probabilities or frequency data are available) instead as situation of reliable, confirmed *risk* (for which reliable probabilities and frequency data are available). Mischaracterizing uncertainty as risk, scientists often claim low risks for breaching million-year nuclear-waste repositories, for the groundwater transmission of hazardous wastes, or for the thousand-year vulnerability of chemical facilities to terrorist attack. The chapter (1) summarizes the difference between Bayesian risk and uncertainty, (2) gives three examples showing how prominent scientists and engineers misuse QRAs that employ flawed computer models, (3) outlines key scientific and ethical problems associated with using QRA computer models to mischaracterize potentially harmful, million-year situations of deep *uncertainty* instead as situations of *risk*, and (4) offers several practical ways to avoid these uncertainty-related scientific biases that result in massive threats to human welfare.

BAYESIAN UNCERTAINTY, RISK, AND MISREPRESENTATIONS OF UNCERTAINTY

Researchers and computer modelers doing welfare-related science frequently mischaracterize situations of Bayesian uncertainty and risk. Scientists who assess

technological risk, through techniques such as QRA, typically define risk as the annual probability that some damaging effect will occur, an effect such as a nuclear-reactor core melt or an effect such as a leak from a hazardous-waste facility. If scientists are overconfident about their computer-modeled risks, often they claim more reliability for their risk predictions and probabilities than is defensible. After all, scientists do not use models when they have adequate empirical data. When they have adequate data, they can simply use them to predict future outcomes. However when empirical data are lacking, that is exactly the situation in which scientists are forced to estimate future risks, on the basis of strongly theoretical and uncertain computer models. Hence, by definition, scientists and mathematicians have limited grounds for claiming they have accurate risk probabilities, when they really face situations of uncertainty (Shrader-Frechette 1993).

Computer modelers often mischaracterize situations of Bayesian uncertainty and risk in one of two ways, (A) and (B). Both uncertainty-related errors, (A) and (B), tend to occur more often when scientists and engineers are overconfident about their knowledge of risky new technologies. Frequently either (A) they misrepresent cases of Bayesian mathematical-scientific *uncertainty* (defined in terms of purely-subjective probabilities) as cases of *risk* (defined in terms of reliable, often frequency-based, probabilities), or (B) they claim that their computer-modeled estimates of risk are more reliable than they are, sometimes because they fail to do uncertainty analysis. Uncertainty analysis is a statistical assessment of the reliability of scientific or engineering judgments about the values attributable to estimates or computer models, often of risk. Whenever such values are untestable, rely on unknowns, or reflect cumulative effects of data variability, uncertainty analysis can assess both random error and bias (Jordaan 2005; Shrader-Frechette 2007:76–112; 2017).

Uncertainty analysis is especially needed when scientists or engineers estimate long-term, inaccessible, or difficult-to-predict harmful effects, such as 10,000-year effects of climate change—or the timing, route, and volume of pollutants that may escape from a hazardous-waste site. Otherwise, experts' well-documented overconfidence, representativeness, anchoring, and other cognitive biases could compromise sound science and threaten public health (Kahneman et al. 1982).

THE FLAWED MIT REACTOR STUDY

Unfortunately, even well-known scientific and engineering analyses, like the classic MIT study of commercial-nuclear-reactor-accident probabilities, may misrepresent uncertainty. For instance, they may commit (A) when they confuse risk and uncertainty by making subjective assumptions about how to quantify public-health risk. They may commit (B) when they fail to do uncertainty analysis. The MIT engineers committed (A) because they made the subjective assumptions that they could rely on purely theoretical calculations, could ignore available empirical data about accidents, could presuppose that control-rod and other reactor-failure probabilities were completely independent, yet then could estimate that nuclear-core-melt-accident risks were only 1/17,000 per reactor-year – that is, about 1 in 5 for all US reactors during their lifetimes. Unsurprisingly, the American Physical Society and US Nuclear Regulatory Commission said they do “not regard as reliable” the MIT “numerical estimate of the overall risk of reactor accidents.” Because the distinguished MIT researchers

did not do any uncertainty analysis, they also fell into error (B) (Shrader-Frechette 2014; US Nuclear Regulatory Commission 1975, 1979).

However, US, Dutch, and other engineers showed that the MIT study errs in ignoring empirical data, exhibiting overconfidence biases, and overestimating nuclear safety. When the other researchers compared actual, empirical, US reactor-accident frequencies (tracked by the US government's Oak Ridge, Tennessee Laboratories), with the MIT predictions for the same 7 events, they showed the actual occurrence rates for all 7 accident types were outside MIT's 90-percent-confidence bands. That is, the MIT authors said these repeated accidents had only a 10 percent probability. Simply checking available empirical data and doing uncertainty analyses could have helped MIT avoid this misrepresentation of uncertainty and underestimate of nuclear-reactor threats to health and safety (e.g., Cooke 1982; Shrader-Frechette 1991, 2007; US Nuclear Regulatory Commission 1975).

BIASED US GOVERNMENT STUDIES OF YUCCA MOUNTAIN WASTE REPOSITORY RISKS

Similar misrepresentations occurred when US *Department of Energy* (DOE) engineers assessed the million-year safety of the proposed Yucca Mountain, Nevada, nuclear-waste repository (TRW 2000). After DOE contractors failed to do uncertainty analysis, then made optimistic predictions about repository safety, scientists from the International Atomic Energy Agency used DOE's own data to do uncertainty analysis. The results were damning. DOE's overconfident estimates of future low risks – based on their estimated low radiation doses from Yucca Mountain – were uncertain by 9-12 orders of magnitude. Yet if they had erred by only 2 orders of magnitude, catastrophic numbers of deaths could occur (IAEA 2001; Shrader-Frechette 1993, 2007).

Both the MIT and DOE misrepresentations of uncertainty arguably have contributed to false-negative biases, false assertions that nuclear reactors are not as dangerous to public health and safety and they really are. They also have contributed to building more expensive, risky nuclear plants, as well as to environmental injustice in nuclear-plant siting. This environmental injustice occurs because US commercial reactors are disproportionately sited in predominantly poor, southeastern US communities, under the false assumption – based on models that misrepresent uncertainty – that these communities are not put at any extra risk. Similarly, Yucca Mountain was sited near predominantly Native American and Latino communities, also under the false assumption – based on models that misrepresent uncertainty – that local communities would bear no higher risk (Shrader-Frechette 2011).

THE SCIENTIFICALLY ERRONEOUS US GOVERNMENT MODELS FOR WEST VALLEY, NEW YORK

West Valley, New York presents another dramatic example of how flawed computer models can provide flawed scientific and public-health analyses. West Valley has been the only place in the US where the country did reprocessing of spent nuclear fuel and, as a result,

it is one of the most hazardous sites in the entire country. However, since the 1970s, when West Valley stopped nuclear-fuel reprocessing, the New York state government, national and local citizens groups, and the US federal government have been fighting over how to solve the West Valley dilemma: West Valley radioactive and toxic wastes are not safe where they are, even for a short time, because of site erosion and because the place is the most radioactively contaminated in the US. However, site remediation – for which the US DOE and the state of New York are responsible – will be very expensive, so neither side wants to pay for moving the wastes to a safer site. The US DOE solution? Misrepresent risk and uncertainty so as to underestimate site hazards, ignore the huge plume of radioactive waste moving toward Lake Erie and drinking-water supplies, fail to do any adequate uncertainty analyses, then issue a 2010 *environmental impact statement* (EIS) that declares the lethal waste to be safe where it is onsite – even for 10,000 to a million years (Napoleon et al. 2008; Shrader-Frechette 2016; US DOE 2010;).

How did DOE come to the strange conclusion that this US site, with more long-lived radioactive contamination than any in the US, could be left alone, largely “as is,” and cause no health harm? DOE made at least three scientifically questionable moves in its computer models. It (1) confused risk and uncertainty; (2) avoided doing any classic uncertainty analysis to assist in decision making, and it (3) arbitrarily redefined the meaning of “uncertainty analysis” so that it could claim to have done this analysis, allegedly showing that by the time lethal amounts of waste migrated, they would cause only minor harm.

West Valley Background

It is puzzling that US government computer modelers claimed that their models showed West Valley would be harmless for the next 10,000 years. Already in 1983, scientists discovered a West Valley plutonium-239 leak that was already 63 feet offsite. It has been traveling through subsurface fractures and sand and is radioactively contaminating Lake Ontario and Lake Erie (source of drinking water for communities like Buffalo, New York) at levels beyond federal radioactivity limits. Given the plutonium-239 half-life of 24,110 years, this leak will cause contamination and risk for hundreds of thousands of years (Napoleon et al. 2008).

Assessing West Valley radioactive dangers, Cambridge, Massachusetts scientists warned in the first decade of the 21st century that “radionuclide doses calculated for a person drinking [local water near the site]...were substantial and well in excess of the federal and state [safety] standards.... [As a result, this West Valley pollution will cause....] up to 334...people...to die of cancer as a result of their exposure to [radioactively] contaminated water from Lake Erie” (Napoleon et al. 2008). “Adverse health effects as well as unnecessary deaths from cancer [will occur] due solely to radiation exposure coming from the West Valley site” [19]. At least 30 years ago, scientists documented that the West-Valley-contaminated local creeks have contaminated Lake Erie (and its drinking-water supplies) which, in turn, have contaminated both the Niagara River and Lake Ontario (Joshi 1988a, 1988b; Napoleon et al. 2008).

Apart from existing contamination of New York water supplies, the West Valley site has a massive groundwater-contamination plume of strontium-90 that not only violates

government safety regulations but also will expand and cause risks for at least another 300 years because of the long strontium-90 half-life. Besides multiple leaks of long-lived, radioactive, groundwater contaminants, West Valley waste-site soil also is eroding at a rate of 1 foot per year, threatening to unearth the shallow land burial of the improperly dumped West Valley radioactive wastes, (Napoleon et al. 2008: 12, 13, 37, 44-45, 54-64, 107).

Mischaracterizing Risk and Uncertainty in West Valley Computer Models

Instead of admitting the severity of the West Valley site risks, in 2010 the US DOE EIS claimed that minor cleanup, plus leaving most of the lethal waste buried onsite, will be safe for the next tens'-to-hundreds of thousands of years. The US DOE concluded that if it merely leaves much of the long-lived nuclear waste onsite at West Valley, without any government-institutional management such as fences, monitoring, and erosion controls, the maximum annual future dose to any person offsite will be only 0.2 mrem or 0.002 mSv – about 1/2500 of normal background radiation. Even with completely uncontrolled erosion, DOE also says that future yearly maximum offsite radiation dose would be only 4 mrem – less than one percent of normal background radiation (US DOE 2010).

The preceding claims are surprising conclusions for at least two reasons. The first reason is that distinguished economists have shown that the least-expensive, long-term strategy is to move West Valley wastes to a safer, drier location (Napoleon et al. 2008). Why doesn't US DOE accept the cheapest long-term solution? The main reason is that annual West Valley Congressional budget allotments from the US DOE cover only minor cleanup and site maintenance, US DOE has been reducing annual West Valley budgets, and US DOE and the Congress have not given the greater, one-time, West Valley funding needed for full site cleanup – which would dwarf annual available, budgeted site monies (Napoleon et al. 2008: 9, 12, 26, 39, 63, 108, 128-130).

The second reason the DOE West Valley claims are surprising is that there is no scientific way to predict such tiny risks and precise radiation exposures, up to a million years into the future. Besides, if future West Valley risks would really be so low, why does the US government today say that it would not allow siting a nuclear-waste facility at West Valley because of its severe erosion problems? Scientific peer reviewers consider US DOE radiation-risk predictions from the West Valley site, including the maximum dose of 0.2 mrem/year, highly unlikely (Napoleon et al. 2008; NYSERDA 2010). Moreover, the US National Academy of Sciences has pointed out that scientists agree that it is impossible to make precise risk predictions about site historical, hydrological, geological, and meteorological events tens of thousands of years in the future (US National Research Council 1995).

But if so, how does the DOE get its risk predictions? A key way that the US DOE's 2010 EIS claims reliable, 10,000-year "predictions" of low risk is that it ignores massive long-term uncertainty and instead employs a largely subjective, "best estimate" set of mostly deterministic predictions about future site safety. It also uses single values, rather than a range of probable values, for model inputs and parameters. Without any documentation or defense of its "estimates," the US DOE next begs the question when it asserts that these guestimated risk-input values are "conservative." Given such question-begging, subjective, risk-

probability estimates, US DOE ignores massive, long-term uncertainty about the site (NYSERDA 2010; Shrader-Frechette 2016; US DOE 2010).

Regarding parameter uncertainty, for example, although the EIS admits that erosion is the main way that site radionuclides are likely to be transported, it gives neither error estimates nor confidence intervals for the parameter values it uses to predict in erosion risk – the most essential of all predictions for ensuring site safety. Yet, US DOE admits that these parameters have a large potential range. For instance, although the EIS shows no gully erosion in the South Plateau over the next 10,000 years, his conclusion is “wholly inconsistent” with the observed topography and observed, long-term, continuing, severe erosion and stream downcutting at the site. In other words, the US DOE conclusions about 10,000-year, site-erosion risk not only ignore long-term uncertainty and fail to have any mathematical justification, but they also contradict existing, short-term (30 years) frequency data on massive site erosion. These are some of the reasons that the long-term, site-parameter predictions of risk in the EIS are not reliable (Shrader-Frechette 2016; US DOE 2010).

Avoiding Uncertainty Analysis of West Valley Computer Models

Thus, despite the dominance of uncertainty in long-term hydrogeological prediction, and despite DOE’s providing EIS uncertainty analyses only for a handful of the hundreds of relevant West Valley parameters, it concludes that the site will be safe for the long-term future. DOE also does no uncertainty analysis of its model predictions, and it ignores uncertainties that arise from factors such as spatial variability at the site (US DOE 2010).

For instance, the US DOE EIS could have done uncertainty analysis of its model predictions, but it did not. Likewise it could have qualitatively assessed the uncertainties in its main computer model – a landscape-evolution model – by listing all major assumptions, questionable predictions, idealizations, and application problems. Again the EIS did not do even this qualitative analysis. Instead it used a crude landscape-evolution model for long-term site prediction – although scientists agree they are unsuitable for long-term prediction. As in the earlier Yucca Mountain case, this is another example of risk assessors and computer modelers using a fundamentally “explanatory” model of a site as if it were a “predictive” model (Shmueli 2010). Because the EIS admits such explanatory, landscape-evolution site models cannot predict locations of streams, gullies, and landslides; cannot address stream wandering, over time; and cannot predict knickpoint erosion that is causing rapid downcutting erosion of stream channels and increased gullying, it is puzzling that the EIS used such admittedly crude models for its claimed precise, long-term predictions (Shrader-Frechette 2016).

Similarly, the EIS used a crude, one dimensional model of groundwater transport at the site to predict future radiation doses to humans, for 10,000-1,000,000 years (US DOE 2010), although such models cannot be validated or verified (Bredehoeft 2005; Bredehoeft and Konikow 1992), and although a three-dimensional model likely would have been more reliable than the US DOE one-dimensional model. Yet, never did the EIS present a compelling argument for why it chose to use simplified one-dimensional flow-and-transport models for the purposes of calculating something as important as long-term radiation dose. Never did the West Valley EIS defend its generating nearly worthless computer-model

predictions whose reliability has never been assessed. In fact, even the EIS short-term computer models of the site are nearly worthless, because none of them is able even to correctly predict current-time gully erosion. Yet gully erosion is the principal surface threat to the radioactive wastes. Never did the EIS do model verification or validation by comparing model output with actual field data available for the short term. For all these reasons, the US DOE decision to avoid uncertainty analysis is highly questionable (Shrader-Frechette 2016).

Relying on Non-Standard Accounts of Classic Scientific Terms and Methods

The US DOE 2010 West Valley EIS also erred in failing to employ the standard scientific meaning of terms such as “uncertainty analysis” when it used them. In other words, rather than admit all these sources of West Valley EIS uncertainty, and rather than do an uncertainty analysis, the DOE West Valley EIS simply redefines various scientific terms in ways that cover up the flaws in the document and the failure of the authors to do standard uncertainty analysis. For instance, while its use of the term “best estimate” suggests a reasoned, empirical assessment, the EIS and computer model use the term in a way that is contrary to standard scientific use. Scientists usually employ the term to mean the average or mean of a distribution or some other optimum, such as a median. However, the DOE EIS uses “best estimate” to mean merely some estimate, subjectively considered by the authors (without any justification provided) to be conservative (US DOE 2010). Yet nowhere does the EIS explain or argue why its’ supposed analyses are conservative. Indeed, given all the gratuitous guestimates and undocumented claims, it is impossible to check the alleged conservatism of the EIS scenarios (Shrader-Frechette 2016).

One alleged conservative best estimate of US DOE, for instance, is that “the probable maximum flood floodplain is very similar to the 100-year floodplain” (US DOE 2010). Yet by definition, the maximum flood over 50,000 years has more extreme, therefore more dangerous, values than over 1/500 of that time span, namely 100 years. Likewise, the EIS says it provides a conservative estimate of West Valley radiation in drinking water because its “drinking-water dose analysis conservatively assumes no radionuclide removal in the water treatment system” (US DOE 2010). Yet such an assumption is not conservative, but typical. US water-treatment facilities typically do nothing except add chlorine to the water to kill bacteria. They are not equipped to remove radionuclides or any other contaminants. Hence to assume no such removal is not conservative but typical (Shrader-Frechette 2016).

Similarly the EIS says it presents a conservative “best estimate” for West Valley radiological accidents because it presents the estimated worker “accidents and fatalities that could occur from actions planned for each of the proposed alternatives. These estimates were projected using data from DOE’s historical database for worker injuries and fatalities at its facilities” (US DOE 2010). Yet employer databases typically underestimate health problems and accidents, both because they include no long-term follow-up of workers and because workers are reluctant to admit either their radiation accidents or excessive dose levels, because they fear losing their jobs. Given the EIS misnomer of “best estimates,” the pro-nuclear scientific peer reviewers of the EIS warned: “it appears to us that a more apt description” of many of these alleged EIS “best estimate” cases would be “nominal and non-conservative” (Bredehoeft et al. 2006).

Likewise the West Valley EIS repeatedly claims to have presented an uncertainty analysis of its conclusions. Yet according to standard scientific usage, an uncertainty analysis assesses the degree to which any particular conclusions and input parameters are reliable. The West Valley EIS, however, does not employ the term “uncertainty analysis” in this way.

Instead, as the pro-nuclear scientific peer reviewers point out, the West Valley EIS uses this term to mean simply presenting several different deterministic cases – in fact, only two of them. The reviewers warn that although the EIS “considers presenting three sets of cases to constitute an analysis of uncertainty,” it “cannot substitute for a comprehensive uncertainty analysis” (Bredehoeft et al. 2006; see Shrader-Frechette 2016). Because nothing in the EIS justifies choosing these two sets of deterministic, non-probabilistic assumptions rather than others, because there is no probabilistic analysis that could provide the basis for quantifying uncertainty, the EIS provides little basis for confidence in the quality of its conclusions, little basis for precisely or reliably understanding the contributors to uncertainty (Shrader-Frechette 2016).

QUESTIONABLE TREATMENT OF UNCERTAINTY IN COMPUTER MODELS AND HOW TO AVOID IT

Perhaps the most scientifically and ethically worrisome thing about the West Valley modelers’ treatment of risk and uncertainty is that essentially the same US government agencies, responsible for US public health and safety from ionizing radiation, have been making the same fundamental mathematical and scientific modeling mistakes for nearly half a century—at least since the 1975 flawed studies already mentioned. The longevity of such errors suggests it is especially important to develop ways to avoid such flawed scientific modeling, especially modeling that underestimates serious public-health threats.

Epidemiologist David Michaels, former President Obama’s assistant secretary of labor, seems to agree. He claims the US health-regulatory system is broken. As a result, he says flawed science and engineering dominate it. He shows how unscrupulous product-defense, contract-research, and private consultants, along with US regulatory agencies like DOE – that are dominated by the entities that they regulate – misuse analytic techniques, ignore dangerous uncertainty at places like Yucca Mountain, “manufacture” uncertainty about obvious and certain product/pollutant harm, control the scientific literature, and thus derail needed protections and regulations (Michaels 2008).

Whether or not Michaels is correct –and many US scientists say that he is, e.g., (Cranor 2011; McGarity and Wagner 2008; Shrader-Frechette 2014), there are ways to make computer modeling of health and safety threats better. Especially any time science is used in ways that affect human welfare or regulations, there should be clear standards for valid science, risk assessment, and computer models. Yet, for more than half a century, there have been clear legal and ethical requirements for research affecting human subjects, but there no comparable legal, scientific, and methodological requirements for research – like computer models used in human-health risk assessment – that affect human welfare (e.g., EPA 2006: 6160).

In failing to articulate scientific standards for welfare-affecting or regulatory research, federal agencies like US EPA, US DOE, and US NRC err. The whole point of science is that

its principles are universal, not just case-specific. As any good scientist knows, two key factors that undercut scientific validity are using low-power or small-sample studies and short-term studies – both of which make studies likely to falsely conclude that there are no (or limited) negative health effects from some exposure (Shrader-Frechette 2016).

Indeed, a primary failing of studies like US DOE 2010 West Valley risk assessments and computer models are that they both frequently ignore short-term frequency and empirical data showing that their risk-assessment models likely are wrong, and they never admit the impossibility of long-term prediction in the absence of long-term data. Thus, one obvious scientific-default rule might be: “Accept no low-power, short-term, or million-year studies claiming minor harmful impacts, unless these claims are clearly scientifically substantiated and approved by independent peer reviewers and the predominance of all available frequency data” see (Moyer and Finney 2005: 307). Versions of this rule are enshrined in virtually all statistics, public-health, and epidemiology textbooks, yet regulators do not require it, and studies like those from US DOE violate it (Shrader-Frechette 2016).

Such scientific rules are particularly needed for two main reasons (Shrader-Frechette 2016). One reason is that both the US National Academies of Sciences, the US EPA (external) Science Advisory Board, and other scientists have urged government to adopt specific scientific norms for all research used for regulatory purposes – and to provide a mechanism to ensure compliance with these norms. However, such norms arguably are needed for any research related to regulatory protection of humans from any dangerous pollutants – including nuclear waste (EPA Science Advisory Board 2000; National Research Council 2004; Oleskey et al. 2004).

Another reason that scientific and computer-modeling rules are needed is that both Congressional and government studies reveal that regulated entities routinely submit scientific studies – for use in setting regulations – -that are severely scientifically flawed (Shrader-Frechette 2016). They typically are short term, or low power studies, or have other obvious false-negative biases against finding any harm from their own industrial products or pollutants (EPA Science Advisory Board 2000; US House of Representatives 2005). However, instead of addressing these well documented biases, EPA and other government agencies ignore these scientific flaws that lead to ethical bias (EPA 2006). Yet as the National Academy warns, “a study cannot be ethically acceptable if it is scientifically invalid” (National Research Council 2004).

CONCLUSION

As these MIT, Yucca Mountain, and West Valley computer models reveal, flawed methods may be used not only by corporations, seeking to protect profits, but also by allegedly democratic governments that appear unwilling to spend the necessary monies to actually protect citizens from technological risks. Such government misuse of science and computer modeling may be even more deadly than corporate misuse of modeling because typically citizens cannot sue government, the way they can sue corporations or citizens who harm them. Implementing norms for regulation-related and welfare-related risk assessment and computer modeling is thus essential.

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Chapter 527

PORK FOODBORNE PARASITES OF PUBLIC HEALTH INTEREST IN MEXICO

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ABSTRACT

The ingestion of raw or undercooked pork poses a public health risk, since pork is the main transmitter of parasites, which include the protozoa *Toxoplasma gondii* (*T. gondii*) and the helminths *Trichinella spiralis* (*T. spiralis*) and *Taenia solium* (*T. solium*). These three ‘T’ porkborne parasites have been responsible for most of the porkborne illnesses throughout history; they are still endemic, and therefore are important public-health concerns, in developing countries. In Mexico, these three ‘T’ porkborne parasites are considered re-emerging parasites, and they represents a risk for the population that consumes large quantities of pork. Currently, inspection procedures are effective in eliminating the majority of the risks from *T. spiralis* and *T. solium* in certified slaughterhouses, due to the training of inspectors in the detection of tissue cysts. However, there are still clandestine slaughterhouses that do not have adequate surveillance methods to identify these parasites. Furthermore, for *T. gondii* no suitable methods for post-slaughter detection are available, where intervention measures at the animal level may be key to successful prevention. Early detection of the parasite is not easy, and the implementation of molecular techniques must be improved and made available mainly in endemic areas, in order to establish an accurate diagnosis, because isolation procedures are long, more expensive and often not sufficiently sensitive. The objectives of this chapter are to describe the epidemiological situation of these three

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parasites transmitted by pork in Mexico, outline the main lines of prevention, and describe the molecular methods that can be used for the early and accurate detection.

Keywords: pig-meat, zoonosis, parasites, Mexico, molecular detection, prevention

INTRODUCTION

Foodborne zoonoses have been estimated to annually affect 10% of the global population, among which zoonotic parasites constitute an important class of aetiological agents [1]. Foodborne parasites are expected to have a strong impact on public health in the future, particularly with the increase in meat consumption that is taking place in the world and the recognition that billions of people lack basic water services [2]. Pork is one of the main transmitters of parasites that include the protozoa *Toxoplasma gondii* (*T. gondii*) and the helminths *Trichinella spiralis* (*T. spiralis*) and *Taenia solium* (*T. solium*). These three ‘T’ parasites have been responsible for most porkborne illnesses throughout history; they are still endemic, and therefore are important public health concerns, in developing countries [1]. They are important because pork has long been the most consumed meat globally, and the projections of the future global pork demand remain robust [3]. The disability adjusted life-years (DALYs) have been estimated for human cysticercosis, toxoplasmosis and trichinellosis, with 2.78 million DALYs (95% UI 2.14–3.61 million), 825,000 DALYs (95% UI 561,000–1.26 million) and 550 (95% UI 285–934), respectively [4]. The United States has improved demonstrably over recent decades in pork safety due to the changes in swine production methods. The implementation of intensive confinement production systems has eliminated the risk of foodborne parasites [5]. The environment in which animals are kept determines the course and severity of disease expression; a highly contaminated environment for animals with a weakened immune system often tips the balance and makes a disease clinical [6]. The potential sources of infection at the farm level for these three parasites include water, feed, soil/organic material contaminated with oocysts or eggs, feed contaminated with infected animal tissue, and exposure to and ingestion of tissue from rodents, pigs, or wildlife carcasses [7]. The culinary preferences for fresh, slightly cooked, and ready-to-eat food and the increasing demands for meat in developing countries are increasing the risks posed by foodborne parasites [8]. In addition, pigs raised in outdoor systems inherently confront higher risks of exposure to foodborne parasites, particularly *T. gondii* [5].

Several endemic countries (such as some countries in Asia, Eastern Europe, and South America) cannot avoid human infection due to inadequate quality control in meat production [2]. In México, reporting the occurrence of these three parasites is considered mandatory by monthly notification to the official dependencies of animal health of the country [9]. According to the Mexican regulation (NOM-SSA1-2004), pork must be free of *Trichinella spiralis*, *Taenia solium* and other parasites; however, trichinoscopy is not mandatory [10]. Regarding, *T. gondii*, there are no official regulations that required the identification of tissue cysts in the carcasses. In the country, the Federal Inspection Type Certification, (abbreviated TIF), is an acknowledgment granted by SAGARPA (Secretary of Agriculture, Livestock, Rural Development, Fisheries and Food), that performs a thorough inspection procedure and supervises and traces industrial establishments that are dedicated to produce, store, sacrifice,

process and distribute all kinds of meats and their derivatives. The TIF recognition opens the possibility of international trade, since these establishments are the only ones eligible to export. Currently, in Mexico there are 457 TIF slaughterhouses where the surveillance of the meat is guaranteed [11]. However, in local markets in the central region of Mexico, it has been reported that 11.3% of the meat sold comes from pigs raised at home, which are illegally slaughtered [12]. In rural regions of Mexico, it is common to raise backyard pigs without adequate sanitary conditions, and these animals are slaughtered in unhealthy facilities that are not inspected for pathogens that may be encysted in the animal tissues. Unfortunately, there is no record of the illegal slaughterhouses established in Mexico, where proper inspection of the pig carcasses is not carried out, representing a risk for consumers. In addition, it has been shown that methods of direct observation of meat have low sensitivity, so the frequency of these porkborne parasites in Mexico may be underestimated [13]. Efforts to maintain innocuous pork meat ensure that the population is free to acquire these parasitic infections. The implementation of efficient, accessible, and controllable inspection policies for livestock, slaughterhouses, and meat processing and packaging companies is highly recommended [14].

In this chapter, we present epidemiological data reported for these three “T” pork parasites of public health interest in Mexico. Additionally, we described the main molecular methods used for the detection of these parasites in pork meat, as well as the prevention measures.

METHODS

Epidemiology of *Taenia solium*

Taenia solium is a hermaphrodite cestode parasite that infects humans and pigs. Worldwide, it is estimated that approximately 2 to 3 million people are infected with *T. solium*, and it is thought that some 50,000 people die annually from this parasitosis due to complications in the nervous system or heart failure [15]. *T. solium* is endemic in tropical regions of the world (Latin America, Southeast Asia and Africa). Normally, the cycle life of *T. solium* involves two hosts (human and pig) in which this parasite completes its life cycle. The disease is known as taeniasis and is more common in rural communities where domestic pigs are raised under free conditions, allowed to roam in the backyards and feed on fecal matter deposited by people in backyards because of a lack of sanitary infrastructure [15, 16]. Humans become infected by *T. solium* when eating inadequately cooked pork that contains the larvae. Once consumed, the larvae restart their development to the adult forms in the small intestine of humans, specifically the duodenum (5 to 12 weeks of patency). *T. solium* attach to the wall of the small intestine using the scolex armed with 4 suckers and 2 rows of large and small hooks [15, 16, 17]. Each segment or proglottids of *T. solium* have different degrees of development (immature, mature and gravid). The last segments are called gravid proglottids that contain infective eggs; these segments detach from the strobila (the main body of the parasite) and are shed in the environment through the feces. Adult *T. solium* can eliminate up to 300,000 eggs per day. These segments remain active and show movements. *T. solium* could reach 2 to 7 meters in length and live less than 5 years but occasionally could persist nearly 25 years. The infection of adults with *T. solium* is often asymptomatic, but the

presence in many adults can cause mucosal irritation, abdominal pain, diarrhea, constipation, weight loss and obstruction of the intestinal lumen [15, 16, 17].

The natural intermediate host for *T. solium* is the pig; however, the parasite can occasionally be found in dogs, cats, sheep, camels, monkeys and humans (Figure 1, *Life cycle image courtesy of DPDx*) [18]. Pigs are infected through the consumption of the eggs of *T. solium* scattered by wind or rain that contaminate the water or their food. In the interior of the host, the embryo is activated and leaves the egg, penetrates the intestinal mucosa, enters blood circulation and disperses to other tissues between 24 and 72 hours after ingestion [15, 18]. Once in the tissue, the embryo is transformed into cysticerci with the shape of an ovoid vesicle [18]. In the pig, the cysticercus is located in the striated or cardiac muscle. In humans, cysticerci can invade different types of muscle (striated and cardiac), the central nervous system (brain), the subcutaneous tissue and other tissues of the host, such as the liver, lungs, abdominal cavity and eye orbit [15, 18]. The most common cases of cysticercosis in humans are detected in the central nervous system. The presence of cysticerci in the tissue unchains many mechanisms in the human body such as inflammation, fibrosis and some calcification. In the brain, this immunological reaction produces neurological signs such as epilepsy, seizures, headaches, nausea, visual disturbance, focal weakness, and paresthesias. The neurological form of the disease is called neurocysticercosis and is the most serious form of the disease [18, 19]. Regardless of the source of the infection, the lack of hygienic habits, such as washing hands after going to the bathroom and before consuming meals, are the main reasons for the presentation of cysticercosis in humans (*Taenia* and *Cysti*). Other factors, such as the use of wastewater for irrigation or the consumption of contaminated water from rivers, could contribute to the spread of the eggs [18].

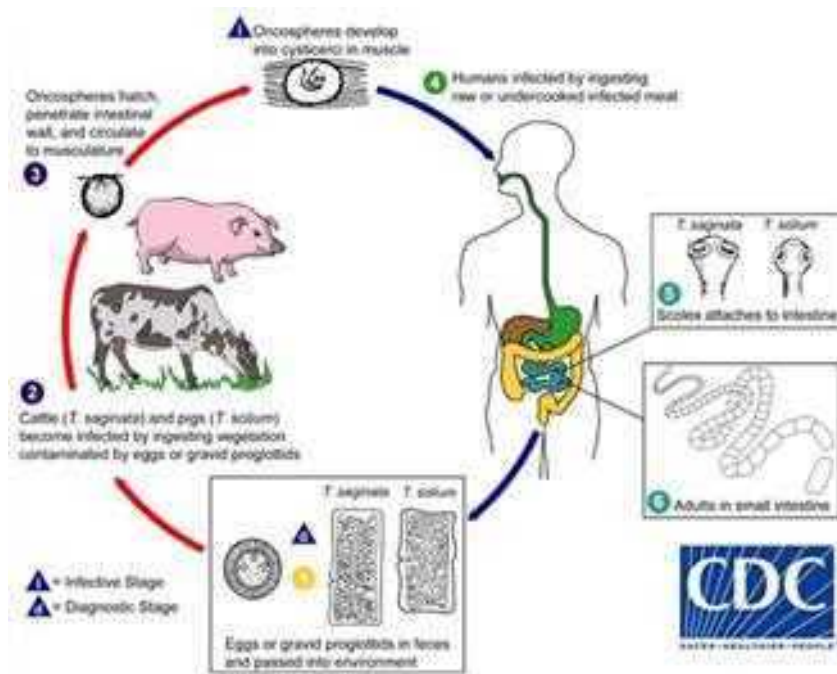


Figure 1. Life cycle of *Taenia* spp (image courtesy of DPDx) www.cdc.gov/parasites/(<http://www.cdc.gov/parasites/>).

Table 1. Studies of *Taenia solium* in pigs from Mexico

<i>Taenia solium</i>					
Sample	Origin	Assay	Positivity	State	Reference
Tongue	Backyard	Direct palpation	25%	Hidalgo	[23]
Tongue	Backyard	Direct palpation	4%	Morelos	[24]
Tongue	Backyard	Direct palpation	6.5%	Michoacán	[28]
Tongue	Backyard	Direct palpation	2.6%	Morelos	[25]
Serum	Backyard	Western Blot	5.2%	Morelos	[25]
Serum	Backyard	Western Blot	23%	Yucatan	[20]
	Semi intensive		25%		
	Intensive reared		2%		
Serum	Backyard	Western Blot	35%	Yucatan	[21]
Tongue		Direct palpation	23%		
Serum	Backyard	Western blot	29%	Yucatan	[22]
Tongue	Backyard	Direct palpation	13.3%	Morelos	[26]
Tongue	Backyard	Direct palpation	7%	Guerrero	[29]
Body Serum		Ultrasound	3.6%		
		ELISA	17.7%		
Serum	Backyard	ELISA	19.0%	Morelos	[27]

Taenia solium in Pigs in Mexico

In Mexico, the epidemiological studies that have focused on binomial taeniasis/cysticercosis in humans. However, most of studies were conducted prior to the year 2000. At the national level, the actual prevalence of this parasitosis associated with poverty conditions is still unknown. Many of the existing studies carried out in Mexico have been isolated, focusing on some states, and few have jointly evaluated the positivity of people and pigs. Table 1 shows the results of different studies in which infection by *T. solium* cysticerci was diagnosed in pigs reared in rural communities in Mexico. The highest prevalence of pigs infected by cysticerci was found in pigs from Yucatán State (southeast region), with a prevalence of 23 to 35% [20, 21, 22]. In central Mexico, a prevalence of 25% was reported from Hidalgo State [23] and 2.6% to 13.3% was reported for the state of Morelos [24, 25, 26, 27]. For the Pacific coast, prevalence rates of 6.5% and 17.7% were reported for Michoacan and Guerrero State, respectively [28, 29]. In Mexico it is estimated that 2.1 million pigs live in rural areas, inside backyard systems [30]. Considering the percentage of infected pigs in some studies conducted in the country, the risk of acquiring taeniasis and cysticercosis is high.

Approximately, 4,328 cases of human cysticercosis have been reported between 2000 and 2010 [31]. Recently, in 2017, 227 and 179 cases of Taeniasis and Cysticercosis have been reported, respectively. In the January-October period of 2018, 139 cases of Taeniasis and 187 cases of Cysticercosis have been reported [32]. The persistence of cases diagnosed in humans in different states of the country suggests that the prevalence of this disease in pigs reared in backyards could be underestimated. In Mexico, the lack of sanitary infrastructure, the availability of decent housing with latrines, the low economic income of families in rural communities, the backyard rising of animals for self-consumption and the saturation of health centers contribute to the persistence of this parasitosis.

Epidemiology of *Toxoplasma gondii*

Toxoplasma gondii is an apicomplexan protozoan intracellular parasite with a widespread distribution in both developed and developing countries [33]. *T. gondii* has veterinary and medical importance, because it may cause abortion or congenital disease in its intermediate hosts [34]. Additionally, *T. gondii* can cause severe illness in immunocompromised individuals [35], and ocular toxoplasmosis is frequently observed in immunocompetent patients [36]. Felids are the only definitive hosts in which the parasite can complete its sexual cycle and spread millions of oocysts into the environment. Although the number of oocysts produced is a key element in environmental contamination and consequently in parasite transmission, *T. gondii* is also able to rely on its asexual cycle in all warm-blooded animals (mammals and birds) and humans [35]. Initial infection of a host is usually accomplished by the rapidly replicating form of the organism called tachyzoites. However, in an immune competent host following the activation of the immune system, the tachyzoites undergo a conversion to the slowly replicating form of the organism called bradyzoites, which cluster to form tissue cysts. These tissue cysts can persist in the brain and other organs for extended periods of time without the generation of an apparent immune response. At various times, a portion of these tissue cysts can reactivate into tachyzoites and, if the immune response is adequate, subsequently reconvert into bradyzoites containing tissue cysts. Through these interconversions, *T. gondii* can establish life-long persistence in immune competent hosts [33].

There are two major modes of transmission of *T. gondii*: infection may occur by the ingestion of food or water contaminated with oocysts excreted by infected cats or by ingesting uncooked or undercooked meat containing tissue cysts (Figure 2, *Life cycle image courtesy of DPDx*). The proportion of the human population that acquires an infection by the ingestion of oocysts in the environment or by eating contaminated meat is not known, and there are no tests available that can determine the infection source. However, sero-epidemiologic data suggest that ingesting improperly cooked meat containing *T. gondii* is a major source of infection for humans in the United States [37, 38]. In addition, pregnant women in Europe identified meat ingestion as the major source of *T. gondii* infection (30–63% of cases) [39].

It has been reported that in meat-producing animals, tissue cysts of *T. gondii* are most frequently observed in these tissues of infected pigs, sheep, and goats, and are less frequently in infected poultry, rabbits, dogs, and horses, with pork being the major source of *T. gondii* infection [34]. These animals harbor tissue cysts, and human consumers can be infected by ingestion of these cysts in raw or undercooked meat [40]. Virtually all edible portions of an animal can harbor viable *T. gondii* tissue cysts [41], and tissue cysts can survive in food animals for years [40]. It has been shown that a single *T. gondii* oocyst is capable of producing an infection in pigs, and among the most parasitized organs with tissue cysts are the tongue, brain and heart [42].

The reduction of the risk of *T. gondii* infections in pigs is possible, using intensive farm management with adequate measures of hygiene, confinement, and prevention [34]. In contrast, pigs reared on organic farms have shown to have a higher *T. gondii* prevalence than pigs from conventional farms [35].

The first report of *T. gondii* in pigs in Mexico was in the central region, where they analyzed 6 to 10-month-old pigs weighing 90-100 kg from an abattoir of Morelos State, and they found a prevalence of 8.9% using ELISA [45]. Another study conducted in Jalisco State (west region that borders the Pacific Ocean), they analyzed 48 pork samples from butcher shops and found that all the samples were negative by histology and by PCR; however, a positivity of antibodies against *T. gondii* of 2.1% in pork meat was detected through bioassay [46]. In Veracruz State (eastern region and the coastline on the Gulf of Mexico) a seroprevalence of 45.3% was reported in domestic pigs raised in backyards using the Microscopic Agglutination Test (MAT), showing that a tropical-humid climate, feeding with leftovers, storing pig food in the owner's home, and free ranging was associated with *T. gondii* seropositivity in pigs [47].

Table 2. Studies of *Toxoplasma gondii* in pigs from Mexico

Toxoplasma gondii					
Sample	Origin	Assay	Positivity	State	Reference
Serum	Abattoir	ELISA	IgG 8.9%	Morelos	[45]
Muscle	Butcher shops	Bioassay	IgG 2.1%	Jalisco	[46]
Serum	Farms with cats	ELISA	IgG 100%	Yucatán	[48]
Serum	Backyard ND	MAT	IgG 16%	Durango	[43]
			IgG 9.1%	Sonora	
Serum	Backyard Farm	MAT	IgG 17.2% IgG 0.5%	Oaxaca	[53]
Serum	Farm	ELISA	IgM 92.5% IgG 95.8%	Yucatán	[49]
Blood		PCR	DNA 50.8%		
Serum	Backyard	ELISA	IgG 75%	Yucatán	[50]
Serum	Backyard	MAT	IgG 45.3 %	Veracruz	[47]
Serum	Backyard	MAT	IgG 13%	Baja California	[44]
Serum Tongue Loin	Backyard	ELISA nPCR	IgG 96.6% Tongue 23.21% Loin 7%	Yucatán	[51]
Serum Tissue	Semi-extensive breeding	ELISA qPCR	IgG 53% DNA 5.3%	Yucatán	[52]

ND: Not data.

In the southern region, the Yucatan State (northern part of the Yucatan peninsula) has carried out the largest number of studies of *T. gondii* in these animals, finding high seroprevalences in pigs reared on farms as well as pigs reared in backyards. A study in this region analyzed the infection dynamics of *T. gondii* in two fattening pig farms exposed to high and low cat densities and found that 100% of finished pigs had contact with the *T. gondii* regardless of the relative density of the cats [48]. Another study in Yucatan, reported a positivity of *T. gondii* DNA in 50.8% of the blood samples and a seroprevalence of 96% in pigs reared on farms, indicating a high circulation of the parasite [49]. In addition, backyard pigs have reported seroprevalences of 75% from the same region [50]. The high circulation of *T. gondii* in pigs intended for human consumption in Yucatan has led to investigations of the presence of DNA in pork using PCR. Regarding the presence of the parasite in pork, the first report in the southeast of Mexico found a positivity through an nPCR of 23.2% and 7% for samples of tongue and loin tissue, respectively [51]. Subsequently, the parasitic burden of *T. gondii* in Mexican hairless pig (*Sus scrofa*) tissues using quantitative real-time PCR (qPCR) was determined, finding a positivity of 5.3% of the tissue samples with an average of 2.5 ± 2.71 , 0.26 ± 0.39 and 0.31 ± 0.37 parasites per gram for the leg muscle, heart and tongue tissue, respectively [52]. In Oaxaca State, a seroprevalence in pigs raised in backyards of 17.2% and in pigs raised on farms of 0.5% was reported, confirming that the management system (outdoor vs. indoor with biosecurity) is a key factor in the epidemiology of swine toxoplasmosis [53]. The relevance between these studies is that the southern region is endemic to toxoplasmosis, with a high prevalence in the human population and in different animal species [54].

Epidemiology of *Trichinella spiralis*

Trichinella is one of the most widespread parasites infecting people and other mammals all over the world in most climates, except for deserts [55]. Trichinellosis infection follows the ingestion of raw or undercooked meat containing *Trichinella* larvae [56], mainly from pigs, wild boar or horses [57, 58]. *Trichinella spiralis* (*T. spiralis*) has a cosmopolitan distribution, and it affects domestic and wild mammals [59]. In Central and South America, the etiological agent of human trichinellosis has been reported to be *T. spiralis*; however, only in a few cases has the parasite species been properly identified [60]. Its clinical manifestations are not specific; thus, the diagnosis of trichinellosis is not easy to make [61]. The life cycle begins when the larvae are released after gastric digestion and mature into adult worms that penetrate the mucosa of the intestine. After fertilization, the female sheds new larvae that disseminate throughout the host to find their definitive location, the striated muscle, where they encyst. This larval migration may result in severe lesions, particularly when larvae migrate to the heart or the brain [55]. Encystment is completed in 4 to 5 weeks, and the encysted larvae may remain viable for several years. Ingestion of the encysted larvae perpetuates the cycle. Rats and rodents are primarily responsible for maintaining the endemicity of this infection. Carnivorous/omnivorous animals, such as pigs or bears, feed on infected rodents or meat from other animals (Image 3, *Life cycle image courtesy of DPDx*).

Worldwide, data from 1986 to 2009 implicated domestic pigs as the major source of infection (53%) in outbreaks [62], most of them in Eastern Europe and Argentina, where the traditional small, “backyard” rearing of pigs for household and local use often involve high risk rearing practices, especially the feeding of food waste. Although commercially produced pork under controlled management now accounts for approximately half of the world’s pork production, the demand by consumers, especially in Europe and North America, for free-range pork is increasing [63]. In addition, Trichinellosis is common in some rural areas of South America and Asia but is quite infrequent in urban regions [55]. In Mexico, 453 human cases of trichinosis have been reported from 1893 to 1995, which were confirmed by the finding of larval *T. spiralis* in diaphragm tissue. Chihuahua State, have been reported the largest outbreak in humans, which was associated with the consumption of pork sausage, even though the anatomical parts of the infected animals presented health check seals [64].

In pigs, very few studies have found pigs infected with *T. spiralis*; however, these data are not reliable since they have not been investigated in other states of the country, especially in production systems with unsanitary conditions [65]. Despite the scarcity of studies on *T. spiralis*, so far in 2018, there have been 9 cases of trichinosis in the human population in Mexico [32]. In rural areas of Mexico, it is common to have pigs as part of the family economy. Unfortunately, pigs are left to breed freely, and they go where they can find food, which is in spaces where there is garbage and the presence of the domestic rat, which is part of the transmission cycle of this parasite (rat-pig-human) [66]. In addition, the clandestine slaughter of backyard animals is frequent [67].

Trichinella spiralis in Pigs in Mexico

Most of the studies on pigs are very old. In a review, from 1909 to 1999 there was a positivity of 0-6% of *T. spiralis* in pig carcasses, mainly from trichinoscopy and artificial digestion techniques. In 1989, samples from backyard pigs were analyzed by ELISA, and

seroprevalences of <1%, 14% and 24% were found for the state of Michoacan, Veracruz and the State of Mexico, respectively [68]. However, there have been few states where these investigations have been made, mainly in Mexico City, the State of Mexico, Tamaulipas, Jalisco, Sonora, Michoacan, Veracruz and Zacatecas [60]. Recent epidemiological studies of *T. spiralis* in pigs are scarce, which could contribute to an underestimation of the occurrence of this parasite in pigs destined for consumption, especially those that are reared in backyards and do not have adequate sanitary conditions, representing a risk for consumers. The few studies that have been conducted on *T. spiralis* in pigs are located in the center of the country (Table 3). One of the studies that analyzed pork samples from butchers and local markets, found all the negative samples through trichinostomy [69]. Another study, used serological tests (ELISA and Western blot) and found a seroprevalence of 12.4% in farm and backyard pigs [70]. The last report we have analyzed samples of pork sausage, finding a positivity of 3.4 and 4% by artificial digestion and by trichinostomy, respectively [65].

Table 3. Studies of *Trichinella spiralis* in pigs from Mexico from the year 2000 to date

Trichinella spiralis					
Sample	Origin	Assay	Positivity	State	Reference
Pork	Butcher Public market Ambulatory market	Trichinostomy	0%	Distrito Federal	[69]
Serum	Farm/ Backyard	ELISA/WB	12.4%	State of Mexico	[70]
Chop sausage	ND	Artificial digestion Trichinostomy	3.4% 4%	State of Mexico Michoacán Hidalgo Morelos	[65]

ND. Not data.

Diagnostic Methods for the Detection of Pork Parasites

Diagnostic Methods of Taenia solium in Pork

At the field level, several detection methods of *T. solium* in pigs are used, including the following: 1) Palpation. Tactile inspection is made in search of cysticerci in the body of the pigs and can be performed before the animals are slaughtered. This method consists of palpating the surface of the tongue to determine the presence of nodules of *T. solium* cysticerci. It has been reported that this method has a sensitivity of 70% and a specificity of 100% [71]. 2) Direct observation. Direct inspection of organs and pig carcasses in search of cysticerci and is carried out during the slaughter stage of animals at certified slaughterhouses. This inspection is carried out by trained veterinary personnel for this purpose [29]. 3) ELISA and Western blot. These techniques allow the detection of antibodies against *T. solium* in samples of serum from pigs. The Western blot technique is commonly used as a confirmatory test due to its high sensitivity (97%) and specificity (100%) [72]. The ELISA demonstrated a sensitivity of 83.7 to 86% and a specificity of 95.7 to 95.9% [73]. 4) Ultrasound. This method consists of observing the presence of cysticerci through portable ultrasound equipment by examining the anatomical regions where cysticerci is located, offering greater sensitivity than

visual inspection and palpation. This technique can be applied in both live animals and animal carcasses [74].

Diagnostic Methods of *Toxoplasma gondii* in Pork

In Mexico, *T. gondii* is not among the mandatory inspection diseases in slaughterhouses. However, the main diagnostic tests for this agent are the following: 1) Serology. This method allows for the detection of antibodies in animals. Among the serological tests used for the rapid diagnosis of toxoplasmosis there is an ELISA and MAT. In addition, Western blot (sensitivity of 84.7% and a specificity of 96.7%) [75] and the Indirect immunofluorescent antibody test (IFAT) could be employed to diagnose of this disease [76]. The latter has been used with a cut-off point of 1:64 and in the 80% of the positive cases, and it has been possible to isolate *T. gondii* by inoculation in mice [77]. Currently, there are commercial ELISA kits for the detection of antibodies against *T. gondii* in porcine serum samples [78]. With respect to the detection of *T. gondii* in pork samples, the MAT has been proposed for examining tissue fluid and has had good results for detection [79]. 2) Molecular biology. With respect to molecular diagnosis, PCR variants have been developed as a real-time PCR, PCR point for the detection of *T. gondii* in blood and tissue samples [80] and nested PCR [81]. In addition, a protocol that includes the magnetic capture of *T. gondii* DNA and a real-time PCR have been developed, which examine large samples of pork (100g) with a limit of detection of 230 tachyzoites, and this method has been validated by ISO 17025 certification [82, 83].

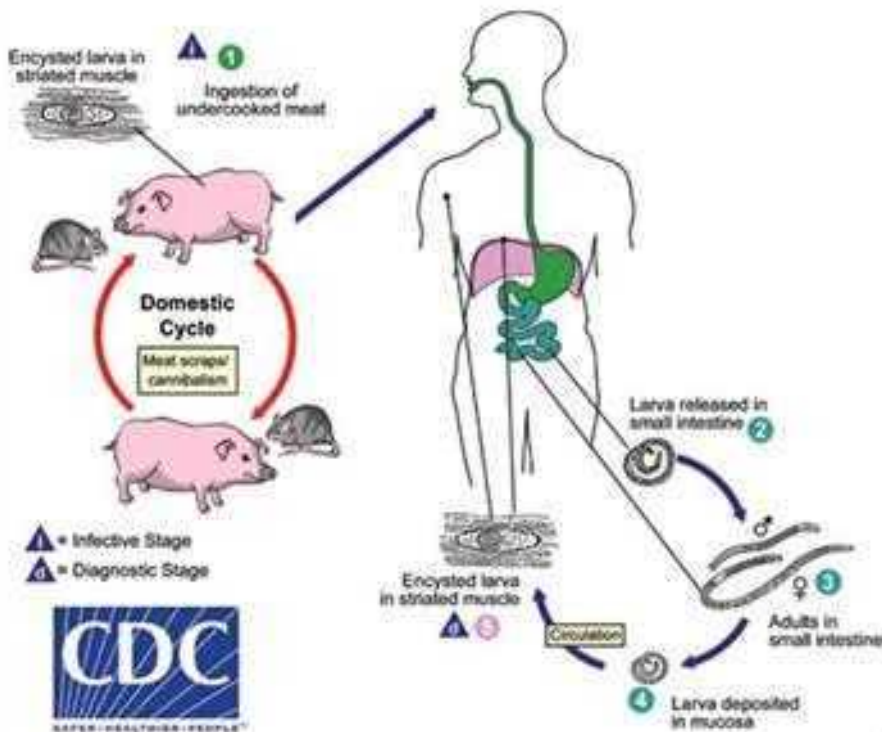


Figure 3. Life cycle of *Trichinella spiralis* (image courtesy of DPDx) www.cdc.gov/parasites/(<https://www.cdc.gov/parasites/>).

Diagnostic Methods of Trichinella spiralis in Pork

The main techniques used for the detection of *T. spiralis* in pork are the following: 1) Trichinoscopy. This involves examining a sample of tissue in which the cystic form of the parasite is observed placed between two sheets of glass under a microscope. This method is applied in the slaughterhouses but show low sensitivity when parasitic loads are less than 2 larvae per gram of meat [84]. 2) Artificial Digestion. This technique consists of dissolving the muscle tissue using pepsin, protease and hydrochloric acid to detect the encysted larvae of *T. spiralis*. Currently, there is a commercial kit for this purpose (PrioCHECK™ Trichinella AAD Kit) that complies with international standards and produces a faster and less risky digestion for operators compared to the conventional method [85]. 3) Serological tests. ELISA assays and immunochromatography have been developed and applied in research but not for field-level diagnosis. However, these tests have been effective for the detection of *T. spiralis* in natural and artificially infected pigs [86, 87]. 4) Molecular biology. As in other infectious agents, there are protocols to perform conventional PCR, real-time PCR and loop mediation isothermal amplification to detect *T. spiralis* in naturally infected wild and domestic pigs [88, 89].

Prevention

Prevention implies taking measures at different levels, both in breeding and surveillance systems, as well as in the personal hygiene habits of people who consume pork. Some measures can be used to reduce the risk of infection for the consumption of infected meat in rural communities where pigs are maintained in backyard systems [18, 90, 91]:

- *In the backyard system.* Keep pigs raised in barnyards made with local materials and that prevent the access of pigs to areas that could be contaminated with pathogens such as *Toxoplasma gondii*, *Taenia solium* and *Trichinella spiralis*. Avoid areas where pigs could be in contact with cats and mice. Do not implement the outdoor bathroom.
- *Personal habits.* Implement personal hygiene habits, such as washing hands with soap and water before eating, after going to the bathroom and after handling raw, meat as well as washing hands after handling pets, such as like cats.
- *Food preparation.* Cook pork meat at a temperature of 71°C before consumption and avoid ingesting half-cooked meat; wash and disinfect raw fruits and vegetables and consume UV-treated water or boil and wash all kitchen utensils that have had contact with raw meat. Keep food out of reach of cats, and avoid the consumption of meat and organs such as the tongue and viscera that have visible nodules.
- *Personal health.* Deworm twice a year. All members of the family must be dewormed.

With simple actions implemented in communities with backyard systems, the risk of infection can be greatly reduced, and this ensures that backyard systems are a safe source of protein for people.

ABOUT OUR RESEARCH

In our experience, we carried out studies of *T. gondii* in samples of serum and tissue from pigs in southeastern Mexico. We will describe the methodologies of *T. gondii* detection that we carried out in our laboratory.

Determination of Anti-Igg Antibodies against *T. Gondii* through an Enzyme-Linked Immunosorbent Assay (ELISA)

Blood samples from the cava vein (Vacutainer tubes without anticoagulant) of pigs were collected at slaughter, and the samples were kept in refrigerated until they reached the laboratory. To obtain the serum, the samples were centrifuged for 10 min at 448 g. The serum samples were individually labeled and stored at -20°C until they were processed. The presence of IgG specific antibodies against *T. gondii* was determined using an indirect ELISA test (Human-GmbH, Wiesbaden, GER). The technique has been adapted according to Figueroa-Castillo [92] using a secondary antibody, anti-swine IgG-HRP (Catalog no. J3007, Santa Cruz, Inc., CA). The serum samples were evaluated at a concentration of 1:100, and IgG secondary antibodies were used at a dilution of 1:5000 [48]. A commercial normal swine serum (Catalog no. B2613; Santa Cruz, Inc., CA) was used as a negative control, and a serum from pigs previously tested by nested PCR (nPCR) as positive (in tissue sample), and an ELISA seropositive was used as the positive control. The optical density was measured at 450 nm using a spectrophotometer (xMark, Bio-Rad). The cutoff point was the average of the negative control plus three standard deviations.

Molecular Test

DNA Extraction from Pork Samples

DNA from tissue samples was predigested in pepsin solution, which was previously described (Table 4) [93]. Then, the protocol of the commercial kit, DNeasy Blood and Tissue (QIAGEN GmbH, Hilden, Germany), was followed. To assess the absence of endogenous inhibitors for PCR amplification, a housekeeping gene, glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was analyzed in each DNA sample with real-time PCR [94].

*Protocol for the Detection of *T. gondii* DNA in Pork Samples through a Nested Polymerase Chain Reaction (nPCR)*

After the DNA extraction step, nPCR was performed to amplify a fragment of 390 bp of the SAG1 gene (encoding the main surface protein of *T. gondii*) [81], using a 96-well Veriti thermocycler (Applied Biosystems). The primers used were external forward 5'-GTTCTAACCACGCACCCTGAG-3' and external reverse 5'-AAGAGTGGGAGGCTCTGTGA-3'. In the second amplification, the internal primers used were inner forward 5'-CAATGTGCACCTGTAGGAAGC-3' and inner reverse 5'-GTGGT TCTCCGTCGGTGTGAG-3'. The first amplification conditions were as follows: 1X Colorless GoTaq Flexi

Table 4. Materials used for isolation of DNA in pork samples in the southeast of Mexico

Sample	Materials and methods
Isolation of DNA in pork samples (50 grs)	Predigestion whit acid pepsin solution [93]* *Acid pepsin solution (Pepsin 2.6 g; NaCl, 5.0 g; HCl 7.0 mL and distilled water to make 500 ml, pH ~ 1.10-1.20). Phosphate buffered saline (PBS, pH 7.2) Sodium bicarbonate (pH ~ 8.3) Saline solution Blender Plastic jar Layers of gauze Plastic pipettes Follow the protocol for Tissue samples of DNeasy Blood and Tissue Kit (QIAGEN)
General consumables	Pipets and filter tips Vortex Microcentrifuge tubes (1.5mL) Microcentrifuge Centrifuge Thermomixer for heating at 56°C Reagents of DNeasy Blood and Tissue Kit (QIAGEN) Ethanol (96-100%)

Buffer (PROMEGA); 2mM MgCl₂; 0.8 mM dNTPs; 0.5 µM for both the forward and reverse primers; 1.5 U Taq polymerase (GoTaq Flexi DNA Polymerase); and a 2 µL DNA sample in a final volume of 25 µL. The second amplification conditions had the same conditions as the first PCR, except that in this case, the concentration used for the forward and reverse primers was modified to 0.3 µM and as a template for the second round, 2 µL of the product was used from the first round of PCR. The nPCR conditions in the first run were 95°C for 5 min, followed by 30 cycles of 94°C for 30 s, 55°C for 1 min, and 72°C for 2 min. In the second run, the conditions were 95°C for 5 min, followed by 35 cycles of 94°C for 30 s, 60°C for 1 min, and 72°C for 1.5 min. The DNA from *T. gondii* axenic tachyzoite culture was used as a positive control, and a reaction without DNA was used as a negative control in each round of nPCR. The amplification products were observed on 1.5% agarose gel stained with ethidium bromide (10 mg/mL in H₂O).

Protocol for Detection of T. gondii DNA in Pork Samples through a Real Time Quantitative Polymerase Chain Reaction (qPCR)

The primers and Taqman probe amplified a fragment of 62 bp of the B1 gene of *T. gondii*, and the conditions have been previously described [95]. The specific primers used are GENE B1 TG-TX2F(5'-CTAGTATCGTGCGCAATGTG-3') and GENE B1 TG-TX2R(5'-GGCAGCGTCTCTTCCTCTTTT-3') and a TaqMan probe (5'-(6-FAM)-CCACCTCGCC TCTTGG-(NFQ-MGB)-3'). Each qPCR reaction was carried out in a final volume of 25 µL. The reaction conditions were as follow: 1X TaqMan Universal PCR Master Mix (PE Applied Biosystems) at an adjusted MgCl₂ concentration of 5 mM, 0.90 µM of each primer, 0.25 µL of the marker probe and 100 ng of purified DNA from the tissue. The amplification conditions were the following: initial incubation for 2 min at 50°C, followed by 10 min at

95°C, followed by 40 cycles of 95°C for 15 s and 60°C for 1 min. For the absolute quantification of the parasites, serial dilutions (from 1×10^{-2} to 1×10^5 parasites/mL) were performed by duplicated with known amounts of parasites/mL (tachyzoites) to construct the standard curves for *T. gondii* quantification. The parasite load determinations were performed by a linear regression analysis of the Ct values from known amounts of protozoan DNA to determine the *T. gondii* cell equivalents. The parasite load found in each tissue (estimated as a function of the Ct relative position from each sample with the Ct of the standard curve values) was divided per g of the sample to obtain the parasites/g by tissue. The results were expressed as *T. gondii* – equivalents (1 parasite equivalent = 68 femtograms of *T. gondii* DNA).

CONCLUSION

The human population is increasing every day and with it the demand for food of animal origin. Despite the fact that the implementation of intensive systems in the raising of pigs has drastically reduced the prevalence of *T. solium*, *T. gondii* and *T. spiralis* in developed countries, in rural regions of Mexico, it is still common to raise animals in backyard systems. Backyard farming systems are characterized by unhealthy conditions, a lack of confinement facilities, animals with poor diet, and inadequate health care. In addition, these animals are commonly slaughtered in the same homes where they are raised; therefore the rigorous inspection processes for the search of the cysts in their tissues are not carried out with cysts passing from their meat directly to the local consumers. This represents a high risk of infection for the population if this meat is consumed raw or undercooked.

In Mexico, studies of these three parasites *T. solium*, *T. gondii* and *T. spiralis*, in pigs are scarce dated, which makes it difficult to know the current epidemiological status of these agents. Moreover, it is alarming that in the country there are still outbreaks of cysticercosis/taeniasis, toxoplasmosis and trichinosis in the human population, which could indicate that the presence of these parasites in pigs for consumption is being underestimated. The data found in the literature show that these three agents in pork have a high impact on the health of the population; however, their detection is not mandatory. Unfortunately, the raising of backyard pigs is the key to the maintenance of these zoonoses. In addition, until measures are taken to improve production systems, the cycle of *T. solium*, *T. gondii* and *T. spiralis* will continue in the food chain. On the other hand, the breeding tendencies of animals in friendly conditions, free from stress and grazing, have made this parasite reemerge due to the greater exposure of pigs to the contaminated environments.

Prevention measures should be taken when cooking pork carcasses at optimal temperatures (71°C or 160°F) to inactivate the tissue cysts of *T. solium*, *T. gondii* and *T. spiralis* and thus avoid the risk of infection. Other measures for the prevention of these diseases can be contribute to reducing outbreaks in Mexico by increasing the infrastructure in health services in marginalized communities, the implementation of dissemination campaigns regarding the epidemiology of these diseases among communities, and fostering habits of personal hygiene and good practices in breeding of pigs in backyard systems.

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Chapter 528

THE LIBERIAN PUBLIC HEALTH SYSTEM

Veronica Fynn Bruey

INTRODUCTION

A brief historical account of Liberia is fundamental to understanding the apparently haphazard approach used to develop a relatively poor public health system in Liberia, which is evidently in need of comprehensive reform after the Ebola virus disease outbreak that occurred between 2014 and 2016. The modern state of Liberia is Africa's oldest republic that was founded by the ACS. The ACS, a philanthropic organisation, was founded in 1816, following the enactment of the *Act Prohibiting Importation of Slaves*, 1807 and the *Act in Addition to an Act to Prohibit the Importation of Slaves*, 1819 by the United States Congress. Liberia was birthed out of the need to address the "problem" of freed slaves being placed on the same legal equality with white people in the United States (Huberich 2010: 18). An amount of \$100,000 was granted to the ACS in 1819 to fund, manage and repatriate the African colonisation (McPherson, 2010: 21). Between 1820 and 1904, some 14,996 Black Africans were removed from the United States to the Colony of Liberia (Brown, 1980: 1; Murdza Jr., 1975: 1; Reef, 2002: 14–18).

Prior to the arrival of African American settler-colonists in 1822 and a Declaration of Independence by African-American former slaves in 1847, the area called Liberia today, was home to a number of indigenous or native groups (Fyfe, 1972:150–152; Korvah, 1995:11). The American Colonisation Society (ACS) claimed to have "purchased" and "bargained" for land from the Natives of Liberia to set up its enclave (Ashmun, 1826: 6). However, evidence of violent conflicts and wars between the ACS and the Natives of Liberia indicates otherwise (Huberich, 2010:278–280). Since the initial dispossession of native Liberians of their lands, African-American settler-colonist elites ruled and controlled Liberia and its natives for well over 133 years (1847-1980) (Dunn und Holsoe, 1985: xiv-xix).

This elite oligarchy of African American in Liberia is mainly responsible for the political unrest observed between 1979 and 1989, which escalated into two full-blown civil wars that lasted for about 14 years (Mgbeoji, 2003: 11–19). Having been "debarred by law from all rights and privileges of men" and forced to economically development a country that gave

them no protection, African American settler-colonists to Liberia sought a land of freedom—“an asylum from the most grinding oppression” (Liberia Declaration of Independence, 1847). But, as the oppressed becomes the oppressor (Freire, 2005: 45), it comes as no surprise what African American settler-colonists did to the native peoples of Liberia. Clinton Caldwell Boone, an African-American missionary-doctor, confirms that, “[t]he civilised Liberian, to maintain his standing as a light and a ruler of the country must live in some way aloof from the people it governs. This is the custom in America and it is far more necessary in Africa” (Boone, 1970: 51). French (2004:91) captures the essence of African American settler-colonists to Liberia:

...the old Americo-Liberian elite – the class of freed American slaves that had founded this country in 1847...settled the land, [and] fondly strove to reproduce the only model they knew, the plantation society of the American South. Affecting top hats and morning coats, the freedmen ruled Africa’s first republic in a clannish and conservative manner, established their own curiously paternalistic brand of apartheid, systematically excluding so-called aborigines from positions of privilege and power until 1980, when a coup by an unschooled soldier and ‘man of the soil’ from the Krahn ethnic group, Master Samuel Kanyon Doe, brought this anachronistic little universe to a bloody end.

It would take decades to comprehend the full extent of the devastating impact and consequences of the Liberian civil wars. Although no accurate statistical account is available, some quantification exists especially regarding the persistent health impact, trauma and burden of disease on Liberia’s public health system. From 1989 to 2003, between 250,000 (United Nations, Security Council 2003: 6) and 270,000 people lost their lives either as a direct result of the wars or due to illness exacerbated by the destruction of health facilities (United Nations Development Program, 2006: 12). During the two civil wars, approximately 800,000 persons were internally displaced (United Nations High Commissioner for Refugees, 2006: 3) and over a million persons became refugees (Nmoma, 1997: 4–5), many of whom are still struggling to return home today (Essuman-Johnson, 2011: 117–119; Genoway, 2018).

The United Nation Mission in Liberia helped to disarm some 103,019 ex-combatants, including 11,282 child soldiers (Agencie Catalan de Cooperacio al Desenvolupament, 2008: 3). It is estimated that a third of Liberians participated in the civil war including ~21,000 child soldiers; but only 28,314 arms, 32,530 ammunition, and 7.1 million small arms ammunition were collected during the Disarmament, Demobilisation and Rehabilitation period which took place between 2003 and 2008 (Agencie Catalan de Cooperacio al Desenvolupament, 2008: 6; Johnson et al., 2012: 531; Paes, 2005: 1; Weiss, 2005: 81). In 2004, a preliminary study conducted by the United Nations Development Program (UNDP) and the National Human Rights Center of Liberia found that 60-70 per cent of Liberians (Amnesty International 2004: 4) suffered some form of sexual violence during the civil conflict.

Against this backdrop, the previous brief discussion of the country’s history provides the context for examining the public healthcare system. Thus, the purpose of this chapter is to examine the Liberian public healthcare system. Specifically, the chapter will discuss some of the major public health laws and policies that have been enacted and implemented, since the founding of the country. Further, the chapter will interrogate the state of the country’s public healthcare system.

PUBLIC HEALTH: CONCEPTS AND PRINCIPLES

Conceptualising Public Health

In his report on Public Health in England, Sir Donald Acheson defines public health as the science and art of preventing disease, prolonging life and promoting health through organized efforts of society (Acheson, 1988: 1). Acheson's definition is both generic and sustainable, drawing on principles of interdisciplinarity, social determinants of health, and the ethics of prolonging life, promoting health and preventing illness. The term population health refers to health outcomes and their distribution in a population (Turnock, 2016: 10). After decades of focusing on treatment as a panacea to ill-health, public health incorporated lifestyle and the environment as serious concerns.

In the early 1990s, John Ashton described the “new public health” approach as one which transcends human biology, combines environmental change and individual preventive measures with appropriate medical interventions, but with focus on vulnerable populations (Ashton 1992: 113). A decade later, Tulchinsky and Varavikova (2010:26) asserted that the new public health is “an integrative approach to protecting and promoting the health status of both the individual and the society.” To this end, it is instructive that contemporary perspectives incorporate socio-economic, political and legal factors into developing and sustaining a robust public health system.

Primary Healthcare

The original definition of primary health care centered on health workers providing medical care to patients on first contact. In 1978, at the International Conference on Primary Health Care in Alma-Ata, the concept of primary health care surpassed medical care on first contact to include social, economic and political factors affecting inequality and poverty (Walt und Vaughan, 1982: 1). The Alma-Ata Declaration IV (1978) states that:

primary health care is essential health care based on practical, scientifically sound and socially acceptable methods and technology made universally accessible to individuals and families in the community through their full participation and at a cost that the community and country can afford to maintain at every stage of their development in the spirit of self-reliance and self-determination. It forms an integral part both of the country's health system, of which it is the central function and main focus, and of the overall social and economic development of the community. It is the first level of contact of individuals, the family and community with the national health system bringing health care as close as possible to where people live and work, and constitutes the first element of a continuing health care process.

The socio-economic, political and legal effects of health captured by Acheson and the Alma-Ata Declaration are collectively referred to as the social determinants of health. In order to address the social determinants of health, health promotion strategies must be put in place.

Health Promotion

Building on the progress of the Alma-Ata Declaration, the *Ottawa Charter for Health Promotion* was established during the First International Conference on Health Promotion held on November 21, 1986 in Ottawa, Canada. The *Ottawa Charter*, 1986 (the Ottawa Charter) defines health promotion as the process of enabling people to increase control over

and improve their health. The Ottawa Charter also identifies the fundamental conditions required to instil good health: i.e., peace, shelter, education, food, income, a stable ecosystem, sustainable resources, social justice and equity. These fundamental conditions would later form part of the original ten factors Richard Wilkinson and Michael Marmot earmarked as the social determinants of health.

Social Determinants of Health

Social determinants of health are the conditions in which people are born, grow, live, work and age, but are also shaped by the distribution of money, power and resources at global, national and local levels (Wilkinson und Marmot, 2003: 8). These conditions are (but not limited to): social gradient, stress, early life, social exclusion, work, unemployment, social support, addition, food, and transport (Wilkinson und Marmot, 2003: 10–29). Health disparities and inequities are unfair and avoidable differences in health status seen within countries such as Liberia, where the health system is heavily focused on medical care (or secondary and tertiary care).

Although medical care can increase survival and provide cure for some diseases, the population's health is dependent on the social, economic, political and legal conditions that make people ill (Wilkinson und Marmot, 2003: 7). To reduce global health inequalities and improve population health outcomes, WHO established the Commission on Social Determinants of Health between 2005 and 2008. Over the period of three years, the Commission on Social Determinants of Health aimed at and was successful in understanding the social relationships and factors that influenced health and health systems at the national level (Marmot, 2005: 1099).

THE HISTORY OF PUBLIC HEALTH IN LIBERIA

The history of public health in Liberia has a humble beginning with very little evidence to draw on. The first documented material to infer the existence of some sort of a medical or public health initiative in the Colony of Liberia can be found in the *Statute Laws of the Commonwealth of Liberia and Plan of Civil Government*, 1841 (The Statute Laws of the Commonwealth and the Plan for Civil Government, 1841). Under Article VI of the Statute Laws of the Commonwealth, “All Custom, Port, Infirmary, Medical, Guard, and Police Officers [that were] not appointed by the Managers of the Colonisation Society, and whose services are required and defined by the laws of the Colony, together with the public Measurers, Inspectors, and Appraisers, shall be appointed by the Agent of the Colony” (Statute Laws of the Commonwealth of Liberia and the Plan for Civil Government, 1841). Following was the *Act to Provide for the Support and Employment of the Poor*, 1843, which included aged widows, destitute orphans, poor persons and invalid poor (Constitution and Laws of the Commonwealth of Liberia and the Plan for Civil Government, 1841:39-40). In that same year (1841), an *Act Requiring the Register of Births and Deaths*, 1843 (The Birth and Death Act) appointed a Town Clerk to record and report all births and deaths to the Probate Court. Amended to law in 1857, after Liberia declared independence in 1847, saw the

Births and Death Act, which required the Probate Court to submit collected records to the Secretary of State (Constitution and Laws of the Commonwealth of Liberia and the Plan for Civil Government, 1841:30) rather than the Colonial Secretary. Thus, it can be assumed that the newly formed Liberian State did not have a Ministry of Health even ten years after its independence.

In December 1859, *An Act Approving and Appropriating a Certain Amount of Money Assumed and Expended by the President* authorizes the release of \$300 or \$400 dollars from the Public Treasury to assist with preventing the spread of smallpox in Montserrado county (Act of the National Legislature of Liberia, 1859a:50). The Legislature also released an amount of \$200 to Dr. D. R. Fletcher to help minimize smallpox outbreak in Maryland County (Act of the National Legislature of Liberia, 1859b). The first mention of a hospital made by the Liberian Legislature was a resolution passed during the December 1861 session. The resolution authorized the President of Liberia to allocate \$300 annually to St. Mark's Hospital in Harper, Maryland for a term of 10 years (Act of the National Legislature of Liberia, 1861:83). On January 26, 1870, *An Act Incorporating the Palm Grove Cemetery Company of Monrovia* was approved was passed (Act of the National Legislature, 1870). The Palm Grove Cemetery, positioned next to the public burial ground, allow private citizens to purchase plots for burying the dead. The Palm Grove Cemetery Act was the Liberian Government's effort to manage the disposal of dead persons by containing the spread of disease.

In his Third Annual Message of January 23, 1973, President William R. Tolbert, Jr commented on *The Public Health and Safety Law on the Control of Narcotic and Dangerous Drugs*, 1956 (Public Health and Safety Law, 1956). According to President Tolbert, the Public Health and Safety Law was enacted for the purpose of "discharging more effectively the obligation of the Republic under the international conventions to which it is a party" (President Tolbert, 1973)." Violation of sections 406 (Penalty for illegal traffic in drugs), 407 (Penalty for illegal possession of drugs) and 408 (Penalty for other violations) of the Public Health and Safety Law resulted in imprisonment for up to twenty, two and six years, respectively (Dunn, 2011: 1535). While in previous years, the cost of managing the Public Health and Sanitation Bureau was defrayed by loans and introduction of a Public Health and Sanitation tax in 1931, increased revenue for public health from \$0 to \$1,937.35 by 31 July 1932 was observed (Dunn, 2011: 845). In 1950, Liberia's Public Health and Sanitation Bureau appropriated 12 per cent of its total revenue towards Public Health, the highest for any nation apart from Sweden, which expended 15 per cent of its revenues at the time (Dunn 2011: 1145). By 1966, health expenditure rose to \$2.5 million under Tubman's regime (Dunn, 2011: 1360).

Proposal to amalgamate the hospital and sanitary services was first suggested in 1932 under President Edwin J. Barclay (1930-1944) (Dunn, 2011: 845). Dissatisfied with the conditions at the Government Hospital, President Barclay proposed the first Department of Health and Sanitary Service in 1935 in order to maximize efficiency and economic cost of caring for patients (Dunn, 2011: 915). Additionally, a Child and Maternity Health Clinic and a Clinic for the Poor under the auspices of the Bureau of Health and Sanitation were set up in that same year (Dunn, 2011: 915, 928).

PUBLIC HEALTH STATUS AND TRENDS

Statistical data and measurements are an important source of information for law and policy-makers to implement effective public health intervention and engineer social change. The ability numeration has to contextualise a complex and disorganized world is paramount in decision-making processes. In ordering numbers to simplify our world, quantitative data gives a sense of authority, “objective truth and scientific authority” but can be seductive (Merry, 2016: 1). Reliance on indicators with little commitment to systematic study affect power distribution and tilts international health leadership and control towards the West (Davis et al., 2012: 4). Thus, global health statistics should always be interpreted through a critical lens (Merry, 2016: 1–2).

The last census conducted in 2008, put Liberia’s population at 3.5 million (Liberia Institute of Statistics and Geo-Information Services, 2009: 3), although the UNDP projects a current population of 4.5 million people. Liberia ranks relatively low on the Human Development Index at 177 out of 188 countries (United Nations Development Program, 2016: 200). According to the World Health Organisation (WHO), life expectancy for both sexes at birth is 62 years, which increased over 11 years between 2000 and 2012 (World Health Organisation, 2015a: 1). In 2015, Liberia’s health expenditure as percentage of its Gross Domestic Product (GDP) was 15.2 per cent (World Health Organisation, 2017). In concrete terms, for fiscal year 2017/2018, 13.6 per cent (\$77.4 million) of Liberia’s total budget (\$563 million) was spent on health (Government of Liberia, 2017: iii, xv). The highest budget allocation was given to the Public Administration Sector, which received 31.4 per cent (\$176 million) of the total budget for the fiscal year 2017/2018 (Government of Liberia, 2017: xiv). Aid and donor agencies contributed US \$55 million (9.7 per cent) to Liberia’s budget for fiscal year 2017/2018, of which 20 per cent (US \$144 million) was allocated to the Health Sector. In essence, donor and aid agencies spent an excess of US \$ 67 on the health sector compare with that of the Government of Liberia spending on health (Government of Liberia, 2017: xi, 546).

Compounded by the civil war and the Ebola epidemic outbreak, Liberia has seen improvements in under-five mortality rate from a baseline of 248 per 1,000 live births in 1990 to 16 per 1,000 live births in 2016 (UNICEF, 2017: 148). Similarly, maternal mortality ratio has reduced from 1,200 per 100,000 live births to 725 per 100,000 live births (UNICEF, 2017: 179). In spite of the reduction in infant mortality rates and maternal mortality ratios over a 15-year period (World Health Organisation, 2015b: 53), continuous increase in public health access and services between rural and urban areas places Liberia at a relatively high global ranking of 27 out of 192 countries for Infant mortality rate (UNICEF, 2017: 148–149) and 7 out of 181 countries for maternal mortality rate (World Health Organisation, 2015b: 70–77). In effort to address the poor quality of care as a major cause of relatively high maternal and under-five mortality rates, the World Bank launched the *Liberia Health Systems Strengthening* project in 2013. A grant amount of US \$16 million was allotted to support the *Every Woman Every Child* project in Liberia, which focuses on reproductive, maternal, newborn, child and adolescent health (RMNCAH) (World Bank, 2017b: 1–3).

The top ten causes of death in Liberia in 2012 are listed below in Table 1 (World Health Organisation, 2015a). The top three burden of disease affecting disability-adjusted life years

(DALYs) and years of healthy life lost due to disability (YLD)¹ are: human immune-deficiency virus (HIV), tuberculosis (TB), malaria, maternal, neonatal, nutritional and infectious diseases other than acute respiratory diseases, HIV, TB and malaria.

Table 1. Top ten causes of death in Liberia, 2012

Disease/Condition	# of Deaths (000s)	Percentage
Lower respiratory infections	12.2	4.20
Malaria	8.40	2.90
Tuberculosis	5.60	1.90
HIV/AIDS	5.60	1.90
Stroke	5.30	1.80
Diarrhoeal diseases	4.70	1.60
Birth Asphyxia and trauma	4.00	1.40
Ischaemic heart disease	3.50	1.20
Preterm birth complications	3.50	1.20
Maternal conditions	2.90	1.00

Source: Compiled by the Author.

More than 11,400 persons living with HIV in Liberia were enrolled in care with 8,400 actively receiving anti-retroviral therapy (ART) (Gasasira et al., 2016: 20). In 1989, the Ministry of Health's Department of Preventive Services launched the National Leprosy and Tuberculosis Control Program (Ministry of Health, 2014: 1). To this end, tuberculosis notification reduced from 8,132 in 2012 to 5,849 cases in 2015. In 2016, 77 per cent of the 7,119 tuberculosis cases in Liberia were successfully treated (Gasasira et al., 2016: 20). Malaria, endemic in Liberia are the leading cause of attendance at outpatient hospital care (National Malaria Control Program - Liberia et al., 2016: ix), with a national average prevalence rate of 28 per cent (United States Agency for International Development, 2016: 11). To reduce the burden of malaria in Liberia, the Ministry of Health's National Malaria Control Program, in its fourth plan, focuses on scaling up malaria prevention and control (Ministry of Health, Liberia, 2016a: 3). According to WHO, some 1.2 million malaria cases were treated with anti-malaria therapy and approximately 103,892 pregnant women received long lasting insecticidal nets in 2016 (Gasasira et al., 2016: 22–23).

LAW, POLICY AND STRATEGIC PLAN

Ministry of Health and Social Welfare Act 1972 to Ministry of Health Act, 2015

In 1972, the Fourth Regular Session of the Forty-Fifth Legislature of Liberia, repealed *Title 33 of the Liberian Code of Laws*, 1956, entitled: "Public Welfare Law." A new Executive Law, Chapter 30, Title 12, *Liberian Code of Laws, Revised*, 1972 established the Ministry of Health and Social Welfare for the first time (see section 30.1). Duties of the

¹ Disability-adjusted life years (DALYs) are the sum of years of life lost due to premature mortality (YL) and years of healthy life lost due to disability (YLD).

Minister of Health and Social Welfare include the prevention and abatement of conditions hazardous to the public health, *inter alia* (section 30.2 (3)).

In 2015, after 43 years of delivering health service, the Liberian Legislature renamed the Ministry of Health and Social Welfare by passing an *Act to Establish the Ministry of Health, 2015* (Ministry of Health Act), which repealed all social welfare provisions.² The main rationale for separating the “Ministry of Health” from that of “Social Welfare” is to “promote planned and sustainable economic development, efficiency in development resources and effectiveness in the delivery of public services” (preamble, Ministry of Health Act). With a mandate focused on health policy, planning, and delivery standards (section 39.3), the new Ministry of Health moves away from primary care, while emphasizing more on secondary and tertiary care. Albeit, the Department of Preventive Services of the Ministry of Health plans and coordinates prevention activities to control diseases that concern the public’s health, including emergencies, monitoring and outbreaks (Ministry of Health, Liberia, 2018).

The Public Health Law, 1976

The Public Health Law, Title 33, Liberian Code of Laws Revised 1976 (the Public Health Law) was first established in 1956, Title 31. In 1977, an Act of the National Legislature set up the Liberian Association of Public Health Inspectors, now called the Liberian Association of Public Health Technicians. The goal of the Liberian Association of Public Health Technicians was to help implement the Public Health Law by protecting Liberians’ health through preventive health measures (Front Page Africa, 2017). The Public Health Law is divided into seven parts: 1) General Provisions, 2) Control of Acute Communicable Diseases and Conditions, 3) Environmental Sanitation, 4) Health Standards of Public and Private Institutions, 5) Regulation of Drugs, 6) Vital Statistics: Disposal of Human Remains, and 7) Regulation and Supervision of Medical and Allied Health Professions. Though considered elaborate at the time, the Public Health Law provides no definition of Public Health and is silent on non-communicable diseases, mental health, or public health emergency preparedness.

Chapter 14.2 of the Public Health Law, invests power in the Minister of Health to make rules regarding a cadre of matters, including but not limited to, 1) conducting house visitation (Chapter 14.2 (b)); 2) preventing any person from leaving an infected area without undergoing medical examination (Chapter 14.2 (d)); 3) establishing hospital and observation camps or stations (Chapter 14.2 (e)); 4) removal of person with the disease and those in contact with such persons (Chapter 14.2 (g)); and 5) removal of corpses (Chapter 14.2 (h)). As indicated above, amidst the Ebola Virus outbreak in 2014, former President Sirleaf asserted that the Public Health Law was inadequate to handle the Ebola epidemic holistically and comprehensively (Johnson-Sirleaf, 2014). Thus, in its current state, the Public Health Law makes no provision for handling public health emergencies whether through quarantine or through other monitoring or surveillance measures (Public Health Law, 1956)³

² Chapter 39, Executive Law, Title 12, Liberian Code of Laws, Revised, 2015

³ Chapter 11(i) and (k) of the Public Health Law defines isolation and quarantine as it pertains the “Control of acute communicable diseases and conditions”. These terms are not used anywhere in Chapter 14: Formidable Epidemic, Endemic or Infectious Diseases.

The Public Health Law criminalises “risky” behaviours and practices. For instance, Chapter 14.6 of the Public Health Act states: “Any person other than a public officer who violates any of the provisions of this chapter or any of the rules made thereunder shall, upon conviction, be liable to a fine not exceeding two hundred dollars or to imprisonment not exceeding thirty days, or to both such fine and imprisonment.” The Public Health Law is further critiqued for being very general and incongruent to the health realities at the time (World Health Organisation, 2005), yet heavily focused on regulating drugs, standards for health workers, and licensing of health professionals. Much needed revision of the Public Health Law started in 2011 with assistance from Jeannette Austin (another individual foreign to the Liberian health system), serving with a team of in country lawyers in developing a new public health law (Austin, 2011).

Ministry of Gender and Development Act, 2001

As noted above, the “Social Welfare” aspects of the old Ministry of Health and Social Welfare is now moved to the Ministry of Gender, Children and Social Protection, formerly known as the Ministry of Gender and Development. Back in 1998, under the leadership of former President Charles Ghankay Taylor, Grace Minor, then Senator of Montserrado County and Chairperson of the Senate Standing Committee on Executive called for the establishment of a Ministry of Gender Affairs in Liberia. Senator’s Minor’s recommendation for establishing a Ministry of Gender was apt then as Liberia was barely recovering from the scourge of its first civil war, which predisposed many girls and women to violence and abuse. The proposed Ministry of Gender Affairs was to “seek the enhancement and protection of women rights...” as women have been marginalised for so long in Liberia and therefore needed to be “educated massively of their rights and roles in this male dominated Liberian society” (Staff Reporter, 1998). In 2001, *An Act to Amend the Executive Law Title 12 (The Gender and Development Act)*, established the Ministry of Gender.

In 2013, overlap between the responsibilities of the Ministry of Health and Social Welfare and that of the Ministry of Gender and Development regarding care of children, led to the Governance Commission’s Bill.⁴ On April 8, 2014, the 53rd Legislature of Liberia amended Chapter 38 of the New Executive to establish the Ministry of Gender, Children and Social Protection (Staff Reporter, 2014a). All functions and powers of the repealed social welfare provisions of the old Ministry of Health and Social Welfare is now transferred to the new Ministry of Gender, Children and Social Protection (Cabran, 2014: 12). Grounded in population health approach by focusing on health outcomes, determinants, policy and intervention of group of individuals (Kindig and Stoddart, 2003: 380), the Ministry of Gender, Children and Social Development mandate is to

promote the development, empowerment and protection of women, girls and children, as well as the welfare and integration of persons with disabilities, the vulnerable, extremely poor, excluded and disadvantaged. Specifically, the Ministry will initiate, develop and implement and/or coordinate policies and programs aimed at women, girls, and children, as well as those physically challenged, marginalised, disadvantaged and excluded, to ensure that their rights are protected and that they are integrated, and contribute

⁴ An Act to Amend Chapter 38 Ministry of Gender and Development, of the Executive Law, to Establish the Ministry of Gender, Children and Social Protection, 2013

to, and benefit from, the peace, stability and socio-economic advancement of the country (Section 38.3, *Ministry of Gender, Children and Social Development Act*, 2014).

Interestingly, the Ministry of Gender, Children and Social Protection has no Department of Social Welfare included in its organisational structure (Cabran, 2014: 12).

Section 7 (e) of the *Ministry of Gender, Children and Social Protection Act*, 2013 transfers all assets, personnel, and remaining budget from the Ministry of Health and Social Welfare's Department of Social Welfare to the Ministry of Gender, Children and Social Protection. The Ministry of Gender, Children and Social Protection leads with mainstreaming government-wide efforts to ensure gender equality and empowerment of women and development of children. The Ministry of Gender, Children and Social Protection is the driving force behind the enforcement of the Universal Declaration of Human Rights, *Convention on the Elimination of All Forms of Discrimination against Women (CEDAW)*, 1989 the Convention on the Rights of the Child, the *Protocol to the African Charter on the Human and Peoples' Rights on the Rights of Women in Africa*, 2003 the African Children's Charter, and the United Nations Security Council 1325 on Women Peace and Security. The roles of both the Ministries of Health and Gender are significantly increasing in the lives of children and women in post-war Liberia (Fuest 2008), especially with the new addition of social protection of children.

Basic Package of Health Services, 2008

The first government health insurance program, the "Hospitalisation Insurance Plan," was introduced in 1936 under the presidency of Barclay where paying a premium of 50 or 60 cents per month entitled a person to free hospital treatment over a specified period (Dunn, 2011: 915). In recent times, with assistance from international donor agencies, the Government of Liberia is gradually moving towards establishing national health coverage program that would expand the population access to public health care. The Basic Package of Health and Social Welfare Services, 2008 (the Basic Package of Health), founded on the fundamental principles of primary health care and decentralisation of health services management; targets maternal, child, adolescent, reproductive, mental health, communicable disease control and emergency care. The main objectives of the Basic Package of Health are to: 1) standardise the service delivery package at the five levels of the Liberian health system; and 2) redistribute essential health services to ensure universal access throughout Liberia (Government of Liberia, 2008: 1–3).

While the goals of the Basic Package of Health appear to be doable, Roberts et al., argue that disruption in care and fragmented health service delivery caused by damaged infrastructure, limited human resources, weak stewardship and proliferation of non-governmental organisations are common symptoms of countries, such as Liberia, emerging from violent conflict (Roberts et al., 2008). Enhancing the implementation of the Basic Package of Health hinges on the idea of continuous assessment. Accreditation is one way to conduct continuous assessment of the Basic Package Health programs as it does not only improve quality of care, but it also facilitates monitoring of trends and evaluation of health systems. While successful accreditation systems have existed in high- and middle-income

countries, many low-income countries such as Liberia, have fallen behind in establishing effective health facilities programs (Cleveland et al., 2011: 272).

For instance, in 2007, the Ministry of Health and Social Welfare did not have basic information about health care in Liberia. With assistance from the Clinton Foundation, a Basic Package of Health Service accreditation program was initiated amidst extreme logistical and implementation challenges (Cleveland et al., 2011: 272). In particular, the Basic Package of Health was designed to track quality improvement or measure of quality of care. Nevertheless, the accreditation program allowed the Ministry of Health to gather unprecedented amounts of information about the current status of service provision across the country, well beyond directly tracking and measuring quality of care (Cleveland et al., 2011: 275).

Mainly due the Ebola Virus Disease epidemic (Kruk et al., 2017), the Government of Liberia mobilised to develop another policy to improve public health intervention programs. Emphasising the fact that health workers experienced a 30 times higher risk of infection compared as to the general population, (i.e., as of 8 April 2015, 372 healthcare workers were infected and 184 had died), *the Investment Plan for Building a Resilient Health System* emerged in 2015 with assistance from the World Bank Group (Ministry of Health and Social Welfare 2015; 2017a). Like the National Health Policy and Plan, the Investment Plan for Building a Resilient Health System (Government of Liberia, 2015: iii and 1) aims to provide universal access to safe and quality services through improved capacity of the health network for provision of safe, quality Essential Packages of Health Services, as well as a robust Health Emergency Risk Management System through building public health capacity for prevention, preparedness, alert and response for disease outbreaks and other health threats. In spite of the aforementioned, a study conducted in 2008 with 1,405 individuals in Nimba country, found that rural communities in Liberia still have limited access to life-saving health care (Kruk et al., 2010: 527).

National Health Policy Plan, 2011

The first-ever National Health and Social Welfare Financing Policy and Plan was established in 2007 to supervise and standardize the finances to implement the National Health and Social Welfare Policy and Plan, 2011–2021 (Ministry of Health and Social Welfare, 2006: 13, 2011: 5). Recognizing that health and social welfare are key determinants of human development, and in the context of national social and economic growth strategy, then Ministry of Health and Social Welfare led the development of one holistic National Health and Social Welfare Policy and Plan, 2011–2021 (Government of Liberia, 2011: 6) with the aim of substantially improving the health and social welfare of Liberia's population health.

Mental Health Act, 2017

Consistent with the National Health Policy and Basic Package of Health, the National Mental Health Policy, 2010 was Liberia's first major attempt to address mental health

problems comprehensively and incorporate it into all areas of health and health delivery service (Ministry of Health and Social Welfare, 2010: 10). In the past, mental illness in Liberia was exclusively limited to severe forms of psychotic disorders treated by traditional and religious leaders who saw the disease as one of witchcraft or demonic possession (Ministry of Health and Social Welfare, 2010: 14). Even after the Catherine Mills Rehabilitation Center was established in the 1960s, mental health patients still roamed the streets of Liberia commonly referred to as “crazy people.” The Catherine Mills Rehabilitation Center, the only psychiatric care facility in the country, was destroyed during the civil war (Ballah, 2016c) but now has 75 beds and provide care for both in- and out-patients (Ministry of Health and Social Welfare, 2010: 14).

In 2016, the Ministry of Health released a new 5-year Mental Health Policy and Strategic Plan for Liberia, 2016-2021 (Mental Health Policy, 2016) that will expand access to mental health clinicians and develop new Wellness Units in every county (Ministry of Health, 2016b: v). Drawing on the Basic Package of Health and the Investment Plan for Building a Resilient Health System 2015-2021, the Mental Health Policy, 2016 emphasizes on secondary and tertiary care. Though, two primary care strategic objective of the Mental Health Policy, 2016 are: 1) sensitize communities about mental health and illness and modify, 2) encourage families of persons with neuropsychiatric disorders to be involved in the care and management of their loved ones (Ministry of Health and Social Welfare, 2010: vi).

Prior to 2017, Liberia had only one psychiatrist (Massachusetts General Hospital, 2018) and no mental health law for protecting its estimated 300,000 persons suffering from mental illnesses (Cooper, 2017) and many more survivors of the 14-year civil war. Now, the country boasts of four psychiatrists and 230 mental health personnel (Cooper, 2017), in addition to enacting a mental health law. On May 23, 2017, the Liberian Legislature unanimously amended the Public Health Law by adding Part VIII, Health and Related Rights, Chapter 2, Mental Health (Ballah, 2017; Sonpon, 2017). On November 30, 2017, the Carter Center in Liberia reported that the Mental Health Act handbill was released and distributed by the Ministry of Foreign Affairs, an indication of the official enactment of “Liberia’s first law to improve health care for people with mental illnesses and prevent discrimination against them” (Cooper, 2017). The new Mental Health Act aims to

provide for and protect the civil, social and health rights of all persons with mental disorders and/or mental disabilities including persons with intellectual disabilities; promotes and regulates equitable and effective access to timely, appropriate and quality mental healthcare, treatment, habilitation and rehabilitation for all persons in the 15 counties, including those with mental disorders and/or mental disabilities; establish and enforce the responsibilities and obligations of the government in carrying out the duties set forth (Sonpon, 2017).

Children’s Act, 2011

Signatory to the *Universal Declaration of Human Rights* (UDHR), 1948; the *Convention on the Rights of the Child* (CRC), 1989; the African Charter on the Rights and Welfare of the Child (the African Children’s Charter), 1990; and the *Convention on the Elimination of All Forms of Discrimination against Women* (CEDAW), 1979; Liberia legislated *An Act to Establish the Children’s Law of Liberia* (the Children’s Law), 2011. According to the United Nations Children’s Fund (UNICEF), “Liberia is one of the first countries to adopt

comprehensive legislation for children that incorporates the UNCRC and the African Charter” (Pradhan, 2012). The Children’s Act covers a broad range of rights and protection that generally speaks to primary care approach of children’s health. Section 8, Article III, of the Children’s Act particularly deals with the right to access medically necessary health care, while Article VII focuses on children’s situations of vulnerability. In spite of progress made with the establishment of the Children’s Law, the vulnerability and risk to ill-health of Liberian are many.

Although there has been some progress with reducing infant and under mortality rates in Liberia as indicated above, a relatively high maternal mortality rate implies that many children die with their mothers inside the womb (UNICEF-Liberia, 2018). Liberia ranks second highest in the first global primary out-of-school rate at 62 per cent of children out of school (UNESCO Institute for Statistics, 2017: 6). Out of school of many children implies increased vulnerability to neglect, violence, abuse and exploitation. According to the United States Department of Labor, Liberian children are engaged in some of the worse forms of child labor including, being trafficked and exploited for commercial sex, forced domestic work, forced begging and performing dangerous tasks in the production of rubber, mining gold and diamonds (Bureau of International Labor Affairs, 2016: 1–2).

National Commission on Disabilities Act, 2005

In 2005, the Liberian Legislature enacted *the National Commission on Disabilities Act* 2005, with a mandate to deal with the general welfare and education of persons with disabilities in Liberia (Swedish International Development Cooperation 2014: 4). Following the set-up of the National Commission on Disability, Liberia signed (March 30, 2007) and ratified (July 26, 2012) the *United Nations Convention on the Rights of Persons with Disabilities*, 2006⁵ (United Nations 2018). The National Commission on Disabilities is an autonomous agency having “*jurisdiction over all matters involving and appertaining to general welfare, wellbeing, education of all disabled persons within the Republic of Liberia.*”⁶ Section 7 of the Act, authorized the Government of Liberia to make budgetary appropriation for the education, social and economic development of all disabled persons within minutes of passing the National Commission on Disabilities Act. Despite its overzealous aspiration, the National Commission on Disabilities continues to struggle (Tamba, 2018). In an address by President Johnson Sirleaf to the National Union of Organisations of the Disabled, the National President, Reverend Fallah S. Boima discloses that,

...the [National Union of Organisations of the Disabled], which is the mother organisation of all disabled persons in Liberia, does not have a stable source of funding to support its activities and programs... That the subsidy provided by government through the National Commission on Disabilities cannot cover the monthly rent of the Union’s office and it stands to be evicted from its office shortly (Executive Mansion, 2015).

⁵ On 30 March 2007, Liberia signed the Optional Protocol to the Convention on the Rights of Persons with Disabilities, 2006 but has not ratified yet.

⁶ Section 2, National Commission on Disabilities Act.

Statistical data on persons with disabilities in Liberia is non-existent. Albeit, a study carried out by the Center for Rehabilitation of the Injured and disabled in 1997 found that 16 per cent of the Liberian population live with a disability (UNICEF-Liberia, 2012: 15). According to a report by the Swedish International Development Agency, approximately 20 per cent (or 800,000 persons) have disability in Liberia as a direct result of the civil war (Swedish International Development Cooperation, 2014: 1). One can only imagine the situation of people with disabilities living in remote Liberia when its centralised location in Monrovia is already at risk for being “homeless” due to lack of funding and budgetary allocation (Swedish International Development Cooperation, 2014: 4). In its National Human Rights Action Plan of Liberia, 2013-2018; the government of Liberia stated two major objectives regarding the rights of persons with disabilities and other vulnerable groups (Government of Liberia, 2013: 23–24):

1. Improve accessibility to disability-specific services and reduce stigmatisation and discrimination against all vulnerable groups; promote their right to be treated equally.
2. Improve protection for marginalised and vulnerable groups at all levels of the administration of justice (police, prison system, courts) and marginalised groups within society and strengthen capacity for response, referral and follow-up of gender-specific issues.

Whether full and comprehensive implementation of the above objectives will be materialised by the end of 2018, is a matter of time, effort and commitment on the part of the government to carry out an evaluation of the human rights action plan. The law, policies and strategic plans listed above promise to create an enabling environment that restores trust in the health authorities’ ability to provide national public health services and delivery through community engagement grounded in leadership, effective governance and accountability at all levels.

PUBLIC HEALTH PROGRAM: SERVICE, INSTITUTION AND TRAINING

Health Facilities and Services

The Government of Liberia has always supported and funded national health initiatives by establishing public health institutions to provide services to its population. In 1943 and 1948, \$37,623.68 and \$248,077, respectively were allocated to the Bureau of Public Health and Sanitation to be used towards health care of 44,647 patients across 15 health centers⁷ across the country (Dunn, 2011: 1088). In 1949, the Bureau of Public Health and Sanitation engaged in swamps drainage program in efforts to combat malaria outside of the City of Monrovia (Dunn, 2011: 1112). In that same year (1949), either a hospital, clinic or special sanitary works were established in Cape Mount, Grand Bassa, Sinoe, Cape Palmas, Webbo, Tchien, Tappita, Sannequellie, Gbarnga, Salala, River Cess, Timbo, Maryland, Voinjama, Bopulu and Clay-Ashland (Dunn, 2011: 1112).

⁷ Monrovia, Bassa, Voinjama, Cape Palmas, Tchien, Tappita, Webbo, Sinoe, Cape Mount, Salala, Crozierville, Gbarnga, River Cess, Marshall and Bopulu Health Centers.

On May 3, 1972, the Liberian Legislature approved an act to create the John F. Kennedy Medical Center (JFK Medical Center) as an autonomous agency of the Government of Liberia.⁸ The JFK Medical Center comprised the John F. Kennedy Memorial Hospital, Maternity Hospital, the Tubman National Institute of Medical Arts (a paramedical and nursing school), and the Catherine Mills Rehabilitation Hospital. Now also repealed (i.e., the JFK Medical Center Act, 1972) the main goal of the JFK Medical Center was to provide medical care to the population of Liberia and serve as a center of training in the medical, paramedical and public health fields.⁹ As such, the JFK Medical Center currently serves as a tertiary health care facility, the main national referral center primary and secondary healthcare, as well as, the teaching hospital for the A. M. Dogliotti School of Medicine (Government of Liberia, 2017: 231).

Table 2. Showing Percentage of Health Access, Public Health Facilities and Health Workers in the 15 Counties of Liberia, 2008

#	County	Population	Access to Healthcare (%)	Public Hospitals	Health Clinics	Doctors	Registered Nurses
1	Grand Bassa	182,937	NA	2	31	0	0
2	Bomi	105,345	<15	1	15	1	10
3	Bong	520,000	NA	2	33	6	28
4	Grand Cape Mount	191,102	NA	1	30	1	35
5	Gbarpolu	129,739	Limited	1	11	0	0
6	Grand Gedeh	140,934	6	0	11	0	1
7	Grand Kru	58,342	Extremely low	1	10	0	1
8	Lofa	416,173	NA	4	31	6	2
9	Margibi	240,996	NA	2	19	0	0
10	Maryland	135,912	NA	1	16	3	19
11	Monterrado	1,277,994	3	6	44	97	188
12	Nimba	732,195	3	2	39	1	89
13	River Cess	124,756	10	0	10	0	?
14	River Gee	50,605	NA	0	11	0	1
15	Sinoe	76,224	NA	1	5	2	1
	TOTAL	4,383,254	NA	24	316	117	375

Source: Compiled by the Author.

The purpose of the newly enacted *John F. Kennedy Memorial Center Act*, 2013 (JFK Memorial Center) is to provide specialist care and services, conduct training programs for health professionals as a teaching hospital, and promote health-related scientific research (Staff Reporter, 2014a). Heavily focused on treatment, cure, and teaching, the JFK Memorial Center does not have a Public Health Division, which attest to the struggle it faced during the Ebola epidemic outbreak. After 46 years of its existence (1972-2018), the historically public-run national hospital, is barely equipped with basic X-rays, emergency room, surgical capabilities, laboratory services provided by very few specialists, and allied health care providers. Although one of two national tertiary care facilities in the country, the JFK Medical Care Center accepts only cash payment from patients. In 2016, Daylue Goah,

⁸ *An Act to Amend the Executive Law to Create the John F. Kennedy Medical Center*, 1972, Government Printing Office Ministry of Foreign Affairs, Monrovia, 6 May 1972.

⁹ Preamble of *An Act to Amend the Executive Law to Create the John F. Kennedy Medical Center*, 1972

formally employed as a Public Relation Officer of the JFK Memorial Center, alleged ongoing corruption and poor services specifically regarding senior staff members stealing donated medication and delivering treatment that resulted in patients' death (Dweh 2016). Daylue's accusation of corruption was recently confirmed by the General Auditing Commission (Dodoo, 2018). In response, Dr. Wannie Scott-McDonald, Head of the JFK Memorial Center, enumerated achievements under her leadership, including staff training, renovations, increase in staff salary and constant supply of medication to patient (Rogers, 2016). That being said, a most recent media report highlighted the breakdown of the largest public health center in Liberia due to budget cuts (Senkpen, 2018). Compiled from individual County Development Agendas released in 2008, Table 2 (below) shows a glimpse of health facilities, practitioners and basis services provided across Liberia.

Health Professionals, Education and Training

Historically, Liberia has struggled with training qualified health personnel as the Country has only one public health school (privately owned), and a medical and a nursing school that is publicly funded. As early as 1948, Liberian health professionals were sponsored by foreign governments. For example, the United States Government sponsored Dr. Joseph N. Togba, Chief of the Bureau of Health and Sanitation, who took up a special post-graduate course in public health and sanitation in the United States in 1948 (Dunn, 2011: 1088). In cases where there were insufficient qualified health practitioners, the Government of Liberia sought the assistance of foreign nationals, a practice still existing today (Staff Reporter, 2018a). For example, in 1949, former President William V. S. Tubman recruited nine doctors from Germany, adding to the already eight government doctors to help increase the number of medical doctors for the growing population of Liberia (Dunn, 2011: 1113). There are a number of private institutions providing health, nursing, and public health education and training. However, the challenge most Liberians face is the ability to afford the cost of attending public health schools and finding a job after completing their educational programs. To date, no PhD programs are offer in Liberia, as such, the conduct of high quality research in Liberia is constrained by many factors, making it difficult to produce and access scholarly resource materials.

Tubman National Institute of Medical Arts

The Tubman National Institute of Medical Arts furthers educational, health and social development in Liberia by training health workers for the rural areas. The Tubman National Institute of Medical Arts was established in 1945 in collaboration with the Liberian National Public Health Services and the United States Mission in Liberia. In 1964, as the need to established a physician assistant program for the development of health workers for the rural areas arose, the Government of Liberia in collaboration with WHO and UNICEF, establish the a two-year training physician assistant program which was later increased to three years in 1976 (Kennedy, 2011). To date, the Tubman National Institute of Medical Arts operates four programs: School of Environmental Health, School of Midwifery, School of Physician Assistant and School of Professional Nursing (Kennedy, 2011). It has graduated over 3000 para-medical health workers as of 2013 (Kennedy, 2011), although not without challenges

(All Africa, 2013; Wolokolie, 2013). However, recent “investment into trained midwives” across the country brings hope for improvement (WHO, 2016) with the launching of the new University of Liberia Nursing School. Until 2014, the Tubman National Institute of Medical Arts was the only publicly funding nursing program in the Country (Staff Reporter, 2014b). In September 2015, the University of Liberia, in collaboration with the JFK Medical Center and the Tubman National Institute of Medical Arts commenced a four-year Bachelor in Nursing and Midwifery with 19 students enrolled (Staff Reporter, 2015).

A. M. Dogliotti Medical School at the University of Liberia

In 1966, then President William V. S. Tubman, with assistance from the Italian Government, the Vatican and the Achille Mario Dogliotti Foundation, established the Monrovia-Torino Medical School in hopes of training medical doctors for Liberia as well as Africa at large (AM Dogliotti College of Medicine, 2010: 3). Initially affiliated with the Faculty of Medicine and Surgery of the University of Turin in Italy, in 1970 the Monrovia-Torino Medical School merged with the University of Liberia and was renamed Achille Mario Dogliotti College of Medicine, becoming the second professional school in Liberia (A. M. Dogliotti College of Medicine 2010: 3). After the inauguration of the John F. Kennedy Memorial Hospital in 1971, the Achille Mario Dogliotti College of Medicine became the teaching hospital of A. M. Dogliotti College of Medicine. From its opening in 1966 until 2009, the A. M. Dogliotti College of Medicine graduated 273 doctors (Executive Mansion, 2009).

A situational and observational report of A. M. Dogliotti College of Medicine highlighted its rickety and neglectful state, noting broken down structures with no access to running water, electricity, or internet (Nyan, 2006). Notwithstanding, in 2016, enrollment at the AM Dogliotti College of Medicine included 231 medical students, 79 pharmacy students, and 20 students in nursing and midwifery (Ballah, 2016b). As not much has changed today (Ballah 2016b), the question remains whether Liberia will ever be prepared for a future epidemic in the face of the lingering possibility of the resurgence of the Ebola Virus Disease.

Cuttington University's Master of Public Health Program

Named in honor of Robert Fulton, Cuttington's Treasurer of the Board of Missions of the Episcopal Church in the United States, the Old Cuttington Collegiate and Divinity School (the Old Cuttington) was founded in 1889, in Cape Palmas, Liberia (Cuttington University, 2018b). At the time, enrollment was limited to only 100 students, all of whom were only men. Due to financial challenges, the Old Cuttington was closed down in 1929 (Cuttington University, 2018b). Re-named, Cuttington College and Divinity School and with guidance from Bishop Bravid W. Harris, then Bishop of Liberia, the New Cuttington opened in 1949 as a co-educational Liberal Arts College (Cuttington University, 2018b). Renamed again in 1977, Cuttington University College, made up of six degree granting colleges, moved to Suakoko, Bong County, on 1,500 acres of rich agricultural land that was donated to the Episcopal Church by the Government of Liberia during the presidency of William V. S. Tubman (Cuttington University, 2018b). A fully accredited university in Liberia, Cuttington University now has seven colleges that offer 13 degrees and 8 certificates in its undergraduate programs, including a Bachelor of Nursing, and offers 11 graduate degrees, including a Master of Nursing Administration, and a Master of Public Health (MPH) (Cuttington University, 2018a).

Located in Oldest Congo Town on Tubman Boulevard in Monrovia, Cuttington University's Department of Community Health offers the MPH degree, and accommodates students with background in natural sciences, health sciences, sociology and other related disciplines (Cuttington University, 2017: 53). The vision of Cuttington University's MPH program is "[t]o train and qualify graduates in Community Health capable of using evidence-based problem-solving approach in dealing with some of the many complex and vexing public health and related issues challenging Liberia and the world at large" (Cuttington University, 2017: 53–54).

ADDRESSING PUBLIC HEALTH EMERGENCY

The government of Liberia first allocated funds to address the outbreak of smallpox in the 1861.¹⁰ Two outbreaks of smallpox in Grand Cape Mount County and the Central Province in 1935, prompted former President Edwin J. Barclay to appoint Dr. Kreuger and Dr. Jung as Medical Officer of Health and Supervisor of the Sanitary Work in both the Western Province and Grand Cape Mount Country, respectively (Dunn, 2011: 908). Dr. Anigstein, an Expert of Tropical Medicine, from the University of Warsaw, was also appointed to advise the Government on matters of sanitation and public health (Dunn, 2011: 908–909). To this end, the Government of Liberia was successful in arresting 186 cases of smallpox and vaccinating 26,427 persons, which rose to 70,177 over a two year period (Dunn, 2011: 908, 914). By 1937, a mild epidemic of Influenza hit the Montserrado area, in addition to 236 cases of smallpox infection sparking the vaccination of 109,950 persons over a period of eight months (Dunn, 2011: 928). Along similar lines, three Leprosy stations we set up across the country to reduce forcible isolation of lepers (Dunn, 2011: 908, 914–915).

In recent times, the Ebola Virus Disease pandemic in West Africa created a new public health challenge never seen before in Liberia. Before the outbreak of the Ebola Virus epidemic in August 2014, Liberia was already stricken by poverty, corruption, hunger and civil war. Growth and development in Liberia was stunted by a 14-year civil war. After the civil war officially ended in 2003, the country's estimated population of 4.1 million was served by 50 licensed Liberian-trained doctors, now upgraded to 298 for 4.5 million people in 2016 (Ballah 2016a: 1) and 437 health facilities as at 2008 (Black et al., 2016: 292). By May 11, 2016, WHO reported 10,666 cases and 4,806 deaths of the Ebola Virus disease in Liberia with a case fatality rate of 72.3 per cent for persons between the ages of 15 and 44 years with a known clinical outcome of the infection (World Health Organisation, 2016).

At the peak of the Ebola crises, former President Ellen Johnson Sirleaf, declared a State of Emergency on August 6, 2014, affirming that public health emergency response measures pursuant to the Public Health Act were inadequate to handle the Ebola epidemic holistically and comprehensively (Johnson-Sirleaf, 2014). To this end, President Sirleaf imposed extraordinary measures, including the suspension of certain rights and privileges of citizens in order to address the Ebola outbreak, which at the time had no cure with a 90 per cent fatality rate. Additionally, then Ministry of Health and Social Welfare released Regulations by the Minister of Health (the "Minister") Governing the Control and Abatement of the Spread and Eradication of the Ebola Virus Disease (EVD) in Liberia (The Anti-Ebola Regulation), 2014.

¹⁰ An Act Passed During the December 1859 Session of the National Legislature of Liberia.

Applied throughout Liberia, the Anti-Ebola Regulation emphasized the duty of local health authority to pick-up, transfer and isolate persons suspected or symptomatic of the Ebola Virus Disease as well as several methods to prevent spread of the disease.¹¹ Since the Ebola Virus epidemic, the Government of Liberia has initiated efforts to build and strengthen a resilient health system in preparing for public health emergency and improving the population's health. Herewith are two key examples:

Integrated Disease Surveillance and Response

In 2006, the Ministry of Health (MOH) adapted a generic integrated disease surveillance and response (IDSR) in collaboration with the World Health Organisation-Regional Office for Africa (AFRO) and the United States Centers for Disease Control and Prevention (CDC) in Atlanta (Centers for Disease Control and Prevention, 2017). The IDSR framework implements the International Health Regulations to effectively respond to severe emergency outbreaks of mostly preventable diseases (Centers for Disease Control and Prevention, 2017). Frimpong et al., (2017:9). suggest that early detection, reporting and response to public health events help to reduce the burden of mortality and morbidity on communities. Therefore, careful analysis of reliable surveillance data is required to implement timely and appropriate public health interventions (Frimpong et al., 2017: 6). For Liberia, sustaining and strengthening a resilient health system is dependent on the collection of high quality IDSR data on both communicable and non-communicable diseases (Ministry of Health, Liberia et al., 2016: 18).

National Public Health Institute of Liberia

In 1967, President Tubman instituted a National Public Health Service, an advisory council on health with the following terms of reference: The Council advised the Chief Executive on all aspects of clinical and preventive medicines and dentistry, including advice on the development, organisation and administrative practice of public health and clinical programs over a 10-year period (Dunn, 2011: 1267).

Decades after the establishment of the National Public Health Service, followed by unprecedented loss of 4,806 lives during the Ebola Virus Disease, Liberia will establish another national public health institution. In January 2017, the National Public Health Institute of Liberia (the National Public Health Institute) was established (Staff Reporter, 2018b; The International Association of National Health Institutes, 2016) with a mission to “prevent and control public health threats by promoting healthy outcomes and serving as a source of knowledge and expertise” (National Public Health Institute of Liberia 2018). In collaboration with the Ministry of Health, the National Public Health Institute also helps to strengthen prevention, surveillance and control of infectious diseases by building public health capacity in responding to outbreaks and monitoring potential epidemic (National Public Health Institute of Liberia, 2018). Since the Ebola epidemic in Liberia, the National Public Health Institute, in partnership with WHO, releases the IDSR Weekly Epidemiology and Surveillance Bulletin (National Public Health Institute of Liberia, 2016).

¹¹ Regulations by the Minister of Health (the “Minister”) Governing the Control and Abatement of the Spread and Eradication of the Ebola Virus Disease (EVD) in Liberia, hereinafter, The Anti-Ebola Regulation (MoHSW/R-001/2014). See, sections 1, 2, 3, 4 and 7.

CONCLUSION

The lack of research and access to resource presented a real challenge in writing this chapter on the Liberian Public Health System. Notwithstanding the limited resources available on public health in Liberia, the chapter demonstrates over and again that the Liberian public health system is not only ad hoc but in dire need of reform, especially regarding access to care in the rural communities. The Government of Liberia's ongoing struggle to develop and maintain functioning health facilities, supply qualified healthcare workers and allocate adequate budgetary funding for public health is a clear reflection of the extremely poor public health system in the country.

Irrespective of some progress made with establishing relevant public health law, policy, strategic plans, institutions and preventive measures after the Ebola Virus Disease epidemic; Liberia still has a long way to go in implementing a resilient and sustainable public health system for the well-being of all Liberians, including vulnerable populations such as women, children and people with disability. It can only be hoped that the newly established Ministry of Health, Ministry of Gender, Children and Social Protection and the National Public Health Institution will combine forces to augment the population health of Liberia within a timely fashion.

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Chapter 529

OPIOID CRISIS: STATUS OF PUBLIC HEALTH EMERGENCY AUTHORITIES*

United States Government Accountability Office

Opioid misuse and related deaths are a serious, growing public health problem in the United States. According to the Department of Health and Human Services' (HHS) Centers for Disease Control and Prevention (CDC), over 42,000 people died from opioid-involved overdoses in 2016. The federal government has launched a number of initiatives to combat the opioid crisis, and HHS issued a five-point Opioid Strategy in April 2017 to guide the department's efforts.¹ We and others have reported on ongoing federal actions to address opioid issues.²

On October 26, 2017, the Acting Secretary of HHS declared the opioid crisis a public health emergency under section 319 of the Public Health Service Act and the declaration was renewed in January, April, and July 2018.³ A public health emergency triggers the availability of certain authorities under federal law that enable federal agencies to take actions such as accessing the Public Health Emergency Fund, temporarily reassigning certain state and local

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¹ The Opioid Strategy's five priority areas are: 1) better access to prevention, treatment, and recovery services; 2) better data on the epidemic; 3) better pain management; 4) better targeting of overdose-reversing drugs; and 5) better research on pain and addiction.

² See, for example, GAO, Prescription Opioids: Medicare Needs Better Information to Reduce the Risk of Harm to Beneficiaries, GAO-18-585T (Washington D.C.: May 29, 2018); Illicit Opioids: While Greater Attention Given to Combating Synthetic Opioids, Agencies Need to Better Assess their Efforts, GAO-18-205 (Washington, D.C.: March 29, 2018); Opioid Use Disorders: HHS Needs Measures to Assess the Effectiveness of Efforts to Expand Access to Medication-Assisted Treatment, GAO-18-44 (Washington, D.C.: Oct. 31, 2017); Newborn Health: Federal Action Needed to Address Neonatal Abstinence Syndrome, GAO-18-32 (Washington D.C.: Oct. 4, 2017); and Prescription Opioids: Medicare Needs to Expand Oversight Efforts to Reduce the Risk of Harm, GAO-18-15, (Washington D.C.: Oct. 6, 2017).

³ A declaration is in effect until the Secretary declares the emergency no longer exists, or 90 days after the declaration, whichever occurs first. A declaration that expires may be renewed by the Secretary. The then-Acting Secretary made the determination for the October 2017 public health emergency declaration for the opioid crisis and the January 2018 renewal of this declaration. The current Secretary made the determination for the April and July 2018 renewals of the declaration.

personnel, and waiving certain administrative requirements. These authorities may allow the federal government to increase support to and reduce administrative burdens on state and local governments and federal grantees affected by or responding to the public health emergency. They may also supplement other federal efforts that are ongoing to address the emergency. While the Secretary of HHS may declare a public health emergency, the use of some authorities requires coordination with other agencies, including the Department of Justice (Justice) and the Department of Labor (Labor). The October 2017 declaration was the first time that a public health emergency declaration was made for the opioid crisis. Public health emergencies have previously been declared for infectious disease outbreaks, such as the Zika and the H1N1 influenza virus outbreaks, as well as for hurricanes and other weather events.⁴

You asked us to review the decision to declare a public health emergency for the opioid crisis, and what actions have been taken under the declaration. In this report, we describe:

1. the factors HHS indicated as affecting its decision to declare and renew the public health emergency for the opioid crisis, and
2. the public health emergency authorities the federal government has used to address the opioid crisis.

To address these objectives, we reviewed relevant HHS statements and decision documents and interviewed HHS officials about the basis for declaring a public health emergency for the opioid crisis. These officials included those from the Substance Abuse and Mental Health Services Administration (SAMHSA), the agency within HHS that leads public health efforts focused on reducing the negative effects of substance abuse and mental illness. In addition, we reviewed the Public Health Service Act and related statutory and regulatory provisions to identify the authorities that become available during a public health emergency. We also reviewed HHS, Labor, and Justice documents and interviewed agency officials to determine which of the available authorities have been used and their status, including reasons that some authorities were not used. In addition, we reviewed information from HHS about other recently declared federal public health emergencies where these authorities were last used. This report focuses on public health emergency authorities and does not examine other federal efforts to combat the opioid crisis.

We conducted this performance audit from March 2018 to September 2018 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

⁴ See GAO, *Emerging Infectious Diseases: Actions Needed to Address the Challenges of Responding to Zika Virus Disease Outbreaks*, GAO-17-445 (Washington, D.C.: May 23, 2017) and *Influenza Pandemic: Lessons from the H1N1 Pandemic Should be Incorporated into Future Planning*, GAO-11-632 (Washington, D.C.: June 27, 2011).

RESULTS IN BRIEF

Increasing rates of opioid-related deaths and opioid use disorder were the primary factors for the declaration of a public health emergency for the opioid crisis on October 26, 2017, and for its renewal on January 19, 2018, according to HHS officials. Officials cited still-increasing rates of opioid-related deaths in 2017 for the declaration's renewal on April 20, 2018, as well as the consideration that a nationwide public health emergency underscores the urgency of ongoing federal, state, and local efforts to combat the opioid crisis. More recently in July, HHS again renewed the declaration due to the continued consequences of the opioid crisis.

Since declaring the opioid crisis a public health emergency, the federal government has used three available authorities. According to HHS officials, one of them allowed HHS to quickly field a survey of more than 13,000 providers to assess prescribing trends for a medication used to treat opioid use disorder and any barriers to prescribing it. HHS used another authority to waive the public notice period for approval of two state Medicaid demonstration projects related to substance use disorder treatment, which is intended to speed up implementation of these projects. HHS also took steps to expedite support for research on opioid use disorder treatments and to disseminate information on opioid misuse and addiction, as required by another authority. In addition to these 3 authorities, we identified 14 other authorities that became available as a result of the public health emergency and have not been used.⁵ According to HHS officials, these additional authorities have not been used for a variety of reasons: for example, HHS officials determined that many are not relevant to the circumstances presented by the opioid crisis. Officials told us they will continue to review the authorities as the opioid crisis evolves and in the context of HHS's other efforts to address the opioid crisis.

BACKGROUND

Opioids, such as hydrocodone, oxycodone, morphine, and methadone, can be prescribed to treat both acute and chronic pain. Because many opioids have a high potential for abuse and may lead to severe psychological or physical dependence, many of them are classified as Schedule II drugs under the Controlled Substances Act.⁶ The misuse of opioids has been associated with serious consequences, including addiction, overdose, and death. Recently, there has been a rise in opioid use in the United States involving both the misuse of prescription drugs and illicit opioids, such as heroin.

The federal government has taken certain actions to address the crisis. For example, we reported on efforts by HHS to expand access to medication-assisted treatment for those who

⁵ We identified authorities that become available as a result of a public health emergency declaration under section 319 of the Public Health Service Act, as well as other authorities that become available when there is a public health emergency, but that do not require a declaration. For the purposes of this report, we refer to these authorities collectively as authorities triggered by a public health emergency.

⁶ Under the Controlled Substance Act, which was enacted in 1970, drugs are classified as controlled substances and placed into one of five schedules based on their currently accepted medical use, potential for abuse, and risk of dependence.

misuse or are addicted to opioids—a condition known as opioid use disorder.⁷ Medication-assisted treatment, which combines behavioral therapy and the use of certain medications (methadone, buprenorphine, and naltrexone), has been shown to reduce opioid use and to increase treatment retention compared with abstinence-based treatment, where patients are treated without medication.⁸ We also recently reported on federal efforts to combat synthetic opioids, such as by limiting their availability and expanding prevention programs and treatment options.⁹ Synthetic opioids, including fentanyl, often have very high potency that can increase the risk of overdose.

In March 2017, the President issued Executive Order 13784 establishing a commission to study the scope and effectiveness of the federal response to drug addiction and the opioid crisis.¹⁰ The President's Commission on Combating Addiction and the Opioid Crisis issued a final report in November 2017, making a number of recommendations to the President to enhance the federal government's response to the opioid problem. Further, on October 26, 2017, the President directed the Acting Secretary of HHS to declare the opioid crisis to be a public health emergency.

Under section 319 of the Public Health Service Act, the Secretary of HHS may declare a public health emergency if the Secretary determines, in consultation with other public health officials as may be necessary, that (1) a disease or disorder presents a public health emergency; or (2) a public health emergency, including significant outbreaks of infectious disease or bioterrorist attacks, otherwise exists.¹¹ Section 319 does not specify any additional requirements or procedures that the Secretary must follow to declare a public health emergency. Under section 319, the Secretary of HHS can take appropriate action in response to a public health emergency, including making grants, providing awards for expenses, entering into contracts, and conducting and supporting investigations into the cause, treatment, or prevention of the underlying disease or disorder. In addition, section 319 includes specific authorities that can be used for such things as extending deadlines for any report required to be submitted under any law administered by HHS and temporary reassignment of state and local personnel whose positions are funded, at least in part, under programs authorized under the Public Health Service Act. Public health emergency declarations also trigger the availability of other authorities outside of section 319. In addition, other authorities may become available when there is a public health emergency but do not require a declaration. The use of these authorities in previous public health emergencies has varied, and some authorities have not been used. Enclosure I lists the authorities available when there is a public health emergency.

⁷ GAO-18-44.

⁸ Methadone and buprenorphine suppress withdrawal symptoms in detoxification therapy and control the craving for opioids in maintenance therapy. Both drugs are opioids that activate opioid receptors and carry risks of misuse. Both drugs can also be used to treat pain. Naltrexone is used for relapse prevention because it suppresses the euphoric effects of opioids, and it carries no known risk of misuse.

⁹ GAO-18-205.

¹⁰ Executive Order No. 13784 of March 29, 2017, 82 Fed. Reg. 16,283 (Apr. 3, 2017).

¹¹ Distinct from a public health emergency declaration are two declarations available to the President under the Robert T. Stafford Disaster Relief and Emergency Assistance Act (Stafford Act): a major disaster declaration and an emergency declaration. The President can issue either type of declaration under the Stafford Act at the request of the governor of an affected state or a chief executive of an affected Indian Tribe. The President may also declare a national emergency under the National Emergencies Act, which authorizes the President to activate existing emergency authorities in other statutes. The President did not make these declarations for the opioid crisis.

The federal government has declared public health emergencies for infectious disease outbreaks, such as the Zika and the H1N1 influenza virus outbreaks, and for hurricanes, such as Hurricane Maria in Puerto Rico, and for other weather-related events. Enclosure II lists other recent public health emergencies.

HHS Officials Cited Increasing Rates of Opioid-Related Deaths and Opioid Use Disorder as Primary Factors for Declaring and Renewing the Public Health Emergency

According to HHS officials, the primary factors for declaring and renewing the public health emergency for the opioid crisis were the increasing rates of opioid-related overdose deaths and opioid use disorder, especially the increase in overdoses as a result of synthetic opioids such as fentanyl.¹² The public health emergency for the opioid crisis was first declared on October 26, 2017, by the Acting Secretary of HHS, who also renewed the declaration in January 2018.¹³ In April 2018, SAMHSA recommended that the Secretary of HHS again renew the public health emergency declaration for the opioid crisis, noting specifically the provisional 2017 estimates from CDC indicating that opioid-related overdose deaths continued to increase in 2017.¹⁴ In addition, SAMHSA's April recommendation cited a March 2018 CDC report stating that emergency department visits due to opioid overdoses—a measure of opioid-related morbidity—had increased significantly in the past year, increasing almost 30 percent from the third quarter (July through September) of 2016 to the third quarter of 2017.¹⁵ In particular, among approximately 91 million emergency department visits captured from July 2016 through September 2017 in the National Syndromic Surveillance Program, a total of 142,557 (15.7 per 10,000 visits) were suspected opioid overdoses.¹⁶ HHS officials told us that in addition to CDC's provisional estimates for opioid-related mortality and the emergency department visit data on suspected opioid-related overdoses, HHS relied on multiple other data sources to inform the public health burden of the opioid crisis.¹⁷

SAMHSA officials noted that the existence of a nationwide public health emergency has spurred additional action across HHS and underscores the urgency of federal, state, and local efforts to combat the opioid crisis, many of which were ongoing prior to the declaration, such as efforts to expand access to medication-assisted treatment. Further, SAMHSA stated that

¹² Synthetic opioids are man-made opioids, such as fentanyl and fentanyl analogues. An analogue is a drug molecule that shares structural similarities with the original compound. It may also share pharmacological similarities. For more information about synthetic opioids and federal agencies' efforts to combat them, see GAO, *Illicit Opioids: Office of National Drug Control Policy and Other Agencies Need to Better Assess Strategic Efforts*, GAO-18-569T (Washington D.C.: May 17, 2018), and GAO-18-205.

¹³ This renewal was declared on January 19, 2018, and effective January 24, 2018.

¹⁴ This renewal was declared on April 20, 2018, and effective April 24, 2018.

¹⁵ Vivolo-Kantor, A.M., Seth, P., Gladden, R.M., et al. "Vital Signs: Trends in Emergency Department Visits for Suspected Opioid Overdoses — United States, July 2016–September 2017." *Morbidity and Mortality Weekly Report* vol. 67:279–285 (2018).

¹⁶ The National Syndromic Surveillance Program promotes the development of a syndromic surveillance system for the timely exchange of syndromic data. Syndromic surveillance uses syndromic data and statistical tools to detect and monitor unusual activity for further public health investigation or response. Syndromic data include patient encounter data from emergency departments, urgent care, ambulatory care, and inpatient healthcare settings, as well as pharmacy and laboratory data. These data are monitored in near real-time as potential indicators of an event, a disease, or an outbreak of public health significance.

¹⁷ The additional data included, among others, data on opioid misuse and use disorder from SAMHSA's National Survey on Drug Use and Health, rising rates of injection drug use among treatment admissions reported into SAMHSA's Treatment Episode Data Set, the Agency for Healthcare Research and Quality's Healthcare Costs and Utilization Project hospitalization and emergency department data, and CDC's data on rising rates of hepatitis C.

renewing the public health emergency declaration provided HHS additional time to consider how the public health emergency authorities might be used to supplement ongoing federal efforts. More recently, the Secretary of HHS again renewed the declaration on July 19, 2018, and stated that the renewal was due to the continued consequences of the opioid crisis.¹⁸

The Federal Government Has Used Three Public Health Emergency Authorities to Help Address the Opioid Crisis

Since declaring the opioid crisis a public health emergency, the federal government has used three public health emergency authorities to help address the crisis, as of July 2018. Specifically, these are:

- *Waiver of Paperwork Reduction Act requirements.* This authority allows the Secretary of HHS to waive requirements under the Paperwork Reduction Act for the voluntary collection of information when necessary to prepare for and respond to a public health emergency.¹⁹ HHS officials told us that, by using this authority, they were quickly able to field a critical survey of more than 13,000 providers to assess prescribing trends of a medication, buprenorphine, used to treat opioid use disorder and any barriers to prescribing it. According to officials, they were able to streamline the survey review process, including bypassing a review by the Office of Management and Budget that is typically required, which allowed HHS officials to deploy the survey in March 2018 and collect more current data in a much shorter timeframe than they would have without the authority. As of April 2018, officials reported receiving over 5,000 responses. Officials told us the results of the survey will inform policy and programmatic decisions related to increasing access to substance abuse treatment.
- *Waiver of public notice procedures for section 1115 Medicaid demonstrations.* This authority allows HHS's Centers for Medicare & Medicaid Services (CMS) to waive federal and state public notice procedures to expedite a decision on a proposed Medicaid section 1115 demonstration project that addresses a public health emergency.²⁰ These demonstrations allow states to test and evaluate new approaches for delivering Medicaid services.²¹ Generally, after receipt of an application from a state to begin or extend a demonstration, CMS must provide for a 30-day public comment period and wait at least 45 days before making a final decision.²² HHS

¹⁸ This renewal was declared on July 19, 2018, and effective July 23, 2018.

¹⁹ The Paperwork Reduction Act was enacted, in part, to minimize the burden for individuals, small businesses, and others resulting from the collection of information by or for the federal government. Among other things, the Act requires federal agencies to justify any collection of information from the public by establishing the need for and intended use of the information, estimating the burden that the collection will impose on the respondents, and showing that the collection is the least burdensome way to gather the information. Paperwork Reduction Act of 1995, Pub. L. No. 104-13, 109 Stat. 163 (1995).

²⁰ Medicaid is a joint federal-state program that finances health care coverage for low-income and medically needy populations. Section 1115(a) of the Social Security Act allows the Secretary of HHS to waive certain federal Medicaid requirements and allow federal funding for items and services that would not otherwise be eligible for federal funding for experimental, pilot, or demonstration projects that, in the Secretary's judgment, are likely to promote Medicaid objectives. The Secretary has delegated the approval and administration of Medicaid section 1115 demonstrations to CMS.

²¹ GAO, *Medicaid Demonstrations: Evaluations Yielded Limited Results, Underscoring Need for Changes to Federal Policies and Procedures*, GAO-18-220, (Washington, D.C.: Jan. 19, 2018).

²² See 42 C.F.R. §§ 431.416(b) and (e) (2017).

officials reported that they waived the public notice requirements for two states—Louisiana and New Hampshire in February 2018 and July 2018, respectively—for the submission of demonstration applications related to substance use disorder treatment.

- *Expedited support for research.* When a public health emergency is in effect, the Secretary of HHS, acting through the Director of the National Institutes of Health (NIH), is required under one of the authorities to take steps to expedite support for research on the disease or disorder underlying the public health emergency and disseminate information on the cause, prevention, and treatment of the disease or disorder.²³ In December 2017, NIH announced expedited procedures for research funding on medication development for opioid use disorder and overdoses. In addition, according to HHS officials, NIH is disseminating information on opioid misuse and addiction through a website about the research goals and funding opportunities of its Helping to End Addiction Long-term (HEAL) initiative, launched in April 2018, and by updating related publications.

In addition to these 3 authorities, we identified 14 other authorities available under a public health emergency. As of July 2018, these 14 authorities have not been used under the public health emergency declaration for the opioid crisis. HHS officials provided reasons for why they were not using these authorities, and we categorized these reasons in table 1 below. (See enclosure I for a list of the 17 available authorities, the source and description of each authority, the reasons agency officials provided for why some authorities were not used during the public health emergency for the opioid crisis, and the last public health emergency declaration during which agency officials identified using the authority.)

Table 1. Reasons cited by agency officials that certain public health emergency authorities have not been used for the opioid crisis, as of July 2018

Reason authorities were not used	Number of authorities
Officials determined authority was not relevant to the opioid crisis; more appropriate to a short, time-limited public health issue or when infrastructure is damaged	5
Officials reported that no eligible entities, such as states, requested the use of this authority	3
Officials determined that other authorities could be used, rather than public health emergency authorities	3a
Officials expressed concerns that use of authority could increase the risk of diversion of medications for improper use	2a
Officials determined authority was not applicable because dependent upon use of the Public Health Emergency Fund, which has not been used	1
Officials determined that the statutory conditions for using the authority have not been met	1

Source: GAO analysis of information from Department of Health and Human Services, Department of Justice, and Department of Labor. | GAO-18-685R.

^a One of the authorities is listed under two reasons.

²³ Health Research Extension Act of 1985, Pub. L. No. 99-158, 99 Stat. 820 (codified as amended at 42 U.S.C. § 289c).

Examples of the authorities, and the reasons that agency officials provided for why they have not been used, include the following:

- **Access to National Dislocated Worker Grants.** This authority allows the Secretary of Labor to award grants to states or other local areas that have been impacted by emergencies, disasters, or major economic dislocations. These grants provide funding to create temporary employment opportunities to assist with clean-up and recovery efforts, among other things. Labor officials reported that no eligible entities have submitted applications for these grants during the public health emergency for the opioid crisis, as of July 2018.²⁴ Officials noted that a number of factors might have affected why potential grantees have not submitted applications for these grants, including that another grant option is available—the National Health Emergency Dislocated Worker Demonstration Grants—which was established to help communities address the economic and workforce-related impacts of the opioid crisis.²⁵
- **Application extensions and waiver of requirements for block grant funding.** This authority allows the Secretary of HHS to provide an application extension for or waive compliance with requirements for mental health and substance abuse block grant funding during a public health emergency.²⁶ HHS officials told us this provision is not relevant to the public health emergency for the opioid crisis, as it is generally used when a local or state health department building is destroyed by a natural disaster, such as an earthquake or hurricane, and grant data is lost.²⁷
- **Modifications to the practice of telemedicine.** During a public health emergency, this authority allows the Secretary of HHS, with concurrence of the Attorney General, to reduce restrictions on the use of telemedicine when prescribing controlled substances, including those used in the treatment of opioid use disorder.²⁸ HHS officials stated that they have not used this authority because federal law provides for other circumstances under which these restrictions do not apply, thereby allowing the use of telemedicine. Officials also expressed concerns about increasing the risk of diversion of medications for improper use and maintaining high quality of care.²⁹
- **Access to the Public Health Emergency Fund.** The Secretary of HHS may access the Public Health Emergency Fund to take action to respond to a public health emergency, including making grants, providing awards for expenses, and entering

²⁴ The National Dislocated Worker Grant authority was last used in September 2016 while the public health emergency declaration for the Zika virus in Puerto Rico was in effect. On September 28, 2016, Labor awarded a \$6 million National Dislocated Worker Grant to the Puerto Rico Department of Labor and Human Resources, to employ temporary workers to assist with recovery efforts to address the Zika outbreak.

²⁵ In July 2018, Labor announced more than \$22 million in National Health Emergency Dislocated Worker Demonstration Grant funding to six state grantees. The grants will be used to provide reemployment services for individuals impacted by the health and economic effects of widespread opioid use, addiction, and overdose.

²⁶ This authority specifically applies to grants for assistance in transition from homelessness, grants for community mental health services, and grants for the prevention and treatment of substance abuse during a public health emergency.

²⁷ As of July 2018, HHS officials reported that they have never used this authority during a public health emergency.

²⁸ Telemedicine generally refers to the use of electronic information and telecommunications technologies to support long-distance health care through technologies such as videoconferencing.

²⁹ As of July 2018, HHS officials told us that they have never used this authority during a public health emergency.

into contracts for conducting and supporting investigations into the cause, treatment, or prevention of the disease or disorder presenting a public health emergency. According to documents provided by HHS, the Public Health Emergency Fund has a balance of about \$57,000. According to HHS officials, HHS has not requested that Congress appropriate money to the Fund for the current public health emergency and, instead, has used other sources of federal funds to address the opioid crisis.³⁰

HHS officials told us they will continue to assess the relevancy of these and other authorities as the opioid overuse issue evolves across the country, in the context of HHS's other efforts to address the opioid crisis.

Agency Comments

We provided a draft of this report to HHS, Labor, and Justice for comment. HHS and Labor provided technical comments, which we incorporated as appropriate. Justice told us that they did not have any comments.

* * *

As agreed with your offices, unless you publicly announce the contents of this report earlier, we plan no further distribution until 30 days from the report date. At that time, we will send copies of this report to the Secretary of Health and Human Services, the Secretary of Labor, the Attorney General, and appropriate congressional committees. In addition, the report will be available at no charge on the GAO website at <http://www.gao.gov>.

If you or your staff have any questions concerning this report, please contact me at (202) 512- 7114 or DeniganMacauleyM@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this report. GAO staff who made key contributions to this report were Will Simerl (Assistant Director), Natalie Herzog (Analyst-in-Charge), Amy Andresen, Kaitlin M. Farquharson, Laurie Pachter, and Carmen Rivera-Lowitt.

Sincerely yours,



Mary Denigan-Macauley
Acting Director,
Health Care

Enclosure(s) – 2

³⁰ HHS officials reported that the Public Health Emergency Fund was last used in 1993 for the Hantavirus outbreak. The Public Health Emergency Fund, established in 1983, is available to the Secretary of HHS without fiscal year limitation to take appropriate action in response to a public health emergency. See Pub. L. No. 98-49, 97 Stat. 245 (1983).

List of Requesters

The Honorable Patty Murray
Ranking Member
Committee on Health, Education, Labor, and Pension
United States Senate

The Honorable Tammy Baldwin
United States Senate

The Honorable Sherrod Brown
United States Senate

The Honorable Richard Blumenthal
United States Senate

The Honorable Cory A. Booker
United States Senate

The Honorable Robert P. Casey, Jr.
United States Senate

The Honorable Joe Donnelly
United States Senate

The Honorable Tammy Duckworth
United States Senate

The Honorable Dianne Feinstein
United States Senate

The Honorable Kirsten Gillibrand
United States Senate

The Honorable Margaret Wood Hassan
United States Senate

The Honorable Tim Kaine
United States Senate

The Honorable Edward J. Markey
United States Senate

The Honorable Bill Nelson
United States Senate

The Honorable Brian Schatz
United States Senate

The Honorable Jeanne Shaheen United
States Senate

The Honorable Debbie Stabenow
United States Senate

The Honorable Elizabeth Warren
United States Senate

The Honorable Sheldon Whitehouse
United States Senate

Enclosure I: Public Health Emergency Authorities

A public health emergency triggers the availability of certain authorities under federal law. These authorities may allow the federal government to increase support to and reduce administrative burdens on state and local governments and federal grantees affected by or responding to the public health emergency. We identified authorities that become available as a result of a public health emergency declaration under section 319 of the Public Health Service Act, as well as other authorities that become available when there is a public health emergency but do not require a declaration. Table 2 lists the public health emergency authorities; the source of the authority; a description of the authority; the reason an authority was not used during the public health emergency for the opioid crisis as of July 2018, according to Department of Health and Human Services and Department of Labor officials; and the last public health emergency declaration during which agency officials identified using the authority.

Table 2. List of federal public health emergency authorities and description of their use under the opioid crisis public health declaration and other public health emergency declarations

Authority	Description
Funding-related authorities	
Access to funds in the Public Health Emergency Fund	•Authority: Pub. L. No. 98-49 (1983) (codified as amended at 42 U.S.C. § 247d(a) and (b)) •Description: This provision allows the Secretary of Health and Human Services to take appropriate action to respond to a public health emergency, including by making grants, providing awards for expenses, entering into contracts, and conducting and supporting investigations into the cause, treatment, or prevention of the disease or disorder. The Secretary may access the Public Health Emergency Fund to carry out these functions if the Secretary has declared a public health emergency. Appropriations made to the Public Health Emergency Fund are available to the Secretary without fiscal year limitation. Such funds may be used to supplement and not supplant other federal, state, and local public funds.

Table 2. (Continued)

Authority	Description
Funding-related authorities	
	•Reason not used for opioid public health emergency: Department of Health and Human Services (HHS) officials determined that other authorities could be used, rather than public health emergency authorities. HHS also provided evidence that the Public Health Emergency Fund currently contains approximately \$57,000. •Last use during a public health emergency: According to. HHS officials, this authority was last used to respond to an outbreak of Hantavirus in 1993
Supplies and services in lieu of award funds	•Authority: Public Health Security and Bioterrorism Preparedness and Response Act of 2002, Pub. L. No. 107-188, § 110 (codified at 42 U.S.C. § 247d-7c) •Description: This provision allows the Secretary of HHS to provide supplies, equipment, services, and HHS personnel to help an award recipient, at the recipient's request, carry out the purposes of the award. The Secretary is required to reduce award payments by an amount equal to the value of the supplies, equipment, services, and personnel. •Reason not used for opioid public health emergency: HHS officials determined this authority is not applicable because it is dependent upon the use of the Public Health Emergency Fund. Specifically, this authority applies to awards under 42 U.S.C. §§ 247d through 247d-7b and 247d-7d. •Last use during a public health emergency: According to HHS officials, this authority has never been used for awards from the Public Health Emergency Fund.
Waiver of certain Ryan White HIV/AIDS program requirements	•Authority: Ryan White HIV/AIDS Treatment Modernization Act of 2006, Pub. L. No. 109-415, § 501 (codified at 42 U.S.C. § 300ff-83) •Description: This provision allows the Secretary of HHS to waive requirements under Title XXVI of the Public Health Service Act, the Ryan White HIV/AIDS Program, to improve the health and safety of those receiving care under the Program and the general public in an area and during a period in which there exists: (1) a public health emergency declared by the Secretary under section 319 of the Public Health Service Act or (2) an emergency or disaster declared by the President under the Robert T. Stafford Disaster Relief and Emergency Assistance Act or the National Emergencies Act. The Secretary may not spend more than five percent of supplemental funds available under each of the Parts A and B to ensure access to care during a public health emergency. •Reason not used for opioid public health emergency: HHS officials reported that no eligible entities, such as states, requested the use of this authority. •Last use during a public health emergency: This authority was last used during the public health emergency declared for Hurricanes Irma and Maria in September 2017.
Access to National Dislocated Worker Grants	•Authority: Workforce Innovation and Opportunity Act, Pub. L. No. 113-128, § 170 (2014) (codified at 29 U.S.C. § 3225) •Description: This provision allows the Secretary of the Department of Labor (Labor) to award grants to eligible entities to provide employment and training assistance to workers in emergency or disaster areas and to those affected by major economic dislocations. Eligible entities may include states and entities capable of responding to the emergency, disaster, or dislocation. Eligible entities may apply for grants in the event of (1) an emergency or major disaster, as defined in the Robert T. Stafford Disaster Relief and Emergency Assistance Act, or (2) an emergency or disaster of national significance that could result in a potentially large loss of employment, as declared by the chief official of a federal agency with jurisdiction over the federal response to the emergency or disaster. •Reason not used for opioid public health emergency: Labor officials reported that no eligible entities, such as states, requested the use of this authority. •Last use during a public health emergency: This authority was last used during the public health emergency declared for the Zika virus outbreak in August 2016.
Medication-related authorities	
Modifications to the practice of telemedicine	•Authority: Ryan Haight Online Pharmacy Consumer Protection Act of 2008, Pub. L. No. 110-425, § 3 (codified at 21 U.S.C. § 802(54)(D)) •Description: The Ryan Haight Online Pharmacy Consumer Protection Act of 2008 generally requires a health care practitioner to have conducted at least one in-person exam prior to prescribing a controlled substance. This provision allows the Secretary of HHS, with the concurrence of the Attorney General, to designate patients located in certain areas and

Authority	Description
Funding-related authorities	
	controlled substances that are excepted from the in-person exam requirement during a public health emergency declared by the Secretary under section 319 of the Public Health Service Act. •Reason not used for opioid public health emergency: HHS determined that other authorities could be used, rather than public health emergency authorities and HHS officials expressed concerns that use of authority could increase the risk of diversion of medications for improper use. •Last use during a public health emergency: According to HHS officials, this authority has never been used.
Exemption from certain drug distribution supply chain requirements	•Authority: Drug Quality and Security Act, Pub. L. No. 113-54, § 202 (2013) (codified at 21 U.S.C. §§ 353(e)(4)(C), 360eee, and 360eee-1(a)(3)) •Description: The Drug Supply Chain Security Act, enacted as Title II of the Drug Quality and Security Act, generally establishes requirements for drug manufacturers, repackagers, wholesale distributors, and dispensers to facilitate the tracing of prescription drugs through the supply chain. Upon a public health emergency declaration under section 319 of the Public Health Service Act, prescription drugs distributed for the public health emergency are excluded from the Act's product tracing and wholesale distribution requirements, including those pertaining to wholesale distribution. In addition, section 360eee-1(a)(3) requires the Secretary of HHS to establish, by guidance, a process for requesting a waiver from these and other requirements related to product tracing and wholesale distribution for emergency medical reasons, such as a public health emergency declaration under section 319 of the Public Health Service Act. •Reason not used for opioid public health emergency: HHS officials expressed concerns that use of authority could increase the risk of diversion of medications for improper use. •Last use during a public health emergency: According to HHS officials, certain Drug Quality and Security Act emergency authorities were last used during the public health emergency declared for Hurricane Maria in September 2017.
Adjustment of Medicare reimbursement for certain Part B drugs	•Authority: Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub.L. No. 108-173, § 303 (codified at 42 U.S.C. § 1395w-3a(e)) •Description: This provision allows the Secretary of HHS to pay the wholesale acquisition cost or other reasonable measure of price instead of the manufacturer's average sales price for a Medicare Part B-covered drug during a public health emergency declaration under section 319 of the Public Health Service Act. These drugs are typically administered under a physician's supervision and include injectable drugs, some oral cancer drugs, and drugs infused or inhaled through durable medical equipment. To exercise this authority, there must be a documented inability to access a drug or biological and a concomitant price increase that is not reflected in the manufacturer's average sales price for one or more quarters. •Reason not used for opioid public health emergency: HHS determined that the statutory requirements for an alternative payment methodology have not been met. •Last use during a public health emergency: According to HHS officials, this authority has never been used.
Research-related authorities	
Research related to public health emergencies ^a	•Authority: Health Research Extension Act of 1985, Pub. L. No. 99-158, § 2 (codified as amended at 42 U.S.C. § 289c) •Description: If the Secretary of HHS determines that a disease or disorder constitutes a public health emergency, this provision requires the Secretary of HHS, acting through the Director of NIH, to (1) expedite review by advisory councils and peer review groups of applications for grant research on the disease or disorder; (2) exercise authority to waive advertising requirements for contract proposals for research on the disease or disorder; and (3) disseminate information to health professionals and the public on the cause, prevention, and treatment of the disease or disorder that has been developed
	through this research. The Secretary may also provide administrative supplemental increases in existing grants and contracts to support new research relevant to the disease or disorder. •Reason not used for opioid public health emergency: Not applicable, because the authority was used. •Last use during a public health emergency: This authority was last used during the public health emergency declared for the opioid crisis in October 2017.

Table 2. (Continued)

Authority	Description
Funding-related authorities	
Temporary reassignment of state and local personnel	•Authority: Pandemic and All-Hazards Preparedness Reauthorization Act of 2013, Pub. L. No. 113-5, § 201 (codified at 42 U.S.C. § 247d(e)) •Description: This provision allows the Secretary of HHS to authorize the temporary reassignment of federally-funded state and local public health department or agency personnel funded under programs authorized under the Public Health Service Act, for purposes of addressing a public health emergency in a state or tribe. The reassignment must occur at the request of a state governor or tribal organization and may not exceed the period of a public health emergency declaration under section 319 of the Public Health Service Act. •Reason not used for opioid public health emergency: HHS officials reported that no eligible entities, such as states, requested the use of this authority. •Last use during a public health emergency: According to HHS officials, this authority has never been used.
Temporary (up to one year or the duration of the emergency) appointments of personnel	•Authority: 5 C.F.R. § 213.3102(i)(3) (2017) •Description: Under this authority, the Secretary of HHS is allowed to make temporary (up to one year or the duration of the emergency) appointments of personnel to positions that directly respond to a public health emergency when the urgency of filling positions prohibits examining applicants through the competitive process. •Reason not used for opioid public health emergency: HHS officials determined that other authorities could be used, rather than public health emergency authorities. •Last use during a public health emergency: This authority was last used during the public health emergency declared for Hurricanes Irma and Harvey in September 2017.
Activation of the National Disaster Medical System (NDMS) ^a	•Authority: Public Health Security and Bioterrorism Preparedness Response Act of 2002, Pub. L. No. 107-188, § 102 (codified as amended at 42 U.S.C. § 300hh-11(a)(3)) •Description: NDMS is a coordinated effort between federal, state, and private entities to respond to public health emergencies. This provision allows the Secretary of HHS to activate NDMS to provide health services, health-related social services, other appropriate human services, and appropriate auxiliary services to respond to the needs of victims of a public health emergency, whether or not a public health emergency declaration under section 319 of the Public Health Service Act has been made. HHS may also activate NDMS in a location that is at-risk of a public health emergency. •Reason not used for opioid public health emergency: HHS officials determined not relevant to the opioid crisis; more appropriate to a short, time-limited public health issue or when infrastructure is damaged. •Last use during a public health emergency: This authority was last used during the public health emergency declared for Hurricanes Irma and Maria in September 2017.
Deployment of the Volunteer Medical Reserve Corps ^a	•Authority: Pandemic and All-Hazards Preparedness Act, Pub. L. No. 109-417, § 303 (2006) (codified at 42 U.S.C. § 300hh-15(e)) •Description: The Secretary is required to build on state, local, and tribal programs to establish and maintain a Volunteer Medical Reserve Corps to provide an adequate supply of volunteers during a public health emergency. This provision allows the Secretary of HHS to activate and deploy willing members of the Volunteer Medical Reserve Corps to areas of need during a public health emergency, taking into consideration the public health and medical expertise required, with the concurrence of the state, local, or tribal officials from the area where the members reside. •Reason not used for opioid public health emergency: HHS officials determined not relevant to the opioid crisis; more appropriate to a short, time-limited public health issue or when infrastructure is damaged. •Last use during a public health emergency: HHS officials did not provide information on when this authority was last used.

Authority	Description
Funding-related authorities	
Deployment of Commissioned Corps Officers ^a	•Authority: Pandemic and All-Hazards Preparedness Act, Pub. L. No. 109-417, § 206(c)(1) (2006) (codified at 42 U.S.C. § 215(e)) •Description: This provision allows the Secretary of HHS to deploy any Commissioned Corps officer to an entity outside of HHS for service under the Secretary's direction in response to an urgent or emergency public health care need. For purposes of this provision, an "urgent or emergency public health care need" includes a health care need arising as a result of (1) a national emergency declared by the President under the National Emergencies Act; (2) an emergency or major disaster declared by the President under the Robert T. Stafford Disaster Relief and Emergency Assistance Act; (3) a public health emergency declared by the Secretary under section 319 of the Public Health Service Act; or (4) any emergency that, in the Secretary's judgment, is appropriate for deployment. •Reason not used for opioid public health emergency: HHS officials determined not relevant to the opioid crisis; more appropriate to a short, time-limited public health issue or when infrastructure is damaged. •Last use during a public health emergency: This authority was last used during the public health emergency declared for Hurricanes Irma and Maria in September 2017.
Paperwork-related authorities	
Waiver of requirements under the Paperwork Reduction Act	•Authority: 21st Century Cures Act, Pub. L. No. 114-255, § 3087 (2016) (codified at 42 U.S.C. § 247d(f)) •Description: This provision allows the Secretary of HHS to waive requirements under the Paperwork Reduction Act for voluntary collection of information when necessary to prepare for and respond to a public health emergency. To exercise this authority, the Secretary must determine (1) that the criteria for a public health emergency have been met or that a disease or disorder is significantly likely to become a public health emergency; and (2) that the circumstances of the existing or potential emergency necessitate a waiver from requirements under the Paperwork Reduction Act. The period of the waiver may not exceed the period of the public health emergency. •Reason not used for opioid public health emergency: Not applicable, because the authority was used. •Last use during a public health emergency: This authority was last used during the public health emergency declared for the opioid crisis in October 2017.
Waiver of public notice process for Medicaid demonstrations under section 1115 of the Social Security Act	•Authority: 42 C.F.R. § 431.416(g) (2017) •Description: This provision allows the Centers for Medicare & Medicaid Services to waive federal and state public notice procedures to expedite a decision on a proposed Medicaid demonstration or demonstration extension request under section 1115(a) of the Social Security Act that addresses a public health emergency. This provision also allows the Secretary of HHS to exempt a state from the normal public notice process or required time constraints when the state demonstrates the existence of unforeseen circumstances resulting from a public health emergency that warrant such an exemption. •Reason not used for opioid public health emergency: Not applicable, because the authority was used. •Last use during a public health emergency: This authority was last used during the public health emergency declared for the opioid crisis in October 2017.
Application extensions and waiver of requirements for block grant funding	•Authority: 21st Century Cures Act, Pub. L. No. 114-255, § 8003 (2016) (codified at 42 U.S.C. § 300x-67) •Description: This provision allows the Secretary of HHS to grant an application extension for or waive compliance with requirements for block grant funding or an allotment authorized under the Protection and Advocacy for Mentally Ill Individuals Act of 1986 during a public health emergency declaration under section 319 of the Public Health Service Act. This authority applies to grants for assistance in the transition from homelessness, grants for community mental health services, and grants for the prevention and treatment of substance abuse and may be exercised, on a state-by-state basis, as the circumstances of the emergency reasonably require. •Reason not used for opioid public health emergency: HHS officials determined not relevant to the opioid crisis; more appropriate to a short, time-limited public health issue or when infrastructure is damaged. •Last use during a public health emergency: According to HHS officials this authority has never been used.

Table 2. (Continued)

Authority	Description
Funding-related authorities	
Extensions or waiver of sanctions related to submission of data or reports required under laws administered by the Secretary of HHS	•Authority: Public Health Security and Bioterrorism Preparedness and Response Act of 2002, Pub. L. No. 107-188, § 141 (codified at 42 U.S.C. § 247d(d)) •Description: This provision allows the Secretary of HHS to grant extensions or waive sanctions related to submission of data or reports required under laws administered by the Secretary of HHS. To exercise this authority, the Secretary must determine that individuals or public or private entities are unable to comply with deadlines for such data or reports due to a public health emergency declared under section 319 of the Public Health Service Act. The Secretary is also required to notify Congress and publish a Federal Register notice before or promptly after granting an extension or waiver. •Reason not used for opioid public health emergency: HHS officials determined not relevant to the opioid crisis; more appropriate to a short, time-limited public health issue or when infrastructure is damaged. •Last use during a public health emergency: According to HHS officials this authority has never been used.

Source: GAO analyses of information from Department of Health and Human Services, Department of Justice, and Department of Labor . | GAO-18-685R.

^aThis authority may become available without a public health emergency declaration under section 319 of the Public Health Service Act.

Enclosure II: Federal Public Health Emergencies, June 2016 through July 2018

The Secretary of Health and Human Services may, under section 319 of the Public Health Service Act, declare a public health emergency if the Secretary determines, in consultation with other public health officials as may be necessary, that: (1) a disease or disorder presents a public health emergency; or (2) a public health emergency, including significant outbreaks of infectious disease or bioterrorist attacks, otherwise exists. A public health emergency declaration is in effect until the Secretary declares the emergency no longer exists or 90 days after the declaration, whichever occurs first. The Secretary may renew the public health emergency declaration for subsequent 90-day periods for as long as the Secretary determines the public health emergency continues to exist. Federal public health emergencies declared since June 2016 are shown in table 3.

Table 3. Federal public health emergencies declared since June 2016

Event	Emergencies declared
Wildfires	•October 15, 2017: Determination that a Public Health Emergency Exists in California •December 11, 2017: Determination that a Public Health Emergency Exists in California
Opioid Crisis	•October 26, 2017: Determination that a Public Health Emergency Exists Nationwide ◦January 19, 2018: Renewal of determination ◦April 20, 2018: Renewal of determination ◦July, 19, 2018: Renewal of determination
Hurricane Nate	•October 8, 2017: Determination that a Public Health Emergency Exists in Alabama •October 8, 2017: Determination that a Public Health Emergency Exists in Florida •October 8, 2017: Determination that a Public Health Emergency Exists in Louisiana • October 8, 2017: Determination that a Public Health Emergency Exists in Mississippi

Event	Emergencies declared
Hurricane Maria	•September 19, 2017: Determination that a Public Health Emergency Exists in the Territory of the U.S. Virgin Islands and the Commonwealth of Puerto Rico ○December 11, 2017: Renewal of determination ○March 15, 2018: Renewal of determination for U.S. Virgin Islands ○March 16, 2018: Renewal of determination for the Commonwealth of Puerto Rico ○June 12, 2018: Renewal of determination for U.S. Virgin Islands
Hurricane Irma	•September 6, 2017: Determination that a Public Health Emergency Exists in the Commonwealth of Puerto Rico and the Territory of the U.S. Virgin Islands •September 7, 2017: Determination that a Public Health Emergency Exists in Florida •September 8, 2017: Determination that a Public Health Emergency Exists in Georgia •September 8, 2017: Determination that a Public Health Emergency Exists in South Carolina
Hurricane Harvey	•August 26, 2017: Determination that a Public Health Emergency Exists in Texas •August 28, 2017: Determination that a Public Health Emergency Exists in Louisiana
Zika Virus Outbreak	•August 12, 2016: Determination that a Public Health Emergency Exists in Puerto Rico ○November 4, 2016: Renewal of determination ○January 31, 2017: Renewal of determination ○April 28, 2017: Renewal of determination

Source: GAO analyses of Department of Health and Human Services information. | GAO-18-685R.

Chapter 530

DISSEMINATION OF ANTIBIOTIC RESISTANCE GENES AS ENVIRONMENTAL CONTAMINANTS: A PUBLIC HEALTH THREAT

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ABSTRACT

Antibiotic resistance and its devastating consequences present us with a growing global healthcare crisis. The extensive use and misuse of antibiotics, in particular, and their dissemination in the environment promote the emergence and dissemination of antibiotic-resistant bacteria, thereby posing risks with respect to public health. An urgent need is growing to improve our understanding of the mechanisms associated with the spread and development of antibiotic resistance genes in clinical and veterinary settings, and natural environments.

Keywords: antibiotic resistance, environmental dissemination, antibiotic resistance gene, horizontal gene transfer

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INTRODUCTION

For more than seven decades antibiotics have been the cornerstones of modern medicine and have changed the healthcare dramatically by significantly reducing the mortality and morbidity due to infections. Consequently, widespread emergence and dissemination of antibiotic resistance is one of the biggest public health threats in the 21st century. It is estimated that deaths because of drug-resistant microbial pathogens could rise from approximately 700,000 per year to 10 million a year by 2050 [1]. The problem is aggravated further due to rather slow or nil developments of new antibiotics during the past 30 years. Uncontrolled use of antibiotics has led to the development and dissemination of antibiotic-resistant genes in the environment, which is an emerging crisis worldwide. Traditionally, healthcare facilities were thought to be the source of dissemination of antibiotic-resistant genes (ARGs), but recently non-clinical environments were also found to play an important part. Over the last decade, increased resistance against antibiotics among bacteria in many different ecological niches such as soil, wastewater treatment plants (WWTPs), river water, drinking water, seawater, sediments, etc. has been recognized. This is a serious threat that limits our ability to treat common infectious diseases [2-10]. In these different environments, antibiotics (AB), antibiotic-resistant bacteria (ARB), and ARGs have consistently been observed. The reasons for this are multifarious, but the uncontrolled increased use and misuse of antibiotics combined with exposure to additional resistance promoting substances, such as disinfectants, biocides, and some heavy metals, are more significant [2, 11, 12].

ENVIRONMENTAL FACTORS AND ANTHROPOGENIC CONTAMINATION WITH ANTIBIOTICS AND ARGs

Antibiotic resistance is a natural phenomenon that occurs either through a mutation that provides the bacteria with new genes allowing them to survive the effects of the antibiotic (natural selection) or acquisition of resistant genes through gene transfer methods as a part of the evolutionary process. Antibiotics prescribed for certain health conditions after being metabolized by the human body are excreted and when these come into contact with the bacteria (present both inside the gut and the outside environment) induces an antibiotic resistance development process. Hence, the greater the use of antibiotics, the larger the magnitude of antibiotic resistance observed due to selection pressure and survival advantage. Antibiotics of anthropogenic origin and their metabolites can enter the environment through a number of different routes (Figure 1). These routes include soil, water, WWTPs, livestock, and gut microbiota, where each scenario is dealt with in the following sections.

These result in environments where antibiotics, ARGs, resistant bacteria, and environmental bacterial flora are mixed. These types of environments are likely resistant hotspots where ARGs proliferate and new resistant strains develop and disseminate by the horizontal gene transfer method.

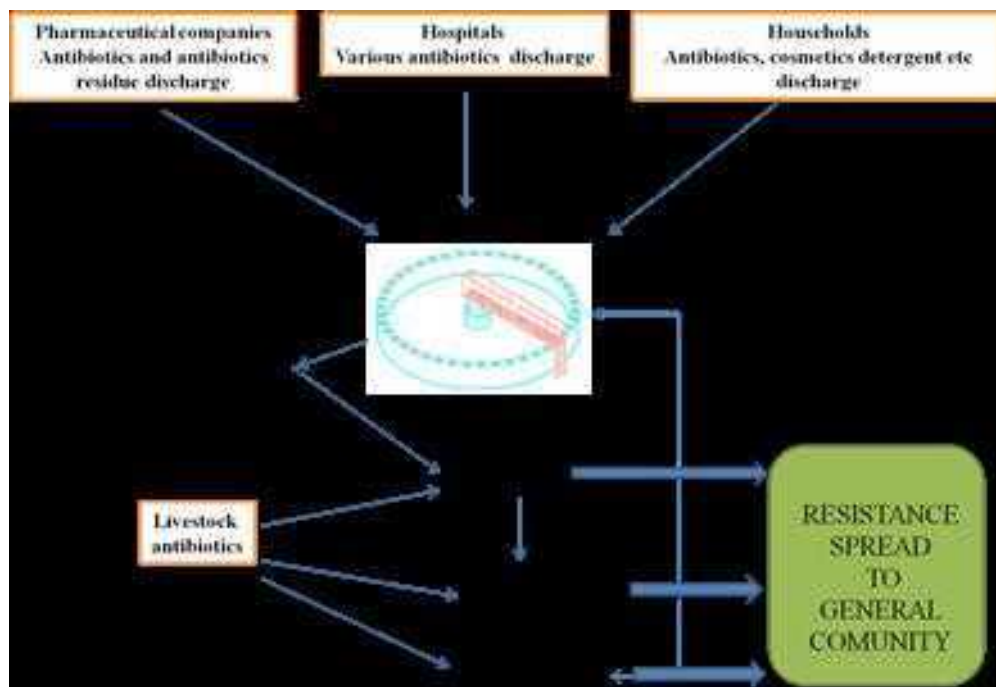


Figure 1. Antibiotics and antibiotic resistance genes (ARGs) can disseminate in humans via the environment by various routes.

Soil, Sediment and Solid Waste

Even though the full extent of ARGs in soil is not known, the existing evidence indicates that the soil acts as a vast reservoir as well as a non-point source of ARG-containing bacteria [13]. Since soil receives a large amount of organic material through the application of manure and sewage sludge as fertilizers as well as by dumping of domestic, hospital, and pharmaceutical waste, it becomes a hotbed of antibiotics from various sources to which indigenous microbes, as well as pathogenic bacteria from human and animal refuse, are exposed. A majority of non-pathogenic soil bacteria are found to be multi-drug resistant, reflecting their evolution in an environment containing a wide variety of bioactive molecules. The antibiotic-resistant genes and proteins in environmental bacteria are also found to be homologous to those in pathogenic bacteria. From this observation, it can be suggested that there could be a possibility of horizontal gene transfer from commensals to pathogens. This is also supported by the fact that opportunistic pathogens such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, etc. are not only highly drug-resistant but have also displayed a remarkable capacity to acquire new ARGs [14]. In addition, it has been demonstrated that some genetic elements can persist in the environment even after the death of the bacteria [15].

Apart from the soil, another environmental milieu that can serve as the ground for development and transfer of ARGs include water reservoirs, sewage treatment plants, solid waste dumping grounds and agricultural practices particularly livestock rearing. Thus the environment acts as a huge reservoir of ARG-containing bacteria. This whole complement of ARGs present in the environment has been termed ‘environmental resistome.’

Water

Water is not only a non-point source for resistant bacteria, but it also acts as a vector for their transport to different places, for example, rivers and streams transport these bacteria, either in the water itself or from the soil, to distant places. Water sources, particularly those that are close to human activities, have high levels of nutrients and other organic matter that promote microbial growth. These aquatic microenvironments, particularly sewage-contaminated water, harbor proliferating bacteria and also promote the development of antibiotic resistance. Antibiotic-resistant bacteria that develop in these microenvironments can be disseminated to humans and animals through contaminated drinking water [16].

Sewage/WWTPs

Antimicrobial resistance genes (ARGs) in ARB have been identified as widespread contaminants of wastewaters and treated drinking water. Most of the antibiotics prescribed to humans are used in households and eventually end up in the sewage. Therefore, urban WWTPs are one of the main sources of both ARB and ARGs that are released into the environment [6, 17-24]. Apart from the sewage, WWTPs receive wastewater from hospitals (after pre-treatment) where antibiotics are applied on a large scale and the prevalence of ARB and ARG might, therefore, increase in such environments [25, 26]. Hence, from the WWTPs, the antibiotics can end up in sludge dispersed on fields as fertilizer, or released as runoff directly into rivers [27, 28]. Sometimes, wastewater is treated by releasing it into the water or lands, thereby releasing antibiotics into the environment, which may ultimately enter the food chain directly or indirectly [29]. Thus, it is clear that antimicrobial resistance (AMR) hotspots are found not only in medical settings but also in environmental compartments that are subject to some anthropogenic activities. These environmental compartments are considered as hotspots for ARB and ARG spread not only because of the potential presence of substances with selective pressure in the WWTP system [8, 30-32] but also because of the presence of nutrient-rich growth conditions to microorganisms during WWT process that may favor events of horizontal gene transfer. This is evidenced by a number of studies that detected AB, ARB, and ARG in samples from WWTPs around the world [6, 20, 24, 33-36]. Since much of the sewage sludge produced by WWTPs is recycled as fertilizer products and used as a soil conditioner on cultivated areas, and on green areas including parks, private gardens, etc. concerns about the increased spread of AMR through this route has been raised [6, 33, 36]. Drinking water often originates from surface water, which is also the discharge point for wastewater [8, 23, 25]. This is supported by the increasing number of studies demonstrating the presence of antibiotics and ARB in the surrounding water sources and the finished drinking water [25, 37-42]. Another contributing factor is that municipal WWTPs are primarily designed and dimensioned to remove organic matter, phosphorus, and possibly nitrogen, but not antibiotics or other pharmaceuticals [3, 5, 7, 43]. In addition, there are studies that demonstrate that the purification process is not appropriate to completely remove resistance genes in the different compartments of WWTPs, meaning that resistant genes also end up in the environment [43].

Livestock

The antibiotics and antibiotic-resistant pathogens are released into the environment through farm animals, abandoned animals (e.g., cattle in India) and stray animals (e.g., dogs, pigs, and birds). This is because many food-producing animals (e.g., poultry, swine, and cattle) are normally treated with antibiotics in order to prevent infections, to promote growth, and to compensate for unsanitary conditions prevailing in commercial farm units. Thus the regular use of antimicrobials in healthy animals during livestock rearing has resulted in the emergence and increase of antimicrobial-resistant bacteria and makes it difficult to treat infectious diseases. India stands fourth highest in antibiotic consumption (3%) in the livestock sector in the world after China (23%), the United States (13%), and Brazil (9%). In the United States, 80% of sold antibiotics are consumed in the livestock sector alone [44-46]. Recently, an increase in antibiotic-resistant bacterial infections has led to public health concerns about the use of antibiotics for non-therapeutic purposes in animals intended for food production [47]. Resistant microorganisms carried by food-producing animals can spread to humans through consumption of contaminated food and drink, from direct contact with animals, or by environmental exposure, for example, contaminated water. The animal pathogens serve as a donor of antimicrobial-resistant genes to pathogens that infect humans. For instance, the use of a glycopeptide, avoparcin, as a growth promoter in animals in Europe resulted in the expansion of vancomycin-resistant enterococci (VRE) in commensal microorganisms in food animals, on meat from these animals, and in the commensal flora of healthy humans. The subsequent ban on the use of avoparcin in food animals in the European Union reduced the incidence of VRE in animals and its occurrence in the general population. The use of fluoroquinolones (e.g., enrofloxacin) in food-producing animals has contributed to the spread of ciprofloxacin-resistant *Salmonella*, *Campylobacter*, and *Escherichia coli*, which have made human infections difficult to treat. Also, AMR affecting the food supply of one country automatically becomes a potential problem in another country through travel and the import and export of food animals and animal products. In view of the developing resistance, many countries, including the European Union have imposed a ban on the use of some antibiotics in feed or as growth promoters [48].

Gut Microbiota

Humans come into contact with resistant microorganisms through numerous routes, including drinking contaminated water, consuming contaminated vegetables, crops, fish, and meat. The human and animal intestines contain non-pathogenic bacterial species, living as commensals or symbionts. Similar to environmental bacteria, these gut microbes also evolve several resistance genes, which may get selected if they offer a survival advantage during intake of antibiotics or the ARB once entered into the human body can spread ARGs to microflora inhabiting the host through the mechanism discussed earlier [27]. Thus, gut microbiome of both humans and animals serve as a reservoir of ARGs. In addition, antibiotics cause dysbiosis of gut microbiota by obliterating the bacteria that offer colonization resistance. Both these mechanisms together create the paradox of increased susceptibility to infection after the use of antibiotics. Analogous to environmental resistome (defined earlier),

the complement of ARGs in gut microbiome has been referred to as ‘gut resistome’ and they act as reservoirs. Since these genes are already present in the organisms, transfer to pathogenic organisms is more likely than from environmental resistome. For example, a study on *Bacteroides* species has found that tetracycline resistance gene *tet*, present on a conjugative transposon, was found in 20%–30% of isolates before the 1970s in contrast to over 80% in 1990s. The DNA sequence analysis of these genes revealed a high degree of similarity between these genes, indicating frequent occurrences of horizontal gene transfers [49].

Future advances in genome sequencing technologies are likely to facilitate high throughput characterization of the resistome by metagenomic sequencing of the microbiome of patients. This may guide the choice of antibiotics for curtailing infections, at least partially, by the composition and relative abundance of the ARGs in gene reservoir in patients. To fully assess the risks that are associated with the selection of ARGs in GI or genitourinary commensals, we foresee that further studies would be helpful to profile ARGs with respect to their possibility for horizontal gene transfer. However, at present individual monitoring in a clinical setting is not feasible due to the high cost involved.

ANTIBIOTICS USE: PRESENT AND FUTURE TRENDS

It is evident that the major factor driving the increased rate of antibiotic resistance is increased by the use of antibiotics. It was estimated that global antibiotic consumption increased by 36% between 2000 and 2010 and more than half of these were cephalosporins and broad-spectrum penicillins. This study also found that India, China, and the United States were the three largest consumers of antibiotics in 2010, respectively [50]. Though these figures represent the population of these countries to some degree, it is evident that the rampant and unregulated use of antibiotics is a matter of global concern. Particularly in middle-income countries, low public health and sanitation measures are an additional driving force for the increase in antibiotics sales. High population and economic burden promote practices such as over-the-counter sales and financial incentives to prescribe more antibiotics. Similarly, there is a greater burden of food production which leads to excessive use of prophylactic antibiotics in animal rearing practice. A recent study has pointed out that antibiotic use in the livestock sector in India is expected to notice the biggest increase, that is, 82% by 2030. It is projected that India will notice the highest growth rate in antibiotics use in animal farms between now and 2030 for the mass production of food animals [51]. Since indiscriminate use of antibiotics is the main reason for the rapid rise of antibiotic resistance, this problem needs to be addressed to slow down the emergence of newer ARGs.

MITIGATING STRATEGIES FOR ANTIBIOTIC RESISTANCE

One Health Concept

Since antibiotic resistance genes are persistent in environmental and human-animal health interfaces, an approach which deals with all the three areas is required, which highlights the

One Health approach [16]. The One Health approach, is defined as ‘the mutual effort of various disciplines – working locally, nationally, and worldwide – to accomplish optimal health for humans, livestock and our environment’ [52]. This approach perceives that human health is linked to the health of animals and the environment and is applicable to the problem of antibiotic resistance as well. Role of livestock in the dissemination of ARGs is due to use of many antibiotics in animal rearing, in sub-therapeutic doses and with elongated exposure periods, these production systems generate perfect milieu for bacteria for horizontal gene transfer that confers resistance. These genes can consequently be transmitted to human-adapted pathogens or to the human gut. The fact that the antibiotics used in human and animal health largely comprise the same molecules would be expected to commute the transmission of resistance between animals and humans, either directly or via the environment.

The One Health approach for dealing with AMR, encircling all three pillars (human health, animal health, and environmental health), will depend on sound knowledge about the ways how all three pillars interrelate in transmission to human and mechanisms involved (Figure 2).

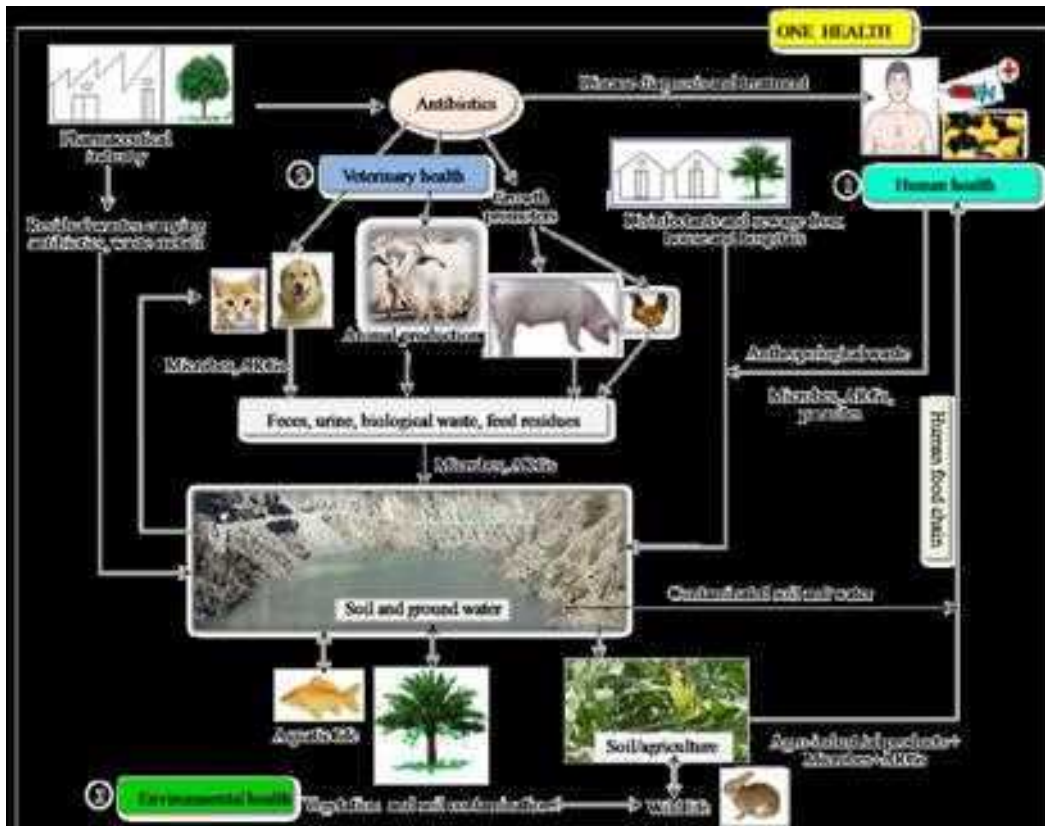


Figure 2. Role of three pillars (human health, animal health, and environmental health) of one health concept in the dissemination of antibiotic residues, antibiotic-resistant bacteria, and antibiotic-resistant genes in the environment.

Surveillance

Antibiotic resistance has its foundation on accelerated misuse and overuse of antibiotics along with poor infection prevention and control. Surveillance to estimate the exact magnitude of this problem, public awareness, and regulation of antibiotic use are the key elements for reducing the escalating rates of antibiotic resistance. In October 2015, WHO launched the Global Antimicrobial Surveillance System (GLASS), allied with WHO Collaborating Centres and existing AMR surveillance networks. So far, 52 countries are enrolled in GLASS out of which 40 countries provided information about their national surveillance systems and 22 countries also provided data on levels of antibiotic resistance for their first report. It has revealed the spread of antibiotic resistance across these 22 countries. The United Nations Interagency Coordination Group on Antimicrobial Resistance has been formed in 2016 with the mandate of providing practical guidance for sustained effective global action to address AMR. In developing nations like India, AMR is of particular concern due to the high burden of infectious diseases and low availability of resources. In 2011, the Health Ministers of the WHO South-East Asia Region pledged to combat drug resistance through the Jaipur Declaration. Since then, there has been a growing awareness of the need for appropriate tracking of drug resistance, and all countries have agreed to contribute information to a regional database. The Indian Council of Medical Research (ICMR) in 2013 set up an AMR surveillance network which is currently networking the tertiary care hospitals in the country. This network has been established with the aims of (i) collecting a nationally representative data on drug resistance and monitor trends across the country, (ii) generating evidence on mechanisms of resistance in different pathogenic groups, (iii) guiding antimicrobial policies for both treatment and prophylaxis, and (iv) directing hospital infection control efforts that facilitate prevention of the spread of resistant organisms.

Filling the vast gap of new antibiotic development is another step that will address this issue. An initiative in this direction is the establishment of the Global Antibiotic Research and Development Partnership, a not-for-profit research and development (R&D) organization. This organization is focused on developing and delivering new or improved antibiotic treatments and endeavoring to ensure their sustainable access at a global level.

Box 1.

- Strengthening of surveillance data
- Increasing public awareness regarding antibiotic resistance
- Strengthening government commitment to improve the practices of antibiotic prescription
- Optimizing the use of antimicrobials and restricting the over-the-counter sale of antibiotics
- Undertaking strategies for improving sanitation, malnutrition, and endemic infections
- Implementing preventive measures against infections, for example, vaccination for reducing clinical trial risk
- Strengthening the regulatory policies of farm feeding of antibiotics
- Formulating and implementing measures to properly dispose of biological waste
- Establishing guidelines for soil and water safety to reduce the pool of antibiotics and ARGs in the ecosystems
- Assuring the quality of generic antibiotics
- Sharing of data as early as possible
- Organizing World Antibiotic Awareness Week
- Establishing global partnerships for coordinated measures

Strong political will is required to formulate and implement regulations regarding antibiotic use. In addition, a collaboration between governments, research organizations, pharmaceutical companies, and healthcare providers is required for rapid communication of information. In summary, the steps required to combat this problem are provided as follows (BOX 1) [53-55].

CONCLUSION AND OUTLOOK

Antibiotic resistance is a natural phenomenon which is promoted by human activities. Lack of awareness and rampant unscientific use of antibiotics for short-term economic gains has escalated antibiotic resistance disproportionately. The assessment of the overall burden of resistance is difficult but mortality is clearly greater in vulnerable groups such as neonates. The environment plays a key role as a reservoir and source of dissemination of ARGs and several environmental regulatory measures are required to adequately address this issue. Preventive measures to reduce infections in the community, as well as reared animals, will go a long way to reduce the ARG pool, as will soil and water safety measures. Political commitment, global partnerships, and public awareness are most essential to tackle this problem systemically. In addition, newer alternative methods of treatment of infections will reduce the use of antibiotics, thus reducing infections as well as the emergence of resistance.

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Chapter 531

**CARTELS AND THE U.S. HEROIN EPIDEMIC:
COMBATING DRUG VIOLENCE AND
PUBLIC HEALTH CRISIS***

Committee on Foreign Relations

THURSDAY, MAY 26, 2016

U.S. SENATE,

SUBCOMMITTEE ON WESTERN HEMISPHERE, TRANSNATIONAL CRIME,
CIVILIAN SECURITY, DEMOCRACY, HUMAN RIGHTS, AND GLOBAL WOMEN'S
ISSUES,

Committee on Foreign Relations

The subcommittee met, pursuant to notice, at 9:03 a.m. in Room SD-419, Dirksen Senate
Office Building, Hon. Marco Rubio, chairman of the subcommittee, presiding.

Present: Senators Rubio, Gardner, Boxer, Kaine, Menendez, and Markey.

**OPENING STATEMENT OF HON. MARCO RUBIO,
U.S. SENATOR FROM FLORIDA**

Senator RUBIO. Good morning. This hearing on the Subcommittee of the Western Hemisphere, Transnational Crime, Civilian Security, Democracy, Human Rights, and Global Women's Issues will come to order. I thank you for being here today.

The title of this hearing is "Cartels and the U.S. Heroin Epidemic: Combating Drug Violence and Public Health Crisis."

* This is an edited, reformatted and augmented version of Hearing before the Subcommittee on Western Hemisphere, Transnational Crime, Democracy, Civilian Security, Human Rights, and Global Women's Issues, Committee on Foreign Relations, United States Senate, One Hundred Fourteenth Congress, Second Session, dated May 26, 2016.

Before we begin the meeting, on a matter of personal privilege, I wanted to acknowledge the contributions of a loyal and a dedicated staffer because behind every one of us here in the Senate, there are loyal and really hardworking people. Literally they sit behind us at these meetings, and they do all the hard work behind the scenes to make sure that we are briefed and prepared to cast votes and advance public policy that makes a difference.

Since 2011, Maggie Dougherty has been an instrumental part of our policy team, and she has logged in countless hours working on all sorts of complex and important issues for our office. She has also logged in countless hours sitting behind us here in these committee meetings, but no longer. Today is Maggie's last Senate Foreign Relations Committee meeting. In a week's time, she will depart our office to even a bigger and better opportunity. So I just briefly wanted to thank her for everything she has done for us. We are very proud of her work. [Applause.]

Senator RUBIO. So the title of this hearing, "Cartels and the U.S. Heroin Epidemic"—we have two panels testifying. The first is an official panel that will feature Mr. Daniel Foote, the Deputy Assistant Secretary of State for the Bureau of International Narcotics and Law Enforcement at the U.S. Department of State, and Mr. Kemp Chester, the Associate Director for the National Heroin Coordination Group for the Office of National Drug Control Policy.

The second panel will present the Honorable Teresa Jacobs, the Mayor of Orange County, Florida, and Mr. Steven Dudley, the Co-Director of InSight Crime.

Thank you all for being here today. We appreciate your time. We appreciate your dedication. I would also like to thank all of those who worked alongside my staff and making this hearing possible.

Drug cartels operate out of countries in the western hemisphere, and they do so by using sophisticated distribution systems that move narcotics into and across the United States. Heroin supplied by these cartels has created a public health epidemic and fueled drug violence across this country.

The heroin epidemic, drug war, and fight against drug violence are, unfortunately, becoming part of everyday events in our society. It is our duty to find the best possible avenues and allocate resources to provide the best tools to equip those on the front lines to fight this public health crisis. We need to examine what the United States, Mexico, and other regional partners are doing to cooperatively address the rise in heroin and in drug trafficking. Promoting the efficacy and proper execution of U.S. initiatives to stop the spread of heroin and combat the drug cartels should be one of our top priorities.

Here are some facts. One of the primary culprits in this fight is called fentanyl. It is a synthetic opiate that is 25 to 40 times more potent than heroin and it may be used to treat pain associated with advanced cancer. While fentanyl is legally prescribed in the United States, the CDC states that most cases of fentanyl-related overdoses are associated with non-pharmaceutical fentanyl. It is a type used as a substitute for heroin or mixed with heroin or other drugs, sometimes without the user's knowledge.

In 2015, the DEA's National Drug Threat Assessment Summary reported that Mexico and China have been cited as the primary source country, though some analogs of fentanyl are manufactured in China. These supplies are often trafficked into the United States across the southwest border or delivered through mail couriers. Transnational criminal organizations also use Florida as the point of arrival for South American cocaine and heroin. Much of the illegally diverted and produced fentanyl is found in the same U.S. markets where white powder heroin is found.

According to the Substance Abuse and Mental Health Services Administration, the estimated number of individuals who used heroin was 914,000 people in 2014.

In addition, there are about 586,000 individuals, or basically .2 percent of the 12 and older population, who had a heroin disorder in 2014.

While there has been an increase in heroin overdoses and heroin-related deaths across the United States, the Midwest and the Northeast regions have been areas of particular concern. To this day despite the administration's efforts, heroin-related overdose deaths increased by 244 percent between 2007 and the year 2013.

The U.S. has responded to such findings by launching the Heroin Response Strategy, leveraging upon the 15 high intensity drug trafficking areas across the country.

Mexico, our regional partner, has displayed willingness to cooperate with U.S. authorities, but despite these operations, the International Narcotics Control Strategy Report estimates that less than 2 percent of cocaine that comes through Mexico is seized by this country's authorities. Under the Merida Initiative, Congress has provided billions in funds to the Mexican Government to improve security and the rule of law, and I applaud the continued efforts of the Mexican Government to continue its drug crop eradication efforts and to arrest drug kingpins. However, we are still far from the finish line.

I think the Congress can continue to work in constructive ways to promote legislation addressing opiate abuse. I am proud to be the cosponsor of the Comprehensive Addiction and Recovery Act, a bipartisan bill that overwhelmingly passed the Senate. I also applaud the House for working to address this issue, and I hope soon we will be able to send this legislation to the President's desk.

It is my hope that today's hearing will shed light on the consequences that this epidemic will have in our society and future generations if left unaddressed and not given proper attention. I am optimistic this hearing will serve as the opportunity to learn about the administration's priorities in combating the heroin epidemic and drug violence. And I hope you will address these issues in your testimony as well.

With that, I will now turn it over to our ranking member, Senator Boxer, for her opening statement.

STATEMENT OF HON. BARBARA BOXER, U.S. SENATOR FROM CALIFORNIA

Senator BOXER. Mr. Chairman, thank you so much for holding this important hearing.

The abuse of illegal and legal drugs in America is an absolute crisis, and to fight it, we need to act on many fronts.

Take the case of opioids. These are legal prescription drugs that are killing approximately 125 people every single day here at home. The CDC says that in 2014, 47,000 people died from opioid abuse. Just imagine that.

We need to do much more than we have done so far to put real dollars behind the effort to stop this madness.

Then there is the issue we will focus on today of illegal drugs being transported into this country.

Recently I visited Costa Rica, and I learned that this peaceful country is very alarmed about drug cartels infiltrating their population. We must help them stop this real threat. And I hope to ask a question about that.

And while we are working cooperatively with the Mexican Government, specifically an initiative called the Merida Initiative, and while we have to date seized more than \$4 billion in narcotics and illicit currency, let us face it. That is a drop in the bucket. We simply have to address the demand in the United States for these lethal products. And I know that is not your job, and I am not going to even ask you about that. But I am making a statement as a United States Senator. We have to address the demand in the United States for these lethal products.

Supply and demand go hand in hand. A long time ago, I was an economics major. It is like economics 101. When people demand a product, we know what happens. The supply will come. And when even more people demand a product, the price will go up and it goes around in a circle.

Years ago, too many to even mention—so I do not even know where my chairman was at that time it was so long ago, very long—when I first came to Congress, I wrote a bill called Treatment on Demand because what I found out, Mr. Chairman and members, is that when there is a person in America with a terrible addiction, at that time—and it is so true today—they wake up one day and they say I have done it, I have had it, I need a new life. They cannot get in anywhere. So people say, very good, come back in 2 weeks. This is an emergency circumstance in many ways, but it is not considered that. So they will go in. Maybe they will get a pat on the back. Come back in 2 weeks. And by then, maybe they have even overdosed.

Now, I know we are working with Colombia and Guatemala helping farmers develop alternatives to opium production. But again, we need to be even more aggressive in our policies regarding drug production, trafficking, and consumption here at home.

In California, we have four of those areas that my chairman spoke about that are designated as high intensity drug trafficking areas by the Obama administration. I am extremely grateful to the administration. We had that help under George Bush as well. When you identify an area, it means you are going to get some attention, some Federal dollars, some Federal help because a lot of these local people, our police forces and so on, really do need that help. So I am very grateful for that.

We have also discovered tunnels from Mexico to San Diego, which act as conduits for thousands of pounds of cocaine. And this points to the continuous challenges we face in dealing with these dangerous cartels. They are really good at what they do, and they intimidate everyone. And that is why this fight is so critical. We need even stronger partnerships with Mexico and other countries in the region.

And I want to say this. Alienating our Latin American neighbors and our Latinos here at home is the worst possible thing we can do, first of all, on a human level because in my view it is prejudice and bigotry. But it does not make sense if we are really trying to crack down on these cartels. We need our friends to work with us. We do not need to escalate some kind of ridiculous debate about walls and all the rest.

I do want to thank our witnesses for being here today. There is a lot of burden on you, and this is very difficult. The war on drugs has not been a success. And I think the reason is we have not done enough on the demand side or on any side. We need to do much better.

And I want to thank my chairman because I think this is really well-timed given what we are facing with the opioid crisis. Thank you.

Senator RUBIO. Thank you, Senator Boxer.

Before we begin with the testimony, I did want to recognize the senior Senator from New Jersey, who has done an extreme amount of work on western hemisphere issues but also issues regarding transnational crime, if he wanted to give any opening comment.

Senator MENENDEZ. No, thank you.

Senator RUBIO. With that, please join me in welcoming our first witness, Mr. Foote. Thank you for your testimony before us here today.

**STATEMENT OF DANIEL L. FOOTE, DEPUTY ASSISTANT SECRETARY
OF STATE, BUREAU OF INTERNATIONAL NARCOTICS AND LAW
ENFORCEMENT U.S. DEPARTMENT OF STATE, WASHINGTON, D.C.**

Mr. FOOTE. Chairman Rubio, Senator Boxer, Senator Menendez, Senator Gardner, thank you for this opportunity to appear before you to discuss the work of the State Department's Bureau of International Narcotics and Law Enforcement Affairs to combat the production and trafficking of heroin particularly by Mexican-based drug trafficking organizations that are responsible for the vast majority of the heroin on America's streets today.

In the United States, we face an epidemic of opioid abuse. Well over half of the more than 47,000 American deaths from last year were due to either domestically produced controlled prescription pain relievers or heroin, which is often combined with other deadly drugs such as fentanyl.

In Mexico, drug trafficking organizations have killed tens of thousands of citizens, and these organizations continue to foment violence, instability, corruption, and addiction.

This scourge is broader than just the United States, and we will not solve it alone.

The overwhelming majority of the heroin in the U.S. is produced or distributed by Mexican drug trafficking organizations. For many years, they have been trafficking not only heroin but also much of the cocaine, methamphetamine, and other illicit drugs that enter our country. Most of these drugs enter through our border with Mexico.

The United States and Mexico developed the Merida Initiative in 2007 with major focus on combating the production and trafficking of illicit drugs across our borders. Today the Pena Nieto and Obama administrations remain committed to Merida's strategic goals. Our Merida partnership, which brings together significant investments and capabilities of both countries, continues to help build Mexico's capacity to fight narcotics trafficking, organized crime, and violence. Together, we are aggressively responding to this threat by putting the leaders of drug trafficking organizations in jail, by seizing their drugs and money, and by dismantling their organizations. Today, through Merida, INL is professionalizing and building the capacity of Mexican law enforcement agencies, supporting the Mexican Government's efforts to strengthen border management and security, and helping advance reform across Mexico's justice sector.

Bilaterally we have agreed that targeting the production and trafficking of heroin, as well as fentanyl and other dangerous synthetic substances, is a top shared priority. To that end, INL and DEA are providing training to law enforcement officers, investigators, and analysts

increasing Mexico's ability to identify, investigate, and dismantle clandestine heroin and fentanyl labs.

With our interagency partners, we are also improving information sharing between our governments on heroin and fentanyl working together to get better assessments on opium poppy cultivation and heroin and fentanyl production in Mexico and continuing to explore other avenues to enhance our bilateral cooperation and effectiveness.

Building strong, effective Mexican justice sector institutions, capable of confronting organized criminal enterprises, is a difficult, long-term challenge. This work must be sustained, for it is only through a committed, coordinated effort that sustainable capacity to deter the cultivation, production, and trafficking of illicit drugs will be strengthened. The significant investments of both of our governments are producing results, and with your continued support, this successful collaboration with Mexico will continue.

Thank you.

[Mr. Foote's prepared statement is located in the Additional Material Submitted for the Record section at the end of this transcript.]

Senator GARDNER [presiding]. Thank you, Mr. Foote.

Mr. Kemp Chester, Associate Director for the National Heroin Coordination Group, please begin your testimony. Thank you.

STATEMENT OF KEMP CHESTER, ASSOCIATE DIRECTOR FOR THE NATIONAL HEROIN COORDINATION GROUP, OFFICE OF NATIONAL DRUG POLICY, WASHINGTON, D.C.

Mr. CHESTER. Chairman Rubio, Ranking Member Boxer, and members of the subcommittee, thank you for inviting me here this morning to discuss the public health and public safety issues resulting from heroin use, the Government of Mexico's efforts to reduce the availability of heroin in the United States, and U.S.-Mexico cooperation to address heroin issues in both countries.

In 2014, the most current year for which we have data, more than 47,000 Americans, or approximately 129 people each day, died from a drug overdose. Of the overdose deaths in 2014, 22 percent involved heroin.

The threat posed by heroin has continued to grow dramatically over the past several years, and since 2007, deaths involving heroin have risen 340 percent from 2,402 in 2007 to 10,574 in 2014.

Heroin use has spread into suburban and rural communities and is growing among most socioeconomic classes, age groups, and races.

Mexico is currently the primary supplier of heroin to the United States with Mexican drug traffickers cultivating opium poppy, producing heroin, and smuggling the finished product into the United States. Poppy cultivation in Mexico has increased substantially in recent years, rising from 17,000 hectares in 2014 to 28,000 hectares in 2015, which could yield potential production of 70 metric tons of pure heroin.

The heroin crisis is being compounded by the reemergence of illicit fentanyl, a powerful synthetic opioid more potent than heroin.

Illicit fentanyl is sometimes mixed with powder heroin to increase its effects or mixed with dilutants and sold as synthetic heroin. Increasingly fentanyl is being pressed into pill form and sold as counterfeit prescription opioid pills. The majority of the illicit fentanyl in the U.S. is clandestinely produced in Mexico or in China.

Fentanyl is extremely dangerous and deadly. In 2014, there were more than 5,544 drug overdose deaths involving synthetic narcotics other than methadone, a category that includes fentanyl. This number has more than doubled from 2 years earlier.

U.S.-Mexico engagement regarding heroin has been robust. In October 2015, ONDCP Director Michael Botticelli participated in a bilateral security dialogue where the importance of increased poppy eradication efforts by the Government of Mexico, as well as drug interdiction, clandestine laboratory destruction, and the disruption of precursor chemical trafficking were all highlighted.

In early March, Director Botticelli, Ambassador William Brownfield, the Assistant Secretary of State for International Narcotics and Law Enforcement Affairs, and I met with the Mexican Attorney General Gomez, and she announced her role as the synchronizer of Mexico's efforts to disrupt the production of heroin and illicit fentanyl. Importantly, we agreed then to jointly develop a focused national plan to concentrate Mexico's efforts against heroin and fentanyl.

The urgent need to sustain progress toward addressing the Nation's heroin and fentanyl crisis requires increased collaboration between Federal agencies and with our partners working at the State, local, and tribal level where the crisis is felt most deeply.

In November 2015, the team that I lead, the National Heroin Coordination Group, was created within the Office of National Drug Control Policy to form the hub of a network of interagency partners who will leverage their home agency authorities and resources and to harmonize interagency activities against the heroin and fentanyl supply chains to the United States.

The ONDCP-funded high intensity drug trafficking areas, or HIDTA program, the locally based program that responds to drug trafficking issues facing specific areas of the country, has also been instrumental. In August 2015, ONDCP committed \$2.5 million in HIDTA funds to develop a heroin response strategy. This innovative project combines prevention, education, intelligence, and enforcement resources to address the heroin threat through seven regional HIDAAs covering 17 States and the District of Columbia.

So while we have laid a firm foundation to address the heroin crisis, much remains to be accomplished. For example, we do have gaps in our capability to detect illicit fentanyl at our borders, and our Mexican partners could certainly do more in the areas of opium poppy eradication and clandestine laboratory identification and neutralization.

And while my remarks have focused on addressing the supply side of the opioid crisis, we must address opioid use disorders with a balanced approach that also regards addiction as a public health matter, using substance abuse prevention and treatment strategies and recovery support services. In his fiscal year 2017 budget, President Obama proposed \$1 billion in new mandatory funding to expand the availability of evidence-based strategies such as medication-assisted treatment and to extend the availability of substance abuse treatment providers.

ONDCP will continue to work with our international partners, Federal Government Departments and agencies, and our partners at the State, local, and tribal levels to reduce

heroin and fentanyl production and trafficking and the profound effect these dangerous drugs are having in our communities.

Thank you for the opportunity to testify today, and I would be happy to answer any of your questions.

[Mr. Chester's prepared statement is located in the Additional Material Submitted for the Record section at the end of this transcript.]

Senator RUBIO [presiding]. Thank you.

And I am going to defer my questions because I know members need to be in other places, and I will basically be here throughout the duration. And so I will turn over to the ranking member for her questions.

Senator BOXER. Thanks. I just have two questions for Mr. Foote. So, Mr. Chester, breathe. You are off the hook here.

Mr. Foote, in 2008, Mexico's Congress passed a series of significant reforms to its criminal procedures, new laws to promote greater access to justice, and strengthened measures to combat organized crime, measures that would make the Mexican justice system look a little bit more like our own. These reforms were intended to be implemented by 2016. Where does the implementation of these judicial reforms stand, and how has the United States assisted in this process? And how do you feel about whether they are really doing what they committed to do?

Mr. FOOTE. Thank you, Senator.

As you know, Mexico committed and passed legislation to implement a new criminal justice system which is an accusatorial justice system, much like ourselves. At this point, of the 32 Mexican states, 24 have implemented this with federal level crimes and I believe 9 have implemented it at state level crimes. Obviously, this is a long-term process, and some of the states in Mexico will not meet next month's deadline.

We remain committed and continue to work closely with them on a number of issues. Thanks to the gracious appropriations of Congress, we have dedicated approximately \$250 million to these efforts between the Department of State and USAID through issues such as training judges, prosecutors, courtroom personnel, law students. Over 4,000 have been trained to date through Department of Justice's OPTAT prosecutorial training program. We also have a number of law school and institutional exchange programs through the American Bar Association and a number of universities here in the United States.

We are preparing law enforcement for their new roles in the accusatorial justice sector. For instance, our Department of Justice partners in ICITAP have trained thousands of law enforcement in crime scene investigations, provided equipment for units and forensics, fingerprinting, and other collection there so that Mexico can comply with international standards.

Senator BOXER. Okay. Thank you. What I am getting from you is that there is progress being made, although not everyone will meet the deadline. It is an optimistic report.

And so that leads me to my final question, which I alluded to in my statement. As we continue to work with the Mexican Government—and that is just critical. We have to. We have to work here at home to reduce the demand. We have to work across the border to reduce the supply. And that is where the rubber meets the road in both of these areas where we need to work with Mexico.

I am concerned about the rhetoric in the presidential campaign describing our relationship with Mexico. I know it is a tough question for you. I just want you to say what you feel in

your heart because we need to know. Mexican officials have said on the record that some of the proposals mentioned on the campaign trail—we know who we are talking about here, a candidate who is talking about building a wall, having Mexico do it, insulting Mexican Americans here at home—that some of the proposals would have a cataclysmic effect on our bilateral relations.

Has this divisive rhetoric affected diplomatic relations with Mexico at this point? Has it impacted the United States' ability to work with the Mexican Government to combat drug trafficking? And are you concerned that that type of rhetoric could just completely undermine what we are trying to do here?

Senator RUBIO. Just for the record, she is not talking about me. [Laughter.]

Senator BOXER. I am so not talking about you.

Mr. FOOTE. Excellent. Well, I will try to strike a balance between answering your question and not entering too deeply into our own domestic politics here.

Senator BOXER. I know it is a tough one, but you know what? When people talk, it has real-life impacts, especially presumptive nominee.

Mr. FOOTE. You have all seen some of the reactions from south of the border from our Mexican brothers and sisters. You have seen President Vicente Fox's reactions and others.

From the embassy bilateral level to date, we continue to work very closely together. In my personal opinion, I do not believe it has gravely affected our ability to do business together. Mexico in the last several months has reiterated its commitment to continuing with the Merida Initiative. Where the populace of Mexico stands on this may be another matter. But we continue to be able to work closely together bilaterally on all——

Senator BOXER. So the words have not had an impact on what is going on at the very top levels in your opinion on the work that you were doing at this point.

Mr. FOOTE. Not in their dealings with us.

Senator BOXER. That is excellent.

Now we have to make sure that those policies never come into effect.

Thank you very much.

Senator RUBIO. Thank you, Senator Boxer.

Senator Menendez?

Senator MENENDEZ. Thank you, Mr. Chairman, for calling the hearing. It is an important one.

And thank you both for your service to our country.

Mr. Foote, how many agencies are involved in interdiction and eradication efforts with respect to Mexico's border with us in our efforts to stop interdiction, stop flows, use intelligence? How many agencies are involved?

Mr. FOOTE. U.S. agencies I hope is what you are asking?

Senator MENENDEZ. U.S. agencies.

Mr. FOOTE. Thank you. INL, Department of State. You have Department of Justice, DEA, FBI to a certain extent. Department of Homeland Security is heavily involved through Customs and Border Protection, Immigration and Customs Enforcement, Homeland Security investigations. Our military supports some of the border efforts of Mexico's military. And then we have some ancillary agencies who are based in Mexico City, but while their chief focus is not the border, they do peripherally work on it such as ATF and the U.S. Marshals.

Senator MENENDEZ. And if you had to guess how much money has been spent on interdiction and eradication efforts in Mexico since the start of the epidemic that we are experiencing here, would you put it at?

Mr. FOOTE. My understanding is \$2.5 billion has been appropriated, of which approximately \$1.5 billion has been obligated or committed to specific projects, of which we still have at this point new initiatives for about \$700 million.

Senator MENENDEZ. Now, are you speaking just Merida specifically?

Mr. FOOTE. Pardon me?

Senator MENENDEZ. Are you speaking just of Merida specifically? Mr. FOOTE. Largely.

Senator MENENDEZ. There is money spent far beyond Merida.

Mr. FOOTE. There certainly is, Senator. I am not in a position to comment on Department of Justice's appropriation. I just do not have the figures. That is something we could get for you.

Senator MENENDEZ. I was not looking just at appropriation. I look at all the agencies you mentioned, your own, INL, Department of Justice, DEA, FBI, Homeland Security, Immigration, military, Alcohol, Tobacco and Firearms. And I think to myself it has to be billions collectively. And I was one of the architects of the Merida Initiative, which I support.

But \$1.5 billion later, billions between all of our respective agencies, and what we have is an opioid epidemic. And as a policy-maker, one has to take a step back and say to themselves, what is not working because something is not working. If billions of dollars later what you see is a spike versus a trend in the other direction, then something is not working. So if I were to say to you, what is not working, what do we need to change, your answer would be?

Mr. FOOTE. First of all, Senator, I think we have in the past few years come to the realization that this is a shared responsibility between the United States and source countries and trafficking countries. I am heartened by the Senate's recent passing of the opioid legislation. It is something that is going to help us. Certainly Mexico-specific, their capacities are far greater than they were when we started the Merida Initiative in 2007. Information sharing and collaboration has led our own U.S. law enforcement agencies to interdict significantly more on our southern border due to Mexico cooperation.

We still do have a way to go. I think we also need to get better here in the United States at demand reduction and treating the health issues of addicted people. It is a shared responsibility and it is no longer just a supply-side issue.

Senator MENENDEZ. So as I listened to your response, it is everything that we are doing except for a more significant effort on demand reduction, but it is not suggesting that there is anything that we are not doing. And all I can look at and say if you are spending billions and instead of the trend going the opposite direction, it is rising, you have to raise the question what is it that we are either doing wrong or what is it that we are not doing that we need to do in order to meet the challenge because otherwise we can appropriate billions and billions, but still find ourselves in a trend that is undesirable.

So the only thing I heard from you in your response to me was doing more demand reduction, which I certainly believe is true. But I did not hear about anything else. So you know, you have to question whether or not the continuation of this type of expenditure in this manner is the right policy.

Let me ask you this. Do you believe that there is sufficient coordination, a seamless coordination between at least on our side of the border as it relates to all the agencies that you suggested are engaged in this fight?

Mr. FOOTE. Senator, obviously, we can always get better at everything we do. Department of State kind of works from the southern border south. So I do not feel that it is our position to comment on interagency coordination north of the border. South of the border, we have robust interagency coordination through the country team at Embassy Mexico City. We can always get a little better there.

Senator MENENDEZ. Your Mexican partners—are they doing everything that they can in order to meet the challenge on their side of the border?

Mr. FOOTE. During the beginning part of President Pena Nieto's administration, there was a pause in Plan Merida as I think we did a mutual assessment of the security relationship, particularly on their side, and over the past year and a half, we have seen much closer collaboration, an unprecedented openness and frankness in our bilateral dialogue.

To answer your question, is Mexico doing everything that they can, they could improve. Some of their efforts are not yet at the optimal level, but we remain optimistic and positive that they are moving in the right direction.

Senator MENENDEZ. Well, I appreciate the optimism, but I am seeking to introduce a little dose of realism into it. And so part of the challenge is that you have lawless states in some of the northern part of Mexico where I have heard U.S. citizens from the region who have come to talk to me say that many who had businesses, longtime relationships on the immediate other side of the border, that basically cannot operate there because the federal government's presence—i.e., the federal government of Mexico's presence—is not there. So if you have lawlessness and if you have uncontrolled states, then you have the opportunity for drug traffickers to avail themselves of that. And it seems to me that while I am an incredibly strong and have been for 25 years supporter of the U.S.-Mexico relationship, we need to be honest in this relationship in order to make sure that we are making the progress that we need here and for Mexico to be able to regain its sovereignty over parts of northern Mexico that it presently does not have.

Thank you, Mr. Chairman.

Senator RUBIO. Thank you.

Let me use some of my time that I yielded just to interject, to follow up on that.

Secretary Foote, how would you assess the assertion made by a group of experts from the Inter-American Commission on Human Rights that there may have been another bus involved in the incident in which 43 students disappeared in Guerrero, Mexico that was packed with heroin bound for the U.S.?

Mr. FOOTE. Senator, thank you for that question. Given that we have not seen the results of the final investigation from Mexico, I am not in a great position to answer that question right now. We would be happy to answer that for the record in writing.

[The material referred to above was not available when this transcript went to press.]

Senator RUBIO. Okay.

Senator KAINE?

Senator KAINE. Thank you, Mr. Chair, and thanks to the witnesses.

First, to get an idea of the scope of this challenge on the Mexican side in terms of the black tar heroin, is the poppy production for this heroin still significantly confined to the state

of Nayarit or is it more broadly distributed? Mexico is a big country. So when we talk about a problem in Mexico, I worry that we are not being specific enough.

Mr. CHESTER. Yes, Senator. Our latest crop estimate that was produced about 2 months ago shows two major growing areas in Mexico, one in the state of Guerrero and then another in what is called the tri-border region up in the northern part of the country. Those are the two major growing areas in Mexico, with very, very small kind of sporadic spots in other parts of the country, but they are basically concentrated in those two areas.

Senator Kaine. And then the fentanyl is made in labs, and I gather that most of the fentanyl that comes in is either coming in— it is made in China and may be transited in through Mexico or also made in labs in Mexico. Are those the two main sources for fentanyl?

Mr. CHESTER. That is correct.

And I will tell you that our understanding and our awareness of fentanyl traffic has evolved dramatically over the last 6 months as we have seen the crisis rise. So in order of magnitude, I cannot tell you, but what I can tell you is that China is a significant supplier of fentanyl to the United States or it is ordered by individuals on the dark web around the Internet and then, using parcel post or the Postal Service, shipped directly to them.

We also know that fentanyl is shipped into Mexico in some cases mixed with dilutants and smuggled across the Southwest border and that there are precursor chemicals that are shipped into Mexico that can be used for the production of clandestine fentanyl in laboratories in Mexico. So as you look at the vectors coming into the United States, those are the two main ones that we see for finished fentanyl coming into the United States or its manufacture in Mexico.

Senator Kaine. I want to talk, Mr. Chester, about your written testimony. I am sorry I did not get here for your entire oral testimony.

But on page 1, there are several principal factors contributing to the current nationwide heroin crisis: the increased availability of heroin in the U.S. market, the availability of pure forms of heroin that allow for non-intravenous use, its relatively low price, and a relatively small percentage of non-medical users of opioid prescription drugs transitioning to heroin.

I am trying to unpack that statement, and I am wondering if your statement puts enough of a finger on the prescription opioid problem. I have heard it stated through Michael Botticelli and others that 80 percent of those who OD on heroin in this country, not fatal ODs but total ODs, started their addiction to opioids by being addicted to prescription opioids and then transition to heroin because they could get it for a lower price. Is that an accurate statement?

Mr. CHESTER. No, Senator. And I am glad you asked that question. Of the numbers of individuals who non-medically use opioids and then transition into heroin, that number is actually relatively small. It is about 3.6 percent.

Senator Kaine. For non-medical use.

Mr. CHESTER. That is correct. So the non-medical use of a prescription opioid like OxyContin and kind of the traditional “got it from the medicine cabinet, got it from friends or family members”—the percentage of those individuals who transition to heroin use is relatively low. It is about 3.6 percent.

But conversely, of individuals who are non-treatment users of heroin, 80 percent of them actually abused a prescription opioid in the past. So while there is not a direct causation between the two, the non-medical use of opioids is a strong risk factor for eventual heroin use.

Senator Kaine. And even the medical use of opioids can be a risk factor for eventual heroin use. Correct?

Mr. Chester. Yes, Senator, that is right. So an opioid in and of itself and its effect on the body—obviously, it is a very addictive drug and affects the body in unique ways, as an opioid. So those individuals who take opioids, whether they get them from a doctor or whether they get them from a friend or a family member for non-medical reasons are at risk for eventual opioid addiction if not used properly. That is correct.

Senator Kaine. And you cite in the testimony the relatively low price of heroin—and that is relatively low compared to past trends but also compared to the cost of opioid-based prescription drugs. Correct?

Mr. Chester. That is correct. So the street price of a gram of heroin compared to the street price, if you will, of an opioid pill or an oxy pill or something of that nature, that is correct. That is what we consider to be one of the contributing factors. So it is the availability and the general low price and then the purity that have all been contributing factors to the current crisis that we are in with heroin. That is correct.

Senator Kaine. Mr. Foote talked about the work that we have done in this body and we are trying to harmonize with the House in this recent CARA, Comprehensive Addiction and Recovery Act. We really believe it here—and I think it is now bipartisan—we are seeing in all of our States that if we do not get a hold of the culture of over-prescription of opioid-based prescription drugs, we are just hollowing out communities, rural, urban, suburban, rich and poor. And this was a drug addiction that came out of the medicine cabinet. In many instances it was a trusted professional in a white coat that was handing somebody this prescription saying this is going to do you good and it is not going to do you harm, driven by inadequate science, driven by frankly marketing scams. And that is inextricably related to this heroin issue. And so I think it is kind of hard to deal with the heroin issue in the abstract without talking about this culture of over-prescription, that hopefully we are working together to reel in.

Last question I want to ask—and it is probably too early to know this. But in terms of the growth of the number of hectares of poppy production in Mexico, do we have any evidence to suggest whether that is at all connected with marijuana legalization in the United States? I actually kind of like this notion of the States as labs and they can experiment and we can see what happens. But I have heard it said—and I do not know whether there is any evidence to back it up—that the legalization of marijuana in some States that has allowed marijuana to be grown has taken hectares of land that were used for marijuana cultivation and, well, we do not have a market for our marijuana anymore because there is competition, so we will switch to something like poppies to produce black tar heroin. Is there any evidence of that?

Mr. Chester. We have actually looked closely kind of at the crop transference to see if there is anything there, and I can tell you at this time, whether it is too early or whether it does not exist, we cannot definitively say that farmers have decided to switch from one crop to another in Mexico. We cannot say that with any degree of authority at this point.

Senator Kaine. But that is something that you are going to continue to monitor.

Mr. Chester. It is something that we do watch, yes.

Senator Kaine. Great.

Thanks, Mr. Chair.

Senator Rubio. To interject on that point, it is my sense—and you are both experts at this—that very few people wake up in the morning and say I am going to go shoot heroin just

for the first time. There is a gateway to the heroin use. A lot of it is being driven by people that were prescribed prescription opiates. They now become physically dependent. The prescription opiate is cut off. They are going through severe withdrawal, and the only thing that addresses that withdrawal, if they are not in treatment, is access to heroin, and that brings all sorts of problems.

Absent that, what is the other gateway? How does someone get dependent on heroin minus the prescription drug gateway, which we have already discussed?

Mr. CHESTER. Senator, it is a difficult question just because you are dealing with a number of variables down at the individual level as to the reasons why people engage in the behavior. We do know a couple things. Heroin in general terms is kind of at the end of a trajectory of long-term drug use and that a high number of heroin users are actually poly-drug users. And so they are not an exclusive heroin user. They get the drugs that are available to them, and because of the high availability of heroin, a lot of times that is heroin.

The other thing that we look at—and we do a number of surveys to look at this. But what we realize is that youth behavior from the ages of about 13 to about 18 is a very strong factor in terms of risk-taking behavior, in terms of underage drinking, tobacco, marijuana, things of that nature in shaping youth attitudes eventually that they carry with them for the rest of their lives in terms of risk-taking behavior for using other drugs.

So what we cannot say is that we can put a finger on this or that particular reason why a person does something, but we do know that the availability of drugs in society obviously increases the chances that an individual who is inclined to use them is going to intersect them at some particular point. And I think that is one of the—with the discussion we had about the availability of heroin being the driving factor.

Senator RUBIO. So just to understand your testimony, we understand the pill problem that leads to that. But what you are basically saying is if someone, especially at some point earlier in their life, begins to use a substance, alcohol, whatever it may be, an intoxicant of some sort, there now starts a potential trend where the next thing is, well, what is out there that is better, what is out there that is stronger. Once you have crossed that barrier, it could unleash this cycle of basically a set of dominoes that ultimately lead you to the heroin point.

Mr. CHESTER. Yes, sir. And again, it is not direct causation, but it certainly is risk-taking behavior and patterns of behavior.

And that is why the prevention strategies, particularly through programs like the Drug Free Communities Program that ONDCP manages are incredibly important because they are locally based, and they allow trusted individuals to be able to speak to people at very, very young ages about things just like that and their attitudes about drugs and foreign substances in the body and things of that nature. So they, through evidence-based prevention strategies, are able to talk to people at those young ages when they are vulnerable in shaping their ideas about drug use that they carry with them for the rest of their lives.

Senator RUBIO. Senator Markey?

Senator MARKEY. Thank you, Mr. Chairman, and thank you for this hearing. I think this is the most important hearing we are going to have on our relations with Mexico and with China this year in the Congress, and I thank you for it.

This issue of fentanyl is to my way of thinking kind of the most important threat that we have to families in the United States at this time. I will just give you some numbers. In Massachusetts, in 2015, 57 percent of the opioid-related overdose deaths in Massachusetts had a positive screen for fentanyl. Specifically of the 1,319 individuals whose deaths were

opioid-related in 2015 where a toxicology screen was available, 754 of them had a positive screen for fentanyl. So we can talk about prescription drugs. We can talk about heroin, but fentanyl is now the issue.

And we—that is, New England—are at the epicenter of it. It comes up from Mexico to Lawrence, Massachusetts, and then it goes out into New Hampshire, other States, but Massachusetts as well.

So the pathway is China into Mexico, then into Lawrence, Massachusetts, into Ohio, into Virginia, into Florida. And when it is over half of the deaths now in Massachusetts, it is clearly a looming threat that is a preview of coming attractions to every single city and town in our country.

So that is why this hearing is so important because it gets to the question of what is Mexico doing in partnership with China. We will start with that, Mr. Foote. What are specifically Mexico and China at the highest governmental levels doing in order to interdict this new synthetic formula that is lacing heroin with a drug 50 times more powerful than heroin, so powerful that the DEA does not even let its dogs any longer sniff for fentanyl for fear that the dog will just die with the first sniff of fentanyl. 3 grams, 3 equivalent of salt grams, could kill a human being if they gained access to it. What are Mexico and China doing in cooperation with you in order to interdict that drug?

Mr. FOOTE. Senator, first, I will touch on Mexico and China's bilateral relationship on this. With our support, Mexico and China are meeting and discussing fentanyl regularly every year. They are both involved in the multilateral side of things. Just last month at the U.N. General Assembly special session on drugs, they were both there. China—their minister of public security led the conclusion statement. They were fully on board. And they are a member, both countries, to the three international drug conventions.

We also sponsor in the United States two annual fentanyl and precursor chemical conferences with Mexico and China.

Senator MARKEY. So how successful is this effort so far?

Mr. FOOTE. That is a good question, Senator. Fentanyl is a new problem for the Department of State and INL, and it is one where we are applying lessons we have learned with other substances in other crime areas over the years, and at this point we are working as hard as we can to have success but I cannot quantify it.

Senator MARKEY. Has it been elevated to the highest level? In other words, with human rights and copyright infringement, is this issue now at the highest level of negotiations with the Chinese Government and with the Mexican Government?

Mr. FOOTE. It is. Mr. Chester went down in March with our folks and spoke to a large interagency group headed by the Attorney General in Mexico on this issue. We regularly engage with China. Our diplomats are going to China next week at a very high level diplomatic engagement where they will raise it. We raise it regularly in the joint liaison group on law enforcement, which has a counter-narcotics working group that meets throughout the year. We have actually seen some positive signs from China.

Senator MARKEY. What is the evidence? If you were going to convict them of doing something, what would the evidence be to convict them?

Mr. FOOTE. To convict?

Senator MARKEY. Convict China of actually doing something to block this from coming into Mexico and then into the United States. What would the evidence be to convict them of doing good?

Mr. FOOTE. Of doing good.

We have seen encouraging progress. There is still plenty to do. Last year, their ministry of public security officially controlled 116 new substances, including several analogs of fentanyl, and they have expressed high receptivity and continue to send information on new synthetic substances to help us to efficiently control them. So they are doing something. There is more that can be done, obviously.

Senator MARKEY. Clearly we have the evidence in 2015 in Massachusetts, and it is going to be worse this year in 2016. There is slim evidence that this thing is being slowed down. In fact, it is very clear that it is intensifying and it is going to kill. It is going to kill ultimately tens of thousands of Americans every year—every year. There is no other threat to our country that even matches that. Every single year, fentanyl is going to be able to do that. So if we do not stop it, it dwarfs every other issue. Every other issue will be a footnote compared to the magnitude of the impact on American families.

Mr. Chester, can we just go to Mexico? What is the level of cooperation that you are getting from the Mexican Government in interdicting fentanyl coming into the United States? We know it is el Chapo and his gang that is responsible for the traffic that comes up to Lawrence, Massachusetts, but pretty much for the whole country. What is your success level with the Mexican Government getting them to understand the magnitude of the threat to the American people?

Mr. CHESTER. Senator, I would tell you that I personally have been down there twice and then have dealt with the Mexican Embassy here in the United States. I will tell you that they understand how seriously we take this issue in the United States. They understand that this is our top illicit drug priority, and they also understand that it is not just heroin but it is heroin and it is fentanyl.

In a meeting down there in February, I put fentanyl on the table. And I will not say it was a “first heard” for them, but they were not really familiar with how serious the issue was in the United States. By the time we had gone down later with Director Botticelli and Ambassador Brownfield, that was part of the problem set that they agreed to work with us moving forward on.

So I will tell you that the Mexicans understand the importance that we place on this issue. They are very engaged on it, and they are willing to conduct a joint planning with us on the issues not only of poppy eradication, which addresses the heroin issue, but also lab identification and neutralization specifically on issues of either fentanyl creation or the milling of fentanyl with dilutants and other inert matter as it is transported across the border.

Senator MARKEY. Well, and it is a little bit disturbing to me if, from your testimony, it is a case of first impression for the principal law enforcement officials in Mexico, that they are just hearing about fentanyl, and it is just getting on their radar screen, and it is February of 2016, given the fact that more than half of all the people who died last year in Massachusetts, opioid-related, had fentanyl in their system. That is kind of a little bit disturbing to me. I am going to be very honest with you, and I do not like it to have just been introduced at that level.

I would like to have heard that President Obama has raised this issue with the president of Mexico, that President Obama has raised this issue with President Xi in China just because of the incredible level of fatalities all across our country. And we know specifically what the source of their death is.

So do you mind if I just continue a little bit? Thank you, Mr. Chairman.

So give me some hope here that there is an aggressive strategy in place on fentanyl and that it has been elevated to a level where there is a no-nonsense conversation going on in terms of what the expectations of our government is.

Mr. CHESTER. Right, Senator. In response to your concern, I know that the President did raise this with President Pena Nieto—the opioid issue with the Government of Mexico.

Senator MARKEY. He raised the fentanyl issue with——

Mr. CHESTER. I will check if it was specifically fentanyl, but I know the heroin issue was raised and the opioid issue——

Senator MARKEY. Well, I am asking about fentanyl here. Fentanyl is the epidemic. Fentanyl is the epidemic. It is not heroin. It is fentanyl. Fentanyl is 50 times more powerful. Fentanyl is what is showing up in a majority of the deaths. So you are not sure whether or not he has raised it.

Mr. CHESTER. And I need to make sure that fentanyl was part of that conversation between the two of them as well.

Senator MARKEY. How about you, Mr. Foote? Has the State Department specifically raised fentanyl at the highest levels with the Chinese Government and the Mexican Government?

Mr. FOOTE. We continue to raise it at the highest levels of dialogue that we have.

Senator MARKEY. What is the highest level?

Mr. FOOTE. Next week, our Deputy Secretary will be in China, and this is high on the agenda, if not top on the agenda. I cannot promise that President Obama raised it with President Xi, but certainly Secretary Kerry has raised it with the Chinese Government.

Senator MARKEY. Thank you, Mr. Chairman.

Senator RUBIO. Thank you.

Just a couple of points that I wanted to raise. First of all, why Lawrence, Massachusetts? Why New Hampshire? Why are these communities specifically targeted? In Florida, for example, central Florida, how does a community wind up targeted by these criminal gangs? What are the characteristics that are making them targets as opposed to some other part of the country?

Mr. CHESTER. Senator, there are a number of variables, one of which is the existing structure, the existing trafficker structure, that is in place in particular areas. In some cases, it is transportation networks. In some cases, the traffickers from Mexico have personal or business relationships with traffickers in a particular area or that geographically a place lends itself to further distribution. There are a lot of reasons why a particular——

Senator RUBIO. But the Northeast is far from the U.S.-Mexico border. I mean, my question is why did they not stop somewhere along I-95 and target there. Is it because of these existing structures that were there before?

Mr. CHESTER. We believe that there is very strong evidence that there are, that it is the existing structures that were there before.

When we specifically talk about fentanyl, one of the things that we have looked at as we have tracked the fentanyl crisis is why the Northeast, why the Eastern United States, why so much not the Western United States. And we believe that one of the strong contributing factors is the fact that fentanyl is more easily mixed into the white powder heroin which was preferred in the eastern part of the United States than it is in the black tar heroin which was preferred in the western part of the United States, and that has traditionally been the heroin market in the United States.

And so fentanyl is being mixed into powder heroin, and therefore it landed in the United States. And increasingly we are starting to see it be pressed into pill form and sold as counterfeit oxy or counterfeit opioids, but fentanyl has found a market in the Eastern United States probably because of those two reasons.

Senator RUBIO. I spent some time in New Hampshire over the last year and from that experience found myself in a lot of small townships, not large places, throughout New England that faced an overwhelming problem, almost as if they were specifically targeted perhaps because trafficking networks knew that they had smaller police departments. If you are a small township, you are not going to have a 1,000-officer department. Is there evidence that some of that is in play for these trafficking networks, that in essence, they look to set up in places where they can overwhelm local law enforcement with numbers and capabilities?

Mr. CHESTER. Senator, I do not know. I do not know whether the size of a population or the size of law enforcement was a particular reason why.

But to your point, it is a matter of deep concern that you find increasing numbers of heroin or fentanyl users in rural areas who are starting to use the product alone, and they are far from treatment and they tend to be further from first responders. Those are all things that make this particular crisis particularly pernicious. It is the fact that it has moved into a lot of rural areas, which is not something that we have seen in previous outbreaks of heroin or—

Senator RUBIO. And I know what I am asking—and perhaps it is more appropriate to the second panel—is more of a domestic issue as opposed to a transnational one. But some of the stuff we used to hear—because the supply is also driving the demand. They are interrelated. In essence, the supply meant these traffickers, who now had the supply on their hands, had to be more aggressive in finding market share. And one of the things I kept hearing a lot were that they were specifically targeting treatment centers, especially outpatient treatment centers where they knew people were getting treatment because of addiction, and they were waiting for them outside to tempt them to buy, that they specifically were targeting recovering individuals for the sale of this. And this is a pernicious, disgusting industry that we are dealing with here.

In that realm, I wanted to ask—you know, since the arrest of el Chapo, Secretary Foote, this is part of Mexico's, I believe, concerted policy to conduct high profile arrests of drug lords. And while it is positive that these organizations are being decapitated, have we seen any evidence that the arrest of a high profile individual impacts the ability of these organizations to continue to function specifically since el Chapo's arrest? Is there any evidence that the operation has been impacted by it, or is it just one of those things that is now functioning the way a corporate entity would, irrespective of who is at the top?

Mr. FOOTE. Senator, my personal experience is far more robust with Colombia where I led our programs several years ago. We have seen where the kingpin being arrested does certainly affect an organization. The question is how big is the structure, how organized is it, and how quickly can it recover. That is a question far better posed to our Drug Enforcement Administration guys than State.

Senator RUBIO. Let me ask you about Colombia. It is not directly related to the opiate issue, but nonetheless cocaine. They suspended their aerial eradication program ostensibly for fear of the impact that the defoliants would have on the population environmentally. There is a counter-argument out there that some have made, in which I find some credibility, that this is also part of the peace process, that in essence, this deforestation effort and the eradication effort was an irritant in the peace process with the FARC and other elements.

As a result, we now see numbers where for the first time in a long time there has been a massive increase in the amount of cocaine production in parts of Colombia that we had not seen in a while, and the assumption is that that cocaine is going to get sold. It is going to go somewhere and that we should expect at some point within the next couple years to see a spike in cocaine sales in the United States.

Do you have a view, irrespective of the reason why they are doing it, of what these new numbers mean for the U.S. in the years to come?

Mr. FOOTE. We are concerned about the suspension of aerial eradication. It is a sovereign decision of President Santos and the Colombian Government obviously. We believe while eradication and aerial eradication are not magic pills, they are valuable tools in any supply-side intervention on narcotics. It has long been a big part of our strategy in Colombia. We continue to work closely with the Colombians on the successor to Plan Colombia, which is Paz Colombia, Peace Colombia, and are in close contact to see which direction they decide to go if and when President Santos gets the peace process resolved.

Senator RUBIO. And here is my final question for the panel. And I thank you both for being here and for your testimony and for your work. The work you do is important and difficult.

We now have two separate but interrelated problems, as the Senators just pointed out a moment ago, the production of synthetic fentanyl, the growth of opiate poppies. My understanding is that the amount of poppy-based opiates grown in the western hemisphere is a small percentage of the overall production in the world. In your view—or do you know this—if a poppy-based opiate is produced or fentanyl is produced somewhere in the western hemisphere, Mexico or anywhere else, what percentage of that is destined for the United States in particular?

Mr. CHESTER. Senator, we believe that Mexico is the primary supplier of heroin to the United States and that the United States is the primary customer for Mexican heroin. That relationship in the western hemisphere is fairly solid. We do not see any widespread evidence of Southwest Asian heroin, Afghan heroin, Burmese heroin coming to the United States, although the Government of Canada does believe that Southwest Asia is its primary supplier of heroin.

So one of the things that we have discovered is a risk and we have identified as a risk is if we are successful against the Mexican drug trafficking organizations in bringing down the supply of Mexican heroin into the United States, do we open up the door for others.

Senator RUBIO. I think it is pretty clear that if you see a heroin overdose in the U.S., that heroin or that fentanyl came from Mexico or maybe in the case of fentanyl, China through the mail. I think that is pretty clear.

Here is my question. Are the opiates being grown or produced in the case of fentanyl in Mexico being sold anywhere else in the world or should we basically assume that virtually all of it that is being grown there—you can see it from the camera—pictures are being taken—all of that is headed to a city near you in the United States?

Mr. CHESTER. That is the assumption we make, Senator. Yes, that is correct.

Senator RUBIO. Well, I want to thank you both for being here. Did you have a final question, Senator Markey?

Senator MARKEY. Thank you so much. Again, for me this is the top topic. It does not get any bigger than this, and these are the gentlemen responsible for it in the United States. So

to have them here and to know that they are the principal people working on the fentanyl issue I think is absolutely central.

So let me just ask you this, Mr. Chester. Your title is Associate Director for the National Heroin Coordination Group. Do you think it is time for us to just change the name to the National Heroin and Fentanyl Coordination Group? Do you think we should change the name just so it advertises correctly what is going on to the American people?

Mr. CHESTER. Senator, when we began our work this fall as the Heroin Coordination Group, and after Director Botticelli stood up this group within ONDCP in order to provide focused efforts against the heroin and the fentanyl problem. In our work what we determined was that we were going to handle heroin and fentanyl as part of the same problem set for a lot of different reasons. What has evolved over time in our work and in our planning and our work with the interagency is that we have discovered the incredible importance of fentanyl more so than what was identified 6 or 8 or 9 months ago.

The other important thing about fentanyl that I would like to bring up is the fact that the emergence and the visibility of fentanyl is driven almost entirely by the postmortem testing that is done on individuals in overdose deaths around the country. And in those areas where the testing is done and fentanyl is tested as part of the toxicology panel, you begin to see more. So it leads us to believe that in looking at both the heroin and fentanyl problem, we have a significant fentanyl problem, as you identified, that we believe was being masked by this increased availability in heroin. So we handled both of them as part of the same problem set simply because it allows us to be able to deal with the trafficking and the supply chain and the effects on communities in the exact same way.

Senator MARKEY. No, I appreciate that. So that is what I am asking. Should we add fentanyl to your title in your opinion? Does that make sense given what you now know and given how little Mexico, it turns out, knows when you had the conversation in February of 2016 about fentanyl? They did not have it on their radar. Did we raise it so that they understand? The same thing is true for the Chinese. What do you think?

Mr. CHESTER. The issue being raised to the Chinese——

Senator MARKEY. No, no. I am talking about Mexico. I am talking specifically here about Mexico right now. They did not know in February.

And by the way, even when I say 57 percent, a lot of experts think that is an understated number because of the poor reporting that goes on in terms of the total number of deaths.

And by the way, it is no secret why they do it. It is like a 300 percent markup—300 percent markup—in terms of their ability to make money off this as opposed to heroin or other drugs.

So again, from my perspective, this is the issue. This dwarfs any terrorist threat to the United States. This is what is going to kill people, tens of thousands, ultimately hundreds of thousands of Americans. It is going to be this fentanyl that comes into our country. You are the front line on this. Mexico just heard about it. I am not sure the Chinese understand the priority that we expect them to deal with this issue.

Mr. Chester, earlier today in your testimony, you said that there are gaps in the interdiction of fentanyl from Mexico coming into the United States. Could you explain in more detail what those gaps are?

Mr. CHESTER. We are speaking primarily about gaps in our ability to be able to detect fentanyl at borders, and what was brought up earlier is the ability of canines, canines being trained in order to be able to detect fentanyl because it is so deadly.

And we work very closely with CBP both in terms of intelligence and in terms of policy to address those gaps to better detect fentanyl not only at the Southwest border but in our air freight locations in the United States whether it is U.S. Postal Service or whether it is a commercial company. That has been an area of ongoing discussion for us so that we can better determine how much fentanyl is getting into the country and to be able to detect it when it does arrive, and whether that is detecting the chemical, the fentanyl itself, or the dilutant with which it is mixed.

Senator RUBIO. Gentlemen, I apologize. We have got to move to the next panel because in about 45 minutes, I have to preside over the floor and I turn into a pumpkin here. Not literally. [Laughter.]

Senator MARKEY. If I may just conclude. I would just strongly recommend to the administration that when the President meets with the president of Canada and Mexico, that he raises fentanyl to the highest level with them and lets them know that that is a threat to our country. And the same thing is true in any communications with the Chinese Government that it has to be at the highest level.

Thank you, Mr. Chairman.

Senator RUBIO. Thank you, Senator Markey. This is an important issue in the Northeast and for the country.

And I thank you both.

We are going to welcome our next panel.

As we will say at the end of the hearing, we keep the record open for a few days. If you receive any questions in writing, if you would respond as quickly as possible so we can close the record. We thank you both for being here.

So as they are getting seated and situated, I am going to, once again, reintroduce the members of our second panel. The Honorable Teresa Jacobs is the Mayor of Orange County, Florida, which we hope, if it has not yet been finalized, will be the site of the Pro Bowl in 2017. Right?

Ms. JACOBS. Yes, it is.

Senator RUBIO. Maybe you can give us an update on that too. We are excited about it.

And, of course, Mr. Steven Dudley, who is the Co-Director of In-Sight Crime.

Mayor, if you are ready—your testimony has been submitted in writing, and we look forward to hearing you as well. Thank you for being here.

STATEMENT OF HON. TERESA JACOBS, MAYOR OF ORANGE COUNTY, FLORIDA

Ms. JACOBS. Thank you, Chairman Rubio. And thank you for calling this very important hearing and allowing me to share a local perspective. The conversation this morning has certainly been informative for me, as I am sure it has been for everyone here.

First, a little background on Orange County, nothing that you do not know, but for the record. Orange County is home to the City of Orlando and 12 other municipalities. We have a strong economy and an exceptional quality of life. We have a population of 1.2 million people that call Orlando home, but we also have 66 million visitors on an annual basis and we continue to shatter national records for tourism. That is the good news.

The bad news and the very sad news is that we, like too many other communities across this country, have seen an alarming increase in the number of heroin overdoses and related deaths. I say heroin. When I say heroin, I mean opioids, opiates, I mean fentanyl, all of them combined. Last year, we lost 85 lives to heroin. We lost 62 lives to fentanyl.

We have heard this morning testimony about the increase in deaths related to opioids and opiates of anywhere from 200 to 400 percent since 2007. In Orange County, we have had a staggering 600 percent increase since 2011 alone, and already this year we have had 90 reported opioid overdoses, about 1 in 10 resulting in death.

Florida's fight against this current wave of opioid addiction began about 5 years ago. You may recall that in 2010, Florida was known as the "pill mill capital" of the country. Florida practitioners were prescribing oxycodone at levels that exceeded all the other States in our Nation combined. At a State and local level, we responded by outlawing unauthorized pain clinics. Yet, today the battlefield has moved. Today we fight heroin. Today we fight fentanyl.

Given the dramatic rise in the flow of heroin and fentanyl into our community, one can only surmise that drug cartels perceived us as a ripe marketplace. Unfortunately, it is nearly impossible to accurately assess the size of the heroin threat in Florida and across States in our Nation. But there are a few things that we do know.

In Orange County, we know that last year approximately 2,000 heroin users moved through our county jail alone, and on any given day, we treat roughly 200 heroin addicts in our jail. We know that in 2015 our county jail housed 100 expectant mothers who were addicted, whose babies will most certainly be born tragically addicted to heroin. We know that over 60 percent of overdose patients are uninsured, and yet we have only one inpatient facility with 26 detox beds available to the uninsured for all four counties in our region, with a combined population of 2.5 million people. Simply put, we know that our county jail has become the treatment center of last resort for far too many people who find themselves addicted to heroin, fentanyl, and other opiates and opioids.

For the good of our citizens, we are fighting back, and here is how. Last summer, we convened the Orange County Heroin Task Force, chaired by myself and our sheriff. Our joint work is having a positive impact, including the passage of the 2016 Florida legislature, which passed a measure allowing naloxone sales without an individual prescription. And while there is no single cure or solution, we know there are some universally effective approaches, many of which have been discussed here today. But I think at the heart of it is that we have to recognize that we must address the demand side while we attack the supply side, and an either/or policy simply will not work.

On the demand side, through our task force, we have joined forces with our K through 12 public education system, our universities, our faith-based communities, our medical communities. Together we are launching a social media campaign to educate the public on the risks of this highly addictive and deadly drug. We are trying to convince our citizens and warn them in advance that this is something that they want to avoid at all costs.

We are also not only treating heroin addicts in our jail, we are implementing a new medically assisted treatment program using Vivitrol. And this is an option for all of our addicts that are leaving our jail.

But we need the Federal Government's help to treat more addicts. As I mentioned a few minutes ago, we are woefully short on beds and other resources.

On the supply side, we are also doing our best to arrest traffickers on our streets. But our local efforts, no matter how highly leveraged and coordinated, are simply no match for the

drug cartels and organized traffickers coming across our country's borders. And that is why we need your help to help stop the influx of drugs across our borders.

To end the crisis, to save lives, to save communities, we each have a role to play. Local governments have a crucial role to play. The State government does and the Federal Government does. But the efforts need to expand beyond government. We need every citizen that is a mother or a father or a friend of an addict—we need our entire communities engaged. We need doctors. We need the clergy. We need counselors. We need teachers. We need all of them to be informed. And that is why I think that we also need a nationwide awareness campaign.

And we have talked briefly about fentanyl. It needs to include the high risk of fentanyl and the low cost. Quite frankly, today it is less expensive for many of our addicts to get high on opioids than it is for them to go and get a Happy Meal. That is a sad state of reality that has to be addressed.

Thank you again so much for this opportunity, Mr. Chairman. Thank you for your and your committee's continued service and leadership on this issue.

[Ms. Jacobs's prepared statement is located in the Additional Material Submitted for the Record section at the end of this transcript.]

Senator RUBIO. Thank you, Mayor, and thank you for your work on this. You have been involved in this for a while now trying to deal with it back when the pill mill problem was going on, and we will talk about that in the questioning section.

Mr. Dudley, thank you for being here. We look forward to your testimony.

STATEMENT OF STEVEN DUDLEY, CO-DIRECTOR, INSIGHT CRIME, WASHINGTON, D.C.

Mr. DUDLEY. Thank you very much, Chairman Rubio.

As we know, as U.S. consumption of heroin has increased significantly in the last few years, the U.S. portion of the world heroin market is quite small by comparison in terms of users but really outsized in terms of potential earnings. The RAND Corporation estimated in 2014 that U.S. consumers spent as much as \$27 billion on heroin each year, an increase from \$20 billion in the year 2000.

Mexican, Guatemalan, and Colombian criminal organizations have reacted to these changes by producing more heroin.

As noted already in the earlier panel, Mexico accounts for the bulk of the poppy production in the region.

Seizure data of heroin along the southwest border also indicate that Mexican criminal groups are moving increasing amounts of heroin into the U.S. market. Mexican criminal organizations are also the key transporters of Colombian heroin to the United States, and they manage and purchase the heroin produced in Guatemala or buy the opium gum wholesale to process it into heroin themselves in Mexico.

Inside the U.S., the trend appears to be the same. The DEA says that Mexican groups are seeking an increasing amount of the market share in the distribution business itself, displacing other wholesalers.

In sum, the picture we have is one of an increasingly lucrative, vertically integrated market with large Mexican criminal organizations managing the product from the point of production to the point of sale and seeking a greater market share of these sales.

The reality of the supply chain, however, is much more complex. While it helps us to use well-worn monikers when talking about these organizations, the truth is that they are not nearly as strong or monolithic as they once were. Names such as the Tijuana Cartel, the Juarez Cartel, the Zetas, or La Familia Michoacana may still evoke fear and sometimes awe, but they are not organizations as much as brand names. In many cases, the individual parts of the organization have as much contact with the bosses as a local Coca-Cola bottling plant manager might have with corporate headquarters.

Even the vaunted Sinaloa Cartel is more horizontally than vertically integrated. Take the recent case of the Flores brothers in Chicago. Before they were arrested, Pedro and Margarito Flores were said to be Sinaloa Cartel distributors in Chicago, one of the areas of greatest interest to this subcommittee. And they were. But as Federal intercepts of their conversations with cartel leaders show, the two brothers negotiated independently with each of the top two members of the Sinaloa criminal organization, obtaining different prices for the product that they were selling. Even after a war started between the Sinaloa Cartel and a rival group called the Beltran Leyva Organization, the Flores brothers continued to purchase drugs from portions of the Beltran Leyva organization and the Sinaloa Cartel.

The Flores case cuts at two different myths about the Sinaloa Cartel: number one, that this is one single organization; and number two, that it is tightly controlled by a single leader or a single group of leaders. The point is that as shipments get further and further from Mexico's wholesale points, the loyalties become more disperse and in some cases completely disappear. This is especially true in the U.S. market where violence is not a viable long-term option to ensure loyalty, win market share, or become a monopoly.

The effectiveness of U.S. law enforcement has made violence terrible for business and made the distribution chain a more democratic, capitalist affair. This is evident in other ways as well. While the amount of seizures indicates that there is more heroin available in the United States, it is still moved in very small quantities. The median seizure for the Los Angeles Field Division of the DEA in 2014, for example, was a single kilogram. In Denver, a 10- to 12-pound shipment is considered large.

The case of the Laredo brothers, recently indicted in the Eastern District of Pennsylvania, is indicative of these trends. The Laredo brothers are charged with moving 1 ton of heroin over a 6-year period. This is about 14 kilos per month. The organization was so subtle and, as one Mexican analyst put it, "mom-and-pop," the Mexican authorities were not even aware of the group.

This brings us to Mexico. The horizontal nature of the distribution chain makes it a difficult law enforcement problem in Mexico as well. As noted, the once monolithic criminal organizations are shells of what they once were. This is in part due to infighting of the type mentioned earlier but also Mexican law enforcement efforts. Many of the fragmented pieces have formed their own criminal organizations and brand names.

The upshot is that the chain of production in Mexico is broken into numerous pieces, including small and large producers of opium poppy plants, the opium gum producers, and processors, the wholesale purchasers, and the transporters. Production, transport, and distribution may all be different organizations. The Laredo brothers, for example, were purchasing opium gum from an independent broker, then processing it themselves, and

distributing it in those small quantities in the U.S. for years without running into trouble with the large, supposedly all-controlling Sinaloa Cartel.

To be sure, violence is still a viable option in Mexico, so the pendulum may swing back towards more monolithic criminal organizations. But for the moment, the reality is that there are literally dozens of small criminal organizations involved in this trade from the point of production to the point of sale.

In sum, while the level of control that the Mexican production and transport groups exert over the supply chain is clear, we are not talking about one or two criminal groups, but dozens of interlocking organizations whose alliances are constantly shifting. The heroin supply chain appears to be a largely horizontal, diversified operation with multiple actors, and one that is obedient to market forces rather than one or two single vertically integrated distributors.

The result is that law enforcement efforts are largely muted. Whether you debilitate the Sinaloa Cartel or the Laredo brothers, you are hindering a small part of the overall production and distribution chain. Even if you did slow the heroin from Mexico, you would face an insurmountable task: stopping the flow from other countries, which would undoubtedly fill the void and account for the bulk of worldwide production anyway. Canada already gets up to 90 percent of its heroin from Afghanistan. And the United States once got all of its heroin from the Asian markets that supply the rest of the world.

Thank you for your time and attention. I look forward to your questions.

[Mr. Dudley's prepared statement is located in the Additional Material Submitted for the Record section at the end of this transcript.]

Senator RUBIO. Thank you both for being here.

I want to begin with one of the questions I alluded during the testimony, and that is—I cannot prove it. I guess it is anecdotal. We do not have a number behind this. But the notion that these criminal groups are specifically targeting people recovering. In essence, they basically station themselves outside of a rehabilitation outpatient center, even an inpatient center, knowing that these people are vulnerable and enticing them to fall back into addiction.

Mayor, have you seen evidence of this? Mr. Dudley, have you heard about this as a recurring issue, a specific practice at the local level of targeting people in recovery for sales?

Ms. JACOBS. Senator, I have not seen evidence of targeting our treatment facilities.

I will say that it certainly appears on the surface that there has been a targeting effort towards which communities to infiltrate with heroin, and certainly I look to the increase in heroin coming into our communities, the increase of fentanyl at the same time that we were restricting access to prescription drugs as suspecting that there is a strong correlation between those two and a causation between those as well. But I do not have direct evidence of it. It just seems hard to imagine that there would not be a direct relationship between them.

Mr. DUDLEY. Thank you, Senator.

I also do not have direct evidence of this activity on a local level. I will say in Mexico that criminal groups have targeted recovery facilities, but more as recruitment centers, not necessarily—— Senator RUBIO. Recruitment centers for?

Mr. DUDLEY. Recruitment centers for them, to basically build out their own criminal operations.

Senator RUBIO. You mean for like dealers?

Mr. DUDLEY. Not for dealers. Just for membership. So people who would participate in the criminal organization. So that has certainly happened especially with regard to La Familia Michoacana, a very famous group there.

The upshot of this is to say whether or not they are targeting to pushing drugs in certain areas I am not sure is as relevant as this sort of whole picture, which is what the Mayor alluded to, which is this idea that this is largely driven from people who use pharmaceutical drugs, and those people you can find all over. And that accounts also for the sort of dispersed nature of this epidemic as opposed to sort of the 1970s where you had it very concentrated in urban areas. Now we have it spread out throughout many different parts of the United States.

Senator RUBIO. So I want to share with you an anecdote. This weekend, I have a personal friend who is a police officer in Miami Dade County, and he recounted a story that he pulled up to a car that was kind of pulled over on the side of the road. And there was a woman in the driver's seat. She was kind of slumped over, and it caught his curiosity. So he pulled over and knocked on the window. This was a nice car, by the way. Obviously, this is a person of financial means. Knocks on the window and the person immediately pops to attention. And he can see that in her arm there was a needle. She was basically shooting up on the side of the road in a luxury vehicle. Knocks on the window. She rolls down the window. They begin to interact. Obviously, he had a decision to make about how to treat her. This is someone who said 10 years ago he would have arrested her and taken her in as a criminal using drugs in the street.

Today his perception has changed because he has had several interactions, including this interaction with a person who, by the way, is a member of the Florida Bar, is a successful, functional attorney whose husband apparently also has a problem. The fundamental challenge he faces: he does not want to take her to jail. He does not view her as a criminal. He views her as someone who has a disease and is in need of treatment to overcome it.

And by the way, her gateway into heroin was the use of a pharmaceutical pain killer for a surgical procedure 6 or 7 years ago, which she lost access to the medicine, and this is what has happened.

And so the concern that I have is twofold, and perhaps you can both opine on this.

Number one, if today you are dependent upon an opiate substance, irrespective of how you got there, but let us say in the case of this person because of the use of a pharmaceutical that led to this point, there is still an extraordinary stigma associated with it as if you are a bad person who is doing a really bad thing and needs to be punished for it.

And second, even if that stigma were to change so that we can get more people into treatment and accepting the fact that I am physically dependent on this substance, in many communities there is nowhere to take them. The only place you can take them potentially is to a jail where you hope their withdrawals are managed but may not be. And in essence, there is nowhere for them to go. We have many places. We just do not have the capacity to meet that reality.

Which leads to the third problem, and that is the number of people who end up in a jail cell for 15 days, go through withdrawal, do not realize they have lost their tolerance, even in that short period of time, and when they fall off the proverbial wagon, they go back to using the levels they were using before they went through withdrawal and it kills them because they lost their tolerance for an opiate.

So given that perspective, I am sure there are hundreds, if not thousand of cases like that. What are the impediments to getting someone who faces this now who—I do not think so, but

could be watching C-SPAN at this very moment. Not many people watch C-SPAN—but are watching this or are hearing us talk about this. What is out there today or what is missing for someone who needs this treatment and just does not know what to do about it next? Because especially for the uninsured, there are not very many options from my understanding.

Ms. JACOBS. Thank you, Mr. Chairman. I think that is a key part of addressing the demand side. Part of it is to educate people and help them make the right choices to avoid overuse of prescription drugs, but the other part is how do we provide the resources to treat people that are addicted. And the treatment options are very limited. For the uninsured, as I pointed out, 26 beds for 2.4 million people. Our jail alone, one out of four jails in the region, we have on average 200 people that we are treating for withdrawal symptoms and offering them a treatment program when they leave. We need more treatment facilities.

When you ask me the question are traffickers, are dealers preying on people coming out of treatment centers, the reality is we do not have enough treatment centers to prey on.

Senator RUBIO. You said in your testimony—and I do not want to interrupt, but you said in your testimony you believe that Florida was specifically targeted because they knew we had the pill mill problem, and once that was cut off, these folks were going to need—

Ms. JACOBS. Exactly. That is what I believe. I do not have empirical evidence. What I have is the evidence of the increase in the flow of heroin and the increases in deaths related to heroin in correlation to our cutting off the pill mills.

Let me also say that while we were dispensing more oxycodone than the rest of the country combined out of Florida, most of that was leaving our State. And most of these pill mills—you could drive up and you could look in the parking lots. The parking lot would be full and only a small percentage of those were local license plates. So the cartels may have misjudged the appetite, but they, no question, have flooded us with very, very cheap drugs.

And the number of youth that I have seen that are struggling with addiction and have turned the corner and have had the good fortune and the money to find treatment, the insured portion of that population, to see that there actually is life after heroin addiction is very encouraging. But what is very discouraging is that most people that are addicts have no idea there is life, and most people that are addicts have no opportunity to get to those treatment centers.

Senator RUBIO. Just to fill in the gaps for those who may not be fully aware of the Florida pill mill problem, we had these facilities. You just basically pulled up and said my neck hurts or my back hurts, and by routine, they would give you a package of prescriptions. It was not just, by the way, oxy. They also put some other stuff in there. And people knew this, and you would have busloads of people actually come in sometimes. It was a huge problem. The Florida legislature closed that loophole that was allowing this to happen. So just to be fair, we are not talking about the oxy prescriptions being driven by a doctor at his or her office. It was these specific facilities that drove it.

Did you want to add something on the treatment part of it? Because I had one more question. I know that Senator Kaine—

Mr. DUDLEY. Just very quickly. I mean, this is obviously framed as a law enforcement debate. And certainly I was asked to talk about the criminal organizations.

But as you rightly pointed out, this is a public health issue. At the heart of it, this is a pharmaceutically driven epidemic, and it is a public health issue. And that is really the difficulty in facing up to this is that it is not necessarily strictly law enforcement. We are not

talking about throwing people into jails. We need to be talking about how to get them better treatment.

Senator RUBIO. And my sense on the human side of it is I do not believe anyone wakes up in the morning and says today is the day I become a heroin addict or an opiate addict. It is not something somebody wants to happen. You just see growing evidence. People do not realize the power of this. There is no responsible way to use this, and its impact on everybody is a little different. We know some people are more sensitive or susceptible to addiction than others, but it basically restructures the brain's chemistry in a way a disease would and it has to be treated as that.

I look at these statistics, for example, in Florida as just an example. Orlando had 83 heroin deaths in 2014. Other communities have large numbers with West Palm Beach at 51, Miami at 60, Sarasota at 55. But that number pops out at you as a place that has been specifically targeted.

And then you see the rise in deaths and kind of the spike we have seen across the country in heroin and opiate deaths where the takeoff point is the introduction of fentanyl which, as we have already seen from testimony today, is an incredibly powerful and lethal substance, which in fact from my understanding is not prescribed outside of a hospital setting to begin with on the pharmaceutical side and is now being laced into——

I want to go to Senator Kaine. So I wanted to leave with this thought. I read the other day a report where someone who was a former—he is now a recovering addict—was asked about this and said, you know, when you hear that someone has died from an overdose that was sold by a particular dealer, it makes you want to buy from that particular dealer because you know what they are selling is the strong stuff. Now, maybe that is just one interview, one line somebody said. But it just kind of tells you the point we have reached here where it is a very difficult and debilitating condition that we have to try to understand here. And I think one of the keys is to remove the stigma associated with it.

And I think many of us would be very surprised at the number of people we interact with on a daily basis that at some level have a dependence problem, maybe not through street heroin, but of some sort as a result of what we have seen happen in this country. And hopefully we can make advances in pharmaceuticals so that we can draw the line and we will be able to treat pain effectively in this country without putting people at risk.

Senator Kaine?

Senator KAINE. Thank you, Mr. Chair.

And thanks to each of you. I am sorry I missed your opening testimony, although I read your written testimony.

And, Mayor, I will start with you. I was a mayor too in Richmond. And it was only when I was mayor that I really fully grasped the depths of the demand side of this challenge. You know, you can arrest a dealer and arrest another dealer and arrest another dealer, but if the demand for drugs is so potent, if it has its hooks in people so deeply, the next dealer will appear tomorrow.

We had a really tough problem in Richmond, and a lot of drug-related homicides were taking place in this little neighborhood near where the church that I go to is. And the number of stories that would appear on the front page of the paper about somebody from the suburbs coming in to buy drugs and getting shot at the corner of 2nd and Maryland or wherever, and you would think about five of those stories, people would quit driving in to buy drugs there. But, no, they would keep driving in to buy drugs.

And that just was evidence of how powerful addiction is, that you would have all this objective evidence that, wow, this is really going to be dangerous for me to go, but much less that the drugs could be dangerous, I could get shot, but the need is so intense that I am still going to go. And it sounds like you have seen that in your community. I was a mayor 20 years ago. The drugs were different. But it is the same thing of this addiction. And that is why the treatment issues are so important.

And the other thing we used to hear anecdotally—I am not an expert in this field, but when somebody who is under the grip of an addiction says I want treatment, that is a window that opens where the treatment, if it is not there, the window can close. And in a month from now when the bed opens up, the individual may be past the point of wanting treatment, may have ODED or may have lapsed back into behaviors not desiring treatment. So I do appreciate what the chair was saying and you were saying too about the need for treatment.

I am curious if you can talk about as a mayor the way to solve some of these challenges is definitely through how the partnership, State, Federal—talk a little bit about what you have done in your county on the partnership side. Do you have the right stakeholders around the table? Are there things we can do from a Federal level to ensure that if we are issuing funds, that we do it in a way that requires regional cooperation or multi-level stakeholder cooperation?

Ms. JACOBS. Thank you, Senator. In Orlando, one of the things that I think we have done very effectively is regional cooperation and collaboration. I think that that is crucial on tackling any large issue such as this. And so one of the reasons that we pulled together the task force that we did is we brought in so many different disciplines to make sure that we could attack this problem from all angles.

It is so important. We have limited resources at all government levels, and it always seems like the demand for resources outpaces supply. So it is important that programs are structured in a way that the funding is put to its best use.

And I do think that collaborative effort is important. We have a Metropolitan Bureau of Investigation that pulls together our FDLE, FDA, our local law enforcement, our police officers, our sheriff, our State attorney's office. That has been very effective for us on the enforcement side of this.

In terms of your comments about that window of opportunity for addicts, I cannot understand it either because I have never experienced a feeling of needing something so badly that I am willing to risk my life to have it. But I do understand that is the reality. I know enough people. Once we formed the task force, enough people came forward, literally walked up to me on the street. You know what it is like being a local mayor. People recognize you. They come up and they pour their heart and soul out to you. And it is a blessing to be at that level where you can really heard firsthand. And I have seen young people that you would never in your wildest imagination have thought were heroin addicts tell me their stories.

And what I also saw—I think I mentioned before you walked in here—was I also saw the other side. I saw that they came out the other side of heroin addiction, and they are living full lives and they are getting college degrees and they are going to be productive members of society.

And I think that most heroin addicts do not believe that is a possibility, and if they have that moment, if it is 15 minutes, if it is 2 hours, if it is 2 days, where they say, gosh, I want to kick this, reality is they are not going to be waiting for 2 weeks or a month. They are going to

be waiting a lot longer in most of our communities to get into a treatment facility unless they have got a substantial amount of money. And that is a huge problem.

And as I said in my testimony, the best option is our county jail right now, and that is a lousy option. Not to say we have a bad jail. We do our best. But having a record does not help the situation.

So we really need to have options available. We need to have education. We need to have hope. We need to have whole communities that are engaged. And as you point out, it is destroying more than lives. It is destroying entire communities.

Thank you, sir.

Senator Kaine. We had, Mr. Chair, a chart recently placed before us at another hearing about opioid-based ODs per capita, the 50 States arrayed. It was unlike any chart I have ever seen ever. If you look at a chart that is usually about some kind of problem or crime or social breakdown, high income States will be at one part of the chart and low income States will be at the other part of the chart. If you looked at the top 10 most affected States, they included some of the poorest States in the country and some of the richest States in the country. And if you looked at the bottom 10 affected States, they included some of the poorest States in the country and some of the richest States in the country. This is really unlike any sort of similar epidemic or law enforcement problem I have ever seen in the traditional demographic data, not at all a predictor. It is rural over the suburban. It is all regions.

I went to a drug court graduation. Kind of the founding drug court in Virginia is in the Roanoke area, and the judge who founded it, who was this super, farsighted thinker about the need for drug courts, had a child who many years later was killed in a drug-related incident. And after I spoke at the graduation, one of the probation officers who helps the court run and has done so as a spectacular advocate for many years came up to me and said this is my second drug court graduation this week. I said, did you have another class? He said no. I went to my son's graduation in a community about 2 hours from here.

This affects every level, and that is why we are now spending the time that we are. But we have not spent time in this committee on it, and it is really important that we do so because this is not—just like it does not have demographic borders, this is not a problem that even has national borders. And we have got to grab a hold of some of the dimensions, Mexico, China, the other nations that are experiencing this, and build those partnerships not even in a metropolitan region, but we have got to build law enforcement and other partnerships internationally.

Thank you for being here, for your testimony.

Thank you, Mr. Chair.

Senator Rubio. Thank you, Senator.

And I just wanted to ask you, Mr. Dudley, about these transnational groups that are targeting us. I think in your testimony you talked about this. So I just want to reiterate it. Whether it is fentanyl being produced synthetically or poppy-based opiates being grown in the Western Hemisphere, in particular in Mexico, they are coming here. This is the almost exclusive market for these trafficking networks. Is that correct?

Mr. Dudley. That is correct, absolutely. There is a small market, local market that they can satisfy, but it is minimal.

Senator Rubio. Because you would think—so logically they are crossing the border, you would think the easiest from a logistical point of view is for them to flood it into Texas or flood it into California or into a border State. But you are hearing where the outbreaks are.

And this is a national problem. There is no community in the country that does face it to some level, but you see these outbreaks in the Northeast in New Hampshire and Massachusetts and in places like central Florida. So it is not even I-10 alone where you would think they would come across.

What is your view of how is it winding up in these pockets? What are the distinguishing characteristics? You heard the previous testimony of the government witnesses. What in your view are the distinguishing characteristics that turn a community into a high- propensity, high-risk area?

Mr. DUDLEY. You know, it is such a new phenomenon because it is so disperse. But the fact that it is so disperse is really what leads to the criminal organizations being so disperse. And the notion that we have one single, all-encompassing enemy that is called the Sinaloa Cartel and once we incarcerate Chapo Guzman, then everything will be resolved is just simply not correct just because of the disperse nature of the market and the way in which these criminal organizations will satisfy that market.

It is an odd thing because in a way there are certain elements of this epidemic that we are victims of our own success. The fact that you would create ways so you cannot tamper with OxyContin, for example, you cannot store it anymore, the way in which it is distributed, well, then that makes it less available to people so then they start to search out other things.

The way in which the Mexican Government, in conjunction with the United States Government, has captured or killed several of the larger leaders of the larger criminal organizations has led to a fragmentation of these groups. So you have groups like you referred to Guerrero earlier. There is a Guerrero Unidos group, which was the group responsible for the massacre or supposed massacre of those 43 students that disappeared, 43 students currently still. You know, this is a group that was an offshoot of a larger group, the Beltran Leyva organization, and there are several like them.

So in order to wrap your hands around this as a law enforcement issue, it is incredibly difficult because the terrain is so much more horizontal than vertical. And even when you take out the larger leaders, what you are left with is a fragmented criminal landscape, and a landscape that does not necessarily—as in the cocaine market, they might depend on getting product from another country. In fact, they do from the Andes region. They need to get their product from other criminal organizations. But they do not have that dependency when it comes to the poppy production which is local and the heroin production which is local. So they can produce all of this themselves, which makes it much more difficult to wrap your hands around as well.

Senator RUBIO. Well, do you have anything further Senator?

I want to thank both of you for being here, for sitting through the previous testimony. I hope that was insightful as you go back and continue your work. And I want to thank you for coming here today and being a part of this hearing as well. This is an important issue. There has been a lot of debate about what is being done domestically on this issue. I am glad we touched on it.

I think this has to be dealt with. There is not like one law we can pass that deals with this. It has to be dealt with comprehensively whether it is on the treatment side for people to recover, on the prevention side, but also by targeting these organizations who are in the business of murder basically, which is what this ultimately is, and not just murdering each other for territory, but the direct murder of Americans by targeting us with the distribution of these products in our country.

So I want to thank all of you for being here.

I also want to ask consent to enter a statement for the record of Jack Riley, who is the Acting Deputy Administrator of the Drug Enforcement Administration. And without objection, I show that ordered.

[Mr. Riley's statement is located in the Additional Material Submitted for the Record section at the end of this transcript.]

Senator RUBIO. The record for this hearing is going to remain open until the close of business on Tuesday, May 31st. You might receive some questions in writing. If possible, I would ask you to respond just so we can close the record on this.

And with that I thank you both for being here, and this meeting is adjourned.

[Whereupon, at 10:55 a.m., the hearing was adjourned.]

ADDITIONAL MATERIAL SUBMITTED FOR THE RECORD

Additional Questions Submitted for the Record by Members of the Committee, Responses to Questions Submitted to Assistant Secretary Daniel Foote by Senator Marco Rubio

Question 1. Mexico has been a very good partner but systemic corruption and other issues, including issues of trust, persist. What is the U.S. government's assessment of Mexico's commitment to truly stopping the Sinaloa cartel, in particular, and the flow of illicit narcotics to the U.S.?

Answer. Our partnership with the Government of Mexico on counternarcotics has led to enhanced collaboration on this important issue. The State Department's Bureau of International Narcotics and Law Enforcement Affairs (INL), under the Merida Initiative, is working with the Government of Mexico to help build the capacity of Mexico's law enforcement and rule of law institutions to disrupt drug trafficking organizations (DTOs) and to stop the flow of drugs from Mexico to the United States, including augmenting their ability to coordinate with U.S. law enforcement agencies. Through Merida, we have provided the Mexican government with the communications equipment and technical assistance to enable the Department of Homeland Security's Customs and Border Protection (CBP) and the Mexican Federal Police to conduct coordinated patrols of our shared border. Merida-supported implementation of the Cross Border Secure Communications Network and Cross Border Coordination Initiative provides direct communication between CBP Sector Offices and Mexico's Federal Police and State Command and Control Centers at ten locations along our shared border. INL also is working in partnership with CBP to provide training to Mexican Federal Police officers assigned to the northern border region.

The United States and Mexico are working to increase communication and information sharing on combating the production and trafficking of heroin and meth-amphetamine. In addition to discussions at the high level Security Cooperation Group meetings, in the last year INL supported U.S. Drug Enforcement Administration-led bimonthly counternarcotics meetings, which bring together experts from both countries to share information and strategies. These efforts to increase cooperation are paying off. Federal and state police in one

of Mexico's northern border states recently arrested two suspects and seized 630 kilograms of methamphetamine, 80 kilograms of heroin, 48 kilograms of cocaine, one semi-automatic weapon, and two AK-47 assault rifles after acting on real-time intelligence provided by U.S. law enforcement. The federal police unit involved in the operation participates in the bimonthly counternarcotics meetings.

In recent years, the Government of Mexico has taken active steps to reduce corruption and other illegal activities in police forces and government institutions by vetting public officials through its Control de Confianza system. INL seeks to strengthen and accredit Mexican vetting institutions by establishing and deploying uniform standards for polygraph administration, background (socio-economic) investigations, and psychological assessments.

Question 2. Mexico has adopted a policy of high profile arrest of drug lords. While it is positive that these organizations are being decapitated, has the drug trade run by the cartels been impacted by these arrests in the way envisioned?

Answer. Capturing and successfully prosecuting high profile traffickers who have committed serious crimes and have operated with relative impunity is essential to maintaining the rule of law. High profile drug lords are responsible for the deaths of tens of thousands, and their sophisticated organizations create violence, generate illegal earnings and influence, and ultimately harm U.S. citizens and interests through cross-border flows of illicit drugs, goods, and people. We refer you to the U.S. Drug Enforcement Administration for additional details on the potential impact on the drug trade resulting from Mexico's high profile arrests.

Recognizing, however, that targeting high profile traffickers alone will not solve Mexico's security dilemma, the State Department's Bureau of International Narcotics and Law Enforcement Affairs (INL) supports Mexico's security and law enforcement efforts more broadly. Combating transnational criminal organizations requires a comprehensive approach that disrupts illicit financial and trafficking networks, combats government corruption, strengthens the rule of law, bolsters judicial systems, and enhances transparency. Under the Merida Initiative, INL focuses not only on disrupting organized criminal groups, but on institutionalizing rule of law, strengthening border security, and building strong and resilient communities in Mexico. INL's efforts to enhance state-level law enforcement professionalization, support Mexico's efforts along its northern and southern borders, and assist Mexico's transition to an accusatory justice system all augment the capacity of Mexico to effectively provide security, disrupt organized crime, and manage its borders.

Question 3. Since the arrest of Joaquin "El Chapo" Guzman, has there been a noticeable drop in narcotics trafficked by his organization? Specifically heroin?

Answer. At this time, the effect of El Chapo's arrest on the amount of narcotics trafficked by the Sinaloa Cartel is unclear. We refer you to the U.S. Drug Enforcement Administration for additional information on shifts in the trafficking of narcotics, including heroin.

The United States is fully committed to working with Mexico to combat the production and trafficking of illicit drugs. Over the past year, our bilateral dialogue, specifically on heroin, has reached an unprecedented level of openness and coordination and we are continuing to work closely with Mexico to increase these efforts.

Question 4. What successes can the U.S. government point to in cooperation with the Mexican government that have yielded concrete results?

Answer. For the past eight years under the Merida Initiative, the U.S. government has worked closely with the Government of Mexico to advance our shared security objectives and these efforts are demonstrating results, including:

Criminal Intelligence and Analysis Program: To support the Government of Mexico in improving criminal investigations to hold drug traffickers and other criminals accountable and boost public confidence in the rule of law, INL is supporting the professionalization of criminal intelligence analysts throughout Mexico. Initial programming has focused on equipping and training analytic units along the Mexico- U.S. border to serve as the primary state-level liaison with U.S. law enforcement entities to develop intelligence related to drug cultivation and trafficking, extortions, kidnappings, and homicides.

INL has trained and equipped five analytic units that have contributed to 1,900 investigations/citizen complaints resulting in more than 200 arrests as of the end of 2015. The units in the cities of Chihuahua and Ciudad Juarez provided intelligence that led to the arrest of a principal leader of the Sinaloa cartel. The Chihuahua unit also assisted in the identification and apprehension of two suspects responsible for an attack on a Ciudad Juarez television station, in addition to six kidnappings and five homicides. This unit also aided the apprehension of suspects responsible for the murder of the sons of two prominent Mexican journalists. The Sonora unit developed tactical intelligence, which led to the arrest of four suspects, identified as former Mexican military and enforcers for the Sinaloa Cartel. It also worked with ICE/HSI on an investigation that resulted in the seizure of five weapons, one grenade, three vehicles, and 450 kilograms of marijuana in Nogales, Sonora in 2015.

Anti-Money Laundering: To assist Mexico in disrupting transnational criminal organizations (TCOs), INL provided over \$16 million in hardware, software, servers, and technical assistance to Mexico's Financial Intelligence Unit (UIF), a division of Mexico's Secretariat of Public Finance and Credit responsible for receiving, analyzing, and disseminating information on suspicious financial transactions. This assistance enhanced the Government of Mexico's ability to combat financial crimes and money laundering activity, resulting in the following successes:

In 2014 alone, the UIF froze 761 suspicious accounts.

Between March 2014 and May 2015, the UIF froze approximately \$41 million in suspicious assets.

The UIF reports it collected as much data in 2015 as in the previous six years combined due to new IT platforms and additional data storage capacity principally provided by INL.

Corrections: Since 2008, the Department of State's Bureau of International Narcotics and Law Enforcement Affairs (INL) and the Government of Mexico have partnered to create a more effective, transparent, and humane prison system, including through accreditation by the American Correctional Association (ACA), which has helped to reduce escapism and mitigate the ability of imprisoned cartel members to fuel organized crime from behind bars. As of May 2016, a total of 30 Mexican correctional facilities have achieved ACA accreditation: six federal prisons, 22 state prisons, one state central office, and the federal training academy. INL plans to work toward having all federal prisons and one quarter of state prisons ACA-accredited by 2021. In a recent National Human Rights Commission (CNDH) evaluation of more than 150 federal and state prisons, ACA-accredited prisons received significantly higher

average scores than non-ACA-accredited facilities. Of the top ten facilities, eight are either accredited or seeking accreditation, and none of the ten lowest scoring facilities in the CNDH evaluation are ACA-affiliated.

The state prison system in Chihuahua is an example of the program's success. In 2010, 216 prisoners in Chihuahua died as a result of prison violence, and the state reported more than 17 escapes. After achieving INL-sponsored ACA accreditation in 2013, there have been only three violent prison deaths, and no escapes from any accredited facility.

Question 5. I believe we should continue to expand military to military cooperation with the Mexican government as long as the Mexicans welcome our contributions. Maritime cooperation between our navies and coast guards seems like an underdeveloped area. Perhaps U.S. Northern Command should look at a role for Mexico to play in NORAD. The U.S. should also work to bring Canadian law enforcement into closer cooperation with Mexican law enforcement to stem illicit trafficking. What other opportunities exist where cooperation between the U.S. and Mexican governments can be improved?

Answer. We have an excellent relationship with the Mexican government and together we are continuously assessing our security relationship and working on ways to improve and enhance our cooperation.

The biannual "Security Cooperation Group" meeting, co-chaired by the National Security Council and Mexico's Center for Investigation and National Security (CISEN), serves as the primary forum for our senior policy makers to work with their Mexican counterparts to devise strategies to combat our shared security threats and identify and reassess strategic priorities, such as continuing the fight against organized crime, enhancing counternarcotics efforts, and jointly managing our 2,000 mile shared border. There are also multiple venues and working groups that facilitate operational and tactical security cooperation, including through the 21st Century Border Management Initiative, bilateral border violence prevention protocols, and other coordination mechanisms.

Specific to our military relationship, U.S. Northern Command works with Mexico on initiatives that not only assist in mitigating the current Transnational Criminal Organization (TCO) threat, but also focus on capacity building. They work with the Mexican Navy (SEMAR) and Army (SEDENA) to build specific capabilities, enhance our bilateral and regional engagement, and prioritize joint activities through programs in aviation, communications, and civil-military operations. SEMAR's participation in exercises, combined and multilateral, is increasing and planning is underway for joint U.S.-Mexican exercises next year that will increase interoperability with U.S. Naval Forces and bolster regional security.

The North American Leaders' Summit, to be attended by President Obama, Mexican President Peña Nieto, and Canadian Prime Minister Trudeau, will take place in Ottawa on June 29. The discussion of the effective exchange of information and coordination among law enforcement authorities will remain essential. We will also discuss continued coordination to pursue areas of cooperation to counter drug trafficking, trafficking in persons, and other illicit trade.

Question 6. Please summarize any progress that has been made as a result of the bilateral talks that have been occurring over the past year on how the U.S. and Mexican government can address heroin cultivation and production in Mexico.

Answer. Over the past year, our bilateral dialogue with the Government of Mexico on heroin has reached an unprecedented level of openness. This has led to enhanced U.S.-Mexico collaboration on this critically important issue, including increased communication and information sharing on heroin. In March 2016, Office of National Drug Control Policy Director Michael Botticelli and the State Department's Bureau of International Narcotics and Law Enforcement Affairs (INL) Assistant Secretary William R. Brownfield participated in meetings hosted by the Mexican Attorney General's Office with high-level officials from each of the Mexican federal government agencies involved in drug enforcement to discuss U.S.-Mexico collaboration on heroin and potential new areas of assistance. INL continues to increase the capacity of law enforcement and justice sector institutions to detect heroin distribution networks and prosecute those involved. INL has hosted seminars with several Mexican agencies to increase information sharing on heroin, and has facilitated a study trip with Mexican officials to Guatemala and Peru to examine poppy eradication best practices. The United States has provided more than \$130 million in non-intrusive inspection equipment, maintenance, technical assistance, and capacity building to enhance the capabilities of Mexican officials at internal checkpoints and points of entry along Mexico's northern and southern border. INL is also working with the U.S. Drug Enforcement Administration (DEA) to provide training to augment Mexico's ability to identify, investigate, and interdict clandestine heroin labs, and better prepare Mexican officials to dismantle them.

This year, the Government of Mexico is expected to finalize its National Drug Control Policy Plan, and to lay out protocols for poppy eradication. Mexico is also working with the United Nations Office on Drugs and Crime (UNODC) on a yield study that will enable more accurate estimates of potential heroin production. Initial reports outlining baseline poppy cultivation estimates will be completed this year. These reports will provide a greater understanding of how Mexican eradication and interdiction responsibilities will be organized going forward, and will help shape the best areas for U.S. assistance. INL will continue to work closely with Mexico to increase efforts to combat heroin.

Question 7. How would you assess the assertion made by a group of experts from the Inter-American Commission on Human Rights, that there may have been another bus involved in the incident in which 43 students disappeared in Guerrero, Mexico, that was packed with heroin bound for the U.S.?

Answer. We strongly support the work of the Interdisciplinary Group of Independent Experts affiliated with the Inter-American Commission on Human Rights and commend the assistance they have provided to the Government of Mexico with respect to the investigation of the September 2014 disappearance of 43 students in Iguala, Mexico. We have encouraged Mexican authorities to incorporate the experts' findings into the ongoing official investigation.

In the reports released in September 2015 and April 2016, the experts noted the organized crime group alleged to be involved in the attack on the students and their disappearance is

connected to drug trafficking to the United States and, specifically, to a case before a federal court in Chicago. The experts hypothesized that the extreme violence against the students and the alleged “missing” fifth bus might be related to this drug trafficking—i.e., that unknown to the students who seized several buses, one of those buses could have contained drugs or drug money, which in turn led to the violent attacks of September 26, 2014. The Department of State is not in a position to evaluate the merits of that hypothesis.

WITNESSES PREPARED STATEMENTS

Prepared Statement of Daniel L. Foote, Deputy Assistant Secretary, Bureau of International Narcotics and Law Enforcement Affairs

Chairman Rubio, Senator Boxer, and distinguished Members of the Subcommittee: thank you for the opportunity to appear before you to discuss U.S. government efforts to combat the production and trafficking of heroin and the violence and instability it brings to our communities, our citizens, and the world in which we live.

The flow of illicit narcotics across our shared border with Mexico threatens citizen security in both countries. Recognizing that we have a shared responsibility to address common challenges, in 2007, the United States forged a comprehensive security partnership with Mexico. Through the Merida Initiative, we work in partnership with Mexico to build the capacity of Mexican institutions to counter organized crime, uphold the rule of law, and protect our shared border from the movement of illicit drugs, money, and goods.

The need for effective collaboration is now more important than ever. Heroin and fentanyl-laced heroin is a public health crisis in the United States, and Mexican drug trafficking organizations are the primary suppliers of heroin to the United States. We must aggressively respond to this growing threat in concert with our broader work through the Merida Initiative to counter all illicit drugs and to end the impunity with which trafficking organizations are able to operate, putting their leaders in jail, seizing their weapons, drugs, and money, and dismantling their illicit businesses.

To date through the Merida Initiative, the United States government has provided nearly \$1.5 billion worth of capacity building assistance to our Mexican partners. This includes training and equipment which complements the significant resources the Government of Mexico has dedicated to our shared security goals. Today there are more than \$700 million in bilaterally agreed upon projects with the Peña Nieto administration, which fully support the Merida Initiative’s strategic framework that underpins the basis of our security cooperation. Most of these projects fall into three priority areas: professionalizing and building the capacity of Mexican law enforcement agencies; supporting the Government of Mexico’s efforts to strengthen border management and security; and helping advance reforms across Mexico’s justice sector.

In partnership with the Department of Justice, INL is building the skills of prosecutors, investigators, and forensic experts in Mexico and preparing them for their responsibilities under the oral accusatory system, the transition to which is well underway throughout Mexico. This includes helping enhance the technical capacity of courtrooms throughout the

country to host oral trials. We are also assisting in the training of the next generation of Mexican attorneys as they learn crucial oral trial skills in Mexican law schools.

Through Merida, INL is enhancing federal, state, and municipal policing capacity throughout Mexico. These programs provide a full range of professionalization activities including: the development of enforceable police standards; basic training and academy accreditation; continuing and leadership education programs; law enforcement vetting programs; and the development of effective internal affairs units. The continued professionalization of Mexican law enforcement will result in a greater observance of and accountability for civil and human rights, increasing trust in these institutions by the people of Mexico, and making them better partners for other law enforcement organizations both within Mexico and with the United States. This is vital to any effort to stem drug trafficking and reduce the capabilities and influence of drug trafficking organizations.

Strengthening border security capacity on Mexico's borders is a priority for both our nations. Our governments have committed to further enhancing Mexico's ability to interdict illicit narcotics, arms, and money. INL has provided more than \$125 million in inspection equipment and more than 340 canine teams deployed at ports of entry, border crossings, and internal checkpoints throughout Mexico. In Mexico's northern border region, INL has provided equipment and technical assistance to improve communications between the Mexican Federal Police and U.S. Customs and Border Protection (CBP). We are working in conjunction with CBP to provide training to Mexico's Federal Police who will be deployed to the northern border region, advancing cooperation between our countries along our shared border.

Through Merida, we continue to make progress with Mexico in targeting heroin production and trafficking. We work with the U.S. Drug Enforcement Administration to provide training to augment Mexico's ability to identify, investigate, and interdict clandestine heroin labs, and better prepare Mexican authorities to dismantle them. We are improving information sharing between our governments on heroin and fentanyl, working together to better assess poppy cultivation and heroin production in Mexico, and with our interagency partners, continuing our high-level focus on exploring other avenues to enhance our bilateral cooperation when it comes to heroin.

At the last high level Security Cooperation Group held in Mexico City in October 2015, heroin was the group's highest priority. We agreed to continue working in partnership on a bilateral approach for combating the cultivation, production, and trafficking of heroin and to determine how U.S. assistance can best support Mexico's efforts in this area.

Building strong, effective justice sector institutions in Mexico capable of confronting organized crime and the violence and corruption for which it is responsible is a difficult, long-term challenge. Our work across numerous institutions and sectors must be sustained, for it is only with a concerted, committed effort that the capacity to deter the cultivation, production, and trafficking of heroin and other illicit drugs in Mexico will be strengthened. Past investments by the American people in this partnership have produced results, and with your continued support, our collaboration with Mexico on this important work will continue.

**PREPARED STATEMENT OF KEMP L. CHESTER,
ASSOCIATE DIRECTOR FOR THE NATIONAL HEROIN
COORDINATION GROUP, OFFICE OF NATIONAL DRUG POLICY**

Chairman Rubio, Ranking Member Boxer, and members of the subcommittee, thank you for inviting me to discuss the public health and public safety issues resulting from heroin use; the Government of Mexico's efforts to reduce the availability of heroin in the United States; and the U.S.-Mexico cooperation to address heroin issues in both countries.

Background

In 2014, more than 47,000 Americans, or approximately 129 people each day, died from a drug overdose. Opioids—a category of drugs that includes heroin and prescription pain medicines like oxycodone, oxymorphone, hydrocodone, and fentanyl—are having a considerable impact on public health and safety in communities across the United States. Of the overdose deaths in 2014, 61 percent (28,647) involved an opioid, 44 percent (20,808) involved prescription pain medicines, and 22 percent (10,574) involved heroin.¹ The threat posed by heroin has continued to grow dramatically over the past several years. Since 2007, deaths involving heroin have risen 340 percent, from 2,402 in 2007 to 10,574 in 2014.²

There are several principal factors contributing to the current nationwide heroin crisis: the increased availability of heroin in the U.S. market,³ the availability of purer forms of heroin that allow for non-intravenous use,⁴ its relatively low price,⁵ and a relatively small percentage of non-medical users of opioid prescription drugs transitioning to heroin.⁶ The purity of retail-level heroin has increased since the 1990s while prices have remained low.⁷ Further increases in purity since 2010 have enabled heroin use by a variety of means including snorting or smoking which broadens the drug's appeal to a large population that is disinclined to inject the drug intravenously. Heroin's relatively low price makes it a viable alternative to many prescription opioids which command higher prices on the street.⁸ Heroin use has spread into suburban and rural communities and is growing among most socioeconomic classes, age groups, and races.⁹

¹ An opioid-related death may involve more than one type of opioid.

² Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death, 1999-2014 on CDC WONDER Online Database, released 2015.

³ Drug Enforcement Administration, El Paso Intelligence Center, National Seizure System, 2008-2014.

⁴ Drug Enforcement Administration. Strategic Intelligence Section. 2015 National Heroin Threat Assessment. DEA-DCT-DIR-039-15.

⁵ Drug Enforcement Administration. System to Retrieve Information from Drug Evidence (STRIDE), Price and Purity Data, 2015.

⁶ Muhuri PK, Gfroerer, JC and Davies, MC. (2013). Associations of nonmedical pain reliever use and initiation of heroin use in the United States. Substance Abuse and Mental Health Services Administration.

⁷ Drug Enforcement Administration. System to Retrieve Information from Drug Evidence (STRIDE), Price and Purity Data, 2015.

⁸ Drug Enforcement Administration. Strategic Intelligence Section. 2015 National Heroin Threat Assessment. DEA-DCT-DIR-039-15.

⁹ Cicero, T., Ellis, MS, Surratt, HL, Kurtz, SP. (2014). The changing face of heroin in the United States: A retrospective analysis of the past 50 years. JAMA Psychiatry, 71(1): 821-826.

The Administration recognizes that the heroin threat is a global issue; however, Mexico is currently the primary supplier of heroin to the United States, with Mexican drug traffickers cultivating opium poppy and producing heroin in Mexico, and smuggling the finished product into the United States.¹⁰ Opium poppy cultivation in Mexico has increased substantially in recent years, rising from 17,000 hectares in 2014, with an estimated potential pure heroin production of 42 metric tons, to 28,000 hectares in 2015 with a potential production of 70 metric tons of pure heroin.¹¹

The reemergence of illicit fentanyl, a powerful Schedule II synthetic opioid more potent than morphine or heroin, exacerbates the heroin crisis.¹² Illicit fentanyl is sometimes mixed with powder heroin to increase its effects or with diluents and sold as “synthetic heroin,” with or without the buyers’ knowledge.¹³ Increasingly, illicit fentanyl is pressed into pill form and sold as counterfeit prescription opioid pills. Illicit fentanyl comes from several sources. The majority of the illicit fentanyl in the U.S. market is smuggled into the country after being clandestinely produced in Mexico or China.¹⁴

Illicit fentanyl is extremely dangerous and deadly. In 2014, there were more than 5,544 drug overdose deaths involving synthetic narcotics other than methadone, a category that includes fentanyl. This number has more than doubled from two years earlier (2,628 in 2012).¹⁵ Moreover, overdose deaths involving opioids like illicit fentanyl are likely undercounted. Of deaths where drug overdose is cited as the underlying cause of death, approximately one-fifth of the death certificates do not list the specific drug(s) involved in the fatal overdose.¹⁶

There are several reasons why it is important that we address concerns regarding heroin and illicit fentanyl in a single problem set. First, traffickers who add illicit fentanyl as an adulterant to boost the effect of their heroin, or mix it with diluents to sell as synthetic heroin, likely utilize the same supply chains and distribution mechanisms for both drugs. Moreover, both heroin and fentanyl belong to the same class of opioid drugs that have similar effects making their illicit user populations one and the same. Second, both heroin and clandestinely-produced fentanyl can be manufactured by the same drug trafficking organizations that can bring both drugs into the country using the same trafficking routes. And finally, addressing both illicit drugs together allows us to address the heroin crisis while avoiding unintended uptick in illicit fentanyl use. If we move too quickly in reducing the availability of heroin

¹⁰ Drug Enforcement Administration. Strategic Intelligence Section. 2015 National Heroin Threat Assessment. DEA-DCT-DIR-039-15.

¹¹ U.S. Department of State, Bureau of International Narcotics and Law Enforcement Affairs. International Narcotics Control Strategy Report—2015 [INCSR] (March 2015) for data from 2013–2014 and unpublished U.S. Government Estimates.

¹² Zuurmond WW, Meert TF, and Noorduyn H. (2002). Partial versus full agonists for opioid-mediated analgesia—focus on fentanyl and buprenorphine. *Acta Anaesthesiol Belg*, 53(3):193–201.

¹³ Drug Enforcement Administration. Strategic Intelligence Section. 2015 National Heroin Threat Assessment. DEA-DCT-DIR-039-15.

¹⁴ Drug Enforcement Administration. Strategic Intelligence Section. 2015 National Heroin Threat Assessment. DEA-DCT-DIR-039-15.

¹⁵ Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999–2014 on CDC WONDER Online Database, released 2015. Data are from the Multiple Cause of Death Files, 1999–2014, as compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program.

¹⁶ Rudd, RA, Aleshire, N, Zibbell, JE, and Gladden, RM. Increases in Drug and Opioid Overdose Deaths—2000–2014. Centers for Disease Control and Prevention: *Mortality and Morbidity Weekly Report*. Jan. 1, 2016. 64(50):1378–82.

without simultaneously addressing illicit fentanyl availability, it could increase the price of heroin, and risk driving more people to use illicit fentanyl—thereby creating the prospect of an additional and potentially more deadly opioid drug threat.^{17,18}

The dramatic increase in the availability and use of heroin and illicit fentanyl is a national security, law enforcement, and public health issue, and it has become the highest priority illicit drug threat to the Nation.¹⁹ Addressing this complex problem demands significant effort, creativity, and interagency collaboration.

The Federal Response

The National Heroin Coordination Group

In November of 2015, the National Security Council (NSC) Transborder Security and Western Hemisphere Directorates Interagency Policy Committee (IPC) on Mexico Security Priorities directed the formation of the National Heroin Coordination Group (NHCG) within the Office of National Drug Control Policy (ONDCP). The NHCG is the hub of a network of interagency partners who leverage their home agency authorities and resources to synchronize interagency activities against the heroin and illicit fentanyl supply chains to the United States. I serve as the Director of the NHCG, which ensures that Federal counterdrug efforts focused on the heroin problem complement the NSC's ongoing work related to Mexico security priorities, and that the NHCG connects the actions taken on the front end of the supply chain with the effects on the domestic market and user population.

Bi-Lateral Engagement

U.S.-Mexico engagement regarding heroin has been robust. In October 2015, ONDCP Director Michael Botticelli participated in a U.S.- Mexico Security Cooperation Group dialogue that included heroin as the first security cooperation agenda topic. The importance of increased poppy eradication efforts by the Government of Mexico, as well as drug interdiction, clandestine laboratory destruction, and disruption of precursor chemical trafficking were all highlighted as crucial issues to be addressed.

Director Botticelli and I traveled to Mexico in early March 2016 with Ambassador William Brownfield, Assistant Secretary of State for International Narcotics and Law Enforcement Affairs (INL), to engage on heroin and illicit fentanyl issues specifically and to impress upon our Mexican partners the urgency with which the United States is addressing the heroin problem. We met with Mexican Attorney General Gómez and senior members of her staff, as well as with senior officers from the Mexican Army, the Mexican Navy, and the Secretariat of the Government. Attorney General Gómez announced her role as the synchronizer of Mexico's efforts to disrupt the production of heroin and illicit fentanyl including poppy eradication and the identification and neutralization of production laboratories.

¹⁷ National Institute for Health Development, Infectious Diseases and Drug Monitoring Centre. 2014 National Report to the EMCDDA by the REITOX National Focal Point. Tallinn, Estonia.

¹⁸ European Monitoring Centre for Drugs and Drug Addiction. Fentanyl in Europe EMCDDA Trendspotter Study: Report from an EMCDDA expert meeting 9 to 10 October 2012. Lisbon, Portugal.

¹⁹ The White House, Strategy to Combat Transnational Organized Crime, 25 July 2011.

Importantly, we agreed to conduct joint planning and to develop a simple and focused national strategy to direct and concentrate Mexico's efforts against heroin and illicit fentanyl. We expect this plan to delineate responsibilities, identify gaps, and help synchronize heroin and illicit fentanyl efforts across the Mexican government. This plan will be beneficial for both countries and we look forward to collaborating on its development. The country team at the U.S. Embassy in Mexico City has led efforts to foster partnerships within the Government of Mexico, and increased information sharing continues to enhance this relationship. The United States continues to work with the Government of Mexico on important efforts under the Merida Initiative, a joint effort to fight transnational criminal organizations and reduce associated violence. Building upon the Mexican Government's own investment in equipment and border security infrastructure, the Merida Initiative will continue to strengthen border security that facilitates the flow of legitimate commerce and travel, while reducing the movement of illicit narcotics, currency, weapons, explosives, black market goods, and undocumented migrants.

U.S. Federal law enforcement agencies are aggressively addressing the heroin and illicit fentanyl issue both here and abroad. The Drug Enforcement Administration and other agencies have co-located Special Agents with international partners in Mexico and throughout Latin America to assist in criminal investigations targeting drug trafficking organizations, and to help their international counterparts develop their capacity to conduct the full range of narcotics interdiction activities within their countries to target both heroin and illicit fentanyl. Our Federal law enforcement agencies, in conjunction with the Department of State, are working with the countries who supply illicit fentanyl and the precursor chemicals used in its manufacture to stem the flow of these dangerous chemicals to the Western Hemisphere.

Interagency Partnerships

Our ability to bring together, contextualize, and synchronize the strategies and partnerships currently taking place at the Federal, state, local, and tribal levels to reduce the availability of heroin in the United States is critical to our overall efforts. The urgent need to sustain progress toward addressing the heroin crisis, combined with the expanding and dynamic nature of the problem itself, requires increased collaboration among Federal agencies, and with our partners working at the state, local and tribal level where the crisis is felt most deeply and where there is an enormous amount of energy and innovation. This cooperation will allow for greater situational awareness to provide more comprehensive understanding of expected changes in the domestic environment related to interagency heroin/illicit fentanyl supply reduction efforts.

The ONDCP funded High Intensity Drug Trafficking Areas (HIDTA) Program is a locally-based program that responds to the drug trafficking issues facing specific areas of the country. Law enforcement agencies at all levels of government share information and implement coordinated enforcement activities; enhance intelligence sharing among Federal, state, local, and tribal law enforcement agencies; provide reliable intelligence to law enforcement agencies to develop effective enforcement strategies and operations; and support coordinated law enforcement strategies to maximize available resources and reduce the supply of illegal drugs in designated areas. In August 2015, ONDCP committed \$2.5 million in HIDTA funds to develop a strategy to respond to the heroin crisis in the United States. This unprecedented project combines prevention, education, intelligence, and enforcement

resources to address the heroin threat across 17 states and the District of Columbia. The effort is carried out through a unique partnership of seven regional HIDTAs—Appalachia, Michigan, New England, New York/New Jersey, Ohio, Philadelphia/Camden, and Washington/Baltimore. The HIDTA heroin response strategy will foster a collaborative network of public health-public safety partnerships, sharing best practices, innovative pilots, and identifying new opportunities to leverage resources.

Along our Southwest border, U.S. Customs and Border Protection (CBP) continues to detect and interdict illicit narcotics entering the United States. CBP reports seizing 1,121,411 kilograms of illegal drugs in 2015. Of that amount, CBP seized 2,745 kilograms of heroin, 25 percent more than CBP seized in 2014.

The Department of Justice's Organized Crime Drug Enforcement Task Forces (OCDETF) partnered with the Federal Bureau of Investigation, Homeland Security Investigations, and the Drug Enforcement Administration target, disrupt, and dismantle international drug trafficking organizations that manufacture, transport, and distribute heroin and illicit fentanyl destined for and distributed across the United States. In addition, OCDETF's National Heroin Initiative, launched in December 2014, seeks to coordinate innovative regional approaches that improve information sharing and data collection to support multi-agency, multi-jurisdictional enforcement actions.

Challenges

While we have worked tirelessly to address the heroin crisis and have laid a firm foundation for future efforts, much remains to be done. We have gaps in our capability to detect illicit fentanyl at our borders and in our air freight package locations, and our Mexican partners could certainly do more to strategically dismantle criminal organizations and conduct opium poppy eradication and clandestine laboratory identification and neutralization.

We are working to close information gaps. Although it is abundantly clear that the number of overdose deaths involving illicit fentanyl nationwide has increased dramatically, it is likely that the overdose numbers underreport the actual number of deaths due to heroin and illicit fentanyl. The ability to detect illicit fentanyl in overdose victims, and the standard inclusion of illicit fentanyl in overdose death toxicology screening, varies widely among localities. This likely results in the undercounting of heroin and illicit fentanyl-related deaths and actual numbers of heroin-related overdoses are probably much higher. In localities where detailed toxicology screening is performed, information suggests higher numbers of illicit fentanyl-related overdose.

We look forward to working with our Federal and state government partners, as well as our international counterparts, to address these problem areas.

Conclusion

We cannot forget that the epidemic of opioid use and overdose deaths is fundamentally a public health problem that is exploited by criminal organizations, and addressing it adequately requires substance use prevention and treatment strategies and recovery support

services. Law enforcement officials are increasingly becoming public health partners, linking individuals with opioid use disorder to treatment.

For this reason, in the FY 2017 budget President Obama proposed \$1 billion in new mandatory funding over two years to expand the availability of opioid use disorder services, target areas of highest need, and allow states to implement evidence-based strategies that best meet local needs, such as medication-assisted treatment and expansion of the availability of substance abuse treatment providers (through enhanced loan repayment for healthcare providers that offer medication-assisted treatment). Such efforts will help individuals seek treatment, successfully complete treatment, and sustain recovery.

ONDCP will continue to work with our Federal government departments and agencies, partners at the state, local and tribal levels, and international counterparts to reduce heroin and illicit fentanyl production and trafficking and to combat the profound effect these dangerous drugs are having in our communities.

Thank you for affording me the opportunity to testify today and for your commitment to this important issue.

PREPARED STATEMENT OF TERESA JACOBS, MAYOR OF ORANGE COUNTY, FLORIDA

Chairman Rubio, Ranking Member Boxer, members of the committee, thank you for calling this important hearing, and for allowing me to share a local perspective on the terrible threat that heroin poses for cities and counties throughout our country.

First a bit about Orange County: We're home to the City of Orlando and 12 other municipalities, with a population of 1.2 million people, a strong economy and an exceptional quality of life. In 2015, we shattered national tourism records, hosting more than 66 million visitors.

No doubt you know us as the vacation capital of the world, but tragically, like too many other states and communities, Orange County has seen an alarming increase in the number of heroin overdoses and related deaths. Last year, we lost 85 lives to heroin—a staggering 600% increase since 2011. Already this year we've had more than 90 heroin overdoses in the county, with about one-in-ten resulting in death.

Florida's fight against this current wave of opioid addiction began about five years ago, in the midst of our battle against the pill mills.

You may remember the shocking statistics from 2010, when it was discovered that Florida practitioners purchased more than 41 million oxycodone pills in the first six months of that year—more than the other 49 states of the union combined.

Like countless cities, towns and counties across the U.S., we worked to outlaw unauthorized pain clinics and provide resources for breaking opioid addiction.

In Florida, the pill mill 'legacy' has impacted us beyond measure. I can't prove it, but I think it's very likely that cartels took notice of what they perceived to be a ripe "marketplace." Today, predatory drug dealers are targeting us with heroin, as well as cheap and deadly strains of fentanyl. Unfortunately, it's nearly impossible to accurately assess the threat in Florida, since no statewide databases exist. Instead, numbers are captured by individual agencies and municipalities—there is simply no mechanism for synergy or sharing.

What we do know? We know that last year, approximately 2,000 heroin users moved through our Orange County jail. Many of those were arrested not for heroin possession, but for other offenses related to heroin addiction.

We know that in 2015, we housed 100 expectant mothers tragically addicted to opiates or heroin, as our Jail has become the treatment center of last resort for so many people.

For the good of our citizens and our community, we are fighting back.

Last summer I convened the Orange County Heroin Task Force, and asked our sheriff to Co-Chair the effort. Our joint work is having a positive impact, including passage in the 2016 Florida Legislature of a measure allowing Naloxone sales without an individual prescription.

We know there is no single solution, but there are some universally effective approaches:

- Enforcement is critical. In a world of increasingly sophisticated technology, our local efforts—no matter how highly leveraged and coordinated—are simply no match against organized traffickers.
- Equally important, and in keeping with what we learned with pill mills, we must be tireless in educating people that addiction is an illness. An illness that requires treatment and support not only for the addict, but also for the families who are ravaged by addiction.

In closing, I respectfully ask for your help:

- *Help to stop the influx of drugs* across the border. We've got our hands full at the local level, and are simply not equipped to fight the cartels. This is where we really need your help—to stop these deadly drugs before they cross our borders.
- *Help to treat more addicts.* With a regional population of 2.5 million, we have one Addictions Receiving Facility with 26 detox beds serving four counties for the uninsured.
- *Help to raise awareness* so more people will choose not to try this deadly drug in the first place.

To end this crisis and save lives, we all need to be engaged. Thank you for your attention to this critical issue and thank you for your leadership and your service.

PREPARED STATEMENT OF STEVEN DUDLEY, CO-DIRECTOR, INSIGHT CRIME

Chairman Rubio, Ranking Member Boxer, and members of the subcommittee: I am grateful for the opportunity to appear before you on behalf of InSight Crime and the Center for Latin American and Latino Studies at American University to discuss the criminal dynamics connected to the illegal opiate market, specifically the heroin market in the United States related to poppy production in Mexico.

Mexico's Increased Market Share

U.S. consumption of heroin has increased significantly in the last few years. The reasons for this are complex but have to do with the increase of prescription drugs in the United States, a rise in prices of these prescription drugs and their black market counterparts, and the subsequent safeguards on this prescription medicine market, specifically OxyContin.

The U.S. portion of the world heroin market is small by comparison in terms of users, but outsized in terms of potential earnings. The Rand Corporation estimated in 2014, that U.S. consumers spend as much as \$27 billion on heroin each year, an increase from \$20 billion per year in 2000.²⁰ Only the marijuana market is worth more in the U.S.²¹

Mexican, Guatemalan and Colombian criminal organizations have reacted to these changes by producing more heroin. Only a small percentage of the world's opium poppy is cultivated in this hemisphere, but after it is processed into heroin, almost all of it is sold in the United States where the number of consumers for the drug has more than doubled since the early 2000s.

Mexico accounts for the bulk of poppy production in the region. According to estimates by the Drug Enforcement Administration (DEA), the production of poppy, the raw ingredient for the production of heroin, increased from 10,500 hectares in 2012 to 17,000 hectares in 2014, giving the groups the potential to produce 42 metric tons, up from 26 metric tons in 2012.²² By comparison, the DEA says Colombia produces only two metric tons per year.²³

Seizure data of heroin along the southwest border also indicate that Mexican criminal groups are moving increasing amounts of heroin into the U.S. market. Mexican criminal organizations are also the key transporters of Colombian heroin to the United States, and they manage and purchase the heroin produced in Guatemala or buy the opium gum wholesale to process it into heroin themselves in Mexico.

Inside the U.S., the trend appears to be the same. The DEA says that Mexican groups are seeking an increasing amount of the market share in the distribution business itself, displacing other wholesalers. In sum, the picture is one of an increasingly lucrative, vertically integrated market, with large Mexican criminal organizations managing the product from the point of production to the point of sale and seeking a greater market share of these sales.

The Reality of the Heroin Supply Chain

The reality of the supply chain is much more complex. While it helps us to use well-worn monikers when talking about these organizations, the truth is that they are not nearly as strong or monolithic as they once were. Names such as the Tijuana Cartel, the Juárez Cartel, the Zetas, or La Familia Michoacana may still evoke fear and sometimes awe, but they are not organizations as much as brand names. In many cases, the individual parts of the organization have as much contact with the bosses as a local Coca-Cola bottling plant manager might have with corporate headquarters.

²⁰ Beau Kilmer, et al., "How Big is the U.S. Market for Illegal Drugs," Rand Corporation (2014).

²¹ Ibid.

²² Drug Enforcement Administration (DEA), "National Drug Threat Assessment 2015," p. 34

²³ . The United Nations' most recent estimate for global heroin production is 526 tons. See: UNODC, "World Drug Report 2015," p. 41. Av.

Even the vaunted Sinaloa Cartel is more horizontally than vertically integrated. Take the recent case of the Flores brothers in Chicago. Before they were arrested, Pedro and Margarito Flores were said to be Sinaloa Cartel distributors in Chicago, one of the areas of greatest interest to this subcommittee. And they were. But as federal intercepts of their conversations with cartel leaders show, the two brothers negotiated independently with each of the top two members of the Sinaloa criminal organization, obtaining different prices with different leaders and managing shipments separately.²⁴ Even after a war started between the Sinaloa Cartel and the Beltrán Leyva Organization, the Flores brothers continued to purchase drugs from portions of the Beltrán Leyva Organization and the Sinaloa Cartel.

The Flores case cuts at two different myths about the Sinaloa Cartel: 1) that this is one single organization; 2) that it is tightly controlled by a single leader or a single group of leaders. The point is that as shipments get further and further from Mexico's wholesale points, the loyalties become more disperse, and in some cases completely disappear. This is especially true in the U.S. market where violence is not a viable long-term option to ensure loyalty, win market share or become a monopoly.

The effectiveness of U.S. law enforcement has made violence terrible for business and made the distribution chain a more democratic, capitalist affair. This is evident in other ways as well. While the amount of seizures indicates that there is more heroin available in the United States, it is still moved in very small quantities. The median seizure for the Los Angeles Field Division of the DEA in 2014, for example, was a kilogram.²⁵ In Denver, a 10 to 12 pound shipment is considered large.²⁶

The amount of profits reaped by these Mexican criminal organizations also raises questions about how much control they exert in the United States. The Rand Corporation estimated in 2010 that Mexican criminal groups earn in the range of \$400 million per year from their heroin exports and possibly another \$700 million for transporting Colombian heroin to the U.S. market.²⁷ While this has undoubtedly increased, there is still the question of where the rest of the over \$20 billion spent on heroin in the U.S. annually goes.

The case of the Laredo brothers, recently indicted in the Eastern District of Pennsylvania, is indicative of these trends. The Laredo brothers are charged with moving one ton of heroin over a six-year period. This is about 14 kilos per month. The organization was so subtle and, as one Mexican analyst put it, "mom-and-pop," the Mexican authorities did not even know it existed.²⁸

This brings us to Mexico. First, it is important to note that, unlike the cocaine market, Mexico is not dependent on other countries for its product. It is home grown. Second, the horizontal nature of the distribution chain makes it a difficult law enforcement problem in that country as well. As noted, the once monolithic criminal organizations are shells of what they once were. This is in part due to in-fighting of the type mentioned earlier but also Mexican law enforcement efforts. Many of the fragmented pieces have formed their own criminal operations and brand names.

²⁴ Michelle Garcia, "Court Docs Raise Questions about Mexico Sinaloa Cartel Narrative," 12 November 2013.

²⁵ DEA, *op. cit.*, p. 37.

²⁶ *Ibid.*

²⁷ Kilmer, et al., "Reducing Drug Trafficking Revenues and Violence in Mexico: Would Legalizing Marijuana in California Help?," Rand Corporation (2010), p. 30.

²⁸ Alejandro Hope, "The Laredo DTO and what it says about the heroin trade," 19 April 2016.

The most well-known is arguably the Guerreros Unidos, the criminal group held responsible for the disappearance of the 43 students in Mexico in 2014. The Guerreros Unidos used to be under the umbrella of the Beltrán Leyva Organization. When the Beltrán Leyva Organization fell to pieces during their war with the Sinaloa Cartel, the Guerreros Unidos became independent, as did several other criminal groups in the embattled state of Guerrero, which is one of the centers of opium cultivation, heroin production, wholesale and transport. Indeed, the mystery of what happened to those students, may hinge on whether the Guerreros Unidos were using commercial buses to move heroin to Chicago.²⁹

The upshot is that the chain of production in Mexico is broken into numerous pieces, including small and large producers of opium poppy plants, the opium gum producers, the processors, the wholesale purchasers, and the transporters. Production, transport and distribution may all be different organizations. The Laredo brothers, for example, were purchasing opium gum from an independent broker then processing it themselves and distributing it in those small quantities in the U.S. for years without running into trouble with the large, supposedly all-controlling Sinaloa Cartel.

To be sure, violence is still a viable option in Mexico, so the pendulum may swing back towards more monolithic criminal organizations. But for the moment, the reality is that there are literally dozens of small criminal organizations involved in this trade from the point of production to the point of sale.

Impact on Law Enforcement Efforts

In sum, while the level of control that the Mexican production and transport groups exert over the supply chain is clear, we are not talking about one or two criminal groups, but dozens of interlocking organizations whose alliances are constantly shifting. The heroin supply chain appears to be a largely horizontal, diversified operation with multiple actors, and one that is obedient to market forces rather than one or two single vertically integrated distributors.

The result is that law enforcement efforts are largely muted. Whether you debilitate the Sinaloa Cartel or the Laredo brothers, you are hindering a small part of the overall production and distribution chain. Even if you did slow the heroin from Mexico, you would face an insurmountable task: stopping the flow from other countries, which would undoubtedly fill the void and account for the bulk of world-wide production. Canada already gets up to 90 percent of its heroin from Afghanistan.³⁰

And the United States once got all of its heroin from the Asian markets that supply the rest of the world.

Thank you for your time and attention. I look forward to your questions.

²⁹ Elyssa Pachico, "Four Questions about the '5th Bus' in Case of Mexico's Missing 43," 27 April 2016.

³⁰ UNODC, *op. cit.*, p. 46.

STATEMENT FOR THE RECORD SUBMITTED BY JACK RILEY, ACTING DEPUTY ADMINISTRATOR, DRUG ENFORCEMENT ADMINISTRATION

Introduction

Chairman Rubio, Ranking Member Boxer, and members of the subcommittee, on behalf of the approximately 9,000 employees of the Drug Enforcement Administration (DEA), thank you for the opportunity to discuss the issue of Cartels, the U.S. heroin epidemic, and DEA's response to combating the drug violence and public health crisis.

Today, Mexican Transnational Criminal Organizations (TCOs) remain the greatest criminal drug threat to the United States; no other group can challenge them in the near term. These Mexican poly-drug organizations traffic heroin, illicit fentanyl, methamphetamine, cocaine, and marijuana throughout the United States, using established transportation routes and distribution networks. They control drug trafficking across the Southwest border (SWB) and are moving to expand their share of U.S. illicit drug markets, particularly heroin markets.

National-level gangs and neighborhood gangs continue to form and expand relationships with Mexican TCOs. Many gangs rely on Mexican TCOs as their primary drug supply source, and Mexican TCOs depend on street-level gangs, many of which already have a customer base, for drug distribution. Additionally, gangs profit through drug transportation activities, enforcement of drug payments, and by securing drug transportation corridors from use by rival gangs.

Mexican TCOs exploit a user population struggling with the disease of addiction. Drug overdoses are the leading cause of injury-related death in the United States, eclipsing deaths from motor vehicle crashes or firearms.³¹ There were over 47,000 overdose deaths in 2014, or approximately 129 per day, over half (61 percent) of which involved either a prescription opioid or heroin.³² These are our family members, friends, neighbors, and colleagues.

The DEA's focus is targeting the most significant, sophisticated, and violent trafficking organizations that profit from exploiting persons with substance use disorders. DEA's strategic priorities include targeting Mexican Consolidated Priority Organization Targets (CPOTs) and Priority Target Organizations (PTOs), which are the most significant international and domestic drug trafficking and money laundering organizations.

Current Assessment of the Threat

Based on active law enforcement cases, the following Mexican TCOs are operating in the United States: the Sinaloa Cartel, Beltrán-Leyva Organization (BLO), New Generation Jalisco Cartel (Cartel de Jalisco Nueva Generación or CJNG), Los Cuinis, Gulf Cartel (Cartel del Golfo or CDG), Juarez Cartel Michoacán Family (La Familia Michoacána or LFM), Knights Templar (Los Caballeros Templarios or LCT), and Los Zetas. While all of these Mexican TCOs transport wholesale quantities of illicit drugs into the United States, the

³¹ Centers for Disease Control and Prevention, Web-based Injury Statistics Query and Reporting System (WISQARS) [online], (2014).

³² Rose A. Rudd, Noah Aleshire, Jon E. Zibbell, R. Matthew Gladden. Increases in Drug and Opioid Overdose Deaths—United States, 2000–2014 *Morbidity and Mortality Weekly Report*, 2016;64:1378–1382.

Sinaloa Cartel remains the most active supplier. The Sinaloa Cartel leverages its expansive resources and organizational structure in Mexico to facilitate the smuggling and transportation of drugs throughout the United States.

Mexican TCO operations in the United States typically take the form of a supply chain system that relies on compartmentalized operators who are only aware of their own specific function, and remain largely unaware of other operational aspects. In most instances, transporters for the drug shipments are independent third parties who work for more than one Mexican TCO. Since operators in the supply chain are insulated from one another, if a transporter is arrested the transporter is easily replaced and unable to reveal the rest of the network to law enforcement.

Mexican TCOs in the United States utilize a network of extended family and friends to conduct their operations. Families affiliated with various Mexican TCOs in Mexico vouch for U.S.-based relatives or friends that are deemed trustworthy to run various aspects of the drug trafficking operations in the United States. Actual members of Mexican TCOs are usually sent to important U.S. hub cities to manage stash houses containing drug shipments and bulk cash drug proceeds. While operating in the United States, Mexican TCOs actively seek to maintain low profiles and avoid violent confrontations between rival TCOs or U.S. law enforcement.

Mexican TCOs transport illicit drugs over the SWB through ports of entry using passenger vehicles or tractor trailers. Illicit drugs are typically secreted in hidden compartments when transported in passenger vehicles or comingled with legitimate goods when transported in tractor trailers. Once across the SWB, Mexican TCOs will initially utilize stash houses in a number of hub cities to include Dallas, Houston, Los Angeles, Atlanta, and Phoenix. The illicit products will then be transported via these same conveyances to distribution groups in the Midwest and on the East Coast. Mexican TCOs also smuggle illicit drugs across the SWB using other methods including tunnels, maritime conveyances, and aircraft.

Heroin Availability to the U.S. Market

There are four major heroin-producing areas in the world, but heroin bound for the U.S. market originates predominantly from Mexico and, to a lesser extent, Colombia. The heroin market in the United States has been historically divided along the Mississippi River, with western markets using Mexican black tar and brown powder heroin, and eastern markets using white powder, which over the last two decades has been sourced primarily from Colombia. The largest, most lucrative heroin markets in the United States are the white powder markets in major East Coast cities: New York City and the surrounding metropolitan areas, Philadelphia, Boston and its surrounding cities, Washington, D.C., Baltimore, as well as Chicago. Given the growing number of individuals with an opioid use disorder in the United States, Mexican TCOs have seized upon a business opportunity to increase their profits. Mexican TCOs are now competing for the East Coast and Mid-Atlantic markets by introducing Mexican brown/black tar heroin, as well as by developing new techniques to produce highly refined white powder heroin.

Poppy cultivation in Mexico increased 160 percent between 2013 and 2015, resulting in an estimated 70 metric tons of potential heroin. Cultivation in Mexico is located primarily in the state of Guerrero and the Mexican ‘Golden Triangle’ which includes the states of Chihuahua, Sinaloa, and Durango. The increased cultivation and trafficking from Mexico to the United States impacts both of our nations by supporting the escalation of heroin use in the United States, as well as the instability and violence associated with drug trafficking in Mexico.

The majority of Mexican and Colombian heroin bound for the United States is smuggled into the United States via the SWB, and heroin seizures at the border have more than doubled, from 1,016 kilograms in 2010 to 2,524 kilograms in 2015.³³ During this time, the average seizure at the Border also increased from 2.0 kilograms to 3.5 kilograms. Most heroin smuggled across the border is transported in privately-owned vehicles, usually through California, as well as through south Texas. In 2014, more than half of U.S. Customs and Border Protection (CBP) heroin seizures at the SWB were in the southern California corridors of San Diego and El Centro. The distribution cells, and the Mexican and South American traffickers who supply them, are the main sources of heroin in the United States today. In Mexico, the threat of these organizations is magnified by the high level of violence associated with their attempts to control and expand drug distribution operations.

DEA has become increasingly alarmed over the addition of fentanyl into heroin sold on the streets as well as the use of fentanyl analogues such as acetyl fentanyl. The more potent opioids like fentanyl³⁴ present a serious risk of overdose death for a user. In addition, this drug can be absorbed by the skin or inhaled, which makes it particularly dangerous for law enforcement, public safety, or health care personnel who encounter the substance during the course of their daily operations. On March 18, 2015, DEA issued a nationwide alert to all U.S. law enforcement officials about the dangers of illicit fentanyl and fentanyl analogues and related compounds. In addition, due to a recent spike in overdose deaths related to the use of acetyl fentanyl, on July 17, 2015, DEA used its emergency scheduling authority to place acetyl fentanyl in Schedule I of the CSA.

DEA Response to the Heroin Threat

DEA’S 360 Strategy

DEA is rolling out the 360 Strategy to address the opioid, heroin, and violent crime crisis. The strategy leverages existing federal, state, and local partnerships to address the problem on three different fronts: law enforcement, diversion control, and community relations. The strategy is founded upon our continued enforcement activities directed at the violent street gangs responsible for feeding the heroin and prescription drug abuse epidemic in our communities.

While law enforcement plays a central role in the 360 Strategy, enforcement actions alone are not enough to make lasting changes in our communities. The 360 Strategy, therefore, also focuses on preventing diversion by providing education and training within the

³³ Drug Enforcement Administration, *Unclassified Summary, 2015 National Drug Threat Assessment*, Pg. 35.

³⁴ Centers for Disease Control, *Emergency Response Safety and Health Database, FENTANYL: Incapacitating Agent*, accessed March 19, 2015; U.S. Department of Justice, *Drug Enforcement Administration, Office of Diversion Control, Drug & Chemical Evaluation Section, Fentanyl*, March 2015.

pharmaceutical community and to pursue those practitioners who are operating outside of the law. The final component of the strategy is a community effort designed to maximize all available resources to help communities turn around the recurring problems that have historically allowed the drug and violent crime problems to resurface after enforcement operations.

Additional Resources in Fiscal Year 2017

DEA plays an important part in the U.S. government's drug control strategy that includes enforcement, treatment, and prevention. While there are complex issues affecting spikes in heroin use and overdoses, including prescription drug abuse, the same significant poly-drug trafficking organizations responsible for other illicit drug threats are also responsible for the vast majority of the heroin supply. Additionally, drug trafficking has a proven linkage to gangs and other violent criminal organizations. The FY 2017 President's Budget request provides \$12.5 million and 42 positions, including 32 special agents, to create new enforcement groups in DEA domestic field divisions.

Heroin Task Force

As directed by Congress, the Department of Justice joined with the Office of National Drug Control Policy (ONDCP) to develop strategies to confront the heroin problem and curtail the escalating overdose epidemic and death rates. DEA and more than 28 Federal agencies and their components participated in this initiative. The task force provided its Report to Congress on December 31, 2015.

International Enforcement: Sensitive Investigative Units

DEA's Sensitive Investigative Units (SIU) program, nine of which are in the Western Hemisphere, helps build effective and vetted host nation units capable of conducting complex investigations targeting major TCOs. DEA, with funding support from the Department of State, currently mentors and supports 13 SIUs, which are staffed by over 900 foreign counterparts. The success of this program has enhanced DEA's ability to fight drug trafficking on a global scale.

International Enforcement: Bilateral Investigations Units

Bilateral Investigations Units (BIUs) are one of DEA's most important tools for targeting, disrupting, and dismantling significant TCOs. The BIUs have used extraterritorial authorities to infiltrate, indict, arrest, and convict previously "untouchable" TCO leaders involved in drug trafficking.

Special Operations Division

Established in 1994, the Special Operations Division (SOD) is a DEA-led multi-agency operations coordination center with participation from Federal law enforcement agencies, the Department of Defense, the Intelligence Community, and international law enforcement partners. SOD's mission is to establish strategies and operations to dismantle national and international trafficking organizations by attacking their command and control communications. Special emphasis is placed on those major drug trafficking and narco-

terrorism organizations that operate across jurisdictional boundaries on a regional, national, and international level.

El Paso Intelligence Center

The El Paso Intelligence Center (EPIC) is a national intelligence center focused on supporting law enforcement efforts in the Western Hemisphere with a significant emphasis on the SWB. Through its 24-hour watch function, EPIC provides law enforcement officers, investigators, and analysts immediate access to participating agencies' databases. This function is critical in the dissemination of relevant information in support of tactical and investigative agencies, deconfliction, and officer safety. EPIC also provides significant tactical, operational, and strategic intelligence support to state and local law enforcement agencies, especially in the areas of clandestine laboratory investigations and highway interdiction.

Cooperation with Mexico

The DEA's presence in Mexico represents our largest international footprint. The ability to have DEA Special Agents assigned to 11 different offices throughout Mexico is a reflection of the level of cooperation that we continue to enjoy with our Mexican counterparts. DEA supports bi-lateral investigations with the Government of Mexico by providing information and intelligence to develop investigations that target leaders of TCOs throughout Mexico.

We view our working relationship with the Mexican Authorities as strong, and getting stronger. In 2014, Mexican law enforcement officials arrested cartel leaders Hector Beltrán-Leyva, Servando Gomez-Martinez, and Omar Trevino Morales. These actions represent significant successes for both the United States and Mexico in our shared struggle against TCOs. The arrests struck at the heart of the leadership structure of the Knights Templar Cartel, the Beltrán-Leyva Organization, and the Los Zetas Cartel; and highlight the continuing cooperation between Mexican and U.S. law enforcement. The United States and Mexico have established a strong and successful security partnership in the last decade and, to that end, the U.S. government stands ready to work with our Mexican partners to provide any assistance, as requested, to build upon these successes.

Conclusion

Mexican TCOs remain the greatest criminal drug threat to the United States. These Mexican poly-drug organizations traffic heroin, methamphetamine, cocaine, and marijuana throughout the United States, using established transportation routes and distribution networks. They control drug trafficking across the SWB and are moving to expand their share of U.S. illicit drug markets. Their influence up and down the supply chain, their ability to enter into new markets, and associations with domestic gangs are of particular concern for the DEA. DEA will continue to address this threat domestically and abroad by attacking the crime and violence perpetrated by the Mexican-based TCOs which inflict tremendous harm to our communities.

Chapter 532

**THE IMPLEMENTATION OF THE COMMON
ASSESSMENT FRAMEWORK IN PUBLIC HEALTHCARE
ORGANIZATIONS: IMPROVING PATIENT SAFETY
THROUGH IMPROVEMENT OF
ORGANIZATIONAL PERFORMANCE**

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ABSTRACT

The Common Assessment Framework (CAF) constitutes a holistic analysis of the performance of one organization, approaching it from different perspectives simultaneously. According to this, the excellent results for the organizational performance, citizens/customers and society rely on leadership, planning/design, human resources, partnerships, resources, as well as administrative processes. CAF is based on 8 basic principles, the so called “Excellence Principles”, namely Results orientation, Focus on citizen/customer, Leadership and Consistency of aim, Management through processes and facts, Development and participation of human resources, Continuous learning, Innovation and improvement, Development of partnerships and Corporate social responsibility. These principles have been incorporated in the CAF structure through 9 criteria, which are further analyzed in 28 subcriteria. Each of the principles has 4 maturity levels, which define over time the course of one organization towards excellence. The CAF 9 criteria represent the main aspects that need to be taken into consideration during the analysis of any organization. These are categorized in 5 criteria- enablers, which cover what the organization does (Leadership, Strategy & Planning, Human Resources,

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Partnerships & Resources and Processes) and 4 criteria- results, which cover what the organization achieves (Citizens/Customers oriented results, Human Resources oriented results, Society oriented results and Key performance results). By conducting a self-assessment Public Organizations may define in their function their strengths, as well as areas for improvement. The self-assessment process is guided by a specific rating system. The CAF implementation is a continuous process, as the conclusions from one assessment should lead to a plan with improvement actions, which, after their implementation, should be re-assessed using the CAF, so to achieve continuous administrative improvement. As a conclusion, the CAF is a Total Quality Management (TQM) tool that Public Organizations can use for free for their self-assessment, aiming at improving their administrative capacity and services, without having to ask for support from external sources.

Keywords: self-assessment of hospital, common assessment framework, quality in healthcare services

INTRODUCTION

The CAF belongs to the TQM tools and in Europe it is used for free as of year 2000 to assist Public Organizations in using TQM techniques in a simple way so that they can improve their administrative capacity and the services provided to citizens and other enterprises.

The CAF constitutes a holistic analysis of one organization, approaching it from different perspectives simultaneously and assessing the results achieved, either by its entirety or by its different divisions, in terms of organizational performance, citizens'/customers' satisfaction and society's satisfaction (EIPA, 2019). By being common for Organizations of the Public Sector, it ensures comparability of results among similar services.

European Public Administration Network (EUPAN) introduced this tool on the principles and philosophy of TQM and Public Management. The CAF is available for free and it is inspired by the European Foundation for Quality Management (EFQM) model, sharing the same 9 criteria. According to fundamental European guidance, all processes of Public Organizations must be part of a quality system, therefore, the implementation of the CAF, in addition to the use of other systems and quality tools, is a topic of first priority for the administrative transformation and the improvement of the Public Sector.

The essence of the CAF use is the continuous administrative improvement through appropriately designed actions or measures. The CAF constitutes a complete study of the structure and function of one Public Organization at a defined point of time. The process of self-assessment is based on real facts and evidence-based views for each criterion/subcriterion. The employees of the organization can perform the assessment themselves, without support from external partners.

The implementation of the CAF is a continuous process, since the results from one assessment should lead to the compilation of a plan with improvement actions, which, after their implementation, are re-assessed based on the same tool, in order to achieve continuous administrative improvement.

Public Organizations can implement the CAF either in their entirety or in specific divisions, yet always as a single tool and never in fragments, with the selective use of specific criteria and subcriteria.

ORIGIN AND DEVELOPMENT OF THE CAF

Public Administration throughout Europe, more than ever in our days, is asked by society to prove and improve the value it brings as far as the maintenance and further development of the societal well-being are concerned. In times of socio-financial austerity, the effectiveness of the public policies, the organizational adequacy and the quality of public services constitute factors of vital importance, which define the response to the changing needs and expectations of citizens and enterprises (Dimitriou and Archontas, 2015).

In the countries-members of the European Union, Public Administration is trying to meet all these societal requirements and has undertaken many initiatives for the implementation of new techniques and methods, aiming at improving its effectiveness, performance, as well as its financial and societal responsibility. To this direction different approaches have taken place in all types of Public Organizations and sectors of public responsibility, at European, national, federal, regional and local level. One of the key factors that affected the results of these initiatives was the lack of a coherent and sustainable approach (Michalopoulos, Polykratis and Dimitriou, 2017).

In 1998 from discussion among the General Managers of Public Administration of countries-members within EUPAN, the need for a common European quality framework arose, to be used across the Public Sector as a self-assessment tool. It was, therefore, decided that this quality framework be jointly developed under the auspices of the Innovative Public Services Group (IPSG), an unofficial working group from experts at national level, established by General Managers of EUPAN.

The first CAF edition was created in 1998 and 1999 from IPSG with the support of EFQM, Speyer Academy and the European Institute of Public Administration (EIPA). Speyer Academy had established the homonymous quality award for the Public Sector in German speaking European countries (Engel, 2002).

The CAF standard was implemented in 2000 during the 1st European Quality Conference in Lisbon. In 2001 in Maastricht, Netherlands the European CAF Resource Center was established in EIPA, as a center of specialization for the CAF implementation with the aim to train, consult and support countries members of the European Union in promoting and further enhancing the CAF.

The first two years of the implementation of CAF were evaluated by a study on its use. The results of the study led to the improved CAF 2002 edition, presented at the 2nd European Quality Conference in Denmark. A further study on the CAF use in 2005 indicated a number of areas requiring further improvement. Such improvements were the increase of the coherence and the simplification of the tool, the increase of user-friendliness with the elaboration of examples and special vocabulary, the development of a better scoring system for specific users and the incorporation of guidance documents about benchlearning. Therefore, the CAF was improved for the second time in 2006 and its new edition, the CAF 2006 edition, was presented at the 4th European Quality Conference in Finland. In 2009 and

2010 the establishment of a process of external feedback on the CAF use followed, along with a special edition for the teaching sector, respectively (Staes et al., 2011).

The most recent edition of CAF is this of year 2013, with the incorporation of changes that arose from observations collected from 400 users of the tool and its national correspondents in the countries-members of the European Union. With this revision, the tool improved significantly, with aim the benefit of all stakeholders of the Public Sector in general and more specifically of citizens (Michalopoulos, Polykratis and Dimitriou, 2017). For example, concepts like the users' orientation, public performance, innovation, ethics, effective collaboration with other organizations and social responsibility have been developed in depth, creating new possibilities for further development of the Public Sector organizations (Dimitriou and Archontas, 2015) (Table 1).

Table 1. The development of CAF

Year	Event
1998	Agreement on the development of the CAF within EUPAN
2000	CAF Implementation
2001	Foundation of European CAF Resource Center in EIPA Institute (Maastricht, Netherlands)
2002	First revision of the standard: Implementation of CAF 2002 edition
2006	Second revision of the standard: Implementation of CAF 2006 edition
2009	Implementation of external feedback process
2010	CAF edition specialized for teaching sector
2013	Third revision of the standard: Implementation of CAF 2013 edition

As far as the adoption of the tool is concerned, 59 European countries have currently implemented the CAF, having in total 3.989 registered users (EIPA, 2019).

OBJECTIVE OF THE CAF STANDARD

The CAF can act as a catalyst for an integrated improvement process within one Public Organization and has five basic objectives (EIPA, 2019) (Dimitriou and Archontas, 2015):

- To introduce Public Organizations in the excellence culture and the TQM principles,
- To guide them gradually to an integrated quality cycle, which consists of the Deming Cycle stages,
- To enable the self-assessment of one Public Organization and support it in diagnosing improvement areas and taking the appropriate actions,
- To act as a bridge between the different standards used for quality management in both Public and Private Sectors &
- To enable the bench learning among different organizations of the Public Sector

The organizations that implement the CAF are aspired to achieve excellent performance. The effective use of the CAF should lead to further development of this culture of excellence within the organization in a short time period.

STRUCTURE OF THE CAF STANDARD

According to the CAF, the excellent results in terms of organizational performance, citizens/customers' satisfaction and society's satisfaction depend on leadership, planning/design, human resources, partnerships, resources, as well as administrative processes.

The CAF is based on 8 basic principles, the so called "Excellence Principles". These principles make the difference between traditional, bureaucratic, Public Organizations and Public Organizations oriented towards Total Quality (Dimitriou and Archontas, 2015).

These principles are the following (Dimitriou and Archontas, 2015) (EIPA, 2019):

1. *Orientation towards results:*

The organization focuses on results, for the benefit of all interested parties (Public Authorities, citizens/customers, partners and human resources of the organization) in conjunction with the objectives set.

2. *Focus on citizen/customer:*

The organization focuses on the needs of both current and potential citizens/customers, promoting their active participation in the development of its products and services and the improvement of its performance.

3. *Leadership and consistency of purpose:*

This principle combines leadership that has vision and inspiration with purpose, which remains consistent in a changing environment. The leadership clearly establishes the mission, vision and values. In addition, it creates and maintains an internal environment in which human resources have the possibility to participate fully to meet the objectives of the organization.

4. *Management through processes and facts:*

The desired outcome comes successfully when relevant resources are managed as process and the effective decisions are driven by the analysis of facts and information.

5. *Development and participation of human resources:*

Human resources at all levels constitute the essence of the organization. The full participation of employees allows the use of their skills for the benefit of the organization. The personnel's contribution should be maximized through their development and participation, as well as through the creation of a working environment of common values, trust, transparency, empowerment and recognition.

6. *Continuous learning, innovation and improvement:*

The excellence constitutes a challenge for the current status and activates change through continuous learning. Therefore, continuous improvement should constitute a permanent objective of the organization.

7. *Development of partnerships:*

The organizations of the Public Sector need other Public Organizations to meet their objectives. Consequently, they should develop and maintain partnerships that add value, through a relationship of interdependence.

8. *Corporate social responsibility:*

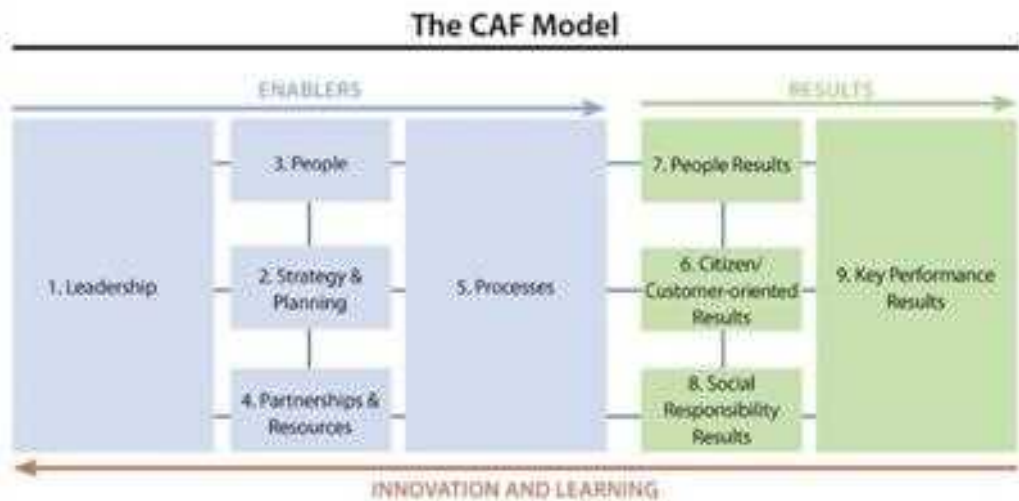
Public Organizations must own their part of social responsibility. This means that they must respect ecological sustainability and try to meet the high expectations and requirements of the local and international community.

The CAF standard incorporates in its structure the Excellence Principles. Each of the principles is consisted by 4 maturity levels. The organization will reach these levels gradually during its course towards excellence through an integrated Quality Cycle, (Deming Cycle/Plan- Do- Check- Act, PDCA) (Figure 1).



Source: Encyclopedia of Production and Manufacturing Management, 2000.

Figure 3. The Deming Plan, Do, Check, Action (PDCA) cycle.



Source: Dimitriou and Archontas, 2015.

Figure 4. The CAF model.

The CAF has 9 criteria that represent the key aspects that need to be taken into account in the analysis of any organization. There are 5 criteria-enablers (Leadership, Strategy & Planning, Human Resources, Partnerships & Resources and Processes) and criteria-results (Results oriented to Citizen/Customer, Results oriented to Human Resources, Results oriented to Society and Key Performance Results) (EIPA, 2019). The criteria-enablers cover what the organization does, while the criteria-results cover what the organization achieves. With the conduct of a self-assessment, the Public Organizations can identify in their function, as well

as in their aspiration for desired results, areas for improvement (Tomazevic, Seljak and Aristovnik, 2014) (Figure 2).

The 9 criteria of the standard are further analyzed in 28 subcriteria, which identify the main issues that need to be addressed when a Public Organization is assessed. Each of these subcriteria comprises a series of examples (EIPA, 2019). These examples reflect a large number of successful practices across Europe. Despite the fact that not all criteria are applicable to all organizations, many of these require special attention during the self-assessment. The incorporation of the conclusions from the assessment of the criteria-enablers and the criteria-results into the administrative practices constitutes the never-ending cycle of innovation and learning, which accompanies organizations on their way to excellence (Dimitriou and Archontas, 2015).

Each organization can adjust freely the CAF to its specific conditions or even exceptional circumstances, yet with all 9 criteria and 28 subcriteria, as presented in Table 2:

Table 2. The CAF criteria

1st Criterion: Leadership	It assesses the way with which people at the helm and managers shape the mission of one Public Organization (P.O.), facilitate its fulfillment and contribute to the realization of the vision. It includes 4 sub-criteria.
Sub-criterion 1.1	The Leadership provides one clear direction of the P.O., developing vision, mission and values.
Sub-criterion 1.2	What the Leadership does to develop and implement a performance management system and changes.
Sub-criterion 1.3	What the Leadership does to encourage, support employees and act as a role model.
Sub-criterion 1.4	How the Leadership manages the relations with the politicians and the rest groups of interest to ensure common responsibilities.
2nd Criterion: Strategy & Planning	It assesses the way the P.O. implement its mission through one specific strategy oriented towards the groups of interest and with the support of public policies, programs, processes, etc. It includes 4 sub-criteria.
Sub-criterion 2.1	What the P.O. does to collect information regarding the current or future needs of the parties involved in its function.
Sub-criterion 2.2	What the P.O. does to develop, revise and update its strategy and planning taking into consideration the needs of all the involved parties in its function and the available resources.
Sub-criterion 2.3	What the P.O. does to implement strategy and planning throughout the organization.
Sub-criterion 2.4	What the P.O. does to design, implement and update its program for modernization and innovation.
3rd Criterion: Human Resources Management	It assesses the way a P.O. manages and develops the knowledge and skills of its personnel. It includes 3 sub-criteria.
Sub-criterion 3.1	What the P.O. does to program, manage and improve human resources with transparency in relation to its strategy and planning.
Sub-criterion 3.2	What the P.O. does to determine, develop and make use of employees' capabilities, harmonizing individual objectives with organizational ones.
Sub-criterion 3.3	What the P.O. does to involve employees by developing open dialogue and empowering them, supporting their well-being.
4th Criterion: Partnerships & Resources	It assesses the way the P.O. designs and manages the external relationships and the internal resources in order to support its policy, strategy and the effective function of its processes. It includes 6 sub-criteria.
Sub-criterion 4.1	What the P.O. does to develop and implement basic relationships of partnerships.

Table 2. (Continued)

Sub-criterion 4.2	What the P.O. does to develop and implement partnerships with citizens/customers.
Sub-criterion 4.3	What the P.O. does to manage finances.
Sub-criterion 4.4	What the P.O. does to manage information and knowledge.
Sub-criterion 4.5	What the P.O. does to manage technology.
Sub-criterion 4.6	What the P.O. does to manage its facilities.
5th Criterion: Management of Processes & Changes	It assesses the way the P.O. manages and improves the processes in order to support its strategy and satisfy its citizens/customers.
Sub-criterion 5.1	What the P.O. does to determine, design and continuously improve its processes.
Sub-criterion 5.2	What the P.O. does to develop and provide services and products oriented to the citizen/customer.
Sub-criterion 5.3	What the P.O. does to develop innovative processes with the citizens' participation.
6th Criterion: Citizens-Oriented rEsults	It assesses the results of the P.O. in relation to the satisfaction of the external and internal customers. It includes 2 sub-criteria.
Sub-criterion 6.1	Results of the citizens'/customers' satisfaction surveys.
Sub-criterion 6.2	Indicators regarding evaluations for citizens/customers.
7th Criterion: Human Resources-oriented Results	It assesses the results that the P.O. achieves in relation to the satisfaction of its human resources. It includes through 2 sub-criteria.
Sub-criterion 7.1	Results of human resources' satisfaction survey.
Sub-criterion 7.2	Indicators of effectiveness of human resources.
8th Criterion: Society-Oriented Results	It assesses what the P.O. achieves for the satisfaction of the needs and expectations of society for topics like the quality of life, the maintenance of global resources, etc. It includes 2 sub-criteria.
Sub-criterion 8.1	What results has the P.O. achieved to address the needs of society in relation to the results of social surveys, as the involved citizens perceive them.
Sub-criterion 8.2	What results has the P.O. achieved to meet the society's needs in relation to indicators of social performance established by the P.O.
9th Criterion: Key Performance Results	It assesses what the P.O. achieves in relation to its constitutional mandate and its defined objectives, as well as in relation to the satisfaction of the needs and expectations of all parties that have a financial interest or participate in the P.O. It includes 2 sub-criteria.
Sub-criterion 9.1	External results. Output- results in relation to the objectives.
Sub-criterion 9.2	Internal results.

Source: (Efkarpidis, 2016).

INTERCONNECTED FUNCTIONS IN THE CONTEXT OF THE CAF STANDARD

The holistic approach of the CAF does not only suggest that one Public Organization's functions are thoroughly assessed but also that all integral elements of the organization are interdependent. The following remarks can be made:

- There is a cause-effect relationship between the left part (conditions- causes) and the right part (results- consequences) of the standard (Figure 2).
- There is a holistic relationship among causes (conditions).

The verification of the interconnection between cause-effect is of fundamental importance for the self-assessment, in the context of which the organization must always check the consistency between certain result or a series of similar results and the evidence arisen from the relevant criteria and sub-criteria regarding conditions. This consistency is sometimes difficult to verify because, due to the holistic character of the organization, the different causes (conditions) interact between each other during the delivery of results. Since the integrity of results is defined largely by the type and intensity of the relationships between conditions, these relationships must be investigated during the assessment. In fact, the intensity of these relationships differs among different organizations and their nature defines largely the quality of the organization.

Apparently the relationships are not limited to the level of criteria. Quite often substantial interactions- relationships exist at the level of sub-criteria.

COMMON EUROPEAN VALUES OF THE PUBLIC SECTOR

The CAF is designed specifically for the Public Sector and this is the differentiating point from the EFQM standard.

Quality in the Public Sector present some unique features compared to the Private Sector, taking into account the basic conditions of the European socio-political and administrative culture (EIPA, 2019).

These conditions are the legitimacy (democratic and parliamentary) and the state of justice and ethics, which are based on common values and principles, like transparency, accountability, participation, diversity, equality, social justice, solidarity, collaboration and the relationships with the stakeholders (EIPA, 2019). All the above constitute elements to be taken into account during the assessment.

Although the CAF focuses mainly on the assessment of the performance of the administration and on the identification of the organizational causes that make improvement possible, the ultimate goal is to contribute to good governance.

THE IMPORTANCE OF EVIDENCE AND MEASUREMENTS OF THE CAF

The self-assessment and the improvement of the Public Organizations become difficult without reliable information from their different functions. The CAF supports Public Organizations in the collection and use of information, yet quite often this information is not available during the first self-assessment. For this reason, the CAF is often seen as measurement that starts from scratch, indicating the important areas for the initiation of the measurement. As long as the Administration is under a process of continuous improvement, information will be increasingly collected and managed in a systemic and gradual manner both in the internal and external environment (Dimitriou and Archontas, 2015).

COMMON ADMINISTRATIVE LANGUAGE AND GLOSSARY OF THE CAF

Many Public Organizations are facing difficulties in understanding Management terminology. The CAF creates a common language allowing the organization's personnel and leadership to discuss about organizational topics in a constructive way. This simple and understandable language by all public employees promotes the dialogue and the bench learning among Public Administrations at European level (Dimitriou and Archontas, 2015).

THE ROLE OF THE ASSESSMENT SYSTEM IN THE CAF

Although the identification of the strengths, the areas for improvements and the relevant improvement actions constitute the most important results of the self-assessment, the CAF scoring system plays an equal special role (Dimitriou and Archontas, 2015).

The scoring of each criterion and sub-criterion of the CAF standard has 4 main objectives:

- To provide an indication for the direction that the Public Organization shall follow as regards improvement actions,
- To measure the improvement of the Public Organization,
- To identify successful practices, as these are determined by the high scores for the conditions and the results &
- To assist in finding the appropriate stakeholders from whom the Public Organization can learn.

SUPPORT IN THE USE OF THE CAF

In 2001 with decision of the responsible General Managers for the Public Administration, a network of national representatives for the CAF was established, as well as the CAF Resource Center, as previously mentioned. This network is responsible at European level for the development and the monitoring of the standard. In addition, it studies new tools and strategies for the promotion of the CAF. CAF Resource Center operates in EIPA in Maastricht, Netherlands and is responsible for the coordination of the network. In addition, it manages the CAF webpage, which is the access point to all CAF-related information and other TQM topics.

In the countries-members of European Union the national representatives take the right initiatives to encourage and support the use of the standard in their countries. The activities of the Center cover a broad spectrum, ranging from the creation of national centers of data management to the construction of specialized web portals and from national or regional projects or programs to national awards or quality conferences based on the CAF standard (Dimitriou and Archontas, 2015).

THE PROCESS OF EXTERNAL FEEDBACK

In order for the Public Organizations to implement the CAF successfully, there is a formal process to provide feedback from the external environment on the overall quality management with the CAF use. This external feedback process, implemented on a voluntary basis, aims at supporting even more the CAF users on their way towards quality, making their efforts visible within and outside the organization. This feedback process relates to the self-assessment process, as well as to the broader vision of the organizations to achieve excellence over time.

The external feedback process aims at achieving the following objectives:

- To support the quality of the CAF implementation and the impact on the organization,
- To investigate whether the organization adopts the TQM principles, as a consequence of the CAF implementation,
- To support and empower the feeling of enthusiasm with continuous improvement inside the organization,
- To promote the assessment and the bench learning from similar organizations,
- To reward the organizations that have started their course towards continuous improvement for achieving excellence in an effective manner, without criticizing their current quality level &
- To enable the participation of the CAF users at the level of excellence of the EFQM model

The process of the external feedback is based on the following 3 pillars:

- Pillar 1: Self-assessment process,
- Pillar 2: Improvement actions process &
- Pillar 3: Maturity of the organization towards TQM

The organizations that have used the CAF effectively may assume the title of “Effective CAF user” given for a duration of 2 years. The process of external feedback and the previous title are at the discretion of countries-members, which create the practical details having as basis a commonly agreed frame but at their own pace. The organizations that wish to submit an application for the title above have to be informed in advance if this possibility exists in their countries (Dimitriou and Archontas, 2015).

ADVANTAGES OF THE CAF STANDARD

The CAF has the following advantages (Michalopoulos, Polykratis and Dimitriou, 2017):

1. It constitutes a first attempt to manage the diversity of the administrative systems of the countries-members of the European Union, setting common criteria and a single

assessment method, so that its conclusions be comparable, commonly accepted and utilizable and common policies be designed if and when conditions allow for it.

2. It allows the development of contacts, communication and cooperation among the agencies of the Public Administration of the countries-members of the European Union, as well as the exchange of experiences for topics of administrative organization and function.
3. It creates the preconditions for the implementation of a broader plan to establish the European Quality Award in the Public Administration.
4. It significantly contributes to the introduction of the philosophy and the concepts of TQM and of Public Management into the Public Organizations.
5. It enforces the participation of the staff of one Public Organization in the process of the assessment of its function, since in principle it is about a self-assessment method.
6. It constitutes a holistic study of the structure and function of one Public Organization at one specific point of time. The self-assessment process is based on real facts and justified conclusions for each aspect under evaluation and it can be carried out by the employees of the Public Organization themselves, without assistance from external partners.
7. Its implementation is a continuous process, since the conclusions of one assessment lead to the implementation of a plan with actions for the improvement of the administrative function, which after their implementation, are re-assessed based on the CAF again.
8. The CAF does not concern the assessment of the public policies that one Public Organization applies, but its administrative function.
9. The CAF is linked in no way with the performance assessment of the personnel of the Public Organization at any hierarchical level of responsibility.
10. The CAF may be implemented either to the whole Organization either to individual units, yet always in an integrated way, as single system and not in a fragmented way with the selective implementation of some criteria and sub-criteria.

CONCLUSION

Concluding on the above observations about the CAF, its implementation is suggested for the Public Organizations, so that they can use a tool for the improvement of their administrative capacity, which belongs to them and they do not necessarily need to refer to external sources for the implementation of some similar integrated methodology.

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Chapter 533

**BRAZILIAN RATTLESNAKE
(*CROTALUS DURISSUS LINNAEUS 1758*) IN
THE ATLANTIC FOREST OF RIO DE JANEIRO
STATE: A CASE OF BIOLOGICAL INVASION
OR A RED ALERT TO PUBLIC HEALTH?**

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ABSTRACT

Crotalus durissus is the snake species within its genus which covers the largest geographic distribution, reaching almost the entire South American territory. This species is widely dispersed and adaptable to open and anthropized environments. *C. durissus* is increasingly entering areas which once belonged to the Atlantic Forest biome and were covered by Ombrophilous (broadleaf) Forest. The main reason this species is establishing in this new environment is due to Atlantic Forest deforestation; initially to establish coffee and sugarcane plantations, and later to establish pastures for livestock. The new environment has become similar to the *Cerrado* biome, which was the original habitat of *C. durissus* in southeastern Brazil. *Cerrado* is one of the most representative biomes in the State of Minas Gerais, and from which several *C. durissus* individuals have migrated from towards the State of Rio de Janeiro. With this new panorama, the species has started

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to cause sanitary and possibly ecological problems such as an increase in number of local residents injured by snakebites (affecting the distribution of snake anti-venom in health posts, and predation and competition with native species). In this chapter, we aim to review and analyze the past and present view of *C. durissus* distribution in the State of Rio de Janeiro through scientific literature review and consultations in the biological collections of the Rio de Janeiro National Museum and Vital Brazil Institute. We also correlated its distribution to the time it took to advance into the State.

Thus, we found *C. durissus* records in 13 municipalities and 11 of them were new records for the State. There was no prior confirmation about the presence of the species in these sites, evidencing that it is increasing its geographical distribution mainly toward degraded areas in the State of Rio de Janeiro. The new *C. durissus* records indicate that it is spreading into Rio de Janeiro through three routes: *Paraíba do Sul* River Valley, mountainous region, and *Serra da Bocaina* in the municipality of *Paraty*. The new rattlesnake records were associated to the Atlantic Forest degradation in these locations. The expansion in the distribution area of this poisonous snake into densely populated areas is expected to increase the number of snakebite accidents, which will require greater production of snake anti-venom. In addition, its expansion is expected to have ecological impacts on the native fauna. More attention should be given to this issue in the State of Rio de Janeiro in order to prevent the species from advancing into new areas.

Keywords: bioinvasion, environmental degradation, geographic distribution, rattlesnake

INTRODUCTION

The planet's Neotropical Region shelters invaluable and great biological diversity due to vicarious effects. Within them there are three main effects which can be drawn: the emergence of the Andes; the Panama isthmus; and the constant climatic changes during and after the Pleistocene epoch, which occurred approximately 1.8 million years ago (e.g., Wing and Sues, 1992, 327-416; Mittermeier et al., 2005; Wüster et al., 2005, 1095-1108).

This last event is the most known and controversial Atlantic Rainforest speciation model known as the Pleistocene Refuge hypothesis (Haffer 1969, 131-137; Vanzolini and Williams 1981, 251-255), during which the Amazon had its dimensions reduced due to climatic fluctuations, specifically at the end of the Pleistocene and Pliocene epoch (Quijada-Mascareñas et al., 2007, 1296-1312). This fact resulted in intense fragmentation of the biome and created geographical barriers which favored allopatric biological diversity formation (Haffer 1969, 131-137; Haffer and Prance 2001, 579-607).

Commonly known as rattlesnakes, serpents of the *Crotalus* genus had their speciation well evidenced with the occurrence of only one species on the south portion of the American continent *Crotalus durissus* (Linnaeus 1758). However, this species has the greatest geographical distribution among the genus, possessing 11 described subspecies (Campbell and Lamar 2004, 539-547), among which six can be encountered in Brazilian territory (Costa and Bérnills 2018, 57). These Brazilian subspecies are: *Crotalus durissus durissus* (Linnaeus 1758), described in the State of Amapá; *Crotalus durissus ruruima* (Hoge 1966), described in the State of Roraima; *Crotalus durissus cascavella* (Wagler in Spix 1824), registered in the States of Maranhão, Piauí, Ceará, Rio Grande do Norte, Paraíba, Pernambuco, Alagoas, Sergipe, Bahia, and Minas Gerais; *Crotalus durissus marajoensis* (Hoge 1966), recorded at Marajó Island (Pará); *Crotalus durissus collilineatus* (Amaral 1926), found in Tocantins,

Mato Grosso, Mato Grosso do Sul, Goiás, Distrito Federal, Minas Gerais, and São Paulo; and lastly, *Crotalus durissus terrificus* (Laurenti 1768), found in Tocantins, Mato Grosso, Minas Gerais, Rio de Janeiro, São Paulo, Santa Catarina, Paraná, and Rio Grande do Sul (Hoge and Romano 1978/79, 491; Campbell and Lamar 2004, 539-547; Dos-Santos et al., 2005, 958-961; Costa and Bérnils 2018, 29). The species inhabits almost all of the Brazilian biomes, especially those with open and dry vegetation such as the Brazilian *Cerrado* (Brazilian Savannah), but they do not inhabit humid tropical forests such as the Amazon and the Atlantic Rainforest. *Crotalus d. terrificus* is the only subspecies with recent records in the State of Rio de Janeiro in the Atlantic Forest domain (e.g., Campbell and Lamar 2004, 539-547; Bastos et al., 2005, 812-815; Costa and Bérnils 2018, 29) (Figures 1 and 2).

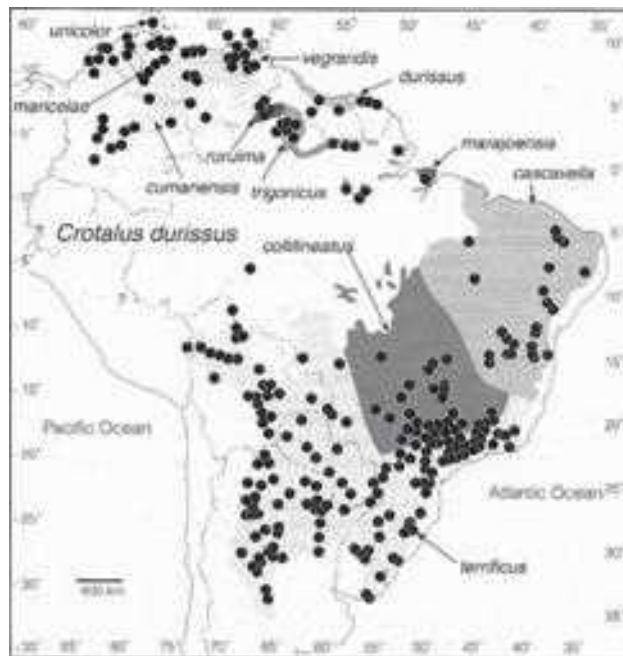


Figure 1. Geographical distribution of *Crotalus durissus* (Linnaeus 1758) in South America (black dots), with locality type (white dot). Map by Campbell and Lamar (2004).



Figure 2. *Crotalus durissus terrificus* (Laurenti, 1768) ♀ in an area of Atlantic Forest, Paraty/Cunha (Rio de Janeiro/São Paulo), Brazil. Photography by Jorge Pontes 2016.

C. durissus is commonly found in areas below 1,000 m altitude, but there is a recorded registry of 2,300 m at Sandia, Peru (Mijares-Urrutia and Arends 2000, 1-30). The species presents variable dorsal coloration in different regions in Brazil (Campbell and Lamar 2004, 539-547). It has the ability to colonize insular areas such as Aruba, and the climate changes and vegetal cover modifications during the Pliocene and Pleistocene epochs had an effect on the species distribution in South America, reaching pastures and coastal open vegetation (Mijares-Urrutia and Arends 2000, 1-30; Campbell and Lamar 2004, 539-547).

Exotic and invasive species are currently one of the greatest causes of native species extinction around the globe (e.g., Gurevich and Padilla 2004, 470-474; Pimentel 2011, 1-7). In competition for resources or by predation of native species, invasive exotic fauna grow rapidly in association with human occupation and other actions (e.g., Pimentel 2011, 1-7; Rocha and Bergallo 2012, 1-2). Several serpent species have become environmental, economic and public health problems in some places around the world (e.g., Jorge and Ribeiro 1992, 347-354; Duarte and Eterovic 2003, 126-135; Warrel 2004, 709-761; Bergstrom et al., 2009, 73-81). Public health problems in Brazil are aggravated by the reduction in the availability of snake anti-venom in health posts, including Rio de Janeiro State (Cardoso and Wen 2003, 3-5; Citeli et al., 2018, 123-124).

The species was not found in the State of Rio de Janeiro before 1940 because this region was not part of its natural geographic distribution and the forest matrix was a barrier for the rattlesnake to enter into the State (Melgarejo 2003, 52-53; Melgarejo 2013, 59; present study). However, *C. durissus* is becoming an invasive species in the Atlantic Rainforest biome, mostly due to deforestation and its aptness to adapt to open surroundings and anthropized environments such as man-made fields and pastures (Marques, Eterovic and Sazima. 2019, 44; Bastos et al., 2005, 812-815; Wüster et al., 2005, 1095-1108; present study). Its oldest record in the institutional collection in Rio de Janeiro State dates from 1988 in the municipality of Itatiaia (present study).

Ever since this time, *Crotalus durissus* has been taking advantage of its new environment, which (despite anthropic influences) resembles its original habitat, the *Cerrado*. Once established in its new habitat, the species begins to not only affect the native fauna, but also the local human population, thereby causing new snakebite accidents being recorded in places in which they did not previously occur. Therefore, this becomes a problem in the Health Ministry's snake anti-venom distribution directive for the incident regions, as *Crotalus durissus* is responsible for 7.7% of the snakebite accidents in Brazil (Duarte and Menezes 2013, 1-4; Melgarejo 2013, 59).

Although this percentage seems relatively low, the mortality rate is 1.84% (Pinho and Pereira 2001, 24-29). This is higher than deaths caused by the *Bothrops* genus (0.45% mortality rate) which is responsible for 90.6% of snakebite incidents in Brazil (Luna and Silva 2011, 130). The remaining incidents of medical importance are attributed to serpents of the *Lachesis* genus (known in Brazil as “*sucurucu*,” “*pico-de-jaca*,” and “*surucutinga*”), accountable for 1.4% of incidents, and the *Micrurus* genus (“*corais-verdadeiras*”), responsible for approximately 0.4% of the incidents (Pinho and Pereira 2001, 24-29).

In view of the above, in this chapter we aimed to compile the most recent records of the occurrence of *Crotalus durissus* in Rio de Janeiro State, as well as to know the situations in which the species advance in its area of occurrence. More specifically, we aimed to clarify when the species began to spread to new municipalities in Rio de Janeiro State, particularly in

the most populous regions, which might become a leading factor for an increase in snakebite accidents.

METHODS

Literature Review

A bibliographic revision was performed in order to identify articles and further publications regarding biogeography, ecology and registry of the *Crotalus durissus* species in the municipalities of the Rio de Janeiro and neighboring States. The criteria used to choose these articles were the keywords regarding the *Crotalus* genus, invasion specimens, snakebites in Rio de Janeiro State, and seasonal activity. Papers used in this study were mainly compiled in academic articles which comprehend *Crotalus durissus* distribution inside or outside of Rio de Janeiro State. Google Scholar, Scielo, ScienceDirect and Web of Science databases were used to search for the articles.

Collection Review

We performed a review on the herpetological collection of the Rio de Janeiro National Museum (MNRJ) and the Vital Brazil Institute, Niterói (IVB) to compile rattlesnake records in the State of Rio de Janeiro and vicinity between 1980 and 2019. The inventory books of the visited institutions contain capture data, local, rostrum-cloacal length (RCL), gender, acronym (record number) and other additional observations. The review at the Vital Brazil Institute was done via digital inventory books using a filter to solely compile the State of Rio de Janeiro and vicinity, as well as individuals which had been run over by vehicles. It was not possible to identify the gender of the animals or the RCL for data collected at the Vital Brazil Institute because the Biological Collection Division was relocated and disorganized at the time of consultations.

A physical inventory book was rearranged at the National Museum using the same filters as in the aforementioned review. A great deal of the deposited specimens in the Museum were collected from roads and their physical condition presented damage to such an extent that the RCL had to be taken by attaching body parts (head, body, and tail) with the use of metric tape. Specimen gender discrimination was performed by visualizing the reproductive organs (when possible) or by consulting the inventory books. We have also included the date and place of collection in the review, and other relevant information observed in the field.

The data gathered in the institutions were processed using Microsoft Excel® software, from which graphics and lists were elaborated using municipality's occurrence as criteria.

Maps

We mapped the invasion of *Crotalus durissus* in municipalities of the State of Rio de Janeiro from 1988 to 2019 through bibliographic data and collection records. The map was

generated via ArcGIS software, entering the geographic coordinates (UTM, SIRGAS 2000) and indicating the species occurrences. A breakthrough in the species distribution in the State of Rio de Janeiro was created by organizing occurrences by decades. Some records, more specifically the roads sampled ($n = 10$), did not have additional information about the exact collection point. Thus, we chose to perform a coordinate approximation according to the indicated locations. When the registry only mentioned the municipality name in the inventory books, we used the central point (coordination) of the city as reference.

RESULTS

We found 77 records of *C. durissus* between 1988 and 2019 for the State of Rio de Janeiro: 58 records were found in the Vital Brazil Institute, 15 records in the National Museum (Figure 3), and four other casual encounters: two in the municipality of Paraty, one in Cunha, and another in Miguel Pereira. The records found in the Vital Brazil and National Museum institutions comprised 13 municipalities, in which eleven were new occurrences (*Nova Friburgo*, *Miguel Pereira*, *Paraty*, *Petrópolis*, *Vassouras*, *Itatiaia*, *Conservatória*, *Levy Gasparian*, *Paraíba do Sul*, *Três Rios*, and *Volta Redonda*). Of the 77 records, 54.5% ($n = 42$) were found in the municipality of *Valença*. An other 9.0% ($n = 7$) were registered in *Três Rios*, 9.0% ($n = 7$) in *Rio das Flores*, 7.8% ($n = 6$) in *Paraíba do Sul*, 3.9% ($n = 3$) in *Levy Gasparian*, 2.6% ($n = 2$) in *Paraty*, 2.6% ($n = 2$) from the BR 040 highway, and 1.3% ($n = 1$) in *Conservatória*, *Volta Redonda*, *Itatiaia*, *Nova Friburgo*, *Petrópolis*, *Miguel Pereira*, *Cunha*, SP/*Paraty*, RJ (border municipalities) and *Vassouras*.

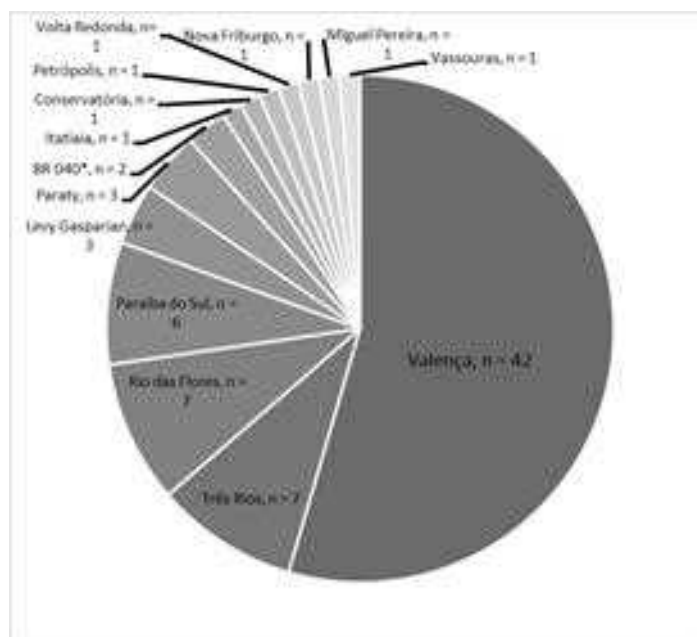


Figure 3. *Crotalus durissus* specimens (n) collected in the State of Rio de Janeiro between 1988 and 2019 and deposited at the Rio de Janeiro National Museum (Rio de Janeiro City) and Vital Brazil Institute collection (Niterói City).

Among the examined specimens, seven were identified at the subspecies level (*Crotalus durissus terrificus*). All of them were found in the municipality of *Rio das Flores*. The number of *C. durissus* collected in the State of Rio de Janeiro and deposited in the institutional collections varied over a period of 31 years (between 1988 and 2019) (arithmetic average 2.3 ± 3.2 individuals per year). Most specimens were collected in the early 1990s and this may be related to collection activities carried out at the *Sítio Divina Providência*. The site is in the municipality of *Valença* and is bordered by the State of Minas Gerais.

A total of 10 *C. durissus* individuals were registered at the BR-040 highway nearby the cities of *Matias Barbosa*, MG ($n = 4$), *Levy Gasparian*, RJ ($n = 1$), *Juiz de Fora*, MG ($n = 2$), *Simão Pereira*, MG ($n = 2$) and *Lima Duarte*, MG ($n = 1$). The oldest record was from 1988 at the *Represa do Funil* in the municipality of *Itatiaia*, albeit the most recent records were found between 2018 and 2019 in *Miguel Pereira*, *Nova Friburgo*, *Petrópolis* and *Três Rios*.

We observed that another *C. durissus* was captured in 2006 in *Rio das Flores* after a 10-year gap. There were six new registries found in 2007. Furthermore, there was a considerable number of these serpents encountered at the roadside ($n = 10$) in the 2010 decade, usually run over by vehicles.

Although *Paraty* has been indicated as a new viable route for southern invasion into the State of Rio de Janeiro, all recent occurrences of *C. durissus* have been recorded in the Rio de Janeiro Metropolitan Region. In addition, an individual was registered in 2019 in the *Miguel Pereira* municipality by Murilo Vicente (personal communication). The taxonomic identity of this specimen was confirmed through photographic evidences (Figure 4).



Figure 4. A *Crotalus durissus* (Linnaeus 1758) individual was registered in the municipality of *Miguel Pereira*, Rio de Janeiro State. Photograph by Murilo Vicente on March 04, 2019.

In 2016, during a study by researchers from the Rio de Janeiro State University in *Paraty*, three *C. durissus* were registered at the *Serra da Bocaina* National Park. One of those individuals was run over on the border of the States of Rio de Janeiro and São Paulo, in the municipality of *Cunha* (Figure 5).



Figure 5. *Crotalus durissus* (Linnaeus 1758) specimen being captured in the SP–171 highway, border of the municipality of *Cunha* (São Paulo State) and *Paraty* (Rio de Janeiro State), near *Serra da Bocaina* National Park. Photography by José Vitor Maciel, 2016.

We observed that the area of occurrence of the species increased between 1988 and 2019, and it is advancing towards the central region of the State of Rio de Janeiro. Advancement through municipalities and all records overlaps deforested and anthropized areas, mainly pasture and secondary vegetation in the early stages of regeneration (Figures 6 and 7).



Figure 6. (Continued).



Figure 6. Forest cover map indicating *Crotalus durissus* (Linnaeus 1758) registries by decade between 1988 and 2019 (a). The occurrence records were extracted from the Rio de Janeiro National Museum (Rio de Janeiro city) and Vital Brazil Institute (Niterói city) Collections. Advance in space and time of *C. durissus* records in the municipalities of Rio de Janeiro State (b).



Figure 7. Aspect of *Serra da Bocaina* on the border of Paraty (Rio de Janeiro State) and *Cunha* (São Paulo State) municipalities. Forest fragmentation and anthropic environments facilitate the entrance of *Crotalus durissus* (Linnaeus 1758) into Paraty, Rio de Janeiro State. Photography by Jorge Pontes, 2011.

DISCUSSION

The advancing area of *Crotalus durissus* occurrence was directly influenced by anthropic actions in the State of Rio de Janeiro, mainly due to deforestation which gave space to coffee and sugarcane plantations, and culminated in a reduction of the Dense Ombrophilous Forest to sparse forest fragments, making way for the serpent species incursion. Almost 80% of the Atlantic Rainforest domain has already been lost (Bastos et al., 2005, 812-815; Castro and Lardosa 2015, 6-27), and pasture areas for cattle ranching have been established in its place. According to Bastos et al., (2005), the presence of *Crotalus durissus* in these regions may be attributed to the great floods in the *Paraíba do Sul* River Basin which occurred in the 1950s and 60s. This argument seems questionable due to the fact that the species indicates its advance regardless of natural disasters, and it is believed that the advance is caused by occupancy of anthropic environments similar to the *Cerrado* biome, which were found at the Vale do Paraíba region due to farming exploitation (Costa and Clemente 2009, 57-65; Melgarejo 2013, 59).

Our study adds eleven new legal municipalities with the occurrence of *C. durissus* to the study by Bastos et al., (2005), where only *Valença*, *Rio das Flores* and *Resende* have some officially registered specimens, with the others being informal records. The records for the studied period (1988-2019) indicate that the species has been advancing to deforested areas and areas replaced by pasture or anthropic fields. This fact is also pointed out by Melgarejo (2003).

This advance form with a high concentration of records in the north of the State may be related to the high rates of land occupation by pasture, livestock and sugarcane plantations in established farms (Rocha et al., 2003, 3-32; Costa and Clemente 2009, 57-65). The advance of *C. durissus* may also be related to deforestation and the fire propagation cycle which lead to secondary vegetation (Tanizaki-Fonseca and Bohrer 2009, 81-90), and creates habitats and passageways for the entry and dispersion of the species.

In addition to the spatial records, the generated maps enable visualizing the expansion of the species to areas which were previously free from *C. durissus* invasion, such as *Miguel Pereira*, *Nova Friburgo* and *Petrópolis*. Interestingly, the aforementioned localities do not present proper climatic patterns for the natural habitat of serpent species (Campbell and Lamar 2004, 539-547; Melgarejo 2003, 52-53), indicating that rattlesnakes are expanding their distribution to colder and damper environments.

There was an increase in the number of rattlesnakes in the 2010s, especially in the highways linking Minas Gerais and Rio de Janeiro. However, another possible invasion route seems to have been established through *Paraty* because the region is vastly occupied by pasture and anthropic fields (Rocha et al., 2003, 3-32; Mittemeier et al., 2005; Santos et al., 2009, 41-56).

Population expansion of *C. durissus* seems evident in the interior of Rio de Janeiro State and throughout the central and coastal areas. Its occupation coincides with more populous areas where some municipalities will be considerably more affected than others. The species is in second place regarding snakebite accidents in Brazil (Araújo, Santa Lucia and Cabral 2003, 7) and the reduction in snakebite anti-venom production, health posts and the lack of organization regarding available information (Bochner and Struchiner 2002, 741-744; Citeli

et al., 2018, 123-124; Ministério da Saúde 2019) could mean an increase in the number of complications due to accidents and even more deaths.

The situation regarding the advance of an exotic species from another Brazilian region which was able to adapt to the Ombrophilous Forest domain is not only creating a concerning panorama for environmental conservation regarding the implications of biological invasion, but also to the healthcare system as a whole in Rio de Janeiro State.

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Chapter 534

MICROBIAL RESISTANCE: A WORLDWIDE PUBLIC HEALTH PROBLEM

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ABSTRACT

The era of antimicrobial resistance is now upon us. Resistance problems are especially visible with hospitalized patients, as resistant infections readily spread among weakened hosts in close contact. But treatment choices are also diminished for some community infections, such as tuberculosis, pneumonia, and sexually transmitted diseases. Managing this new era in medicine is challenging, in part because we rely so heavily on antimicrobials. The problems are exacerbated by global travel, since resistance is readily disseminated. Calls to reduce consumption have raised general awareness and led to some reduction in the prevalence of resistance, but on a global level antimicrobial consumption remains high, both in agriculture and in human populations. Thus, antibiotic resistance will not disappear soon. Since new antimicrobials are becoming increasingly difficult to find, it is likely that we will need new strategies for suppressing resistance and for incentivizing the discovery and development of new antimicrobial therapies.

Keywords: antimicrobial, bacteria, resistance, tuberculosis, hospital infection

INTRODUCTION

In recent years, the problem of antimicrobial resistance has been recognized and addressed by international, regional, and national public health agencies, authorities, and

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professional societies (Carlet et al., 2012; Bell, 2014; Laxminarayan et al., 2014; Shallcross and Davies, 2014). Antibiotics have saved millions of lives and have enabled many other medical advances since their discovery and introduction into clinical practice. The worsening problem of antimicrobial resistance now jeopardizes many of these advances. However, action plans to minimize this threat have been developed by many public health agencies around the globe (CDC, 2013; Kessel and Sharland, 2013; Keown et al., 2014; Paphitou, 2013). This focus is likely to increase among public health agencies in the coming years. Several facets of the problem involve the relationship between human and animal use of antimicrobial agents (Laxminarayan et al., 2014; McIntosh and Dean, 2014). This chapter summarizes the components of the cost of resistance from a public health perspective and contrasts this perspective to other societal perspectives. It then reviews strategies at several different levels of responsibility, ranging from the patient care provider to international agencies. Finally, it considers appropriate public health responses according to the resources available for control.

In an era of globalization, antimicrobial resistance represents an international concern that demands a concerted effort from multiple health and industry sectors. Public health must be at the forefront of these efforts. Antimicrobial resistance is widely recognized as a complex international problem. Antibiotics have saved millions of lives and have enabled many other medical advances since their discovery and introduction into clinical practice. The worsening problem of antimicrobial resistance now jeopardizes many of these advances (Carlet et al., 2011; Carlet et al., 2012; Speck, 2013; Spellberg et al., 2013; Bell, 2014; Keown et al., 2014; Shallcross and Davies, 2014; Paphitou, 2013; Woolhouse and Farrar, 2014). The number of pathogens resistant to multiple classes of antimicrobials has increased worldwide (WHO, 2014).

There have been reports of infections with *Pseudomonas aeruginosa* and *Acinetobacter* species which are resistant to all available antibiotics (Paterson, 2006). Other pathogens, such as *Neisseria gonorrhoeae*, that were previously relatively easy to treat, are now becoming much more difficult to treat due to antimicrobial resistance (Ndowa et al., 2013). There is also evidence that resistant organisms that were previously confined to the acute care hospital setting are now sources of community acquired infections (Dantes et al., 2013). Resistance is not only an issue for bacterial pathogens like Staphylococci, Enterococci, *Escherichia coli*, *Klebsiella*, *Neisseria*, and *Mycobacterium tuberculosis* but also the problem of resistance is increasingly being recognized in nonbacterial pathogens like *Candida*, HIV, malaria, and influenza (WHO, 2014).

The worldwide increase in the prevalence of resistance is a concern because it threatens both the optimal care of patients with infections and the viability of current healthcare systems (DiazGranados et al., 2008). For individual patients, antimicrobial drug resistance has a clear impact on patient morbidity and mortality (Cosgrove, 2006; Neidell et al., 2012; CDC, 2013). Of concern for healthcare systems is the economic impact of resistance (McGowan et al., 2001; Roberts et al., 2009; White, 2011; Neidell et al., 2012). In the United States, resistance is especially costly for the healthcare system and for the third-party payers that support such systems (Roberts et al., 2009; Neidell et al., 2012). Costs are also burdensome for national-based healthcare programs (White, 2011). The incremental cost of caring for patients infected with resistant organisms has several aspects (Cosgrove, 2006; Roberts et al., 2009; Neidell et al., 2012). As the prevalence of resistance increases, physicians often substitute older and less expensive drugs for newer and more expensive

agents (Laxminarayan, 2014). Such costs in the United States are absorbed only in part by third-party payers, which often reimburse on the basis of head count, diagnosis related groups, or other formulas unrelated to specific services provided to an individual patient. Thus, most costs associated with resistant infections must be absorbed by the healthcare system itself (Laxminarayan and Malani, 2007). As the prevalence of drug resistant organism increases, these additional costs will mount and become a threat to the financial stability of local, regional, and national healthcare systems, many of which are already struggling to survive.

PUBLIC HEALTH AS A PERSPECTIVE ON RESISTANCE

Public health involves the population as a whole. It focuses on what we as a society do to assure conditions in which we can be healthy (Institute of Medicine, 1988). The goal of public health, the health of a population, can be distinguished from the goals of medical care, the health of a patient (McGowan, 2012). The public health goal, fueled by an aim of social good, is much broader in scope. It can encompass the health of neighborhoods, cities, countries, or even the entire world (McGowan, 2001). Using the public health perspective of health, a long time frame for evaluation is usually appropriate. Since antimicrobials can both prevent and treat infections in society, society considers them a valuable resource (Carlet and Pittet, 2013). As resistance diminishes this resource, a societal goal should be to minimize resistance and therefore to reduce the forces that produce resistance (Chaudhary et al., 2012; Kessel and Sharland, 2013; Carlet et al., 2014). All use of antimicrobials increases the likelihood of resistance developing (Woolhouse and Farrar, 2014). From a societal viewpoint, the use of antimicrobials to appropriately treat infections would be an appropriate rate of depletion of this valuable resource (Laxminarayan and Malani, 2007; Bartlett, 2011). Overuse or misuse of antimicrobials would be an inappropriately increased depletion of this resource (Bartlett et al., 2013). The costs of resistance from a public health perspective can be summarized as those resulting from treatment of patients infected with resistant organisms, those resulting from treatment of patients not infected with resistant organisms, and those resulting from antimicrobial use in agriculture, animal breeding, aquaculture, and industry.

The impact of antimicrobial resistance includes an increase in morbidity, mortality, and added costs for patients with resistant organisms. The added costs include those derived from the use of scarce healthcare resources: the care of patients with infections of resistant organisms, preventing transmission, maximizing appropriate empiric therapy, and resistance surveillance. In addition, excess loss of productivity and excess intangible costs such as patient and physician anxiety, pain, suffering, and inconvenience are also increased with antimicrobial resistance. Antimicrobial drug markets may also be affected by increasing resistance. Older, cheaper, and more narrow-spectrum drugs often become less useful, while the marketability of newer, more expensive, and more broad-spectrum drugs is favored (Van Boeckel et al., 2014).

Numerous studies have demonstrated that antimicrobial resistant organisms are associated with a higher morbidity and mortality than susceptible organisms. This has been shown for many different types of resistant organisms (Giske et al., 2008; Lode, 2009; de Kraker et al., 2011a; 2011b; 2011c; Pietersen et al., 2014; Pop-Vicas and Opal, 2014).

Invasive infections with methicillin-resistant *Staphylococcus aureus* (MRSA) have frequently been shown to be associated with a higher mortality and an increase in hospital length of stay when compared to methicillin susceptible *Staphylococcus aureus* (MSSA) (Lode, 2009; de Kraker et al., 2011a; 2011b). Similar associations are found when looking at enterococci. Vancomycin-resistant enterococci (VRE) bloodstream infections are associated with a higher mortality than vancomycin susceptible enterococci bloodstream infections (Lode, 2009). Although prior studies had not shown a higher mortality with penicillin-resistant pneumococcal infections (Moroney et al., 2001; Lode, 2009), a more recent meta-analysis has shown penicillin-resistant pneumococcal infections to be associated with a higher mortality compared to penicillin-susceptible infections (Tleyjeh et al., 2006; Lode, 2009). Similar outcomes have been noted for antibiotic-resistant gram-negative infections. *Escherichia coli* and *Klebsiella pneumoniae* strains resistant to extended-spectrum cephalosporins, multidrug-resistant (MDR) *Pseudomonas aeruginosa* strains, and carbapenem-resistant *Acinetobacter* infections have all been associated with an increased length of stay and mortality when compared to their more susceptible counterparts (Giske et al., 2008; de Kraker et al., 2011a; de Kraker et al., 2011c; Lemos et al., 2013). Specifically, this mortality is noted to be higher when study antibiotic-resistant gram negative bacilli in the setting of septic shock (Pop Vicas and Opal, 2014). One plausible reason for this finding is the difficulty in selecting an appropriate empiric antibiotic regimen in the era of highly drug-resistant gram-negative infections. It is well established that the duration of hypotension without appropriate antimicrobial therapy is a crucial factor in the probability of survival in septic shock (Kumar et al., 2006). In addition to gram-positive and gram-negative pathogens, drug-resistant tuberculosis has also been shown to have a higher mortality compared to drug-susceptible tuberculosis (Pietersen et al., 2014).

For all different types of drug-resistant infections, an increase in mortality affects more than just the patient when examined using the public health perspective. Although difficult to quantify, the consequences of premature death include a loss of productivity (number of productive years lost multiplied by the average yearly productivity) and the pain and suffering of family members and friends (Laxminarayan and Malani, 2007).

EVOLUTION OF RESISTANCE

Antimicrobial resistance is a global dilemma that threatens the health and safety of populations in all countries of the world. Urgent actions are needed to be taken before it reaches a critical stage, when large numbers of people in communities cannot be treated for life-threatening infections due to lack of effective drugs. Although the threat is most imminent from antibacterial resistance to commonly used antibiotics for infections seen regularly in intensive care units and hospitals, it is more prevalent and widespread and involves a wide spectrum of microbes.

To understand the evolution of microbial resistance, it is appropriate to review historical aspects. Development of antimicrobial chemotherapy is usually attributed to Paul Ehrlich ["father of chemotherapy"] based on his quest to find a cure for parasitic infections, toward the latter part of the nineteenth century, with natural dyes and heavy metals [mercury and arsenicals]. Penicillin was subsequently discovered in 1928 and administered clinically in the

1940s; sulphonamides were introduced clinically in 1937 (Greenwood et al., 2007). Thus, the “antibiotic era” was under way by the early 1940s. Penicillin and other antibiotics were initially derived from environmental fungi and bacteria, often with improvements made by chemical synthesis. Hence, the origin of antibiotics is through naturally derived substances produced to antagonize or inhibit the growth of other microorganisms, probably due to an evolutionary process that protects environmental niches of the producing organisms.

Streptomycin and the precursor of cephalosporins were also obtained from soil microbes in the 1940s. Penicillin was first used in 1941, and by 1944 penicillinase producing *Staphylococcus aureus* was described. Streptomycin was introduced clinically in 1944 for treatment of tuberculosis, but resistance soon developed during treatment (Davies and Davies, 2010). By the mid-1950s, most of the major antibiotic families, including aminoglycosides, chloramphenicol, tetracycline, and macrolides, had been developed (Greenwood et al., 2007).

Synthetic chemical agents with antibacterial activity were introduced in the early 1950s with para-aminosalicylic acid and isoniazid as antituberculosis agents; nitrofurantoin was found around the same time, followed by trimethoprim in 1956. Nalidixic acid, discovered in the early 1960s, was the precursor of the fluoroquinolones, with norfloxacin and ciprofloxacin developed in the 1980s. Rifampin was introduced for tuberculosis in 1968. The spectacular success of antimicrobial therapy led to widespread use and emergence of resistance. Pharmaceutical companies saw profit in new, more potent derivatives, which gave rise to broad-spectrum antipseudomonal penicillins and second-generation cephalosporins in the 1970s, with subsequent introduction in the 1980s of third generation cephalosporins. Later, beta-lactamase inhibitors combined with broad spectrum penicillins and carbapenems, new glycopeptides, newer macrolides, later generation quinolones, linezolid [a new class of oxazolidinone], and glycylcyclines [tigecycline] were introduced. Currently, there are more than 100 antimicrobial compounds available.

It is important to understand the evolution of antimicrobial resistance in order to tackle the problem. It was initially thought that antimicrobial resistance was a modern, man-made phenomenon. Although penicillinase-producing bacteria were recognized soon after the discovery of penicillin, it was not recognized as a problem until clinical use of penicillin became widespread. By the end of the 1950s, 80% of *Staphylococcus aureus* isolated from hospital patients were penicillin resistant due to β -lactamase production (Greenwood et al., 2007). This observation led to the development of penicillinase-stable penicillins [methicillin, cloxacillin, and oxacillin] which were introduced in the early 1960s to treat *S. aureus*. But resistance to methicillin was seen within a year or so of its clinical introduction. Thus, this was a sign that microbial resistance would be a problem, but in most cases this was overcome with development of new, more potent compounds. Many agents were developed that initially failed to compete well in the marketplace. The lack of use kept resistance from emerging, and now they are being used more frequently to fill a niche. Vancomycin is one of these agents. It was approved for use in 1958, but it was used sparingly due to concerns of toxicity and efficacy.

When methicillin-resistant *S. aureus* [MRSA] appeared in hospitals during the 1970s and then spread to other health-care facilities, vancomycin became more frequently used, beginning in the 1980s (Levine, 2006). Similarly, polymyxins were developed in the 1950s, but toxicity kept them from widespread use for systemic infections. Now they are gaining clinical use with infections caused by *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and carbapenemase-producing *Enterobacteria-ceae* that are resistant to all other antibiotics

(Landman et al., 2008). Full vancomycin resistance among MRSA strains is rare, probably because mutational changes cause impaired fitness for MRSA as susceptibility decreases. As a result, vancomycin-intermediate resistance [VISA] is slowly becoming a problem. Resistance to polymyxins appears to be emerging readily with increased use.

Over the years, development of new antibiotics to counter resistant bacteria led to appearance of novel resistant strains to these new drugs, which become widespread with increasing use of the antibiotics. This pattern has been seen with every new class of antibiotic developed over the years. There is strong correlation between the frequency and quantity of antibiotics used in humans and animals and the rate of development of antibacterial drug resistance. The logarithmic growth of resistant bacteria since the 1970s is reflected by the number of β -lactamase enzymes identified during the antibiotic era. Before 1970, there were only several β -lactamase enzymes described, and now about 900 β -lactamase enzymes have been identified (Davies and Davies, 2010).

Mobile genetic elements, extra chromosomal self-replicating structures [plasmids] and transposons, found in bacterial cells provide a resistance threat that maybe unconquerable. Our understanding of horizontal transfer of bacterial resistance was heralded by the discovery of antibiotic resistance plasmids that could be disseminated by bacterial conjugation in the mid-1950s (Davies and Davies, 2010). Since 1989 we have gained much greater knowledge of the genetics of bacterial resistance following the discovery of integrons. Integrons are versatile genetic elements, commonly found in bacterial genomes that allow efficient capture and expression of exogenous genes.

Plasmids and transposons are considered mobile integrons. Integrons play a major role in the spread of antibiotic resistance, particularly in Gram-negative pathogens; the majority of these pathogens carry integrons with resistant genes (Gillings, 2014). The process of microbial resistance is complex, and besides plasmids and DNA mutations [acquired or heritable and transferable], other mechanisms include biofilms, which harbor hypermutator bacteria that select for resistance more frequently, and phenotypic tolerance, a situation in which bacteria are not killed by antimicrobials (Nathon, 2012). Antibiotic pressure predisposes to resistance and tolerance. Despite the call for intensive research on mechanisms of microbial resistance and development of novel compounds to counteract the spread in 2012 (Nathon, 2012), no innovative agent is on the horizon.

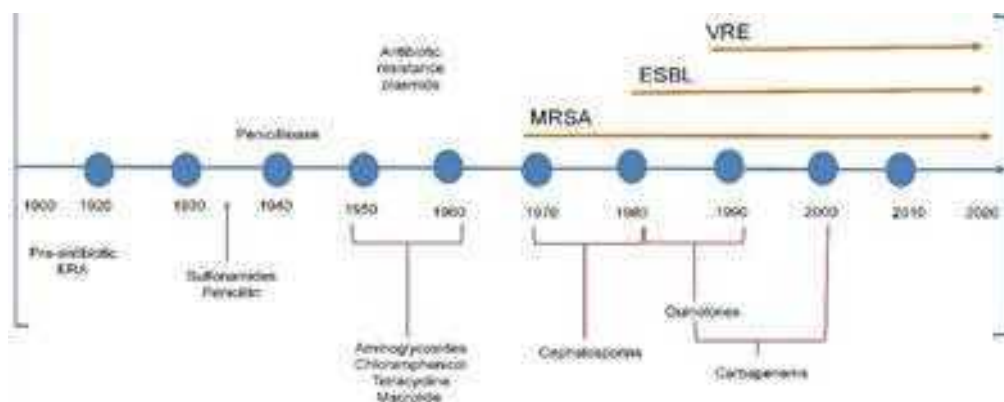


Figure 1. Appearance of antimicrobial resistance. Abbreviations: MRSA methicillin-resistant *S. aureus*, VRE vancomycin-resistant enterococci, ESBL extended β -lactamase.

The origins, evolution, genetics, and biochemistry of antibiotic resistance have been studied over the last 60 years. Figure 1 outlines the history of antibiotic discovery and subsequent development of antibiotic resistance. The emergence of antibiotic resistance of pathogenic bacteria after antibiotic development and clinical use, plus the absence of resistance in bacteria of the pre-antibiotic era (Hughes and Datta, 1983), suggested that resistance is a modern phenomenon. However, metagenomic analyses of authenticated ancient DNA from 30,000-year-old Beringian permafrost sediments identified genes encoding resistance to β -lactam, tetracycline, and glycopeptides antibiotics (D'Costa et al., 2011). Thus, antibiotic resistance is a natural phenomenon that predates the modern selective pressure associated with clinical and animal use. This explains the rapid emergence of resistance to new antibiotics; resistance will continue to emerge with drugs now in development. Hence, it is predictable that new antibiotics will select for preexistent resistance determinants that have been present and circulating in universal, environmental microbial pangenome for hundreds of years (D'Costa et al., 2011). Thus, the era of antibiotics has shifted naturally to the era of antibiotic resistance. The main challenge is to minimize the problem.

CONCLUSION

Human migration, animal and vector movement, and food markets may facilitate the spread of antimicrobial resistance across almost any geographic or political boundary. Methicillin-resistant *Staphylococcus aureus* and vancomycin resistant *Enterococcus* were first reported in the United Kingdom. After becoming widespread in North America and Europe, the same resistance patterns were noted in Asia. Today, novel gram-negative carbapenem resistance mechanisms such as OXA-48 and NDM-1 (New Delhi metallo- β -lactamase) were first discovered in Asia and have since spread to Europe and North America. The global spread of antimicrobial resistance demands effort of multiple health and industry sectors (in both low-resource and high-resource countries) to strengthen multinational/international partnerships and regulations. Public health must be at the forefront of these efforts.

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Chapter 535

STRATEGIC FACILITIES MANAGEMENT APPROACH IN AUSTRALIAN PUBLIC HEALTHCARE ORGANISATION

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ABSTRACT

The objective of this paper is to identify the relationship between Facilities Management Business Operation and facilities management support services delivery (FMssd). A public healthcare organisation in regional Victoria was used as a case study. A quantitative method approach is used with strategies for inquiry that multiples regression technique. The questionnaires were distributed to clinical and non-clinical staffs in the organisation. Three dimensions of healthcare management were evaluated in clusters of variables: business organisation management, facilities management operation system and decision making process. The data was analysed using a statistical tool (SPSS 20). The method used is a standard multiple regression. The healthcare management has to understand the nature of every FMssd item better. This paper has found a strong idea and understanding of the link between operational management and organisational management in order to understand how to effectively manage healthcare buildings facilities better.

Keywords: facilities management, hospital, decision making

INTRODUCTION

In order to ensure facilities management (FM) is strategically managed, the public healthcare management needs to understand a different concept of managing various kinds of buildings. FM theory in organisations lie in three elements, namely process, place and people

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[1]. Firstly, process in FM strategic management is business operations. It is a support service to the core business operation of the organisation. Secondly, the building is the place where the core business runs by FM service delivery support. Thirdly, the building users are people. The objective of this paper is to identify the significant relationship between FM support service delivery (FMssd) and facilities business operation (FBO) for Public Hospital in Australia.

The implementation of strategic facilities management seems to lack in terms of promoting the aspects of integration and holistic approach. Therefore, in the early stages of the FM era, financial indicators were the business' only performance measure [2]. FM is approached in many ways, making it difficult to bridge knowledge and thus creating a coherent body of FM knowledge [3].

How can FM processes be innovative with business strategic management? FM is not about reducing running costs of building or maintaining costs but the business as a whole. Performance measurement is a vital tool; as a means of balancing multiple measures across multiple levels [5]. TQM is one of the most established tools, but an integrated tool is still yet to be explored [4]. Tucker and Pitt [2] trust that the scarcity of a FM holistic approach in business solutions may cause an ineffective application of strategic facilities management.

Mohd Noor and Pitt [6] considered that in order to establish FM organization into business strategic, FM management teams need to provide adequate resources, ample working space and practical guidelines to the operational FM system. However, some healthcare organisations, especially private healthcare may not be able to cope or provide sufficient resources and expertise in FM operation.

STRATEGIC FACILITIES MANAGEMENT APPROACH

Enhancing the decision-making process of HFMs will not only prevent the devastating consequences of error in this area, but will also increase the productivity of the facility and sustainability of the healthcare infrastructure [7].

FM discipline is infancy knowledge-based from the businesses corporate perspective [6]. FM is meant to allocate core business physical resources in a way that allows it to flourish in competitive and dynamic markets. Despite the robust definitions, it is the client's responsibility to ensure how FM can operate in a diligent manner. The client's decision-making has to align with the FM strategic operation in order to gain effectiveness in service delivery. FM is capable of carrying out the strategic role if the FM division has a distinctive knowledge-based on how to source and evaluate between "intra-firm" administrative governance and "inter-firm" contractual arrangements [8].

FM Support Service Delivery

Clients and service providers have indicated that applying the FM outsourcing relationship types improves the quality of the services. Meanwhile, the results from the past literature has found that FM outsourcing relationship types are used in related services; that is, the outsourcing categories of a specific FM outsourcing contract will be achieved through

prediction at the level of substitution of ownership, substitution of control, competitive positions and long term planning [9].

FM support services exist from the user's requirement and the organisation's nature of business [10]. The author claims that the term "support service within FM" needs to be clearly defined. Traditionally, FM support service is understood to be one of the support system to core activities of an organisation. Hence, it can be argued for strategic reasons that support and core are the same, for operational purposes that clarifies services between support and core is best confined within one organisation [10].

Healthcare Strategic FM Efficiency

FM must take certain management challenges that go beyond the current perspective of FM being a mainly engineering- and cost-driven discipline that deals with the built environment into account [11]. Implementation of FM in business strategy creates a substantial holistic culture, and strategy through quality of service [6]. On the other hand, Rogers [12] believes that differences in operational effectiveness between organisations are pervasive.

Business Organization Management

Outsourcing is one of the most effective ways to ensure that healthcare business management can operate without worrying about the non-core support system, which is complicated and requires specialised and highly technical skills. However, outsourcing is not a favourite option to most public healthcare organisations. It is more suitable for private healthcare organisations that are profit-oriented, where there are no compromises on the core or non-core healthcare services. Furthermore, the demands of private healthcare organisations are high and require expertise in order to generate business. Undoubtedly, FM when integrated with business strategies gives a more modern image; reduces unnecessary costs and enhances the working environment [6].

Strategic FM looks into business performance to achieve business objectives. Nevertheless, before they can be achieved, the FM operation has to understand how the buildings perform or behave. Past literatures have discussed FM performance, but less literature is available on building performance itself, or relating both strategic FM service delivery and building performance [13 - 15].

FM Operation System

FM has become very conventional in its approach and purpose. In a business context, FM has played a significant role in strategic decision making to enhance core function of the business. To develop a business function, Atkin and Brooks [21] highlight three stages: (i), analysis stage is to incorporate business objectives, needs and policies, review of resources, processes, system and the physical assets in terms of space, function and

utilisation. (ii), solution stage, which it involves judging options, evaluating the organisation's objectives and developing the FM strategy, and (iii), implementation stage completes the strategy development process through the establishment of an implementation plan through procurement, training and communication. The author then ensures that, upon completion, the FM strategy should form part of the organisation's strategic and operating plan.

Decision Making Process

Study revealed that the need to have a strategic focus on organisation's core goals is the most influential factor for outsourcing FM services, while the need to instil cost transparency and to improve the satisfaction of customers were among the highly rated factors, thus providing a framework for decision-making within organisations [22].

Boussabaine and Kirkham [23] implement the Data Envelopment Analysis (DEA) methodology to examine the organisational management aspect of PM. The efficiency of PM techniques used by the National Health Service (NHS) in United Kingdom was taken as a case study. The study has found that it is important for estate managers to select input variables that demonstrate large effects of inefficiencies in management because organisational changes and decisions for efficiency improvements are costly to implement. Although more comprehensive approaches to linking FM costs are needed in terms of inpatient days or other appropriate output variables, findings from this analysis has proven to be valuable for improving the managerial decision making process. To show more significant contributions into strategic management [24], integrate two domains in Performance Indicators (PIs) namely organisational and operational. The results found that the disconnection between two domains, as well as vast levels of stakeholders, cause absentee in facility maintenance strategic decision making.

METHODOLOGY

To answer the research objective of this paper, quantitative method is used to analyse an agreement levels on business organisation management (BOM), facilities management operation system (FMOS) and decision making process (DMP). Information was gathered from preliminary interviews, a literature review, and BREEAM toolkit (AEDET) and the data was used for subsequent surveys. Adapted from UK NHS Toolkit, AEDET Toolkit Evolution is an assessment to provide comprehensive evaluation of the design of healthcare.

The survey questionnaire is mainly quantitative that comprises of Part 1- Facilities Management Support Services Delivery (FMssd) and Part 2 - Facilities Business Operation (FBO). 360 respondents are from clinical staffs and non-clinical staffs. Completed questionnaires were managed in two ways. For the paper survey, questionnaire surveys were individually coded and filed. Both surveys were entered into the computer database using statistics software called Statistical Package for the Social Science (SPSS Version 20). Based on a large sample size and nature of data (interval level scaling), this study applied a parametric statistics technique. The decision of using parametric technique is based on a few

factors, namely level of measurement, random sampling, and independence of observations, distribution and homogeneity of variance [25].

To ensure this study can use parametric statistics technique, the following steps were taken beforehand [25].

- i. Checking the distribution of scores on all independent and dependent continuous variables
- ii. Test of normality: represented by Kolmogorov-Smirnov statistic.
- iii. Checking for outliers: Outliers can be checked by examining the histogram and boxplot.
- iv. Scatterplots: Scatterplots is used to explore the relationship between continuous variables.

To achieve the result, the parametric technique called the multiple regressions was used. The screening and cleaning data were completed at the early stages before proceeding to statistical analysis to ensure that there are no missing data and, if there were any, the data was rectified.

Standard multiple regression techniques were chosen to explore the relationship between one dependent variable against 3 independent variables (FMssd), which was divided into three constructs; FMcs, FMfs and FMn-cs against predicted outcome (dependent) variable, namely FBO's three factors; (i) business organisation management (BOM), (ii) FM operation system (FMos), and (iii) decision making system (DMS).

Regression analyses are a set of statistic techniques that allow one to access the relationship between one dependent variable and several independent variables [26]. Multiple regressions are selected to predict an outcome variable from several predictor variables. Standard multiple regressions used the following mathematical equation to identify the relationship:

$$\begin{aligned} y &= \text{dependent variables} \\ b_1 &= \text{regression coefficient} \\ x_1 &= \text{independent variables} \end{aligned}$$

To be more precise, considering there will be deviations between the value from Y and the value from X, where the standard regression model will not fit the data perfectly, Field (2012) proposed the equation that considers the residual (deviations) as

$$Y_i = (b_0 + b_1X_i) + \varepsilon_i \quad (1)$$

RESULTS AND DISCUSSIONS

In this study, standard multiple regressions was undertaken to describe how strong each independent variable (FMss, FMfs and FMn-cs) was when evaluated in terms of its predictive power, over and above that was offered by all the other independent variables [25]. Furthermore, this approach explained how much unique variance in the dependent variable

was explained by each of the independent variables. Standard multiple regressions were used because both predictor and dependent variables had been theory tested. The predictor (FMssd) had gone through a preliminary survey. As for dependent variables, the FBO factor with its three constructs (BOM, FMos and DMP) was mentioned in the literature review as one of the gap/issues in strategic FM.

Table 1. Multicollinearity test for FBO for “A”, a public health care organisation

DV	Predictive variables	Tolerance	VIF	Mahalanobis distance	Cook's distance
Business organisation management (BOM)	FMcs	.310	3.321		
	FMfs	.013	4.017	2.977	.008
	FMn-cs	.332	3.008		
FM operation system (FMos)	FMcs	.318	3.145		
	FMfs	.252	3.971	2.039	.018
	FMn-cs	.333	3.000		
Decision making process (DMP)	FMcs	.328	3.053		
	FMfs	.255	3.928	2.009	.025
	FMn-cs	.314	3.184		

Relationship of FMssd to FBO: The Influence of FBO Factors on FMssd for “A”, the Public Health Care Organization

Evaluating the model (FBO_FMssd)

This model is intended to evaluate the FMssd against three FBO constructs, namely: (i) business organisation management (BOM); (ii) the facilities management operation system (FMos); and (iii) the decision-making process (DMP). Evaluating the model generated from this standard multiple regression analysis has provided an idea of the percentage of variance of FMssd against the FBO factors, which can be described as FM organisational management. Adjusted R² used as this sample is considered to be a small to average size sample (119 cases to 128 cases), and indicates the regression equation of percentage variance. Adjusted R² is used to explain how much variance occurs. The model (FMssd) shows (see Table 2) that the highest percentage of variance is “BOM”, presenting 2%, the second is “DMP” which owned 1.9% and the lowest is “FMos” which contributed 1%. Furthermore, it is worth looking at the individual predictor (square from part correlation), where it was found that FMcs was making the largest contribution on all of the constructs. FMcs was found to have contributed 0.2% for BOM, 1.6% for FMos and 0.3% for DMP of variance alone. However, of all the dependent variables, none were found to be statistically significant: (i) BOM ($F(3,173) = 0.149$, $p > 0.05$), (ii) FMos ($F(3,127) = 1.418$, $p > 0.05$), and (iii) DMP ($F(3,119) = 0.256$, $p > 0.05$). Therefore, from this model, FMssd did not happen to predict all FBO constructs.

Evaluating FMss, FMfs and Fmn-cs

All three predictors predicted the FBO construct, namely; BOM, FMos and DMP. The description is as follows:

(i) Business organisation management (BOM)

FMcs ($b = 0.142$, $\beta = 0.072$, $t = 0.456$, $p > 0.05$), FMfs ($b = 0.036$, $\beta = 0.026$, $t = 0.146$, $p > 0.05$) and FMn-cs ($b = -0.156$, $\beta = -0.065$, $t = -0.426$, $p > 0.05$) did not significantly predict “business organisation management” (BOM). For FMfs and FMcs, their beta value indicated that as these constructs increased, the BOM also increased. This result showed that the more important the fundamental and core FM support services, the more efficient the BOM. As for FMn-cs, there was a negative correlation where the more important the non-core FM, the less efficient the BOM. BOM items are related to health care organisational management. Businesses operating such facilities face two choices; either they have to make the operation a core competence of its own, in which case logic dictates that it becomes their core business, or part of it, or else they should be sourcing the business critical services from a firm who has core competence in such services. This result showed that core and fundamental FM services, but not the non-core FM, promote the efficiency of health care organisational management. FM operates in a customised manner, wherein the business support service is designed and accessed according to the strategic needs of the changing business.

(ii) Facilities management operation system (FMos)

FMcs ($b = 0.343$, $\beta = 0.226$, $t = 1.461$, $p > 0.05$), FMfs ($b = 0.039$, $\beta = 0.036$, $t = 0.210$, $p > 0.05$) and FMn-cs ($b = -0.227$, $\beta = -0.124$, $t = -0.822$, $p > 0.05$) did not significantly predict “facilities management business operation” (FMos). For FMfs and FMcs, their beta value indicated that as this construct increased, the FMos also increased. This result showed that, the more important the fundamental and core FM support services, the more efficient the FMos. As for FMn-cs, there was a negative correlation, where the more important the non-core FM, the less efficient the FMos. FMos items are related to the FM system in health care. This result showed that core and fundamental FM services, but not the non-core FM, promote the efficiency of the FM system in health care. Facilities issues can critically affect investment decisions, operational efficiency and cultural attitudes, so bringing them into centre stage can create a comprehensive view of the corporate condition. Furthermore, the facilities department will be organised as a profit centre and will seek to create the relationships that will enable the service to develop, with continual improvement of quality, better value for money and at minimum risk to the organisation.

(iii) Decision-making process

FMcs ($b = 0.142$, $\beta = 0.089$, $t = 0.560$, $p > 0.05$), FMfs ($b = 0.042$, $\beta = 0.037$, $t = 0.205$, $p > 0.05$) and FMn-cs ($b = -0.116$, $\beta = -0.062$, $t = -0.381$, $p > 0.05$) did not significantly predict “decision-making process” (DMP). For FMfs and FMcs, their beta value indicates that as these constructs increased, the DMP also increased. This result showed that, the more important the fundamental and core FM support services, the more efficient the DMP. As for FMn-cs, there was a negative correlation, where the more important the non-core FM, the less efficient the DMP. DMP items are related to the decision-making process in health care organisation management. This result showed that core and fundamental FM services unlike the non-core FM services promote the efficiency of the decision-making process in health care organisational management.

As a conclusion, all FBO constructs seemed to have shown the same result, where all three constructs that resulted with their FMcs and FMfs did have a positive correlation. However, FMn-cs gained a negative correlation against all BOM, FMos and DMP. However, bear in mind that none of these results were significant.

Table 2. Standard multiple regression (FBO)

DV	Variables	Coefficients					ANOVA		Model Summary	
		B	SE	β	T	P	F	Sig.	R ²	Adjusted R ²
Business organisation management (BOM)	FMcs	.142	.312	.072*	.456	.649				
	FMfs	.036	.245	.026	.146	.884	.149	.930	.003	.020
	FMn-cs	-.156	.366	-.065	-.426	.671				
FM operation system (FMos)	FMcs	.343	.234	.226*	1.461	.146				
	FMfs	.039	.185	.036	.210	.834	1.418	.241	.032	.010
	FMn-cs	-.227	.276	-.124	-.822	.412				
Decision-making process (DMP)	FMcs	.142	.254	.089*	.560	.576				
	FMfs	.042	.204	.037	.205	.838	.259	.855	.006	.019
	FMn-cs	-.116	.306	-.062	-.381	.704				

*Indicates largest beta coefficient

CONCLUSION

FMssd was found not to predict all three FBO constructs, namely, BOM, FMos and DMP, as well as FMssd individual constructs, FMcs, FMfs and FMn-cs. The only strong finding was that FMcs has the largest impact of all FBO constructs, namely Business organisation management (BOM), FM operation system (FMos) and Decision-making process (DMP). It can be concluded that the efficiency of FBO is not affected by the importance of any FMssd construct or FMssd as a whole.

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Chapter 536

CLIMATE CHANGE: HHS COULD TAKE FURTHER STEPS TO ENHANCE UNDERSTANDING OF PUBLIC HEALTH RISKS*

United States Government Accountability Office

WHY GAO DID THIS STUDY

The World Health Organization projects climate change will adversely affect health significantly over the next several decades. Some health effects of climate change are already being felt in the United States, according to assessments by the National Research Council, USGCRP, and others. Since the federal government is the nation's largest purchaser of health care services, federal health care expenditures could increase in future years due to climate-related impacts.

GAO was asked to review federal efforts to increase public health system preparedness for climate change. This report addresses (1) federal activities to enhance understanding about the risks climate change poses to public health, (2) federal resources used by selected states and localities to address these risks, and (3) challenges states and localities face and actions federal agencies could take to mitigate them. GAO examined federal, state, and local documents, and interviewed officials from federal agencies such as CDC, NIH, USGCRP, as well as state and local health departments, including all 18 recipients of CDC's Climate Ready States and Cities Initiative award.

* This is an edited, reformatted and augmented version of the United States Government Accountability Office publication, GAO-16-122, dated October 2015.

ABBREVIATIONS

ASTHO	Association of State and Territorial Health Officials
BRACE	Building Resilience Against Climate Effects
CDC	Centers for Disease Control and Prevention
CCHHG	Interagency Crosscutting Group on Climate Change and Human Health
EPA	Environmental Protection Agency
HHS	Department of Health and Human Services
NACCHO	National Association of County and City Health Officials
NASA	National Aeronautics and Space Administration
NCA	National Climate Assessment
NIH	National Institutes of Health
NOAA	National Oceanic and Atmospheric Administration
USGCRP	U.S. Global Change Research Program

WHAT GAO RECOMMENDS

GAO recommends that HHS direct CDC to develop a plan describing when it will be able to issue climate change communications guidance to state and local health departments. CDC generally agreed with the recommendation, stating that it will issue guidance once HHS's climate change communication and outreach strategy is final.

WHAT GAO FOUND

Federal agencies are enhancing understanding of climate-related risks to public health by (1) supporting and conducting research, (2) providing data and informational resources, and (3) communicating about risks. The Department of Health and Human Services' (HHS) National Institutes of Health (NIH) supports a portfolio of research directly related to these risks. NIH reports awarding about \$6 million for such research in fiscal year 2014, including for one study examining health risks posed by heat and air pollution. Federal agencies have also provided data on climate and health issues, such as the number of extreme heat days that state and local officials can use to assess health risks. They have also reported about these risks, such as through the third National Climate Assessment issued in May 2014 by the U.S. Global Change Research Program (USGCRP).

Selected state and local health departments have used resources from HHS's Centers for Disease Control and Prevention (CDC) and other federal agencies to address and plan for the risks of climate change to public health. CDC's Climate Ready States and Cities Initiative awards an average of about \$200,000 per year each to 16 state and two local health departments to implement a risk management framework designed to help incorporate climate projections into public health planning. CDC also requires awardees to increase public awareness of the risks climate change poses to public health. Other federal resources used by

health departments to prepare for these risks include funding provided through CDC's National Environmental Public Health Tracking Program.

When asked to identify challenges they face in addressing and planning for the risks of climate change to public health, state and local health officials identified challenges that GAO grouped into the three most frequently mentioned themes. First, the officials said they face challenges communicating about the public health risks of climate change, due to limited public awareness and the complexity of the issue. These officials reported that enhanced federal leadership could help address this challenge. Although HHS plans to develop a climate change communication and outreach strategy, its development has been delayed by over a year. Also, CDC currently does not have plans to issue climate change communications guidance, which state and local officials said would be helpful. CDC's limited resources are currently focused on resolving methodological and data issues related to its Climate Ready States and Cities Initiative. Given that health departments that have received awards under CDC's initiative are required to take steps to enhance public awareness, such guidance may help awardees better meet this requirement. Issuing such guidance would also be in line with CDC's core functions, which include translating climate change science to inform communities. Second, officials said they face challenges identifying health risks of climate change due to gaps in research and difficulties using climate data. Federal officials told GAO about actions they have taken or plan to take that could help address these challenges, such as issuing an assessment of climate change impacts on health, and creating a national heat health information system. Finally, the officials told GAO about other challenges they face that federal action may not be able to address, such as having insufficient local data on health outcomes, because states may not collect or have access to such data, and having insufficient staff resources for these activities.

October 5, 2015

Congressional Requesters

The effects of a changing climate are viewed as threats to human health in a variety of ways, and, according to assessments by the National Research Council, the U.S. Global Change Research Program (USGCRP), and the Intergovernmental Panel on Climate Change, some effects are already being felt across the world and within the United States.¹ The World Health Organization projects that climate change will have significant adverse effects to health over the next several decades, including an increased number of deaths in 2030 from impacts such as heat exposure, malaria, diarrhea, and childhood malnutrition.² Observations of a changing climate in the United States include trends such as an increase in average temperatures, shifting patterns of rainfall, rising sea levels, and more frequent and intense extreme weather events such as heat waves, heavy downpours, and drought, according to reports from the National Research Council and USGCRP. While it is challenging to link any individual weather event to climate change, the National Research Council and USGCRP, among others, expect these climate trends to continue. According to assessments by the National Research Council and USGCRP, climate change will amplify existing health threats, and populations such as the elderly, children, those who are sick, and those living in poverty

will face disproportionate health risks from climate change in the United States.³ In addition to being the nation's largest purchaser of health care services, the federal government bears the expense of these services for some of the most vulnerable populations to climate change impacts—spending \$815 billion on three such programs in 2014.⁴ As such, federal health care expenditures could increase in future years as a result of climate impacts. A 2006 summer heat wave in California illustrates the types of health impacts that could be associated with climate change, including increased hospitalizations for heat-related illnesses.⁵ In February 2013, we added limiting the federal government's fiscal exposure by better managing climate change risks to our High Risk List, which calls attention to agencies and program areas that are at high risk due to their vulnerabilities to fraud, waste, abuse, or are most in need of transformation.⁶

State and local public health authorities have responsibility for carrying out most public health activities in the United States, but a number of federal agencies also have a role. State and local public health agencies have responsibilities such as disease surveillance and responding to public health emergencies within their jurisdictions, including activities that may be related to climate change.⁷ The federal government's role in addressing public health includes providing high-level leadership through setting and communicating health-related policies, goals, and standards; supporting state and local health department efforts; and financing research and higher education. In addition, federal agencies, such as the Environmental Protection Agency (EPA), Department of Health and Human Services' (HHS) National Institutes of Health (NIH) and Centers for Disease Control and Prevention (CDC), and the Department of Commerce's National Oceanic and Atmospheric Administration (NOAA), support the development of data and other information resources on climate change that others, including state and local health departments, can use to manage public health risks. CDC has also provided support to some state and local health departments to manage these risks.

You asked us to review federal efforts to increase the preparedness of the nation's public health system for the impacts of climate change. In this report, we (1) discuss the types of activities that selected federal agencies have conducted to enhance understanding about the risks that climate change poses to public health; (2) describe federal resources used by selected state and local health departments to address or plan for the risks that climate change poses to public health; and (3) examine challenges, if any, identified by state and local officials to addressing or planning for the risks that climate change poses to public health, and any steps they identified that federal agencies could take to mitigate these challenges.

To describe the types of activities that federal agencies have conducted to enhance understanding about the risks that climate change poses to public health, we reviewed federal documents such as USGCRP's 2014 third National Climate Assessment (NCA) and a 2010 report on climate change and human health research needs.⁸ We interviewed officials from 26 federal agencies, including CDC, EPA, NIH, NOAA, and others participating in a USGCRP working group on climate change and human health.⁹ We also interviewed representatives of 13 stakeholder groups, including public health organizations, such as the American Public Health Association,¹⁰ and academic institutions, such as the Georgetown Climate Center.¹¹ (App. I provides a complete list of agencies and stakeholders interviewed.) In addition, we reviewed NIH data on awards it made for research related to the public health risks of climate change from fiscal year 2011 through fiscal year 2014.¹² To assess the reliability of these data, we discussed them with agency officials, reviewed them for reasonableness and consistency,

and determined that they were sufficiently reliable for our purposes. The results of our work provide examples of federal activities to enhance understanding of the risks that climate change poses to public health, and do not represent an exhaustive list of federal actions in this area.¹³ We did not evaluate the effectiveness of federal efforts to enhance understanding, as this was outside the scope of our review.

To describe federal resources used by selected state and local health departments to address or plan for the risks that climate change poses to public health, we used a variety of approaches to obtain information from state and local health departments. This included information about the activities they have conducted related to climate change and public health, and how they used federal resources to support these efforts. Specifically, we conducted interviews with state and local officials during site visits to two states—California and Maryland—and two cities—New York City and San Francisco—that received awards from CDC’s Climate Ready States and Cities Initiative, which is HHS’s primary investment in climate change adaptation.¹⁴ We selected these four locations from among the 18 awardees of CDC’s Climate Ready States and Cities Initiative to obtain geographic diversity, because climate change impacts are location-specific, and to have a mixture of state and local governments, because states and municipalities may have different approaches in preparing for the public health risks of climate change. We also facilitated four small group discussion sessions with officials from 22 state and local health departments to gather additional information about federal resources used by state and local health officials. We worked with representatives of the Association of State and Territorial Health Officials (ASTHO)¹⁵ and the National Association of County and City Health Officials (NACCHO)¹⁶ to identify state and local public health officials who have expressed interest in climate change issues to participate in these sessions.¹⁷ In a third approach to gather perspectives, we interviewed officials from a nongeneralizable sample of 11 state and local health departments that reflected geographic diversity and that had either recently faced climate-related public health issues, had conducted work to plan for potential future health impacts from climate change, or had concerns about potential future health impacts. In total, through these approaches, we interviewed officials from all 18 state and local health departments that received awards from CDC’s Climate Ready States and Cities Initiative, officials from 7 local health departments in some of those jurisdictions, and health department officials from 13 other states and localities.¹⁸ These interviews and small group discussions included open-ended questions that were not conducive to quantitative analysis. Therefore, using a qualitative approach, we identified examples of the types of federal resources that these officials have used to address and plan for the risks that climate change poses to human health. We also reviewed Climate Ready States and Cities Initiative awardees’ annual progress reports to CDC. To obtain more information about these resources, we reviewed documentation about the types of support they offered, such as from funding opportunity announcements. We also reviewed information on fiscal year 2014 funding for CDC programs cited by state and local officials, as presented in the agency’s congressional budget justification for fiscal year 2016. Furthermore, we interviewed officials from federal agencies, such as CDC and NOAA, and gathered the perspectives of stakeholders through interviews with representatives from groups such as ASTHO and NACCHO. The results of our review do not provide an exhaustive list of federal resources that state and local health departments could use to address and plan for the public health impacts of climate change, but are provided as illustrative examples of such resources.

To examine challenges identified by state and local officials to addressing or planning for the risks that climate change poses to public health, and any steps federal agencies could take to mitigate these challenges, we gathered the views of state and local health department officials during site visits, small group discussion sessions, and individual interviews. Through an inductive analysis of officials' views, we qualitatively grouped them into three themes that were most frequently mentioned about the types of challenges these public health departments face, and, in some cases, the opportunities officials see for federal action to address these challenges.¹⁹ We also gathered the perspectives of stakeholder groups through interviews with representatives from ASTHO, NACCHO, and the Council of State and Territorial Epidemiologists. To gather information about steps federal agencies could take to mitigate these challenges, we interviewed officials from federal agencies such as CDC, NIH, and NOAA, as well as representatives from stakeholder groups. We examined federal documents, including those describing ongoing and planned federal actions aimed at reducing the impact of climate change on public health. We reviewed prior GAO work on the federal role in addressing challenges related to climate change, including challenges faced by state and local officials.

We conducted this performance audit from June 2014 to September 2015 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

BACKGROUND

Climate changes, including rising temperatures and shifting patterns of rainfall, are expected to impact public health across the nation in a variety of ways. Though state and local governments have primary responsibility for protecting the public health in their jurisdictions, the federal government also plays an important role in supporting state and local efforts by, for example, providing health departments with technical support and other resources. The federal government has also taken other targeted actions to help prepare the nation for climate change impacts, such as by issuing a number of orders, actions, and plans to provide state and local decision makers with information they need to manage such impacts, including impacts to public health.

Climate Change Impacts in the United States

Impacts from climate change in the United States have been observed, are projected to continue, and are likely to accelerate over the next several decades, with impacts varying considerably by region, according to assessments by the National Research Council and USGCRP.²⁰ According to USGCRP's third NCA, observed impacts in the United States include increases in average temperatures and precipitation, as well as changes to precipitation extremes, with variation across regions (see table 1). These and other climate

changes are projected to continue over this century and beyond, according to USGCRP's third NCA. The magnitude of climate change beyond the next few decades depends primarily on the amount of heat-trapping gasses emitted globally, and how sensitive the Earth's climate is to those emissions, according to USGCRP's third NCA.²¹

Table 1. Observed and projected impacts of climate change in the United States

	Observed and projected impacts
Temperature	• Observed impact: The last decade was the warmest on record for the contiguous United States, with 2012 as the warmest year on record.^a The average temperature has risen by 1.3 to 1.9 degrees Fahrenheit since record keeping began in 1895, with most of this increase occurring since 1970. • Projected impact: Temperature increases are projected for all regions of the country during this century, with projected increases of 2 to 4 degrees Fahrenheit in the next few decades in most areas.
Precipitation	• Observed impact: Precipitation has increased by an average of about 5 percent since 1900, with variation across regions. Heavy downpours have been increasing nationally in recent decades, with the largest increases in the Midwest and Northeast. • Projected impact: More winter and spring precipitation is projected for the northern United States, and less for the Southwest, during this century. Increases in the frequency and intensity of extreme precipitation events are projected for all regions.
Sea levels	• Observed impact: Global sea level has risen by about 8 inches over the last century. • Projected impact: Global sea level is projected to rise another 1 to 4 feet by 2100, with additional increases well beyond this century.
Extreme weather events and impacts from storms	• Observed impact: Some types of extreme weather events—such as heat waves and regional droughts—have become more frequent and intense in recent decades. • Projected impact: Droughts in the Southwest and heat waves everywhere are projected to become more intense. Rainfall from storms such as hurricanes is expected to increase, and sea level rise is expected to magnify the adverse impact of storm surges on some coastal communities.

Source: U.S. Global Change Research Program's third National Climate Assessment. | GAO-16-122

^a The National Oceanic and Atmospheric Administration and the National Aeronautics and Space Administration have since declared 2014 as the warmest year on record since 1880.

WHAT IS A VECTOR-BORNE DISEASE?



Vector-borne diseases are transmitted by mosquitoes, ticks, and fleas. West Nile virus is one type of vector-borne disease and is most commonly transmitted to people by the bite of infected mosquitoes. First detected in North America in 1999, it has since spread to all states except Alaska and Hawaii, with outbreaks occurring every summer. Most people who are infected with West Nile virus experience no symptoms, but one in five infected people will develop a fever with other symptoms such as headaches and body aches, and a very small number of infected people—less than 1 percent—will develop a severe neurological illness that can result in paralysis or death. People who work or play outside are especially vulnerable because of greater exposures to mosquitoes.

Source: Centers for Disease Control and Prevention/James Gathany. | GAO-16-122.

Climate Change and Human Health

According to USGCRP’s third NCA, climate change is expected to impact human health in the United States by exacerbating some existing health threats and by posing new risks. For example, projected changes in temperature are expected to increase the length of pollen seasons, which could increase allergies and asthma episodes. According to USGCRP’s third NCA, extreme weather events, which are expected to become more common with climate change, are linked with increases in injuries, deaths, and mental health problems, such as anxiety and posttraumatic stress disorder. Furthermore, according to this assessment, changes in the climate may contribute to the spread of vector-borne diseases that are transmitted to humans by animals, including invertebrate animals such as mosquitoes and ticks. Examples of vector-borne diseases that currently pose health risks in some regions of North America include chikungunya virus, dengue, Lyme disease, Rocky Mountain spotted fever, and West Nile virus.²² Table 2 summarizes these and additional risks that climate change poses to human health.

WHY ARE CHILDREN ESPECIALLY VULNERABLE TO SOME HEALTH RISKS FROM CLIMATE CHANGE?

Children are more vulnerable than adults to some health risks from environmental hazards— including hazards exacerbated by climate change—because of differences in their biology and behavior. Children breathe more air relative to their body mass than adults do and their natural defenses are less developed, which makes them especially vulnerable to health impacts from decreased air quality. Asthma is one of the most common serious chronic diseases among children, and can be aggravated by poor air quality. Children also behave differently from adults, such as by spending more time outdoors and playing closer to the ground, which makes them especially vulnerable to mosquito and tick bites that can cause disease.



Source: Environmental Protection Agency. | GAO-16-122.

The type and severity of health impacts that communities and individuals face from climate change will depend on a variety of factors, and not everyone is equally at risk, according to assessments by the National Research Council, USGCRP, and others. Populations of special concern include children, the elderly, those who are sick, those who are living in poverty, those who work outdoors, some communities of color, and Native American communities.²³ According to the National Research Council and USGCRP’s third NCA, key factors in determining health risks include the following:

- **Location.** Because climate change impacts are expected to vary across the country, people will face different risks depending on where they live, work, and travel. People located in cities may be at increased risk for heat-related illnesses (e.g., heat

stroke or heat-sensitive conditions such as cardiovascular disease), for example, because land cover changes associated with urbanization, including increases in the amount of paved areas, can result in higher air temperatures compared to the surrounding rural areas, according to USGCRP's third NCA. Those who work outdoors, such as farmers, fishermen, firefighters, and utility workers, may be adversely affected by climate impacts because they have more frequent, intense, and longer exposures to the climate than the general public, according to CDC's website. For example, as extreme weather events such as floods become more frequent and severe, outdoor workers could be at increased risk of traumatic injury. Figure 1 provides examples of potential impacts by region.

Table 2. Examples of health risks posed by climate change in the United States

Health risk	Exposure or event posing health risk	Reason for increased risk from climate change
Allergies, asthma, and other adverse respiratory impacts	Pollen, smoke from wildfires, and ground-level ozone (a key component of smog)	Pollen seasons are becoming longer because of climatic changes, such as increases in the number of frost-free days. Wildfires are projected to increase in some regions in part because of drought and other stressors exacerbated by climate change. Rising temperatures can also lead to higher levels of ozone pollution.
Food-borne and water-borne illnesses	Pathogens such as disease-causing bacteria, viruses, and parasites from untreated water or other sources	Factors that contribute to flooding, such as more extreme downpours, sea level rise, storm surges, and more rapid spring snowmelt may increase releases of sewage to surface waters. In addition, diarrheal diseases caused by pathogens such as Salmonella are more common when temperatures are high.
Heat-related illnesses and deaths ^a	Unusually high temperatures, including prolonged heat waves	Extreme heat events are expected to become more frequent and intense in coming decades because of climate change.
Injuries and deaths	Extreme weather events—such as winter storms and heavy precipitation—and their aftermaths, and changes to natural or built environments that introduce hazards	Some types of extreme weather events are expected to become more frequent and severe because of climate change. Extreme weather events may result in direct injury and impact natural or built environments in ways that increase risk of injury. Heavy precipitation events may result in flash floods, which can lead to drownings.
Mental health and stress-related disorders	Any adverse change to an individual's environment, way of life, or health, such as displacement following a disaster	Climate-related disasters such as floods, heat waves, and wildfires may result in increases in mental health problems, such as anxiety and post-traumatic stress disorder.
Vector-borne diseases	Pathogens spread by vectors—including fleas, ticks, and mosquitoes—cause diseases such as dengue, Lyme disease, Rocky Mountain spotted fever, and West Nile virus	Habitats of some pathogen-carrying vectors may expand into previously unaffected regions, in part because of climate change.

Source: U.S. Global Change Research Program's third National Climate Assessment. | GAO-16-122.

^a Heat-related illnesses and deaths may result from heat stroke or heat-sensitive conditions such as cardiovascular disease, kidney disease, cerebrovascular disease, and other conditions exacerbated by exposure to extreme heat.

- **Age.** A person's age also plays a role in determining his or her vulnerability to health impacts, including those related to climate change, according to USGCRP's third NCA. For example, children suffer disproportionately from the effects of heat waves and other environmental hazards associated with climate change, according to USGCRP's third NCA. One reason is that children playing outside during heat waves

may not be aware that they need to drink more water as a preventative measure, according to EPA.²⁴ Older adults are also vulnerable to some climate-related impacts, according to USGCRP's third NCA. Specifically, this assessment states that limited mobility among older adults can increase their flood-related health risks, and that older people are at much higher risk of dying during extreme heat events.

- **Adaptive capacity.** The extent to which people and communities have the capacity to successfully adapt to adverse events also affects the health risks they face, and is influenced by characteristics such as disabilities and socioeconomic status. For example, according to USGCRP's third NCA, limited economic resources for adapting to or escaping from health-sensitive situations will place the poor at higher risk of health impacts from climate change than higher-income groups. In contrast, communities that have access to early warning systems, such as for forecasting and alerting people about impending heavy precipitation events and flooding, may be better positioned to reduce health risks from such adverse events.

Roles and Responsibilities for Managing Public Health Risks in the United States

State, local, territorial, and tribal governments have primary responsibility for managing public health risks within their jurisdiction. Public health departments vary greatly in their size, responsibilities, and resource levels, among other factors.²⁵ Activities that public health departments may undertake to help promote health and well-being include monitoring and investigating health problems, educating people about health issues, developing plans to support health efforts, and researching new solutions to health problems, among other activities.

The federal government's role in managing public health includes providing leadership through setting and communicating health-related policies, goals, and standards. Federal agencies also finance research and higher education, support state and local health department efforts, and support the development of data and decision support resources that decision makers can use to manage for risks to public health, including from climate change.²⁶ For example, through its various programs, CDC provides technical and financial support to state and local health departments to enhance their capacity to monitor and promote public health, including preparing for the risks posed by climate change. The agency's Climate and Health Program, established in 2009, supports state and local health department efforts to plan for and address the health risks posed by climate change. According to CDC, the program's three core functions are to translate climate change science into health policy for action by health departments and communities, create decision support resources to build capacity, and serve as a credible leader in planning for the public health impacts of climate change.

Federal Efforts to Enhance Resilience to Climate Change Impacts

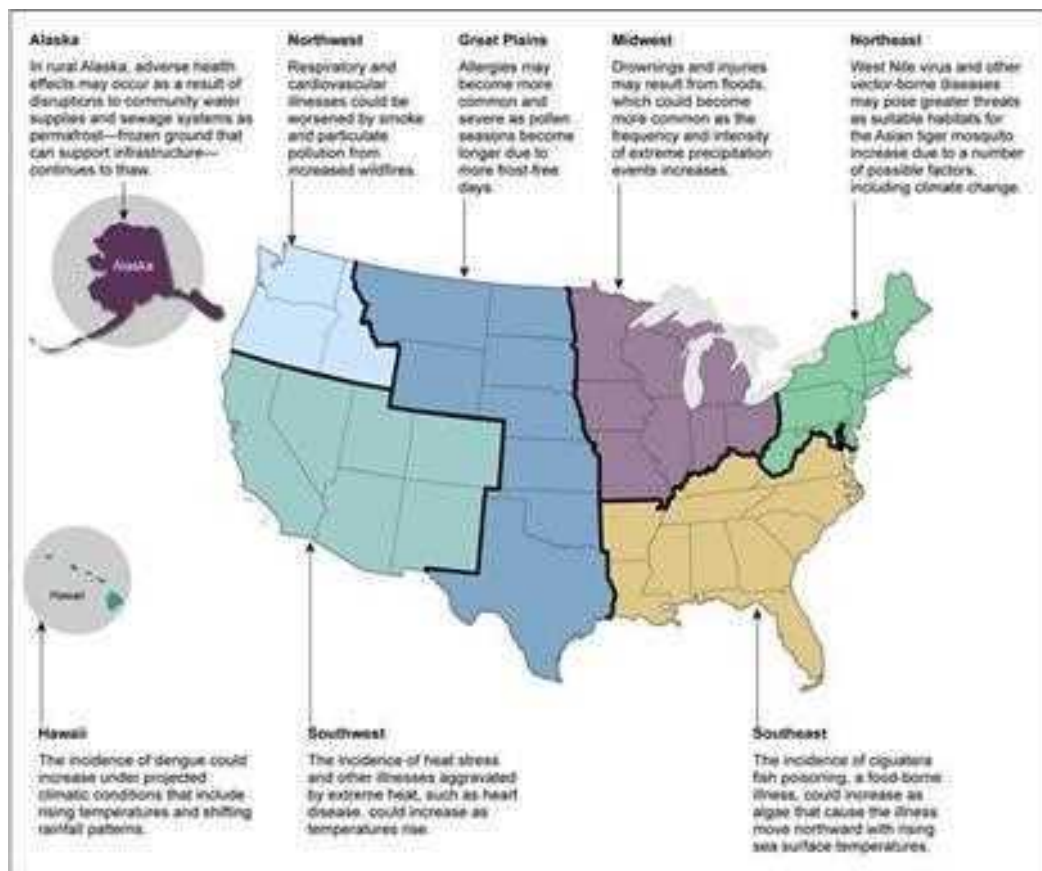
The federal government has undertaken a number of efforts to enhance the nation's resilience to climate change impacts, such as strengthening federal agencies' adaptation

planning and providing states and localities with information for managing risks posed by climate change. In July 2014, we reported that investing in resilience—actions to reduce potential future losses rather than waiting for an event to occur and paying for recovery afterward—can reduce the potential impacts of climate-related events.²⁷ To facilitate federal efforts, the federal government has issued the following orders, actions, and plans:

- **Executive Order 13514.** On October 5, 2009, the President issued an executive order calling for federal agencies to participate in the existing interagency Climate Change Adaptation Task Force.²⁸ Based on the task force's recommendations, the Council on Environmental Quality within the Executive Office of the President issued implementing instructions for the executive order,²⁹ directing federal agencies to establish agency climate change adaptation policies, among other things.³⁰
- **The President's Climate Action Plan.** In June 2013, the White House published a climate action plan detailing actions that federal agencies would take to prepare the nation for the impacts of climate change, among other goals.³¹
- **Executive Order 13653.** On November 1, 2013, the President issued an executive order to help prepare the nation for the impacts of climate change.³² Among other things, the order called on certain federal agencies to provide information, data, and decision-support tools on climate preparedness and resilience in support of federal, regional, state, local, tribal, and other efforts to prepare for the impacts of climate change. It also established a State, Local, and Tribal Leaders Task Force on Climate Preparedness and Resilience to inform federal efforts to support climate preparedness and resilience.³³
- **April 2015 Administrative Actions.** On April 7, 2015, the White House announced a series of actions that the administration was taking to better understand, communicate, and address the health impacts of climate change, as well as commitments made by private sector entities and institutes of higher learning to further our knowledge in this area. Among other things, the administration expanded the resources available for analyzing the climate change impacts on health. (App. II provides a summary of these actions.)
- **June 2015 Climate and Health Summit and Administrative Actions.** On June 18, 2015, the White House hosted a summit on climate change and health, which included the participation of the President, the Surgeon General, and the HHS Assistant Secretary for Preparedness and Response.³⁴ At the summit, the administration announced a set of actions to protect communities from the health impacts of climate change that cannot be avoided. (App. III provides a summary of these actions.)

In addition, USGCRP has undertaken efforts to support scientific research with the goal of improving understanding of and response to climate change and its impacts on the United States. To help address climate change impacts on human health, USGCRP coordinates an Interagency Crosscutting Group on Climate Change and Human Health (CCHHG); officials from CDC, NIH, and NOAA chair this group. The mission of CCHHG is to promote and protect the nation's public health by leading and coordinating federal scientific activities related to climate change and human health, from basic research through public health

practice. CCHHG's activities include working to address key gaps in understanding of the health-related impacts of climate change and developing informational resources.³⁵



Sources: GAO analysis of U.S. Global Change Research Program's third National Climate Assessment Map Resource (map). | GAO-16-122

Note: Impacts described for certain regions do not imply that they do or can occur only in those regions.

Figure 1. Examples of potential health impacts from climate change in the United States, by region.

FEDERAL AGENCIES HAVE UNDERTAKEN VARIOUS ACTIVITIES TO ENHANCE UNDERSTANDING OF CLIMATE CHANGE RISKS TO PUBLIC HEALTH

Federal agencies have undertaken activities to enhance understanding about the risks that climate change poses to public health, including supporting and conducting research on or related to these risks. Agencies have also provided some data and decision support resources, such as guidance and tools, for state and local officials and others to use in examining public health-related risks from climate change and potential actions to address these risks. Agencies have also communicated about such risks through reporting and outreach efforts to public health officials and the general public.

Supporting and Conducting Research on or Related to the Risks Climate Change Poses to Public Health

To enhance understanding of the risks that climate change poses to public health, many of the federal agencies included in our review have supported and conducted research on or related to these risks. While governmentwide data on funding for such research is not available, NIH, which awards financial assistance for research, reports that it awarded about \$6 million to support research on the health impacts of climate change in fiscal year 2014.³⁶ This amount comprised a relatively small portion—about 0.025 percent—of the approximately \$24 billion that NIH awarded for research that year. Some of this research originated from an NIH funding opportunity—a solicitation for exploratory research projects on the health impacts of climate change—through which the agency awarded a total of about \$8.3 million for research from fiscal year 2011 through fiscal year 2014 for 21 projects. One of these projects, for example, examined the relationship between climate change and pediatric asthma.³⁷ NIH officials told us that the agency has not issued additional funding opportunities for research on climate change. These officials said that they hoped researchers who received awards from this opportunity would be better positioned to submit proposals in the future through NIH's most common submission process, in which researchers submit unsolicited proposals based on the program interests of one or more of the agency's institutes or centers.³⁸

In addition to NIH, other federal agencies, such as the National Aeronautics and Space Administration (NASA), have also conducted or supported research on or related to the risks that climate change poses to public health, including by making awards for relevant research projects and providing financial support for research teams or postdoctoral students conducting relevant work. For example, NASA made an award to aid in the development of climate change indicators related to heat waves in urban areas through its 2012 research announcement entitled "Research Opportunities in Space and Earth Sciences" that intended to, among other things, facilitate the application of scientific knowledge to management decisions.³⁹ Indicators developed through this program may be used by health officials to identify urban areas with increased vulnerabilities to health impacts due to a lack of cooling green spaces and other factors. Additionally, EPA sponsored a review of the effects of climate change on the indoor environment and health, which concluded, among other things, that climate change may worsen existing indoor environmental problems that are known to exacerbate illnesses such as asthma and allergies, and create new problems that have adverse health impacts.⁴⁰

Officials from some of the federal agencies included in our review told us that while their agencies have conducted or supported research that is useful for advancing understanding of climate change impacts to public health, the link to this topic is often indirect. For example, federally-funded research about health impacts from natural disasters, such as floods, does not always explicitly consider the associated impacts from climate change but can help advance understanding of these impacts, according to federal officials we spoke with. Appendix IV provides additional examples of research on or related to the risks of climate change to public health that some of the federal agencies included in our review have conducted or supported.

Providing Data and Decision Support Resources for Examining Risks

Federal agencies have provided some data and decision support resources—such as guidance and tools—that state and local officials, and others, can use to examine public health-related risks from climate change and potential actions to address these risks. Table 3 provides examples of these data and decision support resources.

Table 3. Examples of federal data and decision support resources for examining the risks that climate change poses to public health

Federal agency	Description of data or decision support resource
Environmental Protection Agency (EPA)	EPA published a software tool in 2010—referred to as the Climate Resilience Evaluation & Awareness Tool—to assist drinking water and wastewater utility owners and operators in understanding and addressing potential climate change risks at their utilities to continue to protect public health, among other reasons.
Department of Health and Human Services (HHS)	In December 2014, HHS published a best practices document to promote resilience of health care facility infrastructure to climate change impacts—primarily from extreme weather events, as part of its Sustainable Climate Resilient Health Care Facilities Initiative. To help users implement the guidance, the agency subsequently published an online toolkit with links to individual tools. In June 2015, HHS released its emPOWER map, an online interactive tool that displays information about vulnerable populations that rely on electricity-dependent medical equipment, to support state, local, and community partner emergency planning and response activities.
National Aeronautics and Space Administration (NASA)	NASA collects data on land surface temperature and other climate-sensitive environmental factors that may affect public health by, among other mechanisms, impacting the range of animals that can transmit harmful diseases to humans. The agency reports some data online and provides other data upon request.
National Oceanic and Atmospheric Administration (NOAA)	NOAA’s National Weather Service and its partners collect environmental data and provide decision support services to aid decision makers in their examination of the potential public health impacts of weather, water, and climate events.
U.S. Global Change Research Program (USGCRP)	In 2013, USGCRP introduced the Metadata Access Tool for Climate and Health, or MATCH, an online clearinghouse that provides links to thousands of government-held datasets related to health, the environment, and climate science.

Source: GAO. | GAO-16-122

Users of these data and decision support resources may include public health officials or decision makers with responsibility for managing systems that are necessary for protecting public health, such as hospital administrators or wastewater management system operators, among others. Other users may include researchers, community organizations, or other interested individuals. The following are two key interagency mechanisms that federal agencies leverage to provide climate and health data and decision support resources to potential users:

- **Data.gov.** In April 2015, data.gov, the federal government’s site for open data, launched a theme page on climate and health that provides information about data sources and tools maintained by federal agencies.⁴¹ The site includes links to data on climate, weather, and health from many federal agencies. One data source included on the theme page is CDC’s National Environmental Public Health Tracking Network, which includes heat-related health data, including national data on the number of extreme heat days and future projections of extreme heat.⁴² Another data source included on the theme page is NOAA’s Climate Data Online, which includes

data on precipitation amounts, as well as a mapping tool and other decision support resources.

- **The U.S. Climate Resilience Toolkit.** The toolkit is an online portal that is intended to help individuals, communities (including tribal nations), and others respond to risks from climate change. Human health is one of the topics highlighted in the toolkit.⁴³ One tool available in the toolkit is the Agency for Toxic Substances and Disease Registry's Social Vulnerability Index, which uses U.S. Census Bureau variables to identify communities that may need support in preparing for climate-related or other hazards or recovering from disasters, and includes a mapping feature and downloadable data. Another tool available in the toolkit is a software package developed by EPA that allows users to predict levels of disease-causing pathogens at specific beach sites, where outbreaks can result from climate change-related effects such as warming waters and intense precipitation.⁴⁴

CDC has also developed some decision support resources intended to help state and local public health officials identify and address risks from climate change. In June 2014, CDC officials authored a journal article which described a five-step risk management framework that the agency developed for health officials to use in preparing for the health effects of climate change.⁴⁵ In July 2014, CDC issued a more detailed guide for health departments on how to assess the vulnerability of their constituent populations to the health impacts of climate change—a critical step for health departments in planning for climate change risks to public health, according to CDC.⁴⁶ The guide includes a case study detailing how CDC conducted a vulnerability assessment on heat impacts in the state of Georgia. In addition, CDC's National Environmental Public Health Tracking Program published a communication toolkit in 2012 that focuses on the relationship among climate change, public health, and extreme heat—which is the only climate change-related area for which the tracking network provides data.⁴⁷ Among other things, the communication toolkit provides health officials and other potential users with key messages and tips for using social media to communicate effectively about this topic.

Communicating through Reporting and Outreach

Federal agencies in our review have communicated information about the risks that climate change poses to public health through reporting and outreach efforts directed at multiple audiences, such as public health officials and the general public. In several key communication efforts, federal agencies have collaborated to report on what is known about these risks. For example, in the third NCA published in May 2014, USGCRP reported on the impacts of climate change on the United States, including risks to human health. The report was the result of a large multiagency effort that included the 13 agencies participating in the USGCRP as well as other agencies that chose to support the production of the report.⁴⁸ It includes a chapter on human health—prepared collaboratively by officials from several federal agencies participating in CCHHG, as well as experts from outside the federal government—summarizing what is known about how climate change threatens human health and well-being, populations that are at greatest risk, the extent to which public health actions

can help address these risks, and opportunities to improve human health while combating climate change.⁴⁹ CCHHG is expanding upon this information in a report that is intended to provide a comprehensive, evidence-based, and, where possible, quantitative estimation of observed and projected climate change related health impacts in the United States. The report, referred to as the USGCRP Climate and Health Assessment, is being developed through a multiagency effort and is expected to be finalized in 2016.⁵⁰ The American Public Health Association, with the support of CDC, recently reported on threats that climate change poses to human health, and how state and local public health departments have responded to these threats using CDC resources.⁵¹ In addition to preparing reports, federal agencies have also reported on the risks that climate change poses to public health through their websites and through social media, and federal officials have reported on these risks in peer-reviewed journal articles and other publications.⁵²

Federal agencies have conducted outreach to inform public health officials, as well as the general public, about the risks that climate change poses to public health. Some ways in which federal agencies have recently done so include the following:

- In August 2014, HHS held a departmentwide briefing on climate change risks to public health.⁵³
- In December 2014, CDC addressed climate change in its Public Health Grand Rounds—a publicly-available webcast that is intended to foster discussion on major public health issues.⁵⁴

In addition, senior officials within HHS and EPA have also conducted outreach on certain occasions about the risks that climate change poses to public health. In April 2015, the Surgeon General spoke publicly about climate change impacts to health following a roundtable discussion on the topic with the President, the EPA Administrator, and others, and also used social media to solicit and respond to questions about health impacts from climate change. The EPA Administrator has also communicated about these risks to a variety of audiences, citing climate change as among the most significant threats to public health.⁵⁵ App. V provides additional information about federal activities related to climate change risks to public health.

STATE AND LOCAL HEALTH DEPARTMENTS HAVE USED CDC AND OTHER FEDERAL RESOURCES TO ADDRESS THE RISKS THAT CLIMATE CHANGE POSES TO PUBLIC HEALTH

Selected state and local health departments included in our review have used a CDC climate and health award that addresses the risks that climate change poses to public health, as well as other federal resources, to address and plan for the public health risks from climate change.

Selected Health Departments Have Used a CDC Award to Directly Address and Plan for the Risks that Climate Change Poses to Public Health

Sixteen state and two local health departments have used awards from CDC's Climate Ready States and Cities Initiative to address and plan for the risks that climate change poses to public health.⁵⁶ The initiative is the federal government's primary investment in supporting state and local health departments in addressing the risks that climate change poses to public health, and is the only HHS financial resource that has been offered to state and local public health departments that directly targets these risks. In fiscal year 2014, Initiative awards to state and local health departments totaled \$3.6 million, with individual awards averaging about \$200,000.⁵⁷ Figure 2 displays Initiative awardees as of fiscal year 2015.



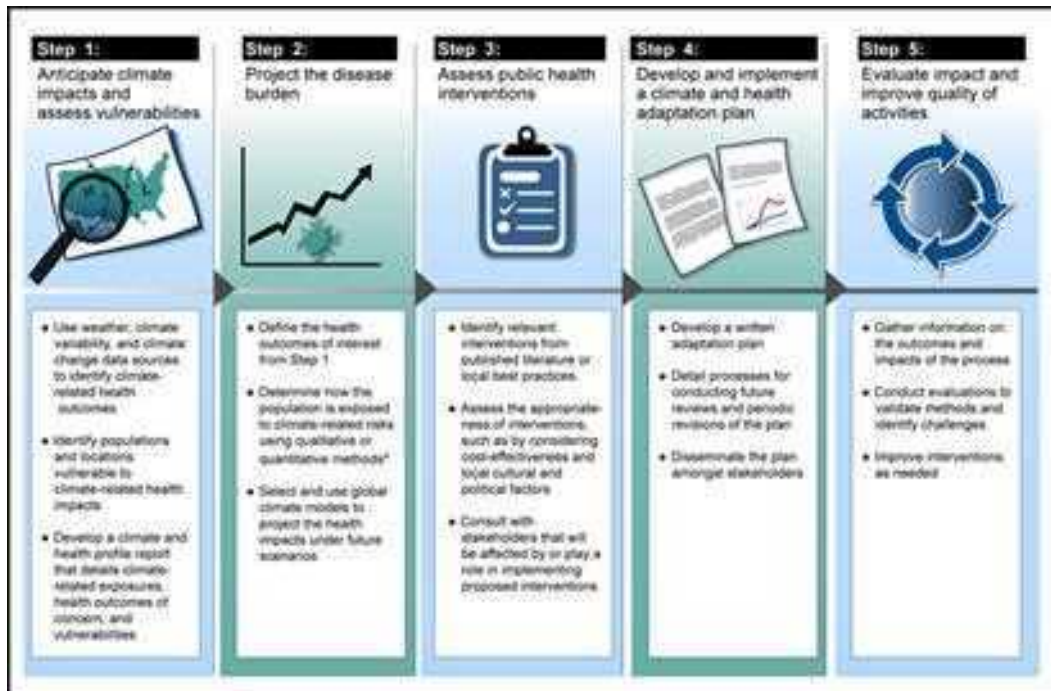
Source: Centers for Disease Control and Prevention; Map Resources (map). | GAO-16-122

Figure 2. CDC Climate ready states and cities initiative awardees, fiscal year 2015.

CDC's Climate and Health Program administers the Climate Ready States and Cities Initiative. Under the initiative, CDC program staff are substantially involved in program activities, above and beyond routine grant monitoring. CDC activities for this program are described as providing ongoing guidance, resources, consultation, technical assistance, and training related to awardee activities.

Under the initiative, CDC requires awardees to implement CDC's Building Resilience Against Climate Effects (BRACE) framework—a five-step risk management process intended to help public health departments identify and prepare for the public health impacts of climate change by, among other things, incorporating atmospheric data and climate projections into public health planning. To implement the framework, CDC requires awardees to work with internal and external stakeholders to forecast climate trends, identify disease

risks and vulnerable populations, and develop action plans for addressing these risks, among other things. Figure 3 describes the five steps of the framework and provides examples of activities that can be included in its implementation.⁵⁸ CDC officials told us that they developed the BRACE framework to assist state and local health departments in preparing for the public health impacts of climate change. (App. VI provides information on the types of activities undertaken by awardees in implementing the BRACE framework, and app. VII provides information on activities by other selected state and local health departments).



Sources: GAO analysis of Centers for Disease Control and Prevention information and Art Explosion (image). | GAO-16-122

Note: According to CDC officials, the Building Resilience Against Climate Effects (BRACE) framework is iterative and enables the incorporation of learning into future decisions by encouraging users to revisit prior steps to reevaluate risks and management priorities.

^a According to CDC, qualitative methods may be used to provide a general impression of how climate change may affect the risk for certain outcomes, at least capturing general climatic trends and environmental exposures, population vulnerability, and expected human health impacts. Quantitative methods may be used, for example, to quantify existing climate and health exposure pathways, or to project disease impacts.

Figure 3. Steps and examples of activities conducted under CDC's building resilience against climate effects framework.

Under the initiative, CDC requires awardees to complete a range of activities that complement their work implementing the BRACE framework. For example, CDC requires that awardees take steps to increase awareness among the public and decision makers about the risks that climate change poses to public health, making use of available CDC resources.

Awardees provided examples of the types of guidance and support that CDC's Climate and Health Program has provided to assist them in implementing the BRACE framework and addressing climate and health information needs in their jurisdictions. For example, CDC created guidance for awardees on how to develop a Climate and Health Profile—a report detailing a jurisdiction's climate-related exposures, health outcomes of concern, and vulnerabilities of certain populations—a required component of the first step of the BRACE framework. CDC officials told us that they plan to issue guidance describing how to approach each step of the BRACE framework. As of June 2015, CDC has issued two guidance documents on the first step of the framework.⁵⁹ Awardees also told us about other types of support provided by CDC, including tools that CDC developed in response to awardees' specific requests for assistance, such as a database of peer-reviewed literature on climate change and public health impacts and a graphic summarizing the impacts of climate change to public health.⁶⁰ CDC has also organized several communities of practice among awardees as forums to discuss issues related to the implementation of the BRACE framework.⁶¹ According to CDC officials, some public health departments that have not received the Climate Ready States and Cities Initiative award have expressed interest in implementing the BRACE framework, and such departments are able to do so using the resources available on CDC's website.

Although awardees told us that they are in various stages of implementing the framework, they also noted that they have already observed a variety of benefits from the award. Specifically, awardees we spoke with told us that the CDC award has enabled them to work on climate change and health issues in a formalized way that would otherwise not have been possible given, for example, competing priorities and limited staff time. According to our analysis of awardee reports to CDC, nearly all 18 awardees have created a climate and health program with dedicated staff within their departments to work on this issue, although doing so is not a requirement of the award. Awardees also reported that the program allows them to address specific needs in their jurisdictions and consider certain areas of interest while implementing the framework. For example, some awardees in state health departments told us that they have provided subawards to a small number of local health departments in their jurisdictions to participate in the implementation of the BRACE framework, such as by providing feedback on the usefulness of materials developed by the state, or to develop their own initiatives on or related to climate change and public health. Officials in these states told us that the award allows staff in the local jurisdictions to spend time considering the risks that climate change poses to public health and how these risks may impact existing priorities in their health departments. Additionally, some awardees have identified specific risks that climate change poses to public health and are interested in exploring these issues in further detail. For example, some awardees are examining potential health affects related to climate change impacts on food security—that is, the availability and affordability of nutritious and quality foods.

Furthermore, awardees told us that the CDC award has allowed for their programs to build relationships and engage with partners, such as officials from other departments in their jurisdictions or regional partners from federal agencies, in ways that could not be accomplished without such awards or without a formalized climate and health program. For example, officials from the New York City Department of Health and Mental Hygiene told us that through the department's climate and health program, they worked collaboratively with their regional National Weather Service office to study the appropriateness of the thresholds

used to issue heat advisories and warnings. According to these officials, the National Weather Service had been using a Heat Health Watch and Warning System in addition to heat index forecasts to determine when to issue heat advisories and warnings; however, health officials were concerned that this method was not sensitive enough for use in predicting public health outcomes during excessive heat events.⁶² The health department completed a retrospective study of heat-related deaths to evaluate metrics that could be used to estimate risks, and it found that maximum heat index is a useful metric for assessing public health risks due to hot weather in New York City. The officials said that they have changed the threshold at which warnings are set as a result of this study, and they have continued to develop a working relationship with the National Weather Service.

Selected Health Departments Reported Leveraging Other Federal Resources to Address and Plan for Risks

State and local public health officials we interviewed reported leveraging a variety of other federal resources, including funding and information sources, to address and plan for the risks that climate change poses to public health. In most cases, these federal resources were not specifically designed for addressing and planning for these risks, but the resources could be used in ways that support such efforts. State and local public health officials we interviewed most commonly mentioned leveraging resources provided by CDC's National Environmental Public Health Tracking Program to support their work in addressing and planning for the public health risks of climate change. CDC's Tracking Program made awards to 25 states and one city to develop local tracking networks, analyze data on local environmental exposures and related health outcomes, and supply selected data to a national tracking network.⁶³ The national network includes indicators on climate change, among other environmental hazards, related to extreme heat exposure.⁶⁴ State and local health officials we interviewed reported that this award provides an important core source of funding for data infrastructure and environmental health surveillance activities in their jurisdictions, which can be leveraged to include activities such as monitoring patterns of heat-related illness. Awards provided to state and local health departments for the tracking program vary; in fiscal year 2014, awards totaled \$22.6 million to participating states and localities, ranging from about \$500,000 to \$1.2 million, with an average award of about \$870,000.⁶⁵

State and local health officials also provided examples of how their jurisdictions have leveraged funding resources from other CDC programs to address and plan for the risks that climate change poses to public health. For example, state and local health officials told us that they have leveraged awards from CDC's Public Health Emergency Preparedness program—which provides state, local, tribal, and territorial health departments across the country with resources to build public health preparedness capabilities—to help consider climate change in emergency preparedness planning or develop systems that can be used to monitor climate-related public health risks. Awards provided to state and local health departments vary; in fiscal year 2014, for example, awards ranged from \$325,000 to approximately \$42.5 million, with an average award of approximately \$9.9 million and a total of about \$611.8 million.⁶⁶ Climate change is not a specific focus of the program, but CDC officials responsible for administering this program told us that awardees have flexibility in determining how to use

the funds while meeting CDC's requirements.⁶⁷ State health officials also told us that they have used awards from CDC's National Institute for Occupational Safety and Health to consider the impacts of climate change on worker safety and health, such as by monitoring heat-related illnesses and deaths among worker populations or specific industries.⁶⁸ Officials from the National Institute for Occupational Safety and Health also noted that, while climate change is not a specific focus of the program, the award could be used to support activities in this area.

Some public health officials we interviewed also reported leveraging federal resources from agencies other than from CDC to address or consider the risks that climate change poses to public health. Specifically, officials provided examples of other awards and informational resources that they had used in their work on this issue. For example, an official from one state told us that the state used an award from U.S. Geological Survey to assess the vulnerability and health risks of the state's watersheds to flooding and drought under a changing climate. Some state and local health officials reported using the health and regional chapters of USGCRP's third NCA as key sources of information. Some officials also told us that they have relied on a variety of NOAA information resources, such as those provided through NOAA's National Centers for Environmental Information or through NOAA-funded Regional Integrated Sciences and Assessment teams.⁶⁹ For example, one state health official told us that the state has relied on support from a NOAA Regional Integrated Sciences and Assessment team to translate technical information about climate change. In conducting work to address the risks that climate change poses to public health, local health officials from one jurisdiction also provided an example of using demographic information from the American Community Survey—an official U.S. Census Bureau survey that is part of the Decennial Census Program—to identify populations in its locality that are vulnerable to the health-related impacts of climate change.

STATE AND LOCAL HEALTH OFFICIALS IDENTIFIED MULTIPLE CHALLENGES, SOME OF WHICH THEY SAID COULD BE ADDRESSED BY FEDERAL ACTION

When asked to identify challenges related to their work planning for and addressing the risks that climate change poses to public health, state and local public health officials we interviewed identified challenges that we grouped into the three most frequently reported themes, noting that some of these challenges could be addressed by federal action, while others could not. According to state and local officials, they face challenges communicating about the risks that climate change poses to public health. Officials identified related opportunities for federal agencies to enhance public understanding of these risks. The officials also stated that they face challenges in identifying potential health risks of climate change, for example, as a result of research gaps. Officials said that federal agencies may be able to address this challenge by continuing to advance research and enhance decision support resources. Finally, state and local public health officials said they face other challenges that federal action may not be able to address, such as having insufficient data on health impacts in areas where agreements between states and hospitals limit access by health departments.

Selected Health Officials Face Challenges Communicating about the Risks That Climate Change Poses to Public Health and Identified Opportunities for Federal Action

According to our discussions with selected state and local health officials, officials face challenges communicating about the risks that climate change poses to public health, in part because of limited awareness about climate change as a public health issue. The officials also identified opportunities for federal agencies to address these communication challenges.

Challenges Identified

Selected state and local health officials told us during interviews, site visits, and small group discussion sessions that they face challenges resulting from limited awareness about climate change as a public health issue within their own health departments, among other state and local partners, such as other agencies in their jurisdictions, and among the public. As we have previously found, public awareness can play an important role in the prioritization of climate change adaptation efforts.⁷⁰

In addition, if public health officials are aware of the risks that climate change poses to public health, they can better assess the importance of these risks and allocate resources appropriately. However, health department leadership and staff are often not aware of the public health impacts of climate change, or do not understand how the issue fits into the health department's priorities, according to state and local health officials.⁷¹ This observation is consistent with results from a 2012 NACCHO survey of 174 local health department officials, which showed that just over one-third of respondents thought that other relevant senior managers in their health departments were knowledgeable about the potential public health impacts of climate change.⁷²

Some local health officials also reported that officials from other sectors of government in their jurisdictions, such as environmental agencies responsible for climate change adaptation planning efforts, have a limited awareness of climate change as a public health issue. This has resulted in health officials having limited involvement in climate change adaptation planning within their localities, according to officials we interviewed. Some officials believe that progress has been made in this area in recent years, but, according to our review of a 2014 analysis of states' climate change adaptation planning activities, only about one-quarter of all states have incorporated public health considerations into their statewide climate change adaptation plans.⁷³

In addition, health officials told us that stakeholders and the public have limited awareness about climate change as a public health issue, in part because climate change has historically been framed as an environmental issue. State and local health officials discussed climate change impacts on health as an emerging issue that they became aware of within the last decade, in part as a result of educational efforts of the American Public Health Association. In 2008, for example, the association made climate change a focus of its National Public Health Week, issuing communications to highlight climate change as a public health issue.⁷⁴

State and local health officials also told us that they face challenges in communicating or enhancing awareness about projected changes to local climate that can impact public health because of the complexity of the issue.⁷⁵ Specifically, officials told us that it is difficult to

develop messages about climate change impacts on health because of uncertainties inherent in climate change projections. For example, officials from one state health department told us that the state has faced challenges describing climate projections for its jurisdiction in a way that is accurate but not overly technical, while adequately acknowledging the uncertainties of these projections. State and local health officials also said that it is challenging for them to communicate about the risks that climate change poses to public health because some of the potential effects have not yet been observed in their jurisdictions and, therefore, are not perceived by the public as risks. For example, officials in some states that do not frequently experience heat waves told us that they face challenges convincing their constituents that the risks of heat-related illnesses will increase. Officials told us that they have used a variety of strategies to attempt to interest their constituents and stakeholders in these risks, such as framing the issue as planning for emergency preparedness or severe weather events. However, state and local health officials find it difficult to communicate and bring attention to long-term issues, such as climate change, when there are more immediate public health concerns drawing attention, such as the 2014 Ebola virus outbreak.⁷⁶

Opportunities Identified

State and local health officials, as well as representatives from associations representing these officials, identified opportunities for federal action to help address challenges the officials face in communicating about the risks that climate change poses to public health. These opportunities were generally in two areas: enhancing public awareness on climate change as a public health issue, and providing guidance and tools on how to communicate about this issue.

Concerning enhancing public awareness, state and local health officials, as well as representatives from associations representing these officials, told us that federal agencies could help address this challenge by taking a sustained leadership role in enhancing public and stakeholder awareness and understanding. Specifically, officials told us that a federally-led public awareness campaign on this issue could assist in informing decision makers and the public. They also said a campaign could help and provide legitimacy to the work of public health officials in addressing and planning for these risks. Officials particularly pointed to the need for a sustained leadership role from HHS and its component agencies, which could draw on the department's experience from engaging in previous successful public health campaigns, such as the campaign to reduce tobacco use. In a November 2014 report, the President's State, Local, and Tribal Task Force on Climate Preparedness and Resilience also recommended actions that federal agencies should take to increase climate literacy and public awareness, among other things.⁷⁷ These actions included coordinating federal communications on climate change to develop clear, consistent and unified messages, and ensuring that communications resources are accessible to state and local governments. (See app. VII for a summary of the task force's health-related recommendations.)

Federal officials, including those from HHS, told us that they are taking steps to enhance public awareness. For example, as previously mentioned, the White House held a climate change and health summit in June 2015, which included the participation of the U.S. Surgeon General, the HHS Assistant Secretary for Preparedness and Response, and the EPA Administrator. In addition, CDC officials told us that through awards the agency provides, the FrameWorks Institute is developing a series of fact sheets for the general public that explain various impacts of climate change on human health.⁷⁸ In its 2014 Climate Adaptation Plan,

HHS reported that it considers climate change to be one of the top public health challenges of our time, and it noted that its Office of the Assistant Secretary for Health will develop a climate change communication and outreach strategy to, among other things, promote outreach and awareness among its stakeholders about climate change and its impact on public health.⁷⁹ The plan further notes that outreach and communication to at-risk populations will be a significant part of this strategy, and that the department will leverage its comprehensive network of stakeholders involved in the receipt or delivery of health and human services to disseminate climate change and health information. HHS reported in its Strategic Sustainability Performance Plan that the strategy was to be developed by the fall of 2014.⁸⁰ In March 2015, a senior HHS official from the HHS component responsible for developing this strategy told us that limited progress had been made in developing the strategy, and that the strategy was not anticipated to be formalized in a written document. However, in July 2015, HHS officials told us that they plan to refine and document the strategy over the next 12 months.

Concerning guidance and tools, state and local health officials, as well as a representative from an association representing them told us it would be helpful if federal agencies, including CDC, developed communications guidance on a number of topics. For example, they said they could benefit from guidance on how to frame climate change as a public health issue or communicate based on best practices from the social sciences. They also suggested the development of communication tools, such as talking points or training on how to communicate about this issue. Because protecting public health requires the participation of a variety of stakeholders—including state and local public health departments and other state and local entities—enhancing stakeholder awareness and understanding about climate change as a public health issue could bolster state and local preparedness for the risks that climate change poses. In addition, as noted earlier in this report, enhancing awareness among the public and decision makers about the risks that climate change poses to health is a requirement of the Climate Ready States and Cities Initiative. According to state and local health officials, including Initiative awardees, communication guidance and tools would help them enhance stakeholder awareness and understanding of the risks climate change poses to public health.

CDC has developed limited guidance regarding communicating the risks that climate change poses to public health for state and local health officials. CDC has developed a toolkit related to communicating the connections between climate change, extreme heat, and health. However, the content of this document is focused on how awardees and partners of the National Environmental Public Health Tracking Network can use Tracking Network data to communicate about this issue, and is therefore not as applicable to a wider audience.⁸¹ CDC officials were not aware of any other agency guidance documents on communicating about the risks climate change poses to public health.⁸² Officials from CDC's Climate and Health Program acknowledged that a commitment to communicating about the risks that climate change poses to public health is needed, and they identified some actions to help Climate Ready States and Cities Initiative awardees address this challenge, such as reviewing and sharing research findings on best practices for communicating about climate change and providing technical assistance to state and local health departments regarding communication upon their request. However, these officials also told us that they do not currently have plans to develop communication guidance for state and local health departments on how to communicate about climate change because they do not have the resources or capacity to

develop such guidance at this time. CDC officials told us that they have been focusing on assisting awardees with resolving methodological and data issues related to implementing the BRACE framework, such as identifying models for use in developing projections of climate change in their jurisdictions.

As we noted earlier, the agency's Climate and Health Program supports state and local health department efforts to plan for and address the health risks posed by climate change. CDC's website states that the program's core functions involve translating climate change science to inform health departments and communities, serving as a credible leader in planning for the public health impacts of climate change, and creating decision support resources to assist officials in preparing for climate change.⁸³ As the administrator of the Climate Ready States and Cities Initiative, CDC is to provide ongoing guidance, resources, and technical assistance, among other things, related to awardee activities. Because CDC requires that awardees of this initiative take steps to enhance public awareness of the risks that climate change poses to human health, developing communications guidance would support their efforts. While CDC's current resources are focused on addressing methodological and data issues related to the implementation of the BRACE framework, it is also critical for the agency to establish a plan describing when it will develop future communications guidance, to help ensure that health officials have the tools they need to effectively implement the BRACE framework and address required aspects of the award.

Selected Health Officials Face Challenges Identifying Potential Health Risks of Climate Change and Identified Opportunities for Federal Action

According to our discussions with selected state and local health officials, they face challenges identifying potential health risks from climate change and have identified related opportunities for federal action. Specifically, officials noted how gaps in research have made it difficult for them to understand and plan for potential health impacts. For example, some state and local public health officials said that limited research has been conducted on how climate change may affect certain aspects of public health, such as the spread of vector-borne diseases, the costs of climate change impacts on human health, and the effectiveness of specific management options. Other officials we interviewed told us that they had difficulty using some of the climate-related data that federal agencies have made available for decision makers. Officials we interviewed explained that they typically do not have the scientific or technical expertise to fully understand or use some federal data, particularly those related to climatology. Public health officials have generally not been trained in using geographic information systems, atmospheric data, and climate projections, according to officials.⁸⁴ In addition, conducting analyses with these data can be complex and time-intensive. Consequently, they said that the availability of technical assistance in using such data, as well as in translating the results so that officials can apply them at the local level, has been very helpful.⁸⁵

State and local public health officials we interviewed said that federal agencies could help address these challenges by continuing to advance the research they support, and by enhancing decision support resources, including resources to assist decision makers in using federal datasets. State officials noted that an expansion of interagency research opportunities

on the public health impacts of climate change, which is a crosscutting research area, could be helpful. State and local public health officials we interviewed said that federal agencies could also enhance the decision support resources they provide, including through technical assistance that would better position public health departments to effectively use available datasets. For example, a Climate Ready States and Cities Initiative awardee said that it would be helpful if CDC could provide awardees with programming language to assist them in using federal datasets to assess health vulnerabilities associated with climate change.

Officials from federal agencies told us about actions that they have taken or that they have planned that could help address some of these challenges. Specifically, federal officials have acknowledged the need for additional research on the public health impacts of climate change and have taken some steps to fill those needs. In 2010, an ad hoc interagency working group on climate change and health developed a white paper summarizing research needs on the human health effects of climate change.⁸⁶ The intent of this paper was to provide a baseline picture of research needs in this area that agencies could then build upon as new information became available, according to the paper. Subsequently, NIH officials analyzed the agency's portfolio of research on climate change and health, and summarized their results in an article published in 2013.⁸⁷ The article includes a discussion of challenges related to conducting this research and opportunities to advance the research, including opportunities to take a multidisciplinary approach through enhanced interagency research opportunities.⁸⁸ More recently, in an April 2015 *Federal Register* notice, EPA, on behalf of USGCRP, announced that a draft of the CCHHG assessment of climate change impacts on health was available for comment.⁸⁹ According to the CCHHG co-chairs, the report contains results that should advance the research in some needed areas, and is likely to include some information on research needs. The CCHHG co-chairs told us that they hope to use information on research needs included in the final assessment to help inform the development of a prioritized and focused research agenda for use in addressing research needs. CCHHG officials also told that they would like to continue to help foster a collaborative interagency approach to researching climate change impacts on health.

Federal agencies, such as HHS, EPA, and NOAA, have also recently taken steps to enhance data and decision support resources available to state and local decision makers, for example, by enhancing air quality surveillance and creating a national heat health information system. These enhanced resources may address some needs of state and local decision makers. CCHHG officials said that they have plans to solicit feedback from state and local decision makers about these enhanced decision support resources through town hall meetings and other mechanisms.

Selected State and Local Health Officials Face Other Challenges That Federal Action May Not Be Able to Address

According to selected state and local public health officials we interviewed, they face a range of other challenges related to planning for and addressing the health impacts of climate change that federal action may not be able to address. For example, they said that insufficient data and inadequate resources impede their ability to address or plan for these risks. While some federal programs collect local data and provide financial resources to selected states and

localities, such as CDC's National Environmental Public Health Tracking Program, the federal government does not collect local data on climate impacts or health outcomes in all locations, and does not make awards to support the climate and health activities of all state and local health departments.

State and local public health officials told us that some environmental surveillance data that could help inform research on the health risks of climate change—such as data on air quality, water quality, and pollen—are often not collected by their states and localities given limited surveillance systems. Additionally, state and local officials explained that some health outcome data can be difficult to obtain. State officials explained that their access to health outcome data, such as the medical conditions cited for emergency room visits, is limited by agreements that states have with hospitals regarding the amount and type of information that hospitals will share with state officials.

Some state and local officials told us that their health departments did not have dedicated staff or funding to address and plan for climate change impacts or that their staff resources and funding were not sufficient for maintaining the ideal quality or quantity of work in this area. These statements are consistent with findings from NACCHO's 2012 survey of local health department officials, in which less than 10 percent of respondents said that their health departments had sufficient resources to effectively protect local residents from the health impacts of climate change, and less than 20 percent of respondents said their health departments had sufficient expertise to assess the potential impacts from climate change.⁹⁰

CONCLUSION

Federal agencies have taken steps to enhance understanding about the risks of climate change to public health. They have also supported state and local efforts to address and plan for these risks, in keeping with an executive order that calls on federal agencies to provide them with data, information, and decision support tools on climate preparedness and resilience. Nevertheless, state and local officials face challenges resulting from limited awareness of climate change as a public health issue among their own departments and the public. As we have previously found, public awareness can play an important role in the prioritization of work on climate change. HHS has acknowledged climate change as one of the top public health challenges of our time and is developing a climate change communication and outreach strategy, which has been delayed by over a year, but is expected to be finalized by July 2016.

CDC requires public health departments participating in its Climate Ready States and Cities Initiative to take steps to raise public awareness about the risks that climate change poses to public health, and also engage stakeholders in their planning. As the administrator of the Climate Ready States and Cities Initiative, CDC is to provide ongoing guidance, resources, and technical assistance to support state and local health department work on this issue. Although the agency has provided guidance on some topics, such as extreme heat events, it has not provided specific guidance on how public health departments should communicate about the risks that climate change poses to public health. Officials from CDC's Climate and Health Program acknowledged that a commitment to communicating about the risks that climate change poses to public health is needed. However, the agency does not

currently have plans to develop guidance on this topic, as it has been focused on other priorities. Issuing such guidance would also be in line with the core functions of CDC's Climate and Health Program, which include translating climate change science to inform communities. By developing such guidance, CDC may help public health departments better meet the requirements of the Climate Ready States and Cities Initiative and better position all health departments to make progress in planning for the health impacts of climate change.

RECOMMENDATION FOR EXECUTIVE ACTION

To enhance HHS's ability to protect public health from the impacts of climate change, we recommend that the Secretary of HHS direct CDC to develop a plan describing when it will be able to issue climate change communication guidance to state and local health departments, to better position relevant officials to effectively communicate about the risks that climate change poses to public health and address requirements of the Climate Ready States and Cities Initiative.

AGENCY COMMENTS AND OUR EVALUATION

We provided a draft of this product to HHS, EPA, NOAA, USGCRP, the Council on Environmental Quality, the Department of the Interior, and the National Science Foundation for comment. In its written comments HHS stated that CDC generally concurred with our recommendation. CDC noted its plans to develop and issue climate change communication guidance to state and local health departments after HHS finalizes its climate change communication and outreach strategy, which is expected by July 2016. CDC stated that it would use HHS's strategy to inform their development of guidance, and to build off of the same strategy. CDC said that the agency currently provides support and technical assistance to state and local health departments regarding communication upon their request, and would continue to do so while HHS finalizes its strategy. CDC remarked that the agency is also working with partner and professional organizations to disseminate messages on the health impacts of climate change.

We also received technical comments from HHS, EPA, NOAA, USGCRP, the Council on Environmental Quality, the Department of the Interior, and the National Science Foundation, which we incorporated as appropriate

J. Alfredo Gómez
Director, Natural Resources and Environment

Marcia Crosse
Director, Health Care

APPENDIX I: LIST OF AGENCIES AND STAKEHOLDERS INTERVIEWED

We interviewed officials from federal, state, and local government agencies, as well as representatives of stakeholder groups involved in public health and climate change.

Government Agencies

Federal Agencies and Entities

1. Department of Commerce, National Oceanic and Atmospheric Administration
2. Department of Defense, Defense Health Agency
3. Department of Health and Human Services
 - Office of the Assistant Secretary for Preparedness and Response
 - Centers for Disease Control and Prevention
 - Indian Health Service
 - National Institutes of Health
 - Office of the Assistant Secretary for Health
4. Department of Homeland Security
 - Federal Emergency Management Agency
 - Office of Health Affairs
5. Department of the Interior
 - Bureau of Indian Affairs
 - Office of Insular Affairs
 - U.S. Geological Survey
6. Environmental Protection Agency
7. National Aeronautic and Space Administration
8. National Science Foundation
9. Smithsonian Institution
10. United States Department of Agriculture
 - Agricultural Marketing Service
 - Animal and Plant Health Inspection Service
 - Agricultural Research Service
 - National Institute of Food and Agriculture
 - Economic Research Service
 - Forest Service
 - Natural Resources Conservation Service
 - Office of the Chief Economist
11. United States Global Change Research Program
12. Council on Environmental Quality

State Public Health Departments

1. Alaska
2. Arizona
3. California
4. Florida
5. Hawaii
6. Illinois
7. Louisiana
8. Maine
9. Maryland
10. Massachusetts
11. Michigan
12. Minnesota
13. New Hampshire
14. New York
15. North Carolina
16. Oregon
17. Rhode Island
18. Utah
19. Vermont
20. Washington
21. Wisconsin

Local Public Health Departments

1. Baltimore (MD)
2. Benton County (OR)
3. Columbus (OH)
4. Dallas County (TX)
5. Houston (TX)
6. Multnomah County (OR)
7. New York City (NY)
8. Portsmouth (VA)
9. Salt Lake County (UT)
10. San Diego County (CA)
11. San Francisco (CA)
12. San Luis Obispo County (CA)
13. Shelby County (TN)
14. Summit County (OH)
15. Toledo-Lucas County (OH)
16. Washington County (MD)
17. Wicomico County (MD)

Stakeholder Groups

1. American Lung Association
2. American Public Health Association
3. Association of State and Territorial Health Officials
4. Council of State and Territorial Epidemiologists
5. George Mason University Center for Climate Change Communication
6. Georgetown Climate Center
7. Health Care Without Harm
8. National Association of County and City Health Officials
9. National Resources Defense Council
10. Public Health Institute
11. Trust for America's Health
12. Yale Climate and Energy Institute
13. Selected Lead Authors of the Third National Climate Assessment's Chapter on Human Health⁹¹

APPENDIX II: SUMMARY OF ACTIONS ANNOUNCED BY THE ADMINISTRATION IN APRIL 2015 TO ADDRESS THE HEALTH IMPACTS OF CLIMATE CHANGE

In April 2015, the administration announced a series of actions and commitments that were intended to enhance the nation's ability to understand, communicate, and reduce the health impacts of climate change.⁹² Specifically, the administration announced the following 12 actions that it plans to take to address this issue:

1. hosting a climate change and health summit at the White House;
2. issuing a report highlighting actions taken by state and local leaders to reduce the impact of climate change on public health;⁹³
3. releasing a health care facilities toolkit consisting of fact sheets, checklists, case studies, and other resources to assist local decision makers in promoting resilient health care infrastructure;⁹⁴
4. circulating a draft climate and health assessment report that is intended to synthesize the best available information on the public health impacts of climate change;⁹⁵
5. holding a community, culture, and mental health workshop to identify factors that enhance resilience to climate change;
6. integrating climate considerations into the Department of the Interior's health and safety policies;
7. hosting a climate and health data challenge, whereby coders, analysts, and researchers will use available government datasets to generate insights into unresolved questions about the health impacts of climate change;
8. offer climate and health data to participants during the national day of civic hacking (June 6, 2015) to encourage participants to develop new climate and health solutions;

9. improving air quality data with the Environmental Protection Agency's release of six new village green stations that measure air quality and meteorological data;
10. challenging researchers to develop new models to forecast epidemics of dengue and other infectious diseases through the consolidation of federal and nonfederal data sets;
11. awarding prizes to those who have developed predictive modeling capabilities that can assist government and health organizations to predict the spread of chikungunya, a vector-borne disease; and
12. measuring nutrient pollution through a competition whereby federal datasets are leveraged to develop educational and decision support resources.

Additionally, the administration announced that it has secured commitments with 14 businesses and other organizations to collect and share data regarding the health impacts of climate change. For example, Microsoft has committed to improve vector-borne disease surveillance capabilities by developing and deploying drones that are capable of collecting large amounts of mosquitos and automatically analyzing them for various pathogens. Finally, the administration announced that a coalition of deans from 30 medical, nursing, and public health schools had committed to train their students to address the health impacts of climate change.

APPENDIX III: SUMMARY OF ACTIONS ANNOUNCED BY THE ADMINISTRATION IN JUNE 2015 TO ADDRESS THE HEALTH IMPACTS OF CLIMATE CHANGE

In June 2015, the administration announced a set of actions and commitments that were intended to protect our communities from the health impacts of climate change.⁹⁶ Specifically, the administration announced the following actions to address this issue:

1. creation of a map tool by the Department of Health and Human Services to improve the ability of health officials and emergency managers to rapidly identify residential areas where people who depend on electricity to power life-critical durable medical equipment live;
2. development of a national integrated heat health information system by the Centers for Disease Control and Prevention and the National Oceanic and Atmospheric Administration, which is intended to provide a suite of decision support resources that better serve public health needs;
3. launch of a climate and health innovation challenge series by the National Institutes of Health and others to promote innovative approaches and highlight technologies available for understanding the health implications of climate change and improving resilience to adverse effects;
4. creation of a climate change impacts subcommittee within the Federal Interagency Working Group on Environmental Justice, and the workgroup's launch of a climate justice initiative that is focused on incorporating equity into climate adaptation planning;

5. announcement of a local climate and energy webcast series on climate change, heat islands, and public health, to be hosted by the Environmental Protection Agency;
6. plans to highlight examples of policy actions related to children's health during national Children's Health Month;
7. a commitment by CDP, a private organization, to release publicly disclosed data from 61 U.S. cities that summarize the climate risks that the cities are facing and the actions they are taking to improve resilience; and
8. an expansion in the number of medical, public health, and nursing schools that have committed to educate and train their students about the risks of climate change to public health.

APPENDIX IV: EXAMPLES OF CLIMATE CHANGE AND HEALTH RESEARCH CONDUCTED OR SUPPORTED BY FEDERAL AGENCIES

Federal agencies conduct or support research on a range of topics that can enhance understanding of the risks that climate change poses to public health. In conducting our work, we interviewed officials from some federal agencies involved in the United States Global Change Research Program's Interagency Crosscutting Group on Climate Change and Human Health. Specifically, we spoke with officials from those agencies whose focus was on understanding climate change risks to populations within the United States. Table 4 provides examples of research some of the federal agencies involved in this group have conducted or supported on or related to the risks that climate change poses to public health.

Table 4. Examples of federal agencies supporting or conducting research on or related to the risks that climate change

Federal agency	Examples of agency actions to support or conduct research
Environmental Protection Agency (EPA)	• Through its Science to Achieve Results program, EPA has made research awards to assess climate change impacts to health, including those related to air and water quality as well as impacts to tribal populations. For example, one project reviewed the relationship between extreme weather events and combined sewer overflows, which can enhance understanding of how climate change may affect risks from water-borne diseases associated with such overflows. Another project assessed a tribe's vulnerability to waterborne disease risks. • EPA has conducted research on how weather events associated with climate change—including heat, flooding and droughts—alter the risk of health impacts associated with air and water pollution, heat exposure, allergens, and water-borne and infectious diseases. For example, the agency's National Health and Environmental Effects Research Laboratory has conducted research on how the combination of air pollutants and elevated temperatures affect human health, including in populations that may be especially sensitive to such effects. • EPA has published information on observed trends in health-relevant indicators of climate change, including changes in high and low temperatures, heat-related mortality, Lyme disease, length of the ragweed pollen season, and extreme weather events.
Department of Health and Human Services (HHS)	• NIH has made research awards on or related to climate change and public health. For example, beginning in FY 2013, NIH made an award for a research project on climate change and heat-related morbidity among vulnerable populations in Atlanta.

Table 4. (Continued)

Federal agency	Examples of agency actions to support or conduct research
National Aeronautics and Space Administration (NASA)	• NASA assisted the New York City Panel on Climate Change in researching the impacts of climate change on New York City and the surrounding metropolitan region, including impacts to public health.
National Oceanic and Atmospheric Administration (NOAA)	• Some of NOAA’s regional research teams (referred to as Regional Integrated Science and Assessment teams) have partnered with local decision makers to provide actionable information related to the health impacts of climate change. For example, the team for the Great Lakes region has worked with local decision makers to develop a tool intended to help decision makers examine options for reducing morbidity and mortality related to extreme heat events in Michigan under changing climate conditions. • NOAA’s Ecological Forecasting Roadmap team partners with federal and state decision makers to integrate climate information into predictions for harmful algal blooms and pathogens such as <i>vibrio parahaemolyticus</i>.
National Science Foundation (NSF) ^a	• Since 2000, NSF has led a collaborative effort with other federal agencies to solicit proposals for research on the ecology and evolution of infectious disease. Among other things, the influence of environmental factors such as climate is listed as a factor that researchers may wish to consider as they design their work. Through this program, NSF made a research award focused on examining why the occurrence of Lyme disease varies significantly across regions of the eastern United States where blacklegged ticks, which transmit the disease to humans, are found. The researchers intended, in part, to help advance predictions of how climate change could impact the risk associated with Lyme disease.
Smithsonian Institution	• Researchers with the Smithsonian Institution have conducted research on the relationship between environmental factors, including rainfall and vegetation cover, and infestations of fleas, which are known vectors for a variety of pathogens, including plague.
U.S. Department of Agriculture	• The Department’s Agricultural Research Service has conducted research on the relationship between climate change and a variety of factors that can impact human health, including crop growth, levels of allergenic plant pollens, food availability, and water quantity.

Source: GAO. | GAO-16-122

^a NSF does not typically make awards for research on the cause, diagnosis, or treatment of physical or mental disease in human beings, as research in these areas is supported by the National Institutes of Health.

APPENDIX V: EXAMPLES OF FEDERAL AGENCY ACTIVITIES ON OR RELATED TO THE PUBLIC HEALTH IMPACTS OF CLIMATE CHANGE

Federal agencies have conducted a range of activities related to understanding, communicating, and managing for the public health impacts of climate change. In conducting our work, we interviewed officials from 26 federal agencies, including some of those involved in the United States Global Change Research Program’s Interagency Crosscutting Group on Climate Change and Human Health. Specifically, we interviewed officials from agencies whose focus was on understanding or managing for climate change risks to populations within the United States. We also interviewed officials from the United States Global Change Research Program and the Council on Environmental Quality. Table 5 provides information about activities conducted by these selected agencies.

Table 5. Examples of Activities Conducted by Selected Federal Agencies on or Related to Public Health Impacts of Climate Change

Department and component agency or office	Summary of work related to climate change and health	Examples of activities
Department of Commerce		
National Oceanic and Atmospheric Administration (NOAA)	Collects and provides data, collaborates in research, and develops decision support resources to aid decision makers in examining and addressing the potential health impacts of climate-related events.	• Develops climate change projections, including those used in the third National Climate Assessment. • Maintains the Climate.gov portal, which includes scientific information and materials about climate change, including impacts to public health. • Works with public health officials through its National Weather Service to revise thresholds for issuing heat alerts, and through its Climate Program Office to understand and provide climate information as part of an integrated heat health information system. • Through its National Weather Service, works with federal, state, and local authorities to support hospital and community preparedness efforts. • Developed the Coastal Flood Exposure Mapper, a tool that allows users to access maps showing populations, places, and natural resources exposed to coastal flood hazards.
Department of Defense		
Defense Health Agency	Routinely assesses and addresses health risks to personnel through disease surveillance activities, including health risks related to extreme heat and cold.	• Plans to review and, as needed, modify health surveillance programs to better integrate climate change considerations into the department's efforts to address health and safety risks to its personnel.
Department of Health and Human Services		
Office of the Assistant Secretary for Health	Coordinates intra- and interagency activities related to climate change and health.	• Plans to develop a climate change communication and outreach strategy. • Held a departmentwide briefing on climate change and health in August 2014.
Assistant Secretary for Preparedness and Response	Leads the department's efforts to prevent, prepare for, and respond to public health emergencies, some of which may stem from climate change	• Leads science preparedness efforts aimed at establishing and sustaining a research framework that communities can leverage to better identify, collect, and analyze data and information that may be available only before, during, or immediately following a public health emergency. • Provides awards for examining the long-term recovery of health systems and communities impacted by Hurricane Sandy. • Provides federal support, including medical professionals, through its National Disaster Medical System, to augment state and local capabilities during an emergency or disaster. • Through its emPOWER map, provides data regarding vulnerable populations that rely upon electricity-dependent medical equipment, to support state, local and community partner emergency planning and response activities.
Centers for Disease Control and Prevention	Works with state and local health departments through a variety of programs to enhance capacity to protect public health, including from the impacts of climate change.	• Through its Climate and Health Program, manages the Climate Ready States and Cities Initiative, which provides awards and technical resources to 18 state and local health departments to incorporate climate change considerations into public health planning, including by implementing a five-step risk management framework.

Table 5. (Continued)

Department and component agency or office	Summary of work related to climate change and health	Examples of activities
		• Supports a network of 26 health departments to collect and make available health, exposure, and hazard data, including on climate change indicators, measures, and data related to extreme heat, through the National Environmental Public Health Tracking Program. • Works with state and local health departments to prepare for and respond to public health emergencies, including by providing awards for emergency preparedness planning to all 50 states, eight territories, and four large cities. • Through its National Institute for Occupational Safety and Health, established a climate change initiative to, among other things, make recommendations for worker safety and health improvements related to climate change. The Institute also seeks to identify workers and facilities at an increased risk to severe weather events.
Indian Health Service	Provides primary health care and disease prevention services to American Indian and Alaska Native people.	• Provided an award to the Alaskan Native Tribal Health Consortium to assess the impacts of climate change on sanitation facilities, including determining data gaps for health- and safety- related parameters.
National Institutes of Health	Funds research on the health impacts of climate change.	• Issued a trans-institute research solicitation in 2010 on the public health impacts of climate change that resulted in awards for 21 new research projects. • Led an ad hoc interagency working group in developing a white paper on research needs for health impacts that may be exacerbated by climate change. • Through its Worker Training Program, hosted a workshop on the health risks that hazardous waste workers face as a consequence of climate change.
Department of Homeland Security		
Office of Health Affairs	Works with communities nationwide to prepare for and respond to emergencies, including by assisting officials in understanding health risks during emergencies.	• Developed a Community Health Resilience Initiative Guide and Toolset, which provides local decision makers with information needed to strengthen community resilience from a variety of impacts, including health impacts related to climate change. • Reviews climate change impacts to its field-based departmental workforce, such as those working for U.S. Customs and Border Protection. • Oversees the National Biosurveillance Integration Center, an interagency center that tracks patterns of disease, disease vectors, food- and water- borne pathogens, among other factors that could influence public health.
Federal Emergency Management Agency	Works to enhance the nation's capability to prepare for, protect against, respond to, recover from, and mitigate all hazards, including by providing data and tools.	• Provides data and tools such as the National Flood Hazard Layer, which allows users to identify base flood elevation and other data that can be used by local decision makers to identify vulnerable populations. • Provides awards to state, local, tribal, and territorial governments to enhance their ability to prevent, respond to, mitigate, and recover from all hazards, including those related to climate change.

Department and component agency or office	Summary of work related to climate change and health	Examples of activities
Department of the Interior		
U.S. Geological Survey	Provides scientific information to describe and understand the Earth and to minimize loss of life and property from natural disasters, among other functions.	• Through its Climate Science Centers, studies the impact of climate change on fish, wildlife, and their habitats to help decision makers address the impacts of climate change, some of which can impact human health and well-being. • Developed the Coastal Vulnerability Index, which provides a preliminary overview, at a national scale, of the relative vulnerability of the nation's coast to sea-level rise, a climate change impact that may affect public health, including mental health in impacted communities. • Provides the Disease Maps Web page, which includes seasonal tracking of seven vector-borne diseases in the United States and territories, including West Nile virus and dengue, which may be impacted by climate change.
Bureau of Indian Affairs	Provides awards for some tribes to conduct climate change adaptation planning, training, and capacity building, which could help these tribes address related risks to public health.	• Provided an award to a regional tribal community partnership in southeast Alaska to monitor beaches and shellfish for toxins from harmful algal blooms.
Office of Insular Affairs	Coordinates federal policy in the territories of American Samoa, Guam, the U.S. Virgin Islands and the Commonwealth of the Northern Mariana Islands.	• Hosted its first stakeholder meeting on climate change in June 2015 for federal officials and leaders from the territories that the office engages with to discuss climate change adaptation efforts in those territories.
Environmental Protection Agency		
	Collects and disseminates environmental data, studies the impact of environmental exposures on human health, and provides decision support resources to state and local decision makers that can assist them in preparing for the impacts of climate change, among other functions.	• Developed a community edition of its Benefits Mapping and Analysis Program, an open-source computer program that helps users estimate the health impacts and economic value of changes in air quality. • Provides awards for Pediatric Environmental Health Specialty Units to educate health professionals and others about environmental health risks, including some that may be exacerbated by climate change. • Provides awards to states and tribes for drinking water and wastewater system projects that can help address some risks from climate change, such as from altered precipitation and runoff patterns. • Worked with the Institute for Tribal Environmental Professionals at Northern Arizona University to develop a national training program and online resources to assist tribal leaders in developing adaptation plans to prepare for the impacts of climate change, including human health impacts.
National Aeronautics and Space Administration (NASA)		
	Through its Applied Sciences Program, partners with public and private organizations on ways to apply agency data in their decision-making activities.	• Collects and analyzes remote sensing data, including data on air quality, extreme weather, biodiversity, and changes in land cover, which may be used by decision makers to assess climate change impacts on health. • Working with NOAA's National Weather Service, provided awards for projects in three U.S. cities to develop more effective heat advisory thresholds by using NASA land surface data to identify extreme hotspots and data about morbidity and mortality to identify neighborhoods at the highest risk for health effects from heat waves.

Table 5. (Continued)

Department and component agency or office	Summary of work related to climate change and health	Examples of activities
National Science Foundation		
	Funds a wide array of scientific research that could be useful in understanding climate change and, less directly, its impacts on human health.	• Provided awards for research on climate change and oceans, such as impacts on rising ocean temperatures and increased ocean acidity resulting from absorption of atmospheric emissions, which alter the characteristics of the most fundamental organisms of the ocean food chain. • Provided awards for research on how people make decisions, including those related to climate change, during times of uncertainty. • Provided awards for research on the ecology and evolution of infectious disease, including research related to the spread of Lyme disease in ticks.
Smithsonian Institution		
	Provides knowledge about nature and culture through research, collections, exhibitions, and education efforts, among other functions.	• Hosted a 1-day symposium in October 2014 on climate and health, among other topics, which included a panel on health in a changing climate. • Planned and organized a June 2014 webinar on food security in the Arctic, which included a discussion of challenges to food security posed by climate change.
U.S. Department of Agriculture		
Office of the Chief Economist	Coordinates the department's responses to climate change.	• Initiated an evaluation of possible changes to the food system, and thus to food security outcomes, as a result of changes in weather and climate, both historically and over the next 25 to 100 years.
Agricultural Research Service	Conducts research on agricultural problems of high national priority, and provides information to ensure high-quality, safe food and assess the nutritional needs of Americans, among other functions.	• Helped support research on improving models for evaluating the effects of climate change and adaptation on crop production, a topic that could be useful for understanding how climate change may affect food availability and prices, which may impact human health.
Animal and Plant Health Inspection Service	Administers the Animal Welfare Act and carries out wildlife damage management activities, among other functions.	• During emergencies, including any that may be caused or exacerbated by climate change, supports the evacuation of people with their pets, which officials told us was essential because some people will not evacuate without their pets.
Economic Research Service	Conducts economic research and provides information related to issues including agriculture, food, and the environment.	• Issues a Cost Estimates of Food-borne Illnesses data product, which includes data about the costs of major food-borne illnesses in the United States, including for illnesses that may increase as a result of climate change.
Forest Service	Aims to achieve quality land management by, among other things, protecting and managing national forests and helping states and communities to use their forests wisely.	• Provides an online climate change resource center for land managers and decision makers interested in learning more about climate change and what they can do. The site focuses on forests and other ecosystems, but includes some information related to human health.
National Institute of Food and Agriculture	Provides leadership and funding for programs that advance agriculture-related sciences.	• Provided awards for basic and applied research related to climate change, such as research on how climate change may affect the water quality functions of on-site wastewater treatment systems, and identifies climate change as a priority research area for research it manages.

Department and component agency or office	Summary of work related to climate change and health	Examples of activities
Natural Resources Conservation Service	Provides farmers and ranchers with financial and technical assistance to voluntarily enact conservation measures.	Through its National Water and Climate Center, monitors and provides information on droughts and water supplies critical for both agricultural and urban uses.
U.S. Global Change Research Program		
	Aims to build a knowledge base that informs human responses to climate and global change through coordinated and integrated federal programs of research, education, communication, and decision support resources.	Included a health chapter in its third National Climate Assessment, published in May 2014, and, through its Interagency Crosscutting Group on Climate Change and Human Health, initiated a scientific assessment of the human health impacts of climate change, a draft of which was released for public comment in April 2015.
Council on Environmental Quality		
	Coordinates federal environmental efforts and works closely with agencies and other White House offices in the development of environmental policies and initiatives.	- Co-chaired the State, Local, and Tribal Leaders Task Force on Climate Preparedness and Resilience, which published a final report in November 2014 that included recommendations for federal action on climate change and public health. - Reviewed federal agencies' climate change adaptation plans, which include information on how climate change could impact the health and well-being of their employees.

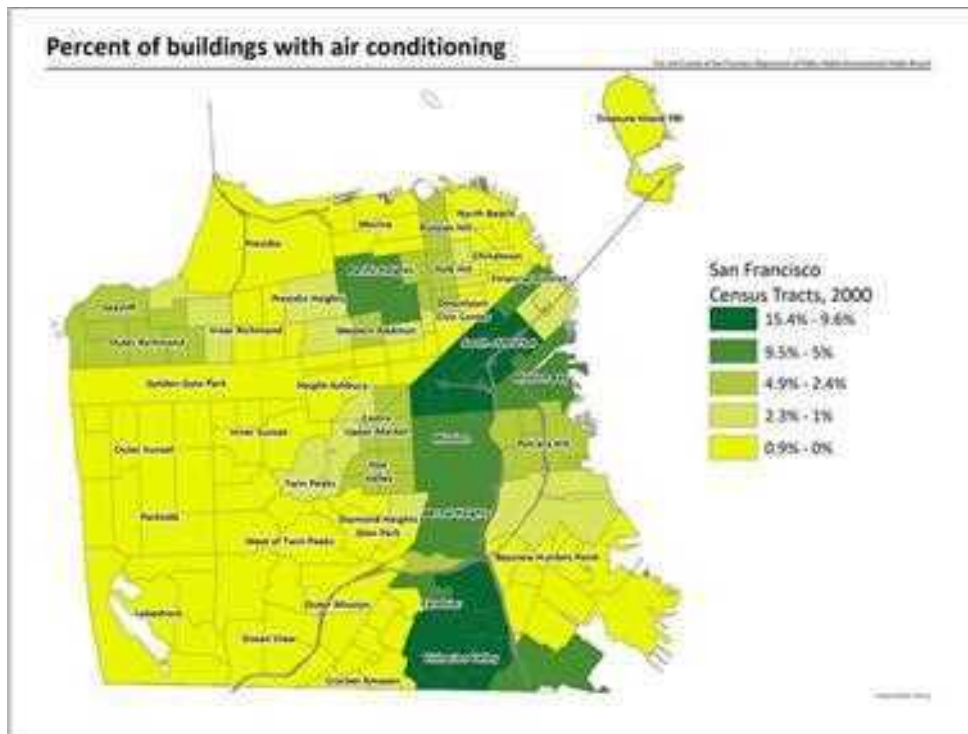
Source: GAO. | GAO-16-122

APPENDIX VI: EXAMPLES OF ACTIVITIES CONDUCTED BY Awardees of CDC's Climate Ready States and Cities Initiative

State and local health officials from the 16 state and two local health departments receiving awards through the Center for Disease Control and Prevention's (CDC) Climate Ready States and Cities Initiative told us that they have conducted a variety of activities to address and plan for the risks that climate change poses to public health. These activities support awardees' efforts to implement CDC's Building Resilience Against Climate Effects (BRACE) framework—a five-step risk management approach intended to help public health departments identify and prepare for the public health impacts of climate change by, among other things, incorporating atmospheric data and climate projections into public health planning. Examples of these activities include the following:

- Developing community vulnerability and resilience indicators.** Awardees have developed indicators to measure community vulnerability and resilience. Florida, for example, developed indicators to identify relationships between measures of social and medical vulnerabilities, such as age and access to health care facilities, with risks to climate-related hazards in the state including hurricane winds and wildland fire.⁹⁷ Officials from the city of San Francisco also created a series of community resilience indicators to provide quantitative measurements of vulnerability to climate change stressors in the city, by neighborhood.⁹⁸ Indicators were developed in a variety of categories, including in areas related to the environment, health, housing, and the

economy, and then mapped by census tract. See figure 4 for an example of a map developed to display areas of vulnerability to extreme heat based on the percentage of buildings with air-conditioning.



Source: San Francisco Department of Public Health (image). | GAO-16-122

Note: According to the San Francisco Department of Public Health, in housing stock without other forms of ventilation, air conditioning can prevent the health effects of extreme heat. Residents in buildings with centralized air conditioning units are at far lesser risk of heat stress. In multiunit buildings without centralized air, personal units often place the financial burden of cooling on low-income residents and incentivize disuse.

Figure 4. Example of a community resilience map illustrating vulnerabilities to extreme heat in San Francisco.

- **Enhancing surveillance.** Some awardees described taking efforts to enhance the amount and type of surveillance data they collect. For example, Vermont developed Web-based tools for the public to report surveillance information related to the spread of ticks and algal blooms. Specifically, through its interactive tick tracker, the public can share information about where and what kinds of ticks have been observed, in order to better prevent the occurrence of tick bites in others.
- **Incorporating climate change into emergency preparedness planning.** Awardees told us that they have incorporated climate change considerations into emergency preparedness planning, such as by developing plans for hazards related to climate change, which can include heat waves or other extreme weather events. For example, Arizona created outreach materials on extreme heat and flooding emergencies to support local health departments. In addition, the state provided technical assistance

to a county to create an extreme weather response plan, which included responding to extreme heat events. Illinois also incorporated climate change considerations into emergency preparedness planning by requiring that local health departments demonstrate that they are planning for an increase in the frequency and severity of extreme weather events in order to obtain public health emergency preparedness funding from the state.

- **Developing communication materials.** Awardees have developed communication materials to share information on the risks that climate change poses to public health in their jurisdictions, such as through websites for their Climate and Health programs. Officials from one county receiving funds through California's Climate and Health Program told us that its jurisdiction developed a climate change communications campaign for the purpose of educating health department staff and the community. As part of this effort, county health officials developed public service announcements to air on county-based radio stations—in English and in Spanish—that explain climate change and health-related topics, such as food, transportation, and energy.
- **Engaging communities.** Awardees described efforts to engage communities, particularly those vulnerable to the risks that climate change poses to public health. For example, officials from New York City described conducting focus groups with seniors and their caregivers to obtain their perspectives on awareness of heat warnings, prevention behaviors, and air-conditioning prevalence and use during heat waves. Officials from San Francisco also reported holding town hall style meetings with community groups from selected neighborhoods to discuss issues related to climate and health, including heat, sea level rise, and vulnerable populations in these specific areas.
- **Partnering with academic institutions.** Awardees reported forming partnerships with academic institutions to, among other things, develop vulnerability assessments and translate climate science information. In some cases, these partnerships were the result of the health department providing a small amount of funding to the university to conduct these assessments, according to officials. For example, officials from Maryland told us that they are collaborating with researchers at the University of Maryland to develop vulnerability assessments and develop county-level projections of the burden of disease from climate change on particular health impacts, such as asthma and waterborne illness. Maryland officials noted the importance of partnering with the University to conduct this work, given the limited resources of the health department and difficulties associated with hiring staff to conduct this assessment.
- **Collaborating with other state or local entities.** Awardees have developed relationships with other state or local departments in conducting activities related to addressing and preparing for the risks that climate change poses to public health. Awardees mentioned that these partnerships help others gain a better perspective of the health impacts of climate change, which will help them to consider health impacts as they make decisions in their respective fields. Awardees also noted that they have shared information with partners or worked collaboratively on projects. For example, officials from the Michigan Department of Community Health reported partnering with the state's Department of Environmental Quality to receive data on topics related to air or water quality. Some awardees also noted the importance of

developing partnerships with their state climatologist to provide their health departments with technical assistance in interpreting climate data.

APPENDIX VII: ACTIVITIES OF OTHER SELECTED STATE AND LOCAL HEALTH DEPARTMENTS RELATED TO PREPARING FOR THE PUBLIC HEALTH IMPACTS OF CLIMATE CHANGE

Officials from some of 13 state and local health departments that we interviewed that have not received an award through the Centers for Disease Control and Prevention's (CDC) Climate Ready States and Cities Initiative have conducted some activities related to addressing and planning for the risks that climate change poses to public health, to the extent that they have resources available.⁹⁹ Some of these state and local health department officials began working on this issue as a result of receiving leadership direction to do so, whereas others did so in the absence of leadership direction, because they believe it is an important issue or because they have identified the need to acknowledge the issue based on knowledge of climate change risks in their jurisdictions.

While some departments have conducted work in this area, others did not have the resources to begin or sustain a robust level of activity. State and local health officials told us that they have few staff to work on such activities, and that those staff also have other assignments and responsibilities. Efforts related to preparing for climate change risks to human health are often conducted in an ad hoc manner compared to those receiving awards through CDC's Climate Ready States and Cities Initiative. Some officials also told us that they have partnered with or received support from academic institutions and nonprofit organizations, which has been beneficial in beginning their work in this area since they have few resources to devote to this issue within their health departments.

State and local health departments not receiving the award that have begun planning for the risks that climate change poses to public health have undertaken activities such as conducting research on health impacts associated with climate change, such as heat-related illness or asthma, participating in workgroups, holding forums to raise awareness, and producing reports. Among the state and local health departments that we interviewed, Alaska and Washington were among those not receiving the CDC initiative award that had undertaken a number of activities directly related to preparing for the public health impacts of climate change.

- **Alaska.** Officials from the Alaska Department of Health and the Alaska Native Tribal Health Consortium—a nonprofit tribal health organization—told us that they have engaged in a number of activities to address and plan for the risks that climate change poses to public health, given that Alaska residents are already seeing climate change impacts to their health and livelihoods. The state's Department of Health is in the early stages of developing a health impact assessment that seeks to identify the potential costs of climate change to health, ways in which to minimize adverse health effects, and ways in which to maximize potential health benefits. The results of this assessment will serve as a baseline for future climate change planning and preparedness activities in the state. Officials from the Department of Health were

also involved in studying an outbreak of *vibrio parahaemolyticus* in July 2004, due, in part, to rising ocean temperatures.¹⁰⁰ The Alaska Native Tribal Health Consortium has also conducted activities related to climate change and health. Through an award provided by HHS's Indian Health Service, the center has conducted assessments to understand the broad range of community impacts from climate change, including changes in disease, mental health, food and water security, and infrastructure. The center is integrating the results of these assessments into construction design, operations, and maintenance considerations for specific health facility improvements, such as new filtration systems for water treatment plants. The center also developed a Local Environmental Observers network, consisting of tribal environmental, natural resources, and health professionals, to enhance monitoring of unusual events that are climate change-related or climate-sensitive. Observations are mapped on a Google maps platform and are communicated through an electronic newsletter to provide information to decision makers on current risks.¹⁰¹

- **Washington.** The Washington State Department of Health has recently started to engage in activities related to climate change and health at the direction of its Secretary of Health, who identified climate change as a priority issue. The department is working to identify how to measure and track the impacts of climate change, particularly in the areas of food, water, and air quality, through its Washington Tracking Network, which is funded by CDC's Environmental Public Health Tracking Network. The department also conducted a survey to characterize local health jurisdiction's perceptions, activities, and needs related to climate change, and compared the results to similar surveys of local health departments on this topic.

APPENDIX VIII: SUMMARY OF HEALTH-RELATED RECOMMENDATIONS MADE BY THE PRESIDENT'S TASK FORCE ON CLIMATE PREPAREDNESS AND RESILIENCE

In November 2013, the President issued Executive Order 13653, *Preparing the United States for the Impacts of Climate Change*, which, among other things, established the State, Local, and Tribal Leaders Task Force on Climate Preparedness and Resilience. The mission of the task force was to provide recommendations to the President and interagency council on how the federal government could, among other things, support state, local, and tribal preparedness for and resilience to climate change.

The task force issued a report to the President in November 2014, noting that the federal government has an essential and unique role to play in preparing for and responding to climate change impacts.¹⁰² Its report includes 35 recommendations to the President across seven themes, and it also listed suggested actions that federal agencies could take to implement the recommendations. The themes addressed in the report are (1) building resilient communities, (2) improving resilience in the nation's infrastructure, (3) ensuring resilience of natural resources, (4) preserving human health and supporting resilient populations, (5) supporting climate-smart hazard mitigation and disaster preparedness and recovery, (6) understanding and acting on the economics of resilience, and (7) building capacity. Table 6

summarizes selected health-related recommendations and suggested actions listed across various themes of the report.

Table 6. Summary of selected health-related recommendations and suggested actions from the President’s state, local and tribal leaders task force report on climate preparedness and resilience

Theme	Recommendation	Examples of suggested actions to address the recommendation
Preserving human health and supporting resilient populations		
	Address the needs of vulnerable populations	• Develop guidance and tools to identify those most at risk the effects of climate change. • Ensure that federal programs that serve vulnerable populations (for example, housing and senior assistance programs) evaluate how climate change will impact needs and service delivery.
	Improve capacity to protect public health	• Expand and build on the Centers for Disease Control and Prevention’s (CDC) Climate-Ready States and Cities Initiative, to include mechanisms for grantees to share their experience and best practices with nongrantees, including all local governments. • Encourage recipients of CDC’s Public Health Emergency Preparedness funding to consider climate change impacts when developing their required vulnerability assessments. • Develop climate-sensitive health tracking and surveillance tools. • Improve awareness of mental health impacts associated with climate change impacts, including by incorporating such impacts in preparedness and response planning.
	Assist communities in building food system security.	• U.S. Department of Agriculture should work with the Department of Health and Human Services and others to support research on climate change-related risks to food supply chains.
	Improve disaster preparedness for communities most at-risk.	• Provide enhanced access to predisaster training on federal response and recovery programs. • Develop health-sensitive extreme weather event warning systems that enhance response activities for at-risk populations.
	Explore the federal role in addressing climate change-related displacement.	• Establish a framework for responding to climate-related displacement.
Building capacity for resilience		
	Increase climate literacy and public awareness.	• Ensure that senior federal health officials such as the U.S. Surgeon General and the Director of CDC draw attention to the public health impacts of climate change. • Coordinate federal communications on climate change to develop clear, consistent, and unified messages, including on the impacts of climate change to human health, and ensure that communications tools are provided to state and local governments.
Ensuring the resilience of natural resources		
	Combat the spread of invasive species, pests, and diseases.	• Increase regional monitoring efforts, including by enhancing related research, identification, interagency coordination, and education efforts.

Source: President’s State, Local and Tribal Leader’s Task Force Report on Climate Preparedness and Resilience, Recommendations to the President (Washington, D.C.: Nov. 17, 2014). | GAO-16-122.

The task force also developed five overarching principles for all federal agencies to consider as a means to advance climate preparedness and resiliency. These include:

1. Require consideration of climate-related risks and vulnerabilities as part of all federal policies, practices, investments, and regulatory or other programs.
2. Maximize opportunities to take actions that have dual benefits of increasing community resilience and reducing greenhouse gas emissions.
3. Strengthen coordination and partnerships among federal agencies, and across federal, state, local, and tribal jurisdictions and economic sectors.
4. Provide actionable data and information on climate change impacts and related tools and assistance to support decision making.
5. Consult and cooperate with tribes and indigenous communities on all aspects of federal climate preparedness and resilience efforts, and encourage states and local communities to do the same.

END NOTES

¹ National Research Council, *America's Climate Choices: Panel on Adapting to the Impacts of Climate Change, Adapting to the Impacts of Climate Change* (Washington, D.C.: 2010); Jerry M. Melillo, Terese (T.C.) Richmond, and Gary W. Yohe, eds., *Climate Change Impacts in the United States: The Third National Climate Assessment*, U.S. Global Change Research Program (Washington, D.C.: May 2014); and K.R. Smith, K.R., et al., *Human Health: Impacts, Adaptation, and Co-Benefits in Climate Change 2014: Impacts, Adaptation, and Vulnerability. Part A: Global and Sectoral Aspects. Contribution of Working Group II to the Fifth Assessment Report of the Intergovernmental Panel on Climate Change* (Cambridge, United Kingdom: 2014). The National Research Council is the principal operating agency of the National Academy of Sciences and the National Academy of Engineering. USGCRP coordinates and integrates the activities of 13 federal agencies that conduct research on changes in the global environment and their implications for the United States. USGCRP began as a presidential initiative in 1989 and was codified in the Global Change Research Act of 1990 (Pub. L. No. 101-606, § 103 (1990)). The act requires USGCRP to periodically prepare a scientific assessment—known as the National Climate Assessment—which is an important resource for understanding and communicating climate change science and impacts in the United States. The Intergovernmental Panel on Climate Change is a scientific body under the auspices of the United Nations that was designed to assess the scientific, environmental, and socioeconomic aspects of climate change.

² World Health Organization, *Quantitative Risk Assessment of the Effects of Climate Change on Selected Causes of Death, 2030s and 2050s* (Geneva, Switzerland: 2014). The World Health Organization directs and coordinates international health within the United Nations system. In this study, WHO modeling and simulation results estimate 240,000 additional deaths worldwide in 2030 due to the health effects of a changing climate.

³ While climate change poses health risks worldwide, this report focuses on the risks that climate change poses to human health within the United States.

⁴ In 2014, the federal government spent \$815 billion on Medicare, Medicaid, and the Children's Health Insurance Program, which provide coverage for the elderly, low-income individuals, and children, respectively. Office of Management and Budget, *Analytical Perspectives, Budget of the United States Government, Fiscal Year 2016* (Washington, D.C.: Feb. 2, 2015).

⁵ During this 16-day heat wave, more than 10 times the number of hospitalizations for heat-related illnesses occurred statewide, and more than 23 times the number of emergency department visits for heat-related illnesses occurred in the most affected region, as had been recorded in 6 days prior and 10 days following the event. One study estimated that this heat wave resulted in nearly \$180 million in additional health care costs. K. Knowlton, et al., "The 2006 California Heat Wave: Impacts of Hospitalizations and Emergency Department Visits," *Environmental Health Perspectives* 117 (2009) and K. Knowlton, et al., "Six Climate Change-Related Events in the United States Accounted for About \$14 Billion in Lost Lives and Health Costs," *Health Affairs* 30, no. 11 (2011).

⁶ GAO, *High-Risk Series: An Update*, GAO-13-283 (Washington, D.C.: Feb. 14, 2013).

⁷ Disease surveillance is the process of reporting, collecting, analyzing, and exchanging information related to cases of infectious diseases. For more information on state and local public health agency activities related to

climate change, see H. Frumkin, et al., “Climate Change: The Public Health Response,” *American Journal of Public Health* 98, no. 3 (2008).

- ⁸ The 2014 assessment summarizes the impacts of climate change on the United States, now and in the future. A team of several hundred experts guided by a 60-member Federal Advisory Committee produced the report, which was extensively reviewed by the public and experts, including federal agencies and a panel of the National Academy of Sciences. The 2010 report, developed by an ad hoc interagency working group on climate change and health, summarizes research needs on the human health effects of climate change. See, Interagency Working Group on Climate Change and Health, *A Human Health Perspective on Climate Change: A Report Outlining the Research Needs on the Human Health Effects of Climate Change*, National Institute of Environmental Health Sciences (Research Triangle Park, N.C.: April 2010).
- ⁹ Specifically, we interviewed officials from 26 federal agencies: Department of Commerce’s National Oceanic and Atmospheric Administration; Department of Defense’s Defense Health Agency, Department of Health and Human Services’ Assistant Secretary for Preparedness and Response, Centers for Disease Control and Prevention, Indian Health Service, National Institutes of Health, and Office of the Assistant Secretary for Health; the Department of Homeland Security’s Federal Emergency Management Agency and Office of Health Affairs; Department of the Interior’s Bureau of Indian Affairs, Office of Insular Affairs, and U.S. Geological Survey; Environmental Protection Agency; National Aeronautic and Space Administration; National Science Foundation, and the U.S. Department of Agriculture’s Agricultural Marketing Service, Animal and Plant Health Inspection Service, Agricultural Research Service, National Institute of Food and Agriculture, Economic Research Service, Forest Service, Natural Resources Conservation Service, and the Office of the Chief Economist, USGCRP, and the Council on Environmental Quality. These agencies include those that participate in USGCRP’s Interagency Crosscutting Group on Climate Change and Human Health and whose focus is on understanding risks to populations within the United States.
- ¹⁰ The American Public Health Association is a national nonprofit organization representing public health officials, whose mission is to improve the health of the public and achieve equity in health status.
- ¹¹ The Georgetown Climate Center, a nonpartisan organization of Georgetown University Law Center, seeks to advance policies that reduce greenhouse gas emissions and help communities adapt to climate change.
- ¹² We did not review governmentwide data on funding for such research because such data were not readily available.
- ¹³ In identifying these examples, we did not limit the scope of our work to a specific time period.
- ¹⁴ Adaptation refers to adjustments to natural or human systems that are made in response to actual or expected climate changes. While our report focuses on activities taken to adapt to the potential health impacts of climate change, federal agencies and others are also involved in climate change mitigation—that is, taking actions to limit the magnitude or rate of climate change. EPA recently reported on the physical and monetary benefits in the United States of global mitigation, including that it is projected to reduce the impact of climate change on air quality and the corresponding adverse health effects related to air pollution, avoiding 57,000 premature deaths in 2100. EPA, *Climate Change in the United States: Benefits of Global Action* (Washington, D.C.: June 2015).
- ¹⁵ ASTHO is a national nonprofit organization representing public health agencies in the United States, the U.S. Territories, and the District of Columbia, and over 100,000 public health professionals these agencies employ. ASTHO’s primary function is to track, evaluate, and advise members on the impact and formation of public or private health policy that may affect them and to provide them with guidance and technical assistance on improving the nation’s health.
- ¹⁶ NACCHO’s mission is to be a leader, partner, catalyst, and voice for the 2,800 local health departments across the United States in order to ensure the conditions that promote health and equity, combat disease, and improve the quality and length of all lives.
- ¹⁷ We conducted one small group discussion session in person with state health department officials during the American Public Health Association’s annual meeting, and we conducted three additional sessions by teleconference with state and local health department officials, to capture the perspectives of those who were unable to attend our in-person session. In total, we conducted three sessions with state health department officials and one session with local health department officials. In addition to working with ASTHO and NACCHO to identify potential participants, we also conducted some targeted recruitment of officials from state and local health departments receiving awards through CDC’s Climate Ready States and Cities Initiative to include these jurisdictions in our small group discussion sessions.
- ¹⁸ We interviewed officials from all 16 states and two cities that were awarded funding through CDC’s Climate Ready States and Cities Initiative—Arizona, California, Florida, Illinois, Maine, Maryland, Massachusetts, Michigan, Minnesota, New Hampshire, New York, North Carolina, Oregon, Rhode Island, Vermont, Wisconsin, as well as New York City and San Francisco. In addition, we interviewed officials from seven local health departments located in states that received the CDC award, including Baltimore (MD), Benton County (OR), Multnomah County (OR), San Diego County (CA), San Luis Obispo County (CA), Washington County (MD), and Wicomico County (MD). We also interviewed officials from five other state and eight other local health departments: Alaska, Hawaii, Louisiana, Utah, and Washington, as well as Columbus (OH),

Dallas County (TX), Houston (TX), Portsmouth (VA), Salt Lake County (UT), Shelby County (TN), Summit County (OH), and Toledo (OH). We interviewed officials from a few state and local health departments twice, through different approaches.

- ¹⁹ The results from our analysis identify the three themes that were commonly reported by a diverse group of state and local health departments. These results are not generalizable to other state and local health departments and do not necessarily include all challenges that public health departments may face.
- ²⁰ National Research Council, *America's Climate Choices: Panel on Adapting to the Impacts of Climate Change, Adapting to the Impacts of Climate Change* (Washington, D.C.: 2010); and Melillo, Richmond, and Yohe, eds., *Climate Change Impacts in the United States: The Third National Climate Assessment*.
- ²¹ Because of greenhouse gases already in the atmosphere, another 0.5 degree Fahrenheit increase would occur even if all emissions from human activities were suddenly stopped, according to USGCRP's third NCA.
- ²² Chikungunya is a viral disease spread to people by the bite of infected mosquitoes. According to CDC, the first locally acquired cases of chikungunya were reported in Florida in 2014. Dengue is caused by any one of four related viruses transmitted by mosquitoes. According to CDC, dengue is endemic to Puerto Rico and the Pacific Islands, and occurs only infrequently in the United States. Lyme disease is a bacterial disease that is transmitted to humans through the bite of infected blacklegged ticks. Most Lyme disease cases reported to CDC through national surveillance are concentrated heavily in the Northeast and upper Midwest. West Nile virus is most commonly transmitted to humans by mosquitoes. According to CDC, the virus has been detected in all of the 48 contiguous United States, but not in Hawaii or Alaska.
- ²³ For example, Native American communities' vulnerabilities to climate change impacts are exacerbated by poor socioeconomic conditions, according to USGCRP's third NCA.
- ²⁴ EPA, *Climate Change and Children's Health* (Washington, D.C.: December 2009). In a prior report, we noted that as children's bodies are still developing, they can be more vulnerable than adults to certain environmental hazards, including air pollutants. See GAO, *Environmental Health: EPA Has Made Substantial Progress but Could Improve Processes for Considering Children's Health*, GAO-13-254 (Washington, D.C.: Aug. 12, 2013).
- ²⁵ Each of the 50 states has a state health department and according to NACCHO, about 2,800 local health departments exist across the nation, including those that function at the city, county, or multicounty level.
- ²⁶ Decision support resources—including tools and decision-making frameworks—can help decision makers to understand and apply scientific information to a particular scenario, and identify and assess the costs and benefits of taking various actions, among other things.
- ²⁷ Implementing resilience measures creates additional up-front costs but could also confer benefits, such as a reduction in future damages from climate-related events. See GAO, *Budget Issues: Opportunities to Reduce Federal Fiscal Exposures Through Greater Resilience to Climate Change and Extreme Weather*, GAO-14-504T (Washington, D.C.: July 29, 2014).
- ²⁸ Executive Order 13514, *Federal Leadership in Environmental, Energy, and Economic Performance* (Oct. 5, 2009). This Executive Order was revoked by Executive Order 13693 on March 19, 2015; however, an Executive Order issued in 2013 directed agencies to continue developing, updating, and implementing agency adaptation plans. Executive Order 13653, *Preparing the United States for the Impacts of Climate Change* (Nov. 1, 2013).
- ²⁹ The Council on Environmental Quality coordinates federal environmental efforts and works with agencies and other White House offices in the development of environmental policies and initiatives.
- ³⁰ *Instructions for Implementing Climate Change Adaptation Planning in Accordance with Executive Order 13514 "Federal Leadership in Environmental, Energy, and Economic Performance,"* (Mar. 4, 2011).
- ³¹ *The President's Climate Action Plan* (June 2013).
- ³² Executive Order 13653, *Preparing the United States for the Impacts of Climate Change* (Nov. 1, 2013).
- ³³ The task force consisted of 26 governors, mayors, county officials, and tribal leaders from across the United States, and was co-chaired by the Chair of the White House Council on Environmental Quality and the Director of the White House Office of Intergovernmental Affairs.
- ³⁴ The recording of the summit is available online at [https:// www.whitehouse.gov/ blog/ 2015/ 06/18/public-health-climate-summit](https://www.whitehouse.gov/blog/2015/06/18/public-health-climate-summit).
- ³⁵ Additional federal agencies participating in the CCHHG are the U.S. Departments of Agriculture, Defense, Interior, State; EPA; National Aeronautics and Space Administration; the Smithsonian Institution; and the U.S. Agency for International Development.
- ³⁶ Examples of funded projects include a study examining the health risks of heat and air pollution, and a study examining the impacts of extreme heat on inner-city minority children with asthma and older adults with chronic obstructive pulmonary disease.
- ³⁷ The funding opportunity for exploratory research was issued in 2010 by National Institute of Environmental Health Sciences with the participation of the Fogarty International Center, National Cancer Institute, National Center on Minority Health and Health Disparities, National Heart, Lung, and Blood Institute, National Institute on Aging, National Institute on Biomedical Imaging and Bioengineering, National Institute of Child

Health and Human Development, National Institute of General Medical Sciences, National Library of Medicine, and the Office of Behavioral and Social Sciences Research.

- ³⁸ NIH reported awarding a total of about \$28 million for research on the health impacts of climate change for fiscal year 2011 through fiscal year 2014, which includes nearly all of the projects funded through the NIH solicitation for research proposals, as well as other unsolicited research. For this period, NIH also reported awarding about \$579 million for research on exposures or conditions that are related to climate, such as research on melanoma. Because these categories are not mutually exclusive, funding for some research is included in both groups.
- ³⁹ An indicator is an observation or calculation that allows scientists, analysts, decision makers, and others to track environmental trends, understand key factors that influence the environment, and identify effects on ecosystems and society.
- ⁴⁰ Institutes of Medicine, *Climate Change, the Indoor Environment, and Health* (Washington, D.C.: 2011).
- ⁴¹ Executive Order 13653 directed the establishment of a data.gov portal on climate issues. The portal's theme page on climate and health is available online at <http://www.data.gov/climate/humanhealth/>.
- ⁴² The network—which is part of CDC's National Environmental Public Health Tracking Program—is a system of integrated health, exposure, and hazard information and data from a variety of national, state, and city sources. CDC makes awards to 26 state and local health departments to develop local tracking networks, which feed into the national network.
- ⁴³ The U.S. Climate Resilience Toolkit was developed in 2014 by a partnership of federal agencies and organizations in response to the President's Climate Action Plan and Executive Order 13653. The toolkit's page on human health is available online at <http://toolkit.climate.gov/topics/human-health>.
- ⁴⁴ EPA's tool, Virtual Beach, helps users to predict levels of disease causing pathogens such as *Escherichia coli* and enterococci at freshwater and saltwater beaches.
- ⁴⁵ G.D. Marinucci, et al., "Building Resilience Against Climate Effects—A Novel Framework to Facilitate Climate Readiness in Public Health Agencies," *International Journal of Environmental Research and Public Health* 11, no. 6 (2014).
- ⁴⁶ Centers for Disease Control and Prevention, *Assessing Health Vulnerability to Climate Change: A Guide for Health Departments* (2014).
- ⁴⁷ The communication toolkit, entitled "Climate Change, Extreme Heat, and Health: A Tool Kit," is available online at http://ephtracking.cdc.gov/docs/CDC_ClimateChange_Final.pdf.
- ⁴⁸ Melillo, Richmond, and Yohe, eds., *Climate Change Impacts in the United States: The Third National Climate Assessment*.
- ⁴⁹ G. Luber, et al., Ch. 9: Human Health. *Climate Change Impacts in the United States: The Third National Climate Assessment*, J.M. Melillo, Terese (T.C.) Richmond, and G. W. Yohe, eds. U.S. Global Change Research Program (Washington, D.C.: U.S. Government Printing Office, 2014).
- ⁵⁰ Additional information about USGCRP's Climate and Health Assessment can be found at <http://www.globalchange.gov/health-assessment>.
- ⁵¹ American Public Health Association, *Adaptation in Action: Grantee Success Stories from CDC's Climate and Health Program* (Washington, D.C.: March 2015).
- ⁵² For example, CDC's website includes information on climate change effects on health; see <http://www.cdc.gov/climateandhealth/effects/default.htm>. In addition, EPA has posted information about climate impacts to human health to its Facebook page; see <https://www.facebook.com/EPA/videos/vb.39637302228/10152857564172229/?type=2&theater>.
- ⁵³ This briefing is available online at <http://videocast.nih.gov/summary.asp?Live=14490&bhcp=1>.
- ⁵⁴ This presentation is available online at <http://www.cdc.gov/cdcgrandrounds/archives/2014/december2014.htm>.
- ⁵⁵ EPA, "Speeches by Date," Administrator Gina McCarthy, *Keynote Remarks at the University of Michigan Environmental Law and Public Health Conference, As Prepared*, <http://yosemite.epa.gov/opa/admpress.nsf/8d49f7ad4bbcf4ef852573590040b7f6/ac6b9218ba9e1e2885257bf2005a41cb1?OpenDocument> (accessed April 2, 2015).
- ⁵⁶ In conducting this work, we spoke with officials from all 18 health departments receiving the award—who we refer to as awardees—about the activities they have conducted related to climate change and public health.
- ⁵⁷ In fiscal year 2014, individual awards ranged from \$173,000 to \$250,000. According to CDC officials, funding for awardees varies by award cycle, as awardees are funded under two cooperative agreement mechanisms—a fiscal year 2012 agreement funded 8 awardees for 4 years, through fiscal year 2016, and a fiscal year 2013 agreement funded 10 awardees for 3 years, through fiscal year 2016.
- ⁵⁸ Officials from CDC's Climate and Health Program told us that they make information about the BRACE framework available on the program's website and through a peer-reviewed journal article. See <http://www.cdc.gov/climateandhealth/brace.htm> and G.D. Marinucci, et al., "Building Resilience against Climate Effects—A Novel Framework to Facilitate Climate Readiness in Public Health Agencies," *International Journal of Environmental Research and Public Health* 11, no.6 (2014).

- ⁵⁹ See Centers for Disease Control and Prevention, *Climate Models and the Use of Climate Projections: A Brief Overview for Health Departments* (2014), and Centers for Disease Control and Prevention, *Assessing Health Vulnerability to Climate Change: A Guide for Health Departments* (2014).
- ⁶⁰ CDC also makes some of these resources available on its Climate and Health Program website, see http://www.cdc.gov/climateandhealth/site_resources.htm.
- ⁶¹ According to CDC officials, as of May 2015, there are five communities of practice, related to vector-borne diseases, water-borne diseases, conducting vulnerability assessments, developing disease projections, and developing evaluation plans.
- ⁶² According to officials from the New York City Department of Health and Mental Hygiene, a Heat Health Watch and Warning System uses daily forecasts of the dominant local weather pattern to calculate predicted excess deaths from periods of excessive heat based on location-specific historical data.
- ⁶³ CDC's National Environmental Public Health Tracking Network Reporting Tool is available online at <http://ephrtracking.cdc.gov/QueryPanel/EPHTNQuery/EPHTQuery.html?c=-1&i=-1&m=-1>.
- ⁶⁴ Specifically, these indicators use historical weather and health data to identify extreme temperatures, extreme heat days and events, deaths that might be related to heat, and conditions that make people vulnerable to heat. They also project future extreme heat events to help estimate the burden of heat-related illness in the next century. Data for these indicators and associated measures are available at the national, state, or county level, depending on the indicator and measure. According to CDC officials, the program is planning to adopt additional climate change-related indicators in the future.
- ⁶⁵ The program made 26 awards to state and local programs in fiscal year 2014 for a 3- year award cycle. Thirteen of the 18 Climate Ready States and Cities Initiative awardees also received National Environmental Public Health Tracking Network awards in fiscal year 2015.
- ⁶⁶ CDC's Public Health Emergency Preparedness program makes awards to public health departments in all 50 states, four major metropolitan areas (Chicago, Los Angeles County, New York City and Washington, D.C.), and eight U.S. territories and freely associated states (American Samoa, Guam, U.S. Virgin Islands, Northern Mariana Islands, Puerto Rico, Federated States of Micronesia, Republic of the Marshall Islands, and Republic of Palau).
- ⁶⁷ Specifically, awardees are required to build and sustain their public health preparedness capabilities according to standards developed by CDC. Awardees are also required to review their preparedness status annually by using information from a variety of sources, such as jurisdictional risk assessments.
- ⁶⁸ Through its State-Based Occupational Health and Safety Surveillance program, the National Institute for Occupational Safety and Health provides awards to 23 states to collect data on occupational safety and health hazards and effects, identify new sources of occupational safety and health data, conduct surveillance, interpret findings, and develop or recommend related interventions. According to officials from the National Institute for Occupational Safety and Health, the program awarded nearly \$6.5 million to state health departments in fiscal year 2014, with individual awards ranging from about \$100,000 to nearly \$900,000. Twelve of the 18 Climate Ready States and Cities Initiative awardees were also awardees of the State-Based Occupational Health and Safety Surveillance program in fiscal year 2014.
- ⁶⁹ NOAA's Regional Integrated Sciences and Assessment teams are university-based research partnerships that help build the nation's capacity to prepare for and adapt to climate variability and change.
- ⁷⁰ GAO, *Climate Change Adaptation: Strategic Federal Planning Could Help Government Officials Make More Informed Decisions*, GAO-10-113 (Washington, D.C.: Oct. 7, 2009).
- ⁷¹ Some awardees of CDC's Climate Ready States and Cities Initiative told us that they have begun to provide briefings or trainings on climate and health issues for departmental staff.
- ⁷² National Association of County and City Health Officials. *Are We Ready? Report 2 Preparing for the Public Health Challenges of Climate Change* (Washington, D.C.: 2014).
- ⁷³ According to our review of this analysis, 22 states have finalized climate change adaptation plans or have such planning underway. See Georgetown Climate Center, *State and Local Adaptation Plans*, <http://www.georgetownclimate.org/adaptation/state-and-local-plans> (accessed May 15, 2015).
- ⁷⁴ See American Public Health Association, *Climate Change Is a Public Health Issue* (Washington, D.C.: 2008), and American Public Health Association, *Climate Change: Our Health in the Balance. National Public Health Week 2008 Partner Toolkit* (Washington, D.C.: 2008).
- ⁷⁵ In our previous work on climate change adaptation, we also found that climate change adaptation is a complicated issue to communicate with the public because the impacts vary by location and may occur well into the future. See GAO-10-113.
- ⁷⁶ While Ebola did not present a significant risk to the U.S. public, two imported cases, and two locally acquired cases in health care workers were reported in the United States. According to ASTHO and NACCHO, state and local health departments worked to enhance preparedness in their jurisdictions, including by collaborating with health care providers in their jurisdictions to ensure they had adequate information on screening, isolating, and diagnosing potential patients, reiterating the importance of infection control procedures for health care givers, working with laboratories to provide guidance on safe handling of specimens, and creating and providing timely and consistent messages for the public about the disease.

- ⁷⁷ President's State, Local, and Tribal Leaders Task Force on Climate Preparedness and Resilience, *Recommendations to the President* (Washington, D.C.: Nov. 17, 2014). The task force was established by Executive Order 13653.
- ⁷⁸ The FrameWorks Institute is an independent nonprofit organization with a mission of advancing the nonprofit sector's communications capacity by identifying, translating and modeling relevant scholarly research for framing the public discourse about social problems. As of August 11, 2015, these fact sheets had not yet been finalized. CDC is providing funding for this effort through a cooperative agreement with the American Public Health Association.
- ⁷⁹ See HHS, *HHS Climate Adaptation Plan 2014* (Washington, D.C., July 3, 2014), p.7. A senior HHS official from HHS component responsible for developing this strategy also told us that the strategy is intended to have multiple goals, including communicating to the general public on the risks that climate change poses to public health, as well as multiple audiences such as health care providers, public health officials, and other decision makers.
- ⁸⁰ See HHS, *Strategic Sustainability Performance Plan* (Washington, D.C.; July 17, 2014), p.50.
- ⁸¹ Centers for Disease Control and Prevention, *Climate Change, Extreme Heat, and Health: A Tool Kit*, http://ephtracking.cdc.gov/docs/CDC_ClimateChange_Final.pdf (accessed May 1, 2015).
- ⁸² CDC has issued a document that describes the risks posed by extreme heat events, and includes some information that could be used in developing communications to the public about heat. However, this document is not focused on how to communicate on a broader level about the risks climate change poses to public health. Centers for Disease Control and Prevention, *Climate Change and Extreme Heat Events*, <http://www.cdc.gov/climateandhealth/pubs/ClimateChangeandExtremeHeatEvents.pdf> (accessed July 16, 2015).
- ⁸³ The program has also identified priority actions to meet these core functions, such as communicating the health-related aspects of climate change, including risks and ways to reduce those risks, to the public, decision makers, and healthcare providers.
- ⁸⁴ According to HHS officials, geographic information systems can be used to overlay public health disease data with climatic datasets, such as temperature and precipitation information, to determine if associations exist.
- ⁸⁵ We previously reported that future federal adaptation efforts could better focus on providing local climate change assistance, including with regard to translating climate data for decision makers. See GAO, *Climate Change: Future Federal Adaptation Efforts Could Better Support Local Infrastructure Decision Makers*, GAO-13-242 (Washington, D.C.: Apr. 12, 2013).
- ⁸⁶ Interagency Working Group on Climate Change and Health, *A Human Health Perspective on Climate Change: A Report Outlining the Research Needs on the Human Health Effects of Climate Change*.
- ⁸⁷ C. Jessup, et al., "Climate Change, Human Health, and Biomedical Research: Analysis of the National Institutes of Health Research Portfolio," *Environmental Health Perspectives* 121, no. 4 (2013).
- ⁸⁸ Among other things, the authors noted that research in this area requires multidisciplinary teams that can include meteorologists, climatologists, mathematicians, statisticians, computational scientists, and a diversity of health scientists, and most researchers are not cross-trained to meet these needs.
- ⁸⁹ The goals of the assessment, which is expected to be finalized in 2016, are to summarize the state of the science for climate change impacts to health, and to quantitatively assess observed and projected impacts for selected impacts. Release of this report and other federal actions discussed here were taken after we met with and obtained most information from state and local public health officials for this report. 80 Fed. Reg. 18619 (Apr. 7, 2015).
- ⁹⁰ National Association of County and City Health Officials. *Are We Ready? Report 2 Preparing for the Public Health Challenges of Climate Change* (Washington, D.C.: 2014).
- ⁹¹ Each of the individual chapters of the third National Climate Assessment were developed by a team of convening lead authors and lead authors.
- ⁹² The White House, "Administration Announces Actions To Protect Communities From The Impacts Of Climate Change" (Washington, D.C.: Apr. 7, 2015).
- ⁹³ American Public Health Association, *Adaptation in Action: Grantee Success Stories from CDC's Climate and Health Program* (Washington, D.C.: March 2015).
- ⁹⁴ The Sustainable and Climate Resilient Health Care Facilities Toolkit is available online at <http://toolkit.climate.gov/tool/sustainable-and-climate-resilient-health-care-facilities-toolkit>.
- ⁹⁵ The draft assessment report was published for public comment in April 2015. 80 Fed. Reg. 18619 (Apr. 7, 2015).
- ⁹⁶ The White House, "Fact Sheet: Obama Administration Announces Actions to Protect Communities from the Health Impacts of Climate Change at White House Summit" (Washington, D.C.: June 23, 2015).
- ⁹⁷ See C. Emrich, D. Morath, G. Bowser, R. Reeves, *Climate-Sensitive Hazards in Florida: Identifying and Prioritizing Threats to Build Resilience against Climate Effects*. <http://www.floridahealth.gov/environmental-health/climate-and-health/documents/climate-sensitive-hazards-in-florida-final-report.pdf> (accessed September 10, 2014).
- ⁹⁸ See San Francisco Department of Public Health. San Francisco Climate & Health Profile. http://www.sfclimatehealth.org/wp-content/uploads/2015/01/SFDPH_ClimateHealth_Profile_FinalDraft.pdf (accessed April 15, 2015). According to officials from San Francisco, information sources used to develop the indicators

included data from the U.S. Census Bureau and the American Community Survey, and many of the indicators are based on those established by the University of South Carolina's Social Vulnerability Index, which measures the social vulnerability of U.S. counties to environmental hazards. Data used in the development of the indicators were also made available for researchers, decision makers, and the public, in an effort to promote transparency and encourage the development of tools to address climate change.

⁹⁹ According to these officials, resources used to conduct this work include federal and state funding sources, as well as partnerships with academic institutions or nongovernmental organizations.

¹⁰⁰ Specifically, in July 2004, over 60 passengers aboard cruise ships near Alaska became ill after eating raw oysters, resulting in one of the largest known outbreaks of *vibrio parahaemolyticus* ever reported in the United States. During this outbreak, Department of Health officials worked to study the disease and process oyster samples, and later published the results of their study. See J. McLaughlin, et al., "Outbreak of *Vibrio parahaemolyticus* Gastroenteritis Associated with Alaskan Oysters," *The New England Journal of Medicine* 353, no. 14 (2005).

¹⁰¹ The Local Environmental Observers network was developed by the Alaska Native Tribal Health Consortium's Center for Climate and Health with funding from EPA and the Western Alaska Landscape Conservation Cooperative—a partnership of federal agencies and other stakeholders addressing climate change impacts on the nation's landscapes.

¹⁰² President's State, Local, and Tribal Leaders Task Force on Climate Preparedness and Resilience, *Recommendations to the President* (Washington, D.C.: Nov. 17, 2014). The task force terminated 6 months after it provided its recommendations. In July 2015, the administration issued a progress report, providing examples of federal actions taken to address these recommendations. The White House, *Progress Report: Highlighting Federal Actions Addressing the Recommendations of the State, Local, and Tribal Leaders Task Force on Climate Preparedness and Resilience* (Washington, D.C.: July 2015).

Chapter 537

**TESTIMONY OF ANTHONY S. FAUCI,
DIRECTOR, NATIONAL INSTITUTE OF ALLERGY AND
INFECTIOUS DISEASES, NATIONAL INSTITUTES OF
HEALTH. HEARING ON “EXAMINING THE U.S.
PUBLIC HEALTH RESPONSE TO THE ZIKA VIRUS”***

Mr. Chairman, Ranking Member DeGette, and Members of the Subcommittee:

Thank you for the opportunity to discuss the National Institutes of Health (NIH) research response to Zika virus, an emerging public health threat of international concern. I direct the National Institute of Allergy and Infectious Diseases (NIAID), the lead NIH institute for conducting and supporting research on emerging and re-emerging infectious diseases, including those caused by flaviviruses such as Zika virus.

The Administration is taking appropriate action to protect the American people and, as you know, it announced a request to Congress for approximately \$1.9 billion in emergency funding to enhance ongoing efforts to prepare for and respond to outbreaks of the Zika virus, both domestically and internationally. This includes funding for work on the development of vaccines and diagnostics and to improve scientific understanding of the disease.

The overarching mission of NIAID is to conduct and support research to better understand, treat, and prevent infectious and immunologic diseases. This is accomplished through a spectrum of research, from basic studies of the mechanisms of disease to applied research focused on developing interventions such as diagnostics, therapeutics, and vaccines. As part of this mission, NIAID has a dual mandate encompassing both research on ongoing public health issues and the capability to respond rapidly to newly emerging and re-emerging infections such as Zika virus.

These emerging and re-emerging disease threats, whether man-made or naturally occurring, are perpetual challenges, in part due to the capacity of microbial pathogens to evolve rapidly and adapt to new ecological niches. To address the challenges posed by

* This is an edited, reformatted and augmented version of testimony presented March 2, 2016 before the House Committee on Energy and Commerce, Subcommittee on Oversight and Investigations.

emerging infectious diseases, NIAID employs both targeted, disease-specific research as well as broad-spectrum approaches. NIAID maximizes its efforts by prioritizing the development of drugs effective against multiple bacteria or viruses, and “platform” technologies to facilitate rapid development of vaccines and diagnostics applicable to multiple infections.

NIAID is well-positioned to rapidly respond to infectious disease threats as they emerge by leveraging fundamental, basic research efforts; domestic and international research infrastructure that can be quickly mobilized; and productive partnerships with industry. NIAID provides preclinical research resources to scientists in academia and private industry worldwide to advance translational research against emerging and re-emerging infectious diseases. These resources are designed to bridge gaps in the product development pipeline and lower the scientific, technical, and financial risks incurred by industry in order to incentivize them to partner with us in the advanced development of effective countermeasures. NIAID also supports our Vaccine and Treatment Evaluation Units (VTEUs), a research network that conducts clinical trials to quickly investigate promising therapeutic and vaccine candidates when public health needs arise. NIAID collaborations with other federal agencies, including those undertaken within the Department of Health and Human Services (HHS) Public Health Emergency Medical Countermeasures Enterprise (PHEMCE), help advance progress against newly emerging public health threats. In addition, partnerships with academia, the biotechnology and pharmaceutical industries, and international researchers and organizations such as the World Health Organization (WHO) and WHO’s regional office, the Pan American Health Organization (PAHO), are integral to these efforts.

OVERVIEW OF ZIKA VIRUS

Zika virus is a flavivirus. These viruses typically are transmitted by mosquitoes and often have the ability to spread quickly to new geographic locations because of the widespread prevalence of these vectors. Other well-known flaviviruses include dengue virus and yellow fever virus; like Zika virus they are transmitted by *Aedes* mosquitoes. Zika virus was discovered in monkeys in Uganda in 1947 and is now endemic to Africa and Southeast Asia. During the past decade it has emerged in other areas of the world, including Oceania, the Caribbean, and Central and South America, where countries, notably Brazil, are currently experiencing unprecedented Zika transmission.

Infections caused by Zika virus are usually asymptomatic. About 20 percent of infected individuals experience clinical symptoms such as fever, rash, joint pain, and conjunctivitis (red eyes). Symptoms of Zika virus infection in humans are typically mild and brief, with very low hospitalization and fatality rates. The recent outbreak of Zika virus disease in Brazil has coincided with a reported increase in the number of infants born with microcephaly, a birth defect characterized by an abnormally small head resulting from an underdeveloped and/or damaged brain. In addition, increases in suspected cases of Guillain-Barré syndrome (GBS), a rare, acute, immune-mediated peripheral nerve disease that leads to weakness, sometimes paralysis, and infrequently, respiratory failure and death, have been noted in Brazil and other countries in the Americas.

Further research is needed to better understand the effect of Zika virus infection on the body, particularly during pregnancy; to investigate the potential relationship between Zika infection and congenital abnormalities including microcephaly, as well as to explore the potential relationship between Zika infection and GBS; and to develop better diagnostics, vaccines and treatments, and new methods of vector control. Currently, no vaccines or specific therapeutics are available to prevent or treat Zika virus disease. Improved diagnostic tests also are needed because Zika virus infection causes non-specific symptoms or no symptoms at all and can be difficult to distinguish by antibody screening tests from other mosquito-borne infections such as dengue, malaria, and chikungunya. Moreover, current antibody screening tests can be falsely positive or inconclusive if the individual was previously infected with related viruses such as dengue, which is prevalent in South America and the Caribbean. Therefore, a positive result with the antibody screening test requires an additional test to confirm the diagnosis.

NIH RESEARCH ON ZIKA VIRUS

NIAID has a longstanding commitment to flavivirus research, including extensive efforts to combat diseases such as dengue, West Nile virus, and yellow fever. This research has informed our understanding of the viral genetics, vector biology, and pathogenesis of flaviviruses and provides a strong foundation for our efforts to learn more about Zika virus. NIAID has responded to the newly emerging Zika virus disease outbreak by expanding our portfolio of basic research on Zika virus and other flaviviruses. NIAID also is accelerating efforts to develop improved diagnostics and candidate therapies for Zika virus as well as prioritizing the development of Zika virus vaccines. In addition, screening tests and pathogen reduction technologies are critically important to assure safety of the U.S. blood supply.

The emergency funding for NIH would support development of vaccines to prevent Zika virus infection, from the discovery phase through preclinical and eventually clinical testing. In addition, the funds would support basic research to understand the natural history, viral biology and pathogenesis, including potential links to microcephaly; establishment of animal models to test candidate countermeasures; development of rapid, sensitive, and specific diagnostic tests; and discovery and preclinical development of new therapeutics to treat disease caused by Zika virus. This research is necessary to better understand this emerging infection and uncover the best ways to diagnose, treat, and prevent Zika virus disease.

In January 2016, NIAID issued a notice to researchers highlighting NIH's interest in supporting research and product development to combat Zika virus. Areas of high priority include basic research to understand viral replication, pathogenesis, and transmission, as well as the biology of the mosquito vectors; potential interactions with co-infections such as dengue and yellow fever viruses; animal models of Zika virus infection; and novel vector control methods. In addition, NIH is soliciting Zika virus research to develop sensitive, specific, and rapid clinical diagnostic tests; drugs against Zika virus as well as broad spectrum therapeutics against multiple flaviviruses; and effective vaccines and vaccination strategies.

NIAID also is partnering with other NIH institutes, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), the National Institute of Neurological Disorders and Stroke (NINDS), and the National Institute of Dental and

Craniofacial Research, to accelerate Zika virus research as it relates to the mother-infant pair. The Institutes issued a notice that indicates NIH's interest in supporting research to understand transmission, optimal screening and management in pregnancy, and the mechanisms by which Zika virus affects the developing nervous system, including potential links to microcephaly and other congenital abnormalities.

DEVELOPING TOOLS TO COMBAT ZIKA VIRUS

In response to public health concerns about Zika virus, NIAID has accelerated ongoing flavivirus research efforts to speed the development of tools that could help control current and future outbreaks of Zika virus.

Vector Control

For many years, NIAID has supported extensive research to understand the biology of mosquitoes to help develop tools to limit the spread of deadly mosquito-borne diseases such as dengue and malaria. This research aids in vector control strategies to reduce mosquito bites or limit mosquito populations. In the Americas, Zika virus is transmitted primarily by *Aedes aegypti* mosquitoes, and vector control or other methods to prevent exposure to these mosquitoes are currently the only ways to prevent Zika infection. NIAID plans to support vector competence studies to test various mosquito species for their ability to carry and transmit Zika virus and for insecticide resistance. Understanding the specific mosquito species involved in Zika outbreaks and which insecticides may be effective against them will aid current vector control efforts and may inform novel mosquito control strategies in the future.

Diagnostics

Accurate diagnostic tests for Zika virus infection are needed to distinguish it from other flavivirus infections and to identify women who have been infected with Zika virus during pregnancy and may be at risk for developing fetal complications. Blood, organ, and tissue donor screening tests are also needed to assure the safety of transfusion and transplantation in areas of active mosquito-borne virus transmission. Currently, Zika virus itself can often be detected during the acute phase of infection and up to seven days after the onset of symptoms using diagnostic tests for viral RNA (RT-PCR test). While prior infection can be detected by testing for the presence of antibodies against Zika virus, assays for Zika antibodies may also detect or cross-react with antibodies against other flaviviruses, particularly dengue virus. For this reason, a positive antibody test does not definitively confirm prior Zika virus infection in the setting of possible co-infection or prior infection with dengue and other related viruses, and separate confirmatory testing is required. This is a particular concern in South America where there is a high level of exposure to other flaviviruses, particularly dengue virus.

To facilitate the development of improved Zika virus diagnostic tests, NIAID grantees are working to generate antibodies that can distinguish between Zika virus and dengue virus. They also are working to identify biosignatures unique to Zika infection that could form the basis of additional rapid, specific, and sensitive diagnostic tests. In addition, NIAID is pursuing the development of a mouse model of Zika virus infection that could be used to test new diagnostic and therapeutic tools.

Vaccines

A safe and effective Zika vaccine would be a very valuable tool to help stop the spread of infection and prevent future outbreaks. NIAID is investigating multiple Zika virus vaccine candidates, including vaccines based on technologies that have shown promise in targeting other flaviviruses. The NIAID Vaccine Research Center (VRC) is pursuing a DNA-based vaccine for Zika virus that is similar to a West Nile virus vaccine previously developed by NIAID. The West Nile vaccine candidate was shown in Phase 1 testing to be safe and generated a strong immune response in humans, offering a model for Zika vaccine development. NIAID scientists also are designing a live, attenuated vaccine, using an approach similar to that used for making a vaccine against the closely related dengue virus. The dengue vaccine candidate showed an excellent safety profile and generated strong immune responses in early-phase clinical trials. In January, a large Phase 3 trial assessing the dengue vaccine candidate was launched in Brazil in collaboration with the Butantan Institute. In addition, NIAID grantees are in the early stages of developing a Zika virus vaccine based on a recombinant vesicular stomatitis virus – the same animal virus used successfully to create an investigational Ebola vaccine. Plans are underway to evaluate this potential vaccine construct in tissue culture and animal models.

While these approaches are promising, it is important to realize that the development of investigational vaccines and the clinical testing to establish whether they are safe and effective takes time. Although a safe and effective, fully licensed Zika vaccine will likely not be available for a few years, we plan to begin early-stage clinical testing of one or more NIAID-supported vaccine candidates in 2016.

Therapeutics

NIAID has an active program to screen for antiviral drugs active against viruses in the flavivirus family, including dengue, West Nile, yellow fever, and Japanese encephalitis viruses, as well as the closely related hepatitis C virus. NIAID has enhanced these efforts with the recent development of an assay to test compounds for antiviral activity against Zika virus. NIAID will make this test available to the research community and will soon test 10 antiviral compounds with activity against other flaviviruses to determine if they are effective against Zika virus. Promising drug candidates identified by the assay could be further tested in a small animal model of Zika virus infection developed with NIAID support. The ultimate goal of NIAID-supported flavivirus therapeutic research is to develop a broad-spectrum antiviral drug that could be used against a variety of flaviviruses, including Zika.

Emergency Request for Vaccine Research and Diagnostic Development and Procurement

As I noted in the introduction to my testimony, the Administration has announced an emergency funding request of approximately \$1.9 billion to combat the Zika virus both domestically and internationally. Included in the request are resources for Zika-related vaccine research, rapid advanced development, and commercialization of new vaccines and diagnostic tests for Zika virus. The funding will allow NIH to build upon existing resources and work to develop a vaccine for Zika virus and the chikungunya virus, which is spread by the same type of mosquito. Funding will accelerate this work and improve scientific understanding of the disease to inform the development of additional tools to combat it. The request also includes resources for FDA to support Zika virus medical product development, including the next-generation diagnostic devices. We look forward to working with the Congress to implement this request.

COLLABORATIONS

Investigation of emerging and re-emerging infectious diseases requires expertise from a variety of fields. In the case of Zika virus, studies of virology, immunology, natural history, neurology, and neonatology will be required to fully understand the pathogenesis of this infection. As mentioned previously, NIAID is partnering with other NIH institutes including NICHD and NINDS to better understand the potential association between Zika virus infection and neonatal defects, particularly microcephaly.

NIAID also is employing partnerships with research institutions in South America to advance research on Zika virus infection; additional collaborations with academic, industry, and government partners are under active exploration. NIAID held a joint meeting in December 2015 with Brazilian research institute Fiocruz in which Zika was a key area of concentration. In addition, NIAID is collaborating with other HHS agencies in responding to the Zika epidemic. For example, NIAID, CDC, BARDA, ASPR, and FDA are jointly convening a Zika virus workshop on March 28-29, 2016, where the latest information on Zika virus will be discussed by experts from Federal Agencies, academia, and pharmaceutical and biotechnology companies. Topics to be addressed at the workshop include virology, epidemiology, possible links to microcephaly, and efforts to develop diagnostics, therapeutics, and vaccines.

CONCLUSION

NIH is committed to continued collaboration with HHS agencies and other partners across the U.S. government in advancing research to address Zika virus infection, and we look forward to working with the Congress to implement the President's emergency funding request. As part of its mission to respond rapidly to emerging and re-emerging infectious diseases throughout the world, NIAID is expanding our efforts to elucidate the biology of

Zika virus and employ this knowledge to develop needed tools to diagnose, treat, and prevent disease caused by this virus. In particular, NIAID will pursue the development of safe, effective vaccines to prevent disease caused by Zika and chikungunya viruses.

Chapter 538

**TESTIMONY OF JOSEPH M. CONLON, TECHNICAL
ADVISOR, AMERICAN MOSQUITO CONTROL
ASSOCIATION. HEARING ON “EXAMINING THE U.S.
PUBLIC HEALTH RESPONSE TO THE ZIKA VIRUS”***

Good morning, Mr. Chairman and Members of the Subcommittee. My name is Joseph Conlon and I am a retired U.S. Navy medical entomologist serving as Technical Advisor for the American Mosquito Control Association (AMCA), a nonprofit organization of 1600 members dedicated to enhancing health and quality of life through the suppression of mosquitoes and other vectors of public health importance. I welcome this opportunity to provide a mosquito control perspective to the deliberations of this committee concerning Zika Virus and will limit my testimony to mosquito management methodologies that contribute to its control.

The introduction and spread of Zika Virus in Central and South America and the Caribbean in 2014 reawakened in the United States an appreciation of mosquitoes as vectors of diseases. I use the term “reawakened” advisedly, for mosquito-borne diseases such as malaria and yellow fever were once quite prevalent in the United States and, indeed, played a major part in shaping our nation’s destiny. These diseases no longer claim victims in the United States as a matter of course largely due to the exemplary efforts of organized mosquito control agencies, in conjunction with an enlightened and effective public health infrastructure. But other mosquito-borne diseases are on the horizon and public health agencies need to be prepared to meet the challenges they present.

Progress continues in defining the transmission dynamics of Zika Virus so as to allow for its prevention and control. However, considering that it is a comparatively recent epidemiological phenomenon, there remains much to learn in order to establish and verify baseline data. The virus is thought to be primarily transmitted from human to human by the bite of infected *Aedes aegypti* and (possibly) *Aedes albopictus* species of mosquitoes. Of these, *Aedes aegypti* has been primarily responsible for transmitting the disease due to its preference to bite humans both day and night and its predilection for biting the lower

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extremities. Moreover, females frequently take multiple partial bloodmeals, often from different individual humans, not only increasing the likelihood of feeding on an infectious human but also leading to single infectious females potentially feeding on and infecting multiple humans within a relatively short time period.

Aedes aegypti and *Aedes albopictus* are notoriously difficult to prevent or kill. They live inside our houses under furniture, beds and in closets; their eggs can withstand months of drying, and their young can develop in water containers as small as a bottle cap. Virtually any collection of stagnant water in containers, treeholes, leaf axils, etc. can serve as egg-laying habitat for these species. Thus, draining wet areas doesn't prevent their development around our homes and yards; predators do not consume enough to provide effective control; and repellents, while protecting individuals, just redirect the adult mosquitoes to bite somebody else.

Aedes aegypti has been found in isolated areas of California, and from Arizona, New Mexico, Texas, Louisiana, Mississippi, Alabama, Florida, Georgia and South Carolina. *Aedes albopictus* is a more cold-hardy species and its range includes those states but extends northward to Illinois and New York. Its range is thought to be defined by an average winter temperature of 50 degrees Fahrenheit.

MOSQUITO CONTROL AS CURRENTLY PRACTICED IN THE UNITED STATES

The first mosquito control districts were established in NJ in 1912. California and Florida followed suit in 1915 and 1925, respectively. In the ensuing years, mosquito control districts and state agencies were established nationwide so that there are now more than 700 recognized districts within the United States along with over 1000 control entities within municipal service programs.

The integrated mosquito management methods currently employed by these organized control agencies and endorsed by the CDC and EPA are comprehensive and specifically tailored to safely counter each stage of the mosquito life cycle. Larval control through water management and source reduction, where compatible with other land management uses, is a prudent pest management alternative - as is use of the environmentally friendly EPA-approved larvicides currently available. When source elimination or larval control measures are clearly inadequate, or in the case of imminent disease, the EPA and CDC have emphasized in a published joint statement the need for considered application of adulticides by certified applicators trained in the special handling characteristics of these products.

In 2009 the AMCA published its "Best Management Practices for Integrated Mosquito Management" and promulgated it to its membership as a set of guidelines for safe, effective and efficient vector control programs. The AMCA is currently in the process of developing guidelines specifically geared toward control of *Aedes aegypti* and *Aedes albopictus*. This will emphasize urban mosquito control and the paradigm shift in control practices from floodwater/salt marsh mosquitoes (predictable habitats) to container-inhabiting mosquitoes (unpredictable and ubiquitous in the peridomestic environment). In addition, the unique manpower, resources, and funding needed for proactive urban control will be covered. AMCA hopes to have a finalized version available as early as possible in 2016/2017 timeframe.

States thought to be particularly susceptible to Zika introduction, such as Florida, California, and Texas, have excellent integrated mosquito control programs in many areas, but emergency funds to respond to a Zika outbreak are needed if timely interventions to contain outbreaks in these districts and elsewhere are to be realized. Critically, many potential ports of entry throughout the U.S. have limited or no mosquito control available and there is a pressing need for funding to establish sustainable mosquito control programs in these areas.

Components of successful mosquito-borne disease control programs as currently practiced in the United States include, but are not limited to, the following:

Prevention

Surveillance - A sustained, consistent surveillance program targets the particular vector species, mapping their larval habitats by season, and documents the need for control through larval and adult trapping regimens. It thus also monitors the effectiveness of the control program. Appropriate and timely response to surveillance data is the key to preventing human disease associated with Zika. Control activity should then be intensified in response to evidence of virus in imported cases, as deemed necessary by the local statutory authority.

Public Information and Outreach – Studies have shown that information programs, while crucial to the overall prevention/control strategy, only exert a moderate effect on modifying population behaviors related to personal protective measures. Effective programs include development of a community task force, interventions to improve access to window screening materials or repellents, and social marketing to reinforce preventive behaviors. These are critical components of any mosquito control program, but cannot, in and of themselves, replace established prevention/control methodologies.

Source Reduction - Removing breeding habitat is the most effective long-term mosquito preventative/control and includes activities as simple as the proper disposal of used tires, paint cans and trash, in addition to the cleaning of rain gutters and bird baths, by individual property owners.

Control

Reducing the contact between the vector mosquito and humans - This is accomplished through removing, modifying or treating larval habitats; modification or removal of adult mosquito resting areas, adulticide treatments when indicated, and use of repellents. All of these interventions can be problematic regarding control of *Aedes aegypti*.

Best Management Practices (BMP) - Most larger mosquito control districts in states having potential ports of entry, such as California, Texas and Florida, usually employ a phased response based upon mosquito trapping data. Such programs consist of public education emphasizing personal protection and residential source reduction; municipal larval control to prevent repopulation of the area with competent vectors; adult mosquito control to decrease the density of infected, adult mosquitoes in the area; and continued surveillance to monitor virus activity and efficacy of control measures.

How Mosquito Control Can Be Improved

- Mosquito surveillance tools for adult *Aedes aegypti* are ineffective for small populations and need to be improved and made more widely available to marginally funded programs.
- Training in the use and interpretation of survey results should be made available to both program managers and public health officials as continuing education adjuncts.
- Additional training resources and comprehensive participation in workshops and professional mosquito control conferences are key components of program upgrades.
- Faster and more efficient communications between public health laboratories and vector control programs need to be explored and implemented. The speed with which the public health sector can respond to either imported or locally-acquired cases will ultimately depend on the turnaround time between testing of suspect cases, laboratory confirmation and promulgation of surveillance results. In addition, variable interpretations of the Health Insurance Portability and Accountability Act (HIPAA) may delay release of results, further restricting timely interventions by vector control agencies. Mechanisms need to be developed that require health departments at all levels to disclose to local vector control agencies the location of suspect cases of Zika while not violating HIPAA provisions. This will ensure more timely and targeted initiation of intervention measures that will prevent or rapidly contain outbreaks.
- Materials and training regarding pesticide resistance testing should be implemented nationwide.
- Funds should be made available to underwrite new data call-ins that might influence a pesticide registrant's decision to keep products on the market
- New chemical, genetic, and biological control methodologies and means of dispersal should be developed and field validated.
- Conventional pesticides are losing ground to resistance. New tools are in development (spatial repellents, ATSB, lethal ovitraps, intracellular biological control (*Wolbachia*), RNAi, GMO mosquitoes, and new pesticide chemical classes require more field validation prior to widespread use.
- Rapid diagnostic tests for Zika and other arboviral agents need development and deployment to mosquito control entities to provide timely notification of infected mosquitoes prior to human cases.

THE ROLE OF FEDERAL GOVERNMENT

The federal government has a crucial role to play in how vector control is accomplished. Several agencies either conduct (e.g., USDA and to a lesser degree CDC) research on applied vector control topics, or fund (NIH) projects (e.g., *Wolbachia*) into novel technologies, FEMA supports large-scale vector control in declared disasters (under Stafford Act stipulations).

In addition, the Centers for Disease Control and Prevention (CDC) Division of Vector-borne Disease provides national expertise in mosquito-borne disease prevention and control

in concert with members of the AMCA. They have also served as an effective conduit via the Expanded Laboratory Capacity (ELC) program for funding that can increase arboviral testing capacities at both state and local levels. To this end, we encourage Congress to authorize supplemental funding for 2016 and increased funding in FY 2017 to support vector-borne disease surveillance. Funding should be allocated through the Centers for Disease Control and Prevention's (CDC's) Division of Vector-Borne Diseases for dispersal to localities most vulnerable to disease introduction while lacking the capabilities.

The Mosquito Abatement for Public Health Act (MASH), Public Law 108-75, was passed during the first session of the 108th Congress but has not received appropriations for its implementation. This Act is a mechanism by which local governments could receive matching federal funds up to \$100,000 for the establishment and/or enhancement of a mosquito abatement program through the CDC. The MASH Act authorized \$100,000,000 in funds for FY 2003, but, as of this hearing, Congress has still not appropriated any funds to cover its provisions. In addition, it requires NIEHS to conduct or support research into methods to control the population of insects and vermin that transmit dangerous diseases to humans. The AMCA fully supports the MASH Act and requests action to appropriate the funds for its full implementation to bolster long-term vector surveillance and control.

The critical challenge for the nation's public health system will be modifying the behavior of the US population to eliminate oviposition sites for these species. Vector control agencies do not possess the resources to provide the sustained service for each resident in their jurisdiction that is required to successfully control invasive *Aedes*. To accomplish that end via source reduction will entail a national effort, along the lines of the "buckle up" seat belt, Smoky the Bear, and "don't be a litterbug" campaigns of the 1960s. A sustained national program will require continued funding into the foreseeable future if the benefits from reduced introduction and spread of exotic mosquito-borne diseases are to be realized.

We further see a federal government role in maintaining our present, proven chemical tools at risk of losing their registration. In 1996 Congress unanimously approved the Food Quality Protection Act (FQPA) (PL 104-170) to modernize the regulation of pesticides and expand data requirements to demonstrate their safety to people and the environment. A key element was authorization to use federal funds when the cost of new data for public health pesticides was more than their producers could afford, putting registration at risk. Unfortunately, these essential funds have never been appropriated, and we are now losing critical public health tools because the cost to prove their safety is higher than return on investment.

CONCLUSION

Vector-borne diseases, whether ancient like malaria or relatively new like Zika, are an unfortunate reality, and Zika won't be the last to challenge our vector-borne disease control capabilities. There are many factors that contribute to the emergence of novel vector-borne diseases, including poverty, climate change, and global trade. They will require long-term solutions.

Mosquito control capabilities in the United States are the finest in the world, but in many cases, fall short of providing the level of protection needed to prevent outbreaks of mosquito-

borne disease in all potential ports of entry. Increased tourism and trade make continual introductions of exotic diseases inevitable and resources for sustainable prevention and control programs must be made available so that future imported cases of exotic diseases beyond Zika can be contained and eliminated before their establishment and spread. Our citizenry deserves no less.

SUMMARY

- Capacities to address mosquito-borne diseases in the U.S. are better than in the past, but require significant improvement to successfully meet the mosquito-borne disease threats such as Zika Virus surely to come our way in the future.
- Increased capacity must include capabilities to address survey control strategies applicable to the widest possible variety of vector-borne disease transmission cycles.
- The unique bionomics of *Aedes aegypti* require better surveillance and prevention/control tools and strategies over the long-term.
- The Federal role should consist of exploring and implementing funding mechanisms devoted to increasing sustainable integrated vector surveillance and control capabilities in areas with organized mosquito control and to develop startup programs in areas of potential risk.
- The MASH act proposes just that sort of thing – providing support for developing new vector control where lacking, and enhancing capacities where they exist but are inadequate.
- Fully fund the Food Quality Protection Act provisions to use federal funds when the cost of new data for existing public health pesticides is more than their producers can afford, putting their registration at risk.
- Increase the CDC/DVBD annual budget to levels that allow funds to be allocated directly for testing of mosquito pools conducted at the local mosquito control program level or intrastate testing collaborative below the state level.

Chapter 539

**STATEMENT OF DR. LUCIANA BORIO, ACTING CHIEF
SCIENTIST, U.S. FOOD AND DRUG ADMINISTRATION.
HEARING ON “EXAMINING THE U.S. PUBLIC
HEALTH RESPONSE TO THE ZIKA VIRUS”***

INTRODUCTION

Good morning Chairman Murphy, Ranking Member DeGette, and members of the Subcommittee. I am Dr. Luciana Borio, Acting Chief Scientist at the Food and Drug Administration (FDA or the Agency). Thank you for the opportunity to appear today to discuss FDA’s actions in response to the Zika virus outbreak.

As you know, Zika virus was first identified in 1947 in Uganda. Since then, sporadic cases and a few outbreaks have been recognized in a number of locations, including parts of Africa, Asia, and the Pacific. However, the situation has changed dramatically since May 2015, when the first local transmission of Zika virus in the Americas was confirmed in Brazil. By December 2015, Brazil had reported more than 56,000 suspected cases of Zika virus and has since stopped counting cases due to the magnitude of the outbreak, which Brazilian national authorities estimate to encompass from approximately 500,000 to 1.5 million cases.

Zika virus is now spreading throughout Latin America and the Caribbean, as well as in parts of the Pacific and Africa. As of February 25, 2016, 34 countries and territories, including the Commonwealth of Puerto Rico, the U.S. Virgin Islands, and American Samoa, have active, local transmission of Zika virus.

Potential links between Zika virus infection and neurological complications (e.g., Guillain-Barré Syndrome), as well as microcephaly and other poor pregnancy outcomes in babies of mothers who were infected with Zika virus during their pregnancy have dramatically increased concerns about the risks associated with Zika virus. On February 1, 2016, the World Health Organization (WHO) declared the recent clusters of microcephaly and other neurological disorders a public health emergency of international concern.

* This is an edited, reformatted and augmented version of a statement presented March 2, 2016 before the House Committee on Energy and Commerce, Subcommittee on Oversight and Investigations.

No locally transmitted mosquito-borne Zika virus disease cases have been reported in the continental United States to date. There have, however, been travel-associated cases, as well as local cases of sexual transmission to women whose only known risk factor was sexual contact with an infected male partner who traveled to an area with active transmission. These imported cases have the potential to result in local spread of Zika virus in areas of the United States where *Aedes* mosquitoes that transmit Zika virus are found. CDC and state, local, and territorial health departments are monitoring for any such events.

FDA RESPONSE TO THE ZIKA VIRUS OUTBREAK

FDA is working in collaboration with other components of the Department of Health and Human Services (HHS), including the Office of the Assistant Secretary for Preparedness and Response (ASPR) and its Biomedical Advanced Research and Development Authority (BARDA), the National Institutes of Health (NIH), and the Centers for Disease Control and Prevention (CDC), as well as with partners across the U.S. Government and with international partners to respond to the Zika virus outbreak. FDA's primary areas of activity include: (1) protecting the safety of the nation's blood supply and tissues for transplantation; (2) facilitating the development of donor screening and medical diagnostic tests that may be useful for identifying the presence of, or prior exposure to, Zika virus; (3) supporting the development of investigational vaccines and therapies; (4) reviewing proposals for the use of innovative strategies to help suppress the population of virus-carrying mosquitoes; and (5) protecting the public from fraudulent products that claim to prevent, diagnose, treat, or cure Zika virus disease.

Blood Supply and Tissue Safety

In the absence of an available donor screening assay, the risk of transmission of Zika virus by blood transfusion is considered likely, based on the most current scientific evidence of how Zika virus and other flaviviruses (including West Nile and dengue) are spread, as well as recent reports of transfusion-associated infection outside of the United States. Realizing this risk, and to better protect the U.S. blood supply, FDA issued new Zika-related blood donor guidance. In areas with active Zika virus transmission, FDA recommends that whole blood and blood components for transfusion be obtained from areas of the United States without active transmission. Blood establishments may continue collecting and preparing platelets and plasma if an FDA-approved, pathogen-reduction device is used. FDA also recommends deferral from donating blood for four weeks for individuals in areas without active Zika transmission if they a) have been to areas with active Zika virus transmission; b) have recovered from an illness with symptoms suggestive of Zika virus infection that developed within two weeks of exposure in an affected area; or c) have had sexual contact with a man who has traveled to, or resided in, an area with active Zika virus transmission during the prior three months. The guidance also recommends that blood establishments update donor education materials with information about Zika virus signs and symptoms, ask potentially affected donors to refrain from giving blood, and update the donor history

questionnaire to elicit information on recent exposure to an affected area. FDA is working with public health authorities in territories with confirmed Zika virus to take rapid and appropriate steps to ensure that safe blood is available.

In addition, to advance blood safety against Zika virus, FDA is facilitating the development of screening tests for identifying the presence of the virus in donated blood and pathogen-reduction technologies to kill viruses in blood components through establishment of reference materials, clarification of regulatory pathways, and interactive review of sponsor-submitted data.

Furthermore, FDA is developing guidance that will address appropriate donor deferral measures for human cells, tissues, and cellular and tissue-based products. This guidance is particularly important given evidence of sexual transmission of Zika virus.

Diagnostic Tests

Unfortunately, there are no commercially available diagnostic tests cleared by FDA for the detection of Zika virus. Two types of diagnostic tests are needed for Zika virus: (1) a test to diagnose acute infection; and (2) a test to assess whether individuals, especially pregnant women, who were potentially exposed to Zika virus were actually infected. In keeping with FDA's practice for responding to emerging infectious disease outbreaks, FDA has been reaching out to potential diagnostic manufacturers to encourage them to develop needed diagnostic tests for Zika virus. In addition, FDA is working interactively with diagnostic manufacturers interested in developing diagnostic tests for Zika virus to help accelerate development programs, including clarifying data requirements for the authorization of the use of Zika diagnostic tests under FDA's Emergency Use Authorization authority (EUA). FDA has authorized the use of a Zika virus diagnostic test developed by CDC under EUA for the qualitative detection of Zika virus-specific immunoglobulin M (IgM) antibodies by qualified laboratories. This diagnostic test can help expand domestic readiness for Zika virus by enabling the identification of patients recently infected with Zika virus in support of response efforts. The authorized test has already been made available to 19 states and territories. FDA is ready to authorize the use of additional

Zika virus diagnostic tests under our EUA authority as soon as we receive data regarding the accuracy and precision of the test from a diagnostic manufacturer to enable such authorization.

Vaccines and Therapies

There are no vaccines or treatments in advanced development for Zika virus at this time. Development programs for investigational vaccines and therapies are in the very early stages and FDA is actively engaged with NIH and BARDA to help accelerate development programs. FDA stands ready to work with medical product developers to provide technical support and clarify regulatory and data requirements necessary to move products forward in development as quickly as possible.

Vector Control

In the United States, mosquito control is typically achieved by a multi-faceted approach that includes a range of tools, including surveillance of mosquito activity, reduction in breeding sites, and the use of chemical and biological control methods. There has been public discussion of a new method to potentially help control mosquito populations through the use of a genetically engineered (GE) line of the mosquito *Aedes aegypti* (OX513A) developed by Oxitec, Ltd. The release of male Oxitec GE mosquitoes is intended to cause suppression of the mosquito population in a release area over time because the offspring resulting from the mating of male GE mosquitoes with wild type females do not develop to adulthood. The Brazilian National Biosafety Commission found the Oxitec GE mosquito safe for use in Brazil in 2014 after extensive field testing, and open field trials of these GE mosquitoes have also been conducted in the Cayman Islands, Panama, and Malaysia. Although multiple pilot studies have been authorized in Brazil, the country's national regulatory authority, the Agência Nacional de Vigilância Sanitária (ANVISA), is currently reviewing Oxitec's request to approve its product for commercial sale.

FDA is reviewing information in an Investigational New Animal Drug (INAD) file from Oxitec regarding the potential use of the company's GE mosquito with the intent of suppressing the population of *Aedes aegypti* mosquitoes at the release site(s). FDA ordinarily cannot acknowledge or discuss INAD files due to confidentiality concerns; however, FDA is able to do so in this case because Oxitec has publicly announced that they have opened an INAD file.

Oxitec is seeking to conduct a field trial to determine whether the release of its GE mosquito will suppress the local *Aedes aegypti* mosquito population in the release area at Key Haven, Florida. As with similar applications, FDA plans to release for public comment a draft environmental assessment submitted by Oxitec that assesses the potential environmental impacts of conducting a field trial in Key Haven with the GE mosquitoes. A field trial of the GE mosquito may only be authorized if—after a draft environmental assessment has been released for public comment and the Agency has had the opportunity to review those comments—FDA issues a final environmental assessment and Finding of No Significant Impact on the environment, or FDA prepares an Environmental Impact Statement. If such a trial is authorized and conducted, Oxitec could use the results from a field trial in an application for approval if the company decides to pursue one in the future.

Fraudulent Product Claims

Unfortunately, during emerging infectious disease outbreaks such as this, fraudulent products that claim to prevent, treat, or cure a disease rapidly appear on the market. FDA is actively monitoring for fraudulent products and false product claims related to Zika virus and will implement enforcement actions, as warranted, to protect the public health.

CONCLUSION

FDA is fully committed to remaining highly responsive and adaptive to the complex range of issues the Zika virus outbreak has presented and will continue to present. Developing the medical products necessary to help bring this outbreak under control is highly complex and will, unfortunately, take time. Close cooperation and collaboration within FDA, within the U.S. Government, with our international partners, and with product developers, is essential to help facilitate the development and availability of medical products to respond to Zika virus. There is an urgent need to accelerate medical product development programs, and FDA anticipates that—similar to the Ebola epidemic in West Africa—there will be a strong desire for access to investigational medical products as soon as they become available.

While the Ebola and Zika viruses have important differences, the response to the Ebola epidemic demonstrated that the typical, phased approach to medical product development can be accelerated and streamlined as appropriate, for the particular health circumstance; it may be appropriate in certain emergency circumstances to accept a greater than usual degree of uncertainty and risk in order to move rapidly to clinical trials, with the goal of getting safe, effective therapies or vaccine products to patients sooner. However, while greater risks may be acceptable during a public health emergency or when there is the potential for a public health emergency, the responsibility to protect patient welfare never ceases. The Ebola epidemic highlighted the importance of determining whether investigational products may help patients, do nothing, or cause unintentional harm. Thus, it is essential that clinical trials be designed to provide interpretable data—with respect to both safety and efficacy—that will enable the global community to learn whether investigational products are safe and effective for broader use.

FDA is fully prepared to leverage its authorities to the fullest extent practicable to help accelerate the development and availability of safe and effective products with the potential to help mitigate the Zika virus outbreak as quickly as the science will allow.

Thank you. I am happy to answer your questions.

Chapter 540

**TESTIMONY OF DR. THOMAS R. FRIEDEN,
DIRECTOR, CENTERS FOR DISEASE CONTROL AND
PREVENTION. HEARING ON “EXAMINING THE U.S.
PUBLIC HEALTH RESPONSE TO THE ZIKA VIRUS”***

INTRODUCTION

Good morning Chairman Murphy, Ranking Member DeGette, and members of the Subcommittee. Thank you for the opportunity to testify before you today on Centers for Disease Control and Prevention’s (CDC’s) efforts to prepare for and respond to the Zika virus outbreak, which threatens the United States and the rest of the Americas.

The Administration has requested approximately \$1.9 billion in emergency funding to respond to the Zika virus outbreak, including \$828 million for CDC, in support of both the domestic and international response, with particular attention to emergency assistance to the Commonwealth of Puerto Rico and other U.S. Territories and States with local transmission of Zika virus.

CDC is the nation’s health protection agency, working 24-7 to save lives and protect people against unpredictable threats such as the Zika virus. Nature is a formidable adversary, and Zika is our newest threat, particularly to pregnant women. CDC has some of the world’s leading experts both in diseases spread by mosquitos and in birth defects. We must act swiftly to stop the spread of the Zika virus, both domestically and globally. While we are learning more about the Zika virus every day, there are many things we do not know yet about Zika. These include our understanding of the spectrum of effects of Zika infection during pregnancy, the risk the virus may play in microcephaly, Guillain-Barré syndrome and other possible complications, the duration of Zika infectivity in semen, and determining what other factors may play a part in the consequences associated with the virus. In addition to answering these questions, we are also working to accelerate optimal mosquito control strategies, improve testing and assure preparedness for rapid detection, control, and prevention within the United States and U.S. territories.

* This is an edited, reformatted and augmented version of testimony presented March 2, 2016 before the House Committee on Energy and Commerce, Subcommittee on Oversight and Investigations.

We are making advancements in these areas and will need the additional requested funding to do so. We are figuring out more about Zika literally every day, and will share information – and adjust our guidelines and recommendations – as we learn more. That is the nature of a scientific response to an emerging health threat. The doctors, scientists, entomologists, and others at CDC are working nonstop to protect Americans from this and other health threats. We have already made significant progress identifying the Zika virus in brain tissue of affected deceased infants, developing new diagnostic tests, issuing guidance, conducting epidemiological investigations along with affected countries, and improving monitoring and surveillance in the United States including in the Commonwealth of Puerto Rico and the other U.S. territories. Much of what we know about Zika and similar viruses today is based on the work that's been done by CDC scientists. But there are still many things we do not yet know. We will continue to use the best of modern science to protect the American people. I understand that Zika virus and the emergence of serious birth defects cause concern. We are committed to providing the American people with the most accurate and timely information about Zika virus and the current outbreak.

CDC is working in collaboration with other components of the Department of Health and Human Services (HHS), including the Office of the Assistant Secretary for Preparedness and Response (ASPR) and its Biomedical Advanced Research and Development Authority (BARDA), the National Institutes of Health, and the Food and Drug Administration (FDA). We are also working with partners across the U.S. Government to communicate with travelers and health care providers, update travel alerts and clinical guidance, and develop improved mosquito-control methods.

ZIKA AND ITS HISTORY

Zika is a flavivirus, which is closely related to dengue, yellow fever and West Nile viruses. Zika virus is primarily spread to people through the bite of infected *Aedes* species mosquitos, particularly *Aedes aegypti*. The *Aedes aegypti* mosquitos, which also transmit dengue and chikungunya viruses, are extremely difficult to control. They bite during the day, indoors and outdoors, and they preferentially feed on humans. And they need only the smallest bit of water to breed – just a bottle cap is enough. The mosquitos become infected when they bite a person with Zika virus. These infected mosquitos can then spread the virus to other people through bites. Case reports of other modes of transmission include spread through sexual transmission and blood transfusion. Of great concern, Zika virus infection in a pregnant woman has been linked to issues in fetal development, and the virus has been detected in association with fatal brain malformation in newborns as well as in miscarriages.

While its adverse effects were unforeseen, Zika is not a new virus. It was first recognized in 1947 and has caused occasional illness in Africa and Asia, but the first outbreak we know of occurred in 2007 in the small Pacific island of Yap. Last May, the first local transmission of Zika in the Americas was reported in Brazil, and by the end of 2015, Brazilian authorities estimated that the outbreak there involved perhaps a million suspected cases of Zika virus. In recent months, the virus has spread rapidly throughout Latin America and the Caribbean, as well as to parts of the Pacific. As of February 18, 2016, 32 countries and territories, including

the Commonwealth of Puerto Rico, a United States Territory, the U.S. Virgin Islands, and American Samoa have reported local transmission of the Zika virus.

SYMPTOMS AND ADVERSE OUTCOMES

Many people exposed to Zika virus will have only mild symptoms - such as fever, rash, joint pain, and red eyes or conjunctivitis - that will last no more than a week. In past outbreaks, about four out of five people infected with Zika appear not to have had symptoms at all, although we do not know if that is the pattern in this outbreak.

Increasing evidence suggests that Zika virus infection may be associated with more serious health outcomes. In October 2015, Brazilian authorities recognized a concerning increase in microcephaly, which has occurred in close sequence to Brazil's outbreak of Zika virus. Microcephaly is a usually rare, serious condition where a baby's head is smaller than expected based on age and sex. Microcephaly is not a diagnosis in and of itself, but a sign that the brain did not develop as it should in the womb. Babies with microcephaly can have a range of problems, including seizures, developmental delay, feeding problems and hearing loss. In some cases these problems can be fatal.

Laboratory tests at CDC strongly suggest a link between Zika virus infection during pregnancy and microcephaly.

We do not fully understand the nature of this relationship, or if there are important cofactors. We also do not know what, if any, other outcomes might be associated with Zika infection during pregnancy among infants who do not have microcephaly. Microcephaly in infants can be devastating to the affected families, and this ongoing outbreak is concerning to everyone, especially for pregnant women, and their families who may travel to or live in the infected areas. The association between Zika virus and microcephaly is unexpected. A new infectious cause of fetal malformations has not been identified in decades. Zika virus spread in the Americas and its effect on pregnancy are developments that we are working with partners to better understand.

Our key priority at this point is to reduce the risk to pregnant women of Zika virus infection. Given the potential risks associated with maternal Zika infection, prevention is key for this response, with a parallel approach of acting based on what we know now and, at the same time, discovering more so that we can better prevent adverse health outcomes in the future. That's why, during the same week we identified Zika in brain tissue specimens from affected infants, we issued a warning to advise pregnant women not to travel to affected areas. That's why we are working intensively with the Commonwealth of Puerto Rico and other areas to get support to women who are or who may become pregnant and do what we can to reduce the threat of Zika there. And that's why we are engaging in studies with international partners so that we can more fully understand the magnitude of risk and the range of outcomes associated with Zika virus infection during pregnancy.

Health authorities in Brazil and elsewhere have also reported an increase in suspected cases of Guillain-Barré syndrome, a rare neurologic disorder in which a person's own immune system damages nerve cells, leading to nerve damage or paralysis that lasts for several weeks or several months. Most people fully recover, but it can take a few months or even years to do so. Some people with Guillain-Barré syndrome have permanent damage and, in rare cases,

people have died. It is difficult to determine if any particular pathogen “caused” or “triggered” Guillain-Barré syndrome. Currently, we do not know if Zika virus infection causes Guillain-Barré syndrome.

However, the development of Guillain-Barré syndrome is a recognized after-effect of a variety of different infections. CDC is currently collaborating with public health officials in Brazil to investigate whether there is any causal link between Zika infection and Guillain-Barré syndrome.

Domestic Activities

While we are working to better understand these health outcomes, transmission, diagnostics, and mosquito control, CDC is moving quickly to respond. We have moved our Emergency Operations Center to the highest alert level for Zika virus to further enhance our response activities in areas with current local transmission and to accelerate preparedness efforts in anticipation of local transmission in the continental United States.

For the Commonwealth of Puerto Rico as well as the U.S. Virgin Islands and American Samoa, a surge in resources is urgently needed. The population of *Aedes aegypti* mosquitos is widespread on these islands, protective environmental factors such as window screens are not as prominent, and the density of people puts people there at high risk for transmission. All three areas have already reported local Zika transmission, with Puerto Rico alone reporting at least 30 cases. Furthermore, recent outbreaks of dengue and chikungunya suggest that Zika virus may spread extensively and rapidly in these areas. CDC has deployed staff to the U.S. Virgin Islands, American Samoa, and Puerto Rico to support response activities and provide technical assistance to health departments there. CDC and the CDC Foundation are also partnering to create Zika prevention kits.

Containing educational materials, and initial supplies of prevention tools such as insect repellent, the purpose of these kits is to help pregnant women in areas with local Zika transmission protect themselves and their pregnancies. Five thousand of these kits have been dispatched to the Commonwealth of Puerto Rico, the U.S. Virgin Islands, and American Samoa; and CDC plans to distribute more than 45,000 kits to these areas in the future.

While we have not yet seen transmission of the Zika virus by mosquitos within the continental United States, we expect many returning travelers will have Zika infection. As a potential benchmark, we received reports of 3,270 travelers from 49 states with laboratory confirmed cases of chikungunya infection in 2014 and 2015. There are about 40 million people travelling between the continental U.S. and Zika-affected areas each year. Therefore, all U.S. jurisdictions must be prepared to evaluate, test, and manage patients with potential Zika virus infection, particularly pregnant women. Furthermore, *Aedes aegypti* is found in many areas of the United States, raising the risk of local transmission. The most recent data available suggest that *Aedes aegypti* are found in 13 states and *Aedes albopictus* are found in 31 states and the District of Columbia. Recent chikungunya and dengue clusters in the United States suggest that Zika outbreaks in the U.S. mainland may be relatively small and localized due to protective factors like window screens and less dense living conditions; however, any local outbreaks will be of deep concern to the people living there, and we must be prepared for different scenarios including more extensive transmission risk.

CDC is working with health departments across the country to ensure coordination and to expand capacity for detecting and responding to Zika virus. Surveillance is essential to monitor and quickly identify areas with local transmission. We conduct multi-faceted surveillance for arboviruses, including Zika, through ArboNET, an integrated network which funds, through our Epidemiology and Laboratory Capacity cooperative agreements, staff in 49 states, the Commonwealth of Puerto Rico, and six large municipalities to conduct human case investigations, collect and test mosquitos, and perform laboratory analysis on arboviruses including Zika. Zika virus is now a nationally notifiable disease, meaning states report the virus to CDC, which will aid Zika surveillance efforts. CDC is also working with several states and the Commonwealth of Puerto Rico to determine a baseline prevalence of microcephaly so that any increase, should it occur, can be quickly and accurately identified.

With support from the President's emergency request, CDC will build on its current efforts to provide financial and technical resources to states and territories through its cooperative agreements to strengthen their capacity to prepare for and respond to emerging insect-borne threats such as Zika virus. These resources may be used to help health departments expand their capability to manage cases of local Zika virus transmission in their areas and to implement community education and prevention programs to reduce human-mosquito contact and subsequently, the risk of Zika transmission. Resources will also be used to implement mosquito control strategies, including mosquito surveillance. Current mosquito surveillance capacity is uneven across the country, which makes our knowledge about the locations of the two mosquito vectors that transmit Zika virus potentially incomplete. To effectively track the spread of the outbreak, it is critical that states and territories receive specimens and test for Zika virus to diagnose and report travel-related and locally acquired cases of Zika. Under the emergency request CDC will expand its efforts to assist public-health labs nationwide to test for Zika and to provide the guidance on how to interpret test results. In addition, CDC is available to provide testing of any Zika samples upon request.

We are working to expand the number of health departments that have the ability to perform testing, but will need to increase the existing capacity to meet the projected demand for Zika testing. Given that, last year, it is estimated that approximately 500,000 travelers to areas of current Zika transmission were pregnant women and 36,000 pregnant women are currently living in the Commonwealth of Puerto Rico, the expansion of testing capacity in public health labs nationwide, included in the request, is urgently needed in order to ensure that every pregnant woman needing testing for Zika virus has access.

Recognizing the potential for Zika virus transmission through blood transfusions, CDC is collaborating with FDA to ensure the safety of the blood supply from Zika virus, particularly in regions experiencing local outbreaks.

CDC has sent experts to the Commonwealth of Puerto Rico to assess the steps needed to assure both that Puerto Rico's blood supply needs are met and that transfusion-transmitted Zika is prevented.

CDC experts are working intensively to learn more about the outbreak and provide people with the information they need to protect themselves. We will continue to issue travel alerts for the affected areas as confirmation of the virus is reported, and we'll keep the American people informed as the situation changes. We recognize people are eager for information, and our website has exceeded half a million views in recent days.

CDC has also provided guidance for doctors and other clinicians on evaluation, treatment and follow-up care of pregnant women and infants with possible exposure to Zika virus,

partnering with organizations from around the health care community to help distribute this information as widely as possible. Our guidance will continue to be updated as our knowledge increases. We have recently updated our guidance to provide recommendations for the clinical care and management of pregnant women living in areas where Zika transmission is widespread, with special consideration to the ongoing risk of maternal Zika virus infection throughout pregnancy. These guidance documents were prepared in consultation with the American College of Obstetricians and Gynecologists, the Society for Maternal Fetal-Medicine, and the American Academy of Pediatrics.

CDC also wants to ensure that the general public knows what it can do to protect itself. Pregnant women should postpone travel to regions with ongoing Zika virus transmission. If they must travel, or if they live in affected areas, CDC recommends pregnant women talk to their doctors or other healthcare providers first and strictly follow steps to prevent mosquito bites. Reducing exposure to mosquitos is important for anyone traveling to or residing in areas where the virus is circulating. Wearing long sleeves, long pants, using EPA-registered repellents such as DEET and permethrin-treated clothing (both of which are safe to use in pregnancy), and using other protections such as air-conditioning will reduce exposure to mosquito bites. Given the potential for Zika virus to be spread through sex, pregnant women and their male partners living in or who have been to Zika-affected areas should abstain from sex or use condoms for the duration of pregnancy. This is a rapidly changing situation and our understanding of the risks concerning Zika virus infection is incomplete and evolving. As we get new information, we will update our advice.

Global Activities

On February 1, the World Health Organization (WHO) declared the recent cluster of microcephaly cases and other neurological disorders (such as Guillain-Barré syndrome) and their possible association with Zika virus, a public health emergency of international concern, a reflection of the seriousness of this unfolding health threat.

CDC is coordinating its response with the U.S. Agency for International Development, as well as the Pan American Health Organization (PAHO), the regional arm of the World Health Organization (WHO), and other parts of WHO, and is collaborating with many international partners to learn more about this outbreak. We are working with the Brazilian Ministry of Health on investigation and research partnerships. Specifically, one partnership involves studying the link between Zika virus infection and microcephaly, while another is examining the relationship between Zika virus and Guillain-Barré syndrome. Research teams from CDC are also in other countries, including Colombia, to explore collaborations that will shed light on the risk of microcephaly in relation to Zika virus infection during pregnancy.

In addition, CDC is offering support to all countries so that they can test samples from microcephaly cases for serologic evidence of Zika virus infection, and CDC is helping countries throughout the Americas establish in-country diagnostic capacity. To that end, we are currently, and in conjunction with PAHO, providing training to laboratorians in South and Central America on diagnostic tests, including two recent workshops in Brazil and Nicaragua.

CDC's Central American office has also facilitated the verification of Zika cases in several countries throughout Latin America, including Colombia, Venezuela, and Nicaragua.

At the request of the Department of State's Bureau of Medical Services, staff from CDC's Global Disease Detection Center in Guatemala has been involved in communication efforts to ensure that new information regarding Zika virus and its possible link to birth defects is communicated to U.S. Mission Health Unit staff throughout the Americas.

The Global Health Security Agenda, with critical support from Congress, is collaborating with countries around the world so that we can find, stop, and prevent health threats when and where they first emerge. Zika has been present in Africa for decades, and it's possible that it could become linked to microcephaly there as well. The sooner we detect a problem, wherever it occurs, the more rapidly we can respond to it and prevent it from spreading. It is in all of our best interests to work with others to improve public health capacity around the world.

IMPROVING THE TOOLS AND INFORMATION FOR RESPONDING TO ZIKA

We need a better understanding of the epidemiology of Zika and potential Zika-associated birth defects and other adverse health outcomes. We need better diagnostic methods that can quickly and clearly differentiate between similar viruses to detect evidence of past Zika infection. Testing for current Zika infection is only reliable in the first week of illness. A Reverse Transcription-Polymerase Chain Reaction (RT-PCR) test can provide a definitive diagnosis of Zika, but only if it is performed within about seven days of symptom onset. The tests we have available for Zika in persons who are no longer ill may have cross-reactivity with similar flaviviruses, particularly dengue, which can lead to false-positive or inconclusive results and confirmatory testing is required. Diagnosis is particularly challenging with Zika virus since most people will not experience symptoms. We also need to determine how long a man who has been infected with Zika may continue to be able to sexually transmit the virus to a partner, and we need better tools to screen the blood supply.

We also need to advance our ability to control the mosquito population. Existing methods for mosquito control all have shortcomings, especially in areas where the population of *Aedes* mosquitos is rampant. Furthermore, in some areas like the Commonwealth of Puerto Rico, mosquitos may have developed resistance to certain insecticides, which could reduce the range of substances that can be used to effectively decrease mosquito populations. We need to implement the best tools we have today, improve current vector control strategies, and identify better options. We also need better mosquito surveillance to determine the location of mosquitos and areas with mosquito resistance to insecticides, which would inform the implementation of new mosquito control techniques.

Finally, a vaccine is needed to protect people at risk of Zika virus infections, particularly preventing infection among women of childbearing age. At CDC, our scientists developed both a West Nile virus vaccine, which is currently in use for animal protection in the United States, and a dengue vaccine, which is currently in clinical trials. The President's request will increase Zika research, improve diagnostics and support advancements in vector control methods. Although availability of a licensed Zika vaccine is several years away, we do not know how long Zika will be a problem in the Americas nor whether the mosquito control efforts that must be implemented will yield durable results.

CONCLUSION

Microbes continue to be formidable adversaries. To protect Americans, the Zika emergency request invests in the laboratories, disease detectives, disease tracking systems, mosquito control, and investigations needed to continue to improve these essential tools.

The emergence and reemergence of health threats, including those spread by mosquitos and other vectors is not a unique event but something we expect to continue to see in the future. These outbreaks cannot be expected to occur in isolation of one another. The Commonwealth of Puerto Rico and Hawaii were already responding to outbreaks of dengue when Zika virus arose as an urgent health threat. We need to address the threat of mosquitoborne diseases systematically, rather than episodically. Thank you again for the opportunity to appear before you today. I appreciate your attention to this concerning outbreak and I look forward to answering your questions.

Chapter 541

**TESTIMONY OF LAWRENCE O. GOSTIN,
FACULTY DIRECTOR, O'NEILL INSTITUTE FOR
NATIONAL AND GLOBAL HEALTH LAW. HEARING ON
“EXAMINING THE U.S. PUBLIC HEALTH RESPONSE
TO THE ZIKA VIRUS”***

EXECUTIVE SUMMARY

Following the 2014/15 Ebola epidemic, the World Health Organization (WHO) was widely criticized for its delay in taking decisive action and leadership to protect global health. Four international panels found that the WHO unreasonably delayed declaring Ebola a Public Health Emergency of International Concern (PHEIC) to call the international community to action in providing financial and technical resources for the global health humanitarian and security threat posed by Ebola.

The WHO appeared to learn from the Ebola experience. On February 1st, 2016, the Director-General, Margaret Chan, declared the clusters of microcephaly and neurological syndromes (including Guillain-Barré Syndrome) associated with Zika virus infection a PHEIC. The link between Zika virus infection and microcephaly and Guillain-Barré Syndrome is not yet proven, although suspected. Now the international community, including the United States, must answer the call to action to ensure global health security and equity against the risk posed by the spread of Zika virus.

As the only developed country in the Americas with the *Aedes aegypti* mosquito, the United States bears not only a unique responsibility to take leadership for global health in our region, but also to protect the health of United States residents. The Zika virus is already embedded in Puerto Rico, and it is likely that by the summer time there will be local transmissions in Florida and the Gulf Coast. During the summer, the *Aedes aegypti* mosquito has been observed as far north as Washington, DC,¹ and the *Aedes albopictus* mosquito, believed to also transmit the Zika virus, is found in at least 32 states in the United States.²

* This is an edited, reformatted and augmented version of testimony presented March 2, 2016 before the House Committee on Energy and Commerce, Subcommittee on Oversight and Investigations.

As Ebola demonstrated, the health security of the United States is intrinsically tied to ensuring strong health systems and a coordinated international response at the source of the outbreak. Furthermore, as a global leader for humanitarian action, the United States can provide the financial and technical resources necessary to address the Zika epidemic and protect global health. The work of the United States military and the Centers for Disease Control and Prevention (CDC) during Ebola proved to be transformative. The Ebola response was made possible by a special appropriation during the height of the epidemic, as requested by the President and allocated by Congress.

I fully support President Obama's FY2016 emergency supplemental appropriations request of \$1.86 billion to respond to the Zika virus domestically and internationally. This must be in addition to existing global health security funding – including unobligated Ebola funding – to ensure flexibility to respond to the United States' needs as we progress towards Summer and the threat of domestic mosquito-borne transmission.

The Global Response to the Zika Epidemic

I have served on several high-level panels reviewing the WHO and international community's response to the 2014/15 Ebola outbreak including on the Harvard-London Hygiene and Tropical Medicine Independent Panel on the Global Response to Ebola and the National Academy of Sciences Global Health Risk Framework Commission. I also closely advised the United Nations Secretary General's High Level Panel on Global Health Crises. The WHO's failure to act quickly and decisively cost thousands of lives.³ Of particular concern was the unreasonable delay in the convening of an Emergency Committee to advise to the WHO Director-General whether she should declare the Ebola outbreak a Public Health Emergency of International Concern (PHEIC) under the International Health Regulations (2005). The Director-General was also late in mobilizing the international financing needed to prevent international spread of the Ebola Virus.

Despite these critiques from numerous independent panels as well as implementing internal reforms, the WHO delayed taking its leadership role in response to Zika. The CDC and Pan American Health Organization had been working actively on Zika, in collaboration with the Brazilian government for months prior to the WHO's active engagement. Given the broad, global distribution of the mosquitoes that transmit Zika virus, and in the absence of rapid diagnostic tests or a vaccine, on January 27, 2016, my colleague Daniel Lucey MD and I called for the WHO to not repeat its mistakes from Ebola, and for the WHO Director-General to immediately convene an Emergency Committee on Zika virus to assess whether a PHEIC should be declared.⁴ On January 28, 2016, the WHO announced that the Director-General would convene an Emergency Committee on Zika virus and the observed increase in neurological disorders and neonatal malformations.⁵

Following this announcement, the WHO acted decisively and with leadership. On February 1st, 2016, the WHO Director-General Margaret Chan declared the clusters of microcephaly and neurological syndromes including Guillain-Barré Syndrome a PHEIC.⁶ This was the fourth PHEIC the WHO Director-General has declared since the International Health Regulations (2005) came into effect in June 2007, including for Influenza A (H1N1), polio, and Ebola.⁷ While a causal relationship between these clusters and Zika virus is

strongly suspected, it is not yet scientifically proven. Nonetheless, the declaration of a PHEIC reflects the pressing need for the coordination and resourcing of international efforts to address the Zika epidemic.

Accompanying the PHEIC, the Director-General issued temporary recommendations to countries on handling the Zika epidemic. While not legally binding, these temporary recommendations have significant normative weight and are issued in accordance with the legally binding International Health Regulations (2005). The recommendations advise countries to enhance surveillance for Zika virus infections, develop diagnostic tools, communicate the risks of Zika virus infection, aggressively implement vector control and personal protective measures, and ensure reproductive health services, including access to contraception (including emergency contraception) and maternal health care.

On February 16th, 2016, the WHO released its “Zika Strategic Response Framework & Joint Operations Plan”.⁸ This plan is a critically important step towards an effective response to the Zika epidemic. It is also a critical step towards re-establishing the WHO’s global health credibility which was significantly undermined during Ebola. The plan estimates that \$56 million will be required for the Zika epidemic response.⁹ The majority of the funding is for risk communication and community engagement (\$15.5 million) and care for those affected (\$14.2 million). Given the vital role that the Pan American Health Organization (PAHO) plays in leading the global health response in the Americas, a large amount of the funding under this plan is appropriately earmarked for PAHO (\$8.1m), including \$1.5 million for surveillance and \$2.25 million for vector control measures. Yet, despite this estimate of the needs, the WHO has yet to mobilize the required funding. That is still another reason to support the President’s proposed emergency Zika appropriation.

While the WHO’s commitment to raising funds needed for the global response is positive, the estimate of \$56 million is far less than that required to stem the Zika epidemic in the Americas.

Major global funding is needed for aggressive mosquito control, surveillance, and research. Under the WHO’s plan, the overall estimates for these strategies are \$6.4 million, \$7.1 million, and \$6.4 million respectively. The Zika epidemic is likely to spread to many regions of the world beyond the Americas, which will require considerably greater funding. During the Ebola outbreak, the WHO released financing estimates that were far from adequate, requiring repeated increased cost estimates as the Ebola outbreak unfolded. Overly conservative estimates for the Zika epidemic response could result in the same mistakes seen with Ebola: waiting until a global emergency to mobilize funding will always be too little, too late. The WHO must have access to a much larger emergency contingency fund. The trigger for use of this fund would be the declaration of a PHEIC.

The Global Health Risk Framework Commission (on which I served) estimated that it would cost \$4.5 billion annually to truly reduce pandemic risks.¹⁰ While this may appear to be a great deal of money, it pales in comparison to the global costs of a pandemic. Previous epidemics have demonstrated that states with major emerging disease outbreaks experience a loss in GDP of up to 10%. Brazil is may experience a similar economic impact with the upcoming 2016 Olympics and Paralympics in Rio de Janeiro. The World Bank has advised that while initial estimates of the short-term economic impact of the Zika epidemic in the Latin American and Caribbean region is 0.06% of GDP, such estimates are based on a swift, coordinated international response. The World Bank however advises such estimates could be significantly larger given the high dependence on tourism in the region if the virus is not

promptly contained, if a causal association between Zika virus and clusters of microcephaly and Guillain-Barré Syndrome is established, and if public perceptions of the risks of Zika change.¹¹

In addition to the financial and technical resources dedicated by the WHO, it is vital that the WHO use its normative power for global public health. The WHO was criticized for prioritizing politics over public health during the Ebola outbreak. It must not let the same happen with the Zika epidemic, which disproportionately burdens women and the poor. In particular, calls by governments that women avoid getting pregnant – including Brazil, Honduras, Colombia, and El Salvador – without providing access to reproductive health and rights services, are not only ineffective but also unfair to women. In Central and South America, there is limited access to contraception – especially in poorer communities most at risk of Zika virus infection and cultural and religious norms still restrict the availability and use of contraception. Nearly all countries in the Americas currently experiencing or likely to experience Zika virus cases have laws preventing women from accessing reproductive health services such as emergency contraception and abortion. In addition, the quality, accessibility, and affordability of maternal health care systems vary greatly between and within countries, with varying degrees of post-partum support services for children born with disabilities. Pope Francis recently supported the expanded use of contraception in the face of potential harms to pregnant women from Zika virus infection.

Both the WHO and the international community's response to the Zika epidemic must therefore be comprehensive, equitable, and substantial.

The United States' Domestic Response

The Risk to the United States

The mosquitoes that transmits Zika virus – *Aedes aegypti* (primary vector) and *Aedes albopictus* – is present in the United States and its territories.¹² One recent study modeling possible Zika spread estimates that more than 60% of the US population lives in areas conducive to seasonal Zika virus transmission,¹³ with Florida and Southern Texas at risk of year round transmission. The United States is the only high-income country in the Americas at risk of local Zika virus transmission.¹⁴ As a result, the United States domestic response must cover not only returning travelers who may be infected and local transmission of Zika virus from sexual intercourse, but also local transmission of Zika virus due to infected mosquitoes.

On February 3, 2016, the CDC's Emergency Operations Center (EOC) moved into Level 1 activation to accelerate domestic preparedness in anticipation of local Zika virus transmission by mosquitoes in the Continental United States.¹⁵ Level 1 is the EOC's highest level of activation, reserved for critical emergencies. This involves assignment of the largest number of staff possible to work on a response. There have been three previous EOC Level 1 responses: the Ebola outbreak, Influenza A H1N1 outbreak, and Hurricane Katrina. Moving to this level of response demonstrates the importance of preparedness for the Zika outbreak and supports the development of laboratory tests to diagnose Zika infection, studies to investigate the association between Zika virus and microcephaly and Guillain Barré

syndrome, surveillance in the United States and its territories, and support of efforts in Puerto Rico, Brazil, and Colombia.

Travel Advisories and Restrictions

The CDC has issued Level 2 (Alert: Practice enhanced precautions) general travel advisories for Zika virus in areas with local transmission such as South America, Central America, Mexico, Pacific Islands, and the Caribbean.¹⁶ In addition, these Level 2 travel alerts include specific interim recommendations that pregnant women should consider postponing any travel to affected regions. The CDC has not issued any Level 3 (Warning: Avoid all non-essential travel) travel advisories which would indicate danger to all travelers, not only travelers with specific risk factors, such as pregnancy.

Travel advisories are important for ensuring that individuals traveling to Zika virus affected countries have adequate information to decide whether to travel and what steps they should take to prevent Zika infection while in affected countries and upon return to the United States. Given the typically mild symptoms of Zika virus in healthy, non-pregnant individuals, Level 3 travel warnings are not currently warranted. Priority should be given to continuing the current information sharing process to travelers on how to prevent mosquito bites, such as through the use of EPA-registered insect repellents, the covering of exposed skin, and sleeping in screened or air-conditioned rooms, and how to prevent possible infection of pregnant partners through sexual intercourse upon return to the United States.

Notably, the CDC and WHO have different advice to pregnant women traveling to Zika affected countries. The CDC's response is more proactive and one that I strongly support.

Travel bans are not warranted, including specific bans for pregnant women at any stage during pregnancy, which would be unnecessarily discriminatory and intrusive. It is important that the CDC is supported in its efforts to set, continually review, and update travel advisories as the public health circumstances change. The WHO Director-General's temporary recommendations issued with the PHEIC declaration specifically advise against travel or trade restrictions to prevent the spread of Zika virus.

Quarantine and Isolation

As a vector-borne disease, Zika virus is predominately transmitted through the bite of an infected female *Aedes aegypti* mosquito. In addition, most individuals infected with Zika do not show symptoms, making identification of individuals for isolation very difficult. The quarantine of persons suspected of Zika virus infection, or isolation of persons with Zika virus infection, is therefore not an effective or warranted public health strategy. While there is evidence of sexual transmission of Zika, this mode of transmission would also not be favorable to quarantine or isolation measures. As a result, the use of quarantine and isolation in response to Zika is unfounded and therefore likely to be considered an unreasonable and unnecessary burden on individuals' liberty that does not have justification in public health. In the temporary recommendations issued with the PHEIC, the WHO Director-General has advised against restrictions such as quarantine and isolation to prevent the spread of Zika virus. Control efforts should therefore focus on mosquito eradication, education about the measures individuals can take to protect themselves from infection, and funding the development of a vaccine.

Vector-Control

It is a public health priority that the main source of Zika virus transmission — principally the *Aedes aegypti* mosquito — is subject to aggressive vector control efforts. In addition to the physical removal of stagnant water that serves as mosquito breeding sites, the use of safe, effective and approved insecticides is necessary. However, insecticide resistance is growing and the WHO is investigating novel mosquito control strategies, such as the use of transgenic mosquitoes to reduce local mosquito populations.¹⁷

Given the public health impact of the *Aedes aegypti* mosquito, I support the watchful use of transgenic mosquitoes through a carefully controlled release that monitors the effects on mosquito-borne diseases — including Zika, Dengue, and Chikungunya viruses — as well as any potential ecological harms. Trials so far have demonstrated promising results in drastically reducing local mosquito populations that carry these diseases without causing other harms. There is also little evidence that transgenic mosquitos cause ecological harms, although potential harms need to be closely watched and controlled for.

Ensuring Equity and Justice in the United States' Health System

Given the disproportionate impact of the Zika epidemic on women, it is essential that women in the United States are guaranteed access to reproductive health services including contraception, emergency contraception, and maternal healthcare. Where it is lawful, pregnant women with a fetus known to have microcephaly should be offered the opportunity to abort the pregnancy.

Given the possible sexual transmission of Zika virus, condoms must be readily available and accessible to both men and women in the United States. In addition, concerns about fetal health cannot stop at birth: infant, child, and ongoing healthcare and support services for babies that may be affected by the Zika epidemic must be guaranteed. The Federal and States Governments must act to protect the health of US citizens, and meet their obligations under international health and human rights law.

Ensuring Financing for Response Efforts: President Obama's Supplementary Funding Request

On February 22nd, 2016, President Obama submitted a FY 2016 emergency supplemental appropriations request of \$1.86 billion to respond to the Zika virus domestically and internationally.¹⁸ The vast majority of this funding request is directed to the Department of Health and Human Services — \$1.48 billion, \$828 million of which is directed to the CDC. This funding includes \$200 million to support the development of a vaccine through to commercialization with the National Institutes of Health and product development and approvals with the Food and Drug Administration. The United States Agency for International Development (USAID) would receive \$335 million for targeted activities in South America, Central America, and the Caribbean. Finally, \$41 million would be directed to the Department of State to *inter alia* support WHO, PAHO, and UNICEF public health efforts to address the Zika virus in affected countries while ensuring United States health security. Given the unknowns of the health humanitarian and security risk posed by Zika — especially as we transition to Summer — this funding is essential to ensure flexibility to respond to the United States' needs, including beyond that already identified.

Use of Unobligated Ebola Emergency Funds for the Zika Response

While it may seem appealing to use money previously allocated to the Ebola outbreak, such a move risks making the United States more vulnerable to infectious disease threats. Failure to develop and secure health systems in developing countries – whether in West Africa or South America – risks the health, safety, and security of the United States.

Ensuring global public health is not simply about a rapid response, but a sustainable response. Reallocating money from one infectious disease outbreak to another undermines efforts to ensure surveillance, detection, response, and control strategies are not only operational but sustainable in countries at risk of outbreaks. While infectious diseases may appear quickly, the efforts to prevent and respond to them cannot simply be about extinguishing fires, but rather preventing them from flaring up and occurring again in the future. Given the economic impact of outbreaks, sustainable and systems-wide technical and financial resources are essential to ensure taxpayers' money is utilized effectively. Furthermore, reallocating money from one infectious disease outbreak to another infectious disease outbreak risks the long-term health, safety, and security of the United States. It is important to note that the USAID funding request in President Obama's FY2016 emergency supplemental appropriations request would provide flexibility in the use of remaining USAID Ebola funds.¹⁹

Global health security and public health is grossly underfunded. I strongly advise that the Zika supplementary budget request is funded independently from unobligated past emergency funds.

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Chapter 542

EPIDEMIOLOGICAL CONCEPTS, PUBLIC HEALTH AND Q FEVER

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ABSTRACT

In this chapter, we define epidemiological concepts commonly used when describing zoonotic infectious diseases and relate these to Q fever. The aim is to promote the understanding of the remaining chapters, in particular for readers less familiarized with epidemiological and biomedical terminology. After a brief description of the epidemiology of coxiellosis, the distinction between infection and disease is highlighted, as only a proportion of *Coxiella burnetii* infections result in clinical disease in humans and animals. Q fever is considered a zoonosis, i.e., an infection/disease naturally transmitted between vertebrate animals and humans. A key characteristic is that once transmitted to humans, the *C. burnetii* infection dies out quickly as human host populations are inefficient in maintaining the transmission chain. Q fever has been coined an emerging or re-emerging disease on one hand, and a neglected zoonosis on the other. The emergence of coxiellosis may in some cases be genuine, and in others partly be explained by higher awareness rather than by true emergence. Disease emergence can be driven by multiple factors such as pathogen and host characteristics, population dynamics, ecological and environmental factors. The ability to infect multiple hosts seems to be determinant. This is the case of *C. burnetii*, which is a generalist agent that can infect many species, including wildlife, reptiles, fish, birds and ticks. Interestingly, despite *C. burnetii* being a multi-host pathogen, important species-specific particularities exist regarding the transmission and pathogenesis in humans and ruminants. Regarding disease occurrence, Q fever may be sporadic, endemic or epidemic, depending on the presence of specific risk factors. Due to the potentially large impact of major outbreaks, Q fever is a notifiable disease in many countries. Despite recommendations of notification at international level, national legal frameworks vary and notification is not compulsory in all countries. Some examples of Q fever case definitions for reporting

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purposes are given. The development of surveillance systems in human and animal populations is considered desirable, although challenging, as nonspecific clinical signs may lead to underreporting and because *C. burnetii* is a multi-host pathogen. The impact of Q fever on public health, e.g., measured in DALY's or by economic assessments, may change quickly from very low in endemicity to very high during major outbreaks, as illustrated here by some examples.

Keywords: epidemiological concepts, public health, reservoirs, surveillance, transmission

INTRODUCTION

In this chapter, we define epidemiological concepts commonly used when describing (zoonotic) infectious diseases and relate these to the disease. We present a brief description of the epidemiology of coxiellosis and then illustrate issues regarding the transmission, types of hosts, factors which drive the emergence of disease, detection, case definitions, monitoring and surveillance, and the assessment of public health impact of Q fever.

This chapter aims to promote a better understanding of other more specialized chapters of this book, especially for readers who might be less familiarized with epidemiological and biomedical terminology.

BRIEF DESCRIPTION OF THE EPIDEMIOLOGY OF COXIELLOSIS

Details on the infection and the disease itself can be found in the scientific literature [1–4] as well as in this book. Briefly, infection with *Coxiella burnetii* in animals is widespread in many husbandry systems and countries throughout the world. Domestic ruminants, in particular goats and sheep, are considered the main reservoirs [2]. The occurrence of the clinical form of coxiellosis in small ruminants is not easily detectable or is sporadic, although outbreaks with severe economic impact may occur. Disease in ruminants is characterized by reproductive disorders such as abortions in late pregnancy. High loads of infectious *C. burnetii* are shed by infected animals in birth products and aborted fetuses, and less so in milk and faeces [2, 5, 6]. Excreted *C. burnetii* are highly resistant in the environment and may become aerosolized. Humans may become infected via the inhalation of contaminated aerosols. Most cases of infection in humans result from spillover of *C. burnetii* infections from domestic small ruminants, as transmission between humans is not a feature [3].

Risk factors for zoonotic transmission may vary and include proximity between animal and human populations, farm management and husbandry factors such as the seasonality of parturition and specific climatic conditions, among others [2, 6]. The role of foodborne transmission, environmental persistence, and wildlife or tick reservoirs as sources of infection in humans is considered minor [2]. Exposure of susceptible humans to *C. burnetii* may result in infection and, in only a proportion of individuals, in disease. Q fever clinical symptoms in humans may be classified as acute or chronic [1, 2, 4, 7]. Symptoms of acute Q fever are usually non-specific and often relatively mild, mainly related to fever and headache, but severe disease such as pneumonia and hepatitis may occur. Risk groups such as pregnant women, immunocompromised patients and those with pre-existing cardio-vascular

conditions, have an enhanced risk of serious clinical manifestation, as well as of developing chronic Q fever [1, 7–9]. The main presentation of chronic Q fever is chronic fatigue and endocarditis. Human Q fever cases and outbreaks have been controlled by treating human cases with antimicrobial therapy and by implementing different disease control measures on farms [2, 10].

To bring the essence of a complex disease such as Q fever into one concise sentence is a challenge. Q fever has been described as “disease of humans, caused by *C. burnetii*, and a large range of animals can be infected” [3], “bacterial zoonosis, caused by the intracellular bacteria *C. burnetii*” [11], “a zoonotic disease caused by the ubiquitous pathogen *C. burnetii* responsible for acute and chronic clinical manifestations” [1], “zoonosis with many manifestations” [12], and many others. Common terms such as infection, disease, reservoir, risk factor, host and zoonosis arise in the descriptions of Q fever, warranting definitions, explanations and sometimes reflections.

INFECTION AND DISEASE

Infection is said to occur when infectious organism invade a host, and multiply within it [13]. Infections may remain localized in a particular tissue or organ, or they may spread to distant tissues/organs, causing a disseminated infection. But not all infections automatically result in what we denominate disease. Defining health and disease is not straightforward [14, 15]. Disease may be described as “any departure from health” or “any impairment that interferes with or modifies the performance of normal functions” [16], or “clinical consequences, whether mild or severe” [13]. So, some infections remain asymptomatic or subclinical, whereas others result in “overt disease,” i.e., the infections become symptomatic or clinical. In asymptomatic infections, despite replication of the agent within the host, the interference within it is too mild to induce perceivable signs or symptoms, i.e., the host remains apparently healthy and the infection goes unnoticed, but the host may still transmit the infection to others. On the other hand, in symptomatic infections, the interference with the normal structure or function of a tissue or organ is large enough to induce signs or symptoms that are clinically apparent. This may lead to (veterinary) medical attention seeking and further diagnostic investigation. When talking about symptoms and clinical signs, one has to bear in mind that a symptom is a subjective feeling or perception, whereas a clinical sign is something that can be observed or measured objectively by others. Therefore, in the context of human medicine, both, clinical signs and symptoms are commonly referred to, whereas strictly speaking, only clinical signs are described for animals.

Within the context of Q fever, the line between infection and disease may become blurred. Sometimes the term Q fever is used to specifically describe in humans [3, 4, 17]. On other occasions, the term is extended to describe disease occurrence in animals [2, 18, 19]. And sometimes the distinction between infection and disease becomes less clear and the term Q fever is also used to describe asymptomatic infections by *C. burnetii* [20]. These slight variations in the terminology on Q fever and coxiellosis are common, as universally accepted definitions are lacking, despite trends of harmonization mostly for reporting purposes [5, 19, 21]. The reader is thus invited to keep an open mind when reading on the subject.

TRANSMISSION OF ZOONOSES

Q fever is considered an infectious disease because it is caused by an infectious agent. But is *C. burnetii* also a contagious or communicable disease, i.e., is it transmissible? Transmission of infection or infectious agents from an infected to a susceptible individual may occur by direct or indirect contact [13, 22]. Direct contact requires close proximity, and may occur, for example, by the respiratory or oral route, whereas indirect contact may occur by vectors, contaminated objects or the environment. Indirect transmission involving widespread contamination of the environment may provide more opportunities to infect different hosts, than direct contact [23]. Many pathogens can be transmitted by more than one route. *C. burnetii* can be transmitted by both, direct transmission - predominantly by the respiratory route - and indirect transmission - by exposure to contaminated environment or ticks [1].

Regarding the sources of infectious agents, diseases may be classified as anthroponoses or zoonoses, according to whether the pathogens are predominantly transmissible from human to human or between animals and humans, respectively. The term sapronose is used for agents which can replicate in the environment, and from where they can infect humans [24, 25]. Q fever is considered a zoonosis, defined as any disease that is transmitted from animals to humans, or vice versa [26]. It is neither an anthroponosis nor a sapronosis, as it does not readily transmit between humans, nor is it capable of replicating in the environment, despite being able to survive for weeks in the environment. Within zoonoses, a further distinction can be made according to the predominant direction of transmission. Anthropozoonoses are those where the disease or infection spreads from animals to humans, whereas with zooanthroponoses the spread is the other way round [25, 26]. This distinction is not recommended anymore and the term zoonosis should be preferentially used to describe any disease or infection that is naturally transmissible between vertebrate animals and humans [2, 5, 25, 27]. One important feature of several zoonoses, including Q fever, is that once transmitted to humans, the infection dies out quickly, as human host populations are rather inefficient in maintaining the transmission chain [25, 28].

EMERGING, RE-EMERGING AND NEGLECTED ZOONOSES

An emerging zoonosis or pathogen can be defined as “a pathogen that is newly recognized or has newly evolved, or that has occurred previously but shows an increase in incidence or expansion in geographical, host or vector range” (see www.who.int/zoonoses/emerging_zoonoses/en). On the other hand, a re-emerging pathogen is one whose incidence is increasing in an existing host population as a result of long-term changes in its underlying epidemiology [24, 29]. Pathogens may sometimes be labelled as emerging grounded on subjective criteria, or associated to increased awareness, improved diagnosis, characterization of previously unrecognized aetiological agents, and the interests of researcher, as much as any objective epidemiological data [24]. The majority of emerging and re-emerging human pathogens (>75%) are zoonotic [24]. Of these over 71% have wildlife origins [29].

Zoonotic pathogens are almost twice as likely as non-zoonotic pathogens to be regarded as emerging. They are not strongly associated with any particular reservoir species, but can be associated with both, the taxonomic and ecological amplitude of host range [24]. Transmissibility between humans is a risk factor for the emergence of zoonotic pathogens. We have a poorer understanding of the epidemiology of multi-host pathogens than simpler single-host systems. This scarcity of understanding is a particular problem with emerging diseases, since most emerging human, domestic animal and wildlife diseases infect multiple hosts. Reservoirs should be defined with reference to particular target populations [30].

Through constant modifications in human and animal demographics, such as the intensification of farming and concentration of animals, as well as environmental fluctuations, new and recurring diseases are likely to continue to emerge [29, 31]. They may also be classified as opportunistic, since the opportunity of spread to human hosts may rise due to factors such as changing patterns of lifestyle, farming, transportation, etc. [24, 29, 32]. Since more resources are allocated to disease-related research and treatment in the northern hemisphere, the number of hosts and pathogens “discovered” in these countries tends to increase [32–34]. In the case of Q fever the number of publications on outbreaks has been growing since 1999. This increase may reflect a higher attentiveness to the disease rather than a true emergence. The so called re-emergence of Q fever could be explained by an enhanced vigilance and the increased dedication of more resources to the improvement of the diagnosis for which serological and PCR tests allow an accurate detection of the infected flocks [35].

Q fever has been coined an emerging or re-emerging disease [35, 36] on one hand, and a neglected zoonosis on the other [20, 37, 38]. The concept of neglected zoonosis is commonly associated with poverty, disproportionately affecting neglected populations and less developed countries [29, 37, 39, 40]. However, Q fever can also be termed a neglected zoonosis in the sense of underdiagnosis and underreporting due to lack of awareness or lack of surveillance systems [20].

DRIVERS OF DISEASE EMERGENCE

Several factors have been proposed to explain disease emergence, including pathogen characteristics (mutation, recombination and genetic drifts), host characteristics (immunosuppression), host population characteristics (population size, behaviour and movements) and ecological and environmental factors (land use, changes in agriculture, deforestation and urbanization) [24, 41]. Within pathogen characteristics, the ability to infect multiple hosts seems to be determinant, since multiple host pathogens are very prevalent among human pathogens (61.6%), even more among domestic mammal pathogens (livestock 77.3% and carnivores 90.0%) [30, 32]. Host range and biodiversity are also associated with disease emergence, since more zoonotic host species are expected to occur in regions with high biodiversity. Nevertheless, in terms of emergence, the majority of human infectious diseases appeared for the first time in northerly latitudes, with a hotspot in Europe [32].

The reservoir species also play an important role in the emergence of zoonosis. Ungulate reservoirs of zoonotic disease have been of particular interest because of high human contact rates through hunting, and the degree of contact or relatedness between wild and domesticated species (livestock). The time since domestication correlates positively with the number of

zoonotic infections shared between ungulates and humans, and the fact that species with the longest history of domestication carry more zoonotic pathogens and also may transmit infection to a greater diversity of alternative host species [32]. Many zoonotic pathogens fall into the category of generalist agents exhibiting extensive host diversity. *C. burnetii* is a good example as it can infect hosts ranging from domestic animals to wildlife, reptiles, fish, birds and ticks.

TYPES OF HOSTS AND RESERVOIRS

C. burnetii is a generalist or multi-host pathogen [2, 5, 19, 29]. And, generally speaking, the epidemiology of these pathogens is complex [30, 42]. Despite *C. burnetii* being able to infect multiple species, interestingly, important species-specific traits exist regarding transmission and pathogenesis. As described above, transmission occurs predominantly from animals to humans. Transmission between certain animal species, in particular ruminants, occurs readily, whereas between humans it does not, i.e., the infection cycle can be more efficiently maintained within certain animal populations such as ruminants, but less between others. Consequently, in the context of Q fever, ruminants are considered the maintenance (reservoir) hosts, whereas humans are considered accidental (incidental hosts or dead-end hosts). Incidental (accidental or dead-end hosts) are those that can be infected, but usually do not further transmit the infection [22].

Sometimes a distinction is made between the terms maintenance host and reservoir. A maintenance host, also denominated primary or natural host, is a species which can maintain an infection in an area, whereas in a reservoir host, the agent multiplies and represents a common source of infection for others [22]. However, frequently, both terms are used interchangeably. For example, small ruminants can be considered maintenance hosts or reservoirs for *C. burnetii*, as their abortions are an important source of environmental contamination and/or direct transmission to other animals or humans [19, 20]. More recently and within the context of generalist or multi-host pathogens, the term reservoir has been subject to discussion and redefinition, moving away from the single-species single-host concept, and allowing for interaction between multiple species and also the environment. Haydon et al. [30] defined a reservoir as “one or more epidemiologically connected populations or environments in which the pathogen can be permanently maintained and from which infection is transmitted to the defined target population.” According to Ashford [43], the above definition implies that the reservoir includes all hosts equally, irrespective of its role in transmission to the target host and argues that incidental and maintenance hosts should be considered differently. He refined the definition of reservoirs of infection as ecologic systems that include all different host populations, environmental components, as well as quantitative requisites such as critical community size, necessary to maintain the agent indefinitely. The reservoir for *C. burnetii* can thus be seen as the ecologic system that includes different host species (e.g., ruminants as maintenance hosts and humans as incidental hosts), an environmental compartment (e.g., resistance in the environment and easy spread by the windborne route) and critical community size (e.g., herd size, and geographical proximity between farms and human settlements) [23, 44–46].

The term pathogen spillover also is frequently used in the context of Q fever, and other emerging infectious diseases. Spillover is said to occur when transmission from a reservoir population to a given (incidental) host population leads to epidemics [32, 41, 47]. Q fever epidemics in humans are a good example of spillover infections from infected sheep and goats to humans [2, 48].

Summarizing, *C. burnetii* it is a multi-host pathogen with an environmental component [20, 28]. Domestic goats and sheep (also cattle) are considered maintenance hosts, as they maintain infection by excreting high numbers of bacteria, especially during abortions. Resistance of the agent allows survival in the environment. Other susceptible hosts such as horses, cats, birds and ticks, as well as humans, may get infected either by direct contact with infected goats or by indirect contact (inhalation) with aerosolized particles from the environment. These are considered dead-end hosts, and infection is said to occur by spillover from maintenance hosts.

DISEASE OCCURRENCE: SPORADIC, ENDEMIC AND EPIDEMIC

Depending on the context, the occurrence of Q fever can be described as sporadic, endemic or epidemic. An infection or disease is said to be endemic when it occurs regularly [13, 22]. Q fever (*C. burnetii* infection) is often described as being endemic in ruminants [49–51]. After infection, whether symptomatic or asymptomatic, animals and humans mount a humoral immune response, i.e., antibodies specific to *C. burnetii*, and these persist for many months or years and can easily be measured [10, 52, 53]. If a high proportion of animals have antibodies to *C. burnetii*, i.e., seroprevalence is high, it is inferred that the agent is circulating and consequently that the infection is endemic [10, 20, 49, 54].

On the other hand, outbreaks or epidemics are said to occur when there is a sudden increase in frequency of disease above endemic levels [13, 22]. These terms typically are related to the occurrence of disease – either in animals and/or in humans - and not solely to infection [10, 23, 55, 56]. Disease or outbreaks may occur sporadically, i.e., irregularly and haphazardly in single animals of a single farm, or they may occur in clusters of animals/farms more or less prolonged in time, such as the 2007-2010 outbreak in the Netherlands [3, 5, 22, 49].

DETERMINANTS OF DISEASE OR RISK FACTORS

How can it then be explained, that despite infection by *C. burnetii* being so widespread, the disease occurrence in animals as well as in humans is mostly only sporadic? And why does it sometimes, but not always, lead to outbreaks? The development of disease following *C. burnetii* infection is – as in many other infections - influenced by so-called determinants of disease or risk factors. The presence of risk factors increases the probability of high levels of bacterial excretion, environmental contamination, and (zoonotic) spread of infection, development of clinical disease etc.

What are the risk factors for the development of clinical disease (Q fever) in animals? In ruminants, most infections by *C. burnetii* are asymptomatic, and the main clinical

manifestation is abortion. Consequently, two of the most obvious risk factors are being female and being pregnant [2, 3]. Clinical manifestations such as abortions may be sporadic in herds where few breeding females are present, whereas outbreaks may result in farms where many pregnant females are present, as is the case of intensive dairy sheep and goat farms, especially when reproduction is synchronized [10, 53, 56, 57]. Intensification of animal husbandry systems is thus considered an important risk factor for Q fever outbreaks [10, 20, 58].

In humans, clinical signs are different; they may be unspecific and quite variable. Abortions may occur, but they are not a main feature. Risk factors for the development of human disease are different from those of sheep and goats [1, 9]. For example, risk factors for the development of chronic Q fever, which may develop after primary acute infection (whether symptomatic or not), are pre-existing cardio-vascular conditions [2, 59]. Two important risk factors for the occurrence of Q fever outbreaks in humans are close proximity (< 5km) of humans to infected small ruminant farms, and intensive management systems of sheep/goat farms [3, 10, 52, 58, 60, 61]. Under certain circumstances, occupational exposure may play a role as a risk factor for *C. burnetii* infection and development of Q fever [4, 10, 62, 63]. Under others, such as outbreaks due to windborne spread, occupational exposure may play a minor role [3, 10, 58, 64].

NOTIFICATION, CASE DEFINITIONS AND SURVEILLANCE SYSTEMS

Public health surveillance has been defined by the World Health Organization (WHO) as “the continuous, systematic collection, analysis and interpretation of health-related data needed for the planning, implementation, and evaluation of public health practice” (see www.who.org). The objectives of surveillance systems include serving as an early warning system for impending public health emergencies; documenting the impact of an intervention or tracking progress towards specified goals; and monitoring and clarifying the epidemiology of health problems, to allow setting of priorities and to inform public health policy and strategies (also see www.who.org).

Notification

Q fever is a notifiable disease in many countries. Notifiable or reportable diseases have a legal framework by which they should be reported to official health authorities. Notification may be due at national, regional and/or international level [4, 18, 65–68]. Importantly, despite recommendations of notification at international level, national legal frameworks vary and notification is not compulsory in all countries [21]. For example, within 24 EU member states, Q fever is reportable in humans and animals in 17 and 15 member states, respectively [19]. The reasons for these discrepancies in reporting among countries may be at least two-fold.

On one hand, the relative importance of Q fever as compared to other health-related conditions varies with time and among countries [3, 37]. For example, in Kenya, Q fever is currently neither a notifiable disease, nor is it on the list of zoonotic disease of priority, as

there are other conditions with higher impact on animal and public health [37]. In the Netherlands, Q fever is notifiable since 1978, and until 2007 on average 17 cases were notified per year [49, 69]. The relative importance of Q fever increased in the Netherlands during the 2007-2010 outbreaks, when it jumped from a sporadic occurrence to an epidemic (outbreak) with an important public health impact on urban resident populations.

The second major reason for discrepancies in reporting Q fever can be related to difficulties in diagnosing the condition and on setting case definitions. The majority of infections with *C. burnetii* in humans and animals either run an asymptomatic course or are characterized by transient mild and nonspecific signs. These infections are generally (dis-) missed, especially in situations of low endemicity, when awareness regarding Q fever among medical and veterinary practitioners is low [3, 19]. On the other hand, it may be desirable to have monitoring activities in place at all times to allow early detection of outbreaks and rapid implementation of control measures to minimize public and animal health impact.

Case Definitions

Reporting systems require case definitions. A case definition states “when the sample is considered to be positive for the zoonotic agent or when the person, animal, herd or flock is considered to be infected with the zoonotic agent” [19]. Case definitions vary according to the objective of the study, so case definitions for seroepidemiological studies may differ from those for clinical diagnosis or from those of monitoring and surveillance purposes [4]. Importantly, mild cases may remain undetected if the patient does not seek medical attention, as only then and depending on medical awareness, it may be referred for laboratory confirmation [4, 7, 8, 70]. Underreporting is a very important feature of Q fever. During the large Q fever outbreak in the Netherlands, it was estimated that approximately 9 of every 10 infections were not notified [59].

Regarding human Q fever, case definitions for reporting purposes have been laid out, for example, by the European Commission to facilitate uniform reporting by member states [21]. Accordingly, Q fever (*C. burnetii*) diagnosis is based on clinical, laboratory and epidemiological criteria. At least one of the following three clinical symptoms: fever, pneumonia and/or hepatitis must be present. Additionally, at least one of the following laboratory criteria must be met: isolation of *C. burnetii* or detection of its nucleic acid from a clinical specimen, or a specific antibody response (IgG or IgM phase II). Finally, at least one of two epidemiological links must be present: exposure to a common source or animal to human transmission. Based upon these criteria, cases of Q fever in humans may be classified as “probable” if clinical and epidemiological criteria are fulfilled, or as “confirmed” if clinical and laboratory criteria are fulfilled. One potential drawback of these case definitions is that they mostly focus on acute Q fever. In the aftermath of major Q fever outbreaks, the necessity of early detection of chronic Q fever cases for treatment purposes increases [9, 59, 71]. The lack of precedence of large Q fever outbreaks in the past partly explains the focus of some notification systems on acute Q fever. In response to the large Q fever outbreak in the Netherlands new follow-up strategies of early detection for chronic Q fever in general populations were developed [7, 9, 71]. The distinction between acute and chronic Q fever is made in the criteria for surveillance purposes by the Centre of Disease Control, where cases

are defined as “confirmed” and “probable” based on clinical evidence as well as laboratory “confirmed” and laboratory “supportive” criteria [4].

For the purpose of diagnosis of human Q fever in a clinical context, case definitions are nearly always specified for acute and chronic manifestations. For example, acute Q fever may be suspected based on clinical signs such as fever, muscle pain, headache, pneumonia and other symptoms, especially if epidemiological links exist [1, 70]. Only once suspected, laboratory confirmation can be carried out [12, 56, 64, 71]. Chronic Q fever cases may be detected by screening high risk group patients, e.g., those with pre-existing cardiovascular conditions [9, 59, 71].

Regarding animal health, Q fever is listed as notifiable by the World Animal Health Organization [68]. Recommended diagnostic procedures and case definitions are laid out in the Manual of diagnostic tests and vaccines for terrestrial animals [5]. Similar as for humans, the diagnosis of Q fever in animals is based upon a combination of serology and PCR assays. But, although identification of *C. burnetii* from an individual animal could confirm diagnosis (similar as for humans), as a general principle, diagnostic test results should be interpreted at herd/flock level, together with its clinical history [5]. A positive Q fever case in animals is thus defined by the OIE as a herd or flock with clinical signs (abortion and/or stillbirth) for which the presence of the agent has been confirmed [2, 5, 19]. For monitoring and reporting purposes of Q fever in animals in EU member states, a Q fever case definition was proposed as a herd/flock with clinical pattern of coxiellosis (abortion and/or stillbirth), confirmation of the agents` presence and positive serology [19]. A distinction is made between “probable” cases where clinical signs (abortion and/or stillbirth) and positive serology was observed, and “confirmed” cases, where the presence of the agent has to be demonstrated.

Surveillance Systems

Surveillance and monitoring has been described as the “key defence against emerging pathogens,” often required to be “integrated across human, domestic animal and wildlife populations” [24, 72]. This could be illustrated by the 2007-2010 epidemic of Q fever in the Netherlands, whose magnitude and impact at animal and human health level could be estimated through monitoring and surveillance systems [49]. Monitoring can be defined as an intermittent performance and analysis of routine measurements and observations, aiming to detect changes in the environment or health status of a population [73], or as a system of collecting, analysing and disseminating data on the occurrence of zoonoses, zoonotic agents and antimicrobial resistance (Directive 2003/99/EC) [19]. Surveillance is the systematic ongoing collection, collation, and analysis of information related to animal health and the timely dissemination of information so that action can be taken [73]. Both, monitoring and surveillance are similar in the continuous observation of health related parameters, but only in surveillance systems, active control measures are taken when positive cases are detected [19, 73]. Because the distinction between monitoring and surveillance can be difficult, the single term monitoring and surveillance system (MOSS) has been proposed [24, 72].

As a consequence of the large Q fever outbreak in the Netherlands, harmonised schemes for the monitoring and reporting of Q fever in animals in the European Union were developed [19]. As Q fever outbreaks in humans are most frequently associated with *C. burnetii*

infection in domestic ruminants, passive and active monitoring systems were described which focus on domestic cattle, sheep and goats. Passive monitoring schemes aim to detect clinically affected herds/flocks of domestic ruminants by encouraging the inclusion of Q fever in differential diagnostic testing in all herds/flocks with abortions. Active monitoring, on the other hand, can be applied when the aim is to estimate the prevalence of *C. burnetii* infections in animal populations, e.g., when disease frequency in humans or animals is suspected to be high. Generally, large sample sizes are required for active monitoring, which turns it labour- and cost-intensive [19].

Q fever outbreak investigations represent excellent examples of multidisciplinary teamwork and practical application of the “One Health” concept [23, 45, 64, 74]. Similar to other recent major outbreaks of zoonoses, such as avian influenza, they illustrate the complexity and high scientific level of outbreak investigation nowadays, using methods such as molecular epidemiology [75], spatial modelling [46, 51, 74], vaccine effectiveness modelling [76] and atmospheric dispersion modelling [23].

IMPACT ON PUBLIC HEALTH

Public health is concerned with protecting the health of populations, and can be defined as “the science of protecting and improving the health of families and communities through promotion of healthy lifestyles, research for disease and injury prevention and detection and control of infectious diseases” (see www.cdcfoundation.org/). Veterinary public health is an essential part of public health linking the various disciplines of the epidemiological triad human-animal-environment. It can be defined as “the sum of all contributions to the physical, mental and social well-being of humans through an understanding and application of veterinary science” [77].

The estimation of the impact or burden of Q fever on public health can be a challenge. As mentioned above, unspecific clinical pictures and variability in disease awareness may lead to considerable underreporting. As opposed to mild *C. burnetii* infections or the occurrence of sporadic Q fever, major (relevant) public health impacts are usually related to outbreaks [19, 78]. For example, the large Q fever epidemic in the Netherlands resulted in a serious burden of disease, which can be described qualitatively by the hospitalisation of acute cases and, in the longer term, by the intense medical treatment and eventual premature death of chronic cases [9, 20, 79]. The impact on public health of Q fever has been measured by instruments such as the Nijmegen Clinical Screening Instrument (NCSI) or Short Form 36 (SF-36) [80–82]. These instruments are particularly useful for assessing the long term or chronic consequences of Q fever infections such as severe chronic fatigue [79, 82–84].

Quantitative assessments of the impact of diseases on animal and public health can also be made by different metrics. Economic impact studies assess lost labour productivity due to human illness or reduced tourism to affected areas, or, in the case of animal diseases, the reduced productivity and consequent reduced food production for human consumption [28]. In a recent economic impact assessment of the Q fever outbreak in the Netherlands, the biggest losses were observed in the public (human health) sector, with an estimated 222 Million Euro [50]. Interestingly, income losses due to chronic fatigue syndrome and chronic Q fever were considered substantial, as they accumulated over time, whereas treatment costs

accounted for less than 2% of the total human health costs. The second highest cost, of approximately 85 Million Euro, was related to disease control in the agricultural sector, whereas production losses on infected farms were considered relatively minor [50].

The impact and ranking of different diseases in terms of public health is commonly assessed using disability-adjusted life years (DALY). One DALY can be seen as one year of “healthy” life lost due to a specific disease (see www.who.int). For example, for the large Q fever outbreak in the Netherlands, the burden for human health was estimated to be 2,462 DALY’s, with chronic fatigue syndrome as the most prominent contribution [50]. Linking this estimate with the economic evaluation, the total intervention cost in agriculture was estimated as 35,000 Euro per DALY (85 Million Euro/2462 DALY) [50]. The use of DALYs further allows the comparison of different diseases. For example, for the year 2009 in the Netherlands, seasonal influenza by A(H1N1)pdm09 was estimated to cause approximately four times more DALYs than Q fever, but Q fever was shown to be 8 to 28 times more severe than influenza, because of the long-term sequelae of Q fever, whereas influenza’s burden was largely due to mortality [85].

CONCLUSION

Infections by *C. burnetii* and Q fever are very complex in terms of biology, epidemiology, diagnosis and control. In this chapter, a brief overview on the disease was given and relevant epidemiological terminology was defined and illustrated within the context of Q fever/coxiellosis. Transmission cycles between different hosts systems, the importance of distinguishing between infection and disease as well as the importance of case definitions for monitoring and surveillance systems were described. The impact of Q fever on public health may very quickly change from very low in sporadic single cases to very high in the case of major outbreaks. This chapter serves as an aid for the understanding for the remaining chapters.

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Chapter 543

PHARMACOGENOMICS, REGULATORY AFFAIRS AND PUBLIC HEALTH

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ABSTRACT

The science of pharmacogenomics has advanced significantly in the last five years. The Pharmacogenomics helps identify interindividual variabilities in drug response (both toxicity and effectiveness). This information will make it possible to individualize therapy with the intent of maximizing effectiveness and minimizing risk. The objective of this chapter is to present an overview about the international regulations about this topic and to present briefly the introduction of this science in Cuba. It was done a revision in the international literature about the existing regulations, guidance, concept paper, etc. The chapter illustrates the general requirements for regulation, e.g., reception, codification and sample storage, biomarkers, ethical consideration as well as it is explained the relation of this discipline with pharmacokinetics studies, bioequivalence trials and pharmacovigilance systems. Cuban guidance will be introduced which is focused to pharmacogenetic studies during the clinical phases of drug development. Pharmacogenetic has several advantages in order to get rational use of drugs but still there are many challenges which will be shown in this work. The hope for the future is that through personalized medicine, doctors and patients will be able to make better-informed choices about treatment. This treatment will avoid the adverse drug reaction to the medication and will improve the diagnosis diseases as well as the prevention and treatment of diseases.

Keywords: pharmacogenetics, pharmacogenomics, pharmacovigilance, regulatory, public health

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INTRODUCTION

Pharmacogenetics, one of the cornerstones of personalized medicine, has the potential to change the way in which health care is offered by stratifying patients into various pretreatment categories, such as likely responders, likely non-responders or likely to experience adverse drug reactions. In order to advance drug development and regulatory science, regulatory agencies globally have promulgated guidelines on pharmacogenetics for nearly a decade (Evans, 2003).

Pharmacogenomics helps in identifying inter-individual variability in drug response (both toxicity and effectiveness). This information will make it possible to individualize therapy with the intent of maximizing effectiveness and minimizing risk beside that, pharmacogenomics allows optimize pharmacovigilance by identifying risk of adverse reactions and to improve the design of clinical trials by stratifying group population. Thus, it is important to regulate this subject in order to minimize the adverse drug reactions, make decisions based on risk benefit criteria, and allow the rational use of drugs based on other criteria and to avoid the discrimination of people (Gibbsburg & Willard, 2009).

The main mission of any regulatory agency is to control the quality, safety and efficacy of drugs. The main regulatory agencies around the world: Food and Drug Administration (FDA) from United States of America, Health Canada (Canada), European Medicines Agency (EMA) from Europe and Pharmaceuticals and Medical Devices Agency (PMDA) from Japan have issued guidance's about pharmacogenomics as well as the International Conference on Harmonization (ICH) which is integrated by FDA, EMA, PMDA and Pharmaceutical companies.

There are different regulatory dispositions related with pharmacogenomic studies; for example: concept paper, reflection paper, drafts, position paper, which explains how to implement the regulations and guidance about pharmacogenomic assays (FDA, 2016).

EMA is the regulatory agency with more regulations about this topic, followed by FDA and International Conference of Harmonization (ICH). These documents explain about the samples reception, the codification, the use of biomarkers. Recently, EMA published a new guide in relation with good practices for pharmacogenomic moreover there are guides which include the importance of Pharmacogenomic in the prescription as well as the drug rescue from the market and pharmacogenetic methodologies in pharmacokinetics studies, etc. On the other side, World Health Organization, in the technical report series, appears as potential risk the declaration of genetic polymorphism for its importance in the drug metabolized by polymorphic enzymes e.g. Cytochrome P-450 (CYP) 3A4 metabolize Indinavir and nelfinavir and promethazine is metabolized by CYP 2D6 (WHO, 2006).

Each regulatory agency has settled their guides according to the rational use of drug for their population, the safety and efficacy of the drugs and taking into account the context of every country for the further implementation.

In general the guidance's published are formed by the following chapters (EMA, 2006):

- Introduction
- Background
- Objectives and Scope

- Terms and Definitions
- Regulatory Requirements

Introduction: In this chapter it is explained a general summary of the regulatory disposition.

Background: Refers about the previous report about the topic of the guidance.

Objectives and Scope: Specify the aims of the regulatory disposition, and its scope should indicate whether the guideline concern a selected area of medicinal product development where limited experience is available and knowledge is fast evolving requiring the need for easy updates and flexibility.

Concerning to the regulatory requirements is mentioned the requirements recommended or demanded related with the codification of samples, the obligation in the use of biomarkers, ethical aspects, etc.

MAIN ITEMS IN THE GUIDELINES

Terms and Definitions

The uses of terms in this subject have been harmonized and these have been accepted by the international scientific community (Regulatory, academics, ethical committee, and health professionals).

Actually the terms pharmacogenomic and pharmacogenetics are frequently used interchangeably. The achievement of widely accepted working definitions of the two would be a useful first approach to applying pharmacogenetics and pharmacogenomics in clinical trials. It is important to single out pharmacogenetics and pharmacogenomics from the wider field of genetic testing as the latter encompasses different level of concerns especially in terms of sensitivity of sample handling, data and trial results management (ICH, 2016).

Pharmacogenetics: is the study of interindividual variations in DNA sequence related to drug response.

Pharmacogenomics: is the study of the variability of the expression of individual genes relevant to disease susceptibility as well as drug response at cellular, tissue, individual or population level. The term is broadly applicable to drug design discovery, and clinical development.

Other terms are also identified like, Mutation, Alleles, Single nucleotide polymorphism, Genomic Biomarker, Gene, Genotype, Phenotype, Locus (EMA, 2016).

MANAGEMENT AND STORAGE SAMPLES

The sample identification is very important for getting traceability of the results. According the guidelines published related with pharmacogenomic studies the samples and data can be identified in 4 general categories (Ricci et al., 2011).

- 1) Identified data: The samples are identified with personal identifiers such as (name, identification numbers, like social security or national insurance number), the right identification offers privacy protection similar to general healthcare confidentiality in everyday medical practice.
- 2) Coded Data and Samples. The data and coded samples are labeled at least with a unique code and do not carry any personal identifiers. These samples can have a unique or second label, the second code offers additional confidentiality, and second code is linked to the first code by a key. It is possible to trace the data or samples back to the individual by the use of both coding keys.
- 3) Anonymised Data and Samples: Anonymous data and samples are initially single or double coded but then the link between the subject's identifiers and the unique code (s) are subsequently deleted. Once the link has been deleted it is no longer possible to trace the data and samples back to the individual through the coding key (s). Anonymisation is intended to prevent subject re-identification.
- 4) Anonymous Data and Samples. Anonymous data and samples are never labelled with personal identifiers and therefore there is no potential to trace back genomic data and samples to an individual subject.

On the other side, the suitable storage is a key aspect for sample preservation, at the same time to the period of time for protecting the sample is very important, which can take several years. The biological samples could have variable quantities of nucleases in certain conditions, for this reason is important that samples have acceptable integrity in the storage conditions selected which should be checked and validated. All these process, reception codification and storage should fulfillment of good pharmacogenomic and clinical practices (EMA, 2016).

USE OF BIOMARKERS

Significant pharmacogenomic research has focused on understanding the molecular mechanism underlying certain adverse reactions and on recognizing biomarkers (BM)s that identify individuals at risk.

A genomic biomarker is a measurable DNA and/or RNA characteristic that is an indicator of normal biologic process, pathogenic processes, and/or response to therapeutic or other interventions (EMA, 2016).

A genomic biomarker could, for example, be a measurement of:

The expression of a gene

The function of a gene

The regulation of a gene.

There are 2 main types of BMs.

- 1) Predictive BMs: Are those that provide clues towards response (safety or efficacy or metabolic) to a particular therapeutic intervention, especially drug therapy. Evaluation of clinical utility of such predictive markers is facilitated by pivotal trials

conducted in defined patient populations, selected and grouped based on the marker (s).

- 2) Prognostic BMs: Those that indicate disease prognosis, that may not have an intrinsic relation to specific intervention, either drug therapy or otherwise. Thus prognostic BM may or may not provide the basis for a clinical decision or influence the decision algorithm for treatment or intervention. However, studies evaluating prognostic GBMs may provide a scientific background of the natural history of the disease, facilitate development of additional other biomarkers (genomic or non-genomic) and contribute to drug development indirectly.

Another important aspect is the critical parameters for the choice Biomarker assay.

The intended use of the BMs should be thought before development and validation of the chosen assay.

CRITICAL PARAMETERS FOR THE CHOICE BIOMARKER ASSAY (EMA, 2016)

- 1) Assay-specific considerations. These include, known attributes of analytical sensitivity, diagnostic sensitivity, specificity, accuracy, repeatability, reproducibility, linear range of quantitative assays including control of known relevant interference, and limits of detection.
- 2) Preanalytical factors: General principles of specimen acquisition regarding BMs, sample type, patient or subject selection criteria, conditions and preparation for sampling, sample handling, e.g., storage conditions, extraction procedure.
- 3) Analytical factors: Assays protocol, assay platform including amplification efficiency, linearity, precision, dynamic range as well as limit of detection, calibrators and software and algorithms used for the interpretation of results, performance variables.
- 4) Post analytical factors: Data handling and processing, relevant published data, meta data and standards available, comparative performance with relevant standard if available or state of the art test.
- 5) Validation steps in the development of an assay for a pharmacogenomic biomarkers: Assay performance evaluation: Validation of analytical performance, validation of in vivo clinical performance as relevant for context and intended uses (i.e sensitivity and specificity in detecting clinically relevant response), further plans in post market surveillance to confirm clinical utility.

Therefore, a biomarker should be qualified as early as possible for promoting its use in drug development when reasonable evidence for a particular context of use is available.

Another important point to consider is that a biomarker should be qualified internationally rather than by a single regulatory agency because most drugs are currently developed globally, and conducting a MRCT has become a standard strategy for drug development. For global drug developments, an internationally qualified biomarker is

necessary so that the data can be submitted to multiple regulatory agencies for a regulatory review and decision-making (EMA, 2016).

A big challenge is ‘biomarker qualification’. A PGx biomarker to be used in drug developments should be qualified and accepted by a regulatory agency because use of an unqualified and unacceptable biomarker may result in misinterpretation of the acquired data due to false signals (false-positive or -negative signal) and, therefore, may not be used in regulatory decision-making. Biomarker qualification by a regulatory agency is an important process to qualify the objective and context of use of the biomarker before it can be widely used in drug development. To confirm the acceptability of the biomarker, each agency – PMDA, the FDA and the EMA – has established a biomarker qualification process. Thus, in many cases the identified biomarkers are used for more than one drug and consequently the same biomarker can be used for different indications, for example, Glivec for several types of leukemia but also for stromal tumours (Otsubo et al., 2013). Figure 1 shows some of the differences in required pharmacogenetics testing between EMA and FDA. The vast majority of drugs/78%) have similar label requirements for diagnostic testing in both geographies.

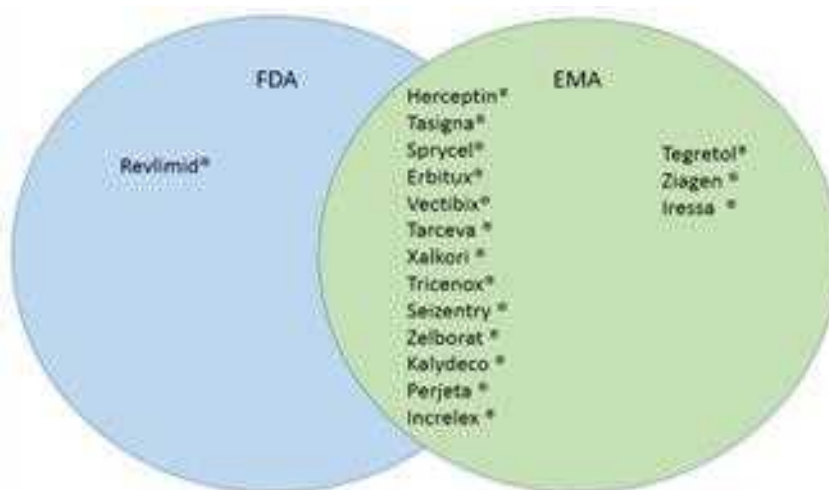


Figure 1. Drug required pharmacogenetic companion diagnostic testing.

Biomarkers open a new era for pharmaceutical companies concerning the Companion diagnostics for drugs mainly for cancer treatment in order to guarantee the safety and efficacy of the drugs and the reduction of the cost (Berryessa et al., 2013).

ETHICAL ISSUES

This is a big challenge in this subject, particularly as science and technology continue to advance very rapidly. Whole genome sequencing, for example, is poised to eliminate the need for individual genetic tests, thus raising ethical concerns about the creation of genetic information which individuals may or may not want to know and which may or may not remain privately secured. Ethical Committee has a great responsibility, should approve the pharmacogenomic studies taking into account, Balancing risk-benefit, Ethical responsibilities

of all the participants in the study, The patients need all necessary information to make the own decision. All anticipatable information of expected benefits or expected harms. Concern of individual participants regarding anonymity, privacy and confidentiality should be respected and should be addressed in a research agreement the discrimination should not be allowed and the protocol should always refer the alternative treatment in case the patient according the result cannot take the drug assayed (Issa et al., 2002).

Another important point is the Investigation in biological samples with genetic material because (Berryessa et al., 2013):

- 1) Genetic material is unique for each person and does not change along the time. It means that patient will be potentially identified.
- 2) Because DNA is stable. Would be capable of multiple researches. Many of them are not in related to the goals for which they were gotten.
- 3) The samples that will be taken for pharmacogenomic assays could be useful in order to know the diseases which the subject does not want to know.
- 4) Because genetic material is common for parents and brothers, the finding could have implications for subject relatives what shows as results individual ethical problems.

Pharmacogenetics allows researchers to conduct gene profiling to answer questions about patient responses to medicines, which results in the design of safer and more effective medicines. The science and its applications are real today and will be increasingly utilized in coming years. While it is extremely unlikely that individuals will be excluded from health insurance because of their response (or lack) to a particular drug, or that they will be subject to employment exclusions (in hiring, promoting or job responsibilities), ethical issues are central to policy debate about the appropriate use of pharmacogenetic testing and its related benefits (Berryessa et al., 2013).

The European regulatory strategy adopted in recent years to raise awareness via informing health-care professionals by adding pharmacogenomic information in drug label is evolving and is now increasingly providing practical guidance on why, when and how to obtain pharmacogenomic individual patient's data to facilitate pharmacogenomics (PGx)-guided drug treatment.

To further promote the scientifically sound integration of PGx in product development and consequently the product label and patient treatment, the EMA sets recommendations and requirements for the investigation and incorporation of PGx in drug development and surveillance/ pharmacovigilance.

In addition, the Agency has elaborated guidance on the importance of identification and validation of genomic biomarkers 10–13 and established a number of activities (Ehrman et al., 2015).

Drug labels form an intrinsic and integral part of the marketing authorization and are intended to guide patient treatment.

The Summary product characteristics (SmPC) is the basis of information for health-care professionals on how to use the medicinal product safely and effectively and the SmPC thus sets out key elements of drug benefits and risks relevant to the clinical use of the product defined during the medicine regulatory assessment process. Regulatory recommendations on how pharmacogenomic information shall be presented in the EU labels have been published (EC, 2016).

The description and place of pharmacogenomic information in the label (SmPC section) has also an important impact on reimbursement not only for the drug but also for the related companion diagnostic test used and potentially liability implications for the treating health-care professionals.

Almost 15% of EMA-evaluated medicines contain pharmacogenomic information in their label that directly impacts patient treatment. These sections include Therapeutic indications, Posology and method of administration and Contraindications etc. (EC, 2016).

In Table 1 it is shown, the information in each chapter.

Table 1. Types of PGx information for labeling

Section of Label.	Pharmacogenomic (PG) information.
Therapeutic indications	If the product's indication depends on a particular genotype or the expression of a gene or a particular phenotype, then this should be stated in the indication.
Dosage and administration.	Where necessary, dosage adjustments in patients with a particular genotype should be stated (with cross-reference to other relevant sections for further detail as appropriate).
Contraindications.	Linked to a particular genotype.
Special warning and precautions	Subjects or patients with a specific genotype or phenotype might either not respond to the treatment or be at risk of a pronounced pharmacodynamic effect or adverse reaction. These may arise because of non-functioning enzyme alleles, alternative metabolic pathways (governed by specific alleles) or transporter deficiencies. Such situations should be clearly described if known.
Drug Interactions.	If interactions with other medicinal products depend on polymorphisms of metabolizing enzymes or certain genotypes, then this should be stated.
Undesirable effects.	This section may include information on any clinically relevant differences specifically observed in patients with a specific genotype.
Overdose.	If applicable, counteractive measures based on genetic factors should be described.
Pharmacodynamic properties.	Any relevant pharmacogenetics information from clinical studies may be mentioned here. This should include any data showing a difference in benefit or risk depending on a particular genotype or phenotype.
Pharmacokinetic properties.	Variations with respect to polymorphic metabolism should be described, if clinically relevant, in quantitative terms.

More than 200 drug labels in the US, corresponding to about 10% of drugs approved by the FDA, contain pharmacogenetics information, still a relatively small figure. But it shows that a significant number of relationships between genetic markers and pharmacokinetic or drug response phenotypes are potentially relevant. Both at Food and Drug Administration and

at European Medicines Agency (EMA) pharmacogenomic information in drug labels is increasingly present and consequently tailored drug therapy to patients' genetic make-up can lead to improved benefit-risk balance of drug treatment by optimization of the target population and by tailored choice of drug treatment and drug dosages resulting in improved drug efficacy including minimization of adverse drug reactions (ADRs) (Eichelbaum et al., 2006).

There are several differences in how the main agencies deal with critical issues in the application of pharmacogenetics to pharmacokinetics parameters and these are highlighted in Table 2.

Table 2. Summary of differences between the three regulatory guidelines on pharmacogenetics. (Malliepard et al., 2013)

Issue	Regulatory agency.		
	European Medicinal Agency.	Pharmaceutical and Medical Devices Agency, Japan.	US Food and Drug Administration.
Development phases covered in guideline or guidance.	Preclinical and clinical development (Phase I-IV, focusing on PK).	Clinical development (Phases I-IV).	Early clinical development (Phases I and II).
Banking of DNA samples.	Highly recommended.	Recommended.	Recommended.
Genomic testing	Required	Recommended	Recommended
In vitro cut-off values*	> 50%	None	None
In vitro cut-off values*	> 25%	None	None

*It is firm requirement only when in vitro (> 50%) or in vivo (> 25%) cut-off values are met. For when pharmacogenetics-related testing is required in pharmacokinetics studies.

Health Canada, the Canada Regulatory Agency, has adopted ICH guidance Definitions for Genomic Biomarkers, Pharmacogenomics, Genomic Data and Sample Coding Categories E-15. In general the regulatory agencies have exchanged through different meeting, working party about Pharmacogenomic. There is consensus among the regulatory authorities concerning this topic.

Current Status of Pharmacogenomics in Latin-American Countries

Several studies have been done with Latin-American population related with the study of the variability of pheno- and genotypes in Hispanics. Most of these studies have been carried out through Ibero American Network of Pharmacogenomic and Pharmacogenetic. Studies related with the polymorphism of CYP isoenzymes (CYP 2C9, 2C19, 2D6) and variability in the drugs response have been done with population from Costa Rica, Peru, Uruguay, Cuba, Argentina, Nicaragua, Ecuador, Chile, Colombia, México. One of the studies describes the frequency of the most relevant pharmacogenetic biomarkers and metabolic phenotypes in

Central American healthy volunteers and to determine its interethnic variability. Twenty-six original research articles on allelic, genotypes or metabolic phenotype frequencies were analyzed, in which a total number of 7611 Central American healthy volunteers were included (6118 were analyzed for genotype and 1799 for metabolic phenotype). No reports were available for population from Belize and Honduras. The CYP2D6*4 and *5 frequencies in Amerindian populations from Costa Rica have shown to be among the highest frequencies so far reported in the world. Furthermore, NAT2*5 and *6 presented high frequencies in admixed populations than in Amerindians, but, inversely, the NAT2*7 was more frequent in Amerindians compared to an admixed population. Likewise, different patterns of distribution have been shown in HLA-A*02, *03 and HLA-B*07 among Native populations from Latin America. Reports on Central American populations were also found for the CYP2C19, LDLR, CYP2E1, MDR1, G6PD, TP53, CYP1A2, CYP3A4 and CYP3A5 biomarkers, but no data were available for the other 91 pharmacogenetic biomarkers revised in Central American populations. Differences in the frequency of some pharmacogenetic biomarkers and metabolic phenotypes were found, showing interethnic variability within Central American and with other Latin American populations (Céspedes-Garro et al., 2014, Rodeiro et al., 2012).

The main implications for the implementation in Latin-American are: the population are very heterogeneous, so that there is great variability in the drug response, another important aspect is the access to the drugs for every people is not equal is limited, according to the economical support, for this reason, the persons could be discriminated for using specific drugs, it means that people need the medicines and they cannot get them. There is a fragmentation of health care system according the health insurance. Latin-American is a continent which imports drugs and posologies, the drugs are sold in these countries but they have not assayed in them, another barrier is related to the need for clear guidelines for the use of pharmacogenomics in clinical practice due to the cost of trials.

Some of the possible solutions are: to create global development programmes, in several countries rather use bridging studies, the vital need is the education of health professional and the community, particular attention for special populations, like children and geriatrics patients, other relevant aspect is access to the information, and trials for the populations of Latin American countries. Pharmacogenetics should be introduced with the focus on the benefit for the majority of the population (Quiñones et al., 2014; Llerena, 2015).

CONSIDERATIONS ABOUT CUBA

Cuba is a country with heterogeneous population, with a growing development of biological product, which are subject to pharmacogenomic studies, these products are mainly for cancer treatment, for this reason is very important the right response to the patients (25). On the other side there are some pharmacogenetic studies with Cuban population through Pharmacogenetic Iberoamerican Network. Some of them are: It was demonstrated on debrisoquine hydroxylation in a Cuban population, moreover, differences on the frequency of ultrarapid metabolizers. The frequency of poor and ultrarapids metabolizers between Cubans and Spaniards have been determined, these results could explain inter-individual and

interethnic differences on drug response such as side effects or the therapeutic failures among Cuban patients receiving treatment with CYP2D6 substrates (Gonzalez et al., 2007).

The role of CYP2D6 activity variation in a sample of Cuban women with regard to their risk of eating disorder symptoms was evaluated and the results showed that there is a relationship between individual at risk of bulimia symptoms and increased CYP2D6 hydroxylation capacity in healthy Cuban women which supported previous finding about the relationship between eating disorders and CYP2D6 active genes (Lledó et al., 2012).

Taking into account the previous resulted and development of Cuban biotechnology, The Cuban Regulatory Agency, has clinical regulatory framework, which involves 5 main guidance (CECMED, 2016).

- 1) Requirements for authorization and modification of clinical trials.
- 2) Good Clinical Practices in Cuba.
- 3) Requirements for notification and reports of serious and unexpected adverse events in the clinical trials.
- 4) Requirements for clinical trials phase I and II with local products under investigation destined to the Cancer and AIDS treatment.
- 5) Requirements for availability and bioequivalence studies.

Recently it has been elaborated a guidance for carrying out pharmacogenetic studies during the clinical phases of drug development, it is oriented to the Industry, and this guide is focused to give some recommendations about this assays for example the use and type of biomarkers, sample codification, ethical aspect, a proposal of consent informed is proposed. This guide is about to be approved.

OTHER IMPORTANT ASPECTS FOR PHARMACOGENOMIC REGULATIONS

Bioequivalence Studies

In bioequivalence studies, intra-individual variability (CV_w) is critical in determining sample size. In particular, highly variable drugs may require enrolment of a greater number of subjects. We hypothesize that a strategy to reduce pharmacokinetic CV_w and hence sample size and costs would be to include subjects with decreased metabolic enzyme capacity for the drug under study. Regulatory agencies indicate that bioequivalence studies must be conducted in homogeneous but representative samples of the general population, ensuring external validity of the results. The pharmacogenomic assays are very useful for bioequivalence studies so that if the metabolic enzymatic capacity of the subjects is known for the assayed drug, this is clearly essential for the analysis of drug safety and efficacy to ensure that the results can be generalized to the whole population. However, as the main purpose of bioequivalence studies is to assess differences among drug products' bioavailabilities, decreasing intra-individual variability might increase the accuracy of determinations of drug-related factors (González-Vacarezza et al., 2012).

Use of Pharmacogenomic Methodologies in the Pharmacovigilance Evaluation of Medicinal Products

Some genomic biomarkers may predict drug exposure or the risk status of a patient related to adverse drug reactions (ADR). Genomic factors may play a role in the pathogenesis of both predictable and unpredictable ADRs as well as in clinical progression of diseases and rescue drug withdrawn from the market. Currently, there is limited information on the utilization of a genomic biomarker during follow up (post marketing) or on the effect of labeling with genomic information.

It is proposed guidelines to further discuss the following aspects (EMA, 2016).

- 1) Systematic consideration of pharmacogenomic effects and the implications of genomic biomarker use in the target population in the risk management plan (RMP) for:
 - a. Suspected/identified lack of efficacy/effectiveness of a relevant medicinal product related to the use of a genomic biomarker.
 - b. Safety concerns of a relevant medicinal product related to the use of a genomics biomarker.
- 2) Early consideration of when post authorization genomic data may need to be monitored or collected to confirm appropriate dose and co-medication, as well as to provide information or advice based on identified genomic biomarkers.
- 3) Collection and storage of genomic material (e.g., DNA or other) during clinical trials and upon the occurrence of serious ADR, lack effectiveness post authorization or unexpected worsening of the condition.
- 4) Methodologies for post authorization safety studies and post authorization efficacy/effectiveness studies regarding pharmacogenomic and biomarkers related issues (for adverse drug reaction and for lack of effectiveness) in the post marketing setting.
- 5) Consideration of the level and type of evidence for identification of signals, and how to report to the competent authorities (e.g., in RMP updates, periodic safety update reports published studies etc).
- 6) Consideration of risk minimization measures depending upon the importance of the possible clinical implications.
- 7) Labelling issues
 - a. What pharmacogenomic information to include in the product information (PI) and in which sections.
 - b. Assessing the impact of information in the product information on the use of the medicinal products.
 - c. Consideration of monitoring the effectiveness of genomic biomarker use in a clinical setting if there are requirements or recommendations in the product information on the use of genomic biomarkers.

The document is expected to provide for both industry and Regulatory Authorities regarding the application of pharmacogenomic methodologies in the pharmacovigilance evaluation of medicinal products and to support the development of methodologies for monitoring of the effectiveness of genetic biomarker use in the clinical setting.

Use of Pharmacogenetic Methodologies in the Pharmacokinetics Evaluation of Medicinal Products

The pharmacokinetics of many medicinal products is prone to interindividual variability, which is caused by several factors such as gender, age, weight, impaired renal and hepatic function and genetics. For drugs where pharmacogenetics is important, for pharmacokinetic variability there are guidelines which recommend that pharmacogenetics should be implemented in the drug development process. Genetic variants can influence a drug pharmacodynamics but also the absorption, distribution, metabolism and excretion of a drug. Furthermore, pharmacogenetics may also influence the formation, distribution and elimination of metabolites and this should be remembered if there are metabolites that may affect the efficacy and/or safety of the administered drug. Genotypes leading to absent decreased or increased enzyme or transport protein activity affecting the pharmacokinetics of the investigated drug and major pharmacologically active metabolites should be considered. Studies of the effect of pharmacogenetics on the pharmacokinetics of an active substance (parent and/or active metabolite) and its implication for efficacy and safety during development are generally required when the magnitude of the interindividual variation in drug exposure is so high as to likely influence the safety and/or efficacy of the drug in genetically variable populations. Factors that identify such a situation are (EMA, 2016):

- a. In vitro and/or in vivo studies indicate that known functionally polymorphic enzyme or transporter is likely to represent an important pathway in the metabolism or distribution of the drug or
- b. In vitro and/or in vivo studies that known functionally polymorphic enzyme or transporter is likely to represent an important pathway in the formation, elimination or distribution of a pharmacologically active or toxic metabolite, or
- c. In vivo studies indicate substantial interindividual differences in the pharmacokinetics of the drug likely to influence the efficacy or safety of the drug in the variable subpopulation, which cannot be explained by other intrinsic or extrinsic factor:

Studies on the effect of pharmacogenetics on the pharmacokinetics of an active substance and its implications for efficacy and safety are generally recommended during development if:

- a. Available in vitro data indicate that a human polymorphic enzyme or transporter contributes to the pharmacokinetics of the active substances but the quantitative role may be low based on the in vitro data or,
- b. There is high interindividual pharmacokinetic variability or there are pharmacokinetics outliers with higher or lower exposure to the active substance which cannot attributed to other known intrinsic or extrinsic factors, but which possibly can give rise to clinical efficacy and safety concerns based on the existing knowledge, or
- c. Major differences in pharmacokinetics are observed in different ethnic groups, which cannot be attributed to other known intrinsic or extrinsic factors.

Other recommendations have been made on how to implement pharmacogenetics during the different phases of clinical development, starting with in vitro studies conducted before investigation of the medicinal product in man. As a general rule, genotyping of the population included in a drug-drug interaction study for a relevant gene is recommended when pharmacogenetics are expected to affect the pharmacokinetics of any of the drugs included in the study. Because interactions might differ in subgroups of different pharmacogenetic genotypes, genotyping for the enzymes and transporters involved in the interaction should be carried out when appropriate (van Schie et al., 2011)).

CONCLUSION

Consideration of pharmacogenetics is also important in global drug development. Pharmacogenetic analysis in multi-regional clinical trials (MRCTs) will provide useful scientific data for understanding similarities and differences in drug responses (efficacy and/or safety) among various ethnicities. Specifically, when large differences in pharmacokinetics (PK) parameters among different populations is observed, pharmacogenetic analyses are useful for the examination of the reason or reasons for the differences and to set an appropriate dose for each population in later clinical trials (such as an exploratory dose-finding study) (Warner et al., 2011).

Pharmacogenomics-guided drug development has been implemented in practice in the last decade, resulting in increased labeling of drugs with pharmacogenomic information. However, there are still many challenges remaining in utilizing this process.

Main Challenges

- Education for health professionals and the community.
- Lack of familiarity with pharmacogenomics data.
- Resistance to the routine use of pharmacogenomics in medical care.
- Legal assurance.
- Interaction of the parties involved (patients, health-care professionals, authorities, health insurance companies and scientists).

As it comes to clinical translation, PGx is faced with big hopes and high expectations by everybody involved: patients who demand effective treatment free of adverse effects; physicians in need of guidance for selecting the most appropriate drug and the right dose for the patient; health care providers who have to find ways to improve medical care while reducing cost at the same time; regulatory agencies who need proof of concept to issue guidelines and laws, and also drug developers who are in fear of losing their costly drug candidates due to unforeseen toxicity in late stages of development (34).

In short integration of pharmacogenomics in clinical practice needs training of healthcare professionals and citizens, moreover legal and regulatory guidelines and safeguards will be needed. The answers to the questions of which patient should receive which drug and dose will be not easy, but we believe that the approach offered by pharmacogenomics should be

incorporated into the decision-making process. A more rational use of expensive treatment drugs together with actions to minimize patient toxic events and its consequences, would dramatically reduce medical costs as an added benefit.

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Chapter 544

THE OFFER OF ALTERNATIVE/COMPLEMENTARY THERAPIES IN THE BRAZILIAN PUBLIC HEALTH SYSTEM AND CONSIDERATIONS ABOUT THE LIMITS OF THE NEW AGE

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ABSTRACT

The author explores the public health system in Brazil and its relationship with the field of alternative and complementary therapies. In his article, he said that the recent availability of alternative therapies in Brazil's public health system is a result of the 971 Interministerial Order which, in 2006, established the National Policy of Integrative and Complementary Practices (PNPIC). Such policy aims at ensuring and promoting access, through the Unified Health System (SUS), to traditional Chinese medicine, homeopathy, phytotherapy, thermalism, and anthroposophical medicine. The announcement of the PNPIC created the opportunity for states and municipalities to elaborate their own policies and guidelines regarding the provision and use of Integrative and Complementary practices (ICPs) in the SUS.

In this chapter, whose focus is on the policies of ICPs, Toniol investigates the processes of legitimation and regulation of such therapeutic practices within SUS, as well as their implementation routines in health care units, clinics and public hospital in Rio Grande do Sul. The author begins by analyzing the invention of Integrative and Complementary Practices (ICPs). Invention of ICPs refers here equally to the production of bureaucratic state records that are specific to such policy, and to the daily work of therapists, physicians and managers who strive to turn alternative/complementary therapies into ICPs. With this in mind, Toniol concludes that the ICPs policies, in addition to legitimizing the availability of alternative/complementary therapies within SUS, likewise create the regulatory tools for carrying out such practices. In the second part, the author looks into the ties established between ICPs, spirituality and health. Here

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he explores both the normativity of these links by surveying documents produced by health care managing organizations, and the policy's practical implementation in clinics. Contending that the category of spirituality deserves attention on its own, Toniol demonstrate that the notion of "spirituality" has been mobilized agents and institutions involved in the provision of alternative/complementary therapies within SUS. The author indicates, lastly, that the provision of ICPs within SUS has become an official means of drawing attention to the spiritual dimension of health.

Keywords: alternative/complementary therapies, health system, Brazil

INTRODUCTION

Anthropological criticism customarily identifies substantial ties between so-called alternative therapies and the new age.¹ Two sets of parallel – although connected – arguments reinforce this understanding. The first is the affirmation that there is a historic relationship between the rise and popularization of some of these therapies and the new age movement. After all, it had been in the realm of the countercultural movements that therapeutic practices such as meditation, yoga and oriental healthcare modalities expanded in the West (see Kemp; Lewis 2007). The second is that beyond a historic connection, there was an ontological compatibility between new age principles and the form of understanding the relationship between health and disease that supports alternative therapies. I have already closely addressed the delineation of these characteristics in other texts (Toniol 2015a), here, I will merely indicate that alternative therapies constitute, according to a significant part of the literature, the privileged form of healthcare for subjects and groups identified with the new age. Moreover, the association made between the new age, health and alternative therapies, forms a type of tautological connection, in which the therapies themselves serve to establish the marks of what would be the new age and the new age is used to explain the phenomenon of alternative therapies.

The attention that social scientists of religion have given to delineating new age phenomenon have benefitted studies about alternative therapies, given that it considered them as objects pertinent to anthropological analysis. It is not by chance that the period of emergence of the investigations dedicated to the therapies coincides with the main moment of interest in the new age, which took place particularly during the 1990s and early 2000s. At the same time, the presumption of – or the insistent analytical emphasis on – the link between alternative therapies and the esotericism of the new age made it difficult for anthropologists to focus on processes that were progressively taking place in Brazil, and which to some degree were counter to the perspectives that conceived these practices as being deinstitutionalized, non-modern, counter-hegemonic, etc. I refer to processes that have been realized at least since the mid-1990s, such as the emergence of unions of holistic therapists, the rise of a political agenda in the national congress dedicated to regulating the profession, the teaching of alternative therapies in healthcare courses in public universities and, finally, support for the

¹ A first version of this article was published in Portuguese in number 16, volume 2, of the journal *Revista de Estudos da Religião*.

promotion and offer of these practices under the public federal Unified Health System (SUS).²

My purpose is not to deny the historic relevance of the association between the new age and alternative therapies. But I will affirm that it is important to not treat this relationship as an analytical *a priori*. Therefore, I insist on the need to question understandings that see a supposed tie with the new age to any modality of use and offer of alternative therapies. Despite the apparent triviality of this argument, its explicit enunciation is necessary, given that in the literature of the social sciences of religion there are few contributions that identify modes of existence of alternative therapies outside the empiric scope and analytical-conceptual language of the new age. The argument that I present in this text can be synthesized in the following idea: the indiscriminate use of the analytical focus of the new age does not illuminate, but makes invisible important processes and transformations in the field of alternative therapies. In this case, using a frequent concept from the field, what is at stake is recognizing that the new age as an analytical category, beyond being a mystic-esoteric nebula, as Françoise Champion suggested in an effort to affirm the porosity of the phenomenon (1993), may also have become a smoke screen for social scientists of religion (Tonio 2015b; 2016).

In the sections that follow I give visibility to other configurations and modes of existence of the so-called alternative therapies. I will emphasize the condition of alternative therapies as officialized and legitimated in the scientific-political field and supported by law. Based on these cases, I will present configurations of the use and offer of alternative therapies that shift the analytical rhetoric of the new age in at least three dimensions: a) in these configurations, the offer of alternative therapies is not aimed at a middle class, urban educated user and is not concentrated in the central neighborhoods of large cities. To the contrary, new agers here, at least in the Brazilian case, are users of Brazil's public healthcare system;³ b) for the public legitimation of these therapeutic practices, their experts mainly mobilize texts from the resolutions, laws and public policies promulgated by healthcare agencies (state and municipal secretariats of health and the World Health Organization), and rarely make reference to contact with a master or guru; c) the scientific-political legitimation of alternative therapies involves a necessary denial of proximity with the new age and, as a complement, the enactment of long-term institutional processes through which the World Health Organization (WHO) recognized the so-called traditional medicines, for example.

I insist that what is at stake here is not to deny the historic ties between alternative therapies and the new age phenomenon, but to ponder the uses of these ties as a justification for the use of the conceptual-analytical language of the new age to address any modality of realization of alternative therapies. In a more immediate plane, therefore, the sections that follow serve to differentiate a set of terms such as alternative/complementary therapies, traditional medicine, integrative and complementary practices and alternative and complementary medicine and indicate the existence of distinct configurations for the reality of each one of them. Moreover, an important argument will remain latent throughout this text: the variety of the phenomenon described as characteristic of the new age, allied to the

² The thesis by Fátima Tavares, *Alquimistas da cura*, is one of the exceptions in this field. Originally presented in 1998, this text conducts a seminal analysis about the beginning of the formation of holistic therapist unions in Rio de Janeiro and São Paulo (Tavares 2012).

³ The Unified Health System is the public healthcare system available throughout Brazil in a free and universal form, it is the world's largest public healthcare system.

insistent tendency of social scientists of religion to impute the category in their ethnographies, is what allows questioning if the systematic use of this analytical language has imprisoned the multiplicity of the realities observed in a fiction used to describe them.

The sections that follow synthesize part of the official path of legitimation and regulation of the offer and use of alternative therapies in Brazil, which has been my object of analysis for the past five years. The data presented result from this research and come mainly from participant observation in commissions dedicated to the issue in official entities that coordinate and plan Brazil's national and public SUS, from interviews conducted with public administrators and healthcare practitioners as well as official documents. I will focus on the terms used by the policies for integrative and complementary practices, which were capable of legitimizing the offer of alternative therapies in the SUS. I then associate the Brazilian process to the steps that have already been taken by the World Health Organization to recognize traditional medicine and complementary and alternative medicine as healthcare practices.

THE CONVERSION OF ALTERNATIVE/COMPLEMENTARY THERAPIES INTO INTEGRATIVE AND COMPLEMENTARY PRACTICES

On December 2013 the southern Brazilian state of Rio Grande do Sul approved the State Policy for Integrative and Complementary Practices (PEPIC/RS).⁴ In conformity with the text drafted by a commission of technicians and specialists in the field, the state secretariat of health published a decree that assured the implementation of the following practices in the state's healthcare network: floral therapies, integrative corporal practices, manual and manipulative therapies, community therapy and diet-therapy. In addition, the same document also recommended the insertion of meditation, chromotherapy, music-therapy, aromatherapy and geotherapy to care provided at health clinics and hospitals in the state. These therapeutic practices are combined with those that were already approved in 2006 when the National Policy for Integrative and Complementary Practices established the guidelines for implementation of phytotherapy, acupuncture, homeopathy, crenotherapy and anthroposophic medicine, in the entire network of the country's Unified Health System.⁵

Like Rio Grande do Sul, other states have also approved their own policies for integrative and complementary practices, and with this have added new practices to those already included in the national policy. This is the case of Minas Gerais, Santa Catarina, Rio Grande do Norte and Espírito Santo, to mention just a few examples. In the wake of enactment of the National Policy for Integrative and Complementary Practices, a series of municipal laws and decrees have been issued dedicated to these therapeutic practices. The municipal government of Santo Angelo in the interior of Rio Grande do Sul, for example, instituted, the municipal natural therapies program, in a decree. The main objective of the program is to implement, in

⁴ See Rio Grande do Sul 2014.

⁵ In 2017 the National Policy for Integrative and Complementary Practices was reformulated and also came to call for the offer of shantala, reiki, reflex-therapy, chiropractic, integrative community therapy, naturopathy, osteopathy, Yoga, circular dance, biodance, Ayurveda and art therapy.

the municipal health clinics, service based on practices such as: biotherapy, bioenergetics, iridology, hypnosis, alphatherapy, oligotherapy therapy, radiesthesia and others.⁶

The publication of the National Policy for Integrative and Complementary Practices in 2006 encouraged states and municipalities to produce their own policies and guidelines related to the offer and use of the integrative and complementary practices in the SUS. My interest is not in discussing the effectiveness of each one of these policies or to evaluate if they have had concrete repercussions on the routine of healthcare units in the country. My objectives are related to the specific terms that these policies for promotion of the integrative and complementary practices use to legitimate and regulate what they call integrative and complementary practices. Thus I begin with the understanding that, at the same time as the public policies dedicated to the integrative and complementary practices legitimate these therapies as part of the official healthcare service, they also inscribe them in a specific regime of classification and regulation. Using as a predominant reference the National Policy for Integrative and Complementary Practices, in the following sections I will problematize the terminology used by the policy that is, the categories mobilized to justify and frame the offer of these practices in SUS.

As a regulatory instrument, the National Policy for Integrative and Complementary Practices produces a series of demarcations. The most evident is the very broad category integrative and complementary practices. The term was created by members of a commission charged with developing that policy and competes with a long list of others, such as alternative, complementary, natural, and parallel therapies as well as romantic, complementary and alternative, non-hegemonic or non-formal medicines. If on one hand, all of these categories converge on some aspects of the practices that they designate, on the other, their multiplicity does not only raise a problem of a nominal order. They also indicate specific relations with the state and with its modalities of regulation that define how and who is authorized to treat, diagnose and cure. As Waleska Aureliano (2011, 168) affirms, the difficulty created by constructing broad classifications for these other medicines is related not only to the plurality of practices to which they refer, but above all, to the fact that they involve distinct modes of relation with the official spaces of healthcare. These, in turn, are based on the differentiated modes with which they historically construct and negotiate their legitimacy with the state.

Thus, I consider it necessary to reflect on how to denominate the so-called alternative therapies. The mode of designating these therapeutic practices is important for two main reasons: first because the use of certain broad categories immediately inscribe the practices analyzed in certain theoretical perspectives – this is the case of designating them as medical rationalities,⁷ for example. Second, because some of these terms are summarily rejected by part of their practitioners – for example, by acupuncturists who refuse the category alternative therapy because it establishes a relation of divergence with a principal therapy. For this reason, I opt here for a terminology that seeks not to make invisible this nominal permanent tension, by using the composite term alternative/complementary therapies. The solution is only partial, but serves to indicate the unstable and controversial character of the designation of these practices. In addition, by referring to the category as alternative/complementary therapies, I benefit from the possibility of indicating their difference in relation to the official

⁶ I am referring to lei n° 3.597, of 23 March 2012 (mimeo).

⁷ The term relates to debates about the topic conducted in the field of collective healthcare (see Luz 1996).

term, which was recently established - integrated and complementary practices. More than differentiating them, as I demonstrated in other texts (2015c) it is necessary to show that a lot of work and bureaucracy (laws, decrees, state agents and regulations) is involved in the difficult task of transforming an alternative/complementary therapy into an integrative and complementary practice.⁸ To some degree, this passage, from alternative/complementary therapies to integrative and complementary practices synthesizes the process of making these practices official within the Unified Health System. I will now look at how and with what terms this process took place.

INTEGRATIVE AND COMPLEMENTARY PRACTICES

In September 2003 a commission of technicians, doctors and specialists in alternative/complementary therapies was formed by Brazil's Ministry of Health to produce a national healthcare policy about the issue. Nearly two years later, in February 2005, this commission prepared a draft of the proposed National Policy on Natural Medicine and Complementary Practices, and submit it to technical chambers of national councils, state and municipal healthcare secretariats. Months later, in September, the document was presented in an ordinary meeting of the National Council of Health (CNS) and to its Commission on Sanitary Inspection and Pharmacology. In these two bodies, the policy was approved with some technical restrictions and others concerning the title of the policy. Carmem De Simoni, who participated in the group responsible for the preparation of the policy and who later, in the implementation period, was its first coordinator, commented on the problem raised by the National Healthcare Council in relation to the name initially proposed for the policy and the solution found to resolve it:

“Until then the name was the National Policy for Natural Medicine and Complementary Practices. When it reached the Council [CNS], the name medicine was not approved. This was because of the same questions raised about Chinese medicine. In the end, it did not pass. They said: ‘AH! You want to pass the policy?’ Yes, we do. ‘Then you must change the name!’ We said, ‘very well, we will’. Well, then we entered a small room, 5 people, and we began to think of a name. At some point [someone] entered and said, ‘but this is taking too long. Why don’t you use integrative practices?’ And that’s how it happened. It was Divaldo Dias who entered that room and gave the name to the policy. And it was a very good name!”(Carmem De Simone, interview, May 2013)

With the new name and with the technical changes incorporated to the text, the National Policy of Integrative and Complementary Practices was approved by the National Healthcare Council in February 2006 and the decree that established it was published on May 3 of that year.

⁸ I reiterate that this is a precarious solution and clarify that I do not use the term *alternative/complementary therapies* to fix the therapeutic practices that are not regulated by the state in this pairing of specific opposition or in the regimes of configuration that each one of the terms (alternative and complementary) admit. Here, the terminology *alternative/complementary* was the way I found precisely to indicate the multiverse character of the configurations that these therapies have. It is also necessary to mention that there are cases in which state and municipal policies recognize as integrative and complementary practices some alternative/complementary therapies that are not identified as such by the official policy. For this reason I may also alternate in considering a specific practice as complementary and integrated or as alternative/complementary.

The somewhat anecdotal case about the choice of name for the policy is indicative of contingent decisions not always based on technical principles and bureaucratic rationalization of the state that accompany the development of public policies. I mention it here mostly to emphasize that the name of the policy, or the terms it uses, were a condition for the document's approval. And once enacted, the National Policy for Integrative and Complementary Practices established, based on these terms, a regulatory regime for the therapies that it describes. Below I will address each one of the words in the policy's title. To do so, I will use as an analytical recourse, some comparisons between the terms used in this policy and others that are used in other regulatory regimes for alternative/complementary therapies.⁹

PRACTICES AND MEDICINES: COMPLEMENTARY AND ALTERNATIVE

In mid-2009, the Doctor's Union of Rio Grande do Sul (SIMERS) filed a public civil suit against the Escola Superior de Ciências Tradicionais e Ambientais [College of Traditional and Environmental Sciences] (Escam), which operates as a center for education in natural medicine in the city of Porto Alegre. The suit says little about the content of the courses offered and is more associated to the use of the term medicine in the promotional materials for the services offered, even if they are always accompanied by the words traditional or natural. The term doctor according to the ruling of the appeals court judge, is only for those who have been educated and registered by the competent professional council.¹⁰ In one of his decisions the judge ordered that the school abstains from using the expression 'doctor' or 'medicine' in its propaganda.¹¹

Also in 2009 the doctor's union of Rio Grande do Sul launched an advertising campaign, broadcast on radio, television and in print media, with the following content:

"Considering the recent offering of courses in Traditional, Ayurvedic, Environmental, Chinese and Ecological Medicine among others, SIMERS informs: 1. There is only one form of Medicine. To practice it in the country, it is necessary to comply with the educational legislation and be registered in the Regional Council of Medicine. 2. Any other exercise of Medicine is illegal, a crime punished with a prison term, according to art. 282 of the Penal Code. (...) Truth is good for your health."¹²

The monopoly on the term medicine in Brazil has a broad trajectory, which goes hand in hand with the establishment of doctors as a professional category in the country. As other authors have shown, in the past century, the exercise of medicine and the title of doctor have been defended against charlatans, mediums, religious people, healers and many others who tried to appropriate them (see: Giumbelli 1997; Weber 2003; Maggie 1992). The case described is only one example of many in which the use of the terms was denied to holistic therapists. To it we can associate the imbroglio, mentioned by Carmem De Simone, about the denomination traditional Chinese medicine to designate the exercise of techniques and procedures not recognized by the Federal Council of Medicine in Brazil, for example.

⁹ In an attempt to mark the permanent tension between various social actors by the definition of the status of these therapists, I will use as a narrative strategy the term *alternative/complementary* therapies.

¹⁰ Apelação cível nº 0033780-12.2006.404.7100/RS.

¹¹ Ação civil pública nº 2006.71.00.033780-3/RS.

¹² Source: <http://goo.gl/qCjmhM> (Consulted on 22/06/2014).

Considering this controversy, it is evident how the use of the term practices in the National Policy for Integrative and Complementary Practices is used to avoid the category medicine, for which doctors have a monopoly of use that is repeatedly assured by the state. To recognize the therapies as a practice was essential to the approval and legitimation of the National Policy for Integrative and Complementary Practices, situating it, at least in terms of its name – which is important – outside the marks that regulate medicine in Brazil. The change in name, from natural medicine to integrative and complementary practices was thus essential for the National Policy for Integrative and Complementary Practices to acquire the capacity to produce its own regulations about alternative/complementary therapies, without which these practices would be denounced for appropriation (of the terms) of medicine.

The notion of complementarity, in turn, is constantly used as an encompassing term that is capable of designating the broad set of therapeutic practices included by the policies for the integrative and complementary practices. To situate the therapies supported by and offered in the official SUS as complementary practices signifies establishing the integrative and complementary practices based on a specific mode of relation with that which they complement - biomedicine. In this case, complementarity does not describe something that pertains to the substantive content of the therapies, but is a category that expresses how these therapies should relate with other modalities of healthcare. There is, therefore, an hierarchical relationship implicit to the term and which, in a certain sense, is a counterpoint to the designation alternative therapies. The practices regulated by the National Policy for Integrative and Complementary Practices are complementary and not alternative because they must be allied to biomedical treatment and made compatible to it, and not be alternative to it.

If, on one hand, the category complementary submits the therapies/practices/medicines that it describes to the modalities of healthcare that are complemented by it, on the other, researchers who analyze the category have emphasized the incongruence or even inoperativeness of the ideal of complementarity in some situations (White 2014). This is because not all of the associations of therapeutic practices complementary to biomedicine allow maintaining the principle of complementarity, as a type of policy of harmonious coexistence between different forms of treatment. This is what Ruth Barcan suggests (2011) when describing the impossibility of articulation, for example, between therapies to increase fertility based on diets of detoxification from industrialized products and biomedical treatments for the same purpose which is linked to the consumption of allopathic medications.

In the National Policy for Integrative and Complementary Practices, complementarity is not a quality that varies situationally, that is, according to the capacity of the association of the therapeutic models used in a specific situation. More than that, it is a policy of complementarity that, by decree, should always prevail, regardless of the forms or principles of the therapies in question. When inscribed in the policy regime of complementarity, the therapies give up a claim, at least on the formal plane, to the possibility of becoming alternatives (to biomedicine, mainly). In addition to this distinction between the two terms – complementary and alternative – it is necessary to emphasize that the option for the first and not the second in the National Policy for Integrative and Complementary Practices is also related to the dense historic load that the idea of alternative therapies has in Brazil. This is because it is primarily associated to esoteric practices, with little scientific proof and low acceptance among healthcare professionals. Here I only want to emphasize that to avoid the category alternative also meant the possibility of at least in a first moment, shifting the integrative and complementary practices from the universe of esoteric new age references,

thus operating a new possibility for alignment of these practices, which come to be approximated to the field of legitimate and official medicine.

As I have argued, the terms practices and complementary used in the National Policy for Integrative and Complementary Practices are broad categories that inscribe the therapies to which they refer in a regime of legitimation and specific regulation. These terms say little about the characteristics of the therapies themselves. Instead, they establish how they should relate with other therapeutic modalities.

Integrative is the other term used to name the policy. I suggest that it has a differentiated status from the other two described until now because it does not only concern the relation between the integrative and complementary practices with biomedicine, but is also related to how these therapies are integrated to the SUS. At the same time, as I will show below, it is a term that is key for making reference, without being explicit, to an idea that is central to these therapeutic practices, that is: a holistic quality.

INTEGRALITY, SUS AND HOLISTICNESS

Brazil's Unified Health System was established in 1990 under decree law 8080 which presents the objectives, attributions, guidelines, organization and administration of the country's healthcare services. This document also established, in chapter II, the three fundamental principles of the system: universality, equity and integrality. The first refers to the universality of the access to healthcare services at all levels of assistance, the second concerns the guarantee of equality of healthcare assistance, without prejudice or privilege of any kind. I want to focus on the third principle, that of integrality, whose definition in the decree cited establishes it as the model of assistance, understood as the articulated and continuous group of preventive and curative actions and services, individual and collective, required for each case at all levels of complexity of the system. Integrality, in this configuration, is an attribute of the healthcare model that stipulates, at a first moment, the integration, for each act of care, of the different entities within the Unified Health System, for prevention of risks and harm to healthcare and recovery. Carmen Teixeira, who is a researcher at the Collective Healthcare Institute of the Federal University at Bahia, affirmed in a text presented by the Ministry of Health:

"An integral model, therefore, is that which has establishments, care providing units, trained personnel and the resources needed for the production of healthcare actions that range from nonspecific actions for promoting health in defined population groups, to specific actions of environmental, sanitary and epidemiological inspection aimed at controlling risks and damages, to actions of assistance and recovery for sick individuals, or actions for the precocious detection of disease, or actions of diagnosis, treatment and rehabilitation." (Teixeira 2011, 7-8)

Beyond the strictly formal marks of the principle of integrality in the Unified Health System, established by law 8080, this category has a long political trajectory in the struggle for public healthcare services in Brazil, and also an academic one, having been the main analytical focus for many research projects.

The origins of the debate about the theme in the country relate to the history of the Movement for Sanitary Reform, which during the 1970s and 1980s, embraced different movements of struggle for better living conditions and better conditions for work in

healthcare and for the formulation of specific care policies for users (Pinheiro 2006, 255). When understood based on these movements, integrality concerns a type of amalgam-concept, as suggested by Ruben Mattos (2006, 46), which does not “seek to make a final definition, given that by establishing a definition we can abort some of the meanings of the term and in this way silence some of the questioning from social actors who struggle with us for a more just society”. For Kenneth Camargo (2003) the lack of a true definition of “integrality” is simultaneously a weakness and an opportunity for the category. This lack of definition appears to be accommodated in the affirmation of another researcher of the issue, José Ricardo Ayres (2006, 11): the principle of universality drives us to construct access for everyone, that of equity requires guaranteeing everyone to meet each one’s needs, but integrality challenges us to know and do “what” can be realized and “how” in healthcare to universally respond to each person’s needs.

Considering the recognition of the non-definition of the term, the analytical solution proposed by authors such as Ruben Matos (2006) has been to identify the uses and therefore the meanings of integrality situationally. I revive these considerations about the category of integrality to treat the term integrative which is part of the name of the National Policy for Integrative and Complementary Practices. Although the terms are not necessarily synonymous, the use of the category integrative in the National Policy for Integrative and Complementary Practices relates, at times, to integrality, as a principle of the SUS. In this sense, integrative appears to be another consequence of the undefined character of integrality.

The term integrative was incorporated to the National Policy for Integrative and Complementary Practices by the suggestion of one of the members of the National Council of Health, during the approval process for the policy. At that time, according to the minutes of the council’s 160th meeting, Francisco das Chagas Monteiro presented, in name of the Federal Council of Medicine, the suggestion:

“To substitute the term “Policy for Natural Medicine” for “Policy of Integrative Medicine”, which consists of medicine that uses conventional scientific knowledge aggregated to traditional knowledge (millenary or centenary), which is also scientific, excluding alternative practices based on creed, myths and magic and is associated to complementary therapeutic models, such as acupuncture, homeopathy and phytotherapy, in addition to propaedeutic models such as anthroposophic medicine.”¹³

Integrative, in this case, refers to the quality of a practice that integrates scientific and traditional knowledge, maintaining them, however, free of creeds. The suggestion was accepted and the term was incorporated to the title of the policy. In the text of the decree, however, and for the first national coordinator of the National Policy for Integrative and Complementary Practices, the meaning attributed to it is far from that proposed by the council member.

“This idea of integrative is ambivalent. First it is the principle of integrality of the Unified Health System, which is the vision of a policy that tends to comprehend the social, economic and cultural insertion of the creature in society. But together and simultaneously, integrative is also the holistic vision that these therapies have about the individual. This is there in the policy.” (Carmem De Simone, interview May 2013)

¹³ Source: 160th meeting of the CNS. Available at: <http://goo.gl/Bo3geB> (consulted on 14/01/2014).

The first dimension mentioned by de Simone appears at the very beginning of the presentation of the National Policy for Integrative and Complementary Practices, written and signed by the then minister José Gomes Temporão:

“In compliance with its responsibility to coordinate the SUS and establish policies to guarantee integrality in healthcare, the Ministry of Health presented the National Policy for Integrative and Complementary Practices within the SUS, and whose implementation involves justifications of a political, technical, economic, social and cultural nature.” (Brasil 2006, 4)

In this plan, the association between the Policy for Integrative and Complementary Practices and the principle of integrality of the Unified Health System is based on the characteristics of the policy itself.

In other portions of the document, however, this meaning is shifted and is used not to justify the National Policy for Integrative and Complementary Practices in the SUS, but to refer to how subjects treated by the integrative and complementary practices are understood as integral beings. In other words, integrative/integrality is no longer a quality of the National Policy for Integrative and Complementary Practices and becomes the perspective by which the user of the policy is conceived by the therapeutic practices the policy promotes.

“Upon acting in the fields of prevention against harm and the promotion, maintenance and recovery of health based on a model of humanized care focused on the integrality of the individual, the National Policy for Integrative and Complementary Practices contributes to strengthening the principal foundations of the SUS.” (Brasil 2006: 7)

“Considering the individual in his global dimension (...), the National Policy for Integrative and Complementary Practices corroborates to the integrality of healthcare (...).” (Brasil 2006, 3-4)

“Integrative and Complementary Practices are those for the promotion, protection and recovery of health, which presuppose users/patients in their physical, mental, emotional, social, environmental and spiritual integrality.” (Rio Grande do Sul 2014, 15)¹⁴

The categories of integrality and integrative that focus on the subject is thus approximated to a concept that is central to the alternative/complementary therapies: holism. In terms of the differences in the understanding about how holism can be therapeutically addressed (Kemp and Lewis 2007, 119), the use of the term indicates an opposition to medical therapies and perspectives that conceive the possibility of treating subjects in a fragmented form by specialists in a single part of the body.

What is at stake, therefore, is to observe how the category integrative, used in the National Policy for Integrative and Complementary Practices, operates on at least three levels. First, it is related to the evaluations that the National Council of Health made about the policy. Originally, according to the initial suggestions of the members of this council, the integrative character of the National Policy for Integrative and Complementary Practices refers to the integrating quality of these therapeutic practices that could combine traditional and scientific knowledge. In the text of the policy, however, integrative is associated to the principle of integrality of the Unified Health System, so that the National Policy for

¹⁴ The last portion was extracted from the state plan for integrative and complementary practices (PEPIC) of Rio Grande do Sul and expresses that the association between *integrality* and the holistic mode of treatment of the subject under the policies for the integrated and complementary practices is not restricted to the National Policy.

Integrative and Complementary Practices would find foundation and legitimacy in the very terms that establish the offer of public healthcare in Brazil. There is a third meaning that overlaps these two meanings, which relates the categories integrative and integrality to holism. I opt to make visible these three overlapping meanings without suggesting that one or another has acquired definitive form, thus emphasizing precisely what is undefined in these categories.

The version of the term integrative/integrality as holism also serves here to explain how, based on the terms used in the policy, a principle central to the alternative/complementary therapies according to the new age literature is developed without turning to the history of the countercultural movement but, to the contrary, appeals to the more formal aspects of Brazilian public healthcare. In the next section I will address another configuration of the alternative/complementary therapies in their official form, based on the terms used by the World Health Organization.

THE PROMOTION OF TRADITIONAL MEDICINE AND OF ALTERNATIVE/COMPLEMENTARY THERAPIES BY THE WHO

In the realm of the World Health Organization, two broad categories are those most used to designate the non-biomedical therapies, traditional medicine and alternative and complementary medicine. Although since the mid-1990s official documents from the agency have referred to these practices in a way that establishes equivalence between the terms, and use the initials TM (traditional medicine)/CAM (complementary and alternative medicine), these categories have specific genealogies in the discussions at the WHO. To explain the variations between them in the context of the legitimation and regulation of the use of alternative/complementary therapies by the WHO serves not only to demonstrate how the Brazilian policy for integrative and complementary practices accompanies similar processes in other countries, but also helps to understand the WHO's motivations for promoting these therapies.

One of the first registers of the term traditional medicine in the WHO documents was made in September 1978, at the time of the first conference on primary care, held in the city of Alma Ata, which was then part of the Soviet Union. Although it contained guidelines of various kinds, the final report of this conference was significantly marked by the context of the Cold War and by the systematization of data that express the unequal offer of healthcare technologies, professionals and hospital institutions in various countries of the world. It was based precisely on the recognition of the unavailability of these resources to two-thirds of the world's countries that the WHO identified traditional medicine as an action in healthcare and recommended the formulation of national policies and regulations that refer to the use of traditional medicine of proven effectiveness and exploration of the possibilities to involve those who hold traditional knowledge in primary healthcare activities, providing them corresponding training.¹⁵

Thus, if on one hand, this recognition would contribute to the legitimation of traditional knowledge about health and disease by an agency for global governance, on the other, this

¹⁵ Source: WHO, Conferência Internacional. 6-12 Setembro 1978 – Cuidados primários de saúde: declaração de Alma-Ata. Lisboa: Gabinete de Estudos e Planeamento 1978.

action is associated to the recognition of the scarcity, in certain parts of the world, of human and technological resources needed to provide healthcare, according to the precepts of biomedicine. In this sense, recognizing traditional medicine as a mode of healthcare established the conditions for the WHO to extend its own regulatory capacity to the more than half the planet that at the time did not have the healthcare facilities and institutions upon which the global agency could have influence.

According to the WHO, traditional medicine is the sum total of the knowledge, skills, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness. By the characteristics of its definition and by that which I previously described, it is observed that in this configuration, the exercise of traditional medicine, according to the WHO, occurs mainly outside the West and far from the global north, that is, it is concentrated in the poorest parts of the world. In addition to the geographic perspective, which associates traditional medicine to poor or developing countries, two other characteristics can be gathered from the concept and documents developed by the WHO about the issue. First, traditional medicine is part of a cultural system and, second, these practices are millenary traditions, dating back to before the development of modern Western medicine.

Based on culture, historically situated in a distant past and geographically far from the West, the exercise of traditional medicine appears to be well summarized in the passage below, taken from the document WHO Traditional Medicine Strategy 2002-2005:

“A variety of indigenous TM systems have also been developed throughout history by Asian, African, Arabic, Native American, Oceanic, Central and South American and other cultures. Influenced by factors such as history, personal attitudes and philosophy, their practice may vary greatly from country to country and from region to region. (...) Traditional medicine may be codified, regulated, taught openly and practiced widely and systematically, and benefit from thousands of years of experience.” (WHO 2002, 7)

Considerations like these lead one to believe, as Waleska Aureliano (2011, 175) affirmed, that these practices are static or that they have not undergone significant changes over their history. These winds up characterizing traditional medicines based on stereotyped notions that reify them as millenary or ancestral practices that survive the advances of science.

As I mentioned earlier, traditional medicine is not the sole category used by the WHO to deal with therapeutic practices that are not aligned with Western biomedicine. During the 1990s, and particularly in the decade of 2000, it came to be associated to the term complementary and alternative medicine. Although articulated in some documents as if they are synonyms, this second category concerns the healthcare practices conducted in developed countries that do not share the same epistemological and therapeutic principles as biomedicine.¹⁶ The geographic link of alternative and complementary medicine with the developed countries, as well as the genealogical contrast of the category with that of traditional medicine at the WHO, appears explicitly in a document from the global agency about the use of non-hegemonic therapies:

¹⁶ In the WHO documents *Complementary and Alternative Medicines* are defined as “a broad set of health care practices that are not part of a country’s own tradition or not integrated into its dominant health care system” (WHO 2001).

“TM is widely used and of rapidly growing health system and economic importance. In Africa up to 80% of the population uses TM to help meet their health care needs. In Asia and Latin America, populations continue to use TM as a result of historical circumstances and cultural beliefs. In China, TM accounts for around 40% of all health care delivered.

Meanwhile, in many developed countries, CAM is becoming more and more popular. The percentage of the population which has used CAM at least once is 48% in Australia, 70% in Canada, 42% in USA, 38% in Belgium and 75% in France.” (WHO 2002, 5)

The contrast can be seen, at least in the original sense, between the concepts used by the WHO to designate the non-hegemonic therapeutic practices. First, traditional medicine is associated to contexts in which the offer of healthcare treatments is scarce and has little diversity. The second, complementary and alternative medicine, to the contrary, is associated to the offer of healthcare modalities that are alternatives to the biomedical hegemony. On the state level, the offer of complementary and alternative medicine would express the consolidation of the plural character of medical systems available in the West, while traditional medicine would be the cultural manifestation of regions with scarce and poorly diverse resources.

Also in relation to the two categories, it is worth emphasizing that little by little, in the realm of the WHO, they come to not necessarily qualify the therapeutic practices, but to characterize the relationship between a therapy and the context in which it is used. For the WHO, traditional Chinese medicine, for example, when used in China is an example of traditional medicine. When translated outside its culture of origin, however, and applied in Brazil or the United States, for example, it becomes an alternative and complementary medicine. It is this relationship that guarantees the affirmation, reiterated in the WHO documents, that traditional medicine and complementary and alternative medicine are interchangeable terms. Given that the identification of the therapies with these categories are unstable and provisional. On one hand, I recognize that this provisional character of the tie between the therapies and the categories traditional medicine and complementary and alternative medicine can relativize the binary quality that associates non-hegemonic practices of medicine in developing countries to traditional medicine and those realized in developed countries to complementary and alternative medicine. On the other, I affirm that this relativization does not make invalid the pertinence of identifying the configurations of power that cause each one of these categories (traditional medicine and complementary and alternative medicine) to emerge in the WHO.

Beyond the possibility of being used as synonyms, as affirmed by the WHO (WHO 2002, 2), these two categories also converge in that they use biomedicine as their principal element of reference and in the recognition that the fundamentals and exercise of biomedicine have no culture, time or space, or that these factors do not matter. If, in the original elaboration of these categories (traditional medicine and complementary and alternative medicine) there is an effort to establish a symmetry between the different forms of medical knowledge (which includes biomedicine), this effort involves an attempt to affirm that traditional medicines are culturally located forms of therapeutic medical practices, without, however, submitting biomedicine to the cultural localization of its traditions.

Once recognized and associated, traditional medicine and complementary and alternative medicine become the object of attention of a special department of the WHO, which since 2002, regularly publishes documents with goals and programs related to these therapeutic

practices. In one of the more recent publications about the theme, WHO Traditional Medicine Strategy 2014-2023, the WHO established four central objectives:¹⁷

“policy — integrate TM within national health care systems, where feasible, by developing and implementing national TM policies and programmes.

safety, efficacy and quality — promote the safety, efficacy and quality of TM by expanding the knowledge base, and providing guidance on regulatory and quality assurance standards.

access — increase the availability and affordability of TM, with an emphasis on access for poor populations.

rational use — promote therapeutically sound use of appropriate TM by practitioners and consumers.”
(WHO 2013, 11)

In the same document, Brazil’s National Policy for Integrative and Complementary Practices is mentioned as one of the exemplary experiences of integration of traditional medicine and complementary and alternative medicine in the national healthcare system.¹⁸ Equally exemplary, according to WHO, are the policies adopted in countries such as Belgium, Canada, Cambodia and Australia. Although the list with detailed descriptions about the experiences with the use of traditional medicine and complementary and alternative medicine is restricted in this document,¹⁹ the broader data it presents gives an idea of the scope and number of countries that have adopted specific policies to regulate and introduce these therapies in their healthcare systems. In 2012, 119 countries had regulations about traditional medicine and complementary and alternative medicine, while 69 have specific public policies to guide and promote the incorporation of these practices in their healthcare networks. These numbers are part of a historic series that since 1999, indicates a progressive increase in the number of countries that legitimate and regulate the use of alternative/complementary therapies.

Although the data found in these reports can be analyzed from different perspectives that are capable of presenting distinct forms of grouping the countries that produce national policies about complementary and alternative therapies, I highlight the presence of the variable culture, which was cited in the analysis of the concept of traditional medicine, to explain one of the differentiating perspectives of these policies. My suggestion is that it is possible to distinguish the various policies aimed at traditional medicine and complementary and alternative medicine based on the public that can access them. This is because, in Latin American countries, for example, most of these policies compose a broad range of actions based on the principle of interculturality. In name of recognition of cultural diversity and of the right to medical care according to individual beliefs, interculturality as a principle suggests, for example, that indigenous populations can demand that their care in hospitals, clinics and medical offices be associated to rituals and procedures from their own cosmology. This care, however, is not available for the entire population, but is restricted to subjects who

¹⁷ The document uses only the term traditional medicine. In its initial paragraph, however, the WHO clarifies that it understands there to be an equivalence between the term and alternative and complementary medicine.

¹⁸ The projection intended by the Ministry of Health with the National Policy for Integrative and Complementary Medicine should not be underestimated. The document was translated, printed and made available electronically in Portuguese, English, Spanish and Mandarin. Moreover, in 2008, the I International Seminar on Integrated and Complementary Practices was held, with participation of representatives from Cuba, Mexico, China, Italy, and technicians and members of agencies such as WHO and the Pan American Health Organization.

¹⁹ For an extensive overview from the WHO about the situation of traditional medicine and complementary and alternative medicine policies among its member countries (see WHO 2001).

are culturally identified with these practices. Contrary to these policies restricted to specific cultural groups are those like the National Policy for Integrative and Complementary Practices that have as a principal characteristic the universality of the offer and access to complementary and alternative therapies (see WHO 2001).

The WHO report about traditional medicine describes the Brazilian public policy as an exemplary model for integration of non-hegemonic therapeutic practices in national healthcare systems, but the policy does not legitimate or regulate, for example, healthcare actions aimed at traditional populations, and it does not address the action of midwives in the services of the SUS. The option for this model for the policies of the integrative and complementary practices certainly creates tensions. In Rio Grande do Sul, when I accompanied the process for elaboration of the state policy for integrative and complementary practices (see Toniol 2015c), technicians from the secretariat of health, linked to the healthcare services for the black population²⁰ requested a meeting with the commission responsible for the state policy for integrated and complementary practices. The request was not granted by the commission with the justification that the policy was being prepared for the entire state network of the Unified Health System and not for specific population groups.

RETURN TO A NEW AGE: IN CONCLUSION

I began this text stating the possibility to reflect on the limits of the new age as an analytical resource for understanding the current situation of provision and use of alternative/complementary therapies. Although in other studies (Toniol 2015a and 2015c) I have mobilized the historic references of this phenomenon and also addressed its analytical dimension, here I opted to treat the theme from a reversed viewpoint. That is, I raised a topic that is systematically associated to the new age to point to some of the limits of this perspective. In sum, my argument was that the possible association of some alternative and complementary therapies with counter cultural movements does not justify the deliberate use of the analytical language of the new age to frame and describe these practices. In this sense, what I did in this text was to present a set of other configurations for the provision and use of the alternative/complementary therapies that remain outside the field that is usually described as new age. I thus worked with the expectation that texts such as these can help to establish a principle of precaution, which from a methodological perspective, signifies calling for the analyses about alternative/complementary therapies to invest in describing the historic and conjunctural configurations that make these practices possible, without presuming the new age to be an absolute *a priori*.

This recommendation is necessary given that the literature dedicated to the theme appears to have left us accustomed to identifying any mention of alternative/complementary therapies as the expression of a trait inherited from religious, moral and aesthetic sensibilities of subjects and groups committed to the esoteric principles of the Age of Aquarius and with counterculture ideas.²¹ To make this warning does not imply abdicating a dialog with new age research. It involves indicating my effort to not stabilize the associations described here in a

²⁰ In the structure of the Secretariat of Healthcare of Rio Grande do Sul there is a sector, which is part of the Department of Healthcare Actions, that is specialized in healthcare for the black population.

²¹ Among the exceptions to this trend I highlight the work by Koch and Binder 2013.

category that appears to engage more the social scientists of religion than the subjects observed. Thus, what comes to be at stake is to not assimilate the various cases of offer and use of alternative/complementary therapies to a specific and univocal analytical line, which establishes their contours and characteristics by making them part of an ontological principle that transcends the situations observed. Alternatively, it involves reinforcing the need for studies about the topic that emphasize its variations, making the task of describing how? In what terms? and in what configurations? a constant analytical principle.

Chapter 545

THERAPEUTIC DIVERSITY AND PUBLIC HEALTH POLICIES AMONG VULNERABLE POPULATIONS: A STUDY IN BAHIA, BRAZIL

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ABSTRACT

The authors refer to issues involving health care policies in municipalities that surround the Bay of Todos os Santos (Bahia). It is initially presented some indicators of the Family Health Strategy (ESF) – the national public policy mediated by local implementation, and the main primary care program and disease prevention available in the country – which proposes general procedures about the health of the target population. Recognizing and articulated to some of the municipal health indicators, it highlights some state initiatives around two national health policies: the “National Policy of Comprehensive Health of the Black Population” and the “National Policy of Medicinal Plants and Herbal Medicines,” with special care for the impacts on the populations in situations of socioenvironmental vulnerability of the region. In the case of policy for black people, in addition to the high consideration given to the Afro-Brazilian traditional knowledge, the guidelines also turn to the minimization of inequalities in access to health services for this segment of the population. The policy of medicinal plants and herbal medicines is articulated to broader regulation of the National Integrative and Complementary Practices Policy (PNPIC), which does not focus on a specific segment and has as one of its guidelines the “encouraging of the insertion of Integrative and Complementary Practices at all levels of care, with emphasis on primary care,” thus stimulating the diversity of therapeutic practices in the SUS. Presenting some challenges around the “coexistence” between universalizing guidelines of ESF, in one hand, and of “recognition” policies of the differences in another hand, it will indicate clues to understanding of the processes of recognition of the high value of the knowledge of

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traditional populations indicated by those policies, to the extent that the interlocutors of these policies and diverse opinions involved in the two fields of argumentation are not always the same.

Keywords: public health policies, vulnerable populations, therapeutic diversity

INTRODUCTION

Some of the challenges posed by public health care policies in municipalities¹ in the area of the *Baía de Todos os Santos*², or, simply *Baía*, is the subject of the discussion and analysis in this chapter. More specifically, we address to the difficult relationship between the universalization of biomedical care and the promotion of therapeutic diversity, with the aim to understand which forms of relationship have been interwoven amongst those public policies in this specific context.

With the objective of conducting the proposed analysis, we have taken some indexes of the Family Health Strategy-ESF³ (this is the government agency which defines and formulates the national orientation policy for implementation by the municipalities, resulting in the main program of primary health care and disease prevention available in the country), based on the general questions about the characteristics of the one which is the universalizing health system. With this purpose, we will focus on two national health sub-policies, which are represented by the “National Policy on Integral Health of the Black Population,” and the “National Policy on Medicinal Plants and Herbal Medicine,” we will focus on their initiatives and dilemmas, as well as their impact over the populations in situations of socio-environmental vulnerability in the area we have been conducting our studies.

LOCAL LEVEL HEALTH CARE

Since the late 1990s, new dimensions of health care have been gaining prominence in ESF. These range from normative guidelines valid throughout the national territory, to local arrangements involving management, pedagogical and therapeutic practices disseminated by different segments and professional and community agencies involved with health care in various ways. These orientations are so much more visible when we focus in historical perspective issues that concern the use of health services by these populations since the implantation of SUS. The expansion of health care provision by the Brazilian State, initially through the Program of Community Health. Agents (PACS), and latter by the ESF, did not necessarily result in the reduction of the role and importance community “traditional” knowledge and local health practices; on the contrary, they are transformed, they are

¹ *Municípios*, which stands for municipalities, are the local administrative units in each state of Brazil. They are further divides in *distritos*/districts. Each *município* has a main city, usually having its same name, and the districts will have diferente denominations. In the case that we are discussing there is one exception, represented by the insular município of *Vera Cruz*, whose main and administrative city is *Mar Grande*.

² This bay system encompasses the *Baía de Todos os Santos*, itself, the *Baía de Aratu*, the *Baía de Iguaçu*, and various river estuarine áreas, coves, and 56 islands of various sizes and shapes, being the largest the island of Itaparica. For further information on this see Caroso, Tavares and Pereira (2011).

³ ESF is the acronym for *Estratégia de Saúde da Família* in Portuguese, already translated for English.

contagious among themselves, taking on new forms in the face of the growing demand for rights in different segments of society, especially vulnerable populations and peoples. It is important to highlight that, given the territorial nature of health care, the ESF must deal with a context of diversity of practices that constitutes the therapeutic plurality to which we are referring⁴ to. Recent studies about the daily life of health teams has pointed to the coexistence of care networks that cross and transgress the territorialisation promoted by the ESF (Bonet and Tavares 2006, 2007 and 2008). Some of these are official (stemming from the very implementation of health teams in a territory), but there may also be a multitude of “unofficial”; they can be hierarchical and rhizomatic; visible, and invisible, in short, their striations make up a territory of varying densities (Deleuze and Guatarri 1995 and 1997). Thus, understanding the dynamics of this care policy requires the identification of the networks, identifying the already calibrated paths, the “paths” of the communities, through which it is possible to pursue care practices in its capillarity or landscape rhizomatic (Latour 2006).

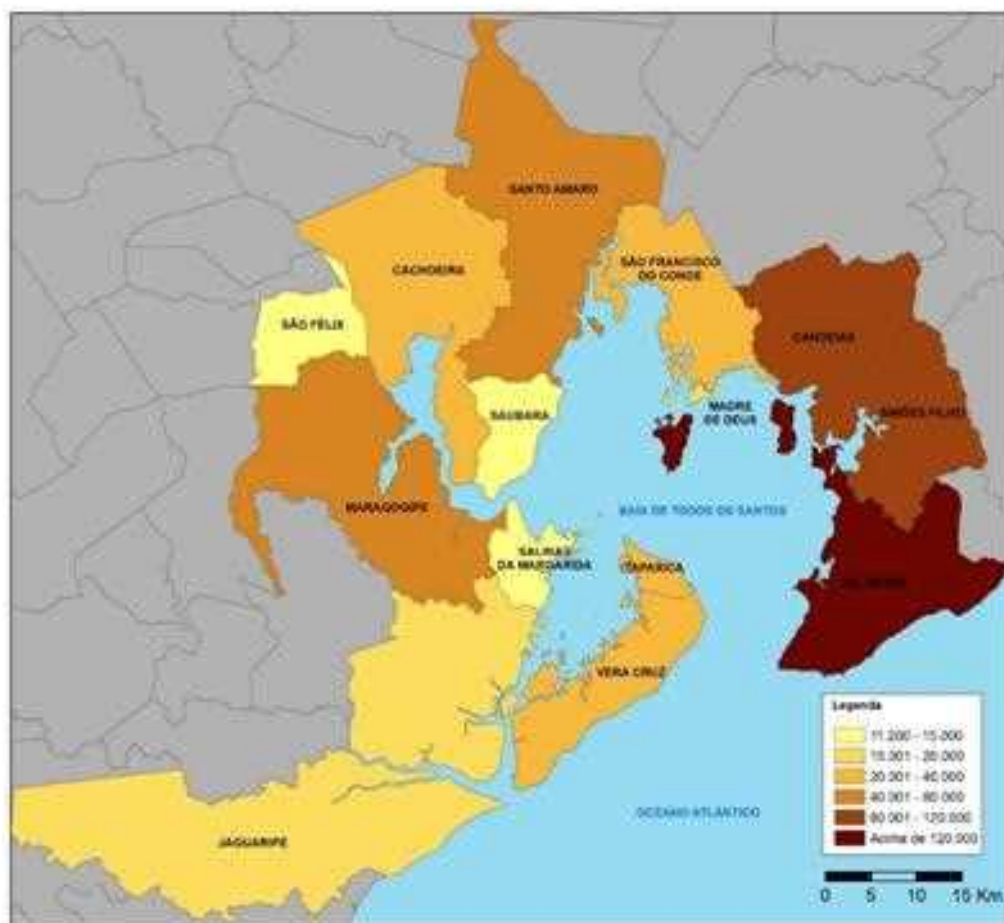
Tensioning the hospital-centered model, the guiding principles of ESF that involve “integrality in health” have been challenged to mobilize an “expanded conception of care” that is not understood only within the limits of the doctor-patient relationship. For this, the ESF guidelines emphasize the need to decentralizing this relationship, disseminating care practices by health teams and seeking to overcome the “traditional” perception of the medical practice that intervenes on the non-situated individual. Categories such as family and community, considered “peripheral” in the “traditional” model, have been gaining relevance in this model (Fontes 2004, 129).

This redirecting of basic health care has been significantly contributing to the formulation of more effective public policies and intervention for various segments of the population, whose social dramas are strongly related to the processes of urbanization and modernization in peripheral regions of large cities, marked by intense inequality of access to public services and low quality of life, such as in municipalities on the edge or on the islands Baía that have been studied by the team of the research group *ObservaBaía*⁵.

The public health network available in the 14 municipalities that make up the research area (as highlighted in the map above), is made up of hospitals, polyclinics and/or specialized clinics and health posts and/or UBSs (Basic Care Health Units) and/or Family Health Units, as shown in Table 1, below. Considering the health care available infrastructure, the municipality that has the greatest need is Jaguaripe, which does not have a general hospital or specialized care facilities. Besides Jaguaripe, Maragogipe also does not have a general hospital and Salinas da Margarida does not have any specialized care (such as polyclinic). These noticeable deficiencies of the health care assistance in Jaguaripe, Salinas da Margarida and Maragogipe, which are contiguous municipalities located in the southwest portion of the Bay, forces a large portion of the population to seek for health care in neighbouring municipalities, such as Cachoeira, Itaparica, Vera Cruz and Salvador, resulting in overdemand and overloading of the latter's health care units.

⁴ In the daily routine of ESF it is possible to identify the “officialised” network by the territory of each one of them. This results from the systematic registration of the resident population within the scope of the work of a health team. A second network, also “official,” refers to each unit of registry, that is to say, the family units. It is at the intersection of these two networks that the therapeutic care interventions are carried out in the daily life of ESF professionals. On this question see Bonet and Tavares (2006).

⁵ More information about the research group: www.observabaia.ufba.br.



Source: Demográfico Censur 2010/ObservaBaía.

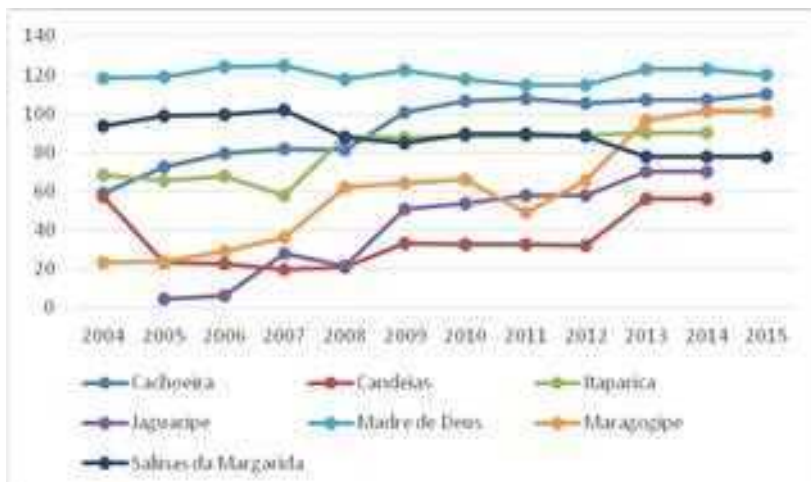
Map 1. Municipalities of the Baía de Todos os Santos and their populations.

Table 1. Public health units in municipalities of the Baía de Todos os Santos

Municipalities	Hospital	Polyclinic	Basic Health Unity
Cachoeira	1	12	13
Candeias	1	21	22
Itaparica	1	2	9
Jaguaripe	-	-	9
Madre de Deus	1	7	7
Maragogipe	-	4	13
Salinas da Margarida	1	-	5
Salvador	28	1405	129
Santo Amaro	2	7	18
São Felix	1	1	6
São Francisco do Conde	1	-	16
Saubara	1	1	4
Simões Filho	1	10	15
Vera Cruz	1	4	18

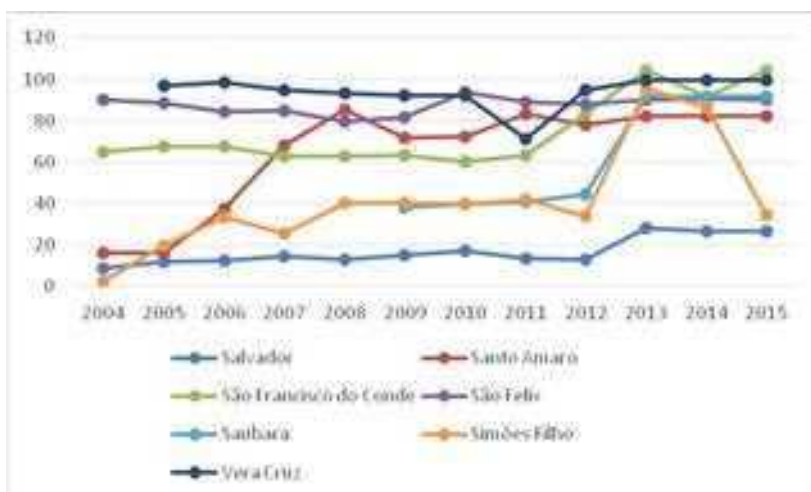
Source: MS/SIAB – CNES; Data from December 2016.

Graphs 1 and 2, below, present the history of ESF implementation by means of the proportion of the population registered by health teams in the municipalities around the Bay, in which one can observe the performance of each one in relation to ESF coverage. The data presented allow us to verify, through the comparative analysis of registration percentages, significant asymmetries in the municipal policies of the ESF.



Source: SESAB.

Graph 1. Proportion of population registered by ESF in Municipalities of Baía de Todos os Santos (1)⁶.



Source: SESAB.

Graph 2. Proportion of population registered by ESF in Municipalities of Baía de Todos os Santos (2).

⁶ The data is presented in the two graphs for greater visual clarity. This index reflects in percentage the population registered by the ESF in the municipalities in relation to the total population of the municipality, based on the population registry of the area of coverage of the Family Health teams registered in the System of Information of Basic Attention-SIAB. The method of calculation is the population registered in the SIAB (model of attention ESF) in a certain location and period $\times 100$ / population in the same place and period. The data refer to December of each year. The municipalities of Candeias, Itaparica and Jaguaripe do not have data available for the year of 2015.

Percentages of attendance above 100% are identified in Cachoeira, São Francisco do Conde and Madre de Deus (in Maragogipe this plus difference is very small), indicating, therefore, the attendance of a non-resident population “officially,” who has been coming to these municipalities expecting to have access to health services. Madre de Deus is especially significant, as this situation occurs throughout the whole statistical series. Salvador (like other Brazilian capitals) and Simões Filho have the lowest percentage of coverage. The services available in the municipality of Madre de Deus, which “receives” many residents of neighboring cities and from the islands of the municipality of Salvador (due to difficulties in accessing the services of their municipalities), ends up “overburdened” with high rates of attendance, both in the system of primary care, and in emergency care, as observed in a previous study by the ObservaBaía (Caroso et al. 2014). Asymmetries like these give us clues about the problems experienced by the populations of these municipalities, but also indicate the extent of the capillarity of the health care networks that seek (and are successful) to transgress the official limits of the municipalities. In the municipalities of São Francisco do Conde, Candeias and the islands of the municipality of Salvador, the limits of municipal territoriality do not constitute a limitation for strategies for obtaining health care in other localities, which are problems more often observed in the small marginal districts than in the seat cities of the municipality (Caroso et al. 2014). Also among some marrons communities in the municipality of Cachoeira (which we have recently studied) similar dissatisfactions are observed about the proposed universality of ESF care (Tavares et al. 2017).

Taking into consideration these references, it is possible to emphasize the existence of a wide coverage of the ESF in whole of the municipalities around and in the interior of the Baía (except Salvador), although the quality of the service may present important variations. In order to understand better these questions that emerge from the previous discussion, we will identify and address to some points of tension between universalizing health care policies and the importance of therapeutic diversity.

HEALTH VULNERABILITIES AND HEALTH CARE POLICIES

The “National Policy on Black Population Health,” and the “National Policy on Medicinal and Phytotherapeutic Plants,” both emerge from within the discussions and formulations of health policies which consider and are directed to socially vulnerable populations. These initiatives from the part of the federal government can be found in the area where we have been conducting our studies, and their declared intention is to value the knowledge, populations, and people found in situations of social vulnerability, but they do so by means of different processes, because the people involved in the discussion do not always present the same characteristics, needs, and demands.

In the case of the social movements focused on black population health, besides the valorization of traditional knowledge, the demands also include the reduction of the inequalities of access to the health services for this segment of the population. In Salvador (and other Brazilian large cities) the demands are more heated within Afro-Brazilian religious communities, but little or no attention has been given to inequities in health care directed to

*quilombola*⁷ communities (such as those located in the municipality of Cachoeira, where we have been carrying out recent studies). This picture does not differ much from other regions of the country, where there is an urgent need for research and directed actions to implement differentiated policies aimed at *quilombolas* communities (Arruti 2008).

The “National Policy on Medicinal and Phytotherapeutic Plants” is articulated with the broader regulation of the “National Policy on Integrative and Complementary Practices” (PNPIC), which does not focus on a specific segment, but has as one of its guidelines the stimulus to plurality (which, of course, includes the ESF).

However, the inclusion of other therapies in the system hegemonized by agencies and practices of the professional health sector agencies face challenges and generates controversies for the valorization of community health sector agencies and practices (Caroso et al. 1997). As it can be understood from the text of the document itself, another guideline refers to “[...] articulation with the National Policy on Attention to Health of Indigenous Peoples and other policies of the Ministry of Health” (PNASI), as emphasized by Ferreira (2012, 267), “Instead of advocating the incorporation of traditional medicines into the national health system, PNASI recommends promoting the articulation of indigenous traditional medicines to health services.”

Within the limits of the Baía, these policies intersect in projects and actions implemented with the black population, precariously incorporating the *quilombola* communities. This is what we will see in more detail, as each of the policies is presented in the following parts of this chapter.

THE HEALTH OF BLACK POPULATION

The public debates involving the access of socially vulnerable populations to health care constitute the arenas of disputes concerning equity and respect, tolerance and religious visibilities, whose controversies present varying degrees of tension⁸. In this sense, the debate about the health of the black population constitutes a “field” of reflections and political interventions where ethnic-racial issues, health, Afro-Brazilian religions and the territoriality of the rural and urban *quilombos* intertwine.

The valorization of the therapeutic practices of *candomblé* configures an ambiguous arena, in which we find attitudes of religious intolerance (usually involving members of neopentecostais religions) amidst social life. Broadly speaking, the disputes that have as a reason the health of the black population are centered around the promotion of equity in health, taking a critical stance to the principle of universality which guides the SUS. Thus, several segments of the black movement demand a health policy that, at the same time, minimizes inequities and promotes the valorization of community-based therapies from African matrix. As Maio and Monteiro (2005) point out, the health policy for the black

⁷ *Quilombo* is the Brazilian denomination for maroon communities, being the *quilombolas* both the members of those communities and those descende of enslaved african populations.

⁸ Departing from the idea that “religion” and “society” are relational domains, rather than being self-referenced, it is necessary to consider the different modalities of configuration of Afro-Brazilian religions in the public space, which is to say that, in certain domains one can observe greater legitimacy than in others. This is the case, for example, of health practices, which can be discriminated against in contrast to festive and cultural practices that have been increasingly valued (Tavares and Caroso 2015).

population is resumed at the beginning of this century as an antiracist and affirmative action policy, which has been reinforcing identities of “racial conscience” with the participation of the State.

In the history of this policy, there is agreement between several authors (Maio and Monteiro 2005; Serra et al. 2009, 2010; Silva 2007), during the Government of Fernando Henrique Cardoso (1994-2002)⁹ Against Racism, Racial Discrimination, Xenophobia and Related Forms of Intolerance (2001), that iniquities in this area have gained visibility. In this context, the first initiative was held in 1996, the Roundtable on Black Population Health, an important meeting held in Rio de Janeiro, which brought together intellectuals, militants and technicians from the Ministry of Health. However, as Maio and Monteiro (2005), this event did not produce directed policies because it did not find, according to the document produced at that time, “technical justification for the creation of several specific public health programs for the black population, as some sectors in the sector intended” (p.2 document, apud Maio and Monteiro 2005)¹⁰. Even so, the balance of the event was to highlight the specificity of the black population's health, generating, in later years, other initiatives for its transformation into differentiated policies. Maio and Monteiro find a turning point in this debate at the Durban Conference in 2001: from then on “new actors took sides in favor of the implementation of “racial politics” (2005, 427). In the same year, the document “National Policy on the Health of the Black Population” was produced, with specific guidelines for the search for equity in health, in addition to demanding the official recognition of popular medicine of African matrix. At that very moment, it turned out clear that the universality of SUS was not enough to overcome racial inequalities.

During the Lula government (2003-2011) some actions have been implemented, such as the creation of the Special Secretariat for the Promotion of Racial Equality (SEPPIR) in 2003, enabling the following year, the constitution of Technical Committee for the Health of the Black Population. The 1st National Seminar on Health of the Black Population, in that same year, broadened the framework of action mentioned in the 2001 document, by valuing a diversity of actions, among which the promotion of health in the *quilombola* communities and recognition of the knowledge of Afro-Brazilians religions. Thus, a field of policies for the racialization of health is consolidated:

“The formation of the field of “black population health” occurs at a time when the debate about racism and the formulation of affirmative action programs are becoming increasingly visible in the Brazilian scene. It is the construction of a sectoral policy, with a racial cut, generating a process of differentiation and search of legitimation - in the scope of public health - of the grievances suffered by the blacks.” (Maio and Monteiro 2005, 438)

Parallel to the movement in the scope of the formulation of public policies, in the year 2003 the segments of the black movement also constituted the National Network of Afro-Brazilian Religions and Health, a fact which occurred during the II National Seminar of Afro-Brazilian Religions and Health, Held in Maranhão. In the historical record drawn by Silva (2007), the “Network” integrates diverse segments of civil society, seeking to valorize and leverage the traditional knowledge of these religions, as well as monitor governmental actions

⁹ As the authors point out, during that government a chapter on the health of the black population was included within the framework of the Interministerial Working Group for the Valorization and Promotion of the Black Population, created in 1995.

¹⁰ The exception was the Sickle Cell Anemia Program (PAF).

directed at these segments. This initiative is part of the anti-racism policies, and establishes partnerships with municipal health secretariats, as well as national seminars. According to the author:

“The Network develops several activities aimed at empowering the leaders of the Afro-Brazilian religious tradition for the exercise of social control of public policies. For this it counts on education and health professionals initiated or sympathizers of the *terreiros* that develop actions in the diverse nuclei spread by the country and *mães* and *pais de santo*¹¹ managing each nucleus of the Network.” (Silva 2007, 175)

Evaluating the Network's trajectory, the author points out that one of the most pressing challenges refers to religious intolerance within SUS: “We found from the beginning certain discomfort in the approach of the SUS to the *terreiros*” (2007, 176). This issue can be observed, for example, in the moments of professional training with the ESF teams, generating therapeutic and religious conflicts¹²:

“[The health agents] did not go into the *terreiros* to make routine visits, because they were scared or afraid that something would happen. The *terreiros* in turn complained that the PSF [currently ESF] did not meet them and thus did not comply with what was guaranteed by law, in the Constitution: the human right to health. Another challenge was to deal with religious intolerance, since most health teams are made up of people of other religions (Catholics and Evangelicals), who often make it difficult for the adepts to access the services offered by SUS. Health workers also complained that some supporters go against the guidelines prescribed by doctors and disrupt treatment. “The adepts trust more fathers and mothers of the saint than in us,” says the doctor.” (Silva 2007, 177)

The inequalities experienced by the black population, considering the principle of universality that guides the SUS and its policies, such as the ESF, qualifies the debate around the search for equity in health and not exactly through focal health policies such as Case of American society (Adorno et al. 2004). The experiences of inequality in treatment extend in different dimensions, as Lopes explains:

“In the case of health, the use of language as a means of maintaining and legitimating social and racial inequalities allows the creation of new mechanisms for the non-availability of a professional, adequate and equitable service. From the user's point of view, mechanisms are created and recreated for the non-perception or non-acceptance of negative attitudes on the part of the professionals. While they simulate egalitarian treatment,

¹¹ *Mãe de santo* and *pai de santo* is how the priests and priestesses of Afro-Brazilian religions are named in Brazil.

¹² Gomes (2010) describes an experience of partnership between an Afro-Brazilian *terreiro* and the Health Coordination of a Programmatic Area of the Municipality of Rio de Janeiro, where she was one of the active professionals. The request of the religious leader was aimed at the implementation of a vaccination unit within the space of the *terreiro* to serve the residents of the region. In the context of the *Posto* implementation process, the author reports that several complaints were presented by a group of women, many of whom were knowledgeable of professionals and users, such as “access difficulties, non-resolution assistance, racial prejudice, prejudices about poverty, maltreatment, prejudice related to the practice of Afro-Brazilian religion” (p. 665). One complaint, however, left the author intrigued: “invisibility,” which was only understood when the experiences of women were known. As the author points out with surprise: “The ‘invisibles’ had access to services, were attended to, accompanied, medicated and examined, but when we saw and heard them, we had the impression that they had never been seen.” (p. 665). The perception of invisibility, due to other difficulties presented, made the researcher recognize the fallacy of equity in health services provided to the population, producing contradictory speeches and interventions that denied poor women, black women and Afro-Brazilian religions their health demands. On the other hand, Lacerda et al. (2008), in a research related to evangelical ACS in the Northern Zone of Rio de Janeiro, point to the issue of religious intolerance as one of the issues addressed. According to the authors, it was observed that there is respect for the Afro-Brazilian religions in the daily work of these professionals, not interfering in the relations established with the families and houses visited.

they pretend not to perceive that they are being mistreated or pretend not to know that they do not have their needs satisfactorily addressed.” (Lopes 2005, 67, emphasis added)

Taking as reference a research carried out with users with hypertension, carried out in Rio de Janeiro and cited by Lopes, one can observe the capillarity of inequalities in health care: “The lack of cordiality on the part of the receptionist was cited by 4.5% of whites and 13.3% of blacks; By the auxiliary of nursing, 4.5% for whites and 5.4% for blacks; By the general practitioner, 4.5% among whites and 13.3% among blacks” (Lopes 2005, 67).

These problems also occur in the services found in the municipalities around the Baía. In a study of the relationship between *candomblé terreiros*¹³, public power and health policies in Salvador, Serra et al. (2010) point out different dimensions in the struggle for recognition of these groups: disputes over the religious dimension, territoriality involved in the management of urban space and the delay in recognizing Afro-Brazilian religions as “health agencies” (p.165).

Simultaneously with the process of constitution of the health policy of the black population at the national level, several initiatives took place in the city of Salvador, such as the 1st *Terreiro da Casa Branca* Health Fair, an event that was part of the activities of the I Seminar on Health of the Black Population¹⁴. Other editions of the fair took place in 2004, and in 2005, the Health Department of the Municipality of Salvador would refer to this project as a systematic activity (Serra et al. 2010, 168)¹⁵. In 2005, the Black Population Health Working Group was set up, an initiative linked to the newly created Municipal Secretariat of Reparation (SEMUR) in conjunction with the Municipal Health Secretariat (SMS). That same year, the SMS held a meeting with members of these secretariats and leaders of the *terreiro* with a view to the elaboration of propositions of activities. As a consequence of these initiatives, in 2007 the 1st Seminar on African Religions and Health was held with representatives of the Municipalities of Salvador and Lauro de Freitas, and the state government. The authors call attention to the central objectives of this meeting: the training of professionals to work in partnership with the *terreiros* and the training of *terreiros* agents (Serra et al. 2010, 169). Another claim of the meeting was the organization of an integrated district network of *candomblé terreiros* by the public health system. Serra et al. indicate that these objectives, still not very effective, sought to sensitize health professionals to the specificities of the *terreiros*, drawing attention to the problems of racism and religious intolerance. The following section synthesizes the intentions of the approach between religious leaderships and public administration from a double movement:

“The desiderata of the new policy that is tried to put into practice is double, as it is easily inferred from what has already been exposed: on the one hand, it is sought to contemplate effectively the people-of-santo in the actions of public health, giving him due Without discrimination; On the other hand, the objective of an alliance between government bodies and communities of *candomblé* is pursued, with a view to improving the health care of the black population (and the people in general).” (Serra et al. 2010, 170)

¹³ The *terreiro* is sacred ground and temple where all religious events happen. The older and more traditional ones are usually part of a *roça*, which includes not only the *terreiro*, but sacred trees and herbal gardens, *assentamentos*, and often a housing compound inhabited by some of the adepts.

¹⁴ The authors point out that the success of this seminar is that it mobilized several segments of the black movement to hold the First National Seminar on Health of the Black Population in 2004, held in Brasília.

¹⁵ Other health fairs were held in Salvador, such as the one that most recently took place in *Terreiro Jeje Savalia Karé Lewi* in June 2015 (Moreno Neto 2017).

On the one hand, health care; on the other, partnership. The terreiros can help in the capillarization of health policies, becoming “attention centers” as a result of the training of health professionals from these segments, seeking, therefore, policies directed and sensitive to the specificities of this population. However, the difficulties pointed out by the authors in the pursuit of this policy have come up against financial questions and religious intolerance. On this last point, Serra et al. (2010) affirm that this is a problem that is constantly approached in different forums that involve the candomblé leaderships and the public power.

“At the meeting just mentioned [I Seminar on African Religions and Health], this problem was clearly posed: community health and zoonotic agents refuse to perform health actions in the *terreiros*. In short, when it comes to meeting *candomblés*, they dodge the performance of routine actions that are their normal business.” (Serra et al. 2010, 171).

As the authors point out, if there are difficulties in the day-to-day care of the “*povo de santo*,” it is difficult to have a partnership, as the agents involved in this policy claim. The basis of this difficulty would be therapeutic prejudice (irrational and backward practices), diffuse racism and religious intolerance, the latter mainly driven by adherents of fundamentalist Pentecostal churches. On this issue, the consequences are severe for the Afro-Brazilian religions, as they clarify:

“One must note: religious intolerance spreading in Bahia is a cause of deprivation and suffering for an important segment of the population of the state, particularly its capital city: the *povo de santo*¹⁶, the priests and worshippers of the *orixás*¹⁷. It thus produces serious negative effects: on the one hand, it embarrasses the performance of a traditional system of action for health that effectively succumbs to the afflictions of many; On the other hand, prevents a more effective action by the public power in this field, in so far as it hinders a collaboration whose importance it is not possible to doubt.” (Serra et al. 2010, 173)

Allied to the difficulties surrounding religious intolerance, it is seen that the disposition of the public power towards the health of the black population is “much more rhetorical than effective” (Serra et al. 2010, 175). Serra et al. (2009), when the authors emphasize that the National Policy on Integral Health of the Black Population, approved in 2008, was assumed by the federal, state and municipal governments, but that in the government of Bahia has not yet been sensitive to the urgent need for a policy specifically directed at the health of the black population. The State Department of Health has agreed on a comprehensive policy of promoting equity, including blacks, indigenous people, homosexuals, *quilombola* communities, fishermen and *assentados*¹⁸, which fails to account for the specific health demands of blacks¹⁹. In this context, Serra et al. (2010) point to the fairs as the most successful experience between candomblés and the Municipal Government of the City of Salvador. They are different fairs from those held in other community spaces: in addition to the provision of services and other educational activities, there are still trade in products,

¹⁶ The adepts of religions of African matrix are known as *povo de santo*, which corresponding to saint's, in this case being *orisha's*, people.

¹⁷ Deities in the African matrix religions in Brazil.

¹⁸ *Assentados* are those rural workers who have benefited from the national agrarian reform program, getting access to land property.

¹⁹ Volochko (2009) presents several difficulties that involve the promotion of health in the *quilombola* communities of São Paulo, which are usually located in peripheral areas and economically poorly developed. In most municipalities, communities share the ESF services with nearby districts, creating numerous difficulties for the displacement of health professionals, high turnover and low qualification of managers. Poor and precarious facilities, as well as inadequate facilities to meet the population, complete the deficiencies.

dances, games, etc. These activities deserve great attention because they are elements that characterize the environment of *candomblé* and the sociability among its supporters and sympathizers.

Table 2. Religious participation in municipal health councils²⁰

Municipalities	Total number of participants	Catholic Representation	Evangelical Representation	Afro-Brazilian religions Representation	Spiritist Representation	Religious Indefinite Representation
Cachoeira	10	1	-	-	-	-
Candeias	12	1	-	-	-	-
Itaparica	12	1	1	-	-	1
Jaguaripe	10	1	1	-	-	-
Madre de Deus	12	-	-	-	-	2
Maragogipe	8	1	-	-	-	-
Salinas da Margarida	12	2	1	-	-	-
Salvador	16	1	-	1	-	-
Santo Amaro	10	1	1	-	-	-
São Félix	8	1	-	-	-	-
São Francisco do Conde	10	1	-	-	-	1
Saubara	10	-	1	-	-	-
Simões Filho	18	1	-	-	1	-
Vera Cruz	10	1	-	-	-	-

Source: SESAB/ CIB, 2017.

If, on the one hand, we have, in the experience of the fairs, as occasional attempts at recognition of therapeutic diversity in a city like Salvador, on the other hand, the invisibility of *candomblé* therapies in health policy is evident in the composition of municipal health councils. The table below indicates the restricted participation of the Afro-Brazilian community in the councils in comparison with other religious segments (especially the Catholic ones): only in Salvador is an Afro-Brazilian representative found. This imbalance certainly results in important consequences in the construction of public policies directed to the “povo de santo.”

THERAPEUTIC DIVERSITY IN SUS

Ministerial Order 971/2006 – “National Policy on Integrative and Complementary Practices in the SUS” and the “National Policy of Medicinal Plants and Phytotherapeutics” - Presidential Decree 5813/2006 - finally came to recognize and stimulate therapeutic diversity and Practice in the field of public health care. Seeking to comply with WHO guidelines, the objective was the inclusion and access of the population to phytotherapy/medicinal plants, acupuncture, homeopathy and termalism/chronotherapy practices. The valorisation of

²⁰ Available in http://www1.saude.ba.gov.br/cib/conselhos_municipais.asp. Accessed on: 12 May 2017.

alternative, community and “traditional” knowledge constitutes a tripartite policy, with responsibilities distributed by the federal, state and municipal governments, in order to increase the resolubility of the public health system.

The implementation of these policies in Bahia has focused more specifically on the issue of medicinal and phytotherapeutic plants and has been mobilizing the efforts of UFBA professors and researchers through the teaching, research and extension center of the Faculty of Pharmacy (*Farmácia da Terra* /UFBA) and the FITOBAHIA/SESAB, nucleus of the state health department. According to Almeida (2011a and 2011b), who is the coordinator of both nuclei, the strategies for the incorporation of complementary practices in the SUS-BA goes through the valorization of traditional cultures, especially African religions and of the identification of limits and possibilities for the insertion of phytotherapy in the public health services. Regarding herbal medicine, the author identifies and enumerates three main lines of action: a) the insertion of phytotherapy in the scope of state health policy; B) the creation of the State Nucleus of Medicinal Plants and Phytotherapy (FITOBAHIA), and c) the designing and implementation of the State Program of Medicinal Plants and Phytotherapy (Almeida 2011b, 31).

According to this author, these objectives have been consolidated, emphasizing that in 2009, *Portaria* No. 1686, instituted the State Nucleus of Integrative and Complementary Practices of SUS and the Nucleus of Medicinal and Phytotherapeutic Plants, as an integral part of the first. In the initial phase of the project of medicinal and phytotherapeutic plants, the municipalities included have been Itacaré, Ilhéus, Itabuna, Palmeiras, Itapetinga, Juazeiro, Igrapiúna and São Francisco do Conde, which is the only municipality among those located around the Baía included in the program (Almeida 2011b, 31). She mentions some challenges which have to be dealt for the implementation of these policies, such as the acquisition of materials, the qualification of professionals, the acquisition of basic knowledge about these therapeutic practices among SUS professionals, managers and users, the need for participatory management, cooperation and national and international exchange and education, evaluation and further research (Almeida 2011b, 32).

It should be considered, however, that the policies of valorization of traditional practices such as those involving medicinal plants need to consider both the epidemiological profile of the populations and the specificities of the therapeutic practices that make use of native plants. Commenting on the formulation of legal frameworks²¹ for the regularization of medicinal plants in Brazil, Almeida and collaborators (2012) indicate that these “milestones” have been giving greater prominence to exotic plants, as can be seen in the last edition of the “Brazilian Pharmacopoeia,” in comparison with the 1929 edition. In this sense, the authors warn that:

“The state of Bahia is divided in 417 municipalities, and it is covered by divers biomes, such as the Atlantic Forest, the *caatinga*, the *cerrado*, the coastal zone vegetation and transition zone of the *cerrado-caatinga*, which justifies considering the epidemiological profile of each municipality, the native species present in each of those biomes, as well as the knowledge and health practices of the local population for the elaboration of the State Relation [of medicinal and phytotherapeutic plants] and Therapeutic Memento. Ethnobotanical surveys carried out in the *Recôncavo Vaiano* indicate that, unlike official lists, Afro-descent

²¹ As to the National List of Medicinal Plants of Interest to SUS (RENISUS) released in February 2009, which includes 71 species of plants, in addition to ANVISA regulations for registration of herbal medicines (RDC 14, October 31, 2010), resolution on (RDC 10, 03/10/2010) and normative instruction (IN-05/2008) of medicinal plants considered as a simplified registration.

communities preferentially use native species for medicinal and ritualistic purposes in the proportion of 52% to 28% of Brazilian legal landmarks.” (Almeida 2012, 244)

In the context of the Baía, the nucleus of UFBA (developing activities since 1995), in partnership with FITOBAHIA/SESAB, conducted in *São Francisco do Conde* a work of insertion of community therapeutic practices in the *Sistema Único de Saúde-SUS*²², through articulation of the health policies for the black population and of the herbal and phytotherapeutic plants. The implementation of this project took place through ethnopharmacological research, training of public network professionals and educational actions with the local population (according to news published on the Internet, the group cataloged more than 60 species of medicinal plants). The localities of the municipality served by the project were Muribeca (due to the large number of elderly) and the *quilombola* community of *Monte Recôncavo* (emphasis on therapeutic practices of African matrix), besides the seat district²³. For the implementation of the herbal medicine program, the UFBA nucleus developed activities ranging from theoretical classes, cultivation of medicinal plants at the Faculty of Pharmacy of UFBA, visits and research to popular fairs and *candomblé terreiros*, follow-up of popular initiatives such as “*Botica da Terra*.” This last project was initiated by a group of women from the suburbs of Salvador, which was stimulated by the city's archdiocese, which sought new practices in education, hygiene and health. The group started its activities in the 1980s, in the neighborhood *Alto da Terezinha*: in addition to several actions in education and health, the group had a home remedy center located since 1997 in *Pelourinho* (currently this project is deactivated).

As it can be seen, both from the situation in the State of Bahia and the Baía region, these policies are still incipient, insofar as they are restricted to a few municipalities and focus on the implementation of medicinal and phytotherapeutic plants. In a meeting of the state coordinators of integrative and complementary practices programs, held in 2011, in Brasília, Almeida (2011b) records the progress of this program in Bahia: only policy regulation. The author also indicates that actions have already been initiated to train professionals and to conduct orientation seminars for SUS users, but there is still no availability of resources for the implementation of the Pharmacobotanical Garden, the “Live Pharmacies” and the Herbal Medicines Processing Centers.

CONCLUSION

Returning to the characteristics highlighted in the two public policies which have been presented, one can identify as a common point the valorization of therapeutic diversity, however, through certain specificities. In policy designed for the black population, in addition to valuing Afro-Brazilian traditional knowledge, the guidelines also focus on minimizing inequalities in access to health services in this segment of the population, that's to say, a demand for “more” universalization “of biomedical care.” However, the policy of herbal and phytotherapeutic plants, which is articulated with the broader regulation of the “National Policy of Integrative and Complementary Practices” (PNPIC), does not focus on a specific

²² Unified Health System of Brazil.

²³ Information available on the website: farmaciadaterra.ufba.br.

segment and has as one of its guidelines the incentive to therapeutic diversity in scope (“inside”) of SUS.

The resumption of this discussion, based on the data on which is based this chapter, has led to the identification, as in practice, of some challenges involving the universal guidelines of the ESF, on the one hand, and the policies of “recognition” of the differences, drawing attention to the need to deepen the discussion and to understand these processes in close interrelation. The policies mentioned highlight processes of valorization of people’s knowledge in complex situations of social, economic and environmental vulnerability, since the policy interlocutors and the diverse opinions involved in the two fields of discussion are not always the same. These are challenges that make it difficult to understand the complexity of situations and, consequently, the need to argue in favor of giving isonomic treatment to the parties, differentiated by means of unequal treatments, that allow those who are in those situations of inequality pointed out in this text to overcome the deficiencies to which they are subjected in all aspects of everyday life, which includes formulation and implementation of affirmative action policies in health care²⁴.

²⁴ Nery Junior (1999, 42) argues that “giving isonomic treatment to the parties means treating equally and unequally the unequal, in the exact measure of their inequalities.”

Chapter 546

MUSSELS AS SENTINEL ORGANISMS IN METAL AND METALLOID CONTAMINATION SCENARIOS: ENVIRONMENTAL AND PUBLIC HEALTH RISK BIOINDICATORS

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ABSTRACT

Among environmental pollutants, metals and metalloids are of particular concern due to their potential toxic effects and the ability to bioaccumulate throughout the aquatic trophic web. However, the simple measurement of chemicals levels present in the environment is often not enough to reveal the actual adverse effects of the contamination, making it necessary to also assess the biological effects of contamination on living organisms, applying bioindicators and biomarker measurements. Mussels have been recognized as one of the best sentinel organisms regarding aquatic environments and have been increasingly used in many worldwide environmental monitoring programs. This chapter will discuss the role of several mussel species in environmental monitoring programs, with emphasis on metal contamination, including metal bioaccumulation and biomarker investigations. In addition, the fact that these organisms may be an important contaminant transfer link to the human population and pose important public health risks will also be discussed.

Keywords: mussels, sentinel organism, metal contamination, biomarkers, oxidative stress, public health risks

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INTRODUCTION

One of the major damaging effects in aquatic environments due to anthropic activities is contamination by chemical pollutants. These contaminants continuously enter the aquatic environment through inadequate waste disposal, incomplete removal by sewage treatment plants, and sewage dumped into water bodies without adequate collection and treatment. Among the many different environmental contaminants present in these ecosystems, those of greatest concern present environmental persistence, bioavailability, a tendency to bioaccumulate in the food chain and the ability to cause toxic effects, such as persistent organic pollutants (Jones and de Voogt, 1999), polycyclic aromatic hydrocarbons (Abdel-Shafy and Mansour, 2016), metals (Singh et al., 2011) and, more recently, emerging contaminants originating from substances used by the human population in daily life, such as pharmaceutical formulations and personal products (Burkhardt-Holm, 2010).

Among environmental pollutants, metals and metalloids are of particular concern due to their potential toxic effects and the ability to bioaccumulate throughout the aquatic trophic web (Censi et al., 2006; MacFarlane and Burchett, 2000; Miller et al., 2002), thus being the subject of many biomonitoring efforts.

Metal and metalloids enter aquatic systems through both natural and man-made processes. The natural processes that most contribute to their presence in aquatic environments are rock weathering and the erosion of soils rich in metals and metalloids, while the main anthropic sources are industrial and mining activities, domestic effluents, surface water runoff from areas cultivated in the presence of chemical fertilizers and agricultural pesticides, and atmospheric precipitation of ash or small particles from fires (Esteves, 1988; Jordão et al., 1999; Mortatti and Probst, 1998; Nriagu and Pacyna, 1988; Ramalho et al., 2000; Yabe and Oliveira, 1998).

In the aquatic environment, metals and metalloids are distributed in both the aqueous (water column and interstitial water) and the solid (suspended and sedimented) phase, as well as in aquatic organisms, with a dynamic exchange between these phases, varying from one ecosystem to another (Conceição, 2004). Aquatic organisms assimilate metals and metalloids from both the aqueous and solid phases, namely water and sediments and, especially, food. These elements may then accumulate in tissues in several orders of magnitude above concentrations found in the water column. Therefore, aquatic organisms are responsible for much of the dynamics of these pollutants in the aquatic environment. It is important to note that the effects of these pollutants can be toxic and/or lethal to all components of the biota, such as phytoplankton, benthos, fish, birds, and, finally, humans that feed on contaminated organisms (Canli and Atli, 2003; Fowler, 1982; Junior et al., 2002; Pfeiffer et al., 1985), through bioaccumulation and bio magnification processes.

METAL AND METALLOID TOXICITY

Metals and metalloids can be classified as essential, non-essential and toxic elements. Essential elements, when present in low concentrations, play an important role in organism metabolism. Non-essential elements and toxic elements, however, do not play any known biological functions. Increasing essential element concentrations, up to a certain range, lead to

improvements in organism development and metabolism. Above this range, these elements become toxic and, beyond a certain limit, lethal. Non-essential elements, on the other hand, are tolerated by the body to a certain extent and, if present above certain concentration limits, follow the same behavior described above, becoming toxic and then lethal to the organism. These differences are displayed in Figure 1.

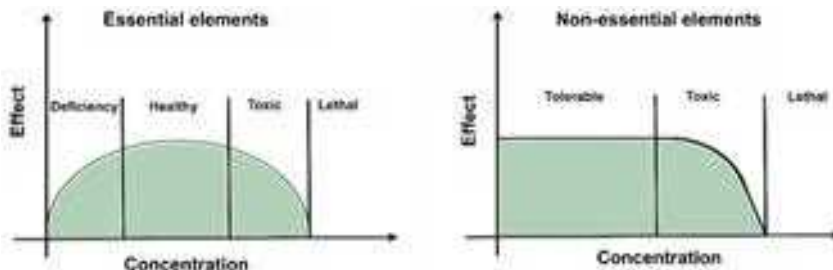


Figure 1. Graphical representation of the relationship between essential and non-essential concentrations and their effects on organisms. Adapted from Galvão (2003).

Element toxicity also depends on the chemical form present, i.e., the bioavailable fraction. Some metals and metalloids, such as Cd, Pb, Hg and As, for example, are non-toxic in the forms of free condensed elements, while, when present in their cation forms and when bonded to short carbon atom chains, become toxic. The amount absorbed by the organism also influences element toxicity, since even essential elements can be toxic when absorbed above limits tolerable for normal organism metabolism, as stated previously (Baird, 2002; Melo, 2003).

Different metal and metalloid toxicity mechanisms have been described, including (i) enzymatic inactivation due to the high reactivity of divalent transition metals with the amino and sulfhydryl groups of proteins; (ii) metal competition with essential elements and their replacement in the enzymatic metabolism - Pb, for example, can replace Zn in several proteins that function as transcription regulators - and (iii) the “cocktail effect,” in which the excess of one element can cause the deficiency of another(s), such as the case of excess of Pb, that interferes in the absorption of Ca, Fe, Cu and Zn, for example (Förstner, 1989; Melo, 2003; Moreira and Moreira, 2004).

Thus, although the determination of metals and metalloids in tissues and organs of different aquatic organisms is an important method to evaluate metal contamination in aquatic ecosystems (Farkas et al., 2001), the simple measurement of metal levels present in the environment is often not enough to reveal the actual adverse effects of the contamination, making it necessary to also assess the biological effects of contamination on living organisms. This is performed through the use of bioindicators, also termed sentinel species, and biomarker measurements.

MUSSELS AS BIOINDICATORS CONCERNING ENVIRONMENTAL METAL AND METALLOID CONTAMINATION

Mussels are widely used as bioindicators for a number of aquatic contaminants, due to their sessile nature, which facilitates their sampling, their worldwide distribution, reasonable

size, known biology and ecology, and filtering feeding habits, leading to the absorbance and retention of solid particles and, consequently, any contaminant adsorbed therein (Lamparelli, 1987; Rainbow, 1995; Resgalla Jr. et al., 2008; Wallner-Kersanach and Bianchini, 2008).

These organisms are able to concentrate contaminants in their tissues and survive, and even, thrive, in contaminated environments and are, therefore responsible for part of pollutant dynamics in the aquatic environment. In addition, they concentrate environmental contaminants proportionally to external (water) concentrations, thus reflecting the contamination history of the environment and, because they settle on shallow water substrates, they are exposed to environmental factors on a local scale, allowing for the comparison of environmental contamination between different locations (Chase et al., 2001; Chou et al., 2004; Dame, 1996; Rainbow, 1995; Storelli et al., 2000; Sun et al., 2004).

Because of these characteristics, mussels have been recognized as one of the best sentinel organisms regarding aquatic environments and have been increasingly used in national and international environmental monitoring programs (Bellotto et al., 2005) for both freshwater and marine ecosystems. For example, the United States National Oceanic and Atmospheric Administration Mussel Watch Program, the nation's longest running continuous coastal contaminant monitoring program, has applied several *Mytilus* species, such as *Mytilus edulis*, *Mytilus californianus*, *Mytilus galloprovincialis* and *Mytilus trossulusto*, to evaluate the contamination status of US coasts (Binelli et al., 2015), while many other species have been applied as bioindicators for metal and metalloid contamination scenarios worldwide.

Several biomarkers have been routinely investigated in these contamination scenarios, in order to evaluate the potentially deleterious effects of metal and metalloids, which shall be discussed further ahead in this chapter. First, however, it is important to understand the subcellular and molecular effects of metal and metalloid exposure in living organisms.

SUBCELLULAR AND MOLECULAR EFFECTS OF METAL AND METALLOID EXPOSURE: REACTIVE OXYGEN SPECIES AND OXIDATIVE STRESS

One of the main deleterious effects of metals and metalloids are alterations in cellular redox regulation or oxidative reaction cycles, producing reactive oxygen species (ROS) and certain non-radicals derived from oxygen capable of generating free radicals, such as hydrogen peroxide and hypochlorous acid, which, in turn, may lead to oxidative stress (Buonocore and Groenendaal, 2007; Halliwell and Gutteridge, 2007).

Free radicals, like ROS, are small molecules with a short half-life that possess one or more unpaired electrons, characterized by high reactivity, sequestering electrons from neighboring molecules in order to become stable (Buonocore and Groenendaal, 2007; Halliwell and Gutteridge, 2007). The main ROS species are usually formed by the main oxygen metabolism route in the body, which is completely reduced to water, integrating four electrons at the end of the electron transport chain inside the mitochondria. The main ROS, superoxide anion, hydrogen peroxide and hydroxyl radical, are produced when the oxygen molecule is reduced, along with a smaller number of electrons along the respiratory chain.

The body, however, possesses natural ROS elimination systems, known as intracellular antioxidant defenses, which are substances that prevent, delay or remove oxidative damage

from a target molecule (Cogo et al., 2009; Halliwell and Gutteridge, 2007). When these antioxidant substances are present in amounts equivalent to ROS concentrations, the metabolism and cellular functioning of living organisms remain unchanged. However, situations where excessive ROS are being produced, and/or cases of failure of antioxidant defenses may lead to oxidative stress, caused by the imbalance between the formation rate of oxidant molecules and antioxidants in the body (Halliwell and Gutteridge, 2007). Oxidative stress may then lead to protein carbonylation, a process by which proteins can undergo reversible and irreversible oxidation and covalent modifications in their amino acids, modifying them into aldehyde or ketone groups, which are harmful to proteins, causing their aggregation, inactivation and degradation, and the produced ROS may interact with lipids, proteins or nucleic acids, resulting in various biochemical or genetic damages (Costa et al., 2002; Ghezzi and Bonetto, 2003; Levine et al., 1990).

The presence of metals and metalloid in biological systems in an uncomplexed form, not as protein co-factor or any other type of protective metal complex, can significantly increase oxidative stress levels (Dalle-Donne et al., 2006). In this context, certain redox-active metals, that undergo redox-cycling reactions, such as Cr, V, Co and Cr, are known to induce oxidative stress, causing damage to mitochondrial respiration (He et al., 2008; He et al., 2007; Valko et al., 2005), while other metals, such as Fe and Cu, are known to produce ROS by the Haber-Weiss (Equation 1) and Fenton (Equation 2) reactions (Barreiros et al., 2006).



The Fenton reaction occurs in the presence of metal ions and hydrogen peroxide, forming the hydroxyl radical, hydroxyl anion and leading to metal oxidation. In the Haber-Weiss reaction, metals can react with the superoxide anion through its reduction, generating molecular oxygen, and the reduced metal the reacts react with the hydrogen peroxide, generating the hydroxyl radical in the Fenton reaction (Leonard et al., 2004).

The generation of these radicals may lead to negative effects if organism defenses are overwhelmed. In this context, biomarker responses, meaning measurable alterations of any physiological, biochemical or behavioral steady state induced by an environmental change, against metal- and metalloid-induced oxidative stress are applied as early warning signs of the possible deleterious effects of these contaminants.

MUSSEL BIOMARKER RESPONSES AGAINST METAL - AND METALLOID-INDUCED OXIDATIVE STRESS

Mussel gills, digestive gland and haemolymph are regarded as excellent candidates for assessing toxic impacts of metal and metalloid exposure, due to their direct contact with the environment (water medium) and the fact that they are the center of metabolic regulations and metal transfer pathways to detoxifying tissues (Chandurvelan et al., 2013). Thus, biomarkers against metal- and metalloid-induced oxidative stress in these tissues are investigated in order

to detect early negative effects and allow for decision-making processes regarding these environmental contaminants.

In this regard, one of the main biomarkers established by monitoring programs developed and implemented in the European community to investigate contamination by metals and metalloids is the metalloprotein metallothionein (MT) (Bebianno et al., 1993; Garrigues et al., 2002; Sarkars et al., 2006).

Metallothioneins are a group of low molecular weight (6 to 7 KDa) metalloproteins (proteins that bind to metals), rich in cysteines and presenting heat stability. They display a high affinity for metal ions and play an important role in several biological functions, such as essential metal homeostasis and detoxification of both non-essential elements and essential elements present in excess in the organism (Freire et al., 2008; Monserrat et al., 2007; Motta, 2012; Sarkars et al., 2006; Viarengo et al., 2007). Their synthesis is induced through the presence of metal and metalloid cations in the body, and the thiol group (-SH) present in this metalloprotein's structure allows binding with these elements, restricting their bioavailability (Freire et al., 2008; Linde et al., 1999; Monserrat et al., 2007; Nicholson and Lam, 2005; Viarengo et al., 2007).

Usually, these proteins bind to 7 equivalents of divalent metal ions, through the formation of metal-sulfhydryl clusters (Figure 2) (Melendez et al., 2012; Motta, 2012), in which the order of affinity is usually $\text{Cd} > \text{Pb} > \text{Cu} > \text{Hg} > \text{Zn} > \text{Ag} > \text{Ni} > \text{Co}$ (Waalkes et al., 1984), although this may vary according to the bioavailability of the metals in the cell.

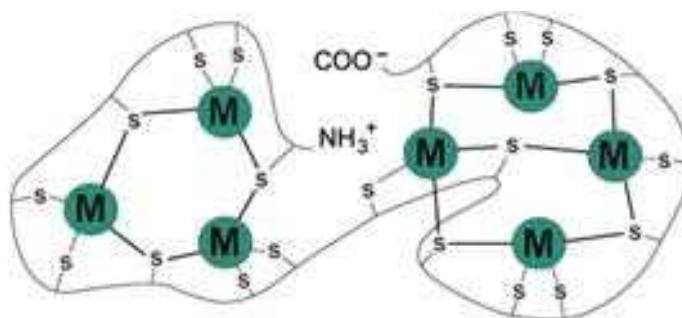


Figure 2. Metal binding sites present in one metallothionein molecule. "M" indicates metal ion binding sites. Adapted from UVED (2015).

Several metals have been shown to induce MT synthesis in mussels. For example, Mourgaud et al. (2002) observed that As, Cd, Cr, Cu, Hg, Ni, Pb and Zn concentrations were significantly correlated to MT in the mussel species *Mytilus galloprovincialis* mussels, while Purina et al. (2013) observed the same for Cd, Pb, Hg, Cu and Zn and MT in the freshwater mussel *Anodonta* spp. In another study, an increase in MTs in *Dreissena polymorpha* was shown to occur at relatively low aqueous Pd concentrations indicating that there is the need for Pd detoxification in these mussel, with significant correlations between MT and Pd associated with adverse effects on the mussels (Frank et al., 2008), while significant correlations were determined between MT induction and metal contamination in the green-lipped mussel, *Perna canaliculus*, indicating that different sampling sites were clearly distinguishable based on the metal contamination profiles and this biomarker response (Chandurvelan et al., 2015).

Tissue-specific responses have been reported for this biomarker, such as in the study conducted by Lavradas and collaborators with *Perna perna* mussels sampled from 3 contaminated areas in an extremely contaminated bay and compared to a reference site in southeastern Brazil, where the digestive gland was shown to be a better bioindicator for metal and metalloid contamination compared to muscle tissue (Lavradas et al., 2016). This was also observed in a study that investigated Cd and MT distribution in different tissues of the freshwater mussel *Anodonta woodiana* following Cd exposure. In this case, the authors report that Cd was distributed in all tissues in the concentration order of gills>mantle>foot>visceral mass>digestive gland, and that the highest Cd accumulation was found in the digestive gland, while MT levels in the gills and mantle increased significantly and were positively correlated to Cd accumulation in the different tissues (Li et al., 2015).

However, it is important to note that variations in MT isoforms may be present, in which one or more may contribute to metal detoxification, while others may not display a function in this regard, or may even be inhibited following metal or metalloid exposure. For example, in one study, *Mytilus edulis* specimens were exposed to Cd and Hg for 21 days and the gills, mantle and digestive gland were evaluated regarding MT isoforms. Size exclusion chromatography showed the presence of an MT monomer and a dimer in gills, of respective apparent molecular weight of about 12 kDa and 20 kDa, which were then resolved into five components by anion exchange chromatography in the gills of control or Hg-treated mussels, whereas a sixth isoform was isolated in the gills of Cd-exposed mussels. In the mantle of mussels, exposed or not, five isoforms were separated, and in the digestive gland of mussels exposed or not, six isoforms were separated (Geret and Cosson, 2002). In another study, different MT isoforms were observed in the digestive gland of control and experimentally Cd-exposed mussels in *Mytilus edulis* ($200\ \mu\text{g L}^{-1}\ \text{Cd}^{2+}$ and $400\ \mu\text{g L}^{-1}\ \text{Cd}^{2+}$; 20 days), where an induction of the dimeric form MT20 II was detected in the $400\ \mu\text{g L}^{-1}$ exposed mussels and an inhibition of the monomeric form MT10 IV was verified (Ciocan and Rotchell, 2004).

It is thus, important to investigate MT expressions in mussels through analytical techniques that allow for isoform differentiation, since different MT isoforms may contribute to different metal and metalloid detoxification mechanisms.

The glutathione metabolism is also extremely important in conferring protection against metal and metalloid toxicity.

Glutathione (γ -L-glutamyl-L-cysteinylglycine) (Figure 3). is a tripeptide with strong antioxidant capacity, determined by the reactive grouping of its cysteine, the thiol group (-SH).

This tripeptide acts directly or indirectly in many biological processes, such as in metabolic and transport processes, acting against the production of free radicals, in thiol homeostasis, maintenance of the redox balance of the cell, defense against xenobiotics and playing a central role in the biotransformation and elimination of electrophilic agents and protecting cells against the toxic effects of a variety of compounds. GSH is used as a substrate in conjugation reactions, catalyzed by glutathione S-transferase enzymes, but is also capable of participating in nonenzymatic conjugations with many xenobiotics (Aquilano et al., 2014).

Several studies demonstrate the induction of metal-GSH complexes in different organisms after exposure to these compounds, through the sulfhydryl group, such as Cu^{2+} and Fe^{3+} , that readily catalyze GSH oxidation, producing several free radical species (Rabestein et al., 1985; Stohs and Bagchi, 1995), and the Cu^{2+} reduction by GSH, that produces a stable Cu^{1+} -SG complex that impedes further redox cycling and leads to the generation of free

radicals (Corazza et al., 1996). Thus, it has been proposed that GSH is able to complex with metals and detoxify organisms soon after the entry of these elements into the cell, representing a first line of defense against metal cytotoxicity (Canesi et al., 1999).

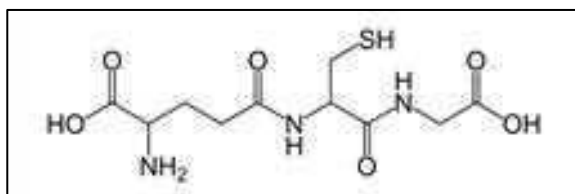


Figure 3. γ -L-glutamyl-L-cysteinylglycine.

The glutathione metabolism also includes several glutathione-based enzymes, such as glutathione S-transferase (GST), glutathione peroxidase (GPx) and glutathione reductase (GR), which have also been implicated in metal and metalloid biomarker responses.

In this regard, research has investigated glutathione metabolism proteins and enzymes in mussels and their responses after metal and metalloid exposure. For example, several studies indicate impairment of the antioxidant system and decreases in GR activity and GSH levels when *Perna perna* mussels were exposed to zinc (Franco et al., 2006; Trevisan et al., 2014). Exposure to sublethal copper concentrations in *Mytilus galloprovincialis* also led to alterations (decreases) in total GSH content in both gills and the digestive gland, while sublethal mercury concentrations in the same species decreased tissue glutathione content when exposure was conducted with the organic mercury form (methylmercury), but did not significantly affect GSH content and metabolism when present in the inorganic form (Canesi et al., 1999), thus indicating that the chemical form of the contaminant is also of importance when evaluating metal and metalloid effects in these organisms. Other studies conducted with environmentally exposed mussels, such as the freshwater *Lasmigona costata* inhabiting a metal gradient, indicate that several biomarkers involving the SH metabolism, namely GSH, SH protein, total SH, GR and GST, were significantly correlated to gill metal concentrations (Machado et al., 2014), while alterations in GR and GPx were detected in the brown mussel *Perna perna* after exposure to 30 and 100 $\mu\text{mol L}^{-1}$ zinc (Franco et al., 2006).

Thus, it is a consensus that the glutathione metabolism plays an essential role in metal- and metalloid-induced responses in these organisms.

Several other enzymes are important in this regard, since they participate in the biotransformation process of xenobiotics, which occurs in two stages, Phase I and Phase II.

Phase I reactions are responsible for exposing or introducing functional chemical groups into xenobiotic molecules leading to an increase in their polarity, which can lead to the loss of toxic potential and their excretion, resulting in detoxification. At this stage reduction reactions catalyzed by the cytochrome P450 enzymes occur, as well as hydrolysis reactions, catalyzed by esterases and amylases, and oxidation reactions. Metabolites resulting from the metabolism of this first phase may subsequently undergo detoxifying during biotransformation in Phase II. During this second phase, conjugation reactions catalyzed by sulfotransferases, glucuronosyltransferases and GST occur, promoting the conjugation of a variety of toxic molecules with endogenous molecules. The conjugates, mostly soluble and often inactive, are then excreted.

However, the mechanism by which metals and metalloids alter the activity of these enzymes is still unknown. Thus, some hypotheses that attempt to explain this phenomenon have been postulated, as follows: (i) Metals and metalloids cause protein denaturation because they alter the ionic interactions existing between the amino acid side chains, causing changes in enzyme conformation, leading to loss of catalytic activity; (ii) Metals and metalloids may bind to an amino acid residue, for example, cysteines, containing the sulfhydryl group and displaying affinity for various metals and metalloids, close to the active site of the enzyme, making it impossible for the substrate to fit into the enzyme for the enzymatic catalysis process (Bainy et al., 2006; Goncalves et al., 2010; Romani et al., 2003; Sant'anna et al., 2011). It is important to emphasize that studies on the effect of metals and metalloids on enzyme activities are discrepant since certain parameters, such as exposure time and test concentrations, can stimulate, diminish or even alter the activity of this group of enzymes in exposed organisms (Bainy et al., 2006; Barata et al., 2004; Najimi et al., 1997; Richetti et al., 2011; Vioque-Fernández et al., 2007).

Several of these enzymatic biomarkers have been evaluated in mussels regarding metal exposure scenarios. In one study, the mussel species *Mytilus galloprovincialis* from the Saronikos Gulf of Greece was applied to monitor metal pollution in three contaminated sites and the results were compared to unpolluted site. Seasonal variations in superoxide dismutase (SOD) and catalase (CAT) activities were observed over three years in relation to concentrations of trace metals mussel gills and mantle, with SOD activity increasing at least 2-fold at the polluted sites, while CAT activity increased 2-3 times at the polluted sites, both compared to the control site (Vlahogianni et al., 2007). Another study investigated the toxic effects of zinc on antioxidant status and stress proteins in the gills of the brown mussel *Perna perna*, and indicated significant induction of CAT activities (Franco et al., 2006).

However, discrepant results in the literature are frequent regarding metal-induced alterations in these organisms. For example, in a study that conducted both a transplantation experiment of these organisms to a contaminated site and laboratory-exposure study to copper with *Mytilus galloprovincialis* polluted organisms (native, transplanted and Cu-exposed) showed significantly lower levels of glutathione and higher activities of glyoxalases (which detoxify reactive α -ketoaldehydes formed in cellular oxidative processes). However, native mussels from both the polluted and control populations exhibited similar GR, GPx, catalase, SOD and alkaline phosphatase activities, whereas, in both transplanted and Cu-exposed mussels, these enzymes showed significant variations. The authors postulate that these findings could suggest the occurrence of an adaptation or compensatory mechanism in chronically polluted organisms. In addition, they state that no clear results were obtained regarding GST, and that other esterases (arylesterases and cholinesterases) appeared not to be affected by metal pollution (Regoli and Principato, 1995).

MUSSEL RESPONSES TO NANOPARTICLE EXPOSURE

Nanotechnology applications have significantly expanded in the last decades, leading to the inevitable release of nanoparticles, mainly metal nanoparticles, into aquatic systems, resulting in growing environmental and human health concerns (Rocha et al., 2015b). Although very small, nanoparticles exhibit a high surface/volume ratio, providing them with a

high reactivity potential and unique physical and chemical properties that differ from conventional forms (Oberdörster et al., 2005).

In this context, research regarding these metal contaminants has increased in the last decades. Most studies expose mussels to both a metal nanoparticle and the dissolved form of the metal, in order to compare mechanisms of action and ecotoxicological effects. For example, *Mytilus galloprovincialis* specimens were exposed to $10 \mu\text{g L}^{-1}$ of Ag nanoparticles (Ag NPs) and ionic silver (Ag^+) for 15 days. Results indicate that both Ag forms, the NPs and ionic form, accumulated in both gills and digestive glands of the organisms. Regarding antioxidant enzymes, activities of superoxide dismutase, catalase and glutathione peroxidase were activated by both Ag NPs and Ag^+ , and displayed different antioxidant patterns in both gills and digestive glands. Moreover, metallothionein was induced in gills, directly related to Ag accumulation, while in the digestive glands only a small fraction of Ag seems to be associated with this protein. Thus, the authors indicate that Ag NPs and Ag^+ cause oxidative stress with distinct modes of action and it is not clear if for Ag NPs the observed effects are due to the free Ag^+ ions associated with the nanoparticle effect (Gomes et al., 2014).

In another study conducted with the same species, *Mytilus galloprovincialis* specimens were exposed to $10 \mu\text{g Cu} \cdot \text{L}^{-1}$ copper nanoparticles (CuO NPs) and Cu^{2+} in gills for 15 days. Results indicate that mussels accumulated copper in gills and responded differently to both copper forms, suggesting distinct modes of action. The CuO NPs induced oxidative stress by overwhelming the antioxidant defense system in gills, while Cu^{2+} exposure led to either unchanged or increased enzymatic activities. MT induction was also observed during both types of exposure, while neurotoxic effects reflected as AChE inhibition were only detected at the end of the exposure period for both copper forms (Gomes et al., 2011).

Tissue-specific responses related to alterations in the antioxidant defense system induced by CdTe quantum dots, in comparison with its dissolved counterpart, using the marine mussel *Mytilus galloprovincialis* have also been conducted. Results indicate that both Cd forms altered mussel antioxidant responses with distinct modes of action, tissue- and time-dependent differences in the biochemical responses to each Cd form, wherein QDs were more pro-oxidant when compared to dissolved Cd. Regarding tissue, the gills were observed as being the main tissue affected by QDs, with effects related to the increase of SOD, GST and GPx activities, while dissolved Cd was associated to increases in CAT activity, Cd accumulation and exposure time. The authors report that the digestive gland was the main tissue for accumulation of both Cd forms, but changes in antioxidant enzyme activities were noted as being lower than in gills. The authors conducted a multivariate analysis, that revealed that the observed antioxidant patterns are tissue dependent, indicating nano-specific effects possibly associated to oxidative stress and changes in redox homeostasis (Rocha et al., 2015a).

Another study on *Mytilus galloprovincialis* evaluated short-term effects on antioxidant enzyme activities and long-term genotoxic and carcinogenic potential of CuO NPs (NPs) in comparison to bulk CuO and ionic copper after 21 days exposure to $10 \mu\text{g Cu L}^{-1}$. After exposure, mussels were kept for up to 122 days in clean water. Results indicate that Cu accumulation depended on the form of the metal and on the exposure time, and that the three Cu forms produced different effects on antioxidant enzyme activities in digestive glands, overall increasing antioxidant activities. In addition, the authors report that CuO NPs significantly induced both catalase and superoxide dismutase activities, with fewer effects observed in gills (Ruiz et al., 2015).

However, nanoparticle studies have mostly been conducted on seawater species, with *Mytilus* genus as the main investigated taxa used as a model system (Rocha et al., 2015b). Thus, scarce literature is available on other species, indicating the need for further research in this regard in order to increase knowledge on the ecotoxicological effects of these emerging contaminants.

Some of the few examples found in the literature conducted with other species include a recent study on the toxicological perturbations resulting from zinc oxide nanoparticle exposure in the *Coelatura aegyptiaca* mussel, where the organisms were exposed to ZnO NPs (2, 10 and 50 mg L⁻¹) for 6 consecutive days. Exposure at 10 and 50 mg L⁻¹ induced a significant increase in malondialdehyde, superoxide dismutase and nitric oxide, with a concomitant decrease in reduced glutathione, glutathione-S-transferase and catalase levels in the haemolymph, digestive glands and gills of the treated mussels, indicating significant oxidative stress mechanisms of action (Fahmy and Sayed, 2017).

Sublethal effects of nanoparticle exposure in the freshwater mussel *Elliptio complanata* have also been evaluated. On study investigated the effects of CdTe quantum (1.6–8 mg L⁻¹) dot exposure in this species, while another, by the same research group, investigated the effects of increasing concentrations of 20-nm and 80-nm silver nanoparticles, as well as dissolved Ag⁺, for 48 h at 15°C. The former observed significant effects on hemocyte immuno competence (phagocytic activity, viability and cell lysis potential), as well as oxidative stress in gills and digestive glands, while a significant decrease in the number of DNA strand breaks was also observed at 4 and 8 mg L⁻¹, indicating inhibition of the DNA repair activity (Gagné et al., 2008). The latter observed that the response pattern of 80 nm nAg was more closely related to ionic Ag⁺ than 20 nm Ag, suggesting higher release of dissolved Ag from the 80 nm nAg. The authors, however, also report that all forms of Ag increased MT and LPO levels, suggesting that the presence of ionic Ag⁺ leads to oxidative stress. The nanoparticles also induced alterations in other proteins, such as ubiquitin, actinomyosin-ATPase, MT, and DNA strand breaks in the digestive gland in a manner different from Ag⁺, while LPO was closely associated with DNA strand breaks in the digestive gland and was not entirely explained by induction of MT, suggesting another type of toxic interaction. It was concluded that the presence of nAg not only increases the toxic loadings of released Ag ions but also generates other and perhaps cumulative effects of nanoparticle-induced toxicity related to size and surface properties (Gagné et al., 2013).

Overall, mussels display significant oxidative stress effects after nanoparticle exposure, and it seems that metals in the nanoparticle form show different mechanisms of action than those in free form, thus creating increased concerns regarding the effects of these emerging contaminants in the aquatic environment.

NECESSARY CONSIDERATIONS WHEN APPLYING MUSSELS AS BIOINDICATORS FOR METAL AND METALLOID EXPOSURE IN AQUATIC ECOSYSTEMS

Seasonal metal accumulation variations may be due to several abiotic factors. For example, increased precipitation in the summer may be responsible for pollutant dilution of pollutants and decreased metal concentrations in the water and, consequently, in mussels,

while differences in water temperature between summer and winter, which may affect mussel physiology and cause changes in metal concentrations in certain tissues (Szefer et al., 2004). In this regard, several factors have been postulated as the cause of the seasonal variations observed for biomarkers in mussels (Petes et al., 2008), including hyperthermia, hyposmotic stress, temperature and dissolved oxygen (Gourgou et al., 2010; Hamer et al., 2008; Jarque et al., 2014), as well as reproductive events, food availability and water temperature, among other factors (Amiard and Berthet, 1996; Mubiana et al., 2005; Wang and Dei, 1999).

In this context, significant seasonal variations have been reported for several antioxidant enzymes in mussel species, and conflicting results have ensued. For example, a study on the green-lipped mussel *Perna viridis* from Goa indicated that, although the oxidative stress status of gills and digestive gland of *P. viridis* expressed in terms of LPX and H₂O₂ were lowest in February, their levels were maximal in gills and digestive gland during May and November, respectively. On the other hand, SOD and GPX activities were low in August, and CAT and GR activities were low in February. GST activity in gills although remained high in February, while elevated values in the digestive gland were recorded in August and November (Verlecar et al., 2008). In another study, *Mytilus galloprovincialis* from the Gulf of Greece displayed seasonal variations in superoxide dismutase (SOD) and catalase (CAT) activities, as well as lipid peroxidation (LP). SOD activity displayed higher activity in spring, whereas CAT activity was highest activity in winter and spring. LP concentration was twice higher at the polluted sites, following the same seasonal pattern. However, trace metal showed only moderate variations along the months, with a winter maximum followed by a summer pre-spawning minimum (Vlahogianni et al., 2007).

Reproductive efforts, in particular, are known to lead to increases in metabolic activity, ROS and, consequently oxidative stress, as a result of reduced energy available for antioxidant defenses (Petes et al., 2008). Therefore, sampling should be avoided during the reproductive period, which is well documented for several commercial species (Mourgau et al., 2002).

In addition, mussel development stage may also be a confounding factor. For example, when comparing adult and juvenile *Mytilus edulis* after cadmium exposure for 20 days, juveniles expressed increased GSTpi expression compared to the adults, revealing variations in the expression of this GST isoform among control and Cd²⁺-exposed mussels of different ages (Ciocan and Rotchell, 2004).

In view of these factors, environmental monitoring studies should take care to conduct sampling efforts under standardized conditions (as much as possible), in order to avoid misinterpretation of biomarker results.

MUSSELS AND PUBLIC HEALTH

Bivalve shellfish culture and production for commercial purposes has been noted as a substantial contribution to the economic development of many countries (Santos et al., 2017).

However, the quality of mussels as food is closely related to the sanitary conditions of the marine environment where these bivalves are found (Oliveira et al., 2016), and public health risks associated with metal concentrations in these organisms have been increasingly reported for several species and geographical areas (Jović and Stanković, 2014). For example, in a

study conducted with *Mytilus galloprovincialis* mussels sampled along the marine coast of Boka Kotorska Bay, Montenegro, in the Adriatic sea, Cd, Co and Pb levels were recognized as limiting factors for mussel consumption by humans for some Adriatic areas in relation to the provisional tolerable weekly intake prescribed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), and the target hazard quotient (*THQ*) for average and high level mussels consumers in order to evaluate possible alert regarding adverse health effects that may be caused by trace metals individually (Jović and Stanković, 2014). A study conducted on *Perna perna* mussels in southern Brazil compared metal concentrations from 3 contaminated areas from the contaminated Guanabara Bay to a reference site, Ilha Grande Bay, and concluded that mussels from all sampling sites were improper for human consumption due to metal contamination (As, Se, Zn, Pb) according to both Brazilian and international standards, including Ilha Grande Bay, which was previously considered a reference site (Lavradas et al., 2016). Another study indicated that the invasive Indo-Pacific green mussel, *Perna viridis* (Linnaeus, 1758) in Jamaica accumulates significantly high levels of Cr and Cd, and that risks to public health through consumption of these mussels from Kingston Harbour are significant, exceeding the European Standards and Guidelines for Trace Metals in fish and shellfish. The authors suggest that depuration of the mussels prior to consumption should be carried out (Buddo et al., 2012).

The presence of metals in seafood depends on several factors including geographic location, species, size, feeding patterns and metal concentrations in the environment, which, in turn, are affected by many abiotic factors, such as solubility, temperature, salinity, dissolved oxygen and pH, among others (Stankovic and Jovic, 2012). Thus, it is clear that biomonitoring applying mussels as bioindicators is vital and directly linked to risk assessments regarding human population health, since these animals are a staple diet for many coastal populations, and, in recent years, have become commercially important seafood species worldwide (Stankovic and Jovic, 2012).

It is very important to note that many reports in the literature indicate no risk to human consumers due to low metal and metalloid levels in the digestive gland or gills of certain mussel species. However, these organisms are almost always ingested whole, so levels in this tissue only cannot be used to indicate public health risks, since total levels would be those present in muscle tissue, digestive gland and gills, summed. Thus, care should be taken in this regard when calculating possible public health risks.

CONCLUSION

Mussels are one of the most important bioindicator species applied to date to investigate the effects of metals and metalloids in the environment. Biomarker responses, such as protein and enzymatic alterations, to metal and metalloid exposure are routinely evaluated in several marine and freshwater species, although research on emerging contaminants, such as metal nanoparticles, is still recent. Public health risks associated with metal concentrations in these organisms have been increasingly reported for several species and geographical areas, since metal contamination in aquatic ecosystems has increased in the last decades, and thus, environmental monitoring efforts applying these organisms is paramount to attempt public decision-making processes regarding environmental metal and metalloid contamination.

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Chapter 547

CLIMATE CHANGE AND ITS POTENTIAL RISKS TOWARDS PUBLIC HEALTH

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ABSTRACT

Climate change refers to any change in climate over time, whether due to natural variability or as a result of human activity. However, the present scenario of climate change is mostly due to anthropogenic or human-made. Humans are integrally related to the climatic changes directly or indirectly both in cause and impacts. The current trend in climate change has both short term as well as long term effects among which most of them are negative effects on humanity. This chapter deals with the potential impacts of present climate change on different aspects of human health and their future repercussion, discusses gaps for further research to generate shreds of evidence that will help in framing effective and proper adaptation and mitigation strategies to avoid the black shadow of climate change.

Keywords: climate change, global warming, disease, health

INTRODUCTION

Human history is intricately related to climatic disparity and change. Nature has already experienced nearly two full glacial and inter-glacial cycles in the history of the earth among which the last glacial period favored the global geographical expansion, massive population increase and worldwide ecological domination of *Homo sapiens* which was furthermore

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extended during the last glacial-interglacial transition. During the past 25,000 years, the Earth system has undergone a series of dramatic transitions. The most recent glacial period peaked 21,500 years ago during the Last Glacial Maximum (LGM) where there was an expansion of ice sheet cover over the globe resulting the global sea level down to 125 meters (410 feet) below today's level with surface temperatures about 5°C (9°F) cooler than today.

Earth's atmosphere is made up of oxygen, a large amount of nitrogen and a small percentage of greenhouse gases (GHGs), such as carbon dioxide (CO₂) and methane. In the 1820s, French mathematician and physicist Joseph Fourier proposed that the green house gases act like a blanket around the Earth and they trap heat from the sun and make life on Earth possible. However, it took nearly 40 years when Irish scientist John Tyndall, in 1860, demonstrated exactly what kinds of gases were most likely to play a role in absorbing sunlight. In 1895, Swedish chemist Svante Arrhenius showed that if CO₂ levels were halved, global temperatures could decrease by about 5°C, explaining the effect of lower global CO₂ level due to decreased volcanic activity on past ice ages. He also suggested that if CO₂ levels were doubled, global temperatures would increase by the same amount, i.e., 5°C. British engineer Guy Stewart Callendar, in 1930s, noted that due to the ongoing "Industrial Revolution" the United States and North Atlantic region had warmed significantly. Callendar's calculations suggested that a doubling of CO₂ in Earth's atmosphere could warm Earth by 2 degrees C (3.6 degrees F) and he put forwarded the theory that warming of the planet due to greenhouse-effect was underway. However, during 1940-1970, due to a postwar boom in aerosol pollutants which reflected back sunlight away from earth, a cooling effect was observed. This was further explained scientifically by Broecker in 1975 [1], where he supported the observation made by Callender and stated that

"This cooling has, over the last three decades, more than compensated for the warming effect produced by the CO₂ released into the atmosphere as a by-product of chemical fuel combustion. By analogy with similar events in the past, the present natural cooling will, however, bottom out during the next decade or so. Once this happens, the CO₂ effect will tend to become a significant factor and by the first decade of the next century we may experience global temperatures warmer than any in the last 1000 years."

Broecker was the first to introduce the term "Global Warming." This led to increased scientific interest and research on this front. Hansen et al. 1988 [2], using a three dimensional climate model, the Goddard Institute for Space Studies (GISS) model II with 8° X 10° horizontal resolution, showed that the global warming within the next several years is predicted to reach and maintain a level of at least three standard deviations (3SD) above the climatic conditions of the 1950s. Understanding these changing scenarios and related consequences, the United Nations established the Intergovernmental Panel on Climate Change (IPCC) in 1989 to provide a scientific view of climate change and its political and economic impacts. According to IPCC, climate change refers to a change in the state of the climate that can be identified (e.g., using statistical tests) by changes in the mean and/or the variability of its properties and that persists for an extended period, typically decades or longer. It refers to any change in climate over time, whether due to natural variability or as a result of human activity [3]. According to the IPCC published landmark report in 2007, there is unequivocal evidence of global warming. Increase in green house gases is attributing towards most of the warming within the past 50 years affecting the physical and biological systems on all continents and oceans [4]. The next few decades are likely to witness more warming. The effect of emissions in the long term is becoming more evident [5].

CLIMATE VS. WEATHER

The concepts of climate and weather are often confused. *Weather* is the state of the atmosphere at any given time and place. Weather patterns vary greatly from year to year and from region to region. Familiar aspects of weather include temperature, precipitation, clouds, and wind that people experience throughout the course of a day. Severe weather conditions include hurricanes, tornadoes, blizzards, and droughts. *Climate* is the average weather conditions that persist over multiple decades or longer. While the weather can change in minutes or hours, identifying a change in climate has required observations over a time period of decades to centuries or longer [6]. According to NOAA, climate is the average of weather over at least a 30 -year period. Climate change encompasses both increases and decreases in temperature as well as shifts in precipitation, changing risks of certain types of severe weather events, and changes to other features of the climate system.

EVIDENCE OF CLIMATE CHANGE

A change in earth's climate is becoming evident with the rising temperatures, shifting rainfall patterns and more extreme climatic events such as heavy rainstorms, heat waves and cold waves. There are ample evidence that these observed changes are linked to the rising levels of carbon dioxide and other greenhouse gases in our atmosphere, caused by human activities. The United States Environmental Protection Agency (EPA) published "*Climate Change Indicators in the United States*," in 2016. This report presents 37 indicators, each describing trends related to the causes and effects of climate change [6]. The evidence includes:

- Increase in global average surface temperature by 2 degrees Fahrenheit ($\sim 1^{\circ}\text{C}$) in the last century (Figure 1). Global average surface temperature has risen at an average rate of 0.15°F (0.09°C) per decade since 1901.
- On average, total annual precipitation has increased over land areas worldwide. Since 1901, global precipitation has increased at an average rate of 0.08 inches per decade. (Figure 2) [8].
- Sea surface temperature increased during the 20th century and continues to rise. From 1901 through 2015, the temperature rose at an average rate of 0.13°F per decade. Sea surface temperature has been consistently higher during the past three decades than at any other time since reliable observations began in 1880.
- Global average sea level rose throughout the 20th century, and the rate of change has accelerated in recent years. When averaged over all of the world's oceans, absolute sea level has risen at an average rate of 0.06 inches per year from 1880 to 2013. Since 1993, however, average sea level has risen at a rate of 0.11 to 0.14 inches per year—roughly twice as fast as the long-term trend.
- Measurements made over the last few decades have demonstrated that ocean carbon dioxide levels have risen in response to increased carbon dioxide in the atmosphere, leading to an increase in acidity (that is, a decrease in pH).

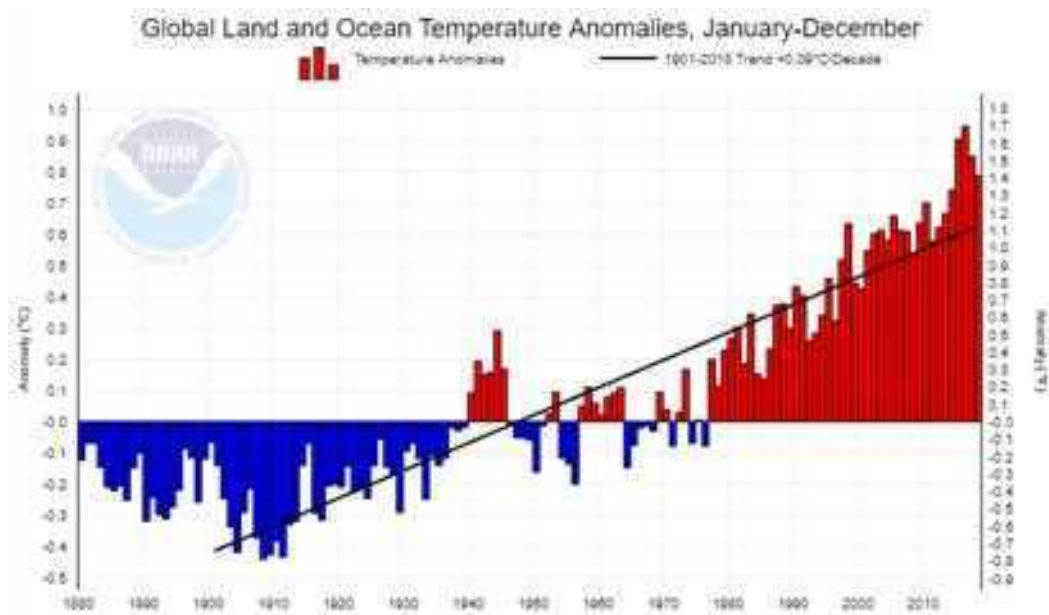


Figure 1. Average annual global temperatures from 1880 to 2018 compared to the long-term average (1901-2000). The zero line represents the long-term average temperature for the whole planet; blue and red bars show the difference above or below average for each year (adapted from [7]).

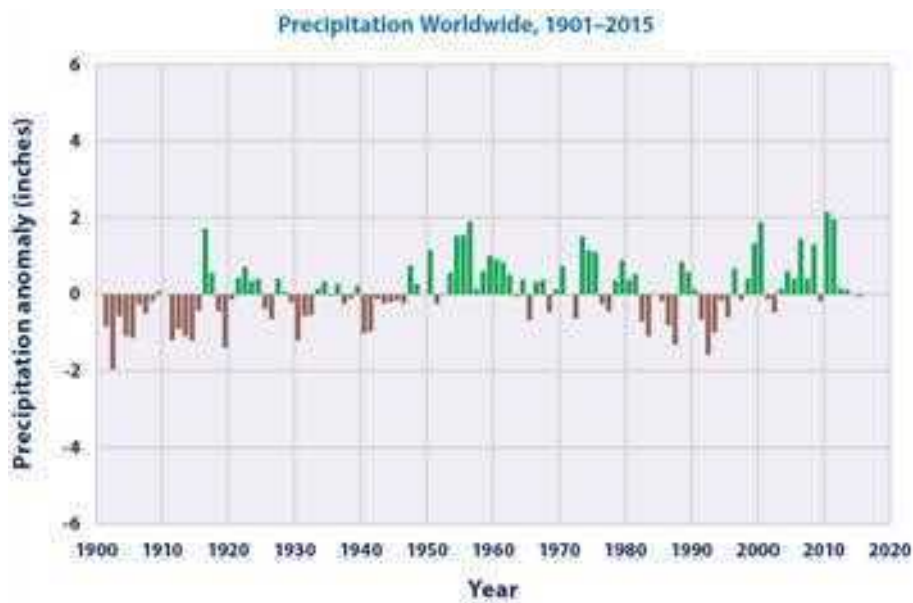


Figure 2. Anomalies in total annual amount of global precipitation change for period 1901-2015. This graph uses the 1901–2000 average as a baseline for depicting change. (Adapted from [8]).

- Reduction of ice caps. Arctic sea ice now starts melting 11 days earlier and it starts refreezing 26 days later than it used to, on average. Overall, the Earth has lost sea ice at an average rate of 13,500 square miles per year since 1979. This decrease affects the Earth’s energy balance.

- On average, glaciers worldwide have been losing mass since at least the 1970s, which in turn has contributed to observed changes in sea level. A longer measurement record from a smaller number of glaciers suggests that they have been shrinking since the 1940s. The rate at which glaciers are losing mass appears to have accelerated over roughly the last decade.

A number of biological changes have also been observed. These include shifts in the ranges of some plant and animal species, earlier timing of spring events such as leaf-unfolding, bird migration and egg-laying for some species. Together these indicators provide clear evidence that the climate is changing.

CLIMATE CHANGE PROJECTIONS

Continued emissions of greenhouse gases will lead to further changes in the prevailing climate over any space. Future changes are expected to include a warmer atmosphere, a warmer and more acidic ocean, higher sea levels, and larger changes in precipitation patterns. The extent of future climate change depends on what we do now to reduce greenhouse gas emissions. The more we emit the larger future changes will be. Projecting future changes to the Earth's climate vary widely based on different climate modeling approaches generating different types of datasets.

Global climate models or general circulation model (GCMs) are the most widely used method to understand what the climate may be like in the future as a result of emissions of greenhouse gases (global warming). They are run on supercomputers that attempt to simulate the complex atmospheric and oceanic processes that determine the climate conditions. Because they work at a global scale, the resolution of GCM results is typically quite coarse (usually about 300 X 300 KM resolution). These projections are helpful for decision makers and resource managers to formulate adaptation policies in response to climate change impacts. Although GCMs provide adequate simulations of atmospheric general circulation at the continental scale, they do not capture the details required for regional and national assessments. Therefore, reliable climate change information is required at finer spatial scales. Regional climate models (RCMs) are applied to smaller spatial areas to produce results with greater local detail (usually about 25 X 50 KM resolution). However, RCMs still rely on GCMs for input data and therefore are not necessarily more reliable or more accurate [9]. GCMs and RCMs are run under different scenarios of future greenhouse gas emissions – from a best-case scenario (if extensive action is taken to reduce emissions levels) to the worst-case (if emissions keep rising with no action taken to reduce them), whereby they generate a number of possible climate futures (projections).

The first Intergovernmental Panel on Climate Change Assessment Report (IPCC FAR) in 1990 discussed three types of scenarios: equilibrium scenarios, in which CO₂ concentration was fixed; transient scenarios, in which CO₂ concentration increased by a fixed percentage each year over the duration of the scenario; and four brand-new Scientific Assessment (SA90) emission scenarios based on World Bank population projections [10]. The standard sets of time-dependent scenarios used by the climate modeling community as input to global climate model simulations provide the basis for the majority of the future projections presented in

IPCC assessment reports and U.S. National Climate Assessments (NCAs). Developed by the integrated assessment modeling community, these sets of standard scenarios have become more comprehensive with each new generation, as the original SA90 scenarios [11] were replaced by the IS92 emission scenarios of the 1990s [12], which were in turn succeeded by the Special Report on Emissions Scenarios in 2000 (SRES) [13] and by the Representative Concentration Pathways (RCPs) in 2010 [14]. Box 1 explains about the different scenarios under SRES and RCP projection scenarios. Based on the SRES and RCP projection scenarios, the future climatic projections for CO₂ emission, concentration and temperature for 2100 is shown in Figure 3 [16].

Box 1.

(A). SRES scenarios

SRES contains 40 scenarios that fall into four qualitative storylines [13]: A1, A2, B1 and B2.

The A1 storyline describes a future world of very rapid economic growth, global population that peaks in the mid twenty-first century and declines thereafter. The A1 family develops into three groups that describe alternative directions of technological change in the energy system. These three: A1FI is fossil intensive (highest), A1T is non-fossil energy sources (mid), and A1B is a balance across all sources (lowest).

The A2 storyline describes a very heterogeneous world. The global population increases continuously and the economic development is primarily regionally oriented and per capita economic growth is more fragmented and slower than in other families.

The B1 storyline describes a convergent world with the same global population that peaks in the mid twenty-first century and declines thereafter, as in the A1 family, but with rapid changes in economic structures toward a service and information economy, with a reduction in material intensity, and the introduction of clean and resource-efficient technologies.

The B2 storyline describes a world in which the emphasis is on local solutions to economic, social, and environmental sustainability. The global population increase is at a lower rate than A2 family, intermediate levels of economic development, and less rapid and more diverse technological change than in the B1 and A1 families. The scenario is oriented towards environmental protection but it focuses on local and regional levels.

(B). RCP scenarios:

Four pathways have been selected for climate modeling and research, which describe different climate futures, all of which are considered possible depending on how much greenhouse gases are emitted in the years to come. The four RCPs, namely RCP2.6, RCP4.5, RCP6, and RCP8.5, are labeled after a possible range of *radiative forcing* values in the year 2100 (2.6, 4.5, 6.0, and 8.5 W/m², respectively) [15].

The RCPs are consistent with a wide range of possible changes in future anthropogenic (i.e., human) *greenhouse gas* (GHG) emissions, and aim to represent their atmospheric concentrations [4].

RCP 2.6 Peak in radiative forcing at ~ 3 W/m² before 2100 and decline

Emissions in RCP 4.5 Stabilization without overshoot pathway to 4.5 W/m² at stabilization after 2100

In RCP 6, Stabilization without overshoot pathway to 6 W/m² at stabilization after 2100

In RCP 8.5, Rising radiative forcing pathway leading to 8.5 W/m² in 2100.

CLIMATE CHANGE IN INDIA

Although India accounts for only 4.5 percent of the world's greenhouse gases, based on the best available pieces of evidence and computer simulation, it is one of the few countries which is going to be influenced by climate change in its extremity in near future because of

its diverse terrain, geography, diverse population characteristics and extremely high dependence on fossil fuels [17-18]. As the natural resources are rapidly exhausting along with the destruction of natural environment mostly due to increased population, urbanization, industrialization and economic growth, the country is expected to experience a serious impact of climate change in many areas such as agriculture, water resources, food safety, cities, coastal ecosystems and on health [19].

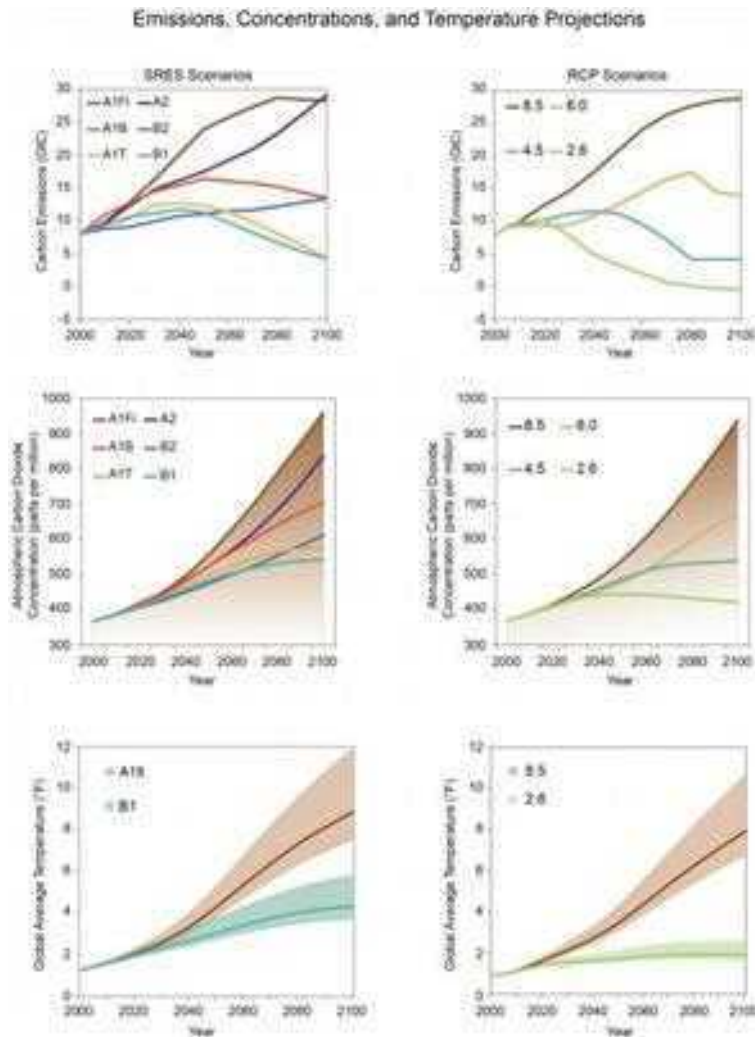
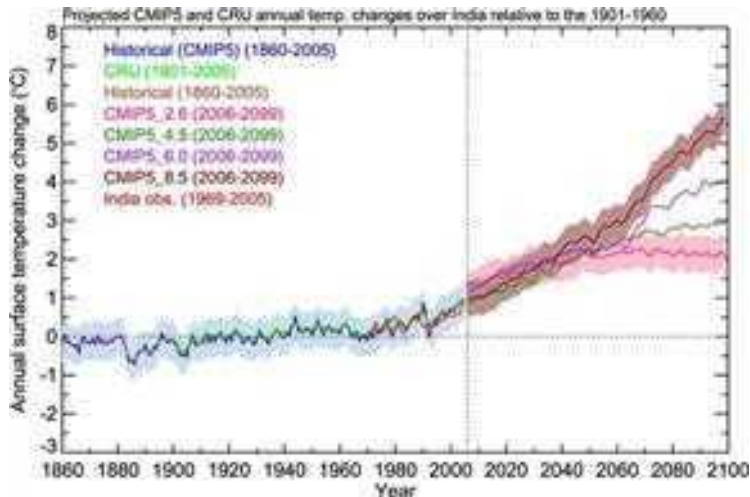


Figure 3. Future CO₂ emission, concentration and temperature projections based on SRES (left) and RCP (right) pathways [adapted from 16].

The latest high-resolution climate change scenarios and projections for India are based on a regional climate modeling system known as PRECIS (Providing Regional Climates for Impact Studies), which was developed by the Hadley Centre (the research centre of the national weather service in the United Kingdom) and applied in India using scenarios developed by the Intergovernmental Panel on Climate Change. The latest projections for India are [20, 21, 22]:

- Annual mean surface temperature will rise by the end of the century, by from 2.5°C to 5°C, with warming more pronounced in the northern parts of India (Figure 4 & 5)
- More than 20% (15-24%) rise in summer monsoon rainfall is projected over all states except Punjab, Rajasthan and Tamil Nadu
- The range of maximum temperatures in any one season is predicted to vary more widely (for example, from between 27°C and 44°C to between 26°C and 45°C); variations in minimum temperature are expected to increase in the same way
- Rainfall is expected to increase substantially, particularly over the west coast of India and west-central India.



Time series of surface air temperature change (°C) (Max. Temp. anomalies, relative to the present day). Projected annual mean surface temperature from multimodel average CMIP5 data for the years 1860–2100 relative to the base period 1901–1960. Adapted from [22].

Figure 4. Projected surface temperature for India over the period of 1860-2100.

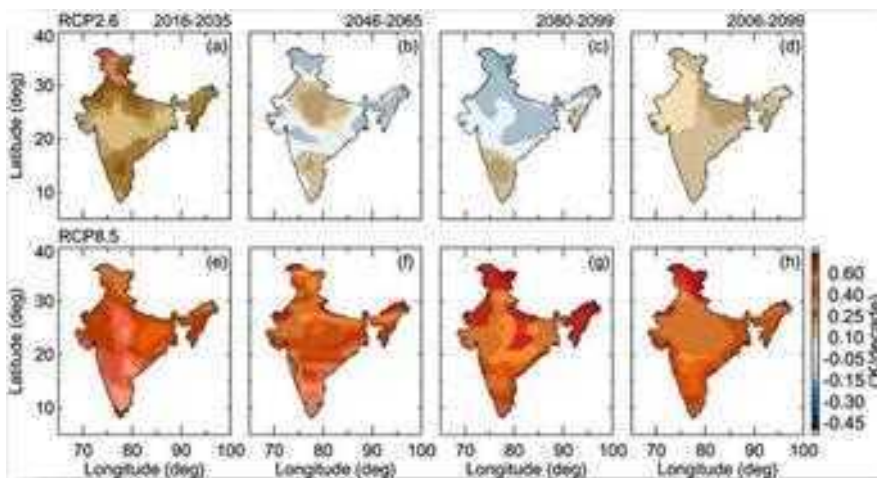


Figure 5. Geographical distribution of surface temperature trends (K/decade) at the 95% confidence level from RCP2.6 and RCP 8.5 for different periods over India for the 21st century. (Adapted from [22]).

IMPACTS OF CLIMATE CHANGE

The impacts of human-caused climate change are already being seen, from polar regions to rising temperature, to communities around the world and to the local environments. Consequences of climate change will affect the biosphere on many levels, from coral bleaching to dying forests, to species extinction. Most of the impacts of Climate change are negative and will be hitting the sectors such as water resources, energy supply and use, transportation, agriculture, ecosystems (forestry & biodiversity), human health, economy and society [23]. Hitz and Smith (2004) [24] found that the relationships between global mean temperature (GMT) and impacts are not consistent across sectors. Some of the sectors such as coastal resources, biodiversity, and possibly marine ecosystem productivity will exhibit increasing adverse impacts with increasing global mean temperature. . Other sectors are characterized by a parabolic relationship between temperature and impacts (benefits at lower global mean temperature increases, damages at higher global mean temperature increases), in particular, agriculture, terrestrial ecosystem productivity, and possibly forestry. The relationship between global impacts and increase in global mean temperature for water, health, energy, and aggregate impacts appears to be uncertain and a matter of thorough research. Overall, it appears likely that there are increasing adverse impacts at higher increases in GMT.

CLIMATE CHANGE AND HUMAN HEALTH

Global climate change has become one of the most visible environmental concerns over the 21st century. Environmental consequences of climate change, such as extreme heat waves, rising sea levels, changes in precipitation resulting in flooding and droughts, intense hurricanes, and degraded air quality, affect directly and indirectly the physical, social, and psychological health of humans (Figure 6). For instance, changes in precipitation are creating changes in the availability and quantity of water, as well as resulting in extreme weather events such as intense hurricanes and flooding. Climate change can be a driver of disease migration, and exacerbate health effects resulting from the release of toxic air pollutants in vulnerable populations such as children, the elderly, and those with asthma or cardiovascular disease.

In September 2015, 193 world leaders committed to achieve 17 sustainable development goals (SDGs) and 169 targets to end extreme poverty, fight inequality and injustice and protect our planet by 2030. Climate change and health featured prominently in this “Agenda 2030 for Sustainable Development” as a new set of goals [25].

However, to date, most climate change research has focused on environmental effects, not on health effects. Evidence-based information generation and understanding of the often indirect, long term and complex interactions of climate change on human health is a top priority research task to be conducted. In 2000, WHO estimated 1,66,000 deaths and about 5.5 million disability-adjusted life years (DALYs) only because of four diseases (cardiovascular disease, malnutrition, diarrhea, and malaria) as well as floods, that were attributable to climate change [26]. To date, the majority of analyses on climate change and health have focused on diseases that predominantly affect people in the developing world, and

therefore, are perceived as less relevant to more developed countries. However, as the recent pandemic of H1N1 virus has shown us, diseases do not respect international boundaries. Climate change can be a driver for disease migration, but even so, such diseases do not represent the broadest range of possible, or even likely, human health effects of climate change, nor do they reflect the likely co-benefits of mitigation and adaptation to climate change, some of which may have their greatest impact in the developed world. There is a substantial gap in our understanding of the complex relationship among climate change, the environment and human health globally [27] which needs to be bridged.

Climate change directly affects five components of the environment: water, air, weather, oceans, and ecosystems. Changes in rainfall pattern, temperature fluctuations, and melting of ice glaciers are already happening and will create changes in the availability and quality of water across the globe over the next 30 years [28]. The air quality is modulated by heat, humidity, the degree of ultraviolet (UV) radiation, and many other factors and changes in any of these can directly reduce air quality, particularly in urban areas, by increasing air concentrations and human exposures to a variety of toxic air pollutants. In many areas of the country, climate change and resulting weather events such as drought and wildfires will reduce general air quality resulting increases in asthma, cardiovascular disease, and other respiratory ailments. Extreme heat also directly increases the risk of injury, illness, and death, as well as indirectly by contributing to illnesses such as those associated with mental health and stress in developing countries [29]. The warming of ocean waters contributes to increases in incidence and severity of toxic algal blooms, alterations in aquatic and estuarine food webs and seafood quality and availability, and effects on sentinel aquatic species. Changes in plant habitat can result in reduced availability of grazing lands for livestock [30]. Global warming is also causing shifts in the ranges of disease vectors that require specific environments to thrive (for example, Lyme disease and dengue vectors) [31] and increasing the threat and incidence in humans of waterborne, vectorborne and zoonotic (those transferred from animals to humans) diseases (Table 1).

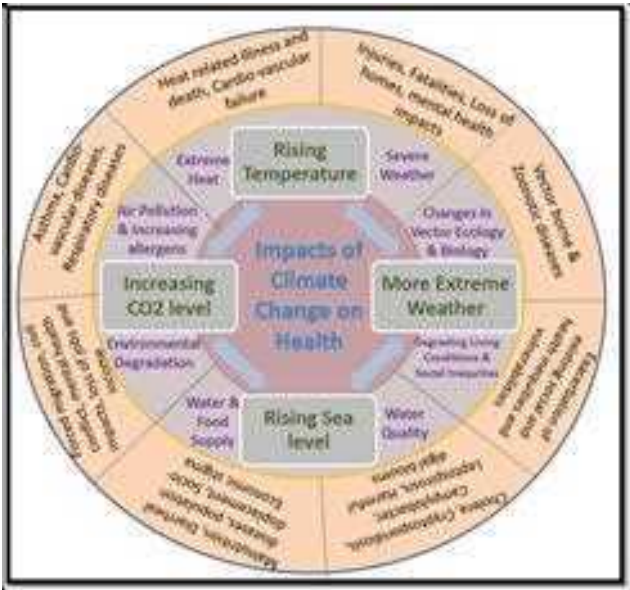


Figure 6. Impact of climate change on human health.

The Interagency Working Group on Climate Change and Health (IWGCCH) in its white paper has identified the following human health categories to be affected by climate change demanding research needs to identify mitigation and adaptation [32].

Asthma, Respiratory Allergies and Airway Diseases

Globally approximately 235 million people suffer from asthma and among these India has an estimated 15-20 million asthmatics with a prevalence of 10-15% in children below 11 years old [33]. In recent decades, the world has seen a sharp rise in prevalence as well as severity of respiratory diseases mostly in low and middle-income countries with environmental factors such as outdoor and indoor air pollution like tobacco smoke as a major risk factor [34] and extended by climate change [35]. In many low and middle-income countries including rural areas of India, people rely on solid fuel (wood, cow dung or crop residues) that they burn in simple stoves or open fires for domestic energy [36].

Table 1. Examples of how diverse environmental changes affect the occurrence of various infectious diseases in humans

Environmental changes	Example diseases	Pathway of effect
Dams, canals, irrigation	Schistosomiasis	☞ Snail host habitat, human contact
	Malaria	☞ Breeding sites for mosquitoes
	Helminthiasis	☞ Larval contact due to moist soil
	River blindness	☞ Blackfly breeding, ☞ disease
Agricultural intensification	Malaria	Crop insecticides and ☞ vector resistance, ☞ disease
	Venezuelan haemorrhagic fever	☞ Rodent abundance, contact
Urbanization, urban crowding	Cholera	☞ Sanitation, hygiene; ☞ water contamination
	Dengue	Water-collecting trash, ☞ Breeding sites for mosquitoes
	Cutaneous leishmaniasis	☞ Proximity, Sandfly vectors
Deforestation and new habitation	Malaria	☞ Breeding sites and vectors, immigration of susceptible people
	Oropouche	☞ Contact, breeding of vectors
	Visceral leishmaniasis	☞ Contact with sandfly vectors
	Dengue	☞ Contact, breeding of vectors
Reforestation	Lyme disease	☞ Tick hosts, outdoor exposure
	Kyasunur Forest Disease	☞ Tick hosts, outdoor exposure
Ocean warming	Red tide	☞ Toxic algal blooms
Elevated precipitation	Rift valley fever	☞ Pools for mosquito breeding
	Hantavirus pulmonary syndrome	☞ Rodent food, habitat, abundance

Many respiratory allergic diseases are seasonal with climate-sensitive components; climate change may increase the incidence and exacerbation of such allergic diseases. While

some risk for respiratory disease can be clearly linked to climate change, for many others the risk attributable to climate change is unclear. In addition to impacts on asthma and other allergic diseases, climate change has the potential to impact airway diseases by increasing ground level ozone and possibly fine particle concentrations. Both ozone, indoor air pollutants (other than tobacco smoke) and $PM_{2.5}$ lead to several cardio-pulmonary disorders like breathing difficulty, worsening of asthma, bronchitis and emphysema, decreased lung function, cardiovascular events and even death. [37, 38, 39]. Cecchi et al. 2010 [40] projected that increasing effect of aeroallergens may imply a greater likelihood of the development of allergic respiratory disease in sensitized subjects and exacerbation of symptomatic patients. There is also a possibility that certain aeroallergens may become more allergenic as temperatures and CO_2 concentrations increase [41, 42, 43, 44]. Another respiratory disease such as “Thunderstorm related Asthma” is found to be linked with humidity, temperature, respirable particulate matter and bioaerosols which are highly influenced by climate change [45, 46]. Research studies found an association of fine particles with cardiovascular outcomes such as heart attacks, formation of deep vein blood clots, and increased mortality [43, 47-52]. These adverse health impacts intensify as temperatures rise [53]. The temperature-mortality relationship has been shown to be established for cardiovascular disease (CVD), followed by respiratory disease and total mortality in temperate countries. These relationships are supported by strong evidence for direct links between high and low temperatures and increased blood pressure, viscosity and heart rate for CVD [54] and broncho-constriction for pulmonary disease [55].

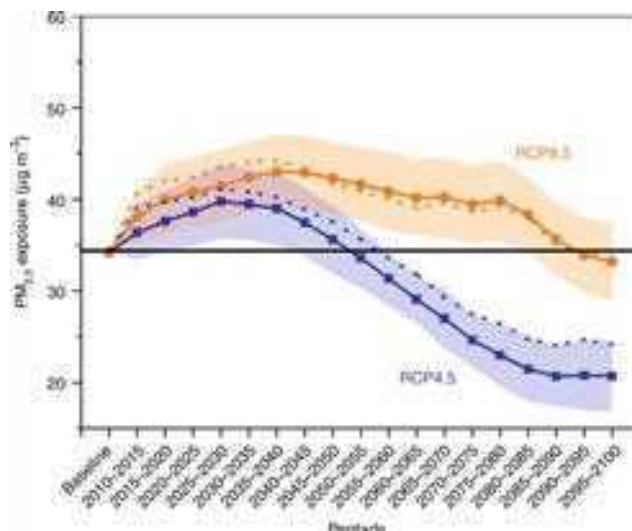


Figure 7. Projected ambient $PM_{2.5}$ exposure over the Indian landmass under both RCP4.5 and RCP8.5 scenarios. Shaded part represents the range (1–99%) in all-India averaged $PM_{2.5}$ across the 13 CMIP5 models. The black line represents the all-India averaged baseline (2001–2005) $PM_{2.5}$ exposure level. (Adapted from [59]).

India is at a higher risk with wide variation in temperature and higher level of air pollutants. However, very limited work has been carried out on this front in India [56]. An investigation on the effects of air pollution on respiratory disease showed that emergency department visits increased by approximately 20% because of high levels of pollutants in Delhi [57]. In another study based in Chennai, India, [58] concluded that short-term exposure

to particulate matter $\leq 10 \mu\text{m}$ in aerodynamic diameter (PM_{10}) resulted in an estimated risk ratio of 1.0044 (95% CI, 1.002–1.007) per a $10 \mu\text{g}/\text{m}^3$ increase in daily average concentrations. Recently, Choudhury et al. 2018 [59] modeled the ambient $\text{PM}_{2.5}$ exposure up to 2100 under the climate change scenario and concluded that ambient $\text{PM}_{2.5}$ exposure is expected to peak in 2030 under the RCP4.5 and in 2040 under the RCP8.5 scenario. Premature mortality burden is expected to be 2.4–4 and 28.5–38.8% higher under RCP8.5 scenario relative to the RCP4.5 scenario in 2031–2040 and 2091–2100, respectively (Figure 7).

Cancer

Cancer is the second leading cause of death globally after cardiovascular diseases [60]. In India, 8.3% (95% uncertainty interval [UI] 7.9–8.6) of the total deaths and 5.0% (4.6–5.5) of the total DALYs in India in 2016 were due to cancer [61]. Climate change has both indirect as well as direct effect on cancer. Due to climate change, ambient temperatures will rise which may increase the transfer of volatile and semi-volatile compounds from water and wastewater into the atmosphere resulting in distribution and exposure of contaminants to places more distant from the sources [62]. Climate change is also expected to increase heavy precipitation and flooding events, which may increase the chance of toxic contamination leaks from storage facilities or runoff into water from land containing toxic chemicals and heavy metals. Very little is known about how such events will affect people's exposure to these chemicals, some of which are known carcinogens, and its ultimate impact on incidence of cancer [63]. On the other hand, some cancer such as lung cancer and skin cancer has a direct connection to climate change. Smoking is considered as the main cause of lung cancer, but air pollution [64] including indoor air pollution and fine particulates [65–67] also contributes to the burden of lung cancers. Another direct effect of climate change is depletion of stratospheric ozone which will result in increased ultra-violet (UV) radiation exposure leading to increased risk of skin cancer [68–69]. Rising temperatures and diurnal temperature were found to be associated with increases in UV exposure due to climate change which may lead to an increase in the incidence of non-melanoma skin cancers [70–72].

Cardiovascular Disease and Stroke

Cardiovascular diseases (CVD) accounts for most of the deaths (~18million) due to non-communicable diseases globally [73]. In India too, mortality due to cardiovascular diseases and stroke made the highest contribution (28.1%) in 2016 increasing by ~34.3% in the last 25 years [74]. Long-term exposure to ambient particulate matter $\text{PM}_{2.5}$ has been considered as a potential risk factor to cardiovascular and respiratory diseases [75]. India is recognized as a hotspot for aerosol loading [76] where ambient $\text{PM}_{2.5}$ exposure was observed to increase rapidly over the past decade (2001–2010) [77]. The annual premature mortality burden from ambient $\text{PM}_{2.5}$ exposure in India is currently estimated to be ~1.0 million [78].

Weather conditions such as extreme heat and extreme cold are evident for several CVDs affecting the incidence of hospital admissions for chest pain, acute coronary syndrome,

stroke, and variations in cardiac dysrhythmias [79-82]. Similarly, stroke and CVD incidences are also found to be increased with increasing temperature specifically in both elderly and isolated individuals [83-84]. There are many indirect impacts of weather, weather variability and climate changes on CVDs. Weather and climate modifies the associations between air quality, especially ozone and particulate matters, and incidence and mortality of CVD., acute myocardial infarction and ischemic heart disease in most of the low and middle-income countries [85-90]. Under the climate change projections, it has been also observed that the increasing temperatures and number of hot day will increase cardiovascular diseases related mortality in Middle East and China including India in near future [91-93]. Although not prevalent in India, Chagas diseases, which is expected to rise due to climate change, will also increase manifestation of stroke and heart failure in South America [94].

Food-Borne Diseases and Nutrition

The potential effects of climate change on food-borne illness, nutrition, and food security are mostly indirect. However, there is a proven link between food security to climate change and it may affect food safety and the incidence of food-borne illness [95]. Extreme weather events, changes in temperature and precipitation patterns resulting in flood or drought can directly damage or destroy crops and thereby impacts food quality, food supplies, interrupt transport and distribution of food. Indirectly, this results to undernutrition or famine resulting from damage to agricultural crops and related trade, economic, and social instability. Food-borne illness results from ingesting food that is spoiled or contaminated with microbes, chemical residues such as pesticides, biotoxins, or other toxic substances.

It was estimated that food-borne diseases caused ~600 million illness including 420000 deaths, mostly in children, globally in 2010. Among the 31 global hazards causing food-borne illness, diarrhoeal diseases are the most common illness resulting from unsafe food accounting for 230000 deaths globally of which ~100000 are under the age of 5 years [96]. It was observed that increased temperature due to climate change impacts the rate of food-borne illness. Checkley et al. 2000 [97] recorded each degree Celsius rise in average ambient temperature increases the incidence of diarrhea in Lima, Peru (Figure 8). A similarly strong positive correlation was also observed between high temperature and *Salmonella* infections by Akil et al. 2014 [98]. Using modeling approaches such as regression analysis and neural network, they have found that an increase of 1°F was shown to result in four cases increase of *Salmonella* in Mississippi. Kim et al. 2015 [99] observed that different food-borne pathogens are affected differently by changes in climatic variables such as temperature and relative humidity. Eight pathogens commonly associated with food-borne diseases were identified and the effect of changes in temperature and relative humidity on each of them was investigated. Pathogenic *Escherichia coli* had the strongest correlation with temperature and relative humidity, followed by *Vibrio parahaemolyticus*, *Campylobacter jejuni*, *Salmonella* spp., and *Bacillus cereus*. On the other hand, Norovirus had a strong negative correlation with temperature and relative humidity, followed by *Clostridium perfringens* and *Staphylococcus aureus*.

Rising temperatures and impacts on other environmental parameters such as ocean acidification may also lead to more virulent strains of existing pathogens and changes in their distribution or the emergence of new pathogens [100].

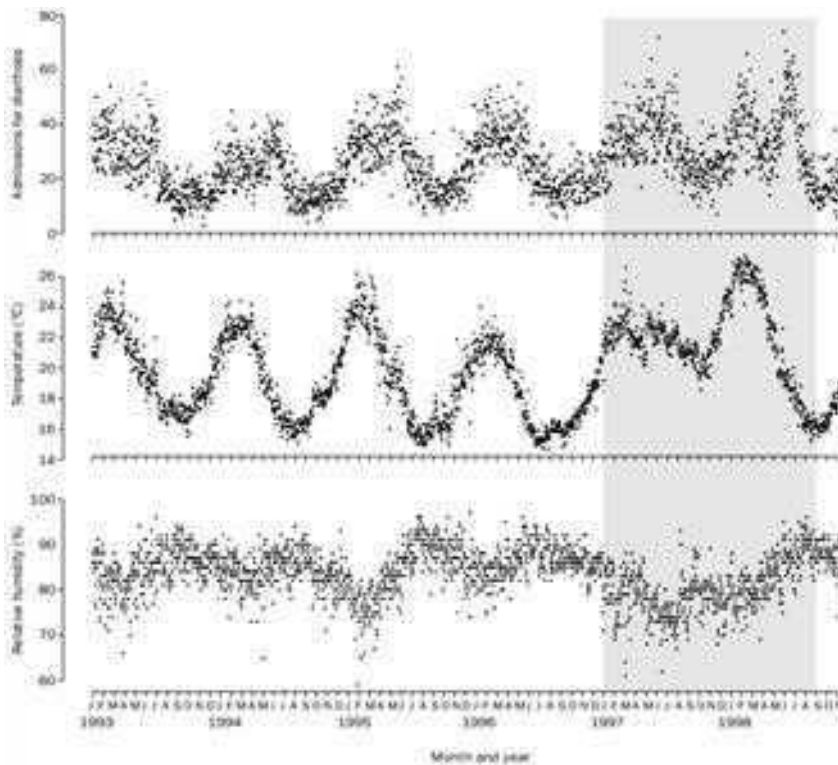


Figure 8. Effect of increase of temperature on diarrhea incidence (adapted from [97]).

In India, the number of foodborne diseases is expected to rise from 100 million in 2011 to ~170 million in 2030 [101]. Therefore, it's a high time to put more emphasis on foodborne diseases research from the point of climate change to identify the mitigation approaches.

Heat-Related Morbidity and Mortality

Due to the anthropogenic climate change, the global mean temperature is increasing and is expected to be increasing far more regardless of the reducing greenhouse gas emissions. It is estimated that human activities have caused approximately 1.0°C rise of global warming above pre-industrial levels, with a *likely* range of 0.8°C to 1.2°C. Global warming is *likely* to reach 1.5°C between 2030 and 2052 if it continues to increase at the current rate [102] and is likely to increase between 1.8 and 4.0°C by 2100 [28]. Climate change is expected to raise overall temperature distribution and contribute to an increase in the frequency of extreme heat events, or heat waves in different parts of the globe [103] which is associated with a wide range of health illness and deaths by exacerbating preexisting chronic conditions such as various respiratory, cerebral, and cardiovascular diseases [104] as well as increasing risk for patients taking psychotropic drug treatment for mental disorders [105] due to the body's impaired ability to regulate temperature. Heat related morbidity and mortality can be due to either direct or indirect effects [104]. Direct effects include a spectrum of heat illness ranging

from heat exhaustion to heat stroke; the indirect effects occur when heat exposure stresses underlying physiological systems and results in other specific manifestations such as renal insufficiency, acute cerebrovascular disease, and exacerbations of pulmonary disease [106].

Among historic heat waves, some have been associated with large numbers of all-cause and cause-specific deaths, notably in France, Europe more broadly, Chicago and California [107-110]. During the 2003 heat wave in France, excess mortality in 13 French cities varied from 4% to 142%, with a majority of cities experiencing excess mortality in the 20–50% range [107, 26]. During the 2006 heat wave in California, there were an estimated 16,166 excess emergency department visits and 1,182 excess hospitalizations state-wide [109]. In 2010, Moscow and Western Russia experienced a heat wave with ambient temperatures exceeding 39°C, and a high number of deaths, though specific estimates of excess morbidity and mortality have not been done [111].

Table 2. Heatwave events in India (Adapted from [115-116])

Sl. No.	Year	No. of heat wave days	Place	Lives lost
1	1979	16	Orissa, Andhra Pradesh, Gangetic West Bengal, Uttar Pradesh, Bihar	365
2	1980	7	Uttar Pradesh, Maharashtra, Tamil Nadu, Andhra Pradesh	106
3	1981	7	Uttar Pradesh, Madhya Pradesh, Bihar	63
4	1982	4	Uttar Pradesh	11
5	1983	11	Bihar, Punjab, Uttar Pradesh, Maharashtra	185
6	1984	11	Punjab, Uttar Pradesh, Maharashtra	58
7	1985	5	Punjab, Bihar	141
8	1986	8	Andhra Pradesh, Punjab, Rajasthan, Himachal Pradesh, Bihar	155
9	1987	6	Orissa, Punjab, Haryana, Uttar Pradesh	90
10	1988	21	Rajasthan, Gujarat, Saurashtra & Kutch, Uttar Pradesh, Punjab	924
11	1989	15	Rajasthan, Madhya Pradesh, Maharashtra	43
12	1990	6	Rajasthan	
13	1991	10	Rajasthan, Madhya Pradesh, Maharashtra, Gujarat	250
14	1992	13	Rajasthan, Madhya Pradesh, Haryana, Bihar, Uttar Pradesh, Maharashtra	114
15	1993	13	Punjab, Haryana, Rajasthan, Uttar Pradesh	73
16	1994	25	Punjab, Haryana, Rajasthan, Uttar Pradesh, Madhya Pradesh, Maharashtra	234
17	1995	29	Haryana, Rajasthan, Punjab, Uttar Pradesh	410
18	1996	9	Rajasthan, Haryana, Uttar Pradesh	17
19	1998	27	Punjab, Rajasthan, Gujarat, Uttar Pradesh, Maharashtra, Orissa, Andhra Pradesh, South Tamil Nadu	1300
20	1999	14	north-west and central India	
21	2003		Andhra Pradesh	3000
22	2010		Ahmedabad	1300
23	2015		Andhra Pradesh, Telengana, Odisha, Uttar Pradesh, West Bengal, Gujarat, Madhya Pradesh, Delhi, Maharashtra, Rajasthan, Chattisgarh, Bihar, Karnataka	2500

In India, heat waves often lead to loss of human and animal life, while enhancing morbidity and discomfort (Table 2). Official records of the India Meteorological Department (IMD) indicate that there have been approximately 223 heatwave incidents between 1978 and 1999, causing more than 5,300 deaths [112]. Premature mortality in India is experienced more in rural populations, particularly among elderly and outdoor workers. Omid et al. 2017 [113]

observed that Mean temperatures across India have risen by more than 0.5°C over the period of 1960-2009, with statistically significant increases in heat waves. Similarly, Concurrent day and nighttime heatwaves can exacerbate human discomfort causing high morbidity and mortality. Mukherjee and Mishra, 2018 [114] reported an increase 12-fold of the current level by the end of 21st century and 4-fold by the mid 21st century under the high emission pathway of RCP 8.5 Concurrent day and nighttime heatwaves. India has had several historic heat waves. Most notably, in May 1998, India experienced a severe heat wave over a 2-week period, which was considered to be the worst in the previous 50 years [115]. The following year, a similar record-breaking event occurred in 1999 in north-west and central India. According to Kalsi et al. 2001 [116], during the summer of 1999, India experienced unprecedented heat in April, with maximum temperatures of 40°C or above for more than 14 days. Another heat wave in 2003 caused more than 3,000 deaths in Andhra Pradesh. Under a 2°C warming scenario, it was observed that the frequency of severe heat waves in India will increase 30-fold by 2100 [117]. According to IMD, a heatwave is considered to be severe when the maximum temperature remains 7 deg or more above its long term normal value for an area having a normal maximum temperature ≤ 40 deg or remains 5 deg or more above its long term normal value for an area having a normal maximum temperature ≤ 40 deg [115].

Human Developmental Effects

Climate change can impact normal human developments through malnutrition during the prenatal and early childhood and through exposure to toxic contaminants and biotoxins due to extreme weather events. Environment is considered as a potential modifier of normal human development and behavior. Human development can be affected by environmental factors including subtle changes such as small reductions in IQ from exposure to lead [118], changes in onset of puberty from exposure to endocrine disrupting chemicals (EDCs) [119], birth defects such as cleft palate due to dioxin-like compounds [120] and fetal loss through exposure-related spontaneous abortion [121]. Birth defects are a leading cause of mortality accounting for 7% of all neonatal deaths and 3.3 million deaths under the age of 5 years. The prevalence of birth defects in India is 6-7% which translates to around 1.7 million birth defects annually [122] and some of these can be attributed to malnutrition arising from environmental causes. Maternal deficiencies of iodine and folic acid and other macro and micro-nutrient found to be associated with birth defects. According to the National Family and Health Survey 4 [123], less than 50% of children below 5 years of age consumed VitA rich food and only 18% consumed iron-rich foods in India. Approximately 23% of women have a BMI below 18.5, indicating a high prevalence of nutritional deficiency. Due to rising levels of CO₂ and climate change, staple crops such as rice and wheat will loss significant nutrition. According to a recent study [124] rising CO₂ levels from human activity could result in 175 million people worldwide becoming zinc deficient and 122 million people becoming protein deficient by the middle of this century and also found that over one billion women and children could lose a large amount of their dietary iron intake, putting them at increased risk of anemia and other diseases. It was also noted that India would bear the greatest burden, with an estimated 50 million people becoming zinc deficient. As many as 38

million people in India are at the risk of becoming protein deficient, and 502 million women and children becoming vulnerable to diseases associated with iron deficiency.

Climate change will lead to changes in agricultural practices and for higher crop yields increase amount of pesticides will be used which have direct human exposure. Similarly, due to the change in temperature and rainfall pattern, ranges of disease-causing mosquitoes will be expanded and control of these mosquito-borne diseases are still highly depended upon the use of a large scale of insecticides such as DDT which persists in nature for a long time. Exposure to high levels of DDT shortened menstrual cycle and reduced chance of getting pregnant. According to Cohen et al. 2003 [125], every 10 milligrams per liter of DDT in mother's serum, the probability of pregnancy for the daughter dropped by 32%. Other pesticides have also been linked to a similar reduction in fertility [126]. Additionally, changes in maternal nutrition and *in utero* exposure to certain chemicals or biotoxins due to climate change may impact the health of future generations through epigenetic changes before conception and during pregnancy.

Mental Health and Stress-Related Disorders

Mental health disorders comprise a broad class of illnesses which may even leads to chronic diseases and death. Stress-related disorders derive from abnormal responses to acute or prolonged anxiety and include diseases such as obsessive-compulsive disorder and post-traumatic stress disorder. Psychological impacts of climate change, ranging from mild stress responses to chronic stress or other mental health disorders, are generally indirect and have only recently been considered among the collection of health impacts of climate change [127]. The effects of climate change in the form of extreme weather events impact the social, economic, and environmental determinants of mental health, with the most severe consequences being felt by communities who were already disadvantaged [128]. It was observed that the tsunami associated with December 26, 2004, Sumatra–Andaman earthquake killed approximately 250000 people along the coastlines of the Indian Ocean produced posttraumatic stress reactions across a wide region of Aceh and North Sumatra [129]. Similarly, John et al. 2007 [130] observed a prevalence of 70.7% for acute posttraumatic stress disorder (PTSD) and 10.9% for delayed onset PTSD. PTSD was more prevalent among girls and more severe among adolescents exposed to loss of life or property in Tamilnadu, India. Similar high stress disorders due to that tsunami were also observed in Thailand [131] and in Sri Lanka [132].

Vector-Borne and Zoonotic Diseases

The socioeconomic development leading to the clearing of forests, reclaiming wasteland for urbanization, etc. are resulting in ecological change leading to altered epidemiology of vectorborne and zoonotic diseases (VBZD). The changes in habitats of wild animals lead to man-vector contact, thus posing a risk to public health. According to IPCC, 2007 [133], climate change is most likely to modify the consequences of vector-borne disease. Importantly, as all vector-borne diseases are extremely sensitive to climate fluctuations, these

might serve as an alert to focus attention on climate change threats [134-135]. There is substantial concern that climate change will make certain environments more suitable for some VBZD, worsening their already significant global burden and potentially reintroducing some diseases into geographic areas where they had been previously eradicated. In recent years, there is increased awareness about the resurgence of zoonotic or other re-emerging diseases in India [136]. Crimean–Congo hemorrhagic fever (CCHF) has been reported from India for the first time in 2010 while West Nile virus (WNV) is making inroads into new areas. Swine flu, which was not known till 2009, emerged in pandemic form throughout the world. The projections on climate change for India [20] indicate an increase in average temperature between 2.5°C and 5°C and an overall increase in the intensity of rainfall between 1 mm and 4 mm/day, except for small areas in north-west India. It is thought that such changes in the climate may affect several characteristics of vector-borne disease, namely their survival and reproduction rates, the intensity and temporal pattern of vector activity and the rates of development, survival, and reproduction of pathogens within vectors [133, 137].

In recent years, vector-borne diseases have emerged as a serious public health problem in countries of the South East Asia region, including India. Many of these diseases, particularly dengue fever and Japanese encephalitis, now occur in epidemic form, almost on an annual basis, causing considerable morbidity and mortality. The risk factors that play a key role in the spread and transmission of dengue and other vector-borne diseases in India and across its borders include globalization, unplanned and uncontrolled urbanization, developmental activities, poor environmental sanitation, poor household water-storage practices, improper drainage of water, widespread traveling and human migration [138]. Even the very recent outbreaks of Zika virus can be linked to the creation of suitable breeding places of Zika vector *Aedes aegypti*. Effect of climate change on different VBZD has been shown in Table 3.

Valid projections on likely impacts of climate change on VBZD are lacking, and a scientific consensus has yet to emerge. Even though we now have the technical knowledge to treat or vaccinate against many VBZD, in the absence of these technologies, some experts believe that population-level mortality from certain disease outbreaks could reach as high as 20–50%. Accordingly, this modeling method has been used particularly for malaria and dengue fever. The malaria modeling shows that small temperature increases can greatly affect transmission potential. Globally, temperature increases of 2-3°C would increase the number of people who are at risk of malaria by around 3-5%. Ultimately, projections must be specific to location, altitude, ecosystem, and host or vector. Health impacts from changing distributions of VBZD are likely to unfold over the next several decades, and prevention and control activities must be developed and honed prior to significant vector range expansion in order to be most effective [158].

Water Borne Diseases

Climate change will affect water availability but at the same time, it will also increase human exposure to unsafe water. Climate change will affect biological, physical and chemical components of water through different paths thus enhancing the risk of waterborne diseases. Water-borne disease such as cholera, diarrhea, giardiasis, salmonellosis, and cryptosporidiosis may be more frequent due to warmer climate [159].

Table 3. Impact of climate change on potential distribution and transmission of VBDs

Sl. No.	Disease	Endemic Region	Global Prevalence of Infection (in Million)	Pathways of Introduction	Vector	Possible changes in distribution as a result of Climate Change
1	Malaria*	Africa, Asia, SE Asia,	219	Infected people	Anopheles mosquitoes	More suitable in the tropical highland regions [139]
2	Lymphatic Filariasis*	Africa, South Asia, SE Asia, Asia Pacific	38,464	Infected people	Mosquitoes of genus Anopheles, Culex and Aedes	Possible expansion in tropical and subtropical regions [140,141]
3	African Trypanosomiasis	sub-Saharan Africa	0.0107	Infected people	tsetse fly (Glossina genus)	epidemics can occur when mean temperatures are between 20.7°C and 26.1°C [142] and a large shift in the geographical extent of the range [142,143]
4	Yellow fever	tropical areas of Africa and Central and South America	0.13	Infected people	Aedes aegypti	Increase in the Americas [144]
5	Muco/cutaneous Leishmaniases*	Americas, the Mediterranean basin, the Middle East and Central Asia	3.9	Infected people	female phlebotomine sandflies	likely to cause an increase in the prevalence, distribution, and severity of leishmaniases [145]
6	Visceral Leishmaniases*	Brazil, East Africa and in South-East Asia	0.061	Infected people	female phlebotomine sandflies	likely to cause an increase in the prevalence, distribution, and severity of leishmaniases [145]
7	Chagas disease	Latin America	6.653	Infected people	Triatomine bugs	A significant possibility of increase in both rural and urban population of North America [146], Decreasing trend of human infection in Latin America [147]
8	Lyme diseases	forested areas of Asia, north-western, central and eastern Europe, and the USA.	0.532	Infected people/Livestock	Ixodes scapularis, I. persulcatus, I. pacificus, I. ricinus	Increase in transmission in the USA [148] and more expansion in Europe [149]
9	Kyasanur Forest Disease	South Asia (Mainly South and West India)	NA	Infected animals (Monkeys)	Haemaphysalis spinigera	Possible range expansion within Indian subcontinent [150]
10	West Nile virus	Africa, Asia, Europe, Australia	0.002588	Migratory or dispersing birds	Mosquitoes of the genus Culex	Expansion into new areas, Increase in transmission intensities [151]
11	Japanese encephalitis virus*	South-East Asia and Western Pacific	0.0425	Infected livestock	Culex species (mainly Culex tritaeniorhynchus)	Likely to cause an increase in the prevalence, distribution, and severity in coastal areas [152]
12	Chikungunya virus*	Africa, Asia	0.693	Infected people	Ae. aegypti and Ae. albopictus	Broader expansion in tropics and subtropics [153]

Sl. No.	Disease	Endemic Region	Global Prevalence of Infection (in Million)	Pathways of Introduction	Vector	Possible changes in distribution as a result of Climate Change
13	Dengue virus*	Southern hemisphere	96	Infected people	Ae. aegypti and Ae. albopictus	Broader expansion in tropics and subtropics [153]
14	Zika virus	Africa	0.5	Infected people	Ae. aegypti and Ae. albopictus	Expected to increase in Geographical expansion due to favorable environmental conditions [154]
15	Onchocerciasis	Africa, Latin America and Yemen	15.531	Infected people	blackflies of the genus Simulium	Increase in transmission rates [155]
16	Schistosomiasis	Africa, the Middle East, the Caribbean, Brazil, Venezuela, Suriname, Indonesia, China, The Philippines	207	Infested water	Snails	Contraction in transmission in Africa [156], possibility of expansion in Asia [157]

Diseases superscripted with * are considered as major VBZD in India with their prevalences in India are: Malaria (9.5 million), Dengue (0.19 million), Chikungunya (0.07 million), Filariasis (23.0 million cses), Japanese encephalitis (0.0022 million) and Leishmaniasis (0.0058 million).

Diarrhoeal disease is one of the most important causes of mortality and morbidity in developing countries including South Asia, particularly among children [160]. It is estimated that diarrhea kills approximately 104643 (95% CI: 89525.9 – 122375.6) with a mortality rate of 84.2/100000 children below 5 years in India [161]. There is strong evidence that diarrhea, particularly the one caused by bacteria and protozoan pathogens, is highly sensitive to variations in both temperature and precipitation [162]. It is, therefore, very likely that long-term climate change will lead to consistent changes in diarrhoeal rates. Climate change can result in increased temperatures in both ocean water and ambient air as well as rise in sea level due to increased temperatures can lead to coastal flooding, which can force the communities to use contaminated water, inadequate sanitation systems, or trigger migration into areas with unsafe water and sanitation availability which can lead to the spread of Cholera [163]. Warm water, moderate salinity, and number of aquatic invertebrates are the conditions influenced by climate change which promote the growth of Cholera species. It was observed that both high and low temperatures, as well as diurnal temperature range, have been found to be associated with childhood diarrhea in Brisbane, Australia [164]. Applying the conceptual framework to the latest regional climate projections for northern India, Moors et al. 2013 [165] showed that there is a chance of increase of 5.6% and 0.4% diarrhea per 1°C rise in temperature and per mm/month decrease in rainfall respectively. The study also projected an average 13.1% increase in diarrhea incidences in north India by the 2040s.

MITIGATION AND ADAPTATION

Climate change is contributing significantly towards the global burden of disease both directly or indirectly and this contribution is expected to grow far more in the near future. According to a WHO assessment, taking into account only a subset of the possible health impacts and assuming continued economic growth and health progress, concluded that climate change is expected to cause approximately 250 000 additional deaths per year between 2030 and 2050; 38 000 due to heat exposure in elderly people, 48 000 due to diarrhoea, 60 000 due to malaria, and 95 000 due to childhood undernutrition (<https://www.who.int/news-room/fact-sheets/detail/climate-change-and-health>). Kovats et al. 2011 [166], using a medium-to-high emission (A1B) scenario with no further climate change or mitigation or adaptation efforts, resulted in estimates of an additional 26,000 deaths per year from heat by the 2020s (2011-2040), rising to 89,000 per year by the 2050s (2041-2070) and 127,000 per year by the 2080s (2071-2100). While heat-related mortality in Europe is projected to increase in all regions, there are relatively higher levels of climate change attributable heat deaths in Southern Europe. As the average mean temperature in India has increased, Mazdiyasni et al. 2017 [167], based on data from the India Meteorological Department between 1960 and 2009, indicated that there has been a substantial increase in mass heat-related deaths. Their “results suggest that even moderate increases in mean temperature may cause a great increase in heat-related mortality.” With an increase in summer mean temperature of 0.5% (to 27.5°C), the probability of these mortality events increases by a factor of 2.5 to 32%. The impacts of climate on human health will be heterogeneous around the world. Peoples living in developing countries, particularly in small island states and thickly populated coastal areas, arid and high mountain zones are considered

to be particularly vulnerable [168]. The Third Assessment Report of IPCC [169] concluded that the extent to which human health is affected depends on the exposures of populations to climate change and its environmental consequences, the sensitivity of the population to the exposure, and the ability of affected systems and populations to adapt. Certain adverse health effects can be minimized or avoided with sound mitigation and adaptation strategies. Strategies for mitigating and adapting to climate change can prevent illness and death in people now, while also protecting the environment and health of future generations. Adaptation [170] can reduce sensitivity to climate change while mitigation can reduce the exposure to climate change, including its rate and extent. Adaptation and mitigation can complement each other and together can significantly reduce the risks of climate change [171]. Appropriate mitigation and adaptation strategies will positively affect both climate change and the environment, and thereby positively affect human health. Some adaptation activities will directly improve human health through changes in our public health and health care infrastructure.

The IPCC special report on global Warming of 1.5°C [172] assesses mitigation pathways by limiting global warming to 1.5°C above pre-industrial levels which depends on the lowering green house gas emission by 2030 and reaching net zero CO₂ emission globally around 2050. The mitigation of GHGs provides a mechanism for slowing, and perhaps eventually halting the build-up of GHGs in the atmosphere. Emission of GHGs can be reduced by more efficient use of energy, reducing dependence on carbon energy and switching to low-carbon energy like solar, hydro, or wind energy, etc. Steps to reduce GHG emissions could have positive health effects. For example, promoting the safe use of public transportation and active movement, such as biking or walking as alternatives to using private vehicles, could reduce carbon dioxide emissions and improve public health. They can not only cut traffic injuries but also air pollution and associated respiratory and cardiovascular diseases. Increased levels of physical activity can lower overall mortality rates [173].

Even if GHG emissions are expected to reduce in the near future, Earth's climate will continue to change. Hence, adaptation strategies must be considered to reduce disease burdens, injuries, disabilities, and deaths. Extreme weather events can have vastly different impacts because of differences in the target population's adaptation capacity. Adaptation enhances a population's coping ability and may protect against current climatic variability as well as against future climatic changes. It includes the strategies, policies, and measures undertaken now and in future to reduce the potential adverse health effects. The rebuilding and maintaining of public health infrastructure are often viewed as the "most important, cost-effective, and urgently needed" adaptation strategy [174]. This includes public health training, more effective surveillance and emergency response systems, and sustainable prevention and control programs. Education, awareness-raising, and the creation of legal frameworks, infrastructures, institutions, and an environment that enables people to make well-informed, long-term, sustainable decisions are also of paramount importance [175] (Climate change and health: Why should India be concerned). The main determinants of a community's adaptive capacity are economic wealth, technology, information and skills, infrastructure, institutions, and equity. Adaptive capacity is also a function of current population health status and pre-existing disease burdens. Developed countries are better to adapt because they have the economic resources to invest and to offset the costs of adaptation. Countries that have contributed the majority of GHG emissions should acknowledge their responsibility for generating climate change and consequent health impacts, reduce their emissions, and support

under-resourced and marginal populations in adapting to climate change, to help ensure the long-term sustainability [176].

RESEARCH NEEDS

It is critical that adaptation and mitigation decisions and policies be developed with a sound basis in the best current science on climate change and its effects. There are gaps in our understanding of the relationship between climate change, the environment, and human health. In its 2010 report, the NIEHS-led Interagency Working Group on Climate Change and Health identified major research areas that need to be further explored and understood [158].

RESEARCH NEED IN INDIAN CONTEXT

With its huge and increasing population (~1.33 billion) and increasing rate of urbanization, India is going to witness the enormous fate of climate change which is going to magnify existing health threats by many fold [177]. A greater understanding of the relationship between climate variability and human health in a country such as India could aid in the development of new prevention strategies and early warning systems, with implications throughout the developing world. Future studies must work to more explicitly define the relationship between climate variability and emerging and reemerging infectious diseases such as dengue, yellow fever, cholera, and the chikungunya virus [178], as well as chronic diseases related to cardiovascular and respiratory illness, asthma, and diabetes [177]. Evaluation of health risks due to climatic variability and subsequent climate change by using innovative and multidisciplinary investigations coupled with environmental epidemiologic methods are important in countries like India. However, such work will require expanded partnerships among researchers, governments, and communities to develop a co-benefit strategy that addresses public health challenges and risks associated with climate change. Adoption and implementation of these research initiatives will provide the necessary tools and infrastructure to pose interesting scientific questions and design effective solutions to the complex issues imposed by climate change.

CONCLUSION

Humans are the most intelligent species on the earth and are highly adaptive. They have proved this by successfully adapting to numerous environmental changes over a long time and improving their life and health by the use of knowledge, science and technologies. These improvements come at a cost which needs to be understood and acknowledged such that human can act on it for their sustainable development. Climate change is now a mainstream issue and must be framed as a public health concern. The costs of not taking appropriate and timely action are high. Therefore, it is urgently needed to find ways to prevent the ill-effects of climate change on health and humanity by finding the knowledge gaps and adopting sustainable approaches.

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Chapter 548

PUBLIC HEALTH CHALLENGES AND OPPORTUNITIES IN LEPROSY CONTROL: FROM THEORY TO IMPLEMENTATION

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ABSTRACT

Despite the availability of multidrug therapy since 1981, leprosy remains a significant public health problem and cause of disability in developing countries. Progress towards the control of leprosy has stagnated: over the last ten years, the global incidence has remained around 200,000 cases, 80% of which occur in India, Brazil, and Indonesia. Control efforts have been stymied by myriad factors, including stigma, which can delay diagnosis and treatment, as well as the paucity of information about where and to what extent transmission is occurring. These challenges are exacerbated by the lack of reliable data, the absence of an appropriate measure of leprosy burden, several gaps in the epidemiological knowledge about the disease, and the high cost of implementing new control measures. To accelerate progress towards a leprosy-free world, the World Health Organization (WHO) launched a global leprosy strategy in 2016 with the goal of achieving zero disability among new pediatric patients and reducing grade-2 disability rate to less than 1 case per 1 million people by 2020. To meet these goals, expanding knowledge about leprosy epidemiology, developing innovative, evidence-based strategies and optimal implementation of current programs are essential. In this chapter, we discuss the current public health challenges that leprosy control faces, and explore the opportunities addressing these challenges that can potentially accelerate progress towards the elimination of leprosy.

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INTRODUCTION

Leprosy is an infectious disease caused by *Mycobacterium leprae* that primarily affects the skin and peripheral nerves. Primary symptoms of leprosy include muscle weakness, skin lesions, and numbness in the arms and legs. Although the mechanism of disease transmission is not known, it is generally accepted that prolonged, close contact with an untreated person is needed to catch the disease [1]. Clinical manifestation of leprosy infection appears after an incubation period ranging from 2 to 20 years [2]. Leprosy patients are divided into three groups based on the number of skin lesions and infected nerves involved: paucibacillary (PB) single-lesion leprosy (one skin lesion), paucibacillary leprosy (2-5 skin lesions) and multibacillary (MB) leprosy (more than five skin lesions) [3]. Symptoms of PB infection include swelling of the nerves, muscle weakness, numbness in the limbs and stuffy nose. Compared to PB leprosy, there are many outward symptoms associated with MB leprosy, including skin lesions, curling of the fingers, ulcers, and absorption of limbs. MB leprosy progresses at a rapid rate compared to PB leprosy, and patients with MB manifestation have a lower life expectancy. MB is also associated with greater life-long disability and has a higher transmission rate than PB. The immune responses and the mechanisms involved in nerve damage caused by leprosy are not well understood, and there is no predictive test to determine the extent of nerve damage as well as the best course of the treatment regimen to minimize the damage. The disabilities caused by leprosy are often irreversible [4]. Consequently, it is necessary to diagnose and treat leprosy infections early.

The first breakthrough of disease control occurred in 1941 when sulfone was introduced as a treatment for leprosy (Figure 1). Patients treated with sulfone were instructed to continue taking the drug in smaller doses after they were released from medical care. This was followed by dapsone in 1950 (Figure 1). Dapsone treatment typically continued for 4-10 years and, in some cases, treatment continued for life. However, *M. leprae* evolved resistance to dapsone in the 1960s, which reduced the effectiveness of dapsone. To combat this problem, multidrug therapy (MDT) was recommended by the World Health Organization (WHO) in 1981 (Figure 1). Current MDT treatment to cure single lesion paucibacillary leprosy includes a combination of rifampicin, ofloxacin, and minocycline. Paucibacillary leprosy is treated with a combination of Rifampicin and dapsone. A combination of Rifampicin, clofazimine, and dapsone is used to treat multibacillary leprosy [5].

Since 1995, the WHO has supplied MDT free of cost to leprosy patients in all endemic countries (Figure 1). MDT helped reduce worldwide prevalence from more than 5.25 million cases to approximately 193,118 since 1985 [6]. Global elimination of leprosy, defined as a registered prevalence of less than 1 case per 10,000 population, was achieved in 2000 [7]. Of the 122 countries previously considered endemic for leprosy, 119 countries had achieved leprosy elimination by 2012 [8]. This dramatic reduction in prevalence is almost entirely due to the shortening of treatment duration to two years. Following evidence of low relapse rates with MDT treatment for 24 months [9], the treatment duration was further reduced to a fixed period of 6 months for PB leprosy and 12 months for MB leprosy. Widespread use of MDT also reduced the long-term cost of treatment to the health system.

Despite the substantial progress made in the last 20 years, leprosy remains a significant public health problem and the leading cause of permanent physical disabilities due to a communicable disease [10]. More than 200,000 cases are still reported worldwide every year,

with India, Brazil, and Indonesia accounting for 80% of the new cases detected globally [11]. While the global incidence of leprosy has declined by 3.4% over the last ten years, the increase in new cases was reported in 7 countries (Bangladesh, Brazil, Comoros, Mozambique, Nepal, Philippines and Sri Lanka) out of the 22 priority countries (Figure 2). Moreover, the number of new cases detected with grade-2 disability in 2017 only declined by 10% over the last 4 years from 12,267 to 11,014, indicating an urgent need to improve early case detection (Figure 3). Clearly, the transmission of leprosy is continuing. Eradication of leprosy will require increased efforts and a multifaceted strategy that addresses the myriad epidemiological, socioeconomic and clinical challenges that contribute to the persistence of leprosy. In this chapter, we review both pressing challenges and potential solutions to control leprosy.

KNOWLEDGE GAPS IN EPIDEMIOLOGY OF LEPROSY

An understanding of the transmission dynamics of leprosy is fundamental to the design and success of control strategies. However, there are gaps in our knowledge about the epidemiology of the disease. Firstly, the mechanism of leprosy transmission is not well understood. Leprosy is generally believed to spread either through direct exposure to infected fluids, indirectly via airborne viral droplets, or through direct or insect-mediated infection from zoonotic or environmental reservoirs [12]. Nasal secretions and skin of untreated leprosy patients are capable of shedding *M. leprae* to the environment. The relative potential of both the sites in establishing infection remains unclear. The ability of the disease to transmit over the course of an infection is also not known. Secondly, there is limited knowledge about risk factors for leprosy infection including genetic predisposition, immune and nutritional status [13]. Finally, there are the proportion of cases attributable to environmental reservoirs and animal hosts such as armadillos in the Americas [14, 15], red squirrels in the British Isles [16] and nonhuman primates [17].

A better understanding of *M. leprae* transmission, as well as the risk factors for infection, is essential to developing effective interventions to interrupt transmission. While the mode of leprosy transmission is unclear, prolonged, close contact with an untreated patient is likely the most common cause of transmission. Contact tracing, which involves reaching out to the contacts of index patients and screening them for signs of leprosy, can be an effective strategy of curbing leprosy transmission by enabling early diagnosis and identifying additional cases [18–21]. Research focusing on the relationship between human genetics and *M. leprae* genome has been crucial towards developing an understanding of how and why people develop leprosy [22]. There have been an increasing number of reports linking genetic regulation of the innate immune response with increased susceptibility to leprosy and also to the development of adverse leprosy reactions [23]. Advanced genome-wide association studies have provided clues towards immune-related gene variants that pose as risk factors for leprosy [24–27].

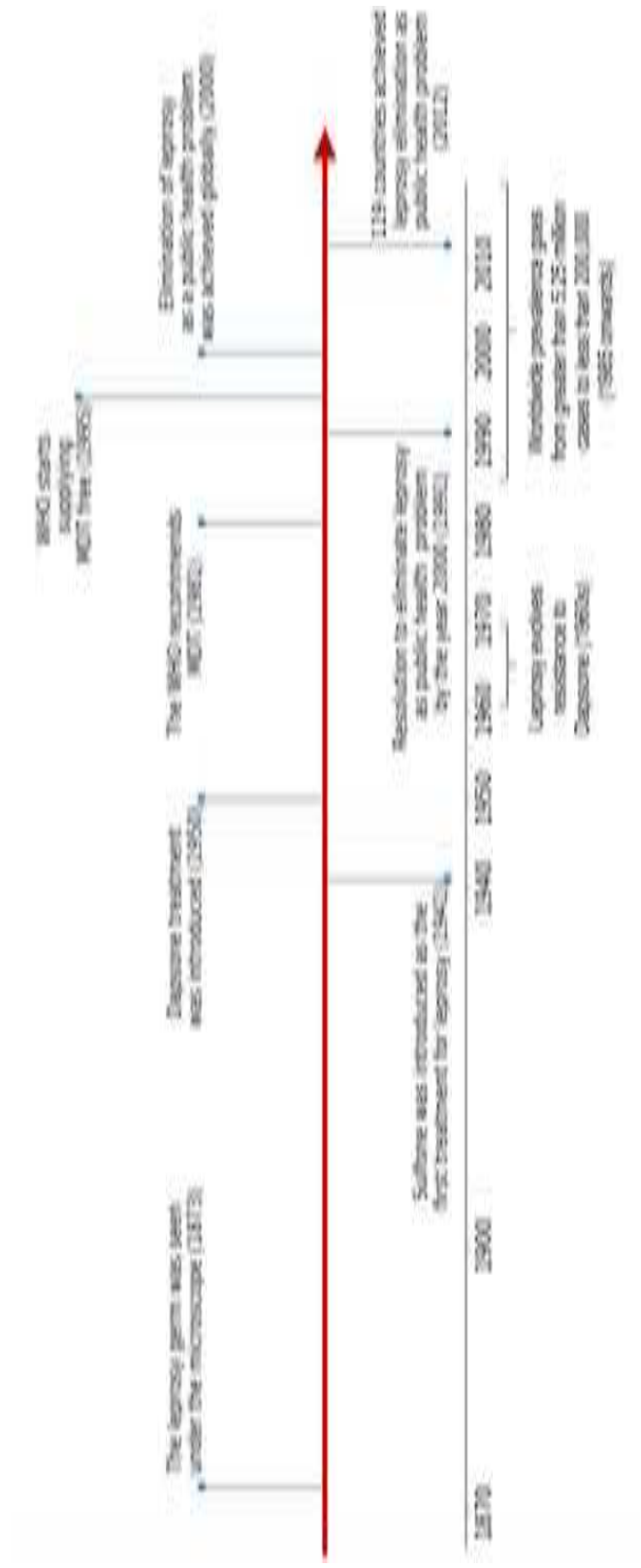


Figure 1. Timeline of key events in the history of leprosy.

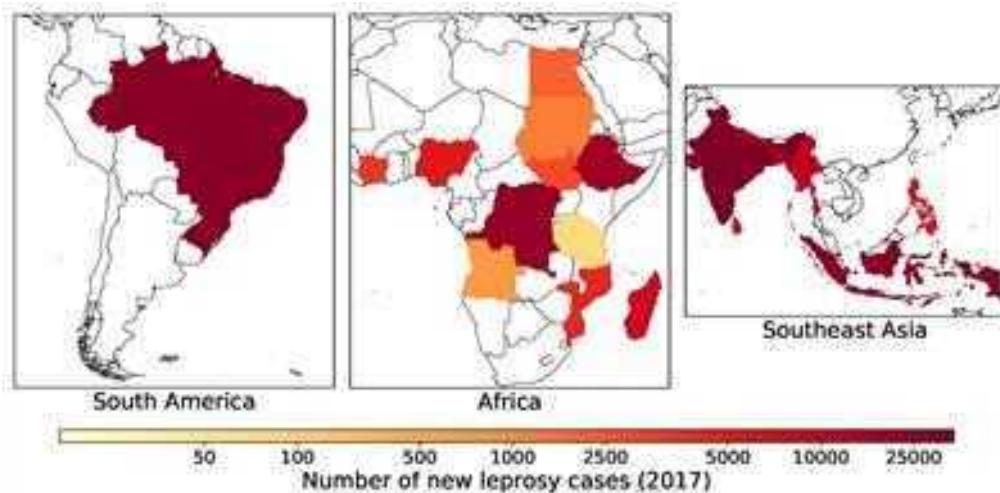


Figure 2. Number of new leprosy cases across the 22 global priority countries in 2017.

CHOOSING A METRIC TO MONITOR LEPROSY CONTROL

An appropriate definition of leprosy control is fundamental to optimize strategic interventions, setting geographical priorities, and estimate the impact of intervention efforts. Prevalence has been one of the most widely used measures of monitoring leprosy burden and control. However, disease prevalence is a poor indicator of leprosy control because it is sensitive to factors such as incubation period of the disease, duration of treatment and case-finding method [28, 29]. Firstly, leprosy has a long incubation period, ranging from 2 to 20 years [30], and technology to detect leprosy at early stage is lacking. New cases therefore continue to become infectious even if prevalence may have been very low in a particular year. Secondly, with MDT, patients are declared cured after treatment and removed from leprosy registers. Consequently, shortening the treatment duration alone can dramatically reduced prevalence without reducing the number of new cases detected annually. For example, the global burden of registered leprosy cases reduced by 50% when the treatment period of leprosy decreased from 24 months to 12 months [31]. Besides prevalence, new case detection rate is increasingly used to report leprosy burden across the world. Both prevalence and new case detection rates suffer as a metric by the fact that they are strongly dependent on the surveillance efforts. Furthermore, as countries are not required to provide evidence of the quality and effectiveness of surveillance efforts, levels of under-reporting remain uncertain.

Challenges in choosing a metric to monitor leprosy control can be overcome by adopting several indicators rather than a single one. Case detection among children provides good evidence for ongoing active transmission of leprosy, and therefore new case reports among children along with disease prevalence data and detection rate can be utilized to better monitor the ongoing transmission as well as inform intervention approaches [32, 33]. Previous modeling studies have highlighted the need for active case detection [34, 35]. Such mathematical models of leprosy transmission can be further utilized to understand the current and future disease burden based on historical data and scientific knowledge about the disease.

Moreover, such studies can allow us to assess the impact of under-reporting and evaluate the effectiveness of current and future intervention strategies to curtail transmission.

SETTING A GLOBAL TARGET FOR LEPROSY CONTROL

In 1991, the WHO defined the goal of eliminating leprosy as reducing the global prevalence rate to less than one case per 10,000 population. Although the global goal was achieved in 2000, India and Brazil failed to meet the deadline. The deadline was extended to 2005 for both India and Brazil that lead to some unintended consequences. For example, India began relying on voluntary reporting and stopped actively seeking new cases and screening contacts. As a result, detection rates fell by 75% between 2003 and 2005 [36]. In India, almost half of the cases were not reported or were staged inappropriately as part of an effort to formally meet the elimination targets of 2005 [37]. Similarly, Brazil achieved the target in 2005 when unregistered patients were omitted from the calculation, which was later retracted after the missing patients were reinstated [36]. The quality of the reported data still remains a concern, especially from low-income countries. The poorest areas tend to have longer detection delays that result in larger numbers of undiagnosed leprosy cases. These undiagnosed cases remain a critical threat to the goal of breaking transmission. When countries are pressured to eliminate leprosy, inaccurate reports can ensue in an attempt to pretend to meet the goal. A study estimated that over 2.6 million cases were missed between 2000 and 2012 due to the decline in new case detection rates for meeting the Leprosy elimination target [37]. Inaccurate and under-reporting of cases not only result in continued transmission and delays in starting treatment, but also a shortage of drugs required for treatment. Therefore, it is essential to ensure that leprosy goals are transparent and widely understandable.

Setting an inappropriate global target of control can also mislead governments, health workers and donors. For example, following the achievement of previous elimination goal in 2000, political commitment, funding, and training of healthcare workers lost momentum, even though more than 700,000 new cases were registered in the same year [10, 36, 38]. The decreased incentive to find new cases may partly explain the 38% increase in grade-2 disability cases from 2004 - 2007. Recognizing these challenges and shortcomings of defining goals based on elimination, the WHO shifted its future goal towards reducing the global burden and reduction of grade-2 disabilities. The 2016-2020 Global Leprosy Strategy aims to reduce the newly detected cases with leprosy-related deformities to below 1 per million population at the global level by 2020 and to reduce leprosy-affected disabilities in children to zero. The WHO's new goal of reducing the grade-2 disability rate will be challenging, considering uncertainties about data quality. Tools and measurement techniques for collecting disability data exist, but their applicability to leprosy-endemic countries needs to be validated [39].

CLINICAL SHORTCOMINGS

Currently, the evidence of acid-fast bacilli in slit-skin smears or the presence of characteristic histological patterns of nerves or skin through biopsy is used to confirm a diagnosis of leprosy. However, the presence of bacilli is rare in the PB forms of the disease and in some cases typical histopathologic changes may not be present [40]. Therefore, there is no gold standard for accurately diagnosing and classifying leprosy so far. Moreover, there are no serologic tests that are available for the routine laboratory diagnosis.

In the absence of any point-of-care test, the initial diagnosis of leprosy commonly relies on the patient's clinical signs and symptoms. In an endemic area, WHO recommends considering an individual as having leprosy if they have skin lesions consistent with definite sensory loss, with or without thickened nerves and positive skin smears. The clinical symptoms are determined by a skin and neurological exam. Additionally, skin biopsies and smears may also be taken to provide a more conclusive diagnosis. Other more uncommon tests include nasal smears, nerve biopsies, and blood exams. Based on the number of bacteria, either PB or MB leprosy is diagnosed [41].

Since leprosy patients have traditionally been in the hands of specialized staff, many healthcare providers are ill-equipped to treat leprosy patients. Success in meeting the World Health Organization's (WHO) goal of eliminating leprosy as a global public health problem by 2005 also led to complacency and a loss of skills in diagnosing and managing leprosy patients. Although the integration of leprosy services into public health services helps reduce stigma, there is a loss of skill in diagnosis and treatment. [42]. Lack of diagnosis and management skills is exacerbated by the fact that, even if a clinical diagnosis is made, there is no good point-of-care test for confirming it. [43]. Tests to confirm a leprosy diagnosis such as skin smears and skin biopsies are only available in facilities that have labs. Unavailability of such facilities can also lead to patients being diagnosed with a disease other than leprosy by their healthcare providers. 42.6% of participants in a study among patients across three states of Brazil were misdiagnosed initially, suggesting a need to increase clinical suspicion of leprosy [44].

In order to both curb transmission and prevent disabilities, it is essential to focus on research aimed at finding practical diagnostic tools that can detect all levels of leprosy infections. Several serological tests for leprosy detection are under development but none of them have achieved sufficient sensitivity and specificity yet [42]. Integrating leprosy services in primary health care can improve case finding and continuity of care, however without appropriate expertise, misdiagnosis of leprosy can not be minimized. Therefore, it is vital to provide clinicians training to recognize and diagnose leprosy, especially in high-risk regions.

STIGMA OF LEPROSY

Although leprosy has had a widespread prevalence since medieval times, and there is evidence of the disease as far back as 1600 BC, it was not until 1873 that *M. leprae* was discovered as the cause of leprosy. While this discovery dispelled the myth that leprosy was hereditary or a curse, the stigma associated with the disease persisted. Fuelling the stigma, legal discrimination against people affected by leprosy played a key role in outcasting leprosy

patients from society. For example, segregation of people with leprosy was required by law in Japan and leprosy patients begged for a living around the temples or shrines. Starting in 1909, the Japanese government started hospitalizing leprosy patients in the leprosy sanatoria, often forcefully. This law lasted until 1996 [45]. Similarly, British India enacted the Leprosy Act of 1898, which institutionalized those affected and segregated them by sex to prevent reproduction. The law also stated that a state government could declare any place as an asylum for people with leprosy. In addition, a sequel to the law said that any person with leprosy who appeared to be poor could be arrested without a warrant. This law was repealed only in 1983 [46].

Although legal discrimination against leprosy patients has reduced significantly across the world, the social stigma against people with leprosy continues to drive affected individuals into further poverty by limiting their employment and educational opportunities. Because MB leprosy shows more outward signs of the disease, people with MB leprosy are stigmatized more than people with PB leprosy. Stigma also deters people from seeking treatment that subsequently leads to irreversible disabilities, such as nerve damage [42]. Delayed treatment also increases the risk of transmission to other people. While active case finding can curb transmission in areas where stigma is widespread, efforts to reduce social stigma towards leprosy patients will have a long-lasting impact on surveillance and control of leprosy.

The stigma associated with the disease is deeply rooted in societies across the world through centuries of misconceptions and myths. The lack of knowledge about the etiology, curability, and transmissibility of the disease remains one of the driving factors of social stigma faced by leprosy patients. Therefore, interventions to raise community awareness by demystifying misconceptions such as leprosy being hereditary or leprosy cases being untouchable can be highly effective. Similarly, it is imperative to train healthcare officials and staff to ensure non-discriminatory behavior of healthcare workers while diagnosing and treating leprosy patients. Integrating leprosy services in general health care aimed towards ‘no isolation-no discrimination’ policy can gradually decrease society’s negative perception as well as provide treatment to leprosy patients closer home.

Fear of social exclusion plays a fundamental role in leprosy patients delaying seeking treatment. The deformity caused by leprosy in a patient not only limits their employment opportunities, but it also results in decreased prospects of marriage for them and their family members. Strategies that primarily focus on reintegration of people with leprosy into society such that they can live with dignity and self-sufficiency are essential to improve their quality of life and to encourage individuals with symptoms to seek early treatment.

The WHO’s Global Leprosy Strategy 2016-2020 calls for several measures to end discrimination towards those affected by leprosy [47]. These measures include empowering the leprosy patients and their communities to actively participate in leprosy programs, providing better access to social and financial support, and promoting community-based rehabilitation for people with leprosy-related disabilities. The WHO has also committed to work towards ending discriminatory laws and promoting policies that facilitate the inclusion of people affected by leprosy.

SOCIOECONOMIC RISK FACTORS

Although leprosy has been identified as a disease of poverty, we still have a limited understanding of the risk factors that link them together. Nationally, new case detection rates do not necessarily correlate with indicators such as GDP or human development index. For example, countries with very low human development index such as Burkina Faso (ranked 183) and Benin (ranked 163) report lower new case detection rates compared to Brazil (ranked 79) that has the second highest new case detection rates [48]. The distribution of leprosy risk is highly heterogeneous even within most affected countries such as India, Brazil and Indonesia where the majority of cases occur in high-risk regions. Living in a crowded household as well as lack of schooling was identified as a risk factor in an individual-level study done in Malawi [49]. Another study conducted in a high endemic area of leprosy in Brazil showed the level of inequality, population growth, and presence of a railroad are associated with higher levels of leprosy [50]. A systematic review and meta-analysis of 39 studies identified poor hygiene, lower levels of education, and food insecurity as risk factors for leprosy [51].

Across all high-endemic regions of leprosy, impoverished communities remain disproportionately affected. Multiple socioeconomic factors drive the association between leprosy and poverty. One of these factors is the lack of physical access to diagnosis and treatment, which occurs due to inadequate access to specialized leprosy clinics. The costs of seeking treatment are another factor. Although MDT is free, other costs such as travel, lost wages, and other incidental expenses must be accounted for. In addition, getting MDT to patients—who are typically located in impoverished remote locations—poses major logistical and distribution challenges. Shortages of MDT at the health center level are a chronic problem due to weak information systems and inadequate planning. Moreover, when the disease has progressed too far, MDT may not be sufficient to prevent permanent disabilities.

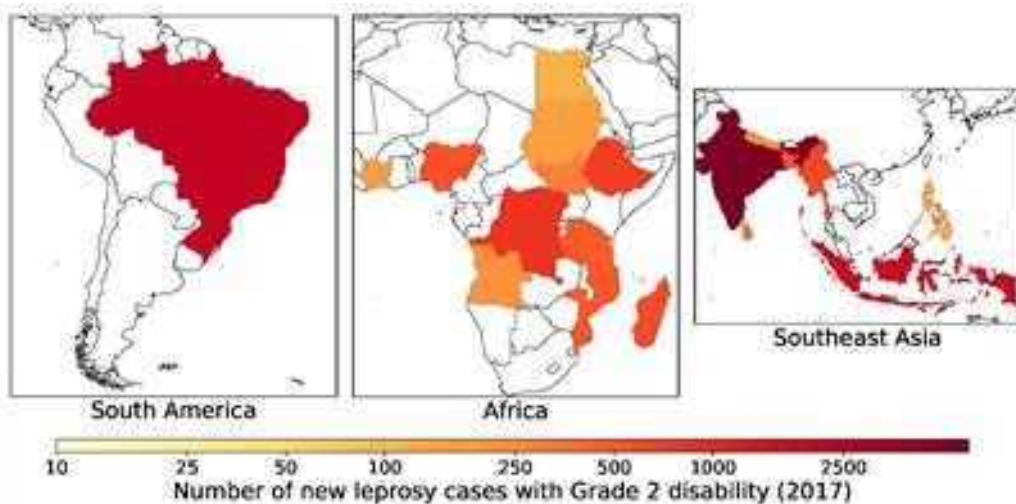


Figure 3. Number of new leprosy cases diagnosed with grade-2 disabilities across the 22 global priority countries in 2017.

Most of these challenges emphasize the importance of efficient, cost-effective case detection in high-endemic regions. The status quo approach of passive case finding that relies on people with symptoms to voluntarily present themselves at health-care facilities is ill-suited to curb transmission. Delayed treatment also increases the risk of permanent disabilities. Targeted strategies of diagnosing cases in high-risk areas have the potential to accelerate leprosy control. By facilitating early diagnosis and treatment, targeted case-finding approaches can substantially curtail transmission and reduce disabilities among leprosy patients. Socioeconomic factors associated with high risk can of leprosy infection be used to target diagnostic efforts and interventions that will be fundamental to curb leprosy transmission. Moreover, improving health-care access and implementing poverty alleviating interventions among the most vulnerable populations in leprosy-endemic regions can facilitate leprosy control.

CONCLUSION

Leprosy, an age-old disease caused by *Mycobacterium leprae*, is no longer causing the level of devastation it had for thousands of years. Since multidrug therapy became available for widespread use in the early 1980s, over 16 million people have been successfully treated for leprosy [52]. Consequently, leprosy prevalence has dropped by 99% over the last thirty years: from 21.1 cases per 10,000 population in 1985 to 0.2 cases per 10,000 population in 2015 [52]. Progress towards leprosy control, however, has stagnated due to continuing and interrelated challenges of clinical uncertainties, knowledge gaps in epidemiology of leprosy, stigma, delayed diagnosis, and socioeconomic risk factors [53].

A multifaceted approach that mitigates the existing challenges and improves early case-detection, provides effective treatment and reintegrates leprosy patients in the society will be required to curtail leprosy at local and global levels. It is vital to identify the pockets of high endemicity in each country. Intervention efforts can be most effectively and efficiently targeted to these areas where high-risk population reside. Innovative technologies are needed to generate high quality and high-resolution data on new case detection rates and prevalence. Epidemiological studies can utilize these data to identify factors that are associated with a high risk of leprosy and to map the regions where control efforts are most needed. For example, a recent systematic review and meta-analysis of socioeconomic determinants revealed several risk factors, including crowded living conditions, food insecurity, household exposure, manual labor, increasing age, lack of sanitation, and lower levels of education [51].

Untrained healthcare professionals contribute substantially to delays in case detection due to both misdiagnoses of early-stage symptoms and discriminatory behavior towards leprosy patients. Training and sensitizing healthcare workers to create a nondiscriminatory healthcare environment will reduce misdiagnosis of cases and encourage patients with symptoms to seek treatment sooner. Delays in diagnosis can also be reduced by alleviating the social stigma faced by patients. Awareness campaigns can aid in reducing societal stigma and contribute to accelerating case-detection and preventing leprosy-related deformities in patients. In the absence of quick point-of-care tests for confirming leprosy, setting up a sufficient number of laboratories with facilities to conduct skin and nerve biopsy and acid-bacilli tests can also

improve case-detection rates. Given that leprosy is a disease of poverty, social development should help to reduce leprosy risks and facilitate eradication.

As leprosy has a very long incubation period, rigorous surveillance and contact tracing are of utmost importance to curb transmission in communities where leprosy cases have been reported. The WHO recommends examining the members of a patient's household for signs of leprosy and educating them on the initial signs. The approach can be further strengthened by continued periodic inspections of family members by medical professionals. At the community level, active case finding should be implemented in areas from leprosy cases are being reported. Awareness campaigns can educate communities to recognize the first signs of symptoms so that they can seek medical care promptly before permanent disabilities occur or there is a further onward transmission. In areas that have previously reported cases, surveillance can be implemented via periodic active case finding among school children to monitor leprosy transmission. The government of countries with leprosy should frame health policies that are geared towards reducing transmission.

The treatment-as-prevention approaches that have been successful in curtailing HIV transmission are applicable to leprosy. Chemoprophylaxis, a treatment that prevents infection for about two years, is an option that can significantly lower the risk of leprosy acquisition among contacts of leprosy patients. However, the widespread use of chemoprophylaxis is still being debated due to ethical and logistical concerns [42, 54]. Two doses of chemoprophylaxis, as opposed to one, would be most effective, but chemoprophylaxis is expensive and is not widely available [54]. Cost-effectiveness studies can evaluate and optimize strategies to treat and household contacts of leprosy patients using chemoprophylaxis. Furthermore, the *Bacillus Calmette–Guérin* (BCG) vaccine, which provides protection against tuberculosis, has also been found to be partially efficacious against leprosy [55]. Thus, BCG vaccination coverage levels should be assessed among populations that are at high risk of leprosy. Improving BCG vaccination among individuals at high risk of leprosy can be a cost-effective strategy for averting cases of leprosy and ultimately reducing prevalence.

Following the introduction of MDT, leprosy prevalence declined sharply between 1980 to 2010. The positive impact of widespread use of MDT appears to have run its course and despite continued efforts, leprosy prevalence has remained stable for the last several years. There is a need for new innovative tools that can detect leprosy infection early, including subclinical infection, and tracking drug resistance. Additionally, new avenues for basic science and clinical research have been opened by genome sequencing of *Mycobacterium leprae* and genome-wide analysis for leprosy cases, which could be instrumental in the development of drugs and vaccines. Until such breakthroughs in clinical research are achieved that can augment the current strategies and facilitate the elimination of leprosy, interrupting leprosy transmission will require bolstering skills in leprosy diagnosis and management, rigorous surveillance and contact tracing of cases, and development of a point-of-care test for confirming leprosy diagnosis.

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Chapter 549

**PUBLIC HEALTH PREPAREDNESS:
HHS SHOULD TAKE ACTIONS TO ENSURE IT HAS AN
ADEQUATE NUMBER OF EFFECTIVELY TRAINED
EMERGENCY RESPONDERS***

United States Government Accountability Office

ABBREVIATIONS

ASPR	Office of the Assistant Secretary for Preparedness and Response
HHS	Department of Health and Human Services
NDMS	National Disaster Medical System

WHY GAO DID THIS STUDY

NDMS is the main program through which HHS enrolls responders to assist with the federal medical and public health response to public health emergencies. HHS deploys NDMS responders to provide, among other things, patient care and movement.

During the 2017 hurricanes, NDMS had a shortage of responders that resulted in HHS relying on other departments, such as the Department of Defense, to provide medical care. As of December 2019, HHS had 3,667 NDMS responders.

The Pandemic and All-Hazards Preparedness and Advancing Innovation Act of 2019 included a provision for GAO to review HHS's responder surge capacity. This report examines (1) the workforce planning for NDMS responders to assist with public health emergencies, and (2) training provided to these responders.

* This is an edited, reformatted and augmented version of United States Government Accountability Office, Report to Congressional Committees, Publication No. GAO-20-525, dated June 2020.

To conduct this work, GAO reviewed agency NDMS planning documentation, including NDMS staffing decisions, team structures, and training materials; compared HHS actions to key workforce planning practices; and interviewed HHS officials.

WHAT GAO RECOMMENDS

GAO is making five recommendations to HHS, including to develop a workforce target that accounts for the critical skills and competencies that are needed to meet current and future programmatic results and to develop processes for evaluating its training to ensure an effectively trained workforce. HHS concurred with our recommendations and generally plans to take action.

WHAT GAO FOUND

Major natural disasters in the past 3 years, as well as the COVID-19 pandemic, have heightened attention to the nation's ability to respond to these types of emergencies. The Department of Health and Human Services (HHS) is responsible for leading the public health and medical response to emergencies. HHS responded to COVID-19, in part, by deploying responders enrolled in the National Disaster Medical System (NDMS). These individuals, such as doctors and nurses, generally work outside the federal government and are federal employees used intermittently. In 2018, HHS developed an enrollment target for NDMS of 6,290 responders, but GAO found HHS did not follow key principles of effective strategic workforce planning in developing this target. For example, HHS did not identify the critical skills and competencies needed of its NDMS workforce to meet current and future programmatic results. Specifically, HHS's target does not take into consideration three key areas: a workforce capable of responding to (1) a nationwide event or multiple concurrent events, (2) the needs of at-risk individuals, and (3) the availability of other medical responders.

Consequently, HHS cannot be sure its target, if achieved, will provide an adequate number of responders with the skill sets needed to effectively respond.



Source: Department of Health and Human Services. | GAO-20-525.

HHS requires responders to take web-based training prior to deployment, such as characteristics of infectious diseases, and also offers optional in-person training, such as care delivery in a severe environment. However, HHS's process to evaluate its training does not align with key practices. As a result, HHS does not have assurance that it is effectively preparing responders for deployment, including keeping them and others safe during an emergency, such as COVID-19. For example, HHS requires a web-based course on donning and doffing personal protective equipment to protect against infectious disease, biological, and chemical threats. However, HHS does not know the training's effectiveness until responders have deployed; at which point, if ineffective, responders could potentially expose themselves to hazards. Further, HHS officials state their in-person training is most beneficial but more costly to provide, limiting its provision. A more effective training evaluation process would help the agency determine which in-person courses are most beneficial and should be prioritized, or even made mandatory, for effective and safe responder deployment.

June 18, 2020

The Honorable Lamar Alexander
Chairman
The Honorable Patty Murray
Ranking Member
Committee on Health, Education, Labor & Pensions
United States Senate

The Honorable Frank Pallone, Jr.
Chairman
The Honorable Greg Walden
Ranking Member
Committee on Energy & Commerce
House of Representatives

On January 31, 2020, the Secretary of Health and Human Services declared a public health emergency for the United States to aid the nation's health care community to respond to Coronavirus Disease 2019 (COVID-19).¹ On March 11, 2020, the World Health Organization characterized COVID-19 as a pandemic. Subsequently, on March 13, 2020, the President declared COVID-19 a national emergency under the National Emergencies Act and an emergency under the Robert T. Stafford Disaster Relief and Emergency Assistance Act.²

To aid the response to COVID-19, as of March 27, 2020, the Office of the Assistant Secretary for Preparedness and Response (ASPR), a division within the Department of Health and Human Services (HHS), deployed about 1,200 public health and medical responders through its National Disaster Medical System (NDMS), according to ASPR officials. These individuals, such as doctors, nurses, and paramedics, work outside the federal government on a day-to-day basis and are federal employees used intermittently to respond to public health

¹ The declaration was retroactive to January 27, 2020.

² The President has also approved major disaster declarations under the Robert T. Stafford Disaster Relief and Emergency Assistance Act for all 50 states, the District of Columbia, and five territories.

emergencies. Some of these responders deployed to help disembark American citizens who were potentially infected with COVID-19 aboard cruise ships, including the Diamond Princess in Japan and the Grand Princess in California, to their quarantine locations in the United States.

ASPR previously deployed these responders to provide surge support as part of the federal public health and medical response to the 2017 hurricanes affecting Texas, Puerto Rico, Florida, and the U.S. Virgin Islands. However, we reported in 2019 that during the hurricane response, ASPR experienced a shortage of NDMS responders and relied on its federal partners, such as the Department of Defense, to provide medical response personnel.³ These events and others have raised questions about ASPR's public health and medical responders, including their capacity to assist during public health emergencies, such as the COVID-19 pandemic, as well as natural disasters, the number of which are predicted to rise as the climate changes.⁴

ASPR leads the nation's medical and public health preparedness for, response to, and recovery from public health emergencies. As part of this role, ASPR aims to enhance medical surge capacity by organizing, training, and equipping federal public health and medical responders, as well as calling upon and deploying these personnel during responses.

The program through which ASPR enrolls responders is NDMS. ASPR may activate NDMS to deploy medical providers, evacuate patients, and provide veterinary services, among other supports.⁵

The Pandemic and All-Hazards Preparedness and Advancing Innovation Act of 2019 included a provision for GAO to review the federal medical provider surge capacity in the event of a public health emergency.⁶ This report examines

1. ASPR's workforce planning for its medical and public health responders to assist with public health emergencies, and
2. ASPR's evaluation of, and planning for, the training it provides to its medical and public health responders.

To examine ASPR's workforce planning for its medical and public health responders to assist with public health emergencies, we reviewed ASPR documentation and interviewed ASPR officials involved with workforce planning for, and hiring of, NDMS responders.

³ GAO, Disaster Response: HHS Should Address Deficiencies Highlighted by Recent Hurricanes in the U.S. Virgin Islands and Puerto Rico, GAO-19-592 (Washington, D.C.: Sept. 20, 2019).

⁴ According to a 2018 report from the U.S. Global Change Research Program, extreme weather and climate-related events are expected to increase in frequency and intensity. U.S. Global Change Research Program, Impacts, Risks, and Adaptation in the United States: Fourth National Climate Assessment, Volume II (Washington, D.C.: 2018). We have also reported that the number of disasters and the reliance on the federal government for disaster assistance will likely continue to rise as the climate changes. GAO, Climate Change: Information on Potential Economic Effects Could Help Guide Federal Efforts to Reduce Fiscal Exposure, GAO-17-720 (Washington, D.C.: Sept. 28, 2017). Managing fiscal exposure due to climate change has been on our high-risk list since 2013, in part, because of concerns about the increasing costs of disaster response and recovery efforts. See GAO, High-Risk Series: Substantial Efforts Needed to Achieve Greater Progress on High-Risk Areas, GAO-19-157SP (Washington, D.C.: March 6, 2019); also http://www.gao.gov/highrisk/limiting_federal_government_fiscal_exposure/why_did_study.

⁵ Under 42 U.S.C. § 300hh-11, NDMS may be activated to provide health services, health-related social services, other appropriate human services, and appropriate auxiliary services to respond to the needs of victims of a public health emergency. ASPR may also activate NDMS in a location that is at-risk of an emergency.

⁶ Pub. L. No. 116-22, § 301(e), 133 Stat. 905, 933-34.

Specifically, we reviewed a June 2018 staffing decision memo signed by the Assistant Secretary for Preparedness and Response outlining ASPR's target for NDMS enrollment—referred to as the NDMS workforce target for the purposes of this report. We reviewed NDMS team structures that the agency developed in March 2018, which include position types and numbers of responders in each position. We also reviewed direct-hire authorities HHS received to hire NDMS responders.⁷ Further, we collected and analyzed ASPR data on the number of enrolled NDMS responders. We assessed the reliability of these data by comparing them to data in other sources, such as agency budget justifications, interviewing knowledgeable agency officials, and performing checks of the data for consistency and completeness. Based on these steps, we found these data to be reliable for our reporting purposes. Lastly, we interviewed ASPR officials to gather information on the capacity factors they considered when establishing the NDMS workforce target and the related workforce planning the agency has conducted. We also interviewed officials from HHS's Staffing Recruitment and Operations Center—the office that conducts all hiring actions on behalf of ASPR and certain other HHS divisions—to gather information on the planning and hiring process for NDMS responders.

We assessed ASPR's workforce planning against key principles of strategic workforce planning that we have identified in previous work, focusing our analysis on those principles that are related to determining current and future workforce needs and establishing strategies to fulfill those needs.⁸ This was a general all-hazards assessment of ASPR's workforce planning and not specific to a single event. In addition to NDMS, the U.S. Public Health Service—an agency within HHS—can also deploy Commissioned Corps officers as a means to help surge during a medical and public health response to an emergency or disaster.⁹ We did not assess the workforce planning of the Public Health Service because the agency is in the process of reorganizing its workforce. This includes plans for implementing a Ready Reserve Corps, which like NDMS, would consist of intermittent employees who could be called-up as needed. For more information on these plans, as well as the number of U.S. Public Health Service Commissioned Corps officers available to provide medical and public health care to humans during a response, see appendix I.

To examine ASPR's evaluation of, and planning for, the training provided to its responders, we reviewed ASPR's current NDMS training catalog, which covers fiscal years 2017-2019 and its draft NDMS training catalog, which the agency plans to implement for

⁷ A direct-hire authority is generally provided to federal agencies when a critical hiring need or severe shortage of candidates exists to expedite hiring by eliminating competitive rating and ranking, among other competitive appointment procedures. HHS received a direct hiring authority for NDMS that ran from February 9, 2018, to November 6, 2018, as part of the Bipartisan Budget Act of 2018. Pub. L. No. 115-123, § 20803, 132 Stat. 64, 95. The Bipartisan Budget Act of 2018 made supplemental appropriations to aid the response to the 2017 hurricane season. HHS received another direct hiring authority as part of the Pandemic and All-Hazards Preparedness and Advancing Innovation Act of 2019. Pub. L. No. 116-22, § 301(a)(3), 133 Stat. 932 (codified at 42 U.S.C. § 300hh-11(c)(4)). This direct hire authority began on June 24, 2019 and ends on September 30, 2021.

⁸ GAO, *Human Capital: Key Principles for Effective Strategic Workforce Planning*, GAO-04-39 (Washington, D.C.: Dec 11, 2003).

⁹ Commissioned Corps officers may be deployed to respond to an urgent or emergency public health care need arising from (1) a national emergency declared by the President under the National Emergencies Act; (2) an emergency or major disaster declared by the President under the Robert T. Stafford Disaster Relief and Emergency Assistance Act; (3) a public health emergency declared by the Secretary of Health and Human Services under the Public Health Service Act; or (4) any emergency that is appropriate for deployment, as determined by the Secretary of Health and Human Services. See 42 U.S.C. §§ 204a(a)(5) and 215(e).

fiscal years 2020-2024 but had not yet implemented at the time of our review. These training catalogs describe mandatory and optional NDMS training courses. We also compared ASPR documentation on the number of optional training courses the agency had planned to provide in fiscal year 2019 against documentation of courses actually provided in that year. Further, we analyzed ASPR's efforts to evaluate its training. This included a review of the survey questions ASPR provides to training participants to evaluate the training they have received. Lastly, we interviewed ASPR officials who oversee NDMS training. We assessed ASPR's planning and evaluation of NDMS responder training against GAO-identified key practices for effective training programs and key principles of strategic workforce planning.¹⁰

We conducted this performance audit from July 2019 to June 2020 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

BACKGROUND

Medical and Public Health Responders

As of December 9, 2019, ASPR had 3,667 enrolled NDMS responders. These responders include physicians, nurses, and paramedics, among other professions, who generally work outside of the government but may be asked to deploy to assist with a federal public health emergency.¹¹ Because these individuals have regular jobs, they may not always be available to deploy. For example, if a response occurs in a state, NDMS responders in that state may already be assisting the response through their civilian jobs, such as through working in hospitals, hindering their ability to deploy.

NDMS responders are organized into five types of NDMS teams. Two of these types—the Disaster Medical Assistance Team and the Trauma and Critical Care Team—are primarily composed of medical providers and focus on providing public health and medical care to individuals during a response. The other three types of teams are the Disaster Mortuary Operational Response Team, the Victim Information Center Team, and the National Veterinary Response Team. See Table 1 for a description of each type of team and number of responders enrolled in each.

¹⁰ See GAO, *Human Capital: A Guide for Assessing Strategic Training and Development Efforts in the Federal Government* (Supersedes GAO-03-893G), GAO-04-546G (Washington, D.C.: Mar. 1, 2004) and GAO-04-39.

¹¹ According to agency officials, responders are federal employees used intermittently and are entitled to the same liability and workforce protections offered to full-time federal employees when deployed due to their positions as intermittent federal employees.

Table 1. Types of National Disaster Medical System (NDMS) responder teams

NDMS Team Name	Team Description	Number of responders ^a
Disaster Medical Assistance Team	Provide patient care to help area health systems during a response. Responders include advanced clinicians (nurse practitioners/physician assistants), physicians, registered nurses, respiratory therapists, paramedics, pharmacists, safety specialists, logistical specialists, information technologists, and communication and administrative specialists.	2,703
Trauma and Critical Care Team	Provide critical, operative, and emergency care to help people during a response. Responders are medical professionals with expertise in trauma care.	212
Disaster Mortuary Operational Response Team	Identify victims and support local mortuary services. Responders include funeral directors, medical examiners, pathologists, forensic anthropologists, fingerprint specialists, forensic odontologists, dental assistants, administrative specialists, and security specialists.	611
Victim Information Center Team	Support local authorities and other NDMS teams in the aftermath of a mass casualty event and may serve as liaison to victims' families. Responders, who include forensic dental officers, pathologists, and victim advocates, collect ante-mortem data, such as pictures, fingerprints, dental X-rays, and other medical records, to help identify the victims.	51
National Veterinary Response Team	Provide veterinary care to working animals, such as search and rescue dogs, during disasters and certain national security events. Responders include veterinarians, animal health technicians, epidemiologists, safety specialists, logisticians, communications specialists, and other support personnel.	90
Total		3,667

Source: GAO summary of data and information from the Office of the Assistant Secretary for Preparedness and Response. | GAO-20-525.

Note: ^aData as of December 9, 2019.

Workforce Planning and Training

We have previously reported that high-performing public organizations have found that maintaining a quality workforce requires them to systematically assess current and future workforce needs and formulate a long-term strategy to attract, retain, develop, and motivate employees.¹² While simple in theory, strategic workforce planning can be difficult to carry out. Agencies must, for example, acquire accurate information on the workforce, including assessing the workforce's ability to assist with mission achievement. Further, agencies must have the internal capabilities to support strategic workforce planning activities. According to our previous work, strategic workforce planning should involve certain key principles that agencies should address, irrespective of the context of the workforce planning. Among these principles are the need to align workforce requirements with agency-wide goals and objectives, identify critical skills and competencies the workforce needs to meet current and future programmatic results, and develop strategies to fill identified gaps in these skills. Effective strategic workforce planning enables an agency to remain aware of, and be prepared for, its current, emerging, and future needs as an organization.¹³

¹² GAO, *Veterinarian Workforce: Actions Are Needed to Ensure Sufficient Capacity of Protecting Public and Animal Health*, GAO-09-178 (Washington, D.C.: February 4, 2009).

¹³ GAO-04-39.

We have also reported that strategic workforce planning includes the training and development of the workforce to eliminate gaps and improve the contribution of critical skills and competencies needed for mission success.¹⁴ Agencies need to ensure that training provided is strategically targeted and not wasted on efforts that are irrelevant, duplicative, or ineffective. Effective training and development programs are an integral part of a learning environment that can enhance the federal government's ability to attract and retain employees with the skills and competencies needed to achieve results for the benefit of the American people.

According to our previous work, key practices for effective training programs involve evaluating training, such as using measures of (1) training participants' reaction to, and satisfaction with, the training program and (2) changes in participants' knowledge, skills, abilities, and on-the-job behavior. Key practices also include planning for training, such as prioritizing training around funding so that an agency can address its most important training needs first.¹⁵

ASPR IS MISSING KEY STEPS IN WORKFORCE PLANNING, LIMITING ASSURANCE THAT IT CAN ADEQUATELY RESPOND TO PUBLIC HEALTH EMERGENCIES

ASPR has not conducted key workforce planning steps for its NDMS responder workforce, and as a result, has limited assurance that it is adequately prepared to respond to public health emergencies. While ASPR has performed some workforce planning, the agency's efforts do not follow the strategic principles that we have identified in prior work as essential for effective workforce planning.

Specifically, ASPR's primary workforce planning efforts focused on developing an NDMS workforce target of 6,290 responders. ASPR data shows that it had reached a little more than half of this target, with 3,667 responders enrolled in NDMS as of December 2019. According to ASPR officials, this workforce target represents the number of responders the agency estimates it needs to enroll in NDMS to position itself to effectively respond to public health emergencies.

ASPR generated this target in June 2018 by multiplying the number of NDMS teams it had at that time by the number of responders planned for each of the five NDMS team types, using NDMS team structures that ASPR developed in March 2018—which include position types and numbers of responders in each position. (See appendix II for the NDMS team structures for each of the five NDMS team types.) See Table 2 for ASPR's workforce target for each of the five NDMS team types.

However, we found that by using this process to determine its workforce needs, ASPR has limited assurance that reaching its NDMS workforce target will be adequate to allow the agency to respond effectively to public health emergencies. This is because, when setting its target, ASPR has not followed two key principles of strategic workforce planning: aligning workforce requirements with agency-wide goals and objectives, and identifying critical skills

¹⁴ GAO-04-546G.

¹⁵ GAO-04-546G.

and competencies the workforce needs to meet current and future programmatic results. Further, even if ASPR’s target is adequate, its ability to achieve this target is limited, because ASPR has not followed a third key strategic workforce planning principle: developing strategies to fill identified gaps in these skills. These key principles are described below, along with an assessment of ASPR’s efforts.

Table 2. ASPR’s workforce target, by National Disaster Medical System team type

Team type	Number of teams as of June 2018	Number of responders ASPR would like, per team	Workforce target = number of teams x number of responders per team
Disaster Medical Assistance Team	57	85	4,845
Trauma and Critical Care Team	3	118	354
Disaster Mortuary Operational Response Team	10	86	860
Victim Identification Team	1	52	52
National Veterinary Response Team	1	179	179
Total			6,290

Source: GAO summary of documentation collected from the Office of the Assistance Secretary for Preparedness and Response (ASPR). | GAO-20-525.

Alignment between ASPR’s NDMS Workforce Target and APSR’s Agency-Wide Goals And Objectives Has Been Limited

According to key principles of effective workforce planning, the process begins with an agency setting a strategic direction and aligning its workforce requirements with agency-wide goals and objectives. However, we found that the extent to which ASPR aligned its NDMS workforce target with APSR’s agency-wide goals and objectives has been limited, because the agency has not had a strategic plan with specific objectives since 2016. According to agency officials, the prior strategic plan expired while the agency was under an acting Secretary, and development of a new strategic plan led by the current Assistant Secretary for Preparedness and Response, who began his role in August 2017, has been delayed due to events, such as the 2017 hurricanes. Agency officials told us that they had planned to release a strategic plan in April 2020, but at the time this report was being prepared to be published, ASPR’s strategic plan had not yet been released.

In lieu of a strategic plan, ASPR officials told us that they aligned the NDMS workforce target with four broad guiding priorities published on ASPR’s website: (1) providing strong leadership, (2) building a regional disaster health response system, (3) sustaining public health security capacity, and (4) enhancing the medical countermeasure enterprise.¹⁶ However, officials provided conflicting information regarding where NDMS responders fit within ASPR’s four priorities. When we asked program officials who oversee NDMS where the program falls within these priorities, these officials told us that NDMS was associated with priority 1 – providing strong leadership, and indirectly related to priority 2 – building a

¹⁶ ASPR, *ASPR Mission and Priorities*, accessed April 24, 2020, <https://www.phe.gov/about/aspr/Pages/About-ASPR.aspx>.

regional disaster health response system. ASPR officials in the Office of Strategy, Policy, Planning and Requirements told us that NDMS falls under priority 2. ASPR officials told us that this misalignment occurred because leadership developing the agency-wide strategic plan had not informed the NDMS program officials of where NDMS fell within the priorities.

In March 2020, ASPR officials provided us with a draft version of the agency's forthcoming strategic plan. In this draft plan, ASPR lists the following four priority goals, which are similar to those the agency has been operating under, albeit in a different order: (1) foster strong leadership, (2) sustain a robust and resilient public health security capacity, (3) advance an innovative medical countermeasure enterprise, and (4) build a regional disaster health response system. From reviewing this plan, it is clear that NDMS falls within priority 4 – building a regional disaster health response system, as one of the objectives is “modernize NDMS.” However, NDMS also falls within an objective under priority 2, “strength response and recovery operations,” as well as an objective under priority 1, “lead adaptive planning and emergency repatriation efforts.” In finalizing this strategic plan, aligning the NDMS workforce target with ASPR goals and objectives would help ensure mission clarity and accountability. Without such an NDMS workforce target, ASPR risks being unable to fulfill its role as the lead agency for public health emergencies, which includes the ability to sufficiently enhance medical surge capacity during a response.

ASPR's NDMS Workforce Target Did Not Adequately Identify Critical Skills and Competencies Needed to Meet Current and Future Programmatic Results

According to key principles of effective workforce planning, an agency should identify the critical skills and competencies needed of its workforce that will position it to meet current and future programmatic results. The NDMS team structures that ASPR developed in March 2018 broadly cover emergency response needs for medical and public health care by including position types and number of responders needed in each position.

However, ASPR's process for calculating its responder workforce target did not take into consideration three key workforce factors: specifically, a workforce capable of responding to (1) a nationwide event or multiple concurrent events, (2) the needs of at-risk individuals, and (3) the availability of other medical responders, all of which would help determine the NDMS workforce skills and competencies needed to meet current and future programmatic results.

- *Number of responders needed for a nationwide event or multiple concurrent events.* ASPR did not consider the number of responders projected to be needed to respond to multiple or concurrent events, such as the 2017 hurricanes, or a national event, such as an infectious disease outbreak, when developing the NDMS workforce target. This is notable given that during the 2017 hurricane season, we found that ASPR experienced a shortage of NDMS responders, which contributed to a reliance on the Department of Defense to provide essential public health and medical service functions.¹⁷ We reported that during such situations, the Department of Defense may be responding to other events and its capacity to assist ASPR's response to a public

¹⁷ GAO-19-592.

health emergency may be limited. Therefore, we recommended that ASPR develop a strategy to demonstrate how the agency can provide a public health and medical services response if the Department of Defense's capacity to respond is limited. ASPR agreed with this recommendation but has not yet taken action to implement it. Further, according to the National Response Framework, the unprecedented scale of recent disasters highlights the need for further progress to build resilient capabilities to respond to disasters of increasing frequency and magnitude.¹⁸ For example, at the time of this report, HHS is responding to the COVID-19 pandemic nationwide and the National Oceanic and Atmospheric Administration has predicted that the 2020 Atlantic hurricane season will be more active than usual.¹⁹

- *Types of responders needed to care for at-risk individuals.* ASPR did not consider the responder types needed to care for at-risk individuals, such as children, the elderly, pregnant women, or individuals with chronic health conditions when developing the workforce target.²⁰ ASPR officials stated that this is not needed because NDMS responders provide medical stabilization to patients and move the patients to another facility for care, if required.²¹ However, the agency's fiscal year 2020 budget justification stated that ASPR had identified existing shortfalls in pediatric care during disasters, including trauma and critical care provided by NDMS. Our prior work in this area also showed that at-risk individuals were a key population requiring medical care during the 2017 hurricanes.²² Further, ASPR is required to take steps to ensure that NDMS includes an appropriate specialized and focused range of responder capabilities, which take into account the needs of at-risk individuals during a public health emergency.²³
- *Number of U.S. Public Health Service Commissioned Corps officers available to provide medical and public health care.* ASPR did not consider the U.S. Public Health Service Commissioned Corps officers or their capabilities when developing the NDMS workforce target, although these officers are available to assist with emergencies and disasters.²⁴ As a result, ASPR's NDMS workforce target may be too high or low (or targeting the wrong positions), depending on the number and type of officers able to provide medical and public health care. While commenting on a draft of this report, ASPR officials stated that Commissioned Corps officers primarily

¹⁸ Department of Homeland Security, *National Response Framework*, Fourth Edition (Washington, D.C.: Oct. 28, 2019).

¹⁹ National Oceanic and Atmospheric Administration, *Busy Atlantic hurricane season predicted for 2020*, accessed May 21, 2020, <https://www.noaa.gov/media-release/busy-atlantic-hurricane-season-predicted-for-2020>.

²⁰ Under 42 U.S.C. § 300hh-1(b)(4)(B), "the term 'at-risk individual' means children, pregnant women, senior citizens, and other individuals who have access or functional needs in the event of a public health emergency, as determined by the Secretary [of Health and Human Services]." The Secretary includes individuals with communication, chronic health, and behavioral health needs, among others, in the definition of at-risk individuals during an emergency or disaster.

²¹ While not specific to the workforce target, ASPR officials stated that they have in the last year given consideration to at-risk populations by, for example, working with organizations that take care of these populations, using subject matter experts for training on Acute Respiratory Infections in these population, and specific to children, working with the International Pediatric Association.

²² See GAO-19-592 and GAO, *Disaster Assistance: FEMA Action Needed to Better Support Individuals Who Are Older or Have Disabilities*, GAO-19-318 (Washington, D.C.: May 14, 2019).

²³ See 42 U.S.C. § 300hh-11(a)(3)(C).

²⁴ See Appendix I for more information on the U.S. Public Health Service Commissioned Corps officers available to assist during a federal emergency or disaster.

serve in administrative roles when deployed or, at best, support basic medical care. However, in recent years, Commissioned Corps officers have played an important response role. For example, the U.S. Public Health Service Commissioned Corps provided assistance during the 2017 hurricanes public health and medical services response by providing support such as managing evacuated patients. Additionally, during the ongoing COVID-19 pandemic, the Assistant Secretary for Preparedness and Response stated that the U.S. Public Health Service Commissioned Corps has been an important asset during the response.²⁵ According to U.S. Public Health Service officials, Commissioned Corps officers have assisted with the return of American citizens from China and Japan, airport screenings to monitor the health of travelers, and providing clinical care surge capacity in nursing facilities and field hospitals, among other COVID-19 response activities. Further, ASPR officials told us they may rely on the U.S. Public Health Service Commissioned Corps' mental health team for the care of individuals with behavioral and mental health needs during a response, making it all the more important that they consider their capabilities.

Regarding the U.S. Public Health Service Commissioned Corps and its relationship to the NDMS workforce target, ASPR officials originally stated that the agency does not have assurance that U.S. Public Health Service Commissioned Corps officers will be able to deploy quickly. As we described in the above paragraph, ASPR officials later commented that Commissioned Corps officers mostly support administrative requirements. With respect to the other critical workforce factors we identified, ASPR officials acknowledged that the agency did not consider these factors when developing the NDMS workforce target, and officials could not provide detailed information as to why they were not considered. For example, beyond building in redundancy to allow for responder availability (e.g., a Disaster Medical Assistance Team deploys with 35 responders, so each team is assigned 85 positions), officials could not tell us how they reached the number of positions for each type of team. Officials stated that to develop the NDMS team structures in the spring of 2018, they used Concept of Operations for each NDMS team type, as well as the Federal Emergency Management Agency's pre-scripted mission assignments, but did not provide further detail on how they used these documents.²⁶ Our analysis of these documents found that the documents do not align, so it is unclear how they were considered or used to develop ASPR's NDMS workforce target. For example, the pre-scripted mission assignments referred to team names and team sizes that were not included in the Disaster Medical Assistance Team concept of operations, and vice versa.

²⁵ CQ Congressional Transcripts, *House Oversight and Reform Committee Holds Hearing on Coronavirus Preparedness and Response, Part 2*, accessed March 31, 2020, <https://plus.cq.com/doc/congressional-transcripts-5859788?2>.

²⁶ The Concept of Operations addresses the mission and role of each NDMS team, deployment configurations, the team structure, requirements for team employees, operations during steady states and active states, and expectations of a deployment environment. According to Federal Emergency Management Agency officials, pre-scripted mission assignments are created prior to an incident to expedite the processing of a mission assignment once it is required. These mission assignments are created for capabilities that involve known or frequently used resources for services, such as logistics, communications, health care, and public safety. The National Response Framework establishes a response structure to coordinate federal resources during emergencies and disasters. Department of Homeland Security, *National Response Framework, Fourth Edition* (Washington, D.C., October 2019).

Nevertheless, the draft version of the agency's forthcoming strategic plan we received in March 2020, identifies the aforementioned workforce factors as important for future consideration. For example, it states that the agency plans to review the NDMS program to identify gaps in specialty care skills, capacity, training, and readiness to respond to multiple, simultaneous events, and national-level public health emergencies. The draft plan also states that medical surge capacity may be further supported through improved alignment across multiple groups of health care professionals, including the U.S. Public Health Service Commissioned Corps. While the draft strategic plan does not mention the development of a revised NDMS workforce target, ASPR's acknowledgement that these are important factors to consider is an important step forward. However, ASPR still needs to finalize its strategic plan, take specific actions to implement its plans to review these three key factors, and then adjust its workforce target accordingly.

ASPR Has Not Developed Strategies to Fill Identified Gaps in Critical Skills to Achieve an NDMS Workforce Target

Without an NDMS workforce target that considers the critical skills and competencies that are needed to meet current and future programmatic results—such as a workforce capable of responding to (1) a nationwide event or multiple concurrent events, (2) the needs of at-risk individuals, and (3) the availability of other medical responders—ASPR risks having an NDMS responder workforce target that is inadequate. For example, one that is too low, is redundant of other responders and therefore could be too high, or has gaps, such as a workforce that is unable to effectively care for all individuals affected by a public health emergency, as occurred during ASPR's response to the 2017 hurricanes.

According to key principles of effective workforce planning, once an agency has identified the critical skills and competencies needed of its workforce, the agency should then develop strategies to address gaps in the number, skills, and competencies of its workforce. Although we believe ASPR still needs to adequately identify the critical skills and competencies needed and related gaps of its NDMS workforce, the agency is operating under a current NDMS workforce target of 6,290.

However, as of December 2019, ASPR was not close to this target—having 3,667 responders enrolled in NDMS—and we found the agency has not developed specific strategies to drive hiring and fill its NDMS workforce gaps to reach its target.

ASPR officials told us that their hiring plan consisted of prioritizing NDMS job postings by posting those of high-priority first rather than posting them all at once. ASPR officials also stated they planned to implement a direct-hire authority, enacted in February 2018, by hiring as many NDMS responders as possible to meet the NDMS workforce target.²⁷ According to

²⁷ ASPR has received two direct-hire authorities for NDMS. The first was enacted as part of the Bipartisan Budget Act of 2018, and ran from February 9, 2018 to November 5, 2018. Pub. L. No. 115-123, § 20803, 132 Stat. 64, 95. The second was enacted as part of the Pandemic and All-Hazards Preparedness and Advancing Innovation Act of 2019 and runs from June 24, 2019 to September 30, 2021. Pub. L. No. 116-22, § 301(a)(3), 133 Stat. 905, 932 (codified at 42 U.S.C. § 300hh-11(c)(4)).

the Office of Personnel Management's website, the purpose of a direct-hire authority is to expedite hiring by eliminating some of the steps required for federal hiring.²⁸

We found that there have been no other strategies or specific intermediate goals for hiring and filling gaps to achieve its current NDMS workforce target. For example, intermediate goals could include milestones detailing the number of responders the agency aims to hire per month, taking into account any hiring resource constraints in order to establish a realistic timeline for completing all hiring, as well as establish an indicator by which they can measure progress. The lack of more detailed strategies may have contributed to the slow hiring that ASPR is currently facing. For example, as of March 2020, some NDMS responders were still going through the hiring process more than 16 months after they received offers from job postings made under the direct-hire authority.

Neither ASPR officials nor officials from HHS's Staffing Recruitment Operations Center (the agency within HHS that conducts all hiring actions on behalf of ASPR) could tell us when hiring will be completed.²⁹ Further, when asked about a plan or strategy to drive hiring under a second direct-hire authority enacted in June 2019, ASPR officials stated that they had started a draft plan. However, they put a hold on further plan development until the hiring under the first direct-hire authority is completed. As of March 18, 2020, 163 of the 1,447 individuals who accepted job offers under this first direct-hire authority are still in the process of being hired, according to ASPR officials.

Further, we found that ASPR is using a 2-year term appointment to hire all of the 1,447 responders under the first direct-hire authority. Because of this decision, Staffing Recruitment Operations Center officials told us that these responders will further burden hiring efforts because they will need to undergo an additional human resources action 2 years after they are hired to renew their appointment for an additional 2-year term. According to the job posting, the term appointment lasts for 2 years and may be extended for another 2 years, for a total of 4 years. If ASPR still has a need for these responders, they will have to rehire for these positions after 4 years. If hired under an indefinite term appointment, as was previously used to hire NDMS responders, this would have allowed these responders to serve for an indefinite amount of time. While officials stated that they will use an indefinite term position for hires under the second direct-hire authority, neither Staffing Recruitment Operations Center nor ASPR officials could tell us how they made the decision to use a 2-year term appointment for the first direct-hire authority. Officials from both agencies stated that the decision came from the other agency, further exemplifying a lack of strategies.

²⁸ Office of Personnel Management, *Hiring Information Direct Hire Authority Fact Sheet*, accessed April 3, 2020, <https://www.opm.gov/policy-data-oversight/hiring-information/direct-hire-authority/#url=Fact-Sheet>.

²⁹ Staffing Recruitment Operations Center officials stated that the center is one of nine human resource centers within HHS, which provides human resources services to HHS agencies that do not have a human resource center, including ASPR.

ASPR DOES NOT HAVE ASSURANCES IT IS EFFECTIVELY TRAINING RESPONDERS

ASPR Requires Web- Based Training and Also Offers In-Person Training, Which It Considers Most Beneficial, but Also More Costly to Provide

In the draft strategic plan provided to us, ASPR states that the agency wants to develop and launch a program to actively recruit medical professionals into NDMS, though there are no specifics included in the plan on how this will be achieved. It will be important for ASPR to develop specific plans. Without strategies to fill gaps to achieve an NDMS workforce target, ASPR continues to risk being unable to provide adequate numbers and types of NDMS responders to effectively respond to public health emergencies. It also risks not being able to take full advantage of the direct-hire authority that expires in September 2021.

ASPR requires NDMS responders to take introductory web-based training courses to be eligible for deployment. It also offers in-person training, which ASPR officials state is most beneficial for deployment preparedness but also more costly to provide. However, the agency does not sufficiently evaluate the quality or effectiveness of its training in preparing responders. Further, ASPR does not have a process or approach for establishing priorities among its in-person training courses.

ASPR requires NDMS responders to take introductory web-based training courses to be eligible for deployment. Specifically, ASPR requires responders to complete seven web-based training courses that are specific to preparedness to be eligible for deployment.³⁰ Many of these courses are required once in an NDMS responder's career. ASPR officials stated that these mandatory courses are intended to be a simple introduction to the topic areas, and the web-based aspect allows them to require these courses without incurring a large cost to the agency.

In recent years, ASPR has increased the number of mandatory courses specific to preparedness. For example, in fiscal year 2019, ASPR added five web-based video courses, many of which ASPR added per an identified need for more training specific to an infectious disease response, according to officials. In addition, based on a draft catalog of NDMS training courses for fiscal years 2020-2024, the agency plans to add an additional five courses, many of which are web-based courses provided by the Federal Emergency Management Agency, but as of March 2020, ASPR officials did not know when they would implement this training. See Table 3 for a description of the seven preparedness-related mandatory training courses, as well as the additional five that ASPR plans to add, including the frequency they are required to be taken.

In addition to the required web-based courses, ASPR also provides in- person training courses. ASPR officials told us that the agency's in- person training courses are the most beneficial, but they cannot require or offer as many in-person training courses as they would

³⁰ In addition to these seven, NDMS responders must also take five other mandatory courses that are general courses required by HHS: 1) Cybersecurity Training, 2) Ethics for Special Government Employees, 3) Ethics for OGE-450 Filers, 4) HHS Travel Charge Card, and 5) Sexual Harassment Prevention for Employees. Additionally, certain NDMS responders involved in patient movement must take a just-in-time refresher course on HHS's Joint Patient Assessment and Tracking System—a patient evacuation tracking system—as needed.

like, due to budget constraints and the cost of in-person courses relative to the web-based mandatory courses. Officials stated that in-person courses are most beneficial since they are more detailed than web-based courses and allow responders to more fully understand topics important for deployment. For example, ASPR brings responders together to be taught by a live instructor, and in some courses, practice using response equipment. Further, some of the courses are exercise-based so responders can practice their role in a simulated real-world scenario.

However, these courses are more expensive to offer. ASPR officials explained, for example, that for in-person training, ASPR compensates the instructors and responders for the time they are participating in the training, as well as pays the travel costs of the responders to the training site, such as flights and hotel costs. See appendix III for the 22 NDMS in-person training courses and their description, as well as those offered in fiscal year 2019.

ASPR Does Not Sufficiently Evaluate Its Training's Effectiveness in Preparing Responders

Our review of ASPR documentation shows that in fiscal year 2019, ASPR provided at least one offering of 14 of the 22 in-person training courses listed in its training catalog. For example, in fiscal year 2019, ASPR offered six Disaster Medical Assistance Team 101 trainings, each designed to provide up to 42 responders hands-on experience for delivering care to a diverse group of patients in a severe environment, including the appropriate use of equipment and supplies, among other topics. ASPR also offered 20 Isolation, Simulation, Quarantine trainings, each designed to teach up to 20 responders how to safely care for patients with highly hazardous communicable diseases in both health care and more austere environments, implement controls to curb the spread of disease, and contain accidental exposure to contamination, among other topics.

We found that ASPR does not sufficiently evaluate the quality or effectiveness of its training in preparing NDMS responders. This is because the agency lacks a process focused on evaluating both its web-based and in-person training. Instead, ASPR's process is to send an email with a link to a survey to responders who participate in the in-person training or those who deploy to real-world events, which would include those who received the required web-based training. The survey is optional (See Table 4 for the four standard questions).

However, the survey does not directly ask about the quality or effectiveness of the training. This approach is inconsistent with GAO-identified key practices for evaluating training, which include using measures of (1) training participants' reaction to, and satisfaction with, the training program and (2) changes in participants' knowledge, skills, abilities, and on-the-job behavior.³¹

³¹ GAO-04-546G.

Table 3. National Disaster Medical System (NDMS) preparedness-related mandatory training web-based courses

Training course	Fiscal year added	Course description	Frequency of required course completion
Psychological First Aid Training	2017	Introduces the concepts of Psychological First Aid and workforce resilience and prepares personnel to provide compassionate care and emotional support during emergencies and disasters.	Every 3 years
Safety 101 Training	2018	Provides initial safety training generally applicable to all responders to meet Department of Labor Occupational Safety and Health Administration requirements and enhance deployment safety.	Once in a responder's career
Pathogens of Concern	2019	Provides NDMS responders information about the characteristics of infectious diseases, specific pathogens and the diseases they cause, as well as how to recognize the signs and symptoms of disease to determine appropriate protection measures.	Once in a responder's career
Personal Protective Equipment Donning and Doffing	2019	Introduces the process of safely donning and doffing level C personal protective equipment providing chemical and biological protections to minimize exposure to hazards while providing care and support during disasters and public health emergencies. ^a	Once in a responder's career
Personal Protective Equipment Selection, Regulations, and Limitations	2019	Trains responders to identify and utilize different types of personal protective equipment and respirators while following federal regulations, as well as how to recognize possible limitations of use.	Once in a responder's career
Strategic National Stockpile Overview	2019	Provides a look at available resources, supplies, and equipment for emergency logistics and planning purposes.	Once in a responder's career
Weapons of Mass Destruction/Terrorism Awareness for Emergency Responders	2019	Provides an all-hazards approach to hazardous material incidents, including acts of terrorism where weapons of mass destruction materials may have been used.	Once in a responder's career
Bloodborne Pathogens Training	Planned	Provides training on bloodborne pathogen incidents in the workplace consistent with Occupational Safety and Health Administration regulation 29 C.F.R. § 1910.1030.	Annually
Federal Emergency Management Agency Introduction to the Incident Command System	Planned	Describes the history, features, principles, and organizational structure of the Incident Command System and provides the foundation for higher level Incident Command System training. ^b	Once in a responder's career
Federal Emergency Management Agency Incident Command System for Single Resources and Initial Action Incidents	Planned	Reviews the Incident Command System, provides the context for Incident Command System within initial response, and supports higher level Incident Command System training.	Once in a responder's career
Federal Emergency Management Agency National Incident Management System, An Introduction to the National Incident Management System	Planned	Provides learners with a basic understanding of the National Incident Management System concepts, principles, and components. ^c	Once in a responder's career
Federal Emergency Management Agency National Response Framework, An Introduction	Planned	Introduces participants to the concepts and principles of the National Response Framework, and its application in actual response situations. ^d	Once in a responder's career

Source: GAO summary of Office of the Assistant Secretary for Preparedness and Response's NDMS training documentation. | GAO-20-525.

Notes: ^aLevel C protection is used when the type and concentration of an airborne substance is known, the criteria for using air-purifying respirators has been met, and skin and eye exposure is unlikely. ^bThe Incident Command System is the organizational management system designed to enable effective and efficient domestic incident management by integrating a combination of facilities, equipment, personnel, procedures, and communications operating within a common organizational structure. ^cThe National Incident Management System is the comprehensive approach guiding the whole community—all levels of government, nongovernmental organizations, and the private sector—to work together seamlessly to prevent, protect against, mitigate, respond to, and recover from the effects of incidents. ^dThe National Response Framework is an all-hazards response structure to coordinate federal resources during emergencies and disasters. It divides the federal response into 15 emergency support functional areas that are most frequently needed during a national response.

According to ASPR officials, although the survey is not specific to training, ASPR still receives feedback about the training courses through that survey, so they do not feel that they are missing any information from using this format to evaluate training. However, reliance on this process does not allow ASPR to understand training participants’ reaction to, and satisfaction with, the training, or whether responders’ knowledge, skills, and abilities or on-the-job behavior are affected if they deploy having received training. For example, it does not allow ASPR to understand whether the Disaster Medical Assistance Team 101 training course has an effect on responders’ ability to effectively provide care during a response. According to the NDMS training catalog, objectives of the Disaster Medical Assistance Team 101 course include that students have learned to use equipment and supplies in accordance with manufacturer instructions, and that those in clinical care positions have learned how to provide medical care to a diverse group of patients, including individuals with special health care needs, in a disaster setting. Effective evaluation questions could include those that specifically ask participants about these objectives and if they felt the objectives were met. For example,

- Did training participants feel that they sufficiently learned how to use the equipment and supplies in preparation for a real event?
- To what extent do training participants feel confident that they can apply the information they learned regarding use of equipment and supplies in a disaster setting, or teach it to others?

Table 4. Survey questions used to evaluate National Disaster Medical System in-person training

Survey question
1. Identify an issue or observation that requires corrective action(s). This should be a simple problem statement of 1 - 2 sentences in length.
2. Describe the issue or observation in detail. What was expected, but did or did not occur? Include the effect, positive or negative, and the consequence that actions had on the situation. Provide specific information that can be used for follow-up (dates, times, location, names, temporary fix, etc.).
3. What action(s) would you recommend to correct/resolve the issue or observation?
4. Submit positive feedback here.

Source: Office of the Assistant Secretary for Preparedness and Response National Disaster Medical System Responder Survey. | GAO-20-525.

Additionally, by relying on survey feedback once deployed to receive any information on the effectiveness of required web-based courses, ASPR does not know if they are effective until after the fact, which can potentially put responders and others at risk. For example, ASPR does not know if its required web-based course on donning and doffing personal protective equipment is effective until responders have deployed. At that point, if the training was not effective, the responder could have potentially exposed themselves and others to hazards, especially during a response to an infectious disease, chemical, or biological threat.

Our prior work has shown that a balanced, multilevel approach to evaluating training and development efforts is most appropriate, and that not all training and development programs

require, or are suitable for, higher levels of evaluation.¹ We acknowledge that higher levels of evaluation can be challenging to conduct because of the difficulty and costs associated with data collection and the complexity in directly linking training and development programs to improved individual and organizational performance. We have reported that factors to consider when deciding the appropriate level of evaluation include estimated costs of the training effort, size of the training audience, management interest, program visibility, and the anticipated “life span” of the effort. ASPR should consider these factors in developing a process that specifically evaluates the web-based and in-person training provided to NDMS responders. Using GAO-identified key practices for evaluating training could help ASPR know the extent to which its training is effective in preparing responders for deployment, including keeping them and others safe during a public health emergency. A process that specifically evaluates the training can also help determine whether the web-based or in-person training courses need to be improved, or whether any of the in-person training courses are so effective that they should be required.

ASPR Does Not Sufficiently Identify Priorities among Its In-Person Training Courses

Similarly, this information will allow ASPR to assess the relative effectiveness of in-person training courses, which is important when planning which of these training courses to offer each year.

We also found that ASPR does not sufficiently prioritize its in-person training. Specifically, ASPR has not sufficiently identified priorities among its in-person training courses that take into account its aforementioned resource constraints to provide this training, because the agency lacks a process or approach for prioritizing its training.

GAO-identified key practices for planning training state that an agency should prioritize training around funding so that the agency can address its most important training needs first.² Further, effective strategic workforce planning means that agency officials should develop training that they can implement with the resources that can be reasonably expected to be available, and be aligned to eliminate gaps and improve the contribution of critical skills and competencies needed for mission success.³

Because ASPR officials have no process or approach for prioritizing the in-person training, we found that ASPR officials could not provide information on how they chose the

¹ See GAO-04-546G. We reported that one commonly recognized four-level model for evaluating training and development efforts is a model conceived by Donald L. Kirkpatrick (author of *Evaluating Training Programs: The Four Levels*). In this model, the first level measures the training participants’ reaction to, and satisfaction with, the training program or planned actions to use new or enhanced competencies. The second level measures the extent to which learning has occurred because of the training effort. The third level measures the application of this learning to the work environment through changes in behavior that trainees exhibit on the job because of the training or development program. The fourth level measures the effect of the training program on the agency’s program or organizational results. The fourth level is sometimes split into two levels with the fifth level representing a comparison of costs and benefits quantified in dollars.

² A key tool to aid this prioritization is an annual training plan that targets developmental areas of greatest need and that outlines the most cost-effective training approaches to address those needs. We have also reported that if training is identified as a solution to improve performance, agencies should compare various training strategies by weighing their estimated costs and anticipated benefits. GAO-04-546G.

³ GAO-04-39.

14 in-person training courses the agency offered in fiscal year 2019, such as whether they prioritized any identified skill or competency gaps when selecting these courses. Further, ASPR officials could not provide documentation to support changes the agency made to training originally scheduled for fiscal year 2019. For example, ASPR documentation indicated that ASPR initially planned to offer an exercise-based Disaster Medical Assistance Team 201 course several times in fiscal year 2019 but did not end up offering the course at all. When asked about this change, ASPR officials attributed to its NDMS training budget. However, officials could not provide documentation showing that (1) their plans for the NDMS training the agency would offer in fiscal year 2019 had taken into account budget constraints, or (2) that the budget had changed subsequent to their plan development. As a result, it is difficult to know if the decision to drop the exercise-based Disaster Medical Assistance Team 201 course was due to budget constraints or due to poor planning, such as the agency not accounting for those constraints when originally determining which courses to offer.

CONCLUSION

A process or approach for identifying priorities among its in-person training courses while taking into account budget constraints, will help ASPR ensure that it is maximizing its available training resources, by providing the training responders need the most for effective deployment during a public health emergency.

The seriousness of recent natural disasters and the COVID-19 pandemic illustrate the importance of having a skilled workforce to respond to public health crises. However, our past work and current review of ASPR's workforce planning and training raise concerns about its efforts to prepare NDMS responders to assist during public health emergencies.

Specifically, ASPR experienced a shortage of NDMS responders to assist with the federal public health and medical response to the 2017 hurricanes. Since that time, the agency has not followed key strategic workforce planning principles to effectively address this response shortfall and prepare for future responses, including natural disasters of increased frequency and magnitude, which are predicted to occur. Until ASPR develops an NDMS workforce target that aligns with agency-wide goals and objectives, it risks being unable to fulfill its role as the lead agency for public health emergencies, which includes the ability to sufficiently enhance medical surge capacity during a response. In addition, until ASPR develops an NDMS workforce target that considers the critical skills and competencies needed to meet current and future programmatic results—such as a workforce capable of responding to (1) a nationwide event or multiple concurrent events, (2) the needs of at-risk individuals, and (3) the availability of other medical responders—ASPR risks having an NDMS responder workforce target that is inadequate.

Furthermore, ASPR has faced slow hiring and has not developed specific strategies to help drive hiring and address workforce gaps. Until ASPR develops strategies to fill gaps to achieve a workforce target, the agency continues to risk being unable to provide adequate numbers and types of NDMS responders to effectively respond to public health emergencies. It also risks not being able to take full advantage of the direct-hire authority that expires in September 2021 that is specifically designed to facilitate hiring.

Finally, ASPR does not have a process to collect information that would allow it to evaluate the effectiveness of the individual courses it offers in its training program nor a process to identify priorities among its in-person training courses. Such processes will help ASPR ensure that it is maximizing its available training resources to provide training most beneficial for effective deployment, including training to keep responders and others safe during a public health emergency.

RECOMMENDATIONS

We are making the following five recommendations to the Assistant Secretary for Preparedness and Response:

1. ASPR should develop an NDMS responder workforce target that aligns with the goals and objectives in ASPR's forthcoming strategic plan. (Recommendation 1)
2. ASPR should develop an NDMS responder workforce target that accounts for the critical skills and competencies that are needed to meet current and future programmatic results, such as a workforce target that considers (1) a nationwide event or multiple concurrent events, (2) the needs of at-risk individuals, and (3) the availability of other medical responders. (Recommendation 2)
3. ASPR should develop strategies to fill gaps to achieve its revised workforce target. (Recommendation 3)
4. ASPR should develop a process to evaluate the web-based and in-person training provided to NDMS responders using GAO-identified key practices for evaluating training. (Recommendation 4)
5. ASPR should develop a process or approach to prioritize various in-person training needs for its NDMS responders while taking into account budget constraints. (Recommendation 5)

AGENCY COMMENTS AND OUR EVALUATION

We provided a draft of this report for advance review and comment to HHS. HHS provided written comments, which we have reprinted in appendix IV. HHS concurred with our five recommendations and generally plans to take action.

Although HHS concurred with our five recommendations, the agency expressed concern about our references to the COVID-19 response in the draft report. Specifically, HHS noted that a pandemic response is outside the primary scope of NDMS—as its responders should be assisting the response through their civilian jobs, such as through working in hospitals—and for that reason COVID-19 pandemic planning did not include NDMS. While HHS states that it did not include NDMS in its COVID-19 planning, as we also state in our report, the agency has deployed more than 1,200 NDMS responders to assist in the COVID-19 response. Also in its comments, HHS stated that any assessment of NDMS in the ongoing response would be premature. Our review did not assess NDMS's response to COVID-19, rather we assessed

ASPR's workforce planning more generally for all-hazards events. We clarified this in the report.

HHS also commented on our concerns with HHS's evaluation of the training provided to NDMS responders. Specifically, the agency stated that we did not ground, in context or examples, our assertion that responders may be at risk since ASPR does not receive feedback on training until after deployment. We stand by our statement that there is the potential for this risk to occur given that HHS does not collect specific feedback on its trainings' quality or effectiveness and does not collect any feedback on mandatory training until after a responder has been deployed. As discussed in the report, an example is the mandatory web- based training on donning and doffing personal protective equipment.

ASPR does not know if this training course is effective until responders have deployed. At that point, if the training was not effective, responders could have potentially exposed themselves and others to hazards, especially during a response to an infectious disease, chemical, or biological threat.

HHS also provided technical comments, which we incorporated as appropriate.

Mary Denigan-Macauley
Director, Health Care

APPENDIX I: U.S. PUBLIC HEALTH SERVICE COMMISSIONED CORPS OFFICERS AND THE READY RESERVE CORPS

Current Number of Officers Who Provide Medical Care to Humans during a Response

The U.S. Public Health Service, an agency under the Department of Health and Human Services (HHS), comprises Commissioned Corps officers who are available to assist with emergencies and disasters.⁴ Commissioned Corps officers' duty stations are typically within the federal government, including agencies within HHS such as the Centers for Disease Control and Prevention, Food and Drug Administration, and National Institutes of Health, but these officers can be temporarily assigned to HHS's Office of the Assistant Secretary for Preparedness and Response to assist with a federal response.

There are a number of types of Commissioned Corps officers, including those who are deployed to provide medical care to humans during a response and fall within four professional categories—dental officer, health services officer, medical officer, and nurse officer.⁵ As of October 4, 2019, the U.S. Public Health Service had 2,127 of these types of officers available to assist with emergencies and disasters (See Table 5).

⁴ Commissioned Corps officers may be deployed to respond to an urgent or emergency public health care need arising from (1) a national emergency declared by the President under the National Emergencies Act; (2) an emergency or major disaster declared by the President under the Robert T. Stafford Disaster Relief and Emergency Assistance Act; (3) a public health emergency declared by the Secretary of Health and Human Services under the Public Health Service Act; or (4) any emergency that is appropriate for deployment, as determined by the Secretary of Health and Human Services. See 42 U.S.C. §§ 204a(a)(5) and 215(e).

⁵ There are 11 professional categories for Commissioned Corps officers: physicians, dentists, clinical and rehabilitation therapists, dietitians, engineers, environmental health, health service, nurses, pharmacists,

Table 5. U.S. Public Health Service Commissioned Corp Officers available to provide medical care to humans during a response, by provider type

Professional category	Number of responders	Percent of total number of responders
Dental officer	141	6.6
Health Services officer	156	7.3
Medical officer	460	21.6
Nurse officer	1,370	64.4
Total	2,127	99.9 ^a

Source: GAO analysis of U.S. Public Health Service data as of Oct. 4, 2019. | GAO-20-525.

Note: ^aThe total percentage does not sum to 100 due to rounding.

Table 6. U.S. Public Health Service Commissioned Corps Officers available to provide medical care to humans during a response, by deployment team

Team name	Team description	Number of officers available to provide medical care to humans
Rapid Deployment Force	Health and medical services to support a Federal Medical Station. ^a	300
Capital Area Provider	Health and medical services to support national special security events in the national capital region.	96
Mental Health	Behavioral health services for impacted citizens and deployment teams.	29
Applied Public Health	Public health services to augment state and local public health departments.	39
Regional Incident Support	Incident support services focused on liaison and information management.	45
National Incident Support	Incident support services focused on assisting command and control.	16
Services Access	Assist impacted citizens and federal partners with access to follow-on services. ^b	63
Tier 3	Augment any of the above teams once deployed.	1,539
Total		2,127

Source: GAO analysis of U.S. Public Health Service data as of Oct. 4, 2019. | GAO-20-525.

Notes: ^aA Federal Medical Station is a Health and Human Services deployable health care facility that has a 3-day supply of medical and pharmaceutical resources to sustain from 50 to 250 patients who require medical services.

^bFollow-on services can range from providing support to health care institutions on the discharge planning process to connecting individuals affected by a disaster or emergency to services such as housing or home health care.

These officers are assigned to deployment teams that provide both direct and indirect health care services to humans. The deployment teams provide support ranging from providing medical services to connecting affected individuals with community services, such as home health care. See Table 6 for the number of U.S. Public Health Service Commission Corps officers available to provide medical care to humans during a response, by deployment team.

science and research health professions, and veterinary medicine. As of September 9, 2019, these officers totaled to approximately 6,200 Commissioned Corps. According to Public Health Service officials, as of March 2020, ASPR had only requested four of these 11 professional categories to help provide medical care to humans during a response to a disaster or emergency—dental, health services, medical, and nurse officers. Medical officers are physicians. Health services officers include allied clinical care providers, such as physician assistants and optometrists, and those that serve in other roles, such as health information managers and public health educators and administrators.

PLANS FOR A READY RESERVE CORPS

To augment capacity, the U.S. Public Health Service is in the process of implementing a Ready Reserve Corps, but plans are still in development.⁶ The Ready Reserve Corps would consist of intermittent employees who could be called up as needed. Implementing a Ready Reserve is part of a broader plan to modernize the U.S. Public Health Service Commissioned Corps announced by the Assistant Secretary for Health in March 2018. A contractor hired to assist with the modernization effort assessed the agency and concluded in April 2019 that, among other things, establishing a Ready Reserve Corps will give the U.S. Public Health Service Commissioned Corps the needed bandwidth to meet demand for its services. The contractor stated that the demand for services is likely to increase in the future based on multiple demand signals (e.g., natural disasters, biological pathogens, the opioid epidemic and suicide clusters, and international and immigrant-related situations).

In September 2019, the U.S. Public Health Service tasked the contractor with developing a plan by June 10, 2020, to establish the Ready Reserve Corps, including an organization infrastructure design plan and recruitment strategy. It also included the development of a training plan applicable to Commissioned Corps Officers.

U.S. Public Health Service officials we spoke with agreed that the introduction of a Ready Reserve Corps would dramatically help their ability and capacity to respond to emergencies and disasters, especially given the rise in demand on the agency. According to these officials, the number of U.S. Public Health Service Commissioned Corps deployments has increased 44 percent over 6 years—from calendar year 2013-2018—and officials expect demand to continue to grow. Ready Reserve Corps officers would be deployed or backfill positions of deployed U.S. Public Health Service Commissioned Corps officers.

U.S. Public Health Service officials stated that there is a target of commissioning 100 Ready Reserve Corps officers in fiscal year 2021, which was set based upon fiscal constraints and force management planning factors. According to officials, since the vast majority of the work in the first year of establishing a Ready Reserves Corps will be dedicated to establishing the policies, procedures, information technology, and management infrastructure necessary to recruit, organize, train, and manage a ready reserve component, a conservative target was deemed most prudent. Officials stated that 50 percent of their goal of 100 Ready Reserve Corps officers will be targeted toward retaining already trained officers with significant clinical experience who otherwise would separate completely from the service.

⁶ The Ready Reserve Corps was established in 2010 by the Patient Protection and Affordable Care Act to have additional personnel available to assist the U.S. Public Health Service Commissioned Corps with routine and emergency missions. Pub. L. No. 111-148, § 5210, 124 Stat. 119, 614-15 (2010) (codified as amended at 42 U.S.C. § 204). The CARES Act amends federal law to allow members of the Ready Reserve Corps to receive certain compensation and benefits for their service. See Pub. L. No. 116-136, § 3214(d) 134 Stat. 281, 373 (2020) (to be codified at 42 U.S.C. § 213a).

APPENDIX II: NATIONAL DISASTER MEDICAL SYSTEM TEAM STRUCTURES

The Office of the Assistant Secretary for Preparedness and Response (ASPR) enrolls responders into its National Disaster Medical System (NDMS). Once enrolled, ASPR can deploy these responders to assist with the federal public health and medical response during a public health emergency. There are five types of NDMS responder teams. Two of these types,

Table 7. Team structures for each national disaster medical system team

Position description	Disaster Medical Assistance Team	Disaster Mortuary Operational Response Team	National Veterinary Response Team	Trauma and Critical Care Team	Victim Identification Team
Administrative Specialist	2	2	3	2	2
Animal Health Technician	-	-	100	-	-
Behavioral Health Specialist	2	-	-	2	2
Chaplain	-	2	-	-	-
Dental Assistant (Forensic)	-	3	-	-	-
Dental Officer (Forensic)	-	11	-	-	2
Deputy Team Commander	3	2	3	3	2
Diagnostic Radiologic Technologist	-	4	-	3	-
Fingerprint Specialist	-	2	-	-	-
Forensic Anthropologist	-	4	-	-	-
Health (Autopsy Assistant)	-	2	-	-	-
Health Technician (Paramedic)	15	-	-	8	-
Information Technology Specialist	2	-	-	3	-
Logistics Management Specialist	5	2	3	6	2
Medical Investigator	-	21	-	-	-
Mortuary Specialist	-	18	-	-	-
Nurse Anesthetist	-	-	-	8	-
Nurse Practitioner	6	-	-	5	-
Nurse Specialist (Registered Nurse)	21	-	-	33	-
Pharmacist	6	-	3	4	-
Physician	10	-	-	23	-
Physician (Pathology)	-	6	-	-	-
Physician Assistant	6	-	-	5	-
Respiratory Therapist	2	-	-	5	-
Safety and Occupational Health Specialist	2	2	3	2	-
Security Specialist	-	2	-	-	-
Surgical Technologist	-	-	-	2	-
Team Commander	1	1	1	1	-
Telecommunications Specialist	2	2	3	3	-
Veterinary Medical Officer	-	-	60	-	-
Victim Advocate	-	-	-	-	-
Total	85	86	179	118	-

Legend: — = not applicable.

Source: GAO summary of documentation collected from the Office of the Assistant Secretary for Preparedness and Response. | GAO-20-525.

the Disaster Medical Assistance Team and the Trauma and Critical Care Team, focus on providing public health and medical care to humans during a response. The National Veterinary Response Team provides veterinary care, while the Victim Identification Team and Disaster Mortuary Operational Response Team collect information on victims and support local mortuary services during a response, respectively. In March 2018, ASPR developed team structures for each NDMS team type, which include position types and numbers of responders in each position. See Table 7 for the team structures of each of the five types of NDMS teams.

**APPENDIX III: NATIONAL DISASTER MEDICAL SYSTEM OPTIONAL
TRAINING COURSES FOR RESPONDERS**

The Office of the Assistant Secretary for Preparedness and Response (ASPR) enrolls responders into the National Disaster Medical System (NDMS). Once enrolled, ASPR can deploy these responders to provide medical care, evacuate patients, and provide veterinary services, among other supports.⁷ To prepare these responders for deployment, ASPR offers optional, in-person training throughout the year. This training may be applicable to all responders, or specific to responders on certain of the five types of NDMS teams. Table 8 summarizes the 22 optional training courses that may be available to NDMS responders, though not all courses are available each year.

**Table 8. Optional training courses for National Disaster
Medical System (NDMS) responders**

Course name	Course description	Course capacity (max participants per course offering)	Number of course offerings in fiscal year 2019
Aeromedical Evacuation Team	Develop the skills required of NDMS responders as members of an aeromedical evacuation team expected to deliver care in flight.	25	10
Aeromedical Evacuation Team Critical Care	Develop the skills required of NDMS responders on an aeromedical evacuation critical care team who are expected to deliver critical care in flight.	18	5
Critical Care Air Transport Team Advanced	Develop skills related to the clinical care of the critically ill and injured patients in flight.	18	1
Critical Care Air Transport Team Initial	Teach and test operational concepts, flight and altitude physiology, and critical care knowledge as it applies to air and ground transport of a critically ill or injured patient.	18	7

⁷ Under 42 U.S.C. § 300hh-11, NDMS may be activated to provide health services, health- related social services, other appropriate human services, and appropriate auxiliary services to respond to the needs of victims of a public health emergency. ASPR may also activate NDMS in a location that is at-risk of an emergency.

Course name	Course description	Course capacity (max participants per course offering)	Number of course offerings in fiscal year 2019
Disaster Medical Assistance Team 101	Develop and improve upon the skills required of NDMS Disaster Medical Assistance Team responders to deliver care in a severe environment and familiarize new or not recently deployed personnel on general principles of NDMS deployments.	42	6
Disaster Medical Assistance Team 201 Exercise	Prepare NDMS Disaster Medical Assistance Teams for short-notice disaster relief deployments. The training involves the reporting, mobilization, and demobilization activities that would occur during an actual deployment.	No course capacity maximum indicated	0
Disaster Mortuary Operational Response Teams 101	Allow mortuary specialists—one of the positions on the NDMS Disaster Mortuary Operational Response Teams who identify victims and support local mortuary services—to prepare, train, and enhance the processes, procedures, and practices used during Disaster Mortuary Operational Response Team missions.	100	0
Disaster Mortuary Operational Response Teams 201	Prepare NDMS Disaster Mortuary Operational Response Teams for short-notice disaster relief deployments. The training involves the reporting, mobilization, and demobilization activities that would occur during an actual deployment.	80	
Electronic Medical Records	Update the knowledge, skills, and response capabilities of emergency medical records users in the revised deployment and utilization of the new emergency medical records software.	36	
Highly Infectious Disease Patient Transport	Address the transportation of highly infectious patients to appropriate facilities such as assessment or isolation centers.	No course capacity maximum indicated	
Isolation, Simulation, Quarantine	Provide the knowledge, skills, and abilities to ensure that competencies in the areas of situational awareness, preparedness and planning, infection prevention and control, and crisis and risk communication are met.	20	
Joint Patient Assessment and Tracking System	Improve the knowledge, skills, and response capabilities of responders in the deployment and utilization of the Joint Patient Assessment and Tracking System (a patient evacuation tracking system) software.	36	
Joint Patient Assessment and Tracking System Exercise: Supporting Department of Defense and Veterans Affairs Federal Coordinating Center	Support Federal Coordinating Center exercises conducted by the Departments of Defense and Veterans Affairs with a two-person Joint Patient Assessment and Tracking System Team. ^a These exercises are controlled and scenario-driven trainings for federal responders.	2	

Table 8. (Continued)

Course name	Course description	Course capacity (max participants per course offering)	Number of course offerings in fiscal year 2019
Regional Equipment Familiarization	Prepare responders enrolled in NDMS Disaster Medical Assistance Teams for the challenges of disaster care by supporting familiarization with field equipment.	40	Regional Equipment Familiarization
Logistics Specialist 101	Utilize a combination of classroom and hands-on training to familiarize logistical personnel with equipment used during actual deployments.	50	
NDMS/Department of Defense Outbreak Response Course	Prepare responders to support operations that may involve infectious diseases with high infectivity, morbidity, and mortality.	12	
National Veterinary Response Team Working Animal	Prepare NDMS National Veterinary Response Team responders to properly handle and provide medical support to working animals used in post-disaster environment, public health emergency, or planned national security event.	55	
Trauma Critical Care Team 101	Allow responders enrolled in NDMS Trauma and Critical Care Teams to deliver the highest level of trauma and critical care to victims of disasters in accordance with current clinical standards and NDMS guidelines.	48	
Team Leadership	Improve the knowledge, skills, and response capabilities of NDMS Team Commanders and Deputy Team Commanders to enhance their leadership capabilities. ^b	142	
Safety Specialist 101	Qualify Safety and Occupational Health Specialists—a responder position on all of the NDMS teams except the Victim Identification Team—to perform pre-deployment health and safety activities.	14	
Victim Identification Center 101	Allow the Victim Identification Response team and all 10 NDMS Disaster Mortuary Operational Response Teams to train and prepare for the practice of ante mortem (before death) data collection used during disaster missions. ^c	35	
Trauma and Critical Care Team 201 Exercise	Prepare NDMS Trauma and Critical Care Teams for short-notice disaster relief deployments.	48	

Source: GAO summary of Office of the Assistant Secretary for Preparedness and Response NDMS training documentation. | GAO-20-525.

Notes:

^aFederal Coordinating Centers are activated to receive, triage, stage, track, and transport patients affected by a disaster or national emergency to a participating NDMS medical facility capable of providing the required care to manage the patient's condition.

^bEach NDMS team is led by a Team Leader and a Deputy Team Leader that constitute a team's Command Staff during steady state or day-to-day operations.

^cThe Victim Information Center is a location for local authorities and Disaster Mortuary Operational Response Team members to collect ante-mortem data, such as pictures, fingerprints, dental X-rays, and other medical records, to help identify the victim.

APPENDIX IV: COMMENTS FROM THE DEPARTMENT OF HEALTH AND HUMAN SERVICES



DEPARTMENT OF HEALTH & HUMAN SERVICES

OFFICE OF THE SECRETARY

Assistant Secretary for Legislation
Washington, DC 20201

May 28, 2020

Mary Demigan-Macaulay
Director, Health Care
U.S. Government Accountability Office
441 G Street NW
Washington, DC 20548

Dear Ms. Demigan-Macaulay:

Attached are comments on the U.S. Government Accountability Office's (GAO) report entitled, *"PUBLIC HEALTH PREPAREDNESS: HHS Should Take Actions to Ensure It Has an Adequate Number of Effectively Trained Emergency Responders"* (GAO-20-525).

The Department appreciates the opportunity to review this report prior to publication.

Sincerely,

Sarah C.
Arbes-S

Principal Deputy
Assistant Secretary
for Legislation

Sarah C. Arbes
Assistant Secretary for Legislation

Attachment

GENERAL COMMENTS FROM THE DEPARTMENT OF HEALTH & HUMAN SERVICES ON THE GOVERNMENT ACCOUNTABILITY OFFICE'S DRAFT REPORT ENTITLED -- PUBLIC HEALTH PREPAREDNESS: HHS SHOULD TAKE ACTIONS TO ENSURE IT HAS AN ADEQUATE NUMBER OF EFFECTIVELY TRAINED EMERGENCY RESPONDERS (GAO-20-525)

The U.S. Department of Health & Human Services (HHS) appreciates the opportunity from the Government Accountability Office (GAO) to review and comment on this draft report.

While this report refers to the COVID-19, it is important to note that GAO work on the National Disaster Medical System (NDMS) was well underway prior to the advent of the pandemic. Thus, we raise concerns about COVID-19 references throughout the report. Our chief concern is that pandemic response is outside the primary scope of the NDMS, as NDMS employees should be primarily working in their civilian jobs within the traditional healthcare system. The COVID-19 pandemic planning, therefore, did not include NDMS. The governing assumption was the federal response should not compromise the community healthcare capabilities. Furthermore, HHS remains in the middle of its pandemic response, thus any assessment of NDMS during this time is premature at best.

Secondly, HHS would like to address the GAO's concerns with the training regimen. GAO asserts that collecting feedback about training from providers whom are deployed potentially places them at risk. However, this assertion is made with no examples or grounding in context of the training delivered. Where there is opportunity to improve training, HHS will work diligently to incorporate best practices in the preparation of its NDMS workforce.

Going forward, HHS will work to develop a strategic documented workforce target that considers (1) a nationwide event or multiple concurrent events, (2) the needs of at-risk individuals, and (3) the availability of other medical responders to fill the gaps in workforce target.

Recommendation 1

ASPR should develop an NDMS responder workforce target that aligns with the goals and objectives in ASPR's forthcoming strategic plan.

HHS Response

HHS concurs with GAO's recommendation. ASPR will work to align all goals and objectives to the strategic plan.

Recommendation 2

ASPR should develop an NDMS responder workforce target that accounts for the critical skills and competencies that are needed to meet current and future programmatic results, such as a workforce target that considers (1) a nationwide event or multiple concurrent events, (2) the needs of at-risk individuals, and (3) the availability of other medical responders.

HHS Response

HHS concurs with GAO's recommendation. ASPR will work to develop a strategic documented workforce target that considers (1) a nationwide event or multiple concurrent events, (2) the needs of at-risk individuals, and (3) the availability of other medical responders. ASPR's ability to realize this workforce target will be subject to the availability of funding.

GENERAL COMMENTS FROM THE DEPARTMENT OF HEALTH & HUMAN SERVICES ON THE GOVERNMENT ACCOUNTABILITY OFFICE'S DRAFT REPORT ENTITLED -- PUBLIC HEALTH PREPAREDNESS: HHS SHOULD TAKE ACTIONS TO ENSURE IT HAS AN ADEQUATE NUMBER OF EFFECTIVELY TRAINED EMERGENCY RESPONDERS (GAO-20-525)

Recommendation 3

ASPR should develop strategies to fill gaps to achieve its revised workforce target.

HHS Response

HHS concurs with GAO's recommendation. This recommendation will be subject to the availability of funding.

Recommendation 4

ASPR should develop a process to evaluate the web-based and in-person training provided to NDMS responders using GAO-identified key practices for evaluating training.

HHS Response

HHS concurs with GAO's recommendation. ASPR will work to incorporate GAO-identified key practices into training evaluation.

Recommendation 5

ASPR should develop a process or approach to prioritize various in-person training needs for its NDMS responders while taking into account budget constraints.

HHS Response

HHS concurs with GAO's recommendation. ASPR will continue to prioritize in-person training for NDMS responders.

Chapter 550

PROSOPIS GENUS: POTENTIAL USES AND APPLICATIONS WITH SPECIAL REFERENCE TO PUBLIC HEALTH AND IN VETERINARY MEDICINE

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ABSTRACT

This chapter provides a general overview of the main aspects related to the Fabaceae (Leguminosae) family, focusing on species of the genus *Prosopis* and covering their main aspects, such as nutritional characteristics, beneficial aspects in different social strata as well as their usage as food, traditional medicine and other uses. General information about their physiological and ecological aspects is provided, particularly regarding their role in maintaining the biodiversity of ecosystems. The enormous capability of *Prosopis* species to fix atmospheric nitrogen, retaining soil fertility, and their important contribution to soil remediation as also discussed. Furthermore, chemical aspects of the plant as well as the main secondary metabolites and their implications in the control of a large list of diseases are also discussed. This chapter focuses on the potential use of *Prosopis* species in human health and veterinary medicine. *Prosopis* species offer a wide range of uses and applications in different areas, such as a nutritional supplement, as feed

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for livestock, as a retainer of soil fertility and as an invaluable natural and sustainable medical source in both human and animal health.

INTRODUCTION

The extraordinary richness in plant biodiversity, associated with the soil microbiome, contributes to the stability of ecosystems all over the world (Trivedi et al., 2020). Against the background of a changing climate, most plant species living in different ecosystems are greatly affected, and their permanence under natural conditions mainly depends on their genetic capability for adaptation to such adverse conditions (Minorsky, 2002; Becklin et al., 2016). Leguminosae plants are one of the largest groups of plants in the world, with almost 18,000 species (Al-Tawaha et al., 2020); they are adapted to almost all terrestrial ecosystems and occur as trees, shrubs, vines and annual herbs (Vasconcelos et al., 2020). This group of plants is widely spread in many countries mainly in tropical and subtropical areas around the world (Sacheti and Al-Rawahy, 1998) and plays an important role because of its symbiotic system of atmospheric N₂ fixation through a bacteria-containing root nodule system (Schwember et al., 2019). Leguminous plants can be found in various habitats, where they provide a natural source of shade for humans and animals and are agricultural crops, either as a legume produced for human consumption, pasture, forage, or as silage for livestock and soil-enhancing green manure (Gutiérrez-Urbe et al., 2016).

The genus *Prosopis* is a group of plants belonging to the Leguminosae family and is also called “Fabaceae”, comprising 44 species (Burkart, 1976). It is widespread in arid and semi-arid regions around the world, including Central and North Africa, South and North America and the Caribbean region (Asaf et al., 2020). Species belonging to this group of plants have been considered in some countries to be invasive plants (Shackleton et al., 2015), threatening indigenous plant species and putting the biodiversity in some regions at risk (Muturi, 2009, Rejmánek and Richardson, 2013).

In some regions, this genus is highly valued because of its beneficial properties, whereas in other regions, it is considered an undesirable weed (Shackleton et al., 2014). Some studies have demonstrated that *Prosopis* species are necessary to achieve an environmental equilibrium, where plants of this group play an important role in erosion control and biodiversity support (Kumar-Prusty, 2009). *Prosopis* trees have been considered a valuable resource to reforest arid zones (de la Vega et al., 1996).

In many other countries, *Prosopis* species are highly appreciated and used as fast-growing ornamental trees in landscapes (Brown, 1991).

Other important uses for species of this genus are as a source of fuel for communities; they often are the major source of firewood and charcoal and a source of energy for refugee communities (Gianvenuti et al., 2018).

Tree species of this genus have also been used for bioethanol production (Sindhu and Gnanavel, 2016).

Prosopis species also serve as a valuable source of nutrients for wild animals since they contain protein, fibre and sugars (Ruiz-Nieto et al., 2020). These nutrients also play an important nutritional role in livestock feeding (Pasiiecznik et al., 2001; Santos et al., 2015).

Other *Prosopis* species, i.e., Mesquite, are used for human consumption, and many dishes made with this plant are prepared in Central American countries and include bread, syrup,

sweets and sweeteners, alcoholic beverages and a sort of coffee substitute (Gutteridge and Shelton, 1994). Additionally, in the culinary industry, the flour of *Prosopis* species is used because of its nutritive and bioactive properties in breadmaking (Gonzales-Barron et al., 2020).

Prosopis species contain various medicinal properties and are applied as natural remedies in the general health sector and in veterinary.

Recent studies exploring the metabolomics aspects of this interesting group of plants have identified molecules with the potential for the control of diseases either in humans or animals (Sharifi-Rad et al., 2019; Miri et al., 2020; Delgado-Núñez et al., 2020). A list of phytochemical compounds, such as alkaloids, tannins, phenolics, steroids, terpenes and flavonoids associated with medicinal properties, has recently been published (Ruiz-Nieto et al., 2020).

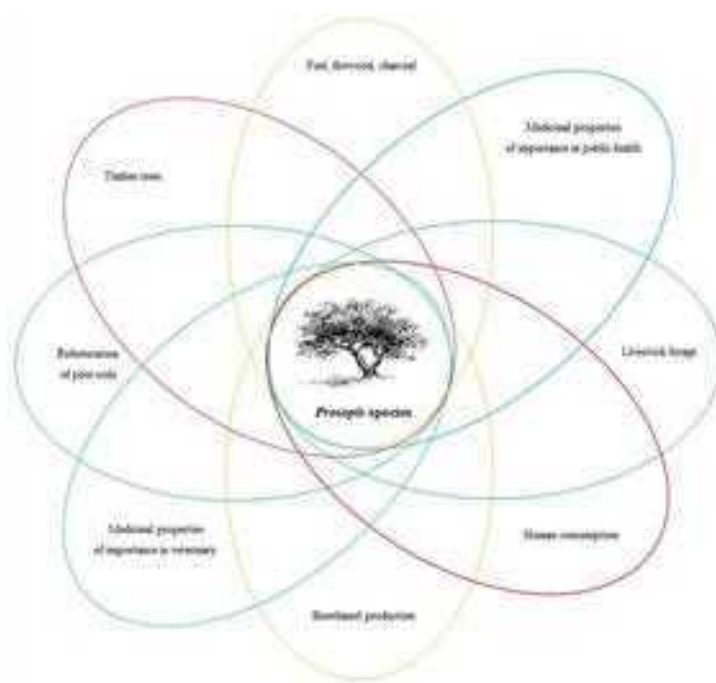


Figure 1. Diagram about some of the most frequent uses and applications of *Prosopis* species around the world.

Figure 1 shows the most beneficial characteristics of *Prosopis* species for humans. The circles represent every one of the potential uses of the plant with impact on a wide diversity of fields that benefit not only humans and animals, but also the larger environment.

Plants of this genus are considered valuable crops and are currently attracting increased interest from researchers on a global level. This chapter presents a general view of the most important aspects of the genus *Prosopis*, with special reference to its potential use in public health and veterinary medicine.

ADAPTABILITY OF *PROSOPIS* SPECIES TO ECOSYSTEMS

The genus *Prosopis* genus has an extraordinary capability for physiological adaptation to inhospitable ecosystems, and it is common to see species growing under severely adverse conditions, particularly in semiarid and arid climates of the Americas, Asia and Africa (Pasiecznik et al., 2004). *Prosopis* species can survive in different xeric environments, where, over time, some species have developed specific ecophysiological mechanisms to be able to survive under such hostile conditions (Carevic, 2014). Likewise, *Prosopis* species can synthesise chemical defense molecules with implication as nutraceuticals and phytopharmaceutical compounds (Persia et al., 2016), providing a range of competitive ecological advantages that allow them to widely self-establish in physiognomic territories, mainly under hydric deficit conditions (Passera, 2000). This group of plants can tolerate drought and adverse edaphic conditions such as salinity and alkalinity as well as having an extraordinary adaptation to herbivory. These are the main reasons why these plants have gained a dominant position in the woody vegetation of arid and semiarid zones of the Americas (Villagra, 2000; Meloni et al., 2004). Due to their abundance and ecological behaviour, *Prosopis* species play a crucial economical role, mainly in rural zones (Argaw, 2015). *Prosopis* species are also important in maintaining some ecosystem balance in cases of deforestation because of firewood gathering and charcoal production, where *Prosopis* facilitates natural reforestation by massive plant propagation, preserving its species and genetic features (Rivera et al., 2020). In South America, the relationship between *Prosopis* species and humans can be traced back to pre-Columbian ages, where these species constituted the main food for humans and animals (Roig, 1993). It can grow on sand dunes (Hennessy et al., 1985), ephemeral xero-riparian washes (Warren and Anderson, 1985), abandoned lakebeds and edges of lakes (Jarrel and Virginia, 1990) and river floodplains. Only under riparian conditions, *Prosopis* trees or “mesquite” trees grow to reach their maximum height, mainly in dense woodlands.

Mesquite is a Mexican tree whose name is derived from the Náhuatl native language (Mizquilt). The species grows in semi-desert zones with low rainfall and can be found in arid and semiarid regions in Southeast Sonora, the northern part of the Sinaloa, Chihuahua Mexican states and in other arid regions of Mexico (Rodríguez and Maldonado, 1996).

These trees grow better in the confluences of rivers and along the alluvial plains of large rivers with a low slope and along rivers that flow through wide valleys with no restrictions (Szaro, 1990). Mezquite woodlands (*Prosopis* spp.) in the United States of America have spread to southeastern Utah, southwestern Kansas, southern Texas and southeastern California. Historically, *Prosopis* trees have represented one of the most abundant riparian communities, but nowadays, they are reduced to a remnant state. This tree community is localised in high alluvial plains of 2 to 15 m above sea level. Inside riparian ecosystems, which historically covered several kilometres in width, they extended their territory along hundreds of kilometres in the lower parts of rivers (Ellsworth et al., 2018).

In other countries, different species of the genus *Prosopis* have been described. For instance, in Mexico, eleven mesquite species have been identified in almost all regions of the country, mainly in arid and semiarid regions. In Mexico, the following species of *Prosopis* have been identified: *P. odorata*, *P. glandulosa*, *P. velutina*, *P. articulate*, *P. tamaulipana*, *P.*

yaquiana, *P. mayana*, *P. vidaliana*, *P. laevigata*, *P. mezcalana* and *P. juliflora* (Palacios, 2006).

On the other hand, the density of the trees is important for the growth of *Prosopis* species. It should be considered that many decades ago, the woodland areas worldwide were considerably larger, whereas nowadays, they are reduced in size and composed of dense stands of trees that are younger and smaller compared to their potential size of 18 m in height and 1.5 m in stem diameter (Ansley et al., 1997). The woodland overstory is dominated by mesquite species, but the underground woodlands can support a diverse set of bushes, climbing plants and herbaceous plants (Ansley et al., 2010). Mesquite trees are characterised by high productivity due to the combination of a deep root system that extends almost to the riparian phreatic level and nitrogen-fixing symbiotic bacteria (Kulkarni and Nautiyal, 1999). Productivity is high, with abundant flower and fruit production, allowing colonisation by diverse and abundant animal species. For example, mesquite woodlands harbour one of the highest densities of reproductive chickens of any habitat (Boggie et al., 2017). Woodlands are continuously threatened by human activities such as groundwater pumping, surface water diversion, forest clearing and cutting trees for wood, as well as soil changes for livestock grazing (Felker, 1990). *Prosopis* species have also been considered a suitable plant to prevent soil erosion (Al-Assaf et al., 2020).

PHYTOCHEMISTRY AND BIOLOGICAL ACTIVITY OF THE GENUS *PROSOPIS*

As previously stated, *Prosopis* species are not only a crucial source of nutrients in the diet of humans, but are also traditionally used because of the medicinal properties (Luna-Nemecio, 2019; Gallegos, 2016; Dardón and Retana, 2017). Most of the medicinal uses were originally employed on an empirical basis. However, studies of the chemistry and metabolomics of *Prosopis* species have led to the identification of several secondary metabolites, resulting in a long list of chemical compounds used in different industrial sectors, including cosmetics, pharmaceuticals or medicines (Damasceno et al., 2020). In the last decades, some phytochemicals from *Prosopis* species of medicinal importance, including alkaloids and phenolic compounds such as flavonoids, terpenes, tannins and saponins, have been reported (Ibrahim et al., 2013). These findings contribute to the scientific search for other alternative curative tools against a range of pathogens and diseases. For example, *P. glandulosae* has antimicrobial activity against *Vibrio cholerae*, one of the most dangerous enteric pathogenic bacteria responsible for cholera; it has been estimated that each year, there are 1.3 to 4.0 million cases of cholera, with 21,000 to 143,000 deaths worldwide (FAO, 2019).

The chemical composition as well as the pharmacological activity of *P. juliflora* Swartz DC, which is one of the most abundantly spread species and one of the most studied ones, has recently been reported. Due to its high content of flavonoids, *P. juliflora* can be considered as an important natural anticancer source according to Odero et al. (2017). These authors also reported the presence of a compound called “mesquitol” (Figure 2) as a major compound in this species, associated with antioxidant activity. The presence of alkaloids (3.6%) in this plant supports its use as analgesic, antispasmodic and bactericidal compound (Ibrahim et al.,

2013; Dey et al., 2020). Quantitative analysis of this species revealed a 2.2% saponin content in *P. juliflora* leaves. In this regard, some authors have explored other medicinal properties of saponins, and particularly steroids have shown antimicrobial (Sobolewska et al., 2020), antiprotozoal (Henciya et al., 2017), cytotoxic and anticancer (Persia et al., 2020), molluscicidal (Ukande et al., 2019), antitumour and fungicidal (Sharifi-Rad et al., 2019), insecticidal and acaricidal activities (Brito-Mancero et al., 2019).

The phenolic compounds present in *P. juliflora* and *P. pallida* have been associated with nutraceutical and antioxidant properties (Suárez-Rebaza et al., 2019). The most important phenolic compounds found in *P. juliflora* belong to the following groups: flavonoids (quercetin, kaempferol, myricetin and isorhamnetin) and phenolic acids (gallic, coumaric, caffeic and chlorogenic). These compounds possess a synergistic effect with flavonoids and together achieve an enhanced effect as antioxidant and anticancer agents. Some chemical structures as well as the part of the plant used and their pharmacological properties are shown in Figure 2. The tannin concentration is generally low.

Some authors have stated that the consumption of plants containing such metabolites leads to a significant reduction in the risk of contracting some chronic diseases (Afrin et al., 2016). The consumption of plants of the genus *Prosopis* is therefore recommended to increase general health.

A wide range of biological applications of *Prosopis* species, particularly because of their pharmacological potential as well as the variety and abundance of phytochemical compounds, has been reported. Various bioactive substances with medicinal effects, including alkaloids (juliflorine, juliprosopine, prosoflorine, julisopropine, patulitrin and piperidine) as well as flavonoids (mesquitol) and tannins such as antraquinones and quinones have been reported for *P. juliflora* (Ukande et al., 2019). The activities described for these compounds varied from inhibition of acetylcholinesterase, blocking calcium channels, gas production inhibition during ruminal digestion, anti-lung cancer activity, antioxidant activity, inhibition of drug-resistant fungi, glial cell activation and inhibition of H⁺, K⁺ and ATPase of *Helicobacter pylori*. These findings could be useful when establishing the ethnopharmacological basis for *Prosopis* plant species for future phytochemical and pharmacological studies focusing on the treatment of several diseases of importance in public health. Similarly, other secondary metabolites have been identified in other *Prosopis* species; most of them correspond to a piperidine alkaloids known as “prosopinine” (isolated from *P. juliflora*), which has been used as a local anaesthetic, and “Prosopine” (isolated from *P. africana* and used as a stimulant of the central nervous system. Alkaloids from this genus are used as analgesic and anti-paludism agents (Khuong-Huu et al., 1972; Ratle et al., 1966) (Figure 3).

The main structural tissue constituents of *P. laevigata* pods and duramen are sugars, i.e., saccharose, glucose, fructose and xylose, as well as sulphur amino acids and phenolic compounds (Carrillo-Parra et al., 2008; Díaz-Batalla et al., 2018). In an acetone/water extract, three flavonoids, namely (-)-epicatechin (+)-catechin and taxifolin, were identified by HPLC (Carrillo-Parra et al., 2008) (Figure 4).

Chemical analysis of mesquite flour obtained from the tree pods revealed the presence of six fatty acids: palmitic (C16:0), palmitoleic (C16:1), stearic (C18:0), oleic (C18:1), linoleic (C18:2) and linolenic acid (C18:3). Some of these fatty acids i.e., linoleic, palmitic and stearic acids play an important role in multiple functions in the body; for instance, an influx in the brain function, in cardiovascular system health, digestion, allergies, immunity and vision (Cruz-Gracida et al., 2019).

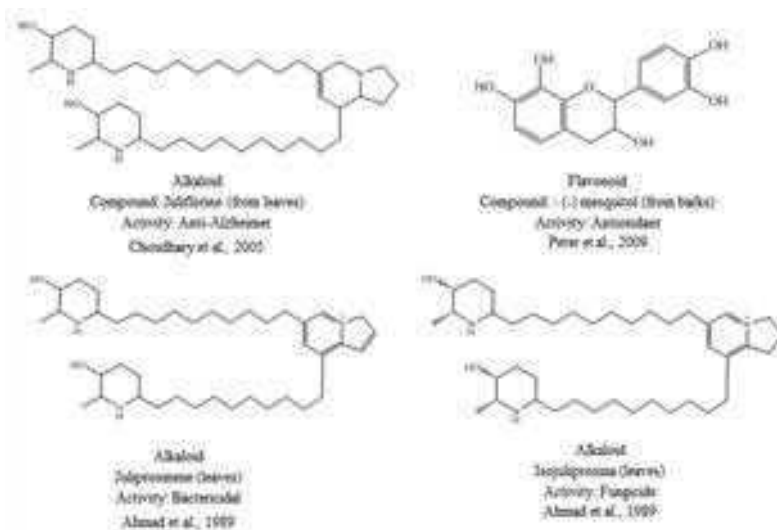


Figure 2. Compounds identified in different parts of *Prosopis juliflora* and their pharmacological properties.

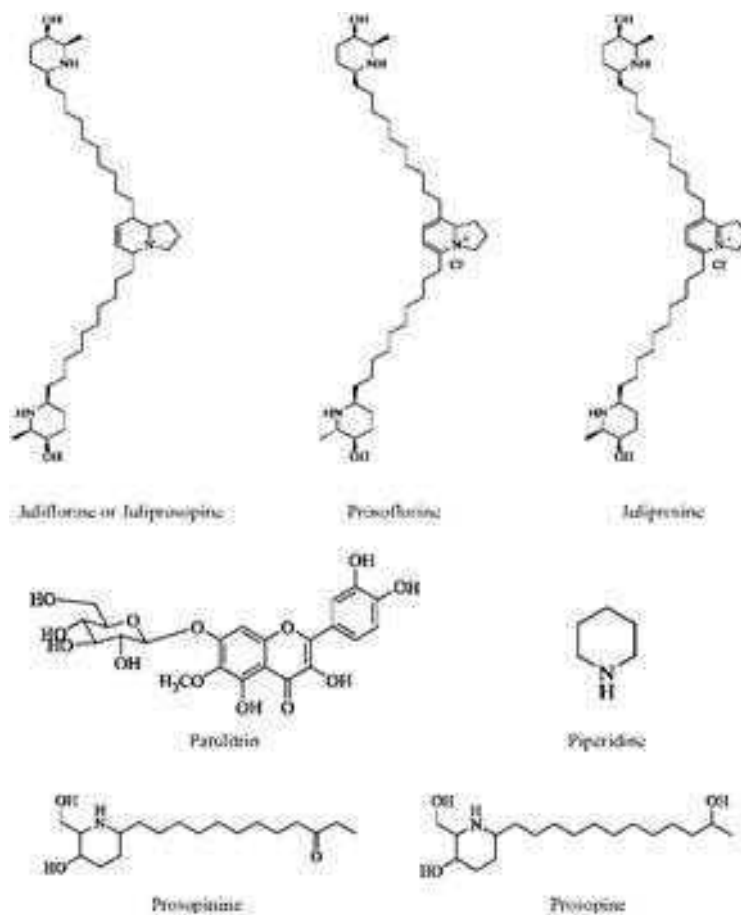


Figure 3. Chemical structures elucidated from *Prosopis* species.

The antibacterial activity of two bipeptides isolated from *Prosopis* seeds (obtained inside the tree pods) against the pathogenic bacteria *Bacillus cereus* has recently been reported (Acosta-Salas et al., 2020).

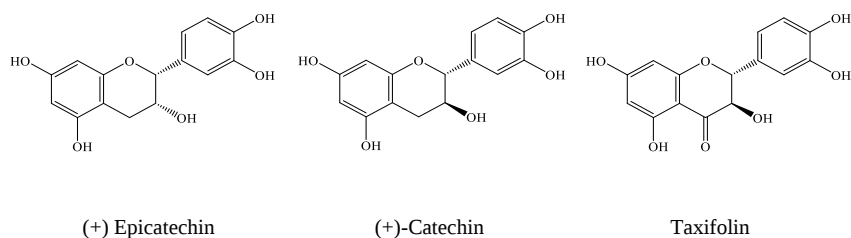


Figure 4. Chemical structures of Epicatechin, Catechin and Taxifolin identified in *Prosopis laevigata*.

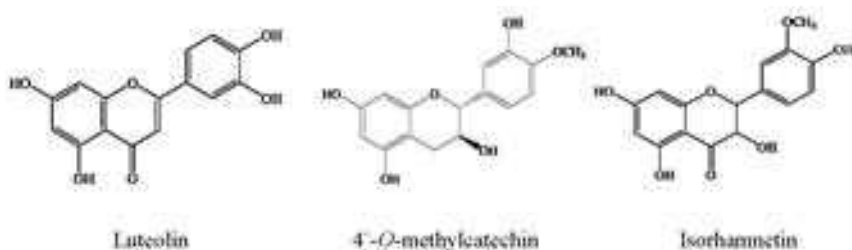


Figure 5. Chemical structures of compounds isolated from in *P. laevigata*.

In a recent study, the anthelmintic activity of a hydroalcoholic extract obtained from *P. laevigata* leaves was assessed against *Haemonchus contortus*, one of the most pathogenic agents affecting small ruminants all over the world; the extract had 100% *in vitro* ovicidal and larvicidal activity and contained three known flavonoids: isorhamnetin, luteolin and 4'-O-methylcatechin from an ethyl acetate fraction. Isorhamnetin was the compound identified as responsible for the nematocidal activity (Delgado-Núñez et al., 2020) (Figure 5). *Prosopis* spp. offer a wide variety of compounds with enormous medicinal potential, and this interesting Fabaceae plant should be further explored to increase its potential use in public health.

ETHNOPHARMACOLOGICAL USES OF *PROSOPIS* SPECIES

Plants have been used in the control of various diseases for ages, mainly on an empirical basis, contributing to public health particularly in rural zones. This knowledge has been passed down from generation to generation, and nowadays, such “alternative” methods are considered highly valuable. For instance, in India, *P. juliflora* is frequently used to cure rheumatism, as an astringent and as a cure against scorpion stings and snakebites (Wassel et al., 1972). Additionally, *Prosopis* species have been used in India as a diuretic and in the treatment of liver and eye diseases (Chopra et al., 1956). In Pakistan, pregnant women consume powdered *Prosopis* flowers mixed with sugar to prevent spontaneous abortion (Kirtikar and Basu, 1984; Marwat et al., 2011). Additionally, species of *Prosopis* have been

reported to cure some sexually transmitted diseases such as gonorrhoea caused by *Neisseria gonorrhoeae* (Cáceres et al., 1995). Other empirical applications are associated with *P. cineraria*, for example, the use of the plant as an anthelmintic and against leprosy, dysentery and asthma symptoms in the Tharr Desert, India (Garg et al., 2003).

Ethnopharmacological studies have shown that some species of *Prosopis*, such as *P. africana*, *P. alba*, *P. cineraria*, *P. farcta*, *P. glandulosa*, *P. juliflora*, *P. nigra*, *P. ruscifolia* and *P. spicigera*, are commonly used in traditional medicine in several parts of the world to treat various diseases (Table 1). Nevertheless, the species with the highest benefits in public health are *P. juliflora*, *P. africana* and *P. cineraria* (Ahmed et al., 2015; Yaseen, et al., 2015; Suroowan et al., 2017; Umair et al., 2017; Aziz et al., 2018; Younis et al., 2018; Suárez et al., 2019).

POTENTIAL USE OF *PROSOPIS* SPECIES IN DISEASE CONTROL

In the last decades, the medicinal use of plants of the genus *Prosopis* has been widely studied, and nowadays, there is a wide and detailed catalogue of information about the secondary metabolites of pharmacological relevance, particularly against some specific diseases. Plants survive under various biotic and abiotic stress conditions and have developed different barriers of defence; some of these are chemical responses against wounds caused by the attack of pathogenic microorganisms, which trigger the synthesis of compounds called secondary metabolites (Sepúlveda-Jiménez et al., 2003). As previously mentioned, various studies report phytoconstituents such as alkaloids, tannins, phenolic compounds, steroids, terpenes and flavonoids with importance in public health (Ruiz-Nieto et al., 2020). In this context, using natural compounds obtained from plants with medicinal properties, i.e., *Prosopis* species, offers an alternative focus against certain diseases and pathogenic microorganisms of medicinal importance. For example, *in vitro* bactericidal activity of *Prosopis glandulosa* against *Vibrio cholera*, *Salmonella* spp., *Salmonella thypimurium*, *Streptococcus agalactiae* and *Enterococcus faecium* has been recorded by Sánchez et al. (2010) and Valenzuela-Balderas et al. (2017). Reports about the chemical and pharmacological composition of some *Prosopis* species, such as, *P. juliflora*, *P. africana* and *P. cineraria*, include a long list of uses and applications as well as their nutritional benefits and effectiveness as traditional medicine. These species are considered suitable candidates for deeper phytochemical analysis searching for natural medicinal phytochemicals. Some *Prosopis* species share phytochemical and secondary metabolite characteristics that have been associated with several diseases as well as a wide pharmacological response in certain cases. Some *Prosopis* species, as well as their aerial parts, metabolites and pharmacological activities, are listed in Table 2.

Bactericidal and fungicidal activity has been associated with specific alkaloids: juliprosinene and isojuliprosine, as recorded by Ahmad et al. (1989) and Nakano (2010), respectively. Juliflorine also shows activity against Alzheimer's, according to Choudhary et al. (2005), and some flavonoids with antioxidant effects, i.e., α -mesquitol, have been reported (Sirmah et al., 2009). These benefits of phytochemical compounds significantly contribute to reducing the effects of various diseases, including chronic diseases, all over the world (Afrin et al., 2016). *Prosopis* species have been successfully used in traditional

medicine for about 1,000 years to cure many diseases (Giovannetti et al., 2008). In recent decades, scientific studies have explored and corroborated the medicinal properties of this group of plants. The pharmacological potential of secondary metabolites of *Prosopis* species is an important alternative tool of control diseases, and studies on the bioactive molecules from this genus contribute to the development of more natural and practical approaches in public health.

PROSOPIS SPECIES IN THE CONTROL OF DISEASES OF ANIMALS

Since remote times, farmers closely working with animals have been facing numerous health problems in their flocks, forcing them to learn how to restore the health of their animals. This continues practice has allowed them to gain experience in the development of ethnoveterinary tools. Ethnic farmers have established a set of traditional medicinal recipes, which have been handed down through generations (Dassou et al., 2020). When we think of traditional medicine applied to animals, it is important to consider that ethnoveterinary medicine has been existing since remote times, since humans closely living with animals have learned from animals based on their self-treatment behaviour by selecting and feeding on herbs (Miara et al., 2019).

Most medicinal compounds used in the control of human diseases are being used in a similar way in animals. Interestingly, some phytotherapies were initially used in animals and only later in humans and/or vice versa, using the same herbs, compounds and manipulative techniques (McCorkle and Mathis-Mundy, 1992).

As we have mentioned early in this chapter, the genus *Prosopis* is used in a wide of applications, many of them only on an empirical basis by humans, mainly in rural zones in many countries around the world.

The genus *Prosopis*, similar to other members of the Fabaceae family, contains important nutritional components. For example, the various species are an excellent source of crude protein, energy and structural carbohydrates, making them (*per se*) an important natural stimulant of unspecific immunological response associated with the self-defence of cells against several diseases (Ketcha-Wanda et al., 2014). Additionally, plants of the genus *Prosopis* produce several bioactive compounds derived from their secondary metabolism, including condensed tannins, flavonoids, saponins and other phenolic compounds that have been associated with a significant medicinal activity (Ram et al., 2020). These benefits make *Prosopis* plants as viable option as nutraceutical food for cattle and small ruminants (Malik et al., 2013). *Prosopis* spp. leaves (mesquite) have been successfully used in ruminant diets as a nutritional supplement at inclusion levels of 20–40% (Yasin and Animut, 2014; Ruiz-Nieto et al., 2020). Likewise, *Prosopis* species have numerous medicinal properties, including antimicrobial (Yarkwan, 2020), anti-inflammatory (Abodola et al., 2015, Nodushan et al., 2020), antifungal (Miri et al., 2020), skin wound curative (Yadav et al., 2018), antidiabetic (George et al., 2011; Alsaadi et al., 2015), antiprotozoal, cestocidal (Faten and Al-Azziz, 2011) and nematocidal activities (Delgado-Núñez et al., 2020).

Table 1. Traditional use of Prosopis species against various diseases

Species	Part of the plant	Disease/bioactive effect	Mode of use	Location	References
<i>P. juliflora</i>	Bark	Asthma	Oral	Madhya Pradesh, India	Wagh et al., 2018
	Xerophyte shrub	Asthma, cough	Unspecific	Pakistan	Younis et al., 2018
	Leaves, gum	Analgesic, boils, conjunctivitis, toner, muscle pain	Oral	Sindh Desert, Pakistan	Yaseen et al., 2015
	Leaves	Lactation and expectorant	Oral	Pakistan	Aziz et al., 2018
	Leaves, stems, fruits	Eye problems Traumatism Aphrodisiac, intestinal worms	Eye drops Rum macerated balsam	Paraguana Peninsula, Venezuela	Taïma, 2017
	The whole plant, flowers stems, leaves	Galactagogo, kidney stones, toothache, breast cancer asthma, boils	Oral, topic, as a teeth brush	Punjab, Pakistan	Umair et al., 2017
	Branches and leaves	Diabetes	Unspecific	Durango and Coahuila, Mexico	Landeros et al., 2018
<i>P. cineraria</i>	Leaves, bark, flowers, Pods and timber	Menstrual disorders, contraceptive, abortion prevention	Oral	Pakistan	Tariq et al., 2018
	Fruits and pods	Asthma	Unspecific	Pakistan	Younis et al., 2018
	Leaves, bark, stems, flowers fruits	Liver tonic, boils and ampules, pancreatic stones, leucorrhoea, calculus, chronic dysentery, eye cataracts	Oral, topic, eye drops	Punjab, Pakistan	Umair et al., 2017
	Fruits	Body tonic, leucorrhoea	Oral	Thar Dessert (Sindh), Pakistan	Yaseen et al., 2015
	Flowers	Rheumatism	Oral	Pakistan	Suroowan et al., 2017
	Fruits	Asthma, cutaneous eruption	Topic	Southern Kerman, Iran	Sadat-Hosseini et al., 2017
	Leaves and stems	Spasms, diabetes, liver infection, diarrhoea, kidney stone extraction bladder and pancreas fever, flu	Oral	Bahawalnagar, Punjab, Pakistan	Ahmed et al., 2015
<i>P. alba</i>	Leaves Pods Bark	Eye cataracts, dyspepsia, earache, toothache, bone fracture pain relief	Eye drops Oral Ointment	Oman (Arabia)	Ghazanfar and Alsabahi et al., 1993
	Resin	Conjunctivitis, post-abortion pain	Oral	Wichi Village, de Salta Province, Argentina	Suárez, 2019
	Leaves	Malaria	Oral	Nigeria	Wagh et al., 2018
<i>P. africana</i>	Leaves, bark, roots	Pregnancy pains, delivery, lactation, newborn diseases, cutaneous inflammation (wounds and burns)	Unspecific	Guinea-Bissau	Catarino et al., 2016
	Bark from stems	Malaria	Oral, shower	Sub-district of Sélingué, Mali	Diarra et al., 2015
	Roots	Analgesic anti-inflammatory	Oral	Nigeria	Salihi et al., 2018
<i>P. glandulosa</i> Torr	Inflorescences	Stomach ache	Oral	Nuevo Leon, Mexico	Estrada-Castillón et al., 2018
<i>P. ruscifolia</i>	Leaves	Conjunctivitis, stomach-ache, skin pimples, cutaneous eruption, scabies, calluses, fever, birth delivery and post-birth delivery, diarrhoea, pediculosis, otitis	Oral	Wichi Village, de Salta Province, Argentina	Suárez, 2019
	Fruits	Constipation and antipyretic	Oral	Jahrom, Iran	Nasab and Esmailpour, 2018
<i>P. farcta</i>	Roots	Hypoglycaemic and hypotensive	Unspecific	Jordania	Afifi et al., 1993
	Bark, leaves, flowers	Asthma	Unspecific	Pakistan	Younis et al., 2018

Table 1. (Continued)

	Pods, Bark, Flowers	Astringent, pectoral, demulcent Anti-inflammatory, anti-rheumatic Spontaneous abortion preventive	Decoction	India	Khare, 2007
<i>P. nigra</i>	Resin	Eye traumatism, conjunctivitis	Oral	Wichí Village, de Salta Province, Argentina	Suárez, 2019
<i>P. laevigata</i>	Leaves	Indigestion Eye problems Delivery	Oral Eye drops	San Rafael Coxcatlán, Puebla, Mexico	Canales et al., 2005

Table 2. Some Prosopis species, as well as their aerial parts, metabolites and pharmacological activities, used in public health

Species	Aerial part	Metabolites	Pharmacological activity	References
<i>P. cineraria</i>	Leaves Flowers Pods	Tannins (gallic acid), steroids (stigmasterol, campesterol, sitosterol, etc.), derivatives from flavonones (prosopetin A, B, C, D and E), alkaloids (spicigerine, prosophylline)	Antipyretic, anti-hyperglycaemic, antioxidant, anti-hypercholesterolemia, antitumour	Garg and Mittal, 2013
<i>P. pallida</i>	Fruits	Phenolic compounds	Anti-hyperglycaemic	Pinto et al., 2009
<i>P. glandulosa</i> var. <i>glandulosa</i>	Leaves	$\Delta^{1,6}$ -Juliprosopine	Anti-infectious, antiparasitic	Astudillo, 2000 Rahman, 2011
<i>P. juliflora</i>	Leaves	Juliflorine	Inhibition of acetylcholinesterase Calcium channel blockade and antidermatophytic	Choudhary, 2005
	Leaves Pods	Juliprosopine Prosopiflorine Juliprosopine	Diminishing gas production during ruminal digestion	dos Santos et al., 2013
	Fruits	Patulitrin	Antilung cancer	Sathiya et al., 2010
	Wood	(-)-Mesquitol, quercitrin, quercetin, caffeic acid	Antioxidant	Sirmah et al., 2011 Almaraz-Abarca et al., 2007
	Leaves	Piperidine alkaloids	Inhibition of drug-resistant fungi Glial cell activation	Valli et al., 2014 Silva et al., 2013
	Seeds Leaves	Alkaloids, flavonoids, tannins, antraquinones, quinones	Inhibition of H ⁺ , K ⁺ , ATPase of <i>H. pylori</i>	Gobinath et al., 2013
<i>P. flexuosa</i>	Aerial parts	Catechin	Antioxidant	Tapia et al., 2000
<i>P. alpatarco</i>	Seeds	Pentacyclic triterpenes	Antibacterial	Mazzuca et al., 2003
<i>P. tamarugo</i> <i>P. alba</i>	Leaves and pods	Catechin	Antioxidant	Astudillo et al., 2000
<i>P. cineraria</i>	Whole plant	Alkaloids	Anticonvulsive activity Anti-hyperglycaemia and antioxidant	Sachdeva et al., 2014
<i>P. africana</i>	Leaves, roots and stems Bark of stems	Tannins, flavonoids	Antitrypanosomal	Atawodi et al., 2009
<i>P. chilensis</i>	Leaves	β -Phenethylamine, tryptamine	DNA binding activity	Astudillo et al., 2000

Table 3. Examples of medicinal effects of Prosopis species against different diseases in animals and under different experimental conditions

Prosopis species	Isolated compound	Activity	Animal specie	Author
<i>P. juliflora</i> (pods)	Alkaloid-enriched extracts	Antimicrobial, feed additive for ruminants	<i>In vitro</i> study	dos Santos et al., 2013
<i>P. farcta</i> (fruits)	Ethanollic extract	Antidiabetic	Male rats (Wistar rats)	Dashtban et al., 2016
<i>P. glandulosa</i>	2,3-dihydro-1H-indolizinium alkaloid-prosopilosidine	Antifungal (<i>Cryptococcus neoformans</i>)	Mice (murine model)	Ashfaq et al., 2018
<i>P. juliflora</i> (pods and leaves)	Julifloridine and juliprosopine	Antimalarial	Mice (murine model)	Batista et al., 2018
<i>P. juliflora</i> (leaves)	Methanolic extract	Anticancer	Mice	Utage et al., 2018
<i>P. juliflora</i> (leaves)	Alkaloids	(Antibacterial) Sub-clinical mastitis	Cows	Shah et al., 2018

Based on an extensive revision of the available literature about *Prosopis* spp., most publications have focussed on investigating their medicinal properties. However, other studies have explored its potential use in the control of diseases of animals. It is important to remark that some species of *Prosopis* have beneficial effects in animals, improving or restoring the health of laboratory animals, which is crucial when exploring their use either in animals and/or in diseases of importance in public health. For example, a wound care curative effect was observed using a methanolic extract obtained from *P. africana* stem bark, which reduced the bleeding/clotting and coagulation time in rats (Ezike et al., 2009). Additionally, a hypoglycaemic effect has been reported for 24-methylencycloartan-3-one, a compound obtained from *P. juliflora* pods, in alloxan-induced diabetic rabbits (Alsaadi et al., 2015). An antipyretic effect of a *P. juliflora* ethanolic extract prepared in Brewer's yeast in rats has been reported by Gobinath et al. (2013), whereas an anti-ulcer effect has been observed in ethanol-induced gastric ulcers in rats treated with *P. juliflora* ethanolic extract (Reddy et al., 2014). In another study, an anodyne effect (pain reliever), using a *P. glandulosa* paste prepared with leaves and fruits of the plant and applied to painful bone fractures in animals, has been observed (Khan et al., 2009), and in another study, *P. glandulosa* demonstrated antidiabetic activity in rats with diabetes and in insulin resistance models (George et al., 2011). Other *Prosopis* species, i.e., *P. farcta* (roots), are a promising natural drug for cardiovascular disorders in traditional medicine. In this regard, studies assessing an aqueous extract of *P. farcta* root have been performed using rabbits with high-cholesterol-diet-induced hypercholesterolemia as a study model (Saidi et al., 2016).

A list of medicinal properties of *Prosopis* species against different diseases either under *in vitro* or *in vivo* in different animal species is shown in Table 3.

EXPLORING THE POTENTIAL USE OF *PROSOPIS* SPECIES AS A NATURAL ANTIPARASITIC IN ANIMALS

Under natural conditions, animals show a selective feeding behaviour, especially when they suffer from certain diseases, including parasitosis (Torres-Fajardo et al., 2019). Such behaviour corresponds to a natural self-deworming system (de Roode, 2013). Some groups of compounds with anti-parasitic activity have been identified in different *Prosopis* species,

including tannins, terpenes, coumarins, phenolic compounds, flavonoids and alkaloids (Prabha et al., 2014). It is important to consider that when animals feed on Fabaceae plants such as *Prosopis*, two natural systems against parasites occur in the organism. First, the high nutritional contribution, mainly protein, offered by these plants strengthens the body's defence system, acting as a natural stimulus of the immune system, as mentioned above. Additionally, the molecules identified in the phytochemical profile of *Prosopis* exert an anthelmintic effect that has been identified in many *in vitro* and *in vivo* studies against veterinary parasites (Rahman et al., 2011). Table 4 provides a list of antiparasitic and anthelmintic properties of *Prosopis* species.

Table 4. Examples of the anti-parasitic effect of *Prosopis* species under different conditions

<i>Prosopis</i> species and part of the plant	Extracts/Compounds	Experimental conditions/Biological activity	Blank parasite	Author
<i>P. farcta</i> (leaves)	Alkaloid-enriched extracts	Scolicidal	<i>In vitro</i> study (<i>Echinococcus granulosus</i>)	Hammoshi et al., 2006
<i>P. juliflora</i> (fruits)	Methanolic extract	Antiplasmodial, antileishmanial and antitrypanosomal	<i>In vitro</i> study	Al-Musayeib et al., 2012
<i>P. juliflora</i> (pods)	---	Antiprotozoal	<i>In vitro</i> study (<i>Leishmania infantum</i> , <i>Trypanosoma brucei</i> , <i>T. cruzi</i>)	Al-Musayeib et al., 2012
<i>P. juliflora</i> (leaves)	Aqueous extract	Anthelmintic	<i>In vivo</i> study (sheep)	Mutembei et al., 2015
<i>P. glandulosa</i> (leaves)	Juliprosopine	Anthelmintic	<i>In vitro</i> study (<i>Haemonchus contortus</i>)	Kipyegon et al., 2015
<i>P. cineraria</i> (bark)	Ethanol extract	Anthelmintic	<i>In vitro</i> study (<i>Cotylophoron cotylophorum</i>)	Manigandan and Veerakumari 2015
<i>P. juliflora</i> (pods)	Julispronine	Anthelmintic	<i>In vitro</i> study (<i>H. contortus</i> , <i>Trichostrongylus</i> spp. and <i>Oesophagostomum</i> spp.)	Lima et al., 2017
<i>P. juliflora</i> (pods and leaves)	Julifloridine and juliprosopine	Antimalarial	<i>In vivo</i> study mice (murine model)	Batista et al., 2018
<i>P. laevigata</i> (leaves)	Isorhamnetin	Anthelmintic	<i>In vitro</i> study (<i>Haemonchus contortus</i>)	Delgado-Núñez et al., 2020

Recently, other studies have investigated the anthelmintic activity of different parts of the plant using different isolation strategies, mainly maceration with organic solvents, to separate groups of compounds by polarity grades, followed by chromatography analysis; the results are promising. *Prosopis laevigata* organic extracts have been explored in terms of anthelmintic activity against one of the most pathogenic parasites of small ruminants, *Haemonchus contortus*. For instance, the *in vitro* mortality of *H. contortus* infective larvae by the action of hexanic extract of *P. laevigata* obtained from leaves and stems was assessed, and 51, 81 and 86% larval mortalities were recorded after 24, 48 and 72 h post-exposure to the extract, respectively (López-Aroche et al., 2008). In another study, an *n*-hexanic extract from *P. laevigata* leaves was evaluated as a natural dewormer against *H. contortus* using gerbils as an *in vivo* model, with 100 µL as a unique intra-peritoneal dose. The authors reported a maximum reduction of 53% in the recovery of worms at necropsy, providing evidence of the anthelmintic effect of this extract (de Jesús-Gabino et al., 2010).

In a recent publication by Delgado-Núñez et al. (2020), a chemical bio-guided study was conducted using a hydroalcoholic extract prepared with dried leaves of *P. laevigata* against *H. contortus*. The authors reported a potent *in vitro* anthelmintic effect of this extract against

two exogenous stages of this parasite (eggs and larvae) and found a compound called isorhamnetin, which was responsible for the nematocidal activity. The contents of constitutive chemical compounds in pods of another *Prosopis* species, *P. juliflora*, have been reported by Lima et al. (2017), who described the presence of an alkaloid compound called juliprosopine. This molecule was associated with ovicidal and larvicidal activity against three gastrointestinal parasitic nematodes of sheep and goats: *H. contortus*, *Trichostrongylus* spp. and *Oesophagostomum* spp. (Lima et al., 2017). Encapsulated ethanolic extracts of *P. juliflora* roots have shown 50% ovicidal activity against *H. contortus*, with only 0.35 and 0.74 mg/mL (Kipyegon et al., 2015). As shown in this present chapter, *Prosopis* species are important due to their use in traditional medicine, and they could be used as a potential tool in the control of many diseases of livestock and other domestic species

CONCLUSION

The wide range of beneficial properties of the Fabaceae *Prosopis* has been used since remote times. The plants play an important role as forage for cattle and small ruminants, as a source of fuel, firewood and charcoal as well as timber trees. The genus is also used in bioethanol production, reforestation and bioremediation. In addition, *Prosopis* species contain several compounds and molecules derived from their secondary metabolism with potential use in public health and veterinary medicine. The medicinal properties of this genus confirm that traditional medicine has correctly used these plants on an empirical basis. Beyond these properties, new biological activities have recently been found and applied in public and veterinary health, offering new alternative tools of control for many diseases from a natural and sustainable perspective.

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Chapter 551

SCHIZOPHRENIA: AN OVERVIEW FROM PUBLIC MENTAL HEALTH PERSPECTIVE

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ABSTRACT

Schizophrenia is a chronic and severely disabling mental illness representing a serious public mental health problem across the globe. It is an illness that has multifarious symptom manifestations across patients, and the cumulative effect is always severe and long-lasting. Schizophrenia unarguably remains one of the most debilitating mental illnesses with multifactorial causes. It creates a burden not only for the patient but also for the family, community, and nation. The chapter discusses etiology, epidemiology, comorbidities, diagnosis, and prognosis. It presents a synthesis of current evidence on treatment modalities - moving from a biomedical approach to a more integrative approach. Schizophrenia is a common psychiatric condition that most clinicians encounter in their routine practice. Early screening and timely treatment is linked with reduced chronicity and severity. However, screening of schizophrenia at community level is not prioritized. The chapter concludes by arguing that community level screening, timely diagnosis and integrating traditional medicine and traditional healing practices rooted in a given cultural and religious context as treatment plans are potential public health strategies. More research is needed to generate evidence on the above areas.

Keywords: schizophrenia, mental illness, psychosis, positive symptoms, negative symptoms, public mental health

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INTRODUCTION

Schizophrenia is a chronic and severe mental illness affecting the most basic human processes of perception, emotion, and judgment. Approximately 20 million people live with schizophrenia globally, which will continue to rise (James et al., 2018). Schizophrenia is associated with considerable disability impacting educational, social, occupational, and economic productivity (Chong et al., 2016; WHO, 2019). People with schizophrenia are more likely to die early than the general population due to comorbidities such as cardiovascular, metabolic, and infectious diseases (Laursen et al., 2014).

Although schizophrenia is treatable, more than 69 percent of people with schizophrenia are not receiving appropriate mental health care (WHO, 2019). Approximately 90% percent of people with untreated schizophrenia are from low- and middle-income countries (WHO, 2019). Restricted access to mental health services is a critical challenge. Research indicated that people with schizophrenia are less likely to seek care than the general population (Lora et al., 2012). Further, stigma, discrimination, and violation of human rights of people with schizophrenia also act as barriers in access to timely appropriate mental health care (Kanak et al., 2017; Poreddi et al., 2013; Singh et al., 2016). Prevalence of schizophrenia, challenges in accessing appropriate and timely mental health care, and stigma make schizophrenia a serious public mental health problem.

This chapter discusses epidemiology, comorbidities, causal factors, diagnosis, prognosis, and treatment modalities by synthesizing current evidence. The chapter gives an overview of different treatment modalities, from a biomedical approach to a more integrative approach that evolved in the last two decades. Authors argue that integrating traditional medicine and traditional healing practices rooted in a given cultural and religious context is imperative in the public health system. Lastly, authors present implications for future research and public health practices.

BRIEF HISTORY AND EVOLUTION OF NOMENCLATURE

The emergence of schizophrenia as a medical condition was noted worth studying only after the eighteenth century. Till then, the general perspective around various psychotic disorders was that of insanity or madness (Sadock & Sadock, 2009). It was Belgian psychiatrist, Benedict Morel (1852), in the late nineteenth century who formally spoke about schizophrenia, addressing it as ‘*démence précoce*.’ Later, the German psychiatrist Emil Kraepelin (1896) introduced the term ‘*dementia praecox*’ to a group of illnesses beginning in adolescence that ended in dementia as the individual progressed into adulthood. Later, Kraepelin further formalised the construct by integrating the contemporary descriptions of catatonia by Kahlbaum (1863), that of ‘*hebephrenia*’ by Hecker (1871), and his own “*dementia paranoia/praecox*” into a single disorder with an early onset, poor prognosis, and 36 psychic or psychological symptoms and 19 bodily or physical symptoms. Kraepelin's description explained the presence of negative symptoms (described as emotional dullness, failure of mental activities, loss of mastery over volition, of endeavor, and the ability for independent action), as well as positive symptoms (described as a loss of the inner unity of the activities of the intellect, emotion, and volition in themselves) (Lavertsky, 2008).

Table 1. Emile Kraepelin's 'clinical forms' (Kraepelin, 1919; Kraepelin, 1990)

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| <ul style="list-style-type: none"> • Dementia praecox simplex: impoverishment and devastation of the whole psychic life, which is accomplished quite imperceptibly. • Hebephrenia: insidious change of personality with shallow capricious affect, senseless and incoherent behaviour, poverty of thought, occasional hallucinations, and fragmentary delusions, progressing to profound dementia. • Depressive dementia praecox (simple and delusional form): the initial state of depression followed by slowly progressive cognitive decline and avolition, with or without hypochondriacal or persecutory delusions • Circular dementia praecox: prodromal depression followed by the gradual onset of auditory hallucinations, delusions, marked fluctuations of mood, and aimless impulsivity. • Agitated dementia praecox: acute onset, perplexity or exaltation, multimodal hallucinations, fantastic delusions. • Periodic dementia praecox: recurrent acute, brief episodes of confused excitement with remissions. • Catatonia: the conjunction of peculiar excitement with catatonic stupor dominates the clinical picture" in this form, but catatonic phenomena frequently occur in otherwise wholly different presentations of dementia praecox. • Paranoid dementia (mild and severe form): the essential symptoms are delusions and hallucinations. The severe form results in a "peculiar disintegration of psychic life," especially emotional and volitional disorders. The mild form is a very slowly evolving "paranoid or hallucinatory weak-mindedness" which "makes it possible for the patient for a long time still to live as an apparently healthy individual. • Schizophasia (confusional speech dementia praecox): cases are meeting the general description of dementia praecox but resulting in an end-state of "an unusually striking disorder of expression in speech, with relatively little impairment of the remaining psychic activities." |
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In 1911, a Swiss psychiatrist, Paul Eugene Bleuler, disagreed with the presentation of dementia in dementia praecox and coined the term 'schizophrenia.' The term schizophrenia has its roots in the early 20th century Latin words, *skhizein* meaning 'to split' and *phren* meaning 'mind.' Thus schizophrenia is understood with a characteristic as the splitting of the mind. Bleuler introduced the symptoms of schizophrenia as primary and secondary symptoms. He called the four primary symptoms as the four As, which included abnormal associations, autistic behaviour and thinking abnormal affect and ambivalence. Bleuler's view of the illness being a dissociative process is fundamental to the conceptualisation of schizophrenia and its symptom manifestations. Schizophrenia is a single disease entity in which there is an extensive similarity in the etiology (cause) and pathophysiology (a mechanism) across all patients with the disorder.

Alternatively, schizophrenia is characterized as a clinical syndrome rather than a single disease entity, often understood as having heterogeneity in presentation. This view holds that although patients with schizophrenia share commonalities of signs and symptoms that are enough to differentiate them from other disorders, more than one disease entity is likely to be found within this syndrome (Sadock & Sadock, 2008). There is extensive variability in clinical presentation, disease course, and how patients respond to pharmacological and psychosocial treatment.

The modern-day understanding of schizophrenia is a neuropsychiatric condition (Gur, 2011), classifying as a debilitating psychiatric illness adversely influencing the development of mental capacities in thought, emotion and behavior. In the illness's active phase, the individual experiences delusions, hallucinations, disorganized speech, trouble with thinking, and lack of motivation (APA, 2020). According to the latest Diagnostic and Statistical Manual of Mental Disorders (DSM) Edition 5, schizophrenia is no more classified as various types (schizophrenia was classified under five subtypes of paranoid, catatonic, residual, undifferentiated, and disorganized-till DSM IV-TR) but diagnosed as a schizophrenia spectrum disorder (DSM 5, 2016).

EPIDEMIOLOGY

Schizophrenia is a public health challenge with no society or culture in the world found free from this impairing mental health condition. It affects about 0.5-1 percent of the world's population (approximately 0.85 percent) (Sadock & Sadock, 2008). It is a mythical conception that schizophrenia has a universal prevalence. Difficult to study the exact demographic differences across time; it is found that the incidence is between 8%-43% (McGrath et al., 2008); however, the lifetime prevalence remains more or less the same throughout the world. The recent (2016) global age-standardized point prevalence of schizophrenia was estimated to be 0.28%. However, the point prevalence of schizophrenia, the proportion of the population at a point in time with the disorder, is about 7/1000 in the global population (McGrath et al., 2008).

Age of Onset

Although schizophrenia can occur at any age, the average age of onset tends to be in the late teens to the early 20s for men and the late 20s to early 30s for women. It is uncommon for schizophrenia to be diagnosed in a younger than 12 years or older than 40 years (National Alliance of Mental Illness, 2020). Schizophrenia in children younger than 12 years, early onset, is referred to as Childhood onset Schizophrenia or COS and is very rare. In children, COS can often be misunderstood for various other diagnoses. The epidemiologic incidence of the diagnosis based on standardized clinical assessments are lacking. It is generally accepted that the incidence of COS is less than 0.04% based on the observations from the National Institutes of Mental Health (NIMH) cohort (Driver et al., 2013).

Ever since the DSM III-R, the late onset of schizophrenia has been anchored at 44 years of age, accounting for 15-20% of all the cases (APA, 1987). The same continues to be accepted for ICD-11 (Gaebel, 2012). Most patients with late onset usually have had an onset in the middle age but may remain mild, remain unidentified or go undiagnosed. Psychosis after the age of 65 years signifies very-late onset schizophrenia; it is most often secondary to medical conditions like dementia or neurodegenerative disorders (Sable et al., 2002).

Gender

The existence of gender differences in the incidence of schizophrenia has been subject to debate. The traditional consideration that the prevalence of schizophrenia is similar among men and women is a myth (Wyatt et al., 1988) and has been challenged to evidence gender differences. Several studies indicate that the incidence rate of schizophrenia is higher in men. The mean age of onset for men is usually 18–25 years, while the mean age of onset in women is 25–35 (Ochoa et al., 2012). A systematic review analysis of 31 studies reveals that the male to female rate ratio can be estimated to be 1.4:1 (McGrath & John, 2005). Though no gender differences have been found in the prevalence of schizophrenia in epidemiological studies, it seems that more new cases of schizophrenia have been detected in men (Ochoa et al., 2012).

Urbanicity and Socio-Economic Status

The incidence of schizophrenia in rural and urban areas are somewhat similar. However, expressly, a greater prevalence of schizophrenia is noted among the urban population and those belonging to the lower socio-economic classes. This difference is generally attributed to the "social drift" phenomenon in which vulnerable individuals tend to lose their occupation which pushes them into pockets of poverty (Sadock & Sadock, 2008). A strong link between socio-economic status and schizophrenia has been highlighted by encompassing income inequality, low parental socio-economic status, migration, and overall socio-economic deprivation (Lee et al., 2018). Studies have also shown correlations between poverty and the incidence of schizophrenia. However, a challenge that remains to pose is the inconsistent methodologies and differing urbanization rates.

Race and Ethnicity

Understanding the prevalence of schizophrenia in the context of race and ethnicity is a challenging task, given that the current diagnostic criteria do not display satisfactory cultural competence. Some studies speak of differences in incidence and symptom presentation of schizophrenia spectrum disorder across racial and ethnic groups. However, more important is to address the nuance if these differences arise more for clinician biases, lack of cultural competence of diagnostic criteria and. Further research is required to clarify the racial/ethnic conundrum in the context of schizophrenia spectrum disorder (Gurak et al., 2018).

ETIOLOGY

The etiological processes of schizophrenia continue to be unknown. It is debatable yet to see if schizophrenia is a neurodevelopmental (impacting brain development) or a neurodegenerative (affecting the normal and healthy developed brain) disorder. Although Kraepelin believed that schizophrenia had an early onset and was a chronic deteriorating disorder, examining the clinical course of the illness has not helped clarify this issue. Clinical

features like subtle neurological manifestations, cognitive dysfunction, and disturbances in affect are some primary symptoms seen in patients with schizophrenia- it remains uncovered whether these arise from an injured brain with lesions or are a function of neurodevelopmental abnormalities of the developing brain. However, a good deal of understanding of the risk factors of schizophrenia becomes a reliable guide to understanding probable causative factors. The heterogeneity of the illness further exacerbates the complexity of etiopathophysiology. Despite this, there are the following plausible etiological considerations to understand the causation of schizophrenia spectrum disorder:

Diathesis Stress Model

One of the fundamental ways of explaining the development of schizophrenia is through the diathesis stress model. It proposes that the individual who develops schizophrenia has a predisposition of biologic vulnerability or 'diathesis' triggered by stress and leads to schizophrenia symptoms. Stress can be biological, psychological, genetic, or environmental.

Genetics

There are single-gene and polygenic theories proposed to understand the development of schizophrenia. Though none of the theories are conclusive, polygenic theories are given more weightage as plausible causative factors.

The risk for schizophrenia is higher in consanguineous families than in the general population. Among twin studies, it is yet higher in monozygotic twins versus dizygotic, with a concordance rate for schizophrenia between 40 to 50 percent with heritability estimates about 80-85%. This concordance rate is 4-5 times that in dizygotic twins or the rate of occurrence found in other first-degree relatives such as siblings, parents, or offspring. Surprisingly, genetic factors have also been found in second- and third-degree relatives in whom generally the genetic load is expected to be lowered (Kavanagh et al., 2015). Adoption studies have also delineated the greater prevalence in biological parents of adoptees with schizophrenia versus adoptive parents. Studies have also found higher rates of schizophrenia when born to unaffected parents but reared by parents with schizophrenia (Leo, 2006).

There has been documentation of robust findings on family, twin and adoptive studies in regards to contribution of genetic factors to the etiology of schizophrenia. Evidence for genetic factors have been established in almost all cases of schizophrenia. However, it is not yet known which specific genes are underlying, nor the contribution of specific proteins is known to the pathophysiology of schizophrenia. Recent linkage analyses have revealed the potential location on chromosome 6 and contributions associated with chromosomes 4, 8, 15. Research studies also talk about microdeletion of a region on chromosome 22, called 22q11, that has been found in cases of schizophrenia and thus a supposed causal factor (Escudero et al., 2014).

Novel technologies such as next-generation sequencing (NGS), genome-wide association studies (GWAS), and the Clustered Regularly Interspaced Short Palindromic Repeats-associated nuclease 9 (CRISPR/Cas9) genome editing platform are capable of interrogating

and editing the genome directly. These efforts have led to identifying essential loci and genes susceptible to schizophrenia (Zhuo et al., 2019).

Findings to date are not conclusive and demand accelerated research to clarify the disorder's heritability and genetic load. Alternatively, Torrey and Yolken (2019) have argued that schizophrenia may be a pseudo-genetic condition with an overestimation of heritability linkages which could be better explained by infectious transfer (Torrey & Yolken, 2019). There is a need for further gene-environmental studies to clarify this stand. In addition, epigenetic findings have surged in research, with time, compared with healthy controls. Many of the findings revealed associations with epigenetic modulations of genes regulating neurotransmission, neurodevelopment, and immune function, as well as differential miRNA expression (Smigielski et al., 2020).

Neurotransmitter Theories

1. Dopamine hypothesis: Dopamine alterations are related to schizophrenia (Wang et al., 2012). An increase of dopaminergic activity in the mesolimbic region and decreased activity in the prefrontal region is implicated in positive and negative symptoms of schizophrenia, respectively (Brisch et al., 2014). Recent research has outlined the dopaminergic activities, and the interaction with other neurochemicals is essential to explain the etiology for schizophrenia. Dopamine receptors D1 through D5 have been identified to play a role in the etiology of the illness. Another oft researched hypothesis is Gamma-aminobutyric acid (GABA), which discusses that patients with schizophrenia have fewer GABAergic neurons in the hippocampal area. Decreased GABA activity has also been found to increase dopamine activity implicated in schizophrenia.
2. Norepinephrine hypothesis. It is another suggestion while understanding the development of schizophrenia that posits a relationship between increased norepinephrine levels and consequent sensitization of sensory inputs. Norepinephrine is also implicated in the impaired capacity of emotional regulation and decreased ability to feel pleasure- anhedonia- symptomatology of schizophrenia.
3. Serotonin hypothesis. Hyperserotoninemia and hyposerotoninemia forms of abnormal serotonin metabolism are reported in patients with schizophrenia. Specifically, antagonism at the serotonin 5-HT₂ receptor has been emphasized. Chronic widespread stress-induced serotonergic overdrive in the anterior cingulate cortex (ACC) and dorsolateral frontal lobe of cerebral cortex in schizophrenia is the primary cause of the disease (Eggers, 2013).
4. Glutamate hypothesis. Hypofunction of the glutamate N-methyl-D-aspartate (NMDA)-type receptor is theorized to cause both positive and negative symptoms of schizophrenia. This hypothesis furthers the explanation with glutamate, including hyperactivity, hypoactivity, and glutamate-induced neurotoxicity that are underpinned in the development of schizophrenia.

Neurodevelopmental Theories

Weinberger, Murray & Lewis formulated the neurodevelopmental hypothesis of schizophrenia. This understanding propounds the development of schizophrenia later in life due to abnormal neuronal functioning and neural development in childhood. Structural brain abnormalities, frequent occurrence of cognitive and motor abnormalities at a young age, and the possible presence of neonatal lesions (Owen et al., 2011) have been some ways of tracing back to understand the development of schizophrenia. There is evidence for abnormal neuronal migration during the second trimester of fetal development (Hwang et al., 2019).

Neuro Immunovirology

The immune and viral hypotheses of schizophrenia have existed for far longer, though with weak empirical efficacy. These theories have been difficult to conduct and study because any potential marker of an immune or viral process associated with schizophrenia is limited in application to few cases. Besides, it is also subject to interpretation where the immunoviral hypothesis could be better explained by conditions associated with the disease (e.g., high rates of exposure in crowded hospitals with chronically ill patients, low socio-economic circumstances, and poor health habits).

Miscellaneous Factors

Some miscellaneous factors that have been hypothesized in the causal explanations for the neurodevelopmental pathological process of schizophrenia include gestational complications and complications during birth, exposure to influenza, Rhesus (Rh) incompatibility, starvation, and births during winter months (Sadock & Sadock, 2008). However, the exact pathophysiological mechanisms associated with these risk factors remain unknown.

PSYCHOSOCIAL THEORIES OF SCHIZOPHRENIA

Various theories embedded in the psychosocial framework have been delineated to understand the roots of the development of the illness (Sadock & Sadock, 2008). Most prominent theories are discussed below.

Psychoanalytic Theories

The classical psychoanalytic foundation laid by Sigmund Freud postulated that early life developmental fixations produce defects in ego development which contribute to the symptoms of schizophrenia. Ego disintegration in schizophrenia represents a return to when the ego was not yet developed or had just begun to be established, explaining the regressive

behavior in schizophrenia. The ego functions are impaired due to how the ego alters the interpretation of reality and the control of inner drives (sex and aggressive instincts). The intrapsychic conflict between fixations from early life and defects in ego fuel psychotic symptoms such as losing touch with reality. As Margaret Mahler explains the child's insecure attachment style, the infant and the mother's reciprocal relationship is distorted. The child fails to grow independent of the mother in the oral phase of development.

Harry Stack Sullivan viewed schizophrenia as a disturbance in interpersonal relatedness. He proposed that schizophrenia is an adaptive method used by patients to avoid panic, terror, and disintegration of the sense of self resulting from cumulative experiential traumas during development.

The psychoanalytic theory also postulates varied symbolism in various symptoms of schizophrenia for individual patients.

Learning Theories

Learning theorists propose that schizophrenia develops in later life in children who learned irrational ways of thinking and behaving to imitate parents with emotional troubles. The presence of poor models in childhood is responsible for the poor interpersonal relationships, which further become a risk factor for the development of schizophrenia.

Double Bind

Gregory Bateson and Donald Jackson coined the double-bind concept to describe a hypothetical family in which children receive opposing and conflicting messages from parents. The messages are centered around behavior, attitudes, and feelings that confuse the child model to follow/learn from. Bateson hypothesizes that children withdraw into a psychotic state to escape the confusion of the double bind, which they find unsolvable. However, the lack of empirical backing does not make the theory fit enough to explain a causal explanation of schizophrenia.

Skewed Families and Family Schism

Theodore Lidz conceptualized two abnormal family behavioral patterns implicated in the development of schizophrenia. There is a prominent divide (schism) between the parents; one parent is overly close to a child of the opposite gender. In the family skew, a skewed relationship between a child and one parent involves a power struggle between the parents and one parent's resulting dominance. Both the family-type dynamics induce stressed adaptation for the person with schizophrenia.

Pseudomutual and Pseudohostile Families

Lyman Wynne described some families suppress emotional expression by consistently using pseudomutual or pseudohostile verbal communication. There is a pretense of cordial communication when there is conflict (pseudomutual), and sometimes families fake conflicts to hide cordiality (pseudo-hostile). In such families, exceptional verbal communication develops, influencing the child's communication patterns. The child fails to integrate messages and is left confused and incomprehensible to the outsiders.

Expressed Emotion

A higher end of emotional expression, especially demonstrated through parental control, over criticism, hostility, and demandingness can trigger the psychotic outbreak in persons with schizophrenia. Many studies have indicated that in families with high levels of expressed emotion, the relapse rate for schizophrenia is high. The assessment of expressed emotion involves analyzing both what is said and how it is said.

PATHOPHYSIOLOGY

The earliest and only way of understanding the neuroanatomy of schizophrenia was the examination of the brain tissue through postmortem. The complexity in discerning the exact neural pathways and pathophysiology of schizophrenia earned it to be "the graveyard of neuropathology," which often caused difficulty understanding if neuropathological findings were a cause or consequence. This is attributed to the heterogeneity of the illness. It is relatively well established that schizophrenia can result from single or multiple disorders of the brain regions. With the understanding of schizophrenia moving away from the gene-based developmental factors, recent research focuses on exploring different neurodevelopmental or environmental causes for the pathophysiology of the illness. Despite the lack of conclusivity, several theories around nature, timing, and the course of the brain change that effort to explain the development of schizophrenia (Lakhan & Vieira, 2009). There has been strong evidence on explaining the linkages between multiple neurotransmitter pathways such as dopaminergic, glutamatergic, GABAergic, and cholinergic neurotransmitter systems with the pathophysiology of schizophrenia (Benes, 2009).

The introduction of neuroleptic drugs for the treatment of schizophrenia and the interest in noninvasive techniques led to further investigation into pathophysiology.

Neuroimaging

Earlier in the years, primary neuroimaging techniques like pneumoencephalography (PEG) and CT scans have provided substantial evidence for enlarged brain ventricles and sulcal widenings, suggesting lesser brain tissue in patients with schizophrenia as compared to controls. Electroencephalography or EEG provided information on cortical surface electrical

activity. Conclusively, PEG, CT nor EEG techniques fell short of providing functional information about the brain.

Decreased cortical gray matter in the temporal cortex, decreased volume of limbic system structures, and increased volumes of basal ganglia nuclei have been found in studies employing magnetic resonance imaging (MRI). Functional imaging studies provide real time functional data, like, recording abnormal patterns of glucose metabolism/blood flow while cognitive tasks were being performed.

Neural Circuits

The biochemistry of the brain plays a fundamental role in the disruptions of brain function involved in schizophrenia, given that information is processed through neurons and neuronal networks (Benes, 2009). An integrative approach of the neuroanatomical understanding with biochemical disruptions is considerable to trace the pathophysiology of schizophrenia. Over the last 30 years, schizophrenia has grown from being conceptualized as a disorder that involves discrete brain areas to a view that schizophrenia is a disorder of neural circuitry in the brain. This paradigm shift in understanding the pathophysiology schizophrenia posits the plausible presence of a structural or functional lesion in the neural circuit that causes various dysfunctions as seen in the illness.

Studies done on the pathophysiology of schizophrenia using postmortem and structural/functional studies have implicated the limbic cortex, especially in the hippocampus (HC) and the anterior cingulate cortex (ACC), with the involvement of abnormal regional cerebral blood flow (rCBF). Each neurocircuitry is responsible for a different set of functions. Dysfunction of one neurocircuitry is independent of that of another. Some symptoms of schizophrenia, such as task difficulty and cognitive symptoms, are mediated as a possible dysfunction of the neuronal activity in the ACC and HC. It has been hypothesized that dysfunction of the anterior cingulate basal ganglia-thalamocortical circuit underlies the production of psychotic symptoms, and dysfunction of the dorsolateral prefrontal circuit underlies the production of primary enduring negative or deficit symptoms (Lakhan & Vieira, 2009).

The production of hallucinations, delusions, and positive formal thought disorder are a function of Wernicke's and Broca's areas and associated cortical and subcortical structures. Although the pathophysiology of schizophrenia remains unknown, clues about its mechanisms are emerging and evolving. (Tamminga et al., 2002).

CLINICAL FEATURES

The clinical features, signs, and symptoms of schizophrenia are not pathognomonic but are commonly found overlapping with those of other psychiatric disorders. Thus, signs and symptoms are not diagnostic in nature without the context of case history and MSE. It is also crucial to incorporate the educational level, intellectual capability, and socio-cultural framework to formulate the diagnosis. Additionally, it is vital to understand and note symptoms' temporal nature while case history taking and examination.

As part of understanding the clinical features of schizophrenia, it is relevant to understand the prodrome phase of schizophrenia. With multiple understandings, prodrome, as described by Keith and Matthews (1991), refers to a 'heterogeneous group of behaviors temporally related to the onset of psychosis' (George et al., 2017). The DSM III (1987) included nine characteristics of the prodrome, as listed below:

1. Marked social isolation or withdrawal
2. Marked impairment in role functioning
3. Markedly peculiar behavior
4. Marked impairment in personal hygiene and grooming
5. Blunted or inappropriate affect
6. Digressive, vague, overelaborate or circumstantial speech, or poverty of speech, or poverty of content of speech
7. Odd beliefs or magical thinking
8. Unusual perceptual experiences
9. Marked lack of initiative, interests, or energy.

However, this has been dropped from DSM IV and ICD-10 onwards and remains characteristic of its illness. Though met with a diagnostic dilemma, it is said that about 75% of patients experience this phase before developing the full-blown illness. A subclinical threshold of symptoms and non-specific anxiety and affective disturbance are seen at least one year before the full blow episode of psychosis. Current estimates say that 1 in 4 of the high-risk patients will progress to schizophrenia (George et al., 2017).

Some experienced clinicians express a *precox feeling*, that is, their inability to establish an emotional rapport with the patients. Anecdotally, it is frequently reported but lacks empirical backing to confirm it as a marker for diagnosing schizophrenia.

Symptoms of schizophrenia are most conveniently understood by desiccating them into positive and negative symptoms. Positive symptoms are abnormally present complaints that cause distress to patients, leading to the experience of not being in touch with reality. Positive symptoms usually classify to be perceptual differences. The most vivid positive symptoms are hallucinations and delusion.

Hallucinations, experienced by nearly 70-75% of patients, are perceptual disturbances affecting any individual's five senses. Auditory hallucinations are the commonest reported hallucination, followed by visual hallucinations, followed by tactile and olfactory. The least reported hallucination is that of taste or gustatory hallucinations. Delusions are more common than hallucinations, observed in more than 90% of patients. A delusion is a false belief that indicates an abnormality in the content of thought. The false belief is not accounted for by the person's cultural or religious background or intelligence level. Based on content (Kiran & Chaudhury, 2009), delusions are categorized as a delusion of persecution (the most frequently encountered delusion), grandiose delusions (also called expansive delusion, all forms of hallucinations can occur), a delusion of infertility (referred to as sexual jealousy by Emile Kraepelin), a delusion of love (erotomania, commoner in women), religious delusion (formed a higher proportion in the nineteenth century than in the twentieth century and are still prevalent in developing countries), nihilistic delusion (reverse of grandiose delusion) and delusion of guilt and unworthiness (may lead to suicide).

Disorganized symptoms include confused and disordered thinking and speech, trouble with logical thinking, and sometimes bizarre behavior or abnormal movements. Disorganized symptoms encompass disorganized thought, speech, and behavior which are incoherent, unrelated, illogical, and sometimes even bizarre.

Negative symptoms signify a lost function or absence of function. Theoretically, there can be a large number of potential negative symptoms. Given the variety of cognitive, emotional, and socio-occupational deficits seen in schizophrenia, excepting defects in the domain of emotion, the rest are not defined as negative symptoms (Sadock & Sadock, 2008), some of the primary ones being:

- Affective flattening/blunting
- Unchanged facial expressions
- Decreased spontaneous movements
- Paucity of expressive gesture
- Poor eye contact
- Affective non-responsivity
- Inappropriate affect
- Lack of vocal inflections

There are additional symptoms to the negative symptoms recognized as associated symptoms called *alogia* (poverty of speech, content of speech, blocking, increased latency of response), *avolition-apathy* (grooming and hygiene, absence at work/school, lack of energy), *anhedonia-asocial* (lack of motivation, lack of interest in interpersonal relationships) and *attention* (social inattentiveness, disorientation). Signs and symptoms must present for at-least six months to make a diagnosis.

COMORBIDITIES

Physical and psychiatric comorbidities are common among patients with schizophrenia. The most predominant comorbid condition seen with schizophrenia is substance abuse, seen in about 47% at lifetime prevalence. A comorbid diagnosis of anxiety and depressive symptoms is also widespread throughout the course of illness. Research (Buckey et al., 2009) shows an estimated prevalence of 15% for panic disorder, 29% for posttraumatic stress disorder, 23% for obsessive-compulsive disorder, and comorbid depression occurs in 50% of patients.

Obesity and metabolic syndrome are among the significant medical comorbidities in schizophrenia, with evidence of a relationship between weight gain or metabolic syndrome and antipsychotic medications (Norlelawati et al., 2012). People with schizophrenia are also at higher risk for hepatitis, cardiovascular diseases, diabetes, sexual dysfunction, and obstetric complications (Santos et al., 2017).

Diagnosis

Schizophrenia is a disorder whose diagnosis is based on the patient's observation and description. Abnormalities are often present on most components of the mental status examination. There are no pathognomonic signs or symptoms. According to the Diagnostic Statistical Manual of Mental Disorders -fifth edition (DSM-5), at-least two of the following five symptoms must present for at least one month. (1) Hallucinations; (2) delusions; (3) disorganized speech; (4) disorganized behavior; or (5) negative symptoms (e.g., flat affect, abulia).

The diagnosis of schizophrenia is often misunderstood leading to erroneous conclusions. Throughout most of the twentieth century, there has been substantial agreement among diagnosticians throughout the world, using seemingly divergent diagnostic approaches, in recognition of typical cases of schizophrenia. There has also been no difficulty in distinguishing schizophrenia from normality.

The identification of several diagnostic issues identified in a body of research in the 1960s and 1970s warranted for developing an adequate diagnostic system which was implemented in DSM-III. This was retained till DSM IV TR and ICD 10. The advent of DSM 5 saw some changes in the way schizophrenia was diagnosed.

The following is the exhaustive criteria of diagnosis according to DSM 5 (DSM 5, 2013).

Table 2. DSM 5 diagnostic classification of schizophrenia

A.	Overall functioning. Level of functioning declines or fails to achieve the expected level.
B.	Thought content. Abnormal (e.g., delusions, ideas of reference, poverty of content). Delusion and hallucinations are not necessary to diagnose if other signs and symptoms are present.
C.	Form of thought. It is illogical (e.g., derailment, loosening of associations, incoherence, circumstantially, tangentiality, over-inclusiveness, neologisms, blocking, echolalia—all incorporated as a thought disorder).
D.	Perception. Distorted (e.g., hallucinations: visual, olfactory, tactile, and, most frequently, auditory).
E.	Affect. Abnormal (e.g., flat, blunted, silly, labile, inappropriate).
F.	Sense of self. Impaired (e.g., loss of ego boundaries, gender confusion, inability to distinguish internal from external reality).
G.	Volition. Altered (e.g., inadequate drive or motivation and marked ambivalence).
H.	Interpersonal functioning. Impaired (e.g., social withdrawal and emotional detachment, aggressiveness, sexual inappropriateness).
I.	Psychomotor behavior. Abnormal or changed (e.g., agitation vs. withdrawal, grimacing, posturing, rituals, catatonia).
J.	Cognition. Impaired (e.g., concreteness, inattention, impaired information processing).

DSM-5 no longer classifies schizophrenia based on subtypes.

Differential Diagnoses

Disorders considered as the differential diagnosis for schizophrenia are primarily divided into medical- neurologic conditions, medical conditions, and psychiatric conditions. However, to further detail, the categorization can also spread across- anatomic lesions, metabolic syndromes, endocrine disorders, infectious illnesses, and vitamin deficiencies.

Some studies have confirmed that schizophrenia can be over-diagnosed, with up to 50% of patients being misdiagnosed as schizophrenia (John Hopkins Medicine, 2019). The following are some essential diagnoses to ensure the sanctity of diagnosis.

Medical-Neurologic Conditions

- Substance-induced—amphetamine, hallucinogens, belladonna alkaloids, alcohol hallucinosis, barbiturate withdrawal, cocaine, phencyclidine
- Epilepsy—especially temporal lobe epilepsy

Neoplasm, cerebrovascular disease, or trauma—especially frontal or limbic

- Other Medical Conditions Acute intermittent porphyria
- AIDS
- Vitamin B12 deficiency
- Carbon monoxide poisoning
- Cerebral lipoidosis
- Creutzfeldt–Jakob disease
- Fabry's disease
- Fahr's disease
- Hallervorden–Spatz disease
- Heavy metal poisoning
- Herpes encephalitis
- Homocystinuria
- Huntington's disease
- Metachromatic leukodystrophy
- Neurosyphilis
- Normal pressure hydrocephalus
- Pellagra
- Systemic lupus erythematosus
- Wernicke–Korsakoff syndrome

Wilson's Disease

- Psychiatric Conditions Atypical psychosis
- Autistic disorder
- Brief psychotic disorder
- Delusional disorder
- Factitious disorder with predominant psychological presentation
- Malingering
- Mood disorders- major depressive disorder & bipolar disorder
- Obsessive-compulsive disorder
- Cluster A and B personality disorders
- Schizoaffective disorder

Schizophreniform Disorder

Diagnostic concepts play a critical role in identifying risk factors, etiology, assess comorbidities, and end-goal of management and treatment of schizophrenia patients. This is met with an inherent challenge of the heterogeneity of the illness and the weakness of the diagnostic concept of the illness as a result of the unknown pathophysiology, etiology, and the wavering presentation of symptomatology. However, the utility of diagnosis is maintained with the spectrum-based understanding of the illness that allows addressing overt symptoms and patient-reported concerns. (Jablensky, 2006).

Diagnostic Tools for Schizophrenia

The first step in diagnosing the illness involves ruling out other mental health disorders and determining that symptoms are not a function of a comorbid condition. Determining a diagnosis of schizophrenia may include:

- i. Case history and MSE: to get a detailed understanding of the presentation of symptoms, onset, and course of illness along with personal, past, and family histories. MSE can help gauge the present status of illness presentation, temporally, in the patient.
- ii. Physical examination: to help rule out any medical problems that could be causing overlapping or similar symptoms and check for any medical complications, if any.
- iii. Screening tests: to rule out differential diagnoses and screen for possible symptomatology that could hint towards the psychosis presentation.
- iv. Diagnostic criteria for schizophrenia: a mental health professional may use the criteria in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) to confirm the illness presentation.

Clinical psychological assessment is also carried out for patients with schizophrenia to understand their motivations and presentation of the illness. These tests generally include projective testing techniques such as the Rorschach Inkblot Test, Thematic Apperception Test, and Drawing tests. Apart from these, several other rating scales can be used to confirm the presence of symptoms of the illness for a surer evaluation. Some of them being the following (Kumari et al., 2017):

1. *Positive and Negative Syndrome Scale (PANSS)*: Often referred to as the "gold standard" for measuring treatment progress. The PANSS scale involves an interview of about 30-40 minutes taken by the clinician, interviewing the caregivers, and reporting their symptoms (positive and negative).
2. *SANS and SAPS Tests*: SANS (Scale for the Assessment of Negative Symptoms) and SAPS (Scale for the Assessment of Positive Symptoms) check for the presence and effect of positive and negative symptoms in patients. It measures 25 negative symptoms of schizophrenia. SAPS test is a Scale for the assessment of 34 positive symptoms.

3. *Brief Psychiatric Rating Scale (BPRS)*: It is one of the most typical tests psychiatrists use to check the severity of schizophrenia using a checklist of 18 symptoms or behaviors.
4. *Clinical Global Impression-Schizophrenia (CGI-SCH)*: This test has been adapted from the more general Clinical Global Impression score, which is used to diagnose other psychiatric illnesses. Like the PANSS, this scale also assesses the progress of treatment but, contrastingly, can be used with a group of patients. The CGI-SCH measures two things: severity of schizophrenia and improvement on symptoms since the last check-up.

COURSE OF ILLNESS AND PROGNOSIS

With the severity of the illness, the course of the illness varies from patient to patient, depending on the frequency and intensity of symptom presentation, age of onset, severity of course, available emotional and social support, and treatment options. Though schizophrenia does not always end up in an excruciatingly debilitating condition, adverse effects of the illness indeed cripple most persons living with schizophrenia.

The course of the illness can be divided into four significant epochs: premorbid adjustment, the onset of illness, middle course, and late course. The premorbid adjustment refers to symptoms that appear prior to positive symptoms. Premorbid adjustment is manifested as poor social and academic adjustment, lack of social drive, decreased emotional responsiveness, social isolation, introversion, suspiciousness, or impulsive behavior among the cluster of symptoms, seen in about 25-50% of patients.

The onset of illness, the second epoch, typically refers to the onset of positive symptoms (i.e., hallucinations, delusions, and formal thought disorder). The onset of positive symptoms is insidious in about 50% of the patients, with the earliest signs showing several years before a full-blown episode of psychosis. This is usually indicative of a poor, intermediate course and poor prognosis. In cases where onset is relatively sudden or acute, in patients with typical development, the outcome and prognosis are generally more robust and positive. Childhood onset of the illness is a poor prognostic indicator for the illness.

The third epoch or middle course of illness has two sub epochs: the first has multiple exacerbations of positive symptoms and the second sub epoch (plateau phase), brings some stabilisation for the patients and a decrease in symptom exacerbations. Studies have shown that deterioration seen in the course of illness happens in the first or middle of the course rather than the remaining in the illness (Emsley et al., 2013). However, it must have adhered to the fact that schizophrenia remains a severe social and occupational burden regardless of the degree of recovery.

In the late course of illness (last epoch), there is a tendency for the intensity of positive symptoms to diminish. Improvement of social and occupational competence is seen in many patients with long-term impairments. Though the illness is less disruptive and easier to manage, it remains challenging to overcome the effects of years of dysfunction from the past. The years of life lost to disability and thus, impacting the quality of life is a loss that cannot be compensated for. Conclusively, in addition to the poor recovery outcomes, people with schizophrenia have a significantly reduced life expectancy and high excess mortality

compared to healthy controls (Charlson et al., 2016). Approximately 55% of patients with schizophrenia have moderately good outcomes, and 45% have severe outcomes (Häfner, 2015). It is promising to rely on these results for two reasons: the sample selection was representative, and that effective treatments with moderate and long-term benefits were administered.

TREATMENT MODALITIES

Schizophrenia is not curable but treatable and manageable with medication and psychological, behavioral interventions when diagnosed early and treated without a break. Treatment modalities of schizophrenia typically include psychotropic drugs to reduce the symptoms, psychosocial interventions, cognitive-behavioral therapy, which can help "train" patient social skills once symptoms are reduced. Psychopharmacological interventions are dominant in the public health system.

Recent evidence highlights that patients undergoing regular psychosocial interventions comply better with medication and have fewer relapses and hospitalizations (Chien et al., 2013; Loh et al., 2017; Saha et al., 2020). A stronger alliance with a patient with schizophrenia may offer a reliable source of information about schizophrenia and empathy, encouragement, and hope. Social networks and family member support have also been shown to be helpful.

Recent clinical researches have increasingly indicated significant improvement in patients' long-term health outcomes with community-based psychosocial interventions (Asher et al., 2017). Recent research and systematic reviews indicate that both psychiatric and psychosocial treatment offered early can improve their prognosis and even help prevent their worsening severity (Bellack, 2001; Chien et al., 2013).

Evidence suggests that health outcomes may be related to the time interval between the initial detection of schizophrenia and the initiation of psychotropic drug intervention. The timely diagnosis and treatment is associated with less severity of illnesses and positive prognosis. It confirms the importance of early screening of schizophrenia and the need for intensive therapeutic interventions, combining pharmacological and psychosocial treatments to ascertain positive health outcomes.

There is also considerable evidence suggesting the prophylactic use of psychotropic medication significantly reduces the relapse rate (Brissos et al., 2014). This potentially makes it possible to substantially reduce the load of inpatient care in favor of brief hospital stay, crisis intervention, and community-based treatment. It is well documented that an integrated approach including early identification and treatment of schizophrenia symptoms, a collaboration between patients and caregivers in managing treatment, family and social supports, and training in social skills improve the course and outcome of schizophrenia (especially symptoms, recurrence, social functioning, and quality of life).

TRADITIONAL MEDICINE AND HEALING PRACTICES

In many countries, schizophrenia is characterized as insanity or a mental problem due to possession by ghosts or evil spirits, thus approaching traditional healers for the treatment. A study conducted in Uganda, Egypt, found that a combination of modern psychiatry and traditional healing brings promising health outcomes (Abbo, 2011; Ibrahim Awaad, 2020). A recent study from India echoed similar findings, which complement existing primary health care services (Saha et al., 2021). Such approaches provide modern medicine access without compromising patients' religious and spiritual practices. A comprehensive review of scientific literature showed that several medicinal plants had been scientifically validated for the treatment of schizophrenia (Ahmed et al., 2014; Hoenders et al., 2018). Few studies from India have explored the role of Ayurveda (Indian medicine system) schizophrenia and found it complementary to psychotropic intervention (Agarwal et al., 2007; Ramu et al., 1992; Sarkar et al., 2012). Much robust evidence is required to explore the potential of traditional medicine to treat schizophrenia.

REHABILITATION AND REINTEGRATION

People living with schizophrenia require rehabilitation and reintegration to preserve a sense of physical wellness, mental, social, and economic well-being. Adequate daily exercise also forms part of a healthier daily routine and facilitates sleep patterns. For example, a study conducted by Saha and colleagues in India found that psychiatric rehabilitation of people living with chronic mental illness improves recovery (Saha et al., 2020).

Several approaches have been developed aiming at reducing the stigma associated with schizophrenia. Amongst major approaches, including social movement, mental health education, and educating people living with schizophrenia, the latter two approaches showed considerable reduction in the stigma (Corrigan et al., 2012; Stuart, 2016). These approaches must be included in an integrated approach to treat schizophrenia within the public health system.

CONCLUSION

The World Health Organization describes schizophrenia as one of the most severe and challenging psychiatric diseases. Although people with schizophrenia and affected people can lead a productive social life, limited numbers of people access appropriate and timely mental health care services. Evidence indicates a critical role of psychosocial intervention in recovery, rehabilitation & reintegration for delaying relapses. Additionally, traditional medicine and healing practices also play a crucial role in recovery; however, it needs more research in this area. In summary, schizophrenia still demands strong efforts to manage schizophrenia more effectively.

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